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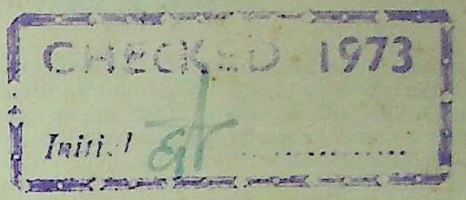

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VOLUME 79 MAY 7, 1957 NUMBER 9

PHYSICAL AND INORGANIC CHEMISTRY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

Precipitation of Calcite and Aragonite

BY JOHN L. WRAY AND FARRINGTON DANIELS

RECEIVED OCTOBER 22, 1956

The two common polymorphs of calcium carbonate, calcite and aragonite, have been precipitated by mixing soluble carbonate solutions with solutions of calcium ions under conditions of controlled temperature, concentration and aging. Results from these experiments have provided new information regarding the factors affecting the formation of these two crystalline varieties.

Introduction

Although the preparation of calcium carbonate has been described many times in the chemical and geological literature, the products usually have not been well defined and they have varied considerably with the experimental conditions. Among the important early workers who have attempted to determine the factors controlling the formation of the various crystalline varieties of calcium carbonate are Credner,[1] and Johnson, Merwin and Williamson.[2] A comprehensive summary of much of the early work was compiled by Mellor.[3] More recently, studies of artificial calcium carbonate have been made by deKeyser and Dugueldre.[4] Calcium carbonate can be precipitated in the laboratory in different crystalline forms as calcite, aragonite or vaterite, although calcite is the only thermodynamically stable form of pure $CaCO_3$ at room temperature and atmospheric pressure. The factors which are involved in the formation of the polymorphs of $CaCO_3$ apply then to the kinetics of metastable forms, rather than to equilibrium conditions.

The purpose of this investigation was to determine the conditions necessary to precipitate pure calcite, pure aragonite, or specific mixtures of the two. There is practical significance also for such a study. Calcium carbonate is finding extensive use in chromatography and the efficiency in such work depends not only on the size of the particles, but also on the calcite–aragonite ratio. Again, calcite and aragonite are found in nature and their origin is important in the interpretation of geologic phenomena.

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Experimental

Calcium carbonate was precipitated in 500-ml. round-bottom flasks by mixing soluble carbonate solutions with solutions of calcium ions with rapid mixing by a motor-driven stirrer. Reagent grade calcium nitrate manufactured by Merck and Co. was used. Spectrographic analysis of selected impurities in this material given in parts per million are as follows: MgO, 80; Fe_2O_3, 20; MnO, 3; SrO, 30; Pb <3; and BaO <3. Sodium carbonate manufactured by the Baker Chemical Co. gave MgO <10, Fe_2O_3 <10, MnO <3, SrO <3, Pb <5, and BaO <3. The experiments were carried out at temperatures from 30 to 70 ±1° and the precipitates were aged for periods from 6 minutes to 18 hours. The solutions were mixed to give precipitates of calcium carbonate as shown in Table I.

TABLE I

CONCENTRATIONS OF SOLUTIONS USED IN PRECIPITATING $CaCO_3$

Expt. series	Soln. added	Addn. rate, ml./min.	Soln. in flask
1	20 ml. 1.0 *M* $Ca(NO_3)_2$	5	200 ml. 0.1 *M* Na_2CO_3
2	20 ml. 1.0 *M* Na_2CO_3	5	200 ml. 0.1 *M* $Ca(NO_3)_2$

Additional experiments were performed in which 1.0 *M* $Ca(NO_3)_2$ and 1.0 *M* Na_2CO_3 were mixed. At selected temperatures and aging periods, calcium chloride was substituted for calcium nitrate in experiment series 1 and 2.

The *p*H of each solution was determined with a glass electrode. At the end of each aging period the precipitate was filtered immediately through a Büchner filter, thoroughly washed with distilled water, and dried at room temperature.

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The per cent. of calcite, aragonite and vaterite in the precipitates was determined by X-ray diffraction measurements and by examination with a petrographic microscope, in which the relative areas of rhombs of calcite, needles of aragonite, and spherulitic growths of vaterite were estimated with the aid of a linear scale. The limits of error in these determinations, both by X-ray diffractometer and petrographic microscope, may be as great as ±15%.

Results

Table II gives the results of experiment series 1.

TABLE II

CRYSTAL PHASES PRODUCED BY ADDING 1 *M* $Ca(NO_3)_2$ TO 0.1 *M* Na_2CO_3

Temp., °C.	Digestion time, hr.	Crystal phase (%) Aragonite	Calcite	Vaterite
30	0.1	..	5	95
	0.5	..	10	90
	3.0	..	20	80
	10.0	..	20	80
	18.0	..	100	..
40	0.1	5	95	..
	0.5	..	100	..
	3.0	..	100	..
	10.0	..	100	..
	18.0	..	100	..
45	0.1	70	30	..
	0.5	30	70	..
	3.0	2	98	..
	10.0	..	100	..
	18.0	..	100	..
50	0.1	100	..	..
	0.5	100	..	..
	3.0	95	5	..
	10.0	85	15	..
	18.0	70	30	..
70	0.1	100	..	..
	0.5	100	..	..
	3.0	100	..	..
	10.0	100	..	..
	18.0	100	..	..

The *p*H of the initial sodium carbonate solution was 10.9 at 30° and after complete precipitation with calcium nitrate it was 9.1. The sizes of the $CaCO_3$ particles ranged from about 10 to 15 μ.

The aragonite–calcite components of this series after various periods of aging, which are given in Table II between 40 and 50°, are shown graphically in Fig. 1.

Table III gives the results of experiment series 2.

The *p*H of the 0.1 *M* $Ca(NO_3)_2$ was 6.3 at 30° and increased to 9.1 with the addition of the 1 *M* Na_2CO_3. The grain size varied from about 10 to 20 μ.

The effect of increasing the concentrations of the reagents, using 1 *M* solutions of both $Ca(NO_3)_2$ and Na_2CO_3, was to give a finer grained precipitate (5–10 μ) and products that contain a much greater proportion of calcite and vaterite than aragonite when precipitated at high temperatures and allowed to age only for brief periods. For example, a precipitate containing 70% calcite, 20% vaterite and 10% aragonite was obtained at 70° after 6 minutes aging when 100 ml. of 1 *M* Na_2CO_3 was added to 100 ml. of 1 *M* $Ca(NO_3)_2$.

TABLE III

CRYSTAL PHASES PRODUCED BY ADDING 1 *M* Na_2CO_3 TO 0.1 *M* $Ca(NO_3)_2$

Temp., °C.	Digestion time, hr.	Crystal phase (%) Aragonite	Calcite	Vaterite
30	0.1	..	5	95
	0.5	..	5	95
	3.0	..	5	95
	18.0	..	25	75
40	0.1	..	15	85
	0.5	5	45	50
	3.0	5	95	..
	18.0	..	100	..
50	0.1	30	70	..
	0.5	25	75	..
	3.0	20	80	..
	10.0	10	90	..
	18.0	..	100	..
60	0.1	95	5	..
	0.5	95	5	..
	3.0	90	10	..
	10.0	50	50	..
	18.0	..	100	..
70	0.1	100	..	..
	0.5	100	..	..
	3.0	100	..	..
	10.0	..	100	..
	18.0	..	100	..

Essentially the same results, as shown in Tables II and III, were obtained when calcium chloride was substituted for calcium nitrate. This reagent grade material was manufactured by Mallinckrodt Chemical Works and analyzed (in p.p.m.): MgO, 25; Fe_2O_3, 25; MnO < 3; SrO, 60; Pb < 3; BaO < 3.

Many of the precipitations in experiment series 1 and 2 were repeated with reagent grade calcium nitrate manufactured by the General Chemical Company. This material analyzed (in p.p.m.): MgO, 25; Fe_2O_3, 35; MnO, 3; SrO, 40; Pb < 3; BaO < 3. These results were within ± 15% of the products obtained with the Merck calcium nitrate shown in Tables II and III.

Discussion

It is evident from the results of this investigation that it is easy to control temperature, *p*H and time so as to get either calcite or aragonite. It is surprising to find, as shown in Fig. 1, that the temperature range is so small and so critical. At 40° the precipitate is nearly pure calcite. At 45° it is 30% calcite and 70% aragonite, but changes during two hours digestion to more than 90% calcite. At 50° the precipitate is mostly aragonite. At temperatures between 45 and 50°, with suitable periods of digestion, one can obtain practically any ratio of calcite to aragonite. Although the precipitate suspended in solution may go rather rapidly to the more stable calcite, this change is stopped by filtering and drying the material. The rate of change in the dry state is indefinitely slow in the laboratory.

The temperature at which dry aragonite changes spontaneously into calcite at atmospheric pressure is quite high (usually above 400°). At very high pressures, aragonite is thermodynamically stable

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at lower temperatures, even at room temperature. The phase equilibrium diagram for the different crystalline varieties of calcium carbonate has been fully worked out.[5]

There is much geological and laboratory evidence to show that the aragonite crystal structure is favored by the inclusion in its lattice of cations as impurities which are larger than the calcium ion, such as strontium, barium, and lead.[6,7]

The ionic radii of the cations of the calcite and aragonite groups are given in Table IV.

TABLE IV

IONIC RADII OF CATIONS, ÅNGSTRÖM UNITS[8]

	Mg	Fe	Zn	Mn	Cd	Ca	Sr	Pb	Ba
Calcite type	0.78	0.83	0.83	0.91	1.03	1.06	..	..	..
Aragonite type	..	..	..	..	..	1.06	1.27	1.32	1.43

In this Laboratory, it was found[9] that aragonite generally has a higher content of strontium than calcite, and that the formation of aragonite is induced by adding strontium, barium or lead under conditions, namely, high *p*H, such that they will be co-precipitated with the calcium carbonate. Only in case these ions are incorporated into the lattice would they be expected to produce the aragonite. It was pointed out that the presence of these larger ions under the proper conditions tends to produce the aragonite, rather than that the aragonite is produced from other causes and takes up the strontium, barium, or lead which happen to be in solution.

In studying the aging process, it is important to distinguish three different stages[10] in the mechanics of crystallization: (a) an aggregation velocity in which the ions are brought together and precipitated; (b) an orientation velocity in which the ions in colloidal or amorphous material of the precipitated particles form crystals; and (c) a rate of recrystallization.

In the present work the aggregation velocity is considered to be infinitely rapid, the orientation is probably complete in a few seconds or minutes, and the recrystallization takes place in minutes, hours or days, and longer depending on conditions.

With the facts and generalizations discussed here, it is possible to explain the experimental results and to point out the factors which affect the production of calcite or aragonite.

The formation of the unstable aragonite having a larger crystal structure than calcite is favored by the incorporation of larger-sized cations, Sr^{++}, Ba^{++} or Pb^{++}, into the $CaCO_3$ lattice. The concentration of these ions may be very low, because once a seed crystal of aragonite or calcite is formed, the rest of the crystal growth tends to follow the same crystal pattern.

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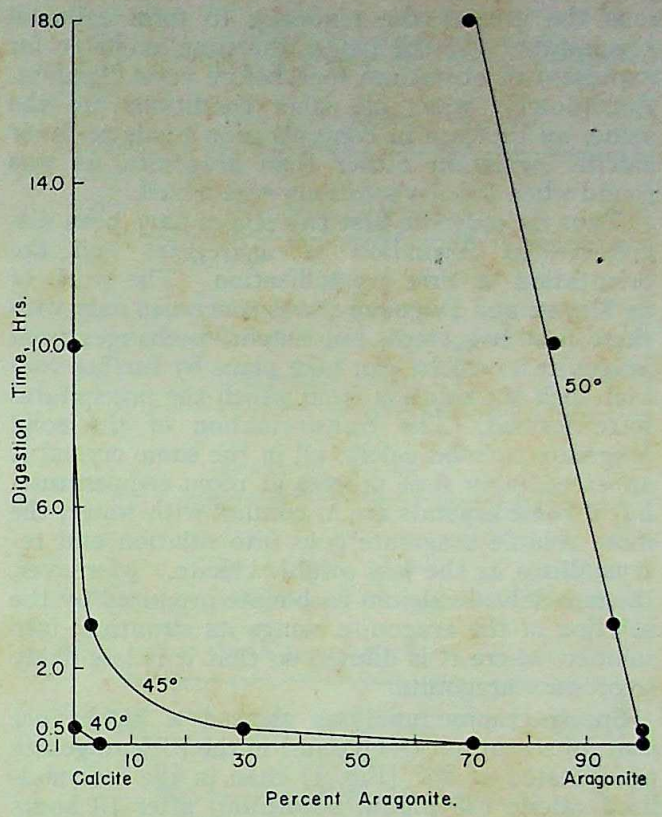

Fig. 1.—Influence of temperature and aging on the crystal form of precipitated calcium carbonate.

At low *p*H values, strontium, barium and lead carbonates do not precipitate, and the first colloidal particles of calcium carbonate to form do not contain these larger ions. Calcite is precipitated under these conditions. At higher *p*H values, however, these larger ions are co-precipitated with the calcium carbonate and there is a tendency to form aragonite.

At the instant of precipitation, the strontium ions as well as the calcium ions are brought from a large volume of solution into the small volume of the first colloid particles to form, thus giving in these aggregates a high concentration. In a matter of seconds or minutes, the colloid aggregate undergoes orientation leading to crystal formation. If there is sufficient time between precipitation and crystallization, the strontium (and barium and lead) ions can diffuse out of the colloidal particles into the strontium-depleted solution which surrounds them. Factors which tend to shorten this time for escape of strontium ions tend to produce aragonite, and those which lengthen the time before crystallization give more opportunity for the escape of strontium ions and thus tend to produce calcite.

At the higher temperatures, the rate of crystallization is accelerated rapidly and the strontium ions do not have time to escape and thus they are incorporated into the $CaCO_3$ lattice giving the larger structure—aragonite. In series 1, calcite is formed at temperatures below 40° and aragonite is formed at temperatures above 50°. At temperatures between these limits, the incorporation of strontium in the lattice is intermediate and a mixture of aragonite and calcite is formed.

The greater the concentration of precipitating

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ions the greater the tendency to form colloidal precipitates and the longer the time available for expulsion of strontium ions before crystallization. Accordingly, when all other conditions are the same, an increase in concentration tends to favor calcite formation rather than aragonite, as was found when 1 molar solutions were mixed.

Thus far only the first two stages have been discussed—the formation of aggregates and the orientation or first crystallization. The work of de Keyser and Dugueldre[4] was concerned only with these first two steps, but extensive changes from aragonite to calcite can take place by further contact with the solution from which the precipitates were formed. The transformation of the solid aragonite to solid calcite all in the same crystal is an exceedingly slow process at room temperature, but if these crystals are in contact with water, the more soluble aragonite goes into solution and recrystallizes as the less soluble calcite. Moreover, the redissolved calcium carbonate produced by the solution of the aragonite brings its strontium into solution where it is diluted so that it is less likely to produce aragonite.

Spectrographic analyses showed a higher per cent. of strontium (80 p.p.m.) in the 70% aragonite precipitated at 45° (Fig. 1) than in the recrystallized calcite (25 p.p.m. strontium) after 10 hours of standing in the solution.

The removal of strontium ions from aragonite which is undergoing recrystallization is believed responsible for the formation of calcite. This hypothesis was confirmed with additional experiments. Pure aragonite precipitated at 50° and its surrounding solution was divided equally and placed in two separate flasks and maintained at 50°. To one of these was added 100 ml. of 0.1 *M* $Sr(NO_3)_2$. In this flask there was no trace of calcite formation after 20 hours, whereas in the flask to which strontium nitrate had not been added, about 50% of the aragonite had changed to calcite in the same period of time.

The fact that similar results were obtained with calcium nitrate of two different manufacturers probably indicates that after a certain minimum concentration of strontium and other critical impurities are reached, higher concentrations have but little further effect.

At first sight, it would be expected that the recrystallization from aragonite to calcite would go faster at high temperatures, but an examination of Fig. 1 shows that at 40° the 95% calcite changes to 100% calcite in half an hour, at 45° it changes from 30 to 100% in about 10 hours, and at 50° it changes only from zero to about 35% in 18 hours. The number of calcite crystals to act as nuclei for further growth is much less in the precipitates formed at the higher temperatures. The slowness to go from aragonite to calcite at the higher temperatures is thus explained as due to the relative absence of calcite seed crystals. This hypothesis was checked by taking out a precipitate of 50% aragonite and 50% calcite slowly changing at 45°. When this precipitate in its solution was heated to 70° the change to calcite was complete in two hours, whereas at 45° it required ten hours. If sufficient seed crystals are present, the higher temperature does give a faster rate of transformation to the stable calcite, as would be expected.

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MADISON, WISCONSIN

[CONTRIBUTION FROM THE OAK RIDGE NATIONAL LABORATORY, CHEMISTRY DIVISION, OAK RIDGE, TENN.]

Equilibrium Ultracentrifugations of Acidic Hg(I), Hg(II), In(III), and Au(III) Solutions[1]

BY JAMES S. JOHNSON AND KURT A. KRAUS

RECEIVED DECEMBER 1, 1956

Equilibrium ultracentrifugations confirm that In(III) in HBr and Au(III) in HCl exist as mononuclear complexes. The results contradict recent suggestions based on solvent extraction data that dimers of In(III) and Au(III) exist in the aqueous phase. The method was checked by comparing apparent molecular weights of Hg(I) and Hg(II) in nitrate solutions.

In recent years the extractability of several metal ions from aqueous into organic phases has been reported to increase with decreasing concentration of the metal. For example, from 3.7 *M* HCl, the extraction coefficient of Ga(III) into bis-2-chloroethyl ether increases manyfold as the aqueous Ga(III) concentration is decreased from 10^{-2} *M* to 10^{-3} *M*.[2] Similar changes in extractability have been observed for Au(III) in HCl, In(III) in HBr and Tl(III) in HCl.[3] It has been suggested[2] that such results could be explained by the formation of unextractable dimers of the metal ion species in the aqueous phase at the higher metal concentrations, but alternate explanations have also been advanced.[4-6] Recently Irving and Rossotti have attributed this change in extractability for In(III) from HBr solutions to dimerization.[7]

We have attempted to decide between alternate explanations by molecular weight measurements with the equilibrium ultracentrifuge.

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Experimental

Centrifugation techniques have been described earlier.[8,9] All centrifugations were carried out in an excess of supporting electrolyte to diminish the effect of charge. Equilibrium temperatures were 30 ± 2° in all cases. Density measurements were made with a pycnometer. Bromide analysis of $InBr_3$, kindly supplied us by Dr. J. W. Irvine, Jr., indicated 67.2% Br (theoretical 67.6%). Merck reagent grade $AuCl_3 \cdot HCl \cdot 3H_2O$ was used; chloride and gold analysis indicated an empirical formula $HAuCl_4 \cdot 3.3H_2O$. Reagent grades of Hg(I) and Hg(II) nitrates were employed, and the compositions established by mercury and nitrate analyses. All other chemicals were also reagent grade.

Results and Discussion

The optical system of the centrifuge measures the refractive index gradients (dn/dx) as a function of the radius, x. The gradients displace the shadow of an inclined bar, and the results are in terms of a displacement, Z^* (corrected for background) assumed proportional to the concentration gradient dc/dx for the solute of interest.[9] For all experiments, the values of $\ln (Z^*/x)$ at equilibrium were plotted against x^2, and the slopes, S_e, of the curves at the average radius of the cell obtained. These values of S_e and the experimental conditions are summarized in Table I.

TABLE I

ULTRACENTRIFUGATION OF $HgNO_3$, $Hg(NO_3)_2$, $HAuCl_4$ AND $InBr_3$ SOLUTIONS NEAR 30°

Solute and formula wt.	Concn. (M)	Supporting electrolyte	S_e	M_e	Conditions[a]
$HgNO_3$	0.035	0.1 M HNO_3–	0.0705	505	D-2
(262.6)	.116	1.9 M $NaNO_3$	.0689	495	G-2
$Hg(NO_3)_2$	.042	2 M HNO_3	.0435	315	C-2
(324.6)	.103		.0403	295	F-2
$InBr_3$	.023		.0313	300	B-1
(354.5)	.049	2 M HBr	.0269	260	A-1
	.093		.0256	245	E-1
$HAuCl_4$	.056	3 M HCl	.0394	330	A-2
(340.0)					

[a] Bar angle: A, 35°; B, 40°; C, 45°; D, 50°; E, 55°; F, 60°; G, 65°. Approximate speed of rotation (r.p.m.): (1) 24,600; (2) 27,670.

For an ideal solution of an uncharged, monodisperse solute, a straight line should be obtained, *i.e.*, S_e constant. Further, $S_e = d \ln (Z^*/x)/d(x^2)$ would also equal $d \ln c_2/d(x^2)$, where c_2 is the concentration of the solute of interest. For all experiments reported here, S_e was essentially constant. (See Fig. 1, a deviation plot of $\log (Z^*/x) - (S_e/2.303)\, x^2$ *vs.* x^2.) From the values of S_e, apparent molecular weights, M_e, defined by the equation

$$M_e = \frac{2RT}{(1 - \bar{v}_2\rho)\omega^2} S_e \qquad (1)$$

were computed (Table I). In this expression, R is the gas constant; T, the absolute temperature; $\bar{v}_2$, the partial specific volume of the solute of interest; ρ, the solution density; and ω, the angular velocity. The term "apparent molecular weight" is used because zero charge (*i.e.*, the solute is not dissociated into ions) is assumed in the derivation of equation 1. Ignoring charge leads to values of M_e which are lower limits of the actual molecular weights.[10] In principle, it is possible to estimate the charge or, conversely, the average degree of complexing by anions, from the decrease of S_e with concentration in one or more equilibrium centrifugations. We do not feel that the present data are accurate enough for such a detailed analysis, even if other necessary assumptions could be made. For the experiments reported here, however, estimates of the charge indicate that in no cases is it large enough to lead to confusion between monomeric and dimeric species.

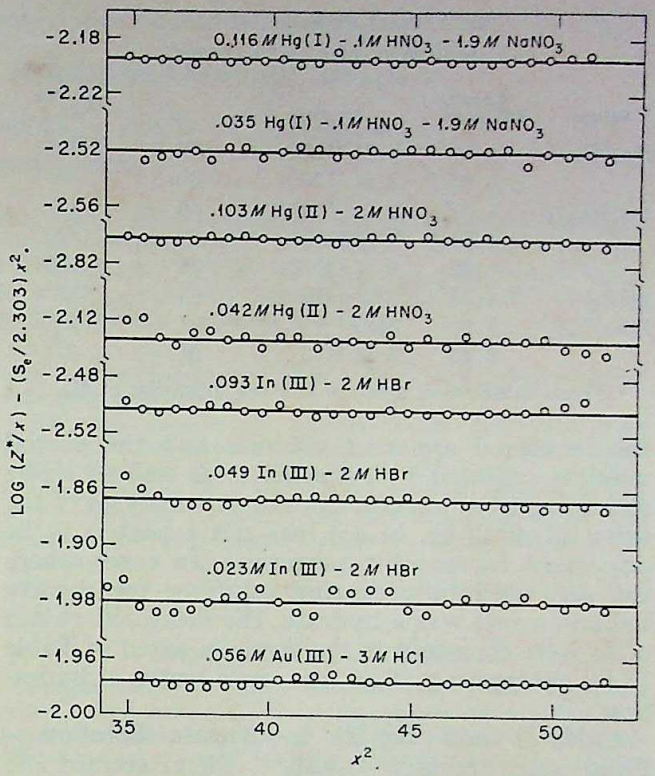

Fig. 1.—Test of constancy of S_e.

Equation 1 requires the partial specific volume of the solute in question. Density values for solutions of all these compounds are in the literature.[11] Extreme accuracy is not required for present purposes, since the quantity $(1 - \bar{v}_2\rho)$ does not differ greatly from unity. However, the literature values are rather old, and, in the case of the mercury compounds, the density measurements indicate the rather surprising result that the molar volume of $HgNO_3$ is greater than that of $Hg(NO_3)_2$. We have, therefore, made a few measurements of apparent molal volumes, ϕ_v, of these salts (Table II). Our results agree fairly well with those computed from literature values of solution densities for $InBr_3$ (*ca.* 60 cc./mole in water[11c]), and $HgNO_3$ (*ca.* 39 cc./mole[11b]), but disagree rather strongly with those for $HAuCl_4$ (*ca.* 126 cc./mole[11a]), and $Hg(NO_3)_2$ (*ca.* 35 cc./mole[11b]).

In the computation of molecular weights we have used for $\bar{v}_2$ the apparent specific volumes measured under conditions closest to those of the centrifugations (Table II). Differences between

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TABLE II

APPARENT MOLAL VOLUMES

Solute	Concn. (% by wt.)	Medium	ϕ_v	Apparent specific vol.
$HgNO_3$	4.87	1 M HNO_3	35.5	0.135
	4.35	2 M HNO_3	36.5	.14[a]
$Hg(NO_3)_2$	4.57	0.1 M HNO_3	46	.14
	4.51	1 M HNO_3	50	.155
	4.62	2 M HNO_3	53	.165[a]
$InBr_3$	1.54	2 M HBr	63	.18[a]
$HAuCl_4$	7.90	H_2O	91	.27
	3.46	3 M HCl	91	.27[a]

[a] These values were used for $\bar{v}_2$ in computation of M_e.

the measured apparent volumes and the partial volumes required by equation 1, as well as errors stemming from uncertainties in the analyses of the salts (about 3 cc. in ϕ_v), are not expected to be important for present purposes. In cases where the salt used in preparing solutions for density measurements was a hydrate, the measured values of ϕ_v were corrected to the formula listed in Table II by subtracting 18 cc. per mole water of hydration.

1. Hg(I) and Hg(II) in Nitrate Solution.—From our previous results[8,9] there seemed no reason to doubt that a clear distinction could be made between monomeric and dimeric species of the ions in question by equilibrium ultracentrifugation. Nevertheless, it appeared advisable to test this on a known system of a similar type. Nitrate solutions of Hg(I) and Hg(II) were selected. Hg(I) is known to form dimers in solution, and Hg(II) is generally considered to be monomeric. The experiments were carried out in 2 M nitrate, and acidities selected to preclude interference from hydrolysis.[12] For 0.116 M Hg(I) in 0.1 M HNO_3–1.9 M $NaNO_3$ the apparent molecular weight computed by equation 1 is 495; for an initial concentration of 0.035 M Hg(I) in the same supporting electrolyte, 505 is obtained. These may be compared with 525, the formula weight for $(HgNO_3)_2$. The experimental values are not much different from each other, nor much lower than the theoretical value for the dimer; *i.e.*, there is little interference from a charge effect.

For 0.103 M Hg(II) in 2 M HNO_3 we find M_e = 295; for 0.042 M Hg(II) the value is 315. The formula weight of $Hg(NO_3)_2$ is 325. The method thus definitely distinguishes between a monomeric Hg(II) and a dimeric Hg(I) species of mercury.

2. In(III) in HBr.—The solvent extraction measurements of Irving and Rossotti,[7] which indicated dimerization of In(III) in aqueous bromide solutions, were carried out with 1M HBr solutions. For the centrifugations, 2M HBr solutions were used. With the stability constants reported for In(III) bromide complexes[13] and with constants for dimerization given by Irving and Rossotti,[7] one concludes that most of the In(III) should be dimerized even at the lowest In(III) concentrations encountered in the centrifugations.

Centrifugations were carried out at initial In(III) concentrations 0.023, 0.049 and 0.093 M. The values of M_e obtained were 300, 260 and 245, respectively. Comparison with the formula weight of $InBr_3$, 355, indicates that no appreciable fraction of the indium is dimeric under these conditions. The substantial decrease of M_e with increasing In(III) concentration, and the lowness of all values with relation to the formula weight suggest that the average number of bromide ions complexed by In(III) is not as great as estimated by Irving and Rossotti.[13b] More accurate results are required, however, before the charge of such complexes can be determined with confidence.

3. Au(III) in HCl.—A single centrifugation of Au(III) in 3M HCl was carried out at an initial gold concentration of 0.056M. The observed value of M_e was 330; the formula weight of $HAuCl_4$ is 340, *i.e.*, Au(III) is not dimerized in these solutions.

4. General Discussion.—The results of the equilibrium ultracentrifugations leave little doubt that both the In(III) bromide and Au(III) chloride complexes are monomeric (mononuclear) under conditions where anomalies in solvent extraction data have been interpreted in terms of formation of dimeric complexes in the aqueous phase. The explanation for the non-constancy of the extraction coefficients (increase with decreasing metal concentration) for these and similar complex salts must, therefore, be sought in the properties of the organic phase, *i.e.*, in a decrease of the stoichiometric activity coefficients γ_0 of the distributing components (*e.g.*, $HAuCl_4$ or $HInBr_4$) in the organic phase. This could result from various dissociation reactions as, for example, proposed by Saldick.[5]

The low concentration extraction anomaly which gave rise to this study limits the region where solvent extraction substantially follows Nernst's law (concentration independence of extraction coefficients) in much the same way that a similar anomaly limits it, at least for some systems, at high metal concentrations.[14] In these cases, extractability increases with metal concentration. There is apparently now general agreement that the deviations from Nernst's law at high concentrations also stem from a decrease of the stoichiometric activity coefficients γ_0 in the organic phase[15] (polymerization in the organic phase), though for a short time variations of the activity coefficients in the aqueous phase had been held responsible.[16]

Acknowledgment.—We wish to thank Miss Neva E. Harrison and Mrs. A. S. Dworkin for technical assistance.

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[CONTRIBUTION FROM THE UNIVERSITY OF CALIFORNIA, LOS ALAMOS SCIENTIFIC LABORATORY]

Dimorphic Modifications of Beryllium Diiodide, BeI_2[1]

BY ROWLAND E. JOHNSON, E. STARITZKY AND R. M. DOUGLASS

RECEIVED AUGUST 9, 1956

Two polymorphic modifications of beryllium diiodide have been found. Form I apparently corresponds to the previously described phase, and form II is a heretofore undescribed high-temperature phase stable above 350°. Form I is tetragonal. Powder X-ray diffraction data indicate cell dimensions $a_0 = 6.12 \pm 0.01$ Å., $c_0 = 10.63 \pm 0.02$ Å., $Z = 4$. Form II is orthorhombic with cell dimensions $a_0 = 16.48 \pm 0.02$ Å., $b_0 = 16.702 \pm <0.01$ Å., $c_0 = 11.629 \pm <0.01$ Å., $Z = 32$. Volume per formular unit and Lorentz–Lorenz refraction, respectively, of the two forms are nearly identical.

Introduction

In view of recent work on the subhalides of other elements, particularly aluminum iodide,[2] attempts were made to prepare sub- and superiodides of beryllium. The attempts were unsuccessful, but in the course of this work two polymorphic modifications of beryllium diiodide were found, hereafter designated form I and form II. It seems likely that the previously reported beryllium diiodide[3] corresponds to form I, and that form II is a previously unrecognized high-temperature modification. Because beryllium diiodide is extremely hygroscopic all operations were carried out in sealed glass tubes or in an inert-atmosphere box.

Beryllium Diiodide Form I

Preparation.—Beryllium diiodide form I was prepared by heating beryllium metal chips or diberyllium carbide in a stream of hydrogen and iodine, after the method of Messerknecht and Biltz.[3] Slight modifications permitted use of high-vacuum techniques. Reaction was carried out in silica-glass tubes at various temperatures between 750 and 1100°, and in this range temperature did not appear to affect yield. The products were sealed off in evacuated bulbs fitted with small side arms. On heating the bulbs to about 85° small amounts of silicon tetraiodide impurity (identified by melting point and spectral analysis) sublimed into the side arms which were then sealed off and discarded. The contents of several bulbs were combined and sublimed under vacuum. This product gave a positive test for iodide and gave on analysis 3.39% by weight beryllium, to be compared with 3.43% calculated for BeI_2. No optical or X-ray evidence of inhomogeneity of the product was observed.

Properties.—Most preparations examined consisted of colorless, anhedral grains without pronounced cleavage. One preparation, however, contained some euhedral crystals which were tetragonal dipyramids {112} with basal pinacoid {001} and prism {100}. Lack of suitable material made it impossible to obtain single-crystal X-ray data. The powder X-ray diffraction pattern (Table I) was indexed in terms of a primitive tetragonal cell with dimensions $a_0 = 6.12 \pm 0.01$ Å., $c_0 = 10.63 \pm 0.02$ Å., $c/a = 1.73_7$. All observed diffraction lines of type $0kl$ had k even and $(h + k)$ was even for all lines of type $hk0$, suggesting space group $P4/nbm$ (D^3_{4h}) in which the number of formular units per cell must be an integral multiple of two. Assuming four formular units per cell gives a volume per formular unit of $99._5$ Å.^{3} and a calculated density (formula weight 262.85; weight of unit atomic weight 1.6602×10^{-24} g.) of 4.38 g. per cc. For beryllium diiodide prepared in like manner and purified by sublimation, and therefore probably corresponding to form I of the present paper, Messerknecht and Biltz[3] reported a measured density of 4.325 g. per cc.

The crystals were optically uniaxial positive with very low birefringence and refractive indices for the ordinary and extraordinary rays near 1.99. The Lorentz–Lorenz refraction is $29._8$ cc.

Although samples for powder X-ray diffraction were prepared in an inert-atmosphere box with dew point below −60°, this form of beryllium diiodide exhibited a tendency to decompose on grinding in a mortar. Extreme care had to be exercised to avoid such decomposition which was evidenced by development of brown color in streaks corresponding to the more vigorous strokes of the pestle. No such tendency to decompose on grinding was observed with form II described below.

Beryllium Diiodide Form II

Preparation.—Beryllium diiodide form I and beryllium metal chips were sealed in borosilicate-glass tubes and heated for various lengths of time at various temperatures. When heated above 350° for a few hours form I was converted to form II. Attempts to separate form II from the metal chips by sublimation proved unsuccessful; when heated to about 450° form II sublimed, form I appearing as the condensation product. Although this might appear to indicate that form I is the high-temperature modification, the temperature at which crystal growth took place on condensation was believed to be well below 350°, the approximate temperature at which form I changed to form II on heating. Therefore form II is regarded as the high-temperature polymorph.

Beryllium diiodide form I and iodine sealed in borosilicate-glass tubes and heated to about 300° overnight gave form II and iodine. Most of the excess iodine was removed on heating this product under vacuum at about 150°. Analysis of the material thus purified gave 3.60% by weight beryllium. If the remainder is assumed to be iodine this corresponds to an iodine-to-beryllium ratio of 1.9. The fact that the same crystal species resulted from heating beryllium diiodide form I with excess beryllium and with excess iodine makes it highly improbable that this deviation from the stoichiometric ratio of 2 is significant; it is believed attributable to difficulty in analyzing such extremely hygroscopic materials. As will be shown, the two beryllium iodides have nearly identical molecular volumes and Lorentz–Lorenz refractions, this lending further support to the contention that they do not differ in composition.

Properties.—Calibrated Weissenberg and precession photographs indicate, with the exception of two faint reflections, diffraction symbol mmmB-ab, otherwise diffraction symbol mmmP-an, and give cell dimensions $a_0 = 16.48 \pm 0.02$ Å., $b_0 = 16.702 \pm <0.01$ Å., $c_0 = 11.629 \pm <0.01$ Å.; volume per formular unit 100 Å.^{3}; $a:b:c = 0.987:1:0.696$. The density calculated assuming 32 formular units per cell is 4.36 g. per cc.

The crystals exhibit prominent cleavage parallel to {010} and less prominent cleavage parallel to {001}. They are colorless and optically biaxial positive with optic axial angle 25° for sodium light and very weak dispersion $r < v$. The principal refractive indices for sodium light are 1.952 ± 0.005, 1.954 ± 0.005, 1.988 ± 0.005; geometric mean 1.965; Lorentz–Lorenz refraction 29.4 cc. The optic orientation is $X = c$, $Y = b$, $Z = a$.

Structural Considerations.—All prominent X-ray diffraction spots appearing in single-crystal photographs, and all the diffraction lines appearing in the powder pattern (Table II), have indices satisfying the conditions $h = 4n$, $k = 4n$, $h/4 + k/4 + l/2 = 2n$. This indicates a monomolecular orthorhombic pseudocell with dimensions $a_0' = 4.120$, $b_0' = 4.176$, $c_0' = 5.815$ Å. (obtained from the true cell by the transformation 1/4, 0, 0/0, 1/4, 0/0, 0, 1/2) with an

(1) Work done under the auspices of the Atomic Energy Commission.

(2) J. D. Corbett and S. von Winbush, THIS JOURNAL, **77**, 3964 (1955).

(3) C. Messerknecht and W. Biltz, *Z. anorg. allgem. Chem.*, **148**, 152 (1925).

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TABLE I

PARTIAL POWDER X-RAY DIFFRACTION PATTERN OF BERYLLIUM DIIODIDE, FORM I

hkl	*d*, Å. Calcd.	*d*, Å. Obsd.[a]	I/I_1[b]
110	4.33	4.31	10
112	3.36	3.33	100
200	3.06	3.04	35
201	2.941	2.925	15
004	2.658		
202	2.652	2.646	20
211	2.650		
212	2.433	2.424	5
213	2.166	2.157	15
220	2.164		
005	2.126	2.112	5
221	2.120		
204	2.006	2.001	40
222	2.004		
310	1.935	1.931	5
115	1.908		
214	1.907	1.900	15
311	1.904		
223	1.847	1.842	5
312	1.819	1.814	35
006	1.772	1.763	10
205	1.746	1.734	10
313	1.698	1.693	5
215	1.679		
224	1.678	1.673	25
321	1.676		
116	1.640	1.634	20
322	1.617	1.614	10
314	1.564	1.555	5
206	1.533		
323	1.531	1.528	5
400	1.530		
007	1.519		
225	1.516	1.512	10
401	1.514		
216	1.487	1.483	10
402	1.470	1.467	10
411	1.470		
117	1.433		
315	1.431		
324	1.430	1.429	5
412	1.430		
331	1.429		
332	1.392	1.390	5
226	1.371		
413	1.369	1.369	5
420	1.368		
207	1.360	1.356	5
421	1.357		
008	1.329		
217	1.328		
325	1.326	1.325	10
404	1.326		
422	1.325		
316	1.307	1.305	15
414	1.296	1.294	10

[a] Philips 114.6 mm. diameter powder camera, Straumanis mounting; λ(Cu Kα) = 1.5418 Å. [b] Relative peak intensities above background from densitometer measurements.

TABLE II

PARTIAL POWDER X-RAY DIFFRACTION PATTERN OF BERYLLIUM DIIODIDE, FORM II

HKL[a]	*hkl*[b]	*d*, Å. Calcd.	*d*, Å. Obsd.[c]	I/I_1[d]
111	042	3.392	3.37	100
	402	3.362	3.35	55
200	440	2.933	2.92	30
	004	2.907	2.89	60
	080	2.088	2.080	45
220	444	2.065	2.058	60
	800	2.060		
	482	1.774	1.772	35
311	842	1.761	1.752	70
	046	1.758		
	406	1.754		
222	084	1.696	1.691	10
	804	1.681	1.675	15
400	880	1.4663	1.463	10
	008	1.4536	1.453	20
	0·12·2	1.3535	1.352	20
331	486	1.3428	1.340	5
	846	1.3372	1.336	25
	12·0·2	1.3364		
	4·12·0	1.3187	1.318	5
420	884	1.3092	1.307	5
	12·4·0	1.3046		
	448	1.3023	1.301	20
	4·12·4	1.2008	1.201	5
422	088	1.1929	1.189	10
	12·4·4	1.1904		
	808	1.1879		
	8·12·2	1.1314	1.131	5
	0·12·6	1.1305		
333,	12·8·2	1.1256	1.119	5
511	12·0·6	1.1207		
	0·4·10	1.1203		
	4·0·10	1.1194		
	0·16·0	1.0439	1.032	5
440	888	1.0323		
	16·0·0	1.0300		
	4·16·2	0.9969	0.9979	5
	8·12·6	.9911		
	12·8·6	.9873	0.9856	10
531	4·8·10	.9864		
	16·4·2	.9855		
	8·4·10	.9842		
	0·16·4	.9824	0.9776	<5
	12·12·0	.9775		
600,	4·12·8	.9767		
442	12·4·8	.9709		
	16·0·4	.9709	.9704	5
	0·0·12	.9691		

[a] Indices of the face-centered-cubic pseudocell derived from the true cell by the transformation 1/4, 1/4, 0/1/4, 1/4, 0/0, 0, 1/2. [b] Indices of the true, orthorhombic unit cell. [c] Philips 114.6 mm. diameter powder camera, Straumanis mounting; λ(Cu Kα) = 1.5418 Å. [d] Relative peak intensities above background from densitometer measurements.

approximate body-centered arrangement of iodine ions. Further, the ratios of c_0' to a_0' and b_0' (1.61 and 1.59, respectively) approximate the square root of two. By the transformation 1, 1, 0/1, $\bar{1}$, 0/0, 0, 1 the above body-centered arrangement of iodine ions may be described as a face-centered-monoclinic arrangement with unit dimensions $a_0'' = 5.866$, $b_0'' = 5.866$, $c_0'' = 5.815$ Å., $\gamma = 90° 46'$. This may be regarded as a distorted face-centered-cubic arrangement of iodine ions, *i.e.*, a distorted cubic-close-

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packed arrangement. The relation between the true orthorhombic unit cell and the cubic pseudocell is apparent in Table II. Calculated and observed d spacings are closely grouped corresponding to possible spacings of the face-centered-cubic pseudocell.

Acknowledgment.—Thanks are due Mr. C. E. Holley of this Laboratory for suggesting and encouraging this work.

LOS ALAMOS, NEW MEXICO

[CONTRIBUTION FROM THE IBM WATSON LABORATORY AT COLUMBIA UNIVERSITY]

Chemistry of the Group VB Pentoxides. VI. The Polymorphism of Nb_2O_5

BY FREDERIC HOLTZBERG, ARNOLD REISMAN, MARGARET BERRY AND MELVIN BERKENBLIT

RECEIVED SEPTEMBER 21, 1956

The polymorphism of Nb_2O_5 has been reinvestigated. Experimental results indicate the definite existence of two modifications and the possible existence of a third. The δ-modification recently reported has been shown to be a poorly crystallized state of the γ-phase. It is proposed that the α- and β-phases are identical, with the β-modification existing as a two-dimensional array. Transformation temperatures were found to be: amorphous to γ 435°, γ to α 830°. The densities are: amorphous 4.36 g./cm.^{3} at 25°, γ, 5.17 g./cm.^{3} at 25° and α, 4.55 g./cm.^{3} at 25°. None of the transformations was reversible. The α-phase was reindexed on the basis of a monoclinic unit cell with a = 21.34 Å., b = 2.816 Å., c = 19.47 Å. and $\sphericalangle \beta$ = 120°20′ having 14 molecules/unit cell and an X-ray density of 4.52 g./cm.^{3}. The freezing point of Nb_2O_5 obtained in the study was 1491°.

Previous investigations pertaining to the chemistry of the Group VB pentoxides and their reactions with alkali oxides and carbonates have included studies of the polymorphism of Ta_2O_5[1] and V_2O_5.[2] Examination of the temperature–phase relationships of Nb_2O_5, in addition to completing the study of the comparative polymorphism of the pentoxides, may help explain the non-model behavior exhibited by the systems K_2O–Ta_2O_5[1] and K_2O–Nb_2O_5.[3]

In 1941, Brauer[4] reported that Nb_2O_5 existed in three crystalline modifications having the following transformations: amorphous to γ 500°, γ to β 1000° and β to α 1100°.[5] In 1951 Hahn[6] published X-ray data for an unspecified form of Nb_2O_5. The pattern did not correspond to Brauer's α-, β- or γ-forms. Subsequently Schäfer, *et al.*,[7,8] presented the results of a partial X-ray investigation of the system Nb_2O_5–Ta_2O_5 in which a study of the polymorphism of Nb_2O_5 was included. This work confirmed the α-, β- and γ-polymorphs reported by Brauer: however, the transformation temperatures were significantly different. Furthermore, contrary to evidence given by Brauer, the γ to β transformation was found to be reversible. The reversibility of the α to β transformation was not clarified. Schäfer also observed that the crystallization of the amorphous oxide sometimes results in a mixture of β- and γ-Nb_2O_5. Lapitskiĭ, *et al.*,[9] showed with thermal analysis that the amorphous pentoxide exhibited an exotherm at 609°. The temperature of this heat effect is not coincidental with any of the reported transition temperatures. Recently, Frevel and Rinn[10] reported a δ-form which was indexed on the basis of a pseudohexagonal unit cell. The δ-form is apparently converted to the γ-phase at 700°, a contradiction of Brauer's results. The method of preparation of the δ-form was not specified.

In order to resolve the uncertainties concerning the number of polymorphs of Nb_2O_5, and the temperatures and reversibilities of transformations between phases, it was felt that a complete re-evaluation of previously reported data was in order.

Experimental Procedure

Preparation of Reagents.—Sublimed $NbCl_5$ prepared from high purity niobium[11] was used for the preparation of Nb_2O_5. The pentachloride was hydrolyzed in distilled water and the precipitated Nb_2O_5 was washed until the filtrate was free of chloride ion. The washings, with intermediate digestions at boiling temperatures, were continued through five further cycles. After drying for 24 hours at 100° the pentoxide was found to be amorphous to X-rays. The excessive washing and digestion treatment was employed because, as will be shown, the transformation temperatures of the different pentoxide phases were impurity sensitive.

"High Purity"[12] Nb_2O_5 was used in experiments designed to determine the reversibility of phase transformations. Prior to use the oxide was heated at 1200° for 24 hours to ensure complete conversion to the high temperature form. A portion of the Nb_2O_5 was fused with K_2CO_3, dissolved in water and amorphous hydrated Nb_2O_5 was precipitated as described in an earlier paper.[13] X-Ray analysis indicated that this material was also amorphous.

Differential Thermal Analysis.—A large number of furnaces specifically designed for heating curve analysis have been described in the literature. The general construction involves the use of a mobile furnace which rolls into position over a fixed sample holder and thermocouple assembly. The holder and thermocouple assembly are often difficult to clean and frequently require refabrication for each analysis. In addition the apparatus is costly, requiring elaborate engineering. The problems inherent in the standard

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(2) F. Holtzberg, A. Reisman, M. Berry and M. Berkenblit, *ibid.*, **78**, 1536 (1956).

(3) A. Reisman and F. Holtzberg, *ibid.*, **77**, 2115 (1955).

(4) G. Brauer, *Z. anorg. allgem. Chem.*, **248**, 1 (1941).

(5) Consistent with accepted nomenclature, the highest temperature phase will be denoted as α which corresponds to Brauer's "Hochform."

(6) R. B. Hahn, THIS JOURNAL, **73**, 5091 (1951).

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(9) A. V. Lapitskiĭ, Y. P. Simanov and E. I. Yarembash, *J. Phys. Chem. Moskav*, **26**, 56 (1952).

(10) L. K. Frevel and H. N. Rinn, *Anal. Chem.*, **27**, 1329 (1955).

(11) The $NbCl_5$ was obtained from the A. D. Mackay Co. The niobium from which the pentachloride was prepared was Fansteel High Purity Grade containing a maximum impurity of 0.2% Ta.

(12) The high purity of Nb_2O_5 was obtained from the Fansteel Metallurgical Co. and contained as a maximum impurity 0.2% Ta.

(13) (a) A. Reisman, F. Holtzberg, S. Triebwasser and M. Berkenblit, THIS JOURNAL, **78**, 719 (1956); (b) See Errata for ref. 11 in THIS JOURNAL, **78**, 6423 (1956).

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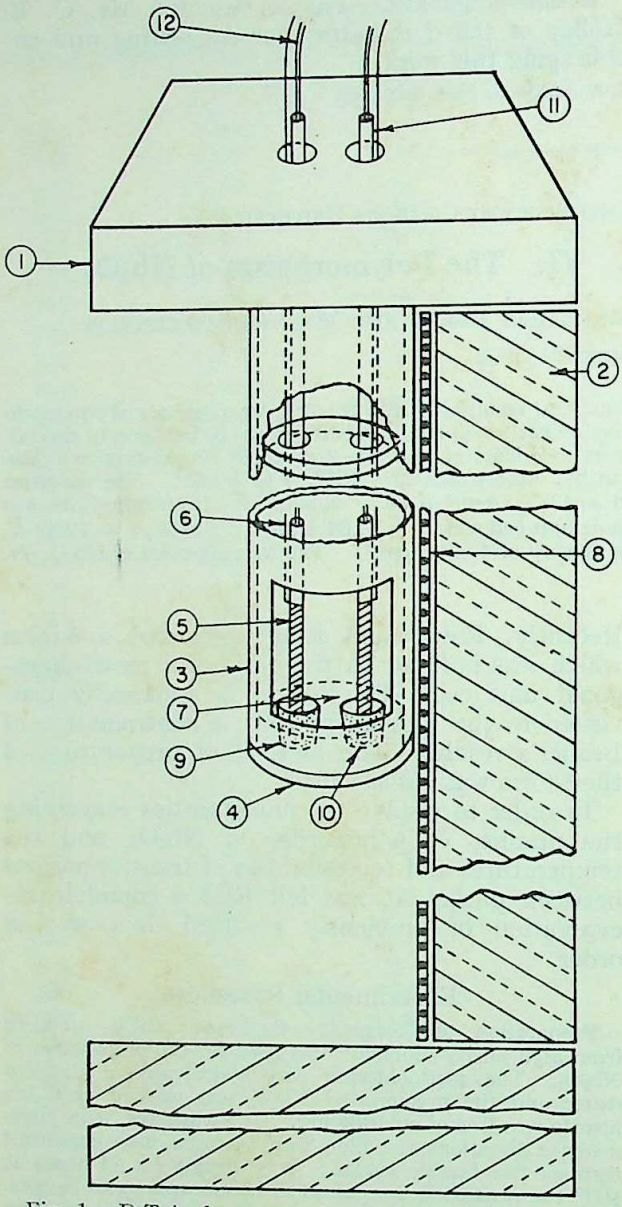

Fig. 1.—D.T.A. furnace and sample assembly: 1, firebrick, air-dry cement coated; 2, firebrick; 3, alumina; 4, alumina; 5, platinum protecting capsule; 6, platinum 20 mil ground wire; 7, firebrick crucible seat; 8, alumina 1/6″ pitch furnace tube; 9, 1-cc. platinum crucible with 90-mesh Alundum powder; 10, 1-cc. platinum crucible with sample; 11, 1/8″ 2-hole thermocouple tubing; 12, Pt–10 Rh B & S #28 wire.

design have been eliminated with the construction of a new D.T.A. apparatus, Fig. 1. A stationary furnace consisting of a 12 in. Kanthal wound $1^1/_2$ in. i.d. core set into 4 in. × 8 in. firebrick is mounted vertically. The sample holder and thermocouple assembly are mounted in a $1^3/_{16}$ in o.d. ceramic hollow cylinder which slides into the furnace and seats at the appropriate height. The thermocouples are supported in 1/8 in. two-hole alumina insulating rods that are guided through centering holes located in two parallel ceramic discs. Such an arrangement permits removal of the thermocouples after a heating curve. 0.2–0.5 g. charges contained in 1-cc. platinum crucibles are easily loaded into the holder through a port cut in the alumina cylinder. The time required for manipulation of the equipment prior to a run is approximately 1 minute. The electronic components of the D.T.A. apparatus have been previously described.[1-3] Heating rates were of the order 0.5–2°/minute with 5–34 × amplification of the differential signal.

The freezing point of Nb_2O_5 was determined using cooling curves as previously described.[1-3]

Sensitivity of D.T.A. Equipment.—In order to evaluate the smallest spontaneous heat change that could be detected with D.T.A. apparatus, potassium metaniobate was used as a calibrant. $KNbO_3$ has two solid state transformations, one at 215° and the other at 425°. The latent heat associated with the orthorhombic to tetragonal transformation at the lower temperature is 69 ± 5 cal./mole and that of the tetragonal to cubic transformation is 134 ± 5 cal./mole.[14] Consequently a 0.5-g. sample would absorb 0.2 cal. at 215° and 0.4 cal. at 425°. The signal-to-noise ratio for the lower endotherm was approximately 3 and thus it is estimated that a spontaneous heat change of 0.1 cal. can be readily detected.

Heat Treatments and X-Ray Analysis.—Samples contained in platinum crucibles were placed in furnaces whose temperatures were controlled to within ±5° throughout the heating period. Temperatures were measured with Pt–10 Rh thermocouples. All X-ray traces were obtained with a General Electric XRD-5 diffractometer using nickel filtered copper radiation.

Single crystals of α-Nb_2O_5 were obtained by cooling the molten oxide. The resulting crystals were twinned, strained and exhibited poor external morphology; however, sufficient X-ray data were collected with a precession camera to establish the crystal class and unit cell size. It was not possible to obtain single crystals of lower temperature phases because, as will be shown, the transformations are not reversible.

Discussion of Experimental Results

A. The Amorphous to Crystalline Transformation.—Figure 2 is a D.T.A. heating curve starting with the amorphous Nb_2O_5 prepared by the hydrolysis of $NbCl_5$ as previously described. The first broad endotherm corresponds to the evolution of surface water. The endotherm extends from room temperature to 400°. Although very slow heating rates were used, static experiments were

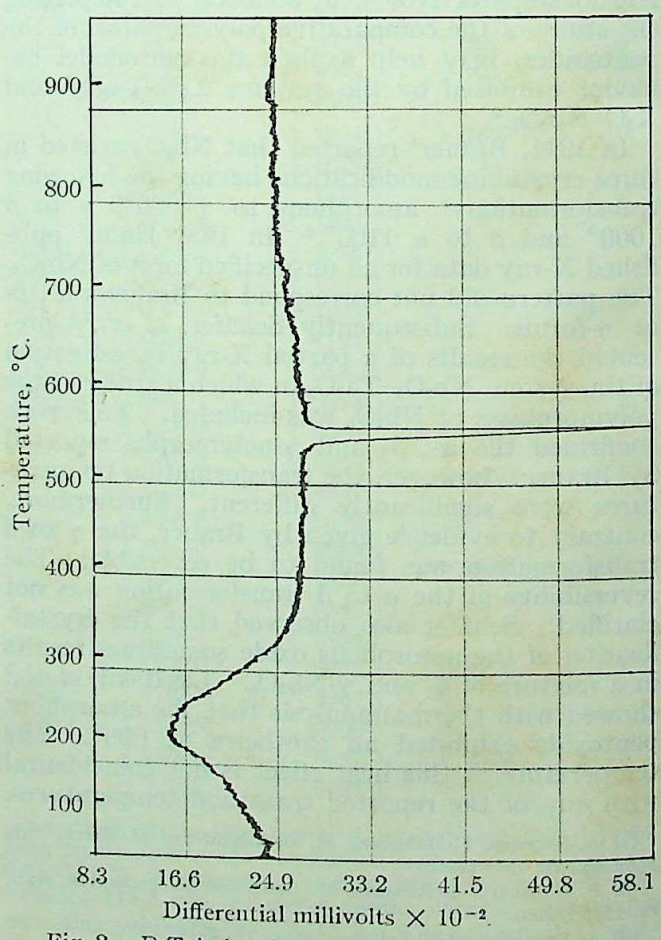

Fig. 2.—D.T.A. heating curve of amorphous Nb_2O_5.

(14) S. Triebwasser and J. Halpern, *Phys. Rev.*, **98**, 1562 (1955).

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necessary in order to more nearly approximate equilibrium conditions. Constant temperature weight loss experiments showed that surface absorbed water is completely removed at 400°; Table I, part A.

TABLE I

HEAT TREATMENT EXPERIMENTS

PART A

A[a] dried at 100° 24 hr.	Temp., °C.	Time, hr.	Cumulative % wt. loss
	120	16	1.77
	150	16	4.04
	300	16	9.52
	400	16	9.86
	450	24	9.86
	500	22	9.86
	520	22	9.86

PART B

Orig. phase	Temp., °C.	Time, hr.	Final phase
A	440	23	A
A	440	64	γ
A	430	96	A
A	430	215	A

PART C

Orig. phase	Temp., °C.	Time, hr.	Final phase
A	702	23	γ
A	645	23	γ
A	602	23	[b]$\gamma' + \gamma$
A	550	24	γ'
A	550	72	$\gamma' + \gamma$
A	540	138	$\gamma' + \gamma$
A	520	72	γ'
A	520	140	γ'
A	520	232	γ'
A	520	328	$\gamma' + \gamma$
A	510	528	$\gamma' + \gamma$
A	488	96	γ'
A	488	165	γ'
A	488	550	$\gamma' + \gamma$
A	463	23	γ'

PART D

Orig. phase	Temp., °C.	Time, hr.	Final phase
A	956	23	$\alpha + \alpha'$
A	905	23	$\alpha + \alpha'$
A	857	67	$\alpha + \alpha'$
A	833	168	$\alpha + \alpha'$
A	818	116	γ
A	804	120	γ
A	795	144	γ
$\alpha + \alpha'$	1145	12	α
$\alpha + \alpha'$	1095	23	α
$\alpha + \alpha'$	1050	23	$\alpha + \alpha'$
$\alpha + \alpha'$	1000	432	$\alpha + \alpha'$
$\alpha + \alpha'$	997	23	$\alpha + \alpha'$

PART E

Orig. phase	Temp., °C.	Time, hr.	Final phase
α	1150	336	α
α	995	384	α
α	905	384	α
α	850	384	α
α	798	336	α
α	754	336	α
α	706	336	α
α	644	168	α
α	600	360	α
α	500	336	α
α	477	216	α
α	430	120	α
α	−80	124	α
α	−196	120	α
$\alpha + \alpha'$[c]	1150	408	α
$\alpha + \alpha'$	1050	144	α
$\alpha + \alpha'$	997	432	$\alpha + \alpha'$
$\alpha + \alpha'$	909	336	$\alpha + \alpha'$
$\alpha + \alpha'$	850	230	$\alpha + \alpha'$
$\alpha + \alpha'$	798	456	$\alpha + \alpha'$
$\alpha + \alpha'$	754	336	$\alpha + \alpha'$
$\alpha + \alpha'$	706	336	$\alpha + \alpha'$
$\alpha + \alpha'$	595	480	$\alpha + \alpha'$
$\alpha + \alpha'$	430	168	$\alpha + \alpha'$
$\alpha + \alpha' + \gamma$	500	168	$\alpha + \alpha' + \gamma$
$\alpha + \alpha' + \gamma$	477	168	$\alpha + \alpha' + \gamma$
$\alpha + \alpha' + \gamma$	−200	166	$\alpha + \alpha' + \gamma$
$\alpha + \gamma$	477	216	$\alpha + \gamma$
$\alpha + \gamma$	−200	168	$\alpha + \gamma$

[a] A, amorphous Nb_2O_5. [b] γ' refers to poorly crystallized γ. [c] α', 2-dimensional α.

The second heat effect is exothermal and coincides with the first appearance of crystallinity. It should be noted that the conversion temperature of amorphous to crystalline Nb_2O_5 obtained with D.T.A. is a function of heating rate. Thus, at 5°/minute the transformation occurred at 580°. At 3°/minute the transformation temperature was 520°. The exotherm is probably the same one observed by Lapitskii[9] at 609°. It is evident that D.T.A. serves only to indicate the presence of a latent heat associated with the amorphous–crystalline transition, and not the true temperature of the phase change. In addition to being rate dependent the inversion temperature was found to be impurity sensitive. For example, if the amorphous Nb_2O_5 prepared by precipitation from carbonate solution is not thoroughly washed, NH_4Cl remains as a contaminant. Approximately 0.5 wt. % NH_4Cl lowered the transition temperature amorphous to crystalline about 200°. This behavior, which is not uncommon, necessitated the excessive washing and digestion procedure used in the preparation of the amorphous oxide.

The "equilibrium" transformation temperature was determined using static methods. Table I, part B, describes the results. The samples of amorphous oxide were heat-treated at the different temperatures for varying lengths of time and then air-quenched. X-Ray diffractometer and Debye Scherrer techniques were then used to determine the phase present. It is seen that 64 hours at 440° showed conversion amorphous–crystalline, 96 hours at 430° showed no conversion. Within the time limits specified the transformation temperature could not be lowered and the "equilibrium" temperature was chosen at 435 ± 5°. It would appear, on the basis of the thermal and X-ray evidence, that the precipitated Nb_2O_5 has no rudimentary crystallinity. If some degree of periodicity were present, heating would serve only to increase crystallite size, and any heat effect would ex-

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tend over a large temperature interval making the exotherm undetectable.

What is most interesting about Fig. 2 is that no further heat effects are observed above the exotherm. However, successive heating experiments with fresh samples up to given temperatures, at rates of 1–2°/minute, followed by X-ray examination of the quenched samples, indicated the appearance of new phases. The absence of latent heat concurrent with the appearance of new phases probably indicates that the transformations are second order. It was only possible to isolate the "pure" β-form characterized by Brauer[4] during these relatively non-equilibrium heating experiments. This behavior will be discussed more fully below.

B. Question of the Existence of δ- and γ-Polymorphs.—Above 440° the δ-modification reported by Frevel and Rinn[10] was found by X-ray analysis. The apparent temperature of transition of the δ form[15] to Brauer's γ-form was lowered by successively longer heat treatments at lower temperatures. These results are listed in Table I, part C. It is seen that progressively longer treatment at each of the transformation temperatures finally results in simultaneous appearance of γ- and δ-phases. On the basis of these results, it is believed that the δ-modification is a less crystalline state of the γ-phase. Examination of X-ray diffractometer traces shows that all of the maxima of the δ-form are characteristic of a material with poorly defined crystallinity. All of the δ-reflections occur as the major lines in the γ-form with increased sharpness, and the additional diffraction lines of the γ-form are all of low intensity. Low intensity maxima would not be observable in the diffuse pattern given by a poorly crystallized material. For example, as shown in Fig. 3, the broad maxima at 2θ equals 28.34 and 36.53° become resolved into sharp peaks at 28.32, 28.88, 36.52 and 36.98°, respectively. In fact upon careful inspection of the diffractometer traces of the δ-form, it is possible to see evidence of overlap of two diffraction maxima, Fig. 3, points a and b. It is evident, therefore, that the δ- and γ-modifications represent different degrees of crystallinity of the same polymorph.

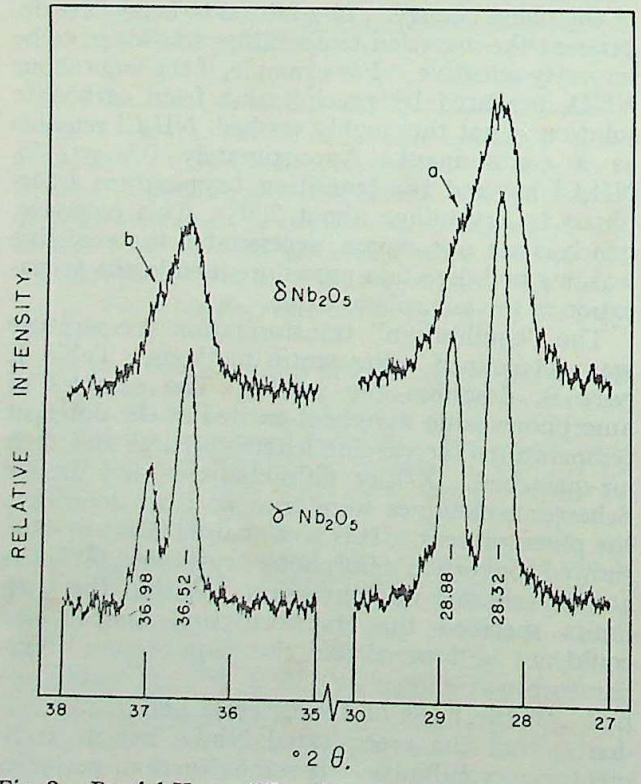

Fig. 3.—Partial X-ray diffraction pattern of γ- and δ-Nb_2O_5.

C. Question of the Existence of β- and α-Polymorphs.—Table I, part D, indicates that the γ-polymorph undergoes a transformation at 830 ± 5°. This temperature is in agreement with the upper limits reported by Schäfer, *et al.*, for the appearance of Brauer's β-phase. In the transition of γ to the next modification, one observes the phenomenon of a highly crystalline substance transforming into a material of low crystallinity. As pointed out, the transformation occurs in the absence of an observable latent heat. What is of greatest import is that under equilibrium conditions the γ-polymorph always transformed into a mixture of Brauer's β- and α-forms and, although these modifications appeared simultaneously, further treatment at approximately 1000° for 18 days did not result in complete conversion to the α-form. At 1095°, however, complete conversion of the β- or α'-phase to α was observable.

The question arises as to whether this is the same type of behavior observed for the development of crystallinity in the lower temperature polymorph or whether two crystalline forms exist. From the point of view of X-rays the apparent equilibrium transformation involves the simultaneous formation of two crystalline entities. As previously pointed out pure β-Nb_2O_5 was obtained only under non-equilibrium conditions. The characteristic pattern of the β-form shows broad as well as sharp maxima, and the sharp peaks are identical with peaks occurring in the α-form. The broad maxima can be traced into the formation of sharp doublets in the α-form, and it is difficult to attribute the doublet formation to the same phenomena observed in the lower temperature case because of the large displacement of the center of gravity of the broad maxima in the formation of doublets. One might postulate the occurrence of a two-dimensional periodicity in the apparent drastic structural changes in the transformation γ to α' and α. In such a situation the α'-polymorph might be thought of as a transitional phase. In view of the fact that all of the sharp lines that occur in the α'-form are also present in the α-form, it is conceivable that the sharp lines represent the two-dimensional periodicity of the α-form in the transitional phase. The broad maxima would then be attributable to a disordered structure in the third dimension. Such a hypothesis appears to reconcile the apparent paradox presented between heat treatment data which indicate identity of forms, and X-ray data which indicate two distinct forms.

D. Reversibility of Phases.—It can be seen from Table I, part E, that prolonged heat treatment of the various forms and mixtures of them at

(15) In Table I the δ-phase is referred to as γ'.

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TABLE II

POWDER DIFFRACTION DATA FOR α-Nb_2O_5

d = interplanar spacing. I/I_1 = relative peak intensity obtained by normalizing with respect to the strongest line. Peak height measured in counts above background. hkl = plane indices. The monoclinic unit cell contains 14 molecules, a = 21.34 Å., b = 3.816 Å., c = 19.47 Å., β = 120°20′.

d Å. meas.	I/I_1	d Å. calcd.	hkl	d Å. meas.	I/I_1	d Å. calcd.	hkl	d Å. meas.	I/I_1	d Å. calcd.	hkl
16.9	10	16.8	001	3.28	<10	3.28	$21\bar{3}$	2.319	10	2.318	$20\bar{8}$
10.6	20	10.7	$20\bar{1}$			3.27	$11\bar{3}$	2.181	<10	2.184	$81\bar{4}$
9.7	10	9.7	$10\bar{2}$	3.17	<10	3.16	$20\bar{6}$			2.177	$81\bar{3}$
9.2	<10	9.2	200	3.09	<10	3.10	$41\bar{2}$	2.112	<10	2.116	513
8.4	<10	8.4	002	3.01	<10	3.00	$10\bar{6}$			2.109	414
6.32	10	6.32	$10\bar{3}$	2.84	10	2.84	$51\bar{2}$	2.079	10	2.081	207
5.60	<10	5.60	003	2.83	10	2.83	$70\bar{1}$	2.041	20	2.042	$10.0.\bar{7}$
5.29	<10	5.33	$40\bar{2}$	2.78	20	2.78	$51\bar{1}$			2.039	$80\bar{9}$
5.13	20	5.15	$40\bar{1}$	2.71	20	2.71	$21\bar{5}$	2.037	10	2.036	604
4.74	<10	4.73	103	2.677	<10	2.681	$41\bar{5}$	1.934	<10	1.932	117
4.63	20	4.64	$10\bar{4}$			2.677	$20\bar{7}$	1.915	20	1.914	712
3.83	<10	3.82	010	2.635	<10	2.637	$11\bar{5}$	1.876	<10	1.878	$22\bar{1}$
3.75	70	3.77	$40\bar{5}$	2.549	10	2.552	$10\bar{7}$	1.857	<10	1.858	$10.1.\bar{4}$
3.74	50	3.74	110	2.537	<10	1.544	503			1.855	208
3.65	100	3.65	$10\bar{5}$			2.531	404	1.822	10	1.822	320
3.56	<10	3.57	111			2.531	412	1.793	10	1.791	902
		3.55	$11\bar{2}$	2.529	<10	2.528	313	1.762	<10	1.761	$10.0.\bar{10}$
3.49	50	3.50	$21\bar{2}$	2.496	10	2.504	$80\bar{6}$	1.744	10	1.743	$11\bar{9}$
3.41	<10	3.44	$60\bar{4}$	2.483	<10	2.482	511	1.694	10	1.694	520
		3.38	402	2.457	<10	2.459	$61\bar{5}$	1.685	10	1.687	$3.1.\bar{10}$
3.36	10	3.36	005	2.451	<10	2.453	$80\bar{1}$	1.590	<10	1.591	522
3.32	<10	3.32	211	2.340	<10	2.340	$90\bar{3}$	1.584	10	1.582	10.1.1
								1.557	10	1.556	904

varying temperature increments beneath their transformation temperatures did not result in reversal of transformations, which is in agreement with the results obtained by Brauer.

In view of the inability to invert higher to lower temperature polymorphs, the term "equilibrium" as employed in this paper refers only to the results obtained within the limits of the experiments tabulated in Table I.

The densities of the polymorphs of Nb_2O_5, determined using the method previously described,[1] are as follows: amorphous 4.36 g./cm.^{3} at 25°, γ, 5.17 g./cm.^{3} at 25°, α 4.55 g./cm.^{3} at 25°.

The freezing point obtained in this study using D.T.A. cooling curve techniques was 1491 ± 2° which is slightly higher than the value originally reported.[3]

Magneli and Lagergren[16] indexed α-Nb_2O_5 on the basis of a monoclinic unit cell using data obtained with a Guinier focusing camera. They reported a = 21.50 Å., b = 3.825 Å., c = 20.60 Å. and $\sphericalangle\ \beta$ = 121°45′. Using these parameters the cell was found to contain 14 molecules with an X-ray density of 4.29 g./cm.^{3}. Apparently an error is present in the A.S.T.M. card since the indices recorded are not consistent with the above lattice constants. Using the data obtained from single crystal precession photographs the powder lines listed in Table II were reindexed. The monoclinic cell was found to have a = 21.34 Å., b = 3.816 Å., c = 19.47 Å. and $\sphericalangle\ \beta$ = 120°20′ with 14 molecules/unit cell. The X-ray density is 4.52 g./cm.^{3}.

Frevel and Rinn indexed the γ-phase on the basis of a monoclinic unit cell with a = 7.31 Å., b = 15.72 Å., c = 10.75 Å., $\sphericalangle\ \beta$ = 120°41′ with 12 molecules per unit cell. The X-ray density calculated from their data is 4.99 g./cm.^{3}, which is in poor agreement with the pycnometric density reported above. Attempts to reindex the γ-form directly from powder data were unsuccessful. Although heat treatment of the γ-phase for a month just below the γ- to α-transformation temperature appreciably improved the sharpness of diffraction maxima, the resolution was still insufficient to enable unequivocal indexing of this form. Consequently until a method is devised for growth of single crystals of this phase, the choice of unit cell is questionable.

The difference between the high temperature Nb_2O_5 and Ta_2O_5 phases indicated that the mixed oxide system would probably not form a continuous series of solid solutions. Preliminary investigation of this system, contrary to Schäfer's observations, showed a miscibility gap at approximately 25 mole % Ta_2O_5.

A complete investigation of the heterogeneous equilibria in the system Ta_2O_5–Nb_2O_5 is presently in progress and will be reported at a later date.

(16) A. Magneli and S. Lagergren A.S.T.M. #5-0379.

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[CONTRIBUTION FROM THE MALLINCKRODT LABORATORY, HARVARD UNIVERSITY]

Heats of Combustion and Formation of Metal Carbonyls. II. Nickel Carbonyl[1]

BY A. K. FISCHER, F. A. COTTON[2] AND G. WILKINSON

RECEIVED DECEMBER 10, 1956

The heat of combustion of liquid nickel carbonyl, $Ni(CO)_4$, has been determined as $\Delta H°_{298} = -282.2 \pm 0.5$ kcal./mole. For the reaction Ni(s) + 4CO (g, 1 atm.) = $Ni(CO)_4$ (g, 1 atm.) a value of -39.1 ± 0.5 kcal./mole is calculated for $\Delta H°_{298}$ (the error does not include errors in auxiliary data). The relation of these values to the various highly divergent results previously reported is discussed.

Introduction

The unsatisfactory status of the value of $\Delta H°$ for the reaction Ni(s) + 4CO(g) = $Ni(CO)_4$(g) was recently emphasized by Spice, Staveley and Harrow,[3] who surveyed the field, checked some of the earlier calculations, and tabulated the values which they recalculated so as to be consistent among themselves in respect to the various supplementary quantities. They indicated that values for $\Delta H°$, as determined by several methods, ranged from -26.0 to -52.6 kcal./mole, with the more recent values tending to center toward -35 kcal./mole, and this figure was accepted as the best then available. Because of possible uncertainties attending equilibrium studies involving finely divided nickel metal, it seemed that combustion calorimetry might assist a resolution of the difficulties. Shortly after the paper by Spice, *et al.*, there appeared a report of a combustion study by Smagina and Ormont[4] giving the value of $\Delta H°$ as -47.3 ± 1 kcal./mole. This Russian work appeared to be of doubtful reliability not only because of a paucity of experimental data and inadequately described experimental technique, but also because of the rather large deviation of their result from the region in which the value might be expected to lie as a result of the discussion by Spice, *et al.* The discordance therefore remained, and a redetermination of the heat of combustion of nickel carbonyl was included in the present series of combustion studies.

Experimental

The nickel carbonyl used in this work was obtained from a cylinder bottled by The Matheson Co., Inc., and was purified by repeated bulb-to-bulb distillation *in vacuo*. The purified nickel carbonyl was shown not to contain iron by testing with thiocyanate. Immediately before use, the samples were distilled into thin-walled Pyrex bulbs about 1.5 cm. in diameter. Two types of bulb (see below) were used, and the stems of either type were fused to a standard taper joint fitting into the vacuum system. After degassing the sample by means of thawing followed by freezing and pumping, the bulb was sealed by touching a small flame to the constricted stem about 1.5 cm. above the bulb at the same time that the bulb was drawn aside with tweezers. During this operation the sample was kept frozen by having the bulb just immersed in liquid nitrogen; also, the space above the sample was evacuated. Heat was further kept away from the sample by several layers of slotted asbestos paper slipped around the bulb stem. Nevertheless, slight decomposition of carbonyl vapor occurred just at the point of sealing, but analysis showed that the resulting nickel mirror weighed only 0.1 to 0.2 mg.; in a 1 to 2-g. sample the error thus introduced is negligible.

The calorimetric apparatus and technique were the same as described previously.[1] In the first of two series of combustions which were performed, the sample was fired with the aid of a benzoic acid pellet placed next to the bulb. In the second series, bulbs with 4.0 cm. of electrically heated no. 32 platinum wire sealed in (Fig. 1) were used in order to check on the hydration effect of the water present in the first set.[5]

Although incomplete combustion represented by unburned nickel metal in the final state was the rule, in a few preliminary runs a more serious difficulty was encountered in the form of residual nickel carbonyl; this was evident from the abnormally small temperature rises and spontaneous ignition upon venting the bomb gases. Subsequently, therefore, all runs were checked for residual nickel carbonyl and for unburned carbon monoxide by slowly releasing the bomb gases into a train consisting, in order, of a Dry Ice trap, an iodine pentoxide tube maintained at 150°, and two carbon tetrachloride traps. The Dry Ice trap serves to condense out any nickel carbonyl, and any carbon monoxide reacts in the iodine pentoxide tube: $5CO + I_2O_5 = I_2 + 5CO_2$.[6] Carbon dioxide and oxygen from the bomb then sweep any liberated iodine into the carbon tetrachloride traps where the characteristic violet color should develop. Nickel carbonyl was tested for by removing the Dry Ice and adding bromine water to the still cold trap; after debromination by boiling, the resulting solution was tested with dimethylglyoxime. Any run which revealed residual nickel carbonyl or unburned carbon monoxide was rejected. Three of the twenty-one runs done failed this test; none in the internally fired series did so.

The solid combustion products consisting of NiO and some unburned nickel metal were found in the combustion cup and on the bomb walls with the nickel metal concentrated as a black underlying layer almost exclusively on the lower half of the walls and in the cup. The solids were brushed out so as to recover all of the nickel metal and most of the nickel oxide, weighed and dissolved in concentrated nitric acid. To recover any traces of nickel metal occluded in fused glass, the glass was pulverized and leached with concentrated hydrochloric acid. The total nickel in these solutions was determined gravimetrically with dimethylglyoxime. To calculate the quantity of unburned metal, it was assumed that a fraction x of the solid material is nickel metal and a fraction $1 - x$ is nickel oxide; the nickel content expressed in terms of x was equated to the total nickel determined and the operation solved for x. The weight of unburned nickel metal was used to calculate a correction for incomplete combustion of nickel, using -57.3 kcal./mole as the enthalpy of formation of nickel oxide.[7]

No X-ray studies were made on the solid combustion products, but the presence of significant amounts of higher oxides of nickel was unlikely. Smagina and Ormont,[4] in runs made under conditions similar to those employed here, reported that X-ray powder patterns of the products of combustion were consistent with the presence of only NiO and

(1) Part I: F. A. Cotton, A. K. Fischer and G. Wilkinson, THIS JOURNAL, **78**, 5168 (1956).

(2) Chemistry Department, Massachusetts Institute of Technology, Cambridge 39, Massachusetts.

(3) J. E. Spice, L. A. K. Staveley and G. A. Harrow, *J. Chem. Soc.*, 100 (1955).

(4) E. I. Smagina and B. F. Ormont, *J. Gen. Chem. U.S.S.R.*, **25**, 207 (1955). (In the English translation edition published by Consultants Bureau, Inc., New York, N. Y.)

(5) A few runs (not reported) were made with magnesium ribbon as a fuse, but this mode of operation was abandoned when it was realized that unknown heat effects might attend the possible formation of mixed oxides of magnesium and nickel and, indeed, the $\Delta H°$ values for the carbonyl obtained in these runs were well outside the ranges of the ones reported below.

(6) M. C. Teague, *Ind. Eng. Chem.*, **12**, 964 (1920).

(7) B. J. Boyle, E. G. King and K. C. Conway, THIS JOURNAL, **76**, 3825 (1954).

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TABLE I

DATA FOR COMBUSTION OF $Ni(CO)_4$ WITH BENZOIC ACID FUSE

Run	Vac. wt. sample, g.	Cor. temp. change, °C.	Uncor. heat of combustion, kcal./mole	Cor. for incomplete combustion, kcal./mole	Fuse cor. kcal./mole	Washburn cor. kcal./mole	Fully cor. $\Delta E^{comb.}_{298°}$
1	1.86885	1.4278	−305.42	−11.12	+33.68	+0.48	−283.03[a]
2	1.71979	1.2955	−301.05	−14.70	+24.79	+ .48	−290.48
3	2.32480	1.7571	−302.04	−11.68	+28.28	+ .48	−284.96
4	2.40332	1.8752	−311.81	−13.98	+41.07	+ .47	−284.25
5	1.96039	1.7171	−350.01	−10.75	+75.89	+ .45	−284.42
6	1.25641	1.9568	−336.22	−11.02	+63.26	+ .46	−283.52

[a] This value includes a correction of −0.15 kcal. for the reduction to 25° (see text).

TABLE II

DATA FOR COMBUSTION OF $Ni(CO)_4$ WITH INTERNAL FIRING

Run	Vac. wt. sample, g.	Cor. temp. change, °C.	Uncor. heat of combustion, kcal./mole	Cor. for incomplete combustion, kcal./mole	Washburn cor. kcal./mole	Fully cor. $\Delta E^{comb.}_{298°}$
1	2.45808	1.6979	−276.03	− 4.87	+0.50	−280.40
2	2.65744	1.8163	−273.11	−10.16	+ .50	−282.77
3	2.16307	1.4761	−272.66	− 8.75	+ .50	−280.91
4	2.10515	1.5186	−287.86	− 5.95	+ .50	−293.31
5	2.95059	1.9963	−270.32	−14.34	+ .50	−284.16

Ni. Moreover, higher oxides of nickel are said not to exist in the anhydrous state.[8] Hence, although the non-anhydrous final state resulting in the runs fired with benzoic acid might conceivably permit slightly higher oxide formation, the borderline significance of the difference between this series of runs and the internally fired series would belie this; indeed, the difference can in greater likelihood be ascribed to hydration effects.

The heat input (*e.i.t.*) correction for the internally fired series was estimated in control runs with an empty sample bulb and its enclosed fuse wire in the following way. The slopes of the time *vs.* resistance curves for the fore- and after-periods, together with an allowance of an average time of 7 minutes for attainment of maximum temperature rise in a combustion run, permitted calculation of the correction, using the method of Dickenson.[9] This heat effect is such as to raise the resistance of the platinum resistance thermometer 0.0004 ohm and is included in the corrected temperature rise in Table II. Washburn corrections were calculated in one case by the original method of Washburn[10] which applies to 20° and also by the modified method of Hubbard, *et al.*,[11] which applies to 25°. The difference between the two values was insignificant for the present purposes, and all subsequent calculations were made by Washburn's simpler method. It was found that the correction differs negligibly from run to run and the same value, +0.50 kcal./mole, was applied to all.[12]

In Table I, run no. 2, and in Table II, run no. 4 were rejected as being obviously out of line with the other values. Thus, the remaining values in Table I give a mean value for $\Delta E^{comb.}_{298°}$ of −284.00 kcal./mole with an average deviation from the mean of ±0.61 kcal./mole and a standard deviation of the mean of ±0.34 kcal./mole. The mean of the remaining values in Table II is −282.06 kcal./mole with an average deviation from the mean of ±1.41 kcal./mole and a standard deviation of the mean of ±0.87 kcal./mole.

(8) N. V. Sidgwick, "The Chemical Elements and their Compounds," Oxford University Press, Oxford, England, 1951, p. 1450.

(9) H. C. Dickenson, *Bull. Bur. Standards*, **11**, 189 (1914).

(10) E. W. Washburn, *Bur. Standards J. Research*, **10**, 525 (1933).

(11) W. N. Hubbard, D. W. Scott and G. Waddington, *J. Phys. Chem.*, **58**, 152 (1954).

(12) For the benzoic acid fired series, the fuse correction was calculated from the heat of combustion of benzoic acid under the standard conditions specified by the National Bureau of Standards. The actual conditions here, however, differed from the standard ones in that 1 ml. of water was omitted from the bomb. It can be calculated that this gives rise to a correction of −0.060% of the fuse correction. This has been included in Table I with the general Washburn corrections thus lowering them from 0.50 to the values listed. The effect is seen to be practically negligible, but has been treated to avoid uncertainty in the matter.

Results

An analysis of errors in the various operations leads to a maximum expected random error of ±0.80 kcal./mole in the benzoic acid ignited runs, and an error of ±0.90 kcal./mole in the internally fired series. In the latter case, the error is larger because of uncertainties in the *e.i.t.* correction. The error in the determination of unburned nickel metal is taken as ±0.006 g., leading to an error in ΔE of ±0.50 kcal./mole for an average 2-g. sample. The percentage of nickel metal in the solid combustion products varies from 16 to 21% in the benzoic acid fired series, and from 9 to 21% in the internally fired series; this is also about the range reported by Smagina and Ormont.[4]

Initial temperatures for the accepted runs ranged from 21.6° for run no. 1 in Table I to 27.9° for run no. 5 in Table II, but calculation of the temperature coefficients of these runs showed that neglecting to reduce the data to 25° introduced an error of −0.15 kcal./mole for the former and only 0.02 kcal./mole for the latter. Therefore, the temperature being assigned to the measured reaction is 25°, run no. 1 in Table I being corrected to this temperature and the other runs standing as they are.[13]

Discussion

If the means are expressed as −284.0 and −282.1 kcal./mole for the series with and without benzoic acid, respectively, and if allowance is made for the expected maximum random error, these values fail to coincide by 0.2 kcal./mole, and the separation is 0.7 kcal./mole if the standard deviations are considered. It is doubtful if much significance can be attributed to or explanation given for this difference at the present time, save ascribing it to slight, exothermic hydration of the NiO by the water produced from the combustion of benzoic acid, and/or, less likely, to the formation of a small amount of a higher oxide of nickel in the same runs. If it is assumed that the two series do indeed measure the same thing, then together they have a mean of $\Delta E^{comb.}_{298°}$ = −283.1 kcal./mole with a standard deviation of the mean[14] of ±0.5 kcal./mole; this grand average was used in the subsequent calculations.

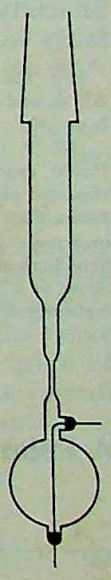

Fig. 1.

For the reaction

$$Ni(CO)_4(l) + 5/2O_2\ (g,\ 1\ atm.) = NiO(s) + 4CO_2\ (g,\ 1\ atm.)$$

$$\Delta H°_{298} = -282.2 \pm 0.5\ kcal./mole$$

(13) Calculation of the correction utilized heat capacity data from National Bureau of Standards Circular 500, except for $Ni(CO)_4$, for which the value $C_p^{298°}$ = 48.9 cal./mole was taken from reference 2.

(14) In part I a typographical error occurred in the definition of this quantity. The reported standard deviations of the means were calculated from the correct expression involving Σd_i^2.

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For the reaction

$$Ni(s) + 4CO(g, 1 atm.) = Ni(CO)_4(g, 1 atm.),$$
$$\Delta H°_{298} = -39.1 \pm 0.5 \text{ kcal./mole}^{15}$$

The enthalpies of formation used in the calculations are from reference 13 for CO and CO_2 and from reference 7 for NiO. The heat of vaporization of $Ni(CO)_4$ was taken as 6.5 kcal./mole.[3] From the foregoing, $\Delta Hf°_{298} = -145.1$ kcal./mole was calculated for the reaction Ni(s) + 4C (graphite) + $2O_2$ (g, 1 atm.) = $Ni(CO)_4$ (g, 1 atm.). Taking $S°_{298}$ of nickel carbonyl as 96.0 cal./°mole,[16] $\Delta Ff°_{298} = -140.0$ kcal./mole was calculated for the same reaction. The values quoted for Mittasch's work are those recalculated by Spice, *et al.*, from the corrected mathematical expressions; Reicher's value had also been recalculated by the same authors using more modern values for the relevant heats of formation and for the heat of vaporization of $Ni(CO)_4$. Of the listed figures, Reicher's is the most divergent and since the technique used is of doubtful reliability, this value perhaps need not be considered further.

The results obtained from equilibrium studies involving finely divided nickel metal may, as Spice, *et al.*, pointed out, suffer from an effect demonstrated by Giauque,[22] namely, that sometimes it may be impossible to identify equilibrium data obtained with finely divided solids with the equilibrium obtaining with the macrocrystalline phase, presumably because of the higher energy content of the more open structure of the finer material. The direct determination and the heat of combustion studies should be free from this difficulty. Mittasch's direct determination agrees fairly well with Smagina and Ormont's combustion value, but Mittasch's result conflicts markedly with the more modern direct determinations by Tomlinson and by the Mond Nickel Company, the latter agreeing well and contrasting with Mittasch's 30% higher figure. Smagina and Ormont's value was based on only three combustion runs, the average of which can be expressed to only two-figure significance and the result appears to be of doubtful reliability. In the present work, pains were taken to eliminate systematic errors, one noteworthy source of which could be incomplete detection of unburned nickel metal; an error of this sort would lead to a high value for $\Delta H°$. Consequently, it appears reasonable to regard previous values greater than −40 kcal. as erroneous.

(15) The ±0.5 kcal. represents the standard deviation of the mean in $\Delta E°_{298}$ and does not include errors in the auxiliary data from refs. 3, 7 and 13.

(16) B. L. Crawford, Jr., and P. C. Cross, *J. Chem. Phys.*, **6**, 525 (1938), report a spectroscopically determined value of 97.0 e.u. The expected error was stated as not greater than 2%. Recently L. H. Jones, *ibid.*, **23**, 2448 (1955), reinvestigated the infrared spectrum and in a preliminary report suggests some reassignments of bands in the neighborhood of 300–400 $cm.^{-1}$ which may lower the entropy value. Spice, *et al.*,[3] found 95.4 (probably ±2 e.u.) calorimetrically, the uncertainty arising in a long low temperature extrapolation.

TABLE III

SUMMARY OF $\Delta H°$ VALUES FOR Ni(s) + 4CO(g) = $Ni(CO)_4$(g) (IN KCAL./MOLE)

Mittasch—direct determination[17]	−45.7
Tomlinson—direct determination[18]	−32.0
Mond Nickel Co.—direct determination[19]	−34.5
Mittasch—equilibrium study[17]	−26.0
Mittasch—equilibrium study[17]	−27.5
Mittasch—equilibrium study[17]	−30.0
Sykes and Townshend—indirect determination[20]	−36.3
Reicher—heat of combustion study[21]	−52.6
Smagina and Ormont—heat of combustion study[4]	−47.3
This research—heat of combustion study	−39.1

Acknowledgment.—One of us (A.K.F.) wishes to express his thanks to the Mallinckrodt Chemical Company for a grant toward research expenses.

(17) A. Mittasch, *Z. physik. Chem.*, **40**, 1 (1902).

(18) J. R. Tomlinson, Abstract of Papers Presented at the 125th Meeting of the American Chemical Society, March, 1954, p. 18-Q.

(19) Private communication to Spice, *et al.*, see reference 3.

(20) K. W. Sykes and S. C. Townshend, *J. Chem. Soc.*, 2528 (1955). In line 2, p. 2529, a typographical error omitted a factor of 4 from the denominator of the expression for *C*, but the result was obtained from the correct formula.

(21) R. Reicher, "Werken von het Genootschap ter befordering der naturgenees-en heelkunde," Amsterdam, 2nd series, Vol. II, 1896, p. 296.

(22) W. F. Giauque, THIS JOURNAL, **71**, 3192 (1949).

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE HALL LABORATORY OF CHEMISTRY, WESLEYAN UNIVERSITY]

A Polarographic Study of the Formate Complexes of Cadmium, Copper, Lead, Thallium and Zinc[1]

BY HERBERT M. HERSHENSON,[2] RUTH THOMPSON BROOKS AND MARY E. MURPHY

RECEIVED OCTOBER 8, 1956

Cadmium, lead and zinc have been found to form weak but definite complexes of the types $M(HCOO)^+$, $M(HCOO)_2$, $M(HCOO)_3^-$ and $M(HCOO)_4^=$ with formate ion concentrations ranging from 0 to 1.98 *M* in solutions held at a constant ionic strength of 2.00 with perchlorate. Copper forms similar complexes which appear to be more stable, while thallium shows no complexing tendency except at very high formate concentrations. The formation constants at 25° for the $M(HCOO)^+$, $M(HCOO)_2$, $M(HCOO)_3^-$ and $M(HCOO)_4^=$ complexes, respectively, were determined to be 3, 13, 22 and 16 for cadmium, 6, 23, 27 and 15 for lead, 4, 9, 3 and 6 for zinc and 37, 116, 112 and 283 for copper. No constants could be determined for thallium.

Introduction

The formate complexes of metal ions have not been investigated extensively; however, a few complex formates of iron and chromium have been

(1) Presented before the Division of Physical and Inorganic Chemistry at the 130th Meeting of the American Chemical Society, Atlantic City, N. J., September 20, 1956. Taken from the M.S. dissertations of Ruth Thompson Brooks, June, 1954, and Mary E. Murphy, June, 1956.

(2) Fox Project, Pratt & Whitney Aircraft, East Hartford, Conn.

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known for some time.[3-5] Brintzinger and co-workers[5] employed dialysis measurements to establish the existence of the following complexes: $Cd(HCOO)_4^=$, $Cu(HCOO)_4^=$ and $M(HCOO)_6^{-4}$ where M may be Co^{++}, Ni^{++} or Zn^{++}.

As part of a program involving the complexing tendencies of certain anions in aqueous solution, the formate complexes of cadmium, copper, lead, thallium and zinc have been studied using the polarographic technique developed by DeFord and Hume.[6]

Experimental

Half-wave Potential Measurements.—A Sargent Recording Polarograph, Model XXI, was used throughout this study. The span voltage was normally set at 0.5 volt, the sensitivity at 0.040 μa./mm. and no damping was employed. The initial and final applied voltages were measured to ±0.1 mv. with a Rubicon potentiometer and the resistance of the cell system was determined by means of an Industrial Instruments conductivity bridge. A Beckman Model G *p*H meter was used to determine the acidity of all solutions. Nitrogen was bubbled through the sample solution before each run in order to remove dissolved oxygen. All polarograms were run at 25.0 ± 0.2°. The method employed for determining the half-wave potential, slope and diffusion current for each polarogram was essentially that described by Hume and co-workers.[7]

Electrode Assembly.—The dropping mercury electrode, made from Corning marine barometer tubing, served as cathode. Because of the possibility of precipitation of potassium perchlorate,[8] it was decided to avoid the use of a conventional saturated calomel reference electrode. Instead a reference solution saturated with quinhydrone and hydroquinone was used. The sample solution, containing 0.001 *M* metal ion, 0.01 *M* perchloric acid, and various concentrations of sodium perchlorate and sodium formate, was placed in one arm of a U-shaped cell. The other arm, separated by a sintered-glass disk, contained the reference solution and 100 cm. of 0.0014″ platinum wire wound into a 3″ coil. The reference solution consisted of the same concentrations of perchloric acid, sodium perchlorate and sodium formate as in the sample solution, but contained no metal ion, and was saturated with quinhydrone and hydroquinone by shaking with the solids immediately before use. This assembly had the advantage of reducing to a minimum the unknown junction potential. Since the *p*H of the reference solution varies with the sodium formate concentration, it was necessary to measure the *p*H of each solution in order to calculate the potential of the reference electrode in each case. The standard potential of the quinhydrone–hydroquinone electrode was taken as +0.6123 volt *vs.* hydrogen.[9] Half-wave potential values were converted to S.C.E. as reference.

Chemicals.—All chemicals were reagent grade except for C.P. quinhydrone and hydroquinone. The nitrate salts were used to supply the metal ions, sodium formate to supply the formate ions and sodium perchlorate to adjust the ionic strength.

Results and Discussion

It is generally true that, if the half-wave potential of a metal ion shifts in a more negative direction as the concentration of ligand is increased, formation of complexes is indicated. Experiments were performed, therefore, to discover the direction and magnitude of the half-wave potential shift for each metal as the concentration of formate was increased. The results are shown in Fig. 1. It may be seen that in each case except thallium, there was a pronounced shift to more negative potentials with increasing formate concentration. Thus it appeared that complex formation does occur with

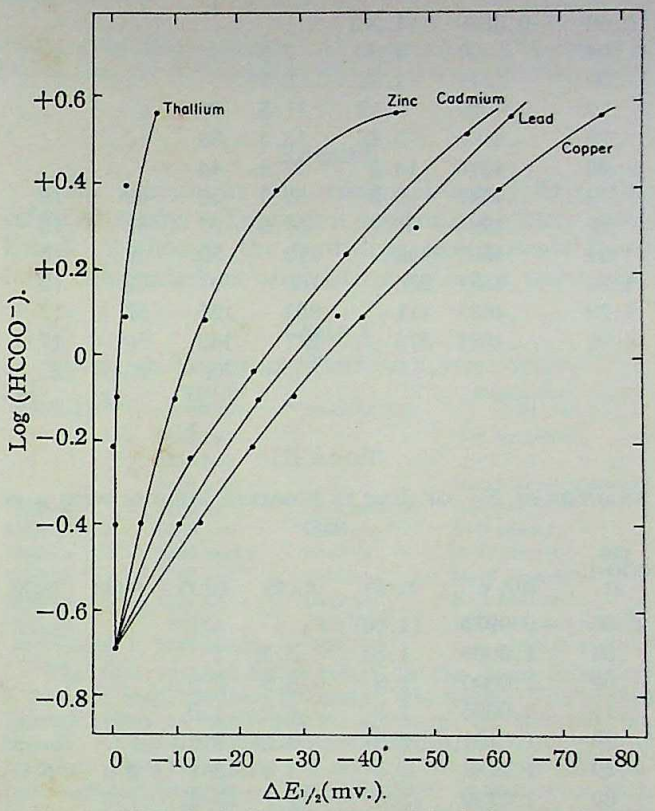

Fig. 1.—Shift in half-wave potential of the metals as a function of sodium formate concentration (based arbitrarily on the half-wave potential in 0.20 *M* formate as the initial value).

cadmium, copper, lead and zinc. However, the observed shift in half-wave potential is due to two factors: the increased amount of complex formation at higher formate concentrations and the change in activity coefficients due to changing ionic strength. In order to obtain quantitative results, another series of determinations was performed for each metal during which the ionic strength was maintained at a constant value of 2.00 while the formate concentration was varied. The data obtained were calculated and plotted as directed by DeFord and Hume.[6] The analysis of the data is shown in Tables I, II, III and IV.

TABLE I

ANALYSIS OF $E_{1/2}$ OF CADMIUM IN FORMATE MEDIUM WITH $\mu = 2.00$

(HCOO⁻), *M*	$E_{1/2}$, v.	$F_0(X)$	$F_1(X)$	$F_2(X)$	$F_3(X)$	$F_4(X)$
0.00	−0.5687	(1.00)	...	...	...	...
.09	.5730	1.40	4.4	16	...	...
.19	.5790	2.28	6.7	19	...	...
.49	.5965	9.53	17.4	29	33	...
.79	.6102	26.6	32.4	37	30	10
.89	.6140	37.0	40.4	42	33	12
.99	.6193	55.2	54.8	52	39	17
1.79	.6421	349	194	107	53	17
1.98	.6465	525	265	132	60	19
			K_1 =	K_2 =	K_3 =	K_4 =
			3	13	22	16

(3) R. Weinland and H. Reihlen, *Ber.*, **46**, 3144 (1913).

(4) W. D. Treadwell and W. Fisch, *Helv. Chim. Acta*, **13**, 1219 (1930).

(5) H. Brintzinger, H. Plessing and W. Rudolph, *Z. anorg. Chem.*, **242**, 197 (1939).

(6) D. D. DeFord and D. N. Hume, THIS JOURNAL, **73**, 5321 (1951).

(7) D. N. Hume, D. D. DeFord and G. C. B. Cave, *ibid.*, **73**, 5323 (1951).

(8) H. M. Hershenson, M. E. Smith and D. N. Hume, *ibid.*, **75**, 507 (1953).

(9) J. B. Conant and L. F. Fieser, *ibid.*, **46**, 1858 (1924).

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TABLE II

ANALYSIS OF $E_{1/2}$ OF LEAD IN FORMATE MEDIUM WITH μ = 2.00

(HCOO⁻), M	$E_{1/2}$ v.	$F_0(X)$	$F_1(X)$	$F_2(X)$	$F_3(X)$	$F_4(X)$
0.00	−0.3890	(1.00)	...	...	...	...
.04	.3921	1.30	7.5	...	...	...
.09	.3917	1.32	3.6	...	...	...
.19	.4029	3.18	11.5	29	...	...
.29	.4100	5.48	15.5	33	...	...
.49	.4216	14.5	27.6	44	...	...
.79	.4347	40.5	50.0	56	42	19
.89	.4384	51.7	57.0	57	38	12
1.29	.4507	146	112	82	46	15
1.59	.4581	256	160	97	47	13
1.79	.4637	411	229	125	57	17
1.98	.4681	570	287	142	60	17
			K_1 =	K_2 =	K_3 =	K_4 =
			6	23	27	15

TABLE III

ANALYSIS OF $E_{1/2}$ OF ZINC IN FORMATE MEDIUM WITH μ = 2.00

(HCOO⁻), M	$E_{1/2}$ v.	$F_0(X)$	$F_1(X)$	$F_2(X)$	$F_3(X)$	$F_4(X)$
0.00	−0.9975	(1.00)	...	...	...	...
.04	1.0009	1.34	8.5	...	...	...
.09	1.0090	1.8	8.9	5.5	...	...
.19	1.0095	1.8	4.2	1.0	...	...
.29	1.0101	2.8	6.2	7.6	...	...
.49	1.0183	5.4	8.4	10.1	4.3	6.7
.69	1.0239	12.8	17.1	13.2	1.6	...
.89	1.0318	16.0	16.9	14.5	7.3	7.1
1.09	1.0386	23.3	20.5	13.7	3.4	3.1
1.29	1.0425	37.9	28.6	19.1	8.6	5.9
1.49	1.0503	68.8	45.5	27.8	13.3	8.2
1.69	1.0531	88.7	51.9	28.3	12.1	6.7
1.84	1.0597	145	78.5	40.5	17.7	9.1
1.98	1.0667	259	130	66.0	29.3	14.8
			K_1 =	K_2 =	K_3 =	K_4 =
			4	9	3	6

Plots of the calculated values of $F(X)$ against the formate ion concentration for each of the elements resulted in straight lines for $F_3(X)$ and $F_4(X)$. This indicates the presence of complexes of the forms $M(HCOO)^+$, $M(HCOO)_2$, $M(HCOO)_3^-$ and $M(HCOO)_4^=$ in each case.

The formation constants for the formate complexes and their estimated uncertainties are summarized in Table V. These uncertainties are primarily the result of the difficulty in determining very precisely half-wave potential shifts ranging from 10 to 100 mv. Examination of the data in

TABLE IV

ANALYSIS OF $E_{1/2}$ OF COPPER IN FORMATE MEDIUM WITH μ = 2.00

(HCOO⁻), M	$E_{1/2}$ v.	$F_0(X)$	$F_1(X)$	$F_2(X)$	$F_3(X)$	$F_4(X)$
0.00	+0.0318	(1.00)	...	...	...	...
.04	.0198	2.96	48	...	...	...
.19	.0024	10.3	49	68	...	...
.29	− .0128	34	114	236	242	448
.49	.0246	87	175	284	240	261
.69	.0366	226	326	420	369	370
.89	.0445	421	472	490	364	283
1.09	.0527	799	731	630	425	286
1.29	.0652	2197	1700	1290	870	510
1.49	.0625	1807	1210	790	419	210
1.69	.0746	4550	2685	1570	830	424
1.84	.0747	4630	2510	1320	630	282
1.98	.0809	7725	3900	1960	956	428
			K_1 =	K_2 =	K_3 =	K_4 =
			37	166	112	283

Table V will show that the order of complexing with formate is Cu >> Pb > Cd > Zn >> Tl. This agrees with the order predictable from the results of the preliminary experiment shown in Fig. 1.

TABLE V

CALCULATED FORMATION CONSTANTS FOR FORMATE COMPLEXES AT 25°

Complex type	Zinc	Cadmium	Lead	Copper
$M(HCOO)^+$	4 ± 1	3 ± 1	6 ± 1	37 ± 8
$M(HCOO)_2$	9 ± 2	13 ± 1	23 ± 4	166 ± 22
$M(HCOO)_3^-$	3 ± 1	22 ± 7	27 ± 10	112 ± 40
$M(HCOO)_4^-$	6 ± 3	16 ± 4	15 ± 4	283 ± 23

Burns and Hume[10] have reported recently that lead forms only the $Pb(OAc)^+$, $Pb(OAc)_2$ and $Pb(OAc)_3^-$ complexes with acetate under comparable conditions. However, the evidence for the presence of the tetraformato complex at high formate concentrations is quite definite. Also, the $Cd(HCOO)_4^=$ and $Cu(HCOO)_4^=$ complexes identified by Brintzinger and co-workers[5] have been confirmed but no indication of a $Zn(HCOO)_6^{-4}$ complex was observed.

The formate complexes of cadmium, lead and particularly zinc are obviously very weak. The validity of the constants is therefore somewhat questionable. Nevertheless, the data presented strongly suggest the tendency for complex formation with formate and represent at least a reasonable measure of the magnitude of this tendency.

MIDDLETOWN, CONN.

(10) E. A. Burns and D. N. Hume, THIS JOURNAL, **78**, 3958 (1956).

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[CONTRIBUTION FROM THE W. A. NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

Infrared Spectra of the Salts of the Dinitrososulfite Ion (Nitrosohydroxylaminesulfonates)

BY RUSSELL S. DRAGO

RECEIVED NOVEMBER 30, 1956

The infrared spectra of the sodium, potassium and ammonium salts of the dinitrososulfite ion are reported. Differences in the spectra of these three salts are interpreted. It is also concluded that the N–N bond in this ion has considerably more single bond character in it than previously proposed.

The synthesis of several materials containing the dinitrososulfite ion can be accomplished by passing nitric oxide into a basic solution containing sulfite ion.[1,2] The reactions that the dinitrososulfites undergo are very complex and, as a result, attempts to deduce a structure from the chemical behavior led to conflicting results.[2–5] A single crystal, X-ray diffraction investigation was undertaken and the structures of the potassium, ammonium and thallium salts were determined.[6] An accurate determination of the bond orders could not be ascertained from these studies and recently there have been attempts[7,8] to explain the electronic structure of the dinitrososulfites from chemical behavior. Evans and Gergeley[9] have also proposed a structure based upon a molecular orbital system of bonding throughout the N_2O_2 group. The infrared spectra were obtained in order to gain additional information concerning the structures of these salts.

An X-ray study of the sodium salt was not undertaken by Cox, *et al.* Difficulties were encountered[5] in attempts to prepare single crystals of this salt because of its much greater solubility. In view of this surprising solubility, the infrared spectrum of the sodium salt also was studied in order to obtain evidence concerning its structure.

Experimental

The sodium and potassium salts were prepared by methods described by Weitz and Achterberg.[2] The ammonium salt was prepared by a metathesis reaction based on the insolubility of ammonium dinitrososulfite relative to the sodium salt. In this procedure excess ammonium chloride and ammonium hydroxide are added to the reactants used to prepare the sodium salt. The crude ammonium salt precipitates out as the reaction proceeds. The salt is purified by methods previously described.[2] The potassium salt can also be prepared by a similar type reaction. The purity of the salts employed in this study are indicated by the following analyses: Calcd. for $K_2SO_3N_2O_2$: N, 12.83; K, 35.84. Found: N, 12.74; K, 35.67. Calcd. for $Na_2SO_3N_2O_2$: N, 15.01; Na, 24.73. Found: N, 14.38; Na, 24.73. Calcd. for $(NH_4)_2SO_3N_2O_2$: N, 31.82. Found: N, 31.80.

Nujol mulls of the compounds were examined using a Perkin–Elmer model 21 infrared spectrometer with sodium chloride optics. The potassium salt was also examined in perfluorokerosene mull.

Results

Table I contains the results obtained from the infrared study. Tentative assignments have been listed. Although the tentative assignments have been designated as originating within a particular bond, it should be pointed out that the group frequency vibrations in the 1300–650 region are not completely localized within the bond designated. There is only limited information available to support the assignment of the bond at 925 cm.$^{-1}$. Fortunately the doubtful assignment does not seriously affect the conclusions that can be drawn regarding the structure of these salts.

TABLE I

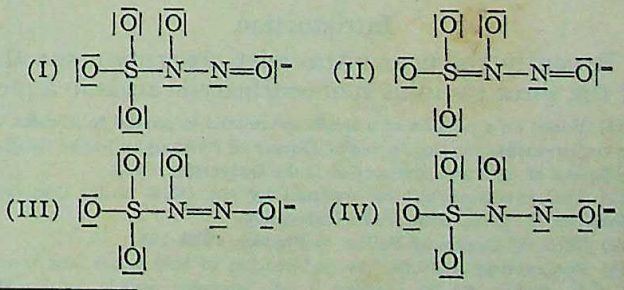
INFRARED BANDS AND TENTATIVE ASSIGNMENTS[a]

$K_2SO_3 \cdot 2NO$	$(NH_4)_2SO_3 \cdot 2NO$	$Na_2SO_3 \cdot 2NO$	Assignments and lit. ref.
	3250 i,s		NH stretch[10]
	3110 i,m		
	1435 i,m		NH_4^+ bending mode[10]
1322 i,s	1330 i,s	1345 med,m	NO stretch[12]
1265–85 i,m	1282 i,m	1280 i,m	S–O stretch[11]
1230 i,s	1202 med,s	1240 i,s	N–O stretch[12]
1130 i,s	1132 i,s	1147 i,s	N–N stretch[12]
1055 i,s	1057 i,s	1060 i,s	S–O stretch[11]
922 i,s	925 i,s	934 i,s	(S–N–N) vibration[b]
625 med,br	625 med,br	625 i,br	S–O bending mode[11]

[a] The first symbol listed refers to the bond intensity: i, intense; med, medium intensity; wk, weak. The second symbol refers to band width: s, sharp, m, medium, br, broad. [b] Very little information is available on this type of linkage. This bond does not occur in compounds that contain only one nitrogen on the sulfur.[11,13] It does occur both in the compounds reported above and in hydrazinosulfuric acid.[13] The parentheses indicate this assignment is questionable and requires further investigation.

Discussion

The following structures are possible for the dinitrososulfite ion. (Resonance forms for the $-SO_3$ group are not included.)



(1) J. Pelouze, *Ann. Pharm.*, **15**, 240 (1835).
(2) E. Weitz and F. Achterberg, *Ber.*, **66B**, 1718 (1933).
(3) F. Raschig, *Ann.*, **241**, 232 (1887).
(4) E. Divers and T. Haga, *J. Chem. Soc.*, **67**, 452 (1895); **69**, 1610 (1896).
(5) A. Hantzsch, *Ber.*, **27**, 3264 (1894).
(6) E. G. Cox, G. A. Jeffrey and H. P. Stadler, *J. Chem. Soc.*, 1783 (1949); *Nature*, **162**, 770 (1948); G. A. Jeffrey and H. P. Stadler, *J. Chem. Soc.*, 1467 (1951).
(7) M. Goehring and R. Otto, *Z. anorg. allgem. Chem.*, **280**, 143 (1955).
(8) E. Degener and F. Seel, *ibid.*, **285**, 129 (1956).
(9) M. G. Evans and J. Gergeley, *Nature*, **162**, 771 (1948).
(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 285.
(11) H. J. Hofmann and K. R. Andress, *Naturwissenschaften*, **41**, 94 (1954).
(12) R. N. Haszeldine and J. Jander, *J. Chem. Soc.*, 691 (1954), Errata, *ibid.*, 4778 (1954); R. N. Haszeldine and B. J. H. Mattinson, *ibid.*, 4172 (1955).
(13) S. West, Ph.D. Thesis, University of Illinois, 1955.

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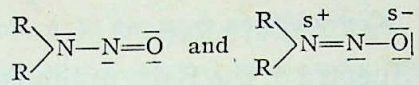
The actual structure undoubtedly is a resonance hybrid consisting of most of these forms. From the X-ray study it was concluded that structure III is of greatest significance in contributing to the final structure and in other publications[7] structure III was the only one indicated.

The absence of absorption in the 1500 cm.$^{-1}$ region indicates that the N–N bond has a considerable amount of single bond character in it. This would indicate that other structures (I or I and II) are quite significant in determining the final state of the molecule. The Raman and infrared spectra of hyponitrite ion have been reported[14] and absorption at 1392 cm.$^{-1}$ was attributed to the N–N bond. The authors interpreted this as indication of a considerable amount of single bond character in the N–N bond. Using similar arguments these studies indicate that the N–N bond in the dinitrososulfite ion has more single bond character than the N–N bond in hyponitrite for the spectra of the potassium salt in perfluorokerosene shows the absence of absorption up to 1322 cm.$^{-1}$.

The tentative assignments have been made for N–O and N–N absorption by considering the bond types to be similar to those in the dialkyl nitrosamines.[12] The following assignments have been reported for N–O and N–N vibrations in these compounds[12]: two vibrations for N–O stretch: 1315–1165 and 1265^{-1} cm.$^{-1}$; the N–N vibration between 1135–1190 cm.$^{-1}$. The structures of the nitrosamines were regarded as a hybrid of the forms



Absorptions from N=O do not occur at higher frequencies because of this resonance.

It should be kept in mind that in this study the spectra were obtained on Nujol mulls of the solid dinitrososulfites. It would be most desirable to check these measurements with Raman data on these compounds in solution to evaluate further the above assignments.

The spectra of the potassium, ammonium and sodium salts are all similar enough to indicate that the structure of the sodium salt is similar to that of the potassium and ammonium salt. With the exception of the NH_4^+ vibrations and the absorption at 1230 cm.$^{-1}$, the spectra of the potassium and ammonium salts are very much alike. The difference in the N–O vibration at 1230 cm.$^{-1}$ can be attributed to effects caused by hydrogen bonding in the ammonium salt. The existence of hydrogen bonding is further substantiated by the splitting of the N–H stretching vibration in the 3200 cm.$^{-1}$ region.

The shifts observed in the infrared spectra of the sodium salt compared to the other salts is interesting in view of the larger solubility of the sodium salt. The shifts probably arise from differences in crystal stability resulting from either anion–anion contact or from a different kind of crystal lattice in the case of the sodium salt.

URBANA, ILL.

(14) L. Kuhn and E. L. Lippincott, THIS JOURNAL, **78**, 1820 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICS OF DUKE UNIVERSITY]

Near Ultraviolet Absorption Spectra of the Pyridine Monocarboxylic Acids in Water and Ethanol Solutions[1,2]

BY HAROLD P. STEPHENSON[3] AND H. SPONER

RECEIVED DECEMBER 26, 1956

The near ultraviolet absorption spectra of picolinic, nicotinic and isonicotinic acids (2-, 3- and 4-pyridinecarboxylic acids) have been measured in 95% ethanol and distilled water solutions, and for isonicotinic acid, also for several mixtures of these two solvents. Changes in the spectra which occur when the solvent is changed from ethanol to water have been interpreted to show that the pyridine monocarboxylic acids exist primarily in the neutral, undissociated form in ethanol, and in the anion and zwitterion forms in water.[4] The spectra of the several species are discussed with regard to rather limited theoretical information concerning the effects of a carboxyl substituent on the spectrum of benzene or pyridine.

Introduction

Recently the near ultraviolet absorption spectra of the three pyridine monocarboxylic acids in aqueous solution have been reported in a number of papers,[5–7] the spectra having been observed in order to determine the acid and base dissociation constants of these substances. In each of these papers the possible zwitterion forms of the molecules were considered unimportant for an interpretation of the observed spectra. However, Jaffé[8] has discussed the tautometric equilibria of a number of substituted pyridines and their 1-oxides in aqueous solution and has concluded that nico-

(1) Based on a portion of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Arts and Sciences of Duke University, 1952.

(2) This investigation was assisted by the ONR under Contract N6ori-107, T. O. I., with Duke University.

(3) Shell Oil Company Fellow in Physics, 1950–1951.

(4) For external reasons, the publication of this paper was much delayed. Before finally sending it off, a recent article by R. W. Green and H. K. Tong on "The Constitution of the Pyridine Monocarboxylic Acids in their Isoelectric Forms" (THIS JOURNAL, **78**, 4896 (1956)) has come to our attention, in which these authors came to the same conclusions about the species of these acids in aqueous solutions as are presented in this paper. However, since our approach to this problem came more from the spectroscopic side, this paper contains additional spectroscopic information which supplements the paper by Green and Tong.

(5) E. B. Hughes, H. H. G. Jellinek and B. A. Ambrose, *J. Phys. Colloid Chem.*, **53**, 414 (1949).

(6) R. F. Evans, E. F. G. Herington and W. Kynaston, *Trans. Faraday Soc.*, **49**, 1284 (1953).

(7) H. H. G. Jellinek and J. R. Urwin, *J. Phys. Chem.*, **58**, 548 (1954).

(8) H. H. Jaffé, THIS JOURNAL, **77**, 4445 (1955).

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tinic acid and isonicotinic acid exist predominantly in the zwitterion form at the isoelectric point and that the thermodynamic constants K_a and K_b for these substances have been misinterpreted in the previous papers. Platt[9] has included nicotinic acid in a study of the "spectroscopic moments" of a large number of substituent groups and has suggested that observed anomalous intensities in the ultraviolet spectra of nicotinic acid may be due to zwitterion formation. In part, Platt based his conclusions on data from a spectrum which was reported to have been measured in isoöctane solution (non-polar solvent) but has since been found to have been taken in water solution instead.[10]

In this paper the near ultraviolet absorption spectra of picolinic, nicotinic and isonicotinic acids (2-, 3-, 4-pyridinecarboxylic acids) measured in this Laboratory in both ethanol and water solutions[11] will be reported which augment and clarify the arguments of Jaffé and Platt and afford an opportunity to discuss the spectra of what we think are the truly neutral species of these substances.

Experimental

The picolinic acid (melting point designated as 136°) was kindly given to us by Mr. L. Szabo of the Wyeth Institute of Applied Biochemistry. Since only a small quantity of the acid was available, it was found impossible to recrystallize any useful amount of the sample on account of the very high solubility of picolinic acid in cold water. Both the nicotinic and isonicotinic acids were purest-grade Eastman Kodak products and were used after recrystallization. In water solution where the extent of dissociation of these acids appears not to be the same for all observers, it is difficult to judge the purity of the samples by a comparison of the spectra. The absorption strength of both picolinic[12] and nicotinic[10] acid as reported by previous authors is somewhat smaller than that reported here. We have measured the spectrum of nicotinic acid both before and after recrystallization and have observed that low molar extinction values are characteristic of an unpurified sample. Better agreement between the results of different laboratories is to be expected for spectra measured in ethanol solutions, but apparently an ethanol solution spectrum has been published elsewhere only for nicotinic acid. In this case there is excellent agreement between our measured maximum molar extinction value of 2840 and an earlier value of 2820 reported by Miller.[13] All the spectra recorded in the previously mentioned papers[6-7] were measured in solutions of controlled *p*H and may not therefore be used to judge the purity of our samples.

The solutions used in this research were prepared from distilled water or 95% ethanol by ordinary procedures, and the spectral measurements were made at room temperature with a Beckman quartz spectrophotometer. Readings were taken over the wave length range from about 210 mμ up to about 320 mμ. For the concentrations used to cover most of this range (4×10^{-3} to 4×10^{-4} mole/l.) there appeared to be no significant concentration effects which could not be attributed to non-linearity of the optical density scale. The results of this paper indicate, however, that a careful study of such effects over a much wider range of concentrations in water solution would undoubtedly be very worthwhile for the pyridine carboxylic acids. For isonicotinic acid an interesting band shifting effect was discovered which seemed to warrant our taking measurements in various mixtures of ethanol and water. The proportions of 95% ethanol and water were in this case measured volumetrically.

Molar extinction coefficients ϵ were calculated from the usual equation $I = I_0 \times 10^{-\epsilon cl}$, where c refers to the total concentration of the solute in moles per liter and l is the absorbing path length, absorption cells 1 cm. long being used throughout this research. The spectra are plotted in Figs. 1, 2 and 3 with wave numbers ν (reciprocal centimeters) as the abscissae and molar extinction coefficients as the ordinates. For convenient comparison the spectra of

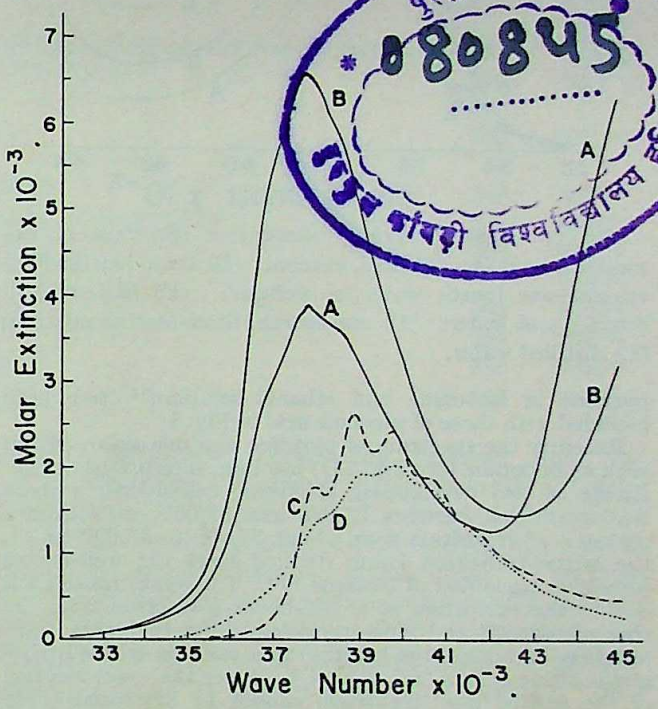

Fig. 1.—Near ultraviolet absorption spectra of: (A) picolinic acid in 95% ethanol; (B) picolinic acid in distilled water; (C) pyridine in 95% ethanol; (D) pyridine in isoöctane.

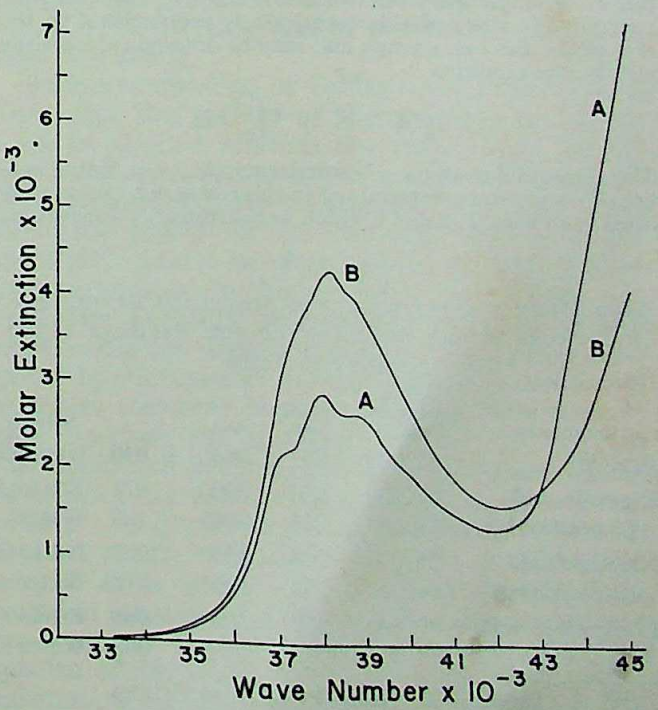

Fig. 2.—Near ultraviolet absorption spectrum of nicotinic acid in: (A) ethanol; (B) water.

(9) J. R. Platt, *J. Chem. Phys.*, **19**, 263 (1951).

(10) API Research Project 44 at the NBS. Catalog of Ultraviolet Spectrograms. Serial No. 110, Nicotinic Acid (water solution[a]) contributed by the California Research Corporation. [a] Private communication to this Laboratory from the California Research Corporation. This spectrogram was incorrectly labelled "Solution in Isoöctane."

(11) Some of the results given here have previously been contributed to the API Catalog of Ultraviolet Spectrograms. *Cf.* Serial Nos. 231, 232, 233, 483, 484, 485.

(12) H. Hünecke, *Ber.*, **B60**, 1451 (1927).

(13) E. Miller, "Qualitative Biological Spectroscopy," Vol. I, Burgess Publishing Co., Minneapolis, Minn., 1940, p. 201.

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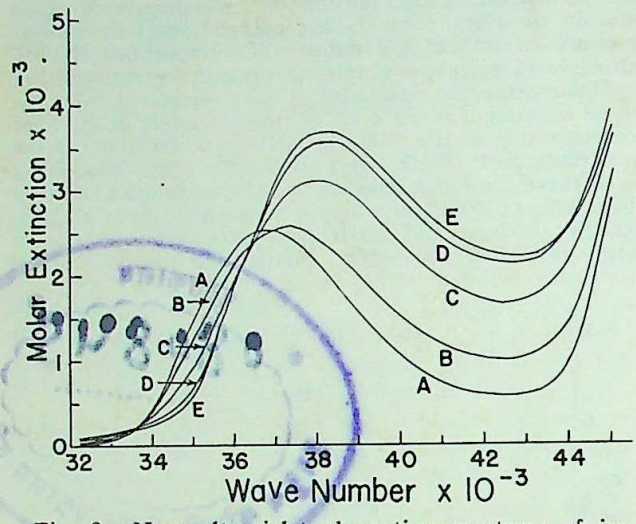


Fig. 3.—Near ultraviolet absorption spectrum of isonicotinic acid in: (A) 95% ethanol; (B) three-fourths 95% ethanol–one fourth water by volume; (C) half-and-half ethanol and water; (D) one-fourth, three-fourths mixture; (E) distilled water.

pyridine in isoöctane and ethanol solutions[14] have been included with those of picolinic acid in Fig. 1.

Recently the spectrum of pyridine in a non-polar solvent such as isoöctane (see Fig. 1D) has been interpreted as consisting of two overlapping electronic transitions, a weak n-π^* transition between 35,000 and 38,000 cm.$^{-1}$, and a strong π-π^* transition from about 37,000 to 45,000 cm.$^{-1}$, the latter transition being derived from the well-known forbidden transition of benzene.[14,15] The weak transition is due to the excitation of a non-bonding electron from the ring nitrogen,[16] and this transition shifts to higher wave numbers (shorter wave lengths) in a solution where hydrogen-bonding occurs (see Fig. 1C). Since the exact location of the shifted n-π^* transition cannot be determined, the near ultraviolet absorption spectrum of pyridine in either ethanol or water solution[17] is assumed, therefore, to be due to a single π-π^* transition of a ring π-electron.

It is likewise very probable that the single strong band appearing with a maximum at about 38,000 cm.$^{-1}$ in the spectra of the pyridine carboxylic acids is also primarily due to a single π-π^* electronic transition. The oscillator strength (f-value) of this transition is proportional to the area under the ϵ *vs.* ν graph and may be determined from the well-known equation

$$f = 4.32 \times 10^{-9} \int_0^\infty \epsilon d\nu$$

The f-values for the π-π^* transitions of the pyridine carboxylic acids were determined in this research by measuring areas from Figs. 1, 2 and 3 which were arbitrarily determined on the high wave number side by drawing a vertical line through the minimum of absorption around 43,000 cm.$^{-1}$. The results of the f-value determinations are listed in Table I together with the wave numbers, wave lengths and molar extinction coefficients of the band maxima.

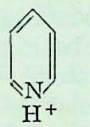
TABLE I

BAND MAXIMA AND OSCILLATOR STRENGTHS OF THE π-π^* TRANSITIONS IN THE SPECTRUM OF THE PYRIDINE MONOCARBOXYLIC ACIDS

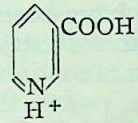
Compound	Max. wave no., cm.$^{-1}$	λ_{max}, mμ	ϵ_{max}	f	Solvent
Pyridine	38,900	257	2630	0.049	Ethanol
Picolinic acid	37,900	264	3900	.071	Ethanol
(2-position)	37,000	265	6600	.120	Water
Nicotinic acid	38,000	263	2840	.052	Ethanol
(3-position)	38,200	262	4230	.073	Water
Isonicotinic acid	36,800	272	2520	.055	Ethanol
(4-position)	38,200	262	3650	.093	Water

Discussion

Molecular Species in Solution.—Earlier authors[5] have called attention to the fact that the spectrum of nicotinic acid is very similar to that of pyridine and not to benzoic acid.[18] Especially impressive is the similarity of the spectra of the cations

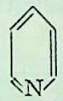


I, λ_{max} = 256 mμ
ϵ_{max} = 5320[19]
= 5290[20]

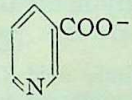


II, λ_{max} = 262 mμ
ϵ_{max} = 5500[5]
= 5000[6]

The spectra of the neutral and anion species existing in a highly basic aqueous solution (0.1 *N* NaOH) are likewise very similar

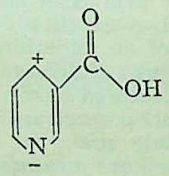


III, λ_{max} = 256 mμ
ϵ_{max} = 2660[19]
= 2750[20]



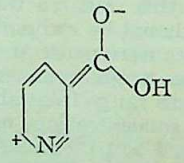
IV, λ_{max} = 262 mμ
ϵ_{max} = 2960[5]
= 3100[6]

This comparison between the spectra of pyridine and nicotinic acid indicates that the nature of the π-π^* transition in the acid is determined largely by the ring nitrogen and not by the carboxyl group. Using the symbolism of valence-bond theory, one concludes that ionic resonance structures with migration of charge to the nitrogen atom, *viz.*



V

characterize the π-π^* transition to a much larger extent than do resonance structures with migration of charge to the carboxyl group, *viz.*



VI

That structure VI plays some role in the absorption is indicated by the red shift of about 6 mμ in the maximum of the acid spectrum relative to the pyridine spectrum.[21] The corresponding red shift is particularly pronounced for isonicotinic acid and will be discussed further in the last section of this paper.

Since there is the possibility that the observed enhancement of intensity for nicotinic acid cation over that of the anion is primarily due to the addi-

(14) H. P. Stephenson, *J. Chem. Phys.*, **22**, 1077 (1954).
(15) J. H. Rush and H. Sponer, *ibid.*, **20**, 1847 (1952).
(16) M. Kasha, *Disc. Faraday Soc.*, **9**, 14 (1950).
(17) P. Krumholz, THIS JOURNAL, **73**, 3487 (1951).
(18) H. E. Ungnade and R. W. Lamb, *ibid.*, **74**, 3789 (1952).
(19) E. B. Hughes, H. H. G. Jellinek and B. A. Ambrose, *J. Phys. Colloid Chem.*, **53**, 410 (1949).
(20) H. C. Brown and X. R. Mihn, THIS JOURNAL, **77**, 1723 (1955).
(21) (a) W. D. Kumler and L. A. Strait, *ibid.*, **65**, 2349 (1943); (b) W. F. Hammer and F. A. Matsen, *ibid.*, **70**, 2482 (1948).

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TABLE II

COMPARISON OF THE ABSORPTION SPECTRA OF THE PYRIDINE MONOCARBOXYLIC ACID ANIONS AND CATIONS WITH THE SPECTRA OF OTHER DERIVATIVES NOT POSSESSING A CARBOXYL SUBSTITUENT

Compd. with carboxyl group	λ_{max}, mμ	ϵ_{max}	Compd. without carboxyl group	λ_{max}, mμ	ϵ_{max}
Picolinic acid anion	265	4000[6]	2-Picoline in 0.1 *N* NaOH	262	3560[20]
Picolinic acid cation	265	7600[6]	Same in ethanol	262	3520[14]
			Same in 0.1 *N* HCl	263	6630[20]
			2-Fluoropyridine in 0.013 *N* NaOH	257	3300[22]
			Same in ethanol	258	3200[14]
					3250[23]
			Same in 1.2 *N* HCl, complete protonation not reached	260	5800[22]
Nicotinic acid anion	262	3100[6]	3-Picoline in 0.1 *N* NaOH	263	3110[20]
		2960[5]			
Nicotinic acid cation	262	5000[6]	Same in ethanol	263	3080[14]
		5500[5]			
			Same in 0.1 *N* HCl	263	5470[20]
			3-Fluoropyridine in 0.013 *N* NaOH	262	3300[22]
			Same in ethanol	262	2990[14]
					3050[23]
			Same in 1.2 *N* HCl	262	5800[22]
Isonicotinic acid anion	266	2400[6]	4-Picoline in 0.1 *N* NaOH	255	2090[20]
Isonicotinic acid cation	272	4600[6]	Same in ethanol	256	2095[14]
			Same in 0.1 *N* HCl	253	4510[20]

tion of the proton to the carboxyl group rather than to the ring nitrogen, comparison data for all three of the pyridine carboxylic acids and a number of other simple pyridine derivatives not possessing a carboxyl substituent are given in Table II. The data for the fluoropyridines and picolines demonstrate that the nitrogen protonation effect is not only approximately independent of the nature of the pyridine ring substituent, but is also approximately independent of the initial degree of binding of the nitrogen non-bonding electrons. Spectral evidence[14] as well as dissociation constant measurements[22] have proved that for the *ortho*-substituted halopyridines the nitrogen non-bonding electrons are very tightly bound by an inductive effect. Whether these electrons are tightly bound or loosely bound as in the picolines,[14,20] the addition of a proton to the ring nitrogen of a pyridine derivative generally has the effect of approximately doubling the absorption intensity of the π-π^* transition in the near ultraviolet.

What the independent effect of adding or removing a proton from the carboxyl group alone would be may be estimated from the recent work of Ungnade and Lamb on benzoic acid.[18] They found that the ionization of benzoic acid in 95% ethanol solution is negligible and that ϵ_{max} is 900 at λ_{max} of 272 mμ for the π-π^* transition corresponding to the transition under discussion for the pyridine compounds. In 0.01 *N* HCl aqueous solution ϵ_{max} is 1020 at λ_{max} of 274 mμ, and in 0.01 *N* NaOH solution, where the molecule is entirely in the anion form, ϵ_{max} is 490 at λ_{max} of 268 mμ. In water solutions for which the *p*H is determined by the dissociation of the acid itself, the maximum extinction coefficient varies from 940 at a concentration of 1.748×10^{-3} mole/l. to 780 at a concentration of 0.0715×10^{-3} mole/l., for which there is considerable ionization. Thus for benzoic acid, in which the carboxyl group causes about a 5-fold intensification of the originally forbidden benzene spectrum, the relative effect of removing the proton from the carboxyl group is rather large. The relative effect will not be expected to be nearly as large for the pyridine monocarboxylic acids, however, because the *f*-value of pyridine itself is already some 50 times as large as that for benzene,[14] and the *f*-values in Table I show that the addition of the carboxyl group to pyridine serves only to increase slightly the absolute degree of absorption intensity, not its order of magnitude. One might estimate that the effect of removing a proton from the carboxyl group of the pyridine carboxylic acids would be to decrease ϵ_{max} by several hundred, possibly 200 to 500.

With a comparison of Tables I and II it becomes clear that the spectra of the pyridine carboxylic acids in ethanol solution are very similar to the spectra of the aqueous-solution anions (species IV, for example) of these substances. In spite of the fact that nearly all the carboxyl groups would, therefore, have to be dissociated, the ethanol solutions appear to be highly basic, not acidic. At first this situation seemed puzzling. It is well known that the acidity of the carboxyl group is reduced by as much as 5 pK_a units whenever many acids are dissolved in ethanol rather than water,[24] and therefore the spectral evidence of Ungnade and Lamb that benzoic acid is negligibly dissociated in ethanol, as well as other alcohols, is not surprising. In consequence of these facts for benzoic acid, it seems reasonable that the pyridine carboxylic acids would likewise be negligibly dissociated in ethanol solutions and that the corresponding spectra in Figs. 1, 2 and 3 actually represent the spectra of the completely neutral forms of these substances, not the anion forms. The reason the spectra are so similar to the anion spectra in all

(22) H. C. Brown and D. H. McDaniel, THIS JOURNAL, **77**, 3752 (1955).

(23) W. K. Miller, S. B. Knight and A. Roe, *ibid.*, **78**, 1629 (1956).

(24) A. J. Deyrup, *ibid.*, **56**, 60 (1934).

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cases is simply that the π-electron systems of picolinic, nicotinic and isonicotinic acids are very little affected by the presence of a proton on the carboxyl group. In fact, we see that the ϵ_{max} values for all the neutral molecules in ethanol solution are actually somewhat smaller than the ϵ_{max} values for the corresponding anions in basic water solution, rather than larger as we would have predicted. A similar situation prevails for all the other pyridine compounds listed in Table II except 4-picoline.

In water solution where some ionization of the pyridine acids is now expected, one sees from Figs. 1, 2 and 3 that the intensity of absorption of these acids increases with carboxyl dissociation rather than decreases as does the intensity of the benzoid acid spectrum.[18] Consequently it becomes clear why it is necessary to have established the primary importance of proton attachment at the ring nitrogen as the determining factor in the intensity changes. Every proton that detaches itself from a carboxyl group must decrease the intensity of absorption by a much smaller extent than it subsequently increases the intensity when it becomes attached to a ring nitrogen. Furthermore, there must be a large percentage of such attachments in water solution, a situation which agrees with the opinion of Jaffé[8] that these acids must exist primarily as zwitterions in water solution. According to Jaffé the neutral uncharged forms of the molecules contribute only about 5% to the equilibrium mixtures at the isoelectric points, which in each case are mixtures of rather high acidity: picolinic acid, pH 3.21; nicotinic acid, pH 3.42; isonicotinic acid, pH 3.31.[6] The pH of the water solutions used in this research will be expected to be somewhat higher than those values.

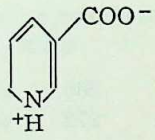
By making measurements near the isoelectric points, Evans, Herington and Kynaston[6] were able to derive spectral curves for what they called the undissociated molecular species of the acids. The curves are closely similar to the water spectra given in Figs. 1, 2 and 3, with the following values for ϵ_{max}: 7400 for picolinic acid; 4800 for nicotinic acid; 4500 for isonicotinic acid. It is significant that these ϵ_{max} values are just 200 to 300 less than the ϵ_{max} values of the corresponding cations listed in Table II, a difference corresponding to the change expected with the removal of a proton from the carboxyl group. Thus the evidence is rather convincing that the dissociated molecular species is formed by removing a carboxyl proton, not the ring nitrogen proton, from the cation species II. Evans, Herington and Kynaston realized that the undissociated molecular species might be an admixture of the neutral form and the zwitterion form, but they stated that it is unnecessary to discriminate between them. Such a point of view is permissible for the measurement of the apparent dissociation constants of these dibasic compounds, but the work of Jaffé shows that some discrimination is necessary for the interpretation of these constants in order to calculate the thermodynamic dissociation constants K_a and K_b.

In each of the papers[5-7] on the dissociation constants of pyridine and its derivatives the following

stants which were determined experimentally were defined by the equations

$$K_1 = \frac{a \times [HA]}{[H_2A]} \text{ and } K_2 = \frac{a \times [A]}{[HA]}$$

where "a" is the hydrogen ion concentration, [HA] the concentration of the undissociated molecular species, [H_2A] the concentration of the cation species, and [A] the concentration of the anion species. If the species HA is predominantly represented by the neutral, uncharged molecule, then K_1 would be referred to as the apparent dissociation constant of the conjugate acid of the base, and K_2 would be referred to as the apparent dissociation constant of the acid. These constants were thought of in these terms by the previous authors.[5-7] On the other hand, if the species HA is predominantly represented by the zwitterion form of the molecule, for example



VII

then K_1 must be referred to as the apparent dissociation constant of the acid and K_2 as the apparent dissociation constant of the conjugate acid of the base.

From their assumptions about K_1 and K_2 the previous authors have further calculated the thermodynamic constants K_a and K_b. The most accurate results seem to be those of Evans, Herington and Kynaston, and these are summarized in Table III. According to these values of K_a and K_b, the carboxyl groups of these acids donate a proton with slightly less facility than does benzoic acid, $K_a = 6.86 \times 10^{-5}$,[18] and the basic property of the ring nitrogen is greatly reduced with respect to pyridine itself, $K_b = 1.44 \times 10^{-9}$.[25] That the basic property of the ring nitrogen appears so weak for nicotinic acid, as well as in the other two acids is the reason why Hughes, Jellinek and Ambrose[5] were the first to conclude that nicotinic acid cannot exist as a zwitterion in water solution.

TABLE III

DISSOCIATION CONSTANTS OF THE PYRIDINE MONOCARBOXYLIC ACIDS ACCORDING TO EVANS, HERINGTON AND KYNASTON[6]

Compound	pK_1	pK_2	10^5K_a	$10^{12}K_b$
Picolinic acid	1.08	5.32	0.403	0.102
Nicotinic acid	2.09	4.72	1.50	1.04
Isonicotinic acid	1.82	4.78	1.46	0.59

Jaffé has pointed out that one must know the extent of zwitterion formation before the correct values of K_a and K_b may be determined precisely from the measured K_1 and K_2 values, even when the correct interpretation of the constants is made. He finds that for nicotinic acid and isonicotinic acid the corrections are quite small because of the predominant formation of the zwitterions. With the altered interpretation of K_1 and K_2, new values of K_a and K_b may now be determined from the

(25) E. F. G. Herington, *Disc. Faraday Soc.*, 9, 26 (1950). See also ref. 20.

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same equations used by Evans, Herington and Kynaston, namely

$$pK_a = pK_2 - \log_{10} \gamma^-$$
$$pK_b = 13.997 - pK_1 - \log_{10} \gamma^+,$$

where the values used for the activity coefficient terms were about −0.10. When the apparent dissociation constants K_1 and K_2 are interchanged in the equations, the results listed in Table IV are obtained. For example, in the case of picolinic acid

$$pK_a = 1.08 + 0.10 = 1.18$$

and consequently

$$K_a = 6.61 \times 10^{-2}$$

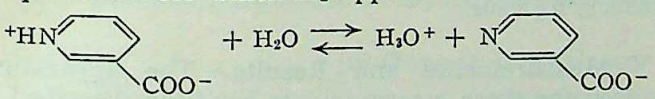
TABLE IV

DISSOCIATION CONSTANTS OF THE PYRIDINE MONOCARBOXYLIC ACIDS WITH THE ASSUMPTION THAT ZWITTERION FORMATION IS PREDOMINANT IN WATER SOLUTION

Compound	pK_a	10^2K_a	pK_b	10^9K_b
Picolinic acid	1.18	6.61	8.78	1.66
Nicotinic acid	2.19	0.646	9.38	0.417
Isonicotinic acid	1.92	1.20	9.32	0.479

These results show that the basicity of the ring nitrogen is changed very little by the introduction of the carboxyl group, but that the acidity of the carboxyl group itself is greatly enhanced by the presence of the nitrogen. These conclusions are in agreement with the spectral evidence that the ring nitrogen acts almost independently of the carboxyl substituent, preventing large migration of negative charge on to the carboxyl group as shown in resonance structure VI.

Because of the almost complete dissociation of the carboxyl groups, the pH of the water solutions used in this research must have been determined chiefly by the value of the dissociation constant K_2. That is, we are chiefly concerned with the equilibrium for which K_2 applies. Under this as-



VII IV

sumption it is possible to use the data from the paper of Evans, Herington and Kynaston to calculate theoretical values for the molar extinction coefficients of the pyridine acids in water solution. The results of these calculations are summarized in Table V. The maximum molar extinction values for the zwitterions were taken to be identical with the coefficients for the "undissociated molecular species."[6] There is good agreement between the calculated and observed values of ϵ_{max}, but for each acid the observed molar extinction coefficient is lower than the calculated value, a fact which indicates that the neutral undissociated molecular species is making a small contribution to the absorption. By assigning ϵ_{max} values to these neutral species corresponding to those obtained in ethanol solution (the values in water solution must still be considered uncertain), it appears that the neutral form makes up about 10, 5 and 15% of the *total* solute mixture in the case of picolinic, nicotinic and isonicotinic acids, respectively.

Comparison of the Spectra.—It is well known that, because of their strong electron attracting character as illustrated by the resonance structures V and VI, both a carboxyl group and a ring nitrogen are *meta*-directing substituents in benzene and pyridine. Sklar[26] has studied the effects which

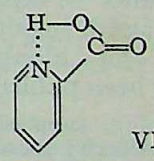
TABLE V

THEORETICAL CONCENTRATIONS OF VARIOUS SPECIES AND ϵ_{max} VALUES FOR WATER SOLUTIONS OF THE PYRIDINE ACIDS AT A TOTAL CONCENTRATION OF 2×10^{-4} MOLE/L.

Compound	Zwitterion concn., $\times 10^4$, mole/l.	Anion concn., $\times 10^4$, mole/l.	pH	Calcd. ϵ_{max}	Measd. ϵ_{max}
Picolinic acid	1.71	0.29	4.54	6910	6600
Nicotinic acid	1.48	.52	4.28	4360	4230
Isonicotinic acid	1.50	.50	4.30	3980	3650

electron-attracting or electron-donating substituents have on the near ultraviolet π-π^* electronic transition in benzene, and was able to predict the relative intensities of the spectra of a number of isomeric disubstituted benzenes for which first-order calculations applied. While neither a ring nitrogen nor the carboxyl group fits the theoretical restrictions of the Sklar theory, Platt[9] has noted that these groups do act in a manner expected of *meta*-directing substituents in all observed cases except nicotinic acid. According to the simple Sklar treatment, one expects the oscillator strengths of the *o*- and *m*-pyridine carboxylic acids to be equal to each other and to be slightly smaller than that of pyridine itself, while the oscillator strength of *p*-pyridine monocarboxylic acid is expected to be larger than any of the other two or of pyridine itself. The equality of the oscillator strengths of the *ortho*- and *meta*-substituted compounds is predicted by the theory also for the case where the orienting powers of the substituents are different.

Now it is significant that the oscillator strength of the electronic transition in picolinic acid should be so much larger than that of nicotinic and isonicotinic acids, regardless of whether the molecules are in their neutral forms or in the zwitterion forms characteristic of water solutions (*cf.* Table I). It is tempting to say that picolinic acid occurs predominantly in the chelated[27] form



VIII

in alcohol solution, but then it is not understandable why the oscillator strength of picolinic acid cation should continue to be so much more intense than that of nicotinic or isonicotinic acid cations. The addition of a proton to the ring nitrogen of the latter substances ought to have the effect of evening up the discrepancies between the intensities.

That the oscillator strength of isonicotinic acid should be slightly larger than that of nicotinic acid in ethanol agrees qualitatively with the results expected from the Sklar theory for two *meta*-directing substituents. This agreement must be considered very inconclusive, however, in view of the difficul-

(26) A. L. Sklar, *J. Chem. Phys.*, **10**, 135 (1942), and *Rev., Modern Phys.*, **14**, 232 (1942).

(27) N. H. Cantwell and E. V. Brown, THIS JOURNAL, **74**, 5967 (1952).

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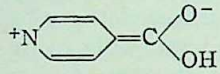
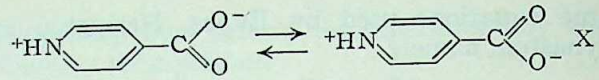
ties with the picolinic acid intensity. The observed violet shift of about 1700 cm.$^{-1}$ (*cf.* Fig. 3) which occurs for isonicotinic acid when the solution is changed from ethanol to water bears a close resemblance to the type of blue shift expected for an n-π^* transition,[14,28] but it is highly probable that the correct explanation for this blue shift is one that involves a discussion of π-electrons only. Kumler and Strait[21a] have pointed out in a discussion of the spectra of benzoic acid and *p*-aminobenzoic acid that resonance (migration of negative charge) between the carboxyl group and the ring is restricted whenever internal carboxyl resonance itself is enhanced by removal of the proton. Whereas, therefore, one expects some contribution from ionic resonance structures such as



IX (similar to VI)

in ethanol solutions, such structures will be restricted in water solution because of the added importance of the resonance



That is, one expects a greater migration of charge out of the ring in the neutral isonicotinic acid species than for the corresponding zwitterion species. The greater migration in the former case is a well-known explanation for the resulting shift of the π-absorption band to longer wave lengths.[21b] Since the shifts for picolinic and nicotinic acids are not so large, it can be assumed that the ionic structure IX is more important in determining the absorption by isonicotinic acid than is the corresponding structure VI for nicotinic acid (and picolinic acid). In the *ortho* and *meta*-positions the nitrogen atom undoubtedly restricts the degree of electron migration to the carboxyl group. A theoretical treatment of the perturbation effect of the carboxyl group when substituted on simple aromatic rings like benzene and pyridine is evidently very desirable.

DURHAM, NORTH CAROLINA

(28) G. J. Brealey and M. Kasha, THIS JOURNAL, **77**, 4462 (1955).

[CONTRIBUTION FROM THE MINERALS THERMODYNAMICS EXPERIMENT STATION, REGION II, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

Low Temperature Heat Capacities and Entropies at 298.15° K. of Cryolite, Anhydrous Aluminum Fluoride and Sodium Fluoride

BY E. G. KING

RECEIVED NOVEMBER 28, 1956

Heat capacities of cryolite (Na_3AlF_6), sodium fluoride and aluminum fluoride were measured in the temperature range 51 to 298°K. All showed normal behavior. The 298.15°K. entropies are: cryolite, 57.0 ± 0.4 cal./deg. mole; sodium fluoride, 12.26 ± 0.07 cal./deg. mole; and aluminum fluoride, 15.89 ± 0.08 cal./deg. mole.

This paper reports the results of heat capacity measurements throughout the temperature range 51–298°K., with derived entropies, for cryolite and its constituent fluorides. Thermodynamic values for these substances are of importance in the usual electrolytic process for aluminum production. No similar data have been published previously.

Materials.—The cryolite, supplied by the Aluminum Company of America Research Laboratories, New Kensington, Pa., consisted of hand-picked crystals of natural Greenland cryolite. The analysis by ALCOA showed 32.76% sodium (theoretical, 32.85%) and 13.01% aluminum (theoretical, 12.85%). As impurities there were 0.036% potassium and 0.007% lithium. For the purpose of the present work, the substance was considered as $Na_{2.959}AlF_{5.959}$, and the heat-capacity results were corrected to stoichiometric composition. This correlation ranged from 0.1 to 0.2%.

The sodium fluoride was Mallinckrodt analytical reagent powder meeting A.C.S. specifications. No treatment of the sample was made other than heating to 700° immediately before use.

The aluminum fluoride was a vacuum-sublimed product, prepared especially for this work by the Reduction Research Laboratory, Kaiser Aluminum and Chemical Corp., Permanente, Calif. The sample analyzed 32.12% aluminum (theoretical, 32.13%). Impurities, measured spectrographically by the Kaiser Laboratories, were: Si, 0.008%; Fe, 0.008%; Mg, 0.005%; Na, 0.05%; Ti, 0.003%; and Ca, 0.06%. All other impurities were present in amounts less than 0.003%.

Measurements and Results.—The apparatus used for these measurements has been described.[1] Sample masses employed were: cryolite, 214.48 g.; sodium fluoride, 130.08 g.; and aluminum fluoride, 241.49 g.

The heat capacities are expressed in defined calories (1 defined calorie = 4.1840 absolute joules). The measured values are given in Table I. Molecular weights accord with the 1953 International Atomic Weights.[2]

All three compounds showed normal behavior over the entire measured temperature range. It is of interest to compare the heat capacity of cryolite with that of the stoichiometric summation of sodium and aluminum fluorides. Cryolite has 60% greater heat capacity at 50°K. However, the difference decreases rapidly with temperature, becoming 7% at 100°K., less than 0.2% at 200°K., and less than 0.2% for the entire range from 200 to 298.15°K.

Entropies at 298.15°K.—The entropy increments for the measured range, 51–298°K., were obtained by Simpson-rule integrations of C_p *vs.* log T plots.

(1) K. K. Kelley, B. F. Naylor and C. H. Shomate, Bur. Mines Tech. Paper, 686, 1946.

(2) E. Wichers, THIS JOURNAL, **76**, 2033 (1954).

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TABLE I

HEAT CAPACITIES (CAL./DEG.-MOLE)

T, °K.	C_p	T, °K.	C_p	T, °K.	C_p
NaF (mol. wt., 41.991)					
54.01	1.659	114.61	6.434	216.14	10.08
58.57	2.025	124.46	7.007	225.80	10.27
62.80	2.380	135.98	7.606	235.96	10.44
67.29	2.770	145.74	8.060	245.66	10.57
71.81	3.165	155.77	8.460	256.40	10.73
76.33	3.555	165.84	8.815	266.20	10.91
80.98	3.955	175.84	9.124	276.20	10.97
85.79	4.355	186.05	9.413	287.15	11.09
95.40	5.110	195.79	9.650	295.86	11.17
105.04	5.808	205.89	9.882	298.15	(11.19)
AlF_3 (mol. wt., 83.98)					
53.65	1.774	114.53	7.268	215.91	14.48
56.69	2.013	124.39	8.131	226.20	15.02
57.89	2.110	135.56	9.077	235.93	15.50
61.01	2.380	145.35	9.879	245.55	15.92
65.62	2.782	155.75	10.68	256.18	16.39
70.32	3.206	165.58	11.38	266.31	16.80
74.88	3.623	175.81	12.08	276.22	17.19
82.19	4.304	185.93	12.75	286.59	17.54
86.30	4.685	195.84	13.35	296.10	17.88
94.60	5.463	206.14	13.93	298.15	(17.95)
104.82	6.404				
Na_3AlF_6 (mol. wt., 209.953)					
53.66	10.10	114.69	27.62	216.05	44.67
57.94	11.39	124.69	29.95	226.06	45.70
62.32	12.76	136.00	32.37	236.20	46.70
66.53	14.13	145.51	34.35	245.81	47.63
70.94	15.54	155.82	36.27	256.33	48.53
75.55	17.00	165.66	37.91	266.23	49.30
80.79	18.55	175.91	39.50	276.24	50.02
84.45	19.61	185.85	40.90	286.47	50.76
94.77	22.46	195.95	42.25	296.00	51.49
105.20	25.24	206.18	43.58	298.15	(51.60)

The curves were extrapolated below 51°K. by means of the following Debye and Einstein function sums, which fit the measured data within the limits of temperature and percentage of the heat capacity shown below

Na_3AlF_6: $D(144/T) + 4E(236/T) + 5E(568/T)$ (51–298°K., 1.7%)

NaF: $D(340/T) + E(391/T)$ (51–115°K., 0.2%)

AlF_3: $D(326/T) + E(385/T) + 2E(767/T)$ (51–298°K., 0.8%)

The entropy values are listed in Table II. The extrapolated portions of the total entropies at 298.15°K. are cryolite, 7.2%; sodium fluoride, 4.1%; and aluminum fluoride, 3.5%.

TABLE II

ENTROPIES AT 298.15°K. (CAL./DEG.-MOLE)

	Na_3AlF_6	NaF	AlF_3
0–51°K. (extrap.)	4.12	0.50	0.56
51–298.15°K.	52.86	11.76	15.33
$S^\circ_{298.15}$	57.0 ± 0.4	12.26 ± 0.07	15.89 ± 0.08

The entropy of formation of cryolite from sodium and aluminum fluorides is 4.3 ± 0.5 cal./deg. mole at 298.15° K.

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[CONTRIBUTION FROM THE WRIGHT AIR DEVELOPMENT CENTER]

Infrared Spectra of Cyclopentamethylenedialkylsilanes[1] in the 2–35–Region

BY GORDON D. OSHESKY AND FREEMAN F. BENTLEY

RECEIVED NOVEMBER 28, 1956

The infrared absorption spectra of 21 cyclopentamethylenedialkylsilanes have been obtained from 2–35 μ and empirical assignments made for specific vibrations. The series begins with cyclopentamethylene-silane and ends with cyclpentamethylenedioctadecylsilane. Absorption bands at 10.93 to 11.00 and 20.20 to 20.85 μ are tentatively assigned to vibrations arising from the heterocyclic ring. All the observed absorption bands are given in a table showing their position and relative intensities.

This paper presents infrared absorption spectra of a series of cyclopentamethylenedialkylsilanes in the liquid state from 2 to 35 μ. This series of compounds was studied by this Laboratory for the purpose of correlating various physical properties with molecular structure.[2] This paper will deal solely with the infrared absorption bands of this and mainly with the tentative band assignment of the organosilicon ring vibration.

Experimental

Apparatus and Technique.—The infrared spectra in the 2 to 15 μ region were obtained with a Baird Associates, Model B, automatic recording spectrophotometer equipped with a sodium chloride prism. This instrument was calibrated to within ±0.05 μ by using ammonia and polystyrene. The liquid samples were recorded in a 0.028 mm. cell with sodium chloride windows. The thin capillary thicknesses were obtained by placing a drop of liquid between two rock salt plates, which were then fastened tightly together.

The spectra in the 15–35 μ region were obtained on a Perkin–Elmer Model 21, double beam recording spectrophotom ter equipped with cesium bromide optics. This prism was calibrated by using atmospheric carbon dioxide and water vapor bands. The accuracy of the wave lengths as recorded here is probably better than ±0.05 μ, which in this region of the spectrum is equivalent to about ±1.5 cm.$^{-1}$. The liquid samples were measured in 0.510 and 0.053 mm. cells with cesium bromide windows. All measurements in the 2 to 35 μ region were made at 24.0 ± 0.5° and at a relative humidity of 35 ± 5%.

Due to insufficient sample the spectra of the diethyl and 2-ethylbutyl derivatives could not be obtained in the 15 to 35 μ region.

(1) Opinions expressed are those of the authors and do not necessarily express the official opinions of the U. S. Air Force or the Wright Air Development Center.

(2) This series of compounds was prepared by Dr. Christ Tamborski, Dr. Harold Rosenberg and Mr. James Groves, and the details of their physical properties and preparation will be published elsewhere.

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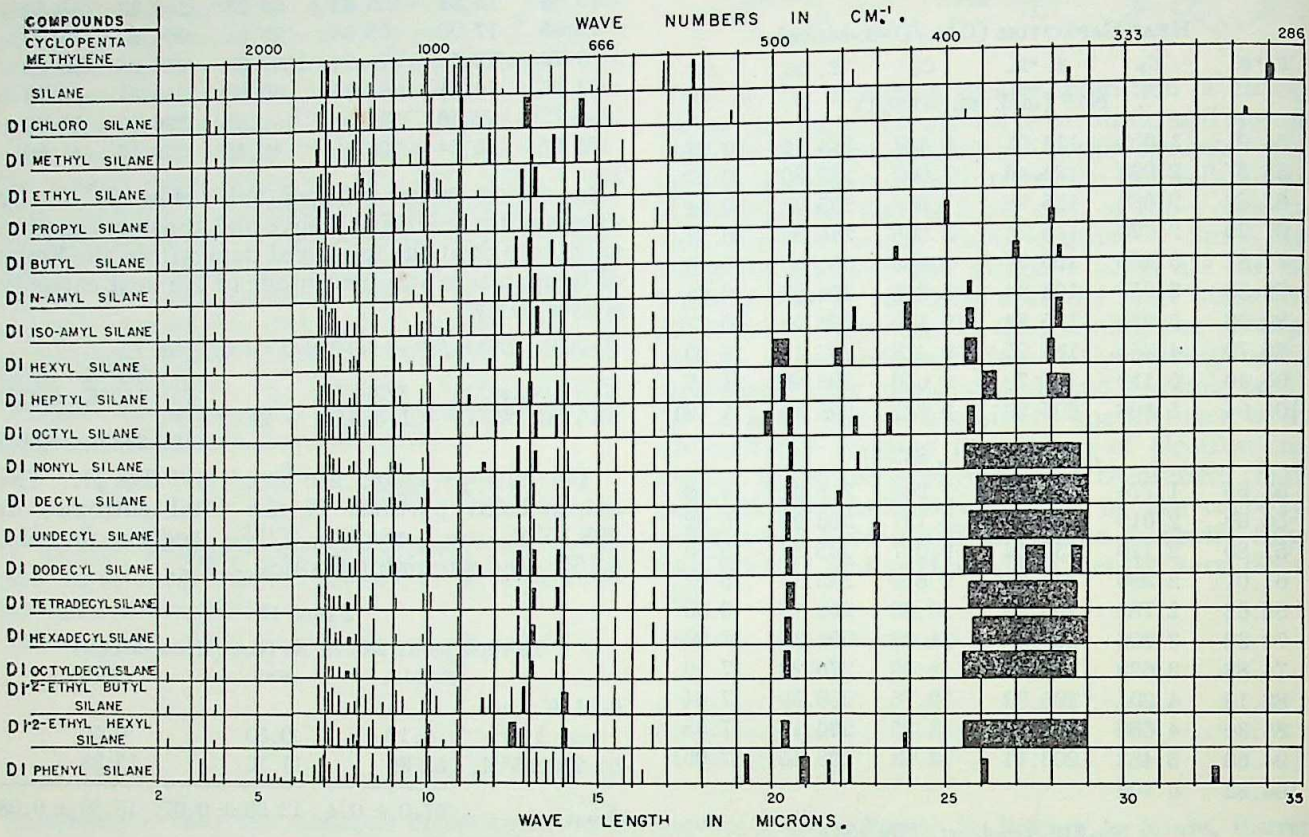

Fig. 1.—Tabulated absorption frequencies of 21 cyclopentamethylenedialkylsilane derivatives.

Materials.—The cyclopentamethylenedialkylsilanes used in this study were fractionated through a 30-cm. short-path Vigreux column. Carbon, hydrogen and silicon analyses were performed on each compound of this series and they were found to be 99% pure. The compounds were analyzed by the Schwarzkopf Microanalytical Laboratory.

Results and Discussion

The difficulty in establishing the presence of a ring in organic molecules by chemical means has promoted interest in identifying the presence of cyclic structures by infrared techniques. Saturated cyclic systems have characteristic frequencies arising from the bond stretching and valence angle modes which occur in the fundamental region. There is a great number of articles in the literature dealing with attempts to characterize alicyclic systems, particularly cyclopropane and cyclobutane, from the infrared spectra, but the situation is still obscure.[3-5] With the possible exception of cyclopropane[6] no certain means of identifying ring systems by the out-of-plane and torsional bending modes beyond 20 μ has so far been realized. A few band assignments for some of the saturated cyclic hydrocarbons are given in Table I.

Tentative frequency assignments have been made for the cyclopentamethylenedialkylsilanes investigated in these studies. Figure 1 lists the 21 compounds recorded and pictorially indicates the band positions and their relative intensities. The infrared spectra of eight of the derivatives of this series are shown in Figs. 2 to 5, inclusively.

Carbon–Hydrogen Deformation Frequencies.—Absorption arising from the CH deformation frequencies of these molecules present some interesting correlations. Absorption bands at 6.85 μ in the spectra of cyclopentamethylenesilane and cyclopentamethylenedichlorosilane are apparently due to the CH_2 bending modes of the heterocyclic ring. The position of this band remains constant throughout the series. It is masked to a degree by the CH_2 deformation and CH_3 asymmetrical deformation absorption of the large alkyl substituents on the silicon atom. Absorbance due to the sym-

TABLE I

Structure	Assigned ring vibrations	Ref.
Cyclopropyl ring	9.8–10.00	7–11
Cyclobutyl ring	10.9–11	12–14
Cyclopentyl ring	10.8–11.3	15, 16
Cyclohexyl ring	9.95–10.5, 9.5–10	15, 16
Cyclopentamethylene silicon ring	10.93–11.00[a]	

[a] Based on the infrared spectra of the cyclic silanes studied in this series.

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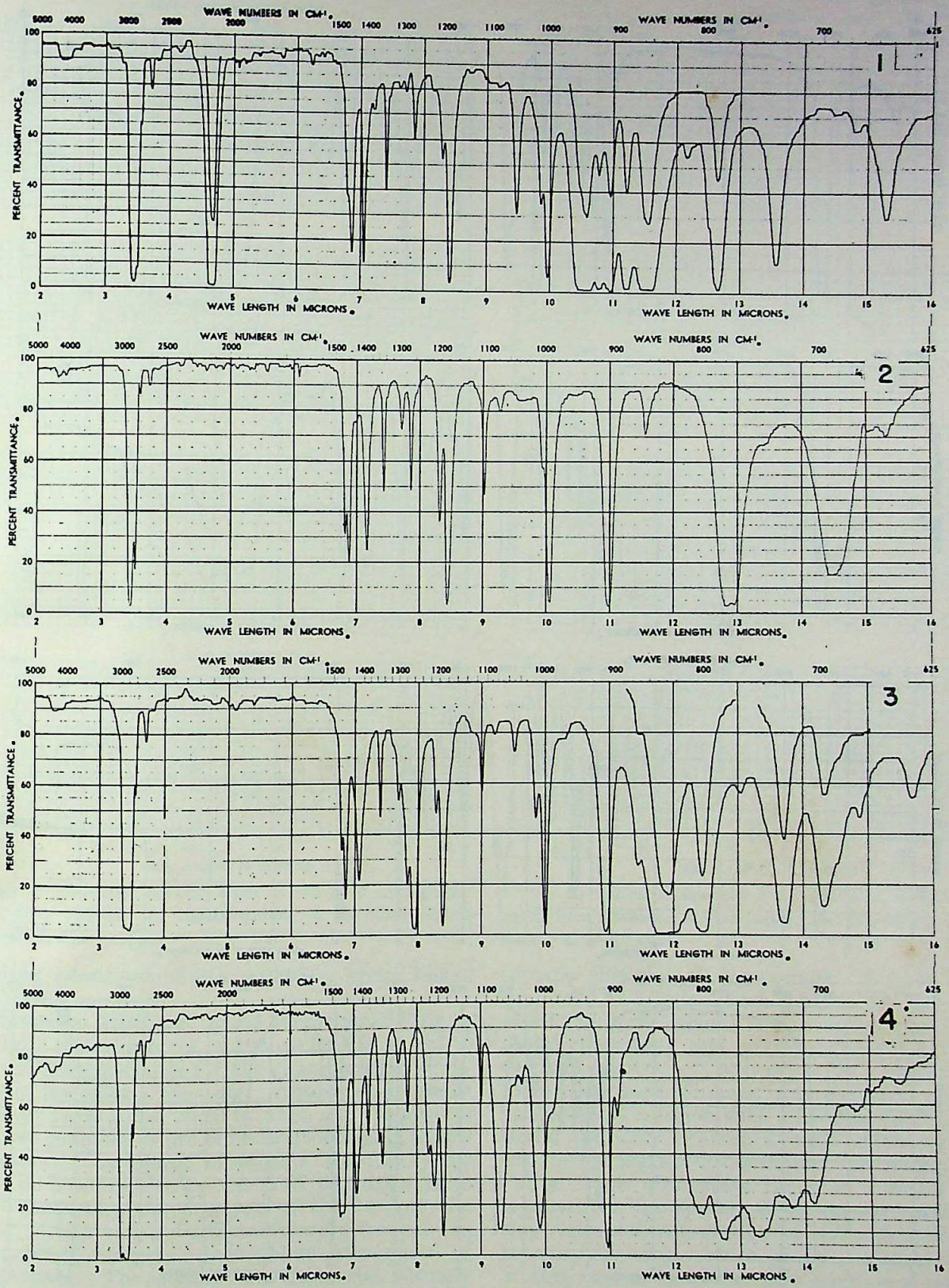

Fig. 2.—Infrared spectra from 2–16 μ of cyclopentamethylene silanes: 1, unsubstituted; 2, dichloro; 3, dimethyl; 4, di-*n*-propyl.

metrical bending vibration of the CH_3–C group at 7.23 μ is clearly present in the spectra of all the molecules of this series containing this group. The intensity of this absorption band gives some indication as to the number of methyl groups present in the molecule. In the spectrum of cyclopentamethylenediisoamylsilane the absorption band is split due to the isopropyl group.[17,18] As would be expected the absorption band at 7.23 μ is not present in the spectrum of cyclopentamethylenedimethylsilane where the methyl group is linked to a silicon atom.

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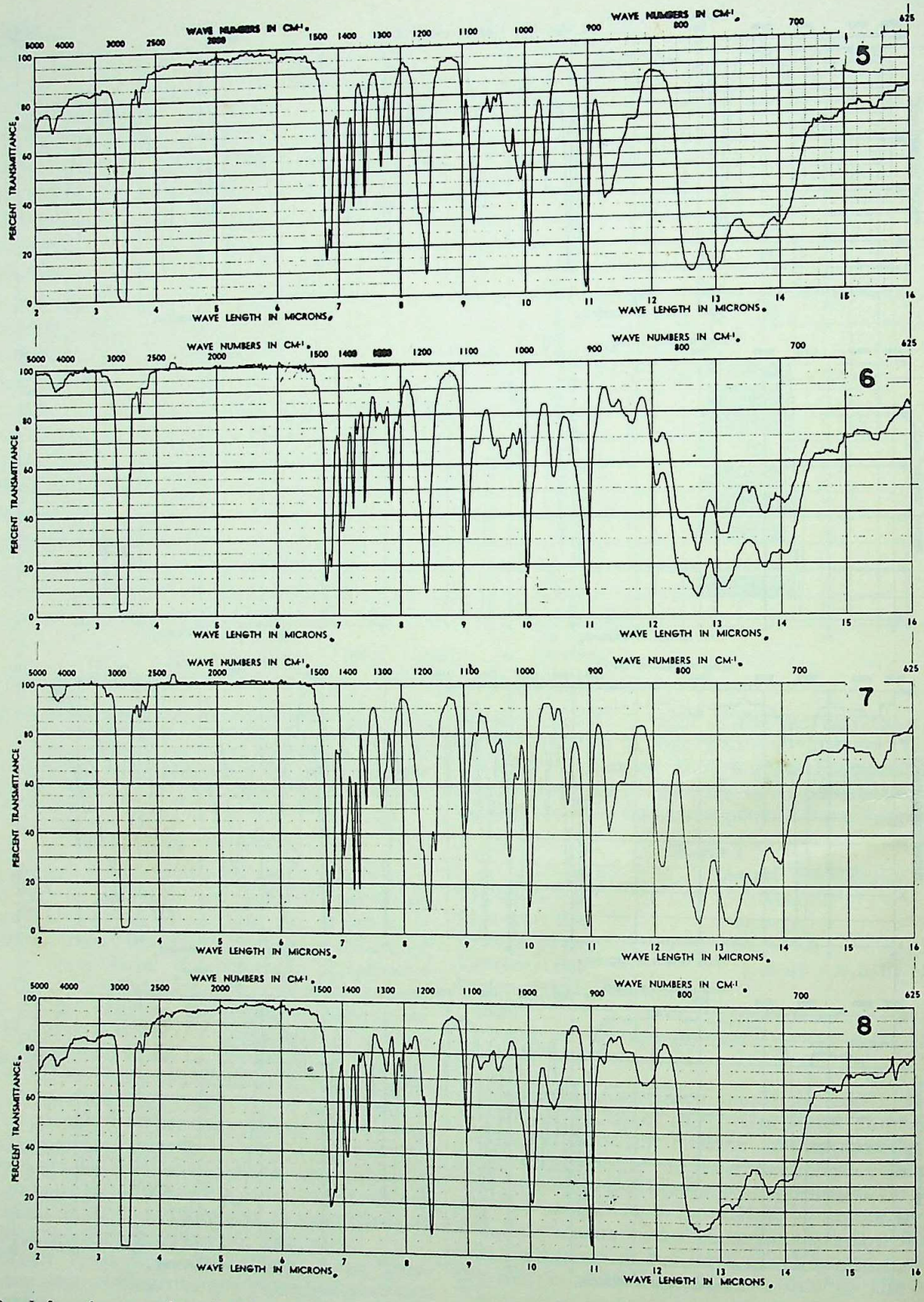

Fig. 3.—Infrared spectra from 2–16 μ of cyclopentamethylene silanes: 5, di-*n*-butyl; 6, di-*n*-amyl; 7, diisoamyl; 8, di-*n*-hexyl.

The strong absorption in the 7.03 to 7.10 μ region is attributed to the deformation vibrations of the CH_2 group linked to the silicon atom. The CH bending vibration of the $Si–CH_3$ group was observed by Wright and Hunter[19] and all the tetraalkylsilanes (more than 30) studied in this Laboratory absorb in this region. Young and co-workers[20] also observed an absorption band at 7.08 μ in the spectra of cyclic disubstituted siloxanes containing $Si–CH_3$ and $Si–CH_2CH_3$ linkages. They tentatively assigned this band to the carbon–hydrogen

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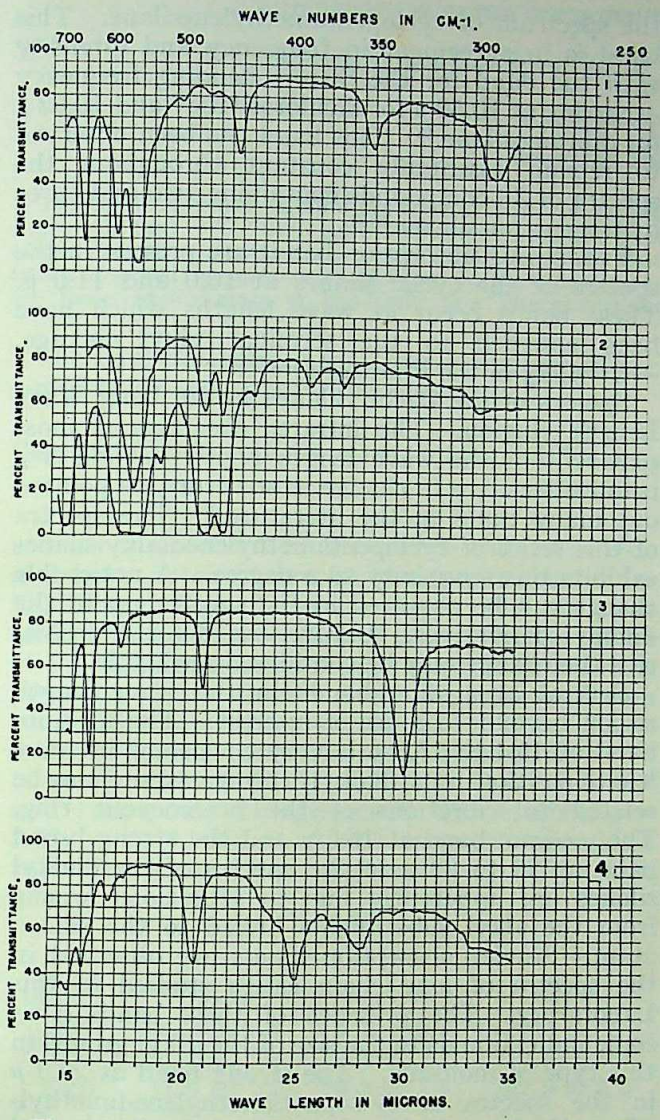

Fig. 4.—Infrared spectra from 15–35 μ of cyclopentamethylene silanes: 1, unsubstituted; 2, dichloro; 3, dimethyl; 4, di-*n*-propyl.

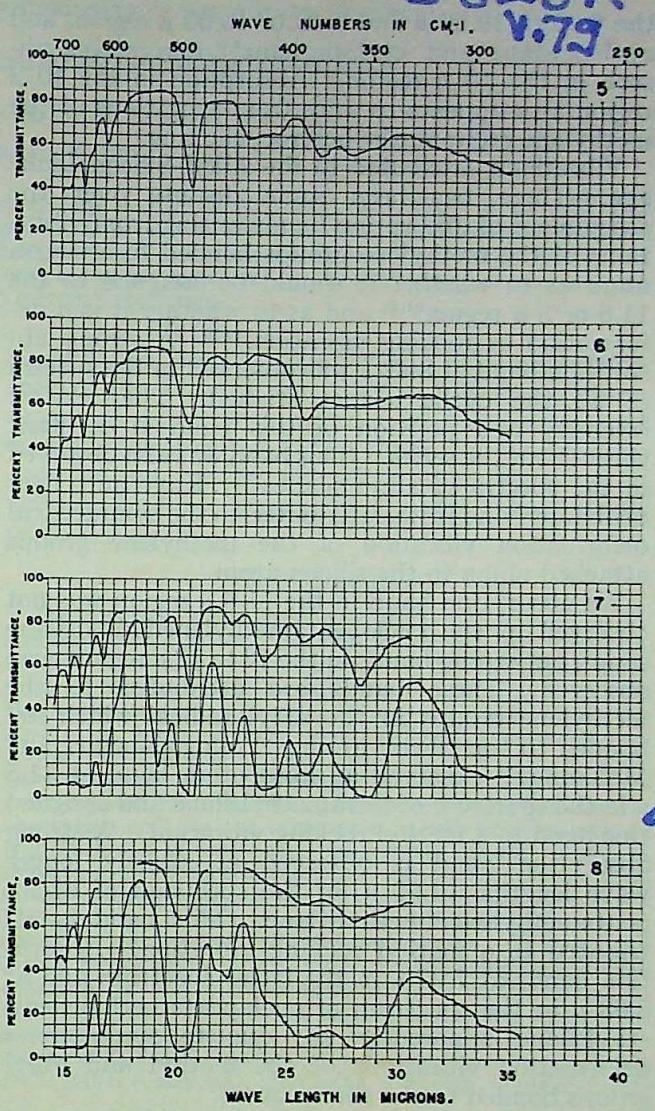

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Fig. 5.—Infrared spectra from 15–35 μ of cyclopentamethylene silanes: 5, di-*n*-butyl; 6, di-*n*-amyl; 7, diisoamyl; 8, di-*n*-hexyl.

bending vibrations of the methylene group linked to the silicon atom.

Vibrations Attributed to the Heterocyclic Ring.—Analysis of the spectra of the cyclic silanes led to empirical assignments for the characteristic vibrations of the heterocyclic ring. Absorption bands at 10.93 to 11.00 μ and 20.20 to 20.85 μ in the spectra of these compounds are tentatively assigned to this structure. The sharp absorption band at 10.93 to 11.00 μ appears to be the most promising band for determining the presence of the heterocyclic ring. It is a strong band and is very constant in wave length position throughout this series of compounds. The second band absorbs strongly at 20.20 to 20.85 μ and is present in the spectra of all the cyclic silanes except cyclopentamethylenesilane and cyclopentamethylenediphenylsilane. In the latter spectrum the band is at 21.00 μ, just outside the above range, but in the spectrum of the silane it has shifted to longer wave lengths at 22.30 μ. This band is attributed to the out-of-plane bending mode of the heterocyclic ring.

Several other absorption bands in the spectra of these cyclic silanes appear to be characteristic of the cyclopentamethylene silicon ring, and serve to identify this class of compounds. A weak absorption band at 3.70 to 3.75 μ is present in the spectra of all the cyclic silanes in this series, and most of the cyclopentane and cyclohexane derivatives in the API spectra. It appears to be a characteristic feature of these aliphatic ring systems. A study in the 3 to 4 μ region with a lithium fluoride prism would probably disclose a band characteristic of the C–H vibration of the heterocyclic ring.

The weak absorption band at 7.83 to 7.90 μ is present in the spectra of all the cyclic silanes in this series and appears to be characteristic of the heterocyclic ring. Since Si–CH_3 always absorbs in this region, however, this band is a risky one for other correlations. Cyclohexane has an absorption band at 7.95 μ and most of its derivatives absorb in this region. The 7.83 to 7.90 μ band appears to be associated with the vibrations of the methylene linkage in the heterocyclic ring.

The strong absorption band at 9.95 to 10.05 μ decreases in intensity as heavier alkyl substituents are linked to the silicon atom. The relative position of this band is constant throughout the series. Marrison[15] has noted that most of the published spectra of cyclohexane derivatives show bands in

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the 9.95 to 10.50 μ and 9.48 to 10.00 μ region, and cyclopentane and cyclopropane[8,9] derivatives absorb in the 10 μ region. Absorption in the 10 μ region also appears to arise from vibrations of the methylene group in the heterocyclic ring.

Vibrations Attributed to the Alkyl-Silicon Linkage.—There has been some dispute over the assignment of absorption bands arising from vibrations of the methylene groups bonded to a silicon atom as to whether it should be assigned to the 11.6 or 8 μ region[21,22] and as to whether it is a deformation or rocking vibration.[19,20] A strong absorption band at 8.42 μ was observed in the spectra of all the cyclic silanes studied. The relative intensity and position of this band is constant throughout the series. This band was also observed in the spectra of alkyl silanes by Kaye and Tannenbaum[23] and it was attributed to the symmetrical deformation vibration of the methylene groups attached alpha to the silicon atom.

An absorption band in the 11.6 μ region was not observed in the cyclopentamethylenedialkylsilane series, but strong bands in the 12 to 13 μ region were observed. These bands are attributed to the methylene groups in the alkyl radical which are bonded to the silicon atom. Young, Koehler and McKinney[24] observed an absorption band at 11.5 μ in the spectrum of tetramethylsilane and assigned this band to a methyl rocking vibration. A strong absorption band is observed at slightly longer wave lengths, 11.90 μ, in the spectrum of cyclopentamethylenedimethylsilane. This band is attributed to a methyl rocking vibration. Absorption bands at 7.97 μ in the latter spectrum and at 8.03 μ in the spectrum of cyclopentamethylenediethylsilane apparently are due to symmetrical deformation vibrations of the methyl and ethyl groups bonded to the silicon atom.

Absorption Characteristic of Disubstituted Silanes.—An absorption band in the 10.6 to 10.7 μ region, characteristic of disubstituted silanes, was observed and reported by West and Rochow,[25] but no frequency assignments were made in that paper. A strong band in this region was also observed by Opitz[26] in the spectra of monosubstituted silanes. He assigned the 10.60 to 10.90 μ region, which is common to disubstituted silanes, to a deformation mode of the SiH_2= group. An absorption band has been observed at 10.58 μ in the spectrum of cyclopentamethylenesilane. This band is in agreement in frequency and intensity with the band for the SiH_2= bending frequency occurring at 10.50 μ for dichlorosilane[27] and 10.62 μ for dibromosilane.[28] This band has been observed to remain essentially constant throughout the spectra of 38 compounds containing two and three hydrogens on silicon.[29,30]

Two strong absorption bands are present in the spectra of the cyclic silanes at 10.0 and 11.0 μ. These bands occur at wave lengths which have been assigned to the terminal vinyl linkage, —C=CH_2, in the litarature.[31,32]

Spectra of the Cyclic Silanes in the Long Wave Length Region.—The infrared spectrum of most materials in the wave length region beyond 8 μ is quite sensitive to change in structure, as pointed out many times in the literature.[33] The spectra of this series of cyclopentamethylenedialkylsilanes exhibits this sensitivity to a degree. A noticeable change can be observed in the spectra up to the dinonyl derivatives. Beyond the dinonyl derivative the change may be considered negligible.

Several absorption bands in the wave length region beyond 15 μ are of interest. The medium band at 15.4 to 15.8 μ is very consistent in wave length position in the dialkyl derivatives, and may be related to vibrations of the heterocyclic ring. The medium band at 16.6 μ and the strong broad band at 26 to 29 μ in the spectra of the dialkyl silanes are apparently due to vibrations arising from the alkyl substituents linked to the silicon atom. Similar absorption bands are observed in the spectra of long chain esters studied in this Laboratory. The presence of these bands gives some indication as to the size of the alkyl groups in this type of molecule. The strong band at 29.9 μ in the spectra of cyclopentamethylenedimethylsilane is observed in the spectra of toluene and other cyclic systems containing methyl groups and may be indicative of this group.

Acknowledgments.—The authors wish to thank Dr. C. Tamborski, Dr. H. Rosenberg and Mr. J. Groves of this Laboratory for preparing the samples used in this investigation.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF BRYN MAWR COLLEGE]

Equilibria and Spectra of Aqueous Chlorine Solutions

BY G. ZIMMERMAN AND F. C. STRONG[1]

RECEIVED DECEMBER 20, 1956

The thermodynamic equilibrium constants for the reactions: $Cl_2(aq) + H_2O = HOCl(aq) + H^+(aq) + Cl^-(aq)$, $Cl_2(aq) + Cl^-(aq) = Cl_3^-(aq)$, have been determined by a spectrophotometric method which involved accurate determinations of the absorption spectra of aqueous Cl_2, HOCl and Cl_3^- from 2000 to 3900 Å. The second, shorter wave length absorption bands observed for aqueous Cl_2 and Cl_3^- (in the former case, absent in the gas spectrum) can be interpreted as excitation to an "ionic" excited state, or, less likely, as a "charge transfer to solvent" spectrum.

We have determined spectrophotometrically the equilibrium constants for the reactions

$$Cl_2(aq.) + H_2O(l) \overset{K_1}{=} HOCl(aq.) + Cl^-(aq.) + H^+(aq.) \quad (1)$$

$$Cl_2(aq.) + Cl^-(aq.) \overset{K_2}{=} Cl_3^-(aq.) \quad (2)$$

and have obtained precise absorption spectra for HOCl(aq.), Cl_2(aq.) and Cl_3^-(aq.). The work was undertaken partly because of interest in the nature of the absorption spectra and partly to verify the presently accepted values of the two equilibrium constants, namely, $K_1 = 3.90 \times 10^{-4}$,[2] and $K_2 = 0.176$.[3] Several other recorded values of K_1 [(4.75×10^{-4}),[4] (2.09×10^{-4})[5] at 25° and (1.55×10^{-4})[6] at 0°] show only fair agreement. Our results ($K_1 = 3.35 \times 10^{-4}$, $K_2 = 0.191$) support Jakowkin's value for K_1 and are consistent (*vide infra*) with Sherrill and Izard's value for K_2. The absorption spectra for Cl_2(aq.) and Cl_3^-(aq.) have not been separated properly hitherto; in pure water and even in concentrated H_2SO_4 there is a considerable contribution to the net absorption spectrum of chlorine by Cl_3^-, especially at short wave lengths (<2800 Å.).

TABLE I

ABSORPTIVITIES

Wave length, Å.	a_{HOCl}	a_{Cl_2}	$a_{Cl_3^-}$
2537	59.0 ± 0.4	5.0 ± 0.5	3311 ± 78
2885	27.0 ± .2	26.3 ± .2	180.4 ± 1.7
3250	11.0 ± .2	75.3 ± .3	192.9 ± 5.0

Experimental

Absorbancies[7] were measured with a Beckman D.U. spectrophotometer for solutions of HOCl, OCl^- and Cl_2 in pure water and for solutions of Cl_2 in HCl–$HClO_4$ solutions of constant ionic strength (μ = 1.000) and varying HCl concentration. In order to prevent loss of Cl_2 during absorption measurements and analysis, two techniques giving identical results were used. In one case, a hypodermic syringe was connected, through a stopcock and ground joints, to a standard, Beckman, 1 cm. path quartz absorption cell; in the other case, a cell was designed to trap (below a ground joint) an exactly known volume of solution in the absorption cell and, subsequent to absorption measurements, to release the solution under the surface of a KI solution. In both cases liberated I_2 was titrated with carefully standardized thiosulfate solution. In this way highly reproducible (0.5% average deviation) values were obtained for A/bc[7] (c = total chlorine concentration in moles per liter of solution at 25°). During absorption measurements, solutions were held at 25.0 ± 0.1° in a thermostated cell holder. Pure commercially available HCl (Baker Analyzed), $HClO_4$ (G. F. Smith, triple distilled) and Cl_2 (Ohio Chemical Co.) were used; all chlorine solutions were made up immediately before using, and never kept for more than 1 or 2 hours. No detectable decomposition of the chlorine solutions was found, however, over considerably longer periods of time in strong artificial light. Pure HOCl solutions were prepared[8] by adding the stoichiometrically correct amount of NaOH solution to an aqueous chlorine solution, vacuum distilling on to Ag_2SO_4, and redistilling. The spectrum of this solution agreed with that of the original half-neutralized solution. As an additional check, the spectrum of OCl^- (prepared by adding the correct amount of chlorine to pure, carbonate-free NaOH solution) was determined carefully and compared with the spectra of HOCl–OCl^- mixtures. The longer wave length, weaker band in the HOCl spectrum definitely belongs to HOCl

TABLE II

EQUILIBRIUM CONSTANTS FROM ABSORPTION OF AQUEOUS CHLORINE SOLUTIONS

c	A_{3130}	A_{2537}	(HOCl)	(Cl_2)	(Cl_3^-) × 10^5	$K_1 \times 10^4$	K_2
0.01971	0.604	0.893	0.01372	0.00598	1.569	3.44 ± 0.11	0.191 ± 0.016
.02301	.774	1.006	.01496	.00803	2.439	3.29	.203
.02631	.942	1.115	.01622	.01006	3.147	3.32	.193
.02964	1.122	1.223	.01734	.01226	4.054	3.31	.191
.03290	1.294	1.322	.01849	.01436	4.651	3.40	.175
						Av. 3.35 ± 0.11	0.191 ± 0.016

(1) Taken from a dissertation submitted by F. C. Strong to the Graduate School of Bryn Mawr College in partial fulfillment of the requirements for the Ph.D. degree, June, 1954. This work was supported by funds from the Plan for the Coördination of the Sciences of Bryn Mawr College and was presented at the first Delaware Valley Regional meeting of the American Chemical Society, Feb. 1956.

(2) A. A. Jakowkin, *Z. physik. Chem.*, **29**, 613 (1899). This value was obtained by recalculating Jakowkin's original conductance data, using recent values for the activity coefficient of HCl taken from "Electrochemical Data" by B. E. Conway, Elsevier Publishing Co., Amsterdam, 1952. The above value is substantially lower than the one usually tabulated; for example, see "Oxidation Potentials," by W. M. Latimer, 2nd edition, Prentice–Hall, New York, N. Y., 1952.

(3) M. S. Sherrill and E. F. Izard, THIS JOURNAL, **53**, 1667 (1931). This value was recalculated from Sherrill and Izard's data to apply to reaction 1 as written here.

(4) S. N. Shilov and E. A. Solodushenkov, *Compt. rend. acad. sci. U.R.S.S.*, **3**, 17 (No. 1, 1936); *Acta Physicochim. U.R.S.S.*, **20**, 667 (No. 5, 1945).

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(7) The terms and symbols used here are those recommended by the Joint Committee on Nomenclature on Applied Spectroscopy in *Anal. Chem.*, **24**, 1349 (1952); A = absorbance, b = thickness of absorbing layer in cm.; a = absorptivity.

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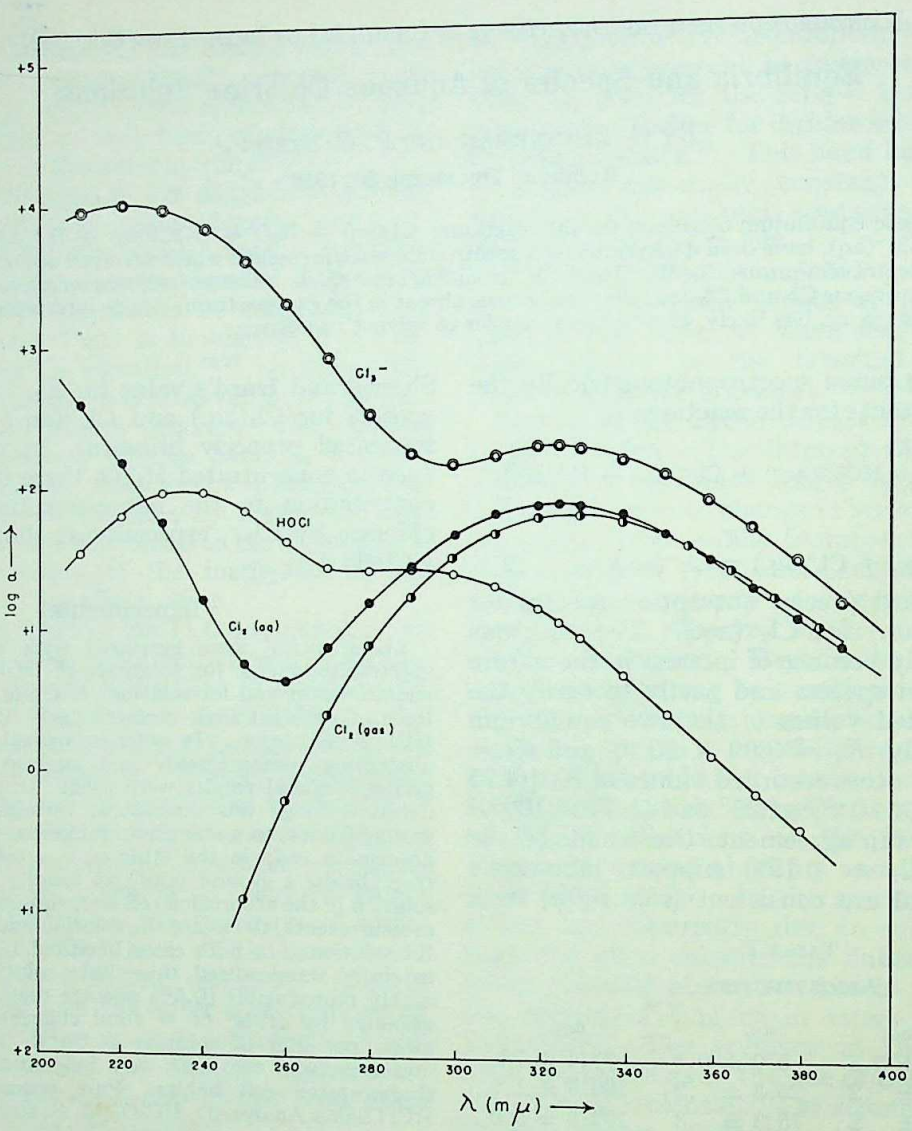

Fig. 1.—Absorption spectra.

and not to OCl^-, which happens to have a maximum absorption at the same wave length.

Results

The absorption spectrum of HOCl(aq.) shown in Fig. 1) (precise data for several wave lengths are given in Table I) is essentially the same as previously obtained[8,9,10] and was repeated mainly in order to obtain more precise values of the absorption coefficients. For solutions of chlorine in HCl–$HClO_4$ mixtures of ionic strength unity and with the initial concentration of HCl (U_0) larger than 0.02 molar, the concentration of HOCl becomes negligibly small and assuming Beer's law to hold for the two species, Cl_2(aq.) and Cl_3^-(aq.), it can be shown easily that (to better than 0.1%) the relation holds

$$A/bc = a_{Cl_2} + K_2(a_{Cl_3^-} - a_{Cl_2})\frac{U_0}{1 + K_2'(U_0 + c)}$$

where the a's are molar absorptivities[7] and $K_2' = (Cl_3^-)/(Cl_2)(Cl^-)$ for $\mu = 1.000$; parenthesis ( ) indicate molar concentrations. Figure 2 shows some typical plots of A/bc against $U_0/[1 + K_2' \cdot (U_0 + c)]$ for three wave lengths, and Table I gives the values and probable errors for a_{Cl_2} and $a_{Cl_3^-}$ obtained from least square calculations. All of the points for the corresponding spectra in Fig. 1 were obtained in the same way. For these calculations the value of 0.176 for K_2' from Sherrill and Izard's work[3] was used as representing the best value of K_2' for an ionic strength of 1.000.

Absorbances of solutions of Cl_2 in pure water are given in Fig. 3 and Table II. From the former there appears to be an isosbestic point at 2885 Å. ($A/bc = 27.02$) for $0.015 < c < 0.034$ mole/liter. It is not a true isosbestic point since all three species, HOCl, Cl_2 and Cl_3^- contribute significantly to the absorption (see Table I). However for the above limited range of c values and with no added electrolytes, A/bc for this "isosbestic" wave length is constant to within the limits of experimental accuracy and can be used conveniently to determine c from absorption measurements. In order to determine K_1 and K_2 from the data in Table II the three equations

$$A/bc = a_{HOCl}(HOCl) + a_{Cl_2}(Cl_2) + a_{Cl_3^-}(Cl_3^-) \text{ for the 2 wave lengths 2537 and 3250 Å.}$$

$$c = (HOCl) + (Cl_2) + (Cl_3^-)^{11}$$

were solved for the three concentrations, and the K's calculated using accurate values for the activ-

(9) H. L. Friedman, *J. Chem. Phys.*, **21**, 319 (1953).
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(11) c was usually determined from a measurement of A/bc at the isosbestic wave length."

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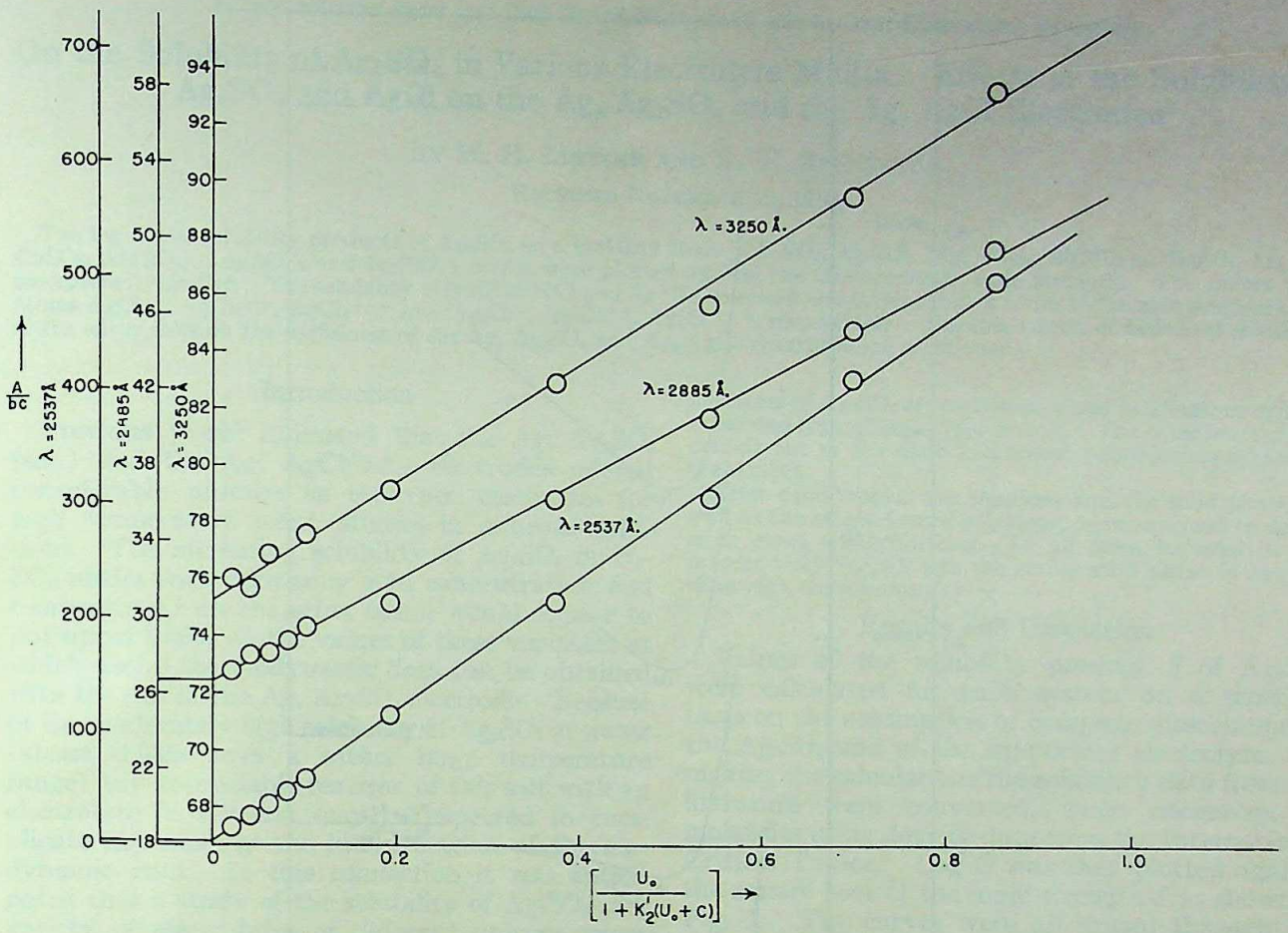

Fig. 2.—Absorption of chlorine in HCl–$HClO_4$ solutions.

ity coefficient of aqueous HCl[2] and making all other activity coefficients unity. The uncertainties (probable errors) in the individual K's in Table II are all essentially the same and result mainly from the uncertainties in the a's in Table I; the uncertainties in the a's also mainly determine the uncertainty in the average K's.

Aqueous Chlorine and Trichloride Ion Spectra.—In the Cl_2(aq.) absorption spectrum (see Fig. 1) the longer wave length band clearly corresponds to the similar known $^1\Pi_{Lu} \leftarrow {}^1\Sigma_g^+$ band for the gas[12,13]; the band which begins to appear at shorter wave lengths and which must involve fairly strong solvent-excited state interaction (since it differs greatly from the gas spectrum) probably represents either a transition to an "ionic" excited state of Cl_2[14–16] or to an excited state involving neighboring solvent molecules roughly similar to the case of aqueous halide and certain other ions.[17–19] This latter sort of excitation has been referred to frequently as "electron transfer" to solvent molecules. A semi-quantitative explanation can be based on the first assumption. Thus Fig. 4 shows the various possible levels for the separated nuclei and potential curves for (a) the ground ($^1\Sigma_g^+$) state, (b) the $^1\Pi_{1u}$

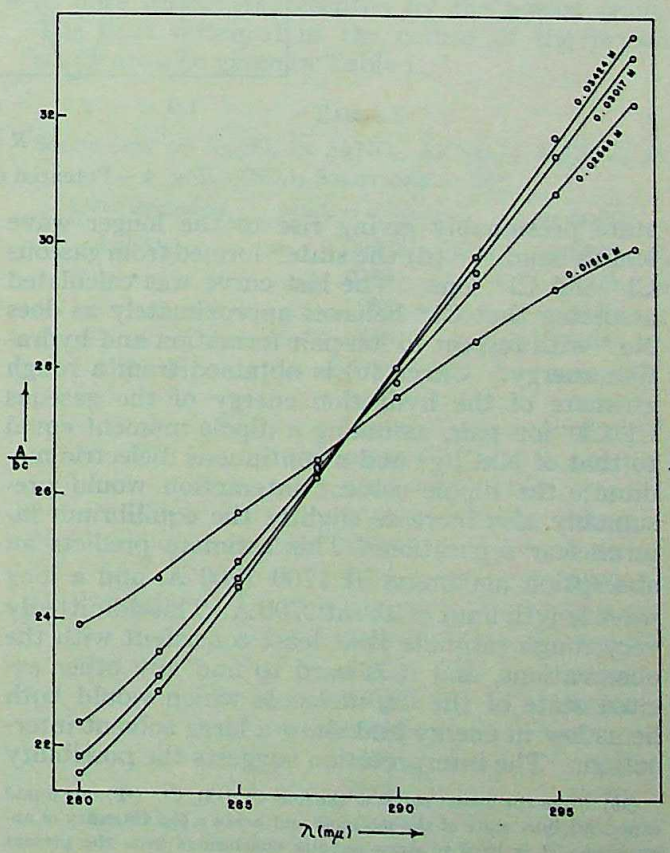

Fig. 3.—Absorption in aqueous chlorine solutions.

(12) Gerhard Herzberg, "Molecular Spectra and Molecular Structure," Vol. 1, Second Ed., D. Van Nostrand Co., New York, N. Y., pp. 390–394.
(13) G. E. Gibson and N. S. Bayliss, *Phys. Rev.*, **44**, 191 (1938).
(14) R. S. Mulliken, *J. Chem. Phys.*, **7**, 14, 20 (1939).
(15) R. S. Mulliken, *ibid.*, **8**, 234, 382 (1940).
(16) See also the discussion for I_2 by L. Mathieson and A. L. G. Rees, *ibid.*, **25**, 753 (1956).
(17) E. Rabinowich, *Rev. Mod. Phys.*, **14**, 112 (1942).
(18) L. E. Orgel, *Quart. Rev.*, **8**, 422 (1954).
(19) R. Platzman and J. Franck, "L. Farkas Memorial Volume," Research Council of Israel, Special Publication No. 1, 1952.

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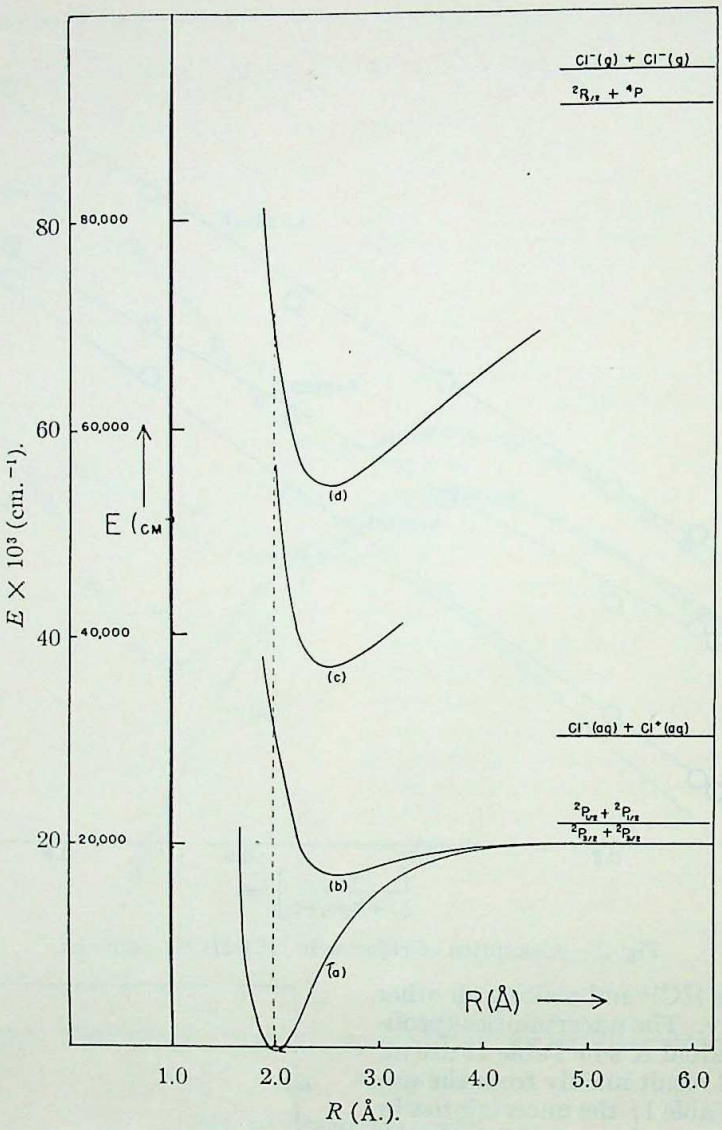

Fig. 4.—Potential energy curves for Cl_2.

state presumably giving rise to the longer wave length band,[12,13] (d) the state[20] formed from gaseous Cl^- and Cl^+ ions. The last curve was calculated assuming that Cl^+ behaves approximately as does Na^+ with respect to ion-pair formation and hydration energy. Curve (c) is obtained from a rough estimate of the hydration energy of the gaseous Cl^+Cl^- ion pair, assuming a dipole moment equal to that of NaCl(g) and a continuous dielectric medium; the dipole–solvent interaction would presumably also increase slightly the equilibrium internuclear separation. This estimate predicts an absorption maximum at 1700–1800 Å. and a long wave length limit of about 2700 Å. This admittedly very rough estimate is at least consistent with the observations, and it is hard to find any other excited state of the Cl_2 molecule which would both lie as low in energy and show a large solvent interaction. The interpretation suggests the possibility of dissociation into ions in solution by the absorption of the shorter wave lengths. In Cl_3^- the interaction of the Cl_2 and Cl^- is so weak (about 2 kcal.)[21] that one can think of the spectrum as that of Cl_2 perturbed by a close Cl^- neighbor. Thus absorption within the longer wave length band would lead to dissociation into $Cl_2 + Cl^-$ as suggested by existing photochemical evidence,[22,23] while in the lower band the upper state would be an ion triplet, $Cl^-Cl^+Cl^-$, the additional ion–dipole interaction shifting the maximum further toward the red. It would be interesting to see whether the photochemical behavior of Cl_2(aq.) for wave lengths less than about 2200 Å. would contribute to the present picture.

We wish to acknowledge the advice and suggestions of the late Professor J. L. Crenshaw under whose direction the work was begun.

BRYN MAWR, PA.

(20) From the lowest states of the ions $Cl^-(^1S)$, $Cl^+(^3P)$ one would expect a triplet state of the molecule and hence a low intensity of absorption. It is hard to draw definite conclusions from the present data concerning the intensity; more knowledge could prove to be a serious objection to the above suggested explanation.

(21) Obtained from the known equilibrium constant and a semi-empirical estimate of the entropy of Cl_3^- (aq.).

(22) A. C. Rutenberg and H. Taube, THIS JOURNAL, **72**, 5561 (1950)

(23) A. C. Rutenberg and H. Taube, *ibid.*, **73**, 4426 (1951).

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[CONTRIBUTION FROM THE OAK RIDGE NATIONAL LABORATORY, CHEMISTRY DIVISION]

On the Solubility of Ag_2SO_4 in Various Electrolyte Media. Effects of the Solubility of Ag_2SO_4 and AgCl on the Ag, Ag_2SO_4 and the Ag, AgCl Electrodes[1]

BY M. H. LIETZKE AND R. W. STOUGHTON

RECEIVED NOVEMBER 19, 1956

The log of the solubility products of Ag_2SO_4 on a molality basis in KNO_3, $AgNO_3$, $Mg(NO_3)_2$, $Al(NO_3)_3$, Na_2SO_4, $MgSO_4$, $CuSO_4$, $Al_2(SO_4)_3$, $La_2(SO_4)_3$ and $In_2(SO_4)_3$ media were plotted against the stoichiometric ionic strength. The curves were unexpectedly similar. The solubility of AgCl in HCl and $AgNO_3$ solutions was interpreted in terms of the mononuclear complexes $AgCl_2^-$, $AgCl_3^{--}$, $AgCl_4^{---}$ and Ag_2Cl^+, Ag_3Cl^{++}, Ag_4Cl^{+++}, respectively. Possible effects of increased solubility of the silver salts on the usefulness of the Ag, Ag_2SO_4 and Ag, AgCl electrodes are mentioned.

Introduction

Previous work[2] indicated that the Ag, Ag_2SO_4 (sat.) and the Ag, AgCl(sat.) electrodes offered considerable promise as reference electrodes for high temperature e.m.f. studies in aqueous solutions. The increasing solubility of Ag_2SO_4 in H_2SO_4 media with increasing acid concentration and temperature,[3] on the other hand, would appear to put upper limits on the values of these variables at which useful thermodynamic data can be obtained with the use of the Ag, Ag_2SO_4 electrode. Because of the moderately high solubility of Ag_2SO_4 in water (about $0.03m$ over a rather large temperature range) any appreciable reaction of this salt with an electrolyte in solution may be expected to complicate significantly the interpretation of thermodynamic data. In this connection it was anticipated that a study of the solubility of Ag_2SO_4 in a variety of electrolytes of different valence types even at room temperature might elucidate the general problem of such interpretations.

Data for the solubility of Ag_2SO_4 in $AgNO_3$, $Al(NO_3)_3$, $Al_2(SO_4)_3$ and $La_2(SO_4)_3$ solutions at 25° were obtained experimentally for this study, while data for the solubility of Ag_2SO_4 in $Mg(NO_3)_2$,[4] Na_2SO_4,[5] $MgSO_4$,[6] $CuSO_4$[6] and $In_2(SO_4)_3$[7] solutions were obtained from the literature. The determinations in $AgNO_3$ solutions were made because, as will be shown later, the literature values for this system[4] appeared to be inconsistent with the other data. Solubility data for AgCl in HCl, $AgNO_3$ and HNO_3 media were also obtained from the literature in order to compare the common ion effect on this salt with that on Ag_2SO_4.

Experimental

The Ag_2SO_4 used in the solubility measurements was prepared according to the method described by Archibald.[8] The $La_2(SO_4)_3$ was prepared from Fisher Scientific Company $La(NO_3)_3 \cdot 6H_2O$ by treating the nitrate with Baker analyzed concentrated H_2SO_4, fuming off the excess H_2SO_4, and igniting the $La_2(SO_4)_3$ in a muffle furnace at 500°. The $Al(NO_3)_3$, $Al_2(SO_4)_3$ and $AgNO_3$ were all Baker Analyzed Reagent grade chemicals. In each case a series of stock solutions was prepared covering the desired concentration range. Ten-ml. aliquots of the stock solutions along with an excess of Ag_2SO_4 crystals were sealed in 15-ml. centrifuge tubes and rotated at 25° for 5 days. The equilibration was carried out in the dark to prevent photodecomposition of the Ag_2SO_4.

After equilibration the solutions and the solid phase, as well as the original stock solutions, were analyzed to determine exact concentrations. In all cases included in the present work Ag_2SO_4 was the stable solid phase in equilibrium with the solution.

Results and Discussion

Values of the solubility product S of Ag_2SO_4 were calculated for each system on a molality basis on the assumption of complete dissociation of the Ag_2SO_4 and of the supporting electrolyte. In making the calculations the solubility data from the literature were converted, when necessary, to molalities using density data from the International Critical Tables.[9] Log S was then plotted against the square root of the ionic strength I as shown in Fig. 1. The curves were all drawn through the value of the log of the solubility product of Ag_2SO_4 in pure water[6] (represented by the lowest point). The data obtained in the course of the present study are also given in Table I.

TABLE I

SOLUBILITY OF Ag_2SO_4 IN $AgNO_3$, $Al(NO_3)_3$, $Al_2(SO_4)_3$ AND $La_2(SO_4)_3$ SOLUTIONS AT 25°

Added electrolyte	m added electrolyte	m Ag_2SO_4
$AgNO_3$	0.00983	0.0238
	.0174	.0211
	.0268	.0180
	.0448	.0130
$Al(NO_3)_3$	0.00527	0.02950
	.01029	.03180
	.03014	.03923
	.05035	.04493
	.1005	.05595
	.3044	.08166
	.4787	.1022
	.8774	.1382
$Al_2(SO_4)_3$	0.00221	0.02741
	.00531	.02692
	.01030	.02664
	.03048	.02644
	.05072	.02672
	.1010	.02785
	.2712	.03091
$La_2(SO_4)_3$	0.001999	0.02733
	.004938	.02747
	.009819	.02769

(1) This document is based on work performed for the U. S. Atomic Energy Commission at the Oak Ridge National Laboratory.

(2) M. H. Lietzke and R. W. Stoughton, THIS JOURNAL, **75**, 5226 (1953); M. H. Lietzke and J. V. Vaughen, *ibid.*, **77**, 876 (1955).

(3) M. H. Lietzke and R. W. Stoughton, *ibid.*, **78**, 3023 (1956).

(4) W. D. Harkins, *ibid.*, **33**, 1807 (1911).

(5) M. Barre, *Compt. rend.*, **150**, 1321 (1910).

(6) G. Åkerlöf and H. C. Thomas, THIS JOURNAL, **56**, 593 (1934).

(7) M. H. Lietzke and R. W. Stoughton, *ibid.*, **78**, 4520 (1956).

(8) E. H. Archibald, "The Preparation of Pure Inorganic Substances," John Wiley and Sons, Inc., New York, N. Y., 1942.

(9) "International Critical Tables," First Edition, McGraw-Hill Book Co., Inc., New York, N. Y., 1936.

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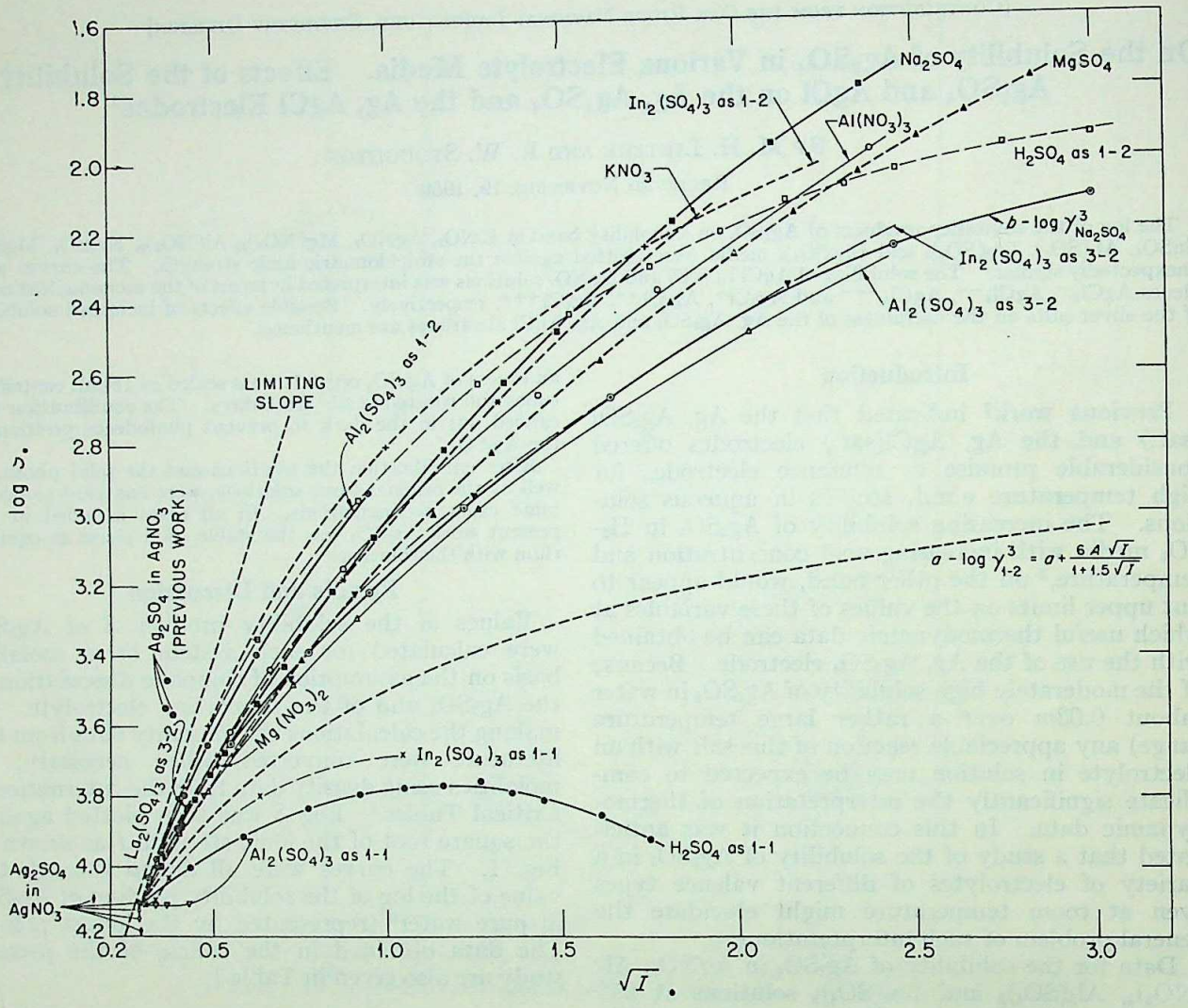

Fig. 1.—The apparent solubility product of Ag_2SO_4 in various electrolyte media.

As can be seen in Fig. 1 the solubility products on a molality basis vary in a surprisingly similar manner with the stoichiometric ionic strength whether or not the "supporting electrolyte" contains sulfate ions. The solubility data of Ag_2SO_4 in $AgNO_3$ solutions obtained in this study appear to be generally consistent with the other data, while the values obtained by Harkins[4] fall considerably above the limiting slope. It is interesting to note that the ionic strength in this case is essentially independent of $AgNO_3$ concentration.

For purposes of comparison, plots of log $\gamma_{\pm}^3$ for Na_2SO_4[10] and a generalized average activity coefficient function are also shown in Fig. 1. These two curves were shifted vertically to make them go through the point representing the solubility product of Ag_2SO_4 in pure water. The generalized average activity coefficient function (equation 2) was obtained by calculating log $\gamma_{\pm}^3$ for a 1–2 electrolyte from equation 1 which relates log γ of an ion to the ionic strength I, the charge of the ion Z_i, and the Debye–Hückel limiting slope A. The factor 1.5 in the denominator of equation 1 was suggested by Scatchard[11] as being more useful in many cases than the value unity used by Guggenheim.

$$\log \gamma_i = -\frac{AZ_i I^{1/2}}{1 + 1.5I^{1/2}} \qquad (1)$$

For a 1–2 electrolyte

$$\log \gamma_{\pm}^3 = -\frac{6AI^{1/2}}{1 + 1.5I^{1/2}} \qquad (2)$$

As can be seen the activity coefficient of Na_2SO_4 varies with its stoichiometric ionic strength in a manner very similar to that in which the activity coefficient of Ag_2SO_4 varies with the stoichiometric ionic strength in the various mixed electrolyte solutions. Two interesting conclusions can be drawn concerning all the curves based on the assumption of complete dissociation: (1) they all lie closer to the limiting law slope than do most activity coefficient curves, and (2) they are surprisingly close together compared to activity coefficient curves for strong electrolytes picked at random (after multiplication by the proper factors to correct for different valence types).

These two statements can be seen clearly to be true by noting the position of the hypothetical "average" 1–2 electrolyte curve, denoted as $a - \log\gamma^3_{1-2}$ in Fig. 1, or by an actual comparison with a plot of strong electrolyte activity coefficients.

Originally it had been hoped that some qualitative conclusions concerning the degree of dissocia-

(10) R. H. Stokes, *Trans. Faraday Soc.*, **44**, 295 (1948).
(11) G. Scatchard, private communication.

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tion of electrolytes such as the 3–2 sulfates might result from inspection of the curves in Fig. 1. For this reason the 3–2 sulfates were assumed to dissociate "completely" on three separate bases

$$\text{3–2} \quad M_2(SO_4)_3 = 2M^{+3} + 3SO_4^{--}$$
$$\text{1–2} \quad M_2(SO_4)_3 = 2MSO_4^{+} + SO_4^{--}$$
$$\text{1–1} \quad M_2(SO_4)_3 = MSO_4^{+} + M(SO_4)_2^{-}$$

Values of S and I were then determined on each of these three bases. As can be seen from Fig. 1, basis 3–2 gives the best agreement with the other curves. Basis 1–2 causes deviations from the other curves in a direction consistent with greater association or complexing of either the Ag^+ or SO_4^{--} (or both) up to an ionic strength of about 2.3 (*i.e.*, an $I^{1/2}$ of about 1.5). Basis 1–1 shows effects entirely unlike the 1–1 salt KNO_3. At least in the case of $In_2(SO_4)_3$ it is surprising that the three different bases do not cause more widely differing curves. Apparently the ionic strength effect and the common ion effect approximately cancel each other when a comparison of the three bases is made. It is not believed that the fact that basis 3–2 gives best agreement with the other curves should be interpreted as indicating that the principal species in solution are M^{+3} and SO_4^{--}. For example, in a previous paper,[7] evidence was presented to show that $In_2(SO_4)_3$ is by no means completely dissociated into In^{+3} and SO_4^{--} ions in the concentration range indicated.

In the case of the solubility of Ag_2SO_4 in H_2SO_4 media two bases of dissociation were considered

$$\text{1–2} \quad H_2SO_4 = 2H^+ + SO_4^{--}$$

and

$$\text{1–1} \quad H_2SO_4 = H^+ + HSO_4^-$$

It is known that the second equation more nearly represents the principal species in H_2SO_4 solutions in the concentration range of interest than does the first. According to Fig. 1 basis 1–2 indicates an activity coefficient for Ag_2SO_4 which varies with ionic strength almost exactly as it does in $Al_2(SO_4)_3$ and $In_2(SO_4)_3$ media on basis 1–2. Such a close similarity in these three different cases is surprising. When H_2SO_4 is treated as a strong 1–1 electrolyte the plot of the Ag_2SO_4 activity coefficient varies with ionic strength in a manner distinctly different from the other curves in Fig. 1 and similar to some of the 1–1 halide curves.

It would be interesting to calculate S and I for the Ag_2SO_4–H_2SO_4 system on an actual ionic basis using the data of T. F. Young[12] for the values of the concentration quotient K for HSO_4^- dissociation as a function of ionic strength calculated from the actual ionic concentrations in pure H_2SO_4 solutions. However, both the calculation and its interpretation would be complicated since the ionic strength on this basis must be calculated by a reiterative process; the equilibrium quotients vary, in general, with species in solution as well as with ionic strength (especially at higher values of the latter); and, as shown in Fig. 1, log S appears to be to a good approximation a function of the stoichiometric ionic strength alone. The calculation may be even further complicated by the existence of Ag^+-SO_4^{--} complex ions.

A calculation similar to the one just discussed was carried out in an attempt to calculate Ag_2SO_4 solubilities in H_2SO_4 media more accurately than was done previously.[3] The previous calculation involved the assumptions that (1) only the species Ag^+, H^+, HSO_4^- and SO_4^{--} existed in solution, (2) that S and K varied with ionic strength (calculated from actual ionic concentrations) in a manner predictable by equation 1, and (3) that only A in equation 1 varied with temperature or dielectric constant. In the current calculation assumption (2) was altered in that log S was assumed to vary with I (in this calculation I being determined by the actual ionic concentrations) in a manner represented by the average of the curves in Fig. 1 where the supporting electrolytes were assumed to dissociate completely into their simple ions, *i.e.*, basis 1–2 for H_2SO_4, basis 3–2 for $Al_2(SO_4)_3$, etc. The log S curve at any other temperature was assumed to be given in terms of that at 25° by equation 3

$$\log S(t,I) = \frac{A(t)}{A(25°)} \log S(25°, I) \qquad (3)$$

The variation of K with I (on an ionic concentration basis) at 25° was obtained from the data of Young[12] and the relation given by equation 3 was also assumed to hold for log K, *i.e.*

$$\log K(t,I) = \frac{A(t)}{A(25°)} \log K(25°,I) \qquad (4)$$

These calculations were carried out for 25 and 150° and for 0.1, 0.5 and 1.0m H_2SO_4 based on the solubilities in pure water. Contrary to expectation the agreement with the experimental values was not noticeably better than in the previous calculations. Nor was better agreement obtained when similar calculations were made in which I was calculated from the stoichiometric concentrations of the ions.

In contrast to the Ag_2SO_4 system where possible complexing of Ag^+ or SO_4^{--} with ions of the supporting electrolyte cannot be deduced definitively from the solubility data, the solubility of AgCl in electrolyte solutions containing a common ion shows a dramatic behavior. From the data of Forbes[13]; Pinkus and Timmermans[14]; Pinkus, Frederic and Shepmans[15]; and Pinkus and Shepmans[16] for the solubility of AgCl in HCl, $AgNO_3$ and HNO_3, respectively, the solubility products were calculated on a molality basis and on the basis of complete dissociation into simple ions. A plot of log S was then made against the square root of the stoichiometric ionic strength as shown in Fig. 2. In the case of HNO_3 media log S approaches the Debye–Hückel limiting slope at low ionic strengths and deviates at higher ionic strengths in a manner expected from the behavior of strong 1-1 electrolyte activity coefficients. In the cases of HCl and $AgNO_3$ media the deviations from the limiting law slope clearly show strong complexing. Further the two curves are, surprisingly enough, almost coincident which strongly implies complexing

(12) T. F. Young, private communication.

(13) G. S. Forbes, THIS JOURNAL, **33**, 1937 (1911).

(14) A. Pinkus and A. M. Timmermans, *Bull. soc. chim. belg.*, **46**, 46 (1937).

(15) A. Pinkus, S. Frederic and R. Shepmans, *ibid.*, **47**, 304 (1938).

(16) A. Pinkus and R. Shepmans, *ibid.*, **47**, 337 (1938).

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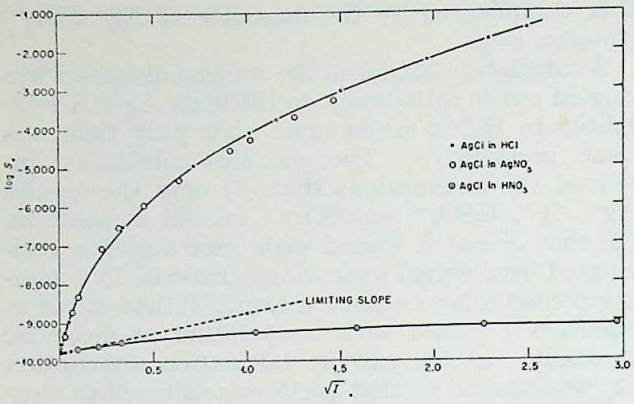

Fig. 2.—The apparent solubility product of AgCl in HCl, HNO_3 and $AgNO_3$ media.

(with excess Ag^+ or Cl^-) that is both symmetrical and that takes place to the same degree in both cases.

Some idea of the extent of complexing may be obtained in the AgCl–HCl system by making the assumption that only mononuclear complexes exist and then plotting the data in the form of log S *vs.* log m_{HCl}. On the basis of this assumption the observed S in terms of the molal solubility s and the species assumed to exist is given by

$$S = (m + s)s \qquad (5)$$

when $m \gg s$

$$S = ms = m([Ag^+] + [AgCl]_{(aq)} + [AgCl_2^-] + [AgCl_3^-] + \ldots) \qquad (6)$$

Letting S_i (where $i = 1, 2, \ldots n$) represent the molality solubility quotients for the assumed ionic equilibria

$$\underline{AgCl} = Ag^+ + Cl^- \quad S_0$$
$$\underline{AgCl} = AgCl_{(aq)} \quad S_1$$
$$\underline{AgCl} + Cl^- = AgCl_2^- \quad S_2$$
$$\ldots\ldots\ldots\ldots\ldots\ldots \quad \ldots$$
$$\underline{AgCl} + (n-1)Cl^- = AgCl_n^{-n+1} \quad S_n$$

equation 6 becomes

$$S = S_0 + mS_1 + m^2S_2 + \ldots m^nS_n \qquad (7)$$

If a single silver species predominates in any HCl concentration range then the slope of a log S *vs.* log m curve in that region gives the number of chlorides in the predominant species, and an extrapolation of that slope to $m = 1$ gives the appropriate log S_i. For an accurate treatment of the data corrections would have to be made for activity coefficient changes throughout the region under consideration. However, for a qualitative interpretation it may be assumed that activity coefficient changes are of the order of magnitude of the changes in the AgCl–HNO_3 curve with ionic strength and hence may be neglected.

In general, more than one species may exist to an appreciable extent in any region and hence the slope will give an average of i. The simplest interpretation where the slope lies between i and $i + 1$ is to assume that $AgCl_i^{-i+1}$ and $AgCl_{i+1}^{-i}$ are the principal species. If such an interpretation is made it appears that $AgCl_2^-$, $AgCl_3^{--}$ and $AgCl_4^{---}$ become significant species above about 0.002, 0.1 and 1 m HCl, respectively. Since there is no extended region where the slope is equal to a single integral value of i it appears that more than one species is important throughout the whole range studied except perhaps at the lowest ionic strength values. Consistent with the interpretation given here is that of Barney, Argersinger and Reynolds[17] who interpreted their solubility data to give a $Ag^+/AgCl_2^-$ ratio of about unity at 0.0015 m KCl.

The similarity between the AgCl–HCl and AgCl–$AgNO_3$ curves suggests the existence of species like Ag_2Cl^+, Ag_3Cl^{+2} and Ag_4Cl^{+3} in the presence of excess Ag^+ at approximately the same ionic strength values where $AgCl_2^-$, $AgCl_3^{--}$ and $AgCl_4^{---}$ appear to exist in the presence of excess Cl^-. Actually, in either or both systems polynuclear complexes may exist. Additional information is needed to settle the question definitively.

Berne and Leden[18] interpreted the solubility data for AgCl in chloride media and in $AgNO_3$ media in a manner consistent with that given above. Moreover, MacDougall[19] has shown impressive solubility evidence for the existence of the positive silver acetate complex $Ag_2(C_2H_3O_2)^+$ in solutions containing excess silver ion.

While the effect of the complexing described above on the solubility of AgCl at room temperature is not sufficiently great to alter appreciably an HCl or a $AgNO_3$ medium, the situation may be much more unfavorable to interpretation of Ag, AgCl (sat.) electrode results at elevated temperatures. It is known, for example, that the solubility of AgCl in pure water increases about tenfold in raising the temperature from 25 to 100°. If then the complex formation constants were temperature independent the solubility in HCl or $AgNO_3$ media would be about 10 times higher at 100° than it is at 25°. Actually the complex formation tendency may increase with temperature, and the solubility probably continues to increase with temperature above 100°. Thus it will be necessary to investigate the solubility of AgCl in water and in media containing a common ion at elevated temperatures before interpretation of e.m.f. data under such conditions can be taken seriously.

Conclusions

The molality solubility product of Ag_2SO_4 appears to a good approximation to be a function of the stoichiometric ionic strength alone. The fact that this is true to an ionic strength of over unity in widely different media and in the presence or absence of a common ion is difficult to explain. Nothing can be concluded definitively concerning the existence of complex ions from the solubility data alone, although at least in the case of $In_2(SO_4)_3$ considerable complexing was previously shown to obtain. Reasonable and surprisingly similar curves are obtained whether $In_2(SO_4)_3$ is assumed to dissociate "completely" as a 3-2, a 1-2, or a 1-1 electrolyte. Apparently, in this case, the common ion effect and the ionic strength effect

(17) J. E. Barney, II, W. J. Argersinger, Jr., and C. A. Reynolds, THIS JOURNAL, **73**, 3785 (1951).

(18) E. Berne and I. Leden, *Svensk Kem. Tidskr.*, **65**, 88 (1953).

(19) F. H. MacDougall, *J. Phys. Chem.*, **46**, 738 (1942).

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cancel each other to a first approximation. In contrast, the solubility of AgCl in the presence of either common ion clearly shows complexing. Interestingly enough the complexing of Ag^+ by Cl^- and of Cl^- by Ag^+ appear to be remarkably similar. The large extent of this complexing at room temperature combined with the known increasing solubility of AgCl in water with temperature suggest the necessity of obtaining AgCl solubilities in media containing a common ion before making definitive interpretations concerning thermodynamic data involving the Ag, AgCl (sat.) electrode in such media.

Acknowledgment.—We wish to express our appreciation to P. F. Thomason and co-workers of the Ionic Research and Development Group of the Analytical Chemical Division of the Oak Ridge National Laboratory for all analytical work in connection with our solubility program.

OAK RIDGE, TENN.

[CONTRIBUTION FROM THE JOHNSON FOUNDATION FOR MEDICAL PHYSICS, UNIVERSITY OF PENNSYLVANIA]

Some Phase Relationships in the Three-component Liquid System CO_2–H_2O–C_2H_5OH at High Pressures

BY LOUIS C. W. BAKER[1] AND THOMAS F. ANDERSON

RECEIVED JUNE 15, 1956

Phase diagrams for the liquid system CO_2–H_2O–C_2H_5OH are reported covering the temperature range 10 to 50° at pressures from 3000 lb./in.² down to the vapor pressures of the respective mixtures. Liquid–vapor critical data are included. In most respects the diagrams are typical of systems wherein one component (C_2H_5OH) is completely miscible with each of the other two components while the latter are only sparingly soluble in one another. However, for ternary mixtures containing a given C_2H_5OH:H_2O molar ratio, isobaric temperature rise causes first an increase and later a decrease in the extent of the region wherein only one liquid phase exists. The temperature of maximum extent of the region of one liquid phase increases with increasing pressure and decreases with increasing C_2H_5OH:H_2O molar ratio. These effects are attributable to temperature-dependent variation in the extent of molecular association.

The properties of liquid carbon dioxide solutions have received relatively little study[2] although the liquid has potentialities for considerable interest as a solvent. The linear CO_2 molecule has no over-all dipole moment and the liquid has a very low dielectric constant.[3] However, the ends of the molecule are undoubtedly considerably more negative than its center, offering opportunities for hydrogen bonding and other forms of molecular association. It is challenging to consider the following facts, for example: (1) water is practically insoluble in liquid CO_2, although the solid $CO_2 \cdot 8H_2O$ is stable, at elevated pressures, at temperatures up to 8° and perhaps higher[4–6]; (2) this paper shows ethyl alcohol to be miscible with liquid CO_2, marked diminution in total molal volume taking place upon mixing[4,7]; (3) measurements with the propyl and butyl alcohols indicate rapidly decreasing solubility with increasing carbon chain length[7]; but (4) glycerol is practically insoluble in liquid CO_2.[8] Several examples of minimum critical solution temperatures have been reported for liquid CO_2 solutions of organic substances.[7]

This paper reports phase diagrams, determined with moderate accuracy, for the liquid system CO_2–H_2O–C_2H_5OH, at temperatures from 10 to 50° and at pressures from 3000 lb./in.² down to the vapor pressures of the mixtures. Liquid–vapor critical data, within that range of conditions, are included. The results are potentially useful in the "critical point drying method" for electron microscope specimens.[9] The experimental approach has novel features.

Pure water and pure liquid CO_2 exhibit very limited mutual solubility. However, the latter was found to be completely miscible with absolute ethyl alcohol, as anticipated on the basis of frag-

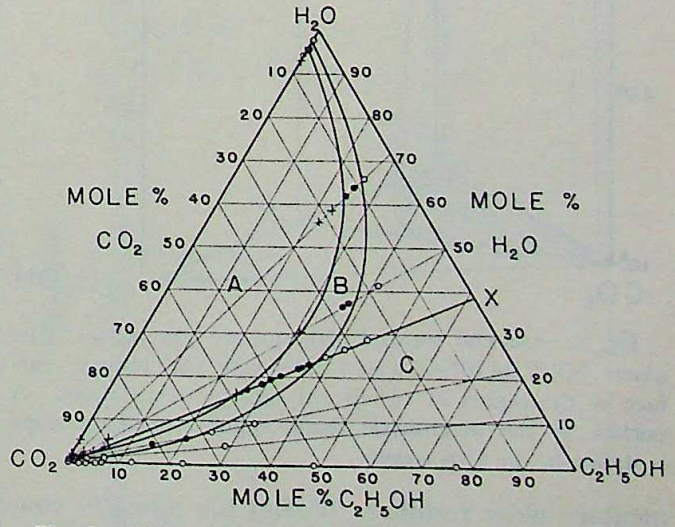

Fig. 1.—Within the ranges of conditions cited: A, area of two liquid phases; C, area of one liquid phase; B, area of one or two liquid phases depending upon temperature and pressure. Experimental points are indicated.

(1) Department of Chemistry, Boston University, Boston 15, Massachusetts.

(2) E. L. Quinn and C. L. Jones, "Carbon Dioxide," Am. Chem. Soc. Monograph No. 72, Reinhold Publ. Co., New York, N. Y., 1936, p. 94–112.

(3) F. Linde, *Wied. Ann.*, **56**, 546 (1895); H. Riegger, *Ann. Phys.*, **59**, 753 (1919); W. Herz, *Z. physik. Chem.*, **103**, 269 (1922); F. G. Keyes and J. G. Kirkwood, *Phys. Rev.*, **36**, 754 (1930).

(4) W. Hempel and J. Seidel, *Ber.*, **31**, 2997 (1898).

(5) S. Wroblewsky, *Wied. Ann.*, **17**, 103 (1892); *Compt. rend.*, **94**, 212 (1882).

(6) P. Villard, *ibid.*, **119**, 368 (1894); *Ann. chim. phys.*, **11**, 355 (1897).

(7) E. H. Büchner, *Z. physik. Chem.*, **54**, 665 (1906).

(8) E. L. Quinn, *Ind. Eng. Chem.*, **20**, 735 (1928).

(9) T. F. Anderson, *J. Appl. Phys.*, **21**, 724 (1950); *Trans. N. Y. Acad. Sci.*, [II] **13**, 130 (1951).

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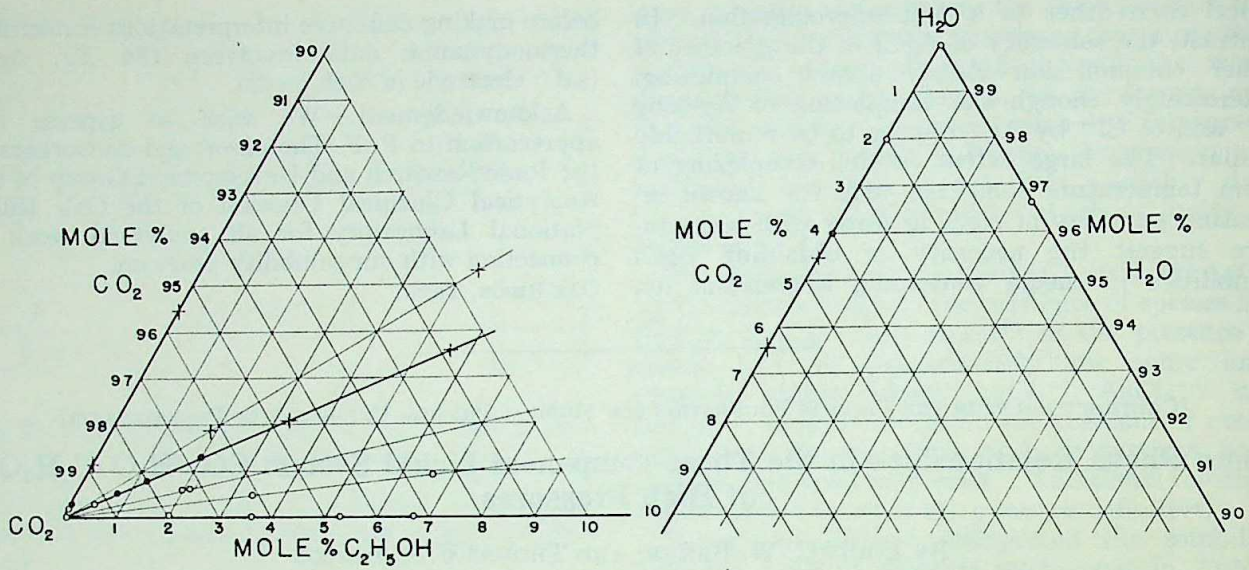

Fig. 2.—Details of corners of Fig. 1: ×, points in area A; ●, points in area B; ○, points in area C. Critical conditions were determined for most of the latter in the CO_2-rich corner.

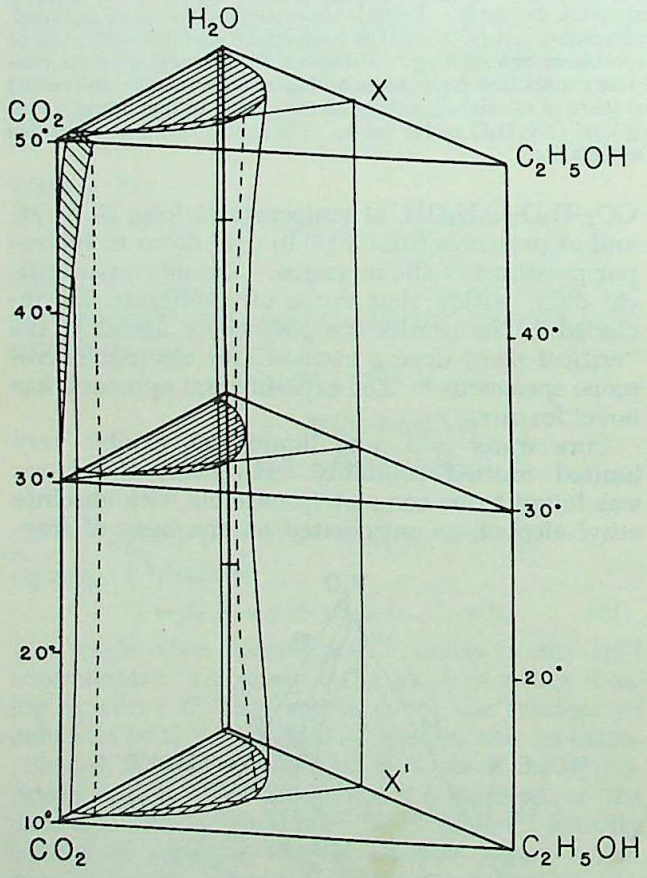

Fig. 3.—General form of diagram, see text below. The plane $XX'CO_2(10°)CO_2(50°)$ intersects the isobaric surface of the region of two liquids at the dotted lines. A portion of the heterobaric liquid–vapor critical envelope is shown in the CO_2 corner.

mentary older results.[7] Within the range of conditions cited, a 95 weight % solution of ethyl alcohol in water is also completely miscible with liquid CO_2.

The general findings are summarized by Figs. 1 and 2.

Figure 3 represents the general form of the phase diagrams of which Fig. 1 is a projection. The lower end of the liquid–vapor critical envelope is seen in the CO_2 corner. That envelope, of course, is not isobaric. It is composed of the "second critical points" of the mixtures[10] (*i.e.*, the points at which the distinction between the gaseous phase and the liquid phase vanishes). The vertical columnar volume represents the region of two liquids. One of the isobaric surfaces of that region is represented. A slight indentation in that surface, locating temperatures of maximum extent of the region of one liquid phase, runs as a broad shallow valley in a counterclockwise helical path up that surface. The valley's depth appears to be negligible near its ends. As the pressure is raised the region of two liquids is slightly decreased in size and the location of the helical valley is displaced upward, sometimes to temperature ranges higher than those illustrated.

Experimental

An extremely sturdy glass-and-steel liquid level gage,[11] manufactured for service on very high-pressure steam boilers, was adapted for use as a glass-walled bomb. The interior volume (about 35 cc.) was all visible between the two 1.0 inch-thick pre-strained Pyrex glass plates which formed opposite sides of the bomb. Each plate covered a 1.3 cm.-wide side of the interior chamber. The bomb, containing a large ball bearing, was mounted on a motor-driven rocking mechanism which was submerged in a well-stirred water-bath. As the bomb rocked slowly, the steel ball rolled from one end of the interior chamber to the other, providing efficient stirring. A powerful light was shone, by means of a submerged mirror, through the glass walls of the bomb chamber and toward the observer. The contents of the bomb could be watched through a window in the side of the water-bath. One end of the bomb was fitted with an aneroid high pressure gage, of negligible volume, which was calibrated in place and periodically checked against an hydraulic dead-weight balance. The other end of the bomb was fitted with a fine-bore high pressure valve of negligible volume.

Solutions were prepared, in relatively large amounts, from known weights of absolute ethyl alcohol and recently boiled distilled water.

A typical run was made as follows. The water-bath was emptied and the dried bomb-chamber was swept out with

(10) J. P. Keunen, *Phil. Mag.*, **40**, 173 (1895); H. C. Weber, "Thermodynamics for Chemical Engineers," John Wiley and Sons, Inc., New York, N. Y., 1939, p. 33–43.

(11) Jerguson Gage and Valve Co., Somerville, Massachusetts. Catalogue Unit No. 264, p. 3, Gauge No. 11-T-30.

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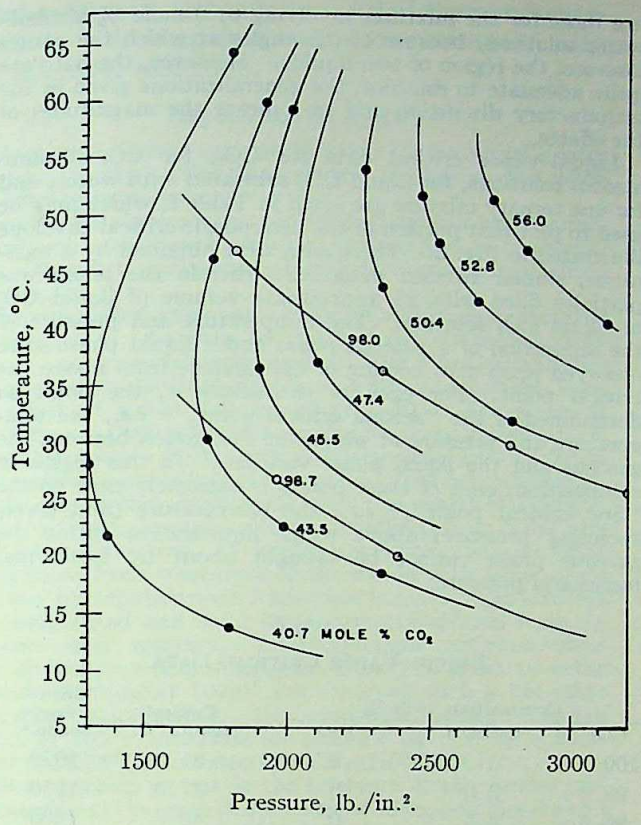

Fig. 4.—Temperatures and pressures of phase separations for various mixtures *made with* 61.0 mole % solution of alcohol in water. These mixtures all lie on line CO_2-X, Fig. 1. The mole % CO_2 is indicated for each. The two types of curves shown lie on opposite sides of the intersection of the line CO_2-X with area A, Fig. 1. (For mixtures containing about 50 mole % CO_2, the CO_2-rich liquid phase is the more dense of the two liquid phases below 10°; and it is the less dense liquid phase above that temperature.)

CO_2. Then a known weight of a given alcohol–water solution was injected with a calibrated syringe, the nozzle of which was temporarily inserted through the open valve into the bomb chamber. A high pressure stainless steel tube, running from an inverted cylinder of C.P. liquid CO_2, was swept out and connected to the valve on the bomb. The water-bath was then filled with ice-water. Liquid CO_2 (under its room temperature vapor pressure) was thereupon run into the bomb chamber, filling it at 0°. This procedure ensured that only liquid phases would be present after the temperature was raised as described below. The valve on the bomb was closed and the mixture was rocked to stir it at 0°. The pressure fell during this stirring, it being obvious that a marked decrease in total molal volume accompanied the dissolution.[4] More CO_2 was then admitted and the contents were stirred as before. The line to the CO_2 tank was then disconnected and, in its place, a rubber tube was fitted to the valve on the bomb. This tube led to a precision "wet test meter"[12] containing several liters of water through which CO_2 had just been bubbled for 20 minutes. While the bomb rocked, the temperature of the bath was rapidly raised until only one liquid phase was present, provided the temperature required was not over 60°. The temperature was then lowered fairly rapidly to determine roughly the temperature of separation of two liquid phases. The point of separation of the two phases was then determined accurately by covering again the appropriate portion of the temperature range very slowly. Reproducibility was consistently within 0.1°. The thermometer used was calibrated against one recently checked by the U. S. Bureau of Standards. The temperature and pressure at which the two phases separated were noted. The bath was then raised to 60°, and the valve on the bomb was cracked, allowing a little of the homogeneous mixture within the bomb to blow off very slowly through the wet test meter. The valve was closed again, and the temperature and pressure of separation of two liquid phases were again determined for that portion of the mixture remaining in the bomb. This partial blowing off procedure was repeated several times; and for each ternary mixture within area B, Fig. 1, several points were thus obtained. Observations were discontinued when the pressure was so low that a vapor phase appeared. The remaining CO_2 in the bomb was then blown off slowly through the wet test meter. The total reading on that instrument then showed the amount of CO_2 which had been in the bomb originally, measured as volume of water-saturated gas at the current atmospheric pressure and at the temperature of the water within the meter. Thus the over-all mole fraction could be calculated. Most of the alcohol and water generally remained in the bomb (not much being swept out during the final blow off); but the small amounts of these compounds which entered the wet test meter dissolved, when the gas was bubbled through it, in the large volume of water the meter contained. Excellent reproducibility was obtained on duplicate runs.

(12) "Fisher's Modern Laboratory Appliances," Fisher Scientific Co. Catalogue, New York, N. Y., 1952, p. 497, No. 11–165.

Construction of Diagrams

For a given run, the temperatures and pressures of liquid phase separations were plotted against one another and a smooth curve was drawn through the points (Fig. 4). Different runs involving varying proportions of CO_2 but the same C_2H_5OH:H_2O ratio (*e.g.*, 61.0 mole % alcohol) thus gave a family of curves (Fig. 4) from which temperatures of separation at a given pressure can be read. Alternatively one may ascertain pressures of separation at a given temperature.

The point X, Fig. 1, represents a specific (*i.e.*, 61.0 mole %) alcohol–water solution. All mixtures made by injecting varying quantities of that solution into the bomb, as described in the above procedure, have compositions falling on the line joining X and the CO_2 corner. In Fig. 3 these compositions coincide with the plane $XX'CO_2(10°)CO_2(50°)$. The dotted lines, Fig. 3, representing the intersections of this plane with an isobaric surface of the region of two liquids, may be plotted by reading temperatures from Fig. 4 at the pressure in question. Figure 5 represents the plane $XX'CO_2(10°)CO_2(50°)$, with such intersections plotted for three different pressures. The locations of temperatures of maximum extent of the region of one phase are obvious in Fig. 5.

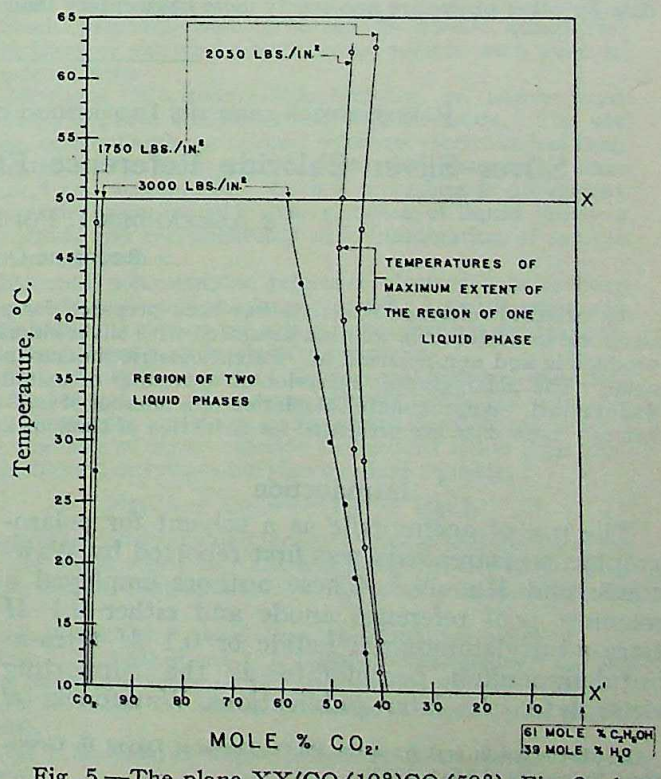

Fig. 5.—The plane $XX'CO_2(10°)CO_2(50°)$, Fig. 3, showing three of the isobaric intersections of the plane with the region of two liquids. Plotted with readings from Fig. 4.

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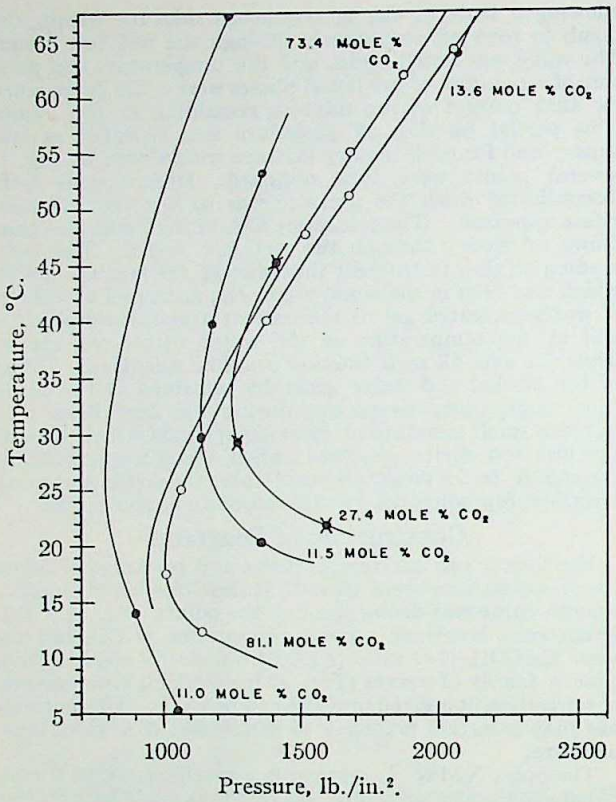

Fig. 6.—○, points on *PT* curves for mixtures *made with* 77.9 mole % alcohol–water solution; ●, points determined for mixtures *made with* 28.1 mole % alcohol–water solution; ✕, points determined for mixture *made with* 50.0 mole % alcohol–water solution.

The isobaric intersections of the region of two liquids with other planes, radiating from the CO_2 corner of Fig. 3, may be similarly plotted from the data obtained using other alcohol–water proportions (Fig. 6). An assemblage of such planes determines the surfaces of the region of two liquids. The data for other planes are necessarily more fragmentary than are those for the mixtures involving 61.0 mole % alcohol–water solutions, because of the angles at which the planes intersect the region of two liquids. However, the data are quite adequate to establish the generalizations given in the introductory discussion and to indicate the magnitudes of the effects.

Liquid–vapor critical data for CO_2, for CO_2–absolute alcohol solutions, for liquid CO_2 saturated with water, and for one ternary mixture are listed in Table I, which may be used to plot that portion of the heterobaric critical envelope illustrated in Fig. 3. These data were obtained by a technique, similar to that described, wherein the bomb was partially filled with an appropriate volume of liquid CO_2 or liquid CO_2 solution. The temperature and pressure of the separation of a gaseous phase and a liquid phase were observed upon slow cooling of the mixture from above the critical point. For each of the solutions, the point so determined is the "second critical point,"[10] *i.e.*, the temperature and pressure at which the distinction between the gaseous and the liquid phase vanishes. In this region of composition, each of these points is extremely close to the "first critical point",[10] *i.e.*, the temperature (and corresponding pressure) above which liquefication within the gaseous phase cannot be brought about by isothermal increase of pressure.

TABLE I

LIQUID–VAPOR CRITICAL DATA

Composition, mole %			Critical temp., °C.	Critical pressure, lb./in.²
CO_2	C_2H_5OH	H_2O		
100	0	0	31.0	1070
98.0	2.0	0	37.9	1150
96.4	3.6	0	40.7	1200
94.7	5.3	0	45.6	1300
93.3	6.7	0	47.8	1345
99.8	0	0.2 (satd.)	31.7	..
97.5	2.0	0.6	38.1	1195

Acknowledgment.—This work was supported by a contract (NR-135-197) between the Office of Naval Research, Department of the Navy, and the University of Pennsylvania.

PHILADELPHIA 4, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Silver–Silver Chloride Reference Electrode in Acetonitrile Polarography[1]

BY ALEXANDER I. POPOV AND DAVID H. GESKE[2]

RECEIVED OCTOBER 24, 1956

An external reference electrode has been prepared for polarographic studies in acetonitrile. A silver–silver chloride electrode in acetonitrile solution saturated with silver chloride and trimethylethylammonium chloride was found to be reproducible and non-polarizable. Potentiometric measurements were made to relate the reference electrode to Pleskov's scale. The polarographic behavior of a number of metallic perchlorates in 0.1 *M* tetra-*n*-butylammonium perchlorate was studied. Approximate calculation of a number of half-wave potentials was done and comparison made with observed values. New data are presented for reduction of thallous and stannous ions.

Introduction

The use of acetonitrile as a solvent for polarographic measurements was first reported by Wawzonek and Runner.[3] These authors employed a mercury pool reference anode and either 0.1 *M* tetra-*n*-butylammonium iodide or 0.1 *M* tetra-*n*-butylammonium perchlorate as the supporting electrolyte. In later publications Wawzonek, *et al.*,[4] reported polarographic measurements on some organic compounds in the same solvent. The study of hydrogen ion reduction in acetonitrile has been described recently by Vlcek.[5]

After the work reported in this paper was completed, a dissertation by Coetzee[6,7] reported a comprehensive polarographic study of a number of

(1) Abstracted in part from the Ph.D. Thesis of David H. Geske, State University of Iowa, 1957.

(2) National Science Foundation Predoctoral Fellow.

(3) S. Wawzonek and M. E. Runner, *J. Electrochem. Soc.*, **99**, 457 (1952).

(4) S. Wawzonek, E. W. Blaha, R. Berkey and M. E. Runner, *ibid.*, **102**, 235 (1955); **103**, 456 (1956).

(5) A. A. Vlcek, *Chem. Listy*, **48**, 1741 (1954); *Coll. Czech. Chem. Comm.*, **20**, 636 (1955).

(6) J. F. Coetzee, *Diss. Abs.* (Minnesota), **16**, 1071 (1956).

(7) J. F. Coetzee, Ph.D. Thesis, University of Minnesota; I. M. Kolthoff and J. F. Coetzee, THIS JOURNAL, **79**, 870 (1957).

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metal cations in acetonitrile. All of these measurements were done against an aqueous saturated calomel reference electrode.

Experimental Part

Reagents.—Source and purification of acetonitrile were given previously.[8] The final solvent distillation was made in a nitrogen atmosphere.

Tetra-*n*-butylammonium iodide[9] and tetra-*n*-butylammonium perchlorate[10] were prepared as described in the literature. Reagent grade potassium iodide was recrystallized from water.

Trimethylethylammonium chloride was prepared in the following way. Aqueous sodium hydroxide is added dropwise to aqueous trimethylamine. The reaction mixture was warmed to distil trimethylamine into an alcoholic solution of ethyl iodide maintained at −50°. The alcoholic solution was then allowed to warm to room temperature. Since the reaction is exothermic it is necessary to moderate the reaction to avoid loss of reactants. The trimethylethylammonium iodide is filtered from the reaction mixture, rinsed with ethyl acetate and recrystallized from ethyl acetate–ethanol mixture. Trimethylethylammonium chloride is produced from treatment of the iodide with silver oxide followed by titration with hydrochloric acid. The solution was evaporated and solid material recrystallized from an acetone–water mixture. Trimethylethylammonium chloride undergoes a transformation from non-cubic to cubic crystal structure at 100.0° (as observed with a hot-stage polarizing microscope). Decomposition without fusion begins at 290°. Analysis for chloride gave 28.57% compared to 28.68% calculated for $(CH_3)_3N(C_2H_5)Cl$.

Silver chloride for use in the reference electrode was precipitated from acetonitrile solutions of silver perchlorate and tetra-*n*-butylammonium chloride and washed on the filter with acetonitrile.

Silver nitrate was purified from reagent grade material by recrystallization from water followed by fusion. Anhydrous potassium, sodium, barium, strontium and silver perchlorates (G. F. Smith and Co.) were dried *in vacuo* at 25°. Anhydrous lithium perchlorate was obtained by dehydration of lithium perchlorate trihydrate.

Anhydrous lead perchlorate was obtained by preparing the hydrated material from lead monoxide and 70% perchloric acid and then dehydrating in a vacuum oven at 180°.[11] No chloride was present after the dehydration. Analysis for lead by electrodeposition of lead dioxide gave 51.5% compared to 51.02% for $Pb(ClO_4)_2$.

Thallium perchlorate was prepared anhydrous by dissolving thallium metal in perchloric acid and drying the resulting crystals at 120°. Analysis for thallium by gravimetric chromate gave 66.5% compared to 67.27% for $TlClO_4$.

Anhydrous cadmium perchlorate was prepared by dissolving cadmium oxide in perchloric acid to obtain the hexahydrate, dehydrating to the dihydrate at 25° *in vacuo*, and finally to the anhydrous compound at 120° *in vacuo*.[12] Analysis for perchlorate by precipitation of potassium perchlorate in ethanol[12] gave 63.6% perchlorate compared to 63.89% for $Cd(ClO_4)_2$.

Calcium perchlorate was obtained anhydrous by dissolving calcium hydroxide in perchloric acid and dehydrating the resulting dihydrate by heating *in vacuo* at 180°.[12] Analysis for calcium by standard Versenate titration gave 16.5% calcium compared to 16.77% for $Ca(ClO_4)_2$.

Nickel, cobaltous, ferric, ferrous, cupric and chromic perchlorates (hexahydrate) and mercuric perchlorate trihydrate (all obtained from G. F. Smith and Co.) were dried over phosphorus pentoxide *in vacuo* at 25°. Compositions were checked by precipitation of potassium perchlorate in ethanol,[12] except in the case of the cupric salt where copper was determined electrometrically. The ferrous salt was found to be free of ferric by polarographic analysis. Zinc and manganese perchlorates (hexahydrate) were prepared by action of perchloric acid on the oxide. The zinc salt was analyzed by the gravimetric perchlorate method. The manganese salt was analyzed by gravimetric determination of manganese sulfate obtained by repeated fuming with sulfuric acid. Aluminum perchlorate hexahydrate (chloride free), was obtained by action of perchloric acid on aluminum dust and was analyzed by the gravimetric perchlorate method.

The compound stannous perchlorate diacetonitrile was prepared as described by Schmidt[13] but was found to detonate on handling. It was possible to prepare an acetonitrile solution of stannous perchlorate by electrolyzing an acetonitrile solution of silver perchlorate using a tin anode. Concentration was determined from the amount of silver replaced by tin.

The perchloric acid solution used for polarographic study was prepared by dilution of 70% stock followed by titration against standard base.

Tank nitrogen was purified by passage through concentrated sulfuric acid, barium oxide, hot copper turnings, another barium oxide column, and finally an acetonitrile presaturator.

Apparatus.—A Sargent Model XXI recording polarograph was used to obtain all data reported here. Calibration of current sensitivity was done as described by Kolthoff and Lingane.[14] Current measurements were made by using the average of the pen deflections with the instrument circuit undamped. Recorder lag was negligible with the circuit undamped. Potential settings for scanning were checked with a potentiometer. Polarograms were corrected for iR drop through the cell and instrument resistances.

The dropping mercury electrode had a drop time of t = 4.02 sec. and m = 1.75 mg. sec.$^{-1}$ at a pressure of 60.0 cm. Hg (uncor.) on open circuit in 0.1 M tetra-*n*-butylammonium perchlorate solution. Diffusion current constants were evaluated using m and t values obtained at the potential of the reduction wave.

Resistance measurements were made using a Wheatstone bridge powered by a 1000 cycle audio oscillator. Resistance of the cell circuit was taken at maximum mercury drop size.

Electromotive force measurements of circuits of high resistance were made using a Leeds and Northrup #7673 thermionic amplifier and a type K potentiometer.

Temperature of polarographic cell was maintained at 25.0 ± 0.1° by circulation of water from a constant temperature reservoir through a smaller auxiliary bath in which the cell was placed.

Stock solutions were prepared in 50-ml. quantities. Weighings of extremely hygroscopic solutes were done in stoppered vials.

Reference Electrode.—Polarography in non-aqueous solvents requires a suitable reference electrode. The use of an external aqueous calomel reference electrode has been reported with formamide,[15] acetamide–formamide mixtures,[16] and acetonitrile.[7] Such a procedure is convenient but nevertheless magnifies the question of liquid junction potentials and the possibility of contamination of sample system with water.

External polarographic reference electrodes have been prepared in acetone[17] and formic acid.[18] A search was made for a half-cell reaction suitable for use as an external polarographic reference electrode in acetonitrile.

An acetonitrile analog of the aqueous calomel electrode was investigated. Mercurous chloride, although insoluble in acetonitrile, undergoes a disproportionation reaction in the presence of excess chloride ion present either from lithium chloride or tetra-*n*-butylammonium chloride.

$$Hg_2Cl_2 + Cl^- \longrightarrow Hg^0 + HgCl_3^-$$

Particles of finely divided mercury appear and mercuric ion is detected in solution. The enhanced stability of the chloromercurate complex anion is apparently responsible for

(8) A. I. Popov and N. E. Skelly, THIS JOURNAL, **76**, 5309 (1954).

(9) H. A. Laitinen and S. Wawzonek, *ibid.*, **64**, 1765 (1942).

(10) W. F. Luder, P. B. Kraus, C. A. Kraus and R. M. Fuoss, *ibid.*, **58**, 255 (1936).

(11) V. A. Pleskov, *Zhur. Fiz. Khim.*, **22**, 351 (1948).

(12) A. L. Chaney and C. A. Mann, *J. Phys. Chem.*, **35**, 2289 (1931).

(13) H. Schmidt, *Z. anorg. allgem. Chem.*, **271**, 305 (1953).

(14) I. M. Kolthoff and J. J. Lingane, "Polarography," 2nd edition, Interscience Publishers, Inc., New York, N. Y., 1952, p. 320.

(15) H. Letaw, Jr., and A. H. Gropp, *J. Phys. Chem.*, **57**, 964 (1953).

(16) J. H. Hook, H. Letaw, Jr., and A. H. Gropp, *ibid.*, **58**, 81 (1954).

(17) P. Arthur and H. Lyons, *Anal. Chem.*, **24**, 1422 (1952).

(18) T. G. Bonner and D. Sebba, THIS JOURNAL, **78**, 2095 (1956).

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this reaction in acetonitrile as well as in a number of other organic solvents. These observations agree with those reported by Ulich and Spiegel[19] and Cruse, Goertz and Petermoller.[20]

The mercury–mercurous sulfate electrode, with sulfate ion furnished by tetraethylammonium sulfate, was found to be entirely unsatisfactory.

A silver–silver nitrate electrode was unsatisfactory because of polarization when current flowed.

Janz and Taniguchi[21] comment that the tendency of silver chloride to form complexes in acetonitrile makes the silver–silver chloride electrode unsuitable as a reference electrode. A preliminary study in this Laboratory indicated that the solubility of silver chloride is indeed greatly increased in the presence of free chloride ion, thus indicating complex formation. This increased stability of silver polychloride anions in acetonitrile by comparison with water is in accord with observations by Kratohvil.[22] However it was found possible to achieve equilibrium conditions such that the potential of a silver–silver chloride electrode did not change.

A silver electrode was prepared by deposition of silver on a platinum cylinder with a surface area of 23.4 cm.^{2}. The silver deposition was done as described by Brown.[23]

The reference electrode consisted of the silver electrode placed in acetonitrile saturated with respect to silver chloride and trimethylethylammonium chloride. The solubility of silver chloride in acetonitrile is limited by the amount of free chloride ion present, which in turn is governed by the solubility of trimethylethylammonium chloride. It is this saturation condition that prevents the electrode potential from drifting as further complexation occurs. Equilibrium conditions for a 250-ml. quantity of reference electrolyte are achieved in approximately 80 hours at 25°.

Analysis of such solutions equilibrated at 25.0° was carried out by digesting an aliquot portion in aqueous nitric acid and filtering. This gave the amount of silver chloride present. Excess chloride was determined in the filtrate by the usual means. The composition of the reference electrolyte was found to be 0.015 *M* silver chloride and 0.118 *M* trimethylethylammonium chloride.

Performance of the electrode was tested by placing identical half-cells in the arms of an H cell with a fine sintered glass frit separating the arms. A linear current–voltage relationship was found from 0 to 2 volts and 0 to 100 μa. Polarization was less than 1 mv. on such a run, and less than 2 mv. when a current of 100 μa. was passed through the cell for 20 minutes. There was no variation of potential on shaking the cell. These results indicated that the electrode was suitable as a non-polarizable polarographic reference electrode.

Pleskov[11] has measured formal electrode potentials in acetonitrile using a silver–silver nitrate (0.01 *M*) half-cell as a primary zero reference. It seemed desirable to relate the saturated silver chloride electrode to this primary reference, thus allowing comparison of half-wave potentials with electrode potentials.

This measurement was made in an H cell whose arms were separated by a ground glass plug. Junction between the two half-cells formed around the plug. The high resistance of the cell necessitated the use of the amplified potentiometer circuit previously described.

Six measurements with different electrolyte preparations over a period of six months gave a value of 0.638 ± 0.001 v. for this cell at 25.0°.

$$-\text{Ag, AgCl (0.015 } M\text{), } Me_3NEt^+Cl^- \text{ (0.118 } M\text{)//AgNO}_3 \text{ (0.01 } M\text{), Ag} +$$

The temperature coefficient was 0.6 mv. deg.$^{-1}$. Half-wave potentials reported in this paper are all referred to the silver–silver nitrate scale by the above measurement.

Following completion of this investigation a publication by Hanselman and Streuli[24] reported use of a silver–silver chloride in saturated lithium chloride as a potentiometric reference electrode in acetonitrile. Pavlopoulos and Strehlow[25] found the solubility of lithium chloride in acetonitrile to be 0.14 g./100 ml. at 25°, corresponding to a 0.026 *M* solution. It appears reasonable that a silver chloride electrode saturated with lithium chloride could be adapted for use as a polarographic reference electrode. Such an electrode would undoubtedly have a higher resistance than the cell employing trimethylethylammonium chloride as electrolyte. On the other hand, lithium chloride is more readily available. Transference numbers for estimation of liquid junction potentials are not available for ionic species in the reference electrolyte. The following limiting ionic conductances were reported by Walden[26] and are of interest here: lithium, 59.3; chloride, 88.8; tetramethylammonium, 92.9; and tetraethylammonium, 86.1 (trimethylethylammonium limiting conductance assumed intermediate to tetraethyl- and tetramethylammonium ions). From these data it seems probable that the saturated solution of trimethylethylammonium chloride minimizes the liquid junction potential more effectively than a saturated solution of lithium chloride.

Cell Construction.—A satisfactory polarographic cell was obtained by modification of the design of Pecsok and Juvet.[27] Reference electrolyte and electrode are separated from a junction compartment by a sintered glass disk (fine porosity). The junction compartment is in turn separated from the test solution by another disk (coarse porosity).

Formation of the liquid–liquid junction in this manner proved quite successful. There was no contamination of the test solution by chloride ion from the reference electrolyte.

An external electrical contact into the test solution compartment was provided for the studies of the mercury pool reference electrode. Resistance of the cell using the external reference electrode was 1500 ohms.

A gravity-flow closed system was designed in which it was possible to distil solvent, prepare and dilute solutions and transfer into the polarographic cell under dry nitrogen. It was found unnecessary to use this apparatus since the solvent which had been distilled under nitrogen required only ten minutes of degassing to remove traces of oxygen. The minor effect of small amounts of water is described later.

Results

Polarographic data were obtained in acetonitrile using the reference electrode described above. These data are summarized in Table I, with half-wave potentials reported *versus* the silver–silver nitrate (0.01 *M*) electrode. Data presented represent the average of at least three determinations. Diffusion current was proportional to concentration in the range studied, 1 to 0.1 millimolar. All polarographic waves were examined by plotting log $i/(i_d - i)$ *vs.* the applied e.m.f. corrected for iR drop (except for ferrous ion reduction, where $\log(i_d - i)$ *vs.* ϵ was plotted). The slope of such lines gives $n\alpha/0.059$. Values of $n\alpha$ are listed in Table I for those waves which gave straight line plots. The effect of addition of 0.5% water on half-wave potential is also listed in Table I.

Previous workers[3] have obtained half-wave potentials of various cations in 0.1 *M* tetra-*n*-butylammonium iodide employing a mercury pool anode. It is of interest to correlate these data with those reported in this paper. Measurement of the half-wave potential of potassium ion (in iodide supporting electrolyte) *versus* both the mercury pool and silver–silver chloride reference electrodes showed a difference of 0.25 v. Combining this measurement with the potential of the cell, $Ag,AgCl,Me_3NEtCl(satd.)\ //\ AgNO_3$ (0.01 *M*), Ag, the half-wave potentials in 0.1 *M* iodide are referred to the silver nitrate electrode by addition of

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TABLE I

POLAROGRAPHIC DATA

Compound	$-E_{1/2}$, volts Ref. 7[a]	$-E_{1/2}$, volts This paper[b]	I[c]	$n\alpha$	Effect of water[e]
$LiClO_4$	2.24	2.26	2.68	0.90	0.04
$KClO_4$		2.24	3.23	0.95	0.00
$NaClO_4$	2.14	2.14	3.00	0.94	
$Ca(ClO_4)_2$	2.11	2.14	4.34	..	
$Sr(ClO_4)_2$	2.05	(2.08)[f]	4.56	..[f]	
$Ba(ClO_4)_2$	1.92	1.92	4.62	1.68	
$Al(ClO_4)_3 \cdot 6H_2O$	1.71	1.64	5.22	0.64	
$Mn(ClO_4)_2 \cdot 6H_2O$	1.41	1.40	4.44	1.89	
$Cr(ClO_4)_3 \cdot 6H_2O$	1.41	1.39	3.79	1.27	
	0.29	(0.3)	..	..	
$Fe(ClO_4)_2 \cdot 6H_2O$	1.29	1.33	4.25	..[g]	0.13
$Fe(ClO_4)_3 \cdot 6H_2O$	1.29	1.33	4.25	..[g]	
		>-0.36	1.91	..[h]	
$Co(ClO_4)_2 \cdot 6H_2O$	0.94	0.96	4.55	1.45	
$Zn(ClO_4)_2 \cdot 6H_2O$	0.99	0.91	4.59	0.94	0.07
$HClO_4$	0.70	0.78	1.65	1.08	0.68
$Cu(ClO_4)_2 \cdot 6H_2O$	0.65	0.62	2.54	0.96	-0.01
		>-0.36	2.27	..[h]	
$TlClO_4$		0.55	3.19	0.93	
$Cd(ClO_4)_2$	0.56	0.55	4.10	1.89	0.03
$Pb(ClO_4)_2$		0.33	5.38	1.25	0.03
$Sn(ClO_4)_2$		0.23	4.50	1.63	
$AgClO_4$	-0.03	-0.13	3.10	0.94	0.005
$Hg(ClO_4)_2 \cdot 3H_2O$		>-0.36	4.70	..[h]	

[a] Metallic perchlorates in 0.1 M sodium perchlorate, except Li, Na, Ca, Sr, Ba in 0.1 M tetraethylammonium perchlorate. [b] Metallic perchlorates in 0.1 M tetra-n-butylammonium perchlorate. [c] $I = i_d/cm^{2/3}t^{1/6}$. Where multiple waves occur, I values given for separate waves, not total wave. [d] Slope value defined in text. [e] Values given are for $E_{1/2} - E_{1/2}^{H_2O}$ where $E_{1/2}^{H_2O}$ is the half-wave potential for solutions containing 0.5% water (except $HClO_4$, where 1% water was added). [f] Maxima. [g] No straight line when $\log (i_d - i)$ plotted *vs.* ϵ. [h] Current phenomenon described in text.

-0.89 volt. Potentiometric measurement of the cell, Hg, Bu_4NI(0.10 M) // $AgNO_3$(0.01 M), Ag, also gave 0.89 v. These recalculated values are shown in Table II.

TABLE II

COMPARISON OF HALF-WAVE POTENTIALS

Ion	Present work[a]	$-E_{1/2}$ Ref. 3[b]	Ref. 7
Li	2.26	2.31	2.24[d]
Na	2.14	2.14	2.14[d]
K	2.24	2.23	2.23[b]
Rb		2.25	2.24[b]
Cs		(2.23)[c]	
Ca	2.14	2.13	2.11[d]

[a] Metallic perchlorates in 0.1 M tetra-n-butylammonium perchlorate. [b] Metallic halides in 0.1 M tetra-n-butylammonium iodide. [c] Maxima. [d] Metallic perchlorate in 0.1 M tetraethylammonium perchlorate.

Half-wave potentials for a number of ions in 0.1 M tetra-n-butylammonium perchlorate measured with a mercury pool anode have been reported.[3] Comparison of these data with data in this publication did not show an exactly constant difference between the two sets of measurements. The possibility that the mercury pool anode was polarizable was verified by passing a current of 50 μa. for 2 minutes through the cell: Ag, AgCl reference / / 0.1 M Bu_4NClO_4, Hg. Polarization of 60 mv. occurred.

The potential of the mercury pool anode in iodide media is controlled by the activity of mercuric ion present largely as tetraiodomercurate, $HgI_4^=$. In the case of perchlorate media, the absence of mercury complexes may account for the polarizability of the pool electrode.

Polarographic measurements were made by Coetzee[7] using 0.1 M solutions of tetraethylammonium perchlorate and sodium perchlorate as supporting electrolyte. These measurements were related to Pleskov's electromotive force series[11] by measurement of the cell, saturated calomel-(aq.) / / $AgNO_3$(0.01 M)$_{CH_3CN}$ Ag; $E = 0.29$ volt.

Although both this measurement and the polarographic measurements involve an unknown liquid junction potential, if the junction potentials are assumed equal, the half-wave potentials obtained by Coetzee[7] are satisfactorily placed on the silver–silver nitrate (acetonitrile) scale. Thus comparison may be made between Coetzee's work (listed in Tables I and II) and the data in this paper.

Generally good agreement is found between the two sets of data, even though the supporting electrolytes were not the same.

Coetzee[7] reports a well-defined wave for the chromic–chromous reduction, while in this work the wave is ill-defined ($E_{1/2}$ approximate only) and the diffusion current plateau was not accurately measurable.

Difficulty was encountered in the study of nickel perchlorate. Two reducible species appeared to be present, since one wave occurred at -0.69 v. and another at -1.22 v. The total diffusion current was proportional to concentration but the height of the individual waves was not reproducible.

A systematic study has been made by Vlcek[5] of the effect of small amounts of water on the reduction of hydrogen ion. By using potassium as a pilot ion, hydrogen ion reductions were carried out in acetonitrile–water solutions of up to 6.2% water. The solution was saturated with tetramethylammonium iodide to provide supporting electrolyte. The reduction wave shifted to increasingly negative potentials with increasing water concentration. A plot of difference between half-wave potentials of potassium and hydrogen ions ($\Delta E_{1/2}$) *vs.* water concentration was extrapolated to zero water concentration. This value 1.55 v., represented the $\Delta E_{1/2}$ in anhydrous acetonitrile. In practice, in the solution of lowest water content, 0.05%, Vlcek found that the hydrogen ion reduction wave did not show a knee, but the current rose sharply from zero applied voltage (*vs.* mercury pool). At slightly higher water concentrations, 0.2%, the wave was normally formed.

The present work in 0.1 M perchlorate media shows a $\Delta E_{1/2}$ (as defined above) of 1.46 v. with the wave normally formed. Similarly, addition of 1% water shifted the half-wave potential 0.68 v. to more negative potentials. It has been suggested[3] that reduction waves observed for copper, cadmium and zinc perchlorates might actually be due to hydrogen ion reduction. Table I includes data for the shift of these reduction waves upon addition of 0.5% water. It is seen that these shifts are extremely small compared to the shift observed with addition of water to perchloric acid solution. This seems to offer conclusive proof

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that the reduction waves observed for the metallic cations are due to that cation and not a hydrogen ion reduction.

Stannous perchlorate shows only a single reduction wave and no oxidation to stannic ion in the potential range studied (limited by anodic dissolution of mercury).

A curious current phenomenon was encountered in the case of mercuric, cupric (first step) and ferric (first step) ion reductions. Polarograms were scanned both from the most positive potential possible (limited by anodic dissolution of mercury) toward more negative potentials and *vice versa*. In the case of the ions mentioned, at the higher concentrations (approximately 1×10^{-3} *M*) the current rose sharply at the most positive potentials and then broke abruptly several hundred millivolts more negative to a limiting current plateau. The behavior of copper as shown in Fig. 1 is typical. This behavior is

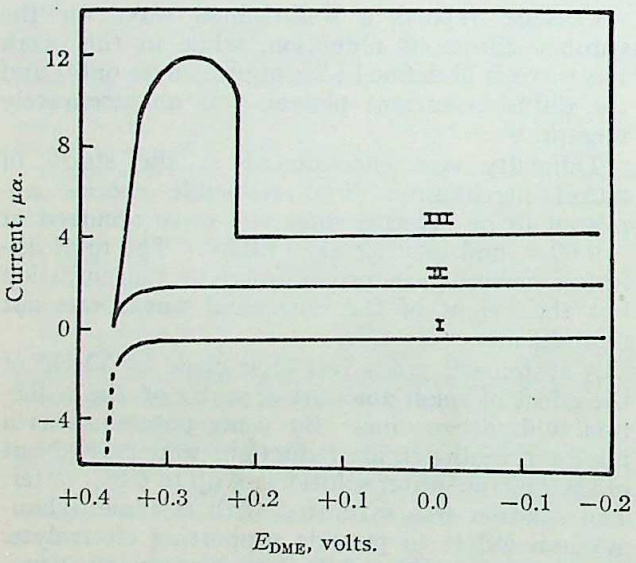

Fig. 1.—Polarograms, current *vs.* applied voltage: I, residual current, 0.1 *M* tetra-*n*-butylammonium perchlorate; II, cupric perchlorate, 0.55×10^{-3} *M*; III, cupric perchlorate, 1.10×10^{-3} *M*.

somewhat similar to that described by Bachman and Astle,[28] who suggest that the discontinuity is due to adsorption processes. A more likely explanation is that there is interaction of the oxidants with the mercury drop causing a "mercury" maxima. Adsorption reactions would not account for the current in excess of the diffusion current. No studies were made in the present work to differentiate between diffusion and kinetic control of the limiting currents. At concentrations of less than approximately 5×10^{-4} *M* the discontinuous current rise was absent and the wave appeared to be normal. However, subtraction of residual current obtained from polarogram of the supporting electrolyte showed that the apparent wave was caused by the beginning of the mercury dissolution. From this it is concluded that actual half-wave potentials of cupric and ferric ions occur at more positive potentials than +0.36 v.

Discussion

The half-wave potentials observed in acetonitrile are generally in the same order as in aqueous solution (non-complexing supporting electrolyte). Two important exceptions are copper and silver. While the reduction of silver in water occurs at such positive potentials that mercury oxidation occurs first, the reduction is observed easily in acetonitrile. An indication of the solvated nature of silver ion in acetonitrile is seen in the fact that dipyridinesilver(I) perchlorate shows the same half-wave potential as silver perchlorate (the coordinated pyridines are undoubtedly largely displaced by acetonitrile).

Stabilization of the cuprous state in acetonitrile, as indicated by the two-step reduction of cupric ion, is shown by other observations. Morgan[29] isolated cuprous nitrate tetra-acetonitrile, $CuNO_3 \cdot 4CH_3CN$, from reaction between an acetonitrile solution of silver nitrate and metallic copper.

It is of interest to compare observed half-wave potentials with calculated values. Where measurements are made with solid metal electrodes, the half-wave potential is given by the expression[14]

$$E_{1/2} \backsimeq E^0_M + E_S + \frac{0.059}{n} \log C_{satd} f_{satd}$$

The normal electrode potential is given by E^0_M, E_S is the potential of the cell, $M(s)/M^{n+}/M\text{-}(Hg)_{satd}$, and C_{satd} and f_{satd} are the concentration and activity coefficient, respectively, of the metal in the saturated amalgam. Since these last three terms are independent of solvent, calculation of half-wave potentials only requires evaluation of E^0_M.

Values of E^0_M were obtained by assuming the Nernst equation to hold, and then calculating E^0_M from e.m.f. data for the lowest concentration of solute as given in the publication by Pleskov.[11] This estimate of E^0_M should be reasonably accurate since the activity coefficient approaches unity at zero concentration.

Using Pleskov's[11] data for 5×10^{-4} *N* CdI_2 with $E = -0.7327$ v. (*vs.* $AgNO_3$ reference), E^0 is −0.626 v. For cadmium $E_S = 0.051$ v.,[30] $C_{satd} = 6.40$ moles/l.,[31] $f_{satd} = 1.15$[32] giving a calculated half-wave potential of −0.550 v. which compares favorably to the observed −0.553 v. Similar calculations can be made for zinc and lead but are not presented here since the polarographic waves are irreversible.

Calculation of half-wave potentials of some metal ions in acetonitrile from Pleskov's amalgam electrodes has been done.[7] Employing the expression developed by von Stackelberg[33] and using Pleskov's[11] potentiometric data, the half-wave potential of cesium is found to be −2.20 v., which compares well with the recalculated value, −2.23 v., given in Table II as obtained by Wawzonek and Runner.[3]

Vlcek[34] has suggested that the half-wave potential of potassium is the same in all solvents. Un-

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der this assumption, comparison of reduction of cations in differing solvents can be made by noting the difference, $\Delta E_{1/2}$, between the potassium half-wave potential and the half-wave potential of the particular metal. This is at least a reasonable approach to absolute comparison of half-wave potentials. Tabulation of these data for acetonitrile and aqueous solutions (non-complexing supporting electrolyte) shows several interesting points. Of the ions studied (outside of the alkali metals) the $\Delta E_{1/2}$ values are most similar for thallium, 1.70 v. in acetonitrile and 1.66 v. in water. This is reasonable when one considers that thallous ion does not form complex ions and presumably is not highly solvated, or at least the degree of solvation is the same in water as in acetonitrile.

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IOWA CITY, IOWA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF ARKANSAS]

The Neutral and Acid Hydrolysis of Ethyl Dibromoacetate in Acetone–Water Solvents[1]

BY FREDERICK N. HORNYAK AND EDWARD S. AMIS

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The neutral and acid hydrolysis of ethyl dibromoacetate was carried out at three temperatures and in water–acetone solvents containing various percentages of acetone. In the neutral hydrolysis the acid formed produced a departure from the first-order law at greater than 8% reaction. The acid-catalyzed runs followed the pseudo first-order law strictly for at least 85% of completion of reaction. The parameters of the Arrhenius equation are presented and discussed. The dependence of the rates on the dielectric constant of the media is compared with that of the acid hydrolysis of ethyl dichloroacetate in acetone–water solvent.

Introduction

As part of the general problem of the effect of solvent and molecular substituent changes upon reaction rate in solution, a study of the neutral and acid-catalyzed hydrolysis of ethyl dibromoacetate was carried out.

Experimental

Materials.—All water was twice distilled; the last distillation employed alkaline potassium permanganate. The water was then boiled to ensure carbon dioxide removal and was stored and delivered from vessels protected with ascarite tubes.

A. C. S. reagent grade acetone was purified according to the procedure of Åkerlöf.[2]

Ethyl dibromoacetate (product of Sapon Laboratories, Inc.) was washed briefly with concentrated sodium bicarbonate and then with calcium chloride solution. After drying over drierite, distillation at 14.5 mm. gave the ester with b.p. 81–82.5° (reported[3] 66–70° at 7 mm.); d^{22} 1.9081; $n^{22}D$ 1.4973; $n^{12.5}D$ 1.5018 (reported[4] d^{20}_{20} 1.9025; $n^{12.5}D$ 1.50167). Observed molar refraction and neutralization equivalent were 37.72 and 244 ± 2, respectively (calculated 37.86 and 246).

Barium hydroxide solutions, 0.002500 and 0.02500 *N*, were made up periodically from concentrated stock solution and were checked frequently against aliquots of standard potassium acid phthalate solutions. The hydrochloric acid solution was 0.3700 *N*. C.P. chemicals were used and all normalities were determined to four significant figures.

Methods and Apparatus.—Reaction temperatures were kept constant to ±0.03° and were determined with a NBS thermometer.

All pipets and burets were calibrated.

Hydrolysis were carried out in glass-stoppered 100-ml. volumetric flasks. By lightly greasing the stoppers (Fisher Rubber Compound Stopcock Lubricant) and fastening them down with rubber bands evaporation of solvent was made negligible. The grease was insoluble and had no apparent effect.

The reaction solution for a kinetic study was prepared as follows. Appropriate amounts of acetone, water and hydrochloric acid (if any) were weighed into a tared volumetric flask. The flask was then stoppered and placed in the constant temperature bath for several hours to reach thermal equilibrium. Weighings were made to 0.02 g. and the weight of hydrogen chloride (if any) was taken into account when calculating the weight of water present. The reaction was started by adding 10.00 ml. of a standard acetone–ester solution and adjusting to the mark with water at the temperature of the experiment. The flask was then shaken and the time noted. At convenient intervals 10.00-ml. samples were withdrawn, run into 25 ml. of ice-cold water and titrated with standard base. Sufficient accuracy in the times of starting and of sample withdrawal was easily attained because of the slowness of the reaction. The actual sample volume delivered by the pipetting procedure was checked by weight and also by titration and allowance was made in subsequent calculations.

The concentration of ester in all runs was 0.0500 molar and the concentration of hydrochloric acid in the acid runs was 0.0500 molar. The acetone percentages employed are shown in the tables of results.

In this work it was found that the standard base, during the titration of an ice-cold reaction sample, reacted in part with unhydrolyzed ester giving an acid value that was too high. It was found that identical samples of reaction mixture gave widely different acid values depending on the strength of the base used; the stronger base gave the highest value. In the titration of standard acid with standard base the addition of pure ester and acetone vitiated the results even under ice-cold conditions. An ester solution alone, without the presence of acid showed a zero acid value on titration with standard base (immediate end-point).

Because of these facts it was necessary to standardize the titration procedure and determine the errors involved. The titrating base solution was run in always at approximately the same rate and the reaction sample was stirred constantly in an ice-bath.

A series of mixtures of standard acid phthalate, acetone, water and ester were made up to correspond to compositions which would be obtained for titration at various stages of reaction. These mixtures were freshly made up and titrated ice-cold in the same manner as the actual run samples. The errors obtained were reproducible and found for acid hydrolyses to be a linear function of the amount of unhydrolyzed ester present. These corrections were applied to the actual run titrations to determine the true amount of acid present.

The acid runs employed the stronger 0.02500 *N* base and the titration error was about 5% in the early stages of reaction where the amount of unhydrolyzed ester is large.

(1) The authors wish to thank the National Science Foundation for a grant which made this research possible.

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TABLE I

NEUTRAL HYDROLYSIS, K_H IN LITERS MOLE^{-1} AND k_m IN HOUR^{-1}

Temp., °C.	Wt. % acetone	D	$k_m \times 10^6$	$k_H \times 10^6$
34.61	31.1	57.5	747	20.9
	38.7	52.8	332	10.6
	48.0	47.2	149	5.76
	77.8	29.4	6.09	0.592
35.04	58.3	40.8	53.5	2.63
44.83	31.1	54.8	1230	34.6
	38.6	50.5	563	18.1
	4.84	44.7	262	10.3
	58.1	39.0	124	6.09
	78.3	27.8	12.4	1.25
51.29	30.8	53.3	1540	43.3
	38.4	49.0	782	25.1
	47.9	43.6	372	14.5
	57.6	38.2	157	7.70
	77.2	27.4	18.9	1.83

TABLE II

ACID HYDROLYSIS, k^1 IN HOUR^{-1} AND k_a IN LITERS MOLE^{-1} HOUR^{-1}

Temp., °C.	Wt. % acetone	D	$k^1 \times 10^4$	$k_a \times 10^2$
35.04	31.1	57.4	44.2	7.34
	38.7	52.8	31.9	5.72
	47.6	47.4	23.5	4.40
	58.3	40.8	15.6	3.01
	78.6	28.8	9.45	1.88
44.83	31.0	54.8	99.1	17.4
	38.5	50.5	69.7	12.8
	47.9	45.0	49.4	9.35
	58.1	39.0	34.8	6.72
	77.6	28.2	24.9	4.95
51.29	31.0	54.2	170	31.0
	38.6	49.0	112	20.8
	48.05	43.5	84.0	16.1
	57.9	38.1	62.3	21.1
	77.6	27.2	45.2	9.00

The neutral runs employed the 0.00250 N base and the titration error was found to be less than 1%.

The pseudo first-order rate constants k_m and k^1 for neutral and acid-catalyzed runs, respectively, were obtained from plots of log $(M_\infty - M)$ against t where M and M_∞ are the corrected milliliters of standard base required for neutralization of formed acid at time t and time infinity, respectively. M_∞ was calculated.

The second-order rate constants k_H and k_a for the neutral and acid hydrolysis, respectively, were calculated employing the relationship

$$k^1 = k_a(0.0500) + k_H(H_2O)$$

activation parameters were obtained from plots of log k_H and log k_a *versus* $1/T$.

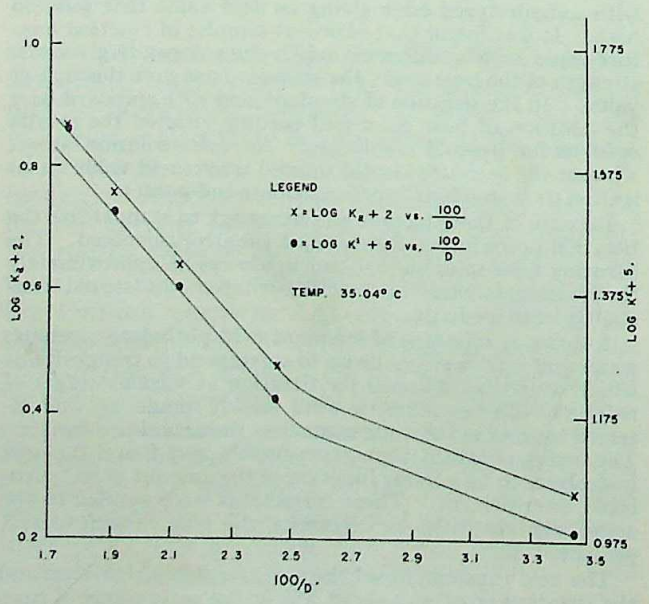

Fig. 1.

Discussion

The neutral hydrolyses proceeded very slowly so that 0.00250 N base was used to measure the production of small amounts of acid. The normality of this base could not be as accurately determined as that of the stronger base and the sensitivity of the indicator was decreased but these disadvantages were outweighed by the greatly increased accuracy of buret readings. Readings could be made to 0.1 ml. easily and end-points were easy to observe.

In the neutral hydrolyses the dibromo acid formed produced a departure from the first-order law at greater than 8% of reaction. The weak base enabled the reaction to be followed with accuracy to this small extent so that fairly good first-order constants were obtained. Acid catalysis by the dibromo acid is to be expected because the electronegative substituents make the acid very much stronger than acetic acid. The rate constants obtained varied with solvent composition and temperature in a reasonable way. Duplicate and triplicate rate constants checked to within ±5–12% generally.

TABLE III

ACTIVATION PARAMETERS[a]

Wt. % acetone	Neutral hydrolysis Log$_{10}$ Z	Neutral hydrolysis ΔE, kcal.	Acid hydrolysis Log$_{10}$ Z	Acid hydrolysis ΔE, kcal.
31	7.2	8.25	13.4	17.6
39	8.3	10.3	12.0	15.8
48	8.6	11.0	11.8	15.8
58	8.6	11.5	12.6	17.1
78	9.1	13.1	13.8	19.1

[a] Based on the second-order rate constants k_H and k_a.

The acid-catalyzed runs followed the pseudo first-order law very strictly for at least 85% of completion of reaction. Apparently the ionization of the produced dibromo acid is insignificant in the presence of the very strong hydrochloric acid. Pseudo first-order rate constants were very reproducible and duplicate runs checked within 2–5%. Also ln k_a *versus* $1/T$ plots were very accurately linear.

The activation energies for the neutral runs showed an increase with increasing acetone percentage. The statistical errors for these activation energies range from 0.9 to 2.1 kcal. per mole.

The activation energies for the acid-catalyzed runs show a minimum at about 45% acetone. This observed minimum might not be real since the statistical errors in these activation energies were from 0.3 to 0.9 kcal. per mole.

The activation energies increased as log Z increased.

In Fig. 1, log k_a and log k^1 are plotted *versus* $100/D$ for 35.04°. In this region of higher dielectric constants, these plots are straight lines of negative slope as was found by Nair and Amis[5] for the acid

[5] P. M. Nair and E. S. Amis, THIS JOURNAL, 77, 3452 (1955).

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hydrolysis of ethyl dichloroacetate in acetone–water mixtures. The present curves have a less negative slope in regions of lower dielectric constant instead of changing to a positive slope as was found by Nair and Amis.

FAYETTEVILLE, ARK.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Pyrolysis of Lead Oxalate; Isotope Effects and Product Composition

BY PETER E. YANKWICH AND JAMES L. COPELAND

RECEIVED NOVEMBER 14, 1956

The composition and isotopic constitution of the gaseous products of the pyrolysis of lead oxalate have been studied for reaction between 350 and 625°. Variations with temperature of the ratio of carbon dioxide to carbon monoxide in the product gases and of carbon isotope distribution are considered in terms of simple models in which: (a) it is assumed that the primary products are modified by a secondary reaction among themselves which competes with escape of the gaseous products from the decomposing mass, or (b) oxygen abstraction and C–C bond rupturing processes are presumed to compete. Models in group (a) are shown to correspond to temperature dependences of the molar yield ratio of gaseous products which are not in accord with observation. Consideration of models in group (b) is based primarily on the Bigeleisen–Wolfsberg treatment of three center reactions; satisfactory agreement with experiment is obtained for a model of the activated complex which includes a lead atom.

Introduction

Several investigations have been made of the products obtained when crystalline lead oxalate is decomposed thermally. At temperatures of pyrolysis above about 250° all of the carbon can be obtained as carbon dioxide or monoxide, but there is little unanimity concerning the molar ratio, Y, of these gases in the products. Maumene[1] finds $Y = 2$ and records the stoichiometry $3PbC_2O_4 = 2PbO + Pb + 4CO_2 + 2CO$, while mentioning that previous workers observed Y to be 3. Maumene reported that at higher temperatures some reduction of lead oxide to metal may occur; Sveda[2] studied the pyrolysis in an initially evacuated vessel and found that the extent of this reduction was proportional to the time of contact between solid and gaseous products of the primary reaction.

Denham[3] found that there was no reaction between the solid product (which he and Pascal and Minne[4] believed to be a lead suboxide) and the carbon monoxide produced if the total pressure was below 5 cm. at 270°; he reported $Y = 3$.

Bircumshaw and Harris[5] studied the products of the decomposition at temperatures in the range 310–470°. They found a dioxide/monoxide ratio of 2, established by X-ray and electrical conductivity measurements that the solid was a mixture of metallic lead and red tetragonal lead oxide, and observed that removal of the gaseous products by continuous pumping had only a slight effect on their composition. In a second paper[6] the kinetics of the pyrolysis was studied at temperatures between 309 and 350°. The rate data conformed to predictions based on a model in which decomposition starts at nuclei and spreads through branching chains along paths of lateral strain; the strain is relieved by the formation of Smekal cracks along which the decomposition is favored.

In the present paper we report a study of the composition and isotopic constitution of the gaseous products over the temperature range 350–625°. The study was carried out to elucidate the character of the molecular mechanism of the process, and no kinetics measurements were made.

(1) E. J. Maumene, *Bull. soc. chim.*, **13**, 194 (1870).
(2) J. Sveda, *Chem. Listy*, **17**, 47, 81, 112 (1923).
(3) H. G. Denham, *J. Chem. Soc.*, 29 (1917).
(4) P. Pascal and P. Minne, *Compt. rend.*, **193**, 1303 (1931).
(5) L. L. Bircumshaw and I. Harris, *J. Chem. Soc.*, 1637 (1939).
(6) L. L. Bircumshaw and I. Harris, *ibid.*, 1898 (1948).

Experimental

Lead Oxalate.—A slight excess of aqueous reagent oxalic acid was added slowly with constant stirring to a 1 M aqueous solution of reagent grade lead nitrate; after standing in contact with the supernatant for one hour at room temperature, the lead oxalate was removed by filtration, washed with distilled water, then dried in air for 3 hours at 110°.

Apparatus and Procedure.—The pyrolyses were carried out in a stream of dry, oxygen-free helium. The train employed was made up as follows. Sample decomposition took place in a 2 cm. i.d. Vycor tube, the second half of which passed through an electric furnace which maintained a predetermined temperature constant to 2°; the gaseous products passed first through a trap cooled in liquid nitrogen, thence to a combustion tube at 750° filled with copper oxide wire, and finally through another trap cooled in liquid nitrogen. Preliminary tests showed that carbon monoxide and carbon dioxide were separated quantitatively in the first trap at the helium flow rate employed (50 cc. per min.). In a typical experiment 0.45–0.50 g. of lead oxalate was weighed into a shallow platinum boat which was placed in the unheated end of the pyrolysis tube. The train was assembled and the helium flow maintained for one hour to remove traces of oxygen. At the start of most of the runs the pyrolysis tube was tipped, causing the boat to slide into the heated zone. Since the reaction becomes very rapid at the higher temperatures employed, a few runs in that region were made in which the contents of the boat were dumped by an externally operated tipper onto a thick platinum foil in the heated zone to ensure the most rapid possible heating to the run temperature. At 350° the decomposition is complete in 40 minutes[6]; so that no time variable would be introduced, the helium sweep was maintained for 60 minutes in all runs. The two gaseous samples were measured manometrically, then reserved for mass spectrometric analysis.

Isotope Analyses.—The procedures and calculation methods used for the carbon isotope ratio determinations have been detailed in previous publications from this Laboratory.[7,8] The final oxygen isotope ratios were obtained by applying to the observed values of the ratio $(m/q\ 46)/(m/q\ 44 + 45)$ corrections for the magnitude of $(m/q\ 45)/(m/q\ 44)$, and for daily variations in the response of the mass spectrometer; analysis showed that corrections to these ratios for incomplete resolution and the contribution to the peak at m/q 46 of the species $C^{13}O^{16}O^{17}$ (assumed

(7) P. E. Yankwich and R. L. Belford, THIS JOURNAL, **75**, 4178 (1953).
(8) P. E. Yankwich and R. L. Belford, *ibid.*, **76**, 3067 (1954).

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constant) were so small that considerable uncertainty in them produced no variation in the final corrected ratio.

Results

The corrected carbon and oxygen isotope ratios of the samples of carbon dioxide and carbon monoxide (measured in the form of the dioxide) products are given in Table I. In Table II are collected the calculated values of the ratios $R_r = (R^c_{CO_2}/R^c_{CO})$ and Y = (moles CO_2 product/moles CO product) for each run. The average values of Y and R_r are plotted against each other in Fig. 1; the horizontal

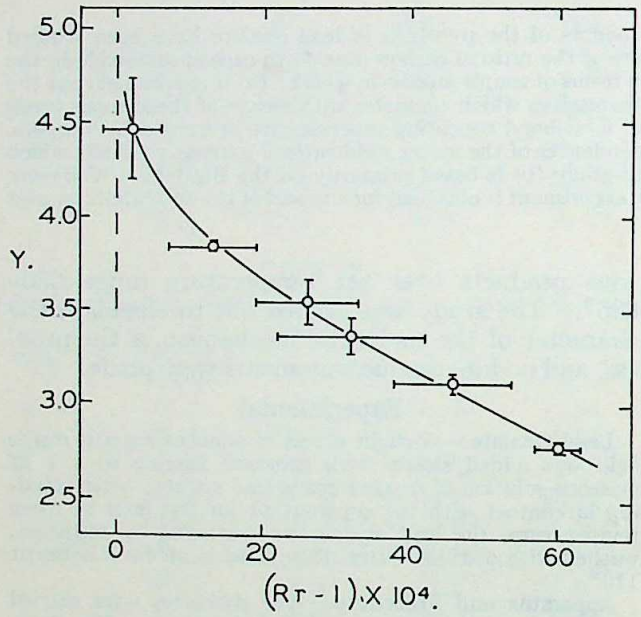

Fig. 1.—Molar ratio CO_2/CO, Y, *vs.* ratio of carbon isotope ratios, R_r.

and vertical bars represent the errors given in Table II.

Table I

Corrected Carbon (C^{13}/C^{12}) and Oxygen (O^{18}/O^{16}) Isotope Ratios of Carbon Dioxide and Carbon Monoxide Product Gases

(All R values have been multiplied by 10^6)

Temp., °C.	Run	$R^c_{CO_2}$	R^c_{CO}	$R^0_{CO_2}$	R^0_{CO}
350	7	10846[9]	10779	4257[9]	4208
	8	10848	10784	4258	4208
400	10	10864	10796	4256	4197
	11	10842	10800	4250	4193
	12	10841	10798	4255	4203
	13	10821	10775	4246	4202
450	14	10828	10805	4250	4196
	15	10833	10790	4244	4201
	16	10848	10807	4254	4201
	17	10842	10797	4253	4202
	31	10830	10810	4252	4204
500	18	10832	10803	4249	4202
	19	10835	10800	4253	4206
	20	10841	10809	4251	4201
	32	10837	10822	4251	4202
550	21	10827	10821	4244	4194
	22	10837	10814	4247	4200
	23	10835	10822	4248	4199
625	24	10828	10828	4249	4198
		10832	10828	4246	4198
Tank CO_2		10789		4180	

(9) The uncertainty in a ratio is ±2 or less in the last digit.

Table II

Values of the Ratios $R^0_r = (R^c_{CO_2}/R^c_{CO})$ and Y = (Moles CO_2/Moles CO) for the Gaseous Products

Temp., °C.		R_r	Y
350		1.0062	2.79
		1.0059	2.75
	Av.	1.0060 ± 0.0003[10]	2.77 ± 0.02[11]
400		1.0063	3.06
		1.0039	3.14
		1.0040	3.07
		1.0043	3.16
	Av.	1.0046 ± 0.0008	3.11 ± 0.04
450		1.0021	3.52
		1.0040	3.31
		1.0038	3.32
		1.0042	3.19
		1.0019	3.44
	Av.	1.0032 ± 0.0010	3.36 ± 0.10
500		1.0027	3.43
		1.0032	3.41
		1.0030	3.60
		1.0014	3.73
	Av.	1.0026 ± 0.0007	3.54 ± 0.12
550		1.0006	3.80
		1.0021	3.87
		1.0012	3.81
	Av.	1.0013 ± 0.0006	3.83 ± 0.03
625		1.0000	4.73
		1.0004	4.19
	Av.	1.0002 ± 0.0004	4.46 ± 0.27

At the helium flow rate of 50 cc. per min. the mean contact time of product gases with the decomposing sample is about 8 seconds; the residence time of the burning carbon monoxide in the combustion tube is 60–65 seconds. Titani, Nakata and Kanome[12] observed the exchange of O^{18} between carbon dioxide and cupric oxide after a contact time of 75 seconds to be 15% complete at 430° and 48% complete at 530°.[13] It is probable then that the carbon dioxide obtained from combustion of the product carbon monoxide is in exchange equilibrium with the copper oxide with respect to O^{18}; if this situation obtains, the differences between R^0_{CO} and the value of $R^0_{CO_2}$ for tank carbon dioxide should be constant. Examination of the data in Table I shows this conclusion to be valid, except for the runs at 350°.

While the oxygen isotope ratio data for carbon monoxide product furnish no useful information about the pyrolysis, those for carbon dioxide may if there is no appreciable exchange between dioxide and monoxide in the pyrolysis tube. The carbon dioxide–carbon monoxide exchange is extremely slow at 800° in quartz vessels[14]; any exchange under the conditions of our experiments presumably would be catalyzed by the decomposing solid.

(10) Includes the uncertainty in the isotope ratios.

(11) Average deviation from the mean.

(12) T. Titani, S. Nakata and A. Kanome, *Bull. Chem. Soc. Japan*, **17**, 288 (1942).

(13) Exchange of about 40% was observed at 580 and 630°, but their analytical method was not of high precision. For our purpose, the important fact is that the exchange is reasonably rapid at temperatures above 400°.

(14) T. H. Norris and S. Ruben, *J. Chem. Phys.*, **18**, 1595 (1950); F. Hovorka, *Bull. Chem. Soc. Japan*, **26**, 165 (1953).

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This point can be tested by comparing the observed values of R_r as a function of temperature with those calculated for exchange equilibrium from the data of Urey[15]; since the mechanism of the exchange involves oxygen atom transfer, carbon and oxygen isotope exchanges must occur simultaneously.[16] It is observed that, at all temperatures, the value of R_r is much smaller than that calculated for complete exchange (at 350°: obsd. 1.0060, calcd. 1.0275; at 625°: obsd. 1.0002, calcd. 1.0160); further, if the exchange were very rapid at the higher temperatures employed, one would expect a plot of ln R_r *versus* $1/T$ to exhibit a positive second derivative since the value of R_r must approach from below that calculated for complete exchange. We conclude that exchange of carbon and oxygen between carbon dioxide and carbon monoxide products is inappreciable under the conditions of the pyrolysis.

Discussion

Variation of Y with Temperature.—While it has been found that the proportions of the product gases are altered if the pressure in the system is maintained at a low value by pumping, the data of Bircumshaw and Harris[5] indicate that the effect is small compared with the variations observed in this research. The kinetics study of the same workers[6] shows that the reaction does not take place in the bulk of the crystals, but in cracks on the surfaces and at imperfections. Consider two situations in which the primary products are modified by a secondary *reaction* among themselves, which competes with *escape* of the gaseous products from the decomposing mass: case I—lead and carbon dioxide primary products, subsequent partial reduction of the carbon dioxide to the monoxide; case II—a simple oxygen abstraction primary process yielding equimolar amounts of lead oxide and the two carbon oxides, subsequent partial oxidation of carbon monoxide to the dioxide. Ignoring the isotope effect, assume that both the *reaction* and *escape* processes may be considered pseudo-first order with respect to carbon; then define the appropriate rate constants as k_r and k_e, respectively, and let $(k_e/k_r) = (1 - \alpha)/\alpha$. For case I, $Y = (1 - \alpha)/\alpha$; for case II, $Y = (1 + \alpha)/(1 - \alpha)$. It seems likely that the activation energy of the forward or reverse of the reaction $Pb(s) + CO_2(g) = PbO(s) + CO(g)$ is of the order of 40–50 kcal. per mole. The escape process may be similar to any of these: simple unactivated diffusion through the interstices of the decomposing powder mass, activated surface diffusion, desorption from an original chemisorbed state, or diffusion through the bulk of individual crystallites from a depth of at least a few tens of ion layers; the maximum apparent activation energy associated with any of these is of the order of 15–20 kcal. per mole, which would require that α increase rapidly with increasing temperature. For case I, Y would decrease with increasing temperature; for case II, Y would increase very rapidly with temperature. Neither situation corresponds to that observed, so we reject those models which require competition between escape and secondary reaction.

It is possible that the mechanism of the decomposition involves an intra-ionic competition between two processes, one which results in conversion of an oxalate ion into two molecules of carbon dioxide and another, with a somewhat lower activation energy, which results in the formation of one molecule each of carbon monoxide and dioxide. In suggesting such a model we presume that no chemical process occurs during the diffusion of the product gases out of the solid mass. If the intra-ionic reactions are assumed to be first order, and the specific rate constants are k and k', respectively, then $Y = (2k + 4k')/(4k')$ and the activation energy difference obtained from the observed temperature dependence of Y is 2.7 ± 0.1 kcal. If the required electron transfer from oxalate ion to lead takes place before gross bond ruptures within the ion, this activation energy difference can be related to the C–C bond energy in the first reaction and the energy of the C–O bond, or of motion of O in a triad such as C–O–Pb, in the second. In the absence of more information we conclude only that the second reaction probably involves something more complex than rupture of a simple C–O linkage since the activation energy difference in that case would be more than a few kcal. per mole.

Calculation of Isotope Effects through Two-center and Three-center Models.—Methods for the calculation of the ratios of isotopic rate constants have been developed by Bigeleisen[17] extending the work of Bigeleisen and Mayer.[18] The usual application, which has been successful in a number of cases,[19] involves the assumption of a two-center model, the effective masses of the activated molecules along the coördinate of decomposition in the transition state being calculated by the method of Slater.[20] As a refinement, Bigeleisen and Wolfsberg[21,22] derived these effective mass ratios, μ, for the three-center system A–B–C, in which a bond between atoms B and C is broken and a bond between atoms A and B is formed. The final corrected formula for these temperature independent factors[22] involves a term whose coefficient is (−cos ABC), and depends on atomic masses and a parameter p which, for this situation, is the square of (amount of bond formation between A and B)/(amount of bond extension between B and C). By analogy, it follows that the original formula[21] which was incorrect for the three-center system formulated above (and in which the sign of the cosine term is positive), applies to the three-center system in which the motion about B is symmetrical rather than asymmetrical, *i.e.*, to the

(15) H. C. Urey, *J. Chem. Soc.*, 562 (1947).

(16) Use of figures for C^{12} and C^{13} is required because the carbon isotope content of the carbon monoxide fraction is unaffected by combustion and the comparison of either carbon or oxygen isotope contents of carbon dioxide and carbon monoxide by direct mass spectrometric measurements is very imprecise due to differences between these two gases of the effect of isotope substitution upon ionization probabilities.

(17) J. Bigeleisen, *J. Chem. Phys.*, **17**, 675 (1949).

(18) J. Bigeleisen and M. G. Mayer, *ibid.*, **15**, 261 (1947).

(19) J. Bigeleisen, *J. Phys. Chem.*, **56**, S23 (1952).

(20) N. B. Slater, *Proc. Roy. Soc.* (*London*), **194**, 113 (1948).

(21) J. Bigeleisen and M. Wolfsberg, *J. Chem. Phys.*, **21**, 1972 (1953).

(22) J. Bigeleisen and M. Wolfsberg, *ibid.*, **22**, 1264 (1954).

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three-center situation in which both A–B and B–C bonds are being made or broken.[23]

In application of the three-center model it is assumed that a single vibration gives rise to the motion in the reaction coördinate, most simply either the symmetric or asymmetric mode in the imaginary triatomic system ABC.

In an earlier publication[24] it was shown that one could obtain, from isotopic rate constant ratio data taken over a sufficiently wide range of temperatures, a value for μ of reasonable precision. Since knowledge of this quantity permits direct computation of the temperature dependent part of such ratios, it is of interest to speculate on the information concerning the differences between the vibrational motions of the reactant and activated states which can be derived from such calculated results.

As detailed by Bigeleisen and Wolfsberg,[21] the vibration lost upon activation generates the quantity μ. Now, it will be possible usually to calculate the temperature dependent part of a ratio of isotopic rate constants in terms of a single frequency, which may have no relation whatsoever to any actual vibrational frequency in the reactant molecule or activated complex, and its isotopic companion, *i.e.*, in terms of an ω and a value for the ratio ω/ω_i (the subscript i denoting the frequency in the molecule labeled with the heavier atom of the isotopic pair).[25] Two simple approaches suggest themselves. First, one could set ω/ω_i equal to μ, then calculate the value of ω required to reproduce the observed temperature dependence; this is what has been done in some two-center cases.[8,19] Second, one could set up a three-center or more complicated model for the reaction, and employing distances, angles and force constants of reasonable magnitudes, compute a set of ω's and ω_i's. An appropriate value of ω/ω_i is estimated by comparison of the various normal modes of the model with the reaction coördinate motion assumed; the estimated ω/ω_i is then used in the calculation of a value for the ω to be lost upon activation which will reproduce the observed temperature dependence. The utility of the calculation lies in the possible similarity of this artificial ω to that for some normal mode in the model or the actual reactant molecule which involves motion like that in the assumed reaction coördinate. Where such similarity is observed one would take some confidence in the choice for reaction coördinate motion; were such correspondence not observed, the calculation would not have yielded a helpful result.

Intra-ionic Competition Models.—The simplest model for the decomposition of oxalate ion into two molecules of carbon dioxide is the two center C–C system; the competing process yielding carbon monoxide and carbon dioxide will be treated as a C–O two-center system in which C–C bond rupture follows the rate-determining oxygen abstraction, as a C–C–O three-center system involving symmetric motion, and as the O–C–O or C–O–Pb triads involving asymmetric motion. The following notation is adopted for the several rate constants

$$\begin{array}{l} C^{12}OO^- \xrightarrow{k_4} C^{12}O + C^{12}O_2 \\ \quad\vdots \\ C^{12}OO^- \xrightarrow{k_1} 2C^{12}O_2 \end{array} \qquad (1)$$

$$\begin{array}{l} C^{12}OO^- \xrightarrow{k_4'} C^{12}O + C^{13}O_2 \\ \quad\vdots \\ \quad\vdots \xrightarrow{k_2} C^{12}O_2 + C^{13}O_2 \\ \quad\vdots \\ C^{13}OO^- \xrightarrow{k_5} C^{13}O + C^{12}O_2 \end{array}$$

It is impossible to obtain the appropriate ratios of these isotopic rate constants from the data available. We choose to assume values for k_1/k_2 and with the average values for R_r at each temperature calculate k_4/k_5, or other related ratio; we then compute the temperature independent part of k_4/k_5, examine its value in terms of some simple models, then carry out a very approximate treatment of the temperature dependent part.

Where a three-center model for the process competing with C–C bond rupture contains only one of the carbon atoms, $k_4/k_4' = 1$; if both of the carbon atoms are involved, as in a C–C–O system, this ratio will depend upon the relative involvement of the C–C and C–O bonds in the reaction coördinate motion, *i.e.*, upon the value of the parameter p. For $p = 0.3$ or less, the values of μ for k_4/k_4' are not very different from unity (Fig. 2, curve C), which suggests that k_4/k_4' is near unity in this range; in the whole range of p from 1 to ∞ the ratio of the μ's for k_4/k_4' and k_4/k_5 (Fig. 2, curves C and B, respectively) deviates from unity less than does that for k_4/k_4' at $p = 0.3$. As a matter of convenience, then, we make the following approximations: for p small compared with unity, $k_4/k_4' = 1$ and $k_4/k_5 \neq 1$; from $p = 1$ to ∞, $k_4/k_4' = k_4/k_5 \neq 1$.

In performing the integrations and in the equations below for R_r we employ the approximation $Y = 1 + (k_1/2k_4)$; this generates an error in R_r smaller than that due to imprecisions in the mass spectrometric measurements. For situations where one carbon atom is involved in the three-center model, where a C–O two-center model is considered, or where p is small for the C–C–O three-center model

$$R_r = \frac{C\left[\frac{M}{D}+2\right]\left[2A_0\left(\frac{M}{D}+\frac{2}{C}+2\right)+B_0(M+4)\right]}{\left[2A_0(M+2)\left(\frac{M}{D}+\frac{2}{C}+2\right)+B_0(M+4)\left(\frac{M}{D}+\frac{2}{C}\right)\right]} \qquad (3)$$

where $M = k_1/k_4 = 2(Y-1)$, $D = k_1/k_2$, $C = k_4/k_5 = k_4'/k_5$, A_0 = mole fraction of C^{12}–C^{12} oxalate in the original material, and B_0 = the corresponding mole fraction for C^{12}–C^{13} oxalate.[26] For the three center C–C–O model with p between 1 and ∞

(23) J. Bigeleisen, *Can. J. Chem.*, **30**, 443 (1952).

(24) P. E. Yankwich and H. S. Weber, THIS JOURNAL, **78**, 564 (1956).

(25) This statement is a generalization to complicated models of a practice already found to be successful in two-center systems[19]: there a stretching frequency of the bond ruptured is presumed lost and, following the diatomic molecule argument,[20] ω/ω_i is taken as the ratio of the reduced masses of the imaginary triatomic.

(26) Neglect of the oxalate species C^{13}–C^{13} introduces imperceptible error.

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$$R_r = \frac{\left[\frac{M}{D}+\frac{2}{C}\right]\left[2A_0\,C\left(\frac{M}{D}+\frac{4}{C}\right)+B_0(M+4)\right]}{\left[2A_0(M+2)\left(\frac{M}{D}+\frac{4}{C}\right)+B_0\left(\frac{M}{D}+\frac{2}{C}\right)(M+4)\right]} \quad (4)$$

where $C = k_4/k_5 = k_4/k_4'$, but the other symbols have the same meaning as in equation 3.

In Fig. 3 are plotted as functions of temperature values of k_4/k_5 derived from the experimental data by application of equations 3 and 4; curves C and C′ show the relative insensitivity of the k_4/k_5 values to that assumed for the frequency of the C–C stretching vibration. The temperature dependence of k_4/k_5 as graphed in curve A is very large for an isotope effect of that magnitude; further, the values of μ obtained from the curve range smoothly from 1.009 at $(1000/T) = 1.5$ to 1.018 at $(1000/T) = 1.1$. The temperature dependent part of k_4/k_5 calculated by equation 4 exhibits a similar anomalous dependence upon temperature. For these reasons we reject the C–C–O three-center model involving asymmetric motion and large values of p.

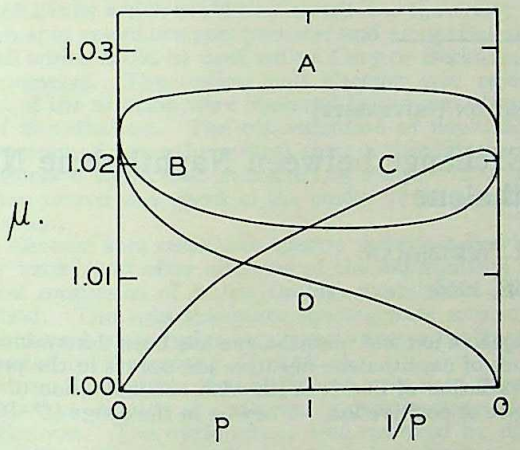

Fig. 2.—Temperature-independent factor, μ, in isotopic rate constant ratio as a function of p.[21] For asymmetric motion about B, curves A and D:

$$\mu = \left[\frac{(m_B^{-1}+m_C^{-1})+p(m_B^{-1}+m_A^{-1})-2p^{1/2}m_B^{-1}(\cos ABC)}{(m_{B_i}^{-1}+m_{C_i}^{-1})+p(m_{B_i}^{-1}+m_{A_i}^{-1})-2p^{1/2}m_{B_i}^{-1}\times(\cos A_iB_iC_i)}\right]$$

for symmetric motion, curves B and C, the minus sign to the cos term is replaced with +. Curve A, O–C–O system: $ABC = A_iB_iC_i = 120°$; $m_A = m_{A_i} = m_O = m_{C_i} = 16$; $m_B = 12$, $m_{B_i} = 13$. Curve B, C–C–O system: $ABC = A_iB_iC_i = 120°$; $m_A = m_{A_i} = m_B = 12$; $m_{B_i} = 13$; $m_C = m_{C_i} = 16$. Curve C, C–C–O system: $ABC = A_iB_iC_i = 120°$; $m_A = m_B = m_{B_i} = 12$; $m_{A_i} = 13$; $m_C = m_{C_i} = 16$. Curve D, Pb–O–C system: $ABC = A_iB_iC_i = 180°$; $m_A = m_{A_i} = 207$; $m_B = m_{B_i} = 16$; $m_C = 12$, $m_{C_i} = 13$.

We consider seriatim the four models described above for the oxygen atom abstraction process competing with simple C–C bond rupture. The values of μ obtained for k_4/k_5 from curves C and C' are 1.0138 and 1.0134, respectively; if these values are assumed for ω/ω_i, the artificial frequency ω is calculated to be 1220 cm.$^{-1}$ for curve C and 1230 cm.$^{-1}$ for curve C′. Each of these groups of μ, ω/ω_i and ω values reproduces the plot of calculated k_4/k_5 within ± 0.0005 over the temperature range covered by the experiments. The C–C stretching

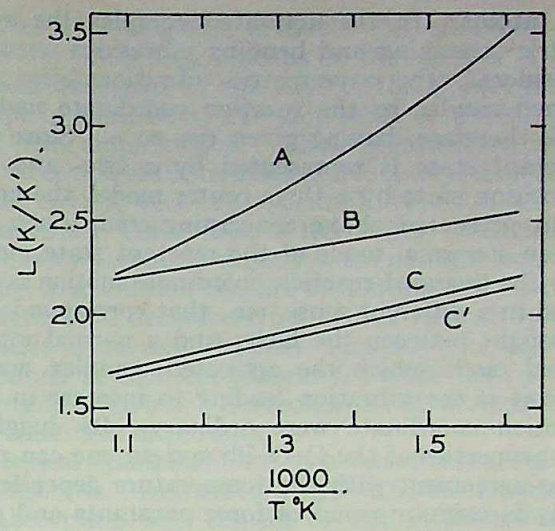

Fig. 3.—Calculated isotopic rate constant ratios; $L(k/k')$ *versus* $1000/T$°K., $L = 100\ ln$. Curve A, k_4/k_5 by equation 4; values for k_1/k_2 taken from curve B. Curve B, k_1/k_2, two-center model; $\mu = \omega/\omega = 1.0198$, $\omega_{C-C} = 850$ cm.$^{-1}$. Curve C, k_4/k_5 by equation 3; values for k_1/k_2 assume $\omega_{C-C} = 850$ cm.$^{-1}$. Curve C′, k_4/k_5 by equation 3; values for k_1/k_2 assume $\omega_{C-C} = 750$ cm.$^{-1}$.

force constant in oxalate ion[27] leads to a calculated stretching frequency near 700 cm.$^{-1}$, and we adopt a value of 1.014, for the μ of k_4/k_5. The values of μ for the C–O two-center system and for asymmetric motion in the O–C–O system with bond angle (120°) near that observed for crystalline oxalates (Fig. 2, curve A) are equal to or greater than 1.0227, leading to rejection of these models. The calculated μ for symmetric motion in the C–C–O system (Fig. 2, curve B) is close to 1.014 for values of p in the vicinity of unity; however, the original approximations leading to equations 3 and 4 require that p be less than 0.2–0.3 in the present instance, so this model is unsatisfactory. Consideration of the vibrations of C–C–O would lead us to the same end, for with force constants of reasonable magnitude chosen for this fragment of the oxalate ion a temperature dependent part of k_4/k_5 is predicted which is much larger at all temperatures than that "observed" (*i.e.*, than that calculated on the basis that k_1/k_2 is appropriately estimated in terms of the C–C two-center model).

We consider finally the linear C–O–Pb triad, for which values have been plotted in Fig. 2, curve D, the motion assumed being asymmetric. In this case we are not limited by the kinetics analysis to p values in any particular range, and the calculated value of μ for the system becomes 1.014 near $p = 0.3$, which implies that the amount of bond extension between C and O is about twice the amount of bond formation between O and Pb. This bond involvement situation seems reasonable for such an oxygen atom transfer. Less clarity is evident when we consider the temperature dependent part of k_4/k_5 which one calculates for this model. The *reactant* state requires consideration only of the stretching vibration between the carbon and oxy-

(27) F. Douville, C. Duval and J. Lecomte, *Bull. soc. chim. France*, **9**, 548 (1942); see also H. Murata and K. Kawai, *J. Chem. Phys.*, **25**, 589 (1956).

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gen atoms. In the activated complex the symmetric stretching and bending vibrations must be considered, the asymmetric vibration being assumed similar to the reaction coördinate motion and, therefore, having given rise to μ. Since the reactant state is represented by a two- and the transition state by a three-center model, the argument presented above concerning comparison between a normal mode of the reactant state model and the assumed reaction coördinate motion is applied in a different sense, *viz.*, that correspondence is sought between the latter and a normal vibrational mode which the activated complex would exhibit *if* the vibration leading to increase in the reaction coördinate were ordinary. By juggling the properties of the C–O–Pb system one can produce agreement with the temperature dependence of k_4/k_5 using a group of force constants and distances having reasonable magnitudes, provided that the asymmetric normal mode is selected as the reaction coördinate motion.

An alternate choice for the process leading to C–C bond rupture is asymmetric motion in the three-center system C–C–O, bond extension taking place between C and C, and bond formation between C and O. In effect this adds still another parameter to the over-all picture, *i.e.*, p for this triad, and does not further illuminate the situation.

In Table I the total change in $R^0_{CO_2}$ is only $(11 \pm 5) \times 10^{-6}$; for none of the models considered above is the change predicted in O^{18} content of product carbon dioxide outside the limits defined by this figure. Thus the O^{18} isotope effect is not a useful adjunct to evaluation of these models.

Acknowledgment.—We are indebted to Mrs. Beverly Thomas for the mass spectrometric determinations, and to Professor H. S. Gutowsky and Dr. Martin Karplus for stimulating discussion. Dr. James Y. Tong and the staff of the University of Illinois Digital Computer Laboratory have performed calculations which permitted checking of several ideas. This research was sponsored by the U. S. Atomic Energy Commission.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE WASHINGTON UNIVERSITY]

Electron Spin Resonance Study of the Electron Exchange between Naphthalene Negative Ion and Naphthalene[1]

BY R. L. WARD[2] AND S. I. WEISSMAN

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The rate of the electron exchange reaction between naphthalene negative ion and naphthalene has been determined by a spectroscopic method. Broadening of the electron spin resonance lines of naphthalene negative ion occurs in the presence of naphthalene. Bimolecular rate constants are deduced from the variation of line breadth with concentration of added naphthalene. The rate constants vary with solvent and with the choice of positive ion. They lie in the range 10^7–10^9 liter mole^{-1} sec.$^{-1}$.

Introduction

The rate of a chemical reaction is usually determined by a sequence of measurements in time of properties which vary as the reaction proceeds. Such measurements yield directly the net changes in the quantities of reactants and products. Individual rates of production and consumption are inferred from the net rates and these inferred rates are sometimes subject to considerable uncertainties. Direct determination of rates of production and consumption of participants in a reaction has become possible in certain cases by the recent development of radiofrequency and microwave spectroscopic techniques of high resolving power.

The measurements depend on the fact that the shape of a spectroscopic line associated with a transition between a pair of states is affected by the mean life of the states. The essential ideas involved in the relations between lifetimes and line breadths were worked out by Lorentz in his treatments of the effects of collisions on the breadth of spectral lines.[3] Many authors have further developed the subject.[4–11] The theoretical treatment of P. W. Anderson[8a] appears to be the most readily applicable to the interpretation of the kinds of experiments which we shall describe here.

These experiments consist of observations of the electron spin resonance spectra of naphthalene negative ion (to be referred to as naphthalenide) in the presence of naphthalene.

In the concentration range 10^{-4}–10^{-3} M in tetrahydrofuran (THF) or 1,2-dimethoxyethane (DME), the spectrum of naphthalenide consists of a set of seventeen hyperfine components extending over a field interval of 27.2 oersteds. The breadth of each line is about 0.9 oersteds between points of extreme slope. This description applies to the spectrum of lithium, potassium, rubidium or cesium naphthalenide. Sodium naphthalenide, on the other hand, behaves differently. In DME its spectrum is

(1) This research was supported in part by the United States Air Force through the Office of Scientific Research of the Air Research and Development Command.

(2) E. I. du Pont de Nemours Post-Graduate Fellow, 1955–1956.

(3) H. A. Lorentz, *Proc. Acad. Amst.*, **8**, 591 (1906).

(4) (a) V. Weisskopf, *Z. Physik.*, **75**, 287 (1932); (b) J. H. Van Vleck and V. Weisskopf, *Rev. Mod. Phys.*, **17**, 227 (1945).

(5) H. M. Foley, *Phys. Rev.*, **69**, 616 (1946).

(6) H. S. Gutowsky and A. Saika, *J. Chem. Phys.*, **21**, 1688 (1953).

(7) P. W. Anderson and P. R. Weiss, *Rev. Mod. Phys.*, **25**, 269 (1953).

(8) (a) P. W. Anderson, *J. Phys. Soc. Japan*, **9**, 316 (1954); (b) R. Kubo and K. Tomita, *ibid.*, **9**, 888 (1954).

(9) D. Pines and C. P. Slichter, *Phys. Rev.*, **100**, 1014 (1955).

(10) J. T. Arnold, *ibid.*, **102**, 136 (1956).

(11) H. M. McConnell and H. Weaver, *J. Chem. Phys.*, **25**, 307 (1956).

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similar except for a markedly greater line breadth to that of the other salts, while in THF it is completely different in structure.[12] At concentrations lower than 10^{-5} M the normal spectrum of seventeen lines is further resolved into one of twenty-three lines. The contribution of each of the protons in naphthalenide to the hyperfine splitting has been determined.[12]

As naphthalene is added to a solution of naphthalenide, a broadening of the hyperfine components of the ion occurs.[13] As more naphthalene is added, the lines merge into a single broad band which in some cases continues to broaden with further addition of naphthalene and in others becomes narrower. From the broadening at the lower concentration of added naphthalene a rate constant for the electron exchange reaction between naphthalene and naphthalene negative ion may be obtained.

Experimental Methods

Solutions of naphthalenide salts were prepared in high vacuum by methods already described.[14] The apparatus included a tube which could be inserted into the cavity of the electron spin resonance spectrometer and an optical absorption cell which could be used with a Cary or Beckman spectrophotometer. The optical and electron spin resonance spectra of the solution were observed before and after addition of naphthalene. The concentration of naphthalenide was determined from the optical spectra through the use of the extinction coefficients measured by Paul.[15] The optical spectrum served as a check of the purity of the naphthalenide solution.

The electron spin resonance spectra were recorded immediately before and after addition of the naphthalene under identical conditions of cavity tuning, modulation and amplification. The spin resonance spectra were measured at nine thousand megacycles in a spectrometer designed and constructed by Professor J. Townsend.

When small amounts of naphthalene were used they were introduced as aliquots of a solution in cyclohexane of known concentration. The cyclohexane was removed by distillation. When large amounts of naphthalene were required, they were purified and introduced into the apparatus by the methods described by Paul. The naphthalene was contained in an evacuated side arm separated from the rest of the apparatus by a break seal. The concentration of naphthalene, when it could not be added in known amount at the beginning of the experiment, was determined by analysis after completion of the spectroscopic measurements.

Results and Discussion

The small broadenings of the hyperfine components which occur at low naphthalene concentrations are not easily determined by direct measurement of line width. They are better determined indirectly from the intensities of the lines. The spin resonance spectra were recorded as derivative of absorption X'' with respect to magnetic field H against the field. It may be shown that the intensity of a single peak as measured by the difference in values of dX''/dH at maximum and minimum varies inversely as the square of the line breadth, provided the shape of the line remains unchanged, *i.e.*, that the absorption may be represented by a single function of field $X''[(H - H_0)/\delta H]$ where H_0 is the field at the center of the line and δH is a line breadth. In addition, the intensity of the line depends on the number of free radical molecules in the cavity, the Q and filling factor of the cavity, the amplitude of modulation and the amplification. These parameters, with the exception of the number of free radical molecules in the cavity, were kept constant in each of our experiments. The number of free radical molecules in the cavity decreased slightly when naphthalene was added to a solution because of dilution and because of occasional decomposition of free radical by impurities in the naphthalene. This decrease was determined in each experiment from the optical absorption spectrum. Correction for it was made in the treatment of the data.

Typical examples of the observed effects are given in Figs. 1–3. In each case, dX''/dH, the derivative of absorption with respect to field is plotted as a function of field H. In Fig. 1 is shown the effect of addition of naphthalene at 0.103 M to a solution of potassium naphthalenide 1.36×10^{-3} M in THF. A small broadening results. It is observed in two ways. The intensities of the individual peaks are reduced and the resolution of adjacent peaks is diminished. While the derivative changes signs between all pairs of adjacent peaks in the unbroadened spectrum, it does not do so in the broadened spectrum.

In Fig. 2 is shown the effect of addition of naphthalene at 0.218 M to a solution of potassium naphthalenide at 1.4×10^{-3} M in DME. An example of exchange narrowing is shown in Fig. 3.

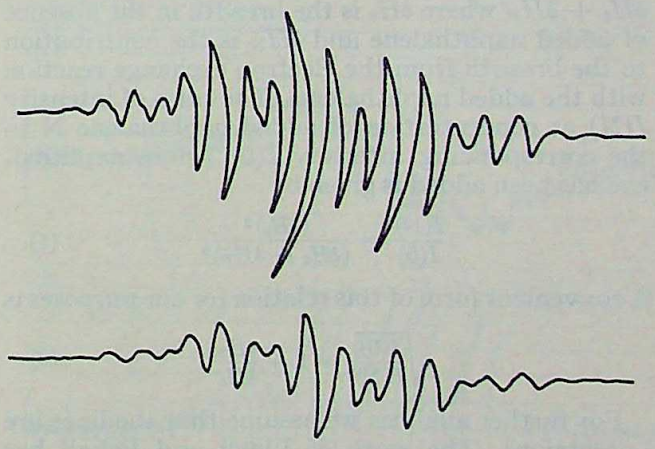

Fig. 1.—Spin resonance spectrum of 1.36×10^{-3} M potassium naphthalenide in THF: above, no added naphthalene; below, naphthalene added at 0.103 M.

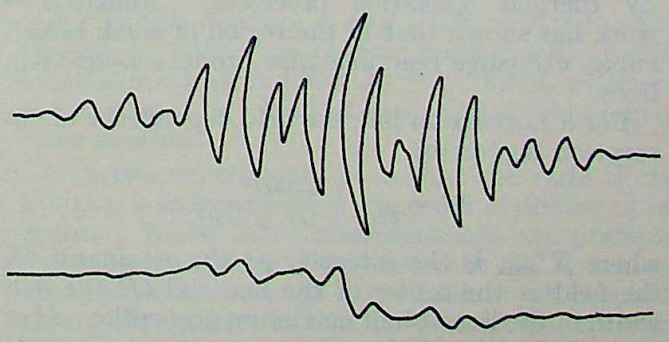

Fig. 2.—Spin resonance spectrum of 1.4×10^{-3} M potassium naphthalenide in DME: above, no added naphthalene; below, naphthalene added at 0.218 M.

(12) T. R. Tuttle, R. L. Ward and S. I. Weissman, *J. Chem. Phys.*, **25**, 189 (1956).

(13) R. L. Ward and S. I. Weissman, THIS JOURNAL, **76**, 3612 (1954).

(14) D. E. Paul, D. Lipkin and S. I. Weissman, *ibid.*, **78**, 116 (1956).

(15) D. E. Paul, Ph.D. thesis, Washington University, 1954.

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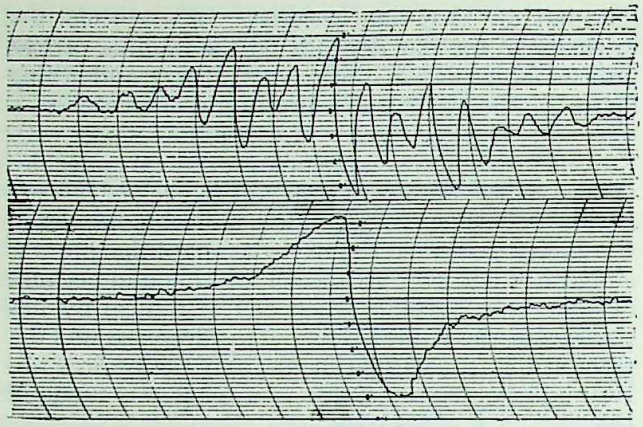

Fig. 3.—Spin resonance of 1.0×10^{-3} M lithium naphthalenide in THF: above, no added naphthalene; below, naphthalene added at 0.405 M.

Here naphthalene at 0.405 M was added to a solution of lithium naphthalenide at 1.0×10^{-3} M in THF.

From the spectra, of which those described in the preceding paragraph are typical, we wish to deduce information concerning the electron exchange reaction. We assume that in the region of small line broadenings (broadenings small compared with the separation betweeen lines), the contributions to the line breadth from individual broadening mechanisms are additive. This assumption corresponds to the more familiar one of additivity of rates.

We write, then, for the breadth of a line $\delta H = \delta H_0 + \delta H_N$ where δH_0 is the breadth in the absence of added naphthalene and δH_N is the contribution to the breadth from the electron exchange reaction with the added naphthalene. The ratio of intensity $I(N)$ at concentration of added naphthalene N to the corresponding intensity $I(0)$ before naphthalene has been added is given by

$$\frac{I(N)}{I(0)} = \frac{(\delta H_0)^2}{(\delta H_0 + \delta H_N)^2} \qquad (1)$$

A convenient form of this relation for our purposes is

$$\sqrt{\frac{I(0)}{I(N)}} = 1 + \frac{\delta H_N}{\delta H_0} \qquad (2)$$

For further analysis we assume that the lines are Lorentzian. The work of Lloyd and Pake[16] has shown that in dilute solutions of the free radical peroxylamine disulfonate the lines are close to Lorentzian and that their breadth is accounted for by thermal relaxation processes. Anderson's[8a] work has shown that in the region of small broadening, exchange reactions also produce Lorentzian lines.

For a Lorentzian line the field dependence of absorption is given by

$$X'' = \frac{X''_{max}\delta H^2}{\delta H^2 + (H - H_0)^2}$$

where X''_{max} is the intensity at the maximum, H_0 the field at the center of the line and δH the half width of the line at half maximum absorption. H in oersteds is related, for a pure electron spin resonance of the type studied here to the frequency V by

$$V = \frac{g\mu_0 H}{h} = 2.83 \times 10^{4} H$$

g is the spectroscopic splitting factor for an electron spin, μ_0 is the Bohr magneton, h Planck's constant.

Anderson's theory which is based on a frequency modulation model (as well as the theories based on the Bloch equations) indicate that in the region of line broadenings small compared with the separation between lines, the contribution to the line breadth δV of the exchange process is given by

$$\frac{1}{\tau} = 2\pi\delta V \qquad (3)$$

where τ is the mean time between electron exchanges, and δV is the half width at half maximum. In Anderson's theory the assumption is made that the exchange process is Markoffian.[17] This assumption seems to be a reasonable one. We should emphasize Anderson's result that the lines are Lorentzian with contributions to the breadth δV given by the last equation only when the mean frequency of exchange $1/\tau$ is small compared with $V_i - V_j$ where V_i and V_j are the frequencies of adjacent lines. When $1/\tau > V_i - V_j$ exchange narrowing may occur.

In naphthalene negative ion each line in the spectrum arises from an electron spin transition in a molecule of specified proton spin quantum numbers. Although there are eight protons, because of symmetry only two proton quantum numbers—M_α, the sum of the projections on the field of the spins of the α protons, and M_β, a similar sum for the β protons—fix the position of the electron spin resonance line. When the electron jumps from one naphthalene to another, it usually finds different values M_α, M_β in the second site from the first.

The central peak in the hyperfine pattern of naphthalene negative ion arises from electron spin transitions in molecules with $M_\alpha = M_\beta = 0$. This peak is the most intense one in the spectrum and it is single. The data to be presented in the following paragraphs are obtained almost exclusively from this peak.

If τ_{N^-} is the mean time between exchanges for a naphthalene negative ion, and τ_N the corresponding time for naphthalene, for a bimolecular exchange where k is the rate constant and (N) and (N^-) are concentrations of naphthalene and naphthalene negative ion

$$\frac{(N^-)}{\tau_{N^-}} = \frac{(N)}{\tau_N} = k(N)(N^-)$$

Hence

$$\frac{1}{\tau_{N^-}} = k(N); \quad \frac{1}{\tau_N} = k(N^-)$$

If ΔH_N is the line breadth as measured between points of extreme slope

$$\frac{1}{\tau_{N^-}} = (2\pi)(2.83 \times 10^{6}) \frac{\sqrt{3}}{2} \Delta H_N = k(N)$$

($\sqrt{3}/2$ is the proportionality factor between half width at half maximum and width between points of extreme slope.) We then find a relationship between the line breadth (between points of extreme

(16) J. P. Lloyd and G. E. Pake, *Phys. Rev.*, 94, 579 (1954).

(17) An essential feature of a Markoffian process is that the probabilities of transition at a given time do not depend on past history.

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slope) produced by exchange, ΔH_N, and the second-order rate constant

$$k = \sqrt{3}\,\pi\, 2.83 \times 10^6 \frac{\Delta H_N}{(N)} \qquad (4)$$

From (2) and (4) we find

$$\sqrt{\frac{I(0)}{I(N)}} = 1 + \frac{k(N)}{\sqrt{3}\pi\, 2.83 \times 10^6 \Delta H_0}$$

In the curves given in Figs. 4–8 we plot the measured values of $\sqrt{I(0)/I(N)}$ against $(N)/\Delta H_0$. ΔH_0 in each case was found from direct measurement of the central line before naphthalene was added. Each point represents a separate preparation of naphthalenide and addition of naphthalene to it.

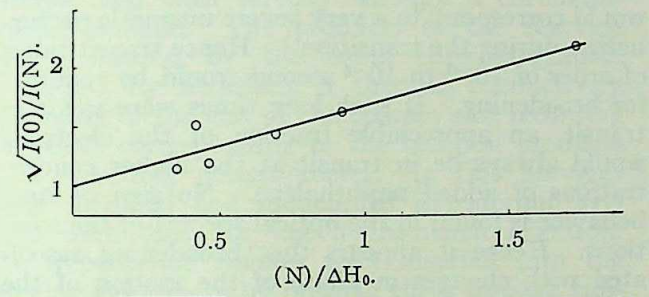

Fig. 4.—$\sqrt{I(0)/I(N)}$ *vs.* $(N)/\Delta H_0$ for sodium naphthalenide in THF.

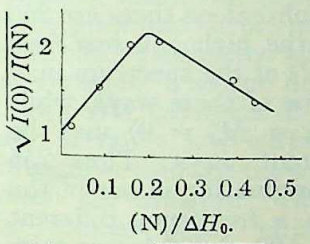

Fig. 5.—$\sqrt{I(0)/I(N)}$ *vs.* $(N)/\Delta H_0$ for potassium naphthalenide in DME.

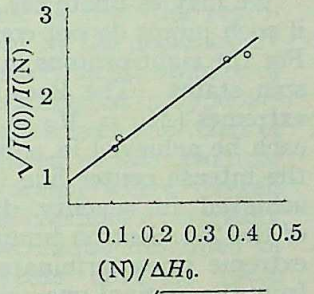

Fig. 6.—$\sqrt{I(0)/I(N)}$ *vs.* $(N)/\Delta H_0$ for potassium naphthalenide in THF.

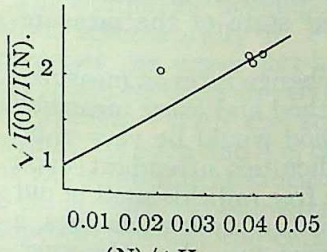

Fig. 7.—$\sqrt{I(0)/I(N)}$ *vs.* $(N)/\Delta H_0$ for lithium naphthalenide in THF.

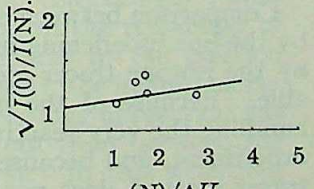

Fig. 8.—$\sqrt{I(0)/I(N)}$ *vs.* $(N)/\Delta H_0$ for sodium naphthalenide in DME.

A second-order rate constant is determined from the slope of the curve at low concentration of added naphthalene.

A summary of the rate constants for the exchange for the various combinations of cation and solvent used in these experiments is given in Table I.

All the experiments summarized in Table I were at temperatures between 30 and 35°. Several experiments were performed with the lithium and potassium salts in tetrahydrofuran at −70° and one was performed with the sodium salt in THF at 60°. All showed no observable effects of temperature. Because our apparatus was not well suited for reliable measurements at these temperatures, a rough upper limit of 2600 cal. mole^{-1} was established for the activation energy.

The reasons for the dependence of rate on the nature of the cation are not clear to us. It will be noticed that the rate constant for the sodium salt in dimethoxyethane is much higher than for the potassium salt. The following experiments were performed in connection with this point. To a solution of potassium naphthalenide in 1,2-dimethoxyethane was added naphthalene at 1.3×10^{-2} *M*. This concentration produces little broadening for the potassium salt. To the solution containing potassium naphthalenide and naphthalene, a large excess (0.22 *M*) of sodium iodide was added. A barely perceptible broadening occurred. In another experiment naphthalene at 1.8×10^{-2} *M* was added to sodium naphthalenide at 0.96×10^{-3} *M* in DME to produce an easily observed broadening. To this solution 1.8×10^{-3} *M* potassium iodide was added. The spectrum reverted to the unbroadened spectrum of the potassium salt. This set of spectra is shown in Fig. 9.

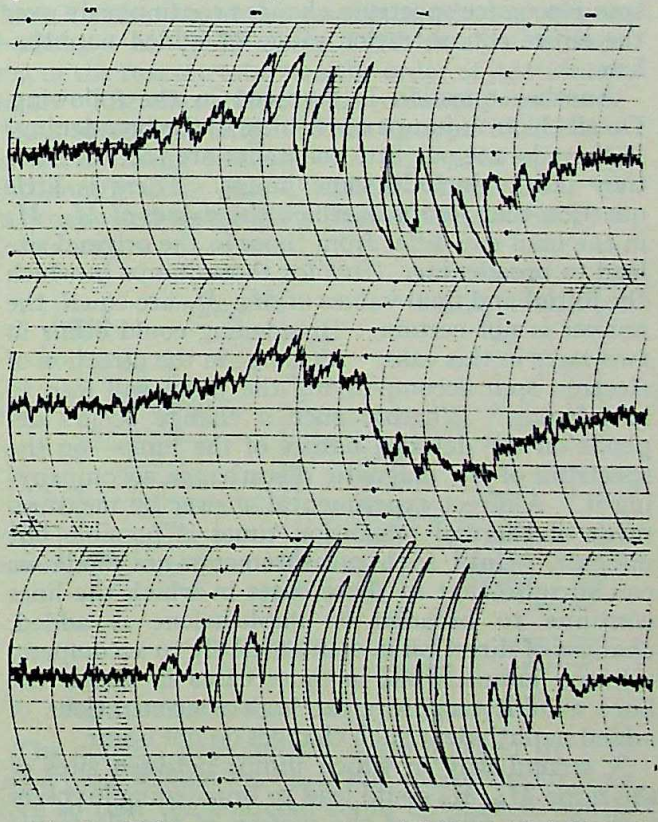

Fig. 9.—Spin resonance spectra of 0.96×10^{-3} *M* naphthalenide in DME: above, pure sodium salt; center, naphthalene added at 1.8×10^{-2} *M*; below, potassium iodide at 1.8×10^{-3} *M* added to solution which had given center spectrum.

The two experiments show that the state of the solution is independent of the order of adding of reagents. While other interpretations are possible, the experiments are consistent with the statement that the rapid exchange of the sodium salt proceeds through ion pairs and that the equilibrium constant for the reaction

$$Na^+C_{10}H_8^- + KI = Na^+I^- + K^+C_{10}H_8^-$$

is at least 10^4

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TABLE I

RATE CONSTANTS FOR ELECTRON TRANSFER BETWEEN NAPHTHALENIDE ION AND NAPHTHALENE

Positive ion	Solvent	k (l. mole^{-1} sec.$^{-1}$)
K^+	DME	$(7.6 \pm 3) \times 10^7$
K^+	THF	$(5.7 \pm 1) \times 10^7$
Na^+	DME	$(1 +3 -0.7) \times 10^9$
Na^+	THF	$(1 +3 -0.6) \times 10^7$
Li^+	THF	$(4.6 \pm 3) \times 10^8$

There are a few points concerning interpretation of the results which may be further discussed. One involves the possibility that the formation of stable complexes between naphthalene negative ion and naphthalene is responsible for the observed phenomena. Such a possibility is contradicted by several observations. First, no observable change in the optical spectrum of naphthalenide occurs even in the presence of a thousand-fold excess of naphthalene. Second, if a stable complex were formed, a superposition of the electron spin resonance spectra of the complex and the uncomplexed species would be expected. No sign of such superposition is observed. Third is the fact that the electron spin resonance spectrum changes continuously over the entire concentration range of added naphthalene.

Another question is involved in the following. Do all electron jumps contribute to the broadening? If they do not our rate constants are too low since they fail to include some jumps. There is little question that jumps in which the values of M_α, M_β in the final site differ from those in the original site lead to broadening. But for those jumps in which the initial and final values of M_α, M_β are equal, the answer is not certain. Broadening could occur in two ways in this case. A change in the direction of electron spin accompanying the jump will lead to broadening. Whether such a change occurs depends on the detailed nature of the jump—on the spectrum of the magnetic disturbance accompanying it. A direct experimental answer by measurement of thermal relaxation times is possible but difficult. Until such measurements are made we can surmise that in those cases in which the lines continue to broaden as naphthalene is added, changes of direction in spin are likely to accompany electron jumps, while in those cases in which the lines exhibit narrowing at high concentrations of added naphthalene such changes do not occur.

A second way in which jumps between sites of the same M_α, M_β could lead to broadening involves a change in phase of the motion of the electronic moment without change in direction of spin. A classical description of the problem similar to one given by McConnell and Weaver[11] is the following. If the phase of the Larmor precession of the electron spin at some instant after the jump differs by an appreciable fraction of a radian from the value it would have had at that instant if the jump had not occurred, broadening results. If V_0 is the frequency in the site between which the jumps occur, V^* the average frequency in transit, and τ the time spent in transit, the condition for broadening is

$$\tau > \left| \frac{1}{V_0 - V^*} \right|$$

In the cases studied by us it is unlikely that $V^* - V_0$ would be greater than 10^8 or 10^9 cycles per second (50–500 oersteds). (A value of 10^9 cycles would correspond to a very severe magnetic perturbation during the transition.) Hence transit times of order of 10^{-9} to 10^{-8} second would be required for broadening. If such long times were spent in transit, an appreciable fraction of the electrons would always be in transit at the higher concentrations of added naphthalene. No sign of such behavior is found in the optical spectra of the solutions. Hence it appears that broadening associated with changes in phase of the motion of the electron spin during jumps between sites of the same M_α, M_β are not significant.

We may estimate the error in our rate constants if such jumps do not contribute to the broadening. For the eight protons in naphthalene there are 256 spin states. The lines at the high and low field extremes ($M_\alpha = M_\beta = \pm 2$) of the spectrum may each be achieved in only one of these ways, while the intense center line ($M_\alpha = M_\beta = 0$) may be achieved in seventy different ways. Thus 255 of the 256 electron jumps originating in one of the extreme lines terminate in a frequency different from the original one, while 196 of 256 jumps originating in the central line terminate in a different frequency. Use of the central line may underestimate the exchange rate by about 27%—not a very serious error in the present state of the measurements.

Comparison between exchange rates as measured by the line broadening method and those measured by the isotope tracer method would be very valuable. Because of the difficulties attendant upon handling the very reactive free radicals used in our experiment, and because of the rapid exchanges, a tracer method does not seem feasible. However, in certain other rapid exchanges, especially those studied by Wahl and his collaborators, it may be possible to study the reactions by both methods.

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[CONTRIBUTION FROM MULTIPLE FELLOWSHIP OF GULF RESEARCH & DEVELOPMENT COMPANY, MELLON INSTITUTE]

An Improved Microcatalytic Technique

BY W. KEITH HALL AND P. H. EMMETT*

RECEIVED OCTOBER 10, 1956

An improved new microcatalytic technique, capable of yielding reproducible catalyst testing data, is outlined. Data describing the utility of the method in a kinetic study of the catalytic hydrogenation of ethylene are presented, and advantages of the technique over conventional methods are discussed.

In a recent communication from this Laboratory,[1] a new microcatalytic technique was outlined. This technique involved the injection of gaseous or liquid hydrocarbon reactants into a carrying gas stream which was passing over a catalyst and then directly through a chromatographic column. The products of the reaction were measured by the usual chromatographic technique, by attaching a thermal conductivity apparatus to the exit of the column and recording the peaks corresponding to the reaction products on a recording potentiometer. In this previous work, modified and unmodified hypodermic syringes were used for the hydrocarbon injection. The hypodermic needles were inserted into the carrying gas stream by pushing them through rubber serum caps. While this technique is probably adequate for many studies, it has two serious drawbacks: the first of these is that the reproducibility obtainable is limited by the accuracy by which gases and/or the extremely small samples of liquid can be measured and transferred in hypodermic syringes; a second limitation is encountered in studies over catalysts of reduced metals (particularly of fairly low surface areas) where oxygen diffusing in through the serum cap may irreversibly poison the catalyst. The technique described in the present paper circumvents both of these difficulties and in addition provides a means of preparing synthetic blends that may be used either in calibration or in the actual catalytic studies.

The equipment developed in the present work is shown schematically in Fig. 1; the doser device comprises the upper left-hand (blocked-in) corner and is shown there in relation to the remainder of the system. With the stopcocks in the position shown (3 is open and 4 is closed), the helium carrying gas is pushing the measured slug of reactant gas (8 cc. in these experiments) out from between the stopcocks toward the catalyst. In this situation, the by-pass stopcock for the carrying gas (4) is in the closed position. By reversing the doser stopcocks (1 and 2) by 180°, the by-passed stream of reactant gas could be run through the doser (close 3), while in turn, the helium carrying gas would be by-passed (open 4). Thus by proper manipulation, measured volumes of the flowing synthesis gas could be trapped between the doser stopcocks and in turn carried over the catalyst by the stream of carrying gas. The volume between the stopcocks, in which the gas is trapped, was calibrated gravimetrically with mercury before the doser device was sealed into the system. By an obvious modification, the doser volume may be varied by making this part of the assembly interchangeable.

Provision was also made for evacuation of the measured volume and the filling of it with gas blends of known composition from a gas buret attached to a manometric system as shown in Fig. 1. This feature was especially convenient in calibration.

As an example of the utility and reproducibility of this equipment, data will be presented below for an experiment in which a mixture of 60% hydrogen–40% ethylene was passed over a copper–nickel alloy catalyst. These data comprise part of a study which will be reported in more detail elsewhere.[2] The slug of the gas mixture had a volume of about 8 cc. (NTP); the total catalyst surface area in the reactor tube was the order of one square meter. The chromatographic column was made from a seven foot length of one quarter inch stainless steel tubing packed with high area charcoal (Pittsburgh Coke and Chemical "Type B"). It was connected to the glass part of the system by a Kovar seal.

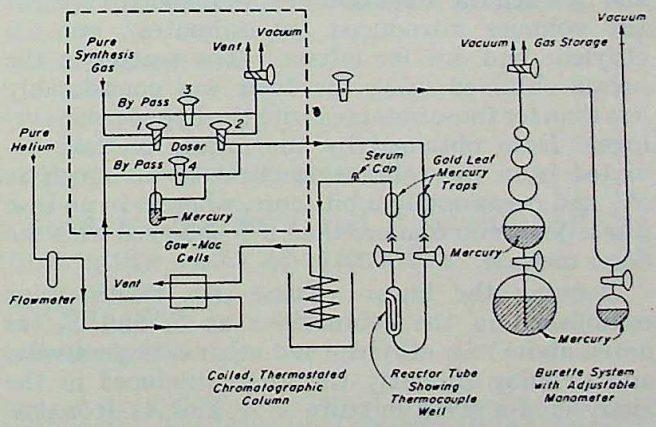

Fig. 1.—Flow sheet of microcatalytic system.

The column packing was accomplished by putting a plug of glass wool into one end of the straight piece so that the charcoal could be packed tightly into the column a little at a time while the tube was vigorously vibrated with an electric Vibra-tool. When the packing was completed, the upper end of the column was plugged with another piece of glass wool. The column was then formed into a coil which fit into a large Dewar flask where it was thermostated at 136°, using a conventional relay circuit. The exit end of the column was connected directly into the Gow–Mac thermal conductivity cell. It should be noted that the metered carrying gas passed through the other side of the Gow–Mac cell before reaching the doser.

* Johns Hopkins University, Baltimore, Md.

(1) R. J. Kokes, H. Tobin, Jr., and P. H. Emmett, THIS JOURNAL, 77, 5860 (1955).

(2) W. K. Hall and P. H. Emmett, "The Hydrogenation of Ethylene Over Copper–Nickel Alloys," to be published.

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An a.c. bridge circuit, developed and supplied by the Department of Instrumentation of the Mellon Institute, was used to link the output of the Gow–Mac cell to the unmodified Speedomax recording potentiometer. It proved to be both flexible and highly stable.

With reference to Fig. 1, the reactant gas was carried from the doser through the gold leaf mercury traps and over the catalyst. As the slug containing the reactant gases emerged from the catalyst, it passed directly over the charcoal chromatographic column and then through the Gow–Mac thermal conductivity cell.

The record obtained was, in effect, a plot of the concentration of hydrogen, ethylene and ethane passing out of the chromatographic column as a function of time. Quantitative measurements of the volume of the various components were obtained by integration of the peak areas using a planimeter. Calibrations to establish the area–volume relationships were made in several ways. First, ethylene and ethane were measured out separately or together in a hypodermic syringe and injected through the serum cap indicated in Fig. 1; the areas obtained from integration of the peaks obtained on the Speedomax record were plotted as abscissas against the volumes of gas injected as ordinates. Second, various gases of known compositions were used to fill the doser and the data obtained when these slugs were carried through the column were plotted on the same graph. The data obtained by both methods served to define two straight lines characterized by the slopes S_1 and S_2 when the areas obtained were plotted against the volumes introduced (as ordinates), one for ethylene and one for ethane. The scatter in the points obtained using the doser was considerably less than for those obtained with the hypodermic syringe. Data obtained by the former method deviated from the calibration curve by as much as 5% and occasionally a bit more, whereas in no case was a deviation of more than 2% observed with the doser method.

Defining the linear volume–area relationships established in the calibrations as S_1 and S_2 (as noted above) for ethylene and ethane, respectively, and defining similarly the areas produced in the analysis of a given mixture as A_1 and A_2, it is possible to write for the fraction ethane, r, in the mixture

$$r = S_2A_2/(S_1A_1 + S_2A_2) = A_2/[(S_1/S_2)A_1 + A_2] \quad (1)$$

When the doser is filled with a mixture of hydrogen and ethylene, and this slug is passed over the catalyst and partially converted, the percentage of ethane in the ethylene plus ethane mixture is a measure of the reaction rate. Thus equation 1 defines the reaction rate, r, which is sought. The ratio of the slopes of the volume–area calibration curves, S_1 to S_2, was found to be 1.012. It should be noted that this ratio would be expected to be less sensitive to uncontrolled external variables such as room temperature, atmospheric pressure, etc., than either S_1 or S_2 separately. It was found, however, that the calibrations were moderately sensitive to the flow rate of the gas, so that it was more convenient to design a series of experiments with a constant flow rate of approximately 40 cc. per minute.

The data in Fig. 2 exemplify the reproducibility of the data obtained in actual catalyst testing. In this expt., the catalyst was contained in the all-glass reactor tube shown in Fig. 1. The catalyst was reduced *in situ* with carefully purified hydrogen; the stopcocks for this are not shown in this schematic drawing. The catalyst was cooled from the reduction temperature of 250° in hydrogen, and then was flushed out with the purified helium carrying gas at the reaction temperature of −69.3°. The data shown in Fig. 2 were then obtained by passing 15 successive slugs of synthesis gas over the catalyst and permanent chromatographic tracings from the Speedomax were obtained. The temperature of the thermostatting cryostat was changed between successive slugs according to a schedule reflected in Fig. 2, where lines connect points taken at the same temperature. The cumulative errors in these data are due not only to the errors in the calibration data, but also to those in reproducing the temperatures and to those in the inherent reproducibility of the catalyst. When this is taken into account, the data shown are gratifying.

If points are picked off the curves shown in Fig. 2 at any given slug number and plotted against the reciprocals of the absolute temperatures, a conventional activation energy curve is obtained. Figure 3 was constructed in this manner from the data for the twelfth slug.

In the course of the experimental work[2] over an entire series of catalysts similar to that outlined above, some additional advantages were discovered. These are listed separately below.

(1) When this technique was employed, the glass reaction vessels became nearly isothermal reactors. With the 8-cc. slugs which were passed over the catalyst, even at complete conversion no more than two calories of heat could be liberated. In attempts at steady-state reaction, it was found that at even moderate conversions it was difficult to control the reaction, but in these same tubes, using the microcatalytic technique, there was no evidence of local overheating of the catalyst.

(2) Semi-quantitative estimates of the results obtained by passing a single slug over the catalyst could be made before the next slug was sent over the catalyst. Experimentally this was found to be a great advantage because in a single experiment the information obtained on the first slug could be used immediately to establish conditions for the second, and so on.

(3) The technique was found useful for determining the effects of small amounts of poisons. In this case, data such as shown in Fig. 2 would not be independent of slug number but would constitute a family of curves, falling with slug number.

(4) Similarly, the technique was quite useful, for studies involving changes in activity occurring as catalysts are lined out (brought into a steady state).

(5) With obvious modifications, the same equipment could be used to study steady-state reaction

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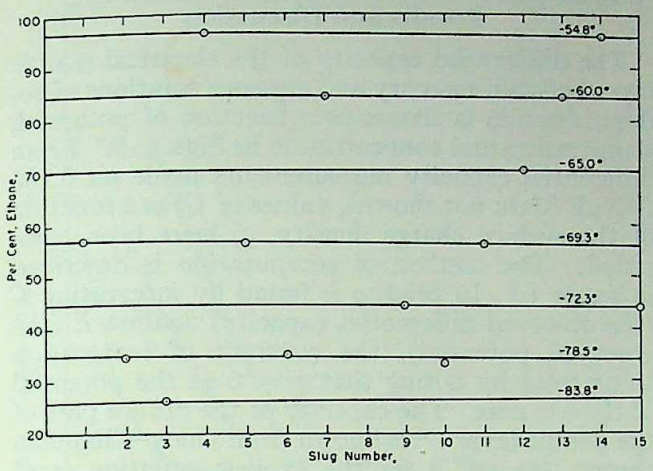

Fig. 2.—Testing data for catalyst IX.

conditions. In this case, a stream of synthesis gas would be passed over the catalyst and the doser would be used to collect measured volumes of the tail gas. This in turn would be carried through the chromatographic column as before, so that most of the advantages listed above would be applicable.

(6) In the present work, adsorption chromatography[3-6] was used because it was most convenient in dealing with the low molecular weight gases of interest. Vapor phase chromatography[5-11] would be preferable for studies involving molecules of higher molecular weight.

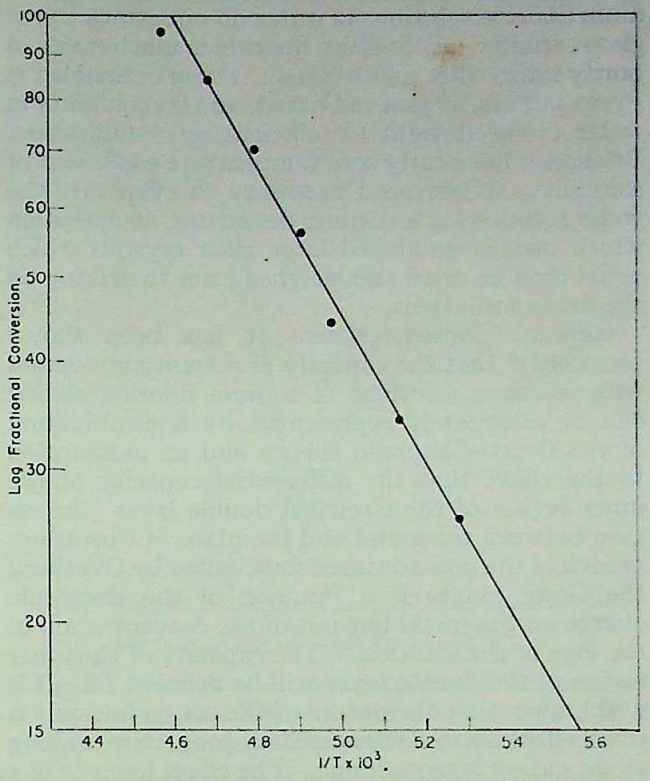

Fig. 3.—Activation energy data picked from Fig. 2 at the twelfth slug.

(3) H. W. Patton, J. S. Lewis and W. I. Kaye, *Anal. Chem.*, **27**, 170 (1945).
(4) J. Griffiths, D. H. James and C. S. G. Phillips, *Analyst*, **77**, 879 (1952).
(5) D. H. James and C. S. G. Phillips, *J. Chem. Soc.*, 1600 (1953).
(6) F. T. Eggertsen, H. S. Knight and S. Groennings, *Anal. Chem.*, **28**, 303 (1956).
(7) A. T. James and A. J. P. Martin, *Biochem. J.*, **50**, 679 (1952).
(8) N. H. Ray, *J. Appl. Chem.*, **4**, 21 (1954).
(9) E. M. Fredericks and F. R. Brooks, *Anal. Chem.*, **28**, 297 (1956).
(10) M. Dimbat, P. E. Porter and F. H. Stross, *ibid.*, **28**, 290 (1956).
(11) D. H. Lichtenfels, S. A. Fleck and F. H. Burow, *ibid.*, **27**, 1510 (1955).

PITTSBURGH, PENNA.

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

Capacity of the Electrical Double Layer between Mercury and Aqueous Sodium Fluoride. II. Effect of Temperature and Concentration

BY DAVID C. GRAHAME

RECEIVED NOVEMBER 12, 1956

The differential capacity of the electrical double layer between mercury and aqueous solutions of sodium fluoride has been measured at five different temperatures and four different concentrations. The results are in agreement with a theory previously proposed. The results also provide several clues to the anomalous behavior of the electrical double layer and suggest a new theory according to which the rise in the capacity on the *anodic* side of the potential of the electrocapillary maximum is attributed to electrostriction. The "hump" is attributed to the formation of a pseudo-crystalline semi-rigid layer through which anions pass only with difficulty, but without activation energy. The solvent next to the metal never achieves a state of free rotation comparable to that which it enjoys in the bulk of the liquid, which is offered as a partial explanation for the fact that the dielectric coefficient of the substance making up the inner layer is so much lower than that of pure water.

Introduction

The fluoride ion is unique among the univalent anions so far investigated in that it exhibits little or no specific adsorption on mercury even when the latter is positively charged.[1-3] This makes it particularly useful as a tool for studying the properties of the electrical double layer on mercury, since it eliminates the most complicating factor.

The choice of a positive ion is dictated largely by convenience, since monatomic cations are never observed to be chemisorbed on mercury. The sodium ion has several advantages for this investigation as follows: (1) its mobility in water is nearly the same as that of the fluoride ion,[4] which tends to reduce or eliminate liquid junction potentials between two concentrations of aqueous sodium fluoride, or between sodium fluoride and potassium chloride in solution. (2) Unlike KF and NH_4F, so-

(1) D. C. Grahame and B. A. Soderberg, *J. Chem. Phys.*, **22**, 449 (1954).
(2) D. C. Grahame, THIS JOURNAL, **76**, 4819 (1954).
(3) D. C. Grahame, *Z. Elektrochem.*, **59**, 740 (1955).
(4) H. Hartley and H. R. Raikes, *Trans. Faraday Soc.*, **23**, 393 (1927).

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dium fluoride solutions in water do not attack Pyrex glass rapidly. (3) Sodium fluoride is much easier to purify than either KF or NH_4F. It can be handled in Pyrex vessels, as just indicated, and its solubility in water is about right for efficient recrystallization. Because it has nearly zero temperature coefficient of solubility, it has been necessary to evaporate the water solutions in a vacuum desiccator, an operation which usually produced large clear crystals which could then be dried and weighed prior to making up the desired solutions.

General Considerations.—It has been shown previously[2] that the capacity of mercury in contact with aqueous solutions of sodium fluoride at 25° can be adequately represented by a combination of the Gouy–Chapman theory and an assumption to the effect that the differential capacity of the inner region of the electrical double layer (the region between the metal and the plane of closest approach of the non-adsorbed ions, called by Overbeek the Gouy plane) is a function of the electronic charge on the metal but not of the concentration of the ions in the solution. The capacity of the inner region of the double layer will be denoted C^0. It is well known that the nature of the cation has only a small effect upon electrocapillary properties, so long as the cation is monatomic. The effect upon C^0 of a change of temperature is dealt with in the present paper. The effect of changing the solvent (from water to methanol) has been reported elsewhere.[3] It is found that in methanol the above-mentioned theory of the electrical double layer works very well, and that the capacity C^0 changes with potential in a manner which is qualitatively similar to that found for water solutions at elevated temperatures. In all cases C^0 goes through a pronounced minimum when plotted as a function of the potential or of the surface charge density q, and in methanol solutions there is no trace of the "hump" which is so characteristic a feature of differential capacity curves of mercury in contact with aqueous solutions at room temperature.

Experimental Details

The experimental procedure was the same as that described in part I.[2] For measurements at elevated temperatures, the solution was jacketed by a stirred water-bath of the desired temperature. For measurements at 0°, the jacket of the cell was packed in ice, covered with a minimum of water, and stirred gently with a stream of air bubbling up through the mixture.

The reference electrode was a normal calomel electrode held at 25°. This is better practice than changing the temperature of the reference electrode. The uncertainty in the absolute value of the potential is of no consequence, since no use is made of the *absolute* value of the recorded potential.

The mode of purification of the sodium fluoride has been mentioned above. Solutions were made up in conductivity water of specific conductance 1.0×10^{-6} or better. Special care was taken to prevent the contamination of the fluoride solutions by chloride ions from the calomel electrode. This is of particular importance in the present work because the chloride ion is chemisorbed on positively charged mercury.

The potential of the electrocapillary maximum (e.c. max.) was found by the drop weight method described earlier (method III of ref. 5) or from the potential of the capacity minimum in rather dilute ($\sim$0.01 N) solutions.[6] The latter method is somewhat more reliable in practice.

(5) D. C. Grahame, R. P. Larsen and M. A. Poth, This Journal, 71, 2978 (1949).

(6) To be precise about this matter, it was not the capacity minimum which was used but the minimum in the C^0–E curve, part of the double layer, C^d, as determined from an analysis of the capacity curves for 0.01 N solutions. C^d goes through a minimum when dC/dE is the same as dC^0/dE. The latter is known from measurements in more concentrated solutions, as described in the text.

(7) Tables of values corresponding to these figures, and also tables of values of q, the surface charge density, will be printed up separately and will then be available on request.

Results and Discussion

The differential capacity of the electrical double layer between mercury and aqueous solutions of sodium fluoride is shown as a function of potential, temperature and concentration in Figs. 1–5.[7] From differential capacity measurements made on 0.795 N NaF (data not shown), values of C^0 as a function of the surface charge density, q, have been computed. The method of computation is described in paper I.[2] In brief, q is found by integrating C (the observed differential capacity) against E (the observed potential), the constant of integration being fixed by noting that $q = 0$ at the potential of the e.c. max. The capacity of the diffuse part of the double layer C^d is known from Gouy–Chapman theory (see ref. 3 for the explicit equation most readily applicable), and the capacity of the inner region, C^0, is found by regarding the observed capacity C as the series capacitance of C^d and C^0. That is to say

$$1/C = 1/C^d + 1/C^0 \qquad (1)$$

This equation may be regarded as a definition of C^0. It is derived from more theoretical considerations in another place which in point of logic, therefore, give physical meaning to the C^0 defined by the equation.

The results of the computation are shown in Fig. 6. The first point to be noted in Fig. 6 is the convergence of the curves at the capacity minimum. This observation suggests and probably requires the assumption of complete dielectric saturation of the inner region at the point of convergence. To the right of the point of convergence (*i.e.*, on stronger cathodic polarization), the curves remain sensibly coincident in spite of the very considerable increase in the capacity. There is hardly room for doubt that this coincidence results from dielectric saturation of the inner region over this whole range of potentials in question.

To the left of the point of convergence the separation of the curves is also consistent with this interpretation. The capacity is lower at the higher temperature, as expected, and the ratios of the capacities at, say, $q = -4$ μcoul./cm.^{2} are about equal to the ratios of the dielectric constants of water at the various temperatures. No precise agreement is to be expected.

The folding over of the low temperature curves is manifestly related to the "hump" which forms so conspicuous a part of the differential capacity curves of most electrolytes in water. The results show that it is not a consequence of the specific adsorption of the anion, as was previously informally supposed, since the beginning of the hump is clearly observed at 25°, where specific adsorption of fluoride ions is surely absent.

Further evidence to the effect that specific adsorption is not responsible for the hump comes from the observation that the hump in solutions of

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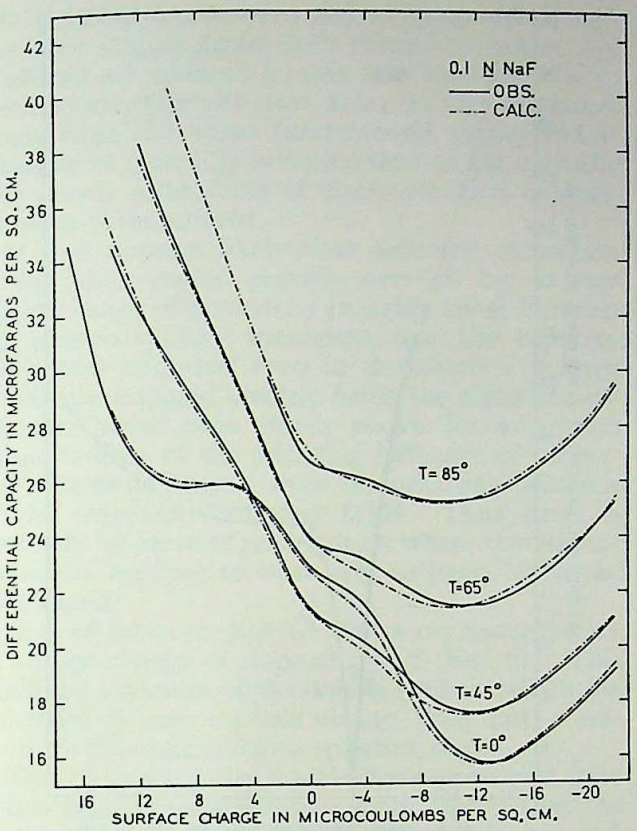

Fig. 1.—Observed and calculated values of the capacity of the electrical double layer between mercury and 0.1 *N* solutions of sodium fluoride at various temperatures. Calculated values depend upon measurements made with 0.8 *N* NaF solutions at same temperature.

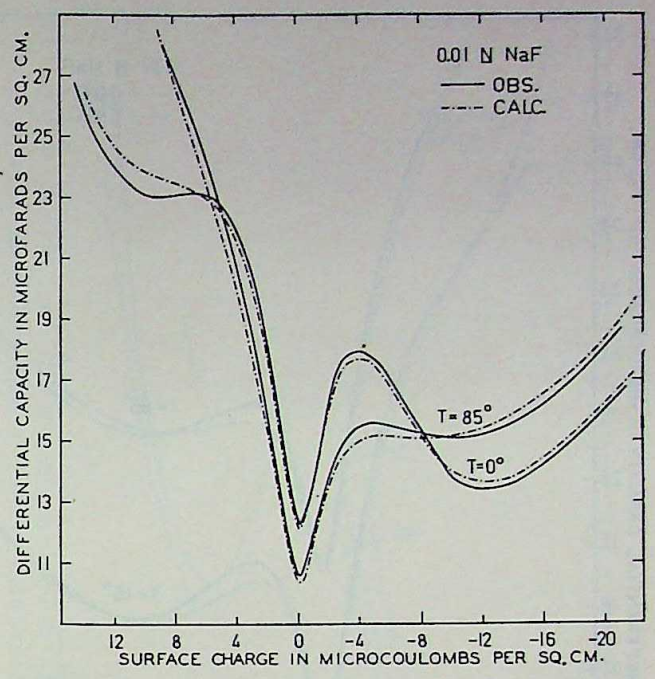

Fig. 2.—Observed and calculated values of the capacity of the electrical double layer between mercury and 0.01 *N* solutions of sodium fluoride at two temperatures.

chlorides vanishes above about 85°[8] although the specific adsorption of the ion is still strong, as evidenced by comparison of the capacity curves with those of fluorides.

A clue to the cause of the "hump" is furnished by the observation that at values of q more positive than about 6 μcoulombs/cm.^{2} the capacity of the inner region is larger at high temperatures than at low (Fig. 6). This means that comparatively weak forces (sufficient to be influenced by the *average* kinetic energies of the ions or molecules) are involved. In the absence of specific adsorption, the only two ways of increasing the capacity per unit area of the inner region are (1) increasing the dielectric coefficient of the region and (2) decreasing its thickness.

It is difficult to assess the dielectric coefficient of the inner region without knowing either its field strength or its thickness, but an increase with temperature of dielectric coefficient is seemingly unknown in any other context. Moreover, the comparatively normal variation with temperature of the dielectric coefficient to the right of the hump makes it unlikely that the dielectric coefficient behaves so very abnormally elsewhere.

A much more plausible explanation of the phenomena observed is found by exploring the second possibility, namely, that the thickness of the inner region may increase with decreasing temperature, a statement which immediately brings to mind the possibility that the surface may be covered with what the author has called[9] a "pseudo-crystalline ice-like" layer of solvent. The expression "ice-like" is not to be interpreted literally, since there is no assurance that the layer is hydrogen bonded. The significant property of the layer, and the only one for which we have any experimental evidence, is its ability to exclude anions, some more than others. With all these restrictions in mind, it is still convenient to speak of an ice-like layer and to refer to the theory as the ice-layer theory. A more accurate description would be to speak of the anion-excluding-layer theory.

The "ice-like" layer must have the property of "melting," not abruptly, like ice, but gradually, like tar. This property is indicated by the *gradual* disappearance of the hump as the temperature is raised (Fig. 6). The layer must also have the property of excluding certain anions, such as nitrate, more easily than it excludes others, such as fluoride. This is evident from the curves shown in Fig. 7, where even at 89° the "hump" has not completely disappeared.

It is natural to assume that the "ice-like" layer is composed of water molecules oriented with their oxygen atoms weakly chemisorbed to the positively charged mercury. This is a form of dielectric saturation, of course, and suggests that the rise of C^0 on strong anodic polarization may have the same cause as the rise of C^0 on strong cathodic polarization. The latter can be explained as the result of electrostriction compressing the solvent and making the inner region thinner.[10]

(8) D. C. Grahame, unpublished results.

(9) D. C. Grahame, *J. Chem. Phys.*, **25**, 364 (1956).

(10) In ref. 3 the author attributed this effect to the increase in the dipole moment of the solvent molecules in the high field. This now seems to be a concurrent but less important effect than the simple compression of the dielectric by the field. The compressed dielectric allows the ions to move closer, thereby increasing the capacity of the inner layer. Macdonald (*J. Chem. Phys.*, **25**, 364 (1956)) takes the position that the ions themselves compress the solvent.

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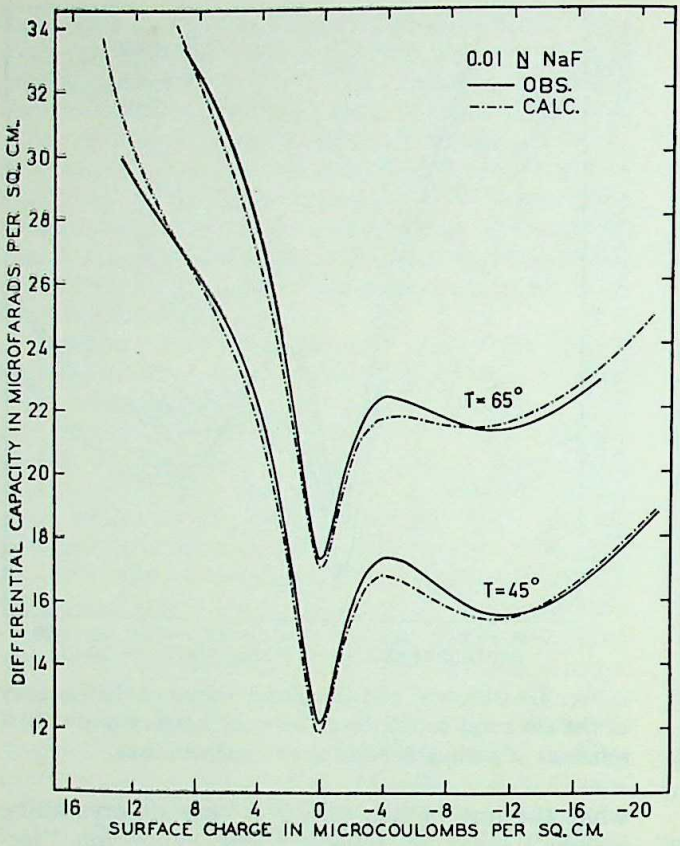

Fig. 3.—Observed and calculated values of the capacity of the electrical double layer between mercury and 0.01 *N* solutions of sodium fluoride at two temperatures.

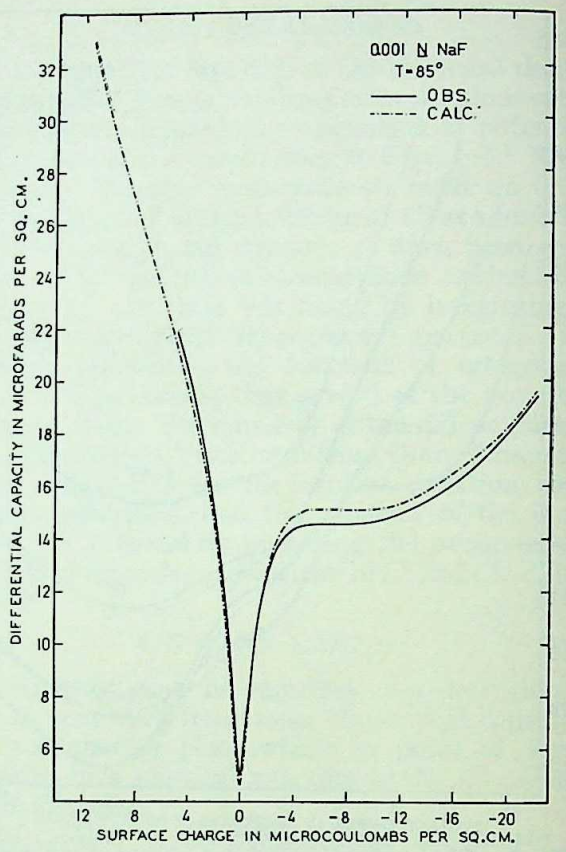

Fig. 5.—Observed and calculated values of the capacity of the electrical double layer between mercury and 0.001 *N* sodium fluoride at 85°.

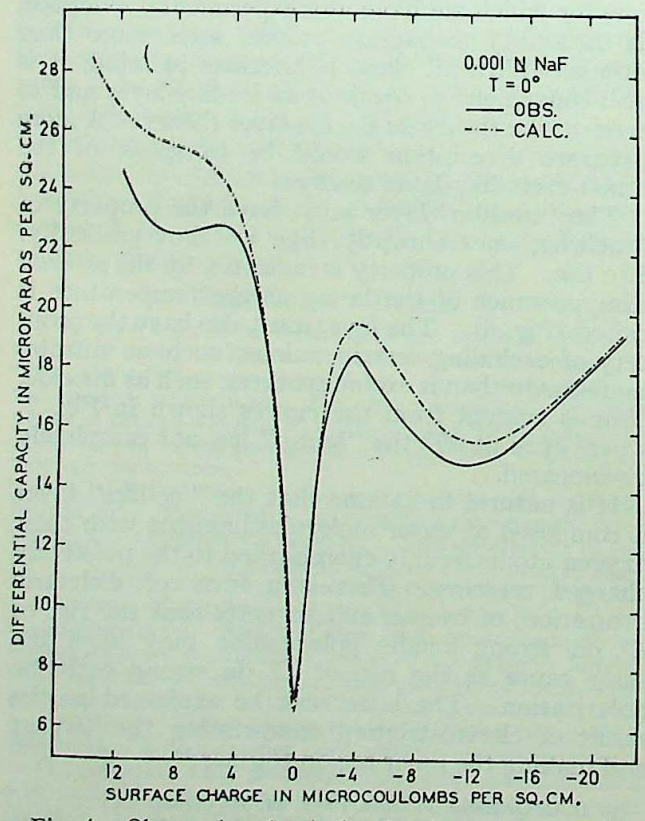

Fig. 4.—Observed and calculated values of the capacity of the electrical double layer between mercury and 0.001 *N* sodium fluoride at 0°.

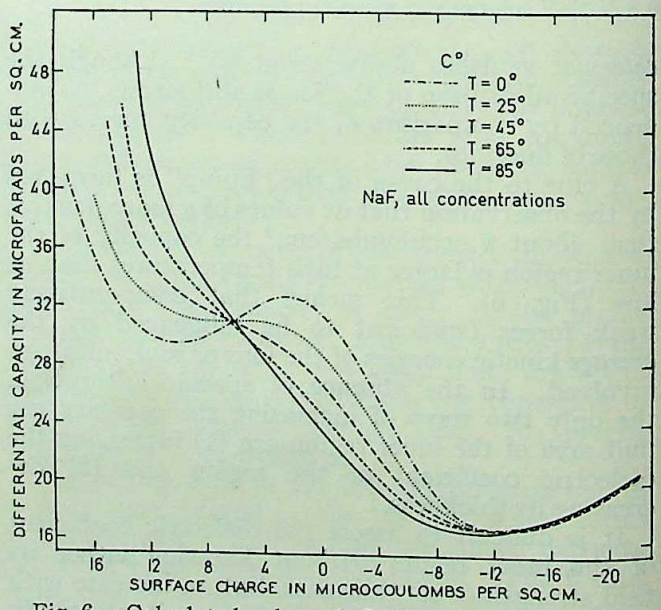

Fig. 6.—Calculated values of C^0, the differential capacity of the inner part of the electrical double layer, between mercury and aqueous solutions of sodium fluoride at several temperatures. Calculations made from data obtained with 0.8 *N* solutions.

Considerable support for the view that electrostriction is largely responsible for the capacity rise on *both* branches of the curve (and in the absence of specific adsorption, which overwhelms the effect in question on the anodic branch) is found in data already presented on the capacity of the double layer in methanol.[3] Here the "ice-layer" is absent and the compressibility of the solvent is large (a point already made by Macdonald[11]), with the re-

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(11) J. Macdonald, *J. Chem. Phys.*, **25**, 364 (1956).

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sult that the curves are nearly symmetrical and rise very steeply from their minimum values. It is almost self-evident in this case that the rise in the capacity on the two sides of the minimum stems from the same fundamental cause, and it seems to be generally accepted that on the cathodic side this is some form of electrostriction or compression of the solvent.

It now appears likely that dielectric saturation of the inner region prevails over all but a very limited range of potentials (roughly those between the electrocapillary maximum and the capacity minimum) and that even in the absence of large externally imposed electric fields the dielectric coefficient never rises much above its saturation value because of the orienting influence of "chemical" forces as distinct from the orienting influence of the externally imposed fields. Thus there is probably no state of polarization where the solvent molecules are free to turn over as freely as in the bulk liquid.

It is of interest that C^0 shows no discontinuity or abrupt change of slope at $q = 0$ (Fig. 6). This again fits a picture of the double layer in which the potential of zero surface charge does not correspond to a condition of no orienting forces.

The concept of the double layer presented here differs from that published a year ago[3] in that the "natural" field of the metal is no longer called upon to account for the lack of a maximum in the plot of C^0 *vs.* q. The role of the "natural" field is now left unspecified; it may well turn out to be of no particular importance. The change in the potential of the electrocapillary maximum when the solvent is changed may now be attributed, as formerly,[12] to changes in the amount of dielectric orientation and to changes in the dipole moment of the solvent molecules.

What emerges from the above considerations is a qualitative but reasonably self-consistent picture of the electrical double layer. The "ice-layer" turns out to be a layer of oriented solvent molecules (not hydrogen bonded to one another) which excludes large anions at room temperature and even small anions (F^-) at lower temperatures. The "hump" in the capacity curves marks the formation of the layer, and its disappearance at elevated temperatures marks the "melting" of the layer. Electrostriction is responsible for the rise in the capacity both on the anodic and cathodic ends of the curve, although relaxation of dielectric saturation also makes a contribution to this rise over a limited range of potentials, as mentioned above.

The Effect of Concentration.—It has already been stated that at 25° C^0 was found to be a function of the surface charge density, q, and not of the concentration. It was of interest to see to what extent this result holds at higher and lower temperatures and also how the potential of the electrocapillary maximum varies with temperature.

The most satisfactory method of testing the constancy of C^0 is to calculate the capacity of the whole double layer, using eq. 1 and diffuse double layer theory in the classical manner, and then to compare the calculated and observed results.

(12) A. Frumkin, *Colloid Symp. Ann.*, **7**, 89 (1930).

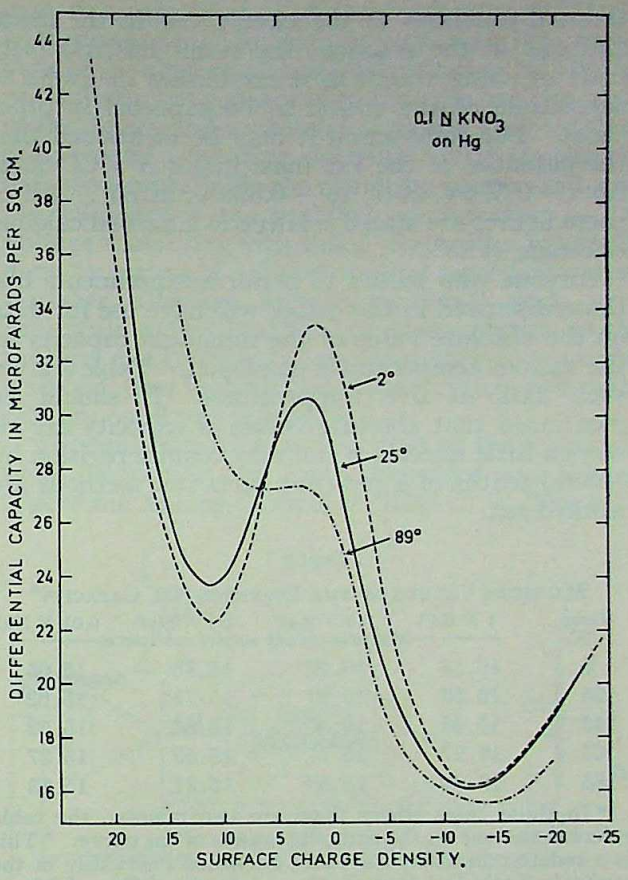

Fig. 7.—Observed values of the differential capacity of the electrical double layer between mercury and aqueous 0.1 N solutions of potassium nitrate at three temperatures.

This procedure has the advantage that it does not magnify errors in the observations or errors in the theory of the diffuse double layer in such a way as to produce uninterpretable results. The results of the calculations are shown in Figs. 1–5. The agreement is as good as one could expect, bearing in mind that the accuracy of the measurements falls off as one goes away from room temperature. Where the disagreement is systematic, this is attributable to small errors in the measurement at the highest concentration, which affects all the other results at that temperature.

The relatively good agreement between theory and experiment at 0° provides the first evidence that the fluoride ion is not adsorbed (strongly) on positively charged mercury at that temperature. It was self-evident that the adsorption at temperatures above 25° would not exceed that at 25°, a fact which these observations tend to confirm.

There is always some disagreement between theory and experiment on the anodic end of the curves. This disagreement is no worse at low temperatures than at high temperatures, a result which indicates that specific adsorption of the fluoride ion is not responsible for the disagreement.[13]

The potential of the e.c. max. varied from −0.48 v. at 0° to −0.44 v. at 85°.[14] Since there are two

(13) If fluoride ion were specifically adsorbed on positively charged mercury, the adsorption would certainly be expected to diminish at elevated temperatures.

(14) This result is independent of concentration within the limits of error of the measurements. At 45° the value is −0.46 v. and at 65° it is −0.455 v.

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thermal junctions in the circuit, one in the metal and one in the solution, the result has relatively little meaning except as it establishes the order of magnitude of the effects to be expected in other cases. For comparison it may be mentioned that the potential of the e.c. max. in 1.0 *N* KCl varies from −0.574 v. at 0° to −0.522 v. at 85°. All of these figures are stated relative to a normal calomel electrode at 25°.

Anyone who wishes to perform experiments like those discussed in this paper will have use for data on the absolute value of the minimum capacity at the various temperatures employed. Table I gives such data at five temperatures. It should be mentioned that absolute values of capacity are always a little uncertain and may require revision by several tenths of a per cent. as better methods are worked out.

TABLE I

MINIMUM VALUES OF THE DIFFERENTIAL CAPACITY[a]

Temp., °C.	1 *N* KCl	0.8 *N* NaF	0.1 *N* NaF	0.01 *N* NaF
	Microfarads per square centimeter			
0	16.58	16.00	15.76	15.65
25	16.50	15.97	15.74[b]	15.62[b]
45	16.43	15.90	15.66	15.52
65	16.27	15.77	15.52	15.37
85	16.08	15.56	15.31	15.13

[a] In those cases where there are two minima, the table refers to the one on the cathodic branch of the curve. [b] This is a redetermination of a value published previously in the author's Technical Report No. 14 to the Office of Naval Research, dated February 18, 1954.

It is a great convenience in this work to have values of the surface charge density, q, at some sufficiently cathodic potential that the effect of the anion is virtually eliminated. For this purpose Table II gives values of q at a potential of −1.205 v. This potential is sufficiently cathodic for all but the most strongly adsorbed anions (I^-, SCN^-, $S^=$) and is convenient for the integration of capacity data by the trapezoidal rule using potential intervals of 0.01 v. These data, like those in Table I, are a little uncertain in absolute value but give correct results for the potential of the e.c. max. when used together.

TABLE II

SURFACE CHARGE DENSITY, q, AT POTENTIAL AT −1.205 VOLTS[a]

Temp., °C.	1 *N* KCl	0.8 *N* NaF	0.1 *N* NaF	0.01 *N* NaF
	Microcoulombs per square centimeter			
0	14.60	14.20	13.58	12.73
25	14.22	13.73	13.03	12.14
45	13.86	13.49	12.79	11.83
65	13.51	13.14	12.40	11.47
85	13.28	12.86	12.10	11.14

[a] All potentials measured relative to a normal calomel electrode at 25°.

Conclusion

The investigation of the capacity of the electrical double layer in aqueous solutions of sodium fluoride in contact with mercury at several temperatures has provided a clue to the behavior and structure of the double layer. This has permitted the formulation of a theory which is at least qualitatively understandable and for which the next step will be to provide a quantitative expression. The author wishes to make it clear that he is merely *proposing* a theory and is not yet prepared to underwrite it.

Acknowledgments.—The author is grateful to Professor Earle S. Scott for stimulating discussions leading to the formulation of the theory proposed in this paper. He is indebted to Miss Vera Brewus for making many of the measurements and to the Office of Naval Research for the support of the project of which this work forms a part.

AMHERST, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Primary Quantum Yield for the Dissociation of Iodine Molecules in Carbon Tetrachloride Solution and the Rate Constant for the Recombination Reaction[1]

BY R. L. STRONG AND J. E. WILLARD

RECEIVED NOVEMBER 24, 1956

The quantum yield for the dissociation of iodine molecules in carbon tetrachloride solution at room temperature by a continuous spectrum of visible light has been found to be 0.13 ± 0.04. The determination has been made by the flash photolysis technique with a d.c. analog computer used to aid in correcting for the fact that the duration of the flash is appreciable relative to the time of recombination of I atoms. The recombination rate constant obtained is $k = 5.7 \pm 0.5 \times 10^9$ liters mole^{-1} sec.$^{-1}$ where $d[I_2]/dt = k[I]^2$. The relative extinction coefficients of iodine in the gas phase and in carbon tetrachloride solution and the visible spectrum of the xenon flash lamp have been determined.

Introduction

When a gaseous iodine molecule in the presence of a foreign gas absorbs a quantum of visible light, it always dissociates.[2] If, however, it is surrounded by a "cage" of solvent molecules, the atoms may lose their energy to the cage walls and immediately recombine[3] or they may recombine by diffusion after having escaped only a molecular diameter or so from each other.[4]

Knowledge of the quantum yield for the escape of such atoms from each other is relevant in interpretations of the over-all quantum yields of photochemical reactions, in reasoning about caging ef-

(1) R. L. Strong and J. E. Willard, Abstracts of the New York Meeting of the American Chemical Society, Sept., 1954, p. 26-R.

(2) W. A. Noyes and P. A. Leighton, "The Photochemistry of Gases," Reinhold Publ. Corp., New York, N. Y., 1941.

(3) J. Franck and E. Rabinowitch, *Trans. Faraday Soc.*, **30**, 120 (1934).

(4) R. M. Noyes, *J. Chem. Phys.*, **18**, 999 (1950).

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fects which may occur in the tracks of ionizing radiations[5a] and atoms activated by nuclear processes,[5] and in considerations of diffusion controlled kinetics[6] in general.

In principle this quantum yield can be determined by flash photolysis experiments in which the rate of recombination of iodine atoms in a solution is measured by the change in transmittance of an analyzing beam immediately after the iodine has absorbed a known number of quanta from an intense short-duration flash. Extrapolation of the recombination curve (on the straight line plot of $1/[I]$ *vs.* time) to zero time would give the concentration of iodine atoms initially produced (and escaping parent recombination) if the flash were instantaneous. In practice the rates of recombination in solution are so fast, and minimum flash times so long, that appreciable recombination occurs before the flash is over, thus invalidating a simple extrapolation and making it necessary to solve for the quantum yield ϕ in the equation

$$-d[I_2]/dt = (1/2)(d[I]/dt) = \phi(I_a) - k[I]^2 \quad (1)$$

where I_a is the rate of light absorption, which varies with time. We have done this with the aid of an analog computer.

The method employed here is more quantitative than that employed for similar determinations by Marshall and Davidson[7] and differs radically in approach from that used by Lampe and Noyes.[8]

Methods and Results

Equipment and Materials.—The flash photolysis equipment used in the present work has been described elsewhere.[9]

The carbon tetrachloride solvent was Mallinckrodt AR low sulfur grade further purified by degassing and distilling through a phosphorus pentoxide train on the vacuum system used for filling the reaction cell. Mallinckrodt AR grade iodine was further purified by grinding with reagent grade potassium iodide followed by sublimation from the mixture through phosphorus pentoxide on the vacuum system.

Solution of the Differential Equation.—The value of ϕ in eq. 1 can be determined with the aid of a d. c. analog computer if I_a (the rate of light absorption in quanta cc.$^{-1}$ sec.$^{-1}$) is known as a function of time, if k has been determined, and if the iodine atom concentration is known at time t (these determinations will be described below).

In a d. c. analog computer, voltages are made to behave in a manner analogous to that prescribed by the variables and coefficients in the given differential equation.[10] To accomplish this, several computing elements, each consisting of a very high gain d. c. amplifier modified by input and feed back components in such a way that its output voltage is some mathematical function of the input voltage, are connected so that the various parts of the differential equation are represented by operations in the computing elements. With time as the independent variable the computer is operated, and the solutions of the problem are recorded as the voltage variations with time. Recording is usually done by means of a direct-writing recording potentiometer, although some computers[11] work on a time scale so fast that the complete solution to the problem can be repeated automatically many times a second, thus making visual observation on a cathode-ray oscilloscope possible.

The computer setup represented by the schematic block diagram in Fig. 1 was assembled on a Reeves Electronic Analog Computer (REAC).[12] The voltage corresponding to $d[I]/dt$ was treated as if it were known and was fed into the integrator computing element. Its output, $-[I]$ (each electronic integration results in a change of sign), was applied to a squaring unit that consisted of a servodriven potentiometer. The voltage corresponding to $-[I]^2$ was finally multiplied by the constant $2k$ by means of a potentiometer and amplifier, giving $-2k[I]^2$. This was fed into the integrator input along with the light intensity function (I_a) multiplied by 2ϕ. As defined by the differential equation, the sum of these two quantities ($2\phi I_a - 2k[I]^2$) is equal to $d[I]/dt$, which has been assumed to be the input to the integrator. Thus the voltage corresponding to $[I]$ must vary as prescribed by the differential equation. The value for ϕ was obtained by recording the voltage representing $[I]$ as a function of time (output 1) and adjusting the potentiometer (2ϕ) until

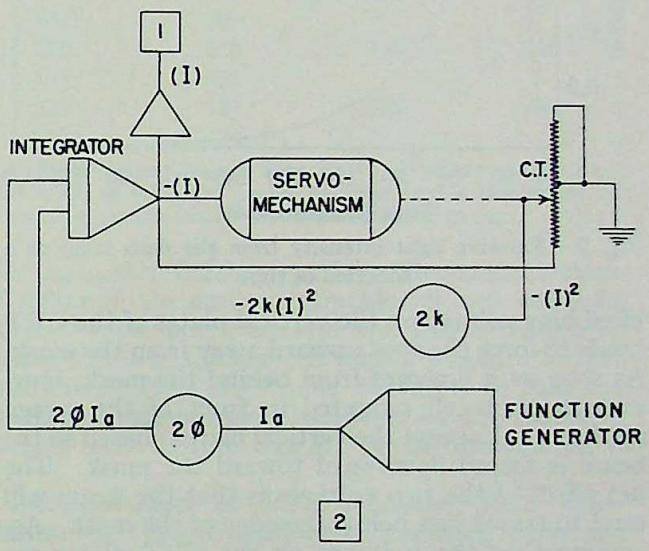

Fig. 1.—Computer block diagram.

(5) Discussion of reactions of this type and references are given by J. E. Willard in (a) *Ann. Rev. Phys. Chem.*, **6**, 141 (1955); (b) *Ann. Rev. Nucl. Sci.*, **3**, 193 (1953).

(6) See, for example: R. M. Noyes, *J. Chem. Phys.*, **22**, 1349 (1954); J. C. Roy, R. R. Williams, Jr., and W. H. Hamill, THIS JOURNAL, **76**, 3274 (1954).

(7) R. Marshall and N. Davidson, *J. Chem. Phys.*, **21**, 2086 (1953).

(8) F. W. Lampe and R. M. Noyes, THIS JOURNAL, **76**, 2140 (1954).

(9) R. L. Strong, J. C. W. Chien, P. Graf and J. E. Willard, *J. Chem. Phys.*, in press.

(10) A thorough discussion of the construction and operation of analog computers is given by G. A. Korn and T. M. Korn, "Electronic Analog Computers," McGraw–Hill Book Co., Inc., New York, N. Y., 1952.

(11) For example, the Philbrick Repetitive Analog Computer, developed by the George A. Philbrick Researches, Inc., Boston, Massachusetts.

(12) Reeves Instrument Corporation, New York, N. Y. We are indebted to Mr. W. G. McClintock and the staff of the Computer Laboratory, Rensselaer Polytechnic Institute, Troy, N. Y., for their valuable aid in setting up and operating the REAC Computer. We are also grateful to Prof. H. A. Peterson, Chairman of the Department of Electrical Engineering, the University of Wisconsin, and to Mr. M. G. Spooner for their aid in making preliminary measurements on a Philbrick Repetitive Computer.

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the voltage corresponded to the experimentally determined value of the iodine atom concentration at 150 microseconds.

The change in the relative light intensity of the flash as a function of time is shown in Fig. 2. This curve was adequately generated by a cathode-ray function generator, or photoformer,[13] in which an opaque mask shaped like the function is placed over the lower portion of a cathode-ray screen. As the electron beam sweeps across the tube face, an applied bias voltage on the vertical plates of the CRT tends to force the spot upward away from the mask. As soon as it emerges from behind the mask, however, a photocell mounted in front of the screen applies a voltage on the vertical plates phased so the beam is forced downward toward the mask. The net effect of the two voltages is that the beam will tend to travel just below the edge of the mask. Assuming that the voltages on the CRT plates are proportional to the deflections, the voltage on the vertical plates is forced to vary as a function of the voltage on the horizontal plates, the function being determined by the shape of the mask boundary. This voltage was fed into the computer as representative of I_a, and observed at output 2 (Fig. 1).

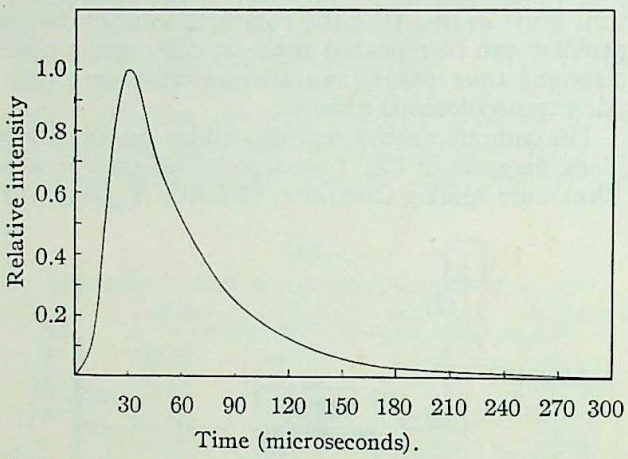

Fig. 2.—Relative light intensity from the flash lamp as a function of time.

The independently variable quantity in a machine such as the REAC is time (τ). The dependently variable quantities are voltages and potentiometer settings, designated below as capital letters. By convention, 100 volts = 1 computer unit. The following transformation equations were used to transform the variables in eq. 1 to machine variables: $\tau = \alpha t$; $Y = a_y[I]$; and $Z = a_z I_a$, where α, a_y and a_z are scale factors. Equation 1 thus becomes

$$dY/d\tau = 2\phi Z(a_y/\alpha a_z) - 2kY^2/\alpha a_y \qquad (2)$$

in terms of machine variables. The time scale factor (α) is numerically equal to the number of seconds representing the unit of the independent variable under consideration. In this case it was desirable to let the machine operate for 15 seconds corresponding to 150 microseconds problem time, so that $\alpha = 10^5$. A maximum rate of light absorption by the iodine in carbon tetrachloride was found to be 1.2×10^{20} quanta cc.$^{-1}$ sec.$^{-1}$ (as discussed below); the function generator was adjusted so that its output at the maximum of the curve was 0.75 computer unit (75 v.), giving $a_z = 6.25 \times 10^{-21}$ (computer units) (quanta cc.$^{-1}$ sec.$^{-1}$)$^{-1}$. Assuming a maximum iodine atom concentration of less than 10^{15} atoms cc.$^{-1}$, a value for a_y of 10^{-15} (computer units) (atoms cc.$^{-1}$)$^{-1}$ was chosen so that $Y = 1$ computer unit when $[I] = 10^{15}$ atoms cc.$^{-1}$.

Experimentally, it had been found (see Table II) that $k = 5.7 \times 10^9$ liters mole^{-1} sec.$^{-1}$ $= 9.5 \times 10^{-12}$ cc. molecule^{-1} sec.$^{-1}$, and $[I] = 9.2 \times 10^{-7}$ moles liter^{-1} $= 5.54 \times 10^{14}$ atoms cc.$^{-1}$ at 150 microseconds. Equation 2 then becomes $dY/d\tau = 3.2\phi Z - 0.19Y^2$ and $Y = 0.554$ computer unit (55.4 v.) at 150 microseconds. The scale factor potentiometer corresponding to 3.2ϕ was varied until this voltage was obtained, resulting in a value for ϕ of 0.13. A maximum error of ± 0.04 was determined by feeding into the computer, maximum and minimum experimental values for k and the iodine atom concentration at 150 microseconds, and estimated maximum and minimum values for the light intensity function.

As shown by the recording for Y *vs.* τ, the iodine atom concentration reached a maximum value of *ca.* 1.4×10^{-6} mole per liter at 65 microseconds, although the light intensity from the flash lamp was at a maximum at only 30 microseconds.

Rate of Light Absorption.—The number of quanta absorbed from a flash of the flash lamp by the iodine in a Pyrex cell 10 cm. long and 25 mm. i.d. containing gaseous iodine at 1.07×10^{-5} mole per liter was 3.49×10^{15} per cc. This was determined by assuming a yield of two iodine atoms per photon absorbed and extrapolating a plot of $1/[I]$ back to the time of initiation of the flash,[14] a valid procedure since the time required for atom recombination in the *gas* is long compared to the duration of the flash. On the basis of the fact that this value is the area enclosed by a curve identical in shape to that shown in Fig. 2, it can be shown by graphical methods that the peak rate of light absorption in the gas phase cell was 5.74×10^{19} quanta cc.$^{-1}$ sec.$^{-1}$.

To find the light absorption by a carbon tetrachloride solution of iodine in a cell placed in the same position and flashed with the same intensity as the gas cell, comparison was made of the extinction coefficients of gaseous and dissolved iodine (Table I), and the spectral distribution of the light from the flash lamp (Fig. 3) was determined. The experimental comparison was necessary because there are large inconsistencies in the extinction coefficient

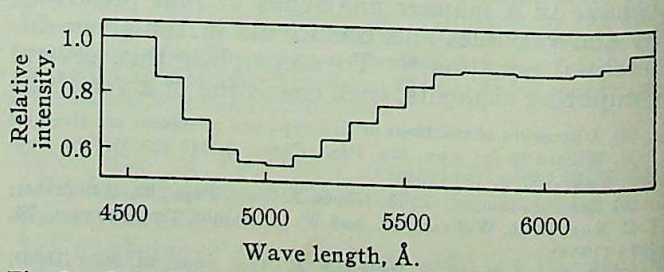

Fig. 3.—Spectral distribution of light from the flash lamp.

(13) Reference 10, page 248.

(14) Additional details of this work are given in the Ph.D. Thesis of R. L. Strong, filed with the University of Wisconsin library in 1954.

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values in the literature. Measurements of optical density as a function of wave length on gaseous iodine (using a Beckman DU spectrophotometer) were compared with similar measurements on the same iodine dissolved in a weighed amount of carbon tetrachloride. By assuming a value of 905[8,15] for the extinction coefficient of iodine in carbon tetrachloride at 5200 Å., its wave length of maximum absorption, the concentration in the carbon tetrachloride solution and the extinction coefficients at the other wave lengths were calculated.[14]

At wave lengths greater than 4995 Å. the spectrum of iodine gas consists of bands rather than a continuum[2] even at an argon pressure of 710 mm. Therefore, relatively large fluctuations in the measured values of the extinction coefficients were obtained at the longer wave lengths because of the use of a narrow spectrophotometer effective band width.

The relative intensity of the flash lamps[9] (containing 70 mm. of Xe and flashed at 27 μf. and 9000 v.) for successive 100 Å. bands from 4400 to 6500 Å. shown in Fig. 2 was determined with the aid of an Applied Research Laboratories 150 cm. grating spectrograph and an ARL projector densitometer.[14,16,17]

The rate of radiant energy absorption may be expressed as $I_a' = I_0(1 - 10^{-\epsilon\, cd}) = I_0(1 - e^{-2.3\epsilon\, cd})$ in units of quanta traversing unit area per sec. Expanding the exponential term in a series gives $(1 - e^{-2.3\epsilon\, cd}) = 2.3\epsilon\, cd - (2.3\epsilon\, cd)^2/2! \ldots$; for small absorption ($\epsilon\, cd << 1$) the higher power terms may be neglected, so that $I_a' = I_0(2.3\epsilon\, cd)$. The average number of quanta absorbed per unit volume per second, I_a, is given by $I_a = (A/V)I_0(2.3\epsilon\, cd)$, where A is the area of the cross-section of the radiation beam and V is the volume of the vessel, (A and V will cancel out when the comparison is made between the light absorbed by the gas and solution cells under identical experimental conditions, assuming no differences in incident light at the interface surfaces.) It follows, then, that

$$(I_a)_{gas} \cong (A/V)\, 2.3[I_2]_{gas}\, d\Sigma(I_0)_\lambda\, (\epsilon_{\lambda,\,gas})(\lambda/hc)$$

$$(I_a)_{soln} \cong (A/V)\, 2.3[I_2]_{soln}\, d\Sigma(I_0)_\lambda\, (\epsilon_{\lambda,\,soln})(\lambda/hc)$$

where λ is the average wave length of a 100 Å. band, and λ/hc is the conversion factor from ergs to quanta at each wave length. Therefore

$$(I_a)_{soln} = (I_a)_{gas} \frac{[I_2]_{soln}\, \Sigma(I_0)_\lambda\, (\epsilon_{\lambda,\,soln})\lambda}{[I_2]_{gas}\, \Sigma(I_0)_\lambda\, (\epsilon_{\lambda,\,gas})\lambda}$$

Average values for the extinction coefficients for each 100 Å. band for iodine gas and iodine in carbon tetrachloride solution were calculated from the extinction coefficients measured in this work (Table I) and values of $(I_0)_\lambda$ were determined from Fig. 3. A value of 1.22 was calculated for the ratio: $(\Sigma (I_0)\, (\epsilon_{\lambda,\,soln})\lambda)/(\Sigma(I_0)_\lambda(\epsilon_{\lambda,\,gas})\lambda)$. The concentration of iodine in the carbon tetrachloride cell was 1.84×10^{-5} mole per liter, and the concentration of iodine in the gas phase cell (argon pressure = 532 mm.) was 1.07×10^{-5} mole per liter, so that the maximum rate of light absorption by the iodine in carbon tetrachloride was 1.2×10^{20} quanta cc.$^{-1}$ sec.$^{-1}$.

TABLE I

EXTINCTION COEFFICIENTS FOR IODINE AT ROOM TEMPERATURE

Å.	Extinction coefficients[a] In CCl_4 soln.	In the gas phase 480 mm.[b]	710 mm.[b]
4400	82	74	60
4500	150	104	
4600	243	157	155
4700	369	224	216
4800	517	335	332
4900	663	447	445
5000	804	577	579
5100	882	676	683
5200	905	724	745
5300	863	709	708
5400	763	660	641
5500	633	606	656
5600	487	472	489
5700	361		
5800	263	335	318
5900	181		
6000	131	125	101
6200	74		

[a] ϵ from the expression $I = I_0\, 10^{-\epsilon\, cd}$ where c is the concentration of iodine in moles per liter and d the length of absorbing path in cm. [b] Pressure of argon in mm.

Determination of Recombination Rate Constants.—A typical oscillogram resulting from the recombination of iodine atoms in carbon tetrachloride at room temperature, compared with the scattered light trace (obtained by flashing the activating light with the filled reaction cell at the light axis and the analyzing beam off) is given in Fig. 4. The vertical difference between the

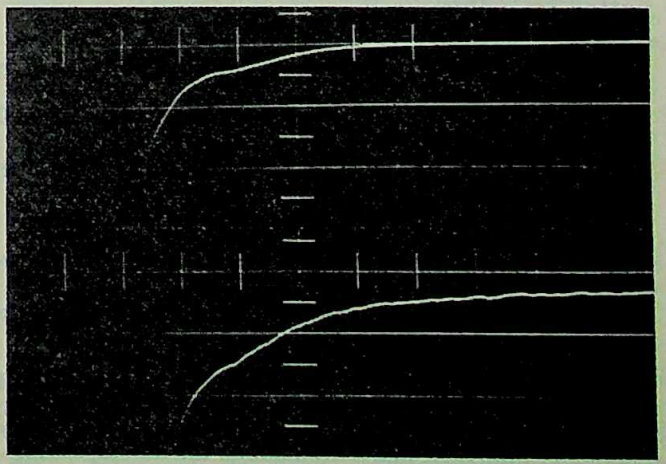

Fig. 4.—Oscillograms for recombination of iodine atoms in carbon tetrachloride solution. The top panel, taken without the analyzing beam on, shows the deflection due to scattered light; the bottom panel shows the sum of the deflections due to scattered light and to dissociation of the iodine. Sweep time, 50 μsec./1 cm. scale division; vertical sensitivity, 0.40 volt/cm., $[I_2]_0$, 1.84×10^{-5} mole/liter.

(15) (a) G. Groh and S. Papp, *Z. physik. Chem.*, **A149**, 153 (1930); (b) W. R. Brode, THIS JOURNAL, **48**, 1877 (1926); (c) O. J. Walker, *Trans. Faraday Soc.*, **31**, 1432 (1935); (d) H. A. Benesi and J. H. Hildebrand, THIS JOURNAL, 2703 (1949); (e) A. I. Popov, K. C. Brinker, L. Campanaro and R. W. Rinehart, *ibid.*, **73**, 514 (1951).

(16) We are indebted to Dr. V. W. Meloche and Dr. Irving Shain of the Analytical Chemistry Division for making this equipment available and for assistance in its use.

(17) M. J. Christie and G. Porter, *Proc. Roy. Soc.* (*London*), **A212**, 398 (1952), have made extensive investigations of the spectral characteristics of the flash discharge in the region of 2600 to 4400 Å., which is below the wave lengths of interest in the present work.

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scattered light trace and the recombination trace is proportional to the iodine atom concentration. The precision of these results was less than for those in the gas phase[9,14] because of the smaller per cent. initial dissociation, resulting from the caging effect, and the faster rate of recombination, resulting from the constant presence of solvent molecules to serve as the "third body." Nevertheless, the best curve through the $1/[I]$ *vs.* time plot clearly showed a second-order dependence of the rate on the iodine atom concentration. Values of k in the relation $d[I_2]/dt = k[I]^2$ were calculated as previously described[9,14] and are given in Table II for 20 determinations. Included in the table are the values obtained for the iodine atom concentration at 150 microseconds, which were used in the calculation of the primary quantum yield.

TABLE II

RECOMBINATION RATE CONSTANTS FOR IODINE IN CARBON TETRACHLORIDE AT ROOM TEMPERATURE

$[I_2]_0 = 1.84 \times 10^{-5}$ mole/liter

$k \times 10^{-9}$, l. mole^{-1} sec.$^{-1}$	$[I] \times 10^7$ at $t = 150$ μsec. mole/l.	$k \times 10^{-9}$, l. mole^{-1} sec.$^{-1}$	$[I] \times 10^7$ at $t = 150$ μsec. mole/l.
5.16	7.6	5.96	9.7
5.48	9.0	5.96	9.7
6.30	10.2	5.31	8.8
5.74	10.3	6.66	9.5
6.71	9.8	5.27	8.5
5.86	8.8	5.11	9.4
5.40	9.7	6.47	8.3
5.96	11.0	5.27	9.0
5.10	7.7	5.39	9.1
5.96	9.7	5.39	9.5

Av. of k values = $5.7 \pm 0.5 \times 10^9$ l. mole^{-1} sec^{-1}.

Discussion

The procedures outlined above gave a value of 0.13 for the fraction of the iodine molecules in carbon tetrachloride solution which, having absorbed a photon, produce iodine atoms which escape recombination to the parent partnership. The light used was the full light of the xenon flash lamp transmitted by a Pyrex cell.

Marshall and Davidson,[7] also using the flash technique, but making no attempt to correct quantitatively for the time dependence of the flash intensity or for the difference in the absorption spectra of iodine in the gas and in solution, and using only light of wave lengths greater than 5000 Å., obtained 0.19 molecule dissociated per quantum. From a determination of the quantum yield for disappearance of iodine in air-saturated solutions of allyl iodide in carbon tetrachloride solution, Lampe and Noyes[8] have obtained a value of 0.14 for the quantum yield of I atom escape from the parent partnership. This determination was made with 4368 Å. light. It is presumed that the allyl iodide reacts with all of the iodine atoms which escape recombination and that the radicals so formed are removed from further chemical activity by reaction with oxygen.

The fact that three laboratories using two widely different techniques obtain values as close together as those cited above is convincing evidence that the true value lies in the region indicated. It, together with the values which have been obtained for iodine in hexane[7,8] (0.41, 0.66) and in hexachlorobutadiene[9] (0.075), offers the most direct experimental evidence yet obtained for the "cage effect."[3] It will be desirable if it is possible for the direct measurements by the flash photolysis technique to be extended to determine the effect of wave length and of a variety of solvents. Use of the analog computer technique described in this paper makes quantitative determinations of this type possible even when the duration of the flash is necessarily appreciable relative to the time required for atom recombination.

Acknowledgment.—This work was supported in part by the United States Atomic Energy Commission, and by the University Research Committee with funds made available by the Wisconsin Alumni Research Foundation. It also was aided by fellowships supported by the United States Rubber Co. and the Minnesota Mining and Manufacturing Co.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Thermal Decomposition of Methyl *n*-Butyl Ketone[1,2]

BY WILLIAM T. BARRY, JR., AND W. D. WALTERS

RECEIVED DECEMBER 13, 1956

The gas-phase thermal decomposition of methyl *n*-butyl ketone has been studied in the neighborhood of 430–500°. The principal products of the reaction during the early stages are: (a) propylene and acetone, (b) ethane and methyl vinyl ketone and (c) methane, carbon monoxide and 1-butene. A small quantity of ethylene also has been found. Acid-forming constituents, *e.g.*, ketenes, are present in only small amounts. The order of the decomposition is about 1.3 and the variation of the rate with temperature gives an apparent activation energy of approximately 52 ± 3 kcal./mole for 200 mm. experiments. The reaction is predominantly homogeneous although it is inhibited to a slight extent by packing the reaction vessel. The addition of propylene markedly inhibits the decomposition. Small quantities of added biacetyl at 475° or ethylene oxide at 450° accelerate the decomposition.

The thermal decomposition of methyl *n*-butyl ketone over a copper–aluminum oxide catalyst has been reported by Mailhe.[3] The composition of the gaseous products was found to be carbon monoxide (18.9%), hydrogen (8.0%), methane (23.5%), saturated hydrocarbons (16.5%) and

(1) This work was supported by the Office of Naval Research.

(2) Abstracted from the Ph.D. thesis submitted by William T. Barry, Jr.

(3) A. Mailhe, *Bull. soc. chem. France*, **31**, 863 (1922).

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unsaturated hydrocarbons (33%). The unsaturated fraction consisted of ethylene, propylene and 1-butene. A liquid product fraction boiling below 90° was obtained, but not identified. The photolysis of methyl *n*-butyl ketone has been studied rather extensively[4] and the chief products at low temperatures are acetone and propylene. Davis and Noyes[4b] found that the acetone yield is relatively constant under all conditions indicating that acetone and propylene are formed in a single step. It was of interest to investigate the homogeneous thermal decomposition in order to make a comparison with the photochemical studies and with the thermal decompositions of the lower ketones.

Experimental

Materials and Apparatus.—Methyl *n*-butyl ketone was prepared in this Laboratory (a) by the reaction[5] of *n*-butylmagnesium bromide with an excess of acetic anhydride at −70° and (b) by converting *n*-butylmagnesium bromide to the cadmium alkyl with anhydrous cadmium chloride and treating the cadmium alkyl with acetyl chloride.[6] Methyl *n*-butyl ketone (c) which had been prepared by the chromic acid oxidation of 2-hexanol was purchased from Paul C. Kletzke Co.

Materials (a) and (b) were purified by recrystallization of the semicarbazone and the regenerated samples of the ketone (aI and bI) were dried over anhydrous calcium sulfate, filtered and fractionated. In one instance, material (a) was purified by conversion to the bisulfite addition compound and regeneration of the ketone gave sample (aII). Material (c) was shaken with pure mercury for 24 hours to remove peroxides, distilled once, and then fractionated. All of the samples were fractionated (usually twice) in an atmosphere of pure, dry nitrogen. Similar results were obtained with the various samples described above. The indices of refraction of the purified samples were: $n^{24}D$ for sample (aI) 1.3991; $n^{20}D$ for (bI) 1.4006, (aII) 1.4009, and (c) 1.4006. A value of 1.4008 for $n^{20}D$ has been reported previously.[7]

Ethylene oxide was obtained from the Dow Chemical Co. Biacetyl from the Eastman Kodak Co. was purified by fractionation under vacuum. Propylene (99.5%, Ohio) was used without further purification other than thorough degassing at −196°. Nitrogen (99.99%) was supplied by Linde Air Products Co. Nitric oxide (Matheson) was passed through three traps at −160°, and before each use it was frozen at −196°, degassed and distilled from a −78° bath.

The apparatus was almost identical with the one used in an earlier study.[8] The rate of pressure rise was measured usually with a heated mercury manometer, but in some experiments a click gage or a mirror gage was used.

Analysis of the Products.—Infrared measurements, conventional gas analysis involving absorption and combustion techniques and mass spectrometric analyses[9] were used to identify the gaseous products. To establish the identity of butene the more volatile products from a series of static experiments were removed by vaporization at low temperatures; the infrared absorption curve for the less volatile portion of the gases indicated that the main C_4 hydrocarbon is 1-butene. Prior to the quantitative analyses the gaseous products were separated usually into a fraction volatile at −196° and another volatile at −78°.

Tests for formaldehyde[10] and for higher homologs[11] did not reveal the presence of any aldehyde. A solution of the products in water showed a slight acid reaction, indicating the presence of ketene, substituted ketenes or other acidic substances. By titration with standard base it was found that after 10–20% pressure increase at 450° for 250 mm. experiments ketenes are present to the extent of less than 1% of the gaseous products. For an initial pressure of about 120 mm. at 512° with a pressure increase of 58–64% the acidic constituents amounted to 3.4% of the gaseous products.

In order to secure sufficient amounts of the liquid products for identification a series of static experiments (250–300 mm., 525°, 40–75% pressure increase) was performed. The liquid portion of the reaction mixture was fractionated in a semi-micro column. The boiling point and the index of refraction were measured for each fraction. Since the evidence indicated the presence of acetone and methyl vinyl ketone as important products (formed in comparable amounts), the semicarbazones of the appropriate fractions were prepared, recrystallized and compared with the semicarbazones from the pure ketones. The data are summarized in Table I. The infrared curves of fraction I4 and I8 agreed with the curves for acetone and methyl vinyl ketone, respectively. There appeared to be a trace of acetone in I8. Some evidence was obtained for the presence of another substance which came over in the first fraction of the distillation along with 1-butene and acetone. It had a maximum in its ultraviolet absorption at 223 mμ, but due to the minute quantity an infrared identification could not be made.

TABLE I

Fraction	B.p., °C.	$n^{20}D$	M.p., °C. Semicarbazone	M.p., °C. Mixed
I4	55.8[a]	1.3610	184–188	184–187
I8	80[a]	1.4096	140–144	141–143
Acetone	56.2[b]	1.3591[b]	184–187	
Methyl vinyl ketone	81[c]	1.4095[c]	141–143	

[a] 744 mm. [b] From reference 12a, b.p. at 760 mm. [c] From reference 12b, refractive index at 22°.

The amount of methyl vinyl ketone in the products was determined by two methods. The products which had not volatilized at −78° were dissolved in a 0.1 *N* potassium chloride solution (90% water–10% methanol). A portion of this solution was used for polarographic measurements[13] carried out with a Fisher Elecdropode. A second portion of the solution was diluted with water and the optical density was determined at 210 mμ with a Beckman DU spectrophotometer. For each method standard solutions of methyl vinyl ketone were used for calibration purposes.

Acetone in the products was estimated by a colorimetric method involving the reaction with vanillin.[14] A wave length of 540 mμ was employed and the contributions resulting from the methyl vinyl ketone and the unreacted methyl *n*-butyl ketone were taken into account. The acetone analyses seemed to be satisfactory for a comparison between experiments on a relative basis, but the absolute values may have been in error by 20–25%.

Results

Products of the Reaction.—The results from the mass spectrometric analyses of the gaseous products formed at 450 and 475° are plotted in Fig. 1. The data from two other series of experiments analyzed by conventional gas analytical procedures were in good agreement with those shown in Fig. 1. In the initial stages of the decomposition propylene and ethane are the most important gaseous products. For comparison a plot of (pressure of methyl vinyl ketone/pressure of gaseous products) for a

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(9) Performed by the Mass Spectrometry Section of the U. S. Bureau of Standards under the direction of Dr. F. L. Mohler.

(10) J. F. Walker, "Formaldehyde," Reinhold Publ. Corp., New York, N. Y., 1944, pp. 246 and 263.

(11) L. Lewin, *Ber.*, **32**, 3388 (1899).

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(14) H. I. J. Backstrom, *Z. anal. Chem.*, **123**, 96 (1941).

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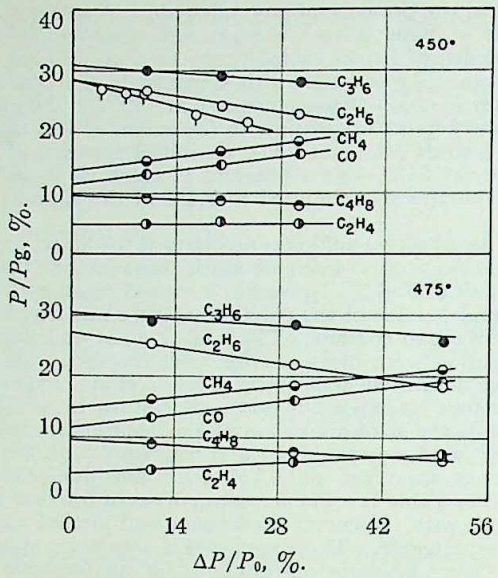

Fig. 1.—Products formed during the decomposition of methyl *n*-butyl ketone, 250 mm. at 450° and 160 mm. at 475°. *P*/*P*g represents the ratio of the amount of each substance to the total amount of gaseous products in % for various percentages of pressure increase ($\Delta P/P_0$, %). ♀ gives the ratio of methyl vinyl ketone to gaseous products for experiments at 200 mm.

series of 200 mm. experiments at 450° is shown also in Fig. 1. The agreement between the ethane and methyl vinyl ketone at the start of the decomposition indicates that one of the reactions is

$$CH_3COC_4H_9 \longrightarrow CH_3COCH{=}CH_2 + C_2H_6 \quad (1)$$

The acetone determined for 200 mm. experiments at 450° by the colorimetric method appeared to be about 80–85% of the percentage of propylene shown in Fig. 1. In view of the difficulties inherent in the colorimetric method in the presence of other ketones the results point toward the occurrence of

$$CH_3COC_4H_9 \longrightarrow CH_2{=}CHCH_3 + CH_3COCH_3 \quad (2)$$

The fact that the lines for methane, carbon monoxide and butene extrapolate to percentages of comparable magnitudes at the beginning of the reaction gives evidence for the reaction

$$CH_3COC_4H_9 \longrightarrow C_4H_8 + CH_4 + CO \quad (3)$$

Since methane and carbon monoxide grow in importance during the decomposition, they are probably formed also by the decomposition of intermediate products. It might be expected that in the presence of undecomposed ketone and liquid products some of the butene may remain in the −78° trap. Two experiments employing a more elaborate procedure of separation by fractional condensation and volatilization indicated that as much as eight parts per hundred of the butene might have been retained, but the loss of other gases was negligible. Thus the amount of butene may be somewhat closer to the carbon monoxide than the data in Fig. 1 show.

The presence of ethylene in the initial portion of the decomposition points toward the occurrence of at least one other reaction of lesser importance, as will be considered in the Discussion. For the experiments at 450 and 475° other products not shown in Fig. 1 were found in the gases by the mass spectrometric analyses: H_2, 0.3–0.8%; C_3H_8, 0.2–1.7%; C_5-C_6 hydrocarbons, 0.1–0.3%; CH_3COCH_3, 0.2–0.4% (most of the acetone is in the condensed fraction).

It was observed that the relative proportions of the products change as the decomposition proceeds, but for a given percentage of pressure increase the composition, particularly in the early stages, does not depend appreciably upon the initial pressure or temperature over the range used in this study. This finding indicated that the pressure increase could be used for the investigation of the kinetics of the reaction.

To study the appearance of methyl vinyl ketone during the decomposition both the spectrophotometric and the polarographic methods were used and the data are summarized in Fig. 2. The pressure of methyl vinyl ketone rises rapidly at first, reaches a maximum and then gradually diminishes in the later stages of the decomposition. In the early portion the points representing the polarographic and spectrophotometric measurements are essentially coincident, but at the higher percentages of pressure increase ($\Delta P/P_0$) where the reaction times are considerably longer, there are differences probably due to the ultraviolet absorptions of secondary products.

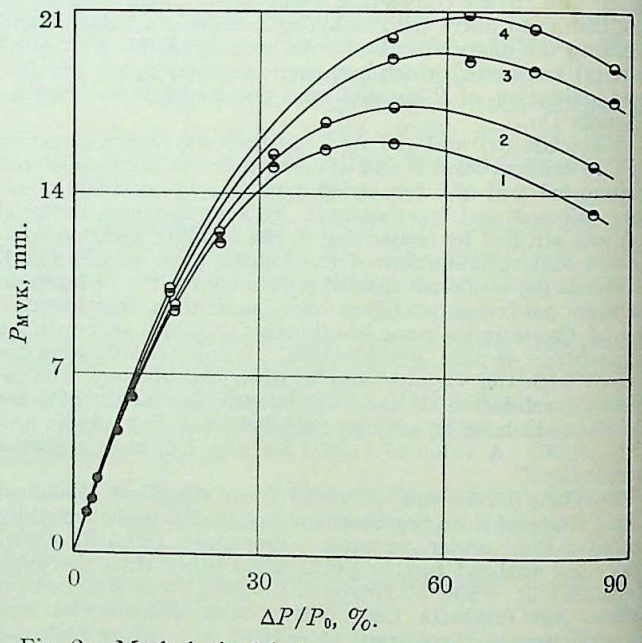

Fig. 2.—Methyl vinyl ketone present during the decomposition of methyl *n*-butyl ketone: Curves 1 and 2, ~200 mm. of $C_6H_{12}O$ at 450°; curves 3 and 4, ~198 mm. of $C_6H_{12}O$ at 495°. Pressure of methyl vinyl ketone based on polarographic measurements, ⊖ ; on the ultraviolet absorption of a solution of the reaction mixture at 210 mμ, ◒ .

Pressure–Time Curve and Homogeneity.—The change of pressure with time at 450° is shown in curve 1, Fig. 3. The slope of the curve decreases more than expected during the first ten minutes and then remains almost constant to about 60% pressure increase. The decrease in the initial stages may be due to the formation of products, such as propylene, which can inhibit the reaction. Later, secondary reactions involving the products initially formed will be occurring.

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Curve 2 in Fig. 3 shows that a 22-fold increase in the surface to volume ratio reduces the rate of pressure rise. This decrease may result from the increase in the termination of free radical chains due to packing. Analyses after 40 min. at 450° showed that methyl vinyl ketone in the packed vessel is about 90% of that in the unpacked vessel for similar experiments at 200 mm. In view of the large difference in the total surface between the packed and unpacked vessels it is probable that surface effects play a relatively insignificant role in the unpacked bulb under the conditions used.

Influence of Added Substances.—The effect of the addition of propylene upon the rate of pressure rise is shown in curve 3, Figure 3. It was observed that as little as 4 mm. produces some decrease in the initial rate and the addition of 150 mm. propylene inhibits about 80% or more of the initial rate of pressure increase. Analyses were performed in order to ascertain whether this decrease in the rate of pressure rise is associated with a real inhibition of the decomposition. The amounts of methyl vinyl ketone present at 475° with and without added propylene are shown in Table II.

TABLE II

EFFECT OF PROPYLENE UPON THE APPEARANCE OF METHYL VINYL KETONE AT 475°

Propylene added, mm.	0	150	200	250
Reaction time, min.	Methyl vinyl ketone present, mm.			
2.5	3.2	0.75	0.67	0.49
11.5	9.8	3.9	3.5	3.1

P_0 (methyl *n*-butyl ketone) = 200 ± 4 mm.

A similar inhibiting effect of propylene upon the build-up of methyl vinyl ketone was observed at 450°. The results show that the major portion of the methyl vinyl ketone is formed by a chain process which is markedly inhibited by propylene. It is to be noted that the addition of 100 mm. of nitrogen to 200 mm. of methyl *n*-butyl ketone at 450° produced no appreciable effect upon the pressure–time curve or upon the amounts of methyl vinyl ketone and acetone formed in 40 min.

To find out whether the formation of other products is affected by propylene, gas analyses were made on reaction mixtures from experiments in the presence of propylene and the quantities of products were compared with the quantities from pure methyl *n*-butyl ketone under similar conditions (Table III). It is apparent from these results

TABLE III

AMOUNTS OF PRODUCTS FORMED WITH ADDED PROPYLENE RELATIVE TO THE AMOUNTS FROM PURE METHYL *n*-BUTYL KETONE (200 MM.) AT 450°

Propylene, mm.	$\Delta P_i/\Delta P_n$[a]	CO	CH_4	Higher saturates	Unsaturates
	Reaction time, 40 min.				
80	0.45[a]	0.38	0.45	0.52	0.3
160	.38[a]	.38	.42	.50	.4

[a] Ratio of the pressure increases in the presence and absence of propylene.

that the processes producing carbon monoxide and methane are inhibited by propylene. Since ethane is the principal higher saturated hydrocarbon, the formation of ethane is presumably decreased also.

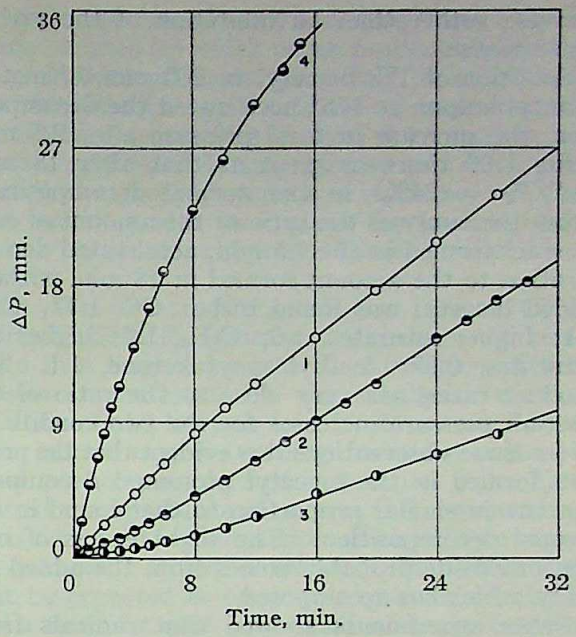

Fig. 3.—Pressure increase during the decomposition of 200 mm. of methyl *n*-butyl ketone at 450°: ○, pure ketone; ◓, packed bulb (other curves from unpacked bulb); ◑, 105 mm. of propylene added; ◒, 1% ethylene oxide and 99% ketone.

The values for the unsaturates are subject to considerable error since they were obtained by subtraction of the amount of added propylene, but the rate of production of olefins seems definitely lower in the presence of propylene.

The effect of propylene upon the formation of acetone was evaluated semi-quantitatively in two ways. The colorimetric method was used for (a) two experiments with 200 mm. of methyl *n*-butyl ketone at 475° for 2.5 min. with 151 and 201 mm. of added propylene and (b) the experiments shown in Table III (greater percentages of decomposition and smaller pressures of propylene). It was estimated that the acetone in the presence of propylene compared to that in the normal decomposition probably does not exceed a value of 15% in the case of the (a) experiments and is not greater than 45% for the experiments shown in Table III. The infrared absorption technique was employed for experiments with 200 mm. of methyl *n*-butyl ketone in the presence and absence of 260 mm. of propylene for reaction times of 40 and 56 min. at 450°. In each case a sample of vapor removed from the liquid portion of the reaction mixture by volatilization was examined in the region of 8.2μ where acetone absorbs quite strongly and the absorptions of methyl vinyl ketone and methyl *n*-butyl ketone are relatively weak. The absorption observed for acetone (after correction for the absorption of methyl *n*-butyl ketone) in the inhibited experiments seemed to be not more than 30–35% of the absorption of samples for the experiments without added propylene. On the basis of these results it can be concluded that the added propylene under the above conditions inhibits at least 60% of the acetone formation.

Experiments with 0.3–7.0 mm. of nitric oxide added to 200 mm. of methyl *n*-butyl ketone at 450° gave a decrease in the time for 10% pressure

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increase rather than an inhibition of the rate of pressure rise.

Addition of 1% biacetyl to 200 mm. of methyl *n*-butyl ketone at 475° accelerated the decomposition, the increase in total pressure after 9.5 min. being 1.06 times as great as that after 18 min. ($\Delta P/P_0$ = 24%) in the normal decomposition. From the analyses the ratio of the amount of each product formed in the 9.5 min. accelerated decomposition to the amount formed in 18 min. without added biacetyl was found to be: CO, 1.17; CH_4, 1.1; higher saturates, 1.0; C_2H_4, 1.1; higher unsaturates, 0.97; methyl vinyl ketone, 1.1. The product ratios are very close to the ratio of the over-all pressure increases for the two conditions. From these observations it is evident that the products formed in the biacetyl promoted decomposition are in similar proportion to that found in the normal decomposition. The slight excess of carbon monoxide probably comes from the added biacetyl which has decomposed.

Other experiments showed that radicals from decomposing ethylene oxide can sensitize the decomposition. The influence of added ethylene oxide is shown in curve 4, Fig. 3. For a 200 mm. mixture of methyl *n*-butyl ketone and 1% ethylene oxide the increase in the total pressure at 450° after 15 min. was 1.03 times as large as that observed for 200 mm. pure ketone in 40 min. ($\Delta P/P_0$ = 16.5%). Ratios of the amounts of the products formed in the 15 min. sensitized decomposition to those in the 40 min. normal decomposition were: CO, 1.1; CH_4, 1.16; higher saturates, 1.0; C_2H_4, 1.1; higher unsaturates, 1.1; methyl vinyl ketone, 1.0. The ratio is approximately the same for every product and is close to the value of 1.03 for the ratio of the observed pressure increases. These results also give evidence for the similarity of the products in the normal and sensitized decompositions.

Kinetics.—In experiments at 450° with pressures from 50 to 300 mm. the initial slope of the pressure–time curve $(dP/dt)_0$ and the rate of pressure rise in the region of essentially constant slope (after 6% pressure increase at 450°) were measured and their logarithms were plotted against the logarithm of the initial pressure (Fig. 4). Likewise the average rate of build-up of metal vinyl ketone during the first 8 min. ($\Delta P_{MVK}/\Delta t$) was measured and the data are shown in Fig. 4. The slopes of the three lines are almost the same and all lie within the range 1.30 ± 0.06. Thus an order of about 1.3 is indicated for the over-all reaction and for the build-up of methyl vinyl ketone.

Figure 5 summarizes the data showing the temperature variation of the reaction over the range 430–495° at a constant pressure of 200 ± 2 mm. (or corrected to this value). Each point in Fig. 5 represents two or more experiments. For methyl vinyl ketone in Figs. 4 and 5, each point is the

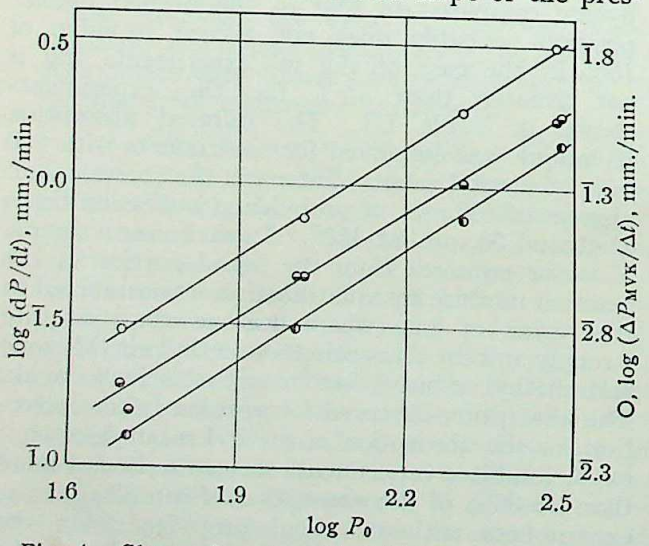

Fig. 4.—Change in rate with initial pressure, P_0: ◒, $(dp/dt)_0$, initial rate of pressure rise; ◐, $(dp/dt)_c$, rate of pressure rise after ~6% pressure increase; O, $(\Delta P_{MVK}/\Delta t)$, average rate of build-up of methyl vinyl ketone during the first 8 min. Each point showing the rate of pressure rise at 200 mm. represents the average of three runs.

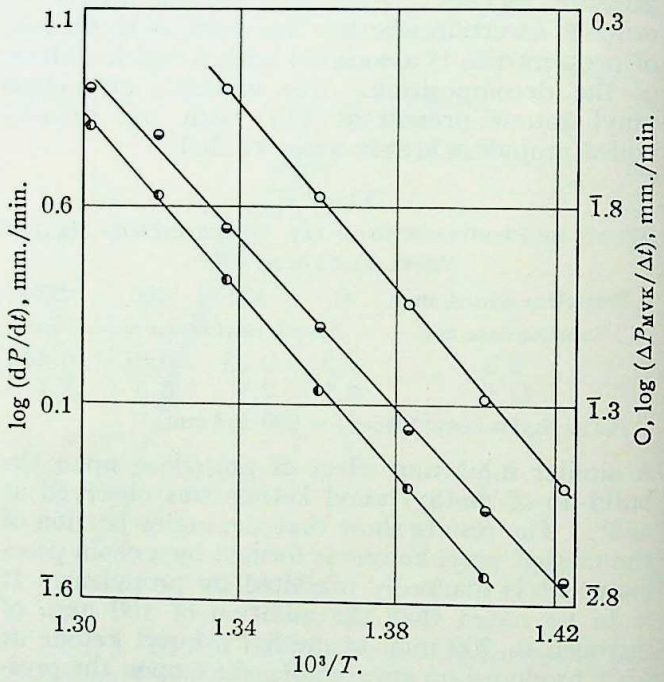

Fig. 5.—Variation of rate with temperature: ◒, $(dP/dt)_0$, initial rate of pressure rise; ◐, $(dP/dt)_c$, rate of pressure rise after ~10% pressure increase; O, $(\Delta P_{MVK}/\Delta t)$ initial rate of appearance of methyl vinyl ketone.

average of the spectrophotometric and polarographic analyses, the former being on the average about 5% higher. If one assumes that for a constant initial pressure each of the rates can be represented by an expression involving a constant multiplied by $e^{-E/RT}$, the values for E obtained from the data shown in Fig. 5 are: 50 ± 2 kcal./mole from $(dP/dt)_0$, 52 ± 1 kcal./mole from $(dP/dt)_c$, and 53.5 ± 1 kcal./mole from $(\Delta P_{MVK}/\Delta t)$. It is to be noted that for the measurement of $(\Delta P_{MVK}/\Delta t)$ the reaction time at each temperature was kept sufficiently short to permit the build-up of only 2.7-3.1 mm. of methyl vinyl ketone. Due to secondary reactions the observed rate of build-up will not be identical with the rate of formation, but the difference should be small. In the evaluation of the temperature variation and the order by the use of $(\Delta P_{MVK}/\Delta t)$ a compensating factor is that approximately similar percentages of methyl vinyl ketone may disappear in the various experiments.

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To estimate the importance of the disappearance of methyl vinyl ketone for the kinetic studies above, two experiments with 11 mm. of this compound plus 200 mm. nitrogen were allowed to proceed for 8 min. at 450°. Analyses did not reveal any significant loss, but the disappearance of about 5% might have escaped detection. Small amounts (12 mm.) of methyl vinyl ketone were added to 200 mm. of methyl *n*-butyl ketone and analyses were made after 8, 24 and 40 min. at 450°. The influence of added methyl vinyl ketone upon its own formation is not known, but it is estimated that the disappearance of methyl vinyl ketone probably is not in excess of 1% per minute in the initial stages of the reaction.

Discussion.—The experimental results indicate that even in the initial stages the homogeneous thermal decomposition of methyl *n*-butyl ketone is not a simple reaction, but involves three major reactions designated above as (1), (2) and (3). However, the order and the temperature coefficient of the reaction producing methyl vinyl ketone are approximately the same as the order and temperature coefficient obtained from the rate of pressure increase. Furthermore it has been shown that the three reactions given above can be inhibited by propylene and sensitized by free radicals to form the products in nearly the same proportions as in the normal reaction. The rate of pressure rise is also reduced by an increase in the surface to volume ratio of the reaction vessel. To explain the results a free radical chain mechanism of the Rice–Herzfeld type can be used. Although the exact nature of the primary radical producing process is not known, the rupture of any carbon–carbon bond in methyl *n*-butyl ketone can produce free radicals. The abstraction of a hydrogen atom from the ketone by a radical can then lead to a chain reaction

$$R + CH_3COCH_2CH_2CH_2CH_3 \longrightarrow RH + C_6H_{11}O$$

$$C_6H_{11}O \longrightarrow M + R'$$

$$R' \left(\begin{matrix}\text{or smaller}\\ \text{radical}\end{matrix}\right) + C_6H_{12}O \longrightarrow R'H + C_6H_{11}O$$

The formulas for M and R′ will depend upon the particular hydrogen atom abstracted. In some cases R′ will decompose before abstracting a hydrogen atom. The chain products which could be formed by the type of mechanism given above are shown in Table IV.

TABLE IV

Carbon atom from which H is abstracted	M	Products from reaction of R	
3	$CH_3COCH{=}CH_2$	C_2H_6	(A)
4	$CH_2{=}CHCH_2CH_3$	$CH_4 + CO$	(B)
5	$CH_2{=}CHCH_3$	CH_3COCH_3	(C)
1	$CH_2{=}CO$	$C_2H_4 + C_2H_6$	(D)
6	C_2H_4	$C_2H_4 + CH_4 + CO$	(E)

It is apparent that processes (A), (B) and (C) lead to the formation of the major products. Reactions (A), (B) and (C) would be expected to be important on the basis of the fact that they involve the abstraction of secondary hydrogen atoms and in the case of (A) the hydrogen is on a carbon atom adjacent to a carbonyl group.[15] After the abstraction of hydrogen there are in certain cases alternative routes by which other products might be formed instead of those given in Table IV, but from theoretical considerations or experimental evidence they appear less likely. For example, an alternative to methyl vinyl ketone and ethane in (A) might be propyl ketene and methane, but the experimental results have given no positive evidence for the presence of propyl ketene in important amounts.

That the decomposition of the radical $CH_2COCH_2CH_2CH_2CH_3$ (reaction (D)) does not contribute to a large extent to the formation of the products is indicated by the smallness of the quantities of the ketenes found. Moreover, some of the ketene may be coming from the acetonyl radical (or acetone) formed in reaction (C). The apparent unimportance of process (D) is somewhat surprising since the abstraction of a hydrogen atom from carbon 1 which is adjacent to a carbonyl might be expected to occur to a greater extent.[15a] From a spatial model of the radical it can be seen that there is a position in which carbon atom 1 is close to the hydrogens on carbon 5 so that it may be possible for $CH_2COCH_2CH_2CH_2CH_3$ to isomerize by an intramolecular hydrogen abstraction to $CH_3COCH_2CH_2CHCH_3$.[16] Decomposition of the latter radical would lead to an enhancement of reaction (C) at the expense of reaction (D) and would tend to make the products from (C) more important than (B) as is observed experimentally.

Reaction (E) which produces two molecules of ethylene probably can account for the ethylene formed in addition to that from reaction (D). Since the initial percentage of ethylene is not more than 5% (see Fig. 1), reaction (E), which involves the abstraction of a primary hydrogen atom, does not seem to be as important as (A), (B) or (C).

The decomposition of methyl *n*-butyl ketone appears to have considerable similarity to the decompositions of the lower methyl alkyl ketones particularly with respect to the occurrence of chain processes which are inhibited by propylene.[17] However, with methyl *n*-butyl ketone the reactions leading to the formation of ketenes seem to be less important. The activation energies observed in the present case are close to those (51–53 kcal./mole) found for methyl *n*-propyl ketone.[17d] The order of the reaction of methyl *n*-butyl ketone seems to be somewhat higher than the first order behavior found for the lower ketones; this could be due to the existence of several types of chain termination which might lead to an order between 1 and 1.5.[18]

Although propylene and acetone are among the

(15) (a) F. O. Rice and K. K. Rice, "The Aliphatic Free Radicals," Johns Hopkins Press, Baltimore, Md., 1935, pp. 91 and 108; (b) F. W. R. Steacie, "Atomic and Free Radical Reactions," 2nd Ed., Reinhold Publ. Corp., New York, N. Y., 1954, p. 499–500; (c) C. N. Hinshelwood, *Disc. Faraday Soc.*, **10**, 266 (1951).

(16) A similar type of isomerization has been suggested by A. Kossiakoff and F. O. Rice, THIS JOURNAL, **65**, 590 (1943), for the 1-hexyl radical.

(17) (a) F. O. Rice and O. L. Polly, *J. Chem. Phys.*, **6**, 273 (1938); (b) J. R. E. Smith and C. N. Hinshelwood, *Proc. Roy. Soc.* (*London*), **A183**, 33 (1944); (c) C. E. Waring and M. Spector, THIS JOURNAL, **77**, 6453 (1955); (d) V. L. Garik, Ph.D. thesis, Univ. of Connecticut, 1953, Univ. Microfilms Pub. No. 6328, Ann Arbor, Mich.

(18) That the chain terminating step is complex in the acetone pyrolysis has been reported by J. R. McNesby, T. W. Davis and A. S. Gordon, THIS JOURNAL, **76**, 823 (1954).

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important pyrolytic products from methyl *n*-butyl ketone, in contrast to the photochemical decomposition at low temperatures there are other products formed in comparable amounts. Moreover, the results from the experiments with added inhibitor show that in the thermal decomposition acetone and propylene are formed mainly by a free radical chain process rather than by a single-step reaction.

A detailed treatment of the kinetics of a free radical mechanism has not been attempted on account of the complexity of the chain decomposition which probably involves the participation of a number of different radicals. The inhibiting effect of propylene indicates that even in the relatively early stages of the decomposition a partial inhibition of the reaction by the products should be taken into account. In the later stages the subsequent reaction of several of the primary products would be expected to introduce additional complicating factors.

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ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Carbonium Ions. V. The Nature of the *t*-Butyl Cation as Indicated by a Study of the Formation of N-*t*-Butylacrylamide[1]

BY N. C. DENO, TOM EDWARDS AND CARL PERIZZOLO

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The kinetics of the acid-catalyzed formation of N-*t*-butylacrylamide from *t*-butyl alcohol and acrylonitrile have been studied from 20–69% sulfuric acid. The rate is proportional to the first powers of the acrylonitrile concentration, the *t*-butyl alcohol concentration and the Hammett h_0 function. The rate constants for the reactions of protonated *t*-butyl alcohol with water, acrylonitrile and propionitrile were found to be identical within a factor of three. The combined results are interpreted in terms of transition states in which the incoming group is so weakly bonded to the transition state that its nature has only a small effect on the rate. The results do not support the concept of a free *t*-butyl cation. The rate of hydrolysis of acrylonitrile was studied from 28–85% sulfuric acid. The rate is proportional to the concentration of acrylonitrile and the h_0 function.

Since Whitmore[2] first introduced the concept of aliphatic cations, considerable controversy has existed as to their exact nature.

On the basis that methanolysis of hydrogen 2,4-dimethylhexyl-4-phthalate proceeded with 55% inversion and 45% racemization, Doering and Zeiss[3] concluded that no free alkyl cation was an intermediate. Their argument was that if the *t*-alkyl cation was not free enough to racemize, it is difficult to conceive of a transition state in which there is no covalent participation by the incoming group. Their conclusion is strongly supported by the failure to observe a mass-law effect in the solvolysis of *t*-alkyl halides.[4]

The strongest arguments proposed in favor of free *t*-alkyl cations are the studies of Winstein, Grunwald and Jones[5] on the variation of rate with solvent. We interpret these studies as showing that there is nearly complete charge separation in the transition state, a situation that can be accommodated by transition states of the type described by Doering and Zeiss.

In our work, a study of the acid-catalyzed reactions of *t*-butyl alcohol was initiated with the expectation that it would provide evidence as to the existence of the *t*-butyl cation as a reaction intermediate. It was first necessary to develop acidity function theory and this was the concern of an earlier paper.[6]

The reaction chosen for study was the formation of N-*t*-butylacrylamide from *t*-butyl alcohol and acrylonitrile. This reaction is of a type extensively studied by Ritter,[7] who demonstrated that it was a remarkably general reaction between alcohols and nitriles.

Experimental

Extinction Coefficients.—In order to determine the concentration of N-*t*-butylacrylamide spectroscopically, it was necessary to know the extinction coefficients for *t*-butyl alcohol and acrylonitrile (the reactants), N-*t*-butylacrylamide (the product), acrylamide (a side product) and acrylic acid (the hydrolysis product of acrylamide or N-*t*-butylacrylamide). The *t*-butyl alcohol and acrylonitrile showed no measurable absorption in the region of wave lengths greater than 220 mμ at the concentrations employed in the kinetic runs. Their absorptions were thus neglected. The absorption spectra of the remaining compounds are summarized in Table I.

Kinetic Measurements.—The kinetics of the reaction between *t*-butyl alcohol and acrylonitrile were studied in 20–69% sulfuric acid. The formation of the product, N-*t*-butylacrylamide, was determined spectroscopically with a Beckman DU spectrophotometer. Measurements were made at 260–280 mμ. The cells of the spectrophotometer were thermostated at 25 ± 0.1° by means of thermospacers. Rapid runs were conducted entirely in the spectrophotometer cells whereas slow runs were held in thermostated volumetric flasks from which a portion was periodically introduced into the cells.

(1) Grateful acknowledgment is made of the support of this research by a grant from the Petroleum Research Fund of the American Chemical Society.

(2) F. C. Whitmore, *Ind. Eng. Chem.*, **26**, 94 (1934).

(3) W. E. Doering and H. Zeiss, THIS JOURNAL, **75**, 4733 (1953).

(4) L. Bateman, M. Church, E. Hughes, C. Ingold and N. Taher, *J. Chem. Soc.*, 979 (1940). Note comments of J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1956, pp. 103–105.

(5) E. Grunwald and S. Winstein, THIS JOURNAL, **70**, 846 (1948); S. Winstein, E. Grunwald and N. W. Jones, *ibid.*, **73**, 2700 (1951).

(6) N. Deno and C. Perizzolo, *ibid.*, **79**, 1345 (1957).

(7) J. Ritter and co-workers, *ibid.*, **70**, 4045, 4048 (1948); **71**, 4128, 4130 (1949); **73**, 4076 (1951); **74**, 763 (1952).

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TABLE I

ABSORPTION SPECTRA OF N-*t*-BUTYLACRYLAMIDE, ACRYLAMIDE AND ACRYLIC ACID IN 41 AND 55% SULFURIC ACIDS

Wave length (mμ)	Extinction coefficient[a] N-*t*-Butylacrylamide		Acrylamide		Acrylic acid	
225			3340	4290	373	418
230			1660	1990	217	222
235			770	755	146	147
240	2700		360	355	104	109
250	840	872	90	86	63	70
260	169	164			30	37
270	27	22				

[a] Under each compound, the values in the first column are for 41% sulfuric acid and those in the second column are for 55% acid.

All runs were conducted as pseudo first-order reactions by using at least tenfold excess of either reactant, acrylonitrile or *t*-butyl alcohol. The fit of the data with first-order kinetics is demonstrated in Table II for two typical runs in which *t*-butyl alcohol was in excess and a run in which acrylonitrile was in excess.

TABLE II

DEMONSTRATION OF FIRST-ORDER KINETICS FOR FORMATION OF N-*t*-BUTYLACRYLAMIDE AT 30.0 AND 69.1% H_2SO_4 WITH EXCESS *t*-BUTYL ALCOHOL AND AT 41.0% H_2SO_4 WITH EXCESS ACRYLONITRILE

% Completion	Time (days)	Optical[a] density, 260 mμ	$k \times 10^6$, l. mole^{-1} sec.$^{-1}$
	30.0% H_2SO_4, $c_{t\text{-buOH}}/c_{RCN}$ = 11.7		
0	0	0	
10	2.60	.300	2.24
20	5.40	.600	2.29
30	8.70	.900	2.27
40	12.30	1.200	2.30
50	16.70	1.500	2.30
60	22.2	1.800	2.29
70	29.6	2.10	2.26
80	39.3	2.40	2.27
85.7	45.3	2.57	2.37
100		3.00	
	69.1% H_2SO_4, $c_{t\text{-buOH}}/c_{RCN}$ = 11.7		
	Time (min.)		
0	0	0	
10	14.5	.300	580
20	31.0	.600	575
30	50.0	.900	570
40	71.5	1.200	571
100		3.00	
	41.0% H_2SO_4, $c_{t\text{-buOH}}/c_{RCN}$ = 0.0715		
	Time (hr.)		
0	0	0	
10	56	.042	14.4
20	117	.085	14.5
30	183	.127	14.8
40	265	.169	14.7
50	360	.222	14.6
60	490	.254	14.2
70		.296	
80		.338	
100		.423	

[a] The values are taken from a smooth curve drawn through a plot of optical density against time. Observations at 270 and 280 mμ were converted to the equivalent at 260 mμ. The value at 100% completion was calculated from the extinction coefficient of the product, N-*t*-butylacrylamide, and the initial concentrations of reactants.

The rate constants, which are summarized in Table III, were calculated from integrated forms of the equation $dc_{product}/dt = kc_{RCN}c_{t\text{-BuOH}}$. The added *t*-butyl alcohol significantly lowered the acidity of the reaction mixtures similar to the effect of adding 2-propanol to water–sulfuric acid.[8] It was necessary to make small corrections for this effect in computing the rate constants since varying concentrations of *t*-butyl alcohol were used in different runs. For this purpose the Hammett H_0 function[9] was measured as a function of added *t*-butyl alcohol at several concentrations of sulfuric acid. The data are summarized in Table IV. The method of computing the correction for k was to determine d log k/dH_0 at each % H_2SO_4 from the variation of rate with % H_2SO_4. The change in log k due to the added *t*-butyl alcohol could then be estimated from the data in Table IV.

TABLE III

RATE CONSTANTS FOR THE FORMATION OF N-*t*-BUTYLACRYLAMIDE

Run	% H_2SO_4	Initial molarities $CH_2{=}CHCN$	Initial molarities *t*-BuOH	$(k \times 10^6)$,[a] l. mole^{-1} sec.$^{-1}$	% Completion[b]
1	20.0	0.0178	0.209	0.49	25
2	25.0	.0178	.209	1.15	60
3	30.0	.0178	.209	2.58	80
4	35.0	.0178	.209	4.48	80
5	37.0	.0178	.209	7.05	70
6	39.0	.0178	.209	8.15	90
7	41.0	.0178	.209	13.4	60
8	41.0	.0175	.410	12.7	5
9	41.0	.0356	.00255	12.6	50
10	45.3	.0178	.209	22.9	30
11	49.5	.0178	.209	53.6	8
12	54.8	.0178	.209	98.8	15
13	54.8	.0175	.410	98.2	25
14	54.8	.0356	.209	91.3	13
15	55.3	.0178	.209	103	30
16	57.3	.0178	.209	140	15
17	57.3	.0356	.00255	126[c]	85
18	59.5	.0178	.209	182	13
19	61.3	.0178	.209	191	25
20	62.8	.0178	.209	220	15
21	64.4	.0178	.209	274	30
22	64.9	.0178	.209	350	20
23	65.8	.0178	.209	488	25
24	68.0	.0178	.209	560	30
25	69.1	.0178	.209	628	40

[a] The values of k were calculated from integrated forms of the equation $dc_{amide}/dt = kc_{RCN}c_{t\text{-BuOH}}$. The concentrations used in this equation were the stoichiometric concentrations. All values of k were corrected for the small change in acidity due to the added *t*-butyl alcohol. [b] The rate constants did not vary by more then 10% out to the % completion listed in this column. The runs at 20 and 25% H_2SO_4 were inconveniently slow to carry to completion. The runs at 40–50% acid were arbitrarily stopped at the % completion listed. For runs at acid concentrations greater than 50%, no observations were made beyond the % completion listed in this column because of the appearance of cloudiness. [c] In this run where the acrylonitrile was in excess, about 17% of the *t*-butyl alcohol disappeared in some reaction other than the formation of N-*t*-butylacrylamide as judged by the final constant optical density reading. When a correction was made based on the assumption that the side reaction involved a bimolecular reaction between two derivatives of *t*-butyl alcohol, the calculated values of k were constant within 10% out to 85% completion. For these reasons this value of k must be considered uncertain.

Evidence for the Validity of the Kinetic Data.—Although Ritter[7] has shown that under certain conditions acryloni-

(8) P. D. Bartlett and J. D. McCollum, THIS JOURNAL, **78**, 1441 (1956).

(9) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, Chapter IX.

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TABLE IV

VARIATION IN H_0 ON ADDITION OF *t*-BUTYL ALCOHOL TO FOUR DIFFERENT CONCENTRATIONS OF SULFURIC ACID

Ml. of *t*-butyl alcohol per l. of soln.	H_0[a] A	B	C	D
0	1.28	0.31	−0.92	−4.36
10	1.30	.32		
20	1.36	.36	− .86	−4.32
40	1.46	.40	− .78	−4.26
60	1.54	.44		
80	1.58	.46		
100	1.63	.51		

[a] The data in column A refer to addition of *t*-butyl alcohol to a 0.45% solution of sulfuric acid, column B to 4.39% acid, column C to 20.35% acid and column D to 60.3% acid. The indicators used were 2-nitroaniline at 0.45 and 4.39% acid, 4-chloro-4-nitroaniline at 20.35% acid and 2,4-dinitroaniline at 60.3% acid.

trile and *t*-butyl alcohol react to give high yields of N-*t*-butylacrylamide, it was necessary to demonstrate that this was true under the conditions of the kinetic experiments. Related to this problem was the fact that both reactants and the product undergo hydrolysis or dehydration–polymerization in at least some of the regions of acidity studied. Particular emphasis was thus placed on demonstrating that the spectrophotometer data really measured the formation of N-*t*-butylacrylamide and that its formation was nearly quantitative.

The most direct evidence was that crystalline N-*t*-butylacrylamide was isolated in runs at 41 and 55% sulfuric acids in amounts equal to 80% of that calculated from the rate data.

The side reactions, hydrolysis of acrylonitrile and N-*t*-butylacrylamide, were investigated independently. Both of these reactions were found to be sufficiently slow under the conditions employed so that they did not interfere with measurements on the formation of N-*t*-butylacrylamide.

The behavior of *t*-butyl alcohol alone in the various concentrations of sulfuric acid was investigated spectroscopically to be certain that no significant absorption due to isobutene polymers or oxidation products was present during the time that the kinetic data were recorded. The behavior of the *t*-butyl alcohol in the various concentrations of sulfuric acid also was observed visually to see whether any cloudiness developed. No measurements were taken after any cloudiness developed.

The most convincing evidence was the spectrophotometric measurements. Below 45% sulfuric acid where formation and polymerization of isobutene was absent, the final optical density reading was generally at least 95% of that calculated for complete conversion of the reactants to the product, N-*t*-butylacrylamide. The calculated values were based on the extinction coefficient of the product (Table I) and the initial concentrations of reactants. In addition the calculated values of the rate constant, k, were constant until either the reaction was complete or cloudiness prevented further measurements.

Hydrolysis of Acrylonitrile to Acrylamide.—The rate of formation of acrylamide from acrylonitrile was determined from 25–85% H_2SO_4. The concentration of acrylamide was followed by measurements of the optical density at 230–250 mμ. The further hydrolysis of acrylamide to acrylic acid was sufficiently slow so that it did not interfere.

The rate constants, k, were calculated from the integrated form of the equation $-dc_{RCN}/dt = kc_{RCN}$. In all cases values of k were constant to within 5% at all stages of the reaction. The data are summarized in Table V.

Competition Experiments.—The relative rate of reaction of *t*-butyl alcohol with acrylonitrile and propionitrile was determined at 50.3% H_2SO_4. The initial concentrations were made sufficiently large so that the first-order direct hydrolysis of acrylonitrile did not interfere. Although no direct measurements were made on the rate of hydrolysis of propionitrile, this reaction was slow enough so as not to interfere. The evidence for this was that the ratio of rates was constant although the ratio of initial concentrations of the two nitriles was varied from 2.42/1 to 0.58/1. The data are summarized in Table VI.

TABLE V

RATE CONSTANTS AND THEIR VARIATION WITH SULFURIC ACID CONCENTRATION FOR THE HYDRATION OF ACRYLONITRILE TO ACRYLAMIDE

% H_2SO_4	$k \times 10^5$, sec.$^{-1}$	% Completion[a]	$\frac{d \log k}{d\ \%\ H_2SO_4}$	$\frac{-dH_0}{d\ \%\ H_2SO_4}$	$\frac{d \log c_{H_3O^+}}{d\ \%\ H_2SO_4}$
25.5	4.27	0.5	0.04	0.065	0.021
41.3	22.2	5	.061	.087	.013
54.8	188	40	.078	.110	.010
72.0	5960	90	.112	.124	
85.0	82800	90	.112	.134	

[a] The runs were arbitrarily stopped at the % completion listed in this column.

TABLE VI

RELATIVE RATES OF REACTION OF *t*-BUTYL ALCOHOL WITH ACRYLONITRILE AND PROPIONITRILES IN 50.3% H_2SO_4

t-Butyl alcohol	Initial molarities: Acrylonitrile	Propionitrile	Final optical[a] density: Calcd.	Obsd.	$\frac{k_{propionitrile}}{k_{acrylonitrile}}$[b]
0.102	0.184	0.304	16.9	4.43	1.78
.109	.171	.295	18.1	4.87	1.72
.111	.227	.225	18.4	6.92	1.90
.093	.128	.130	15.4	5.67	1.97
.100	.377	.156	16.6	9.00	2.02

[a] The calcd. values were obtained by assuming that the *t*-butyl alcohol was completely converted to N-*t*-butylacrylamide. The observed values were obtained by multiplying the optical density of diluted reaction mixtures by the dilution factor. [b] The calculation of this ratio was made by the equivalent of a graphical integration which took into account that the ratio of the concentrations of the two nitriles changed during the course of the reaction and that the two nitriles disappeared at different rates.

Discussion

Rate Law for the Formation of N-*t*-Butylacrylamide.—At constant concentration of sulfuric acid, the rate law was found to be eq. 1. The majority of reactions were conducted

$$dc_{amide}/dt = kc_{RCN}c_{t\text{-buOH}} \qquad (1)$$

using an 11.7/1 ratio of *t*-butyl alcohol concentration to acrylonitrile concentration. In these runs, the rate constant calculated by eq. 2 was constant (Table II) to within 10% out to the % completions listed in Table III.

$$k = (2.3)(\log c_{RCN}/c'_{RCN})/(c_{t\text{-buOH}})(t) \qquad (2)$$

This demonstrated that the rate was proportional to the first power of the acrylonitrile concentration.

The proportionality of the rate to the first power of the *t*-butyl alcohol concentration was demonstrated in two ways. First, when the concentration of *t*-butyl alcohol was doubled (runs 8 and 13), the value of k was unchanged providing that it was computed by eq. 2. Secondly, in two runs (runs 9 and 17, Table III) the procedure was reversed in that a 14/1 excess of acrylonitrile was employed. In run 9 the plot of log $c_{t\text{-buOH}}$ against time was linear. This was also true for run 17 providing a correction (*cf.* footnote *c*, Table III) was made for the 17% of the *t*-butyl alcohol which disappeared by an uninvestigated side reaction.

In summary, eq. 1 was obeyed over a 330-fold variation in the ratio of *t*-butyl alcohol concentration to acrylonitrile concentration. This range probably could have been extended greatly by using lower acrylonitrile concentrations, but exten-

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sion in this direction was not critical to the arguments to be considered.

From 20–40% sulfuric acid, the variation of rate with acid concentration was expressed accurately by eq. 3 as shown by the data in Table VII. In this eq. as with all others that follow in this paper, all derivatives are taken in respect to % H_2SO_4 unless otherwise specified. Thus d log k stands for d log k/d % H_2SO_4.

$$\mathrm{d} \log k = -\mathrm{d}H_0 \qquad (3)$$

TABLE VII

VARIATION OF RATE CONSTANTS WITH SULFURIC ACID CONCENTRATION FOR THE FORMATION OF N-*t*-BUTYLACRYLAMIDE

% H_2SO_4	$\frac{\mathrm{d} \log k}{\mathrm{d}\ \%\ H_2SO_4}$	$\frac{\mathrm{d} \log k'^{a}}{\mathrm{d}\ \%\ H_2SO_4}$	$\frac{-\mathrm{d}H_0}{\mathrm{d}\ \%\ H_2SO_4}$	$\frac{-\mathrm{d}C_0}{\mathrm{d}\ \%\ H_2SO_4}$
20	0.068	0.068	0.068	0.12
25	.068	.068	.065	.13
30	.068	.068	.068	.14
35	.068	.068	.074	.16
40	.068	.072	.084	.16
45	.066	.081	.096	.18
50	.062	.091	.106	.20
55	.061	.102	.110	.23
60	.060	.120	.110	.26
65	.060	.170	.116	.26

[a] The calculation of k' differed from that of k in that instead of using the stoichiometric concentration of *t*-butyl alcohol in eq. 2, a concentration of *t*-butyl alcohol was used which was corrected for the equilibrium between alcohol and protonated alcohol. This correction was calculated on the hypothesis that $pK = -3.8$ for *t*-butyl alcohol. It was not felt necessary to tabulate values of k'.

From 40–70% sulfuric acid the variation became more complex. This was anticipated because Bartlett and McCollum have found that ethanol has $pK = -2.2$,[10] which means that it is half-protonated in 40% H_2SO_4. For 2-propanol, $pK = -3.2$,[8] which means that it is half-protonated in 50% H_2SO_4. It was thus expected that *t*-butyl alcohol would be half-protonated near 60% H_2SO_4, and that this protonation of the alcohol would affect the fit of the kinetics with eq. 3.

If a $pK = -3.8$ ($H_0 = -3.8$ at 55% H_2SO_4) is assumed for *t*-butyl alcohol and the concentration of free *t*-butyl alcohol computed on this basis, the kinetic data now fit eq. 2 from 20–65% H_2SO_4 as shown in Table VII. The fit is not sensitive to the value chosen for the pK so that the value -3.8 must be considered at best an estimate precise to perhaps ± 0.4.

The complete rate eq. is thus given by eq. 4 where h_0 is the $-$antilog H_0.

$$\mathrm{d}c_{\mathrm{amide}}/\mathrm{d}t = kc_{\mathrm{RCN}}c_{t\text{-BuOH}}\,h_0 \qquad (4)$$

Significance of Eq. 3.—On the basis of limited work, there appear to be two groups of cations for which d log f in sulfuric acid is dependent only on the sulfuric acid concentration.[6] The first group are cations of a type (type I) exemplified by Ar_3C^+, $(C_6H_5)_4P^+$ and Bu_4N^+ in which the common character is a positive charge well shielded by non-polar groups. The second group are cations of the general formula BH^+ (type II) where the common character is a positive charge on the periphery of a non-polar moiety.

(10) Unpublished results.

By the development previously presented,[6] the fact that the data fit eq. 3 and 4 would be interpreted to mean that the transition state resembles type II, BH^+, close enough so that d log (f_{BH^+}/f^*) is negligible. Generally this would be more likely to happen if the transition state were composed of acrylonitrile and protonated *t*-butyl alcohol rather than some other derivative of *t*-butyl alcohol (such as the *t*-butyl cation) and this is our tentative interpretation.

Relative Rates of Reaction.—In a typical SN1 reaction involving a stable cation intermediate such as the triphenylmethyl cation, the relative rate of formation of triphenylmethyl azide and triphenylmethanol is 2.8×10^5.[11] The wide range of rate constants in SN2 reactions is too well known to merit examples. In contrast, a unique feature of the substitution reactions of *t*-butyl derivatives is that their rate constants are so similar.

Using the data of Ingold, *et al.*, Swain, Scott and Lohmann[11] calculated the relative rate of formation of *t*-butyl azide to the rate of formation of *t*-butyl alcohol (from the solvolysis of *t*-butyl chloride in 10% water–90% acetone at 50°) as being 3.9.

Another example of similar rates is the ratio of *t*-butyl thiocyanate to *t*-butyl isothiocyanate formed in solvolysis of *t*-butyl chloride in the presence of thiocyanate ions. Taft and Cannell[12] found the ratio to be 71/29 at 38°. The same authors found that the ratio of the same products was 65/35 when *t*-butylamine was treated with nitrous acid in the presence of thiocyanate ion.[12]

In our work we found that the relative rates of reaction of propionitrile and acrylonitrile with *t*-butyl alcohol in the acid-catalyzed Ritter reaction was 1.9/1 (Table VI).

A more striking example is a comparison of the rates of oxygen exchange on *t*-butyl alcohol with the rate of reaction of acrylonitrile with *t*-butyl alcohol. Dostrovsky and Klein[13] measured the oxygen exchange rate. Their data at 55 and 75° in 0.45 M H_2SO_4 and one molar *t*-butyl alcohol can be extrapolated to 25° to give a rate constant equal to 2.42×10^{-7} sec.$^{-1}$. If this reaction is assumed to be of the same type as the formation of N-*t*-butylacrylamide, the rate constant must be divided by the molarity of water (about 51 M) to reduce the rate constant to that for unit concentration of water and *t*-butyl alcohol. The rate constant then becomes 4.8×10^{-9} l. mole^{-1} sec.$^{-1}$. This rate constant can be compared with the rate constant, $k = 1.7 \times 10^{-9}$ l. mole^{-1} sec.$^{-1}$, calculated for the formation of N-*t*-butylacrylamide at the same value of H_0 ($H_0 = 1.60$ for 0.45 M H_2SO_4 and 1 M *t*-butyl alcohol). The relative rates are 2.8/1 and this is interpreted to mean that the protonated *t*-butyl alcohol reacts 2.8 times as fast with water as with acrylonitrile. With propionitrile, water reacts about 1.4 times as fast.

The similarity in rates in itself could be interpreted as due to an unstable cation intermediate which is not selective in its reactions or it could

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equally well be interpreted as due to weak bonding of the incoming group which thus has a relatively small effect on the free energy of the transition state. The latter interpretation is more in accord with eq. 4 and the experiments of Doering and Zeiss.[3]

These results on *t*-butyl alcohol make it probable that the oxygen exchanges on 2-butanol are simple displacements on the protonated alcohol by water. The result that each exchange proceeds with inversion[14] is thus a most natural result. The author's conclusion that water was not covalently bonded to the transition state was based on the Hammett-Zucker hypothesis which is now suspect.[6]

It is of interest that substitution reactions of even triphenylmethyl derivatives become displacement reactions in non-ionizing media.[15] In these circumstances, the reactions are like those of the *t*-butyl derivatives discussed above in that the rate shows little variation with the nature of the incoming group.[16] It is hard to see how these reactions can proceed in any other way than with inversion of configuration and we are currently studying this problem.

Although we have interpreted the reactions of *t*-butyl derivatives as an extreme type of displacement reaction (SN2), some of the characteristics closely resemble those of an ideal SN1 reaction. Thus the rates depend primarily on the structure of the *t*-alkyl group and may parallel the cation stability as has been shown for solvolysis of diarylmethyl derivatives.[17] Also the large charge separation in the transition state will cause the variation of rate with media to be similar to that found for an ideal SN1 reaction. This intermediate type of nucleophilic displacement reaction as exemplified by the substitution reactions on *t*-butyl alcohol have a unique character of their own and it may be convenient to term them SN(int.) reactions.

Hydrolysis of Acrylonitrile to Acrylamide.—The data in Table V show that to within 10–30% $d \log k = -dH_0$. The transition state contains acrylonitrile and a proton. The presence or absence of water is undecided.

Acknowledgment.—We wish to acknowledge discussions with Dr. R. W. Taft, Jr.

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[CONTRIBUTION FROM THE GEORGETOWN UNIVERSITY AND NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

The Binding of Ions to the Muscle Proteins. Measurements on the Binding of Potassium and Sodium Ions to Myosin A, Myosin B and Actin[1,2]

BY M. S. LEWIS AND H. A. SAROFF

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The binding of sodium and potassium ions to myosin A, myosin B, actin and bovine and human serum albumin was studied using electrodes made of collodion membranes which were permselective to cations. Data showing *p*H dependence, concentration dependence and temperature dependence were obtained. It was found that myosin A and myosin B bound sodium and potassium, but that the other proteins did not. The imidazol and amino groups appear to control the binding of sodium and potassium to myosin A and B. The values of the equilibrium constants for the interaction of sodium and potassium with the myosins were determined, and values for $\Delta F°$ and $\Delta H°$, were calculated.

Introduction

The interaction of potassium and sodium ions with the proteins of muscle is undoubtedly of considerable importance in the contractile processes in muscle. The extent of these interactions has been studied by several investigators by measuring the amount of the ion adsorbed by threads of myosin.[3–6] Their data present certain difficulties in interpretation because the threads represent a phase different from that of the solution in which they were equilibrated. This study was carried out on the viscous solutions and suspensions of the muscle proteins rather than on the precipitated thread. Other evidence for sodium and potassium ion binding to myosin can be found in Mihalyi's[7] hydrogen ion titration data at different salt concentrations.

When a suitable electrode exists for a certain ion, it is possible to determine the extent of the interaction of that ion with a protein by determining the activity of the ion in the presence of the protein. Hydrogen ion interactions with proteins have been studied using the hydrogen and glass electrodes. Scatchard, Scheinberg and Armstrong[8] studied the binding of chloride to serum albumin using silver–silver chloride electrodes. Carr has used permselective membranes as membrane electrodes to study the binding of cations and anions to a wide variety of proteins.[9]

(1) Taken in part from a doctoral thesis submitted by M. S. Lewis to the faculty of Georgetown University in partial fulfillment of requirements for the degree of Doctor of Philosophy, June, 1955.

(2) Presented before the American Physiological Society at the 40th Annual Meeting of the Federation of American Societies for Experimental Biology, April 17, 1956, Atlantic City, N. J.

(3) L. J. Mullins, *Federation Proc.*, **1**, 61 (1942).

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Because permselective membranes selectively permit the transfer of only a single ion species from one solution to another solution of the same electrolyte, they act as a reversible electrode for that ion species.[10,11] This makes it possible to determine the activities of ions for which no specific reversible electrodes exist or where the use of such conventional electrodes offers considerable difficulty. This method was used in the studies described here to determine the activities of potassium and sodium in the presence of muscle proteins, and thus to determine the extent of their interaction.

Experimental

Myosin A was prepared by a modification of the procedure of Kessler and Spicer.[12] Five hundred grams of chilled, ground rabbit muscle was extracted for 10 minutes with 1500 cc. of ice-cold solution of 0.3 *M* KCl and 0.15 *M* *p*H 6.5 phosphate buffer. After 10 minutes, 6 liters of ice-cold water was added and the suspension was strained through gauze. The residue was used for the preparation of actin. The filtrate then was diluted slowly with 10 liters of cold water and the precipitated myosin allowed to settle. The supernatant was removed by aspiration and the precipitate was centrifuged. The separated precipitate was dissolved in 0.6 *M* KCl. This solution was diluted to 0.12 *M* by the addition of 4 volumes of cold water and clarified by centrifugation. Myosin was precipitated from the supernatant by dilution of the KCl to 0.03 *M* by the addition of 3 volumes of cold water. The myosin was collected by centrifugation and then re-dissolved in 0.6 *M* KCl. The myosin was stored at 0°.

At the time it was used the myosin solution was diluted to 0.12 *M* KCl and clarified by centrifugation. It was noted that the amount of insoluble material increased with the age of the preparation until after about seven days, no myosin would remain in solution. Whether this was essentially denatured myosin or some aggregate of myosin is not known. After centrifugation, the supernatant was diluted with 20 volumes of cold water, the *p*H adjusted to 5.4, and the myosin allowed to settle. The supernatant was removed by aspiration and the myosin concentrated by centrifugation. This procedure gave a protein concentration of 0.8 to 1.0% with a potassium content of about 0.006 *M*. Myosin A prepared in this manner was found to be homogeneous electrophoretically and in the ultracentrifuge. Measurements were made on the myosin within a period of 5 hours after the completion of the preparation.

Myosin B (natural actomyosin) was prepared[13] by extracting the ground muscle for 5 hours with an ice-cold solution of 0.75 *M* KCl, 0.01 *M* Na_2CO_3 and 0.04 *M* $NaHCO_3$. After extraction, the mixture was strained through gauze and then clarified by centrifugation. The binding activity of this protein was found to remain constant for at least three weeks when stored at 0°. The myosin was precipitated by diluting the solution with 30–40 volumes of cold water, and adjusting the *p*H to 6.8. After the myosin settled, the supernatant was removed and the precipitate concentrated by centrifugation. It was then redispersed in 30–40 volumes of cold water, the *p*H adjusted to 5.3, and the myosin allowed to settle again. The supernatant was removed and the precipitate was again concentrated by centrifugation. This gave a myosin concentration of 1.5 to 2.5% and with a potassium ion content of 0.001 *M* or less. This preparation was homogeneous neither electrophoretically nor in the ultracentrifuge.

Actin was prepared by the method of Tsao and Bailey.[14] The G-actin thus prepared was then clarified prior to use by centrifugation for 30 minutes at 75,000 × gravity. The amount of active polymerizable actin in the solutions thus produced was determined by measuring the protein content of the sample, polymerizing the actin, centrifuging down the gel, and determining the protein content of the supernatant which should be free of polymerized actin. Actin solutions prepared by this procedure and tested as described above had a protein concentration of about 2%, of which about one-half was active polymerizable actin.

The bovine serum albumin was the Armour crystalline product. The human serum albumin was fraction V obtained from the American Red Cross. These were dialyzed before use.

Membranes.—The strong acid type (negatively charged) collodion-base membranes used as the membrane electrodes were prepared by the method described by Neihof.[15] The solution used to prepare the membranes contained 0.15% sulfonated polystrene (mol. wt. ~70,000) and 3% collodion in a 50–50 alcohol–ether solution. The membranes were prepared by pouring this solution over 25 × 100 mm. test-tubes rotated in a horizontal position. Three layers were cast with an interval of five minutes between each layer. After the membranes were dried on the forms overnight, they were soaked in water for 30 minutes and water was forced between the membrane and the glass to facilitate removal of the membrane from the form. Glass rings were fitted to the membranes at their open end. After being dried for one hour in an oven at 60–70°, the membranes were stored in 0.1 *N* KCl or NaCl for at least three days before use.

These membranes were clear, colorless and free of wrinkles. They were approximately 50 μ thick and their resistance was approximately 200 ohms/sq. cm. in 0.1 *M* KCl. These membranes gave an average potential of 15.55 mv. (corrected for difference in liquid junction potential) with 0.2 *M* KCl on one side of the membrane and 0.4 *M* KCl on the other. This compares well with the theoretical maximum of 16.00 mv. at 27°, and indicates a high degree of selectivity.

Saturated calomel cells were used as indifferent reference electrodes in the measurement of the potentials. Agar-saturated KCl bridges were used to connect these cells to the solutions on each side of the membrane. Both cells were maintained at the same temperature in a bath to avoid thermal asymmetry potentials. The potentials were measured with a Leeds and Northrup type K potentiometer.

In the determination of the concentration of the potassium or sodium ion in a solution,[10,11] the solution of unknown concentration was placed inside the membrane tube and the membrane was immersed to about two-thirds of its length in 100 ml. of water in a 150-ml. beaker and clamped in position. Various volumes of 1.00 *M* KCl or NaCl were added to the external solution, the external solution stirred thoroughly, and the potential measured. Slight asymmetries in the liquid junction potential were found even when the solution was the same on both sides of the membrane. This difference was measured over a range of concentrations, and used to correct the measured potentials. If the potentials obtained are plotted against the logarithm of the concentration, a straight line will result. At the zero potential obtained from their graph, the activities of the critical ion inside and outside the membrane are the same, and it has been assumed here that their concentrations are the same. In this manner it was possible to determine the concentration of an unbound ion in the presence of a protein, and since the total quantity of that ion present could be readily determined, the amount bound could be calculated.

Twenty cc. ±0.02 cc. samples of the protein solutions were used. These were weighed out because the viscosity of the protein solutions made accurate pipetting difficult. The temperature of the solution was adjusted just before use, the desired amount of 1.00 *N* KCl or NaCl added, and the *p*H adjusted with dilute KOH or NaOH of known concentration. The *p*H was adjusted to within ±0.05 *p*H unit. The salts used to adjust the K^+ or Na^+ content were recrystallized three times to remove traces of impurities which produced erratic results. The protein concentrations were determined by dry weights of samples of known volumes. The residual potassium or sodium content of the protein solutions was determined with the flame photometer.

Experimental Errors.—For myosin B at *p*H 7.7, and at a free concentration of 0.01 *M* K^+, the standard error in $\bar{\nu}_K$ is 1.5%, and at 0.1 *M* K^+ is ±7.5%. For myosin A, which was used at a lower protein concentration, the error at 0.01 *M* K^+ is ±2.5%, and at 0.1 *M* K^+ is ±18%. These errors are somewhat higher at *p*H 6.4 and lower at *p*H 9.0. These

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are the errors intrinsic in a single measurement. The errors in the apparent constants n' and k'_K were calculated from the scatter of the experimentally determined values of $\bar{\nu}_K$, after assuming that the data at pH 6.4 and pH 9.0 were essentially representative of the first and second sets of sites, respectively (see below). The errors in the apparent constants were determined by applying the least squares procedure using the equation

$$\frac{1}{\bar{\nu}_K} = \frac{1}{n'k'_K c_K} + \frac{1}{n'}$$

The values of $1/\bar{\nu}_K$ were so weighted that the variance of $1/\bar{\nu}_K$ was proportional to $1/c_K$. This was necessary to give equal weight to each value of $\bar{\nu}_K$. If this is not done, the low values of $\bar{\nu}_K$ have a much greater weight than high values of $\bar{\nu}_K$, and unrealistic variances of n' and k' result. It is shown in eq. 6 below that the apparent constant multiplied by $(1 + k_{H_1}c_H)$ gives the constant k_{K_1} when n and n' are assumed to be equal. Thus, the values of k'_{K_1} and k'_{K_2} multiplied by $(1 + k_{H_1}c_H)$ for the first set of sites (pH 6.4) and by $(1 + k_{H_2}c_H)$ for the second set of sites (pH 9.0) yield the values of k_{K_1} and k_{K_2} with their associated errors. This operation required an additional estimate of the errors in k_{H_1} and k_{H_2} and their inclusion in the calculation. The range in error of k_{H_1} and k_{H_2} was determined to be ± 0.2 pK unit from the curves shown in Fig. 1. (A change in 0.5 pK unit, the dotted curves, shifted the curve of the pH 7.7 binding by 0.3 of a pK unit too far out of a fit.) The errors shown in Tables II and III were thus calculated with the assumption that k'_K was independent of k_H.

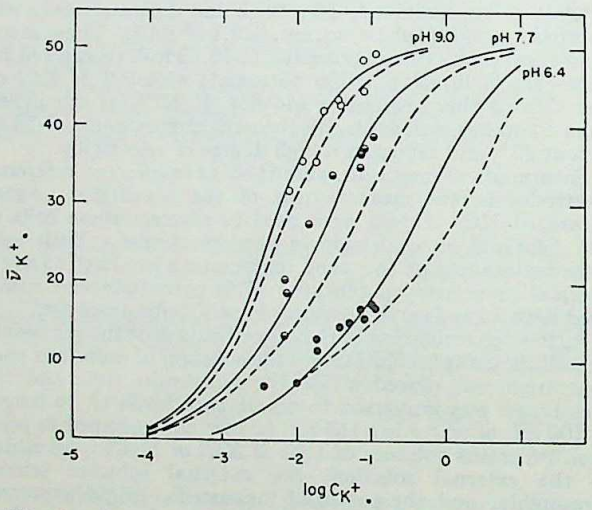

Fig. 1.—Concentration dependence data for the binding of potassium ions to myosin at 5°: ●, pH 6.4; ⊖, pH 7.7; ○, pH 9.0. Solid curves calculated from the constants shown in Table II using eq. 6. Dotted curves calculated from eq. 6 with the same constants except that the value of k_{H_2} has been changed to 10^9.

Myosin A—Results

Binding of potassium and sodium ions to myosin A was measured at 5°. It was important to avoid even brief exposures of myosin A to elevated temperatures. An exposure of a few hours at 27° resulted in a complete loss in binding ability of myosin A for potassium ions. Warming myosin A solutions to room temperature also brings about changes in sedimentation value.[16] The experimental points in Fig. 1 summarize our data on the concentration dependence of K^+ binding to myosin A at the pH values of 6.4, 7.7 and 9.0. Additional experiments were done at a free KCl concentration of 0.100 M at the pH values of 4.7, 5.2, 5.8, 6.4 and 7.0 to complete a pH dependence survey, the data for which are summarized in the experimental points of Fig. 2.

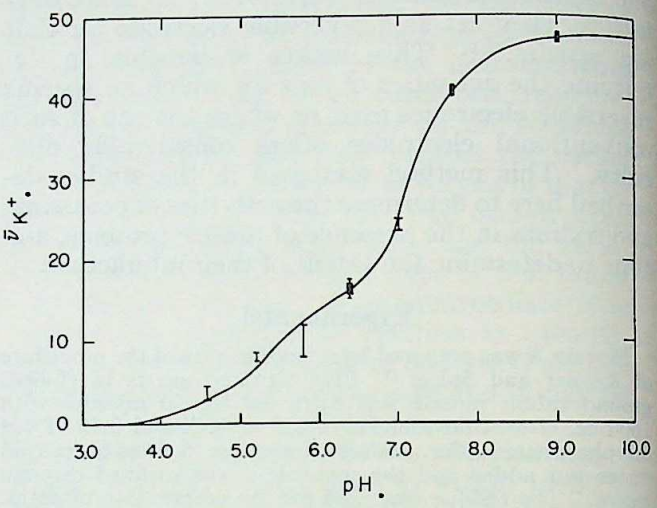

Fig. 2.—pH dependence data for the binding of potassium ions to myosin A at 5°. Concentration of free potassium ion was 0.100 M. Each symbol, I, represents the range of values from 3 to 4 measurements. The symbols, ▮, represent values found by interpolation of the concentration dependence data. The curve is calculated from eq. 6 and the constants in Table II.

Sodium ion binds to myosin A more strongly than does the potassium ion. A study of the concentration dependence of Na^+ binding to myosin A at 5° was made at pH 7.7. The data are represented in the experimental points of Fig. 3.

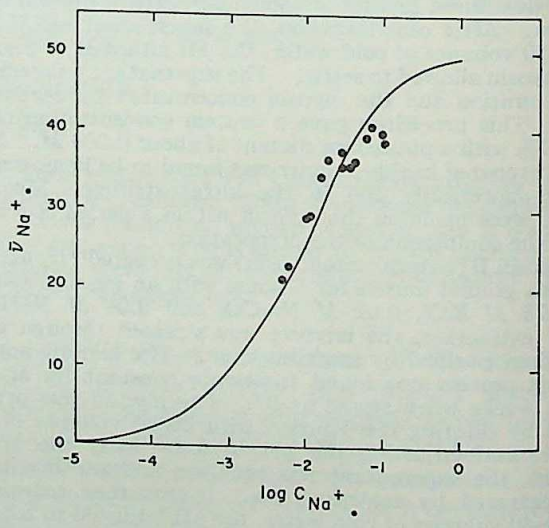

Fig. 3.—Concentration dependence data for the binding of sodium ions to myosin A at 5°, pH 7.7. The curve is that calculated from eq. 6 with the constants in Table II.

Effect of Actin on Binding of Potassium Ions to Myosin A.—To study the effect of actin upon the potassium binding of myosin A, various quantities of G-actin were added to samples of myosin A, the desired quantity of KCl was added, the pH adjusted to the desired value with KOH, and the free K^+ ion measured as previously described. The result of such an experiment is given in Fig. 4. If molecular weights of approximately 70,000 and 420,000 are taken for the actin and myosin A, respectively, then the potassium binding to the resulting actomyosin is at the same level as potas-

(16) K. Laki and W. R. Carroll, *Nature*, **175**, 389 (1955).

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sium binding to myosin B (see below) when the molar ratio of actin to myosin A is 0.5:1 or greater. The binding of potassium to actin alone was studied at pH's 7.7 and 9.0 over the concentration range of 0.004 to 0.100 M K^+. Under these conditions, no binding of potassium to actin could be detected.

Interpretation of Myosin A Data

Apparent association constants, k'_K, and apparent maximum number of sites available n', may be evaluated from the concentration dependence data of Fig. 1 and the use of the mass law expression[17]

$$\bar{\nu}_K = \frac{k'_K c_K n'}{1 + k'_K c_K} \qquad (1)$$

where $\bar{\nu}_K$ is the average number of potassium ions found per mole of myosin, c_K is the concentration of the free potassium ions in solution, n' is the apparent maximum number of binding sites, and k'_K is the apparent intrinsic association constant. The usual methods of evaluating these constants are to plot $1/\bar{\nu}$ as a function of $1/c$,[17] or to plot $\bar{\nu}/c$ as a function of $\bar{\nu}$.[18] The values of k'_K and n' are determined from the extrapolated intercepts and slopes. Table I lists the values of k'_K and n' found in this manner from the concentration dependence curves at the three pH values. In Table I are listed, also, the values of k'_K calculated[8] from the k_{K_1} and k_{K_2} values of eq. 6 below. Both the variation of n' and k' with pH and the pH dependence data in Fig. 2 indicate the possibility of competition with hydrogen ion for the site to which the potassium ion is bound.

TABLE I

APPARENT BINDING CONSTANTS FOR MYOSIN A AT 5°

Bound ion	pH	n'	k'_K	$\frac{k_{K_1}}{1 + k_{H_1}c_H}$	$\frac{k_{K_2}}{1 + k_{H_2}c_H}$
K^+	6.4	18 ± 0.8	124 ± 24	89	..
K^+	7.7	43 ± 1.1	98 ± 11	..	..
K^+	9.0	50 ± 1.2	200 ± 33	..	150
Na^+	7.7	42 ± 0.6	225 ± 22	..	..

The following treatment involves the assumption of direct competition between hydrogen and potassium ion for the same site.[19,20]

Equations describing the competition at a single site are

$$\text{Site} + H^+ = (\text{Site } H^+)$$
$$\text{Site} + K^+ = (\text{Site } K^+) \qquad (2)$$

For a group of n sites per mole of protein, neglecting electrostatic corrections, the expression for the number of hydrogen ions bound per mole of protein, $\bar{\nu}_H$, becomes

$$\bar{\nu}_H = \frac{k_H c_H (n - \bar{\nu}_K)}{1 + k_H c_H} \qquad (3)$$

where k_H is the intrinsic association constant of the specific site ($k_H = 10^{pK}$) for hydrogen ion, c_H represents the concentration of the free hydrogen ion in solution, and $\bar{\nu}_K$ represents the number of

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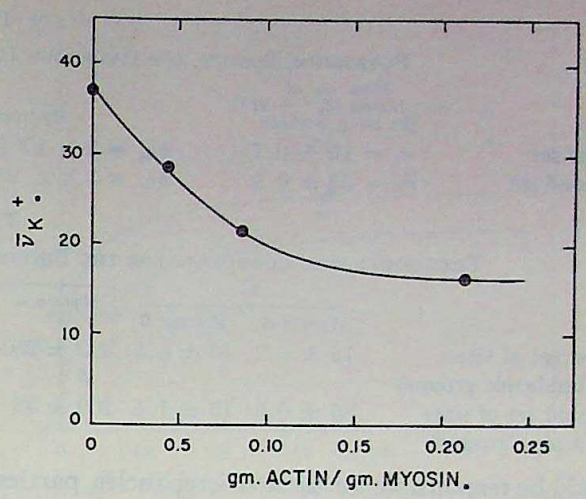

Fig. 4.—The effect of actin on the binding of potassium ions to myosin A at 5°, free K^+ concentration = 0.075 ± 0.002. (The curve is not a calculated one.)

potassium ions bound per mole of protein. The analogous expression for potassium ions is

$$\bar{\nu}_K = \frac{k_K c_K (n - \bar{\nu}_H)}{1 + k_K c_K} \qquad (4)$$

where k_K is the intrinsic association constant for the potassium ion, and c_K is the concentration of the free potassium ion. The solution of eq. 3 and 4 for $\bar{\nu}_K$ gives the expression

$$\bar{\nu}_K = \frac{k_K c_K n}{1 + k_K c_K + k_H c_H} \qquad (5)$$

If more than one set of sites is involved, equation 5 may be written

$$\bar{\nu}_K \text{ (total)} = \sum_i \bar{\nu}_{K_i} = \sum_i \frac{k_{K_i} c_{K_i} n_i}{1 + k_{K_i} c_K + k_{H_i} c_H} \qquad (6)$$

Thus, for this competitive concept, $k_{K_i} = k'_{K_i}(1 + k_{H_i} c_H)$ when n and n' are assumed to be equal.

Examination of the pH dependence data (Fig. 2) reveals that two sets of sites are probably active in potassium ion binding to myosin. When, therefore, two sets of sites, the first with $n = 15$ and the second with $n = 35$, are applied to eq. 6 the solid curves shown in Figs. 1 and 2 are calculated. These curves represent a satisfactory fit to the experimental data. Table II gives the values for n_1, n_2, k_{K_1}, k_{K_2}, k_{H_1} and k_{H_2} required for these calculated curves to fit the data on the assumption that there is competition as described by the eq. 2 and 6.

It is not too difficult to assign reasonable sets of ionizing groups to the pK and n values in Table II. Amino acid analysis[21] indicates that there are 15 histidine residues per 10^5 g. of myosin A. Mihalyi's titration data[7] indicate a pK of approximately 7 for imidazole groups at 25° (7.3 at 5°). Mihalyi's data also indicate approximately 25 amino groups with a pK of about 7.6 at 25° (8.2 at 5°) as well as a larger number at a pK between 10 and 11. The minor discrepancies between these values and the values of $n_2 = 35$ and $k_{H_2} = 3.3 \times 10^8$ (pK 8.5) found here may be at least partly attributable to the differences in the protein preparations used here and in Mihalyi's experiments. Differences of even small amounts of actin in the preparations

(21) D. R. Kominz, A. Hough, P. Symonds and K. Laki, *Arch. Biochem. Biophys.*, 50, 148 (1954).

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TABLE II

POTASSIUM, SODIUM AND HYDROGEN ION BINDING CONSTANTS FOR MYOSIN A AT 5°

	Max. no. of ions bound ($K^+ + H^+$) per 10^5 g. myosin	Association constants: Hydrogen ion	Potassium ion	Sodium ion
First set	$n_1 = 15 \pm 0.7$	$k_{H_1} = 2 \times 10^7$ ($pK_1 = 7.3$)	$k_{K_1} = 800 \pm 250$	$k_{K_1} = 1600 \pm 500$
Second set	$n_2 = 35 \pm 0.9$	$k_{H_2} = 3.3 \times 10^8$ ($pK_2 = 8.52$)	$k_{K_2} = 200 \pm 36$	$k_{K_2} = 400 \pm 72$

TABLE III

THERMODYNAMIC CONSTANTS FOR THE BINDING OF POTASSIUM IONS TO MYOSIN A AND MYOSIN B

	n_K		k_K			$\Delta F°_K$, cal./mole		$\Delta H°_K$, cal./mole av., 16°
	Myosin A	Myosin B	Myosin A 5°	Myosin B 5°	Myosin B 27°	5°	27°	
First set of sites (imidazole groups)	15 ± 0.7	10 ± 0.5	800 ± 250	800 ± 210	800 ± 210	−3690 ± 180	−3980 ± 160	0 ± 3100
Second set of sites (amino groups)	35 ± 0.9	15 ± 1.5	200 ± 36	200 ± 52	50 ± 10	−2930 ± 150	−2330 ± 120	−10,300 ± 2500

could be responsible for these discrepancies, particularly that in the value of n. Studies on myosin B, see below, support this line of reasoning.

Two other competitive mechanisms have been considered, particularly in an attempt to explain the anomalously high association constants for the binding of Na^+ and K^+ to myosin.[22] These mechanisms involve hydrogen bonding and may be described by the reactions

$$—COO^-....H_3^+N- + K^+ = -COOK + H_3^+N- \quad (7)$$

$$—COO^-....H_3^+N- + K^- = -COO^-..K^+..H_2N- + H^+ \quad (8)$$

Equation 7 represents competition between the potassium and ammonium (or imidazolium) ions for the carboxylate ion. Equation 8 represents competition between H^+ and K^+ for the hydrogen bonded and chelated positions, respectively.

Application of the binding expression derived from the idea in equation 7 can result in a satisfactory fit of the experimental data. However, the binding constants required for the fit were such as to result in abandoning the reaction of equation 7 as an explanation for Na^+ and K^+ binding.

The chelation mechanism of equation 8 results in a binding expression which not only fits the data but does so with values of the binding constants approaching those found for the direct competitive reaction of eq. 6. This chelation mechanism, while not changing the binding constants appreciably, makes the values of these constants more acceptable in light of our knowledge of the chelation of small compounds with Li^+, Na^+ and K^+.[23]

Myosin B—Results and Interpretation

The instability of preparations of myosin A at temperatures above 5° makes difficult a study of the temperature dependence of the potassium ion binding. Myosin B may be considered to be a complex of myosin A and actin and was, therefore, chosen as the protein to study for temperature dependence of the binding. Myosin A is the protein of choice for binding studies because this protein appears monodisperse on examination in both centrifugal and electrical force fields. However, myosin B, while stable at room temperature, is polydisperse under the conditions of these potassium ion binding studies. The heterogeneity of myosin B prepared in these studies was found to increase at pH 9.0. Blum[24] has reported a study of the dissociation of myosin B occurring at pH 9 and at relatively high salt concentrations.

Measurements were made at the pH values of 6.4, 7.7 and 9.0, and at the temperatures of 5 and 27°. The experimental points of Figs. 5 and 6 represent these data. Figure 7 summarizes all the experimental data collected at pH 9.0. The data with the free potassium ion concentration above 0.06 M at pH 9.0 were not used in the interpretation of the myosin B binding since we believe that the irregularities noted were caused by the dissociation and heterogeneity phenomena. The solid curves drawn in Figs. 5, 6 and 7 for the data at 5° are calculated curves derived from eq. 6 with the same association constants as those found for myosin A but with $n_1 = 10$ and $n_2 = 15$ for myosin B. (This lower number of binding sites may be attributed to the actin content.) The data fit well the calculated curves at pH 6.4 and 7.7, while there is a discrepancy of one order of magnitude for the value of k_{K_2} at pH 9.0.

The following procedure was used in evaluating the association constants for myosin B at 27°. First, the shifts in pK values for the hydrogen ions from 5 to 27° were calculated using the van't Hoff expression

$$\Delta H°_{ion} = -4.579 \frac{T_1T_2}{T_1 - T_2}(pK_2 - pK_1) \quad (9)$$

The values of $\Delta H°_{ion}$ used were 6,000 cal. for the imidazole groups and 11,000 cal. for the amino groups. This gave association constants at 27° of $k_{H_1} = 1 \times 10^7$ (pK 7.0) and $k_{H_2} = 8.7 \times 10^7$ (pK 7.94). Then, values of n and k_K at 27° were found to fit the experimental data. These were found to be $n_1 = 10$, $k_{K_1} = 800$, and $n_2 = 15$, $k_{K_2} = 50$.

The calculated curves and experimental data show satisfactory agreement except, again, for some of the data at pH 9. With the reservation that the discrepancies at pH 9.0 must be adequately explained, it appears reasonable to assume that similar sites in both myosin A and B bind potassium ions. The difference appears to lie in the number of sites available for binding. With the assumption that eq. 1 and 6 describe the binding reaction of potassium ions to myosin and that the extrapola-

(22) A detailed treatment by H. A. S. of these competitive mechanisms will appear elsewhere.

(23) A. E. Martell and M. Calvin, "Chemistry of the Metal Chelate Compounds," Prentice–Hall, Inc., New York, N. Y., 1952, Appendix I.

(24) J. Blum, *Biochem. Biophys.*, 43, 176 (1953).

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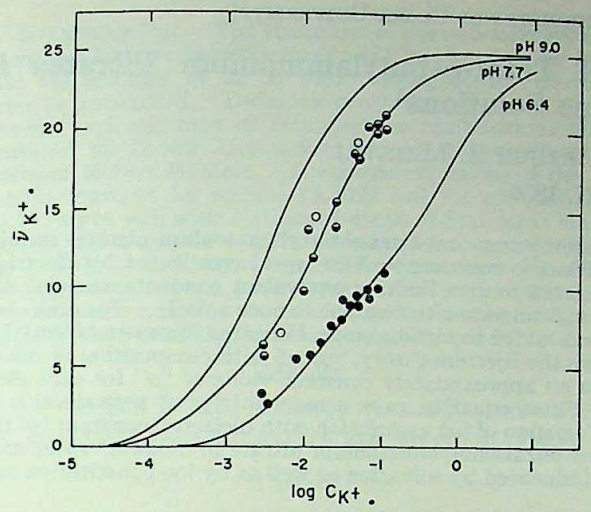

Fig. 5.—Concentration dependence data for the binding of potassium ions to myosin B at 5°: ●, *p*H 6.4; ◒, *p*H 7.7; ○, *p*H 9.0. Curves calculated from eq. 6 and the constants in Table III (k_H values from Table II).

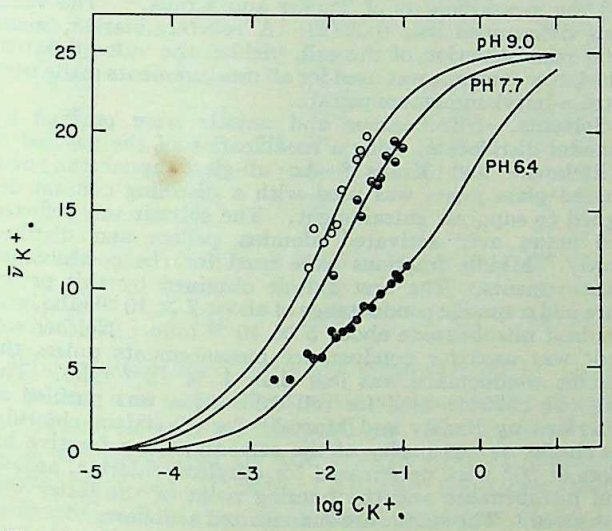

Fig. 6.—Concentration dependence data for the binding of potassium ions to myosin B at 27°, ●, *p*H 6.4; ◒, *p*H 7.7; ○, *p*H 9.0. Curves calculated from eq. 6 and the constants in Table III (the k_H values were calculated as explained in the text from the van't Hoff expression).

tion from myosin A to myosin B is legitimate, the values of $\Delta F°$ and $\Delta H°$, for the binding of K^+ to the imidazole and amino groups of myosin A and B were calculated using the relations

$$\Delta F°_K = -RT \ln k_K \qquad (10)$$

$$\Delta H°_K = RT^2 \left(\frac{\partial \ln k}{\partial T}\right)_P \qquad (11)$$

Table III summarizes the values for the binding sites of myosin.

Serum albumin, both human and bovine were studied at 27° in the *p*H range from 5 to 9 and in a concentration range from 0.01 to 0.09 *M* KCl. No binding ($\bar{\nu} = 0 \pm 1$) of potassium ions was found to occur under these conditions.

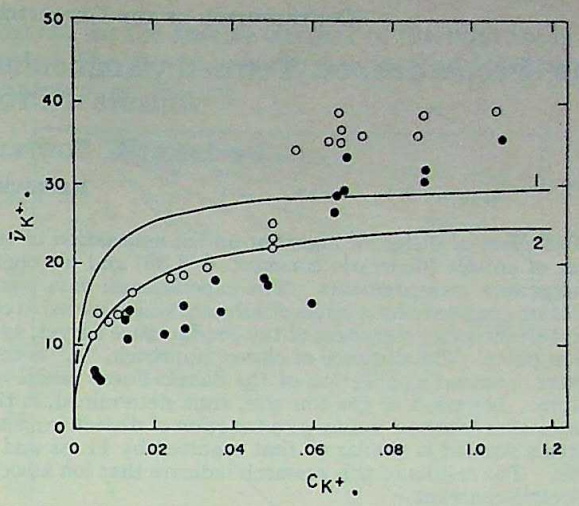

Fig. 7.—The binding of potassium ions to myosin B at *p*H 9.0: ●, 27°; ○, 5°. Curve 1 calculated for 27°, curve 2 calculated for 5° from eq. 6 with the same constants as in Figs. 5 and 6.

Actin was studied at 27° and at *p*H 7.7 and 9.0. No binding of potassium ions was found in the concentration range from 0.005 to 0.09 *M* KCl.

Discussion

The validity of the assumption that the activity coefficients of the free potassium and sodium ions are not affected seriously by the myosin is supported by the following observations: (1) the binding of sodium ions is stronger than that of the potassium ions, and (2) warming the myosin A solutions to room temperature destroys the binding properties of the protein. The second supporting argument requires the qualification that large changes in what constitutes the domain of the molecule (per unit weight) in solution do not occur in the warming process. Additional study of the temperature effect will be required to describe completely the change in myosin, particularly in light of the proposed chelation mechanism.

The temperature dependence data are subject to the limitations already described. The $\Delta H°_K$ for the first set of sites (imidazole groups) is similar to that found for association reactions between ions where it is assumed that oriented water of hydration is lost to give an increase in entropy. It is difficult to speculate on the reasons for the positive $\Delta H°_K$ value for the second set of sites (amino groups) in light of the uncertainties in the *p*H 9.0 data for myosin B. The difficulties in obtaining good temperature dependence data for binding to a protein such as myosin are intrinsic in the nature of this protein.

Acknowledgment.—The authors are indebted to Dr. G. Scatchard, Dr. R. Neihof and Dr. M. Morales for their valuable comments, criticism and assistance.

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[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY OF CLARK UNIVERSITY]

The Properties of Tetraethylammonium and Tetra-*n*-butylammonium Picrates in Anisole–Nitrobenzene Solutions[1]

BY ARNET L. POWELL[2] AND ARTHUR E. MARTELL

RECEIVED JULY 27, 1956

The effect of dielectric constant on ion association of tetraethylammonium and tetra-*n*-butylammonium picrates in mixtures of anisole (dielectric constant = 4.30) and nitrobenzene (dielectric constant = 34.9) was investigated by electrical conductance measurements. The experimental data were extrapolated to give limiting equivalent conductances and dissociation constants for a series of solvents which varied in composition from pure nitrobenzene to pure anisole. For each electrolyte, increasing steepness of the conductance curves, as anisole was added to nitrobenzene, indicated increasing formation of ion pairs. The distance of closest approach, "*a*," computed from the Bjerrum theory, varied with composition of mixed solvent, whereas application of the Sadek–Fuoss model resulted in an approximately constant value of "*a*" for each electrolyte. Insertion of the ion size, thus determined, in the Sadek–Fuoss equation gave a reaonably good reproduction of dissociation constant values as a function of dielectric constant. Variation of ion association with dielectric constant for the systems studied is similar to that reported by Fuoss and Kraus for tetraisoamylammonium nitrate in dioxane–water mixtures. The results of this research indicate that ion association is influenced by solvation as well as by ion constitution and dielectric constant.

Fuoss and co-workers[3–8] have conducted a series of investigations of electrolye–solvent interactions, using the single electrolyte, tetrabutylammonium bromide, in a variety of solvent mixtures. They found that the Bjerrum model was not satisfactory for all systems investigated, the values of the ion size "*a*" calculated from dissociation constants varying with composition of the solvent mixtures. In a number of cases, changes in ion association, observed for intermediate solvent compositions, were attributed to specific electrolyte–solvent interactions.

In this investigation, two quaternary ammonium salts—tetraethylammonium picrate and tetra-*n*-butylammonium picrate—are studied in mixtures of anisole and nitrobenzene. By variation of the solvent composition over the whole range, a variation of dielectric constant from 34.9 to 4.3 is possible. This combination of solvents offers the additional advantage of providing an opportunity of studying the effect of dielectric constant on solution conductance in a non-aqueous aprotic solvent relatively free of solute–solvent and solvent–solvent interactions. A study of conductance and ion association in such a medium would be of interest for comparison with the results of Fuoss and Kraus[9] for tetraisoamylammonium nitrate in dioxane–water mixtures.

Experimental

Apparatus.—The conductance bridge employed was a modification[10] of the design described by Foy and Martell.[11] A 0–20,000 cycle audio oscillator (General Radio No. 913-G) was used in all measurements. Temperature of the conductance cell was maintained at 25° within ±0.003° by means of a thermostatically-controlled constant-temperature oil-bath. Measurement and bath control were aided by dehumidification and regulation of room temperature in the range of 21–22°. The conductance cell was designed according to the specifications of Kraus and Fuoss,[12] and the cell constant was determined by measurement of the conductances of tetraethylammonium and tetra-*n*-propylammonium picrates in ethylene chloride, taking as standard the measurements of Tucker and Kraus.[13] The value thus determined was 0.03410. A redetermination, made after reconstruction of the cell, yielded the value 0.04163. The latter constant was used for all measurements made with tetra-*n*-butylammonium picrate.

Solvents.—Nitrobenzene and anisole were purified by vacuum distillation, using a modification of the method of Witschonke and Kraus.[14] An all-glass apparatus with ground glass joints was used with a distilling column designed to suppress entrainment. The solvent was refluxed 4–6 hours over activated alumina pellets and distilled slowly. Middle fractions were used for the conductance measurements. The best anisole obtained by this procedure had a specific conductance of about 7×10^{-11} mho, and the best nitrobenzene about 5×10^{-10} mho. Neither solvent was used for conductance measurements unless the specific conductance was less than 1×10^{-9} mho. The ethylene chloride used for cell calibration was purified as described by Healey and Martell[15] for ethylidene chloride. As checks on the purity of the solvents, the refractive indices at 20° were determined for ethylene chloride, anisole and nitrobenzene and the freezing point of the latter was measured. The results are summarized as follows

Solvent	$n^{20}D$ Measured	$n^{20}D$ Lit.	F. p., °C. Measured	F. p., °C. Lit.
Anisole	1.5170	1.5170[16]		
Ethylene chloride	1.4444	1.4443[17]		
Nitrobenzene	1.5524	1.5529[18]	5.82	5.72[19]
				5.50–5.85[20]

Measurements.—Densities of the solvents and solvent mixtures were determined in a 5-ml. pycnometer at 25 ± 0.01°. Doubly distilled water was used as the calibrating liquid. In the case of nitrobenzene, the best literature value of the density, 1.1987 g./ml.,[21] was used in the calculations in place of the measured value, 1.1983 g./ml. For anisole, the measured density, 0.9888 g./ml., was employed; Bien, Kraus and Fuoss[22] reported that the density of anisole at

(1) Abstracted from a Dissertation submitted by Arnet L. Powell to the Faculty of Clark University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1956.
(2) Office of Naval Research, Boston, Mass.
(3) H. Sadek and R. M. Fuoss, THIS JOURNAL, **72**, 301 (1950).
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(13) L. M. Tucker and C. A. Kraus, *ibid.*, **69**, 454 (1947).
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(16) "International Critical Tables," Vol. I, McGraw–Hill Book Co. Inc., New York, N. Y., 1926, p. 277.
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(18) Ref. 16, p. 38.
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(20) Landolt–Bornstein, "Physikalisch–Chemische Tabellen," 5th ed., Julius Springer, Berlin, 1935, 3rd supplement, p. 342.
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(22) G. S. Bien, C. A. Kraus and R. M. Fuoss, THIS JOURNAL, **56**, 1860 (1934).

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25° is 0.9890 g./ml. The viscosities of the two solvents and a series of intermediate mixtures were measured in an Ostwald viscosimeter at 25 ± 0.01°, using doubly distilled water as a standard. Dielectric constants of anisole, nitrobenzene and mixtures of intermediate compositions were measured at Brown University through the courtesy of Professor Robert H. Cole. The measured values of the dielectric constant for anisole (4.302) and for nitrobenzene (34.91) agree well with National Bureau of Standards measurements (D of anisole = 4.33, D of nitrobenzene = 34.82).[23] The salts used had been prepared by previous workers.[10,15] Melting points were in good agreement with the literature. The procedure used for the conductance measurements was similar to that described by Healey and Martell.[15]

Results

The results of the density, viscosity and dielectric constant measurements are given in Table I.

TABLE I

PROPERTIES OF ANISOLE–NITROBENZENE MIXTURES AT 25°

Nitrobenzene, wt. %	Nitrobenzene, mole fraction	Density, g./ml.	Viscosity, poise	Dielectric constant
0.00	0.0000	0.9888	0.01008	4.30
8.30	.0736	1.0032	.01040	5.82
19.81	.1783	1.0240	.01091	8.00
29.20	.2659	1.0418	.01145	10.04
33.34	.3052	1.0502	.01170	11.02
40.61	.3752	1.0664	.01219	12.80
42.93	.3978	1.0709	.01234	13.43
49.59	.4635	1.0842	.01279	15.27
56.85	.5364	1.0981	.01330	17.55
69.72	.6691	1.1266	.01434	21.77
80.92	.7884	1.1526	.01546	26.00
88.95	.8760	1.1710	.01646	29.59
100.00	1.0000	1.1987	.01823	34.91

The conductance data are summarized in Table II, where Λ is equivalent conductance and c is concentration in equivalents per liter. The various systems are identified by the weight % nitrobenzene above each set of data. All the solutions were sufficiently dilute so that their densities could be taken as that of the solvent without incurring appreciable error. Corrections for solvent conductance were negligible even in the most dilute solutions.

Discussion

In order to eliminate the effects of changing viscosity from mixture to mixture so that attention could be directed to the effect of variation in dielectric constant, the conductances in Table II were divided by the appropriate values of Λ_0, and Λ/Λ_0 was plotted against the square root of concentration.[6] The results are illustrated in Figs. 1 and 2.

To avoid crowding in these graphs, the curves for the 100% anisole and for the 88.95% nitrobenzene–11.05% anisole mixture in the tetraethylammonium picrate series and the curve for the 93.38% nitrobenzene–6.62% anisole mixture in the tetra-*n*-butylammonium picrate series were omitted. The limiting tangent determined from the Onsager equation is shown on each figure. As anisole is added to nitrobenzene, the dielectric constant of the mixture decreases, and an increase in ion association at a given concentration is observed (Figs. 1 and 2). In nitrobenzene, the curves are approximately straight lines and lie only a little below the limiting tangent. As the anisole content of the mixture is increased, the curves become progressively steeper at a given concentration.

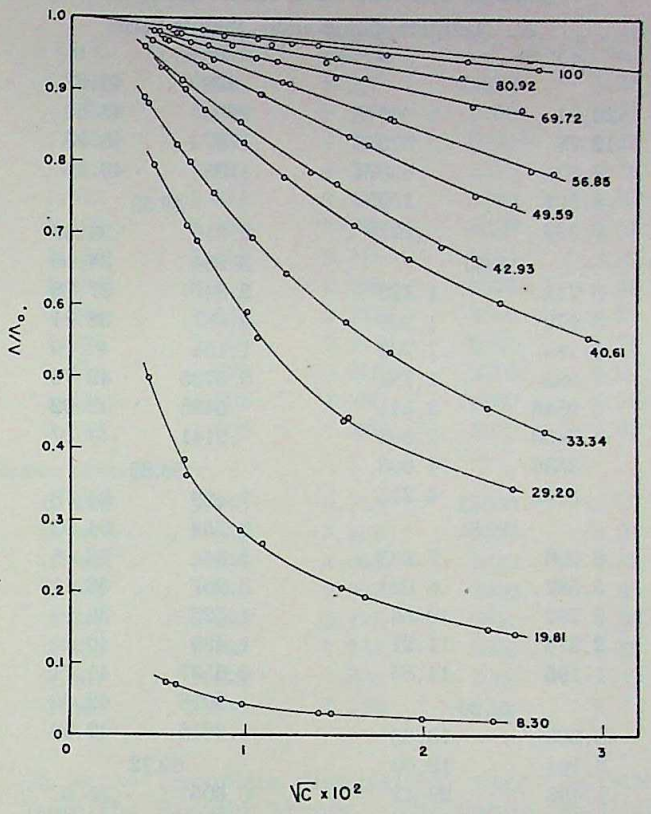

Fig. 1.—Reduced conductance curves: tetraethylammonium picrate in anisole–nitrobenzene mixtures. Figures to right of curves are weight % nitrobenzene.

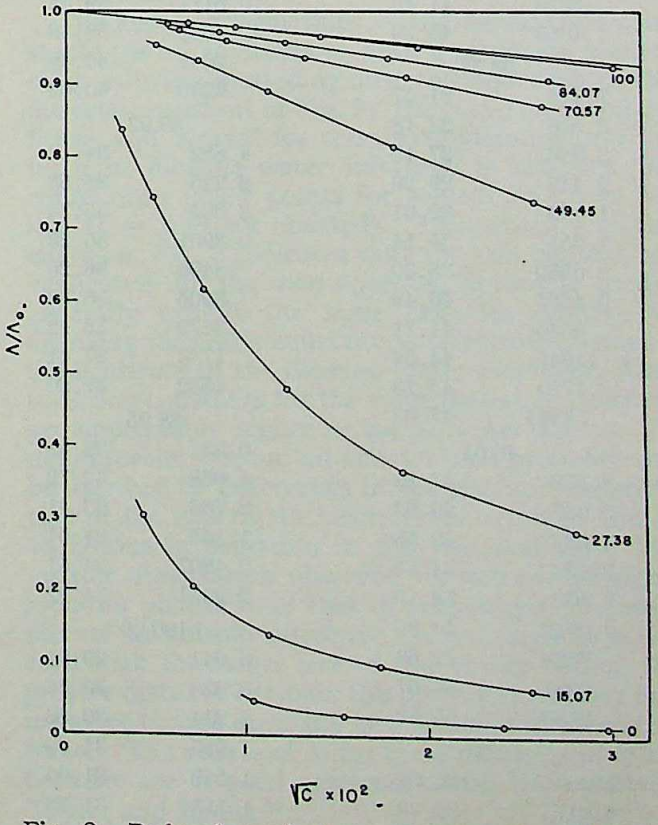

Fig. 2.—Reduced conductance curves: tetra-*n*-butylammonium picrate in anisole–nitrobenzene mixtures. Figures to right of curves are weight % nitrobenzene.

(23) Natl. Bur. Standards Circular No. 514, 1951, pp. 18, 23.

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TABLE II

CONDUCTANCE OF QUATERNARY AMMONIUM PICRATES IN ANISOLE–NITROBENZENE MIXTURES AT 25°

A. Tetraethylammonium Picrate Series

$c \times 10^4$	Λ	$c \times 10^4$	Λ
0.00		.3938	43.83
20.91	0.06675	.2905	44.60
12.78	.07275	.1767	46.08
7.839	.08374	.1135	46.58
4.521	.1025	49.59	
2.699	.1219	6.310	33.97
8.30		5.254	34.55
5.718	1.123	2.847	37.78
3.972	1.309	2.487	38.31
2.189	1.706	1.154	40.99
1.982	1.783	0.5736	42.75
0.9546	2.511	.5496	42.92
.7406	2.802	.2141	44.37
.3530	4.008	56.85	
.3052	4.215	7.429	34.78
19.81		6.753	34.93
6.296	7.683	3.344	38.06
5.587	8.024	3.267	38.11
2.792	10.53	1.525	39.88
2.375	11.21	1.439	40.24
1.195	14.55	0.6537	41.71
29.20		.3018	42.89
6.263	18.06	.2816	42.90
6.194	18.09	69.72	
2.496	23.42	6.505	35.67
1.063	28.86	5.043	35.78
1.006	30.82	2.762	37.42
0.5082	35.94	1.374	38.37
.4384	37.01	1.096	38.56
.2220	41.40	0.6111	39.32
.1083	45.29	.4632	39.38
33.34		.2641	40.06
7.176	21.57	.2230	40.09
5.596	23.18	80.92	
3.288	27.15	4.882	34.59
2.442	29.29	2.246	35.58
1.499	32.61	2.094	35.34
1.051	35.14	0.8901	36.28
0.6580	38.30	.8496	36.20
0.4584	40.49	.3906	36.83
.3640	41.71	.3679	36.92
.1945	44.64	.1733	37.41
.1729	45.13	.1532	37.60
.08464	47.62	88.95	
40.61		6.381	32.48
8.578	27.22	4.968	32.72
5.907	29.62	2.788	33.41
3.683	32.58	1.165	34.01
2.578	34.81	0.4967	34.61
1.463	38.15	0.2341	34.97
0.9642	40.46	100.00	
.7628	42.68	6.941	29.91
.3981	44.07	5.028	30.36
.2580	45.53	3.214	30.56
42.93		1.955	31.00
5.203	32.08	1.559	31.06
4.417	32.78	1.118	31.33
2.270	36.88	0.7551	31.39
1.857	37.72	.5595	31.68
0.9286	41.05	.3125	31.73

B. Tetra-*n*-butylammonium picrate series

0.00		70.57	
14.35	0.05606	7.014	29.76
8.838	.06567	3.611	31.15
5.772	.07698	1.804	32.06
15.07		0.8095	32.87
6.559	3.232	.4010	33.35
3.017	4.453	84.07	
1.285	6.398	7.216	28.44
0.5143	9.413	3.251	29.38
.1917	14.05	1.498	30.05
27.38		0.7360	30.50
7.890	12.42	.3194	30.91
3.509	16.19	93.38	
1.533	20.99	7.608	26.37
0.5886	27.15	2.793	27.17
.2352	32.79	1.194	27.57
.1010	36.97	0.5442	28.16
49.45		.2251	28.55
6.785	28.23	100.00	
3.357	31.13	17.65	25.05
1.279	34.08	9.321	25.82
0.5484	35.83	3.860	26.56
.2556	36.61	2.022	26.97
.1158	37.49	0.9015	27.39
		.4603	27.55

The conductance data for solutions of both picrates in the solvent mixtures with $D \geqq 10$ were extrapolated by use of the Shedlovsky equation[24,25] to obtain limiting conductances and dissociation constants. The values obtained are given in Table III.

The values of Λ for anisole and for the solvent mixtures with $D < 10$ were approximated by use of Walden's rule.[26] The Walden products were computed for each quaternary ammonium picrate for all solvent mixtures with $D > 10$ and plotted *versus* mole fraction nitrobenzene.

Since approximately linear relationships were obtained for each picrate, it was possible to approximate Walden products for mixtures with lower dielectric constants by extrapolation. From these, Λ_0 was calculated for each solution by dividing by the appropriate viscosity. The values of the dissociation constant K were determined by application of the Ostwald dilution law.[9,27] The values of Λ_0 and K determined in this way are included in Table III as are Walden products $\Lambda_0\eta_0$ for all solvents and solvent mixtures investigated.

The free energy of dissociation for each solution of each picrate was computed from

$$\Delta E = 2.303RT \log K$$

The results, which are given in Table III, tend to approach the thermal energy of the solvent molecules ($\Delta E = RT = 596$ cal.) as the dielectric constant increases. The dielectric constant at the point of closest approach represents the critical value, and is in both cases beyond the highest dielec-

(24) T. Shedlovsky, *J. Franklin Inst.*, **225**, 739 (1938).

(25) R. M. Fuoss and T. Shedlovsky, THIS JOURNAL, **71**, 1496 (1949).

(26) C. Walden, *Z. physik. Chem.*, **55**, 207 (1906).

(27) T. A. Kraus and W. C. Bray, THIS JOURNAL, **35**, 1315 (1913).

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TABLE III

PROPERTIES DERIVED FROM CONDUCTANCE DATA FOR NITROBENZENE–ANISOLE MIXTURES AT 25°

A. Tetraethylammonium picrate

Nitrobenzene, mole fraction	Λ_0	$\Lambda_{0.70}$	K	log D	$-\log K$ (exptl.)	$-\log K$ (calcd.)	ΔE, cal.	$a \times 10^8$, cm.
0.0000	59.62[a]	0.6010[a]	9.40×10^{-10}	0.6335	9.025	9.025	12300	5.55
.0736	57.70[a]	.6000[a]	1.80×10^{-7}	.7649	6.745	6.530	9200	5.29
.1783	54.54[a]	.5950[a]	1.12×10^{-5}	.9031	4.951	4.947	6760	5.23
.2659	52.19	.5976	6.50×10^{-5}	1.002	4.187	4.094	5710	4.72
.3052	50.71	.5933	1.44×10^{-4}	1.042	3.842	3.820	5240	4.67
.3752	48.97	.5969	3.98×10^{-4}	1.107	3.400	3.432	4640	4.51
.3978	48.00	.5923	5.51×10^{-4}	1.128	3.259	3.315	4450	4.49
.4635	45.83	.5862	1.23×10^{-3}	1.184	2.910	3.025	3970	4.45
.5364	44.21	.5893	2.38×10^{-3}	1.244	2.623	2.745	3580	4.22
.6691	40.78	.5848	5.90×10^{-3}	1.338	2.229	2.313	3040	3.78
.7884	37.61	.5814	1.05×10^{-2}	1.415	1.979	1.956	2700	3.23
.8760	35.34	.5817	1.58×10^{-2}	1.471	1.801	1.690	2460	2.87
1.0000	32.15	.5861	3.02×10^{-2}	1.543	1.520	1.326	2070	2.65

B. Tetra-*n*-butylammonium picrate

0.0000	49.60[a]	0.5000[a]	1.09×10^{-9}	0.6335	8.963	8.705	12200	5.59
.1349	46.52[a]	.4970[a]	2.65×10^{-6}	0.8476	5.583	5.402	7620	5.31
.2487	44.21	.5009	4.92×10^{-5}	0.9827	4.308	4.095	5880	4.86
.4621	38.37	.4904	1.38×10^{-3}	1.183	2.860	2.929	3900	4.65
.6781	34.26	.4940	8.30×10^{-3}	1.344	2.081	2.183	2840	4.38
.8225	31.42	.4974	1.85×10^{-2}	1.438	1.733	1.742	2360	3.88
.9253	28.69	.4915	3.01×10^{-2}	1.501	1.521	1.433	2080	3.46
1.0000	27.97	.5099	7.67×10^{-2}	1.543	1.115	1.188	1520	4.67

[a] Estimated using Walden's rule.

tric constant available from the solvent system (D of nitrobenzene = 34.9).

The ion sizes "a" for each quaternary ammonium picrate were computed from the value of K for each solution by application of the Bjerrum equation.[28] The values of "a" for each salt thus obtained were not constant but varied with the composition of the solvent, as can be seen by referring to Table III. Hence, it was not possible to evaluate the mean ionic diameter by taking an average value, as was done by Fuoss and Kraus,[9] and the modified "sphere-in-continuum" theory of Sadek and Fuoss[8] was employed to obtain constant values of "a" for each solute. The relationship given by Sadek and Fuoss is

$$K = k_D/(1 + k_s)$$

where K is the ion-pair dissociation constant obtained by extrapolating the conductance data, K_D is the solvated ion pair dissociation constant calculated from the Bjerrum equation, and k_s is an empirically-derived "solvation constant" for the expulsion of the intervening solvent from an incipient ion pair. By the use of this method, "a" for tetraethylammonium picrate was found to be 5.8×10^{-8} cm., and for tetra-*n*-butylammonium picrate, 6.0×10^{-8} cm. The computed dissociation constants agree reasonably well with the experimentally-determined values, as can be seen by comparison of the $-\log K$ (exptl.) and $-\log K$ (calcd.) values in Table III. For both picrates, the average difference between the calculated and experimental values of $-\log K$ is 3.4%.

The values of the dielectric constant for each solute–solvent system corresponding to $K = 1$ and $K = \infty$ (complete dissociation) were computed from the Bjerrum theory. The values for tetraethylammonium picrate in anisole–nitrobenzene mixtures were 44 and 48, respectively; for tetra-*n*-butylammonium picrate, the corresponding values were 43 and 47.

The negative logarithms of the dissociation constants for all solutions of both quaternary ammonium salts are plotted against the logarithm of the dielectric constant in Fig. 3; the curve obtained by Fuoss and Kraus[9] for tetraisoamylammonium nitrate in dioxane–water mixtures is included for comparison (their points for solvent mixtures below $D = 3.48$ are omitted). Examination of the curves in Fig. 3 indicates that the two picrates investigated in the non-aqueous, aprotonic media generally exhibit the same behavior relative to changing dielectric constant as tetraisoamylammonium nitrate in the dioxane–water mixtures. Dissociation constants for the same dielectric constant are appreciably higher in the aqueous than in the non-aqueous system, an effect which probably can be ascribed to differences in the size and constitution of the ions of the electrolytes involved and to variations in solvation in the two systems. The greater dissociation observed for tetra-*n*-butylammonium picrate over that of tetraethylammonium picrate in anisole–nitrobenzene mixtures is in accord with the larger size of the former cation, the greater distance between the centers of positive and negative charge resulting in a decrease in attractive force. The values of Λ_0 for these two salts in nitrobenzene are in good agreement with the results of Taylor and Kraus.[29]

The values of the dielectric constant for $K = 1$

(28) N. Bjerrum, *Kgl. Danske Videnskab. Selskab, Mat.-Phys. Medd.*, 7, No. 9 (1926).

(29) H. S. Taylor and C. A. Kraus, THIS JOURNAL, 69, 1731 (1947).

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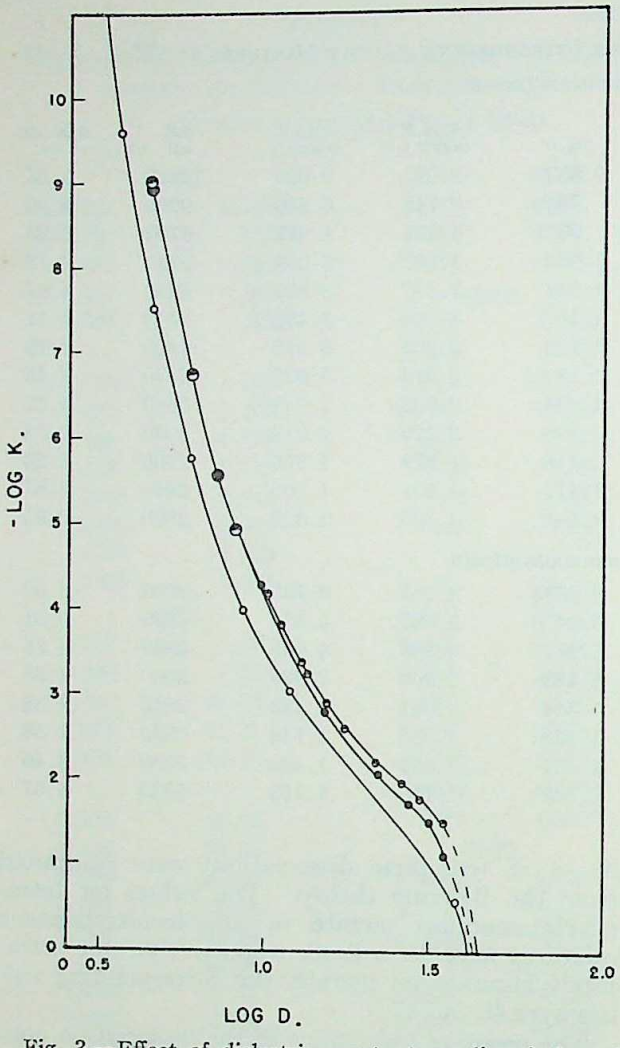

Fig. 3.—Effect of dielectric constant on dissociation of electrolytes in mixed solvents: ⊖, tetraethylammonium picrate in anisole–nitrobenzene mixtures; ●, tetra-*n*-butylammonium picrate in anisole–nitrobenzene mixtures; ○, tetraisoamylammonium nitrate in dioxane–water mixtures.

for each quaternary ammonium picrate in the anisole–nitrobenzene solvent system calculated using the "*a*" values derived from the Sadek–Fuoss model[8] appear to be reasonably close to the results which would be obtained by extrapolating the $-\log K$ *vs.* $\log D$ curves. In any event, these D values and the corresponding critical dielectric constants are only approximate, being limited by the uncertainties in the larger values of K as well as the validity of the assumptions underlying the Sadek–Fuoss model. Fuoss[6,8] and Kraus[30,31] have pointed out that reliable values of dissociation constants from conductance measurements cannot be obtained for $K > 0.01$ because of uncertainties in the magnitudes of the c and $c \log c$ terms in the Onsager equation.

Densities and molar volumes of the solvent mixtures change smoothly from anisole to nitrobenzene, and deviations from volume additivity are small, the maximum being about 0.16%. The values of dielectric constant also vary smoothly with composition of the solvent mixtures. The viscosities of the solvent mixtures change continuously from the less viscous anisole to nitrobenzene and the curve shows little structure. There is no evidence of specific interactions leading to sharp changes in ion association at intermediate solvent composition of the type observed by Fuoss, *et al.*[3–8] and by Kortum and co-workers.[32,33] Since the conductance–viscosity products are approximately constant for both systems investigated (Table III), it could be expected that Stokes' law would hold and that, at least hydrodynamically, the "sphere-in-continuum" model would be a good representation of the physical facts. Constancy of the Walden products requires that the effective ionic volumes should be constant: that is, the ion size "*a*" should not change for that particular system. However, the values of "*a*" calculated from the experimentally determined dissociation constants are not the same but vary continuously, decreasing with increasing nitrobenzene content.

There are two possible explanations which may be advanced to account for this situation. The first of these is that a solvation effect is involved. The observed increase of effective ion size with rising anisole content is consistent with an increase in solvation. Kraus[34] has shown that even large ions, such as quaternary ammonium ions, show specific differences in going from solvent to solvent and that frequently Stokes' law does not apply. Fuoss[8] has raised a possible objection to an explanation on a solvation basis in that this would require that the solvate shall remain intact in the ion pair. Regardless of the validity of this argument, the constancy of the $\Lambda_0\eta_0$ values for the systems investigated indicated that approximately constant ion sizes were to be expected.

The second explanation involves the assumption that the Bjerrum model does not apply to this system. When an anion and a cation are separated by appreciable distances, it seems reasonable to assume that the macroscopic dielectric constant of the medium is a good approximation for calculating the potential energy of the two ions approaching to form a pair. However, upon closer approach of the two ions, it is likely that such an approximation can no longer hold since the solvent molecules will be polarized by the intense electric fields of the ions. The Sadek–Fuoss model is an attempt, on an empirical basis, to solve this problem. It apparently works very well for tetrabutylammonium bromide in nitrobenzene–carbon tetrachloride mixtures[8] and reasonably well in this case for tetraethylammonium picrate and tetra-*n*-butylammonium picrate in anisole–nitrobenzene mixtures.

The results of this research confirm Kraus'[31] conclusion that the variation in ion size with changing dielectric constant cannot be attributed to experimental error. It is much more likely that the mean diameter of the solvated ions cannot be expressed precisely by the Bjerrum theory, and that some additional concept is required for the interpretation of experimentally-derived ion-pair dis-

(30) C. A. Kraus, *J. Phys. Chem.*, **58**, 673 (1954).
(31) C. A. Kraus, *ibid.*, **60**, 129 (1956).
(32) G. Kortum, S. D. Gorkhale and H. Wilski, *Z. physik. Chem., Neue Folge*, **4**, 286 (1955).
(33) G. Kortum and H. Wilski, *ibid.*, **5**, 333 (1955).
(34) C. A. Kraus, *Ann. N. Y. Acad. Sci.*, **51**, 789 (1949).

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sociation constants. Indeed, Azzari and Kraus[35] have shown recently that the Bjerrum equation fails completely in solutions of higher dielectric constant.

Acknowledgments.—The authors are indebted to Dr. C. A. Kraus of Brown University for suggesting this research topic and for valuable discussions and advice. Thanks are also due to Professor Robert H. Cole of Brown University for the use of his apparatus to measure dielectric constants of the solvent mixtures. Appreciation is expressed for solvents to The Dow Chemical Company for ethylene chloride, and the Calco Chemical Company for nitrobenzene.

WORCESTER, MASS.

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[CONTRIBUTION FROM THE BIOLOGICAL LABORATORIES, HARVARD UNIVERSITY, AND THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

The Association of 4-Methylimidazole with the Ions of Cupric Copper and Zinc; with Some Observations on 2,4-Dimethylimidazole

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The 4-methyl and the 2,4-dimethyl derivatives of imidazole have been studied in their interactions with hydrogen, cupric and zinc ions, at different temperatures. The *p*H titrations, in the absence of Cu or Zn ions, gave pK' values which were extrapolated to zero ionic strength. Heats of reaction and standard entropies associated with these pK values were also determined. ($\Delta H°$ is in the range 8.5 ± 0.7 kcal./mole and $\Delta S°$ in the range −6.5 ± 0.8 cal. deg.$^{-1}$ mole^{-1}.) Similar titrations, in the presence of Cu(II) and Zn(II), showed that the number of molecules of both imidazole derivatives, bound to either of these ions, approached an upper limit of 4, at high imidazole concentrations. This number is the same as for unsubstituted imidazole. The intrinsic association constants log $\kappa_i (i = 1,2,3,4)$ at 25° were found for 4-methylimidazole to be 3.53, 3.31, 3.05 and 2.56, respectively, for combination with Cu(II), and 1.84, 2.35, 2.82 and 2.98 for combination with Zn(II). Approximate values for $\Delta H°$ in the combination of 4-methylimidazole with these ions have been estimated. Incomplete studies on the binding of 2,4-dimethylimidazole to copper indicated association constants of the same order of magnitude, but somewhat smaller, than those for 4-methylimidazole. A discussion is given of the stereochemistry of the copper and zinc complexes, and of some of the structural implications of the observed association constants.

The reactivity of the imidazole group of the histidyl residue in proteins has assumed great importance for the understanding of interactions between proteins and several metallic ions.[4-6] A previous report described the application of a method suggested by Scatchard to the interpretation of the equilibria between the parent imidazole and Cu(II) and Zn(II) ions.[7] A similar study has now been made of the corresponding equilibria of the 4-methyl derivative of imidazole, chosen because it is substituted in the same position as the imidazole ring in the histidyl residue, and thus represents a step toward the study of the metal-binding behavior of the histidyl residue in peptide chains. A fragmentary study has also been made of 2,4-dimethylimidazole, in order to determine whether the additional methyl group, attached to the carbon atom between the two nitrogens of the imidazole ring, would significantly alter the binding of the imidazole molecule to the metallic ions.

Materials and Methods

4-Methylimidazole was prepared as the crystalline salt, 4-methylimidazolium nitrate, by a modification of the method of Weidenhagen and Herrmann.[8] The free base was prepared, in the manner described by them, from acetol acetate, aqueous ammonia and formaldehyde in the presence of cupric acetate. The resulting copper complex of 4-methylimidazole was decomposed, and the copper precipitated as sulfide, by treatment with hydrogen sulfide at 50°. After removal of the precipitate, and cooling, dilute nitric acid was added cautiously to the solution, with constant stirring, until a *p*H between 2 and 3 was attained. (Further addition of nitric acid decreases both the yield and the purity of the product.) The solution was concentrated by evaporation to a small volume, *in vacuo* at 45–55°, filtered with charcoal and dried in a desiccator. The resulting crude product was recrystallized two or three times from acetone. The material was colorless and melted at 110.5–111.5°. Dedichen[9] reported a melting point of 110°. The purity of the material obtained by us was confirmed also by the constancy of the value of pK' obtained in the *p*H titrations (see below) for widely varying ratios of the concentration of free base to that of the conjugate imidazolium ion.

2,4-Dimethylimidazole also was prepared by the method of Weidenhagen and Herrmann[8]; the base released on removal of Cu(I) by sulfide was converted directly to the nitrate and the product was obtained by evaporation to dryness at low temperature. Recrystallization was from acetone or acetone–ether mixtures. Thrice recrystallized 2,4-dimethylimidazolium nitrate melted at 133–134°. The purity of the product was confirmed by the *p*H titrations discussed below.

The preparation of mixtures of methylimidazolium nitrates and Cu(II) or Zn(II) nitrates and their titration with NaOH were carried out as previously described.[7] The *p*H of each mixture was determined with a Beckman

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(3) Requests for reprints and inquiries concerning this paper should be addressed to Dr. J. T. Edsall, Biological Laboratories, Harvard University, Cambridge 38, Massachusetts.

(4) F. R. N. Gurd and D. S. Goodman, THIS JOURNAL, **74**, 670 (1952).

(5) C. Tanford, *ibid.*, **74**, 211 (1952).

(6) F. R. N. Gurd and P. E. Wilcox, *Advances in Protein Chem.*, **11**, 311 (1956).

(7) J. T. Edsall, G. Felsenfeld, D. S. Goodman and F. R. N. Gurd, THIS JOURNAL, **76**, 3054 (1954).

(8) R. Weidenhagen and R. Herrmann, *Ber.*, **68**, 1953 (1935). See also K. Hofmann, "Imidazole and its Derivatives" Part I, Interscience Publishers, Inc., New York, N. Y., 1953, Chapter II.

(9) G. Dedichen, *Ber.*, **39**, 1831 (1906).

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Model G pH meter, first at 2.5° in a cold room and again at laboratory temperature. The instrument and solutions were allowed to reach temperature equilibrium for several hours before readings were taken. Measurements were repeated at five-minute intervals and care was taken to maintain the precision of the measurements at ±0.01 pH unit. The buffer described by Bates and Acree[10] containing 0.02M KH_2PO_4, 0.03M Na_2HPO_4 and 0.02M NaCl was used for calibration. The pH values assigned to this buffer at various temperatures were obtained by interpolation in Table II of the publication of Bates and Acree.[10]

Results

Dissociation of Hydrogen Ions.—Table I shows the pK' values for the dissociation of 4-methylimidazole and of 2,4-dimethylimidazole. The values for the former were obtained at 2.5 and 29°, and for the latter at 4 and 22°. Interpolated or extrapolated pK' values are given at 25°. Solutions were made up to 0.02M in total imidazole derivative and the ionic strength adjusted with sodium nitrate. The titration of 4-methylimidazole was carried out, at each ionic strength and temperature, for seven different ratios of imidazolium ion to free base, ranging from 6 to 0.17. The calculated pK' values for the seven solutions agreed within ±0.01, except occasionally at the extreme ends of the curve, where the deviation was sometimes twice as great. The titrations of 2,4-dimethylimidazole are somewhat less accurate, with a probable error of perhaps ±0.025 in the reported pK' values.

The results are given for several different ionic strengths ($\Gamma/2$) and are extrapolated to zero ionic strength according to a simplified version of the Debye–Hückel equation previously employed by Kirby and Neuberger.[11]

$$pK = pK' - 0.5\sqrt{\Gamma/2}/(1 + \sqrt{\Gamma/2})$$

The results of the present study are compared in Table II with their measurements, in which the hydrogen electrode was used. The results agree within experimental error.[12]

TABLE I

APPARENT DISSOCIATION CONSTANTS, pK', AT VARIOUS TEMPERATURES AND IONIC STRENGTHS FOR THE CONJUGATE ACIDS OF TWO IMIDAZOLE BASES

Ionic strength	Temp., °C. 2.5	29	25
	4-Methylimidazolium ion		
0.16	8.20	7.60	7.69
.076	8.17	7.56	7.65
.034	8.15	7.55	7.64
.00	8.06	7.46	7.55
	2,4-Dimethylimidazolium ion		
	4	22	25
0.16	9.05	8.59	8.52
0.00	8.91	8.45	8.38

The values of $\Delta H°$ in Table II range from 7.7 to 9.2 kcal./mole. These values are somewhat larger than those which usually have been assumed as typical for imidazole groups.[13] The standard entropy of ionization is in all cases negative and of the order of −6 cal. deg.$^{-1}$mole^{-1}. In attempting to interpret these values, we note that the process involved is the transfer of a proton from an imidazolium ion to a water molecule to form an H_3O^+ ion. Both the imidazolium ion and the H_3O^+ ion tend to attract and orient water molecules, with an accompanying entropy decrease, around a positively charged center, but the orientation around the positively charged imidazolium nitrogen will be obstructed to some extent by the adjoining atoms of the ring; whereas no such obstruction exists around the H_3O^+ ion. Hence a moderate negative value of $\Delta S°$ is to be expected for a proton transfer of this type.[14]

TABLE II

THERMODYNAMIC VALUES FOR THE HYDROGEN ION EQUILIBRIA OF VARIOUS IMIDAZOLES AT 25°

Conjugate acid of	pK at $\Gamma/2 = 0$	$\Delta F°$, kcal./mole	$\Delta H°$, kcal./mole	$\Delta S°$, cal. deg.$^{-1}$ mole^{-1}
Imidazole	6.95[a]; 6.97[b]	+ 9.5	+7.7[f]	−6.0
1-Methylimidazole	7.06[c]	+ 9.6		
2-Methylimidazole	7.86[a]	+10.7		
4-Methylimidazole	7.52[a]; 7.54[d]	+10.3	+8.6	−5.7
2,4-Dimethylimidazole	8.36[a]; 8.38[d]	+11.4	+9.2	−7.4
2,4,5-Trimethylimidazole	8.92[e]	+12.2		

[a] A. H. M. Kirby and A. Neuberger, *Biochem. J.*, **32**, 1146 (1938). [b] J. T. Edsall, G. Felsenfeld, D. S. Goodman and F. R. N. Gurd, THIS JOURNAL, **76**, 3054 (1954). [c] N. C. Li, J. M. White and E. Doody, *ibid.*, **76**, 6219 (1954). [d] Present investigation. [e] R. W. Cowgill and W. M. Clark, *J. Biol. Chem.*, 198, 33 (1952), give a pK' for this substance of 8.86 in 23.3% ethanol at 30° and ionic strength 0.2. Following their calculation, we have taken the value in water, at 25° and zero ionic strength, as 0.06 greater than this. [f] In reference 6, the value of $\Delta H°$ for imidazole was given incorrectly as 6.0 kcal./mole. The value listed here is based on the data given in that reference, and the calculation has been corrected. Values for $\Delta H°$ and $\Delta S°$ are based on temperature coefficients of pK values determined in the present investigation, or in reference *b* above.

Association of Cu(II) and Zn(II) with 4-Methylimidazole.—The results of the titration of mixtures of 4-methylimidazole with $Cu(NO_3)_2$ and $Zn(NO_3)_2$ are summarized in Tables III and IV. Throughout these measurements the ionic strength was maintained at 0.15–0.16. The first three columns in Table III, and the subhead and first column of Table IV, define the compositions of the mixtures; the next three columns show the results at 2.5°; and the last three show the results at 29 and 27°, respectively. The concentration of the imidazole derivative in the free base form is expressed as its negative logarithm, pA, and the average number of 4-methylimidazole molecules bound per metal ion is denoted by $\bar{\nu}$. The values of pA and $\bar{\nu}$ were obtained from the data by the method previously employed with imidazole.[7]

(10) R. G. Bates and S. F. Acree, *J. Research Natl. Bur. Standards*, **30**, 129 (1943).

(11) A. H. M. Kirby and A. Neuberger, *Biochem. J.*, **32**, 1146 (1938). Concerning the extrapolation of pK' values to zero ionic strength, see also A. Neuberger, *Proc. Roy. Soc.* (*London*), **A158**, 68 (1937).

(12) Much of the difference of about 0.02 unit may be due in any case to differences in methods of standardization. See also R. G. Bates, "Electrometric pH Determinations," John Wiley and Sons, Inc., New York, N. Y., 1954, Chap. 4.

(13) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943, Chapters 4 and 5.

(14) Compare the discussion by E. J. King and G. W. King, THIS JOURNAL, **76**, 1089 (1954), especially pp. 1095–1098.

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TABLE III

TITRATION OF MIXTURES OF 4-METHYLIMIDAZOLIUM NITRATE (4-MeIm$^+$NO$_3^-$) AND CUPRIC NITRATE

Total molar concn. of 4-MeIm$^+$NO$_3^-$	Cu(NO$_3$)$_2$	NaOH	Results at 2.5° pK' = 8.20 pH	pA	$\bar{\nu}$	Result at 29° pK' = 7.60 pH	pA	$\bar{\nu}$
0.1354	0.0113	0.002377	3.93	5.15	0.21	3.82	4.66	0.21
.1354	.0113	.004754	4.28	4.80	0.42	4.16	4.32	0.42
.1354	.0113	.007131	4.50	4.59	0.63	4.39	4.10	0.62
.1354	.0113	.009508	4.72	4.38	0.84	4.58	3.92	0.83
.1354	.0113	.01664	5.25	3.88	1.46	5.09	3.44	1.44
.1354	.0113	.02377	5.70	3.45	2.08	5.48	3.07	2.03
.1354	.0113	.03090	6.16	3.02	2.65	5.90	2.68	2.55
.1354	.0113	.04041	6.76	2.46	3.27	6.38	2.24	3.08
.1354	.0113	.04754	7.13	2.13	3.55	6.65	2.01	3.34
.1354	.0113	.05705	7.48	1.83	3.73	6.95	1.76	3.50
.0200[a]	.0214	.007132	5.15	4.94	0.32	5.00	4.49	0.33
.0300[a]	.0136	.007132	5.18	4.66	0.52	5.02	4.22	0.52
.0600[a]	.0186	.02377	5.62	4.02	1.27	5.44	3.60	1.27
.0600[a]	.0186	.03090	5.99	3.75	1.65	5.80	3.34	1.64
.0600[a]	.0135	.03090	6.39	3.35	2.25	6.15	2.99	2.21
.0600[a]	.0186	.04754	6.96	3.14	2.52	6.72	2.79	2.41

[a] $NaNO_3$ added to bring total ionic strength to 0.15–0.16. The symbol pA, here and elsewhere in this paper, denotes the negative logarithm of the concentration of free basic imidazole.

TABLE IV

TITRATION OF MIXTURES OF 4-METHYLIMIDAZOLIUM NITRATE (4-MeIm$^+$NO$_3^-$) AND ZINC NITRATE

Total molar concentration of 4-MeIm$^+$NO$_3^-$ was 0.1354 and that of Zn(NO$_3$)$_2$ was 0.0111 in all solutions reported here.

Total NaOH added (mole/l.)	Results at 2.5° pK' = 8.20 pH	pA	$\bar{\nu}$	Results at 27° pK' = 7.64 pH	pA	$\bar{\nu}$
0.001418	5.43	3.64	0.11	5.01	3.50	0.10
.002836	5.70	3.38	.22	5.28	3.24	.20
.005138	5.90	3.19	.40	5.50	3.03	.38
.01028	6.13	2.93	.83	5.74	2.80	.78
.01541	6.26	2.86	1.27	5.88	2.68	1.20
.02055	6.38	2.76	1.69	6.00	2.58	1.61
.02569	6.48	2.68	2.13	6.10	2.50	2.03
.03084	6.60	2.58	2.54	6.20	2.42	2.44
.03597	6.74	2.46	2.93	6.33	2.31	2.80
.04614	7.08	2.17	3.55	6.62	2.07	3.39
.06166	7.61	1.72	3.85	7.07	1.72	3.77

From the data in Tables III and IV plots of $\bar{\nu}$ against pA (Bjerrum's "formation function") may be constructed. The curves so formed are nearly symmetrical about $\bar{\nu} = 2$, and it appears reasonable to assume that $\bar{\nu}$ approaches a limiting value of 4 at high concentrations of free 4-methylimidazole. The justification for this assumption lies partly in the approximate symmetry about $\bar{\nu} = 2$, referred to above, and partly in the extensive evidence that coördination complexes of Cu(II) and Zn(II) with nitrogenous bases generally approach a $\bar{\nu}$ value of 4. Similar conclusions concerning the Cu(II)–imidazole system[7] have been confirmed by the polarographic technique.[15]

The data in Tables III and IV have been analyzed by the method of Scatchard[7] from plots of log Q *versus* $\bar{\nu}$ where

$$Q = \bar{\nu}/(4 - \bar{\nu})\,(A) \qquad (1)$$

These plots are shown in Figs. 1 and 2, derived from the data of Tables III and IV, respectively. The open circles represent points observed at 29 and 27°, respectively, and the closed circles at 2.5°. The

(15) N. C. Li, J. M. White and E. Doody, THIS JOURNAL, 76, 6219 (1954).

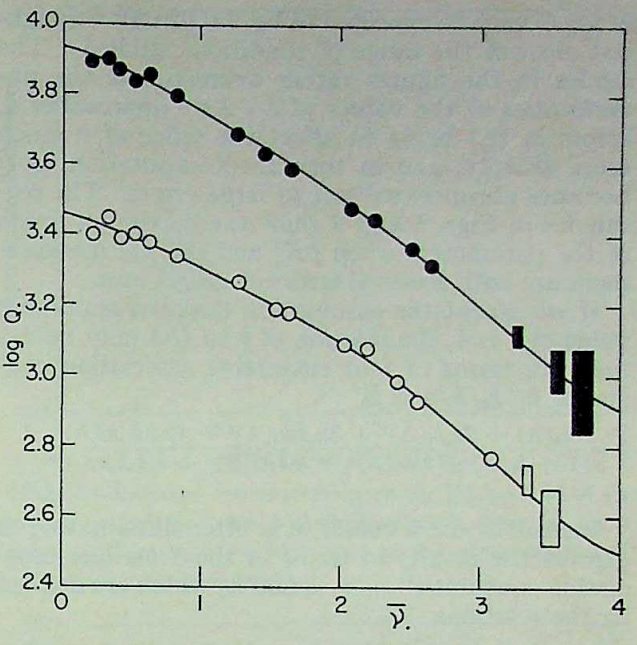

Fig. 1.—Values of the Scatchard function log Q for the binding of Cu(II) to 4-methylimidazole as a function of the mean number ($\bar{\nu}$) of imidazole molecules bound per Cu ion: upper curve data at 2.5°; lower curve data at 29°. Increased probable error of the data at high $\bar{\nu}$ values is indicated by the increased height of the rectangles on the right-hand side of the curves. Circles and rectangles are experimental values; curves are drawn on the basis of the constants listed in Table V.

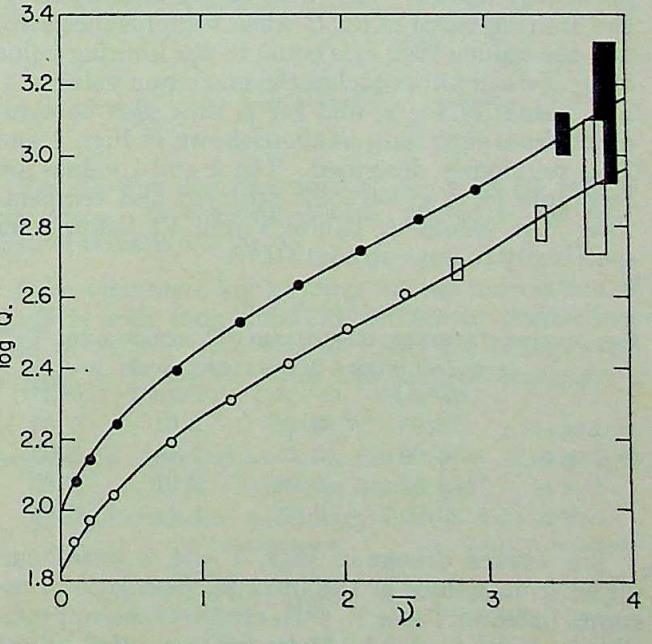

Fig. 2.—Log Q for the binding of Zn(II) to 4-methylimidazole. The data should be compared with those for Cu(II) in Fig. 1: upper curve data at 2.5°; lower curve data at 27°.

circles are drawn to represent the probable accuracy with which log Q is measured. Errors in the pH measurements affect most directly the value of (A) in equation 1. The computed value of (A) depends both on the measurement of the pH in the experimental mixture and on the value of pK' determined separately. Taking the precision of both values as ±0.01 unit, the uncertainty in the value

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of log Q may be expected to be ± 0.02 unit throughout most of the range of conditions studied. The circles in the figures rather overestimate the uncertainties in the values of $\bar{\nu}$. As $\bar{\nu}$ approaches 4, errors in (A) begin to affect the value of $\bar{\nu}$ much more sharply, and in turn the computation of Q becomes abruptly subject to large errors. The rectangles in Figs. 1 and 2 show the maximum limits of the parameters when pK' and the pH measurement are both ascribed errors of ± 0.01 unit.

If we accept the assumption that the maximum value of $\bar{\nu}$ is 4, the relation of $\bar{\nu}$ to (A) may be defined[7] in terms of four successive association constants, k_1, k_2, k_3 and k_4

$$\bar{\nu} = \frac{k_1(A) + 2k_1k_2(A)^2 + 3k_1k_2k_3(A)^3 + 4k_1k_2k_3k_4(A)^4}{1 + k_1(A) + k_1k_2(A)^2 + k_1k_2k_3(A)^3 + k_1k_2k_3k_4(A)^4} \quad (2)$$

Instead of the k values, it is often illuminating to express the results in terms of the "intrinsic association constants," κ_1, κ_2, κ_3 and κ_4, which are defined by the relations

$$\kappa_1 = k_1/4;\ \kappa_2 = 2k_2/3;\ \kappa_3 = 3k_3/2;\ \kappa_4 = 4k_4 \quad (3)$$

The factors $^1/_4$, $^2/_3$, $^3/_2$ and 4 in (3) are statistical factors. For a system in which all the ligand sites are equivalent and also react independently with the ligand, all the four κ values would be identical. In the systems studied here, this is far from being the case, and the differences in the successive κ values give a measure of the character of the interactions in the binding of the ligand molecules. As previously shown,[7] the value of log κ_1 is equal to the limiting value of log Q when $\bar{\nu}$ approaches zero, and the value of log κ_4 is equal to the limiting value of log Q when $\bar{\nu}$ approaches the maximum value of 4. The values of log κ_2 and log κ_3 may also be computed from such data as those shown in Figs. 1 and 2, as previously described. The k and κ values are constants for a given ionic strength and temperature; the values in Tables V and VI below refer specifically to ionic strength 0.16.

TABLE V

CALCULATED INTRINSIC ASSOCIATION CONSTANTS FOR Cu^{II} AND Zn^{II} WITH 4-METHYLIMIDAZOLE

	Cu^{II}(2.5°)	Cu^{II}(29°)	Zn^{II}(2.5°)	Zn^{II}(27°)
Log κ_1	3.93	3.46	2.01	1.83
Log κ_2	3.69	3.24	2.53	2.33
Log κ_3	3.36	2.99	3.01	2.80
Log κ_4	2.90	2.50	3.15	2.95

The curves drawn in Figs. 1 and 2 were computed from values of the intrinsic association constants listed in Table V. To obtain these, approximate values of κ_1 and κ_4 were first obtained by extrapolation and values of κ_2 and κ_3 were estimated roughly from the values of log Q corresponding to $\bar{\nu} = 1.5$ and $\bar{\nu} = 2.5$, respectively. The values reported in Table V were obtained by successive approximations, to give the best fit between the observed and calculated curves.

In general, a plot of log Q *versus* $\bar{\nu}$ yields most directly the values of κ_1 and κ_4. In the present study, based on pH measurements, κ_1 may be determined with considerable accuracy but, as Figs. 1 and 2 show, the extrapolation to obtain κ_4 is more uncertain. The uncertainty in κ_4 corresponds to about [illegible] of general applicability for estimating temporary values of κ_2 and κ_3 from limiting slopes[7,16] cannot be exploited conveniently. It was found that the value of the product $\kappa_2\kappa_3$ was fixed by the experimental data with considerably less uncertainty than the value of either κ_2 or κ_3 alone. The same point has been emphasized by the very careful studies of Roughton, Otis and Lyster[17] on the combination of sheep hemoglobin with oxygen—a problem mathematically identical with that considered here, if we substitute hemoglobin for Cu(II) or Zn(II), and the concentration of free oxygen in solution, or its partial pressure, for (A).

We estimate the probable range of error of the successive log κ values given in Table V to be ± 0.04, ± 0.10, ± 0.10 and ± 0.20, respectively. The error in the product log $(\kappa_2\kappa_3)$, however, is estimated at ± 0.05–0.06. If anything, we believe that this estimate overstates the probable errors. Standard enthalpy changes, $\Delta H°$, for the first three steps of the complex formation with Cu(II) are computed to be -6.7, -6.4 and -5.3 kcal./mole and with Zn(II) are -2.8, -3.1 and -3.1 kcal./mole. The values for the first step are subject to an uncertainty of about ± 1 kcal./mole, and for the second and third steps they may be as great as ± 3 kcal./mole. No significance can be attached to the apparent trend in the values for the successive steps. The calculation of $\Delta H°$ values for the fourth step scarcely appears justified, in view of the probable errors in the values of κ_4. For imidazole[7] the corresponding value for the first stage of the interaction with Cu is approximately -4.9 kcal./mole, while the value for imidazole and Zn is also negative but decidedly smaller.[18] We note that the combination of a Cu or a Zn ion with an imidazole nitrogen —or rather the displacement of a water molecule and its substitution by an imidazole molecule at one of the coördination positions around the ion— is thus an exothermic process. The heat liberated in the reaction, however, is significantly less than that produced by the combination of a proton with a basic nitrogen of imidazole or one of its methylated derivatives (see Table II). In view of the uncertainty of the data it appears unprofitable to calculate standard entropy changes ($\Delta S°$) for the interactions of 4-methylimidazole with Cu and Zn ions. It may be estimated with some confidence, however, that for the first step of the complex formation with Cu(II) $\Delta S°$ is probably negative.

Association of Cu(II) with 2,4-Dimethylimidazole.—Because of the high pK value of the 2,4-dimethyl derivative (Table II) and the tendency of uncomplexed Cu(II) to hydrolyze at pH values above about 6,[6] only the first step of the association could be determined with assurance. The measurements were made at ionic strength 0.16 and at 26 or 20.5°. Three values of $\bar{\nu}$ between 0.23 and 0.44 were obtained at pH values ranging between 5.37 and 5.72, and the values of log k_1 were

(16) For a general discussion of these and other methods see J. Z. Hearon and J. B. Gilbert, THIS JOURNAL, **77**, 2594 (1955).

(17) F. J. W. Roughton, A. B. Otis, and R. L. J. Lyster, *Proc. Roy. Soc.* (*London*), B144, 29 (1955). Also personal communications from F. J. W. Roughton to J. T. Edsall.

(18) The value for the copper–imidazole interaction was incorrectly given in our previous paper[7] as -2.2 kcal./mole.

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computed to be 3.89, 3.91 and 3.95. Since some contribution from the second step of association was to be expected, judging from analogy with the 4-methylimidazole system (see Fig. 3, below), we estimate that the value of log k_1 at about 25° is 3.8 ± 0.1. This is equivalent to log κ_1 = 3.2 ± 0.1.[7] Very rough estimates from the titration data gave values for log κ_2, log κ_3 and log κ_4 which were of the order of 3.0, 2.6 and 2.4, respectively. These values, however, should not be taken as indicating anything more than the order of magnitude of the constants involved. Values of $\bar{\nu}$ as high as 3.6 were estimated for the solutions containing the highest concentrations of 2,4-dimethylimidazole relative to Cu, but the *p*H in these solutions was as high as 7.8–7.9. Although by working at low total concentrations of cupric ion—of the order of 0.006 *M*—it was possible to attain such high *p*H values without precipitation of cupric oxide, accurate evaluation of the data would require careful correction for the binding of some of the added hydroxyl ion by copper (see the detailed discussion in reference 7). We have therefore refrained from presenting the detailed data for the 2,4-dimethylimidazole system. The available evidence indicates that the association constants involved are all of the same order of magnitude but somewhat lower than those found for imidazole and 4-methylimidazole.[19]

Discussion

The results of the present study with 4-methylimidazole show the same striking contrast in behavior between Cu(II) and Zn(II) as was found in the study with unsubstituted imidazole.[7] In both cases the imidazole compound shows increasing affinity for Zn(II) as the degree of complex formation increases; in other words there are "positive interactions" between the coördinated imidazole groups. With Cu(II) the opposite behavior is seen and the interactions are negative. This contrasting behavior appears to be the rule with all the simple imidazoles that have been tested, including the 1-methyl derivative,[15] and is indeed characteristic of the behavior of other systems in which nitrogen is the donor atom of the ligand molecule.[6]

A consequence of the contrasting behavior with Cu(II) and with Zn(II) is illustrated in Figs. 3 and 4 which show the per cent. of each metal ion in each complex as a function of the concentration of the free base 4-methylimidazole. The curves were computed from the *k* values for 29 and 27° corresponding to the κ values given in Table V. The conversion from κ values to *k* values was made according to equation 3. Noteworthy is the much greater overlapping of the regions of existence of the Zn(II) complexes. Indeed the Zn(II) system moves from 50% in the form of the uncomplexed ion to 50% in the form of the quaternary complex when the concentration of the uncombined base is increased about fivefold. By contrast the corresponding change in the Cu(II) system requires an increase of approximately 200-fold.

(19) Further details concerning the work on 2,4-dimethylimidazole are given in the Honors Thesis of Raymond F. Chen, submitted to the Board of Tutors in Biochemical Sciences, Harvard University, 1955.

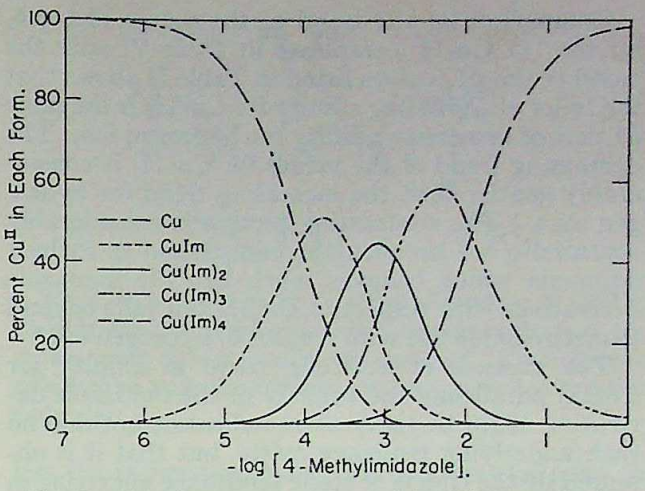

Fig. 3.—Relative concentrations of Cu(II) ion and of its various complexes with 4-methylimidazole, plotted as a function of the negative logarithm of the concentration of free basic 4-methylimidazole.

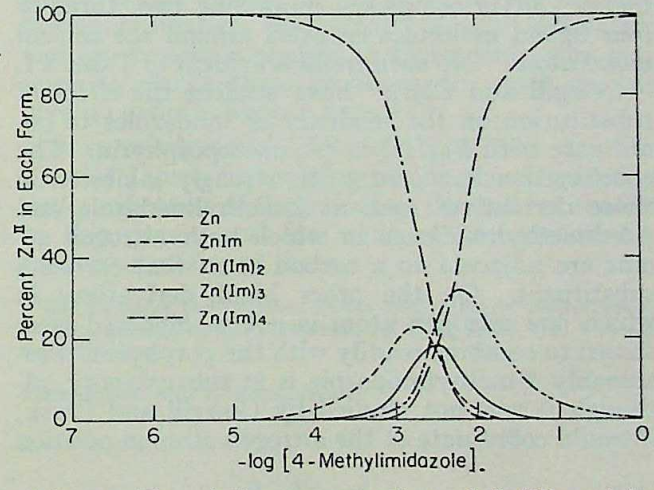

Fig. 4.—The relative concentrations of Zn(II) and its complexes with 4-methylimidazole, plotted in the same manner as the data of Fig. 3.

The successive log *k* values for the association of Cu(II) with four different imidazole derivatives and of Zn(II) with two of them are brought together in Table VI. For the sake of comparison the values are extrapolated or interpolated to correspond with 25° and in each case the ionic strength is 0.15–0.16.

TABLE VI

SUCCESSIVE ASSOCIATION CONSTANTS FOR Cu(II) AND Zn(II) WITH SOME IMIDAZOLES[a]

Log *k* values for ionic strength 0.15–0.16 and 25°

	Cu(II) complexes				Zn(II) complexes	
	Imidazole[b]	1-Methylimidazole[c]	4-Methylimidazole	2,4-Dimethylimidazole	Imidazole[b]	4-Methylimidazole
Log k_1	4.33	4.22	4.13	3.8	2.57	2.44
Log k_2	3.54	3.54	3.49		2.36	2.53
Log k_3	2.82	2.89	2.87		2.22	2.64
Log k_4	2.03	2.21	1.96		2.01	2.38

[a] Note that the values given in this table are log *k* values as defined by equation 2. They are related by equation 3 to the log κ values given in Table V. [b] J. T. Edsall, G. Felsenfeld, D. S. Goodman and F. R. N. Gurd, THIS JOURNAL, 76, 3054 (1954). [c] N. C. Li, J. M. White and E. Doody, *ibid.*, 76, 6219 (1954).

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Comparison of the trend of the values of log k_1 for the 1:1 Cu(II) complexes in Table VI with the trend of the pK values listed in Table II shows that the order of *decreasing* affinity for Cu(II) is the same as that of *increasing* affinity for hydrogen ion. The decreasing trend of the values for Cu(II) is considerably gentler than the increasing trend for hydrogen ions. The contrasting picture is considerably accented if we broaden the comparison to include ammonia which behaves much like the imidazole derivatives with respect to Cu(II) but falls beyond trimethylimidazole with respect to hydrogen ion.[6]

The absence of a strong trend in affinity for Cu(II) paralleling the basicity of the imidazole derivative might be taken as an indication not that no such underlying tendency exists, but that it is obscured by the effects of steric hindrance operating in the opposite sense. However, if steric hindrance were such a powerful factor in the formation of the 1:1 complexes we should expect that far larger effects would be evident in the formation of the higher Cu(II) complexes containing two, three or four ligand molecules crowded around the central metal atom. No such trend is evident in Table VI.

Cowgill and Clark[20] have studied the effect of substitution on the tendency of imidazoles to coordinate with Fe(III) in ferrimesoporphyrin. The coördination appeared to be strongly inhibited in those derivatives such as 2-methylimidazole and 4,5-dimethylimidazole in which both nitrogen atoms are adjacent to a carbon atom that carries a substituent. On the other hand, derivatives in which one nitrogen atom is not so hindered were shown to combine readily with the porphyrin. Presumably 4-methylimidazole is in this category, although it was not studied by Cowgill and Clark; it would coördinate at the nitrogen atom in position 1 (in the alternative numbering system these positions would be 5 and 3, respectively), and so on. Possibly there is some tendency for similar preferences in the coördination of imidazole derivatives with free metal ions. The analogy should not be carried far, however, because Cowgill and Clark also showed that among those imidazole derivatives that were effective in forming complexes there was a general tendency for the strength of coördination to increase with increasing pK', an effect opposite to that found in the present study.

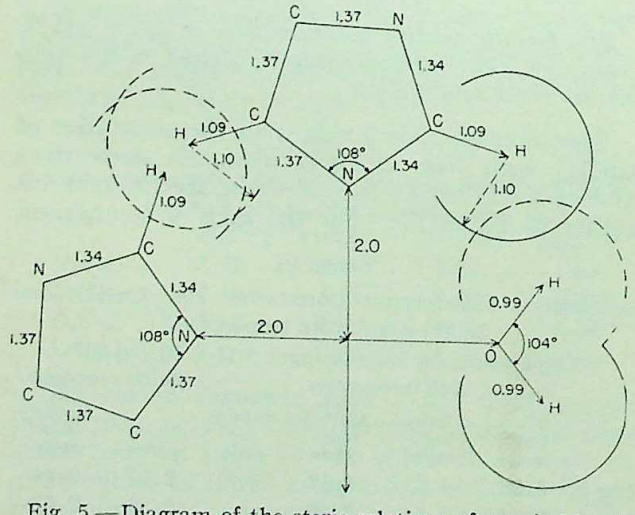

Fig. 5.—Diagram of the steric relations of two imidazole rings and a water molecule, coördinated around a central Cu ion. The Cu–N bonds and the Cu–O bond are assumed to be 2.0 Å. long. In the drawing all these bonds are assumed coplanar. The dotted arcs of circles on the upper left indicate the overlapping van der Waals radii of the hydrogen atoms on two adjoining imidazole rings. A slight overlapping is also shown to exist between the van der Waals radii of the hydrogen atoms of the attached water molecule on the right and the neighboring imidazole ring (see text).

Some further comments on the stereochemistry of these complexes may be offered. In general, tetra-coördinated zinc complexes are tetrahedral, while those of copper are generally planar[6,21] but may sometimes correspond to a more or less distorted tetrahedron. The strongly positive interactions which are apparent in the binding of many organic bases to the Zn(II) ion are present to about the same extent in imidazole and 4-methylimidazole; the extra methyl group apparently produces no added hindrance to the binding of the successive imidazole molecules to the zinc ion. This appears not unreasonable if the methyl groups in the complex are oriented outward, away from the nitrogen which is attached to the copper, which must then be the nitrogen in position 1. On the other hand if the Cu(II) complexes are square and planar, some difficult steric problems arise, in the placing of three or four imidazole rings about a central cupric ion. We take the Cu–N distance as approximately 2.0 Å., which appears reasonable in the light of available data.[22] In constructing a model for the imidazole ring, the detailed X-ray diffraction study by Donohue, Lavine and Rollett[23] of histidine hydrochloride monohydrate gives by far the most definite information available. The imidazole ring in this crystal is in the positively charged (imidazolium) form. The Cu(II) imidazole complexes should be fairly closely similar in electron distribution because of the positive charge on the copper (basic imidazole may well be considerably different in structure, since the removal of the positive charge should have important repercussions on the electron distribution in the ring). We may adopt a simplified model suggested by Donohue, *et al.*, as being compatible with their data within the limits of experimental error. It is illustrated in the two imidazole groups around the Cu atom in Fig. 5. All the internal bond angles are taken as being very close to 108°, and all C and N atoms shown are coplanar within very narrow limits (within 0.017 Å. in the case of histidine hydrochloride monohydrate). An attached carbon in the 4-position, as in histidine and 4-methylimidazole, is also coplanar with the atoms of the ring. Allowing for the usual C–H bond distances and van der Waals radii for the hydrogen atoms, it proves to be impossible to place four imidazole rings, even without substituent

(20) R. W. Cowgill and W. M. Clark, *J. Biol. Chem.*, **198**, 33 (1952).

(21) See, for instance, A. F. Wells, "Structural Inorganic Chemistry," 2nd Ed., Oxford, 1950; also J. C. Bailar, Jr. (editor) "The Chemistry of the Coördination Compounds," Reinhold Publ. Corp., New York, N. Y., 1956.

(22) See, for instance, the discussion by J. Bjerrum, C. J. Ballhausen and C. I. Jørgensen, *Acta Chem. Scand.*, **8**, 1275 (1954).

(23) J. Donohue, L. R. Lavine and J. S. Rollett, *Acta Cryst.*, **9**, 655 (1956).

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methyl groups, around the central Cu(II) ion, if it is assumed that all the rings are coplanar, and lie in the plane defined by the C–N bonds. The nature of the steric hindrance involved is shown in Fig. 5, in which the C–H distance is taken as 1.09 Å., and the van der Waals radius of the hydrogen atoms as 1.10 Å. The marked overlapping shown between the van der Waals radii of the adjacent imidazole rings in Fig. 5 obviously cannot be obviated by any reasonable change in the assumed dimensions. Presumably some or all of the imidazole rings must be rotated out of the plane of the figure, around the Cu–N bonds, so as to make mutual accommodation easier. Probably there is also some distortion of the orientation of the Cu–N bonds, so that they do not all lie in a single plane.[24]

The insertion of a methyl group in the 4-position on the ring gives rise to new stereochemical problems and also to new possibilities of isomerism, as illustrated in Fig. 6. To minimize steric hindrance it seems probable that the binding will occur chiefly with the 1-nitrogen, as for the imidazole ring shown on the right hand side of Fig. 6. This places the methyl group as far away as possible from the central copper ion. In the binding of 2,4-dimethylimidazole, however, it is inevitable that one of the methyl groups must be on a nitrogen atom immediately adjacent to the copper ion. Nevertheless the rather incomplete studies reported here on 2,4-dimethylimidazole indicate only a slight decrease in its tendency to coördinate with copper as compared with imidazole or 4-methylimidazole. These findings reinforce the conclusion that the Cu–N bonds cannot be coplanar in the tri- and tetra-coördinated complexes. X-ray diffraction and spectroscopic studies on these complexes may serve to clarify these problems, to which we can give no definite answer here.[25]

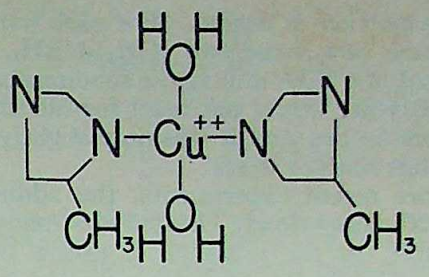

Fig. 6.—Combination of 4-methylimidazole with Cu(II), showing the two possible isomeric arrangements; the one shown on the right is presumably preferred. The other two coördination positions are shown as being occupied by water molecules.

Acknowledgment.—We are indebted to Mr. Charles Lipson for much work on the preparation and purification of the imidazole derivatives studied in this paper, and for some of the preliminary measurements upon them.

(24) Bjerrum, *et al.*,[22] conclude that the $Cu(NH_3)_4^{++}$ complex, and other analogous complexes, are distorted octahedral structures, with attached water molecules above and below the plane defined by the 4 Cu–N bonds. If this is true for the imidazole complexes, the stereochemical problem is not very much changed from that outlined in the text here. The two attached water molecules, however, may make the attachment of 4 imidazole molecules involve an even tighter fit than we have suggested.

(25) Compare the structure of the $CuCl_4^-$ ion in cesium chlorocuprate, reported by L. F. Helmholz and R. F. Kruh, THIS JOURNAL, **74**, 1176 (1952).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Amine Chemistry of the Pentaborane B_5H_9

BY ANTON B. BURG

RECEIVED NOVEMBER 13, 1956

The structure of B_5H_9 suggests certain modes of reaction which its amine chemistry appears to confirm. It adds trimethylamine at −78° to form $B_5H_9 \cdot 2Me_3N$, which on heating *in vacuo* is partly dissociated into the original components and partly converted to Me_3NBH_3 and $(BH)_x$. On heating with excess Me_3N, the adduct yields $2Me_3NBH_3$ and BH polymers incorporating Me_3N, which lends thermoplastic character. Either Me_2NH or aminoboron hydrides such as Me_2NBH_2 or $(Me_2N)_2BH$ remove BH_3 from B_5H_9 on heating, and much of the new $(Me_2N)_3B_3H_4$ (m.p. 95°; b.p. est. 220°) is formed. Small yields of the new liquid $(Me_2N)_2B_4H_6$, of similar volatility, also are obtained. Both compounds, which seem to represent a large new class, are presumed to have cross-ring structures wherein all B and N atoms are four-coördinate. The $(Me_2N)_2B_3H_4$ is especially unreactive and thermally stable but can be converted by heat to still more inert new materials.

The structure of the pentaborane B_5H_9[1,2] is such that the removal of two BH_3 groups from the molecule—as by the use of a tertiary amine to form $2R_3NBH_3$—could occur by breaking only bonds of order less than one, and without shifting any hydrogen atoms from one boron atom to another. The remainder of the molecule then would be a B_3H_3 unit which could not persist as a simple B–B–B chain hydride, but would convert immediately to a high-polymer form. These ideas correlate with some experimental results obtained by the author in the year 1937, during a period of collaboration with Professor H. I. Schlesinger at the University of Chicago. It was found that the adduct $B_5H_9 \cdot 2(CH_3)_3N$ would form slowly at −79° and upon warming *in vacuo* it would decompose in two ways: dissociation into the original components and the formation of $(CH_3)_3NBH_3$ and a yellow residue. The two ways of decomposition, occurring simultaneously, suggested the possibility that the adduct had two forms with different types and strengths of bonding. On heating with more trimethylamine, the yellow solid became almost colorless, with slight production of $(CH_3)_3NBH_3$, and approached the composition $(BH)_x$, containing only a very

(1) K. Hedberg, M. E. Jones and V. Schomaker, THIS JOURNAL, **73**, 3538 (1951).

(2) W. J. Dulmage and W. N. Lipscomb, *ibid.*, **73**, 3539 (1951).

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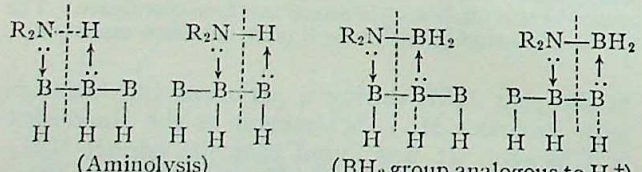
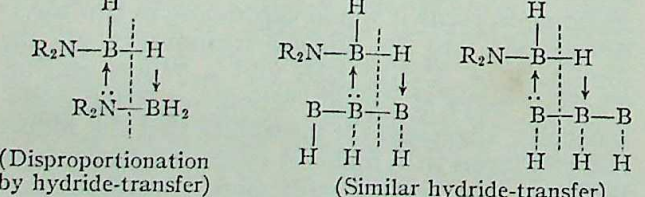
small proportion of amine. For each unrecovered B_5H_9 there now were two $(CH_3)_3NBH_3$, and the equivalent of a B_3H_3 unit in the solid residue. This $(BH)_x$ polymer would not react further on heating with more amine, and it was only slightly affected by aqueous acids or bases.

In more recent experiments, the adduct $B_5H_9 \cdot 2(CH_3)_3N$ was slowly heated to temperatures above 100° in the presence of excess trimethylamine, again always producing $2(CH_3)_3NBH_3$ per B_5H_9. In such experiments some of the excess amine became incorporated in the polymer, which exhibited thermoplastic behavior above 100°. This effect can be understood by assuming that a $(BH)_x$ polymer has a highly cross-linked chain structure of icosahedral or possibly octahedral boron hydride clumps, the interlinking of which can be decreased by amine-complex bonding to boron. Thus it would be possible to have a rubber-like chain instead of a stiff network. Polymers of similar composition were obtained earlier from the reaction of tetraborane with trimethylamine,[3] although their physical character was not closely observed.

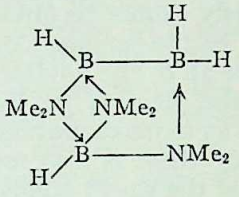
Such aminated boron hydride polymers, ranging from three to five BH units per amine molecule, can neither absorb nor lose amine on heating; indeed one sample was heated *in vacuo* to 400°, losing methane rather than trimethylamine, and forming a very difficultly volatile sublimate. This product would seem to be a dimethylaminopolyborane, a member of a new class of compounds whose prototype was obtained by experiments using dimethylamine.

The reaction of pentaborane with dimethylamine present in excess led only to the previously known aminoboron hydrides,[4] but the reaction with a carefully limited proportion of this amine produced new volatile products wherein direct B–B bonding can be recognized. The yields of such products were improved by the use of the compounds $(CH_3)_2NBH_2$ and $[(CH_3)_2N]_2BH$ with pentaborane, for these pick up the BH_3 group to form $(CH_3)_2NB_2H_5$ and $(CH_3)_2NBH_2$, respectively[4]; and they can react with the B_3H_3 remainder with no net destruction of B–B bonding. The latter aspect can be recognized by comparing with aminolysis or hydride-transfer reactions the attack by an aminoborine upon the B_3H_3 remainder, thus

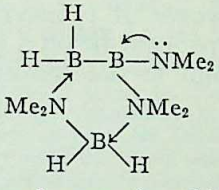




A major product of such reactions was shown by analyses and a molecular weight determination to have the molecular formula $[(CH_3)_2N]_3B_3H_4$. It is a slightly volatile white solid, reasonably stable in the open air, and on heating to 300°, both thermally stable and unreactive toward hydrogen. The only molecular structure which seems both appropriate and sterically possible would be



wherein the two nitrogen atoms in the B_2N_2 ring would be in a line perpendicular to the plane of the B_3N chain. However, it seems necessary to find some explanation for the failure of the substance to react with diborane at 90°, as happens when the B^N_NB ring dimer of $(CH_3)_2NBH_2$ is converted to $(CH_3)_2NB_2H_5$. But this difficulty would seem greater if one considered the conceivable alternative pattern



In any case a formal name for this new compound would be cumbersome; hence in this paper it will be called simply the triaminotriborane, the -ane ending being adopted in view of the probable analogy to a hydrocarbon somewhat like pinane.

Another product of the aminoborine–pentaborane reaction is a somewhat less stable and more reactive liquid, slightly more volatile than the solid triaminotriborane. Its molecular formula was determined as $[(CH_3)_2N]_2B_4H_6$. If it be assumed that B and N always are four-coördinate in such compounds, the following five structural patterns might be considered.

The last three of these structures are sterically not favored, and the second would be less stable than the first, by analogy to the reaction of $[(CH_3)_2NBH_2]_2$ with B_2H_6 to form $(CH_3)_2NB_2H_5$. However, the first pattern might well be less stable than still another form wherein the B–B bonds are along opposite edges of a B_4-tetrahedron. A second pair of opposite edges would be B^HB bridged and the third pair of edges would be B^NB bridged. A final decision on the structure must come from physical methods, for which it will be necessary to find a way to make larger samples. Hereinafter the compound will be designated as diamino-bis-diborane.

Experimental

The Reaction of Pentaborane with Trimethylamine.—In the 1937 experiment, 0.504 mmole of B_5H_9 and 13.12 mmoles of $(CH_3)_3N$ were allowed to react during 10 days at −79°. Then 12.05 mmoles of the amine could be recovered by distillation at −79°, leaving a loose white solid of average composition $B_5H_9 \cdot 2.12(CH_3)_3N$. This was warmed to room temperature under high vacuum, with the vapors led through a fractional-condensation train, and finally with warming to 66°. The volatile products were 0.290 mmole

(3) A. B. Burg and F. G. A. Stone, THIS JOURNAL, **75**, 228 (1953).

(4) A. B. Burg and C. L. Randolph, Jr., *ibid.*, **73**, 953 (1951), and earlier papers there cited.

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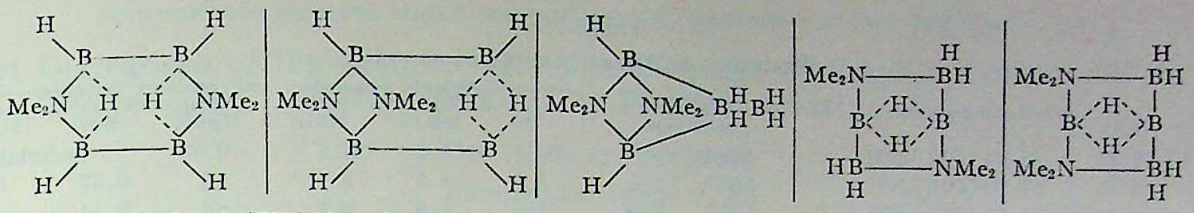

of B_5H_9, 0.629 mmole of $(CH_3)_3N$ and 0.361 mmole of $(CH_3)_3NBH_3$. Thus 58% of the 2:1 adduct was recovered as the original reactants, while the remainder was partially converted to $(CH_3)_3NBH_3$. The glassy brilliant-yellow residue next was heated for 8 hr. at 100°, in an atmosphere of 3.00 mmoles of amine, converting 0.063 mmole of this to $(CH_3)_3NBH_3$ and leaving a nearly-white residue of composition $(BH)_x$ with possibly as much as 3 mole % of amine content. The yield of $(CH_3)_3NBH_3$ was 1.98 per unrecovered B_5H_9. The polymer did not react further with trimethylamine, but aqueous hydrochloric acid attacked it slightly, giving off 0.09 mmole of hydrogen, and a sodium hydroxide solution first turned it slightly brown, and then white, without appreciable dissolving.

In more recent experiments the 2:1 adduct was formed in 50 ml. sealed tubes at −78° and simply allowed to warm slowly to room temperature or higher, usually in the presence of excess amine. At intervals in the course of heating to higher temperatures, the volatile products were removed and determined, and the residue was heated further in the resealed tube or with connection to an automatic Sprengel pump for collection of non-condensable gases. The results of four such experiments are shown in Table I.

In all of these experiments the initial heating (usually slowly, to 100°) gave a polymer-residue having a B:H ratio near to 1:1 and this changed very little on heating up to the 200° range. When there was plenty of amine, this initial heating always produced very nearly $2(CH_3)_3NBH_3$ per B_5H_9. However in the exceptional expt. 2 the excess amine had been removed at −78°, establishing the composition of the adduct as $2.04(CH_3)_3N$ per B_5H_9, and then the initial heating of this adduct (24 hr. in a sealed tube at 102°) gave only $1.3(CH_3)_3NBH_3$ per B_5H_9, and 0.494 mmole of H_2 was produced. Thus it appears that the forming polymer competes with BH_3 groups for possession of the amine; but once formed, the polymer does not absorb any significant proportion of amine after being formed with a low amine content. And from expt. 4 it is apparent that the amine cannot be removed from its incorporation in the polymer by vacuum heating; instead there is a loss of methane to produce some $(CH_3)_2NBH_2$ and a far less volatile sublimate, presumably formed at the expense of the N–CH_3 and B–H linkages. Attempts to analyze this sublimate have not been successful, and there is no evidence that it is a pure substance.

Experiment 1 was of special interest because the polymer showed plastic character in the range 100–165°: in losing traces of volatile products *in vacuo* it slowly formed large bubbles which slowly collapsed and reformed in the manner of bubble gum. At room temperature the material was a brittle solid, very slightly yellow, and apparently unaffected by the open air. Thermoplastic behavior in such materials may be critically dependent upon their amine content, for in expt. 4 (B:N ratio, 5.16) the only such effect was the temporary appearance of a fine foam during the vacuum heating to 200°.

Formation of Aminoboron Compounds from Pentaborane.—The experiments on the reactions of B_5H_9 with dimethylamine and with dimethylaminoboron compounds are summarized in Table II. Experiment 1 was done in a vertical tube having an internal cold finger at 0° and attached to the high-vacuum manifold. The others were done in sealed tubes which could be opened to the vacuum system for isolation and measurement of the volatile products and possible reheatings of the residues with volatile materials in the resealed tubes. It is apparent that the best conversion of B_5H_9 to the triaminotriborane occurred in expt. 5, wherein more than two-thirds of the boron was recovered in that form. The sixth run did nearly as well, and gave also some of the diamino-bis-diborane—a product which could not be expected from expt. 5 because it has been found to react with $[(CH_3)_2N]_2BH$. Methods for obtaining high yields of this diamino-bis-diborane are yet to be found.

Physical Properties of the Aminopolyboranes.—The triaminotriborane and the diamino-bis-diborane apparently have nearly the same normal boiling point, but their vapor tensions at room temperature or lower are so different as to permit easy separation under high vacuum. The triaminotriborane was purified by fractional condensation at 15–20°, and the diamino-bis-diborane was isolated from it by a slow distillation from a tube at 0°.

The triaminotriborane melted sharply at 95.0°, and the vapor tensions of the solid, shown in Table III, determined the equation $\log_{10} p_{mm.} = 11.424 - 3723/T$. Assuming a normal value of the Trouton constant, the normal b.p. would be estimated as 220° and the heat of fusion approximately 6750 cal./mole. A preliminary crystal-structure determination by Professor Jerry Donohue showed orthorhombic symmetry and a density of 0.945 for a unit cell containing four molecules (a_0 = 8.03 Å.; b_0 = 11.14 Å.; c_0 = 13.22 Å., all ±0.8%). A complete structure determination from the X-ray data would be very time-consuming, but it could be argued from the Weissenberg photographs that the space group could be either C_{2v}^5-Pbc or D_{2h}^{11}-Pbcm— the latter affording the possibility of a mirror-plane in accord with the preferred molecular pattern.

The melting point of the diamino-bis-diborane was uncertain, for the transition from a glassy state to a viscous oil was hard to observe. There seemed to be melting in the range 11–15°. The vapor tensions of the liquid, shown in Table IV, determined the equation $\log_{10} p_{mm} = 8.070 - 2475/T$. This would imply a normal boiling point near 203°—probably lower than the true value, since the Trouton constant has the high value 23.8 cal./deg. mole.

Proofs of Formulas.—The molecular weights of the new aminoboron hydrides were determined from their gas densities: for the triaminotriborane the result was 169.3 (calcd., 168.7); for the diamino-bis-diborane, 140 ± 2 (calcd., 137.5). Each of these compounds was analyzed by heating with methanol and a measured quantity of HCl, in a sealed glass tube at 80–90°. The resulting H_2 was Sprengel-pumped into a gas-measuring tube. Methyl chloride, representing

TABLE I

THE PENTABORANE–TRIMETHYLAMINE REACTION

Expt. no.	Reactants (mmoles) B_5H_9	Reactants (mmoles) $(CH_3)_3N$	Latest heat treatment	Volatile components (mmoles) $(CH_3)_3N$	Volatile components (mmoles) $(CH_3)_2NBH_2$	Composition of residue (mmoles) H_2	B	H	$(CH_3)_3N$
1	0.988	4.149	30 min., 165°	1.446	1.936	0.098	3.003	2.887	0.769
2	1.013	2.681	10 min., 210°	0.576	1.363	.569	3.703	3.890	0.742
3	1.630	5.684	10 min., 200°	1.031	3.165	.140	4.985	4.895	1.488
4	1.542	11.29	70 hr., 208°	7.11	3.11[a]	.127	4.60	4.29	1.07
			2 hr., vac. 210°	7.14	3.27[a]	.146	4.44	3.77	0.86
			2 hr., vac., 290°	7.24	3.28[a]	.525	4.43	2.63	.75
			3 hr., vac. ⟶ 402°	7.25	3.28[a]	1.087	4.43	1.04	.74

[a] Includes 0.29 mmole converted to $(CH_3)_2NBH_2$ and CH_4; the next-to-last heating of the residue gave 0.36 mmole of CH_4 and no other volatile products, and the final heating gave 0.46 mmole more CH_4; total CH_4 from residue, 1.11 mmoles.

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TABLE II

REACTIONS OF AMINO COMPOUNDS WITH B_5H_9

Expt. no.	B_5H_9	Reactants (mmoles)	Heating conditions	Volatile remainders and products (mmoles) H_2	$(CH_3)_2NB_2H_5$	$(CH_3)_2NBH_2$	$[(CH_3)_2N]_2BH$	$[(CH_3)_2N]_3B_3H_4$	$[(CH_3)_2N]_2B_4H_6$
1	11.13	49.34 $(CH_3)_2NH$	See below	30.8	2.3	21.7	0.38	uncertain	
2	5.76	17.20 $(CH_3)_2NH$	160°, 72 hr.	4.5	8.3	3.4	nil.	0.57	0.10
3	4.46	13.38 $(CH_3)_2NH$	150°, 2 hr.	4.0	5.8	0.5	nil.	0.14	nil.
4	1.42	3.03 $(CH_3)_2NBH_2$	100°, 14 hr.	0.06	0.37	2.22	0.02	present	0.20
5	1.41	3.95 $[(CH_3)_2N]_2BH$	111°, 94 hr.	.15	.03	1.62	0.01	1.57	nil.
		+1.71 $[(CH_3)_2N]_2BH$	112°, 282 hr.	.003	..	..	1.62	trace	..
6	7.384	36.23 $(CH_3)_2NBH_2$	95°, 21 hr.	3.12	7.91	5.77[a]	nil.	6.58	0.64
		+5.77 $(CH_3)_2NBH_2$	133°, 96 hr.	1.5	..	1.74	..	1.50	..

[a] Same sample re-used on the glassy residue. Expt. 1 (cold-finger apparatus): first, 15 hr. at 95–100° with frequent removal of volatile products; finally 20 min. at 150°; cold-finger always at 0°.

TABLE III

VAPOR TENSIONS OF SOLID $[(CH_3)_2N]_3B_3H_4$

t(°C.)	Obsd. p_{mm}	Calcd. p_{mm}
43.3	0.41	0.46
54.0	1.10	1.11
69.0	3.52	3.49
80.2	7.76	7.73
87.8	12.6	12.9
90.9	15.66	15.77
97.3	24.0 (l.)	23.7 (s.)

TABLE IV

VAPOR TENSIONS OF LIQUID $[(CH_3)_2N]_2B_4H_6$

t (°C.)	Obsd. p_{mm}	Calcd. p_{mm}
8.3	0.18	0.19
13.1	0.27	.27
27.0	.69	.68
33.3	1.02	1.00
36.4	1.20	1.21
51.3	2.82	2.82
66.0	6.04	6.03
73.1	8.48	8.52
82.1	12.92	12.92
86.5	15.6	15.7

the excess of the HCl over the amine, was isolated and measured. Methyl borate was distilled into water and titrated as the mannitol boro-spirane. In various experiments the amine hydrochloride was determined by direct weighing, by a micro-Kjeldahl analysis, by a chloride titration, or from the decrease of volatile chloride.

For the triaminotriborane, the two samples averaged 2.94 amine, 2.92 boron and 5.08 H_2 per molecule, no deviation being higher than 0.17 unit. These results uniquely require the equation $[(CH_3)_2N]_3B_3H_4 + 9\ CH_3OH + 3\ HCl \longrightarrow 5H_2 + 3(CH_3O)_3B + 3(CH_3)_2NH_2Cl$, for conformity to the observed molecular weight of the compound.

For the diamino-bis-diborane the ratio of amine to B to H_2 was 200:370:803. Boron usually runs a little low by the method here employed, for Pyrex glass is avoided and the formation of CH_3Cl from CH_3OH and the excess HCl produces a trace of water which interferes with the complete volatilization of boron as methyl borate. The results are consistent only with the equation $[(CH_3)_2N]_2B_4H_6 + 12CH_3OH + 2HCl \longrightarrow 8H_2 + 4(CH_3O)_3B + 2(CH_3)_2NH_2Cl$, requiring that the compound have two B–B links per molecule.

Chemical Behavior of the Aminopolyboranes.—The triaminotriborane $[(CH_3)_2N]_3B_3H_4$ proved to be inert toward water, acid, and methanol at room temperature, requiring many hours of heating for the analytical break-down by acid methanolysis. With an equi-molar proportion of dimethylamine in a sealed tube it failed to react during 100 hr. at 180°; but after 102 hr. at 300° the mixture had formed mole-for-mole yields of H_2, $(CH_3)_2NBH_2$ and $[(CH_3)_2N]_2BH$, the remaining aminoboron material appearing as a colorless non-volatile film on the tube-wall. Unlike some other B–B compounds,[5] the triaminotriborane is inert toward hydrogen, for a 0.245-mmole sample, after a series of heatings with 1.56 mmoles of H_2 (ending with 24 hr. at 300°) still had the same melting point. After 102 hr. at 360°, however, there was a considerable formation of a colorless oily film and the H_2 had increased to 1.88 mmoles. There was also 0.14 mmole of CH_4 and a trace of $(CH_3)_2NBH_2$. Thus it appears that the triaminotriborane is stable at 300°, but at 360° is converted to a still more stable material—probably a high polymer.

With 0.141 mmole of diborane, a 0.128-mmole sample of the triaminotriborane showed no effect of heating in a space of 130 ml. for 3 hr. at 99°; the recovery of diborane was 0.137 mmole. This result indicates that the nitrogen atoms are very firmly bonded in a four-coördinate situation, contrasting with the comparatively reactive state of nitrogen in $[(CH_3)_2NBH_2]_2$.

Little is known of the chemistry of the diamino-bis-diborane, for the samples so far have been too small for extensive study; but it does seem to be considerably less stable and more reactive than the triaminotriborane. Its presumed structure would permit the possibility of conversion to the triaminotriborane by reaction with $[(CH_3)_2N]_2BH$ but when 0.763 mmole of this was heated with 0.348 mmole of the diamino-bis-diborane for 5 hr. at 95°, only 2.2 mg. (0.013 mmole) of the triaminotriborane could be found, the main yield being a yellow resinous solid.

Such a yellow resinous solid was the chief by-product of the preparation of the triaminotriborane in expts. 5 and 6, Table II. From the reaction-balance of expt. 6 (first part), its empirical formula would be approximately $[(CH_3)_2N]_4B_{11}H_{16}$. As indicated in Table II, its further treatment with the bis-aminoborine gave a further yield of dimethylaminoborine and the triaminotriborane. At various points in this study trace amounts of very difficultly volatile aminoboron hydrides were noticed, indicating that a considerable variety of such compounds, probably merging into polymeric types, can be produced.

Acknowledgment.—The generous support of this work by the Office of Naval Research is gratefully acknowledged. Reproduction of this paper in whole or in part is permitted for any purpose of the United States Government.

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(5) G. Urry, T. Wartik, R. E. Moore and H. I. Schlesinger, THIS JOURNAL, **76**, 5293 (1954).

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[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY AT HARVARD UNIVERSITY]

Vinyl Derivatives of the Metals. II. The Cleavage of Vinyltin Compounds by the Halogens and by Protonic Acids[1]

BY DIETMAR SEYFERTH

RECEIVED NOVEMBER 1, 1956

The halogens, hydrogen bromide, hydrogen chloride, organic acids and mercaptans cleave the vinyl group in vinyl derivatives of tin. No addition reactions were observed with these reagents. This behavior is attributed to the relatively low tin–carbon bond energy. Product studies of cleavage reactions of compounds of the type $R_2Sn(CH{=}CH_2)_2$ have shown that the vinyl group is cleaved more readily than normal alkyl groups but less readily than the phenyl group. Phenyldivinyltin halides have been found to undergo thermal redistribution, yielding trivinyltin halide and triphenyltin halide.

As part of a broad study of the reactions of the vinyl derivatives of tin,[1] we have investigated the behavior of these compounds toward the halogens and toward protonic acids. Such a study was of particular interest in view of the addition reactions that vinylsilicon compounds undergo when treated with these reagents.[2]

We have found that in all cases where completely alkylated vinyltin compounds are treated with the halogens or with protonic acids, such as the hydrogen halides, organic acids and mercaptans, *cleavage of one or more of the vinyl groups* occurs in preference to addition to the vinyl double bond, giving the corresponding organotin halide (or ester or sulfide) and the vinyl halide or ethylene, respectively

$$R_3SnCH{=}CH_2 + X_2 \longrightarrow R_3SnX + CH_2{=}CHX \quad (1)$$
$$(X = Cl, Br, I)$$
$$R_3SnCH{=}CH_2 + HX \longrightarrow R_3SnX + CH_2{=}CH_2 \quad (2)$$
$$(X = Cl, Br, O_2CR', SR')$$

An already extensive Kharasch-type[3] cleavage series for organotin compounds is known.[4] It was of theoretical interest to determine the position of the vinyl group in this series. We have carried out careful product studies of the cleavage reactions of compounds of the type $R_2Sn(CH{=}CH_2)_2$, where R is methyl, *n*-butyl and phenyl, with one equivalent of iodine in refluxing ether solution, with hydrogen bromide at −78° and with hydrogen chloride in chloroform solution at 50–60°. Use of the symmetrical $R_2Sn(CH{=}CH_2)_2$ compounds eliminated any possible probability factors which might obtain in the cleavage reactions of $R_3SnCH{=}CH_2$ and $RSn(CH{=}CH_2)_3$ compounds.

These studies, the results of which are summarized in Table I, show that the position of the vinyl group in the cleavage series is

$$C_6H_5 > CH_2{=}CH > CH_3 > C_2H_5 > n\text{-}C_3H_7 > n\text{-}C_4H_9$$

since vinyl group cleavage is the only observed reaction with dimethyl- and di-*n*-butyldivinyltin, while the phenyl group is cleaved in the case of diphenyldivinyltin.

TABLE I

PRODUCT STUDIES OF THE CLEAVAGE OF $R_2Sn(CH{=}CH_2)_2$ COMPOUNDS

R	Cleavage agent	Cleavage product	Yield, %
CH_3	I_2	$(CH_3)_2(CH_2{=}CH)SnI$	74
CH_3	HCl	$(CH_3)_2(CH_2{=}CH)SnCl$	70
CH_3	HBr	$(CH_3)_2(CH_2{=}CH)SnBr$	77
$n\text{-}C_4H_9$	I_2	$n\text{-}(C_4H_9)_2(CH_2{=}CH)SnI$	82
$n\text{-}C_4H_9$	HCl	$n\text{-}(C_4H_9)_2(CH_2{=}CH)SnCl$	79
$n\text{-}C_4H_9$	HBr	$n\text{-}(C_4H_9)_2(CH_2{=}CH)SnBr$	76
C_6H_5	I_2	C_6H_5I	88
C_6H_5	HBr	C_6H_6	100
$CH_2{=}CH$	I_2	$(CH_2{=}CH)_3SnI$	71

Extreme difficulties were encountered in the study of the cleavage reactions of diphenyldivinyltin by iodine, hydrogen bromide and hydrogen chloride. A careful study of the reaction of diphenyldivinyltin with iodine on a larger scale showed that thermal redistribution of the phenyldivinyltin iodide formed in the reaction had occurred during distillation of the reaction mixture

$$(C_6H_5)_2Sn(CH{=}CH_2)_2 + I_2 \longrightarrow C_6H_5(CH_2{=}CH)_2SnI + C_6H_5I \quad (3)$$
$$3C_6H_5(CH_2{=}CH)_2SnI \longrightarrow 2(CH_2{=}CH)_3SnI + (C_6H_5)_3SnI \quad (4)$$

The results of this product study are shown in Table II.

TABLE II

PRODUCT STUDY OF THE CLEAVAGE OF $(C_6H_5)_2Sn(CH{=}CH_2)_2$ AND OF THE REDISTRIBUTION OF $(C_6H_5)(CH_2{=}CH)_2SnI$

Isolated products	Yield, g. Calcd.[a]	Found
C_6H_5I	31.2	27.5
$(CH_2{=}CH)_3SnI$	32.6	28.2
$(C_6H_5)_3SnI$	24.4	24.2

[a] Calculated on the basis of reactions (3) and (4).

Similar results were obtained in the cleavage of diphenyldivinyltin by hydrogen bromide and hydrogen chloride.

No reports of such redistributions have appeared in the literature thus far. However, Luitjen and

(1) Part I, D. Seyferth and F. G. A. Stone, THIS JOURNAL, **79**, 515 (1957).

(2) (a) C. A. Burkhard, *ibid.*, **72**, 1078 (1950); (b) E. Larsson, *Trans. Chalmers Univ. Technology*, **115**, 21, 25 (1951); (c) R. Nagel and H. W. Post, *J. Org. Chem.*, **17**, 1379 (1952); (d) G. H. Wagner, D. L. Bailey, A. N. Pines, M. L. Dunhan and D. B. McIntire, *Ind. Eng. Chem.*, **45**, 367 (1953); (e) L. H. Sommer, D. L. Bailey, G. M. Goldberg, C. E. Buck, T. S. Bye, F. J. Evans and F. C. Whitmore, THIS JOURNAL, **76**, 1613 (1954); (f) M. Kanazashi, *Bull. Chem. Soc. Japan*, **28**, 44 (1955).

(3) M. S. Kharasch and R. Marker, THIS JOURNAL, **48**, 3130 (1926).

(4) For a comprehensive survey of the cleavage reactions of organotin compounds see: J. G. A. Luitjen and G. J. M. van der Kerk, *Investigations in the Field of Organotin Chemistry*, Tin Research Institute, Greenford, England, 1955, pp. 75–81.

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TABLE III

VINYL DERIVATIVES OF TIN PREPARED BY CLEAVAGE REACTIONS

Compound	B.p. °C.	Mm.	M.p., °C.	d^{25}_4	$n^{25}D$	Carbon, %[a] Calcd.	Carbon, %[a] Found	Hydrogen, %[a] Calcd.	Hydrogen, %[a] Found
$(CH_3)_2(CH_2{=}CH)SnI$	57.5–59	5.2–5.3		2.033	1.5762	15.87	16.08	3.00	3.01
$(n\text{-}C_4H_9)_2(CH_2{=}CH)SnI$	108.5–109.8	1.75		1.556	1.5384	31.04	31.30	5.47	5.34
$(CH_2{=}CH)_3SnI$	60	1.8–1.9		1.898	1.5828	22.05	22.35	2.78	2.96
$(CH_3)_2(CH_2{=}CH)SnBr$	59–61	9.5		1.838	1.5350	18.79	18.54	3.55	3.57
$(n\text{-}C_4H_9)_2(CH_2{=}CH)SnBr$	96	0.65–0.45		1.416	1.5102	35.34	35.51	6.23	6.37
$(CH_3)_2(CH_2{=}CH)SnCl$	73–75	27.0		1.575	1.5105	22.74	22.95	4.29	4.36
$(n\text{-}C_4H_9)_2(CH_2{=}CH)SnCl$	82–83	0.6		1.273	1.4973	40.75	40.60	7.17	7.19
$(CH_2{=}CH)_3SnF$			>300°			32.93	33.02	4.15	4.37
$(C_6H_5)_2(CH_2{=}CH)SnF$			>300°[c]			52.72	52.76	3.37	3.43
$C_6H_5(CH_2{=}CH)_2SnF$			>300°[d]			44.66	44.52	4.12	4.05
$(CH_3)_2(CH_2{=}CH)SnO_2CCHBrCH_3$			79–81			26.65	26.37	4.00	4.19
$(C_2H_5)_3SnSCH_2CO_2C_2H_5$[b]	107–109	1.0			1.5101	38.69	38.55	6.82	6.74

[a] All analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. [b] % S: calcd., 9.86; found, 10.13. [c] Turns brown and shrinks above 285°. [d] Turns tan and shrinks above 210°.

van der Kerk (ref. 4, p. 120) mention the possibility of such reactions in their discussion of the preparation of unsymmetrical organotin iodides.

Preliminary experiments have shown that organic acids cleave the vinyl group as well

$$R_3SnCH{=}CH_2 + R'CO_2H \longrightarrow R_3SnO_2CR' + CH_2{=}CH_2 \quad (5)$$

Indeed, this is an excellent method for preparing pure organotin esters in quantitative yield, and this reaction will be discussed in greater detail in a later communication. Qualitative observations of the reaction rate show that the greater the dissociation constant of the organic acid used, the faster is the cleavage of the vinyl group. Thus acetic acid reacts only very slowly with dimethyldivinyltin at room temperature, while dichloroacetic acid reacts exceedingly vigorously with the same compound.

Even weak acids such as mercaptans liberated ethylene from vinyltin compounds. When equivalent quantities of triethylvinyltin and ethyl mercaptoacetate were mixed and left to stand at room temperature for four days an 11% yield of ethyl S-(triethylstannyl)-mercaptoacetate thus resulted. Heating the reactants at 90–95° for ten hours gave a 41% yield of this cleavage product. This observed cleavage reaction again is in marked contrast to the well-known addition of mercaptans to vinylsilicon compounds.[2a,b] The structure of the cleavage product was proven by its independent synthesis by the reaction of bis-(triethyltin) oxide with ethyl mercaptoacetate

$$[(C_2H_5)_3Sn]_2O + 2HSCH_2CO_2C_2H_5 \longrightarrow 2(C_2H_5)_3SnSCH_2CO_2C_2H_5 + H_2O$$

Discussion

The results of this work are in accord with the extensive literature concerning cleavage reactions of organotin compounds.[4] However, an explanation of the ready cleavage of the vinyl group from tin, in contrast to the well-defined addition reactions exhibited by vinylsilanes, can no longer be sought in terms of a more polar metal–carbon bond in the case of organotin compounds. The most recent determinations of electronegativity[5] of the Group IVB elements have shown that the electronegativities of tin and silicon in their tetravalent organometallic compounds are about the same. The greatest differences, relevant to this discussion, between the organic compounds of silicon and tin lie in (a) the lower metal–carbon bond energy in the case of tin[6] and (b) the larger covalent radius of tin.[7] Of these, the former is probably the main contributor to the observed differences in the reactions of vinylsilicon and vinyltin compounds with the halogens and with protonic acids. Cleavage is clearly the thermodynamically favored reaction in the case of the tin compounds.

A detailed explanation of the cleavage series of organotin compounds and of the position of the vinyl group in this series must await kinetic studies which would give us an understanding of the transition state of the cleavage reaction. However, the results of this study are in harmony with that of Winstein and Traylor[8] on electrophilic substitution on saturated carbon atoms by means of acetic acid cleavage of dialkylmercury compounds. The anticipation of these authors that the rates of electrophilic substitution on carbon will fall off as attack is on: (a) an aromatic or vinyl carbon atom and (b) a saturated carbon atom, is borne out by the cleavage series for organotin compounds and by the position of the vinyl group in this series.

New compounds obtained by these reactions, their physical properties and analytical data are listed in Table III.

Experimental

1. Starting Materials.—The preparation of the vinyltin compounds used in this study, with the exception of diphenyldivinyltin, has been described previously.[1] **Diphenyldivinyltin** was prepared in 68% yield by treatment of 0.7 mole of crude diphenyltin dichloride with 2.0 mole of vinylmagnesium bromide[9] in tetrahydrofuran solution for 20

(5) L. A. Allred, Ph.D. Thesis, Harvard University, 1956.

(6) For instance, the Si–C mean bond energies in tetramethyl- and tetraethylsilane are 75 and 62 kcal./mole, respectively, (*cf.* S. Tannenbaum, THIS JOURNAL, **76**, 1027 (1954)), while the Sn–C mean bond energies in tetramethyl- and tetraethyltin are 44.8 and 49.5 kcal./mole, respectively (calculated from heats of combustion reported by C. R. Dillard, Final Report, U. S. Office of Naval Research Contract N9-onr-95700, August 31, 1952).

(7) T. Moeller, "Inorganic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1952, p. 135.

(8) S. Winstein and T. G. Traylor, THIS JOURNAL, **77**, 3747 (1955).

(9) [illegible], *Compt. rend.*, **239**, 1510 (1954).

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hours at reflux. Hydrolysis with a saturated aqueous solution of ammonium chloride, followed by distillation of the decanted organic layer, gave 152 g. of diphenyldivinyltin, b.p. 121.5° at 0.4 mm., d^{25}_4 1.334, $n^{25}D$ 1.5929.

Anal. Calcd. for $C_{16}H_{16}Sn$: C, 58.76; H, 4.93. Found: C, 58.88; H, 4.98.

2. **Iodine Cleavage Reactions. a. Dimethyldivinyltin, Di-*n*-butyldivinyltin and Tetravinyltin.**—The same procedure was used in the iodine cleavage of these three compounds. One such reaction is given as an example.

To a solution of 25 g. (0.123 mole) of dimethyldivinyltin in 500 ml. of diethyl ether was added 31.1 g. (0.123 mole) of iodine, and the mixture was refluxed for eight hours. A colorless solution resulted. The ether was distilled at atmospheric pressure, and the residue was distilled at reduced pressure to give 27.3 g. (74%) of dimethylvinyltin iodide.

b. **Diphenyldivinyltin.**—To a solution of 50 g. (0.153 mole) of diphenyldivinyltin in 400 ml. of ether was added 38.8 g. (0.153 mole) of iodine. After the mixture had been refluxed for eight hours the iodine color was discharged. The ether was removed at atmospheric pressure and then the distillation was continued at reduced pressure to give the following fractions: iodobenzene, b.p. 60.5–62° at 8.7 mm., $n^{24.5}D$ 1.6160, 27.5 g.; impure trivinyltin iodide, boiling from 54° at 1.3 mm. to 60° at 0.7 mm., $n^{25}D$ 1.5897, 28.2 g.; triphenyltin iodide, solid residue, 24.2 g. The latter was recrystallized from ether and identified by analysis:

Anal. Calcd. for $C_{18}H_{15}ISn$: C, 45.3; H, 3.17. Found: C, 45.00; H, 3.21.

The crude trivinyltin iodide was redistilled to give 25 g. of material, b.p. 60–62° at 1.8 mm., $n^{25}D$ 1.5835.

c. **Triphenylvinyltin.**—To a solution of 20 g. (0.053 mole) of triphenylvinyltin in 350 ml. of ether was added 13.5 g. (0.053 mole) of iodine, and the mixture was refluxed for 15 hours. The ether and part of the iodobenzene were removed by distillation. The residue could not be crystallized and for this reason it was treated with an excess of neutral aqueous-alcoholic potassium fluoride solution. Recrystallization of the precipitated organotin fluoride from a tetrahydrofuran–acetone–ethanol mixture gave pure **diphenylvinyltin fluoride**, 13 g., a yield of 77%.

3. **Bromine Cleavage Reactions.**—To a 25-g. (0.079 mole) sample of tri-*n*-butylvinyltin at −78° was added dropwise 12.6 g. (0.079 mole) of bromine. The bromine was decolorized immediately as it was added. After the addition had been completed the mixture was allowed to warm to room temperature. Distillation of the reaction mixture yielded: 1,1,2-tribromoethane, boiling from 58° at 4 mm. to 53° at 1.9 mm., $n^{25}D$ 1.5855, 8 g.; a center fraction boiling from 98° at 2.5 mm. to 110° at 1.8 mm.; tri-*n*-butyltin bromide, b.p. 120° at 1.8 mm. to 122° at 1.6 mm., d^{25}_4 1.338, $n^{25}D$ 1.5022; MR_D found, 81.64, calcd., 81.40, 15 g., a yield of 51.4%. Jones, *et al.*,[10] report d^{20}_4 1.3365 and $n^{20}D$ 1.5000 for tri-*n*-butyltin bromide. When a 100% excess of bromine was used, a 76% yield of tri-*n*-butyltin bromide resulted.

4. **Chlorine Cleavage Reactions.**—Into 23.5 g. (0.074 mole) of tri-*n*-butylvinyltin at −78° was bubbled 5.5 g. (0.08 mole) of dry chlorine. The reaction mixture subsequently was warmed up to room temperature and was fractionally distilled to give 20.4 g. (86.4%) of tri-*n*-butyltin chloride, b.p. 98° at 0.45 mm. to 100° at 0.35 mm., $n^{25}D$ 1.4903; $n^{22}D$ 1.4908 is reported by Manulkin[11] for this compound.

5. **Hydrogen Bromide Cleavage Reactions.** (a) **Dimethyldivinyltin.**—Into a cold trap at −78° was charged 25 g. (0.123 mole) of dimethyldivinyltin. The exit arm of the trap led to an Ascarite-filled tube which was connected to another trap containing a solution of 16 g. (0.1 mole) of bromine in chloroform. Hydrogen bromide gas was slowly bubbled into the organotin compound until the latter had nearly solidified. The organotin compound was then warmed up to −40°, and the addition of hydrogen bromide was continued until the bromine solution was completely decolorized. Fractional distillation of the reaction mixture gave 24.2 g. (77%) of dimethylvinyltin bromide. A small amount of dimethyltin dibromide (m.p. 74° after recrystallization from ether; m.p. in the literature,[12] 75–77°) remained in the still pot, indicating that the second vinyl group is more susceptible to cleavage than are the methyl groups after one vinyl group has been removed.

A similar procedure was followed in the hydrogen bromide cleavage of di-*n*-butyldivinyltin. In the latter case the 1,2-dibromoethane formed in the end trap was recovered in 80% yield by distillation, b.p. 129–130°.

b. **Diphenyldivinyltin.** (i).—Eight grams (0.10 mole) of liquid hydrogen bromide was allowed to vaporize slowly and was bubbled into 30 g. (0.0918 mole) of diphenyldivinyltin, initially at −78°. The organotin compound began to form a solid slush in the later stages of the reaction and therefore was warmed to −40°. Distillation at atmospheric pressure gave 8 g. (100% yield) of benzene, b.p. 79–80°.

(ii).—A similar procedure was used when 25 g. (0.0765 mole) of diphenyldivinyltin was treated with 6.2 g. (0.0765 mole) of hydrogen bromide. Fractional distillation of the high boiling organotin products gave: impure **trivinyltin bromide**, boiling from 54° at 0.4 mm. to 53° at 0.3 mm., 9 g.; a yellow oil, distilling continuously from 86° at 0.35 mm. to 132° at 0.35 mm., 10 g.; a solid residue, 4.5 g. The latter was recrystallized from ether to give triphenyltin bromide, m.p. 118–120°; m.p. reported by Krause,[13] 120.5°. The impure trivinyltin bromide was converted to pure **trivinyltin fluoride** by the potassium fluoride method.

(iii).—To 20 g. (0.061 mole) of diphenyldivinyltin was added 5 g. (0.061 mole) of hydrogen bromide in the manner described above. When the reaction mixture had warmed to room temperature it was treated with an excess of neutral aqueous-alcoholic potassium fluoride solution. A white, oily solid resulted that could be extracted with ether. Evaporation of the ethereal extracts yielded 8 g. of pure **phenyldivinyltin fluoride**. No attempt was made to recover the remaining portion of this fluoride from the precipitation solvent medium.

6. **Hydrogen Chloride Cleavage Reactions. a. Di-*n*-butyldivinyltin.**—A solution of 28.7 g. (0.1 mole) of di-*n*-butyldivinyltin in chloroform was prepared in a trap. The exit arm of the trap led to a tube filled with Ascarite which was connected to a trap containing 12.8 g. (0.08 mole) of bromine in chloroform solution. The di-*n*-butyldivinyltin solution was maintained at 50–60° with a hot water-bath and hydrogen chloride gas was bubbled through the solution until the bromine in the end trap was decolorized. The chloroform was removed by rapid distillation and the residue was fractionally distilled, giving 23.4 g. (79.3%) of di-*n*-butylvinyltin chloride, b.p. 82–83° at 0.6 mm.

A similar procedure was used in the hydrogen chloride cleavage of dimethyldivinyltin.

b. **Diphenyldivinyltin.**—Into a solution of 21.5 g. (0.0657 mole) of diphenyldivinyltin in chloroform, maintained at 60–70°, was bubbled about 2.4 g. (0.066 mole) of hydrogen chloride gas. After removal of the chloroform by rapid distillation the residue was distilled at reduced pressure. The following fractions were collected: 44° at 0.5 mm. to 64° at 0.35 mm., 4 g.; 65–68° at 0.35 mm., 5 g.; 83–105° at 0.35 mm., 3 g.; a solid residue, 4 g. The latter was recrystallized from ether to give fairly pure triphenyltin chloride, m.p. 100–102°; m.p. reported[14] 105–106°.

7. **Cleavage by Organic Acids. a. Acetic Acid.**—To 10 g. (0.0428 mole) of triethylvinyltin was added 2.57 g. (0.0428 mole) of glacial acetic acid. The reactants were heated on the steam-bath for 1.5 hours and then cooled to give a quantitative yield of triethyltin acetate, m.p. 132–134°; Luitjen and van der Kerk (ref. 10, p. 99) report a m.p. of 134–135°.

b. **α-Bromopropionic Acid.**—The same procedure was followed in the reaction of 5 g. (0.0243 mole) of dimethyldivinyltin with 3.06 g. (0.02 mole) of α-bromopropionic acid. A quantitative yield of dimethylvinyltin α-bromopropionate resulted after the crystals were washed with chilled petroleum ether and dried.

8. **Cleavage by Mercaptans.**—To 23.3 g. (0.1 mole) of triethylvinyltin was added 36.0 g. (0.3 mole) of ethyl mercaptoacetate. The mixture was heated on the steam-bath

(10) W. J. Jones, D. P. Evans, T. Gullwell and D. C. Griffiths, *J. Chem. Soc.*, 39 (1935).

(11) Z. M. Manulkin, *J. Gen. Chem.* (*U.S.S.R.*), **18**, 299 (1948).

(12) A. C. Smith, Jr., and E. G. Rochow, THIS JOURNAL, **75**, 4105 (1953).

(13) E. Krause, *Ber.*, **51**, 912 (1918).

(14) K. A. Kocheshkov, *ibid.*, **67**, 1348 (1934).

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for ten hours. Fractional distillation gave 27.5 g. of a mixture of unreacted starting materials, boiling from 44° to 52° at 8.9, mm, and 14.5 g. of ethyl S-(triethylstannyl)-mercaptoacetate, boiling from 99° at 0.44 mm. to 110° at 0.65 mm. This fraction was redistilled (107–109° at 1.0 mm.) to give the pure compound. Reference to the analytical data in Table III shows that this is not the addition product, $Et_3SnCH_2CH_2SCH_2CO_2Et$. (Calcd. for the addition product: C, 40.82; H, 7.42; S, 9.08.)

9. **Ethyl S-(Triethylstannyl)-mercaptoacetate: Proof of Structure.**—The method of Sasin[15] was used. To 6.2 g. (0.0144 mole) of bis-(triethyltin) oxide was added 5.2 g. (0.432 mole) of ethyl mercaptoacetate. After the initially vigorous reaction had subsided the mixture was refluxed for one hour and then was distilled to give a small fraction boiling at 115–117° at 1.5 mm., $n^{25}D$ 1.5099, whose infrared absorption spectrum was identical with that of the cleavage product described above.

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(15) G. Sasin, *J. Org. Chem.*, **18**, 1142 (1953).

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ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE RAHWAY RESEARCH LABORATORY OF THE METAL AND THERMIT CORPORATION]

The Preparation of Some Vinyltin Compounds with Vinylmagnesium Chloride

BY SANDERS D. ROSENBERG, AMBROSE J. GIBBONS, JR., AND HUGH E. RAMSDEN

RECEIVED OCTOBER 29, 1956

Tetravinyltin, dibutyldivinyltin, dimethyldivinyltin, diphenyldivinyltin, tributylvinyltin, triphenylvinyltin, butylvinyltin dichloride, dibutylvinyltin chloride and divinylbutyltin chloride have been prepared by the reaction of vinylmagnesium chloride with appropriate tin chlorides. In addition, dibutyldivinyltin and tributylvinyltin have been synthesized from vinylmagnesium chloride and dibutyltin oxide and bistributyltin oxide, respectively.

The development of vinylmagnesium chloride in this Laboratory[1] has made possible the synthesis of vinyltin compounds by classical Grignard techniques. The only vinyltin compounds previously reported in the literature are vinyltin tribromide[2] and several 2-chlorovinyltin compounds.[3,4]

Four general methods have been developed for the synthesis of organotin compounds: 1, the complete replacement of the halogen of tin tetrachloride or organotin halides by use of an active organometallic compound; 2, the stepwise partial replacement of the halogen of organotin halides by use of an active organometallic compound; 3, the disproportionation of symmetrical tetrasubstituted organotin compounds with tin tetrachloride; 4, the cleavage of organotin compounds with halogen or halogen acid. The use of the first two methods in the preparation of vinyltin compounds will be reported here and of the last two in a subsequent article.

Tetravinyltin (82%), di-*n*-butyldivinyltin (89%), dimethyldivinyltin (75%), diphenyldivinyltin (73%), tri-*n*-butylvinyltin (82%) and triphenylvinyltin (79%) have been prepared by the reaction of vinylmagnesium chloride in tetrahydrofuran solution with the appropriate tin halide in a hydrocarbon solvent. These compounds, with the exception of triphenylvinyltin, were purified by distillation under reduced pressure to give colorless liquids. Triphenylvinyltin, a colorless solid, was crystallized from ethanol.

$$4CH_2{=}CHMgCl + SnCl_4 \longrightarrow (CH_2{=}CH)_4Sn + 4MgCl_2$$

$$2CH_2{=}CHMgCl + (n\text{-}C_4H_9)_2SnCl_2 \longrightarrow (n\text{-}C_4H_9)_2Sn(CH{=}CH_2)_2 + 2MgCl_2$$

$$CH_2{=}CHMgCl + (C_6H_5)_3SnCl \longrightarrow (C_6H_5)_3SnCH{=}CH_2 + MgCl_2$$

n-Butylvinyltin dichloride (54%), divinyl-*n*-butyltin chloride (50%) and di-*n*-butylvinyltin chloride (56%) have been synthesized by the stepwise substitution of *n*-butyltin trichloride and di-*n*-butyltin dichloride, respectively, with vinylmagnesium chloride. The problem in this approach was one of limiting the substitution to a stepwise vinylation. Failure to do this led to a separation step in which the product had to be won from unreacted starting material and/or the completely substituted vinyltin compound. It was this difficult separation that caused the yield of desired product to be lower than in the preparation of completely substituted compounds.

$$CH_2{=}CHMgCl + n\text{-}C_4H_9SnCl_3 \longrightarrow (n\text{-}C_4H_9)(CH_2{=}CH)SnCl_2 + MgCl_2$$

$$2CH_2{=}CHMgCl + n\text{-}C_4H_9SnCl_3 \longrightarrow (CH_2{=}CH)_2(n\text{-}C_4H_9)SnCl + 2MgCl_2$$

$$CH_2{=}CHMgCl + (n\text{-}C_4H_9)_2SnCl_2 \longrightarrow (n\text{-}C_4H_9)_2(CH_2{=}CH)SnCl + MgCl_2$$

In a search for a shorter preparative method, it was found that di-*n*-butyldivinyltin could be prepared in a 58% yield from di-*n*-butyltin oxide[5] and vinylmagnesium chloride. Similarly tri-*n*-butylvinyltin (85%) was synthesized from bistri-*n*-butyltin oxide[5] and vinylmagnesium chloride.

$$2CH_2{=}CHMgCl + (n\text{-}C_4H_9)_2SnO \longrightarrow (n\text{-}C_4H_9)_2Sn(CH{=}CH_2)_2 + (MgCl)_2O$$

$$2CH_2{=}CHMgCl + (n\text{-}C_4H_9)_6Sn_2O \longrightarrow 2(n\text{-}C_4H_9)_3SnCH{=}CH_2 + (MgCl)_2O$$

These results demonstrate that the oxide bond in organotin compounds, and most likely in other similar organometallic compounds, is very different from those encountered in the chemistry of carbon. These oxides behave like the halides and esters of silicon and tin and undergo similar nucleophilic substitution reactions.

Experimental

Starting Materials.—Commercial tin tetrachloride was redistilled through a short column. Du Pont tetrahydrofuran and Matheson vinyl chloride were used without additional purification. Dow Grignard grade magnesium turnings were used. Triphenyltin chloride, diphenyltin dichloride, butyl trichloride, dibutyltin dichloride, tributyltin chloride and dimethyltin dichloride were obtained by disproportionation of the corresponding tetrasubstituted compounds.[6,7]

1. Tetravinyltin.—In a 22.0-l. flask[8] was placed 394.0 g. (16.2 g. atoms) of magnesium turnings. To this was added 100 ml. of a solution of 1212 g. (19.4 moles) of vinyl chloride in 3460 g. (48 moles) of tetrahydrofuran. The reaction was initiated by heating the flask to cause reflux, followed by the addition of 2.0 ml. of ethyl bromide. Once thoroughly initiated, the heating was stopped and the remainder of the mix added at a rate to maintain a pot temperature of 48–56°. The addition took 6.0 hr. The tem-

(1) H. E. Ramsden, J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. E. Balint and R. Cserr, unpublished.

(2) A. Solerio, *Gazz. chim. ital.*, **85**, 61 (1955).

(3) A. N. Nesmeyanov, A. E. Borisov and A. N. Abramova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 647 (1946).

(4) We have learned in a private communication from Dr. D. Seyferth of the Chemistry Department of Harvard University that several vinyltin compounds have been synthesized recently by his group utilizing vinylmagnesium bromide, THIS JOURNAL, **79**, 2133 (1957).

(5) This compound is commercially available at the Rahway Chemical Plant of the Metal and Thermit Corporation.

(6) H. Gilman and S. D. Rosenberg, THIS JOURNAL, **74**, 5580 (1952).

(7) E. W. Johnson and J. M. Church, U. S. Patent 2,672,471, 1954.

(8) The flask was equipped with a swivel anchor stirrer (3/8" blade on 3/8" shaft, stainless steel), a 2.0-l. dropping funnel, an extra large Dry Ice–acetone cold condenser and a thermometer.

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TABLE I
VINYLTIN COMPOUNDS

Compound	B.p. or m.p. °C.	Mm.	d^{25}_4	$n^{25}D$	Analyses, % Calcd. Cl	Calcd. Sn	Found Cl	Found Sn
Tetravinyltin	55–57	17	1.267	1.4993		52.32		51.77
Di-*n*-butyldivinyltin	78–80	2	1.127	1.4824		41.36		41.20
Dimethyldivinyltin	120–121	760	1.284	1.4720		58.50		58.29
Diphenyldivinyltin	153–154	5	1.3195	1.5949		36.30		36.30
Tri-*n*-butylvinyltin	114	3	1.085	1.4761		37.44		37.37
Triphenylvinyltin	M. 39–40					31.48		31.11
n-Butylvinyltin dichloride	99–101	3	1.533	1.5254	25.90	43.36	24.80	42.85
Divinyl-*n*-butyltin chloride	M. 27–28 82–84	3	1.370	1.4970	13.36	44.73	13.33	44.51
Di-*n*-butylvinyltin chloride	112–114	4	1.266(20°)	1.4987(20°)	12.00	40.18	11.30	40.31

perature was maintained for 3.0 hr. longer by heating. Then a solution of 663.6 g. (3.5 moles) of tin tetrachloride in 10.8 l. of pentane was added at a rate to maintain reflux.[9] The addition took 4.0 hr. The mixture was refluxed for 5.0 hr.

On cooling, the reaction mixture was partially hydrolyzed by the cautious addition of 2.8 l. of 10% aqueous hydrochloric acid. At this point, a heavy solid[10] dropped out of the organic layer. The organic layer was decanted from the solid into a 22.0-l. flask. The hydrolysis was completed by the addition of 2.0 l. of water to the solid and two liquid phases resulted. The organic layer (*ca.* 300 ml.) was separated and added to the 22.0-l. flask. The solvents, pentane and tetrahydrofuran, were removed by rapid distillation at 1.0 atm. on a steam-bath. The residue was transferred to a 1.0-l. flask and carefully fractionally distilled under reduced pressure to yield: cut 1, b. 25–30° (100–120 mm.), 150 g. of tetrahydrofuran; cut 2, b. 55–57° (17 mm.), 642 g. (82%) of tetravinyltin.

2. **Di-*n*-butyldivinyltin.**—In a 5.0-l. flask equipped as above was placed 303.8 g. (1.0 mole) of di-*n*-butyltin dichloride in 2.0 l. of heptane. To this was added, at reflux, 2.5 moles of vinylmagnesium chloride in tetrahydrofuran over a 2.0-hr. period. The mix was refluxed an additional 4.0 hr. and worked-up as above to yield 254.0 g. (89%) of di-*n*-butyldivinyltin distilling at 78–80° (2.0 mm.).

3. **Triphenylvinyltin.**—In a 3.0-l. flask was placed 385.5 g. (1.0 mole) of triphenyltin chloride in 1.0 l. of heptane. Then 1.2 moles of vinylmagnesium chloride in tetrahydrofuran was added over a 2.0-hr. period at reflux followed by a 3.0-hr. reflux. The mix was hydrolyzed as above. The solvents were distilled at 1.0 atm. with the last traces taken off at water-pump pressure (20 mm.). A solid residue of 362.0 g. (93%) of crude product melting at 31–35° was obtained. This was recrystallized from methanol to yield 298.0 g. (79%) of triphenylvinyltin melting at 39–40°.

4. **Tri-*n*-butylvinyltin.**—In a 5.0-l. flask was placed 592.1 g. (1.0 mole) of bistri-*n*-butyltin oxide in 2.0 l. of heptane. Then 2.2 moles of vinylmagnesium chloride in tetrahydrofuran was added at a temperature of 70–80°. The mix was refluxed for 3.0 hr. and worked-up to yield 541.0 g. (85%) of tri-*n*-butylvinyltin distilling at 114° (3.0 mm.).

5. ***n*-Butylvinyltin Dichloride.**—In a 5.0-l. flask was placed 282.2 g. (1.0 mole) of *n*-butyltin trichloride in 2.5 l. of heptane. Then 1.0 mole of vinylmagnesium chloride in tetrahydrofuran was added over a 2.0-hr. period with the reaction temperature maintained between 25–40°. The mix was stirred for 3.0 hr. and filtered by suction through a Buchner funnel. The solvents were removed at 1.0 atm. and the residue carefully fractionally distilled under reduced pressure to yield 146.0 g. (53.5%) of *n*-butylvinyltin dichloride distilling at 99–101° (3.0 mm.).

6. **Divinyl-*n*-butyltin Chloride.**—In a 5.0-l. flask was placed 339.0 g. (1.2 moles) of *n*-butyltin trichloride in 2.5 l. of heptane. Then 2.4 moles of vinylmagnesium chloride in tetrahydrofuran was added, at reflux, over a 3.0-hr. period with stirring. On completion of addition, the mix was refluxed for 1.0 hr. and allowed to cool. Hydrolysis was accomplished as above. The organic phase was dried on sodium sulfate, freed of solvents at 1.0 atm. and carefully fractionally distilled under reduced pressure to yield 159.0 g. (50%) of divinyl-*n*-butyltin chloride distilling at 82–84° (3.0 mm.).

Acknowledgment.—The authors wish to thank Dr. Marie Farnsworth and her co-workers in the Physical and Analytical Section of this Laboratory for their assistance throughout this work.

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(9) At this point, two large water condensers were substituted for the thermometer and cold condenser, and the excess vinyl chloride was allowed to vent up the hood. A thorough study of solvent systems has been made and pentane at this relative concentration was found to give maximum yield of product.

(10) The solid is thought to be $MgCl_2 \cdot 6H_2O$.

[CONTRIBUTION FROM THE RAHWAY RESEARCH LABORATORY OF THE METAL AND THERMIT CORPORATION]

The Disproportionation of Tetravinyltin with Tin Tetrachloride and the Cleavage of Some Vinyltin Compounds with Bromine

BY SANDERS D. ROSENBERG AND AMBROSE J. GIBBONS, JR.

RECEIVED OCTOBER 29, 1956

Vinyltin trichloride, divinyltin dichloride and trivinyltin chloride have been prepared in excellent yields by the low temperature disproportionation of tetravinyltin with tin tetrachloride. Dibutyldivinyltin, dimethyldivinyltin and diphenyldivinyltin have been subjected to bromine cleavage, and it has been found that the ease of displacement of these groups from tin is phenyl > vinyl > methyl > butyl. Divinyltin oxide and trivinyltin hydroxide have been prepared by the hydrolysis of divinyltin dichloride and trivinyltin chloride, respectively, with aqueous sodium hydroxide.

The preparation of organotin chlorides by the disproportionation of symmetrical tetrasubstituted organotin compounds with tin tetrachloride has been reported by a number of workers.[1-3] Conditions have been outlined for the synthesis of such compounds as di-*n*-butyltin dichloride,[1,3] di-*n*-hexyltin dichloride[3] and triphenyltin chloride.[2]

(1) W. J. Jones, W. C. Davies, S. T. Bowden, C. Edwards, V. E. Davies and L. H. Thomas, *J. Chem. Soc.*, 1043 (1947).

(2) H. Gilman and S. D. Rosenberg, THIS JOURNAL, 74, 5580 (1952).

(3) O. W. Johnson and J. M. Church, U. S. Patent 2,672,471, 1954.

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In general the method involves heating the tetra-substituted organotin compound with tin tetrachloride at 200–240° for 1–3 hr. at 1.0 atmosphere.

$$3R_4Sn + SnCl_4 \longrightarrow 4R_3SnCl$$

$$R_4Sn + SnCl_4 \longrightarrow 2R_2SnCl_2$$

The product is purified by distillation under reduced pressure and/or recrystallization from a suitable solvent.

In the course of research in this Laboratory on the preparation of vinyltin compounds,[4] a need arose for vinyltin chlorides. As it was known that tetravinyltin was not stable at temperatures over 200°, it was decided to investigate the utility of the disproportionation reaction at low temperatures. It was found that vinyltin trichloride, divinyltin dichloride and trivinyltin chloride could be prepared in virtually quantitative yields simply by stirring tetravinyltin with tin tetrachloride, in stoichiometric quantities, for several hours and

$$(CH_2{=}CH)_4Sn + 3SnCl_4 \xrightarrow{75\text{–}90^\circ} 4CH_2{=}CHSnCl_3$$

$$(CH_2{=}CH)_4Sn + SnCl_4 \xrightarrow{0\text{–}10^\circ} 2(CH_2{=}CH)_2SnCl_2$$

$$3(CH_2{=}CH)_4Sn + SnCl_4 \xrightarrow{35\text{–}40^\circ} 4(CH_2{=}CH)_3SnCl$$

isolating the products by distillation under reduced pressure. The disproportionation took place with equal facility over a wide temperature range (0–150°).

Vinyltin trichloride and divinyltin dichloride are stable compounds, but it was found, after a series of vacuum distillations on a 3′-glass helix packed column, that trivinyltin chloride tends to rearrange to form divinyltin dichloride and tetravinyltin. Therefore, it is suggested that the crude trivinyltin chloride be used as such for the preparation of derivatives.

$$2(CH_2{=}CH)_3SnCl \longrightarrow (CH_2{=}CH)_2SnCl_2 + (CH_2{=}CH)_4Sn$$

Cleavage studies on organotin compounds with halogen[5] and halogen acid[6] have shown that the ease of displacement of organic groups from tin is α-thienyl > p-tolyl > phenyl > methyl > n-butyl > n-octyl. It was of interest to ascertain the relative position of the vinyl group in this series. Di-n-butyldivinyltin, dimethyldivinyltin and diphenyldivinyltin were allowed to react with bromine at 10–15°. The results are summarized in Table I. It was found that the preferential order of cleavage of these groups from tin is phenyl > vinyl > methyl > butyl.

$$R_2R_2'Sn + Br_2 \rightarrow \begin{cases} R_2R'SnBr + R'Br \\ RR'_2SnBr + RBr \end{cases}$$

Experimental

1. Vinyltin Trichloride.—In a 500-ml. flask was placed 50.0 g. (0.22 mole) of tetravinyltin. To this was added, with good stirring and over a 2.25-hr. period, 187.6 g. (0.66 mole plus 10%) of tin tetrachloride at a pot temperature of 30°. The solution was then heated to and maintained at 70° for 2.0 hr. and distilled to yield: cut 1, b.p. 115–125° (760 mm.), 32 g. of crude tin tetrachloride; cut 2, b.p. 64–65° (15 mm.), 190.0 g. (86%) of vinyltin trichloride.

Anal. Calcd. for $C_2H_3Cl_3Sn$: Cl, 42.19; Sn, 47.08. Found: Cl, 41.55; Sn, 47.13; $n^{25}D$ 1.5361; d^{25}_4 1.9981.

2. Divinyltin Dichloride.—In a 2.0-l. flask was placed 340.5 g. (1.5 moles) of tetravinyltin. To this was added, with good stirring and over a 2.25-hr. period, 390.8 g. (1.5 moles) of tin tetrachloride at a pot temperature of 30°. The solution was then stirred for 2.0 hr. and carefully fractionally distilled under reduced pressure to yield 718.0 g. (98%) of divinyltin dichloride distilling at 54–56° (3.0 mm.).

Anal. Calcd. for $C_4H_6Cl_2Sn$: Cl, 29.10; Sn, 48.71. Found: Cl, 28.81; Sn, 48.71; m.p. 13.2°; $n^{25}D$ 1.5490; d^{20}_4 1.7645.

3. Trivinyltin Chloride.—In a 2.0-l. flask was placed 600.0 g. (2.64 moles) of tetravinyltin. To this was added, with good stirring and over a 1.0-hr. period, 229.0 g. (0.88 mole) of tin tetrachloride at a pot temperature of 30°. The solution was stirred for 2.0 hr. and rapidly distilled under reduced pressure to yield 795.0 g. (96%) of trivinyltin chloride distilling at 59–60° (6.0 mm.).

Anal. Calcd. for C_6H_9ClSn: Cl, 15.07; Sn, 50.45. Found: Cl, 14.68; Sn, 50.50; $n^{25}D$ 1.5235; d^{20}_4 1.5139.

4. Di-n-butylvinyltin Bromide.—In a 500-ml. flask was placed 102.6 g. (0.358 mole) of di-n-butyldivinyltin. To this was added, with good stirring and over a 2.0-hr. period, 57.0 g. (0.357 mole) of bromine. Each drop of bromine was decolorized instantly on reaching the solution and the reaction was vigorous.

The solution was then carefully fractionally distilled in an adequately trapped system to yield: cut 1, b.p. 14–17° (760 mm.), 22.7 g. (59.5%) of vinyl bromide; cut 2, b.p. 72–73° (0.03 mm.), 82.7 g. (68.4%) of di-n-butylvinyltin bromide; cut 3, pot residue, 13.4 g. (9.1%) of crude di-n-butyltin dibromide.

Anal. Calcd. for $C_{10}H_{21}BrSn$: Br, 23.55; Sn, 34.98. Found: Br, 24.28; Sn, 34.63; $n^{25}D$ 1.4970; d^{25}_4 1.3913. Calcd. for $C_8H_{18}Br_2Sn$: Br, 40.60; Sn, 30.18. Found: Br, 39.58; Sn, 30.54.

In a second run 58.6 g. (0.368 mole) of bromine in 184 ml. of CCl_4 was added to 105.3 g. (0.368 mole) of di-n-butyldivinyltin in 184 ml. of CCl_4 with good stirring over a 2.0-hr. period at 15°. A total of 99.5 g. (78%) of di-n-butylvinyltin bromide and 17.3 g. (12%) of di-n-butyltin dibromide was obtained.

5. Trivinyltin Hydroxide and Divinyltin Oxide.—In a 500-ml. flask was placed 25.0 g. (0.625 mole) of sodium hydroxide in 300 ml. of water. To this was added, with good stirring and over a 0.5-hr. period, 100.0 g. (0.425 mole) of trivinyltin chloride. A white solid formed immediately. After stirring for 1.0 hr., the solid filtered from the reaction solution under nitrogen was dried under reduced pressure over potassium hydroxide pellets in a vacuum desiccator. A total of 68.0 g. (74%) of trivinyltin hydroxide melting at 67.5–69.0° was obtained.

TABLE I

REACTION OF VINYLTIN COMPOUNDS WITH BROMINE

Vinyltin compound	Products isolated
$(n\text{-}C_4H_9)_2Sn(CH{=}CH_2)_2$	$CH_2{=}CHBr$ (60%)
	$(n\text{-}C_4H_9)_2(CH_2{=}CH)SnBr$ (78%)
$(CH_3)_2Sn(CH{=}CH_2)_2$	$CH_2{=}CHBr$ (69%)
	$(CH_2{=}CH)(CH_3)_2SnBr$ (88%)[a]
$(C_6H_5)_2Sn(CH{=}CH_2)_2$	C_6H_5Br (90%)
	$(CH_2{=}CH)_2(C_6H_5)SnBr$[b]

[a] *Anal.* Calcd. for C_4H_9BrSn: Br, 31.25. Found: Br, 30.92; b.p. 72° (21.0 mm.). This compound gave evidence of disproportionation on prolonged distillation under reduced pressure. [b] This compound was not isolated as it apparently disproportionated on distillation under reduced pressure (20 mm.). The main products isolated were diphenyltin dibromide, divinyltin dibromide and trivinyltin bromide.

(4) S. D. Rosenberg, A. J. Gibbons, Jr., and H. E. Ramsden, THIS JOURNAL, 79, 2137 (1957).

(5) Z. M. Manulkin, *J. Gen. Chem.* (*U.S.S.R.*), 11, 386 (1941); 13, 42 (1943); 14, 1047 (1944); 16, 235 (1946).

(6) Ch. Bobashinskaya and K. A. Kocheshkov, *ibid.*, 8, 1550 (1938).

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Anal. Calcd. for $C_6H_{10}OSn$: Sn, 54.75. Found: Sn, 54.11.

Similarly divinyltin oxide (42%) has been prepared from divinyltin dichloride and aqueous sodium hydroxide.

Anal. Calcd. for C_4H_6OSn: Sn, 62.95. Found: Sn, 62.60.

Acknowledgments.—The authors wish to thank Dr. Marie Farnsworth and her co-workers in the Physical and Analytical Section of this Laboratory for their assistance throughout this work.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES OF THE AMERICAN SMELTING AND REFINING COMPANY AND THE RESEARCH LABORATORIES OF E. F. HOUGHTON & CO.]

Arsonosiloxanes[1]

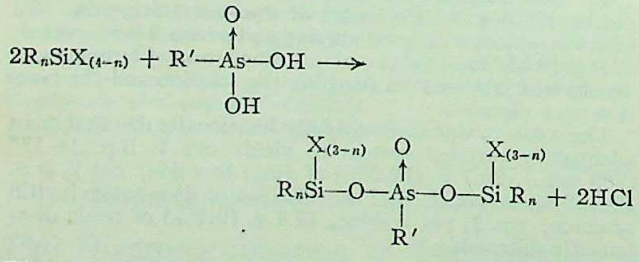
BY ROLAND M. KARY AND KURT C. FRISCH

RECEIVED APRIL 25, 1956

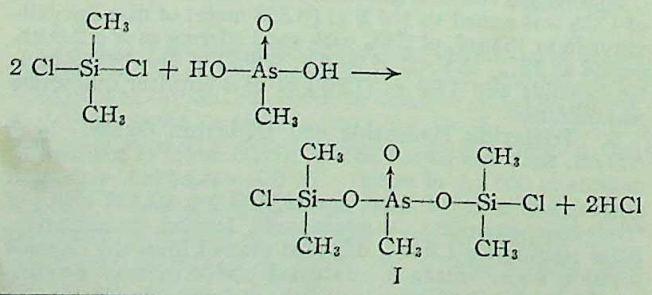
The well-known silicones, such as polymethylsiloxanes, do not exhibit pesticidal properties. Organic arsenical siloxanes could be used to control pest organism in addition to already existing utilities of conventional silicones. It was found that arsenic can be incorporated into siloxane structures by formation of Si–O–As bonds from a novel reaction between organic chlorosilanes and organic arsonic acids. Formation of arsonosiloxane polymers from hydrolysis of chlorosilylarsonates appears to be feasible. Methyl- and phenylchlorosilylarsonates were synthesized and hydrolyzed to the corresponding arsenical siloxane derivatives. Compounds found were identified by chemical analysis and infrared absorption characteristics.

The well-known utilities of silicones, particularly of methylsilicones, do not include action toward pest organisms. Organic arsenical siloxane derivatives could conceivably exhibit pesticidal properties which would add numerous possibilities of applications to those already existing. Therefore, the investigation of organic arsenical silanes and siloxane derivatives was undertaken in order to prepare compounds containing Si–O–As bonds. It was found that methyl- and phenylchlorosilanes react with methyl- and phenylarsonic acids in the presence of an inert solvent such as benzene or carbon tetrachloride, at the temperature of 80° at which these solvents are kept refluxing for about 24 hr. under agitation.

As is shown by the following equation, 2 moles of chlorosilane react with one mole arsonic acid to form a "bis" or neutral chlorosilylarsonate and 2 moles of hydrochloric acid

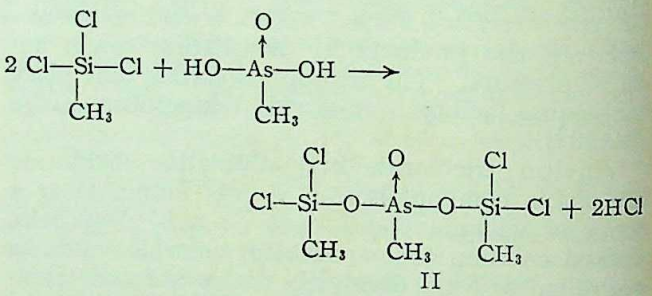


Thus, the reaction between dimethyldichlorosilane and methylarsonic acid resulted in bis-(dimethylchlorosilyl)-methylarsonate (I), shown by the equation



I

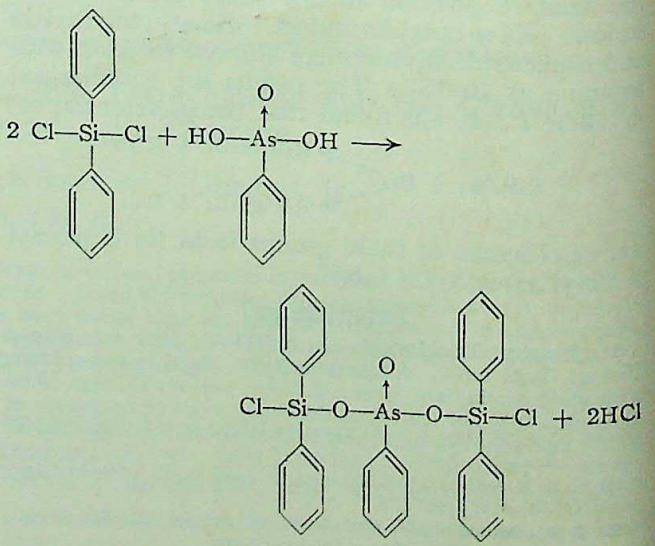
In similar manner, bis-(methyldichlorosilyl)-methylarsonate (II) was prepared from methyltrichlorosilane and methylarsonic acid



II

These reactions were carried out in 2:1 molar ratio of chlorosilane and methylarsonic acid. If a 1:1 molar ratio was employed, poor yields of the "bis" compounds were obtained, together with considerable amounts of unreacted starting materials.

Essentially, the same method was used to prepare the corresponding phenyl derivatives. Bis-(diphenylchlorosilyl)-phenylarsonate (III) was synthesized from diphenyldichlorosilane and phenyl arsonic acid



III

(1) Presented at the 129th Meeting of The American Chemical Society, Dallas, Texas.

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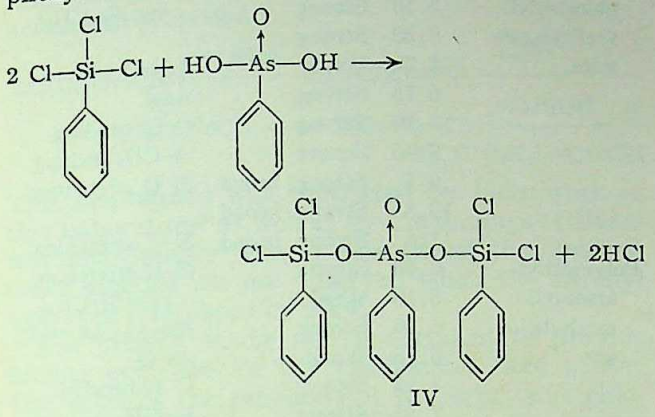
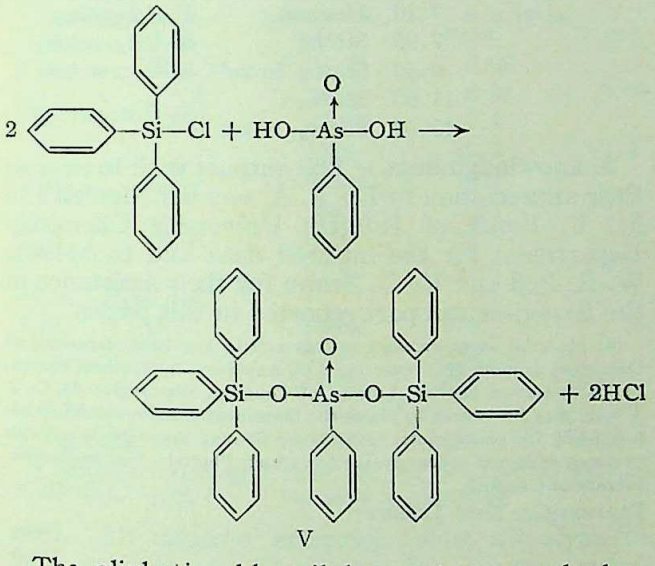
Similarly, bis-(phenyldichlorosilyl)-phenylarsonate (IV) was made, using phenyltrichlorosilane and phenylarsonic acid



IV

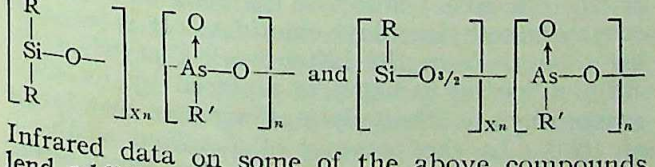
Bis-(triphenylsilyl)-phenylarsonate (V) was synthesized by treating triphenylchlorosilane with phenylarsonic acid, using pyridine as a hydrohalogen acceptor



V

The aliphatic chlorosilylarsonates were hydrolyzed either in water alone or in mixtures of their carbon tetrachloride solutions and water of a volume ratio of 1:3. The aromatic chlorosilylarsonates were hydrolyzed in mixtures of their chloro- or bromobenzene solutions and water of the same ratio. Upon removal of the solvents the recovered hydrolysis products ranged from transparent, rubbery materials to fine, white powders.

From the elementary analysis of the recovered products, it became apparent that some cleavage of the Si–O–As bond had taken place as could be expected from theoretical considerations. However, the resulting hydrolysis products still contained both arsenic and silicon, even after repeated washing with water, and appeared to be copolymers of the general formulas:



Infrared data on some of the above compounds lend additional evidence to the postulated structures.

Experimental

Methylarsonic Acid.—Methylarsonic acid was obtained as its disodium salt, according to Meyer's reaction from sodium arsenite and methyl chloride.[2] The free acid was isolated through the calcium salt by decomposition of the latter with sulfuric acid, followed by precipitation upon concentrating the filtrate (from $CaSO_4$), and recrystallization from ethanol.

Phenylarsonic Acid.—Phenylarsonic acid was used as the available "D.P.I.—Eastman Kodak—Benzenearsonic Acid" without further purification.

Methyl- and Phenylchlorosilanes.—The methyl- and phenylchlorosilanes were used as the available Linde Air Products or General Electric Co. preparations without further purification.

Bis-(dimethylchlorosilyl)-methylarsonate (I).—Seventy g. (0.5 mole) of methylarsonic acid was suspended in 400 ml. of dry benzene by stirring at room temperature. One hundred and twenty-nine g. of dichlorodimethylsilane was added slowly from a separatory funnel, so as to keep the ensuing exothermic increase in temperature to a minimum of 10–15°. After the initial reaction, indicated by a considerable evolution of HCl gas, had abated, the mixture was refluxed for 24 hr., under a drying tube containing "Drierite." Upon cooling to room temperature, the amount of unreacted methylarsonic acid, which is practically insoluble in benzene, was found to be 8%. It was subsequently removed by filtration.

After removal of the solvent under atmospheric and reduced pressure, 111 g. of I or 68% was obtained in form of a pale-yellow oil.

Anal. Calcd. for $C_5H_{15}O_3Cl_2Si_2As$: Si, 17.3; As, 23.1; Cl, 21.8; C, 17.8; H, 4.6. Found: Si, 17.4; As, 22.7; Cl, 21.9; C, 18.5; H, 5.4.

Bis-(methyldichlorosilyl)-methylarsonate (II).—Seventy g. (0.5 mole) of methylarsonic acid reacted with 150 g. (1.0 mole) of methyltrichlorosilane in the same manner as described before.

Removal of the solvent yielded II, a resinous, somewhat transparent solid. The yield was 154 g., corresponding to 84% of the theoretical. Since the purification of this material proved to be extremely difficult, the resulting product was hydrolyzed directly to the corresponding polymer VII.

Bis-(diphenylchlorosilyl)-phenylarsonate (III).—Twenty and two-tenths g. (0.1 mole) of phenylarsonic acid reacted in the same manner as described before with 50.6 g. (0.2 mole) of diphenyldichlorosilane resulting in formation of III as a white, amorphous solid. The yield was 51 g. or 80% of the theoretical.

Anal. Calcd. for $C_{30}H_{25}O_3Cl_2Si_2As$: Si, 8.8; As, 11.8; Cl, 11.2; C, 56.7; H, 4.0. Found: Si, 8.6; As, 11.8; Cl, 11.0; C, 57.0; H, 4.7.

Bis-(phenyldichlorosilyl)-phenylarsonate (IV).—Twenty and two-tenths g. (0.1 mole) of phenylarsonic acid reacted in the same manner as described before with 42.3 g. (0.2 mole) of phenyltrichlorosilane which resulted in formation of IV as a somewhat resinous, amorphous solid. The yield was 43 g. or 78.2% of the theoretical.

Here, again, purification of the resulting dichlorosilyl derivative presented some serious obstacles, and the product was hydrolyzed directly to the corresponding polymer.

Bis-(triphenylsilyl)-phenylarsonate (V).—Twenty and two-tenths g. (0.1 mole) of phenylarsonic acid was suspended in 400 ml. of dry benzene containing 79.1 g. of pyridine which latter is an excess over the theoretically required 15.8 g. (0.2 mole). To this mixture 59.0 g. (0.2 mole) of triphenylchlorosilane dissolved in 400 ml. of dry benzene was added gradually. The formation of a precipitate accompanied by an exothermic temperature increase of 7° was observed. The mixture was then heated to reflux (80–82°) which was maintained for 24 hr. After cooling to room temperature, the precipitate was filtered off and dried. It consisted almost entirely of pyridine monohydrochloride. The filtrate was subjected to solvent removal under atmospheric and reduced pressure upon which 66.5 g. or 92.6% was recovered as a white, waxy solid.

Anal. Calcd. for $C_{42}H_{35}O_3Si_2As$: Si, 7.8; As, 10.4; C, 70.3; H, 4.9. Found: Si, 7.0; As, 10.3; C, 69.6; H, 4.3.

(2) G. Meyer, *Ber.*, **16**, 1440 (1883); G. E. Miller and S. G. Seaton, U. S. Patent 2,442,373 (1948); *C. A.*, **42**, 6842 (1948); U. S. Patent 2,695,306 (1954).

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Polymethylarsonodimethylsiloxane (VI).—Ten g. of bis-(dimethylchlorosilyl)-methylarsonate was dissolved in 100 ml. of carbon tetrachloride and added gradually from a separatory funnel through a tube reaching into 100 ml. of CCl_4 agitated with 300 ml. of water, at about 40–50°, during 25–35 minutes. After cooling to room temperature and subsequent washing with water to remove hydrochloric acid found during hydrolysis, the CCl_4 (bottom) layer was drawn off, dried over anhydrous Na_2SO_4 and the solvent removed under atmospheric and reduced pressure. Three and six-tenths g. of VI, a translucent, rubbery material was obtained.

Anal. Calcd. for $C_{25}H_{75}O_{14}Si_{12}As$: Si, 33.3; As, 7.4; C, 29.7; H, 7.4. Found: Si, 33.6; As, 7.7; C, 29.8; H, 8.1.

Polymethylarsonomethylsiloxane (VII).—One hundred and nine g. of bis-(methyldichlorosilyl)-methylarsonate was leached with boiling water for about 1 hr., washed thoroughly with water of room temperature, filtered off and dried. Forty-five g. of VII, a fine white powder, was obtained.

Anal. Calcd. for $C_{13}H_{39}O_{20}Si_{12}As$: Si, 36.3; As, 8.1; C, 15.5; H, 3.9. Found: Si, 37.1; As, 7.5; C, 15.8; H, 4.6.

The above VI and VII thus appear to be copolymers of the previously given formula where X is about 12.

The aromatic chlorosilylarsonates were found to be soluble in bromobenzene which is a suitable solvent for this type of controlled hydrolysis.[3] Essentially, the same method of hydrolysis was performed as described before. So far only impure polymers have been obtained as the result of this hydrolysis. The infrared data were obtained by means of a Perkin–Elmer Double Beam Recording Infrared Spectrophotometer, Model 21. Data on infrared absorption maxima, characteristic for regular siloxane compounds, were available from the literature.[4] Unpublished data on infrared absorption maxima, characteristic for organoarsenic compounds, were available from known or novel organic arsenicals, such as methylarsonic acid, arsenomethane As-1,2-disulfide[5] and others. Compound I was examined as liquid film in capillary thickness, whereas compound VII had to be used as 2% solution in chloroform. Polydimethylsiloxane, General Electric Co.—SF-96 (300), was used as a standard reference.

(3) C. E. Welsh and N. G. Holdstock, U. S. Patent 2,661,348 (1953); *C. A.*, **48**, 3063 (1954).

(4) N. Wright and M. J. Hunter, THIS JOURNAL, **69**, 803 (1947).

(5) R. M. Kary, U. S. Patent 2,646,440 (1953).

INFRARED ABSORPTION CHARACTERISTICS[6]

Compound	Microns	Intensity	Assignment
Bis-(dimethylchlorosilyl) methylarsonate	3.40	Strong	C–H stretching (for Si–CH_3)
	5.10	Strong	
	5.50	Strong	
	6.20	Weak	As=O (As → O)
	6.75	Strong	As–C
	7.10	Strong	C–H bending
	7.95	Strong	Si–CH_3 rocking
	9.5	Strong, broad	Si–O stretching
	10.8	Strong, broad	
	11.6	Strong, broad	Si–C stretching
Polymethylarsonodimethylsiloxane	3.40	Strong	C–H stretching (for Si–CH_3)
	5.10	Weak	
	6.20	Strong	As=O (As → O)
	6.75	Weak	As–C
	7.15	Strong	C–H bending
	7.95	Strong	Si–CH_3 rocking
	9.50	Strong, broad	Si–O stretching
	11.65	Strong, broad	Si–C stretching
Polydimethylsiloxane	3.40	Strong	C–H stretching (for Si–CH_3)
	7.10	Medium	C–H bending
	7.95	Strong	Si–CH_3 rocking
	9.50	Strong, broad	Si–O stretching
	11.60	Medium	Si–C stretching
	12.50	Strong, broad	Si–C stretching

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(6) Material supplementary to this article has been deposited as Document number 5076 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting $1.25 for photoprints, or $1.25 for 35-mm. microfilm in advance by check or money order payable to: Chief, Photoduplication Service, Library of Congress.

PLAINFIELD, NEW JERSEY

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

The Kinetics of the Hydrolysis of Acetylenic Chlorides and Their Reactions with Primary and Secondary Aliphatic Amines[1]

BY G. F. HENNION AND KENNETH W. NELSON[2]

RECEIVED NOVEMBER 30, 1956

Acetylenic chlorides of the type RR'C(Cl)—C≡CH undergo very slow solvolysis in 80% ethanol at 25°. The rate is accelerated by addition of sodium hydroxide, and the reactions then commonly follow second-order kinetics. Primary and secondary aliphatic amines are smoothly alkylated by these halides. The mechanisms of these reactions are discussed.

Discussion

It was reported in a previous paper[3] in this series that 3-chloro-3-methyl-1-butyne undergoes extremely slow solvolysis in 80% ethanol at 25° ($k_1 = 7.4 \times 10^{-4}$ hr.$^{-1}$). This was attributed to lack of steric strain, despite the tertiary structure, and the inductive (electron-withdrawing) effect of the ethynyl group. Burawoy and Spinner[4] have verified these findings (k_1 said to be 8.48×10^{-4} hr.$^{-1}$) in a recent study of the behavior of alkylethynyldimethylcarbinyl chlorides. It is interesting to note from the latter work that when the ethynyl hydrogen atom is replaced by an alkyl group, the rate of solvolysis is increased by a factor of 1000. In the presence of dissolved alkali, 3-chloro-3-methyl-1-butyne reacts by second-order

(1) Paper LXIV on substituted acetylenes; previous paper, *J. Org. Chem.*, **21**, 1142 (1956).

(2) Miles Laboratories Fellow, 1954–1955; Reilly Fellow, 1955–1956. Abstracted from the Ph.D. Dissertation of K. W. N., 1956.

(3) G. F. Hennion and D. E. Maloney, THIS JOURNAL, **73**, 4735 (1951).

(4) A. Burawoy and E. Spinner, *J. Chem. Soc.*, 3752 (1954).

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kinetics.[3,4] The product of this reaction is the unexpected 3-ethoxy-3-methyl-1-butyne.[3] To account for this product as well as the second-order rate observed for the reaction, the following mechanism was proposed.[3]

$$R_2C(Cl)C{\equiv}CH \xrightarrow{+OH^\ominus} R_2C(Cl)C{\equiv}C^\ominus \xrightarrow{-Cl^\ominus} (R_2\overset{\oplus}{C}C{\equiv}C^\ominus \longleftrightarrow R_2C{=}C{=}C:) \xrightarrow{C_2H_5OH} R_2C(OC_2H_5){-}C{\equiv}CH$$

This mechanism was supported by later work in this Laboratory[5] as well as by the findings of Burawoy and Spinner[4] who demonstrated that second-order kinetics are *not* observed when the ethynyl hydrogen is replaced by alkyl.

The present study was undertaken to provide further evidence for the mechanism cited above. The rates of the reactions of the acetylenic chlorides listed in Tables I and II have now been measured. All undergo extremely slow solvolysis in 80% ethanol at 25° (Table I). In two cases, namely, 1-ethynylcyclohexyl chloride and 3-chloro-1-hexyne, the rate was too slow to measure. Reinvestigation of the solvolysis of 3-chloro-3-methyl-1-butyne gave a rate constant of 9.0×10^{-4} hr.$^{-1}$ in agreement with the previously published values.[3,4] This rate is 1/61 of that for *t*-amyl chloride, the saturated analog, under the same conditions.[6] Likewise, the ratio of the rate of solvolysis of 3-chloro-3-methyl-1-pentyne to that of 3-chloro-3-methylpentane is 1/69, and the ratio of the rate for 3-chloro-3-ethyl-1-pentyne to that of 3-chloro-3-ethylpentane is 1/62. The unique stabilizing influence of the ethynyl group is thus clearly demonstrated. When sodium hydroxide was added, other conditions remaining the same, the reactions were faster and usually followed clean second-order kinetics (Table II). In the case of 3-chloro-3-methyl-1-butyne, the rate constant was 1.29 l./mole hr. in excellent agreement with the earlier value[3] (1.2–1.4 l./mole hr.) but in only fair agreement with the Burawoy and Spinner measurement[4] (2.56 l./mole hr.). In two cases, namely, 3-chloro-1-hexyne and 3-chloro-3-phenyl-1-propyne, both secondary halides, clean second-order kinetics could not be obtained.

TABLE I

THE SOLVOLYSIS OF ETHYNYLCARBINYL CHLORIDES, RR′C(Cl)C≡CH, IN 80% ETHANOL AT 25°

RR′C(Cl)C≡CH R	R′	Initial concn., mole/l.	$k_1 \times 10^4$ hr.$^{-1}$ Exptl.	Mean
CH_3	CH_3	0.08336	9.02	
		.1430	8.98	9.00
CH_3	C_2H_5	.07764	12.4	
		.1049	12.3	12.4
C_2H_5	C_2H_5	.06834	16.1	
		.08623	16.1	16.1
CH_3	i-C_4H_9	.07002	35.5	
		.07002	34.8	35.2
$-CH_2(CH_2)_3CH_2-$[a]		[c]		
C_6H_5	H	.09684	1670	
		.1267	1680	
		.09752	1690	1680
n-C_3H_7	H	[c]		
t-Amyl chloride		.06213	530	530[b]

[a] 1-Ethynylcyclohexyl chloride. [b] Literature value, 550 $\times 10^{-4}$ hr.$^{-1}$ (ref. 6). [c] Too slow to measure.

TABLE II

THE REACTIONS OF ETHYNYLCARBINYL CHLORIDES WITH SODIUM HYDROXIDE IN 80% ETHANOL AT 25°

RR′C(Cl)C≡CH R	R′	c_0 RCl, mole/l.	c_0 NaOH, mole/l.	k_2, l./mole. hr. Exptl.	Mean
CH_3	CH_3	0.1800	0.08968	1.26	
		.09000	.08968	1.30	
		.09000	.08968	1.29	
		.09000	.1789	1.25	
		.09000	.1804	1.26	1.27
CH_3	C_2H_5	.1433	.07104	1.13	
		.1433	.07180	1.13	
		.07168	.07180	1.16	
		.07168	.07164	1.17	
		.07168	.1440	1.12	1.14
C_2H_5	C_2H_5	.1428	.07116	1.08	
		.07141	.07141	1.04	
		.07141	.07141	1.07	1.06
$-CH_2(CH_2)_3CH_2-$		.1875	.09143	0.240	
		.09375	.09375	.234	
		.09375	.1789	.218	
		.09375	.1793	.218	0.227
CH_3	i-C_4H_9	.08229	.08241	2.67	
		.08229	.08220	2.64	2.66
C_6H_5	H	No clean second-order reaction			
n-C_3H_7	H	No clean second-order reaction			

While these data are in complete agreement with the mechanism cited above, additional evidence for this mechanism was sought and was found in the reactions of the acetylenic chlorides with primary and with secondary amines. It is well known that tertiary aliphatic halides are not suitable for the alkylation of amines since such halides are too sensitive to HX elimination. It has been stated[7] without qualification that "amines of tertiary alkyl groups are not obtainable from the halide." The mechanism pictured above suggests *a priori* that amines which are strong bases and good nucleophilic reagents should be alkylated by acetylenic halides. This has now been found to be true and the simple reaction

$$RR'C(Cl){-}C{\equiv}CH + 2R_2NH \longrightarrow RR'C(NR_2){-}C{\equiv}CH + R_2NH{\cdot}HCl$$

gives good yields of products in a variety of applications (Table III).

The reaction of 3-chloro-3-ethyl-1-pentyne with aqueous ammonia was tried in an attempt to prepare 3-amino-3-ethyl-1-pentyne. The reaction was carried out at 100° in an autoclave. Approximately 30% of the starting material suffered HCl elimination to produce 3-ethyl-3-pentene-1-yne, the remainder being hydrolyzed to the corresponding carbinol, 3-ethyl-1-pentyne-3-ol. It appears therefore that aqueous ammonia is not sufficiently basic, even though less steric hindrance is involved in comparison with the amines used, to initiate the mechanism necessary for amine formation.

(5) G. F. Hennion and E. G. Teach, THIS JOURNAL, 75, 1653 (1953).

(6) H. C. Brown and R. S. Fletcher, *ibid.*, 71, 1845 (1949).

(7) F. C. Whitmore, "Organic Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1937, p. 76.

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Further work is in progress, particularly to determine the limitations of alkylation reactions with acetylenic halides.

Experimental

Acetylenic Carbinols.—Generous samples of 3-methyl-1-butyne-3-ol, 3-methyl-1-pentyne-3-ol, 3-ethyl-1-pentyne-3-ol, 3,5-dimethyl-1-hexyne-3-ol and 1-ethynyl-cyclohexanol were obtained from Air Reduction Chemical Co. and from Reilly Tar and Chemical Co. 1-Hexyne-3-ol was prepared by the reaction of freshly distilled butyraldehyde and sodium acetylide in anhydrous liquid ammonia as previously described.[8] Likewise, 3-phenyl-1-propyne-3-ol was prepared by the reaction of freshly distilled benzaldehyde with sodium acetylide in anhydrous liquid ammonia.

All fractional distillations, except as noted, were carried out with a 40 × 1.2 cm. column fitted with a total reflux, partial take-off distilling head, hereafter referred to as column A. All boiling points and melting points are uncorrected.

Preparation of 3-Chloro-3-methyl-1-butyne.—This compound was prepared by the reaction of 1300 ml. (15 moles) of cold concentrated hydrochloric acid (0°) containing three moles of anhydrous calcium chloride with three moles of 3-methyl-1-butyne-3-ol as described earlier.[9] The crude chloride was distilled from potassium carbonate through column A; yield, 138 g. (45%), b.p. 33–36° (175 mm.). Triple distilled material, b.p. 75.5–75.6°, $n^{25}D$ 1.4145, was used for kinetic studies.

Preparation of 3-Chloro-3-methyl-1-pentyne and 3-Chloro-3-ethyl-1-pentyne.—These compounds were prepared by the reaction of 3-methyl-1-pentyne-3-ol and 3-ethyl-1-pentyne-3-ol with five times the theoretical amount of cold concentrated hydrochloric acid as described previously.[5] Crude 3-chloro-3-methyl-1-pentyne was obtained in 53% yield, b.p. 51–54° (120 mm.). Triple distilled material, b.p. 51.9–52.2° (115 mm.), $n^{25}D$ 1.4307, was used for kinetic studies. Crude 3-chloro-3-ethyl-1-pentyne was obtained in 62% yield, b.p. 70–75° (100 mm.). Triple distilled material, b.p. 71.9–72.2° (101 mm.), $n^{25}D$ 1.4396, was used for kinetic studies.

Preparation of 3-Chloro-1-hexyne.—This compound was prepared by the reaction of 1 mole (100 g.) of 1-hexyne-3-ol with 1.1 moles (130 g.) of thionyl chloride, using 5 g. of pyridine as a catalyst.[8] Fifty-one grams (43% yield) of crude product, b.p. 61–65° (100 mm.), was obtained in this manner. Triple distilled material, b.p. 63.1–63.4° (97 mm.), $n^{25}D$ 1.4366, was used for the kinetic work.

Preparation of 3-Chloro-3-phenyl-1-propyne.—This compound was prepared by the reaction of 1.14 moles (150 g.) of 3-phenyl-1-propyne-3-ol with 1.25 moles (150 g.) of thionyl chloride using five grams of pyridine as a catalyst; yield 70 g. (41%), b.p. 100–104° (18 mm.). Triple distilled material, b.p. 45.8–46.0° (1.0 mm.), $n^{25}D$ 1.5478, was used for kinetic studies.

Preparation of 1-Ethynylcyclohexyl Chloride.—Approximately 0.2 mole of freshly prepared cuprous chloride (CuCl) was dissolved in 430 ml. (5 moles) of cold concentrated hydrochloric acid contained in a 2-l. separatory funnel. One hundred and twenty-four grams (1 mole) of freshly distilled 1-ethynylcyclohexanol was then added. After 1 hr. of intermittent shaking, the lower layer was separated and discarded. The upper layer was washed twice with 200-ml. portions of concentrated hydrochloric acid to remove most of the adhering cuprous chloride and then shaken with anhydrous potassium carbonate. After this preliminary neutralization, the reaction mixture was dried overnight over a fresh layer of anhydrous potassium carbonate. Distillation through column A gave 100 g. (70% yield) of crude 1-ethynylcyclohexyl chloride, b.p. 56–58° (10 mm.). Triple distilled material, b.p. 55.0° (13 mm.), $n^{25}D$ 1.4795, was used for kinetic studies.

Preparation of 3-Chloro-3,5-dimethyl-1-hexyne.—One hundred and twenty-six grams (1 mole) of 3,5-dimethyl-1-hexyne-3-ol and 5 ml. of concentrated hydrochloric acid were placed in a 500-ml. three-neck round-bottom flask fitted with a stirrer, gas inlet tube and thermometer. Dry hydrogen chloride gas was passed into the carbinol at a rate of approximately 4 to 5 bubbles per second. The reaction mixture was periodically cooled with running water to maintain the temperature at 20–25°. After 52 g. of hydrogen chloride had been absorbed, the addition of the gas was terminated. The reaction mixture was placed in a separatory funnel and the small water layer was removed. After two washings with 200 ml. of water, the organic layer was dried overnight with anhydrous potassium carbonate. Distillation through column A gave 55 g. (38%) of chloride, b.p. 56–63° (39 mm.). The first fractions from this distillation were found to contain a considerable amount of an unidentified impurity containing a conjugated double bond system as indicated by the infrared spectrum. Five distillations were required to give a product which was suitable for kinetic studies; b.p. 56.7–57.0° (39 mm.), $n^{25}D$ 1.4370.

Preparation of Solutions for Kinetic Studies.—The ethanol (80%) was prepared by mixing four volumes of absolute ethanol and one volume of freshly boiled distilled water. The densities of two batches prepared in this manner were found to be 0.8495 and 0.8498 at 25.0°. A carbonate-free solution of sodium hydroxide in 80% ethanol was prepared by dissolving approximately 17 g. of crushed sodium hydroxide pellets in 100 ml. of 80% ethanol. Filtration of this solution through a sintered glass funnel and dilution with one liter of 80% ethanol gave an approximately 0.4*N* sodium hydroxide solution. Standardization of the above solution as well as that of aqueous hydrochloric acid and aqueous sodium hydroxide were performed with potassium acid phthalate and sodium carbonate using as an indicator a mixture consisting of two parts of 0.1% methyl red solution and three parts of 0.1% brom cresol green solution, both in absolute ethanol.[10]

General Kinetic Procedures, First-order Rate Constants.—A sample of halide (*ca.* 1–2 g.) was weighed in a thin-walled glass ampoule and sealed. The ampoule was crushed under solvent previously adjusted to 25.0°. The solution was rapidly transferred to a 100-ml. volumetric flask, diluted to the mark with more solvent, mixed and returned to the constant temperature bath. Periodically, approximately every 24 hr., 10-ml. aliquots were removed by a pipet, quenched in 50 ml. of absolute methanol and titrated immediately with standard sodium hydroxide using the forementioned indicator. A total of six to eight aliquots were taken from each reaction, following the first 30–60% reaction. The first-order rate constants were calculated from the integrated rate expression.

Second-order Rate Constants.—A sample of halide (*ca.* 4–5 g.) was weighed in a 50-ml. volumetric flask. The flask was then filled to the mark with 80% ethanol, the temperature of which was previously adjusted to 25°; 5- or 10-ml. aliquots of this solution were placed in 100-ml. flasks. A predetermined amount of standard sodium hydroxide in 80% ethanol (delivered from a buret) was added to the 100-ml. flasks, and the flasks were filled to the mark with 80% ethanol, shaken and returned to the constant temperature bath. Periodically, approximately every hour, 10-ml. aliquots were removed and quenched in 5 or 10 ml. of standard acid dissolved in absolute methanol. Each aliquot was then back-titrated with standard base. A total of six to eight aliquots were taken from each reaction covering the first 30–70% reaction. The second-order rate constants were calculated from the appropriate integrated rate expressions.

Preparation of 3-Dimethylamino-3-methyl-1-butyne Hydrochloride.—Ten grams of 3-chloro-3-methyl-1-butyne and 50 ml. of 40% aqueous dimethylamine were placed in a stout bottle and shaken mechanically for a period of 15 hr. The orange colored solid was collected by filtration, dissolved in 100 ml. of ether and dried over potassium hydroxide pellets. The hydrochloride of this amine was precipitated by addition of excess hydrogen chloride dissolved in absolute ether. After collection by suction filtration, this material was recrystallized from an ethyl acetate–ethanol mixture; yield 10 g. (70%) of material melting at 241–242.5° dec. A small sample of the free base was isolated and purified by sublimation, m.p. 99–102°.

Preparation of 3-Pyrrolidino-3-methyl-1-butyne.—Twenty-five grams of 3-chloro-3-methyl-1-butyne, 60 ml. of pyrrolidine and 20 ml. of water were placed in a 125-ml. erlenmeyer flask and set aside for 24 hr. The product was collected by filtration and washed with water. Recrys-

(8) G. F. Hennion and J. J. Sheehan, THIS JOURNAL, **71**, 1964 (1949).

(9) G. F. Hennion, *et al.*, *ibid.*, **72**, 3542 (1950).

(10) H. C. Brown, *ibid.*, **76**, 4515 (1954).

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TABLE III

ACETYLENIC AMINES FROM ACETYLENIC CHLORIDES

Cmpd.	R^1	R^2	R^3	R^4	B.p., °C.	B.p., Mm.	M.p., °C.	$n^{25}D$	d^{25}	Yield, %
I[a]	CH_3	CH_3	CH_3	CH_3			99–102			70
II	CH_3	CH_3	$(CH_2)_4$				76–78			62
III	$(CH_2)_5$		$(CH_2)_4$				65–66.5			73
IV	$(CH_2)_5$		$(CH_2)_5$				94–95.5			60
V	$(CH_2)_5$		CH_3	CH_3			57–58.5			68
VI[b]	CH_3	C_2H_5	C_2H_5	H	74–79	120		1.4308		52
VII	C_3H_7	H	$(CH_2)_4$		70–72	11		1.4597	0.8693	63
VIII	C_3H_7	H	C_4H_9	H	71–72	11		1.4365	0.8043	56

[a] *Cf.* G. F. Hennion and J. M. Campbell, *J. Org. Chem.*, 21, 792 (1956). [b] *Cf.* G. F. Hennion and E. G. Teach, THIS JOURNAL, 75, 4298 (1953).

TABLE IV

ACETYLENIC AMINE DERIVATIVES AND ANALYTICAL DATA

Cmpd.	Mol. formula	Nitrogen, % Calcd.	Nitrogen, % Obsd.	Hydrochloride M.p., °C.	Hydrochloride Nitrogen, % Calcd.	Hydrochloride Nitrogen, % Obsd.	Methiodide M.p., °C.	Methiodide Nitrogen, % Calcd.	Methiodide Nitrogen, % Obsd.
I	$C_7H_{13}N$[a]			241–242.5	9.49	9.69			
II	$C_9H_{15}N$[a]			232–233	8.07	8.30	181–182	5.02	5.12
III	$C_{12}H_{19}N$	7.90	8.02	235–236	6.55	6.78	155–157	4.39	4.30
IV	$C_{13}H_{21}N$	7.32	7.50	239-240	6.15	5.87	181–182	4.20	4.29
V	$C_{10}H_{17}N$[a]			222–223	7.46[b]	7.46	175	4.78	4.50
VII	$C_{10}H_{17}N$	9.26	9.37	176–177	7.46	7.59	131–133	4.78	4.64
VIII	$C_{10}H_{19}N$	9.14	9.35	166	7.38	7.21			

[a] Too volatile for analysis. [b] Calcd. for $C_{10}H_{18}NCl$: C, 63.98; H, 9.67. Found: C, 63.88; H, 9.73.

tallization from a water–ethanol mixture gave 21 g. (62%) of material melting at 76–78°.

Preparation of 1-Pyrrolidino-1-ethynylcyclohexane.—Ten grams of 1-ethynylcyclohexyl chloride, 20 ml. of pyrrolidine and 10 ml. of water were placed in a 50 ml. erlenmeyer flask and set aside for 24 hr. The solid material was collected by filtration, washed with water and recrystallized from an ethanol–water mixture; yield 8 g. (73%) of material melting at 65–66.5°.

Preparation of 1-Piperidino-1-ethynylcyclohexane.—Twenty grams of 1-ethynylcyclohexyl chloride, 40 ml. of piperidine and 20 ml. of water were placed in a 125-ml. erlenmeyer flask. After 48 hr. had elapsed, the solid material was collected by filtration, washed with water and recrystallized from aqueous acetone; yield 16 g. (60%) of material melting at 94.5–95.5°.

Preparation of 1-Dimethylamino-1-ethynylcyclohexane.—Twenty grams of 1-ethynylcyclohexyl chloride, 60 ml. of 40% aqueous dimethylamine and 55 ml. of acetone were placed in a 125-ml. erlenmeyer flask. After 24 hr., 60 ml. of volatile solvent was removed by distillation. Solidification of the desired product resulted when the two-phase residue was cooled to approximately −10°. Filtration of the solid material and subsequent recrystallization from aqueous alcohol gave 14.5 g. (68%) of material melting at 57–58.5°.

Preparation of 3-Ethylamino-3-methyl-1-pentyne.—One hundred and fifty ml. of 70% aqueous ethylamine and 40 g. of 3-chloro-3-methyl-1-pentyne were placed in a stout bottle. After 12 hr., the reaction mixture appeared in two layers. The mixture was then shaken mechanically for an additional period of 30 hr. The upper layer was separated and the bottom layer was diluted with an equal volume of water. The upper layer was again separated and added to the first. After adding 100 ml. of ether and washing twice with water, the solution was dried over potassium hydroxide pellets. Distillation gave a 25.5-g. fraction, b.p. 70–79° (120 mm.). Redistillation gave 22 g. (52%), b.p. 74–79° (120 mm.), $n^{25}D$ 1.4308.

Preparation of 3-Pyrrolidino-1-hexyne.—Thirty grams of 3-chloro-1-hexyne, 90 ml. of pyrrolidine and 30 ml. of water were refluxed for 18 hr. (inside temperature, 95°). The upper layer was separated and the bottom layer was diluted with an equal volume of water. The upper layer was again separated and combined with the first. An equal volume of ether was added and the ether solution was washed twice with water and dried overnight over potassium hydroxide pellets. Distillation gave 25 g. (63%) of material boiling at 71–72° (12 mm.), $n^{25}D$ 1.4597, d^{25} 0.8693.

Preparation of 3-*n*-Butylamino-1-hexyne.—Thirty-four grams of 3-chloro-1-hexyne, 90 ml. of *n*-butylamine and 30 ml. of water were placed in a 300-ml. round-bottom flask and heated at about 65° for 5 days.

The upper layer was separated and the bottom layer was diluted with an equal amount of water. The upper layer was again separated and combined with the first. After an equal volume of ether had been added, the solution was washed with water and dried over potassium hydroxide pellets. Distillation gave a 29.5-g. fraction, b.p. 68–72.5° (11 mm.). Redistillation gave a fraction weighing 25 g. (56%) of material, b.p. 71–72° (11 mm.), $n^{25}D$ 1.4365, d^{25} 0.8043.

As derivatives, the hydrochlorides and methiodides of most of the amines were prepared. The hydrochlorides were prepared by treating 1 g. of the amine dissolved in 25 ml. of absolute ether with excess ethereal hydrogen chloride. Purification was achieved by recrystallization from an ethyl acetate–ethanol mixture. The methiodides were prepared by treating 1 g. of the amine dissolved in 15 ml. of absolute ethyl acetate with twice the theoretical amount of methyl iodide. They were crystallized from an ethyl acetate–ethanol mixture.

The physical properties and analyses of the amines and their derivatives are shown in Tables III and IV.

Acknowledgments.—The authors are indebted to Dr. F. E. Cislak, Reilly Tar and Chemical Corp., Indianapolis, Ind., and to Dr. C. O. Herman, Air Reduction Chemical Co., New York, for generous supplies of acetylenic carbinols. Thanks are due to G. M. Maciak and Miss Gloria Beckman of the Lilly Research Laboratories, Indianapolis, for the analyses reported in Table IV.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

The Preparation of *t*-Acetylenic Carbinol Esters and Related Compounds[1]

BY G. F. HENNION AND S. OLIVIA BARRETT[2]

RECEIVED NOVEMBER 30, 1956

Acetylenic carbinols, notably the tertiary isomers, may be esterified with certain aromatic carboxylic acids in pyridine solution in the presence of *p*-toluenesulfonyl chloride (Brewster's method, ref. 3). *p*-Nitrobenzoic acid in particular gives excellent results, generally affording nicely crystalline derivatives of characteristic melting points in good yields. The esters may be semi-hydrogenated to the corresponding vinyl carbinol esters with 5% Pd–$BaCO_3$ in ethyl acetate.

Discussion

In connection with other problems under investigation in this Laboratory, need arose for a variety of acetylenic carbinol esters and their semi- and fully hydrogenated analogs, *i.e.*, the corresponding vinyl- and ethylcarbinyl compounds. Solid esters amenable to careful purification (for studies in kinetics) were particularly desired. Brewster's method[3] has been found to be exceptionally well suited for this purpose.

Excellent yields of 3,5-dinitrobenzoates were obtained when *p*-toluenesulfonyl chloride was mixed with pyridine solutions of the acid and a variety of tertiary alcohols at ice-bath temperature (Table III). Surprisingly, the attempted syntheses of the corresponding *p*-nitrobenzoates gave almost quantitative yields of the crystalline anhydride and no esters. The relative insolubility of this anhydride in cold pyridine in contrast to the dinitro anhydride seemed a reasonable explanation, since Brewster had suggested that this synthesis is actually a pyridine–acid anhydride esterification, the anhydride being formed *in situ*. Accordingly, the Brewster procedure when carried out at steam-bath temperature (thus maintaining homogeneity throughout the reaction time) proved satisfactory for the preparation of a large variety of *p*-nitrobenzoates and several monobromobenzoates (Tables I and IV). Anisic acid, however, at steam and ice-bath temperatures gave a quantitative yield of the anhydride, although this anhydride is soluble in both hot and cold pyridine. Apparently homogeneity is not the controlling factor.

Chemical stability of the "intermediate anhydride" probably determines the course of the reaction. The question arises, however, as to whether the reactive intermediate is a symmetrical anhydride as proposed by Brewster[3] or a mixed anhydride. Pyridine-catalyzed esterifications of 3-methyl-1-butyn-3-ol with anisic, *p*-chlorobenzoic and *p*-nitrobenzoic anhydrides at steam-bath temperature were unsatisfactory. The ester was isolated only in the case of the *p*-nitrobenzoate; and the yield, less than 10% in twice the normal reaction time, was not comparable to the 94% yield obtained in the presence of *p*-toluenesulfonyl chloride.

Furthermore, the trend of reactivity for the Brewster procedure is related to the acidic dissociation constants of the reacting acids—the stronger the acid the more facile the esterification. Reactions were on a 0.01-molar scale and the results are summarized in Table V.

TABLE I

ACETYLENIC CARBINOL *p*-NITROBENZOATES, $RR'C(C{\equiv}CH)OCOC_6H_4NO_2$

Cmpd.	R	R′	Formula	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	CH_3	CH_3	$C_{12}H_{11}NO_4$	94	126–127	61.79	61.42	4.75	4.81
II	CH_3	C_2H_5	$C_{13}H_{13}NO_4$	82	72[a]	63.16	63.00	5.29	5.47
III	H	*n*-C_3H_7	$C_{13}H_{13}NO_4$	63	53–54	63.16	63.31	5.29	5.63
IV	C_2H_5	C_2H_5	$C_{14}H_{15}NO_4$	91	77	64.36	64.60	5.79	5.91
V	CH_3	*n*-C_3H_7	$C_{14}H_{15}NO_4$	87	72–73	64.36	64.47	5.79	5.71
VI	CH_3	*i*-C_3H_7	$C_{14}H_{15}NO_4$	80	88–89	64.36	65.00	5.79	5.96
VII	CH_3	C_2H_5[b]	$C_{14}H_{15}NO_4$	96	72	64.36	64.18	5.79	5.96
VIII	$CH_2(CH_2)_3CH_2$[c]		$C_{15}H_{15}NO_4$	95	66	65.90	66.04	5.53	5.77
IX	C_2H_5	*n*-C_3H_7	$C_{15}H_{17}NO_4$	93	62	65.43	65.73	6.23	6.32
X	CH_3	*i*-C_4H_9	$C_{15}H_{17}NO_4$	88	54–55	65.43	65.76	6.23	6.42
XI	H	C_6H_5	$C_{16}H_{11}NO_4$	93	73	68.32	68.58	3.94	4.19
XII	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{19}NO_4$	93	49	66.41	66.51	6.62	6.37
XIII	C_2H_5	*n*-C_4H_9	$C_{16}H_{19}NO_4$	90	52–53	66.41	66.31	6.62	6.73
XIV	CH_3	*i*-C_5H_{11}	$C_{16}H_{19}NO_4$	87	72–73	66.41	66.51	6.62	6.75
XV	CH_3	C_6H_5	$C_{17}H_{13}NO_4$	60	104–105	69.15	69.43	4.44	4.61
XVI	CH_3	C_6H_{13}	$C_{17}H_{21}NO_4$	89	72–73	67.32	67.33	6.98	6.80
XVII	CH_3	C_7H_{15}	$C_{18}H_{23}NO_4$	91	84	68.11	68.02	7.31	7.54
XVIII	*t*-$C_4H_9(C_5H_9)$[d]		$C_{19}H_{23}NO_4$	94	107–109	69.28	69.23	7.04	7.17

[a] Lit. m.p. 68–69° (J. R. Hickman and J. Kenyon, *J. Chem. Soc.*, 2051 (1955)). [b] 4-Methyl-2-hexyn-4-yl *p*-nitrobenzoate, $CH_3(C_2H_5)C(C{\equiv}C{-}CH_3)OCOC_6H_4NO_2$. [c] 1-Ethynylcyclohexyl *p*-nitrobenzoate; lit. m.p. 64–64.5° (J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 61 (1938)). [d] 4-*t*-Butyl-1-ethynylcyclohexyl *p*-nitrobenzoate.

(1) Paper LXV on substituted acetylenes; previous paper, THIS JOURNAL, 79, 2142 (1957).

(2) Abstracted from the Ph.D. Dissertation of Sr. M. Olivia Barrett, R.S.M.

(3) J. H. Brewster and C. J. Ciotti, Jr., THIS JOURNAL, 77, 6214 1955).

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TABLE II

VINYLCARBINOL *p*-NITROBENZOATES, $RR'C(CH{=}CH_2)OCOC_6H_4NO_2$

Cmpd.	R	R′	Formula	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
XIX	CH_3	CH_3	$C_{12}H_{13}NO_4$	88	106–108	61.27	61.30	5.57	5.43
XX	CH_3	C_2H_5	$C_{13}H_{15}NO_4$	90	93–94	62.64	62.73	6.07	6.08
XXI	$CH_2(CH_2)_3CH_2$[a]		$C_{15}H_{17}NO_4$	85	102–103[a]	65.44	65.33	6.23	6.46
XXII	CH_3	C_6H_5	$C_{17}H_{15}NO_4$	98	87	68.68	68.52	5.09	5.13

[a] 1-Vinylcyclohexyl *p*-nitrobenzoate; lit. m.p. 101–102° (J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 61 (1938)).

TABLE III

ACETYLENIC CARBINOL 3,5-DINITROBENZOATES, $RR'C(C{\equiv}CH)OCOC_6H_3(NO_2)_2$

Cmpd.	R	R′	Formula	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
XXIII	CH_3	CH_3	$C_{12}H_{10}N_2O_6$	87	112	51.80	51.83	3.62	3.68
XXIV	CH_3	C_2H_5	$C_{13}H_{12}N_2O_6$	86	72–73	53.42	53.67	4.14	4.28
XXV	C_2H_5	C_2H_5	$C_{14}H_{14}N_2O_6$	78	72–73	54.90	54.93	4.61	4.61
XXVI	CH_3	*n*-C_3H_7	$C_{14}H_{14}N_2O_6$	47	64–66	54.90	54.63	4.61	4.69
XXVII	CH_3	*i*-C_3H_7	$C_{14}H_{14}N_2O_6$	72	62–63	54.90	54.69	4.61	4.76
XXVIII	$CH_2(CH_2)_3CH_2$[a]		$C_{15}H_{14}N_2O_6$	98	109–110[a]	56.60	56.28	4.34	4.64
XXIX	CH_3	*i*-C_5H_{11}	$C_{16}H_{18}N_2O_6$	65	72–73	57.47	57.53	5.42	5.56
XXX	CH_3	C_6H_5	$C_{17}H_{12}N_2O_6$	87	112	59.99	60.03	3.55	3.86
XXXI	CH_3	*n*-C_6H_{13}	$C_{17}H_{20}N_2O_6$	85	59	58.61	58.66	5.79	5.84
XXXII	CH_3	*n*-C_7H_{15}	$C_{18}H_{22}N_2O_6$	92	55–56	59.66	60.05	6.12	6.39
XXXIII	4-*t*-$C_4H_9(C_5H_9)$[b]		$C_{19}H_{22}N_2O_6$	74	154–155	60.95	60.76	5.92	6.04

[a] 1-Ethynylcyclohexyl 3,5-dinitrobenzoate; lit. m.p. 104.5–106° (J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 61 (1938)). [b] 4-*t*-Butyl-1-ethynylcyclohexyl 3,5-dinitrobenzoate.

TABLE IV

ACETYLENIC CARBINOL MONOBROMOBENZOATES, $RR'C(C{\equiv}CH)OCOC_6H_4Br$

Cmpd.	R	R′	Formula	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
XXXIV	CH_3	CH_3	$C_{12}H_{11}BrO_2$[a]	89	63–64	53.95	53.93	4.15	4.38
XXXV	CH_3	C_2H_5	$C_{13}H_{13}BrO_2$[a]	74	65	55.53	55.48	4.66	4.95
XXXVI	C_2H_5	C_2H_5	$C_{14}H_{15}BrO_2$[a]	71	41–42	56.97	56.54	5.12	5.43
XXXVII	$CH_2(CH_2)_3CH_2$[b]		$C_{15}H_{15}BrO_2$[a]	80	86–87	58.64	58.58	4.92	5.30
XXXVIII	CH_3	C_6H_5	$C_{17}H_{13}BrO_2$[a]	75	85	62.02	62.13	3.98	3.93
XXXIX	*t*-C_4H_9-(C_5H_9)[c]		$C_{19}H_{21}BrO_2$[a]	74	103	62.81	62.83	6.38	6.36
XL	CH_3	CH_3	$C_{12}H_{11}BrO_2$[d]	67	46–47	53.95	53.97	4.15	4.31
XLI	CH_3	C_6H_5	$C_{17}H_{13}BrO_2$[d]	32	80–81	62.02	63.02	3.98	4.70

[a] *m*-Bromobenzoate. [b] 1-Ethynylcyclohexyl *m*-bromobenzoate. [c] 4-*t*-Butyl-1-ethynylcyclohexyl *m*-bromobenzoate. [d] *p*-Bromobenzoate.

TABLE V

ESTERIFICATION OF 3-METHYL-1-BUTYN-3-OL: INFLUENCE OF K_a ON REACTION

Substituted benzoic acid	K_a	Product formed: Ice-bath	Product formed: Steam-bath
3,5-Dinitro	1.6×10^{-3}	Ester	Ester[a]
2,4-Dichloro	$>1.3 \times 10^{-3}$	Ester	Ester
2-Chloro	1.3×10^{-3}	Oil[b]	Oil[b]
4-Nitro	4.0×10^{-4}	Ester + anhyd.	Ester
3-Bromo	1.4×10^{-4}	Anhydride	Ester
4-Chloro	9.3×10^{-5}	Anhydride	Ester
4-Bromo	6.6×10^{-5}	Anhydride	Ester
4-Methyl	4.5×10^{-5}	Anhydride	Anhydride
4-Methoxy	3.2×10^{-5}	Anhydride	Anhydride

[a] Room temperature. [b] Probably liquid ester.

The dialkylvinylcarbinyl esters (Table II) were prepared by two independent routes, the esterification of the vinyl alcohol by the procedure just considered and the semi-hydrogenation of the tertiary acetylenic esters. Identity of products indicates that the Brewster procedure does not involve an allylic rearrangement.

Recently 5% palladium supported on barium carbonate was reported to be an excellent semi-hydrogenation catalyst for both acetylenic carbinols and their acetates.[4] Using ethyl acetate as the solvent, reduction of the tertiary acetylenic *p*-nitrobenzoates at room temperature was complete with the addition of two atoms of hydrogen per molecule. The yields are reported in Table II and in each case are 15 to 20% higher than the yields obtained by esterification of the vinyl alcohol.

Experimental

Carbinols.—Generous samples of 3-methyl-1-butyn-3-ol, 3-methyl-1-pentyn-3-ol, 3,5-dimethyl-1-hexyn-3-ol, 3-ethyl-1-pentyn-3-ol and 1-ethynylcyclohexanol were obtained from Air Reduction Chemical Co. and Reilly Tar and Chemical Corporation. Air Reduction Chemical Co. also supplied samples of 3,4-dimethyl-1-pentyn-3-ol, 3-methyl-1-hexyn-3-ol, 3,6-dimethyl-1-heptyn-3-ol, 3-methyl-1-nonyn-3-ol, 3-methyl-1-decyn-3-ol, 3-ethyl-1-heptyn-3-ol, 3-ethyl-1-octyn-3-ol, 3-phenyl-1-butyn-3-ol and 4-*t*-butyl-1-ethynylcyclohexanol. 4-Methyl-2-hexyn-4-ol was supplied by Dr. Raymond Fleck, St. Edwards University, Austin, Texas. 1-Hexyn-3-ol and 3-phenyl-1-propyn-3-ol as well as 3-ethyl-1-hexyn-3-ol and 3-propyl-1-hexyn-3-ol were prepared by the reaction of sodium acetylide in anhydrous liquid ammonia with the appropriate carbonyl compound and were supplied by Drs. Kenneth Nelson[1] and Eugene Teach.[5] 3-Phenyl-1-buten-3-ol, 3-methyl-1-penten-3-ol and

(4) G. F. Hennion *et al.*, *J. Org. Chem.*, **21**, 1142 (1956).
(5) G. F. Hennion and E. G. Teach, THIS JOURNAL, **75**, 1653 (1953).

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1-vinylcyclohexanol were prepared by the semihydrogenation of the corresponding acetylenic alcohols.[4]

Preparation of 3,5-Dinitrobenzoates.—These esters were prepared by the procedure described by Brewster.[3]

Preparation of *p*-Nitrobenzoates and Monobromobenzoates.—Molecular equivalents (0.05 mole) of acid and alcohol were dissolved in dry pyridine (*ca.* 65 ml.) by placing the mixture on a steam-bath. About 0.05–0.08 mole of *p*-toluenesulfonyl chloride was added and after 2 hr. at steam-bath temperature, the cooled solution was poured into three volumes of ice and water. The crude crystals were collected, washed with ice-water and usually recrystallized from aqueous ethanol.

Semi-hydrogenation of *p*-Nitrobenzoates.—Two-hundredths mole of the ester was dissolved in 50 ml. of ethyl acetate, and 5% Pd–$BaCO_3$ (0.03–0.08 g.) was added. The reduction was carried out at room temperature and an initial pressure of *ca.* 50 p.s.i.g. The solution was filtered and the filtrate allowed to evaporate at room temperature. The crude crystals were recrystallized from aqueous ethanol with the exception of 3-phenyl-1-buten-3-yl *p*-nitrobenzoate (XXII). This ester is very sensitive to solvolysis; consequently, recrystallization was most efficient using petroleum ether.

Acknowledgments.—The authors are indebted to Dr. F. E. Cislak, Reilly Tar and Chemical Corp., Indianapolis, Ind., and to Dr. C. O. Herman, Air Reduction Chemical Co., New York, for generous supplies of acetylenic carbinols. Appreciation is also expressed to G. M. Maciak and H. L. Hunter of the Lilly Research Laboratories, Indianapolis, for the analyses reported in Tables I–IV.

NOTRE DAME, INDIANA

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

The Kinetics of the Saponification of Acetylenic Carbinol Esters and Related Compounds[1]

BY G. F. HENNION AND S. OLIVIA BARRETT[2]

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Acetylenic carbinol esters, RR′C(C≡CH)OCOR″, undergo extremely slow solvolysis in mixed aqueous solvents, as do the chlorides, RR′C(Cl)C≡CH, and rapid saponification in the presence of base. The semi- and fully hydrogenated analogs (—CH=CH_2 and —CH_2CH_3 in place of —C≡CH) solvolyze more rapidly and saponify more slowly. Variations in R and R′ do not alter the saponification rates so significantly. In the acetylene series the ester group, —OCOR″, is not comparable to —Cl in reactions with bases.

Discussion

Tertiary acetylenic chlorides, RR′C(Cl)C≡CH, undergo remarkably slow solvolysis in aqueous solvents and react much more rapidly by second-order kinetics in the presence of base.[3,4] There is considerable evidence that the reactions with bases are initiated by attack on the acetylenic hydrogen atom.[3–5] It was, therefore, of interest to ascertain if acetylenic carbinol esters behave in a similar manner. The solvolysis of a variety of such compounds (as well as their hydrogenation products) and their behavior in alkaline solutions have now been studied.

In solvolytic reactions there is good correlation between halide and ester reactivities, the order of ease of carbonium ion formation in polar solvents being the same, vinyl >> ethyl > ethynyl. The stability of the carbon–halogen and carbon–oxygen bonds is considerably different, however. The solvolysis of 3-chloro-3-methyl-1-butyne at 25° in 80% aqueous ethanol is extremely slow but easily detectable[3,4] while 0.01 *N* solutions of the corresponding 3-bromobenzoate, 4-bromobenzoate, 4-chlorobenzoate, 4-nitrobenzoate and 2,4-dichlorobenzoate in 90% aqueous ethanol at room temperature were neutral to litmus after a period of 8 months. Solvolysis was evident only in the case of the 3,5-dinitrobenzoate. Moreover, the corresponding acetate was recovered in almost quantitative yield after boiling for 50 hr. in absolute ethanol. In 80% aqueous ethanol, 3-methyl-1-pentyn-3-yl *p*-nitrobenzoate was recovered in 96% yield after 50 hr. of refluxing. The corresponding vinyl ester under comparable conditions underwent considerable solvolysis. The order of solvolysis is more evident when one compares the reactivity of 3-phenyl-1-butyn-3-yl *p*-nitrobenzoate and the corresponding semi-hydrogenated ester. Introduction of a phenyl group facilitated alkyl–oxygen heterolysis in both compounds. Boiling the ethynyl compound in absolute ethanol for only 2.5 hr. gave *p*-nitrobenzoic acid in 59% yield. The vinyl ester, 3-phenyl-1-buten-3-yl *p*-nitrobenzoate, was still more sensitive to solvolysis. Recrystallization from aqueous solvents or absolute ethanol resulted in decomposition of the ester, and solvolysis in absolute methanol at room temperature was rapid (82% decomposition in four days.) Although the saturated esters were not included in this study, Cohen and Schneider[6] have demonstrated the sensitivity of *t*-butyl benzoate to alkyl–oxygen fission. When this ester was boiled for 4 days in absolute methanol, a 60% yield of *t*-butyl methyl ether was obtained.[6]

Product studies of tertiary acetylenic esters under saponification conditions clearly demonstrated the reaction to be a normal nucleophilic attack on the carbonyl carbon rather than on the acetylenic hydrogen atom. Both the acetate and the 3,5-dinitrobenzoate of 3-methyl-1-butyn-3-ol were saponified in aqueous ethanol at room temperature; the ethyl ether, the expected product of alkyl–oxygen fission,[3] was not produced. It may be concluded that the strong electrophilic character of

(1) Paper LXVI on substituted acetylenes; previous paper, THIS JOURNAL, **79**, 2146 (1957).

(2) Abstracted from the Ph.D. Dissertation of Sr. M. Olivia Barrett, R.S.M.

(3) G. F. Hennion and D. E. Maloney, THIS JOURNAL, **73**, 4735 (1951).

(4) G. F. Hennion and K. W. Nelson, *ibid.*, **79**, 2142 (1957).

(5) G. F. Hennion and E. G. Teach, *ibid.*, **75**, 1958 (1953).

(6) S. Cohen and A. Schneider, *ibid.*, **63**, 3383 (1941).

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the ester carbonyl controls the mechanism and in effect eliminates the possibility of attack at the acetylenic hydrogen.

The data recorded in Table I indicate a remarkable similarity in saponification rate for all *p*-nitrobenzoates of the general type RR'C(OPNB)-C≡CH, regardless of the nature of R and R'. Presumably the linear electron-withdrawing ethynyl group influences the rate to the extent that steric and polar variations in R and R' affect the reaction less than in saturated tertiary esters (Table II).[7-9]

TABLE I

SAPONIFICATION RATES OF *p*-NITROBENZOATES, RR'C(C≡CH)OCOC$_6$H$_4$NO$_2$, IN 70% AQUEOUS ACETONE AT 25°

R	R'	Initial concn., mole/liter	k_2, l./mole-sec. × 10² Exptl.	Mean
CH_3	CH_3	0.0170	4.03	
		.0139	4.02	4.03
CH_3	C_2H_5	.0171	2.47	
		.0177	2.46	2.47
CH_3	n-C_3H_7	.0168	1.99	
		.0165	1.93	1.96
CH_3	i-C_3H_7	.0057	1.87	
		.0168	1.86	1.87
CH_3	n-C_7H_{15}	.0111	1.88	
		.0110	1.89	1.89
CH_3	C_6H_5	.0141	4.07	
		.0141	4.00	4.04
n-C_3H_7	n-C_3H_7	.0180	0.972	
		.0181	0.967	0.970
$-CH_2(CH_2)_3CH_2-$[a]		.0162	1.97	
		.0173	2.07	2.02
t-$C_4H_9(C_5H_9)$[b]		.0181	1.99	
		.0180	2.03	2.01

[a] 1-Ethynylcyclohexyl *p*-nitrobenzoate. [b] 4-*t*-Butyl-1-ethynylcyclohexyl *p*-nitrobenzoate.

The rate constants listed in Table II for the saponification of several yne–ene–ane series of *p*-nitrobenzoates confirms the trend observed by Meyers,[10] namely, ethynyl > vinyl > ethyl. The acetylenic ester reacts most rapidly, and there is a greater change in rate in replacing ethynyl by vinyl than vinyl by ethyl. Since the rate-controlling step in every case is an attack on the carbonyl carbon, the acetylenic esters react fastest because steric hindrance is at a minimum and electron distribution most favorable.

Kinetic rates of tertiary acetylenic benzoates, listed in Table III, illustrate again the importance of inductive and mesomeric as well as steric factors in the saponification of a variety of substituted benzoates. Although the acid dissociation constant of 2,4-dichlorobenzoic acid predicts rapid saponification, faster than that of the *p*-nitrobenzoate, the relatively slow rate indicates that the bulk of the *o*-chlorine is sufficient to hinder nucleophilic attack at the carbonyl carbon.[11]

TABLE II

SAPONIFICATION RATES OF *p*-NITROBENZOATES, RR'CR''(OCOC$_6$H$_4$NO$_2$), IN 70% AQUEOUS ACETONE AT 25°

R	R'	R'' and k_2, l./mole-sec. × 10⁴ C≡CH	CH=CH$_2$	CH$_2$–CH$_3$	H
CH_3	CH_3	402.5	40.5	9.23	535
CH_3	C_2H_5	246.5	24.2	3.25	..
CH_3	C_6H_5	404	115.5	15.4	..
$-CH_2(CH_2)_3CH_2-$[a]		202	*ca.* 7	Too slow	374

[a] 1-Ethylnylcyclohexyl *p*-nitrobenzoate.

TABLE III

SAPONIFICATION RATES OF SUBSTITUTED BENZOATES OF 3-METHYL-1-BUTYN-3-OL IN 70% AQUEOUS ACETONE AT 25°

Substituent	k_2, l./mole-sec. × 10³	K_a
4-Nitro	40.25	4.0×10^{-4}
2,4-Dichloro	2.01	$>1.3 \times 10^{-3}$
3-Bromo	1.84	1.4×10^{-4}
4-Bromo	1.30	6.6×10^{-5}

It should be noted also (Table IV) that changes in the solvent and/or the water content thereof affect the saponification rates of the acetylenic carbinol esters precisely as in the case of other aliphatic alcohol esters.

TABLE IV

VARIATIONS IN SAPONIFICATION RATES WITH SOLVENT CHANGES (k_2 IN L./MOLE-SEC. × 10²)

p-Nitrobenzoate	Solvent	k_2
C_2H_5OPNB	80% ethanol	8.85
	85% ethanol	7.14
	60% acetone	24.5
	70% acetone	30.85
$(CH_3)_2C(OPNB)C\equiv CH$	70% acetone	4.03
	75% acetone	4.49
	80% acetone	5.00
	90% ethanol	2.70
	70% dioxane	3.23
$(CH_3)_2C(OPNB)CH=CH_2$	70% acetone	0.405
	75% acetone	.485
$(CH_3)_2C(OPNB)C_2H_5$	70% acetone	.0923
	75% acetone	.118
$CH_3(C_2H_5)C(OPNB)C\equiv CH$	70% acetone	2.47
	75% acetone	3.11
	90% ethanol	2.14
	70% dioxane	2.10
$CH_3(C_2H_5)C(OPNB)C\equiv C-CH_3$	70% acetone	1.08
	75% acetone	1.33
$CH_3(n\text{-}C_3H_7)C(OPNB)C\equiv CH$	70% acetone	1.96
	90% ethanol	1.86
$(CH_2)_5C(OPNB)C\equiv CH$	70% acetone	2.02
	70% dioxane	1.67

Experimental

Preparation of Esters.—The esters were prepared as described in the previous paper[1] and were recrystallized at least three times.

Preparation of Solutions for Kinetic Studies.—The acetone was prepared by distilling C.P. acetone from an excess of potassium permanganate and allowing the distillate to stand at least one day over anhydrous potassium carbonate before redistillation through a Vigreux column. Car-

(7) *Cf.* M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N.Y., 1956, p. 222.

(8) The close agreement between the specific rates for 1-ethynylcyclohexyl *p*-nitrobenzoate and one of the isomers of the 4-*t*-butyl-1-ethynylcyclohexyl ester suggests comparable conformations for the carboxylate group, probably equatorial. This matter is now being studied.

(9) Surprisingly, replacement of the acetylenic hydrogen by methyl reduces the rate only by one-half; see Table IV.

(10) R. T. Meyers, A. R. Collett and C. L. Lazzell, *J. Phys. Chem.*, **56**, 461 (1952).

(11) Failure of the Hammett relationship in saponification of *o*-substituted ethyl esters has been discussed by R. W. Taft, ref. 7, p. 583.

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bonate-free alkali solutions were prepared by carefully pipetting the required amounts of clear solution from above the precipitated carbonate of a saturated sodium hydroxide solution. These were diluted with freshly boiled water and standardized against potassium acid phthalate using brom thymol blue. The approximately 0.05*N* hydrochloric acid was standardized with standard alkali.

General Kinetic Procedure.—The method was similar to that of Tommila and Hinshelwood.[12] The specific rates were determined by mixing equal volumes of alkali and ester solutions of the same concentration at the desired temperature, withdrawing aliquots at specific time intervals and quenching these in an excess of standard acid. The excess acid was back-titrated with standard base (*ca.* 0.03 *N*) using brom thymol blue.

The 70% acetone solution of alkali was prepared by diluting exactly 30.00 ml. of aqueous standard sodium hydroxide (*ca.* 0.1*N*) to 100 ml. of solution at 25° using purified acetone.

(12) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1802 (1938).

The ester solution was made by weighing on counterpoised watch glasses a quantity of ester exactly equivalent to 30.00 ml. of the standard alkali. This ester was quantitatively transferred to a 100-ml. volumetric flask with acetone; 30 ml. of water was added and the solution brought to volume at 25° with acetone.

Mixing was effected by simultaneously pouring the solutions through a powder funnel into a 250-ml. ground-glass stoppered erlenmeyer flask. An aliquot was withdrawn immediately, quenched in an ice-cold mixture of 5 ml. of standard hydrochloric acid and 10 ml. of acetone and back-titrated against standard alkali. Zero time was considered to be the contact time of this first aliquot and all time intervals were determined in a similar manner. The concentration of alkali in this first aliquot was considered to be the initial concentration (*a*). A total of 6 to 10 aliquots were withdrawn from each reaction mixture, following the first 30–50% reaction. The second-order rate constants were calculated from the customary equation for equal initial concentrations.

NOTRE DAME, INDIANA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, IOWA STATE COLLEGE]

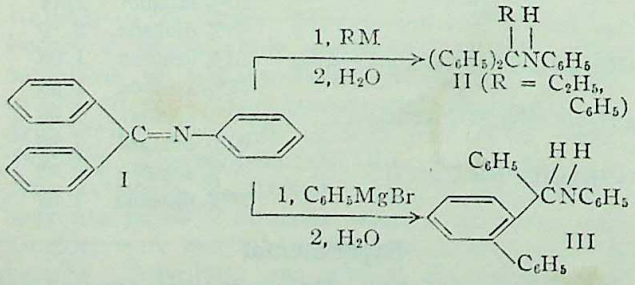
1,2-Addition of Allylmagnesium Bromide to N-Diphenylmethyleneaniline and Structurally Related Systems

BY HENRY GILMAN AND JOHN EISCH

RECEIVED NOVEMBER 24, 1956

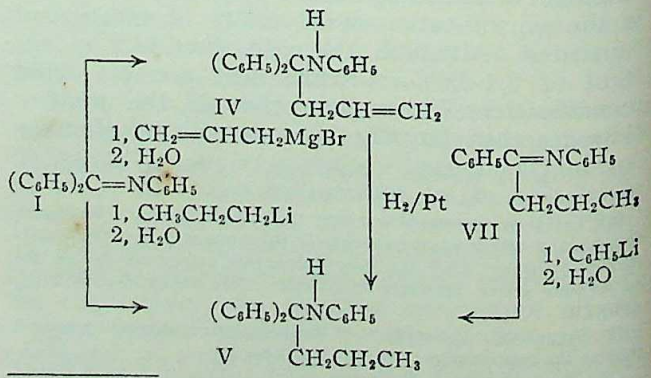
Allylmagnesium bromide readily added in a 1,2-manner to the structurally related systems, N-diphenylmethyleneaniline (I), fluorenone anil (VIII) and 6-phenylphenanthridine (IX). The structure of the product from I was demonstrated by an unambiguous synthesis. The mechanism of 1,2-addition to the azomethine linkage is discussed and an explanation is advanced for the abnormal 1,4-addition of phenylmagnesium bromide to I.

The interaction of organometallic compounds with the –C=N– linkage in N-diphenylmethyleneaniline (I) (benzophenone anil) has received considerable study due to the peculiar behavior of this system. Although the organometallic compounds of lithium,[1,2] potassium,[3] sodium,[3] calcium,[4] barium[2] and strontium[2] add to the system in a 1,2-manner (II), the ordinary Grignard reagents fail to react with this azomethine linkage in refluxing ether.[5,6] Indeed, when the reaction between phenylmagnesium bromide and N-diphenylmethyleneaniline is forced by running it in ether–toluene solution at 90–105°, the only isolable product is the result of an apparent 1,4-addition (III).[5]



Previous studies in this Laboratory have demonstrated that the allyl Grignard reagent in its interactions with aza-aromatic heterocycles exhibits an exceptionally high order of reactivity when compared with that of ordinary Grignard reagents.[7] Consequently, its behavior with N-diphenylmethyleneaniline was investigated in order to see whether it would parallel the behavior of phenyllithium or phenylmagnesium bromide toward this system.

Surprisingly enough, it was found that allylmagnesium bromide reacted readily with N-diphenylmethyleneaniline in refluxing ether to give a 95% yield of product which was shown to be 1-allyl-1,1-diphenylmethylaniline (IV) in the following rigorous manner. By catalytic hydrogenation it was converted to the same substance (V) as obtained by the interaction of propyllithium and N-diphenylmethyleneaniline. Although this demonstrated that both reagents reacted with N-diphenylmethyleneaniline in the same manner, confirmation that indeed 1,2-addition had taken place was obtained by synthesizing V unambiguously.



(1) Gilman and R. H. Kirby, THIS JOURNAL, **57**, 1267 (1935).
(2) Gilman, Haubein, O'Donnell and Woods, *ibid.*, **67**, 922 (1945).
(3) Gilman and R. H. Kirby, *ibid.*, **63**, 2046 (1941).
(4) Gilman, R. H. Kirby, Lichtenwalter and Young, *Rec. trav chim.*, **55**, 79 (1936).
(5) Gilman, J. E. Kirby and Kinney, THIS JOURNAL, **51**, 2252 (1929).
(6) Short and Watt, *J. Chem. Soc.*, 2030 (1939).
(7) Gilman, Eisch and Soddy, THIS JOURNAL, **79**, 1245 (1957).

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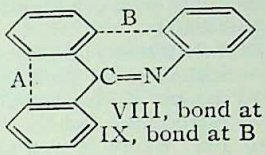
Thus butyrophenone (VI) was converted to its anil VII and the latter compound treated with phenyllithium. The 1-propyl-1,1-diphenylmethylaniline obtained upon hydrolysis was identical with that from the hydrogenation of IV.

The ease with which N-diphenylmethyleneaniline reacted with allylmagnesium bromide suggested that the azomethine linkage in related compounds also would be attacked readily. Chosen for this study were fluorenone anil (VIII) and 6-phenylphenanthridine (IX), as the former is formally derived from N-diphenylmethyleneaniline by forming bond A, while the latter results from forming bond B.

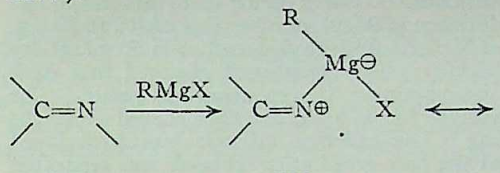


VIII, bond at A
IX, bond at B

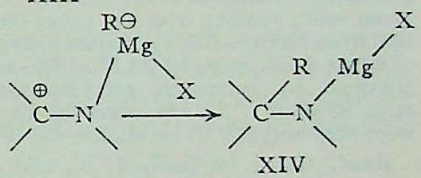
Allylmagnesium bromide added to the azomethine linkage of fluorenone anil extremely rapidly to yield α-allylfluorenylaniline (X) in 93% yield. 6-Phenylphenanthridine was attacked somewhat less readily to give 6-allyl-6-phenyl-5,6-dihydrophenanthridine (XI) in 67% yield. In the latter case it is remarkable that this endocyclic azomethine linkage reacts with such facility with this Grignard reagent. Previous studies have shown that the unsubstituted phenanthridine also has a heightened reactivity toward allylmagnesium bromide in comparison with pyridine, quinoline and isoquinoline.[7]

Based upon the previously observed behavior of N-diphenylmethyleneaniline with phenyllithium and with phenylmagnesium bromide, it was suggested that the abnormal 1,4-addition of the latter reagent might be owed to the greater steric demands of the Grignard reagent.[1,5] Subsequently, it was found that phenylcalcium iodide reacted with N-diphenylmethyleneaniline in a 1,2-manner[4] and this fact seriously weakened the case for steric hindrance. The steric bulk of the calcium and iodine atoms was not reflected in the mode of addition. In the course of studies employing N-diphenylmethyleneaniline and benzalacetophenone to index the reactivity of related organometallic compounds, it was concluded that the more reactive organometallic reagents added in a 1,2-manner, while the less reactive tended to add in a 1,4-fashion.[3] The present study shows that allylmagnesium bromide may well be classified among the more reactive organometallic reagents and that not only the metal but also the organic moiety can greatly influence the reactivity of the composite organometallic reagent. In support of this conclusion N-diphenylmethyleneaniline was allowed to react, in turn, with methylmagnesium iodide[6,8] and with propylmagnesium bromide under the conditions so successful with allylmagnesium bromide. However, almost all starting material was recovered with no sign of reaction.

In light of present knowledge it seems reasonable to view the mechanism of 1,2-addition to the azomethine linkage as proceeding through a nucleophilic attack of the organic anion of the reagent on the positive-polarized carbon atom adjacent to the nitrogen. The resonance stabilization of the allylic anion in allylmagnesium bromide seems to favor heterolysis of the magnesium–carbon bond and hence rationalizes the greater reactivity of this Grignard reagent. With certain organometallic reagents, especially those of the alkaline earth metals, it is quite probable that the reagent preliminarily complexes with the nitrogen[9] (XII → XIV).

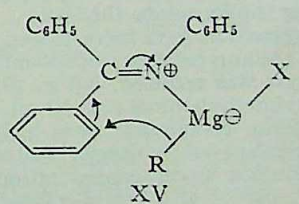


XII XIII



XIV

The abnormal 1,4-addition to N-diphenylmethyleneaniline by phenylmagnesium bromide can also be considered as a nucleophilic attack of $R^{\ominus}$ at the *o*-position of the benzene ring proceeding through a six-membered cyclic complex (XV). However,



XV

the stringent conditions necessary to obtain such a reaction make it quite probable that here radical processes play a part. Thus Kharasch, Goldberg and Mayo[10] have shown that aromatic Grignard reagents when heated in aromatic solvents yield products indicative of attack by aromatic radicals. It is therefore conceivable that 1,4-addition on N-diphenylmethyleneaniline may proceed by attack of phenyl radicals and that other phenylated isomers may also be formed.

Experimental

The melting points were determined on an electrically heated copper block and are corrected. Operations involved in the preparation and reactions of organometallic compounds were conducted in an atmosphere of dry oxygen-free nitrogen.

1-Allyl-1,1-diphenylmethylaniline (IV).—To 43.3 g. (0.169 mole) of N-diphenylmethyleneaniline partially dissolved in 100 ml. of dry ether was added 0.215 mole of allylmagnesium bromide[11] in 190 ml. of ether. During the 25-minute addition period the N-diphenylmethyleneaniline dissolved and spontaneous reflux set in. Toward the end, however, a white solid settled out of solution. After the mixture was stirred at the reflux temperature for 18 hours, it was hydrolyzed with 500 ml. of saturated ammonium chloride solution. The pale yellow ethereal layer, upon separation

(8) Maginnity and Cloke, THIS JOURNAL, **73**, 49 (1951), as well as Short and Watt (ref. 6) have isolated only starting material from the reaction between N-diphenylmethyleneaniline and methylmagnesium iodide.

(9) Sachs and Sachs, *Ber.*, **37**, 3088 (1904).

(10) Kharasch, Goldberg and Mayo, THIS JOURNAL, **60**, 2004 (1938).

(11) Gilman and McGlumphy, *Bull. soc. chim. France*, **43**, 1325 (1928).

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and drying with anhydrous sodium sulfate, was distilled to remove the solvent. Chilling of the residual oil gave 48.1 g. (95%) of light tan solid, melting over the range 72–78°. Recrystallization from 200 ml. of 95% ethanol afforded 44.0 g. (87%) of white, close-packed crystals, m.p. 78.5–80°, and further recrystallizations did not alter the melting point.

Anal. Calcd. for $C_{22}H_{21}N$: N, 4.67. Found: N, 4.70.

The infrared spectrum in bromoform exhibited a sharp –NH band at 3.0 μ, but did not indicate the presence of any disubstituted benzene ring.

1-Propyl-1,1-diphenylmethylaniline (V). (a) From Propyllithium and N-Diphenylmethyleneaniline.—Propyllithium was prepared in 83% yield by adapting the published directions for butyllithium.[12] Over a period of 45 minutes, 0.097 mole of propyllithium in 90 ml. of ether was added to 20.0 g. (0.078 mole) of N-diphenylmethyleneaniline in 50 ml. of dry ether. The initially yellow suspension changed to a dark red solution accompanied by spontaneous reflux. The solution was refluxed for six hours and then stirred overnight without heating. The reaction mixture was hydrolyzed with water and the pale green ethereal layer was separated and dried. Removal of the ether left 21.2 g. (91%) of pale green solid, melting over the range 69–74°. Recrystallization from 100 ml. of 95% ethanol (Norit) gave 18.0 g. (77%) of white solid, m.p. 83–84.5°. The analytical sample was obtained by successive recrystallizations from ethanol, m.p. 85–85.5°. It was observed that the purer samples were very sluggish to crystallize out of solution.

Anal. Calcd. for $C_{22}H_{23}N$: N, 4.64. Found: N, 4.73.

The infrared spectrum in bromoform had a distinct band at 3.0 μ, but as with the product from allylmagnesium bromide and N-diphenylmethyleneaniline, no bands indicative of a disubstituted benzene ring.

(b) From 1-Allyl-1,1-diphenylmethylaniline (IV).—The hydrolyzed allyl Grignard adduct of N-diphenylmethyleneaniline was correlated with the hydrolyzed propyllithium adduct by reducing the former to the latter.

In the hydrogenation flask were placed 30 mg. of platinum(IV) oxide (Adams catalyst) and 50 ml. of 95% ethanol. After the catalyst was reduced, 3.0 g. (0.010 mole) of 1-allyl-1,1-diphenylmethylaniline and 50 ml. of ethyl acetate were added. The compound was hydrogenated until one molar equivalent of hydrogen had been taken up. The filtered solution upon concentration and refrigeration gave 2.5 g. (83%) of a cream-colored solid, m.p. 83–85°. This was shown to be identical with the 1-propyl-1,1-diphenylmethylaniline prepared in part a by a mixture melting point determination and comparison of infrared spectra. This verified that allylmagnesium bromide and propyllithium both added to N-diphenylmethyleneaniline in the same fashion. It remained to be confirmed that this was 1,2-addition.

(c) From Butyrophenone Anil (VII).—Phenyllithium was prepared in 99% yield according to published directions[13] by the interaction of 2.2 g. (0.33 g. atom) of lithium wire and 22.8 g. (0.145 mole) of bromobenzene in dry ether.

To 0.144 mole of phenyllithium in 100 ml. of dry ether was added a solution of 15.5 g. (0.069 mole) of butyrophenone anil in 75 ml. of dry ether over the course of 50 minutes. The mixture was stirred for four hours and then hydrolyzed. The ether layer upon separation, drying and removal of the solvent gave 22 g. of a somewhat sticky, pale yellow solid. After recrystallization from 100 ml. of 95% ethanol 12.4 g. (59%) of cream-colored solid was obtained, m.p. 80–83°. Additional recrystallizations from ethanol gave a white product, m.p. 83–84°. This solid was identical with the 1-propyl-1,1-diphenylmethylaniline obtained in parts a and b, as evidenced by mixture melting points and infrared spectra.

Butyrophenone (VI).—This compound was conveniently prepared by adaptation of procedures for the preparation of other aliphatic-aromatic ketones.[14]

To 0.60 mole of filtered propylmagnesium bromide in 600 ml. of ether was added a solution of 50.0 g. (0.485 mole) of redistilled benzonitrile in 60 ml. of dry ether during a 45-minute period. The dark yellow solution was refluxed overnight and subsequently poured into a mixture of 200 ml. of 6 *N* sulfuric acid and ice. The biphasic mixture was heated to distil off the ether and to hydrolyze the ketimine. The cooled mixture was then extracted with ether. The extracts were dried over anhydrous sodium sulfate and the ether distilled off. The residual oil was distilled under reduced pressure to yield 64.0 g. (90%) of colorless butyrophenone, b.p. 106.5–107° (13 mm.), lit.[14] b.p. 128° (27 mm.).

Butyrophenone Anil (VII).—This procedure is adapted from Reddelien's directions for acetophenone anil.[15] The necessary aniline–zinc chloride complex was prepared by adding 25 ml. of freshly distilled aniline to a solution of 25.0 g. of zinc chloride dihydrate in 40 ml. of water, 20 ml. of ethanol and 10 ml. of concentrated hydrochloric acid. The white suspension was stirred thoroughly and then filtered. The solid was washed twice with ether and upon drying the white complex weighed 30.0 g.

Freshly distilled aniline (30 ml.) and butyrophenone (30.0 g., 0.202 mole) were heated up to 100° (oil-bath) in a distillation flask. Two grams of the powdered aniline–zinc chloride complex was introduced and the bath temperature was raised slowly to 160° where it was maintained for 15 minutes. Steam began to evolve and continued to do so when the temperature was raised to 180° and held there for 30 minutes. The cooled reaction mixture was taken up in 200 ml. of chloroform and the undissolved zinc salts were filtered off. The filtrate was distilled to remove, in turn, chloroform and then the excess aniline and butyrophenone. Finally the butyrophenone anil came over as a clear yellow liquid weighing 15.8 g. (35% conversion), b.p. 183–185° (13 mm.), 128° (1.1 mm.), $n^{25}D$ 1.5926.

Anal. Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.96; H, 7.83; N, 6.22.

α-Allylfluorenylaniline (X).—To a yellow solution of 25.5 g. (0.100 mole) of fluorenone anil in 100 ml. of dry ether was added an equimolar quantity of allylmagnesium bromide in 110 ml. of ether during 20 minutes. Immediate reaction was evidenced by the discharge of the yellow color and occurrence of spontaneous reflux. After the solution was stirred at room temperature for an additional two hours, it was hydrolyzed with ammonium chloride solution. The ethereal layer upon drying and removal of the solvent yielded a tan solid melting over the range 130–134°, 27.6 g. (93%). Recrystallized from ethanol (Norit), the solid formed long, glistening white needles, 25.7 g. (87%), m.p. 136.5–137.5°.

Anal. Calcd. for $C_{22}H_{19}N$: N, 4.71. Found: N, 4.71.

6-Allyl-6-phenyl-5,6-dihydrophenanthridine (XI).—To 25.5 g. (0.100 mole) of 6-phenylphenanthridine[16] suspended in 150 ml. of dry ether was added 0.125 mole of allylmagnesium bromide in 125 ml. of ether over the course of 30 minutes. Upon heating at the reflux temperature overnight the reaction mixture formed a dark green, fluorescent solution. The cooled reaction mixture was hydrolyzed in the usual fashion and from the ethereal layer was obtained 28.1 g. of crude white product, melting over the range 90–100°. This product was difficult to free from contamination with 6-phenylphenanthridine (m.p. 107°) due to the similar properties of the product and starting material. Repeated recrystallization from 95% ethanol in excess afforded 20 g. (67%) of shiny white platelets, m.p. 101–103°. The analytical sample melted at 103–104.5°. As is characteristic of 5,6-dihydrophenanthridine types,[17] this compound in ethanolic solution possessed a marked blue fluorescence.

Anal. Calcd. for $C_{22}H_{19}N$: C, 88.84; H, 6.44; N, 4.71. Found: C, 89.14; H, 6.23; N, 4.66.

Reaction of Grignard Reagents with N-Diphenylmethyleneaniline.—Neither the methyl nor the propyl Grignard reagent reacted with N-diphenylmethyleneaniline under the conditions successful with allylmagnesium bromide. Thus, when 18.0 g. (0.070 mole) of N-diphenylmethyleneaniline in 100 ml. of dry ether was heated for 18 hours with 0.10 mole of either methylmagnesium iodide or propylmagnesium bromide in ether, the usual work-up yielded

(12) Gilman, Beel, Brannen, Bullock, Dunn and Miller, THIS JOURNAL, **71**, 1499 (1949).

(13) Gilman and Morton in Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1954, Vol. VIII, p. 286.

(14) Birch, Dean, Fidler and Lowry, THIS JOURNAL, **71**, 1362 (1949).

(15) Reddelien, *Ber.*, **43**, 2476 (1910).

(16) Morgan and Walls, *J. Chem. Soc.*, 2447 (1931).

(17) Callaway, Copp and Walls, *ibid.*, 2698 (1950).

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only about 16–17 g. (88–95% recovery) of starting material.

Acknowledgments.—The authors are grateful to Dr. V. A. Fassel and Mr. R. McCord of the Institute for Atomic Research for the infrared determinations.

AMES, IOWA

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

A Kinetic Study of the Leuchs Anhydrides in Aqueous Solution. I[1]

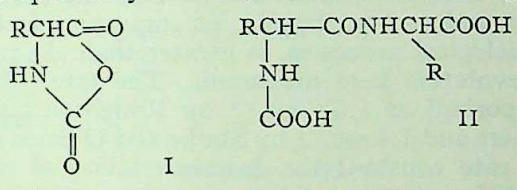
BY PAUL D. BARTLETT AND RICHARD H. JONES

RECEIVED SEPTEMBER 7, 1956

The reaction of an anhydro-N-carboxy-amino acid (Leuchs anhydride) with water is subject to general basic catalysis and is not catalyzed by acids. The reaction with the amino group of an amino acid anion is so rapid that it can compete successfully with hydrolysis. The reactions of anhydro-N-carboxyglycine, anhydro-N-carboxy-D- and L-alanine and anhydro-N-carboxy-α-aminoisobutyric acid with water and some amino acids have been followed kinetically by carbon dioxide evolution and their rate constants determined (Tables II and III). The possibility of controlled peptide synthesis in aqueous solution from the Leuchs anhydrides is discussed and experiments are reported showing the limitations of such a procedure.

Introduction

The anhydrides (I) of N-carboxy-α-amino-acids, first prepared by Leuchs,[2] have been investigated



I II

chiefly in inert solvents where with controlled amounts of active-hydrogen compounds as initiators they lead to polypeptides[3] of moderate or high molecular weight while at very low temperatures the decarboxylation of the initial carbamic acid (II) can be repressed sufficiently by salt formation[4] to afford good yields of simple peptides. Even more attractive possibilities of control of this reaction would present themselves if it were possible to operate in aqueous solutions; with this in mind, we have studied the nature and rates of the reactions of some simple N-carboxy-anhydrides in water.

Reactions of N-Carboxy-anhydrides with Water.—The N-carboxy-anhydrides of glycine, *dl*-alanine and α-amino-isobutyric acid, on solution in water at 0°, evolve carbon dioxide at a rate convenient for measurement. The reactions were followed by observing the increase in pressure in a closed, initially evacuated system; with the first and last of these anhydrides a rate measurement by following volume increase at constant pressure agreed with the results of the pressure method. Except for a short initial period (see below) the reactions, as followed in this manner, were of the first order, yielding rate constants as shown in Table I. Reactions of anhydro-N-carboxy-α-aminoisobutyric acid in 0.1 *M* barium chloride, 0.1 *M* hydrochloric acid and 1.0 *M* sulfuric acid yielded the same average rate constant, 2.4×10^{-3} sec.$^{-1}$, as the reaction in pure water, with a mean deviation of $\pm 0.07 \times 10^{-3}$. The effect of acid catalysis upon the hydrolysis of the anhydride is therefore negligible.

TABLE I

RATE CONSTANTS FOR UNCATALYZED HYDROLYSIS AT 0°

N-Carboxy-anhydride of	No. of runs	Concentration range	k_1, sec.$^{-1}$ $\times 10^3$	Mean deviation
Glycine	6	0.01– 0.028	4.1	0.23
dl-Alanine	3	.022– .028	6.4	.23
α-Aminoisobutyric acid	5	.019– .028	2.4	.12

Carbon dioxide is not evolved when a carboxy-anhydride reacts with two or more equivalents of sodium or barium hydroxide. An attempt was made to measure the rate of the reaction of anhydro-N-carboxyglycine with hydroxyl ion by following the conductivity of a solution of barium hydroxide to which the anhydride was added. There was a very rapid reaction which produced 74% of the expected change in conductivity within the first 40 seconds, followed by a slower process to which a second-order rate constant of 0.30 l./mole sec. could be assigned. The latter process is far too slow to be the reaction of anhydride with hydroxyl ion, as a later experiment proves. According to Stadie and O'Brien,[5] carbamates such as the Siegfried salts come rapidly to equilibrium with carbon dioxide and amino acid anion, but the carbon dioxide is much more slowly equilibrated with bicarbonate and carbonate. The calculated equilibrium concentration of carbonate ion during the preparation of a Siegfried barium salt is more than sufficient to precipitate barium carbonate; the non-appearance of such a precipitate is evidently the result of slow attainment of the carbonate equilibrium. The slow reaction observed in the conductivity experiments may well be the conversion of hydroxyl ion into carbonate.

Hydrolysis of N-Carboxy-anhydrides in Buffer Solutions.—During this work it became apparent that the amino acid formed by hydrolysis of the

(1) This work was supported by the Office of Naval Research under Contract No. N5ori-07653 with Harvard University, 1952–1953.

(2) H. Leuchs, *Ber.*, **39**, 857 (1906).

(3) For a review see E. Katchalski, "Advances in Protein Chemistry," Vol. VI, Academic Press, Inc., New York, N. Y., 1951, pp. 123–185. More recent work: D. G. H. Ballard and C. H. Bamford, "Symposium on Peptide Chemistry," Special Publication No. 2, Chemical Society, London, 1955, pp. 25–48; E. R. Blout and R. H. Karlson, THIS JOURNAL, **78**, 941 (1956); P. Doty and R. D. Lundberg, *ibid.*, **78**, 4810 (1956); E. R. Blout and M. Idelson, *ibid.*, **78**, 3857 (1956).

(4) J. Leggett Bailey, *J. Chem. Soc.*, 3466 (1950).

(5) W. C. Stadie and H. O'Brien, *J. Biol. Chem.*, **103**, 521 (1933); **112**, 193 (1936).

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anhydride was itself competing appreciably with water, especially in the case of glycine, for reaction with the anhydride after the reaction was under way. The effect of this competition could be reduced by operating either in excess base to prevent decarboxylation of N-carboxy-glycine or in a buffer solution sufficiently acid to keep the amino group of the amino acid overwhelmingly in the ammonium ion form. An acetate buffer was adopted containing 1.00 *M* sodium acetate and 0.875 *M* acetic acid and having a *p*H of 4.76. The experiments described above indicated that the hydrolysis of an N-carboxy-anhydride is subject to basic but not to acid catalysis. In view of the possibility of general basic catalysis (*e.g.*, catalysis by acetate ions as well as by hydroxyl ions), a series of rate determinations were made in which anhydro-N-carboxyglycine was hydrolyzed at 0° at concentrations from 0.023 to 0.026 *M* in this acetate buffer at various buffer dilutions up to tenfold, the ionic strength being maintained constant at 1.00 by means of potassium chloride. The results fit the equation

$$k = 0.00028 + 0.00049[OAc^-] \text{ (time in sec.)}$$

closely. That this is catalysis by the acetate ion and not by acetic acid is already indicated by the complete insensitivity of the rate to strong acids in the case of anhydro-N-carboxy-α-aminoisobutyric acid. From this result it appears that about 30% of the rate measured in pure water was due to the overlaying of the hydrolysis by a reaction with amino acid formed during the hydrolysis and existing at a varying *p*H during the reaction, which did not produce a clear deviation from first-order kinetics. Later work verified this indication that the carboxy-anhydrides do indeed react preferentially with amino groups even in aqueous solution.

Kinetic Salt Effect.—The salt effect on the hydrolysis of anhydro-N-carboxyglycine is negative, as shown by the first-order rate constants in buffer solutions consisting of 0.1 *M* sodium acetate and 0.0875 *M* acetic acid alone (k 0.00043 sec.$^{-1}$). No study was made to apportion this between "primary" and "secondary" kinetic salt effect.

The "Induction Period."—Most of the manometric runs had an initial period of ten minutes during which the reaction appeared to be very slow, before the uniform first-order rate of gas evolution was attained. Since the carbon dioxide is the product of the second of two successive reactions

$$I \longrightarrow \underset{\underset{NHCOOH}{|}}{RCHCOOH} \longrightarrow \underset{\underset{NH_2}{|}}{RCHCOOH} + CO_2$$

we considered the possibility that the decarboxylation of the carbamic acid was a slow enough reaction to account for this effect. This was tested by taking advantage of the fact that a stable salt of glycine N-carboxylic acid can be prepared[6] by saturating a solution of barium glycinate with carbon dioxide. At 0°, in the absence of excess barium hydroxide, this saturation was accomplished without any precipitation of barium carbonate. The decarboxylation of N-carboxyglycine was now observed by the rapid addition to the stable Siegfried salt of enough acetic acid to make an acetate buffer of *p*H 4.76, or in other experiments to give an unbuffered solution of *p*H 0–2. The evolution of carbon dioxide in these experiments followed an approximately first-order course with k_1 varying from 0.023 to 0.042 sec.$^{-1}$. However, when a solution of sodium carbonate was acidified in the same manner, similar results were obtained, k_1 being again from 0.023 to 0.042 sec.$^{-1}$. That the measurable reaction was just the rate of evolution of carbon dioxide from aqueous solution was verified in a series of experiments in which the rate constants varied from 0.005 to 0.030 sec.$^{-1}$ as the speed of the magnetic stirrer in the apparatus was varied over an approximately fivefold range. We conclude that the slow approach to linearity in the kinetic curves is due to the appreciable time required for the establishment of liquid–vapor equilibrium, a steady state being approached as the carbon dioxide evolved in a period of a few minutes becomes a smaller fraction of the total present.

The rate of equilibration of carbonic acid with water and carbon dioxide, an important factor in physiological processes, is greater than the rate of gas evolution here measured. The rate constant is reported[7] as 1.97 sec.$^{-1}$ by Roughton and coworkers and 1.4 sec.$^{-1}$ by Stadie and O'Brien at 0°. The rate constant for decarboxylation of unsubstituted carbamic acid at this temperature is reported[8] to be even greater, 80 sec.$^{-1}$. It appears that whatever the position of the equilibrium in the carbonation of glycine, this equilibrium is attained rapidly in comparison with the reactions whose rates are being measured here.

Reaction of N-Carboxy-anhydrides with Amino Acids.—With the information at hand it was possible to measure the rates of reaction of the N-carboxyanhydrides with various amino acids in aqueous systems. For this purpose it was not possible to suppress the hydrolysis of the anhydride entirely, but the rate constant of this process could be accurately evaluated and subtracted from the over-all pseudo-unimolecular rate constant observed in the presence of an excess of amino acid in the same buffer solution. The reactivity of an amino acid toward an N-carboxyanhydride resides entirely in the free amino group, and the fraction of the amino acid molecules possessing such a free amino group is controlled by the buffer solution. By knowing the second acid dissociation constant of an amino acid and the *p*H of the buffer, it should therefore be possible to determine the rate constant for reaction of an N-carboxyanhydride with the free-base form of any amino acid. In the 0.1 *M* acetate buffer of *p*H 4.74 the pseudo-unimolecular rate constant k_{obs} was used as follows to determine the second-order rate constant k_{AA} for the reaction of anhydro-N-carboxyglycine with amino acid

$$k_{obs} = 0.00043 + k_{AA} \text{ (amino acid)}$$

and for anhydro-N-carboxyalanine

$$k_{obs} = 0.00071 + k_{AA} \text{ (amino acid)}$$

(6) M. Siegfried, *Z. physiol. Chem.*, **44**, 85 (1905).

(7) R. Brinkman, R. Maragria and F. J. W. Roughton, *Phil. Trans. Roy. Soc.*, **A232**, 65 (1933); W. C. Stadie and H. O'Brien, *J. Biol. Chem.*, **103**, 521 (1933).

(8) F. J. W. Roughton, THIS JOURNAL, **63**, 2834 (1941).

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In the latter case the correction to be made for hydrolysis rate amounted to as much as 80% of the quantity being measured; in most cases the relative rates were more favorable than this. An idea of the degree of reliability of the results may be had from the data in Table II, which were determined in order to learn how great the selectivity might be between the optical isomers of alanine in reaction with *d*- or *l*-anhydro-N-carboxyalanine.

TABLE II

OPTICALLY ACTIVE ANHYDRO-N-CARBOXY-ALANINES AND OPTICALLY ACTIVE ALANINES IN ACETATE BUFFER AT 0°

0.100 *M* NaOAc, 0.0875 *M* HOAc

Anhydride concentration	Alanine concentration	k_1, sec.$^{-1}$ × 10^3	$\frac{k_1 - 0.00071}{\text{(alanine)}}$ l./mole sec. × 10^3
	L-Alanine anhydride alone		
0.0396	0	0.70	
.0426	0	.71	
.0465	0	.70	
	Average	0.70	
	D-Alanine anhydride alone		
0.0454	0	0.71	
.0423	0	.72	
.0446	0	.72	
	Average	0.72	
	L-Alanine anhydride + L-alanine		
0.0408	0.225	1.02	1.29
.0416	.449	1.31	1.33
.0442	.449	1.31	1.33
	Average		1.32
	D-Alanine anhydride + D-alanine		
0.0454	0.337	1.15	1.30
0.0439	0.449	1.31	1.33
	Average		1.32
	D-Alanine anhydride + L-alanine		
0.0456	0.225	0.96	1.12
.4038	.337	1.07	1.06
.0422	.449	1.04	1.10
	Average		1.09
	L-Alanine + D-alanine		
0.0420	0.225	0.96	1.13
.0438	.449	1.16	1.00
.0411	.449	1.19	1.07
.0449	.337	1.07	1.07
	Average		1.10

The four possible pairs were run in triplicate, with mean deviations of 1–3% in the second-order rate constants determined. There was agreement between the values for *d*-anhydride with *d*-alanine and for *l*-anhydride with *l*-alanine and also between the constant for *d*-anhydride with *l*-alanine and that for *l*-anhydride with *d*-alanine. In each case the reaction between the configurationally similar reactants was about 20% faster than that between the configurationally opposite reactants. It is not surprising that the difference is small, since neither reacting center is itself asymmetric.

Table III summarizes the second-order rate constants for reaction of anhydro-N-carboxyglycine and alanine with several amino acids and peptides. These measurements are made under conditions where only a minute fraction of the amino acid exists with its amino group in the free-

TABLE III

ANHYDRO-N-CARBOXYGLYCINE AND AMINO ACIDS AT 0° IN ACETATE BUFFER

0.1 *M* sodium acetate, 0.0875 *M* acetic acid

Amino acid	k_{AA}, l./mole sec. × 10^3	pK_2^0	$(k_{AA})^-$ corr.
Glycine	3.8 ± 0.25	10.53[a]	2330
dl-Alanine	1.10 ± .12	10.62[a]	830
α-Aminoisobutyric acid	0.265 ± .045	10.57[a]	179
l-Leucine	1.85 ± .13	10.73[a]	1800
Glycylglycine	23.7 ± .17	8.86[b]	311
Triglycine	29.0 ± .17	(8.58)[c]	200
	Anhydro-N-carboxy-*d*-alanine		
dl-Alanine	1.2	10.62[a]	917
dl-Alanylalanine	4.4 ± 0.7	(9.17)[c]	118
l-Leucine	1.11	10.73[a]	1100

[a] From an equation of H. S. Harned and R. A. Robinson, *Trans. Faraday Soc.*, **36**, 973 (1940), and data selected by J. T. Edsall in Cohn and Edsall, "Amino Acids, Peptides and Proteins," Reinhold Publ. Corp., New York, N. Y., 1943, p. 79. [b] J. Greenstein, *J. Biol. Chem.*, 101, 603 (1933). [c] Estimated assuming the same temperature coefficient as for the amino acids, from data in Cohn and Edsall, p. 84.

base form, yet even under these conditions the amino acid competes successfully with the water for reaction with the N-carboxyanhydride. It is of interest to calculate how fast the active form of the amino acid (having its amino group free) is reacting with the anhydride. For this purpose there are two molecular species to be considered, the anion $H_2NCHRCOO^-$ and the unfavored uncharged form $H_2NCHRCOOH$. The fraction of the former species present in our buffer solution is $10^{(4.74 - pK_2)}$, and the fraction of the latter species is 10^{pK_z} where K_2 is the second ionization constant of the amino acid, and K_z is the equilibrium constant between the dipolar ion and the uncharged amino acid.[9] The latter quantity has been evaluated by Edsall and Blanchard for most of the amino acids with which we are concerned. If for glycine we extrapolate their value of pK_z from 25 to 0° by means of their value of ΔH = 11,500 cal., we find that pK_z under our conditions is −5.79, and this leads to an estimate of the fraction of neutral glycine present at *p*H 4.74 as 1/1,500,000. From the values of pK_2 at 0° given in Table III, the fraction of anion has been estimated; for glycine it is 1/620,000. Thus about two-thirds of the free amino group which is responsible for the reaction with N-carboxyanhydride at *p*H 4.74 is situated on the glycine anion, and the other third is on neutral glycine. These are by no means accurate figures in view of the assumptions underlying the estimate of K_z, but they suggest that we should not be too far wrong in calculating the bimolecular rate constant for reaction between N-carboxyanhydride and glycine anion if we were to attribute all the reaction ob-

(9) J. T. Edsall and M. H. Blanchard, THIS JOURNAL, **55**, 2344 (1933).

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served at pH 4.74 to this species. In favor of this approximation is the expectation that a negative charge on the carboxyl group might enhance the nucleophilic reactivity of the amino group, so that the anion would be inherently more reactive than the neutral form. Against this is the possibility that an undissociated carboxyl group in the amino acid might be strategically located to assist catalytically in the reaction of its amino group with the carbonyl group in the anhydride, which might enhance the importance of the rare neutral species in contributing to the observed rate. In a series of experiments in acetate buffers at constant acetate concentration and ionic strength but varying acetic acid concentration and pH, the rate of reaction was inversely proportional to the acetic acid concentration.

This provides evidence that the amino acid anion is the dominant species in the reaction with anhydro-N-carboxyglycine, rather than the neutral form which is present at constant concentration in this series of buffers.

Accordingly, in Table III the corrected bimolecular rate constant for reaction of anhydride with each amino acid anion has been computed by multiplying k_{AA} by the factor $10^{(pK_2 - 4.74)}$. It will be seen that these rate constants are very large, indicating a surprising ability of the amino group to compete with solvent water. More will be said of this in a later section.

The rate constants for reaction of anhydro-N-carboxyglycine with glycine, glycylglycine and glycylglycylglycine are in the ratio of 1:6:7.5. This means experimentally that in the acetate buffer there is a strong tendency toward the formation of higher peptides through competition of the glycylglycine already formed during a run with the glycine added and so on for the higher peptides. As the last two columns show, *this is not due to an inherently higher reactivity of the peptide anions* toward the anhydride in comparison with glycine, but rather to the fact that the second ionization of di- and triglycine occurs at less basic pH values and there is more anion in proportion present at pH 4.74. The *corrected rate constants*, referred to the anions, are in the *reverse order:* 12:1.6:1. Likewise, anhydro-N-carboxyalanine reacts more than three times as fast with alanylalanine at pH 4.74 as with alanine, although the anion of the latter is the more reactive by a factor of almost eight.

A regularity is discernible in the anion rate constants when a "Brønsted plot" is made of the logarithms of the rate constants *referred to pure anion* against the logarithms of the second ionization constants, the measure of the thermodynamic basicity of the amino groups. The table contains data for three compounds with amino groups on primary carbon atoms reacting with anhydro-N-carboxyglycine and for three compounds with amino groups on secondary carbon atoms reacting with anhydro-N-carboxyalanine. Each class of amino compound determines a straight line (Fig. 1), the rates for the secondary amino acids and peptides being slower than for comparably basic primary compounds. In the case of the one amino acid examined which has an amino group on a tertiary carbon atom, the point if plotted would lie below either line. Toward alanine and leucine the reactivities of anhydro-N-carboxyglycine and the corresponding alanine derivative do not appear to be very different. Also plotted in Fig. 1 are the rate constants for three reactants in the "secondary" class, from Part II (see following paper).

The Possibility of Controlled Peptide Syntheses in Aqueous Solution.—The selective reaction of anhydro-N-carboxyglycine with amino acids in aqueous solution raises the question whether it would be possible to control this process with enough precision to synthesize a peptide step by step by the successive addition of a series of N-carboxyanhydrides to a growing peptide in solution in water without isolating the peptide at each step. Obviously this would require very high yields in each step in order to be feasible for chains of any length. Our measurements show that there are two competing reactions of importance to interfere with the clean production of a desired peptide. One of these is the reaction of the anhydride with hydroxyl ion, the other is the reaction of the product peptide with anhydride to give the peptide of one more amino acid unit. The rate of uncatalyzed or buffer-catalyzed hydrolysis can be negligible in the pH range above 7.

As far as the reaction with hydroxyl ion is concerned, we did not succeed in measuring its rate. We might attempt to estimate it by taking advantage of the relationship, shown in Fig. 1, between the strength of the basic amino group of an amino acid or peptide and its rate of attack on anhydro-N-carboxyglycine, extrapolating the glycine line to the right to an abscissa of 15.74 corresponding to the basic strength of the hydroxyl ion. This is an unjustified procedure, since the Brønsted relation holds only among acids or bases of the same chemical type, and there is reason to think that for a given basic strength a primary amine should be a more powerful reagent in attack on an anhydride carbonyl group than a corresponding oxygen reagent. The rate constant estimated in this way, 1.6×10^6 l./mole sec., is probably a generous upper limit for purposes of predicting the favorable conditions for producing dipeptide with a minimum of hydrolysis.

Since we know the rate constants for uncatalyzed hydrolysis and for reaction of the anhydride with glycine as a function of pH, we can make a hypothetical calculation to the effect that

$$\text{rate of hydrolysis} = [\text{A}]0.00041 + k_{OH}10^{pH-15.74}$$

$$\text{rate of diglycine formation} = \frac{2330\ [\text{A}]\,[\text{G}]}{1 + 10^{10.53-pH}}$$

By differentiating to make the ratio of the second rate to the first a maximum, we find that the pH should be most favorable around 8, at which point diglycine formation should be favored over hydrolysis by a factor of 3.3 times the glycine concentration. This factor is not very sensitive to pH in this region, being adversely affected by the constant water hydrolysis in the more acid media and by the fact that the hydroxyl ion concentration continues rising beyond pH 10–11 where the concentration of the reactive form of the amino acid ceases to in-

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crease. The results reported below (Table IV) show that hydrolysis by hydroxyl ion cannot be as extensive as this, so that $K_{OH} < 1.6 \times 10^6$.

TABLE IV

ATTEMPTS AT SYNTHESIS OF DIPEPTIDES FROM ANHYDRO-N-CARBOXYGLYCINE AND GLYCINE AT 0°

Solution	*p*H[a]	% polymer with anhydride alone	G = final concn. glycine,[b] $M \times 10^2$	100 (1–50 G) % dipeptide (side reaction → triglycine)[d]	100 (1–12.5 G) % dipeptide (side reaction → glycine)[d]
0.174 N $Ba(OH)_2$	(13.2)	11	5.5	0	31
0.50 M Na_2CO_3	11.71	18	5.4	0	33
1.0 M NaH_2BO_3 + 0.2 M H_3BO_3	10.89	31	0.65	68	91
0.5 M NaH_2BO_3	10.61	50	0.35	83	96
0.5 M Na_2CO_3 + 0.5 M $NaHCO_3$	(10.3)	10	>5.5	0	31
Catalytic amount $Ba(OH)_2$	(9.5)	98	3.0[c]	0	63

[a] *p*H values are those of the solution before the addition of anhydride or amino acids. Values in parentheses are calculated. Others were measured at 28° using a Beckman *p*H meter with glass electrode for solutions of *p*H 10. [b] Initial concentrations of all solutions: 4.0×10^{-2} M glycine and 4×10^{-2} M N-carboxyglycine anhydride. [c] Calculated from a reaction where two portions of glycine anhydride were used in an attempt to synthesize triglycine. [d] If anhydride (A) reacts exclusively with either glycine (G) to yield diglycine (GG) or diglycine to yield triglycine (GGG) and zero subscripts denote concentrations at t =0, then at the end of the reaction: (G) + 2(GG) + 3(GGG) = $(A)_0 + (G)_0 = 0.08$. Since $(A)_0 = (G)_0$ in all cases, (G) = (GGG), and 4(G) + 2(GG) = 0.08, so that (GG) = 0.04 − 2(G) and $(GG)/(A)_0 = (0.04 - 2(G))/0.04 = 1 - 50(G)$. In similar fashion, if A reacts only with hydroxyl ion to yield G or with G to yield GG, then (G) + 2(GG) = 0.08, (GG) = 0.04 − (G)/2 and $(GG)/(A)_0 = 1 - 12.5(G)$.

The competition between glycine and the desired product, glycylglycine, for reaction with the N-carboxyanhydride can be estimated more reliably and is more serious. We have observed that because of the lower basicity of glycylglycine (pK_2 8.86) in comparison to glycine (pK_2 10.53), the dipeptide appears to be the stronger competitor toward the anhydride when examined in the buffer of *p*H 4.75. This situation should be reversed at *p*H 10–11, where both amino compounds are largely in their reactive forms, but the ratio between the rates of formation of diglycine and triglycine can never exceed 2330/311 (= 7.5) times the ratio of glycine and diglycine concentrations present (Table III). For this reaction to be useful, it would be necessary that we start with equivalent amounts of glycine (or other desired starting material) and N-carboxyanhydride. The concentration of diglycine in this example would start at zero and would approach a concentration whose ratio to that of glycine was equal to k_G/k_{GG} the ratio of the two rate constants. At the time of total consumption of the anhydride, an amount of tripeptide would have been formed which was equal to that of the glycine remaining unattacked, in this case 12% of the total hydrolysis being neglected. For higher peptides, where the differences between members of the series become less, the outlook is correspondingly less encouraging.

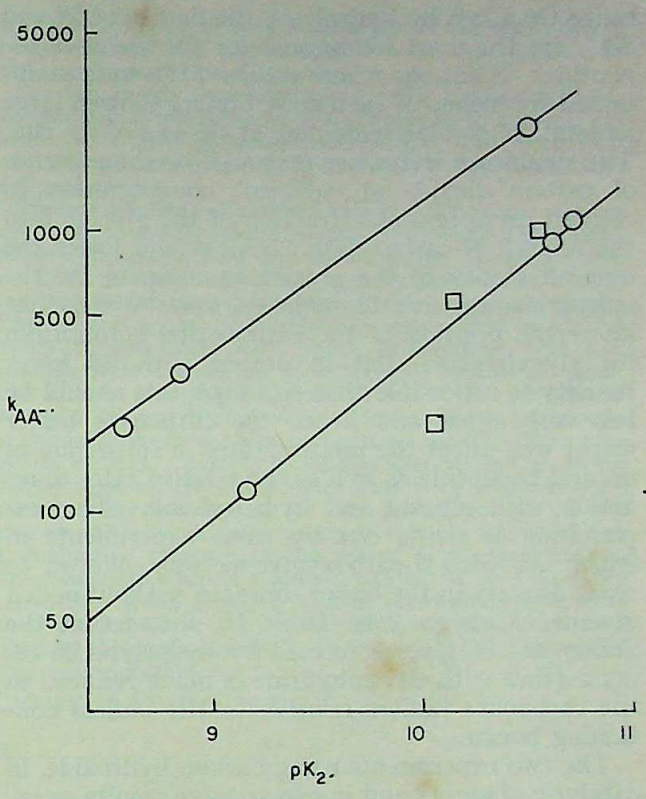

Fig. 1.—Logarithmic relationship between k_{AA^-}, the second-order rate constant for reaction in water at 0° between an anhydro-N-carboxy-amino-acid and an amino acid or peptide anion, and pK_2, the second ionization constant of the amino acid: upper line, anhydro-N-carboxyglycine with triglycine, glycylglycine and glycine anions; lower line, anhydro-N-carboxyalanine with alanylalanine, alanine and leucine (see Table III); square points, data from Part II, THIS JOURNAL, 79, 2159 (1957): phenylalanine, methionine, aspartic acid.

The experiments on peptide synthesis in water bear out these conclusions in general. Quantitative experiments were made in which, in each of a series of solutions of different *p*H, equimolar amounts of glycine and anhydro-N-carboxyglycine were introduced and the reaction was allowed to run to completion. The remaining glycine was then determined by the Van Slyke ninhydrin technique, by which amino acid can be estimated in the presence of peptides which do not evolve carbon dioxide on treatment with the reagent. Table IV lists the results obtained.

In a reaction yielding only hydrolysis and dipeptide formation there will be two molecules of amino acid remaining in excess for each anhydride molecule hydrolyzed, for this reaction not only wastes anhydride but adds to the store of amino acid. In a reaction yielding only di- and tripeptide, the amount of tripeptide will be equal to the amount of amino acid remaining unattacked. In Table IV the yield of the desired dipeptide has been computed on both assumptions and recorded in the last two columns.

Two solutions in which the *p*H was controlled by borate buffers at *p*H's of 10.89 and 10.61 gave results in the expected range. The above considerations having shown that competition from tr peptide formation is more important in this *p*

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range than loss by hydrolysis, the figures of 68 and 83% are the most likely ones for the yields of dipeptide. Solutions where similar *p*H's were maintained by means of carbonate buffers showed large amounts of glycine remaining at the end of the run. The significant difference may well be the presence of carbon dioxide at sufficient concentration to convert an appreciable fraction of the glycine into the related N-carboxylate. This would lower the over-all ability of the glycine to compete for the anhydride, relative to hydroxyl ion. We do not know the position of the carbonation equilibrium for glycylglycine, but in accord with its lower basicity it is possible that this dipeptide should be less carbonated and hence the carbonate buffer might well affect the relative rates of formation of di- and tripeptide as well as the relative rates of reaction with glycine and hydroxyl ion. This explanation is borne out by some experiments in which anhydro-N-carboxyglycine was allowed to react directly in the buffer solutions without added glycine. Column 3 of Table IV shows that the ability of the glycine formed by hydrolysis to react further with the anhydride is much reduced in the carbonate buffers relative to the buffers containing borate.

The two experiments using barium hydroxide, in catalytic amounts and in excess, gave results as expected from the above kinetic discussion. With the small amount of base, the *p*H began at 9.5 and dropped. Polymerization was so important that only 2% of amino acid remained in the control experiment without added glycine. Obviously here the formation of tri- and higher peptides is the important side reaction and the yield of dipeptide from the 1:1 reaction mixture is zero, as indicated in column 5. In 0.174 *N* barium hydroxide, anhydride alone yields 89% of glycine. Hydrolysis is therefore rapid, as expected, and the results from the 1:1 experiment mean a 31% yield of diglycine. The upshot of these experiments is that the conditions for selective formation of glycylglycine are rather critical, and the selectivity is not sufficient to make this a useful general method for the stepwise synthesis of polypeptides.

Experimental

Reagents.—Various methods were used for preparing the Leuchs anhydrides but by far the most satisfactory was the method of Ben-Ishai and Katchalski[10] using the N-carbobenzoxy-amino acids and phosphorus tribromide. The purity of the anhydrides was best determined by the quantitative measurement of the carbon dioxide liberated. This was done during each kinetic run and consistent values were obtained from the various samples of anhydrides used. The anhydrides were stored in a desiccator over phosphorus pentoxide, being stable under these conditions for several weeks. In practice, however, the anhydrides were used within three days of the final recrystallization.

Benzyl chloroformate was obtained from three sources. It was prepared[11] by the method of reference 11, some was purchased from the Mann Research Laboratories and some was kindly donated by Dr. E. R. Blout.

N-Carbobenzoxyglycine was prepared from benzyl chloroformate and glycine by the method of reference 11.

N-Carbomethoxyglycine was prepared by the method described[12] by Schramm.

N-Carbethoxyglycine was prepared from ethyl chloroformate and glycine in a procedure similar to that used for N-carbomethoxyglycine; the melting point of the crude material was 74–78°.

Anhydro-N-carboxyglycine was prepared by the method of Katchalski. The crude product was recrystallized four or five times from dry ethyl acetate. Good yields of the anhydride were also obtained with 20.9 g. of N-carbobenzoxyglycine and 25 g. of phosphorus pentachloride dissolved in 150 ml. of dry ethyl acetate at 0°. The mixture was shaken every two or three minutes and the temperature maintained at 0° for 0.5 hr. The solution was allowed to warm to room temperature and was filtered to remove excess phosphorus pentachloride. The ethyl acetate was removed under vacuum at temperatures up to 60°. After the removal of most of the ethyl acetate, the residue was recrystallized from ethyl acetate.

N-Carbomethoxy-α-aminoisobutyric acid was prepared by the method of Schramm.

Anhydro-N-carboxy-α-aminoisobutyric acid was made from N-carbomethoxy-α-aminoisobutyric acid and thionyl chloride, according to the method of Schramm. The product was recrystallized six times from a benzene–cyclohexane mixture.

N-Carbomethoxy-*dl*-alanine, m.p. 75–77°, was prepared according to the method of Schramm.

N-Carbobenzoxy-*dl*-alanine, N-carbobenzoxy-*d*-alanine and N-carbobenzoxy-*l*-alanine were prepared in 90% yield by the "Organic Syntheses" procedure, described for N-carbobenzoxyglycine. The product was recrystallized by dissolving in chloroform and adding petroleum ether. The melting points were 111–115°, 85.2–86.0° and 85.0–85.5°, respectively.

Anhydro-N-carboxy-*dl*-alanine was prepared from N-carbobenzoxy-*dl*-alanine and phosphorus pentachloride, following Schramm's directions for the preparation using N-carbomethoxy-*dl*-alanine. The product was recrystallized several times from dry benzene, although it was necessary to seed each time. Several attempted preparations from the N-carbomethoxy-amino acid were unsuccessful, as was the attempted use of thionyl chloride or phosphorus tribromide on the N-carbobenzoxy-*dl*-alanine.

Anhydro-N-carboxy-*d*-alanine and anhydro-N-carboxy-*l*-alanine were prepared easily by the method of Katchalski from the corresponding N-carbobenzoxyalanine and phosphorus tribromide. The product was recrystallized three or more times from dry benzene. It was occasionally necessary to add dry petroleum ether to cause crystallization of the anhydrides.

Benzene, ether and petroleum ether (30–60°) were reagent grade dried over sodium wire.

Cyclohexane was Eastman Kodak Co. technical grade distilled and dried over sodium wire.

Reagent quality ethyl acetate was dried over calcium hydride and distilled.

Glycine and *dl*-alanine were obtained from the Eastman Kodak Co. and were twice recrystallized from ethyl alcohol–water solution, before being used in kinetic runs. These and all the other amino acids and peptides were dried at 110° before use.

α-Aminoisobutyric acid and *l*-leucine were obtained from Eastman Kodak Co. and were recrystallized once from an ethyl alcohol–water solution before being used in kinetic runs.

d-Alanine was obtained from Schwartz Laboratories and was used without further purification; $\alpha^{25}D$ −14.8 (c = 2 in 2 *N* hydrochloric acid).

l-Alanine was obtained from Schwartz Laboratories, $\alpha^{25}D$ +14.3° (c = 2 in 2 *N* hydrochloric acid).

Glycylglycine was obtained from the Nutritional Biochemical Corporation and was recrystallized from 50% ethyl alcohol before use.

Glycylglycylglycine was obtained from the Nutritional Biochemical Corporation and was recrystallized from water.

dl-Alanyl-*dl*-alanine was obtained from the Nutritional Biochemical Corporation and was used without further purification.

Kinetic Procedure.—The reaction vessel was a 250-ml. erlenmeyer flask equipped with a side arm to which a mercury manometer could be attached through a 10/30 joint. The mercury manometer was made of 1-mm. capillary tubing with a reservoir made of 20-mm. tubing, so that the change in height in the reservoir would be negligible during

(10) E. Ben-Ishai and E. Katchalski, THIS JOURNAL, **74**, 3688 (1952).

(11) *Org. Syntheses*, **23**, 13 (1943).

(12) C. H. Schramm, Thesis, Harvard University, 1947.

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the course of a run. Evacuation was accomplished through a stopcock attached to the arm between the flask and the manometer. The erlenmeyer flask was closed with a 24/40 cap equipped with a glass hook from which a glass bucket containing the anhydro-N-carboxy-amino acid could be suspended by a platinum wire.

First the weighed amino acid or peptide, when any was used, was added to the erlenmeyer flask, followed by the water or buffered solution (50 ml. for the runs with optically active anhydro-N-carboxy-alanine and 100 ml. in all other cases). The system was assembled using silicone stopcock grease, and the reaction flask was immersed in an ice-bath for 1 hr. before the start of the run. The ice-bath, stirred by air and surrounded by two concentric beakers, was so arranged as to permit magnetic stirring through the bottom by means of an Arthur H. Thomas Co. magnetic stirrer and a plastic coated magnet within the reaction flask.

After the attainment of thermal equilibrium, a weighed amount of the anhydride was suspended from the cap and the system was evacuated. After three or four minutes, the anhydride was dropped into the solution by agitation of the reaction vessel and the run was begun. The manometer was always tapped immediately before reading and its response characteristics were determined before use. The pressure at infinite time was that observed after at least ten times the half-life.

In studying the decomposition of the Siegfried salts, a solution of amino acid in barium hydroxide was placed in the reaction flask and carbon dioxide was bubbled through the solution until added phenolphthalein turned colorless. In this instance, acetic acid or sulfuric acid was suspended in the glass bucket and was dropped into the basic solution at zero time to start the reaction.

For the kinetic experiments using the volume method, the manometer was replaced by a connection to a 50-ml. gas buret and a butyl phthalate manometer. The connection was made almost completely from glass with two short joints of Tygon tubing.

Product Studies.—Exactly 5 ml. of 0.400 molar glycine and 50 ml. of an appropriate buffer were placed in a stoppered 250 ml. erlenmeyer flask and cooled to 0°. Exactly 0.202 g. (0.002 mol.) of anhydro-N-carboxy-glycine was added, and the mixture was rapidly stirred with a magnetic stirrer. After several hours the solution was neutralized to *p*H 7.0 (brom thymol blue) with dilute hydrochloric acid and quantitatively transferred to a 250 ml. volumetric flask. The solution was acidified with 50 ml. of *p*H 4.5 acetate buffer (1 *M*) and diluted with water to 250 ml. A sample of the solution (5 ml.) was analyzed by the Van Slyke ninhydrin method. Acetate buffer was used instead of citrate buffers since all the kinetic runs that were analyzed were already buffered with acetate. The procedure used did not give quantitative yields of carbon dioxide but was helpful as a qualitative measure of the amino acid concentration. Thus standard alanine solutions yielded 98 ± 1% of the calculated carbon dioxide, whereas standard glycine solutions yielded 92 ± 3%. Glycylglycylglycine, when analyzed by this method, gave 0.074 mole of glycine per mole of glycylglycylglycine.

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

A Kinetic Study of the Leuchs Anhydrides in Aqueous Solution. II[1]

BY PAUL D. BARTLETT AND DONALD C. DITTMER

RECEIVED SEPTEMBER 7, 1956

Rate constants are reported for the reaction in water at 0° between anhydro-N-carboxy-DL-alanine and DL-phenylalanine, DL-methionine, DL-aspartic acid, L-histidine, L-cysteine and glutathione. Cysteine reacts 45 times as fast as methionine. In the reaction of cysteine with anhydro-N-carboxy-DL-phenylalanine, the concentration of free SH groups shows an initial decline followed by a return to its original value. This is interpreted as an initial reaction of the anhydride with the thiol group followed by an intramolecular transfer of the phenylalanyl group from sulfur to nitrogen. Glutathione shows a similar rapid reaction, but the thiol titer drops much more and is slow to return, as would be expected from the less favorable location of groups for an intramolecular acylation. The effect of conditions upon the reaction of alanine with both anhydro-N-carboxy-DL-alanine and anhydro-N-carboxy-DL-phenylalanine in aqueous solution has been studied.

It was shown in Part I[2] that the anhydro-N-carboxy derivatives of certain amino acids reacted in aqueous solution with amino groups so rapidly as to raise the hope that this might be a useful method for controlled, stepwise peptide synthesis. In a further exploration of systems of this kind, we have measured the rate constants listed in Table I between anhydro-N-carboxy-DL-alanine and amino acids of different types. The rate constants were determined as described in Part I.[2] An attempt has been made in Table I, as in the cases previously reported, to refer the rate constants to the active anion of the amino acid by means of the published second ionization constants of the amino acids in question.

Table I shows that cysteine and glutathione react substantially faster with anhydro-N-carboxy-alanine than does the closely comparable methionine which lacks the sulfhydryl group. Some experiments were carried out in which the sulfhydryl group was titrated with iodine during the reaction between cysteine and anhydro-N-carboxy-DL-phenylalanine. The results are shown in Fig. 1, together with the results of a similar run on the tripeptide glutathione. In both cases there is an initial attack of the carboxy-anhydride on the sulfhydryl group. In the case of cysteine, the sulf-

TABLE I

REACTIONS OF ANHYDRO-N-CARBOXY-DL-ALANINE AT 0° IN ACETATE BUFFER (0.102 *M* NaOAc, 0.0875 *M* HOAc) AT *p*H 4.75

Added compound	k_1, sec.$^{-1}$ × 10^3	k_{AA} l./mole sec. × 10^3	pK_2[c]	k_{AA^-}, l./mole sec.
None	0.715			
DL-Phenylalanine	.772	1.0	10.06	200[d]
DL-Methionine	.988	2.3	10.14	565[d]
DL-Aspartic acid	.837	1.4	10.53	840[d]
L-Cysteine	14.8[a]	103	9.11	1770
L-Histidine	6.25	61[b]	10.10	1370
Glutathione	2.83	68	9.59	4640

[a] Did not show clean first-order kinetics. [b] *p*H increased during run. [c] E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publishing Corp., New York, N. Y., 1943, p. 84 ff., assuming same temperature coefficient as for glycine and alanine. [d] Plotted in Fig. 1, Part I, THIS JOURNAL, 79, 2153 (1957).

(1) This work was supported by the Office of Naval Research under Contract No. N5ori-07653, Task 53, with Harvard University, 1953–1954.

(2) P. D. Bartlett and R. H. Jones, THIS JOURNAL, 79, 2153 (1957).

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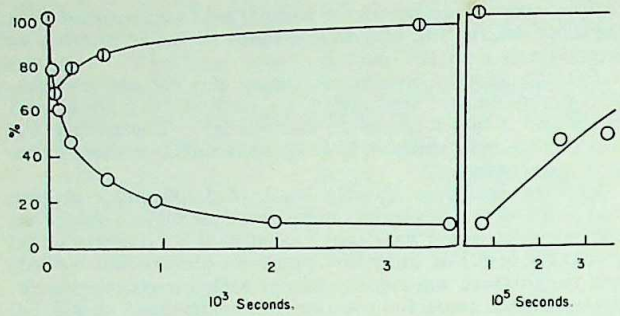

Fig. 1.—Decline and return of sulfhydryl titer during reaction of anhydro-N-carboxy-*dl*-phenylalanine with cysteine (dashed circles) and with glutathione (open circles). Note break in time scale.

hydryl titer had dropped at the end of one minute to 67% of that initially present but had already begun to rise again. The rapid formation of thioester evidently is followed up immediately by a transfer of the acyl group from sulfur to nitrogen with the formation of a normal peptide. Such transfer reactions have been observed before,[3] being a consequence of the reactivity of thioesters and the fact that such a transfer can take place here by way of a six-membered cyclic transition state.

In the case of glutathione the sulfhydryl titer also drops but does not return nearly so rapidly. At the end of an hour the sulfhydryl titer has reached 9% of that initially present and appears to be still dropping. After 20 hr. the titer is again 9%; after three days it has risen again to 45%. The difference between the cases of cysteine and glutathione would appear to be largely the less favorable situation in the latter case for the transfer of an alanyl group from sulfur to nitrogen internally.

The attempts reported in Part I to achieve high yields in the formation of specific peptides were extended to the use of anhydro-N-carboxy-DL-alanine and anhydro-N-carboxy-DL-phenylalanine. As judged by the amount of amino acid remaining after reaction, the yields obtained from these anhydrides and alanine were never as high as the best yields of glycylglycine under comparable conditions. Experiments were conducted at *p*H 9, 10, 11 and 12, the *p*H being generally controlled by the use of a Beckman auto-titrator. With anhydro-N-carboxy alanine as with anhydro-N-carboxyglycine, the highest yields of dipeptide were obtained at *p*H 10, but these yields never reached 90%. The presence or absence of a borate or phosphate buffer and the use of lithium, sodium or thallium hydroxide as the titrating base produced no marked effect upon the course of the reaction. In the case of anhydro-N-carboxy-*dl*-phenylalanine the yields were consistently below 80% and the sensitivity to *p*H appeared to be somewhat less. These results are all consistent with the view that the aqueous reactions of the anhydro-N-carboxyamino acids are determined by a set of protonation and carboxylation equilibria which are established rapidly compared to the speed of the attack of the water or amino acids upon the anhydride.

(3) T. Wieland, E. Bokelmann, L. Bauer, H. U. Lang and H. Lau, *Ann.*, **583**, 129 (1953).

Experimental

Materials.—DL-Alanine, DL-methionine and DL-aspartic acid were Eastman Kodak Co. White Label grades. DL-Phenylalanine was the C.P. grade obtained from H. M. Co., Ltd. L-Cysteine, glutathione and L-histidine were from the Nutritional Biochemicals Corporation. Benzyl chloroformate was from Mann Biochemicals. N-Carbobenzoxy-DL-alanine and N-carbobenzoxy-DL-phenylalanine were prepared by the method of reference 4. Anhydro-N-carboxy-DL-alanine and anhydro-N-carboxy-DL-phenylalanine were prepared from the corresponding N-carbobenzoxy derivatives and phosphorus tribromide by the method of Ben-Ishai and Katchalski.[5] They were recrystallized from ethyl acetate and petroleum ether. Ethyl acetate was Merck reagent grade dried over calcium hydride.

The manometric kinetic determinations were carried out as described in Part I.

The reactions of L-cysteine and glutathione with anhydro-N-carboxy-DL-phenylalanine were done in an acetic acid–sodium acetate buffer (*p*H 4.66) at 0°. The anhydride was added in 10 ml. of dimethylformamide. Aliquots were taken at various times, quenched in 2 *N* hydrochloric acid and cooled in an ice-bath. A measured amount of standard iodine solution was added to react with the excess SH groups and the excess of iodine was back titrated with standard sodium thiosulfate solution using starch as an indicator. There was no reaction between cysteine and dimethylformamide under the reaction conditions employed. The accuracy of the glutathione reactions was impaired by precipitation early in the reaction.

The solution of the product of reaction between L-cysteine and anhydro-N-carboxy-DL-phenylalanine was oxidized with hydrogen peroxide. The resulting material was submitted to paper chromatography with butanol–acetic acid[6] resulting in three ninhydrin-positive spots. Two of these readily were identified as DL-phenylalanine and cysteic acid. From a large number of paper chromatograms carried out on small aliquots of the solution, the area of the unknown spot was cut out and eluted. The solution of the unknown was evaporated and the α-amino group of the peptide was removed with nitrosyl chloride.[7] The product was then hydrolyzed and chromatographed on paper. One ninhydrin-positive spot appeared which had the same R_f value as cysteic acid. The original dipeptide was accordingly probably DL-phenylalanylcysteine.

CAMBRIDGE, MASSACHUSETTS

(4) H. Carter, R. Frank and H. Johnston, *Org. Syntheses*, **23**, 13 (1943).

(5) E. Ben-Ishai and E. Katchalski, THIS JOURNAL, **74**, 688 (1952).

(6) K. Slotta and J. Primosigh, *Nature*, **168**, 696 (1951).

(7) R. Consden, A. Gordon and A. Martin, *Biochem. J.*, **41**, 590 (1947); F. Sanger and H. Tuppy, *ibid.*, **49**, 463 (1951).

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[Contribution from the Division of Chemistry and Division of Pathology and Microbiology, Medical Units, University of Tennessee]

Seroflocculating Steroids. II.[1] General[2]

By Frederic C. Chang, Robert T. Blickenstaff, Aaron Feldstein,[3a] Jane Ransom Gray, George S. McCaleb[3b] and Douglas H. Sprunt

Received November 20, 1956

The chemical basis for the possible use of a new type of seroflocculation reaction, either for the detection of a disease like cancer or as a general health clearance test, is discussed. In this paper a program of study of the seroflocculating activity of certain steroids is outlined with these alternatives as the goal, and a first report of screening results is given. Accompanying papers III and IV of this series deal with the chemistry and synthesis of compounds reported here.

Although seroflocculation reactions are widely used in medicine for detection of disease, little fundamental knowledge concerning these reactions is available.[4] An understanding of the mechanism of such a reaction entails studying initially: (1) the nature of the substances that function as seroflocculating agents (seroflocculants), (2) the nature of the serum components that are flocculated, (3) the composition of the flocculated material (flocculates) and (4) the conditions under which the reaction takes place. We have been considering some of these factors in a new type of seroflocculation reaction[1,5] which is given by a high percentage of the sera of patients with moderately advanced cancer and of moderately advanced cases of other diseases such as tuberculosis.

Tests on three seroflocculants, the non-saponifiable fraction of cancerous livers,[5] ethyl choladienate[6] and ethyl 3β-chloro-11-cholenate[1] show that they can all be used to detect moderately advanced cancer and other diseases with good precision, but their "sensitivity"[7] was low in many diseases at an early stage, particularly in cancer, and their "selectivity"[7] seemed to decrease with increase in sensitivity. Whether this inverse relationship between sensitivity and selectivity is an inherent property of this series of seroflocculants will determine what applications can be made of the reaction for detection of disease.

Development of the reaction could give rise to two different uses in the detection of disease, depending on which of two alternative chemical situations exists in the serum. Ideally, the reaction would be used to detect specific diseases, or secondarily it might be able to distinguish normal sera from those of a group of diseases and thus be useful as a general health screening test.

From a chemical point of view, the problem can be stated as follows: if the flocculable material in the serum is a component uniquely associated with a specific disease, it would be potentially possible to detect that disease by finding a seroflocculant which will react with the unique component. On the other hand, if the serum component participating in the flocculation reaction is one produced by any of a group of diseases or by a process not necessarily limited to a single disease, then the reaction will be non-specific. In this case, any differences in activity found in flocculants of varying chemical structure will merely be measures of how effectively they combine with the common serum component. Thus, sensitivity appears to be a problem basic to the chemical structure of the flocculant, whereas selectivity is one that concerns the serum component primarily.

There is *a priori* no way of knowing which of these alternative situations prevails for any particular disease. In syphilis, at least, a unique component (or situation) apparently exists since a serological reaction for detection of syphilis is known and widely used. For cancer, there is no previous evidence of a unique cancer component detectable serologically. But because of the obvious importance of a good test for the detection of cancer, the existence of evidence that can be interpreted favorably,[8] and because we have a feasible method of study through the finding of a seroflocculant of known structure, an investigation of this problem appears to be desirable.

Our program involves a search for a sensitive flocculant based on the assumption that the seroflocculation reaction is a useful method of detecting early disease. The completed research will furnish information as to whether it will be possible to detect a specific disease like cancer or whether it will be useful as a health clearance test.

The two substances[6] first studied in this reaction were both oils. The chemical composition of the liver fraction is complex and largely unknown,[9] and

(1) Paper I of this series, This Journal, **76**, 3213 (1954).

(2) This investigation was supported in part by grants (CS-9053 and C-2249) from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

(3) (a) Worcester Foundation for Experimental Biology, Shrewsbury, Mass.; (b) Department of Chemistry, University of Arkansas, Fayetteville, Ark.

(4) L. J. Zeldis and S. C. Madden, *Ann. Review Biochem.*, **17**, 340 (1948); A. Saifer, *Am. J. Med.*, **13**, 730 (1952).

(5) H. S. Penn, *J. Natl. Cancer Inst.*, **12**, 1389 (1952).

(6) A. H. Dowdy, H. S. Penn, G. Hall and A. Bellamy, *Proc. Am. Assoc. for Cancer Research*, **1**, 12 (1954).

(7) The term "sensitivity" is used to indicate efficiency in confirming cancer (diagnosed by biopsy); "selectivity" to denote the degree with which a test is free from giving "false positives." Quotation marks will be omitted when these terms are used subsequently in this paper.

(8) C-Reactive protein antiserum parallels ethyl 3β-chloro-11-cholenate in activity [D. H. Sprunt, W. M. Hale, F. C. Chang, S. G. Richmond, C. C. Erickson, *Science*, **122**, 273 (1955)], but there are differences suggestive that C-Reactive protein and a cancer component are similar but not identical. Orosomucoid, a glycoprotein known to increase in the sera of patients with carcinoma [H. Goodman, S. Brennan and W. J. Simpson, *Proc. Am. Assoc. for Cancer Research*, **2** 111 (1956)], is immunologically distinct from C-Reactive protein. Both orosomucoid and C-Reactive protein seem to belong to a group of abnormal protein substances, another one of which might be unique for cancer. Furthermore, the inverse sensitivity and selectivity relationship mentioned earlier with seroflocculants tested does not hold strictly, suggesting that the serum components flocculated have chemical differences.

(9) R. F. Riley, M. Hokama, P. Kratz and H. S. Penn [*Federation Proc.*, **15**, 636 (1956)] recently reported preliminary results on the

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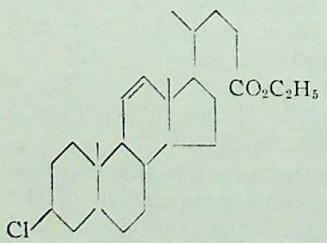
our experience with the desoxycholic acid-derived "antigen"[6,10]—an uncrystallizable oil of variable activity and stability—convinced us of its heterogeneous nature, although it is without doubt chiefly a mixture of ethyl choladienates. Thus it was desirable to find a stable active compound of known structure and our attention was first directed toward the preparation of a pure ethyl choladienate.

The pyrolytic methods used by Wieland[11] when applied to ethyl desoxycholate indeed gave active, crystalline material but appeared unpromising as a means of obtaining a pure isomer. Since elimination reactions involving ionic mechanisms have produced mixtures differing from products of pyrolysis, we decided to try dehydrotosylation, a method often used for introducing unsaturation in steroids.[12] When ethyl Δ^{11}-lithocholenate,[1] refluxed with *p*-toluenesulfonyl chloride in pyridine, yielded a crystalline product of constant melting point and good activity, we naturally assumed that we had in hand an ethyl choladienate. However, the material contained chlorine and was demonstrated to be a constant melting mixture of ethyl 3β-chloro-11-cholenate (28)[13] and unsaturated matter. A separate synthesis of 28 confirmed this. This compound 28, which showed the best seroflocculating activity of all the substances we had tested, was the first active compound of defined structure. Moreover, it had the requisite characteristics of stability, availability and reproducibility to use as a comparison standard for evaluation of other substances.

The preparation of a pure ethyl choladienate was pursued further and ethyl 3,11-choladienate (45) has been obtained by a satisfactory method.[14] Compound 45 when pure turned out to be somewhat too insoluble to be tested satisfactorily by the original test conditions, but the corresponding methyl ester (46) was found to have good activity. With 28 and 46, two compounds of known structure to serve as basic models, it was possible to plan a structure–activity study on a less empirical basis than a random screening would be.



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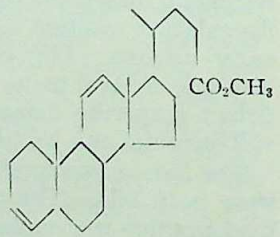

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The program followed is to prepare (or collect) accessible structural variations of these two substances and to test these related compounds for seroflocculating activity in a short screening test. The test, described briefly below, is designed to find compounds with the highest general sensitivity without regard in the first instance to their selectivity. This information, which has given some indications of the structural features associated with good activity, will be a guide in further work. When a sufficient number of representative compounds of high sensitivity but of different chemical structure is found, a parallel clinical test on a larger scale using these compounds will show whether they show selectivity and incidentally answer the question of the existence of a unique cancer component. The results, furthermore, should point to the significant molecular structural features which would be incorporated in the designing of more efficient flocculants. These in turn should facilitate the isolation of the hypothetical cancer component, the study of which would be of fundamental biochemical importance.

This paper is an interim report giving results of the screening to date. The two accompanying papers are concerned with the syntheses of compounds reported here.

Screening Method.—(Only a summary of the method is given; the testing particulars will be described in detail elsewhere.) The tests were performed by a modification of the original method[5]; only one-half the amount of flocculant and different serum dilutions are used. The test is a simple one to perform: a suspension, prepared from an alcoholic solution of the flocculant, a trace of cholesterol and buffered saline solution, is combined with the test serum, diluted serially and centrifuged. The tubes are shaken and read. A good positive test is one in which floccules are formed and the solution remains sparkling clear; a negative test is one in which there are no floccules and the solution is turbid.

Test sera used in the screening varied from three to ten depending on the supply of flocculant available. Cancer sera and normal sera were included in the same test run. Test cancer sera are from cancers (confirmed by biopsy) that give good tests with the standard flocculant, ethyl 3β-chloro-11-cholenate[14a] (28); test normal sera are from apparently healthy individuals and have given consistently negative tests with 28.

Screening Results.—Compounds are classified below in three groups. Group A consists of compounds which clearly can distinguish between test positives and normals and therefore have the same order of activity as the standard 28. Group B are compounds that show differences between the positive and normal standards but not as distinctly as those in group A. In general, there are floccules in the positive tubes but the solution is not clear. These are substances classified as lower activity compounds. Group C compounds do not distinguish between positive and normal sera; almost all give tests that remain turbid and have no floccules. A few flocculants which give positive tests on all sera indiscriminately are also included among this group.

(10) We are indebted to Drs. Dowdy and Penn for making available to us procedures for preparing this "antigen."

(11) H. Wieland and W. Kapitel, *Z. physiol. Chem.*, **212**, 269 (1932).

(12) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 692.

(13) Compounds mentioned in this series of papers are numbered according to the consecutive order in which they are described in the Experimental Sections of papers III and IV.

(14) Paper IV of this series, THIS JOURNAL, **79**, 2167 (1957).

(14a) Merck and Company, through the kindness of Dr. K. Pfister, 3rd, provided a generous supply of the compound for these tests.

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Group A

No.	Compound	Source (ref. no.)
28	Ethyl 3β-chloro-11-cholenate	15
27	Methyl 3β-chloro-11-cholenate	15
31	Ethyl 3β-chloro-9(11)-cholenate	15
30	Methyl 3β-chloro-9(11)-cholenate	15
47	Methyl 3,9(11)-choladienate	14
45	Ethyl 3,11-choladienate	14
46	Methyl 3,11-choladienate	14
38	Ethyl 3β-chloro-5-bisnorcholenate[16]	15
17	Ethyl 3α,12α-diacetoxycholanate	15
19	Ethyl 3β-chloro-12α-acetoxycholanate	15

Group B

	Ethyl cholanate	17
48	Methyl 3-cholenate	14
49	Ethyl 3-cholenate	14
50	Methyl 9(11)-cholenate	14
51	Methyl 11-cholenate	14
52	Ethyl 11-cholenate	14
	Methyl 3α-acetoxy-9(11)-cholenate	18
12	Ethyl 3α-acetoxy-9(11)-cholenate	15
11	Ethyl 3α-acetoxy-11-cholenate	15
13	Methyl 12α-acetoxy-3-cholenate	15
14	Ethyl 12α-acetoxy-3-cholenate	15
	Methyl 3α,12α-diacetoxycholanate	19
	Ethyl 3β-chlorocholanate	1
21	Ethyl 3α-tosyloxycholanate	15
18	Methyl 3β-chloro-12α-acetoxycholanate	15

Group C

1	Methyl lithocholate	15
2	Ethyl lithocholate	15
3	Methyl 12α-hydroxycholanate	15
4	Ethyl 12α-hydroxycholanate	15
5	Ethyl 3α-hydroxy-9(11)-cholenate	15
	Methyl 3α-hydroxy-11-cholenate	20
	Ethyl 3α-hydroxy-11-cholenate	1
6	Methyl 3β-hydroxy-5-bisnorcholenate[21]	15
7	Ethyl 3β-hydroxy-5-bisnorcholenate[21]	15
8	Ethyl 3α-acetoxycholanate	15
9	Methyl 12α-acetoxycholanate	15
10	Ethyl 12α-acetoxycholanate	15
15	Methyl 3β-acetoxy-5-bisnorcholenate	15
16	Ethyl 3β-acetoxy-5-bisnorcholenate	15
20	Methyl 3α-tosyloxycholanate	15
22	Methyl 3α-tosyloxy-9(11)-cholenate	15
23	Methyl 3α-tosyloxy-11-cholenate	15
24	Ethyl 3α-tosyloxy-11-cholenate	15
	Ethyl desoxycholate	22
25	Methyl 3α-tosyloxy-12α-hydroxycholanate	15
26	Ethyl 3α-tosyloxy-12α-hydroxycholanate	15
29	3β-Chloro-11-cholenic acid	15
32	3β-Chloro-9(11)-cholenic acid	15
33	Methyl 3β-chlorocholanate	15
34	3β-Chlorocholanic acid	15
35	Methyl 3β-chloro-12α-hydroxycholanate	15
36	Ethyl 3β-chloro-12α-hydroxycholanate	15
39	Ethyl 12α-benzoxycholanate	15
	Methyl 3α-benzoxy-12α-hydroxycholanate	23
40	Ethyl 3α-benzoxy-12α-hydroxycholanate	15
41	Ethyl 3α-12α-dibenzoxycholanate	15
42	Ethyl 3-ketocholanate	15
	3-Ketocholanic acid	24
43	Methyl 3-keto-9(11)-cholenate	15
44	Methyl 3-keto-11-cholenate	15
	Methyl 3α-carbethoxyoxy-12-keto-9(11)-cholenate	25
53	Methyl 12α-hydroxy-3-cholenate	14
54	Ethyl 12α-hydroxy-3-cholenate	14

Tentative Conclusions.—The compounds reported here are all derivatives of cholanic acid with the exception of several bisnorcholanic acid compounds. Compounds derived from other parent steroids are also being investigated and will be reported in the future. Many of the compounds on these lists were intermediates prepared during the course of synthesis of certain desired structures but were nevertheless included in the testing to provide additional information. Although speculation, at this stage, of the basic nature of the flocculation reaction seems premature and many more structurally different compounds should be examined before profitable conclusions can be drawn, certain empirical deductions already stand out: (1) only esters show activity, free acids are inactive; (2) with one exception (3,11-choladienate) the ethyl esters are more active than the corresponding methyl esters; (3) active groupings are unsaturation, chloro and acetoxy, and two such groups are needed for high activity; (4) inactive groups are hydroxy, tosyloxy, benzoxy and keto, and one such group can counteract the effect of an active group.

Whether a correlation exists between some well-defined physical property of the flocculants and their seroflocculating activity has not been investigated, and obviously this can be done more intelligently when the best flocculants have been discovered. However, from purely qualitative observations made during the handling of these compounds, it can be said that most likely there is no simple relationship between their solubilities and activity.

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Memphis 3, Tenn.

(15) Paper III of this series, This Journal, **79**, 2164 (1957).

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[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY AND DIVISION OF PATHOLOGY AND MICROBIOLOGY, MEDICAL UNITS, UNIVERSITY OF TENNESSEE]

Seroflocculating Steroids. III.[1] Chloro and Other Bile Acid Derivatives[2]

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For study of their seroflocculating activity, a number of 3β-chloro bile acid derivatives were prepared by a new method involving replacement of a tosylate group in pyridine with pyridinium chloride. Several new acetates, tosylates and other related compounds are reported.

When the synthesis of ethyl 3β-chloro-11-cholenate (28)[4] by the method previously described[5] was attempted on a larger scale, the yield and quality of product were found to be considerably lowered. Various other direct methods for preparing halides also proved unsatisfactory for this compound. The presence of 28 among the products of a tosyl chloride reaction in pyridine described in the preceding paper[1] furnished a clue for a satisfactory new method for preparing the compound.

Since 28 obviously resulted from an intermediate tosylate, the commonly used reaction of a tosylate with lithium chloride in acetone (and in dioxane) was tried on the tosylate of ethyl 3α-hydroxy-11-cholenate. Intractable mixtures of unsaturated and chloro compound resulted. However, by substituting pyridine and pyridine hydrochloride for the solvent–halide system, a good quality chloro product was obtained in 51% yield. The yield is only moderate, and the superiority of the method lies in the purity of the product, which is very little contaminated by dienic impurity. A mixture of chloro compound containing more than traces of diene is separated only with much difficulty; the inferior products obtained in other halogenation methods are such mixtures. The reaction temperature is an important factor, as previous studies on replacement reactions would suggest,[6] and at elevated temperatures undesirable mixtures of chloro and dienic compounds are obtained. At temperatures between 78 and 90° the substitution reaction proceeds at a satisfactory rate, with little competition from the elimination reaction.

Methyl 3β-chlorocholanate, methyl and ethyl 3β-chloro-11-cholenate, methyl 3β-chloro-9(11)-cholenate and methyl 3β-chloro-12α-hydroxycholanate have all been prepared by this method, which we are studying further with the view of its use as a general method of preparing halides.[7]

For the preparation of ethyl 3β-chloro-9(11)-cholenate, because of the low melting points and poor crystallizing behavior of the corresponding 3α-hydroxy and 3α-tosyloxy compounds which are intermediates in the synthesis, conversion from the methyl ester is preferred. The sequence of reactions, part of which is also illustrative of other chloro compounds mentioned above, is shown.

Puzzling changes in melting point were encountered during crystallizations of several of the ethyl ester tosylates when methanol was used as solvent at 50°. Since the fractions continued to give correct analyses, replacement of tosylate group was not taking place, and ester interchange was not suspected, because numerous other ethyl esters in this related group of compounds can be crystallized unchanged from methanol. However, ester interchange did take place, as was evident when the supposed ethyl ester tosylate 24 was converted into methyl 3β-chloro-11-cholenate. Apparently a trace of *p*-toluenesulfonic acid resulting from hydrolysis of the 3-tosylate group (it is known that esters of the 3-hydroxy steroids are easily hydrolyzed) catalyzes the ester interchange. By adding *p*-toluenesulfonic acid to the refluxing methanol solution during crystallization, conversion of ethyl to methyl ester is fairly rapid and complete. The facile ester interchange of the bile acid esters might have been expected from the marked ease with which cholenic and substituted cholanic acids are esterified. For instance, 3α-hydroxy-11-cholenic acid is completely esterified in 40 minutes by methanol containing small amounts of aqueous hydrochloric acid at room temperature.[8] Yamasaki, Rosnati, Fieser and Fieser[9] recently encountered an ester interchange during the reduction of methyl 4β-bromodehydrolithocholate by sodium borohydride in the presence of ethanol. They also converted ethyl 3,4-dibromocholanate into the methyl ester by refluxing in methanol containing concentrated hydrochloric acid. Several of our esters underwent interchange similarly when refluxed, but a purer product usually resulted when the reaction was left at room temperature for 10 to 18 days. Ethyl 3β-chloro-11-cholenate (28) prepared in this way crystallized directly from the

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(3) (a) Worcester Foundation for Experimental Biology, Shrewsbury, Mass.; (b) Department of Chemistry, University of Arkansas, Fayetteville, Ark.

(4) Numbered according to the consecutive order in which the compounds are described in the Experimental sections of this (III) and the accompanying paper (IV).

(5) Paper I of this series, THIS JOURNAL, **76**, 3213 (1954).

(6) E. D. Hughes and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941).

(7) Organic halides have been obtained often as a result of reaction between alcohols and tosyl (and mesyl) chlorides in pyridine [*e.g.*, C. R. Noller, C. A. Luchetti, E. M. Acton and R. A. Bernhard, THIS JOURNAL, **75**, 3851 (1953)], but the use of pyridine base and pyridinium halide on a tosylate appears to be novel. F. Drahowzal and D. Klamann [*Monatsh.*, **82**, 460 (1951)] record failure to obtain *n*-butyl and *n*-octyl chlorides from the tosylates under conditions similar to ours except for a considerably smaller proportion of pyridine, but they describe successful preparations of halides using pyridinium chloride without solvent and with carbon tetrachloride as solvent.

(8) L. L. Engel, V. R. Mattox, B. F. McKenzie, W. F. McGuckin and E. C. Kendall, *J. Biol. Chem.*, **162**, 565 (1946).

(9) K. Yamasaki, V. Rosnati, M. Fieser and L. F. Fieser, THIS JOURNAL, **77**, 3308 (1955).

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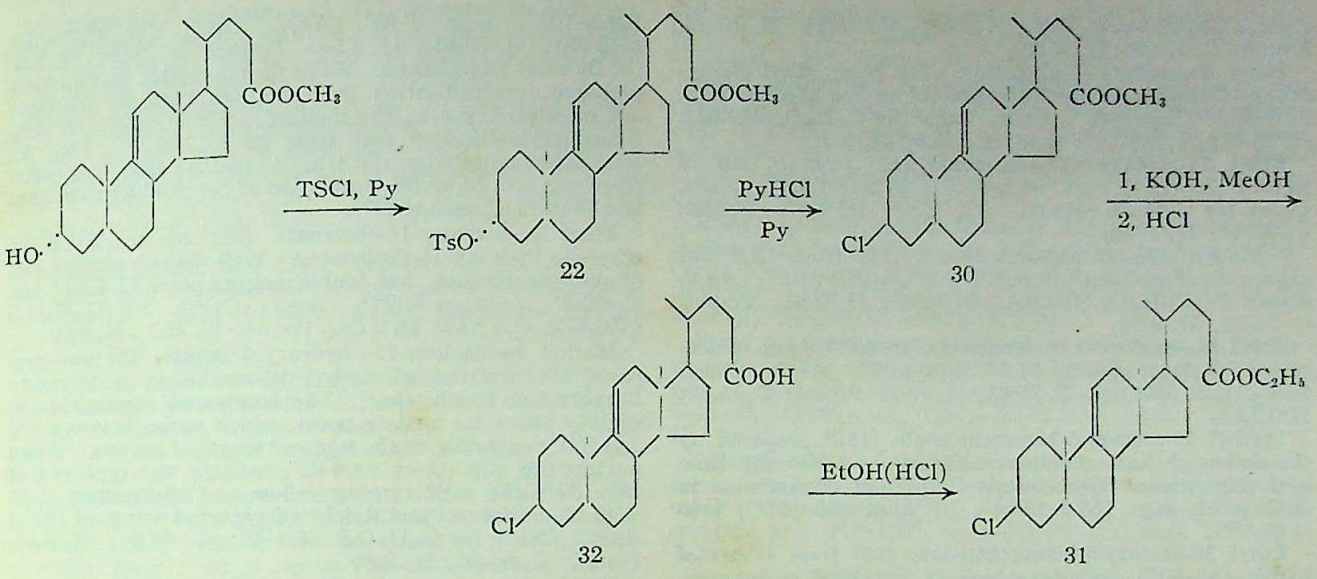

reaction mixture in a state of highest purity in near quantitative yield. This ester interchange constitutes a good method for preparing higher esters of the bile acids from the often more readily available methyl esters.

The extreme ease of esterification of the C_{24}-bile acids is in contrast to the considerable resistance exhibited by the bisnorcholanic acids to this reaction. 3β-Hydroxy-5-bisnorcholenic acid forms the methyl and ethyl esters in poor yield even after several days of reflux with the respective alcohols. Perhaps for this reason, only the methyl ester prepared with diazomethane has been reported. The expected difference in the rates of reaction between the C_{20}-secondary and C_{23}-primary carboxyl groups is doubtless intensified considerably by the interference offered by the steroid nucleus.

Experimental[10,11]

ESTERS OF HYDROXY ACIDS. Esterification of Hydroxy Acids.—All of the C_{24}-acids were esterified readily by using the proportion of 1 g. of acid:10 ml. of absolute (methyl or ethyl) alcohol:0.1 ml. of concd. HCl. (The alcoholic solution is approximately 0.12 *N* in HCl.) With the 10:1 ratio of solvent to acid, the reaction is rapid and complete.

Methyl lithocholate (1),[12] was obtained from lithocholic acid in quantitative yield as large needles, m.p. 129–130°; recrystallized from methanol–water and dried at 100° (1 mm.) for 24 hr. for analysis, m.p. 125–127.5°, $[\alpha]_D$ +22°. *Anal.* Calcd. for $C_{25}H_{42}O_3$ (390.59): C, 76.87; H, 10.84. Found: C, 76.6; H, 10.8. This conflicts with the Reindel report[12] that the 125–127° melting product contains 1.5 moles of methanol as solvent of crystallization. Fieser and Ettore[13] reported m.p. 125–127°; Fieser and Rajagopalan,[14] 129–130°, $[\alpha]_D$ +29 ±2° (diox.).

Ethyl Lithocholate (2).[12] **By ester interchange** from 1 by refluxing 1.5 hr. in ethanol and concentrated hydrochloric acid; 74% of 92–95° melting product. Recrystallized from methanol–water, m.p. 94.5–96° (lit. m.p. 92–93°), $[\alpha]_D$ +28.8°*. *Anal.* Calcd. for $C_{26}H_{44}O_3$ (404.60): C, 77.18; H, 10.96. Found: C, 77.18; H, 10.84.

Methyl 12α-hydroxycholanate (3) was prepared according to Barnett and Reichstein,[15] m.p. 119.5–120.0° (lit. 120–121°), $[\alpha]_D$ +39°.

Ethyl 12α-hydroxycholanate (4) was prepared by the same method from ethyl 12α-hydroxy-3-cholenate (54)[16] in quantitative yield; crystallized from absolute ethanol, m.p. 135–136.5°, $[\alpha]_D$ +46°. *Anal.* Calcd. for $C_{26}H_{44}O_3$ (404.60): C, 77.2; H, 11.0. Found: C, 77.1; H, 10.9.

Compound 4 was also prepared by esterification of 12α-hydroxycholanic acid, m.p. 135–136.5°.

Ethyl 3α-hydroxy-9(11)-cholenate (5) was prepared by esterification of 3α-hydroxy-9(11)-cholenic acid,[17] m.p. 75.0–76.5°, $[\alpha]_D$ +35.6°. *Anal.* Calcd. for $C_{26}H_{42}O_3$ (402.60): C, 77.56; H, 10.52. Found: C, 77.25; H, 10.44.

Compound 5 also was obtained from methyl 3α-acetoxy-9(11)-cholenate (12) by treatment with ethanol and hydrochloric acid.

Methyl 3β-hydroxy-5-bisnorcholenate (6) was prepared by refluxing the corresponding acid in methanol and concd. hydrochloric acid for two days; 54% yield of product melting 140–144° out of ligroin (63–70°). A chromatographed sample for analysis melted at 142–143.7°, $[\alpha]_D$ −55.4°*. (This compound was previously prepared by use of diazomethane by Fernholz,[18] m.p. 140°.) *Anal.* Calcd. for $C_{23}H_{36}O_3$ (360.52): C, 76.62; H, 10.07. Found: C, 76.95; H. 9.97.

Ethyl 3β-Hydroxy-5-bisnorcholenate (7).—Two grams of 3β-hydroxy-5-bisnorcholenic acid (Nutritional Biochemical Corp.) in 150 ml. of absolute ethanol and 2 ml. of concd. sulfuric acid was refluxed for 45 hr. After usual processing a product melting at 162–164° was obtained in 34% yield, after recrystallization from ligroin (63–70°), $[\alpha]_D$ −65.6°. *Anal.* Calcd. for $C_{24}H_{38}O_3$(374.54): C, 76.96; H, 10.23. Found: C, 77.2; H, 10.5.

ACETATES.—The 3-acetates were made by room temperature acetylation using acetic anhydride and pyridine; the 12-acetates required heating to 100°, with the exception of those prepared using *p*-toluenesulfonic acid as catalyst (see compounds 18 and 19).

Ethyl 3α-acetoxycholanate (8)[12] was obtained from ethyl lithocholate, out of ethanol, m.p. 95–98° (lit. 90–91°), $[\alpha]_D$ +38.2°. *Anal.* Calcd. for $C_{28}H_{46}O_4$ (446.65): C, 75.29; H, 10.38. Found: C, 75.48; H, 10.56.

Methyl 12α-acetoxycholanate (9) from 3, heavy prisms out of methanol, m.p. 95.5–96.5°, $[\alpha]_D$ +69°. *Anal.* Calcd. for $C_{27}H_{44}O_4$ (432.62): C, 74.95; H, 10.25. Found: C, 75.03; H, 10.14.

Ethyl 12α-acetoxycholanate (10) from 4, out of absolute ethanol as short, thick prisms, m.p. 63–64°, $[\alpha]_D$ +69.9°.

(10) Microanalyses by the Microchemical Laboratory of New York University, and by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(11) Melting points were taken on an electrical micro-hotstage and are uncorrected. Optical rotations were determined in 1–2% chloroform solutions at about 25°, except where noted, using a Schmidt and Haensch polarimeter, and values are accurate to ±1°. The values marked with an asterisk (*) were obtained with a Keston polarimeter attachment (Standard Polarimeter Co., 225 E. 54th Street, N. Y. C.) to a Beckman DU spectrophotometer with accuracy estimated to be better than ±2°.

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Anal. Calcd. for $C_{28}H_{46}O_4$ (446.65): C, 75.29; H, 10.38. Found: C, 75.33; H, 10.36.

Ethyl 3α-acetoxy-11-cholenate (11) from ethyl 3α-hydroxy-11-cholenate,[5] out of methanol as fine needles, m.p. 91.5–93.7°, $[\alpha]_D$ +42°. *Anal.* Calcd. for $C_{28}H_{44}O_4$ (444.63): C, 75.63; H, 9.97. Found: C, 75.6; H, 9.9.

Ethyl 3α-acetoxy-9(11)-cholenate (12) from 5, out of legroin (35–60°), m.p. 96.5–97.5°, $[\alpha]_D$ +64.8°. *Anal.* Calcd. for $C_{28}H_{44}O_4$ (444.63): C, 75.63; H, 9.97. Found: C, 75.44; H, 10.35.

Methyl 12α-acetoxy-3-cholenate (13) from 53,[16] flat prisms out of methanol, m.p. 107–108°, $[\alpha]_D$ +63.9°. *Anal.* Calcd. for $C_{27}H_{42}O_4$ (430.61): C, 75.31; H, 9.83. Found: C, 75.23; H, 9.72.

Ethyl 12α-acetoxy-3-cholenate (14) from 54,[16] out of acetone–H_2O (3:1), m.p. 86–87.5°, $[\alpha]_D$ +62°. *Anal.* Calcd. for $C_{28}H_{44}O_4$ (444.63): C, 75.63; H, 9.97. Found: C, 75.52; H, 10.12.

Methyl 3β-acetoxy-5-bisnorcholenate (15)[18] prepared by the action of diazomethane on 3β-acetoxy-5-bisnorcholenic acid (Nutritional Biochemicals Corp.) out of methanol in 76% yield, m.p. 153.5–156.5° (lit. m.p. 156–157°), $[\alpha]_D$ +63.4°*.

Ethyl 3β-acetoxy-5-bisnorcholenate (16) from 7 out of ligroin (35–60°), leaflets, which at 124–125° were transformed into needles, m.p. 129–130.5°, $[\alpha]_D$ +63.0°*. *Anal.*[19] Calcd. for $C_{26}H_{40}O_4$(416.58): C, 74.96; H, 9.68. Found: C, 75.13; H, 9.67.

Ethyl 3α,12α-diacetoxycholanate (17) was prepared from ethyl desoxycholate by refluxing in acetic anhydride and pyridine. All attempts at crystallization failed. This distilled as colorless oil in a molecular still at 0.07 mm., $[\alpha]_D$ +89.7° (*c* 2.05, chf); +98.2° (*c* 2.06, ethanol). *Anal.* Calcd. for $C_{30}H_{48}O_6$ (504.68): C, 71.39; H, 9.59. Found: C, 71.73, 71.86; H, 9.91, 9.93.

Methyl 3β-chloro-12α-acetoxycholanate (18) was obtained by the method recently reported[20] for difficultly acetylated hydroxyl groups, using acetic acid, acetic anhydride and *p*-toluenesulfonic acid at room temperature, as colorless needles when crystallized from methanol, m.p. 129–130°, $[\alpha]_D$ +56.8°*. *Anal.* Calcd. for $C_{27}H_{43}O_4Cl$(467.07): C, 69.43; H, 9.28; Cl, 7.59. Found: C, 69.32; H, 9.30; Cl, 7.53.

Ethyl 3β-chloro-12α-acetoxycholanate (19) was prepared as for 18, from 36, crystallizing from ethanol–water (3:1) as colorless needles, m.p. 82.0–83.5°, $[\alpha]_D$ +72.2°*. *Anal.* Calcd. for $C_{28}H_{45}O_4Cl$ (481.10): C, 69.89; H, 9.43; Cl, 7.37. Found: C, 70.00; H, 9.46; Cl, 7.35.

When prepared by the acetic anhydride and pyridine method at 100°, the product was poor.

TOSYLATES.—All are 3α-tosylates, prepared by room temperature addition of *p*-toluenesulfonyl chloride and pyridine to the 3-hydroxy compound. In general, yields were nearly quantitative. Where they were lower than expected, it was possible to increase the yield by first drying the hydroxy compound by an azeotropic distillation in benzene.

Methyl 3α-tosyloxycholanate (methyl lithocholate tosylate) (20)[21] from methyl lithocholate, out of methanol as lovely, light-refracting, thin, square plates, m.p. 120–121.5° (lit.[21] 107–109°), $[\alpha]_D$ +35°. *Anal.* Calcd. for $C_{32}H_{48}O_5S$ (544.75): C, 70.56; H, 8.88. Found: C, 70.6; H, 8.9.

Ethyl 3α-tosyloxy cholanate (21) by ester interchange of 20 in ethanol and HCl by 2-hr. reflux, a low yield of crystalline material out of hexane, m.p. 94.5–95.5°. *Anal.* Calcd. for $C_{33}H_{50}O_5S$ (558.8): C, 70.93; H, 9.02; S, 5.74. Found: C, 71.25; H, 9.17; S, 5.65, $[\alpha]_D$ +33.0°*.

Methyl 3α-tosyloxy-9(11)-cholenate (22)[21] was prepared by tosylation of methyl 3α-hydroxy-9(11)-cholenate at room temperature, out of methanol or acetone as colorless crystals, m.p. 112.5–114°, $[\alpha]_D$ +33° (lit. 111–112°). *Anal.* Calcd. for $C_{32}H_{46}O_5S$ (542.69): C, 70.82; H, 8.54; S, 5.90. Found: C, 70.60; H, 8.61; S, 5.77.

Methyl 3α-tosyloxy-11-cholenate (23) was prepared by (a) tosylation of methyl 3α-hydroxy-11-cholenate to give a 91% yield of lustrous plates, m.p. 103–107°, from methanol. Recrystallized from warm methanol (not refluxed), m.p. 104.5–107°, $[\alpha]_D$ +40°. *Anal.* Calcd. for $C_{32}H_{46}O_5S$ (542.69): C, 70.81; H, 8.54. Found: C, 70.9; H, 8.9. (b) **By ester interchange**: When the ethyl ester (24) was first prepared, crystallization from methanol at 50° brought out colorless crystals, the melting point of which on continued crystallization rose from 65 to 104.5°. That an ester interchange from the ethyl to methyl ester had taken place was proved by the conversion of the product to methyl 3β-chloro-11-cholenate (27).

Ethyl 3α-tosyloxy-11-cholenate (24) by tosylation of ethyl 3α-hydroxy-11-cholenate.[5] Well-shaped needles out of absolute ethanol; has double melting point 57.5–61° and 95–96.5°, $[\alpha]_D$ +30.2°*. *Anal.* Calcd. for $C_{33}H_{48}O_5S$ (556.77): C, 71.18; H, 8.69. Found: C, 71.1; H, 8.90.

Methyl 3α-tosyloxy-12α-hydroxycholanate (25) was prepared by tosylation of methyl desoxycholate according to Barnett and Reichstein.[15] The compound decomposes at slightly above its melting point, which varies between 139 and 150° depending on the rate and length of heating. When put on the m.p. block at 149°, melting was observed at 149–150°, the melt turning yellow and effervescing, $[\alpha]_D$ +40.4°. (Barnett and Reichstein reported a m.p. of 149°.) *Anal.* Calcd. for $C_{32}H_{48}O_6S$ (560.70): C, 68.54; H, 8.63. Found: C, 68.36; H, 8.89.

Ethyl 3α-tosyloxy-12α-hydroxycholanate (26) was obtained by tosylation at room temperature of ethyl desoxycholate (crystallized originally from ether but had been on the shelf for about one year) in poor yield. A second tosylation using ethyl desoxycholate that had first received a preliminary azeotropic distillation with benzene gave a nearly quantitative yield of product of melting point 98–100°. Recrystallization out of ether–Skellysolve F (1:1) gave good, colorless needles, m.p. 101–103.5°. Dissolved in benzene and diluted with ligroin (63–70°), long needles separated, m.p. 114–116.5°, $[\alpha]_D$ +38.8°. *Anal.* Calcd. for $C_{33}H_{50}O_6S$ (574.8): C, 69.00; H, 8.78; S, 5.59. Found: C, 68.81; H, 8.73; S, 5.5.

CHLORO COMPOUNDS.—The 3-chlorocholanic acid derivatives were made by the pyridine–pyridine hydrochloride method; the bisnorcholenic acid compounds were made with thionyl chloride. The pyridinium chloride method is described in detail only for the preparation of compound 27.

Methyl 3β-chloro-11-cholenate (27) was made by the pyridinium chloride method. The tosylate 23 (1.4 g.) was heated for 21 hr. at 90° in 12 ml. of pyridine containing 1.4 g. of pyridine hydrochloride. Chips of ice and water were added and the mixture was stirred and refrigerated. The solid which precipitated was shaken with cold 3% hydrochloric acid and filtered. After washing with water and drying, the solid was crystallized from methanol. A small amount of insoluble material was first removed and the clear methanol solution deposited thin flakes, 446 mg. (42.5%), m.p. 96–100°. Two crystallizations raised the m.p. to 100.5–102°, $[\alpha]_D$ +24.5°. (Another run starting with 400 mg. of tosylate, and heated at 90° for 11 hr. gave a 53.5% yield of comparable product.) *Anal.* Calcd. for $C_{24}H_{37}O_2Cl$ (407.02): C, 73.77; H, 9.66. Found: C, 73.6; H, 9.8.

Ethyl 3β-Chloro-11-cholenate (28).[5]—(a) By the pyridinium chloride method from the tosylate (24), from 95% ethanol in 51% yield, in long laths with hexagonal ends, m.p. 78.5–79.5°, $[\alpha]_D$ +25°. *Anal.* Calcd. for $C_{26}H_{41}O_2Cl$(421.05): C, 74.16; H, 9.82. Found: C, 73.9; H, 9.7.

(b) By esterification of the acid 29, long prismatic needles by slow crystallization out of dilute 95% ethanol solution, m.p. 78–79.5°.

3β-Chloro-11-cholenic acid (29) was obtained in nearly quantitative yield by hydrolysis of the methyl ester and was recrystallized from acetic acid as well-shaped elongated prisms, m.p. 167–170.5°, $[\alpha]_D$ +24.5°. *Anal.* Calcd. for $C_{24}H_{37}O_2Cl$ (393.00): C, 73.34; H, 9.49. Found: C, 73.7; H, 9.5.

Methyl 3β-chloro-9(11)-cholenate (30) was obtained by the pyridinium chloride method on the tosylate 22 at 76.5° for 26 hr., as crystals from methanol in 51.5% yield, m.p. 86.5–88°, $[\alpha]_D$ +31°. *Anal.* Calcd. for $C_{25}H_{39}O_2Cl$ (407.02): C, 73.75; H, 9.66. Found: C, 74.2; H, 9.9.

Ethyl 3β-chloro-9(11)-cholenate (31) by esterification of the acid 32. Recrystallization in 95% ethanol gave colorless prisms, m.p. 67–68°, $[\alpha]_D$ +33.0°. *Anal.* Calcd. for $C_{26}H_{41}O_2Cl$ (421.05): C, 74.16; H, 9.82. Found: C, 73.8; H, 10.0.

(19) Analyses by Oakwold Laboratories, Alexandria, Va.

(20) R. B. Turner, THIS JOURNAL, **74**, 4220 (1952); Huang-Minlon, E. Wilson, N. L. Wendler and M. Tishler, *ibid.*, **74**, 5394 (1952); E. P. Oliveto, C. Gerold, L. Weber, H. E. Jorgensen, R. Rausser and E. B. Hershberg, *ibid.*, **75**, 5486 (1953).

(21) J. C. Babcock and L. F. Fieser, *ibid.*, **74**, 5471 (1952).

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3β-Chloro-9(11)-cholenic acid (32), prepared by hydrolysis of its methyl ester, crystallized from ethanol, m.p. 150–153°, $[\alpha]_D$ +33.4°. *Anal.* Calcd. for $C_{24}H_{37}O_2Cl$ (393.00): C, 73.34; H, 9.49. Found: C, 73.4; H, 9.8.

Methyl 3β-chlorocholanate (33) by pyridinium chloride method on methyl lithocholate tosylate (20), in 80% yield of crude product melting about 80°. After recrystallization from methanol, well-shaped, elongated prisms of m.p. 86–87.5° were obtained, $[\alpha]_D$ +17°. *Anal.* Calcd. for $C_{25}H_{41}O_2Cl$ (409.03): C, 73.41; H, 10.1. Found: H, 73.1; H, 9.8.

3β-Chlorocholanic acid (34), prepared by hydrolysis of the methyl ester 33, separated in long needles, from acetone, m.p. 186–190°, $[\alpha]_D$ +14.3°. *Anal.* Calcd. for $C_{24}H_{39}O_2Cl$ (395.01): C, 72.97; H, 9.95; Cl, 8.98. Found: C, 73.22; H, 9.91; Cl, 9.07.

Methyl 3β-chloro-12α-hydroxycholanate (35), by pyridinium chloride on the tosylate 25, crystallized out of methanol as transparent, dense prisms, m.p. 141.5–143°, $[\alpha]_D$ +29.6°*. *Anal.* Calcd. for $C_{26}H_{41}O_3Cl$ (425.04): C, 70.64; H, 9.72; Cl, 8.34. Found: C, 70.81; H, 9.85; Cl, 8.28.

Ethyl 3β-chloro-12α-hydroxycholanate (36) by ester interchange on 35, by refluxing for 3.5 hr. with hydrochloric acid in ethanol, 86% yield of fine needles, m.p. 116.5–118.8°. Analytical sample out of ligroin (35–60°)–benzene (20:1), m.p. 117.5–118.8°, $[\alpha]_D$ +28.6°*. *Anal.* Calcd. for $C_{26}H_{43}O_3Cl$ (439.06): C, 71.12; H, 9.87; Cl, 8.08. Found: C, 71.05; H, 9.73; Cl, 7.96.

Methyl 3β-chloro-5-bisnorcholenate (37) by the action of thionyl chloride on the 3β-hydroxy compound, m.p. 130–133°, out of methanol in 79% yield, $[\alpha]_D$ −48°. *Anal.* Calcd. for $C_{23}H_{35}O_2Cl$ (378.97): C, 72.89; H, 9.31; Cl, 9.36. Found: C, 72.96; H, 9.01; Cl, 9.44.

Ethyl 3β-chloro-5-bisnorcholenate (38) was prepared in a room temperature reaction of thionyl chloride on the hydroxy ester 7 to give a crystalline product from ethanol, m.p. 120–123°, $[\alpha]_D$ −47.3°. *Anal.* Calcd. for $C_{24}H_{37}O_2Cl$ (393.00): C, 73.34; H, 9.49; Cl, 9.02. Found: C, 73.5; H, 9.5; Cl, 8.9.

OTHER COMPOUNDS.—**Ethyl 12α-benzoxycholanate** (39) by reaction of benzoyl chloride in pyridine on the 12-hydroxy compound 4, 4 hr. reflux. The oil, after processing and chromatography, did not crystallize; distilled at 0.1 mm., $[\alpha]_D$ +51°. *Anal.* Calcd. for $C_{23}H_{48}O_4$ (508.7): C, 77.91; H, 9.51. Found: C, 78.0; H, 9.6.

Ethyl 3α-benzoxy-12α-hydroxycholanate (40) was prepared by benzoylation in pyridine at room temperature; 75% of product, m.p. 103–114°. Recrystallization from methanol, m.p. 118.8–120.7°, $[\alpha]_D$ +51.9°*. *Anal.* Calcd. for $C_{33}H_{48}O_5$ (524.68): C, 75.53; H, 9.22. Found: C, 75.80; H, 9.28.

Ethyl 3α,12α-dibenzoxycholanate (41) from ethyl desoxycholate with benzoyl chloride and pyridine by 3 hr. reflux, crystalline product from ethanol, m.p. 139.2–141.4°, $[\alpha]_D$ +89.7°*. *Anal.* Calcd. for $C_{40}H_{52}O_6$ (628.80): C, 76.40; H, 8.33. Found: C, 76.43; H, 8.59.

Ethyl 3-ketocholanate (42)[22] by esterification of 3-ketocholanic acid,[23] crystallized out of ethanol–water as dense prisms, m.p. 94.5–95.5°, $[\alpha]_D$ +28.9°. *Anal.* Calcd. for $C_{26}H_{42}O_3$ (402.60): C, 77.56; H, 10.52. Found: C, 77.52; H, 10.70.

Methyl 3-keto-9(11)-cholenate (43)[21] was prepared from methyl 3α-hydroxy-9(11)-cholenate by the chromium trioxide–pyridine method[24] to give an 82% yield of colorless crystals, m.p. 117–120°, $[\alpha]_D$ +31.3° (lit. m.p. 117–119°, $[\alpha]_D$ +35°).

Methyl 3-keto-11-cholenate (44)[25] from chromium trioxide–pyridine oxidation of the corresponding 3α-hydroxy compound, out of isopropyl ether–acetone (9:1) giving transparent flat plates, m.p. 125–127° (lit. m.p. 125.5–126°), $[\alpha]_D$ +37.3°. *Anal.* Calcd. for $C_{25}H_{38}O_3$ (386.55): C, 77.67; H, 9.91. Found: C, 77.4; H, 10.2.

(22) This compound is mentioned among other carbonyl compounds [H. Reich, K. F. Crane and S. J. Sanfilippo, *J. Org. Chem.*, **18**, 822 (1953)] without indication of its source or properties.

(23) H. Wieland and P. Weyland, *Z. physiol. Chem.*, **110**, 123 (1920).

(24) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(25) V. Burckhardt and T. Reichstein, *Helv. Chim. Acta*, **25**, 821 (1942).

MEMPHIS 3, TENN.

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, AND THE DIVISION OF PATHOLOGY AND MICROBIOLOGY, MEDICAL UNITS. UNIVERSITY OF TENNESSEE]

Seroflocculating Steroids. IV.[1] Unsaturated Bile Acid Esters[2]

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For study of their seroflocculating activity, methyl and ethyl 3;11-choladienate, methyl 3,9(11)-choladienate, methyl and ethyl 3-cholenate, methyl and ethyl 12α-hydroxy-3-cholenate were prepared by elimination of suitably constituted 3α-tosylates. Each elimination reaction appears to give a single (or highly predominant) olefinic product. The assignment of the Δ^3-structure to these compounds is based on the identity of our methyl cholenate with the product prepared previously by Fieser and Ettore and proved by them to be methyl 3-cholenate.

Our first attempts to prepare a pure ethyl cholaienate for seroflocculation studies were by pyrolysis of diacyl derivatives of ethyl desoxycholate by the methods used by Wieland[4] and subsequently by Reichstein.[5] Solid products were obtained readily enough, but isolation of pure material by crystallization, or even by chromatography and crystallization, was tedious and gave low yield. For example, with ethyl 3α,12α-dibenzoxycholanate, the pyrolysis product yielded a minute amount of pure material only after chromatography and eight crystallizations. The diacyl methyl esters were no more amenable than the ethyl compounds.

The difficulty of isolation of pure product induced us to try an elimination reaction on a tosylate. Dehydrotosylation in a pyridine base which presumably takes place through a heterolytic mechanism might be expected to yield a different and possibly more tractable mixture than that resulting from pyrolysis. This method of producing unsaturation in steroids has been applied frequently,[6] but the

(1) Paper III of this series, THIS JOURNAL, **79**, 2164 (1957).

(2) This investigation was supported in part by grants (CS-9053 and C-2249) from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

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(4) H. Wieland and W. Kapitel, *Z. physiol. Chem.*, **212**, 269 (1932).

(5) A. Lardon, P. Grandjean, J. Press, H. Reich and T. Reichstein, *Helv. Chim. Acta*, **25**, 1444 (1942).

(6) J. von Euw and T. Reichstein, *ibid.*, **29**, 654 (1946).

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composition of the olefinic products obtained in the elimination of cholestanyl tosylates has been studied only recently.[7] And no similar information is available on the A-ring unsaturated products resulting from the 3-tosylates of the coprostane (A/B *cis*) series.

To limit the number of derived products, an ethyl desoxycholate derivative with the preformed 11-unsaturated group, ethyl 3α-hydroxy-11-cholenate[8] was chosen as the starting material. By reflux with tosyl chloride in pyridine solution, a nicely crystalline product was obtained, which, however, proved to be a difficultly separable mixture of diene and 3β-chloro compound, as described in paper II.[9]

When the tosylate 24[10] was first prepared and refluxed in 2,6-lutidine, a solid dienic product was obtained readily from the reaction mixture, but first efforts at purification by fractional crystallization seemed to indicate that, as with the pyrolysis products, the mixture yielded to separation reluctantly. However, by simply passing the material through an alumina column in ligroin, the persistent contaminant was removed and an excellent yield of homogeneous product could be achieved after one or two crystallizations.[10a] The impurity is a minor component that remains adsorbed on the alumina and apparently is not an isomeric diene.

Methyl 3,11-choladienate, methyl 3,9(11)-choladienate, methyl and ethyl 3-cholenate and methyl and ethyl 12α-hydroxy-3-cholenate were all prepared from the respective 3-tosylates in lutidine and purified in analogous manner satisfactorily. Methyl 12α-hydroxy-3-cholenate was obtained in pyridine in only 32% as compared with a 98% yield when lutidine was used. The improved yield when lutidine is used as dehydrotosylation medium in place of pyridine may be attributed partly to the increase in temperature of reaction (pyridine, b.p. 116°; 2,6-lutidine, 143°) but may also possibly be due to the greater steric strain in the transition state required for the formation of the salt when lutidine is the base, as suggested in a similar previous study by King.[11] The replacement reaction competing with elimination would result in the lutidinium (or pyridinium) salt.

Assignment of the Δ^3-Structure.—Fieser and Ettore[12] prepared methyl 3-cholenate by the zinc treatment of the methyl 3-hydroxy-4-bromocholanates, and Yamasaki, Rosnati, Fieser and Fieser[13] showed that it is identical with the methyl ester of an unsaturated acid (originally given the assignment of 2-cholenic acid by Wieland)[14] obtained by pyrolysis of lithocholic acid. They further confirmed the 3-unsaturation by conversion of the methyl cholenate to a 3,4-diol with osmium tetroxide and oxidation of this diol to lithobilianic acid.

Our methyl cholenate obtained from the dehydrotosylation reaction has been compared with the Fieser compound,[13] and the identity of the two preparations was established by comparisons of melting points, optical rotations and infrared spectra and by a mixed melting point determination. Moreover, our compound was converted to the ethyl ester which in turn was shown to be identical with authentic ethyl 3-cholenate provided by Professor Fieser.[13]

The Δ^3-compounds appear to be the sole olefin products of the dehydrotosylation reaction; no Δ^2-isomers were isolated. Wieland[14] reported a 9:1 ratio of isomers in the pyrolysis of lithocholic acid, and in fact his isolation and characterization of the minor component as 3-cholenic acid (now 2-cholenic acid) were extremely tentative. Therefore, the Δ^3-isomer appears to be the sole or highly predominant olefinic product[15] of both the pyrolysis and dehydrotosylation reactions. This is in interesting contrast to the situation of the cholestanyl derivatives; pyrolysis of the 3β-benzoates[16] gave both Δ^2- and Δ^3-cholestene, and elimination of 3α- and 3β-tosylates both afforded a Δ^2- and Δ^3-cholestene mixture in 1:1 ratio.

Consequently, the Δ^3-structure has been assigned to the other compounds made through the dehydrotosylation reaction: ethyl 3-cholenate, methyl 3,9(11)-choladienate, methyl and ethyl 3,11-choladienate, methyl and ethyl 12α-hydroxy-3-cholenate. Methyl 3,11-choladienate, also prepared by the pyrolysis of methyl desoxycholate dibenzoate and brought to satisfactory purity after fourteen recrystallizations, is probably identical with the material reported (m.p. 86°) obtained by Wieland and Kapitel[4] by a similar pyrolysis after "repeated" crystallizations and is most likely the methyl ester of choladienic acid-A. Choladienic acid-A was tentatively considered to be the $\Delta^{2,11}$-compound by Wieland, but Fieser[13] has recently proposed revision to the $\Delta^{3,11}$-structure. Reichstein and his coworkers[5] obtained as a side-product in a pyrolysis reaction of methyl 3α-acetoxy-12α-benzoxycholanate a 76° melting product which they regarded as a mixture of the methyl 2,11- and 3,11-choladienates. The unsaturated compound made by Barnett and Reichstein[17] by dehydrotosylation in pyridine is undoubtedly identical with our methyl 12α-hydroxy-3-cholenate. No supporting evidence or comment was given in the designation of the Δ^3-structure of their product; the preparation appar-

(7) H. R. Nace, THIS JOURNAL, **74**, 5937 (1952).

(8) We are indebted to Dr. K. Pfister and Merck and Co., Inc., for a generous supply of 3α-hydroxy-11-cholenic acid.

(9) F. C. Chang, *et al.*, THIS JOURNAL, **79**, 2161 (1957).

(10) Numbered according to the consecutive order in which the compounds are described in the Experimental sections of this paper IV and the accompanying paper III of this series.

(10a) ADDED IN PROOF.—S. Bernstein and M. V. Querry in U. S. Patent 2,725,388 [*C.A.* **50**, 15605 (1956)] report the preparation of ethyl choladienate by a method similar to ours with the differences that the tosylate was not isolated and the dehydrotosylation medium was pyridine. The yield of product considered to be a mixture of the $\Delta^{2,11}$- and $\Delta^{3,11}$-isomers was about 27%.

(11) L. C. King and B. M. Regan, THIS JOURNAL, **74**, 5617 (1952).

(12) L. F. Fieser and R. Ettore, *ibid.*, **75**, 1700 (1953).

(13) K. Yamasaki, V. Rosnati, M. Fieser and L. F. Fieser, *ibid.*, **77**, 3308 (1955). We wish to thank Professor Fieser for making available to us a copy of the paper before publication and for providing comparison samples of methyl and ethyl 3-cholenate, and Dr. Wei-yuan Huang for valuable help in infrared studies.

(14) H. Wieland, K. Kraus, H. Keller and H. Ottawa, *Z. physiol. Chem.*, **241**, 47 (1936).

(15) R. T. Bridgewater and C. W. Shoppee [*J. Chem. Soc.*, 1700 (1953)] also reported an exclusive coprostene product in the pyrolysis of 3α- and 3β-coprostanyl benzoates as well as in elimination reactions on several 3β-coprostanyl halides, although their preference is for the Δ^2-structure.

(16) D. H. R. Barton and W. J. Rosenfelder, *ibid.*, 1048 (1951).

(17) J. Barnett and T. Reichstein, *Helv. Chim. Acta*, **21**, 92[illegible] (1938).

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ently served only as intermediary in the synthesis of 12α-hydroxycholanic acid.

The 9(11)-cholenic acid methyl ester was conveniently prepared from the 3,9(11)-dienic compound by selective hydrogenation; the 9(11)-double bond was not hydrogenated with platinum oxide catalyst. Methyl 9(11)-cholenate had been prepared previously by Reich and Reichstein[18] and by Fieser, Heymann and Rajagopalan.[19]

Experimental[20,21]

Dehydrotosylation.—This method is used in the preparation of several compounds reported in this paper. Only the first preparation will be given in detail. In the case of the methyl esters, the procedure becomes simpler in that solid (usually crystalline) product separated from the lutidine reaction mixture on addition of ice chips. By washing the solid on a filter with ice-cold 3% hydrochloric acid, a satisfactory preliminary purification is effected.

Ethyl 3,11-Choladienate (45).—(a) Ethyl 3α-tosyloxy-11-cholenate (24),[1] 3.0 g., was refluxed for 3 hr. in 36 ml. of 2,6-lutidine (Eastman Kodak Co. practical grade). Large colorless crystals of lutidine *p*-toluenesulfonate separated on cooling the mixture to room temperature and redissolved when chips of ice were added. The mixture was transferred to a separatory funnel with ether and extracted in order with ice-cold 3% hydrochloric acid, 10% $NaHCO_3$ solution and water to neutrality. The ethereal solution was dried with Drierite and evaporated to a clear residual oil weighing 2.04 g. The oil was dissolved in purified ligroin (63–70°) and chromatographed, using alumina (Fisher) in the ratio of 30:1. ligroin (63–70°) eluted material amounting to 1.32 g. (64%) was dissolved in 95% ethanol and seeded, yielding good crystals. One crystallization gave colorless hexagonal plates with m.p. 67–68.5°, $[\alpha]_D$ + 32.4°*.

Anal. Calcd for $C_{26}H_{40}O_2$ (384.58): C, 81.20; H, 10.48. Found: C, 80.98; H, 10.72.

(b) **By Pyrolysis.**—Ethyl 3α,12α-dibenzoxycholanate (41), 5.0 g., was pyrolyzed at 200–350° for 160 min. at 28 mm. to yield 3.01 g. of oil. Chromatography of 1.78 g. of the oil gave 218 mg. of a ligroin (35–60°) eluted material of m.p. 45–54°. After eight recrystallizations, 41 mg. of colorless needles of m.p. 68–69° was obtained. A mixed m.p. with material obtained in (a) gave no depression.

Anal. Calcd. for $C_{26}H_{40}O_2$: C, 81.20; H, 10.48. Found: C, 81.44; H, 10.62.

(c) **By Esterification.**—Saponification of methyl 3,11-choladienate (46) in methanolic KOH, acidification and re-esterification of the resulting acid in absolute ethanol containing concentrated HCl gave dense, colorless prisms, m.p. 66–68°, melting point not depressed when mixed with (a).

Methyl 3,11-Choladienate (46). (a) **By Dehydrotosylation.**—Three grams of methyl 3α-tosyloxy-11-cholenate (23) gave 1.97 g. (95%) of colorless solid with m.p. 76–78° on addition of ice chips to the lutidine mixture. Fractional crystallization in methanol raised the melting point very gradually, although after several crystallizations the product assumed a regular flat hexagonal form. After eleven recrystallizations the top material melted 82.5–83.5°, weight 116 mg. However, by passing the crude solid dissolved in ligroin (63–70°) through an alumina column, the persistent impurity was removed and shiny flat hexagons melting at 83.5–84.5° were obtained after two crystallizations, $[\alpha]_D$ +33.4°*.

Anal. Calcd. for $C_{25}H_{38}O_2$ (370.55): C, 81.03; H, 10.34. Found: C, 80.8; H, 10.1.

(b) **By Pyrolysis.**[4]—The product of pyrolysis of 10 g. of methyl 3α,12α-dibenzoxycholanate[22] after chromatography melted 50–75° and weighed 2.54 g. After fourteen crystallizations, colorless needles melting 84–85° were obtained, mixed m.p. with product in (a), no depression.

Methyl 3,9(11)-choladienate (47) was prepared by dehydrotosylation of methyl 3α-tosyloxy-9(11)-cholenate (22)[1] in 75% yield as colorless needles when crystallized from methanol, m.p. 61–63°, $[\alpha]_D$ +21.4°*.

Anal. Calcd. for $C_{25}H_{38}O_2$ (370.55): C, 81.03; H, 10.34. Found: C, 80.9; H, 10.5.

Methyl 3-Cholenate (48).—By dehydrotosylation of methyl 3-tosyloxycholanate (methyl lithocholate tosylate) (20), a 95% yield of solid with m.p. 69–72.5° separated on addition of water to the lutidine solution. After chromatography and one crystallization in methanol, shiny, thin rectangular plates, m.p. 74.5–75°, resulted, $[\alpha]_D$ +17.0°.

Anal. Calcd. for $C_{25}H_{40}O_2$ (372.57): C, 80.59; H, 10.82. Found: C, 80.4; H, 10.8.

Admixed with authentic methyl 3-cholenate,[13] m.p. 73–74°, $[\alpha]_D$ +19°, no depression in melting point was found, and the infrared spectra of the two preparations were identical.

Ethyl 3-Cholenate (49).—(a) Dehydrotosylation of ethyl lithocholate tosylate (21) resulted in 52% yield of product melting at 76–80°, after crystallization from aqueous methanol, not chromatographed. (b) By ester interchange: Two hundred mg. of methyl 3-cholenate (48) of m.p. 74.5–75° in 16 ml. of an ethanolic HCl solution (made up by addition of 0.4 ml. of concd. HCl to 25 ml. of absolute ethanol) after standing at room temperature (25–28°) for 18 days, when diluted with water to near turbidity, afforded feathery needles melting at 80–81.5° which recrystallized from aqueous ethanol as colorless needles, m.p. 82.5–83.5°, $[\alpha]_D$ +16.7°. No depression in a mixed m.p. determination with authentic ethyl 3-cholenate[13] (m.p. 82–83°).

Anal. Calcd. for $C_{26}H_{42}O_2$ (386.60): C, 80.77; H, 10.95. Found: C, 80.5; H, 11.0.

Methyl 9(11)-cholenate (50), prepared by partial hydrogenation of methyl 3,9(11)-choladienate (47) in methanol and Adams catalyst, was crystallized from methanol, m.p. 68.5–72°. Chromatographed, it crystallized from methanol and melted at 45–49°; but from a dilute solution, separated slowly as long, colorless needles, m.p. 72–72.8°, giving a positive tetranitromethane test, $[\alpha]_D$ +34.8°*. (Reich and Reichstein's product[18] prepared by another method melted 49.5–50°, 67–67.5°; the preparation of Fieser, Heymann and Rajagopalan[19] had a m.p. of 67.4–68.2°.)

Anal.[23] Calcd. for $C_{25}H_{40}O_2$ (372.57): C, 80.59; H, 10.82. Found: C, 80.62; H, 11.00.

Methyl 11-cholenate (51) was prepared in poor yield following the pyrolysis method of Alther and Reichstein.[24] The product which recrystallized from methanol melted at 58–59°, $[\alpha]_D$ +29.0°.

Anal.[23] Calcd. for $C_{25}H_{40}O_2$ (372.57): C, 80.59; H, 10.82. Found: C, 80.44; H, 10.69. (Analysis on material dried at room temperature and 1 mm. indicates solvation with 0.5 mole of CH_3OH.)

Ethyl 11-cholenate (52) was made by hydrolysis of methyl 11-cholenate (51) to 11-cholenic acid and subsequent esterification of the acid (not crystallized) with ethanol (HCl). Crystallization from absolute ethanol first yielded needles melting at 33–34.5°. These low-melting crystals after standing in a desiccator melted 51–52° and when recrystallized retained the 52° m.p., $[\alpha]_D$ +30.8°.

Anal.[23] Calcd. for $C_{26}H_{42}O_2$: C, 80.77; H, 10.95. Found: C, 80.80; H, 10.85.

Methyl 12α-Hydroxy-3-cholenate (53).—(a) By dehydrotosylation of methyl 3α-tosyloxy-12α-hydroxycholanate (25) a product melting 102–109° was obtained in 90% yield.

(18) H. Reich and T. Reichstein, *Helv. Chim. Acta.*, **26**, 562 (1943).

(19) L. F. Fieser, H. Heymann and S. Rajagopalan, THIS JOURNAL, **72**, 2306 (1950).

(20) Microanalysis by the Microchemical Laboratory of New York University, and by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(21) Melting points were taken on an electrical micro-hotstage and are uncorrected. Optical rotations were determined in 1–2% chloroform solutions at about 25°, except where noted, using a Schmidt and Haensch polarimeter, and values are accurate to ±1°. The values marked with an asterisk (*) were obtained with a Keston polarimeter attachment (Standard Polarimeter Co., 225 E. 54th St., N. Y. C.) to a Beckman DU spectrophotometer with accuracy estimated to be better than ±2°.

(22) B. F. McKenzie, W. F. McGuckin and E. C. Kendall, *J. Biol. Chem.*, **162**, 555 (1946).

(23) Sample melted at 80° in vacuum before analysis.

(24) H. B. Alther and T. Reichstein, *Helv. Chim. Acta*, **25**, 805 (1942).

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Two crystallizations from methanol brought the m.p. to 111–112°, not raised by further recrystallization, $[\alpha]_D$ +24.0°. *Anal.* Calcd. for $C_{25}H_{40}O_3$ (388.6): C, 77.27; H, 10.38. Found: C, 77.1; H, 10.2. This was probably identical with the product of Barnett and Reichstein[17] prepared similarly but with pyridine as solvent and assigned the Δ^3-structure with no comment. Their material had m.p. 110–111° out of methanol; no rotation reported. (b) By pyrolysis of methyl desoxycholate 3-cathylate,[25] a product in 88% yield, m.p. 106.5–109° after recrystallization from methanol, was obtained.

(25) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **72**, 5530 (1950).

Ethyl 12α-Hydroxy-3-cholenate (54).—(a) By dehydrotosylation of ethyl 3α-tosyloxy-12α-hydroxycholanate (26) a 98% yield of 92–95° melting material was produced, which, when recrystallized from methanol, melted at 92–97°. When pyridine was used instead of lutidine, the yield of product dropped to 32%. (b) By ester interchange: After 13 days at room temperature in ethanolic HCl methyl 12α-hydroxy-3-cholenate (53) gave a 60% yield of product melting 96–99° out of ethanol–H_2O (2:1). After chromatography, the m.p. was 97.5–99.2°, $[\alpha]_D$ +27.0°*.

Anal. Calcd. for $C_{26}H_{42}O_3$ (402.60): C, 77.56; H, 10.52. Found: C, 77.53; H, 10.26.

MEMPHIS 3, TENN.

[CONTRIBUTION FROM THE DEPT. OF PATHOLOGY, UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE]

Potentiometric Study of Gelatin and its Methyl Ester[1a-c]

BY SAM KATZ AND PAUL H. MAURER

RECEIVED NOVEMBER 9, 1956

The proton dissociation isotherm for gelatin was established by both titration and equilibration techniques at 37.0 ± 0.02°, 0.15 ionic strength. It was demonstrated that even though the isotherms obtained by titration were reproducible and reversible they were approximately 10% lower than those obtained by the equilibration technique. Similar curves evaluated from equilibration data were analyzed in terms of the number and dissociation constants of the constituent prototropic groups. The resulting values are in good accord with those established by amino acid analyses. A method is proposed for the quantitative determination of the degree of esterification of the methyl ester of gelatin. This is based on the selective alkaline hydrolysis of the ester linkages. The analytical values are considered accurate to 4%.

Introduction

In the course of the investigation of gelatin and some of its derivatives as possible plasma expanders, it was observed that the solubility and gelation properties of the methyl ester of gelatin were markedly different from the parent material.[2] This observation suggested that if this effect were real, *i.e.*, not due to the hydrolysis of gelatin during the esterification procedure, some information relevant to gelation might be derived.

The information derived from potentiometric titrations is important for the interpretation of the results obtained from the other physical techniques such as viscosity, osmometry, etc.[3] From these data a provisional estimate of the electrostatic charge of the gelatin as a function of *p*H may be made. Furthermore, the analysis of the dissociation isotherm will reveal not only the number and the dissociation constants of the prototropic groups but also their relative distribution as a function of *p*H. By comparison of the titration curves of the original and modified gelatins, a quantitative measure of the extent of reaction can be made. If extensive hydrolysis of the protein were to occur, this would be reflected by an increase either in the number of the carboxyl and/or amino groups.

Experimental

Materials.—The beef bone gelatin, lot #148-1B, was kindly supplied by Dr. D. Tourtellote of the Knox Gelatine Company. Analytical grade reagents were utilized without further purification. The standard solutions of NaOH (0.2 *N*) and HCl (0.2 *N*) were prepared by diluting Stansol solutions (Standard Solution Company, Menasha, Wisconsin) to the desired concentrations and restandardized before use. The NaOH was protected from the atmosphere by a tube packed with activated Alumina and Caroxite, a CO_2 absorbent. Nitrogen, water pumped, stated as being 99.6% pure was employed whenever necessary.

Prior to titration, the gelatin solutions were dialyzed at 37° in the presence of toluene against 6 changes of solvent (0.15 *M* KCl) for at least 3 days; the ratio of the gelatin (inner solution) to the solvent being 1:4. The dialysis sac was rotated during this period.

Protein concentrations were determined by dried weight at 115 ± 5°, correcting for the salt content. The validity of this correction was established by demonstrating that the dry weight of the outer solution differed from that of the 0.15 *M* KCl by less than 0.1%.

The methyl ester of gelatin (Metgel) was prepared by the procedure of Fraenkel-Conrat and Olcott.[4] The preparation was washed once with methanol and then repeatedly with acetone. The solvent was removed *in vacuo* at room temperature. The product, which was obtained in 80% yield, was identical in gross appearance to the parent substance.

Equipment.—The *p*H was determined with a Beckman Model G *p*H meter with a type E-2 all-*p*H glass electrode in conjunction with a saturated calomel electrode. The instrument was calibrated at 37° against 0.05 *M* potassium hydrogen phthalate, *p*H 4.03,[5] and at 6.98 and 9.88 using 2 standard buffers.

The iso-ionic *p*H for gelatin was established by electrodialysis employing both parchment paper membrane and Amberplex ion resin membranes (donated by Rohm and Haas).

Titration.—The standard acid or alkali was introduced with a Koch micro-buret, 5-ml. capacity, into 15.00 ml. of 2% gelatin solution contained in a 50-ml. water-jacketed beaker. The temperature was maintained at 37.0 ± 0.2°. Control experiments in which the protein was eliminated were performed in order to evaluate the activity coefficient of the reactants. Prior to the initiation of any experiment, the electrodes were standardized against two of the buffers, and upon completion of the run they were rechecked. In any case, where the drift in reading exceeded 0.03 *p*H unit the experiment was discarded. In the alkaline range of ti-

(1) (a) This investigation was supported by a grant from the Office of the Surgeon General, Department of the Army, Contract No. DA-49-007-MD-248, upon the recommendation of the Subcommittee of Shock of the National Research Council. (b) Presented in part at the 130th Meeting of the American Chemical Society, Atlantic City, New Jersey, Sept., 1956. (c) Publication No. 95 of the Department of Pathology, University of Pittsburgh School of Medicine.

(2) P. H. Maurer, *Arch. Biochem. et Biophys.*, **58**, 205 (1955).

(3) S. Katz and P. H. Maurer in preparation.

(4) H. A. Fraenkel-Conrat and H. S. Olcott, *J. Biol. Chem.*, **161**, 259 (1945).

(5) National Bureau of Standards, Letter Circular LC 933 (1948).

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tration, absorption of atmospheric CO_2 was minimized by continuously bubbling nitrogen gas through the system. The reversibility of the reaction was demonstrated by back-titration and agreed to within 4% of theoretical values. The resulting isotherms were calculated in the conventional manner making the customary assumptions with respect to the additivity of volumes, junction potentials and activity coefficients.[6]

Equilibration.—The equilibration method for determining the association isotherm for gelatin was performed by adding measured quantities of reagents to 50-ml. weighing bottles so that the total volume was 20.0 ml. and the resultant gelatin concentration was about 2%. The system was equilibrated at 37 ± 0.02° for about 24 hr. before *p*H measurements. The electrodes were standardized at frequent intervals. The deviation of any individual reading about the average as a rule did not exceed 0.01 *p*H unit at *p*H values lower than 5. When alkali was added a nitrogen atmosphere was maintained as previously described. The reversibility of the process was established by addition of the appropriate reagent to the equilibrated system, after which another equilibration period was allowed before *p*H measurement. The results agreed within 3% on the acid and 5% on the alkaline[7] sections of the curve.

Alkaline Hydrolysis.—The alkaline hydrolytic method for assaying the methoxyl content of Metgel was performed as follows. A measured excess of NaOH was added to 50.00-ml. aliquots previously adjusted to *p*H 6.2. The solution was then transferred to a 100-ml. volumetric flask, sealed with a greased stopper and allowed to equilibrate for 24 hr. at 37°. The residual alkali was determined by back-titration of 25.00-ml. aliquots.

Formol Titrations.—The procedure was essentially similar to that reported in the review by French and Edsall.[8] In order to determine the α- and ε-ammonium residues and minimize the imidazolium contribution, the solution of gelatin was adjusted to *p*H 7.8. To aliquots containing approximately 2% gelatin, measured volumes of 36% reagent grade formaldehyde, *p*H 7.0, were added so that the final formaldehyde concentration was 8 ± 1%. The end-point was determined by plotting Δ *p*H/Δ ml., the incremental change of *p*H with respect to alkali, *versus* ml. of NaOH added.[9]

Results and Discussion

The iso-ionic point[10] for beef bone gelatin was found to be 4.96 ± 0.02 at 37° by electrodialysis. Equilibration required 24 hr. when parchment-paper membranes were used; however, with ion-exchange resins, Amberplex C-1 and A-1, the time was decreased to 5 hr. When a 2% salt-free gelatin solution was made 0.15 *M* with respect to KCl the resultant iso-ionic *p*H of 4.94 indicated little or no binding of KCl by gelatin, in agreement with Carr and Topol.[11]

Potentiometric Titrations.—The proton dissociation curves for gelatin are given in Fig. 1. The titration isotherm represented by the lower curve was reproducible to within 3% and was found to be reversible. However, when compared with the data obtained by equilibration these proved to be 10% too low. Subsequent investigation revealed that the 30-min. period allowed for reaction during titration was not sufficient to permit equilibration. In contrast with these findings, Kenchington and Ward[12] titrated another type of gelatin successfully; however, the time allowed for equilibration was not indicated. It is difficult to attribute this deviation to heat effects, change of ionic strength (the change was less than 4%), or the 20% dilution of the protein. Assuming the absence of systematic errors, the most plausible explanation is that equilibration of the gelatin with the acid requires an appreciable time. It should be noted that a variation of 0.10 *p*H unit at *p*H 2.2 for the system studied would be equivalent to a change of 0.08 milliequivalent protons bound per g. gelatin. On this basis, no attempt was made to analyze the gelatin isotherms derived from titration.

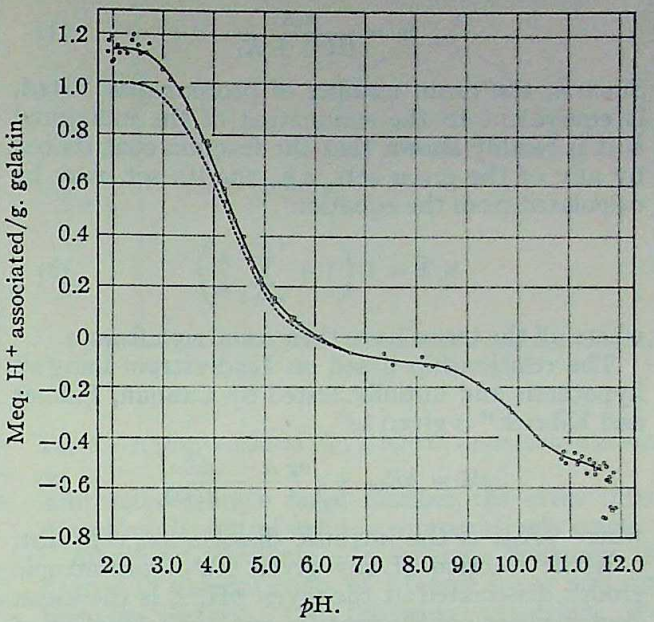

Fig. 1.—The proton association isotherm for beef bone gelatin as determined at 37°; μ = 0.15. The titration data are represented by the broken line; the equilibration data by the curve through the open circles.

The equilibration isotherm, upper curve, is typical for this process,[12,13a-c] except for the region more alkaline than *p*H 11.5. That the downward trend of the data is due to the effect of the guanidinium residues and not due to the experimental error was demonstrated by reversibility experiments.

The theory of the analysis of similar isotherms has been the subject of many reviews[14a-c]; therefore, this aspect of the discussion will be limited to some of the essential equations.

The relationship between h_i, the number of protons dissociated from the ith set of n proton donor groups and the apparent dissociation constant, K_i, for any statistically equivalent unit in this set is given by equation 1 where (H^+) is the proton concentration.

(6) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943, pp. 444–502.
(7) No correction was made for the slight change in ionic strength.
(8) M. Levy, *J. Biol. Chem.*, **105**, 157 (1934); R. A. Kekwick and R. K. Cannan, *Biochem. J.*, **30**, 235 (1936); D. French and J. T. Edsall in M. L. Anson and J. T. Edsall, "Advances in Protein Chemistry," Vol. 2, Academic Press, Inc., New York, N. Y., 1945, pp. 302–317.
(9) M. S. Dunn and A. Loshakoff, *J. Biol. Chem.*, **113**, 359 (1936).
(10) S. P. L. Sørensen, K. U. Linderstrøm-Lang and E. Lund, *J. Gen. Physiol.*, **8**, 543 (1927); G. Scatchard and E. S. Black, *J. Phys. Chem.*, **53**, 88 (1949).
(11) C. W. Carr and L. Topol, *ibid.*, **54**, 176 (1950).
(12) A. W. Kenchington and A. G. Ward, *Biochem. J.*, **58**, 202 (1954).
(13) (a) J. H. Bowes and R. H. Kenten, *ibid.*, **43**, 358 (1948); (b) W. M. Ames, *J. Sci. Food Agr.*, **12**, 579 (1952); (c) J. Salvinien and S. Combet, *Compt. rend.*, **242**, 114 (1956).
(14) (a) R. K. Cannan, *Chem. Revs.*, **30**, 395 (1942); (b) E. J. Cohn and J. T. Edsall, *ibid.*, **30**, 395 (1942); (c) J. Steinhardt and E. M. Zaiser in M. L. Anson, K. Bailey and J. T. Edsall, "Advances in Protein Chemistry," Academic Press, Inc., New York, N. Y., Vol. 10, 1955, pp. 152–226.

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$$h_i = \frac{n_i K_i}{(H^+) + K_i} \qquad (1)$$

Since $\bar{h}$, the mean number of protons dissociated, is equivalent to the summation of the individual h_i it is readily shown that the fraction contributed by any of the given sets, *e.g.*, the lth set, may be calculated from the equation

$$h_1/\bar{h} = 1/\left(1 + \sum_{i=2}^{i=n} \frac{h_i}{h_1}\right) \qquad (2)$$

where all the terms have their usual significance.

The relationship based on Linderstrøm-Lang's[15] hypothesis and initially tested by Cannan, Palmer and Kibrick[16] is given as

$$p\mathrm{H} = pK_{\mathrm{int}} + \frac{\log \alpha}{1-\alpha} - \frac{2\bar{Z}\omega}{2.303} \qquad (3)$$

where pK_{int} is the intrinsic dissociation constant, α is the fraction of any given set of prototropic groups dissociated at the given pH, $\bar{Z}$ is the mean electric charge of the protein, and ω is a function of electrostatic potential of the protein species involved.[14a]

In order to evaluate the contribution of the imidazolium groups a tentative assignment of the α-ammonium groups was made on the premise that the gelatin studied was essentially a linear polymer with a number average molecular weight of about 50,000.[13a,17,18] The number and the pK's of the imidazolium and the α-ammonium groups were obtained by solving simultaneous equations[19] for values of $\bar{h}$ at pH 6.5 and 7.5.

The number of ϵ-ammonium groups was determined from the titration values between pH 8.0 and 11.25 as corrected for the residual contribution of the α-ammonium, imidazolium and guanidinium groups. The greatest single source of error is the difficulty in ascertaining the guanidinium contribution since its pK is not well established even at 25°, while the extrapolation to 37° (van't Hoff equation) introduces another element of error. If the pK were taken as being 13.0 then its contribution would be 0.009 meq./g., if it were 12.5 the corresponding value would be 0.027 meq./g., and similarly for pK 12 it would be 0.078 meq./g. By inspection of the curve it appeared that the value of about 12.5 would be justified for this calculation.

The pK_{int} of the carboxylate groups (uncorrected for α-carboxyl) was determined by plotting $p\mathrm{H} - \log \alpha/(1-\alpha)$ as ordinate *versus* $\bar{Z}^*$, the electronic charge of the protein calculated on a gram basis. The term $\bar{Z}^*$ was calculated from the titration curve, implicitly omitting any salt correction.[11] From Fig. 2, the value for pK_{int} of 4.35 ± 0.04 at 37° was determined in good agreement with that of 4.28, at 25° reported by Salvinien and Combet.[13c] The plot is linear over 80% of the range. The reversal of the curve is too large to be attributed to the α-carboxyl contribution and must be ascribed to higher order effects which have been neglected in the simple model used. A similar plot for the ϵ-ammonium groups is given in Fig. 3. The apparently anomalous behavior may be explained by considering that the ϵ-ammonium groups are contributed by both the lysine and hydroxylysine residues whose pK's are 10.28 and 9.50, respectively.[20] Therefore it is apparent that equation 4 is not applicable.

A comparison of the number of dissociable groups deduced from titration data with that determined by Eastoe[21] from amino acid analysis is offered in Table I. The titration value for the free carboxyl groups (inclusive of the α-carboxyl) of 1.13 ± 0.03 meq./g. gelatin, is in excellent accord with Eastoe's. The figure for the imidazolium residues obtained by titration, though corrected for the α-ammonium contribution, is somewhat high but within the experimental error. If the titration value for the ϵ-ammonium groups is adjusted for the tyrosyl hydroxyls the resulting value of 0.37 meq./g. is again in excellent accord with the English work. This is further corroborated by the value of 0.36 meq./g. obtained by formol titrations. The number of guanidinium residues, 0.46 meq./g., was calculated from the difference between the maximum acid binding quantity, 0.923 meq./g., and the anionic basic groups. This value is lower than that established by amino acid analysis. Furthermore it must be recognized that the initial quantity is more suspect due to incorporation of accumulative errors.

TABLE I

IONIZABLE GROUPS—BEEF BONE GELATIN

Group	Meq. per gram: Titration[a]	Meq. per gram: Analysis[b]	pK: This study	pK: Lit.[c]
Carboxyl (free)	1.13[d]	1.12[e]	4.35 ± 0.04[f]	3.0–4.7
Imidazolium	0.075	0.045	6.7	5.4–6.8
α-Ammonium	.019	...	8.2	7.3–8.1
ϵ-Ammonium	.38[g]	.346	...	9.1–10.3
Phenolic hydroxyl	...	.013	...	.....
Guanidinium	.46	.52	...	.....

[a] Determined at 37.0 ± 0.02°, μ = 0.15. [b] J. E. Eastoe, *Biochem. J.*, 61, 589 (1955). [c] These values, corrected to 37°, are from E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943, p. 445. [d] This includes the contribution of the α-carboxyl groups. [e] This value is corrected for the amide contribution. [f] This corresponds to pK_{int}. [g] This includes the phenolic hydroxyl contribution.

(15) K. U. Linderstrøm-Lang, *Compt. rend. trav. lab. Carlsberg*, **15**, No. 7 (1925).

(16) R. K. Cannan, A. H. Palmer and A. C. Kibrick, *J. Biol. Chem.*, **142**, 803 (1942).

(17) A. Courts, *Biochem. J.*, **59**, 382 (1955); J. W. Williams, W. M. Saunders and J. S. Cicirelli, *J. Phys. Chem.*, **58**, 774 (1954); J. Pouradier and A. M. Venet, *J. Chim. Phys.*, **47**, 11 (1950); G. Scatchard, J. L. Oncley, J. W. Williams and A. Brown, THIS JOURNAL, **66**, 1980 (1944).

(18) If the gelatin contains an appreciable fraction with a molecular weight much less than 30,000 the validity of this assumption is seriously compromised. However, the trend to the other extreme would not introduce as serious an error.

(19) The equations used were

at pH 6.5

$$2 = \frac{K_1}{3.16 \times 10^{-7} + K_1} + \frac{5K_2}{3.16 \times 10^{-7} + K_2}$$

at pH 7.5 =

$$4.5 = \frac{K_1}{3.16 \times 10^{-8} \times K_1} + \frac{5K_2}{3.16 \times 10^{-8} + K_2}$$

The values for h were corrected for carboxyl contribution. Even though these equations are based on an estimated molecular weight of 50,000, the results are independent of this assumption.

(20) D. D. Van Slyke, A. Hiller, J. A. Macfayden, A. B. Hastings and R. M. Kleinhardt, *J. Biol. Chem.*, **133**, 287 (1940).

(21) J. E. Eastoe, *Biochem. J.*, **61**, 589 (1955).

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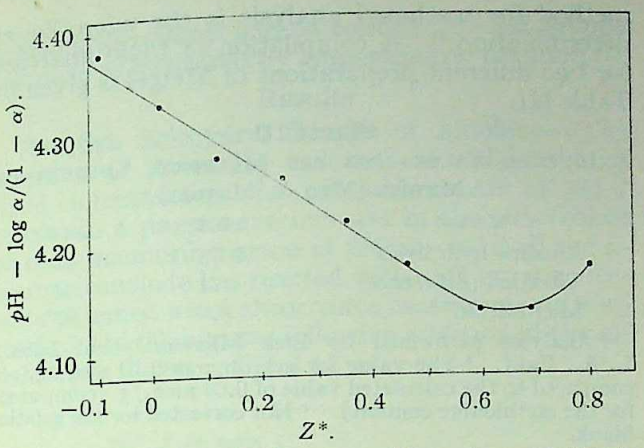

Fig. 2.—The plot of pH − log $\alpha/(1-\alpha)$ *versus* Z^*, the mean electric charge on gelatin calculated on a gram basis. This curve is for the free carboxyl group of beef bone gelatin at 37°, $\pi = 0.15$.

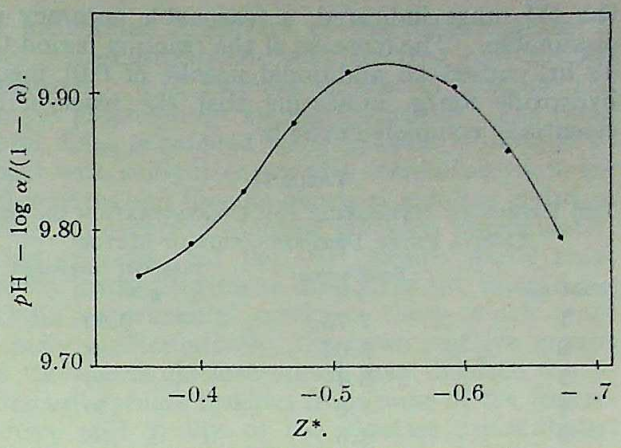

Fig. 3.—A plot, similar to Fig. 2, for the ϵ-ammonium groups.

Another method for interpreting this isotherm is the approach of Cannan, *et al.*,[14a,16] whereby certain arbitrary sections of the titration curve are attributed to given acidic groups. This analysis gave the following results: 1.145 meq./g. for the carboxyl groups (pH 2.0–6.125), 0.10 meq./g. for the imidazolium and α-ammonium groups (pH 6.125–8.0), 0.395 meq./g. for the ϵ-ammonium and phenolic hydroxyl groups (pH 8.0–11.25) and the calculated value for guanidinium was 0.44 meq./g. Thus it may be concluded that this approach is a successful first approximation.

Metgel.—From the difference between the carboxyl content of the original and modified proteins as determined potentiometrically, the extent of esterification of these polar groups may be evaluated. However, when the equilibration method was attempted for Metgel, it was observed that the readings were apparently stable at pH values lower than 5 but that there was a negative drift at higher pH values, *e.g.*, at pH 6.9 the rate of decrease was about 0.01 pH unit/min. When Metgel, with an initial pH of 4.4, was electrodialyzed the pH reached a maximum of about 9; however, upon prolonged electrodialysis the pH dropped asymptotically to 5. These observations are in general agreement with the findings of Saroff, *et al.*,[22b] for the methylated ester of bovine serum albumin which were interpreted as an indication of the lability of the methyl ester linkage in alkaline medium.

On this basis, the titration technique was employed to determine the acid section of the isotherm since it could be completed before extensive hydrolysis would occur. Even though the resulting data did not deviate more than 5% about the mean, no attempt was made to evaluate the reliability of these results due to the variables involved. Yet, if reference is made to Table III, where the degree of methylation was determined using these somewhat doubtful results, the conclusions appear to be quite satisfactory. This apparent anomaly may be rationalized by recognition of the fact that when a small value with a relatively large uncertainty is subtracted from a large number the error introduced by the initial value is comparatively small.

Alkaline Hydrolysis.—In order to determine the degree of esterification of Metgel by a less ambiguous method, the following procedure was developed which is based on the lability of the methyl ester bond in an excess of base.

The stoichiometry of the alkaline hydrolysis of the methyl ester bond in Metgel is indicated by the equation

$$\text{G—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—OR} + \text{OH}^- \longrightarrow \text{G—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—O}^- + \text{ROH} \quad (4)$$

For quantitative results, an excess of alkali must be employed in order to drive the reaction to the right. The possibility exists that this determination might be complicated by the competitive hydrolysis of either amide and/or peptide bonds. However, Bowes and Kenten[23] have shown that the peptide bond is resistant to alkaline hydrolysis under conditions more drastic than those used here, but that the amide group is somewhat more labile. If peptide hydrolysis were to occur it is evident that the back-titration to pH 6.2 would compensate for this effect since the liberated amino groups would be titrated. Evidence indicating that the ester hydrolysis was quantitative was the observation that the value for the free carboxyl groups as determined by continuing the titration to pH 2.1[24] agreed with that for the original gelatin (±2%). The possibility exists that this agreement may have been due to a fortuitous combination of incomplete ester hydrolysis coupled with amide and/or peptide cleavage. However, the fact that the latter effect was negligible was demonstrated by the results of formol titrations on regenerated Metgel, *i.e.*, Metgel neutralized after exposure to alkali, which were about 0.015 meq./g. higher than that of gelatin. Further corroboration was offered by the observation that a 24 hr. exposure of gelatin at pH 13, 37°, resulted in a consumption of ± 0.015 meq. alkali/g.

The effect of different concentrations of hydroxide ion on the ester hydrolysis is summarized in Table II. From these data it appears that providing the final hydroxide ion concentration is in

(22a) S. Blackburn, E. G. H. Carter and H. Phillips, *Biochem. J.*, **35**, 627 (1941); (b) H. A. Saroff, N. R. Rosenthal, E. R. Adamik, N. Hages and H. A. Scheraga, *J. Biol. Chem.*, **205**, 753 (1953).

(23) J. H. Bowes and R. H. Kenten, *Biochem. J.*, **43**, 365 (1948).

(24) Sufficient time should be allowed in order to ensure that equilib-

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the *p*H range indicated, a reasonable accuracy is obtainable. The increase of the reaction period to 48 hr. caused an additional uptake of 0.01 meq. hydroxide ion/g. indicating that the reaction is essentially completed in 24 hr.

TABLE II

THE EFFECT OF HYDROXIDE ION CONCENTRATION ON THE METHYL ESTER DETERMINATION OF METGEL

Expt. no.	Equilibrium[a] *p*H	Meq. OH^- consumed / g. Metgel
1	7.75	0.90
2	8.00	.88
3	8.4	.90
4	8.5	.90
5	8.5	.93
6	9.0	.94
		.91

[a] The *p*H of the system after 24 hr. incubation.

A check of the validity of this technique is offered by a comparison of these results with those derived by other methods. The methyl ester content of Metgel may be calculated from the difference in the titration curves of the initial and final materials. The validity of these results has been discussed in a previous section. Still another method for methoxyl analysis is the micro-Zeisel determination.[25] A compilation of these analyses for two different preparations of Metgel is given in Table III.

TABLE III

ANALYTICAL VALUES FOR THE METHOXYL CONTENT OF METGEL (MEQ./G. METGEL)

Method	Lot 2	Lot 3
Alkaline hydrolysis	0.71	0.91
Titration (difference)	.71	.94
Micro-Zeisel[a,b]	..	.87[c]

[a] Analyses performed by Elek Microanalytical Labs., L. A., Calif. [b] The value for gelatin was 0.10 meq./g. as compared to the calculated value of 0.04 meq./g. (computed for the methionine content). [c] Not corrected for the gelatin blank.

From these data it may be concluded that the alkaline hydrolysis method for methoxyl analysis is relatively simple and reliable to ± 4%.

Acknowledgment.—The authors wish to acknowledge the able assistance of Mr. Trayon Onett in the latter phase of this problem.

(25) J. B. Niederl and V. Niederl, "Micromethods of Quantitative Organic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 239–244.

PITTSBURGH, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF MINNESOTA]

Sulfhydryl Groups in Relation to Aldolase Structure and Catalytic Activity[1]

BY A. D. SWENSON AND P. D. BOYER

RECEIVED OCTOBER 26, 1956

Spectrophotometric measurements readily reveal a graded reactivity of *p*-mercuribenzoate with the –SH groups of rabbit muscle aldolase; some react rapidly at *p*H 7 and 25°, some react much more slowly, and others react only in the presence of urea. With 4.8 *M* or higher urea concentrations, 28 *p*-mercuribenzoate molecules react rapidly per aldolase molecule. The catalytic activity is progressively decreased to 0 as urea concentration is increased up to 3.6 *M;* inactivation by up to 4 *M* urea is completely reversible upon dilution. The rate and extent of reaction with *p*-mercuribenzoate is not influenced by the presence of an excess of substrates. Up to 10 –SH groups per mole of aldolase can react with *p*-mercuribenzoate without decrease in the catalytic activity. Additional reaction with *p*-mercuribenzoate causes a reversible loss of catalytic activity which appears to be associated with structural changes in the aldolase.

Introduction

Considerable information has been accumulated about the status of sulfhydryl groups in enzymes and their catalytic activity.[2] For example, the pioneering studies of Hellerman, *et al.*,[3] with urease showed that the most reactive –SH groups were not essential for catalytic activity but that reaction of additional –SH groups resulted in marked activity loss. Quantitative observations on the relationships between enzyme structure, number of –SH groups reacted with a particular reagent, and the catalytic activity have been limited. Particularly lacking are results which give a clear indication of whether the essential –SH groups have a primary role in the catalysis or whether reaction of the –SH groups results in secondary changes leading to loss of activity. The latter possibility has been suggested by others, including Desnuelle and Rovery[4] and Nygaard.[5]

The rate and extent of the reaction of –SH groups of proteins with the mercaptide forming agent, *p*-mercuribenzoate, at neutral *p*H and under mild conditions, may be measured conveniently by a spectrophotometric technique.[6] This paper gives results of application of the spectrophotometric procedure to measurements of the –SH groups of rabbit muscle aldolase together with catalytic activity measurements in the presence and absence of various urea concentrations. Rabbit muscle aldolase was chosen for study because it is readily obtainable in pure form,[7] conveniently assayed, and has been reported to be inhibited by reaction with

(1) Supported in part by research grant 1783 of the National Science Foundation and by the Hill Family Foundation.

(2) E. S. G. Barron, *Advances in Enzymol.*, **11**, 201 (1951).

(3) L. Hellerman, F. P. Chinard and V. R. Dietz, *J. Biol. Chem.*, **147**, 443 (1943).

(4) P. Desnuelle and M. Rovery, *Biochem. Biophys. Acta*, **3**, 26 (1949).

(5) A. P. Nygaard, *Acta Chem. Scand.*, **10**, 397 (1956).

(6) P. D. Boyer, THIS JOURNAL, **76**, 4331 (1954).

(7) J. F. Taylor, A. A. Green and G. T. Cori, *J. Biol. Chem.*, **147**, 521 (1948).

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p-mercuribenzoate[8] and to contain 29 –SH groups per mole as measured by amperometric titration.[9]

Results

Reactive Sulfhydryl Groups of Aldolase.—The addition of increasing amounts of aldolase to a fixed concentration of *p*-mercuribenzoate at *p*H 7 results in a progressive increase in the absorbance of the *p*-mercuribenzoate at 250 mμ until all the *p*-mercuribenzoate has reacted with –SH groups. Results obtained when absorbance measurements were made 3 and 60 minutes following addition of the aldolase are shown in Fig. 1A.

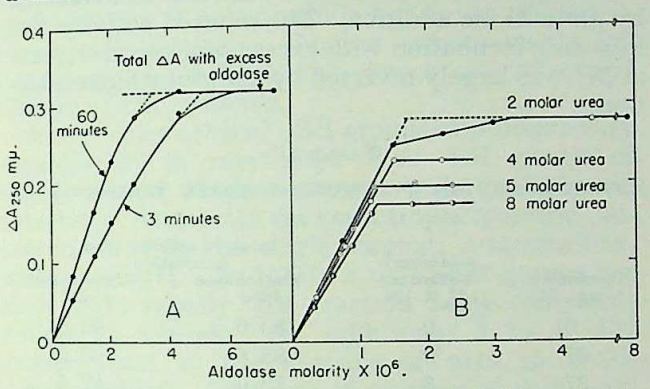

Fig. 1.—Spectrophotometric shift from addition of aldolase to *p*-mercuribenzoate in (A) 0.05 *M* phosphate buffer and 3.5×10^{-5} *M* *p*-mercuribenzoate *p*H 7.0, 25°, and (B) as in A but with indicated urea concentrations.

The presence of urea increases both the rate and the extent of reaction of aldolase –SH groups with *p*-mercuribenzoate. Figure 1B shows results obtained with various urea concentrations after the maximum spectral shift had been obtained. This was 3 minutes or less when 5 *M* or greater urea was present; with 2 *M* urea readings were at 180 minutes. Data showing the cause of the decrease in the total ΔA_{250} in the presence of urea will be presented later.

The fraction of the *p*-mercuribenzoate which has reacted with aldolase under a given set of conditions may be taken as approximately equal to the ratio of the observed ΔA_{250} to the total possible ΔA_{250}. This calculation will give an accurate value for the number of –SH groups reacted only if the absorbance at 250 mμ is the same for each –SH which reacts or if all –SH groups have a statistically equal reactivity with *p*-mercuribenzoate. Different proteins show a variation in the spectral shift at 250 mμ accompanying mercaptide formation,[2] and it thus seems feasible that variation may be encountered with different –SH groups on the same protein. One or both of the aforementioned requisites is met within experimental error for aldolase in the presence of 4 *M* or greater urea concentration, as shown by the straight line relationship between ΔA_{250} and aldolase concentration until a maximum is reached (for example, curve 4, Fig. 1). The lack of a straight line relationship for the experiments in the absence of urea is principally and perhaps entirely a reflection of the decrease in rate of mercaptide formation as the concentration of free *p*-mercuribenzoate and reactive –SH groups decreases; with increase in time of reaction the curves progressively approach linearity. The same total ΔA_{250} is reached when aldolase is allowed to react with a slight excess of *p*-mercuribenzoate for 60 minutes and then an excess of aldolase added as when an excess of aldolase is added immediately. This suggests that the –SH groups which react slowly in the absence of urea show the same ΔA_{250} within experimental error, as those which react rapidly. Alternatively, the more reactive groups of the excess aldolase added may displace the *p*-mercuribenzoate residues from some of the less reactive –SH groups of the aldolase preincubated with excess *p*-mercuribenzoate.

From the fraction of the *p*-mercuribenzoate which has reacted, the number of –SH groups per mole of aldolase which have formed mercaptides can be calculated readily. Figure 2 shows the –SH groups reacted per mole of aldolase as a function of urea concentration and of time. Readings made under comparable conditions 15 seconds after addition of an excess of *p*-mercuribenzoate to aldolase without urea present showed, in various trials, 5 to 7 –SH groups per mole which reacted within this period. These groups are clearly distinct in their reactivity from those reacting slowly over a several hour period. They are likely those responsible for the positive nitroprusside test mentioned by Racker.[10]

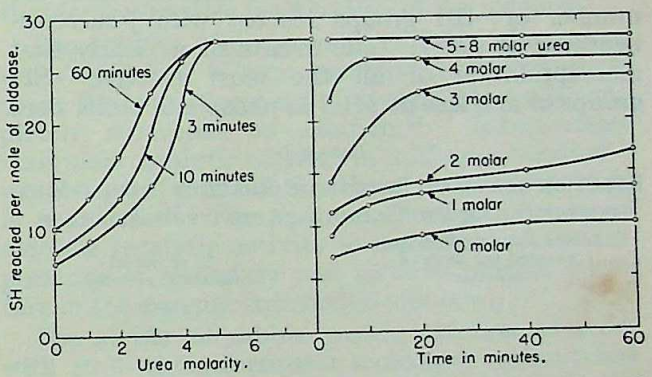

Fig. 2.—Effect of urea on rate and extent of reaction of aldolase SH groups with *p*-mercuribenzoate. Reaction mixtures contained 0.05 *M* phosphate buffer, 3.5×10^{-5} *M* *p*-mercuribenzoate, and urea as indicated, *p*H 7.0, 25°.

The effect of urea in decreasing the ΔA_{250} noted in Fig. 1B results from an increase in the absorbance of the *p*-mercuribenzoate in the presence of the urea, as shown in Fig. 3. The absorbance of the mercaptide of *p*-mercuribenzoate at 250 mμ is not increased by urea; this is illustrated in Fig. 3 for the mercaptide with glutathione. The increase in the absorbance of the *p*-mercuribenzoate undoubtedly results from formation of a urea-*p*-mercuribenzoate compound, very likely involving the mercury, which, on the appearance of the SH compound, gives way to the formation of the mercaptide with the *p*-mercuribenzoate.

Role of Aldolase –SH Groups in the Catalytic Activity.—The data in Table I summarize the

(8) K. Bailey and B. B. Marsh, *Biochim. Biophys. Acta*, 9, 133 (1952).

(9) R. E. Benesch, H. A. Lardy and R. Benesch, *J. Biol. Chem.*, 216, 663 (1955).

(10) E. Racker in Colowick, *et al.*, "Glutathione," Academic Press, New York, N. Y., 1954, p. 101.

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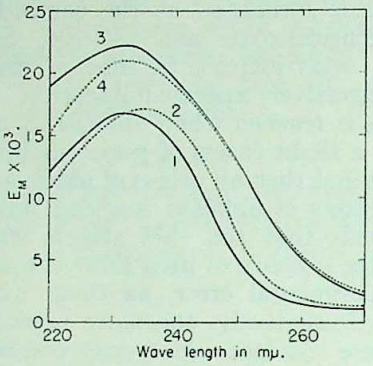

Fig. 3.—Effect of urea on the absorbance of *p*-mercuribenzoate and its glutathione mercaptide: curve 1, 5.7×10^{-5} *M* *p*-mercuribenzoate in 0.05 *M* phosphate *p*H 7.0; curve 2, as 1 but with 8 *M* urea added; curve 3, as 1 but with 10^{-4} *M* glutathione added; curve 4, as 3 but with 8 *M* urea added.

relation between the catalytic activity and the number of –SH groups reacted with *p*-mercuribenzoate at *p*H 7. The results show clearly that mercaptidation of all the most reactive –SH groups of aldolase at *p*H 7 in phosphate buffer does

TABLE I

RELATION BETWEEN EXTENT OF REACTION WITH *p*-MERCURIBENZOATE AND CATALYTIC ACTIVITY OF ALDOLASE

Moles *p*-mercuribenzoate reacted per mole of aldolase	% of initial catalytic activity
0	100
6	98
8	99
10.5	98
12	70
14	32

not significantly decrease the catalytic activity. Exposure at 37° for 1 hour was necessary to get 12 –SH groups to react in the absence of urea and to show a definite decrease (30%) in catalytic activity.

In Fig. 4 are shown data on the rate of reaction of aldolase with *p*-mercuribenzoate in the presence

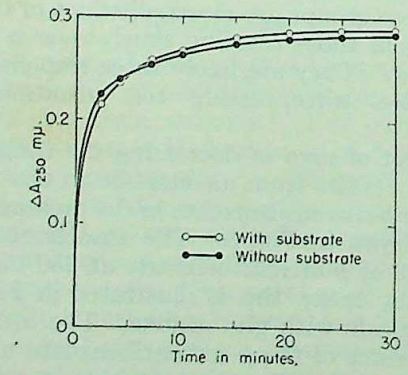

Fig. 4.—Lack of effect of substrate on the reaction of aldolase with *p*-mercuribenzoate. Reaction mixtures contained 0.05 *M* phosphate buffer, 2.6×10^{-6} *M* aldolase, 3.6×10^{-5} *M* *p*-mercuribenzoate with or without 0.07 *M* fructose, 6-diphosphate, *p*H 7.0, 25°.

and absence of substrates. With the concentration of enzyme used, the 0.07 *M* added fructose 1,6-diphosphate would be converted to an equilibrium mixture of the fructose and triose phosphates.[11] Clearly the presence of substrates in relatively high concentration had no effect within experimental error on the rate or extent of reaction of aldolase –SH with *p*-mercuribenzoate.

Reversibility of Aldolase Inactivation.—Table II gives results obtained when aldolase was incubated with or without *p*-mercuribenzoate present, followed by activity tests in the presence and absence of added glutathione. A control sample without *p*-mercuribenzoate incubated 1 hour at 0° showed no loss of activity, and that incubated at 37° a slight loss of activity. This loss was restored by glutathione addition. The marked activity loss following incubation with excess *p*-mercuribenzoate at 37° was largely reversed by the glutathione addition.

TABLE II[a]

REVERSAL OF THE *p*-MERCURIBENZOATE INHIBITION OF ALDOLASE

Incubation temp., °C.	*p*-Mercuribenzoate, $M \times 10^5$	Relative activity after incubation: No glutathione added	Relative activity after incubation: Glutathione added
0	0	100.0	99.0
37	0	88.5	100.0
37	3	12.0	87.5
37	3	12.5	88.0

[a] See Experimental section for details.

Effect of Urea on Aldolase Activity.—The catalytic activity of aldolase when assayed in the presence of urea progressively decreases as the urea concentration increases and falls rather abruptly to zero as the urea level reaches 3.6 *M* (Fig. 5).

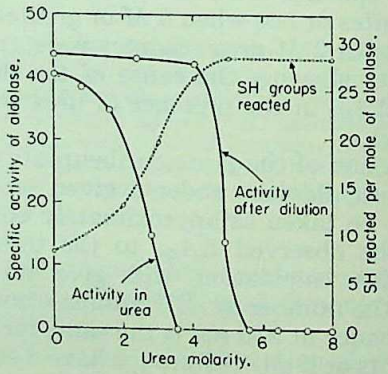

Fig. 5.—The effect of urea on the catalytic activity of aldolase. For details see the experimental section.

The loss in activity resulting from exposure to urea up to 4.0 *M* is essentially completely reversible as shown by the activity measured after a 100-fold dilution of the urea (Fig. 5). The extent of reversal of urea denaturation fell off sharply above 4.0 *M*; only 30% of the original activity was regained after exposure to 4.8 *M* urea, and exposure to 5.6 *M* urea or higher resulted in irretrievable activity loss. The loss in activity with exposure to 5.6 *M* urea varied with aldolase concentration; with $^1/_{10}$ as much aldolase as used for the experiments reported in Fig. 5, approximately $^1/_4$ of the activity was regained following dilution.

(11) D. Herbert, A. H. Gordon, V. Subrahmanyan and D. E. Green, *Biochem. J.*, **34**, 1108 (1940).

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Discussion

The data show that in the presence of 5.0 *M* or higher urea concentration 28 moles of *p*-mercuribenzoate react rapidly with one mole of aldolase. This figure likely represents the total number of –SH present in the aldolase, and agrees well with the value of 29 –SH per mole reported by Benesch, *et al.*, from amperometric Ag titration measurements in 8 *M* urea solution[9] using the same values for molecular weight and absorbance at 280 mμ for determination of aldolase molarity. These values for total –SH considerably exceed the number of reported half-cysteine residues per mole,[12] and suggest that few if any disulfide bonds are present in the native aldolase. Further measurements are necessary to establish this important structural feature of the molecule.

As noted by others,[2] –SH groups of proteins vary considerably in reactivity. The –SH groups of rabbit muscle aldolase show a wide gradation in reactivity detectable by spectrophotometric observations with the single reagent, *p*-mercuribenzoate. At *p*H 7 and 25°, 5 to 7 –SH groups per mole react rapidly, the reaction being completed within 15 seconds. An additional 3 to 4 –SH groups react in the absence of urea in a 90-minute period. The rate of reaction of these –SH groups is sufficiently slow to distinguish them clearly from those which react in 15 seconds. The addition of urea is required to bring about reaction of the remaining –SH groups. Further, differences in the reactivity of these –SH groups can also readily be recognized. This is shown by the increase in total number of –SH groups reacting in the presence of 3, 4 and 5 *M* urea (Fig. 2).

The graded reactivity of the aldolase –SH groups and the ability of urea to increase their reactivity strongly suggests that the lack of reactivity of the aldolase –SH groups results from their unfavorable steric position within the molecule. Similar interpretations have been suggested earlier for "sluggish" –SH groups of proteins.[2,9] Although Benesch, Benesch and Rogers[13] have shown that urea may increase the reactivity of the –SH of glutathione toward nitroprusside, glutathione and other low molecular weight thiols react very rapidly with *p*-mercuribenzoate. Therefore structural features of the protein molecule likely account for reduced reactivity of some –SH groups.

That the –SH groups of the muscle aldolase may not participate directly in the enzyme catalysis is suggested by three facets of the experimental data. First, up to 10 –SH groups per mole, which includes all the rapidly reacting –SH groups, can react with *p*-mercuribenzoate without decrease in the catalytic activity; second, an excess of substrate fails to diminish the reactivity of the –SH groups with *p*-mercuribenzoate; and third, the decrease in catalytic activity occurs only when the less reactive –SH groups combine with *p*-mercuribenzoate. Such combination could logically result in changes of the secondary structure of the aldolase molecule. This possibility also draws support from correlations of the effects of urea and *p*-mercuribenzoate on the enzyme. Such correlations are well shown by the data of Fig. 5, which further define the relationship between structure, –SH reactivity and catalytic activity. The loss of activity resulting from increase in urea concentration is roughly paralleled by an increase in reactivity of the –SH groups. Sufficient structural change to cause complete loss of catalytic activity occurs well before complete reaction of the –SH groups. Exposure to 4.0 *M* urea allows reaction of all but approximately 3 of the –SH groups with *p*-mercuribenzoate, yet the effect on catalytic activity is entirely reversible. Thus the aldolase molecule in 4.0 *M* urea retains sufficient structure to allow the molecule to regain the original configuration or a comparably effective configuration of the active center. Likewise, aldolase inactivated by reaction with *p*-mercuribenzoate at 37° retains sufficient structure for regaining of catalytic activity (Table II). The urea concentration required for complete reaction of the –SH corresponds approximately to that for irreversible inactivation of the aldolase.

The activity of enzymes is variably affected by urea. Aldolase is more sensitive than trypsin to urea; the loss of trypsin activity in 8 *M* urea is completely recovered on dilution.[14] Ribonuclease maintains catalytic activity in 8 *M* urea solution,[15] pepsin in 4 *M* urea solution,[16] and carboxypeptidase in 6 *M* urea.[17] The pronounced effect of urea on aldolase catalytic activity is indicative of the importance of secondary and tertiary protein structure in the enzymic function of aldolase.

The ability of rabbit muscle aldolase to react with 10 *p*-mercuribenzoate molecules without loss of catalytic activity (Table I) was not an expected result. However, as mentioned earlier the most reactive groups of urease are not essential for catalytic activity.[3] The type of result obtained with aldolase and urease may prove to be a more general phenomenon. Desnuelle and Rovery noted that the loss of activity of urease occurred concomitantly with combination of the less reactive groups with phenyl isocyanate.[4] They argued cogently for the interpretation similar to that presented herein for aldolase, namely, that the inactivation resulted from reversible structural changes accompanying reaction of the –SH groups. Nygaard has suggested that some of the effects of *p*-mercuribenzoate on lactic dehydrogenase may result from structural alteration.[5] The results with aldolase are in contrast to the finding of Wallenfels and Sund[18] that the loss of activity of liver alcohol dehydrogenase is strictly proportional to the extent of reaction with *p*-mercuribenzoate.

The frequent interpretation that inactivation accompanied by blocking of –SH group implies a primary role of the –SH groups in enzyme catalysis is open to serious question. Enzymes showing such inactivation, particularly where the inactivation is

(12) S. F. Velick and E. Ronzoni, *J. Biol. Chem.*, **173**, 627 (1948).

(13) R. Benesch, R. E. Benesch and W. I. Rogers, "Glutathione," Academic Press, New York, N. Y., 1954, p. 31.

(14) J. I. Harris, *Nature*, **177**, 471 (1956); H. O. Michel, *Federation Proc.*, **15**, 315 (1956).

(15) C. B. Anfinsen, W. F. Harrington, A. Hoidt, K. Linderstrom-Lang, M. Ottenson and J. Schellman, *Biochem. Biophys. Acta*, **17**, 141 (1955).

(16) J. Steinhardt, *J. Biol. Chem.*, **123**, 543 (1938).

(17) Y. Halsey and H. Neurath, *ibid.*, **217**, 247 (1955).

(18) K. Wallenfels and H. Sund, *Angew. Chem.*, **67**, 517 (1955).

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reversible, have been termed "sulfhydryl enzymes."[2] Such classification should not carry the implication of a primary function of the –SH groups in catalysis. The demonstration of a primary function for –SH groups is difficult. The probability of a primary function would follow from information as to how the –SH participates, as has been obtained for glyceraldehyde 3-phosphate dehydrogenase,[19] or the establishment that the inactivation is not accompanied by secondary structural changes. Such information is lacking for most "sulfhydryl enzymes."

Experimental

Special Reagents.—Aldolase was crystallized from rabbit muscle by the method of Taylor, *et al.*,[7,20] except that all solutions for extraction and crystallization contained 10^{-4} *M* ethylenediaminetetraacetate and were prepared in distilled water passed through a mixed ion-exchange resin bed (Rohm and Haas Amberlite Monobed 3) to remove ionic impurities. The enzyme used was crystallized 4 times to a constant specific activity. When stored as a suspension in the crystallizing medium at 5° the enzyme maintained full activity for at least three months. The molar concentration of aldolase was determined from its absorbance at 280 mμ (A_{280}/0.910 equal grams of aldolase per liter[20]) and its molecular weight of 147,000.[20] The more recent figure of 149,000[21] would not significantly change the values of –SH groups per mole reported herein.

Fructose 1,6-diphosphate solutions were prepared from the magnesium salt (Nutritional Biochemicals) by passing a 0.02 *M* solution through a Dowex 50-H column after which the *p*H was brought to 7.4 with 2 *M* NaOH.

Purification of urea was deemed advisable to minimize possible acceleration of –SH oxidation by any heavy metal contaminants present. For most of the studies urea was purified by passage of 8 *M* solutions through small beds of mixed ion-exchange resin. However, this procedure resulted in a prominent initial elution followed by a slower continuous elution from the column of material giving small absorption at 220–260 mμ. This material did not give a spectral shift with *p*-mercuribenzoate. Also, different batches of urea of the same grade and source differed in their content of ultraviolet absorbing impurities. These could be removed by recrystallization twice from hot 95% ethanol, and urea purified in this manner rather than by the ion exchange resins was used for some later studies.

Aldolase Catalytic Activity Assay.—The catalytic activity assay used is a modification[22] of that of Sibley and Lehninger.[23] One ml. of aldolase solution, recently brought to 30° and containing approximately 10 μg. of aldolase, was added to 0.5 ml. of 0.02 *M* fructose 1,6-diphosphate, *p*H 7.4, and 0.5 ml. of 0.5 *M* hydrazine sulfate, *p*H 7.4, at 30°. At the end of 10 minutes the reaction was stopped with 1 ml. of 0.005 *M* 2,4-dinitrophenylhydrazine in 2 *M* HCl. The development of chromogen proceeded for another 10 minutes at 30° at which time 7 ml. of 0.375 *M* NaOH was added and the system removed from the bath to stand at room temperature. After standing exactly 10 minutes at room temperature the absorbance of 525 mμ was read using a blank in which the sequence of addition of enzyme and 2,4-dinitrophenylhydrazine was reversed. The absorbance at 525 mμ divided by the calculated absorbance of the enzyme at 280 mμ in the assay system is defined herein as the specific activity of the enzyme. For values as measured on the Beckman DU spectrophotometer, using 1 cm. light paths, the 4 times crystallized enzyme had a specific activity of 46–50. Absorbance measurements in routine assays were made with a Bausch and Lomb Spectronic 20 colorimeter and converted to the equivalent Beckman readings by use of appropriate conversion factors.

Although the aldolase assay procedure used has only approximately 1/10 the sensitivity of Beck's modification[24] of the Sibley–Lehninger[23] method, it is considerably simpler, readily reproducible, and could be used because sensitivity was not a limitation of the experimental procedures. Removal of protein by trichloroacetic acid precipitation is not necessary when working with the purified enzyme; the acidic 2,4-dinitrophenylhydrazine solution serves to stop the enzyme action.

Urea caused a marked depression of color development in the aldolase assay. For example, the presence of 4 *M* urea in the assay mixture decreased the absorbance at 525 mμ by 79%. To accommodate this effect when assay samples contained urea, the procedure was altered to include the same concentration of urea in all of a given series of samples during color development. This was done as follows. At the end of the 10-minute incubation period of the enzyme and substrate, a 1-ml. aliquot was removed and added to a solution containing 1 ml. of the 2,4-dinitrophenylhydrazine reagent and 1 ml. of a urea solution of sufficient concentration to bring all samples to the urea level of that of the highest urea content of the series under investigation. Color development then proceeded as previously described.

Reactive Sulfhydryl Determinations.—The spectrophotometric method of Boyer[6] was used for measurement of the amount of *p*-mercuribenzoate reacting with –SH groups. The *p*-mercuribenzoate was reprecipitated four times,[6] and a sufficient amount dissolved in 0.05 *M* tetrasodium pyrophosphate to give stock solutions containing approximately 2×10^{-3} *M* *p*-mercuribenzoate. The concentration of solutions was accurately determined from the absorbance at 232 mμ[6] of appropriate dilutions. In all –SH determinations, requisite corrections were made for the absorbance of aldolase at 250 mμ.

Assays in the presence of urea were made by the same procedure, with consideration of the effect of the urea on the extent of the spectrophotometric shift accompanying mercaptide formation, as noted in the section on results. Assays in 8 *M* urea necessitated making all solutions to be used 8 *M* in urea.

Effect of Urea on Catalytic Activity of Aldolase.—For measurements of the catalytic activity of aldolase in the presence of urea, as reported in Fig. 5, the following conditions were used: 0.1 ml. of aliquots of an aldolase solution, 400 μg. per ml., were incubated 30° for 10 minutes with 0.9 ml. of 0 to 8 *M* urea solution and 0.5 ml. of 0.5 *M* hydrazine, *p*H 7.4. Then 0.5 ml. of 0.02 *M* fructose 1,6-diphosphate, *p*H 7.4, was added, with the resultant urea concentrations during the period of enzyme action as shown in Fig. 5. After 10 minutes a 1-ml. aliquot was removed from the reaction mixture and added to a mixture of 1.0 ml. of 0.005 *M* 2,4-dinitrophenylhydrazine in 2 *N* HCl, and 1.0 ml. of a urea solution of sufficient coucentration to bring the urea level of each mixture to that of the highest in the series under study. This was necessary to have all tubes at equal urea concentration for subsequent color development. This procedure was checked using glyceraldehyde in place of enzyme and substrate and was shown to be accurately reproducible.

The experiments on recovery of activity following dilution of urea (Fig. 5) were performed as follows: 2-mg. portions of crystalline aldolase, freshly centrifuged from ammonium sulfate suspension and well drained, were dissolved in 1 ml. of urea solution of the concentration indicated by Fig. 5. The small volume of the centrifuged aldolase suspension would decrease the molarity of the urea by considerably less than 5%. The solutions were allowed to stand at 30° for 10 minutes, and then diluted 100 times with water containing sufficient urea to bring all samples to 0.08 *M* urea; this concentration of urea was known from other studies to have no effect on catalytic activity. Catalytic activity measurements were made 10 minutes after dilution. Longer periods of standing after dilution did not result in increase in catalytic activity. One-ml. aliquots of the diluted solutions were added to the substrate and hydrazine and the assay carried out as previously described. The data reported in Fig. 5 are for solutions with no added buffer; the *p*H of these solutions was approximately 7.2. Closely similar results were obtained when the urea solutions contained 0.05 *M*

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(20) J. F. Taylor, "Methods in Enzymology," Vol. I, Academic Press, New York, N. Y., p. 310.

(21) J. F. Taylor and C. Lowry, *Biochim Biophys. Acta*, **20**, 109 (1956).

(22) Helen H. Sakanashi, M.S. Thesis, University of Minnesota, 1953.

(23) John A. Sibley and A. L. Lehninger, *J. Biol. Chem.*, **177**, 859 (1949).

(24) William S. Beck, *ibid.*, **212**, 847 (1955).

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phosphate buffer *p*H 7.4 and 10^{-4} *M* ethylenediaminetetraacetate.

Correlation of Loss of Catalytic Activity with Extent of Reaction with *p*-Mercuribenzoate.—For these experiments, from 1 to 5 × 10^{-6} *M* aldolase was incubated with 3 × 10^{-5} *M* *p*-mercuribenzoate and 0.15 *M* phosphate buffer, *p*H 7.0. At room temperature, only approximately 8 –SH groups per mole of aldolase reacted within a 3-hour period. Exposure at 37° for 1 hour was necessary to obtain reaction with 12 –SH groups and exposure for 3 hours resulted in reaction of 14 groups. Longer exposure periods usually resulted in appearance of turbidity from protein precipitation. Subsequent to the desired incubation with the *p*-mercuribenzoate, samples were diluted with water to give solutions containing 20 μg. of aldolase per ml., and the activity was determined by the usual procedure. No compensation was necessary for differences in unreacted *p*-mercuribenzoate in the diluted samples because the low residual concentrations did not affect the catalytic assay. Aldolase samples incubated at 37° for three hours in the phosphate buffer without addition of *p*-mercuribenzoate showed little or no loss of catalytic activity. The loss observed in the presence of *p*-mercuribenzoate could thus be ascribed to reaction of the enzyme with the mercurial.

Reversal of the *p*-Mercuribenzoate Inactivation of Aldolase.—Samples of 1 ml. total volume containing 1 × 10^{-6} *M* aldolase and 0.12 *M* phosphate buffer *p*H 7.2 with or without 3 × 10^{-5} *M* *p*-mercuribenzoate were incubated at 0 or 37° as indicated in Table II. Then either 0.2 ml. of water or of 0.05 *M* glutathione, *p*H 7, was added, the samples allowed to stand 20 minutes at room temperature, and placed in an ice-bath. Catalytic activity assays were then made on appropriate aliquots as described previously.

MINNEAPOLIS, MINN.

[CONTRIBUTION NO. 2077 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

The α-Chymotrypsin-catalyzed Hydrolysis of a Series of Hydrazides. I. Determination of *p*H Optima and their Dependence upon Temperature[1]

BY RALPH LUTWACK,[2] HOWARD F. MOWER[3] AND CARL NIEMANN[4]

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It has been found that the α-chymotrypsin-catalyzed hydrolysis of L-tyrosinhydrazide and of six α-N-acylated-L-tyrosinhydrazides can be followed quantitatively by the spectrophotometric determination of the liberated hydrazine in the form of a protonated bis-*p*-dimethylaminobenzalazine. With this procedure it has been shown that for aqueous solutions at 25° the *p*H optimum for the α-chymotrypsin-catalyzed hydrolysis of L-tyrosinhydrazide is 7.05 ± 0.15 and that the *p*H optima for the comparable reactions involving the six α-N-acylated-L-tyrosinhydrazides lie in a more basic region, *i.e.*, *ca.* 7.7 to 8.0. It also has been observed that the *p*H optima for the α-chymotrypsin-catalyzed hydrolysis of three representative α-N-acylated-L-tyrosinhydrazides are strikingly temperature dependent in the region between 25 and 40° and that an increase in temperature from 25 to 40° causes the *p*H optima to be shifted to a more acidic region, *i.e.*, from *ca.* 7.8 to *ca.* 6.8.

The knowledge that α-N-nicotinyl-L-tyrosinhydrazide and presumably α-N-acetyl-L-phenylalaninhydrazide are hydrolyzed in the presence of α-chymotrypsin[5–7] led us to consider the usefulness of the hydrazides of certain α-amino acids and acylated α-amino acids as specific substrates in studies involving the above enzyme. While MacAllister and Niemann[5] had followed the α-chymotrypsin-catalyzed hydrolysis of α-N-nicotinyl-L-tyrosinhydrazide, in aqueous solutions at 25° and *p*H 7.9 and 0.02 *M* in the EDA[8] component of an EDA–HCl buffer, with the aid of a formol titration[9] and Goldenberg, Goldenberg and McLaren[6] had determined the extent of the α-chymotrypsin catalyzed hydrolysis of α-N-acetyl-DL-phenylalaninhydrazide, in aqueous solutions at 24.6° and *p*H 7.3 and 0.05 *M* in an unspecified phosphate buffer, with a Grassmann–Heyde titration[10] neither of these procedures was employed in the present study because it was anticipated that for many α-amino acid and α-N-acylated amino acid hydrazides any titrimetric procedure based upon the determination of liberated carboxyl groups would not be sufficiently sensitive to be used for determining their rates of hydrolysis by α-chymotrypsin.

Goldenberg, Goldenberg and McLaren[7] were aware of the limitations of the above titrimetric procedures when applied to the hydrazides and these investigators devised a colorimetric procedure for the qualitative recognition of the α-chymotrypsin-catalyzed hydrolysis of α-N-acetyl-DL-phenylalaninhydrazide, which was based upon the reduction of phosphomolybdate ion to the so-called molybdenum blue by the liberated hydrazine. While it was stated[7] that this latter procedure was capable of detecting an extent of hydrolysis of 1 to 2% at specific substrate concentrations of 0.03 to 0.05 *M* no attempt appears to have been made to develop the procedure to the point where it could be used for quantitative measurements.

An alternative colorimetric procedure for determining the extent of the α-chymotrypsin-catalyzed hydrolysis of α-amino acid and α-N-acylated α-amino acid hydrazides, and one that promised exceptional sensitivity, was suggested by the observation of Pesez and Pelit[11] that hydrazine reacts with *p*-dimethylaminobenzaldehyde in aqueous acidic media to give a protonated bis-*p*-dimethylaminobenzalazine with an absorption maximum

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(5) R. V. MacAllister and C. Niemann, THIS JOURNAL, **71**, 3854 (1949).

(6) V. Goldenberg, H. Goldenberg and A. D. McLaren, *ibid.*, **72**, 5317 (1950).

(7) V. Goldenberg, H. Goldenberg and A. D. McLaren, *Biochem. Biophys. Acta*, **7**, 110 (1951).

(8) Ethylenediamine.

(9) B. M. Iselin and C. Niemann, *J. Biol. Chem.*, **182**, 821 (1950).

(10) W. Grassmann and W. Heyde, *Z. physiol. Chem.*, **183**, 32 (1929).

(11) M. Pesez and A. Pelit, *Bull. soc. chim.*, 122 (1947).

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in the region of 455 mμ. Therefore, a procedure for the spectrophotometric determination of hydrazine which was based upon the above reaction was developed and although it was anticipated, and in a sense improved, by Watt and Crisp[12] and by Wood[13] it was employed in its original form in all of the studies described in this communication. With the availability of this latter procedure, which was capable of determining quantities of hydrazine of the order of 10^{-6} to 10^{-7} M in contrast to the lower limits of 10^{-3} to 10^{-4} M encountered in the determination of carboxylate groups with the formol titration,[9] it was possible to determine the extent of the α-chymotrypsin-catalyzed hydrolysis of seven α-amino acid and α-N-acylated α-amino acid hydrazides to carboxylate ion and hydrazine under conditions that involved only a limited extent of hydrolysis.

The seven specific substrates employed in the present investigation were, respectively, L-tyrosinhydrazide and the formyl-, acetyl-, trimethylacetyl-, dichloroacetyl-, benzoyl-, and nicotinyl-α-N-acyl derivatives of L-tyrosinhydrazide. All of these compounds were prepared from the corresponding esters and were found to be stable in the absence of α-chymotrypsin under the conditions employed in the enzymatic studies. In every instance it was found possible to establish conditions that would permit the demonstration of an enzyme-catalyzed hydrolysis. In view of the fact that α-N-benzoyl-L-tyrosinhydrazide, a compound which was previously reported[14] to be ineffective as a competitive inhibitor of the α-chymotrypsin-catalyzed hydrolysis of benzoyl-L-tyrosinamide, or of benzoyl-L-tyrosine ethyl ester, has now been shown to be a specific substrate of this enzyme it is clear that the inference that benzoyl-L-tyrosinhydrazide is incapable of interacting with the catalytically active site of α-chymotrypsin can no longer be maintained.

In view of the general dependence of enzyme-catalyzed reactions upon hydrogen ion concentration the *p*H optima of systems containing α-chymotrypsin and the seven specific substrates listed above were determined for each enzyme–substrate pair in aqueous solutions at 25° and 0.02 M in the THAM[15] component of a THAM–HCl buffer.[16] The results obtained in these studies are given in Table I along with comparable values for the corresponding amides and hydroxamides.[17]

It will be seen from the values summarized in Table I that the *p*H optima for the six α-N-acylated-L-tyrosinhydrazides, in aqueous solutions at 25°, are identical, within the limits of experimental error, with those of the four acylated-L-tyrosinamides, which were studied under comparable conditions, and that in general the optimum *p*H with respect to the attainment of the maximum extent of reaction in aqueous solutions at 25° in a given time interval is approximately 7.8 for both the acylated-L-tyrosinamides and the α-N-acylated-L-tyrosinhydrazides. The observation that the *p*H optimum for the reaction involving acetyl-L-tyrosinhydroxamide, *i.e.*, 7.60 ± 0.05, lies in a more acidic region than that observed for the comparable reaction involving either acetyl-L-tyrosinamide, *i.e.*, 7.90 ± 0.10, or acetyl-L-tyrosinhydrazide, *i.e.*, 7.95 ± 0.20, is not unexpected since of these three specific substrates only acetyl-L-tyrosinhydroxamide is capable of partial ionization in the region of the *p*H optimum and to thus cause a shift of the *p*H optimum in the direction noted.[18]

TABLE I

*p*H OPTIMA AT 25°[a]

–CH(CH₂C₆H₄OH)CO–	–NHOH	–NH₂	–NHNH₂
H₂N–	6.95 ± 0.05[b]	.....	7.05 ± 0.15
HCONH–	.....	.....	7.70 ± .20
CH₃CONH–	7.60 ± .05[c]	7.90 ± 0.10	7.95 ± .20
C(CH₃)₃CONH–	.....	.....	7.65 ± .20
CF₃CONH–	.....	7.85 ± .05	.....
CH₂ClCONH–	.....	7.75 ± .05	.....
CHCl₂CONH–	.....	.....	7.85 ± .20
(C₆H₅)CONH–	.....	.....	8.0 ± .20
β-(C₅H₄N)CONH–	.....	7.90 ± .05	7.80 ± .20

[a] With respect to the α-chymotrypsin-catalyzed hydrolysis of a series of derivatives of L-tyrosine in aqueous solutions 0.02 M in the THAM component of a THAM–HCl buffer unless otherwise noted. [b] 0.1 M THAM. [c] 0.3 M THAM.

From an argument[19] developed to explain the difference in *p*H optima for the α-chymotrypsin-catalyzed hydrolysis in aqueous solutions at 25° of acetyl-L-tyrosinhydroxamide, *i.e.*, 7.60 ± 0.05, and L-tyrosinhydroxamide, *i.e.*, 6.95 ± 0.05, it would be expected that the *p*H optimum for the α-chymotrypsin-catalyzed hydrolysis of acetyl-L-tyrosinhydrazide, *i.e.*, 7.95 ± 0.20, would lie in a more basic region than that observed for the comparable reaction with L-tyrosinhydrazide, *i.e.*, 7.05 ± 0.15. While this expectation has been realized it should be noted that Schwert[20] has suggested that the *p*H optimum reported[17,19] for the α-chymotrypsin-catalyzed hydrolysis of L-tyrosinhydroxamide, in aqueous solutions at 25°, *i.e.*, 6.95 ± 0.05, is to be associated with a transpeptidation reaction rather than with the assumed hydrolytic reaction. Since the absence of pertinent information does not permit us at this time to affirm or deny what appears to us to be an unlikely possibility we have undertaken a study of the importance of transpeptidation reactions under the conditions ordinarily employed for the evaluation of the kinetic constants of α-chymotrypsin-catalyzed hydrolyses of α-amino acid esters, hydroxamides, amides and hydrazides. These studies are now in progress.

The observation that the *p*H optima for the α-chymotrypsin catalyzed hydrolysis of L-tyrosinhydrazide and of L-tyrosinhydroxamide,[17,19] in aqueous solutions at 25°, are identical, within the limits of experimental error, *i.e.*, *ca.* 7.0, and that this latter value is greater than the value of 6.25

(12) G. W. Watt and J. D. Crisp, *Anal. Chem.*, **24**, 2006 (1952).

(13) P. R. Wood, *ibid.*, **25**, 1879 (1953).

(14) S. Kaufman, H. Neurath and G. W. Schwert, *J. Biol. Chem.*, **177**, 793 (1949).

(15) Tris-(hydroxymethyl)-aminomethane.

(16) In a few instances a cacodylic acid–sodium cacodylate buffer which was 0.02 M in added cacodylic acid was employed in the region below *p*H 7.

(17) R. J. Foster and C. Niemann, THIS JOURNAL, **77**, 1886 (1955).

(18) D. S. Hogness and C. Niemann, *ibid.*, **75**, 884 (1953).

(19) R. J. Foster, R. R. Jennings and C. Niemann, *ibid.*, **76**, 3142 (1954).

(20) G. W. Schwert, *Ann. Rev. Biochem.*, **24**, 99 (1955).

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which has been reported[21,22] for the *p*H optimum for the equivalent reaction involving L-tyrosine ethyl ester raises the question as to whether the difference just noted is real or is the result of a variation in procedure.

We may assume that the ammonium group present in a monoprotonated α-amino acid ester, hydroxamide or hydrazide will have a pK'_A value of 7.4 ± 0.4.[19,23,24] Therefore, in aqueous solutions at 25° and between *p*H 6.0 and 9.0 one may expect to encounter significant amounts of the monoprotonated, *i.e.*, $H_3\overset{+}{N}CHRCOY$, and unprotonated, *i.e.*, $H_2NCHRCOY$, species of each of the above specific substrates[25] with the relative concentrations of the two species being dependent upon the *p*H of the particular system under investigation. Thus, with all three of the above specific substrates it is clear that the over-all dependence of relative activity upon *p*H is much more complicated than the case involving interaction of the enzyme with a single substrate species in systems of varying *p*H since in the former instance one is confronted not only with the added problem of multiple and competitive specific substrates[26] but also by the fact that their relative concentrations are varying with the *p*H of the systems. Consequently with situations of such complexity it is imperative that in the first instance significance be given only to those differences that can be observed through the use of comparable experimental procedures.

It will be noted that the *p*H optima for L-tyrosinhydrazide and L-tyrosinhydroxamide which are given above were evaluated under conditions where in each reaction system the extent of reaction arising from the interaction of the enzyme with all substrate species derived from either of the above added specific substrates was collectively determined. In contrast to these two cases the *p*H optimum for L-tyrosine ethyl ester which is given above was evaluated by a procedure which measured only the extent of reaction of the monoprotonated L-tyrosine ethyl ester in a given reaction system.

Balls and his co-workers[21,22,27] in their studies on α-chymotrypsin and modified α-chymotrypsin catalyzed hydrolyses of L-tyrosine ethyl ester employed an analytical procedure which was developed earlier[28] for following the enzyme-catalyzed hydrolysis of acylated α-amino acid esters. In this procedure, which may be represented by eq. 1 and 2, the reaction system was maintained at a constant, or nearly constant, *p*H by the frequent addition of standard alkali and the amount of the latter reagent added was taken to be proportional to the extent of reaction. However, in solutions

$$RCONHCHR'CO_2R'' + H_2O \longrightarrow RCONHCHR'CO_2^- + R''OH + H^+ \quad (1)$$

$$H^+ + OH^- \longrightarrow H_2O \quad (2)$$

containing added α-amino acid ester and in the *p*H region with which we are concerned one is confronted with a situation represented not only by eq. 3 and 2 but also by eq. 4. Therefore, when the

$$H_3{}^+NCHR'CO_2R'' + HOH^- \longrightarrow \overset{+}{H_3}NCHR'CO_2^- + R''OH + H^+ \quad (3)$$

$$H_2NCHR'CO_2R'' + HOH \longrightarrow \overset{+}{H_3}NCHR'CO_2^- + R''OH \quad (4)$$

procedure of Schwert, *et al.*,[28] is used with α-amino acid esters in the *p*H region where both monoprotonated and unprotonated species are present only the extent of reaction of the monoprotonated species can be determined.

Having established the fact that the procedure used by Balls and his co-workers[21,22,27] for the evaluation of the *p*H optimum of L-tyrosine ethyl ester differs in principle from those employed for the evaluation of the *p*H optima of L-tyrosinhydrazide and L-tyrosinhydroxamide the question that arises is whether the difference in *p*H optima noted above may or may not be due to the difference in procedures.

If it is assumed that the monoprotonated species derived from L-tyrosine ethyl ester is hydrolyzed at a faster rate than the corresponding unprotonated species[19] and that the pK'_A value of the monoprotonated L-tyrosine ethyl ester is *ca.* 7.3[29] it may be inferred that had Balls and his co-workers[21,22,27] employed a procedure that was comparable to those used for the evaluation of the *p*H optima of L-tyrosinhydrazide and L-tyrosinhydroxamide they would have observed with L-tyrosine ethyl ester that the relative activities in the region between *p*H 6.3 and 6.9 did not decrease, within the limits of experimental error, with increasing *p*H and thus would have obtained a *p*H activity relationship with a relatively flat maximum extending from *ca.* *p*H 6.3 to 6.9. Since the location of the *p*H optimum would be somewhat arbitrary in a case of this kind all that can be said with certainty is that the *p*H optimum evaluated by measurement of the cumulative extent of reaction embracing all reactive species would lie in a more basic region than the *p*H optimum evaluated by determining the extent of reaction of only the monoprotonated species. Thus, we may conclude that the difference in the *p*H optima of L-tyrosine ethyl ester and of L-tyrosinhydrazide and L-tyrosinhydroxamide which was noted earlier may not be real since the difference could arise either wholly or in part from a difference in procedures. In this connection it may be recalled that Goldenberg, Goldenberg and McLaren[7] have noted that the *p*H optimum for the α-chymotrypsin-catalyzed hydrolysis of L-leucine ethyl ester in aqueous solutions at 25° appears to

(21) E. F. Jansen, M. D. Fellows-Nutting, R. Jang and A. K. Balls, *J. Biol. Chem.*, **185**, 209 (1950).

(22) E. F. Jansen, A. L. Curl and A. K. Balls, *ibid.*, **189**, 671 (1951).

(23) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides as Ions and Dipolar Ions," Reinhold Publ. Corp., New York, N. Y., 1948.

(24) R. J. Kerr, Ph.D. Thesis, Calif. Inst. Tech., Pasadena, Calif., 1957.

(25) With L-tyrosinhydroxamide the additional species $H_3\overset{+}{N}CHRCONHO^-$ and $H_2NCHRCONHO^-$ will be present in the more alkaline solutions. However, in systems more acid than *p*H 7.5 their contribution will be negligible.

(26) R. J. Foster and C. Niemann, THIS JOURNAL, **73**, 1552 (1951).

(27) E. F. Jansen, M. D. Fellows-Nutting, R. Jang and A. K. Balls, *J. Biol. Chem.*, **179**, 189 (1949).

(28) G. W. Schwert, H. Neurath, S. Kaufman and J. E. Snoke, *ibid.*, **172**, 221 (1948).

(29) The pK'_A value of monoprotonated L-tyrosine ethyl ester does not appear to have been determined. However, the monoprotonated L-phenylalanine methyl ester is known to have a pK'_A value of 7.3.[24]

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be *ca.* 6.8 when determined by the procedure used by Balls and his co-workers[21,22,27] for L-tyrosine ethyl ester and to be *ca.* 7.2 when determined by a procedure which would be expected to reveal the cumulative extent of reaction of both the unprotonated and monoprotonated L-leucine ethyl ester. Although it has been suggested[30] that the difference in *p*H optima noted above may be a consequence of a transpeptidation reaction we believe that the argument given above provides a more likely explanation of the observation of Goldenberg, Goldenberg and McLaren[7] and it may be added that the shift in the *p*H optima noted by these authors[7] is in the direction anticipated on the basis of this argument.

The absence of information with respect to the dependency of the *p*H optima of α-chymotrypsin-catalyzed hydrolyses upon temperature led us to determine the *p*H optima for the α-chymotrypsin-catalyzed hydrolysis of α-N-acetyl-, α-N-benzoyl- and α-N-nicotinyl-L-tyrosinhydrazide in aqueous solutions at 10, 25 and 40° and those of L-tyrosinhydrazide in aqueous solutions at 25 and 40°. It will be seen from the data summarized in Table II that the *p*H optima for the α-chymotrypsin-catalyzed hydrolysis of the above three α-N-acylated-L-tyrosinhydrazides in aqueous solutions at 10° are identical, within the limits of experimental error, with those observed at 25°. However, when the values observed at 25° are compared with those observed at 40° it is seen that an increase in temperature from 25 to 40° causes a shift in the *p*H optima from *ca.* 7.9 at 25° to *ca.* 6.8 at 40° for all three of the above α-N-acylated-L-tyrosinhydrazides. In contrast to the behavior of the α-N-acylated-L-tyrosinhydrazides it was found, *cf.* Table II, that the *p*H optimum for the α-chymotrypsin-catalyzed hydrolysis of L-tyrosinhydrazide in aqueous solutions at 25°, *i.e.*, 7.05 ± 0.15, is identical, within the limits of experimental error, with that observed in aqueous solutions at 40°, *i.e.*, 6.85 ± 0.15. It is noteworthy that in aqueous solutions at 40° the *p*H optimum for the α-chymotrypsin catalyzed hydrolysis of L-tyrosinhydrazide is practically the same as that observed for any one of the three α-N-acylated-L-tyrosinhydrazides considered in this study.

TABLE II

VARIATION OF *p*H OPTIMA WITH TEMPERATURE[a]

$-CH(CH_2C_6H_4OH)-CONHNH_2$	10°	25°	40°
H_2N	.....	7.05 ± 0.15	6.85 ± 0.15
CH_3CONH-	7.85 ± 0.25	7.95 ± .20	6.75 ± .15
$(C_6H_5)CONH-$	7.80 ± .25	8.0 ± .20	6.75 ± .20
β-$(C_5H_4N)CONH-$	7.80 ± .25	7.80 ± .20	6.75 ± .20

[a] With respect to the α-chymotrypsin-catalyzed hydrolysis of L-tyrosinhydrazide and of three α-N-acylated-L-tyrosinhydrazides in aqueous solutions 0.02 *M* in the THAM component of a THAM–HCl buffer.

When it is realized that the *p*H optimum of an enzyme-catalyzed reaction is a reflection of the effect of *p*H upon a relatively large number of independent reaction parameters, that each of these dependencies may in turn possess different temperature dependencies and that one may also encounter temperature dependencies which are independent of the *p*H of the reaction system it is clear that in the absence of knowledge of the magnitude and direction of each of the above dependencies one must regard the *p*H optimum and its dependence upon temperature simply as the summation of all of the above effects. Therefore, in view of the nature of the information reflected in knowledge of the *p*H optimum and its dependence upon temperature in the case of the α-chymotrypsin-catalyzed hydrolysis of L-tyrosinhydrazide and of α-N-acetyl-, α-N-benzoyl-, and α-N-nicotinyl-L-tyrosinhydrazide in aqueous solutions at 10, 25 and 40° one can only note that the practice of evaluating the thermodynamic constants of similar α-chymotrypsin catalyzed reactions[14,31] by studying such reactions at a constant *p*H, *i.e.*, 7.8, appears to contain more elements of uncertainty than those already envisaged[14,31] even though such reactions were studied in the temperature range from *ca.* 10 to 30° but in solutions containing 30% aqueous methanol.

Experimental[32,33]

L-Tyrosinhydrazide.[34]—This compound was prepared by the reaction of L-tyrosine methyl ester in methanol solution with hydrazine hydrate essentially as described[34] for the equivalent reaction of the ethyl ester. The product which crystallized from the reaction mixture was twice recrystallized from ethanol and dried *in vacuo* over phosphorus pentoxide to give L-tyrosinhydrazide, m.p. 193–194°. Curtius[34] gives a m.p. of 195.5° for the same compound and a m.p. of 171° for DL-tyrosinhydrazide.

Anal. Calcd. for $C_9H_{12}O_2N_3$ (195): C, 55.4; H, 6.7; N, 21.5. Found: C, 55.4; H, 6.8; N, 21.4.

α-N-Formyl-L-tyrosinhydrazide.—To a well-stirred solution of 10.5 g. of L-tyrosine ethyl ester, m.p. 108.5–109.5°, in 250 ml. of 80% formic acid was added 43 ml. of acetic anhydride at a rate such that the temperature of the reaction mixture remained below 70°. After the reaction mixture had stood overnight at room temperature the solution was evaporated to dryness *in vacuo*, the sirupy residue taken up in 200 ml. of ethyl acetate, the ethyl acetate solution successively washed with 3 *N* aqueous sodium hydroxide, 6 *N* aqueous hydrochloric acid and with water, dried over anhydrous potassium carbonate, the solvent removed *in vacuo* and the 7.1 g. of sirupy residue taken up in 20 ml. of methanol. To the boiling methanol solution was added 2.25 g. of hydrazine hydrate, the reaction mixture allowed to stand overnight prior to concentration, the concentrate allowed to crystallize, the crystalline product recrystallized from aqueous methanol and dried *in vacuo* over phosphorus pentoxide to give 1.7 g. of α-N-formyl-L-tyrosinhydrazide, m.p. 218° with decomp., $[\alpha]^{25}D$ +21.4° (in 30% aqueous ethanol).

Anal. Calcd. for $C_{10}H_{14}O_3N_3$ (224): C, 53.8; H, 6.0; N, 18.9. Found: C, 53.7; H, 6.0; N, 18.8.

α-N-Acetyl-L-tyrosinhydrazide.—This compound was obtained from L-tyrosine by the same procedure used by Hogness and Niemann[18] for the preparation of the D-isomer for which a m.p. of 236–236.5° was erroneously reported instead of the correct value of 226–226.5°. The crude α-N-acetyl-L-tyrosinhydrazide recovered from the reaction mixture was recrystallized twice from methanol and dried *in vacuo* over phosphorus pentoxide to give α-N-acetyl-L-tyrosinhydrazide, m.p. 227–228°.

Anal. Calcd. for $C_{11}H_{16}O_3N_3$ (237): C, 55.7; H, 6.4; N, 17.7. Found: C, 55.7; H, 6.3; N, 17.8.

α-N-Trimethylacetyl-L-tyrosinhydrazide.—A vigorously agitated solution of 10.5 g. of L-tyrosine ethyl ester in 300 ml. of ethyl acetate was cooled to −5° prior to the addition of 2.75 g. of trimethylacetyl chloride, b.p. 104–105°, pre-

(30) H. M. Green and H. Neurath in H. Neurath and K. Bailey, "The Proteins," Vol. IIB, Academic Press, Inc., New York, N. Y., 1954, p. 1104.

(31) J. E. Snoke and H. Neurath, *J. Biol. Chem.*, **182**, 577 (1950).

(32) All melting points reported are corrected.

(33) Microanalyses by Dr. A. Elek.

(34) T. Curtius, *J. prakt. Chem.*, [2] **95**, 349 (1917).

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pared in 35% yield by the reaction of trimethylacetic acid with benzoyl chloride.[35] Two minutes after the addition of the above amount of acid chloride 50 ml. of 0.05 *N* aqueous potassium carbonate was added to the cold and vigorously agitated reaction mixture and the process repeated until four portions of acid chloride and of aqueous potassium carbonate solution had been introduced. The cold solution was then allowed to separate into two phases, the ethyl acetate phase collected, washed with 6 *N* aqueous hydrochloric acid and then twice with water prior to drying over anhydrous potassium carbonate. Removal of the solvent *in vacuo* gave 7.2 g. of a sirupy residue which was taken up in 20 ml. of methanol and allowed to react with 2 g. of hydrazine hydrate as described for the preparation of the α-N-formyl derivative, *vide ante*, to give 5.4 g. of the crude hydrazide which was recrystallized twice from aqueous methanol and dried *in vacuo* over phosphorus pentoxide to give 2.5 g. of α-N-trimethylacetyl-L-tyrosinhydrazide, m.p. 179–180°, $[\alpha]^{25}D$ +29° (in water).

Anal. Calcd. for $C_{14}H_{21}O_3N_3$ (247): C, 60.2; H, 7.5; N, 15.1. Found: C, 60.2; H, 7.5; N, 15.1.

α-N-Dichloroacetyl-L-tyrosinhydrazide.—L-Tyrosine ethyl ester, 10.5 g. in 300 ml. of ethyl acetate was acylated with 14.7 g. of dichloroacetyl chloride, b.p. 106–107.5°, and 200 ml. of 0.05 *N* aqueous potassium carbonate as described for the preparation of α-N-trimethylacetyl-L-tyrosine ethyl ester, *vide ante*, and the 7.7 g. of crude α-N-dichloroacetyl-L-tyrosine ethyl ester obtained as a gummy solid was taken up in 15 ml. of methanol and allowed to react with 1.8 g. of hydrazide hydrate to give 5.9 g. of the crude hydrazide which was recrystallized twice from aqueous methanol and dried *in vacuo* over phosphorus pentoxide to give 2.0 g. of α-N-dichloroacetyl-L-tyrosinhydrazide, m.p. 193–193.5°, $[\alpha]^{25}D$ +12.5° (in 40% aqueous ethanol).

Anal. Calcd. for $C_{11}H_{13}O_3N_3Cl_2$ (306): C, 43.2; H, 4.3; N, 13.7; Cl, 23.2. Found: C, 43.2; H, 4.2; N, 13.8; Cl, 23.3.

α-N-Benzoyl-L-tyrosinhydrazide.—This compound was prepared essentially as described by Bergmann and Fruton.[36] The crude hydrazide was recrystallized twice from methanol and dried *in vacuo* over phosphorus pentoxide to give α-N-benzoyl-L-tyrosinhydrazide, m.p. 247–248°. Bergmann and Fruton[36] report a m.p. of *ca.* 255°.

Anal. Calcd. for $C_{16}H_{19}O_3N_3$ (301): C, 64.2; H, 5.7; N, 14.0. Found: C, 64.2; H, 5.6; N, 14.1.

α-N-Nicotinyl-L-tyrosinhydrazide.—This compound was prepared as described by MacAllister and Niemann[5] from α-N-nicotinyl-L-tyrosine ethyl ester, m.p. 147–149°.[37] The crude hydrazide was recrystallized twice from methanol and dried *in vacuo* over phosphorus pentoxide to give α-N-nicotinyl-L-tyrosinhydrazide, m.p. 242–243°.[5]

Anal. Calcd. for $C_{15}H_{16}O_3N_4$ (300): C, 60.0; H, 5.4; N, 18.7. Found: C, 60.1; H, 5.4; N, 18.8.

Buffer Solutions.—Aqueous stock solutions were prepared from THAM, m.p. 169–169.5°, which had been recrystallized twice from aqueous methanol. These stock solutions were 0.20 *M* with respect to the THAM component and were adjusted to the desired *p*H by the dropwise addition of concd. hydrochloric acid at the temperature at which they were to be used and prior to adjustment to the final volume. In every case the *p*H was checked upon a 1:10 dilution of the above stock solutions and the *p*H readjusted if necessary. All reaction systems were 0.02 *M* with respect to the THAM component.

In a few cases a sodium cacodylate–cacodylic acid buffer, which was 0.02 *M* in cacodylic acid when present in the reaction system, was employed. Some evidence was obtained that a 0.02 *M* THAM–HCl buffer and a 0.02 *M* sodium cacodylate–cacodylic acid buffer of identical *p*H may not be exactly equivalent in the reaction systems considered in this communication. However, the differences observed with these two buffer systems were of minor significance.

***p*-Dimethylaminobenzaldehyde Reagent.**—The *p*-dimethylaminobenzaldehyde, m.p. 74.5–75°, was prepared from a reagent grade product by recrystallization from aqueous methanol or from a practical grade product by precipitation with aqueous sodium hydroxide from a hydrochloric acid solution followed by two recrystallizations from aqueous methanol. The reagent employed contained 1.0 g. of the aldehyde in 100 ml. of absolute ethanol. This solution was stable for periods up to 1 week when stored in sealed brown glass containers.

Enzyme Stock Solutions.—The aqueous enzyme stock solutions were prepared, usually in 5-ml. volumetric flasks, from crystalline bovine α-chymotrypsin, Armour preparations No. 10705 and 00592, but in no case was a stock solution used after it had stood at 25° for more than 1 hour. In every case the stock solutions were equilibrated for not less than 15 minutes at the temperature employed for the examination of a particular system.

A set of experiments were conducted to determine whether there was a significant change in activity when enzyme solutions were maintained at 40° for 1 hour by holding the enzyme in aqueous solutions at 40° and *p*H 7.8 and 0.02 *M* in the THAM component of a THAM–HCl buffer for periods up to 1 hour and then determining the activity at 25° and *p*H 7.8 using α-N-nicotinyl-L-tyrosinhydrazide as the specific substrate and comparing it with the activity of an equivalent enzyme solution that had been kept at 25° and *p*H 7.8 for the same period. The results obtained from these experiments gave no indication that there was a significant change in activity when the enzyme was maintained at 40° for 1 hour under the conditions specified.

Specific Substrate Stock Solutions.—Aqueous stock solutions of the various specific substrates were prepared at concentrations such as to permit the addition of the desired amount of specific substrate to the reaction system in the form of an 8.0-ml. aliquot.

Reaction System.—To a 10-ml. volumetric flask was added, at 25°, 8.0 ml. of the specific substrate stock solution and 1.0 ml. of the 0.2 *M* buffer stock solution and the mixture equilibrated for 30 minutes in a constant temperature bath maintained within ±0.1° of the selected temperature. At zero time a 1.0-ml. aliquot of the enzyme stock solution was added to the flask containing the buffered specific substrate solution and the solution mixed by gentle inversion six or seven times. Aliquots were then withdrawn from the reaction system at selected time intervals and analyzed as described below. A summary of representative reaction systems employed in this study is given in Table III.

TABLE III

REPRESENTATIVE REACTION CONDITIONS USED IN *p*H OPTIMUM STUDIES[a]

Hydrazide	*T*, °C.	[E], mg. P.N/ml.	$[S]_0 \times 10^2$, *M*	*t*, min.
L-Tyrosin-	25	0.104[b]	1.65	60
	40	.104[b]	1.65	60
α-N-Formyl-L-tyrosin-	25	.144[c]	0.12	135
α-N-Acetyl-L-tyrosin-	10	.104[b]	.45	60
	25	.104[b]	.45	60
	40	.104[b]	.49	15
α-N-Trimethylacetyl-L-tyrosin-	25	.144[c]	2.56	122
α-N-Dichloroacetyl-L-tyrosin-	25	.144[c]	0.60	40
α-N-Benzoyl-L-tyrosin-	10	.052[b]	.24	45
	25	.052[b]	.16	30
	40	.052[b]	.19	45
α-N-Nicotinyl-L-tyrosin-	10	.052[b]	.17	60
	25	.052[b]	.93	17
	40	.052[b]	.33	50

[a] In aqueous solutions 0.02 *M* in the THAM component of a THAM-HCl buffer except in a few cases below *p*H 7.0 where a sodium cacodylate–cacodylic acid buffer 0.02 *M* in cacodylic acid was employed. [b] Armour lot no. 10705. [c] Armour lot no. 00592.

Analysis of Reaction System.—At preselected time intervals an aliquot, usually 1.0 ml., was withdrawn from the reaction system and transferred to a 10-ml. volumetric flask containing 1.0 ml. of the *p*-dimethylaminobenzalde-

(35) H. C. Brown, THIS JOURNAL, **60**, 1325 (1938).
(36) M. Bergmann and J. S. Fruton, *J. Biol. Chem.*, **124**, 321 (1938).
(37) B. M. Iselin, H. T. Huang, R. V. MacAllister and C. Niemann, THIS JOURNAL, **72**, 1729 (1950).

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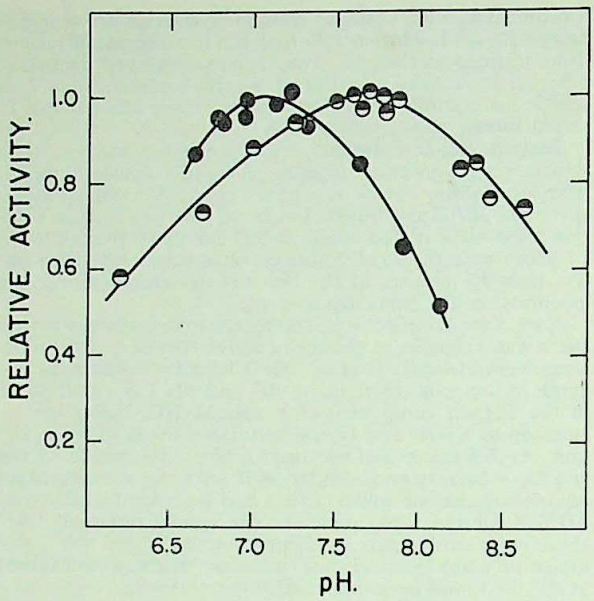

Fig. 1.—Relative activity *vs.* *p*H for the α-chymotrypsin-catalyzed hydrolysis of L-tyrosinhydrazide, ●, and of α-N-formyl-L-tyrosinhydrazide, ◒, in aqueous solutions at 25° and 0.02 *M* in the THAM component of a THAM–HCl buffer.

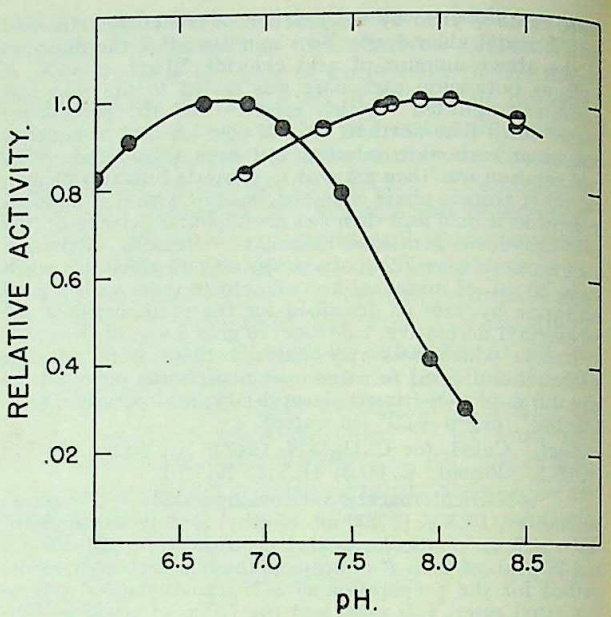

Fig. 2.—Relative activity *vs.* *p*H for the α-chymotrypsin-catalyzed hydrolysis of α-N-benzoyl-L-tyrosinhydrazide at 40°, ●, and at 25°, ◒, in aqueous solutions 0.02 *M* in the THAM component of a THAM–HCl buffer.

hyde reagent, 1.0 ml. of 1.72 *N* aqueous hydrochloric acid and *ca.* 5 ml. of water. The above solution was then made up to 10.0 ml. with water and allowed to stand for a period of 15–45 minutes before the optical density of the solution, contained in a 1-cm. quartz cell, was determined at 455 mμ using a Beckman Model B spectrophotometer equipped with a thermostated cell compartment maintained at 25°. It was found that the absorption at this wave length, *i.e.*, 455 mμ, followed Beer's law when the concentration of hydrazine was between 1 and 50 × 10^{-5} *M*. The size of the aliquot withdrawn from the reaction mixture was adjusted so the amount of hydrazine determined was between these limits.

With regard to blank corrections it should be noted that none of the specific substrates considered in this study were hydrolyzed in the absence of the enzyme under the conditions employed. However, a small blank correction was frequently made because of the presence of trace quantities of hydrazine in the specific substrates and because of a turbidity arising from the presence of a small amount of denatured enzyme in the solution of the azine.

Results.—The primary data obtained from analysis of the various reaction systems were recorded in terms of optical density, *i.e.*, extent of reaction, observed after a constant time interval for systems of varying hydrogen ion concentration with all other factors, *i.e.*, enzyme concentration, specific substrate concentration, time and temperature being maintained constant for any one specific substrate. Because the rather large variability in the susceptibility to hydrolysis of the various specific substrates resulted in a lack of uniformity, particularly with respect to enzyme and specific substrate concentrations, which had to be separately established for almost each specific substrate in order to obtain a significant extent of hydrolysis in a reasonable time interval, all of the primary data were normalized in order to facilitate presentation of the principal results of this study. In the normalization process the maximum optical density observed with any one specific substrate was assigned a value of unity and all other optical densities observed with the same specific substrate, where the only variable was the hydrogen ion concentration, were assigned values between zero and unity which were proportional to the respective observed optical densities relative to the observed maximum optical density. The plots given in Figs. 1 and 2 are representative examples of the derived data used for estimating the *p*H optima which are summarized in Tables I and II.

Acknowledgment.—The authors wish to express their indebtedness to Drs. R. M. Bock, J. T. Braunholtz, R. Kerr and W. E. M. Lands for their assistance during various stages of this study.

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[CONTRIBUTION FROM THE KETTERING–MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. III. Hydrazino Analogs of Biologically Active Purines[2]

BY JOHN A. MONTGOMERY AND LEE B. HOLUM

RECEIVED JUNE 11, 1956

Several hydrazinopurines have been prepared from the appropriate chloropurines. One compound, 2-amino-6-hydrazinopurine, could not be prepared from 2-chloro-6-hydrazinopurine, but was obtained from 2-amino-6-methylmercaptopurine.

There are several purines of biological importance which contain primary amino groups. Among them are adenine, guanine and 2,6-diaminopurine. Adenine and guanine occur naturally in cell nuclei, whereas 2,6-diaminopurine is, curiously enough, incorporated into nucleic acid guanine better than guanine itself[3] and has shown some anticancer activity.[4]

In view of the striking activity produced when the amino group of certain amino acids is replaced by a hydrazino group,[5] it is reasonable to assume that some interesting anticancer agents might result if the amino groups of the above-mentioned compounds are replaced by hydrazino groups (II, III, VI, X and XIV).

Of these compounds, 6-hydrazinopurine (II) has been reported previously,[6] but the method of preparation is inconvenient since it involves heating a sealed tube for 16 hours. In addition to these compounds, 2-hydrazinopurine (V) seemed worthy of synthesis for biological testing.

Two methods of introducing a hydrazino group into the desired positions of the purine ring appeared feasible: the replacement of a methylmercapto group and the replacement of a chlorine atom.

This replacement might be done either before or after ring closure of the appropriate 4,5-diaminopyrimidines to purines, since a new ring closure[7] has made the necessary chloropurines readily available.

The introduction of the hydrazino group prior to ring closure is undesirable for two reasons: the hydrazino group in the 6 position presents the possibility of closure involving the hydrazino group rather than the 4-amino group giving rise to 9-aminopurines, since 6-alkylamino-4,5-diaminopyrimidines give 9-alkylpurines[8]; the intermediate purines such as 2-chloro-6-hydrazinopurine would be more interesting for screening than the intermediate 4,5-diaminopyrimidines such as 2-chloro-4,5-diamino-6-hydrazinopyrimidine.[9]

Although the mercapto group in the 6-position of the purine ring cannot be replaced by amines or hydrazine, the 6-methylmercapto group can be replaced under rather strenuous conditions.[6] Since the chlorine atom is generally more susceptible to nucleophilic attack than the methylmercapto group,[10] it seemed probable that the replacement of the chlorine atom constituted a more desirable method of preparation of 6-hydrazinopurine. Therefore, the preparation of 6-hydrazinopurine *via* 6-chloropurine was attempted; it was found that replacement of the chlorine atom in anhydrous hydrazine took place smoothly at room temperature giving a 92% yield of pure 6-hydrazinopurine, showing that indeed the chlorine atom is more reactive.

It is well known that the substituents in the 2-position of purine are less reactive than substituents in the 6-position. Because of this the chlorine atom in this position, rather than the methylmercapto group, is an even more logical choice for replacement by the hydrazino group. Indeed Todd, *et al.*,[11] found that it was not possible to prepare 2,6-diaminopurine from 2-methylthioadenine under any conditions tried. Hydrazine, while more reactive than ammonia, is still not apt to replace the 2-thio or 2-methylthio group readily, unless an activating group is present in the 6-position.[12] Therefore, 2-chloropurine was chosen as the precursor to 2-hydrazinopurine, and the replacement with hydrazine carried out; although, as predicted, more strenuous conditions than those employed with 6-chloropurine were necessary.

The difference in reactivity of the chloro group in the 2- and 6-position of purine shows up distinctly in the reactions of 2,6-dichloropurine (VIII). This difference is much more pronounced than in the case of the chlorine atoms of 2,4-dichloropyrimidine[14]; it follows closely the comparison of 2-chloropurine and 6-chloropurine. When allowed to react with anhydrous hydrazine, the chlorine atoms of 2,6-dichloropurine are replaced stepwise.

(1) Affiliated with Sloan–Kettering Institute. This work was supported by funds from the C. F. Kettering Foundation. Part II, J. A. Johnson and H. S. Thomas, THIS JOURNAL, **78**, 3863 (1956).

(2) Presented at the Southwide Chemical Conference at Memphis, Tennessee, in December, 1956.

(3) L. L. Bennett, Jr., H. E. Skipper, C. C. Stock and C. P. Rhoads, *Cancer Research*, **15**, 485 (1955).

(4) J. H. Burchenal, A. Bendich, G. B. Brown, G. B. Elion and G. H. Hitchings, *Cancer*, **2**, 119 (1949).

(5) R. W. Brockman, Southern Research Institute, private communication.

(6) G. B. Elion, E. Burgi and G. H. Hitchings, THIS JOURNAL, **74**, 411 (1952).

(7) J. A. Montgomery, *ibid.*, **78**, 1928 (1956).

(8) J. W. Daly and B. E. Christensen, *J. Org. Chem.*, **21**, 177 (1956).

(9) This conclusion is based on the results obtained in screening numerous purines and pyrimidines at Southern Research Institute and Sloan–Kettering Institute for Cancer Research.

(10) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 294 (1951).

(11) K. J. M. Andrews, N. Anand, A. R. Todd and A. Topham, *J. Chem. Soc.*, 2490 (1949).

(12) Since this work was begun Elion, Lange and Hitchings[13] have reported that, in contrast to the behavior of 2-methylmercapto-6-aminopurine, the methylmercapto group of 2-methylmercapto-6-hydroxypurine can be replaced by amines. We have found that this is also true for hydrazine, although a better yield of 2-hydrazino-6-hydroxypyrine was obtained from 2-chloro-6-hydroxypurine under milder conditions.

(13) G. B. Elion, W. H. Lange and G. H. Hitchings, THIS JOURNAL **78**, 218 (1956).

(14) G. E. Hilbert and T. B. Johnson, *ibid.*, **52**, 1154 (1930).

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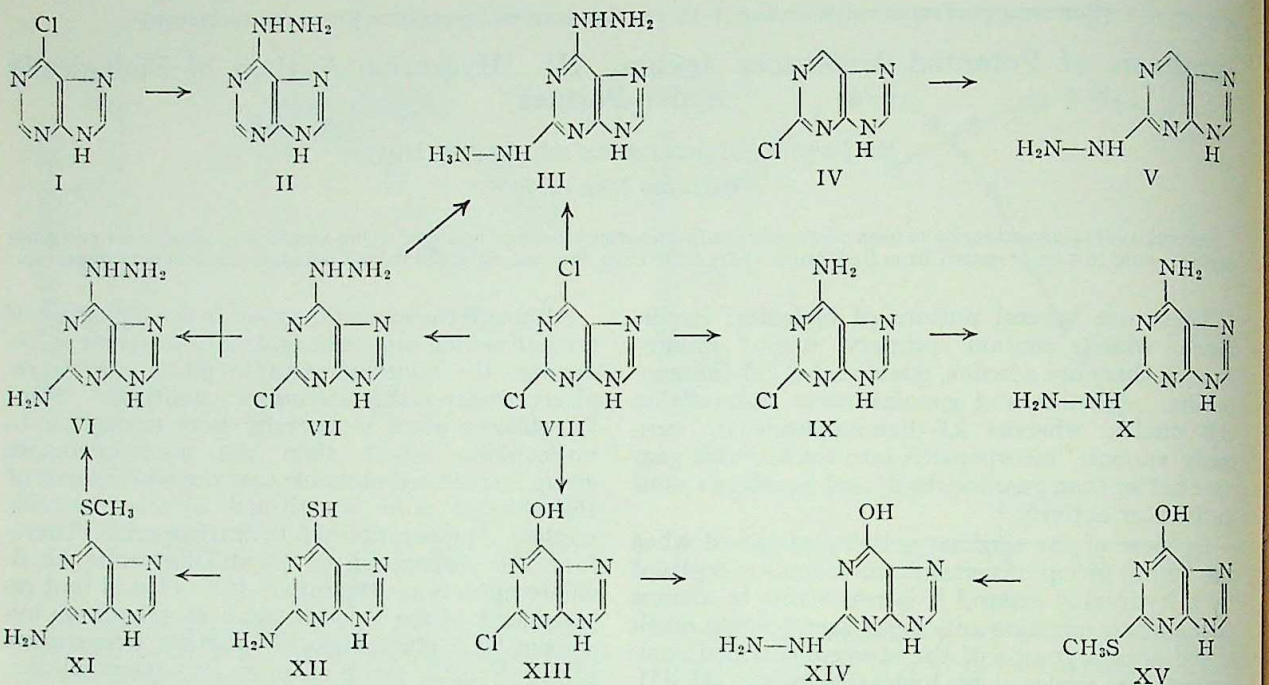

2-Chloro-6-hydrazinopurine (VII)[15] is obtained at room temperature and it is necessary to heat the solution of 2,6-dichloropurine in anhydrous hydrazine to 80° for 12 hours to obtain 2,6-dihydrazinopurine (III).

Attempts to prepare 2-amino-6-hydrazinopurine (VI) by the reaction of 2-chloro-6-hydrazinopurine (VII) with ammonia failed; only starting material was recovered. These findings agree with those of Adams and Whitmore[16] concerning the reactivity of the 2-chloro group of 6-N-substituted-amino-2-chloro-7-methylpurines. This compound (VI) was successfully prepared from 6-thioguanine (XII) *via* 2-amino-6-methylmercaptopurine (XI). The methylation of thioguanine with dimethyl sulfate worked well, but replacement of the 6-methylmercapto group was slow and the yield was low compared to the replacement of the 6-chloro group.

The synthesis of 6-amino-2-hydrazinopurine (X) was accomplished more readily. 2-Chloroadenine (IX) was prepared by the amination of 2,6-dichloropurine[17]; replacement of the 2-chloro group was accomplished by use of the same reaction conditions employed for the preparation of 2-hydrazinopurine and 2,6-dihydrazinopurine.

The preparation of the hydrazino analog of guanine (XIV) involved the selective hydrolysis of the 6-chlorine of 2,6-dichloropurine followed by reaction of the 2-chloro group with anhydrous hydrazine, as described for the other 2-hydrazinopurines.

The hydrolysis of 2,6-dichloropurine in 0.1 *N* acid or base is much slower than that of 6-chloropurine,[18] but proceeds readily in 1 *N* acid or base. Acid hydrolysis yields xanthine, while basic hydrolysis gives 2-chloro-6-hydroxypurine (XIII). Since XIII, when treated with hydrazine, yields the same compound (XIV) as does 6-hydroxy-2-methylmercaptopurine, this constitutes a chemical proof of structure of XIII. The ultraviolet and infrared spectra of this compound are quite similar to those of hypoxanthine and different from those of 2-hydroxypurine.

Absorption Spectra.—The effect of the hydrazino group on the ultraviolet spectrum of purine is about the same as that of the amino group. The only two comparisons available of the effect of the hydrazino group and the methylamino group (6-methylaminopurine: 6-hydrazinopurine and 6-hydroxy-2-methylaminopurine: 2-hydrazino-6-hydroxypurine) show that these two groups are also similar, as might be expected.

The hydrazino or amino group in the 6-position of the purine nucleus has only a slight effect on the position of the peak, but both groups do exert a pronounced hyperchromic effect.

In the 2-position they produce a large bathochromic effect and a slight hypsochromic effect, although in most cases the bathochromic effect of the 2-hydrazino group is less than that of the 2-amino group. Table I shows these comparisons plainly.

The extreme insolubility of the hydrazino purines in water or the common organic solvents makes the accurate determinations of molar absorbancies difficult; their instability in basic solution precludes entirely the accurate determination of their spectra at the higher *p*H.

As in the case of the ultraviolet absorption spectra, the hydrazino group and the amino group have a very similar effect on the infrared spectrum of purine. The spectra of these hydrazino and amino purines typically exhibit strong broad absorption between 3400–2900 cm.$^{-1}$ due primarily to NH vibrations and to a small extent to CH vibrations.

(15) The assignment of the structure of VII as 2-chloro-6-hydrazinopurine instead of 6-chloro-2-hydrazinopurine was made indirectly on the basis of the compound's ultraviolet and infrared spectra (see Table I and Experimental section), and on the chemical behavior of 2,6-dichloropurine in other instances, *i.e.*, the formation of 2-chloroadenine and 2-chloro-6-hydroxypurine (see Experimental).

(16) R. R. Adams and F. C. Whitmore, *ibid.*, **67**, 1271 (1945).

(17) G. B. Brown, private communication.

(18) A. Bendich, P. J. Russell, Jr., and J. J. Fox, THIS JOURNAL, **76**, 6073 (1954).

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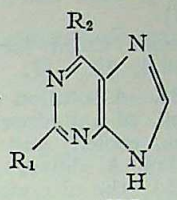
TABLE I

ULTRAVIOLET ABSORPTION SPECTRA



		pH 1		pH 7	
R_1	R_2	λ_{max}, mμ	$a_M \times 10^{-3}$	λ_{max}, mμ	$a_M \times 10^{-3}$
H	H	260	6.2	263	7.95
H	HN_2	263	12.6[a]	260	13.5[b]
H	CH_3NH	267[c]	15.1[b]	266	16.2[b]
H	NH_2NH	267	13.7[d]	262	9.4
Cl	NH_2	266	12	266	12
Cl	NH_2NH	267	10.5	271	10.4
NH_2	H	314	4.1	304	6.1[b]
NH_2NH	H	297	5.0	309	4.7
NH_2	NH_2	241[e]	10.0[f]	247[g]	7.0[f]
		282	9.9	280	8.8
NH_2	NH_2NH	238[h]	8.3	240[h]	7.5
		284.5	7.6	283	7.1
NH_2NH	NH_2	267.5	10.2	263	9.85
NH_2NH	NH_2NH	275.5	7.85	272.5	6.45
NH_2	OH	247[i]	10.5[f]	246[j]	10.8[f]
				275	8.6
CH_3NH	OH	250	12.3[k]	..	..
		280	6.9	..	..
NH_2NH	OH	248	10.6	248	10.0
				271[h]	6.5

[a] R. K. Robins, K. J. Dille, C. H. Willits and B. E. Christensen, THIS JOURNAL 75, 263 (1953). [b] S. F. Mason, *J. Chem. Soc.*, 2071 (1954). [c] *p*H 2.02. [d] See footnote 6. [e] *p*H 1.97. [f] L. F. Cavalieri, A. Bendich, J. F. Tinker and G. B. Brown, THIS JOURNAL, 70, 3878 (1948). [g] *p*H 6.49. [h] Point of inflection. [i] *p*H 1.93. [j] *p*H 5.99. [k] G. B. Elion, W. H. Lange and G. H. Hitchings, THIS JOURNAL, 78, 217 (1956).

The characteristic purine absorption between 2900–2400 cm.$^{-1}$ (due to acidic NH) is present in all cases. The most useful region of the spectrum is between 1700–1500 cm.$^{-1}$. In this region absorption due to NH deformation and C=C and C=N vibrations occurs, and differentiation between 2-substituted, 6-substituted, and 2,6-disubstituted (amino or hydrazino) purines is possibly due to the different modes in which the amino (or hydrazino) group interacts with the ring vibrations when in the 2- and in the 6-position. In the 6-position either group causes splitting of the strong absorption band and two distinct peaks occur, one at 1670–1640 cm.$^{-1}$ and the other at 1605–1590 cm.$^{-1}$. In the 2-position either group interacts to give one broad band about 1650 cm.$^{-1}$. The spectra of the 2,6-disubstituted compounds resemble more closely those of the 2-substituted purines, but the peak of the one broad band in this case is found at 1600–1590 cm.$^{-1}$. All these compounds show a weak to medium absorption peak about 1460–1430 cm.$^{-1}$ and one or two weak to medium peaks 960–900 cm.$^{-1}$, the absorption in both regions being due to CH. They also show a medium to strong band at 1340–1300 cm.$^{-1}$ from C–N deformation. The principal absorption maximum of each compound is listed in the Experimental section under the preparation of the compound.

Acknowledgment.—The authors are indebted to Mr. J. P. Holmquist for the microanalytical results reported, to Mr. J. W. Murphy and Mr. J. B. McBrayer for the ultraviolet and infrared spectral determinations, and in particular to Dr. B. R. Baker for his helpful suggestions and encouragement in this work. Some of the Dumas nitrogen determinations were carried out by the Galbraith Microanalytical Laboratories, Knoxville, Tennessee.

Experimental

Spectral Data.—The ultraviolet spectra were first determined with a Beckman Model DK-2 spectrophotometer, but the optical densities at the maxima were determined with a Beckman DU. The infrared spectra were run in pressed potassium bromide pellets with a Perkin–Elmer Model 21 spectrophotometer.

6-Hydrazinopurine (II).—6-Chloropurine[7,18] (5 g., 32.2 m*M*) was added in small portions with stirring to 25 ml. of anhydrous hydrazine over a period of 15–20 minutes. The solution became warm and turned purple so that it was necessary to moderate the reaction with an ice-bath. After standing for half an hour the solution deposited a large amount of fine crystals of 6-hydrazinopurine. The solid was removed by filtration and washed thoroughly with cold *n*-propyl alcohol. The yield of crude material was 4.76 g., m.p. 206–208° dec. (uncor.). Recrystallization of this material from 250 ml. of water gave 4.25 g. of white crystals, m.p. 246–247.5° dec. (cor.) (lit. 244–245°).[6] On standing the reaction mixture deposited more 6-hydrazinopurine. Purification gave 0.22 g. of additional material making the total yield 4.47 g. (92%); γ_{max} 3328 cm.$^{-1}$ (secondary NH), 3230 and 3175 cm.$^{-1}$ (NH_2), 2960 cm.$^{-1}$ (CH), 2800–2400 cm.$^{-1}$ (acidic NH), 1640 cm.$^{-1}$ (NH), 1605 cm.$^{-1}$ (C=C, C=N), 1455 cm.$^{-1}$ (CH), 1322 cm.$^{-1}$ (C–N), 942 cm.$^{-1}$ (CH).

2-Hydrazinopurine (V).—A solution of 2-chloropurine[7] (500 mg.) in 10 ml. of hydrazine was heated for 12 hours at 80°. The excess hydrazine was removed *in vacuo*. The cream-colored residue was triturated with water, removed by filtration, and dried *in vacuo* over P_2O_5 at 80°; yield 280 mg. (57.7%), m.p. >300°; γ_{max} 3265 cm.$^{-1}$ (secondary NH), 3160 cm.$^{-1}$ (NH_2), 2930 cm.$^{-1}$ (CH), 2800–2500 cm.$^{-1}$ (acidic NH), 1655, 1626 (sh) cm.$^{-1}$ (NH), 1585 and 1538 cm.$^{-1}$ (C=C, C=N), 1432 cm.$^{-1}$ (CH), 1328 cm.$^{-1}$ (C–N), 930 cm.$^{-1}$ (CH).

The ultraviolet and infrared absorption spectra of a sample recrystallized from water for analysis were essentially the same as those of the unrecrystallized material.

Anal. Calcd. for $C_5H_6N_6$: C, 40.0; H, 4.00; N, 56.0. Found: C, 40.1; H, 4.05; N, 56.4.

2,6-Dihydrazinopurine (III) (A).—A solution of 2-chloro-6-hydrazinopurine (500 mg.) in 10 ml. of anhydrous hydrazine upon heating at 80° for four hours deposited a white solid which was removed by filtration, washed with water, and dried *in vacuo* over P_2O_5; yield 175 mg., m.p. > 300°; γ_{max} 3215 cm.$^{-1}$ (secondary NH), 3140 and 3000 cm.$^{-1}$ (NH), 2920 cm.$^{-1}$ (CH), 2800–2400 cm.$^{-1}$ (acidic NH), 1650 (sh) and 1625 (sh) cm.$^{-1}$ (NH), 1600 cm.$^{-1}$ (NH and C=C, C=N), 1550 cm.$^{-1}$ (C=C, C=N), 1435 cm.$^{-1}$ (CH), 1325 cm.$^{-1}$ (C–N), 923 cm.$^{-1}$ (C–H).

Anal. Calcd. for $C_5H_8N_8$: C, 33.3; H, 4.45; N, 62.2. Found: C, 33.1; H, 4.42; N, 62.1.

The hydrazine filtrate from above was taken to dryness *in vacuo* and the residue triturated with water, filtered and dried. The yield was 25 mg., λ_{max}^{pH1} 276 mμ ($a_M \times 10^{-3}$ 7), λ_{max}^{pH7} 275 mμ ($a_M \times 10^{-3}$ 6.08). The total yield of 2,6-dihydrazinopurine was 200 mg. (41%).

(B).—2,6-Dichloropurine[7] (1 g.) was added slowly to 11 ml. of anhydrous hydrazine with intermittent cooling. After standing overnight at room temperature, the solution was heated at 80° for 12 hours. The precipitate which formed during the reaction was removed by filtration, washed with cold water, and dried *in vacuo* over P_2O_5; yield 760 mg. Another 20 mg. of product was obtained by concentration of the hydrazine filtrate from above making the total yield 780 mg. (82%). The ultraviolet and infrared spectra of this material were identical with that of the material prepared by A.

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6-Amino-2-hydrazinopurine (X).—A solution of 2-chloroadenine[17] (440 mg.) in 15 ml. of anhydrous hydrazine was heated at 80° for 12 hours. The excess hydrazine was removed under reduced pressure and the resultant gray solid triturated with warm water, removed by filtration, and dried *in vacuo* over P_2O_5; yield 200 mg. (47%), m.p. >300°; γ_{max} 3300 cm.$^{-1}$ (secondary NH), 3100 cm.$^{-1}$ (NH_2), 2980 cm.$^{-1}$ (CH), 2800–2500 cm.$^{-1}$ (acidic NH), 1655 cm.$^{-1}$ (NH), 1600 and 1545 cm.$^{-1}$ (C=C, C=N), 1450 cm.$^{-1}$ (CH), 1331 cm.$^{-1}$ (C–N), 934 cm.$^{-1}$ (CH).

A small sample was recrystallized from water for analysis.

Anal. Calcd. for $C_5H_7N_7$: C, 36.40; H, 4.25; N, 59.5. Found: C, 36.2; H, 4.55; N, 60.34.

2-Chloro-6-hydrazinopurine (VII).—2,6-Dichloropurine (2.5 g.) was added to 15 ml. of anhydrous hydrazine with stirring and intermittent cooling. After standing overnight at room temperature the mixture was evaporated under reduced pressure and the solid residue boiled with 25 ml. of distilled water. The suspension was then cooled and the solid removed by filtration and dried *in vacuo* over P_2O_5; yield 1.98 g. (81%), m.p. >300°; γ_{max} 3340 cm.$^{-1}$ (secondary NH), 3250, 3100 cm.$^{-1}$ (NH), 2800–2400 cm.$^{-1}$ (acidic NH), 1665 and 1655 (sh) cm.$^{-1}$ (NH), 1605 cm.$^{-1}$ (C=C, C=N), 1450 cm.$^{-1}$ (CH), 1305 cm.$^{-1}$ (CN), 925 cm.$^{-1}$ (CH).

The ultraviolet and infrared spectra of a small sample recrystallized from water for analysis were practically unchanged.

Anal. Calcd. for $C_5H_5ClN_6$: C, 32.50; H, 2.75; Cl, 19.25. Found: C, 32.6; H, 2.87; Cl, 19.4.

2-Chloro-6-hydroxypurine (XIII).—A solution of 2,6-dichloropurine (500 mg.) in 25 ml. of 1 *N* sodium hydroxide was refluxed for one hour, cooled, neutralized with acetic acid, and allowed to stand in a refrigerator overnight. The light yellow crystals were removed by filtration, washed with ice water, and dried *in vacuo* over P_2O_5; yield of almost pure material, 300 mg. (66%), m.p. >300°.

A small sample was recrystallized from water for analysis; λ_{max}^{pH1} 250 mμ ($a_M \times 10^{-3}$ 11.2), λ_{max}^{pH7} 259 mμ ($a_M \times 10^{-3}$ 10.1), λ_{max}^{pH13} 265 mμ ($a_M \times 10^{-3}$ 11.6); γ_{max} 3020 cm.$^{-1}$ (NH), 2900 cm.$^{-1}$ (CH), 2800–2300 cm.$^{-1}$ (acidic H), 1680 cm.$^{-1}$ (C=O), 1562, 1530 (sh) cm.$^{-1}$ (C=C, C=N), 950 cm.$^{-1}$ (CH).

Anal. Calcd. for $C_5H_3ClN_4O$: C, 35.20; H, 1.76; N, 32.82. Found: C, 35.4; H, 1.93; N, 32.65.

2-Hydrazino-6-hydroxypurine (XIV) (A).—A solution of 6-hydroxy-2-methylmercaptopurine[18] (720 mg.) in 10 ml. of anhydrous hydrazine was refluxed for 20 hours, cooled, and the excess hydrazine removed at reduced pressure. The gray residue was triturated with water, removed by filtration, and dried *in vacuo* over P_2O_5; yield of almost pure material, 200 mg. (30%). A small sample of this material was recrystallized from water for analysis, m.p. >300°; γ_{max} 3305 cm.$^{-1}$ (secondary NH), 3160 cm.$^{-1}$ (NH), 3000 cm.$^{-1}$ (CH), 2800–2300 cm.$^{-1}$ (acidic NH), 1665 cm.$^{-1}$ (NH and C=O), 1600, 1590 (sh), 1537 (sh) cm.$^{-1}$ (C=C, C=N), 1455 cm.$^{-1}$ (CH), 1308 cm.$^{-1}$ (CN), 942 cm.$^{-1}$ (CH).

Anal. Calcd. for $C_5H_6N_6O$: C, 36.2; H, 3.62. Found: C, 36.4; H, 4.17.

(B).—A solution of 2-chloro-6-hydroxypurine (3.5 g.) in 25 ml. of anhydrous hydrazine was heated at 80° for 14 hours, cooled, and the product isolated as described in Method A above; yield of almost pure material, 3.1 g. (91%); the ultraviolet and infrared spectra were identical with that of the material obtained by Method A above.

A 100-mg. sample was recrystallized from 200 ml. of water and dried over P_2O_5 *in vacuo* at 110°; yield 65 mg.

Anal. Calcd. for $C_5H_6N_6O$: C, 36.2; H, 3.62; N, 50.60. Found: C, 36.25; H, 4.13; N, 50.05.

2-Amino-6-methylmercaptopurine (XI).—Thioguanine[19] (5 g., 30 m*M*) was dissolved with heating in 253 ml. of 0.115 *N* sodium hydroxide (30 m*M*). This solution was cooled to 30–40° and dimethyl sulfate (3.79 g., 2.8 ml., 30 m*M*) added dropwise with stirring. After stirring the mixture for another hour, the material which had precipitated was removed by filtration and dried. The yield of almost pure material was 3.5 g., m.p. 239–239.5°; λ_{max}^{pH1} 241, 272, 318 mμ ($a_M \times 10^{-3}$ 6.72, 9.6, 12.4), λ_{max}^{pH7} 242, 310 mμ ($a_M \times 10^{-3}$ 12.1, 10.6), λ_{max}^{pH13} 227, 314 mμ ($a_M \times 10^{-3}$ 19.9, 10.3). An additional gram of material, m.p. 239–240°, was obtained by concentration of the mother liquor.

A small sample of the material was recrystallized from water and dried *in vacuo* at 80–100° for about 6 hours, m.p. 239.5–240°; λ_{max}^{pH1} 241, 273, 317 mμ ($a_M \times 10^{-3}$ 7.0, 10, 13), λ_{max}^{pH7} 242, 309 mμ ($a_M \times 10^{-3}$ 12.7, 11.0), λ_{max}^{pH13} 228, 313 mμ ($a_M \times 10^{-3}$ 20.2, 10.6); γ_{max} 3350–3050 cm.$^{-1}$ (NH), 2960 cm.$^{-1}$ (CH_3), 2800–2400 cm.$^{-1}$ (acidic NH), 1635 (sh) cm.$^{-1}$ (NH), 1600 and 1556 cm.$^{-1}$ (C=C, C=N), 1450 cm.$^{-1}$ (CH), 1308 cm.$^{-1}$ (C–N), 911 cm.$^{-1}$ (CH).

Anal. Calcd. for $C_6H_7N_5S$: C, 39.8; H, 3.86. Found: C, 39.8; H, 3.91.

2-Amino-6-hydrazinopurine (X).—A solution of 2-amino-6-methylmercaptopurine (505 mg.) in 10 ml. of anhydrous hydrazine was refluxed for 12 hours. Most of the excess hydrazine was removed under reduced pressure and 10 ml. of *n*-propanol added to the residue. The resultant gray solid was removed by filtration, triturated with boiling water, again collected by filtration and dried *in vacuo* over P_2O_5 at 100° for 3 hours; yield of almost pure material, 310 mg. (67%). A small amount of this material was recrystallized from water for analysis and dried *in vacuo* over P_2O_5 for 3 hours at 100°, m.p. >300°; γ_{max} 3345 cm.$^{-1}$ (secondary NH), 3250 and 3140 cm.$^{-1}$ (NH), 2930 cm.$^{-1}$ (CH), 2800–2500 cm.$^{-1}$ (acidic NH), 1645 (sh) and 1625 (sh) cm.$^{-1}$ (NH and C=C, C=N), 1590 cm.$^{-1}$ (C=C, C=N), 1436 cm.$^{-1}$ (CH), 1332 cm.$^{-1}$ (C–N), 930 cm.$^{-1}$ (CH).

Anal. Calcd. for $C_5H_7N_7$: C, 36.38; H, 4.23; N, 59.5. Found: C, 36.05; H, 4.29; N, 59.2.

(19) Francis Earle Laboratories.

BIRMINGHAM 5, ALABAMA

[CONTRIBUTION FROM THE KETTERING–MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. IV. 4-Nitro- and 4-Amino-5-imidazole Sulfones

BY L. L. BENNETT, JR., AND HARRY T. BAKER

RECEIVED NOVEMBER 19, 1956

A number of 4-nitro- and 4-amino-5-imidazole sulfones have been prepared as potential antagonists of 4-amino-5-imidazolecarboxamide. Attempts to prepare 4-amino-5-imidazolesulfonamide by several methods were unsuccessful. A convenient preparation of 4-acetamidoimidazole is described.

The synthesis of compounds designed to interfere with purine metabolism has been the subject of considerable recent literature.[2] Most of the com-

(1) Affiliated with Sloan–Kettering Institute. This work was supported by grants from the C. F. Kettering Foundation and the Alfred P. Sloan Foundation, Inc. For the preceding paper in this series, see J. A. Montgomery and L. B. Holum, THIS JOURNAL, **79**, 2185 (1957).

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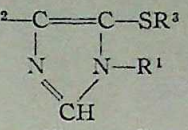
TABLE I

4-NITRO-5-IMIDAZOLE SULFIDES AND 4-AMINO-5-IMIDAZOLE SULFIDES



R	R^2	R^3	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
H	NO_2	CH_3	70	187–189	30.19	30.54	3.17	3.33	26.41	26.00	20.12	20.00
H	NO_2	C_2H_5	60	196–198	34.68	34.99	4.08	4.12	24.27	24.19		
H	NO_2	n-C_3H_7	55	159–161	38.50	38.52	4.85	4.62	22.45	23.18		
H	NO_2	n-C_4H_9	75	215–216	41.79	42.07	5.51	5.94	20.89	20.95		
H	NO_2	$C_6H_5CH_2$	90	212–213	51.06	51.43	3.86	3.97	17.87	18.42	13.61	13.30
CH_3	NO_2	CH_3	90	119–120	34.68	34.53	4.08	4.13	24.27	25.64	18.44	18.25
CH_3	NO_2	C_2H_5	98	68–70	38.50	38.54	4.85	4.62	22.45	22.94		
CH_3	NO_2	n-C_3H_7	80	43–44	41.79	42.56	5.51	5.60	20.89	20.85		
CH_3	NO_2	n-C_4H_9	92	45–46	44.64	44.98	6.09	6.09	19.53	19.46		
CH_3	NO_2	C_6H_5	95	77–78	51.06	51.43	3.86	3.87	17.87	17.48	13.61	13.42
CH_3	NO_2	o-$NH_2C_6H_4$	95	129–132	48.00	48.05	4.02	3.97	22.39	22.31		
CH_3	NO_2	o-$(CH_3CONH)C_6H_4$	65	162–163	49.31	49.39	4.14	4.15	19.17	19.09	10.94	10.90
CH_3	NO_2	$C_6H_5CH_2$	90	113–115	53.01	52.94	4.45	4.47	16.86	16.77		
CH_3	NH_2·HCl	C_6H_5	70	210–211	49.68	49.50	4.97	4.84	17.38	17.11		
CH_3	NH_2·HCl	$C_6H_5CH_2$	60	181–182	51.65	51.04	5.52	5.48	16.43	16.20		

pounds prepared for this purpose have been analogs or derivatives of purines and their ribosides. Although imidazole ribotides have been implicated for some time as intermediates in the biosynthesis of purines,[3–5] there have been no reports of attempts to prepare imidazoles as antagonists of 4-aminoimidazole or 4-amino-5-imidazolecarboxamide which, as their ribotides, occur as intermediates in *de novo* synthesis of purines.[3–5] This paper is concerned with the synthesis of certain 4-amino-5-imidazole sulfones and related compounds as potential antagonists of 4-amino-5-imidazolecarboxamide.

A number of 2-mercaptoimidazoles are known, but only a few 4-mercaptoimidazoles are recorded in the literature.[6] A series of sulfones derived from 2-mercaptoimidazole has been reported recently,[7] but there have been no reports of sulfones derived from 4-mercaptoimidazoles.

In the present work, two series of imidazole sulfides and sulfones were prepared: one derived from 4-nitro-5-mercaptoimidazole and one from 1-methyl-4-nitro-5-mercaptoimidazole. 1-Methyl-4-nitro-5-chloroimidazole[8] and 4-nitro-5-bromoimidazole[9] were converted to the ammonium salts of 1-methyl-4-nitro-5-mercaptoimidazole and 4-nitro-5-mercaptoimidazole, respectively, by reaction with hydrogen sulfide in ammoniacal methanol, a method used by Bhagwat and Pyman[10] for the synthesis of 2-methyl-4-nitro-5-mercaptoimidazole. The nitroimidazole mercaptans were then alkylated in methanolic sodium methoxide, and the resulting sulfides were oxidized to the sulfones with hydrogen peroxide in glacial acetic acid. The nitroimidazole sulfones finally were reduced to 4-amino-5-imidazole sulfones by Raney nickel in absolute ethanol. In the 1-methyl series the sulfides also were prepared easily from the reaction of 1-methyl-4-nitro-5-chloroimidazole with mercaptans in ammoniacal ethanol, but 4-nitro-5-bromoimidazole failed to react with a variety of mercaptans under these conditions. 1-Methyl-4-nitro-5-(*p*-acetamidophenylsulfonyl)-imidazole was prepared by reaction of 1-methyl-4-nitro-5-chloroimidazole with *p*-acetamidobenzenesulfinic acid[11] under the conditions used by Baker, *et al.*,[12] for the preparation of 2,4-dinitro-4′-acetamidodiphenyl sulfone. The sulfides and sulfones prepared are listed in Tables I and II.

In the course of this work, a number of attempts were made to prepare 4-amino-5-imidazolesulfonamides. 1-Methyl-4-nitro-5-imidazolesulfonic acid[13] failed to react with phosphorus pentachloride, phosphorus pentachloride–phosphorus oxychloride mixtures, thionyl chloride, or chlorosulfonic acid under a variety of conditions; this failure was anticipated from the unsuccessful attempts of Pyman and co-workers[14,15] to prepare sulfonyl chlorides from other imidazolesulfonic acids. Chlorosulfonic acid at 190–200° converted 4-bromoimidazole[9] to 4-bromo-5-imidazolesulfonyl chloride which was converted readily to the corresponding sulfonamide. However, the bromine atom in this sulfonamide and in its derivative, 4-bromoimidazole-5-N,N-dibenzylsulfonamide, was inert toward ammonia and amines under a variety of conditions. Considerable inertness to replacement by hydroxyl groups has been observed by Eliel and Nelson[16] in studies with *p*-chlorobenzenesulfonamides.

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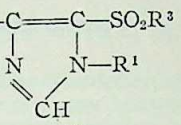
TABLE II

4-NITRO-5-IMIDAZOLE SULFONES AND 4-AMINO-5-IMIDAZOLE SULFONES



R^1	R^2	R^3	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
H	NO_2	CH_3	80	276–277	25.17	25.24	2.64	2.94	21.99	22.33	16.75	16.85
H	NO_2	C_2H_5	90	246.5–247	29.27	29.51	3.44	3.61	20.49	20.53		
H	NO_2	n-C_3H_7	60	215–217	32.88	32.58	4.14	3.98	19.18	19.25		
H	NO_2	$C_6H_5CH_2$	85	252–256	44.95	45.22	3.40	3.67	15.73	15.96	11.98	11.56
CH_3	NO_2	CH_3	25	160–161	29.27	29.55	3.44	3.68	20.49	20.47		
CH_3	NO_2	C_2H_5	85	158–160	32.88	32.37	4.14	4.17	19.18	18.22		
CH_3	NO_2	n-C_3H_7	90	165–166	36.05	35.83	4.76	4.78	18.02	17.93		
CH_3	NO_2	n-C_4H_9	60	82–84	38.87	38.99	5.30	5.33	17.00	16.15	12.94	12.79
CH_3	NO_2	C_6H_5	80	130–133	44.95	45.08	3.40	3.42	15.73	15.53	11.98	11.48
CH_3	$NO_2 \cdot H_2O$	p-$(CH_3CONH)C_6H_4$	55	125–127	42.11	42.49	4.12	3.91	16.37	16.35		
CH_3	NO_2	$C_6H_5CH_2$	70	161–162.5	46.98	46.78	3.94	3.97	14.94	15.10	11.38	11.84
H	$NH_2 \cdot HCl$	CH_3	65	193–195	24.31	24.03	4.08	3.92	21.26	20.98	16.23	16.12
H	$NH_2 \cdot HCl$	$C_6H_5CH_2$	25	208–210	43.87	43.82	4.42	4.94	15.35	15.79		
CH_3	$NH_2 \cdot HCl \cdot H_2O$	CH_3	80	207–208	26.14	26.37	5.27	4.97	18.29	18.44	13.96	13.90
CH_3	$NH_2 \cdot HCl \cdot H_2O$	n-C_4H_9	70	165–167	35.35	35.12	6.67	6.46	15.46	16.21		
CH_3	NH_2	p-$(CH_3CONH)C_6H_4$	60	220–222	48.96	48.71	4.79	4.81	18.36	18.66		
CH_3	$NH_2 \cdot HCl$	$C_6H_5CH_2$	60	221–222	45.90	45.44	4.90	4.94	14.60	14.75	(Cl) 12.38	(Cl) 12.19

Attempted chlorosulfonation of 4-acetamidoimidazole[17] led only to decomposition products from which no sulfonyl chloride could be isolated. Unsuccessful attempts were also made to convert 1-methyl-4-nitro-5-mercaptoimidazole to the sulfonamide *via* the sulfenamide, a method recently used with success by Greenbaum[18] for the conversion of 6-mercaptouracil to uracil-6-sulfonamide.

4-Acetamidoimidazole, used for the attempted chlorosulfonation mentioned above, was prepared by reduction of 4-nitroimidazole[19] with Raney nickel in a mixture of acetic anhydride and acetic acid, a method considerably more convenient for the preparation of this compound in quantity than the stannous chloride reduction method of Hunter and Nelson.[17] Under the conditions of the Raney nickel reduction, 4-aminoimidazole was isolated as a diacetyl derivative, which on the basis of a comparison of its infrared spectrum with that of an authentic sample of 1-acetylimidazole,[20] was assigned the structure of 1(or 3)-acetyl-4-acetamidoimidazole. Boiling water readily removed the ring acetyl group, giving 4-acetamidoimidazole in 88% yield from the diacetyl compound.

Acknowledgments.—The authors are indebted to Dr. B. R. Baker, Dr. J. A. Montgomery and Miss K. Hewson for helpful discussions; to Mr. J. P. Holmquist for elemental analyses; and to Dr. W. C. Coburn and Mr. J. W. Murphy for infrared spectra determinations.

Experimental

All melting points are uncorrected. The infrared spectra were run in pressed potassium bromide pellets with a Perkin-Elmer model 21 spectrophotometer.

4-Nitro-5-mercaptoimidazole.—This compound was prepared by the same method used by Bhagwat and Pyman[10] for 2-methyl-4-nitro-5-mercaptoimidazole.

4-Nitro-5-bromoimidazole[9] (2.0 g.) was dissolved in 20 ml. of warm 5 *N* ammonium hydroxide and hydrogen sulfide was bubbled through the solution for 15 min. The ammonium salt of the mercaptoimidazole separated as bright orange needles, m.p. >300°, yield 1.9 g. (82%). The crude product was crystallized from methanol.

Anal. Calcd. for $C_3H_6N_4O_2S$: C, 22.20; H, 3.73; N, 34.52; S, 19.75. Found: C, 22.11; H, 3.54; N, 34.37; S, 19.58.

The ammonium salt of 1-methyl-4-nitro-5-mercaptoimidazole, m.p. 197–198°, was prepared similarly in 58% yield and purified by crystallization from methanol by the addition of ether.

Anal. Calcd. for $C_4H_8N_4O_2S$: C, 27.27; H, 4.58; N, 31.78; S, 18.19. Found: C, 27.70; H, 4.46; N, 31.79; S, 18.14.

4-Nitro-5-imidazole Sulfides.—The imidazole sulfides were prepared either by alkylation of the mercaptoimidazole or by reaction between the 4-nitro-5-haloimidazole and mercaptans.

Alkylation of Mercaptoimidazoles.—The ammonium salt (2.0 g.) of the 4-nitro-5-mercaptoimidazole was dissolved in 50 ml. of methanol containing about 1 g. of sodium methoxide. The alkyl halide (5–10% excess) was added and the mixture was refluxed for two hours. After the solvent had been removed by evaporation in a stream of nitrogen, the residue was crystallized from water or aqueous ethanol.

Reaction of 4-Nitro-5-haloimidazoles with Mercaptans.—This reaction, which was used only in the 1-methyl series, was carried out under the conditions reported by Overberger, *et al.*,[21] for the synthesis of *p*-nitrobenzyl sulfide.

To a solution of 1-methyl-4-nitro-5-chloroimidazole[8] (10.0 g.) in 200 ml. of warm ethanol there was added an equimolar amount of the mercaptan, and ammonia was bubbled through the solution for two hours. The reaction mixture was allowed to stand overnight after which the solution was evaporated to dryness and the residue was crystallized from aqueous ethanol.

4-Nitro-5-imidazole Sulfones.—The imidazole sulfide was dissolved in a small volume (about 10 ml./g. sulfide) of glacial acetic acid at 60°, and oxidized by the dropwise addition of 30% hydrogen peroxide[21] (10 ml./g. sulfide). After the yellow color of the original solution had disappeared, the solution was warmed at 80° for 30 min. The sulfone usually crystallized at this point or upon standing overnight; in some cases it was necessary to concentrate the solution or to add water or ethanol to cause precipitation. The sulfones were purified by crystallization from water or ethanol.

1-Methyl-4-nitro-5-(*p*-acetamidophenylsulfonyl)-imidazole.—A solution of 1-methyl-4-nitro-5-chloroimidazole (5.0 g.) and 6.2 g. of *p*-acetamidobenzenesulfinic acid in 25 ml. of ethanol and 5 ml. of 6 *N* NaOH was refluxed for 30 min. After the mixture had been cooled to room temperature, 200 ml. of water was added. The precipitated yellow solid was washed with water and alcohol and dried; wt. 5.4 g., m.p. 120–125°. Recrystallization of the sulfone

(17) G. Hunter and J. A. Nelson, *Can. J. Research*, **19B**, 296 (1941).

(18) S. B. Greenbaum, THIS JOURNAL, **76**, 6052 (1954).

(19) R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, **115**, 217 (1919).

(20) J. H. Boyer, "Biochemical Preparations," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 50.

(21) C. G. Overberger, S. P. Ligthelm and E. A. Swire, THIS JOURNAL, **72**, 2856 (1950).

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from alcohol with charcoal treatment gave white needles, m.p. 125–127°, which analyzed as a monohydrate (Table II).

4-Amino-5-imidazole Sulfones.—The 4-nitroimidazole sulfone was suspended in dry ethanol (100 ml./g. sulfone) containing Raney nickel which had been washed repeatedly with dry ethanol. The suspension was reduced in a Parr hydrogenation apparatus at atmospheric pressure until the theoretical amount of hydrogen was taken up (about 15 min. required). While air was excluded by a nitrogen atmosphere, the catalyst was removed, four volumes of anhydrous ether were added, and dry hydrogen chloride was bubbled through the solution for 30 min. After the solvents had been removed by evaporation at 40–60° in a stream of nitrogen, the residue was taken up in 2–3 ml. of dry ethanol, decolorized with charcoal, and the amine hydrochloride was precipitated by addition of a large volume of dry ether. When 1-methyl-4-nitro-5-(*p*-acetamidophenylsulfonyl)-imidazole was reduced, the free base began to precipitate from the reaction mixture, and was obtained in a pure state by removing the catalyst and evaporating the ethanol *in vacuo*.

The 4-amino-5-imidazole sulfides reported (Table I) were prepared similarly by reduction of the nitro compounds.

Infrared Spectra.—All of the reaction products described above were characterized by infrared spectra which were compared with the spectra of known imidazoles. Reduction of 4-nitro-5-imidazole sulfones caused the disappearance of bands in the ranges 1460–1550 and 1360–1380 cm.$^{-1}$; these ranges correspond fairly well to those in which the aromatic nitro group is known to absorb.[22] Concurrent with the disappearance of the nitro group there appeared a strong amino band at 1630–1650 cm.$^{-1}$ and increased NH absorption in the range 3100–3400 cm.$^{-1}$. Oxidation of 4-nitro-5-imidazole sulfides to sulfones caused the appearance of new bands in the ranges 1120–1170 cm.$^{-1}$ and 1300–1330 cm.$^{-1}$, regions in which sulfones are known to absorb.[22] When these compounds were reduced, strong bands were retained in the ranges 1120–1170 and 1300–1330 cm.$^{-1}$. It was difficult, however, to make a definite assignment of the sulfone absorption, since the 4-nitro-5-imidazole sulfides showed some absorption in the same regions, and since there was apparently some interaction between the sulfone and nitro groups.

4-Bromo-5-imidazolesulfonamide.—To 10 ml. of chlorosulfonic acid in a small flask was added 2.0 g. of 4-bromoimidazole.[9] With exclusion of moisture, the mixture was heated slowly to 190–200° and kept at this temperature for 2 hr. The mixture was then poured onto 50 g. of crushed ice, and the colorless sulfonyl chloride, which precipitated, was removed and dried in air; m.p. 186–188° (dec.), wt. 1.7 g. (51%). For preparation of the amide, the crude acid chloride was dissolved in 20 ml. of concd. NH_4OH at room temperature. After 10 min., excess ammonium was removed by gentle warming in a stream of nitrogen and the solution was acidified with HCl. The precipitate weighed 0.76 g. (55%), m.p. 243–244°. After crystallization from water, the m.p. was 246–247°.

Anal. Calcd. for $C_3H_4BrN_3O_2S$: C, 15.92; H, 1.77; N, 18.60; Br, 35.40; S, 14.18. Found: C, 15.99; H, 1.79; N, 18.47; Br, 35.34; S, 14.25.

(22) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Company Ltd., London, 1954

The anilide and the N,N-dibenzylamide were prepared by the Schotten–Baumann method. *Anal.* Calcd. for anilide: $C_9H_8BrN_3O_2S$: C, 35.79; H, 2.65; N, 13.90; Br, 26.94; S, 10.60. Found: C, 35.37; H, 2.62; N, 13.99; Br, 26.37; S, 10.69. Calcd. for dibenzylamide: $C_{17}H_{16}BrN_3O_2S$: C, 50.20; H, 3.94. Found: C, 50.14; H, 4.12.

Treatment of the amide with nitrous acid[23] gave the sulfonic acid, m.p. 265–267°. *Anal.* Calcd. for $C_3H_3BrN_2O_3S$: C, 15.88; H, 1.32; N, 12.32. Found: C, 15.72; H, 1.40; N, 12.40.

A sample of 4-bromo-5-imidazolesulfonic acid, prepared by sulfonation of 4-bromoimidazole according to Balaban and Pyman,[9] melted at 270–271°; a mixed melting point of this sample with that prepared above was 265–267°. The infrared spectra of the two samples were identical in the fingerprint region.

1(or 3)-Acetyl-4-acetamidoimidazole and 4-Acetamidoimidazole.—4-Nitroimidazole[19] (2.3 g.) was suspended in 50 ml. of acetic anhydride to which was added 20 ml. of glacial acetic acid and 1 teaspoonful of Raney nickel slurry. The mixture was shaken in a Parr hydrogenation apparatus at 31 p.s.i. initial pressure until the theoretical pressure drop occurred (about 2 hr. required). Raney nickel was removed and, while air was excluded by blowing dry nitrogen on the surface, the clear solution was evaporated to dryness on a steam-bath. The black residue was treated with cold water; a gray insoluble residue, which was removed by filtration, weighed 1.2 g. and melted at 225–227°. After crystallization from dioxane with charcoal treatment, the product was obtained colorless and melted at 227.5–228.5°. The infrared spectrum showed a strong band at 1680 cm.$^{-1}$, characteristic of the amide carbonyl group, and an additional band at 1720 cm.$^{-1}$. Since 1-acetylimidazole[20] was found to have a strong band at 1725 cm.$^{-1}$, the compound was assigned the structure of 1(or 3)-acetyl-4-acetamidoimidazole. The infrared spectrum of N-acetylimidazole has also been determined recently by Otting[24] who reported a peak at 1747 cm.$^{-1}$ for the N-acetyl group.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.30; H, 5.38; N, 25.12. Found: C, 50.37; H, 5.36; N, 25.06.

When the above compound was treated with a solution of picric acid in aqueous ethanol, a picrate was formed which analyzed as the picrate of 4-acetamidoimidazole, m.p. 202°, reported[17] 208°.

Anal. Calcd. for $C_{11}H_{10}N_6O_8$: C, 37.29; H, 2.82; N, 23.73. Found: C, 37.12; H, 3.08; N, 23.25.

For conversion to 4-acetamidoimidazole, a sample of the diacetyl compound was boiled in water for 30 min., after which the solution was evaporated to dryness *in vacuo* on a steam-bath. The residue was crystallized from dioxane to yield white crystals which were dried *in vacuo* at 140° and 1 mm. pressure; m.p. 220°, reported m.p. 226°[17]; yield 88% from the diacetyl derivative.

Anal. Calcd. for $C_5H_7N_3O$: C, 48.00; H, 5.60; N, 33.59. Found: C, 47.77; H, 5.36; N, 33.28.

(23) F. Muth, in "Methoden der Organischen Chemie," IV Auflage, Vol. IX, edited by E. Müller, Georg Thieme, Stuttgart, 1955, p. 531.

(24) W. Otting, *Chem. Ber.*, **89**, 1940 (1956).

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Alkaloids of the Amaryllidaceae. X. The Structure of Caranine[1]

BY E. W. WARNHOFF AND W. C. WILDMAN

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A combination of degradative experiments substantiates the structure I for the alkaloid caranine.

In previous papers[2,3] of this series the alkaloid caranine, isolated from *Amaryllis belladonna* L., was characterized as a base, $C_{16}H_{17}NO_3$. One of the two simplest Amaryllidaceae alkaloids, it contained a methylenedioxyphenyl group, a hydroxyl group, a tertiary nitrogen atom and one double bond.

Preliminary tests on caranine have now shown it to be unaffected by hot 10% hydrochloric acid, hot 90% formic acid, hot 10% ethanolic potassium hydroxide and lithium aluminum hydride. The alkaloid was not oxidized to an α,β-unsaturated ketone by active manganese dioxide although part of the base was destroyed by the reagent. Caranine contained no N-methyl or methoxyl groups, and a Rast molecular weight determination showed the molecular formula to be $C_{16}H_{17}NO_3$.

Hydrogenation of caranine in acetic acid over platinum gave α-dihydrocaranine (IV), m.p. 170.5–172°, $[\alpha]D$ −126°, which proved to be different from β-dihydrocaranine (V), m.p. 166.5–168°, $[\alpha]D$ −191°, obtained from the reduction of caranine in ethanol over palladium.[2]

On the basis of an unusual, but reproducible, modified Oppenauer oxidation of caranine to the phenanthridinium compound II,[3] the base I was postulated to have the lycorine[4] carbon skeleton with a hydroxyl group in the 1-position. The unprecedented nature of the above oxidation does not exclude the possibility of a molecular rearrangement or the possibility that the hydroxyl present in II is not that originally present in caranine but may have been introduced by the air oxidation occurring during the reaction work-up. Hence it was felt desirable to provide additional evidence for each structural feature and in particular for the size of each ring of caranine.

Potassium permanganate oxidation of caranine (I) gave hydrastic acid isolated as its anhydride III, m.p. 179–180.5°, to establish the nature and position of the substituents on ring A.

The size of the B-ring of caranine was determined in the same way as for lycorine.[5] Acetylation of α-dihydrocaranine or hydrogenation of acetylcaranine in acetic acid over platinum gave the same α-dihydroacetylcaranine (VI). This was oxidized with permanganate to the lactam VII whose infrared spectrum in chloroform showed a peak at 6.10 μ characteristic of a 6-membered lactam ring.[5] The lactam was reduced with lithium aluminum hydride to α-dihydrocaranine (IV) to prove that no rearrangement had taken place.

Ring C was investigated through the ketone α-dihydrocaranone (VIII). When a benzene solution of α-dihydrocaranine was stirred for 1.5 hours at room temperature with potassium *t*-butoxide and fluorenone, a 65% yield of pure α-dihydrocaranone was isolated. Its chloroform infrared spectrum had a carbonyl peak at 5.87 μ characteristic of a ketone in a six-membered ring. From the oxidation, in addition to the ketone VIII, there was obtained, in 3% yield, a neutral keto-lactam, $C_{16}H_{13}NO_4$, m.p. 251.5–253°, which must have the structure IX since its complex ultraviolet spectrum is almost identical with the model compound X prepared previously.[3,6]

The isolation of the keto-lactam IX provides additional evidence for the placement of the caranine hydroxyl group in the 1-position. Unequivocal evidence for this point was obtained when the treatment of α-dihydrocaranone with acetic anhydride gave an enol acetate conjugated with the aromatic ring, λ_{max} 264 mμ (ϵ 12,000), possible only with a 1-keto structure. The enol acetate proved too sensitive to oxidation and hydrolysis to be separated from a second product of the reaction, the neutral keto-amide XII, which could have been formed either by direct attack of the anhydride on the nitrogen atom of VIII or by acetylation of the nitrogen after its β-elimination from the C-ring.

The results of the Hofmann degradation of caranine are consistent with the above findings Caranine, like lycorine,[7] gives an α- and a β-methiodide XIII but in the proportion of 2:1. The β-methiodide, m.p. 312–314°, $[\alpha]D$ +62°, crystallized from ethanol–water while the α-methiodide, m.p. 254–255°, $[\alpha]D$ −111°, could be obtained from the filtrates by evaporation to dryness and trituration with ethanol. The Hofmann reaction on the mixture of methiodides was carried out at 120°. The optically inactive caranine anhydromethine, $C_{17}H_{17}NO_2$, m.p. 92–92.5°, obtained by chromatography of the crude product contained no hydroxyl group and did not absorb hydrogen in the presence of palladium. The oxidation of the anhydromethine to 4,5-methylenedioxy-2,3′-biphenyldicarboxylic acid (XVa), m.p. 262.5–263.5°, together with the fact that the nitrogen atom is benzylic to the methylenedioxyphenyl ring

(1) Paper IX, H. M. Fales and W. C. Wildman, THIS JOURNAL, **78**, 4151 (1956).

(2) L. H. Mason, E. R. Puschett and W. C. Wildman, *ibid.*, **77**, 1253 (1955).

(3) H. M. Fales, E. W. Warnhoff and W. C. Wildman, *ibid.*, **77**, 5885 (1955).

(4) L. G. Humber, *et al.*, *J. Chem. Soc.*, 4622 (1954).

(5) K. Wiesner, W. I. Taylor and S. Uyeo, *Chemistry & Industry*, 46 (1954), found the lactam infrared peak of dihydrolycorinone at 6.13 μ compared to 6.10 μ for N-methyloxyhydrastinine and 5.97 μ for N-methyl-1-oxo-2,3-dihydroisoindole.

(6) Probably IX was formed by air oxidation. In acidic or basic solution α-dihydrocaranone absorbs oxygen rapidly. See also the ultraviolet spectrum of a similar compound from lycorine, S. Takagi, W. I. Taylor, S. Uyeo and M. Yajima, *J. Chem. Soc.*, 4003 (1955).

(7) H. Kondo, H. Katsura and S. Uyeo, *Ber.*, **71**, 1529 (1938).

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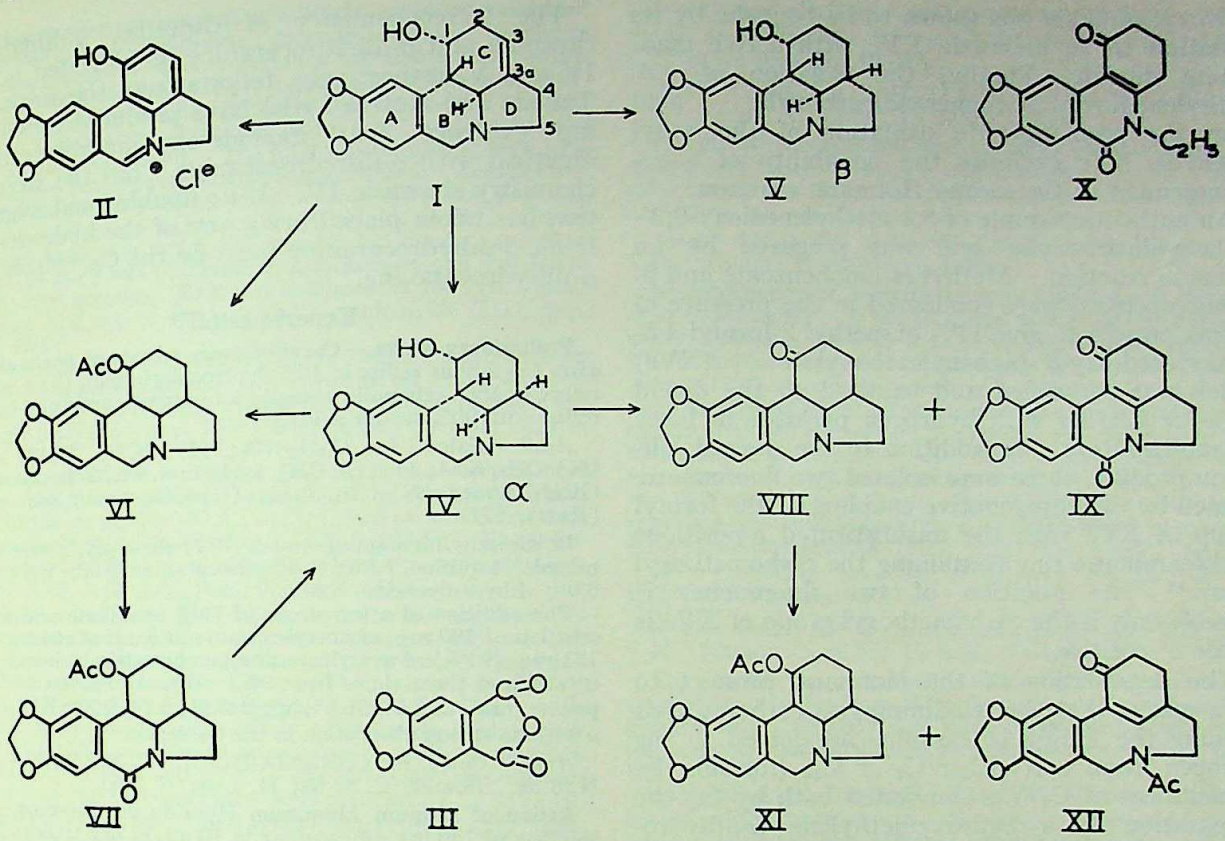
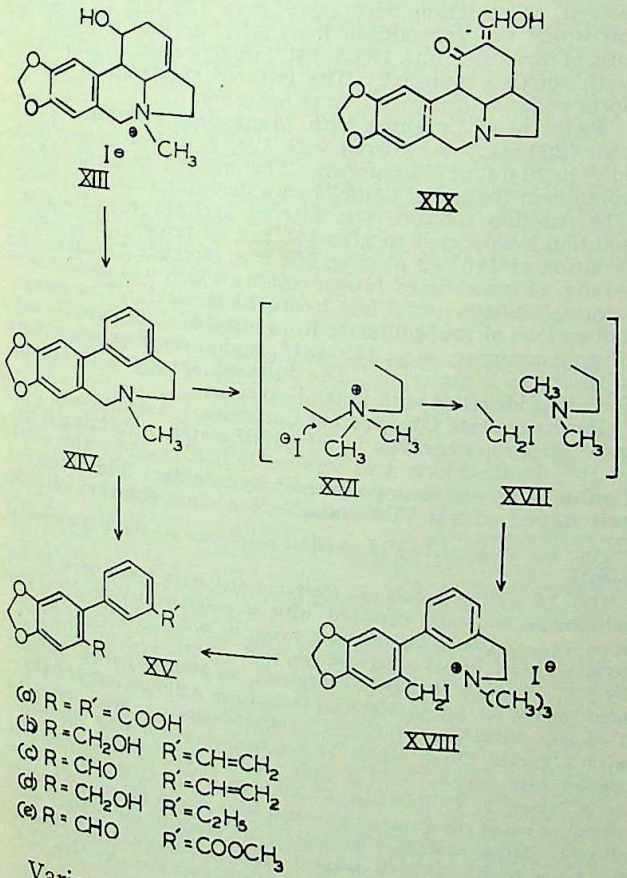


(as shown by formation of lactam VII) proves the structure to be XIV.



Various attempts to prepare the methiodide of caranine anhydromethine failed until its sensitive nature was realized.[8] The best procedure was to allow a methyl iodide solution of the methine to stand at room temperature until a crystalline precipitate slowly settled. This proved to be the product XVIII of reaction of two molecules of methyl iodide with the anhydromethine. Undoubtedly the first reaction was the formation of the normal methiodide XVI which then underwent nucleophilic attack by the iodide ion at the benzylic carbon.[9] The resulting iodo-tertiary amine XVII was quaternized by another molecule of methyl iodide to give XVIII. When this methiodide was subjected to the Hofmann reaction with two equivalents of silver oxide, the vinyl benzyl alcohol XVb was formed.[10] The other product of the reaction, trimethylamine, was isolated as its picrate when the quaternary salt XVIII was heated with aqueous base.

The presence of a vinyl group in XVb was shown by the strong infrared absorption at 10.98 μ[11] which disappeared on hydrogenation with the absorption of one equivalent of hydrogen. The

(8) The strain introduced into the biphenyl system of XIV by the four-atom bridge renders the anhydromethine extremely sensitive to nucleophilic attack at the benzylic carbon bonded to the nitrogen atom when this nitrogen is quaternized by a proton or an alkyl group. This will be elaborated in a later publication.

(9) *Cf.* the formation of 6-phenylpiperonyl iodide from tazettine methine (6-phenylpiperonyl dimethylglycinate) on heating in acetone with methyl iodide at 100°. *Cf.* (a) G. R. Clemo and M. Hoggarth, *Chemistry & Industry*, 1046 (1954); (b) G. R. Clemo and R. Robinson, *ibid.*, 1086 (1955); (c) W. I. Taylor, S. Uyeo and H. Yajima, *J. Chem. Soc.*, 2962 (1955).

(10) A second, crystalline compound, $C_{31}H_{36}O_5$, was isolated from the Hofmann reaction on oily anhydromethine methiodide prepared in acetone at 95°. This was apparently the ether of two molecules of XVb.

(11) R. S. Hampton, *Anal. Chem.*, **21**, 923 (1949). See also reference cited in L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 42–43.

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hydroxyl of XVb was shown to be benzylic by its oxidation to an aldehyde XVc with active manganese dioxide. Finally, the isolation of 4,5-methylenedioxy-2,3′-biphenyldicarboxylic acid from the permanganate oxidation of the vinyl aldehyde XVc excludes the possibility of a rearrangement in the second Hofmann reaction.

An authentic sample of 3,4-methylenedioxy-2,3′-biphenyldicarboxylic acid was prepared by an Ullmann reaction. Methyl *m*-iodobenzoate and 6-bromopiperonal were condensed in the presence of copper powder to give 14% of methyl 2-formyl-4,5-methylenedioxy-3′-biphenylcarboxylate (XVe) which was saponified and oxidized to the diacid XVa by heating with hydrogen peroxide in basic ethanol solution. In addition to the desired Ullmann product, there were isolated two fluorenones, formed by dehydrogenative coupling of the formyl group of XVe with the unsubstituted *o*-positions of the aromatic ring containing the carbomethoxyl group.[12] The isolation of two fluorenones is possible only if the carbomethoxyl group of XVe is in the 3′-position.

The degradation of the Hofmann product to XVa means that the remaining two carbon atoms forming the D-ring of caranine are joined to the nitrogen atom and either C_2 or C_{3a} (formula I). Attachment at C_2 was eliminated both by (a) the preparation of a hydroxymethylene α-dihydrocaranone (XIX) which had the same ultraviolet absorption peak at 275 mμ, after subtraction of the methylenedioxyphenyl contribution, as a simple α-hydroxymethylene ketone[13] and by (b) Takeda and Kotera's conversion of dihydrolycorine to α-dihydrocaranine.[14,14a]

The position of the double bond in caranine is as yet fixed only by negative evidence. The double bond is not conjugated with the aromatic ring. The failure of caranine to yield an α,β-unsaturated ketone on stirring with manganese dioxide[15] and, more important, the formation of two dihydrocaranines preclude the 2,3-position for the double bond. Nor is the double bond α,β to the nitrogen atom since (a) caranine is not reduced by lithium aluminum hydride, (b) neither the perchlorate of caranine nor of acetylcaranine shows strong infrared absorption in the 6 μ region[16] and (c) the pK_a of α-dihydrocaranine is higher than that of caranine.[17] The double bond must be at least trisubstituted since two isomers were obtained on hydrogenation of caranine. Of the two possible positions 3,3a or 3a,4 for the double bond, the 3,3a-isomer more readily accommodates the oxidation of caranine to II.

(12) For other examples of this reaction see S. Uyeo, *Ber.*, **73**, 661 (1940).

(13) For example, hydroxymethylene taraxerone, λ_{max} 275 mμ, E. Koller, A. Hiestand, P. Dietrich and O. Jeger, *Helv. Chim. Acta*, **33**, 1050 (1950).

(14) K. Takeda and K. Kotera, *Chemistry & Industry*, 347 (1956).

(14a) ADDED IN PROOF.—A third and most convincing argument for the lycorine ring system in caranine is the conversion of lycorine to caranine with sodium and amyl alcohol (W. C. Wildman and H. M. Fales, unpublished observation).

(15) (a) B. C. L. Weedon, *Ann. Repts.*, **49**, 142 (1952); **50**, 169 (1953); (b) F. Sondheimer, E. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5932 (1953).

(16) N. J. Leonard and V. W. Gash, *ibid.*, **76**, 2781 (1954).

(17) R. Adams and J. E. Mahan, *ibid.*, **64**, 2588 (1942).

The stereochemistry of caranine, α-dihydrocaranine and β-dihydrocaranine as indicated in I, IV and V, respectively, follows from the work of Takeda and Kotera[14] who have produced convincing evidence that monodesoxydihydrolycorine, identical with α-dihydrocaranine,[18] has the stereochemistry shown in IV. If no double bond migration has taken place during any of the hydrogenations, β-dihydrocaranine must be the C_{3a} epimer of α-dihydrocaranine.

Experimental[19]

Preliminary Tests.—Caranine was recovered unchanged after (a) 2-hour reflux in 10% hydrochloric acid, (b) 1-hour reflux in 10% ethanolic potassium hydroxide and (c) 4-hour reflux with 90% formic acid.

Anal. Calcd. for $C_{16}H_{17}NO_3$: (1) OCH_3, 11.43; (1) (N)–CH_3, 5.54; (1) (C)–CH_3, 5.54; mol. wt., 271. Found: OCH_3, none; (N)–CH_3, 0.53; (C)–CH_3, none; mol. wt. (Rast), 277.

In dimethylformamide-water (3:7) these pK_a's were obtained: caranine, 7.60; α-dihydrocaranine, 9.00; lycorine, 6.90; dihydrolycorine, 8.67.

The addition of a few drops of 70% perchloric acid to a solution of 100 mg. of acetylcaranine in 5 ml. of ether gave 123 mg. (93%) of **acetylcaranine perchlorate** which was recrystallized three times from 99% ethanol to give colorless prisms, m.p. 259.5–261.5°, λ_{max}^{Nujol} 2.91, 5.77, 9.72 and 10.80 μ with no strong absorption in the 6 μ region.

Anal. Calcd. for $C_{18}H_{19}NO_4 \cdot HClO_4$: C, 52.24; H, 4.87; N, 3.38. Found: C, 52.58; H, 4.98; N, 3.50.

Action of Lithium Aluminum Hydride on Caranine.—A solution of 150 mg. of caranine in 10 ml. of dry tetrahydrofuran was refluxed with 150 mg. of lithium aluminum hydride for 25 hours. The excess hydride was destroyed with ethyl acetate and concentrated aqueous sodium hydroxide was added until the precipitated aluminum hydroxide dissolved. Extraction with ether gave 138 mg. of colorless oil which was crystallized from ethyl acetate to yield 111 mg. of caranine, m.p. 178.5–181°, undepressed on admixture with starting material. The infrared spectrum in chloroform was identical with that of caranine.

Reaction of Caranine with Manganese Dioxide.—Caranine (200 mg.) was stirred with 1.00 g. of manganese dioxide[20] in 10 ml. of chloroform. The infrared spectrum of the solution at the end of 1 and 2 hours showed no carbonyl band. The reaction mixture was filtered and the emerald-green solution evaporated to give 146 mg. of brown glass. Sublimation at 145° (2 μ) gave 106 mg. of crude caranine and 40 mg. of unsublimed brown residue which was insoluble in organic solvents and dilute hydrochloric acid. Two recrystallizations of the sublimate from ethyl acetate gave 62 mg. of pure caranine, m.p. 179–181°, undepressed on admixture with starting material. The infrared spectrum in chloroform was identical with that of caranine.

Permanganate Oxidation of Caranine.—A solution of 1.00 g. of caranine dissolved in 50 ml. of water containing 6 ml. of 10% hydrochloric acid was made just basic by the addition of 10% aqueous potassium hydroxide. This solution was stirred with a Vibro-mischer[21] while a solution of 5.00

(18) For a comparison of physical properties see the Experimental section.

(19) All melting points are corrected and were taken on a Kofler microscope hot-stage equipped with a polarizer unless otherwise specified. Optical rotations were taken in a 2-dm. tube on chloroform solutions unless otherwise specified. Analyses were performed by J. F. Alicino, Metuchen, New Jersey; W. Manser, Zurich, Switzerland; and W. C. Alford, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer and ultraviolet spectra were recorded with a Cary Model 11MS spectrophotometer by F. Byers, F. C. Bateman, C. Monaghan and C. Smith. Unless otherwise noted the ultraviolet spectra were run in Pharmco absolute ethanol. Molar extinction coefficients are given in parentheses after the wave length. Merck reagent grade chromatographic alumina (*p*H 10) was used. The pK_a measurements were made by Mrs. L. E. Giuffrida.

(20) J. Attenburrow, *et al.*, *J. Chem. Soc.*, 1094 (1952).

(21) AG für Chemie Apparatebau, Zurich, Switzerland.

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g. of potassium permanganate in 250 ml. of water was added dropwise during 45 minutes. After an additional 15-minute stirring period the reaction mixture was treated with sulfur dioxide until solution of the manganese dioxide was effected. A few milliliters of dilute sulfuric acid was added and the yellow solution was extracted with ethyl acetate to give 413 mg. of yellow solid. The solid was triturated with 10% potassium bicarbonate solution and filtered. Acidification of the filtrate followed by ethyl acetate extraction gave 178 mg. of solid which was refluxed with 8 ml. of 20% aqueous sodium hydroxide under nitrogen for 3.5 hours. A yellow gum (84 mg.) was obtained on acidification and extraction with ethyl acetate. This was sublimed at 160° (0.3 mm.) to give 12.5 mg. of crude hydrastic anhydride (III), m.p. 168–175°.

Continuous ether extraction of the original aqueous layer from the oxidation gave 83 mg. of brown oil which was sublimed at 160° (0.3 mm.) to give 8.5 mg. more of crude hydrastic anhydride, m.p. 140–155°, bringing the total yield to 3%.

A sample of the sublimate (4.5 mg.) was recrystallized from cyclohexane–acetone to give 3.0 mg. of pure **hydrastic anhydride**, m.p. 179–180.5°, undepressed on admixture with an authentic specimen[22] of m.p. 179.5–180.5°. The infrared spectra of the two samples in chloroform were identical, $\lambda_{max}^{CHCl_3}$ 5.40, 5.49, 5.65, 6.28, 9.70 and 10.69 μ.

Another sample of the crude anhydride (8.0 mg.) was triturated in a sublimation tube with 2 drops of 30% aqueous ethylamine. The tube was heated to drive off the water and the residue was sublimed at 160° (0.3 mm.) to give 8.0 mg. of **N-ethylhydrastimide**, m.p. 150–164°. Recrystallization from ethanol gave 5 mg. of colorless blades, m.p. 168.5–169.5°, undepressed on admixture with an authentic specimen[23] of m.p. 169–170°. The ultraviolet and infrared spectra of the two specimens were identical, λ_{max} 245 (41,100), 302 (1860), 313 (1810) and 341 mμ (1010); $\lambda_{max}^{CHCl_3}$ 5.64, 5.85, 6.23, 9.66 and 10.66 μ.

Hydrogenation of Caranine in Acetic Acid with Platinum.—A solution of 5.000 g. of caranine in 30 ml. of glacial acetic acid was added to a suspension of 400 mg. of reduced platinum oxide in 5 ml. of glacial acetic acid. The reduction stopped in two hours after 0.96 equivalent of hydrogen was absorbed at atmospheric pressure and room temperature. Most of the acetic acid was evaporated from the solution after filtration and the residue was basified with 10% aqueous potassium hydroxide before extraction with ethyl acetate. Concentration of the dried solution gave 3.626 g. (72%) of **α-dihydrocaranine** (IV), m.p. 169–172°. A second crop of 0.300 g. (6%), m.p. 168–172°, brought the total yield to 78%. Three recrystallizations from ethyl acetate gave colorless prisms, m.p. 170.5–172°, $[\alpha]^{26}D$ −126° (*c* 0.441), λ_{inf} 233 mμ (4400) and λ_{max} 291 mμ (4700); $\lambda_{max}^{CHCl_3}$ 2.77, 9.65 and 10.70 μ.

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.44; H, 6.95; H, 5.27.

The picrate was prepared with ethanolic picric acid and recrystallized three times from acetone–ethanol to give clusters of yellow needles, m.p. 149–150° and 172–173° dec.

Anal. Calcd. for $C_{16}H_{19}NO_3 \cdot C_6H_3N_3O_7$: C, 52.59; H, 4.41; N, 11.15. Found: C, 52.65; H, 4.60; N, 11.23.

A sample of **monodesoxydihydrolycorine** kindly supplied by Dr. Takeda[14] had m.p. 170.5–172.5°, $[\alpha]^{24}D$ −126° (*c* 0.610). The mixture melting point with α-dihydrocaranine was 170.5–172.5°. The infrared spectra of the two compounds in chloroform were identical. The mixture melting point of the monodesoxydihydrolycorine and β-dihydrocaranine was depressed to 141–160°.

Hydrogenation of Caranine in Ethanol with Palladium.—A solution of 300 mg. of caranine in 9 ml. of ethanol in the presence of 100 mg. of 10% palladium-on-carbon catalyst took up one mole of hydrogen at room temperature and atmospheric pressure. Filtration of the solution and evaporation of the solvent gave 290 mg. of colorless glass. This was crystallized from ethyl acetate to give 96 mg. (32%) of β-dihydrocaranine (V), m.p. 157–163°. A second crop of 41 mg. (14%), m.p. 156–162°, brought the total yield to 46%. Five recrystallizations from ethyl acetate–cyclohexane gave colorless prisms, m.p. 166.5–168° (depressed to 142–164° on admixture with α-dihydrocaranine), $[\alpha]^{25}D$ −191° (*c* 0.520), λ_{inf} 233 mμ (3720), λ_{max} 292 mμ (4650); $\lambda_{max}^{CHCl_3}$ 2.75, 9.65 and 10.69 μ.

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.64; H, 7.00; N, 5.08.

The picrate was prepared with ethanolic picric acid and recrystallized twice from chloroform–ethanol to give yellow spherulites, m.p. 174–175° dec., depressed to 163–171° on admixture with α-dihydrocaranine picrate.

Anal. Calcd. for $C_{16}H_{19}NO_3 \cdot C_6H_3N_3O_7$: C, 52.59; H, 4.41. Found: C, 52.65; H, 4.35.

Hydrogenation of Acetylcaranine.—A solution of 230 mg. of acetylcaranine in 8 ml. of glacial acetic acid was stirred under hydrogen with 72 mg. of platinum oxide catalyst. The reduction stopped in 20 minutes after the absorption of 20 ml. (108% of one equivalent) of hydrogen. The catalyst was removed by filtration and most of the acetic acid evaporated at reduced pressure. The residue was dissolved in 2% hydrochloric acid, washed with ethyl acetate, basified and extracted with ethyl acetate to give 220 mg. (95%) of colorless oil which crystallized. Five recrystallizations from ethyl acetate–cyclohexane gave colorless felted needles of **α-dihydroacetylcaranine** (VI), m.p. 193.5–195°, $[\alpha]^{23.5}D$ −121° (*c* 0.332), λ_{max} 235 (3950) and 293 mμ (4770); $\lambda_{max}^{CHCl_3}$ 5.77, 9.64 and 10.67 μ.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.65; H, 6.81; N, 4.46.

The picrate was prepared in ethanol solution and when crystallized rapidly from chloroform–ethanol gave feathery needles, m.p. 182–184°, but when crystallized slowly from the same solvent gave micaceous yellow plates, m.p. 188–189°.

Acetylation of α-Dihydrocaranine (IV).—A solution of 200 mg. of α-dihydrocaranine in 3 ml. of dry pyridine and 1 ml. of acetic anhydride was refluxed for 3 hours. Most of the acetylation mixture was removed at reduced pressure. The residue was taken up in chloroform, washed with aqueous potassium carbonate solution, dried and evaporated to give 225 mg. of yellow oil which was chromatographed on 7 g. of alumina. Benzene and benzene–ethyl acetate (49:1) eluted 183 mg. (80%) of α-dihydroacetylcaranine (VI) which crystallized.

A solution of 50 mg. of the acetate in ethanol gave 79 mg. (92%) of **picrate**, m.p. 183–192°, on treatment with ethanolic picric acid. Four recrystallizations from chloroform–ethanol gave yellow micaceous plates, m.p. 188–189°, λ_{max} 237 (15,200), 292.5 (6450) and 359 mμ (15,700).

Anal. Calcd. for $C_{18}H_{21}NO_4 \cdot C_6H_3N_3O_7$: C, 52.94; H, 4.44; N, 10.29. Found: C, 52.73; H, 4.51; N, 10.15.

This picrate exhibited the same polymorphic behavior as the picrate in the preceding experiment and the mixture melting point of the two was undepressed. The infrared spectra of the two picrates in chloroform were identical.

Oxidation of α-Dihydroacetylcaranine.—A solution of 290 mg. (0.92 mmole) of α-dihydroacetylcaranine in 8 ml. of reagent-grade acetone was cooled to 1–2° in an ice–salt bath. A solution of 194 mg. (1.23 mmoles) of potassium permanganate in 19 ml. of water was cooled to 5° and added dropwise over a period of 20 minutes to the stirred acetone solution. At the end of the addition period all permanganate had been reduced. The reaction mixture was filtered through Celite and the manganese dioxide washed with acetone. The filtrates were evaporated to dryness and taken up in ether–chloroform before washing with dilute hydrochloric acid. Concentration of the dried organic layer gave 135 mg. (44% crude yield) of oily **α-dihydroacetylcaranine lactam** (VII) which crystallized on trituration with ethyl acetate, m.p. 180°. Four recrystallizations from ethyl acetate–cyclohexane gave irregular prisms, m.p. 192–194°; $[\alpha]^{23}D$ −171° (*c* 0.595); λ_{max} 222 (29,900), 251 (5150), 265 (4600) and 305 mμ (6940); $\lambda_{max}^{CHCl_3}$ 5.80, 6.11, 6.25, 9.67 and 10.70 μ.

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.39; H, 5.63; N, 4.21.

Reduction of α-Dihydroacetylcaranine Lactam.—A solution of 30 mg. of the lactam VII, m.p. 189–193°, in 10 ml. of ether was refluxed with lithium aluminum hydride for 22 hours. The excess hydride was decomposed with dilute hydrochloric acid and the aqueous solution was washed with ether. Basification of the acid solution followed by extrac-

(22) M. Freund, *Ann.*, **271**, 375 (1892).
(23) E. Späth and F. Kuffner, *Ber.*, **64**, 3000, 3120 (1931).

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tion with ether gave 19 mg. of crystals, m.p. 168°. Recrystallization from ethyl acetate gave 5 mg. of **α-dihydrocaranine** (IV), m.p. 170–172.5°, undepressed on admixture with an authentic sample of m.p. 170.5–172°. The infrared spectra of the two samples in chloroform were identical.

Modified Oppenauer Oxidation of α-Dihydrocaranine (IV).—Potassium *t*-butoxide was prepared from 2.30 g. of potassium and 75 ml. of dry *t*-butyl alcohol. The excess alcohol was evaporated at reduced pressure. To the dry alkoxide were added a magnetic stirring bar, 65 ml. of benzene, 5.00 g. of fluorenone and 3.000 g. (11.0 mmoles) of α-dihydrocaranine, m.p. 169–172°. The reaction mixture was put under nitrogen and stirred at room temperature. The color changed from orange to a dark brown within the first few seconds after mixing. At the end of 1.5 hours water was added to the brown mixture whereupon the color lightened to an orange-yellow. The aqueous layer was separated and washed twice with ether. The combined organic layers were washed once with water and extracted with three portions of 5% hydrochloric acid. The combined acid layers were washed with ether and basified with concentrated sodium hydroxide solution. The oil which precipitated was extracted with ether to give 2.873 g. (96% crude yield) of crystalline α-dihydrocaranone (VIII). Recrystallization from methanol gave 1.945 g. (65%) of long colorless prisms, m.p. 140–149°. The analytical sample after three more recrystallizations from methanol had m.p. 141–148°, unchanged when taken in a nitrogen atmosphere, $[\alpha]^{25}D$ 0°, $[\alpha]^{25}_{436}$ +24° (*c* 0.849); λ_{inf} 226 mμ (5660), λ_{max} 289 mμ (4600); $\lambda_{max}^{CHCl_3}$ 5.87, 9.68 and 10.70 μ.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.97; H, 6.44; N, 5.25.

A solution of 40 mg. of the ketone and 50 mg. of 2,4-dinitrophenylhydrazine in 4 ml. of glacial acetic acid was warmed on a steam-bath and allowed to stand at room temperature overnight. Dilution of the solution with water and neutralization of the acid precipitated 71 mg. of 2,4-dinitrophenylhydrazone which was recrystallized twice from chloroform–ethanol to give felted orange needles which decomposed with a yellow flash at *ca.* 270° on a Kofler Heizbank, $\lambda_{max}^{CHCl_3}$ 3.01, 6.19, 6.28, 9.67 and 10.70 μ.

Anal. Calcd. for $C_{22}H_{21}N_5O_6$: C, 58.53; H, 4.69; N, 15.52. Found: C, 58.90; H, 4.46; N, 16.04.

The material in the mother liquor from recrystallization of the ketone was taken up in ether–ethyl acetate and washed with three portions of 5% hydrochloric acid, dried and evaporated to give 100 mg. (3%) of neutral keto-lactam (IX), m.p. 220–250°, which was recrystallized three times from chloroform–methanol to give small felted needles, m.p. 251.5–253°, $[\alpha]^{26}D$ −21.5° $[\alpha]^{26}_{436}$ −92° (*c* 1.01), λ_{max} 214 (12,600), 247 (30,900), 265 (28,000), 303 (7140), 330 (9480) and 344 mμ (9480); $\lambda_{max}^{CHCl_3}$ 6.09, 6.18, 6.30, 9.65 and 10.65 μ. The model compound X[3] had λ_{max} 216 (11,700), 246 (30,500), 265, (27,400), 316 (8380), 331 (9600) and 345 mμ (8200).

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.95. Found: C, 67.84; H, 4.70; N, 4.88.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized twice from dimethylformamide as felted red needles, m.p. 299–302° dec.

Anal. Calcd. for $C_{22}H_{17}N_5O_7$: C, 57.02; H, 3.70; N, 15.11. Found: C, 56.89; H, 3.77; N, 15.34.

Reaction of Acetic Anhydride with α-Dihydrocaranone.—A solution of 400 mg. of α-dihydrocaranone (VIII) and three drops of triethylamine in 2 ml. of acetic anhydride was kept under nitrogen at 90° for 2 hours. The clear brown solution was evaporated to dryness *in vacuo*. The infrared spectrum of the crude material in chloroform showed carbonyl absorption at 5.73, 5.99, and 6.10 μ which indicated a mixture of enol acetate XI and keto amide XII. The brown glass was dissolved in ethyl acetate, washed with 5% hydrochloric acid and 5% potassium hydroxide solution, dried and evaporated to give 252 mg. (55%) of oily keto-amide XII which crystallized on trituration with ethyl acetate. Three recrystallizations from ethyl acetate–cyclohexane gave colorless prisms, m.p. 182.5–184.5°, $[\alpha]^{27}D$ +242° (*c* 0.565); λ_{max} 245 mμ (10,300), λ_{inf} 260 (7350) and 292 mμ (3910); $\lambda_{max}^{CHCl_3}$ 5.99, 6.12, 9.66 and 10.72 μ.

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47; (N)-$COCH_3$, 13.73. Found: C, 68.89; H, 6.22; N, 4.44; (N)-$COCH_3$, 14.52.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized twice from dimethylformamide to give small red needles, m.p. 300–301° dec., in amount insufficient for analysis.

Attempts to isolate the pure enol acetate XI from acetylations under milder conditions by fractional sublimation, crystallization and rapid chromatography failed because of the sensitivity of the compound to oxidation and hydrolysis. A sample of the crude enol acetate containing very little XII had λ_{max} 263 (12,000) and λ_{max} 304 mμ (5720) compared to λ_{max} 260 (11,800) and 305 mμ (5200) for isosafrole. The infrared spectrum in chloroform had λ_{max} 5.72, 9.65 and 10.70 μ with weaker peaks at 6.00 and 6.11 μ.

Caranine α- and β-Methiodides (XIII).—To a refluxing solution of 6.00 g. (22.1 mmoles) of caranine, m.p. 178.5–180.5°, in 130 ml. of benzene was added 20 ml. of redistilled methyl iodide. A white precipitate formed immediately. The reaction mixture was cooled and filtered to give 9.15 g. (100%) of crude methiodide, m.p. 270–275° dec., $[\alpha]^{28}D$ −60° (*c* 0.34, 1:1 water–dimethylformamide).

A 200-mg. sample was recrystallized from water–ethanol to give 76 mg. (38%) of colorless blades, m.p. 305–308° dec. Two more recrystallizations from water–ethanol gave pure **caranine β-methiodide**, m.p. 312–314° dec. (reported[2] 316–318° dec.), $[\alpha]^{28}D$ +62° (*c* 0.28, 1:1 water–dimethylformamide); λ_{max} 291 mμ (4740); λ_{max}^{KBr} 2.90, 9.69 and 10.75 μ.

The filtrates from the first recrystallization of the methiodide were evaporated to dryness and the resulting glass triturated with ethanol whereupon it crystallized. Recrystallization from 99% ethanol gave 98 mg. (49%) of **caranine α-methiodide**, m.p. 255–256° dec. Three more recrystallizations from 99% ethanol gave colorless felted needles, m.p. 254–255° dec., $[\alpha]^{25}D$ −111° (*c* 0.459, 1:1 water–dimethylformamide); λ_{max} 293 mμ (4600); λ_{max}^{KBr} 2.92, 9.70 and 10.72 μ.

Anal. Calcd. for $C_{17}H_{20}NO_3I$: C, 49.40; H, 4.88; N, 3.39. Found: C, 49.68; H, 5.17; N, 3.49.

The proportion of α- to β-methiodide calculated from rotation data is 70:30 whereas that calculated from the fractional crystallization is 62:38.

The Hofmann Reaction on Caranine Methiodide.—To a suspension of 8.95 g. (21.6 mmoles) of a mixture of caranine α- and β-methiodides in 80 ml. of water was added neutral silver oxide prepared from 3.900 g. (22.9 mmoles) of silver nitrate. The formation of the methohydroxide was shown to be complete within a few minutes when a centrifuged sample of the mixture gave no precipitate with silver nitrate–nitric acid solution. The silver salts were removed by filtration through Celite. The clear filtrate was evaporated under reduced pressure at 50°. The flask containing the greenish residual oil was put under nitrogen and immersed in an oil-bath at 120° for 40 minutes. The water given off was removed at reduced pressure, and the brown glass dried in a desiccator to give 5.76 g. (99%).

The product was partitioned between ether and 5% hydrochloric acid. The acid solution was washed with ether, cooled in an ice-bath and basified with concentrated sodium hydroxide solution. Ether extraction gave 4.80 g. of brown oil which was dissolved in cyclohexane and chromatographed on a column of 120 g. of alumina. Elution with cyclohexane:benzene (49:1) gave 2.22 g. of colorless oil which solidified. Recrystallization from methanol gave 1.95 g. (33%) of **caranine anhydromethine** (XIV), m.p. 91–92.5°.

The material eluted with cyclohexane:benzene (3:1) was rechromatographed to give an additional 208 mg., m.p. 91–92.5° after recrystallization from methanol, bringing the total yield to 37%.

Three additional recrystallizations from methanol gave white flakes, m.p. 92–92.5°, $[\alpha]^{24}D$ 0°, $[\alpha]^{24}_{436}$ 0° (*c* 0.835); λ_{max} 255 (8460) and 302 mμ (7080); $\lambda_{max}^{CHCl_3}$ 6.25, 6.37, 9.67 and 10.76 μ.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24; (N)-CH_3, 5.62. Found: C, 76.25; H, 6.36; N, 5.11; (N)-CH_3, 4.07; (C)-CH_3, none.

The anhydromethine (42 mg.) gave 75 mg. (96%) of picrate, m.p. 124–148° when treated with ethanolic picric acid. The derivative was recrystallized twice by solution

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in a small volume of acetone at room temperature followed by addition of ethanol and chilling to −20° to give the pure picrate, m.p. 130–152°, λ_{max} 304 (10,200) and 358 mμ (16,100).

Anal. Calcd. for $C_{17}H_{17}NO_2 \cdot C_6H_3N_3O_7$: C, 55.64; H, 4.06; N, 11.29. Found: C, 55.68; H, 4.02; N, 11.20.

When the salt was warmed above *ca.* 50° in aqueous or alcoholic solution, an acid-catalyzed rearrangement occurred. Presumably the low and wide melting point of the picrate is also due to this rearrangement taking place.

A solution of 100 mg. of the anhydromethine in 8 ml. of 99% ethanol with 100 mg. of 10% palladium-on-carbon did not absorb any hydrogen in two hours. The anhydromethine was recovered unchanged on evaporation of the alcohol.

Oxidation of Caranine Anhydromethine.—To a solution of 400 mg. (1.50 mmoles) of caranine anhydromethine (XIV) in 50 ml. of water containing 3 ml. of 10% hydrochloric acid was added 10% aqueous potassium hydroxide until the solution was neutral and there was only a faint turbidity. This solution was warmed to 70°, and a solution of 1.895 g. (12.0 mmoles) of potassium permanganate in 100 ml. of water was added dropwise during 0.5 hour with stirring by a Vibro-mischer.[21] A few minutes after addition was over all the permanganate had been reduced. The reaction mixture was cooled and sulfur dioxide bubbled in until solution of the manganese dioxide was effected. The solution was extracted continuously with ethyl acetate after the addition of 5 ml. of 10% sulfuric acid. Evaporation of the ethyl acetate gave 233 mg. of brown gum which after trituration with chloroform left 53 mg. of insoluble acid. The chloroform solution containing 180 mg. was chromatographed on 15 g. of Mallinckrodt silicic acid. Chloroform–methanol (99:1) eluted 69 mg. of the same crude acid which had not dissolved in chloroform. This material could not be completely purified by recrystallization from ethyl acetate. Some of the purer crops of crystals were combined (44 mg.) in ethyl acetate and converted to the methyl ester with ethereal diazomethane. Evaporation of the solvent and chromatography of the residue on 2.5 g. of alumina gave 24 mg. of crystalline ester eluted with benzene. The ester was dissolved in 3 ml. of methanol and refluxed for 1 hour with 2 ml. of water containing 0.8 g. of sodium hydroxide. The methanol was boiled off and the cooled aqueous solution acidified with dilute sulfuric acid. The resulting white precipitate was filtered, washed and dried to give 19 mg. of **4,5-methylenedioxy-2,3′-biphenyldicarboxylic acid** (XVa) which was recrystallized from ethyl acetate–benzene to give 17 mg. (4%) of small white prisms, m.p. 262.5–263.5°. The mixture melting point with an authentic specimen, m.p. 262.5–263.5°, prepared as described below, was 261–263.5°. The infrared and ultraviolet spectra of the two compounds were identical, λ_{max} 226 (37,200), 267.5 (6750) and 295 mμ (5950); λ_{max}^{KBr} 3.70–3.95, 5.92, 6.20, 9.72 and 10.81 μ.

Anal. Calcd. for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52. Found: C, 62.84; H, 3.61.

Caranine Anhydromethine Bis-methiodide (XVIII).—Caranine anhydromethine (1.000 g., 3.74 mmoles) was dissolved in 13 ml. of redistilled methyl iodide and allowed to stand at room temperature protected from light. After 17 hours 600 mg. (29%) of tan solid was removed by filtration. After another 8 hours 157 mg. (7.6%) of almost colorless matted needles separated. Further crops collected over a period of several days gave 1.181 g. (57%) more bis-methiodide for a total yield of 93% of XVIII. The salt decomposed on warming with solvents. A sample prepared for analysis by washing a colorless crop of the matted needles several times with benzene before drying at room temperature *in vacuo* had m.p. 199–201° dec., λ_{max} 295 mμ (6700).

Anal. Calcd. for $C_{19}H_{23}NO_2I_2$: C, 41.39; H, 4.20; N, 2.54; I, 46.05; (3) (N)–CH_3, 8.18. Found: C, 41.01; H, 4.12; N, 2.67; I, 44.83; (N)–CH_3, 8.18.

Isolation of Trimethylamine from Caranine Anhydromethine Bis-methiodide.—A mixture of 135 mg. of the bis-methiodide XVIII and 10 ml. of 10% potassium hydroxide solution was heated to reflux in an oil-bath. Nitrogen was passed through the solution and the effluent gas bubbled through an ethanolic solution of picric acid. A slow precipitation of trimethylamine picrate occurred. The picrate was recrystallized twice from ethanol to give long yellow prisms, m.p. 213–216° (sealed capillary), undepressed on admixture with an authentic specimen of trimethylamine picrate, m.p. 214–217° (sealed capillary). The infrared spectra of the two picrates in chloroform were identical. The organic material in the potassium hydroxide solution was an intractable brown gum.

The Hofmann Reaction on Caranine Anhydromethine Bis-methiodide.—To a suspension of 1.246 g. (2.26 mmoles) of the crystalline bis-methiodide XVIII in 15 ml. of water was added the neutral silver oxide from 800 mg. (4.71 mmoles) of silver nitrate. The mixture was stirred until a sample of the supernatant liquid gave no precipitate with silver nitrate–nitric acid solution. The silver salts were separated by centrifugation and the opalescent solution of quaternary amine hydroxide decanted and evaporated to dryness *in vacuo* at 60°. An aspirator was attached to the flask which was immersed in an oil-bath at 120° for 30 minutes. The dark brown residue was taken up in benzene, washed twice with dilute hydrochloric acid, dried and evaporated to give 280 mg. (48%) of neutral yellow oil. This was combined with 47 mg. of oil from a smaller scale reaction, dissolved in benzene and chromatographed on 10 g. of alumina. Elution with benzene–ethyl acetate (1:1) gave 270 mg. of colorless **2-hydroxymethyl-4,5-methylenedioxy-3′-vinylbiphenyl** (XVb) which did not crystallize on trituration with various solvents. A sample was evaporatively distilled at 140° (0.025 mm.); λ_{max} 251 (22,100) and 293 mμ (5900); $\lambda_{max}^{CHCl_3}$ 2.76, 2.90, 6.19, 6.26, 6.31, 9.66, 10.73 and 10.98 μ.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.69; H, 5.52.

From a Hofmann reaction on the crude bis-methiodide prepared by heating crude, non-crystalline caranine anhydromethine with methyl iodide in acetone at 95° was obtained by chromatography on alumina a neutral, nitrogen-free compound which was apparently the ether derived from two molecules of XVb, m.p. 111–113° after three recrystallizations from 99% ethanol, λ_{max} 252 (41,400) and 293 mμ (11,400); $\lambda_{max}^{CHCl_3}$ 6.18; 6.25; 6.35, 9.65, 10.72 and 11.00 μ.

Anal. Calcd. for $C_{32}H_{26}O_5$: C, 78.35; H, 5.34. Found: C, 78.27; H, 5.44; N, 0.0.

Hydrogenation of 2-Hydroxymethyl-4,5-methylenedioxy-3′-vinylbiphenyl.—A solution of 71 mg. of XVb in 5 ml. of 99% ethanol absorbed 7.0 ml. (92% of one equivalent) of hydrogen over 40 mg. of 10% palladium-on-carbon catalyst in 8 minutes at room temperature and atmospheric pressure. Filtration of the solution and evaporation of the solvent gave 62 mg. of **2-hydroxymethyl-4,5-methylenedioxy-3′-ethylbiphenyl** (XVd), a colorless liquid, which was evaporatively distilled at 140° (0.03 mm.); λ_{max} 257 (7210) and 293 mμ (5400); $\lambda_{max}^{CHCl_3}$ 2.76, 2.90, 6.19, 6.25, 6.33, 9.65 and 10.72 μ.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.53; H, 6.25.

The ultraviolet spectrum of 6-phenylpiperonyl alcohol has λ_{max} 257.5 (7150) and 293 mμ (5410) for comparison.

An attempt to prepare a 3,5-dinitrobenzoate of the alcohol by allowing the alcohol in pyridine to react with 3,5-dinitrobenzoyl chloride at room temperature for 4 days gave recovered starting material.

2-Formyl-4,5-methylenedioxy-3′-vinylbiphenyl (XVc).—Manganese dioxide[20] (700 mg.) was added to a solution of 146 mg. of the benzyl alcohol XVb in 10 ml. of chloroform. The mixture was stirred for three hours at the end of which time the solution showed strong carbonyl absorption at 5.95 μ and no hydroxyl absorption. The solution was filtered and evaporated to give 137 mg. of colorless oil. Chromatography over 4 g. of alumina gave 116 mg. (80%) of XVc in the benzene eluate. The aldehyde crystallized from ethanol at −78° but after separation from solvent liquefied at room temperature. Evaporative distillation at 140° (0.025 mm.) gave a colorless glass, λ_{max} 247 (40,000) and 325 mμ (6630); $\lambda_{max}^{CHCl_3}$ 5.97, 6.20, 9.66, 10.70 and 10.96 μ.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 76.38; H, 5.04.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized four times from chloroform–ethanol to give small felted orange needles, m.p. 215.5–216.5°, $\lambda_{max}^{CHCl_3}$ 396 mμ (30,400); $\lambda_{max}^{CHCl_3}$ 3.04, 6.21, 6.28, 9.67, and 10.72 μ.

Anal. Calcd. for $C_{22}H_{16}N_4O_6$: C, 61.11; H, 3.73; N, 12.96. Found: C, 60.95; H, 3.94; N, 12.95.

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Oxidation of 2-Formyl-4,5-methylenedioxy-3′-vinylbiphenyl.—To a solution of 48 mg. of the aldehyde XVc in 6 ml. of reagent-grade acetone stirred with a magnetic stirring bar was added a solution of 90 mg. of potassium permanganate in 3 ml. of water. After the 2-minute addition period the brown reaction mixture was allowed to stir for 30 minutes. Sulfur dioxide was added until solution of the manganese dioxide. Most of the acetone was blown off in an air jet and the residual aqueous solution was extracted continuously with ethyl acetate. The ethyl acetate was evaporated and to the residue was added 3 ml. of ethanol, 3 ml. of water and 1 g. of sodium hydroxide. This mixture was warmed for 45 minutes on the steam-bath during the dropwise addition of 12 ml. of 30% hydrogen peroxide. Acidification of the cooled solution gave 33 mg. of white precipitate, m.p. 240–252°. This acid was converted to the methyl ester with ethereal diazomethane and chromatographed on 2 g. of alumina. The benzene eluate (24.5 mg.) was saponified with methanolic sodium hydroxide. Acidification of the solution and recrystallization of the white precipitate from ethyl acetate–benzene gave 12.5 mg. (23%) of **4,5-methylenedioxy-2,3′-biphenyldicarboxylic acid** XVa, m.p. 262.5–263.5°, undepressed on admixture with an authentic specimen of m.p. 262.5–263.5°, prepared as described below. The infrared spectra of the two acids were identical, λ_{max}^{KBr} 3.70–3.95, 5.93, 6.22, 9.73 and 10.83 μ.

2-Hydroxymethylene-α-dihydrocaranone (XIX).—A solution of 654 mg. of α-dihydrocaranone in 6 ml. of benzene and 3 ml. of redistilled ethyl formate was refluxed under nitrogen with 335 mg. of sodium methoxide for 3 hours. The reaction mixture was diluted with water and benzene. The benzene solution was separated and washed with two portions of 10% aqueous potassium hydroxide. The combined basic aqueous solutions were washed with benzene, acidified to *p*H 7 with dilute hydrochloric acid and extracted with three portions of ethyl acetate. Evaporation of the dried ethyl acetate solution gave 461 mg. (64%) of hydroxymethylene ketone (XIX). A portion was recrystallized thrice from absolute ethanol to give almost colorless prisms, m.p. 131–133°, $\lambda_{max}^{CHCl_3}$ 5.98, 6.24, 9.60 and 10.70 μ, which gave a deep violet ferric chloride test.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73. Found: C, 68.59; H, 5.95.

In absolute ethanol containing 2 drops of 10% hydrochloric acid per 10 ml. the derivative had λ_{max} 280 mμ (16,600). Subtraction of the spectrum of α-dihydrocaranone gave λ_{max} 275 mμ (13,700). The absorption peak of XIX was shifted to 304 mμ (24,700) in absolute ethanol containing 2 drops of 10% aqueous potassium hydroxide per 10 ml.

Methyl 2-Formyl-4,5-methylenedioxy-3′-biphenylcarboxylate (XVe).—In a 50-ml. pear-shaped flask equipped with a stirrer and nitrogen inlet were placed 26.2 g. (0.10 mole) of methyl *m*-iodobenzoate, m.p. 45.5–48.5°, and 22.9 g. (0.10 mole) of 6-bromopiperonal,[24] m.p. 122–128°. A small flask containing 50 g. of copper powder was attached to the third neck of the flask by a piece of rubber tubing and the whole apparatus was flushed with nitrogen. The flask was heated to 230–250° in a Woods metal-bath while the copper powder was added in small portions to the stirred liquid during one-half hour. The reaction was kept at 230–250° for another hour. The contents of the cooled flask were dissolved in benzene and filtered. Benzene was removed by distillation and 5.5 g. of recovered methyl *m*-iodobenzoate was distilled at 150° (0.8 mm.). The 22.1 g. of residue in the flask was taken up in benzene and chromatographed on 500 g. of alumina. Benzene eluted 4.0 g. of methyl *m*-iodobenzoate and 1.0 g. of impure 6-bromopiperonal. Benzene–ethyl acetate (49:1) eluted 3.62 g. of yellow oil which crystallized on trituration with ether. Further elution with the same solvent gave 1.04 g. of an orange fluorenone (a) while elution with pure ethyl acetate gave a different orange fluorenone (b).

The 3.62 g. of partially crystalline material was triturated with benzene and filtered to remove some insoluble fluorenone. The benzene of the filtrate was replaced by methanol and the solution concentrated to give 1.66 g. of **methyl 2-formyl-4,5-methylenedioxy-3′-carboxylate** (XVe), m.p., 129.5–131°. A second crop of 0.93 g., m.p. 126–131°, brought the yield to 14% based on recovered methyl *m*-iodobenzoate. A sample was recrystallized twice more from methanol to give colorless prisms, m.p. 130–131°, λ_{max} 242.5 (30,900), 281 (6580) and 324 mμ (6670); $\lambda_{max}^{CHCl_3}$ 5.82, 5.98, 6.21, 9.66 and 10.71 μ.

Anal. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.42; H, 4.39.

A sample of the orange fluorenone (a) was recrystallized three times from dimethylformamide and sublimed at 200° (0.05 mm.) to give bright orange prisms of **2,3-methylenedioxy-6(or 8)-carbomethoxyfluorenone**, m.p. 287–288° with sublimation, $\lambda_{max}^{CHCl_3}$ 277 (46,100), 331 (2780) and 437 mμ (610); $\lambda_{inf}^{CHCl_3}$ 316 (3960) and 344 mμ (1180); λ_{max}^{Nujol} 5.82, 5.86, 6.26, 9.70 and 10.88 μ.

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.08; H, 3.57. Found: C, 67.90; H, 3.81.

A specimen of the orange fluorenone (b) was recrystallized three times from chloroform–ethanol to give pale orange felted needles of **2,3-methylenedioxy-8(or 6)-carbomethoxyfluorenone**, m.p. 247–249° and 272.5–275° with sublimation, $\lambda_{max}^{CHCl_3}$ 282 (64,500), 340 (4550), 356 (3550) and 448 mμ (590); $\lambda_{inf}^{CHCl_3}$ 275 (45,500) and 313 mμ (8970); λ_{max}^{Nujol} 5.80, 5.85, 6.25, 9.63 and 10.80 μ.

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.08; H, 3.57. Found: C, 67.89; H, 3.52.

4,5-Methylenedioxy-2,3′-biphenyldicarboxylic Acid (XVa).—A solution of 91 mg. of the Ullmann product XVe, m.p. 129–131°, from the above reaction in 10 ml. of ethanol and 2 ml. of water containing five potassium hydroxide pellets was warmed on a steam-bath. The addition of 5 ml. of 30% hydrogen peroxide caused a vigorous reaction. After subsidence of gas evolution another 5 ml. of peroxide was added. The solution was heated for another 30 minutes, concentrated to one-third its original volume, cooled and acidified with 10% hydrochloric acid. The white precipitate was collected on a filter, washed with water and dried to give 78 mg. (85%) of 4,5-methylenedioxy-2,3′-biphenyldicarboxylic acid (XVa), m.p. 248–263°. Three recrystallizations from ethyl acetate–benzene gave small colorless prisms, m.p. 262.5–263.5°, λ_{max} 226 (36,800), 268 (6750) and 295 mμ (5970); λ_{max}^{KBr} 3.70–3.95, 5.92, 6.20, 9.70 and 10.81 μ.

Anal. Calcd. for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52. Found: C, 62.97; H, 3.46.

BETHESDA, MARYLAND

(24) R. G. Naik and T. S. Wheeler, *J. Chem. Soc.*, 1780 (1938).

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, PEARL RIVER LABORATORIES, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

The Preparation of Some Merimine Derivatives[1]

BY WILLIAM B. WRIGHT, JR., JOHN S. WEBB AND JAMES M. SMITH, JR.

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The preparation and properties of a number of derivatives of 6-methylmerimine have been described.

The compound 2,3-dihydro-1H-pyrrolo[3,4-c]-pyridine was prepared by Gabriel and Colman,[2] in 1902, by the hydrogen iodide and phosphorus reduction of the γ-lactam of 3-aminomethylisonicotinic acid and was named merimine. The only other compounds of this bicyclic ring structure known in the literature are the imides and lactams derived from substituted pyridinecarboxylic acids.

7-Amino-6-methylmerimine (I) was prepared by the lithium aluminum hydride reduction of the γ-lactam of 3-amino-5-aminomethyl-2-methylisonicotinic acid (II).[3] Compound I was used as the basic raw material in the preparation of the series of compounds outlined in Chart I.

When compound I was treated with nitrous acid, dark tars were obtained. When the 2-position was blocked by a carbethoxy (III) or a benzoyl (IV) group, the primary amino group was easily diazotized and a variety of 2,7-disubstituted derivatives (V-X) could be obtained by standard procedures. Hydrolysis with either acid or alkali resulted in the 7-substituted-6-methylmerimines (XI-XV). These merimines, unsubstituted in the 2-position, are strong bases which absorb carbon dioxide on standing. They are best stored as the high melting dihydrochlorides.

When 7-methoxy-6-methylmerimine (XI) was heated with 48% hydrobromic acid, 7-hydroxy-6-methylmerimine (XII) dihydrobromide was obtained. Catalytic reduction converted 7-bromo-6-methylmerimine dihydrochloride (XIV) to 6-methylmerimine dihydrochloride (XV). 2-Benzoyl-7-iodo-6-methylmerimine (XVI) and 2-benzoyl-7-bromo-6-methylmerimine (XVII) were not prepared easily by diazotization of IV, but were obtained in excellent yield by the Schotten–Baumann reaction on XIII and XIV.

Typical reactions of merimines unsubstituted in the 2-position are illustrated with 7-methoxy-6-methylmerimine (XI) in Chart II. The 2-guanyl (XVIII) and 2-imidazolinyl (XIX) derivatives were prepared by reaction with thiuronium salts, 2-carbamyl derivatives (XXI) by reaction with potassium cyanate, and 2-dialkylsulfamyl derivatives (XX) by reaction with dialkylsulfamyl chlorides. When XI was treated with acetic anhydride, the 2-acetyl derivative XXII was formed and this was converted easily to the methiodide XXIII. The 2-*p*-acetylsulfanilyl derivative XXIV was prepared and was hydrolyzed to the unacetylated derivative XXV.

Similar derivatives were prepared from other 2-unsubstituted merimines and additional examples are described in the Experimental section.

Experimental

7-Amino-6-methylmerimine Dihydrochloride (I).—A solution of 2.0 g. of lithium aluminum hydride in 100 ml. of tetrahydrofuran was stirred under nitrogen at a temperature of 45–50° while a solution of 1.0 g. of the γ-lactam of 3-amino-5-aminomethyl-2-methylisonicotinic acid (II) in 200 ml. of tetrahydrofuran was added. The reaction mixture was heated at 60–65° for seven hours and then allowed to stand at room temperature overnight. A solution of 4 ml. of water in 50 ml. of tetrahydrofuran was added and the insoluble portion was filtered off and washed with ethanol. The filtrate was acidified with concentrated hydrochloric acid and the precipitate which separated was filtered and oven-dried. The yield was 0.77 g. of brown powder. This powder was dissolved in 10 ml. of water and treated with activated charcoal. The solution was concentrated to dryness and then diluted with 1 ml. of concentrated hydrochloric acid and 10 ml. of ethanol. The precipitate was filtered and washed with ethanol. The product was dissolved once more in 1.5 ml. of water and then diluted with 0.4 ml. of concentrated hydrochloric acid. The precipitate which separated was filtered, washed with ethanol and dried. The yield of 7-amino-6-methylmerimine dihydrochloride was 0.21 g. (15%).

Anal. Calcd. for $C_8H_{13}Cl_2N_3$: C, 43.3; H, 5.90; Cl, 32.0; N, 18.9. Found: C, 43.1; H, 5.86; Cl, 31.7; N, 18.9.

7-Amino-6-methylmerimine.—A mixture of 4.55 g. of the dihydrochloride, 2.16 g. of sodium methylate and 20 ml. of absolute ethanol was stirred under nitrogen for 2 hours at room temperature. The mixture was heated to the boil and filtered. The filtrate was concentrated *in vacuo* until heavy precipitation occurred and then diluted with ether. The mixture was filtered and the cake was washed with ether and dried. Two grams of 7-amino-6-methylmerimine (67%), m.p. 167–169°, was obtained.

Anal. Calcd. for $C_8H_{11}N_3$: C, 64.4; H, 7.43; N, 28.2. Found: C, 64.3; H, 7.47; N, 28.1.

7-Amino-2-carbethoxy-6-methylmerimine (III).—A solution of 448 g. of 7-amino-6-methylmerimine dihydrochloride in 2,500 ml. of water and 800 ml. of 5 *N* sodium hydroxide was cooled to 10° and 194 ml. of ethyl chloroformate and 400 ml. of 5 *N* sodium hydroxide were added simultaneously over a 15-minute period while allowing the temperature to rise to 20°. The reaction mixture was stirred for 1.5 hours longer and then filtered. The cake was washed with ice-water and then recrystallized from ethanol. A 65% yield of 7-amino-2-carbethoxy-6-methylmerimine monohydrate, m.p. 182–183°, was obtained.

Anal. Calcd. for $C_{11}H_{17}N_3O_3$: C, 55.2; H, 7.16; N, 17.6. Found: C, 55.2; H, 6.85; N, 17.9.

7-Amino-2-benzoyl-6-methylmerimine (IV).—A solution of 280 g. of 7-amino-6-methylmerimine dihydrochloride and 150 g. of sodium hydroxide in 2,400 ml. of water was adjusted to 33° and 165 g. of benzoyl chloride was added over a 40-minute period at 30–35°. The mixture was stirred for two hours longer at this temperature and the insoluble product was filtered, washed with water and dried at 50°. Recrystallization from ethanol resulted in a 61% yield of 7-amino-2-benzoyl-6-methylmerimine, m.p. 202–203°.

Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.1; H, 5.97; N, 16.6. Found: C, 71.0; H, 5.98; N, 16.5.

2-Carbethoxy-7-hydroxy-6-methylmerimine Hydrochloride (V).—A mixture of 95.5 g. of 7-amino-2-carbethoxy-6-methylmerimine monohydrate, 320 ml. of 5 *N* hydrochloric

(1) Presented in part at the 126th Meeting of the American Chemical Society in New York City, September, 1954.

(2) S. Gabriel and J. Colman, *Ber.*, **35**, 2832 (1902).

(3) L. Velluz and G. Amiard, *Bull. soc. chim.*, [5] **14**, 196 (1947).

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CHART I

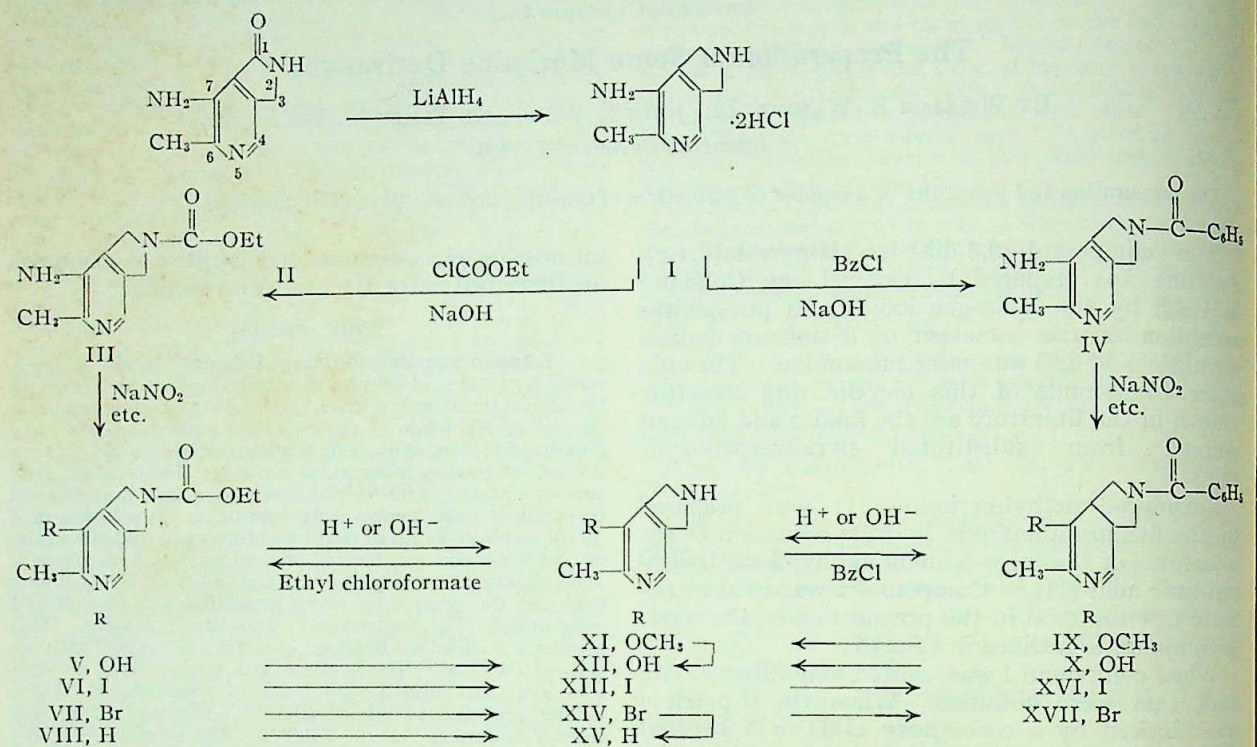
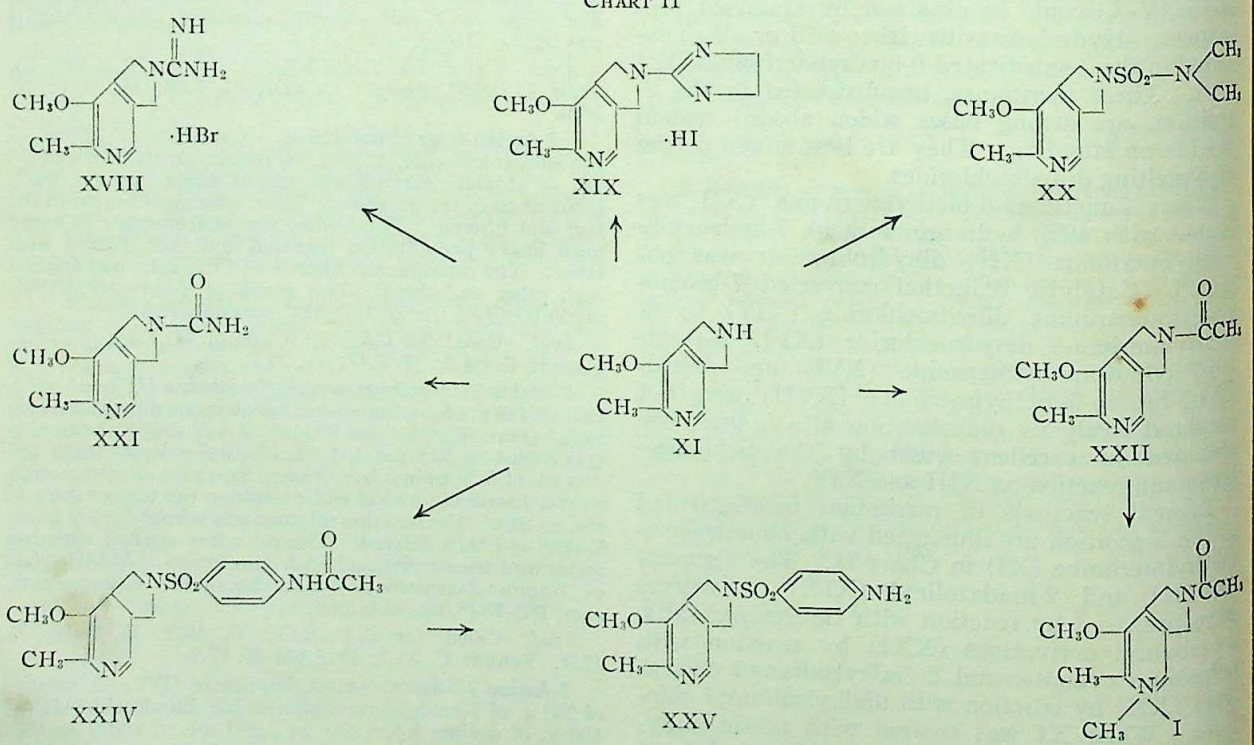


CHART II



acid and 4 liters of ice and water was cooled to 0° and a solution of 29 g. of sodium nitrite in 150 ml. of water was added over ten minutes. The reaction mixture was allowed to warm to 25° over a 3-hour period and was then adjusted with sodium hydroxide to a *p*H of 3. The mixture was concentrated to dryness *in vacuo* and then boiled with 400 ml. of ethanol and filtered hot to remove the salt. On cooling the filtrate, 71.5 g. (69%) of product was obtained. Recrystallization from ethanol yielded pure 2-carbethoxy-7-hydroxy-6-methylmerimine hydrochloride, m.p. 246° dec.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_3$: C, 51.1; H, 5.85; Cl, 13.7; N, 10.8. Found: C, 51.2; H, 5.87; Cl, 13.6; N, 11.1.

2-Carbethoxy-7-iodo-6-methylmerimine (VI).—A solution of 72 g. of sodium nitrite in 300 ml. of water was added over 5 minutes at −2 to −5° to a mixture of 239 g. of 7-amino-2-carbethoxy-6-methylmerimine monohydrate, 1,200 ml. of 5 *N* sulfuric acid and 6,200 ml. of water. The reaction mixture was stirred at this temperature for 20 minutes longer and then poured into a solution of 176 g. of po-

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tassium iodide in 500 ml. of water. The mixture was warmed over a 4-hour period to 25–30° and then filtered to remove some brown insoluble material. The filtrate was treated with sodium bicarbonate and filtered to remove the precipitate. This was washed with water, dried and recrystallized twice from ethanol. The yield of 2-carbethoxy-7-iodo-6-methylmerimine, m.p. 130–131°, was 34%.

Anal. Calcd. for $C_{11}H_{13}IN_2O_2$: C, 39.8; H, 3.95; I, 38.2. Found: C, 39.8; H, 3.86; I, 38.0.

7-Bromo-2-carbethoxy-6-methylmerimine (VII).—A solution of 2.9 g. of sodium nitrite in 30 ml. of water was added over a 5-minute period at −1 to −4° to a mixture of 9.56 g. of 7-amino-2-carbethoxy-6-methylmerimine monohydrate, 15 ml. of 48% HBr and 150 ml. of water. The reaction mixture was held at this temperature for 20 minutes and then poured into a solution of 7 g. of cuprous bromide in 25 ml. of 48% HBr and 15 ml. of water. The dark brown foamy mixture was left at room temperature overnight and then warmed to 60° and filtered. The filtrate was treated with activated carbon and then with hydrogen sulfide gas. After filtration, the light colored filtrate was treated with sodium bicarbonate. An oil separated and gradually solidified. The precipitate was filtered off and washed with water. The yield of 7-bromo-2-carbethoxy-6-methylmerimine was 3.2 g. (28%). After recrystallization from ether the melting point was 93–94°.

Anal. Calcd. for $C_{11}H_{13}BrN_2O_2$: C, 46.4; H, 4.60; Br, 28.0. Found: C, 46.4; H, 4.02; Br, 27.7.

A purer product, m.p. 99–101°, was prepared by treating 7-bromo-6-methylmerimine (XIV) with ethyl chloroformate in aqueous alkali; yield 78%. Found: C, 46.6; H, 4.62; Br, 27.9.

2-Carbethoxy-6-methylmerimine Hydrochloride (VIII).—A solution of 2.17 g. of sodium nitrite in 10 ml. of water was added over a 10-minute period to a solution of 7.17 g. of 7-amino-2-carbethoxy-6-methylmerimine monohydrate and 24 ml. of 5 *N* hydrochloric acid in 200 ml. of water while holding the temperature at 0 to −5°. The reaction mixture was stirred for 5 minutes longer and 19.8 g. of 50% hypophosphorous acid was then added. The temperature was allowed to rise to 22° over a 7-hour period and sodium bicarbonate was then added until foaming no longer occurred. The solution was concentrated to a low volume, extracted with ether, and the ether layer was dried over sodium sulfate. On addition of hydrogen chloride 2-carbethoxy-6-methylmerimine hydrochloride separated. On recrystallization from alcohol and ether, 3.3 g. (45%), m.p. 219–220° dec., was obtained.

The same compound, m.p. 221–223° dec., was obtained in 67% yield by treating 6-methylmerimine dihydrochloride with ethyl chloroformate in aqueous alkali.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2$: C, 54.4; H, 6.25; N, 11.5. Found: C, 54.3; H, 6.40; N, 11.7.

2-Benzoyl-7-methoxy-6-methylmerimine (IX).—A mixture of 101 g. of 7-amino-2-benzoyl-6-methylmerimine, 4 liters of methanol and 166 ml. of concentrated hydrochloric acid was heated to 48° and a solution of 56 g. of sodium nitrite in 160 ml. of water was added over a 1-hour period at 48–59°. The reaction mixture was held for one hour longer at this temperature and then partially concentrated. The mixture was diluted with water, neutralized with sodium carbonate to a *p*H of about 8, and then concentrated further to remove all methanol. The precipitate which separated was filtered off and then dissolved in water adjusted to *p*H 3 with hydrochloric acid. The solution was treated with activated carbon and clarified and the filtrate was adjusted with sodium carbonate to *p*H 5.2. The product was filtered off and recrystallized first from ethanol and then from a mixture of ethanol and isopropyl acetate. The yield of 2-benzoyl-7-methoxy-6-methylmerimine, m.p. 149–151°, was 38%.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.6; H, 6.01; N, 10.4. Found: C, 71.6; H, 5.95; N, 10.6.

2-Benzoyl-7-hydroxy-6-methylmerimine Hydrochloride (X).—A mixture of 76 g. of 7-amino-2-benzoyl-6-methylmerimine, 3,500 ml. of water and 240 ml. of 5 *N* hydrochloric acid was cooled to 0 to −5° and a solution of 21 g. of sodium nitrite in 100 ml. of water was added over a 30-minute period at this temperature. The reaction mixture was allowed to gradually warm over a two hour period to 28°. The mixture was adjusted with 5 *N* sodium hydroxide to a *p*H of about 3 and then concentrated *in vacuo* until heavy precipitation occurred. The precipitate was filtered off and washed with acetone. On recrystallization from ethanol, 2-benzoyl-7-hydroxy-6-methylmerimine hydrochloride, m.p. 228–230°, was obtained in 59% yield.

Anal. Calcd. for $C_{15}H_{15}ClN_2O_2$: C, 62.0; H, 5.20; Cl, 12.2; N, 9.64. Found: C, 61.7; H, 5.26; Cl, 12.4; N, 9.93.

7-Methoxy-6-methylmerimine Dihydrochloride (XI).—A mixture of 295 g. of 2-benzoyl-7-methoxy-6-methylmerimine, 1,100 ml. of 5 *N* sodium hydroxide and 1,800 ml. of ethanol was heated on the steam-bath for three hours, cooled, neutralized with 475 ml. of concentrated hydrochloric acid, concentrated to remove the ethanol and then further acidified with a mixture of 200 ml. of concentrated HCl and 400 ml. of water. The precipitated benzoic acid was filtered off and the filtrate was then treated with 530 ml. of 5 *N* sodium hydroxide and concentrated to remove as much water as possible. The residue was boiled with 400 ml. of ethanol, filtered hot and the salt cake washed with 300 ml. of ethanol. The filtrate was concentrated to a thick mush. This was dissolved in 500 ml. of water and the solution was treated with activated carbon and then acidified with 210 ml. of concentrated hydrochloric acid and further diluted with 500 ml. of ethanol. The crystalline product was filtered, washed with ethanol and dried. The yield of 7-methoxy-6-methylmerimine dihydrochloride, m.p. about 290° dec., was 65%. On concentration of the filtrate, an additional 25% was obtained.

Anal. Calcd. for $C_9H_{14}Cl_2N_2O$: C, 45.6; H, 5.95; Cl, 29.9; N, 11.8. Found: C, 45.5; H, 5.73; Cl, 29.7; N, 11.9.

7-Methoxy-6-methylmerimine Base.—A mixture of 166 g. of the dihydrochloride, 75.5 g. of sodium methylate and 1,500 ml. of ethanol was refluxed under nitrogen for three hours. The reaction mixture was filtered hot to remove the salt and the filtrate was concentrated to an oil. The 7-methoxy-6-methylmerimine was distilled at 125–130° (2 mm.), yield 76%. On cooling, it solidified as white crystals which melted at 57–59°.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.8; H, 7.37; N, 17.1. Found: C, 65.6; H, 7.23; N, 17.2.

7-Hydroxy-6-methylmerimine Dihydrochloride (XII).

A. By Acid Hydrolysis.—A mixture of 10 g. of 2-benzoyl-7-hydroxy-6-methylmerimine hydrochloride and 80 ml. of 5 *N* hydrochloric acid was heated on the steam-bath for five hours. The reaction mixture was cooled and the benzoic acid was filtered off. The filtrate was treated with activated carbon and then concentrated until solidification occurred. The product was filtered, washed with alcohol and dried at 60°. The yield of 7-hydroxy-6-methylmerimine dihydrochloride, m.p. above 290°, was 91%.

Anal. Calcd. for $C_8H_{12}Cl_2N_2O$: C, 43.1; H, 5.42; Cl, 31.8; N, 12.6. Found: C, 42.9; H, 5.49; Cl, 31.8; N, 12.8.

B. By Alkaline Hydrolysis.—The same product was isolated in 68% yield by the alkaline hydrolysis of 2-carbethoxy-7-hydroxy-6-methylmerimine monohydrochloride.

C. From 7-Methoxy-6-methylmerimine.—When 7-methoxy-6-methylmerimine was heated on the steam-bath with 48% hydrobromic acid for 16 hours a 70% yield of 7-hydroxy-6-methylmerimine dihydrobromide, m.p. above 290°, was isolated.

Anal. Calcd. for $C_8H_{12}Br_2N_2O$: Br, 51.2; N, 8.98. Found: Br, 51.8; N, 8.89; CH_3O, 0.0.

7-Bromo-6-methylmerimine Dihydrochloride (XIV). A. Alkaline Hydrolysis of 7-Bromo-2-carbethoxy-6-methylmerimine.—A mixture of 86 g. of 7-bromo-2-carbethoxy-6-methylmerimine, 267 ml. of 4.5 *N* sodium hydroxide and 333 ml. of ethanol was heated on the steam-bath for 2.5 hours. The reaction mixture was cooled and the precipitate was filtered off. The filtrate was acidified with 125 ml. of concentrated hydrochloric acid and clarified with activated charcoal. The solution was concentrated to dryness and the solid residue was washed into a filter with ethanol. The cake was mixed with 26.4 g. of sodium methylate and 500 ml. of ethanol and the mixture was stirred at room temperature for one hour and heated at reflux for 30 min. and then filtered to remove the salt. The filtrate was cooled and HCl gas was passed through to precipitate 7-bromo-6-methylmerimine dihydrochloride as a light tan powder;

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yield 72 g. (84%). Recrystallization from 85% ethanol resulted in an almost white powder which decomposed about 275°.

Anal. Calcd. for $C_8H_{11}BrCl_2N_2$: C, 33.6; H, 3.88; Br, 27.9; Cl, 24.8; N, 9.80. Found: C, 33.6; H, 3.88; Br, 27.7; Cl, 24.6; N, 9.90.

B. Acid Hydrolysis of 7-Bromo-2-carbethoxy-6-methylmerimine.—A mixture of 113 g. of 7-bromo-2-carbethoxy-6-methylmerimine and 500 ml. of concentrated hydrochloric acid was heated on the steam-bath for 30 hours and then concentrated to dryness *in vacuo*. The light brown residue was washed onto a filter with ethanol and then recrystallized from 85% ethanol. A 67% yield of 7-bromo-6-methylmerimine dihydrochloride was obtained as almost white crystals which decomposed about 275°.

7-Iodo-6-methylmerimine Dihydrochloride (XIII).—Alkaline hydrolysis of 2-carbethoxy-7-iodo-6-methylmerimine as described above resulted in a 28% yield of 7-iodo-6-methylmerimine dihydrochloride, m.p. 257° dec. Recrystallization was from aqueous acetone.

Anal. Calcd. for $C_8H_{11}Cl_2IN_2$: C, 28.9; H, 3.33; Cl, 21.3. Found: C, 29.2; H, 3.52; Cl, 21.0.

6-Methylmerimine Dihydrochloride (XV). A. From 2-Carbethoxy-6-methylmerimine Hydrochloride.—A 76% yield of 6-methylmerimine dihydrochloride, m.p. 280° dec., was obtained by the acid hydrolysis of 2-carbethoxy-6-methylmerimine. A 30% yield of pure product was obtained by alkaline hydrolysis of the same compound.

Anal. Calcd. for $C_8H_{12}Cl_2N_2$: C, 46.4; H, 5.84; Cl, 34.3; N, 13.5. Found: C, 46.2; H, 5.96; Cl, 34.1; N, 13.6.

B. From 7-Bromo-6-methylmerimine Dihydrochloride.—A mixture of 5.72 g. of 7-bromo-6-methylmerimine dihydrochloride, 50 ml. of water and 1.0 g. of palladium-on-carbon catalyst was reduced in a Parr shaker. One molar equivalent of hydrogen was absorbed in 15 min. The reaction mixture was filtered and concentrated to dryness. Alcoholic HCl was added and the mixture was again concentrated to dryness. The white crystals were washed into a filter with alcohol and dried at 60°; crude yield 92%. Analysis indicated a mixed hydrochloride hydrobromide salt of 6-methylmerimine.

The above product was dissolved in 5 *N* NaOH and the base was extracted with ether. The extract was treated with HCl gas and the 6-methylmerimine dihydrochloride so obtained did not depress the melting point of the product prepared by method A.

2-Benzoyl-7-iodo-6-methylmerimine (XVI).—The Schotten–Baumann reaction of benzoyl chloride and 7-iodo-6-methylmerimine dihydrochloride yielded 2-benzoyl-7-iodo-5-methylmerimine as white crystals which melted at 193–195° dec.

Anal. Calcd. for $C_{15}H_{13}IN_2O$: C, 49.5; H, 3.60; I, 34.9; N, 7.70. Found: C, 49.9; H, 3.58; I, 34.8; N, 7.62.

2-Benzoyl-7-bromo-6-methylmerimine (XVII).—The Schotten–Baumann reaction of benzoyl chloride and 7-bromo-6-methylmerimine dihydrochloride yielded 2-benzoyl-7-bromo-6-methylmerimine as white crystals which melted at 174–176°.

Anal. Calcd. for $C_{15}H_{13}BrN_2O$: C, 56.8; H, 4.13; Br, 25.2; N, 8.84. Found: C, 56.9; H, 3.65; Br, 25.6; N, 8.91.

2-Guanyl-7-methoxy-6-methylmerimine Hydrobromide (XVIII).—A solution of 1.7 g. of 7-methoxy-6-methylmerimine and 1.85 g. of S-ethylthiuronium bromide in 10 ml. of ethanol was allowed to stand at room temperature for 2 hours and then heated on the steam-bath for 1 hour. The mixture was cooled and filtered and then recrystallized from dilute ethanol. An 87% yield of 2-guanyl-7-methoxy-6-methylmerimine hydrobromide was obtained. This material darkened about 260° but was of indefinite melting point.

Anal. Calcd. for $C_{10}H_{15}BrN_4O$: C, 41.9; H, 5.27; Br, 27.8; N, 19.5. Found: C, 41.8; H, 5.10; Br, 27.9; N, 19.7.

7-Amino-2-guanyl-6-methylmerimine Hydrobromide.—This compound was prepared as above from 7-amino-6-methylmerimine and S-ethylthiuronium bromide. A white product of indefinite melting point was obtained after two recrystallizations from water.

Anal. Calcd. for $C_9H_{14}BrN_5$: C, 39.7; H, 5.18; Br, 29.4; N, 25.7. Found: C, 39.4; H, 4.74; Br, 28.9; N, 25.5.

2-(2-Imidazolinyl)-7-methoxy-6-methylmerimine Hydroiodide (XIX).—This compound was prepared as above from 7-methoxy-6-methylmerimine and 2-methylmercaptoimidazoline hydroiodide. The yield of 2-(2-imidazolinyl)-7-methoxy-6-methylmerimine hydroiodide was 89%.

Anal. Calcd. for $C_{12}H_{17}IN_4O$: C, 40.0; H, 4.76; I, 35.2; N, 15.5. Found: C, 39.7; H, 4.70; I, 34.9; N, 15.7.

2-Dimethylsulfamyl-7-methoxy-6-methylmerimine (XX).—A solution of 2.37 g. of 7-methoxy-6-methylmerimine dihydrochloride in 20 ml. of 1 *N* sodium hydroxide was treated with 1.08 ml. of dimethylsulfamyl chloride. After one hour, 10 ml. of 1 *N* sodium hydroxide was added and the precipitate which separated was filtered and recrystallized from aqueous ethanol. The yield of 2-dimethylsulfamyl-7-methoxy-6-methylmerimine, m.p. 100–103°, was 33%.

Anal. Calcd. for $C_{11}H_{17}N_3O_3S$: C, 48.7; H, 6.32; N, 15.5; S, 11.8. Found: C, 48.6; H, 6.23; N, 15.3; S, 12.1.

2-Dimethylsulfamyl-7-hydroxy-6-methylmerimine.—This compound was prepared as above from 7-hydroxy-6-methylmerimine dihydrochloride and dimethylsulfamyl chloride. Recrystallization from ethanol resulted in a 33% yield of white powder of indefinite melting point.

Anal. Calcd. for $C_{10}H_{15}N_3O_3S$: C, 46.7; H, 5.88; N, 16.3; S, 12.4. Found: C, 46.4; H, 5.80; N, 16.4; S, 12.4.

2-Diethylsulfamyl-7-hydroxy-6-methylmerimine.—A 22% yield of 2-diethylsulfamyl-7-hydroxy-6-methylmerimine, m.p. 195–197°, was obtained when 7-hydroxy-6-methylmerimine dihydrochloride and diethylsulfamyl chloride were allowed to react as above.

Anal. Calcd. for $C_{12}H_{19}N_3O_3S$: C, 50.5; H, 6.71; N, 14.7; S, 11.2. Found: C, 50.2; H, 6.78; N, 14.8; S, 10.9.

2-Carbamyl-7-methoxy-6-methylmerimine (XXI).—A mixture of 32.8 g. of 7-methoxy-6-methylmerimine, 200 ml. of 1 *N* hydrochloric acid and 16.2 g. of potassium cyanate was allowed to stand overnight at room temperature and was then heated on the steam-bath for 30 minutes. The solution was treated with activated carbon and cooled. The precipitate was filtered, washed with water, and then dried at 100°. The yield of 2-carbamyl-7-methoxy-6-methylmerimine, m.p. 233° dec., was 40 g. (97%).

Anal. Calcd. for $C_{10}H_{13}N_3O_2$: C, 58.0; H, 6.32; N, 20.3. Found: C, 58.1; H, 6.18; N, 20.4.

The following compounds were prepared by essentially the same procedure:

7-Amino-2-carbamyl-6-methylmerimine: yield 95%, m.p. 275° dec. *Anal.* Calcd. for $C_9H_{12}N_4O$: C, 56.2; H, 6.29; N, 29.2. Found: C, 56.3; H, 6.30; N, 29.0.

2-Carbamyl-7-hydroxy-6-methylmerimine: yield 82%, m.p. above 275°. *Anal.* Calcd. for $C_9H_{11}N_3O_2$: C, 56.0; H, 5.74; N, 21.8. Found: C, 56.0; H, 5.74; N, 21.8.

7-Bromo-2-carbamyl-6-methylmerimine: yield 58%, m.p. 243–244°. *Anal.* Calcd. for $C_9H_{10}BrN_3O$: C, 42.2; H, 3.94; Br, 31.2; N, 16.4. Found: C, 42.0; H, 3.57; Br, 31.2; N, 16.3.

2-Carbamyl-7-iodo-6-methylmerimine: yield 56%, m.p. 232–234° dec. *Anal.* Calcd. for $C_9H_{10}IN_3O$: C, 35.7; H, 3.34; I, 41.9; N, 13.9. Found: C, 35.6; H, 3.18; I, 41.9; N, 13.7.

2-Acetyl-7-methoxy-6-methylmerimine (XXII).—A mixture of 49.3 g. of 7-methoxy-6-methylmerimine and 150 ml. of acetic anhydride was heated on the steam-bath for 90 min. and then concentrated to a dark oil. Ether was added and a precipitate separated and was filtered off. After recrystallization from ethanol, the yield of 2-acetyl-7-methoxy-6-methylmerimine, m.p. 115–116°, was 35 g. (70%).

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.84; N, 13.6. Found: C, 64.0; H, 6.89; N, 13.7.

The following were prepared by the same general procedure:

7-Acetoxy-2-acetyl-6-methylmerimine: yield 26%, m.p. 143–144°. *Anal.* Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.5; H, 6.02; N, 12.0. Found: C, 61.3; H, 5.74; N, 12.3.

7-Acetamido-2-acetyl-6-methylmerimine: yield 71%, m.p. 226–228°. *Anal.* Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.8; H, 6.48; N, 18.0. Found: C, 61.5; H, 6.48; N, 17.9.

2-Acetyl-7-methoxy-6-methylmerimine Methiodide (XXIII).—A mixture of 2.06 g. of 2-acetyl-7-methoxy-6-

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methylmerimine, 1.87 ml. of methyl iodide and 15 ml. of ethanol was allowed to stand at room temperature for 5 days and was then heated at reflux for 90 min. The solution was concentrated and then diluted with ether. The precipitate which separated was filtered off and recrystallized from ethanol. The yield of 2-acetyl-7-methoxy-6-methylmerimine methiodide, m.p. 175–177°, was 89%.

Anal. Calcd. for $C_{12}H_{17}IN_2O_2$: C, 41.4; H, 4.92; I, 36.5; N, 8.05. Found: C, 41.4; H, 4.71; I, 36.5; N, 8.27.

The following were prepared by the same general procedure:

7-Acetoxy-2-acetyl-6-methylmerimine methiodide: yield 61%, m.p. 222–224°. *Anal.* Calcd. for $C_{13}H_{17}IN_2O_3$: C, 41.5; H, 4.56; I, 33.8; N, 7.45. Found: C, 41.4; H, 4.53; I, 33.6; N, 7.55.

7-Acetamido-2-acetyl-6-methylmerimine methiodide: yield 41%, m.p. 198–199°. *Anal.* Calcd. for $C_{13}H_{18}IN_3O_2$: C, 41.6; H, 4.84; I, 33.8; N, 11.2. Found: C, 41.7; H, 4.88; I, 32.9; N, 11.0.

2-Carbethoxy-6-methylmerimine methiodide: yield 54%, m.p. 183–185°. *Anal.* Calcd. for $C_{12}H_{17}IN_2O_2$: C, 41.4; H, 4.92; I, 36.5; N, 8.05. Found: C, 41.1; H, 4.62; I, 36.4; N, 7.78.

2-(*p*-Acetylsulfanilyl)-7-methoxy-6-methylmerimine (XXIV).—A mixture of 1.18 g. of 7-methoxy-6-methylmerimine dihydrochloride, 1.23 g. of *p*-acetylsulfanilyl chloride and 30 ml. of 1 *N* sodium hydroxide was allowed to react at 30–35° for one hour and then heated on the steam-bath for two hours. The precipitate was filtered hot, washed with water, dried and then recrystallized from ethanol. The yield of 2-(*p*-acetylsulfanilyl)-7-methoxy-6-methylmerimine, m.p. 212–213°, was 0.7 g. (44%).

Anal. Calcd. for $C_{17}H_{19}N_3O_4S$: C, 56.5; H, 5.30; N, 11.6; S, 8.85. Found: C, 56.7; H, 5.14; N, 11.4; S, 8.85.

The following compounds were prepared by the same general procedure:

2-(*p*-Acetylsulfanilyl)-7-hydroxy-6-methylmerimine: yield 35%, m.p. above 250°. *Anal.* Calcd. for $C_{16}H_{17}N_3O_4S$: C, 55.3; H, 4.93; N, 12.1; S, 9.23. Found: C, 55.2; H, 4.93; N, 11.9; S, 9.03.

2-(*p*-Acetylsulfanilyl)-7-amino-6-methylmerimine hemihydrate: yield 75%, m.p. above 280°. *Anal.* Calcd. for $C_{16}H_{18}N_4O_3S \cdot 0.5H_2O$: C, 54.1; H, 5.38; N, 15.8; S, 9.02. Found: C, 54.4; H, 5.05; N, 15.7; S, 8.85.

7-Methoxy-6-methyl-2-(*p*-sulfanilyl)-merimine (XXV).—A mixture of 1.08 g. of the above acetyl derivative, 20 ml. of ethanol and 5 ml. of 5 *N* sodium hydroxide was heated on the steam-bath for one hour. The reaction mixture was concentrated and diluted with water and the precipitate was filtered. On recrystallization from ethanol, 0.55 g. (58%) of 7-methoxy-6-methyl-2-(*p*-sulfanilyl)-merimine, m.p. 204–205°, was obtained.

Anal. Calcd. for $C_{15}H_{17}N_3O_3S$: C, 56.4; H, 5.37; N, 13.2; S, 10.0. Found: C, 56.4; H, 5.11; N, 13.5; S, 9.60.

7-Amino-6-methyl-2-(*p*-sulfanilyl)-merimine.—This compound was prepared as above from 2-(*p*-acetylsulfanilyl)-7-amino-6-methylmerimine. The yield was 80%, m.p. 217° dec.

Anal. Calcd. for $C_{14}H_{16}N_4O_2S$: C, 55.2; H, 5.30; N, 18.4; S, 10.5. Found: C, 55.0; H, 5.32; N, 18.6; S, 10.9.

Acknowledgment.—We are indebted to Mr. O. Sundberg and co-workers for the microanalyses.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

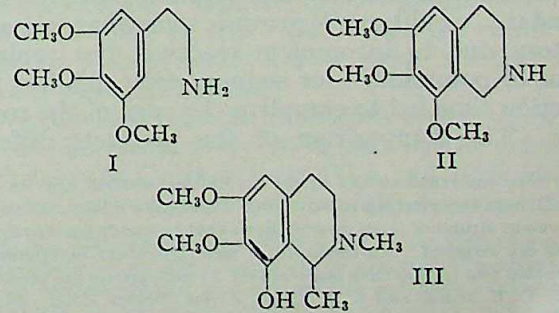
Alkaloid Studies. XVII.[1] The Structure of the Cactus Alkaloid Pilocereine[2]

BY CARL DJERASSI, S. K. FIGDOR,[3a] J. M. BOBBITT[3b] AND F. X. MARKLEY[3c]

RECEIVED OCTOBER 11, 1956

In contrast to the hitherto known cactus alkaloids which are based on a β-phenylethylamine or tetrahydroisoquinoline skeleton, pilocereine consists of two tetrahydroisoquinoline nuclei fused by an ether linkage. Its exact structure (XIIIa) was elucidated by diaryl ether cleavage of pilocereine methyl and ethyl ether with potassium in liquid ammonia and identification of all of the cleavage products. Attention is called to the presence of the 1-isobutyl substituent, which appears to be unique in alkaloid chemistry, and to certain side reactions in the potassium–ammonia cleavage of diaryl ethers.

The most remarkable chemical feature of the hitherto studied cactus alkaloids[4] is the simplicity of the various structures which are all based on β-phenylethylamine or 1,2,3,4-tetrahydroisoquinoline. Mescaline (I) and anhalinine (II) can be offered as two examples which also illustrate their close biogenetic origin[5] and even the most complicated cactus alkaloid, pellotine (III) contains only thirteen carbon atoms and one nitrogen atom.



Consequently, it was of particular interest to elucidate the structure of pilocereine, an alkaloid found[6–8] in various giant cacti and possessing the unusually high (at least for a cactus alkaloid)

(1) Paper XVI, C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney and S. C. Pakrashi, THIS JOURNAL, **79**, 1217 (1957).

(2) Our initial studies in this field were supported by a grant-in-aid from the American Heart Association, Inc. Subsequently, financial assistance was provided by the National Heart Institute ot fhe U. S. Public Health Service (Grant No. H-2040).

(3) (a) Postdoctorate Research Fellow, 1953–1954; (b) Postdoctorate Research Fellow, 1955–1956; (c) Predoctorate Research Fellow, 1955–1956.

(4) For recent reviews see L. Reti in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. VI, Springer, Vienna, 1950, pp. 242–289, and L. Reti in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. IV, Academic Press, Inc., New York, N. Y., 1954, pp. 7–28.

(5) It is now generally accepted that 1,2,3,4-tetrahydroisoquinolines are formed in the plant from substituted β-phenylethylamines and an appropriate amino acid or equivalent (α-keto acid, aldehyde, etc.), the latter providing carbon atom 1 and any substituent attached to it. For pertinent review see R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, 1955.

(6) G. Heyl, *Arch. Pharm.*, **239**, 451 (1901). Heyl did not obtain the alkaloid in crystalline form, but he did arrive at the correct empirical formula (*cf.* ref. 9).

(7) C. Djerassi, N. Frick and L. E. Geller, THIS JOURNAL, **75**, 3632 (1953).

(8) C. Djerassi, C. R. Smith, S. P. Marfey, R. N. McDonald, A. J. Lemin, S. N. Isidoro and H. Estrada, *ibid.*, **76**, 3215 (1954).

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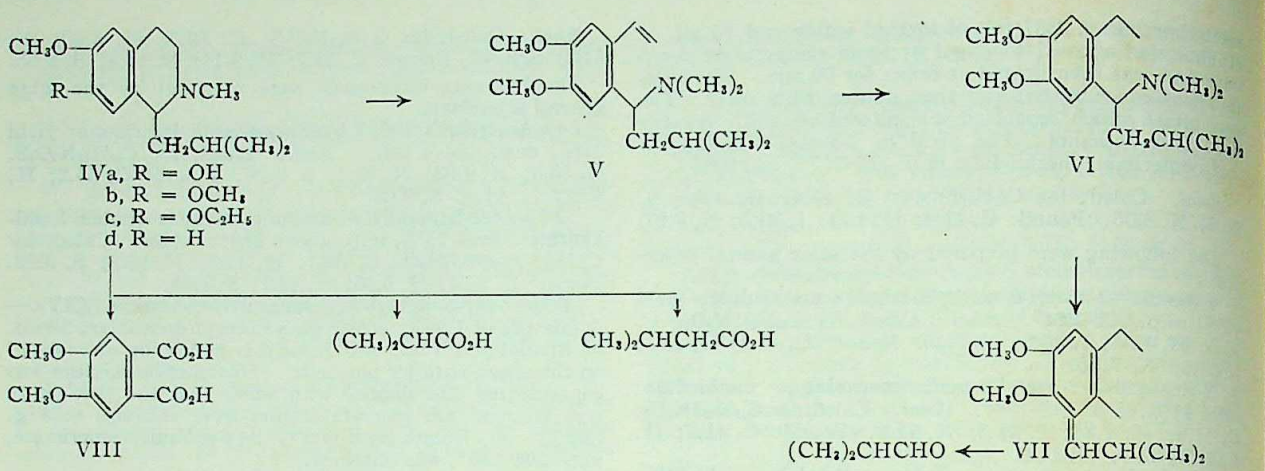

empirical formula $C_{30}H_{44}N_2O_4$.[9] The pharmacology of this alkaloid already has been reported,[10] and we should now like to describe the relevant experiments[11] which lead us to propose structure XIIIa as a complete expression for pilocereine.

Of the four oxygen atoms in pilocereine, two are present as methoxyl groups, one as a kryptophenol and the remaining one was believed[7] to be involved in an ether linkage since no infrared hydroxyl or carbonyl bands were noted in pilocereine methyl ether. Further support could now be provided by the observation that while pilocereine contains one active hydrogen atom (kryptophenol), none is present in its methyl ether. The alkaloid remained unchanged after catalytic hydrogenation in ethanol solution using either platinum oxide or palladium–charcoal. Various oxidations led to no conclusive results except for a permanganate oxidation of its methyl ether which furnished as the only recognizable products[12] isobutyric and isovaleric acids, thus implying that pilocereine must contain at least an isobutyl fragment attached to carbon.

The most promising point of attack seemed to be the still uncharacterized ether linkage involving the fourth oxygen atom. On the supposition that this might be a diaryl ether type, we resorted to the sodium–liquid ammonia procedure[13] which has proved to be so fruitful in the field of the bisbenzyl isoquinoline alkaloids and related bases.[14] The standard conditions[13] proved somewhat unsatisfactory due to incomplete reaction, but replacement of potassium[14] for sodium and extending the reaction time led to complete cleavage of the molecule. The composition of the products differed depending upon the reaction temperature (−60° as compared to −30°), but in each case separation into phenolic and non-phenolic (including kryptophenolic) material could be accomplished by taking advantage of the differing solubility in alkali.

Irrespective of the temperature at which the potassium–ammonia cleavage of pilocereine was conducted, the principal, phenolic, basic component proved to be an oil which could not be converted into a crystalline derivative. However, after methylation with diazomethane in ether–methanol solution,[15] the oil could be characterized as a crystalline picrate and styphnate. The analytical results were consistent with the formulation $C_{16}H_{25}NO_2$, and since functional group analysis indicated the presence of two methoxyl[16] and one N-methyl group, it was clear that one-half of the cleaved pilocereine molecule had now been isolated.

The structure elucidation of the methylated, phenolic cleavage fragment (IVb) of pilocereine proceeded in a straightforward manner along the following lines. Hofmann degradation of IVb led to a methine (V) which furnished formaldehyde upon ozonolysis. Hydrogenation of the methine (V) and repeated Hofmann degradation of VI gave trimethylamine and a neutral substance (VII); ozonolysis of the latter produced isobutyraldehyde. Potassium permanganate oxidation of the original methyl ether IVb yielded a mixture of volatile stench acids (isobutyric and isovaleric acids) and a crystalline acid which was identified as *m*-hemipinic acid (VIII). This sequence of reactions is only compatible with structure IVb, and this was confirmed by direct comparison with a synthetic specimen of 1-isobutyl-2-methyl-6,7-dimethoxytetrahydroisoquinoline (IVb).[17] In order to define the exact position (C-6 or C-7) of the free phenolic group in the original cleavage product, the substance was ethylated with diazoethane and com-

(9) The analytical results of the crystalline alkaloid and its salts (ref. 7) were in better agreement with a $C_{30}H_{42}N_2O_4$ formulation, but the present structure proof clearly shows that two additional hydrogen atoms are required. Furthermore, a new N-methyl determination shows that two (rather than one—see ref. 7) such groups are present.

(10) C. E. Powell and K. K. Chen, *J. Am. Pharm. Assoc.*, **45**, 559 (1956).

(11) A preliminary communication concerning part of this work has already been published (C. Djerassi, S. K. Figdor, J. M. Bobbitt and F. X. Markley, THIS JOURNAL, **78**, 3861 (1956)).

(12) This observation was first made in this Laboratory by Dr. Nelly Frick while working on the initial characterization of pilocereine (ref. 7).

(13) P. A. Sartoretto and F. J. Sowa, THIS JOURNAL, **59**, 603 (1937); A. L. Kranzfelder, J. J. Verbanc and F. J. Sowa, *ibid.*, **59**, 1488 (1937); F. C. Weber and F. J. Sowa, *ibid.*, **60**, 94 (1938).

(14) For leading references see M. Tomita in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. IX. Springer, Vienna, 1952, pp. 175–224.

(15) It was reported earlier (ref. 7) that pilocereine was not methylated in ethereal solution by diazomethane (24 hr.) and that the Rodionow methylation procedure had to be used. Subsequently, it was found (see Experimental portion of this paper) that methylation could be achieved in ether–*methanol* in 3–7 days and all of the methylations were conducted in this manner even though the phenolic cleavage product IVa could also be methylated in ether without added methanol.

(16) Only one of the two methoxyl groups originated from the alkaloid while the second one was introduced by methylation of the newly formed phenolic function.

(17) C. Djerassi, J. J. Beereboom, S. P. Marfey and S. K. Figdor, THIS JOURNAL, **77**, 484 (1955).

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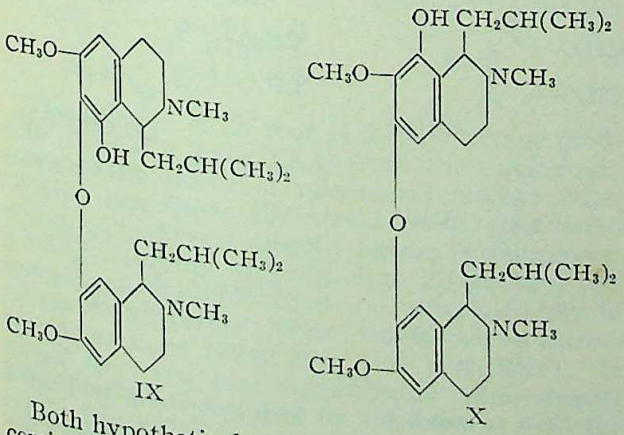
pared with the two possible isomers which had recently been synthesized.[18] The product was shown to be identical with 1-isobutyl-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline (IVc) thus proving unequivocally that the free phenolic group was located at C-7 (IVa).

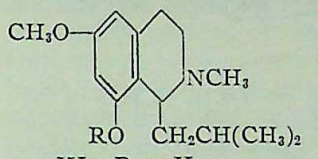
The composition of the alkali-insoluble portion from the pilocereine cleavage was affected by the temperature at which the reaction was conducted. At *ca.* −60°, two substances were isolated; the minor constituent, characterized as a crystalline picrate, corresponded to the empirical formula $C_{15}H_{23}NO$ (one methoxyl group). If this fragment had arisen from the same portion of the pilocereine molecule as the phenolic fragment IVa, it would have to be 1-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IVd). This assumption was confirmed by direct comparison with a synthetic specimen.[18]

The second and major base-insoluble component formed a picrate, the analysis of which indicated the empirical formula $C_{15}H_{23}NO_2$ for the base. Since the substance possessed only one methoxyl group, it was presumably kryptophenolic (infrared hydroxyl band), and this was established by prolonged methylation with diazomethane[15] to a new ether lacking free hydroxyl absorption in the infrared. When this methylated, kryptophenolic fragment was subjected to the same reactions (Hofmann degradations and permanganate oxidations) as described above (IVb → VIII) for its phenolic counterpart IVa, the same results were observed (isolation of, respectively, formaldehyde, isobutyraldehyde, isobutyric acid and isovaleric acid) except that no substituted phthalic acid could be obtained. At this stage of the investigation it was simply assumed that the inability to isolate in this case a substituted phthalic acid may have been due to destruction of the aromatic ring activated by methoxyl substituents. Since the phenolic (IVa) and kryptophenolic cleavage products each corresponded to $C_{15}H_{23}NO_2$, it appeared that both fragments of the pilocereine molecule ($C_{30}H_{44}N_2O_4$) had been secured and that only two structures—IX and X—needed to be considered for the alkaloid.

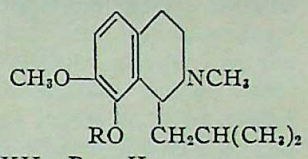


IX X

Both hypothetical structures IX and X for pilocereine appeared to be consistent with the cleavage results and with the general properties of the alkaloid. Thus ether cleavage would yield the two fragments IVa and IVd,[19] already identified by degradation and synthesis, while the kryptophenolic portion would then be represented by either XIa or XIIa. The kryptophenolic character of such a cleavage product and of pilocereine itself could be ascribed to steric hindrance imposed by the bulky isobutyl substituent *peri* to it. However, synthesis[18] of the methyl ethers XIb and XIIb proved conclusively that pilocereine could not possibly be represented by either IX or X since the synthetic products were different from the methylated, kryptophenolic cleavage base.



XIa, R = H
b, R = CH_3



XIIa, R = H
b, R = CH_3

An explanation for this apparent inconsistency appeared when the potassium–ammonia cleavage of pilocereine was carried out near −30°. Under those conditions, in addition to the phenolic (IVa) and "kryptophenolic" fragments,[20] there was formed an appreciable amount of a colorless, crystalline (m.p. 178°) substance (named "desmethylisopilocereine"). The high melting point and in particular the analytical figures ($C_{29}H_{42}N_2O_4$) demonstrated that this substance was not a cleavage product of pilocereine but rather closely related to it. In fact, it differed from the parent alkaloid only by the absence of one methoxyl group and it was first assumed that it simply represented partially demethylated pilocereine. However, methylation of this substance with diazomethane in ether–methanol yielded an oily substance, the infrared spectrum of which was identical with that of the methylated, kryptophenolic cleavage product "isopilocereine" methyl ether. When a partial methylation was attempted with diazomethane in ether alone, some of the above kryptophenol was isolated as the crystalline picrate. It then became apparent that the kryptophenol ("isopilocereine") isolated in the original −60° (as well as in part in the −30°) cleavage could not possibly possess structures of type XI and XII since it was still dimeric.[21]

We conclude that the potassium–ammonia cleavage of pilocereine proceeds in part by the expected path to yield C_{15} fragments (IVa and IVd) and in part by rearrangement or possibly dimerization of

(18) C. Djerassi, F. X. Markley and R. Ehrlich, *J. Org. Chem.*, **21**, 975 (1956).

(19) Cleavage of an unsymmetrical aryl ether can yield all four possible products (*cf.* ref. 13). The fourth (trioxygenated) product would contain two free phenolic groups in one ring and might be expected to be unstable. It was never isolated in the cleavage of pilocereine, but it was encountered when the reaction was performed with the methyl ether where no labile polyphenols would be formed.

(20) 1-Isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IVd) was not encountered in those experiments.

(21) Unfortunately, while the kryptophenol itself gave a crystalline picrate on which a complete analysis (including functional groups) was performed, its methylation product was oily and only C, H and N analyses were secured. When the dimeric nature was recognized, a methoxyl determination was carried out which clearly showed the presence of three methoxyl functions. The methoxyl analysis of the kryptophenol itself was of no help in this connection since it contained two methoxyl groups based on a C_{30} formula or one methoxyl based on C_{60}, in agreement with the hypothetical structures XI or XII.

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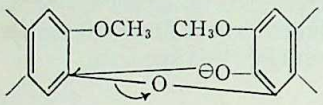
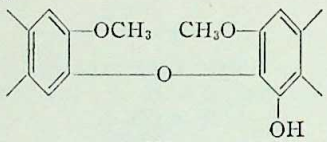
initially formed C_{15} components to yield an isomer of pilocereine in which the phenolic group is still kryptophenolic (repeated cleavage of this dimer with potassium in liquid ammonia failed). It should be noticed that at the higher temperature (−30°), rearrangement (or dimerization) is also accompanied by demethylation. The structure of the rearrangement product has not been established, but it is possible that it should be represented by IX[22] as a consequence of the transformation



XIIIa

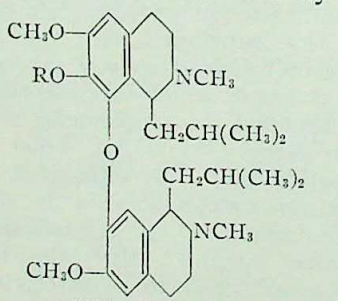


IX

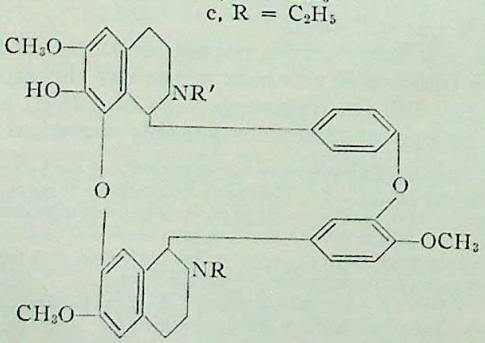
The high-melting, crystalline product would then be a demethylation product of IX, and it appears quite likely that the two phenolic groups are in different rings since the substance appears to be reasonably stable to oxidation.

The above discussion shows that the only cleavage products of structural value are IVa and IVd. In fact, the absence of any other C_{15} fragments raises the question whether the principal product—1-isobutyl-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (IVa)—might not represent *both* halves of pilocereine. Such a hypothesis would be accommodated by structure XIIIa for pilocereine, which would also be eminently satisfactory from a biogenetic viewpoint since exactly the same type of oxygenation is encountered in a variety of bisbenzylisoquinoline alkaloids[14] such as daphnandrine (XIV).[23]

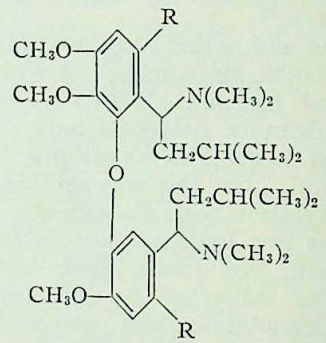
A direct connection between pilocereine (XIIIa) and the bisbenzylisoquinoline alkaloids appeared feasible since the latter (*e.g.*, oxyacanthine) have been degraded[14,24] to the dialdehyde XVIII. Hofmann degradation of pilocereine methyl ether (XIIIb) proceeded smoothly and the resulting methine XV[25] was hydrogenated to the corresponding crystalline tetrahydro derivative XVI. All attempts to isolate a normal second stage Hofmann product XVII[26] or to oxidize the crude total product to the aldehyde XVIII failed in spite of elimination of trimethylamine. It appears that the predom-



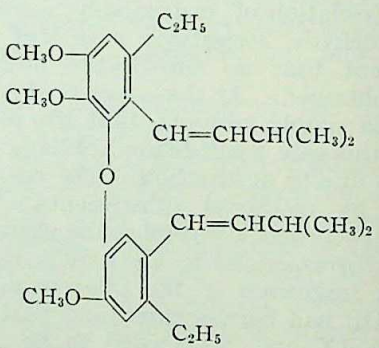
XIIIa, R = H
b, R = CH_3
c, R = C_2H_5



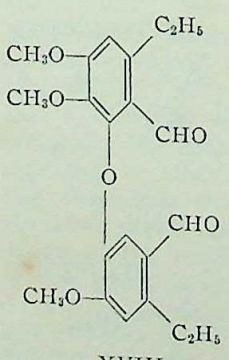
XIV, R = CH_3; R′ = H or
R = H; R′ = CH_3



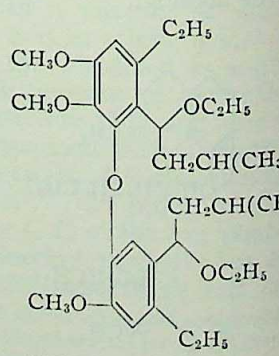
XV, R = CH = CH_2
XVI, R = C_2H_5



XVII



XVIII



XIX

(22) Such a reaction (related to the Smiles rearrangement) has been observed (*cf.* J. D. Loudon, J. R. Robertson, J. N. Watson and S. D. Aiton, *J. Chem. Soc.*, 55 (1950)) in an *o*-hydroxydiphenyl ether with a *p*′-nitro group. In the present case the driving force would have to be ascribed to steric factors since no electron-withdrawing substituents are present.

(23) I. R. C. Bick, E. S. Ewen and A. R. Todd, *J. Chem. Soc.*, 2767 (1949).

(24) *Cf.* F. v. Bruchhausen, H. Oberembt and A. Feldhaus, *Ann.*, **507**, 144 (1933).

(25) Its structure was confirmed by ozonolysis to formaldehyde without any formation of isobutyraldehyde.

(26) Only traces of isobutyraldehyde were obtained when the crude reaction product was ozonized.

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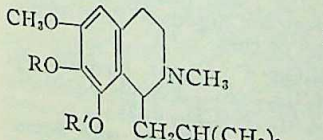
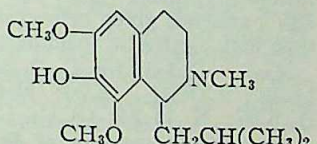
inant course of the reaction was solvolysis[27] aided by the *p*-methoxy substituent, and in one reaction conducted in the presence of ethanol, a product corresponding by analysis to the ethyl ether XIX was isolated.

In view of the unsuccessful Hofmann degradation sequence, attention was directed to the potassium–ammonia cleavage of pilocereine methyl ether (XIIIb). It was felt that if the rearrangement mechanism (XIIIa → IX) or a similar one did indeed obtain in the case of pilocereine (XIIIa), this would be inhibited in pilocereine methyl ether (XIIIb) and furthermore, it might be possible to isolate all of the possible cleavage products.[19] Indeed, the "non-phenolic" portion of such a cleavage of XIIIb could be resolved by chromatography into 1-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IVd), 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVb) and an oily substance which after methylation[15] afforded the known[18] 1-isobutyl-2-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (XXb). The phenolic components of the pilocereine methyl ether cleavage were separated *after methylation* into 6,7-dimethoxy- (IVb) and 6,7,8-trimethoxy- (XXb) 1-isobutyl-2-methyl-1,2,3,4-tetrahydroisoquinoline.

The fact that the trioxygenated cleavage product was isolated in both the phenolic and non-phenolic portions indicates that the phenolic group in that compound is rather hindered. This would be consistent with structure XXa—hindrance being due to the *peri*-isobutyl substituent as well as to the adjacent methoxyl group—but could conceivably also apply to a phenol such as XXI in which the free phenol is flanked by methoxyl groups on either side. While either XXa or XXI would afford the same methylation product XXb (the identity of which was established rigorously by synthesis[18]) it should be noted that the presence (*prior to methylation*) of the 6,7-dimethoxy derivative IVb in the non-phenolic portion requires structure XXa.



XXa, R = CH_3; R′ = H
b, R = R′ = CH_3
c, R = C_2H_5; R′ = H



XXI

The isolation of all four possible cleavage products (IVa, IVb, IVd, XXa) from the potassium–ammonia treatment of pilocereine methyl ether (XIIIb) establishes the structure of that compound. The kryptophenolic nature of pilocereine is compatible only with structure XIIIa, and this was proved rigorously by diaryl ether cleavage of pilocereine *ethyl* ether (XIIIc) which yielded the expected products (IVa, IVc, IVd and XXc). It should be noted that considerably more drastic conditions were required in the cleavage of the ethyl ether XIIIc as compared to the lower homolog XIIIb.

(27) *Cf.* G. Norcross and H. T. Openshaw, *J. Chem. Soc.*, 1174 (1949); A. R. Battersby and H. T. Openshaw, *ibid.*, S59 (1949); A. R. Battersby and R. Binks, *ibid.*, 2889 (1955).

While according to structure XIIIa, pilocereine contains two asymmetric centers, it was nevertheless isolated in an optically inactive form.[28] Späth and Kesztler[29] already have called attention to the fact that several cactus alkaloids are isolated in the *d,l*-form[30] and they noted that synthetic, resolved pellotine (III) racemized quite readily, particularly in acid solution. It is impossible to state, therefore, whether pilocereine was racemized during the isolation process or whether it exists in the racemic form in the plant.

The presence of an isobutyl fragment at C-1, as observed in pilocereine (XIIIa), is unique among isoquinoline alkaloids. It strongly points toward the participation of leucine (or its biogenetic equivalent) in the synthesis of this alkaloid in the plant,[5] and it is not impossible that simple 1-isobutyltetrahydroisoquinolines (such as IVa) might be found in those cacti in which pilocereine has been encountered.[6–8] This would seem particularly likely in the event that diphenyl ether formation[31] should follow tetrahydroisoquinoline ring closure, and we are presently concerned with a search among cacti for such precursors. While isobutyl groups are fairly common among alkaloids, they are usually present as esters[32] and the direct connection of an isobutyl fragment to a non-oxygenated carbon atom does not appear to have been encountered before among alkaloids.

Experimental[33]

Pilocereine (XIIIa) and Pilocereine Methyl Ether (XIIIb).[34]—In order to establish the optical inactivity of pilocereine, its rotation was examined in methanol solution in a Rudolph spectropolarimeter over the range 600–350 mμ and no perceptible rotation was noted. New functional group analysis (see ref. 7) indicated the presence of two C-methyl and two N-methyl groups in the alkaloid.

Anal. Calcd. for $C_{20}H_{44}N_2O_4$: $-CH_3$, 3.03. Found: $C-CH_3$, 4.76, 5.18; $N-CH_3$, 5.16; active hydrogen, 0.95.

An alternative method[35] for the methylation of pilocereine proceeded as follows: pilocereine (8.5 g.) in methanol (200 cc.)–ether (280 cc.) solution was left for six days at 0° with 2.2 g. of distilled diazomethane. After adding an additional 2.2 g. of diazomethane and letting stand at 0° for 3 more days, the solvent was removed and the residue was recrystallized from hexane; yield 6.5 g. (in two crops), m.p. 92–105°, then resolidification and sharp melting at 153–155°. The infrared spectrum (no hydroxyl band) of this methyl ether (XIIIb) was identical with that of the earlier described[7,35] analytical sample.

(28) In order to make sure that the substance does not just happen to have zero rotation at the sodium D line, it was examined in a spectropolarimeter down to 350 mμ without observing any perceptible rotation.

(29) E. Späth and F. Kesztler, *Ber.*, **69**, 755 (1936).

(30) This is not limited to alkaloids with a free 8-hydroxyl group since this also applies to carnegine (1,2-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline).

(31) See in particular p. 85 of ref. 5.

(32) For a recent example see W. Deckers and J. Maier, *Ber.*, **86**, 1423 (1953).

(33) Melting points were determined on the Kofler block. We are indebted to Mrs. Dolores Phillips for all infrared spectra. Microanalyses were carried out by Dr. Alfred Bernhardt (Mülheim, Germany), Geller Laboratories (Hackensack, N. J.) and Spang Microanalytical Laboratory (Plymouth, Mich.).

(34) In order to secure adequate amounts of pilocereine for the degradation experiments described in this paper, over 100 kg. of the cactus was collected by Dr. R. R. Humphrey (University of Arizona), and the preliminary processing was carried out in the pilot plant of Chas. Pfizer and Co. (Brooklyn, N. Y.). We are grateful for this very valuable assistance.

(35) Application of the Rodionow procedure to pilocereine has al-

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Anal. Calcd. for $C_{31}H_{46}N_2O_4$: active hydrogen, 0.0. Found: active hydrogen, 0.0.

Pilocereine methyl ether with m.p. 153–155° could be transformed by recrystallization from ethyl acetate into a second crystalline form with m.p. 133–135°. The transformation was reversed by recrystallization from hexane.

Pilocereine Ethyl Ether (XIIIc).—Pilocereine (3.0 g.) in 100 cc. of absolute ethanol was treated with 3.6 g. of distilled diazoethane[36] in 150 cc. of ether. After 24 hr. at room temperature, an additional 3.6 g. of diazoethane in ether was added, and the mixture was left in the refrigerator for 6 days. Evaporation of the solvent and recrystallization from hexane gave 2.07 g. of the ethyl ether with m.p. 149–151°. An additional 0.32 g. (m.p. 143–148°) was secured by chromatography of the mother liquors. The analytical sample, recrystallized from hexane, showed a dual m. p. 90–95° and 152–153°.

Anal. Calcd. for $C_{32}H_{48}N_2O_4$: C, 73.24; H, 9.22; N, 5.34; O, 12.20; 2 N-CH_3, 5.72. Found: C, 72.64; H, 9.23; N, 5.37; O, 12.68; N-CH_3, 5.86.

Regeneration of Bases from Picrates and Styphnates by Ion Exchange Method.[37]—The following procedure was used throughout this work for the regeneration of amines from their picrate or styphnate salts: The bicarbonate salt (IRA-400-HCO_3) of the strongly basic anion exchange resin IRA-400 was prepared by passing 500 cc. of 50% sodium hydroxide solution over 200 g. of IRA-400 hydrochloride followed by 2 l. of water and 250 g. of sodium bicarbonate in saturated aqueous solution. The resin was washed with 12–16 l. of distilled water and stored under distilled water.

The styphnate or picrate salt was dissolved in acetone (or ethanol) containing about 5% of water and passed dropwise over a column of IRA-400-HCO_3. The spent resin turned bright red when acetone was used as the solvent. The column was washed with twice its volume of 10% aqueous acetone, the acetone was removed *in vacuo*, acid was added, the aqueous solution was washed with ether (discarded), made basic with ammonia and the free base was extracted with ether.

Permanganate Oxidation of Pilocereine Methyl Ether (XIIIb).—A solution of 2.5 g. of pilocereine methyl ether in 100 cc. of 10% sulfuric acid was made just alkaline with 2 *N* sodium hydroxide and then treated dropwise at room temperature with 2% aqueous potassium permanganate solution until a purple color persisted (250 cc.). After standing overnight, the colorless solution was acidified with sulfuric acid, extracted continuously with ether and the resulting acids were transformed *via* their acid chlorides (thionyl chloride procedure) into the anilides. Chromatography in the earlier described manner[17] yielded 35 mg. of isobutyric acid anilide and 10 mg. of isovaleric acid anilide. Identification was accomplished by mixture melting point determination and infrared comparison with authentic specimens. It should be noted that it has already been demonstrated[17] that oxidation of isovaleric acid under these conditions does not yield isobutyric acid.

Reductive Cleavage of Pilocereine (XIIIa) with Potassium in Liquid Ammonia at −60°.—A solution of 5.0 g. of pilocereine in 200 cc. of dry ether was added slowly with stirring to 1.5 l. of redistilled liquid ammonia cooled to −60°. Potassium metal (6 g.) was then added rapidly in small pieces and after continued stirring at −60° for 5 hr., the temperature was allowed to rise to −30° over a period of 3 hr. Anhydrous ammonium chloride was added cautiously until the blue color had been discharged. Stirring was stopped, the solvent was allowed to evaporate overnight and the residue was partitioned between ether and 3% sodium hydroxide solution. The alkaline layer was acidified with 40% sulfuric acid, extracted with ether to remove a trace of colored phenolic, non-basic material and then made basic with concentrated ammonium hydroxide. Extraction with ether, washing with water, drying and evaporation yielded 2.46 g. of *phenolic, basic* oil.

The original ether layer was extracted with 10% hydrochloric acid, dried and evaporated to yield a small amount of non-phenolic, non-basic oil which was discarded. The acid extracts were made basic with ammonium hydroxide and extracted with ether to furnish 2.40 g. of a "*non-phenolic,*" *basic* glassy (rather than mobile) fraction.

This non-phenolic, basic fraction consisted chiefly of one substance—"**isopilocereine**" (IX)—as demonstrated by chromatography and infrared examination of various fractions. It could be converted without chromatography into a crystalline, yellow *dipicrate* which melted at 235–237° after recrystallization from acetone.

Anal. Calcd. for $C_{42}H_{50}N_8O_{18}$: C, 52.82; H, 5.28; N, 11.73; 2 OCH_3, 6.51; 2 N-CH_3, 3.15. Found: C, 53.20; H, 5.36; N, 11.73; OCH_3, 6.48; N-CH_3, 3.19.

For subsequent degradation experiments with "isopilocereine," it was necessary to protect the kryptophenolic group, and 3.5 g. of "isopilocereine" picrate was converted into the free base by means of lithium hydroxide[38] and then methylated with diazomethane in ether–methanol by the procedure described above for pilocereine. The resulting "**isopilocereine" methyl ether** (55% yield) was evaporatively distilled at 180–190° and 0.005 mm. and analyzed directly since no crystalline salts could be obtained.

Anal. Calcd. for $C_{31}H_{46}N_2O_4$: C, 72.90; H, 9.08; N, 5.49; 3 OCH_3, 18.28; 2 N-CH_3, 5.88. Found: C, 72.58; H, 9.21; N, 5.40; OCH_3, 17.76; N-CH_3, 5.63.

In one experiment where rearrangement to "isopilocereine" (IX) was very much reduced and cleavage of the molecule appeared to be nearly complete,[39] treatment of a 75-mg. aliquot of the non-phenolic, basic fraction with picric acid (40 mg.) led to a new picrate (70 mg.), which after two recrystallizations from methanol exhibited m.p. 150–151°. It was identified by mixture melting point determination with a sample of synthetic picrate[18] and by infrared comparison of the free bases as **1-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline** (IVd) picrate.

Anal. Calcd. for $C_{21}H_{26}N_4O_8$: C, 54.54; H, 5.67; N, 12.12. Found: C, 54.96; H, 5.85; N, 12.03.

A 0.26-g. portion of the phenolic, basic cleavage product, which could not be converted into a crystalline salt, was treated with ethereal diazomethane (containing a small amount of methanol) for 6 days at 0°. The solvent was evaporated, the residue extracted with ether and washed with 3% sodium hydroxide solution to give 0.2 g. of an oil which was chromatographed on 9 g. of neutral alumina and eluted in 9 fractions. Fractions 1 and 2, eluted with benzene, weighed 0.155 g., $n^{25}D$ 1.5284, and exhibited an infrared spectrum which was indistinguishable from that of synthetic[17] **1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline** (IVb). The melting points of the crystalline styphnate (m.p. 212–213°) and picrate (m.p. 184–185°, analysis given below) were not depressed upon admixture with synthetic specimens[17] of these salts.

Anal. Calcd. for $C_{22}H_{28}N_4O_9$: C, 53.65; H, 5.73; N, 11.38; 2 OCH_3, 12.70; N-CH_3, 3.26. Found: C, 54.17; H, 5.67; N, 11.74; OCH_3, 12.51; N-CH_3, 3.20.

Reductive Cleavage of Pilocereine (XIIIa) with Potassium in Liquid Ammonia at −30°.—The cleavage of 5 g. of pilocereine in 1.5 l. of redistilled (from sodium) ammonia with 6 g. of potassium was carried out exactly as described above except that the reaction was conducted at −30°. After separation into its components, there was obtained 1.79 g. of "non-phenolic" basic and 2.68 g. of phenolic, basic fractions. When a dried, ethereal solution of the latter was concentrated to a small volume, a white, crystalline substance (1.45 g.) precipitated. After two recrystallizations from ethanol the product ("**desmethylisopilocereine**") melted at 177.5–178°, depressed to 150° upon admixture with pilocereine, and showed significant differences in the infrared spectrum, especially the hydroxyl region. The other products were the same as those found in the −60° cleavage.

Anal. Calcd. for $C_{29}H_{42}N_2O_4$: C, 72.16; H, 8.77; N, 5.80; O, 13.26; OCH_3, 6.44; 2 N-CH_3, 6.23; mol. wt., 482. Found: C, 72.20; H, 8.86; N, 5.89; O, 13.85; OCH_3, 6.72; N-CH_3, 6.30; neut. equiv. (perchloric acid titration), 244; Rast mol. wt., 383.

(36) Prepared from 13 g. of N-ethyl-N-nitrosourethan according to A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948), and H. von Pechmann, *Ber.*, **31**, 2640 (1898).

(37) The general utility of this procedure is being investigated further by J.M.B. at the University of Connecticut.

(38) A. Burger, THIS JOURNAL, **67**, 1615 (1945).

(39) We can offer no explanation for this difference since the experimental conditions were the same as far as could be determined.

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Desmethyl-isopilocereine probably contains the two phenolic groups in two different rings since the substance was recovered unchanged after attempted oxidation with silver oxide.[40]

Partial methylation of desmethyl-isopilocereine was accomplished by treating 100 mg. with excess diazomethane in ether solution (no methanol present) for 2 days at 0°. Evaporative distillation of the product yielded 81 mg. of a glass, the infrared spectrum of which closely resembled that of "isopilocereine" (IX); treatment with picric acid furnished a small amount of isopilocereine picrate, identified by infrared comparison and mixture melting point determination.

Complete methylation of 210 mg. of desmethyl-isopilocereine could be carried out in methanol–ether solution for 7 days, and distillation gave 120 mg. of isopilocereine methyl ether, the infrared spectrum of which was superimposable upon that of the diazomethane methylation product of isopilocereine.

Ethylation of Phenolic, Basic Cleavage Product (1-Isobutyl-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (IVa)) Derived from Pilocereine (XIIIa).—A 300-mg. portion of the phenolic, basic cleavage product (consisting chiefly of IVa) was ethylated with 0.84 g. of diazoethane in ether solution for 7 days at room temperature. The product was freed of unreacted phenolic contaminants by washing with alkali, and it was then transformed into its picrate, m.p. 151.5–152.5°, undepressed upon admixture with a synthetic specimen[18] of **1-isobutyl-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline** (IVc) picrate. Identity was established further by infrared comparison of the respective free bases.

Anal. Calcd. for $C_{23}H_{20}N_4O_9$: C, 54.54; H, 5.97; N, 11.06. Found: C, 54.66; H, 5.94; N, 11.07.

Degradation of Methylated, Phenolic, Basic Cleavage Product (1-Isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVb)) Derived from Pilocereine (XIIIa).—The permanganate oxidation of natural 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVb) was carried out before the substance had ever been synthesized, since it formed part of the structure proof of this degradation product. However, the experimental details of this oxidation already have been reported[17] for the synthetic substance and hence will not be repeated here for the pilocereine cleavage product. By the reported[17] procedure 2.2 g. of IVb yielded 310 mg. of *m*-hemipinic acid (*Anal.* Calcd. for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46; neut. equiv., 113. Found: C, 53.36; H, 4.65; neut. equiv., 117), which was further characterized as the dimethyl ester, m.p. 89.5–90°. Isobutyric and isovaleric acids, the other products of this oxidation, were identified as their anilides.

The Hofmann degradation was performed on 2.47 g. of methyl ether IVb which was converted into its gummy methiodide by standing overnight at room temperature with 10 cc. of methyl iodide. The methiodide (5.17 g.) was dissolved in a small amount of water, added to 120 cc. of 50% aqueous potassium hydroxide solution and heated under reflux for 2 hr. Isolation in the usual manner yielded 2.05 g. of oily methine V.

A 185-mg. portion of the methine was ozonized in glacial acetic acid at 15° for 30 minutes, and the reaction mixture was steam distilled into a methanol (distilled from 2,4-dinitrophenylhydrazine) solution of dimedone. After 24 hr. at 0°, 39 mg. (25%) of the formaldehyde derivative crystallized, m.p. and mixture m.p. 193–195°.

The bulk (1.87 g.) of the methine V was hydrogenated in methanol solution with 5% palladized charcoal catalyst, 1 hr. being required for the uptake of one equivalent of hydrogen. The catalyst was filtered, the solvent was removed and the reduced methine VI was evaporatively distilled at 0.1 mm.

Anal. Calcd. for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 72.81; H, 10.02; N, 4.96.

Conversion of the methine VI to the gummy methiodide (3.94 g.) and repeated decomposition by boiling with 50% aqueous potassium hydroxide yielded 1.06 g. of a neutral, nitrogen-free oil, evidently VII. A 90-mg. portion of it was ozonized as described above for V, and the reaction mixture was steam distilled into acidified aqueous 2,4-dinitrophenylhydrazine solution. Extraction with benzene and chromatography on neutral alumina yielded by elution with benzene 20 mg. of isobutyraldehyde 2,4-dinitrophenylhydrazone, m.p. 181–183° (recrystallized from methanol), which was not depressed when mixed with an authentic specimen.

Degradation of "Isopilocereine" Methyl Ether.—The permanganate oxidation of isopilocereine methyl ether was carried out in the manner described for pilocereine (XIIIa) and 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVb), but except for the volatile stench acids, isobutyric and isovaleric acids, no other acidic fragment could be characterized

For the Hofmann degradation, 104 mg. of isopilocereine methyl ether was treated in benzene solution for 4.5 hr. with 1 cc. of methyl iodide yielding 153 mg. of dimethiodide, m.p. 191–194° after recrystallization from hexane–acetone.

Anal. Calcd. for $C_{33}H_{52}N_2I_2O_4$: C, 49.82; H, 6.59; N, 3.52. Found: C, 50.01; H, 7.12; N, 3.10.

The methiodide (150 mg.) was dissolved in 5 cc. of methanol and 20 cc. of water and passed four times over a column (12 × 300 mm.) of IRA-400-OH anion exchange resin.[41] The column was washed with 20 cc. of 50% aqueous methanol, and the residue from the combined eluates was distilled at 170–175° and 0.005 mm. yielding 89 mg. of a gummy methine.

Anal. Calcd. for $C_{33}H_{50}N_2O_4$: C, 73.56; H, 9.35; N, 5.20; 2 C–CH_3, 5.59. Found: C, 73.44; H, 9.43; N, 5.12; C–CH_3, 3.97.

The above methine (100 mg.) was ozonized in chloroform solution at −60° yielding 55 mg. (51%) of the formaldehyde dimedone derivative. Another portion of the methine (500 mg.) was hydrogenated (10 minutes) in ethanol solution with palladized charcoal catalyst, and the reduced methine was distilled at a bath temperature of 160° and 0.005 mm., yield 450 mg.

Anal. Calcd. for $C_{33}H_{54}N_2O_4$: C, 73.02; H, 10.03; N, 5.16; O, 11.79; 3 OCH_3, 17.18. Found: C, 72.31; H, 9.87; N, 5.19; O, 12.46; OCH_3, 17.91.

The reduced methine (130 mg.) was transformed into its dimethiodide (180 mg.) with methyl iodide in ether solution, and it was decomposed without further purification[42] by the ion exchange resin method[41] as described above for the first stage Hofmann degradation. The resulting neutral olefin (76 mg.), which was distilled at 160–180° and 0.005 mm., was again ozonized at −60° in chloroform solution, and the distillate was passed into 2,4-dinitrophenylhydrazine solution yielding 44% of isobutyraldehyde 2,4-dinitrophenylhydrazone. Efforts to isolate any substituted diphenyl ether acids from the non-volatile ozonolysis products proved fruitless.

Hofmann Degradation of Pilocereine Methyl Ether (XIIIb).—Pilocereine methyl ether (2.56 g.) was transformed in quantitative yield into its methiodide (3.9 g., m.p. 137–150° dec.) which without further purification was added as a powdered solid to 100 cc. of refluxing 40% sodium hydroxide solution and boiled for 2.5 hr. Structure XV for the resulting methine (2.0 g., 77% yield) was established by ozonolysis of a 160-mg. portion in acetic acid solution and steam distillation into 2,4-dinitrophenylhydrazine solution. Only formaldehyde 2,4-dinitrophenylhydrazone (47 mg., 56% yield) was isolated, uncontaminated by any isobutyraldehyde derivative.

Pilocereine methyl ether methine (XV) (1.9 g.) was hydrogenated in 50 cc. of 95% ethanol with 300 mg. of 10% palladized charcoal catalyst and the product (1.85 g.) was recrystallized several times from acetonitrile to yield 0.92 g. of the reduced methine XVI, m.p. 101.5–103.5°.

Anal. Calcd. for $C_{33}H_{54}N_2O_4$: C, 73.02; H, 10.03; N, 5.16; O, 11.79; 3 OCH_3, 17.18. Found: C, 72.37; H, 9.88; N, 5.49; O, 11.53; OCH_3, 15.38.

The second stage Hofmann degradation was carried out with 1.21 g. of crystalline reduced methine XVI and was performed exactly as described above (XIIIb → XV).

(40) *Cf.* N. D. Cheronis, "Micro and Semimicro Methods" in A. Weissberger's "Technique of Organic Chemistry," Vol. VI, Interscience Publishers, Inc., New York, N. Y., 1954, pp. 270–276.

(41) *Cf.* J. Weinstock and V. Boekelheide, THIS JOURNAL, **75**, 2546 (1953).

(42) Excessive handling of this substance was avoided since it was noted by R. Mirza in this Laboratory in some preliminary abortive experiments that heating with methanol during attempted recrystallization yielded some tetramethylammonium iodide (m.p. 228°).

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Elimination of trimethylamine proceeded smoothly as demonstrated by the isolation of 0.45 g. (75%) of trimethylamine picrate (m.p. 206–210°), but the nitrogen-free degradation product (0.84 g.) apparently contained very little of the desired olefin XVII since treatment with one equivalent of ozone in ethyl acetate solution at −60° by the inverse technique[43] (which worked satisfactorily in a model experiment with isoeugenol methyl ether) followed by decomposition of the ozonide with zinc in acetic acid (24 hr., room temperature) yielded only 3% of isobutyraldehyde 2,4-dinitrophenylhydrazone after chromatography on bentonite–kieselguhr.[44] Careful examination of the non-volatile portion including chromatography did not yield any of the desired aldehyde XVIII[24] even though seed crystals of authentic dialdehyde (derived from an intermediate[23] kindly provided by Sir A. R. Todd, Cambridge University) were available.

In another experiment, in which the Hofmann degradation of the dimethiodide of 1.72 g. of crystalline reduced methine XVI was carried out as described above with the modification that the dimethiodide was first dissolved in ethanol (rather than being added in the solid state to the alkaline medium), a substance was isolated which on the basis of the analysis of a distilled (155–170° at 0.005 mm.) sample (no infrared hydroxyl absorption) appeared to be the diethyl ether XIX arising by solvolysis.

Anal. Calcd. for $C_{33}H_{52}O_6$: C, 72.75; H, 9.62; O, 17.62. Found: C, 73.24; H, 9.39; O, 17.04.

Reductive Cleavage of Pilocereine Methyl Ether (XIIIb) with Potassium in Liquid Ammonia.—The cleavage of 1.98 g. of pilocereine methyl ether (XIIIb) was carried out in the manner described above with 90 cc. of ether, 600 cc. of liquid ammonia and 2.5 g. of potassium at −60° for 7 hr. and furnished 1.30 g. of "non-phenolic," basic and 0.67 g. of phenolic, basic fractions. The "non-phenolic," basic portion was dissolved in 20 cc. of hexane and chromatographed on 80 g. of alumina (deactivated with 2.4 cc. of 10% acetic acid), collecting a total of 114 fractions.

Fractions 20–46, eluted with hexane up to 1:1 hexane–benzene mixtures, upon treatment with picric acid in ethanol gave 0.53 g. (29%) of the picrate of **1-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IVd)**, m.p. 152–153°, undepressed when mixed with a sample of the synthetic[18] picrate. Identity was confirmed by converting a portion of the picrate by the above-described ion-exchange method to the free base and comparing its infrared spectrum with that of the synthetic base.

Anal. Calcd. for $C_{21}H_{26}N_4O_8$: C, 54.54; H, 5.67. Found: C, 54.21; H, 5.90.

Fractions 47–83 were eluted with mixtures ranging from 1:1 hexane–benzene to 99:1 benzene–ether and after treatment with ethanolic picric acid solution, yielded 0.196 g. (10%) of **1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVb) picrate**, m.p. 183–185°. Identity was established by mixture melting point determination of the picrates as well as by infrared comparison of the synthetic[17] and natural bases (regenerated from its picrate by the ion exchange method).

Fractions 100–112, eluted with 9:1 benzene–ether, furnished only with great difficulty a picrate (10% yield, m.p. 150–155°) which on the basis of its analysis, kryptophenolic behavior and identification of its methylation product (see below) must be **1-isobutyl-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (XXa) picrate.**

Anal. Calcd. for $C_{22}H_{28}N_4O_{10}$: C, 51.96; H, 5.55; N, 11.02; 2 OCH_3, 12.20. Found: C, 51.51; H, 5.69; N, 11.05; OCH_3, 11.98.

A 73-mg. sample of the above base XXa, regenerated from its picrate by the ion exchange procedure, was methylated for 10 days at 0° with diazomethane in ether–methanol. The product was converted into its crystalline picrate, m.p. 132–134°, which proved to be identical by mixture melting point determination and infrared comparison of the respective free bases with a synthetic[18] specimen of **1-isobutyl-2-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (XXb)**.

Fractions 112–114 were eluted with ether and with 9:1 ether–methanol. The picrate of the residue melting unsharply above 210° could not be resolved into a pure component; it may represent dimeric material.

The phenolic, basic cleavage products (0.67 g.) were methylated with diazomethane in ether–methanol for 8 days in the refrigerator. The crystalline picrate (0.43 g., 23% yield, m.p. 181–184°) of **1-isobutyl-2-methyl-6,7-dimethoxytetrahydroisoquinoline (IVb)** could be separated directly without having to resort to chromatography, and identity with synthetic material[17] was established in the usual manner.

Anal. Calcd. for $C_{22}H_{28}N_4O_9$: C, 53.65; H, 5.73; N, 11.38; 2 OCH_3, 12.60; N–CH_3, 3.05. Found: C, 54.17; H, 5.67; N, 11.74; OCH_3, 12.51; N–CH_3, 3.20.

The mother liquors from the above picrate preparation were transformed into the free amine by the ion exchange method and then chromatographed on deactivated alumina leading to 0.164 g. of an oil. Treatment with picric acid furnished 0.175 g. (9%) of the picrate of **1-isobutyl-2-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (XXb)**, thus raising the total yield of the trioxygenated cleavage product XXa to 19%.

Reductive Cleavage of Pilocereine Ethyl Ether (XIIIc) with Potassium in Liquid Ammonia.—The ethyl ether XIIIc (2.04 g.) was cleaved in 80 cc. of ether and 600 cc. of ammonia with 3.3 g. of potassium at −60°. The reaction time had to be extended to 24 hr. (in contrast to pilocereine or its methyl ether) since incomplete cleavage was observed when the time was shortened. The usual processing gave 1.30 g. of "non-phenolic," basic and 0.51 g. of phenolic, basic fractions.

Careful chromatography of the "non-phenolic" portion as described above for the methyl ether cleavage gave in order of increased polarity 0.576 g. (32%) of **1-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IVd)** picrate, m.p. 151–153°, 0.227 g. (11.5%) of **1-isobutyl-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline (IVc) picrate**, m.p. 152–153°, and 0.244 g. (12%) of **1-isobutyl-2-methyl-6-methoxy-7-ethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (XXc) picrate**, m.p. 153–154°. Identity of the first two compounds was established by mixture melting point determination of the picrates as well as by infrared comparison of the free bases with those of synthetic samples.[18] The structure of the third compound follows from its analysis, the presence of a free hydroxyl band in the infrared spectrum of the free base and from the constitution of pilocereine itself.

Anal. Calcd. for $C_{23}H_{30}N_4O_{10}$: C, 52.87; H, 5.79; N, 10.72; O, 30.62. Found: C, 52.67; H, 5.99; N, 10.54; O, 30.35.

Methylation of the phenolic, basic cleavage fraction (0.51 g.) in the standard manner and treatment with picric acid gave 0.356 g. (19%) of the pure picrate (m.p. 183–185°) of **1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline**, identical in all respects with a synthetic[17] sample.

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(43) *Cf.* P. Bladon, H. B. Henbest, E. R. H. Jones, G. W. Wood and G. F. Woods, *J. Chem. Soc.*, 4890 (1956).

(44) J. A. Elvidge and M. Whalley, *Chemistry & Industry*, 589 (1955).

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Quaternary Piperazines with Anti-pinworm Activity[1]

BY M. HARFENIST

RECEIVED NOVEMBER 13, 1956

The syntheses and properties of 100 piperazine monoquaternary salts prepared for a study of their anthelmintic activities, and of some related compounds, are reported. Most were prepared by standard methods, but attempts to decarbethoxylate three 1-carbethoxy-4-benzylquaternaries (table, lines 42, 49, 50) led to debenzylation. Anthelmintic activity (*Syphacia obvelata* in the mouse) is discussed briefly as a function of structure.

Consideration of the structures of a number of compounds active in a screening test (*Syphacia obvelata* in the mouse)[2] designed to find substances active against the pinworm of humans, *Enterobius vermicularis*, suggested that two structural features were common to piperazine, gentian violet and several other active series of compounds: all appeared likely to exist largely in the cationic form at physiological acidities,[3] and all had a ring structure near the positive charge. It was thought of interest to prepare some other compounds combining these structural features. The piperazine ring, which occurs in many physiologically active compounds, was therefore given the positive charge induced by quaternization at one nitrogen. It was also anticipated that the well-known tendency of quaternary salts to be poorly absorbed on oral administration would result in negligible systemic toxicity to the host. The high therapeutic index of some of the first compounds prepared led to the synthesis of a large number of diverse piperazine monoquaternaries, whose properties are tabulated.

The thoroughly explored route to unsymmetrical piperazines by alkylation of 1-carbethoxypiperazine[1] was used to prepare most of the compounds. The quaternizations were done in acetone at about room temperature, since some of the higher quaternaries could not be crystallized readily from alcoholic solvents. Further, solvolysis of some halides competed with the slower quaternizations especially in methanol.

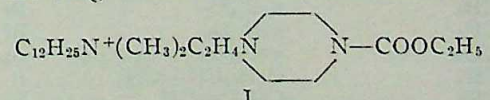
It was convenient to prepare large batches of the 1-carbethoxy-4-alkylpiperazines substituted with the smaller alkyl group and to then quaternize each of these with a number of larger alkyl bromides. In some cases, the alkyl iodides were used as quaternizing agents to speed up the reactions, but they were not as satisfactory since the hydriodides of the starting tertiary amines were sometimes the only isolable products.[4]

The quaternization of 1-carbethoxy-4-propargylpiperazine, *e.g.*, with dodecyl bromide, was so slow as to be essentially unusable. This is, of course, an example of the well-known electron-attracting ability of the ethinyl group. Propargyl bromide was therefore used to prepare quaternaries such as those on lines 38 and 71–79 of the table, and reacted rapidly as anticipated.[5] Indeed, the dipropargyl quaternary was prepared readily (line 76).

To prepare the 1,1-dialkylpiperazinium halides without an amide function at N_4 (lines 1–10 of the table) decarbethoxylation of the corresponding 4-carbethoxy quaternaries by constant-boiling aqueous hydrochloric acid was generally used.[6] The quaternary function at the other nitrogen did not appear to increase the rate of hydrolysis at the carbethoxy group appreciably more than the activation conferred by protonation of a tertiary nitrogen in this strongly acidic medium.

In the case of the attempted acid hydrolysis of 1-carbethoxy-4-methyl-4-benzylpiperazinium chloride and its 4-methyl-4-*p*-chlorobenzyl congener (table, lines 42 and 44), this treatment led to destruction of the quaternary with formation of 1-methylpiperazine (characterized both by benzoylation and by formation of the phenylthiourea) and steam-distillable material resembling the corresponding benzyl halide. The related 1-carbethoxy-4-methyl-4-*p*-anisylpiperazinium chloride (table, line 50) gave what appeared to be a polymer in addition to the 1-methylpiperazine. Raney nickel-catalyzed hydrogenolysis[7] of the 1-nitroso quaternary (table, line 100) was therefore used to prepare 1-methyl-1-benzylpiperazinium chloride.[7,8]

The 1-alkyl-4-amides (other than the carbethoxy compounds) required for preparation of the corresponding quaternaries (table, groups B, C, D, F, G) were in general prepared by the methods previously reported.[9] One exception is the preparation of the compound I, required to determine whether placing the quaternary grouping further from the ring would affect anthelmintic activity.



I

This was prepared from the commercially available aminoethylpiperazine which, on heating with benz-

(1) This paper is No. X on unsymmetrical piperazines from these laboratories. For the previous paper, see R. Baltzly, W. S. Ide and E. Lorz, THIS JOURNAL, **77**, 4809 (1955).

(2) K-F. Chan, *Am. J. Hyg.*, **56**, 22 (1952).

(3) The glycinamide quaternaries of A. J. Rachlin, *et al.*, A.C.S. Div. of Med. Chem. Abstracts, P.5M. (Apr. 8, 1956) also fit this category, as does cyanine dye No. 715 [*cf.* E. Perez-Santiago, J. Oliver-González and C. J. Thillet, *Am. J. Trop. Med. Hyg.*, **2**, 307 (1953)].

(4) E. D. Hughes and U. G. Shapiro, *J. Chem. Soc.*, 1177 (1937), have shown that the ratio of the E_2 elimination to the S_N2 hydrolysis of isopropyl iodide in alkaline ethanol–water solution is greater than for isopropyl bromide.

(5) The rapid reactions of propargyl chloride with ethoxide and with radioactive chloride have been reported by C. A. Vernon, *J. Chem. Soc.*, 4462 (1954), and that with ethoxide by L. F. Hatch and V. Chiola, THIS JOURNAL, **73**, 360 (1951). However, the occurrence of side reactions led to inconstancy of the rate, or incomplete reaction. Since the theoretical titer of acetylenic hydrogen is found in the quaternaries readily isolated in excellent yield from our quaternizations with propargyl bromide, it is hoped to measure the rate of this reaction more precisely as time permits.

(6) T. S. Moore, M. Boyle and V. M. Thorne, *J. Chem. Soc.*, 39 (1929).

(7) E. Lorz and R. Baltzly, THIS JOURNAL, **73**, 93 (1951).

(8) Details of this and of the other protecting methods studied will be reported separately.

(9) M. Harfenist, THIS JOURNAL, **76**, 4991 (1954).

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TABLE I

PROPERTIES OF PIPERAZINE QUATERNARIES

	R	R′	X⁻	M.p., °C.	Recrystn. solvents[a]	Analyses, % Calculated C	Calculated H	Found C	Found H
				A: Compounds of type HN(CH2CH2)2NRR′·X⁻·HX					
1	CH_3	CH_3	Cl	219–220	W–M	38.51	8.62	38.57	8.79
						Cl⁻ 37.90		Cl⁻ 38.19	
2	CH_3	n-C_8H_{17}	Cl	178	A–B–E	Cl⁻ 24.87		Cl⁻ 24.87	
3	CH_3	n-$C_{11}H_{23}$	I	175.5–177	A–B–E	I⁻ 49.73		I⁻ 50.00	
4	CH_3	n-$C_{12}H_{25}$	Cl	158–159	A–Ac	Cl⁻ 20.77		Cl⁻ 20.60	
5	CH_3	n-$C_{13}H_{27}$	Cl	109–120	A–Ac	Cl⁻ 19.95		Cl⁻ 19.96	
6	CH_3	n-$C_{14}H_{29}$	Cl	144–145	A–EA–E	Cl⁻ 19.19		Cl⁻ 18.83	
7	CH_3	n-$C_{16}H_{33}$	Br	105–108	A–EA	Br⁻ 32.88		Br⁻ 33.52	
8	CH_3	$CH_2C_6H_5$	Cl	172–175[c]	A–B–E	Cl⁻ 27.02		Cl⁻ 27.12	
9	C_2H_5	n-C_8H_{17}	Cl	188–195	A–B–E	Cl⁻ 23.68		Cl⁻ 24.43	
10	C_4H_9	n-$C_{10}H_{21}$	Cl	167.5–168	B–E	Cl⁻ 19.95		Cl⁻ 20.23	
11	CH_3	CH_2COOH[b]	Cl	230	W–Ip	36.37	6.98	36.22	7.53
				B: Compounds of type CH2(C=O)N(CH2CH2)2NRR′·X⁻					
12	CH_3	n-$C_{14}H_{29}$	Br	166.5	Ac–E	Br⁻ 19.06		Br⁻ 19.11	
13	CH_3	$CH_2C_6H_5$	Cl	225–226	Ac–E	Cl⁻ 13.20		Cl⁻ 13.34	
				C: Compounds of type C6H5(C=O)N(CH2CH2)2NRR′·X⁻					
14	CH_3	CH_3	I	216.5–217.5	AW–A	45.10	5.53	44.83	5.42
15	CH_3	n-C_4H_9	I	140–142	TBW–TB	49.49	6.49	49.08	6.25
16	CH_3	n-$C_{12}H_{25}$	Br	174.5–175.5	Ac–B–E	63.56	9.11	63.72	9.10
17	CH_3	$CH_2C_6H_5$	Cl	116–117	A–AE–E	Cl⁻ 10.24		Cl⁻ 10.48	
				D: Compounds of type CH3OOCN(CH2CH2)2NRR′·X⁻					
18	CH_3	n-$C_{12}H_{25}$	Br	192–193	MA	56.01	9.65	56.22	9.99
				E: Compounds of type C2H5OOCN(CH2CH2)2NRR′·X⁻					
19	CH_3	CH_3	I	197–199	A–E	34.40	6.10	34.55	6.46
20	CH_3	C_2H_5	Br	170.5–171.5	A–EA–E	42.82	7.72	42.71	7.53
21	CH_3	n-C_3H_7	I	123.5–124.5	A–EA	38.60	6.77	38.58	6.62
22	CH_3	i-C_3H_7	I	178	A–EA	38.60	6.77	38.17	7.04
23	CH_3	n-C_4H_9	I	104–107.5	A–EA–E	40.45	7.07	40.48	7.01
24	CH_3	n-C_5H_{11}	I	131.5–132.5	Ac–EA	42.17	7.35	42.48	7.74
25	CH_3	i-C_5H_{11}	I	133.5–134	A–EA–E	42.17	7.35	42.00	7.11
26	CH_3	n-C_6H_{13}	I	115–117.5	A–EA–E	43.75	7.61	43.87	7.49
27	CH_3	n-C_7H_{15}	Br	161–162	A–EA–E	51.27	8.89	50.75	8.81
28	CH_3	n-C_8H_{17}	Br	183–184	A–EA–E	52.59	9.10	52.67	9.10
29	CH_3	n-C_9H_{19}	I	107–108.5	A–EA	47.91	8.30	48.04	7.92
30	CH_3	n-$C_{10}H_{21}$	Br	203.5–204.5	Ac–EA	54.95	9.48	54.75	9.44
31	CH_3	n-$C_{11}H_{23}$	Br	198.5–199	Ac–EA	56.01	9.65	55.79	10.02
32	CH_3	n-$C_{12}H_{25}$	Br	216	D	56.99	9.81	56.56	10.08
33	CH_3	n-$C_{13}H_{27}$	Br	215.5–218.5	D	Br⁻ 18.36		Br⁻ 18.75	
34	CH_3	n-$C_{14}H_{29}$	Br	203–203.5	A–EA–E	57.98	10.36	57.51	10.12
35	CH_3	n-$C_{15}H_{31}$	Br	201–202.5	Ac–EA; N–EA	59.63	10.23	59.30	10.32
36	CH_3	n-$C_{16}H_{33}$	Br	219–221	D	60.40	10.35	60.58	10.44
37	CH_3	$C_9H_{18}CH{=}CH_2$	I	111–113	EA	50.48	8.22	50.44	8.16
38	CH_3	$CH_2C{\equiv}CH$	Br	151–152	A–EA	45.37	6.58	45.52	6.78
39	CH_3	$CH_2CH_2C{\equiv}CH$	Tos[d]	146–148	Ac–E	57.63	7.12	57.74	7.08
40	CH_3	$CH_2C{\equiv}C{-}C_4H_9$	Br	123–125	Ac–B–E	Br⁻ 22.92		Br⁻ 22.48	
41	CH_3	C_6H_5	I	137.5–138.5	A–Ac–E	I⁻ 33.81		I⁻ 34.23	
42	CH_3	$CH_2C_6H_5$	Cl	185.5–186.5	A–EA–E	Cl⁻ 11.66		Cl⁻ 11.87	
43	CH_3	$CH_2C_6H_4Cl(2)$	Cl	165–167.5	Ac–E	Cl⁻ 10.65		Cl⁻ 10.60	
44	CH_3	$CH_2C_6H_4Cl(4)$	Cl	189	A–Ac–E	54.04	6.62	54.34	6.70
45	CH_3	$CH_2C_6H_3Cl_2(2,4)$	Cl	178.3–179	A–B–E	Cl⁻ 9.64		Cl⁻ 9.21	
46	CH_3	$CH_2C_6H_3Cl_2(3,4)$	Cl	170–171	Ac–E	Cl⁻ 9.64		Cl⁻ 9.62	
47	CH_3	$CH_2C_6H_4CH_3(2)$	Br	200.5–202.5	A–Ac–E	Br⁻ 22.38		Br⁻ 22.63	
48	CH_3	$CH_2C_6H_4CH_3(3)$	Br	176–178	A–EA–E	Br⁻ 22.38		Br⁻ 22.32	
49	CH_3	$CH_2C_6H_4CH_3(4)$	Br	189–190	A–B–E	Br⁻ 22.38		Br⁻ 22.59	
50	CH_3	$CH_2C_6H_4OCH_3(4)$	Cl	189	N–EA	58.55	7.68	58.45	7.92
51	CH_3	$(CH_2)_2C_6H_5$	I	194.5–195.5	A–EA–E; W	I⁻ 31.40		I⁻ 31.42	
52	CH_3	$(CH_2)_3C_6H_5$	Br	138.5–139.5	N–Ac–E	Br⁻ 21.52		Br⁻ 21.81	
53	CH_3	$CH_2CH{=}CHC_6H_5$[e]	Cl	157–158	Ac–EA–E	Cl⁻ 10.92		Cl⁻ 10.87	
54	CH_3	C(=O)CH2CH2C(=O)	Cl	164–165	A–EA–E	Cl⁻ 11.64		Cl⁻ 11.62	

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TABLE I (*continued*)

	R	R′	X⁻	M.p., °C.	Recrystn. solvents[a]	Analyses, % Calculated C	Calculated H	Found C	Found H
				E: Compounds of type $C_2H_5OOCN\langle\rangle^{+}NRR'\cdot X^-$					
55	CH_3	$CH_2C(=O)N(C_6H_5)C(=O)S$	Br	138–145	A–EA	Br⁻ 22.88		Br⁻ 22.68	
		$CH_2C(=O)C_6H_5$	Br	172.5–175	N–EA	51.78	6.24	51.53	6.04
56	CH_3	CH_2COOCH_3	Cl	143–145	M–Ac–E	47.05	7.54	46.60	7.36
57	CH_3	$CH_2COOC_2H_5$	Cl	145.5–146.5	A–B–EA–E	48.89	7.86	48.68	7.90
58	CH_3	$CH_2COOC_{12}H_{25}$	Cl	113.5–116	M–B–E	Cl⁻ 8.15		Cl⁻ 8.26	
59	CH_3	$CH(CH_3)COOC_{12}H_{25}$	Cl	75–77	Ac–E	Br⁻ 16.20		Br⁻ 16.25	
60	CH_3	C_2H_5	I	154–156	A–B–EA	38.60	6.77	38.35	7.04
61	C_2H_5	n-C_8H_{17}	I	106–109	Ac–E	47.88	8.27	48.29	8.55
62	C_2H_5	$CH_2C_6H_5$	Cl	133.5–134.5	N–Ac–E	Cl⁻ 11.34		Cl⁻ 11.14	
63	C_2H_5	n-$C_{10}H_{21}$	I	155.5–156.5	A–EA	52.18	8.98	52.55	8.92
64	C_4H_9	n-C_8H_{17}	Br	154.5–155.5	Ac–E	Br⁻ 20.42		Br⁻ 20.58	
65	$CH_2CH{=}CH_2$	n-$C_{10}H_{21}$	Br	169	Ac–E	Br⁻ 19.50		Br⁻ 19.21	
66	$CH_2CH{=}CH_2$	n-$C_{12}H_{25}$	Br	177–177.5	Ac–E	Br⁻ 17.86		Br⁻ 18.05	
67	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	Br	172–173	A–Ac–E	Br⁻ 25.04		Br⁻ 25.00	
68	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	Cl	154–158	A–Ac–E	Cl⁻ 12.91		Cl⁻ 12.88	
69	$CH_2CH{=}CH_2$	$CH(CH_3)COOC_2H_5$	Br	114.5–116	A–B–E	Br⁻ 21.08		Br⁻ 21.23	
70	$CH_2C{\equiv}CH$	n-C_8H_{17}	Br	125–126	Ac–EA–E	Br⁻ 20.52		Br⁻ 20.85	
71	$CH_2C{\equiv}CH$	n-$C_{10}H_{21}$	Br	125–127	Ac–EA	Br⁻ 19.15		Br⁻ 19.10	
72	$CH_2C{\equiv}CH$	n-$C_{11}H_{23}$	Br	140.5–142.5	Ac–EA	Br⁻ 18.53		Br⁻ 18.36	
73	$CH_2C{\equiv}CH$	n-$C_{12}H_{25}$	I	87–91	EA–B–E	I⁻ 25.78		I⁻ 25.23	
74	$CH_2C{\equiv}CH$	$CH_2CH{=}CH_2$	Br	166–167	A–Ac–E	Br⁻ 25.20		Br⁻ 24.80	
75	$CH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	Br	193.3–194.3	A–B	0.635%[f]		0.641%[f]	
76	$CH_2C{\equiv}CH$	$CH_2C{\equiv}C{-}C_4H_9$	Br	119–121	Ac–EA–E	Br⁻ 21.57		Br⁻ 21.58	
77	$CH_2C{\equiv}CH$	C_6H_5	Br	174.5–175.5	AW–Ac–E	Br⁻ 22.62		Br⁻ 22.77	
78	$CH_2C{\equiv}CH$	$CH_2C_6H_5$	Cl	165–165.5	A–EA–E	63.39	7.12	63.31	7.05
79	$CH_2C{\equiv}CH$	n-C_8H_{17}	Tos[d]	178–181	Ac–EA	N 5.65		N[g] 5.38	
80	$CH_2CH_2C{\equiv}CH$	n-$C_{10}H_{21}$	Tos[d]	193.5–195.5	Ac–EA	64.33	9.05	64.09	9.19
81	$CH_2CH_2C{\equiv}CH$	$CH_2C(=O)N(CH_2)C(=O)S$	Br	163.5–166.5	A–B–E	Br⁻ 18.79		Br⁻ 18.71	
82	$CH_2C_6H_5$	n-$C_{12}H_{25}$	I	111–114	EA–E	I⁻ 22.71		I⁻ 22.22	
83	$CH_2CH_2C_6H_5$	$CH_2C_6H_5$	Cl	181.5–183	A–EA–E	Cl⁻ 9.12		Cl⁻ 9.13	
84	$CH_2CH_2C_6H_5$	n-$C_{12}H_{25}$	I	142–143.5	Ac–E	I⁻ 26.20		I⁻ 26.30	
85	OCH_3	n-$C_{16}H_{33}$	Br	100–101	Ac	Br⁻ 15.76		Br⁻ 15.70	
86	CH_2CH_2OH								
				F: Compounds of type $H_2NCON\langle\rangle^{+}NRR'\cdot X^-$					
87	CH_3	CH_3	I	232.5–233.5	W–A–Ac	I⁻ 44.50		I⁻ 44.31	
88	CH_3	CH_3	Cl	247–247.5	M–Ac	Cl⁻ 18.31		Cl⁻ 18.55	
89	CH_3	$CH_2C_6H_5$	Cl	203[h]	A–Ac	57.91	7.48	58.15	7.82
				G: Compounds of type $(CH_3)_2NC(=O)N\langle\rangle^{+}NRR'\cdot X^-$					
90	CH_3	CH_3	I	213–214	A–Ac–E	I⁻ 40.51		I⁻ 40.42	
91	CH_3	n-C_4H_9	I	136–137	A–Ac–E	40.57	7.38	40.51	7.26
92	CH_3	n-$C_{12}H_{25}$	Br	187–190	D	Br⁻ 19.02		Br⁻ 19.07	
93	CH_3	$CH_2C_6H_5$	Cl	175	A–Ac	Cl⁻ 11.91		Cl⁻ 11.59	
				H: Compounds of type $(C_2H_5)_2NC(=O)N\langle\rangle^{+}NRR'\cdot X^-$					
94	CH_3	n-$C_{10}H_{21}$	Br	158–163	Ac–E	Br⁻ 19.00		Br⁻ 18.97	
95	CH_3	n-$C_{12}H_{25}$	Br	167–169	Ac–EA	Br⁻ 17.81		Br⁻ 17.71	
96	CH_3	n-$C_{14}H_{29}$	Br	169–174	Ac–EA	Br⁻ 16.78		Br⁻ 17.39	
				I: Compounds of type $ONN\langle\rangle^{+}NRR'\cdot X^-$					
97	CH_3	CH_3	I	219–223	N–E	I⁻ 46.78		I⁻ 45.95	
98	CH_3	CH_3	Cl	257	M–Ac	Cl⁻ 19.72		Cl⁻ 19.96	
99	CH_3	n-$C_{12}H_{25}$	I	182.5–183	A–EA	48.07	8.52	47.97	8.40
100	CH_3	$CH_2C_6H_5$	Cl	197	A–EA–E	56.40	7.09	56.30	7.20
						Cl⁻ 13.86		Cl⁻ 14.11	

[a] Recrystallization solvents were: A = absolute ethanol; AW = 95% ethanol; Ac = acetone; B = benzene; D = dioxane (purified); E = absolute ether; EA = ethyl acetate; Ip = isopropyl alcohol; M = methanol; MA = methyl acetate; N = nitromethane; TB = *t*-butyl alcohol; TBW = 2% water in TB; W = water. [b] Prepared by hydrolysis of the 1-carbethoxy esters, lines 57 and 58. [c] Hydrate had m.p. 116°. [d] Tos = *p*-toluenesulfonate. [e] Assumed, but not proved to have been produced without allylic rearrangement. [f] Acetylenic H by method given in S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 55. The compound puffs on attempted microanalysis by standard methods for C and H. [g] Kjeldahl nitrogen, performed by Mrs. R. Purdey. [h] M.p. 215° on rapid heating.

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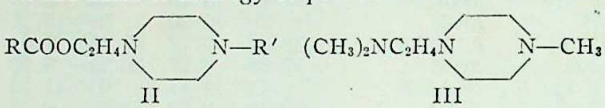
aldehyde, gave the Schiff base. On treatment of this with ethyl chlorocarbonate, it was carbethoxylated to the unstable carbethoxy Schiff base hydrochloride which, on steam distillation of the crude reaction mixture, lost its benzal group to give 1-(2′-aminoethyl)-4-carbethoxypiperazine hydrochloride. Dimethylation (Clarke–Eschweiler) and quaternization of the resulting tertiary amine led to the desired quaternary. Details of these reactions are given in the Experimental section. That quaternization occurs on the side-chain nitrogen is indicated on the basis of analogy to previous work[10] which in-



II III

dicates that the piperazines II quaternize preferentially at N–R′ and that only the bis-quaternary is produced on refluxing III with methanolic methyl iodide.[11]

The amine oxide methiodide (table, line 85) was prepared by quaternization of the oxide produced readily by hydrogen peroxide treatment of 1-carbethoxy-4-*n*-dodecylpiperazine as given in the Experimental section.

Anthelmintic Activity.—Results of the anthelmintic tests will be published in detail elsewhere. They may be summarized in part as showing that a maximum in therapeutic index occurs in the mouse at about the 4-methyl-4-tridecyl- or tetradecylpiperazinium halides. To a first approximation, the position of this maximum is independent of the amide substituent. Of these N-1-amide substituents, the carbethoxy and the diethylcarbamyl groups seem to be best[12] while the 1-nitroso and, surprisingly, the 1-carbamyl quaternaries are inactive (groups F and I). Compound 34, the best of this series, is comparable to piperazine in therapeutic index in these tests.

Activities of 1-methyl quaternaries in which the other 1-substituent is unsaturated, aryl, aralkyl or heterocyclic follow no obvious order. The therapeutic indices of those few quaternaries in which the 1-methyl group was replaced by larger groups seem lower than those of the corresponding 1-methyl quaternaries.

Acknowledgment.—We thank Mr. Samuel W. Blackman for the carbon–hydrogen analyses reported here, and Mr. Ernest Magnien for preparation of certain of the intermediates.

Experimental

Analyses for Halides.—Chlorides were determined by the exceptionally convenient method using phenosafranin as adsorption indicator in dilute nitric acid solution. Bromides and occasionally iodides were also done by this method when a spot test indicated its applicability, otherwise by use of eosin as adsorption indicator or by the Volhard titration.

Melting Points.—These normally occurred with decomposition and frequently were a function of the rate of heating, which therefore was maintained at 3°/min.

1-Carbethoxy-4-dodecylpiperazine-4-oxide.—Fifteen grams (0.13 mole) of 30% hydrogen peroxide was added to a solution of 27 g. (0.083 mole) of 1-carbethoxy-4-*n*-dodecylpiperazine in 116 ml. of glacial acetic acid maintained at about 40°. An equal amount of peroxide was added after 24 hr., and the solution was kept for 3.5 more days. Only a faint positive test with iodide–starch was obtained at this time. The solution was evaporated to a small volume on the steam-bath at 20 mm. pressure, made strongly basic with excess of saturated aqueous potassium carbonate and the resulting oil extracted with two portions of ether. The ethereal solution was dried over magnesium sulfate and concentrated and the residue crystallized from acetone–Skellysolve B. Three crops totaling 23 g. were taken and recrystallized from acetone–Skellysolve A to give 17 g. (two crops), m.p. 139.5°.

Anal. Calcd. for $C_{19}H_{38}N_2O_3$: C, 66.63; H, 11.18. Found: C, 66.95; H, 11.33.

1-Dodecylpiperazine-1-oxide.—A solution of 12 g. (0.035 mole) of the carbethoxypiperazine oxide was heated under reflux with 120 ml. of water containing 12 g. (0.07 mole) of barium hydroxide for 3 hr. Barium ion was removed from the solution by passing in an excess of carbon dioxide and then boiling the solution briefly (*cf.* ref. 9). Evaporation *in vacuo* of the filtrate from this operation gave 8 g. of white solid, which was recrystallized readily from acetone–Skellysolve B to give 5.2 g., m.p. *ca.* 68.5°. This was hygroscopic and apparently light-sensitive and so was converted to the dihydrochloride, m.p. 153–159°.

Anal. Calcd. for $C_{16}H_{36}N_2OCl_2$: Cl^-, 20.62. Found: Cl^-, 20.52.

1-(2′-Benzalaminoethyl)-piperazine.—Addition of 116 g. (1.1 moles) of freshly purified benzaldehyde in a thin stream during four minutes to a well-stirred 129 g. (1 mole if pure) of 2-aminoethylpiperazine (Carbide and Carbon Chemical Co., Inc., "95%") led to spontaneous evolution of steam from the mixture. The remaining water was distilled off at the water-pump until the bath temperature reached 160°. The remaining amber oil was distilled retaining fractions boiling at 140° at 0.2 mm. to 180° at 0.1 mm., totaling 187 g. Redistillation gave 133.5 g. boiling at 130–133° at 0.005 mm. A hard pitch was found as the boiler residue of both distillations, presumably a result of thermal decomposition of the Schiff base. The titration curve of the distillate showed only one inflection point between *p*H 11.5 and 1.5, on titration with hydrochloric acid.

Anal. Calcd. for $C_{13}H_{19}N_3$: equiv. wt., 108.5. Found: equiv. wt., 115.

1-Carbethoxy-4-(2′-aminoethyl)-piperazine.—One hundred grams (0.94 mole) of redistilled ethyl chlorocarbonate was added during 20 minutes to a stirred, cooled solution of 127 g. (0.59 mole) of 1-(2′-benzalaminoethyl)-piperazine in 1 l. of absolute ethanol maintained at 20°. After an additional 0.75 hr. of stirring, the solvent was distilled off at the water-pump, finally on a steam-bath. Distillation of 700 ml. of water from the residue at the water-pump (85% of theory of benzaldehyde was recovered) and similar distillation of 1.1 l. of 1.2 *N* HCl was followed by recrystallization of the residual oil from absolute ethanol by addition of carbon tetrachloride to faint turbidity at 40°. From 77 g. of crude product there was obtained after three recrystallizations 28.2 g. of white solid, m.p. 157.5–158.5.

Anal. Calcd. for $C_9H_{21}N_3O_2Cl_2$: Cl^-, 25.68. Found: Cl^-, 25.70.

1-Carbethoxy-4-(2′-dimethylaminoethyl)-piperazine.—Twenty grams (0.072 mole) of 1-carbethoxy-4-(2′-aminoethylpiperazine) dihydrochloride and 4.3 g. (0.041 mole) of sodium carbonate were added to 38 ml. of 98–100% formic acid, and half of 45 ml. of 38% formaldehyde was added to the mixture. It was then heated under reflux for 6 hr., treated with the rest of the formaldehyde and again refluxed for 6 hr. The reaction mixture was then acidified with 25 ml. of concentrated hydrochloric acid and evaporated on a steam-bath at the water-pump. The residue was dissolved in water, the water saturated with potassium carbonate with cooling and the resulting oil taken into 2 portions of ether. Removal of the ether, acidification with ethanolic hydrogen chloride and dilution with ether gave a white solid. This was recrystallized by addition of acetone to its solution in hot 10% aqueous ethanol. It sublimed when heated over 240° and had m.p. 282–285 when rapidly heated on a hot-stage. The yield was quantitative.

(10) W. S. Ide, E. Lorz and R. Baltzly, THIS JOURNAL, **76**, 1122 (1954).

(11) Personal communication from Dr. A. P. Phillips.

(12) Compare the results of anti-filarid tests reported by S. Kushner, *et al.*, *J. Org. Chem.*, **13**, 144 (1948).

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Anal. Calcd. for $C_{11}H_{25}N_3O_2Cl_2$: Cl^-, 23.41. Found: Cl^-, 23.50.

2-(4′-Carbethoxypiperazino)-ethyldimethyldodecylammonium Bromide (I).—The hydrochloride of the dimethyl tertiary base (above) was converted to the base by excess of aqueous potassium carbonate and subsequent ether extraction and treated with a 100% excess of *n*-dodecyl bromide in acetone at 40° for 19 days. The *extremely hygroscopic* solid produced by dilution with ether was recrystallized twice from ethyl acetate, m.p. 67°.

Anal. Calcd. for $C_{23}H_{48}N_3O_2Br$: Br^-, 16.71. Found: Br^-, 16.58.

The picrate had m.p. 124° (mixed m.p. depression with picric acid).

TUCKAHOE 7, NEW YORK

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Protecting Groups in the Synthesis of Unsymmetrical Piperazines[1]

BY M. HARFENIST AND E. MAGNIEN

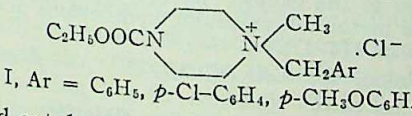
RECEIVED NOVEMBER 17, 1956

Methods for removing various groups useful in protecting one of the two nitrogens of substituted piperazines were studied using piperazine quaternaries with the following N-substituting protective groups: carbethoxyl (removal by aqueous barium hydroxide), acetyl (removal by acid), nitroso (removal by hydrogenolysis catalyzed by Raney nickel) and nitroso with an equivalent of carbamyl (removal of nitroso as nitrous acid, destroyed by the carbamyl function). The relative utility of these methods is briefly considered.

Syntheses in the field of unsymmetrical piperazines are based to a considerable extent on the mono-carbethoxylation of piperazine[2] to protect one nitrogen, although the direct preparations of other mono-amides, and even of alkyl and aralkyl piperazines,[3] have been reported.

The carbethoxy group may be removed either by heating the carbethoxypiperazines with constant-boiling (approx. 6 *N*) aqueous hydrochloric acid at its boiling point (approx. 110°) for two to three days or much more rapidly, as would be anticipated on theoretical grounds, by heating them with alkali.[2,4]

The requirement of protective groups other than carbethoxy became urgent when attempts to hydrolyze the unsymmetrical 1-carbethoxy-4-methyl-4-benzylpiperazinium chlorides (I)[1] by the hydrochloric acid method led to loss, not only of the carbethoxyl, but also of the benzyl group.[5] Further,



I, Ar = C_6H_5, *p*-Cl–C_6H_4, *p*-$CH_3OC_6H_4$–

the acid-catalyzed decarbethoxylation of 1-carbethoxy-4-methyl-4-propargylpiperazinium chloride gave a product containing an impurity of lower halide content, which could not be removed by repeated crystallization.

Although it was felt that the basicity required for saponification of the carbethoxyl group might lead to decomposition of the quaternaries, the rate of the saponification of the propargyl quaternary (I for Ar put C≡CH) by aqueous barium hydroxide was studied. At about 50°, an excess of 0.4 *N* aqueous barium hydroxide gave 85% hydrolysis of the carbethoxyl function (by acidimetric titration of aliquots) in 1 hr. The decarbethoxylated 1-methyl-1-propargylpiperazinium chloride isolated in fair yield after 140 min. under reflux or remaining overnight at 50° was moderately pure and readily gave analytically pure product on recrystallization, although each recrystallization was accompanied by great loss of material.

Theoretical considerations indicated that acid hydrolysis of a 1-acylpiperazine should be rapid, especially under conditions in which the 4-nitrogen, if not quaternized, would be protonated. As anticipated, the de-acetylations of the test substances 1-acetyl-4,4-dimethylpiperazinium chloride and 1-acetyl-4-methyl-4-benzylpiperazinium chloride had been completed (titration) after 30–40 minutes at 95° in the presence of two equivalents of 2 *N* hydrochloric acid and, indeed, were about half completed after four days at room temperature. Hydrolysis of the carbethoxy group of the 1-carbethoxy-4,4-dimethyl quaternary, in contrast, was undetectable after 24 hr. at 95°, in the presence of the same excess of acid. Although the hydrolysis mixture of the acetylmethylbenzyl quaternary had a faint odor resembling benzyl chloride (or alcohol), the appropriate de-acetylated quaternary was isolated in excellent yield from it as well as from the dimethyl analog.

The Raney nickel-catalyzed hydrogenolysis of the nitroso group[6] from 1-nitroso quaternaries was studied with 1-nitroso-4-methyl-4-dodecylpiperazinium iodide which readily gave an 86% yield of analytically pure de-nitrosated quaternary. The corresponding 1-nitroso-4-methyl-4-benzylpiperazinium chloride absorbed the theoretical amount of hydrogen rapidly, and then absorption nearly stopped. Yields averaging 75% were obtained, but the product was contaminated by nickel ion. This was removed by treatment of the reduction filtrate

(1) This is paper No. 11 in a series on unsymmetrical piperazines from these laboratories. For the preceding paper, see M. Harfenist, THIS JOURNAL, **79**, 2211 (1957).

(2) T. S. Moore, M. Boyle and V. M. Thorne, *J. Chem. Soc.*, 39 (1929).

(3) *Cf.* R. Baltzly, THIS JOURNAL, **76**, 1164 (1954), and references given there.

(4) M. Harfenist, *ibid.*, **76**, 4991 (1954).

(5) A related reaction, the spontaneous loss of the 4-methoxybenzhydryl group from 1-(4′-methoxybenzhydryl)-4-methylpiperazine dihydrochloride has been reported by R. Baltzly, S. DuBreuil, W. S. Ide and E. Lorz, *J. Org. Chem.*, **14**, 775 (1942). However, the *p*-methoxy group appeared to be necessary for decomposition under these mild conditions, even though a benzhydryl group should be lost more readily than the benzyl group present in the compounds reported here.

(6) E. Lorz and R. Baltzly, THIS JOURNAL, **73**, 93 (1951).

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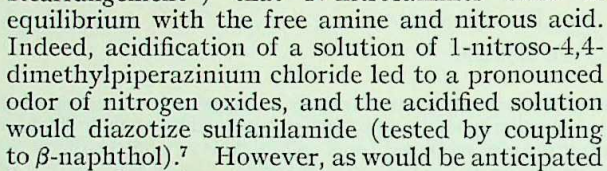
with dimethylglyoxime, as outlined in the Experimental section. However, since no source of anion for the nickel other than the quaternary chloride is evident, it is likely that slight hydrogenolysis had occurred at the quaternary nitrogen in this case. This point was not investigated further.

Another route used successfully for pilot preparations of both dimethyl- and methylbenzylpiperazinium chlorides also utilized the 1-nitrosopiperazinium compounds. It was anticipated on the basis of extension of the known intermolecular nature of rearrangements of N-nitrosamines ("Fisher–Hepp Rearrangement") that N-nitrosamines exist in equilibrium with the free amine and nitrous acid. Indeed, acidification of a solution of 1-nitroso-4,4-dimethylpiperazinium chloride led to a pronounced odor of nitrogen oxides, and the acidified solution would diazotize sulfanilamide (tested by coupling to β-naphthol).[7] However, as would be anticipated from the fact that amines are usually nitrosated in acid solution, the equilibrium strongly favors the nitrosamine, and no appreciable hydrolysis of this one could be found after several days in 2 *N* hydrochloric acid at 95°. A nitrous acid acceptor would therefore be required to make acidic de-nitrosation practical. To avoid introducing extraneous substances, the nitrous acid acceptor selected was the 1-carbamyl derivative of the same piperazine quaternary whose nitroso-derivative was used. The reaction



a, R = CH_3 = R′
b, R = CH_3; R′ = $CH_2C_6H_5$

was complete, as determined by the drop in acid titer, after 30–40 minutes at 95° in the presence of 4 equivalents (100% excess) of 2 *N* hydrochloric acid. Nearly quantitative yields of the expected quaternaries were isolated from these reactions. The rate of hydrolysis of the carbamyl compound under these conditions was separately determined and was found to be negligible by comparison. The product of such hydrolysis, ammonium chloride, would of course also react with nitrous acid rapidly.[8]

Conclusions.—Use of the N-acetyl function as a protective group, and its hydrolytic removal in the presence of mineral acid, is probably the mildest and most convenient of the protective methods discussed here. The use of a mixture of equivalent amounts of N-nitroso- and N-carbamylpiperazine requires the preparation of both, but is otherwise very satisfactory except, presumably, for compounds which might react with nitrous acid irreversibly at a rate comparable to that of the carbamyl group. The barium hydroxide method is best suited to compounds soluble in the basic aqueous solution and stable to alkali for several hours at a temperature somewhat over room temperature. The limits of the Raney nickel-catalyzed hydrogenolytic de-nitrosation have not been determined. The potential utility of this method is great, since reduction of the very readily reduced nitroso function probably would be more rapid than that of most other functional groups.

Acknowledgment.—We thank Dr. R. Baltzly for many helpful discussions during the course of the work.

Experimental

1-Propargyl-1-methylpiperazinium Bromide (Barium Hydroxide Method).—A filtered solution of 295 ml. of 0.4 *N* barium hydroxide in water at 50° was treated with 10 g. of 1-carbethoxy-4-methyl-4-propargylpiperazinium bromide.[1] Aliquots removed after 1 hr. and 5 hr. at 50° revealed an uptake of base corresponding to 86 and 100%, respectively, of the ultimate total base uptake (after 17 hr.). Analogously, 0.35 *N* aqueous barium hydroxide under reflux gave about 70% of the ultimate base uptake after 27 minutes and a base titer after 80 minutes not changed by an additional hour of heating.

This latter alkaline solution was treated with an excess of carbon dioxide and then heated on a steam-bath while nitrogen was bubbled through it to reprecipitate the barium as carbonate. It was then filtered and evaporated on the steam-bath *in vacuo*. The remaining dark oil was dissolved in absolute ethanol, an equal volume of acetone was added and the solution was cooled and filtered from inorganic solids. The hydrobromide of the quaternary was precipitated by addition of 9 g. of 30% hydrobromic acid in acetic acid followed by ether. The resulting 6.5 g. of tan solid had m.p. 160°, after much preliminary sintering. It was recrystallized with difficulty from ethanol (95%)–acetone–ether, yielding 1.5 g., melting with decomposition about 177–180°. The workup of batches decarbethoxylated at 50° was the same in all essentials.

Anal. Calcd. for $C_8H_{16}N_2Br_2$: Br^-, 53.35. Found: Br^-, 53.10.

The compound, in contrast with acetylenic piperazine amines and quaternaries with the other nitrogen present as part of an amide function, gave no usable end-point on titration for acetylenic hydrogen,[1] although qualitative tests were positive for that function.

Conversion to the chloride by the use of silver chloride suspended in methanol containing hydrochloric acid gave a product of m.p. 171–172°.

Anal. Calcd. for $C_8H_{16}N_2Cl_2$: Cl^-, 33.57. Found: Cl^-, 32.70.

1-Methyl-1-benzylpiperazinium Chloride (Nitroso-compound with Hydrogen and Raney Nickel).—A solution of 12.5 g. (0.05 mole) of 1-nitroso-4-methyl-4-benzylpiperazinium chloride[1] dissolved in 50 ml. of methanol was treated with approximately 4 g. (dry weight) of Raney nickel, and hydrogen initially at 40 pounds over-pressure in a Parr hydrogenator at room temperature (28°). The initial rapid reduction slowed markedly when very nearly the theoretical amount of hydrogen had been absorbed, but reduction was continued until the rate fell below 1% of the initial value (3.5 hr.). The green solution was filtered from catalyst and treated with a bit over the theoretical amount of solid dimethylglyoxime (determined by portionwise addition to an aliquot), refiltered and concentrated on the steam-bath *in vacuo*. The resulting pink solid was recrystallized from ethanol–ether, converted to the hydrochloride and that recrystallized from absolute ethanol–benzene–ether. Another recrystallization gave 7.2 g., m.p. 116°, apparently a monohydrate.

Anal. Calcd. for $C_{12}H_{20}N_2Cl_2 \cdot H_2O$: Cl^-, 25.20. Found: Cl^-, 25.10.

Drying for 2 hr. at room temperature and 0.01 mm. gave a product of m.p. 172–175°.

Anal. Calcd. for $C_{12}H_{20}N_2Cl_2$: Cl^-, 26.92. Found: Cl^-, 27.12.

(7) The application of a similar reaction as a spot test has been published since completion of this work; F. Feigl and C. C. Neto, *Anal. Chem.*, **28**, 1311 (1956).

(8) It should be remembered that iodides react with nitrites in acid solution. Iodides can be converted to chlorides, bromides or methanesulfonates under neutral conditions by use of the appropriate silver salt.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of the 2-Amino-3-(3-indolyl)-butyric Acids (β-Methyltryptophans)

BY H. R. SNYDER AND DONALD S. MATTESON[1]

RECEIVED OCTOBER 11, 1956

Indole adds to ethylideneisopropylamine to form 3-(isopropylaminoethylidene)-indole, a substance similar to a Mannich base but having an ethylidene group in place of the methylene residue. Dibenzyl acetamidomalonate is prepared from diethyl acetamidomalonate and alkylated with the new base. Hydrogenolysis of the alkylation product yields the substituted malonic acid, which is converted to 2-amino-3-(3-indolyl)-butyric acid upon decarboxylation followed by hydrolysis of the acetamido group. The amino acid is separated into its two diastereoisomeric *dl*-pairs, and it is shown that these are not structural isomers nor merely different crystalline forms of one compound.

A convenient synthesis of *dl*-tryptophan[2,3] begins with gramine (the Mannich base from indole, formaldehyde and dimethylamine). It appeared likely that β-methyltryptophan (V) could be synthesized *via* a similar route if a way could be found to condense indole, acetaldehyde and an amine to form the base I.

Attempts to employ aldehydes other than formaldehyde in reactions of the Mannich type have met with only limited success; perhaps the best examples of such reactions are those which lead to cyclic products.[4] However, simple bases of the Mannich type have been obtained by the addition of active methylene compounds to aldimines. Benzalaniline has been condensed with acetoacetic ester,[5] malonic ester[6] and related compounds,[7] indoles,[8] pyrazolones,[9] β-naphthol[6] and, in the presence of boron fluoride, with methyl ketones.[10] Recently, indole has been added to Δ^1-piperideine (stable as the trimer) and to 3,4-dihydroquinoline.[11] Indole also has been condensed with the cyanohydrins of acetaldehyde and of acetone and with acetone and chloroform.[12]

The recent observation by Hurwitz[13] that *t*-butylamine forms stable aldimines with aliphatic aldehydes suggested the possibility of adding indole to ethylidene-*t*-butylamine to prepare 3-(*t*-butylaminoethylidene)-indole (Ia).

Before an attempt was made to condense indole with ethylidene-*t*-butylamine, experiments were performed to determine whether *t*-butylamine would participate in normal Mannich reactions. Under typical Mannich conditions,[4] *t*-butylamine hydrochloride, paraformaldehyde and indole give a moderate yield of 3-(*t*-butylaminomethyl)-indole; this secondary amine is the only product. When simpler primary amines are used in Mannich reactions under these conditions, the secondary amine formed condenses with an additional mole of indole and formaldehyde to form a tertiary amine[4]; the formation of a mixture of products severely limits the usefulness of primary amines as reagents for Mannich reactions. In the present case, it appears that the bulky *t*-butyl group shields the amino nitrogen from the second reaction.

To gather preliminary data that might point to a suitable method for condensing ethylidene-*t*-butylamine with indole, methylene-*t*-butylamine and indole were allowed to react under a variety of conditions, most of which resembled those for usual Mannich reactions. Moderate yields of 3-(*t*-butylaminomethyl)-indole generally were obtained.

However, only one method was successful for the reaction of ethylidene-*t*-butylamine with indole. When the reaction was allowed to take place at 0° in a solvent mixture of 75% glacial acetic acid and 25% benzene, 15% yields of the base Ia were obtained. Numerous attempts were made to improve the procedure. The acetic acid was dried by distillation from acetyl borate,[14] but without effect upon the yield. With other variations the reaction failed entirely; an apparently trivial change, the substitution of ether for benzene in the solvent mixture, was one of these.

At this point, it appeared likely that the steric hindrance caused by the *t*-butyl group was so great as to severely repress the condensation. Examination of a Fisher–Taylor–Hirschfelder model indicated that the base Ia has very few unstrained configurations, thus a low entropy of internal rotation both in the molecule itself and in the transition state leading to its formation. An isopropyl group (Ib) allows more rotational freedom in the side chain. The steric properties of isopropyl and *t*-butyl groups are similar enough so that ethylideneisopropylamine should be a fairly stable aldimine; this stability has been observed experimentally by Tiollais.[15]

When ethylideneisopropylamine and indole were allowed to react in acetic acid–benzene at 0°, the yield of 3-(isopropylaminoethylidene)-indole (Ib) was 60%. In addition, direct condensation of indole, acetaldehyde and isopropylamine gave a 40% yield of the base (Ib) under similar conditions.

The structure of the base Ib was confirmed by hydrogenation to 3-ethylindole.

The second step in the *dl*-tryptophan synthesis is the alkylation of diethyl acetamidomalonate by gramine.[2] The properties of 3-(*t*-butylaminomethyl)-, 3-(*t*-butylaminoethylidene)- and 3-(iso-

(1) National Science Foundation Fellow, 1954–1956.
(2) E. E. Howe, A. J. Zambito, H. R. Snyder and M. Tishler, THIS JOURNAL, **67**, 38 (1945).
(3) H. R. Snyder and C. W. Smith, *ibid.*, **66**, 350 (1944).
(4) F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 303–341.
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(6) M. Betti, *Gazz. chim. ital.*, **30**, II, 301 (1900).
(7) C. Lazzareschi, *ibid.*, **67**, 371 (1937).
(8) M. Passerini and T. Bonciani, *ibid.*, **63**, 138 (1933).
(9) M. Passerini and G. Ragni, *ibid.*, **66**, 684 (1936).
(10) H. R. Snyder, H. A. Kornberg and J. R. Romig, THIS JOURNAL, **61**, 3556 (1939).
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(12) H. Erdtmann and Å. Jönsson, *Acta Chem. Scand.*, **8**, 119 (1954).
(13) M. D. Hurwitz, U. S. Patent 2,582,128, Jan. 8, 1952.
(14) W. C. Eichelberger and V. K. LaMer, THIS JOURNAL, **55**, 3633 (1933).
(15) R. Tiollais, *Bull. soc. chim. France*, 716 (1947).

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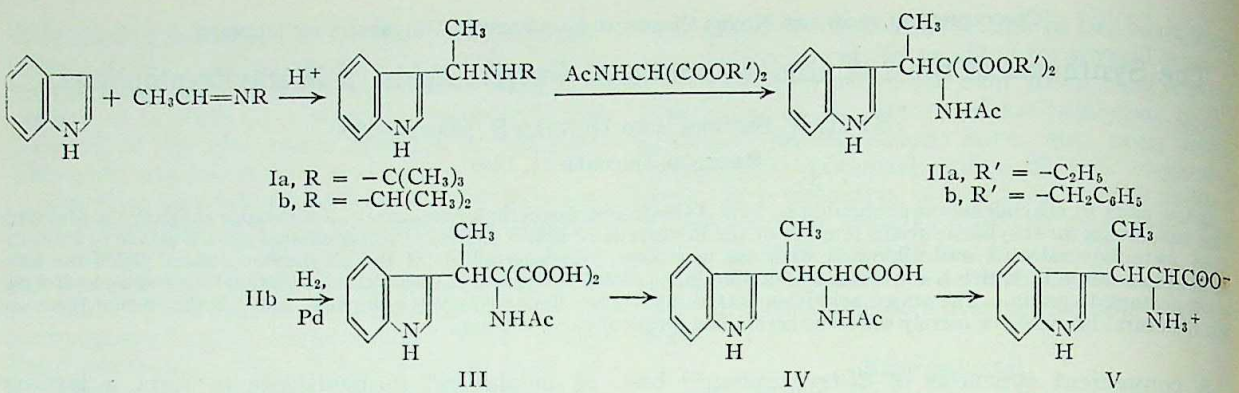

III IV V

propylaminoethylidene)-indole as alkylating agents were investigated. The reaction rates were easily followed semi-quantitatively by titration of the volatile amine evolved. The most rapid alkylation occurred with 3-(*t*-butylaminoethylidene)-indole; the other two reagents gave approximately equal rates. Each requires a lower temperature or shorter time than reported[2] for gramine. Yields are excellent.

The next step, the alkaline hydrolysis of diethyl (3-indolylethylidene)-acetamidomalonate (IIa), took an unexpected course. Instead of the desired acid III, acetylglycine was obtained. Further investigation of this anomalous hydrolysis is being carried out, and, it is hoped, will be reported in a separate article.

This difficulty with the hydrolysis step was eliminated by the use of the dibenzyl ester IIb. Dibenzyl acetamidomalonate was prepared from diethyl acetamidomalonate by transesterification with benzyl alcohol and was alkylated by the base Ib. Dibenzyl (3-indolylethylidene)-acetamidomalonate was converted by hydrogen over a palladium–charcoal catalyst to (3-indolylethylidene)-acetamidomalonic acid (III), isolated and characterized as the ammonium salt.

Decarboxylation of the malonic acid III would be expected to yield two diastereoisomeric *dl*-pairs of 2-acetamido-3-(3-indolyl)-butyric acid (acetyl-β-methyltryptophan) (IV). Only one *dl*-pair was obtained in crystalline form; the other failed to crystallize upon treatment with various solvents, sublimation or partition chromatography (chloroform–water) on silicic acid. The crystalline *dl*-pair was produced in about 30% yields from decarboxylation of either the malonic acid III or its ammonium salt in several different solvents. Since the free acid III was difficult to crystallize, it seemed desirable to decarboxylate the ammonium salt directly. A minimum of discoloration occurred when a pyridine–water solvent was employed.

The crystalline and non-crystalline isomers of acetyl-β-methyltryptophan (IV) were separated and hydrolyzed with 4 *N* sulfuric acid, to avoid the likelihood of racemization encountered with alkaline hydrolysis. Each *dl*-pair of diastereoisomers of 2-amino-3-(3-indolyl)-butyric acid (β-methyltryptophan) (V) was obtained. The first *dl*-pair of V, hereinafter referred to as isomer A, was obtained upon hydrolysis of the crystalline acetyl-amino acid IV; the other *dl*-pair of V, referred to below as isomer B, came from the amorphous material IV. Both isomers had nearly the same decomposition point, but a mixture of the two melted considerably lower. The infrared spectra (Nujol) showed marked differences, and the gross crystalline forms were different.

Two approaches were used to prove that the isomers A and B were not merely different crystalline forms. The α-naphthylurea derivatives were prepared. Although the derivatives had the same decomposition point and gave no depression upon mixing, the infrared spectra (Nujol) were distinctly different. Other evidence was gained from a semi-quantitative determination of the solubilities of the amino acids (V) in 95% ethanol. Isomer A is soluble to the extent of at least 20 mg. per ml., while isomer B has a maximum solubility of not more than 5.5 mg. per ml. at room temperature. In addition, isomer B dissolves to the same extent in a solution of 20 mg. of isomer A per ml. as it does in pure 95% ethanol.

These solubility properties are important in the separation of the isomers, since isomer B is prepared from an impure acetylamino acid IV, but due to its lower solubility in water it is easily separated from any isomer A present by recrystallization. The isomer A, prepared from the crystalline acetylamino acid IV, is presumably free of isomer B to begin with.

To show that the isomers A and B are diastereoisomers, not structural isomers, advantage was taken of the fact that acetylation of tryptophan[16] and other amino acids[17] with excess acetic anhydride leads to racemization at the α-carbon atom; an azlactone is a probable intermediate.[18] Acetylation of isomer B gave the crystalline acetyl derivative of isomer A (28% yield).

Experimental[19]

Aldimines.—Ethylideneisopropylamine was made from acetaldehyde and isopropylamine by the general method for preparing aliphatic aldimines.[20] The most important modifications of the procedure were a final drying of the aldimine over a small amount of barium oxide and distillation at reduced pressure and room temperature with

(16) V. du Vigneaud and R. R. Sealock, *J. Biol. Chem.*, **96**, 511 (1932).

(17) V. du Vigneaud and C. E. Meyer, *ibid.*, **98**, 295 (1932).

(18) V. du Vigneaud and C. E. Meyer, *ibid.*, **99**, 143 (1932).

(19) All melting points are corrected. Infrared spectra were determined by Mr. James Brader. Analyses were performed by Mr. Joseph Nemeth and his associates.

(20) K. N. Campbell, A. H. Sommers and B. K. Campbell, This Journal, **66**, 82 (1944).

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condensation of the aldimine by a Dry Ice–acetone-bath. The yield of ethylidene-isopropylamine (1-mole scale) was 86%, $n^{19.9}$D 1.3877, reported[15] n^{14}D 1.3963; infrared C=N, 1677 cm.$^{-1}$, reported[21] 1672 cm.$^{-1}$. After storage for two months at 0° in an alkali-washed bottle, the refractive index was essentially unchanged, $n^{25.4}$D 1.3862.

A similar procedure with acetaldehyde and *t*-butylamine furnished an 82% yield of ethylidene-*t*-butylamine, $n^{19.2}$D 1.4005. No physical constants were reported by Hurwitz.[13]

Methylene-*t*-butylamine was prepared by the method of Hurwitz.[13] Freshly distilled material was used in all experiments. Contrary to the reported stability of this aldimine,[13] it was observed that the density and refractive index increased considerably after a few days storage at 0°. A sample which had been stored several months at room temperature showed no infrared absorption between 2500 and 1500 cm.$^{-1}$.

3-(*t*-Butylaminomethyl)-indole.—A hot solution of 27.4 g. (0.25 mole) of *t*-butylamine hydrochloride in 175 ml. of abs. ethanol was neutralized (*p*H 6–7) with 0.5 ml. of *t*-butylamine, and 7.51 g. (0.25 mole) of paraformaldehyde was added. The mixture was stirred and refluxed while a solution of 29.3 g. (0.25 mole) of indole in 75 ml. of abs. ethanol was added during 1 hr. Refluxing was continued for 1.5 hr., and the mixture was stored overnight in the refrigerator. The crystalline amine hydrochloride was shaken with 200 ml. of ether and 250 ml. of 1 *N* sodium hydroxide until it dissolved. The ether layer was dried over magnesium sulfate, and the ether was distilled (water-pump). The solid residue was recrystallized from ethanol–water. The yield of 3-(*t*-butylaminomethyl)-indole, m.p. 113–120°, was 19.8 g. (39%). An analytical sample was prepared by two recrystallizations from methylcyclohexane and three from methanol, m.p. 115.5–119°.

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.20; H, 8.97; N, 13.85. Found: C, 77.37; H, 9.23, N, 14.03.

Reaction of Methylene-*t*-butylamine and Indole.—In each experiment, 0.05 mole of indole and 0.055 to 0.06 mole of methylene-*t*-butylamine were used; the product, 3-(*t*-butylaminomethyl)-indole, was isolated by extraction of basic material from aqueous solution with ether, evaporation of the ether, and recrystallization from methylcyclohexane or ethanol–water. The solvents, catalysts, reaction times, temperatures and yields are summarized as follows: 30 ml. abs. ethanol, 20 hr., reflux, 47%; 30 ml. glacial acetic acid, 10 ml. benzene, 0.5 hr., 50°, 33%; 50 ml. glacial acetic acid, 10 ml. benzene, 42 hr., 25°, 26%; 25 ml. abs. ethanol, 0.1 ml. concd. sulfuric acid, 4 hr. reflux, 31%; 25 ml. abs. ethanol, 0.2 ml. glacial acetic acid, 2 hr. reflux, 31%; 30 ml. abs. ethanol, 2 hr., reflux, 6%; 25 ml. methylcyclohexane, 16 hr., reflux, 12%.

3-(Isopropylaminoethylidene)-indole (Ib).—A solution of 29.3 g. (0.25 mole) of indole in 150 ml. of glacial acetic acid was stirred and kept below 15° while a mixture of 23.4 g. (0.275 mole) of ethylideneisopropylamine and 50 ml. of benzene was added dropwise during about 10 min. The solution was then allowed to stand at 0° for 2 to 4 days. The reaction mixture was poured into 500 ml. of ice-water and 50 ml. of ether. The ether layer was separated and extracted with two 100-ml. portions of 1 *M* potassium bisulfate. The combined aqueous solutions were washed with two 50-ml. portions of ether, then made basic with 10 *N* sodium hydroxide; during addition of the alkali, the temperature was kept below 25°. At this point, an oily layer formed and the base began to crystallize from it. To promote crystallization, 100 ml. of methylcyclohexane was added, and the mixture was allowed to stand at 5° for 3 hr. The crystals were collected and dried at room temperature. The yield of 3-(isopropylaminoethylidene)-indole (Ib), m.p. 108–114°, was 30.6 g. (60%). An analytical sample was prepared by two recrystallizations from toluene and one from acetone–toluene, m.p. 113–117.5°.

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.39, H, 9.11; N, 13.39.

3-(*t*-Butylaminoethylidene)-indole (Ia).—The procedure used, starting with indole and ethylidene-*t*-butylamine, was similar to that described above for the preparation of 3-(isopropylaminoethylidene)-indole (Ib), except that a different method of isolating the product had to be used. After the acidic solution of the amine Ia was made basic with sodium hydroxide, the product did not crystallize, but was extracted with ether, the solution was dried with magnesium sulfate and the ether was distilled (water-pump). The oily residue was taken up in methylcyclohexane; crystallization required several days at 0°. The yields of Ia, m.p. 68–72°, were 10 to 18%. An analytical sample was prepared by five recrystallizations from methylcyclohexane, m.p. 69.5–72°.

Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.7; H, 9.31; N, 12.97. Found: C, 77.83; H, 9.53; N, 13.20.

Reaction of Indole, Acetaldehyde and Isopropylamine.—A solution of 5.86 g. (0.05 mole) of indole in 30 ml. of glacial acetic acid was chilled and stirred while 3.3 g. (0.055 mole) of isopropylamine was added. To this cold solution was added a solution of 2.3 g. (0.052 mole) of acetaldehyde in 10 ml. of benzene. The mixture was allowed to stand 2 days at 0°. The product was isolated in the manner described above for 3-(*t*-butylaminoethylidene)-indole (Ia). The yield of 3-(isopropylaminoethylidene)-indole (Ib), m.p. 110–117°, was 3.94 g., 39%.

Reduction of the Base (Ib) to 3-Ethylindole.—A solution of 3-(isopropylaminoethylidene)-indole (Ib) (2 g.) in 95% ethanol (25 ml.) was hydrogenated at 3 atm. over 0.06 g. of 30% Pd/C catalyst at 60–80° for 48 hr. (The apparatus used could not measure the small hydrogen absorption.) The 3-ethylindole was purified by vacuum distillation.

An authentic sample of 3-ethylindole was prepared by a modification of the method of Plancher and Carrasco,[22] a Fischer indole synthesis with phenylhydrazine and butyraldehyde. The reaction was run at about 190° in diethylene glycol until ammonia evolution ceased. Purified by distillation, the 3-ethylindole melted just above room temperature, reported[22] m.p. 43°.

The infrared spectra of the two samples indicated that they were identical.

Dibenzyl Acetamidomalonate.—A solution of 21.7 g. (0.1 mole) of diethyl acetamidomalonate[23] in 60 ml. of benzyl alcohol was heated with an oil-bath to 190–210°. A slow stream of nitrogen was bubbled through the solution, and ethanol was distilled out through a short Vigreux column. After 2 to 3 hr., 11 ml. of ethanol had distilled (theoretical: 0.2 mole, 11.5 ml.). The benzyl alcohol was then distilled at 20 mm.; the bath temperature was raised gradually to 185–190°, where distillation became slow. The residue was crystallized twice from 75 ml. of 2-propanol. The yield of dibenzyl acetamidomalonate, m.p. 110–113°, was 22.1 g. (65%). An analytical sample was prepared by one recrystallization from 2-propanol and two from toluene, m.p. 112–113°.

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.9; H, 5.61; N, 4.10. Found: C, 67.11; H, 5.64; N, 4.06.

Dibenzyl (3-Indolylethylidene)-acetamidomalonate (IIb).—A mixture of 10.11 g. (0.05 mole) of 3-(isopropylaminoethylidene)-indole, 17.07 g. (0.05 mole) of dibenzyl acetamidomalonate, 65 ml. of toluene and approx. 0.01 g. of sodium methoxide was heated at 85–95° with an oil-bath. A slow stream of nitrogen bubbled through the reaction mixture swept out the isopropylamine generated, and the rate of its evolution was followed by titration. The reaction was 95% complete in 6 to 8 hr. Crystallization was induced by scratching and allowed to proceed overnight. The yield of dibenzyl (3-indolylethylidene)-acetamidomalonate was 23.4–23.6 g. (97%), m.p. 120–125°, solidified, second m.p. 161–163°. An analytical sample was prepared by recrystallizations from 2-propanol, acetone, toluene–acetone and toluene, m.p. 166–178°.

Anal. Calcd. for $C_{29}H_{28}N_2O_5$: C, 71.9; H, 5.83; N, 5.79. Found: C, 72.22; H, 5.76; N, 5.82.

Other Alkylations.—The same general procedure described above for the preparation of dibenzyl (3-indolylethylidene)-acetamidomalonate (IIb) was used in all cases with only slight modifications.

Diethyl skatylacetamidomalonate was prepared from diethyl acetamidomalonate and 3-(*t*-butylaminomethyl)-indole at 105° in 71% yield. A low melting form, m.p. 144–145°, was obtained. When recrystallized and seeded

(21) L. Kahovec, *Acta Phys. Austriaca*, **1**, 307 (1948); *C. A.*, **42**, 6665 (1948).

(22) Beilstein, "Handbuch der Organischen Chemie," Vol. XX, 4th Ed., Julius Springer, Berlin, 1935, p. 319.

(23) The Dow Chemical Co., Midland, Michigan.

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with an authentic sample[2] of m.p. 159°, the m.p. rose to 160–161°, not depressed by mixing with the known sample.

Diethyl (3-indolylethylidene)-acetamidomalonate (IIa), m.p. 163–167°, was prepared in 97% yield from diethyl acetamidomalonate and 3-(*t*-butylaminoethylidene)-indole (Ia) at 72–75°. An analytical sample was prepared by three recrystallizations from ethanol, m.p. 176.5–178°.

Anal. Calcd. for $C_{19}H_{24}N_2O_5$: C, 63.3; H, 6.71; N, 7.76. Found: C, 63.18; H, 6.58; N, 7.94.

Dibenzyl (3-indolylethylidene)-acetamidomalonate (IIb) (see preparation above) was also prepared from 3-(*t*-butylaminoethylidene)-indole (Ia) and dibenzyl acetamidomalonate in 91% yield.

Ammonium (3-Indolylethylidene)-acetamidomalonate (Ammonium Salt of III).—Dibenzyl (3-indolylethylidene)-acetamidomalonate (35.7 g., 0.074 mole) (free from lumps) was placed in a heavy-walled bottle with 125 ml. of 95% ethanol and 0.75 g. of 30% Pd/C catalyst. The mixture was shaken under 3–4 atm. of hydrogen until the theoretical amount of hydrogen was absorbed (1 hr.). The catalyst was removed and 15 ml. of ammonium hydroxide was added. Crystallization was allowed to proceed at 0° overnight. The crystals were collected, washed with acetone and dried to constant weight at room temperature. The yield of ammonium (3-indolylethylidene)-acetamidomalonate, m.p. 160–165° dec., was 21.9 g. (87%). An analytical sample was prepared by dissolving the salt in a small amount of water (25°) and recrystallizing it by adding ethanol, m.p. 159–162° dec.

Anal. Calcd. for $C_{15}H_{22}N_4O_5$: C, 53.24; H, 6.56; N, 16.56. Found: C, 53.16; H, 6.81; N, 16.40.

2-Acetamido-3-(3-indolyl)-butyric Acids (Acetyl-β-methyltryptophans) (IV).—A solution of 92.9 g. (0.279 mole) of ammonium (3-indolylethylidene)-acetamidomalonate in 93 ml. of water and 93 ml. of pyridine was refluxed for 5 hr. in a nitrogen atmosphere. Ammonium carbonate deposited in the reflux condenser. The solution was diluted with 465 ml. of water and filtered, then acidified with 46.5 ml. of sulfuric acid dissolved in 465 ml. of water. During acidification, the solution was heated sufficiently to prevent the product from separating as an oil, and crystallization was induced by scratching when about 60% of the acid had been added (*p*H 3). Crystallization was allowed to proceed at 0° overnight.

The yield of crystalline acetyl-β-methyltryptophan, isomer A, m.p. 211–215°, was 32.2 g. (44%). This crude material did not give satisfactory yields of the amino acid on hydrolysis. It was dissolved in 64 ml. of warm dimethylformamide and recrystallized by addition of 96 ml. of water. The yield of purified material, m.p. 214–218°, was 25.0 g. (34%). An analytical sample was prepared by dissolving the crude material in ethanol and crystallizing it by adding ethyl acetate, m.p. 216–218°.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.6; H, 6.20; N, 10.78. Found: C, 64.77; H, 6.12; N, 10.63.

The mother liquor, which contained isomer B, was extracted with four 230-ml. portions of ethyl acetate. The ethyl acetate solution was washed with two 115-ml. portions of water and extracted with two 230-ml. portions of 10% sodium bicarbonate solution. The aqueous solution was acidified with 4 *N* sulfuric acid and extracted with three 115-ml. portions of ethyl acetate. The ethyl acetate solution was washed with two 55-ml. portions of water and was concentrated under reduced pressure until a foamy gum, which weighed about 40 g., remained. This crude acetyl-β-methyltryptophan, isomer B, was satisfactory for hydrolysis to the amino acid.

2-Amino-3-(3-indolyl)-butyric Acids (β-Methyltryptophans) (V).—The purified acetyl-β-methyltryptophan (IV), isomer A described above (25.0 g.), was ground in a mortar, then refluxed under nitrogen with 150 ml. of 4 *N* sulfuric acid and 1.5 ml. of 1-octanol until it completely dissolved (about 20 hr.). The crude isomer B of IV described above (approx. 40 g.) was refluxed under nitrogen with 210 ml. of 4 *N* sulfuric acid for 5 hr. In each case, after the reflux period was complete, the sulfuric acid was neutralized (*p*H 8) with 0.4 *N* barium hydroxide. A little 1-octanol was added to prevent foaming, Dry Ice was added to precipitate excess barium ion, and the mixture was heated to boiling. The barium sulfate was filtered from the hot solution and the filtrate was concentrated to approx. 360 ml. under reduced pressure; foaming was controlled with 1-octanol. The warm solution was treated with charcoal and filtered, then concentrated to about 150 ml., at which point the amino acid began to crystallize. The product was allowed to crystallize at 0° overnight, then collected and dried under 0.1 mm. at room temperature. The yield of β-methyltryptophan (V), isomer A, from the first crop, m.p. 245–251° dec. (loses water of crystallization approx. 190°), was 14.3 g. It was recrystallized from 110 ml. of water, yield 11.2 g., m.p. 248–250° dec. An additional 1.7 g. of recrystallized isomer A, m.p. 246–250° dec., was obtained from the second crop. The yield of isomer B, m.p. 236–242° dec., was 20.7 g. It was recrystallized from 300 ml. of water, yield 13.8 g., m.p. 247–251° dec. It appeared that water of crystallization was lost at 0.5 mm. at room temperature.

Treatment of the combined aqueous mother liquors with acetic anhydride and sodium acetate yielded 4.6 g. of acetyl β-methyltryptophan (IV), isomer A, plus some of the noncrystalline isomer B. Much barium was found in these mother liquors by precipitation with sulfuric acid.

Analytical samples were prepared by dissolving the amino acid in glacial acetic acid, precipitating the acetate salt with benzene and converting the salt to the free amino acid by crystallization from water at *p*H 5. The amino acid was then recrystallized one or two times from water and dried 24 hr. at 100° (0.1 mm.) over phosphorus pentoxide; isomer A, m.p. 232–235° dec., 238–242° dec., isomer B, m.p. 237–240° dec., 246–248° dec., mixture m.p. 218–225° dec.

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 66.0; H, 6.45; N, 12.85. Isomer A, found: C, 66.20; H, 6.73; N, 12.58, 12.75. Isomer B, found: C, 66.31; H, 6.48; N, 12.57, 12.96.

α-Naphthylurea Derivatives of the β-Methyltryptophans.—The customary procedure[24] was followed. The sodium salt of the α-naphthylurea derivative of isomer B was only slightly soluble in water, but dissolved upon warming. Both α-naphthylurea derivatives were first obtained as amorphous solids but crystallized when warmed with ethylene dichloride. Analytical samples were recrystallized twice from 2-propanol–water: isomer A, m.p. 191–193° dec., isomer B, m.p. 192–194° dec.

Anal. Calcd. for $C_{23}H_{21}N_3O_3$: C, 71.3; H, 5.46; N, 10.88. Isomer A, found: C, 71.22; H, 5.61; N, 10.61. Isomer B, found: C, 71.62; H, 5.74; N, 10.77.

The melting point was not significantly depressed upon mixing the two isomers, but the infrared spectra (Nujol) showed large differences.

Racemization of β-Methyltryptophan by Acetylation.—To a solution of 0.10 g. of isomer B of β-methyltryptophan (V) (m.p. 244–247° dec.) and 0.5 g. of sodium bicarbonate in 5 ml. of water was added 1.0 ml. of acetic anhydride, and the mixture was agitated and warmed until a clear solution resulted. Sulfuric acid (4 *N*) was added until the solution was strongly acidic, and crystallization was induced by scratching. The yield of isomer A of acetyl β-methyltryptophan (IV), m.p. 214–218° (not depressed upon mixing with an authentic sample), was 33 mg. (28%). The infrared spectrum (potassium bromide pellet) was identical to that of a known sample. When isomer B of β-methyltryptophan was acetylated with the theoretical amount of acetic anhydride in the presence of excess sodium hydroxide, conditions which do not lead to racemization,[16] no solid acetyl derivative was obtained.

Solubility of β-Methyltryptophan Isomers.—A 20-mg. sample of the amino acid was weighed into a small vial and 1.00 ml. of 95% ethanol was added. After 2 days at room temperature (occasional shaking), the ethanol was withdrawn with a hypodermic syringe; the volume withdrawn was used in calculating solubility. The vial was dried in the oven and weighed. The solubility of isomer A was at least 20 mg./ml. The solubility of isomer B was 5.5 mg./ml.; this value was checked by dissolving the solid in hot ethanol (solubility apparently less than 15 mg./ml.) and allowing it to crystallize. The solubility of isomer B was the same in a solution of 20 mg./ml. of isomer A as in pure 95% ethanol.

(3-Indolylethylidene)-acetamidomalonic Acid (III).—An aqueous solution of the ammonium salt of III was acidified

(24) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Thomas Y. Crowell Co., New York, N. Y., 1947, p. 270.

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and extracted with ethyl acetate. A small amount of chloroform was added and crystallization was induced by scratching. An analytical sample was not obtained.

The free acid III was decarboxylated by heating in several solvents, including methyl ethyl ketone, 2-propanol, acetonitrile and pyridine. The yield of crystalline acetyl β-methyltryptophan was always near 30%. Decarboxylation in water or toluene, which did not dissolve the acid III, led to red tar.

URBANA, ILL.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, RESEARCH DIVISION, LEDERLE LABORATORIES, AMERICAN CYANAMID COMPANY]

Vasodilator and Adrenergic Blocking Agents. I. 1,4-Disubstituted Piperazines and Related N-Phenylethylenediamine Derivatives

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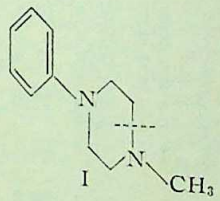
The syntheses and physiological properties of a series of 1,4-disubstituted piperazines and N-phenylethylenediamine derivatives are described. Also a discussion dealing with the importance of the phenyl and pyridylpiperazine nuclei in developing strong adrenergic blocking agents of this type is included.

In recent years a considerable number of compounds exhibiting strong vasodilator or adrenergic blocking action have been described in the literature.[1] However, because of undesirable side effects and poor oral activity, very few of these agents have found therapeutic application in the treatment of peripheral vascular disease. Two classes of compounds which have received considerable attention for their ability to inhibit responses to epinephrine are the β-diaralkylaminoethyl chlorides and the aralkylimidazolines. In our laboratories, pharmacological testing indicates that 1-methyl-4-phenylpiperazine (I) is also an effective vasodilator and adrenergic blocking agent.

To elucidate the structural requirements necessary for activity in this compound, we prepared a series of N-phenylethylenediamine derivatives. These diamines are related to products which would be formed by a scission of the piperazine ring of the active structure[2] I. The diamines were



I

synthesized by the interaction of one molecular equivalent of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride with two molecular equivalents of the appropriate primary or secondary amine in a refluxing water–ethanol solution. Derivatives of a similar nature have been tested as antihistamines.[3,4] The fact that structural similarities exist between adrenergic blocking agents and compounds which antagonize spasmogenic substances, such as acetylcholine and histamine, has been discussed by Burger.[5] As shown in Table I, the simple isosteres derived from the parent compound I where one amino group is substituted by lower alkyls were relatively inactive[6] when compared to Priscoline[7] which was used as a standard. However, a marked increase in vasodilator activity was observed when these substituents were replaced by di-*n*-propyl or benzyl groups.

An extension of this work was the reconstitution of a piperazine ring to include one of the terminal N-atoms of the N-phenylethylenediamine structure. This led to the synthesis of a series of 1-[β-(N-ethyl-N-phenylamino)-ethyl]-4-substituted piperazines which are described in Table II. Preparation of these compounds involved a condensation between the β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 1-substituted piperazines in refluxing ethanol using sodium bicarbonate as an acid acceptor. The biphenylpiperazine analog was synthesized stepwise by condensing the appropriate haloalkylamine with diethanolamine to yield N-ethyl-N′,N′-di-(β-hydroxyethyl)-N-phenylethylenediamine. In the next step, reductive cyclization of the di-(β-hydroxyethyl)-amino portion of the molecule with 4-aminobiphenyl was accomplished in poor yield by subjecting a solution of the two reactants in dioxane over copper chromite to approximately 93 atmospheres of hydrogen for 7 hr. at 250°. An inspection of the activity ratings listed in Table II reveals a sharp change in biological response when the N-methyl, acetyl and carbethoxy groups in the piperazine moiety are replaced by phenyl, 2-pyridyl or 2-(6-methyl)-pyridyl radicals. Based on these findings a study of the scission products of I has by a circuitous route established the importance of not only the phenyl piperazine but also the pyridyl piperazine nucleus as a center of activity. It is also apparent that strong vasodilatation and adrenergic blocking action[8] are obtained when the simple alkyl substituent in I is replaced by a β-(N-ethyl-N-phenylamino)-ethyl chain II. Preliminary studies indicate that compound II is orally active in the test animal.

(1) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 2nd Ed., The Macmillan Co., New York, N. Y., 1955, (Bibliography), pp. 592–595.
(2) W. T. Forsee and C. B. Pollard, THIS JOURNAL, **57**, 1788 (1935).
(3) A. M. Staub, *Ann. Inst. Pasteur*, **63**, 400, 420, 485 (1939).
(4) B. N. Halpern, *Arch. Intern. Pharmacodynamie*, **68**, 339 (1942).
(5) A. Burger, "Medicinal Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, p. 359.
(6) See footnote (a), Table I, for explanation of vasodilator activity.
(7) 2-Benzyl-4,5-imidazoline monohydrochloride.
(8) See footnotes *b* and *c*, Table I, for explanation of adrenergic blocking action.

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TABLE I

$C_6H_5N(C_2H_5)CH_2CH_2R$

R	Yield, %	M.p. or b.p., °C.	Mm.	Empirical formula	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl	Vasodilator[a] activity	Adrenergic blocking action I[b]	D[c]
$-NHCH_3$[h]	48	179–181[d]		$C_{11}H_{20}Cl_2N_2$	52.6	8.0	11.2	28.3	52.4	8.1	11.0	27.9	1+	0	0
$-N(CH_3)_2$[e,h]	60	199–200[d]		$C_{12}H_{22}Cl_2N_2$	54.3	8.3	10.6	26.8	54.5	8.5	10.6	26.2	2+	0	0
$-N(CH_2CH_2OH)_2$[f,h]	58	195–200	1.5	$C_{14}H_{24}N_2O_2$	66.7	9.5	11.1		66.3	10.0	10.8		1+	1+	>1+[g]
$-N(n\text{-}C_3H_7)_2$[f]	28	121–122	0.5	$C_{16}H_{28}N_2$	77.5	11.3	11.3		76.9	11.1	11.7		4+	0	0
$-NHCH_2C_6H_5$	31	157–162	0.5	$C_{17}H_{22}N_2$	80.3	8.7	11.0		80.6	9.0	11.1				
	52	185–188		$C_{17}H_{24}Cl_2N_2$[i]	62.3	7.7	8.6	21.7	62.2	7.7	8.9	21.5	4+	1+	1+

[a] Vasodilator activity was determined in the isolated perfused rabbit ear (all compounds tested as hydrochlorides in 0.1% solution using buffered, perfusion fluid as diluent). The vessels of the ear were constricted by the addition of epinephrine to the perfusion fluid and the increase of venous effluent measured by a drop recorder was the index of vasodilator or adrenergic blocking action. Ratings of 0, 1, 2, 3 or 4+ were assigned to compounds which showed, respectively, 0–5, 6–69, 70–120, 121–170 or >170% of Priscoline activity. [b] When a compound showed strong vasodilator activity in initial screening, the possibility of adrenergic blocking activity was investigated in the anesthetized dog. I represents intensity of adrenergic blockade measured in % inhibition or reversal of intravenous epinephrine pressor response. A rating of 0, 1 or 2+ was assigned to 0–19, 20–50 or 51–100% inhibition. Partial reversal and complete reversal were rated 3+ and 4+, respectively. [c] D represents duration of adrenergic blockade. A rating of 1, 2, 3 or 4+ was assigned to durations of <2, 2–3, 3–4 or >4 hours. [d] Melts with sintering and evolution of gas. [e] Tested as an antihistamine, ref. 4. [f] Compounds submitted for testing as dihydrochlorides in 1.0% aqueous solution. [g] The sign > was used when an experiment was discontinued before duration of action ended. [h] See Experimental. [i] Dihydrochloride prepared by passing hydrogen chloride through ethereal solution of basic material.

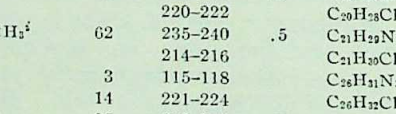
TABLE II

$C_6H_5N(C_2H_5)CH_2CH_2N$ (piperazine) $N-R$

R	Yield, %	M.p. or b.p., °C.	Mm.	Empirical formula	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl	Vasodilator activity[a]	Adrenergic blocking action I[b]	D[c]
$-CH_3$[d]	25	138–142	0.5	$C_{16}H_{25}N_3$[e]	73.0	10.1	17.0		72.7	10.3	16.8		2+	1+	2+
$-COCH_3$	26	192–197	.5	$C_{16}H_{25}N_3O$	69.8	9.1	15.3		69.8	9.4	15.2				
	95[f]	214–216		$C_{16}H_{26}ClN_3O$	61.7	8.1	13.5	11.4	61.7	8.3	13.6	11.4	2+	1+	>1+
$-COOC_2H_5$	49	186–189	.5	$C_{17}H_{27}N_3O_2$	66.9	8.9	13.8		66.6	9.2	13.7				
		200–202		$C_{17}H_{29}Cl_2N_3O_2$	54.0	7.7	11.1	18.8	53.6	8.3	11.5	18.7	2+	0	0
$-C_6H_5$[g]	51	205–210	.2	$C_{20}H_{27}N_3$	77.7	8.7	13.6		77.9	9.1	13.5				
		223–224		$C_{20}H_{28}ClN_3$	69.7	8.1	12.2	10.1	69.4	7.8	12.4	10.2	4+	4+	4+
$-p\text{-}C_6H_4Cl$[g]	59	225–227	.5	$C_{20}H_{27}ClN_3$	69.5	7.8	12.2	10.3	69.8	7.8	12.4	10.2			
		225–228		$C_{20}H_{26}Cl_2N_3$	63.0	7.3	11.0	18.6	62.7	7.3	11.4	18.3	4+	4+	>1+
$-m\text{-}C_6H_4Cl$[h]	39	218–220	.5	$C_{20}H_{27}ClN_3$	69.5	7.8	12.2	10.3	69.6	7.8	12.4	10.6			
		220–222		$C_{20}H_{26}Cl_2N_3$	63.0	7.4	11.0	18.7	62.9	7.1	11.4	18.5	..[q]	1+	>1+
$-p\text{-}C_6H_4OCH_3$[i]	62	235–240	.5	$C_{21}H_{29}N_3O$	74.3	8.6	12.4		74.4	8.8	12.2				
		214–216		$C_{21}H_{30}ClN_3O$	67.2	8.0	11.2	9.7	67.0	8.3	11.0	9.4	4+	1+	>1+
$-C_{12}H_9$[j,g]	3	115–118		$C_{26}H_{31}N_3$	81.0	8.1	10.9		80.8	8.4	11.2				
	14	221–224		$C_{26}H_{32}ClN_3$			10.0	8.4			10.0	8.8	..[k]	..	..
$-C_5H_4N$[l,m]	35	210–215	.5	$C_{19}H_{28}N_4$	73.6	8.4	18.1		73.3	8.4	18.3				
		213–215		$C_{19}H_{27}ClN_4$	65.8	7.8	16.2	10.2	66.0	8.0	16.0	10.4	4+	4+	4+
$-C_6H_6N$[n,g]	63	205–210	.1	$C_{20}H_{28}N_4$	74.1	8.6	17.3		74.1	8.7	17.0				
		212–214		$C_{20}H_{29}ClN_4$	66.6	8.3	15.5	9.8	66.4	8.2	15.8	9.8	4+	2+	>3+
$-C_4H_3N_2O$[o,m]	31	225–230	2.0	$C_{18}H_{25}N_5$	69.1	8.6	22.4		69.2	8.3	22.4				
				$C_{18}H_{26}ClN_5$	61.8	8.0	20.0	10.3	61.6	7.6	20.4	10.0	3+	1+	>1+
$-C_3H_2NS$[p,m]	29	216–218	0.5	$C_{16}H_{22}N_4S$[r]	63.5	7.3	18.5		64.1	7.1	18.2				
		221–224		$C_{16}H_{23}ClN_4S$[s]	56.8	6.8	16.5	10.5	56.6	7.0	16.7	10.8	2+	1+	>2+
C_2H_5 | $-(CH_2)_2NC_6H_5$[g]	38	200–204		$C_{24}H_{40}Cl_4N_4$			10.7	26.7			10.7	26.2	4+	1+	>2+

[a,b,c] See Table I. [d] A general method for preparing these compounds is given in Experimental section. [e] Basic material was acidified with one molar equivalent of hydrochloric acid and submitted for testing in a 1.0% aqueous solution. [f] All hydrochlorides recrystallized from warm ethanol in yields of 90% or better unless otherwise indicated. [g] See Experimental. [h] Intermediate 1-*p*(and *m*)-chlorophenylpiperazine prepared as described by C. B. Pollard and T. H. Wicker, Jr., THIS JOURNAL, 76, 1853 (1954). [i] Intermediate 1-*p*-methoxyphenylpiperazine prepared as described by E. Cerkovnikov and P. Stern, *Arhiv. Kem.*, 18, 12 (1936). [j] 4-Biphenyl. [k] Hydrochloride too insoluble for testing. [l] 2-Pyridyl. [m] 1-Heterocyclic piperazine intermediates prepared according to procedure of M. E. Hultquist and K. L. Howard, U. S. Patent 2,606,906 (August 12, 1952). [n] 2-(6-Methyl)-pyridyl. [o] 2-Pyrimidyl. [p] 2-Thiazolyl. [q] Vasodilator activity data not available. [r] *Anal.* calcd. S, 10.6; found S, 10.6. [s] *Anal.* calcd. S, 9.8; found S, 9.3.

Compounds in Table III were derived from II by keeping the phenylpiperazine portion of the



II, R = $-C_2H_5$; n = 2
III, R = $-H$; n = 2
IV, R = $-C_2H_5$; n = 3

molecule intact while substituents on the terminal N-atom of the β-aminoethyl moiety were varied. Compound III[9] offered a convenient starting point for direct acylation and alkylation as described in the Experimental section. In order to incorporate some of the structural features of Dibenamine[10] in one of these congeners, we condensed the appropriate β-chloroethyldiaralkylamine with 1-phenylpiperazine. This derivative was rated[6] 4+ as a vasodilator but was not considered a strong adrenergic blocking agent.

(9) J. van Alphen, *Rec. trav. chim.*, **56**, 1009 (1937).
(10) β-Chloroethyldibenzylamine hydrochloride.

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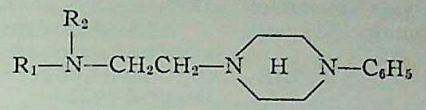
TABLE III



R_1	R_2	Yield, %	M.p. or b.p., °C.	Mm.	Empirical formula	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl	Vasodilator activity[a]	Adrenergic blocking action I^b	D^c
-H	$-C_6H_5$[d,e]	85	175–180	0.5	$C_{18}H_{22}N_2$	76.9	8.2	14.9		76.7	8.1	15.3		4+	4+	2+
$-CH_3$	$-C_6H_5$[f]	90[g]	220–222		$C_{19}H_{26}ClN_3$	68.8	7.8	12.7	10.7	68.4	7.4	13.2	10.6	4+	4+	>1+
$-C_7H_{15}$	$-C_6H_5$	31	235–240	.5	$C_{25}H_{37}N_3$	79.3	9.8	11.1		79.2	10.1	11.2				
			186–188		$C_{25}H_{38}BrN_3$[h]	65.3	8.3	9.1		64.9	8.5	9.1		0	1+	>2+
$-CH_2C_6H_5$	$-CH_3$	49	190–195	.5	$C_{20}H_{27}N_3$	77.7	8.7	13.6		77.4	8.7	13.6				
			243–245		$C_{20}H_{29}Cl_2N_3$	62.8	7.6	11.0	18.6	62.7	7.9	11.1	18.3	3+	1+	2+
$-CH_2C_6H_5$	$-CH_2C_6H_5$	92	88–91		$C_{26}H_{31}N_3$	81.2	8.1	10.9		81.4	7.8	10.7				
			210–212		$C_{26}H_{33}Cl_2N_3$	68.1	7.2	9.2	15.5	68.4	7.1	9.3	15.1	4+	1+	>2+
$-COCH_3$	$-C_6H_5$	80	245–252	.1	$C_{20}H_{25}N_3O$	73.4	8.9	12.9		73.7	8.6	12.6				
		30	168–171		$C_{20}H_{26}ClN_3O$	66.8	7.2	11.7	9.9	66.8	7.2	11.6	9.8	..[i]	4+	>1+
$-COC_6H_4I$[k]	$-C_6H_5$	80	209–211		$C_{25}H_{27}ClIN_3O$[j]	54.8	4.9	7.7	6.5	54.8	5.2	7.8	6.5	4+	2+	>1+
$-(CH_2)_2-N\langle H\rangle N-C_6H_5$	-H	32	195–198		$C_{24}H_{36}ClN_5$	67.1	8.4	16.3		67.3	8.6	16.0		1+	0	0

[a,b,c] See Table I. [d] See ref. 9. [e] See Table II. [f] Preparation of compounds in this table included in the Experimental. [g] See Table II, footnote *f*. [h] *Anal.* calcd. Br, 17.4; found, Br, 18.0. [i] See Table II, footnote *q*. [j] *Anal.* calcd. I, 23.2; found I, 23.2. [k] *o*-Iodobenzoyl.

Several miscellaneous compounds were synthesized to determine the pharmacodynamic effect of chain lengthening IV and piperazine ring substitution. None of these structural changes resulted in activity comparable to II.

Pharmacology.—The authors are grateful to Dr. W. D. Gray and his staff of this Laboratory for their evaluation of these compounds. A pharmacological interpretation of the results obtained in this program will be published elsewhere.

Acknowledgment.—We wish to thank L. Brancone and staff for the analyses contained within.

Experimental[11]

1-Substituted Piperazines.—References for the preparation of these intermediates are given in the footnotes of Table II.

β-Disubstituted Aminoethyl Chloride Monohydrochlorides.—The following preparation of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride is similar to the procedure described by Dehnert.[12] Forty grams (0.24 mole) of N-ethyl-N-(β-hydroxyethyl)-aniline was dissolved in 150 ml. of chloroform, cooled to 0° and treated with thionyl chloride (20 ml.) which was added dropwise with stirring. The reaction mixture was allowed to warm to room temperature and then refluxed for 4 hr. After this time the solvent was removed and the crystalline mass was triturated with dry ether; 48.0 g. (90%). The material obtained in this manner (crude m.p. 125–128°) was suitable for use as an intermediate.

This procedure was also used in the preparation of β-(N-methyl-N-phenylamino)-ethyl chloride monohydrochloride (crude m.p. 100–105°) and β-(N-benzyl-N-methylamino)-ethyl chloride monohydrochloride (crude m.p. 135–138°).

N-Ethyl-N′-methyl-N-phenylethylenediamine Dihydrochloride.—Twenty-six grams (0.117 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride hydrochloride was warmed at the steam-cone with 100 ml. of methylamine in water (25%) for 3 hr. after which time an oily layer separated. Ethanol was added until a clear solution was obtained and the mixture was refluxed an additional 3 hr. The residual oil remaining after concentration was extracted with ether, dried over anhydrous magnesium sulfate and distilled, b.p. 148–150° (20 mm.). The dihydrochloride was formed by adding 10 ml. of concentrated hydrochloric acid in 100 ml. of ethanol to 9.0 g. (0.05 mole) of the basic material. Recrystallization from an ethyl acetate–ethanol solution yielded the pure product.

N,N-Dimethyl-N′-ethyl-N′-phenylethylenediamine Dihydrochloride.—This compound was prepared as described above without distilling the basic product. The residual oil from the reaction was acidified with an excess of concentrated hydrochloric acid and the resulting salt was recrystallized from an ethyl acetate–ethanol solution.

N-Ethyl-N′,N′-di-(β-hydroxyethyl)-N-phenyl-ethylenediamine.—Preparation of the remaining ethylenediamine derivatives in Table I is illustrated by the following procedure. β-(N-Ethyl-N-phenylamino)-ethyl chloride monohydrochloride (13.0 g., 0.058 mole) was refluxed with 6.09 g. (0.058 mole) of diethanolamine and 16.8 g. (0.20 mole) of sodium bicarbonate in 100 ml. of ethanol for 15 hr. After removing the solvent the semi-crystalline residue was made strongly alkaline with 5.0 ml. of concentrated potassium hydroxide solution and extracted with two 50-ml. portions of warm chloroform. The combined extracts were decolorized with Norit and concentrated to a residual oil which was fractionated *in vacuo* to yield 8.0 g. of pure product.

1-[β-(N-Ethyl-N-phenylamino)-ethyl]-4-phenylpiperazine (II).—The preparation of the 1,4-disubstituted piperazines and their salts (Table II) is illustrated by the following example. To a solution of 1-phenylpiperazine (17.8 g., 0.11 mole) in 150 ml. of ethanol was added 20.0 g. (0.11 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 27.7 g. (0.33 mole) of sodium bicarbonate. After a reflux period of approximately 15 hr., the reaction mixture was concentrated to a semi-crystalline mass and then treated as described in the above procedure. The pure product boiled at 205–210° (0.2 mm.), 15.7 g. (51%). On standing this material solidified and could be recrystallized from ether; m.p. 64–66°.

The monohydrochloride was prepared by treating 30.9 g. (0.10 mole) of the basic material with 33.5 ml. (0.099 mole) of 2.98 *N* hydrochloric acid. The salt was then dissolved in 150 ml. of warm water, decolorized with Norit, filtered and concentrated to dryness; 32.0 g. (92%). A pure sample of this product was obtained after two recrystallizations from warm ethanol.

1-[β-(N-Ethyl-N-phenylamino)-ethyl]-4-(4-biphenyl)-piperazine.—A suspension consisting of 25.0 g. (0.10 mole) of N-ethyl-N′,N′-di-(β-hydroxyethyl)-N-phenylethylenediamine, 16.9 g. (0.10 mole) of 4-aminobiphenyl and 5.0 g. of copper chromite catalyst in 75 ml. of dry dioxane was placed in a steel bomb and autoclaved at 250° under 93 atmospheres of hydrogen for 7 hr. After this period of time the dioxane was removed under reduced pressure at 90–100°, leaving a residual oil. This residue was distilled *in vacuo* until a distillate boiling at 190° (0.3 mm.) was obtained. Distillation was then discontinued and the pot residue (2.0 g.) was taken up in 25 ml. of ethanol, decolorized with Norit and filtered. When the filtrate was concentrated to three-quarters of the original volume and allowed to cool, a tan, granular precipitate was deposited. This material (0.329 g.) was collected and air-dried; m.p. 115–118°.

(11) The melting and boiling points are uncorrected.

(12) H. Dehnert, German Patent 650,259.

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A monohydrochloride of this material was formed by treating 0.329 g. of the base with a calculated amount of 2.98 *N* hydrochloric acid in 20 ml. of ethanol. The salt was collected as fine, white needles, m.p. 221–224°.

1-[β-(N-Ethyl-N-phenylamino)-ethyl]-4-[2-(6-methyl)-pyridyl]-piperazine.—Following a procedure developed by Hultquist,[13] a solution consisting of 200.0 g. (1.16 moles) of 1-bromo-6-methylpyridine, 244.8 g. (2.84 moles) of anhydrous piperazine and 171 g. (2.20 moles) of pyridine was heated 6 hr. at 155° in a rocking autoclave. After cooling the autoclave, the brown reaction mass was taken up in water, the aqueous solution made strongly alkaline (1.0 l. of 10 *N* sodium hydroxide) and extracted with ether. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, concentrated and the residual oil was fractionated. The desired product was a yellow oil boiling at 125–127° (1.5 mm.); 133.0 g. (65%).

A suspension of 15.0 g. (0.085 mole) of 1-[2-(6-methyl)-pyridyl]-piperazine, 18.7 g. (0.085 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 21.4 g. (0.255 mole) of sodium bicarbonate in 100 ml. of ethanol was refluxed 15 hr. The desired basic material and monohydrochloride were obtained using the procedure described for the preparation of II.

1,4-Bis-[β-(N-Ethyl-N-phenylamino)-ethyl]-piperazine Tetrahydrochloride.—A solution consisting of 1.82 g. (0.021 mole) of anhydrous piperazine and 9.35 g. (0.043 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride in 75 ml. of absolute ethanol was refluxed 7 hr. The solvent was then removed and the crystalline mass triturated with two 50-ml. portions of acetone to yield 6.0 g. (52%) of the tetrahydrochloride, m.p. 200–204°.

1-β-(N-Phenylamino)-ethyl-4-phenylpiperazine (III).—This substance was prepared by refluxing a mixture of aniline and tri-(β-chloroethyl)-amine hydrochloride for 3 hr. according to process described by van Alphen.[9]

1-[β-(N-Phenyl-N-methylamino)-ethyl]-4-phenylpiperazine.—This derivative was prepared according to the procedure described for II. β-(N-Phenyl-N-methylamino)-ethyl chloride monohydrochloride (11.2 g., 0.066 mole), 10.7 g. (0.066 mole) of 1-phenylpiperazine and 11.0 g. (0.132 mole) of sodium bicarbonate were refluxed in 150 ml. of ethanol for 15 hr. The basic material boiled at 203–208° (0.5 mm.) and was characterized as a monohydrochloride, m.p. 220–222°.

1-[β-(N-Benzyl-N-methylamino)-ethyl]-4-phenylpiperazine.—This substance was prepared as described above from β-(N-benzyl-N-methylamino)-ethyl chloride and 1-phenylpiperazine. The basic material was characterized as a dihydrochloride, m.p. 243–245°.

1-(β-Dibenzylaminoethyl)-4-phenylpiperazine.—β-Dibenzylaminoethyl chloride monohydrochloride (32.3 g., 0.109 mole) was added to 17.6 g. (0.109 mole) of 1-phenylpiperazine, 18.4 g. (0.218 mole) of sodium bicarbonate in 50 ml. of water and 50 ml. of ethanol. The reaction mixture was refluxed 12 hr. and then concentrated to a heavy brown oil which was dissolved in chloroform and decolorized with Norit. Concentration of the chloroform solution yielded a dark-yellow oil which solidified on standing. This waxy material was triturated with water until release of the white, crystalline product was complete; 38.5 g. (92%). An analytical sample was obtained after two recrystallizations from warm ethanol; m.p. 88–91°.

The dihydrochloride was formed by dissolving 4.50 g. (0.012 mole) of the base in 30 ml. of warm ethanol and 2.0 ml. of 11.7 *N* hydrochloric acid. On standing the solution deposited a crystalline material melting at 210–212°.

1-[β-(N-*n*-Heptyl-N-phenylamino)-ethyl]-4-phenylpiperazine.—A suspension consisting of 15.0 g. (0.05 mole) of III and 5.0 g. (0.12 mole) of sodamide in 100 ml. of dry toluene was refluxed 7 hr. At the end of this period of reflux, 9.0 g. (0.05 mole) of *n*-heptyl bromide was added and the mixture refluxed an additional 15 hr. The suspension was filtered hot, the filtrate decolorized with Norit and then concentrated to a heavy, brown oil. Fractionation yielded 6.2 g. (31%) of the crude product, b.p. 220–240° (0.3–0.5 mm.). A pure sample was obtained by refractionation; b.p. 235–240° (0.5 mm.).

A solid monohydrobromide salt of this substance was prepared by treating one molar equivalent of the base with one molar equivalent of hydrobromic acid in ethanol; m.p. 186–188°.

1-[β-(N-Acetyl-N-phenylamino)-ethyl]-4-phenylpiperazine.—Acetic anhydride (16.2 g., 0.159 mole) and 16.9 g. (0.06 mole) of III were mixed in a distilling flask and fractionated *in vacuo*. The acetylated derivative was collected as a viscous, yellow oil boiling at 247–252° (0.1 mm.); 15.7 g. (80%).

A calculated amount of hydrochloric acid was added to 1.69 g. of the base, and the acidic solution was concentrated to a gummy residue. A crystalline material was isolated by taking the residue up in ethanol, treating the solution with decolorizing charcoal, filtering and adding petroleum ether (90–100°) to the filtrate until turbidity. The crystalline precipitate weighed 1.6 g. (93%); m.p. 168–171°.

1-[β-(N-*o*-Iodobenzoyl-N-phenylamino)-ethyl]-4-phenylpiperazine Monohydrochloride.—Eight grams (0.029 mole) of III, 7.6 g. (0.029 mole) of *o*-iodobenzoyl chloride and 100 ml. of toluene were refluxed 2 hr. On cooling the solution deposited a crystalline precipitate which was collected and dried in an evacuated desiccator over solid potassium hydroxide. The salt obtained in this manner weighed 12.5 g. (80%); m.p. 208–210°. Two recrystallizations from warm ethanol yielded a pure salt, m.p. 209–211°.

Di-{β-[1-(4-Phenyl)-piperazinyl]-ethyl}-amine Monohydrochloride.—A suspension consisting of 4.05 g. (0.025 mole) of 1-phenylpiperazine and 4.46 g. (0.025 mole) of di-(β-chloroethyl)-amine hydrochloride was refluxed overnight in 50 ml. of absolute ethanol. The reaction mixture was then diluted with 10 ml. of water and the insoluble, quasi-crystalline material which separated was collected and triturated with two 25-ml. portions of acetone. The platelets obtained after trituration melted at 195–196° with decomposition; 1.5 g. (14%).

The more soluble trihydrochloride was prepared by adding two additional molecular equivalents of hydrochloric acid to the monohydrochloride in ethanol.

Anal. Calcd. for $C_{24}H_{38}N_5Cl_3$: N, 14.0. Found: N, 14.0.

1-(γ-Chloropropyl)-4-phenylpiperazine.—To 70.9 g. (0.340 mole) of phosphorus pentachloride in 200 ml. of chloroform was added portionwise 50.0 g. (0.227 mole) of 1-(γ-hydroxypropyl)-4-phenylpiperazine. During this addition the reaction temperature was maintained at 10–20°. The resulting dark-brown, solution was refluxed for 1 hr. at 95° and then poured on 300.0 g. of ice. The chloroform layer was separated, concentrated to a semi-crystalline mass and the residual material dissolved in warm water. The combined aqueous, acidic solutions were then treated with decolorizing charcoal and evaporated to dryness. When the residue was triturated with acetone 54.1 g. of the crude hydrochloride remained.

Twenty-seven grams (0.983 mole) of the crude salt, dissolved in 50 ml. of water, was then neutralized in the cold with 25% potassium hydroxide solution. Two 50-ml. portions of chloroform were used to extract the organic base which was isolated as a yellow oil after removing the solvent. A pure product was obtained by fractionating the oil and collecting the portion boiling at 146–150° (0.1 mm.).

Anal. Calcd. for $C_{13}H_{19}ClN_2$: C, 65.3; H, 8.0; N, 11.7; Cl, 14.9. Found: C, 65.2; H, 8.2; N, 11.9; Cl, 14.9.

1-[γ-(N-Ethyl-N-phenylamino)-propyl]-4-phenylpiperazine (IV).—Ethylaniline (3.3 g., 0.03 mole) was refluxed with 1.1 g. (0.03 mole) of sodamide in 75 ml. of dry toluene for 15 hr. After this time 6.5 g. (0.03 mole) of 1-(γ-chloropropyl)-4-phenylpiperazine was added and refluxing continued an additional 7 hr. The reaction mixture was then cooled, filtered and concentrated to a brown oil. Fractional distillation *in vacuo* yielded a pure product boiling at 198–205° (0.1 mm.).

Anal. Calcd. for $C_{21}H_{29}N_3$: N, 13.0. Found: N, 12.8.

The monohydrochloride of this material melted at 205–207°.

Anal. Calcd. for $C_{21}H_{30}ClN_3$: C, 70.0; H, 8.3; N, 11.7; Cl, 9.9. Found: C, 69.5; H, 8.3; N, 11.5; Cl, 9.7.

3,5-Dimethyl-1-[β-(N-ethyl-N-phenylamino)-ethyl]-4-phenylpiperazine.—The 2,6-dimethyl-1-phenylpiperazine used as an intermediate was prepared according to a procedure described by Pollard and Wicker.[14] This involved dis-

(13) See Table II, footnote *m*.

(14) C. B. Pollard and T. H. Wicker, Jr., This Journal, **76**, 1853

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tilling water from a mixture of diisopropanolamine and aniline which had been made slightly acidic with concentrated hydrochloric acid. The crude piperazine derivative boiling at 120–125° (1.0 mm.) was used in the next step without further purification.

A suspension consisting of 9.0 g. (0.047 mole) of 2,6-dimethyl-1-phenyl-piperazine, 8.7 g. (0.047 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 10.9 g. (0.13 mole) of sodium bicarbonate in 100 ml. of ethanol was refluxed for 12 hr. The basic derivative was isolated following the procedure used in synthesizing the compounds reported in Table II. This substance boiled at 215–220° (0.4 mm.); 3.9 g. (25%).

Anal. Calcd. for $C_{22}H_{31}N_3$: C, 78.4; H, 9.2; N, 12.5. Found: C, 78.1; H, 9.4; N, 12.2.

The base was not characterized as a hydrochloride because of the hygroscopicity of the salt.

2-Hydroxymethyl-piperazine Dihydrobromide.—This intermediate was prepared by the interaction of 2,3-dibromopropanol-1 and the disodio derivative of N,N′-di-*p*-tosylethylenediamine in refluxing ethanol following the procedure previously described by Bach, Kushner and Williams,[1] m.p. 254–260° dec.

Anal. Calcd. for $C_5H_{14}Br_2N_2O$: C, 21.6; H, 5.0; Br, 57.6; N, 10.1. Found: C, 22.1; H, 5.3; Br, 58.0; N, 9.8.

1,4-Di-[β-(N-Ethyl-N-phenylamino)-ethyl]-2-hydroxymethylpiperazine.—A suspension consisting of 11.8 g. (0.0425 mole) of 2-hydroxymethylpiperazine dihydrobromide, 15.7 g. (0.085 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 42.0 g. (0.50 mole) of sodium bicarbonate in 100 ml. of ethanol was refluxed for 15 hr. After this period of time the reaction mixture was concentrated to a semi-crystalline residue and the desired product was obtained following the procedure outlined for the isolation of compounds described in Table II. This derivative was an oil distilling at 245–250° (1.5 mm.); 4.5 g. (25%).

Anal. Calcd. for $C_{25}H_{38}N_4O$: N, 13.7. Found: N, 13.6. The dihydrochloride of this material was extremely hygroscopic.

(15) F. L. Bach, Jr., S. Kushner and J. H. Williams, THIS JOURNAL, **77**, 6049 (1955).

PEARL RIVER, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

Reactions with Substituted Xanthones. III. Reactions with Hydroxy-9-xanthenones

BY AHMED MUSTAFA AND ORKEDE HASSAN HISHMAT[1]

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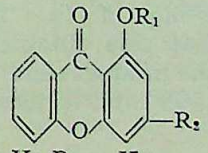
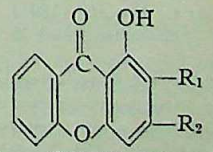
1-Hydroxy-9-xanthenone (Ia) condenses with the acyl and arylsulfonyl chlorides in the presence of aluminum chloride to give 2-acylated-1-hydroxy-9-xanthenones (Table II). The acyl, aroyl and benzenesulfonyl derivatives of Ia and of 1-hydroxy-3-methyl-9-xanthenone (Ii) undergo Fries migration of the acyl group under the influence of aluminum chloride to give the corresponding 2-acyl derivatives (Table II). 1-(β-Naphthoyloxy)-4-benzoyloxy-9-xanthenone and 4-benzoyloxy-1-methyl-10-thiaxanthenone undergo elimination reaction when treated with aluminum chloride under the Fries reaction conditions, yielding the corresponding hydroxy-9-xanthenone and hydroxy-10-thiaxanthenone derivatives, respectively, together with, *e.g.*, β-naphthoic in the case of the naphthoyl ester. Benzoyl esters of 2-hydroxy-3-methyl- and of 2-hydroxy-4-methyl-10-thiaxanthenones proved to be stable toward the action of aluminum chloride under similar conditions. Nencki's reaction offers a convenient method for the preparation of the new 1-hydroxybenzo[b]xanthene-12-one (IIIa), using resorcinol and 2-hydroxy-3-naphthoic acid. The same reaction, using salicylic acid and resacetophenone and/or 2,4-dihydroxybenzophenone, resulted in the formation of Ia in each case together with the removal of the acetyl- and/or the benzoyl group.

Previous work[2] on the study of reactions of substituted xanthenones now has been continued. Hydroxyxanthones, *e.g.*, 1-hydroxy-9-xanthenone (Ia), show the typical reactions of phenols[3] and it should be expected that they undergo the Friedel–Crafts as well as the Fries rearrangement, resulting in the formation of acylated derivatives of hydroxy-9-xanthenones which so far as we are aware[4] have not been synthesized and, meanwhile, constitute important intermediates for the syntheses of naturally occurring substances. Thus, when Ia is treated with acetyl chloride in the presence of aluminum chloride (2.5 moles), using anhydrous nitrobenzene as a solvent, on a steam-bath for three hours and kept aside at room temperature overnight, 2-acetyl-1-hydroxy-9-xanthenone (IIa) is obtained in *ca.* 50% yield. IIa forms a benzoyl derivative with benzoyl chloride in pyridine.

Although substitution may occur in more than one way, we have only been able to isolate one



Ia, R_1 = H; R_2 = H
b, R_1 = $COCH_3$; R_2 = H
c, R_1 = COC_6H_5; R_2 = H
d, R_1 = $COC_6H_4NO_2$-*p*; R_2 = H
e, R_1 = $SO_2C_6H_5$; R_2 = H
f, R_1 = $COC_{10}H_7(\beta)$; R_2 = H
g, R_1 = CH_3; R_2 = H
h, R_1 = $CH_2{\cdot}CH{:}CH_2$; R_2 = H
i, R_1 = H; R_2 = CH_3
j, R_1 = COC_6H_5; R_2 = CH_3
k, R_1 = $COC_6H_4NO_2$-*p*; R_2 = CH_3
l, R_1 = $SO_2C_6H_5$; R_2 = CH_3



IIa, R_1 = $COCH_3$; R_2 = H
b, R_1 = COC_6H_5; R_2 = H
c, R_1 = $COC_6H_4NO_2$-*p*; R_2 = H
d, R_1 = $SO_2C_6H_5$; R_2 = H
e, R_1 = COC_6H_5; R_2 = CH_3
f, R_1 = $SO_2C_6H_5$; R_2 = CH_3

(1) Abstracted from a portion of the dissertation to be submitted by Orkede H. Hishmat in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) A. Mustafa, W. Asker and M. E. E. Sobhy, THIS JOURNAL, **77**, 5121 (1955).

(3) *Cf.* R. C. Elderfield, "Heterocyclic Compounds," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 439.

(4) A perusal of the literature revealed that hardly any work has been done on the migration of esters of condensed heterocyclic ring system phenols, though migration has been reported recently in the case of 1-acetoxy-9-xanthenone (*cf.* ref. 8).

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product (IIa) in a pure form for analytical purposes. The Friedel–Crafts reaction seems to be of preparative nature for the *o*-isomer as we have not been able to demonstrate the presence of the *p*-isomer, since fractional crystallization of the mother liquors leads to difficultly separable mixtures of the probable isomers.

The ready acylation of Ia with acyl chloride and aluminum chloride and the stability of 9-xanthenone toward the same reagent may be attributed to the activating effect of the hydroxyl group.[5] Moreover, it seems very probable that the inhibiting action of the ketone group in xanthone toward Friedel–Crafts acylation nullifies the activating effect of the heterocyclic oxygen atom; a fact which is favored by the observation that xanthene condenses with benzoyl chloride in the presence of aluminum chloride to give 2-benzoylxanthene[6] and the ready acylation of dibenzofuran upon treatment with acetyl chloride and aluminum chloride to give 4-acetyldibenzofuran.[7]

Similar results have now been obtained by Fries rearrangement of 1-acetoxy-9-xanthenone (Ib) with aluminum chloride in hot nitrobenzene (at 130–140° for one hour, then at room temperature overnight). IIa is obtained in *ca.* 55% yield.

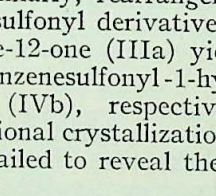
While our investigations were in progress, a publication by Davies and co-workers[8] appeared describing the preparation of IIa, by similar procedure, as an intermediate compound for the preparation of analogs of biologically active chromones, such as khellin. Though the compound IIa reported by them proved to be identical with that prepared by us, there were some points of difference,[9] however, and new material which may be of interest in view of the paucity of information pertaining to this system. IIa was synthesized according to the Friedel–Crafts procedure after Davies and co-workers[8] and we were unable to obtain the unidentified isomeric ketone (m.p. 200°), reported to be obtained in small amount and to depress the m.p. of IIa. The highest m.p. of a substance that was obtained by fractional crystallization of the product contained in the ether extract[10] was 197–198° and it does not depress the m.p. of IIa.

When 1-benzoyloxy-9-xanthenone (Ic) is allowed to undergo the Friedel–Crafts acylation reaction with acetic anhydride, the benzoyl group is eliminated and 2-acetyl-1-hydroxy-9-xanthenone (IIa) is obtained in 71% yield. It appears that the main product is the only one present in appreciable amount. The production of IIa, not contaminated with the 2-benzoyl derivatives[11] (IIb), by treatment with aluminum chloride at 130–140° is unusual in that Ic is isomerized into IIb by treatment with aluminum chloride (see below).

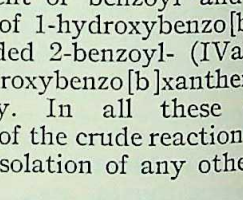
The Friedel–Crafts acylation reaction with Ia now has been extended, using benzoyl and benzenesulfonyl chlorides as acylating agents, under the same experimental conditions described for the acylation of Ia in the presence of aluminum chloride and the corresponding acylated products, believed by analogy to be 2-benzoyl- (IIb) and 2-benzenesulfonyl-1-hydroxy-9-xanthenone (IId), respectively, have been obtained. IIb and IId are obtained in 52 and 58% yield, respectively, and no other isomer was isolated in analytically pure form.

Fries rearrangement of benzoyl (Ic), *p*-nitrobenzoyl (Id) and benzenesulfonyl (Ie) derivatives of Ia, and benzoyl and benzenesulfonyl derivatives (Ij, Il, respectively) of 1-hydroxy-3-methyl-9-xanthenone (Ii), under the same experimental conditions described for the rearrangement of Ib, gave, by analogy, the corresponding 2-aroyl and 2-benzenesulfonyl derivatives (IIb-d and IIe-f, respectively). The *p*-nitrobenzoyl rearranged product IIc is obtained in 17% yield, whereas IIb is obtained in 50% yield. The marked *ortho* shift in the rearrangement of Id may agree with the observation of Baltzly and co-workers,[12] that the *para* shift is discouraged by electron-attracting substitution in the acyl portion. IIb forms a benzoyl derivative with benzoyl chloride in pyridine and a monohydrazone derivative with hydrazine hydrate.

Similarly, rearrangement of benzoyl and benzenesulfonyl derivatives of 1-hydroxybenzo[b]xanthene-12-one (IIIa) yielded 2-benzoyl- (IVa) and 2-benzenesulfonyl-1-hydroxybenzo[b]xanthene-12-one (IVb), respectively. In all these cases, fractional crystallization of the crude reaction product failed to reveal the isolation of any other isomer.



IIIa, R = H
b, R = COC_6H_5
c, R = $SO_2C_6H_5$



IVa, R = COC_6H_5
b, R = $SO_2C_6H_5$

When 1-(β-naphthoyloxy)-9-xanthenone (If) is allowed to undergo Fries rearrangement under similar conditions, the β-naphthoyl group is eliminated and Ia is obtained almost quantitatively.[13] A similar elimination reaction also has been ob-

(5) *Cf.* C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941, p. 360.

(6) J. Heller and St. v. Kostanecki, *Ber.*, **41**, 1324 (1908).

(7) von P. Galewsky, *Ann.*, **264**, 187 (1891).

(8) J. S. H. Davies, F. Scheinmann and H. Susceshitzky, *J. Chem. Soc.*, 2140 (1956).

(9) Davies and co-workers (ref. 8) reported 14% yield of 2-acetyl-1-hydroxy-9-xanthenone by Fries rearrangement of 1-acetoxy-9-xanthenone with aluminum chloride at room temperature for 60 hours and 24% yield at 80° for three hours. The Friedel–Crafts acylation with acetic anhydride in *sym*-tetrachloroethane on the steam-bath for three hours gave 41% yield, whereas 36% yield was reported when acetyl chloride in nitrobenzene at room temperature for 5 days was used.

(10) *Cf.* ref. 8, p. 2142. The m.p. of the crude product after evaporation of the ether was 160–165°.

(11) *Cf.* the same observation in the case of N-phenylsulfonyl-1,8-naphthosultam which undergoes the Friedel-Crafts acetylation reaction to give the 4-acetyl derivative, not contaminated with the 4-benzenesulfonyl derivative (A. Mustafa and M. I. Ali, THIS JOURNAL, **77**, 4593 (1955)).

(12) R. Baltzly, W. S. Ide and A. P. Phillips, *ibid.*, **77**, 2522 (1955).

(13) The elimination of the naphthoyl group and the inhibition of the Fries rearrangement may be attributed to the increase in the size of the acyl group (*cf.* A. H. Blatt, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 342); *cf.* also the formation of free acid and not a ketone on treatment of *o*-cresyl-1-naphthoate with aluminum chloride at 160° (G. S. Saharia, *J. Sci. Indust. Res.*, **13B**, 541 (1954)).

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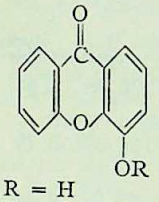
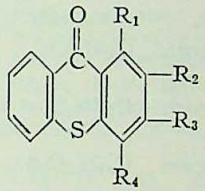
served when 4-benzoyloxy-9-xanthenone (Vb) is subjected to rearrangement with aluminum chloride, under the given conditions, yielding 4-hydroxy-9-xanthenone (Va). We now have found that, whereas elimination reaction takes place when 1-methyl-4-benzoyloxy-10-thiaxanthenone (VIb) is treated with aluminum chloride yielding 1-methyl-4-hydroxy-10-thiaxanthenone (VIa), 3-methyl-2-benzoyloxy-(VId) and 4-methyl-2-benzoyloxy-10-thiaxanthenone (VIf) are recovered almost quantitatively when treated with aluminum chloride under similar conditions. It seems very probable that the benzoyl esters of methyl substituted 2-hydroxy-10-thiaxanthenones (VId, VIf) are comparatively more stable than the benzoyl esters of VIa, Ia, and of Va toward the action of aluminum chloride under the same experimental conditions.



Va, R = H
b, R = COC_6H_5



VIa, $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = OH$
b, $R_1 = CH_3$; $R_3 = R_2 = H$; $R_4 = OCOC_6H_5$
c, $R_1 = R_4 = H$; $R_2 = OH$; $R_3 = CH_3$
d, $R_1 = R_4 = H$; $R_2 = OCOC_6H_5$; $R_3 = CH_3$
e, $R_1 = R_3 = H$; $R_2 = OH$; $R_4 = CH_3$
f, $R_1 = R_3 = H$; $R_2 = OCOC_6H_5$; $R_4 = CH_3$

The observation that as the temperature of the reaction rises the *ortho* shift increases,[14] may agree with the general observation that high temperatures favor the *ortho* shift using nitrobenzene as solvent.[15] Moreover, that the *ortho* shift is favored at high temperatures, leading to an increase in the yield of IIa, may be attributed to the steric factors which do favor an *ortho* shift.[12] The formation of IIa at room temperature in nitrobenzene solution—under which conditions[15] the formation of the *p*-isomer is usually favored—may be paralleled to the known observation that aliphatic esters of *m*-cresol afford *o*-hydroxyketones at room temperature.[16]

Methods of Preparation.—The utilization of the Nencki reaction for the preparation of hydroxy-9-xanthenones after the procedure described by Pankajamani and Seshadri[17] now has been followed for the preparation of the new substituted xanthenone derivative IIIa.[18] Using freshly fused zinc chloride, the reaction has been effected at 230° for five minutes and at 200° for four hours. Making use of the separation of the 3-hydroxy isomer by its ready solubility in sodium carbonate,[17] does not reveal the presence of the other isomer. IIIa is insoluble in aqueous sodium carbonate, but gives an insoluble yellowish orange sodium salt when treated with cold aqueous sodium hydroxide solution, and is slightly soluble on warming. Acidification of its alkaline solution regenerates IIIa almost quantitatively. It gives a brownish color with alcoholic ferric chloride solution and forms with benzoyl or benzenesulfonyl chlorides in pyridine the corresponding derivatives.

Aroylation of the hydroxyl group in the hydroxy-9-xanthenones, used in this investigation, has been accomplished by means of the corresponding aroyl chloride in pyridine. For the acetylation reaction acetic anhydride in the presence of fused sodium acetate is used. VIb is prepared by the action of benzoyl chloride and alkali on VIa.

VIc and VIe were prepared according to the method of Sen and Sen-Gupta[19] and were reported to have m.p. 210–212° for VIc and 190° for VIe. However, the samples of VIc and VIe in our hands have m.p. 321–322° and 273–274°, respectively, and give the correct analytical values. They are partially soluble in hot aqueous sodium hydroxide solution and form readily the corresponding benzoyl derivatives VId and VIf.

Attempts to prepare acylated derivatives of Ia by condensing salicylic acid with resacetophenone, under the same conditions described for the condensation of salicyclic acid with resorcinol, resulted in elimination of the acetyl group and the formation of Ia. The same result has been obtained when 2,4-dihydroxybenzophenone was used for resacetophenone. The elimination reaction, observed in the case of resacetophenone and 2,4-dihydroxybenzophenone, has been observed when they were treated, independently, with fused zinc chloride under the same experimental conditions described for the preparation of Ia; resorcinol was isolated in every case (identified as the monobenzoyl derivative), together with marked smell of acetic acid in the case of resacetophenone and the isolation of benzoic acid in the case of 2,4-dihydroxybenzophenone.

Ia now has been further identified by preparing the corresponding methyl ether Ig by the action of dimethyl sulfate in the presence of anhydrous potassium carbonate on an acetone solution of Ia.[20] Similarly, the allyl ether of 1-hydroxy-9-xanthenone (Ih) has been obtained by the action of allyl bromide on an acetone solution of Ia in the presence of anhydrous potassium carbonate. The rearrangement of Ih is now under investigation.

Experimental

Preparation of 1-Hydroxybenzo[b]xanthene-12-one (IIIa).—A mixture of 6.8 g. of 3-hydroxy-2-naphthoic acid, 5 g. of resorcinol and 10 g. of freshly fused zinc chloride was heated at 230° (metal-bath temperature) and maintained at that temperature for five minutes to bring it to a molten

(14) *Cf.* the rise in the yield of IIa from 14% at room temperature to 55% at 130–140°.

(15) *Cf.* K. W. Rosenmund and W. Schnurr, *Ann.*, **460**, 56 (1928); A. H. Blatt, *Chem. Revs.*, **27**, 429 (1940); "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 342; M. R. Bhatt and N. M. Shah, *J. Indian Chem. Soc.*, **33**, 318 (1956).

(16) C. E. Coulthard, J. Marshall and F. L. Pyman, *J. Chem. Soc.*, 280 (1930); R. Baltzly and A. Bass, THIS JOURNAL, **55**, 4292 (1933).

(17) K. S. Pankajamani and T. R. Seshadri, *J. Sci. Industr. Res.*, **13B**, 396 (1954).

(18) For the structure of IIIa, *cf.* the formation of benzo[b]xanthene-12-one by the condensation of 2-iodo-3-naphthoic acid with sodium phenate, followed by ring closure (von W. Dilthey and F. Quint, *J. prakt. Chem.*, **141**, 306 (1934)); *cf.* also E. Strohbach, *Ber.*, **34**, 4136 (1901), for the preparation of the 2-methyl substituted derivative.

(19) R. N. Sen and S. C. Sen-Gupta, *J. Indian Chem. Soc.*, **6**, 267 (1929).

(20) The same procedure has been followed by K. V. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **26A**, 288 (1947); *C. A.*, **42**, 3393 (1948), for the preparation of the methyl ether of euxanthone.

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TABLE I

ESTERS OF HYDROXYXANTHENONES

Ester	M.p.,[a] °C.	Yield, %	Color with H_2SO_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Id	231	87	Yellow	$C_{20}H_{11}O_6N$	66.48	66.39	3.04	3.14	..	..	3.88	3.92
Ie	148	81	Yellow[b]	$C_{19}H_{12}O_5S$	64.77	64.88	3.41	3.56	9.09	8.30	..	..
If	212–213	72	Canary-yellow	$C_{24}H_{14}O_4$	78.68	78.21	3.82	3.59	..	..	..	..
Ij	187–188	90	Yellow	$C_{21}H_{14}O_4$	76.36	75.87	4.24	4.11	..	..	..	..
Ik	236	85	Yellow	$C_{21}H_{13}O_6N$	67.20	67.09	3.46	3.91	..	..	3.73	4.04
Il	201	88	Yellow	$C_{20}H_{14}O_5S$	65.57	65.74	3.82	3.82	8.75	8.86	..	..
IIIb	203	78	Blood-red	$C_{24}H_{14}O_4$	78.68	78.62	3.82	3.75	..	..	..	..
IIIc	192	75	Red-violet	$C_{23}H_{14}O_5S$	68.65	67.77	3.48	3.61	7.95	7.97	..	..
VId	182	77	Orange-yellow[b]	$C_{21}H_{14}O_3S$	72.83	71.89	4.05	3.98	9.25	8.34	..	..
VIf	179–180	80	Orange[b]	$C_{21}H_{14}O_3S$	72.83	72.77	4.05	4.32	9.25	9.23	..	..

[a] Melting points are uncorrected. [b] The color is accompanied with green fluorescence.

TABLE II

2-ACYLATED-9-XANTHENONES

Xanthenone deriv.	Reaction product	Method of prepn.	M.p.,[a] °C.	Yield, %	Solvent for crystn.	Color with H_2SO_4	Color with $FeCl_3$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ia	IIa	A	202–203	50	1	Olive green	Red-brown	$C_{15}H_{10}O_4$	70.87	70.89	3.94	4.17
Ib[b]		B	202–203	55	1							
Ia	IIb	A	178	52	1	Green	Red-brown	$C_{20}H_{12}O_4$	75.95	75.57	3.79	3.86
Ic[c]		B	178	50	1							
Ia	IId	A	239	58	1	Yellow, green fluor.	Red-brown	$C_{19}H_{12}O_5S$	64.77	65.05	3.41 9.09[e]	3.67 8.61[e]
Ie		B	239	56	1							
Id	IIc	B	263–264	71	2	Yellow	Brown	$C_{20}H_{11}O_6N$[d]	66.48	66.18	3.05	2.88
Ij	IIe	B	175–176	58	3	Brown-yellow	Olive green	$C_{21}H_{14}O_4$	76.36	75.80	4.24	4.18
Il	IIf	B	208–209	60	1	Green	Olive green	$C_{20}H_{14}O_5S$	65.57	65.59	3.83 8.74[e]	3.67 8.26[e]
IIIb	IVa	B	261–262	54	1	Orange-red	Pale brown	$C_{24}H_{14}O_4$	78.69	78.62	3.83	3.89
IIIc	IVb	B	278	56	2	Blood-red	Pale brown	$C_{23}H_{14}O_5S$	68.66	68.12	3.48 7.96[e]	3.45 7.98[e]

[a] Melting points are uncorrected. [b] Michael (*Amer. Chem. J.*, 5, 94 (1883)). [c] *Cf.* ref. 21. [d] Calcd.: N, 3.88. Found: N, 3.71. [e] Sulfur, %. [f] 1, benzene; 2, acetic acid; 3, ethyl alcohol.

state. Then the temperature was brought down to 200° and maintained for four hours. The product was repeatedly washed with hot water and the residue was ground up with a solution of sodium carbonate. The insoluble residue was treated with aqueous sodium hydroxide solution (10%) and the sodium salt of IIIa separated out. It was filtered off, suspended in water containing concentrated hydrochloric acid enough for acidification and the reaction mixture was boiled for 10 minutes. IIIa separated out as a dirty-yellow mass. It crystallized from acetone in the form of yellow needles, m.p. 307°, yield *ca.* 27%.

Anal. Calcd. for $C_{17}H_{10}O_3$: C, 77.86; H, 3.81. Found: C, 77.56; H, 3.68.

An acetone solution of IIIa gave a brownish color with alcoholic ferric chloride solution. IIIa is soluble in acetone and hot chloroform, but difficultly soluble in most of the common organic solvents; it gives deep reddish orange color with concentrated sulfuric acid, and is insoluble in hot aqueous sodium carbonate solution.

Acidification of the sodium carbonate extract resulted in the separation of a small amount of an unidentified substance.

Preparation of VIc and VIe.—Crude VIc, obtained after pouring the reaction[19] mixture into ice-cold water, was washed with 40 ml. of 10% aqueous sodium hydroxide and was then suspended in dilute hydrochloric acid. The resulting yellow solid, which was thoroughly washed with water and dried, was crystallized from acetic acid; yield 31% of yellow crystals, m.p. 321–322°.

Anal. Calcd. for $C_{14}H_{10}O_2S$: C, 69.42; H, 4.13; S, 13.22. Found: C, 69.02; H, 3.98; S, 13.65.

VIe, obtained in 37% yield, melted at 273–274°. *Anal.* Calcd. for $C_{14}H_{10}O_2S$: C, 69.42; H, 4.13; S, 13.22. Found: C, 69.17; H, 4.11; S, 13.26.

They were soluble in hot chloroform, hot acetic acid, but sparingly in cold alcohol. They were insoluble in aqueous sodium carbonate, but were partially soluble in hot aqueous sodium hydroxide. They gave with concentrated sulfuric acid a deep orange color.

Preparation of Esters of Hydroxyxanthenones and Hydroxy-10-thiaxanthenones.—A solution of 0.005 mole of the hydroxy-9-xanthenone in 30 ml. of freshly distilled pyridine was treated with 0.006 mole of the acyl chloride: namely, benzoyl, *p*-nitrobenzoyl, β-naphthoyl and benzenesulfonyl chlorides, respectively. The reaction mixture was heated for one hour (steam-bath), cooled, and the crystals that separated were filtered off and washed with cold alcohol.

The aroyl derivatives of hydroxy-10-thiaxanthenones were prepared by treating a solution of 0.003 mole of the thiaxanthenone derivative in aqueous sodium hydroxide (10%) with 0.006 mole of benzoyl chloride (Schotten-Baumann). The reaction mixture was shaken vigorously at room temperature for 20 minutes, cooled and the separated solid was collected by filtration.

The properties of the above new aroyl and benzene-sulfonyl derivatives are recorded in Table I. They were generally soluble in hot common solvents, formed colorless crystals and were crystallized readily from a mixture of ethyl alcohol and chloroform.

2-Acylated-9-xanthenones. Method A. General Friedel-Crafts Procedure.—In all experiments described in Table II, 0.01 mole of 1-hydroxy-9-xanthenone[17] (Ia) and 0.025 mole of aluminum chloride were used. A solution of Ia in 25 ml. of freshly distilled nitrobenzene and 0.02 mole of the acyl chloride was treated with aluminum chloride in portions as rapidly as it dissolved. The reaction mixture was heated for three hours (steam-bath) and kept aside at room temperature overnight. It was poured into 150 ml. of ice-water containing 25 ml. of concentrated hydrochloric acid, and steam distilled. The solid residue was then extracted with hot petroleum ether (b.p. 100–120°). Concentration

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of the petroleum ether extract, by slow evaporation, gave the 2-acyl derivative of Ia which was crystallized from the solvent specified in Table II.

In the case of 2-acetyl-1-hydroxy-9-xanthenone (IIa) the crude product, after evaporation of the petroleum ether, melted at 180–185°. Fractional crystallization of the 2-substituted acyl derivatives (*cf.* Table II) did not raise the m.p.

IIa-d, when treated with cold aqueous sodium hydroxide solution, formed the corresponding deep yellow sodium salt. They formed yellow crystals which were soluble in hot benzene, but sparingly in alcohol, ether and light petroleum (b.p. 40–60°).

Identification of IIa was carried out by m.p. and mixed m.p. determinations with authentic specimens of IIa and of its 2,4-dinitrophenylhydrazone derivative.[8]

Benzoylation of 0.2 g. of IIa with 0.4 g. of benzoyl chloride and 10 ml. of freshly distilled pyridine, as described above, gave a colorless solid on cooling. It was crystallized from alcohol, m.p. 168°, in almost quantitative yield. 2-Acetyl-1-benzoyloxy-9-xanthenone gave no color with alcoholic ferric chloride and developed a yellow color with slight green fluorescence with concentrated sulfuric acid.

Anal. Calcd. for $C_{22}H_{14}O_5$: C, 73.74; H, 3.91. Found: C, 73.57; H, 3.88.

2-Benzoyl-1-benzoyloxy-9-xanthenone, obtained similarly from 0.65 g. of IIb, 0.85 g. of benzoyl chloride and 25 ml. of pyridine, separated from a mixture of ethanol and chloroform in nearly colorless crystals, m.p. 212–213°, yield 86%. It gave a yellow color with concentrated sulfuric acid and was soluble in hot chloroform and benzene, but sparingly in alcohol.

Anal. Calcd. for $C_{27}H_{16}O_5$: C, 77.14; H, 3.81. Found: C, 76.73; H, 3.72.

A solution of 0.5 g. of IIb in 30 ml. of ethyl alcohol was treated with 4 ml. of hydrazine hydrate. The reaction mixture was refluxed on the steam-bath for 6 hours. The solid, obtained on cooling, was collected and crystallized from ethyl alcohol in canary yellow crystals, m.p. 160–161°. The yield was almost quantitative.

Anal. Calcd. for $C_{20}H_{14}O_3N_2$: C, 72.72; H, 4.24; N, 8.48. Found: C, 72.46; H, 4.50; N, 8.80.

The monohydrazone derivative of IIb was soluble in hot ethyl alcohol, and benzene, but slightly in light petroleum. It gave reddish brown color with alcoholic ferric chloride and yellowish orange color with concentrated sulfuric acid, and formed a canary yellow insoluble sodium salt when treated with hot aqueous sodium hydroxide.

2-Acylated-9-xanthenones. Method B. Fries Rearrangement with Aluminum Chloride of Acyl, Aroyl and Benzenesulfonyl Derivatives of Hydroxy-9-xanthenones.—The rearrangement of Ib-e, Ij, Il and IIIb-c was carried out by heating a solution of 0.01 mole of each in 25 ml. of nitrobenzene and 0.025 mole of aluminum chloride in an oil-bath maintained at 130–140° (bath-temp.) for one hour. The reaction mixture was kept aside at room temperature overnight. The dark colored reaction mixture was cooled, decomposed with 100 ml. of cold dilute hydrochloric acid, and steam distilled. The solid residue so obtained was worked out as described above in the Friedel–Crafts procedure. The properties of the reaction products (IIa–d, IIe–f and IVa–b) are recorded in Table II. When treated with cold aqueous sodium hydroxide (10%) they gave the corresponding yellow colored sodium salt.

When 0.5 g. of IIe, obtained by method B, was treated with benzoyl chloride in pyridine in the usual procedure, 3-methyl-1-benzoyloxy-2-benzoyl-9-xanthenone was obtained in 74% yield as colorless crystals from ethyl alcohol–chloroform mixture, m.p. 214–215°.

Anal. Calcd. for $C_{28}H_{18}O_5$: C, 77.41; H, 4.14. Found: C, 77.06; H, 4.23.

3-Methyl-1-benzoyloxy-2-benzenesulfonyl-9-xanthenone was similarly obtained by the action of benzoyl chloride on 0.5 g. of IIf in pyridine. The benzoyl derivative formed colorless crystals from ethyl alcohol–chloroform mixture, m.p. 239–240°.

Anal. Calcd. for $C_{27}H_{18}O_6S$: C, 68.94; H, 3.83; S, 6.81. Found: C, 68.21; H, 3.93; S, 7.39.

When 1 g. of each of If, Vb[21] and VIb,[19] was treated with aluminum chloride at 130–140°, under the same experimental conditions described above for the Fries rearrangement, followed by working out the reaction products in a similar manner, Ia, Va and VIa were obtained in 82, 87 and 79% yield, respectively. β-Naphthoic acid was isolated in appreciable amounts (m.p. and mixed m.p. determination) in the case of If.

VId and VIf were recovered almost quantitatively when 1 g. of each was treated with aluminum chloride under the same experimental conditions.

Action of Acetic Anhydride on Ic in Presence of Aluminum Chloride.—A mixture of 1.1 g. of Ic, 25 ml. of nitrobenzene and 1.1 g. of freshly distilled acetic anhydride was treated portionwise with 1.2 g. of aluminum chloride. The reaction mixture temperature was maintained at 80° during the addition of aluminum chloride. It was raised slowly to 130–140° (bath-temp.) and the reaction mixture was kept at that temperature for one hour. It was kept aside at room temperature overnight, and was then worked out as described above in the general Friedel–Crafts procedure. IIa was obtained in 71% yield, and was identified by m.p. and mixed m.p. determination with an authentic specimen of IIa,[8] and of 2-acetyl-1-benzoyloxy-9-xanthenone.

Fractional crystallization of the crude product obtained by evaporation of the mother liquors did not reveal the presence of any other isomer. Melting point of the crude product, obtained after evaporation of the petroleum ether, was 193°.

Action of Zinc Chloride on: (a) A Mixture of Salicylic Acid and Resacetophenone.—A mixture of 5 g. of resacetophenone, 5 g. of salicylic acid and 10 g. of freshly fused zinc chloride was heated to 200° and maintained at that temperature for 5 minutes. Then the temperature was brought down to 180° and maintained for four hours. On working up the reaction product as described for the preparation of IIIa, yellow crystals of Ia were obtained in 22% yield. Identification was carried out by m.p. and mixed m.p. determination.

Ia was further identified by preparation of its methyl ether (Ig): To a solution of 1.5 g. of Ia in 50 ml. of dry acetone was added 2 ml. of dimethyl sulfate and 5 g. of anhydrous potassium carbonate. The reaction mixture was refluxed on a steam-bath for six hours and cooled. It was poured into ice-cold water and the solid so obtained was collected by filtration, washed thoroughly with cold water, and crystallized from petroleum ether (b.p. 100–120°). It formed colorless crystals, m.p. 136°, identified by m.p. and mixed m.p. determination with an authentic specimen of Ig.[22]

Five grams of resacetophenone was heated with 10 g. of fused zinc chloride at 130–140° under the same experimental conditions described above. The alkaline extract of the reaction mixture was treated with excess of benzoyl chloride (Schotten–Baumann) and the colorless solid so obtained was crystallized from ethyl alcohol; identified as benzoyl resorcinol (m.p. and mixed m.p. with an authentic sample). A marked smell of acetic acid was noticed on decomposition of the reaction mixture.

(b) A Mixture of Salicylic Acid and 2,4-Dihydroxybenzophenone.—Similarly, a mixture of 5 g. of 2,4-dihydroxybenzophenone, 5 g. of salicylic acid and 10 g. of fused zinc chloride was heated as described in the case of resacetophenone. On working up the reaction mixture, Ia was obtained in *ca.* 23% yield.

A solution of 1.6 g. of Ia (obtained after the above procedure) in 50 ml. of dry acetone, was treated with 2.2 g. of allyl bromide and 5 g. of anhydrous potassium carbonate. The reaction mixture was refluxed for eight hours and cooled. It was poured into ice-cold water, extracted with ether, dried and evaporated. The solid residue (1.1 g.) so obtained was crystallized from petroleum ether (b.p. 80–100°) in colorless crystals, m.p. 86–87°. 1-Allyloxy-9-xanthenone (Ih) was easily soluble in benzene, but sparingly in light petroleum. It gives yellow-brown color with concentrated sulfuric acid.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.19; H, 4.76. Found: C, 76.08; H, 4.98.

2,4-Dihydroxybenzophenone (5 g.) was treated with 10 g. of fused zinc chloride as described in the case of resacetophenone. The cold reaction mixture was poured into ice-

(21) E. König and St. v. Kostanecki, *Ber.*, **27**, 1996 (1894).

(22) J. Nagbor, *Rec. trav.*, **29**, 1883 (1910).

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cold dilute hydrochloric acid and the solid so obtained was extracted with cold aqueous sodium carbonate solution. The insoluble portion was benzoylated with benzoyl chloride in the presence of sodium hydroxide solution and benzoylresorcinol was obtained (1.1 g.).

Acidification of the carbonate solution followed by crystallization of the separated product gave colorless crystals (0.9 g.), identified as benzoic acid.

GIZA, CAIRO, EGYPT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Researches on Pyrimidines. Certain Derivatives of 2-Propylpyrimidine[1]

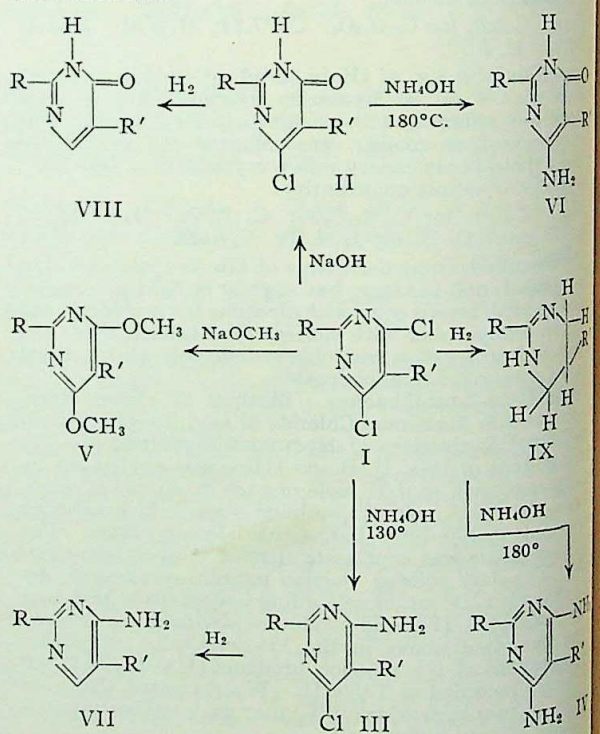
BY HENRY R. HENZE AND STANLEY O. WINTHROP[2]

RECEIVED OCTOBER 8, 1956

Series of 2-propyl-4,6(1,5)-tetrahydropyrimidinediones and 2-propyl-4,6-dichloropyrimidines have been synthesized. The dichloropyrimidines are useful starting materials for the synthesis of various pyrimidine derivatives, some of which are described.

In continuation of our investigation of the synthesis of pyrimidine derivatives through condensation of amidines with malonic esters,[3,4] we have now studied the interaction of butamidine with ethyl malonate and five ethyl alkylmalonates. The 2-propyl-4,6(1,5)-tetrahydropyrimidinediones thus obtained were converted into 4,6-dichloro derivatives by treatment with phosphorus oxychloride. With the appropriate reagents and reaction conditions, as shown below, the 4,6-dichloropyrimidines (I) yielded the corresponding 6-chloro-4(3)-dihydropyrimidones(II), 4-amino-6-chloropyrimidines (III), 4,6-diaminopyrimidines (IV) and 4,6-dimethoxypyrimidines (V). These derivatives in their turn gave 6-amino-4(3)-dihydropyrimidones (VI), 4-aminopyrimidines (VII) and 4(3)-dihydropyrimidones (VIII).

Catalytic hydrogenolysis of the monochloropyrimidines took place with ease. It was noted, however, that in each case there was an amino or keto substituent present which could have the effect of stabilizing the ring against reduction. Catalytic hydrogenolysis of the dichloropyrimidines did not stop at dechlorination but proceeded with the reduction of the pyrimidine ring. Instead of the anticipated 2-propylpyrimidine, the catalytic hydrogenolysis of 2-propyl-4,6-dichloropyrimidine, in the presence of barium oxide,[5] gave a product which analyzed for a 2-propyltetrahydropyrimidine[6] hydrochloride (IX). A search of the literature reveals little on the chemistry of partially reduced pyrimidines and usually the latter have been prepared directly through condensation reactions, rather than as a direct result of hydrogenation of pyrimidines. Thus, Aspinall[7] has reported the preparation of 2-methyl-1,4,5,6-tetrahydropyrimidine by the interaction of trimethylenediamine and ethylacetate. Naff and Christensen[8] have described a dihydrobenzopyrimidine and its conversion by catalytic dehydrogenation to the more stable benzopyrimidine. Attempts to convert our tetrahydropyrimidine to 2-propylpyrimidine by a similar catalytic dehydrogenation were not successful.



Experimental

Butamidine Hydrochloride.—The procedure utilized followed that of Derby's modification[9] of the method of Pinner[10] for the preparation of amidines. A solution was prepared containing 345 g. (5 moles) of butyronitrile, 230 g. (5 moles) of absolute ethanol, 600 ml. of dry ether and 182.5 g. (5 moles) of dry hydrogen chloride. It was stirred for four days at 0°. After standing for two weeks in the cold the imido ester hydrochloride separated and was removed by filtration. The filtrate, on standing in the cold an additional week, produced a second crop of crystals. The initial crop of imido ester was dissolved in 300 ml. of absolute ethanol, 1000 ml. of 10% alcoholic ammonia was

(1) From the Ph.D. dissertation of Stanley O. Winthrop, University of Texas, 1952.

(2) Humble Oil and Refining Co. Fellow in Chemistry, 1951–1952.

(3) H. R. Henze, W. J. Clegg and C. W. Smart, *J. Org. Chem.*, **17**, 1320 (1952).

(4) H. R. Henze and J. L. McPherson, *ibid.*, **18**, 653 (1953).

(5) After this work had been completed, a paper by N. Whittaker (*J. Chem. Soc.*, 1565 (1950)) came to our attention. This investigator showed that catalytic hydrogenolysis of 2,4,6-trichloropyrimidine in the presence of sodium acetate took place with the uptake of five equivalents of hydrogen indicating the formation of a tetrahydropyrimidine, while in the presence of magnesium oxide, only three equivalents of hydrogen were taken up, and pyrimidine was isolated as a mercuric chloride addition complex.

(6) The position of the remaining double bond has not been proven. The compound is most likely a 1,4,5,6-tetrahydropyrimidine.

(7) (a) S. R. Aspinall, THIS JOURNAL, **62**, 2160 (1940); (b) G. S. Skinner and P. R. Wunz, *ibid.*, **73**, 1314 (1951).

(8) M. B. Naff and B. E. Christensen, *ibid.*, **73**, 1372 (1951).

(9) I. H. Derby, *Am. Chem. J.*, **39**, 437 (1908).

(10) A. Pinner and F. Klein, *Ber.*, **11**, 1484 (1878).

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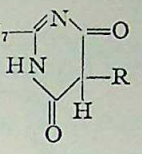
TABLE I

2-PROPYL-4,6(1,5)PYRIMIDINEDIONES C_3H_7



R	M. p., °C	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Hydrogen	[a]	71	$C_7H_{10}N_2O_2$	54.33	54.30	6.53	6.81
Methyl	[a]	73.5	$C_8H_{12}N_2O_2$	57.14	57.45	7.14	6.87[d]
Ethyl[b,c]	[a]	85.5	$C_9H_{14}N_2O_2$	59.32	59.15	7.74	7.61
Propyl[b]	[a]	72	$C_{10}H_{16}N_2O_2$	61.19	61.08	8.22	7.70
Butyl[b]	[a]	94	$C_{11}H_{18}N_2O_2$	62.82	62.67	8.61	8.52
Amyl[b]	[a]	69.5	$C_{12}H_{20}N_2O_2$	64.27	64.36	8.99	8.84
Hexyl	[a]	75.5	$C_{13}H_{22}N_2O_2$	65.51	65.30	9.30	9.45[e]

[a] Does not melt below 300° and decomposes slowly at that temperature. [b] Analysis by Clark Microanalytical Laboratories, Urbana, Ill. [b] This compound has been previously reported by F. G. P. Remfry (*J. Chem. Soc.*, 99, 620 (1906)), who prepared it by interaction of ethylmalonamide and ethyl ethylmalonate. [d] Calcd.: N, 16.67. Found: N, 16.89. [e] Calcd.: N, 11.75. Found: N, 11.71.

5-Alkyl-2-propyl-4,6(1,5)-pyrimidinediones (Table I).—The pyrimidinediones were prepared by interaction of butamidine hydrochloride and ethyl alkylmalonates.[3,4]

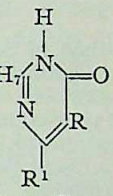
5-Alkyl-2-propyl-4,6-dichloropyrimidines (Table III).—The dichloropyrimidines were prepared from interaction of the pyrimidinediones and phosphorus oxychloride.[3]

5-Alkyl-6-chloro-2-propyl-4(3)-pyrimidones (Table II).—The chloropyrimidones were prepared by the controlled hydrolysis of the corresponding dichloropyrimidines. The 5-alkyl-4,6-dichloro-2-propylpyrimidine (0.05 mole) was refluxed for approximately 48 hr. with 4 g. (0.1 mole) of sodium hydroxide in 70 ml. of water; the reaction was considered complete when all the dichloropyrimidine had gone into solution. Upon cooling, the solution was acidified by addition of glacial acetic acid and the chloropyrimidone precipitated. The product was purified by recrystallization from aqueous ethanol or benzene.

In the case of the 5-hexyl derivative, hydrolysis with sodium hydroxide gave very poor yields of product, and the major portion of the starting material was recovered. It was found that acid hydrolysis gave better yields. A mixture of 3.5 g. (0.015 mole) of 4,6-dichloro-5-hexyl-2-propylpyrimidine, 20 ml. of concentrated hydrochloric acid and 50 ml. of water was refluxed for 12 hr. During this period, the dichloropyrimidine layer disappeared and a solid settled out on the sides of the flask. Upon cooling, an additional amount of solid separated. The solid product was removed by filtration and purified by recrystallization from methanol.

TABLE II

2-PROPYL-4(3)-PYRIMIDONES C_3H_7

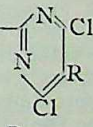


R	R^1	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Hydrogen	Cl	168–169	72	$C_7H_9ClN_2O$	16.23	16.48				
Methyl	Cl	170–171	75	$C_8H_{11}ClN_2O$	15.02	15.11	51.45	50.90	5.89	5.98
Hexyl[a]	Cl	114–115	46	$C_{13}H_{21}ClN_2O$	10.89	10.78				
Hydrogen	NH_2	293–295 d.	32	$C_7H_{11}N_3O$	27.47	27.32	57.45	57.48	7.78	7.85
Methyl	NH_2	209–210	64	$C_8H_{13}N_3O$	25.15	25.27				
Hexyl	NH_2	199–200	81	$C_{13}H_{23}N_3O$	17.70	17.95				
Hydrogen[b]	H	106–107	25	$C_7H_{10}N_2O$	20.31	20.62				
Methyl	H	145–146	81	$C_8H_{12}N_2O$	18.41	18.12	63.12	62.70	7.94	7.86
Hexyl[b]	H	65–67	72	$C_{13}H_{22}N_2O$	12.54	12.82				

[a] This compound was prepared by acid hydrolysis of the dichloropyrimidine. [b] These compounds were purified by vacuum sublimation.

TABLE III

4,6-DICHLORO-2-PROPYLPYRIMIDINES C_3H_7



R	B.p. °C.	Mm.	Yield, %	$n^{20}D$	d^{20}_4	M. R. Calcd.	M. R. Found	Formula	Chlorine, % Calcd.	Chlorine, % Found
Hydrogen	98–99	12	65	1.5206	1.2435	46.82	46.73	$C_7H_8Cl_2N$	37.18	36.75
Methyl[a]	100–101	5	61	1.5203[b]	1.2146[b]	51.44	51.33	$C_8H_{10}Cl_2N_2$	34.63	34.90
Ethyl[c]	115–116	7	53	1.5208	1.1841	56.06	56.20	$C_9H_{12}Cl_2N_2$	32.37	32.02
Propyl[c]	119–120	5	50	1.5165	1.1552	60.68	61.15	$C_{10}H_{14}Cl_2N_2$	30.41	30.40
Butyl[c]	130–131	5	44.5	1.5123	1.1258	65.30	65.93	$C_{11}H_{16}Cl_2N_2$	28.68	28.77
Amyl[c]	153–154	9	46	1.5083	1.1102	69.92	70.17	$C_{12}H_{18}Cl_2N_2$	27.15	27.28
Hexyl	160–161	7	45	1.5060	1.0881	74.54	75.15	$C_{13}H_{20}Cl_2N_2$	25.76	25.35

[a] M.p. 24–26°. [b] Taken at 30°. [c] Analysis by Clark Microanalytical Laboratories, Urbana, Ill.

5-Alkyl-6-amino-2-propyl-4(3)-pyrimidones (Table II).—The chloropyrimidone (1–2 g.) and 50 ml. of concentrated ammonium hydroxide were placed in the glass liner of a small steel pressure vessel and heated at 180–190° for 10 hr. When cool, the bomb was opened and the solid material was removed and recrystallized from aqueous ethanol.

5-Alkyl-6-propyl-4(3)-pyrimidones (Table II).—The pyrimidones were prepared by catalytic hydrogenolysis of the chloropyrimidones. Palladium supported

added and the mixture was stirred for 24 hr. The ammonium chloride, which had separated, was removed by filtration. Approximately 800 ml. of ethanol was removed from the filtrate by distillation to leave a heavy, viscous liquid which solidified on cooling. The second crop of imido ester was worked through in the same manner. The butamidine hydrochloride weighed 372 g. (62% yield) and melted from 95–98° in agreement with the datum recorded in the literature.[11]

(11) Richter, "Beilstein Handbuch der Organischen Chimie," Vol. II, 4th Ed., Springer Verlag, Berlin, 1920, p. 276, recorded a m.p. of 96° for butamidine hydrochloride.

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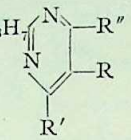
TABLE IV

2-PROPYLPYRIMIDINES C_3H_7



R	R′	R″	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Hydrogen	NH_2	Cl	127–128.5	58	$C_7H_{10}ClN_3O$	24.06	24.28				
Methyl	NH_2	Cl	171–172	67	$C_8H_{12}ClN_3O$	22.65	22.96	51.75	51.76	6.47	6.72
Hexyl	NH_2	Cl	101–102	94	$C_{13}H_{22}ClN_3O$	16.46	16.45				
Hydrogen	NH_2	NH_2	202–203	81	$C_7H_{12}N_4$	35.97	35.67				
Methyl	NH_2	NH_2	181–182	66	$C_8H_{14}N_4$	33.74	33.34	57.81	57.98	8.45	7.93
Hexyl	NH_2	NH_2	139–140	87	$C_{13}H_{24}N_4$	23.71	23.50				
Hydrogen[a,e]	NH_2	H	78–79	60	$C_7H_{11}N_3$	30.62	30.86				
Methyl	NH_2	H	129–130	62	$C_8H_{13}N_3$	27.77	27.69	63.55	63.90	8.68	9.06
Hexyl	NH_2	H	84–85	52	$C_{13}H_{23}N_3$	18.98	19.33				
Hydrogen[c]	CH_3O	CH_3O	93–94[b] (7.5)	59	$C_9H_{14}N_2O_2$	15.34	15.23				
Ethyl[d]	CH_3O	CH_3O	106–107[b] (7)	58	$C_{11}H_{18}N_2O_2$	13.33	13.10				

[a] Molecular weight; calcd. 137, found 142. [b] Boiling points (mm.). [c] $n^{20}D$ 1.4840, d^{20}_4 1.0480; *MR* calcd. 49.62, found 49.86. [d] $n^{20}D$ 1.4870, d^{20}_4 1.0212; *MR* calcd. 58.86, found 59.25; methoxyl, calcd. 2.0, found 1.8. [e] Final purification by vacuum sublimation.

on barium sulfate, prepared by the method of Schmidt,[12] was found to be a suitable catalyst. One gram of catalyst and 1 g. of chloropyrimidone dissolved in 100 ml. of ethanol were shaken with hydrogen at an initial pressure of 60 cm. at room temperature; the calculated amount of hydrogen was taken up in from 1 to 4 hr. It was found that unless the ethanol solution of the chloropyrimidone was first shaken in the cold with some Raney nickel, to remove catalyst poisons, the reduction would take place only very slowly if at all. When the hydrogen uptake had ceased, the catalyst was removed by filtration and the solution evaporated to about 10 ml. On cooling, the solid product precipitated. Ethyl acetate was found to be a suitable solvent for recrystallization. In some cases, an analytical sample was prepared by vacuum sublimation.

5-Alkyl-6-amino-4-chloro-2-propylpyrimidines (Table IV).—The dichloropyrimidine (2–5 g.) and 50 ml. of concentrated ammonium hydroxide were placed in the glass liner of a small steel pressure vessel and heated at 130–140° for 12 hr. Upon cooling to room temperature, the bomb was opened and the solid product removed by filtration and recrystallized from dilute alcohol.

5-Alkyl-4,6-diamino-2-propylpyrimidines (Table IV).—The diaminopyrimidines were prepared in the same manner as the aminochloropyrimidines. A temperature of 180–190° was required for replacement of both chloro substituents by amino. Upon cooling, the product separated and was purified by recrystallizations from water or aqueous ethanol. In the case of the 4,6-diamino-2-propylpyrimidine, it was found necessary to evaporate the solution to about 20 ml. and then to add approximately 20 ml. of 30% sodium hydroxide solution in order to cause the product to separate.

5-Alkyl-4-amino-2-propylpyrimidines (Table IV).—The monoaminopyrimidines were prepared by catalytic hydrogenolysis of the corresponding aminochloropyrimidines. The same conditions and catalyst were used as in the preparation of the pyrimidines from the chloropyrimidines. When the hydrogenation was complete, the catalyst was removed by filtration and the solution evaporated down to a volume of 15 ml. The addition of 25 ml. of concentrated ammonium hydroxide caused the product to precipitate. Recrystallization from benzene gave an analytically pure aminopyrimidine.

5-Alkyl-4,6-dimethoxy-2-propylpyrimidines (Table IV).—The dimethoxypyrimidines were prepared by the interaction of the dichloropyrimidines with sodium methoxide. The dichloropyrimidine (0.04 mole), dissolved in 10 ml. of methanol, was added dropwise to a solution of 2.3 g. (0.1 g. atom) of sodium in 50 ml. of methanol. Reaction took place immediately with the evolution of heat, and sodium chloride separated from solution. When all the dichloropyrimidine had been added, the reaction mixture was refluxed for 14 hr. Methanol was then removed *in vacuo* and the residue taken up in ether. Sodium chloride was filtered off and the ether solution dried over sodium sulfate. Ether was removed *in vacuo* and the product purified by vacuum distillation.

2-Propyltetrahydropyrimidine Hydrochloride.—4,6-Dichloro-2-propylpyrimidine 13.7 g. (0.072 mole), was dissolved in 50 ml. of butanol. The solution was shaken with Raney nickel and allowed to stand at 0° for 12 hr. This procedure was found necessary to remove catalyst poisons which made the subsequent hydrogenation difficult. The Raney nickel was removed by filtration and the filtrate, together with 10.9 g. (0.02 mole) of barium oxide and 10 g. of fresh catalyst, was subjected to hydrogenation in the same manner as described for the monochloropyrimidines. The hydrogenation was considered complete after 4 hr. with the uptake of 0.25 mole (3.6 equivalents) of hydrogen. The catalyst and other solid material was removed by centrifugation and the butanol by distillation. A heavy, viscous oil remained which solidified on cooling. It was recrystallized from acetone to give 5.0 g. (43% yield) of 2-propyltetrahydropyrimidine hydrochloride as hygroscopic white crystals, m.p. 98–100°. *Anal.* Calcd. for $C_7H_{15}ClN_2$: C, 51.65; H, 9.29; N, 17.22; Cl, 21.78. Found: C, 51.28; H, 9.44; N, 16.88; Cl, 21.50.

A picrate was prepared in the usual manner. Two recrystallizations from hot water gave long yellow needles of m.p. 107–109°. *Anal.* Calcd. for $C_{13}H_{17}N_5O_7$: C, 43.94; H, 4.82; N, 19.72. Found: C, 43.84; H, 4.65; N, 19.50.

(12) E. Schmidt, *Ber.*, **52**, 409 (1919).

AUSTIN, TEXAS

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

Pyrimidine N-Oxides and Their Infrared Absorption Characteristics

BY RICHARD H. WILEY AND STEPHEN C. SLAYMAKER

RECEIVED OCTOBER 11, 1956

The infrared spectra for several pyridines and pyrimidines and their N-oxides have been analyzed. Structural correlations and assignments have been made for the C–H stretching and C–H planar deformations and the ring vibrations in the parents. The N-oxides show a strong band at 1255–1300 cm.$^{-1}$ assigned to the N–O stretching frequency. A second band, also characteristic of the N-oxides, appears at 847–872 cm.$^{-1}$. Evidence for the hydrogen bonding of the N-oxide with proton donors is observed in the infrared spectra of the N-oxides in which a band near 2960 cm.$^{-1}$ appears in chloroform but not carbon tetrachloride solutions. This has been correlated with shifts in the ultraviolet absorption maxima of the N-oxides in solvents of varying donor ability.

Although a few pyrimidine N-oxides have been described in the recent literature,[1,2] the possibility of utilizing pyrimidine N-oxides in substitution and rearrangement reactions similar to those which have been developed for the pyridine N-oxides[3,4] warrants additional study of this class of compounds. We have prepared and characterized the previously unknown N-oxides of pyrimidine and its 2-methyl, 5-methyl and 2,4,6-trimethyl derivatives. The infrared spectra of these along with that of the known 4-methylpyrimidine N-oxide[1,2] and pyridine and the picoline N-oxides have been obtained. This report will present the results of these studies.

The pyrimidines were obtained in over-all yields of 43–51% from the palladium-on-charcoal[5,6] reductive dehalogenation of dichloropyrimidines obtained in turn from the corresponding dihydroxy compounds. The N-oxides, described in Table I, were prepared using hydrogen peroxide in glacial acetic acid as described previously[3] for the preparation of pyridine N-oxides although in somewhat lower yields (11–36%). The highly deliquescent nature of the pyrimidine N-oxides coupled with their tendency to sublime *in vacuo* requires that they be handled carefully.

As a preliminary to a consideration of the infrared spectra of the N-oxides, we have evaluated the assignments for a number of the ring vibrations in the pyridines and pyrimidines listed in Table II. The vibrational spectrum of pyridine itself has been fully discussed in the literature.[7,8] As compared to benzene, the introduction of nitrogen into the ring changes the symmetry group from D_{6h} to C_{2v}, with the result that the doubly degenerate benzene ring vibrations are split. The loss of one atom in the benzene–pyridine comparison also requires that three fundamental vibrations be absent in pyridine. Pyrimidine belongs to the symmetry point group C_{2v} also, and although few changes would be expected in the ring vibrations, the loss of three more fundamentals—one C–H stretching, one C–H planar deformation and one C–H out of plane deformation—would be expected. In accordance with this, pyridines normally show two bands in the aromatic C–H stretching region and the pyrimidines show only a single, rather sharp band at 3048 cm.$^{-1}$. Furthermore, the solution spectrum of pyridine clearly shows four medium strength bands (1214, 1144, 1068, 1031 cm.$^{-1}$) in the region where planar hydrogen deformations might be expected and only three bands appear in the same region in pyrimidine (1221, 1155, 1070 cm.$^{-1}$). The third band expected to be lost is a species A_2 C–H out-of-plane deformation which would be inactive in the infrared spectrum of pyridine. The ring vibrations from substituted pyrimidines, with no hydroxyl or amino substituents, have previously been assigned to single absorption bands at 1580–1520 and 990 cm.$^{-1}$.[9] For pyrimidine itself further correlations have been made[9,10] which agree for the most part with those found in this Laboratory.

Assignments for the ring vibrations, v1, v8a, v8b, v19a and v19b[11] for pyridine, the picolines and eight pyrimidines are given in Table II. The location of the v8 and v19 pairs of ring deformation vibrations appears to be quite characteristic, with a slight shift to lower frequencies in both pairs of vibrations in going from the pyridines to the pyrimidines and another shift to still lower frequencies upon chlorine substitution on the pyrimidine ring. The intensities of these four vibrations vary widely, but at least one band in each pair is strong in all of the compounds studied. The v1 band, which can be thought of as a ring "breathing" vibration, appears in the range 1001–986 cm.$^{-1}$ in 10 of the 12 compounds studied.

The spectra of several tertiary amine oxides have been reported by Mathis-Neol[12] who examined five compounds and placed the absorption of the N–O stretching vibration in the range 970–950 cm.$^{-1}$. Goubeau and Fromme[13] have assigned a band at 947 cm.$^{-1}$ in the Raman spectra of one compound to this vibration. Ito and Hata[14] have assigned a band at 832 cm.$^{-1}$ to the N–O

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TABLE I

PYRIMIDINE N-OXIDES

N-Oxide substituent	M.p.,[a] °C.	M.p. $HgCl_2$[b] complex, °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
..	85–88C	.....	11			29.16[c]	28.98
							29.22
2-Methyl	*ca.* 50D	165–169M	31	15.73[d]	15.83	1.59	1.70
					15.90		1.74
4-Methyl[e]	78–79C	146–147W	31			25.44[c]	25.08
							25.10
5-Methyl	113–116C	170–170.5W	36	15.73[d]	15.79	1.59	1.65
					15.69		1.60
2,4,6-Trimethyl[f]	67–72D	143.5–145W	30	15.39[g]	15.58	1.85	1.89
					15.65		1.86

[a] C, recrystallized from carbon tetrachloride; D, purified by distillation and desiccation. [b] M, recrystallized from methanol; W, recrystallized from water. [c] Analysis for nitrogen. [d] As $C_5H_6N_2O \cdot HgCl_2$ complex. 5-Methylpyrimidine N-oxide calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 53.94; H, 5.54; N, 24.68. [e] B.p. 110–113° (3 mm.); reported b.p. 90–110° (bath.) (0.014 mm.), m.p. 74–78°. [f] B.p. 100–102° (1 mm.). [g] As $C_7H_{10}N_2 \cdot 1.5HgCl_2$.

TABLE II[a]

ASSIGNED RING VIBRATIONS FOR PYRIDINES AND PYRIMIDINES

Compound	v8a	v8b	v19a	v19b	v1
Pyridine	1600m[b]	1582s	1484m	1441f	991m
α-Picoline	1597s	1572m	1479s	1433m	996m
β-Picoline	1597w	1580s	1479s	1416s	1029s
γ-Picoline	1605s	1563m	1497w	1416s	996m
Pyrimidine	1613w	1567s	1466m	1401s	990m
2-Methylpyrimidine	1585s	1565s	1441vs[c]	1399m	995m
4-Methylpyrimidine	1590s	1553m	1479m	1391s	998m
5-Methylpyrimidine	1585w	1563s	[d]	1410s	986w
2,4,6-Trimethyl-	1590s	1555m	[d]	1401m	992w
2,4-Dichloro-5-methyl-	1563m	1520s	1399s	1376vs	1001m
2,4-Dichloro-6-methyl-	1565s	1534s	[d]	[d]	1008w
4,6-Dichloro-2-methyl-	1555sh	1536s	1406s	1537s	1000m

[a] Values are in frequencies (cm.$^{-1}$); s = strong, m = medium, w = weak, sh = shoulder, vs = very strong. All are in carbon tetrachloride. [b] Kline and Turkevich[7] and Corrsin[8] assign the 8a and 8b vibrations in pyridine in a slightly different manner. They find a difficultly resolvable doublet at 1570–1580 cm.$^{-1}$ which they attribute to the v8a and v8b vibrations. They find also a band at 1597 cm.$^{-1}$ which they attribute to a combination tone strengthened by resonance with the v8 vibrations. These studies were conducted in the gas phase and in pure liquid pyridine. It would seem possible that the solution spectra used in our series of measurements could effect a further separation of the bands. It seems highly improbable that all of the bands in the first column can be attributed to a combination band since in γ-picoline and again in 2,4,6-trimethylpyrimidine the first band is far stronger than any other band in either spectra. [c] This extremely strong band probably involves some contribution from the asymmetric carbon hydrogen deformation bands expected in this region. The other methyl-containing compounds in this list show this to be a band of medium strength falling very near 1449 cm.$^{-1}$. The symmetric methyl deformation appears in the range 1390–1370 cm.$^{-1}$ in all of the methyl-containing compounds. [d] Bands not assigned.

stretching vibration in pyridine N-oxide on the basis that acetoxime shows an absorption in this same range which may also be attributed to an O–N stretching vibration. The absorption characteristics of the nine N-oxides studied are given in Table IV. All show an extremely strong band near 1266 cm.$^{-1}$ in carbon tetrachloride solution. For pyridine N-oxide itself and in α- and γ-picoline N-oxides this band falls at 1264–1260 cm.$^{-1}$. In β-picoline N-oxide, where the methyl group is not attached to an electron-deficient carbon, the band appears at 1290 cm.$^{-1}$. The location of this band [illegible] cm.$^{-1}$ in chloroform. Since chloroform itself ab-

is similar in the pyrimidine N-oxides but is often more complex. It is split into two strong bands in both 2- and 4-methylpyrimidine N-oxides. 2,4,6-Trimethylpyrimidine N-oxide shows a shift to 1255 cm.$^{-1}$. As in the case of β-picoline N-oxide, 5-methylpyrimidine N-oxide shows a shift to higher frequencies with its absorption appearing at 1300 cm.$^{-1}$. Pyrimidine N-oxide itself, although not sufficiently soluble to obtain a spectrum in carbon tetrachloride, shows a strong band at 1261 cm.$^{-1}$ in chloroform. The exact position of this band is affected by the formation of hydrogen bonds with the solvent. This has been shown to produce a

TABLE III

THE ULTRAVIOLET SPECTRA OF γ-PICOLINE N-OXIDE IN VARIOUS SOLVENTS

Solvent	Wave length, mμ	log ε
Water[15]	256	4.155
Methanol	264.5	4.059
50 mole % $CHCl_3$ in methanol	267.5	4.261
Chloroform	276.5	4.368
Carbon tetrachloride	288	4.489

TABLE IV

PRINCIPAL ABSORPTION BANDS IN INFRARED SPECTRA OF PYRIDINE AND PYRIMIDINE N-OXIDES[a]

Pyridine	1608m, 1488sh, 1464s, 1266vs, 841s
α-Picoline	1616m, 1497s, 1462s, 1420m, 1385m, 1266vs, 856s
β-Picoline	1610m, 1567w, 1490m, 1466m, 1433m, 1389w, 1290vs, 856m
γ-Picoline[b]	1490s, 1453m, 1264s, 856m
Pyrimidine[c]	1577w, 1534m, 1468m, 1410s, 1261s, 845s
2-Me-pyrimidine	1536w, 1488m, 1431s, 1402s, 1287s, 1272s, 872s
4-Me-pyrimidine	1603m, 1565w, 1524m, 1490m, 1439s, 1416m, 1274vs, 1266vs, 858s
5-Me-pyrimidine	1582m, 1548w, 1497w, 1379s, 1300s, 858m
2,4,6-Trimethyl	1608s, 1531m, 1445s, 1416m, 1255vs, 860m

[a] Values are frequencies in cm.$^{-1}$; s = strong, m = medium, w = weak, vs = very strong, sh = shoulder. In carbon tetrachloride except as noted. [b] Owing to the limited solubility of this compound in carbon tetrachloride, only the stronger bands were visible. [c] Chloroform.

shift to lower frequencies in other N-oxides. Thus, pyridine N-oxide shows the band at 1264 cm.$^{-1}$ in carbon tetrachloride and 1252 cm.$^{-1}$ in chloroform, and γ-picoline N-oxide shows the band at 1264 cm.$^{-1}$ in carbon tetrachloride and 1248

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sorbs strongly near this region, the resulting loss of resolution encountered makes the assignment somewhat approximate in the case of pyrimidine N-oxide.

The strength of this band near 1266 cm.$^{-1}$ and the solvent shift have caused us to assign this band to the N–O stretching frequency in these compounds despite the previous assignments.[12–14] This need not be an inconsistency, since it is well known that other physical and chemical properties of the heterocyclic N-oxides differ greatly from those of the trialkyl amine oxides. A number of ionic resonance forms are possible in the heterocyclic N-oxides, and these would give the N–O bond considerable double bond character. The pyrimidine and pyridine N-oxides show no consistent absorption in the 950 cm.$^{-1}$ region previously stated to be characteristic of the N–O stretching vibration.

A second band which appears to be characteristic of the heterocyclic N-oxides is found near 847 cm.$^{-1}$. In pyridine N-oxide this band occurs at 841 cm.$^{-1}$, while in pyrimidine N-oxide the absorption occurs at 845 cm.$^{-1}$. All of the methyl-containing compounds show this band in the narrow range 860–855 cm.$^{-1}$ with the exception of 2-methylpyrimidine N-oxide where the band falls at 872 cm.$^{-1}$. This band is in the region tentatively assigned previously[14] to the O–N stretching vibration. Since it is not subject to the displacement in chloroform as is the 1260 cm.$^{-1}$ band, it now seems advisable to revise this assignment.

An interesting phenomena is observed in the spectra of chloroform solutions of N-oxides. A sharp and unusually strong band occurs near 2960 cm.$^{-1}$ which is absent from the spectra obtained in carbon tetrachloride solutions. This is probably due to the absorption associated with the C–H stretching vibration in chloroform which is shifted to longer wave lengths by hydrogen bonding. A number of other compounds capable of acting as donors have been shown to produce shifts in this band. Quinoline, for example, is known to produce a shift from 3067 to 2960 cm.$^{-1}$ as well as a fourfold strengthening of the absorption.[15] A shift of this magnitude would bring the chloroform frequency to a point where the compensating cell would not eliminate it, thus introducing an entirely spurious band in the N-oxide spectra. Further indication of hydrogen bonding is found in the ultraviolet spectra. Thus, the absorption band for γ-picoline N-oxide shows a strong hypsochromic shift in going from non-polar solvents to polar solvents (see Table III). It has been suggested[16] that this band arises from a $\pi \rightarrow \pi^*$ transition. This type of transition has usually been known to produce a bathochromic (red) shift under the effect of solvation.[17] Large hypsochromic (blue) shifts normally are evidence of $n \rightarrow \pi^*$ transitions,[17] but such a transition is inconsistent with the high intensity of the absorption.

In contrast with the similarities previously noted[12] between the infrared spectra of tertiary amine N-oxide and the corresponding amine, the spectra of the heterocycles and their N-oxides are not greatly similar. While pyridine, pyrimidine and their methyl derivatives show characteristic ring vibrations which are strong and easily assigned, the N-oxides show much less regularity. There is a striking weakening of absorption below 1490 cm.$^{-1}$ as compared to the parent compounds. A number of the bands found in these N-oxides are listed in Table IV. Although the spectrum of pyrimidine shows many resemblances to that of pyridine, the spectra of the N-oxides show fewer resemblances between the two ring systems.

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Experimental

Details of typical procedures are given in the following paragraphs. Complete data are given in Table I. Combustion analyses were performed by Micro Tech Laboratories, Skokie, Ill.

The pyridine, picolines and their N-oxides used in the spectroscopic studies were generously furnished by Reilly Tar and Chemical Co. These compounds were redistilled or recrystallized before use. The tetraethoxypropane was generously donated by Carbide and Carbon Chemical Co. and was used as received.

5-Methylpyrimidine.—Forty-eight grams (0.3 mole) of 4,6-dichloro-5-methylpyrimidine was divided into three portions of 16.0 g., and each portion was hydrogenated in a Parr hydrogenation apparatus with 10.0 g. of powdered magnesium oxide and 2.0 g. of 5% palladium-on-charcoal catalyst in 300 ml. of 50% aqueous methanol. From an initial pressure of about 50 pounds the theoretical amount of hydrogen was absorbed smoothly in 90 minutes. The filtered solution was poured into 1500 ml. of hot water containing 180 g. of mercuric chloride. The thick white precipitate was collected on a filter after cooling, then was dried and placed in a 2000-ml. distilling flask containing 600 ml. of water and 85 g. of sodium sulfide. After removal of 400 ml. of distillate, saturation with sodium hydroxide caused the amine layer to form. This layer was separated and the aqueous solution extracted with three 80-ml. portions of ether. The combined ether fractions and the amine were dried over calcium sulfate, concentrated to 40 ml. and distilled. After removing a small amount of ether, a rather large forerun was collected (b.p. 80–150°), followed by the methylpyrimidine, b.p. 150–155°. The forerun was dried over potassium hydroxide and redistilled to give more of the crude methylpyrimidine. Redistillation gave 15.5 g. (55%) of 5-methylpyrimidine, b.p. 152–154° (760 mm.). The clear, colorless liquid solidified on chilling, m.p. 28–30°; reported[18] b.p. 151.5° (735 mm.), m.p 30.5°.

Other pyrimidines were prepared similarly: pyrimidine (48% from uracil), b.p. 121–123° (760 mm.), $n^{23}D$ 1.4983 (reported[8] b.p. 123–124° (762 mm.); 2-methylpyrimidine (43% from 2-methyl-4,6-dihydroxypyrimidine), b.p. 129–133° (760 mm.), $n^{26}D$ 1.4878 (reported[19] b.p. 130–131° (750 mm.); 4-methylpyrimidine (51% from 4-methyluracil), b.p 139–141° (760 mm), $n^{29}D$ 1.4918 (reported[6] b.p. 141–145° (760 mm.), n_D 1.4940). 2,4,6-Trimethylpyrimidine was prepared in 26% yield from acetamidine and acetylacetone,[20] b.p. 84–87° (45 mm.). The direct condensation of tetraethoxypyropane with acetamidine in hydrochloric acid saturated ethanol gave only a 2% yield of 2-methylpyrimidine isolated as the mercuric chloride complex.

2,4,6-Trimethylpyrimidine N-Oxide.—Six and one-tenth grams (0.05 mole) of 2,4,6-trimethylpyrimidine was heated with 30 ml. of glacial acetic acid and 8 ml. of 30% hydrogen peroxide at 70° for 5 hr. Six additional ml. of peroxide was

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added and the temperature maintained for 16 hr. Evaporation to 10 ml., addition of 20 ml. of water and evaporation again to 10 ml. gave a yellow oil which was saturated with sodium carbonate and extracted with five 20-ml. portions of chloroform. The chloroform extracts were dried with calcium sulfate and evaporated in vacuum to leave a viscous oil. Distillation of this gave 2.3 g. of crude product, b.p. 100–102° (1 mm.), which partially solidified to white crystals in the receiver. Careful drying on a clay plate in a desiccator gave crystals, m.p. 67–72°. The product was very hygroscopic and formed a solid complex with mercuric chloride. One recrystallization of this complex from water gave crystals, m.p. 143.5–145°.

5-Methylpyrimidine N-Oxide.—Seven and five one-hundredth grams (0.075 mole) of 5-methylpyrimidine was heated at 70° for 6 hr. in 30 ml. of glacial acetic acid containing 8 ml. of hydrogen peroxide solution (30%). Eight additional ml. of peroxide was added and the heating continued for 20 hr. The resulting solution was treated as before. The crude solid from the chloroform extracts was recrystallized from carbon tetrachloride to yield white, hygroscopic crystals, m.p. 113–116°. A mercuric chloride complex, m.p. 170–170.5°, was obtained.

The infrared spectra were obtained with a Baird double beam recording spectrophotometer equipped with sodium chloride optics using 0.1-mm. sodium chloride cells. All measurements were calibrated against the 3.419 band of polystyrene. The ultraviolet spectra were obtained using a Beckman DU spectrophotometer in 1-cm. quartz cells.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Reaction of 2-Bromopyridine N-Oxides with Active Methylene Compounds

BY ROGER ADAMS AND WALTER REIFSCHNEIDER

RECEIVED NOVEMBER 10, 1956

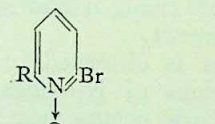
2-Bromopyridine N-oxides condense with active methylene compounds holding a carboalkoxy group to give derivatives of 2-isoxazolono[2,3-a]pyridines. These products react with aqueous alkali; the isoxazolone ring is opened and carbon dioxide is lost with formation of the 2-substituted pyridine N-oxides. 2-Carbethoxy-2-isoxazolono[2,3-a]pyridine is hydrogenated with platinum oxide catalyst to 3-carbethoxy-2-isoxazolono[2,3-a]piperidine.

The electron-attracting power of the ring nitrogen accounts for the facile attack of halogen in the 2- and 4-halopyridines by nucleophilic reagents. In spite of this reactivity, the bromine atom in 2-bromopyridine fails to respond to treatment with diethyl sodiomalonate.[1] The introduction of the malonic ester group in the 2-position of pyridine was achieved[2] by using 5-nitro-2-chloropyridine in which the halogen is further activated by the electron-withdrawing nature of the nitro group.

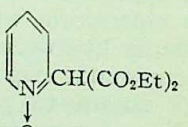
The introduction of an N-oxide into the pyridine system also is known to increase the reactivity of the 2-, 4- and 6-positions of the ring. A reaction between 2-bromopyridine 1-oxide (I) and diethyl sodiomalonate might therefore be expected. A reaction does take place between these reagents under relatively mild conditions, but diethyl 2-pyridylmalonate 1-oxide (III) is not isolated. Instead, a compound of the formula $C_{10}H_9NO_4$ results. The reaction apparently does not stop after the initial condensation but loss of ethanol occurs to form 3-carbethoxy-2-isoxazolono[2,3-a]pyridine (IV).

To demonstrate the generality of this reaction, 2-bromopyridine 1-oxide (I) and 2-bromo-6-methylpyridine 1-oxide (II) were subjected to the action of various active methylene compounds. 2-Bromo-6-methylpyridine 1-oxide (II) is a stable compound in comparison with 2-bromopyridine 1-oxide (I) and therefore was more often used in this study. Upon addition of ethyl sodioacetoacetate and ethyl sodiobenzoylacetate to 2-bromopyridine 1-oxide (I) and 2-bromo-6-methylpyridine 1-oxide (II) the expected cyclized products V, VI, IX and X were obtained.

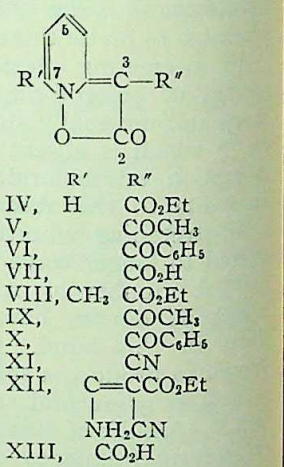
When ethyl sodiocyanoacetate was treated with 2-bromo-6-methylpyridine 1-oxide (II) and benzene was used as the solvent, three compounds were isolated, (1) 2-imino-3-carbethoxy-7-methylisoxazolo[2,3-a]pyridine (XIV), (2) 3-cyano-7-methyl-2-isoxazolono[2,3-a]pyridine (XI) and (3) ethyl [α-cyano-β-amino-β-(7-methyl-2-isoxazolono[2,3-a]pyridyl-3)]-acrylate (XII).



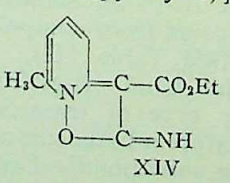
I, R = H
II, R = CH_3



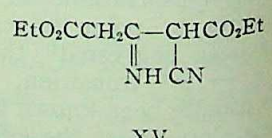
III



	R′	R″
IV,	H	CO_2Et
V,		$COCH_3$
VI,		COC_6H_5
VII,		CO_2H
VIII,	CH_3	CO_2Et
IX,		$COCH_3$
X,		COC_6H_5
XI,		CN
XII,		$C(=CCO_2Et)(NH_2CN)$
XIII,		CO_2H



XIV



XV

The structure of the first compound XIV, a yellow product, was established by analysis ($C_{11}H_{12}N_2O_3$) and the presence in the infrared spectrum of an N–H band at 3285 $cm.^{-1}$ and a conjugated ester band at 1688 $cm.^{-1}$.

The second compound XI was a colorless product with the empirical formula $C_9H_6N_2O_2$ and showed bands in its infrared spectrum for CN at

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2220 cm.$^{-1}$ and for an isoxazolone-CO at 1766 cm.$^{-1}$.

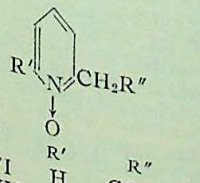
The third product XII, $C_{14}H_{13}N_3O_4$, was colorless but turned yellow upon exposure to light. The infrared spectrum showed bands for NH_2 at 3225 and 3375 cm.$^{-1}$, for CN at 2205 cm.$^{-1}$, for an isoxazolone-CO at 1745 cm.$^{-1}$ and for a conjugated ester at 1672 cm.$^{-1}$. The structure assigned assumes initial formation of a dimer of the ethyl cyanoacetate which then reacted with 2-bromo-6-methylpyridine 1-oxide. This was confirmed by dimerizing ethyl cyanoacetate[3] and condensing it with the 2-bromo-6-methylpyridine 1-oxide to give the same product.

If the condensation of ethyl sodiocyanoacetate with 2-bromo-6-methylpyridine 1-oxide (II) was carried out in dioxane, only compounds XI and XII could be isolated.

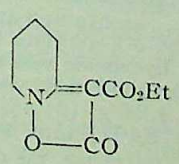
Attempts to achieve reaction between 2-bromo-6-methylpyridine 1-oxide (II) and the sodium salts of acetylacetone, benzoylacetone or dibenzoylmethane failed.

The derivatives of 2-isoxazolono[2,3-a]pyridine were all subjected to hydrolysis with 5% aqueous sodium hydroxide. In both 3-acetyl-7-methyl-2-isoxazolono[2,3-a]pyridine (IX) and 3-benzoyl-7-methyl-2-isoxazolono[2,3-a]pyridine (X) opening of the isoxazolone ring and decarboxylation occurred leading to formation of 6-methyl-2-acetonylpyridine 1-oxide (XVIII) and 6-methyl-2-benzoylmethylpyridine 1-oxide (XIX), respectively. Upon hydrolysis of 3-cyano-7-methyl-2-isoxazolono[2,3-a]pyridine (XI), 6-methyl-2-pyridylacetic acid 1-oxide (XVII) was obtained; besides ring opening and decarboxylation the nitrile group underwent hydrolysis. 6-Methyl-2-pyridylacetic acid 1-oxide (XVII) also resulted from hydrolysis of ethyl [α-cyano-β-amino-β-(7-methyl-2-isoxazolono[2,3-a]-pyridyl-3-)]-acrylate (XII). Hydrolysis of both 3-carbethoxy-2-isoxazolono[2,3-a]pyridine (IV) and its 7-methyl derivative VIII resulted in a mixture of two compounds. 3-Carboxy-2-isoxazolono-[2,3-a]pyridine (VII) and 2-pyridylacetic acid 1-oxide (XVI) were obtained from IV, while the corresponding methyl analogs (XIII and XVII) were formed from VIII. The ratio of the two products in each case is dependent on the duration of the hydrolysis.

2-Pyridylacetic acid 1-oxide (XVI) and 6-methyl-2-pyridylacetic acid 1-oxide (XVII) are much more stable than 2-pyridylacetic acid and 6-methyl-2-pyridylacetic acid. The former do not decompose with loss of carbon dioxide to form 2-picoline 1-oxide and 2,6-dimethylpyridine 1-oxide until their melting points are reached.



	R′	R″
XVI	H	CO_2H
XVII	CH_3	CO_2H
XVIII		$COCH_3$
XIX		COC_6H_5



XX

3-Carbethoxy-2-isoxazolono[2,3-a]pyridine (IV) was hydrogenated using a platinum oxide catalyst. Two moles of hydrogen were absorbed and 3-carbethoxy-2-isoxazolono[2,3-a]piperidine (XX) was formed.

Experimental Part

2-Bromo-6-methylpyridine 1-Oxide (II).—To a solution of 172 g. of 2-bromo-6-methylpyridine[4] in 150 ml. of glacial acetic acid was added 310 ml. of 40% peracetic acid. The temperature rose and was kept below 50° by external cooling. After the initial reaction subsided the solution was heated for 5 hours at 50° and then overnight at 70°. After concentration of the solution *in vacuo* on the water-bath to about 200 ml., it was poured onto ice and made strongly alkaline by adding 40% aqueous potassium hydroxide. An oil separated. The solution was extracted thrice with chloroform. The combined chloroform solutions were dried over potassium carbonate, filtered and the chloroform was removed under reduced pressure on the water-bath. Addition of ether to the oily residue and cooling yielded crystalline 2-bromo-6-methylpyridine 1-oxide. It was recrystallized from ethanol–ether, m.p. 70°. The yield was 181.0 g. (96.3%).

Anal. Calcd. for C_6H_6BrNO: C, 38.32; H, 3.22. Found: C, 38.44; H, 3.17.

Hydrochloride, m.p. 196–197° (lit.[5] m.p. 185–186°).

Anal. Calcd. for $C_6H_7BrClNO$: C, 32.10; H, 3.14. Found: C, 31.98; H, 3.09.

2-Bromopyridine 1-Oxide (I).—The procedure described for making 2-bromo-6-methylpyridine 1-oxide (II) was used. The product was obtained in 72.4% yield. It was recrystallized from ethanol–ether, m.p. 64°; hydrochloride, m.p. 132–135° (lit.[5] m.p. 130–135°).

Anal. Calcd. for C_5H_4BrNO: C, 34.51; H, 2.32. Found: C, 34.55; H, 2.40.

2-Bromopyridine 1-oxide is unstable at room temperature. A sample detonated without apparent cause on standing at room temperature for several days.

Reaction of Active Methylene Compounds with 2-Bromo-6-methylpyridine 1-Oxide and 2-Bromopyridine 1-Oxide. General Procedure.—The sodium salt of an active methylene compound was prepared by adding 0.1 mole of the active methylene compound to 2.4 g. (0.1 mole) of sodium hydride kept under 100 ml. of dioxane, benzene or ether. To this was added 0.1 mole of 2-bromo-6-methylpyridine 1-oxide (II) or 2-bromopyridine 1-oxide (I), and the mixture was heated under reflux for 24 hours. After cooling, the solid part of the reaction mixture was collected by filtration, and the filtrate was evaporated to dryness under reduced pressure on the water-bath. The combined residues were triturated with about 100 ml. of water. The insoluble portion was collected by filtration, washed with water and recrystallized from ethanol.

To recover any unreacted N-oxide, the filtrate was extracted with three 80-ml. portions of chloroform and the combined chloroform extracts were extracted with three 50-ml. portions of 20% hydrochloric acid. The hydrochloric acid solution was concentrated *in vacuo* on the steam-bath until the N-oxide hydrochloride began to crystallize. After cooling, the N-oxide hydrochloride was collected by filtration and was recrystallized from ether.

See Table I for constants of the products.

Hydrolysis of 3-Acetyl-7-methyl-2-isoxazolono[2,3-a]-pyridine (IX): 2-Acetonyl-6-methylpyridine 1-Oxide (XVIII).—A mixture of 2.0 g. of 3-acetyl-7-methyl-2-isoxazolono-[2,3-a]pyridine (IX) and 10 ml. of 5% aqueous sodium hydroxide was boiled under reflux until a clear solution was obtained (about 70 min.). After cooling, the solution was extracted with three 10-ml. portions of chloroform. The combined chloroform extracts were dried over potassium carbonate, and the chloroform then removed under reduced pressure. The residual oil was dissolved in warm ether which on cooling yielded 1.6 g. (92.5%) of colorless needles. The substance was recrystallized from ether, m.p. 67–68°.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.71; H, 6.95; N, 8.49.

(3) S. R. Best and J. F. Thorpe, *J. Chem. Soc.*, 95, 1901 (1909).

(4) R. Adams and S. Miyano, THIS JOURNAL, **76**, 3168 (1954).

(5) E. Shaw, J. Bernstein, K. Losee and W. A. Lott, *ibid.*, **72**, 4362 (1950).

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TABLE I

CONDENSATION PRODUCTS OF 2-BROMOPYRIDINE 1-OXIDES AND ACTIVE METHYLENE COMPOUNDS

Active methylene compound	Solvent	Reaction product	Yield, %	Recovd. starting material, %	Yield based on N-oxide used in the reacn., %	M.p., °C.	Analyses, % Calcd.	Found
		2-Bromopyridine 1-oxide (I)						
Diethyl malonate	Ether	3-Carbethoxy-2-isoxazolono[2,3-a]-pyridine (IV)	40.2	39.5	66.4	181	C, 57.97	57.98
							H, 4.38	4.41
							N, 6.76	6.92
Ethyl acetoacetate	Benzene	3-Acetyl-2-isoxazolono[2,3-a]pyridine (V)	24.8	50.2	48.8	188–190	C, 61.02	60.72
							H, 3.98	4.11
							N, 7.91	7.66
Ethyl benzoylacetate	Benzene	3-Benzoyl-2-isoxazolono[2,3-a]pyridine (VI)	20.1	36.2	31.5	193–194	C, 70.29	70.71
							H, 3.79	3.92
							N, 5.86	5.90
		2-Bromo-6-methyl pyridine 1-oxide (II)						
Diethyl malonate	Benzene or dioxane	3-Carbethoxy-7-methyl-2-isoxazolono-[2,3-a]pyridine (VIII)	44.7	17.6	54.3	175–176	C, 59.72	59.87
							H, 5.01	5.21
							N, 6.34	6.49
Ethyl acetoacetate	Benzene or dioxane	3-Acetyl-7-methyl-2-isoxazolono[2,3-a]pyridine (IX)	24.3	50.8	49.5	200	C, 62.82	62.97
							H, 4.74	4.51
							N, 7.33	7.37
Ethyl benzoylacetate	Dioxane	3-Benzoyl-7-methyl-2-isoxazolono[2,3-a]pyridine (X)	22.1	50.1	44.2	208–209	C, 71.14	71.04
							H, 4.38	4.27
							N, 5.35	5.46
Ethyl cyanoacetate	Benzene[a,b]	2-Imino-3-carbethoxy-7-methyl-isoxazolono[2,3-a]pyridine (XIV)	10.8	18.2	13.3	128 d.	C, 59.99	60.15
							H, 5.49	5.46
							N, 12.72	13.16
		3-Cyano-7-methyl-2-isoxazolono[2,3-a]pyridine (XI)	5.75		7.0	217–219 (dec.)	C, 62.07	62.13
							H, 3.47	3.31
							N, 16.09	15.85
		Ethyl [α-cyano-β-amino-β-(7-methyl-2-isoxazolono[2,3-a]pyridyl-3-)] acrylate (XII)	4.2		5.1	209–212 (dec.)	C, 58.53	58.57
							H, 4.56	4.65
							N, 14.63	14.64
	Dioxane[b]	3-Cyano-7-methyl-2-isoxazolono[2,3-a]pyridine (XI)	16.7	20.5	21.0	217–219 (dec.)		
		Ethyl [α-cyano-β-amino-β-(7-methyl-2-isoxazolono[2,3-a]pyridyl-3-)]-acrylate (XII)	9.1		11.4	209–212 (dec.)		
Diethyl β-imino-α-cyanoglutarate (XV)	Dioxane	Ethyl [α-cyano-β-amino-β-(7-methyl-2-isoxazolono[2,3-a]pyridyl-3-)]-acrylate (XII)	46.2	18.4	56.5	209–212 (dec.)	C, 58.53	58.64
							H, 4.56	4.52

[a] Compound XIV was isolated from the solid part of the reaction mixture. It was recrystallized from water. Compounds XI and XII were isolated from the residue after removing the benzene under reduced pressure. [b] Compounds XI and XII were separated by fractional crystallization from chloroform.

Hydrolysis of 3-Benzoyl-7-methyl-2-isoxazolono[2,3-a]-pyridine (X): 2-Benzoylmethyl-6-methylpyridine 1-Oxide (XIX).—A suspension of 0.7 g. of 3-benzoyl-7-methyl-2-isoxazolono[2,3-a]pyridine (X) in 8 ml. of 5% aqueous sodium hydroxide was boiled under reflux for 1.5 hours. The clear solution was treated in the same manner as described for 6-methyl-2-acetonylpyridine 1-oxide to yield 0.61 g. (97.1%) of white crystals. The substance was recrystallized from ethanol–ether, m.p. 143–145°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.17. Found: C, 74.11; H, 5.74; N, 6.21.

Hydrolysis of 3-Cyano-7-methyl-2-isoxazolono[2,3-a]-pyridine (XI): 6-Methyl-2-pyridylacetic Acid 1-Oxide (XVII).—A mixture of 1.15 g. of 3-cyano-7-methyl-2-isoxazolono[2,3-a]pyridine (XI) and 15 ml. of 5% aqueous sodium hydroxide was boiled under reflux until a clear solution was obtained (1 hr.). After cooling, the solution was acidified with 2 *N* sulfuric acid and then exhaustively extracted with chloroform. The chloroform extracts were dried over magnesium sulfate and the chloroform was removed under reduced pressure. A crystalline residue was obtained and was recrystallized from ethanol, m.p. 147–148° dec. The yield was 1.05 g. (95%).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.81; H, 5.66; N, 8.66.

Hydrolysis of Ethyl [α-Cyano-β-amino-β-(7-methyl-2-isoxazolono[2,3-a]pyridyl-3-)]-acrylate (XII): 6-Methyl-2-pyridylacetic Acid 1-Oxide (XVII).—A mixture of 2.4 g. of ethyl [α-cyano-β-amino-β-(7-methyl-2-isoxazolono[2,3-a]-pyridyl-3-)]-acrylate (XII) and 50 ml. of 5% aqueous sodium hydroxide was treated as described for the hydrolysis of 3-cyano-7-methyl-2-isoxazolono[2,3-a]pyridine (XI) to yield 1.28 g. (91.4%) of 6-methyl-2-pyridylacetic acid 1-oxide (XVII), m.p. 147–148° dec.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43. Found: C, 57.53; H, 5.35.

Hydrolysis of 3-Carbethoxy-7-methyl-2-isoxazolono[2,3-a]pyridine (VIII): 3-Carboxy-7-methyl-2-isoxazolono[2,3-a]pyridine (XIII) and 6-Methyl-2-pyridylacetic Acid 1-oxide (XVII).—A suspension of 3.3 g. of 3-carbethoxy-7-methyl-2-isoxazolono[2,3-a]pyridine (VIII) in 40 ml. of

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5% aqueous sodium hydroxide was boiled under reflux for one hour. The clear solution was cooled and then acidified with 2 *N* sulfuric acid. The white substance which precipitated was collected by filtration and washed with water. The material was recrystallized from ethanol, m.p. 211–212° dec. The yield was 1.5 g. (52.1%).

Anal. Calcd. for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.67; H, 3.74; N, 7.54.

The filtrate, after removal of 3-carboxy-7-methyl-2-isoxazolono[2,3-a]pyridine, was exhaustively extracted with chloroform. The chloroform extracts were dried over magnesium sulfate and the chloroform removed under reduced pressure. The crystalline residue was recrystallized from ethanol. The yield was 1.1 g. (44.2%) of 6-methyl-2-pyridylacetic acid 1-oxide (XVII), m.p. 146–147° dec.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43. Found: C, 57.86; H, 5.37.

Hydrolysis of 3-Carbethoxy-2-isoxazolono[2,3-a]pyridine (IV): 3-Carboxy-2-isoxazolono[2,3-a]pyridine (VII) and 2-Pyridylacetic Acid 1-Oxide (XVI).—A mixture of 3.0 g. of 3-carbethoxy-2-isoxazolono[2,3-a]pyridine (IV) and 30 ml. of 5% aqueous sodium hydroxide was treated as described for its 7-methyl derivative. A yield of 0.8 g. (30.9%) of 3-carboxy-2-isoxazolono[2,3-a]pyridine (VII), m.p. 204–205° dec., resulted from acidification of the alkaline solution.

Anal. Calcd. for $C_8H_5NO_4$: C, 53.64; H, 2.81; N, 7.82. Found: C, 53.67; H, 2.78; N, 7.73.

From the filtrate 0.4 g. (18.0%) of 2-pyridylacetic acid 1-oxide (XVI), m.p. 140° dec., was obtained.

Anal. Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.14. Found: C, 54.60; H, 4.54; N, 8.82.

Hydrogenation of 3-Carbethoxy-2-isoxazolono[2,3-a]pyridine (IV): 3-Carbethoxy-2-isoxazolono[2,3-a]piperidine (XX).—A suspension of 0.4 g. of 3-carbethoxy-2-isoxazolono[2,3-a]pyridine (IV) in 100 ml. of ethanol was hydrogenated in the presence of platinum oxide catalyst. An uptake of 92 ml. of hydrogen at 24° and 745 mm. was observed (theoretical for 2 moles at 24° and 745 mm. is 96.0 ml.) The catalyst was removed by filtration and the filtrate was concentrated until the substance started to crystallize. Ether was added and after cooling the compound was collected by filtration. It was recrystallized from ethanol–ether, m.p. 157–158°.

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.64. Found: C, 56.71; H, 6.23; N, 6.37.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Alkaloids of *Lunasia amara* Blanco. 4-Methoxy-2-phenylquinoline

BY SIDNEY GOODWIN, A. F. SMITH AND E. C. HORNING

RECEIVED SEPTEMBER 16, 1956

From the leaves of *Lunasia amara* Blanco there was isolated an alkaloid which did not correspond to any of the previously reported *Lunasia* alkaloids. It was identified as 4-methoxy-2-phenylquinoline. This substance has not hitherto been reported to occur in nature.

Alkaloids of the genus *Lunasia* (fam. *Rutaceae*) have been investigated on several occasions since their discovery by Lewin[1] and by Boorsma.[1] Several alkaloids of unknown structure were described by Steldt and Chen,[2] who found that, contrary to previous reports, the alkaloids did not possess a digitalis-like action. Pertinent early references are given by Steldt and Chen.

In the present work, a number of alkaloids were isolated from leaves of *Lunasia amara* Blanco obtained from the Philippine Islands.[3] Of the total of seven compounds isolated by chromatography on alumina, only the one eluted first will be discussed in this paper. This material, with an empirical formula $C_{16}H_{13}ON$, crystallized from pentane in colorless, optically inactive needles melting at 66–67°. It was identified through its reactions and by synthesis as 4-methoxy-2-phenylquinoline (I). This substance has not heretofore been reported as a naturally occurring compound, and it was not observed in earlier *Lunasia* work.

An interesting property of this compound, which provided one of the first keys to its structure, was observed through the melting point behavior of the hydrochloride. The salt melted with effervescence to a colorless liquid which resolidified and thereafter melted above 240°. These effects suggested a thermal demethylation to yield a 2- or 4-quinolone. Salts of cusparine (a 4-methoxyquinoline) were reported to yield a 4-quinolone on heating to decomposition temperature,[4] and a preparative pyrolysis of the *Lunasia* alkaloid hydrochloride

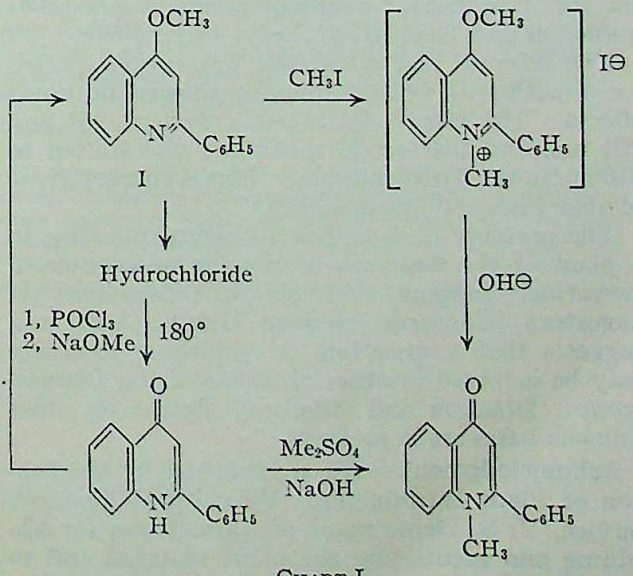

CHART I

was therefore carried out. The high-melting (256–258°) product, later recognized as 2-phenyl-

(1) L. Lewin, "Lehrbuch der Toxikologie," 2nd Ed., Urban and Schwarzenberg, Vienna and Leipzig, 1897, p. 271; W. G. Boorsma, *Bull. Inst. Bot. Buitenzorg*, **6**, 15 (1900).

(2) F. A. Steldt and K. K. Chen, *J. Am. Pharm. Assoc., Sci. Ed.*, **32**, 107 (1943).

(3) S. H. Kooders and T. Valeton (*Meededeel. uit's Lands Plant.*, **17**, 226 (1896)) suggest that the species found in the Malayan and Philippine archipelagoes and described by Miquel are actually varieties of *L. amara*. Steldt and Chen used *L. amara* bark [illegible]

(4) J. Troger and W. Beck, *Arch. Pharm.*, **251**, 246 (113); J. Troger and W. Müller, *ibid.*, **252**, 459 (1914).

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4-quinolone, was obtained in good yield in this way.

The methiodide of the alkaloid was prepared in nearly quantitative yield by heating the base with methyl iodide at 100°. Under these circumstances, some methoxyquinolines are converted into N-methylquinolones; this is true, for example, for dictamnine. Since the immediate reaction product in this instance was the methiodide, it was treated in aqueous solution with dilute sodium hydroxide, and an *iso*alkaloid separated in excellent yield. These results pointed to a 4-methoxyquinoline structure.

The chief problem in selecting the most likely structure for synthesis involved a few points of non-correspondence with the literature. 4-Methoxy-2-phenylquinoline was described about fifty years ago by Knorr[5] with a melting point (69–70°) very close to that found for the *Lunasia* alkaloid, but treatment with methyl iodide at 90° was reported to give 1-methyl-2-phenyl-4-quinolone directly. This behavior was not duplicated in our experience. In addition, the N-methylquinolone was reported as melting at both 85°[5] and 136°,[6] while the reaction product obtained in this work melted at 143.5–144.5°. The first structural comparison selected for investigation was that for 2-phenyl-4-quinolone (the pyrolysis product); the materials derived from synthesis and from the alkaloid were found to be identical. 4-Methoxy-2-phenylquinoline was then prepared, and identity was established for the synthetic and natural substances.

The synthetic route followed Fuson and Burness[7] in the preparation of 2-phenyl-4-quinolone from ethyl anthranilate and acetophenone diethyl ketal. Treatment of the quinolone with phosphorus oxychloride gave the 4-chloro compound, and this was converted to the 4-methoxy compound by sodium methoxide in methanol at 100°. Relationships between the synthetic and natural series are indicated in the reaction chart. Comparisons were made by mixed m.p., infrared and ultraviolet spectra for 4-methoxy-2-phenylquinoline, 2-phenyl-4-quinolone and 1-methyl-2-phenyl-4-quinolone.

The infrared and ultraviolet absorption spectra for 4-methoxy-2-phenylquinoline showed no novel effects. The ultraviolet maxima were at 254 and 294 mμ, and the second maximum was shifted to 316 mμ in the hydrochloride. This is characteristic of quinolines and isoquinolines.[8]

The presence of 4-methoxy-2-phenylquinoline in a plant of the *Rutaceae* recalls the occurrence of cusparine, galipine and simpler quinolines in angostura (*Cusparia febrifuga* Humb.) bark and suggests that a quinoline or quinolone structure may be involved in other alkaloids of the *Lunasia* group. Isolation and structural studies on other *Lunasia* bases are in progress.

Acknowledgment.—We are indebted to the Section of Plant Introduction, Agricultural Research Service, U. S. Department of Agriculture, for obtaining and identifying the plant material and to Dr. Felipe R. Amos, Director, Bureau of Forestry, Department of Agriculture, Republic of the Philippines, for making available the collections. Extractions were carried out by Mr. D. L. Rogerson and Mr. J. Link. The instrumental work was carried out by Mr. H. F. Byers and Miss Catherine Monaghan. Analyses were performed in the laboratories of Mr. W. Manser, Zurich, Switzerland, and Dr. W. C. Alford, National Institute of Arthritis and Metabolic Diseases.

Experimental[9]

Natural Series. Isolation of 4-Methoxy-2-phenylquinoline from *Lunasia amara* Leaves.—A 20-kg. quantity of dried, ground leaves was extracted with 30 gal. of 95% ethanol at 50–60° for 1 hr. The treatment was repeated, and the combined extracts were concentrated under reduced pressure to a volume of 8 l. The concentrate was processed in two parts. To 4 l. of concentrate there was added 3 l. of water and 1 l. of 2 *N* sulfuric acid, and the mixture was filtered (Supercel). The combined filtrate and filtrate washings (500 ml. of 2 *N* sulfuric acid and 500 ml. of water) were extracted with trichloroethylene (the wash contained no alkaloids and was discarded). The solution was made alkaline with sodium carbonate, and an organic base fraction was separated by extraction with trichloroethylene (fifteen 200-ml. portions) and by continuous extraction with chloroform. From the combined organic solvent phases from the entire run there was obtained 300 g. (1.5%) of black viscous residue.

An 80-g. portion of this residue was dissolved in 200 ml. of ethanol, and this was added with rapid stirring to 2 l. of 1% hydrochloric acid at 50°. After filtration (Supercel), the combined filtrate and washings (500 ml. of water at 70°) were cooled and washed with ether to yield 6.8 g. of discolored, viscous oil which gave weak positive tests with Mayer and silicotungstic acid reagents. The aqueous solution was made alkaline (potassium carbonate) and the organic bases were extracted with chloroform to yield 42 g. of crude, mixed alkaloids.

This residue was treated with 400 ml. of warm benzene (about 1 g. of insoluble material remained); the benzene solution was filtered and used for chromatography with 1400 g. of alumina (Merck, acid-washed). Sixty fractions were collected. Fractions 1–6 (benzene, 1.5 l. total) gave 0.19 g. of non-basic oil; fractions 7–14 (benzene, 3.5 l. total) gave 2.02 g. of colorless oil which soon solidified.[10] Recrystallization from pentane gave colorless needles, m.p. 66–67°.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.42; H, 5.47; N, 5.90.

Alkaloid Derivatives.—The hydrochloride was prepared from 200 mg. of the base with hydrogen chloride in methanol. Recrystallization from methanol–ether gave an analytical sample whose melting point exhibited an unusual behavior. The crystalline material sintered at 110–120° and melted at 148–151° with gas evolution; the colorless melt solidified on cooling and thereafter melted at 240–243°. The latter m.p. is close to that of 2-phenyl-4-quinolinol (2-phenyl-4-quinolone), indicating that demethylation occurred during the heating period.

Anal. Calcd. for $C_{16}H_{13}ON \cdot HCl \cdot H_2O$: C, 66.31; H, 5.62; N, 4.84; OMe, 10.71. Found: C, 66.28; H, 5.54; N, 4.87; OCH_3, 10.62; NCH_3, none.

The perchlorate was prepared from 160 mg. of base in ethanol with perchloric acid. Recrystallization from ethanol gave an analytical sample; colorless rods, m.p. 215–218°.

Anal. Calcd. for $C_{16}H_{13}ON \cdot HClO_4$: C, 57.23; H, 4.20; N, 4.17. Found: C, 57.30; H, 4.32; N, 4.17.

The methiodide was prepared from 500 mg. of the base by heating in methyl iodide (2 ml.) at 100° for 18 hr. The product (780 mg.) was recrystallized from methanol to yield bright yellow needles, m.p. 148–151°.

Anal. Calcd. for $C_{17}H_{16}ONI$: C, 54.12; H, 4.28; N, 3.71. Found: C, 54.12; H, 4.39; N, 3.73.

(5) L. Knorr and E. Fertig, *Ber.*, **30**, 937 (1897).

(6) B. Witkop and J. B. Patrick, THIS JOURNAL, **74**, 3855 (1952).

(7) R. C. Fuson and D. M. Burness, *ibid.*, **68**, 1270 (1946).

(8) G. W. Ewing and E. A. Steck, *ibid.*, **68**, 2181 (1946).

(9) All melting points were taken with a Kofler stage.

(10) Continuing elution of the column with the usual solvent mixtures gave a series of fractions from which six additional compounds, in varying states of purity, were obtained. These will be described in connection with structural studies.

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2-Phenyl-4-quinolinol (2-Phenyl-4-quinolone).—A small sample (50 mg.) of the base hydrochloride was heated (oil-bath) at 180° for 5 minutes (the material melted and resolidified). The product was dissolved in 1 *N* sodium hydroxide solution (2 ml.), precipitated by acidification with acetic acid, and recrystallized from aqueous ethanol to give 32 mg. of colorless needles, m.p. 256–258° with crystal transformations at 215° and at 247–251° (partial melting and resolidification occurred at the latter temperature).

A mixed m.p. with synthetic material showed the same effects, and the infrared spectra (potassium bromide disks) of the synthetic material and that obtained *via* the plant alkaloid were identical.

1-Methyl-2-phenyl-4-quinolone.—To a solution of 160 mg. of the alkaloid methiodide in 10 ml. of warm water there was added 2 ml. of 1 *N* sodium hydroxide solution. After warming (steam) for 10 minutes, the product was collected, dried (crude yield, 91%) and recrystallized from ethyl acetate–pentane to give 62 mg. of colorless needles, m.p. 142.5–144.5°. Further crystallization from ethyl acetate gave a sample with m.p. 143.5–144.5°.

Synthetic Series. 2-Phenyl-4-quinolinol (2-Phenyl-4-quinolone).—This compound was prepared according to Fuson and Burness[7] from acetophenone diethyl ketal and ethyl anthranilate. The crude product (74%, m.p. 249–251°) was recrystallized from aqueous ethanol to give colorless needles, m.p. 257–258°, with crystal transformations at 243° and 250° (reported[7] m.p. 259–260°).

2-Phenyl-4-chloroquinoline.—2-Phenyl-4-quinolone was converted to the 4-chloro compound by heating with phosphorus oxychloride according to Knorr.[5] The product (crude yield 97%) was recrystallized from ethanol; colorless needles, m.p. 60–61.5° (reported[5] m.p. 63–64°).

4-Methoxy-2-phenylquinoline (I).—To a solution of 2.7 g. of sodium in 65 ml. of anhydrous methanol there was added 5.0 g. of the 4-chloro compound. After 48 hr. at 90–100° the product was isolated by the usual manipulations. A 4.5-g. (92%) yield of colorless needles, m.p. 66–67° (from pentane) was obtained. This material was unchanged in melting point on further recrystallization from pentane (reported[5] m.p. 69–70°). A mixed melting point with the natural alkaloid was not depressed. The ultraviolet and infrared absorption spectra of this material were found to be identical with those of the natural alkaloid.

1-Methyl-2-phenyl-4-quinolone.—One gram of 2-phenyl-4-quinolone was methylated with dimethyl sulfate, using a total of 80 ml. of 20% sodium hydroxide solution and 25 ml. of dimethyl sulfate. The crude product (1.0 g., 92%) was recrystallized several times from ethyl acetate to yield colorless rods, m.p. 143.5–144.5°, which proved to be identical (mixed m.p., ultraviolet and infrared spectra) with the corresponding material obtained as described in the previous section.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.39; H, 5.71; N, 6.03.

This melting point is not in complete agreement with literature values.[5,6] It was found that crystallization from aqueous ethanol formed a labile material, m.p. 70–79°, followed by resolidification and remelting at 142–145°. The infrared spectrum of this material in chloroform was essentially the same as that of the usual product, but in a Nujol mull two new medium intensity bands at 2.91 and 5.97 μ were noted. After drying *in vacuo* only the higher m.p. was observed, and the Nujol mull spectrum was identical with that of the product obtained from ethyl acetate. In one experiment a sample melting at 136° was obtained.

Ultraviolet absorption spectra were taken with a Cary model 11 spectrophotometer. Values for significant compounds are in Table I.

TABLE I

ULTRAVIOLET SPECTRA DATA

λ_{max}, mμ	log max.	λ_{min}, mμ	log min.
4-Methoxy-2-phenylquinoline (95% ethanol)			
254	4.64	230	4.32
294	4.01	276	3.97
4-Methoxy-2-phenylquinoline hydrochloride (95% ethanol)			
231	4.37	239	4.31
254	4.51	283	3.90
316	4.16		
1-Methyl-2-phenyl-4-quinolone (95% ethanol)			
251	4.52	227	4.24
326	4.12	285	3.40
338	4.18	330	4.11
1-Methyl-2-phenyl-4-quinolone (0.9 *N* hydrochloric acid)			
234	4.65	282	3.64
314	4.17		
2-Phenyl-4-quinolone (95% ethanol)			
257	4.55	227	4.13
310 sh	3.90	285	3.64
325 sh	4.06		
334	4.08		
2-Phenyl-4-quinolone (1 *N* hydrogen chloride in ethanol)			
231	4.36	216	4.30
250 sh	4.36	240	4.24
268	4.49	283	3.79
318	4.28		
2-Phenyl-4-quinolone (1 *N* potassium hydroxide in 90% ethanol)			
262	4.27	234	3.94
325	3.59	290	3.30

Infrared absorption spectra were taken with a Perkin–Elmer model 21 instrument. Reference spectra[11] were obtained for 4-methoxy-2-phenylquinoline (chf.), 4-methoxy-2-phenylquinoline hydrochloride (Nujol) and 1-methyl-2-phenyl-4-quinolone (chf.).

BETHESDA 14, MD.

(11) These spectra have been deposited as Document Number 5075 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting in advance $1.25 for photoprints or $1.25 for 35 mm. microfilm, by check or money order payable to Chief, Photoduplication Service, Library of Congress

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[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE]

Synthesis of Allothreonine–Threonine from Acetaldehyde and Glycine by a Rat Liver Enzyme[1]

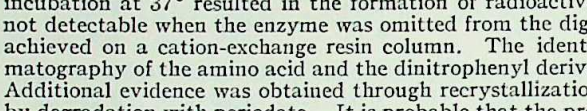
BY JAMES B. GILBERT[2]

RECEIVED OCTOBER 22, 1956

Addition of acetaldehyde and radioactive glycine to a buffered (*p*H 7.9) aqueous solution of a rat liver fraction followed by incubation at 37° resulted in the formation of radioactive allothreonine–threonine.[3] This β-hydroxy-α-amino acid[3] was not detectable when the enzyme was omitted from the digest. Separation of the radioactive products of the reaction was achieved on a cation-exchange resin column. The identification of allothreonine–threonine was accomplished by chromatography of the amino acid and the dinitrophenyl derivative of the amino acid with the respective authentic compounds. Additional evidence was obtained through recrystallization to constant specific activity with carrier DL-allothreonine, and by degradation with periodate. It is probable that the predominant end product of the reaction was one or both isomers of allothreonine. The significance of this finding in relation to intermediary metabolism is discussed.

I. Introduction

A relationship between glycine and β-hydroxy-α-amino acid metabolism was first stated by Knoop.[4] The hypothesis that β-phenylserine was cleaved *in vivo* to benzoic acid and glycine was made on the evidence of the isolation of hippuric acid as the excretory product of this β-hydroxy-α-amino acid. Considerably later, Braunshtein[5] described the enzymatic conversion of several β-hydroxy-α-amino acids, including threonine but not serine,[6] to glycine and the corresponding aldehyde.



(1)

The reaction consisted of cleavage of the bond between the second and third carbon atoms; *e.g.*, β-phenylserine yielded glycine and benzaldehyde as end products.[7] The same reaction was also observed non-enzymatically. For example, in strongly alkaline solutions, β-hydroxy-α-amino acids yielded glycine.[8,9]

The interesting and suggestive finding that a reversible splitting of threonine occurred in the presence of pyridoxal and certain metal ions in aqueous solution was described by Metzler, Longenecker and Snell.[10] It therefore appeared of interest to examine the reversibility of the reaction, eq. 1, when the enzyme was the catalyst. Indeed, this might well be the synthetic route suggested by the work from several sources[11–13] that demonstrated that glycine was a precursor of threonine in yeast. This enzyme which has been variously termed "glycinogenase"[5] and "threonine aldolase"[14] has been shown to be present in liver and kidney tissue of numerous mammals and the pigeon,[5] and probably in Neurospora.[15,16]

II. Experimental

Enzymatic Digests.—The rat liver fractions employed were prepared as previously described.[7] Activities of the three enzyme preparations used were expressed as 20, 26 and 33 μmoles benzaldehyde/hr./mg. N, with *erythro*-β-phenyl-DL-serine as substrate under conditions previously specified.[7] The reaction mixtures consisted of 200 μmoles of glycine plus a trace amount of glycine-2-C^{14} or glycine-1-C^{14}, 200 μmoles of acetaldehyde, and 10 mg. of the purified rat liver enzyme in a volume of 5 ml. of which 3 ml. were 0.15 *M* borate buffer, *p*H 8.0. The digests were incubated at 37° under aerobic conditions with agitation for 4 hours. The final *p*H of the digests was 7.9. The reaction was stopped by addition of 1 ml. of a 5% solution of trichloroacetic acid (aqueous). After precipitation of the protein, the solutions were lightly centrifuged and the supernatant decanted. Two types of controls accompanied the above, consisting of (1) enzyme (10 mg.) plus 3 ml. of borate buffer plus a trace of labeled glycine and (2) 200 μmoles of acetaldehyde and glycine each, plus a tracer amount of radioactive glycine.

Compounds.—Glycine-1-C^{14} and glycine-2-C^{14} were commercially obtained (Nuclear Instrument and Chemical, and Tracerlab, Inc., respectively). They were purified by Dowex 50 column chromatography followed by unidimensional paper chromatography in "formix" followed by elution. After these procedures, the purity was tested by two-dimensional paper chromatography. A radioautograph and a test of the chromatogram for ninhydrin positive areas were made. No spots other than that of glycine were present. Threonine-C^{14} (uniformly labeled) was a Schwarz Laboratory product. The specific activities of the three radioactive amino acids were 39, 18 and 0.8 μC./mg., respectively. The glycine, DL-threonine and DL-allothreonine used were recrystallized commercial compounds with correct analytical values. Dinitrophenyl (DNP) derivatives of several amino acids were kindly supplied by Dr. H. Sober.[17]

Chromatographic Materials and Technique.—Dowex 50 (200 mesh) was used in a column measuring 2.2 × 50 cm.

(1) The subject matter of this paper was presented at the 127th National Meeting of the American Chemical Society at Cincinnati, Ohio, March, 1955, Abstracts of Papers, p. 26-C.

(2) Biochemical Institute, Department of Chemistry, University of Texas, Austin 12, Texas.

(3) Allothreonine–threonine will be employed as the designation for any one or more of the four possible optical isomers of α-amino-β-hydroxybutyric acid without distinction.

(4) F. Knoop, *Z. physiol. Chem.*, **89**, 151 (1914).

(5) A. E. Braunshtein and G. Ia. Vilenkina, *Doklady Akad. Nauk S.S.S.R.*, **66**, 243 (1949); G. Ia. Vilenkina, *ibid.*, **84**, 559 (1952).

(6) The enzyme as so far characterized also has been shown to have no activity with respect to α-methylserine (see reference in footnote 7).

(7) J. B. Gilbert, THIS JOURNAL, **76**, 4183 (1954).

(8) T. Wieland and L. Wirth, *Ber.*, **82**, 468 (1949).

(9) J. M. Bremner, *Nature*, **168**, 518 (1951).

(10) D. E. Metzler, J. B. Longenecker and E. E. Snell, THIS JOURNAL, **76**, 639 (1954)

(11) F. Kogl and W. A. F. Borg, *Z. physiol. Chem.*, **269**, 97 (1941).

(12) I. A. Rossi and C. Cennamo, *Boll. soc. ital. biol. sper.*, **20**, 194 (1945).

(13) A. R. Fanelli, *Farmaco sci. e tec.* (*Pavia*), **1**, 6 (1946).

(14) S. C. Lin and D. M. Greenberg, *J. Gen. Physiol.* **38**, 181 (1954). Note also the recent report, M. A. Karasek and D. M. Greenberg, *Federation Proc.*, **15**, 284 (1956), that sheep liver contained two enzymes, one cleaving L-allothreonine, and the other L-threonine. The enzyme active with respect to the former compound was activated by pyridoxal phosphate.

(15) R. P. Wagner and A. Bergquist, *J. Biol. Chem.*, **216**, 251 (1955).

(16) A preliminary report indicated the presence of the enzyme in *Tetrahymena pyriformis*. V. C. Dewey and G. W. Kidder, Resumes of Communications, International Congress of Biochemistry, 3rd, Brussels, 1955, p. 92.

(17) E. R. Blout and H. Sober, THIS JOURNAL, **76**, 1328 (1954).

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at a flow rate of 7.5 ml./hr. Size of fractions cut was approximately 9–10 ml.; 1.5 *N* HCl was used as the eluting agent throughout.[18]

All two-dimensional chromatograms employed 17 in. squares of Whatman no. 1 paper. Unidimensional chromatograms were either on this size paper or on paper strips 1/4 in. wide and 15 in. long. Solvents employed were (a) for amino acids (1) phenol, H_2O (the phenol was saturated with respect to a 10% sodium citrate aqueous solution) followed by (2) formic acid, *t*-butyl alcohol, H_2O ("formix") (volume proportions 15:70:15); (b) for DNP-amino acids (1) toluene, chloroethanol, pyridine, 0.8 *N* NH_3 (5:3:1.5:3)[19] (2) 1.5 *M* phosphate (*p*H 6).[19] The dinitrophenyl derivative of enzymatically synthesized allothreonine–threonine was prepared by the procedure of Sanger.[20]

Assay of Radioactivity.—Counting of radioactive samples was accomplished on a continuous-flow windowless counter using helium (98.7%)-butane (1.3%) as the self-quenching gas mixture. Only aluminum planchets were employed for $BaCO_3$ samples. All other samples were plated directly on ground glass or aluminum planchets. Where measurement of low activities was important, *e.g.*, Fig. 4, a Robinson counter with background of 3.8–4.0 c.p.m. was employed. Counting was for such a period of time as to make the standard error 5% or less on the corrected sample measurements.

Degradation of Threonine.—Allothreonine–threonine was degraded by the periodate method[21] with some modification. The periodate oxidation flask was connected to two ice-cold bubblers containing 0.1% 2,4-dinitrophenylhydrazine in 2 *N* HCl, followed by a bubbler containing 0.5 *N* sodium hydroxide. The acetaldehyde, as the 2,4-dinitrophenylhydrazone, was filtered, plated and counted. Carbonate from the sodium hydroxide bubbler was precipitated by addition of ammonium chloride and $BaCl_2$.[22]

III. Results

After removal of the protein, an aliquot of the enzymatic digest containing acetaldehyde and glycine-C^{14} was chromatographed in two dimensions (Fig. 1) with the result that a ninhydrin positive, radioactive spot (labeled B) was observed in addition to the glycine area (A). No such spot appeared in a control from which enzyme had been excluded.

The protein-free reaction mixtures, originally incubated with and without enzyme added to the initial incubation mixtures, were placed on a Dowex 50 resin column and eluted with 1.5 *N* HCl. The results (Fig. 2) indicated that where enzyme was originally present, two peaks appeared at 340 and 360 ml., respectively. When the rat liver fraction was absent, only the peak at 360 ml. was present. The two peaks at 360 ml. contained approximately equal amounts of radioactivity. The radioactivity contained in the 490–600 ml. fractions represented glycine.

The several fractions representing the peaks at 340 and 360 ml. were combined and chromatographed in two dimensions with the result shown in Fig. 3. It was noted that when carrier DL-threonine was added, the radioactivity was congruent with this spot when enzyme was present in the incubation mixture. In the other chromatogram, where no enzyme was added, no radioactivity was present; only the ninhydrin positive carrier, DL-threonine area, was demonstrable.[23] The identity of the second component was not ascertained. However, it was present predominantly

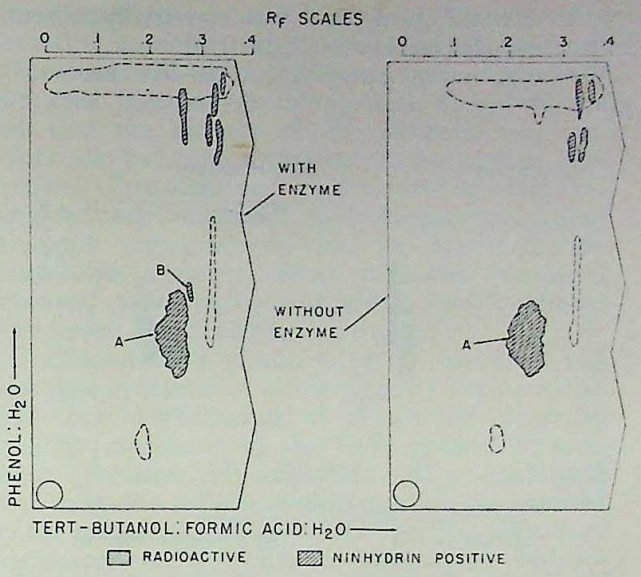

Fig. 1.—Two-dimensional paper chromatograms of aliquots from reaction mixtures of glycine-2-C^{14} and acetaldehyde, with and without enzyme added. Areas of color development following application of ninhydrin are indicated as well as optical densities on a coincident radioautograph. The origin is designated by the circle at the lower left corner in both instances. The chromatograms have been interrupted in the *t*-butyl alcohol:formic acid:H_2O dimension and R_f scales substituted: A, glycine; B, area suggesting synthesis of allothreonine–threonine; radioactive areas in upper right portion are unidentified; areas enclosed by dashed line represent light radioactive or ninhydrin positive areas which may be ignored.

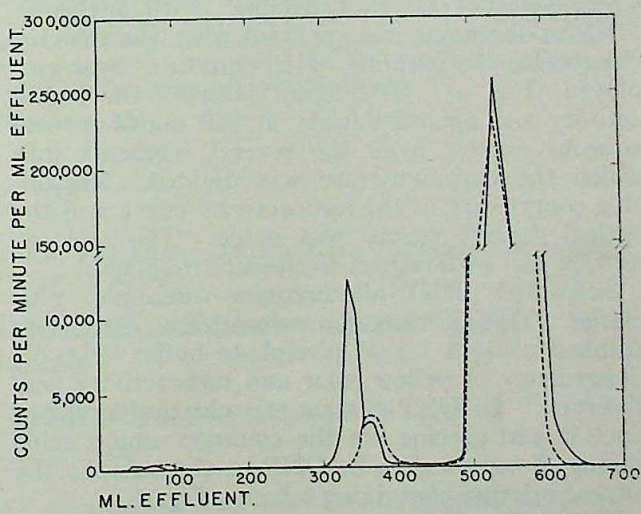

Fig. 2.—Separation on Dowex 50 column of products of reaction of acetaldehyde with glycine-1-C^{14}, 1.5 *N* HCl employed as eluant: ——, original incubation mixture contained enzyme; – – –, enzyme absent from the initial digest.

(18) W. H. Stein and S. Moore, *Cold Spring Harbor Symposia Quant. Biol.*, **14**, 179 (1949).
(19) A. L. Levy, *Nature*, **174**, 126 (1954).
(20) F. Sanger, *Biochem. J.*, **45**, 563 (1949).
(21) A. M. Delluva, *Arch. Biochem. Biophys.*, **45**, 443 (1953).
(22) M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert and P. E. Yankwich, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 85.
(23) The second type of control, which contained enzyme and radioactive glycine only, was also subjected to column and paper chromatography. Essentially no radioactivity was found in the 300–400 ml. interval from the cation-exchange resin column. One-third of this interval volume was concentrated and examined by two-dimensional paper chromatography. No ninhydrin color was located in the chromatograms. It was concluded that the enzyme was a negligible source of threonine, if it contributed any at all.

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in the 360 ml. peak and was essentially absent from the early fractions of the 340 ml. peak.

The area marked threonine on the left chromatogram of Fig. 3 was eluted and reacted with 1-

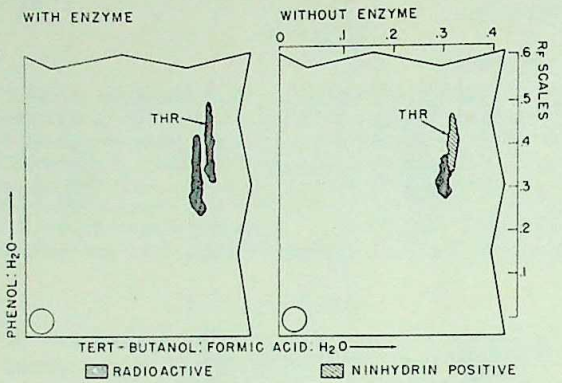

Fig. 3.—Two-dimensional paper chromatograms of aliquots from the radioactive fractions eluted from Dowex-50 column in the interval 300 to 400 ml., inclusive (*cf.* Fig. 2). Carrier DL-threonine added and location indicated (THR). Conventions as in Fig. 1 except that chromatograms have been interrupted in both solvent dimensions and approximate R_f scales substituted. The "with enzyme" chromatogram is drawn to the same R_f scale as the chromatogram on the right.

fluoro-2,4-dinitrobenzene. The resulting dinitrophenyl derivative was chromatographed unidimensionally in two solvent systems: toluene, chloroethanol, pyridine, NH_3 and phosphate buffer. Coincidence of DNP-"threonine" with authentic DNP-DL-threonine was apparent when the toluene, chloroethanol, pyridine, NH_3 mixture was employed (Fig. 4). The figure presents the radioactivity and optical density at 360 mμ of several aqueous eluates from the several segments into which the chromatogram was divided. Reasonable congruency of the radioactivity curve and the optical density curves was noted. The sole exception was with respect to the dinitrophenol.

Suspected DNP–allothreonine–threonine plus carrier DNP-DL-threonine were also chromatographed using a 1.5 *M* phosphate buffer (Fig. 5). Congruency of yellow color and radioactivity was observed. Di-DNP-cystine was chromatographed since it and glycine are the common amino acids having R_f values close to DNP-DL-threonine in the solvent mixture containing toluene (Fig. 4).

The radioactivity corresponding to allothreonine–threonine was eluted from a paper chromatogram and recrystallized with DL-threonine. This was effected by addition of absolute alcohol to an aqueous solution of the amino acid. The result was: original solution, 44 c.p.m./mg. DL-threonine; first crystallization, 37; third, 30; sixth, 22; ninth, 17. When eluted allothreonine–threonine was recrystallized with DL-allothreonine, the result was: original solution, 118 c.p.m./mg. DL-allothreonine; third crystallization, 108; fifth, 110; sixth, 105.

Degradation of allothreonine–threonine-1-C^{14}, *i.e.*, initial substrate glycine-1-C^{14}, together with carrier by the periodate method yielded the following data: % of activity of original allothreonine–threonine in C-1, 70%; C-2, < 1%; C-3,4, <1%.[24] This localization of the isotope is compatible with

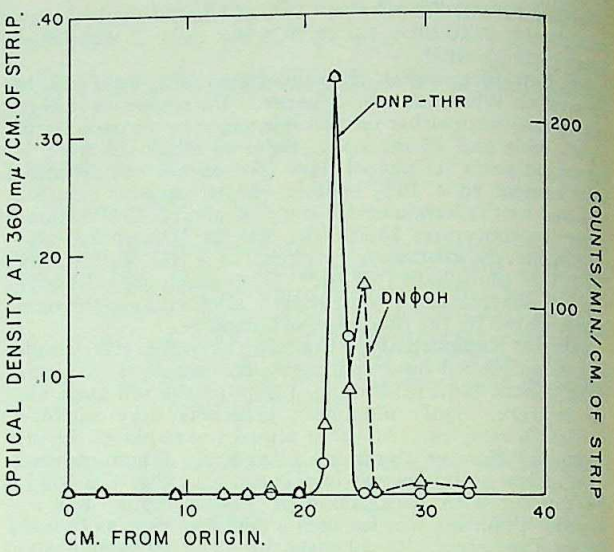

Fig. 4.—Radioactivity and yellow color recorded as a function of distance along a unidimensional paper chromatogram to which was added DNP-"threonine" and authentic carrier DNP-DL-threonine, prior to development in the toluene, chloroethanol, pyridine, NH_3 solvent system. DNP-"threonine" = a fraction from an enzymatic digest which was purified and tentatively identified as allothreonine-threonine by the procedures indicated in Figs. 2 and 3, and which reacted with fluorodinitrobenzene. DNφOH, dinitrophenol: Δ---Δ, optical density; O——O, radioactivity. Chromatogram divided into segments prior to elution and measurement of data. Abscissa points represent distance of midpoint of each segment from origin.

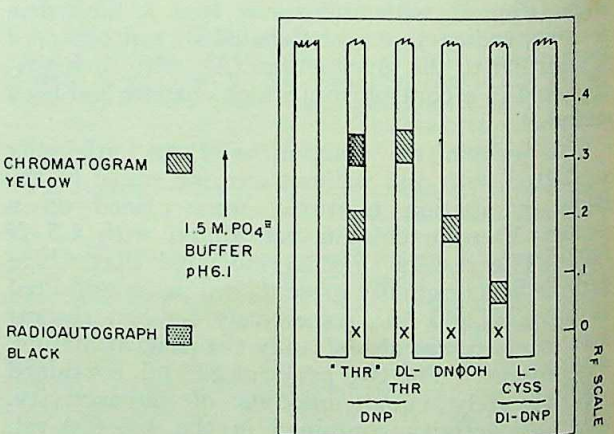

Fig. 5.—Unidimensional chromatogram of several DNP-derivatives: developing solvent, 1.5 *M* phosphate buffer, *p*H 6.1. Except for DNP-"THR," the compounds were authentic. DI-DNP-L-CYSS, di-DNP derivative of L-cystine. Other compounds identified by convention of Fig. 4. Origin on each of the narrow strips is at X.

(24) The recovery of radioactivity of carbons one and two of threonine was somewhat low in our experience. Yield was approximately 70% whereas Delluva[21] reported a yield of 85% for carbon two but made no mention of recovery of carbon one. For example, L-threonine-C^{14} (uniformly labeled—checked by specific activity determination by this periodate method, and stated in arbitrary units: C-1 0.68; C-2, 0.66; C-3,4, 0.76) yielded a recovery of 72% in C-1 and 69% in C-2. However, yield is adequate to prove localization.

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the reaction proceeding as a simple reversal of eq. 1. More devious routes might well introduce randomization.

The conclusion reached from these results is that the predominant product of this enzymatic reaction *in vitro* is an isomer or isomers of DL-allothreonine. Indeed, this may be the only product. However DL-threonine (or L- or D-threonine) could be present in rather large proportion and not be detected. The specific stereoisomer(s) produced awaits future recrystallization, microbiological experiments, etc., in order to determine its configuration.

IV. Discussion

Inasmuch as allothreonine has not been identified in biological material, it obviously is impossible to relate this compound to present schemes of intermediary metabolism. The present findings do suggest the possible natural occurrence of this diastereoisomer, however.[25]

It is worth reiterating that no serious attempt has been made in this present work to identify D- or L-threonine except as a large component. The compound might well escape detection if present in less than approximately 30% of the total amount of threonine. Indeed suggestive of the probability of this occurrence, but in lower forms of life, is the previously cited evidence obtained in yeast.[11-13,26]

Also suggestive is the fact that L-allothreonine was cleaved at approximately seven times the rate that L-threonine was split by the enzyme concerned[5] (prepared from rat liver).[14] So it may well be true that the kinetics of the synthetic reaction, favors allothreonine formation in some such proportion. Furthermore, in the corresponding reversible model reaction[10] both threonine and allothreonine are produced and in approximately comparable amounts. Since both are pyridoxal catalyzed, a somewhat similar relationship should be expected for the enzymatic reaction.

The essentiality of threonine for mammals implies that synthesis of L-threonine by such a route, if it does indeed occur, is of a relatively small quantity compared to the daily growth requirement. Perhaps the availability of acetaldehyde may limit the utility of this reaction in animals. By the same token in yeast, the reaction may be of importance as a synthetic mechanism because acetaldehyde is a major metabolite.

Acknowledgment.—The author wishes to thank Dr. J. P. Greenstein for his interest, Drs. H. Sober and E. Peterson for their advice on chromatography, Mr. R. J. Koegel for the elemental analyses, and Dr. M. Calvin for the opportunity to acquire experience in radioactive isotopic procedure some time ago.

(25) Relative to metabolic utilization, if not metabolic occurrence, D-allothreonine was used by certain mutant microörganisms in the biosynthesis of isoleucine and threonine [H. E. Umbarger and E. A. Adelberg, *J. Biol. Chem.*, **192**, 883 (1951)]. Therefore, this enzyme present in certain lower forms may well serve the production of a precursor of certain amino acids in such microörganisms. However, in the rat it is well established that only one isomer, L-threonine, is utilized for growth purposes [H. D. West and H. E. Carter, *ibid.*, **122**, 611 (1938)].

(26) A more remote possibility is suggested by a *Neurospora crassa* mutant which revealed properties which may be explained by an alternate metabolic pathway for the synthesis of threonine [E. A. Adelberg, C. A. Coughlin and R. W. Barratt, *J. Biol. Chem.*, **216**, 425 (1955)]. This is suggested inasmuch as this double mutant was blocked as follows: homoserine —¦→ threonine ⟶ α,β-dihydroxy-β-ethylbutyric acid —¦→ α-keto-β-ethylbutyric acid. It, in minimal medium, synthesized threonine at a slow rate. That one strain of this species, at least, has the enzyme in question, has been reasonably well authenticated by Wagner and Bergquist (footnote 15). However, glycine did not stimulate production of α,β-dihydroxy-β-ethylbutyric acid. Compare also discussions of the possibility of L-threonine synthesis by this condensation reaction in *Escherichia coli* [J. O. Meinhart and S. Simmonds, *J. Biol. Chem.*, **213**, 329 (1955)] and in *Clostridium kluyveri* [N. Tomlinson, *ibid.*, **209**, 597 (1954)].

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE FRANCIS DELAFIELD HOSPITAL]

Some New *o*-Phenylenediamines and the Related Benzimidazoles, Benzotriazoles and Quinoxalines

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The synthesis of 3,4-diamino-5-nitrophenetole and 3,4-diamino-2-nitroanisole is described. These *o*-diamines have been used to prepare the related benzimidazoles, benzotriazoles and quinoxalines which were needed to continue an investigation of the inhibition of developing *R. pipiens* embryos by such heterocyclic compounds. Derivatives of 3,4-diamino-2-nitroanisole have served as useful reference compounds for the solution of several problems of structure.

Among a number of benzimidazoles, benzotriazoles and quinoxalines previously reported,[1,2] several have shown interesting properties as inhibitors of developing *R. pipiens* embryos. The most active of these were 4-methoxy-6-nitrobenzimidazole, 4-methoxy-6-nitrobenzotriazole and 5-methoxy-7-nitroquinoxaline.[3] Isomers of these heterocyclic compounds, in which the nitro and methoxy groups were interchanged, exhibited an approximately equal level of activity.[4] It seemed of interest, therefore, to investigate whether the activity of such compounds might be enhanced or diminished by changing the methoxy group to ethoxy and changing the relative configuration of the nitro and methoxy groups to *ortho* rather than *meta*. The synthesis of the desired substances required the preparation of two new substituted *o*-phenyl-

(1) H. Gillespie, M. Engelman and S. Graff, THIS JOURNAL, **76**, 3531 (1954).

(2) H. Gillespie, M. Engelman and S. Graff, *ibid.*, **78**, 2445 (1956).

(3) K. Liedke, M. Engelman and S. Graff, *J. Exp. Zool.*, **127**, 201 (1954).

(4) K. Liedke, private communication.

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enediamine intermediates, 3,4-diamino-5-nitrophenetole and 3,4-diamino-2-nitroanisole.

4-Amino-3,5-dinitrophenetole was obtained by nitration of an alcoholic suspension of *p*-toluenesulfonyl-*p*-phenetidide according to the procedure of King and Beer[5] for the preparation of 3,5-dinitro-4-*p*-toluenesulfonamidoanisole and hydrolysis of the intermediate 3,5-dinitro-4-*p*-toluenesulfonamidophenetole. This procedure was more effective than the hydrolysis of the nitration product of 3-nitro-4-*p*-toluenesulfonamidophenetole.[6] Reduction of the 4-amino-3,5-dinitrophenetole by ammonium sulfide gave a 70% yield of 3,4-diamino-5-nitrophenetole. The *o*-diamine was treated with formic acid, nitrous acid, glyoxal and diacetyl to give, respectively, 6-ethoxy-4-nitrobenzimidazole, 6-ethoxy-4-nitrobenzotriazole, 7-ethoxy-5-nitroquinoxaline and 2,3-dimethyl-7-ethoxy-5-nitroquinoxaline. Amino derivatives were prepared by catalytic reduction of the nitro group.

Attempts to obtain 3,4-diamino-2-nitroanisole by ammonium sulfide reduction of 4-amino-2,3-dinitroanisole yielded only resinous products. The *o*-diamine, however, was isolated readily as the hydrochloride on treating the aminodinitroanisole in alcohol with the calculated quantity of stannous chloride and hydrochloric acid for the reduction of one nitro group. The product was shown to be an *o*-diamine by reaction with benzil to give 2,3-diphenyl-6-methoxy-5-nitroquinoxaline. The desired 5-methoxy-4-nitrobenzimidazole, 5-methoxy-4-nitrobenzotriazole, 6-methoxy-5-nitroquinoxaline and 2,3-dimethyl-6-methoxy-5-nitroquinoxaline were obtained by ring closure of the *o*-diamine with appropriate reagents as indicated in the case of 3,4-diamine-5-nitrophenetole. The 5-methoxy-4-nitrobenzotriazole obtained in this fashion was identical with that prepared earlier[7] by nitration of 1-acetyl-5-methoxybenzotriazole, thus confirming the previous assignment of structure. Hydrolysis of the methoxynitrobenzimidazole and benzotriazole by 48% hydrobromic acid gave the corresponding hydroxy compounds.

Meldola and Eyre[8] obtained 2,3,4-triaminoanisole in the form of a crude hydrochloride by complete reduction of 4-amino-2,3-dinitroanisole with tin and hydrochloric acid. The triamine condensed with benzil to yield an aminomethoxydiphenylquinoxaline, m.p. 215°. This product could be either 5-amino-6-methoxy- or 5-amino-8-methoxy-2,3-diphenylquinoxaline. A definite assignment of structure at that time was not possible for lack of reference compounds. Catalytic reduction of 2,3-diphenyl-6-methoxy-5-nitroquinoxaline gave the 5-amino-6-methoxy derivative having m.p. 156–157°. To obtain the 5,8-isomer, 4-acetamido-2,3-dinitroanisole was reduced by hydrogen at atmospheric pressure in the presence of palladium-on-carbon. The crude 4-acetamido-2,3-diaminoanisole thus produced reacted with benzil to give 5-acetamido - 2,3 - diphenyl -8 - methoxyquinoxaline which was hydrolyzed by alcoholic hydrogen chloride to the free amino compound, m.p. 214–215°. The product obtained by Meldola and Eyre must have been 5-amino-2,3-diphenyl-8-methoxyquinoxaline.

Nitration of 3,4-diacetamidoanisole in acetic acid with concentrated nitric acid yielded a mononitro derivative, m.p. 224–227°. This could be any one of three compounds: namely, 3,4-diacetamido-2-nitroanisole (A), 3,4-diacetamido-5-nitroanisole (B) or 4,5-diacetamido-2-nitroanisole (C). Attempts to prepare A and B by acetylation of 3,4-diamino-2-nitroanisole and 3,4-diamino-5-nitroanisole, respectively, led to mixtures difficult to purify. These mixtures undoubtedly contained some of the monoacetyl derivatives along with the diacetyl derivatives and also traces of 2-methylbenzimidazoles. Phillips[9] has shown that mono- and diacetyl derivatives of *o*-diamines readily cyclize to 2-methylbenzimidazoles. The structure of the nitration product was elucidated by the preparation of the isomeric 2-methylbenzimidazoles. A modification of Phillips' procedure for the preparation of 2-substituted benzimidazoles was employed to convert 3,4-diamino-2-nitroanisole to 5-methoxy-2-methyl-4-nitrobenzimidazole, m.p. 204–205°, and 3,4-diamino-5-nitroanisole yielded 6-methoxy-2-methyl-4-nitrobenzimidazole, m.p. 226–227°. When the nitration product was heated with hydrochloric acid, it cyclized to a 2-methylbenzimidazole, m.p. 172–174°. This must be 5-methoxy-2-methyl-6-nitrobenzimidazole, since the melting point eliminates the other two possibilities. The nitration product is therefore 4,5-diacetamido-2-nitroanisole (C).

All of the benzimidazoles, benzotriazoles and quinoxalines here reported are being biologically screened against various test systems. The results of the biological work will be reported elsewhere.

Experimental[10]

3,5-Dinitro-4-*p*-toluenesulfonamidophenetole.—A stirred suspension of 39 g. of *p*-toluenesulfonyl-*p*-phenetidide[11] in 150 ml. of ethanol was treated dropwise during a 2-hr. period with 85 ml. of concentrated (d. 1.4) nitric acid. The suspended material dissolved when approximately one-third of the acid had been added, and shortly thereafter the dinitro derivative began to separate. After all the acid had been added, the mixture was stirred for 1 hr. at room temperature, refluxed for 1 hr. and cooled. The product was collected, washed with 50% ethanol and recrystallized from 1.5 liters of 50% acetic acid. The 3,5-dinitro-4-*p*-toluenesulfonamidophenetole separated as light yellow needles melting at 161–163°. The yield was 30 g. (60%).

Anal. Calcd. for $C_{15}H_{15}O_7N_3S$: N, 11.02; S, 8.40. Found: N, 10.86; S, 8.30.

4-Amino-3,5-dinitrophenetole.—A solution of 20 g. of 3,5-dinitro-4-*p*-toluenesulfonamidophenetole in 50 ml. of sulfuric acid (90%) was kept at room temperature overnight, poured onto ice and diluted with water to one liter. The bright red precipitate of 4-amino-3,5-dinitrophenetole was collected and washed with water. It crystallized as needles (10.7 g., 90%) from hot 50% acetic acid (500 ml.); m.p. 136–139° (lit.[6] m.p. 138–139°).

3,4-Diamino-5-nitrophenetole.—To 260 ml. of freshly prepared 10% ammonium sulfide, there was added 520 ml. of ethanol and 11.4 g. (0.05 mole) of 4-amino-3,5-dinitrophenetole. The reaction mixture was kept at 50–60° and mechanically stirred for 2 hr. After cooling, the crude

(5) F. E. King and R. J. S. Beer, *J. Chem. Soc.*, 792 (1945).

(6) F. Reverdin and L. Furstenberg, *J. prakt. Chem.*, [2] **88**, 321 (1913).

(7) H. Gillespie, M. Engelman and S. Graff, THIS JOURNAL, **78**, 1651 (1956).

(8) R. Meldola and J. V. Eyre, *J. Chem. Soc.*, **81**, 1288 (1902).

(9) M. A. Phillips, *ibid.*, 2393 (1928).

(10) All melting points are corrected.

(11) Prepared according to A. P. Crepieux, *Ber.*, **34**, 3002 (1901).

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product was collected and washed successively with 25-ml. portions of carbon disulfide and 50% ethanol. The *o*-diamine was recrystallized from ethanol (400 ml.). It separated as dark red needles having m.p. 144–146°. The yield was 7.0 g. (70%).

Anal. Calcd. for $C_8H_{11}O_3N_3$: C, 48.73; H, 5.59; N, 21.32. Found: C, 48.81; H, 5.78; N, 21.13.

2,3-Diphenyl-7-ethoxy-5-nitroquinoxaline.—A mixture of 579 mg. (3 mmoles) of 3,4-diamino-5-nitrophenetole, 630 mg. of benzil and 500 mg. of anhydrous sodium acetate in 150 ml. of ethanol was refluxed for 3 hr. The dark red solution was concentrated to 50 ml. and cooled. The 2,3-diphenyl-7-ethoxy-5-nitroquinoxaline (381 mg.) crystallized from ethanol (30 ml.) as light yellow needles, m.p. 142–144°.

Anal. Calcd. for $C_{22}H_{17}O_3N_3$: C, 71.16; H, 4.85; N, 11.32. Found: C, 71.33; H, 4.70; N, 10.99.

6-Ethoxy-4-nitrobenzimidazole.—To 1.5 g. of 3,4-diamino-5-nitrophenetole in 20 ml. of 3 *N* hydrochloric acid, there was added 1 ml. of 98% formic acid. After refluxing for 0.5 hr., another 1-ml. portion of formic acid was added and heating was continued for 30 minutes more. The hot solution was diluted with boiling water to 200 ml. and filtered. The filtrate was made slightly alkaline by cautious addition of concentrated (28%) aqueous ammonia. When cold, the crude 6-ethoxy-4-nitrobenzimidazole was collected and washed with water. The yield was 1.5 g. The compound crystallized from ethanol (400 ml., Nuchar) as tiny bright yellow needles melting at 268–269°. A sample for analysis was sublimed at 210–225° under reduced pressure.

Anal. Calcd. for $C_9H_9O_3N_3$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.29; H, 4.37; N, 19.83.

4-Amino-6-ethoxybenzimidazole.—A solution of 420 mg. (2 mmoles) of 6-ethoxy-4-nitrobenzimidazole in 200 ml. of ethanol was stirred in the presence of 90 mg. of palladium-on-carbon (10%) and hydrogen at one atmosphere pressure for 3 hr. when reduction was complete. The catalyst was removed by filtration and the filtrate concentrated to dryness *in vacuo* in the absence of air. This procedure was employed for all other catalytic reductions which follow. The 4-amino-6-ethoxybenzimidazole (340 mg., 96%) was recrystallized from a small volume (6 ml.) of water; white crystals, m.p. 144–145°.

Anal. Calcd. for $C_9H_{11}ON_3$: C, 61.01; H, 6.21; N, 23.73. Found: C, 61.17; H, 6.50; N, 23.80.

6-Ethoxy-4-nitrobenzotriazole.—A solution of 1 g. of 3,4-diamino-5-nitrophenetole in 100 ml. of hot 2 *N* sulfuric acid was cooled to 5°. The sulfate of the base separated. Keeping the temperature at 5°, there was added gradually with stirring, a solution of 500 mg. of sodium nitrite in 5 ml. of water. After standing overnight at room temperature, the black product (1.01 g.) was collected and washed with water. It was finely powdered and heated under reflux for 1.5 hr. with 250 ml. of 50% ethanol. The hot solution was treated with Nuchar and filtered. After cooling, the 6-ethoxy-4-nitrobenzotriazole (648 mg., 61%) was collected and recrystallized to constant m.p. 240–242°.

Anal. Calcd. for $C_8H_8O_3N_4$: C, 46.15; H, 3.85; N, 26.94. Found: C, 46.35; H, 4.04; N, 26.87.

4-Amino-6-ethoxybenzotriazole.—Catalytic reduction of 970 mg. (4.8 mmoles) of 6-ethoxy-4-nitrobenzotriazole in 200 ml. of ethanol yielded 800 mg. (96%) of crude 4-amino-6-ethoxybenzotriazole. A solution of the crude product in 20 ml. of hot 1 *N* sulfuric acid was boiled briefly with Darco and filtered. The free base precipitated on making the filtrate slightly alkaline (*p*H 8.0) by adding concentrated (28%) aqueous ammonia. It was recrystallized from hot water and separated as pink plates which had m.p. 120–122°, with previous shrinking at 88°. Analysis was done on a sample dried at 110°.

Anal. Calcd. for $C_8H_{10}ON_4$: C, 53.93; H, 5.62; N, 31.46. Found: C, 54.20; H, 5.50; N, 31.84.

7-Ethoxy-5-nitroquinoxaline.—A mixture of 2 g. of 3,4-diamino-5-nitrophenetole, 46.5 ml. of absolute ethanol and 3.5 ml. of a 30% aqueous solution of glyoxal was refluxed for 1 hr. and the hot solution filtered. On cooling there was obtained 930 mg. of crude 7-ethoxy-5-nitroquinoxaline. It was recrystallized from ethanol and separated as yellow needles, m.p. 142–144°. The yield was 611 mg. (27.5%).

Anal. Calcd. for $C_{10}H_9O_3N_3$: C, 54.79; H, 4.11; N, 19.17. Found: C, 54.95; H, 3.78; N, 19.26.

5-Acetamido-7-ethoxyquinoxaline.—Two millimoles (440 mg.) of 7-ethoxy-5-nitroquinoxaline in 150 ml. of ethanol was catalytically reduced as previously described. The product was a brown oil which would not crystallize. The oil was dissolved in 5 ml. of hot acetic anhydride. The solution was refluxed for 15 minutes and poured onto ice. After standing overnight, there was collected 211 mg. of 5-acetamido-7-ethoxyquinoxaline. It was recrystallized from 25% ethanol; white needles, m.p. 190–191°.

Anal. Calcd. for $C_{12}H_{13}O_2N_3$: C, 62.34; H, 5.63; N, 18.18. Found: C, 62.37; H, 5.58; N, 18.00.

2,3-Dimethyl-7-ethoxy-5-nitroquinoxaline.—A suspension of 1 g. of 3,4-diamino-5-nitrophenetole in 50 ml. of 25% acetic acid was stirred and heated on the steam-bath while a solution of 528 mg. of diacetyl in 4 ml. of 10% acetic acid was added dropwise during 20 minutes. On cooling the resultant solution, there separated 1.08 g. of 2,3-dimethyl-7-ethoxy-5-nitroquinoxaline which was collected and washed with water. The compound could be recrystallized from either 50% acetic acid or 50% ethanol, m.p. 151–153°. The yield was 822 mg. (66%).

Anal. Calcd. for $C_{12}H_{13}O_3N_3$: C, 58.30; H, 5.26; N, 17.00. Found: C, 58.26; H, 5.37; N, 16.91.

3,4-Diamino-2-nitroanisole Hydrochloride.—To a solution of 13.6 g. (60 mmoles) of stannous chloride in 100 ml. of ethanol, there was added 4.2 g. (20 mmoles) of 4-amino-2,3-dinitroanisole.[8] The base was kept in suspension by stirring while adding dropwise 25 ml. of concentrated hydrochloric acid. The temperature of the reaction mixture gradually rose to 45°. From the resulting clear, red solution, the monohydrochloride of 3,4-diamino-2-nitroanisole separated on cooling as a felted mass of yellow needles. The crude product was collected, washed with ethanol and recrystallized from 3 *N* hydrochloric acid.

Anal. Calcd. for $C_7H_9O_3N_3 \cdot HCl$: N, 19.14; Cl, 16.13. Found: N, 19.28; Cl, 16.03.

3,4-Diamino-2-nitroanisole.—Concentrated (28%) aqueous ammonia was cautiously added to a solution of 537 mg. of 3,4-diamino-2-nitroanisole hydrochloride in 30 ml. of hot water until the *p*H was approximately 8. The free base separated, on cooling, as a felted mass of dark red needles. The 3,4-diamino-2-nitroanisole was recrystallized from 25 ml. of water, m.p. 116–117°. The yield was 366 mg. (85%).

Anal. Calcd. for $C_7H_9O_3N_3$: C, 45.90; H, 4.92; N, 22.95. Found: C, 46.01; H, 4.86; N, 23.02.

2,3-Diphenyl-6-methoxy-5-nitroquinoxaline.—A mixture of 366 mg. of 3,4-diamino-2-nitroanisole hydrochloride, 180 mg. of anhydrous sodium acetate and 335 mg. of benzil in 25 ml. of 50% ethanol was heated under reflux for 1 hr. The resultant solution, on cooling, deposited 508 mg. (85%) of 2,3-diphenyl-6-methoxy-5-nitroquinoxaline which was recrystallized from ethanol (100 ml.), m.p. 216–217°.

Anal. Calcd. for $C_{21}H_{15}O_3N_3$: C, 70.59; H, 4.20; N, 11.77. Found: C, 70.72; H, 4.10; N, 11.77.

5-Methoxy-4-nitrobenzotriazole.—Ten millimoles (2.2 g.) of 3,4-diamino-2-nitroanisole hydrochloride was suspended by stirring in 100 ml. of ice-cold 1 *N* hydrochloric acid while a solution of 800 mg. of sodium nitrite in 5 ml. of water was being added dropwise. After 1 hr., the crude 5-methoxy-4-nitrobenzotriazole was collected and washed with water. It was recrystallized from ethanol (300 ml.), m.p. 237–238°. The yield was 1.5 g. (80%).

Anal. Calcd. for $C_7H_6O_3N_3$: C, 43.29; H, 3.09; N, 28.87. Found: C, 43.50; H, 3.13; N, 29.42.

5-Hydroxy-4-nitrobenzotriazole.—A solution of 938 mg. (4.8 mmoles) of 5-methoxy-4-nitrobenzotriazole in 10 ml. of hydrobromic acid (48%) was refluxed for 5 hr., cooled and diluted with 50 ml. of water. The precipitate was collected, dissolved in 25 ml. of 1 *N* sodium hydroxide and the solution filtered. A yellow precipitate of 5-hydroxy-4-nitrobenzotriazole (786 mg., 90%) was obtained when the filtrate was acidified with acetic acid. The compound decomposed at about 210°. A sample for analysis was sublimed at 200° under reduced pressure.

Anal. Calcd. for $C_6H_4O_3N_3$: C, 40.00; H, 2.22; N, 31.11. Found: C, 40.23; H, 1.98; N, 31.54.

5-Methoxy-4-nitrobenzimidazole.—This compound was obtained in almost quantitative crude yield from 1.83 g.

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(10 mmoles) of 3,4-diamino-2-nitroanisole by the procedure described for 6-ethoxy-4-nitrobenzimidazole. The 5-methoxy-4-nitrobenzimidazole was recrystallized from 250 ml. of 50% ethanol, m.p. 245–247°.

Anal. Calcd. for $C_8H_7O_3N_3$: C, 49.74; H, 3.63; N, 21.76. Found: C, 50.05; H, 3.67; N, 22.23.

5-Hydroxy-4-nitrobenzimidazole.—Three millimoles (549 mg.) of 5-methoxy-4-nitrobenzimidazole was dissolved in a hot mixture of 5 ml. of acetic acid and 5 ml. of hydrobromic acid (48%). The solution was refluxed for 5 hr., diluted with 50 ml. of boiling water, treated with Darco and filtered. The hot filtrate was made slightly alkaline (*p*H about 8.0) by adding concentrated (28%) aqueous ammonia. After cooling, the yellow precipitate of 5-hydroxy-4-nitrobenzimidazole was collected and washed with water. The yield was 525 mg. (97%). It was recrystallized from boiling water. The compound decomposed at about 220°. A sample for analysis was sublimed at 200–210° under reduced pressure.

Anal. Calcd. for $C_7H_5O_3N_3$: C, 46.93; H, 2.79; N, 23.46. Found: C, 47.18; H, 3.00; N, 23.07.

2,3-Dimethyl-6-methoxy-5-nitroquinoxaline.—A mixture of 1 g. (11.6 mmoles) of diacetyl and 1.83 g. (10 mmoles) of 3,4-diamino-2-nitroanisole in 200 ml. of 35% ethanol was refluxed for 1 hr. The solution, on cooling, deposited 2.14 g. (92%) of crude 2,3-diphenyl-6-methoxy-5-nitroquinoxaline. It was recrystallized from 35% ethanol (Nuchar) and separated as tiny, almost colorless needles, m.p. 145–146°.

Anal. Calcd. for $C_{11}H_{11}O_3N_3$: C, 56.66; H, 4.72; N, 18.03. Found: C, 57.03; H, 4.41; N, 18.33.

5-Amino-2,3-dimethyl-6-methoxyquinoxaline.—The catalytic reduction of 466 mg. (2 mmoles) of 2,3-dimethyl-6-methoxy-5-nitroquinoxaline in 50 ml. of ethanol by the usual procedure required 2 hr. A solution of the crude product in 50 ml. of hot 0.5 *N* hydrochloric acid was treated with Darco and filtered. On adding concentrated (28%) aqueous ammonia to the filtrate until slightly alkaline (*p*H 8.0), the 5-amino-2,3-dimethyl-6-methoxyquinoxaline precipitated. It recrystallized from 60 ml. of water and separated as yellow needles, m.p. 135–136°. The yield was 209 mg. (50%).

Anal. Calcd. for $C_{11}H_{13}O_3N_3$: C, 65.02; H, 6.40; N, 20.69. Found: C, 65.05; H, 6.23; N, 20.92.

5-Amino-2,3-diphenyl-6-methoxyquinoxaline.—One millimole (357 mg.) of 2,3-diphenyl-6-methoxy-5-nitroquinoxaline suspended in 75 ml. of ethanol was catalytically reduced in the usual manner. The crude 5-amino-2,3-diphenyl-6-methoxyquinoxaline was recrystallized from 50 ml. of ethanol (Nuchar), m.p. 156–157°. The yield was 266 mg. (81%).

Anal. Calcd. for $C_{21}H_{17}ON_3$: C, 77.07; H, 5.19; N, 12.84. Found: C, 77.27; H, 5.11; N, 12.82.

5-Acetamido-2,3-diphenyl-8-methoxyquinoxaline.—Two millimoles (510 mg.) of 4-acetamido-2,3-dinitroanisole[8] in 50 ml. of ethanol was reduced in the usual manner in 4 hr. The catalyst was removed by filtration. To the alcoholic solution of 4-acetamido-2,3-diaminoanisole, there was added 420 mg. (2 mmoles) of benzil, and the mixture was refluxed for 1 hr. On cooling, there was obtained 427 mg. (58%) of 5-acetamido-2,3-diphenyl-8-methoxyquinoxaline. It was recrystallized from ethanol (Nuchar) and separated as bright yellow needles, m.p. 236–237°.

Anal. Calcd. for $C_{23}H_{19}O_2N_3$: C, 74.80; H, 5.15; N, 11.38. Found: C, 75.10; H, 4.91; N, 11.10.

5-Amino-2,3-diphenyl-8-methoxyquinoxaline.—To a mixture of 27 ml. of absolute ethanol and 3 ml. of concentrated hydrochloric acid, there was added 376 mg. (1.02 mmoles) of 5-acetamido-2,3-diphenyl-8-methoxyquinoxaline. The acetamido compound gradually dissolved when the mixture was refluxed for 1 hr. The solution was concentrated to dryness *in vacuo*. The residue was washed with 3% aqueous ammonia and recrystallized from ethanol (30 ml., Nuchar). The 5-amino-2,3-diphenyl-8-methoxyquinoxaline (275 mg., 84%) separated as tiny reddish-orange needles, m.p. 214–215°.

Anal. Calcd. for $C_{21}H_{17}ON_3$: C, 77.07; H, 5.19; N, 12.84. Found: C, 77.12; H, 5.24; N, 12.92.

5-Methoxy-2-methyl-4-nitrobenzimidazole.—Four millimoles (738 mg.) of 3,4-diamino-2-nitroanisole dissolved in 5 ml. of acetic anhydride was warmed on the steam-bath. To the solution there was added slowly 15 ml. of 3 *N* hydrochloric acid. The mixture was refluxed for 20 minutes, diluted with 30 ml. of hot water, boiled briefly with Darco and filtered. Concentrated (28%) aqueous ammonia was added to the hot filtrate until slightly alkaline (*p*H 8.0). After cooling, the yellow precipitate of 5-methoxy-2-methyl-4-nitrobenzimidazole was collected and washed with water. The yield was almost quantitative. It was recrystallized from 50% ethanol, m.p. 204–205°.

Anal. Calcd. for $C_9H_9O_3N_3$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.23; H, 4.09; N, 20.25.

6-Methoxy-2-methyl-4-nitrobenzimidazole.—This compound was prepared by the procedure given above from 369 mg. (2 mmoles) of 3,4-diamino-5-nitroanisole.[12] The crude product was recrystallized from 25% ethanol, m.p. 226–227°. The yield of 6-methoxy-2-methyl-4-nitrobenzimidazole was 319 mg. (77%).

Anal. Calcd. for $C_9H_9O_3N_3$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.51; H, 4.03; N, 20.35.

3,4-Diacetamidoanisole.—To a solution of 1.16 g. of 4-acetamido-3-aminoanisole[13] in 3 ml. of acetic acid, there was added 1.5 ml. of acetic anhydride. The reaction mixture became warm and the product soon began to crystallize. After standing at room temperature for 30 minutes, the almost solid mass was stirred up with 10 ml. of 1-butanol and filtered. The crude product (1.18 g., 82.5%) was recrystallized from approximately 20 ml. of water. The 3,4-diacetamidoanisole separated as short needles having a pinkish tinge, m.p. 182–184°.

Anal. Calcd. for $C_{11}H_{14}O_3N_2$: C, 59.46; H, 6.31; N, 12.61. Found: C, 59.61; H, 6.30; N, 12.50.

4,5-Diacetamido-2-nitroanisole.—One gram of 3,4-diacetamidoanisole was suspended by stirring in 5 ml. of glacial acetic acid while a mixture of 0.8 ml. of concentrated (d. 1.4) nitric acid and 1.5 ml. of acetic acid was gradually added. When approximately one-half of the mixed acids had been added, the diacetamidoanisole was almost completely in solution. The reaction mixture became warm as the remainder of the mixed acids was added and the nitro derivative began to crystallize. After all the nitric acid had been added, the mixture was stirred at room temperature for 30 minutes before pouring onto ice and diluting with water to approximately 75 ml. The yellow precipitate of 4,5-diacetamido-2-nitroanisole (1.04 g., 87%) was collected, washed with water and recrystallized from 50 ml. of 50% ethanol, m.p. 225–227°.

Anal. Calcd. for $C_{11}H_{13}O_5N_3$: C, 49.44; H, 4.87; N, 15.73. Found: C, 49.64; H, 5.12; N, 15.66.

5-Methoxy-2-methyl-6-nitrobenzimidazole.—A mixture of 2 g. of 4,5-diacetamido-2-nitroanisole and 50 ml. of 2 *N* sulfuric acid was heated under reflux until a complete solution resulted. The hot, red solution was filtered. The filtrate was diluted with an equal volume of hot water, made slightly basic by adding concentrated (28%) aqueous ammonia and kept at 5° overnight. The precipitated 5-methoxy-2-methyl-6-nitrobenzimidazole (1.4 g., 90%) was collected, washed with water and recrystallized from 25% ethanol (125 ml.) with the aid of Nuchar. The purified material was dried at 110° and had m.p. 172–174°.

The diacetamidonitroanisole also cyclized to the 2-methylbenzimidazole when heated in alcoholic potassium hydroxide.

Anal. Calcd. for $C_9H_9O_3N_3$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.01; H, 4.33; N, 19.47.

Acknowledgments.—The authors are indebted to the Damon Runyon Memorial Fund and The American Cancer Society for support of this work.

NEW YORK 32, N. Y.

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(13) V. A. Izmailskii and A. M. Simonov, *J. Gen. Chem. (USSR)*, **10**, 1580 (1940); *C. A.*, **35**, 2871[3] (1941).

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

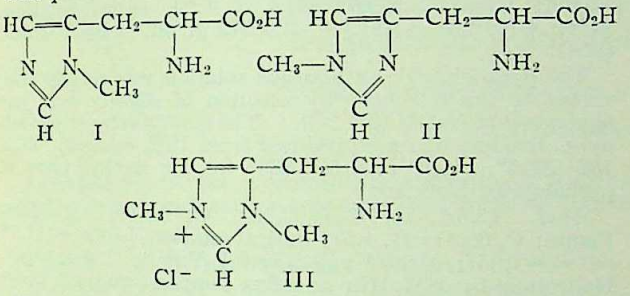
A Synthesis of Radioactive Methylhistidines[1]

BY ROBERT W. COWGILL[2]

RECEIVED NOVEMBER 9, 1956

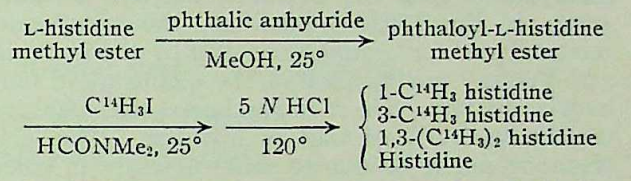
The methyl ester of phthaloyl-L-histidine was synthesized. This ester was methylated with $C^{14}H_3I$, and then acid hydrolysis was employed to remove the phthaloyl and ester groups. The products were separated by ion-exchange chromatography; they were 1-$C^{14}H_3$-L-histidine, 3-$C^{14}H_3$ histidine, 1,3-$(C^{14}H_3)_2$-L-histidine chloride and histidine.

Biochemical studies of the function and the metabolism of methyl-L-histidine compounds in animals would be facilitated by the availability of 1-methyl-L-histidine (I), 3-methyl-L-histidine (II) and 1,3-dimethyl-4-(β-carboxyl-β-aminoethyl)-imidazolium chloride or 1,3-dimethyl-L-histidine (Cl^-) (III) labeled with C^{14} in the methyl groups. The present methods were developed to provide an



efficient path for the synthesis of these labeled compounds; a path free of undesirable by-products with the C^{14}-methyl substituent on the α-amino nitrogen.

Early attempts[3] to synthesize the methylhistidines by methylation of phthaloyl histidine were thwarted by difficulties in the separation of products. Syntheses which did not involve L-histidine as an intermediate led to racemic products.[4] More recently, both 1-Me- and 3-Me-L-histidines have been prepared by methylation of L-histidine in liquid ammonia.[5] However, the existence of by-products methylated on the α-amino nitrogen renders this procedure unpromising for the specific incorporation of $C^{14}H_3$- groups on the imidazole ring. Protection of the α-amino group during methylation would be necessary in order to eliminate products methylated at the α-amino position. Tallan, Stein and Moore[5] methylated phthaloylhistidine but they reported that racemization occurred during the formation of the phthaloylhistidine. Attempts by this writer to form phthaloyl-L-histidine by heating an intimate mixture of L-histidine and phthalic anhydride[6] to 180° or by reaction of this mixture in boiling glacial acetic acid[7] led to racemization. However, it was found that the methyl ester of phthaloyl-L-histidine could be formed by reaction of the methyl ester of L-histidine and phthalic anhydride in anhydrous methanol by the general procedure of King and Kidd[8] for phthaloylamino acids.



Methylation of the methyl ester of phthaloyl-L-histidine occurred smoothly in dimethylformamide. The product, following hydrolysis of the phthaloyl and methyl ester groups, was a mixture of 1-methyl-L-histidine, 3-methylhistidine,[9] 1,3-dimethyl-L-histidine (Cl^-) and histidine. These amino acids were separated on a Dowex 50 (Na^+) ion-exchange column[5] and a representative separation is depicted in Fig. 1. The per cent. recovery of

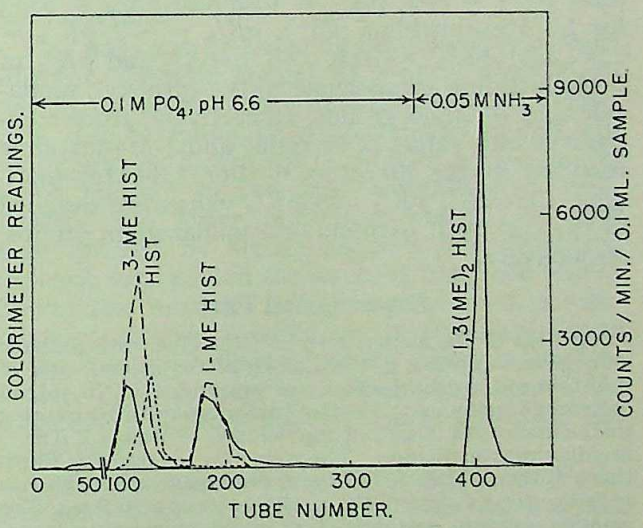


Fig. 1.—Separation of the methylhistidines on a column of Dowex 50 (Na^+); --- quantitative ninhydrin analysis[11]; - - - - Pauly diazo analysis[12]; —— radioactivity.

amino acids introduced into the column was 75% and the per cent. recovery of radioactive compounds was 78%. The average composition of the products of five preparations was 40% histidine and 20% each of 1-Me-histidine, 3-Me-histidine and 1,3-$(Me)_2$-histidine (Cl^-).

The methylhistidines were characterized by paper chromatography,[10] by the ninhydrin analy-

(1) This research was supported in part by a grant from the National Science Foundation.

(2) Department of Biochemistry, University of Colorado School of Medicine, Denver, Colorado.

(3) W. Keil, *Z. physiol. Chem.*, **208**, 67 (1932).

(4) (a) W. Sakami and D. W. Wilson, *J. Biol. Chem.*, **154**, 215 (1944); (b) R. G. Jones and K. C. McLaughlin, THIS JOURNAL, **71**, 2444 (1949).

(5) H. H. Tallan, W. H. Stein and S. Moore, *J. Biol. Chem.*, **206**, 825 (1954).

(6) J. C. Sheehan and V. S. Frank, THIS JOURNAL, **71**, 1856 (1949).

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(8) F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 3315 (1949).

(9) The specific optical rotation of the 3-Me-histidine could not be determined, for the preparation was not completely free of histidine (10%). However, the route of synthesis would indicate that only the L-isomer was formed.

(10) (a) R. W. Cowgill, *Anal. Chem.*, **27**, 1519 (1956); (b) R. W. Cowgill and B. Freeburg, *Arch. Biochem. & Biophys.*, in press.

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sis[11] for free α-amino nitrogen, and by analysis[12] for histidine unsubstituted on the ring nitrogen. Preparations that contained C^{14} were also analyzed by radioactivity techniques. Both the 1-Me- and 3-Me-histidines were found to move on paper chromatograms in five solvent systems[10b] at rates identical with those of authentic samples of the compounds.[13] The 1-Me-, 3-Me- and 1,3-$(Me)_2$-histidines all gave spots on paper chromatograms that were radioactive, gave a blue-green color with the ninhydrin spray,[14] but gave no color with the Pauly diazo spray[15] that is reactive only with those imidazole compounds that bear no substituent on the imidazole ring nitrogen. To ensure that methylation had not occurred on the α-amino group of the 1,3$(Me)_2$-histidine, this compound was analyzed for α-amino nitrogen by the Cocking and Yemm[11] modification of the quantitative ninhydrin method. On a molar basis, the color intensity was 80% of that of histidine. This discrepancy might be due to some decrease in color formation by the presence of the imidazolium structure of the 1,3-$(Me)_2$-histidine (Cl^-), but the difference in color intensity is not of the magnitude that would be anticipated if the α-amino group were methylated. The quaternary-base character of this compound was shown by the fact that it did not migrate toward the anode during electrophoresis at *p*H 9.5, and by titration data. pK values were determined in 0.1 M KCl. For 1-Me-histidine, $pK'_1 = \sim 2$, $pK'_2 = 6.58$ and $pK'_3 = 8.60$; for 1,3$(Me)_2$-histidine (Cl^-), $pK'_1 = \sim 2$, $pK'_2 = 7.95$, and $pK'_3 > 10.5$. pK'_1, pK'_2 and pK'_3 of 1-Me-histidine are assigned to the carboxyl, imidazole and α-amino groups, respectively, from comparison with values of histidine and 1-Me-histidine reported in the literature.[16] For 1,3-$(Me)_2$-histidine, the pK'_1, pK'_2 and pK'_3 values are assigned to the carboxyl, α-amino and imidazolium groups, respectively.

Experimental Part

Reaction of the methyl ester of L-histidine with phthalic anhydride.[8] Twelve g. (0.05 mole) of the methyl ester of L-histidine dihydrochloride[17] was suspended in 75 ml. of anhydrous methanol. The free base was formed by treating this solution with 60 ml. (damp volume) of Dowex 2 (OH^-) in anhydrous methanol. The resin was removed by filtration and then 14.2 g. (0.057 mole) of phthalic anhydride was added to the solution of the methyl ester of histidine. The reaction mixture was stored at room temperature overnight, before it was concentrated on a bath at 70° to about 30 ml. First acetone (about 170 ml.) and then ether were added slowly to bring about precipitation of 13 g. of the products as crystalline or oily material. (The product was usually an oil unless the solution was seeded.) A further 1.5 g. of oil was obtained on concentration of the mother liquor and addition of more ether. Total yield was 93.5%. The product was crystallized from water as clear, cubic crystals. A 24-tube countercurrent distribution of this product between 0.1 M aqueous phosphate buffer of *p*H 6.5 and benzene revealed that it was a mixture of approximately 85% as the methyl ester of phthaloyl-L-histidine and 15% as the methyl ester of *o*-carboxybenzoyl-N-histidine. The proportions of these two compounds in the crude product varied from batch to batch and in four preparations ranged from 50–95% as the methyl ester of phthaloylhistidine.

Conversion of the methyl ester of *o*-carboxybenzoyl-N-histidine to the methyl ester of phthaloylhistidine.[8] Ten ml. of freshly distilled thionyl chloride was dissolved in 40 ml. of benzene and 5 g. of the mixture of methyl esters of *o*-carboxybenzoyl-N-histidine and phthaloylhistidine was added slowly and with stirring. The suspension of fine, white, granular precipitate was allowed to stand at room temperature overnight. The solvent was evaporated and the residual product was crystallized from a mixture of anhydrous methanol and ether. The white crystals of methyl ester of phthaloyl-L-histidine hydrochloride amounted to 3.3 g. (63% yield). The product was recrystallized from 10% ethanol; m.p. 200–200.7°; Keil[3] reported 238–240° for the methyl ester of phthaloyl-DL-histidine·HCl.

Anal. Calcd. for $C_{15}H_{14}O_4N_3Cl$: C, 53.66; H, 4.20. Found: C, 53.63, 54.07; H, 4.52, 4.29, optical rotation, $[\alpha]^{20}D$ −101° ($\alpha = -1.96$; 0.00972 g./ml. in H_2O; 2 dm. tube).

The hydrochloride in aqueous solution was readily converted to the free base by addition of slightly over one equivalent of NaOH (*p*H > 9). The methyl ester of phthaloyl-L-histidine was recrystallized from 10% ethanol; m.p. 182–182.5°; Keil[3] reported 188° for the methyl ester of phthaloyl-DL-histidine.

Anal. Calcd. for $C_{15}H_{13}O_4N_3$: C, 60.19; H, 4.38. Found: C, 60.31; H, 4.57; optical rotation, $[\alpha]^{20}D$ −111.7° ($\alpha = -1.65°$; 0.0074 g./ml. in 0.1 N HCl; 2 dm. tube). Hydrolysis by 48% HBr at reflux temperature for 9 hours gave histidine of $[\alpha]^{20}D$ −40° (H_2O).

Methylation of the methyl ester of phthaloyl-L-histidine. One and one-half g. (0.005 mole) of the methyl ester of phthaloyl-L-histidine free base was dissolved in 7 ml. of dimethylformamide. Methyl iodide (0.005 mole that contained 0.5 millicurie of C^{14}) was added and the flask was securely stoppered. The mixture was stored at room temperature for three days, and then it was concentrated *in vacuo* at 50° to a sirup. The sirup was dissolved in 3 ml. of constant boiling hydrochloric acid and was heated in an autoclave at 15 p.s.i. (121°) for 7 hours. The solution then was concentrated *in vacuo* at 50° to yellow salts, and the salts were extracted with a total of 10 ml. of water. The residue of phthalic acid amounted to 0.916 g.; 110% of theory, as phthalic acid. The solution of methylated products contained a total of 3.96×10^7 c.p.m.,[18] which represents 71% of the initial activity of the methyl iodide.

Separation of the methylation products on an ion-exchange column. The mixture of methylhistidines and histidine was introduced into a 7 × 35 cm. column of Dowex 50 (Na^+) described by Tallan, Stein and Moore,[5] and elution was made with 0.1 M phosphate of *p*H 6.6. The progress of the elution is shown in Fig. 1. The 1,3-dimethylhistidine was held tightly on the column but could be removed by 0.05 M ammonia.

Each fraction in the eluate was desalted and recovered by the procedure of Tallan, Stein and Moore.[5] Of the 3.96×10^7 c.p.m. introduced onto the column, 16% was recovered as 3-methylhistidine, 18% as 1-methylhistidine and 44% as 1,3-dimethylhistidine. This represents about 0.62×10^5 ct./min./mg. for 1-Me- and 3-Me-histidines and 1.0×10^5 ct./min./mg. for 1,3-$(Me)_2$-histidine (Cl^-).

1-Methyl-L-histidine·2HCl.—The desalted fraction from the ion-exchange column which contained the 1-methylhistidine (300 mg.) as the dihydrochloride salt was dissolved in 1.0 ml. of water and 1-Me-histidine·2HCl crystallized upon addition of ten volumes of 1:1:: acetone: absolute ethanol. This salt was recrystallized from 99% ethanol.

Anal. Calcd. for $C_7H_{13}O_2N_3Cl_2$: C, 34.72; H, 5.41. Found: C, 34.95; H, 5.47; $[\alpha]^{20}D$ −17.6° ± 3.0° ($\alpha = -0.0058°$; 0.0066 g. as free base/ml. in H_2O of *p*H 9; 0.5 dm. tube). Linnewek and Linnewek[19] reported $[\alpha]^{18}D$

(11) E. C. Cocking and E. W. Yemm, *Biochem. J.*, **58**, XII (1954).

(12) K. K. Koessler and M. T. Hanke, *J. Biol. Chem.*, **39**, 497 (1919).

(13) Samples of 1-Me-histidine for comparison were a sample of 1-Me-L-histidine obtained by hydrolysis of anserine and a sample of 1-Me-DL-histidine prepared by a different synthetic path (California Foundation for Biochemical Research). An authentic sample of 3-Me-L-histidine was kindly supplied by Dr. H. H. Tallan.

(14) 0.1% ninhydrin in 95% ethanol that contained 5% collidine. The sprayed paper was heated at 100–110° to bring out the colors.

(15) B. N. Ames and H. K. Mitchell, THIS JOURNAL, **74**, 252 (1952).

(16) A. Deutsch and P. Eggleton, *Biochem. J.*, **32**, 209 (1938).

(17) E. Fischer and L. H. Cone, *Ann.*, **363**, 107 (1908).

(18) Counter efficiency was 5% and all counts are expressed as measured at this efficiency.

(19) W. Linnewek and F. Linnewek, *Z. physiol. Chem.*, **189**, 80 (1930).

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$-25.8°$ (H_2O) for 1-Me-L-histidine free base isolated from the hydrolysis of anserine.

1-Methyl-L-histidine Diflavianate.—The diflavianate salt was formed by the general method of Vickery,[20] and it was recrystallized from water; m.p. 234.7° dec.

Anal. Calcd. for $C_{27}H_{23}O_{18}N_7S_2$: C, 40.65; H, 2.92; N, 12.29. Found: C, 40.45; H, 3.08; N, 12.09.

3-Methylhistidine.—The 3-Me-histidine fraction from the ion-exchange column contained 10% histidine. In the radioactive tracer experiments for which this preparation was to be used,[10b] the contamination by histidine was not deleterious, and no further purification was attempted.

1,3-Dimethyl-L-histidine (Cl^-) or 1,3,-Dimethyl-4-(β-carboxyl-β-aminoethyl)-imidazolium Chloride.—The dry, desalted fraction from the ion-exchange column that contained 1,3-$(Me)_2$-histidine was taken up in about 1.0 ml. of H_2O, treated with Norite, filtered and adjusted to about *p*H 8 with ammonia. Acetone was added to the appearance of fluffy white crystals upon cooling the mixture. The crystals were washed on the filter funnel with acetone and dried *in vacuo* at 80°. The hygroscopic salt must be stored under desiccation.

Anal. Calcd. for $C_8H_{15}O_2N_3Cl$: C, 43.50; H, 6.86. Found: C, 43.4; H, 6.7. $[\alpha]^{20}D$ $+18.1° \pm 1.6°$ ($\alpha = 0.23°$; 0.0125 g./ml. in 1 *N* HCl; 1 dm. tube).

1,3-Dimethyl-L-histidine Diflavianate.—The diflavianate was prepared by the general method of Vickery,[20] and it was recrystallized from water; m.p. 237.5° dec.

Anal. Calcd. for $C_{29}H_{25}O_{14}N_7S_2 \cdot H_2O$: C, 40.53; H, 3.28. Found: C, 40.58, H, 3.17.

DENVER, COLORADO

(20) H. B. Vickery, *J. Biol. Chem.*, **71**, 303 (1927).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Purines. VII. The Preparation of Certain 6-Alkylamino- and 6-Dialkylaminopurines[1]

BY MELVIN SUTHERLAND AND BERT E. CHRISTENSEN

RECEIVED DECEMBER 5, 1956

The procedures for the preparation and isolation of high molecular weight alkylamino- and dialkylaminopurines are described. Twenty such compounds have been prepared by the methods described herein.

A great deal of interest has centered in the 6-substituted purines following the recent discovery of the biological importance of kinetin[2] and 6-mercaptopurine.[3] This activity has been divided between the development of new synthetic routes to kinetin itself and to the synthesis[4] and testing of many of its analogs.

Miller and co-workers originally prepared 6-furfurylaminopurine by the aminolysis (in a sealed tube) of 6-methylmercaptopurine[2] following the procedure of Elion and Hitchings. Since then a number of other approaches to the synthesis of kinetin have been reported. One of the most recent methods for the preparation of the 6-substituted aminopurines involves the synthesis and reduction of the corresponding 6-amidopurine with lithium aluminum hydride.

In this Laboratory an aminolytic procedure based on the use of 6-chloropurine was successfully applied to the preparation of a number of 6-substituted purines.[4] Since this procedure appeared to have a wide degree of applicability and in view of the possibility of turning up other biologically active analogs, this work has been expanded to include a number of other potentially active purine derivatives. Recently several new 6-substituted aminopurines have been reported to possess activity.[5] Since this activity may be dependent in part on fat solubilities of the compound, this Laboratory has prepared a number of high molecular weight alkylaminopurines with the side chain in the 6-position.

This was done by refluxing the chloropurine with different aliphatic amines in *n*-butyl alcohol according to the procedure described earlier.[4] However, due to solubility characteristics of the aliphatic amines, it was not possible to isolate the reaction product by the usual crystallization techniques. The lower molecular weight homologs were isolated by steam distilling the unreacted aliphatic amine from the aqueous basic solution of the reaction mixture. The course of the steam distillation could be followed by the slow progression of the insoluble aliphatic amine through the condenser. The product was then obtained by the ethereal extraction of the basic media left in the distilling flask.

As the aliphatic side chain increased in length the products became contaminated with traces of the starting amine which could not be removed by continuous distillation with steam.

Attempts to remove the unreacted amine by co-distillation at reduced pressures with diphenyl ether were quite successful but no practical way was found for isolating the product in turn from the diphenyl ether. Co-distillation under similar conditions with ethylene glycol was successfully applied to the isolation of 6-isohexylaminopurine, but the process proved to be impractical for the distillation of the higher homologs.

Finally it was observed that it was possible to remove amines as large as octadecylamine from sirupy mixtures of 6-substituted purines by the use of super-heated steam. This was the procedure which was adopted for the isolation of the higher molecular weight 6-substituted purines.

One rather interesting steric effect was noted in

(1) These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and Oregon State College. Published with the approval of the Monographs Publication Committee, Oregon State College as Research Paper No. 311, School of Science, Department of Chemistry.

(2) C. O. Miller, F. Skoog, F. S. O. Kumura, M. H. Von Saltza and F. M. Strong, THIS JOURNAL, **77**, 2662 (1955).

(3) C. T. Bahner, B. Stump and M. E. Brown, *ibid.*, **75**, 6301 (1953).

(4) J. W. Daly and B. E. Christensen, *J. Org. Chem.*, **21**, 177 (1956); M. W. Bullock, J. W. Hand and E. L. R. Stokstad, THIS JOURNAL, **78**, 3693 (1956).

(5) C. G. Skinner, W. Shive, R. G. Ham, D. C. Fitzgerald, Jr., and R. E. Eakin, *ibid.*, **78**, 5097 (1956); R. G. Ham, R. E. Eakin, C. G. Skinner and W. Shive, *ibid.*, **78**, 2648 (1956).

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TABLE I

Isolation procedure: A, conventional steam distillation; B, modified steam distillation with flask heated 150° and passing super-heated steam through; C, crystallized from reaction mixture. Crystallizing procedure: 1, crystallized from 75–90% ethanol–water solution; 2, crystallized from 100% ethanol; 3, crystallized from water.

Name (compound)	Isolation crystallization	Yield, %	Melting point, °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
6-Monoalkylaminopurines								
6-(*n*-Hexylamino)-purine	A-1	49	176–178	$C_{11}H_{17}N_5$	60.3	60.2	7.76	8.00
6-Cyclohexylaminopurine	B-1	80	210–211	$C_{11}H_{15}N_5$	60.8	60.2	6.92	6.93
6-(*n*-Heptylamino)-purine	A-1	66	168.5–170	$C_{12}H_{19}N_5$	61.8	61.7	8.16	8.42
6-(1-Methylheptylamino)-purine	B-1	82	94–96	$C_{13}H_{21}N_5$	63.2	62.7	8.51	8.35
6-(*n*-Octylamino)-purine	B-1	84	165–167	$C_{13}H_{21}N_5$	63.2	62.7	8.51	8.61
6-(2-Ethylhexylamino)-purine	B-1	65	158–159	$C_{13}H_{21}N_5$	63.2	63.0	8.51	8.4
6-(*n*-Decylamino)-purine	B-2	79	164.5–165.5	$C_{15}H_{25}N_5$	65.5	65.0	9.09	9.31
6-(*n*-Dodecylamino)-purine	B-2	91	156–156.5	$C_{17}H_{29}N_5$	67.3	67.4	9.58	9.79
6-(*n*-Hexadecylamino)-purine	B-2	83	144–145	$C_{21}H_{37}N_5$	70.2	69.9	10.3	10.2
6-(*n*-Octadecylamino)-purine	B-2	95	107–108	$C_{23}H_{41}N_5$	71.4	71.4	10.6	10.6
6-Dialkylaminopurines								
6-(Di-*n*-amylamino)-purine	A-1	90	88.5–89.5	$C_{15}H_{25}N_5$	65.5	65.6	9.09	9.23
6-(Di-isoamylamino)-purine	A-1	95	114.5–115	$C_{15}H_{25}N_5$	65.5	65.2	9.09	9.21
6-(Di-*n*-hexylamino)-purine	A-1	87	95.5–96.0	$C_{17}H_{29}N_5$	67.3	67.4	9.58	9.69
6-(Di-isohexylamino)-purine	A-1	75	89–90	$C_{17}H_{29}N_5$	67.3	67.6	9.57	9.83
6-(Di-2-ethylhexylamino)-purine	B-1	75	83–83.5	$C_{21}H_{37}N_5$	70.2	70.4	10.3	10.4
6-(Di-*n*-heptylamino)-purine	B-1	80	75–76	$C_{19}H_{33}N_5$	68.9	69.1	9.97	10.1
6-(Di-*n*-octylamino)-purine	B-1	85	85–86	$C_{21}H_{37}N_5$	70.2	70.4	10.3	10.49
6-(Di-*n*-nonylamino)-purine	B-1	89	77–78	$C_{23}H_{41}N_5$	71.4	71.2	10.6	10.8
6-(Di-*n*-decylamino)-purine	B-1	87	75–76	$C_{25}H_{45}N_5$	72.2	72.0	10.8	10.9
6-Alkanolaminopurines								
6-(6-Hydroxy-*n*-hexylamino)-purine	C-3	83	175–176	$C_{11}H_{17}N_5O$	56.1	56.1	7.24	7.37

these studies. All the hindered secondary amines (diisopropylamine, di-1-methylbutylamine, di-*sec*-butylamine and dicyclohexylamine) which were treated were found to be unreactive under these conditions of amination. However, the secondary amine di-(2-ethylhexyl)-amine, on the other hand, coupled with the 6-chloropurine.

Furthermore, it is interesting to note that the primary amine 1-methylheptylamine, which might have presented a steric problem, was reactive.

Experimental

Aminolysis Procedure.—One gram of 6-chloropurine (6.4×10^{-3} mole) was suspended in 10 ml. of *n*-butyl alcohol and to this mixture was added 16×10^{-3} mole of the desired amine. The mixture was then refluxed for four hours; the course of the reaction could be followed by the disappearance of the insoluble 6-chloropurine.

Isolation Procedure A.—The reaction mixture was placed in a 500-ml. round-bottomed flask containing 100 ml. of 0.1 *N* sodium hydroxide. This flask was suspended in an oil-bath and the contents were steam distilled until 500 ml. of distillate had been collected. This amount of distillate was sufficient to remove all the unreacted amine as well as the *n*-butyl alcohol. The non-volatile residue was then extracted with ether, which upon evaporation yielded the product. The 6-substituted amine was then in turn recrystallized from one of the several solvents.

Isolation Procedure B.—To the reaction mixture was added 100 ml. of 0.1 *N* sodium hydroxide. The mixture was stirred for 30 minutes and then extracted with ether. This extract was placed in a 500-ml. flask and the ether and butanol removed by distillation. The flask was then immersed in an oil-bath maintained at 150° and then steam distilled with super-heated steam. The steam was prepared by passing ordinary steam, with all condensate removed, through a Fisher super-heater which was maintained at a temperature of 350° with a Fisher burner. Because of the elevated temperatures it was necessary to use metal to glass connections on the discharge side of the super-heater.

Sufficient steam pressure was applied to cause the sirupy product to spread out in a thin film over the bottom of the flask. The distillation was continued until no more unreacted amine could be observed collecting in the condenser. Upon cooling, the product solidified in the flask and was removed by extraction with absolute alcohol.

The results of these experiments are given in Table I.

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[RESEARCH DIVISION CONTRIBUTION NO. 230—JACKSON LABORATORY, ORGANIC CHEMICALS DEPARTMENT, E. I. DU PONT DE NEMOURS AND CO.]

Evidence for Intramolecular Hydrogen Bonding in Aryl Allophanates and Alkyl or Aryl–Alkyl Biurets

BY I. C. KOGON

RECEIVED FEBRUARY 18, 1957

The near infrared absorption spectra of 1-ethyl-3-phenylurea, 1-methyl-1,3-diphenylurea, 1,1,3-triethylurea, ethyl carbanilate, *p*-chlorophenyl and *p*-methoxyphenyl carbamate show a strong absorption band in the region of 6750 cm.$^{-1}$. The band is not exhibited by ethyl α,γ-diphenylallophanate, ethyl α,p-chlorophenyl-γ-phenylallophanate, ethyl α,p-methoxyphenyl-γ-phenylallophanate, 1,3,5,5-tetraethylbiuret and 1-phenyl-3,5,5-triethylbiuret. It is proposed that the absence of this band is due to the presence of an intramolecular hydrogen bond.

Although examples of intramolecular hydrogen bonding in compounds containing an OH group have been demonstrated by means of near infrared spectra studies,[1] no use has been made of this method of investigation for determining intramolecular hydrogen bonding in molecules containing the NH group.

The hydroxyl group has an absorption band in the region of 7000 cm.$^{-1}$ when no intramolecular hydrogen bonding is expected.[2] This represents the first overtone of the fundamental stretching vibration of the OH group. Hilbert, Wulf, Hendricks and Liddel[3,4] found that absorption in this region is absent for a large number of compounds which have configurations that favor the formation of the intramolecular hydrogen bond. They found absorption was present in related compounds, the configuration of which excluded possible formation of such a bond; *e.g.*, in *o*-nitrophenol, absorption in the 7000 cm.$^{-1}$ region is absent, but it is present in *m*- and *p*-nitrophenol.

Correspondingly, the NH group has an absorption band in the region of 6700–6800 cm.$^{-1}$ which has been correlated with the first harmonic of the fundamental NH stretching vibration at 3500 cm.$^{-1}$.[5] We now have found that intramolecular hydrogen bonding can be detected by means of near infrared absorption spectra in α,γ-diaryl allophanates and in *unsym*-aryltrialkyl and *sym*-tetraalkyl biurets.

The aryl and alkyl ureas and aryl carbamates that we have examined exhibited strong absorption bands in the region of 6750, 5000, 4900 and 4850 cm.$^{-1}$ (Table I). The absence of the absorption band at 6750 cm.$^{-1}$ in the spectra of the allophanates (no. 1–7, Table II) and of the biurets (no. 8 and 9, Table II) strongly suggests that these compounds are intramolecularly hydrogen bonded. The molecular weight of the allophanates and biurets (no. 1–9, Table II) indicated these compounds to be in the monomeric state. In the region of 4831–4877 cm.$^{-1}$, a broad absorption band was found for those compounds suspected of having hydrogen bonding. Kaye,[6] in his study of methanol, showed that a broadening of the absorption bands in this region took place when hydrogen bonding increased.

TABLE I

RNHCOR′

No.	R	R′	Concn.[a] moles/liter	Absorption band, cm.$^{-1}$			
1	C_6H_5	OC_2H_5	2.425	6756	5045	4970	4880
2	p-$CH_3OC_6H_5$	OC_2H_5	0.5020	6743	5083	4940	4850
3	p-ClC_6H_5	OC_2H_5	.5150	6748	5038	4945	4855
4	C_6H_5	$N(CH_3)C_6H_5$	.1500	6710	5022	4946	4867
5	C_2H_5	NHC_6H_5	.0500	6725	4915	(broad band)	
6	C_2H_5	$N(C_2H_5)_2$	.7500	6780	4974	4915	4865

[a] All spectra were determined at 26 ± 0.5° and were carried out in 10.00-mm. and 25.00-mm. quartz cells using carbon tetrachloride as the solvent.

Interestingly, *sym*-triethyl and triphenyl biuret exhibited a weak absorption band in the region of 6750 cm.$^{-1}$ (no. 10 and 11, Table II) and showed three distinct absorption bands at 5000–5276, 4920–4943, 4825–4870 cm.$^{-1}$ instead of one broad band. An examination of Fisher–Hirschfelder–Taylor molecular models indicated that only one NH group can be intramolecularly hydrogen bonded at any one time to an oxygen atom, and therefore an absorption band should appear in the region of 6750 cm.$^{-1}$. Thus the three absorption bands are probably due to the unassociated NH of the biuret which completely masks the broad band due to associated NH.

Additional evidence lending support to the theory that the allophanate molecule is intramolecularly hydrogen bonded is found in the reactions of phenyl isocyanate with ethyl carbanilate[7] and cyanic acid with alcohol.[8] The products of the reactions are always the carbanilate and allophanate. No polyallophanate is isolated as might be expected if no intramolecular hydrogen bonding were present to tie up the NH group.

Experimental[9]

Materials.—Ethyl carbanilate, m.p. 48–49°, ethyl *p*-chlorophenylcarbamate, m.p. 66–67°, and ethyl *p*-methoxyphenylcarbamate, m.p. 65°, were prepared by the procedure of Vittenet.[10] Ethyl-α,γ-diphenylallophanate, m.p. 94°, ethyl α,p-chlorophenyl-γ-phenylallophanate, m.p. 89–90°, and ethyl α,p-methoxyphenyl-γ-phenylallophanate were

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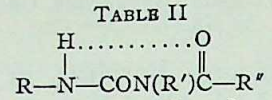
TABLE II



No.	R	R′	R″	Concn.[a] moles/liter	Absorption band, cm.$^{-1}$			
1	C_6H_5	C_6H_5	OC_2H_5	1.056[b]	4843			
2	C_6H_5	C_6H_5	OC_2H_5	0.3520[c]	4843			
3	C_6H_5	C_6H_5	OC_2H_5	.278[b]	4843			
4	C_6H_5	C_6H_5	OC_2H_5	.1408[c]	4843			
5	C_6H_5	C_6H_5	OC_2H_5	.0704[c]	4843			
6	C_6H_5	p-$CH_3OC_6H_5$	OC_2H_5	.1592[c]	4831			
7	C_6H_5	p-ClC_6H_5	OC_2H_5	.3140[c]	4836			
8	C_6H_5	C_2H_5	$N(C_2H_5)_2$	.3800[c]	4877			
9	C_2H_5	C_2H_5	$N(C_2H_5)_2$	.0807[c]	4877			
10	C_6H_5	C_6H_5	NHC_6H_5	.1620[b]	6711	5276	4943	4870
11	C_2H_5	C_2H_5	NHC_2H_5	.1605[c]	6725	5000	4920	4825

[a] All spectra were determined at 26 ± 0.5° and carried out in 10.00- and 25.00-mm. quartz cells. [b] Carbon tetrachloride was used as the solvent. [c] Benzene was used as the solvent.

prepared according to the procedure of Kogon.[11] 1-Ethyl-3-phenylurea was prepared according to the procedure of Thiele and Pickard,[12] m.p. 96–97°. 1-Methyl-1,3-diphenylurea was prepared according to the procedure of Gebhardt[13] m.p. 104°. 1,1,3-Triethylurea was prepared according to the procedure of Hofmann,[14] m.p. 62°. 1,3,5-Triphenylbiuret, m.p. 150–151°, and 1,1,3-triethyl-5-phenylbiuret, m.p. 113–113.5°, were kindly supplied by E. J. Goldberg.[15] 1,3,5-Triethylbiuret[16] (*Anal.* Calcd. for $C_8H_{17}N_3O_2$: N, 22.4. Found: N, 22.6) and 1,1,3,5-tetraethylbiuret (*Anal.* Calcd. for $C_{10}H_{21}N_3O_2$: N, 19.4. Found: N, 19.6) were prepared according to the procedure of Baker and Holdsworth.[17] A boiling point for these compounds was not obtained due to their ease of decomposition.

Preparation of Solutions.—The solutions were carefully made up by weighing the compound directly into a 50-ml. or 100-ml. volumetric flask and diluting with sufficient carbon tetrachloride or benzene to give 50 or 100 ml. of solution. The solution was then added directly to a 100.0- or 25.0-mm. quartz cell. Prior to each run the cells were washed once with acetone, followed by three to five washings with reagent grade carbon tetrachloride, then dried *in vacuo*. The cells were rinsed twice with 2 ml. of the solution to be examined and then filled.

Spectrophotometric Method.—Measurements were made in a 100.0- or 25.0-mm. quartz cell using the Cary spectrophotometer model No. 14. The cell holder was held at a temperature of 26 ± 0.5°. The samples were run at a scan speed of 50 Å./sec., chart speed of 5″/min., and a slit control of 0.15 mm.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WASHINGTON]

Paper Chromatography of Flavins and Flavin Nucleotides[1,2]

BY G. L. KILGOUR[3], S. P. FELTON AND F. M. HUENNEKENS

RECEIVED SEPTEMBER 19, 1956

Methods and solvent systems are described for the paper chromatographic separation and identification of flavins and flavin nucleotides.

Numerous investigations concerned with flavins and flavin nucleotides have been facilitated greatly by the application of chromatographic methods to these problems. Following the work of Crammer,[4] who first separated Rb,[5] FMN and FAD by paper chromatography, this technique has been utilized further in such studies as: the isolation[6–8] and chemical synthesis[9–11] of FAD and FMN, the identification of riboflavinyl glucoside,[12] the identification of Rb analogs,[13] the failure of P^{32}-labeled orthophosphate to be incorporated into FAD by respiring tissue homogenates[14] and the identifica-

(1) Paper IV in the series "Flavin Nucleotides and Flavoproteins"; for paper III, see THIS JOURNAL, **77**, 6716 (1955).
(2) Supported by research grants from Eli Lilly and Co. and Initiative 171, State of Washington.
(3) A portion of this material is taken from the Dissertation of Gordon L. Kilgour offered in partial fulfillment of the requirements for the degree of Doctor of Philosophy.
(4) J. L. Crammer, *Nature*, **161**, 349 (1948).
(5) The following abbreviations will be used: Rb, riboflavin; Lx, lyxoflavin; RbG, riboflavinyl glucoside; GalF, galactoflavin; IsoRb, isoriboflavin; LF, lumiflavin; LC, lumichrome; FMN, riboflavin 5′-phosphate (flavin mononucleotide); cyc-FMN, riboflavin-4′,5′-phosphate (cyclic); RbPP, riboflavin 5′-pyrophosphate; Rb-diP, riboflavin 4′,5′-diphosphate; FAD, flavin-adenine dinucleotide; FAD-X, cyclic analog of FAD.
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tion of the prosthetic group of various flavoproteins.

The present communication describes methods of paper chromatography which are applicable for the separation and identification of known flavins, and which provide information concerning the structure of unknown flavins of natural or synthetic origin.

Experimental

Materials.—Rb and FMN were commercial products from Merck and Co. and Hoffmann-La Roche Inc., respectively. FAD[6] and FAD-X[15] were isolated by methods previously described. LF and LC were prepared by ultraviolet irradiation of neutral and basic solutions of Rb, with subsequent isolation of the products by chloroform extraction of the acidified aqueous phase. Rb-4′,5′-diphosphate was obtained as a by-product in the synthesis of Rb-5′-pyrophosphate; details of these preparations are described in a subsequent communication.[16]

Intestinal phosphatase was purchased from Armour & Co. and nucleotide pyrophosphatase was isolated from potatoes.[17]

The following materials were generously provided for this investigation: Lx by Drs. K. Folkers and E. Snell; IsoRb and GalF by Dr. Folkers; RbG by Dr. L. G. Whitby; and cyc-FMN by Drs. A. R. Todd and G. Kenner.

All solvents were reagent grade commercial products and were used without further purification. Phenol of the required high purity was Merck reagent grade.

Methods.—Paper chromatography was carried out on 28 × 42 cm. sheets of Whatman #1 paper. Spots of approximately 4 mm. diameter were applied at the starting line, and the papers developed either ascending in 15 × 45 cm. cylindrical jars or descending in a Chromatocab. These operations were carried out in very dim light in order to minimize photodegradation of the flavins to LF or LC. An equilibration period of 3 hours was required for all organic systems, but not for aqueous systems.

As little as 0.01 μg. of flavin can be detected by means of its fluorescence under the Mineralight ultraviolet lamp, Model RB-50. When it was desired to locate, in addition, other nucleotides by their dark blue "quenching" spots, the shorter wave length Mineralight lamp, Model V41, was employed. Larger amounts of the dinucleotides, such as FAD, must be used in comparison to Rb or FMN, since the molar fluorescence of FAD is only 10–15% of that of the other two compounds at neutral *p*H.[18] In addition, considerable quenching of the fluorescence of all the flavins is caused by the presence of many organic compounds and metal ions.[19]

Due to the great sensitivity of detection by means of fluorescence, the usual spray reagents are largely unnecessary, and, in fact, are somewhat interfered with by the yellow color of the flavins. Thus, the phosphate reagent of Bandurski and Axelrod[20] yields spots of a greenish shade rather than blue. It is possible by spraying with an alkaline hydrosulfite reagent to bleach temporarily the yellow color of flavins, which are then re-oxidized by air. This serves to distinguish flavins from many other colored materials.

A semi-quantitative estimate of the amount of each flavin on a paper chromatogram may be obtained by photographing the flavins by their own fluorescence, and subsequently analyzing the negative with a Photovolt Model 501A densitometer.[21] The photography is accomplished by illuminating the paper evenly with the ultraviolet light source and using a red (*e.g.*, Wratten A) filter at the camera with Contrast Process Panchromatic Sheet film (Eastman). The picture also provides a permanent record of the chromatogram. An alternate method for obtaining quantitative data consists of treating the paper strip with a light Mineral oil, passing it through a Beckman Model DU spectrophotometer equipped with a paper-strip scanner,[22] Model 2001, and taking optical density readings at 450 mμ.

Results and Discussion

R_f Values and Solvent Systems.—Table I lists a series of acidic, basic and neutral solvents which have been found to be most suitable for the separation and identification of flavins. It is seen that essentially all of the systems readily separate the four *classes* of flavins: (a) degradation products, LC and LF; (b) nucleosides, Rb, Lx, GalF, IsoRb and RbG; (c) mononucleotides, FMN and cyc-FMN; and (d) dinucleotides, FAD and FAD-X. Within a given class, the individual members are usually separable, with the exception of Rb and Lx for which no separation has been devised.[23]

TABLE I

PAPER CHROMATOGRAPHY OF FLAVINS

Substance	R_f Values × 100 in various solvent systems[a] 1	2	3	4	5	6	7	8	9
Dinucleotides									
FAD	5	36	38	20	17	8	4	24	14
FAD-X	16	37	38	41	30	28	20	29	30
Mononucleotides									
FMN	10	33	50	17	4	17	4	17	14
cyc-FMN	13	27	36	49	15	29	12	29	23
Nucleosides									
Rb	31	58	28	79	69	37	41	33	39
Lx	32	55	30	77	64	34	40	32	38
IsoRb	33	55	27	80	74	45	46	35	42
GalF	30	51	41	73	57	37	41	32	39
RbG	23	42	43	59	50	34	35	31	36
Degradation Products									
LF	47	67	18	94	68	34	43	34	44
LC	68	75	7	88	72	61	73	53	58

[a] Composition of solvent systems: 1, *n*-butanol:acetic acid:H_2O (40:10:50)—use organic phase; 2, isobutyric acid:NH_4OH:H_2O (66:1:33); 3, $Na_2HPO_4 \cdot 7H_2O$ (5% in H_2O); 4, phenol:*n*-butanol:H_2O—160 g. of phenol is dissolved with warming in 30 ml. of *n*-butanol. The resulting solution is cooled to room temperature, shaken with 100 ml. of water and the organic phase used. 5, collidine—saturate with H_2O and use organic phase; 6, *t*-butyl alcohol:H_2O (60:40); 7, *t*-butyl alcohol:pyridine:H_2O (60:15:25); 8, *t*-butyl alcohol:NH_4OH:H_2O (60:5:35); 9, *n*-propanol:NH_4OH:H_2O (60:30:10). After being run in solvent system 4 and 5, the dried papers must be washed repeatedly in $CHCl_3$ before the fluorescent spots can be seen.

Solvent system 3, and similar ones employing aqueous buffered solutions, are susceptible to extreme variation in R_f values depending upon both the *p*H and the buffer concentration. The R_f values (× 100) for Rb, FMN and FAD vary with the molar concentration of 1.0, 0.1, 0.01 and 0.001 *M* phosphate buffer, *p*H 8.0, as follows: Rb—19, 32, 34, 32; FMN—40, 75, 76, 89; and FAD—24, 62, 74, 79. The relative order of the compounds does not change in spite of wide variations in their relative separation. This latter finding is not the case, however, when the *p*H is varied using different buffers, but with the buffer concentration held at 0.1 *M*. The R_f of Rb is not greatly influenced from *p*H 2 to 10, while FAD precedes FMN at *p*H values below 5.5, and follows FMN at *p*H values above that. Maximum separation may be ob-

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(22) Research Specialties Co., 1148 Walnut St., Berkeley 7, Calif.
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tained for a mixture of all three components in the *p*H range of 7.0–8.0.

It is possible also in aqueous solvent systems, such as No. 3, to observe a linear relationship, as shown in Fig. 1, between the R_f value of a flavin

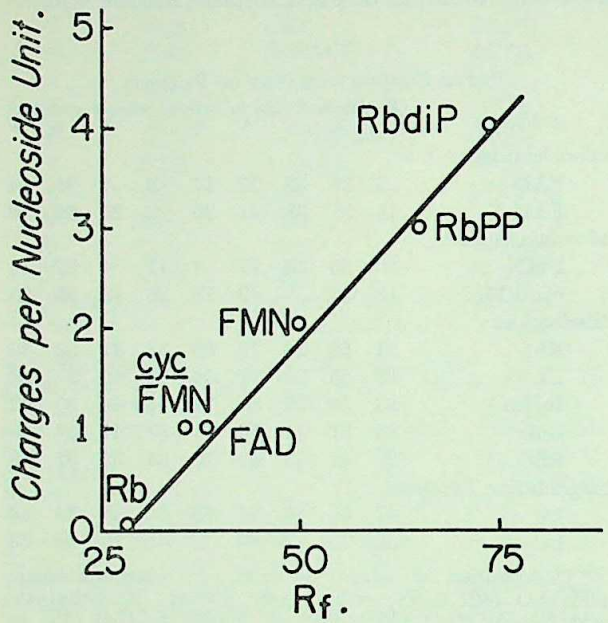

Fig. 1.—R_f value as a function of charge per nucleoside.

and its "charge per nucleoside" ratio. This latter quantity is obtained by dividing the number of negative charges, due to ionization of the phosphate groups, by the total number of nucleoside residues in the molecule. At *p*H 8, these values are 0, 1 and 2, respectively, for Rb, FAD and FMN.

The acidic solvents in Table I have been chosen partially because of the relative stability of sensitive dinucleotides, such as FAD, in these systems. The basic solvents, especially those containing ammonia, all have shown a tendency to cause cyclization of the flavin nucleotides.

Identification of Unknown Flavin Nucleotides.—Considerable information concerning the structure of a flavin prosthetic group or synthetic flavin may be obtained on small amounts of material by the above techniques. All flavoproteins, with the exception of succinic dehydrogenase,[24] have their prosthetic groups readily detached by heat denaturation or treatment in the cold with 10% trichloroacetic or perchloric acid. Heat is preferable both because it minimizes breakdown and because it avoids the addition of extraneous materials. Excess of the two precipitating agents should be removed, however, by ether extraction or neutralization with KOH, respectively. Prior to examination by paper chromatography, the flavins may be concentrated by methods described previously, or by adaptation of paper chromatographic methods, wherein the flavins are run as streaks and eluted with minimum volumes of water. It should be noted that acids, bases, light and some organic solvents, (*e.g.*, acetone and ethyl alcohol), tend to degrade flavins and should be avoided during the concentration procedures.

In addition to obtaining information from chromatography of the intact flavin, it is possible to degrade the material by means of treatment with acid, base or enzymes, and to compare the breakdown products with known standards. For example, after spotting the flavin at the origin, the paper may be exposed to HCl or NH_3 vapors for 1 hour in the dark, and then aerated in a hood for a few minutes before being placed in the solvent. Similarly, the spot may be overlaid with a concentrated solution of intestinal phosphatase or nucleotide pyrophosphatase and the paper suspended in a moist tank for an hour prior to running the chromatogram. Such techniques have been employed previously for establishing the structure of FAD-X.[15]

Acknowledgment.—The authors are indebted to Mrs. Enid Vercamer for her assistance in this problem.

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Chemical Synthesis of Riboflavin 5′-Pyrophosphate[1,2]

BY G. L. KILGOUR[3] AND F. M. HUENNEKENS

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The chemical synthesis of riboflavin 5′-pyrophosphate (RbPP) from readily available riboflavin 5′-phosphate (FMN) has been investigated, using several phosphorylating agents, the most suitable being phosphoric acid in the presence of di-*p*-tolyl carbodiimide (DPTC). By means of these reactions, and subsequent isolation of the product by large-scale, preparative paper chromatography, RbPP has been obtained and characterized.

The chemical synthesis of flavin–adenine dinucleotide (FAD[4]) was first achieved by A. R. Todd and his colleagues[5] through a route utilizing the condensation of the mono-silver salt of FMN with 2′,3′-isopropylidene adenosine-5′-benzyl phos-

(1) Paper V in the series "Flavin Nucleotides and Flavoproteins"; for paper IV see G. L. Kilgour, S. P. Felton and F. M. Huennekens, THIS JOURNAL, **79**, 2254 (1957).

(2) Supported by research grants from Eli Lilly and Co. and Initiative 171, State of Washington.

(3) A portion of this material is taken from the Dissertation of Gordon L. Kilgour offered in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(4) The following abbreviations will be used: LC, lumichrome; LF, lumiflavin; Rb riboflavin; FMN, riboflavin-5′-phosphate; cyc-FMN, riboflavin-4′,5′-(cyclic)-phosphate; FAD, flavin–adenine dinucleotide; RbPP, riboflavin-5′-pyrophosphate; RbdiP, riboflavin diphosphate; RbI, 5′-deoxy-5′-iodo-riboflavin; AdI, 5′-deoxy-5′-iodo-adenosine; DCC, dicyclohexyl carbodiimide; DPTC, di *p*-tolyl carbodiimide.

(5) S. Christie, G. W. Kenner and A. R. Todd, *Nature*, **170**, 924 (1952); *J. Chem. Soc.*, 46 (1954).

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phorochloridate, followed by removal of the protective groups. Subsequently, an alternate procedure was devised in this Laboratory, wherein FMN and AMP are condensed directly using di-*p*-tolyl carbodiimide as the dehydrating agent.[6] Other projected pathways to FAD, not requiring protective groups, would envision either (a) the condensation of RbI with mono-silver ADP, or (b) mono-silver RbPP with AdI.[7] The present communication describes briefly the attempted preparation of RbI and, in more detail, the successful synthesis of RbPP.

Synthesis of RbI would be expected to proceed through replacement of the primary tosyl group, at the 5′-position of riboflavin, with iodine.[8] Preliminary experiments, however, confirmed the finding of Forrest, *et al.*,[9] that neither the 5′-tosyl nor the 5′-mesyl ester of riboflavin could be obtained, even with wide variation in reaction conditions. Attempts to halogenate the 5′-position directly with ICl were likewise unproductive; accordingly the first route was not explored further.

The preparation of RbPP was approached in several ways. It was decided first to attempt the condensation of the silver salt of FMN with $POCl_3$ at temperatures below 0° in anhydrous dimethylformamide. Upon chromatographing an aliquot of the resulting solution in 5% Na_2HPO_4 and determining the amount of each component by quantitative densitometry,[1] three products were found in addition to unreacted FMN (R_f = 0.57, 18% yield) and large quantities of cyc-FMN (R_f = 0.36, 63% yield). Following purification by means of large-scale paper chromatography, one product (R_f = 0.66, 6% yield) was identified as RbPP. It was found to exhibit a P_7:P_{tot}:flavin ratio[10] of 1:2:1, and upon treatment with dilute H^+, NH_3 or Ba^{++}, was hydrolyzed to FMN (with NH_3, some cyc-FMN was formed also). The second flavin product (R_f = 0.73, 8% yield) is believed to be riboflavin-4′,5′diphosphate by the P_{tot}:flavin ratio of 2:1, the absence of any acid-labile phosphate, and the positive periodate reaction.[11] This second compound has been detected also in small amounts (*ca.* 3–6%) by paper chromatography of commercial FMN. The third flavin (R_f = 0.60, 5% yield) has been designated tentatively as Rb-4′,5′-cyc-diphosphate because of its chromatographic behavior, ease of hydrolysis in dilute acids to yield Rb-4′,5′-diphosphate, and positive reaction to the periodate reagent.

The yield of RbPP could not be increased, nor could the amount of unwanted cyc-FMN be decreased, by substituting monochlorophosphoric acid[12] or diphenylphosphoryl chloride for $POCl_3$.

The synthesis of ATP and ADP from AMP and H_3PO_4 using dicyclohexyl carbodiimide[13] suggested the possibility of RbPP synthesis from FMN and H_3PO_4 by this method. However, DCC reacted rapidly and completely with FMN to give only cyc-FMN. When the less reactive DPTC was substituted for the dicyclohexyl derivative, the reduced reaction rate permitted the hydroxyl group of the entering phosphate to compete with the sterically preferred 4′-hydroxyl of FMN. In addition to FMN and cyc-FMN, the products included one compound chromatographically and chemically indistinguishable from the RbPP prepared previously by condensation of Ag_2FMN and $POCl_3$. Several other flavins obtained in lower yield appeared to be, on the basis of R_f values and acid hydrolysis to FMN, higher polyphosphates of riboflavin, Rb(P)x, analogous to the ATP and adenosine tetraphosphate obtained by Khorana[13] in the synthesis of ADP.

Experimental

Materials and Methods.—Commercial chemicals used in this investigation were obtained from the following sources: monosodium FMN, Hoffman–LaRoche, Inc.; Rb, Nutritional Biochemical Co.; DCC, Dajac Laboratories; Florisil, Floridin Company; ICl, Eastman Kodak Co. DPTC was prepared by the method of Khorana.[14] Cyc-FMN was prepared by the method of Forrest and Todd.[15]

Paper chromatography was carried out as described previously.[1]

Preparation of Disilver FMN.—NaFMN (1.0 g., 2.1 mmoles) was dissolved in 10 ml. of water and a solution of 1.0 g. (6.0 mmoles) of $AgNO_3$ in 10 ml. of water added. To the resultant bright red solution was added 10 ml. of absolute methanol. At this point a flocculent red precipitate formed and was centrifuged readily from the pale yellow supernatant solution. The precipitate was washed twice with absolute methanol, twice with dry ether, and dried under vacuum at room temperature to yield 1.080 g. of a fine, red powder. Found: Ag = 33.17%; Calcd. for AgFMN, Ag = 19.04%; for Ag_2 FMN, Ag = 31.73%; for Ag_3FMN, Ag = 41.70%.

Synthesis of RbPP Using H_3PO_4 and Carbodiimide.—Ten mg. of NaFMN was dissolved in 0.1 ml. of water and 0.5 ml. of pyridine was added. To this was added a solution of 500 mg. of DPTC in 0.5 ml. of pyridine. Finally, 0.25 ml. of 85% H_3PO_4 was added with shaking, and the final mixture was shaken mechanically in the dark at room temperature for 24 hours. Addition of water (*ca.* 2 ml.) to the mixture caused precipitation of unreacted DPTC and the by-product, di-*p*-tolylurea. These materials were removed by filtration and the resulting clear solution analyzed by paper chromatography in order to ascertain the amount of RbPP present. Quantitative densitometry of the paper chromatograms revealed that 17% of the total flavin was RbPP. Decreasing the amount of H_3PO_4 or water, increasing the amount of pyridine (to 3.0 ml.), or substitution of FMN (free acid) for NaFMN, greatly diminished the yield of RbPP, while increasing the time beyond 24 hours appeared to have no significant effect. Shorter times were found to result in increased amounts of unreacted FMN.

(6) F. M. Huennekens and G. L. Kilgour, THIS JOURNAL, **77**, 6716 (1955).

(7) Since the difficulties of preparing AdI by the conventional route through the condensation of 2′,3′-isopropylidene-5′-tosyladenosine with NaI are well recognized (J. Baddiley, *J. Chem. Soc.*, 1349 (1951); V. M. Clark, A. R. Todd and V. Zussman, *ibid.*, 2952 (1951)), this pathway would be useful only if an alternate route to AdI were available. The analog, flavin-inosine dinucleotide, previously synthesized by another route,[8] could be prepared, however, in this manner, since the synthesis of inosine-5′-iodide is reported to proceed smoothly by NaI treatment of the tosyl intermediate.

(8) J. W. H. Oldham and J. K. Rutherford, THIS JOURNAL, **54**, 366 (1932); P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 317 (1933).

(9) H. S. Forrest, H. S. Mason and A. R. Todd, *J. Chem. Soc.*, 2530 (1952).

(10) P_7 = moles phosphate released in 7 minutes at 100° in 1 *N* acid/mole flavin; P_{tot} = total moles phosphate present/mole flavin.

(11) J. G. Buchanan, C. A. Dekker and A. G. Long, *J. Chem. Soc.*, 3162 (1950).

(12) L. A. Flexser and W. G. Farkas, 12th International Congress of Pure and Applied Chemistry, New York, Sept. 1951, Abstracts, p. 71.

(13) H. G. Khorana, THIS JOURNAL, **76**, 3517 (1954).

(14) H. G. Khorana, *Can. J. Chem.*, **32**, 230 (1954).

(15) H. S. Forrest and A. R. Todd, *J. Chem. Soc.*, 3295 (1950).

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RbPP was isolated from the above mixture of flavins by the following procedure. The solution was diluted to 50 ml. with water and was shaken three times with four volumes of $CHCl_3$ in order to remove most of the pyridine. Removal of inorganic impurities was carried out by adsorption of the flavins on a Florisil column. The solution was acidified to *p*H 5 with acetic acid and passed through a washed column of Florisil (*ca.* 10 × 30 cm.). The column was washed with acetic acid, water and pyridine, as described previously,[16] and the flavins removed by elution with 5% pyridine. Pyridine was removed by shaking with $CHCl_3$, giving a clear yellow solution of the flavins.

The solution was concentrated to a small volume by lyophilization. Bulk separation of the flavins was achieved by applying the concentrated flavin solution to the starting line of Munktell's Cremer–Tiselius paper[6] (*ca.* 50 mg. per sheet) and developing the chromatogram in 5% Na_2HPO_4. The separate bands were located by inspection under a Mineralite, cut out, and eluted with water. Inorganic phosphate was removed from each fraction as follows. First, the solutions were stored at 0–5° for several days in order to crystallize out excess phosphate. Silver nitrate was then added in slight excess, with stirring, and the solution was adjusted with dilute acetic acid until the flavin went back into solution as a red complex. The residual silver phosphate was removed by centrifugation and the red supernatant solution passed through a short, chilled column of IR-120(H^+) cation exchange resin to remove silver. The effluent was collected in a tube immersed in a bath of acetone and Dry Ice and was thus frozen immediately. The solution was later thawed and adjusted immediately to *p*H 7 with dilute NaOH. Large-scale paper chromatography was repeated as above but employing *t*-BuOH:water (60:40) as the solvent system.[6] The pure components thus obtained, with the exception of FMN and cyc-FMN, were present in amounts too small to handle conveniently in the dry state, and the analyses and characterization were carried out using concentrated solutions. At this point, all of the flavins including RbPP behaved chromatographically as single components having the R_f values given previously. RbPP was obtained after purification in *ca.* 5% over-all yield, based upon the original NaFMN. The P_i:$P_{tot.}$: flavin ratio was 1.13:2.07:1 and 1.09:2.17:1 in duplicate analyses, and upon gentle acid hydrolysis there was quantitative conversion to FMN.

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(16) E. Dimant, D. R. Sanadi and F. M. Huennekens, THIS JOURNAL, **74**, 5440 (1952).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WASHINGTON, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

Lyxoflavin Nucleotides[1,2]

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L. lactis cells, grown on lyxoflavin, incorporate the vitamin into lyxoflavin mononucleotide (LMN) and dinucleotide (LAD), which can be isolated by means of chromatography on Florisil and paper columns. LMN and LAD can be distinguished from their riboflavin analogs by means of a differential microbiological assay using *L. lactis* and *L. casei*. They cannot be distinguished, however, by means of paper chromatography. In TPNH cytochrome c apo-reductase from yeast FMN is utilized preferentially to LMN, although the latter exhibits appreciable activity. In a D-amino acid apo-oxidase from pig kidney, FAD is utilized preferentially to LAD.

In 1949 Pallares and Garza[3] reported the isolation of L-lyxoflavin from human cardiac muscle. The proof of its structure, and its non-identity with D-riboflavin, rested principally upon the preparation of the tetraacetyl derivative, whose melting point agreed with that of Lx,[4] but not Rb. Synthetic Lx was first prepared by these authors, using a modification of the Karrer procedure[5] and, subsequently, by other independent routes.

The failure of other workers[6,7] to find Lx in a variety of animal tissues has cast doubt as to the natural occurrence of this substance. In addition, Gardner, *et al.*,[7] have pointed out the difficulty in distinguishing Lx and Rb on the basis of a single derivative.

In spite of the doubtful natural occurrence of Lx, other investigations have been carried out with the synthetic material. The addition of Lx to experimental rations increased the growth of rats,[8,9] chicks[9,10] and pigs.[11] Snell, *et al.*,[6] have shown that Lx does not support growth of *Lactobacillus casei* in the absence of Rb, but that low concentrations of Lx increase the growth response to limiting amounts of Rb. Under the latter conditions it was shown that Lx was not deposited in cells of *L. casei*, and that it actually decreased the concentration of Rb deposited in such cells. In contrast, the similar organism, *Lactobacillus lactis*, grew in the absence of Rb when Lx was supplied to the medium.[6,12] In this case, cells grown with Lx contain no Rb, but do contain Lx; *i.e.*, Lx apparently can fulfill the essential metabolic roles normally played by Rb. The growth requirements of these two organisms made it possible to determine Lx and Rb by means of a differential microbiological assay.[6]

Since it had been established that *L. lactis* utilized Lx directly for growth, it seemed possible that the Lx was being incorporated into the cellular flavin nucleotides. In the present study, the

(1) Paper VI in the series "Flavin Nucleotides and Flavoproteins." For paper V see G. L. Kilgour and F. M. Huennekens, THIS JOURNAL, **79**, 2256 (1956).

(2) Supported by grants from Eli Lilly and Co. and Initiative 171, State of Washington.

(3) E. S. Pallares and H. M. Garza, *Arch. Biochem.*, **22**, 63 (1949).

(4) The following abbreviations will be used: Lx, lyxoflavin; Rb, riboflavin; LMN and FMN, lyxoflavin and riboflavin mononucleotides; LAD and FAD, lyxoflavin- and riboflavin–adenine dinucleotides.

(5) P. Karrer, H. Salmon, K. Schopp, F. Benz and B. Becker, *Helv. Chim. Acta*, **18**, 910 (1935).

(6) E. E. Snell, O. A. Klatt, H. W. Bruins and W. W. Cravens, *Proc. Soc. Exp. Biol. Med.*, **82**, 583 (1953).

(7) T. S. Gardner, E. Wenis and J. Lee, *Arch. Biochem. Biophys.*, **34**, 98 (1951).

(8) G. A. Emerson and K. Folkers, THIS JOURNAL, **73**, 2398, 5335 (1951).

(9) J. M. Cooperman, W. L. Marsuick, J. Scheiner, L. Drekter, E. DeRitter and S. H. Rubin, *Proc. Soc. Exp. Biol. Med.*, **81**, 57 (1952).

(10) H. W. Bruins, M. L. Sunde, W. W. Cravens and E. E. Snell, *ibid.*, **78**, 535 (1951).

(11) R. C. Wahlstrom and B. C. Johnson, *ibid.*, **79**, 636 (1952).

(12) M. S. Sheridan, *ibid.*, **79**, 611 (1952).

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flavin nucleotides have been isolated from *L. lactis* cells grown on Lx, and shown to be the corresponding counterparts of FMN and FAD. Although the Lx and Rb nucleotides are similar in many chemical aspects, including migration on paper in various solvent systems, they can be distinguished by their behavior as coenzymes in enzymatic assay systems.

Experimental

Materials.—Lx was generously provided by Drs. Karl Folkers and J. M. Cooperman. FAD was prepared by the method of Dimant, *et al.*,[13] FMN was obtained from Hoffmann-LaRoche, Inc., and was recrystallized from an acidic aqueous solution. Cytochrome-c and TPN were obtained from the Sigma Chemical Company. TPNH was prepared by the enzymatic reduction of TPN using the glucose 6-phosphate dehydrogenase system.

Synthetic LMN was prepared as follows[14]: 5 mg. of Lx was added to a mixture of 0.15 ml. of $POCl_3$ and 0.01 ml. of water at room temperature. After 20 minutes the solid had dissolved to yield a dark red-brown solution. Twenty ml. of ether was then added and the resulting precipitate was recovered by centrifugation, washed twice with ether and dried *in vacuo*. The solid was dissolved in 1.5 ml. of water, neutralized with NaOH and subjected to large-scale paper chromatography, using 5% aqueous Na_2HPO_4 as the solvent system. The LMN band, which separated cleanly, was cut out, eluted and standardized spectrophotometrically in solution[15]; yield, *ca.* 25% of theory. The molal extinction coefficient, ϵ, for LMN is assumed to be the same as for FMN,[16] *i.e.*, 12.2×10^6 cm.^{2}/mole.

D-Amino acid apo-oxidase and TPNH-cytochrome-*c* apo-reductase were prepared from pig kidney and baker's yeast, respectively.[17] The growth media for both *L. casei* and *L. lactis* has been described previously by Snell, *et al.*[6]

Methods.—Absorption spectra were determined with a Beckman spectrophotometer, Model DU. Enzymatic assays[17] for FAD and FMN and the differential microbiological assay[6] for Rb and Lx have been described previously.

Using a great variety of solvent systems, or even borate-treated papers, it has not been possible to effect a satisfactory separation of Rb and Lx, or the corresponding nucleotides, by means of paper chromatography.[18]

The isolation of the flavin nucleotide fraction from *L. lactis* cells by means of chromatography on Florisil was carried out as follows: 10 g. of washed, harvested and lyophilized cells were mixed with 30 ml. of water and 4.7 ml. of 50% trichloroacetic acid and homogenized for 1 minute in a Waring blendor. The slurry was centrifuged for 5 minutes at 2300 × *g* in the cold, and the supernatant fluid was removed by decantation. The residue was homogenized twice with 35 ml. of 6.7% trichloroacetic acid, and the supernatant fluids separated by centrifugation. The combined supernatant fluids (77 ml.) exhibited optical density values of log I_0/I = 0.195 at 450 mμ and 1.095 at 260 mμ. The trichloroacetic acid extract was passed through a Florisil column (3.4 × 14.5 cm.), and, after adsorption of the flavins at the top, the column was washed, in turn, with 1 l. of 2% acetic acid, 2 l. of water and one l. of 0.5% pyridine. The flavins were then eluted with 200 ml. of 5% pyridine. After removal of the pyridine by extraction with chloroform, there remained a volume of 160 ml. which had optical density values of 0.035 at 450 mμ and 0.565 at 260 mμ. This would correspond to 5.0×10^{-4} mmole of flavin, or a recovery of about 38% of that originally placed on the column. The solution was then lyophilized to yield a light yellow powder weighing 35 mg.

Separation of the Lx nucleotides was effected by means of adsorption chromatography on a paper pulp column. Solka-floc[19] was slurried in acetone and packed into a column (1.1 × 23 cm.) under gentle air pressure. The column was washed with 0.05 *M* phosphate buffer (*p*H 8.0) until all of the acetone had been removed, and the column was completely equilibrated with the buffer. The column was taken to incipient dryness and the above lyophilized flavin material, dissolved in 1.5 ml. of water, was added to the top of the column. Separation of the flavins was achieved by developing the column with phosphate buffer. The flow rate was about 2 drops per minute, and the effluent was collected in an automatic fraction collector. The contents of each tube was diluted up to 3 ml. with water and the optical density determined at 450 mμ. The resulting column profile is shown in Fig. 1.

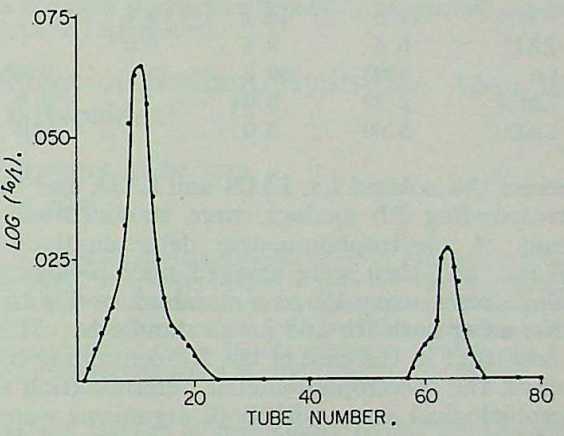

Fig. 1.—Separation of flavins on Solka-floc column. Column effluent was collected in test-tubes using a Technicon Time-Flow Automatic fraction collector, pre-set for 5 drops per tube from 1–56 and 10 drops per tube from 57–80. The contents of each tube was diluted to 3.0 ml. with water and the light absorption log (I_0/I) determined at 450 mμ.

Paper chromatography[15] revealed that tubes 8–13 contained only LMN, whereas tubes 14–19 contained both LMN and LAD. The latter group were pooled, lyophilized to dryness, and the material chromatographed on sheets of No. 1 Whatman paper using 5% $NaHPO_4$ as the solvent system. The separated bands of LMN and LAD were cut out, eluted, and the LMN fraction combined with the contents of tubes 8–13. Assayed spectrophotometrically, the amounts of lyxoflavin-containing materials were: Lx, 0.44 × 10^{-4} mmole; LMN, 1.21 × 10^{-4} mmole; and LAD, 0.14 × 10^{-4} mmole; total, 1.79 × 10^{-4} mmole; recovery, 36%. About 75% of the flavin is in the mono- or dinucleotide form, the remaining 25% being the free vitamin concentrated within the cell. In animal tissues essentially all of the flavin is distributed between the nucleotide forms.[13]

Results and Discussion

Isolation of Lx Nucleotides.—The total amount of flavin contained in cells of *L. lactis* grown on Lx may be calculated from the data obtained in the Florisil chromatography step. In the pyridine eluate fraction about 230 μg. of flavin was obtained from 10 g. of dried cells, or about 23 mg. of flavin per kg. of dried cells. For pig liver or yeast the value is about 200 mg. per kg.[12] It is probable that the amount of flavin calculated from the pyridine eluate is more accurate than that obtained on the original trichloroacetic acid extract, since the original extract may have contained substances

(13) E. Dimant, D. R. Sanadi and F. M. Huennekens, THIS JOURNAL, **74**, 5440 (1952).

(14) We are indebted to Dr. G. L. Kilgour for carrying out this synthesis.

(15) It has been shown previously that treatment of Rb with (a) $POCl_3$ (H. S. Forrest and A. R. Todd, *J. Chem. Soc.*, 3295 (1950)), or (b) monochlorophosphoric acid (L. A. Flexser and W. G. Farkas, 12th International Congress of Pure and Applied Chemistry, New York, N. Y., Sept. 1951, Abstracts p. 71) results in phosphorylation only at the 5′-position.

(16) L. G. Whitby, *Biochem. J.*, **54**, 437 (1953).

(17) F. M. Huennekens and S. P. Felton in "Methods in Enzymology," Vol. III, ed. by S. P. Colowick and N. O. Kaplan, Academic Press, New York, N. Y., 1957, p. 950.

(18) G. L. Kilgour, S. P. Felton and F. M. Huennekens, THIS JOURNAL, **79**, 2255 (1957).

(19) Solka-floc Paper Pulp, BW 200, was obtained from the Brown Co., 150 Causeway St., Boston 14, Mass.

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other than flavin capable of absorbing light at 450 mμ.

Microbiological Assay of Lyxoflavin Nucleotides.—It was of interest to carry out on the isolated Lx nucleotides a differential microbiological assay similar to that which had been done previously on the total Lx-containing compounds in *L. lactis* cells.[6] Table I contains the results of the assay,

TABLE I

FLAVIN CONTENT BY SPECTROPHOTOMETRIC AND MICROBIOLOGICAL ASSAY

Compound	Spectrophotometric assay, μg./ml.	Microbiological assay, μg./ml. *L. casei* Rb Std.	*L. lactis* Rb Std.	*L. lactis* Lx Std.
Rb	19.4	18.4	18.0	
FMN	14.9	14.1	15.9	
FAD	9.5	9.6	8.0	
Lx	0.92	0.0		0.42
LMN	2.22	0.04		2.0
LAD	3.60	0.0		0.0

wherein the isolated Lx, LMN and LAD, and their corresponding Rb analogs, were standardized by means of spectrophotometric determinations at 450 mμ, and then were assayed microbiologically with *L. casei*, using Rb as a standard, and with *L. lactis*, using both Rb and Lx as standards. It can be seen that in the case of the Rb-containing compounds, the spectrophotometric determination and microbiological assay with both organisms were in good agreement. In the case of the Lx analogs, however, there was no apparent response in the *L. casei* assay. Of interest also is the fact that the Lx materials did not function equally well in the microbiological assay with *L. lactis*. Both Lx and LMN showed agreement between the microbiological and spectrophotometric assays, but LAD gave no response in the microbiological assay.

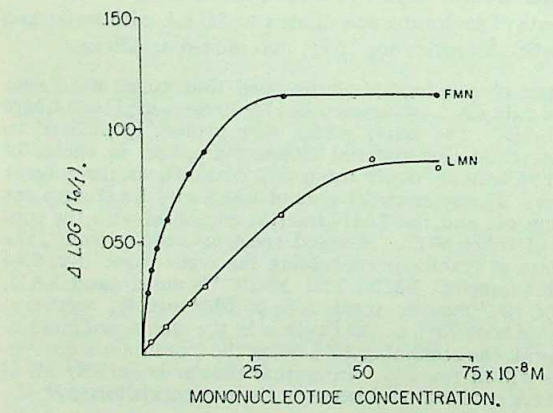

Fig. 2.—Comparison of FMN and LMN as coenzymes for TPNH-cytochrome-C reductase. The following components were added to a Corex cuvette having a light path of 1 cm.: 20 μmoles of phosphate buffer, *p*H 7.3, 0.08 μmole of cytochrome-c, 0.05 μmole of TPNH, the indicated amount of FMN (⊙) or LMN (△) and water to make 2.9 ml. The blank cell was identical except for the omission of cytochrome-c. After taking an initial reading at 550 mμ, 0.1 ml. of the apo-reductase was added to both cuvettes and the readings taken at 1-min. intervals for 6 min. Since the change in optical density was linear over the entire period, the total change, expressed as log (I_0/I) for 6 min., is plotted on the ordinate. All experimental values have been corrected for an additional blank wherein no FMN was added. This value, representing the residual, conjugated enzyme in the preparation, was about one-fourth the experimental value.

Enzymatic Activity of LMN.—The dissociated TPNH-cytochrome-*c* reductase from baker's yeast was chosen as a suitable test system for examining the relative coenzymatic activity of the two mononucleotides. As shown in Fig. 2, FMN restored full activity to the enzyme at a level of about 150 μg. per ml., and has a Michaelis constant K_m, of 5.2×10^{-8} *M*. LMN was less effective than FMN, but at high concentrations it reached a maximum activity about 75% of that shown by FMN. The K_m value for LMN was 6.4×10^{-7} *M*. Further evidence that the isolated LMN is, in fact, the 5′-phosphate derivative of Lx, was afforded by an experiment wherein a synthetic sample of LMN, prepared by the direct phosphorylation of Lx in the 5′-position, was assayed in the above enzymatic system. A K_m value of 8.8×10^{-7} *M* was obtained. The somewhat higher value for the synthetic LMN may have been due to the presence of inhibitory substances carried along from the synthetic reaction mixture.

Enzymatic Activity of LAD.—The D-amino acid oxidase of pig kidney was chosen for a comparison of FAD and LAD. Using the customary manometric assay, the effect of FAD concentration upon activity is shown in Fig. 3. The Michaelis

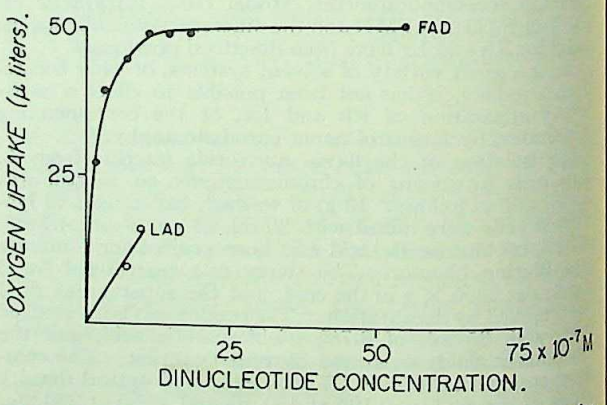

Fig. 3.—Comparison of FAD and LAD as coenzymes for D-amino acid oxidase. The manometer cups contained 25 μmoles of pyrophosphate buffer, *p*H 8.3, 100 μmoles of DL-alanine, *p*H 8.3, 0.5 ml. of D-amino acid apo-oxidase, FAD (⊙) or LAD (△) at the indicated concentration, and water to make 2.8 ml. The center well contained 0.2 ml. of 6 *N* NaOH. The blank cups were identical except for the omission of alanine. The cups were gassed with oxygen and equilibrated for 10 min. with the stopcocks open. Oxygen uptake values are expressed as μliters for the first 10-min. period after the stopcocks were closed. All values are corrected for the blanks without substrate and without added FAD. The blank was about 20% of the experimental values; bath temperature, 30°.

constant, K_m, is calculated to be 1.6×10^{-7} *M*. LAD, on the other hand, was quite inactive in this system at concentrations where FAD had saturated the enzyme, although there was a progressive increase in activity as the concentration was in-

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creased. The small amount of LAD available for this study made it impossible to test the activity at higher concentrations.[20]

The results with both enzymatic assay systems give further convincing evidence of the remarkable ability of enzyme systems to distinguish between closely related substances. In this respect, it would be of interest to isolate typical flavoprotein enzymes from *L. lactis* cells, and to determine the relative efficiency of Rb and Lx nucleotides in these systems. Since Lx nucleotides satisfy the requirements of all of the flavoprotein enzymes of this organism that are essential for its growth, they may approach their Rb counterparts more closely in activity. Even in this organism Rb promotes growth at substantially lower concentrations than Lx,[6] and it is unlikely that the Lx coenzymes function as efficiently as the Rb coenzymes.

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(20) The present evidence does not constitute unequivocal proof that the material in question is actually lyxoflavin–*adenine* dinucleotide. By all criteria of paper and column chromatography, the material is clearly a lyxoflavin *dinucleotide*. After acid degradation, LMN could be identified by paper chromatography, but the equally minute amount of purine mononucleotide could not be located on the paper chromatograms.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, LOUISIANA STATE UNIVERSITY SCHOOL OF MEDICINE, AND THE DEPARTMENT OF CHEMISTRY, TULANE UNIVERSITY]

The Shape of Pyranoside Rings. II. The Effect of Sodium Hydroxide upon the Optical Rotation of Glycosides[1]

BY RICHARD E. REEVES AND FLORINE A. BLOUIN

RECEIVED OCTOBER 25, 1956

The optical rotation of many glycosides is essentially the same in neutral aqueous solution or in *N* sodium hydroxide solution. However, there are some glycosides which show relatively large, reversible changes in optical rotation at sodium hydroxide concentrations greater than approximately 0.01 *N*. The observation that these changes are reversible argues against their being due to hydrolysis or to degradation reactions. The possibility is considered that these alkali-sensitive substances might undergo an alteration in the fine structure (conformation) of the molecules arising as a result of a tendency of axially oriented hydroxyl groups to shift toward an equatorial orientation under strongly alkaline conditions.

In a continuing search for an understanding of the effect of alkali upon the optical rotation of amylose,[2] we have been led to a general investigation of the effect of alkali upon the rotation of simple glycosides. The literature contains few observations of an effect of alkali upon the rotation of "alkali-stable" sugar derivatives, and no survey of this effect seems to have been reported. An unusual temperature dependence of optical rotation has been noted for a class of glycosides, the acylated *o*-nitrophenyl glycosides, and this had led to the development of ideas regarding the fine structure of these substances.[3] However, no significance has hitherto been attached to the fact that some glycosides are quite alkali-sensitive while others are not.

Experimental

The glycosides employed in this work possessed melting points and specific rotations in close agreement with the best values reported in the literature.

To avoid the possibility that the different optical rotations observed for neutral and alkaline aqueous solutions might be due to ionic strength differences, we have observed optical rotations in molar sodium chloride and in normal sodium hydroxide. When a substance with different rotations in water and in alkali was encountered, solutions of equal concentration were prepared in molar saline and in normal sodium hydroxide, and the solutions were mixed in various proportions in a sealed-end polarimeter tube made with a side-arm bulb to allow for mixing. Additive volumes were assumed for these solutions. In some instances observations were made at alkali concentrations greater than normal and these solutions were separately prepared in volumetric flasks. The reversibility of the alkali-induced shifts in rotation was checked by neutralizing normal or half-normal sodium hydroxide solutions with hydrochloric acid and observing the rotations of the neutralized solutions.

The observations were made with the sodium D-line at 27.5 ± 2.5° using either a 1- or a 2-dm. polarimeter cell. Because of the fixed volume requirements of the cells and the widely different availability of pure samples of the substances employed, the measurements are not uniformly precise. However, it seems to us that the greatest uncertainty due to experimental error in the difference between specific rotation in saline and in normal sodium hydroxide should not exceed 1°.

In the preparation of a solution of methyl β-D-altropyranoside the crystalline tetraacetate was dissolved in an excess of aqueous sodium hydroxide at room temperature. Back titration with standard hydrochloric acid provided assurance that all four acetate groups had been saponified. The saline and alkaline solutions were prepared from this neutralized stock solution and contained 0.53 *M* sodium acetate in addition to the sodium chloride and sodium hydroxide.

Results

The simple glycopyranosides so far examined in saline and in normal sodium hydroxide solution have fallen into two classes: those which show differences in specific rotations amounting to less than 2.5° and those which show differences greater than 7.0°. These substances are listed in Table I together with the approximate concentrations employed, their observed rotations in molar sodium chloride solution, in normal sodium hydroxide solution and the difference, sp. rot. (NaCl) minus sp. rot. (NaOH). For the first class of substances some of the differences are within the experimental error of the observations, but others, for example that of methyl β-D-glucoside, appear to lie slightly outside the experimental error. Almost an order of magnitude greater are the differences attributed to the second class of substances, described as being alkali-sensitive. These five substances have spe-

(1) Some of the data reported herein were presented before the Division of Carbohydrate Chemistry at the 127th Meeting of the American Chemical Society, Cincinnati, Ohio, March–April, 1955.

(2) R. E. Reeves, THIS JOURNAL, **76**, 4595 (1954).

(3) W. W. Pigman, *J. Research Natl. Bur. Standards*, **33**, 129 (1944).

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cific rotations which are appreciably altered by the presence of alkali. Upon neutralization each of these specific rotations in alkali returned to the value characteristic of a directly prepared neutral solution. Observations on the disaccharides sucrose[4] and trehalose are included in the table for comparison with the simple glycosides. An interesting aspect of the rotation of sucrose in alkaline solution will be considered below.

In Fig. 1 is plotted the change in specific rotation *versus* the log sodium hydroxide concentration for

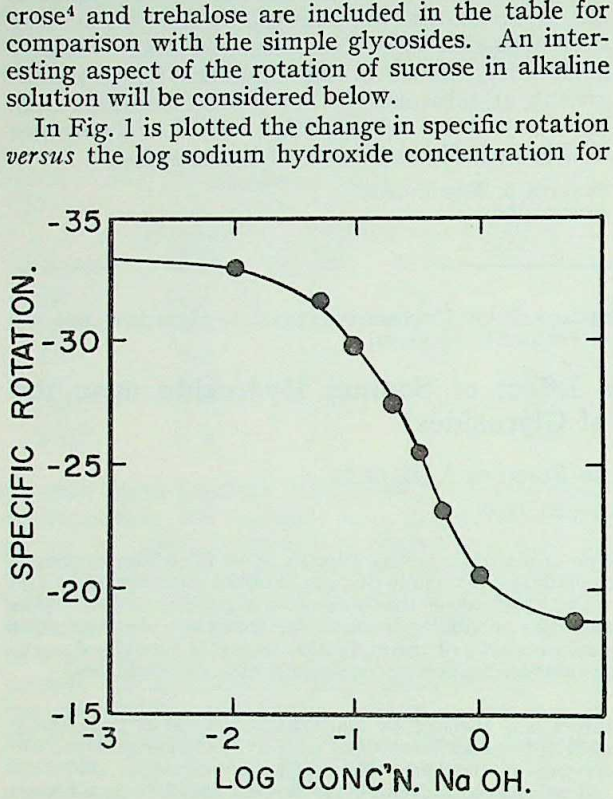

Fig. 1.—The effect of sodium hydroxide upon the optical rotation of methyl β-D-altropyranoside.

methyl β-D-altropyranoside, a member of the group possessing alkali-sensitive rotations. All observations save the one at the highest alkali concentration were made at constant ionic strength. The point of inflection of this curve lies in the vicinity of log *N* NaOH, −0.4. All other members of this group gave curves of similar shape and location on the *x*-axis.

In Fig. 2 is plotted the change in specific rotation *versus* the log sodium hydroxide concentration for sucrose. The solid circles represent observations made in the present work, at unit ionic strength up to the normal sodium hydroxide concentration. The triangles represent data reported by Thomsen in 1881.[5] Although Thomsen did not comment upon the fact, his data clearly showed the minimum occurring at 1.57 *N* alkali concentration. The highest alkali concentration employed by this worker was 2.14 *N*, and at this point the specific rotation had risen only 0.1° above the minimum; the pronounced rise at still higher alkali concentrations apparently was not observed. Thomsen did note an evolution of heat when sucrose was added to sodium hydroxide solution.

(4) It is noted that the specific rotation of 10% sucrose in molar sodium chloride is one degree lower than its rotation in water as required by the formula proposed by Brown, *Ind. Eng. Chem.*, **17**, 39 (1925).

(5) Th. Thomsen, *Ber.*, **14**, 1647 (1881).

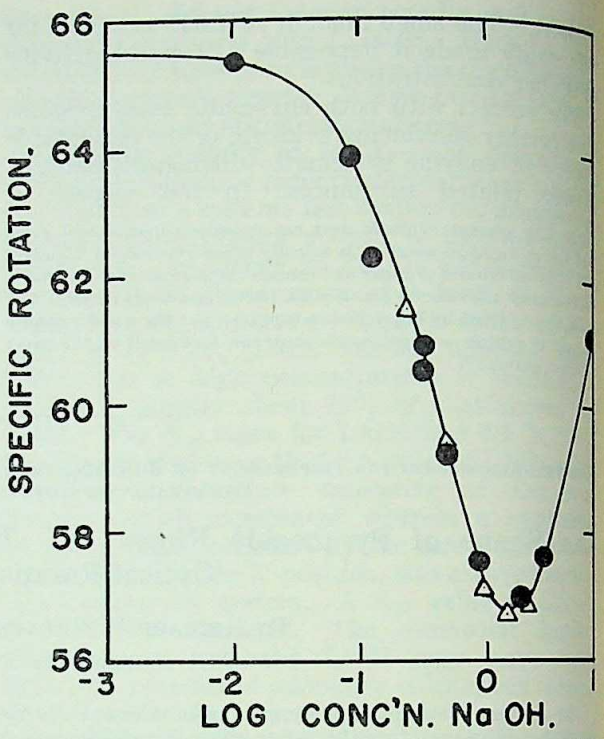

Fig. 2.—The effect of sodium hydroxide upon the optical rotation of sucrose; triangles represent observations made by Thomsen.[5]

Discussion

The position on the alkalinity scale and the general shape of the curves of alkali-sensitive substances suggest the possibility that the ionization of hydroxyl groups may be involved in these rotational shifts. Yet there are closely related glyco-

TABLE I

OPTICAL ROTATIONS OF GLYCOSIDES IN NEUTRAL AND ALKALINE SOLUTIONS

Substance	Approx. concn., %	Specific rotation, degrees *M* NaCl	*N* NaOH	Diff.
Alkali-stable pyranosides				
Methyl α-D-glucoside	2	157.8	157.8	0.0
Methyl β-D-glucoside	2	−32.8	−31.1	−1.7
Cyclohexyl α-D-glucoside	1.2	140.1	139.2	0.9
Phenyl α-D-glucoside	2.3	178.7	179.7	−1.0
Phenyl β-D-glucoside	3	−71.5	−71.0	−0.5
Methyl α-D-xyloside	11	155.9	154.3	1.6
Methyl β-D-xyloside	13	−63.7	−64.9	1.2
Methyl α-D-mannoside	2	76.1	76.6	−0.5
Methyl α-L-rhamnoside	2	−61.0	−60.5	−0.5
Methyl α-D-altroside	1	123	121	2
Methyl α-D-lyxoside	5	58.0	60.4	−2.4
Methyl α-D-guloside·H_2O	2	104.4	103.0	1.4
Alkali-sensitive pyranosides				
Methyl α-D-galactoside·H_2O	4.7	177.3	170.0	7.3
Methyl β-D-galactoside	2	3.0	− 6.6	9.6
Methyl β-D-mannoside	1.2	−69.4	−60.1	− 9.3
Methyl β-D-altroside	2.6	−33.2	−20.5	−12.7
Methyl β-L-arabinoside	2	243	233	10
Disaccharides				
Sucrose	10	65.4	57.6	7.8
Trehalose $2H_2O$	2	179.4	180.8	−1.4

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sides which are not alkali-sensitive. In searching for an explanation for the difference between the two classes of glycosides, it was considered possible that axially oriented hydroxyl groups might tend to produce a ring strain or a conformation shift at high alkali concentrations. Since charged RO^- groups would be more strongly solvated and have a greater effective volume than neutral ROH groups, it might be supposed that under ionizing conditions there would be a tendency for the ring to adopt a shape placing as many as possible of the ring hydroxyls in the equatorial positions where there is less steric hindrance than is afforded by the axial positions. We have chosen to accept the hypothesis that hydroxyl groups which are axially oriented in neutral solution may produce reversible rotational changes due to their tendency to move to equatorial positions at high alkalinity and to examine the implications of this hypothesis in the light of the present observations.

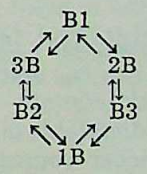
Except for the α-1,4-linked glucose polysaccharides, there is no reason to doubt that the C1 conformation is the favored shape of the D-glucopyranoside ring. In this conformation there are no axially oriented hydroxyl groups and, in agreement with the hypothesis, all the simple glucosides (and xylosides) yet examined have exhibited optical rotations which were similar in neutral and alkaline solution.

In the D-galactose (L-arabinose) series the favored conformation again appears to be C1,[6] but in this series there is an axial hydroxyl group at carbon atom 4. Both α- and β-galactosides and the arabinoside were alkali-sensitive. In agreement with the hypothesis this might be due to a strain imposed upon the C1 ring, or to displacement of an equilibrium in the direction of a form possessing fewer axial hydroxyl groups. In the latter event the effect produced by alkali might be to shift a C1 $\rightleftarrows$ B2 equilibrium to the right. In the B2 conformation the hydroxyl groups at carbon atoms 2, 3 and 4 are equatorial in the D-galactose series.

It is observed that the methyl α-pyranosides of D-mannose, D-altrose, D-lyxose and L-rhamnose fall into the alkali-stable class. Each of these configurations would possess one or more axial hydroxyl groups if it existed in a chair form. But for each of these α-anomers there is a boat-form conformation with *no* axial substituents: D-mannose and D-lyxose, B1; D-altrose, 2B; and L-rhamnose, 1B. These forms may be reconciled with the cuprammonium-complexing behavior of these glycosides as well as the previously suggested chair forms.[7]

To argue, as the present hypothesis appears to require, that boat-form rings represent the lowest energy state for some pyranosides brings into question a previous hypothesis that "Pyranose rings assume a chair form in preference to any boat form whenever both are structurally possible."[7] It may be the case that although chair forms are generally of lower energy than boat forms, the difference is more than offset when a boat form allows *all* ring substituents (other than hydrogen) to be equatorial. It should be remarked that in simple pyranosides geometrically regular boat forms are unlikely because of the high energy resulting from the eclipsed valence angles on some of the adjacent atoms. Therefore, the suggestion that methyl α-D-mannoside may prefer the B1 conformation should be construed to mean that it may take a shape approximating that of the pure B1 form but distorted into the region where the tendency of the large groups to move into the equatorial plane is balanced by the repulsion brought about by approaching the eclipsed valence position. There is already experimental evidence that some of these glucosides do not take a pure boat form, for to do so would place two adjacent hydroxyl groups in the true *cis* position where they should be almost instantly cleaved (titratable) with lead tetraacetate. It has been shown that this does not occur in the case of methyl α-D-mannoside, α-D-lyxoside or α-D-altroside.[7]

Boat-form rings are unlike chair forms in possessing a flexibility so that positions intermediate between Reeves' designated forms can occur without greatly increased ring strain. There is a sequence in which one boat form may be changed into another, as is shown in the following diagram. Unless certain of the forms are prohibited by steric interference of the substituents, boat forms may shift in either direction around the ring shown in the diagram.



Faced with increasing evidence that boat-form rings may have an important role in carbohydrate chemistry, it would be desirable to give further consideration to the problem of designating the various ring shapes. It now seems clear that Reeves' designations B1, 1B, etc., will not be sufficiently precise. However, until a better system is devised it is proposed to describe the boat forms as *e.g.* "approximating" a particular conformation; or as intermediate between B1 and 3B, or between such other forms as are adjacent to each other in the above diagram.

The β-mannose and β-altrose configurations differ from their anomers in having no conformation which places all ring substituents in the equatorial position. Without attempting, for the present, to assign most stable ring conformations to these substances, it would appear that neutral aqueous solutions might contain some finite proportion of axial hydroxyl groups and that this proportion might be reduced by ring shifts at high alkali concentrations.

The alkali-stability of the optical rotation of methyl α-D-guloside presents some unusual aspects. Any of the conformations compatible with the cuprammonium complexing behavior of this substance[7] require at least one axial hydroxyl group. As far as the hitherto recognized factors governing ring stability are concerned, the guloside could as well shift from C1 toward 1B under the influence of alkali as the galactosides might shift from C1 toward B2. However, inspection of scale

(6) R. E. Reeves, THIS JOURNAL, **71**, 1737 (1949).
(7) R. E. Reeves, *ibid.*, **72**, 1499 (1950).

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models of α-D-hexosides reveals extensive interference between the hydrogen atom of carbon 4 and the oxygen atom at carbon 1 in the 1B conformation, an interference not present in the proposed galactoside shift C1 ⇄ B2. It may be that the 1B conformation is prohibited for steric reasons in the α-D-hexose (and pentose) series, or its energy level is so much greater than that of the other forms that it cannot be overcome by the tendency of a charged axial hydroxyl group to move to the equatorial position. It is noted that methyl β-D-guloside might be expected to show an alkali-sensitive rotation due to the shift of a C1 ⇄ 1B equilibrium.

The hypothesis that hydroxyl groups which are axially oriented in neutral solution move to equatorial positions under conditions of high alkalinity requires further confirmation. Work to prove or disprove the concept is in progress. No attempt will be made at this time to interpret the alkali-sensitive behavior of the disaccharide sucrose, beyond observing that since the simple α-glucopyranosides (and trehalose) fail to show the same type of behavior, it would be logical to attribute the observed effect to changes in the fructofuranoside portion of the sucrose molecule.

Acknowledgment.—Some of the glycosides employed in this work were supplied by Drs. N. K. Richtmyer and H. S. Isbell.

NEW ORLEANS, LA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

4-Allylveratrole from *Anemopsis californica*

BY W. J. HORTON AND E. G. PAUL

RECEIVED NOVEMBER 5, 1956

The steam distillable oil from rhizomes of *Anemopsis californica* contains 4-allylveratrole which contributes the pungency to the odor of the oil. A second compound of unknown nature greatly masks the spice-like odor. A number of 4-alkylveratroles and their 5-sulfonamides were prepared in an effort to identify the sulfonamide (2-propyl-4,5-dimethoxybenzenesulfonamide) derived from the natural oil.

Anemopsis californica has a distinctive odor with a faint undertone of a spicy material. Both leaves and rootstock contain the odorant which resides in the steam distillable oil. Since the woody rhizome was the richer source, oil was obtained from this portion of the plant and submitted to fractional distillation using a small Vigreux column. A redistilled sample gave analytical data in excellent agreement with $C_{12}H_{16}O_2$. Catalytic hydrogenation indicated a single olefinic bond and oxidation produced veratric acid which was confirmed by the preparation of veratramide. The ultraviolet absorption also suggested the veratryl ring[1] with the olefinic bond in a non-conjugated position. Synthetic work was therefore designed so as to determine the nature of the butyl group in hydrogenated *Anemopsis* oil. A comparison of synthetic 4-butylveratroles (Table II) with the alkylveratrole derived from the oil was facilitated by the preparation of a crystalline sulfonamide from the hydrogenated oil. However, re-examination of the original analysis became necessary when none of the synthetic 4-butylveratroles nor isoamylveratrole gave a sulfonamide identical to the unknown sulfonamide (Table III). Furthermore the analytical values obtained from the unknown sulfonamide indicated a propyl group rather than a butyl group. Subsequent samples of the oil submitted to analysis pointed to contamination in the original oil by compounds of higher carbon content so as to make the excellent agreement with the formula $C_{12}H_{16}O_2$ fortuitous. The preparation of 4-propylveratrole (Table II) and its sulfonamide together with the ultraviolet spectra identify this part of the original oil as 4-allylveratrole.

The acyl-3,4-dimethoxyphenones were prepared by the excellent procedure of Gardner[2] and are collected in Table I. Clemmensen reduction gave the corresponding 4-alkylveratroles (Table II) whose sulfonamides are presented in Table III.

We are greatly indebted to Prof. Walter P. Cottom of our Department of Botany for discussions and to Mr. L. Woodbury at Dixie College, St. George, Utah, who so kindly provided the plant material.

Experimental[3]

The plant material collected in the vicinity of St. George, Utah, was divided into rhizomes and stems, the rhizomes were washed in water to remove adhering soil and thoroughly air-dried. They were then passed through a food chopper to produce material of the appearance of a brown sawdust. A 200-g. portion was steam distilled until 6 l. of distillate was obtained. The distillate was saturated with sodium chloride and extracted with ether. The residual oil on distillation of the dried ether extract weighed 17.4 g. (8.7%). This oil was divided into three fractions by distillation: (a) 6.22 g. of pale yellow, b.p. 137–141° (23 mm.); (b) 5.38 g. of yellow green, b.p. 141–146° (23 mm.); and (c) 2.44 g. of green, b.p. 147–155° (23 mm.). All fractions gave a brown color with tetranitromethane and a negative test with ferric chloride except (c) which was dubious. Fraction (a) gave a red complex with picric acid but a solid picrate could not be obtained.

In a similar manner from 500 g. of rhizomes the following fractions were collected by distillation at 23 mm. through a 25-cm. Vigreux column: 0.40 g., 90–106°; 16.16 g., 135–141.5°; "Fraction C" 8.09 g., 141–143°; 11.67 g., 144–151° (total yield 7.3%).

By distillation of fraction b above, a sample was obtained for analysis.

(1) *Cf.* R. Adams, C. K. Cain and H. Wolff, THIS JOURNAL, **62**, 732 (1940), who give the absorption curves for 4-methyl- and 4-*n*-amylveratrole.

(2) P. D. Gardner, *ibid.*, **76**, 4550 (1954).

(3) Melting points on analytical samples are corrected. Microanalyses are by Dr. K. W. Zimmerman, University of Melbourne.

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TABLE I

3,4-DIMETHOXYPHENYL ALKYL KETONES

Alkyl	Yield,[a] %	M.p. or b.p., °C.	Mm.		Carbon, % Calcd.	Carbon, % Analyses, Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ethyl	97.9	54.5–60.5[b]						
n-Propyl	91	52–57[c]		$C_{12}H_{16}O_3$	69.20	69.64	7.75	7.74
i-Propyl	87.3	117–126	0.1–0.7[d]					
i-Butyl	91.6[e]	143–141.5	0.22–0.16[f]	$C_{13}H_{18}O_3$	70.24	70.49	8.16	8.20

[a] Prepared (ref. 2) using 0.403 mole of veratrole, polyphosphoric acid and the appropriate acid at 60° for 2.5 hr. [b] Softens at 47.5°; reported m.p. 58–59° by R. C. Fuson, R. Gaertner and D. H. Chadwick, *J. Org. Chem.*, **13**, 489 (1948). [c] The analytical sample from aqueous ethanol and from ligroin melted at 54.4–55.2°. The oxime from aqueous ethanol and from petroleum ether (30–80°) followed by sublimation at 0.1 mm. melted at 73.3–74.5°. *Anal.* Calcd. for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68. Found: C, 64.58; H, 7.52. [d] Reported as a colorless liquid b.p. 116–117° (0.2 mm). The semicarbazone melted at 146.5–148°; reported m.p. 149–150° by G. Norcross and H. T. Openshaw, *J. Chem. Soc.*, 1174 (1949). [e] Pale yellow oil; from 0.215 mole of veratrole. [f] The analytical sample boiled at 134.5° (0.37 mm.). The oxime was an oil. The semicarbazone formed colorless short thick prisms, m.p. 183.4–185.7°. *Anal.* Calcd. for $C_{14}H_{21}O_3N_3$: C, 60.19; H, 7.58. Found: C, 60.43; H, 7.43.

TABLE II

4-ALKYLVERATROLES

Alkyl	Yield[a] % (mole of ketone)	B.p. °C.	Mm.	$n^{25}D$	d^{25}_4	λ_{max}^{EtOH}	log ε		Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-Propyl	84.4 (0.2)	137.5–138[b]	21	1.5150	1.006	280	3.52	$C_{11}H_{16}O_2$	73.30	73.58	8.95	9.12
						229	3.94					
n-Butyl	73 (0.0481)	149–152[c]	23	1.5121	0.9918	280	3.58	$C_{12}H_{18}O_2$	74.19	74.25	9.34	9.32
						228	4.00					
i-Butyl	81.3 (0.0481)	134–136[d]	16	1.50935	0.9848	280	3.51			74.46		9.33
						228	3.96					
i-Amyl	68.3 (0.10)	143–141.5[e]	0.22–0.16	1.50735	0.9795	280	3.54	$C_{13}H_{20}O_2$	74.96	75.09	9.68	9.63
						228	3.97					

[a] By Clemmensen reduction from the ketone (Table I). [b] The analytical sample boiled at 147.5° (34 mm.); reported b.p. 244–245° (763 mm.) by Wl. Ipatjew, *Ber.*, **46**, 3589 (1913). [c] The analytical sample boiled at 156–156.5° (28 mm.); reported b.p. 126–129° (7 mm.) by A. Ya. Berlin and S. M. Sherlin, *Zhur. Obshcheĭ Khim.*, **18**, 1386 (1948) (*C. A.*, **43**, 2185f (1949)). [d] The analytical sample boiled at 150–151° (31 mm.). [e] The analytical sample boiled at 168–169° (34 mm.).

TABLE III

2-ALKYL-4,5-DIMETHOXYBENZENESULFONAMIDES[a]

Alkyl	M.p., °C. (cor.)		Analyses, % Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
n-Propyl[b]	169.6–170.8[c]	$C_{11}H_{17}O_4NS$	50.94	6.61	5.40	12.36	51.17	6.73	5.10	12.25
n-Propyl	166–170[d]									
n-Butyl	135–135.4[e]	$C_{12}H_{19}O_4NS$	52.72	7.01	5.13	11.73	52.79	6.89	4.68	11.62
i-Butyl	152.7–153.7						52.78	7.00	4.83	11.24
s-Butyl	120.2–122[f]						52.57	6.93	4.71	11.53
i-Amyl	164.6–166.8[g]	$C_{13}H_{21}O_4NS$	54.33	7.37	4.87	11.16	54.27	7.28	4.41	11.08

[a] Prepared according to R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., p. 246. [b] From the hydrogenation of *Anemopsis* oil. [c] Colorless groups of thin rods. [d] Uncorrected; mixed with the compound above, m.p. 166.5–170.5° (uncor.). [e] Softens sharply at 116°; colorless flat diamonds. [f] Colorless short thick rods from aqueous ethanol. [g] Colorless short rods.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39; O, 16.64. Found: C, 74.89; H, 8.34; O, 17.0.

The fraction b.p. 144–151° (23 mm.) was redistilled collecting a portion, b.p. 129–130° (14 mm.). From the latter a cut, b.p. 146.5° (29 mm.), was analyzed; $n^{25}D$ 1.52925, d^{25}_4 1.028; $\lambda_{max}^{ethanol}$ 230 mμ (log ε 3.83), 280 mμ (log ε 3.39).

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95. Found: C, 74.66; H, 8.22; O, 17.4.

Catalytic Hydrogenation of "Fraction C."—A redistilled portion (7.55 g.) of the 8.09-g. middle cut above with 60 ml. of absolute ethanol and 300 mg. of platinum oxide was shaken with hydrogen at slightly above atmospheric pressure. After absorption of one mole of gas, the reaction stopped. The catalyst was removed by filtration, and the alcohol was distilled *in vacuo*. Distillation of the residue gave a middle cut, b.p. 164–164.5° (66 mm.), $n^{25}D$ 1.5131.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34; O, 16.47. Found: C, 74.92; H, 9.31; O, 16.0.

The residual material boiled at 144–145° (29 mm.) and was later redistilled for analysis, b.p. 143–144° (29.5 mm.), $n^{25}D$ 1.5125, d^{25}_4 0.9969, $\lambda_{max}^{ethanol}$ 278 mμ (log ε 3.62), 228 mμ (log ε 4.05).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; O, 17.75. Found: C, 74.64; H, 9.07; O, 16.6.

Oxidation with Permanganate.—The reaction of 3.84 g. of the original oil with powdered potassium permanganate in aqueous pyridine[4] gave 1.5 g. of acid, m.p. 172–178°. The neutral equivalent was 177; for veratric acid, 182. After sublimation (0.17 mm.) and crystallization from benzene, it melted at 171.5–179.5°. On mixing with veratric acid from authentic veratraldehyde (m.p. 176.5–180°), the melting point was 176–181.5°.

The amide prepared from the acid melted at 162.5–167° and mixed with authentic veratramide (m.p. 162–165°) melted at 161–164°.

2-(3,4-Dimethoxyphenyl)-2-butene.—Methylmagnesium iodide from 5.62 g. (0.231 mole) of magnesium in 150 ml. of ether was allowed to react with 15 g. (0.0774 mole) of 3,4-dimethoxypropiophenone dissolved in 70 ml. of

(4) J. U. Nef, this JOURNAL, **32**, 374 (1910).

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benzene. After refluxing for 1 hr. the product was isolated by the usual procedure. Material with a cinnamon-like odor, b.p. 147–167° (20–18 mm.), was divided by redistillation into a colorless liquid with a flower-like odor (2.3 g.), b.p. 120–155° (23–22 mm.), and a greenish-yellow liquid of similar odor, b.p. 154.5–159° (20–19.5 mm.). A sample of the latter on redistillation was colorless, b.p. 163° (27 mm.), $n^{25}D$ 1.5507, d^{25}_4 1.040, $\lambda_{max}^{ethanol}$ 254 mμ (log ε 4.10) and end absorption.[6]

(5) The shift to shorter wave length when an olefinic bond is conjugated at the 4-position of the veratryl ring system confirms the report on 4-propenylveratole; A. Hillmer and P. Schorning, *Z. physik. Chem.*, **168A**, 81 (1934).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.64; H, 8.50.

2-*sec*-Butyl-4,5-dimethoxybenzenesulfonamide.—Catalytic hydrogenation of 1.0 g. of the above olefin with 500 mg. of 5% palladium–carbon in 50 ml. of ethanol consumed 148 ml. of gas; calculated volume 138 ml. After filtration of the catalyst and distillation of the solvent, the residual oil was converted to the sulfonamide (0.63 g.) as indicated in Table III.

SALT LAKE CITY 12, UTAH

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

2-Pyrones. XXVI. Alkylidene Methylglutaconic Acids and 3,6-Dialkyl-5-carboxy-5,6-dihydro-2-pyrones from Methyl β-Methylglutaconate and Ethyl Isodehydroacetate and their Isomerization and Decarboxylation

BY RICHARD H. WILEY AND H. G. ELLERT

RECEIVED NOVEMBER 1, 1956

The condensation of aliphatic aldehydes with methyl β-methylglutaconate gives alkylidene glutaconic acids (III) and carboxy-δ-lactones (IV). Comparable yields are obtained using ethyl isodehydroacetate in place of the glutaconate. Short-chain and branched-chain aldehydes give diacids (III); longer chain and unbranched aldehydes give carboxylactones (IV). Decarboxylation of these products gives the dienonoic acids VI and δ-lactones V. The lactones can be hydrolyzed to the corresponding acids and the preferred route to the isoprenoid acid, 3,7-dimethyl-2,4-octadienoic acid, is *via* decarboxylation of the dipotassium salt to the lactone which is then hydrolyzed. The carboxy isoprenoid acid, γ-isoamylidene-β-methylglutaconic acid, has been obtained in three forms, m.p. 149–150, 163° and 181–184°. The isomer m.p. 149–150° has been assigned the 4-*cis*-2-*trans* structure; the isomer m.p. 181–184° has been assigned the 2-*trans*-4-*trans* structure on the basis of comparisons of their infrared spectra with those of *cis* and *trans* β-methylglutaconic acid. The δ-lactone structure has been established by conversion to the tetrahydro-2-pyrone structure with properties similar to those of other known tetrahydro-2-pyrones.

One of the few known methods for adding an isoprenoid unit to an organic structure involves the base-catalyzed condensation of dimethyl β-methylglutaconate (II) with an aldehyde[1–4] to give γ-arylidene or alkylidene-β-methylglutaconic acids (III). Although previously utilized principally for the synthesis of vitamin A, this method also makes possible the synthesis of acyclic isoprenoid acids of 10 or 15 carbons, which are of current interest as possible intermediates in the biosynthesis of cholesterol[5–8] with varying substituents, notably a 4-carboxyl group. Since previous studies of the reaction have not included comprehensive studies of the scope of the reaction using aliphatic aldehydes, we have undertaken a study of such reactions which we wish to record here along with our observations on the previously unreported accompanying cyclization to lactones (IV), the decarboxylation, and the geometrical isomerism of the γ-alkylidene-β-methylglutaconic acids (III). Particular attention has been directed to 3,7-dimethyl-2,4-octadienoic acid—an isomer of geranic acid and its 4-carboxy derivative.

The condensation reaction previously has been conducted using the aldehyde and dimethyl β-methylglutaconate (II) in methanolic potassium hydroxide. With aliphatic aldehydes the reaction is exothermic and the crystalline potassium salt of the product begins to precipitate shortly after mixing the reactants. The products from aliphatic aldehydes have been isolated in 51–91% yields (Table I). Since the β-methylglutaconate itself is formed readily from ethyl isodehydroacetate (I) by the action of methanolic potassium hydroxide, the utilization of the latter in place of the β-methylglutaconate to give the products directly in one step has been examined and found to be satisfactory. The products obtained by the two processes are comparable in all respects observed. This reaction is also exothermic and gives comparable yields with hexaldehyde (55 as compared to 58%), heptaldehyde (48 as compared to 51%), and pelargonaldehyde (61 as compared to 76%). With isobutyraldehyde (59 as compared to 91%) and isovaleraldehyde (43 as compared to 84%), the yield is noticeably poorer. Allowance for a 75% yield from isodehydroacetate to β-methylglutaconate indicates that the one-step process gives comparable yields with considerable saving of effort by avoiding isolation of the intermediate ester. The combined one-step process has been used with several other aliphatic and aromatic aldehydes listed in Table II. β-Ethoxypropionaldehyde, tiglic aldehyde and acetaldehyde failed to give characterizable products.

A unique feature of this reaction, which has not been recognized previously, is that not only diacids IV but also the isomeric carboxylactones IV are

(1) F. Feist and O. Beyer, *Ann.*, **345**, 117 (1906).
(2) C. D. Hurd and J. L. Abernethy, THIS JOURNAL, **63**, 976 (1941).
(3) V. Petrow and O. Stephenson, *J. Chem. Soc.*, 1310 (1950).
(4) J. D. Cawley, THIS JOURNAL, **77**, 4125 (1955).
(5) H. Rudney, *ibid.*, **76**, 2595 (1954); **77**, 1698 (1955).
(6) J. L. Rabinowitz and S. Gurin, *ibid.*, **77**, 1295 (1955); **76**, 3037, 5168 (1954).
(7) K. Bloch, L. C. Clark and I. Harary, *J. Biol. Chem.*, **211**, 687 (1954).
(8) S. Gurin, *et al.*, *Federation Proc.*, **14**, 752 ff. (1955).

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TABLE I

γ-ALKYLIDENE-β-METHYLGLUTACONIC ACIDS AND CARBOXYLACTONES FROM METHYL β-METHYLGLUTACONATE

R of formula III or IV	Yield, %	M.p.,[a] °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Neut. equiv. Calcd.	Neut. equiv. Found
Isopropyl	91[b]	157–158 A	60.59	60.64	7.12	7.18	102.1	99.0
Isobutyl	84[b]	149 A	62.25	62.23	7.60	7.78	106.2	105.3
n-Amyl	58[c]	127–129 P	63.70	63.52	8.02	7.99	226.3	229.0
n-Hexyl	52[c]	124–126 P	64.98	64.88	8.39	8.38	240.3	243.6
n-Octyl	76[c]	105–106 P	67.13	67.08	9.02	9.12	268.3	268.8

[a] Recrystallized from A, methanol–water; E, ether–petroleum ether; P, ethyl acetate–petroleum ether. [b] Diacid III. [c] Lactone IV.

TABLE II

γ-ALKYLIDENE-β-METHYLGLUTACONIC ACIDS AND CARBOXYLACTONES FROM ETHYL ISODEHYDROACETATE

R of formula III or IV	Yield, %	M.p.,[a] °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Neut. equiv. Calcd.	Neut. equiv. Found
n-Propyl	37[b]	127–128 E	60.59	60.76	7.12	7.36	99.1	105.8
Isopropyl	59[b]	157–158 A	60.59	60.64	7.12	7.26	99.1	100.8
Isobutyl	43[b]	149–150 A	62.25	62.21	7.60	7.82	106.2	105.3
1′-Ethylpropyl	86[b]	216–220 B	63.70	63.66	8.02	8.04	113.1	114.2
1′-Ethylpentyl	60[b]	148 A	66.11	66.23	8.72	8.63	127.2	128.6
Phenyl[d]	48[b]	190–191 A					116.1	115.9
3,4-Dimethoxyphenyl[d]	50[b]	184–185 C						
p-Chlorophenyl[d]	66[b]	193–195 A						
n-Butyl	21[c]	123–124 P	62.26	62.20	7.60	7.62	212.2	214.9
n-Amyl	55[c]	127–129 E	63.70	63.52	8.02	7.99	226.3	229.0
n-Hexyl	48[c]	124–126 A	64.98	64.88	8.39	8.38	240.3	243.6
n-Heptyl	25[c]	115–117 A	66.11	66.42	8.72	8.75	254.3	256.8
n-Octyl	61[c]	105–106 P	67.13	67.08	9.02	9.12	268.3	268.8

[a] Recrystallized from A, methanol–water; B, methanol; C, ethyl acetate; E, petroleum ether–ether; P, ethyl acetate–petroleum ether. [b] Diacid III. [c] Carboxylactone IV. [d] See ref. 4. [e] In cm.$^{-1}$.

formed. It appears that the short chain and branched-chain aliphatic aldehydes and aromatic aldehydes give exclusively the diacid products III and that the longer chain, unbranched aldehydes give principally the carboxylactones IV as products. The contrast in behavior in this respect between valeraldehyde and isovaleraldehyde and between *n*-octaldehyde and 2-ethylhexaldehyde is striking. Assuming that the 2-*cis* form is needed for cyclization and that the 2-*trans* form is customarily obtained[4] in this reaction, isomerization and subsequent lactonization must take place more readily under the conditions used in the reaction with the unbranched types. It is difficult to assign a reason for this in the absence of additional data about the conditions required for geometrical isomerization of these structures. With some of these materials it is possible to lactonize the dibasic acids, although in low yield. Thus, γ-isoamylidene-β-methylglutaconic acid (III, R = isobutyl) is lactonized in 16% yield by treatment with acid. With others it is possible to obtain mixtures of both isomers. Thus, the potassium salt obtained from the hexaldehyde reaction (III, R = *n*-amyl) gives a mixture of the lactone IV and the dibasic acid III when exactly neutralized at 0°. The two types of products formed in this reaction are readily distinguished by their neutral equivalents. The infrared absorption characteristics of the dibasic acids show typical carboxyl carbonyl absorption bands at 1690–1680, at 1455–1445, 1430–1425 and at 950–935 cm.$^{-1}$. The lactones show a strong carbonyl absorption at 1730–1725 cm.$^{-1}$ typical of δ-lactones. The δ-lactone structure is further confirmed by the conversion described in following paragraphs of one derivative to a similar tetrahydro-2-pyrone obtained by another synthetic route. These considerations eliminate the alternative γ-lactone structure.

During the process of decarboxylation the dibasic acids and the carboxylactones give either acids such as VI or lactones (5,6-dihydro-2-pyrones) such as V. The dibasic acids (R = isopropyl, isobutyl) decarboxylate in 10–12% yields using 2,4-lutidine and cupric acetate as the catalyst. These products are assumed to have lost the carboxyl groups on the 4-carbon atom, by analogy with previously reported data,[9] to give dienoic acids. These acids are unstable toward oxygen and readily form peroxides. Their purification is difficult and this accounts in part for the low yields in the decarboxylation. Although reactions of these acids with bromine and with maleic anhydride have not given readily characterizable derivatives, the benzylthiuronium salts readily are formed and crystallize nicely.

When the crude dipotassium salts are heated in glacial acetic acid, decarboxylation occurs and the product is the lactone (V, R = isobutyl, *n*-amyl or 2′,6′-dimethyl-5′-heptenyl). Using lutidine and cupric acetate for the decarboxylation, a mixture of lactone V and acid VI results from other dibasic acids (R = propyl, 1′-ethylamyl) and from the carboxylactone (IV, R = butyl). Two of the lactones obtained by decarboxylation (V, R = isobutyl, propyl) have been converted to the open-chain acids by hydrolysis with alcoholic potassium hydroxide. This hydrolysis gave 38% of 3,7-dimethyl-2,4-octadienoic acid (VI, R = isobutyl) and this route *via* dibasic acid salt, decarboxylation to the lactone (71%) and hydrolysis (38%) is pre-

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ferred to that *via* the decarboxylation of the dibasic acid (12%) since the yield is better and the isolation of the dicarboxylic acid is avoided.

The lactone or 5,6-dihydro-2-pyrone structure assigned to the compounds IV and V has been confirmed by catalytic reduction of 6-butyl-4-methyl-5,6-dihydro-2-pyrone to 6-butyl-4-methyltetrahydro-2-pyrone with infrared absorption characteristics identical in all significant respects with that of 4,6-dimethyltetrahydro-2-pyrone prepared previously.[10] Carbon–hydrogen absorption at 2960 cm.$^{-1}$, a carbonyl doublet at 1735–1710 cm.$^{-1}$ and the ester carbon–oxygen absorption at 1240 cm.$^{-1}$ are the most prominent bands and are at the same location in the spectra of both of these compounds.

The geometric isomerism of acids such as γ-isoamylidene-β-methylglutaconic acid is of considerable significance. This acid is a carboxy isoprenoid acid which by virtue of its structural relation to β-methylglutaconic acid is of interest as a possible intermediate in the biosynthesis of cholesterol. The fact that only *trans*-, not *cis*-, β-methylglutaconic acid is an effective intermediate in this process and that squalene, another apparent intermediate, is of the *trans* configuration, suggest that geometric isomers of the acid should be available for biosynthetic examination.

Attempts to isomerize the acids, m.p. 149–150°, with iodine and ultraviolet light gave an isomer, m.p. 163°, which was also obtained by slow recrystallization of the acid, m.p. 149–150°, from ether–ligroin. The facts that no depression of the melting point of the acid, m.p. 149–150°, is observed with mixtures of the two and that the infrared spectra of the two materials are apparently identical indicates that these two forms may be isomorphic. This does not eliminate the possibility that they are geometric isomers or mixtures thereof.

An isomer of γ-isoamylidene-β-methylglutaconic acid has been obtained by altering the conditions used in the preparation of this acid from methyl β-methylglutaconate. If double the amount of potassium hydroxide is used in a procedure otherwise similar, a product is obtained which melts at 181–184°. This gives a mixed m.p. of 144–151° with the isomer, m.p. 150°. The infrared spectra of the two (Fig. 1) are substantially identical except in the 1285 cm.$^{-1}$ (C–O stretching or O–H deformation) and 1175 cm.$^{-1}$ (band progression) regions where certain minor differences can be correlated with differences in the infrared spectra for *cis*- and *trans*-β-methylglutaconic acid (Fig. 2). There is no substantial difference in the C–H out-of-plane deformation region where disubstituted *cis–trans*-ethylenes show marked differences,[11] but it has previously been noted[12] that trisubstituted ethylenes do not show such differences. *cis*-β-Methylglutaconic acid shows maxima at 1277 and 1148 cm.$^{-1}$ shifted to 1264 and 1167 cm.$^{-1}$, with a shoulder at 1152 cm.$^{-1}$ in the *trans*-acid. The isomer, m.p. 150°, shows maxima at 1289 cm.$^{-1}$ shifted to 1284 cm.$^{-1}$ with shoulders at 1295 and 1310 cm.$^{-1}$ and a new band at 1263 cm.$^{-1}$

(10) R. H. Wiley and A. J. Hart, This Journal, **77**, 2340 (1955).
(11) R. N. Jones, *ibid.*, **72**, 5322 (1950).
(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 36.

Table III

Infrared Absorption Maxima[a]

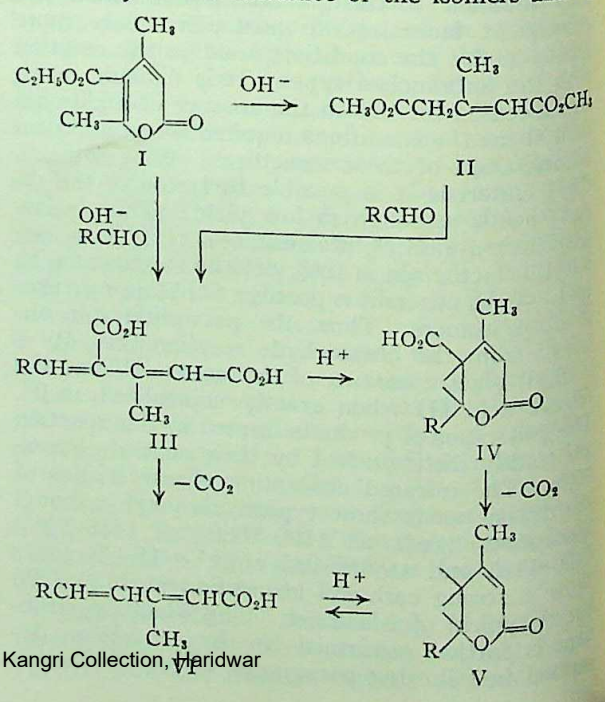
R of formula III	C=O stretching[b]	C=C stretching[c]		Out-of-plane deformation: OH	CH
γ-Alkylidene-β-methylglutaconic acids					
n-Propyl	1689	1645	1623	935	869
Isopropyl	1689	1650	1623	958	882
Isobutyl	1686	1658	1626	930	877
n-Amyl	1684	1647	1618	936	864
1′-Ethylpentyl	1689	1653	1623	935	866
Phenyl	1684	1639	1608	935	867
3,4-Dimethoxyphenyl	1678	1653	1608	942	871

R of formula IV			
γ-Carboxy-δ-lactones			
Isobutyl	1718/1664	1634	
n-Amyl	1721/1664	1634	
n-Hexyl	1721/1664	1634	
n-Heptyl	1718/1667	1634	

R of formula V			C—O stretching
δ-Lactones			
n-Propyl[d]	1724	1639	1242
Isobutyl[d]	1724	1639	1242
n-Amyl[d]	1727	1642	1252
2,6-Dimethyl-5-heptenyl[d]	1727	1645	1247

[a] In cm.$^{-1}$ as potassium bromide pellets except as noted. [b] All bands of strong intensity. [c] All bands of medium intensity. [d] In carbon tetrachloride.

in the isomer, m.p. 181–184°. The band at 1167 cm.$^{-1}$ in the 150° isomer appears at 1174 cm.$^{-1}$ with a shoulder at 1157 cm.$^{-1}$ in the 181–184° isomer. These differences, although minor in themselves, constitute a total absorption picture in this region which serves to distinguish the isomers rather clearly and, furthermore, resembles the differences in the spectra of *cis*- and *trans*-β-methylglutaconic acids. This would appear to establish the reality of the existence of the isomers and to



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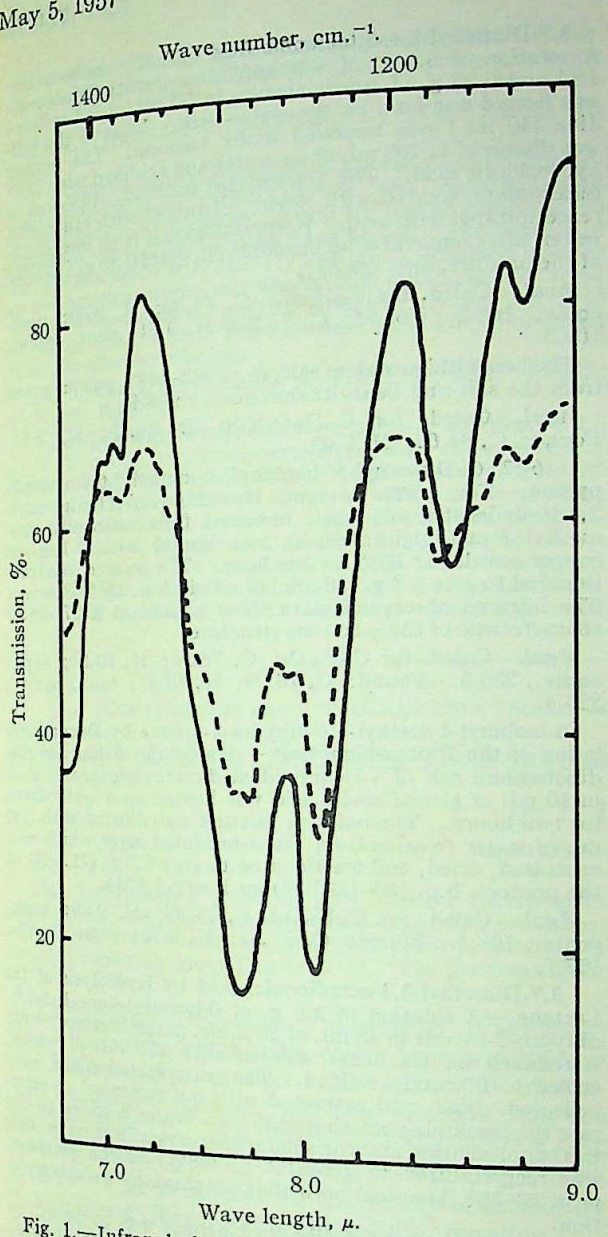

Fig. 1.—Infrared absorption of γ-isoamylidene-β-methylglutaconic acids: m.p. 149–150° (——); m.p. 181–184° (- - - -).

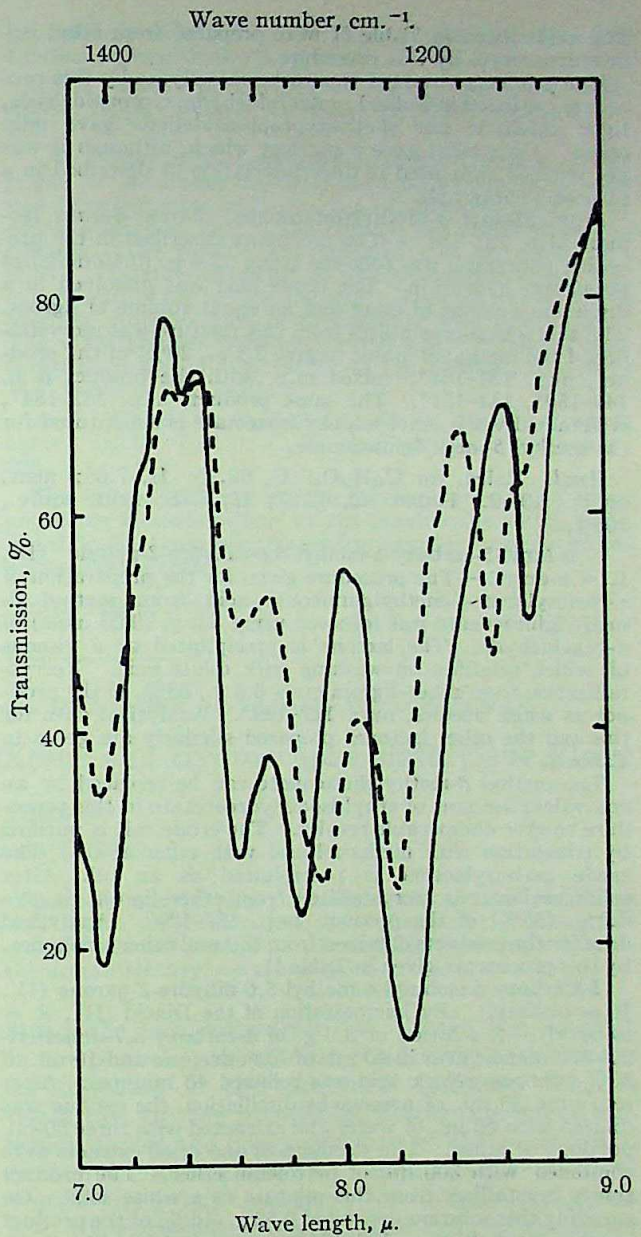

Fig. 2.—Infrared absorption of *cis*- (——) and *trans*- (- - - -) β-methylglutaconic acids.

support a tentative assignment of the *trans–trans* structure to the isomer, m.p. 181–184°, on the basis that the *cis–cis* structure would have undergone lactonization. The 4-*cis*-2-*trans* structure may be tentatively assigned to the isomer, m.p. 150°, on the basis of reasons previously analyzed.[4,9]

Acknowledgment.—The authors wish to acknowledge with appreciation partial support of this research by a grant (NSF-G1918) from the National Science Foundation.

Experimental[13]

The ethyl isodehydroacetate,[14] b.p. 139–142° (5 mm.), and the methyl β-methylglutaconate,[15] b.p. 142° (30 mm.), used in these studies were prepared by the methods previously given. The authors are indebted to the Tennessee Eastman Co. for additional supplies of ethyl isodehydroacetate. The aldehydes were commercial samples and were distilled prior to use. Details of typical reactions will be given. Data on other reactions and characterization of the products are presented in the Tables.

γ-Isoamylidene-β-methylglutaconic Acid (III, R = isobutyl). **From Methyl β-Methylglutaconate. 4-*cis*-2-*trans* Isomer, M.p. 149–150°.**—To a solution of 4.3 g. (0.05 mole) of freshly distilled isovaleraldehyde and 8.6 g. (0.05 mole) of methyl β-methylglutaconate in 10 ml. of methanol was added a filtered solution of 11.2 g. (0.2 mole) of potassium hydroxide in 30 ml of methanol. An immediate exothermic reaction was followed by precipitation of the dipotassium salt of the acid. After six hours the mixture was cooled to 0° and filtered. The salt was washed with cold methanol, dried, and dissolved in water. Acidification with concd. hydrochloric acid precipitated the crude product. Recrystallization from methanol–water gave 8.9 g., 84.6%, of the product, m.p. 149–150°. Analytical data are given in Table I. Slow recrystallization from ether–ligroin gives the acid in a form which has m.p. 163°.

The methyl β-methylglutaconate can be replaced with an equivalent amount of ethyl isodehydroacetate. The crude salt is triturated at 0° first with methanol then with ether before conversion to the acid. Recrystallization of the acid gives 6 g. (43.3%) of the product, m.p. 149–150°.

(13) Analysis by Micro Tech Laboratories, Skokie, Ill., m.p.'s are uncorrected.
(14) R. H. Wiley and N. R. Smith, This Journal, **74**, 3893 (1952).
(15) F. R. Goss, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, **123**, 327 (1923).

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The acids listed in Table II were prepared from ethyl isodehydroacetate by this procedure.

The products obtained from other aldehydes by this procedure are listed in Table I. Acetaldehyde, crotonaldehyde, tiglic aldehyde and β-ethoxypropionaldehyde gave only resins. Citronellal gave a product which, although it was not purified, was used in decarboxylation as described in a following paragraph.

From Methyl β-Methylglutaconate. 2-*trans*-4-*trans* Isomer, M.p. 181–184°.—The procedure described in the preceding paragraph was followed using 22.4 g. (0.40 mole) of potassium hydroxide. The crude acid was dissolved in a minimum amount of ether and an equal volume of ligroin. The acid which crystallizes from this mixture was recrystallized from methanol–water to give 2.1 g., 20%, of the product, m.p. 181–184°; mixed m.p. with the product m.p. 149–150°, 144–151°. The same product, m.p. 181–184°, is obtained when ethyl isodehydroacetate is substituted for the methyl β-methylglutaconate.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60; neut. equiv., 106.2. Found: C, 62.27; H, 7.75; neut. equiv., 106.1.

6-Amyl-5-carboxy-4-methyl-5,6-dihydro-2-pyrone (IV, R = *n*-amyl).—The procedure given for the preparation of γ-isoamylidene-β-methylglutaconic acid from methyl β-methylglutaconate was followed using 5.0 g. (0.05 mole) of *n*-hexaldehyde. The lactone is precipitated as a viscous oil which solidifies on washing with dilute acid. Recrystallization from ether–ligroin gives 6.5 g., 58%, of the product as white needles, m.p. 127–129°. Analytical data for this and the other lactones prepared similarly are given in Table I.

The methyl β-methylglutaconate can be replaced by an equivalent amount of ethyl isodehydroacetate in this procedure to give comparable results. The crude salt is purified by trituration with methanol and with ether at 0°. The crude carboxylactone is precipitated as an oil. After solidification it is recrystallized from ether–ligroin to give 6.2 g. (55%) of the product, m.p. 127–129°. Analytical data for the products obtained from this and other aldehydes, by this process are given in Table II.

5-Carboxy-6-isobutyl-4-methyl-5,6-dihydro-2-pyrone (IV, R = isobutyl). **By Lactonization of the Diacid** (III, R = isobutyl).—A solution of 2.0 g. of 4-carboxy-3,7-dimethyl-2,4-octadienoic acid in 40 ml. of C.P. acetone and 10 ml. of 50% aqueous sulfuric acid was refluxed 45 minutes. After removing 30 ml. of acetone by distillation, the residue was diluted with 50 ml. of water and extracted with three 50-ml. portions of ether. The decolorized and dried extracts were combined with 300 ml. of petroleum ether. The product slowly crystallizes from this mixture as a white solid. On standing this solution deposited 0.32 g. (16%) of the product as white crystals, m.p. 133–134°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60; neut. equiv., 212.2. Found: C, 62.75; H, 7.93; neut. equiv., 212.5.

γ-Hexylidene-β-methylglutaconic Acid (III, R = *n*-amyl).—This acid was obtained by careful acidification of the crude salt obtained in the reaction of *n*-hexaldehyde with ethyl isodehydroacetate as described above. The neutralization of the salt is carried out by the dropwise addition of the calculated amount of 0.1 *N* hydrochloric acid. The precipitated product is a mixture of the carboxylactone and dicarboxylic acid. Fractional recrystallization from ether–ligroin gives 27% of the dibasic acid, m.p. 110–112°, as the less soluble fraction.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02; neut. equiv., 113.1. Found: C, 63.74; H, 8.07; neut. equiv., 115.6.

3,6-Dimethyl-2,4-heptadienoic Acid (VI, R = isopropyl).—A solution of 5.0 g. of γ-isobutylidene-β-methylglutaconic acid and 0.125 g. of cupric acetate in 25 g. of 2,4-lutidine was heated in a water-bath for one hour. The lutidine was removed under vacuum. Dilution of the residue with 25 ml. of water followed by acidification precipitated the crude acid in 68% yield. Recrystallization gave 0.40 g. (10.4%) of the product, m.p. 82–86°.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15; neut. equiv., 154.2. Found: C, 70.07; H, 9.19; neut. equiv., 157.3.

3,7-Dimethyl-2,4-octadienoic Acid (VI, R = isobutyl).—A solution of 8.0 g. of γ-isoamylidene-β-methylglutaconic acid and 0.25 g. of cupric acetate in 50 ml. of 2,4-lutidine was heated one hour on the water-bath. Most of the lutidine (40 ml.) was removed under vacuum. The residue was dissolved in 100 ml. of ice-water and acidified with 12 *N* hydrochloric acid. The precipitated solid was dissolved in bicarbonate, treated with Norite, extracted with ether, and reprecipitated with acid. Recrystallization from methanol-water, after removal of an insoluble oil, gives 0.80 g. (12.6%) of the product, m.p. 50–53°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; neut. equiv., 168.2. Found: C, 71.26; H, 9.71; neut. equiv., 169.2.

The benzylthiouronium salt, m.p. 143–144°, was prepared from the salt and benzylthiouronium chloride.

Anal. Calcd. for $C_{18}H_{26}O_2N_2S$: C, 64.65; H, 7.81. Found: C, 64.62; H, 7.92.

6-(2′,6′-Dimethyl-5′-heptenyl)-4-methyl-5,6-dihydro-2-pyrone.—Ten grams of crude 4-carboxy-3,7,11-trimethyl-2,4,10-dodecatrienoic acid, obtained from citronellal and methyl β-methylglutaconate, was heated with 0.1 g. of copper powder at 165° for one hour. The residue was fractionated to give 3.2 g. (38.2%) of an oil, b.p. 155° (3 mm.). The infrared absorption data show a band at 1727 cm.$^{-1}$ characteristic of the γ-lactone structure.

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24; sapn. equiv., 236.3. Found: C, 76.09; H, 10.41; sapn. equiv., 226.4.

6-Isobutyl-4-methyl-5,6-dihydro-2-pyrone by Decarboxylation of the Dipotassium Salt.—A solution of 10 g. of the dipotassium salt of γ-isoamylidene-β-methylglutaconic acid in 10 ml. of glacial acetic acid was heated on a water-bath for two hours. The reaction mixture was diluted with 300 ml. of water to separate a water-insoluble layer which was separated, dried, and fractionated to give 4.3 g. (71.5%) of the product, b.p. 130–133° (8 mm.), $n^{26}D$ 1.4754.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; sapn. equiv., 168.1. Found: C, 71.27; H, 9.71; sapn. equiv., 167.7.

3,7-Dimethyl-2,4-octadienoic Acid by Hydrolysis of Its Lactone.—A solution of 3.0 g. of 6-isobutyl-4-methyl-5,6-dihydro-2-pyrone in 45 ml. of 20% alc. potassium hydroxide is refluxed for six hours, diluted with 100 ml. of water, cooled to 0°, and acidified. The precipitated solids were collected, dried, and extracted with hot methanol to separate the insoluble potassium sulfate. Water is added to the methanol solution and the solid which crystallizes on cooling was recrystallized to give 1.1 g. (38%) of the product, m.p. 50–53°, identical with that obtained by decarboxylation.

6-Amyl-4-methyl-5,6-dihydro-2-pyrone was prepared by the process given above for the 6-isobutyl analog. Fractionation gave 66.7% of the product, b.p. 134° (5 mm.), $n^{25}D$ 1.4705.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96; sapn. equiv., 182.2. Found: C, 72.30; H, 10.16; sapn. equiv., 176.

4-Methyl-6-propyl-5,6-dihydro-2-pyrone.—A solution of 20 g. of γ-butylidene-β-methylglutaconic acid and 0.25 g. of cupric acetate in 45 ml. of 2,4-lutidine was heated at 100° for 45 minutes. Addition of ice and acidification precipitates an oil which was taken up in ether. The crude product obtained from these ether extracts was fractionated to give 7.5 g. of material, b.p. 112–135° (6 mm.), which showed the infrared carbonyl absorption characteristics of a mixture of the δ-lactone and unsaturated acid (1738 and 1680 cm.$^{-1}$). The mixture was dissolved in water, neutralized, and extracted with ether to obtain 2.1 g. (13.5%) of the pure 2-pyrone, b.p. 124° (7 mm.), $n^{30}D$ 1.4821.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.09; H, 9.15; sapn. equiv., 154.2. Found: C, 70.05; H, 9.23; sapn. equiv., 154.

3-Methyl-2,4-octadienoic Acid Benzylthiouronium Salt.—A solution of 0.5 g. of 4-methyl-6-propyl-5,6-dihydro-2-pyrone in 10 ml. of methanol is refluxed for one hour with a solution of 0.2 g. of potassium hydroxide in 5 ml. of water. Neutralization precipitated the 3-methyl-2,4-octadienoic acid as a crude oil which could not be purified by crystallization or distillation. Addition of a slight excess of benzyl-

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thiouronium chloride in methanol precipitated the salt. Recrystallization gave 0.75 g. (68%) of the product as white needles, m.p. 150°.

Anal. Calcd. for $C_{17}H_{24}O_2N_2S$: N, 8.74. Found: N, 8.98.

6-Butyl-4-methyl-5,6-dihydro-2-pyrone.—5-Carboxy-6-butyl-4-methyl-5,6-dihydro-2-pyrone was decarboxylated in 2,4-lutidine with cupric acetate by the procedure given above for the 6-propyl analog given above. The mixture of lactone and acid, b.p. 115–117° (4 mm.), obtained from 20 g. of starting material was dissolved in alkali and extracted with ether to obtain 6.7 g. (42.5%) of the product, b.p. 124° (4 mm.), $n^{11}D$ 1.4935. The pure acid could not be obtained from the alkaline solution.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.88; H, 9.73.

6-Butyl-4-methyltetrahydro-2-pyrone.—A solution of 4.5 g. of the crude dihydro-2-pyrone obtained as described in the preceding paragraph in 50 ml. of ether was hydrogenated over palladium-on-charcoal catalyst. The crude product was neutralized and extracted with ether. The ether extracted oil was fractionated to give 1.6 g. (35%) of the product, b.p. 114° (4 mm.), $n^{10}D$ 1.4517. This compound shows infrared absorption bands in carbon tetrachloride at 2959 (C–H stretching), 1712 (carbonyl stretching), 1381 (unassigned) and 1238 cm.$^{-1}$ (C–O stretching) as does also 4,6-dimethyltetrahydro-2-pyrone.[10]

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; sapn. equiv., 170.2. Found: C, 70.37; H, 10.64; sapn. equiv., 169.

6-(1′-Ethylamyl)-4-methyl-5,6-dihydro-2-pyrone.—Four grams of 4-carboxy-6-ethyl-3-methyl-2,4-dodecanoic acid was decarboxylated in 10 ml. of 2,4-lutidine with 0.01 g. of cupric acetate at 100°. The lutidine was removed by distillation. The residue was acidified and extracted with ether. The ether-extracted oil on fractionation gave 2.6 g. of a mixture of the lactone and acid. The acid was extracted from an ether solution of the mixture with dilute alkali. The ether extracts were evaporated and the residue fractionated to give 1.7 g. (51%) of the product, b.p. 141–143° (5 mm.), $n^{25}D$ 1.4641.

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54; sapn. equiv., 210.3. Found: C, 74.38; H, 10.48; sapn. equiv., 205.

The infrared absorption spectra were determined using potassium bromide pellets, except as otherwise noted, and a Baird double beam recording infrared spectrometer with sodium chloride optics.

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[CONTRIBUTION FROM THE CHARLOTTE DRAKE CARDEZA FOUNDATION, JEFFERSON MEDICAL COLLEGE]

Synthesis of Acids Containing Hydrophenanthrene and Hydroacephenanthrylene Rings

BY D. L. TURNER

RECEIVED OCTOBER 25, 1956

The Reformatsky reaction with methyl 3-carbomethoxy-2-keto-3-methyl-6-phenylcyclohexane-1-acetate yields an unsaturated acid which can be cyclized either to a keto-anhydride (IV) or to an acephenanthrylene phenol (VI). The structure of the latter was shown by an independent synthesis from the α-form of 2-methyl-2-carbomethoxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid. The β-stereoisomer of the acephenanthrylene also was prepared.

The cyclic keto-ester I described previously[1] was allowed to react with ethyl bromoacetate in the Reformatsky reaction. The principal crystalline material obtained from this reaction was the lactone ester II. The presence of the lactone ring was indicated by the infrared spectrum $\lambda_{max}^{CS_2}$ 5.56, 5.75 μ. This is similar to the result obtained by Johnson and Christiansen[2] in a similar reaction.

Hydrolysis of the lactone II with alcoholic potassium bicarbonate gave the unsaturated acid III. The ultraviolet absorption spectrum of this acid showed a band at 209 mμ (ϵ 16520), supporting the structure indicated[3] containing a conjugated double bond. The infrared spectrum of the methyl ester of the acid showed a band at 5.75 μ but no absorption at 5.56 μ and a new weak band, not present in the lactone, at 6.12 μ and probably caused by the double bond. The double bond was resistant to oxidation by permanganate under the conditions described by Johnson and Hunt,[4] a method which proved successful with unhindered double bonds.[1] When III was hydrogenated in acetic acid in the presence of Adams catalyst and hydrochloric acid, a product was obtained in which the aromatic ring was reduced but not the hindered double bond.

The acid III was cyclized with polyphosphoric acid, and the product was not an ester, but instead the keto-anhydride IV. Since the product is not phenolic, the double bond must be exocyclic as indicated in the structural formula. This is confirmed by the ultraviolet absorption spectrum, which shows the characteristics of the phenyl and carbonyl chromophores in conjugation,[5,6] and deviates from the spectrum of 9-keto-1,2,3,4,4a,-9,10,10a-octahydrophenanthrene[7] only at the lower minimum where the molecular extinction is greater, reaching 21000 at 212 mμ, the limit of measurement.

The anhydride IV was recovered unchanged after boiling with alcoholic alkali and acidifying. If the double bond were in the nucleus, the substance might be expected to isomerize to a phenol under these conditions. Another substance that exists only in anhydride form and not as the free acid has been obtained in the α-amyrin series by Ruzicka's group.[8,9] It seems probable that the anhydride IV belongs to the same stereochemical series as the major products described by Johnson and Christiansen[2] and it is of interest that it would then conform to the stereochemical arrangement in the Ruzicka anhydride.

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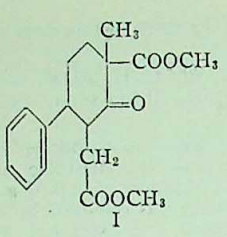
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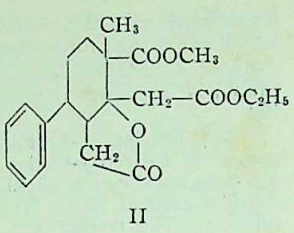
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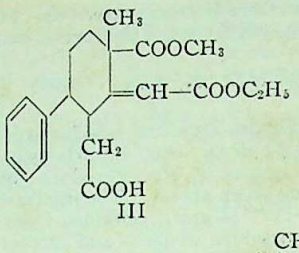
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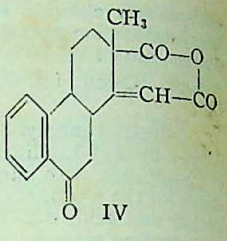
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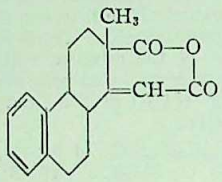
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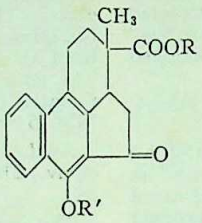
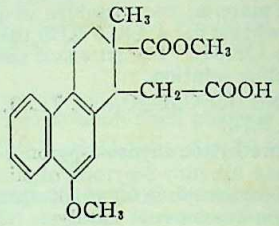

VIa, R = R′ = H
VIb, R = CH_3; R′ = H
VIc, R = R′ = CH_3


VII

The carbonyl group in the anhydride IV was hydrogenated in the presence of perchloric acid[10] to form the anhydride V. This anhydride was dehydrogenated with palladium to 1,2-dimethylphenanthrene. The anhydride V shows the same resistance to reduction of the double bond exhibited by the acid III. Reduction with dissolving alkali metals[11] might be expected to succeed; perhaps it failed because of the extreme insolubility of the alkali metal salts formed from the anhydride.

When the acid III was cyclized by the Friedel–Crafts reaction, the resulting neutral product was a mixture, which was not easily separated. This mixture was hydrolyzed with alkali, producing isomers of the anhydride IV with phenolic properties. The two pure substances resulting from this reaction are assigned the structures VIa and VIb. The substance VIa could be converted to the second product VIb by esterification. These substances were soluble in alkali to give green fluorescent solutions. It was difficult to methylate the phenolic hydroxyl in VIa or VIb, and this could not be done with methyl sulfate or methyl *p*-toluenesulfonate in alkaline solution, but succeeded when diazomethane was employed in an ether–methanol solution. The methyl ether VIc was prepared by an independent method and this constitutes the proof of structure for these substances as acephenanthrylenes.

The monomethyl ester VII of Bachmann and Holmes[12] exists in two stereochemical forms α and β. Both of these were cyclized by the thionyl chloride–stannic chloride method. Since the acid chlorides were prepared at low temperature, it seems improbable that any rearrangement took place[13] and the cyclization products should be the acephenanthrylenes of structure VIc. The identity of the acephenanthrylene derived from the α-acid of Bachmann and Holmes and the product VIc from the Reformatsky acid was established by comparison of melting points and infrared spectra. Hirschmann and Johnson[14] have suggested that the α-series of Bachmann and Holmes has rings C and D fused in the *trans* configuration as in natural estrone.

The ultraviolet absorption spectrum of the methyl ether VIc shows a pronounced hypsochromic shift, when compared with that of the phenolic materials VIa and VIb, which have identical spectra. The hypsochromic shift produced by methylating the phenolic hydroxyl probably indicates chelation in the phenolic substances.[15] This effect is shown in a pronounced form by purpurogallin and its methyl ether,[16] which also has a carbonyl group adjacent to a phenolic hydroxyl. Many substances with this type of structure also show similar chemical properties, particularly characterized by difficulty in methylating the phenolic hydroxyl (quercetin[17]) and easy removal of the methyl group (purpurogallin).[18,19] It should be noted, however, that Haworth[19] ascribes the difficulty in methylating the third phenolic hydroxyl of purpurogallin to steric hindrance, rather than to the chelation effect. The easy removal of the methyl group in VIc was shown by the formation of greenish fluorescent solutions on saponification.

The infrared spectrum of VIa showed bands at 3.0 μ (hydroxyl), 5.93 μ (carboxyl carbonyl) and 6.09 μ (chelate). The band attributed to chelation agrees with the assignment of Bellamy and Beecher[20] for 1-tetralone-2-carboxylate esters. This band disappears in the methyl ether, which has a new band at about 6.2 μ possibly caused by the aromatic system.[21]

Experimental

Ultraviolet absorption spectra were determined in 95% ethanol and infrared spectra in carbon disulfide.

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May 5, 1957

Lactone of Ethyl 2-Carbomethoxy-6-carboxymethyl-1-hydroxy-2-methyl-5-phenylcyclohexane-1-acetate.—A solution of 55 g. of the ester I in 500 ml. of dry ether and 450 ml. of dry benzene was treated with 70 g. of activated zinc[22] and 3 g. of iodine, while stirring and refluxing under nitrogen. Two additional portions of 50 g. of zinc and a crystal of iodine were added at two-hour periods, and the mixture was stirred for a total of six hours. The mixture was treated by the method of Bachmann, Cole and Wilds.[23] After the evaporation of the solvent from the neutral fraction, the product was crystallized from isopropyl alcohol, m.p. 125–127.5°.

Anal. Calcd. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.76; H, 6.98.

Ethyl 2-Carbomethoxy-6-carboxymethyl-2-methyl-5-phenyl-cyclohexylidene-acetate (III) (a).—A solution of the preceding ester (3 g.) in 100 ml. of methanol was refluxed with a solution of 5 g. of potassium bicarbonate in 15 ml. of water. After one hour, the mixture was evaporated *in vacuo*, treated with water, and acidified with 10% hydrochloric acid. The acid fraction was isolated with ether, the ethereal solution was dried and the ether was removed. The residue was crystallized from benzene, giving 1.28 g., m.p. 154–155°, λ_{max} 209 mμ (log ϵ 4.22).

Anal. Calcd. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00; neut. equiv., 374. Found: C, 67.49, 67.41; H, 6.88, 6.83; neut. equiv., 375, 375.

An attempt to oxidize the material by the method of Johnson and Hunt[4] using potassium permanganate in acetone, gave a 63% recovery of the starting material.

(b).—The mother liquors from the preceding Reformatsky reaction were dissolved in 100 ml. of pyridine and refluxed for 45 minutes with 28 ml. of phosphorus oxychloride. After treating with ice and extracting with ether, the ethereal extract was washed with 10% hydrochloric acid, saturated bicarbonate and dried. The residue from the distillation of the ether was hydrolyzed with potassium bicarbonate (30 g.) in 90 ml. of water and 600 ml. of methanol. This gave 6 g. of material, m.p., alone and mixed with (a), 152–154°.

The methyl ester of the acid was made with ethereal diazomethane and crystallized from ethanol; m.p. 70–72°.

Anal. Calcd. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26. Found: C, 67.93, 68.00; H, 7.16, 7.12.

2-Carboxy-6-carboxymethyl-2-methyl-5-phenylcyclohexylideneacetic Acid.—The complete hydrolysis of the preceding acid was effected by refluxing in 5% aqueous sodium hydroxide for four hours. After cooling, it was acidified and isolated with ether in the normal manner. Crystallized from ethyl acetate it melted at 181–183°.

Anal. Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.78; H, 6.27.

The trimethyl ester of this acid, prepared with ethereal diazomethane, was crystallized from ether–pentane; m.p. 65–66°.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 67.36; H, 7.00. Found: C, 67.29; H, 7.12.

Hydrogenation of the Reformatsky Lactone Ester. (II).—The material was recovered unchanged after attempts to hydrogenate using Adams catalyst or palladium catalysts in ethanol or acetic acid.

3-Carbomethoxy-2-keto-3-methyl-6-phenylcyclohexane-1-acetic Acid.—This was prepared for comparison with products of Reformatsky reactions by hydrolysis of the starting ester I using potassium bicarbonate in aqueous methanol as described above. It was crystallized from benzene; m.p. 147–148°.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.63; neut. equiv., 304. Found: C, 67.15; H, 6.57; neut. equiv., 304.

Ethyl 2-Carbomethoxy-5-cyclohexyl-2-methyl-6-carboxymethylcyclohexylidene-1-acetate.—The acid from the bicarbonate hydrolysis of the Reformatsky ester (4.7 g.) was hydrogenated for 2 hours in 100 ml. of acetic acid in the presence of 1 ml. of concentrated hydrochloric acid and 0.5 g. of Adams catalyst. The acetic acid was distilled *in vacuo*, and the residue was purified by a partition chromatograph using nitroethane–heptane on silicic acid–Celite (1:3 by weight)[24] with the nitroethane as the stationary phase.[25] Early eluates gave crystals, m.p. 132–134° after recrystallization from acetone–pentane (1.4 g.).

Anal. Calcd. for $C_{21}H_{34}O_6$ (completely reduced): C, 65.94; H, 8.96; neut. equiv., 382. Calcd. for $C_{21}H_{32}O_6$ (one double bond): C, 66.29; H, 8.48; neut. equiv., 380.5. Found: C, 65.96; H, 8.33; neut. equiv., 374.

Another fraction obtained from later eluates was crystallized from acetone–pentane; m.p. 163–165°.

Anal. Calcd. for $C_{20}H_{32}O_6$ (completely reduced): C, 65.18; H, 8.73; neut. equiv. (dibasic), 246. Calcd. for $C_{20}H_{30}O_6$ (one double bond): C, 65.55; H, 8.25; neut. equiv. (dibasic), 227. Found: C, 65.60; 65.65; H, 8.31, 8.26; neut. equiv., 278.

This substance is considered to be a monoethyl ester because of the analysis and neutralization equivalent. Both of the substances from the chromatograph gave the same acid on hydrolysis.

2-Carboxy-5-cyclohexyl-2-methyl-6-carboxymethylcyclohexylidene-1-acetic Acid.—The preceding dibasic acid was refluxed in 10% aqueous sodium hydroxide solution for 4 hours. The solution was cooled, acidified, and the product filtered. After several recrystallizations from acetone–carbon tetrachloride it had m.p. 184–185.5°. A similar hydrolysis of the preceding monobasic acid gave a substance which was crystallized from acetone–carbon tetrachloride; m.p. 182–184°. The m.p. of a mixture was 182–184°. For analysis, it was crystallized from ether–pentane; m.p. 185–186°.

Anal. Calcd. for $C_{18}H_{28}O_6$: C, 63.89; H, 7.75; neut. equiv. (tribasic), 113. Found: C, 63.99; H, 7.90; neut. equiv., 114.

Anhydride of 2-Carboxy-9-keto-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrylideneacetic Acid.—To 310 g. of phosphorus pentoxide was added 20 ml. of 85% phosphoric acid with cooling. After the reaction had subsided, the mixture was heated on the steam-bath for 2 hours and poured over 26 g. of the Reformatsky unsaturated acid III. The mixture was heated on the steam-bath with frequent swirling for 2 hours and then poured into ice-water. The precipitated solid was filtered, dried and crystallized from ethyl acetate, giving 9.5 g., m.p., 258–260° dec.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44; sapon. equiv., 148.1. Found: C, 73.07; H, 5.54; sapon. equiv., 148.

The substance did not react with diazomethane. The ultraviolet absorption spectrum showed λ_{max} 293, 247 mμ (log ϵ 3.31, 4.10); λ_{min} 275 and 226 mμ (log ϵ 3.12, 3.90). The spectrum resembled that of α-tetralone.

The semicarbazone, m.p. 300° dec., was extremely insoluble in the usual solvents. The **2,4-dinitrophenylhydrazone** was made by the method of Reich, Crane and Sanfilippo[26] and recrystallized from dimethylformamide–ethanol; m.p. 282°. It was extremely insoluble in most solvents.

Anhydride of 2-Carboxy-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrylideneacetic Acid.—The unsaturated anhydride (9 g.) was hydrogenated in the presence of 3 g. of 5% palladium chloride on carbon (Wilkens–Anderson Co.) in 250 ml. of acetic acid and 10 ml. of 60% perchloric acid. The calculated amount of hydrogen was absorbed in three hours. The solution was filtered from the catalyst and poured into 100 ml. of 5% sodium carbonate solution and the product was filtered giving 4.4 g., m.p. 195–210°. This could not be purified by recrystallization. It was treated with ethereal diazomethane and the part which did not react was removed by filtration and crystallized from acetone; m.p. 208–210°, yield 3.4 g.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; sapon. equiv., 141.2. Found: C, 76.52; H, 6.10; sapon. equiv., 149.

This anhydride could not be esterified by the method of Clinton and Laskowski[27] or by the sodium methylate method

(22) L. F. Fieser and W. S. Johnson, THIS JOURNAL, **62**, 575 (1940).

(23) W. E. Bachmann, W. Cole and A. L. Wilds, *ibid.*, **62**, 824 (1940).

(24) Celite no. 545, a product of Johns Manville, Inc.

(25) *Cf.* J. K. N. Jones and S. R. Stitch, *Biochem. J.*, **53**, 679 (1953).

(26) H. Reich, K. F. Crane and S. J. Sanfilippo, *J. Org. Chem.*, **18**, 822 (1953).

(27) R. O. Clinton and S. C. Laskowski, THIS JOURNAL, **70**, 3135 (1948).

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of Herr and Miescher.[28] Attempts to reduce the double bond catalytically failed as with the unsaturated acid III. Sodium and *n*-butyl alcohol was not effective possibly because the anhydride gave a very insoluble sodium salt.

1,2-Dimethylphenanthrene.—The preceding anhydride of carboxy-2-methyloctahydrophenanthrylideneacetic acid (600 mg.) was heated with 1 g. of palladium chloride on Darco, a catalyst containing 5% palladium,[29] to 350° for 20 minutes. The product was dissolved in acetone and filtered from the catalyst. The acetone was evaporated and the residue was crystallized from methanol; m.p. 145°,[30] yield 300 mg.

Anal. Calcd. for $C_{16}H_{14}$: C, 93.18; H, 6.84. Found: C, 92.99; H, 6.93.

The picrate of this hydrocarbon was crystallized from ethanol; m.p. 153–154°.[31]

Anal. Calcd. for $C_{22}H_{17}O_7N_3$: C, 60.69; H, 3.94. Found: C, 60.82; H, 4.08.

Cyclization of Ethyl 2-Carbomethoxy-6-carboxymethyl-2-methyl-5-phenylcyclohexylideneacetate by the Friedel-Crafts Method.—Using the method of Johnson and Glenn,[32] 23 g. of phosphorus pentachloride was added to a solution of 36.8 g. of the acid in 100 ml. of dry benzene. The acid chloride, after the removal of the solvents, was dissolved in 100 ml. of fresh benzene and the solution was added dropwise to a stirred solution of 18.5 g. of aluminum chloride in 50 ml. of benzene at a temperature below 10°. After 2 hours at this temperature and 3 hours at room temperature, the mixture was hydrolyzed with ice and hydrochloric acid, and extracted with ether. The ethereal solution was washed with hydrochloric acid, water, saturated sodium bicarbonate and dried. Partial removal of the ether gave crystals, m.p. 126–135°, yield 27 g. Because this was difficult to purify, it was hydrolyzed by refluxing in 200 ml. of methanol with 30 ml. of 15% sodium hydroxide solution. After 30 minutes, water was added, and the insoluble salt, which separated on cooling, was filtered and treated with 10% hydrochloric acid. The oily yellow crystals produced were filtered and crystallized from benzene; m.p. 159–170° dec., yield 9 g. Repeated recrystallization of this material gave VIa, better prepared by retreatment with alkali as described later.[33] The mother liquor from the benzene solution gave a second crop of 5 g., m.p. 241–248°, which was recrystallized from acetone; m.p. 252–253°. This is **3-carboxy-6-hydroxy-5-keto-3-methyl-1,2,3,3a,4,5-hexahydroacephenanthrylene (VIa).**

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44; neut. equiv. (dibasic), 148. Found: C, 72.87; H, 5.49; neut. equiv., 149.

Alternative Preparation of 3-Carboxy-6-hydroxy-5-keto-3-methyl-1,2,3,3a,4,5-hexanydroacephenanthrylene (VIa).—The intermediate above, m.p. 159–170°, was converted to the phenol by standing in solution, or by the following treatment with alkali. The crystals (600 mg.) were heated on the steam-bath for 1 hour with 10 ml. of 10% sodium hydroxide solution. The solution was acidified with 2 *N* hydrochloric acid, and filtered, giving 0.5 g., m.p. 248–252°. This was recrystallized from acetone–pentane, m.p. alone, and mixed with the phenol from the mother liquor of the starting material, 252–253.5°. The absorption spectrum showed λ_{max} 381, 300, 290, 265 mμ (log ε 3.74, 2.76, 3.64, 4.67).

3-Carbomethoxy-6-hydroxy-5-keto-3-methyl-1,2,3,3a,4,5-hexahydroacephenanthrylene (VIb) (a).—The benzene mother liquor from the hydrolysis of the Friedel–Crafts reaction products was evaporated, and the residue was crystallized from nitromethane, rejecting material insoluble in hot nitromethane. This gave 2.7 g., m.p. 104–109.5°; recrystallized from methanol, m.p. 111–114°.

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.64; H, 5.69.

The ultraviolet absorption spectrum was the same as that of the preceding phenol.

(b).—To 2.1 g. of the free acid VIa, was added 50 ml. of ethylene chloride, 20 ml. of methanol and 2 ml. of concentrated sulfuric acid. This was refluxed for 5 hours, diluted with water and extracted with ethylene chloride.

The ethylene chloride solution was washed with saturated sodium bicarbonate, and dried over sodium sulfate. The solvent was evaporated and the residue was crystallized from ethyl acetate–pentane, m.p., alone and mixed with (a) above 111–114°. The ultraviolet absorption spectrum was identical with that of (a). The yield was 1.1 g. This esterification could also be performed using methanol and boron trifluoride etherate.

This substance, like the free acid, dissolved in alkali to give a greenish-yellow fluorescent solution.

3-Carbomethoxy-5-keto-6-methoxy-3-methyl-1,2,3,3a,4,5-hexahydroacephenanthrylene (VIc).—The phenolic ester VIb was esterified with diazomethane in ether–methanol to give a dark red oil. This was crystallized from isopropyl alcohol and then from methanol; m.p. 106–107°. The very faintly yellow crystals formed a solution in alcohol with violet fluorescence; λ_{max} 372, 311, 299, 257, 221 mμ (log ε 3.62, 3.76, 3.84, 3.67, 4.38).

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22; mol. wt., 324. Found: C, 74.26; H, 6.61; mol. wt. (Rast), 317.

The 2,4-dinitrophenylhydrazone of this keto-ester was prepared by heating in acidified ethanol with Brady's reagent. It had m.p. 273° dec. It was too insoluble to recrystallize and was extracted with hot ethyl acetate and ethanol to purify it.

Anal. Calcd. for $C_{26}H_{24}N_4O_7$: C, 61.90; H, 4.80. Found: C, 61.86; H, 5.02.

Synthesis of the Preceding Acephenanthrylene (VIc) from the α-Form of 2-Methyl-2-carbomethoxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—To 4 g. of the half ester of Bachmann and Holmes[12] was added 125 ml. of anhydrous ether, 10 drops of pyridine and 7 ml. of purified[34] thionyl chloride. After 30 minutes at room temperature, the solvents were distilled *in vacuo* below 35°, 35 ml. of dry benzene was added and the solvents were distilled again. The residual acid chloride was dissolved in 55 ml. of benzene, the solution was cooled until the benzene began to crystallize, and 13 ml. of stannic chloride was added. After swirling for 3 minutes, the mixture was hydrolyzed with ice and hydrochloric acid. The product was taken up in ether and benzene, washed with 10% hydrochloric acid, 4% sodium carbonate solution, water, saturated sodium chloride and then dried. The solvents were removed and the residue was crystallized from methanol, yield 2.9 g. (76%), m.p. 106–107° undepressed when mixed with the preceding acephenanthrylene (VIc). The ultraviolet and infrared absorption spectra of the two substances were identical.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 74.09; H, 6.19.

β-Form of 3-Carbomethoxy-5-keto-6-methoxy-3-methyl-1,2,3,3a,4,5-hexahydroacephenanthrylene.—Using a pro-

(28) J. Heer and K. Miescher, *Helv. Chim. Acta*, **31**, 234 (1948).

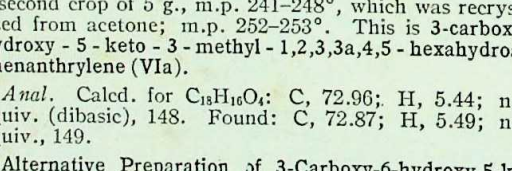
(29) Catalyst C of R. Mozingo, *Org. Syntheses*, **26**, 77 (1946).

(30) Reported 142–143°, A. Butenandt, H. A. Weidlich and H. Thompson, *Ber.*, **66**, 601 (1933); R. D. Haworth, C. R. Marvin and G. Sheldrick, *J. Chem. Soc.*, 457 (1934).

(31) Reported m.p. 153–154° (Haworth, Marvin and Sheldrick).

(32) W. S. Johnson and H. J. Glenn, THIS JOURNAL, **71**, 1094 (1949).

(33) This impure material may contain VIa mixed with an isomer of VIa with the structure of 3-carboxy-5,6-diketo-3-methyl-1,2,3,4,5,-5a-hexahydroacephenanthrylene, easily converted to the phenolic substance VIa by migration of the double bond



The ultraviolet absorption spectrum showed λ_{max} 341 mμ (log ε 3.93), 239 mμ (log ε 4.09) λ_{min} 281 mμ (log ε 3.33), 224 mμ (log ε 3.95). This supports the hypothetical compositon of the material as does the analysis. *Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.88; H, 5.49.

(34) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., 1955, p. 345. This purification is important: *cf.* B. H. Chase and D. H. Hey, *J. Chem. Soc.*, 553 (1952).

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cedure similar to that employed for the α-form, the β-form of 2-methyl-2-carbomethoxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid[12] was converted to the acephenanthrylene in 50% yield. It was crystallized from ethyl acetate; m.p. 173–174°. The ultraviolet absorption spectrum and that of the α-form were identical.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 74.18; H, 6.21.

Acknowledgment.—This work was supported by a grant No. C-1585 from the National Cancer Institute, U. S. Public Health Service. Dr. E. J. Rosenbaum of the Sun Oil Co. gave valuable assistance with the infrared spectra.

PHILADELPHIA, PA.

[CONTRIBUTION FROM LINWOOD LABORATORY, REMINGTON RAND DIVISION, SPERRY RAND CORPORATION]

Cyanine Dyes. I. Absorption of Cyanines Derived from Pyranothiazole and Thiopyranothiazoles[1]

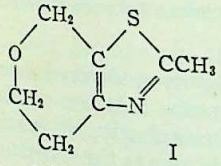
BY ROBERT H. SPRAGUE

RECEIVED JULY 27, 1956

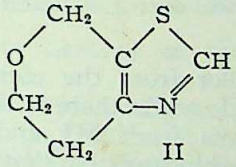
Three new thiazole bases have been prepared by condensing thioacetamide with 3-bromotetrahydro-4-pyrone, 3-bromotetrahydro-1-thio-4-pyrone and 2-bromotetrahydro-1-thio-3-pyrone. Quaternary salts of the products have given rise to new cyanine dyes, some of which are powerful photographic sensitizers. The absorptions of the new dyes are compared with those of similar dyes from benzothiazole and tetrahydrobenzothiazole.

The well known synthesis of 2-methylthiazoles by condensation of thioacetamide with α-haloketones[2] has been employed to prepare thiazole bases from 3-bromotetrahydro-4-pyrone, 3-bromotetrahydro-1-thio-4-pyrone and 2-bromotetrahydro-1-thio-3-pyrone.

Thus 3-bromotetrahydro-4-pyrone was treated with thioacetamide giving 2-methyl-6,7-dihydro-4-H-pyrano[4,3d]thiazole (I). Although (I) has not been reported in the literature, the corresponding unsubstituted thiazole II has been prepared by Sorkin and Erlenmeyer[3] by condensing thioformamide with 3,5-dibromotetrahydro-4-pyrone. The enol forms of the reactants condense with elimination of water and hydrobromic acid.



I



II

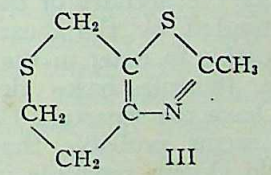
Since the product contained no bromine, Erlenmeyer postulated that the extra bromine atom in the five position of the pyrone ring was eliminated by "reductive splitting" and replaced by hydrogen.

Erlenmeyer isolated only the 3,5-dibromo ketone on treatment of tetrahydro-4-pyrone with N-bromosuccinimide (36% yield, m.p. 156–157°); however, attempts to repeat his work in this Laboratory led to a mixture of the dibromo derivative with a monobromo compound, in which the latter predominated. The mixture was purified by vacuum distillation giving a 24% yield of 3-bromotetrahydro-4-pyrone in the form of a colorless liquid (b.p. 76–80° at 2 mm.) which darkened rapidly and solidified on standing.

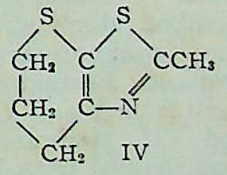
In a second experiment the crude product was recrystallized from ethanol without previous distillation resulting in a small yield of the dibromo compound melting at 159–161°.

Both products condensed readily with thioacetamide in ethanol solution. Contrary to Erlenmeyer's findings in the analogous thioformamide reaction, a bromine-substituted thiazole was obtained from the dibromopyrone. The bases gave crystalline quaternary salts with ethyl iodide and were analyzed in this form.

Bromination of tetrahydro-1-thio-4-pyrone[4] with N-bromosuccinimide gave a very unstable bromoketone, which nevertheless could be condensed with thioacetamide at low temperature. The product, 2-methyl-6,7-dihydro-4-H-thiopyrano[4,3d]thiazole (III), formed quaternary salts with alkyl halides which were very reluctant to crystallize. However, a crystalline hydrochloride was obtained on saturating a solution of the base in ether with hydrogen chloride and this derivative was used for analysis.

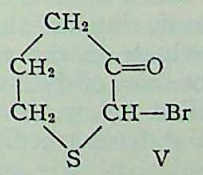


III

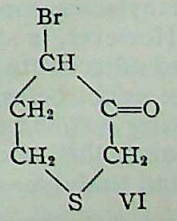


IV

A base IV, isomeric with III, was similarly prepared by condensing thioacetamide with the bromoketone derived from tetrahydro-1-thio-3-pyrone.[5] Of the two possible monobromo derivatives of the latter the product isolated is believed to be the 2-bromo compound V, rather than the 4-bromo isomer VI, for the following reasons:



V



VI

(1) Presented in part before the Organic Division, American Chemical Society, at Minneapolis, Minn., Sept. 12, 1955.

(2) A. Hantzsch, *Ann.*, **250**, 265 (1889).

(3) E. Sorkin and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 96 (1948).

(4) G. M. Bennett and J. V. D. Scorah, *J. Chem. Soc.*, 196 (1927).

(5) E. H. Fehnel, THIS JOURNAL, **74**, 1569 (1952).

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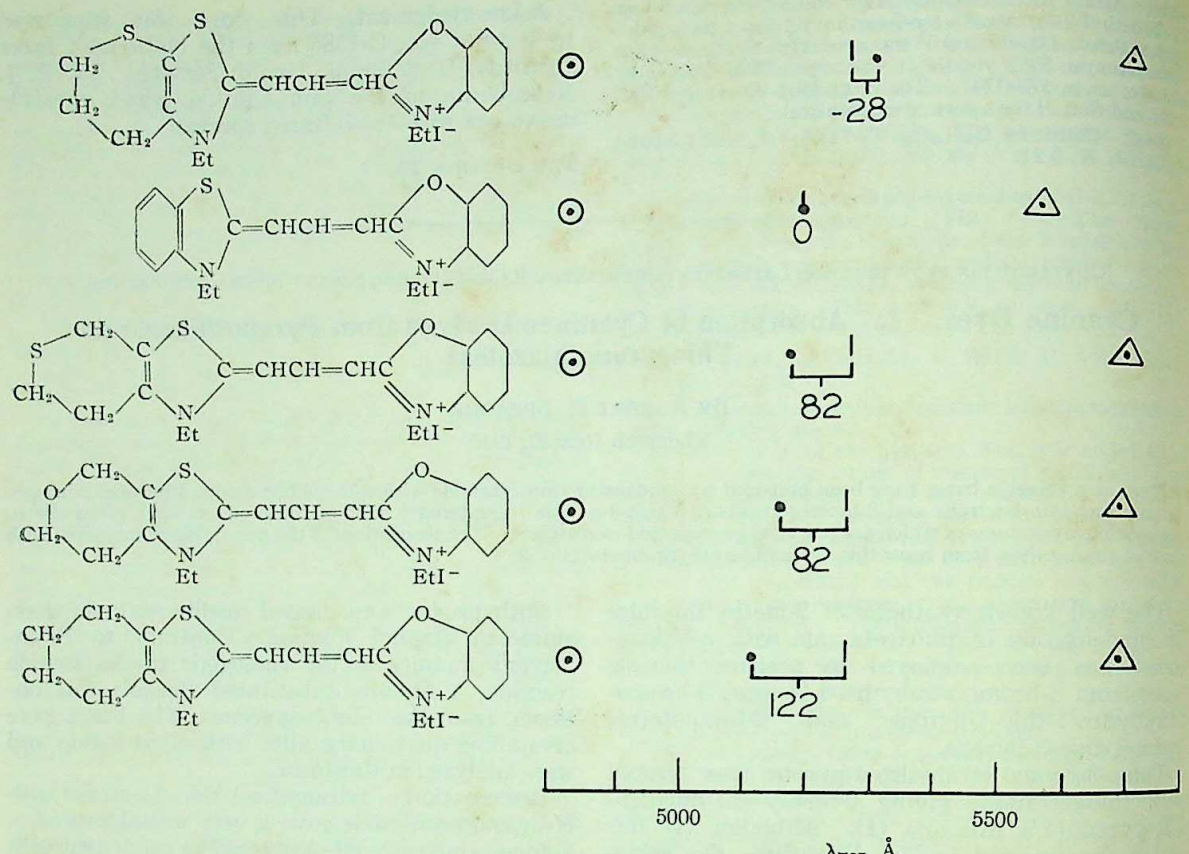
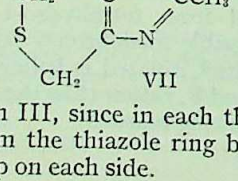


Fig. 1.—Values of $\lambda_{max.}$ of unsymmetrical carbocyanines and related symmetrical dyes: ●, unsymmetrical dye; ⊙, symmetrical oxacarbocyanine (VIII); △, second related symmetrical dye; ⊥, indicates arithmetic mean between ⊙ and △; deviation is indicated by ⊤ and its magnitude is shown in Å.

It has been noted by several workers that the sulfur atom in the system $-\overset{|}{S}-\overset{|}{C}-$ (H) has a considerable proton-releasing effect on the attached carbon atom.[6-8] This would enhance the activity of the 2-carbon atom, already activated by the 3-carbonyl group, causing the bromine to enter in that position. Furthermore, the thiazole bases derived from V and VI would have the structure IV and VII, respectively. It seems probable that dyes derived from VII would closely resemble in



VII

color those from III, since in each the sulfur atom is insulated from the thiazole ring by at least one methylene group on each side.

However, in structure IV the sulfur atom is situated adjacent to that in the thiazole ring and therefore might be expected to participate in the resonating system responsible for the color of dyes containing this nucleus. As detailed below, it was found that dyes derived from IV differ markedly in color from the corresponding dyes derived from III, while there is little difference between similar dyes from III and I. Consequently, it seems highly probable that the new base has the structure IV and therefore its precursor has the structure V. There was no indication that IV was a mixture of two isomers, since the distilled product crystallized readily and quaternary salts prepared from it were sharp melting solids.

Several representative dyes of the various cyanine types were prepared from quaternary salts of the new bases.

Discussion of Absorptions of Dyes

Striking differences are noted when the absorptions of the dyes from the new bases are compared with the corresponding data from tetrahydrobenzothiazole and benzothiazole, using the convenient technique developed by Brooker, *et al.*, in their studies of color and constitution.[9]

Brooker has shown that the color of unsymmetrical cyanine dyes of various types appears to be de-

(6) R. B. Woodward and R. H. Eastman, THIS JOURNAL, **68**, 2232 (1946).

(7) H. Gilman and F. J. Webb, *ibid.*, **62**, 987 (1940).

(8) E. Rothstein, *J. Chem. Soc.*, 1550, 1553, 1558 (1940).

(9) (a) L. G. S. Brooker, R. H. Sprague, C. P. Smyth and G. L. Lewis, THIS JOURNAL, **62**, 1116 (1940); (b) L. G. S. Brooker, F. L. White, G. H. Keyes, C. P. Smyth and P. F. Oesper, *ibid.*, **63**, 3192 (1941); (c) L. G. S. Brooker and R. H. Sprague, *ibid.*, **63**, 3203 (1941); (d) L. G. S. Brooker and R. H. Sprague, *ibid.*, **63**, 3214 (1941); (e) L. G. S. Brooker, G. H. Keyes and W. W. Williams, *ibid.*, **64**, 199 (1942); (f) L. G. S. Brooker and R. H. Sprague, *ibid.*, **67**, 1869 (1945); (g) L. G. S. Brooker, *et al.*, *ibid.*, **67**, 1875 (1945); (h) L. G. S. Brooker, R. H. Sprague and H. W. J. Cressman, *ibid.*, **67**, 1889 (1945); (i) L. G. S. Brooker, F. L. White and R. H. Sprague, *ibid.*, **73**, 1087 (1951); (j) L. G. S. Brooker, *et al.*, *ibid.*, **73**, 5332 (1951).

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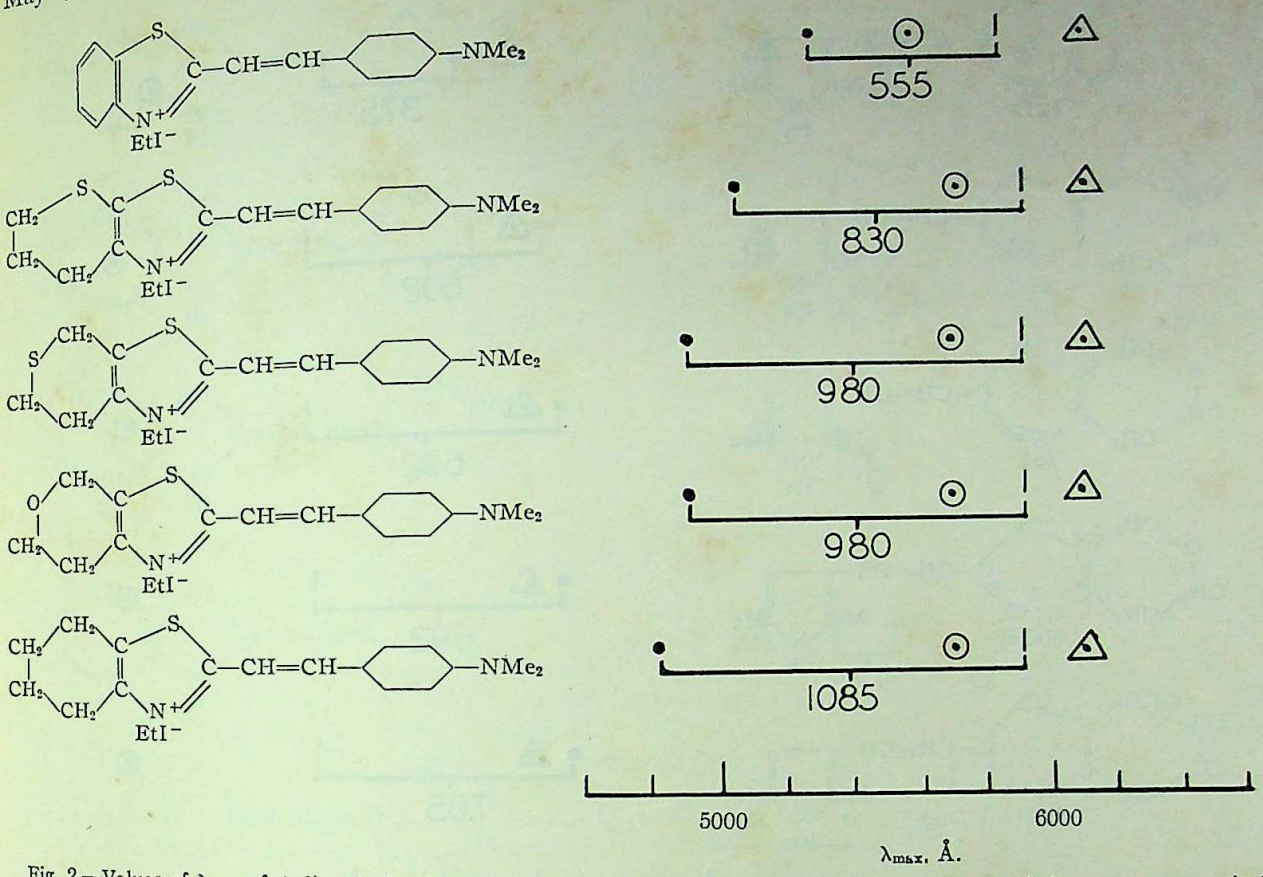
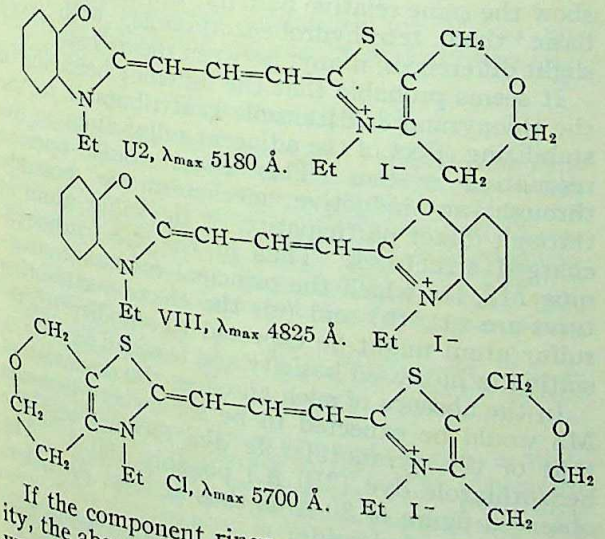


Fig. 2.—Values of λ_{max} of *p*-dimethylaminostyryl dyes and related symmetrical dyes: ●, styryl dye; ⊙, symmetrical carbocyanine; △, Michler hydrol blue; ⊥, arithmetic mean between ⊙ and △; deviation is indicated by ⊤ and its magnitude is shown in Å. For a detailed study of similar dyes see Brooker, *et al.*[9g]

pendent largely on the relative basicity of the heterocyclic rings involved.

For example, the unsymmetrical oxapyranothiazolocarbocyanine (U2) may be considered the structural cross of the symmetrical oxacarbocyanine (VIII) and the symmetrical pyranothiazolocarbocyanine (Cl).



If the component rings are of comparable basicity, the absorption maximum of U2 should be midway between the maxima of the parent dyes, *i.e.*, at 5262 Å. Since the absorption maximum of U2 was found to be 5180 Å., the difference of 82 Å. (called by Brooker the "deviation") indicates that one of the rings is more basic than the other. The corresponding dye from tetrahydrobenzothiazole (U1) gives a similar difference of 122 Å., while the dye from benzothiazole was found by Brooker and co-workers to have zero deviation.[9h] These data together with those for the two isomeric thiopyranothiazole dyes are plotted in Fig. 1.

It already has been pointed out by Brooker[9g,i] that tetrahydrobenzothiazole is considerably more basic than benzothiazole, and since the pyranothiazole and thiopyranothiazoles are structurally very similar to the former, it might be expected that they would closely resemble it in basicity. From Fig. 1 it is seen that the deviations of U2 and U3 are indeed very close to U1 and lie between those of U1 and the corresponding benzothiazole dye. However, dye U4, which is isomeric with U3, has a negative deviation and thus the thiopyrano[3,2d]thiazole nucleus appears to be considerably less basic than tetrahydrobenzothiazole and very similar to benzothiazole, small negative deviations usually being regarded as equivalent to zero.[9j]

On the other hand, data shown in Fig. 2 for the *p*-dimethylaminostyryl series and in Fig. 3 for the pyrrolocarbocyanine series indicate a different order of basicity. In Fig. 2 all three of the new dyes S1, S2 and S3 show deviations lying between those of the tetrahydrobenzothiazole and benzothiazole dyes, S3 again being the least basic of the three but still considerably more basic than benzothiazole. The same order is observed in Fig. 3, the resem-

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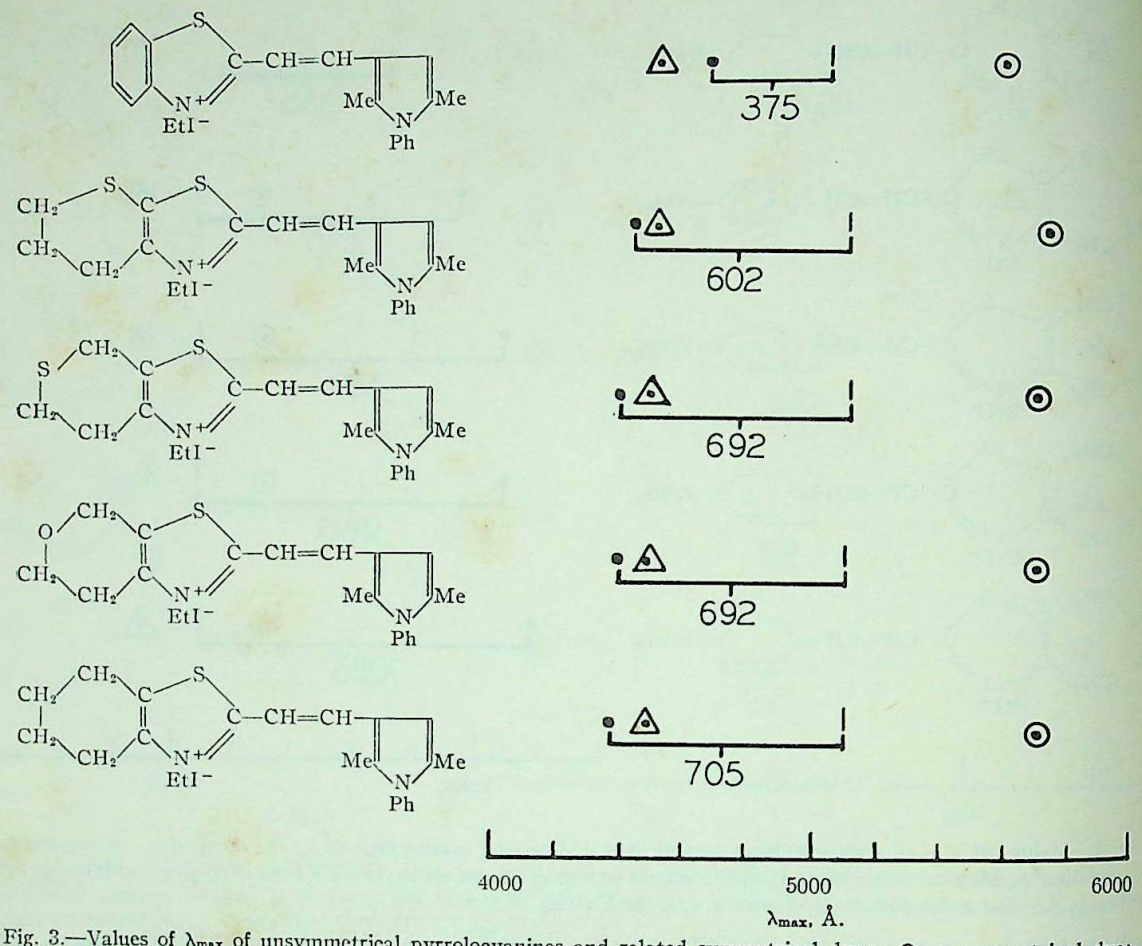
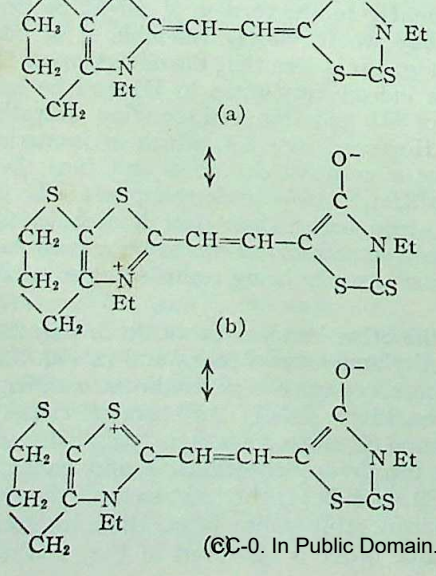


Fig. 3.—Values of λ_{max} of unsymmetrical pyrrolocyanines and related symmetrical dyes: ●, unsymmetrical dye; △, symmetrical cyanine with two pyrrole nuclei; ⊙, second symmetrical cyanine; ⊥, arithmetic mean between ⊙ and △; deviation is indicated by ⊤ and its magnitude is shown in Å. For a detailed study of pyrrolocyanines see Brooker and Sprague.[11]

blance to tetrahydrobenzothiazole being even more marked than in the styryl series.

It is, therefore, all the more interesting to find that in the merocarbocyanine series, as shown in Fig. 4, the order of basicity is reversed, the thiopyrano[3,2d] nucleus now appearing to be more basic than tetrahydrobenzothiazole. It is noteworthy that in all four series pyrano[4,3d]thiazole and thiopyrano[4,3d]thiazole consistently show the same relative basicity, *i.e.*, somewhat less basic than tetrahydrobenzothiazole, with very slight differences, if any, between themselves.



It seems probable that the different behavior of the thiopyrano[3,2d]thiazole is attributable to the stabilizing effect of the adjacent sulfur atom on the resonating system. This effect could operate through an inductive mechanism or possibly through direct participation of the sulfur atom in charged structures. Thus in the merocarbocyanine M3, for which the principal resonance structures are (a), (b) and (c), the electron-attracting sulfur atom might be expected to stabilize (c) resulting in increased basicity and lessened deviation.

In the absence of such an effect the deviation of M3 would be expected to be somewhere between that of the pyranothiazole dye (70 Å.) and the benzothiazole dye (210 Å.) possibly 100 Å. The observed figure of 30 Å. is thus at least 70 Å. less than the expected value.

Too much emphasis on the results shown in Fig. 4 is perhaps not justified since, as Brooker has already stated,[9j] this series does not lend itself readily to differentiation between highly basic nuclei. Nevertheless a difference of 70 Å. between the ob-

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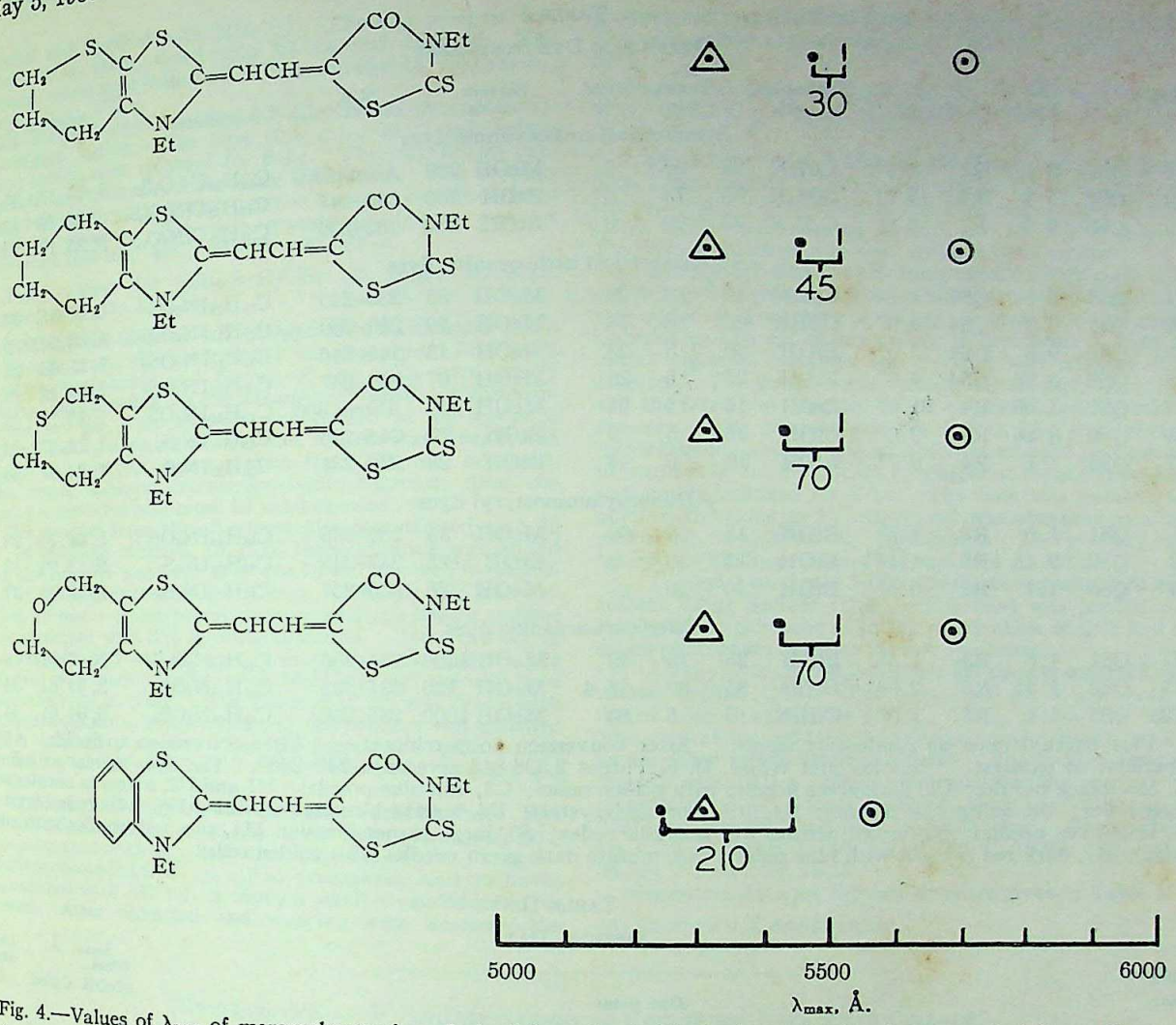

Fig. 4.—Values of λ_{max} of merocarbocyanines derived from 3-ethylrhodanine and related symmetrical dyes: ●, merocarbocyanine; ⊙, symmetrical carbocyanine; △, symmetrical dye with two rhodanine nuclei (oxonol); ⊥, arithmetic mean between ⊙ and △; deviation is indicated by ⊣ and its magnitude is shown in Å. For a detailed study of the merocarbocyanines see Brooker, *et al.*[9i]

served and predicted deviations for M3 is undoubtedly significant and can be explained as suggested above.

Experimental[10]

Quaternary salts used are: QS1, 1-ethyl-2-methyl-6,7-dihydro-4-H-pyrano(4,3d)thiazolium iodide; QS2, 1-ethyl-2-methyl-6,7-dihydro-4-H-thiopyrano(4,3d)thiazolium ethyl sulfate; QS3, 1-ethyl-2-methyl-6,7-dihydro-5-H-thiopyrano(3,2d)thiazolium ethyl sulfate; QS4, 2-(2-acetanilidovinyl)-3-ethylbenzoxazolium iodide; QS5, 1-ethyl-2-methyl-6,7-dihydro-5-H-thiopyrano(3,2d)thiazolium iodide; QS6, 1-ethyl-2-methyl-4,5,6,7-tetrahydrobenzothiazolium *p*-toluenesulfonate.[11]

Other reactants are: R-1, ethyl orthoformate; R-2, *p*-dimethylaminobenzaldehyde; R-3, 5-acetanilidomethylene-3-ethylrhodanine[9j]; R-4, 2,5-dimethyl-1-phenyl-3-pyrrolecarboxaldehyde.[9f]

Details of the preparation of new dyes are given in Table I. These include symmetrical carbocyanines (designated by C), unsymmetrical carbocyanines (U), *p*-dimethylaminostyryl dyes (S) and merocarbocyanines (M). The names of the dyes are given in Table II. In the syntheses the reactants were heated in the solvent indicated for the specified time. The yield of purified dye is given after two crystallizations from the solvent shown in the table.

(10) Melting points are uncorrected. Microanalyses are by Schwarzkopf Microanalytical Laboratory, New York.

(11) L. G. S. Brooker and F. L. White, U. S. Patent 2,336,843.

Details of the preparation of the new bases and their quaternary salts follow.

3-Bromotetrahydro-4-pyrone.—Tetrahydro-4-pyrone[3] (30 g., 1 mol), N-bromosuccinimide (54 g., 1 mol) and 200 ml. of dry CCl_4 were refluxed with stirring under strong ultraviolet light for 20 minutes. A violent reaction occurred after an induction period of 15 minutes. The mixture was chilled, filtered, the solvent evaporated on the steam-bath and the residue distilled under reduced pressure. The fraction boiling at 60–80° at 2 mm. (21 g.) was redistilled. The product was thus obtained as a colorless liquid boiling at 76–80° at 2 mm., yield 13 g., 24%. On standing, the material rapidly darkened to a pinkish-brown and it was therefore used at once in the preparation of the thiazole base. In a later experiment it was found that distillation of the somewhat unstable bromo compound was unnecessary for use in the thiazole condensation. Using the crude bromo derivative an over-all yield of 20% of thiazole was obtained in a large run from 253 g. of tetrahydropyrone.

2-Methyl-6,7-dihydro-4H-pyrano(4,3d)thiazole (I).—3-Bromotetrahydro-4-pyrone (13.0 g., 1 mol), thioacetamide (5.5 g., 1 mol) and absolute ethanol (25 ml.) were heated to boiling under reflux. After the initial vigorous reaction subsided, the mixture was refluxed for 1 hr. The mixture was evaporated nearly to dryness, and the residue was extracted repeatedly with warm dilute HBr. The chilled extract was basified with dilute NH_4OH solution and the oily product was taken up in ether. The ether solution was dried with K_2CO_3, evaporated and the residue was distilled under reduced pressure. The product was

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TABLE I

DETAILS OF DYE SYNTHESES

Dye no.	Reactants, g.				Medium, ml.	Refluxed, min.	Yield, %	Solvent, ml./g.	M.p., °C.		Formula	Analyses, % Calcd.	Found
Symmetrical carbocyanine dyes													
C1	QS1	3.1	R1	3.0	C_5H_5N	25	90	6	MeOH	200	Above 300	$C_{19}H_{25}IN_2O_2S_2$	I, 25.17	25.05
C2	QS2	12.8	R1	14.0[a]	C_5H_5N	35	75	6[b]	EtOH	400	246–247	$C_{19}H_{25}ClN_2O_4S_4$	S, 25.19	25.04
C3	QS3	6.5	R1	6.0	C_5H_5N[a]	32	90	0.3[b]	EtOH	330	233–234	$C_{19}H_{25}ClN_2O_4S_4$	S, 25.19	24.99
Unsymmetrical carbocyanine dyes													
U1	QS6	3.5	QS4	4.34	C_5H_5N	17	15	20	MeOH	55	239–240[e]	$C_{21}H_{25}IN_2OS$	I, 26.45	26.36
U2	QS1	9.3	QS4	13.0[a]	C_5H_5N	90	15	74	MeOH	50	259–260	$C_{20}H_{23}IN_2O_2S$	I, 26.32	26.14
U3	QS2	9.8	QS4	13.0[a]	EtOH	50	5	23[c]	MeOH	43	244–246	$C_{20}H_{23}IN_2OS_2$	I, 25.48	25.66
U4	QS3	3.25	QS4	4.3[a]	EtOH	25	5	29[c]	MeOH	67	246–247	$C_{20}H_{23}IN_2OS_2$	I, 25.48	25.53
U5	QS1	1.55	R4	1.0[d]	EtOH	15	15	61	MeOH	300	Above 300	$C_{22}H_{25}IN_2OS$	I, 25.78	25.75
U6	QS2	3.25	R4	2.0[d]	EtOH	35	5	3	EtOH	70	245–246	$C_{22}H_{26}IN_2S_2$	I, 24.97	24.95
U7	QS5	1.1	R4	0.7[d]	EtOH	10	5	44	EtOH	28	229–231	$C_{22}H_{25}IN_2S_2$	I, 24.97	24.89
***p*-Dimethylaminostyryl dyes**													
S1	QS1	1.6	R2	1.5[d]	EtOH	15	60	59	MeOH	35	233–235	$C_{19}H_{23}IN_2OS$	I, 28.70	28.80
S2	QS2	2.45	R2	1.15[d]	EtOH	15	30	4	EtOH	125	247–249	$C_{18}H_{23}IN_2S_2$	S, 13.99	13.78
S3	QS5	1.1	R2	0.5[d]	EtOH	10	15	67	MeOH	75	256–257	$C_{18}H_{23}IN_2S_2$	I, 27.70	27.90
Merocarbocyanine dyes													
M1	QS1	1.6	R3	1.5[a]	EtOH	25	15	49	MeOH	1200	234–235	$C_{15}H_{18}N_2O_2S_3$	N, 7.91	8.18
M2	QS2	3.25	R3	2.94[a]	EtOH	35	30	5.4	MeOH	125	231–232	$C_{15}H_{18}N_2OS_4$	S, 34.61	34.58
M3	QS5	1.1	R3	1.0[a]	C_5H_5N	10	5	20	MeOH	1000	235-236	$C_{15}H_{18}N_2OS_4$	S, 34.61	34.48

[a] Plus triethylamine as condensing agent. [b] After conversion to perchlorate. [c] After conversion to iodide. [d] Plus piperidine as catalyst. [e] Brooker and White, U. S. Patent 2,336,843 give m.p. 247–248°. The dyes appear as follows: C1, blue-black powder; C2, dark green needles with golden reflex; C3, dull blue powder; U1 and U2, magenta needles with silver reflex; U3, dull purple powder; U4, bright orange crystals; U5, brownish-orange crystals; U6, dull orange crystals; S1, bright red needles; S2, brown needles with metallic reflex; S3, large garnet prisms; M1, tiny red needles with silver reflex; M2, dark red crystals with blue reflex; M3, minute dark green needles with golden reflex.

TABLE II

OPTICAL DATA

Dye no.	Dye name	λmax, Å. Obsd., MeOH	Calcd.	Deviation, Å.
Symmetrical carbocyanine dyes				
C1	1,1′-DiEtbis-(6,7-dihydro-4H-pyrano(4,3d)thiazolo)-carbocyanine iodide	5700		
C2	1,1′-DiEtbis-(6,7-dihydro-4H-thiopyrano(4,3d)thiazolo)-carbocyanine perchlorate	5700		
C3	1,1′-DiEtbis-(6,7-dihydro-5H-thiopyrano(3,2d)thiazolo)-carbocyanine perchlorate	5720		
Unsymmetrical carbocyanine dyes				
U1	3,3′-DiEt-4′,5′,6′,7′-tetrahydro-oxathiacarbocyanine iodide	5140	5262	122
U2	1′,3-DiEt-6′,7′-dihydro-4′H-oxapyrano(4,3d)thiazolocarbocyanine iodide	5180	5262	82
U3	1′,3-DiEt-6′,7′-dihydro-4′H-oxathiopyrano(4,3d)thiazolocarbocyanine iodide	5180	5262	82
U4	1′,3-DiEt-6′,7′-dihydro-5′H-oxathiopyrano(3,2d)thiazolocarbocyanine iodide	5300	5272	−28
U5	1-Et-2′,5′-DiMe-1′-Ph-6,7-dihydro-4H-pyrano(4,3d)thiazolo-3′-pyrrolocarbocyanine iodide	4400	5092	692
U6	1-Et-2′,5′-DiMe-1′-Ph-6,7-dihydro-4H-thiopyrano(4,3d)thiazolo-3′-pyrrolocarbocyanine iodide	4400	5092	692
U7	1-Et-2′,5′-DiMe-1′-Ph-6,7-dihydro-5H-thiopyrano(3,2d)thiazolo-3′-pyrrolocarbocyanine iodide	4500	5102	602
***p*-Dimethylaminostyryl dyes**				
S1	2-*p*-Me2N-styryl-1-Et-6,7-dihydro-4H-pyrano(4,3d)thiazolium iodide	4900	5880	980
S2	2-*p*-Me2N-styryl-1-Et-6,7-dihydro-4H-thiopyrano(4,3d)thiazolium iodide	4900	5880	980
S3	2-*p*-Me2N-styryl-1-Et-6,7-dihydro-5H-thiopyrano(3,2d)thiazolium iodide	5060	5890	830
Merocarbocyanine dyes				
M1	3-Et-5-[(1-Et-6,7-dihydro-4H-pyrano(4,3d)(1H)thiazolylidene)-ethylidene]-rhodanine	5440	5510	70
M2	3-Et-5-[(1-Et-6,7-dihydro-4H-thiopyrano(4,3d)(1H)thiazolylidene)-ethylidene]-rhodanine	5440	5510	70
M3	3-Et-5-[(1-Et-6,7-dihydro-5H-thiopyrano(3,2d)(1H)thiazolylidene)-ethylidene]-rhodanine	5490	5520	30

obtained as a nearly colorless strong smelling oil which boiled at 110 to 115° at 15 mm., yield 4.5 g., 40%.

1-Ethyl-2-methyl-6,7-dihydro-4H-pyrano(4,3d)thiazolium Iodide (QS1).—The base (2.1 g., 1 mol) was refluxed with ethyl iodide (5 g., 1 mol + 150% excess) for 24 hr. The crystalline product was crushed under acetone, chilled and filtered. The nearly colorless crystals melted with decomposition at 142–143°, yield 3.5 g., 83%.

Anal. Calcd. for $C_9H_{14}INOS$: I, 40.80; N, 4.50; S, 10.30. Found: I, 40.84; N, 4.21; S, 10.18.

7-Bromo-2-methyl-6,7-dihydro-4H-pyrano(4,3d)thiazole.—3,5-Dibromotetrahydro-4-pyrone[3] (3.1 g., 1 mol), thioacetamide (1.5 g., 1 mol + excess) and absolute ethanol (25 ml.) were refluxed for 2 hr. The alcohol was evaporated and the residue was extracted with dilute HCl. The acid solution was washed with ether to remove tarry material,

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filtered and basified with NH_4OH. The oily product was taken up in ether, dried with K_2CO_3 and distilled. The product was a pale yellow oil boiling at 140–145° at 15 mm., yield 0.3 g., 9%.

7-Bromo-1-ethyl-2-methyl-6,7-dihydro-4H-pyrano(4,3d)-thiazolium Iodide.—The base (0.3 g., 1 mol) and excess ethyl iodide were refluxed for 6 hr. The oily brown precipitate crystallized on standing overnight. The crystals were collected, washed with acetone and recrystallized from absolute ethanol. The pale orange crystalline product melted at 164–168° dec., yield 50 mg., 10%.

Anal. Calcd. for $C_9H_{13}BrINOS$: N, 3.59; S, 8.22. Found: N, 3.69; S, 8.40.

2-Methyl-6,7-dihydro-4-H-thiopyrano(4,3d)thiazole (III).—Twenty grams of tetrahydro-1-thio-4-pyrone,[4] 30.5 g. of N-bromosuccinimide and 50 ml. of dry CCl_4 were gently warmed under reflux on the steam-bath until a violent reaction set in. The mixture was chilled in an ice-bath, filtered from succinimide and the filtrate was evaporated under water-pump vacuum until the CCl_4 was removed. The crude 3-bromo-tetrahydro-1-thio-4-pyrone thus obtained is unstable and must be used at once.

The product from the above reaction was diluted with 25 ml. of absolute ethanol, 12 g. of thioacetamide was added and the mixture was kept at 0° for 24 hr. followed by standing at room temperature for 3 days. The alcohol was distilled off under water-pump vacuum and the brown residue was extracted with 3% hydrochloric acid. After extracting the acid solution with ether to remove tarry impurities, the solution was made alkaline with $NaHCO_3$ and the oily base was taken up in ether. The ether solution was dried with anhydrous K_2CO_3, evaporated and the product was distilled under reduced pressure. The product was a pale yellow oil boiling at 125–135° at 8 mm. The yield was 5.0 g., 17%.

2-Methyl-6,7-dihydro-4H-thiopyrano(4,3d)thiazole Hydrochloride.—The base (16 g.) in absolute ether (500 ml.) was saturated with dry hydrogen chloride at 0°. The solvent was decanted from the sticky precipitate, and the latter was stirred with 150 ml. of acetone until crystallization occurred. After filtration and washing with acetone, the product was recrystallized from 100 ml. of absolute ethanol. The pale yellow crystals had m.p. 180–181°, yield 12.0 g., 62%.

Anal. Calcd. for $C_7H_{10}ClNS_2$: C, 40.43; H, 4.85; N, 6.74; S, 30.87. Found: C, 40.65; H, 4.88; N, 6.70; S, 31.00.

1-Ethyl-2-methyl-6,7-dihydro-4H-thiopyrano(4,3d)thiazolium Ethyl Sulfate (QS2).—For use in the dye syntheses, equimolecular proportions of the base and freshly distilled ethyl sulfate were heated at 110 to 115° for 5 minutes. The viscous product was used without purification.

2-Methyl-6,7-dihydro-5H-thiopyrano(3,2d)thiazole (IV).—Twenty-five grams (1 mol) of tetrahydro-1-thio-3-pyrone[5] was added to a mixture of 38.2 g. (1 mol) of N-bromosuccinimide and 50 ml. of dry carbon tetrachloride. After the initial vigorous reaction, the mixture was refluxed for 5 minutes. The mixture was chilled, the succinimide filtered and the filtrate evaporated as far as possible under reduced pressure. The product was mixed with 15.0 g. (1 mol) of thioacetamide and 100 ml. of absolute ethanol and allowed to stand at 0° for 3 hr., then overnight at room temperature and finally refluxed for 2 hr. The base was isolated and purified the same as IV above and was obtained as a pale yellow oil, b.p. 90 to 92° at 0.5 mm. The product crystallized on chilling. The yield was 13.4 g., 36%.

1-Ethyl-2-methyl-6,7-dihydro-5H-thiopyrano(3,2d)thiazolium Ethyl Sulfate (QS3).—The base was heated with ethyl sulfate the same as in the preparation of QS2 and the crude product was used in the dye syntheses.

1-Ethyl-2-methyl-6,7-dihydro-5H-thiopyrano(3,2d)thiazolium Iodide (QS5).—The base (10.0 g., 1 mol) was refluxed with ethyl iodide (20 g., 100% excess) for 16 hr. The crystalline product was crushed under ether, washed on the filter with acetone and dried. The yield of light tan crystals was 13.0 g., 68%. For analysis the product was recrystallized twice from absolute ethanol (10 ml. per g.). The pure material had m.p. 150–153° dec. *Anal.* Calcd. for $C_9H_{14}INS_2$: I, 38.80; N, 4.28; S, 19.60. Found: I, 38.51; N, 4.11; S, 19.52.

Absorption data for the new dyes are given in Table II.

MIDDLETOWN, CONNECTICUT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Some Methyl Derivatives of *p*-Quaterphenyl[1]

BY HENRY GILMAN AND EUGENE A. WEIPERT

RECEIVED SEPTEMBER 17, 1956

Condensation of *p*-terphenyl-4-yllithium and 4,4′-biphenylenedilithium with 2-, 3- and 4-methylcyclohexanone, followed by dehydration, has been used to synthesize monomethyltetrahydro-*p*-quaterphenyls and dimethyloctahydro-*p*-quaterphenyls, respectively. The corresponding *p*-quaterphenyl derivatives are formed by dehydrogenation with chloranil. The effect of structure on melting points and on solubilities is discussed.

Chain-type polyaryls have been shown to be superior solutes in liquid solution scintillators.[2–4] The use of hydrocarbons as solutes reaches a limit with *p*-terphenyl because those of higher molecular weight are limited by their sparing solubility in the commonly employed aromatic solvents. The introduction of methyl groups on the terminal rings of *p*-quaterphenyl seemed a direct method of surmounting this limitation in view of an expected decrease in melting point and increase in solubility corresponding to the reduction of symmetry. Also, of significance is the conclusion of Hayes, Ott and Rogers[3] that methyl groups do not generally cause an appreciable change in the scintillation ability of the solute.

Table I shows that this expectation was justified. It is interesting to note the marked correspondence of melting point and solubility in toluene through this series. Among the completely aromatic compounds the one outstanding increase in melting point occurs with the 4,4′′′-dimethyl compound (125° higher than the 3,3′′′-isomer), and this is accompanied by a drop to nearly complete insolubility. The 4-methyl derivative is rather unusual in that it melts higher than the more symmetrical parent hydrocarbon (320°) while it is slightly more soluble. The series of compounds containing cyclohexene rings exhibits the same trends but in more pronounced fashion. While the melting points are somewhat unreliable because of decomposition of those melting above 200°, it is evident that the close grouping of melting points in the three monomethylated compounds is a reflection of a similar situation in the completely aro-

(1) This work was supported by the United States Atomic Energy Commission under Contract No. AT(11-1)-59.
(2) H. Kallman and M. Furst, *Nucleonics*, **8**, No. 3, 32 (1950).
(3) F. Hayes, D. Ott and B. Rogers, *ibid.*, **13**, No. 12, 38 (1955).
(4) F. Hayes, D. Ott and V. Kerr, *ibid.*, **14**, No. 1, 42 (1956)

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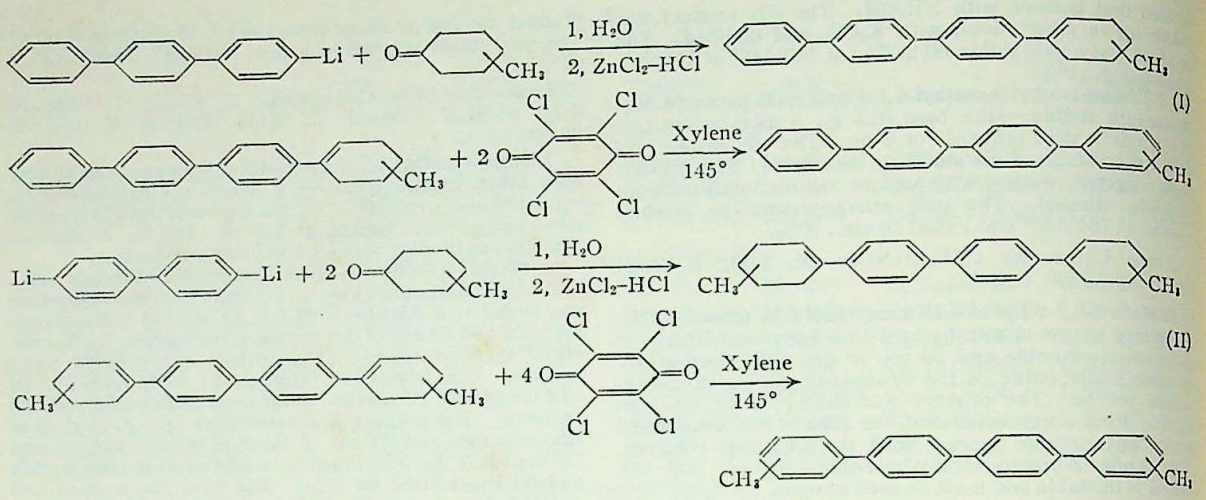

matic series. The melting points of the monomethyl-*p*-quaterphenyls proceed from 172 to 330° and the solubilities drop from 26 g./l. to only 1 g./l. In the partially saturated series the span of melting points is only between 184 and 208° while the solubilities drop from 48 to 4 g./l. With methyl groups on both terminal rings the scope of these variations is greatly magnified: the 4,4‴-derivatives being very high melting and comparatively insoluble, while the 2,2‴-dimethyl compounds have surprisingly low melting points and high solubilities in view of their molecular weight and symmetry.

TABLE I

MELTING POINTS AND SOLUBILITIES OF SOME METHYLATED *p*-QUATERPHENYLS

Substituent	*p*-Quaterphenyl derivative M.p., °C.	*p*-Quaterphenyl derivative Solubility in toluene, g./l.	Tetrahydro (or octahydro) derivative M.p., °C.	Tetrahydro (or octahydro) derivative Solubility in toluene, g./l.
2-Methyl	172–173	26.0	184–185	48.0
3-Methyl	244–245	3.0	200 dec.	10.7
4-Methyl	328–330	1.2	208 dec.	3.8
2,2‴-Dimethyl	150–151	36.0	108–109	86.0
3,3‴-Dimethyl	214–215	6.3	149–150	35.0
4,4‴-Dimethyl	338–340	0.2	225 dec.	2.7
Unsubstituted	320[a]	0.8		

[a] F. Ullmann and G. M. Meyer, *Ann.*, **332**, 52 (1904).

The monomethyl derivatives were prepared by condensation of *p*-terphenyl-4-yllithium with the appropriately substituted methylcyclohexanone, followed by dehydration of the intermediate carbinol and dehydrogenation of the olefin according to scheme I. In analogous fashion the symmetrically dimethylated quaterphenyls were prepared from 4,4′-dilithiobiphenyl according to scheme II.

Of the numerous methods available for dehydration of the intermediate cyclohexanol derivatives, vigorous stirring with Lucas reagent as prescribed by Crawford and Nelson[5] was clearly superior. Most of the more common acid catalysts require conditions that afford poor contact between these intractable carbinols and the reagent. In using the Lucas reagent it is not even necessary to isolate the crude carbinol, since it is dehydrated in the benzene solution resulting directly from the organometallic-ketone reaction.

Dehydrogenation to the aromatic system with sulfur and selenium gave poor yields and led to difficulties in purification. The method of Arnold and Collins[6] employing chloranil as the oxidant in refluxing xylene proved to be much cleaner and provided satisfactory yields. Isolation and purification of the product from this oxidation was more conveniently carried through as suggested by Crawford and Nelson[5] since the products could not be distilled under reasonable conditions.

The compounds described at this time were prepared incidental to a study concerned with organic liquid solution scintillators. Evaluation of the compounds for this purpose is being made by Drs. Wright H. Langham, F. Newton Hayes and Donald G. Ott of the Los Alamos Laboratories who will report the results later.

Experimental[7]

4-(Methyl-1-cyclohexen-1-yl)-*p*-terphenyl.—To a stirred solution of 0.040 mole of *p*-terphenyl-4-yllithium[8] in 130 ml. of ether was added 4.71 g. (0.042 mole) of 2-methylcyclohexanone in 60 ml. of benzene. The suspension was stirred at gentle reflux for 30 minutes, then cooled and hydrolyzed with 50 ml. of 10% hydrochloric acid. An additional 150 ml. of benzene was added, and the layers were separated. The organic layer was distilled until the temperature reached 60° and the remaining benzene suspension stirred at gentle reflux for 2 hr. with 60 ml. of Lucas reagent. The layers were separated and the organic layer washed with water, sodium bicarbonate and water again. Evaporation of the benzene solution left a gummy residue which was crystallized from 150 ml. of 1:1 benzene–ethanol to give 8.70 g. (68%) of white powder, melting over the range 168–174°. After seven recrystallizations from benzene–ethanol there remained 5.50 g. (43%) of white plates, melting at 184–185°. The product turned pale yellow upon exposure to direct sunlight.

Anal. Calcd. for $C_{25}H_{24}$: C, 92.59; H, 7.41. Found: C, 92.50; H, 7.67.

2-Methyl-*p*-quaterphenyl.—A mixture of 3.24 g. (0.010 mole) of 4-(methyl-1-cyclohexen-1-yl)-*p*-terphenyl and 4.96 g. (0.020 mole) of chloranil was heated in 50 ml. of refluxing xylene for 12 hr. The mixture was cooled and diluted with 150 ml. of petroleum ether (b.p. 60–70°). The precipitated brown solid was filtered and extracted with 50 ml. of hot ethyl acetate. This extract was diluted with

(5) H. M. Crawford and H. B. Nelson, THIS JOURNAL, **68**, 1241 (1946).

(6) R. T. Arnold and C. Collins, *ibid.*, **61**, 1407 (1939).

(7) All melting points are uncorrected. Reactions involving organolithium reagents were carried out under an atmosphere of dry, oxygen-free nitrogen and sodium dried solvents.

(8) H. Gilman and E. A. Weipert, *J. Org. Chem.*, **22**, in press (1957).

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50 ml. of benzene and combined with the xylene–ligroin filtrate. The combined organic solution was extracted with three 60-ml. portions of 5% potassium hydroxide, then evaporated to dryness. The residue was crystallized twice from a 1:3 benzene–ethanol mixture to give 1.24 g. (38.7%) of pale yellow material melting at 170–172°. Sublimation of this material at 160° (0.01 mm.) and recrystallization of the sublimate from the same solvent mixture afforded white needles melting at 172–173°.

Anal. Calcd. for $C_{25}H_{20}$: C, 93.75; H, 6.25. Found: C, 93.57; H, 6.39.

4-(Methyl-1-cyclohexen-1-yl)-*p*-terphenyl.—Using the same quantities and conditions as described for the 2-methyl isomer, there was obtained 6.25 g. (49%) of shiny plates from benzene which melted at 200° with decomposition.

Anal. Calcd. for $C_{25}H_{24}$: C, 92.59; H, 7.41. Found: C, 92.31; H, 7.72.

3-Methyl-*p*-quaterphenyl.—Chloranil oxidation as above and recrystallization from benzene afforded a 62% yield of nearly white plates melting at 244–245.5°. The analytical sample was obtained by sublimation at 210° (0.01 mm.) and melted at 245–246°.

Anal. Calcd. for $C_{25}H_{20}$: C, 93.75; H, 6.25. Found: C, 93.43; H, 6.51.

4-(4-Methyl-1-cyclohexen-1-yl)-*p*-terphenyl.—Once again the same quantities and conditions were employed; however, the crude product after treatment with Lucas reagent melted over the range 205–235° and resisted purification by recrystallization. The crude material was sublimed at 200° (0.01 mm.) to provide 3.15 g. (32%) of white material with a melting range of 204–208°. Recrystallization from benzene raised this to 208° with decomposition.

Anal. Calcd. for $C_{25}H_{24}$: C, 92.59; H, 7.41. Found: C, 92.69; H, 7.42.

4-Methyl-*p*-quaterphenyl.—4-(4-Methyl-1-cyclohexen-1-yl)-*p*-terphenyl (1.62 g., 0.005 mole) was dehydrogenated with 2.48 g. (0.010 mole) of chloranil in 25 ml. of xylene by refluxing for 8 hr. Upon dilution of the xylene solution with petroleum ether as before, both the product and the dihydrochloranil precipitated. This mixture was extracted continuously with hot ethanol to remove dihydrochloranil and then with toluene which dissolved the desired product. When cooled, the toluene extract deposited 1.05 g. (65.6%) of nearly white plates having a melting range of 322–329°. Sublimation at 210° (0.01 mm.), followed by recrystallization from toluene, afforded 0.64 g. (38%) of clear plates melting at 328–330°.

Anal. Calcd. for $C_{25}H_{20}$: C, 93.75; H, 6.25. Found: C, 94.04; H, 5.98.

4,4′-Bis-(methyl-1-cyclohexen-1-yl)-biphenyl.—To a solution of 0.025 mole of 4,4′-biphenylenedilithium[9] in 100 ml. of 1:1 benzene–ether was added, over a period of 30 minutes, a solution of 5.72 g. (0.051 mole) of 2-methylcyclohexanone in 50 ml. of benzene. The resulting gray-green suspension was stirred at gentle reflux for 3 hr., then hydrolyzed with 50 ml. of 10% hydrochloric acid. The layers were separated and the organic layer washed with water and filtered from a trace of solid material. This solution was distilled until the temperature had reached 60° and the remaining benzene solution stirred at gentle reflux with 60 ml. of Lucas reagent for 2 hr. The oily solid obtained from the organic layer was crystallized from 100 ml. of ethanol to give 1.51 g. (18%) of shiny plates having a melting range of 98–103°. Two recrystallizations from ethanol raised the melting point to 107–108°. The analytical sample melted at 108.5–109°.

Anal. Calcd. for $C_{26}H_{30}$: C, 91.23; H, 8.77. Found: C, 91.07; H, 8.86.

2,2‴-Dimethyl-*p*-quaterphenyl.—The octahydro derivative (1.37 g., 0.004 mole) was treated with 3.94 g. (0.016 mole) of chloranil in 25 ml. of refluxing xylene for 12 hr. to give 0.59 g. (44%) of crude product melting over the range 125–134°. Sublimation at 120° (0.01 mm.) gave white needles having a melting range of 142–146°. Four recrystallizations from ethanol produced a pure sample melting at 150–151°.

Anal. Calcd. for $C_{26}H_{22}$: C, 93.41; H, 6.59. Found: C, 93.45; H, 6.58.

4,4′-Bis-(methyl-1-cyclohexen-1-yl)-biphenyl.—Employing quantities and conditions identical to those used for the 2-methyl isomer there was obtained 3.32 g. (39%) of pale yellow material melting at 144–146°. After four recrystallizations from 1:1 ethanol–benzene the shiny, white plates melted at 149–150°.

Anal. Calcd. for $C_{26}H_{30}$: C, 91.23; H, 8.77. Found: C, 91.31; H, 8.77.

3,3‴-Dimethyl-*p*-quaterphenyl.—Chloranil oxidation of 1.67 g. (0.005 mole) of 4,4′-bis-(methyl-1-cyclohexen-1-yl)-biphenyl produced 0.41 g. (24%) of nearly white material having a melting range of 210–215°. Sublimation at 210° (0.01 mm.) left 0.30 g. (19%) of clear plates melting at 214–215°.

Anal. Calcd. for $C_{26}H_{22}$: C, 93.41; H, 6.59. Found: C, 93.24; H, 6.64.

4,4′-Bis-(4-methyl-1-cyclohexen-1-yl)-biphenyl.—Again using the same quantities and conditions as in the preparation of the 2-methylcyclohexenyl derivative, there was recovered 2.70 g. (31%) of shiny white plates which gradually melted to a yellow-orange liquid over the range of 215–223°. Two recrystallizations from benzene left 2.20 g. (26%) which decomposed at 225°.

Anal. Calcd. for $C_{26}H_{30}$: C, 91.23; H, 8.77. Found: C, 90.77; H, 8.91.

4,4‴-Dimethyl-*p*-quaterphenyl.—Oxidation of 1.67 g. (0.005 mole) of the bis-cyclohexene compound prepared above with chloranil gave 0.81 g. (58%) of gray powder which charred slowly above 320°. After sublimation at 210° (0.01 mm.) and recrystallization from toluene there was recovered 0.26 g. (18%) of white powder melting at 338–340°. Pummerer and Seligsberger[10] reported 334° for this compound.

(9) H. Gilman, W. Langham and F. W. Moore, THIS JOURNAL, **62**, 2327 (1940).

(10) J. Pummerer and F. Seligsberger, *Ber.*, **64B**, 2485 (1931).

AMES, IOWA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, VETERANS ADMINISTRATION HOSPITAL]

Studies in the Naphthalene Series. III. Synthesis of Apogossypol Hexamethyl Ether[1]

BY J. D. EDWARDS, JR., AND J. L. CASHAW

RECEIVED NOVEMBER 16, 1956

Apogossypol hexamethyl ether, the primary degradation product of gossypol, the pigment and toxic principle in cottonseed, formulated by Adams as 2,2′-bi-5-isopropyl-1,6,7-trimethoxy-3-methylnaphthyl has been synthesized by the oxidative coupling of 5-isopropyl-1,6,7-trimethoxy-3-methyl-1-naphthol and methylation of the resulting binaphthol.

Gossypol, the yellow pigment of cottonseed, has been the subject of extensive work[2] and was for-

(1) Preliminary communication: J. D. Edwards, Jr., and J. L. Cashaw, THIS JOURNAL, **78**, 3224 (1956).

(2) For a review of these studies see F. Mayer and A. H. Cook, "The Chemistry of Natural Coloring Matters," Reinhold Publishing Corp., New York, N. Y., 1943, pp. 114–117; R. D. Haworth, *Ann. Repts. Progr. Chem.* (Chem. Soc. London), **36**, 284 (1939); C. H. Boatner "Cotton Cellulose and Derived Products," edited by A. E. Bailey, Interscience Publishers, Inc., New York, N. Y., 1948, Chap. VI, pp. 213–363.

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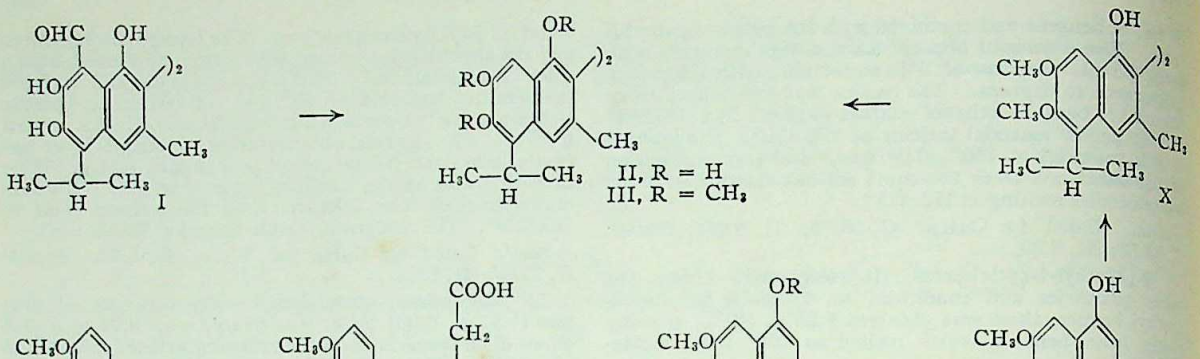

mulated by Adams[3] as 2,2′-bi-1,6,7-trihydroxy-3-methyl-5-isopropyl-8-formylnaphthyl (I), as a result of his degradation studies. The postulated structure of desapogossypolone tetramethyl ether[3] was later shown to be correct by synthesis.[4] Heating of gossypol in concentrated sodium hydroxide results in the formation of apogossypol[5–7] (II), which is very unstable even in the solid state. Methylation gives apogossypol hexamethyl ether (III) which was, to a large extent, used for the degradation studies by Adams.[3]

The synthesis reported in this communication establishes conclusively the correctness of Adams' formulation[3] as to the relationship of the internuclear linkage and the groups at the 1-, 3- and 5-positions in apogossypol and desapogossypol hexamethyl ethers. This relationship has been questioned recently.[8]

The synthesis of 5-isopropyl-6,7-dimethoxy-3-methyl-1-naphthol (IX), the key intermediate in the synthesis here reported, utilized 2-isopropyl-3,4-dimethoxybenzaldehyde (IV)[9] as the starting material. The condensation of IV with diethyl succinate gave the half-ester V. Cyclodehydration of V with sodium acetate and acetic anhydride[10] gave the acetate VI which on saponification yielded 1-hydroxy-5-isopropyl-6,7-dimethoxy-3-naphthoic acid (VII). Reduction of VII with lithium aluminum hydride gave 3-hydroxymethyl-5-isopropyl-6,7-dimethoxy-1-naphthol (VIII). Hydrogenolysis of VIII with palladium-on-charcoal gave the naphthol IX.

In the preliminary studies[1] the oxidative coupling of IX to 2,2′-bi-1-(5-isopropyl-6,7-dimethoxy-3-methyl)-naphthol (X)[11] was achieved in a low yield by use of ferric chloride[12] with purified dioxane as the solvent. Later it was found that the coupling of IX to X occurred in quantitative yield by merely heating IX above its melting point. The over-all yield from IV to X was 26%. Methylation of X using aqueous dioxane as the solvent gave 2,2′-bi-5-isopropyl-1,6,7-trimethoxy-3-methylnaphthyl (III) identical in all respects with apogossypol hexamethyl ether (III) prepared from gossypol.

Acknowledgment.—The encouragement and interest of Professor R. B. Turner is gratefully acknowledged.

Experimental[13]

1-Hydroxy-5-isopropyl-6,7-dimethoxy-3-naphthoic Acid. (a) **Stobbe Condensation.**—To a mixture of 3.8 g. of sodium hydride in 30 ml. of anhydrous benzene there was added with stirring a solution of 27 g. of diethyl succinate and 11 g. of 2-isopropyl-3,4-dimethoxybenzaldehyde[9] in 50 ml. of benzene. This mixture was heated at 50° for 1 hr. after 0.75 ml. of alcohol was added. After cooling, water was added and the mixture extracted with ether. The aqueous phase was acidified and extracted with ether. The two ethereal extracts were combined and extracted with 250 ml. of 5% sodium carbonate solution. The aqueous extract was cooled and acidified with dilute hydrochloric acid. The oily precipitate was taken up in ether and dried over anhydrous sodium sulfate. Evaporation of the ether gave 14.2 g. (80%) of the oily half-ester V.

(b) **Ring Closure and Saponification.**—To 14.2 g. of the crude half ester, there was added 63.5 ml. of acetic acid, 63.5 ml. of acetic anhydride and 3 g. of fused sodium acetate. After refluxing for 4 hr., the light yellow solution was evaporated under a current of air and the semi-crystalline residue treated with 100 ml. of 5% sodium carbonate. The product was extracted with ether, and after drying over sodium sulfate, the ether was removed over a steam-bath. The crude oily product VI was then treated with 350 ml. of methanol and 350 ml. of 10% sodium hydroxide and refluxed for 3 hr. The alcohol was evaporated over a steam-bath and the aqueous extract acidified to give 10.6 g. (86%) of

(3) R. Adams, R. C. Morris, T. A. Giessman, D. J. Butterbaugh and E. C. Kirkpatrick, THIS JOURNAL, **60**, 2193 (1938).

(4) R. Adams and B. R. Baker, *ibid.*, **63**, 535 (1941).

(5) F. E. Carruth, *ibid.*, **40**, 647 (1918).

(6) E. P. Clark, *J. Biol. Chem.*, **78**, 159 (1928).

(7) R. Adams and D. J. Butterbaugh, THIS JOURNAL, **60**, 2174 (1938).

(8) D. A. Shirley and W. L. Dean, *ibid.*, **77**, 6077 (1955).

(9) J. D. Edwards, Jr., and J. L. Cashaw, *ibid.*, **78**, 3821 (1956).

(10) W. S. Johnson and R. B. Graber, *ibid.*, **72**, 933 (1950).

(11) Since methylation of the binaphthol obtained gave a product identical with apogossypol hexamethyl ether, there can be no question that the coupling occurred at the 2-position in IX. This follows since desapogossypolone tetramethyl ether, which is obtained from apogossypol hexamethyl ether, has been shown[3] by synthesis to possess the 2,2′-linkage. A study of Fisher–Taylor–Hirschfelder models also shows that the 4-position in IX is so masked by the methyl and isopropyl groups that no coupling to give the 4,4′-bi-1-naphthol can occur.

(12) J. D. Edwards, Jr., and J. L. Cashaw, THIS JOURNAL, **76**, 6141 (1954).

(13) All analyses were done by the Huffman Microanalytical Laboratories, Wheatridge, Colorado. Melting points are uncorrected and were made on a Fisher–Johns apparatus. The infrared determinations were carried out on a Perkin–Elmer model 21 spectrophotometer, 0.1 mm. cells, solvent chloroform, concentration approximately 7%.

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May 5, 1957

VII. Crystallization from benzene gave material of m.p. 226–227°. The infrared spectrum[13] exhibited carbonyl absorption at 1680 and hydroxyl absorption at 3380 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.18; H, 6.26. Found: C, 66.32; H, 6.23.

3-Hydroxymethyl-5-isopropyl-6,7-dimethoxy-1-naphthol (VIII).—To 4 g. of lithium aluminum hydride in 200 ml. of absolute ether there was added dropwise a solution of 4.5 g. of VII in 100 ml. of ether. The mixture was refluxed for 90 minutes and allowed to stand overnight. After cooling, the mixture was decomposed by the dropwise addition of water and then acidified with dilute hydrochloric acid. After separation, the ethereal extract was washed twice with water and dried over anhydrous sodium sulfate. The ether was removed over a steam-bath and the residue crystallized from benzene to give 3.9 g. (93%) of VIII, m.p. 207–209°. The infrared spectrum[13] showed hydroxyl group absorption at 3420 and 3300 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.53; H, 7.31. Found: C, 69.71; H, 7.20.

5-Isopropyl-6,7-dimethoxy-3-methyl-1-naphthol (IX).—To 0.15 g. of palladium-on-charcoal (10%) in 35 ml. of methanol there was added 0.5 g. of VIII in 65 ml. of methanol. One drop of concd. hydrochloric acid in 1 ml. of water was added to this mixture. It was then hydrogenated for 20 minutes in a Parr low pressure hydrogenator. Anhydrous sodium sulfate was added and the mixture suction filtered. After removal of the methanol over a steam-bath, the product was recrystallized from chloroform–petroleum ether (30–60°) to give 0.192 g. (41%) of IX, m.p. 129–130°. The infrared spectrum[13] showed the presence of an hydroxyl group (sharp band at 3570 and a broad band at 3310 cm.$^{-1}$).

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.76; H, 7.78.

2,2′-Bi-1-(5-isopropyl-6,7-dimethoxy-3-methyl)-naphthol (X).—A test-tube containing 0.2 g. of IX was placed in an oil-bath heated to 150°; the temperature was allowed to rise to 215° and held there for 20 minutes or until the material had melted and solidified. The product was recrystallized from benzene–methanol to give a quantitative yield of X, m.p. 271–274°.

Anal. Calcd. for $C_{32}H_{38}O_6$: C, 74.10; H, 7.38; mol. wt., 518. Found: C, 74.21; H, 7.39; mol. wt. (Rast), 447.

2,2′-Bi-5-isopropyl-1,6,7-trimethoxy-3-methylnaphthyl (III).—To a solution of 0.24 g. of X in 25 ml. of purified dioxane[14] there was added 5 ml. of an aqueous solution of 0.49 g. of potassium hydroxide. To this mixture there was added 1.1 g. of dimethyl sulfate which was then heated under reflux until reaction was complete as indicated by litmus paper. The additions of potassium hydroxide and dimethyl sulfate were repeated two times. After cooling, water was added and the reaction mixture extracted with dichloromethane. The dichloromethane phase was extracted several times with water. After drying over anhydrous sodium sulfate, the dichloromethane was removed over a steam-bath and the residue taken up in 25 ml. of diethyl ether and filtered. Upon standing 0.1 g. (42%) of 2,2′-bi-5-isopropyl-1,6,7-trimethoxy-3-methylnaphthyl (III) crystallized. It was recrystallized several times from benzene–methanol, m.p. 277–279°; mixture m.p. with apogossypol hexamethyl ether prepared from gossypol, 277–278°. The infrared[13] spectra of the natural and synthetic product were indistinguishable.

(14) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p. 285.

HOUSTON, TEXAS

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

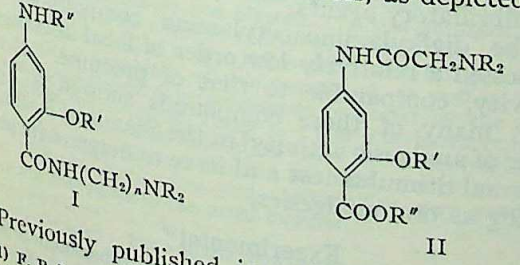
Derivatives of 4-Amino-2-hydroxybenzoic Acid. IV. Amides

BY R. O. CLINTON, S. C. LASKOWSKI, U. J. SALVADOR, HELEN G. BATES AND PATRICIA M. CARROLL

RECEIVED OCTOBER 15, 1956

Several types of amides derived from the 4-amino-2-hydroxybenzoic acid nucleus have been prepared. The first type consisted of N-(dialkylaminoalkyl)-4-amino-2-hydroxybenzamides and the related 2-alkoxy and 4-alkylamino compounds. Several of these compounds possessed outstanding activity as antifibrillatory agents. The second series was of the general type represented by an alkyl 4-(dialkylaminoacetylamino)-2-alkoxybenzoate and its related derivatives. The latter compounds were, in general, only fair local anesthetics but in certain cases possessed substantial analgesic properties. Finally, a series of variants on the 4-amino-2-alkoxybenzamide nucleus were prepared; certain of these compounds were potent oral analgesics.

The observation[1] that a very high degree of local anesthetic activity was associated with certain basic ester and thiol ester derivatives of 4-amino-2-hydroxy- and 2-alkoxybenzoic acids[2] prompted an extension of the synthetic work to two types of basic amides related to these series, as depicted in I and II.



I II

Previously published investigations[3–5] of N-ω-dialkylaminoalkylbenzamides have shown that the simple amides were considerably less active as local anesthetics than their ester counterparts and that even in the cases of 3-alkoxy-[4] or 4-alkoxy-[5] substitution the local anesthetic activity does not surpass that of the esters. However, since in the present series a very high degree of local anesthetic activity was associated with the basic ester counterparts[1] of I, it was felt that a reduction in the degree of local anesthetic activity would not be a serious defect. Further, the increased stability of the amide linkage toward hydrolysis might well be reflected in more desirable physiological properties.

The synthesis of the amides of type II was based upon the premise that the low toxicity associated

(1) F. P. Luduena and J. O. Hoppe, *J. Pharmacol. Exptl. Therap.*, **104**, 40 (1952), and subsequent papers.

(2) (a) R. O. Clinton, S. C. Laskowski, U. J. Salvador and Mary Wilson, THIS JOURNAL, **73**, 3674 (1951); (b) **74**, 592 (1952); (c) R. O. Clinton, U. J. Salvador and S. C. Laskowski, *ibid.*, **76**, 5181 (1954).

(3) H. Wenker, *ibid.*, **60**, 1081 (1938); (4) F. F. Blicke, H. C. Parke and E. L. Jenner, *ibid.*, **62**, 3316 (1940); R. O. Clinton, U. J. Salvador and S. C. Laskowski, *ibid.*, **71**, 3839 (1949).

(4) J. Büchi, E. Stünzi, M. Flury, R. Hirt, P. Labbart and L. Ragaz, *Helv. Chim. Acta*, **34**, 1002 (1951).

(5) A. Kolosy, P. Teyssié and H. Vanderhaeghe, *J. Pharm. Pharmacol.*, **7**, 477 (1955).

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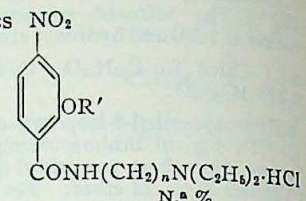
TABLE I

N-(DIETHYLAMINOALKYL)-2-ALKOXY- OR 2-HYDROXY-4-NITROBENZAMIDE HYDROCHLORIDES



n	R′	M.p., °C.	Formula	Chlorine, % Calcd.	Chlorine, % Found	N,[a] % Calcd.[a]	N,[a] % Found[a]
2	H	149.6–150.2	$C_{13}H_{20}ClN_3O_4$	11.16	11.12	[c]	[c]
3	H	137.8–138.8	$C_{14}H_{22}ClN_3O_4$	10.69	10.62	4.22[d]	4.21[d]
4	H	146.0–146.9	$C_{15}H_{24}ClN_3O_4$	10.25	10.09	[e]	[e]
2	CH_3	161.2–162.7	$C_{14}H_{22}ClN_3O_4$	10.69	10.49	4.22	4.14
3	CH_3[g]	149.1–150.0	$C_{15}H_{24}ClN_3O_4$	10.25	10.33	[f]	[f]
4	CH_3	116.4–119.6	$C_{16}H_{26}ClN_3O_4$	9.85	10.10	..	..
[b]	CH_3[h]	153.6–155.0	$C_{15}H_{24}ClN_3O_5$	9.80	9.62	3.87	3.99
3	C_2H_5[i,j]	133.4–135.0	$C_{16}H_{26}ClN_3O_4$	9.85	9.99	3.89	3.83
2	n-C_3H_7[k,l,m]	164.8–167.9	$C_{16}H_{26}ClN_3O_4$	9.85	9.96	3.89	4.14
2	n-C_4H_9[n,o,p]	133.2–134.2	$C_{17}H_{28}ClN_3O_4$	9.48	9.57	3.74	3.74
2	n-C_6H_{13}[q]	90.1–108.9	$C_{19}H_{32}ClN_3O_4$	8.82	8.77	3.49	3.44
2	n-C_8H_{17}[r]	128.0–129.4	$C_{21}H_{36}ClN_3O_4$	8.25	8.35	3.26	3.30

[a] Ref. 10. [b] 3-Diethylamino-2-hydroxy-1-propyl. [c] Calcd.: C, 49.13; H, 6.34. Found: C, 49.35; H, 6.10. [d] Calcd.: C, 50.67; H, 6.68. Found: C, 50.72; H, 6.50. [e] Calcd.: C, 52.09; H, 7.00. Found: C, 52.23; H, 6.70. [f] Calcd.: C, 52.09; H, 7.00. Found: C, 52.16; H, 6.88. [g] Picrate m.p. 152.8–153.8°. Calcd.: neut. equiv., 538; basic N, 2.60. Found: neut. equiv., 546; basic N, 2.62. [h] Picrate m.p. 151.0–152.0°. Calcd.: neut. equiv., 554; basic N, 2.52. Found: neut. equiv., 549; basic N, 2.33. [i] Base, m.p. 62.0–62.9°. Calcd.: N[a], 4.33; basic N, 4.33. Found: N[a], 4.24; basic N, 4.31. [j] Flavianate m.p. 185.9–187.1°. Calcd.: S, 5.03. Found: S, 5.04. [k] Base m.p. 64.4–65.0°. Calcd.: N, 12.99. Found: N, 13.28. [l] Methiodide m.p. 169.8–170.5°. Calcd.: N[a], 3.01; I, 27.28. Found: N[a], 3.05; I, 27.28. [m] Picrate m.p. 161.6–162.6°. Calcd.: neut. equiv., 552; basic N, 2.53. Found: neut. equiv., 546; basic N, 2.48. [n] Base m.p. 49.9–50.9°. Calcd.: N, 12.45. Found: N, 12.32. [o] Methiodide m.p. 136.5–137.6°. Calcd.: N[a], 2.92; I, 26.48. Found: N[a], 3.09; I, 26.40. [p] Picrate m.p. 164.5–165.3°. Calcd.: neut. equiv., 566; basic N, 2.47. Found: neut. equiv., 563; basic N, 2.41. [q] Picrate m.p. 110.2–112.0°. Calcd.: N[a], 9.42. Found: N[a], 9.29. [r] Base m.p. 51.8–52.7°. Calcd.: N, 10.68. Found: N, 10.70.

with Nirvanine[6] [methyl 5-(diethylaminoacetylamino)-2-hydroxybenzoate] might well be retained in the corresponding 4-dialkylaminoacetylamino series, while simultaneously achieving a very desirable reduction in irritation. Since the completion of this investigation, two examples of compounds related to II have been published.[7] Both compounds were hydroxy acids (II, R′ = R″ = H), prepared for testing as antitubercular agents.

In the two formulas shown, I and II, the various indicated substituent R, R′ and R″ groups were varied sufficiently to ensure the attainment, if possible, of a wide range of local anesthetic activity. In addition to the alkyl esters of II, several of the related benzamides and benzoic acids were prepared for comparison.

The benzamides of type I were prepared either by the aminolysis of a 4-nitrosalicylic ester or by the reaction between an alkoxynitrobenzoyl chloride and an amine. Subsequent reduction by conventional means led to the 4-aminobenzamides and thence by reductive alkylation to the 4-alkylaminobenzamides. These compounds are listed in Tables I, II and III and are described in the Experimental section.

The amides of type II were in general prepared by the reaction of an alkyl 2-alkoxy-4-aminobenzoate with chloroacetyl chloride, followed by amination by the appropriate secondary amine. Similar methods were used for the amide types (II, $CONH_2$ in place of COOR″). This series is summarized in Tables IV and V.

The initial observation[8] that 4-amino-2-alkoxybenzamides possessed oral analgesic activity of the order of aminopyrine in the standard Radiant Thermal Stimulus test, prompted the synthesis of a large number of variants on the former nucleus. These compounds were synthesized by straightforward methods with little difficulty; they are summarized in Table VI and in the Experimental section.

Pharmacological testing[9] of the N-dialkylaminoalkyl benzamide types, I, has indicated a high degree of local anesthetic activity for those compounds where R′ is greater than ethyl. In general this activity is less than that found for the corresponding esters, while toxicity and irritancy are similar to those found for the esters. Several of the higher members of the series, in particular N-(2-diethylaminoethyl)-4-amino-2-hexoxybenzamide (Win 8568), have shown outstanding properties as antifibrillatory agents.

The dialkylaminoacetylamino compounds, II, possessed a relatively low order of local anesthetic activity, comparable to that of procaine. However, many of these compounds showed a high order of analgesic activity[8] in the Standard Radiant Thermal Stimulus test and have undergone further testing as oral analgesics.

Experimental[10]

N-(Diethylaminoethyl)-2-hydroxy-4-nitrobenzamide Hydrochloride.—A mixture of 16.7 g. (0.079 mole) of ethyl 4-

(6) A. Einhorn and M. Oppenheimer, *Ann.*, **311**, 155 (1900).

(7) R. Hirt and H. Hurni, *Helv. Chim. Acta*, **32**, 378 (1949); British Patents 665,675 and 676,363.

(8) J. R. Lewis and J. O. Hoppe, to be published.

(9) L. Grumbach and J. O. Hoppe, to be published.

(10) All melting points were determined in a modified Hershberg Apparatus, using total immersion N.B.S. calibrated thermometers

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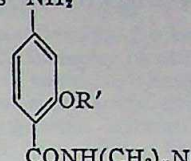
TABLE II

N-DIETHYLAMINOALKYL-4-AMINO-2-ALKOXY- OR 2-HYDROXYBENZAMIDES

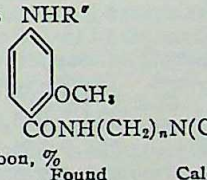


n	R′	M.p. °C.	Formula	Type[a]	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
2	H	179.0–182.0	$C_{14}H_{25}Cl_2N_3O_2$	DH	[b]	[b]	20.96	20.70
3	H	156.8–159.6	$C_{15}H_{26}ClN_3O_2$	H	13.31	13.16	11.23	11.12
4	H	167.9–170.8	$C_{14}H_{26}N_3O_6P$	P	11.56	11.41	26.98[d]	27.35[d]
2	CH_3[c]	212.0–213.1	$C_{15}H_{28}N_2O_6P$	P	11.13	10.91	25.98[d]	25.92[d]
4	CH_3[e]	197.0–199.0	$C_{16}H_{30}N_3O_6P$	P	10.74	10.43	...	...
3	C_2H_5[h]	204.0–205.6	$C_{16}H_{28}ClN_3O_2$	H	12.74	12.75	10.75	10.52
2	n-C_3H_7[i,j]	232.7–233.7	$C_{16}H_{28}ClN_3O_2$	H	12.74	12.72	10.75	10.88
2	n-C_4H_9[k,l]	199.0–199.6	$C_{17}H_{30}ClN_3O_2$	H	12.22	12.24	10.31	10.39
2	n-C_6H_{13}	137.9–139.7	$C_{19}H_{34}ClN_3O_2$	H	11.30	11.38	9.52	9.47
2	n-C_8H_{17}	87.6–90.2	$C_{21}H_{38}ClN_3O_2$	H	10.51	10.55	8.86	8.87

[a] P = phosphate; H = hydrochloride; DH = dihydrochloride. [b] Calcd.: C, 49.71; H, 7.45. Found: C, 49.47; H, 7.27. [c] Flavianate m.p. 199.8–202.8°. Calcd.: N, 12.08. Found: N, 12.08. [d] Phosphoric acid analysis. [e] Flavianate m.p. 186.5–188.2°. Calcd.: S, 5.24. Found: S, 5.26. [f] Calcd.: C, 47.73; H, 6.67. Found: C, 47.74; H, 6.83. [g] Flavianate m.p. 231.2–231.9° dec. Calcd.: neut. equiv., 303; N^a, 4.61. Found: neut. equiv., 298; N^a, 4.54. [h] Flavianate m.p. 208.8–209.1°. Calcd.: S, 5.28. Found: S, 5.40. [i] Diflavianate m.p. 209.0–210.0°. Calcd.: N^a, 6.07. Found: N^a, 5.90. [j] Methiodide m.p. 138.8–141.0°. Calcd.: N, 9.65; I, 29.15. Found: N, 9.66; I, 28.99. [k] Diflavianate m.p. 165.8–167.8°. Calcd.: N^a, 5.98. Found: N^a, 5.78. [l] Methiodide m.p. 173.3–174.5°. Calcd.: C, 48.11; H, 7.17; N, 9.35. Found: C, 48.02; H, 6.97; N, 9.28.

TABLE III

N-(DIETHYLAMINOALKYL)-2-METHOXY-4-ALKYLAMINOBENZAMIDES



n	R″	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2	n-C_4H_9[a]	$C_{18}H_{31}N_3O_2$	13.07	12.78	...	...	...	...
3	n-C_4H_9[b,c]	$C_{19}H_{33}N_3O_2$	12.53	12.33	68.02	68.08	9.91	9.79
3	n-C_5H_{11}[d]	$C_{20}H_{35}N_3O_2$	...	...	68.73	69.06	10.09	9.77
4	$C_5H_{10}O$[e,f]	$C_{20}H_{35}N_3O_3$	...	...	63.43	63.41	9.14	9.08
4	n-C_4H_9	$C_{20}H_{35}N_3O_2$	12.02	12.00	68.73	68.63	10.09	10.26

[a] Dipicrate m.p. 117.0–121.4°. Calcd.: neut. equiv., 390; basic N, 3.59. Found: neut. equiv., 383; basic N, 3.63. [b] Base m.p. 58.4–59.8°. [c] Flavianate m.p. 169.3–171.2°. Calcd.: O, 24.6; N^a, 4.32. Found: O, 25.0; N^a, 4.32. [d] Flavianate m.p. 166.0–166.5°. Calcd.: neut. equiv., 332; N^a, 4.22. Found: neut. equiv., 336; N^a, 4.22. [e] 5-Hydroxyamyl. [f] Flavianate m.p. 140.0–141.7°. Calcd.: neut. equiv., 340; N^a, 4.12. Found: neut. equiv., 346; N^a, 4.18.

nitrosalicylate, 23.2 g. (0.20 mole) of 2-diethylaminoethylamine and 250 ml. of dry toluene was refluxed for 8 hr. On cooling, the orange-colored solution separated into two layers. The toluene was removed *in vacuo* and the residual solid (essentially a phenolate-type salt of the base with excess 2-diethylaminoethylamine)[11] was dissolved in an excess of hot alcoholic hydrogen chloride solution. The solution was cooled, diluted with anhydrous ether and the precipitated hydrochloride was filtered. It was obtained analytically pure after a single recrystallization from absolute alcohol. The yield of bright yellow solid was 18.9 g. (75%). The physical properties of this compound, as well as those of analogous 2-hydroxy compounds prepared by the same procedure, are listed in Table I. The free bases (usually oils) were prepared by liberation from the pure hydrochlorides with potassium carbonate solution, under nitrogen. The picrates, flavianates and methiodides were prepared from the free bases in the usual manner.

N-(Diethylaminoalkyl)-2-alkoxy-4-nitrobenzamides.—Aminolysis of an alkyl 2-alkoxy-4-nitrobenzoate[2b] by means of a dialkylaminoalkylamine as above gave fair to poor yields; the yields decreased as the size of the 2-alkoxy group increased. A better procedure involved the reaction between a 2-alkoxy-4-nitrobenzoyl chloride and the amine in benzene or ether solution.

To a stirred solution of 40.0 g. (0.186 mole) of 2-methoxy-4-nitrobenzoyl chloride[2b] in 250 ml. of dry benzene, there was slowly added a solution of 21.6 g. (0.186 mole) of 2-diethylaminoethylamine in 50 ml. of dry benzene. The addition required about 0.5 hr.; the internal temperature was held at about 20° by means of a cooling bath. The resulting gummy mixture was heated to boiling, diluted with 700 ml. of dry *n*-hexane and cooled. The tan-colored solid was filtered and washed with 1:1 benzene–hexane mixture. After three recrystallizations from an absolute alcohol–*n*-hexane mixture, with decolorization by means of Darco G-60 during the first recrystallization, the product was obtained pure in 77% yield.

With the higher 2-alkoxy-4-nitrobenzoic acids it was necessary to prepare the benzoyl chloride *in situ* in the presence of pyridine, to prevent cleavage of the alkoxyl group.[2b] Under these conditions, wherein a slight initial excess of the acid over thionyl chloride was present, the excess acid was removed by extraction with an ethereal solution of the product before conversion to the hydrochloride.

and are corrected. The analyses were done by Mr. M. E. Auerbach, Mr. K. D. Fleischer and their staffs. In the text and Tables the following abbreviations are used: N^a for nitro-nitrogen by titanous chloride titration; neutral equivalent by titration with sodium methoxide in anhydrous methanol; basic N for nitrogen by titration with perchloric acid in acetic acid.

(11) *Cf.* R. O. Clinton and S. C. Laskowski, THIS JOURNAL, **74**, 2226 (1952).

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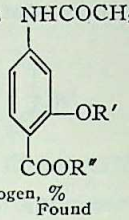
TABLE IV

ALKYL 4-(DIALKYLAMINOACETYLAMINO)-2-ALKOXY- OR -2-HYDROXYBENZOATES

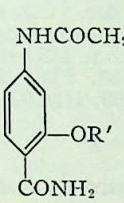


R_2	R′	R″	Type[a]	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
$(C_2H_5)_2$	C_2H_5	C_2H_5[c]	H	171.7–172.5	$C_{17}H_{27}ClN_2O_4$	7.81	7.82	9.88	9.64
C_6H_{12}[b]	C_2H_5	C_2H_5[d]	H	194.4–196.0	$C_{19}H_{29}ClN_2O_4$	7.28	7.22	9.21	9.04
$(C_2H_5)_2$	n-C_4H_9	C_2H_5[e]	H	133.0–134.4	$C_{19}H_{31}ClN_2O_4$	7.24	7.23	9.16	9.30
C_6H_{12}[b]	n-C_4H_9	C_2H_5	B	70.2–71.8	$C_{21}H_{32}N_2O_4$	7.46	7.52	..	..
C_6H_{12}[b]	n-C_4H_9	C_2H_5	H	186.1–187.1	$C_{21}H_{33}ClN_2O_4$	6.78	6.99	8.59	8.82
$(C_2H_5)_2$	C_7H_7[f]	C_2H_5[g]	H	119.8–121.4	$C_{22}H_{29}ClN_2O_4$	6.66	6.68	8.42	8.14
C_6H_{12}[b]	C_7H_7[f]	C_2H_5[h]	H	169.6–171.0	$C_{24}H_{31}ClN_2O_4$	6.27	6.32	7.93	7.90

[a] B = base; H = hydrochloride. [b] 2-Methyl-1-piperidyl. [c] Picrate m.p. 147.8–148.9°. Calcd.: neut. equiv., 552; basic N, 2.54. Found: neut. equiv., 559; basic N, 2.50. [d] Flavianate m.p. 200.1–201.2°. Calcd.: neut. equiv., 332; S, 4.84. Found: neut. equiv., 338; S, 4.94. [e] Picrate m.p. 134.8–135.4°. Calcd.: neut. equiv., 580; basic N, 2.42. Found: neut. equiv., 583; basic N, 2.40. [f] Benzyl. [g] Picrate m.p. 146.2–147.6°. Calcd.: neut. equiv., 614; basic N, 2.28. Found: neut. equiv., 611; basic N, 2.29. [h] Picrate m.p. 154.0–155.2°. Calcd.: neut. equiv., 640; basic N, 2.19. Found: neut. equiv., 652; basic N, 2.19.

TABLE V

4-(DIETHYLAMINOACETYLAMINO)-2-ALKOXY- OR -2-HYDROXYBENZAMIDES

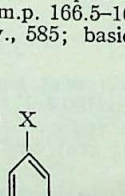


R′	Type[a]	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
C_2H_5[c]	B	138.4–138.8	$C_{15}H_{23}N_3O_3$	14.31	14.32	...	...
C_2H_5	H	234.6–236.0[b]	$C_{15}H_{24}ClN_3O_3$	12.74	12.84	10.75	10.66
n-C_4H_9[d]	B	154.0–155.2	$C_{17}H_{27}N_3O_3$	13.07	13.34	..	..
n-C_4H_9	H	228.6–230.2	$C_{17}H_{28}ClN_3O_3$	11.74	11.59	9.91	9.73
C_7H_7[e,f]	B	137.6–138.0	$C_{20}H_{25}N_3O_3$	11.82	11.55	...	...
C_7H_7	H	199.2–199.6	$C_{20}H_{26}ClN_3O_3$	10.72	10.56	9.05	8.85

[a] B = base; H = hydrochloride. [b] With decomposition. [c] Dipicrate m.p. 155.2–156.4. Calcd.: neut. equiv., 376; basic N, 1.86. Found: neut. equiv., 381; basic N, 1.98. [d] Picrate m.p. 166.5–167.4. Calcd.: N^a, 7.63. Found: N^a; 7.65. [e] Benzyl. [f] Picrate m.p. 179.9–180.9°. Calcd.: neut. equiv., 585; basic N, 2.40. Found: neut. equiv., 590; basic N, 2.64.

TABLE VI

2,4-DISUBSTITUTED BENZAMIDES



X	R′	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
NO_2	CH_3	255.7–256.6	$C_8H_8N_2O_4$	[a]	[a]	..	..	14.28	14.44
NO_2	C_2H_5	188.2–190.0	$C_9H_{10}N_2O_4$	51.42	51.29	4.80	4.68	13.33	13.09
NO_2	n-C_3H_7	191.0–191.7	$C_{10}H_{12}N_2O_4$	[b]	[b]	..	..	12.49	12.23
NO_2	n-C_4H_9	166.6–167.6	$C_{11}H_{14}N_2O_4$	55.45	55.73	5.92	5.65	11.76	11.76
NO_2	i-C_4H_9	198.4–199.4	$C_{11}H_{14}N_2O_4$	55.45	55.43	5.92	5.82	11.76	11.68
NO_2	n-C_6H_{13}	136.3–138.0	$C_{13}H_{18}N_2O_4$	58.63	58.90	6.81	6.52	10.52	10.34
NO_2	C_7H_7[c,d]	180.9–181.9	$C_{14}H_{12}N_2O_4$	61.76	61.75	4.44	4.47	[e]	[e]
NH_2	CH_3	193.9–195.6	$C_8H_{10}N_2O_2$	[f]	[f]	..	..	16.86	16.59
NH_2	C_2H_5	191.6–193.1	$C_9H_{12}N_2O_2$	59.98	60.28	6.71	6.58	15.51	15.56
NH_2	n-C_3H_7	159.6–160.9	$C_{10}H_{14}N_2O_2$	61.83	62.13	7.26	7.39	14.43	14.32
NH_2	n-C_4H_9	178.7–180.2	$C_{11}H_{16}N_2O_2$	63.44	63.62	7.75	7.49	13.45	13.53
NH_2	i-C_4H_9	175.7–177.3	$C_{11}H_{16}N_2O_2$	63.44	63.47	7.75	7.47	13.45	13.12
NH_2	n-C_6H_{13}	127.6–129.0	$C_{13}H_{20}N_2O_2$	66.07	66.09	8.53	8.75	11.86	11.78
NH_2	C_7H_7[c,f]	150.0–151.8	$C_{14}H_{14}N_2O_2$	69.40	69.15	5.82	5.82	11.57	11.27

[a] Calcd.: N^a, 7.19. Found: N^a, 6.96. [b] Calcd.: N^a, 6.25. Found: N^a, 6.24. [c] Benzyl. [d] K. A. Jensen and H. Ingvorsen, *Acta Chem. Scand.*, 6, 161 (1952), reported m.p. 178°. [e] Calcd.: OCH_3, 18.67. Found: OCH_3, 18.50. [f] Reported without physical properties, in British Patent 670,424. [g] Calcd.: N^a, 5.15. Found: N^a, 5.12.

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May 5, 1957

An alternative procedure involved the addition of the benzoyl chloride in alcohol-free chloroform solution to a mixture of the amine, water and sodium bicarbonate.[12] The crude yields obtained by this method were usually somewhat lower than those resulting by the direct reaction mentioned above, but the products in some cases proved to be purified more easily. For example, this method gave excellent results when applied to the preparation of N-(3-diethylamino-2-hydroxy-1-propyl)-2-methoxy-4-nitrobenzamide, whereas the direct reaction in benzene gave an almost inseparable mixture of benzoate and benzamide.

In addition to those compounds listed in Table I, there was prepared: **N-(3-(2-methyl-1-piperidyl)-(propyl)-2-methoxy-4-nitrobenzamide hydrochloride**, from the benzoyl chloride and 3-(2-methyl-1-piperidyl)-propylamine[13] in benzene solution; 82% yield. The compound formed pale yellow prisms from absolute alcohol–*n*-hexane; m.p. 167.5–169.3°.

Anal. Calcd. for $C_{17}H_{26}ClN_3O_4$: N^a, 3.76; Cl, 9.53. Found: N^a, 3.71; Cl, 9.18.

4-Nitro-2-octyloxybenzoic Acid.—The alkylation of ethyl 2-hydroxy-4-nitrobenzoic acid by means of *n*-octyl benzenesulfonate (from *n*-octyl alcohol, benzenesulfonyl chloride and pyridine) was carried out by the method previously described.[2b] Hydrolysis of the crude oily ethyl ester gave a 97% over-all yield of the acid, m.p. 92–93°. The compound crystallized from *n*-hexane in cream-colored feathery needles, m.p. 93.1–94.2°.

Anal. Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.16; N, 4.74. Found: C, 60.94; H, 7.20; N, 4.91.

Conversion to the acid chloride by means of thionyl chloride–pyridine and thence to the ethyl ester, gave the latter as a mobile oil; reduction by means of iron–hydrochloric acid gave a 77% yield of **ethyl 4-amino-2-octyloxybenzoate**, white prisms from *n*-hexane; m.p. 61.8–63.4°.

Anal. Calcd. for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.27; N, 4.77. Found: C, 69.58; H, 9.02; N, 4.82.

N-(Diethylaminoalkyl)-4-amino-2-hydroxybenzamides.—The 2-hydroxy-4-nitrobenzamide hydrochlorides were reduced catalytically by hydrogen in alcoholic solution at 50 lb. pressure and 25°, using 7% palladium chloride on Darco G-60 as catalyst. Precautions were taken in the isolation procedure to minimize air oxidation of the sensitive products.

N-(Dialkylaminoalkyl)-2-alkoxy-4-aminobenzamides.—Reduction of the 2-alkoxy-4-nitrobenzamide hydrochlorides (or the free bases) was carried out by the usual iron–hydrochloric acid procedure.[2b] The isolated bases were converted into the acid salts, picrates, etc., in the usual manner. In the case of N-(3-diethylamino-2-hydroxy-1-propyl)-4-amino-2-methoxybenzamide, the compound was obtained impure (possibly due to some amide–ester interconversion); it was characterized as the picrate, m.p. 88.0–97.0° dec.

Anal. Calcd. for $C_{21}H_{28}N_6O_{10}$: N, 16.00. Found: N, 15.91.

N-(3-(2-Methyl-1-piperidyl)-propyl)-4-amino-2-methoxybenzamide dihydrochloride monohydrate crystallized from absolute alcohol–ether in white needles, m.p. 143.8–146.0°.

Anal. Calcd. for $C_{17}H_{29}Cl_2N_3O_2 \cdot H_2O$: N, 10.60; Cl, 17.89; H_2O, 4.54. Found: N, 10.85; Cl, 17.61; H_2O, 4.57.

The **flavianate** formed yellow cottony needles from dilute alcohol, m.p. 193.8–195.5°. *Anal.* Calcd. for $C_{27}H_{33}N_5O_{10}S$: S, 5.17. Found: S, 5.32.

The 2-alkoxy-4-aminobenzamide methiodides shown in Table II were prepared by the catalytic reduction (platinum oxide) of the nitrobenzamide precursors.

N-(Dialkylaminoalkyl)-4-alkylamino-2-methoxybenzamides.—Reductive alkylation of the 4-amino-2-methoxybenzamides by means of an aldehyde, zinc dust and acetic acid was carried out as usual.[2b] The products in all cases were viscous, high boiling oils; purification was carried out as previously outlined.[2a,b] **N-(3-(2-Methyl-1-piperidyl)-propyl)-4-butylamino-2-methoxybenzamide** was a glassy, straw-colored resin.

Anal. Calcd. for $C_{21}H_{35}N_3O_2$: C, 69.76; H, 9.75; N, 11.62. Found: C, 69.93; H, 9.58; N, 11.31.

The diflavianate crystallized from alcohol in bright yellow prisms, m.p. 160.9–163.9°. *Anal.* Calcd. for $C_{41}H_{47}N_7O_{18}S_2$: N, 9.90. Found: N, 9.84.

Ethyl 4-(Chloroacetylamino)-2-ethoxybenzoate.—To a solution of 20.9 g. (0.10 mole) of ethyl 4-amino-2-ethoxybenzoate in 250 ml. of warm, dry benzene there was added 12.4 g. (0.11 mole) of chloroacetyl chloride in one portion. The resulting heterogeneous mixture, which contained a gelatinous precipitate, was refluxed for 3.5 hr. Solution of the precipitate was completed in 15 minutes; the evolution of hydrogen chloride practically ceased after 2 hr. The mixture was then concentrated to a small volume *in vacuo* and diluted with about five volumes of *n*-hexane. After two recrystallizations from benzene–*n*-hexane, there was obtained 24.8 g. (87%) of pure product which crystallized in brilliant white prisms, m.p. 112.8–113.8°.

Anal. Calcd. for $C_{13}H_{16}ClNO_4$: C, 54.64; H, 5.65; N, 4.90. Found: C, 54.47; H, 5.38; N, 4.91.

With compounds which contained 2-alkoxy groups larger than ethoxy, recourse was had to the acetic acid–sodium acetate methods of Löfgren,[14] in order to prevent alkoxy cleavage.

Ethyl 4-(chloroacetylamino)-2-butoxybenzoate, 81% yield, white prisms from Skellysolve C; m.p. 81.4–83.4°. *Anal.* Calcd. for $C_{15}H_{20}ClNO_4$: Cl, 11.30. Found: Cl, 11.61.

Ethyl 4-(chloroacetylamino)-2-benzoyloxybenzoate, nearly quantitative yield, white prisms from benzene–*n*-hexane, m.p. 120 4–121.6°. *Anal.* Calcd. for $C_{18}H_{18}ClNO_4$: Cl, 10.19; N, 4.03. Found: Cl, 10.42; N, 3.99.

4-(Chloroacetylamino)-2-ethoxybenzamide, obtained in 75% yield from 4-amino-2-ethoxybenzamide (see below) by the acetic acid method, formed white needles from absolute alcohol; m.p. 194.0–198.0° dec. *Anal.* Calcd. for $C_{11}H_{13}ClN_2O_3$: N, 10.91. Found: N, 10.92.

4-(Chloroacetylamino)-2-benzyloxybenzamide, obtained from the amide (see below) by the acetic acid method in 98% yield, rosettes of white needles, from absolute alcohol–ethyl acetate; m.p. 208.0–209.3°. *Anal.* Calcd. for $C_{16}H_{15}ClN_2O_3$: N, 8.79. Found: N, 8.73.

Alkyl 4-(Dialkylaminoacetylamino)-2-alkoxybenzoates.—A mixture of the alkyl 4-(chloroacetylamino)-2-alkoxybenzoate, an amine and the appropriate alcohol was refluxed for 4 to 6 hr. After removal of the alcohol and excess amine *in vacuo*, the product was converted to the base in the usual manner. The yields of the crude bases were 75–85%. The picrates, hydrochlorides, etc., were prepared in the usual manner; *cf.* Table IV.

4-(Dialkylaminoacetylamino)-2-alkoxybenzamides.—The benzamide derivatives were prepared either from the 4-(chloroacetylamino)-benzamide by the above method, or *via* the free acid.

A mixture of 24.5 g. (0.076 mole) of ethyl 4-(diethylaminoacetylamino)-2-ethoxybenzoate, 6.4 g. (0.11 mole) of potassium hydroxide, 200 ml. of alcohol and 100 ml. of water was refluxed for 1 hr. The alcohol was removed *in vacuo* and the aqueous solution was made acidic to congo red paper with hydrochloric acid and saturated with salt. The resulting precipitate was filtered, dried thoroughly and recrystallized from absolute alcohol and from an absolute alcohol–isopropyl alcohol mixture, yielding pure **4-(diethylaminoacetylamino)-2-ethoxybenzoic acid hydrochloride**, m.p. 203.6–204.1° dec.

Anal. Calcd. for $C_{15}H_{23}ClN_2O_4$: Cl, 10.72. Found: Cl, 10.64.

To a stirred suspension of 19.1 g. (0.058 mole) of 4-(diethylaminoacetylamino)-2-ethoxybenzoic acid hydrochloride in 5.2 g. (0.066 mole) of pure pyridine and 200 ml. of dry benzene was added 7.5 g. (0.063 mole) of pure thionyl chloride. The resulting mixture was refluxed and stirred for 15 minutes; solution was not effected. The resulting slurry was poured into a mixture of 200 ml. of concentrated ammonium hydroxide and 500 ml. of water with vigorous stirring. After 15 minutes the benzene layer was separated, washed once with water, dried over Drierite and decolorized with Darco G-60. Evaporation of the benzene gave 13.4 g. of **4-(diethylaminoacetylamino)-2-ethoxybenzamide**, m.p. 135–137°. Two recrystallizations from dilute alcohol gave pure material; *cf.* Table V.

(12) R. O. Clinton, U. J. Salvador, S. C. Laskowski and C. M. Suter, THIS JOURNAL, **70**, 950 (1948).

(13) R. O. Clinton, U. J. Salvador and S. C. Laskowski, *ibid.*, **71**, 3839 (1949).

(14) N. Löfgren, *Arkiv. Kemi, Mineral. Geol.*, **22A**, No. 18 (1946) (*C. A.*, **43**, 1021 (1949)).

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Similarly prepared were: **4-(Diethylaminoacetylamino)-2-butoxybenzoic acid hydrochloride**, m.p. 205.4–206° dec. *Anal.* Calcd. for $C_{17}H_{27}ClN_2O_4$: N, 7.81. Found: N, 7.65.

4-(Diethylaminoacetylamino)-2-benzyloxybenzoic acid hydrochloride, m.p. 180.7–182.0°. *Anal.* Calcd. for $C_{20}H_{25}ClN_2O_4$: N, 7.13; Cl, 9.02. Found: N, 7.34; Cl, 8.90.

2-Methoxy-4-nitrobenzamide.—To 1 liter of cooled, stirred, concentrated ammonium hydroxide (28%) there was added, portionwise, 70 g. of pure 2-methoxy-4-nitrobenzoyl chloride.[2b] When the addition was completed, the resulting suspension was stirred for 15 minutes, filtered and the insoluble product was washed thoroughly with water and dried at 70°. The finely powdered, crude material was stirred at 50° for 15 minutes with 500 ml. of 5% aqueous sodium hydroxide solution and the insoluble material was filtered, washed thoroughly with water and recrystallized twice from glacial acetic acid; *cf.* Table VI.

2-Ethoxy-4-nitrobenzamide.—A mixture of 32 g. (0.166 mole) of 2-ethoxy-4-nitrobenzonitrile[11] and 100 ml. of concentrated sulfuric acid was stirred and heated until the temperature of the mixture was 97°. The heat source was removed; the internal temperature spontaneously rose to 109°. When the internal temperature had dropped to 95°, the mixture was held at 96–97° for a further 1-hr. period. After quenching in 500 ml. of water, the insoluble product was filtered off, washed thoroughly with water and dried at 80°. Three recrystallizations from absolute alcohol furnished 13 g. (37%) of the pure 2-ethoxy-4-nitrobenzamide.

2-Butoxy-4-nitrobenzamide.—General method for alkoxy groups larger than ethoxy: The preparation of 2-butoxy-4-nitrobenzoyl chloride was carried out in benzene solution in the presence of pyridine.[2b] The resulting benzene suspension was added slowly to an excess of concentrated ammonium hydroxide solution, with vigorous stirring. The emulsion was filtered and the insoluble material was washed well with water. The benzene layer was separated from the filtrate and washed with water; evaporation gave a small additional amount of product. The combined fractions, after three recrystallizations from ethyl acetate, gave a 67% yield of pure 2-butoxy-4-nitrobenzamide.

4-Amino-2-alkoxybenzamides.—The reduction of the 2-alkoxy-4-nitrobenzamides was carried out either by means of iron–hydrochloric acid in dilute alcohol[2a] or by catalytic reduction with platinum oxide in alcoholic solution. The yields were good in all cases (80–95%).

RENSSELAER, NEW YORK

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

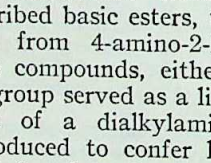
Derivatives of 4-Amino-2-hydroxybenzoic Acid. V. Basic Ethers

BY R. O. CLINTON, S. C. LASKOWSKI, U. J. SALVADOR AND PATRICIA M. CARROLL

RECEIVED OCTOBER 15, 1956

A series of alkyl 4-amino-2-(dialkylaminoalkoxy)-benzoates was prepared for testing as potential local anesthetics. The compounds proved to be good local anesthetics; of more interest was the observation that quaternary salts of these compounds exhibited a high degree of activity as ganglionic blocking agents.

Previous communications[1] from these laboratories have described basic esters, thiol esters and amides derived from 4-amino-2-hydroxybenzoic acids. In these compounds, either the carboxyl or the 4-amino group served as a linkage point for the attachment of a dialkylaminoalkyl chain, which was introduced to confer local anesthetic activity. A third point of attachment for the basic moiety, *viz.*, the 2-hydroxy group, is considered in the present communication. These compounds have the general structure shown by I.



I

Although a compound of type I has not appeared in the literature, a number of related des-amino and des-carboxy analogs have been reported. Chapman, *et al.*,[2] prepared bis-diethylaminoethoxy compounds derived from stilbestrol and hexylresorcinol. Peak and co-workers[3] synthesized several series of basic ethers derived from various chlorinated phenols, catechol, hydroquinone, etc. Furthermore Einhorn and Rothlauf[4] have prepared several alkyl 2- and 4-(2-diethylaminoethoxy)-benzoates and phenolic monobasic ethers, and Rohmann and Friedrich[5] reported the preparation of 4-(2-diethylaminoethoxy)-aniline and a number of its derivatives. In most of these cases pharmacological data have not been reported for the compounds.

Reference should also be made to the dialkylaminoalkoxyaryl compounds and related benzodioxane derivatives, which have been extensively studied by Bovet and co-workers[6] and found to have a wide variety of pharmacodynamic activities.

The alkyl 4-amino-2-(dialkylaminoalkoxy)-benzoates prepared during this investigation were tested for local anesthetic activity[7] by standard methods. In general the compounds were highly active in the intracutaneous wheal and sciatic nerve block tests but less active as corneal local anesthetics. Increasing the side chain length (*e.g.*, from 2-(2-diethylaminoethoxy)- to 2-(3-diethylaminopropoxy)-) or altering the terminal basic moiety (*e.g.*, from dimethylamino to 2-methyl-1-piperidyl) produced a substantial increase in activity. Similarly, changing the ester group from methyl to butyl increased the subcutaneous local anesthetic activity moderately and the topical (corneal) activity markedly. The

(1) (a) R. O. Clinton, S. C. Laskowski, U. J. Salvador, Mary Wilson, Helen Bates and Patricia Carroll, THIS JOURNAL, **73**, 3674 (1951); (b) **74**, 592 (1952); (c) **76**, 5121 (1954); (d) **79**, 2285 (1957).

(2) C. W. Chapman, G. P. Hager and D. E. Shay, *J. Am. Pharm. Assoc.*, **36**, 78 (1947).

(3) D. J. Drain, D. A. Peak and F. F. Whitmore, *J. Chem. Soc.*, 2680 (1949); J. L. Lowe, D. A. Peak and T. I. Watkins, *ibid.*, 3286 (1951).

(4) A. Einhorn and L. Rothlauf, *Ann.*, **382**, 237 (1911); *cf.* C. Rohmann and B. Scheurle, *Arch. Pharm.*, **274**, 110 (1936).

(5) C. Rohmann and K. Friedrich, *Ber.*, **72**, 1333 (1939).

(6) D. Bovet and A. Simon, *Compt. rend. soc. biol.*, **117**, 958 (1934); subsequent papers by D. Bovet, E. Zinz, J. Levy and I. A. M. Staub.

(7) F. P. Luduena and J. O. Hoppe, to be published.

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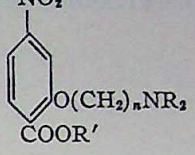
TABLE I

ALKYL 2-(DIALKYLAMINOALKOXY)-4-NITROBENZOATES



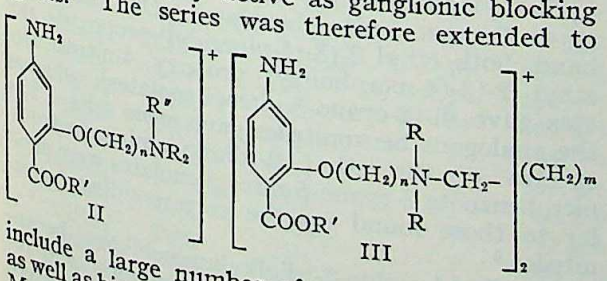
n	R	R′	M.p., °C.	Hydrochloride Formula	Hydrochloride Nitrogen, % Calcd.	Hydrochloride Nitrogen, % Found	Hydrochloride Chlorine, % Calcd.	Hydrochloride Chlorine, % Found	Picrate M.p., °C.	Picrate Nitrogen, % Calcd[a]	Picrate Nitrogen, % Found[a]
2	$(CH_3)_2$	C_2H_5	202.2–202.6	$C_{13}H_{19}ClN_2O_5$	8.79	8.56	11.12	11.10	139.4–140.4	10.96	10.88
2	$(C_2H_5)_2$	CH_3	156.9–159.2	$C_{14}H_{21}ClN_2O_5$	8.42	8.38	10.65	10.50	149.8–150.6	10.68	10.79
2	$(C_2H_5)_2$	C_2H_5	143.9–144.8	$C_{15}H_{23}ClN_2O_5$	4.04[a]	3.79[a]	10.22	10.21	137.8–139.0	10.40	10.18
2	$(C_2H_5)_2$	n-C_3H_7	153.4–155.4	$C_{16}H_{25}ClN_2O_5$	7.77	7.95	9.83	9.83	98.8–100.6	10.12	10.01
2	$(C_2H_5)_2$	n-C_4H_9	117.6–118.6	$C_{17}H_{27}ClN_2O_5$	7.47	7.66	9.46	9.44	120.5–121.6	9.88	9.78
3	$(C_2H_5)_2$	C_2H_5	164.8–165.6	$C_{16}H_{25}ClN_2O_5$	7.77	7.87	9.83	9.72	98.6–99.2	10.12	10.07
2	$(i$-$C_3H_7)_2$[b]	C_2H_5	169.1–170.7	$C_{17}H_{27}ClN_2O_5$	7.47	7.26	9.46	9.40	160.3–163.2	9.87	9.89
2	C_4H_8O[c]	CH_3	206.0–206.4	$C_{14}H_{19}ClN_2O_6$	4.04[a]	4.05[a]	10.22	10.21	161.6–162.2	10.40	10.22
2	C_4H_8O[c]	C_2H_5	207.0–208.0	$C_{15}H_{21}ClN_2O_6$	7.77	7.81	9.83	9.92	154.8–155.6	10.12	10.02
3	C_4H_8O[c]	C_2H_5	142.0–144.6	$C_{16}H_{23}ClN_2O_6$	7.47	7.79	9.46	9.25	133.4–134.2	9.88	9.74
2	C_5H_{10}[d]	C_2H_5	191.0–191.5	$C_{16}H_{23}ClN_2O_5$	7.81	7.82	9.88	9.90	141.7–142.9	10.16	10.02
3	C_5H_{10}[d]	C_2H_5	160.4–161.6	$C_{17}H_{25}ClN_2O_5$	7.52	7.37	9.51	9.33	139.6–140.4	9.92	10.18
2	C_6H_{12}[e]	C_2H_5	180.8–182.6	$C_{17}H_{25}ClN_2O_5$	7.52	7.22	9.51	9.38	138.0–139.0	9.92	9.97
3	C_6H_{12}[e]	C_2H_5	158.2–159.6	$C_{18}H_{27}ClN_2O_5$	7.24	7.03	9.16	8.92	104.6–108.8	9.68	9.65
2	C_7H_{14}[f]	C_2H_5	153.0–154.0	$C_{16}H_{27}ClN_2O_5$	7.24	7.15	9.16	9.14	207.6–209.0	9.68	9.58

[a] N[a], see ref. 10. [b] The base melted at 42.0–48.9°. Calcd.: N, 8.28. Found: N, 8.35. [c] 4-Morpholinyl. [d] 1-Piperidyl. [e] 2-Methyl-1-piperidyl. [f] 2,6-Dimethyl-1-piperidyl.

compounds were, in general, somewhat more toxic and slightly more irritating than their basic ester counterparts[1a,b] and therefore had lower therapeutic indices. Several of the 4-amino compounds possessed a fair degree of oral analgesic activity (*cf.* reference 1d).

The alkyl 4-alkylamino-2-(dialkylaminoalkoxy)-benzoates (I, R″ = butyl, 5-hydroxyamyl, etc.), like their basic ester counterparts,[1a,b], were *less* active than their 4-amino precursors, both subcutaneously and topically (contrast: procaine *vs.* tetracaine). Moreover, the 4-alkylamino derivatives were considerably more irritating than their 4-amino precursors; for this reason only a few examples of the series were prepared. Removal of the ester group with the formation of I (R = H) destroyed all activity.

During the course of the present investigation several quaternary salts derived from I were also prepared (*cf.* II). These quaternary salts, as well as their corresponding 4-nitro precursors, were found to be highly active as ganglionic blocking agents.[8] The series was therefore extended to include a large number of representatives of II, as well as bisquaternary salts of type III (m = 0–4). Most of these compounds were very active, the greatest activity being found with compounds wherein R′ was propyl or butyl, and R and R″ were small (methyl, ethyl, etc.). Activity decreased markedly with the series shown in III as the value of m increased.



The alkyl 2-(dialkylaminoalkoxy)-4-nitrobenzoates were prepared in several ways. The direct reaction between an alkyl 2-hydroxy-4-nitrobenzoate and a dialkylaminoethyl chloride (a modified Horenstein–Pählicke reaction) gave the desired products, although in poor yields. The yields were considerably lower than those obtained previously from 2-hydroxy-4-nitrobenzonitrile[9] by the use of this reaction, indicating the pronounced steric effect of the carbalkoxy grouping.[1a] Moreover, the reaction failed completely with 3-dialkylaminopropyl chlorides, even in the presence of added iodide ion. Considerably better yields were obtained by condensation of sodio-phenolate with a dialkylaminoalkyl chloride in an anhydrous alcoholic solution or in toluene; use of the latter solvent was mandatory with highly reactive halides such as 2-dimethylaminoethyl chloride and in general was the most useful reaction medium.

The route from ethyl 2-(2-chloroethoxy)-4-nitrobenzoate *via* condensation with a secondary amine was also investigated; here again poor overall yields were obtained. The alkyl 2-(dialkylaminoalkoxy)-4-nitrobenzoates as well as their characterizing derivatives, are summarized in Table I.

The alkyl 2-(dialkylaminoalkoxy)-4-nitrobenzoate quaternary salts, listed in Table II, were prepared by the direct condensation of the free base with an alkyl halide or an α,ω-dibromoalkane. Steric effects were quite pronounced. The size of the ester group had no apparent effect since there appeared to be no difference in the rates of reaction of the methyl, ethyl, propyl or butyl esters with, *e.g.*, methyl iodide. The size of the entering R″

(8) J. O. Hoppe, to be published.

(9) R. O. Clinton and S. C. Laskowski, THIS JOURNAL, 74, 2226 (1952).

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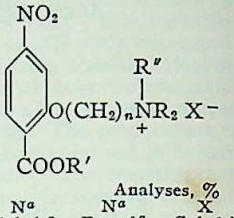
TABLE II

ALKYL 2-(DIALKYLAMINOALKOXY)-4-NITROBENZOATE QUATERNARY SALTS



							Analyses, %			
							N	N	X	X
n	R_2	R′	R″	X	M.p., °C.	Formula	Calcd.[a]	Found[a]	Calcd.[b]	Found[b]
2	$(CH_3)_2$	C_2H_5	CH_3	I	190.2–191.2	$C_{14}H_{21}IN_2O_5$	6.60[c]	6.38[c]	29.92	30.10
2	$(CH_3)_2$	C_2H_5	C_2H_5	I	119.1–120.2	$C_{15}H_{23}IN_2O_5$	3.19	3.22	28.96	28.82
2	$(CH_3)_2$	C_2H_5	i-C_3H_7	Br	180.1–182.4	$C_{16}H_{25}BrN_2O_5$	3.46	3.49	19.71	19.75
2	$(CH_3)_2$	C_2H_5	i-C_4H_9	Br	137.4–148.2	$C_{17}H_{27}BrN_2O_5$	3.34	3.36	19.06	18.62
2	$(CH_3)_2$	C_2H_5	i-C_5H_{11}	Br	150.6–153.0	$C_{18}H_{29}BrN_2O_5$	3.22	3.24	18.44	18.70
2	$(CH_3)_2$	C_2H_5	$-CH_2CH_2OH$	Br	129.7–138.0	$C_{16}H_{23}BrN_2O_6$	3.44	3.59	[d]	[d]
2	$(CH_3)_2$	C_2H_5	C_7H_7[e]	Br	153.3–155.1	$C_{20}H_{25}BrN_2O_5$	3.09	2.98	17.63	17.80
2	$(CH_3)_2$	C_2H_5	C_8H_{15}[f]	Br	121.9–123.5	$C_{21}H_{33}BrN_2O_5$	[g]	[g]	16.88	16.72
2	$(CH_3)_2$	C_2H_5	$-(CH_2)_2-$[h]	Br	164.1–172.0	$C_{28}H_{40}Br_2N_4O_{10}$	3.72	3.76	21.24	21.24
2	$(CH_3)_2$	C_2H_5	$-(CH_2)_3-$[h]	Br	185.1–192.0	$C_{29}H_{42}Br_2N_4O_{10}$	3.65	3.61	20.85	20.42
2	$(CH_3)_2$	C_2H_5	$-(CH_2)_4-$[h]	Br	179.0–186.9	$C_{30}H_{44}Br_2N_4O_{10}$	3.59	3.52	20.48	20.10
2	$(CH_3)_2$	C_2H_5	$-(CH_2)_5-$[h]	Br	[i]	$C_{31}H_{46}Br_2N_4O_{10}$	3.52	3.46	20.12	19.78
2	$(CH_3)_2$	C_2H_5	$-(CH_2)_6-$[h]	Br	192.3–195.9	$C_{32}H_{48}Br_2N_4O_{10}$	3.47	3.35	19.77	19.61
2	$(C_2H_5)_2$	CH_3	CH_3	I	162.5–163.0	$C_{15}H_{23}IN_2O_5$	3.19	3.22	28.96	28.80
2	$(C_2H_5)_2$	C_2H_5	CH_3	Br	150.6–151.6	$C_{16}H_{25}BrN_2O_5$	3.45	3.41	19.72	19.66
2	$(C_2H_5)_2$	C_2H_5	CH_3	I	143.1–144.6	$C_{16}H_{25}IN_2O_5$	6.20[c]	6.16[c]	28.06	28.15
2	$(C_2H_5)_2$	n-C_3H_7	CH_3	I	143.2–144.6	$C_{17}H_{27}IN_2O_5$	3.00	3.04	27.22	27.00
2	$(C_2H_5)_2$	n-C_4H_9	CH_3	I	118.2–120.3	$C_{18}H_{29}IN_2O_5$	2.92	3.11	26.42	26.30
2	$(C_2H_5)_2$	C_2H_5	C_2H_5	I	140.7–141.9	$C_{17}H_{27}IN_2O_5$	3.00	3.02	27.22	27.01
2	$(C_2H_5)_2$	C_2H_5	$-(CH_2)_2-$[h]	Br	146.7–148.7	$C_{32}H_{48}Br_2N_4O_{10}$	3.47	3.50	19.77	20.18
2	$(C_2H_5)_2$	C_2H_5	$-(CH_2)_4$[h]	Br	143.2–146.8	$C_{34}H_{52}Br_2N_4O_{10}$	3.35	3.57	19.11	19.37
2	$(C_2H_5)_2$	C_2H_5	$-(CH_2)_6$[h]	Br	150.7–158.2	$C_{36}H_{56}Br_2N_4O_{10}$	3.24	3.14	18.49	18.21
3	$(C_2H_5)_2$	C_2H_5	CH_3	I	148.0–149.6	$C_{17}H_{27}IN_2O_5$	3.00	3.10	27.22	27.30
2	$(i$-$C_3H_7)_2$	C_2H_5	CH_3	I	183.7–184.2	$C_{18}H_{29}IN_2O_5$	2.91	2.90	26.42	26.18
2	C_4H_8O[j]	CH_3	CH_3	I	209.0–211.0	$C_{15}H_{21}IN_2O_6$	3.09	3.17	28.06	27.88
2	C_4H_8O[j]	C_2H_5	CH_3	I	190.5–191.3	$C_{16}H_{23}IN_2O_6$	3.00	3.02	27.22	26.90
3	C_4H_8O[j]	C_2H_5	CH_3	I	161.1–161.7	$C_{17}H_{25}IN_2O_6$	2.92	2.91	26.42	26.33
2	C_5H_{10}[k]	C_2H_5	CH_3	I	147.7–148.9	$C_{17}H_{25}IN_2O_5$	3.02	3.03	27.34	26.92
3	C_5H_{10}[k]	C_2H_5	CH_3	I	166.9–167.9	$C_{18}H_{27}IN_2O_5$	2.93	2.99	26.53	26.30
2	C_6H_{12}[l]	C_2H_5	CH_3	I	159.8–161.0	$C_{18}H_{27}IN_2O_5$	2.93	2.92	26.53	26.22
3	C_6H_{12}[l]	C_2H_5	CH_3	I	165.5–166.5	$C_{19}H_{29}IN_2O_5$	2.85	2.87	25.78	25.44
2	C_7H_{14}[m]	C_2H_5	CH_3	I	192.3–192.9	$C_{19}H_{29}IN_2O_5$	2.85	2.82	25.78	25.40

[a] See ref. 10. [b] Bromide ion on bromides; iodide ion on iodides. [c] Total nitrogen. [d] Calcd.: C, 44.23; H, 5.69. Found: C, 43.95; H, 5.64. [e] Benzyl. [f] β-Cyclohexylethyl. [g] Calcd.: C, 53.28; H, 7.02. Found: C, 53.03; H, 7.30. [h] Bis-quaternary. [i] M.p. dependent upon immersion point; when immersed at 25° sintered from 152°, melted at 184–187° dec. [j] 4-Morpholinyl. [k] 1-Piperidyl. [l] 2-Methyl-1-piperidyl. [m] 2,6-Dimethyl-1-piperidyl.

group and of the R_2 group(s) (*cf.* II), however, had a marked effect. When NR_2 was 2-methyl-1-piperidyl, for example, the rate of reaction with methyl iodide was only about one-tenth as fast as the reaction with the analogous nitro base wherein NR_2 was diethylamino. Reactions of the α,ω-dibromoalkanes with compounds which contained 2-dimethylaminoethoxy groups took place at a moderate rate in boiling acetonitrile; reaction with compounds which contain 2-diethylaminoethoxy groups was very slow even in boiling nitromethane.

In addition to the picrates of the alkyl 2-(dialkylaminoalkoxy)-4-nitrobenzoates listed in Table I, several 2-cyano-5-nitrophenolates were also synthesized for comparison with the analogous 2-(dialkylaminoalkoxy)-4-nitrobenzonitrile 2-cyano-5-nitrophenolates.[9] Although an extensive series of these salts was not prepared in the present work, it is of interest that the molecular compounds formed are apparently greatly influenced by steric effects, as was previously noted.[9] Ethyl 2-(2-diethylaminoethoxy)-4-nitrobenzoate, similar to 2-(2-diethylaminoethoxy)-4-nitrobenzonitrile, yielded a di-(2-cyano-5-nitrophenolate). On the other hand, both ethyl 2-(3-(1-piperidyl)-propoxy)- and ethyl 2-(3-(4-morpholinyl)-propoxy)-4-nitrobenzoates gave di-(2-cyano-5-nitrophenolates), whereas the analogous benzonitriles gave *mono* salts. The spectra of the ethyl 2-(dialkylaminoalkoxy)-4-nitrobenzoate 2-cyano-5-nitrophenolates were similar to those found for the corresponding benzonitriles.[9]

The alkyl 4-amino-2-(dialkylaminoalkoxy)-benzoates were prepared by iron–hydrochloric acid reduction of the nitro compounds. The bases were obtained crystalline in most cases; they were characterized as their phosphoric and picric acid salts. These compounds are summarized in Table III.

The alkyl 4-amino-2-(dialkylaminoalkoxy)-

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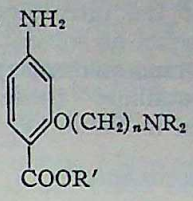
TABLE III

ALKYL 4-AMINO-2-(DIALKYLAMINOALKOXY)-BENZOATES

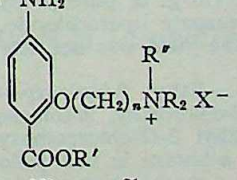


n	R_2	R′	M.p., °C.	Formula	Phosphate Nitrogen, % Calcd.	Found	H_3PO_4, % Calcd.	Found	Picrate M.p., °C.	Nitrogen, % Calcd.[a]	Found[a]
2	$(CH_3)_2$	C_2H_5[b]	176.3–177.3	$C_{13}H_{23}N_2O_7P$	8.00	7.98	27.98	28.10	140.2–141.2	5.82	5.53
2	$(C_2H_5)_2$	CH_3	195.8–196.8	$C_{14}H_{25}N_2O_7P$	7.69	7.61	26.91	27.10	119.0–120.4[c]	11.60[d]	11.39[d]
2	$(C_2H_5)_2$	C_2H_5[e]	168.7–169.6	$C_{15}H_{27}N_2O_7P$	7.40	7.41	25.91	25.30	131.6–133.2	8.43[d]	8.25[d]
2	$(C_2H_5)_2$	n-C_3H_7	153.0–154.0	$C_{16}H_{29}N_2O_7P$	7.14	7.15	24.99	25.23	140.4–141.2	5.36	5.23
2	$(C_2H_5)_2$	n-C_4H_9	154.5–155.5	$C_{17}H_{31}N_2O_7P$	6.88	7.10	24.12	24.15	120.8–122.6	5.22	5.08
3	$(C_2H_5)_2$	C_2H_5	151.5–153.2	$C_{16}H_{29}N_2O_7P$	7.14	7.05	24.99	25.00	146.2–147.0	5.36	5.27
2	$(i$-$C_3H_7)_2$	C_2H_5	186.0–187.0	$C_{17}H_{31}N_2O_7P$	3.44[a]	3.42[a]	24.12	24.70	196.8–197.8[f]	5.15[g]	5.36[g]
2	C_4H_8O[h]	CH_3[i]	151.3–152.1	$C_{14}H_{26}N_2O_{12}P_2$	5.88	5.96	41.16	40.85	168.5–169.7	13.75[i]	13.56[i]
2	C_4H_8O[h]	C_2H_5[k]	196.3–196.9	$C_{15}H_{25}N_2O_8P$	7.14	7.16	24.99	24.50	165.8–166.8	5.35	5.09
3	C_4H_8O[h]	C_2H_5[l]	143.3–144.4	$C_{16}H_{27}N_2O_8P$	6.88	6.65	24.12	24.00	210.4–211.4	5.21	4.95
2	C_5H_{10}[m]	C_2H_5[n]	220.8–221.4	$C_{16}H_{27}N_2O_7P$	7.18	7.17	25.11	25.41	159.0–160.0	5.37	5.07
3	C_5H_{10}[m]	C_2H_5[o]	160.2–161.6	$C_{17}H_{29}N_2O_7P$	6.93	6.83	24.22	24.37	218.0–218.7	5.23	5.07
2	C_6H_{12}[p]	C_2H_5[q]	.....	.....	..	..	...	...	172.4–173.6	5.23	5.18
3	C_6H_{12}[p]	C_2H_5[r]	136.4–138.3	$C_{18}H_{31}N_2O_7P$	6.70	6.56	23.43	23.12	180.8–183.0	5.10	5.16
2	C_7H_{14}[s]	C_2H_5	211.0–211.8	$C_{18}H_{31}N_2O_7P$	6.70	6.67	23.43	23.60	188.8–189.6	5.10	4.88

[a] N_{AP} except as noted; *cf.* ref. 10. [b] The base melted at 94.2–95.6°. Calcd.: N, 11.11. Found: N, 11.14. [c] Dipicrate. [d] N_a, see ref. 10. [e] The dihydrochloride had m.p. 173.6–173.9°. Calcd. for $C_{15}H_{26}Cl_2N_2O_3$: C, 50.99; H, 7.42; Cl, 20.07. Found: C, 51.14; H, 7.36; Cl, 19.90. [f] Flavianate. [g] Sulfur analysis. [h] 4-Morpholinyl. [i] Diphosphate. [j] Total nitrogen. [k] The base had m.p. 98.0–99.8°. Calcd.: N, 9.52. Found: N, 9.42. [l] The base had m.p. 106.8–108.0°. Calcd.: N, 9.09. Found: N, 8.78. [m] 1-Piperidyl. [n] The base had m.p. 107.3–108.5°. Calcd.: N, 9.58. Found: N, 9.40. [o] The base had m.p. 109.2–110.1°. Calcd.: N, 9.14. Found: N, 8.90. [p] 2-Methyl-1-piperidyl. [q] The base had m.p. 91.2–92.4°. Calcd.: N, 9.14. Found: N, 9.26. [r] The base had m.p. 112.4–113.8°. Calcd.: N, 8.74. Found: N, 8.54. [s] 2,6-Dimethyl-1-piperidyl.

TABLE IV

ALKYL 4-AMINO-2-(DIALKYLAMINOALKOXY)-BENZOATE QUATERNARY SALTS



n	R_2	R′	R″	X	M.p., °C.	Formula	Nitrogen, % Calcd.	Found	X, % Calcd.[a]	Found[a]
2	$(CH_3)_2$	C_2H_5	CH_3	I	204.2–205.2	$C_{14}H_{23}IN_2O_3$	7.10	7.13	32.19	31.78
2	$(CH_3)_2$	C_2H_5	C_2H_5	I	172.3–175.3	$C_{15}H_{25}IN_2O_3$	6.86	6.78	31.09	31.03
2	$(CH_3)_2$	C_2H_5	i-C_3H_7	Br	190.0–192.2	$C_{16}H_{27}BrN_2O_3$	7.46	7.39	21.29	21.28
2	$(CH_3)_2$	C_2H_5	CH_2CH_2OH	Br	138.9–142.3	$C_{15}H_{25}BrN_2O_4$	7.42	7.42	21.18	21.20
2	$(CH_3)_2$	C_2H_5	C_8H_{15}[b]	Br	101.6–105.1	$C_{21}H_{35}BrN_2O_3$	6.31	6.23	18.02	17.85
2	$(CH_3)_2$	C_2H_5	$-(CH_2)_2-$[c]	Br	190.0–195[d]	$C_{28}H_{44}Br_2N_4O_6$	8.09	8.01	23.08	23.20
2	$(CH_3)_2$	C_2H_5	$-(CH_2)_4-$[c]	Br	150[e]	$C_{30}H_{48}Br_2N_4O_6$	7.77	7.64	22.18	21.78
2	$(CH_3)_2$	C_2H_5	$-(CH_2)_5-$[c]	Br	125[f]	$C_{31}H_{50}Br_2N_4O_6$	7.62	7.38	21.76	21.50
2	$(C_2H_5)_2$	C_2H_5	$-(CH_2)_6-$[c]	Br	200.7–202.5	$C_{32}H_{52}Br_2N_4O_6$	7.48	7.26	21.35	20.90
2	$(C_2H_5)_2$	CH_3	CH_3	I	127.4–129.0	$C_{15}H_{25}IN_2O_3$	6.86	7.00	31.09	31.50
2	$(C_2H_5)_2$	C_2H_5	CH_3	Br	160.3–162.1	$C_{16}H_{27}BrN_2O_3$	7.46	7.49	21.29	20.95
2	$(C_2H_5)_2$	C_2H_5	CH_3	I	139.2–141.1	$C_{16}H_{27}IN_2O_3$	[g]	[g]	30.05	29.70
2	$(C_2H_5)_2$	n-C_3H_7	CH_3	I	127.4–129.6	$C_{17}H_{29}IN_2O_3$	6.42	6.52	29.09	28.91
3	$(C_2H_5)_2$	C_2H_5	CH_3	I	88.2–92.4	$C_{18}H_{31}IN_2O_3$	6.22	6.33	28.18	28.00
2	C_4H_8O[h]	C_2H_5	C_2H_5	I	141.2–143.8	$C_{17}H_{29}IN_2O_3$	6.42	6.30	29.09	28.94
3	C_4H_8O[h]	C_2H_5	CH_3	I	125.0–126.0	$C_{17}H_{29}IN_2O_3$	6.42	6.35	29.09	29.03
2	C_5H_{10}[i]	C_2H_5	CH_3	I	182.7–183.7	$C_{16}H_{25}IN_2O_4$	6.42	6.40	29.09	29.12
2	C_5H_{10}[i]	C_2H_5	CH_3	I	151.9–153.1	$C_{17}H_{27}IN_2O_4$	6.22	6.25	28.18	28.13
2	C_7H_{14}[j]	C_2H_5	CH_3	I	167.4–168.4	$C_{17}H_{27}IN_2O_3$	6.45	6.30	29.22	29.41
2		C_2H_5	CH_3	I	150.1–150.6	$C_{18}H_{29}IN_2O_3$	6.25	6.09	28.31	28.61
2				I	123.4–126.4	$C_{19}H_{31}IN_2O_3$	6.06	5.84	27.45	27.59

[a] Bromide ion on bromides; iodide ion on iodides. [b] β-Cyclohexylethyl. [c] Bis-quaternary. [d] With decomposition. [e] M.p. indefinite above 160° with decomposition. [f] Monohydrate, above 190° dec. Calcd.: C, 45.50; H, 6.45. Found: C, 45.28; H, 6.58. [g] 4-Morpholinyl. [h] 1-Piperidyl. [i] 2,6-Dimethyl-1-piperidyl.

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benzoate quaternary salts were prepared by the catalytic reduction of the nitro-quaternary salts in the appropriate alcohol as solvent. In a number of cases the 4-amino-quaternary salts could not be obtained crystalline; those which were characterized are listed in Table IV.

Experimental[10]

Alkyl 2-(Dialkylaminoalkoxy)-4-nitrobenzoates.—Several synthetic methods, described below, were used for the preparation of the alkyl 2-(dialkylaminoalkoxy)-4-nitrobenzoates. The compounds prepared are listed in Table I.

Method A.—To a warm solution of 39.4 g. (0.20 mole) of methyl 2-hydroxy-4-nitrobenzoate in 1400 ml. of dry toluene there was added a solution prepared from 4.6 g. (0.20 mole) of sodium and 500 ml. of absolute methanol. The methanol was distilled from the stirred suspension until a constant distillation temperature of 110° was reached. To the red suspension was added 29.8 g. (0.22 mole) of 2-diethylaminoethyl chloride in 500 ml. of dry toluene, and the mixture was stirred and refluxed for 20 hr.; during this period the color faded to pale yellow. The mixture was cooled, filtered, and the insoluble material was washed thoroughly with dry benzene. Distillation of the solvents *in vacuo* left an oily residue of methyl 2-(2-diethylaminoethoxy)-4-nitrobenzoate. Conversion to the hydrochloride was effected by treatment of an ethyl acetate solution of the crude base with an excess of ethereal hydrogen chloride; after one recrystallization from absolute methanol–ethyl acetate, there was obtained an 85% yield of pure material.

This method could be used for the preparation of the majority of the esters in Table I by substituting the appropriate sodium alkoxide–alcohol mixture (depending upon the ester employed) for the sodium methoxide–methanol. The yields were high and as much as two moles of a 2-hydroxy ester could be alkylated by this method on a laboratory scale.

Method B.—A mixture of 24.7 g. (0.11 mole) of propyl 2-hydroxy-4-nitrobenzoate, 16.3 g. (0.12 mole) of 2-diethylaminoethyl chloride and 250 ml. of *n*-propyl alcohol was refluxed and stirred for 8 hr. After the usual procedure there was obtained 1.0 g. of pure propyl 2-(2-diethylaminoethoxy)-4-nitrobenzoate hydrochloride, m.p. and mixed m.p. 153–155°. The yield was not increased by prolonged refluxing.

Method C.—Ethyl 2-hydroxy-4-nitrobenzoate was alkylated by 2-chloroethyl *p*-toluenesulfonate in the usual manner.[1b] **Ethyl 2-(2-chloroethoxy)-4-nitrobenzoate** crystallized from *n*-hexane in pale yellow platelets, m.p. 56.6–57.2°.

Anal. Calcd. for $C_{11}H_{12}ClNO_5$: Cl, 12.96. Found: Cl, 12.62.

When refluxed with an ethanolic solution of a secondary amine in the presence of sodium iodide, there were obtained 50–65% yields of the corresponding ethyl 2-(2-dialkylaminoethoxy)-4-nitrobenzoates.

Method D.—The reaction between an alkyl 2-hydroxy-4-nitrobenzoate, sodium alkoxide and a dialkylaminoalkyl chloride in an alcohol under anhydrous conditions was carried out by substantially the same procedure used with 2-hydroxy-4-nitrobenzonitrile.[9] The only modification necessary was the use of the appropriate alcohol as solvent for the reaction. The effect of the alcohol was indicated by the following yield data, utilizing 2-diethylaminoethyl chloride in each case: methyl ester in methanol: (5%); ethyl ester in ethanol: (71%), propyl ester in *n*-propyl alcohol: (88%); butyl ester in *n*-butyl alcohol: (86%); methyl ester in ethanol: (70%) of *ethyl* ester basic ether (by transesterification).

Alkyl 2-(Dialkylaminoalkoxy)-4-nitrobenzoate Quaternary Salts.—The quaternary salts were prepared in every case from the pure base (liberated from the pure hydrochloride). The following methods were used.

Method A (Methiodides, Methobromides).—To a solution of the base in ethyl acetate, under anhydrous conditions, was added three moles of methyl iodide or bromide. The initially deep orange-colored solution rapidly or slowly changed in color to pale yellow as crystals deposited. After 3–20 hr. at room temperature, the mixture was filtered and the precipitate was washed thoroughly with ethyl acetate. Recrystallization from absolute alcohol or an isopropyl alcohol–ethyl acetate mixture gave a pure quaternary salt.

Ethyl iodide reacted quantitatively with ethyl 2-(2-dimethylaminoethoxy)-4-nitrobenzoate under these conditions, but no product was obtained with the 2-(2-diethylaminoethoxy) homolog at room temperature.

Method B (Alkyl Bromides).—A solution of the base in acetonitrile was mixed with three moles of the alkyl bromide and the mixture was refluxed for 36–72 hr. In the preparation of the bis-quaternaries derived from ethyl 2-(2-dimethylaminoethoxy)-4-nitrobenzoate, similar conditions were used except that a 2.4-to-1 mole ratio of base to the α,ω-dibromoalkane was used. The latter conditions also applied to the preparation of the bis-quaternaries derived from ethyl 2-(2-diethylaminoethoxy)-4-nitrobenzoate which were prepared using nitromethane as solvent; the mixtures were refluxed for 48–72 hr.

Alkyl 2-(Dialkylaminoalkoxy)-4-nitrobenzoate 2-Cyano-5-nitrophenolates.—The 2-cyano-5-nitrophenolate derivatives were prepared[9] from 0.01 mole of the alkyl 2-(dialkylaminoalkoxy)-4-nitrobenzoate and 0.02 mole of 2-hydroxy-4-nitrobenzonitrile, in ethyl acetate solution. The yields were essentially quantitative.

Ethyl 2-(2-diethylaminoethoxy)-4-nitrobenzoate di-(2-cyano-5-nitrophenolate), canary yellow prisms, m.p. 76.0–78.0°. *Anal.* Calcd. for $C_{29}H_{30}N_6O_{11}$: N^a, 6.58; N_{AP}, 2.19. Found: N^a, 6.59; N_{AP}, 2.19.

Ethyl 2-(3-(1-piperidyl)-propoxy)-4-nitrobenzoate di-(2-cyano-5-nitrophenolate), short, blunt orange needles, m.p. 125.2–126.0; λ_{max}^{alc} 234 (inflection), 265, 338, 406 mμ (ε 36,800, 27,770, 8,510, 2,100, respectively).

Anal. Calcd. for $C_{31}H_{32}N_6O_{11}$: N^a, 6.32; N_{AP}, 2.11. Found: N^a, 6.20; N_{AP}, 2.12.

Ethyl 2-(3-(4-morpholinyl)-propoxy)-4-nitrobenzoate di-(2-cyano-5-nitrophenolate), hair-like yellow-orange needles, m.p. 137.2–138.3°; λ_{max}^{alc} 234 (inflection), 265,340 mμ (ε 28,200, 25,000, 9,510, respectively). *Anal.* Calcd. for $C_{30}H_{30}N_6O_{12}$: N^a, 6.30; N_{AP}, 2.10. Found: N^a, 6.49; N_{AP}, 2.16.

2-(2-Diethylaminoethoxy)-4-nitrobenzoic Acid.—A mixture of 15.0 g. (0.043 mole) of ethyl 2-(2-diethylaminoethoxy)-4-nitrobenzoate hydrochloride, 18.3 g. (0.17 mole) of sodium carbonate and 200 ml. of 50% alcohol was stirred and refluxed for 4 hr. The alcohol was removed *in vacuo* and, after filtration, the aqueous residue was acidified to congo red paper with concentrated hydrochloric acid and saturated with ammonium sulfate. The precipitate was filtered and dried *in vacuo* at 70°; yield 13.8 g. (98%), m.p. 211–213°. Recrystallization from methanol gave the pure compound with but little loss, m.p. 212.5–213.9°.

Anal. Calcd. for $C_{13}H_{19}ClN_2O_5$: C, 48.98; H, 6.01; Cl, 11.12; N^a, 4.39. Found: C, 49.28; H, 6.13; Cl, 10.92; N^a, 4.21.

A mixture of 31.9 g. (0.1 mole) of the above hydrochloride, 8.4 g. (0.1 mole) of sodium bicarbonate and 500 ml. of absolute alcohol was stirred and refluxed for 3 hr., cooled, filtered and the filtrate was evaporated to dryness *in vacuo*. Recrystallization from isopropyl alcohol gave 25.0 g. of 2-(2-diethylaminoethoxy)-4-nitrobenzoic acid, m.p. 164.6–166.6°.

Anal. Calcd. for $C_{13}H_{18}N_2O_5$: N_{AP}, 4.97. Found: N_{AP}, 4.93.

The picrate crystallized from alcohol in cottony yellow needles, m.p. 179.2–180.4°. *Anal.* Calcd. for $C_{19}H_{21}N_5O_{12}$: N, 13.70. Found: N, 13.48.

2-(2-Dimethylaminoethoxy)-4-nitrobenzoic acid, prepared by the above method, formed cream colored plates from absolute alcohol, m.p. 193.1–194.1°. *Anal.* Calcd. for $C_{11}H_{14}N_2O_5$: N^a, 5.51. Found: N^a, 5.51.

The hydrochloride crystallized from absolute alcohol in pale yellow needles; m.p. 208.0–209.6°. *Anal.* Calcd. for $C_{11}H_{15}ClN_2O_5$: N_{AP}, 4.82; Cl, 12.20. Found: N^a, 4.70; Cl, 12.06.

(10) All melting points are corrected; they were determined in a modified Hershberg apparatus using total immersion N.B.S. calibrated thermometers. The analyses were done by Mr. M. E. Auerbach, Mr. K. D. Fleischer, and their staffs; absorption spectra by Dr. F. C. Nachod and staff. N^a is used to indicate nitro nitrogen, by titration with titanous chloride; N_{AP} indicates basic nitrogen by titration with perchloric acid; N. E. indicates neutral equivalent by titration with sodium methoxide.

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May 5, 1957

The picrate was prepared by treating an aqueous solution of the hydrochloride with an excess of a saturated aqueous picric acid solution; clusters of yellow needles, m.p. 181.8–182.6°. *Anal.* Calcd. for $C_{17}H_{17}N_5O_{12}$: N^a, 11.60. Found: N^a, 11.51.

2-(3-(1-Piperidyl)-propoxy)-4-nitrobenzoic acid hydrochloride, pale yellow cottony needles from absolute alcohol, m.p. 216.8–217.5°. *Anal.* Calcd. for $C_{15}H_{21}ClN_2O_5$: N, 8.16; Cl, 10.28. Found: N, 8.17; Cl, 10.09.

The picrate, canary yellow needles from absolute alcohol, m.p. 143.0–145.0°. *Anal.* Calcd. for $C_{21}H_{23}N_5O_{12}$: N^a, 10.43. Found: N^a, 10.10.

Alkyl 4-Amino-2-(dialkylaminoalkoxy)-benzoates.—The alkyl 2-(dialkylaminoalkoxy)-4-nitrobenzoate bases or hydrochlorides were reduced by the iron–hydrochloride acid method,[1a] in the appropriate dilute alcohol as solvent, or by catalytic reduction of the hydrochloride (platinum oxide, 25°, alcohol solvent). The crystalline 4-amino bases were recrystallized from benzene or an ethyl acetate–*n*-hexane mixture. The bases did not readily yield crystalline mono- or dihydrochlorides, but the phosphates were easily prepared.[1a,9] The picrates were prepared in the usual manner, using an excess of picric acid. These compounds are listed in Table III.

Alkyl 4-Amino-2-(dialkylaminoalkoxy)-benzoate Quaternary Salts.—The reduction of the alkyl 2-(dialkylaminoalkoxy)-4-nitrobenzoate quaternary salts and bis-quaternary salts was carried out catalytically, using platinum oxide as catalyst, the appropriate alcohol or dilute alcohol as solvent, a temperature of 25° and a pressure of 40 lb. The products were isolated in the usual manner, utilizing a vacuum distillation with ethyl acetate for dehydration prior to crystallization from isopropyl alcohol–ethyl acetate or absolute alcohol. A number of the 4-amino quaternary salts could not be obtained crystalline; in certain cases these were tested as the crude oils. The crystalline 4-amino quaternary salts are listed in Table IV.

4-Amino-2-(dialkylaminoalkoxy)-benzoic Acids.—The 2-(dialkylaminoalkoxy)-4-nitrobenzoic acids or their hydrochlorides were reduced catalytically by the above method.

4-Amino-2-(2-dimethylaminoethoxy)-benzoic acid hydrochloride, white needles from absolute alcohol, m.p. 145.5–147.2° dec. *Anal.* Calcd. for $C_{11}H_{17}ClN_2O_3$: N, 10.75; Cl, 13.60. Found: N, 10.74; Cl, 13.93.

4-Amino-2-(2-diethylaminoethoxy)-benzoic acid, white needles, m.p. 158.0–158.8° dec. *Anal.* Calcd. for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.11. Found: C, 61.88; H, 7.76; N, 11.05.

The picrate, canary yellow needles from alcohol, m.p. 187.5–188.3°. *Anal.* Calcd. for $C_{19}H_{23}N_5O_{10}$: N_{AP}, 5.82. Found: N_{AP}, 5.52.

4-Amino-2-(3-(1-piperidyl)-propoxy)-benzoic acid hydrochloride, tan needles, m.p. 162.1–162.8° dec. *Anal.* Calcd. for $C_{15}H_{23}ClN_2O_3$: N, 8.90; Cl, 11.26. Found: N, 9.20; Cl, 10.96.

4-Alkylamino-2-(dialkylaminoalkoxy)-benzoates.—The reductive alkylation of the 4-amino bases by means of an aldehyde, zinc dust and acetic acid was carried out as previously described.[1a,b]

Ethyl 4-butylamino-2-(2-diethylaminoethoxy)-benzoate hydrochloride, cream-colored needles from absolute alcohol–ethyl acetate, m.p. 160.5–161.8°. *Anal.* Calcd. for $C_{19}H_{33}ClN_2O_3$: N, 7.51; Cl, 9.50. Found: N, 7.36; Cl, 9.45.

The flavianate, yellow-orange plates from alcohol, m.p. 164.6–165.6°. *Anal.* Calcd. for $C_{29}H_{38}N_4O_{11}S$: S, 4.92. Found: S, 4.96.

Ethyl 4-(5-hydroxyamylamino)-2-(2-diethylaminoethoxy)-benzoate hydrochloride, white cottony needles from absolute alcohol–*n*-hexane, m.p. 132.2–133.4°. *Anal.* Calcd. for $C_{20}H_{35}ClN_2O_4$: N, 6.95; Cl, 8.79. Found: N, 7.07; Cl, 9.05.

The flavianate, cottony orange needles, m.p. 126.0–126.4°. *Anal.* Calcd. for $C_{30}H_{40}N_4O_{12}S$: S, 4.71. Found: S, 4.47.

Ethyl 4-(2,2-dimethyl-3-hydroxypropylamino)-2-(2-(2,6-dimethyl-1-piperidyl)-ethoxy)-benzoate, white needles from benzene, m.p. 90.0–91.0°. *Anal.* Calcd. for $C_{23}H_{38}N_2O_4$: C, 67.94; H, 9.42; N, 6.89. Found: C, 68.06; H, 9.31; N, 6.81.

RENSSELAER, N. Y.

[CONTRIBUTION NO. 228 FROM JACKSON LABORATORY, E. I. DU PONT DE NEMOURS AND CO., INC.]

Preparation of N,N′-Disubstituted *p*-Quinonediimine-N,N′-dioxides

BY C. J. PEDERSEN

RECEIVED DECEMBER 3, 1956

Several members of a new class of compounds (I, where R and R′ are alkyl or aryl groups which may or may not be identical) have been prepared by treating either VI or VII with an excess of perbenzoic acid. They are highly colored compounds whose solutions in organic solvents are very sensitive to light. Many of them are good inhibitors of free radical polymerization as well as efficient inhibitors of autoxidation.

During a study of the action of perbenzoic acid on N,N′-disubstituted derivatives of *p*-phenylenediamine, products were obtained which were found to belong to a new class of compounds having structure I.[1] The closest references in the literature are to N-phenyl-*p*-quinoneimine-N-oxide (II),[2] 5,6-bis-(phenylimino)-2-cyclohexene-1,4-dione-N,N′-dioxide (III)[3] and phenazine-N,N′-dioxide (IV).[4]

The two methods of preparing these compounds are shown in Fig. 2. Method I consists in treating one mole of N,N′-disubstituted *p*-quinonediimine (VI) with slightly more than two moles of perbenzoic acid, and method II of treating one mole of N,N′-disubstituted *p*-phenylenediamine (VII) with a little more than three moles of perbenzoic acid.

N-Substituted *p*-nitroanilines (VIII) are obtained as by-products in method II when R or R′, or both, are unsubstituted alkyl groups. The group which comes off the nitrogen atom is always the unsubstituted alkyl group. When both R and R′ are substituted *t*-alkyl or aromatic groups, no derivative of *p*-nitroaniline is formed to any extent.

The establishment of the structure of these compounds is based mainly on work with N,N′-diphenyl-*p*-quinonediimine-N,N′-dioxide. The molecular weight and the elementary analyses of this compound are consistent with the composition of I (R and R′ = phenyl), and its structure is indicated by its hydrogenation to N,N′-diphenyl-*p*-phenylenediamine (VII R and R′ = phenyl).

It is an orange, crystalline compound whose solutions are very sensitive to light.[5] Its visible spectrum, shown in Fig. 3 has a peak at 417 mμ, ε 47,000. Structure X (R and R′ = phenyl) is

(1) C. J. Pedersen, United States Patent 2,681,918, June 22, 1954; C. A., **49**, 7595 (1955).
(2) H. Wieland and K. Roth, *Ber.*, **53B**, 210 (1920).
(3) W. Gündel and R. Pummer, *Ann.*, **529**, 11 (1937).
(4) G. R. Clemo and H. McIlwain, *J. Chem. Soc.*, 479 (1938).
(5) The photochemical reactions of N,N′-disubstituted *p*-quinonediimine-N,N′-dioxides will be discussed in another paper.

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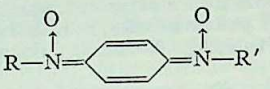
TABLE I

PREPARATION AND PROPERTIES OF 

R	R′	Method	Solvent	Yield, %	Nitrogen, % Calcd.	Found	M.p., °C.[a]
Methyl	Methyl	II	Chloroform	17	16.9	17.0	148
s-Butyl	*s*-Butyl	II	Benzene	11	11.2	11.1	174
α-Cyanoisopropyl	α-Cyanoisopropyl	II	Acetone	52	20.6	20.8	153
α-Carbamoylisopropyl	α-Carbamoylisopropyl	II	Dimethylformamide	57	18.2	18.4	240
α-Carbethoxyisopropyl	α-Carbethoxyisopropyl	II	Dimethylformamide	69	7.7	8.0	129
Cyclohexyl	Cyclohexyl	II	Benzene	77	9.3	9.4	213
1-Cyanocyclohexyl	1-Cyanocyclohexyl	II	Acetone	79	15.9	16.0	196
Cyclohexyl	Phenyl	II	Benzene	30	9.5	9.5	117
Phenyl	Phenyl	I	Chloroform	83	9.7	9.5	205
p-Dodecylphenyl	*p*-Dodecylphenyl	I	Benzene	36	4.5	4.6	116
Phenyl	β-Naphthyl	I	Chloroform	*ca.* 60–80	8.2	8.0	177
β-Naphthyl	β-Naphthyl	I	Benzene	62	7.1	7.4	215
o-Methyl-*m*-chlorophenyl	*o*-Methyl-*m*-chlorophenyl	I	Chloroform	*ca.* 60–80	7.2	7.0	222
p-Anisyl	*p*-Anisyl	I	Chloroform	*ca.* 60–80	8.0	7.8	219
Phenyl[b]	2,4-Dinitrophenyl	II	Benzene	59	14.7	14.7	215

[a] These points were determined on a bronze block and are uncorrected. In general the compounds decomposed on melting and the melting point is not considered a good index of identity for these compounds. [b] A 40% solution of peracetic acid in glacial acetic acid was used instead of perbenzoic acid.

excluded because the spectrum of the "di-isonitrone"[6] should resemble that of *p*-quinone (peaks in ethanol: 244 mμ, ε 19,000; *ca.* 300 mμ, ε 400; 436 mμ, ε 19) and not have such a strong absorption band in the visible region. Its infrared spectrum, shown in Fig. 5, has bands at 8.03 and 13.06 μ which are characteristic for the N,N′-dioxides. The band at 6.3 μ which is characteristic for the *p*-quinonediimines (VI), is either absent or very weak in the spectra of N,N′-dioxides (I).

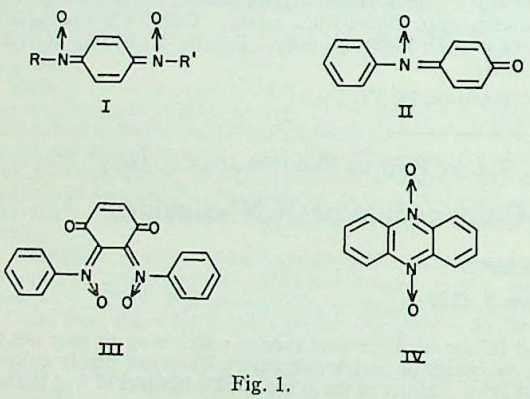


Fig. 1.

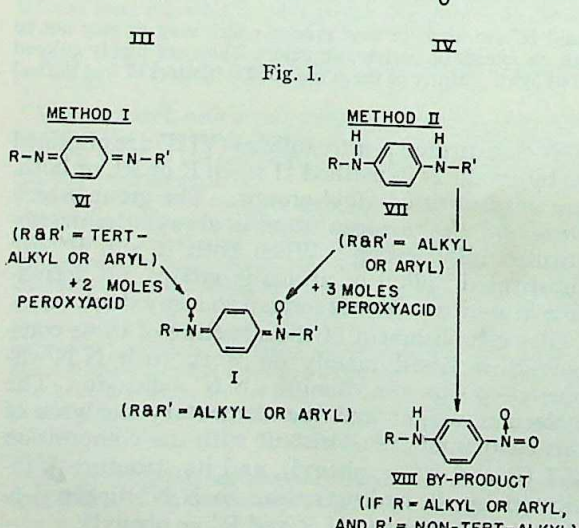


Fig. 2.

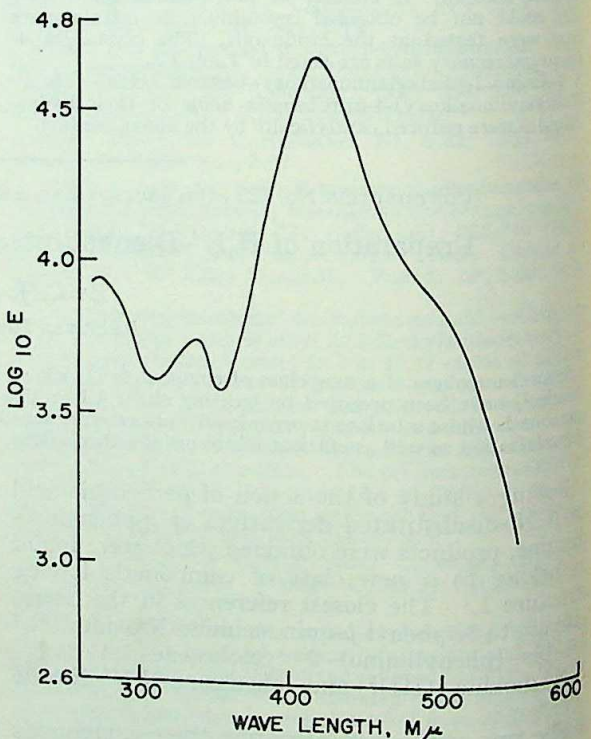


Fig. 3.—Spectrum of N,N′-diphenyl-*p*-quinonediimine-N,N′-dioxide.

Since I (R and R′ = phenyl) is an excellent inhibitor of free radical polymerization and autoxidation,[1] structure XII (R and R′ = phenyl), N,N′-(*p*-phenylene)-bis-(phenylnitroxide), was also considered, but paramagnetic resonance measurements failed to detect the presence of any unpaired electron either in the crystals or in solution. It is concluded, therefore, that I (R and R′ = phenyl) is the correct structure of N,N′-diphenyl-

(6) British Patent 743,940, January 25, 1956.

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TABLE II

VISIBLE ABSORPTION MAXIMA OF R—N(O)=C6H4=N(O)—R′

R	R′	Solvent	Max., mμ[a]	Extinction coeff.
Methyl	Methyl	Methanol	385	17,000
s-Butyl (XIII)	*s*-Butyl	Ethanol	403	66,000
α-Cyanoisopropyl	α-Cyanoisopropyl	Ethanol	406	85,000
α-Carbamoylisopropyl	α-Carbamoylisopropyl	Methanol	410	45,000
α-Carbethoxyisopropyl	α-Carbethoxyisopropyl	Methanol	406	78,000
Cyclohexyl	Cyclohexyl	Methanol	404	65,000
1-Cyanocyclohexyl	1-Cyanocyclohexyl	Chloroform	415	63,000
Cyclohexyl	Phenyl	Chloroform	415	44,000
Phenyl (IX)	Phenyl	Methanol	417	47,000
		Chloroform	423	43,000
Phenyl	β-Naphthyl	Chloroform	432	45,000
β-Naphthyl	β-Naphthyl	Chloroform	435	35,000
o-Methyl-*m*-chlorophenyl	*o*-Methyl-*m*-chlorophenyl	Chloroform	414	62,000
p-Anisyl	*p*-Anisyl	Chloroform	431	40,000
Phenyl	2,4-Dinitrophenyl	Chloroform	408	34,000

[a] Determined with a Cary model 11 recording spectrophotometer. Note that the absorption peaks occur within a relatively narrow range of wave lengths and they are influenced by the substituents on the nitrogen atoms and by the solvent.

TABLE III

CHARACTERISTIC INFRARED ABSORPTION BANDS OF R—N(O)=C6H4=N(O)—R′

R = R′ =	Bands, μ[a]	
s-Butyl	8.17s	12.92w
α-Carbethoxyisopropyl	8.04s	13.06s
Cyclohexyl	8.16s	12.99s
Phenyl	8.03s	13.06s

[a] Determined with a Perkin-Elmer model 12-C spectrophotometer using a NaCl prism and Nujol mulls.

p-quinonediimine-N,N′-dioxide. The compound is a dinitrone and may also be considered the N,N′-diphenyl ether of *p*-quinonedioxime.

The structure of the other compounds of this class is considered also proved because they are prepared in the same way, possess similar properties and their elementary analyses are in accord. They are strongly colored compounds, usually yellow or orange, with molecular extinction coefficients in the visible region, ranging from 17,000 to 85,000. Although their solubility is influenced by the substituents on the nitrogen atoms, they are, in general, moderately soluble at room temperature in organic solvents such as benzene, chloroform, acetone and dimethylformamide, and insoluble in water. Their solutions are rapidly decomposed on exposure to sunlight.[5] Data on these compounds are summarized in Tables I, II and III.

It should be mentioned that no attempt was made to secure maximum yields in these preparations, and it is likely that improved yields could be obtained readily by further work.

Observe that all these spectra contain bands near 8 and 13 μ which are considered to be characteristic for compounds belonging to this class.

It was mentioned previously that derivatives of *p*-nitroaniline are obtained as by-products in certain cases. Those which were identified are listed in Table IV.

N,N′-Dioxides, especially those having aryl substituents on the nitrogen atoms, are inhibitors of

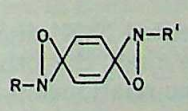
TABLE IV

IDENTIFIED BY-PRODUCTS[a] OBTAINED IN PREPARING R—N(O)=C6H4=N(O)—R′

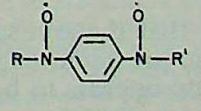
R	R′	By-product	Identified by
Methyl	Methyl	N-Methyl-*p*-nitroaniline	Mixed m.p. 150–151°, spectrum in MeOH 381 mμ, ε 18,000
s-Butyl	*s*-Butyl	N-(*s*-Butyl)-*p*-nitroaniline	Spectrum similar to first compound
Cyclohexyl	Cyclohexyl	N-Cyclohexyl-*p*-nitroaniline	Spectrum similar to first compound
Cyclohexyl	Phenyl	*p*-Nitrodiphenylamine	Mixed m.p. 135°; N, 12.9; spectrum in MeOH 389 mμ, ε 21,000

[a] If any derivative of *p*-nitroaniline had been formed in the other preparations, the quantity was too small for ready identification.

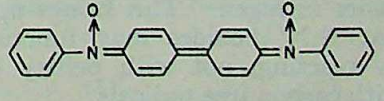
free radical polymerization and autoxidation, and examples of their uses for these purposes have been published.[1] The data in Table V show the effects of several N,N′-dioxides on the induction period of



X



XII



XIV

Fig. 4.

terpinolene autoxidizing in an atmosphere of oxygen. A number of other compounds are included for the purpose of comparison.

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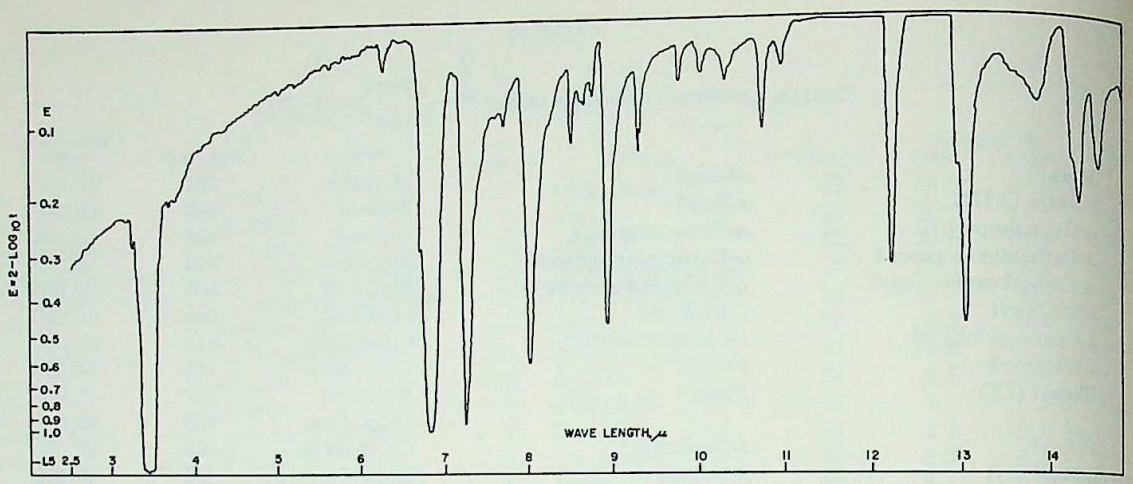

Fig. 5.—Infrared spectrum of N,N′-diphenyl-*p*-quinonediimine-N,N′-dioxide.

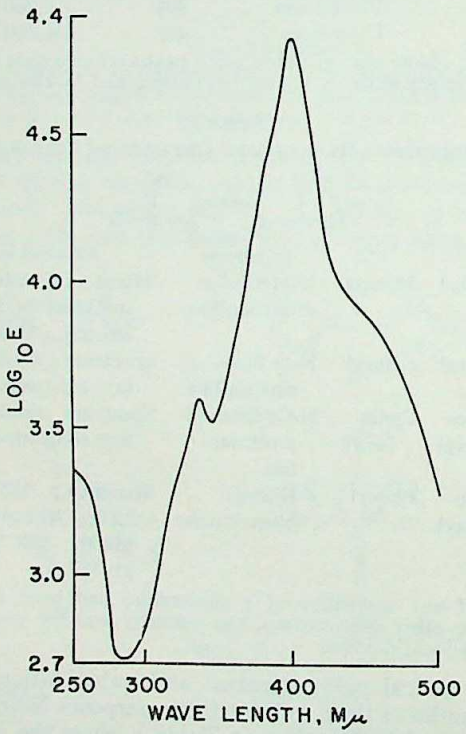

Fig. 6.—Spectrum of N,N′-di-(*sec*-butyl)-*p*-quinonediimine-N,N′-dioxide.

Note that the aryl substituted N,N′-dioxides, as a group, are more effective than the others, but there also appears to be some relationship between efficiency and the ease of removal of the oxygen atom from the nitrogen. It was found that N,N′-diphenyl-*p*-quinonediimine is obtained when N,N′-diphenyl - *p* - quinonediimine - N,N′ - dioxide and N,N′-azo-bis-(α-isobutyronitrile) are refluxed in benzene under nitrogen. This brings up the possibility that N,N′-dioxides may function as inhibitors by reacting, not with peroxy chain-carriers but with carbon free radicals.[7]

Acknowledgment.—The author wishes to thank T. D. Boice and John Willister for preparing many of the compounds; H. S. Jarrett and R. C. Ferguson for the paramagnetic resonance measurements; H. A. Kubitz for interpreting the infrared spectra; and H. E. Schroeder for his advice.

Experimental

Perbenzoic acid was prepared in chloroform or benzene by Braun's method[8] and used directly. All other materials were either laboratory samples or commercially available products.

TABLE V

ANTIOXIDANT ACTION OF R—N(→O)=C6H4=N(→O)—R′[a]

R	R′	Induction period of terpinolene, hours[b]
No additive		1 to 2
Cyclohexyl	Cyclohexyl	3
α-Carbamoylisopropyl	α-Carbamoylisopropyl	3
s-Butyl	*s*-Butyl	10
α-Carbethoxyisopropyl	α-Carbethoxyisoproyl	19
α-Cyanoisopropyl	α-Cyanoisopropyl	28
Cyclohexyl	Phenyl	31
1-Cyanocyclohexyl	1-Cyanocyclohexyl	33
β-Naphthyl	β-Naphthyl	38
o-Methyl-*m*-chlorophenyl	*o*-Methyl-*m*-chlorophenyl	41
p-Anisyl	*p*-Anisyl	58
p-Dodecylphenyl	*p*-Dodecylphenyl	75
Phenyl	β-Naphthyl	87
Phenyl	Phenyl	93
Phenazine-N,N′-dioxide (IV)		1 to 2
N,N′-Bis-(α-carbethoxyisopropyl)-*p*-quinonediimine		2
p-Quinone		3
5,6-Bis-(phenylimino)-2-cyclohexene-1,4-dione-N,N′-dioxide (III)		4
Hydroquinone		5
N,N′-Diphenyl-*p*-quinonediimine		26
N,N′-Diphenyldiphenoquinonediimine-N,N′-dioxide (XIV)		109
N-Phenyl-*p*-quinoneimine-N-oxide (II)		113

[a] All the compounds were tested at 1.6×10^{-5} mole per liter. [b] Terpinolene in an atmosphere of oxygen at 26–28° in the dark.

Method II is applicable to the preparation of all N,N′-dioxides, but method I can be used only if the correspond-

(7) C. J. Pedersen, *Ind. Eng. Chem.*, 48, 1881 (1956).

(8) G. Braun, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431.

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ing *p*-quinonediimine is stable. The preparation of a number of *p*-quinonediimines with aliphatic groups on the nitrogen atoms has been described previously.[9] The *p*-quinonediimines with aromatic groups on the nitrogen atoms can be prepared in nearly quantitative yields by treating a mole of the corresponding *p*-phenylenediamine with a mole of benzoyl peroxide in benzene or chloroform. These solutions can be used for the preparation of the N,N′-dioxides without further ado.

Since the N,N′-dioxides, especially in solution, are extremely sensitive to light, their preparation must be protected from light. This property tends to make it difficult to obtain reproducible analytical and spectral data on these compounds.

N,N′-Diphenyl-*p*-quinonediimine-N,N′-dioxide (Method I).—N,N′-Diphenyl-*p*-quinonediimine (12.9 g., 0.05 mole) in 425 ml. of chloroform was mixed with 250 ml. of benzene containing 15.2 g. of perbenzoic acid (0.11 mole), and allowed to stand for 30 minutes at room temperature. The solution was washed with 500 ml. of water containing 4.8 g. of sodium hydroxide (0.12 mole), twice with water and then dried with anhydrous sodium sulfate. The solution was concentrated to 350 ml. under reduced pressure and added to 600 ml. of petroleum ether (30–60°). The orange crystals which separated overnight were filtered, washed with petroleum ether and dried at room temperature to give 12 g. of product (yield 83%).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.5; H, 4.8; N, 9.7; mol. wt., 290. Found: C, 74.8; H, 5.1; N, 9.5; mol. wt., 288 (elevation of the boiling point of benzene).

An 84% yield of the product was obtained by using a 40% solution of peracetic acid in glacial acetic acid instead of perbenzoic acid in the above method.

N,N′-Diphenyl-*p*-phenylenediamine was obtained by hydrogenating the N,N′-dioxide in methanol with a platinum catalyst. It was identified by mixed melting point (147°), and spectrum (absorption peak in ethanol, 304 mμ, ε 27,000).

N,N′-Diphenyl-*p*-phenylenediamine is also obtained by treating the N,N′-dioxide with ascorbic acid in methanol at room temperature. The N,N′-dioxide is reduced much more slowly than the corresponding quinonediimine by ascorbic acid.

N,N′-Diphenyl-*p*-quinonediimine was obtained (yield over 82%) by refluxing one mole of the N,N′-dioxide with two moles of N,N′-azo-bis-(α-isobutyronitrile) in benzene under nitrogen for three hours. No diimine was formed in the absence of the azo-catalyst. The diimine was identified by mixed melting point (185–186°), and spectrum (absorption peaks in ethanol, 304 mμ, ε 27,000; 442 mμ, ε 7,000).

The visible spectrum of the N,N′-dioxide is shown in Fig. 3. Its spectrum in concentrated sulfuric acid, when fresh, is yellow and has an absorption peak at 468 mμ, ε 1,700, but the solution becomes bright blue within 24 hours at room temperature and has a peak at 670 mμ, ε 44,000. The blue solid product which was recovered from the blue sulfuric acid solution has not yet been identified.

Instead of getting a mole of mono-N-oxide by treating one mole of N,N′-diphenyl-*p*-quinonediimine with one mole of perbenzoic acid, half a mole of the N,N′-dioxide was obtained.

The thermal stability of the N,N′-dioxide was investigated by dissolving 3×10^{-5} mole in one liter of a mixture of trichlorobenzenes, and spectrophotometrically determining the amount of the compound left after exposure to different times and temperatures. The results are shown in Table VI.

N,N′-Dioxides in which both substituents on the nitrogen atoms are aromatic are most conveniently synthesized by first making the *p*-quinonediimine with benzoyl peroxide and using this solution in method I. Method I and method II have been varied by changing the solvent as indicated in Table I. The choice of solvent is dictated by the solubility of the starting compound and the resistance of the solvent to the action of perbenzoic acid.

(9) C. J. Pedersen, United States Patent 2,741,625, April 10, 1956.

TABLE VI

THERMAL STABILITY OF N,N′-DIPHENYL-*p*-QUINONEDIIMINE-N,N′-DIOXIDE IN TRICHLOROBENZENE[a]

Temp., °C.	Minutes at temp.	Decomposed,[b] %
50	10	Nil
94	20	2
152	20	6
176	20	42
202	20	Over 82
202	140	100

[a] Concentration, 3×10^{-5} mole per liter. [b] Determined spectrophotometrically.

N,N′-Bis-(1-cyanocyclohexyl)-*p*-quinonediimine-N,N′-dioxide (Method II).—1,1′-(*p*-Phenylenediimino)-carbonitrile, 3.2 g. (0.01 mole), dissolved in 200 ml. of acetone was added to 118 ml. of benzene containing 4.35 g. of perbenzoic acid (0.0315 mole). The mixture was shaken and allowed to stand overnight at room temperature. On chilling the solution in ice-water, a precipitate formed which was filtered, washed with acetone and dried at room temperature to give 2.8 g. of orange crystals (yield 79%). The properties of this compound are given in the tables.

N,N′-Dicyclohexyl-*p*-quinonediimine-N,N′-dioxide (Method II).—N,N′-Dicyclohexyl-*p*-phenylenediamine (12.2 g., 0.045 mole), dissolved in 100 ml. of benzene was added dropwise with agitation to 468 ml. of benzene containing 19.8 g. of perbenzoic acid (0.143 mole), and kept at 5° with external cooling. The mixture was stirred for 1 hour more and washed three times with 10% aqueous sodium bicarbonate to remove the benzoic acid. The solution was dried with anhydrous sodium sulfate, concentrated under reduced pressure and cooled to yield 10.5 g. of yellow crystals (yield 77%). Other properties of this compound are given in the tables.

Anal. Calcd. for $C_{18}H_{26}N_2O_2$: C, 71.6; H, 8.61; N, 9.3. Found: C, 71.8; H, 8.62; N, 9.4.

N,N′-Diphenyldiphenoquinonediimine-N,N′-dioxide (XIV) (Method II).—N,N′-Diphenylbenzidine (0.5 g., 0.00149 mole) dissolved in 7.5 ml. of dimethylformamide was added with stirring at room temperature to 16.4 ml. of benzene containing 0.678 g. of perbenzoic acid (0.0049 mole). After 22 hours the reaction product which had precipitated was filtered, washed with benzene and petroleum ether, and dried to give 0.45 g. of purplish brown crystals (yield 83%) which melted with decomposition at 280°; maximum absorption in chloroform, 485 mμ, ε 33,000.

Anal. Calcd. for $C_{24}H_{18}N_2O_2$: N, 7.65. Found: N, 7.5.

N-Phenyl-N′-(2,4-dinitrophenyl)-*p*-quinonediimine-N,N′-dioxide (Method II).—N-Phenyl-N′-(2,4-dinitrophenyl)-*p*-phenylenediamine (7 g., 0.02 mole) partially dissolved in 200 ml. of benzene was mixed with 34 g. of 40% solution of peracetic acid in glacial acetic acid (0.179 mole of peracid) and allowed to stand in the dark at room temperature for 12 days. The deposits were filtered, washed with benzene and dried to yield 4.5 g. of maroon crystals (yield 59%). The properties of this compound are given in the tables.

Neither *p*-quinone dibenzenesulfonimide[10] nor N,N′-bis-(2,4-dinitrophenyl)-*p*-phenylenediamine could be converted to the corresponding N,N′-dioxides with perbenzoic acid.

WILMINGTON 99, DEL.

(10) R. Adams and A. S. Nagarkatti, THIS JOURNAL, **72**, 4601 (1950).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OKLAHOMA AGRICULTURAL AND MECHANICAL COLLEGE]

A Study of the Decomposition of *p*-Nitrophenethyltrimethylammonium Iodide by Means of the Hydrogen Isotope Effect[1]

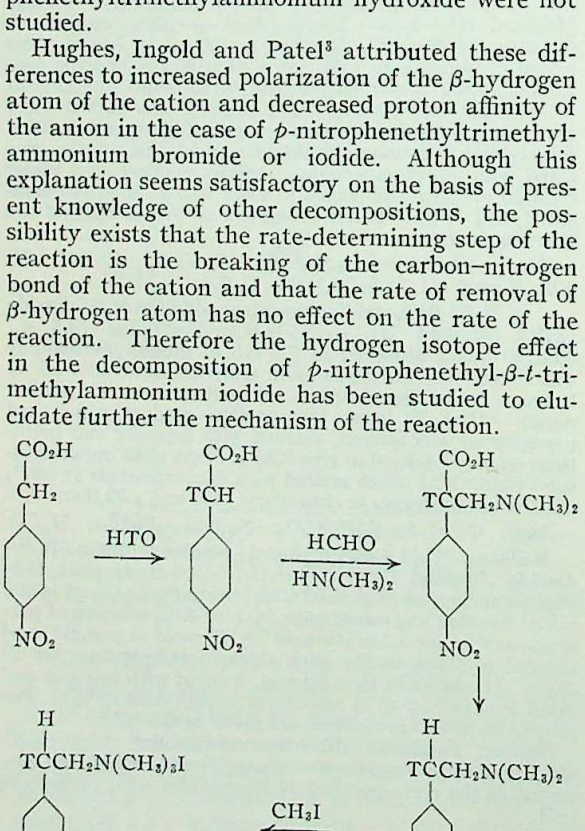
BY ERNEST M. HODNETT AND JOHN J. FLYNN, JR.

RECEIVED NOVEMBER 5, 1956

The hydrogen isotope effect in the decomposition of *p*-nitrophenethyl-β-*t*-trimethylammonium iodide in water at 100° has been measured. A hydrogen atom on the carbon adjacent to the ring is removed from a labeled molecule 7.4 times as rapidly as a tritium atom in the same position. A hydrogen atom in this same position in an inactive molecule is removed 15% faster than a hydrogen atom in the corresponding position of the labeled molecule. The existence of these differences in rate of reaction establishes the mechanism of the decomposition as being that of an attack on the hydrogen atom in the β-position to the ammonium group.

Hughes and Ingold[2] reported that the decomposition of phenethyltrimethylammonium hydroxide in water at 100° is first order in hydroxide ion as well as in the cation. *p*-Nitrophenethyltrimethylammonium iodide and the corresponding bromide each decompose in water at 100° with unimolecular kinetics. These latter decompositions are retarded by acids, unaffected by neutral salts and accelerated by bases although the rate constants were not reported. The kinetics of decomposition of *p*-nitrophenethyltrimethylammonium hydroxide were not studied.

Hughes, Ingold and Patel[3] attributed these differences to increased polarization of the β-hydrogen atom of the cation and decreased proton affinity of the anion in the case of *p*-nitrophenethyltrimethylammonium bromide or iodide. Although this explanation seems satisfactory on the basis of present knowledge of other decompositions, the possibility exists that the rate-determining step of the reaction is the breaking of the carbon–nitrogen bond of the cation and that the rate of removal of β-hydrogen atom has no effect on the rate of the reaction. Therefore the hydrogen isotope effect in the decomposition of *p*-nitrophenethyl-β-*t*-trimethylammonium iodide has been studied to elucidate further the mechanism of the reaction.



p-Nitrophenethyl-β-*t*-trimethylammonium iodide was prepared by the reactions.

Aqueous solutions of the *p*-nitrophenethyl-β-*t*-trimethylammonium iodide were sealed in tubes and held at 100° for various times. The remaining ammonium salt was precipitated as the sparingly soluble picrate and the latter dried and assayed for tritium. For low extents of reaction the product of the reaction was isolated by formation of the dibromide of the *p*-nitrostyrene which was purified and assayed. From these data it was possible to calculate the various isotope effects in the reaction.

Experimental

Preparation of *p*-Nitrophenethyltrimethylammonium Iodide.—Ten grams of phenethylamine was added during 1.5 hr. to 50 ml. of fuming nitric acid at −10°. Nitration occurred immediately; the mixture was allowed to warm slowly to 0° at which point ice and sodium hydroxide were added. The mixture of amines was extracted with ether and isolated as their hydrochlorides. A single crystallization from alcohol gave 6 g. of almost colorless plates of *p*-nitrophenethylamine hydrochloride,[4] m.p. 209–210°.

To the *p*-nitrophenethylamine obtained from 2 g. of the corresponding hydrochloride by neutralization with a base, extraction with ether and evaporation of the ether was added 5 g. of sodium carbonate, 5 ml. of absolute ethyl alcohol and with care 7 ml. of methyl iodide. After the initial vigorous reaction had subsided, it was completed by refluxing the mixture on a water-bath. The carbonate was removed by filtration, washed with ether and neutralized with 47% hydriodic acid. The quaternary ammonium iodide was collected by filtration, washed with acetone and ethyl ether and crystallized from 95% ethyl alcohol. Two grams of feathery lemon-yellow leaflets melting at 206° was obtained. The melting point reported[2] for *p*-nitrophenethyltrimethylammonium iodide is 199°.

Preparation of *p*-Nitrophenethyl-β-*t*-trimethylammonium Iodide.—*p*-Nitrophenylacetic acid (1.8 g., 0.01 mole) was placed in a tube with 1 ml. of tritiated water (7.13 mc./g.). The tube was sealed and placed in a bath at 100° for four days. The tritiated water was recovered by distillation on the vacuum line, and the acid was recrystallized once from water, dried and assayed. With an activity of 77.7 μc./mmole of acid and a recovery of 78%, the activity in the acid was 8.5% of that in the original water, but the actual loss in activity was negligible.

This *p*-nitrophenylacetic-α-*t* acid was shaken with 2 ml. of water and neutralized with a concentrated solution of dimethylamine. One milliliter of formalin was added and the solution was allowed to stand at room temperature for four days. The solid which crystallized on standing was separated by filtration. Unreacted *p*-nitrophenylacetic-α-*t* acid was recovered by acidifying the mixture with hydrochloric acid. The α-(*p*-nitrophenyl)-β-dimethylaminopropionic-α-*t* acid[5] after crystallization from water melted at 164°. The yield was 1 g. or 54% of the theory. The radioactivity of the acid was 54 μc./mmole, representing retention of 69.5% of the initial specific activity. Since on a statistical basis

(1) Supported by the U. S. Atomic Energy Commission under Contract No. AT(11-1)-71, Project No. 5, and the Research Foundation of Oklahoma A. and M. College. Abstracted from the M.S. thesis of John J. Flynn, Jr. Work performed in the Radioisotopes and Radiations Laboratory of the Research Foundation. Presented at the 130th Meeting of the A.C.S., Atlantic City, N. J., September, 1956.

(2) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 523 (1933).

(3) E. D. Hughes, C. K. Ingold and C. S. Patel, *ibid.*, 526 (1933).

(4) R. R. Gross, W. Hanhart and C. K. Ingold, *ibid.*, 255 (1927).

(5) Mannich and L. Stein, *Ber.*, **58**, 2659 (1925).

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one-half of the tritium atoms would be lost in the reaction, this recovery represents a favorable isotope effect.

The amino acid was mixed with 50 mg. of copper carbonate and 1 ml. of pyridine. The mixture was refluxed until evolution of gas had stopped. Water was added to the mixture until a reddish-brown oil separated. The oil layer was washed with water and extracted with ether. Evaporation of the ether gave *p*-nitrophenethyl-β-*t*-dimethylamine.

This amine was treated with 3 ml. of methyl iodide in a water-bath for 1 hr. *p*-Nitrophenethyl-β-*t*-trimethylammonium iodide, which crystallized out on cooling, was filtered off, recrystallized from 95% ethyl alcohol and dried. The yield from 1 g. of the aminopropionic acid was 0.3 g. (21% of theory). The activity was 50 μc./mmole and the melting point was 197°.[2]

Determination of the Isotope Effect.—A solution buffered at *p*H 7 was prepared[6] by diluting a mixture of 29.63 ml. of 0.1 *N* sodium hydroxide and 50 ml. of 0.1 *M* diacid potassium phosphate to 100 ml. Three grams of *p*-nitrophenethyl-β-*t*-trimethylammonium iodide was dissolved in 30 ml. of this buffer solution. Two 1-ml. portions were removed for confirmation of the initial concentration. Two 1-ml. portions and one 2-ml. portion were removed and sealed in small tubes for study of the reaction mixture at 50, 65 and 80% of complete reaction. The remaining solution (24 ml.) and the latter three portions were placed in an oil-bath at 100°. After 45 min. the 24-ml. portion was taken from the bath, and two 1-ml. portions were removed for determination of the extent of the reaction by precipitation of the picrate of the remaining reactant.

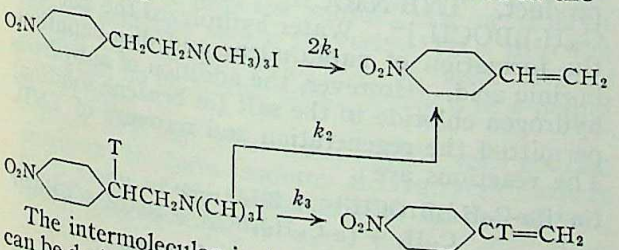
The remainder of the 24-ml. portion of the reaction solution was shaken with petroleum ether to extract *p*-nitrostyrene. The petroleum ether was then evaporated and the residue dissolved in 1 ml. of carbon tetrachloride and treated with 5 drops of bromine. The mixture was heated in a water-bath for 5 min. and the liquid evaporated off with a stream of nitrogen. The residue after recrystallization from aqueous methyl alcohol melted at 71°; m.p. reported[7] for *p*-nitrostyrene, 72–73°.

The other reaction mixtures were removed from the bath at the proper times and the extents of reaction determined by precipitation of the remaining reactant as the picrate. The picrates were assayed for tritium to obtain the molar activity of the remaining reactants.

No exchange of hydrogen atoms occurred between *p*-nitrophenethyl-β-*t*-trimethylammonium iodide and water under the same conditions at which decomposition occurred. This was demonstrated by heating *p*-nitrophenethyltrimethylammonium iodide in tritiated water until one-half of the former had decomposed. Assay of the remaining reactant showed no radioactivity.

Discussion of Results

Three reaction rate constants are involved in the process studied



The intermolecular isotope effect, $2k_1/(k_2 + k_3)$, can be derived from the equation

$$(k_2 + k_3)/2k_1 = 1 + (\log N_1/N_2)/\log (1 - f)$$

where f is the fraction reacted, and N_1/N_2 is the ratio of molar activity of the reactant at a given time to that of the initial reactant.

The secondary isotope effect, k_3/k_1, can be found from

$$k_3/2k_1 = N_3/N_1 \text{ (as } f \to 0)$$

where N_3 is the molar activity of the first product of the reaction.

The intramolecular isotope effect, k_3/k_2, can be determined from the above ratios.

The data obtained in this investigation are summarized in Table I; each figure represents from 2 to 5 assays for which the average deviation is not greater than ±0.5%.

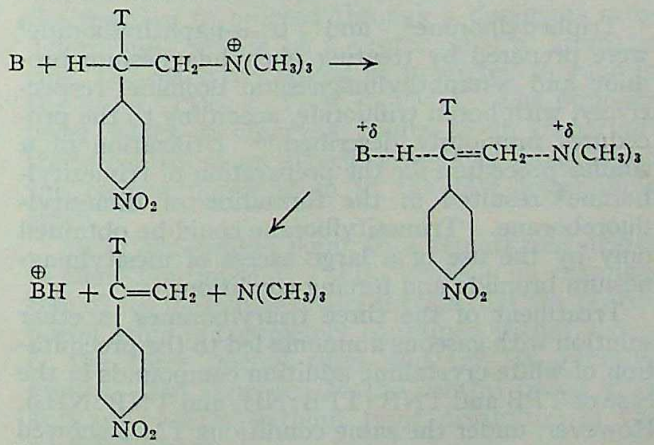
TABLE I

DECOMPOSITION OF *p*-NITROPHENETHYL-β-*t*-TRIMETHYLAMMONIUM IODIDE IN WATER AT 100°

Run	Extent of reacn., %	Activity of picrate, μc./mmole	Activity of *p*-nitrostyrene dibromide, μc./mmole	$\frac{k_3}{2k_1}$	$\frac{k_2 + k_3}{2k_1}$
I	0	11.53			
	17.3	12.33	5.43	0.455	
	43.7	14.95			0.550
	61.8	19.42			.458
II	0	12.33			
	8.6	12.70	5.18	0.414	
	82.6	29.58			0.500
III	0	12.64			
	50.0	18.07			0.484
	65.4	22.43			.459
	71.1	22.80			.510

From these results, the following values for the isotope effects have been calculated together with the average deviations, intermolecular isotope effect, $2k_1/(k_2 + k_3)$, 2.03 ± 0.11; intramolecular isotope effect, k_3/k_2, 7.4 ± 2.8; secondary isotope effect, k_3/k_1, 0.868 ± 0.04.

These ratios show beyond doubt that the decomposition of *p*-nitrophenethyl-β-*t*-trimethylammonium iodide in water at 100° occurs at a rate different from that of the normal compound. This difference proves that the bond between the hydrogen atom and the carbon atom which is adjacent to the ring is broken in the rate-determining step of the reaction. The point of attack on the molecule is therefore a hydrogen atom on the carbon atom beta to the ammonium group, as shown in the reaction scheme



Although Hughes and Ingold[2] found unimolecular kinetics for this reaction, it must be only pseudo-unimolecular.

It seems likely that the hydrogen atoms on the carbon atom adjacent to the ring are activated by the nitro group by the inductive effect as well as by conjugation. These hydrogen atoms may be ac-

(6) W. M. Clark, "The Determination of Hydrogen Ions," 2nd ed., William and Wilkins, Baltimore, Md., 1922, pp. 166–169.
(7) A. Basler, *Ber.*, **16**, 3006 (1883).

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tivated enough to react with molecules as weakly basic as water molecules, thereby producing a pseudo-unimolecular reaction. The exact nature of the attacking molecule, if any, is the subject of further investigation.

STILLWATER, OKLAHOMA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Studies in Stereochemistry. XXII. The Preparation and Reactions of Trimesitylborane. Evidence for the Non-localized Nature of the Odd Electron in Triarylborane Radical Ions and Related Free Radicals[1]

BY HERBERT C. BROWN AND VANCE H. DODSON

RECEIVED AUGUST 13, 1956

Trimesitylborane has been synthesized and its chemical behavior compared with that of triphenyl- and tri-α-naphthylboranes. In contrast to the latter compounds, trimesitylborane is far less reactive toward oxygen and water. Moreover, it fails to add either ammonia or sodium alkoxides. It is concluded that the steric effects of the three mesityl groups are so large as to hinder greatly the approach of a reacting molecule to the central atom. On the other hand, sodium reacts with trimesitylborane to form sodio derivatives analogous to those previously reported for triphenyl- and tri-α-naphthylborane. Since the vacant *p*-orbital of the boron atom is so completely blocked by the three mesityl groups, the ready formation of sodio derivatives in the case of trimesitylborane argues strongly for the entrance of the electron from the sodium atom into a non-localized orbital of the trimesitylborane molecule.

Differences in the chemical behavior of certain trialkylboranes can be correlated with the steric requirements of the alkyl groups in the boron derivative. Thus, trimethylamine forms a more stable addition compound with trimethylborane than does ammonia, whereas the reverse is true in the case of tri-*t*-butylborane.[2] Indeed, in this case trimethylamine exhibits no tendency to unite with the boron component.

It appeared of interest to examine the behavior of a borane derivative which might be expected to be even more hindered than tri-*t*-butylborane. Accordingly, the synthesis of trimesitylborane was undertaken and a study made of its chemical properties. For purposes of comparison, triphenyl- and tri-α-naphthylborane were included in the study. The behavior of these three compounds toward ammonia, sodium methoxide and *t*-butoxide, oxygen, water, sodium hydroxide and sodium metal was compared.

Results

Triphenylborane[3] and tri-α-naphthylborane[3] were prepared by treating phenylmagnesium bromide and α-naphthylmagnesium bromide, respectively, with boron trifluoride, according to the procedures previously described.[4,5] Utilization of a similar procedure for the preparation of trimesitylborane[3] resulted in the formation of dimesitylfluoroborane. Trimesitylborane could be obtained only by the use of a large excess of mesitylmagnesium bromide and forcing conditions.

Treatment of the three triarylboranes in ether solution with gaseous ammonia led to the precipitation of white crystalline addition compounds in the case of TPB and TNB ($TPB:NH_3$ and $TNB:NH_3$). However, under the same conditions TMB showed no tendency to react with ammonia. The data are summarized in Table I.

TABLE I

REACTIONS OF TPB, TNB AND TMB WITH AMMONIA

Triarylboron R_3B	Wt. of R_3B, g.	Wt. of combined ammonia, g.	Wt. of ammonia calcd. for $R_3B:NH_3$, g.
TPB	0.4380	0.0293	0.0308
	0.6753	.0471	.0473
TNB	1.2131	.0518	.0527
	0.5162	.0218	.0224
TMB	.1902	.0004	.0088
	.4458	.0007	.0206

Benzene solutions of TPB and TNB could be titrated stoichiometrically by standard solutions of sodium methoxide in methanol, using phenolphthalein as indicator. In the case of TNB it was demonstrated that the neutralization reaction involved the reaction of a sodium methoxide molecule with the TNB molecule by isolating the product, $TNB{\cdot}NaOCH_3$, presumably $Na^+[(\alpha\text{-}C_{10}H_7)_3BOCH_3]^-$. Water hydrolyzed the salt with the formation of naphthalene and di-α-naphthylborinic acid. However, the addition of anhydrous hydrogen chloride to the salt (in benzene solution) permitted the regeneration and recovery of TNB. The reactions are

$$Na^+[(\alpha\text{-}C_{10}H_7)_3B{:}OCH_3]^- + 2H_2O \longrightarrow C_{10}H_8 + (\alpha\text{-}C_{10}H_7)_2BOH + NaOH + CH_3OH$$

$$Na^+[(\alpha\text{-}C_{10}H_7)_3B{:}OCH_3]^- + HCl \xrightarrow{\text{benzene}} (\alpha\text{-}C_{10}H_7)_3B + NaCl + CH_3OH$$

In titrations of TPB and TNB with sodium *t*-butoxide in *t*-butyl alcohol the indicator changed color when less than 50% of the stoichiometric quantity of base had been added. However, benzene solutions of TMB failed to react with either base. The results of several typical titrations are summarized in Table II.

The reactivities of the triarylboranes toward oxygen were examined in α-bromonaphthalene solution. Both TPB and TNB were found to

(1) Based upon a thesis submitted by Vance H. Dodson in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) H. C. Brown, THIS JOURNAL, 67, 374 (1945).

(3) For convenience the following abbreviations will be used: triphenylborane, TPB; tri-α-naphthylborane, TNB; trimesitylborane, TMB.

(4) E. Krause and R. Nitsche, *Ber.*, 55, 1261 (1922).

(5) H. C. Brown and S. Sujishi, THIS JOURNAL, 70, 2793 (1948).

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TABLE II

REACTION OF TPB AND TNB WITH SODIUM ALKOXIDES WITH PHENOLPHTHALEIN AS INDICATOR

Sodium alkoxide	TPB Ml. base used	TPB Ml. base calcd.	TNB Ml. base used	TNB Ml. base calcd.
Methoxide	11.10[a]	11.05	18.35[b]	18.41
	5.23[a]	5.22	15.60[b]	15.74
t-Butoxide	31.5[c]	68.3	15.1[c]	35.2
	95.2[c]	188.5	21.4[c]	51.4

[a] 0.1511 *M*. [b] 0.1149 *M*. [c] 0.0023 *M*.

react with dry oxygen gas in a molar ratio of 1 O_2 to 2 R_3B. The reaction is presumed to be

$$R_3B + {}^1/_2O_2 \longrightarrow R_2BOR$$

In the case of TPB the absorption of oxygen was complete in approximately 1 hr. at 25°, whereas TNB required 50 days for completion. TMB solutions showed no absorption of oxygen in periods as long as 15 months. The results of typical experiments are summarized in Table III.

TABLE III

REACTION OF TPB AND TNB (IN α-BROMONAPHTHALENE) WITH OXYGEN

TPB[a,c] Time, hr.	TPB[a,c] Oxygen reacted ml. (S.T.P.)	TNB[d,f] Time, days	TNB[d,f] Oxygen reacted, ml. (S.T.P.)
0	0	0	0
0.25	9.9	3	7.9
0.50	11.5	17	11.9
0.75	11.6	42	12.8
1.25	12.4	54	13.2
2.25	12.4	66	13.1[e]
24.0	12.4[b]		

[a] 0.933 mmole. [b] 0.496 mmole. [c] 1.0 O_2/1.9 TPB. [d] 1.116 mmole. [e] 0.526 mmole. [f] 1.0 O_2/2.1 TNB.

TPB hydrolyzed moderately rapidly in cold water, forming a mixture of phenylboric oxide, C_6H_5BO, and phenylboronic acid, $C_6H_5B(OH)_2$. Neither TNB nor TMB showed any significant change after prolonged contact with cold water. However, refluxing water converted TNB partially into naphthalene and α-naphthylboronic acid, $C_{10}H_7B(OH)_2$. Dilute sodium hydroxide rapidly converted TPB into the sodium salt of phenylboronic acid and slowly converted TNB into the sodium salt of α-naphthylboronic acid. Dilute alkali had no noticeable effect on TMB in a period of four days.

Both TPB and TNB react readily with sodium amalgam to form sodium derivatives[6,7] which have many of the characteristics of the triarylmethyl free radicals.[8]

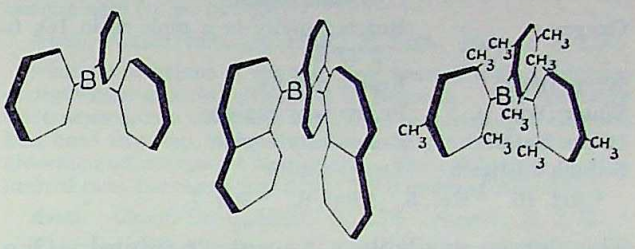
$$(C_6H_5)_3B + Na \longrightarrow [(C_6H_5)_3B\cdot]^-Na^+$$

Treatment of TMB with sodium amalgam in dry ethyl ether led to the take-up of sodium and the formation of a colored addition compound. The amount of sodium reacted could be varied from TMB·Na to TMB·2Na, depending upon the concentration of sodium in the amalgam and the reaction time.[9]

(6) E. Krause and H. Polack, *Ber.*, **59**, 777 (1926).
(7) E. Krause and P. Nobbe, *ibid.*, **63**, 940 (1930).
(8) H. E. Bent, THIS JOURNAL, **57**, 1259 (1935).
(9) A detailed study of the reaction of TMB with sodium has recently appeared; T. L. Chu and T. J. Weismann, *ibid.*, **78**, 23 (1956).

Discussion

Examination of molecular models of the three triarylboranes indicates that the shielding of the boron atom by the three surrounding aryl groups increases in the order TPB < TNB < TMB. Simplified line drawings of the three compounds are shown in Fig. 1.



Triphenylboron Tri-α-naphthylboron Trimesitylboron

Fig. 1.—Diagrams illustrating steric situation of the central boron atom in TPB, TNB and TMB.

Support for this conclusion is provided by the available data summarized in Table IV.

Ammonia reacts with both TPB and TNB, but not with TMB, whereas the more hindered base, trimethylamine, reacts only with TPB. Even sodium methoxide, a very strong base with low steric requirements, fails to react with TMB.

The reaction of oxygen with organoboranes is believed to proceed by a direct attack on the central boron atom by the oxygen molecule.[10] The remarkable difference in the reactivities of TPB, TNB and TMB with oxygen is in accord with this interpretation.

The hydrolysis is catalyzed by acid. In the similar acid-catalyzed solvolysis of aryltrimethylsilanes,[11] it has been shown the reaction proceeds through an attack of a proton on the aromatic ring and a solvent molecule on the silicon atom. If the steric requirements of the groups on the silicon atom are maintained constant, the reaction rate increases with electron-donating substituents in a manner typical of that to be expected for an electrophilic substitution. In the present case, were the reaction to proceed through a dominant rate-determining attack of a proton on the aromatic ring, the reactivity would be predicted to vary in the order, TPB < TNB < TMB. The opposite order which is observed points to an important steric control of an attack of a water molecule on the central boron atom in the rate-determining stage.

All of the results point to a remarkable degree of steric hindrance in TMB. Indeed, an examination of the molecular model reveals that the central boron atom is completely contained within a cage of the three phenyl rings and the six *o*-methyl groups. No approach to the central boron atom appears possible without prior disruption of this protecting cage.

On this basis the ready reaction of sodium amalgam with TMB is particularly interesting.

The three alkyl or aryl groups in a borane derivative, R_3B, are believed to utilize sp^2-hybrid orbitals.

(10) H. C. Brown, H. I. Schlesinger and M. G. VanCampen, *ibid.*, **60**, 121 (1938).
(11) C. Eaborn, *J. Chem. Soc.*, 3148 (1953).

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TABLE IV

A COMPARISON OF THE REACTIONS OF TPB, TNB AND TMB

Reagent	Triphenylborane	Tri-α-naphthylborane	Trimesitylborane
Ammonia	Forms a 1:1 addition compound	Forms a 1:1 addition compound	No reacn.
Trimethylamine	Forms a 1:1 addition compound[a]	No reaction[b]	No reacn.
Sodium methoxide	Forms a sodium methoxide salt	Forms a sodium methoxide salt	No reacn.
Sodium *t*-butoxide	Forms a sodium *t*-butoxide salt to some extent	Forms a sodium *t*-butoxide salt to some extent	No reacn.
Oxygen	Reacts rapidly in a mole ratio $1O_2$ to 2 TPB	Reacts very slowly in a mole ratio $1O_2$ to 2TNB	No reacn.
Water (cold)	Reacts rapidly	No reaction	No reacn.
Water (hot)	Reacts very rapidly	Reacts slowly	No reacn.
Dilute NaOH	Reacts very rapidly	Reacts slowly	No reacn.
Sodium amalgam	Reacts readily[c]	Reacts readily[d]	Reacts readily

[a] Ref. 16. [b] Ref. 5. [c] Ref. 6. [d] Ref. 7.

This leaves available a vacant 2*p*-orbital. One possible interpretation of the reaction with triarylboranes involves the transfer of the electron from sodium to this vacant 2*p*-orbital.

Recently, the magnetic susceptibility of TMB·Na was examined.[9] The results indicate that in dilute solution in tetrahydrofuran the molecule is monomeric and possesses one unpaired electron.

However, there are difficulties in assigning this odd electron to the 2*p*-orbital. The boron atom is so completely surrounded by the three mesityl groups that this does not appear to be a reasonable electronic structure for $[TMB\cdot]^-$ unless the improbable assumption is made that the odd electron has no steric requirements. Partial or complete modification of the structure to sp^3-hybrid orbitals offers no solution to the difficulty. The only reasonable solution to the dilemma involves the assumption that the electron transferred from the sodium atom to the TMB must enter an orbital associated with the entire molecule rather than an orbital associated primarily with the boron atom.[12]

The behavior of TPB, TNB and TMB toward sodium amalgam is qualitatively quite similar. On this basis there appears to be no reason to assign a special structure or interpretation to the TMB derivative. It is concluded, therefore, that the odd electron in the monosodio derivatives of the triarylboranes is probably associated with an orbital common to the entire molecule.

It is tempting to extrapolate this conclusion to the triarylmethyls. This has, of course, been the favored interpretation of the electronic structure of these free radicals.[13] However, recent results of Weissman and Snowden appear to point to another conclusion.[14] As a result of data obtained in a magnetic resonance study of triphenylmethyl, these authors have concluded that the odd electron in this free radical appears to be relatively closely associated with the nucleus of the methyl carbon atom. If this conclusion is supported by further work, it will suggest a major difference in the electronic structures of the triarylborane radical ions and the triarylmethyl free radicals and will require a major revision of present theories regarding the electronic structures of these free radicals. The present results argue strongly for a non-localized configuration for the odd electron in the trimesitylborane radical ion and, presumably, in the related triarylmethyl free radicals.

(12) In the reaction of sodium with polycyclic hydrocarbons in certain ether solvents, the electron is also assumed to enter a vacant orbital within the aromatic system, forming a free radical ion similar to that here postulated for TMB·Na; D. Lipkin, D. E. Paul, J. Townsend and S. I. Weissman, *Science*, **117**, 534 (1953).

(13) G. W. Wheland, "Resonance in Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1955, pp. 381–393.

(14) S. I. Weissman and J. C. Sowden, THIS JOURNAL, **75**, 503 (1953).

Experimental Part

Preparation of Triarylborane Compounds. (A) Triphenylborane.—The procedure used to prepare TPB was essentially that described by Krause.[4] TPB was obtained in yields of approximately 60% as a white crystalline solid, m.p. 138° under nitrogen. The product was stored in sealed tubes and handled in a nitrogen atmosphere in subsequent experiments. The compound was analyzed for boron by the method described by Fowler and Kraus.[15] This same procedure was used in all of the boron analyses reported in this paper.

Anal. Calcd. for $C_{18}H_{15}B$: B, 4.47. Found: B, 4.51.

(B) Tri-α-naphthylboron.—TNB was prepared according to the procedure outlined by Brown and Sujishi.[5] Crude α-bromonaphthalene (Columbia Organic Chemicals Co.) was distilled and the fraction, b.p. 146–148° at 20 mm., was used. The TNB was crystallized from benzene and dried in a stream of nitrogen gas. The benzene of crystallization was removed by slowly warming the solid in a round bottom flask to 160° at 0.5 mm. to a constant weight. The product melted at 205–206°.

Anal. Calcd. for $C_{30}H_{21}B$: B, 2.76. Found: B, 2.74.

(C) Trimesitylboron.—Because of the difficulties experienced in forcing the reaction to proceed to the synthesis of trimesitylboron, the experimental procedure will be described in some detail. A standard 500-ml. three-necked flask (round bottom), equipped with a dropping funnel, ball joint stirrer, and water cooled condenser, was used. In a typical preparation, an anhydrous ethyl ether solution of bromomesitylene (0.240 mole, 47.8 g.), was added dropwise from the funnel to the flask containing magnesium turnings (0.29 g. at., 7.0 g.) and 100 ml. of anhydrous ether. The solution was refluxed during the addition period, which required approximately one hour, and for 4 to 5 hr. after the addition was complete. The solution was then allowed to stand at room temperature overnight. A slow but steady stream of nitrogen was passed through the system during the reflux period and a constant positive pressure of nitrogen gas was maintained in the system during the standing period. Dry toluene (150 ml.) was added to the flask and the mixture was heated to reflux temperature for 30 minutes to dissolve the precipitated Grignard reagent. Freshly distilled boron trifluoride etherate (0.036 mole, 5.1 g.), dissolved in 50 ml. of ether, was transferred to the dropping funnel and added to the stirred and refluxed solution of the Grignard over a period of 30 minutes. The condenser was replaced by a "goose-neck" adapter and the ether was distilled from the reaction flask. The condenser was replaced in the system and 50 ml. of toluene was added to the flask, and the solution was stirred and refluxed for 4 hr. On cooling to

(15) D. Fowler and C. Kraus, *ibid.*, **62**, 1143 (1940).

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room temperature, the solution separated into an upper clear brick red layer and a lower yellow brown viscous layer. The entire reaction mixture was transferred to a 1-liter separatory funnel containing 300 ml. of cold water and crushed ice. After the initial hydrolysis reaction had subsided, 55 ml. of concentrated hydrochloric acid was added to dissolve the insoluble magnesium compounds and unreacted magnesium. Ice was added from time to time to keep the reaction mixture cool. After thoroughly shaking the mixture over a period of 20 minutes, the slightly turbid aqueous layer was withdrawn and the organic layer was washed with three 200-ml. portions of cold water. The yellow organic layer was then placed over calcium chloride to dry. Approximately one-half of the solvent was removed by distillation. The concentrated solution was treated with 150 ml. of 95% ethanol. A white to pale yellow solid immediately precipitated from solution. The solid was filtered and recrystallized from 300 ml. of 95% ethanol. The snow-white product weighed 4.5 g. and melted at 190.5–191.5°. Approximately two more grams of recrystallized product was obtained by evaporating the ethanol solution to one-half its original volume and allowing the solution to stand for 4 hours at room temperature.

Anal. Calcd. for $C_{27}H_{33}B$: B, 2.94; H, 9.03; C, 88.03. Found: B, 2.90; H, 9.10; C, 88.09.

Solubility of TMB.—An excess of solid TMB was added to 40 ml. of the solvent in a vessel, and the vessel was stoppered and placed in a constant temperature bath for 48 hr. During this period the mixture was shaken intermittently to facilitate saturation. Five ml. portions of the clear supernatant solution were withdrawn with a pipet and the solvent was removed by warming the solutions on a hot-plate at 60 to 70°. The results indicated a solubility per 100 ml. of solution at 25° of 6.96 g. in carbon tetrachloride, 1.25 g. in acetone, 0.08 g. in 95% ethanol, 4.98 g. in ethyl ether and 16.5 g. in benzene.

Preparation of Dimesitylboron Fluoride.—Mesitylmagnesium bromide was prepared according to the procedure outlined for TMB. Boron trifluoride etherate (0.073 mole) was added to the Grignard reagent (0.228 mole) over a period of 1.5 hr., and the reaction mixture was refluxed for 2 more hr. After standing at room temperature for 24 hr., the solution separated into two layers. The upper yellow orange ether layer was transferred, under nitrogen pressure, to a 125-ml. claisen flask and the ether was removed by distillation at atmospheric pressure. The residue was distilled at reduced pressure. A colorless liquid which distilled over the range 127–129° at 0.5 mm. pressure solidified in the receiver on cooling. The product melted at 75.5–76.0° in a sealed tube.

Anal. Calcd. for $C_{18}H_{22}BF$: B, 4.04; F, 7.09. Found: B, 3.97; F, 6.99.

When dimesitylboron fluoride was treated with water, dimesitylborinic acid was formed. After recrystallization from petroleum ether, the white crystalline solid melted at 140–141°.

Anal. Calcd. for $C_{18}H_{22}BOH$: C, 81.21; H, 8.73; B, 4.05. Found: C, 80.95; H, 8.99; B, 3.95.

Preparation of Ammonia Addition Compounds.—Anhydrous ether solutions of TPB and TNB were saturated with dry ammonia gas, and the solvent was removed at reduced pressure. The triarylboron compounds showed a gain in weight that checked well with that calculated for TPB:NH_3 and TNB:NH_3. Their melting points were in good agreement with those values given in the literature.[5,16] The very slight gain in weight shown by TMB when treated in a similar way was attributed to occluded solvent and not to reacted ammonia.

Titration with Sodium Alkoxides.—Anhydrous benzene solutions of TPB and TNB were titrated with freshly prepared and standardized sodium methoxide and sodium *t*-butoxide, using phenolphthalein as an indicator. Benzene solutions of TMB turned pink after the addition of the first drop of the alkoxide solution.

Benzene solutions of TNB which had been titrated with sodium methoxide to the phenolphthalein end-point were placed in a vacuum line, and the solvents were removed at reduced pressure. The white solid residue did not melt on heating but turned brown at 155–160° and black at 200°.

Anal. Calcd. for $Na^+[C_{30}H_{21}B{:}OCH_3]^-$: B, 2.42. Found: B, 2.40.

Benzene solutions of the salt were shaken with 50 ml. of distilled water and titrated with standard hydrochloric acid to a phenolphthalein end-point. The amount of titratable material, which was assumed to be sodium hydroxide, was found to be present in a mole ratio of 1:1 with respect to the original TNB. Other products formed by the hydrolysis of the salt were identified as naphthalene and di-α-naphthylborinic acid (m.p. 148–150°).

Anal. Calcd. for $C_{20}H_{14}BOH$: B, 3.85. Found: B, 3.83.

Benzene solutions of the salt were treated with a solution of hydrogen chloride dissolved in benzene. The solutions were heated on a hot-plate until all excess hydrogen chloride had been expelled, then filtered free of precipitated sodium chloride and evacuated to dryness. The solid white residue melted over the range 204–206° (TNB melts at 205–206°).

Anal. Calcd. for $C_{30}H_{21}B$: B, 2.76. Found: B, 2.73.

Reaction with Oxygen.—Weighed samples of TPB were transferred, in a nitrogen atmosphere, to the reaction bulb and dissolved in 20.0 ml. of α-bromonaphthalene. The bulb was attached to the reaction system (ball-joint), and the system was evacuated to a pressure of 0.5 mm. Pure dry oxygen gas was allowed to flow into the system and enough mercury was run into a side-arm U-tube to seal the system. The arm of the U-tube adjacent to the reaction flask was previously calibrated to represent the volume of the reaction flask and glass tubing to the mark on the side arm. A mercury-leveling device was attached to the open side of the U-tube and the pressure of the oxygen in the sealed system was adjusted to that of the atmosphere. The volume, pressure and temperature of the oxygen in the system were recorded at the beginning of the experiment and at various time intervals thereafter. Corrections for the volume of solvent in the reaction bulb were made for each reading. The reacting solution was continually agitated with a magnetic stirrer during the course of the reaction. Solutions of TNB and TMB in the same solvent were treated in a like manner.

A number of organic compounds were investigated and α-bromonaphthalene was found to fit best the needs for a solvent, having a very low vapor pressure and showing little or no signs of reacting with oxygen. A 20.0-ml. volume of the solvent was found to absorb 1.3 ml. of oxygen at S.T.P. This volume was subtracted from the final measured volume of reacted oxygen before calculating the number of moles of oxygen that had reacted.

Reaction with Water.—Mixtures of solid TPB and distilled water were shaken intermittently for a period of 8 hr. at room temperature. A pale brown residue was formed and this was filtered, dried in air and recrystallized from petroleum ether. The recrystallized material melted at 201.5–202.5° and was identified as phenylboric oxide. Evaporation of the aqueous solution produced a small amount of white solid, melting at 215°. The latter product was found to be phenylboronic acid. Refluxing a TPB and water mixture for 20 minutes produced the same materials.

Anal. Calcd. for C_6H_5BO: B, 10.41. Found: B, 10.32. Calcd. for $C_6H_5B(OH)_2$: B, 8.89. Found: B, 8.83.

TNB did not react with distilled water after treatment at room temperature for 8 hr. The melting point of the insoluble residue differed from that of the starting material by less than 1°. After refluxing in water for 1 hr., the insoluble residue was identified as a mixture of naphthalene and unreacted TNB. The aqueous solution yielded a white solid (m.p. 195°) on evaporation to dryness which was identified as α-naphthylboronic acid. A refluxing period of 2.5 hr. was required for complete conversion to these products.

Anal. Calcd. for $C_{10}H_7B(OH)_2$: B, 6.29. Found: B, 6.22.

Samples of TMB failed to react with water at room temperature after 8 hr. and after refluxing for 8 hr. The melting points of the starting material and the final product varied by less than 1°.

Reaction with Aqueous Sodium Hydroxide.—TPB was shaken with 0.05 *N* aqueous sodium hydroxide for a period of 4 hr. at room temperature. At the end of this time the samples had reacted completely and the products had gone into solution. The solution was neutralized with dilute hydrochloric acid and extracted with ether. The ether ex-

(16) E. Krause, *Ber.*, **57**, 813 (1924).

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tract was washed with water and evaporated to dryness. The residue was recrystallized from petroleum ether and identified as phenylboronic acid (m.p. 215°).

TNB was treated in the same way but the mixture was allowed to stand at room temperature for four days. The insoluble residue present was filtered and identified as a mixture of naphthalene and unreacted TNB. The filtrate was neutralized and extracted with ether. A small amount of α-naphthylboronic acid was obtained from the ether extract (m.p. 195°). TMB failed to react with 0.05 *N* sodium hydroxide after a period of 4 days at room temperature.

Reaction with Sodium Metal.—The procedures used were similar to those previously utilized for TPB[6] and TNB.[7] Since a detailed study recently has been described for the reaction of sodium with TMB,[9] we shall give only a brief summary of our observations.

A weighed sample of TMB was added to freshly prepared sodium amalgam in a dry glass bulb, and the bulb was swept out with dry nitrogen gas. Anhydrous ether was added and the bulb was sealed and set aside at room temperature. The bulb was shaken several times during the reaction period. The solution became pink, then purple and finally a yellow solid crystallized from the solution. At the end of the reaction period, the seal was broken and the ether solution was transferred to a flask containing distilled water. The bulb was rinsed several times with ether to remove all of the yellow solid adhering to the walls of the bulb. The rinses were added to the water and the ether was removed from the mixture by warming on a hot-plate. As the ether evaporated from the mixture, a white solid precipitated in the flask. The aqueous residue, containing the white precipitate, was titrated with standard hydrochloric acid to a phenolphthalein end-point. The insoluble residue was identified as TMB. The base was assumed to be sodium hydroxide. For samples that had been allowed to stand for 24 hr. the mole ratio of sodium to TMB varied from 1.09:1 to 1.53:1. A mixture of TMB and sodium amalgam which had been set aside for two months gave a 1.9 (Na) to 1 (TMB) mole ratio. No significant difference was noted between the ease of reaction of sodium with TMB as compared to TPB[6] or TNB.[7]

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

(±)-18-Fluoro-10-methyloctadecanoic Acid (Fluorotuberculostearic Acid)[1]

BY F. L. M. PATTISON AND R. G. WOOLFORD

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Racemic fluorotuberculostearic acid (Vb) was prepared readily from 8-fluoroöctanoic acid by anodic coupling reactions. The sodium salt showed antitubercular activity *in vitro* but not *in vivo*.

From the knowledge gained from the study of fluoroacetates[2] and of other series of toxic compounds,[3] it has become increasingly apparent that certain biological systems are unable to differentiate between organic compounds containing the methyl group (CH_3^-) and the fluoromethyl group (FCH_2^-), respectively. Compounds containing the latter group, once assimilated, may then disturb or block the enzyme systems normally responsible for the metabolism of the non-fluorinated materials.

Occurring in the lipid sheath of the tubercle bacillus are a variety of fatty acids, including the levorotatory isomer of 10-methyloctadecanoic acid (tuberculostearic acid).[4] By applying the above observations regarding the fluoromethyl group to this acid, it was argued that 18-fluoro-10-methyloctadecanoic acid (fluorotuberculostearic acid) might readily be assimilated by the tubercle bacillus and that the toxic action of the fluorine atom might then result in its death. It was for this reason then that fluorotuberculostearic acid was prepared. If the racemic acid had shown high antitubercular activity, its resolution would have been undertaken; since its activity *in vivo* was low, this proved to be unnecessary. All compounds described in this article are therefore in the racemic form.

Fluorotuberculostearic acid was prepared by two routes, as is shown below. The work of Linstead, Lunt and Weedon[5] was of great value in selecting the experimental conditions. Some observations regarding symmetrical and unsymmetrical anodic coupling reactions of ω-fluorocarboxylic acids have been presented earlier.[6]

8-Fluoroöctanoic acid[6,7] (I) and methyl hydrogen β-methylglutarate[5] (II) (100% excess) on electrolysis formed a mixture of methyl 11-fluoro-3-methylundecanoate (IIIa), 1,14-difluorotetradecane and dimethyl β,β′-dimethylsuberate. The crude mixture, after hydrolysis with 10% sodium hydroxide, was separated into neutral and acidic fractions; the former gave 1,14-difluorotetradecane (20%), while the latter gave 11-fluoro-3-methylundecanoic acid (IIIb) (45%) and β,β′-dimethylsuberic acid (37%).

The anodic coupling of IIIb and methyl hydrogen azelate followed by hydrolysis of the resultant mixture gave the two symmetrical products, 1,20-difluoro-9,12-dimethyleicosane (23%) and hexadecanedioic acid (36%); a crude fraction of fluorotuberculostearic acid (Vb) also was obtained; this was found to be contaminated with azelaic acid, which had codistilled during attempted purification. Attempts to remove this impurity by preferential solubility in hot water and by treatment with alcoholic lead acetate[5] were unsuccess-

(1) Issued as DRB Report No. SW-35.

(2) See, for example, M. B. Chenoweth, *J. Pharmacol. Exptl. Therap.*, **97**, 383 (1949); R. A. Peters, *Endeavour*, **13**, 147 (1954).

(3) F. L. M. Pattison, *Nature*, **172**, 1139 (1953); **174**, 737 (1954); F. L. M. Pattison, W. C. Howell, A. J. McNamara, J. C. Schneider and J. F. Walker, *J. Org. Chem.*, **21**, 739 (1956), and subsequent papers in the series.

(4) R. J. Anderson and E. Chargaff, *J. Biol. Chem.*, **85**, 77 (1929); M. A. Spielman, *ibid.*, **106**, 87 (1934); F. S. Prout, J. Cason and A. W. Ingersoll, THIS JOURNAL, **70**, 298 (1948); S. Ställberg-Stenhagen, *Arkiv Kemi, Mineral. Geol.*, **26A**, No. 12, (1948); G. A. Schmidt and D. A. Shirley, THIS JOURNAL, **71**, 3804 (1949).

(5) R. P. Linstead, J. C. Lunt and B. C. L. Weedon, *J. Chem. Soc.*, 3331 (1950).

(6) F. L. M. Pattison, J. B. Stothers and R. G. Woolford, THIS JOURNAL, **78**, 2255 (1956).

(7) F. L. M. Pattison, S. B. D. Hunt and J. B. Stothers, *J. Org. Chem.*, **21**, 883 (1956).

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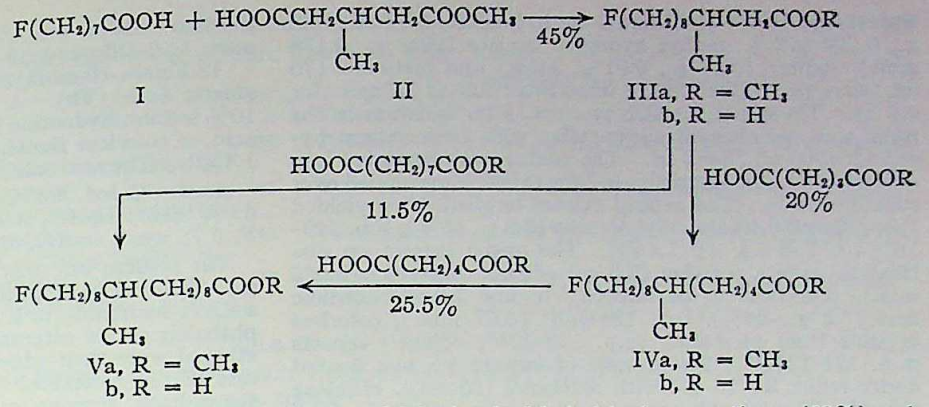

ful. The crude acid was therefore re-esterified and fractionated to give methyl fluorotuberculostearate (Va) (11.5%). A portion of the pure ester was hydrolyzed with 10% sodium hydroxide and fractionated to give the pure fluorotuberculostearic acid (Vb). The acid was converted to the sodium salt for biological testing (see below).

Because of the above purification difficulties, methyl fluorotuberculostearate was prepared from 11-fluoro-3-methylundecanoic acid (IIIb) by a route involving two coupling reactions. The first of these, using methyl hydrogen glutarate, yielded on distillation methyl 14-fluoro-6-methyltetradecanoate (IVa) (20%), dimethyl suberate (57%) and 1,20-difluoro-9,12-dimethyleicosane (21%). The ester IVa was hydrolyzed to the acid IVb (93%), which in turn was coupled with methyl hydrogen adipate to give methyl fluorotuberculostearate (Va) (25.5%); dimethyl sebacate also was isolated (30%). This longer method, while proceeding in lower over-all yield, avoided some of the separation and purification difficulties encountered in the shorter method.

Sodium fluorotuberculostearate was screened[8] against virulent *Mycobacterium tuberculosis* var. *hominis* (strain H37Rv) both *in vitro* and *in vivo*. In the former, it caused complete inhibition of growth at a concentration of 1.25 γ/ml. in the absence of bovine serum but was inactive at a concentration of 20 γ/ml. in a medium containing 10% bovine serum. Because of the high toxicity, the diet concentration for the *in vivo* test was reduced from 0.125% to 0.0125%; at this lower concentration, the compound did not prolong the lives of tuberculous mice and is therefore inactive in what must be considered the crucial test.

Sodium fluorotuberculostearate was found to have an L.D. 50 of 2.7 mg./kg. (intraperitoneal injection into mice). The tolerated diet level of 0.0125% used on the tuberculous mice probably corresponds to just under 25 mg./kg./day. Of the other intermediates and by-products, 11-fluoro-3-methylundecanoic acid (L.D. 50, 2.42 mg./kg.) and 1,20-difluoro-9,12-dimethyleicosane (L.D. 50, 57 mg./kg.) were subjected to the usual toxicological screening by intraperitoneal injection into mice. Some of these results will be discussed in a future communication.

Experimental[9]

Procedure.—The equipment, method and conditions were the same as previously described.[6]

Intermediates.—8-Fluoroöctanoic acid[6,7] was prepared by the oxidation of 8-fluoroöctanol.[10] Methyl hydrogen β-methylglutarate was prepared as described by Linstead, Lunt and Weedon.[5] Methyl hydrogen adipate (62%) and azelate (67%) were prepared by the modified procedure[10] of Swann, Oehler and Buswell.[11] Methyl hydrogen glutarate was prepared from glutaric acid by conversion to the anhydride, followed by treatment with methanol.

11-Fluoro-3-methylundecanoic Acid (IIIb).—A mixture of 8-fluoroöctanoic acid (20.0 g., 0.123 mole), methyl hydrogen β-methylglutarate (40.0 g., 0.25 mole), sodium (0.46 g., 0.02 g. atom) and methanol (70 ml.) was electrolyzed at 1.9 amp. for 6 hr. by the procedure described for unsymmetrical couplings.[6] The crude neutral product, having been isolated in the usual way,[6] was hydrolyzed by heating under reflux with 10% aqueous sodium hydroxide (300 ml.) for 3 hr. The product was separated into neutral and acidic fractions, and the ethereal extracts of each were dried over sodium sulfate. The neutral fraction yielded 1,14-difluorotetradecane (2.9 g., 20%), b.p. 146–147° (10 mm.), n_D^{25} 1.4224. We have previously reported[6] b.p. 148° (11 mm.) and n_D^{25} 1.4218. Fractionation of the acidic fraction through a modified Podbielniak column yielded 11-fluoro-3-methylundecanoic acid (12.0 g., 45%), b.p. 152–153° (2.7 mm.), n_D^{25} 1.4393. *Anal.* Calcd. for $C_{12}H_{23}O_2F$: C, 66.02; H, 10.61. Found: C, 66.27; H, 10.81. Further distillation of the acidic residue through a short Vigreux column yielded β,β'-dimethylsuberic acid (9.3 g., 37%), b.p. 184–186° (1.0 mm.), m.p. 87–90°. Linstead, Lunt and Weedon[12] report m.p. 90–92° for a mixture of stereoisomeric β,β'-dimethylsuberic acids.

14-Fluoro-6-methyltetradecanoic Acid (IVb).—A mixture of 11-fluoro-3-methylundecanoic acid (IIIb) (15.0 g., 0.069 mole), methyl hydrogen glutarate (20.1 g., 0.138 mole), sodium (0.23 g., 0.01 g. atom) and methanol (70 ml.) was electrolyzed at 1.7 amp. for 4.5 hr. The cell contents were diluted with water, neutralized with acetic acid and thoroughly extracted with ether. The extracts were washed with sodium carbonate and with water and were dried over sodium sulfate. After removal of the ether, the residue yielded three products on careful fractionation: (1) dimethyl suberate (7.9 g., 57%) b.p. 142–144° (15 mm.), n_D^{25} 1.4320; Vogel[13] reports b.p. 148° (20 mm.), n_D^{20} 1.43370. (2) Methyl 14-fluoro-6-methyltetradecanoate (IVa) (3.8 g., 20%), b.p. 120–121° (0.10 mm.), n_D^{25} 1.4387. *Anal.* Calcd. for $C_{16}H_{31}O_2F$: C, 70.04; H, 11.39. Found: C, 70.36; H, 11.26. (3) 1,20-Difluoro-9,12-dimethyleicosane (2.45 g., 21%), b.p. 156–157° (0.25 mm.), n_D^{25} 1.4438. *Anal.* Calcd. for $C_{22}H_{44}F_2$: C, 76.23; H, 12.79. Found: C, 76.42; H, 12.55.

The ester IVa (3.0 g., 0.011 mole) was hydrolyzed with 10% sodium hydroxide (50 ml.) by heating under reflux until homogeneous (*ca.* 45 minutes). The solution was cooled, diluted with water, acidified with dilute hydrochloric acid and extracted with ether. The extracts were washed with water and dried over sodium sulfate. After removal of the ether, the residue on fractionation through a short Vigreux column yielded 14-fluoro-6-methyltetradecanoic acid (2.5 g., 93%), b.p. 146° (0.10 mm.), n_D^{25} 1.4454.

Anal. Calcd. for $C_{15}H_{29}O_2F$: C, 69.20; H, 11.23. Found: C, 69.47; H, 11.25.

Methyl 18-Fluoro-10-methyloctadecanoate (Methyl Fluorotuberculostearate) (Va). (a) From 11-Fluoro-3-methyl-

(8) Carried out by Mr. Leonard Doub and Dr. M. W. Fisher, Parke, Davis and Co., Detroit, Mich.

(9) (a) The microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J., and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.; (b) the melting points and boiling points are uncorrected.

(10) F. L. M. Pattison, W. C. Howell, A. J. McNamara, C. C. J. Culvenor, Schneider and J. F. Walker, *J. Org. Chem.*, 21, 739 (1956).

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undecanoic Acid.—11-Fluoro-3-methylundecanoic acid (15.0 g., 0.069 mole), methyl hydrogen azelate (28.0 g., 0.139 mole), sodium (0.23 g., 0.01 g. atom) and methanol (70 ml.) were electrolyzed by the usual procedure at 1.7 amp. for 4.5 hr. The crude reaction product, after isolation in the usual way, was heated under reflux with 10% sodium hydroxide (200 ml.) for 3 hr. The mixture was separated into neutral and acidic fractions, and the extracts were dried over sodium sulfate. The neutral extract on distillation yielded 1,20-difluoro-9,12-dimethyleicosane (2.8 g., 23%), b.p. 149–150° (0.15 mm.), n_D^{25} 1.4438. The acidic extract on distillation gave a fraction (3.6 g.) of b.p. 148–154° (0.025 mm.), presumed to be impure Vb, and hexadecanedioic acid (7.2 g., 36%), b.p. 184–188° (0.07 mm.), colorless crystals from methanol, m.p. 123–124°; Chuit[14] reports m.p. 124–124.2°. The sample of impure Vb was heated under reflux for 16 hr. with methanol (20 ml.), ethylene chloride (25 ml.) and concentrated sulfuric acid (0.2 ml.).[15] After dilution with water, the ethylene chloride layer was separated and distilled through a short Vigreux column to yield methyl fluorotuberculostearate (2.5 g., 11.5%), b.p. 149–150° (0.10 mm.), n_D^{25} 1.4433.

Anal. Calcd. for $C_{20}H_{39}O_2F$: C, 72.68; H, 11.90. Found: C, 72.88; H, 11.90.

(b) **From 14-Fluoro-6-methyltetradecanoic Acid.**—A mixture of 14-fluoro-6-methyltetradecanoic acid (2.0 g., 0.0077 mole), methyl hydrogen adipate (2.5 g., 0.0156 mole), sodium (0.035 g., 0.0015 g. atom) and methanol (75 ml.) was electrolyzed at 1.5 amp. for 50 minutes. Isolation and distillation of the products in the usual way gave two fractions: (1) dimethyl sebacate (1.08 g., 30%), b.p. 76–78° (0.02 mm.), n_D^{25} 1.4368; Stahl and Pessen[16] report n_D^{25} 1.4368. (2) Methyl fluorotuberculostearate (0.62 g., 25.5%), b.p. 126–127° (0.02 mm.), n_D^{25} 1.4433. The distillation residue was too small to allow of the isolation of pure 1,26-difluoro-9,18-dimethylhexacosane.

18-Fluoro-10-methyloctadecanoic Acid (Fluorotuberculostearic Acid) (Vb).—A portion of Va was hydrolyzed with 10% sodium hydroxide in the usual manner to yield the free acid, a colorless liquid of b.p. 159–160° (0.05 mm.), n_D^{25} 1.4500. The acid solidified just below room temperature.

Anal. Calcd. for $C_{19}H_{37}O_2F$: C, 72.10; H, 11.79; F, 6.00; neut. equiv., 316.5. Found: C, 72.14; H, 11.68; F, 5.7; neut. equiv., 318.2.

The sodium salt was prepared as follows: the acid (1.3 g.), dissolved in ethanol (20 ml.), was titrated with 0.25 *N* sodium hydroxide to a faint pink end-point, using phenolphthalein as an external indicator. A few drops of Vb in ethanol were then added to return the solution to the acid side of the indicator. The solution was evaporated on a steam-bath, forming a colorless solid. After drying in a vacuum desiccator, the sodium salt was found to be non-hygroscopic and sufficiently soluble in water for biological testing.

Acknowledgments.—The work described herein was carried out under Contract (DRB X-24) with the Defence Research Board of Canada, to whom grateful acknowledgment is made for financial assistance and for permission to publish this work. The authors wish also to express their indebtedness to the National Research Council of Canada for the award of a bursary to R.G.W.; to Mr. J. B. Stothers for valuable help in the preliminary phases of the investigation; to Dr. I. G. Walker, Defence Research Medical Laboratories, Toronto, for carrying out the toxicity determinations; and to Parke, Davis and Co., Detroit, Mich., for screening sodium fluorotuberculostearate against *M. tuberculosis*.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Toxic Fluorine Compounds. XVI.[1] Branched ω-Fluorocarboxylic Acids

BY F. L. M. PATTISON AND R. G. WOOLFORD

RECEIVED DECEMBER 3, 1956

Six branched ω-fluorocarboxylic acids, $F(CH_2)_nCHMe(CH_2)_mCOOH$, were prepared by anodic coupling reactions. The toxicological results may be explained on the basis of two modes of breakdown: (1) when *m* is odd, the compounds form intermediate oxidation products which in turn break down to give ω-fluorocarboxylic acids containing a total of *n* carbon atoms; (2) when *m* is even, β-oxidation occurs in the usual way, resulting in toxicity figures comparable to those of the unbranched ω-fluorocarboxylic acids, $F(CH_2)_{n+m+1}COOH$. Thus, compounds in which *n* is the same have approximately the same toxicity, irrespective of *m* and hence of the total length of the chain.

The unique pharmacological properties of the ω-fluorine atom in aliphatic compounds have been outlined in earlier reports in this series. By an examination of the toxicity of members of any series $F(CH_2)_nX$, it has been possible to deduce the probable metabolic fate of the group X. As an extension of this work, we have now prepared some branched ω-fluorocarboxylic acids (Table II), in order to obtain information regarding the metabolism of the corresponding unfluorinated branched-chain acids.

The value of unsymmetrical anodic coupling reactions in the synthesis of fluorine compounds has already been indicated.[2,3] The procedure used in the present work to obtain the compounds listed in Table I was essentially the same as that described earlier. In general, ω-fluorocarboxylic acids were electrolyzed in the presence of an excess of the appropriately substituted glutaric acid half-ester

$$F(CH_2)_{n-1}COOH + HOOCCH_2CHMeCH_2COOCH_3 \longrightarrow F(CH_2)_nCHMeCH_2COOCH_3 \longrightarrow F(CH_2)_nCHMeCH_2COOH$$

Simple homologation of II by means of the Arndt–Eistert synthesis yielded 11-fluoro-4-methylundecanoic acid (V). The preparation of 18-fluoro-10-methyloctadecanoic acid (VI) has been described in an earlier report.[3]

The results presented in Table II indicate that compounds in which *n* is odd are non-toxic whereas those in which *n* is even are toxic, irrespective of *m* and hence of the total length of the carbon chain. It is convenient to discuss this observation and the

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TABLE I

UNSYMMETRICAL ANODIC COUPLING REACTIONS

Product	Reactants	Yield, %	Symmetrical by-products (yield, %) ω,ω'-Difluoroalkane	Dicarboxylic acid
$F(CH_2)_5CHMeCH_2COOH$ (I)	$F(CH_2)_4COOH$ + $HOOCCH_2CHMeCH_2COOCH_3$	30	$F(CH_2)_8F$ (10)	$HOOCCH_2CHMe(CH_2)_2CHMeCH_2COOH$ (36)
$F(CH_2)_7CHMeCH_2COOH$ (II)	$F(CH_2)_6COOH$ + $HOOCCH_2CHMeCH_2COOCH_3$	42	$F(CH_2)_{12}F$ (20)	$HOOCCH_2CHMe(CH_2)_2CHMeCH_2COOH$ (35)
$F(CH_2)_8CHMeCH_2COOH$ (III)	$F(CH_2)_7COOH$ + $HOOCCH_2CHMeCH_2COOCH_3$	45	$F(CH_2)_{14}F$ (20)	$HOOCCH_2CHMe(CH_2)_2CHMeCH_2COOH$ (37)
$F(CH_2)_5CMe_2CH_2COOH$ (IV)	$F(CH_2)_4COOH$ + $HOOCCH_2CMe_2CH_2COOCH_3$	30	$F(CH_2)_8F$ (10)	$HOOCCH_2CMe_2(CH_2)_2CMe_2CH_2COOH$ (38)

TABLE II

TOXICOLOGICAL RESULTS AND POSTULATED METABOLIC DEGRADATIONS OF $F(CH_2)_nCHMe(CH_2)_mCOOH$

Acid	L.D. 50,[a] mg./kg.	L.D. 50[a,b] of corresponding unbranched acid,[c] mg./kg.	Suggested metabolic route[d]	Suggested inte mediary metabolite	L.D. 50,[a,b] mg./kg.
$F(CH_2)_5CHMeCH_2COOH$ (I)	118	0.64	1	$F(CH_2)_4COOH$	>100
$F(CH_2)_7CHMeCH_2COOH$ (II)	65	1.5	1	$F(CH_2)_6COOH$[e]	40
$F(CH_2)_8CHMeCH_2COOH$[f] (III)	2.42	57.5	1	$F(CH_2)_7COOH$[g]	0.64
$F(CH_2)_5CMe_2CH_2COOH$ (IV)	121	0.64	Blocked	.....	....
$F(CH_2)_7CHMeCH_2CH_2COOH$ (V)	52	57.5	2	$F(CH_2)_6COOH$	40
$F(CH_2)_8CHMe(CH_2)_8COONa$[f] (VI)	2.7	5.7	2	$F(CH_2)_7COOH$	0.64

[a] Intraperitoneal injection into mice. [b] Reported previously.[4] [c] General formula $F(CH_2)_{n+m+1}COOH$. [d] Outlined in the Discussion. [e] L.D. 50 of 9-fluoro-2-nonanone, $F(CH_2)_7COCH_3$, 16 mg./kg.[5] [f] Reported previously.[3] [g] L.D. 50 of 10-fluoro-2-decanone, $F(CH_2)_8COCH_3$, 1.2 mg./kg.[5]

resultant biochemical conclusions under two main headings.

(1) **When m is Odd (Compounds I–IV).**—The most striking feature apparent in this class of compounds is the pronounced difference in toxicity between the branched and the corresponding unbranched ω-fluorocarboxylic acids. The mere introduction of one or more methyl groups in the β-position results in the complete reversal of the toxicological pattern. Clearly, β-oxidation of the main chain is not occurring in the usual manner. Originally, it was considered likely that methyl ketones were formed[6,7] as intermediates by loss of two carbon atoms ($F(CH_2)_nCHMeCH_2COOH \rightarrow F(CH_2)_nCOMe$). While it is possible that this is indeed the case to a certain extent, it is nevertheless unlikely that methyl ketones are the sole or even the main intermediates, since the toxicities of II and III are not sufficiently similar to those of the anticipated methyl ketones[5] (Table II) to justify drawing any such definite conclusion. Additional evidence against this simple ketone formation is supplied by the report[8] that β-methyl-*n*-valeric acid forms, not methyl ethyl ketone, but acetone. An alternative mode of breakdown is suggested by the observation of Barker,[9] as a result of work with *Clostridium kluyveri* extracts, that fatty acids can give rise to the corresponding β-unsaturated acids; if this mechanism be applied to compounds I–III, the postulated intermediate, $F(CH_2)_{n-1}CH{=}CMeCH_2COOH$, could on subsequent oxidation form the ω-fluorocarboxylic acid containing a total of n carbon atoms. In short, the nature of the intermediary metabolites is uncertain, and the most reasonable interpretation of the toxicity results is that the members under consideration form ω-fluorocarboxylic acids containing a total of n carbon atoms, presumably through the intermediate formation of oxidation products which may or may not include the above-mentioned ketones and unsaturated acids. That the toxic members ultimately form fluoroacetate is indicated[10] by the high citric acid level in the tissues of animals poisoned by III.

$$F(CH_2)_nCHMeCH_2COOH \longrightarrow [\text{intermediate}] \longrightarrow F(CH_2)_{n-1}COOH$$

(2) **When m is Even (Compounds V and VI).**—In contrast to the compounds described above, the toxicity of the two members of this class are very similar to those of the corresponding unbranched acids, within the limits of biological variation. Thus the introduction of the methyl group causes no change in the general toxicological pattern of the unbranched ω-fluorocarboxylic acids. The obvious conclusion is that these branched acids, after initial formation of the thiol-ester of coenzyme A, progressively lose two carbon atoms by β-oxidation until an acid possessing an α-methyl substituent is produced; this can then undergo further β-oxidation, since an α-methyl substituent apparently results in no interference with the normal process.[11–14] Thus the branched acids of this class show toxicity figures very similar to those of the unbranched acids, $F(CH_2)_{n+m+1}COOH$.

$$F(CH_2)_nCHMeCH_2CH_2COOH \longrightarrow F(CH_2)_nCHMeCOOH \longrightarrow F(CH_2)_{n-1}COOH$$

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The fundamental distinction between the above two metabolic mechanisms is well illustrated in the case of the two isomeric acids III and V, which differ only in the position of the methyl group. The simple shift of the methyl group to the adjacent carbon atom results in one acid being over 20 times more toxic than the other.

It is also of interest to consider the progressive substitution of 8-fluoroöctanoic acid. The unsubstituted acid previously has been reported[4] to be very toxic. The substitution of one methyl group on the β-carbon atom (I) results in a remarkable drop in toxicity (nearly 200 fold), as explained by mechanism 1 above. The substitution of two methyl groups on the β-carbon atom results in another non-toxic acid (IV), the lack of toxicity of which probably is associated with complete blockage of the β-oxidation process. The latter derivative (IV) is analogous to ethyl 4-fluoro-3,3-dimethylbutanoate, $FCH_2CMe_2CH_2COOEt$, which previously has been reported[15] to be non-toxic, presumably for the same reason.

It is probably justifiable to extend the above mechanisms of intermediary metabolism to unfluorinated branched acids, $CH_3(CH_2)_nCHMe(CH_2)_mCOOH$. Thus, if m is even, the acid will be metabolized by essentially the same route as the unsubstituted acid, $CH_3(CH_2)_{n+m+1}COOH$; whereas if m is odd, the probable end-products of metabolism will be formed by β-oxidation of $CH_3(CH_2)_{n-1}COOH$.

The results and conclusions presented provide further examples of the ω-fluorine atom acting as a "tag" in the elucidation of metabolic mechanisms. The general method is of wide application, and readily could provide information regarding the metabolism of many different types of branched and unbranched aliphatic compounds.

Experimental[16]

Equipment and Intermediates.—The electrolyses were carried out in the cell and by the general procedure described previously.[2] The ω-fluorocarboxylic acids were prepared[2,4] by hydrolysis of ω-fluoronitriles[17] or by oxidation of ω-fluoroalcohols.[18] Methyl hydrogen β-methylglutarate was prepared as described by Linstead, Lunt and Weedon.[19] Methyl hydrogen β,β-dimethylglutarate (b.p. 153–154° (14 mm.), $n^{25}D$ 1.4398) was prepared from β,β-dimethylglutaric acid[20] by conversion to the anhydride followed by treatment with anhydrous methanol.[21] Diazomethane was prepared[22] from N-methyl-N-nitroso-*p*-toluenesulfonamide.

8-Fluoro-3-methyloctanoic Acid (I).—5-Fluorovaleric acid (20.0 g., 0.167 mole) and methyl hydrogen β-methylglutarate (53.4 g., 0.334 mole) were electrolyzed by the general procedure for unsymmetrical couplings.[2] Methyl hydrogen β-methylglutarate (13.5 g.) and sodium (0.57 g., 0.025 mole) were dissolved in methanol in the electrolysis cell, and a current of 1.7 amp. was applied. A methanolic solution of the remainder of the starting materials was added slowly and at such a rate as to maintain the current at 1.7 amp. Total volume of methanol used was 70 ml. When the reaction solution became slightly alkaline to litmus (*ca.* 10 hours), the electrolysis was stopped. The solution was diluted with water, acidified with glacial acetic acid, and extracted with ether. After removal of the ether, the residue was hydrolyzed by heating under reflux with 10% sodium hydroxide (300 ml.) for three hours. The resultant mixture was separated into neutral and acidic fractions using aqueous sodium carbonate, and the ether extracts of each were dried over sodium sulfate. The neutral fraction on distillation yielded 1,8-difluoroöctane (1.30 g., 10%), b.p. 70° (10 mm.), $n^{25}D$ 1.3943. We have previously reported[2] b.p. 75–75.5° (13 mm.) and $n^{25}D$ 1.3933. Distillation of the acidic fraction through a short Vigreux column gave 8-fluoro-3-methyloctanoic acid (8.9 g., 30%), b.p. 97–98° (0.15 mm.), $n^{25}D$ 1.4287.

Anal. Calcd. for $C_9H_{17}FO_2$: C, 61.35; H, 9.73. Found: C, 61.45; H, 9.53.

Further distillation of the acidic residue yielded β,β'-dimethylsuberic acid (12.2 g., 36%), b.p. 172–174° (0.4 mm.), m.p. 87–90°. Linstead, Lunt and Weedon[23] report m.p. 90–92° for a mixture of stereoisomeric β,β'-dimethylsuberic acids.

10-Fluoro-3-methyldecanoic Acid (II).—A mixture of 7-fluoroheptanoic acid (12.0 g., 0.081 mole), methyl hydrogen β-methylglutarate (26.0 g., 0.163 mole), sodium (0.28 g., 0.012 mole) and methanol (70 ml.) was electrolyzed, as above. The reaction was complete after 4.5 hours at a current of 1.7 amp. After isolation and hydrolysis in the usual way, the resultant mixture was separated into neutral and acidic fractions. The ethereal solution of each was dried over sodium sulfate. The neutral fraction on distillation yielded 1,12-difluorododecane (1.69 g., 20%), b.p. 120° (10 mm.), $n^{25}D$ 1.4177. We have previously reported[2] b.p. 120° (10 mm.) and $n^{25}D$ 1.4170. Distillation of the acidic fraction through a short Vigreux column gave 10-fluoro-3-methyldecanoic acid (7.0 g., 42%), b.p. 120–121° (0.50 mm.), $n^{25}D$ 1.4392.

Anal. Calcd. for $C_{11}H_{21}FO_2$: C, 64.67; H, 10.36. Found: C, 64.85; H, 10.29.

Further distillation of the acidic residue yielded β,β'-dimethylsuberic acid (5.8 g., 35%), with the same physical constants as described above.

11-Fluoro-3-methylundecanoic Acid (III) has been previously described.[2] Its methyl ester, prepared as an intermediate in other work, was obtained as follows. The acid III (15.0 g., 0.069 mole), methanol (25 g.), ethylene chloride (75 ml.) and concd. sulfuric acid (0.8 ml.) were heated under reflux for 16 hours. The mixture was cooled and diluted with water. The ethylene chloride layer was washed with aqueous sodium carbonate and with water. Distillation yielded the methyl ester (14.7 g., 92%), b.p. 95.5–96° (0.2 mm.), $n^{25}D$ 1.4330.

Anal. Calcd. for $C_{13}H_{25}FO_2$: C, 67.20; H, 10.85. Found: C, 67.25; H, 10.90.

8-Fluoro-3,3-dimethyloctanoic Acid (IV).—A mixture of 5-fluorovaleric acid (20.0 g., 0.167 mole), methyl hydrogen β,β-dimethylglutarate (58.0 g., 0.333 mole), sodium (0.57 g., 0.025 mole) and methanol (70 ml.) was electrolyzed, as above. The reaction was complete after 10 hours at a current of 1.7 amp. After isolation and hydrolysis, the resultant mixture was separated into neutral and acidic fractions. The ethereal solution of each was dried over sodium sulfate. The neutral fraction on distillation yielded 1,8-difluoroöctane (1.27 g., 10%), with the same physical constants as described above. Distillation of the acidic fraction through a short Vigreux column gave 8-fluoro-3,3-dimethyloctanoic acid (9.5 g., 30%), b.p. 124–125° (1.0 mm.), $n^{25}D$ 1.4340.

Anal. Calcd. for $C_{10}H_{19}FO_2$: C 63.14; H, 10.07. Found: C, 63.28; H, 9.97.

The acidic residue was recrystallized from methanol to yield $\beta,\beta,\beta',\beta'$-tetramethylsuberic acid (14.6 g., 38%), m.p. 169–170°. Birch, *et al.*,[24] report m.p. 169.5°.

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10-Fluoro-3-methyldecanoyl Chloride.—10-Fluoro-3-methyldecanoic acid (6.0 g., 0.029 mole) was added dropwise to boiling thionyl chloride (4.8 g., 0.040 mole). The resultant mixture was heated for an additional two hours on a steam-bath. Fractional distillation of the product gave 10-fluoro-3-methyldecanoyl chloride (5.3 g., 81.5%), b.p. 112–114° (1.5 mm.), n^{25}D 1.4410.

Anal. Calcd. for $C_{11}H_{20}ClFO$: C, 59.32; H, 9.05; Cl, 15.93. Found: C, 59.38; H, 9.04; Cl, 15.98.

11-Fluoro-4-methylundecanoic Acid (V).—A solution of 10-fluoro-3-methyldecanoyl chloride (5.3 g., 0.024 mole) in anhydrous ether (25 ml.) was added to a stirred ethereal solution of diazomethane (5.9 g., 0.14 mole) cooled in an ice-bath. Stirring was continued for three hours in the cold and then for three hours at 20–25°. The ether was removed *in vacuo* at 20–25°. The residual diazomethyl ketone, a bright yellow liquid, was dissolved in dioxane (100 ml.) and was added dropwise with stirring to a mixture of freshly prepared silver oxide (2 g.), sodium carbonate (5 g.) and sodium thiosulfate (3 g.) in water (200 ml.) at 70°. The mixture was stirred at 70° for two hours with occasional addition of fresh silver oxide. The temperature was then raised to 90° for 10 hours. The black silver residue was removed by filtration, and the filtrate was acidified with dilute nitric acid. The resultant solution was extracted with ether and separated into neutral and acidic fractions. After drying over sodium sulfate and removal of the ether, the acidic fraction was distilled through a short Vigreux column to yield 11-fluoro-4-methylundecanoic acid (1.4 g., 27%), b.p. 150–151° (0.2 mm.), n^{25}D 1.4393.

Anal. Calcd. for $C_{12}H_{23}FO_2$: C, 66.02; H, 10.61. Found: C, 66.02; H, 10.60.

18-Fluoro-10-methyloctadecanoic acid (VI) has been previously described.[3]

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LONDON, ONTARIO, CANADA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Toxic Fluorine Compounds. XVII.[1] Some 1-Fluoroalkanes, ω-Fluoroalkenes and ω-Fluoroalkynes

BY F. L. M. PATTISON AND J. J. NORMAN

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Some 1-fluoroalkanes (*n*-alkyl fluorides), ω-fluoroalkenes and ω-fluoroalkynes were prepared for biochemical studies, and for use as intermediates in the synthesis of other compounds. The even-chain 1-fluoroalkanes are very toxic. Whereas no clear-cut conclusions could be drawn regarding the biochemical breakdown of 1-alkenes, evidence was obtained for ω-oxidation of 1-fluoroalkanes, and, less convincingly, for hydration of 1-alkynes to the corresponding methyl ketones. Ethyl ω-fluorolactate, $FCH_2CH(OH)COOEt$, the preparation of which is described, was found to be non-toxic.

The three classes of monofluorinated hydrocarbons described in this paper were prepared for toxicological studies, and hence to obtain information regarding the breakdown *in vivo* of the unfluorinated analogs. ω-Oxidation had previously been postulated[2] in the biological degradation of certain fluoroketones; it was recognized that the study of 1-fluoroalkanes would provide additional evidence for this mechanism. The results presented here are in conformity with the suggestion. In an earlier report[3] was mentioned the toxicity of 11-fluoro-1-undecene; the inference was drawn that the alkene was converted to the intermediate 11-fluoro-1,2-undecanediol,[4] which in turn was oxidized with loss of one carbon atom. The toxicities of the ω-fluoro-1-alkenes presented below do not tally with this simple mechanism. In regard to the biological fate of the 1-alkynes, hydration to the corresponding methyl ketones was considered most likely; the toxicity figures shown in Table II, supplemented by some studies of citric acid accumulation, lend support for this prediction.

Preparation

The majority of the 1-fluoroalkanes were prepared from alkyl halides or alkyl sulfonates by treatment with potassium fluoride in diethylene glycol.[5–10] Special procedures, for example the cleavage of an alkyl *p*-toluenesulfonate with silver fluoride in acetonitrile, were used in a few instances, but none proved superior to the two above-mentioned methods, both of which already have been described. All the 1-fluoroalkanes have been prepared previously in other laboratories.

The ω-fluoroalkenes listed in Table I were prepared from ω-haloalkenes or from ω-methanesulfonoxyalkenes[10] by treatment with potassium fluoride in diethylene glycol. All four members were prepared by the former method, while 5-fluoro-1-pentene was obtained also by the latter method.[10]

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(2) R. R. Fraser, J. E. Millington and F. L. M. Pattison, *ibid.*, **79**, 1959 (1957).

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(10) F. L. M. Pattison and J. E. Millington, *Can. J. Chem.*, **34**, 757 (1956).

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The ω-fluoroalkynes[3] were prepared either by treatment[11] of the appropriate ω-fluoroalkyl bromides and iodides[12] with sodium acetylide, or by fluorination of the corresponding ω-chloroalkynes[13,14] with potassium fluoride in ethylene glycol or diethylene glycol. By the former method were prepared 5-fluoro-1-pentyne, 6-fluoro-1-hexyne, 7-fluoro-1-heptyne and 8-fluoro-1-octyne, while the latter method yielded 5-fluoro-1-pentyne, 6-fluoro-1-hexyne, 9-fluoro-1-nonyne, 1,4-difluoro-2-butyne and 1-fluoro-4-chloro-2-butyne.

Properties

Chemical.—As has been noted by other workers,[7,8,15] 1-fluoroalkanes are very stable liquids. It is unfortunate that the early misconception[16] regarding the instability of monofluoro aliphatic compounds has persisted for so long. Notwithstanding the growing number of stable monofluoro aliphatic compounds reported in the literature during the last ten years, two recent reviews[17,18] still repeat Henne's observation that a single fluorine atom in an aliphatic compound causes instability. Of some three hundred primary monofluoro compounds prepared in the course of our study of toxic materials, only a handful have proved to be unstable and, in these few instances, the instability was associated almost exclusively with some other functional group in the molecule.

The ω-fluoro-1-alkenes reacted readily with performic acid[19] to yield the corresponding ω-fluoro-1,2-alkanediols; by this means were prepared 5-fluoro-1,2-pentanediol and 11-fluoro-1,2-undecanediol; the former was converted without purification into 4-fluorobutanal.[20] 3-Fluoro-1,2-propanediol was more conveniently prepared by hydrolysis of epifluorohydrin.[21,22] The latter was obtained in 50% yield by fluorination of epichlorohydrin in a stainless steel autoclave at 215–225° using anhydrous potassium fluoride. In most runs, the maximum pressure developed was 190–210 p.s.i., but in one instance, unaccountably, the pressure rose to 3000 p.s.i., with almost total loss of product; it is therefore essential that this reaction be carried out in a pressure vessel equipped with an emergency pressure relief device. Both epifluorohydrin and 3-fluoro-1,2-propanediol on oxidation with nitric acid afforded ω-fluorolactic acid; the crude acid was esterified prior to purification.

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(12) F. L. M. Pattison and W. C. Howell, *J. Org. Chem.*, **21**, 748 (1956).

(13) W. R. Taylor and F. M. Strong, THIS JOURNAL, **72**, 4263 (1950).

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(17) M. Stacey in "Progress in Organic Chemistry," Vol. 2, Editor J. W. Cook, Butterworths Scientific Publications, London, England, 1953, p. 29.

(18) P. Tarrant in "Fluorine Chemistry," Vol. 2, Editor J. H. Simons, Academic Press, Inc., New York, N. Y., 1954, p. 213.

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(20) J. F. K. Wilshire and F. L. M. Pattison, *ibid.*, **78**, 4996 (1956).

(21) E. Gryszkiewicz-Trochimowski, A. Sporzynski and J. Wnuk, *Rec. trav. chim.*, **66**, 413 (1947).

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The ω-fluoro-1-alkynes formed copper, silver and mercuric salts; the last of these served as a convenient means of characterization. The ω-fluoro-1-alkynes tended to lose fluorine in the presence of reactants such as sodamide and Grignard reagents,[23] rather than undergoing the reactions characteristic of the non-fluorinated alkynes. Thus, the reaction of 6-fluoro-1-hexyne with sodamide resulted in an indeterminate mixture of products, and with ethylmagnesium bromide followed by carbon dioxide produced fluorine-free polymers. Whereas 1,4-difluoro-2-butyne was stable, 1-fluoro-4-chloro-2-butyne decomposed extensively when distilled at atmospheric pressure.

Physical.—All the 1-fluoroalkanes listed in Table II have been prepared and examined independently by Vogel and co-workers.[7,8] Since the physical constants obtained were essentially the same in both laboratories, it was mutually agreed that the details would be presented in a forthcoming publication by these workers rather than by us. Physical constants and analytical results of the ω-fluoroalkenes and ω-fluoroalkynes and of some precursors and derivatives are shown in Table I.

Toxicological.—The most striking feature of the figures listed in Table II is the very high toxicity of the 1-fluoroalkanes, and more particularly of the members containing an even number of carbon atoms. They are indeed among the most toxic of the ω-fluoro-compounds; this fact, coupled with their relatively high volatility, emphasizes the need for caution in their manipulation. The hazardous nature of the 1-fluoroalkanes, recorded here for the first time, is the more surprising when contrasted with the outstanding stability of the members, and points a warning to industrial workers who may encounter these materials as by-products in commercial processes.

The alternation in toxicity of the 1-fluoroalkanes indicates the existence of a biochemical degradative mechanism akin to that of the ω-fluorocarboxylates.[24] A reasonable interpretation of this observation consequently points to initial ω-oxidation of the 1-fluoroalkanes, resulting in the formation of ω-fluorocarboxylates containing the same number of carbon atoms ($F(CH_2)_nCH_3 \rightarrow F(CH_2)_nCOOH$); the fluoro-acids, once formed, would then be degraded by β-oxidation.[25] In support of this is the marked similarity in toxicity between the 1-fluoroalkanes, particularly those containing an even number of carbon atoms, and the corresponding ω-fluorocarboxylates.[24] Further evidence in favor of the ω-oxidation mechanism is supplied by high citric acid levels found in animals poisoned by the even chain 1-fluoroalkanes, indicat-

(23) We also have reported loss of fluorine in Grignard reactions involving ω-fluoroalkylmagnesium halides; F. L. M. Pattison and W. C. Howell, *J. Org. Chem.*, **21**, 879 (1956). In a related investigation, we have shown loss of fluorine from 1-fluorohexane by treatment with alkylmagnesium halides; W. J. Cott and F. L. M. Pattison, unpublished results.

(24) F. L. M. Pattison, S. B. D. Hunt and J. B. Stothers, *J. Org. Chem.*, **21**, 883 (1956).

(25) I. G. Walker and J. M. Parker have suggested convincingly that oxidative attack on the 1-fluoroalkanes may occur not only at the end but also in the middle of the chain; this theory, based on studies of citric acid accumulation,[26] will be discussed in a forthcoming publication by these workers.

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TABLE I

PHYSICAL CONSTANTS AND ANALYTICAL RESULTS

Compound	Formula	B.p. °C.	B.p. Mm.	n^{25}D or m.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
5-Fluoro-1-pentene[a]	$F(CH_2)_3CH=CH_2$	61–62	745	1.3748	68.16	68.18	10.29	10.44
6-Fluoro-1-hexene[b]	$F(CH_2)_4CH=CH_2$	91.5	740	1.3874				
11-Fluoro-1-undecene	$F(CH_2)_9CH=CH_2$	84–85	11	1.4236	76.68	76.35	12.29	12.21
1,4-Difluoro-2-butene	$FCH_2CH=CHCH_2F$	73	740	1.3670	52.17	52.44	6.57	6.75
Epifluorohydrin[c]	$FCH_2\underset{\diagdown\,\diagup}{CH}CH_2O$	83–84	742	1.3679				
3-Fluoro-1,2-propanediol	$FCH_2CH(OH)CH_2OH$	100–101	10	1.4220	38.30 20.21[d]	38.40 20.1[d]	7.44	7.22
11-Fluoro-1,2-undecanediol[e]	$F(CH_2)_9CH(OH)CH_2OH$			42–43	64.08	64.03	11.16	11.12
Ethyl ω-fluorolactate	$FCH_2CH(OH)COOEt$	74	12	1.4076	44.12	44.16	6.66	6.85
3,5-dinitrobenzoate[f]	$FCH_2CH(OCOC_6H_3(NO_2)_2)COOEt$			91–91.5	43.64	43.81	3.33	3.30
5-Fluoro-1-pentyne[g]	$F(CH_2)_3C\equiv CH$							
Mercury derivative[f]	$(F(CH_2)_3C\equiv C)_2Hg$			118.5–119	32.38	32.34	3.24	3.29
6-Fluoro-1-hexyne	$F(CH_2)_4C\equiv CH$	106–106.5	745	1.4058	72.00	72.25	9.00	9.09
Mercury derivative[f]	$(F(CH_2)_4C\equiv C)_2Hg$			81–81.5	36.14	36.16	4.04	4.18
7-Fluoro-1-heptyne	$F(CH_2)_5C\equiv CH$	131–131.5	748	1.4103	73.69	73.41	9.65	9.72
Mercury derivative[h]	$(F(CH_2)_5C\equiv C)_2Hg$							
Copper derivative[i]	$F(CH_2)_5C\equiv CCu$			122–123.5[j]	47.58 35.96[k]	47.43 35.99[k]	5.70	5.58
8-Fluoro-1-octyne	$F(CH_2)_6C\equiv CH$	77–78	50	1.4165	74.96	75.05	10.23	10.37
Mercury derivative[f]	$(F(CH_2)_6C\equiv C)_2Hg$			66.5–67	42.23	42.04	5.28	5.11
9-Fluoro-1-nonyne[l]	$F(CH_2)_7C\equiv CH$	66–66.5	12	1.4192	76.05	75.98	10.56	10.57
Mercury derivative[f]	$(F(CH_2)_7C\equiv C)_2Hg$			54.5–55	44.77	44.57	5.80	5.79
1,4-Difluoro-2-butyne[l]	$FCH_2C\equiv CCH_2F$	87–88	742	1.3884	53.33	52.93	4.50	4.98
1-Fluoro-4-chloro-2-butyne[l]	$FCH_2C\equiv CCH_2Cl$	54.5–55	50	1.4455	33.28[m]	32.92[m]		

[a] Hoffmann[28] reports b.p. 61.9–62.1°. [b] Hoffmann[28] reports b.p. 91–92° and n^{26}D 1.3869. [c] Redemann, *et al.*,[29] report b.p. 83.5–84° (753 mm.) and n^{20}D 1.3693; Knunyants, *et al.*,[22] report b.p. 85–86.4° and n^{20}D 1.3730. [d] Fluorine, %. [e] Previously reported.[20] [f] Recrystallized from 95% ethanol. [g] The free alkyne was not isolated. [h] The mercury salt is liquid at room temperature; f.p. *ca.* 15°. The copper derivative is therefore more convenient for characterizing 7-fluoro-1-heptyne. [i] Recrystallized from acetone. [j] Accompanied by extensive decomposition. [k] Copper, %. [l] Because of the very small quantity isolated, physical constants should be regarded only as approximate. [m] Chlorine, %.

ing[26] the ultimate formation of fluoroacetate. In short, ω-oxidation provides a satisfactory explanation of the toxicity results of the 1-fluoroalkanes[25] and of the fluoromethyl alkyl ketones described earlier.[2]

The four ω-fluoroalkenes listed in Table II are all toxic, irrespective of the length of their carbon chains. Hence no clear-cut conclusions can be drawn from these figures regarding the biochemical fate of the alkene grouping. The earlier suggestion[3] that the alkene group was oxidized to the diol and then to the aldehyde ($-CH=CH_2 \rightarrow -CH(OH)-CH_2OH \rightarrow -CHO$) clearly requires modification because of the high toxicity of 6-fluoro-1-hexene; hence a competitive metabolic route, such as ketone[2] formation ($-CH=CH_2 \rightarrow -CH(OH)CH_3 \rightarrow -COCH_3$), also may be available. That the diols, once formed, are indeed oxidized to aldehydes or acids with loss of one carbon atom is supported by the two figures presented in Table II.

Ethyl ω-fluorolactate was found to be non-toxic, as was expected from the low toxicity of the closely related fluoropyruvic acid.[27] This result thus provides evidence that 3-fluoro-1,2-propanediol (toxic) forms some metabolite other than fluorolactate (non-toxic), and at the same time implies that in general α-glycols are not oxidized to the corresponding α-hydroxyacids; this implication is therefore consistent with the oxidative cleavage of α-glycols postulated above.

The alternation in toxicity shown by the ω-fluoro-1-alkynes indicates that the alkyne grouping is attacked *in vivo*. From a comparison of the toxicity pattern of the ω-fluoro-1-alkynes with that previously described for the ω-fluoroalkyl methyl ketones[2] it is suggested that hydration of the alkyne grouping may be the initial step in its degradation

TABLE II

TOXICITY RESULTS

Compound	Formula	L.D. 50 for mice (intraperitoneal), mg./kg.
1-Fluorohexane	$CH_3(CH_2)_5F$	1.7
1-Fluoroheptane	$CH_3(CH_2)_6F$	35
1-Fluoroöctane	$CH_3(CH_2)_7F$	2.7
1-Fluorononane	$CH_3(CH_2)_8F$	21.7
1-Fluorodecane	$CH_3(CH_2)_9F$	1.7
1-Fluoroundecane	$CH_3(CH_2)_{10}F$	15.5
1-Fluorododecane	$CH_3(CH_2)_{11}F$	2.5
5-Fluoro-1-pentene	$F(CH_2)_3CH=CH_2$	5.4
6-Fluoro-1-hexene	$F(CH_2)_4CH=CH_2$	2.8
11-Fluoro-1-undecene	$F(CH_2)_9CH=CH_2$	9.3
1,4-Difluoro-2-butene	$FCH_2CH=CHCH_2F$[a]	6.1
3-Fluoro-1,2-propanediol	$FCH_2CH(OH)CH_2OH$[a]	16.8
11-Fluoro-1,2-undecanediol	$F(CH_2)_9CH(OH)CH_2OH$[b]	1.75
Ethyl ω-fluorolactate	$FCH_2CH(OH)COOEt$[c]	>100
1-Hexyne	$CH_3(CH_2)_3C\equiv CH$	>100
6-Fluoro-1-hexyne	$F(CH_2)_4C\equiv CH$	5.7
7-Fluoro-1-heptyne	$F(CH_2)_5C\equiv CH$	53
8-Fluoro-1-octyne	$F(CH_2)_6C\equiv CH$	7.5
9-Fluoro-1-nonyne	$F(CH_2)_7C\equiv CH$	79

[a] For comparison, FCH_2COOH has L.D. 50, 6.6 mg./kg.[24] [b] For comparison, $F(CH_2)_9CHO$ has L.D. 50, 1.95 mg./kg.[20] and $F(CH_2)_9COOH$ has L.D. 50, 1.5 mg./kg.[24] [c] The high L.D. 50 is consistent with the relatively non-toxic nature of $FCH_2COCOOH$.[27]

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(—C≡CH → —$COCH_3$); the fact that the fluoroalkynes are all rather less toxic than the corresponding fluoroketones may indicate, however, that hydration is not the sole metabolic route. Ultimate formation of fluoroacetate from 6-fluoro-1-hexyne and from 7-fluoro-1-heptyne was shown by citric acid accumulation in the tissues of poisoned animals. That both the even *and* odd members caused citric acid accumulation is a unique point in common between the fluoroalkynes and the fluoroalkyl methyl ketones; moreover, with both classes, the accumulation was greater with the even chain members (on a molar basis). While the toxicity pattern and citric acid levels are thus in substantial agreement with the hydration of the alkyne grouping to the corresponding methyl ketone, independent work is still required to confirm or disprove this postulate.

Experimental[30]

Intermediates.—The ω-fluoroalkyl halides were prepared as described previously.[12] The ω-chloroalkyl iodides were prepared from ω,ω′-dichloroalkanes.[31] 5-Bromo-1-pentene[32] was prepared from 5-hydroxy-1-pentene using phosphorus tribromide; 6-bromo-1-hexene[33] and 11-bromo-1-undecene[34] were prepared similarly from 6-hydroxy-1-hexene[35] and 11-hydroxy-1-undecene,[36] respectively. 1,4-Dichloro-2-butene was purchased commercially.[35] 5-Chloro-1-pentyne[37] was prepared from 5-hydroxy-1-pentyne[38] by treatment with thionyl chloride; the other ω-chloro-1-alkynes were prepared from the appropriate ω-chloroalkyl iodides using sodium acetylide in the usual way.[11] 1,4-Dihydroxy-2-butyne was kindly donated by General Aniline and Film Corporation, 435 Hudson St., New York 14, N. Y. Potassium fluoride and diethylene glycol were purified as described previously.[39]

1-Fluoroalkanes. (a) From *n*-Alkyl Chlorides and Bromides.—The following example is representative of the general method. For the lower members, continuous removal[5,6] of the product gave satisfactory results.

1-Fluoroundecane.—A mixture of anhydrous potassium fluoride (15.0 g., 0.26 mole), diethylene glycol (80 g.) and 1-chloroundecane (34.0 g., 0.18 mole) was heated at 135° for 23 hours with vigorous stirring; the period of heating may be reduced, with slight diminution of yield. The mixture was cooled and diluted with an equal volume of water. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer and extracts were treated with bromine in ether until a faint orange color persisted, and then were washed successively with water, aqueous sodium carbonate and water again. The product, after being dried over sodium sulfate and removal of the ether, was fractionally distilled, yielding 1-fluoroundecane (15.0 g.), b.p. 102–102.5° (23 mm.), $n^{25}D$ 1.4131, and then unchanged 1-chloroundecane (9.0 g.). Gryszkiewicz-Trochimowski, *et al.*,[21] report b.p. 90° (12 mm.). The yield, calculated on reacted 1-chloroundecane, was 66%.

Anal. Calcd. for $C_{11}H_{23}F$: C, 75.80; H, 13.30. Found: C, 75.61; H, 13.03.

By essentially the same procedure were prepared: **1-fluorohexane** (52% yield, from 1-bromohexane, isolated by continuous removal at atmospheric pressure), **1-fluoroheptane** (39% yield, from 1-chloroheptane, isolated by continuous removal under reduced pressure), **1-fluoroöctane** (48% yield, from 1-bromoöctane, isolated by continuous removal under reduced pressure), **1-fluorononane** (31% yield, from 1-chlorononane, isolated by dilution with water) and **1-fluorododecane** (57% yield, from 1-bromododecane, isolated by dilution with water).

(b) From *n*-Alkyl Methanesulfonates.—This previously described procedure[10] was used for the preparation of **1-fluorohexane** (67% yield) and **1-fluorodecane** (48% yield).

ω-Fluoroalkenes and Derivatives. 5-Fluoro-1-pentene.—A mixture of anhydrous potassium fluoride (61.0 g., 1.05 moles) and diethylene glycol (200 g.) was heated to 110° in a three-necked flask equipped with a thermometer, a mercury-seal stirrer and a distillation assembly. 5-Bromo-1-pentene (104.8 g., 0.703 mole) was then added dropwise to the stirred mixture; after about half the quantity had been added, a colorless liquid began to distil at a b.p. of 55–70°. The heating was continued until distillation ceased. The product (35.9 g.) was found to be free of acid, and was therefore fractionated directly through a Todd still, giving 25.8 g. (42%) of a colorless, sweet-smelling liquid. 5-Fluoro-1-pentene may also be obtained from the corresponding methanesulfonoxyalkene.[10]

6-Fluoro-1-hexene.—A mixture of anhydrous potassium fluoride (18.0 g., 0.3 mole), diethylene glycol (70 g.) and 6-bromo-1-hexene (30.0 g., 0.18 mole) was heated at 90° for two hours with vigorous stirring. The pressure was then slowly reduced until a steady, slow rate of distillation resulted. Toward the end of the reaction, the heating was increased and the pressure further reduced until distillation ceased. The residue was heated at 120° for an additional hour at atmospheric pressure, and then was cooled, diluted with water and extracted with ether. The extracts were added to the distillate, and the combined liquids were washed successively with water, aqueous sodium carbonate and water again. The product, after drying over sodium sulfate and removal of the ether, yielded 6-fluoro-1-hexene (5.2 g.) and then unchanged 6-bromo-1-hexene (9.0 g.). The yield, calculated on reacted 6-bromo-1-hexene, was 40%.

11-Fluoro-1-undecene.—A mixture of 11-bromo-1-undecene (62.0 g., 0.28 mole), anhydrous potassium fluoride (33.6 g., 0.58 mole), diethylene glycol (60 g.) and butyl carbitol (60 g.) was heated at 180° for six hours with vigorous stirring. After cooling overnight, the mixture was diluted with water (200 ml.). The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer and extracts were washed and dried, and yielded on fractionation 21.0 g. (46%) of 11-fluoro-1-undecene.

1,4-Difluoro-2-butene.—A mixture of anhydrous potassium fluoride (70.0 g., 1.2 moles), diethylene glycol (150 g.) and 1,4-dichloro-2-butene (46.0 g., 0.37 mole) was heated at 115° for 2.5 hours with continuous stirring. The resultant mixture was cooled, diluted, separated, extracted, dried and fractionated as above, yielding 20.2 g. (60%) of 1,4-difluoro-2-butene. A higher fraction, suspected of being 1-fluoro-4-chloro-2-butene, was found to be unstable.

Epifluorohydrin.—In an electrically heated, stainless-steel autoclave, fitted with a stirrer and an emergency pressure relief device (a rupture disk leading to a fume-hood), was placed a mixture of commercial epichlorohydrin (783 g., 8.5 moles) and anhydrous potassium fluoride (700 g., 12.1 moles). The temperature was raised to 215–225° and maintained in that range for 5.5 hours. The maximum pressure developed was 210 p.s.i. The liquid was distilled from the autoclave leaving only the solids behind. The combined distillates from two identical runs (1165 g.) were fractionated through a Todd still, giving 342 g. of epifluorohydrin and 736 g. of recovered epichlorohydrin. The yield based on reacted epichlorohydrin was 50%.

As mentioned in the Discussion, a serious pressure hazard developed during one run, under apparently identical conditions. When the temperature reached 225°, the pressure had reached 440 p.s.i. The heating was stopped immediately, but within five minutes the temperature had risen spontaneously to 252° and the pressure had passed 1000

(30) (a) The majority of the microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J., and by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. (b) The melting points and boiling points are uncorrected.

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p.s.i. and was rising rapidly. Within another five minutes, the temperature was >255° and the pressure was 3000 p.s.i. The total distillate from 737 g. of epichlorohydrin consisted of 25 g. of a brown liquid. It is therefore essential that the reaction be carried out in a pressure vessel equipped with an emergency pressure relief device.

3-Fluoro-1,2-propanediol.—Epifluorohydrin (20.0 g., 0.213 mole), 10% sulfuric acid (2 ml.) and water (16 ml.) were heated under reflux on a steam-bath for one hour. The solution was allowed to cool, and then was neutralized with solid sodium carbonate. The water was removed under reduced pressure, and the residue was distilled twice, yielding 3-fluoro-1,2-propanediol (18.3 g., 76%).

5-Fluoro-1,2-pentanediol and **11-fluoro-1,2-undecanediol** have been described earlier.[20]

Ethyl ω-Fluorolactate.[40]—Water (58 ml.) and concentrated nitric acid (20 ml.) were placed in a 500-ml. flask fitted with a reflux condenser, a mercury-seal stirrer and a dropping funnel. Epifluorohydrin (58.0 g., 0.76 mole) was added dropwise over 15 minutes to the dilute nitric acid, heated on a steam-bath. A further 100 ml. of concentrated nitric acid was then added, and the mixture was heated for three hours and left overnight at room temperature. Water and nitric acid were distilled off under reduced pressure. The oxalic acid formed during the oxidation was removed by the addition of hot water (1 l.) and then powdered calcium carbonate until effervescence ceased (*ca.* 70 g.). The precipitate was removed by filtration under vacuum at 60°, and the filtrate was acidified with 100 ml. of concentrated hydrochloric acid. The fluorolactic acid was isolated by continuous extraction with ether. Esterification by azeotropic distillation with ethanol and benzene gave ethyl ω-fluorolactate (40.0 g., 39%) as a colorless liquid.

The **3,5-dinitrobenzoate**, recrystallized from 95% ethanol, had m.p. 91–91.5°. Dr. Rivett reported[40] the *p*-bromophenacyl ester to have m.p. 126°, the ***p*-nitrobenzoate** to have m.p. 67–67.5°, and the **benzoate** to be an oil.

ω-Fluoroalkynes.—The following examples are representative of the two general methods. (a) **From ω-Fluoroalkyl Bromides and Iodides. 6-Fluoro-1-hexyne.**—The method was adapted from a previously described procedure.[11] Ferric nitrate (0.3 g. per mole of sodium used) was placed in a 500-ml. flask fitted with a stirrer, a gas inlet tube, and a device for adding sodium.[11] The flask was half-filled with liquid ammonia, and acetylene (scrubbed with concentrated sulfuric acid and dried with calcium chloride) was passed into the system at the rate of 5–10 bubbles per second. After 15 minutes, small pieces of sodium (13.0 g., 0.56 mole) were added to the ammonia solution on a piece of wire at such a rate that metallic sodium solutions were never formed, as indicated by an absence of a blue coloration. The acetylene flow was continued for a further 15 minutes after all the sodium had been added, to decompose any disodium acetylide which might have been formed. 4-Fluorobutyl iodide (100 g., 0.50 mole) was added dropwise to the stirred sodium acetylide solution. The mixture was then stirred for a further five hours to complete the reaction. The volume of the mixture was kept more or less constant by the occasional addition of small portions of liquid ammonia. Ammonium hydroxide (50 ml.) was added to decompose any residual sodium acetylide or sodamide, and the resultant mixture was diluted with water (1 l.). The organic product was isolated by ether extraction. The extracts were washed with dilute hydrochloric acid and then with water, and were dried over calcium chloride. The ether was removed, and the residue was fractionated, yielding 6-fluoro-1-hexyne (44.5 g., 89%) as a colorless, very volatile liquid.

By the above method were prepared **5-fluoro-1-pentyne** (isolated only as the mercury derivative, from 3-fluoropropyl bromide), **7-fluoro-1-heptyne** (53% yield, from 5-fluoroamyl bromide), and **8-fluoro-1-octyne** (63% yield, from 6-fluorohexyl bromide).

(b) **From ω-Chloro-1-alkynes. 6-Fluoro-1-hexyne.**—Ethylene glycol (200 g.) and anhydrous potassium fluoride (52.0 g., 0.90 mole) were placed in a three-necked flask fitted with a mercury-seal stirrer, a dropping funnel and a distillation assembly. The mixture was heated to 120° and 6-chloro-1-hexyne (42.0 g., 0.36 mole) was added dropwise to the vigorously stirred solution. After about one-third of the chloroalkyne had been added, a liquid, boiling at *ca.* 110°, began to distil. When all the chloroalkyne had been added, the temperature of the mixture was gradually raised to maintain the still-head temperature. The distillate was washed with water and was then dried over calcium chloride. Fractional distillation yielded 6-fluoro-1-hexyne (20.8 g., 57%).

By the above method was prepared **5-fluoro-1-pentyne** (isolated only as the mercury derivative).

9-Fluoro-1-nonyne.—9-Chloro-1-nonyne (2.6 g., 0.016 mole), anhydrous potassium fluoride (1.5 g., 0.026 mole) and diethylene glycol (10 g.) were placed in a sealed tube, 10 cm. long and 16 mm. in diameter. The tube was mounted in a mechanical shaker, and was heated electrically at 120° for 24 hours with vigorous shaking. The contents of the tube, after cooling, were diluted with water. The fluoroalkyne was separated using a hypodermic syringe and was dried over calcium chloride. Fractionation gave crude 9-fluoro-1-nonyne of b.p. 70–80° (25 mm.), which, on refractionation through a microdistillation assembly, yielded the pure fluoroalkyne (0.6 g., 26%).

1,4-Difluoro-2-butyne and **1-Fluoro-4-chloro-2-butyne.**—1,4-Dihydroxy-2-butyne was converted to 1,4-dichloro-2-butyne (b.p. 59–60° (13 mm.), n^{25}D 1.5040) in 85% yield using thionyl chloride and pyridine at room temperature. A mixture of anhydrous potassium fluoride (35.0 g., 0.60 mole) and ethylene glycol (200 g.) was heated to 120°, and 1,4-dichloro-2-butyne (49.4 g., 0.41 mole) was added dropwise with vigorous stirring. A brown solid was precipitated, and a very small (*ca.* 5 ml.), two-phase distillate was collected. This was washed with water and dried over calcium chloride. Distillation yielded two fractions, b.p. 70–90° and b.p. 122–130°. The first of these, on fractionation, yielded 1,4-difluoro-2-butyne (0.75 g.), while the second gave 1-fluoro-4-chloro-2-butyne (0.5 g.).

Mercury Derivatives.—Nessler reagent was prepared by dissolving mercuric chloride (66.0 g.) and potassium iodide (163.0 g.) in water (160 ml.) and then adding 10% aqueous sodium hydroxide (125 ml.). The mercury salt was formed by mixing the fluoroalkyne in five volumes of ethanol with an equal volume of Nessler reagent. The white, crystalline precipitate which formed immediately was filtered and recrystallized several times from 95% ethanol. The physical constants and analytical results are listed in Table I. The mercury derivative of 7-fluoro-1-heptyne was found to be liquid at room temperature and to crystallize at *ca.* 15°.

Silver Derivatives.—A 10% solution of the alkyne in alcohol was added to an equal volume of 10% alcoholic silver nitrate solution containing 1% ammonium hydroxide. The insoluble silver salt formed immediately. It was dissolved by gentle heating and crystallized as fine, colorless crystals on cooling. These were filtered and washed with cold alcohol.

Copper Derivatives.—Equimolar quantities of the alkyne and 10% ammoniacal cuprous chloride were mixed and shaken. The insoluble copper salt was filtered, was washed with acetone to remove water, and finally was washed with ether to remove extraneous organic material.

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(40) The preparative details were kindly supplied by Dr. D. E. A. Rivett, National Chemical Research Laboratories, Pretoria, South Africa (April 29 and October 1, 1952), with whose permission they are here recorded.

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LONDON, ONTARIO, CANADA

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES DIVISION OF MERCK & CO., INC.]

Synthesis of DL-3,5-Dihydroxy-3-methylpentanoic Acid (Mevalonic Acid)

BY CARL H. HOFFMAN, ARTHUR F. WAGNER, ANDREW N. WILSON, EDWARD WALTON, CLIFFORD H. SHUNK, DONALD E. WOLF, FREDERICK W. HOLLY AND KARL FOLKERS

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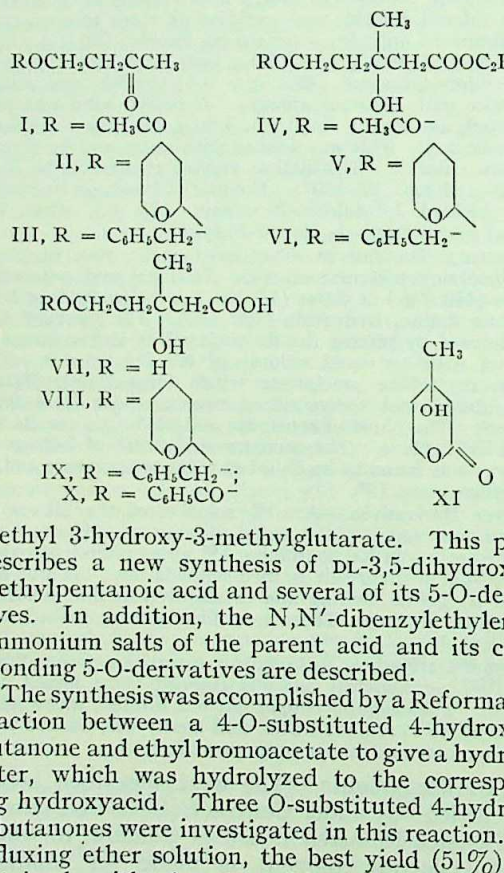
The racemate of a new acetate-replacing factor, DL-3,5-dihydroxy-3-methylpentanoic acid (VII), has been synthesized. The Reformatsky reaction between 4-acetoxy-2-butanone and ethyl bromoacetate gave ethyl 5-acetoxy-3-hydroxy-3-methylpentanoate (IV), which was hydrolyzed by alkali to 3,5-dihydroxy-3-methylpentanoic acid (VII).

A new acetate-replacing factor has been obtained[1] from dried distillers' solubles and has been shown[2] to be 3,5-dihydroxy-3-methylpentanoic acid (XI). The racemate was synthesized[2] from



diethyl 3-hydroxy-3-methylglutarate. This paper describes a new synthesis of DL-3,5-dihydroxy-3-methylpentanoic acid and several of its 5-O-derivatives. In addition, the N,N′-dibenzylethylenediammonium salts of the parent acid and its corresponding 5-O-derivatives are described.

The synthesis was accomplished by a Reformatsky reaction between a 4-O-substituted 4-hydroxy-2-butanone and ethyl bromoacetate to give a hydroxyester, which was hydrolyzed to the corresponding hydroxyacid. Three O-substituted 4-hydroxy-2-butanones were investigated in this reaction. In refluxing ether solution, the best yield (51%) was obtained with 4-acetoxy-2-butanone (I). With the acetal, 4-(2-tetrahydropyranyloxy)-2-butanone (II), the yields were about 20%, while with the ether, 4-benzyloxy-2-butanone (III), the yields were even lower. When the condensation was carried out in refluxing benzene, the yields of hydroxyester were extremely low with both the 4-acetoxy derivative I and the 4-(2-tetrahydropyranyloxy) derivative II.

The hydroxyesters (IV, V, VI) were hydrolyzed with alkali to the corresponding free acids (VII, VIII, IX), which were isolated as oils and purified by conversion to N,N′-dibenzylethylenediammonium salts. Ethyl 5-acetoxy-3-hydroxy-3-methylpentanoate (IV) was hydrolyzed to the corresponding dihydroxyacid VII, which was isolated as an equilibrium mixture of the hydroxyacid and its δ-lactone. The pure lactone XI was isolated from the equilibrium mixture by a short-path distillation. The distilled lactone was crystallized from acetone–ether to yield DL-β-methyl-β-hydroxy-δ-valerolactone (XI), m.p. 27–28°. The acid–lactone mixture was converted by an excess of N,N′-dibenzylethylenediamine in semi-aqueous media into N,N′-dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate).

Both the lactone XI and the salt of VII are fully active in the *Lactobacillus acidophilus* ATCC 4963 assay.[3]

Ethyl 3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate (V) and ethyl 5-benzyloxy-3-hydroxy-3-methylpentanoate (VI) were hydrolyzed with alkali to the corresponding hydroxyacids (VIII and IX), which formed crystalline N,N′-dibenzylethylenediammonium salts. The acetal derivative, N,N′-dibenzylethylenediammonium-bis-[3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate], had 65% of the calculated activity in the L-4963 assay. This derivative is the only one of this series which showed activity in the L-4963 assay. The acetal VIII was converted to the dihydroxyacid VII by acid hydrolysis.

Benzoylation of the 5-hydroxyl group in 3,5-dihydroxy-3-methylpentanoic acid was accomplished in low yield with benzoyl chloride in aqueous alkali. The product, 5-benzoyloxy-3-hydroxy-3-methylpentanoate (X), was isolated as an oil and characterized as the N,N′-dibenzylethylenediammonium salt. This derivative was inactive in the L-4963 assay; alkaline hydrolysis regenerated full activity. Using other acylating reagents, little or none of the 5-acylated products could be isolated. These results indicate that self-acylation to the

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lactone was the preferred reaction under the acylating conditions.

Acknowledgment.—The authors are indebted to Mr. R. N. Boos and associates for elemental analyses and to Dr. L. D. Wright and associates for *Lactobacillus*-4963 assays.

Experimental

4-Acetoxy-2-butanone.—To a mixture of 200 ml. of acetic anhydride and one drop of concentrated sulfuric acid was added 100 g. of 4-hydroxy-2-butanone[4] during a period of one hour. The temperature of the reaction mixture was maintained at 50° by occasional cooling. The reaction mixture was fractionated under reduced pressure and the fraction boiling at 92–95° (25 mm.) was collected yielding 119 g. (80%) of 4-acetoxy-2-butanone, $n^{25}D$ 1.4148.

Anal. Calcd. for $C_6H_{10}O_3$ (130.14): C, 55.37; H, 7.75. Found: C, 55.51; H, 7.79.

4-(2-Tetrahydropyranyloxy)-2-butanone.—Equimolar quantities (0.59 mole) of 4-hydroxy-2-butanone (51.5 g.) and dihydropyran (48.7 g.) were mixed and 4 drops of concentrated hydrochloric acid was added. The mixture was cooled to keep the temperature below 45° and then was allowed to stand overnight at room temperature.

The reaction mixture was dissolved in 500 ml. of ether and the solution was washed with dilute aqueous sodium bicarbonate and then with water. The ether solution was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* yielding 78 g. (78%) of product, $n^{26}D$ 1.4492.

The product was distilled *in vacuo* yielding 57 g. of 4-(2-tetrahydropyranyloxy)-2-butanone, b.p. 60–63° (100 μ), $n^{26}D$ 1.4488.

Anal. Calcd. for $C_9H_{16}O_3$ (172.22): C, 62.77; H, 9.37. Found: C, 62.85; H, 8.99.

4-Benzyloxy-2-butanone.—A solution of 90 g. (0.5 mole) of 4-benzyloxy-2-butanol[5] in 200 ml. of acetic acid was cooled to 10–15°. A solution of 33.3 g. (0.33 mole) of chromium trioxide in 30 ml. of water and 180 ml. of acetic acid was added to the stirred reaction mixture over a period of 2 hours. The reaction mixture was diluted with 1 liter of water and extracted with 3 portions of chloroform. The combined chloroform extracts were washed with water, sodium bicarbonate solution and water. The residue (77 g.) obtained after removal of the chloroform was distilled at reduced pressure yielding 54 g. (60%) of 4-benzyloxy-2-butanone, b.p. 88–91° (0.5 mm.), $n^{28}D$ 1.5040.

Anal. Calcd. for $C_{11}H_{14}O_2$ (178.22): C, 74.13; H, 7.92. Found: C, 74.51; H, 8.19.

Ethyl 5-Acetoxy-3-hydroxy-3-methylpentanoate.—A mixture of 124 g. (0.96 mole) of 4-acetoxy-2-butanone and 166 g. (1.0 mole) of ethyl bromoacetate in 450 ml. of dry ether was added slowly to 120 g. (1.84 moles) of clean, dry, granular zinc. The reaction began immediately and the addition of reagents was regulated so that a gentle refluxing of ether was maintained. The time required for the addition was about 1 hour. The mixture was stirred gently and warmed an additional 2 hours.

The solution was decanted onto an excess of crushed ice, and the mixture was acidified to congo red with concentrated hydrochloric acid. The layers were separated; and the ether phase was washed with sodium bicarbonate solution, then with saturated ammonium sulfate solution, and was dried over sodium sulfate. The aqueous mother liquor and washes were combined, reacidified to congo red and were extracted twice with chloroform. The chloroform extracts were washed with sodium bicarbonate solution and were dried over sodium sulfate. The chloroform and ether extracts were combined and concentrated. The residue was fractionated under reduced pressure and the fraction boiling at 86–87° (0.2 mm.) was collected. The yield of ethyl 5-acetoxy-2-hydroxy-3-methylpentanoate was 106 g. (51%), $n^{25}D$ 1.4458; d^{25}_{25} 1.090, $M^{25}D$ 53.34 (calcd. 53.22).

Anal. Calcd. for $C_{10}H_{18}O_5$ (218.24): C, 55.03; H, 8.31; sapn. equiv., 109. Found: C, 55.32; H, 8.03; sapn. equiv., 114.

Ethyl 3-Hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate.—An equimolar mixture (0.32 mole) of 4-(2-tetrahydropyranyloxy)-2-butanone (55 g.) and ethyl bromoacetate (54 g.) in 200 ml. of ether was added slowly to a stirred mixture of 21 g. of granular zinc in 30 ml. of anhydrous ether. The rate of addition was such that the ether refluxed gently. After all the reactants had been added the mixture was warmed for 3 hours.

The reaction mixture was poured into 200 ml. of cold 2 *N* sulfuric acid. The ether phase was separated and the aqueous phase was extracted with three 150-ml. portions of chloroform. The chloroform and the ether extracts were washed with 10% aqueous sodium bicarbonate, saturated aqueous ammonium sulfate and dried over anhydrous magnesium sulfate. The combined organic phases were concentrated *in vacuo*.

The residue (55.3 g.) was distilled *in vacuo*. After two distillations 28 g. of ethyl 3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate, b.p. 96–98° (100 μ), $n^{25}D$ 1.4562; d^{25}_{25} 1.054, $M^{25}D$ 67.13 (calcd. 66.50), was obtained.

Anal. Calcd. for $C_{13}H_{24}O_5$ (260.32): C, 59.98; H, 9.29. Found: C, 59.29; H, 8.78; sapn. equiv., 255.

N,N′-Dibenzylethylenediammonium Bis-(3,5-dihydroxy-3-methylpentanoate).—Ethyl 5-acetoxy-3-hydroxy-3-methylpentanoate (47.5 g.) was dissolved in 100 ml. of ethanol and 50 ml. of water was added. The solution was warmed to *ca.* 60° and 6 *N* sodium hydroxide was added slowly to the stirred solution keeping the *p*H just at the turning point of phenolphthalein indicator. A total of two equivalents of alkali was added. The solution was cooled to room temperature and two equivalents of 6 *N* hydrochloric acid was added. The aqueous solution was concentrated *in vacuo* and the final traces of water were removed *in vacuo*. The residue was extracted with two 200-ml. portions of chloroform and the insoluble salts were removed by filtration. The combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* yielding a 28.7-g. residue.

The residue was dissolved in 100 ml. of water and a solution of 26 g. of N,N′-dibenzylethylenediamine in 100 ml. of methanol was added; the solution was kept at room temperature about 18 hours. The mixture was concentrated *in vacuo* to remove most of the methanol and the aqueous solution was extracted with 50 ml. of chloroform. The aqueous phase was concentrated *in vacuo* yielding 40 g. of salt.

The salt was dissolved in 125 ml. of hot methanol and 1 liter of ether was added to the warm solution. The product crystallized yielding 22 g. (38%) of N,N′-dibenzylethylenediammonium bis-(3,5-dihydroxy-3-methylpentanoate), m.p. 124–125°.

Anal. Calcd. for $C_{28}H_{44}N_2O_8$ (536.65): C, 62.64; H, 8.26; N, 5.22. Found: C, 62.77; H, 8.24; N, 5.10.

The mother liquors and the chloroform wash of the aqueous solution were combined and concentrated *in vacuo* yielding a 32-g. residue. The residue was taken up in 100 ml. of water and a solution of 25 g. of N,N′-dibenzylethylenediamine in 100 ml. of methanol was added. After standing overnight, the reaction mixture was worked up in the manner described above yielding 9.5 g. (16%) of N,N′-dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate), m.p. 125–126°.

β-Hydroxy-β-methyl-δ-valerolactone.—N,N′-Dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate) (44.4 g., 0.08 mole), was dissolved in *ca.* 100 ml. of water and 170 ml. of 1 *N* sodium hydroxide was added. The N,N′-dibenzylethylenediamine was removed by ether extraction. The aqueous solution of sodium salt was passed through a column of Amberlite resin, IR 120 (H^+), and the eluate was lyophilized. The residue was taken up in chloroform and the solution was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* yielding 20.3 g. of oil.

A sample of the oil was evaporatively distilled at *ca.* 90° (0.3 mm.)[6] to yield the pure lactone, β-hydroxy-β-methyl-δ-valerolactone, $\lambda_{max}^{CHCl_3}$ 2.95 and 5.79 μ.

Anal. Calcd. for $C_6H_{10}O_3$ (130.14): C, 55.37; H, 7.75. Found: C, 55.44; H, 7.56.

A portion of the distilled lactone (0.84 g.) was dissolved in a small amount of acetone, and ether was added to the point of incipient cloudiness. When the solution was cooled in a Dry Ice–acetone-bath, the lactone crystallized. The

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(5) G. G. Mayer and H. Sobotka, THIS JOURNAL, 71, 2588 (1949).

(6) Higher temperatures cause loss of biological activity.

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product was collected by filtration and washed with ether yielding 0.73 g. of β-hydroxy-β-methyl-δ-valerolactone, m.p. 26–28°. Recrystallization of the product gave material melting at 27–28°. The product is hygroscopic.

Anal. Calcd. for $C_6H_{10}O_3$ (130.14): C, 55.37; H, 7.75. Found: C, 55.94; H, 7.75; sapn. equiv., 131.

N,N′-Dibenzylethylenediammonium-bis-(3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate.—Ethyl 3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate (6.1 g.) was dissolved in 30 ml. of ethanol and 10 ml. of 3 *N* sodium hydroxide was added. The mixture was warmed on a steam-cone for 30 minutes.

The mixture was cooled, acidified to *p*H 4 and extracted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* yielding 2.7 g. of oil.

The oil was dissolved in *ca.* 100 ml. of ether and 2.7 g. of N,N′-dibenzylethylenediamine in 20 ml. of ether was added. The salt precipitated and was collected by filtration yielding 3.3 g. of N,N′-dibenzylethylenediammonium-bis-(3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate), m.p. 137–139°.

Anal. Calcd. for $C_{38}H_{60}N_2O_{10}$ (704.88): C, 64.74; H, 8.58; N, 3.98. Found: C, 64.69; H, 8.29; N, 4.46, 4.71.

N,N′-Dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate) from N,N′-Dibenzylethylenediammonium-bis-[3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate].—N,N′-Dibenzylethylenediammonium-bis-[3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate] (3.3 g.) was suspended in 10 ml. of water and 12 ml. of 1 *N* hydrochloric acid was added and warmed on the steam-cone for 10 minutes. The mixture was cooled and 10.8 ml. of 1 *N* sodium hydroxide was added. The mixture was filtered and the filtrate was lyophilized.

The residue was leached with 25 ml. of hot methanol. The methanol solution was cooled and diluted with ether yielding 450 mg. of N,N′-dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate), m.p. 122–123°. A mixture of this sample with an authentic specimen of the salt melted at 122–123°.

N,N′-Dibenzylethylenediammonium-bis-(5-benzyloxy-3-hydroxy-3-methylpentanoate).—A mixture of 40 g. (0.23 mole) of 4-benzyloxy-2-butanone and 37.5 g. (0.23 mole) of ethyl bromoacetate in 100 ml. of ether was added dropwise to 20 g. (0.32 mole) of clean, dry granular zinc. The reaction mixture was stirred at the reflux temperature for about two hours and was then added to a mixture of ice and 30 ml. of concentrated hydrochloric acid. The ether layer was separated and the aqueous phase was extracted with ether. The combined ether layers were washed with saturated sodium chloride solution, sodium bicarbonate solution and, again, with sodium chloride solution. The ether layer was concentrated yielding 40 g. of residual oil. A 30-g. portion of the product was distilled *in vacuo* to give *ca.* 15 g. of material boiling at <70° (0.4 mm.). The residue (14.7 g.) from this distillation was hydrolyzed on the steam-cone with 22 ml. of 1 *N* sodium hydroxide and 50 ml. of methanol. The solution was diluted with 50 ml. of water and concentrated at reduced pressure to a volume of *ca.* 50 ml. The solution was extracted with ether and the ether phase was discarded. The aqueous phase was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was washed with saturated sodium chloride solution, dried and concentrated, yielding 2.2 g. of 5-benzyloxy-3-hydroxy-3-methylpentanoic acid.

A 1.93-g. portion of the acid was dissolved in 5 ml. of methanol and treated with 0.97 g. of N,N′-dibenzylethylenediamine. When *ca.* 75 ml. of ether was added, 1.5 g. of the salt, m.p. 123–127°, crystallized. A 400-mg. portion of the salt was recrystallized from chloroform–ether, chloroform–petroleum ether and finally from methanol–ether yielding 200 mg. of N,N′-dibenzylethylenediammonium-bis-(5-benzyloxy-3-hydroxy-3-methylpentanoate), m.p. 131–133°.

Anal. Calcd. for $C_{42}H_{56}N_2O_8$ (716.89): C, 70.36; H, 7.87; N, 3.91. Found: C, 70.40; H, 7.60; N, 4.14.

5-Benzyloxy-3-hydroxy-3-methylpentanoic Acid.—Four hundred and eighty milligrams of N,N′-dibenzylethylenediammonium-bis-(5-benzyloxy-3-hydroxy-3-methylpentanoate) was suspended in 25 ml. of water and acidified with 2.5 *N* hydrochloric acid. The free acid was extracted into ether and then extracted into aqueous potassium bicarbonate. The bicarbonate solution was acidified and the product was extracted into ether. The ether extract was washed with water, dried and concentrated yielding 169 mg. of 5-benzyloxy-3-hydroxy-3-methylpentanoic acid, $n^{25}D$ 1.5130, neut. equiv. 243 (calcd. 238).

N,N′-Dibenzylethylenediammonium-bis-(5-benzoyloxy-3-hydroxy-3-methylpentanoate).—Ten grams of N,N′-dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate) was dissolved in 37 ml. of 1 *N* sodium hydroxide. The solution was extracted with ether and the ether extract was washed with 15 ml. of water. The combined aqueous phases were stirred and cooled while 6 g. of benzoyl chloride was added dropwise. Sodium hydroxide (1 *N*) was added dropwise during the addition of benzoyl chloride to keep the *p*H at *ca.* 9. After being stirred for one hour, the reaction mixture was washed with chloroform. The aqueous phase was acidified to *p*H 3 with hydrochloric acid and extracted with two 75-ml. portions of chloroform. The combined chloroform extracts were washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*.

The residue was leached with hot petroleum ether and then dissolved in 8 ml. of methanol. N,N′-Dibenzylethylenediamine (2.16 g.) was added, and the solution was diluted with *ca.* 80 ml. of ether. Two grams of N,N′-dibenzylethylenediammonium-bis-(5-benzoyloxy-3-hydroxy-3-methylpentanoate), m.p. 142–143°, crystallized from the solution.

Anal. Calcd. for $C_{42}H_{52}N_2O_{10}$ (744.86): C, 67.70; H, 7.04; N, 3.76. Found: C, 68.42, 68.31; H, 6.76, 6.93; N, 3.71.

RAHWAY, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Light-catalyzed Organic Reactions. VI.[1] The Isomerization of Some Dienones[2,3]

BY G. BÜCHI AND N. C. YANG

RECEIVED NOVEMBER 19, 1956

The isomerization of four dienones has been studied. β-Ionone yielded pyran X and spiroketone IX containing a cyclopropane ring. Irradiation of both pseudoionone and 6-methyl-3,5-heptadiene-2-one led to polymers. *trans–trans*-Crotonylideneacetone was converted to the $\Delta^{3,4}$-*cis* isomer. The changes observed are compared with the isomerization of tachysterol (III) and possible interpretations of the results are discussed.

The conversion of ergosterol (I) to vitamin D_2 (IV) is unquestionably one of the most fascinating photochemical reactions known. The brilliant researches of Windaus and his School have led to the isolation and structure elucidation of lumisterol

(1) Part V, THIS JOURNAL, 78, 876 (1956).

(2) Part of a program of research supported by a grant from the Godfrey L. Cabot Fund, Publication No. 63, M. I. T. Solar Energy Conversion Project.

(3) A preliminary account of this work was reported in *Chemistry & Industry*, 357 (1955).

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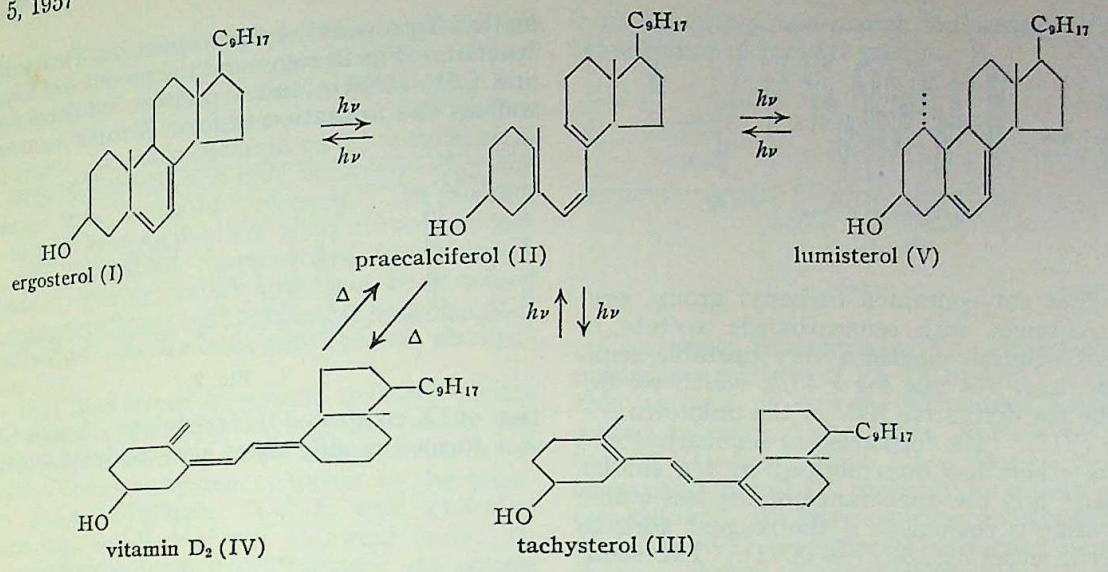


(V) and tachysterol (III), both of which are convertible to vitamin D_2 by further irradiation.[4] The isolation of an additional compound, praecalciferol,[5] present in the mixture obtained on irradiation of ergosterol, has shed some new light on the mechanism of vitamin formation. Velluz recently revealed experimental findings from which he deduced structure II for praecalciferol,[6] which would thus be the *cis* isomer of tachysterol (III). Of even greater interest is the ready conversion of praecalciferol (II) to vitamin D_2 (IV) by moderate heating in neutral solvents in the *absence* of light. The "enesyntheses" of Alder were quoted as analogies in an attempt to rationalize this remarkable change.

It thus appears that the first product formed in the photoisomerization is not V but II which in a subsequent dark reaction is converted to IV. The presence of both I and V in the mixture produced on irradiation of II points strongly to the reversibility of the initial photoreaction. The appearance also of III is easily rationalized by assuming reversible *cis* ⇄ *trans* photoisomerization of II and III, for which there is ample precedent in similar systems.

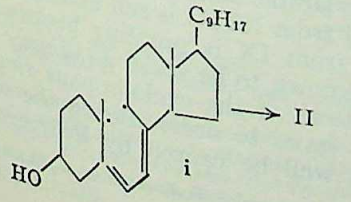
Similarities in the steric as well as electronic structures of tachysterol (III) and *trans*-β-ionone (VI) prompted us to investigate the photochemical isomerization of VI, as a potential synthetic route to γ-ionone[7] (VIII), which in turn should be convertible to a number of compounds with ambergris odor. In this paper we describe the photochemical isomerization of β-ionone and some related dienones.

A solution of β-ionone (VI) in ethanol was irradiated with a low intensity mercury arc and the products separated by fractional distillation. Besides VI (12–22%) and polymers (30–50%), two new compounds, X (22–32%) and IX (2–4%), both isomeric with the starting material were isolated. In analogy to the photoisomerization of *trans*-α-ionone to *cis*-α-ionone[8] and the isomerization of III to II, we had anticipated *cis*-β-ionone (VII) in the low boiling fraction of the reaction product. This notion however was quickly dismissed after an inspection of both the ultraviolet (λ_{max} 286 mμ, log ε 3.68) and infrared spectra (*cf.* Fig. 1) of this fraction (X). The data indicated the presence of an enol ether rather than a ketone. Verification was obtained by catalytic reduction of X to a tetrahydro compound (XI) which was identical with a sample obtained by an unambiguous route.[9] Although the facts presented above show

(4) A recent review of the subject is presented by H. H. Inhoffen and K. Brückner in L. Zechmeister, "Progress in the Chemistry of Organic Natural Products," Vol. XI, Springer, Wien, 1954.

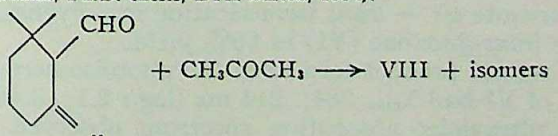
(5) L. Velluz and G. Amiard, *Compt. rend.*, **228**, 692 (1949); E. Havinga, A. L. Koevoet and A. Verloop, *Rec. trav. chim.*, **74**, 788, 1125, 1230 (1955).

(6) L. Velluz, G. Amiard and B. Goffinet, *Bull. soc. chim.*, 1341 (1955). The stereochemical argument presented rests entirely on rather subtle differences in the ultraviolet absorption spectra of II and III. However, it seems reasonable that a transition state (approximately i) should collapse to the *cis*-(II), rather than to the *trans* isomer III.



i

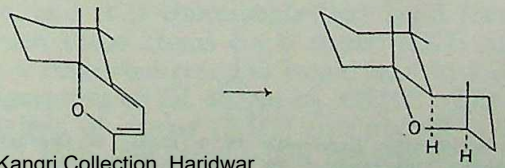
(7) To our knowledge pure γ-ionone has not been described in the literature; however, a mixture of isomeric ionones containing 15% of VIII has been obtained by condensation of ii with acetone (B. Willhalm, Ph.D. thesis, ETH Zurich, 1954).



ii

(8) G. Büchi and N. C. Yang, *Helv. Chim. Acta*, **38**, 1338 (1955).

(9) M. Stoll and P. Bolle, *ibid.*, **33**, 900 (1950); M. Stoll, P. Bolle and L. Ruzicka, *ibid.*, **33**, 1502 (1950). We would like to thank Dr. Max Stoll, Firmenich and Co., Geneva, for providing us with a sample of XI. The configuration of XI is unknown, but it seems safe to assume that catalytic reduction of iii leads to iv.



iii iv

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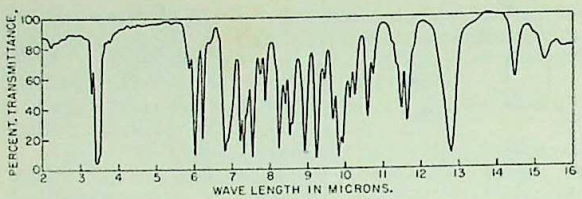
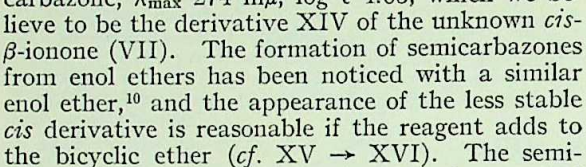
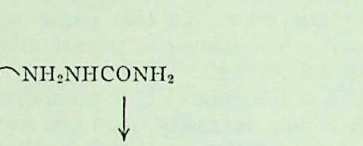


Fig. 1.

that X does not contain a carbonyl group, prolonged treatment with semicarbazide acetate in methanolic solution yielded a very unstable semicarbazone, λ_{max} 274 mμ, log ϵ 4.03, which we believe to be the derivative XIV of the unknown *cis*-β-ionone (VII). The formation of semicarbazones from enol ethers has been noticed with a similar enol ether,[10] and the appearance of the less stable *cis* derivative is reasonable if the reagent adds to the bicyclic ether (*cf.* XV → XVI). The semicarbazone of the *trans*-ketone would be the expected product of addition to the monocyclic ketone.[11]



Semicarbazone XIV was smoothly hydrolyzed by steam distillation in the presence of phthalic acid to the pyran X rather than VII. This finding suggests that the preferred elimination of semicarbazide in the intermediate XVI involves cyclization rather than direct 1,2-elimination (XVII arrows).



Isomerization of X with iodine, a reagent known to promote *cis* → *trans* isomerization in polyenes,[12] gave *trans*-β-ionone (VI) in 60% yield.

A second product formed in the photoisomerization of VI had λ_{max} 284; 214 mμ (log ϵ 2.1; 3.44). The ultraviolet absorption spectrum observed is similar to the one of 1-acetyl-2,2-dimethyl-3-(2-methyl-1-propenyl)-cyclopropane.[13] The infrared spectrum (Fig. 2) suggested the presence of CH_3CO- and $CH_2{=}C(R)_2$, and a positive iodoform test as well as the formation of formaldehyde on ozonization of IX confirmed this postulate. Ionene (XIII) was formed readily upon acid-catalyzed isomeriza-

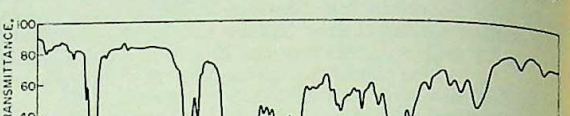
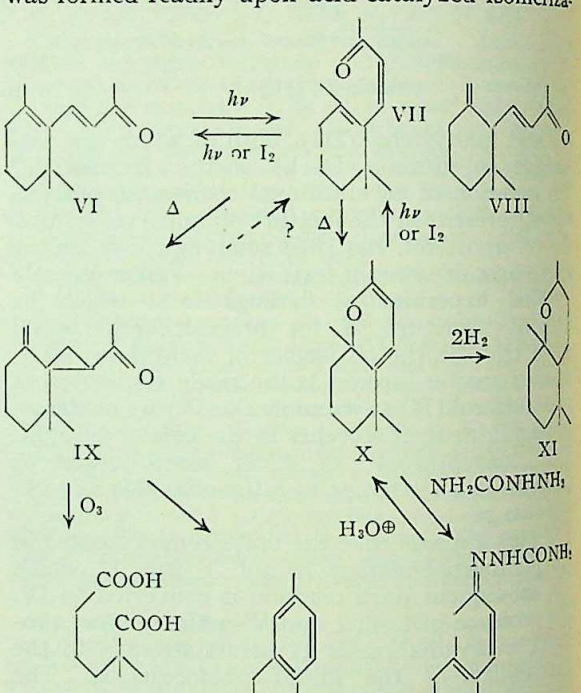


Fig. 2.

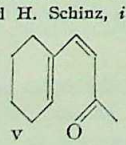


tion of IX, and this finding is interpretable with structures IX and XVIII, both of which contain the unchanged carbon skeleton of VI.

Some insight into the distribution of the functional groups in IX was gained through ozonization experiments which gave formaldehyde (12%) and 2,2-dimethyladipic acid (XII) (40%). The formation of XII from XVIII is self explanatory, but its formation from IX is puzzling because cyclopropanes are known to be stable to ozone. However, the breakdown of the cyclopropane ring does not necessarily have to occur during the ozonization and might well be caused by hydrogen peroxide

(10) M. Stoll, L. Ruzicka and C. F. Seidel, *Helv. Chim. Acta*, **33**, 1245 (1950); M. Stoll and M. Hinder, *ibid.*, **34**, 334 (1951).

(11) In an attempt to prepare the phenylsemicarbazone of v the only isolable derivative was that of the *trans*-ketone [*cf.* W. Surber, V. Theus, L. Colombi and H. Schinz, *ibid.*, **34**, 1299 (1956)].



(12) L. Zechmeister, *Experientia*, **10**, 9 (1954); W. Oroshnik and A. D. Mebane, THIS JOURNAL, **76**, 5719 (1954), and other examples cited in these papers.

(13) R. H. Eastman and S. K. Freeman, *ibid.*, **77**, 6642 (1955), and other papers.

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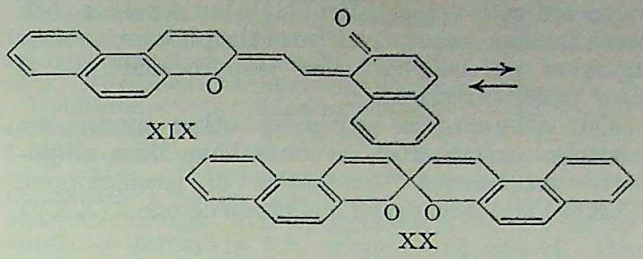
which was used to complete this oxidation.[14] Titration of IX with perbenzoic acid established the presence of only one double bond, and the photoisomer should therefore contain two carbocyclic rings. In sharp contrast to this result catalytic reduction of IX was only complete after the uptake of three moles of hydrogen. The alcohol thus formed was reoxidized with chromium trioxide and the ketone characterized by its semicarbazone. The derivative could not be obtained pure, but no melting point depression was observed on admixture of *cis*-tetrahydroionone semicarbazone.

We were thus forced to assume that our photoisomer contains either (a) two olefinic bonds, one of which is not oxidizable by perbenzoic acid, or (b) a vinylcyclopropane system reducible to the tetrahydro stage. Structure XVIII was excluded through consideration of the following facts: (i) basic conditions sufficiently drastic to cause isomerization of α- to β-ionone[15] did not bring about isomerization of the ketone to VI, and (ii) the ultraviolet absorption observed is scarcely attributable to the conjugated diene chromophore of XVIII because the less highly substituted 1,2-dimethylenecyclohexane has λ_{max} 220 mμ.[16] We therefore favor formula IX with which all of the described facts including the reduction[17] can be rationalized satisfactorily.

Discussion of Results

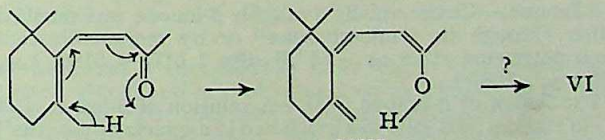
The first step in the conversion of β-ionone (VI) to IX and X is undoubtedly the reversible photoisomerization to *cis*-β-ionone (VII), a reaction for which analogies have been quoted already. We assume that the two products actually isolated are derived from the highly reactive *cis*-ketone VII by two distinct dark reactions (a) and (b). Thus (a), whenever the six atoms present in the chromophore of VII have approached planarity, cyclization can occur to give the bicyclic pyran X. As in the reversible dienone $\rightleftarrows$ pyran interconversion observed with thermochromic spiropyrans (*e.g.*, XIX $\rightleftarrows$ XX),[18] the equilibrium, at room temperature, is very much on the side of the pyran X. This seems reasonable if one compares the resonance energies of the planar pyran X with that of the *cis*-dienone VII which, in the ground state at least, is forced into a non-planar conformation by steric interference of methyl groups.



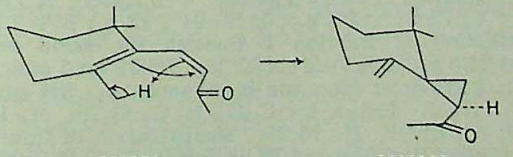
Conversely, irradiation of X in alcoholic solution produces a mixture of VI, IX and X. A considerable amount of energy (ultraviolet light) is required to convert the pyran X back to the *cis*-ketone VII from which VI is formed by photoisomerization and IX probably by a dark reaction (see below). We have no direct evidence that the *cis*-ketone VII → pyran X conversion is indeed a thermal rather than a photochemical reaction, but since the appearance of our preliminary note,[3] Schinz[11] has reported the formation of pyrans by catalytic reduction of two acetylenic ketones in the absence of light. These findings thus support our postulate.

The formation of the *cis*-ketone VII from X is therefore analogous to the photosynthesis of praecalciferol (II) from ergosterol (I); the reverse reaction (X from VII), however, seems to occur very much more readily than the formation of ergosterol (I) and lumisterol (V) from praecalciferol (II).

The question (b) whether the *cis*-ketone VII undergoes an "enesynthesis" analogous to the praecalciferol (II) → vitamin D (IV) change cannot be answered because the product (XXI) from such a reaction might well convert to β-ionone (VI) rather than γ-ionone (VIII).

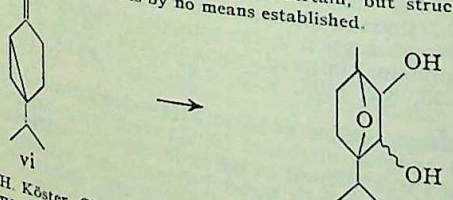


The unstable *cis*-ketone VII apparently can stabilize itself by another route (b) which results in the formation of the spiroketone IX.



The atomic model of the *cis*-ketone XXII shows that in the least strained conformation in which the side chain is approximately perpendicular to the plane of the cyclohexene ring, a methyl hydrogen is close in space to the first carbon atom of the side chain, and it is conceivable that bond formation between these atoms could occur (XXII arrows). Such a concerted reaction would lead to a definite configuration of IX shown in XXIII. The ready formation of ionene (XIII) (see above) is well in accord with this formulation because only in this diastereomer (XXIII) are the carbonyl carbon

(14) The oxidation of sabinene (vi) with hydrogen peroxide in acetic acid has been investigated by G. G. Henderson and A. Robertson [*J. Chem. Soc.*, 1849 (1923); *ibid.*, 2761 (1926)], who have found that two isomeric compounds $C_{10}H_{18}O_3$ were formed. The absence of a cyclopropane ring in the products seems certain, but structure vii advanced by the authors is by no means established.



vi vii

(15) H. Köster, *Chem. Ber.*, **77**, 553 (1944).

(16) W. J. Bailey and H. G. Golden, THIS JOURNAL, **75**, 4780 (1953).

(17) Reductive fission of vinylcyclopropanes is known: *cf.* R. W. Kierstead, R. P. Linstead and B. C. L. Weedon, *J. Chem. Soc.*, 3610 (1952); 1799 (1953), and earlier references cited therein.

(18) For a discussion of this isomerization see C. F. Koelsch, *J. Org. Chem.*, **16**, 1362 (1951).

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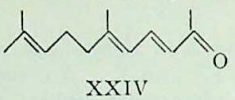
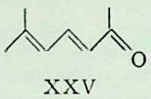
and the terminal methylene group in close spatial proximity. An analogous reaction has not been observed with praecalciferol (II), but whether such a mechanism is operative also in the photoisomerizations of pyrocalciferol and isopyrocalciferol[19] is now under investigation.

Our attempts to synthesize other pyrans by photoisomerization of dienones have been singularly unsuccessful. Irradiation of pseudoionone (XXIV) and 6-methyl-3,5-heptadiene-one-2 (XXV)

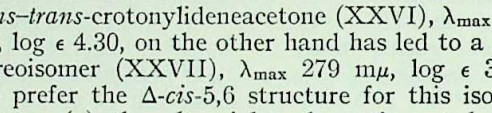


XXIV



XXV

has led to polymeric materials rather than the desired pyrans. We have been unable to determine whether the polymers have originated from the pyrans or the ketones. Photoisomerization of *trans–trans*-crotonylideneacetone (XXVI), λ_{max} 272 mμ, log ϵ 4.30, on the other hand has led to a new stereoisomer (XXVII), λ_{max} 279 mμ, log ϵ 3.99. We prefer the Δ-*cis*-5,6 structure for this isomer because (a) the ultraviolet absorption at longer wave lengths indicates that the newly introduced *cis* double bond is at the end of the chromophore[12] and (b) the $\Delta^{3,4}$-*cis* isomer would be expected to isomerize to the pyran.[11] The aliphatic nature of XXVII was established by hydrogenation to the known 2-heptanone.



XXVI XXVII

Acknowledgment.—The authors wish to acknowledge generous financial assistance from Eli Lilly and Co.

Experimental[20]

β-Ionone.—Commercially available β-ionone was purified either through its semicarbazone[21] or by recrystallization from petroleum ether at −75°,[22] $n^{25}D$ 1.5178–1.5180, λ_{max} 296 mμ, ϵ 10800.

Irradiation of β-Ionone (VI).—A solution of β-ionone (24 g.) in ethanol (600 ml.) was irradiated in a quartz apparatus[23] for 48 hr. at 35–40°. The ethanol was then removed by evaporation under reduced pressure and the residue distilled through a Hickman flask (b.p. 35–60° at 0.05 mm.). The distillates from 5 irradiations (81 g.) were combined and fractionated through a 40-inch spinning band column at 1 mm.: fraction 1, 68–72°, 31.5 g., $n^{25}D$ 1.4980; 2, 71–75°, 2.4 g.; 3, 75–85°, 4.8 g.; 4, 85–94°, 18 g., $n^{25}D$ 1.5060. Redistillation of fraction 1 through the same column yielded 24.5 g. (30% yield) of X, b.p. 70–71° at 1 mm., $n^{25}D$ 1.4992; ultraviolet spectrum in ethanol, λ_{max} 286 mμ, log ϵ 3.86. *Anal.* Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.01; H, 10.25. Redistillation of fraction 3 (17.3 g. combined from six 72-hr. irradiations) through a 1-ft. spinning-band column gave 8.4 g. of IX, b.p. 81–82° at 1 mm., $n^{25}D$ 1.4860, λ_{max} 284 mμ, log ϵ 2.10; 214 mμ, log ϵ 3.44. *Anal.* Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.06; H, 10.51.

The ketone IX was further characterized by a semicarbazone, m.p. 170–171°, recrystallized from ethanol. *Anal.* Calcd. for $C_{14}H_{23}ON_3$: C, 67.43; H, 9.30; N, 16.85. Found: C, 67.29; H, 9.23; N, 16.75.

Treatment with phenylsemicarbazide in methanol gave a derivative, m.p. 144–145°, recrystallized from ethanol. *Anal.* Calcd. for $C_{20}H_{27}ON_3$: C, 73.81; H, 8.36; N, 12.91. Found: C, 73.62; H, 8.52; N, 13.23.

Irradiation of X.—A solution of X (22 g.) in ethanol (650 ml.) was irradiated for 48 hr. at 35° and the organic material isolated as described above. The products (14 g.) were separated by fractionation through a 1-ft. spinning-band column at 1 mm.: fraction 1, b.p. 69–73°, 4.6 g.; 2, 73–75°, 1.2 g.; 3, 75–85°, 3.5 g.; 4, 85–92°, 4.4 g., $n^{25}D$ 1.5108. Fraction 1 was identified as unchanged X by its characteristic infrared spectrum. A semicarbazone prepared from 3 was identical with the corresponding derivative of the bicyclic ketone IX. Fraction 4 consisted mainly of β-ionone (VI) as indicated by its infrared spectrum and the formation of β-ionone semicarbazone, m.p. 147–148°.

Isomerization of X.—To a mixture of X (2 g.) in 40 ml. of benzene was added iodine (100 mg.) and the resulting solution kept at room temperature for 2 hr. After washing with aqueous sodium thiosulfate and evaporation of the solvent, an oil remained which was distilled, b.p. 63–66° (0.02 mm.), 1.2 g., $n^{25}D$ 1.5134, and identified as β-ionone by its infrared spectrum as well as by semicarbazone comparison.

Hydrogenation of X to XI.—A solution of X (1.92 g.) in glacial acetic acid (5 ml.) was stirred with Adams platinum catalyst (0.4 g.) under hydrogen at room temperature. The uptake of hydrogen ceased after 1.96 mole had been absorbed. After removal of the catalyst by filtration, the filtrate was diluted with water (40 ml.) and the product isolated by extraction with petroleum ether. The dried solution was passed over 50 g. of neutral alumina. Removal of the solvent from the eluate yielded a product which after distillation had b.p. 45–48° (0.05 mm.), 1.56 g., $n^{25}D$ 1.4714. *Anal.* Calcd. for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.82; H, 12.06. The infrared spectrum of the product was indistinguishable from the spectrum of authentic epoxy-3,2[3]-tetrahydroionane (XI).

***cis*-β-Ionone Semicarbazone (XIV).**—The pyran X (4.0 g.) was allowed to react with excess semicarbazide–acetate in methanol solution in the absence of oxygen and sunlight. A crystalline precipitate formed slowly and was collected on a filter after 24 hr. After two rapid recrystallizations from aqueous methanol, the compound had m.p. 184–185° (vacuum capillary); λ_{max} 274 mμ, log ϵ 4.03. *Anal.* Calcd. for $C_{14}H_{23}ON_3$: C, 67.43; H, 9.30. Found: C, 67.38; H, 9.28. The infrared spectrum showed that a true semicarbazone was present (5.9, 6.25 μ).

Hydrolysis of *cis*-β-Ionone Semicarbazone (XIV).—The derivative (3.6 g.) was mixed with phthalic anhydride (3.6 g.) by grinding in a mortar and hydrolyzed by steam distillation. The organic material was extracted into petroleum ether and washed successively with aqueous sodium bicarbonate and water, concentrated to a liquid which on distillation gave the pyran X (0.7 g.), identified by b.p., $n^{25}D$ and infrared spectrum.

Air Oxidation of X.—On prolonged standing in the presence of air, X is converted to a crystalline colorless material which after recrystallization from benzene–petroleum ether had m.p. 130° dec. *Anal.* Calcd. for $C_{13}H_{22}O_3$: C, 69.00; H, 9.80. Found: C, 68.96, 69.01, 69.34; H, 9.46, 9.63, 9.55. No absorption in the ultraviolet region of the spectrum; principal infrared bands in KBr: 2.88, 3.05, 3.45, 7.20, 7.35, 8.2, 9.08, 9.25, 9.45, 9.64, 10.05, 10.55 and 11.65 μ.

Acid Isomerization of IX to XIII.—A solution of IX (240 mg.) in aqueous methanol (80%) containing sulfuric acid (400 mg.) was allowed to reflux for 90 min. The mixture was then poured into water (10 ml.) and extracted with ethyl ether. After washing, drying and evaporation, an oil was isolated which was purified successively by chromatography over alumina and vacuum distillation, b.p. 48–50° (0.05 mm.), $n^{25}D$ 1.5205 (*Anal.* Calcd. for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.85; H, 10.10) and shown to be identical by b.p., $n^{25}D$ and infrared spectrum with ionene (XIII).

Oxidation of IX with Perbenzoic Acid.—The bicyclic ketone IX (0.256 g.) was added to a solution of perbenzoic

(19) K. Dimroth, *Chem. Ber.*, **70**, 1631 (1937).

(20) Melting points and boiling points are uncorrected. Analyses by Mmes. N. Alvord and G. Kula and Dr. S. M. Nagy, M.I.T. Microanalytical Department. The infrared spectra were determined with a Baird double beam recording spectrophotometer. Ultraviolet spectra were measured with a Cary recording spectrophotometer.

(21) W. G. Young, S. J. Cristol, L. J. Andrews and S. L. Lindenbaum, THIS JOURNAL, **66**, 855 (1944).

(22) T. G. Drustrup, U. S. Patent 2,638,483 (1951). We would like to thank Dr. Robert Kent, Chas. Pfizer and Co. for calling our attention to this reference.

(23) M. S. Kharasch and H. N. Friedlander, *J. Org. Chem.*, **14**, 239 (1949).

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acid in chloroform (5 ml., 1.17 *N*) and the mixture allowed to stand at 0–5°. Aliquot parts were removed for titration after 6, 8 and 24 hr. The following consumption of perbenzoic acid was observed: 1.02, 1.03 and 1.02 moles.

Hydrogenation of IX.—One gram of IX was hydrogenated in glacial acetic acid (5 ml.) over Adams platinum catalyst (from 0.5 g. of PtO_2) at atmospheric pressure. Hydrogen (368 ml., 3.0 mole equiv.) was absorbed within 12 hr. In two additional reductions, carried out under identical conditions, 2.86 and 2.95 moles of hydrogen was absorbed. Reoxidation of the secondary alcohol(s) thus formed with chromium trioxide in acetic acid solution gave a ketone which was characterized by its semicarbazone, m.p. 173–174°. Repeated recrystallization did not raise the melting point. No depression was observed on admixture of pure *cis*-tetrahydroionone semicarbazone, m.p. 179–180°.

Oxidation of IX with Ozone.—A large excess of ozone (2% in oxygen) was passed through a solution of IX (1 g.) in carbon tetrachloride at 0–5°. The escaping gases were passed through an absorption tube containing water (10 ml.) and after completion of the oxidation, dimedone (1.6 g.) in ethanol (20 ml.) was added to this water. The precipitate which had formed was filtered and on recrystallization yielded the dimedone derivative of formaldehyde, 180 mg., 12%, m.p. 188–190°. The actual reaction mixture was concentrated under reduced pressure and the remaining oil warmed to 85° for 4 hr. after a solution of aqueous hydrogen peroxide (10%) had been added. Aqueous sodium hydroxide was added and the small amount of neutral material extracted with ether. The water layer was then acidified with concd. hydrochloric acid and extracted exhaustively with ether. Purification of the residue obtained after evaporation of the solvent was achieved by chromatography on silica gel (Davison mesh size 28–200, 30 g.). A mixture of chloroform–ethyl acetate (7:3) was used to elute the material which was further purified by recrystallization from acetone–water. The acid (350 mg., 38% yield) had m.p. 86–87° (*Anal.* Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.28; H, 8.00), and was found to be identical by mixture melting point and infrared spectrum with authentic 2,2-dimethyladipic acid (XII).

Attempted Base-catalyzed Isomerization of IX.—A solution of IX in carefully dried ethanol containing 10% sodium ethoxide was allowed to stand for 24 hr. at room temperature. No change in the ultraviolet spectrum was observed.[24]

Irradiation of Crotonylideneacetone (XXVI).—A solution of crotonylideneacetone,[25] 20 g., b.p. 77–78° (24 mm.), $n^{25}D$ 1.5200, λ_{max} 272 mμ, log ε 4.30, was irradiated in ethanol (600 ml.) for 24 hr. The solvent was removed carefully by distillation through a Fenske column and the residue fractionated in a Hickman flask. The distillate was further purified by distillation through a 1-ft. spinning-band column. The first fraction, b.p. 62–77° (24 mm.), yielded 2.3 g. of a light yellow liquid which on redistillation through a semimicro fractionating column gave 700 mg. of XXVII, b.p. 62–64° (21 mm.), $n^{25}D$ 1.5040, λ_{max} 279 mμ, log ε 3.99; principal infrared bands: 3.48, 6.0, 6.15, 12.0, 13.5 and 14.6 μ. *Anal.* Calcd. for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 75.78; H, 9.15. The semicarbazone, m.p. 118–140° dec., decomposed on attempted recrystallization from ethanol.

Hydrogenation of XXVII to 2-Heptanone.—A solution of XXVII (100 mg.) in absolute ethanol (5 ml.) was stirred with 2% palladium-on-calcium carbonate catalyst (100 mg.) under hydrogen at room temperature. The calculated amount of two mole equivs. of hydrogen (100%) was rapidly absorbed. After removal of the catalyst by filtration 2,4-dinitrophenylhydrazine reagent was added. The derivative (160 mg.) had m.p. 73–74° after two recrystallizations from methanol and was identical by mixture melting point determination with an authentic derivative of 2-heptanone.

(24) We would like to thank Dr. Hans Rennhard for performing this experiment.

(25) H. Meerwein, *Ann.*, **358**, 85 (1908).

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Perfluoroalkyl-substituted Dicarboxylic Acids and Derivatives[1,2]

BY E. T. MCBEE, C. W. ROBERTS[3] AND GORDON WILSON, JR.

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The condensation of ethyl malonate with $C_3F_7CH{=}CHCO_2Et$ produced a tricarboxylic ester which was hydrolyzed and decarboxylated to $C_3F_7CH(CH_2CO_2H)_2$. The corresponding ester, glycol and acid chloride were synthesized from the acid. By the same synthetic route $C_7F_{15}CH(CH_2COCl)_2$ also was prepared. The addition of hydrogen sulfide to $C_3F_7CH{=}CHCO_2Et$ produced mainly $S[CH(C_3F_7)CH_2CO_2Et]_2$ with some $C_3F_7CH(SH)CH_2CO_2Et$. The acid, glycol and acid chloride of the sulfide were prepared.

Discussion

Recent interest in elastomers which are not affected by extremes in temperature and by organic solvents has led to investigations of fluorine-containing polyesters. This paper reports several dicarboxylic acids and derivatives containing perfluoroalkyl side chains which were prepared from 3-perfluoroalkylpropenoates and which are convertible to polymers by appropriate reactions.

In earlier investigations, 3-perfluoroalkylpropenoates were prepared by reaction of a perfluoroaldehyde with ethyl bromoacetate in the presence of zinc dust followed by dehydration of the resulting β-hydroxy ester.[4] Higher and more consistent over-all yields of ethyl 4,4,5,5,6,6,6-heptafluoro-2-hexenoate and ethyl 4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-pentadecafluoro-2-decenoate have now been obtained by an alternate procedure in which the perfluoroaldehyde is first condensed with malonic acid in pyridine solution to give a β-hydroxy acid. This Knoevenagel reaction is somewhat surprising since perfluoroaldehydes are readily polymerized by organic bases and, in fact, when the pyridine solution of malonic acid is added to the aldehyde, polymerization occurs rapidly with the evolution of heat. However, as the reaction mixture is heated the polymer slowly dissolves and the condensation proceeds. The stability toward dehydration of β-hydroxy-β-perfluoroalkyl esters[4] and

(1) This investigation was performed on a subcontract with Hooker Electrochemical Co. and was supported in whole by the United States Air Force as part of Contract AF 33(616)-2421 monitored by Materials Laboratory, Directorate of Research, Wright Air Development Center. A paper covering this investigation was presented before the Division of Polymer Chemistry, 130th Meeting of the American Chemical Society, Atlantic City, N. J., 1956.

(2) From a thesis to be submitted by Gordon Wilson, Jr., to the Graduate School, Purdue University, in partial fulfillment for the degree of Doctor of Philosophy.

(3) Dow Chemical Co., Midland, Michigan.

(4) E. T. McBee, O. R. Pierce and D. D. Smith, THIS JOURNAL, **76**, 3722 (1954).

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ketones[5] compared to the non-fluorinated analogs is well known. Thus, although the Knoevenagel reaction usually leads to α,β-unsaturated acids, with perfluoroaldehydes the isolation of the stable β-hydroxy acids is not unusual. The β-hydroxy acids were converted to the α,β-unsaturated esters by esterification followed by dehydration with phosphorus pentoxide.

Several ionic additions to 3-perfluoroalkylpropenoates have been reported[6,7] and in all cases the products were those expected by analogy with similar reactions of non-fluorinated compounds. In the present study, the Michael condensation of ethyl 4,4,5,5,6,6,6-heptafluoro-2-hexenoate with diethyl malonate gave diethyl 2-carbethoxy-3-perfluoropropylpentanedioate. This tricarboxylic ester was hydrolyzed and decarboxylated to 3-perfluoropropylpentanedioic acid. The reaction of phosphorus pentachloride with the acid produced the acid chloride. When the acid was treated with thionyl chloride, however, 3-perfluoropropylpentanedioic anhydride resulted. This is not unusual since 3-phenylpentanedioic anhydride is formed from the corresponding acid by the action of not only thionyl chloride but also phosphorus chlorides.[8] Reduction of the acid, or esterification and then reduction, gave the glycol, 3-perfluoropropyl-1,5-pentanediol. When the glycol was heated with a trace of mineral acid, dehydration occurred and 3-perfluoropropyltetrahydropyran resulted.

3-Perfluoroheptylpentanedioyl chloride was prepared by the same synthetic route. In this case, the tricarboxylic ester resulting from the Michael condensation was not isolated in a pure state but was hydrolyzed and decarboxylated directly to 3-perfluoroheptylpentanedioic acid.

The 3-perfluoroalkyl acids, esters and glycols do not undergo degradation in the presence of acids or bases. Furthermore, they are stable at temperatures as high as 200°. The anhydride and acid chlorides are rapidly hydrolyzed on exposure to moist air. The physical properties are those expected by comparison with the non-fluorinated analogs.[9]

The incorporation of sulfur into the central chain of monomers which contain perfluoroalkyl groups also has been accomplished. Addition of hydrogen sulfide to ethyl 3-perfluoroalkylpropenoates was performed by the method of Barkenbus and coworkers.[10] In the presence of BTA hydroxide[11] and piperidine, ethyl 4,4,5,5,6,6,6-heptafluoro-2-hexenoate and hydrogen sulfide gave primarily diethyl 3,5-bis-(perfluoropropyl)-4-thiaheptanedioate. A by-product of the reaction was ethyl 3-mercapto-4,4,5,5,6,6,6-heptafluorohexanoate. In a similar manner, diethyl 3,5-bis-(perfluoromethyl)-4-thiaheptanedioate was prepared. Acidic hydrolysis of the former ester gave two forms of the dicarboxylic acid. Since there are two identical asymmetric centers, one form is presumed to be the *meso*-acid and the other a racemic modification. 3,5-Bis-(perfluoropropyl)-4-thiaheptanedioyl chloride was prepared from the acid by reaction with thionyl chloride. Reduction of the bis-(perfluoropropyl)-thiaheptanedioate with lithium aluminum hydride gave the glycol, 3,5-bis-(perfluoropropyl)-4-thia-1,7-heptanediol.

Although the sulfide esters are prepared in the presence of a strong base, they are not stable to aqueous base. Even in 5% aqueous sodium hydroxide at room temperature, they decompose to dark red tars in a matter of a few minutes. Traces of impurities appear to cause disproportionation during fractionation but once pure the esters and acid chloride appear to be stable at distillation temperatures. Several attempts at mild oxidation of diethyl 3,5-bis-(perfluoropropyl)-4-thiaheptanedioate were made. In all cases there was apparent cleavage of a carbon–sulfur bond and oxidation to an extremely hygroscopic solid, probably the sulfonic acid.

Experimental[12]

3-Hydroxy-3-perfluoroalkylpropanoic Acids.—A cold solution of 193 g. (1.85 moles) of malonic acid in 1 l. of pyridine was added to 341 g. (1.72 moles) of perfluorobutanal[13] in 400 ml. of dry toluene. The resulting slush of polymerized aldehyde was heated slowly to boiling and refluxed until the evolution of carbon dioxide ceased. The cooled reaction mixture was poured over 4 kg. of ice and 500 ml. of concentrated sulfuric acid. The product was taken up in ether, dried and the ether removed by distillation. Recrystallization of the residue from benzene gave 389 g. (88%) of 3-hydroxy-4,4,5,5,6,6,6-heptafluorohexanoic acid, m.p. 78–80°.[4]

By the same procedure, 159 g. (0.40 mole) of perfluorooctanal[13] and 41.6 g. (0.40 mole) of malonic acid gave 128 g. (68%) of 3-hydroxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-pentadecafluorodecanoic acid, m.p. 123–123.5°.

Anal. Calcd. for $C_{10}H_5F_{15}O_3$: C, 26.21; H, 1.10. Found: C, 25.92; H, 1.13.

Ethyl 3-Hydroxy-3-perfluoroalkylpropanoates.—3-Hydroxy-4,4,5,5,6,6,6-heptafluorohexanoic acid (550 g., 2.13 moles) was dissolved in a large excess (2278 g., 49.1 moles) of absolute ethanol, and hydrogen chloride was bubbled through the solution until 22 g. (0.6 mole) had been absorbed. After standing at room temperature for a day, the solution was refluxed 4 hr. and then distilled. The yield of ethyl 3-hydroxy-4,4,5,5,6,6,6-heptafluorohexanoate was 518 g. (85%), b.p. 92–93° (15 mm.), n^{20}D 1.3538.[4]

In a similar manner, 90 g. (0.196 mole) of 3-hydroxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-pentadecafluorodecanoic acid, 619 g. (13.4 moles) of absolute ethanol and 8 g. (0.22 mole) of hydrogen chloride gave 95.3 g. (86%) of ethyl 3-hydroxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-pentadecafluorodecanoate, b.p. 97° (1.9 mm.), n^{20}D 1.3429.[14]

Ethyl 3-Perfluoroalkylpropenoates.—The dehydration of ethyl 3-hydroxy-3-perfluoroalkylpropanoates with phosphorus pentoxide was conducted by the previously reported method.[4] From 572 g. (2.0 moles) of ethyl 3-hydroxy-4,4,5,5,6,6,6-heptafluorohexanoate there was obtained 451 g. (84%) of the corresponding α,β-unsaturated ester, b.p. 140–141°, n^{20}D 1.3444.[4]

Seventy-five grams (0.155 mole) of the 3-hydroxypentadecafluorodecanoate gave 48 g. (66%) of ethyl 4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-pentadecafluoro-2-decenoate, b.p. 101° (18 mm.), n^{28}D 1.3340.

(5) E. T. McBee, D. H. Campbell, R. J. Kennedy and C. W. Roberts, THIS JOURNAL, **78**, 4597 (1956).

(6) E. T. McBee, O. R. Pierce and D. D. Smith, *ibid.*, **76**, 3725 (1954).

(7) H. M. Walborsky and M. Schwarz, *ibid.*, **75**, 3241 (1953).

(8) J. G. Jackson and J. Kenner, *J. Chem. Soc.*, 573 (1928).

(9) J. N. E. Day and J. F. Thorpe, *ibid.*, 1465 (1920).

(10) C. Barkenbus, V. C. Midkiff and R. M. Newman, *J. Org. Chem.*, **16**, 232 (1951).

(11) A 40% solution of benzyltrimethyl ammonium hydroxide in methanol.

(12) All temperatures are uncorrected. Analyses were made by Clark Microanalytical Laboratory, Urbana, Ill., and Mrs. C. S. Yeh of this Department.

(13) O. R. Pierce and T. G. Kane, THIS JOURNAL, **76**, 300 (1954).

(14) E. T. McBee, O. R. Pierce and D. L. Christman, *ibid.*, [illegible] (1955).

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Anal. Calcd. for $C_{12}H_7F_{15}O_2$: C, 30.78; H, 1.51. Found: C, 30.59; H, 1.57.

Diethyl 2-Carbethoxy-3-perfluoropropylpentanedioate.—Diethyl malonate (23.0 g., 0.144 mole) and 26.8 g. (0.10 mole) of ethyl 4,4,5,5,6,6,6-heptafluoro-2-hexenoate were added to a cold solution of 2.5 g. (0.109 g. atom) of sodium in 100 ml. of absolute ethanol. After 1 hr. at room temperature the mixture was heated under reflux for 1.5 hr., poured into water and made acidic with hydrochloric acid. The product was taken up in ether, dried and distilled to give 38.5 g. (90%) of the triester, b.p. 104° (0.7 mm.), $n^{20}D$ 1.3900, d^{20}_4 1.306.

Anal. Calcd. for $C_{15}H_{19}F_7O_2$: C, 42.06; H, 4.47. Found: C, 41.83; H, 4.61.

3-Perfluoropropylpentanedioic Acid.—A mixture of 133 g. (0.264 mole) of diethyl 2-carbethoxy-3-perfluoropropylpentanedioate and 200 ml. of dilute (1:1) hydrochloric acid was stirred and heated until no further evolution of carbon dioxide could be observed. The water and hydrochloric acid were removed by distillation under reduced pressure and the white solid residue was recrystallized from water to yield 77.2 g. (98%) of product, m.p. 121–122.5°.

Anal. Calcd. for $C_8H_7F_7O_4$: C, 32.00; H, 2.78; F, 44.33. Found: C, 32.02; H, 2.43; F, 43.57.

3-Perfluoroheptylpentanedioic Acid.—Ethyl 4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-pentadecafluoro-2-decenoate was treated with ethyl malonate in the same manner as the ethyl heptafluorohexenoate. The resulting triester was not isolated in pure form but was immediately hydrolyzed and decarboxylated with hydrochloric acid. Since the crude 3-perfluoroheptylpentanedioic acid formed a gel with water, it was recrystallized from toluene. From 90.4 g. (0.20 mole) of pentadecafluorodecenoate there was obtained 53 g. (53%) of 3-perfluoroheptylpentanedioic acid, m.p. 125–126°.

Anal. Calcd. for $C_{12}H_7F_{15}O_4$: C, 28.81; H, 1.41. Found: C, 28.54; H, 1.35.

3-Perfluoropropylpentanedioic Anhydride.—A mixture of 6.0 g. (0.02 mole) of perfluoropropylpentanedioic acid and 9.5 g. (0.071 mole) of thionyl chloride was refluxed for 4 hr. The excess thionyl chloride was removed by distillation under reduced pressure and the residual oil was distilled *in vacuo* to yield 4.9 g. (86%) of the anhydride, b.p. 93–94° (0.2 mm.), m.p. 48.5–49.5°.

Anal. Calcd. for $C_8H_5F_7O_3$: C, 34.04; H, 1.78. Found: C, 34.15; H, 2.00.

3-Perfluoroalkylpentanedioyl Chlorides.—Phosphorus pentachloride (41.6 g., 0.20 mole) was added to 30.0 g. (0.10 mole) of 3-perfluoropropylpentanedioic acid, and the mixture refluxed for 1 hr. The phosphorus oxychloride was removed by distillation at atmospheric pressure and the residue distilled at reduced pressure to yield 29.6 g. (88%) of 3-perfluoropropylpentanedioyl chloride, b.p. 65° (1.6 mm.), $n^{20}D$ 1.3926.

Anal. Calcd. for $C_8H_5F_7Cl_2O_2$: C, 28.48; H, 1.48; Cl, 21.07. Found: C, 28.36; H, 1.69; Cl, 21.45.

In a similar experiment, 25 g. (0.05 mole) of 3-perfluoroheptylpentanedioic acid gave 19.6 g. (73%) of 3-perfluoroheptylpentanedioyl chloride, b.p. 88° (0.7 mm.), $n^{20}D$ 1.3699.

Anal. Calcd. for $C_{12}H_5F_{15}Cl_2O_2$: C, 26.81; H, 0.93; Cl, 13.20. Found: C, 26.57; H, 1.10; Cl, 13.44.

Diethyl 3-Perfluoropropylpentanedioate.—3-Perfluoropropylpentanedioic acid was esterified by dissolving 23 g. (0.07 mole) of the acid and 5.0 g. of hydrogen chloride in 450 ml. of absolute ethanol, allowing the solution to sit 12 hr. and finally refluxing for 1 hr. before removing the excess alcohol. Distillation of the residue gave 22.8 g. (92%) of the ester, b.p. 79–80° (1.5 mm.), $n^{20}D$ 1.3738, $d^{21.5}_4$ 1.320.

Anal. Calcd. for $C_{12}H_{15}F_7O_4$: C, 40.45; H, 4.21. Found: C, 40.41; H, 4.23.

3-Perfluoropropyl-1,5-pentanediol.—To a suspension of 25.0 g. (0.66 mole) of lithium aluminum hydride in 1 lb. of anhydrous ether was added a solution of 60.0 g. (0.20 mole) of 3-perfluoropropylpentanedioic acid in 1 lb. of anhydrous ether. After refluxing for 3 hr., 100 ml. of 95% ethanol was added dropwise, and the partially hydrolyzed mixture was diluted with 500 g. of ice and 45 ml. of concentrated sulfuric acid. The product was taken up in ether, washed with sodium bicarbonate solution and dried. Distillation gave 33.5 g. (62%) of colorless, viscous product, b.p. 82° (0.1 mm.), $n^{20}D$ 1.3752.

Anal. Calcd. for $C_8H_{11}F_7O_2$: C, 35.29; H, 4.07. Found: C, 35.43; H, 4.30.

3-Perfluoropropyltetrahydropyran.—The same reduction procedure as given for the preparation of 3-perfluoropropyl-1,5-pentanediol was used with the exception that the ether extracts of the reaction mixture were not washed with base. After removal of the ether, the residue was refluxed 12 hr. before being distilled. From 35.6 g. (0.10 mole) of diethyl 3-perfluoropropylpentanedioate and 4.56 g. (0.12 mole) of lithium aluminum hydride there resulted 20.4 g. (84%) of 3-perfluoropropyltetrahydropyran, b.p. 114–115°, $n^{20}D$ 1.3527, $d^{20}D$ 1.410.

Anal. Calcd. for $C_8H_9F_7O$: C, 37.78; H, 3.53. Found: C, 37.54; H, 3.84.

Diethyl 3,5-Bis-(perfluoroalkyl)-4-thiaheptanedionates.—The addition of hydrogen sulfide to α,β-unsaturated esters was conducted by the procedure of Barkenbus, Midkiff and Newman.[10] From 43.0 g. (0.256 mole) of ethyl 4,4,4-trifluorobutenoate[4] there was obtained 27 g. (57%) of diethyl 3,5-bis-(perfluoromethyl)-4-thiaheptanedioate, b.p. 114–115° (*ca.* 3 mm.), $n^{20}D$ 1.3737.

Anal. Calcd. for $C_{12}H_{16}F_6O_4S$: C, 38.92; H, 4.32. Found: C, 38.90; H, 4.31.

Ethyl 4,4,5,5,6,6,6-heptafluoro-2-hexenoate (142 g., 0.53 mole) afforded 112 g. (74%) of diethyl 3,5-bis-(perfluoropropyl)-4-thiaheptanedioate, b.p. 100–102° (0.6 mm.), $n^{20}D$ 1.3763, d^{20}_4 1.475.

Anal. Calcd. for $C_{16}H_{16}F_{14}O_4S$: C, 33.68; H, 2.81; F, 46.66; S, 5.62. Found: C, 33.40; H, 2.85; F, 46.31; S, 5.23.

Ethyl 3-Mercapto-4,4,5,5,6,6,6-heptafluorohexanoate.—In the above preparation, a forerun of 9.0 g. (5.5%) of ethyl 3-mercapto-4,4,5,5,6,6,6-heptafluorohexanoate was obtained, b.p. 35–36° (0.6 mm.), $n^{20}D$ 1.3774.

Anal. Calcd. for $C_8H_9F_7O_2S$: C, 31.82; H, 3.00. Found: C, 32.09; H, 2.96.

3,5-Bis-(perfluoropropyl)-4-thiaheptanedioic Acid.—A solution of 42.8 g. (0.075 mole) of diethyl 3,5-bis-(perfluoropropyl)-4-thiaheptanedioate in 150 ml. of concentrated sulfuric acid was warmed on a steam-bath for 45 min. and poured over 600 g. of ice. The product was taken up in ether, dried over Drierite and the ether removed by evaporation on a steam-bath. The residue was recrystallized from toluene to yield 30.0 g. (78%) of fairly pure acid. The most insoluble form melts at 156–157° while the other form melts over the range 108–16° even after repeated recrystallizations.

Anal. Calcd. for $C_{12}H_8F_{14}O_4S$: C, 28.02; H, 1.56. Found: C, 27.68; H, 1.85.

3,5-Bis-(perfluoropropyl)-4-thiaheptanedioyl Chloride.—3,5-Bis-(perfluoropropyl)-4-thiaheptanedioic acid (51.4 g., 0.10 mole) and an excess (100 g., 0.84 mole) of thionyl chloride were refluxed for 1.5 hr. The excess thionyl chloride was removed by distillation at 100 mm. and the residue rectified to give 46.6 g. (85%) of the acid chloride, b.p. 86–88° (0.7 to 0.8 mm.), $n^{20}D$ 1.3892.

Anal. Calcd. for $C_{12}H_6F_{14}Cl_2O_2S$: C, 26.15; H, 1.09; Cl, 12.88. Found: C, 26.12; H, 1.33; Cl, 12.59.

3,5-Bis-(perfluoropropyl)-4-thia-1,7-heptanediol.—By the same procedure given for the reduction of 3-perfluoropropylpentanedioic acid, 114 g. (0.2 mole) of diethyl 3,5-bis-(perfluoropropyl)-4-thiaheptanedioate was reduced with 10 g. (0.26 mole) of lithium aluminum hydride to give 83.7 g. (86%) of the diol, b.p. 109° (0.2 mm.), m.p. 47°, $n^{19.5}D$ 1.3800 (supercooled).

Anal. Calcd. for $C_{12}H_{12}F_{14}O_2S$: C, 29.65; H, 2.27; F, 54.73. Found: C, 29.68; H, 2.42; F, 54.82.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Addition of Trichlorosilane and Methyldichlorosilane to Tetrachloroethylene

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Trichlorosilane and methyldichlorosilane were added to tetrachloroethylene to yield tetrachloroethyltrichlorosilane and trichlorovinyltrichlorosilane. Trichlorovinyltrichlorosilane and trichlorovinyltrimethylsilane undergo addition reactions with trichlorosilane, methyldichlorosilane, chlorine and *p*-toluenethiol. Pentachloroethyltrichlorosilane with ethylmagnesium bromide gave trichlorovinyltriethylsilane.

Discussion

Addition of trichlorosilane to trichloroethylene and the dichloroethylenes to yield olefinic products has been described by Wagner[3] and Agre.[4a–c] While this work was in progress, a patent[5] was issued which describes the addition of chlorosilanes to tetrachloroethylene to produce unsaturated silanes containing the trichlorovinyl group.

This paper reports a study of the addition of trichlorosilane and methyldichlorosilane to tetrachloroethylene and an investigation of the chemical properties of the addition products. High temperatures (600°) at atmospheric pressure, a free radical initiator (*t*-butyl peroxide) at moderate temperatures (125–140°), and ultraviolet irradiation were studied as conditions for the addition. High temperatures gave only trichlorovinyltrichlorosilane (Table I) in agreement with the work of earlier investigators,[3–5] while *t*-butyl peroxide at lower temperatures gave some 1,1,2,2-tetrachloroethyltrichlorosilane. *t*-Butyl peroxide, the best of the catalysts tried (it is a liquid that is miscible with the reactants and generates free radicals at a measurable rate at moderately high temperatures (125°)[6]), gave only low conversions (Table I). Methyldichlorosilane with *t*-butyl peroxide gave the unsaturated addition compound, trichlorovinylmethyldichlorosilane, and a double addition product, 1,2-bis-(methyldichlorosilyl)-1,2-dichloroethene.

Trichlorovinyltrichlorosilane and Grignard reagents gave the corresponding trialkyltrichlorovinylsilane, with no β-elimination involving the chlorine atoms being observed; this is in accordance with the findings of Agre.[4a,7] Addition of chlorine to trichlorovinyltrichlorosilane gave pentachloroethyltrichlorosilane; this compound on treatment with ethylmagnesium bromide lost chlorine to give trichlorovinyltriethylsilane.

Trichlorosilane added in better conversions to trichlorovinyltrichlorosilane (20.9%) and trichlorovinyltrimethylsilane (44.2%) than to tetrachloroethylene (12.6%). This was expected because of the electron-releasing effect of the silicon atom and the resulting easier attack by the silyl radical.[8] The isolated products were again olefins, except in one case where a small amount of 1,2-bis-(trichlorosilyl)-1,1,2-trichloroethane was isolated.

TABLE I

SILANES FROM TETRACHLOROETHYLENE

Method	Conversion, % With $SiHCl_3$ CCl_2-CCl-$SiCl_3$	With $SiHCl_3$ CCl_2HCCl_2-$SiCl_3$	With CH_3SiHCl_2 CCl_2-$CClSi$-$(CH_3)Cl_2$
Hot tube (600°) (A)	14	0	..
Ultraviolet irradiation (B)	7.1	1.1	..
t-Butyl peroxide, Carius tubes, 125–130° (C)	12.6	4.7	8.1
t-Butyl peroxide, nickel autoclave, 120–145° (D)	11.5	2.4	18.8

[a] No saturated addition product could be isolated in pure state, but the double addition product, 1,2-bis-(methyldichlorosilyl)-1,2-dichloroethene, was isolated.

Chlorovinylsilanes are known to be readily attacked by alkali to cleave the carbon–silicon bond,[3] and this was found to be true for the trichlorovinyl compounds. Trichlorovinyltrichlorosilane gave trichloroethylene and some dichloroacetylene with strong aqueous potassium hydroxide. Trichlorovinyltrimethylsilane was more stable toward alkali but was also cleaved after several hours at reflux. 1,2-Bis-(trichlorosilyl)-1,2-dichloroethene was readily attacked and gave a violent explosion, probably caused by chloroacetylene. No dichloroethylene was obtained from this reaction.

Trichlorovinyltrimethylsilane was treated with *p*-toluenethiol and sodium ethoxide in ethanol to prepare the same product obtained from *p*-toluenethiol and trichloroethylene. In view of the structure of the addition compound obtained from trichloroethylene and sodium ethoxide,[10] the product is thought to be *p*-tolylmercapto-1,2-dichloroethene.[11]

During chlorination of trichlorovinyltrimethylsilane most of the methyl hydrogens were sub-

(1) Polymer Research Laboratories, Dow Chemical Co.

(2) A portion of a thesis submitted by G. W. R. Puerckhauer to Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1956.

(3) G. H. Wagner, U. S. Patent 2,637,738 (1953).

(4) (a) C. L. Agre, THIS JOURNAL, **71**, 300 (1949). (b) C. L. Agre and W. Hilling, *ibid.*, **74**, 3895 (1952). (c) C. L. Agre, U. S. Patent 2,682,512 (1954).

(5) J. W. Gilkey, U. S. Patent 2,723,986 (1955).

(6) J. H. Raley, F. F. Rust and W. E. Vaughan, THIS JOURNAL, **70**, 1336 (1948).

(7) However, elimination of chlorine from the trichlorovinyl group was expected, since R. Binaghi, *Gazz. chim. ital.*, **57**, 669 (1927), obtained acetylene from hexachloroethane and ethylmagnesium bromide through a 1,2-dichloroethylene intermediate.

(8) L. H. Sommer, E. W. Pietrusza and F. C. Whitmore, THIS JOURNAL, **69**, 188 (1947). The influence of the methyl groups enhances this electron-releasing effect; hence, the higher yields with trichlorovinyltrimethylsilane.

(9) G. H. Wagner and A. W. Pines, *ibid.*, **71**, 3567 (1949).

(10) O. C. Stephens, *J. Chem. Soc. Ind.*, **43**, 313T (1924).

(11) Treatment of trichlorovinyltrimethylsilane with sodium ethoxide in ethanol gave a similar result, trimethylethoxysilane, 1,2-dichlorovinyl ethyl ether and ethyl chloroacetate being the products. The first two products arose directly from trichlorovinyltrimethylsilane, while ethyl chloroacetate arose from 1,2-dichlorovinyl ether in the basic medium; *cf.* A. Geuther and F. Brockhoff, *J. prakt. Chem.*, [2] **7**, 161 (1873).

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stituted before addition to the double bond occurred. Two products, $CCl_3CCl_2Si(CCl_3)_3$ (I) and $CCl_3CCl_2Si(CCl_3)_2CHCl_2$ (II), were obtained. Compound II was distinguished from the isomeric compounds, $C_2HCl_4Si(CCl_3)_3$ (III), which could arise by addition of hydrogen chloride, formed during the reaction to the trichlorovinyl group, by treatment with alkali. If structure II were correct, tetrachloroethylene would be obtained by this cleavage, whereas structure III would give trichloroethylene or dichloroacetylene. Tetrachloroethylene was isolated confirming structure II.

Experimental

Materials.—Tetrachloroethylene (a gift from E. I. du Pont de Nemours and Co.) was dried over phosphorus pentoxide and rectified. Trichlorosilane and methyldichlorosilane (Pure Grade unless otherwise indicated) were obtained from Anderson Laboratories and used without further purification.

Addition of Trichlorosilane to Tetrachloroethylene. Hot Tube (Method A).—A mixture of 950 g. (5.72 moles) of tetrachloroethylene and 1163 g. (8.6 moles) of technical trichlorosilane was dropped into a Vycor tube of 20 mm. i.d., loosely packed with Raschig rings and heated over a 20-cm. zone in a tube furnace. The temperature, maintained at 570–595°, was measured by a thermocouple inserted between the Vycor tube and heating element. A steady stream of purified nitrogen (Fieser train) was passed through the apparatus during the experiment (presence of oxygen caused explosions). The exit gases were liquefied in an air-cooled and a Dry Ice trap connected in series. The trap contents gave on distillation: unreacted starting materials (91.5 g., 0.68 mole of trichlorosilane and 642 g., 3.9 moles of tetrachloroethylene); 898 g. of by-product silicon tetrachloride and chlorinated disilanes, b.p. 47–111°; 94.5 g. of a carbon-containing by-product, b.p. 170–173°; a forerun; and 139.3 g. (9.2% based on starting olefin) of trichlorovinyltrichlorosilane, b.p. 193° (748 mm.) (reported[5] b.p. 93° (30 mm.)). A silane to olefin ratio of 2:1 gave an improved conversion (*ca.* 14% at 600°).

Below 385° conversion of trichlorosilane to tetrachlorosilane occurred without the formation of trichlorovinyltrichlorosilane and extensive decomposition took place above 670°.

Ultraviolet Initiation (Method B).—A dry 300-ml. quartz flask, connected through a condenser and a Dry Ice trap to a 20-cm. mercury seal,[12] was filled with 83 g. (0.5 mole) of tetrachloroethylene and 203 g. (1.5 moles) of trichlorosilane, swept with nitrogen, and exposed for 90 hr. to the irradiation from a mercury vapor lamp. The flask contents turned red-brown during this period. Trichlorosilane (168 g., 1.2 moles) and tetrachloroethylene (73 g., 0.44 mole) and a small intermediate cut consisting of silicon tetrachloride were obtained by distillation. The residue was rectified to give 9.4 g. (7.1%) of trichlorovinyltrichlorosilane, b.p. 66.5–69.5° (6.5 mm.), and 1.6 g. (1.1%) of 1,1,2,2-tetrachloroethyltrichlorosilane, b.p. 97–98° (2.5 mm.).

Table II

Absorption Bands of Unsaturated Silanes between 6 and 7 μ

Compound	Absorption between 6 and 7 μ[a,b]
Trichlorovinyltrichlorosilane	6.52(s)
Trichlorovinyltrimethylsilane	6.49(s)
Trichlorovinyltriethylsilane	6.50(s), 6.86(m)
1,2-Bis-(trichlorosilyl)-1,2-dichloroethene	6.12(w), 6.72–6.75(s)
1,2-Bis-(methyldichlorosilyl)-1,2-dichloroethene	6.20(vw), 6.64(s)

[a] A Perkin–Elmer no. 21 double beam infrared spectrometer was used. [b] s = strong, m = medium strong, w = weak, vw = very weak.

(12) E. W. Pietrusza, L. H. Sommer and F. C. Whitmore, This Journal, 70, 484 (1948).

t-Butyl Peroxide Initiated (Method C).—Tetrachloroethylene (44 g., 0.27 mole), *t*-butyl peroxide (3.2 g., 0.022 mole) and trichlorosilane (108 g., 0.8 mole) were distributed in equal proportions over 4 Carius tubes, which were sealed under an atmosphere of purified nitrogen (Fieser train) and heated for 60 hr. at 125–130° in a furnace. The contents of the tubes were combined and 92 g. (0.68 mole) of trichlorosilane and 36 g. (0.22 mole) of tetrachloroethylene recovered. The residue was rectified to give 8.9 g. (12.6%) of trichlorovinyltrichlorosilane, b.p. 74° (10 mm.), and 3.8 g. (4.7%) of 1,1,2,2-tetrachloroethyltrichlorosilane, b.p. 97.5–99° (3 mm.).

Method D.—The preceding experiment was repeated in a glass-lined, nickel-clad autoclave. The same proportions of reactants at 125–140° for 60 hr. gave 11.5% of trichlorovinyltrichlorosilane and 2.4% of 1,1,2,2-tetrachloroethyltrichlorosilane.

Trichlorosilane was added to trichlorovinyltrichlorosilane and trichlorovinyltrimethylsilane, methyldichlorosilane to tetrachloroethylene and trichlorovinyltrimethylsilane using method C. Method D gave better results than method C in the addition of methyldichlorosilane to tetrachloroethylene (see Table I).

1,2-Bis-(trichlorosilyl)-1,2-dichloroethane with Alkali.—A concentrated solution of potassium hydroxide (130 g. in 250 ml. of water) was placed in a 500-ml., three-necked flask, and to it was added 28 g. (0.07 mole) of 1,2-bis-(trichlorosilyl)-1,2-dichloroethene. The flask was connected through an ice-cooled trap to the atmosphere. The initially formed white precipitate dissolved on warming. Cooling the flask brought about a violent explosion in the trap and the connecting line. This explosion could have been caused by chloroacetylene formed in this reaction.

Trichlorovinyltrichlorosilane with Alkali.—To a concentrated solution of potassium hydroxide (90 g. in 200 ml. of water) in a 300-ml., three-necked flask was added 22 g. (0.083 mole) of trichlorovinyltrichlorosilane. A white precipitate formed which dissolved on heating and a small layer formed on the bottom of the flask. Several small explosions took place in the flask. After cooling, the small organic layer was separated, dried over Drierite and distilled to give 4 g. (36.7%) of trichloroethylene, b.p. 86.5–86.7° (747 mm.), $n^{20}D$ 1.4773–1.4775. Huntress lists[13] b.p. 86–88°, $n^{20}D$ 1.4775–1.47782.

Trichlorovinyltrimethoxysilane.—From 31.2 g. (0.12 mole) of trichlorovinyltrichlorosilane and a mixture of 13.6 g. (0.43 mole) of methanol and 28.8 g. (0.36 mole) of pyridine there was obtained, using the previously described procedure,[14] 20.5 g. (68%) of trichlorovinyltrimethoxysilane, b.p. 94.5–95° (12 mm.), $n^{20}D$ 1.4646, d^{20}_4 1.345.

This compound did not hydrolyze appreciably with water or dilute acid but was attacked by alkali.

Anal. Calcd. for $C_5H_9Cl_3O_3Si$: C, 23.86; H, 3.58; Cl, 42.34; M_R, 51.24. Found: C, 24.12; H, 3.86; Cl, 42.08; M_R, 51.65.

Grignard Reactions: Preparation of Alkyl Derivatives.—From 14.4 g. (0.054 mole) of trichlorovinyltrichlorosilane and 5.29 g. (0.22 g. atom) of magnesium turnings in 150 ml. of anhydrous ether and 30.9 g. (0.22 mole) of methyl iodide in 50 ml. of anhydrous ether there was obtained[14] 9.3 g. (84.5%) of trichlorovinyltrimethylsilane, b.p. 82° (31 mm.), $n^{20}D$ 1.4890, d^{20}_4 1.189.

Anal. Calcd. for $C_5H_9Cl_3Si$: C, 29.48; H, 4.42; Cl, 52.32; M_R, 48.96. Found: C, 29.51; H, 4.50; Cl, 52.46; M_R, 49.94.

Trichlorovinyltrimethylsilane was prepared in a similar way from trichlorovinyltrimethoxysilane and from trichlorovinylmethyldichlorosilane in 60.6 and 50.9% yields, respectively.

Trichlorovinyltriethylsilane, b.p. 113° (11 mm., $n^{20}D$ 1.4986, d^{20}_4 1.141, was obtained from trichlorovinyltrichlorosilane in 73.7% yield using the same procedure[14] with 7 moles of ethylmagnesium bromide used per mole of silane to make certain any reduction of the β-chlorine substituent would be evidenced; no reduction was observed.

Anal. Calcd. for $C_8H_{15}Cl_3Si$: C, 39.12; H, 6.11; Cl, 43.38; M_R, 62.85. Found: C, 39.30; H, 6.36; Cl, 43.74; M_R, 63.13.

(13) E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948.

(14) T. Meese, C. W. Roberts and G. W. R. Puerckhauer, This Journal, 79, 2329 (1957).

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Table III

Silane Addition Compounds

Compound	B.p.[a] °C.	Mm.	Percentage composition[c] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
CCl_2=$CClSiCl_3$	193	748	9.06	8.99	..	..	80.38	80.38
$CHCl_2CCl_2SiCl_3$	97–98	2.5	7.96	7.78	0.33	0.49	82.09	81.92
CCl_2=$CClSi(CH_3)Cl_2$	105.8–106.6	42	14.73	14.69	1.23	1.47	72.57	72.80
$Cl_2(CH_3)SiCCl$=$CClSi(CH_3)Cl_2$[b]	79.5–80.5	0.8	14.86	14.97	1.86	2.01	65.94	65.89
Cl_3SiCCl=$CClSiCl_3$	87.5–88.3	1.5	6.59	6.60	..	..	78.02	77.81
$Cl_3SiCHClCCl_2SiCl_3$	134.5–138.5	1.6	5.99	6.06	0.25	0.24	79.87	79.62
Cl_3SiCCl=$CClSi(CH_3)_3$	87	3	19.81	19.70	2.98	3.00	58.59	58.69
$Cl_2(CH_3)SiCCl$=$CClSi(CH_3)_3$	94.4–95	6	25.62	25.46	4.27	4.25	50.18	50.31

[a] All boiling points are corrected. [b] This compound was isolated from accumulated distillation residues of the addition of methyldichlorosilane to tetrachloroethylene. [c] All analyses by Dr. Yeh, Purdue University.

Attempted Preparation of 1,2-Bis-(trimethylsilyl)-1,2-dichloroethene.—From 31 g. (0.096 mole) of 1,2-bis-(methyldichlorosilyl)-1,2-dichloroethene in 50 ml. of anhydrous ether and 14 g. (0.58 g. atom) of magnesium turnings in 500 ml. of anhydrous ether and 81.8 g. (0.58 mole) of methyl iodide in 100 ml. of anhydrous ether, no isolable pure product was obtained. An attempt to prepare this compound from 1-(trichlorosilyl)-2-(trimethylsilyl)-1,2-dichloroethene using the same technique also gave no isolable product.

Pentachloroethyltrichlorosilane.—A Carius tube was charged with 9.3 g. (0.13 mole) of dry chlorine and 24 g. (0.09 mole) of trichlorovinyltrichlorosilane and irradiated with light from an AH-1 bulb (Gartner Scientific Co.) for 3 days. After removal of the excess chlorine under reduced pressure, the white solid residue was distilled to give 28.6 g. (94.1%) of pentachloroethyltrichlorosilane, b.p. 98.7° (6 mm.).

Anal. Calcd. for C_2Cl_8Si: C, 7.14; Cl, 84.52. Found: C, 6.98; Cl, 84.32.

Trichlorovinyltriethylsilane from Pentachloroethyltrichlorosilane.—A solution of 28.4 g. (0.085 mole) of pentachloroethyltrichlorosilane in 50 ml. of anhydrous ether was added dropwise at 0° to a solution prepared from 18.5 g. (0.76 g.-atom) of magnesium turnings in 500 ml. of anhydrous ether and 82.9 g. (0.76 mole) of ethyl bromide in 100 ml. of anhydrous ether. The resulting mixture was stirred for 4 hr. at room temperature, 9 hr. at reflux temperature, the ether distilled and the residue heated on a steam-bath for 5 hr. After the ether was returned to the flask, the mixture was decomposed with ice and dilute hydrochloric acid, the aqueous layer extracted with ether and the combined ether layers dried over Drierite. Rectification gave 13.2 g. (63.6%) of trichlorovinyltriethylsilane, b.p. 87.3–88° (3 mm.), $n^{20}D$ 1.4986, d^{20}_4 1.140.

The infrared spectrum of this compound was identical with that of the trichlorovinyltriethylsilane prepared from trichlorovinyltrichlorosilane.

Chlorination of Trichlorovinyltrimethylsilane.—A Carius tube was charged with 5.8 g. (0.08 mole) of chlorine and 2 g. (0.01 mole) of trichlorovinyltrimethylsilane and irradiated for 4 days with light from an AH-1 bulb. From the opened tube there was isolated 4.5 g. of a white solid, m.p. 132–139.5°; this was recrystallized several times from petroleum ether to give the product, m.p. 134.2–135.1°.

Anal. Calcd. for $C_5Cl_{14}Si$: C, 10.26; Cl, 84.94. Found: C, 10.40; Cl, 84.99.

In a subsequent experiment, 4.06 g. (0.02 mole) of trichlorovinyltrimethylsilane and 21 g. (0.3 mole) of chlorine irradiated for 9 days with light from an AH-1 bulb gave 11.7 g. of a white solid, m.p. 130–132°, after one recrystallization from petroleum ether (b.p. 35–37°). On repeated recrystallization from petroleum ether (b.p. 65–67°), the solid had a m.p. 128.3–128.6°. A mixed melting point with the compound obtained in the preceding experiment gave m.p. 129–131.8°.

Anal. Calcd. for $C_5HCl_{14}Si$: C, 10.91; H, 0.18; Cl, 83.82. Found: C, 10.84; H, 0.25; Cl, 83.90, 84.10.

This compound (5.7 g.) was refluxed with a 40% aqueous potassium hydroxide solution. The mixture was steam distilled and the aqueous layer extracted with ether. After drying and removal of the solvent, 0.7 g. of tetrachloroethylene,[13] b.p. 119–120.8°, $n^{20}D$ 1.5064, was obtained.

Attempts to introduce only one chlorine atom into one of the methyl groups of trichlorovinyltrimethylsilane by the above technique and the use of an excess of the silane were unsuccessful, leading to polychlorinated or unreacted materials.

Trichlorovinyltrimethylsilane and *p*-Toluenethiol.—In a 300-ml., three-necked flask (stirrer, addition funnel, Friedrich condenser protected with a calcium chloride tube) was placed 75 ml. of absolute ethanol and 2.53 g. (0.11 mole) of sodium. To this solution was added 12.4 g. (0.1 mole) of *p*-toluenethiol in 60 ml. of absolute ethanol followed by 20.3 g. (0.1 mole) of trichlorovinyltrimethylsilane. The mixture was refluxed for 46 hr. The resulting solid (5 g.) was filtered and proved to be sodium chloride. The filtrate was evaporated to give a yellow liquid, which was separated into two fractions by simple distillation: b.p. 114–127° (3 mm.), 15.2 g., and b.p. 165–270° (3 mm.), 2.7 g.

Part of the lower boiling fraction was rectified to give *p*-tolylmercaptodichloroethene, b.p. 127–127.5° (3 mm.), $n^{25}D$ 1.5966–1.5970, d^{20}_4 1.270.

Anal. Calcd. for $C_9H_8Cl_2S$: C, 49.32; H, 3.66; Cl, 32.42; S, 14.61; M_R, 58.72. Found: C, 49.62; H, 3.65; Cl, 32.15; S, 14.86; M_R, 58.86.

Another part of the lower boiling fraction was oxidized to the sulfone: 2.8 g. (0.013 mole) of *p*-tolylmercaptodichloroethene was refluxed for 2.5 hr. with 95 ml. of glacial acetic acid and 10 ml. of 30% hydrogen peroxide and then allowed to stand overnight. The solution was evaporated and a dark gray mass was left, which gave after recrystallization from ethanol 1.2 g. of a brown solid. Several recrystallizations from ethanol gave a white crystalline product, m.p. 76–77°; reported[15] for the oxidized addition product of *p*-toluenethiol to trichloroethylene, m.p. 74–77°. A mixed melting point of our compound with the one prepared by McManimie gave no depression.

Trichlorovinyltrimethylsilane and Sodium Ethoxide.—Absolute ethanol (400 ml.) and 7.59 g. (0.33 g.-atom) of sodium was placed into a 1000-ml., three-necked flask (stirrer, Friedrich condenser, addition funnel through which dry nitrogen was admitted). To this solution was added 61 g. (0.3 mole) of trichlorovinyltrimethylsilane. The resulting mixture was refluxed for 46 hr. A white precipitate was formed during this period. The solution was filtered and 19 g. (0.32 mole) of sodium chloride remained. The filtrate was rectified to give 37.4 g. of trimethylethoxysilane–ethanol azeotrope, b.p. 66° (744 mm.), $n^{20}D$ 1.3729; an ethanol fraction, b.p. 77.5–78° (744 mm.); and 11.1 g. (30.5%) of ethyl chloroacetate,[13] b.p. 63° (34 mm.), 141.7° (747 mm.), $n^{20}D$ 1.4217, d^{20}_4 1.150.

The trimethylethoxysilane–ethanol azeotrope was poured into water and the silane layer washed with water, dried over Drierite and rectified to give 15.5 g. (43.7%) of trimethylethoxysilane,[16] b.p. 75° (742 mm.), $n^{20}D$ 1.3747, d^{20}_4 0.762.

The first third of the ethanol fraction yielded on dilution with water a heavy layer, which was washed with water, dried over Drierite and rectified to give 10 g. (23.6%) of 1,2-dichlorovinyl ethyl ether,[13] b.p. 42.2° (31 mm.), 126–127.6° (746 mm.), $n^{21}D$ 1.4519, d^{20}_4 1.197.

The infrared spectra of the compounds obtained in this

(15) R. J. McManimie, Ph.D. Thesis, Purdue University, 1953, p. 43.

(16) R. O. Sauer, This Journal, 66, 1707 (1944).

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experiment were identical with the spectra obtained from authentic compounds.

Attempted Addition of Carbon Tetrachloride to Trichlorovinyltrimethylsilane.—Trichlorovinyltrimethylsilane (23.3 g., 0.12 mole) and carbon tetrachloride (70.5 g., 0.46 mole) were placed into a quartz flask and irradiated with light from a mercury vapor lamp for 2 weeks. An atmosphere of purified nitrogen was maintained throughout the experiment. Practically all the starting materials were recovered from the greenish reaction mixture.

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WEST LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Addition of Trichlorosilane and Methyldichlorosilane to Fluorine- and Chlorine-containing Olefins

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Trichlorosilane and methyldichlorosilane were added using ultraviolet irradiation and peroxides to 1,1,2-trichloro-3,3,3-trifluoropropene to give trifluorodichloropropenyltrichlorosilane and trifluorodichloropropenylmethyldichlorosilane, respectively. Trichlorosilane and methyldichlorosilane were added to 3,3,3-trifluoropropene and to 2,3,3,4,4,4-hexafluorobutene, and trichlorosilane was added to chlorotrifluoroethylene to give chlorotrifluoroethyltrichlorosilane. The products were converted to their trimethyl and triethyl derivatives. Trifluorotetrachloropropyltrichlorosilane gave trifluorodichloropropenyltriethylsilane with ethylmagnesium bromide.

Discussion

Trichlorosilane has been added with[3a-e] or without[3f,g] catalysts to olefins. Since this work was initiated, two reports have appeared on the addition of trichlorosilane to fluorine-containing olefins[4,5]; these involve the addition of trichlorosilane to 1,1-difluoroethylene with a platinum-on-charcoal catalyst and to tetrafluoroethylene photochemically.

The addition of methyldichlorosilane to olefins has been less extensively investigated.[3c-f,6a-c] Additions of trichlorosilane and methyldichlorosilane to olefins containing chlorine atoms at the carbon atoms forming the double bond have been shown to form olefinic products[7a-f] by subsequent dehydrohalogenation of the original saturated adduct.

This paper reports the addition of trichlorosilane and methyldichlorosilane to the fluorine-containing olefins, perfluoropropene, 2,3,3,4,4,4-hexafluorobutene and 3,3,3-trifluoropropene, and to the olefins containing both fluorine and chlorine, namely, 1,1,2-trichloro-3,3,3-trifluoropropene and chlorotrifluoroethylene. Ultraviolet irradiation and *t*-butyl peroxide were both used as initiators and the latter proved to be more dependable because it is a liquid miscible with the reactants and generates free radicals at a measurable rate at elevated (125°) temperatures.[8]

The reactivity of the olefins studied increased as the influence of fluorine on the character of the double bond decreased. Thus, 3,3,3-trifluoropropene gave better conversions than 2,3,3,4,4,4-hexafluorobutene, while perfluoropropene gave only traces of an addition compound (Table I). The inertness of perfluoropropene in these reactions was somewhat surprising since it has been reported to add trifluoromethyl iodide[9] and since it adds bromine under the influence of ultraviolet irradiation to give an 83% yield of 1,2-dibromo-1,1,2,-3,3,3-hexafluoropropane.

The proposed mechanism for the addition reaction[10] postulates the formation of a silyl free radical, the addition of this free radical to the olefin, and the removal of a hydrogen from the silane by the resulting radical to generate another silyl radical. This mechanism explains the lesser reactivity of methyldichlorosilane because the silyl free radical may be considered as electrophilic, and if the methyldichlorosilyl radical obtained from methyldichlorosilane is the reactive species in the addition of methyldichlorosilane to olefins, it should be less electrophilic than the trichlorosilyl radical due to the electron-supplying influence of the methyl group.

Although the addition of trichlorosilane and methyldichlorosilane to 1-olefins has been shown to yield the 1-isomer exclusively,[10] the addition compound of trichlorosilane to 3,3,3-trifluoropropene could be either $CF_3CH_2CH_2SiCl_3$ (I) or CF_3-

(1) Polymer Research Laboratories, Dow Chemical Co.

(2) A portion of a thesis submitted by G. W. R. Puerckhauer to Purdue University in partial fulfillment of the requirements of the degree of Doctor of Philosophy, June, 1956.

(3) The following are representative: (a) C. A. Burkhard and R. H. Krieble, THIS JOURNAL, **69**, 2687 (1947); (b) E. W. Pietrusza, L. H. Sommer and F. C. Whitmore, *ibid.*, **70**, 484 (1948); (c) G. H. Wagner and C. O. Strother, U. S. Patent 2,632,013 (1953); (d) D. B. Hatcher, U. S. Patent 2,555,589 (1951); (e) R. D. Lipscomb, U. S. Patent 2,570,462 (1951); (f) A. J. Barry, L. DePree, J. W. Gilkey and D. E. Hook, THIS JOURNAL, **69**, 2916 (1947); (g) E. P. Plueddemann, U. S. Patent 2,642,447 (1953).

(4) G. H. Wagner, U. S. Patent 2,637,738 (1953).

(5) R. N. Haszeldine and R. J. Marlow, *J. Chem. Soc.*, 962 (1956).

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(8) J. H. Raley, F. F. Rust and W. E. Vaughan, THIS JOURNAL, **70**, 1336 (1948). It was shown that *t*-butyl peroxide is superior to acetyl peroxide, benzoyl peroxide or ultraviolet irradiation as an initiator for these additions. Stainless steel retards the addition, hence the reactions were carried out in all-glass apparatus.

(9) R. N. Haszeldine, *J. Chem. Soc.*, 3559 (1953).

(10) E. T. McBee, E. W. Pietrusza and F. C. Whitmore, THIS JOURNAL, **69**, 188 (1947).

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$CH(CH_3)SiCl_3$ (II). In order to distinguish between structures I and II, the product was converted to the trimethoxy derivative; this was found to be identical with 3,3,3-trifluoropropyltrimethoxysilane prepared by a different procedure.[11] By analogy, the addition compound of trichlorosilane to 2,3,3,4,4,4-hexafluorobutene is presumed to be $CF_3CF_2CHFCH_2SiCl_3$ (III).

In comparison to the addition of trichlorosilane to tetrachloroethylene, one would expect the silane to add to 1,1,2-trichloro-3,3,3-trifluoropropene to give an olefinic product[7c]; experimental evidence supported this, and trifluorodichloropropenyltrichlorosilane was isolated. Methyldichlorosilane added less readily and gave also an olefinic product, trifluorodichloropropenylmethyldichlorosilane. The addition product could be either $CF_3CCl{=}CClSiCl_3$ (IV) or $CF_3C(SiCl_3){=}CCl_2$ (V). These compounds were distinguished by alkaline cleavage.[12] Although the physical constants of the resulting olefins are relatively close,[13] the melting point of the olefin obtained by alkaline cleavage of the addition product to 1,1,2-trichloro-3,3,3-trifluoropropene agreed with that for 1,1-dichloro-3,3,3-trifluoropropene and the addition compound is therefore compound V.

The literature and the evidence presented indicate that chlorosilanes will add to chlorinated olefins to give chiefly an unsaturated addition product which arises by the elimination of the elements of hydrogen chloride, while fluorinated olefins such as 2,3,3,4,4,4-hexafluorobutene or 1,1-difluoroethylene gave saturated addition products. It seemed, therefore, of interest to investigate the addition of trichlorosilane to an olefin that contained both fluorine and chlorine at the double bond. Chlorotrifluoroethylene was used and gave a saturated addition product that was somewhat unstable at its boiling point but could be prepared in analytical purity by relatively rapid rectification of a previously distilled sample.

According to the observations made by Sommer and co-workers[14] on the behavior of β-chloroalkylsilanes, 2,3,3,4,4,4-hexafluorobutyltrichlorosilane might be expected to undergo elimination reactions involving the β-fluorine atom with Grignard reagents and bases. However, this β-fluorine is more stable than β-chlorine since even excess of ethylmagnesium bromide with I or III gave the triethyl derivatives with no observed loss of fluorine. Moreover, the products were stable to base under such vigorous conditions as prolonged refluxing with 40% potassium hydroxide. Agre[3] and McBee, *et al.*,[7c] observed that β-chlorovinylsilanes will not undergo reduction or β-elimination with Grignard reagents. Trifluorodichloropropenyltrichlorosilane behaved similarly and the trimethyl and triethyl compounds were prepared by a known procedure[15] with methylmagnesium iodide and ethylmagnesium bromide, respectively.

Chlorine was added in good yields to trifluorodichloropropenyltrichlorosilane to give trifluorotetrachloropropyltrichlorosilane which underwent reduction with ethylmagnesium bromide to give back trifluorodichloropropenyltriethylsilane. This reduction seems to be a general reaction for silanes of this structure as pentachloroethyltrichlorosilane underwent a similar reaction.[7c]

The results of the addition reactions are summarized in Table I and the new compounds in Tables II and III.

Table I

Silane Addition Products

	Addition, % Trichlorosilane		Methyldichlorosilane	
	Ultraviolet	(*t*-BuO)$_2$	Ultraviolet	(*t*-BuO)$_2$
Perfluoropropene	1	1	..	..
2,3,3,4,4,4-Hexafluorobutene	29.3	52.1	8.6[b]	45.8
3,3,3-Trifluoropropene	72	75.3	3.6[c]	69.5
1,1,2-Trichloro-3,3,3-trifluoropropene[a]	9.3	33.5	..	21.2
Chlorotrifluoroethylene	19.1	37.7	..	..

[a] This addition was also brought about by passing a mixture of 1,1,2-trichloro-3,3,3-trifluoropropene (1 mole) and trichlorosilane (1.2 mole) through a horizontal tube (20 mm. interior diameter) that was heated over a 20-cm. zone to 580–620°. Although extensive carbonization took place, 3.9% of trifluorodichloropropenyltrichlorosilane could be obtained; this reaction did not take place below 510°. [b] 8.5 days irradiation. [c] 90 hr. irradiation, impure product.

Experimental

Materials.—3,3,3-Trifluoropropene[16] and 2,3,3,4,4,4-hexafluorobutene[17] were prepared by published methods. Trichlorosilane and methyldichlorosilane (pure grade) were purchased from Anderson Laboratories and used without further purification. 1,1,2-Trichloro-3,3,3-trifluoropropene was obtained from Columbia Organic Chemicals Co., Inc., and chlorotrifluoroethylene from General Chemicals Division, Allied Chemical and Dye Corp.

Addition of Trichlorosilane and Methyldichlorosilane to Olefins.—The following experiments exemplify the different methods used to add trichlorosilane and methyldichlorosilane to 3,3,3-trifluoropropene, 2,3,3,4,4,4-hexafluorobutene, 1,1,2-trichloro-3,3,3-trifluoropropene and chlorotrifluoroethylene.

Ultraviolet Initiation.—A Carius tube was charged with 9.2 g. (0.096 mole) of 3,3,3-trifluoropropene and 39 g. (0.29 mole) of trichlorosilane and exposed to irradiation from an AH-1 bulb (Gartner Scientific Co.) for 90 hr. Olefin (0.9 g.) and trichlorosilane (21.3 g.) were recovered from the tube and 16 g. (72% based on olefin) of 3,3,3-trifluoropropyltrichlorosilane, b.p. 112.9–114.8°, was obtained by rectification.

***t*-Butyl Peroxide Initiation.**—3,3,3-Trifluoropropene (12.8 g., 0.13 mole), *t*-butyl peroxide (1.5 g., 0.01 mole) and trichlorosilane (52.1 g., 0.39 mole) were distributed over three Carius tubes that were sealed under a purified nitrogen atmosphere (Fieser train) and heated in a tube furnace for 60 hr. at 125–130°. The reaction mixture gave 30.3 g. (0.22 mole) of trichlorosilane and 22.3 g. (75.3%) of 3,3,3-trifluoropropyltrichlorosilane, b.p. 112.8–113.7°.

Although attempts to run these reactions in a stainless steel autoclave gave poor conversions, a nickel-clad autoclave was a satisfactory reaction vessel. A glass liner, filled with 219.6 g. (1.1 moles) of 1,1,2-trichloro-3,3,3-trifluoropropene, 12.83 g. (0.088 mole) of *t*-butyl peroxide and 448 g. (3.3 moles) of trichlorosilane was placed in a nickel-clad autoclave

(11) E. T. McBee, C. W. Roberts, G. F. Judd and T. S. Chao, This Journal, **77**, 1292 (1955).

(12) G. H. Wagner and A. N. Pines, *ibid.*, **71**, 3567 (1949).

(13) A. L. Henne, *et al.*, *ibid.*, **63**, 3478 (1941); **64**, 1157 (1942).

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(15) F. C. Whitmore, L. H. Sommer, P. A. DiGiorgio, W. A. Strong, R. E. Van Strien, D. L. Bailey, H. K. Hall, E. W. Pietrusza and C. T. Kerr, *ibid.*, **68**, 476 (1946).

(16) E. T. McBee, C. G. Hsu, O. R. Pierce and C. W. Roberts, *ibid.*, **77**, 915 (1955).

(17) E. T. McBee, D. H. Campbell and C. W. Roberts, *ibid.*, **77**, 3149 (1955).

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TABLE II

TRICHLOROSILANE AND METHYLDICHLOROSILANE ADDUCTS

Compound	B.p.[a] °C.	Mm.	Composition,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Fluorine Calcd.	Fluorine Found
$CF_3CH_2CH_2SiCl_3$	112.8–113.7	751	15.55	15.74	1.73	2.01	46.04	46.04	24.62	21.71
$CF_3CH_2CH_2Si(CH_3)Cl_2$	121–122	737	22.75	22.80	3.31	3.46	33.65	33.50	27.00	25.44
$CF_3CF_2HCFCH_2SiCl_3$	127–127.8	758	16.02	15.80	1.00	1.14	35.56	35.50	38.06	37.02
$CF_3CF_2HCFCH_2Si(CH_3)Cl_2$	128–129.1	746	21.50	21.28	2.15	2.34	25.45	25.48	40.86	40.72
$CF_3C(SiCl_3)=CCl_2$	77.5–78.5	35	12.06	12.22	..	..	59.46	59.31	19.10	19.43
$CF_3C(SiCH_3)=CCl_2$	76–76.5	32	17.27	17.38	1.08	1.38	51.08	50.82	...	...
$CF_3CCl(SiCl_3)CHCl_2$	78–78.5	3.8	10.75	10.76	0.30	0.46	63.58	63.89	17.01	13.61
$C_2HClF_3SiCl_3$	117	746	9.52	9.34	0.40	0.64	56.35	56.40	22.61	22.81

[a] All boiling points are corrected. [b] Carbon, hydrogen and chlorine analyses obtained from Dr. C. S. Yeh, Purdue University. Fluorine analyses obtained from Clark Microanalytical Laboratories, Urbana, Ill.

TABLE III

TETRAALKYL SILANES

Compound	Yield, %	B.p.[c] °C.	Mm.	$n^{20}D$	d^{20}_4	Composition,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Fluorine Calcd.	Fluorine Found	M_r[e] Calcd.	M_r[e] Found
$CF_3CH_2CH_2Si(CH_3)_3$	58[a]	94.3–95.1	750	1.3576	0.896	42.35	42.35	7.65	7.60	33.53	33.69	40.89	41.63
$CF_3CH_2CH_2Si(C_2H_5)_3$	76.1	166.1–167.8	753	1.3962	0.961	50.94	50.91	8.94	8.63	26.87	26.78	53.53	53.07
$C_2F_5CHFCH_2Si(CH_3)_3$	36.3[b]	109.8–111.5	747	1.3441	1.133	35.29	35.04	5.04	5.03	47.90	47.21	44.35	44.51
$C_2F_5CHFCH_2Si(CH_3)(C_2H_5)_2$	64	154–155	747	1.3687	1.115	40.60	40.86	6.01	6.23	42.86	41.37	53.61	53.79
$C_2F_5CHFCH_2Si(C_2H_5)_3$	66.3	173.1	753	1.3800	1.110	42.86	43.12	6.43	6.47	40.71	39.95	58.24	58.45
$CF_3C(Si(CH_3)_3)=CCl_2$	40.4	157	756	1.4322	1.243	30.38	30.17	3.80	3.78	24.05[f]	24.28	49.94	49.48
$CF_3C(Si(C_2H_5)_3)=CCl_2$	72.7	119	28	1.4532[i]	1.193	38.71	38.84	5.38	5.38	20.47[g]	20.42	63.83	63.25
$C_4HClF_3Si(CH_3)_3$	42.9	43–44	43[h]	1.3887–90[i]	1.134	31.50	31.82	5.25	5.18	29.39	29.50	39.84	39.73

[a] From 3,3,3-trifluoropropylmethyldichlorosilane. [b] From 2,3,3,4,4,4-hexafluorobutyltrichlorosilane, 13.4% from 2,3,3,-4,4,4-hexafluorobutylmethyldichlorosilane. [c] All boiling points are corrected. [d] Carbon–hydrogen analyses by Dr. C. S. Yeh, Purdue University; fluorine analyses by Clark Microanalytical Laboratories, Urbana, Ill. [e] Bond refractions calculated by K. G. Denbigh, *Trans. Faraday Soc.*, 36, 936 (1940), and E. L. Warrick, THIS JOURNAL, 68, 2435 (1946), were used. [f] Calcd.: Cl, 29.96. Found: Cl, 30.01. [g] Calcd.: Cl, 25.48. Found: Cl, 25.24. [h] Distilled with decomposition at 117–120° (743 mm.). Calcd.: Cl, 18.63. Found: Cl, 18.20. [i] At 22°.

(750-ml. capacity) and heated at 140–155° (external temperature) for 46 hr. The reaction mixture gave, on rectification, 244.3 g. of chlorosilanes, b.p. 30–80°, 69.4 g. (0.35 mole) of unreacted 1,1,2-trichloro-3,3,3-trifluoropropene and 110 g. (33.5%) of trifluorodichloropropenyltrichlorosilane, b.p. 77.5–78.5° (35 mm.). The residue from this distillation was combined with the residues from other runs and rectified to give the saturated addition product, trifluorotrichloropropyltrichlorosilane.

Structure Proof of Trifluorodichloropropenyltrichlorosilane.—Trifluorodichloropropenyltrichlorosilane (101.6 g., 0.34 mole) was added dropwise to a warm solution of 250 g. of potassium hydroxide in 550 ml. of water. The solution was stirred under a nitrogen atmosphere and the exit gases led into a series of ice and Dry Ice traps. After all of the silane had been added, the reaction mixture was heated and refluxed for 45 min. There was no organic layer in the flask after cooling.

The organic layers from the traps were separated, combined, dried over Drierite and rectified to give 5 g. of 1,1-dichloro-3,3,3-trifluoropropene, b.p. 54.3–55° (uncor.), b.p. 53.5–54.2° (cor.), $n^{21}D$ 1.3682, m.p. −88° to −83° (uncor.); reported[13]: for 1,1-dichloro-3,3,3-trifluoropropene, b.p. 55.1°, 54.5°, $n^{20}D$ 1.3688–1.3690, m.p. −87.2°; for 1,2-dichloro-3,3,3-trifluoropropene, b.p. 53.7°, $n^{20}D$ 1.3670, m.p. −109.2°.

Part of the olefinic product was treated with bromine in carbon tetrachloride to give the dibromide, b.p. 71° (23–24 mm.), $n^{20}D$ 1.4788–1.4791.

Anal. Calcd. for $C_3HBr_2Cl_2F_3$: C, 11.08; H, 0.38; Br, 49.23; Cl, 21.84; F, 17.54. Found: C, 11.36; H, 0.46; Br, 50.81; Cl, 20.07; F, 19.00.

Addition of Trichlorosilane to Perfluoropropene.—Perfluoropropene[18] (48.6 g., 0.32 mole), *t*-butyl peroxide (3.8 g., 0.026 mole) and trichlorosilane (131.7 g., 0.97 mole) were distributed over 4 Carius tubes, which were sealed under an atmosphere of purified nitrogen (Fieser train) and heated in a furnace for 60 hr. at 125–132°. Most of the starting materials were recovered and the residue distilled to give 5.7 g. of fluorine-containing materials, b.p. 95–104°, from which 0.8 g. of a liquid, b.p. 99–99.2°, was isolated. This product contained fluorine and hydrolyzable chlorine atoms and is believed to be the desired addition compound 1,1,-2,3,3,3-hexafluoropropyltrichlorosilane.

(18) L. H. Hals, T. S. Reid and G. H. Smith, THIS JOURNAL, 73, 4054 (1951).

Similar results were obtained, the conversion being always below 1%, with ultraviolet irradiation on 10 weeks exposure, with benzoyl peroxide at various temperatures up to 190°, by passing over silica gel at 250–500°, or without catalyst in an autoclave at 250°. No reaction except some halogen interchange took place with aluminum chloride.

Perfluoroisobutylene did not yield any isolable products when treated with trichlorosilane and *t*-butyl peroxide at 125–130°.

3,3,3-Trifluoropropyltrimethoxysilane.—3,3,3-Trifluoropropyltrichlorosilane (42 g., 0.18 mole) in 160 ml. of dry petroleum ether (b.p. 60–70°) was placed into a 500-ml., three-necked flask (stirrer, Friedrich condenser, addition funnel), and methanol (19.9 g., 0.62 mole) and pyridine (42.9 g., 0.54 mole) were added dropwise at 0°. After standing overnight the pyridine hydrochloride was removed by filtration and the filtrate rectified to give 24.9 g. (63%) of 3,3,3-trifluoropropyltrimethoxysilane, b.p. 141–142° (740 mm.), $n^{21}D$ 1.3546, $d^{20}D$ 1.137.[11]

Attempted conversion of this compound to 3,3,3-trifluoropropyltriethylsilane with ethylmagnesium bromide gave only impure material, the infrared spectrum of which indicated silicon–oxygen bonds.

Alkyl Derivatives.—The following experiment exemplifies the preparation of the alkyl derivatives: a Grignard solution was prepared in a 500-ml. three-necked flask from 9.06 g. (0.37 g.-atom) of magnesium turnings in 250 ml. of anhydrous ether and 40.7 g. (0.37 mole) of ethyl bromide in 50 ml. of anhydrous ether, After this solution was stirred for 2 hr., 27.9 g. (0.093 mole) of 2,3,3,4,4,4-hexafluorobutyltrichlorosilane in 25 ml. of anhydrous ether was added dropwise at 0°. The mixture was stirred for 4 hr. at room temperature and for 12 hr. at reflux temperature. The ether was distilled and the residue heated on a steam-bath for 4 hr. The distilled ether was returned to the flask and the solids broken up and suspended by stirring. The mixture was decomposed with ice and dilute hydrochloric acid. The separated water layer was extracted with ether and the combined ether layers were dried over Drierite. Rectifi-

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cation gave 17.3 g. (66.3%) of 2,3,3,4,4,4-hexafluorobutyltriethylsilane, b.p. 173.1°.

The methyl Grignard reactions were run with a 33% excess of Grignard reagent over the theoretically required amount, while a larger excess was used in ethyl Grignard reactions in order to ensure finding any reaction of the β-halogen substituent.

All the tetraalkyl compounds derived from trifluoropropyltrichlorosilane and hexafluorobutyltrichlorosilane were found to be stable toward concentrated hydrochloric acid and 40% aqueous potassium hydroxide at reflux for 14 hr.

Trifluorotetrachloropropyltrichlorosilane.—A Carius tube was charged with 12.1 g. (0.17 mole) of dry chlorine and 27.8 g. (0.093 mole) of trifluorodichloropropenyltrichlorosilane, sealed under a purified nitrogen atmosphere, and irradiated with light from an AH-1 bulb (Gartner Scientific Co.) for 3 days. After removal of the excess chlorine *in vacuo* the white solid residue was distilled to give 31.7 g. (94.9%) of trifluorotetrachloropropyltrichlorosilane, b.p. 118–120° (8.5 mm.). This compound hydrolyzed only slowly in dilute acid.

Anal. Calcd. for $C_3Cl_7F_3Si$: C, 9.74; Cl, 67.28; F, 15.42. Found: C, 10.02; Cl, 67.01; F, 14.79.

Trifluorodichloropropenyltriethylsilane from Trifluorotetrachloropropyltrichlorosilane.—A solution of 30.5 g. (0.075 mole) of trifluorotetrachloropropyltrichlorosilane in 50 ml. of anhydrous ether was added at 0° to a Grignard solution prepared from 12.81 g. (0.54 g.-atom) of magnesium turnings in 300 ml. of anhydrous ether and 57.7 g. (0.54 mole) of ethyl bromide in 100 ml. of anhydrous ether. The resulting suspension was stirred at reflux temperature for 12 hr., the ether distilled, the residue heated on a steam-bath for 5 hr., the ether added again, the mixture decomposed with ice and hydrochloric acid, the aqueous layer extracted with ether and the combined ether layers dried over Drierite. Rectification gave 11.8 g. (56.2%) of trifluorodichloropropenyltriethylsilane, b.p. 112.5–113.5° (23 mm.), $n^{20}D$ 1.4534–1.4535, d^{20}_4 1.189.

The infrared spectrum of this compound was identical with the one of trifluorodichloropropenyltriethylsilane prepared from trifluorodichloropropenyltrichlorosilane.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

The Cleavage of Ethers by Hydrogen Bromide

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The relative reactivities of several alkyl groups have been determined in the internal competitive reaction RR′O + HBr = (RBr, R′Br) + (R′OH + ROH). With initial mole fraction hydrogen bromide of about 0.65, relative reactivities at 26° are: methyl 11.1, ethyl 1.00, propyl 1.00, butyl 0.93, *i*-butyl 0.053, *i*-propyl 0.87, 3-pentyl 4.2 and cyclopentyl 3.8. The first five groups are cleaved apparently by an SN2 reaction, the last three by a reaction to which there is considerable SN1 contribution. The relative reactivities of secondary alkyl groups in ethers decrease with decreasing mole fraction of hydrogen bromide. In the competitive reaction of butyl ether and propyl alcohol with hydrogen bromide, the ether reacts about 7.5 times faster at an initial mole fraction of hydrogen bromide of 0.63; about 1.4 times faster at an initial mole fraction of 0.32. At the higher initial mole fraction, butyl ether reacts about 12 times faster than isopropyl alcohol.

Despite the importance of the alkyl–oxygen bond in organic chemistry, relatively little mechanistic attention has been given to its cleavage in simple ethers and alcohols. Although both ethers and alcohols involve similar factors, the investigation of ethers offers advantages which will appear in the discussion.

The alkyl–oxygen bond cannot be cleaved by displacement reactions in alkyl ethers and alcohols as such but only in complexes in which considerable positive charge is transferred to the oxygen atom, *e.g.*, in such species as R_2OH^+ and $R_2O{:}BCl_3$.[1] In the present work, hydrogen bromide is employed as the cleaving agent. Cleavage by hydrogen bromide of primary alkyl–oxygen and of tertiary alkyl–oxygen bonds seems to occur by typical SN2 and SN1 reactions, respectively.[1] The nature of the cleavage of secondary alkyl–oxygen bonds is in doubt.

The stoichiometry of the reaction is

$$R'RO + HBr = (R'Br, RBr) + (ROH, R'OH) \quad (1)$$

Determination of the ratio R′Br/RBr in the product gives the relative rates of cleavage of the two alkyl–oxygen bonds in the unsymmetrical ether, R′RO. The relative rates of displacement of two groups attached to the same center is an unusually favorable case of competitive reactions.[2] The present paper reports the results of the cleavage of a number of unsymmetric ethers and of the relative rates of cleavage of butyl ether *vs.* propyl and isopropyl alcohols in conventional competitive reactions.

Experimental Procedure

Materials.—The following ethers were prepared by the Williamson synthesis: methyl butyl, b.p. 69.2°; ethyl butyl, 91.9°; propyl butyl, 116.2°; isobutyl butyl, 138.8°; cyclopentyl butyl, 168°; isopropyl propyl, 80°; isobutyl propyl, 107°; 1-ethylpropyl propyl, 128.5°; and diisobutyl, 120–121°. Since unreacted alcohol usually would form an azeotrope with the ether, gross quantities of alcohol were removed by formation of borate esters[3] followed by distillation. Certain ethers were next chromatographed on silica gel with elution by methanol. The ethers were then fractionated from sodium in a 50-plate Stedman column. Butyl ether (Eastman Kodak Co., White Label) was given the last treatment. The infrared absorption spectra of these and the other compounds employed in this research are presented in the doctoral thesis of Milton E. Fuller, Northwestern University, 1956.

The following alkyl halides were either commercial materials subjected to purification or compounds prepared from the corresponding alcohols by standard methods: butyl bromide and isobutyl bromide, Eastman Kodak Co., White

(1) R. L. Burwell, Jr., *Chem. Revs.*, **54**, 615 (1954).

(2) Such cleavage of ethers resembles the cleavage of unsymmetric dialkylmercury, RR′Hg + HCl = (RH, R′H) + (RHgCl, R′HgCl); M. S. Kharasch and A. L. Flenner, THIS JOURNAL, **54**, 674 (1932).

(3) C. Weygand, "Organic Preparations," Interscience Publishers, Inc., New York, N. Y., 1945, p. 163.

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Label; cyclopentyl bromide, Arapahoe Chemicals, Inc.; ethyl bromide, Fisher Scientific Co., certified reagent; methyl bromide, Matheson; propyl bromide and isopropyl bromide. 2-Pentanol was prepared from acetaldehyde and propylmagnesium bromide, 3-pentanol by the hydrogenation of ethyl ketone on nickel–kieselguhr (Harshaw) at 110°, 100 atm. Both pentanols were converted to the corresponding bromides *via* treatment of the tosylates with sodium bromide.[4] Infrared spectra demonstrated the absence of each bromide in the other.

Ether Cleavage.—About 5 cc. of ether was placed in a tube in the form of the Ostwald–Sprengel pycnometer. Anhydrous hydrogen bromide was passed into the tube leading to the bottom of the bulb while the tube was cooled in ice. At the desired weight increase, the inlet and outlet tubes were sealed off. Saturation of an ether gives a mole fraction of hydrogen bromide close to $^2/_3$.

Analytical Procedures.—The reaction mixture contained unreacted ether and hydrogen bromide, both alcohols and both bromides. The analytical scheme involved the removal of everything except the bromides and then analysis of the bromide mixture for the ratio of the two bromides. The reaction tube was opened and its contents blown into a scrubbing tube containing 85% phosphoric acid. Continued passage of dry air carried the bromides and some of the hydrogen bromide and ether forward. The hydrogen bromide was removed by a tube containing sodium hydroxide. The vapor stream then passed through two scrubbing units containing 96% sulfuric acid to remove ether and any residual alcohols. The sulfuric acid traps were kept at 0° to minimize conjunct polymerization. Bromides were then condensed from the vapor stream in a Dry Ice trap. When methyl and ethyl bromides were present, liquid nitrogen was used as the condensing agent and the sweep gas was purified nitrogen. The procedure was carefully checked with known mixtures. Bromide recoveries of over 90% were obtained. Since there were transfer losses in introducing these mixtures into the purification line and in removing the bromides from the trap, recovery in the purification system was substantially quantitative. We estimate that preferential volatilization leads to changes in the bromide composition of less than 0.5 percentage unit.

Samples of liquid bromide mixtures were analyzed by infrared spectroscopy with the Baird double beam instrument.[5] For example, for cleavage of propyl butyl ether, mixtures containing 48.8, 58.5 and 64.6 mole % propyl bromide and the rest butyl bromide were prepared. With the 58.5 mole % sample in cell A, runs were made in succession with each of the three synthetic samples and the product of an actual ether cleavage in cell B. Plots of the logarithm of the % transmission of the synthetic samples against mole % propyl bromide were prepared for a number of wave lengths. The mole % propyl bromide was then determined at the four most favorable wave lengths and averaged. A number of "known" unknowns of isopropyl and propyl bromides and of butyl and propyl bromides were analyzed by this method. The average deviation of the average from the known value was 0.3 percentage unit. The average maximum deviation of the results at any one wave length from the average of all wave lengths was 1.1 percentage units. We estimate that the reported percentage compositions may involve errors amounting over-all to about 1 percentage unit.

The accuracy of these analyses was checked a number of times by preparing a mixture whose composition was that of the analysis of a reaction product. The infrared spectra of the experimental and synthetic samples were compared by the techniques described above. Agreement was satisfactory.

The infrared technique could not be used with the volatile methyl and ethyl bromides. In these cases analysis was by density determination. A series of about five capillary tubes suspended vertically from a larger tube was provided. The volumes of the bulbs were chosen so that in at least one case the sample of mixed bromides would fill the bulb and part of the capillary. The purified sample of bromides was then totally transferred into the appropriate bulb by vacuum distillation, sealed off and the level of the mixture in the capillary at 0° determined. The density was determined by calibration with butyl bromide. The over-all possible errors are about the same as in the infrared method.

At the very end of this research, vapor phase chromatography became available to us. Results of the density analysis of ethyl butyl ether were checked on the Podbielniak Chromacon using tricresyl phosphate on Celite as the stationary phase and hydrogen as the sweep. Actually, all of our reaction products probably could have been analyzed by this means and without the necessity of isolating the bromide mixture. In the one case which we report, the bromide mixture was isolated before analysis.

Experimental Results

Alcohol–Ether Mixtures.—If the analytical determinations just described are to represent relative rates of cleavage of alkyl–oxygen bonds in ethers, reaction 1 must not be subject to interference with the possible subsequent reaction

$$ROH + HBr = RBr + H_2O \qquad (2)$$

To check this, the bromide ratio in the product of reaction of a mixture of symmetrical ether and alcohol was determined and, in most detail, with butyl ether and propyl alcohol. If the reactions of both species with hydrogen bromide have the same kinetics and if both rates are first order in alcohol or ether, the ratio of the rate constants of the two reactions are

$$k_{ether}/k_{alc} = \log(X^0_{ether}/X_{ether})/\log(X^0_{alc}/X_{alc}) \qquad (3)$$

The assumptions cannot be exactly valid and the reaction also suffers interference from reaction 2. However, equation 3 becomes increasingly valid as total conversions decrease. Results of a series of runs are given in Table I. Times of reaction

TABLE I

RELATIVE RATES OF REACTION OF BUTYL ETHER AND PROPYL ALCOHOL

Mole fraction Ether	Mole fraction Alc.	HBr	Reacted, % Ether	Reacted, % Alc.	$\frac{\log(X^0_{ether}/X_{ether})}{\log(X^0_{alc}/X_{alc})}$
0.56	0.12	0.32	11.4	8.0	1.5
.55	.12	.33	15.3	11.4	1.4
.50	.11	.39	26.0	19.2	1.4
.42	.17	.41	38.6	19.3	2.3
.40	.14	.45	51.1	22.4	2.8
.41	.11	.48	60.1	23.8	3.4
.42	.09	.49	48.2	13.0	4.7
.05	.45	.50	21.9	5.5	4.3
.37	.09	.54	49.6	9.1	7.2
.37	.09	.54	39.0	7.0	6.8
.31	.07	.62	35.6	5.7	7.6
.30	.07	.63	40.5	7.5	6.7
.29	.07	.64	48.5	7.6	8.3

varied from 2 to 26 hr. at ambient temperatures. At $X^0_{HBr} = {}^1/_3$, the ether reacts about 1.4 times as fast as the alcohol. This value increases to 7.5 as X^0_{HBr} increases to $^2/_3$. Higher conversions at low values of X^0_{HBr} result in heterogeneous mixtures. Such runs were discarded since the hydrogen bromide rich layer may preferentially extract alcohol from the other phase. Because of the low concentration of propyl bromide in the product in the last 5 runs of Table I, about 4%, the relative reactivity is subject to an error of about ±1. The probable error for the first 5 runs (about 14% propyl bromide) is ±0.2.

At $X^0_{HBr} = 0.62$, the ratio of the rates of reaction of butyl ether and isopropyl alcohol is about 12.

(4) H. Pines, A. Rudin and V. N. Ipatieff, THIS JOURNAL, **74**, 4063 (1952).

(5) R. L. Burwell, Jr., and A. D. Shields, *ibid.*, **77**, 2766 (1955).

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The relative rate of reaction of alcohols is substantial but, since in cleavage of unsymmetric ethers the ether starts at a finite mole fraction and the alcohol at zero, the effect of reaction 2 can be made negligible by confining the cleavage reaction to low conversions. The data in the next section appear free of interference from reaction 2 to within the estimated experimental error.

Ether Cleavage by Hydrogen Bromide.—The results of ether cleavages are shown in Tables II–V. Reaction temperatures were the ambient, about 26°.

Isomerization During Cleavage.—As shown in Table V, substantial amounts of 2-pentyl bromide appeared in the cleavage of propyl 3-pentyl ether. However, much or all of this isomerization could have occurred during isolation of the bromides. Reaction of hydrogen bromide with a mixture of propyl ether and 3-pentyl bromide yielded a bromide fraction in which about 8% isomerization of the 3-pentyl to 2-pentyl bromide had occurred. Also, on merely carrying a sample of 3-pentyl bromide through the isolation apparatus, 10.7% isomerization occurred.[6] Vapor phase chromatography of the total reaction mixture might yield analyses devoid of accompanying isomerization.

Isobutyl bromide passed through the isolation apparatus without detectable change. No detectable content of *t*-butyl bromide appeared in the products of cleavage of propyl isobutyl and butyl isobutyl ethers (Tables III and IV); however, with the low concentration of isobutyl bromide, this test of isomerization was not sensitive. Accordingly, isobutyl ether was cleaved with hydrogen bromide. About 0.4% *t*-butyl bromide was found in the product.

TABLE II

ETHER CLEAVAGE WITH ANALYSIS BY DENSITY DETERMINATION

X^0_{HBr}	Reacn. time, min.	Conversion,[a] %	Mole % C_4H_9Br	Average mole % C_4H_9Br
Methyl butyl ether				
0.61	12	39	7.5	
0.62	9	34	7.8	7.7
Ethyl butyl ether				
0.62[b]	70	19	48.3	
.63	60	20	48.0	
.65[b]	60	15	46.1	
.68	60	19	49.1	
.69	60	21	48.1	
.70	65	23	46.8	47.7

[a] In terms of total yield of bromide assuming equation 1. [b] Analyzed by vapor phase chromatography.

TABLE III

CLEAVAGE OF BUTYL ETHERS WITH ANALYSIS BY INFRARED ABSORPTION

X^0_{HBr}	Reacn. time, min.	Conversion, %	Mole % C_4H_9Br	Average mole % C_4H_9Br
Propyl butyl ether				
0.27	1340	11	48.5	
.27	2680	26	48.5	
.35	2680	40	47.8	
.66	90	33	47.9	
.67	120	38	48.4	
.67	100	39	47.9	48.2
Isobutyl butyl ether				
0.62	135	23	94.8	
.65	120	23	94.3	
.67	60	11	94.2	
.69	60	10	94.7	94.5
Cyclopentyl butyl ether[a]				
0.44	150	14	32.8[b]	
.59	90	19	35.8[b]	
.65	30	33	20.1	
.66	90	46	21.1	
.67	55	38	15.5	
.69	90	42	23.7	20.1

[a] The vapor pressure of cyclopentyl bromide is so low that the isolation procedure becomes difficult. The analyses here are probably of lower accuracy than in the other runs. In addition, the conversions are too large. [b] Excluded from the average. The average applies to X^0_{HBr} about 0.67.

TABLE IV

ETHER CLEAVAGE WITH ANALYSIS BY INFRARED ABSORPTION

X^0_{HBr}	Reacn. time, min.	Conversion, %	Mole % n-C_4H_9Br	Average mole % C_4H_9Br
Isobutyl propyl ether				
0.61	90	7	94.7	
.64	120	24	94.3	
.64	80	14	94.5	
.65	80	19	93.9	
.65	90	13	94.1	
.66	120	27	93.3	
.66	90	21	94.2	
.69	60	12	93.2	94.0
Isopropyl propyl ether				
0.35	210	9	65.7	
.37[a]	2×10^4	30	66.4	
.50	120	18	62.3	
.65	60	22	55.3	
.67	30	12	53.3	

[a] Temperature of reaction, 5°.

TABLE V

CLEAVAGE OF PROPYL 1-ETHYLPROPYL ETHER, INFRARED ANALYSIS

X^0_{HBr}	Reacn. time, min.	Conversion, %	Product composition, mole % PrBr	2-Pentyl Br	3-Pentyl Br
0.60	25	16	20.0	20.3	59.7
.68	20	15	19.2	25.3	55.5
.71	60	46	19.2	11.5	69.3

Discussion

The reaction mixtures of most of our experiments (initial mole fraction of hydrogen bromide about $^2/_3$, of ether about $^1/_3$) are undoubtedly rather complicated mixtures of various species. The relatively high electrical conductivity[7] and the Raman spectra[8] of ether–hydrogen chloride solutions indicate the presence of dialkylhydronium ions, $RR'HO^+$.

The saturation ratio of about two moles of hydrogen bromide to one of ether suggests that the negative ion $BrHBr^-$ is important.[9] Most of the

(6) See also ref. 4.

(7) O. Maass and D. McIntosh, THIS JOURNAL, **35**, 535 (1913).

(8) G. L. Vidale and R. C. Taylor, *ibid.*, **78**, 294 (1956).

(9) There is evidence for the corresponding chloride ion; H. F. Herbrandson, R. T. Dickerson, Jr., and J. Weinstein, *ibid.*, **76**, 4046 (1954). Also, the low temperature crystalline phase of hydrogen bro-

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ionized species must be involved in ion pairs or in higher aggregates.

Presumably, there will also be substantial concentrations of hydrogen bonded species, RR'O·HBr, particularly at lower concentrations of hydrogen bromide. In any case, the drastically reduced partial pressure of hydrogen bromide from ether solutions (the vapor pressure of pure hydrogen bromide is 12.3 atm. at 0°) indicates strong interaction between ether and hydrogen bromide.

The reactive form of the ether must be the dialkylhydronium ion[1] and the displacing species is presumably an anion such as Br^- or $BrHBr^-$, although, particularly at lower concentrations of hydrogen bromide, RR'O·HBr may be involved.

Bennett and Reynolds[10] investigated the cleavage of the R–O bond by measurement of the rate of reaction between alcohols and hydrogen bromide in aqueous phenol. Variation in basicities of the alcohols must have influenced rates. Such an effect may be small, but it represents an uncontrolled variable. The problem of relative basicities does not enter into an analysis based on equation 1. However, a new uncertainty does; each reaction occurs in a slightly different medium because of the change of ether. In addition, the possibility of steric hindrance of one alkyl group by the other must be considered, but models indicate that such effect is negligible in the ethers under consideration.

Table VI

Relative Rates of Reaction

Methyl	Ethyl	Propyl	Butyl	*i*-Butyl	*i*-Propyl	*s*-Butyl	3-Pentyl	Cyclopentyl
ROR' + HBr at 26°, X^0_{HBr} *Ca.* 0.65								
11.1	1.00	1.00	0.93	0.053	0.87		4.2	3.8
ROH + HBr in aqueous phenol, 83° (ref. 10)								
5.6	1.00	0.87	0.90	0.11	2.30	5.5		
$ROSO_3^-$ + H_2O, first order, 138° (ref. 14)								
1.79	1.00	0.65		0.15	16	19.5		
Br^- + RBr in acetone, 25° (ref. 13)								
76		1.00	0.65		0.033	0.011		

The first line of Table VI presents the relative rate of cleavage compared with ethyl for various alkyl groups at a mole fraction of hydrogen bromide of about 0.65. These are derived from the data on competitive cleavage of unsymmetrical ethers presented in Tables II–V. We did not plan to obtain absolute kinetics, but the data of these tables indicate that the time in minutes required for 20% cleavage of the various ethers at $X_{HBr} = 0.65$ was: ethyl butyl, propyl butyl and isopropyl propyl, 55; methyl butyl, 5 to 6; isobutyl propyl, 90; isobutyl butyl, 110; cyclopentyl butyl and 3-pentyl propyl, 30. These times are in good agreement with the relative rate data of Table VI. The agreement suggests that the change in medium consequent to the change in ether for each competitive cleavage is not too serious, although the variation in medium remains, to some extent, as an uncontrolled variable.

There is some disagreement in the older literature as to the products of the cleavage of propyl isopropyl ether.[1] With the mole fraction of hydrogen bromide about 0.65, both bromides are formed with propyl bromide in slightly the greater quantity. On the basis of Ingold's kinetic criterion[11] then, the isopropyl group is cleaved by a mechanism differing from that of the propyl group. The secondary alkyl groups apparently are cleaved by a reaction to which the form R^+ OHR makes considerable contribution. Similar considerations apply to the reaction between alcohols and hydrogen bromide in aqueous phenol[10] (Table VI, second series).

Relative rates of cleavage of propyl–oxygen *vs.* isopropyl–oxygen bonds are influenced by the initial mole fraction of hydrogen bromide. As shown in Table IV, the reactivity of isopropyl *vs.* propyl decreases from 0.8 at $X^0_{HBr} = 0.66$ to 0.52 at $X^0_{HBr} = 0.35$. A similar effect is observed in the cleavage of butyl cyclopentyl ether (Table III). The decreasing relative rate of cleavage of the *sec*-alkyl–oxygen bond presumably results from the declining polarity of the medium.

To the extent that the three ethers with secondary alkyl groups are cleaved by the same mechanism, the relative figures for the three groups represent relative rate constants. However, in view of the probable change of mechanism, the relative reactivities are not ratios of rate constants in comparisons between primary and secondary groups.

The relative rates in the primary ether sequence, particularly the large value of methyl and the low value of isobutyl, are typical of S$_N$2 reactions[12] such as the exchange reaction between bromide ion and alkyl bromides[13] (Table VI, fourth series). One would not expect the relative reactivities of the primary groups to change substantially with the mole fraction of hydrogen bromide. As shown in Table III, we could detect no difference in the bromide ratio in the cleavage of propyl butyl ether in varying the mole fraction from 0.27 to 0.67. Unlike such reactions as the first-order solvolysis of the alkyl sulfate ion,[14] there is probably no large amount of S$_N$1 character in the sequence of primary alkyl ether cleavages. The near absence of isomerization of isobutyl to *t*-butyl during cleavage of isobutyl ether is consistent with this.

Our data do not establish the exact nature of the cleavage of *sec*-alkyl–oxygen bonds. We attempted to determine the degree of isomerization consequent to the cleavage of the 3-pentyl group but were prevented by the isomerization which accompanied the isolation process. Isomerization during cleavage, if any, stops well short of equilibrium so that the reaction does not involve an extreme form of carbonium ion reaction, but this would hardly be expected. Successful determination of the degree of isomerization of the 3-pentyl group and of the exact stereochemistry in cleavage of the optically active *sec*-butyl group would be of value.

Olefin formation probably does not accompany the cleavage of primary groups since, if it had, the olefin would have reacted with hydrogen bromide

(10) G. M. Bennett and F. M. Reynolds, *J. Chem. Soc.*, 131 (1935).

(11) "Structure and Mechanism in Organic Chemistry," C. K. Ingold, Cornell University Press, Ithaca, N. Y., 1953, p. 316.

(12) Reference 11, Chapter VII, contains numerical data on a number of examples; see also "Physical Organic Chemistry," L. P. Hammett, McGraw–Hill Book Co., Inc., New York, N. Y., 1940, p. 154.

(13) P. B. D de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold and J. D. H. Mackie, *J. Chem. Soc.*, 3200 (1955).

(14) G. M. Calhoun and R. L. Burwell, Jr., This Journal, **77**, 6441 (1955).

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to form secondary alkyl halides. In particular, none was detected in cleavage of propyl butyl ether carried to extensive conversions.

The reactivity in ether cleavage of propyl relative to ethyl, 1.00 (Table VI), is large. The value 0.65 (Table VI) is about the average for a group of halide exchange reactions.[13] In general, the value for propyl is distinctly less than 1.0.[12] Our value depends primarily upon the cleavage of ethyl butyl ether, the analyses for which were performed both by density and by vapor phase chromatography (Table II). The reactivity of propyl in a reaction which also involves a positively charged species, that of alcohols with hydrogen bromide in aqueous phenol,[9] is also large, 0.87. In fact, and not surprisingly, this reaction parallels the ether cleavage rather closely. It has been proposed that the relative reactivity of propyl in general should be about $^2/_3$ on the basis that rotation about the central carbon–carbon bond in propyl compounds would lead the terminal methyl group to obstruct the entering groups in $^1/_3$ of the possible configurations.[15] The effect would appear in the pre-exponential frequency factor.[15,16]

Relative Rates of Reaction of Ethers and Alcohols with Hydrogen Bromide.—Table I presents the first direct data on the relative rates of cleavage of the alkyl–oxygen bond in ethers and in alcohols. Ethers appear to be less basic than alcohols.[17] At concentrations of hydrogen bromide high enough to protonate both ether and alcohol completely, the relative reactivity would be that of the hydronium ions. With decreasing acidity, the ratios of hydronium ions would involve the relative basicities, and the alcohol would become relatively more reactive. The observed data fit this scheme. At a total mole fraction of hydrogen bromide of 0.63, butyl ether reacts 7.5 times as fast as propyl alcohol; at a mole fraction of 0.33, 1.4 times faster. At the higher mole fraction, butyl ether reacts about 12 times faster than isopropyl alcohol. To within the rather low precision of the data, the computed relative reactivities of propyl and isopropyl alcohols are the same as those of propyl and isopropyl groups in propyl isopropyl ether, 0.8 (Table VI). The ether–HBr medium is somewhat more favorable to nucleophilic displacement than hydrogen bromide in aqueous phenol in which isopropyl alcohol reacts 2.6 times faster than propyl alcohol (second series in Table VI).

Acknowledgment.—This research was supported by a grant from the National Science Foundation.

(15) N. Ivanoff and M. Magat, *J. chim. phys.*, **47**, 914 (1950).
(16) See also ref. 13, section (C) and (D).
(17) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 80; J. Hine and M. Hine, THIS JOURNAL, **74**, 5266 (1952); E. F. Pratt and K. Matsuda, *ibid.*, **75**, 3739 (1953).

EVANSTON, ILLINOIS

COMMUNICATIONS TO THE EDITOR

THE POLYMERIZATION OF α-BENZYL-L-GLUTAMATE N-CARBOXY ANHYDRIDE

Sir:

In a recent communication[1] Doty and Lundberg have claimed that during the primary-amine-initiated polymerization of γ-benzyl-L-glutamate N-carboxy anhydride in dioxane solution at 25° two successive stages may be recognized. Using *n*-hexylamine as initiator these authors concluded that the initial part of the polymerization (up to a degree of polymerization of approximately 8) is comparatively slow, with a rate constant of $5–7 \times 10^{-3}$ mole^{-1} l. sec.$^{-1}$. Following this stage in the growth of the polymer an acceleration was reported, the final rate constant being approximately 3×10^{-2} mole^{-1} l. sec.$^{-1}$. The acceleration was correlated with the adoption by the growing polymer chain of an α-helical configuration at a degree of polymerization of about 8. A similar effect, rather smaller in magnitude, was obtained with the DL-anhydride.

We have previously reported[2] that under certain conditions the polymerization of DL-leucine and DL-phenylalanine N-carboxy anhydrides show auto-acceleration. This is in no way connected with the size of the growing polymer, but results from the presence of impurities in the anhydrides. It can be eliminated in these cases by the use of dry-box techniques and purification of the anhydrides by sublimation. In view of these results it appeared desirable to repeat the experiments of Doty and Lundberg, particularly since γ-benzyl-L-glutamate N-carboxy anhydride cannot be purified by sublimation.

We have studied chloride and acid-free samples of the anhydride prepared by phosgenation of the amino acid (the technique apparently used[3] for the anhydrides of Doty and Lundberg) and also from the carbobenzoxy derivative of the amino acid by treatment with phosphorus pentachloride.[4] The materials were crystallized from chloroform in both cases and stored *in vacuo* until required. Dry-box techniques were used throughout, and the rates of reaction were measured in constant-volume and

(1) P. Doty and R. D. Lundberg, THIS JOURNAL, **78**, 4810 (1956).
(2) D. G. H. Ballard and C. H. Bamford, *Proc. Roy. Soc.* (*London*), **A223**, 495 (1954).
(3) E. R. Blunt and R. H. Karlson, THIS JOURNAL, **78**, 941 (1956).
(4) W. E. Hanby, S. G. Waley and J. Watson, *J. Chem. Soc.*, 3009 (1950).

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constant-pressure systems of the type described in reference 2. Dioxane was purified as described by Fieser[5]; the final product showed no reaction with sodium in 24 hr. at room temperatures.

TABLE I

THE POLYMERIZATION OF γ-BENZYL-L-GLUTAMATE N-CARBOXY ANHYDRIDE IN DIOXANE AT 25°

Initiator type	$10^2[X]_0$,[a] mole l.$^{-1}$	$10^2[M]_0$[a] mole l.$^{-1}$	$[M]_0/[X]_0$[a]	10^2 initial propagation rate constant, mole^{-1} l. sec.$^{-1}$	Source of anhydride
n-Hexylamine	0.30	9.3	31	1.5	Phosgenation
	0.31	3.0	9.7	1.5	Phosgenation
	0.5	3.0	6.0	2.2	Phosgenation
	0.95	4.6	4.8	1.6	From carbobenzoxy derivative
	3.4	15.1	4.4	1.2	From carbobenzoxy derivative
	3.4	15.1	4.4	2.5	Phosgenation
4-mer	0.32	3.7	11.5	1.2	Phosgenation
5-mer	1.0	5.0	5.0	1.0	Phosgenation
	1.2	6.1	5.1	1.9	From carbobenzoxy derivative
	1.8	7.5	4.2	1.8	From carbobenzoxy derivative
	4.0	4.0	1.0	1.4	From carbobenzoxy derivative
	4.0	4.2	1.1	1.0	From carbobenzoxy derivative
15-mer	0.31	3.82	12.3	2.4	Phosgenation
	0.37	3.74	10.1	1.8	Phosgenation

[a] $[M]_0$, $[X]_0$ represent the initial anhydride and initiator concentrations, respectively.

(5) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., Boston, 1941, p. 369.

When several recrystallizations were required to obtain chloride-free anhydride it was always found that the polymerization was auto-catalytic. However, the rate constant never increased to more than twice its initial value, and generally the change was much less than this. We have never observed the much larger increases noted by Doty and Lundberg. Our results are in fact those which would be anticipated for an unsublimed anhydride on the basis of our previous work.[2] Moreover, the acceleration was independent of the nature of the initiator, and similar results were obtained by initiation with *n*-hexylamine, and preformed polymers up to a degree of polymerization of 15. The observations are summarized in Table I.

Clearly polymeric initiators both larger and smaller than 8-mers give approximately the same rate constants. It should be noted that anhydrides which have been stored for several days in vacuum desiccators give appreciably higher rates than those in the table.

Recently, by modifying the conditions of preparation using the phosgene technique, we have been able to make an anhydride which required for its purification from chloride and acid only one rapid crystallization. The polymerization of this material showed no acceleration whatever. Figure 1

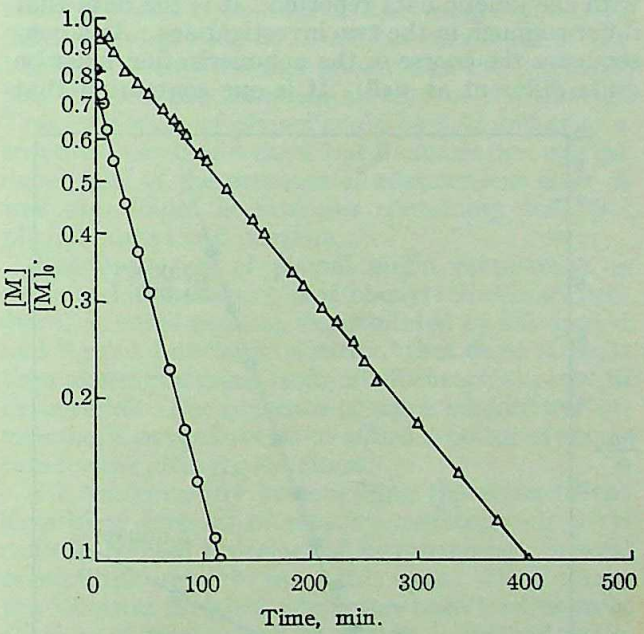

Fig. 1.—The polymerization of γ-benzyl-L-glutamate N-carbonic anhydride initiated by *n*-hexylamine, in dioxane at 25°. Initial anhydride concentration $[M]_0 = 0.151$ mole l.$^{-1}$. *n*-Hexylamine concentrations: ○, 3×10^{-2} mole l.$^{-1}$; △, 1×10^{-2} mole l.$^{-1}$.

indicates the course of the reaction for initiation by *n*-hexylamine, using anhydride to initiator ratios of 5 and 15. In both cases, after the initial rapid reaction of the *n*-hexylamine (this kind of effect has been discussed elsewhere[2]), the reaction was first order over its whole course, with a velocity constant close to 9.5×10^{-3} mole^{-1} l. sec.$^{-1}$. We consider this represents the most reliable value so far obtained for the normal propagation coefficient for this anhydride. These results show definitely that this coefficient does not depend on the length of the

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growing chain (after the first one or two units have been added to the initiator if the latter is not a preformed polymer) and suggest that the propagation reaction is essentially similar to that established for the polymerization of DL-phenylalanine and DL-leucine N-carboxy anhydrides. Similar observations have been made in nitrobenzene and N,N-dimethylformamide solutions.

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D. G. H. BALLARD
C. H. BAMFORD

RECEIVED DECEMBER 17, 1956

POLYPEPTIDES. Xa. ADDITIONAL COMMENTS OF THE AMINE-INITIATED POLYMERIZATION

Sir:

The foregoing communication by Ballard and Bamford[1] disputes our finding of two successive propagation constants in the polymerization of γ-benzyl-L-glutamate N-carboxy-anhydride and thereby casts doubt on the identification we had made of the first, relatively slow propagation with the randomly coiled configuration and the second, faster propagation with the α-helical configuration which is attained by each growing chain when it passes a critical chain length.[2]

In each case the interpretations are consistent with the kinetic data reported: it is the data that differ so much in the two investigations. As a consequence the course of the polymerization must be quite different as well. It is our contention that our N-carboxy anhydride was in such a state of purity that the polymerization consists simply of a rapid initiation followed by chain growth characterized by two successive propagation constants, the second taking over from the first when the chain reaches a length of about eight.

Since there is no indication that Ballard and Bamford[1] have followed precisely the procedure of anhydride preparation and purification[3] we employed, their failure to reproduce our results is not surprising inasmuch as the kinetic effect we have isolated is easily suppressed. On the other hand, we have observed the behavior they report with relatively unpurified anhydride. Since upon sufficient recrystallization the behavior we have reported was always found we have naturally concentrated our attention on what appeared to be the purer and more reproducible anhydride. Although this work is reported in detail in forthcoming papers,[4,5] two particularly relevant points deserve mention here.

(1) If the N-carboxy anhydride is used after its first crystallization a linear first-order behavior similar to that of Ballard and Bamford[1] is observed throughout the polymerization (A in Fig. 1). However, after one recrystallization from methylene dichloride the two successive propagations are clearly evident (B in Fig. 1). Since the HCl content of the unrecrystallized anhydride was 1.0 mole % and since this could react with the initiator, *n*-hexylamine, to produce a possibly "active" impurity, we

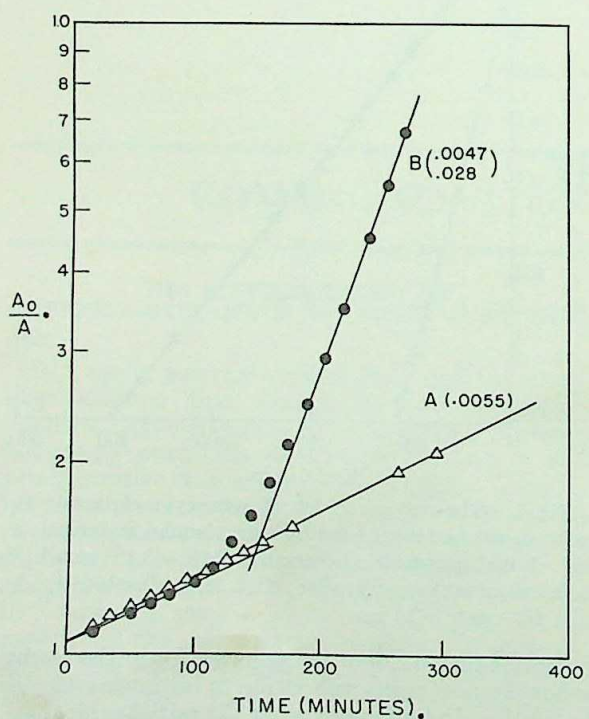

Fig. 1.—Polymerization of γ-benzyl-L-glutamate N-carboxy anhydride initiated with *n*-hexylamine ([A]/[I] = 20) in dioxane solution at concentration of 4 g./100 cc. at 25.0°. Case A corresponds to impure anhydride and case B to the same anhydride after one recrystallization.

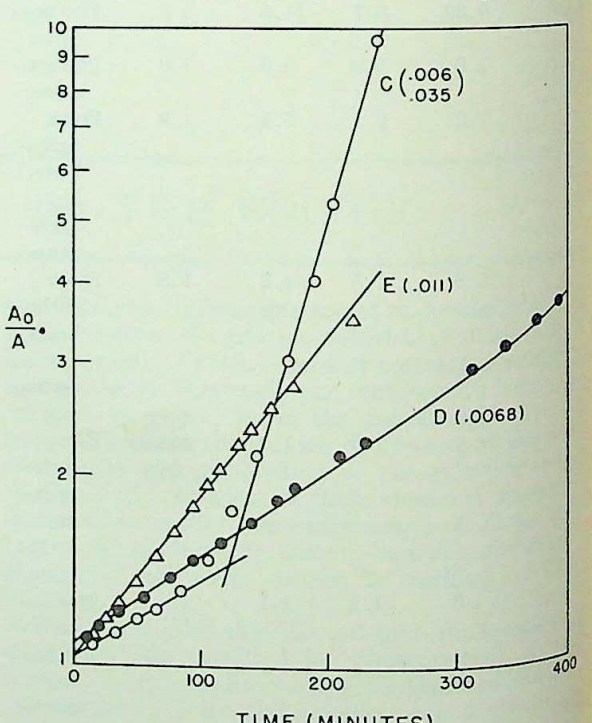

Fig. 2.—Polymerization under same conditions as Fig. 1. Case C is a highly purified anhydride (HCl < 0.1 mole %). Cases D and E correspond to the addition of *n*-hexylamine hydrochloride to the extent of 0.67 and 5.0 mole %, respectively.

(1) D. G. H. Ballard and C. G. Bamford, THIS JOURNAL, 79, 2336 (1957).
(2) P. Doty and R. D. Lundberg, *ibid.*, 78, 4810 (1956).
(3) E. R. Blout and R. H. Karlson, *ibid.*, 78, 941 (1956).
(4) R. D. Lundberg and P. Doty, *ibid.*, in press (1957).
(5) [illegible] and R. H. Karlson, *ibid.*, in press (1957).

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carried out polymerizations with a highly purified anhydride[5] (C in Fig. 2) to which 0.67 and 5.0 mole % of *n*-hexylamine hydrochloride had been added (D and E in Fig. 2). The results show that this adduct eliminates the second propagation step and produces pseudo first-order reactions which bracket the one reported by Ballard and Bamford[1] as "the most reliable thus far obtained." It is evident, therefore, that the results of Ballard and Bamford can be reproduced by impure anhydride or by the addition to highly purified anhydride of one of the impurities removed during its purification. Thus, the sensitivity of this effect to contamination of the anhydride suggests that the presence of *some* impurity is the most likely explanation of their results. Space prevents taking up other possibilities that could arise from not carrying out the purification of the anhydride at −30° as described.[5] Moreover, the premise of Ballard and Bamford concerning the uniqueness of the sublimation in anhydride purification appears invalid inasmuch as we have observed the two successive propagation steps to be even more dramatically exhibited in L-leucine N-carboxy anhydride, both before and after sublimation of the product purified as described.[5] Consequently, we cannot concede that Ballard and Bamford's failure to observe the reported kinetic effect is evidence against its existence.

(2) The kinetic effect we have reported must, of course, be reflected in the molecular weight distribution of the product. In this case, the distribution must be exceedingly broad as we have reported.[2] In case C, for example, the number average DP is 20 and the weight average DP is 170.[6] If, on the other hand, the second propagation step is suppressed as in Case D, the distribution should narrow. This is indeed observed: for case D, $DP_w = 46$, $DP_N = 17.5$. The analysis of the products, therefore, is seen to support the original contention that two successive rate constants are observed under the conditions reported.

We wish to thank Dr. E. R. Blout for his very helpful collaboration in this work.

(6) These measurements were made by Mr. J. C. Mitchell in this Laboratory using the Archibald approach-to-equilibrium technique in ultracentrifugation.

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R. D. Lundberg

Received February 1, 1957

AN ALLEGED FREE RADICAL REACTION IN WHICH BENZENE UNDERGOES ATTACK MORE READILY THAN NITROBENZENE

Sir:

Wieland and Meyer[1] reported that the reaction of triphenylmethyl radical with aromatic substrates, in the presence of benzoyl peroxide, afforded *para*-substituted tetraphenylmethanes. The discovery[2] that these substances were, in reality, *meta* isomers, prompted us to reinvestigate the reaction.

Although nitrobenzene as a substrate was not studied in the original Wieland[1] work, it seemed of special interest to us because of its propensity to participate in free radical reactions with greater ease than benzene itself ($C_6H_5NO_2/C_6H_6)K = 4$).[3]

We found that when triphenylmethyl radicals (in the presence of benzoyl peroxide) were permitted to compete for benzene and nitrobenzene (equimolar mixture) the only products that could be detected were tetraphenylmethane (10%) and *p*-bis-triphenylmethylbenzene, m.p. 330° (9%). (The latter was identical in m.p. and infrared spectrum with material prepared by an independent synthesis.) Both infrared analysis of the crude reaction product and C^{14}-tracer experiments confirmed that nitrotetraphenylmethanes were formed only in trace amounts, if indeed at all.

In conjunction with this work, it was also found that triphenylmethyl radical is not consumed to any appreciable extent by reaction with the nitro function of nitrobenzene in the *absence* of benzoyl peroxide. This is in contradiction to the report by Hammond and Ravve[4] that a quantitative reaction occurs, to afford triphenylcarbinol, azobenzene and phenol among other products.

After a benzene solution of triphenylmethyl (prepared in benzene from triphenylmethyl chloride and mercury) and nitrobenzene had been exposed to diffuse daylight for 24 hours, practically all of the triphenylmethyl was still present and infrared analysis showed the complete absence of azobenzene. Trace amounts of phenol could be detected after a reaction period of 4 days, but its formation was independent of the presence of nitrobenzene since it was also found in mixtures containing only triphenylmethyl and benzene.

The formation of phenol might reasonably be explained by assuming that phenyl radicals are produced in some manner, as postulated by Hammond and Ravve, but the implication[4] that these radicals then abstract oxygen from nitrobenzene appears to be invalid. The presence of trace amounts of atmospheric oxygen seems to afford a better explanation for the phenol production.

We are currently investigating the cause of the surprising reversal of relative reactivity of trityl radicals toward benzene and nitrobenzene. Several possibilities occur to us at this time. (1) Perhaps the Wieland reaction, which has been traditionally considered free radical in nature is instead ionic. (2) The trityl radical may have some carbonium ion character due to the I effects of the three phenyl groups.[5] (3) An ion-pair type complex might form rapidly and reversibly between the easily oxidized trityl radical and nitrobenzene, thus vitiating normal trityl radical attack on that nucleus.

While the first of these explanations cannot be dismissed at this time, it does not seem like an attractive possibility. The Baeyer–Villiger reaction,[6] which almost certainly proceeds *via* a tritylcarbonium ion, occurs only with activated nuclei. Even toluene does not react in a four day period.[2] The

(1) H. Wieland and A. Meyer, *Ann.*, **551**, 249 (1942).
(2) R. A. Benkeser and R. Gosnell, This Journal, **78**, 4314 (1956).
(3) D. H. Hey, *et al.*, *J. Chem. Soc.*, 2094 (1952).
(4) G. S. Hammond and A. Ravve, This Journal, **73**, 1891 (1951).
(5) See R. L. Dannley and M. Sternfeld, *ibid.*, **76**, 4543 (1954), where this general concept was proposed.
(6) A. Baeyer and V. Villiger, *Ber.*, **35**, 3018 (1902).

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Wieland reaction, on the other hand, proceeds successfully with toluene, benzene, chlorobenzene and ethylbenzoate.

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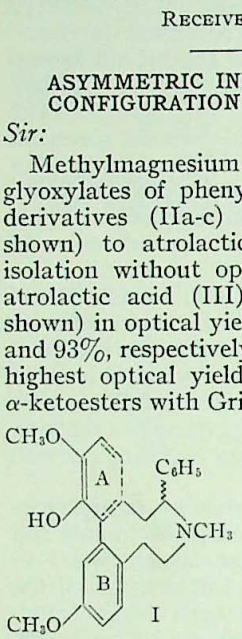
REX B. GOSNELL
WILLIAM SCHROEDER

RECEIVED MARCH 18, 1957

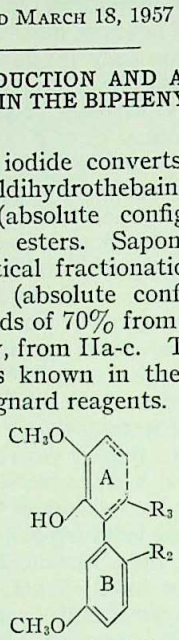
ASYMMETRIC INDUCTION AND ABSOLUTE CONFIGURATION IN THE BIPHENYL SERIES

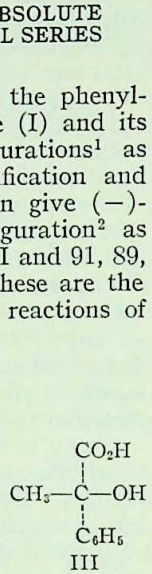
Sir:

Methylmagnesium iodide converts the phenylglyoxylates of phenyldihydrothebaine (I) and its derivatives (IIa-c) (absolute configurations[1] as shown) to atrolactic esters. Saponification and isolation without optical fractionation give (−)-atrolactic acid (III) (absolute configuration[2] as shown) in optical yields of 70% from I and 91, 89, and 93%, respectively, from IIa-c. These are the highest optical yields known in the reactions of α-ketoesters with Grignard reagents.



I

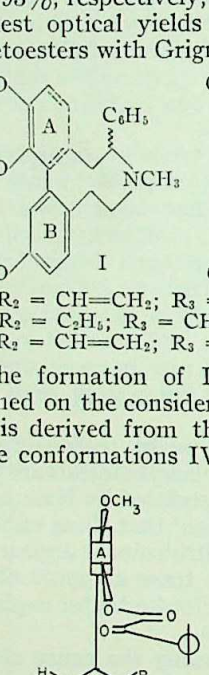




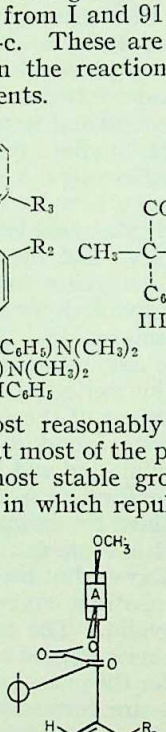
III

IIa, R_2 = CH=CH$_2$; R_3 = $CH_2CH(C_6H_5)N(CH_3)_2$
b, R_2 = C_2H_5; R_3 = $CH_2CH(C_6H_5)N(CH_3)_2$
c, R_2 = CH=CH$_2$; R_3 = CH=CHC_6H_5

The formation of III is most reasonably explained on the consideration that most of the product is derived from the two most stable ground state conformations IV and V, in which repulsive



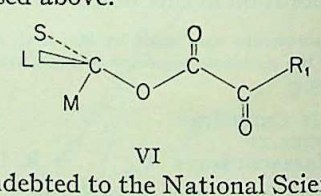
IV



V

interactions are minimized by disposition of the two keto groups coplanar-transoid and the plane of the phenylglyoxylate chain as far away as possible from the ring A methoxyl and ring B, *i.e.*, perpendicular to ring A and at a dihedral angle of 60° with respect to ring B. Approach to the keto carbonyl group in IV and V by the attacking methyl must occur from the direction of ring A, since the underside of the keto group is shielded by ring B. If the rotational barrier between IV and V is high, the major proportion of the product is derived from V, which is more stable than IV because the phenylglyoxylate chain interferes with H instead of R. If the rotational barrier is low compared to the energy of activation for chemical reaction, the product proportions are controlled by the difference in free energy between the transition states derived from IV and V.[3] That from V is the more stable, since in it, the compression of the groups attached to the keto carbonyl as the latter begins to become tetrahedral is against H, whereas in that from IV, this compression is against the large group R. When the effective bulk of R increases (I → II), the stereoselectivity increases. A number of alternative interpretations ascribing special stability to other conformations because of chelate complexing, appear less probable. In particular, the conformation in which each carbonyl group is complexed with a ring methoxyl, and the plane of the phenylglyoxylate residue is perpendicular to ring A and parallel to ring B, would also lead to III. However, in order to explain on this basis the fact that the stereoselectivities with the phenylglyoxylates of IIa-c are 3.5 to 5.8 times greater than with that of I it is necessary to assume that the degree of complexing is less in the latter case. There is no obvious reason why this should be so and, at present, this alternative, while not rigorously excluded, appears unlikely.

In elegant studies, McKenzie, Prelog, Turner and their respective co-workers have examined a large number of reactions of the general type $R_1COCO_2R_a + R_2MgX \rightarrow \rightarrow R_1R_2C(OH)CO_2H$. In eighteen such cases, complete resolution data are available on the product hydroxyacid and, using these, we have now calculated optical yields.[4] For a fixed asymmetric group (R_a), the optical yield is quite insensitive to the size of the incoming group (R_2), but becomes larger as the size of the group (R_1) *already attached* to the keto group increases. This phenomenon requires modification of the previously proposed[5] shielding effect theory of asymmetric induction in α-ketoesters. It is most readily encompassed by the hypothesis that the relative contribution to the total product made by conformation VI diminishes with increasing size of R_1 because of compression effects of the type discussed above.



VI

We are indebted to the National Science Foundation for financial support.

(1) J. A. Berson, THIS JOURNAL, **78**, 4170 (1956).
(2) *Cf.* J. H. Brewster, *ibid.*, **78**, 4061 (1956).
(3) *Cf.* D. Y. Curtin, *Rec. Chem. Progress*, **15**, 111 (1954); D. Y. Curtin and M. C. Crew, THIS JOURNAL, **77**, 354 (1954).
(4) Complete literature references will be given in a forthcoming publication.
(5) V. Prelog, *Bull. soc. chim.*, 987 (1956), and references cited therein.

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JEROME A. BERSON
MICHAEL A. GREENBAUM

RECEIVED FEBRUARY 9, 1957

CYANOCARBON CHEMISTRY—SYNTHESIS AND CHEMISTRY OF TETRACYANOETHYLENE

Sir:

Investigation of cyanocarbons, compounds containing only —C≡N groups attached to carbon,

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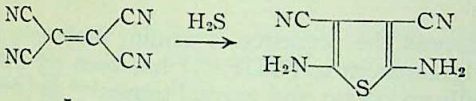
and their derivatives has led to the preparation of tetracyanoethylene (I), the first example of a percyanoölefin. This compound has been shown to be exceptionally reactive and readily undergoes a series of addition and substitution reactions.

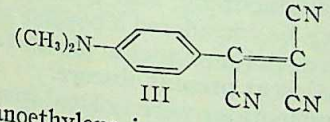
Treatment of dibromomalononitrile–potassium bromide complex[1] with copper powder in benzene under reflux yielded tetracyanoethylene in 65% yield. The product is a white crystalline solid melting at 198–200° in a sealed tube and subliming readily at temperatures above about 120°. (*Anal.* Calcd. for C_6N_4: C, 56.26; N, 43.74; mol. wt., 128. Found: C, 56.42, 56.39; N, 43.23, 43.50; mol. wt., 132.) Tetracyanoethylene is very stable thermally, being unchanged by brief treatment at 600°, and it is resistant to the action of oxygen at moderate temperatures, although it will burn in air.

Tetracyanoethylene is a mild oxidizing agent and converts mercaptans to disulfides, being itself reduced to tetracyanoethane in the process. By treatment with hydrogen sulfide in the presence of pyridine, tetracyanoethylene is converted readily to 2,5-diamino-3,4-dicyanothiophene (II) (92% yield). (*Anal.* Calcd. for $C_6H_4N_4S$: N, 34.13; S, 19.53. Found: N, 34.06, 34.22; S, 19.37.)



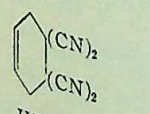
I II

It also reacts with alcohols to give 2,2-dicyanoketene acetals and with N,N-dialkylanilines to give *p*-tricyanovinylaryl amines, a new class of dyes of high tinctorial strength. For example, *p*-tricyanovinyl-N,N-dimethylaniline (III), m.p. 173–175°, has λ_{max} 514 mμ and ϵ_{max} 41,500. (*Anal.* Calcd. for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.31; H, 4.51; N, 25.11.)

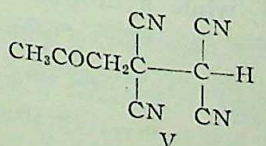


III

Tetracyanoethylene is a very active dienophile, condensing quantitatively with butadiene at 0° to give 4,4,5,5-tetracyanocyclohexene (IV), m.p. 201–202°. (*Anal.* Calcd. for $C_{10}H_6N_4$: C, 65.92; H, 3.32; N, 30.76. Found: C, 65.84, 65.67; H, 3.44, 3.42; N, 30.59, 30.65.)[2] Monoalkylation of ketones having hydrogen alpha to a carbonyl group occurs in the presence of acid catalysts to give α-tetracyanoethyl ketones.[3] For example with acetone in the presence of boron trifluoride at room temperature, 4,4,5,5-tetracyano-2-pentanone (V) is formed in 90% yield; m.p. 118–120° dec. (*Anal.* Calcd. for $C_9H_6N_4O$: C, 58.06; H, 3.25; N, 30.10. Found: C, 58.26, 58.47; H, 3.21, 3.22; N, 30.04, 30.10.)



IV



V

(1) L. Ramberg and S. Wideqvist, *Arkiv. Kemi, Mineral Geol.*, **12A**, No. 22, 12 pp. (1937); *C. A.*, **32**, 2511 (1938).
(2) R. E. Heckert and N. E. Searle, U. S. Patent 2,781,323 (1957).
(3) W. J. Middleton, U. S. Patent 2,762,832 (1956).

Tetracyanoethylene slowly evolves hydrogen cyanide when exposed to moist air at room temperature.

A large number of other reactions of tetracyanoethylene and of related compounds are under investigation, and detailed reports on this research are being prepared for publication.

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R. A. Carboni
D. D. Coffman
V. A. Engelhardt
R. E. Heckert
E. L. Little
Edith G. McGeer
B. C. McKusick
W. J. Middleton

Contribution No. 417 from the Chemical Department, Experimental Station
E. I. du Pont de Nemours and Co.
Wilmington, Delaware

Received March 25, 1957

EFFECTS OF RING SIZE ON THE REACTIONS OF CYCLIC OLEFINS: HALOHYDRINS FROM METHYLENECYCLOALKANES[1]

Sir:

As part of a study of the effects of ring size on the orientations of addition reactions with cyclic olefins, we have included additions of hypohalous acids to a series of methylenecycloalkanes (ring sizes C_4 through C_7). Although we observed no orientation effects when hydrogen bromide was the addend,[2] significant differences were obtained with hypohalous acids. Additions of hypohalous acids to acyclic 1-alkenes always occur predominantly or exclusively with "normal" orientation (primary halogen).[3] We have found however that addition of HOCl to methylenecycloalkanes gives mixtures of chlorohydrins, with "abnormal" orientation predominating with the 4- and 6-membered ring compounds,[4] and that addition of HOBr to these olefins gives only "abnormally" oriented bromohydrins.

Freshly distilled aqueous HOCl or HOBr solution[5] was added in portions to a stirred aqueous suspension of an equivalent amount of methylenecycloalkane at 15°. The mixture was stirred for an hour longer and the layers were separated. The infrared spectrum of the dried organic layer was recorded before distillation. The fractions obtained on distillation were identified by comparison with authentic samples previously synthesized. Both the spectrum taken before distillation and the proportions of distillate in the fractions were used in estimating product distributions. These data are summarized in Table I. From isobutylene and HOBr we obtained a 77% yield of addition product which was about 97% 1-bromo-2-methyl-2-propanol.

(1) This work was supported in part by Research Corporation and in part by the Petroleum Research Fund of the American Chemical Society.

(2) J. G. Traynham and O. S. Pascual, *J. Org. Chem.*, **21**, 1362 (1956).

(3) For example, see P. B. D. la Mare and A. Salama, *J. Chem. Soc.*, 3337 (1956).

(4) Formation of 1-chlorocyclohexylmethanol only from methylenecyclohexane and HOCl has been reported by M. Tiffeneau, P. Weill and B. Tchoubar, *Compt. rend.*, **205**, 144 (1937).

(5) N-Bromosuccinimide could be substituted for HOBr solution without affecting product distributions. See C. O. Guss and R. Rosenthal, This Journal, **77**, 2549 (1955).

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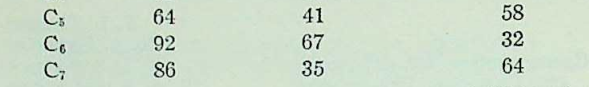
TABLE I

PRODUCT DISTRIBUTIONS IN HYPOHALOUS ACID ADDITIONS TO METHYLENECYCLOALKANES

Ring size	Hypochlorous acid: Total yield, %	Proportion of total, %			Hypobromous acid: Total yield, %	Proportion of total, %	
		>C(Cl)CH₂OH	>C(OH)CH₂OH	Other product		>C(Br)CH₂OH	Other products
C_4	72	60	40	none[a]	78	99	1[b]
C_5	64	41	58	1[b]	67	91	9[c]
C_6	92	67	32	1[b]	89	98	2[d]
C_7	86	35	64	1[b]	87	87	13[d]

[a] No rearrangement products were found. [b] Slight absorption attributable to a carbonyl group (probably in cycloalkanecarboxaldehyde) appeared in the infrared spectrum of the product. [c] Methylenecyclopentane oxide. [d] Cycloalkanecarboxaldehyde.

The preponderance of "abnormally" oriented products from the 4- and 6-membered rings is consistent with the view that trigonal carbons in those rings are unfavored.[6] The initially formed pi-complex (I) may rearrange (as usual) to the conventional carbonium ion (II),[3,7] or it may suffer direct attack by water to give III. Rearrangement of I to II is the less favored path for 4- and 6-membered rings, but is satisfactory for 5- and 7-membered



I II III

rings.[8] The formation of large amounts of III even from 5- and 7-membered rings, when acyclic olefins give corresponding products only in very small amounts, indicates that this explanation is incomplete and suggests an importance of the ring structure itself in directing orientation. That suggestion is further supported by the complete contrast between HOBr additions to methylenecycloalkanes and to isobutylene.

Since "abnormal" products were not obtained with HBr as addend,[2] it appears that the size of the attacking cation (or the "activity" of the attacking particle[9]) may have an important role in determining the actual orientation with these olefins. We hope that our continuing studies will reveal more explicit information about these effects.

Authentic 1-chloromethylcycloalkanols (except for 1-chloromethylcyclobutanol) were synthesized by hydrolysis of the appropriate methylenecycloalkane dichloride with an aqueous suspension of $CaCO_3$.[10] These chlorohydrins all reduced permanganate, gave precipitates with NaI in acetone and with alcoholic $AgNO_3$, produced immediate cloudiness in Lucas reagent and showed infrared absorption near 7.25 μ (tertiary alcohol). Authentic 1-halocycloalkylmethanols were synthesized by the action of hydrochloric or hydrobromic acid on the appropriate olefin oxide. These halohydrins all reduced permanganate, gave precipitates with alcoholic $AgNO_3$ but none with NaI in acetone, gave negative Lucas tests and showed no infrared absorption near 7.25 μ.

COATES CHEMICAL LABORATORIES
LOUISIANA STATE UNIVERSITY JAMES G. TRAYNHAM
BATON ROUGE, LOUISIANA O. S. PASCUAL

RECEIVED MARCH 1, 1957

(6) H. C. Brown, J. H. Brewster and H. Shechter, THIS JOURNAL, 76, 467 (1954).

(7) Rearrangement of the protonated olefin (pi-complex) to a more conventional carbonium ion has been shown to be an important part of acid-catalyzed olefin hydration; R. W. Taft, Jr., *ibid.*, 74, 5372 (1952); R. W. Taft, Jr., E. L. Purlee, P. Riesz and C. A. DeFazio, *ibid.*, 77, 1584 (1955).

(8) A more complete discussion of this point is found in ref. 2.

(9) H. C. Brown and K. L. Nelson, THIS JOURNAL, 75, 6292 (1953).

(10) C. E. Sparks and R. E. Nelson, *ibid.*, 55, 1010 (1933).

URIDINE DIPHOSPHATE N-ACETYLGLUCOSAMINE AND URIDINE DIPHOSPHATE GLUCURONIC ACID IN MUNG BEAN SEEDLINGS

Sir:

Whereas the presence of uridine diphosphate N-acetylglucosamine (UDPaG) has been reported in penicillium, yeast and animal tissues[1-3] and uridine diphosphate glucuronic acid (UDPGuc) in liver tissue, these nucleotides have hitherto been unknown in higher plants.

In the present communication evidence is presented for the existence of UDPaG and UDPGuc in mung bean seedlings. Furthermore, these seedlings contain a hitherto unknown enzyme which catalyzes the reaction between UDPGuc and pyrophosphate to form uridine triphosphate (UTP) and presumably D-glucuronic acid 1-phosphate. While UDPGuc may be considered a possible precursor of the synthesis of polyuronides in plants, the function of the UDPaG is at present obscure.

The two nucleotides were isolated from 10 kg. of mung bean seedlings using methods described by Ginsburg, *et al.*[4] The nucleotide fraction eluted from the Dowex-1-Cl^- column by 0.01 *N* HCl–0.15 *N* NaCl was further purified by paper chromatography.[3] In this way 14 μmoles of a nucleotide (I) corresponding in R_f to authentic UDPaG (R_f 0.45) was separated. A second nucleotide fraction, eluted by 0.01 *N* HCl–0.06 *N* NaCl, was further purified by paper electrophoresis in formate buffer at *p*H 3.5[4,5] to yield 4 μmoles of a nucleotide (II) corresponding to UDPGuc in electrophoretic mobility.

Hydrolysis of both nucleotides with 0.1 *N* HCl at 100° for 10 minutes liberated chiefly uridine diphosphate, while hydrolysis with 1.0 *N* HCl yielded

(1) L. F. Leloir, Proc. 3rd Intern. Congr. Biochem., Brussels, 1955, p. 154.

(2) E. Cabib, L. F. Leloir and C. E. Cardini, *J. Biol. Chem.*, 203, 1055 (1953).

(3) E. E. B. Smith and G. T. Mills, *Biochim. et biophys. Acta*, 13, 393 (1954).

(4) V. Ginsburg, P. K. Stumpf and W. Z. Hassid, *J. Biol. Chem.*, 223, 977 (1956).

(5) A. M. Crestfield and F. W. Allen, *Anal. Chem.*, 27, 422, 424 (1955).

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May 5, 1957

chiefly uridine monophosphate. In both cases a sugar was also set free. The degradation products were identified by paper chromatography and electrophoresis. Hydrolysis of I with 0.05 *N* HCl for 10 minutes at 100° yielded a substance which reacted as an N-acetylhexosamine.[6] It was identified as acetylglucosamine by paper chromatography,[2,7] and by paper electrophoresis at *p*H 5.8 (ammonium acetate) and *p*H 8.6 (borate).[8] Hydrolysis of I with 2 *N* HCl for 2 hours at 100° liberated a substance giving a positive reaction for hexosamine. This was identified as glucosamine by paper chromatography,[7,8] electrophoresis,[8] and by degradation to arabinose with ninhydrin.[7]

Mild acid hydrolysis of II set free a hexuronic acid (carbazole test) which was shown to be glucuronic acid by paper chromatography[9] and by electrophoresis at *p*H 3.5.[4,5] The analyses of the two nucleotides are presented in Table I. It is thus shown that substances I and II are UDPaG and UDPGuc, respectively.

TABLE I

ANALYSES OF NUCLEOTIDES FROM MUNG BEAN SEEDLINGS

	(I) μmole/μmole uridine[a]		(II)	
	Found	Calcd. for UDPaG	Found	Calcd. for UDPGuc
Total P[b]	2.10	2.00	2.02	2.00
Acid labile P[c]	0.98	1.00	0.95	1.00
Glucosamine[d]	0.97	1.00	..	..
Glucuronic acid[e]	..	..	0.93	1.00
Reducing value[f]	0	0	0	0
Reducing value after hydrolysis[g]	0.90	1.00	0.71	1.00

[a] Uridine moiety identified by characteristic ultraviolet spectrum at *p*H 2, 7 and 11. Concentration was determined by the optical density at 260 mμ (*p*H 7) calculated on the basis of a molar extinction of 9.9×10^3. [b] C. H. Fiske and Y. SubbaRow, *J. Biol. Chem.*, 66, 375 (1925). [c] Hydrolysis with 0.1 *N* HCl for 10 minutes at 100°. [d] Z. Dische and E. Borenfreund, *J. Biol. Chem.*, 184, 517 (1950). [e] Z. Dische, *ibid.*, 167, 189 (1947). [f] J. T. Park and M. J. Johnson, *ibid.*, 181, 149 (1949). [g] Hydrolysis with 0.1 *N* HCl for 10 minutes at 100°.

When UDPGuc (0.25 μmole) was incubated with a 55–65% ammonium sulfate fraction from a mung bean seedling extract in the presence of 0.5 μmole of sodium pyrophosphate, 2.5 μmoles of KF and 0.25 μmole of $MgCl_2$ in 0.02 *M* Tris buffer, *p*H 7.5, at 24° in a total volume of 17.5 μl. the formation of UTP could be demonstrated by electrophoresis at *p*H 3.5.[4,5] In analogy with other known UDP-sugar pyrophosphorylases,[10] the reaction may be formulated as

UDPGuc + pyrophosphate $\rightleftharpoons$ UTP + glucuronic acid 1-phosphate

(6) D. Aminoff, W. T. J. Morgan and W. M. Watkins, *Biochem. J.*, 51, 379 (1952).
(7) P. J. Stoffyn and R. W. Jeanloz, *Arch. Biochem. Biophys.*, **52**, 373 (1954).
(8) P. W. Kent and M. W. Whitehouse, "Biochemistry of the Aminosugars," Academic Press, Inc., New York, N. Y., 1955, p. 166.
(9) F. G. Fischer and H. Dörfel, *Z. physiol. Chem.*, **301**, 224 (1955).
(10) E. F. Neufeld, V. Ginsburg, E. W. Putnam, D. Fanshier and W. Z. Hassid, *Arch. Biochem. Biophys.*, in press.

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D. S. FEINGOLD
W. Z. HASSID

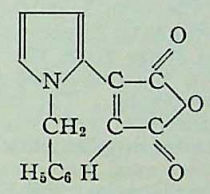
RECEIVED FEBRUARY 27, 1957

THE REACTION OF N-BENZYLPYRROLE WITH ACETYLENEDICARBOXYLIC ACID[1]

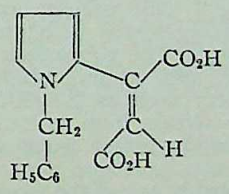
Sir:

The reaction of pyrroles with dienophiles has been shown to lead to substitution in the α-position of the pyrrole and, in some cases, to poly-substitution products such as dihydroindoles.[2] There has been no authenticated report of a pyrrole undergoing a normal Diels–Alder type of addition in the sense that, for example, furan will partake of Diels–Alder addition to dienophiles.[3]

We have found that refluxing an ether solution of N-benzylpyrrole and acetylenedicarboxylic acid for 24 hours gives rise to three products which were separated readily by taking advantage of their varying solubility properties. Two of these products, which had characteristic yellow colors, were shown to be α-substituted pyrroles on the basis of their elemental analyses, neutral equivalents, infrared spectra, common conversion by hydrolysis and hydrogenation to pyrrolidinesuccinic acid, and thus were assigned the structures I and II. This is in accord with the findings of Diels and Alder.[2]

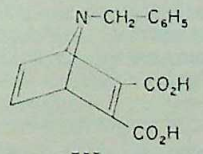


I



II

The third compound, which was colorless, was assigned structure III on the basis of the data given below.



III

The material had an elemental analysis (Calcd. for $C_{15}H_{13}O_4N$: C, 66.4; H, 4.8; N, 5.2. Found: C, 66.0; H, 4.9; N, 5.1.) and neutral equivalent (Calcd. for III: 135.5. Found: 133) which corresponded to a one-to-one adduct. The substance is amphoteric, being soluble in the cold in both dilute sodium bicarbonate and dilute hydrochloric acid, the latter indicative that the pyrrole moiety is no longer intact. On hydrogenation over 5% palladium on carbon at atmospheric pressure and room temperature, *three moles* of hydrogen were absorbed (in contrast to compounds I and II which take up *four moles* of hydrogen under these conditions) thus indicating the presence of a bicyclic skeleton. The material exhibited only end absorption in the ultraviolet (from 210 to 330 mμ) and its infrared spec-

(1) This work was supported by a Frederick Gardner Cottrell grant from Research Corporation.

(2) O. Diels and K. Alder, *Ann.*, **470**, 62 (1929); **486**, 211 (1931); **490**, 267 (1931); **498**, 1 (1932).

(3) H. Hopff and C. W. Rautenstrauch, U. S. Patent 2,262,002 [*C. A.*, **36**, 1046 (1942)] have reported without citing evidence, that N-isobutylphthalimide reacts with pyrrole to yield a tetrahydro-*endo*-phthalimide.

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trum (in KBr) indicated the presence of zwitterion formation.

In accord with this structural assignment, refluxing III for 12 hours in 10% sodium carbonate solution gave rise to N-benzylpyrrole and I.

This represents the first recorded Diels–Alder addition with a pyrrole acting as a diene. We hope to report shortly on further rearrangements of the adduct and its hydrogenation products.

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LEON MANDELL
WESLEY A. BLANCHARD

RECEIVED MARCH 29, 1957

BOOK REVIEWS

Organic Syntheses. Vol. 36. By N. J. LEONARD, Editor-in-Chief, John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 1956. vi + 120 pp. 15.5 × 23.5 cm. Price, $3.75.

"Tried and true" directions for preparing 35 organic compounds are reported in Volume 36 of "Organic Syntheses." This volume maintains the high standards of its predecessors in its editing, experimental directions and indexing. The compounds treated range from the very simple, such as propiolaldehyde, to the somewhat more complex, such as 2-hydroxycyclodecanone. The editors wisely refrain from including syntheses of very complex compounds, which would have limited applicability and interest.

Probably one of the most useful preparations will be the one for diazomethane from *p*-tolylsulfonylmethylnitrosamide. The advantage of this method is that the starting material is stable and soluble in organic solvents.

This new volume will take its place as a worthy addition to the "Organic Syntheses" series, which has for many years been one of the most valuable reference works for the organic chemist.

DEPARTMENT OF CHEMISTRY
ST. JOHN FISHER COLLEGE
ROCHESTER, NEW YORK
CARL J. CLAUS

The Chemistry of Petrochemicals. By MELVIN J. ASTLE, Professor of Chemistry, Case Institute of Technology, Cleveland, Ohio. Reinhold Publishing Corporation, 430 Park Avenue, New York 22, N. Y. 1956. v + 267 pp. 16 × 23.5 cm. Price, $6.50.

This volume is a valuable source of general information and literature references on organic chemical compounds produced from petroleum. The 14 chapters contain 255 pages of text, many equations and tables of data, and 582 literature references. However, there is no author index and the bibliographies for each chapter are not alphabetically arranged.

The discussion is reminiscent of the books of Carleton Ellis. There is much useful information presented in sufficient detail to introduce the reader to the subject. For example, alkylation is covered in 9 pages, 7 on alkylation of paraffins and 2 on alkylation of aromatics. Two and one-half pages are devoted to the theory of alkylation. This section is based almost entirely on the work of Schmerling. The bibliography omits some important papers in this field, particularly those of Dr. P. D. Bartlett and associates.

The discussion of alkylation with hydrogen fluoride starts off with the statement, "Hydrogen Fluoride is increasing in importance as an alkylation catalyst." There is no mention of the fact that HF alkylation was an important process for producing aviation alkylate during World War II, and that nearly all of these HF alkylation plants were shut down, or converted to other use, at the end of the war. In regard to the Ziegler process (p. 103) for polyolefins, it is now more or less generally known that mixed catalyses are better than aluminum alkyls alone.

There are other spots in the text which indicate a lack of familiarity with what has actually been going on in industry. For example, on page 155, a process for concentrating benzene by adsorption is described as though the plant had been built and operated. Actually this process for concentrating benzene by adsorption never got beyond the drawing board stage.

On the scientific side, there is a tendency toward rather loose statements, such as the introductory sentence of chapter 2, which reads, "Inasmuch as petroleum is made up largely of paraffin hydrocarbons, these compounds must be considered to be the ultimate starting materials for the preparation of petrochemicals." Benzene and toluene occur in natural petroleum and have been separated commercially as noted on page 153. It is quite clear that paraffins and cycloparaffins naturally occurring in petroleum are not the "ultimate" starting materials for all petrochemicals. However, it is probably true that on a tonnage basis, the chemicals produced from the paraffin and cycloparaffin constituents of petroleum will probably be more important than those produced from the naturally occurring aromatics in petroleum.

The title of this book illustrates the fact that the word "petrochemical" is better adapted to economic rather than scientific discussion. On page 2 there is an estimate that there will be 35 billion pounds of "petrochemicals" produced in 1956 of which 10.5 billion pounds will be "inorganic petrochemicals." However, the book omits entirely any discussion of the chemistry of the "inorganic petrochemicals" such as ammonia and sulfur.

The word "petrochemical," as used in the petroleum industry, brings together products which are economically related, but not chemically related.

In spite of a certain degree of superficiality, which is perhaps unavoidable in a book covering so wide a range of topics, this book should prove of real value to those who need an introduction to the field of the organic chemistry of hydrocarbons, and the more simple organic compounds derivable from hydrocarbons.

RESEARCH AND DEVELOPMENT DEPT.
SUN OIL COMPANY
MARCUS HOOK, PA.
STEWART S. KURTZ, JR.

Polymer Solutions. By H. TOMPA. Academic Press, Inc., 111 Fifth Avenue, New York 3, N. Y. 1956. xiv + 325 pp. 10.0 × 16.5 cm. Price $8.50.

This is a comprehensive review of current concepts of the solution properties of high polymeric substances. The author has wisely omitted a treatment of polyelectrolytes since this is more properly in the domain of electrolyte theory. Throughout, Dr. Tompa compares theory with experimental results. The book is practically self-contained. All the basic formulas of the thermodynamics of solutions and of the statistics of coiled molecules are derived from first principles. When the author discusses

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viscosity and light scattering, he explains the theories in physical terms but does not derive the formulas since this would require a much larger book.

The author is to be congratulated for the manner in which he has been able to distil the many complicated theories of high polymer solutions down to their essentials. His style is lucid, and his choice of subjects and the extent to which he discusses them is excellent. This book should be studied by everyone concerned with solutions of synthetic high polymers. Workers in the field are looking forward to the day when the properties of the final plastic can be explained in a thorough-going fashion as can now be done for solutions of polymers.

INSTITUTE OF POLYMER RESEARCH
POLYTECHNIC INSTITUTE OF BROOKLYN GERALD OSTER
BROOKLYN, N. Y.

Vacuum Deposition of Thin Films. By L. HOLLAND, Head of the Vacuum Coating Research Laboratory, Edwards High Vacuum Ltd. With a foreword by PROFESSOR S. TOLANSKY, F.R.S. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 1956. xix + 541 pp. + 25 plates. 15 × 23 cm. Price, $10.00.

This book is long overdue. Today, vacuum coating is an important industry and no longer just a laboratory procedure, and Mr. Holland's volume will be useful to every worker in the field. It covers all phases of vacuum coating from the point of view of the technologist. This is not a theoretical treatise but a practical volume written by one with adequate theoretical background and wide experience.

The chapters each stand by themselves without any particular continuity or grouping. The first discusses general techniques and equipment used in the production of high vacuum. The many design sketches and detailed explanations will be of value to those designing their own vacuum evaporators and will increase the understanding of others who purchase commercial units. Sources and the thickness distribution of the deposited films are described in chapters 4 and 5. Distribution functions are derived mathematically and numerous graphs depict the experimental results obtained for different sources and receivers of various shapes.

Cleaning of surfaces prior to coating and the techniques for evaporating metals and alloys are discussed in chapters 3 and 6. Problems of reactions between charge and heater and selective evaporation of alloy components are detailed and tested solutions are given.

The difficulties of degassing plastic materials and coating them are treated in chapters 2 and 12. Systems for handling commercial quantities of materials are described and the vacuum properties of plastics and lacquers used for substrates are tabulated.

The properties of deposited films are discussed in detail and the influence of rate of evaporation, substrate temperature, gas pressure, angle of incidence, etc., is evaluated. This information is carried over into a chapter on the preparation of thin films for electrical purposes in the commercial production of resistors, capacitors and electrodes. Separate chapters are devoted to very detailed treatments of the preparation and properties of aluminum and oxide films.

Chapters 9 and 10 are concerned with optical coatings. Methods of preparing anti-reflection films, high reflection films and interference filters are described. Apparatus for controlling the deposition of optical films and the properties of these coatings is given in detail. In a related vein is a section on shadow-casting and surface replication as used in light and electron microscopy. The emphasis here is on the vacuum techniques and apparatus, not on the microscope applications.

The widely used and poorly understood process of cathodic sputtering is the subject of a complete chapter. The various theories are discussed and their disagreements are enumerated. Properties of films produced by sputtering are described and illustrated graphically, and apparatus for sputtering is shown.

The entire book is admirably documented and the bibliography of 557 references is invaluable. However, considering the large number of topics discussed, an expansion of the index would be very desirable. Also, this reviewer would have appreciated a more thorough discussion of the formation and properties of metallic blacks which are treated only very briefly. Of more commercial interest is the aluminizing of television kinescopes which requires specialized apparatus that might well have been described.

It is to be hoped that subsequent printings will rectify the unusual number of misprints and other minor errors which exist throughout the book, but in no way detract from its value.

RESEARCH DEPARTMENT
CENTRAL SCIENTIFIC COMPANY R. G. PICARD
CHICAGO, ILLINOIS

Advances in Carbohydrate Chemistry. Vol. 11. By MELVILLE L. WOLFROM, Editor, and R. STUART TIPSON, Associate Editor. Academic Press, Inc., Publishers, 111 Fifth Avenue, New York 3, N. Y., 1956. xviii + 465 pp. 15.5 × 23.5 cm. Price, $11.00.

Readers of the previous volumes of this series need only be told that the editors, their board of advisors and the various contributors have joined forces to turn out a work of exceptional interest. This book amply demonstrates that the research worker will find those areas of science most rewarding where different fields of specialization overlap. Enzymology, microbiology, physical chemistry and organic chemistry supply the *leitmotif*.

The chapter dealing with the biosynthesis of the monosaccharides will be read by many grateful people. Sixty five tightly written pages cover all the significant work from Adolf von Baeyer's speculations about the polymerization of formaldehyde to the complex realities of enzyme systems and photochemistry currently under investigation. L. Hough and J. K. N. Jones take leave of their readers with a challenging statement:

> "More than one hundred enzymes, and many of their coenzymes, have been recognized in animal mitochondria. Whether or not such an organization of enzymes is present in such a cell unit for performing a sequence of reactions with carbohydrates remains to be determined."

F. Shafizadeh's chapter dealing with branched-chain sugars of natural origin is an appropriate sequel. His system of naming these compounds is logical, and it could have been used advantageously in the preceding article.

J. M. Bobbitt focusses our attention on the periodate oxidation of carbohydrates, and he brings into relief the functioning of this analytically important reagent. References to other reviews dealing with periodic acid enhance the usefulness of this chapter. S. Bayne and J. A. Fewster supply a comprehensive survey of the chemistry and biochemistry of the osones, and Andrew Beélik discusses the biosynthesis, chemical synthesis and properties of kojic acid. G. R. Barker's chapter on nucleic acids supplements and brings up to date the work published by the associate editor, R. Stuart Tipson, in *Volume I* of this series. Aspects of the Physical Chemistry of Starch, and an Addendum: The Size and Shape of Some Polysaccharide Molecules, by C. T. Greenwood point up the functions of physicochemical techniques in the study of the nature of polysaccharides. The descriptive chemistry of furan, pyrrole and other heterocyclic compounds obtained from condensation reactions of monosaccharides with β-ketonic esters is presented by F. García Gonzáles. A generalized cumulative author and subject index to *Volumes 1–10* is included.

There is an obituary of the late Kurt H. Meyer by R. W. Jeanloz. The current crop of students will find much inspiration in the personal life and achievements of the departed. The diversity of his scientific interests and his warm friendliness are movingly described by his former student.

The reviewer may be considered captious in pointing out a few little motes. Why didn't someone do something about: "Observation of mixed melting points is mandatory." Or, "General consensus of opinion"? There are ambivalent feelings toward the typographical pun in a statement dealing with the use of periodic acid: "Aliquots of the reaction mixture are periodically removed." The author who suggests a system for the naming of branched-chain sugars forgets to use it in a couple of places. Some of the charts would have been easier on the eyes if larger type and more space had been used. In the anniversary year of W. H.

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Perkin, footnote 54 on page 277 as well as the author index refer to the son as W. H. Perkins, Jr. *Eheu fugaces. . . .*

College libraries are advised to chain down this volume or to see to it that they have a sufficient supply to meet the anticipated demand.

DEPARTMENT OF CHEMISTRY
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LOUIS SATTLER

Elementary Wave Mechanics with Applications to Quantum Chemistry. Second Edition. By W. HEITLER, Professor of Theoretical Physics in the University of Zürich. Oxford University Press, 114 Fifth Avenue, New York 11, N. Y. 1956. viii + 193 pp. 12.5 × 19 cm. Price, $2.90.

When a book that is as small as this one is deals with the entire field of "elementary quantum mechanics," and when it also considers the "applications to quantum chemistry," many important topics must unavoidably be slighted or entirely ignored. Consequently, the reader cannot expect here to find more than a general introduction to the basic concepts, and he cannot expect to be brought to the point where he is able to make original contributions to the field.

Even within these limitations, however, there is reason to question whether the author has been successful in presenting the material in such a form that it will be helpful to the "chemists and other non-mathematical readers" for whom, according to the Preface, it is designed. The earliest developments of the theory are expounded clearly and well, but almost nothing that has been added since about 1930 is discussed. Valence, for example, is treated entirely with the aid of first-order perturbation theory, and the variation principle is not mentioned at all. The states of the individual atoms in molecules are described in terms of the spectroscopic symbols that are strictly applicable only to isolated atoms. The concepts of resonance and of molecular orbitals are not explicitly mentioned, although some of the basic principles of these concepts are briefly suggested. The Preface gives the impression that the book should be intelligible to the "non-mathematical reader," but this impression is hardly borne out by the fact that a firm understanding of calculus and at least a bowing acquaintance with the theory of determinants are presupposed.

It is difficult to see for what group of readers this book would be valuable. The chemist or physicist who is already familiar with quantum mechanics might find the discussion of the historical background interesting and informative, but he would probably be disappointed by the inadequate way in which the more recent developments are treated. On the other hand, the reader who is encountering the subject for the first time might be more bewildered than instructed by the necessarily brief and sketchy way in which the complex and rather abstruse principles are presented, and he would almost certainly be left with an incorrect idea of the methods currently employed in the approaches to many important problems.

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PHYSICAL AND INORGANIC CHEMISTRY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

Optical and Electrical Methods of Determining Transference Numbers of Electrolytes in Dilute Solutions by the Moving Boundary Technique

BY J. W. LORIMER, J. R. GRAHAM AND A. R. GORDON

RECEIVED JANUARY 14, 1957

With a view to transference studies in non-aqueous solvents, methods of determining transference numbers at low concentrations have been investigated. The use of rectangular channels permits the identification of the boundary by the conventional optical methods at concentrations well below those permissible in the usual circular channel; there is, however evidence of boundary instability (at 25° at any rate) and with the familiar Tiselius cell, the solvent conductance is sufficiently large and erratic as to render the results at low concentrations valueless. As an alternative, boundary movement in the channel can be followed by measuring the change in resistance across the channel between microelectrodes when the leading solution is replaced between the electrodes by the indicator. A suitable circuit is described, and it is shown that boundary movement can be followed in this way with satisfactory precision. The advantages (and disadvantages) of this technique are discussed.

It has become apparent in recent years[1,2] that the quantity significant in studies of electrolytic transfer in solution is the ionic rather than the equivalent conductance. This implies, in addition to the usual conductance measurement, the determination of the transference number, and even now only a few such data for anhydrous solvents have been reported; the conventional moving boundary measurements with KCl and NaCl in methanol, carried out in this Laboratory,[3] and Smisko and Dawson's KCNS determinations in ethanol[4] suggest the difficulties which may be encountered in non-aqueous solutions. Moreover, if as is the case with many solvents, ion-pair formation occurs, the measurements should be carried to concentrations well below those hitherto used, and this in turn requires improved methods for following boundary movement. The Kohlrausch ratio technique[5] does provide an alternative as far as limiting ion conductances are concerned, but when used as an absolute method suffers under the disadvantage that the resulting limiting ionic quantities are at best no more precise percentually than is the difference in the limiting equivalent conductances of the leading and indicator salts.

This research was therefore undertaken to determine (a) whether optical methods could be employed at high dilutions, and (b) whether alternative criteria could be used to follow boundary movement. The studies of the optical methods are discussed briefly below, the bulk of the paper being concerned with a conductimetric method of following the boundary, which seems to offer distinct advantages.

Experimental

An elementary treatment of the Abegg and Gaus[6] method of observing a sharp boundary between two solutions of different refractive index (sometimes referred to as the total reflection method[7]) shows that, other things being equal, the minimum detectable refractive index difference is roughly inversely proportional to the path length through he cell. This at once suggests the use of a rectangular channel, as in the conventional Tiselius cell, particularly since this would permit, if desirable, the use of more sophisticated optical mthods. The cell chosen was a modified form of the usual 3 mm. × 25 mm. type discussed by Longsworth and MacInnes.[8] It differs in that there are three center sections (labeled II and III in their Fig. 1) the upper two being fused to the header; the third is fused to the bottom section (IV in their figure) thus leaving only one shearing surface to minimize leakage. The electrode compartments were much reduced in size, and the cell was

(1) C. A. Kraus, *Ann. N. Y. Acad. Sci.*, **51**, 789 (1949).
(2) R. E. Jervis, D. R. Muir, J. P. Butler and A. R. Gordon, THIS JOURNAL, **75**, 2855 (1953).
(3) J. A. Davies, R. L. Kay and A. R. Gordon, *J. Chem. Phys.*, **19**, 749 (1951).
(4) J. Smisko and L. R. Dawson, *J. Phys. Chem.*, **59**, 84 (1955).
(5) D. R. Muir, J. R. Graham and A. R. Gordon, THIS JOURNAL, **76**, 2157 (1954).
(6) R. Abegg and W. Gaus, *Z. physik. Chem.*, **40**, 737 (1902).
(7) D. A. MacInnes and L. G. Longsworth, *Chem. Revs.*, **11**, 171 (1932).
(8) L. G. Longsworth and D. A. MacInnes, *ibid.*, **24**, 271 (1939).

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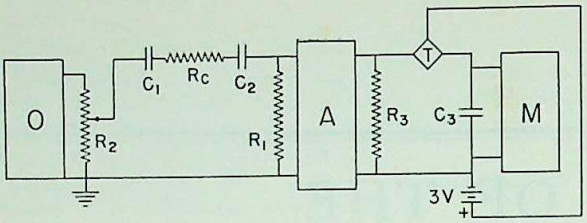

Fig. 1.—Schematic diagram of the alternating current circuit.

mounted in a Rockefeller type of frame (see Fig. 2, ref. 8); we wish to thank Dr. Longsworth for supplying us with the blue prints. The measurements were carried out in a carefully controlled air thermostat placed in a constant temperature room.

To determine the volume swept out by the boundary, two methods were employed. The boundary after passing a reference mark was displaced backward through a known volume by additions of mercury to the closed side of the cell from a calibrated pipet. Alternatively, the channel was calibrated from the known value of t_+ for 0.01 N KCl[9,10] by following boundary movement against a graticuled scale. It was found as expected that while a 0.01 N KCl/KIO_3 boundary is about the most dilute that can be observed satisfactorily in a 2.5 mm. circular channel, a 0.001 N KCl/KIO_3 boundary in the Tiselius cell could be seen with ease. Unfortunately, measurements at high dilutions proved unreliable because of large and erratic solvent conductances determined in the cell; this apparently was due, in part at least, to contamination from slight fissures where the end and side members of the channel are fused together. Moreover, in measurements at 25° in contrast to those near 4°, there was evidence of boundary instability, notably a tendency for the boundary to be arched; this may be due to the non-symmetrical temperature distribution in a channel of this shape.

As an alternative, conventional rising and falling boundary cells were constructed (types V and VIII, see Fig. 1, ref. 11) except that the channel, including that in the shearing stopcock, was of rectangular 2 mm. × 10 mm. glass tubing.[12] The cells were calibrated as to volume with 0.02 and 0.01 N KCl, using KIO_3 and LiCl as indicators for rising and falling boundaries, respectively, and as expected, visible boundaries were obtained at concentrations one quarter to one fifth those for a 2.5 mm. channel. Solvent conductances, determined in the cell, were now reproducible, but again at high dilutions there was some hint of boundary instability; even the volume calibrations showed a scatter of a part in 1500 or so, as compared with a part in 4000 at these concentrations in a 2.5 mm. circular channel. With more dilute solutions, the precision was considerably less; for example, a series of measurements with 0.0025 N KCl and potassium diiodobenzoate as indicator, gave $t_- = 0.5097 \pm 0.0005$.

The Conductimetric Method.—This procedure takes advantage of the fact that there must be a change in resistance across the channel when the leading solution is replaced by the indicator. Preliminary measurements suggested certain obvious conditions to be fulfilled if good precision were to be obtained. In the first place, the electrodes used to determine the conductivity of the solution must be as small as possible in the vertical direction to sharpen the timing of the "event" and to minimize the possibility of their acting as bipolar electrodes to the direct current. Secondly, for continuous recording, the conductance electrodes must be capacity coupled in the a.c. measuring circuit.

To construct the channel, the procedure finally adopted was to stretch a platinum ribbon, 0.07 mm. thick and 1.0 mm. wide, across the upper end of a glass tube, 2.5 mm. i.d. 0.7 mm. wall thickness. Since the ribbon was rather fragile, it was first welded to 0.5 mm. leads of platinum wire, the length of ribbon being so chosen as to leave the leads in close proximity to the glass. Another section of tubing was pressed down on the first, and the two sections were

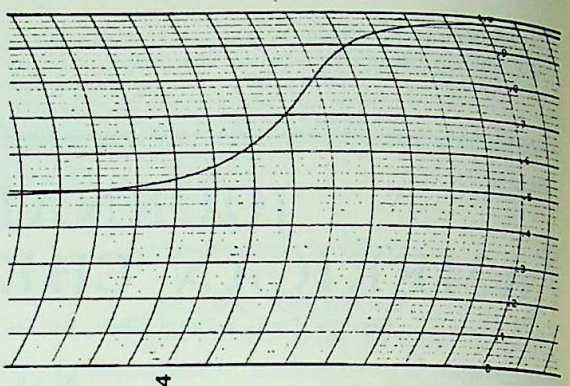

Fig. 2.—Trace on recording milammeter for passage of 0.01 N KCl/0.0069 N KIO_3 boundary; boundary velocity 0.04 mm./sec.

fused at the lowest temperature consistent with obtaining a satisfactory seal, leaving the ribbon extending from wall to wall of the tube. A thin thread of glass was next wound around the lead and fused to it and to the wall of the tube, thus protecting the ribbon from mechanical strains. A sharpened steel rod, slightly smaller than the internal diameter of the tube, was pressed down, cutting the ribbon near the walls, and any protruding platinum was removed with a stiff piano wire coated with carborundum powder and glycerol. It was found, as might be expected, that there was considerable variation in apparent resistance with different pairs of electrodes; accordingly, for reasons discussed below, a "cell factor" (using 0.01 N KCl) was determined for each pair of electrodes, and only those pairs with factors differing by not more than a few per cent. were incorporated in a channel. Each channel had as a rule five pairs of such microelectrodes spaced some 40 mm. apart. It should be noted in passing that even with an ohmic drop as high as 1 volt per mm., due to the passage of the direct current, the voltage drop across the surface of a microelectrode is only 0.07 volt.

In order to test the method in the same cell with both rising and falling boundaries, the earlier designs (after annealing) were fitted with a Type III shearing stopcock[11] at the base of the channel and a Type VIII at the top; subsequent cells, for simplicity, were designed *either* for a rising or a falling boundary. The platinum leads were soldered to stout copper wires which lead to a Lucite distributor plate at the top of the cell; the wires were enclosed in glass tubes which carried the shielding. The distributor plate carried sockets for the electrodes and an additional pair for a variable resistance which permitted the oscillator and amplifier (see below) to operate without passing alternating current through the cell.

The cell was mounted in an oil-bath, operating at 25.00 ± 0.01°, and cadmium and silver–silver chloride electrodes served as anode and cathode. The indicator concentrations were a few per cent. below the Kohlrausch values[5,11] for NaCl and LiCl, and a few per cent. above with KIO_3 and $NaIO_3$; the preparation of the salts and the solutions has been described previously.[2,10] To clean, the cell was washed with redistilled carbon tetrachloride, ethanol and water, then repeatedly with distilled and conductivity water; it was then drained and dried with a stream of dried filtered air. Periodically, before the final washing, the cell was allowed to stand filled with 20% hydrochloric acid to remove surface alkalinity. In general, the solvent conductance measured in the cell differed only negligibly from that of the stabilized conductivity water used in making up the solutions, *viz.*, $0.7–0.8 \times 10^{-6}$.

One essential precaution was the removal of any moisture from the inside of the glass tubes which enclose the copper wires leading from the distributor plate to the microelectrodes. To do this, the tubes were flushed with anhydrous ethanol and dried with dried, filtered air immediately before filling the cell. In addition, particularly in humid weather, it was found necessary to dehumidify the laboratory if leakage of the direct current through the microelectrodes to the grounded shielding on the glass tubes was to be avoided.

(9) L. G. Longsworth, THIS JOURNAL, **54**, 2741 (1932).

(10) R. W. Allgood, D. J. LeRoy and A. R. Gordon, *J. Chem. Phys.*, **8**, 418 (1940).

(11) A. R. Gordon and R. L. Kay, *ibid.*, **21**, 131 (1953).

(12) Supplied by the Fischer and Porter Co., Hatboro, Pa.

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The a.c. circuit is indicated in Fig. 1. Here R_c is the resistance across the channel; C_1 and C_2 are 0.02 μf. condensers (rated at 10,000 working volts, leak resistance >> 50,000 megohms); O is a Hulett–Packard model AB oscillator, normally operating at 20,000 c.p.s.; R_2 is a 6000 ohm voltage divider with taps in 0.05 volt steps up to 1 volt; and R_1 is the amplifier feed resistor. A is a Williamson amplifier (maximum voltage gain 1400 at 20,000 c.p.s., internal input impedance 1.5 megohms); in general, the input, feed resistor and amplification were adjusted to give approximately full scale deflection on the recording ammeter when the leading solution was between the electrodes. R_3 is a 500 ohm load-matching resistor, T a Texas Instrument Co. Type 201 transistor, C_3 an 0.8 μf. condenser, and M an Esterline–Angus Model AW recording ammeter (1 milliamp. full scale deflection, internal resistance 1400 ohms, chart speeds 2.5 mm./sec. and 2.5 mm./minute). We wish to thank Dr. F. S. Goulding of Atomic Energy of Canada Limited, Chalk River, Ont., for suggesting the rectifier circuit to us. To correlate the time scale of the chart with the effective time for the run, a spring-returned stylus was used to record on the chart two datum points, one just before the boundary passed a given pair of electrodes, the second just after it had passed; tests showed that 30 second intervals on the chart were correct to 0.2 sec. or better.

Results

A typical trace for a 0.01 N KCl/0.0069 N KIO_3 boundary is shown in Fig. 2; the current here is 0.36 milliamp. and the actual boundary velocity slightly over 0.04 mm./sec. Zero signal is at the bottom of the chart, which is moving from left to right, the time arcs corresponding to 5 second intervals. At first glance, the duration of the event—approximately 65 seconds—is surprising, but while any calculation of the distribution of the current lines is impossible, an extremely naive estimate of the column of solution involved in the resistance measurement can be made. Since the resistance across the channel for 0.01 N KCl is approximately 12000 ohms, the factor "A/l" is 0.6 mm. If the current were confined vertically to the plane of the electrodes and horizontally to their width, the ratio of length to width would be of the order of 2.5; if this ratio were valid for the actual measurement, the corresponding "height" would be 1.5 mm., which is certainly an underestimate. Moreover, MacInnes and Longsworth's eq. 49 shows[7] that if the thickness of the boundary be taken as the distance from the plane in which the concentration of the indicator is 2% of that of the leading salt, to the plane where the concentration of the leading salt is 2% that of the indicator, the boundary thickness for the conditions obtaining here will be approximately 0.16 mm.; thus the boundary must move at least 1.66 mm. for the transition from leading to indicator solution to be complete, corresponding to an interval of 40 seconds or more—an estimate not inconsistent with the time actually observed.

In addition, if the trace be replotted on rectangular coördinate paper, and the tangent be drawn at the point of inflection, the slope of the tangent should be a measure of boundary velocity near the first moment of the boundary, and for given leading and indicator solutions and fixed a.c. circuit characteristics, the slope should be proportional to the direct current; this is in fact found to be the case.

An approximate circuit analysis shows that with the a.c. circuit components used here, the signal for fixed input voltage should be proportional to $R_1/(R_1 + R_c)$. Thus, with R_1 = 1400 ohms, as in the case in Fig. 2, the ratio of the signal when 0.01 N KCl is between the microelectrodes to that when it has been replaced by 0.0069 N KIO_3 solution,[11] should be 1.80; as is evident from the chart, the actual ratio is some 10% greater than this, and this is in general found to be the case, the observed signal ratio being greater than that computed from R_1, the cell factor and the specific conductances of the two solutions. The explanation lies in the fact, as shown by tests with known resistances in place of R_c, that the response in the circuit is not strictly linear, the recorded signal being somewhat more than proportional to $R_1/(R_1 + R_c)$. However, for given leading and indicator solutions, the observed ratio for a pair of electrodes is reproducible to 1%, is independent of the direct current passing, of the a.c. input voltage, and of the amplification, and varies only a few per cent. from one pair of electrodes to another, *i.e.*, essentially the same phenomenon is occurring at all the electrode pairs.

Since it is the time required for the boundary to move from one electrode pair to another that is the experimentally significant quantity, this suggests that any easily identified point on a trace be used to time the event and thus to compute the interval. The one we have chosen is that corresponding to the average of the signals when only leading or indicator solution is between the electrodes. In Fig. 2, this corresponds to an ordinate of 73.5 units with an uncertainty in the time of less than 0.5 second.

As an example of the results that may be obtained in this way, a volume calibration between two pairs of electrodes is summarized in Table I. With this cell, both rising and falling boundaries could be used; the values of t_+ (to which the appropriate solvent and volume corrections[7] were applied) on which the calibration is based were 0.4902 and 0.3918 for 0.01 N KCl[9,10] and 0.01 N NaCl,[9,13] respectively. It is at once evident from the table that the measured volume is independent of the leading ion, of the indicator, of the direct current employed, whether the boundary is anion or cation, and whether it is rising or falling; in other words, the volume is a function only of the cell geometry. It should be mentioned that with the later cells, designed for use with either a rising or a falling boundary, the reproducibility for a given leading solution was definitely better—a part in four thousand, which is the precision at best of transference data. We believe this was due in these cells to the elimination of the shearing stopcock from the closed side of the cell.

It is naturally pertinent to enquire as to the disadvantages and advantages of the technique as described above—particularly in comparison with optical methods of following boundary movement. Its first and most obvious disadvantage lies in the difficulties always encountered with complicated high resistance circuits—here in particular possible leakage of the direct current through the microelectrodes to ground through the shielding of the a.c. leads. A second is the fact that the recorded trace can give no information as to the actual boundary structure such as is supplied by the famil-

(13) R. W. Allgood and A. R. Gordon, *J. Chem. Phys.*, **10**, 124 (1942).

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iar schlieren technique. On the other hand, there is much greater flexibility here in the choice of indicator ion; the ion must of course be slower than the leading ion and either lighter or heavier depending on the type of boundary, but any requirement as to its optical properties in the solvent disappears. For example, the KCl/LiCl boundary of Table I would be completely invisible under the conditions obtaining here, while the trace obtained is almost indistinguishable from that of Fig. 2. Again, with any optical procedure, there is always a minimum current below which the boundary becomes too diffuse to be observed; here this restriction disappears. It is true that halving the current, for example, and consequently the boundary velocity, roughly doubles the uncertainty in fixing the midpoint of the trace; however, the interval from one electrode pair to the next is also doubled, so that percentually the precision of the computed volume calibration or transference number is unaffected; this can be a matter of real importance where Joule heating is a serious factor. Finally, the method can be employed at concentrations well below those accessible to the optical methods and, as is shown in the accompanying paper, should be generally applicable to non-aqueous solvents.

TABLE I

VOLUME CALIBRATION, CELL λ, 25.00°

Electrode pair No. 2–Electrode pair No. 5

Leading soln., 0.01 *N* KCl			Leading soln., 0.01 *N* KCl		
Indicator	Current, milliamp.	Vol., ml.	Indicator	Current, milliamp.	Vol., ml.
KIO_3	0.11	0.6109	LiCl	0.36	0.6108
KIO_3	.36	.6109	LiCl	.36	.6113
KIO_3	.36	.6112	LiCl	.36	.6114
KIO_3	.36	.6110	Leading soln., 0.01*N* NaCl		
KIO_3	.36	.6106	$NaIO_3$	0.24	0.6112
KIO_3	.66	.6108	$NaIO_3$	.36	.6109
NaCl	.36	.6106	$NaIO_3$	.56	.6109
NaCl	.56	.6110	Mean 0.6110 ± 0.0002		

In conclusion, we wish to express our thanks to the Advisory Committee on Scientific Research of the University of Toronto for a grant in aid, and to the National Research Council of Canada for the award of studentships to J. W. L. and to J. R. G.

TORONTO, ONTARIO, CANADA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

The Transference Numbers of Sodium and Lithium Chlorides in Anhydrous Ethanol at 25°

BY J. R. GRAHAM AND A. R. GORDON

RECEIVED JANUARY 14, 1957

The conductimetric method of following boundary movement has been used to determine the transference numbers for NaCl and LiCl in anhydrous ethanol at concentrations from 0.001 to 0.0025 *N*. Triiodobenzoate served as a satisfactory rising anion indicator, the observed t_- satisfying the usual experimental criteria, but it was not possible to find a satisfactory cation indicator in this solvent. Moreover, even the anion boundaries showed evidence of boundary instability at 0.0005 *N*. However, the Longsworth function, computed on the basis of ionic rather than stoichiometric concentration, is linear in the ionic concentration, thus permitting an unambiguous extrapolation to infinite dilution. While the results are not as precise as those obtained with water and methanol as solvents, they nevertheless demonstrate, we believe, that reasonably reliable transference data can be obtained in many if not most anhydrous solvents.

In this paper we report the results of transference measurements, effected by the technique described in the preceding paper,[1] on sodium and lithium chlorides in anhydrous ethanol at 25°. The reasons for selecting these two salts were (a) that their ions were of the simple noble-gas type, and (b) that transference and ion conductance data were available for them in water[2] (over a range of temperatures) and in methanol.[3] While for purposes of continuity it was desirable to investigate their transport properties in another solvent in the same homologous series, the fact remains that the relatively low solubility of the salts and their low conductivity in ethanol raised special problems—in particular that of finding suitable indicator ions. The fact that it was possible to carry out these measurements at all, argues (we believe) that transference measurements are generally possible with this procedure in non-aqueous solutions subject to certain restrictions discussed below.

Experimental

The general technique already has been described.[1] In general, the amplifier feed resistance R_1 (see Fig. 1 of ref. 1) was set at about one tenth of the resistance across the channel R_c when the leading solution was between the microelectrodes and, owing to the relatively low specific conductance of the solutions, the boundary velocities were considerably lower than those employed in aqueous solutions to minimize Joule heating. The preparation and purification of solvent, salts and solutions are discussed in the accompanying paper.[4] For rising anion boundaries[5] sodium and lithium triiodobenzoate served as suitable indicators; in fact the traces recording boundary passage are almost indistinguishable from those obtained with similar boundary velocities in aqueous solution; see for example Fig. 2 of ref. 1. The 2,3,5-triiodobenzoates were prepared by the pro-

(1) J. W. Lorimer, J. R. Graham and A. R. Gordon, THIS JOURNAL, **79**, 2347 (1957).

(2) (a) H. S. Harned and B. B. Owen "The Physical Chemistry of Electrolytic Solutions," 2nd Edition, Reinhold Publ. Corp., New York, N. Y., 1950, p. 590; (b) G. C. Benson and A. R. Gordon, *J. Chem. Phys.*, **13**, 473 (1945).

(3) (a) J. A. Davies, R. L. Kay and A. R. Gordon, *ibid.*, **19**, 749 (1951); (b) J. P. Butler, H. I. Schiff and A. R. Gordon, *ibid.*, **19**, 752 (1951); (c) R. E. Jervis, D. R. Muir, J. P. Butler and A. R. Gordon, THIS JOURNAL, **75**, 2855 (1953).

(4) J. R. Graham, G. S. Kell and A. R. Gordon, *ibid.*, **79**, 2352 (1957).

(5) The volume calibrations between the various pairs of electrodes are based on the values of t_+ for KCl in aqueous solution at 25° 0.4902 and 0.4901 for 0.01 *N* and 0.02 *N*, respectively; see footnote 3 and Table II of ref. 1.

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cedure described by Davies, Kay and Gordon[3a]; in the case of the lithium salt, however, the reaction between the bicarbonate and the purified acid required digestion at 60° for several hours. It should be noted that the measured transference numbers recorded in the tables are based on the time intervals between electrode pairs 1–4, 2–4, 1–5 and 2–5 to minimize the percentage error in the elapsed time; the intervals 2–3 and 3–4 were only employed to detect any significant change in boundary velocity with boundary movement. Volume corrections for the concentrations employed here are entirely negligible, and solvent corrections amount at most to a few units in the last decimal place.

While the anion transference numbers so obtained satisfied all internal criteria for a stable boundary—absence of "progression," independence of current and of initial indicator concentration over an appreciable concentration range[6]—we were unable to find suitable cation indicators. Falling 0.002 *N* NaCl/LiCl boundaries gave traces approximately ten times as long as those for the anion boundaries, and the duration of the "event" tended to increase as the boundary moved down the channel. Since the duration is primarily a function of the spread of the a.c. current lines,[1] rather than of physical boundary thickness, this raised serious doubts as to whether a boundary in the usual sense of the term existed at all, in spite of the fact that the computed t_+ was consistent within half a per cent. or so with the known value of t_-. If one assumes that cations are more highly solvated than anions, a possible explanation is that the random passage of a cation across the boundary would produce a more serious disturbance than would a similar passage of an anion across an anion boundary, particularly when, as is the case here, density stability is slight. Dodecylammonium chloride as indicator showed similar behavior, while hyamine 1622 chloride with a rising boundary showed an erratic variation of apparent transference number with boundary movement and again a steady increase in the length of the trace. Cadmium chloride as an indicator for rising cation boundaries was eliminated since it proved from rough conductance measurements to be such a weak electrolyte that it was impossible to maintain even an approximately constant direct current during a run.

It should also be noted that when rising 0.0005 *N* NaCl boundaries with triiodobenzoate as indicator were studied, while the traces were not significantly different from those obtained at higher concentrations, the apparent t_- varied erratically as the boundary moved up the channel. This was unquestionably due in part to difficulty in setting the shearing stopcock correctly, since the same behavior was noted at higher concentrations with a definitely incorrect setting; possibly a more sophisticated method of forming the junction such as that employed by Longsworth[7] might eliminate this difficulty, although the possibility of leakage with his apparatus, even with the lithium stearate lubricant[3a] used here, might be serious. A second possibility is that at high dilutions with consequently slight density stability, turbulent electroendosmotic flow may disturb the boundary, the effect being more pronounced the more dilute the solution. If this be the case, it puts a lower limit to the concentration at which moving boundary measurements are possible.

Results

As an example of the reproducibility of the measurements, the individual experimental results for 0.001 *N* NaCl are listed in Table I. Each measurement involves a solution prepared by dilution from a different stock solution[8]; the concentration of the NaCl solutions differed only negligibly from 0.001 *N* as far as variation of t_- with concentration was concerned. The first line of the table gives the initial value of the indicator concentration, the second the current in microamperes and the third the transference number corrected for solvent

(6) To take the case of 0.002 *N* NaCl as an example, the initial indicator concentration was varied from 0.0017 *N*, approximately the Kohlrausch value, to 0.002 *N* without appreciable effect on the measured t_-.

(7) L. G. Longsworth, THIS JOURNAL, **54**, 2741 (1932).

(8) In computing volume from mass concentrations, the density data of ref. 4 were employed.

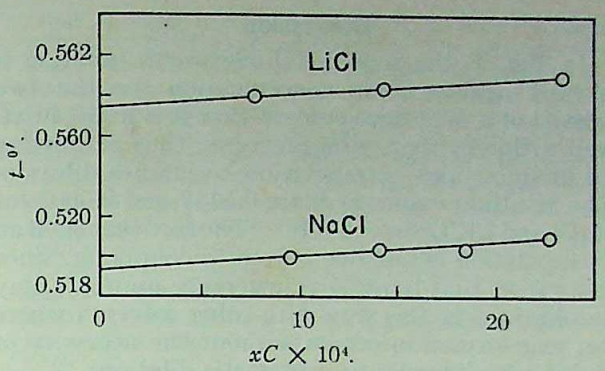

Fig. 1.—The Longsworth function plotted against ionic concentration.

conductance. It is apparent that within experimental precision t_- is independent of initial indicator concentration and of current; it is also evident (and this is generally true of the results obtained) that the reproducibility of the measurements is inferior to that obtained with water and methanol as solvents.

TABLE I

TRANSFERENCE NUMBERS FOR 0.001 *N* NaCl AT 25°

$10^4 C_i^\circ$	9.5	10.5	11.0	9.5	9.5	9.5	10.0
I, μamp	12	17	17	18	18	19	22
t	0.5208	0.5202	0.5205	0.5199	0.5204	0.5208	0.5204

The results for the other solutions are summarized in Table II. The first column gives the concentra-

TABLE II

TRANSFERENCE NUMBERS FOR NaCl AND LiCl IN ETHANOL AT 25°

$10^4 \times C$	No. of meas.	I, μamp.	t_-	x	$t_-^{0\prime}$
Leading soln., NaCl					
10	7	12–22	0.5204(3)	0.954	0.5190
15	4	16–26	.5209(3)	.938	.5192
20	7	22–46	.5212(3)	.925	.5192
25	2	42	.5218(1)	.913	.5195
Leading soln., LiCl					
9	2	12–16	0.5657(3)	0.968	0.5610
15	2	18–31	.5674(1)	.954	.5612
25	5	28–42	.5698(3)	.937	.5615

tion of the leading solution in equivalents/liter, the second the number of independent measurements, the third the current range in microamperes, and the fourth the mean value of t_- corrected for solvent conductance; the figure in brackets indicates the mean absolute deviation of the individual results from the average as printed. The fifth column gives the degree of dissociation of the ion pairs,[9] and the sixth the value of the modified Longsworth function[7] $t_-^{0\prime}$, computed on the basis of ionic rather than stoichiometric concentration

$$t_-^{0\prime} = (t_-\Lambda' + \sigma(xC)^{1/2})/(\Lambda' + 2\sigma(xC)^{1/2}) \quad (1)$$

where $\Lambda' = \Lambda_0 - (\vartheta\Lambda_0 + 2\sigma)(xC)^{1/2}$, and ϑ and σ are the Debye–Onsager coefficients 1.330 and 44.66, respectively.[4]

(9) The values of x were obtained from the values of ΔS of Table II of ref. 4 except for 0.0009 and 0.0025 *N*, when they were computed by means of eq. 4 of ref. 4 from the known value of the dissociation constant.

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Discussion

In Fig. 1, the modified Longsworth function is plotted against ionic concentration for the two salts, and it is at once evident that it is linear in xC well within experimental precision, thus permitting an unambiguous extrapolation to infinite dilution. The resulting values of Λ_0 are 0.5187 and 0.5607 for NaCl and LiCl, respectively. The fact that such an extrapolation is possible here is encouraging, since it suggests that limiting transference numbers may be obtained in this way with other solvents where ion pair formation occurs without the necessity of making measurements at fantastic dilutions.

It should also be noted, in contrast to results in aqueous solution, that although the transference numbers are greater than one half, the limiting slope is approached in both cases from above. Potassium chloride in methanol showed similar behavior,[3a] and we believe that about the only generalization that can be made, based on the results in the three solvents, is that the deviation from the limiting law at finite concentrations is numerically least when the transference numbers are close to one-half.

Smisko and Dawson[10] have recently reported transference numbers for KCNS solutions in ethanol, based on measurements in an autogenic cell; a discussion of the correlation of their results with ours, and of the mutual consistency of our NaCl and LiCl data, is reserved for the accompanying paper.[4] Suffice it to say here that while the ethanol data are not of the precision obtained with water and methanol as solvents, they nevertheless fix a limiting conductance for chloride ion in ethanol which is probably reliable to a few hundredth's of a conductance unit.

In conclusion we wish to express our thanks to the National Research Council of Canada for the award to J. R. G. of two studentships.

(10) J. Smisko and L. R. Dawson, *J. Phys. Chem.*, **59**, 84 (1955).

TORONTO, ONTARIO, CANADA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

Equivalent and Ionic Conductances for Lithium, Sodium and Potassium Chlorides in Anhydrous Ethanol at 25°

BY J. R. GRAHAM, G. S. KELL AND A. R. GORDON

RECEIVED JANUARY 14, 1957

The conductance of lithium, sodium and potassium chlorides in anhydrous ethanol has been determined for concentrations from 0.0001 to 0.0020 N. All three salts show definite ion-pair formation, the dissociation constants for the pairs (determined by the Shedlovsky procedure) being greatest as might be expected for LiCl and least for KCl. In conjunction with the transference numbers, the LiCl and NaCl results yield a limiting conductance for chloride ion of 21.85; this is probably reliable to 0.02 or 0.03 conductance units, and consequently should fix other limiting ion conductances within similar limits. The correlation of the ion conductances in ethanol with those in methanol and water is discussed.

If the transference measurements of the preceding paper[1] are to yield information as to ion conductances in ethanol solution, it is obvious that reliable equivalent conductances are necessary. Previous conductance studies of the alkali halides in ethanol have given an extraordinarily wide variation in conductance values. To take the case of Λ_0 for NaCl as an example, Goldschmidt and Dahll[2] give 46.5, Thomas and Marum[3] 43.0, and Barak and Hartley[4] 42.5. Admittedly, some of the spread is due to the methods of extrapolation employed (see below) but nonetheless such results indicate the necessity for measurements carried out under conditions much more carefully controlled than those obtaining in the earlier work. Here we report conductance data at 25° for lithium, sodium and potassium chlorides.

Experimental

The measurements were effected by the direct current method, developed in this Laboratory, employing the cells previously used with methanol[5] as solvent; their calibrations are based on the Jones and Bradshaw 25° 0.01 demal standard.[6] Bias potentials between the probe electrodes were in general no greater than in water and methanol, but great care had to be exercised, particularly in the more dilute solutions, to avoid the passage of any appreciable current through the probes as the result of significant off-balance in the initial setting of the potentiometer; if this occurred, the probes behaved erratically and had to be reanodized. It was also found impossible to determine the solvent conductance for ethanol by the direct current method; it was accordingly determined in a conventional conductance cell (cell factor 0.1005 cm.$^{-1}$) with an alternating current bridge. Work in methanol[5a] had shown that the two methods were in agreement to better than 1%.

The principal difficulty with ethanol is its preparation as a solvent with, at the same time, low water content and low specific conductance. The starting material was a Gooderham and Worts "anhydrous" alcohol, rectified by ethylene glycol distillation; it contained approximately 0.25% water, 0.01% esters and traces of aldehydes and acids, and its specific conductance was of the order 6×10^{-8} mho/cm. The procedure finally adopted was to reflux 4.5 l. of the starting material overnight under a 30-cm. Allihn condenser (condenser temperature 30°) while a slow stream of nitrogen (from which traces of oxygen, carbon dioxide and water vapor had been removed) bubbled through the charge; this removed the low-boiling impurities, which were taken off by a slight suction applied at the top of the condenser. The subsequent distillation was carried out under a slight positive pressure of the purified nitrogen, only a middle cut of 3 l. being retained. While this procedure left the water content unaltered, the specific conductance of the distillate was in general $0.5–0.8 \times 10^{-8}$ mho/cm.

(1) J. R. Graham and A. R. Gordon, THIS JOURNAL, **79**, 2350 (1957).

(2) H. Goldschmidt and P. Dahll, *Z. physik. Chem.*, **114**, 1 (1925).

(3) L. Thomas and E. Marum, *ibid.*, **143**, 191 (1929).

(4) M. Barak and H. Hartley, *ibid.*, **A165**, 272 (1933).

(5) (a) J. P. Butler, H. I. Schiff and A. R. Gordon, *J. Chem. Phys.*, **19**, 752 (1951); (b) R. E. Jervis, D. R. Muir, J. P. Butler and A. R. Gordon, THIS JOURNAL, **75**, 2815 (1953).

(6) G. Jones and B. B. Bradshaw, *ibid.*, **55**, 1780 (1933).

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To remove the water, a modification of the Lunt and Bjerrum[7] method was used. Grignard quality magnesium turnings were cleaned by refluxing with ethanol and a few iodine crystals for three hours; the liquid was then decanted and discarded, and traces of iodine were removed by repeated washings of the turnings with ethanol. This preliminary cleaning and removal of the iodine are essential, in our experience, if a final product of low specific conductance is to be obtained. The magnesium was then refluxed under purified nitrogen for 24 hours with 1.5 l. of previously dried purified alcohol to permit the magnesium ethoxide to form; the center cut from the first distillation was added, refluxed for 12 hr., and distilled under nitrogen, a center cut of 3 l. being retained. The specific conductance was unaffected by this treatment, but the water content of the distillate, determined by Karl Fischer titration,[8] was reduced in general to 0.001–0.002 weight %. Acid and ester analyses, carried out by A.O.A.C. procedures modified for trace amounts[9] and checked by tests of samples containing known amounts of ester and acid, showed that the distillate was neutral and contained less than 0.002% esters. The mercuric cyanide test of Hartley and Raikes[10] showed negligible amounts of acetone and acetaldehyde, and a spectroscopic analysis for magnesium was negative.

The density of the distillate, determined by means of a Shedlovsky and Brown[11] type pycnometer, at 25.000° was $0.78503_9 \pm 0.00001_2$ g./ml. (8 determinations). Osborne, McKelvey and Bearce[12] report 0.78505_8 for what was almost certainly a somewhat wetter alcohol, and Brunel, Crenshaw and Tobin[13] give 0.78505 for the mean of several drying procedures. If one employs Osborne, McKelvey and Bearce's data for the effect of water on density, our value for the anhydrous alcohol would be 0.78503_5. Any significant study of the effect of solution concentration on density is precluded by the narrow concentration ranges available; however density measurements show that for the concentrations of interest here the solution densities are given within two or three units in the fifth decimal place by $d = 0.78504 + AX$ where X is the salt concentration in moles/kg. solution and A is 0.04, 0.05 and 0.06 for LiCl, NaCl and KCl, respectively.

The salts were prepared as previously described,[5] except that in the final stage they were heated to temperatures slightly below the melting point instead of being fused. This was necessary owing to the extreme slowness with which they dissolved in ethanol; in general, the weighed sample of salt had to be refluxed under purified nitrogen for from 3 to 6 hours in spite of the fact that the strongest stock solutions were only 0.0025 N, well below the values quoted for saturation. The dilution technique, in particular the precautions taken against evaporation losses and contamination with air or water vapor have been previously described.[5]

There is one additional complication with this solvent in that its specific conductance, regardless of the method of storage and of the fact that its water content does not change with time, shows a steady increase (for several days at any rate) of approximately 0.6×10^{-8} mho/cm. per day. Curiously enough, aged samples of pure solvent, refluxed under the conditions obtaining when the salt was dissolved, showed a small but definite decrease in conductance and, for this reason, solvent determinations had to parallel as closely as possible the conditions obtaining in the preparation of the stock solutions and the solvent used for dilution.

Hughes and Hartley[14] report that for exceedingly small additions of water, the viscosity increases by 4% per 1% added water. A series of measurements with 0.001 N NaCl solutions showed that up to approximately 0.015% water content, the conductance decreased per % added water by the same amount, *i.e.*, decrease in conductance for this range of water content is apparently a viscosity effect, as postulated by Hughes and Hartley. The decreases were so slight—at most of the order of 0.02 conductance unit and consequently not much greater than the reproducibility of the measurements—that a detailed presentation of the results is hardly justified, but the effect is unquestionably a real one.[15] For higher water contents, there is a minimum in Λ at about 0.04 wt. %, the minimum being some 0.03 conductance units below the "anhydrous" value, with a subsequent steady increase in Λ until with 0.2% water, Λ has risen to the anhydrous value again; as Hughes and Hartley suggest, this is possibly the result of decreased ion-pair formation. Bezman and Verhoek[16] found somewhat similar behavior with addition of water to ethanolic solutions of ammonium chloride, but their minimum occurs in the neighborhood of 2% water. In any event, with the water contents normally obtaining in our solvents, the water effect on the equivalent conductance is relatively negligible, amounting at most to a few thousandth's of a conductance unit; it has nevertheless been applied where necessary in arriving at the values in the tables.

Results

Owing to the large number of individual measurements, only mean values for round concentrations are recorded. To illustrate the method used in obtaining these, the experimental data for 0.0002 N NaCl are summarized in Table I. The first line gives the concentration in equivalents/liter, each solution being prepared from a different stock solution, and the second the equivalent conductance. The third gives the value of the Shedlovsky function[17]

$$\Lambda'_0 = (\Lambda + 2\sigma C^{1/2})/(1 - \vartheta C^{1/2}) \qquad (1)$$

TABLE I

CONDUCTANCE DATA FOR 0.0002 N NaCl

10^4C	1.9965	1.9983	1.9804	2.0102	2.1404
Λ	39.710	39.719	39.749	39.694	39.613
Λ'_0	41.756	41.766	41.788	41.748	41.732
Λ'_0, 0 = 0.0002	41.756	41.766	(41.785)	41.750	71.756

where $\vartheta = 1.330$ and $\sigma = 44.66$ (see below). It must be emphasized that the Shedlovsky function as defined in eq. 1 has no theoretical significance for a solvent where ion-pair formation occurs, but it does provide a convenient method of interpolation owing to its relatively slight variation with concentration. From a large scale plot of Λ'_0 *vs.* C, $d\Lambda'_0/dC$ at 0.0002 N is -0.17×10^4 for the concentration range of the table, and the resulting values of Λ'_0 for $C = 0.0002$ are given in the last line. Thus, if the bracketed entry be ignored, Λ'_0 for 0.0002 N is 41.757 with a mean average deviation of 0.004; this corresponds to $\Lambda = 39.709$. Table I is typical of the precision and reproducibility of the results entered in Table II. Each entry in Table II is the mean of four or more independent measurements, each involving a different stock solution. The spread covering the individual results for a given concentration is of the same order as that of Table I (or less) for the more concentrated solutions and is not significantly greater for 0.0001 N.

(7) H. Lunt and J. Bjerrum, *Ber.*, **64**, 210 (1931).
(8) K. Fischer, *Z. angew. Chem.*, **48**, 394 (1935).
(9) Assoc. of Official Agric. Chemists "Official and Tentative Methods of Analysis," 6th ed., 1945, Chap. 16.
(10) H. Hartley and H. R. Raikes, *J. Chem. Soc.*, **127**, 524 (1925).
(11) T. Shedlovsky and A. S. Brown, THIS JOURNAL, **56**, 1066 (1934).
(12) N. S. Osborne, E. C. McKelvey and H. W. Bearce, *J. Wash. Acad. Sci.*, *11*, 95 (1912).
(13) R. F. Brunel, J. L. Crenshaw and E. Tobin, THIS JOURNAL, **43**, 561 (1921).
(14) O. L. Hughes and H. Hartley, *Phil. Mag.*, [7] **15**, 610 (1933).

(15) In estimating the effect, Λ was computed using the density data of Osborne, McKelvey and Bearce to correct for water content, and the Shedlovsky function Λ'_0 (see below) was then calculated. This has the advantage that Λ'_0 is relatively insensitive to the small variations in salt concentration inevitable in preparing a series of solutions.
(16) I. I. Bezman and F. H. Verhoek, THIS JOURNAL, **67**, 1330 (1945).
(17) T. Shedlovsky, *ibid.*, **54**, 1405 (1932).

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TABLE II

EQUIVALENT CONDUCTANCE DATA IN ETHANOL AT 25°

10^4C	1	2	5	10	15	20
	LiCl, Λ_0 = 38.90, K = 0.01795					
Λ	37.360	36.695	35.300	33.780	32.650	31.770
ΛS	38.710	38.570	38.135	37.585	37.130	36.780
	NaCl, Λ_0 = 42.16, K = 0.01250					
Λ	40.450	39.710	38.095	36.300	34.970	33.910
ΛS	41.840	41.040	40.995	40.170	39.500	38.945
	KCl, Λ_0 = 45.40, K = 0.00795					
Λ	43.465	42.535	40.530	38.290	36.640	35.350
ΛS	44.890	44.500	43.455	42.135	41.090	40.260

To extrapolate the Shedlovsky procedure[18] was employed. By a short series of successive approximations

$$S = 1 + z + z^2/2 + z^3/8 \qquad (2)$$

is computed where $z = (\vartheta\Lambda_0 + 2\sigma)\ (C\Lambda)^{1/2}/\Lambda_0^{3/2}$, and $\vartheta = 8.204 \times 10^5/(DT)^{3/2}$, $\sigma = 41.21/(\eta \cdot (DT)^{1/2})$.[19] For a solvent of dielectric constant[20] 24.3 and viscosity[21] 0.01084 poise, ϑ and σ are thus 1.330 and 44.66. The degree of dissociation x is then given by

$$x = \Lambda S/\Lambda_0 \qquad (3)$$

ΛS is next plotted against $\Lambda^2S^2f^2C$, where f is the limiting law activity coefficient,[19] given by $\log f = -\alpha(xC)^{1/2}$; here $\alpha = 1.8246 \times 10^6/(DT)^{3/2} = 2.9585$. The plots should be linear, with intercept Λ_0 and a slope given by $-1/K\Lambda_0$, where K, the dissociation constant of the ion pairs is defined by

$$K = f^2x^2C/(1 - x) \qquad (4)$$

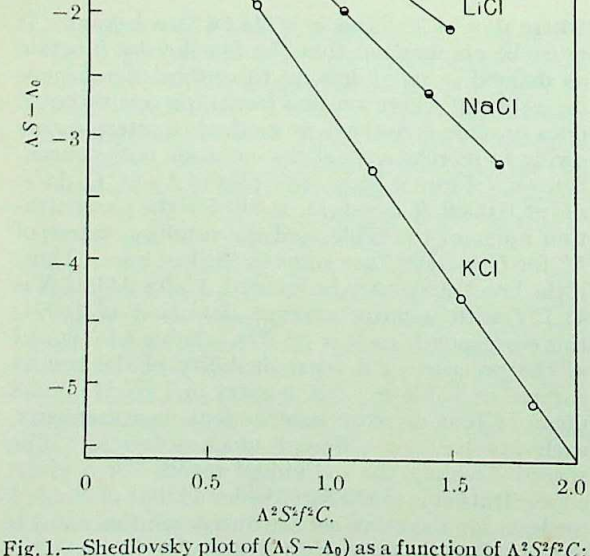

Fig. 1.—Shedlovsky plot of $(\Lambda S - \Lambda_0)$ as a function of $\Lambda^2S^2f^2C$: ○, KCl; ◒, NaCl; ●, LiCl.

Table II gives the values of Λ and of ΛS for the three salts (rounded to the nearest 0.005 conductance unit) as well as the corresponding Λ_0 and K, while Fig. 1 shows the Shedlovsky plot of the data, the ordinates for economy of space being $(\Lambda S - \Lambda_0)$. The agreement is satisfactory, the individual points lying in general within 0.02 conductance unit (or better) of the lines as drawn; the only notable exception is for the most concentrated KCl solution where the discrepancy is 0.06 unit.

It should perhaps be noted that if Λ be plotted against $C^{1/2}$—a procedure frequently employed in the past, for example by Barak and Hartley[4]—the plot is definitely S-shaped. To take the case of NaCl as an example, a "best" straight line can be drawn representing the experimental data within 0.05 conductance unit or so, but the extrapolated Λ_0 is 42.35, a fifth of a unit in error. The result so obtained, however, agrees probably as closely as can be expected with Barak and Hartley's 42.5, and the slope, 190, is in reasonable agreement with the value, 197, quoted in their Table IV. Nevertheless, one must question the validity of conclusions as to ion-pair formation, etc., based on such a procedure.

TABLE III

LIMITING ION CONDUCTANCES AND CONDUCTANCE–VISCOSITY PRODUCTS AT 25°

	Li^+	Na^+	K^+	Cl^-
$\lambda^0_{\pm s}$, C_2H_5OH	17.05	20.31	23.55	21.85
$(\lambda^0_{\pm s} \cdot \eta)$, C_2H_5OH	0.185	0.220	0.255	0.237
$(\lambda^0_{\pm s} \cdot \eta)$, CH_3OH	.217	.246	.285	.285
$(\lambda^0_{\pm s} \cdot \eta)$, H_2O	.346	.448	.658	.683

TABLE IV

LIMITING ION CONDUCTANCE RATIOS

Solvent and temp., °C.	Li^+/Na^+	Na^+/K^+	Na^+/Cl^-	K^+/Cl^-
H_2O, 25	0.772	0.682	0.656	0.963
H_2O, 45	.786	.713	.679	.952
CH_3OH, 25	.881	.863	.863	1.000
C_2H_5OH, 25	.839	.862	.929	1.078

If the values of Λ_0 for NaCl and LiCl be combined with the l^0 of the preceding paper,[1] one obtains 21.87 and 21.82, respectively, as the limiting conductance for chloride ion. The agreement is not as close as was obtained with methanol as solvent,[5a] but the mean, 21.85, is probably reliable to ±0.02 or 0.03 conductance unit. The corresponding λ^0_+ for the cations are summarized in Table III. Smisko and Dawson[22] have reported a limiting conductance for K^+ of 23.4; this is based on their value of l^0_+ for KCNS of 0.4612 and a Λ_0 for the salt of 50.8, computed by them from Barak and Hartley's data[4] by means of a Shedlovsky extrapolation; their result probably agrees with ours as closely as can be expected in view of the uncertainties of the conductance data they were forced to employ.

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(19) G. G. Manov, R. G. Bates, W. J. Hamer and S. F. Acree, *ibid.*, **65**, 1765 (1943).

(20) "Table of the Dielectric Constants of Pure Liquids," Nat. Bureau of Standards Circular No. 514, 1951, p. 8.

(21) H. Goldschmidt and H. Aarflot, *Z. physik. Chem.*, **112**, 371 (1926).

(22) J. Smisko and L. R. Dawson, *J. Phys. Chem.*, **59**, 84 (1955).

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Discussion

Table III gives the limiting conductances and the conductance–viscosity products for the four ions.[23] It is at once apparent that while the Walden rule (as might be expected) is not obeyed, the variation in the product on passing from methanol to ethanol is considerably less than on passing from water to methanol, and is moreover not as great for the three cations as for chloride.

In Table IV are the limiting conductance ratios for the ions in water at 25 and 45° and in the two alcohols. It was earlier pointed[5b] out that viscosity effects on passing from one solvent to another should cancel to some extent in the ratio, if the ions compared were of the same sign and charge. A glance at Table IV shows at once, however, that no simple generalization as to the conductance ratio can be made. In all cases, there is an increase in the ratio of the conductance of the slower to the faster cation with rise in temperature, *i.e.*, with decrease in dielectric constant, and the same is true on going from water to methanol. On passing from methanol to ethanol, a solvent of still lower dielectric constant, however, the Na^+/K^+ ratio is unaltered, while that for Li^+/Na^+ actually decreases. Thus there does not seem any obvious dependence of the ratio on solvent dielectric constant, and this of itself would seem to bargain out any purely electrostatic picture of solvent dipole–cation interaction. It is true that the use of the macroscopic dielectric constant[24] as a rough measure of solvent–ion interaction and consequently of the ion size effective in transport is a gross and possibly unjustifiable simplification. A more sophisticated treatment such as that used by Gilkerson[25] in his recent study of the effect of solvent properties, in particular the dipole moment, on the ion-pair dissociation constant, however, does not seem hopeful, since it would involve assumptions as to the local dielectric constant effective in the interaction between the ion and the innermost layer of solvent dipoles. It should also be noted that while there is a definite trend in the ratio Na^+/Cl^-, this is not the case for K^+/Cl^-. If as relatively simple a quantity as the limiting conductance ratio for a pair of noble gas type ions, shows such individualistic behavior with three solvents as closely related as water and the two alcohols, it indicates (we believe) that any satisfactory answer to the problem of ionic mobility as a function of solvent properties is still remote.

Finally, it should be noted, however, that the ion-pair dissociation constants for the three salts lie in the order expected, *i.e.*, the salt with the smallest crystallographic and consequently the largest solvated radius for the cation shows the smallest tendency toward ion-pair formation.

In conclusion, we wish to express our thanks to the National Research Council of Canada for the award of studentships to J. R. G. and G. S. K.

(23) The water and methanol data are from Tables IV and V of ref. 5b; see also Benson and Gordon, *J. Chem. Phys.*, **13**, 473 (1945).

(24) P. Van Rysselberghe and R. M. Fristrom, THIS JOURNAL, **67**, 680 (1945).

(25) W. R. Gilkerson, *J. Chem. Phys.*, **25**, 1199 (1956).

TORONTO, ONTARIO, CANADA

[CONTRIBUTION FROM THE COATES CHEMICAL LABORATORY, LOUISIANA STATE UNIVERSITY]

Adsorption Kinetics and Electrode Processes

BY PAUL DELAHAY AND ISAAC TRACHTENBERG[1,2]

RECEIVED DECEMBER 11, 1956

The kinetics of adsorption on electrodes is studied for substances which are not reduced or oxidized at the electrode. Adsorption rates are derived for the plane electrode with control by semi-infinite linear diffusion, the streaming mercury electrode, and electrodes in stirred solution. Adsorption at the dropping mercury electrode is also considered briefly. To simplify the treatment it is assumed either (a) that the concentration of adsorbate is so low as to allow linearization of the isotherm, or (b) that the concentration of adsorbate is so large as to correspond to full coverage. In the range of concentrations in which the isotherm can be linearized, adsorption with diffusion control is a slow process and the equilibrium surface concentration is reached only after a long time (perhaps 30 min.). This conclusion is verified experimentally by differential capacity measurements for the adsorption of *n*-hexyl alcohol on a hanging mercury drop in 1 *M* potassium nitrate. Conversely, the streaming mercury electrode is essentially free of adsorbate. Implications are discussed for double layer capacity measurements, electrocapillary curves studies, electrochemical kinetics and polarography. Maxima and minima and other features of current–time curves during drop life in polarographic reductions in presence of an adsorbable species are accounted for; and the dependence of limiting currents on the head of mercury is interpreted. Experimental results are given for the reduction of Cu(II) in 0.5 *M* sodium citrate in presence of quinoline. Experimental methods are discussed, and a simple and accurate bridge for differential capacity measurements without isolation transformer is described.

Introduction

The characteristics of electrode processes often are affected by the adsorption of substances not directly involved in the electrode reaction. For instance, the exchange current and the transfer coefficient for the discharge of cadmium ion on cadmium amalgam vary when hexyl alcohol is added to the cadmium ion solution. The partial coverage of the electrode by the adsorbed substance causes an increase in actual current density and a concomitant increase in overvoltage. The variation of kinetic parameters and the increase in actual current density account for the distortion of current–potential curves which results from the addition of an adsorbable species such as a polar organic substance. If the exchange current is large enough, current–potential curves may not be altered because the decrease in the rate of the electrochemical reaction is not sufficient to cause a

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(2) Predoctoral fellow 1955–1957.

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departure from so-called reversible behavior.[3] Another effect of adsorption of polar organic substances is the decrease of limiting currents which otherwise would be mass transfer controlled.

These effects have been studied in detail[4-13] but, if one excepts studies of adsorption by electrolysis with superimposed alternating current[14-16] (no claim to a comprehensive literature survey is made), mass transfer of the adsorbate has generally not been considered, and it has been assumed tacitly that there is no concentration "polarization" of the adsorbate. In other words it is generally assumed that the surface concentration has the equilibrium value corresponding to the concentration of adsorbable substance in the bulk of the solution far from the electrode. This assumption often cannot be made[17] as will be apparent from this work, and a study of the kinetics of adsorption with mass transfer control is of interest. This study is reported here (a) for control by linear diffusion, (b) for the dropping mercury electrode, (c) for the streaming electrode and (d) for stirred solution. Implications in double layer capacity measurements, electrocapillary curve studies, electrochemical kinetics, and polarography are considered.

Control by Semi-infinite Linear Diffusion

Boundary Value Problem.—We consider the adsorption of a substance on a plane electrode with mass transfer controlled by semi-infinite linear diffusion. The surface of the electrode is supposed to be uncovered initially; the modification in treatment for a partially covered electrode at time zero is trivial. The surface concentration Γ of adsorbable substance at time t is obtained by integrating the flux of adsorbate from 0 to t, *i.e.*

$$\Gamma = \int_0^t D(\partial C/\partial x)_{x=0}\, dt \qquad (1)$$

where D is the diffusion coefficient of the adsorbate, C the concentration of this substance, and x the distance from the electrode. If it is assumed that the adsorption process is so rapid that there is solely diffusion control, the surface concentration Γ is related to the volume concentration at the electrode surface, $C_{x=0}$, by the adsorption isotherm. This simplification is quite justified since it has been found by the alternating current method[14-16] that the adsorption of many polar organic substances on a mercury electrode is purely diffusion controlled. For other metals there might be partial control by the kinetics of adsorption, but this complication will not be considered here. Thus

$$\Gamma = \frac{\Gamma_m C}{a + C} \qquad (2)$$

where Γ_m is the surface concentration for maximum coverage, and a is a parameter which is characteristic of the isotherm.

The combination of (1) and (2) yields the boundary condition for which Fick's equation must be solved. Furthermore, one has $C = C^0$ for $x \geqslant 0$ and $t = 0$; and $C \to C^0$ for $x \to \infty$ and $t \geqslant 0$, C^0 being the bulk concentration of adsorbate.

Solutions are discussed below for the following two cases: (a) The adsorption isotherm can be linearized,[18] *i.e.*

$$\Gamma = KC \text{ with } K = \Gamma_m/a \qquad (3)$$

and (b) the case in which C^0 is so large that $\Gamma \approx \Gamma_m$ even when $C_{x=0} \ll C^0$. The general case is not treated because of mathematical difficulties. A general solution could be obtained by means of computer calculations, but the essential ideas can be presented in a simple treatment.

Variations of Concentration for the Linearized Isotherm.—The ratio of concentrations C/C^0, as obtained by Laplace transformation[19] is

$$\frac{C}{C^0} = 1 - \exp\left[\frac{x}{K} + \frac{Dt}{K^2}\right] \operatorname{erfc}\left[\frac{x}{2D^{1/2}t^{1/2}} + \frac{D^{1/2}t^{1/2}}{K}\right] \qquad (4)$$

where "erfc" represents the complement of the error function. Variations of C/C^0 with the distance from the electrode are shown in Fig. 1 for different times after the beginning of the adsorption process and for the values $D = 0.5 \times 10^{-5}$ cm.^{2} sec.$^{-1}$ and $K = 5 \times 10^{-3}$ cm. (see Experimental Verification). The concentration in the immediate vicinity of the electrode approaches the bulk concentration C^0 only after a long time (1000 sec. or more), and *adsorption equilibrium is slowly attained.* The qualitative interpretation is simple: the gradient of concentration of adsorbate decreases continuously as adsorption proceeds, and the rate of diffusion drops accordingly.

(3) Reversible waves are observed in polarography when the rate constant at the standard potential for the electrode reaction is larger than 10^{-2} cm. sec.$^{-1}$. See P. Delahay, THIS JOURNAL, **75**, 1430 (1953); P. Delahay, "New Instrumental Methods in Electrochemistry," Interscience, New York, N. Y., 1954, pp. 83–85.

(4) J. Heyrovsky, F. Sorm and J. Foretj, *Collection Czechoslov. Chem. Communs.*, **12**, 11 (1947).

(5) K. Wiesner, *ibid.*, **12**, 594 (1947).

(6) M. Matyas, *ibid.*, **16**, 496 (1951).

(7) J. Koryta, *ibid.*, **18**, 206 (1953).

(8) J. Heyrovsky, *ibid.*, **19**, S 58 (1954); contains several references to previous work by this investigator and co-workers; see also references to studies of the effect of gelatin and similar substances.

(9) (a) M. A. Loshkarev and A. A. Kryukova, *Doklady Akad. Nauk SSSR*, **62**, 97 (1948); (b) *Zhur. Fiz. Khim.*, **23**, 209, 221, 1457 (1949); (c) **26**, 731 (1952).

(10) L. Gierst and D. Bermane, paper presented at the National Meeting of the Electrochemical Society, San Francisco, 1956; D. Bermane, Thesis, Brussels, 1955.

(11) V. V. Losev, *Doklady Akad. Nauk SSSR*, **107**, 432 (1956).

(12) For detailed reviews see A. N. Frumkin, *Z. Elektrochem.*, **59**, 807 (1955); *Doklady Akad. Nauk SSSR*, **85**, 373 (1952). Translation of the latter paper was made available by the Naval Research Laboratory, Washington, D. C.

(13) We do not consider the case in which the overvoltage is decreased by the addition of a foreign substance, as for hydrogen evolution upon addition of certain alkaloids.

(14) (a) A. N. Frumkin and V. I. Melik-Gaikazyan, *Doklady Akad. Nauk SSSR*, **77**, 855 (1951); (b) V. I. Melik-Gaikazyan, *Zhur. Fiz. Khim.*, **26**, 560, 1184 (1952). English translations kindly supplied by Dr. D. C. Grahame of Amherst College.

(15) T. Berzins and P. Delahay, *J. Phys. Chem.*, **59**, 906 (1955)

(16) W. Lorenz and F. Möckel, *Z. Elektrochem.*, **60**, 507 (1956).

(17) This does not necessarily invalidate conclusions previously derived because a systematic error on surface concentration may be unimportant.

(18) A linearized adsorption isotherm has been used in the treatment of electrolysis at constant current for an adsorbable reducible (or oxidizable) substance; see W. Lorenz, *Z. Elektrochem.*, **59**, 730 (1955).

(19) Set $u = C^0 - C$. The transform of the solution of Fick's equation is $\bar{u} = A \exp[-(s/D)^{1/2}x]$, A being an integration constant and s the parameter of the transform. The constant A is determined from the transform of (3), and there results $\bar{u} = C^0 \exp[-(s/D)^{1/2}x]/s^{1/2}[(D^{1/2}/K) + s^{1/2}]$. The inverse transform is available in tables; see R. V. Churchill, "Modern Operational Mathematics in Engineering," McGraw-Hill Book Co., Inc., New York, N. Y., 1944.

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May 20, 1957

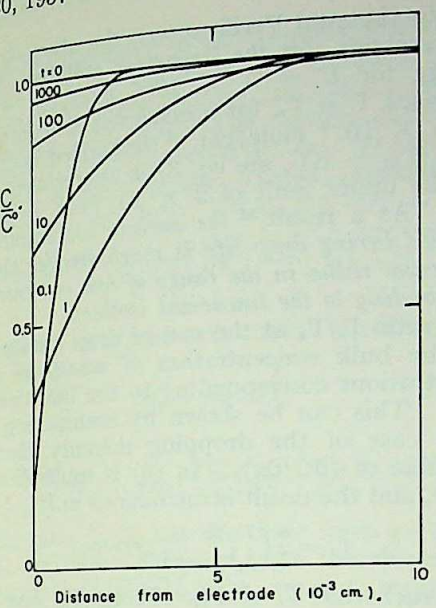

Fig. 1.—Variations of C/C^0 with distance from electrode for different times (in seconds) after the beginning of adsorption and for control by semi-infinite linear diffusion (data in text).

The surface concentration Γ_t at time t is readily obtained from (4) by noting that, according to (3), $\Gamma_t = KC_{x=0}$. Thus

$$\frac{\Gamma_t}{\Gamma_e} = 1 - \exp\left(\frac{Dt}{K^2}\right)\operatorname{erfc}\left(\frac{D^{1/2}t^{1/2}}{K}\right) \qquad (5)$$

where Γ_e is the equilibrium surface concentration for the bulk concentration C^0, *i.e.*, $\Gamma_e = KC^0$ (see eq. 3). The function in (5) is tabulated in Carslaw and Jaeger.[20] The ratio Γ_t/Γ_e, which is equal to zero for $t = 0$, approaches unity as t tends to infinity. The value of the argument for which there is virtually complete coverage is readily deduced from (5). For instance, $\Gamma_t/\Gamma_e \geq 0.99$ when $D^{1/2}t^{1/2}/K \geq 56.5$; *i.e.*, for $t > 1.6 \times 10^4$ sec. for the data of Fig. 1. Actually, convection interferes and shortens the time necessary to attain adsorption equilibrium.

The ratio Γ_t/Γ_e given by (5) is independent of the bulk concentration of adsorbable substance because the adsorption isotherm is linearized in this treatment. Thus, the rate of diffusion is doubled when C^0 is changed to $2C^0$, but Γ_e is also doubled and, consequently, Γ_t/Γ_e is independent of C^0. Actually, one would find that the time required to reach a given value of Γ_t/Γ_e decreases as C^0 increases if the *complete* adsorption isotherm (equation 2) were used.

Variations of Concentration for the Case in which $\Gamma_e \approx \Gamma_m$ even for $C_{x=0} << C^0$.—This case can be treated readily by the Ilkovic equation, as written for the case of semi-infinite linear diffusion.[21,22] It is assumed that the rate of diffusion is the same as for a process in which $C_{x=0} = 0$ for $t > 0$ and $C_{x=0} = C^0$ for $t = 0$. This major *simplification* is justified when the bulk concentration of adsorbate, C^0, is so large that the maximum coverage Γ_m is reached even when the volume concentration of adsorbate at the electrode surface is much smaller than C^0. One then has[23] per unit area

$$\left(\frac{\partial C}{\partial x}\right)_{x=0} = \frac{C^0}{(\pi Dt)^{1/2}} \qquad (6)$$

and in view of (1)

$$\Gamma_t = \frac{2D^{1/2}C^0}{\pi^{1/2}}t^{1/2} \qquad (7)$$

Equation 7 holds only for values for t for which $\Gamma_t \leq \Gamma_m$. The time τ at which $\Gamma_t = \Gamma_m$ is readily computed from (7). Actually, the value Γ_m is approached asymptotically and τ should be infinite, but a finite value is obtained in this very approximate derivation. Note that τ is inversely proportional to the square of the bulk concentration C^0.

Experimental Verification.—The differential capacity of an electrode is markedly changed by the adsorption of polar organic substances. The double layer can be represented by an equivalent circuit composed of two capacities in parallel: one capacity for the covered fraction of the electrode, and the other capacity for the uncovered fraction. On the basis of this model one can write

$$C = C_{\theta=1} + (C_{\theta=0} - C_{\theta=1})(1 - \theta) \qquad (8)$$

θ being the electrode coverage. Equation 8 holds for the range of potentials in which $c_{\theta=0} > c_{\theta=1}$. At time t, one has $\theta = \Gamma_t/\Gamma_m$, Γ_m being the maximum surface concentration of adsorbate. Likewise, $\theta = \Gamma_e/\Gamma_m$ for $t \to \infty$. Hence

$$\frac{\Gamma_t}{\Gamma_e} = \frac{C_{\theta=0} - C_t}{C_{\theta=0} - C_{t\to\infty}} \qquad (9)$$

Relationship 9 was applied to the adsorption of *n*-hexyl alcohol on a mercury hanging drop in 1 *M* potassium nitrate. Differential capacities were measured with an a.c. bridge (see Experimental). Values of $c_{t\to\infty}$ measured at -0.700 v. (*vs.* S.C.E.) are shown in Fig. 2. These values were

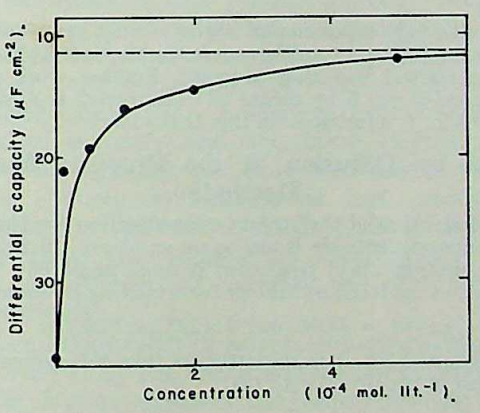

Fig. 2.—Differential capacity of hanging mercury drop in 1 *M* potassium nitrate with varying amounts of *n*-hexyl alcohol. Capacities were measured at -0.700 v. (*vs.* S.C.E.) and 25°.

reached after 30 to 60 minutes. The curve and the asymptote were traced to fit a Langmuir isotherm ($\Gamma_m = 8 \times 10^{-10}$ moles cm.$^{-2}$, $a = 2 \times 10^{-8}$ moles cm.$^{-3}$, see eq. 2). The capacity c_t was followed during adsorption, and the corresponding values of Γ_t/Γ_e (Fig. 3) were computed from (9).

The theoretical curve deduced from eq. 5 is also traced in Fig. 3 for the value $D^{1/2}/K = 0.05$ sec.$^{-1/2}$, *i.e.*, for $K = 4 \times 10^{-2}$ cm. with $D = 0.4 \times 10^{-5}$ cm.^{2} sec.$^{-1}$. This value of K corresponds to $\Gamma = \Gamma_m$ for $C = 2 \times 10^{-8}$ moles cm.$^{-3}$ for the linearized isotherm (Fig. 2). The value $\Gamma_m = 8 \times 10^{-10}$ mole cm.$^{-2}$, used in the calculation of K, was computed from the coverage of 21×10^{-16} cm.^{2} per molecule quoted by Adam[24] for the adsorption of an aliphatic alcohol with no compression of the film.

The marked departure from theory in Fig. 3 is to be expected since the theoretical curve corresponds to linear dif-

(20) H. S. Carslaw and J. C. Jaeger, "Conduction of Heat in Solids," Oxford University Press, London, 1947, p. 373.

(21) Private communication from Dr. J. E. B. Randles of the University of Birmingham, England.

(22) P. Corbusier and L. Gierst, *Anal. Chim. Acta*, **15**, 254 (1956), also evaluated the surface coverage on the dropping mercury electrode by application of the Ilkovic equation. See also ref. 7.

(23) (a) D. Ilkovic, *Collection Czechoslov. Chem. Communs.*, **6**, 498 (1934); (b) *J. chim. phys.*, **35**, 129 (1938).

(24) N. K. Adam, "The Physics and Chemistry of Surfaces," 3rd ed., Oxford University Press, London, 1941, p. 50.

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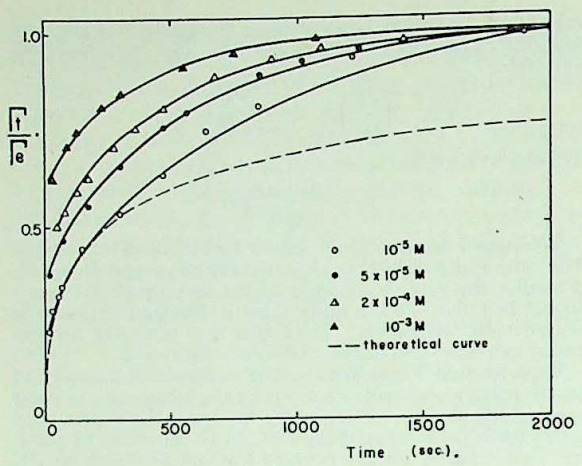

Fig. 3.—Variations of Γ_t/Γ_e with time for the conditions of Fig. 2. The theoretical curve is for the plane electrode.

fusion whereas the experimental results were obtained with a spherical electrode. The disagreement is in the right direction since the rate of diffusion for a spherical electrode is higher than for a plane electrode, all other conditions being the same. Convection also increased the rate of mass transfer of *n*-hexyl alcohol. Similar experiments were made with a mercury pool electrode, but the results were unreliable probably because of wetting of the mercury in contact with the wall of the container.

Figure 3 also shows that Γ_e is reached more rapidly when the bulk concentration of adsorbate is increased, *e.g.*, when the isotherm departs markedly from the linearized form (Fig. 2).

Although this experimental study is only semi-quantitative it definitely bears out the conclusion that adsorption with diffusion control is a slow process. Further work on the verification of eq. 5 by means of radiotracers is now being done by Mr. J. Truemper in this Laboratory.

Control by Diffusion at the Dropping Mercury Electrode

The derivation of the surface concentration for the dropping mercury electrode is the same as above, in principle, but the mathematical treatment is more involved. Fick's equation, as modified by Ilkovic for a moving boundary[23b]

$$\partial C/\partial t = D\partial^2 C/\partial x^2 + (2/3)(x/t)\partial C/\partial x \qquad (10)$$

is applied, and eq. 1 is rewritten to take into account the expansion of the drop (with $t^{2/3}$)

$$\Gamma = \frac{1}{t^{2/3}} \int_0^t Dt^{2/3}(\partial C/\partial x)_{x=0}\, dt \qquad (11)$$

This problem possibly could be solved by computer calculations or by making the same transformations that Smutek[25] used in his elegant treatment of irreversible polarographic waves. Calculations would be laborious, and only a simple analysis will be made here.

The rate of diffusion is increased because of the expansion of the drop, and Γ_t/Γ_e approaches unity more rapidly than eq. 5 predicts for linear diffusion. However, the time required to reach a given Γ_t/Γ_e should be of the same order of magnitude in both cases. From (5) one deduces that $\Gamma_t/\Gamma_e \approx 1$ for $(Dt)^{1/2}/K > 20$, *i.e.*, $D^{1/2}/K > 10$ sec.$^{-1/2}$ for a normal drop time of 4 sec. Since D is of the order of 0.5×10^{-5} cm.^{2} sec.$^{-1}$ in most cases (not for polyelectrolytes), the preceding condition becomes $K < 2 \times 10^{-4}$ cm. If one takes the realistic approximate value of $\Gamma_m = 10^{-9}$ mole cm.$^{-2}$ (see Experimental Verification), the above limit of K corresponds, *for the linearized isotherm*, to full coverage for $C = 5 \times 10^{-6}$ mole/cm.$^{-3}$. In most cases, $\Gamma \approx \Gamma_m$ for much lower concentrations than 5×10^{-6} mole/cm.$^{-3}$ (linearized isotherm), and K ($\Gamma_m = KC$, see eq. 3) is appreciably larger than the upper limit of 2×10^{-4} cm. prescribed above. As a result,[26] *the surface concentration of adsorbate during drop life is much smaller than the equilibrium value in the range of low concentrations corresponding to the linearized isotherm.*

The ratio Γ_t/Γ_e at the end of drop life increases with the bulk concentration of adsorbate above concentrations corresponding to the linearized isotherm. This can be shown by transposing eq. 7 to the case of the dropping mercury electrode. The value of $(\partial C/\partial x)_{x=0}$ in (6) is multiplied[23] by $(7/3)^{1/2}$, and the result is introduced in (11). Thus

$$\Gamma_t = \frac{6}{7}\left(\frac{7}{3}\right)^{1/2} \frac{1}{\pi^{1/2}} C^0 D^{1/2} t^{1/2} \qquad (12)$$

with t such that $\Gamma_t \leqslant \Gamma_m$. From (12) one calculates that the time τ at which $\Gamma_t = \Gamma_m$ is 0.3 sec. for $D = 0.4 \times 10^{-5}$ cm.^{2}/sec.$^{-1}$ and $C^0 = 10^{-4}$ mole/cm.$^{-3}$. This calculation which is *very* approximate corresponds to the most favorable conditions for equilibrium attainment.

Control by Mass Transfer at the Streaming Mercury Electrode

The electrode surface is continuously renewed at the streaming mercury electrode, and it is of interest to determine to what extent the mercury surface is free of adsorbable substance and can be regarded as "clean" in applications in electrochemical kinetics.

The surface concentration of adsorbate will be derived by adaptation of the result for linear diffusion as was done by Koryta[27] in his treatment of the limiting current for the streaming mercury electrode. On the basis of the assumptions listed below, Koryta obtained the simplified form of the equation for the limiting current which had been derived more rigorously by Rius and co-workers.[28,29]

The following assumptions are made: (a) the layer of solution which is adjacent to the mercury column moves at the same velocity as mercury; (b) this layer is thicker than the diffusion layer; (c) there is virtually no concentration gradient in this layer in the direction parallel to the axis of the mercury jet; (d) diffusion in the layer in the immediate vicinity of the mercury column is treated by Fick's equation for linear diffusion.

The number of moles adsorbed on the electrode is

$$N = \int_0^L D\left(\frac{\partial C}{\partial x}\right)_{x=0} 2\pi r\, dl \qquad (13)$$

where L is the length of the mercury column (supposed to be cylindric), l is the distance from the

(25) M. Smutek, *Collection Czechoslov. Chem. Communs.*, **20**, 247 (1955); see also H. Matsuda and Y. Ayabe, *Bull. Chem. Soc. Japan*, **28**, 422 (1955).

(26) One deduces from (5) that $\Gamma_t/\Gamma_e = 0.10$ for $D^{1/2}/K = 0.05$ sec.$^{-1/2}$ and $t = 4$ sec. This corresponds to the data used in the calculation of the theoretical curve in Fig. 3.

(27) J. Koryta, *Collection Czechoslov. Chem. Communs.*, **19**, 433 (1954).

(28) A. Rius, S. Polo and J. Llopis, *Anal. fis. y quim.* (Madrid), **45**, 1029 (1949).

(29) For a more precise analysis than that of Rius *et al.*, see J. S. Weaver and R. W. Parry, THIS JOURNAL, **76**, 6258 (1954); [illegible]

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tip of the capillary to the annular zone of height dl and r is the radius of the mercury jet. The gradient of concentration $(\partial C/\partial x)_{x=0}$ in (13) is evaluated from (4). The latter contains the variable t which is converted to l by noting that $t = l/v$ where v is the velocity (assumed to be uniform) of mercury. Thus, for $l = L$ one has

$$N = 2\pi rLKC^0\left\{1 - \exp\left(\frac{DL}{K^2v}\right)\operatorname{erfc}\left[\frac{1}{K}\left(\frac{DL}{v}\right)^{1/2}\right]\right\} \quad (14)$$

The value of N_e for adsorption equilibrium is in view of (3)

$$N_e = 2\pi rLKC^0 \quad (15)$$

and

$$\frac{N}{N_e} = 1 - \exp\left(\frac{DL}{K^2v}\right)\operatorname{erfc}\left[\frac{1}{K}\left(\frac{DL}{v}\right)^{1/2}\right] \quad (16)$$

The ratio N/N_e has the same form as the value Γ_t/Γ_e for linear diffusion, and the dimensionless parameter $(1/K)(DL/v)^{1/2}$ simply replaces the group $(Dt)^{1/2}/K$.

Because of the assumptions underlying eq. 16, this formula is only approximate but the order of magnitude of N/N_e can be evaluated from it. One has $N/N_e = 0.6\%$ for $D^{1/2}/K = 0.05$ sec.$^{-1/2}$ (see experimental part above), $L = 0.5$ cm., and $v = 50$ cm. sec.$^{-1}$. The electrode is thus essentially free of adsorbate. This could be advantageous in electrochemical kinetics where contamination of electrodes (even mercury or amalgam electrodes) is a serious obstacle to the precise determination of kinetic parameters for electrode processes.

The case in which the bulk concentration of adsorbable substance is so large as to correspond to virtual saturation of the electrode surface can be analyzed by following the same procedure as for linear diffusion. Details will not be given here because the result is of little practical value.

Control by Mass Transfer in Stirred Solution

The surface concentration of adsorbate is easily obtained on the basis of the concept of the Nernst diffusion layer. Thus

$$(\partial C/\partial x)_{x=0} = (C^0 - C_{x=0})/\delta \quad (17)$$

where δ is the thickness of the diffusion layer. By substituting in eq. 1 the gradient from (17) and by differentiating the result with respect to t, there follows a differential equation. The solution is

$$C = C^0\left[1 - \exp\left(-\frac{Dt}{K\delta}\right)\right] \quad (18)$$

Hence (see eq. 3), one has for the linearized isotherm

$$\frac{\Gamma_t}{\Gamma} = 1 - \exp\left(-\frac{Dt}{K\delta}\right) \quad (19)$$

The electrode is rather rapidly covered: $\Gamma_t/\Gamma_e = 0.98$ for $t = 120$ sec. and $D^{1/2}/K = 0.05$ sec.$^{-1/2}$ (see experimental part above), *i.e.*, for $D = 0.4 \times 10^{-5}$ cm.^{2} sec.$^{-1}$, and $\delta = 0.003$ cm. (an order of magnitude for not too vigorous a stirring).

Implications

Double Layer Capacity Measurements.—Double layer capacity measurements are somewhat in error when adsorption equilibrium is not attained for adsorbable species. This is the case in the study of the adsorption of polar organic molecules on mercury, when the differential capacity is measured with a dropping mercury electrode and the concentration of the organic substance is low. The correct dependence of the differential capacity on frequency is nevertheless obtained because the diffusion layer is much thicker than the layer in which the concentration of adsorbate varies periodically with time. However, the surface concentration of adsorbate is smaller than the equilibrium value corresponding to the bulk concentration. It is observed that the characteristic two desorption peaks in the curve differential capacity against potential disappear as the concentration of adsorbate is decreased. When adsorption equilibrium is not attained with the dropping mercury electrode, the peaks should disappear at higher concentrations than for curves obtained with the hanging mercury drop.

Likewise, differential capacities measured with the dropping mercury electrode for *low* electrolyte concentration (10^{-3} M or less) could be somewhat erroneous when the anion (or cation) is adsorbed. The theoretical analysis made above does not apply to this case because of complications resulting from migration and the structure of the double layer, but the conclusion about the slowness of adsorption is still qualitatively valid. The same comment can be made for polyelectrolytes.[30] Fortunately, most measurements of differential capacity for pure electrolytes are made at concentrations at which adsorption equilibrium is attained.

The value of the parameter $(Dt)^{1/2}/K$ for the system being investigated can serve as a guide in deciding whether adsorption equilibrium is attained: the condition $(Dt)^{1/2}/K > 20$ should be fulfilled (see eq. 5). A simpler test is to change the head of mercury and determine whether the differential capacity per unit area varies with drop time. When equilibrium is not attained, the coverage at the end of the drop life decreases with drop time (see section on Polarography below), and the differential capacity per unit area varies accordingly.

Non-attainment of adsorption equilibrium could be avoided by the use of a stationary mercury electrode, but progressive contamination of the electrode by traces of impurities might be very difficult to avoid. The hanging mercury drop is preferable to the mercury pool[31] because of better reproducibility of area. Another possible solution is the use of the rotating dropping mercury electrode developed for voltammetric studies by Stricks and Kolthoff.[32] However, the use of this electrode in precise measurements of differential capacities might not be practical.

Electrocapillary Curves.—The foregoing considerations can be transposed to the "drop weight" method for the determination of electrocapillary curves. Somewhat erroneous results can be expected particularly in studies at low concentration of electrocapillary active substances. Although results are then affected by a systematic error, they

(30) I. R. Miller and D. C. Grahame, THIS JOURNAL, **78**, 3577 (1956).

(31) A mercury pool electrode was recently used in differential capacity measurements: R. S. Hansen, R. E. Minturn and D. A. Hickson, *J. Phys. Chem.*, **60**, 1153 (1956).

(32) W. Stricks and I. M. Kolthoff, THIS JOURNAL, **78**, 2085 (1956).

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can be precise and analytical application is possible.[22]

Electrochemical Kinetics.—In general, traces of adsorbed impurities strongly affect kinetic parameters for electrode processes (exchange current and transfer coefficient). This source of error often cannot be entirely eliminated by careful purification of solution, and electrodes in which contamination is minimized are advantageous. The streaming mercury electrode is the best in this respect, but it is not very practical. The dropping mercury (amalgam) electrode is better than the hanging mercury drop because of the short duration of measurements and the continuous renewal of the mercury surface. It is suggested that kinetic parameters be measured for different times of the drop life (synchronization system), and that results be extrapolated to zero time to minimize the effect of impurity adsorption. This procedure should prove useful in the application of relaxation methods (potential- or current-step methods, electrolysis with superimposed a.c. component). The extrapolation method probably would fail for electrode reactions with gas evolution (hydrogen or oxygen overvoltage) because of the necessity of attainment of a steady state for the electrode coverage by gas. The dropping mercury electrode cannot be utilized in such a case anyhow.

The advantage of the dropping mercury electrode over the hanging mercury drop can be inferred from the recent work of Gerischer and Staubach[33] on the kinetics of the mercurous ion–mercury electrode. These authors observed that exchange currents obtained with a dropping mercury electrode for different concentrations of mercurous ion were about three times larger than the values for the hanging mercury drop. Two different methods, a.c. electrolysis and the potential-step method, were applied in these two sets of measurements and this might account for the discrepancy on the exchange current values. However, the lesser contamination of the dropping mercury electrode may well be the explanation of the difference between the two sets of results.

Polarography.—The departure from adsorption equilibrium (with respect to the bulk concentration) at the dropping mercury electrode may be relevant in a variety of polarographic studies: maximum suppressors, catalytic waves of alkaloids, distortion of waves, and depression of limiting currents by adsorption of foreign substances, etc. Implications will be considered here for current–time curves for electrode reactions in presence of an adsorbable organic substance that is not reduced or oxidized. This study was made for the reduction of Cu(II) in 0.5 *M* sodium citrate in presence of quinoline. Tracings of current–potential curves (maximum current during drop life) are given in Fig. 4. The range of markedly cathodic potentials at which quinoline should be desorbed could not be explored because of reduction of this substance.[34] Current–time curves during drop life are shown in Fig. 5 with the pertaining data in Table I. The following effects will be discussed: effects of drop time, quinoline concentration, and potential.

Since the area of the mercury drop (sphere) increases with $t^{2/3}$, t being the time during drop life, the rate of drop growth depends on $t^{-1/3}$ and decreases continuously. In the initial stage of the drop life, the drop grows too rapidly to be fully covered and the faradaic current is not too markedly hindered. The drop becomes progressively covered with adsorbate, and the current decreases at the end of the drop life (Fig. 5A). If the drop time is long enough (perhaps 10 sec.), the decrease in current is soon over-compensated by the increase in area, and the current increases again (Fig. 5B).

The rate of adsorption increases with the volume concentration of adsorbate. Hence, the minimum in current–time curves is shifted toward shorter times as the concentration of adsorbate increases (Fig. 5C and 5D). The minimum in current–time curves disappears at large concentrations of adsorbable species.

The electrode coverage can be adjusted at will by variation of the potential,[35,36] all other conditions being identical; and the shape of current–time curves changes with potential.[37] If the potential is sufficiently close to one of the two desorption peaks of the differential capacity curve, the coverage is small, and the minimum in the current–time curves disappears (Fig. 5E). Compare plates B, D and E of Fig. 5 which were obtained under identical conditions except that the potential was changed.

If the limiting current is relatively small in comparison with the diffusion current which would be observed in the absence of adsorbed substance, "blocking" by the film primarily controls the current. There is little concentration polarization for the reducible substance, and the limiting current is essentially proportional to the electrode area. The limiting current then is practically independent of the head of mercury.[38] Conversely, when the limiting current is almost equal to the diffusion current, mass transfer is rate determining, and the limiting current virtually obeys the Ilkovic equation. Under these conditions, the limiting current is essentially proportional to the square root of the head of mercury. The intermediate behavior is more complex and corresponds to current–time curves with a minimum.

The foregoing conclusions are borne out experimentally, and it is observed that the relationship between maximum current during drop life and the head of mercury depends on the concentration of adsorbable substance (Fig. 6). Limiting currents of Fig. 6 were measured at the minimum of current–potential curves (see Fig. 4).

Experimental

Cell, Solutions and Procedure for Differential Capacity Measurements.—A hanging mercury drop similar to that developed by Gerischer was utilized.[39,40] Mercury drops were collected in a glass spoon and then, by rotation of the spoon, hung on a fine gold-plated platinum wire[41] sealed in a

(33) H. Gerischer and K. E. Staubach, *Z. physik. Chem., N.F.*, **6**, 118 (1956).

(34) I. M. Kolthoff and J. J. Lingane, "Polarography," 2nd ed., Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1952, p. 818.

(35) A. Frumkin, *Z. Physik*, **35**, 792 (1926).

(36) J. A. V. Butler, *Proc. Roy. Soc.* (*London*), **122A**, 339 (1929).

(37) Another reason is the current-time dependence for irreversible waves.

(38) The limiting current is proportional to $(mt)^{2/3}$, and m is proportional to H while t is inversely proportional to H, H being the head of mercury corrected for the back pressure.

(39) H. Gerischer, *Z. physik. Chem.*, **202**, 302 (1953).

(40) T. Berzins and P. Delahay, This Journal, **77**, 6448 (1955).

(41) Instead of hanging the drop on a gold-plated platinum wire, one can use a mercury-plated platinum wire and thus prevent contamination of the mercury pool. This procedure was developed by J. W. Ross, R. D. DeMars and I. Shain, *Anal. Chem.*, **28**, 1768 (1956).

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May 20, 1957

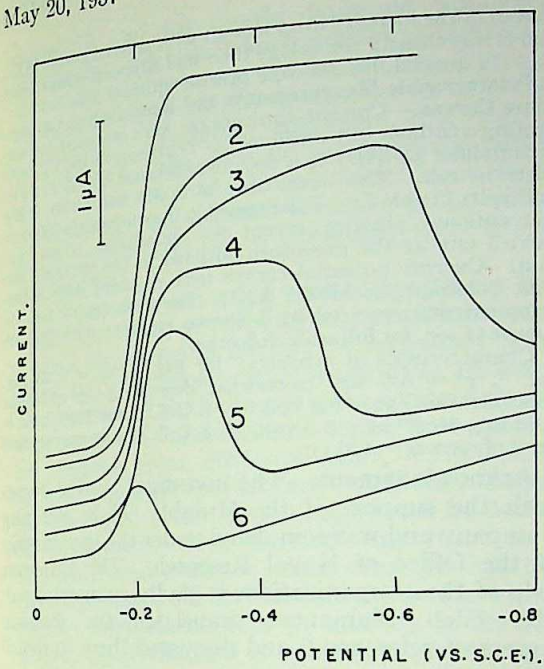

Fig. 4.—Polarograms of 1 millimolar Cu(II) in 0.5 *M* sodium citrate with varying amounts of quinoline. Millimolar concentrations of quinoline are: (1) 0; (2) 0.1; (3) 0.5; (4) 1; (5) 2.5; (6) 5; temperature, 25°.

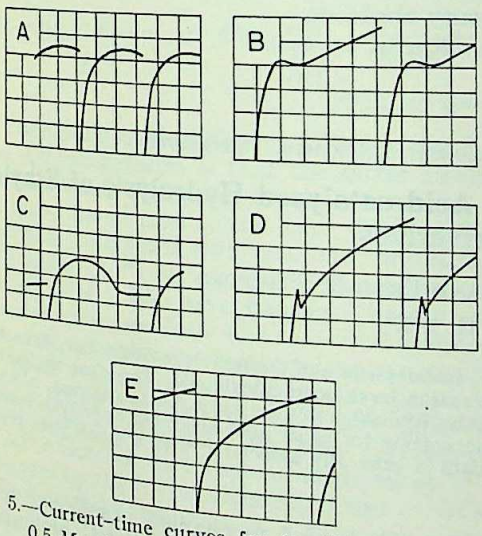

Fig. 5.—Current-time curves for 1 millimolar Cu(II) in 0.5 *M* sodium citrate. See data in Table I.

drawn-out glass tube. This method proved more practical than the one used by Gerischer. The tip of the glass tube was drawn out to avoid shielding of the mercury drop and the resulting dispersion of differential capacity with frequency. The cell was quite similar to that devised by Grahame.[42] The mercury drop was surrounded by a cylinder of platinum foil (diameter, 1 cm.; length 1.5 cm.) which was connected to the a.c. bridge. The potential of the mercury drop was adjusted against a saturated calomel electrode. Solutions were freed of oxygen by nitrogen. To avoid evaporation of the substance being adsorbed on the electrode (*n*-hexyl alcohol), the pure electrolyte was first freed of oxygen, and a small volume (1 ml. in general) of an aqueous solution of *n*-hexyl alcohol was added afterwards. No nitrogen was passed through the solution after the addition of *n*-hexyl alcohol. Solutions were prepared with bidistilled water because traces of organic impurities interfered, especially at low concentrations (10^{-5} *M*) of *n*-hexyl alcohol.

(42) D. C. Grahame, THIS JOURNAL, **71**, 2975 (1949).

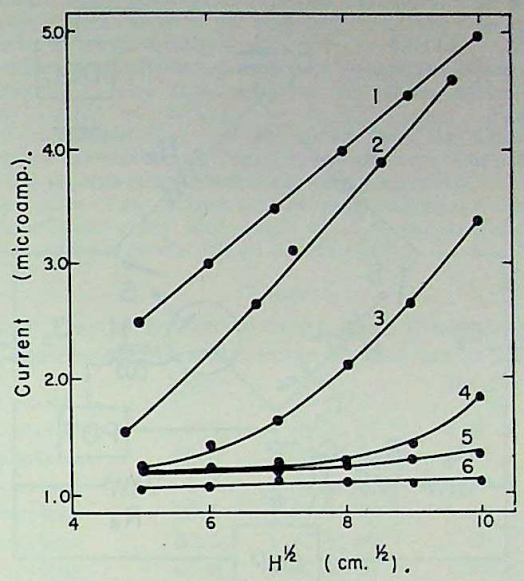

Fig. 6.—Limiting current at 25° against head of mercury for the reduction of 1 millimolar Cu(II) in 0.5 *M* sodium citrate in presence of quinoline. Millimolar concentrations of quinoline are: curve (1), 0; (2) 0.3; (3) 0.4; (4) 0.6; (5) 1; (6) 3.

The procedure was as follows. After preparation of the solution in the cell and proper setting of the potential of the mercury drop electrode (see bridge below), a mercury drop was rapidly hung and the differential capacity was measured within 20–30 sec. The bridge was set approximately at the correct resistance and capacity in advance to speed up measurements. The differential capacity was followed until a steady reading was obtained. This required at least 30 min. with the more dilute solution of hexyl alcohol.

Bridge.—The bridge of Fig. 7 was utilized.[43-45] It is described here because it is simpler than bridges with isolation transformers (in the input and detector circuits) often utilized in differential capacity measurements.[42]

Components were as follows: R_1 and R_2, matched 100 ohm resistances; R_3 and R_4, 1 megohm; R_5, 0–999.9 ohms decade box; R_6, 0–1 megohm variable resistance; C_1, 0.5 microfarad; C_2 and C_3, 0.05 microfarad; C_4, 0–11 microfarad decade box in 0.001 microfarad steps; C_5, 0–500 microfarads, adjustable; H, 32 henry inductance; POT, Leeds and Northrup student potentiometer; OSC, Hulett–Packard oscillator, Model 650A; AMP, Tektronix preamplifier, Model 122; CRO, Dumont oscilloscope, Model 304A; FIL, General Radio filter, Model 1231-P5.

TABLE I

DATA[a] FOR FIG. 5

Plate	*C*,[b] mmole. $l.^{-1}$	$-E$, v. *vs.* S.C.E.	*H*,[c] cm.	Abscissa scale, sec./ square	Ordinate scale, mv./ square	*R*[d],
A	0.6	0.588	81	1	1	800
B	.6	.588	25	2	1	2000
C	.3	.887	25	2	1	1000
D	.6	.816	25	2	1	2000
E	.6	.415	25	2	1	1500

[a] m = 2.23 mg. $sec.^{-1}$ at −0.80 volt (*vs.* S.C.E.) and for H = 81 cm. [b] Concentration of quinoline. [c] Head of mercury. [d] Resistance (in series with cell) connected to cathode-ray oscilloscope. [e] Temperature, 25°.

(43) We are indebted to Dr. W. Vielstich, formerly Research Associate in this Laboratory, for having suggested the use of this simple bridge. See W. Vielstich, Thesis, Göttingen, 1954.

(44) For a general review of a.c. bridge measurements in electrochemistry see H. Gerischer, *Z. Elektrochem.*, **58**, 9 (1954).

(45) See also the bridge developed by J. E. B. Randles, *Trans. Faraday Soc.*, **50**, 1246 (1954).

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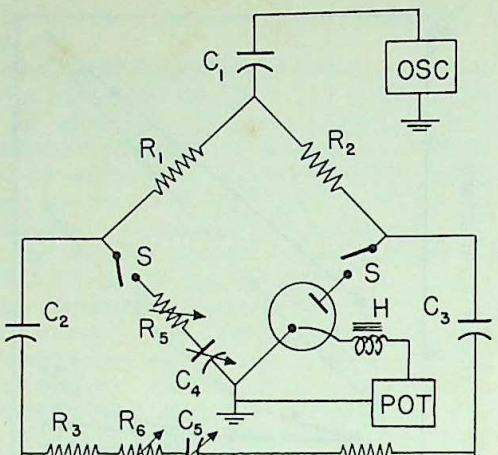


Fig. 7.—Bridge for differential capacity measurements.

The procedure was as follows: the voltage (peak voltage) applied to the bridge was set approximately at 5 mv. at 2000 c.p.s.; the earth compensation was first adjusted with R_6 and C_5 to achieve balance, switch S being open; the potential of the mercury drop was set with potentiometer POT, and S was closed; the bridge then was adjusted with R_5 and C_4. In general, results were precise within 0.1%.

Polarographic Measurements and Recording of Current-Time Curves.—Current–time curves were recorded by connecting a cathode-ray oscilloscope (Tektronix model 531 with preamplifier 53-54D) to a decade resistance box R in series with the cell. The ohmic drop in R did not exceed a few millivolts (Table I). Polarographic measurements followed conventional practice except for deaeration which was carried out by the procedure outlined in the previous section. Current–potential curves were recorded with a Sargent polarograph, Model XXI. The recorder of this instrument was replaced by a Brown recorder with fast response (1 sec. for full scale deflection).

Characteristics of capillary: for Fig. 4, m = 1.23 mg. sec.$^{-1}$, τ = 5.0 sec. (somewhat dependent on quinoline concentration) at −0.8 volt (*vs.* S.C.E.); for Fig. 6, m = 2.23 mg. sec.$^{-1}$ at −0.8 volt (*vs.* S.C.E.) for an uncorrected head of mercury of 81 cm.

Acknowledgment.—The investigation was begun with the support of the Humble Oil & Refining Company and was completed under the sponsorship of the Office of Naval Research. The generous help of these organizations is gladly acknowledged. Mr. Gleb Mamantov translated the Russian papers of reference 9 and discussed them in detail with us.

ADDED IN PROOF.—Arrangements have been made with the Oak Ridge Institute of Nuclear Studies to carry out computer calculations for the complete isotherm for the plane electrode and the dropping mercury electrode.

BATON ROUGE, LOUISIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

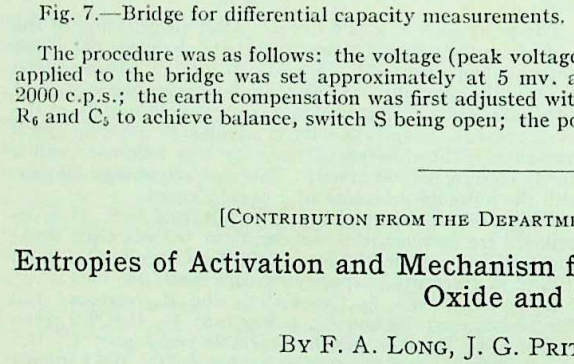
Entropies of Activation and Mechanism for the Acid-catalyzed Hydrolysis of Ethylene Oxide and its Derivatives[1]

BY F. A. LONG, J. G. PRITCHARD AND FRED E. STAFFORD

RECEIVED JANUARY 17, 1957

The rates of the acid-catalyzed hydrolysis of ethylene, propylene, isobutylene and trimethylene oxides have been measured at several temperatures and the energies and entropies of activation have been calculated. The close similarity in the entropy of activation values strongly suggests that all of the oxides hydrolyze by the same A-1 mechanism, which has been proposed previously for epoxides. A survey of entropies of activation for other acid-catalyzed hydrolysis reactions indicates that within similar classes of compounds the A-1 mechanism is generally associated with a much more positive entropy of activation than the A-2 mechanism.

Recent studies on the acid-catalyzed hydrolysis of epoxides have led to the conclusion that this reaction follows an A-1 mechanism in which the rate-determining step is the formation of a carbonium ion.[2–4] In the case of 1,1-disubstituted oxides, the evidence for the A-1 mechanism is sufficient to exclude all others. Thus: (a) the preliminary equilibrium step (1) is established[4] from rate studies in deuterium oxide; (b) the rate-determining spontaneous opening of the epoxide ring in step (2) is shown by the fact that the rates of reaction of several epoxides in strong aqueous solutions of perchloric acid show a good correlation[3] with the Hammett acidity function, h_0; (c) H_2O^{18} has been shown to enter the isobutylene oxide molecule in the tertiary position in accord with step (2)[2]; and (d) the reaction rate is significantly faster for epoxides having electron releasing substituent groups R_1 and R_2, and slower for those with electron withdrawing groups. The same points of evidence have also been established for monosubstituted oxides (R_2 = H). However, for the symmetrical parent compound, ethylene oxide (R_1 = R_2 = H), only items (a) and (b) have been established since



(1) Work supported in part by a grant from the Atomic Energy Commission.

(2) F. A. Long and J. G. Pritchard, THIS JOURNAL, **78**, 2663 (1956).

(3) J. G. Pritchard and F. A. Long, *ibid.*, **78**, 2667 (1956).

(4) J. G. Pritchard and F. A. Long, *ibid.*, **78**, 6008 (1956).

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items (c) and (d) clearly have no application. Hence, the only significant evidence in favor of the formation of a primary carbonium ion during the acid-catalysed hydrolysis of ethylene oxide is the h_0 correlation.[3] (Actually, regarding (d), the rate for ethylene oxide does lie intermediate between the rates for monosubstituted oxides have electron withdrawing and electron releasing group substituents, respectively, as is *consistent* with a single mechanism.)

It is generally accepted that (other things being equal) the order of stability of carbonium ions of various structures is tertiary > secondary > primary, and very few examples of the latter are known. The presence of the hydroxyl group at the β-position with respect to the carbonium center in the primary ion derived from ethylene oxide, $CH_2OHCH_2^+$, should render it particularly unstable. Indeed, the existence of such an ion might well be doubted on this ground. It is therefore important to obtain additional evidence concerning the acid catalyzed hydrolysis of ethylene oxide to decide whether the A-1 mechanism, steps (1) and (2), or the alternative A-2 mechanism is operative. In the latter mechanisms, steps (1) and (3), no carbonium ion would be involved since the rate-determining step would be a simple nucleophilic attack of the solvent molecules on the conjugate acid of the oxide.

$$CH_2(OH^+)-CH_2 + H_2O \xrightarrow{\text{slow}} CH_2(OH)-CH(OH_2^+) \xrightarrow{\text{fast}} \xrightarrow[via\ H_2O]{} \text{Glycol} + H^+ \quad (3)$$

The characteristic difference between the A-1 and the A-2 mechanisms is that the latter involves a specific water molecule in the transition state whereas the former does not. This difference should be reflected in a difference in the entropies of activation (ΔS^*) for the two mechanisms as discussed later. We have therefore measured ΔS^* values for the perchloric acid catalyzed hydrolysis of ethylene, propylene and isobutylene oxides in order to make a comparison for a primary, a secondary and a tertiary epoxide to see if any difference in mechanism is indicated. We have also determined a ΔS^* value for trimethylene oxide since, if it hydrolyzes by the A-1 mechanism,[5,6] this oxide should afford another example of a primary carbonium ion, $CH_2OH{\cdot}CH_2{\cdot}CH_2^+$, and should be of interest for comparison with the results for the epoxides.

Experimental

Rates were measured dilatometrically using the procedures previously described.[3] Chemicals were of reagent grade and all experiments were carried out in water-baths whose temperatures were controlled to $\pm 0.01°$. In the experiments with the very reactive isobutylene oxide, rate measurements were made at 0 and 25° using concentrations of perchloric acid varying between 10^{-2} and 10^{-5} molar, as determined with a standardized Beckman pH meter at the end of each dilatometric run. A value of k_{H+} for $C_{H+} = 10^{-3}$ molar at each temperature was then obtained by graphical interpolation. For each of the other three oxides, a single stock solution of aqueous perchloric acid was prepared, standardized at 25° and used for all the rate measurements, at temperatures ranging from *ca.* 0 to 40°. (Changes in acid concentrations caused by temperature changes were neglected.) The rate equation for these hydrolyses is $-dC_{oxide}/dt = k_1 C_{oxide} = k_{H^+} C_{H^+} C_{oxide}$. First-order rate-coefficients (k_1) were calculated from the dilatometric data by the method of Guggenheim and were then converted to the second-order coefficients (k_{H+}) recorded in Table I. The values of k_{H+} shown are the mean values of at least four determinations for each oxide at each temperature. The results were reproducible to within ±2%.

(5) L. Smith, G. Wode and T. Widhe, *Z. physik. Chem.*, **130**, 154 (1927).

(6) J. G. Pritchard and F. A. Long, to be published. An excellent correlation between the first-order reaction rate and h_0 has been found for the acid-catalyzed hydrolysis of trimethylene oxide in 1 to 4 molar aqueous perchloric acid.

TABLE I

MEAN VALUES OF SECOND-ORDER RATE COEFFICIENTS FOR PERCHLORIC ACID-CATALYZED HYDROLYSIS OF OXIDES

Oxide	Temp. (°C.)	C_{H+} (M)	k_{H+} (l. mole^{-1} sec.$^{-1}$)
Isobutylene	0.0	1.00×10^{-3}	3.80×10^{-1}
Isobutylene	25.0	1.00×10^{-3}	4.60
Propylene	1.0	1.97×10^{-2}	2.79×10^{-2}
Propylene	10.1	1.97×10^{-2}	8.46×10^{-3}
Propylene	30.0	1.97×10^{-2}	7.45×10^{-2}
Propylene	40.0	1.97×10^{-2}	1.99×10^{-1}
Ethylene	1.0	9.45×10^{-2}	5.79×10^{-4}
Ethylene	10.1	9.45×10^{-2}	1.84×10^{-3}
Ethylene	30.0	9.45×10^{-2}	1.69×10^{-2}
Ethylene	40.1	9.45×10^{-2}	4.36×10^{-2}
Trimethylene	1.0	7.02×10^{-1}	7.20×10^{-5}
Trimethylene	10.1	7.02×10^{-1}	2.42×10^{-4}
Trimethylene	30.0	7.02×10^{-1}	1.93×10^{-3}
Trimethylene	35.1	7.02×10^{-1}	4.72×10^{-3}
Trimethylene	40.1	7.02×10^{-1}	7.71×10^{-3}

Values of the Arrhenius energy of activation (E) were obtained in the usual fashion from the gradients of plots of log k_{H^+} *vs.* the reciprocal of the absolute temperature. In all cases, the data were well fitted by straight lines. Values of ΔS^* were calculated from the Eyring equation 4 where the logarithms are to the natural base "e" and the other symbols have their usual significance.

$$\ln k_{H^+} = \ln (ekT/h) + \Delta S^*/R - E/RT \quad (4)$$

Our estimate is that the ΔS^* values are accurate to within ±1 e.u. except for isobutylene oxide where the accuracy may be two- or threefold less, since for this oxide rate measurements were recorded at only two temperatures. The values of ΔS^* recorded in both Tables II and III are for liter mole^{-1} sec.$^{-1}$ rate units.

Results and Discussion

In a discussion of the acid-catalyzed hydration of olefins Taft and co-workers[7,8] suggested that reaction by the A-1 mechanism should be characterized by a relatively more positive entropy of activation than reaction by the A-2 mechanism since the latter involves a relative increase of constraint on the reaction system in the transition state due to the orientation and reaction of a specific water molecule from the solvent. The work of Stimson[9] on the rates of acid-catalyzed hydrolysis of *t*-butyl esters is a good example of the application of this entropy criterion. Thus, the hydrolyses of *t*-butyl benzoate and *t*-butyl formate in acidified 60% acetone–water give ΔS^* values of +9.5 and −23.7 e.u., respectively, suggesting that the former hydrolysis proceeds by an A-1 mechanism and the latter by an A-2.

(7) R. W. Taft, Jr., THIS JOURNAL, **74**, 5374 (1952).

(8) R. W. Taft, Jr., E. L. Purlee, P. Riesz and G. A. De Fazio, *ibid.*, **77**, 1584 (1955).

(9) V. R. Stimson, *J. Chem. Soc.*, 4020 (1955), and refs. therein cited.

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TABLE II

VALUES OF ΔS^* AT 25° FOR SEVERAL A-1 AND A-2 ACID-CATALYZED HYDROLYSIS REACTIONS IN AQUEOUS SOLUTION

Substrate	Mechanism	ΔS^* (e.u.)
Ethyl orthoformate[10]	A-1[11]	+ 5.8
Sucrose[12]	A-1[11]	+ 7.9
Ethylal[13]	A-1[14]	+ 7.3
t-Butyl mesitoate[15]	A-1[15]	+ 9.
Methyl acetate[12]	A-2[16]	−21.3
Ethyl acetate[12]	A-2[16]	−23.0
γ-Valerolactone[17]	A-2[18]	−24.6
γ-Butyrolactone[17]	A-2[18]	−20.9

TABLE III

VALUES OF E AND ΔS^* AT 25° FOR ACID-CATALYZED HYDROLYSIS OF OXIDES

Oxide	$10^3 k_H{}^+$ at 25° (l. mole^{-1} sec.$^{-1}$)	E (kcal./mole)	ΔS^* (cal. mole^{-1} °C.$^{-1}$)
Isobutylene	4600	16.1	−4
Propylene	44.7	18.62	−4.3
Ethylene	9.86	18.99	−6.1
Trimethylene	1.57	20.73	−3.9

To find further examples of this ΔS^*-mechanism relationship, we have calculated ΔS^* values from available data for several acid-catalyzed reactions for which the mechanisms are quite well known. Table II shows that these ΔS^* values fall into two distinct groups separated by some 25 to 30 entropy units, corresponding to the two types of mechanism. The criterion that A-1 and A-2 reactions within the same class of compounds should be characterized by a difference in ΔS^* amounting to from 20 to 30 entropy units therefore appears to be quite general.

The results of the ΔS^* measurements for oxides are given in Table III which includes the appropriate rate and Arrhenius energy of activation data. It is evident that the large variations in hydrolysis rates for these oxides are almost entirely due to changes in the energy of activation and that the values of ΔS^* are almost constant. The observed values of E for the epoxides are in the order expected from a consideration of the stability of both the conjugate acids and the carbonium ions derived from the epoxides. Also, the less strained ring of trimethylene oxide would be expected to require a larger activation energy for opening than the epoxides.

The observed close similarity of the ΔS^* values in Table III provides strong evidence that the mechanism of reaction for all of the oxides is the same. By the argument of the previous paragraphs, the ΔS^* values for the primary oxides would be at least 20 entropy units lower than those for the substituted oxides if there were a change of mechanism from A-1 to A-2. This is clearly not the case. Therefore, since the A-1 mechanism is quite well established for the substituted oxides, we conclude that this same mechanism almost certainly holds for ethylene oxide and for trimethylene oxide.

While the ΔS^* values for the epoxides are closer to the absolute values for the A-1 rather than for the A-2 reactions of Table II, the fact that the values for epoxides are intermediate requires some comment. This may be due to a uniquely higher degree of solvation of the conjugate acids or the transition states in the case of the epoxides, or it may be that in A-1 hydrolyses the restriction of rotation about the breaking bond in the transition state for a cyclic structure leads to a more negative entropy change compared to linear structures. However, further study on this is required.

In view of the great instability of the carbonium ion derived from ethylene oxide, it is probable that the union of a water molecule from the solvation shell with a carbon atom of the epoxide ring, forming a covalent bond, occurs almost immediately after the conjugate acid has reached its free energy maximum in the breaking of one of the carbon–oxygen bonds in the ethylene oxide ring. Some realization of the relative stability of carbonium ions derived from the substituted epoxides of Table III may be obtained from the results of previous hydrolysis studies.[2] Thus, the glycol isolated from the A-1 hydrolysis of propylene oxide in water labeled with H_2O^{18} contained $CH_3{\cdot}CHO^{18}H{\cdot}CH_2OH$ and $CH_3{\cdot}CHOH{\cdot}CH_2O^{18}H$ molecules in a ratio close to 2:1. This result strongly suggests that the conjugate acid of propylene oxide yields the unstable ions $CH_3{\cdot}C^+H{\cdot}CH_2OH$ and $CH_3{\cdot}CHOH{\cdot}CH_2^+$ in this same ratio. Also, the A-1 hydrolysis of isobutylene oxide under similar conditions yielded a product labeled only in the tertiary position, $(CH_3)_2{=}CO^{18}H{\cdot}CH_2OH$, showing that the tertiary ion is preferred in this structure to an extent excluding the primary.

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(15) V. R. Stimson and E. J. Watson, *J. Chem. Soc.*, 2848 (1954).

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(18) F. A. Long, F. B. Dunkle and W. F. McDevit, *J. Phys. Colloid Chem.*, **59**, 829 (1951).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

Some Buffer Solutions with Low Nucleophilic Activity[1]

BY J. G. PRITCHARD AND F. A. LONG

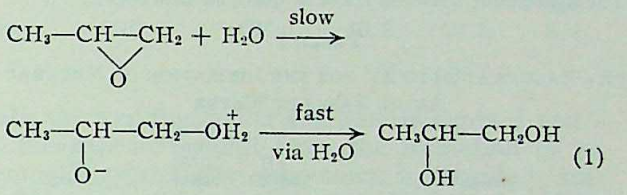
RECEIVED JANUARY 17, 1957

2,6-Dimethylpyridine, 2,4,6-trimethylpyridine, 2-methylquinoline and N-(2-hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidine are shown by kinetic measurements to be unreactive toward propylene oxide in dilute aqueous solution at 50°. These amines may therefore be used, in conjunction with perchloric acid, to form buffer solutions of very low nucleophilic activity for use in the study of reactions sensitive to nucleophilic reagents. In contrast, *cis*-2,6-dimethylpiperidine is found to react readily with propylene oxide and isobutylene oxide. The structure and nucleophilicity of these amines are discussed and details of the preparation and properties of the amine perchlorates are recorded.

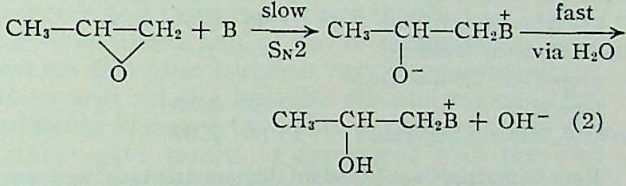
Introduction

In the course of recent investigations on the path of the uncatalyzed hydrolysis of epoxides,[2,3] it was found desirable to control the hydrogen ion concentration of the reaction solutions at values in the range of *p*H 6 to 12. However, for many epoxides, hydrolysis in distilled water is accompanied by a fast drift of the *p*H toward the acid region. Since the reactive epoxides combine readily with nucleophilic reagents of all types[4-8] including the anions of common buffer solution components,[9] the introduction of these into the reaction solution gives rise to both rate and product complications. It was found necessary, therefore, to design buffer solutions which would have a negligible nucleophilic activity. We have examined qualitatively, by a simple dilatometric method, the nucleophilic activity of various hindered amines[10] toward propylene oxide in buffered aqueous solutions, in a manner similar to that used by Eastham and co-workers[5] in their studies with ethylene oxide and various nucleophilic amines. Perchloric acid was used in conjunction with the amines to form the buffer solutions since the low nucleophilic activity of the perchlorate ion is well established.[11]

The hydrolysis of propylene oxide in pure water is known to proceed at a constant rate over the *p*H range 6 to 12, most probably by a scheme similar to that shown in equation 1.[3]



As expected from consideration of the higher densities of glycols compared to the corresponding epoxides, reaction 1 is accompanied by a marked diminution in the volume of the reaction mixture which is proportional to the percentage reaction for dilute solutions of reactants. Tertiary amines such as pyridine should also add to epoxides, to form quaternary ammonium hydroxides as in equation 2.



This reaction should also be accompanied by a diminution in the total volume of the reacting solution. Hence, in our experiments, nucleophilic character in the tertiary amine B should be shown by two criteria. Firstly, if the neutral amine is consumed in reaction with excess of propylene oxide, so producing hydroxide ions, the *p*H of the reaction solution should increase throughout the reaction. Secondly, the apparent dilatometric rate of neutral hydrolysis of the propylene oxide should increase with increasing concentration of the free amine in the buffer solution. In contrast, the hydrolysis of propylene oxide in a solution buffered by a truly anucleophilic amine should show ideally a constant rate for all concentrations of buffer and a constant *p*H throughout the reaction.

In this paper, we report the results of these rate studies together with details of the preparation and properties of the perchlorates of some amines of low nucleophilic activity toward propylene oxide. It is suggested that these and similar compounds may find application as buffer solution components in other fields of research.

Experimental

The Buffer Solutions.—Recrystallization of their salts offered the best means of purifying pyridine and its derivatives. Therefore, it was convenient to make up the buffer solutions from weighed samples of the pure amine perchlorates. These were dissolved, partially neutralized with potassium hydroxide solution and made up to a known volume. The *p*H values of these buffer solutions were recorded, using a standardized Beckman *p*H meter with a glass electrode, at the time of preparation and again at room temperature at the conclusion of the kinetic run with propylene oxide (after *ca.* 36 hours).

Values for the basic ionization constants (K_B) for the amines under study were calculated from the observed *p*H

(1) Work supported by a grant from the Atomic Energy Commission.

(2) J. G. Pritchard and F. A. Long, THIS JOURNAL, **78**, 6008 (1956).

(3) F. A. Long and J. G. Pritchard, *ibid.*, **78**, 2663 (1956).

(4) *Halide ions, thiosulfate ion.* J. N. Bronsted, M. Kilpatrick and M. Kilpatrick, *ibid.*, **51**, 428 (1929).

(5) *Pyridine, aliphatic amines.* M. Eastham, B. de B. Darwent and P. W. Beaubien, *Can. J. Chem.*, **29**, 575, 585 (1951).

(6) *Azide ion.* C. A. VanderWerf, R. Y. Heisler and W. E. McEwen, THIS JOURNAL, **76**, 1231 (1954).

(7) *Nitrate ion.* W. L. Petty and P. L. Nichols, Jr., *ibid.*, **76**, 4385 (1954).

(8) *Thiocyanate ion.* P. L. Nichols, Jr., and J. D. Ingham, *ibid.*, **77**, 6547 (1955).

(9) *Acetate and benzoate ions.* W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

(10) We were prompted to tests derivatives of pyridine in which the nitrogen atom is hindered by substituents in the 2,6-positions by some work of S. Seltzer and F. H. Westheimer (private communication) in which 2,6-dimethylpyridine was used successfully to form a non-chelating buffer solution for the study of the metal ion promoted decarboxylation of dimethyloxaloacetic acid.

(11) *Cf.* K. A. Hoffmann, G. A. Zedwitz and H. Wagner, *Ber.*, **42**, 4390 (1909).

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values of aqueous solutions containing the amine perchlorates (0.0050 *M*) and exactly one-half of an equivalent of potassium hydroxide (0.0025 *M*) in each case. The definitions of K_B and pK_B are shown from the equations

$$B + H_2O \rightleftharpoons BH^+ + OH^- \quad (3)$$

$$K_B = C_{BH^+}C_{OH^-}/C_B, \qquad pK_B = -\log_{10} K_B \quad (4)$$

$$pK_B = 14.0 - pH + \log_{10} C_B/C_{BH^+} \quad (5)$$

For the first four bases in Table I, the equilibrium concentration of OH^- is so small compared to C_B and C_{BH^+} that C_B remains essentially equal to C_{BH^+} and the last term on the right-hand side of equation 5 is zero. For the derivatives of piperidine, which buffer in the *p*H range 10.5–11.0, the value of C_B/C_{BH^+} was calculated from equation 3 and included in the calculation of pK_B by equation 5. Table I records the results of our measurements (at 22 ± 2°) together with some literature values of pK_B where available. The agreement between these is quite satisfactory.

TABLE I

pK_B VALUES AT 20 TO 25° FOR THE IONIZATION OF NEUTRAL AMINE BASES IN WATER

Amine	*p*H 50/50	pK_B from 50/50 buffer	pK_B Lit. values
Pyridine	5.20	8.80	8.85[12]; 8.77[13]
2-Methylquinoline	5.74	8.26	8.6[14]; 8.2[15]
2,6-Dimethylpyridine	6.72	7.28	7.41[12]; 7.38[13]
2,4,6-Trimethylpyridine	7.46	6.54	6.55[13]
N-(2-Hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidine	10.53	3.35	.....
cis-2,6-Dimethylpiperidine	10.86	2.69	.....

Rate Comparisons.—Standard dilatometric technique was used[2,16] with dilatometers of *ca.* 8-ml. capacity. All buffer solutions were thoroughly degassed before addition of propylene oxide The complete hydrolysis of 8 ml. of 0.3 molar propylene oxide gave a meniscus displacement of *ca.* 15 cm. in capillaries of 0.05 cm. internal diameter. The rate equation for the hydrolysis reaction of equation 1 is $-dC_{oxide}/dt = k_1 C_{oxide}$. First-order rate coefficients in sec.$^{-1}$ units were calculated by the Guggenheim method. For those runs with pyridine and 2,6-dimethylpiperidine which involved an abnormally large volume change in the dilatometer due to the nucleophilic activity of these compounds, relative initial rates were calculated by extrapolating the volume diminution data back to the time of mixing the reactants at 50°. Except for these abnormal runs, all rate data gave good straight-line Guggenheim plots. The temperature of the water-bath was controlled at 50 ± 0.01°.

Materials.—Reagent grade inorganic chemicals were used throughout. Reagent grade propylene oxide was distilled before use: b.p. 35°, $n^{25}D$ 1.3638. The perchlorates of the amine bases were prepared and purified as described below, giving good yields except where stated.

Pyridine perchlorate was purified by crystallization from ethyl alcohol giving white crystals of m.p. 289–290°.[17] A solution of 10.5 ml. of 60% perchloric acid and 12 ml. of technical (90%) 2,6-lutidine in 100 ml. of ethyl alcohol was evaporated at 100° and allowed to crystallize. Recrystallization of the product from acetone gave white, crystalline **2,6-dimethylpyridinium perchlorate**, m.p. 110–111°; found C = 40.4%, H = 4.8%, N = 6.7%, as required by $C_7H_{10}O_4NCl$. 11.5 ml. of reagent grade 2,4,6-trimethylpyridine treated as above gave white, crystalline **2,4,6-trimethylpyridinium perchlorate**, m.p. 239–240°; found C = 43.5%, H = 5.4%, N = 6.2%, as required for $C_8H_{12}O_4NCl$ (N = 6.3%). (This substance assumed a faint orange color on exposure to light.) Evaporation of a solution containing 11 ml. of reagent grade quinaldine and 10.5 ml. of 60% perchloric acid in 50 ml. of ethyl alcohol gave a red wine-colored crystalline mass. Repeated recrystallization from alcohol gave straw-colored crystals of **2-methylquinolinium perchlorate**, m.p. 129–130°; found C = 49.1%, H = 4.1%, N = 5.5% ($C_{10}H_{10}O_4NCl$ requires C = 49.2%, H = 4.3%, N = 5.7%).

A solution containing 10 ml. of (*cis*)-2,6-dimethylpiperidine[18] and 9.5 ml. of 60% perchloric acid in 25 ml. of ethyl alcohol was evaporated at 100° and allowed to crystallize. The product was recrystallized from 1,4-dioxane giving fine, white needles of ***cis*-2,6-dimethylpiperidinium perchlorate**, m.p. 186–187°; found C = 39.5%, H = 7.7%, N = 6.4% ($C_7H_{16}O_4NCl$ requires C = 39.4%, H = 7.5%, N = 6.5%).

A solution containing 15 ml. of *cis*-2,6-dimethylpiperidine and 11 ml. of isobutylene oxide in 200 ml. of water was allowed to stand overnight at room temperature. The oily layer which had formed above the aqueous phase was separated and neutralized with alcoholic 20% perchloric acid solution. Evaporation of the alcohol and water present gave a crystalline mass of which only a small part was soluble in ethyl acetate. After washing with boiling ethyl acetate, to remove unreacted 2,6-dimethylpiperidine, the product was recrystallized from a solvent containing equal volumes of ethyl alcohol and ethyl acetate, and gave 2 g. of **N-(2-hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidinium perchlorate**, m.p. 200°; found C = 46.4%, H = 8.4%, N = 4.85%. ($C_{11}H_{24}O_5NCl$ requires C = 46.2%, H = 8.4%, N = 4.9%.)[19] It should be noted that the formation of N-(1,1-dimethyl-2-hydroxyethyl)-*cis*-2,6-dimethylpiperidine in this last reaction may be excluded immediately on steric grounds since the nucleophilic reaction of even the small hydroxide ion with isobutylene oxide occurs almost exclusively at the primary carbon atom of the epoxide ring.[3]

Results

Table II gives the observed first-order rate coefficients for reaction of 0.3 molar propylene oxide at 50° in a series of buffer solutions having two general ranges of concentration. The initial concentrations of free amine in the solutions were calculated using the pK_B values of Table I and the observed initial *p*H values of the reaction solutions.

Since pyridine is known to react readily with propylene oxide[20,21] the results of expts. 1 and 7 exemplify the behavior of a typical nucleophile. In both experiments there is observed a large drift of the *p*H during the reaction, and the rate of volume diminution in the dilatometer is increased about sevenfold on increasing the initial free pyridine concentration from 0.002 to 0.08 molar. A similar behavior is shown by *cis*-2,6-dimethylpiperidine in expts. 2 and 8, and we therefore conclude that this compound exerts a nucleophilic activity similar to that of pyridine.

Completely contrasting behavior is observed for the hindered amines of expts. 4, 5 and 6. For these cases, the *p*H is constant throughout each reaction and the three values of k_1 are identical and somewhat lower than those obtained in expts. 1 and 2. The results of expts. 10, 11 and 12 show that for in-

(12) E. F. G. Herington, *Faraday Soc. Disc.*, **9**, 26 (1950).

(13) A. Gero and J. J. Markham, *J. Org. Chem.*, **16**, 1835 (1951).

(14) W. A. Felsing and B. S. Biggs, THIS JOURNAL, **55**, 3624 (1933).

(15) C. Golumbic and M. Orchin, *ibid.*, **72**, 4145 (1950).

(16) J. G. Pritchard and F. A. Long, *ibid.*, **78**, 2667 (1956).

(17) F. Arndt and P. Nachtwey, *Ber.*, **59B**, 446–448 (1926), give m.p. 288°.

(18) We are indebted to the Reilly Tar and Chemical Corporation for a sample of 2,6-dimethylpiperidine which had b.p. 128°, $n^{20}D$ 1.4370 and which gave a unique hydrochloride of m.p. 278–279° (first crystallization). The sample therefore almost certainly had the *cis* configuration since it was identical with 2,6-dimethylpiperidine prepared by the catalytic reduction of 2,6-dimethylpyridine by hydrogen over nickel. *Cf.* A. Marcuse and R. Wolffenstein, *Ber.*, **32**, 2526 (1899); H. Adkins, L. F. Kuick, M. Farlow and B. Wojcik, THIS JOURNAL, **56**, 2427 (1934).

(19) Microanalyses were by the Schwarzkopf Microanalytical Laboratory, 56-19—37th Avenue, Woodside 77, N. Y.

(20) J. Hansson, *Svensk Kem. Tid.*, **60**, 183 (1948).

(21) L. Smith, S. Mattsson and S. Andersson, *C. A.*, **41**, 6455i (1947).

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TABLE II

DILATOMETRIC RATE COEFFICIENTS FOR WATER REACTION OF 0.3 MOLAR PROPYLENE OXIDE IN A SERIES OF AMINE BUFFER SOLUTIONS AT 50°

Expt.	Amine	Buffer ratio C_B/C_{BH^+}	Approx. free amine concn. (C_B)	pH initial	pH final	$10^6 k_1$ (sec.$^{-1}$)
1	Pyridine	2/3[a]	0.002[a]	5.0	11.0	10.4
2	*cis*-2,6-Dimethylpiperidine	2/3[a]	.002[a]	11.0	10.2	10.6
3	2-Methylquinoline	1	.0025	5.7	5.7	10.7
4	2,6-Dimethylpyridine	2/3	.002	6.4	6.5	8.6
5	2,4,6-Trimethylpyridine	2/3	.002	7.3	7.3	8.6
6	N-(2-Hydroxy 2-methylpropyl)-*cis*-2,6-dimethylpiperidine	3/7	.0015	10.3	10.2	8.5
7	Pyridine	2/3[a]	.08[a]	5.0	12.0	65[b]
8	*cis*-2,6-Dimethylpiperidine	2/3[a]	.08[a]	11.0	10.4	58[b]
9	2-Methylquinoline	1	.025	5.7	5.7	12.1
10	2,6-Dimethylpyridine	1	.10	6.7	6.7	9.3
11	2,4,6-Trimethylpyridine	2/3	.08	7.3	7.3	8.8
12	N-(2-Hydroxy 2-methylpropyl)-*cis*-2,6-dimethylpiperidine	4/5	.016	10.6	10.5	8.4

[a] Initially. [b] Comparative initial rates.

creased concentrations of the same hindered amines, the pH values of the reaction solutions still remain constant and the k_1 values are essentially the same as those obtained in expts. 4, 5 and 6. The small variations in k_1 for these last three expts. of Table II were not outside the *possible* experimental error (± *ca.* 10%) but may actually have been due to small kinetic salt effects. In expts. 9 and 12, the maximum buffer concentrations were limited for solubility reasons. Nevertheless, the free amine concentration of about 0.02 molar was considered adequate to detect dilatometrically any nucleophilic activity. (A comparison of the expts. 1 and 2 with expts. 4, 5 and 6 shows that a concentration of as little as 0.002 molar of a strongly nucleophilic amine gives rise to a detectable increase in the observed value of k_1.) We conclude that the true rate of the uncatalyzed hydrolysis of propylene oxide at 50° is 8.6×10^{-6} sec.$^{-1}$. The good reproducibility of the dilatometric rates leads us to believe that this figure is correct to within ±3%. We conclude also that the hindered amines 2,6-dimethyl- and 2,4,6-trimethylpyridine and N-(2-hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidine have a low nucleophilic activity with respect to propylene oxide.

The case of 2-methylquinoline might appear to be anomalous since it gives k_1 values which are consistently high while the pH during the reaction remains constant at a value of 5.7. The high k_1 values are almost certainly due to the incursion of a small contribution from the acid-catalyzed mode of hydrolysis which would be expected to enter with propylene oxide at pH values below *ca.* 6.0.[3,4] However, the constancy of the pH in both expts. 3 and 9 gives very strong evidence for the very low nucleophilic activity of 2-methylquinoline. In expt. 1 with pyridine, a larger k_1 value might possibly have been expected for the same reason since the reaction was started at pH 5, in the acid-catalyzed region. However, it is highly probable that the pH of the solution drifted into the "neutral" region (pH 6 to 12) during the first few minutes of the reaction, before the first reading of the dilatometer.

Reaction of the Nucleophilic Amines.—The increase of pH for the reaction of propylene oxide with the pyridine buffer solutions in expts. 1 and 7 is the expected result from the formation of an aromatic quaternary ammonium hydroxide.[5] Initially, for such a reaction, the pH drift should be small since the hydroxide ion produced would be almost wholly neutralized by the pyridinium ion. However, this process increases the C_B/C_{BH^+} ratio, and when about half of the total amine has been used up this ratio becomes very large, causing the pH to drift rapidly into the alkaline region. Experiments designed to isolate a product from this reaction gave results in agreement with previous work on similar systems. Namely, the N-(2-hydroxypropyl)-pyridinium hydroxide cannot be isolated as it polymerizes, especially in contact with air, to a dark bro n viscous substance[22]; and whereas the N-(2-hydroxypropyl)-pyridinium halides are reported to be crystallizable,[23,24] the perchlorate salt was found to remain as a viscous oil.[25] The matter was not pursued beyond these qualitative observations.

The pH drift accompanying the nucleophilic reaction of *cis*-2,6-dimethylpiperidine with propylene oxide is directed toward the acid region. Since 2,6-dimethylpiperidine is a secondary amine the product of this reaction by equation 2 should be a tertiary amine and there should be no production of hydroxide ion. Hence, the observed direction of the pH drift in expts. 2 and 8 is consistent with the fact that tertiary amines are generally less basic than the secondary amines from which they are derived. A pertinent example of this is shown by a comparison of the pK_B values in Table I for *cis*-2,6-dimethylpiperidine and its tertiary N-(2-hydroxy-2-methylpropyl) derivative, which was obtained by reaction of isobutylene oxide with the *cis*-2,6-dimethylpiperidine. In this one case, the tertiary amine was prepared in quantity and isolated as its perchlorate since it promised and proved to be a good anucleophilic buffer component for pH *ca.* 10. Experiments are in progress to investigate other members of this class of compounds.

(22) H. Lohmann, *J. prakt. Chem.*, **153**, 57 (1939).
(23) A. M. Eastham, *J. Chem. Soc.*, 1936 (1952).
(24) F. N. Hayes, L. C. King and D. E. Peterson, THIS JOURNAL, **78**, 2527 (1956).
(25) K. C. Kolwyck, J. H. Billman and W. W. Hayes, *ibid.*, **71**, 3498 (1949).

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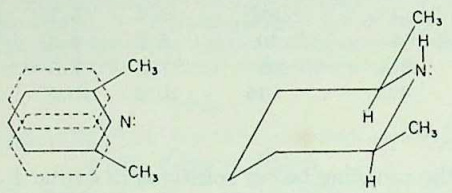
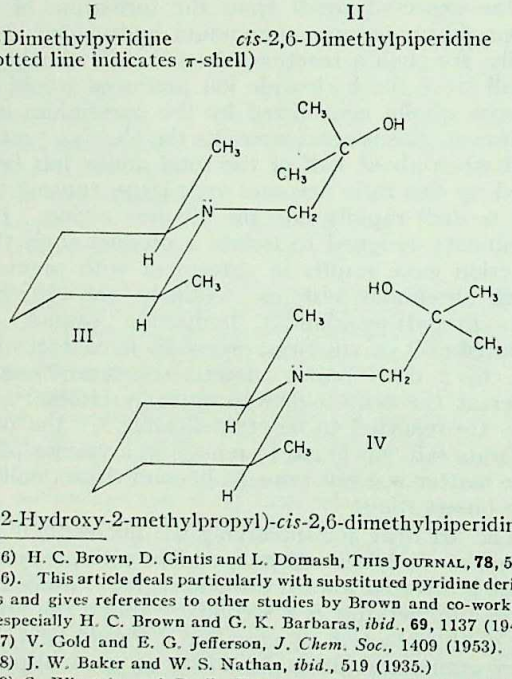
Structural Considerations.—The observed sharp drop in reactivity with propylene oxide on going from pyridine to 2,6-dimethylpyridine (I) is entirely consistent with many other studies of steric effects[26–28] and suggests that the steric requirements for reaction of I with epoxides are quite specific. In an S_N2 reaction involving opening of the epoxide ring in the *trans* sense,[29] the nitrogen atom in I is probably so well shielded by the methyl substituents and the two branches of the π-electron shell of the pyridine ring that this reaction is very slow. The same applies to 2,4,6-trimethylpyridine and to 2-methylquinoline.



I II

2,6-Dimethylpyridine *cis*-2,6-Dimethylpiperidine
(Dotted line indicates π-shell)



III IV

N-(2-Hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidine

The observed high reactivity of *cis*-2,6-dimethylpiperidine (represented by II for one of the four possible configurations) is interesting since from an examination of scale models there appears to be no obvious structural reason why the nucleophilic activities of I and II should be so different toward propylene oxide. However, in I the unshared electrons of the nitrogen atom lie in a plane trigonal sp^2 hybrid orbital directed along the axis of symmetry of I, but in II they lie in a tetrahedral sp^3 orbital which may be directed with respect to the piperidine ring either equatorially as shown in II or axially, depending on inversion of the configuration about the nitrogen atom. Also, owing to their greater "p" character, sp^3 orbitals extend out further from the atomic nucleus than do sp^2 orbitals. The nucleophilic electrons on II should thus be more available than those in I, leading to the much higher basicity and nucleophilic activity of II.[30] From a consideration of models, we consider that the S_N2 reaction of isobutylene oxide with *cis*-2,6-dimethylpiperidine would be most likely to occur through configuration II. Hence, the product from *trans* addition to the epoxide ring would at first be expected to have the structure III. However, the stable modification of this molecule may be the less congested and possibly weakly hydrogen bonded structure IV, since C–C bond rotations in both structures are restricted. The formation of a tertiary ammonium ion by reaction of III or IV with a molecule as large as propylene oxide appears almost impossible on steric grounds, so that the demonstration in this paper of the low or undetectably nucleophilic activity of N-(2-hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidine is easily understood.

As H. C. Brown and co-workers point out,[26] the actual magnitude of a steric effect is dependent on the particular steric requirements of the reaction considered. However, since the epoxide ring is generally considered to be very sensitive to nucleophiles, it is probable that the low nucleophilic activity of the hindered amines discussed in this paper is general toward most types of organic substrate containing two or more carbon atoms.

ITHACA, N. Y.

(26) H. C. Brown, D. Gintis and L. Domash, THIS JOURNAL, **78**, 5387 (1956). This article deals particularly with substituted pyridine derivatives and gives references to other studies by Brown and co-workers: see especially H. C. Brown and G. K. Barbaras, *ibid.*, **69**, 1137 (1947).

(27) V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1409 (1953).

(28) J. W. Baker and W. S. Nathan, *ibid.*, 519 (1935.)

(29) S. Winstein and R. B. Henderson, in Elderfield's "Heterocyclic Compounds," Vol. I, John Wiley and Sons, New York, N. Y., 1950, p. 29.

(30) *Cf.* C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 174.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA, BERKELEY]

The Volumetric and Thermodynamic Properties of Fluids. III. Empirical Equation for the Second Virial Coefficient[1]

BY KENNETH S. PITZER AND R. F. CURL, JR.

RECEIVED DECEMBER 22, 1956

An equation has been developed to represent the second virial coefficient of a normal fluid: $BP_c/RT_c = (0.1445 + 0.073\omega) - (0.330 - 0.46\omega)T_r^{-1} - (0.1385 + 0.50\omega)T_r^{-2} - (0.0121 + 0.097\omega)T_r^{-3} - 0.0073\omega T_r^{-8}$ where ω is the acentric factor (defined by $\omega = -\log (P/P_c)_{sat} - 1.000$ at $T_r = 0.7$) which was discussed in an earlier paper. This equation not only fits the volumetric data with considerable accuracy but its second derivative also yields agreement with measured values of the pressure derivative of the gas heat capacity.

In 1907 Berthelot[2] proposed a simple reduced equation for the second virial coefficient which has been of great value in correcting the properties of real gases at low pressures to the ideal gas state. We know, however, that real gases do not follow accurately the principle of corresponding states, hence any such equation is of limited accuracy. In the earlier papers of this series[3] we have shown that the introduction of the acentric factor as an additional parameter increases the accuracy of possible correlation by about one order of magnitude.

In this paper we present an empirical equation for the second virial coefficient in reduced form which includes the acentric factor dependence.

Basic Data.—In addition to the second virial coefficient values based on volumetric measurements,[4] we calculated the volume of the saturated vapor from vapor pressure, heat of vaporization and liquid volume data in several cases.[5]

We also used the information on the change with pressure of the gas heat capacity.[6] If the second virial coefficient is B, thermodynamics yields the equation

$$\lim_{P \to 0} \left(\frac{\partial C_p}{\partial P}\right)_T = -T \frac{\partial^2 B}{\partial T^2} \qquad (1)$$

Consequently, the pressure dependence of the heat capacity offers a very sensitive test of any equation for B.

Selection of the Equation.—Our earlier studies[3] indicated that an equation linear in the acentric factor was usually adequate and we find this to be the case for the second virial coefficient. We have then, in reduced dimensionless form

$$\frac{BP_c}{RT_c} = \frac{B^{(0)}P_c}{RT_c} + \omega \frac{B^{(1)}P_c}{RT_c}$$

where $B^{(0)}$ and $B^{(1)}$ are functions of the reduced temperature, and ω is the acentric factor. Although ω was defined as

$$\omega = -\log P_r - 1.000 \qquad (2)$$

where P_r is the reduced vapor pressure (P/P_c) at $T_r = 0.7$, it may be evaluated readily from any vapor pressure value well removed from the critical point by the use of Table VI of Paper II of this series.[3]

The simple fluids of zero acentric factor are the heavier inert gases A, Kr, Xe. We know their properties are quite well represented by a Lennard-Jones intermolecular potential. Consequently, we took the equation of Stockmayer and Beattie[7] as a point of departure. This was converted from the molecular potential constants to the macroscopic critical constants and then modified slightly to improve the fit at the lowest temperatures by the addition of a small T^{-3} term and other small adjustments. The resulting equation is

$$\frac{B^{(0)}P_c}{RT_c} = 0.1445 - \frac{0.330}{T_r} - \frac{0.1385}{T_r^2} - \frac{0.0121}{T_r^3} \qquad (3)$$

Figure 1 shows the reduced virial coefficient data for a number of substances together with calculated curves. The agreement of the curve for $\omega = 0$ with the points for A, Kr and Xe demonstrates the adequacy of equation 3.

It is impractical to show all of the data considered in the development of the equation for $B^{(1)}$. The resulting fit with the data for benzene and for n-heptane is shown on Fig. 1 for B and on Fig. 2 for the pressure derivative of the heat capacity. Similar agreement is obtained for other substances. The resulting equations are

$$B = B^{(0)} + \omega B^{(1)} \qquad (4)$$

$$\frac{B^{(1)}P_c}{RT_c} = 0.073 + \frac{0.46}{T_r} - \frac{0.50}{T_r^2} - \frac{0.097}{T_r^3} - \frac{0.0073}{T_r^8} \qquad (5)$$

The selection of a term in T_r^{-8} is, of course, somewhat arbitrary, but a very high power is required to fit the data at low temperatures.

(1) This research was part of the program of Research Project 50 of the American Petroleum Institute.

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(6) *n*-Heptane: G. Waddington, S. Todd and H. Huffman, THIS JOURNAL, **69**, 22 (1947); C_8H_8: D. W. Scott, G. Waddington, J. C. Smith and H. M. Huffman, *J. Chem. Phys.*, **15**, 565 (1947); 2,2,3-trimethylbutane: G. Waddington, S. Todd and H. Huffman, THIS JOURNAL, **69**, 22 (1947); ethanethiol: J. P. McCullough *et al.*, *ibid.*, **74**, 2801 (1952).

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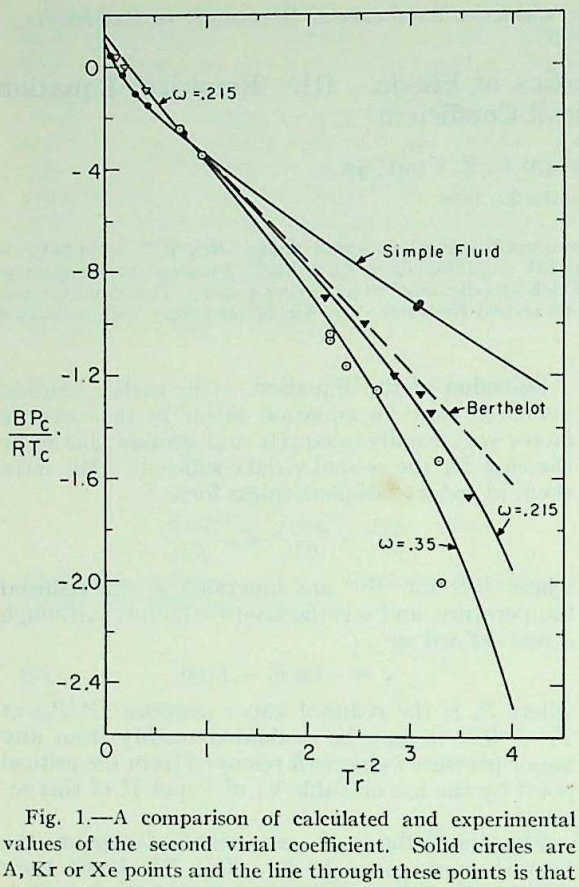

Fig. 1.—A comparison of calculated and experimental values of the second virial coefficient. Solid circles are A, Kr or Xe points and the line through these points is that of equation 3. The open triangles are CO_2 and solid triangles are benzene points. These are to be compared with the line for $\omega = 0.215$. The open circles are points for *n*-heptane ($\omega = 0.35$). It is to be noted that the Berthelot equation yields excellent agreement for ω in the range 0.15 to 0.20.

The work leading to the selection of equation 5 indicated certain small changes in the previously published values of $z^{(1)}$, the term in the compressibility factor expression which is multiplied by ω. The revised values are given in Table I (the upper right-hand portion of each section is unchanged but included for convenience).

TABLE I

REVISED VALUES OF Z^1 FOR COMPRESSIBILITY FACTOR CALCULATION (SEE TABLE IV, PAPER II)

T_r	P_r 0.2	0.4	0.6	0.8	1.0
1.20	0.009	0.018	0.028	0.044	0.069
1.25	.011	.023	.036	.050	.069
1.3	.013	.027	.041	.055	.072
1.4	.016	.032	.049	.065	.082
1.5	.017	.035	.052	.070	.088
1.6	.018	.036	.054	.072	.090

T_r	P_r 1	2	3	4	5	6	7	8	9
1.7	0.09	0.16	0.21	0.24	0.25	0.26	0.25	0.24	0.22
1.8	.09	.16	.21	.26	.29	.31	.32	.32	.30
1.9	.09	.16	.21	.26	.30	.35	.38	.40	.40
2.0	.08	.15	.21	.26	.30	.35	.40	.43	.45
2.5	.07	.13	.20	.25	.30	.35	.40	.45	.50
3.0	.06	.11	.17	.23	.28	.34	.38	.45	.50
3.5	.05	.09	.14	.19	.24	.28	.33	.38	.42
4.0	.04	.08	.12	.16	.20	.25	.29	.34	.38

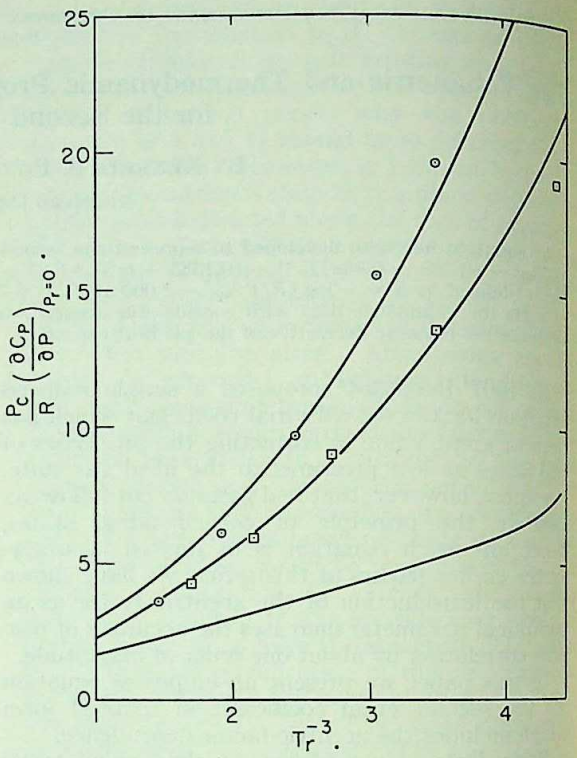

Fig. 2.—A comparison of calculated and experimental values of the pressure derivative of the heat capacity. The circles and upper curve are for *n*-heptane ($\omega = 0.35$); the squares and intermediate curve are for benzene ($\omega = 0.215$). The bottom curve is for $\omega = 0$, but no experimental data are available for comparison.

Discussion.—This equation should be valuable for the estimation of gas imperfection corrections to various data on gases at low pressures. The substances which can be expected to conform are those forming normal liquids. Metals and hydrogen bonding substances must be excluded. The limitations are discussed in greater detail in Papers I and II.[3] The final equations for various properties are readily derived from thermodynamics. In these equations H^*, S^*, C_p^* refer to the properties of the hypothetical ideal gas at the same pressure as the real gas; f is the fugacity.

$$\frac{BP_c}{RT_c} = (0.1445 + 0.073\omega) - (0.330 - 0.46\omega)T_r^{-1} - (0.1385 + 0.50\omega)T_r^{-2} - (0.0121 + 0.097\omega)T_r^{-3} - 0.0073\omega T_r^{-8} \quad (6)$$

$$\log\left(\frac{f}{P}\right) = \left(\frac{P_r}{2.303}\right)[(0.1445 + 0.073\omega)T_r^{-1} - (0.330 - 0.46\omega)T_r^{-2} - (0.1385 + 0.50\omega)T_r^{-3} - (0.0121 + 0.097\omega)T_r^{-4} - 0.0073\omega T_r^{-9}] \quad (7)$$

$$\frac{H - H^*}{RT} = P_r[(0.1445 + 0.073\omega)T_r^{-1} - (0.660 - 0.92\omega)T_r^{-2} - (0.4155 + 1.50\omega)T_r^{-3} - (0.0484 + 0.388\omega)T_r^{-4} - 0.0657\omega T_r^{-9}] \quad (8)$$

$$\frac{S - S^*}{R} = P_r[-(0.330 - 0.46\omega)T_r^{-2} - (0.2770 + 1.00\omega)T_r^{-3} - (0.0363 + 0.29\omega)T_r^{-4} - 0.0584\omega T_r^{-9}] \quad (9)$$

$$\frac{C_p - C_p^*}{R} = P_r[(0.660 - 0.92\omega)T_r^{-2} + (0.831 + 3.0\omega)T_r^{-3} + (0.145 + 1.16\omega)T_r^{-4} + 0.526\omega T_r^{-9}] \quad (10)$$

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

Application of the Glass Electrode to the Determination of the Thermodynamic Ionization Constants of *p*-Aminobenzoic Acid

BY MARVIN L. DEVINEY, JR.,[1] R. C. ANDERSON AND W. A. FELSING[2]

RECEIVED NOVEMBER 15, 1956

The thermodynamic ionization constants of *p*-aminobenzoic acid have been determined in water at 25° by use of cells without liquid junction using the commercial Beckman "General-Purpose" glass electrode. The values of pK_{A_1} and pK_{A_2} obtained were, respectively, 2.50_1 and 4.87_4.

In this investigation a method was developed for determining the first and second dissociation constants of *p*-aminobenzoic acid by the electromotive force method, using cells without liquid junction. The Beckman "General-Purpose" glass electrode was employed in measuring the hydrogen ion activity because the application of the hydrogen electrode or the quinhydrone electrode was found not to be practicable in this case. This is an extension of previous work in this Laboratory on the dissociation of weak electrolytes, which includes studies on propionic acid,[3,4] *n*-butyric acid[5] and β-alanine.[6]

Experimental

p-Aminobenzoic Acid Buffer Solutions.—The K_{A1} buffer solutions were prepared from *p*-aminobenzoic acid, repurified hydrochloric acid and conductivity water; the K_{A2} buffer solutions were prepared from potassium *p*-aminobenzoate, repurified hydrochloric acid and conductivity water. The *p*-aminobenzoic acid, twice recrystallized Eastman Kodak Company White Label grade, melted sharply at 187° in agreement with the best value from the literature[7]; it was not hygroscopic. The potassium *p*-aminobenzoate, prepared from *p*-aminobenzoic acid and potassium hydroxide, was carefully purified; it was found to be free of carbonate and non-hygroscopic.

A stock solution was prepared in the highest concentration possible (about 0.035 *M* in *p*-aminobenzoic acid); and the various solutions for measurement were prepared by weight dilution, with the same buffer ratio being maintained. All solutions were deaerated immediately after preparation with solvent-saturated, high-purity nitrogen. The repurified hydrochloric acid, 0.1 to 0.3 *N*, was standardized gravimetrically.

Glass Electrode Standardization Solutions.—Three different reference buffer solutions, prepared, respectively, from reagent grade glycine, potassium tetraborate and propionic acid, were used for the standardization of the glass electrodes against hydrogen electrodes. The solutions were deoxygenated and stored under repurified electrolytic hydrogen.

Electromotive Force Measurements.—The measuring circuit consisted of a Leeds and Northrup Type K2 potentiometer (recently calibrated by the manufacturer); a Leeds and Northrup thermionic amplifier, modified internally to make it sensitive to ±0.01 millivolt; and a Leeds and Northrup Type R moving-coil galvanometer. Three standard cells were used, all recently calibrated by the Bureau of Standards. Temperature control was maintained to ±0.01° in a kerosene thermostat.

The preparation of the hydrogen electrodes and the thermal decomposition type silver–silver chloride electrodes has been previously described.[8] Each "General-Purpose" glass electrode selected for use was tested for several days to ensure a minimum drift in asymmetry potential. All glass electrode measurements were made in triplicate.

The electromotive force cells were of special design and contained four side arms. Presaturators with sintered-glass cylinders were used whenever the hydrogen electrode was employed. The cells were filled with the appropriate solutions by employing an oxygen-excluding vacuum technique. A special sweep system (for hydrogen or nitrogen) built into the cell allowed removal of any air which entered during the insertion of the glass electrodes, after the vacuum loading procedure.

The actual procedure of measurement consisted of standardization by measuring the potential of the three glass electrodes against duplicate hydrogen electrodes for at least two hours, followed by transfer of the glass electrodes to the *p*-aminobenzoic acid–buffer cell and measurement of its potential until equilibrium was reached. The glass electrodes were then transferred back to the standardization cell for recheck of their calibration. Agreement was almost always obtained to ±0.10 millivolt for the six glass electrode calibration readings, and similar agreement was obtained between the three glass electrodes in *p*-aminobenzoic acid–buffer solutions.

Calculations

The first and second dissociation reactions of *p*-aminobenzoic acid may be written $HQH^+ \rightleftarrows H^+ + HQ$ and $HQ \rightleftarrows H^+ + Q^-$, where HQ represents the neutral-molecule structure of *p*-aminobenzoic acid. Although aliphatic amino acids are usually 99.99% or more in the zwitterion form, Klotz and Gruen[9] have shown that *p*-aminobenzoic acid exists in solution predominantly (91–97%) in the neutral molecule form. pK_{A1} as determined in this investigation really represents a mixture, in the structural sense, of the predominant neutral-molecule species with a small portion of the dipolar species; the same is true in the case of pK_{A2}. Although the simultaneous presence of both species affects the kinetics of the ionization of *p*-aminobenzoic acid by introducing a second dissociation mechanism, it does not affect the final equilibrium or thermodynamic properties of the solution.[10]

From cells of the type

Glass electrode	*p*-Aminobenzoic acid (m_1), Hydrochloride of *p*-aminobenzoic acid (m_2)	AgCl	Ag

the first thermodynamic ionization constant, K_{A1}, is given by

$$-\log K_{A1} = \frac{E + E^0_{Ag,Cl^-,AgCl} - E_g(1\text{ atm.})}{2.303(RT/F)} + \log \frac{m_{HQH} m_{Cl^-}}{m_{HQ}} + \log \frac{\gamma_{HQH}\gamma_{Cl^-}}{\gamma_{HQ}} \quad (1)$$

(1) (a) This paper represents part of a dissertation submitted by Marvin L. Deviney, Jr., in partial fulfillment of the requirements for the Ph.D. degree at the University of Texas, June, 1956. (b) Holder of the Humble Oil and Refining Company Fellowship in Chemistry, 1953–1954.

(2) Deceased October 5, 1952.

(3) A. Patterson, Jr., with W. A. Felsing, THIS JOURNAL, **64**, 1480 (1942).

(4) R. L. Moore and W. A. Felsing, *ibid.*, **69**, 2420 (1947).

(5) W. A. Felsing and M. May, *ibid.*, **70**, 2904 (1948).

(6) M. May and W. A. Felsing, *ibid.*, **73**, 406 (1951).

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(10) L. Michaelis, "Techniques of Organic Chemistry, Vol. I. Physical Methods of Organic Chemistry," Part II, edited by A. Weissberger, Interscience Publishers, Inc., New York, N. Y., 1949, p. 1747.

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where E is the measured voltage of the cell, $E^0_{Ag,Cl^-,AgCl}$ is the molal potential of the silver–silver chloride electrode at 25°,[11] E_g(1 atm) is the glass electrode constant as measured directly against a platinum–black hydrogen electrode (corrected to 1 atmosphere hydrogen pressure) immediately before and after each measurement of E, m is the weight molality and γ is the activity coefficient. The physical constants used in this investigation were the latest and most accurate values available.

The treatment of data used in this Laboratory for the evaluation of the thermodynamic ionization constants of amino acids has been previously described in detail.[6] In the case of *p*-amino-benzoic acid, however, additional calculations were necessary in order to correct for slight concentration changes caused by the overlap of the K_{A1} and K_{A2} ionization reactions. This overlap phenomenon occurs for dibasic-type acids whenever the ratio $K_{A1}/K_{A2} < 10^3$ ($pK_{A2} - pK_{A1} < 3$).[12] Equations were derived to correct for this overlap effect following the principles used by Hamer, Pinching and Acree[13,14] for a dicarboxylic acid (*o*-phthalic acid) and by Smith and Smith[15] for a dicarboxylic amino acid (aspartic acid).

K_{A2} may be determined from cells of the type

Glass electrode	*p*-Aminobenzoic acid (m_3) Potassium *p*-aminobenzoate (m_4) Potassium chloride (m_5)	AgCl	Ag

and the pK_{A2} expression is

$$-\log K_{A2} = \frac{E + E^0_{Ag,Cl^-,AgCl} - E_g(1\text{ atm.})}{2.303(RT/F)} + \log \frac{m_{Cl}m_{HQ}}{m_Q} + \log \frac{\gamma_{Cl}\gamma_{HQ}}{\gamma_Q} \quad (2)$$

The evaluation of K_{A2} was made following the methods referred to in the preceding paragraph.

Results

The data from which the thermodynamic ionization constants of *p*-aminobenzoic acid were calculated were obtained using Beckman "General-Purpose" glass electrodes. It was found in preliminary tests that both the platinized platinum and palladiumized platinum (prepared as recommended by Hamer and Acree[16]) electrodes failed to reach equilibrium in buffer solutions of *p*-aminobenzoic acid and its hydrochloride and in buffer solutions of *p*-aminobenzoic acid and its potassium salt. It was not definitely established in this investigation whether catalytic hydrogenation of *p*-aminobenzoic acid or adsorption on the platinum black and palladium black electrodes was responsible for the instability of the hydrogen electrode. Yoshimura[17] has shown that it is not possible to make accurate electromotive force measurements with the quinhydrone electrode in amino acid solutions because of a condensation reaction between quinone and the amino acid. The mechanism of this reaction has been reported by Posner[18] and Fuson.[19] Although MacInnes and Dole[20] thin-membrane glass electrodes were successfully prepared and tested, it proved to be very difficult to use them because of the extreme fragility of the membrane (on the order of 0.001 mm. thick).

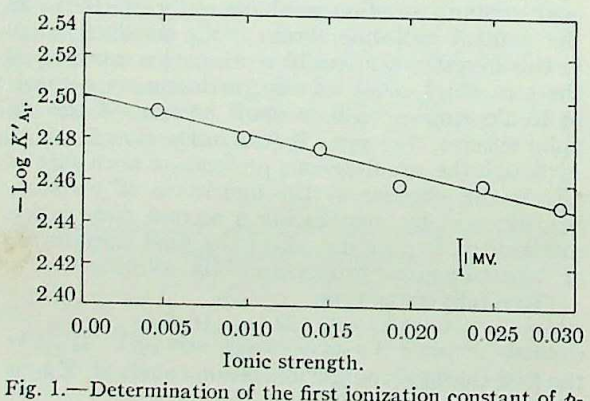

Fig. 1.—Determination of the first ionization constant of *p*-aminobenzoic acid in water at 25°.

In Tables I and II are given the experimental data obtained with the Beckman electrodes for the K_{A1} and K_{A2} determinations, respectively. The E_g (1 atm.) term and the E term represent the average of six and three separate electrode readings, respectively, for the given solution.

TABLE I

EXPERIMENTAL DATA FOR K_{A1} DETERMINATION

Point	m_1	m_2	$E - E_g$(1 atm.)
1	0.029324	0.028928	0.47113
2	.024417	.024089	.47667
3	.019528	.019266	.48267
4	.014463	.014269	.49237
5	.009882	.009750	.50404
6	.004623	.004561	.52996

TABLE II

EXPERIMENTAL DATA FOR K_{A2} DETERMINATION

Point	$m_1 = m_3$	m_2	$E - E_g$(1 atm.)
1	0.028115	0.030664	0.60631
2	.023416	.025539	.61080
3	.018608	.020295	.61659
4	.013754	.015001	.62392
5	.009381	.010231	.63363
6	.007523	.008205	.63936
7	.004722	.005150	.65129
8	.004592	.005008	.65158

The least-squares extrapolation to infinite dilution to determine K_{A1} and K_{A2}, based on the data in the tables, is illustrated in Figs. 1 and 2. The circles in Fig. 2, the K_{A2} determination, are drawn with a radius of ± 0.10 millivolt (or ± 0.002 pK unit, which represents an error in K of 0.4%), and the circles in Fig. 1, the K_{A1} determination, are

(11) R. G. Bates and V. E. Bower, *J. Research Natl. Bur. Standards*, **53**, 283 (1954).

(12) S. Glasstone, "An Introduction of Electrochemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1942, p. 322.

(13) W. J. Hamer and S. F. Acree, *J. Research Natl. Bur. Standards*, **35**, 381 (1945).

(14) W. J. Hamer, G. D. Pinching and S. F. Acree, *ibid.*, **35**, 539 (1945).

(15) E. R. B. Smith and P. K. Smith, *J. Biol. Chem.*, **146**, 187 (1942).

(16) W. J. Hamer and S. F. Acree, *J. Research Natl. Bur. Standards* **33**, 87 (1944).

(17) H. Yoshimura, *J. Biochem. (Japan)*, **23**, 187 (1936).

(18) T. Posner, *Ann. Chem.*, **336**, 85 (1904).

(19) R. C. Fuson, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 497.

(20) D. A. MacInnes and M. Dole, *Ind. Eng. Chem., Anal. Ed.*, **1**, 57 (1929); THIS JOURNAL, **52**, 29 (1930).

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drawn with a radius of ± 0.20 millivolt; these are believed to be the respective accuracies in the two determinations. The values of pK_{A1} and pK_{A2} obtained were, respectively, 2.50_1 (corresponding to $K_{A1} = 3.15_7 \times 10^{-3}$) and 4.87_4 (corresponding to $K_{A2} = 1.33_7 \times 10^{-5}$).

The following comparison of the values of the two ionization constants in water at 25°, as determined in this investigation, can be made with values already reported

	pK_{A1}	pK_{A2}	Method
This investigation	2.501	4.874	Galvanic cells without liquid junction
Klotz and Gruen (1945)[9]	2.504	...	Spectrophotometric
Albert and Goldacre (1942)[21]	2.49	4.83	Potentiometric titration
Kilpi and Harjanne (1948)[22]	2.38	4.89	Buffer capacity min. (liquid junction involved)
Johnston (1906)[23]	2.32	4.92	Catalytic method involving hydrolysis of methyl acetate
Winkelblech (1901)[24] and Walker (1904)[25]	2.32	4.92	Conductance

(21) A. Albert and R. Goldacre, *Nature*, **149**, 245 (1942).
(22) S. Kilpi and P. Harjanne, *Suomen Kemistilehti*, **21B**, 14 (1948).
(23) J. Johnston, *Proc. Roy. Soc.* (*London*), **A18**, 82 (1906).
(24) K. Winkelblech, *Z. physik Chem.*, **36**, 564 (1901).
(25) J. Walker, *ibid.*, **51**, 708 (1904).

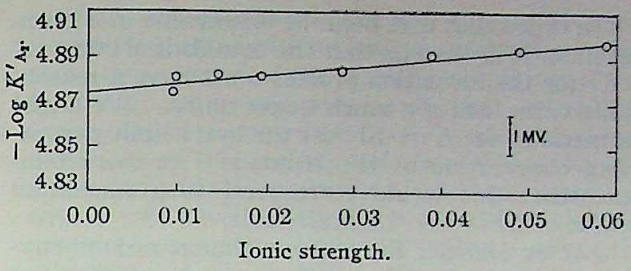

Fig. 2.—Determination of the second ionization constant of *p*-aminobenzoic acid in water at 25°.

The only previous completely thermodynamic method which has been applied to *p*-aminobenzoic acid is the spectrophotometric method, and excellent agreement was obtained between this investigation and the optical method for K_{A1}. The present investigation is apparently the only one in which corrections for the overlap of the dissociation reactions have been applied.

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AUSTIN, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

Inter- and Intramolecular Hydrogen Bonds[1]

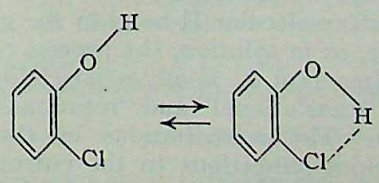
BY H. H. JAFFÉ

RECEIVED SEPTEMBER 24, 1956

The differences in energies of intra- and intermolecular H-bonds are discussed in terms of the entropy changes accompanying H-bond formation.

Since the early work on hydrogen bonds[2] it has generally been accepted that they are usually associated with bond energies in the range of 3 to 7 kcal./mole. These estimates were based almost exclusively on intermolecular hydrogen bonds. In recent years, however, hydrogen bonds have been demonstrated to exist, or at least proposed, for which one would expect appreciably smaller bond energies.[3,4] Most of these cases involve *intra*-molecular hydrogen bonds, many of which could even be demonstrated in solution in polar media,[3] where one might have expected that hydrogen bonding with the solvent might be energetically preferred. It is the purpose of the present paper to call attention to a fundamental thermodynamic difference between *intra*- and *inter*molecular hydrogen bonds which can explain readily why intramolecular H-bonds of much smaller energy than intermolecular ones can be observed.

For the purpose of this discussion, we shall define the process of H-bond formation as the process in which this bond is formed, leaving the molecule (or molecules) otherwise effectively unchanged. For intermolecular H-bonds, this process then is equivalent to association; in case of H-bonds between atoms of the same kind, polymerization or dimerization; in this paper we shall not be concerned with association of more than two molecules, although the arguments presented will hold equally well for more extensive association. For intramolecular H-bonds, the process is represented by reaction 1 (using *o*-chlorophenol as an example) in the forward direction.



(1)

Accordingly, we may consider the process of H-bond formation as an equilibrium reaction, and we wish to examine the thermodynamics of this reaction.

(1) This work was sponsored by the Office of Ordnance Research, U. S. Army.
(2) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 2nd Ed., 1948, Chapter 9.
(3) D. H. McDaniel and H. C. Brown, *Science*, **118**, 370 (1953).
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In order that a H-bond be observable in a given system, it is obvious that the equilibrium constant (K) for the formation process must have a reasonable value, not too much below unity. We might arbitrarily set $K = 10^{-1}$ as the lower limit permitting observation of the H-bond.[5] At room temperature, this would correspond to a maximum value of $\Delta F^\circ \sim +1.5$ kcal./mole.

Let us consider the entropy change accompanying this process. The entropy change accompanying the dimerization of gas molecules can be estimated. The loss of three translational degrees of freedom should involve a loss of entropy of around 40 e.u. for a moderately sized molecule. The loss of three rotational degrees of freedom will involve a smaller decrease of entropy, which we will estimate at about 10 to 15 e.u. The rotational and translational degrees of freedom lost upon dimerization give rise to six vibrational modes and even though most of these vibrations will have fairly low force constants (there will be only one bond stretching mode for each H-bond and two bending modes), it is doubtful that these vibrations make a very appreciable (positive) contribution to the entropy change. Hence the total entropy change should be about -50 e.u., corresponding to a $T\Delta S$ term of about 15 kcal./mole at room temp., and 20 kcal./mole at the lowest temperatures where moderately sized hydrogen bonded molecules exist in the vapor state. Accordingly it is not astonishing that H-bonded dimers in the vapor phase are rarely encountered, and then only when more than one bond is responsible.

The estimation of the entropy changes in solution or in the liquid phase is much more difficult. The translational motion is no longer free, but in solution or in a liquid, may be viewed either as translation in a cage (small volume) or as a vibration about a pseudo-lattice-site. In either way, the translational entropy should be greatly reduced. Rotation of large molecules in a liquid phase is not free; rather the degrees of freedom corresponding to rotation in the gas are probably best described as librations. As such, their contribution to the entropy will also be greatly reduced. In solutions, a further positive change in the entropy of the solvent, due to the fact that the dimer molecule is solvated by slightly fewer solvent molecules, is probably negligible. Thus we see that we should expect a much smaller entropy change in liquids and solutions. Since the lower limit of energies of observable H-bonds are of the order of 3 kcal./mole we may infer that this figure is the probable entropy change (in terms of $T\Delta S$) for dimerization. This value is certainly not unreasonable in the light of the above discussion.

For an intramolecular H-bond in the gaseous or liquid phase, or in solution, the process of H-bond formation (reaction 1) involves no change in the number of "translational" and "rotational" degrees of freedom. The contributions of the various bond stretching vibrations to the entropy of the molecule are undoubtedly so small that even moderate changes in the associated force constants cannot give rise to appreciable entropy effects. Accordingly, using again chlorophenol as an example, it seems evident that the in-plane and out-of-plane bending vibrations of Cl and OH, and the torsional vibration of OH are the only vibrations which could affect the entropy. Altogether, these vibrations do not contribute more than a very few e.u. to the total entropy of the molecule, and while their tightening will lead to a slight decrease in entropy, this decrease is quite insignificant, and can be neglected.

In solution, another possible contribution to ΔS° is due to any change in solvation. The degree of solvation is probably limited by steric relations, and it seems hard to visualize that the number of solvent molecules which can sufficiently closely approach the molecule, is appreciably affected by H-bond formation. Hence, we shall also neglect any contribution to ΔS° from solvation.

Assuming, then, that we can neglect ΔS° for reaction 1, ΔH° and ΔF° are equal, and measurement of either would determine both. Neither of these quantities appear particularly amenable to measurement, and few attempts appear to have been made to determine these quantities for intramolecular H-bonds,[6] and the data obtained invariably refer to the vapor state or to inert solvents. Data in some recent papers,[3,4] however, permit some estimates of ΔF° to be made. For example, in connection with the measurement of the pK's of some *ortho*-substituted benzenephosphonic acids, estimates of the effect of H-bonding on the pK were made, and these are, of course, directly the $-\log K$ applying to eq. 1. The values measured were of the order of 0.25–1.5, and hence lead to enthalpies for reaction 1 of 0.2–1 kcal./mole. These figures are probably slight underestimates, firstly, because the $-\log K$ values were lower limits, and secondly, because ΔS° may well contribute a few tenths of a kcal. However, the arguments seem to show that, in solution, even in highly polar media, extremely weak hydrogen bonds may be observed. Other data of similar nature may be found throughout the modern literature.

It frequently has been pointed out that intramolecular H-bonds are particularly readily formed because other bonds in the molecule constrain the atoms into favorable positions. In this form, this statement, of course, implies the small magnitude of the entropy change. This same constraint also explains certain apparent anomalies, such as the fact that the OH—Cl and OH—Br bonds in *o*-chloro- and *o*-bromobenzenephosphonic acids are of approximately equal strengths, although bromine is generally considered to form much weaker H-bonds than chlorine. The geometry of the molecule, due to the relatively large phosphorus atom, is simply such that the OH—Br distance is much more favorable to H-bonding than the OH—Cl distance, thus overcoming the innate lower H-bonding tendency of Br.

We are now ready to inquire why, even in highly polar solvents, we can find such weak intramolec-

(5) Some recent techniques such as measurement of heats of solution permit demonstration of appreciably weaker H-bonds; *cf.* S. Searles, M. Tamres, F. Block and L. A. Quarterman, THIS JOURNAL, **78**, 4917 (1956), and earlier papers by M. Tamres.

(6) *Cf.* L. R. Zumwalt and R. M. Badger, *ibid.*, **62**, 305 (1940).

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ular H-bonds, formed apparently in preference to possible much stronger intermolecular bonds. One answer to this question is, of course, contained in the comparison of the entropy changes associated with the formation of the two types of H-bonds.

There seems to be a further reason, however, in steric effects. Consider the H-bonded form of *o*-chlorophenol. There is no reason to believe that both the O atom and the Cl atom could not serve as electron donors for H-bonds with as many as two solvent molecules each (the H-bond O-H—Cl is probably so weak that, at equilibrium, not many molecules would be that highly solvated). In the non-bonded form, sufficient electron pairs are available so that the molecule could act as donor for five, and as acceptor for one further H-bond. For steric reasons such an extensive solvation of the substituted region of the molecule seems out of the question; it appears quite likely that steric hindrance would prevent solvation beyond four solvent molecules in this region, and thus leave both the H-bonded and the non-bonded forms approximately equally solvated. Hence the intramolecular H-bonding provides additional energy over the solvation.

Acknowledgment.—The author is indebted to Dr. Robert J. Good for several interesting discussions concerned with this work.

CINCINNATI 21, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WASHINGTON]

Polarized Electronic Absorption Spectrum of Amides with Assignments of Transitions[1]

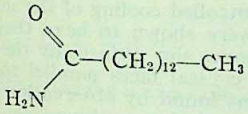
BY DON L. PETERSON[2] AND WILLIAM T. SIMPSON

RECEIVED NOVEMBER 2, 1956

The polarized electronic spectrum of myristamide is obtained to 1600 Å. It is analyzed into n-π; NV_1; Rydberg (2p, 3s) and NV_2 transitions. Emphasis is on obtaining and interpreting the NV_1 transition moment direction.

Introduction

In this investigation the polarized electronic spectrum of myristamide



in the region between 2300 and 1600 Å. was obtained. Starting from the long wave length end there are characterized n-π and NV_1 transitions, a first member of a Rydberg series, and part of the NV_2 transition.

The main result of the paper is considered to be the determination of the direction of polarization of the NV_1 transition, appearing at 1850 Å. In the work on myristamide this direction could not be determined uniquely owing to unfavorable crystal symmetry.[3] Two possible orientations were obtained: one inclined away from the nitrogen–oxygen axis 9.1°, toward the carbon–nitrogen axis; and the other 26.7°, toward the carbon–oxygen axis.[4]

Several methods were employed in an attempt to select the correct direction. The work of Ward on N-acetylglycine was considered first.[5] In addition, an attempt was made to use the results of a π-electron calculation with full configurational interaction in the framework of the ASMO method. During the final stages of this research the crystal structure of N,N′-diacetylhexamethylenediamine was found reported in the literature.[6] This substance has only one molecule per unit cell, a circumstance which made it possible unambiguously to determine the correct polarization direction. The 9.1° value proves to be the correct one, which, gratifyingly was the value selected by the theoretical calculation, and also turns out to be allowed by Ward's experiments.[7]

The theoretical work in this paper is based on calculations described in a collateral paper on the allyl system, particularly allyl anion.[8] Much of the interpretation of the experiments depends on results described in a paper on the nature of resonance force transfer of excitation energy in molecular crystals.[9] Use will also be made of earlier research in which the spectrum of amides in the gas phase down to *ca.* 1300 Å. has been recorded.[10]

I. Experimental

The instrument used in these studies is the same as described elsewhere[11] except for a sliding vane valve situated between the slit compartment and tank.[12]

The calculation of the optical densities of the sample at the various wave lengths was complicated by the fact that there was marked reciprocity failure. Time sensitometry, using numbers of flashes as abscissas, gave characteristic curves which had the usual straight line portion, but with a definite decrease in slope when the intensity was reduced. It was found possible, after a certain amount of trial and error, to assign every density, D, at a given number of flashes, n, an effective gamma determined empirically,

(1) This research was supported in part by The Air Research and Development Command under Contract No. AF 18(600)-375.
(2) National Science Foundation Predoctoral Fellow, 1954–1955.
(3) The crystal structure was determined by J. D. Turner and E. C. Lingafelter, *Acta Cryst.*, **8**, 549 (1955), and refined by R. F. Adamsky and E. C. Lingafelter, private communication.
(4) These possibilities were briefly reported in a Communication to the Editor, D. L. Peterson and W. T. Simpson, THIS JOURNAL, **77**, 3929 (1955).
(5) J. C. Ward, *Proc. Roy. Soc.* (*London*), **A228**, 205 (1955).
(6) M. Bailey, *Acta Cryst.*, **8**, 575 (1955).
(7) Our first interpretation of Ward's results, given in ref. 4, proved to be incorrect.
(8) H. D. Hunt, D. L. Peterson and W. T. Simpson, *J. Chem. Phys.*, in press.
(9) W. T. Simpson and D. L. Peterson, *ibid.*, in press.
(10) H. D. Hunt and W. T. Simpson, THIS JOURNAL, **75**, 4540 (1953).
(11) R. C. Nelson and W. T. Simpson, *J. Chem. Phys.*, **23**, 1146 (1955).
(12) D. L. Peterson, Thesis, University of Washington, 1956.

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$\gamma(D,n)$;[12] whereupon all optical densities expressing absorptivity were determined from the difference, referring to blank, B, and sample, S

$$\frac{D_B}{\gamma_B(D,n)} - \frac{D_S}{\gamma_S(D,n)}$$

Before using this procedure spectra of thick crystals had apparently different shapes than for thin crystals, though with the correction the expected Beer–Lambert behavior was found. The uncertainty in the empirically determined γ's imposes an estimated 5% error in optical densities.

Measurements on Myristamide.—Purified myristamide was obtained from Dr. J. D. Turner.[3] Single crystals were grown by sublimation in shallow, covered petri dishes. Suitable crystals had well developed 001 faces and displayed uniform interference colors in reflected light. The thinnest crystals were colored steel-grey in crossed polaroids.

In preparing a sample for an exposure a crystal was mounted between optically flat, fused quartz cover slips held under slight pressure. The orientation of the crystal was determined either by observation of edges or by location of extinctions under a polarizing microscope. The *a*- and *b*-axes were distinguished by a cleavage running parallel to *b*, and this was confirmed by a zero level X-ray precession photograph of the mounted crystal.[13]

A mounted crystal was placed in the spectrograph with its *a*- and *b*-axes aligned with the polarization directions of the Wollaston prism. An exposure consisted of between 50 and 200 12-kilovolt discharges through a Lyman tube. Each exposure was accompanied on the same plate (to minimize errors due to irregularities in the fluorescent overlay on the plates) by a blank exposure taken under identical conditions including exposure duration, discharge voltage and capillary diameter.

The *a*- and *b*-polarized myristamide spectra below 2100 Å. (Fig. 1) are the averages of separate spectra taken with three crystals of varying thickness. The thicknesses were estimated by converting to an expected vapor spectrum and comparing with that observed for dimethylformamide. They were found to range from 0.3 to 0.5 micron. Above 2100 Å. each spectrum is a composite of spectra for four crystals with estimated thicknesses ranging from 2 to 50 μ. The curves as obtained directly from the spectrograms appeared similar to the wavy curve of Fig. 4 and with this exception have all been smoothed.

The absorption curves for light polarized along the *a*- and *b*-axes are given in Fig. 1. The broken portions signify uncertainty: in the region of the maximum of the D_a curve

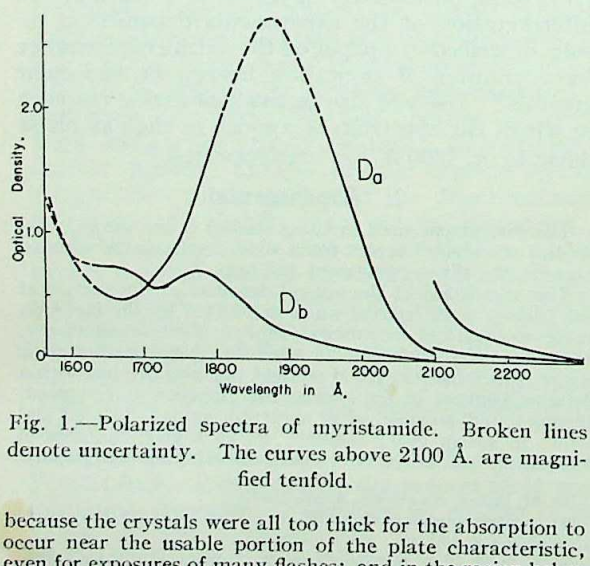

Fig. 1.—Polarized spectra of myristamide. Broken lines denote uncertainty. The curves above 2100 Å. are magnified tenfold.

because the crystals were all too thick for the absorption to occur near the usable portion of the plate characteristic, even for exposures of many flashes; and in the region below 1630 Å. mainly because of anticipated trouble from reflection from the interfaces in the holder assembly. The curves above 2100 Å. are magnified tenfold.

In Fig. 2 the function $\log D_a/D_b$ is plotted against the same abscissa as in Fig. 1 (heavy curve). The expected vapor absorption is also included. It was obtained by introducing artificial random orientation trigonometrically.

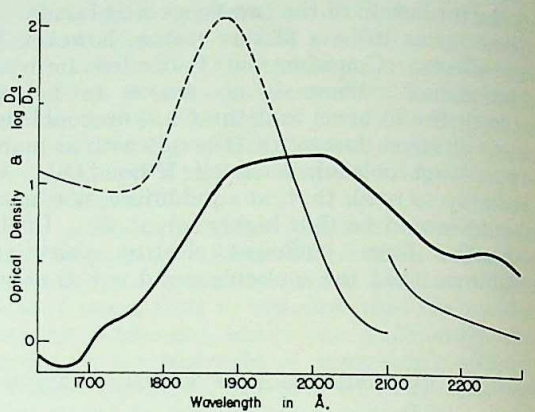

Fig. 2.—Variation of $\log D_a/D_b$ with wave length (heavy curve) and predicted vapor spectrum with region of greatest uncertainty distinguished by a broken curve. The spectrum is magnified tenfold above 2100 Å.

Measurements on N,N′-Diacetylhexamethylenediamine.—The compound was prepared by acetylation[14] of Distillation Products Inc. commercial grade (72%) hexamethylenediamine which was first purified by fractional crystallization. The product was recrystallized from 95% ethanol. In preparing specimens a thin layer of pulverized crystals was enclosed between fused quartz cover slips previously conditioned by immersion in 12 *N* NaOH. Crystallization occurred through controlled cooling of the melt.[15] The crystals so obtained were shown to have their (100) faces in contact with the cover slip surfaces by the identification of the angle "a" in crystal faces parallel to these surfaces.[4] The orientation was found by observation of extinction directions under the polarizing microscope. The extinction direction, *X*, corresponding to the larger refractive index for visible light, was found to be at an angle of 19 ± 2° with the *c*-axis (see Fig. 3). All the molecules are oriented the same way in this material, so that the principal directions are determined by the amide transition moment directly, in the 1900 Å. region.

Only seldom were sufficiently large monocrystalline sections found. The absorption measurements were made on two such sections, the area and thickness of which were estimated to be about 1 mm.^{2} and 0.1 μ. Spectra were recorded for various orientations of the crystals in light polarized in each of the two fixed perpendicular directions of the Wollaston prism. When the orientation was such that the polarization direction of one component of the light was approximately aligned with the projected transition moment direction in the 100 plane, $\vec{m'}$, complete absorption set in below 2100 Å. The crystal may then be regarded as a piece of Polaroid. The angle which $\vec{m'}$ makes with the polarization direction of the other of the two beams could then be obtained easily. Measured from the *X* direction the resulting angle is 5 ± 3° (Fig. 3).

Effect of Varying Polarization of Incident Light.—Crystal spectra must be understood as involving absorption of energy out of two independent beams along the principal directions, or, equivalently, as requiring that the light be represented as a statistical ensemble having parts polarized along the two principal directions. The weights of the two streams of photons, oppositely polarized, are given by the cosine squared law. It is believed that this phenomenon is an example of a disturbance due to the possibility of there having been a "measurement" (absorption of a photon by a crystal oscillator) thus leading to the reduction of the wave function of the light. This point has been considered in

(13) The authors gratefully acknowledge the help of Dr. J. R. Brathovde, Dr. J. D. Brazeale and Professor E. C. Lingafelter in matters having to do with the crystallography.

(14) T. Curtius and H. Clemm, *J. prakt. Chem.*, **62**, 189 (1900).

(15) The apparatus for controlled cooling was constructed by Mr. [illegible] Barnes of this Laboratory.

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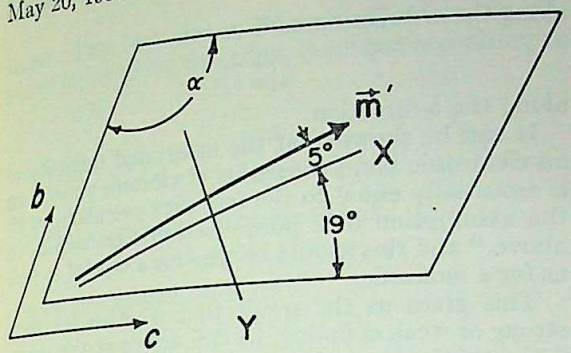

Fig. 3.—The 100 face of the N,N′-diacetylhexamethylenediamine unit cell showing the orientation of the extinction direction, X, and transition moment, m'.

previous work[11,16] and receives a practical verification from the curves in Fig. 4. The dashed curve is obtained by concluding that since the light is polarized in incidence with an angle of 45° to one of the principal directions, it exists with the same polarization inside the crystal. For this situation we project the crystal absorbers onto the electric vector of the light. The D_a and D_b curves from Fig. 1 are thus projected onto this polarization direction, giving for log I/I_0 the average

$$\cos^2 45°\ D_a + \sin^2 45°\ D_b$$

The solid curve is obtained by assuming the polarization of half the beam to be along the a-axis and, in this connection, by using the D_a data from Fig. 1. This gives an intensity I_a' emerging with polarization along the a direction according to

$$\log \frac{I_a'}{I_0/2} = D_a$$

or

$$I_a' = \frac{I_0}{2}\, 10^{D_a}$$

Similarly the intensity emerging in the b direction is given by

$$I_b' = \frac{I_0}{2}\, 10^{D_b}$$

whence the total intensity emerging is the sum

$$I = \frac{I_0}{2}\,(10^{D_a} + 10^{D_b})$$

from which the solid curve is calculated as log I/I_0. The spectrum actually obtained with the light polarized at 45° to the principal directions is the wavy curve, in agreement with the solid curve.

II. The NV_1 Transition

Looking at Figs. 1 and 2 we can see a region from 2050 to 1700 Å. where the absorption is strong, though not with a constant D_a/D_b ratio. This region is interpreted as the crystal absorption associated with the NV_1 electronic band of an isolated myristamide molecule, *e.g.*, as found in the gas phase at low pressures.

It is believed that the long wave length shoulder consists of *vibronic* transitions only weakly split by the resonance force interaction in the myristamide crystal (a situation described as weak coupling). In this region the D_a and D_b curves should be proportional, at low resolution. The ordinates would not be equal because the projection of the transition moment of a typical molecule is unequal on the two principal directions.

When the electronic band half-width, $2V$, for an ideal non-vibrating crystal much exceeds the half-width of the absorption band for isolated

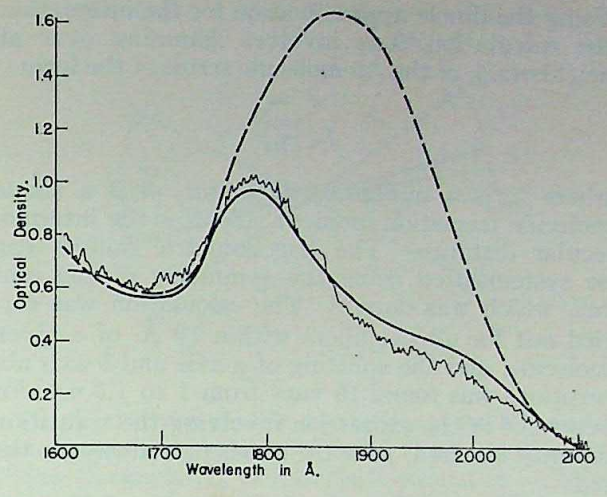

Fig. 4.—Erroneously (broken curve) and properly (heavy curve) calculated myristamide crystal spectrum for light polarized at 45° with the a-axis. The wavy curve is observed.

molecules, Δ, a situation called strong coupling is expected.[9] In this case the D_a and D_b curves would lose their resemblance to one another and to the gas phase spectrum. The separation of the peaks of the two curves would give the crystal splitting of the entire *electronic* transition, just as if vibrations could be disregarded. The separation in Fig. 1 is considered to be an example of this effect though the ratio $2V/\Delta$ is a little less than unity (0.6, see below). It is thought that the middle of the band must be treated as involving strong coupling, even though the wings of the band show weak coupling.

Crystal Spectrum with Strong Coupling.—For strong coupling we assume that the nuclei are fixed and calculate the allowed resonance force spectrum[17] based on the absorption for a single molecule. This requires a knowledge of the strength and direction of the total electronic transition moment. Before the ambiguity about the direction of the NV_1 transition moment was resolved, it was considered that the calculation might aid in the determination, so calculations for all plausible directions were carried out.

Looking at the 001 face of myristamide there will be allowed crystal transitions along the a and b crystallographic axes. Thus only two excited state crystal wave functions need be considered, where the phases for single molecule transitions are picked to reinforce along the respective directions. The upper state functions for a crystal of n molecules are of the form

$$\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \psi_1\psi_1 \ldots \psi_i\dagger \ldots \psi_n$$

where the dagger signifies that the ith molecule is in the V_1 state and the coefficients are approximated as all equal in absolute value (infinite wave length of the light). The expectation value of the interaction operator for an infinite crystal reduces to

$$\int (\psi_1\psi_2 \ldots \psi_i\dagger \ldots \psi_n)^*\, H_{int} \sum_{j=1}^{n} \psi_1\psi_2 \ldots \psi_j\dagger \ldots \psi_n d\tau$$

(16) A. C. Albrecht and W. T. Simpson, *J. Chem. Phys.*, **23**, 1480 (1955).

(17) A. S. Davydov, *J. Exptl. Theoret. Phys.* (*U.S.S.R.*), **18**, 210 (1948).

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Using the dipole approximation for the interaction, the calculation thus involves summing over all neighbors, j, of the ith molecule terms of the form

$$f_{ij}\frac{|\vec{m}|^2}{R^3}$$

where f_{ij} is a trigonometric factor, $\vec{m}$ is a single molecule transition moment, and R is the intermolecular distance. The trigonometric factors can be systematized using the symmetry of the unit cell, which was done.[12] The calculation was carried out for all neighbors within 10 Å. of a given molecule, and the splitting of a-axis and b-axis absorptions was found to vary from 1 to 1.5 e.v. for every Å.^{2} in the expression involving the transition moment squared, with the a-axis part always to the red.

With the transition moment direction 9.1° away from the oxygen–nitrogen line (the value finally found experimentally) and assuming that the transition moment squared is given by[10]

$$|\vec{m}|^2/e^2 = 0.44 \text{ Å.}^2$$

the a-axis absorption is calculated to lie toward the red of the single molecule absorption at 0.11 e.v., while the b-axis absorption should lie to the blue a distance of 0.53 e.v. The calculated splitting is thus 0.64 e.v. or 5.2×10^3 cm.$^{-1}$, with the a-axis part to the red. It is believed that the calculated value is in reasonable agreement with the experimental value (estimated as 0.4 e.v.) when it is considered that the position of the peak of the a-axis absorption is uncertain, and that not all of the single-molecule intensity contributes to the observed crystal splitting, owing to the intervention of the single-molecule vibrations spoiling the resonance.[9]

It has been suggested[9] that the electronic band width parameter for a crystal should be calculated as for a dimer with its molecules disposed according to the strongest interaction in the actual crystal. With the 9.1° angle for the transition moment this calculation leads to

$$2V = 0.4 \text{ e.v.}$$

The single-molecule band width, which is also needed to give the fraction $2V/\Delta$ which determines the nature of the coupling, was taken to be 0.7 e.v.[10] It is the ratio 0.4/0.7 which was used above in this connection.

Direction of the Transition Moment.—Let us consider once again that all the nuclei in the crystal are fixed. The transition moment along either principal direction (provisionally, the a and b crystallographic axes) is then calculated to be a sum of individual molecular moments projected on that direction

$$\frac{1}{\sqrt{n}}\sum_{i=1}^{n}\vec{m_i}\cdot\vec{a}$$

($\vec{a}$ and $\vec{b}$ are unit vectors along the principal directions). Owing to the molecular arrangement in the unit cell, all the terms are the same for an allowed transition in myristamide, so the intensity for strong coupling is given by

$$n|\vec{m}\cdot\vec{a}|^2$$

along the a-direction, and

$$n|\vec{m}\cdot\vec{b}|^2$$

along the b-direction.

It can be shown that the integrated intensity of an electronic band consisting of vibronic transitions is essentially equal to the intensity calculated with the assumption of a pure electronic transition, as above,[18] and this should be true for a crystal as well as for a molecule.

This gives us the result that whether we have strong or weak coupling, we can arrive at the orientation of the transition moment through the ratio of areas of the curves. If there is borrowing, or if the region where one band stops and another starts is ill-defined, this ratio of areas is very likely not going to give an accurate value for the direction. The situation is improved, however, by the fact that with weak coupling the D_a and D_b curves should be proportional in low resolution, so that we have the result

$$\frac{\int D_a d\lambda}{\int D_b d\lambda} = \frac{D_a}{D_b}$$

where the "dichroic ratio" D_a/D_b is independent of wave length. The situation encountered in the case of myristamide is intermediate, but it can be seen that there is a wide region on the long wave length side of the absorption where D_a/D_b is constant, at *ca.* 14.6 (see Figs. 1 and 2, particularly from 2020 to 1890). This region is considered to be the weak coupling part of the NV_1 band (see Fig. 2d of ref. 9). The dichroic ratio for the region gives two possible directions for the orientation of the moment with respect to the amide group: 9.1 and 26.7° with the N–O line, toward the C–N and C–O lines, respectively.[19]

The ambiguity in the work on myristamide has been resolved using the measurements on N,N′-diacetylhexamethylenediamine, and with a new interpretation of the work on N-acetylglycine.[5] In the former compound the direction of $\vec{m'}$ (Fig. 3) is equivalent to a transition moment direction $18 \pm 5°$ away from the N–O line toward the C–N line. This selects the 9.1° value for myristamide.

Unexpectedly, confirmation is provided by working up the results on N-acetylglycine paying attention to the fact that, as with myristamide, there are two values for the polarization, one extraneous. The dichroic ratio was found by Ward to be $D_c/D_b = 20$ to 60 at 2100 Å. for the 100 face,[5] which gives as the correct one of the two possibilities the angle 15° from the N–O line toward the N–C line.

The various angles are all given in Fig. 5, together with arcs indicating estimated experimental uncertainties. It will be noted that the angle for myristamide is more nearly along the N–O line, perhaps outside of experimental uncertainty. (The directions for amides in different environments might well be somewhat different.)

Theoretical Significance of the Polarization.—We take as a starting point a representation of the NV_1 transition for the formate ion, using struc-

(18) H. Sponer and E. Teller, *Revs. Mod. Phys.*, **13**, 75 (1941).

(19) Explanation of the trigonometric formalism used will be given in Part II.

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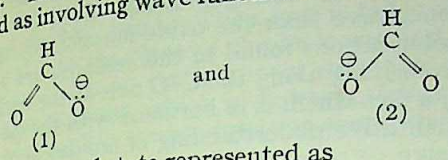
tures. The two states, N and V_1, may be depicted as involving wave functions corresponding to



(1) and (2)

with the normal state represented as

$$\psi_N = 2^{-1/2}(\psi^1 + \psi^2)$$

and the first excited state as[8]

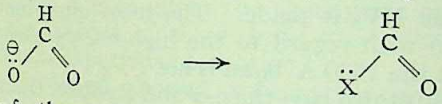
$$\psi_{V_1} = 2^{-1/2}(\psi^1 - \psi^2)$$

(Superscripts refer to structures.) The transition moment is

$$e\int \psi_N \vec{q} \psi_{V_1} d\tau = \frac{e}{2}\left[\int \psi^1 \vec{q} \psi^1 d\tau - \int \psi^2 \vec{q} \psi^2 d\tau\right]$$

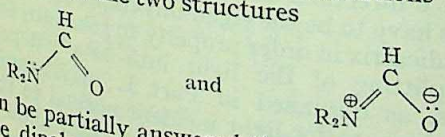
which is just one-half the difference in moments of the structures. This difference is a vector along the O–O line with the length (factor) predicted to be equal to the O–O distance.[20] The transition moment length thus is estimated to be of the order of 1.1 Å., while the value found is *ca.* 0.7 Å.[10]

If the electronegativity of one of the oxygen atoms could be successively increased we should have a *series* of compounds going through the acid all the way, say, to the acid halide, and beyond.



At the furthest extreme the NV_1 transition would be the same as the NV_1 transition for a carbonyl group and so would be polarized along the C–O line. Amides are in or just outside the series, the nitrogen having comparable electronegativity to that of an oxygen with a formal negative charge. It might be expected that the transition moment direction would change monotonically from the O–O to C–O lines in such a series, so that the direction of the moment could be used very simply to characterize the various members.

It is certainly a matter of interest to locate amides in the series. In fact this may be taken as the central question concerning the electronic structure of amides. The question is very closely related to the one regarding the relative contributions to the ground state of the two structures



It can be partially answered through consideration of the dipole moment,[21] infrared intensity,[22] carbonyl force constant,[23] and even the position of the n-π band.[24] It is felt that one of the best approaches is through the Brooker deviation. Brooker in his work on the merocyanine dyes has been able to show convincingly that for vinylogous amides the energy of the charged and uncharged structures

(20) W. H. Zachariasen, *Phys. Rev.*, **53**, 917 (1938).
(21) For a recent discussion see A. Kotera, S. Shibata and K. Sone, THIS JOURNAL, **77**, 6183 (1956).
(22) G. M. Barrow, *J. Chem. Phys.*, **21**, 2008 (1953).
(23) C. G. Cannon, *Mikrochim. Acta*, **2-3**, 555 (1955); *J. Chem. Phys.*, **24**, 491 (1956); and H. Letaw, Jr., and A. H. Gropp, *ibid.*, **21**, 1621 (1953).
(24) S. Nagakura, *Bull. Chem. Soc. Japan*, **25**, 164 (1952).

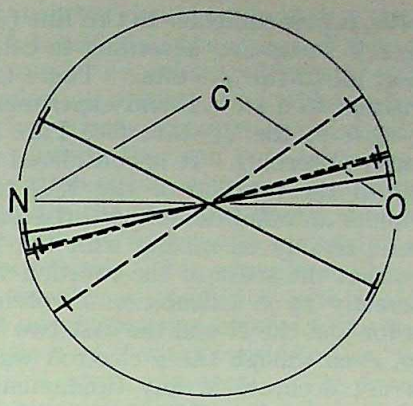


Fig. 5.—The two possible orientations of the NV_1 transition moment for myristamide (solid lines) and N-acetylglycine (broken lines), and the single orientation for N,N′-diacetylhexamethylenediamine (dashed line) as referred to the plane of the amide group. Uncertainties are indicated by the lengths of arcs through the lines.

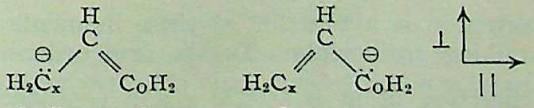
must be nearly equal; for some dyes he has found conditions under which true equality of energy may be demonstrated.[25] The Brooker deviation of a very simple vinylogous amide

$$Me_2\ddot{N}—CH=CH—CH=CH—CH=CH—CH=O$$

has been found to be zero in water, and the color shifts monotonically toward the blue as methanol is added. In pure methanol the deviation is 40 mμ.[26] This positive or normal deviation means that the uncharged structure is the more stable, even in the relatively polar water–methanol environment. That the same conclusion may apply to the amides themselves is easy to imagine, and is borne out by considering the question in detail.

If we now look at the experimental values of the polarizations (Fig. 5) we see that the direction is toward the N–C line, which is surprising considering our expectation for the series. Thus either the amides in their crystalline environment are outside the series, or else the theoretical polarization direction for the series does not vary monotonically between the O–O and the C–O lines. The second alternative is favored by much evidence, including the following calculation.

Theoretical Calculation of the Polarization.—In view of the discussion in the last section, short of having the wave functions for amides themselves, it would be desirable to have good functions for formate ion and apply perturbation theory. We had obtained, in another connection, a set of state wave functions after configurational for allyl anion[8]



We shall use these wave functions as a substitute for the formate functions to represent the start of the series. (The subscripts x and o will be used below to distinguish positions affected differently by a particular perturbation.) The first singlet-singlet transition, NV_1, for the allyl anion is polarized along a line joining the terminal carbons (||) and the

(25) See the series of articles in THIS JOURNAL, beginning with **73**, 5326 (1951).
(26) W. T. Simpson, unpublished research.

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second, NV_2, is perpendicular to this line ($\perp$). The next higher V states are, according to calculation, not close at all to the V_2 state.[8] There is a Rydberg transition to a state found experimentally to be fairly close to the V_2 state (see Part III) but quite weakly absorbing. It is considered that the magnitude of the rotation of the NV_1 transition moment under an infinitesimal perturbation should thus depend mainly on mixing with the V_2 state. It follows that the sense of the rotation would be given correctly by a calculation involving wave functions for just the N and the first two V states. Moreover, even though the π-electron wave functions are not accurate in any fundamental way, they are known empirically to represent positions and intensities of π-electron transitions quite well provided that configurational interaction has been introduced. Perhaps it is not being unrealistic, therefore, to expect the calculation here to provide the correct sense of the rotation. Probably the greatest uncertainty stems from using allyl anion functions for formate ion functions.

What was done was to obtain the abbreviated first-order perturbed wave functions

$$\psi_N = \psi_N^0 - \frac{H'_{NV_1}}{W_{V_1} - W_N}\psi_{V_1}^0 - \frac{H'_{NV_2}}{W_{V_2} - W_N}\psi_{V_2}^0$$

$$\psi_{V_1} = \psi_{V_1}^0 - \frac{H'_{V_2V_1}}{W_{V_2} - W_{V_1}}\psi_{V_2}^0 - \frac{H'_{NV_1}}{W_N - W_{V_1}}\psi_N^0$$

under a perturbation at one of the terminal carbons (labeled C_x, referring to the allyl anion structures above) such that the Coulomb integral for that carbon decreases infinitesimally. This change represents the first increase in electronegativity of x as the series develops, away from formate ion. The functions are found to be

$$\psi_N = \psi_N^0 - 0.0903\epsilon\psi_{V_1}^0 - 0.0318\epsilon\psi_{V_2}^0$$

$$\psi_{V_1} = \psi_{V_1}^0 + 0.0903\epsilon\psi_N^0 - 0.1303\epsilon\psi_{V_2}^0$$

where for atom C_x

$$\int(2p)H'(2p)d\tau = \epsilon < 0$$

The various state moments and transition moments for the unperturbed state functions have to be evaluated paying careful attention to consistency in the selection of phases. They are given in Table I. The NV_1 transition moment after the

TABLE I

THEORETICAL ELECTRIC MOMENT LENGTHS FOR ALLYL ANION IN Å.

	N	V_1	V_2	NV_1	NV_2	V_1V_2
$\parallel$	0	0	0	−1.2994	0	−0.4562
$\perp$	0.8161	0.7418	1.0439	0	−0.4127	0

perturbation is a function of these moments and the mixing coefficients. To the first order in ϵ, the direction of $\vec{m}$ is $0.0605\ \epsilon\ \vec{j} + (-1.2994 + 0\ 0145\ \epsilon)\ \vec{i}$. The $\vec{i}$ vector is parallel ($\parallel$) and the $\vec{j}$ vector perpendicular ($\perp$), with senses as given above in connection with the structures for allyl anion. With $\epsilon < 0$ this gives a twisting away from the parallel direction toward the bond connecting C_x with the center carbon, as found experimentally. Similarly, the NV_2 transition moment is found to twist from $\perp$ toward the $C-C_o$ line.

We may conclude that notwithstanding the observed NV_1 polarizations, amides can still be in the series, with the nitrogen being effectively more electronegative than the oxide ion of formate ion. The polarizations found in this research are a long way from lying along the C–O axis of the carbonyl group, a fact which is in harmony with the customary qualitative understanding of amides in organic chemistry.

III. Absorptions at 2200 and 1660 Å.

Returning again to the consideration of Figs. 1 and 2 we find from the behavior of the polarization that the long wave length tail of the NV_1 absorption may be interpreted as containing a separate electronic transition, which is assigned as n-π[10,27] and called the 2200 Å. band. The region around 1660 Å. is qualitatively different from the NV_1 part and is believed to be the first member of the Rydberg series previously found.[10] It is tentatively assigned as involving a jump of a non-bonding 2p electron on the oxygen to an orbital which is an in-phase linear combination of 3s atomic orbitals. There is a polarization change below 1600, which, however, is in a region where the experimental error is likely to be great. There is an NV_2 transition expected on quite general theoretical grounds in this region, so the tentative assignment of the absorption below 1600 as NV_2 is made. The most important conclusion with regard to the high energy absorption is that the 1660 Å. band is not NV_2.

In this third part the n-π and Rydberg transitions will each be discussed, though first it is convenient to introduce a somewhat formal trigonometric theory connecting the crystal-fixed and molecule-fixed polarization directions.

Trigonometric Analysis of the Dichroic Ratio.—With the assumption of weak coupling one has the following relationships connecting absorption densities along molecule-fixed (x,y,z) and crystal-fixed (a,b,c) axes.[16]

$$\begin{pmatrix} D_x \\ D_y \\ D_z \end{pmatrix} = \mathbf{M}\begin{pmatrix} D_a \\ D_b \\ D_c \end{pmatrix} \text{ or } \begin{pmatrix} D_a \\ D_b \\ D_c \end{pmatrix} = \mathbf{M}^{-1}\begin{pmatrix} D_x \\ D_y \\ D_z \end{pmatrix}$$

In practice the matrix **M** is derived from its inverse, a matrix with elements equal to the squared projections of molecule-fixed unit vectors on the a, b and c directions in the crystal. The a-, b- and c-axes have to be the eigen-directions of a section of the indicatrix in order properly to take into account the splitting of the light into two independent beams, as discussed in Part I. Myristamide is monoclinic, so for light incident normal to the 001 face the principal directions are parallel to the a and b crystallographic axes. For light polarized along the a-axis the E vector inside the crystal is not required by symmetry to lie in a plane containing the 001 face. However considering the orientations of the NV_1 transition moments it is believed that to assume this particular orientation is a good approximation—so that the c-axis is defined here as effectively normal to the 001 plane, and the a- and b-axes as coinciding with the crystallographic a- and b-axes.[28]

(27) J. S. Ham and J. R. Platt, *J. Chem. Phys.*, **20**, 335 (1952).

(28) Detailed consideration of the error introduced by this assumption gives the result that if the correct c-axis were inclined by the unlikely amount of 30° away from the 001 plane the final deter-

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As a simple example of the formal use of the above relationships consider the weak coupling region of the NV_1 band. The z-axis is taken as perpendicular to the plane of the molecule and the x direction is the as yet unknown direction of the transition moment, which is, however, assumed to be in-plane. The inverse equation simplifies to

$$\begin{pmatrix} D_a \\ D_b \\ D_c \end{pmatrix} = \mathbf{M}^{-1} \begin{pmatrix} D_x \\ 0 \\ 0 \end{pmatrix}$$

resulting in an equation for the polarization direction

$$D_a/D_b = M_{11}^{-1}/M_{21}^{-1}$$

It was the observed dichroic ratio combined with this ratio of $\mathbf{M}^{-1}$ elements which led to the angles given in Fig. 5. The fact that the matrix elements are projections squared is to be connected with the fact that the dichroic ratio is always positive, and is of course responsible for the ambiguity.

The n-π Transition.—What is known with certainty about the n-π transition is that a simple orbital approach to the system of 4 π electrons in 3 π orbitals makes the highest filled level non-bonding, so the n-π transition should have approximately the same frequency as the first π-π transition. The 2200 Å. band may then be provisionally assigned as n-π because it is in about the right place and because the analysis of the dichroic ratio is consistent with the expected polarization.

The predicted allowed polarization is out-of-plane, or z, but with a strength depending on the extent to which the lobes of the non-bonding 2p orbital on the oxygen are put out of balance by interaction with the nitrogen, which is long-range. It would therefore be anticipated that except for the zero-zero region there would be a comparatively strong formally forbidden part, polarized like the neighboring NV_1 transition.[5] The z molecular axis does not have an appreciable projection on the a crystal axis in myristamide so the test of the degree of forbiddenness is the deviation of D_a/D_b from zero. Actually D_a/D_b is around 3.6 at 2200, becoming understandably smaller at the long wave length edge.

The expression for the crystal fixed densities with x the NV_1 polarization direction, becomes

$$\begin{pmatrix} D_a \\ D_b \\ D_c \end{pmatrix} = \mathbf{M}^{-1} \begin{pmatrix} D_x \\ 0 \\ D_z \end{pmatrix}$$

giving

$$D_a = M_{11}^{-1}D_x + M_{13}^{-1}D_z$$
$$D_b = M_{21}^{-1}D_x + M_{23}^{-1}D_z$$

The required $\mathbf{M}^{-1}$ elements are known from the work on the NV_1 transition and from the orientation of the molecular plane, so that the ratio of "allowed" to "forbidden" absorption can be computed. It turns out to be

$$D_z/D_x \approx 1/2$$

The Rydberg Transition.—There is a Rydberg series in formamide corresponding to the formula[10]

$$\nu = 82{,}566 - \frac{R}{(n - 0.639)^2} \qquad n = 3, 4, 5, \ldots$$

The first member should be at 1610 Å. and is identified with the 1660 Å. absorption of myristamide.

The formula is written differently than originally[10] following a scheme by which it is expected that the low energy termination point may be predicted.[11] Briefly the plan is to write the formula with an appreciable negative quantum defect. Only then are the quantum numbers presumed to give a correct description of the nodal characteristics of the orbitals. For example, having $n = 3$ as the first member is connected with the fact that there are no unfilled molecular orbitals for amides which have $n = 2$ when considered as "fused," as for a united atom approach. (The fused atomic orbital description of the π orbitals is illustrated in Fig. 6.) We go on now to make a tentative assignment of the Rydberg transition guided by the above considerations.

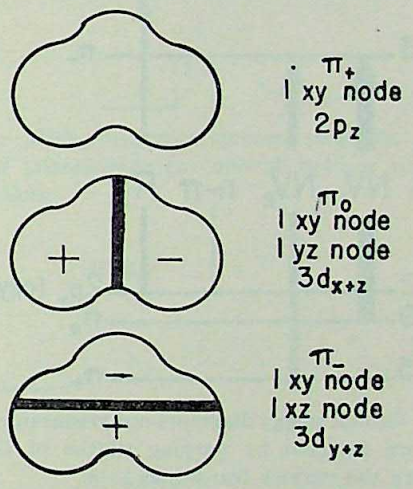

Fig. 6.—Illustration of the fused atomic orbital description for allylic π orbitals.

There are two $n = 3$ empty orbitals, either one of which might be reached in the first transition. One is the anti-bonding $2p_\pi$ orbital, π_-, which is 3d with respect to nodal behavior and the other is a bonding linear combination of 3s AO's which is 3s. These orbitals could well have comparable energies, the anti-bonding character of the π orbital balancing the promotion involved in going to the molecular orbital made up of 3s AO's.

This leaves the question of the originating orbital. It could not be the highest filled or non-bonding π orbital, $\pi\sigma$, because this would lead to the possibilities (fused AO description in parentheses)

$$\pi_0(3d) \longrightarrow \pi_-(3d)$$
$$\pi_0(3d) \longrightarrow 3s(3s)$$

The former is the NV_1 transition and the latter is forbidden provided that amides are considered as having allylic symmetry. The two most plausible possibilities for the originating orbital are considered to be the bonding π orbital, π_+, and the nonbonding oxygen 2p orbital, $2p_y$. The first member of the Rydberg series would then be

$$\left.\begin{matrix} \pi_+(2p) \\ 2p_y(2p) \end{matrix}\right\} \longrightarrow \left.\begin{matrix} \pi_-(3d) \\ 3s(3s) \end{matrix}\right\}$$

Of the four possibilities the one

$$2p_y(2p) \longrightarrow 3s(3s)$$

mination of the angle of the NV_1 polarization direction would be only 5° in error.

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seems to be the most plausible. The $2p_y \rightarrow \pi_-$ transition is the n-π transition assigned to the 2200 Å. region. (It would appear that the experimental results for the 1660 band, polarization and nearness to the NV_1 transition, make it possible to assign the band as n-π; however the allowed intensity is too high. The formally allowed intensity for the n-π transition must, it should be remembered, be quite small.) The $\pi_+ \rightarrow \pi_-$ transition is also the NV_2 transition and on the most general theoretical grounds would not be expected to lie so close to the NV_1 transition. (This closeness is most acutely demonstrated in the spectrum of formamide itself[10] where the absorption around 1600 A. is not even resolved, but shows up as a broadening of the NV_1 band relative to the band

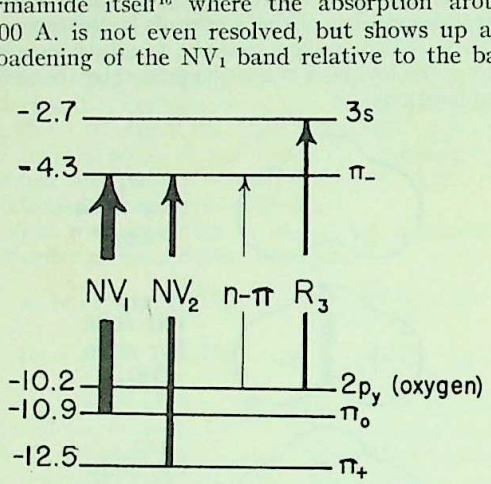

Fig. 7.—Orbital energy diagram for myristamide: (e.v.) intensities are depicted by varying widths of the arrows representing the various transitions.

in dimethylformamide.) The $\pi_+ \rightarrow 3s$ transition would be at shorter wave lengths than the $2p_y \rightarrow 3s$ transition, so unless there is yet another Rydberg band at longer wave lengths the $2p_y \rightarrow 3s$ assignment is to be preferred.

The picture of the orbital reached in the transition is a linear combination of 3s orbitals, all in phase, with perhaps the greatest amplitude on the oxygen, though the higher Rydberg members gradually become more and more like atomic orbitals. The structure in the 1600 Å. region of formamide,[10] with a spacing of 1600 cm.$^{-1}$, may then be interpreted as vibrational intervals corresponding to a carbonyl stretching motion in the upper state (the ground state stretching frequency is 1740 cm.$^{-1}$).[29]

Examination of Fig. 1 shows that the absorption in the 1660 Å. region is likely to be partly from the b-axis component of the NV_1 transition (considered from the strong coupling point of view) and partly from the long wave length part of the band below 1600 Å. Nevertheless the qualitative result

$$D_b > D_a$$

is believed to be a characteristic of the Rydberg member itself. It is found using the trigonometric methods illustrated in the foregoing that this result is consistent with the polarizations expected for all four possibilities considered above, in particular for the possibility which is considered the most likely

$$2p_y \longrightarrow 3s$$

If we adopt this latter process we can, by considering various combinations, represent all the transitions found in this research for myristamide by means of an orbital energy diagram. This is done in Fig. 7. The effective orbital energy of the π_+ orbital is obtained by adopting for the NV_2 absorption a value of 1520 Å. This is estimated by assuming for myristamide an NV_1/NV_2 energy ratio intermediate between the ratio for formamide and dimethylformamide.[10] The zero of energy is taken as the ionization limit for the observed Rydberg series.

(29) J. C. Evans, *J. Chem. Phys.*, **22**, 1228 (1954).

SEATTLE, WASHINGTON

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY, AND CHEMICAL WARFARE LABORATORIES]

Nuclear Magnetic Resonance Study of the B_2D_6–B_5H_9 Exchange Reaction[1]

BY WALTER S. KOSKI, JOYCE J. KAUFMAN AND PAUL C. LAUTERBUR

RECEIVED NOVEMBER 15, 1956

The exchange of deuterium between diborane and pentaborane was investigated by nuclear magnetic resonance. It was found that the exchange proceeded preferentially in the terminal hydrogen positions in pentaborane. The rate of exchange of the apex hydrogen appeared to be within ±10% the same as the exchange rate of the base terminal hydrogen. Under the experimental conditions the bridge hydrogens in pentaborane did not participate in the exchange.

Introduction

Recently we have had occasion to investigate the exchange of deuterium between diborane and pentaborane and we have found that the reaction proceeds through borane, derived from the dissociation of diborane, as an intermediate. By means of a mass spectroscopic study[2] we were able to disentangle the exchange from a complicating reaction due to the pyrolysis of diborane to form pentaborane, and by an infrared study[3] to show that only the five terminal hydrogens participated in the exchange reaction. The bridge hydrogens

(1) This research was supported in part by the United States Air Force through the Office of Scientific Research of the Air Research and Development Command.

(2) W. S. Koski, Joyce J. Kaufman, L. Friedman and A. P. Irsa, *J. Chem. Phys.*, **24**, 221 (1956).

(3) Joyce J. Kaufman and W. S. Koski, *ibid.*, **24**, 403 (1956).

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of pentaborane did not participate in the exchange reaction and neither did the boron atoms under the conditions of the experiments.

The pentaborane molecule has a tetragonal pyramidal arrangement of borons with a hydrogen attached to each boron by a normal boron to hydrogen bond (terminal hydrogens). Four other hydrogens are attached to the base borons by bridge bonds. It was of interest to our program to confirm by an independent technique our previous observations on the difference in the exchangeability of bridge and terminal hydrogens in pentaborane and to determine whether the rate of exchange of the hydrogen attached to the apical boron in pentaborane differed from the exchange rate of a terminal hydrogen attached to the base of the molecule. This report summarizes our study of this exchange using nuclear magnetic resonance as a tool.

Experimental

All of the spectra used in this study were obtained with a Varian Model 4300A high resolution nuclear magnetic resonance spectrometer at a frequency of 40 Mc./sec. and a magnetic field of about 9400 gauss. They were recorded with a Sanborn recorder at a speed of 25 mm./sec. In most cases, the sweep width was 700 milligauss and the sweep rate 70 milligauss/sec. Calibration was made by a water signal modulated at 400 cycles/sec.

The radiofrequency power was kept low enough so that the spectra appeared to be about the same when swept through in either direction. This precaution ensured that saturation effects were largely eliminated.

All of the samples were sealed in Pyrex glass tubes, 5 mm. outside diameter and 3 mm. inside diameter, except for the 55.6% deuterated pentaborane samples which were in tubes 3 mm. outside diameter and 1 mm. inside diameter, because only small quantities were available. The lengths of the samples ranged from 5 to 25 mm. All spectra were taken at room temperature.

Pentaborane of normal isotopic content was prepared by pyrolysis of diborane at 180°. The procedure and purification method has been published previously.[3] The 5% deuterated pentaborane sample was prepared by treating 53.2 cm. of B_2D_6 and 12.55 cm. of B_5H_9 in a 325-cc. bulb at 80° for 2 hours and 50 minutes. The sample, after separation and purification, was sealed in the standard 5 mm. outside diameter tube. The length of this liquid sample was 25 mm. The pentaborane samples containing 26.5 and 55.6% deuterium were prepared in a similar manner except that the reaction times were 11.5 and 48 hours. The latter time actually consisted of two 24-hour contact times with the diborane being replaced with a fresh sample of B_2D_6 at the end of the first 24-hour period. The procedure for separation of the diborane and pentaborane and the purification methods were similar to that previously used.[2] The analysis for total deuterium content was made by decomposing the boron hydride and subjecting the resulting hydrogen–deuterium mixture to a thermal conductivity method.[4] The deuterium content of the B_2D_6 used for deuteration of the pentaborane ranged from 96–98%.

Results and Discussion

The structure of pentaborane has been established by X-ray diffraction of the crystal,[5,6] electron diffraction[7,8] and microwave spectroscopy[9,10] work on the gas. The nuclear magnetic resonance spectra of H and B^{11} in pentaborane have been reported and analyzed by Shoolery[11] and Kelly, Ray and Ogg.[12] The H spectrum of pentaborane of normal isotopic content shown in Figs. 1a and 2a is identical with the ones reported by the earlier observers. Three main sets of peaks are found and

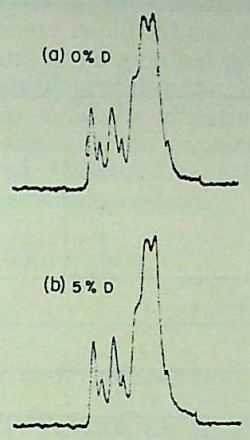

Fig. 1.—High resolution proton magnetic resonance spectra of pentaborane (a) normal isotopic content, (b) 5% deuterium.

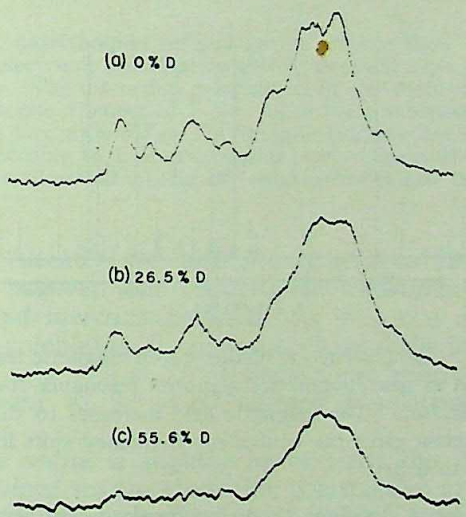

Fig. 2.—High resolution proton magnetic resonance spectra of pentaborane containing (a) normal isotopic abundance, (b) 26.5% deuterium and (c) 55.6% deuterium.

are assigned to hydrogen attached to B^{11} atoms. Other smaller peaks, usually unresolved, arise from those hydrogens bonded to B^{10}. Figure 3 shows a step by step reconstruction of the theoretical spectrum, using the experimentally determined relative chemical shifts and spin couplings estimated on the assumption that there are four large peaks from base terminal hydrogens attached to B^{11}, four small peaks from the apex hydrogen attached to B^{11}, and a broad unresolved peak from the bridge hydrogens. The synthesized spectrum in Fig. 3 has the following contributions: (a) four lines arising from the coupling of the four base terminal protons with B^{11}; (b) four equal lines, one-fourth the intensity of those in (a) representing the apex protons attached to B^{11}; (c) seven lines

(1) W. S. Koski, P. C. Maybury and Joyce J. Kaufman, *Anal. Chem.*, **26**, 1992 (1954).
(2) W. J. Dulmage and W. N. Lipscomb, THIS JOURNAL, **73**, 3539 (1951).
(3) W. J. Dulmage and W. N. Lipscomb, *Acta Cryst.*, **5**, 260 (1952).
(4) K. Hedberg, M. E. Jones and V. Schomaker, THIS JOURNAL, **73**, 3538 (1951).
(5) K. Hedberg, M. E. Jones and V. Schomaker, *Proc. Natl. Acad. Sci. U. S.*, **38**, 679 (1952).
(6) H. J. Hrostowski, R. J. Myers and G. C. Pimentel, *J. Chem. Phys.*, **20**, 518 (1952).
(7) H. J. Hrostowski and R. J. Myers, *ibid.*, **22**, 262 (1954).
(8) H. J. Hrostowski, R. J. Myers and G. C. Pimentel, *J. Chem. Phys.*, **22**, 1483 (1954).
(9) W. J. Lafferty and E. A. Lewis, *ibid.*, **24**, 1128 (1956).
(10) H. J. Hrostowski and R. J. Myers, *ibid.*, **22**, 262 (1954).
(11) J. N. Shoolery, *Disc. Faraday Soc.*, **19**, 215 (1955).
(12) J. Kelly, J. Ray and R. A. Ogg, Jr., *Phys. Rev.*, **94A**, 767 (1954).

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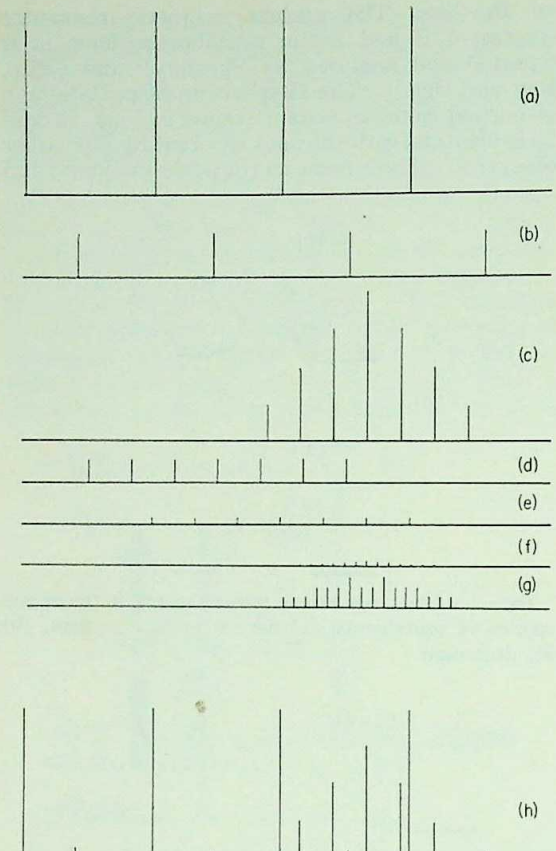

FIG. 3

Fig. 3.—Reconstruction of the proton magnetic resonance spectrum in pentaborane for a proton resonance frequency of 40 Mc./sec. The magnetic field increases to the right. The abscissa gives the equivalent frequency shift in cycles relative to water.

from those bridge protons flanked by two B^{11} atoms; (d) seven lines from the base hydrogens bonded to B^{10}; (e) seven more lines, all equal, from apex protons on B^{10}; (f) a set of small lines arising from the fact that 3.5% of the bridge hydrogens are situated between two B^{10} atoms; (g) this contribution arises from bridge protons joining one B^{10} and one B^{11}; (h) the addition of all these contributions results in a spectrum that compares very well with the experimental results when instrumental resolution is taken into account. In assembling Fig. 3, it was assumed that B^{11} has an isotopic abundance of 81.17%, a nuclear magnetic moment of 2.6880, and a spin of 3/2. B^{10} has an abundance of 18.83%, a magnetic moment of 1.8006, and a spin of 3.

The peaks designated as x and y in Fig. 3h were used in this study to follow the progress of deuteration in the base and apex terminal hydrogen positions, respectively. Our first analysis of the *n-m-r* spectra of partially deuterated pentaborane prepared by exchange was made to obtain a measure of the relative rates of exchange of the terminal and bridge hydrogens in the molecule. It was found that the best place to divide the spectrum in order to separate the two types of hydrogens was between peaks x and y mentioned above, and the rest of the spectrum. A number of spectra of both the undeuterated and deuterated samples were taken and only those which showed no evidence of a field shift or other irregularity were used. Both forward (from low to high field) and backward sweeps were used and the results were calculated separately.

The areas under the peaks were determined by cutting out the entire spectrum, snipping it in two at the minimum after the first two peaks, and weighing for both the forward and backward sweep directions. The ratio of the large area to the smaller one was 7.79 and 7.31 for the forward and backward directions, respectively. The error is estimated as being ± 0.03. The corresponding theoretical ratio as obtained from Fig. 3 was 7.02. The experimental ratios obtained with the 26.5% deuterium sample for the forward and backward sweeps were 10.5 ± 0.1 and 10.0 ± 0.1, respectively. We assume in treating these data that the differences between calculated and observed ratios for the undeuterated pentaborane are possibly caused by the arbitrary process of selecting the point at which to cut the spectrum apart, or more likely the discrepancy probably arises because of a difference in the spin-lattice relaxation times of the different types of protons. We have attempted to minimize this effect by keeping the power level low so as to avoid saturation. The patterns obtained for the forward and backward sweeps indicated an absence of such saturation effects. At any rate the point at which the spectrum was cut was quite far away from any bridge hydrogen lines, so we have further assumed that the ratio of the observed to theoretical values will remain constant in going from one sample to the other. Applying this correction, we get the corrected ratio for the 26.5% deuterium sample as 9.47. Applying simple stoichiometric calculations to these ratios, we find that in the 26.5% sample more than 90% of the deuterium has gone into the terminal hydrogen positions and somewhat less than 10% has gone into the bridge positions. In view of the fact that all of the deuterium in the bridge positions can be accounted for by the pyrolysis of diborane,[1] we conclude that to within experimental error none of the bridge positions in pentaborane participate in the exchange reaction under the conditions of our experiments.

Further qualitative evidence for the difference in rates is provided by the 55.6% deuterium sample, the spectrum of which is shown in Fig. 2c. It is clear that only a trace of the terminal hydrogen remains, whereas the bridge hydrogen peak is still strong.

In view of the fact that the n-m-r technique can, at least partially, resolve the apex and base terminal hydrogens, it is possible to make some deductions on the relative rates of exchange in these positions. Examination of Fig. 3 shows that the small peak y is made up of two lines, one from apex protons on a second smaller contribution from base

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protons on B^{10}. Admittedly this is not a completely satisfactory situation; however, it is the best place in the spectrum to check on progress of deuteration at the apex position.

The procedure chosen was to run somewhat compressed spectra, similar to those shown in Fig. 1. The heights of the two peaks were measured from the base line and the ratio of the second to the first was calculated. Pentaborane samples containing 0, 5 and 26.5% deuterium gave 0.660, 0.675 and 0.681, respectively, as peak ratios. At least five measurements were made for each deuterium content. If we make a rough calculation of the peak height ratio to be expected, taking into account the composite nature of peak y, the differences between the ratios listed above can be accounted for by a 10% difference in the extents of deuteration in the base terminal and apex hydrogen positions. We therefore conclude that as far as terminal hydrogens in pentaborane are concerned the rates of exchange in the base and apex positions are the same to within ±10%.

It should be pointed out that these studies do not permit us to eliminate mechanisms in which only base or apex terminal protons exchange with BD_3 followed by a more rapid intramolecular exchange between base and apex terminal protons. In view of the properties of pentaborane, however, we feel that this is an unlikely situation and a more probable mechanism is the exchange of deuterium between deuterated borane and each of the terminal hydrogen positions independently.

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Interpretation of Abnormalities in Atom Polarization in Terms of Electric Moment

BY C. C. MEREDITH, L. WESTLAND AND GEORGE F WRIGHT

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Dielectric constant determinations of pelletted solid benzoquinone, naphthoquinone and anthraquinone show that the atom polarizations are not abnormally high. Assignment of the non-electronic polarization chiefly as orientation polarization has been confirmed by demonstration of temperature dependence. The distortion polarization of 4,4′-dinitrobiphenyl has also been shown to be normal, so this substance must have an electric moment of 1 *D*. All of these substances must have non-planar and non-linear structures. The so-called abnormal polarization (57 cc.) of ferric acetylacetonate seems to be partly (21 cc.) atomic and partly due to orientation polarization according to dielectric constant determinations of solids and solutions. Since some of these studies contradict earlier evidence the reliability of the measurements and the interpretation is discussed.

A discrepancy has been observed between the total electrostatic polarization and the electronic polarization in certain substances. This discrepancy has been assigned as atom polarization.[1] Typical compounds to which these molecular deformations are attributed are quinones, *p*-substituted biphenyls and metal acetylacetonates, none of which are presumed to contribute to orientation polarization. These types have been considered in the present study.

The Quinones

The difference, $P_T - P_E = 8$–10 cc., for a series of 1,4-benzoquinones would indicate moments of 0.6–0.7 *D* but the orthodox expectation that quinones are planar, as well as the temperature-independent constancy of $P_T - P_E$ among these quinones, has brought forth the theory[2] of an atom polarization due to lateral deformation of "balanced carbonyl dipoles." The apparent dipole moment for 2,5-di-*t*-butylbenzoquinone (= 0.81 ± 0.03 *D* in benzene at 25°)[3] seems to be the only, and minor, exception to this generalization.

In view of this conclusion we sought by use of benzoquinone to test our method[4] for determination of atomic plus electronic polarization by use of solid organic compounds pelletted to maximum density. Already we had found reasonable agreement between our capacitance measurements of pelletted mercuric chloride (P_A = 5 cc.) and the value calculated from vapor phase dielectric constants (P_A = 6 cc.).[5] However our pelletted benzoquinone at 22 ± 2° showed a polarization of 30.1 cc.

This value is slightly lower than the 30.9 cc. determined for the electronic polarization at 5892.6 Å. in benzene solution but is slightly higher than the 28.4 cc. value accepted by many workers[1] and derived from group polarizations (26.8 cc.) plus 1.58 cc. of "exaltation."[6] In any event the derived value deviates from the observed pellet polarization only by the amount expected[7] for normal atom polarization. But this pellet polarization is 7–9 cc. less than the total polarization reported from benzoquinone in solution or in the gaseous state. Therefore the difference cannot be attributed to atom polarization.

In view of this discrepancy we have determined at several temperatures the dielectric constants and specific volumes of a series of solutions of benzoquinone. The precision of these determinations may be judged from Fig. 1 (solutions in benzene) and Fig. 2 (solutions in dioxane) from which the

(1) J. W. Smith, "Electric Dipole Moments," Butterworths, London, 1955, p. 271.
(2) I. E. Coop and L. E. Sutton, *J. Chem. Soc.*, 1269 (1938).
(3) H. Kofod, *Acta Chem. Scand.*, **7**, 928 (1953).
(4) C. C. Meredith and G. F Wright, *Can. J. Technology*, **33**, 182 (1955).
(5) H. Braune and R. Linke, *Z. physik. Chem.*, **31B**, 12 (1935).
(6) G. G. Kikina, Ya. K. Syrkin and E. A. Shott-L'vova, *Izvest. Akad. Nauk. S.S.S.R. Otdel Khim. Nauk*, 563 (1954); *C. A.*, **48**, 13316 (1954).
(7) J. H. Van Vleck, "Theory of Electric and Magnetic Susceptibilities," Oxford Press, London, 1932, p. 46.

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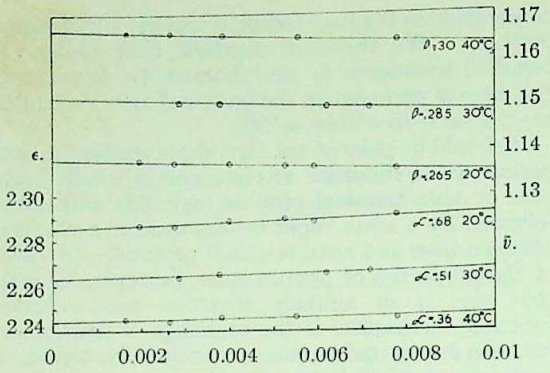
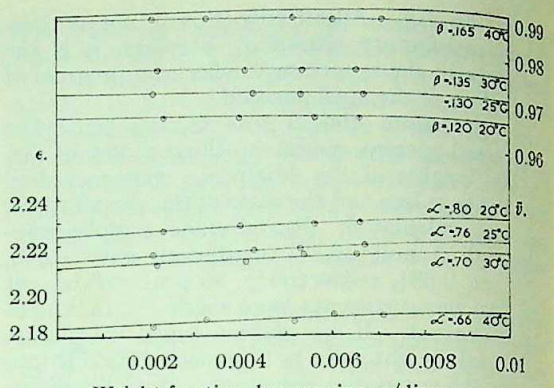


Weight fraction benzoquinone/benzene.

Fig. 1.—Dielectric constants and molar volumes.



Weight fraction, benzoquinone/dioxane.

Fig. 2.—Dielectric constants and molar volumes.

derivatives of dielectric constant ϵ, and specific volume V, with respect to weight fraction (α and β, respectively) may be evaluated. Calculation by the method of Halverstadt and Kumler[8] for total polarization of the solute

$$P_{20} = \left[\frac{3\alpha V_1}{(\epsilon_1 + 2)^2} + \frac{\epsilon - 1}{\epsilon + 2}(V_1 + \beta)\right] M$$

leads to the polarization values in Table I. This method of calculation seems to be reliable since the dielectric constants for the pure solvents are in close numerical agreement (Table I) with ϵ obtained by extrapolation (Fig. 1 and 2) of $\delta\epsilon/\delta\omega$ to zero weight fraction ω. The maximum deviation shown in Table I (detd. − extrap./$\Delta\epsilon$) is 1%. This would lead to an error (largely from the slope of β) not exceeding 0.5 cc. in P_{20} for benzoquinone where M is 108. Thus there is no necessity for application of the corrections suggested by Smith[1] and the polarizations in Table I have been calculated by use of V, and ϵ of pure solvent. It

TABLE I

POLARIZATIONS AND ELECTRIC MOMENTS OF BENZOQUINONE AT 500 Kc.

Temp., °C.	ϵ, benzene Detd.	Extrap.	Polarization, cc., in Benzene	Dioxane	ϵ, dioxane Detd.	Extrap.	Moments, D, in Benzene	Dioxane
20	2.284	2.285	41.9	40.6	2.224	2.224	0.75	0.70
25				39.7	2.216	2.213		.68
30	2.262	2.263	38.2	38.7	2.210	2.210	.63	.65
35	2.253	2.252	36.4				.56[a]	
40	2.245	2.244	35.1	37.3	2.189	2.184	.50	.60

[a] This value is reduced to 0.55 D when the polarization (36.1 cc.) is determined at 2600 kc.

is apparent that the polarization is not temperature independent, either in benzene or dioxane. Unfortunately a plot of these polarizations against reciprocal absolute temperature cannot be used to find, by extrapolation to $1/T = 0$, the intercept corresponding to distortion polarization because the Debye relationship is inadequate in this respect for solutions. Nevertheless an orientation polarization rather than an abnormal distortion (atom) polarization seems to be indicated by the temperature dependence.

In order to test this observation further we have determined the dielectric constant of anthraquinone. Previously a moment of 0.6 D was reported without detail[9] but subsequently it was stated that the moment of this substance in the same solvent (benzene) was zero.[10] Actually the solubility in benzene is too low for precise measurement of dielectric constant. According to our study in dioxane at 30° the total solute polarization is 71.5 cc. There is some doubt about the electronic polarization. Fischer and Rogowski give the value 64 ± 2 cc. without stating their source or method. The refraction measured in a 0.3% solution in pyridine gives an electronic polarization for anthraquinone of 61.7 cc.[11] Our extrapolation of apparent dielectric constant *versus* pellet thickness gives a value of P_{E+A} of 61.1 cc. and from this value (and a density at 20° by flotation of 1.44) we calculate the electric moment to be 0.71 D.

We have found that 1,4-naphthoquinone behaves similarly with benzo- and anthraquinone. The combined electron and atom polarization deduced from pellet studies is close (45.9 cc.) to that expected (46.1 cc.) by group moment subtractive calculation from the observed P_E for anthraquinone. When this polarization of the solid is subtracted from the total solute polarization (77.0 cc.) of 1,4-naphthoquinone in benzene at 20° the corresponding moment is found to be 1.21 D. This value differs from that of benzoquinone by about the same amount (0.46 D) as was found in benzene at 25° for 1,2-benzoquinone (5.1 D) and 1,2-naphthaquinone (5.67 D).[12]

It is of interest to consider the source of the apparent moments of these quinones since temperature dependence seems to exclude an abnormal atom polarization. Orientation polarization has been considered previously in terms of molecular distortion due to thermal agitation.[13] Hampson, Hammick and Jenkins have observed that a deviation from planarity of 8° in benzoquinone due to thermal agitation would not be energetically absurd despite the resonance stabilization (13 kcal./mole) reported for benzoquinone.[14] However they aban-

(8) I. F. Halverstadt and W. D. Kumler, THIS JOURNAL, **64**, 2988 (1942).

(9) R. J. W. LeFevre, "Dipole Moments," Methuen, London, 1938, pp. 73 and 93.

(10) E. Fisher and F. Rogowski, *Physik. Z.*, **40**, 331 (1939).

(11) J. Schuyler, L. Blom and D. W. van Krevelen, *Trans. Faraday Soc.*, **49**, 1391 (1953).

(12) S. Nagakura and A. Kuboyama, THIS JOURNAL, **76**, 1003 (1954).

(13) D. L. Hammick, G. C. Hampson and G. I. Jenkins, *J. Chem. Soc.*, 1263 (1938).

(14) [illegible] Berthier, Harriman, *J. Chem. Phys.*, **1**, 614 (1933).

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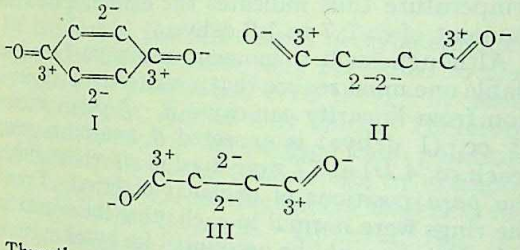
don this explanation because the period of carbonyl bending calculated from the infrared absorption at 120 cm.$^{-1}$ is too small (10^{-13} sec.) to contribute to the orientation polarization.

Of course there is implied in this reservation the common-sense expectation that benzoquinone will be planar in its unactivated, and especially in the orbitally degenerate, state expected for such substances. However, the present experimental evidence requires a factual rather than a common-sense attitude, and some explanation of a permanent moment must be devised. If the group moment for each carbonyl is taken as 2.5 D then the moment for benzoquinone in the vapor phase[2] (0.67 D) may be accounted for by a 6° deviation of these groups from planarity.

In this circumstance a "boat" type of structure may be postulated in which the atom cores may be disposed in an electronic field such as is described as structure I, in Fajans' sense.[15] The 3$^+$C atom cores may then be considered to be disposed symmetrically within the field, forming a constellation such as II (boat) rather than the chair form III, in which a lesser symmetry obtains, especially with respect to the 3$^+$C atoms.



I II III

Thus the non-planar structure II has been defined, like that of water or ammonia, as the lowest energy state of free benzoquinone. This structure might also be considered as a distortion caused by interaction with the solvent, and therefore might resemble iodine in polarizable solvents.[16,17] This latter relationship is doubtful. The excess of polarization over that accountable as electronic, which we have found for benzoquinone to be temperature dependent, has previously been observed in carbon tetrachloride, hexane and in the vapor state.[1,2] Under these conditions iodine does not exhibit orientation polarization. Furthermore the behavior of benzoquinone in solvents like benzene and dioxane (in which iodine has a moment) is unique with respect to the type of temperature dependence that has been observed.

Although it is recognized that the extrapolation of total polarization *versus* reciprocal temperature to $1/T = 0$ is applicable only in vapor-phase studies we have plotted the polarizations of Table I against $1/T$ in Fig. 3. It may be seen that the benzoquinone polarizations in benzene (A, slope 31×10^3) intersect the line (B, slope 15×10^3) joining the polarizations determined in dioxane at a point corresponding to a polarization of 39.3 cc. By reference to Fig. 4 in which these data (after subtraction of $P_{E+A} = 30.1$ cc.) are expressed in terms of electric moments *versus* temperature,

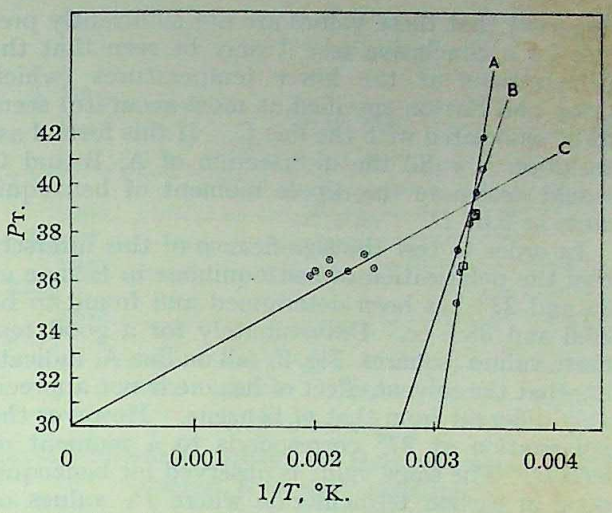


Fig. 3.—Total polarization *vs.* reciprocal temperature, benzoquinone.

it may be seen that the deviations from the moment (0.67 D) calculated from vapor phase studies indicate both positive and negative solvent effect. It is of interest that the model, II, suggested for benzoquinone is of a type (where the axis normal to the dipolar axis is relatively long) for which such deviations are expected.[18]

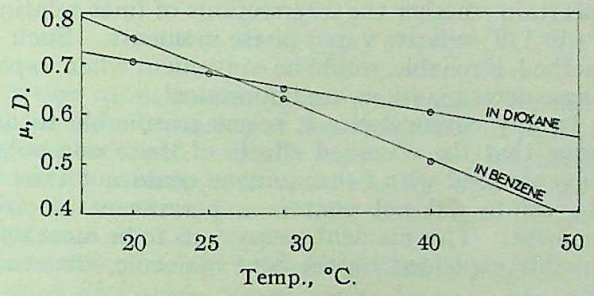


Fig. 4.—Dipole moments *vs.* temperature, benzoquinone.

One should not infer that benzoquinone is abnormal because of these moment variations with respect to temperature and solvent. Such variations are characteristic of most polarization studies but they seem insignificant except when the moment is the square root of a small number. Nevertheless efforts have been made to find theoretical justification for solvent effects (ref. 1, p. 127). However, no useful quantitative generalizations have been found because the electrostatic fields surrounding the molecules cannot be defined precisely.

In view of the difficulty of discovering molecular geometry which might rationalize the solvent effect (ref. 1, p. 145) we have utilized an empirical relationship shown in Fig. 3. We suggest that the intersection of the polarization lines A (benzene solutions) and B (dioxane solutions) may specify the point where solvent effects are minimal or absent. A line, C, has been drawn between the intersection and the point at $1/T = 0$ which represents the distortion polarization (30.1 cc.) determined from the dielectric constants of benzoquinone pellets. The points along this line, C, record the polarization data determined by Coop and Sutton for benzoquinone in the vapor phase. Although it is

(15) K. Fajans, *Chem. Eng. News*, **27**, 900 (1949).
(16) F. Fairbrother, *J. Chem. Soc.*, 1051 (1948).
(17) G. Kortum and H. Walz, *Z. Elektrochem.*, **57**, 73 (1953).
(18) F. C. Frank, *Proc. Roy. Soc.* (*London*), **A152**, 171 (1935).

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apparent that these values are not sufficiently precise for a conclusive test it may be seen that the polarizations at the lower temperatures (which Coop and Sutton specified as most accurate) seem to be associated with the line C. If this formal association is valid the intersection of A, B and C would designate the dipole moment of benzoquinone as 0.67 *D*.

In order to test the significance of this intersection the polarization of benzoquinone in hexane at 35 and 27° has been determined and found to be 36.6 and 38.7 cc. Unfortunately for a good test these values (squares, Fig. 3) fall on line A, indicating that the solvent effect of hexane is not appreciably different from that of benzene. However the polarization at 27° corresponds to a moment of 0.65 *D*. The same value is observed for benzoquinone in carbon tetrachloride where P_T values of 41.0, 38.8 and 36.0 cc. are obtained at 20, 27 and 40°, respectively. Therefore our results designate the benzoquinone moment as 0.65–0.67 *D*.

Of course some rational alternative to the Debye relationship must eventually be found to equate $\delta P/\delta T$ (11.146) for benzoquinone in benzene and $\delta P/\delta T$ (5.409) in dioxane with the slope of line C in Fig. 3. Meanwhile it seems worthwhile in future to examine the polarizations of candidate substances in several solvents at different temperatures in order to ascertain whether the intersections of lines relating P_T to $1/T$ indicate vapor phase moments. Such a method, if reliable, would be convenient when vapor phase determinations are impractical.

In any circumstance it seems reasonable to assume that the observed effects of these non-polar solvents used with benzoquinone could not exist if the solute did not contain a permanent electric moment. This moment seems to us to be most reasonably explained by the bent molecule, structure II.

The evidence from dielectric constant evaluation of pelletted benzoquinone, which has led us eventually to an assignment of electric moment in this compound, was not entirely unexpected. Previously a small discrepancy between total and electronic polarization of diphenylmercury[19] was shown by measurement of pellets not to be due to abnormal atom polarization.[20] The $P_T - P_E$ difference was interpreted as an electric moment due to angularity in the C–Hg–C bond. Although this condition might seem to be unusual it may reasonably be attributed to the distortion of the "O" shell of the bulky mercury atom.

4,4′-Dinitrobiphenyl

The foregoing examples seem to show that planarity and linearity are not always necessary for electronic orbital degeneracy. It has seemed worthwhile to re-investigate other substances to which abnormal atom polarization has been assigned largely on the reasonable belief that they were geometrically planar or linear. We have chosen 4,4′-dinitrobiphenyl for which the difference between the total polarization and that part attributable to electron polarization (87.5 cc. minus 66 cc.) was designated as a high atom polarization of 21.5 cc. The alternative dipole moment (1.0 *D*) was considered only as an apparent one, because of the expectation that the substance would have axial symmetry.[21]

We have prepared pellets from 4,4′-dinitrobiphenyl and have extrapolated the ratios of apparent dielectric constant with respect to thickness to obtain the dielectric constant, free from edge-effect error. This extrapolation (A), together with those of benzoquinone (B), naphthoquinone (C), anthraquinone (E), mercuric chloride (F) and ferric acetylacetonate (G), are shown in Fig. 5. Calculation gives P_{E+A} for 4,4′-dinitrobiphenyl as 66.8 cc., or only 0.8 cc. higher than that ascribed to electronic polarization. Therefore the atom polarization is not abnormal.

In order to confirm that the polarization in excess of P_{E+A} is due to an electric dipole in 4,4′-dinitrobiphenyl we have determined the dielectric constants of benzene and dioxane solutions at 40°. The total polarizations at this temperature are 77.7 and 80.3 cc., the former being about 10 cc. lower than was observed by LeFèvre and Vine at 25° in benzene.[21] The dependence of polarization upon temperature thus indicates the existence of a real moment of *ca* 0.7 to 1.0 debye.

Although such a moment seems to be appreciable one must realize that a relatively small deviation from linearity can cause it. A polarization of 21 cc. (1 debye) is expected if two nitro groups (each *ca*. 4 *D*) at 7° were fixed in *cis* relationship at the *para* positions of coplanar biphenyl. Even if the rings were normal to each other the orientation polarization could be accounted for by nitro groups at an angle of 14.5° from the planes of the rings.

Actually this non-linearity is predicted in a sense by X-ray crystallographic studies. The space group assigned to crystalline 4,4′-dinitrobiphenyl[22] is the non-centrosymmetric "Pc." As Bunn has pointed out[23] centrosymmetrical molecules do not in fact assume non-centrosymmetrical space group arrangements. Furthermore the nitro groups in *meta*-dinitrobenzene are thought to be inclined from the plane of the benzene ring.[24]

Metal Acetonylacetates

Perhaps the most important examples of high atom polarization have been those of the metal acetylacetonates. A difference between total and electronic polarization at one temperature was first observed by Smith and Angus[25] for beryllium acetylacetonate. Later a careful study in a series of solvents at one temperature showed the total polarization to be reasonably constant,[26] thus excluding solvent effect as a cause of the difference between total and electronic polarization. Furthermore the same authors found that in decalin over a temperature range of 298–415° only a small down-

(19) G. C. Hampson, *Trans. Faraday Soc.*, **30**, 877 (1934).

(20) J. C. Sipos, H. Sawatzky and G. F. Wright, THIS JOURNAL, **77**, 2759 (1955).

(21) R. J. W. LeFèvre and H. Vine, *J. Chem. Soc.*, 1878 (1938).

(22) J. N. von Niekerk, *Proc. Roy. Soc.* (*London*), **A181**, 314 (1943).

(23) C. W. Bunn, "Chemical Crystallography," Oxford Press, New York, N. Y., 1946, p. 251.

(24) E. M. Archer, *Proc. Roy. Soc.* (*London*), **A188**, 51 (1946).

(25) J. W. Smith and W. R. Angus, *ibid.*, **137A**, 372 (1932).

(26) A. E. Finn, G. C. Hampson and L. E. Sutton, *J. Chem. Soc.*, 1254 (1938).

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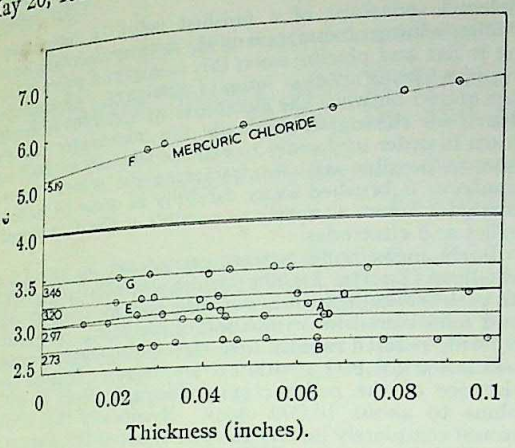


Fig. 5.—Dielectric constant *vs.* thickness of pellets.

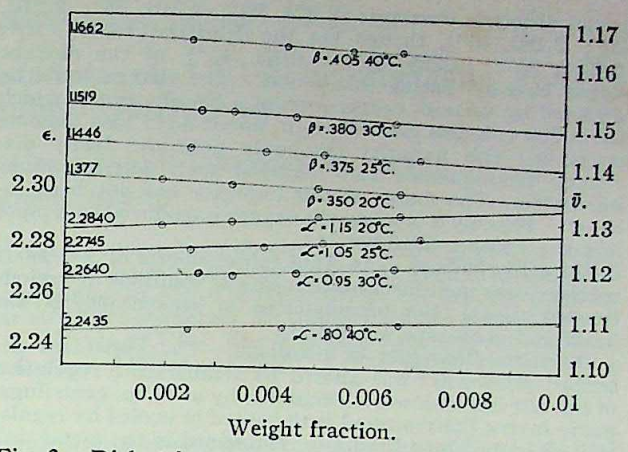


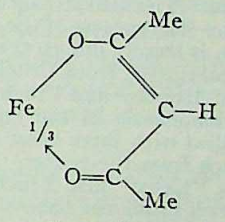
Fig. 6.—Dielectric constants and molar volumes *vs.* weight fraction, ferric acetylacetonate.

ward drift (86.91 to 85.10 cc.) in total polarization occurred. This temperature independence was confirmed[2] by vapor phase measurements from which the drift in total polarization was found to be even less (86.6 to 86.0 cc. from 185 to 255°) than was found for the solution measurements. Upon this evidence the difference between total and electric polarization (25–28 cc.) was designated as atom polarization.

By implication the other eight acetylacetonates examined by these workers were presumed to display high atom polarization even though no temperature coefficient studies were made. Therefore we expected to confirm the assigned atom polarization of 57 cc. for ferric acetylacetonate by extrapolation of our dielectric constant-pellet thickness ratios to zero pellet thickness. However, Fig. 5G shows a dielectric constant of 3.46. Since the density of ferric acetylacetonate is found to be 1.41 the P_{E+A} value by this measurement is only 112.7 cc. If the electronic polarization value (91.5 cc.) of Finn, Hampson and Sutton is subtracted from this number an atom polarization value of 21.2 cc. remains, by contrast to 57 cc.

In view of this large discrepancy we have determined the total polarization of benzene solutions of ferric acetylacetonate at 20, 25, 30 and 40° and have indeed found a temperature dependence corresponding to total polarization (calculated from α and β of Fig. 6) of 158.8, 150.6, 144.5 and 133.6 cc., respectively. These polarizations correspond to permanent moments of 1.48, 1.35, 1.25 and 1.05 D. With reference to the vapor phase study[2] these moments include solvent effects, both positive and negative, depending on the temperature. Therefore according to these experiments ferric acetylacetonate contributes both atomic and orientation polarization in the electric field. Perhaps it is fortuitous that the atomic polarization 21.2 cc. is approximate to that of beryllium acetylacetonate which has been shown not to have (and on the basis of the tetrahedral symmetry of beryllium would not be expected to have) a permanent moment.

The structural feature of ferric acetylacetonate which gives rise to an electric moment cannot be specified with assurance. In absence of orientation polarization one is tempted to attribute complete bonding degeneracy to the system, as was proposed by Finn, Hampson and Sutton. In the face of an observed orientation polarization one can in resonance theory easily rescind this attitude. Furthermore as Smith (p. 279) has pointed out[1] the constellar oscillation of the non-planar six-membered rings in this coördinate structure may give rise



to either atom or orientation polarization depending on the relationship of this frequency to that of the applied field. Finally there is no compelling reason to assume that the electronic and nuclear fields are centrosymmetrically coincident in this substance.

The authors wish to thank the National Research Council of Canada for generous financial support and Mr. Henry Sawatzky for experimental aid.

Experimental

Reagents.—Mercuric chloride was Mallinckrodt reagent, used as received. Benzoquinone was purified by repeated crystallization from 95% ethanol, m.p. 113.5°, d^{20}_4 1.313. Naphthoquinone, obtained as a by-product in naphthalene oxidation to phthalic acid, was five times crystallized from 95% ethanol using Darco decolorization, m.p. 148.4°, d^{20}_4 1.385. Anthraquinone (Kahlbaum) was twice crystallized from chloroform (38 ml. per g.), m.p. 281°, d^{20}_4 1.440. The 4,4′-dinitrobiphenyl was crystallized from ethanol (with Darco) and benzene, m.p. 240.9–241.8°, d^{20}_4 1.445. The ferric acetylacetonate was prepared by Claisen's method[27] in 82% yield, m.p. 179–180°, and was thrice purified by solution in benzene (3.5 ml. per g.) and then addition of petroleum ether (b.p. 60–70°, 4 ml. per g.), m.p. 181.5°, d^{20}_4. All melting points are corrected against reliable standards. The melting points were found to be identical when these substances were recovered after determinations of dielectric constant except for benzoquinone where the melting point was decreased to 112.5°. All recoveries from solution were effected by vacuum evaporation at room temperature.

Solvents.—Benzene and dioxane were purified as described previously but were maintained and delivered under positive pressure of nitrogen freed from oxygen, water and carbon dioxide. No metallic sodium was used in the storage containers. The initial dielectric constant (2.284, 20°; 2.262, 30°; 2.245, 40°) and densities (0.8788, 20°; 0.8681, 30°; 0.8628, 35°; 0.8575, 40°) of the benzene were unchanged after six months of such storage. However the

[27] C. Hurtzsch and C. H. Desch, *Ann.*, **323**, 13 (1902).

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initial dielectric constants (2.224, 20°; 2.216, 25°; 2.210, 30°; 2.189, 40°), though not the densities (1.0336, 20°; 1.0278, 25°; 1.0225, 30°; 1.0109, 40°), of the dioxane slowly changed during this period. The change could be detected by vacuum evaporation of a 50-ml. aliquot which left a few colorless crystals, m.p. about 45°; also dioxane containing this impurity (probably peroxide) badly discolored benzoquinone and rendered such determinations unreliable. The source of this impurity has not been located. Possibly it involves the oxygen introduced by a pipet into the nitrogen-filled bottle.

Refractive Indices.—An Abbé refractometer of ±0.00002 precision was used for measurements of solutions of various concentrations. For benzoquinone in benzene $\delta n/\delta\omega$ was 0.042 and in dioxane was 0.120.

Dielectric Constants of Solutions.—The apparatus described previously[4] was altered by temperature regulation of the test cell with water circulated by a 3/4 hp. centrifugal pump from a thermostated bath heated or cooled by regulation prescribed by a thermistor embedded in the metal wall of the test cell. This thermistor was balanced in a Wheatstone bridge against a second, matched, thermistor immersed in the master bath (±0.01°) in which the density determinations were made. The stray inductance errors in the measuring system were evaluated by the substitution method and were found to cause a positive capacitance error at the standard condenser of 16–22% (non-linear) at 5 mc., 3.6–5% (non-linear) at 2.6 mc., but only 0.1% at 500 kc. and 0.002% at 220 kc. All measurements but one have been carried out at 500 kc. The field strength is about 1 e.s.u.

The Pellet Press.—The success of the solid dielectric constant determination is largely due to the quality of this device. This die is fabricated from Crucible Steel Co. "Ketos" bar 2 inches in diameter and 1 inch long axially drilled centrally for accommodation of the finely powdered substance and also drilled with three holes spaced equally at a distance of 0.75 inch from the center. These holes match threaded holes in a "Ketos" disc 2 inches in diameter and 0.75 inch thick which forms the base of the die. The two pieces are held tightly together by means of three 0.125 × 1.7 inch cap screws. Both pieces are hardened to Rockwell C of 60 and the flat surfaces are finely surface-ground. The axially central hole also is ground to size after hardening.

The surface-ground surfaces between which the powder is compressed to a pellet are presented by two pieces of hardened drill rod finely turned to the exact (+0.000–0.0001 inches internal) diameter of the centrally axial hole in the top member of the die assembly. The bottom piece of drill rod is 0.125–0.375 inch long depending on the life of the die, which gradually expands after long usage where the powder is compressed. This short piece of drill rod is expelled in front of the finished pellet after removal of the bottom plate. Pressure both for compression of the powder and extrusion of the pellet is provided by the other piece of drill rod which is 1.25 inch long; its upper surface obviously need not be surface ground since it receives the ram of the hydraulic press.

All metal parts should be washed with an efficient solvent (usually acetone) after each pellet extrusion, then liberally oiled. The oil is thoroughly wiped away before preparation of the next pellet.

Pellets.—The consolidation of pellets either 0.2500 inch or 0.2675 inch in diameter and of various thicknesses is accomplished as has been described previously[4] under a hydraulic pressure of 10,000 p.s.i. but not *in vacuo*. It is important that the finely powdered substance be distributed uniformly in the die, by twisting the pressing pin without appreciable load, before the hydraulic ram is applied. The dielectric constant of a finished pellet is determined by placing a lump of amalgam on the bottom electrode, smoothing it flat and placing upon this amalgam a pellet upon the top of which is another lump of amalgam. After the pellet is centered between the electrodes by means of a chamfered sleeve on the upper electrode the micrometer is screwed down in order uniformly to extrude laterally as much amalgam as possible without fracturing the pellet. Excess of amalgam is brushed away carefully in order to leave both amalgam layers as nearly as possible at the diameter of the pellet and electrodes.

Early measurements were carried out by use of a zinc amalgam (Zn:Hg, 1 g.:6 g.) which was sufficiently inert that all pellets except those of mercuric chloride could be cleaned and remeasured for evaluation of precision. The mercuric chloride reacted rapidly with the zinc amalgam, preventing oscillation (V.F.O.) within a few minutes because the resistance of the pellet rapidly decreased from 80–100,000 ohms to about 10,000 ohms. Eventually this amalgam would completely liquefy the pellet, but at the moment that the V.F.O. ceased to function because of conductivity the pellet face was apparently unaffected when the amalgam was completely brushed from it. However the cleaned pellet was still a conductor when an inert (tin) amalgam replaced that of zinc. This phenomenon has not been explained. Successful measurements of new mercuric chloride pellets can be made either directly with tin amalgam or with zinc amalgam if the surfaces of the pellets are first coated with an invisible layer of Vaseline.

Amalgams.—The zinc amalgams deteriorate after a few days in contact with air so amalgams with other metals have been examined. Indium and iron amalgams are gritty while silver amalgam is too resilient. Copper amalgam is satisfactory but best is a tin amalgam (1 g. Sn:3 g. Hg) which is always briefly ground, before each application, in the mortar in which it has been prepared by grinding together the two metals. This amalgam is stable for weeks.

Dielectric Constants of Solids.—Determinations have been carried out with the apparatus described previously and also with a duplicate circuit in which the precision was increased fivefold by reducing the variable capacitance in the V.F.O. to 110 pf. The determinations were made in a room at 20 ± 1° with 45 R.H. In order to avoid stray capacitance–inductance errors the dielectric constant determination[4] was altered. The thickness of the pellet was first determined with the pellet test condenser. Then the pellet and amalgam were installed and the V.F.O. was balanced to zero beat with respect to the 500 kc. crystal-controlled oscillator. The pellet and amalgam were then removed quickly and thoroughly and the pellet condenser readjusted to zero beat. In a convenient variation of this technique both adjustments rapidly could be made 50 cycles off zero beat by inclusion of a Hewlett–Packard frequency meter into the circuit. In either circumstance the dielectric constant was evaluated as: thickness of pellet *versus* equivalent thickness of air.

Dipole Moments of 4,4′-Dinitrobiphenyl.—Dioxane solutions at 40° gave a value of $d\epsilon/d\omega = 1.00$ extrapolating smoothly to $\epsilon_1 = 2.1914$ and of $dV/d\omega = 0.425$ extrapolating to $V_1 = 0.9895$. Total polarization (80.3 cc.) thus may be expressed after deduction of $P_{E+A} = 66.9$ cc. as $\mu = 0.83\ D$. Benzene solutions at 40° behaved erratically but a least squares evaluation of 12 analyses gave $d\epsilon/d\omega = 0.55$ extrapolating to $\epsilon_1 = 2.2419$ and $dV/d\omega = 0.445$ extrapolating to $V_1 = 1.1667$. The calculated total polarization (77.7 cc.) thus leads to a moment of 0.74 D.

TORONTO, CANADA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Microwave Spectra and Molecular Structure of 1,1,1-Trifluoroethane and its Mono-, Di- and Trideutero Derivatives[1]

BY WALTER F. EDGELL, GEORGE B. MILLER[2] AND JONATHAN W. AMY

RECEIVED OCTOBER 22, 1956

The microwave spectra of CF_3CH_3, CF_3CH_2D, CF_2CD_2H and CF_3CD_3 have been observed in a Stark modulated sweep spectrometer of the Hughes and Wilson type. The frequencies of R-branch transitions in all four molecules are given and an extensive number of Q-branch transition band-heads corresponding to $J \geq 9$ are reported for the asymmetric molecules. Moments of inertia have been evaluated and a molecular structure consistent with these data has been calculated assuming a rigid rotor model and also that C–H = C–D and ∠CCH = ∠CCD. The following structure was obtained: C-C = 1.530 ± 0.005 Å., C–F = 1.335 ± 0.005 Å., C–H = C–D = 1.085 ± 0.008 Å., ∠CCF = 111°02′ ± 17′ and ∠CCH = CCD = 108°19′ ± 35′.

Introduction

The molecular structure of methylfluoroform has been investigated by use of electron diffraction[3–5] and microwave spectroscopy.[6] The results of the electron diffraction work are summarized in Table I, together with a set of parameters which is compatible with, but not proved by the microwave data of reference 6.

TABLE I

PREVIOUS RESULTS ON CF_3CH_3

	Ref. 3	Ref. 4	Ref. 5	Ref. 6
C-C, Å.	1.45 ± 0.04	1.53 ± 0.04	1.52 ± 0.04	1.54
C-F, Å.	1.35 ± 0.03	1.36 ± 0.02	1.33 ± 0.02	1.33
C-H, Å.	.....	.....	.....	1.093
∠FCF	108.5 ± 2°	107 ± 3°	.....	109°
∠HCH	.....	.....	.....	109°28′
∠CCF	112 ± 2°	.....	111.5 ± 1.5°	.....

Because of the inconsistencies in the results listed above, it seemed desirable to investigate the microwave spectra of methylfluoroform and its deuterated derivatives in order to establish a definitive set of structural parameters. This effort is part of a larger program dealing with the study of the structure of simple fluorinated molecules and it is hoped that the results herein described will be helpful in extending present day knowledge and understanding of the nature of chemical bonding in such molecular species.

Experimental

The spectrometer used in this investigation has been described elsewhere.[7] Comparison with previous measurements made on the ammonia inversion spectrum[8] indicates that the spectrometer has a precision of ±0.2 mc. or better and is sensitive enough to detect lines having an absorption coefficient of 10^{-7} cm.$^{-1}$. All measurements in this work were made in a K-band wave guide cell. Quantitative intensity measurements were not made.

The samples used by us were prepared in this Laboratory[9] for a study of the Raman and infrared spectra of these molecules. Mass spectral analysis showed that the deuterated samples contained not more than 12% of the other molecular isotopes as impurities. Although the compounds were not further purified, no lines were found to be common to more than one spectrum.

Interpretation of the Spectra

In order to predict the main features of the spectra of these four molecules, the structural parameters of reference 5 were assumed to be correct. It was found that the K-band spectrum (*ca.* 17,000–37,000 mc.) of each symmetric top should consist of only two R-branch transitions, corresponding to $J:1 \rightarrow 2$ and $J:2 \rightarrow 3$, and, perhaps, some satellites involving the expected low frequency torsional modes.[10,11]

The two asymmetric rotors should deviate only slightly from a prolate symmetric top ($\kappa = -0.90$ for CF_3CH_2D and $\kappa = -0.82$ for CF_3CD_2H). Accordingly, each of the R-branch lines of the symmetric rotors is replaced by a pattern consisting of three closely spaced lines for the $J:1 \rightarrow 2$ transition and five for $J:2 \rightarrow 3$. These lines should still be accompanied by some torsional satellites. In addition, a rather extensive, although not necessarily complicated, Q-branch structure should occur. These transitions were predicted to form bands having very close line spacing. Bands associated with transitions involving $J \geq 9$ were expected to appear throughout the K-band.

The only lines from which definite assignments were made were in the R-branches of all four molecules. The extreme simplicity of the R-branch structure made identification very straightforward. Torsional satellites were identified by comparing their relative intensities at room and Dry Ice temperatures. Table II gives the observed frequencies and their assignments. Rotational constants evaluated from these assigned frequencies are presented in Table III. The calculated frequencies listed in Table II are based on these constants.

As indicated in Table III, there is a rather large uncertainty in the constants, A. This is due to the fact that, as mentioned previously, CF_3CH_2D and CF_3CD_2H are only very slightly asymmetric rotors. For such small asymmetries the frequencies of the $^aR_{0,1}$ transitions depend on the rotational constants in such a way that an error of the order of 0.01 mc. in frequency is sufficient to cause an error of the order of 1 mc. in the rotational constant, A.

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(2) Purdue Research Foundation Fellow in Chemistry, 1954–1955, and Procter and Gamble Graduate Fellow in Chemistry, 1955–1956.

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TABLE II

R-BRANCH SPECTRA

f, mc. Obsd.	f, mc. Calcd.	Assignment
	CF_3CH_3	
20,742.3	20,742.3	$1 \rightarrow 2$
31,114.1	31,113.5	$2 \rightarrow 3$
	CF_3CD_3	
18,423.6	18,423.6	$1 \rightarrow 2$
27,510.5	.....	[a]
27,563.0	.....	[a]
27,597.5	.....	[a]
27,635.9	27,635.4	$2 \rightarrow 3$
	CF_3CH_2D	
19,818.9	19,818.6	$1_0 \rightarrow 2_{-1}$
19,846.6	19,846.3	$1_{-1} \rightarrow 2_{-2}$
19,876.6	19,876.2	$1_1 \rightarrow 2_0$
29,695.6	.....	[a]
29,727.4	29,727.2	$2_{-1} \rightarrow 3_{-2}$
29,766.6	29,776.8	$2_{-2} \rightarrow 3_{-3}$
29,770.8	29,771.1	$2_1 \rightarrow 3_0$
29,775.5	29,775.4	$2_2 \rightarrow 3_1$
29,814.7	29,813.7	$2_0 \rightarrow 3_{-1}$
	CF_3CD_2H	
19,034.7	19,034.7	$1_0 \rightarrow 2_{-1}$
19,090.0	19,091.8	$1_{-1} \rightarrow 2_{-2}$
19,157.8	19,157.8	$1_1 \rightarrow 2_0$
	CF_3CD_2H	
28,519.5	.....	[a]
28,549.1	28,549.4	$2_{-1} \rightarrow 3_{-2}$
28,607.4	.....	[a]
28,625.8	28,626.7	$2_{-2} \rightarrow 3_{-3}$
28,645.7	28,644.4	$2_1 \rightarrow 3_0$
28,661.7	28,662.1	$2_2 \rightarrow 3_1$
28,705.6	.....	[a]
28,734.7	28,733.8	$2_0 \rightarrow 3_{-1}$

[a] Excited torsional states.

TABLE III

THE ROTATIONAL CONSTANTS, MC.

CF_3CH_3	$B = (5185.58 \pm 0.04)$
CF_3CD_3	$B = (4605.90) \pm 0.04)$
CF_3CH_2D	$A = (5545 \pm 240)$
	$B = (4976.27 \pm 0.04)$
CF_3CD_2H	$C = (4947.43 \pm 0.04)$
	$A = (5409 \pm 240)$
	$B = (4804.83 \pm 0.04)$
	$C = (4743.29 \pm 0.04)$

The use of the Q-branch spectra to eliminate the uncertainty in these constants, A, was found to be unsatisfactory due to the difficulty of making proper assignment to each individual line within the various series. In order to make specific assignments of these lines it would be necessary to be sure that the observed band-heads were the true ones. The distribution of intensities within each series, however, is such that it is by no means certain that the true band-head was observed. An alternative method of assignment would involve making precise assumptions as to the effect of centrifugal distortion but, in view of the lack of relevant experimental data, such assumptions did not appear to be justified.

In order to obtain frequencies leading to a precise evaluation of A, one would have to observe transitions associated with the component of the dipole moment along the axis perpendicular to the a-axis and lying in the molecular plane of symmetry. These would be ${}^bR_{1,1}$ transitions for CF_3CH_2D and ${}^cR_{1,0}$ transitions for CF_3CD_2H. Calculations based on the assumed structure and on the measured dipole moment of methylfluoroform[12,13] showed that the dipole components in question could be expected to be about one hundredth the value of the dipole components along the a-axes. Hence, one would expect these transitions to be very weak and, indeed, no such transitions were observed in spite of a careful search of the regions in which they would be expected.

Table IV lists the apparent band-heads and the number of transitions observed in each of the Q-branch series of the asymmetric tops.[14]

The structure and location of each Q-branch series is in good agreement with predictions based on a rigid, slightly asymmetric rotor model. In particular, one expects and finds that the lines will be closely spaced, with separations of a few megacycles, for the lower J-values in each series, and spacing increasing steadily toward higher J's (lower frequencies). From the apparent beginning of each series, the intensities rapidly approach a maximum with increasing J and then drop off gradually as J is further increased.

TABLE IV

APPARENT BAND-HEADS OF THE Q-BRANCH SPECTRA

CF_3CH_2D f(mc.)	No. of lines obsd.	CF_3CD_2H f(mc.)	No. of lines obsd.
22,547.5	28	22,816.8	12
22,832.5	12	24,075.5	27
23,557.6	17	25,312.8	18
24,568.5	27	26,028.0	7
25,575.4	33	26,546.9	31
26,272.5	6	26,739.5	6
26,582.5	25	27,793.7	30
27,589.6	11	29,011.8	20
28,597.8	31		
29,599.2	25		

Determination of the Structure

Methylfluoroform and its deuterated derivatives can be described structurally by the general molecular formula CF_3CX_2Y. Assuming that each molecule is a rigid rotor and that isotopic substitution at any one atom affects only the coördinates of that atom, one finds that seven parameters completely describe the structure above.

From the four isotopic species, microwave data yield a total of eight moments of inertia which are related to the structure of CF_3CX_2Y by eight nonlinear equations containing the seven parameters as unknowns. The exact form of these equations is determined when the parameters are explicitly defined. However, of the eight moments available,

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(13) S. N. Ghosh, R. Trambarulo and W. Gordy, *J. Chem. Phys.*, **20**, 605 (1952); *Phys. Rev.*, **87**, 172A (1952).

(14) The frequencies of the more than 360 individual lines are listed in reference 1.

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only six are known with sufficient accuracy to permit their use in determining the structure. Taking into account also the fact that the moments of inertia are not very sensitive to the locations of the relatively light hydrogen and deuterium atoms, it seemed best to assume that the geometry of the molecule, CF_3CX_2Y, was completely unaffected by isotopic substitution. The configuration then depends on only five parameters which must be evaluated using a method of successive approximations.

The results of these considerations are presented in Table V in the form of a set of bond distances and angles giving the best agreement with the observed moments of inertia. Table VI compares the results of this set with the observed moments. It

TABLE V

MOLECULAR PARAMETERS

C-C, Å.	1.530 ± 0.005
C-F, Å.	1.335 ± 0.005
C-H, Å.	1.085 ± 0.008
∠CCF	111°02′ ± 17′
∠CCH	108°19′ ± 35′

TABLE VI

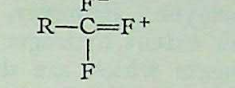
MOMENTS OF INERTIA IN GCM.^{2} × 10^{40}

	Moment	Obsd.	Calcd.
CF_3CH_3	I_b	161.812	161.861
CF_3CD_3	I_b	182.177	182.177
CH_3CH_2D	I_a	151.3[a]	153.3
	I_b	168.618	168.610
	I_c	169.601	169.638
CF_3CD_2H	I_a	155.1[a]	155.3
	I_b	174.634	174.635
	I_c	176.900	176.918

[a] The uncertainty in these moments is ±6.8 whereas the uncertainty in all other moments is ±0.007.

can be seen that the calculated values are in good agreement with the observed ones. The structural parameters determined in this work are in excellent agreement with the values obtained by Brandt and Livingston[5] (Table I).

The C–F bond distance and the CCF angle are consistent with those values found in other molecules containing the CF_3 group.[15] In particular, comparison with the fluoromethane series[16] shows that the C–F bond distance determined for CF_3CH_3 has about the expected value for a singly bonded CF_3 group (C–F = 1.385 Å. in CH_3F, 1.358 Å. in CH_2F_2 and 1.326 Å. in CHF_3). It has been postulated[16] that the slight shortening of the C–F bond and slight closing of the FCF angle in CHF_3 can be associated with the occurrence of resonance structures[17] of the type



(I)

It is certainly conceivable that structures of this type can also contribute to the slight closing of the tetrahedral umbrella of the CF_3 group in CF_3CH_3.

Since the C–H distance in Table V is based upon the assumption that C–H = C–D, it probably represents an average value lying somewhere between the true values of the C–H and C–D bond distances. By analogy with the results obtained by Miller, *et al.*,[18] for the methyl halides, the C–D bond could be expected to be shorter than the C–H bond by perhaps 0.009 Å.

Acknowledgment.—The authors wish to express their thanks to Dr. Norbert Muller for some helpful discussions. They are also grateful to the Proctor and Gamble Company and to the Purdue Research Foundation, acting under Contract AT-(11-1)-164 in coöperation with the Atomic Energy Commission, whose support has made this research possible.

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LAFAYETTE, INDIANA

[CONTRIBUTION NO. 89 FROM THE CRYOGENIC LABORATORY OF THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Heats of Adsorption of Hydrogen and Helium on Prepared Surfaces*

BY WILLIAM A. STEELE AND J. G. ASTON

RECEIVED OCTOBER 31, 1956

Measurements have been made of the heats of adsorption of helium on titanium dioxide powder which had varying amounts of argon preadsorbed on it. Some measurements of the heats of adsorption of hydrogen were also made on similar systems. It is assumed that high energy sites for physical adsorption occur at surface roughnesses and faults. The experimental data are discussed in terms of this model, and it is seen that this work provides an excellent confirmation of this hypothesis.

Introduction

In a recent publication by the authors and Tykodi,[1] an analysis was made of the isotherms and heats of adsorption of a number of rare gases on titanium dioxide. The data were fitted to a model in which lateral interaction in the adsorbate was neglected, but in which the surface heterogeneity of the adsorbent was taken into account. A single site distribution function was taken to characterize the titanium dioxide surface in all cases. The physical considerations underlying the choice of distribution function were as follows: the major portion of the adsorption sites (about 60%) were considered to be those formed by the flat surface of the adsorbent, having energies which could be estimated by calculating the energy due to dis-

(*) This research was carried out under Contract DA-36—061-ORD-509 of the Office of Ordnance Research.

(1) J. G. Aston, R. J. Tykodi and W. A. Steele, *J. Phys. Chem.*, **59**, 1053 (1955).

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persion forces between a gas atom and a planar titanium dioxide surface[2]; the remainder of the adsorption sites were then assumed to be due to imperfections in the surface structure (so-called topographical heterogeneity) such as cracks, holes, grain boundaries, etc. On such a site, an adsorbed atom would have a larger interaction with the solid than on a planar site, due to adjacent surfaces making angles (other than zero) with the planar surface.

This model for adsorption could not be expected to work too well for neon or argon, since these adsorbates exhibit appreciable lateral interaction near the monolayer. However, adsorbed helium, and to a lesser extent hydrogen, should give isotherms and heats which are determined almost exclusively by the site distribution of the adsorbent. The actual site distribution chosen was admittedly a rough approximation to reality, but agreement between experiment and theory was sufficient to inspire further investigation.

The present paper is concerned with an attempt to verify the assumptions made concerning the source of surface heterogeneity of the titanium dioxide used previously. To this end, the heats of adsorption of helium and hydrogen were measured on titanium dioxide powder which had had varying amounts of argon preadsorbed upon it. If the heterogeneity was actually due to imperfections in the surface, a sufficient amount of preadsorbed argon would be expected to fill in the high energy sites, effectively removing them and replacing them by a planar surface composed partly of argon atoms and partly of titanium dioxide molecules. The application of the Kirkwood–Müller formula[3] shows that the energy of interaction of a helium atom with an argon crystal is about the same as that of a helium atom with a titanium dioxide crystal. Thus, the preadsorption of argon on a titanium dioxide surface should produce a roughly uniform surface for helium adsorption. In a preliminary communication[4] it was shown that about one-half layer of argon is sufficient to remove almost all signs of heterogeneity in the heats of adsorption of helium. The results of an extensive investigation of this effect will be presented here, and also the experimental techniques used will be discussed in some detail.

Results and Discussion

Measurements were made of the heat of adsorption of helium on a bare titanium dioxide surface, on titanium dioxide plus 0.36 layer of argon, 0.60 layer and 1.05 layers. The temperatures of measurement were from 10–17°K., and the adsorption pressures of the helium were less than 100 cm. at all times. Under these conditions, no multilayer adsorption can occur, and the correlation of the measured heats with the site distribution in the surface is very nearly complete. The results of these experiments are shown in Fig. 1, where isosteric heats of adsorption of helium in cal./mole are plotted against the amount adsorbed in units of cc.-S.T.P. per gram of adsorbent. Some heats measured by Aston, Mastrangelo and Tykodi[5] on another sample of the same titanium dioxide as that used in this work are included for comparison. The precision of the data is within the estimated 5% (see Experimental), and the corrected calorimetric heats agree well with those calculated from the isotherms. Even the preadsorption of 0.36 layer of argon markedly reduces the heterogeneity of the surface and removes all sites with heat of 400 cal./mole or greater. The heat curves are such that in terms of the topographical model only a small number of sites of energy 250–400 cal./mole are left, and this residue of high energy sites is filled in by 0.25 additional layers of argon.

No significant change can be detected in the shape of the curve of heat of adsorption *versus* coverage when one adds 0.45 layer of argon to a surface which already holds 0.60 layer, although the curve is not quite flat. If the energy of interaction of a helium atom with a titanium dioxide surface was not essentially identical with the energy of interaction with a titanium dioxide substrate covered with a monomolecular layer of argon, one would expect that the heat of adsorption curve would change significantly upon the addition of argon to uncovered titanium dioxide surface. Thus, one may conclude, in agreement with the result calculated from the Kirkwood–Müller formula, that the energy of interaction of an adsorbed atom with titanium dioxide is identical to the interaction energy with titanium dioxide coated with argon, within the accuracy of these experiments.

There is, however, a small decrease in the heat of adsorption with coverage even in the system where a full layer of argon has been preadsorbed. It is suggested that this residual heterogeneity is due to the fact that preferred sites will occur on a perfectly planar surface, due to the periodic nature of the surface potential energy. For instance, the maximum calculated energy due to dispersion forces is roughly 100% greater for a helium atom over the center of a lattice cell in the surface of a simple cubic argon-like crystal than the energy of interaction when the helium atom is over a corner of the lattice cell.[6] Since the energy of interaction of helium with a solid such as titanium dioxide is due mainly to the dispersion energy of the adsorbed atom with the atoms in the solid, one would certainly expect some decrease in the differential molar heats of adsorption of helium on such a solid, independent of any topographic effects.

In Fig. 2 are displayed the heats of adsorption of hydrogen *versus* coverage for two surfaces: bare titanium dioxide and titanium dioxide plus 0.60 layer of preadsorbed argon.

The heats of adsorption of hydrogen on the titanium dioxide plus 0.6 layer of argon show no signs of topographical heterogeneity. The effect of the residual heterogeneity mentioned in the previous paragraph seems to be of the same order of magnitude for hydrogen as for helium. How-

(2) W. A. Steele and G. D. Halsey, Jr., *J. Chem. Phys.*, **22**, 979 (1954).

(3) A. Müller, *Proc. Roy. Soc.* (*London*), **A154**, 624 (1936).

(4) W. A. Steele and J. G. Aston, *Discussions Faraday Soc.*, **23**, 147 (1957).

(5) J. G. Aston, S. V. R. Mastrangelo and R. J. Tykodi, *ibid.*, **31**, 1633 (1955).

(6) W. A. Steele, Thesis, University of Washington, Seattle, Washington, 1955.

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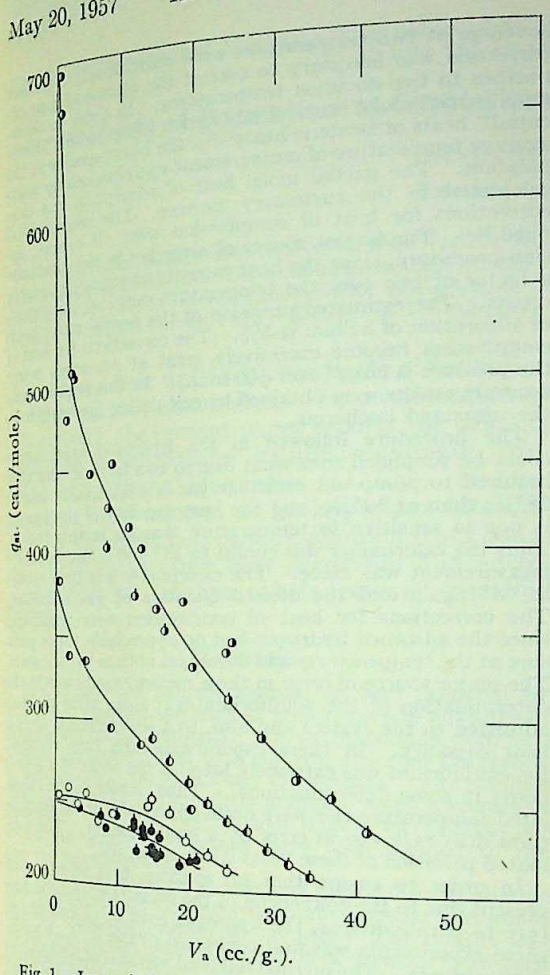

Fig. 1.—Isosteric heats of adsorption of helium on various surfaces: ◑, heats on bare titanium dioxide; ◐, heats on titanium dioxide plus 0.36 layer of preadsorbed argon; ○, heats on titanium dioxide plus 0.60 layer of preadsorbed argon; ●, heats of titanium dioxide plus 1.05 layers of preadsorbed argon. The points without tabs are calorimetric; those with tabs were calculated from the isotherms using the Clausius–Clapeyron equation.

ever, the higher energy sites fill in more rapidly in the case of hydrogen adsorption.

When the heat curves for helium and hydrogen adsorbed on bare titanium dioxide are compared, it is apparent that a large fraction of the high energy sites seems to be absent when the hydrogen is used as an adsorbate. For instance, the number of sites of energy two or more times the energy of adsorption on the flat surface is quite large when helium is adsorbed. However, almost no such states are available for hydrogen adsorption. At first glance, it would seem that such an effect is in contradiction to the hypothesis that the high energy sites are found in cracks or holes in the titanium dioxide crystals. It is unlikely that this unavailability of high energy sites for hydrogen could be due to any great extent to the difference in molecular dimensions, since the two molecules are very similar in size (the collision diameters of hydrogen and helium are 2.9 and 2.6 Å., respectively[7]).

(7) R. H. Fowler and E. A. Guggenheim, "Statistical Thermodynamics," Cambridge University Press, Cambridge, England, 1952, p. 285.

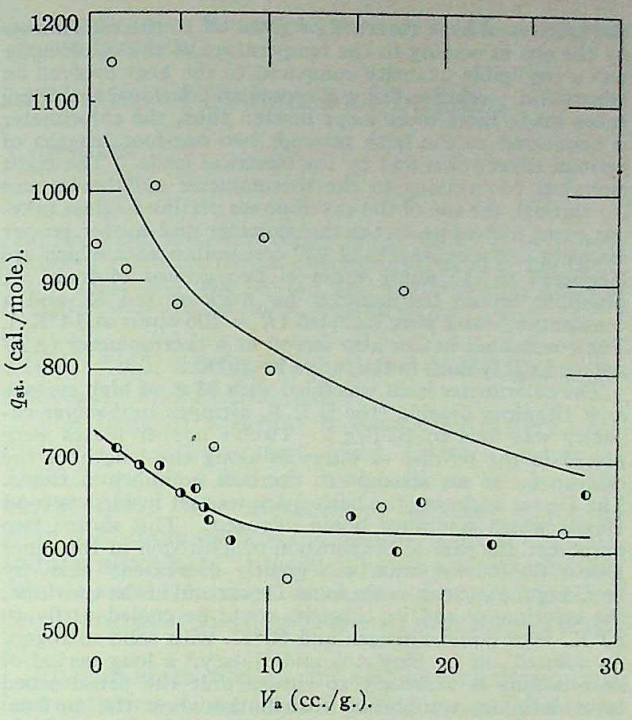

Fig. 2.—Isosteric heat of adsorption of hydrogen on various surfaces: O, parahydrogen on bare titanium dioxide; ◑, parahydrogen on titanium dioxide plus 0.60 layer of preadsorbed argon; ◐, normal (room temperature equilibrium) hydrogen on titanium dioxide plus 0.60 layer of preadsorbed argon.

The most probable explanation has its basis in the fact that the thermal energy of hydrogen molecules at the temperatures of these experiments is quite small compared to the energy of binding to the surface. Thus, the hydrogen will be almost completely immobilized upon adsorption. In particular, the rate of diffusion into the surface faults which give rise to the high energy sites may be negligibly small. Indeed, the adsorbed phase is most probably in a metastable state during the time span of an experiment. This line of reasoning is further supported by the extremely long "equilibrium times" (see Experimental) and by the fact that the scatter of the data for the bare surface is considerably larger than the estimated precision of the method. (For these reasons, it did not seem worthwhile to make any more extensive measurements at low coverages of adsorbed hydrogen than those presented here.)

Experimental

The calorimeter used in this work was a modified version of the one used by Frederikse.[8] This system is designed to operate with the surroundings kept at a constant temperature close to that of the calorimeter by regulating the vapor pressure of the bath. The temperature rise during any process was then found by extrapolation of the equilibrium drift rates. Adequate thermal isolation of the calorimeter from the surroundings could be obtained by maintaining a good vacuum in the envelope which separated the calorimeter from the bath. Two german silver filling tubes were led through the bath space to the top of the vacuum envelope. These tubes make two loops in the bath just above the vacuum envelope to ensure that the incoming gas passes through at least one foot of tubing at the temperature of the bath. In this way, it is believed that the gas was brought sufficiently close to the temperature of the adsorbent that

(8) H. P. R. Frederikse, Thesis, Leiden, 1950.

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the amount of heat absorbed or given off to the calorimeter by the gas in coming to the temperature of the calorimeter was a negligible quantity compared to the heat evolved on adsorption. After entering the vacuum envelope, the filling tubes made three more loops inside: thus, the calorimeter is connected to the bath through two one-foot lengths of german silver tube, and by the electrical leads. The eight electrical connections to the thermometer and heater are led through the top of the envelope *via* platinum–glass take-out caps, and come to the thermometer and heater proper *via* eight one-foot lengths of #29 constantan wire which are lacquered to the filling tubes in two groups of four. A phosphor bronze thermometer for work at 1–4°K. and a constantan heater were included (R = 106 ohms at 14°K.). The constantan heater also served as a thermometer ($\Delta T/\Delta R$ = 6.071°/ohm) in the range 10–20°K.

The calorimeter itself was filled with 83 g. of high surface area titanium dioxide (the B.E.T. nitrogen monolayer capacity was 52.4 cc. STP/g.). Twelve copper plates were placed in the powder at intervals along the length of the calorimeter in an attempt to decrease equilibrium times. The Dewar enclosing the bath space was set inside a second Dewar which contained liquid nitrogen. This served two purposes: the rate of evaporation of hydrogen in the inner Dewar due to radiation was greatly decreased; also, by breaking the vacuum in the inner Dewar and in the envelope, the calorimeter and its contents could be cooled easily to 80°K. with liquid nitrogen and 60°K. with solid nitrogen. As pointed out by Singleton and Halsey,[9] a long period of slow cooling is necessary to ensure that the preadsorbed layer is in an equilibrium distribution over the surface. Since these experiments were made with comparatively small amounts of preadsorbed gas, the gas was more firmly bound to the surface, and the equilibrium process was not quite as sensitive to variations in method as in the experiments of Singleton and Halsey. Allowing small variations in the time and technique of precooling, three runs were made on the system with one-half layer of preadsorbed argon, and two runs on the system with one layer. No significant difference could be detected in isotherms or isosteric heats. In general, the desired quantity of gas was admitted to the calorimeter at 80°K.; the system then was cooled slowly to 60°K. and held at that temperature for at least eight hours. The bath space subsequently was filled with liquid hydrogen and the remainder of the cooling done in 30 minutes or less.

The techniques used in the measurement of the helium heats differed in some respects from those used in the hydrogen work. In the helium experiments, the calorimeter was first cooled to 10°K. The heat capacity of the system was measured; following this, a measured amount of gas was admitted to the calorimeter. After the system had reached thermal equilibrium, a second heat capacity measurement was made. Since these determinations were made without cooling the calorimeter during the sequence, the final temperature was then about 17°. The system was then cooled to 10°K. and the cycle repeated. After applying the usual corrections,[10,11] curves of heat capacity *versus* coverage at two temperatures were constructed; a further correction was necessary to correct the measured heat capacities to two common temperatures. In order to determine partial molal heats of adsorption (often called "differential" heats or isosteric heats[10,11]), the heat capacity at the average temperature of measurement was obtained by interpolation. The partial molal heat of adsorption was then calculated in the customary manner. The conventional corrections for heat of compression were, of course, applied.[10,11] The largest source of error lay in the interpolation procedure, since the heat capacity changed by roughly a factor of two over the temperature range of the experiments. The estimated precision of the partial molal heats of adsorption of helium is 5%. The corrections for heat of compression become excessively great at coverages where the pressure is large (over 100 mm.). In this region, more accurate results were obtained by calculating the heats from the measured isotherms.

The procedure followed in the hydrogen experiments could be simplified somewhat due to two factors: the time required to pump out exchange gas is considerably less at 18°K. than at 10°K., and the heat capacity of the system is not so sensitive to temperature changes in this region. Thus the calorimeter was cooled to 18° and a heat capacity measurement was made. The calorimeter was then cooled to 18° again and the desired quantity of gas admitted. The corrections for heat of compression were negligible, since the adsorbed hydrogen had no appreciable vapor pressure at the temperatures and coverages of these experiments. The major source of error in these measurements was in the determination of the equilibrium drift rates after gas was admitted to the system and also, to a lesser extent, after a heat capacity. In these experiments, the time required for equilibrium was extremely long (of the order of 1.5 to 2 hours in some determinations). Thus, errors in the calculated temperature rise were quite appreciable if the equilibrium drift rate was in error by a small amount. The estimated precision of these heats is also about 5%.

In order to ensure that no spurious heat effects were present due to the conversion of the room temperature mixture to parahydrogen, the hydrogen used in all but one of these experiments was first converted to the 20°K. equilibrium mixture. The method followed was that of Squires and Stewart,[12] who used a catalyst of charcoal plus preadsorbed oxygen at 20°K. They estimated the half-time of the reaction to be 10–20 minutes. In the present work, the hydrogen was left in contact with the catalyst for a minimum of 60 minutes before it was used.

Room temperature equilibrium hydrogen was used in one of the runs on the titanium dioxide plus 0.60 layer of preadsorbed argon to ascertain whether the rotational state of the adsorbed hydrogen had an appreciable effect on the heat of adsorption. It is clear from the data shown in Fig. 2 that the difference in the heats is negligible insofar as these experiments are concerned.

UNIVERSITY PARK, PA.

(9) J. H. Singleton and G. D. Halsey, Jr., *J. Phys. Chem.*, **58**, 330 (1954).

(10) G. L. Kington and J. G. Aston, THIS JOURNAL, **73**, 1929 (1951).

(11) J. A. Morrison, J. M. Los and L. E. Drain, *Trans. Faraday Soc.*, **47**, 1023 (1951).

(12) G. L. Squires and A. T. Stewart, *J. Chem. Phys.*, **22**, 754 (1954).

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[CONTRIBUTION FROM THE MINERALS THERMODYNAMICS EXPERIMENT STATION, REGION II, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

Heats of Formation of Crystalline Aluminates of Sodium and Lithium

BY JAMES P. COUGHLIN

RECEIVED JANUARY 11, 1957

Heat of solution measurements of crystalline $NaAlO_2$, $LiAlO_2$, Al, NaCl and LiCl were conducted at 303.15°K. in 4.360 *m* hydrochloric acid solution. Based upon these data the following heats of formation from the component oxides at 298.15°K. are derived: −20,890 ± 780 cal./mole for $NaAlO_2$ and −12,880 ± 1,030 cal./mole for $LiAlO_2$. Corresponding heats of formation from the elements are −270,840 ± 170 cal./mole and −284,330 ± 210 cal./mole, respectively.

A recent article dealt with the heats of formation of three calcium aluminates.[1] In continuation of this activity, the present paper reports the heats of formation of crystalline sodium aluminate ($NaAlO_2$) and lithium aluminate ($LiAlO_2$). Sodium aluminate is of interest as an important intermediary in the extraction of pure alumina from bauxite. Low temperature heat capacities and entropies at 298.15°K. of these substances were reported by King.[2]

Materials

The sodium and lithium aluminates were prepared by prolonged, repeated sintering of stoichiometric mixtures of appropriate pure ingredients. These compounds were portions of the samples used by King[2] who reported the results of chemical analyses and X-ray diffractions. The samples used in this work contained, in addition, small amounts of moisture (0.11% for $NaAlO_2$ and 0.08% for $LiAlO_2$) for which appropriate corrections have been applied to the thermal measurements.

The lithium aluminate sample was very difficultly soluble and required special treatment to obtain material that would dissolve completely within 90 minutes. The sample was repeatedly ground and elutriated in a stream of oxygen traveling vertically at a rate of 1.2 cm./sec. The maximum particle size, calculated from Stoke's law, was equivalent to a sphere 14 μ in diameter.

Analytical data and heat of solution measurements for aluminum metal already have been reported by the author.[1] Also outlined in that paper are the method of standardizing the hydrochloric acid solution and methods of applying minor corrections to the heat of solution measurements.

The sodium chloride sample was analytical reagent grade, containing less than 0.03% total impurities originally, plus 0.01% moisture picked up in handling.

The lithium chloride sample was also an analytical reagent with original impurities totaling less than 0.55%; the sample picked up 0.08% water in handling for which a correction has been applied. To check the possibility of sample hydrolysis during drying a ten-gram portion which had been dried at 550–600° was titrated with 0.1 *N* acid and the indicated alkalinity, as lithium hydroxide, was found to be only 0.014%. As the total heat of solution was quite small, and the principal impurities are other alkali chlorides, the correction for impurities is considered negligibly small and therefore omitted.

Method and Results

The calorimetric apparatus is essentially the same as described by Southard,[3] with minor improvements by the author.[4] The results are expressed in defined calories (1 cal. = 4.1840 abs. joules), and all molecular weights are based on the 1953 International Atomic Weights.[5] Sample weights were corrected to vacuum using the following densities: Al, 2.70; H_2O, 0.997; 4.360 *m* HCl, 1.062; LiCl, 2.068; NaCl, 2.49; $NaAlO_2$, 2.6 (estimated); and $LiAlO_2$, 2.554.

The heat of solution measurements were conducted in a two-quart glass Dewar containing 1,936.2 g. of 4.360 *m* hydrochloric acid ($HCl \cdot 12.731H_2O$). The amounts of samples employed were 0.02 mole each of aluminum, sodium chloride, sodium aluminate, lithium chloride and lithium aluminate, and requisite amounts of water and hydrochloric acid solution as shown in reactions 6 and 14.

The amounts of water impurities and the equivalent net corrections applied to the various measurements are as follows: sodium aluminate, 0.11% impurity and −64 cal./mole; sodium chloride, 0.01% and −0.3 cal./mole; lithium aluminate, 0.08% and −41 cal./mole; and lithium chloride, 0.08% and −14 cal./mole. A small correction was applied to adjust the electrical calibration measurements to the mean temperatures of the corresponding heat of solution measurements. This correction amounted to −12 cal./mole for sodium aluminate, −10 cal./mole for lithium aluminate, −1 cal./mole for lithium chloride, and was negligible for the other measurements.

All measurements, except one, were made within 0.04° of 30.00° and required no correction to 30.00°. The first measurement of sodium aluminate was made at approximately 29.74°[6] and required a correction of −8 cal./mole.

$NaAlO_2$(c).—Table I gives the skeleton equations for the reactions measured to obtain the heat of formation of sodium aluminate. Reactions 1, 2 and 3 were measured consecutively in the same acid solution; reactions 4 and 5 were measured consecutively in a second portion of acid. Thus the final solution from reactions 1, 2 and 3 and the final solution from reactions 4 and 5 are identical, so that $\Delta H_6 = \Delta H_1 + \Delta H_2 + \Delta H_3 - \Delta H_4 - \Delta H_5$.

Reaction 1 has been discussed in an earlier paper.[1] The molal heat of solution of aluminum in 4.360 *m* hydrochloric acid, including all corrections, is −127,050 ± 120 cal./mole at 303.15°K.

Six measurements were made of the heat of solution of sodium chloride in the final solutions from reaction 1, resulting in +1,924 ± 4 cal./mole as the mean of +1,920, +1,917, +1,920, +1,930, +1,928 and +1,926.

The heat of reaction 3, −1,196 ± 12 cal. for 14.731 moles of water, is the resultant of five meas-

(1) J. P. Coughlin, THIS JOURNAL, **78**, 5479 (1956).
(2) E. G. King, *ibid.*, **77**, 3189 (1955).
(3) J. C. Southard, *Ind. Eng. Chem.*, **32**, 442 (1940).
(4) J. P. Coughlin, THIS JOURNAL, **77**, 868 (1955).
(5) R. Wichers, *ibid.*, **76**, 2033 (1954).

(6) All calorimeter temperature readings were made in terms of microvolt potentials and never converted to degrees. The resistance thermometer was calibrated at one fixed point, 30.00° being equivalent to 8890 ± 10 μv.; the sensitivity was approximately 1180 μv. per de-

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TABLE I

HEAT OF FORMATION OF $NaAlO_2$(c) (CAL./MOLE)

Mol. wt. = 81.97

	Reaction	$\Delta H_{303.15}$	Uncertainty
(1)	$Al(c) + 3H^+(sol) = Al^{+++}(sol) + 3/2\ H_2(g)$	−127,050	±120
(2)	$NaCl(c) = Na^+(sol) + Cl^-(sol)$	+ 1,920	± 10
(3)	$14.731\ H_2O(l) = 14.731\ H_2O(sol)$	− 1,200	± 20
(4)	$NaAlO_2(c) + 4H^+(sol) = Na^+(sol) + Al^{+++}(sol) + 2H_2O(sol)$	− 51,220	± 20
(5)	$HCl{\cdot}12.731\ H_2O(sol) = H^+(sol) + Cl^-(sol) + 12.731\ H_2O(sol)$	− 10	± 10
(6)	$Al(c) + NaCl(c) + 14.731\ H_2O(l) = NaAlO_2(c) + HCl{\cdot}12.731\ H_2O(sol) + 3/2\ H_2(g)$	− 75,100	±130

At 298.15°K., $\Delta H_6 = -74,880 \pm 130$ cal./mole

urements conducted in solutions containing 0.02 mole of aluminum and 0.02 mole of either sodium chloride or lithium chloride (see Table II).

TABLE II

HEAT OF SOLUTION OF H_2O(l) IN SOLUTIONS CONTAINING SODIUM CHLORIDE OR LITHIUM CHLORIDE

H_2O sample size (g.)	NaCl or LiCl	$\Delta H_{303.15}$ (cal./mole)
0.9306	NaCl	−81.0
1.0191	NaCl	−82.0
4.8205	NaCl	−81.9
5.5531	LiCl	−81.3
5.2210	LiCl	−80.0

Mean $\Delta H_{303.15} = -81.2 \pm 0.8$ cal./mole

The heat of reaction appears to be independent of the water sample size and also of whether sodium ion or lithium ion is present in solution. These results agree substantially with similar measurements made in connection with the calcium aluminates.[1]

The heat of reaction 4, −51,220 ± 11 cal./mole, resulted from five measurements, −51,230, −51,230, −51,220, −51,200 and −51,220.

Reaction 5 (the heat of mixing of approximately 5 ml. of the original acid solution with the final solution from reaction 4) required only two measurements to verify that its heat was nearly zero. The first measurement, −7.4 cal./mole, was conducted in the final solution from reaction 4; the second measurement, −5.7 cal./mole, was conducted in the final solution from reaction 12 of Table III. Thus, the rounded value for reaction 5 (and also reaction 13 of Table III) is −10 ± 10 cal./mole.

Reaction 6 represents the heat of formation of sodium aluminate plus aqueous hydrochloric acid from aluminum metal, sodium chloride and water. The heat of reaction was corrected to 298.15°K. using heat capacity data of King,[2] Kelley[7] and Rossini.[8] The heats of formation from the oxides (reaction 7) and from the elements (reaction 8) were obtained by substitution of literature values for sodium chloride and hydrochloric acid,[9] water and sodium oxide[10] and aluminum oxide.[11]

$$^1/_2Na_2O(c) + {}^1/_2Al_2O_3(\alpha) = NaAlO_2(c),$$
$$\Delta H_{298.15} = -20,890 \pm 780 \text{ cal./mole} \quad (7)$$

$$Na(c) + Al(c) + O_2(g) = NaAlO_2(c),$$
$$\Delta H_{298.15} = -270,840 \pm 170 \text{ cal./mole} \quad (8)$$

The free energy changes of these reactions, shown in Table IV, were evaluated using entropy data of Kerr, Johnston and Hallett,[12] King[2] and Kelley.[7]

$LiAlO_2$(c).—Table III shows skeleton equations of the reactions measured to obtain the heat of formation of lithium aluminate.

TABLE III

HEAT OF FORMATION OF $LiAlO_2$(c) (CAL./MOLE)

Mol. wt. = 65.92

	Reaction	$\Delta H_{303.15}$	Uncertainty
(9)	$Al(c) + 3H^+(sol) = Al^{+++}(sol) + 3/2\ H_2(g)$	−127,050	±120
(10)	$LiCl(c) = Li^+(sol) + Cl^-(sol)$	− 6,880	± 10
(11)	$14.731\ H_2O(l) = 14.731\ H_2O(sol)$	− 1,200	± 20
(12)	$LiAlO_2(c) + 4H^+(sol) = Li^+(sol) + Al^{+++}(sol) + 2H_2O(sol)$	− 46,000	± 50
(13)	$HCl{\cdot}12.731\ H_2O(sol) = H^+(sol) + Cl^-(sol) + 12.731\ H_2O(sol)$	− 10	± 10
(14)	$Al(c) + LiCl(c) + 14.731\ H_2O(l) = LiAlO_2(c) + HCl{\cdot}12.731\ H_2O(sol) + 3/2\ H_2(g)$	− 89,120	±140

At 298.15°K., $\Delta H_{14} = -88,900 \pm 140$ cal./mole

Reactions 9, 11 and 13 have been discussed as reactions 1, 3 and 5, respectively. The heat of reaction 10, −6,878 ± 3 cal./mole, is the mean of five measurements, −6,878, −6,876, −6,875, −6,879 and −6,882.

Five measurements of the heat of solution of lithium aluminate, −46,060, −45,960, −45,970, −45,970 and −46,060, yield a mean of −46,000 ± 46 cal./mole. Because of difficulty in preparing large amounts of the finely divided sample, two of the measurements (the second and fourth) were made with samples of one-half the theoretical size, measured consecutively in the same acid solution. Comparison with the other three measurements shows that the heat of solution is independent of sample size, within the limit of experimental error.

Reaction 14 was corrected to 298.15°K., using previously mentioned heat capacity data.[2,7,8] Heat of formation values from other sources[9-11] are used to evaluate reactions 15 and 16, the heats of

(7) K. K. Kelley, U. S. Bur. Mines, Bulletin 477 (1950).

(8) F. D. Rossini, *J. Research* [illegible]

(9) F. D. Rossini, D. D. Wagman, W. H. Evans, S. Levine and I. Jaffe, Natl. Bur. Standards Circular 500 (1952).

(10) J. P. Coughlin, U. S. Bur. Mines Bulletin 542 (1954).

(11) Heat of formation of Al_2O_3 (α,-corundum): $\Delta H_{298.15} = -400,500 \pm 200$ cal./mole. A. D. Mah, unpublished measurements, this Laboratory.

(12) E. C. Kerr, H. L. Johnston and N. C. Hallett, THIS JOURNAL, [illegible]

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TABLE IV

HEATS AND FREE ENERGIES OF FORMATION (KCAL./MOLE)

Substance	From the oxides		From the elements	
	$\Delta H_{298.15}$	$\Delta F°_{298.15}$	$\Delta H_{298.15}$	$\Delta F°_{298.15}$
$NaAlO_2$(c)	−20.89 ± 0.78	−21.58 ± 0.80	−270.84 ± 0.17	−255.60 ± 0.19
$LiAlO_2$(c)	−12.88 ± 1.03	−13.50 ± 1.03	−284.33 ± 0.21	−269.49 ± 0.22

formation of lithium aluminate from the component oxides and from the elements, respectively.

$$\tfrac{1}{2}Li_2O(c) + \tfrac{1}{2}Al_2O_3(\alpha) = LiAlO_2(c), \quad \Delta H_{298.15} = -12{,}880 \pm 1030 \text{ cal./mole} \quad (15)$$

$$Li(c) + Al(c) + O_2(g) = LiAlO_2(c), \quad \Delta H_{298.15} = -284{,}330 \pm 210 \text{ cal./mole} \quad (16)$$

Johnston and Bauer's[13] entropy value for lithium oxide is used, together with entropy data from sources,[2,7,12] to calculate the free energy data in Table IV.

Although no high temperature heat content and entropy increment data are available for these aluminates, the entropies of formation at 298.15°K. indicate that both substances should become increasingly stable with respect to their component oxides with increasing temperature.

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(13) H. L. Johnston and T. W. Bauer, THIS JOURNAL, **73**, 1119 (1951).

[CONTRIBUTION FROM THE MINERALS THERMODYNAMICS EXPERIMENT STATION, REGION II, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

Heat Capacities at Low Temperatures and Entropies at 298.15° K. of Nickelous Oxide, Cobaltous Oxide and Cobalt Spinel

BY E. G. KING

RECEIVED DECEMBER 26, 1956

Heat capacities of nickelous oxide (NiO), cobaltous oxide (CoO) and cobalt spinel (Co_3O_4) were measured throughout the temperature range 51 to 298°K. The heat capacity of cobaltous oxide has a pronounced maximum at 287.3°K. The entropies at 298.15°K. are 9.08 ± 0.04, 12.66 ± 0.08 and 24.5 ± 0.2 cal./deg. mole, respectively.

This paper presents heat capacity measurements in the temperature range 50 to 298°K. and entropy values at 298.15°K. for crystalline nickelous oxide (NiO), cobaltous oxide (CoO) and cobalt spinel (Co_3O_4). No previous similar data exist for the cobalt compounds. Seltz, DeWitt and McDonald[1] have reported low temperature heat capacity data for nickelous oxide.

Materials.—Nickelous oxide[2] was prepared from reagent grade nickelous nitrate hexahydrate and nickelous sulfate hexahydrate. These materials were dissolved in water and precipitated as basic carbonate with ammonium hydroxide and carbon dioxide. The precipitate was heated slowly to 1000° where it was kept for nine days. Analysis showed 99.96% nickelous oxide, 0.05% cobaltous oxide, 0.01% sodium oxide, and 0.02% acid insoluble. Tests showed no calcium or sulfate. The X-ray diffraction pattern agreed with the ASTM catalog.

Cobaltous oxide was obtained from recrystallized, reagent grade cobaltous sulfate heptahydrate as the starting material. After heating slowly to 1000°, it was maintained at this temperature for nine days. Additional treatment involved heating for 16 hours at 1000° and cooling in nitrogen, followed by an additional six hours *in vacuo* at 1000° with cooling in nitrogen. Analysis showed 78.61% cobalt (theoretical, 78.65%). The X-ray pattern was identical with that in the ASTM catalog.

Recrystallized reagent grade cobalt sulfate heptahydrate was the starting material for preparing cobalt spinel. It was heated in air for 15 days at 850° and 16 hours at 900°, after which it was quenched to room temperature. At this point the product contained too much cobalt (73.71%). It was next heated for 16 hours at 720° and finally for 16 hours at 780°, followed by quenching to room temperature. Analysis of the final product gave 73.40% cobalt, as compared with the theoretical 73.42%. The X-ray diffraction pattern agreed with the ASTM catalog.

Heat Capacity Measurements and Results.—The heat capacity calorimeter has been described.[3] Results are given in defined calories (1 cal. = 4.1840 abs. joules). Weighings were reduced to vacuum and molecular weights were obtained using the 1954–55 Report on Atomic Weights.[4] Sample masses were 275.83 g. of nickelous oxide, 396.86 g. of cobaltous oxide and 161.23 g. of cobalt spinel.

The measurements are tabulated in Table I and plotted in Fig. 1. The heat capacity curves of nickelous oxide and cobalt spinel show a regular behavior over the measured range of temperature. A comparison of the heat capacities of nickel oxide with those of Seltz and co-workers[1] shows the present values to be lower. The difference is 2.0% at 75°K., becomes zero at 125°K., then increases again to 1.5% at 258°K., and finally decreases to 0.1% at 298°K.

Cobaltous oxide possesses a peak with the maximum at 287.3°K., at which point the heat capacity is greater than 17.6 cal./deg. mole. As may be seen in Fig. 1, abnormal heat capacities persist for a wide temperature range both above and below the maximum. At the highest measured temperature (307.6°K.) the heat capacity continues to decrease with increasing temperature. Results labeled (a) in Table I were obtained without temperature gaps. In the immediate neighborhood of the peak, runs with temperature rises of only about one degree

(1) H. Seltz, B. J. DeWitt and H. J. McDonald, THIS JOURNAL, **62**, 88 (1940).

(2) All three substances were prepared by K. R. Bonnickson, Chemist, Minerals Thermodynamics Experiment Station, Region II, Bureau of Mines.

(3) K. K. Kelley, B. F. Naylor and C. H. Shomate, U. S. Bur. Mines Tech. Paper 686, 1946.

(4) E. Wichers, THIS JOURNAL, **78**, 3235 (1956).

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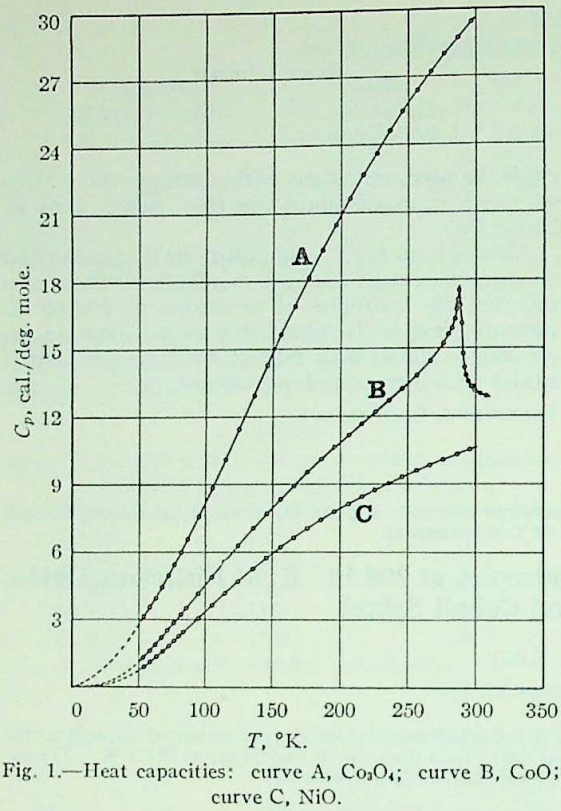

Fig. 1.—Heat capacities: curve A, Co_3O_4; curve B, CoO; curve C, NiO.

were made to better portray the heat capacity curve. This heat capacity maximum is similar to the one found by Todd[5] at 188.5°K. for the compound $Fe_{0.947}O$.

Two separate total heat measurements were made for cobaltous oxide between 280.00 and 294.00°K., enclosing the sharpest part of the peak. The measurements gave identical heat absorptions of 217.9 cal./deg. mole. The runs labeled (a) in Table I also were used (in summation) to obtain this total heat. The latter method gave 219.9 cal./deg. mole, in fair agreement with the total heat runs.

Entropies at 298.15°K.—The entropy of cobaltous oxide between 0 and 51°K. (the extrapolated portion) was calculated from the Debye–Einstein function sum $D(359/T) + E(484/T)$, which fits the measured data within 1.0% between 51 and 100°K. The entropy for the intervals 51–280°K. and 294–298°K. were obtained by graphical integration of a C_p *vs.* log T plots of the data. These increments totaled 11.48 cal./deg. mole. The entropy between 280.00° and 294.00°K. was calculated from the equation

$$\Delta S = \Delta H \frac{\Sigma C_p \Delta T/T}{\Sigma C_p \Delta T}$$

where ΔH is the total heat over the temperature interval and the other two terms were obtained from the consecutive run data marked (a) in Table I. This portion of the entropy was evaluated as 0.76 cal./deg. mole.

The entropy for nickelous oxide below 51°K. was calculated from the function sum $D(422/T) + E(585/T)$, which fits the experimental data below 200°K. within 2.0%. Likewise, the entropy of cobalt spinel below 51°K. was obtained from the function sum $D(219/T) + 3E(485/T) + 3E(926/T)$ which fits the measured data below 200°K. within 1.0%. The entropies between 51 and 298.15°K. for nickelous oxide and cobalt spinel were obtained from C_p *vs.* log T plots.

Table II summarizes the entropy calculations. The present entropy value at 298.15°K. for nickelous oxide is considered more reliable than the value of 9.24 cal./deg. mole calculated by Kelley[6] from the data of Seltz and co-workers.[7]

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TABLE I

HEAT CAPACITIES (CAL./DEG. MOLE)

T, °K.	C_p	T, °K.	C_p	T, °K.	C_p
CoO (mol. wt., 74.94)					
53.61	1.309	165.67	8.939	285.48(a)	16.69
58.27	1.598	175.82	9.526	286.36	16.87
62.80	1.895	185.97	10.12	286.48(a)	17.13
67.20	2.194	195.82	10.63	287.37(a)	17.57
71.72	2.511	206.10	11.16	288.27(a)	16.89
76.31	2.834	215.94	11.67	289.27(a)	16.08
81.76	3.227	225.96	12.19	290.33(a)	14.75
85.71	3.511	235.85	12.69	291.44(a)	14.15
94.37	4.138	245.65	13.19	292.59(a)	13.79
104.79	4.896	256.13	13.79	294.25(a)	13.51
114.22	5.563	266.10	14.43	296.82(a)	13.30
124.28	6.268	276.03	15.19	297.34	13.27
135.71	7.034	279.74(a)	15.60	299.87(a)	13.11
145.57	7.695	282.15(a)	15.89	303.40(a)	12.99
155.66	8.336	284.06(a)	16.28	307.61(a)	12.90
Co_3O_4 (mol. wt., 240.82)					
54.02	3.153	114.67	10.09	216.33	22.68
58.55	3.544	124.81	11.45	226.40	23.68
63.05	3.952	136.03	12.93	236.23	24.62
67.68	4.439	145.76	14.26	245.77	25.46
72.32	4.938	155.91	15.61	256.47	26.37
76.78	5.446	165.95	16.89	266.42	27.19
81.40	5.955	176.02	18.12	276.33	27.98
86.57	6.554	186.06	19.36	286.92	28.70
94.93	7.568	196.03	20.47	296.34	29.29
104.98	8.850	206.38	21.65		
NiO (mol. wt., 74.71)					
54.28	0.900	114.57	4.158	216.19	8.457
58.93	1.112	124.60	4.691	225.85	8.762
63.49	1.341	135.88	5.269	236.07	9.050
68.10	1.582	145.55	5.737	245.63	9.306
72.47	1.818	155.86	6.221	256.29	9.597
76.74	2.051	165.78	6.639	266.15	9.845
80.22	2.248	175.84	7.041	276.01	10.08
83.81	2.444	185.78	7.427	286.43	10.32
94.66	3.056	195.94	7.785	295.94	10.55
104.97	3.639	206.13	8.134		

TABLE II

ENTROPIES AT 298.15°K. (CAL./DEG. MOLE)

	NiO	CoO	Co_3O_4
0–51°K. (extrap.)	0.27	0.42	1.36
51–298.15°K. (measd.)	8.81	12.24	23.18
	9.08 ± 0.04	12.66 ± 0.08	24.5 ± 0.2

(5) S. S. Todd, THIS JOURNAL, 73, 3894 (1951).

(6) K. K. Kelley, U. S. Bur. Mines Bulletin 477 (1950).

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[CONTRIBUTION FROM THE SPECTROSCOPY LABORATORY AND DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Vibrational Spectra and Structure of Cyclobutene and Cyclobutene-d_6[1]

BY R. C. LORD AND D. G. REA[2]

RECEIVED DECEMBER 5, 1956

Cyclobutene and cyclobutene-d_6 have been prepared by the method of Cope, Haven, Ramp and Trumbull.[5] The infrared absorption spectra of both vapor and liquid have been obtained in the range 250–3800 cm.$^{-1}$ and Raman spectra (including semi-quantitative depolarization factors) have been determined for the liquids. Many vibrational frequencies permitted to occur in the Raman effect by selection rules were not observed. The spectra have been interpreted in terms of a C_{2v} structure, for which the chief spectroscopic support is the number and position of infrared bands of type C. In cyclobutene the carbon–carbon double bond frequency is observed at the unusually low value of 1566 cm.$^{-1}$. The Raman line at this frequency is intense but the infrared band is so weak that it could have been ascribed to an overtone.

The cyclobutene molecule contains a C–C double bond in a four-membered ring, and offers the molecular spectroscopist an unusual example of the effect of ring strain on the double bond frequency and the carbon–hydrogen frequencies associated with a double bond. It is also useful in assisting the evaluation of vibrational frequencies of the CH_2 group in small ring compounds as a member of the series cyclopropane-ethylene oxide–cyclobutene-cyclobutane whose spectra have recently been reported together with those of the deuterium analogs.[3] Its structure apparently has not been investigated by X-ray diffraction or by microwave spectroscopy, but a recent study by electron diffraction has been carried out by Goldish, Hedberg and Schomaker.[4]

Experimental

Cyclobutene and cyclobutene-d_6 were obtained as intermediates in the synthesis of cyclobutane and cyclobutane-d_8, respectively. The synthesis was that of Cope, Haven, Ramp and Trumbull,[5] modified to adapt it to the preparation of the deuterium compound.[6] The general method having already been reported, only the purification procedure and the characteristics of the compounds obtained will be given.[7]

The crude cyclobutene (and cyclobutene-d_6 also) was purified by the addition of bromine and fractional distillation of the resultant dibromocyclobutane. Cyclobutene was then regenerated by reduction with zinc in ethanol[8] with a 97% recovery. Unfortunately the infrared spectrum of the regenerated material indicated the presence of an appreciable amount of butadiene, whose boiling point differs by only 5° from that of cyclobutene. The butadiene was removed by bubbling the impure gas four or five times through molten maleic anhydride, the extent of the removal being followed by means of the butadiene infrared bands at 997–1012 cm.$^{-1}$. It was estimated that the final concentration of butadiene was less than 0.1%. The cyclobutene was then distilled once again (at 200°K., condensed at 77°K.) and stored in the vapor phase for spectroscopic study.

Both the cyclobutene prepared in this way and the cyclobutane obtained from it by subsequent hydrogenation were subjected to careful infrared and mass spectrometric analysis.[9] The observed purity of the latter compound confirmed that the original cyclobutene was in excess of 99.9% pure chemically. The isotopic purity of cyclobutene-d_6 by both methods was 99.7 atom-% D.

Spectroscopic Procedures.—Infrared spectra were measured in the range 250–3800 cm.$^{-1}$ on the gaseous compounds and from 400 to 3800 cm.$^{-1}$ for the liquids. The spectrometer was a Perkin–Elmer 12B single-beam instrument, in which prisms of LiF, CaF_2, NaCl, KBr and KRS-5 were employed in their respective regions of optimum dispersion. The low temperature liquid cell was that designed by Lord, McDonald and Miller[10] who also have described the modified optics of the spectrometer used in this work. The liquid was cooled by Dry Ice–acetone slush, and its temperature was probably slightly above −75°.

The spectra are shown in Figs. 1 and 2 and the wave numbers (vac) of the transmission minima in cm.$^{-1}$ in Tables I and II. The precision of wave number measurement is 2 cm.$^{-1}$ or better below 2500 and 5 cm.$^{-1}$ or better above.

Raman spectra of liquid samples were photographed by standard techniques[3] with a Zeiss three-prism spectrograph. Semiquantitative depolarization factors were determined by a single-exposure method.[11] An attempt was made to photograph the Raman spectrum of cyclobutene excited by the mercury resonance line Hg-2537, but decomposition of the sample under intense ultraviolet radiation was sufficiently rapid that inferior spectra were obtained. The results of the Raman work are listed in Table III. The Raman spectrum of cyclobutene has not been reported previously, but there were available to us the results of an earlier study by Slowinski[12] on a cyclobutene sample prepared by a different method.[13] Slowinski's results agree closely with those of Table III both as to frequency and intensity, except that he reported fewer lines and the intensity of the butadiene line at 1635 cm.$^{-1}$ indicated about 5–10% of this substance in his sample. A very weak line found in spectra of some samples during the present work at about 515 cm.$^{-1}$ has been rejected as probably belonging to butadiene since it was not found in spectra from which the 1635 butadiene line was absent.

The infrared spectrum of cyclobutene obtained with the instrument used in the present work has been reported earlier by Roberts and Sauer.[13]

Discussion of Spectroscopic Results

The selection rules for the highest possible symmetry (C_{2v}) for cyclobutene permit all 24 fundamental frequencies to be Raman-active and all but five in the infrared. Thus the assignment of fundamentals has to be carried out with little help from selection-rule arguments. Fortunately the infra-

(1) This paper is based on a thesis submitted by D. G. Rea to the Graduate Department of Chemistry, Massachusetts Institute of Technology, in partial fulfillment of the requirements for the Ph.D. degree, September, 1954. A preliminary oral account was presented at the Pittsburgh Conference on Applied Spectroscopy, March, 1954 (*Anal. Chem.*, **26**, 429 (1954)). Part of the work has been supported by the Office of Ordnance Research under Contract DA-19-020-ORD-896.

(2) Wm. S. Knudsen Fellow, 1953–1954.

(3) (a) A. W. Baker and R. C. Lord, *J. Chem. Phys.*, **23**, 1636 (1955); (b) R. C. Lord and B. Nolin, *ibid.*, **24**, 656 (1956).

(4) E. Goldish, K. Hedberg and V. Schomaker, THIS JOURNAL, **78**, 2714 (1956).

(5) A. C. Cope, A. C. Haven, Jr., F. L. Ramp and E. R. Trumbull, *ibid.*, **74**, 4867 (1952).

(6) R. C. Lord, *J. Chem. Phys.*, **21**, 378 (1953).

(7) Complete details of the synthesis are described in the Ph.D. thesis of D. G. Rea.

(8) G. B. Heisig, THIS JOURNAL, **63**, 1698 (1941).

(9) We are indebted to Dr. Fred Mohler of the National Bureau of Standards for the mass spectrometric analyses. The calibration of the infrared analysis of the high-D sample was based on the infrared and mass spectra of the low-D sample.

(10) R. C. Lord, R. S. McDonald and F. A. Miller, *J. Opt. Soc., Am.*, **42**, 149 (1952).

(11) R. C. Lord and E. Nielsen, *J. Chem. Phys.*, **19**, 1 (1951).

(12) E. J. Slowinski, Jr., Ph.D. thesis, Massachusetts Institute of Technology, September, 1949.

(13) J. D. Roberts and C. W. Sauer, THIS JOURNAL, **71**, 3925 (1949); **74**, 3192 (1952).

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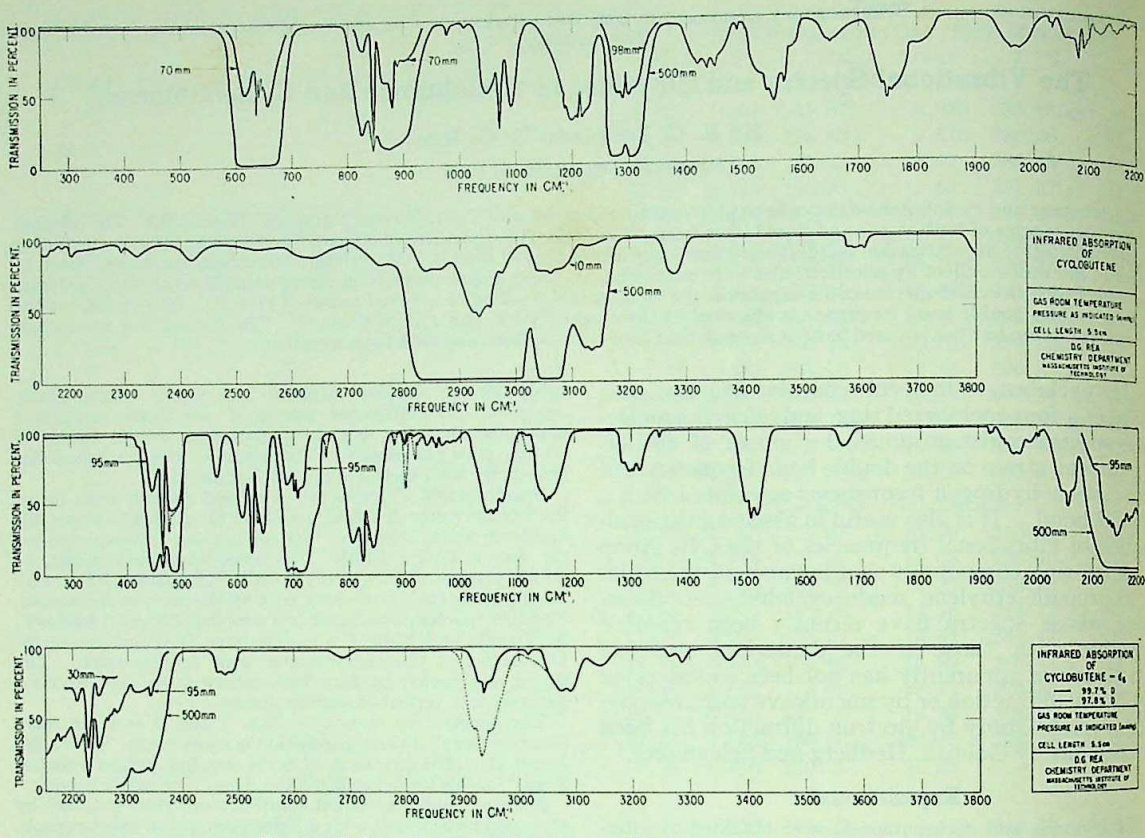

Fig. 1.—Infrared spectra of gaseous cyclobutene and cyclobutene-d_6.

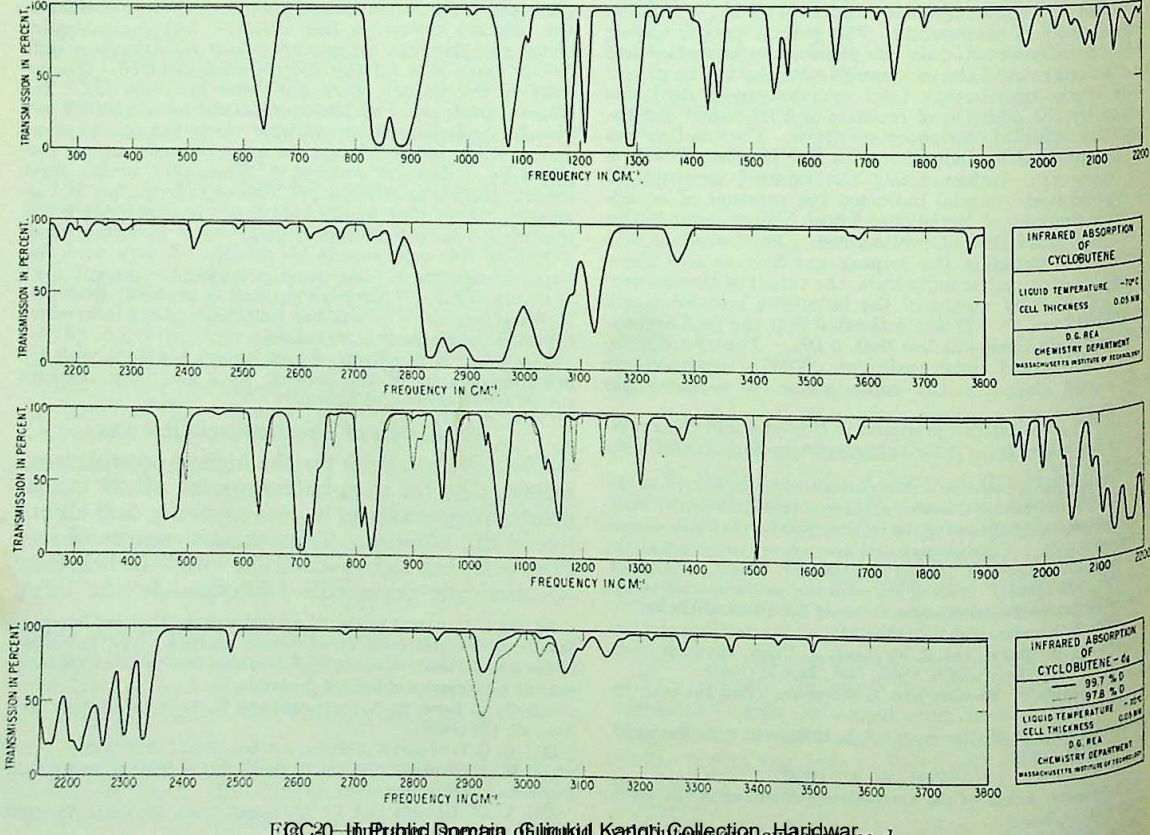

Fig. 2.—Infrared spectra of liquid cyclobutene and cyclobutene-d_6.

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TABLE I

INFRARED SPECTRUM OF CYCLOBUTENE[a]

Vapor ν(cm.$^{-1}$ vac)		Liquid ν(cm.$^{-1}$ vac)	I	Assignment	Vapor ν(cm.$^{-1}$ vac)		Liquid ν(cm.$^{-1}$ vac)	I	Assignment
				$\nu_2 + \nu_{19}$			1400	w	$\nu_{13} + \nu_{22}$
3804	w	3775	w	$\nu_2 + \nu_{23}$			1361	w	?
				?			1337	w	$2\nu_{12}$?
3612	w	3586	w	$\nu_{21} + \nu_{24}$	1304 R	s			
3590	w	3567	w	$\nu_2 + \nu_{24}$	1297 Q′	s,B	1288	s	ν_{17}
		3272	w	$\nu_{13} + \nu_{21}$	1291 Q″				
3278	w	3126	m	ν_{14}	1278 P	s			
3134	m,B	3085	m	?	1224 R	m			
		3043	s	ν_1	1217 Q′	m,B	1210	s	ν_{18}
3060	s,A	2960			1211 Q″				
2975 R	s		vs	ν_{21}	1198 P	m			
2955 Q	s,C				1186	m	1180	s	ν_6
2935 Q	s,A			ν_2	1142	w			
2925 P	s	2900					1109	w	ν_7
2862	s,B	2866	s	$\nu_4 + \nu_{16}$	1094 R	m			
2842		2839	s	$2\nu_{16}$,	1074 Q	m,C	1073	s	ν_{22}
		2830	s	$\nu_3 + \nu_5$	1054 P	m			
1797	w	1801	w	$\nu_6 + \nu_{24}$	978	w	966	w	ν_8?
1762 R	m			$\nu_{13} + \nu_{16}$,	900 R				
1757	m			$\nu_7 + \nu_{24}$	888 Q	s,B	886	s	ν_{20}
1751 Q	m,A?	1747	w	$2\nu_{19}$	883 Q	s,A?			
1740 P	m				866 R	s			
1649	w	1647	m	?	846 Q	s,C	846	s	ν_{23}
1582 R	m				828 P	s			
1570 Q	m	1565 m	m	ν_3	657 R	s			
1554 P	m				645	s			
1540 Q	m	1539	m	$\nu_{13} + \nu_{18}$	640	s			
1529 P	w				635 Q	s,C	636	s	ν_{24}
1450	w	1443	n	ν_4	615 P	s			
1437 Q′	w,B?	1426	m	ν_{16}					
1430 Q″									

[a] Abbreviations: P, Q, Q′, Q″, R refer to the rotational branches of a single band and A, B, C to the band type (see text and Fig. 3). sh = shoulder, v = very, s = strong, m = medium, w = weak for cell thicknesses and pressures shown in Figs. 1 and 2. Overtones which cannot be explained as binary combinations are labeled "?." Between 1800 and 2800 cm.$^{-1}$ there are about 25 weak or very weak overtone bands in the vapor and a similar number (though not always at similar frequencies) in the liquid. For brevity these are not included in Table I. They are recorded in the thesis of D. G. Rea.

red band contours indicate the assignments for a number of frequencies and comparison with the spectra of cyclopropane and ethylene oxide and their deuterium derivatives[3] is also helpful.

The expected modes of vibration for each species are given in column 3 of Table IV. Approximate moments of inertia required for calculation of band contours and product rule values may be obtained from the geometrical parameters of the molecule as determined by Schomaker, *et al.*[4] If one takes the twofold axis (C_{2v} symmetry) as the z-axis with the x-axis perpendicular to the ring plane at the center of gravity, and adopts the values C=C, 1.34 Å.; C–C (perpendicular to C_2^z), 1.57 Å.; C–C ("parallel" to C_2^z), 1.54 Å.; C–H (CH_2), 1.08 Å.; C–H (C=C), 1.07 Å.; ∠HCH, 110°; ∠HC=C, 120°; ∠C–C–C bisected by CH_2 plane, one obtains I_x = 123.8, I_y = 71.5, I_z = 63.0 for cyclobutene and I_x = 158.1, I_y = 95.8, I_z = 83.6 for cyclobutene-d_6, all in units of 10^{-40} g.-cm.^{2}. The band contours and theoretical product-rule ratios are not sensitive to the precise values of the geometrical parameters.[14]

From these values it follows that vibrations of species A_1 (Table IV) should produce bands of type A,[15] species B_1, type B, and species B_2, type C. The shapes of the band contours for room temperature observation have been calculated by the procedure of Badger and Zumwalt[16] and it is found that in cyclobutene, type A bands should have a Q branch of medium intensity and a P–R separation of about 29 cm.$^{-1}$. Type B bands should exhibit a split Q branch (spacing about 7 cm.$^{-1}$) and P–R separation of some 30 cm.$^{-1}$. Type C bands should have a sharp, strong Q branch and P–R spacing of about 40 cm.$^{-1}$. These contours are shown for T = 300°K. in Fig. 3.

Assignment of Frequencies

Although in principle all twenty-four fundamentals are Raman-active, it is apparent from Ta-

(14) The values adopted for the geometrical parameters are not exactly the same as those given by Goldish, Hedberg and Schomaker,[4] though they do lie within or close to the latters' estimates of error. It appears to us that the decreased double bond frequency implies a lower C=C force constant than usual and hence a slightly larger C=C distance. The value given by Goldish, *et al.* (1.325) is slightly smaller than their "standard" value (1.330), but their limits of error (±0.046) are wide enough to include our value of 1.34. The large value appears more reasonable to us in light of the unusually low C=C frequency (1566 cm.$^{-1}$). Quite possibly the C=C distance is even larger than 1.34.

(15) See G. Herzberg, "Infrared and Raman Spectra," D. Van Nostrand Co., New York, N. Y., 1945, p. 469.

(16) R. M. Badger and L. R. Zumwalt, *J. Chem. Phys.*, **6**, 711 (1938).

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TABLE II

INFRARED SPECTRUM OF CYCLOBUTENE-d_6[a]

Vapor ν (cm.$^{-1}$ vac)	I	Liquid ν (cm.$^{-1}$ vac)	I	Assignment
3510	w	3498	w	$\nu_1 + \nu^1$
		3439	w	?
3367	w	3357	w	$\nu_1 + \nu_5$, $\nu_6 + \nu_{21}$
3285	w	3272	w	$\nu_{15} + \nu_{18}$
		3218	w	$\nu_2 + \nu_4$
		3170	w	$\nu_7 + \nu_{21}$
3146	w	3142	w	$\nu_1 + \nu_{19}$
3094	w	3096	w	$\nu_{16} + \nu_{17}$
3077	w	3067	w	$\nu_{14} + \nu_{19}$
2688	w	2682	w	$\nu_{21} + \nu_{24}$
2480	w	2478	w	$\nu_3 + \nu_{17}$
2355 R	s			
2344 Q	s,A?	2335	s	ν_1
2315 P	s			
		2296	s	$2\nu_{18}$
2281 R	s			
2271 Q′, 2266 Q″	S,B	2261	s	ν_{14}
2248 R				
2228 Q, 2210 P	s,C	2221	s	ν_{21}
		2204	s	$\nu_4 + \nu_{18}$
2187 R, 2178 Q, 2168 R		2169	s	ν_2

Vapor ν (cm.$^{-1}$ vac)	I	Liquid ν (cm.$^{-1}$ vac)	I	Assignment
2151 R	s			
2140 Q′, 2135 Q″	s,B	2129	s	ν_{15}
2106 P	s			
		2106	s	$2\nu_4$
		2087	m	$\nu_4 + \nu_5$
2064 R	m			
2055 Q	m,A	2046	m	$2\nu_5$
2045 P	m			
		2032	w	$\nu_4 + \nu_{17}$
		1676	w	$\nu_7 + \nu_8$, $\nu_4 + \nu_{23}$
1669	w	1665	w	$2\nu_{22}$
1521 R	m			
1509 Q	m,A	1504	s	ν_3
1499 P	m			
		1376	w	?
1350	w	1357	w	$\nu_8 + \nu_{23}$
1314 R	w			
1305 Q′, 1298 Q″	w,B	1302	m	$\nu_{11} + \nu_{23}$
1287 P	w			
1157, 1150	m	1155	m	ν_{18}

Vapor ν (cm.$^{-1}$ vac)	I	Liquid ν (cm.$^{-1}$ vac)	I	Assignment
		1135	w	ν_6
		1100	w	$\nu_{13} + \nu_{22}$
1074	m			
1063 R?	m			
1058 Q?	m,B?	1056	s	$\nu_4 + \nu_{16}$
1047 P?	m			
		1031	w	ν_5
991 R	w			
982 Q	w	976	m	ν_{17}
967 R, 956 Q′, 953 Q″, 941 P	w,B?	955	m	ν_7
843 R	s			
826 Q	s,C	826	s	ν_{22}
808 P	s			
		810	s	ν_{19}
745 sh	m	741	m	$\nu_{12} + \nu_{21}$
		722	s	ν_8
718 R	s			
708 Q′, 703 Q″	s,B	702	s	ν_{20}
689 P	s			
642 R	m			
625 Q	m,B	624	m	ν_{23}
608 P	m			
562	vw	552	w	$2\nu_{13}$
475 R	s			
462 Q	s,C	481–453	vs	ν_{24}
446 P	s			
419	w	..		$\nu_{20} - \nu_{21}$

[a] See footnote *a* Table I, for symbols. About a dozen very weak transmission minima observed in the range 1890-2010 cm.$^{-1}$ are omitted from Table II. These can readily be assigned to combinations of the eight fundamentals observed between 810 and 1155 cm.$^{-1}$.

ble III that only a fraction of these, particularly of those expected to lie below 1500 cm.$^{-1}$, have been

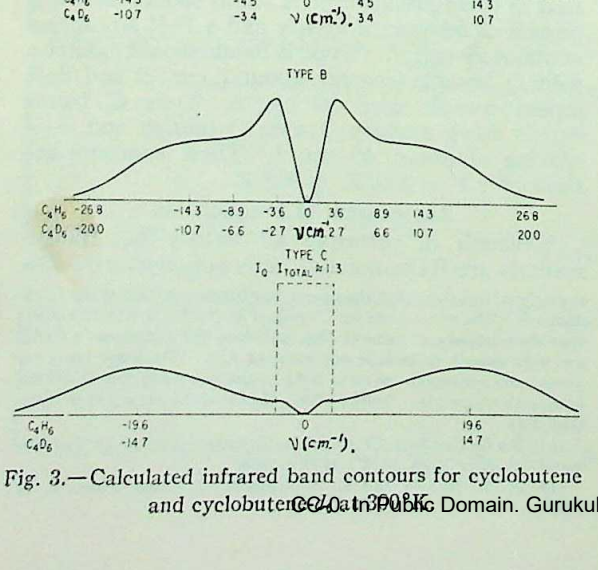

Fig. 3.—Calculated infrared band contours for cyclobutene and cyclobutene-d_6 at 300°K.

TABLE III

RAMAN SPECTRUM OF LIQUID CYCLOBUTENE AND CYCLOBUTENE-d_6

$\Delta\nu$ (cm.$^{-1}$ vac)	I, p (estd.)	Assignment
3129	3 dp	ν_{14}
3058	7 p	ν_1
3047	2 –	?
2933	9 p	ν_2
2916	6 p?	ν_{15}
2876	4 p	$2\nu_4$
2840	5 p	$2\nu_{16}$
2494	1 dp?	$\nu_{17} + \nu_{18}$, $\nu_{16} + \nu_{22}$
1566	10 p	ν_3
1444	5 p	ν_4
1427	4 dp	ν_{16}
1276	1 dp?	ν_5
1182	5 p	ν_6
1113	10 p	ν_7
986	8 dp	ν_8
875	6 dp	ν_{19}
850	1 –	ν_{20}
385		ν_{24}

$\Delta\nu$ (cm.$^{-1}$ vac)	I, p (estd.)	Assignment
2335	7 p	ν_1
2297	1 –	$2\nu_{18}$
2262	5 dp	ν_{14}
2218	3 dp	ν_{21}
2167	7 p	ν_2
2161	7 p	$\nu_5 + \nu_6$
2127	3 dp	$\nu_{17} + \nu_{18}$
2108	4 p	$2\nu_4$
2047	3 p	$2\nu_5$
1947	0 –	$2\nu_{17}$
1504	10 p	ν_3
1136	5 p	ν_6
1054	0 –	ν_4, ν_{16}
1031	0 –	ν_5
953	10 p	ν_7
833	1 dp?	ν_{22}
735	2 dp	$\nu_{12} + \nu_{13}$
723	3 dp	ν_8

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TABLE IV

SYMMETRY SPECIES, SELECTION RULES AND FREQUENCY ASSIGNMENTS FOR C_{2v} STRUCTURE OF CYCLOBUTENE AND CYCLOBUTENE-d_6[a]

Species, selection rules and product rule values	Vibn. No.	Approximate form of vibration	Assignment C_4H_6	Assignment C_4D_6
	1	CX stretching	3058	2335
	2	CX_2 stretching	2933	2164
A_1	3	C=C stretching	1566	1504
$\rho < 6/7$;	4	CX_2 deformation	1444	[1054]
Type-A bands	5	CX in-plane bending	1276	1031
$r_{calcd} = 5.365$				
$r_{obsd} = 5.19$	6	Ring expansion	1182	1136
	7	Ring expansion	1113	953
	8	CX_2 wagging	986	723
	9	CX_2 stretching	(2955)	(2228)
	10	CX_2 twisting	(1100)	(850)
A_2	11	CX out-of-plane bending	(800)	(650)
$\rho = 6/7$; IR-inactive				
$r_{calcd} = 3.472$	12	CX_2 rocking	(640)	(460)
	13	Ring puckering	325	275
	14	CX stretching	3126	2261
B_1	15	CX_2 stretching	2916	2129
$\rho = 6/7$;	16	CX_2 deformation	1426	[1054]
Type-B bands	17	CX in-plane bending	1288	976
$r_{calcd} = 4.75$				
$r_{obsd} = 4.63$	18	Ring expansion	1210	1155
	19	Ring deformation	875	810
	20	CX_2 wagging	850	702
B_2	21	CX_2 stretching	2955	2228
$\rho = 6/7$	22	CX_2 twisting	1074	826
Type-C bands	23	CX out-of-plane bending	846	625
$r_{calcd} = 3.277$				
$r_{obsd} = 3.21$	24	CX_2 rocking	635	462

[a] ρ = depolarization ratio of Raman lines; r_{calcd} = theoretical value of product-rule ratio; r_{obsd} = product-rule ratio of observed frequencies; CX refers to olefinic CX bonds, CX_2 to aliphatic CX_2 group, X = H or D; ( ) means "estimated frequencies," [ ] means "observed frequency assigned to two fundamentals."

observed. Most of the fundamentals must therefore be evaluated from the infrared.

Species A_1.—There are six polarized Raman lines in cyclobutene and five in cyclobutene-d_6 which can be assigned readily as indicated in Table IV. The remaining two A_1 frequencies in cyclobutene are placed at 1276 and 986 on the basis of their expected locations. The former is questionably depolarized and the latter, though observed as depolarized, coincides with a source line which could have influenced the depolarization ratio under the conditions of measurement. In the deuterium compound the lines at 1031 and 1054, though so weak that their depolarization factors could not be measured, are placed in species A_1 because they lie approximately at the plates to which the CH_2 deformation and CH in-plane bending frequencies should shift in cyclobutene-d_6. The remaining frequency—723—is selected from the pair 723–735 because this region is the expected location of CD_2 wagging and the lower of the pair is more intense and gives slightly better agreement with the product rule. The pair 723–735 also occurs in the infrared of liquid cyclobutene with an intensity ratio similar to that in the Raman effect. This fact suggests Fermi resonance, and after attempts to assign 735 as fundamental encountered difficulties, it was attributed to the combination tone $\nu_{12} + \nu_{13}$, in resonance with ν_8.

Species B_1.—If the foregoing assignments are correct, most of the B_1 vibrations must be either unobserved in the Raman effect or in coincidence with A_1 frequencies. However, some of this species can be assigned from the infrared band type (B) and others can be located by elimination, *i.e.*, because their band types are not A or C. In the spectrum of cyclobutene vapor, the bands at 3134, 1294 and 1214 are rather definitely of type B and those at 1434 and 885 are probably of type B, though overlapping of other bands interferes with the identification. In cyclobutene-d_6 the distinction between band types A and B is much less clear-cut and only the band at 706 is sufficiently free from overlapping to be identified as type B. However, the locations of the B_1 fundamentals in cyclobutene and the product rule assist considerably in the assignments. The ones shown in Table IV show good correlation with analogous frequencies in cyclopropane, ethylene oxide and their deuterium analogs.[3] It is interesting that the B_1 vibrations show greater intensity than the A_1 vibrations in the infrared.

Species B_2.—The infrared (type C) bands of this species in both compounds are the most intense of all. This fact together with the distinctive band shape and freedom from overlapping enables all B_2 vibrations to be identified readily. The assignment given in Table IV fits the product rule satisfactorily and correlates well with related molecules.[3]

Species A_2.—This species is inactive in the infrared. Although the A_2 vibrations are formally allowed in the Raman effect, the only observed line which cannot easily be assigned to other species is the extremely weak one at 325 in cyclobutene. This is so low that it can correspond only to the ring-puckering vibration. The analogous frequency in cyclobutene-d_6 is expected at about 275 cm.$^{-1}$, but was not detected in the Raman effect. Certain overtones in the infrared are best explained with the help of an A_2 fundamental of this frequency, and it is therefore entered in Table IV as an observed value.

All the other A_2 modes are similar to the B_2 modes and frequencies are estimated for them by analogy.

Overtones.—In various regions of the infrared spectrum many overlapping overtones are observed. The selection rules are so lax (only species A_2 is forbidden), the overlapping so extensive and the effect of anharmonicity so uncertain that the information obtainable from overtones is limited. Many of the weaker overtone frequencies have been omitted from Tables I and II. Plausible explanations are given for most of those listed in the tables.

Discussion

Since the highest reasonable symmetry for the cyclobutene molecule is C_{2v}, the structural problem from a symmetry standpoint is the rather empty one of distinguishing between C_{2v}, C_2, C_s and C_1

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(no symmetry). In any of these structures, all vibrations would be both infrared- and Raman-active except for the infrared-silent vibrations of species A_2 of C_{2v}. Therefore the vibrational selection rules are unfavorable *a priori* for a structural decision, and in addition the failure of numerous vibrations to appear in the Raman effect renders firm decision impossible.

The most significant structural evidence is furnished by the type-C infrared bands. The number of these found is just that predicted for C_{2v} symmetry for both cyclobutene and cyclobutene-d_6. The frequencies and band shapes (see Fig. 3) are those expected and the frequency product ratio for species B_2 agrees with the theoretical value. To be sure, these things might happen by accident for a structure of lesser symmetry, particularly if the deviation from C_{2v} geometry were rather small. The best one can say is that there is some rather definite evidence in favor of a C_{2v} structure and nothing compelling against it. High-resolution study of the rotation–vibration spectra for bands of all three types in both molecules should furnish sufficient information to evaluate the most important geometrical parameters.

An interesting result of this study is the unusual location and intensity of the double bond frequency. Presumably the low frequency is the result of a decrease in the C=C force constant due to strain in the four-membered ring,[17] as was pointed out above. The high intensity of the double bond vibration in the Raman effect is remarkable, as is the unusually low intensity of the infrared band. The latter, which is weaker than the overtone bands at 1540 and 1760, cannot be used with assurance to indicate the presence of HC=CH in a four-membered ring, and particularly its absence from an infrared spectrum is not an indication of the absence of this group from a molecule. The Raman spectrum is a more reliable guide for this purpose.[18] Substitution of one of the hydrogens by methyl, halogen, or other group will of course affect both the frequency and intensity of the C=C infrared absorption band.

Thermodynamic Functions of Cyclobutene

So far as the authors are aware, no investigation has been made of the heat capacity and heats of transition of cyclobutene. It is therefore not possible to check the assignment given in Table IV by comparison of calculated with measured entropy, free energy or heat capacity. Calculation of these quantities has been carried out by Mr. Alfred Danti of this Laboratory and these results will be published separately.

(17) J. O. Halford (*J. Chem. Phys.*, **24**, 830 (1956)) has shown that a considerable variation in the carbonyl frequency of ketones could result without changing the force constants simply by a change of the bond angles of the carbonyl group. Possibly a similar effect is partially responsible for the low C=C frequency in cyclobutene.

(18) D. E. Applequist and J. D. Roberts (THIS JOURNAL, **78**, 4012 (1956)) have recently published infrared spectra of methylenecyclobutene and certain related compounds. Although the exocyclic double bond of methylenecyclobutene gives a strong infrared absorption band at about 1670 cm.$^{-1}$, no band is reported near 1550 cm.$^{-1}$ for the internal double bond. In the Raman spectrum of this compound, on the other hand (M. V. Evans and R. C. Lord, unpublished results), both double bond frequencies are present, at 1673 and 1530 cm.$^{-1}$, respectively, the latter being considerably stronger.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE CRYOGENIC LABORATORY AND DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

The Surface Catalysis of the Ortho- to Para- Conversion in Hydrogen under Pressure at Low Temperatures

BY DOUGLAS S. CHAPIN[1] AND HERRICK L. JOHNSTON

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The surface catalysis of the ortho- to para- conversion in hydrogen was investigated on a series of catalysts consisting of 0.05 to 2.47% chromia–alumina under pressures in the range 5 to 100 atmospheres at 77°K. and on a 0.05% chromia–alumina catalyst at approximately 29 atm. in the region 55–195°K. For catalysts of lower chromia concentrations the half-life varied linearly with pressure and linearly with the reciprocal of the number of gram-atoms of chromium in the catalyst chamber. The rate data, which were first order with respect to composition, support the theory of Harrison and McDowell[2] who adapted the Wigner[3] theory to the case of conversion in a physically adsorbed hydrogen layer on a paramagnetic surface. The rate constant temperature dependency, in agreement with this theory, was positive for the case of high hydrogen surface coverage investigated in this research. This is in contrast to the negative temperature dependency of the rate constant usually observed for the case of low surface coverage. Absolute rate calculations were made for the case of high surface coverage using Harrison and McDowell's choice of reasonable values for certain constants in the rate expression. Good agreement with experiment was obtained.

Introduction

Though considerable experimental work has been done concerning the surface catalysis of the ortho–para- conversion in hydrogen at pressures of 1 atm. or less, the catalysis at higher pressures and low temperatures has been little studied since the initial experiments of Bonhoeffer and Harteck[4] and Farkas and Bonhoeffer[5] to prove the existence of the heterogeneous catalysis.

Harrison and McDowell,[2] in their study of the para–orthohydrogen conversion on the free radical α,α-diphenyl-β-picrylhydrazyl at low temperatures and pressures, concluded that the conversion takes place by interaction between hydrogen mole-

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(2) L. G. Harrison and C. A. McDowell, *Proc. Roy. Soc.* (*London*), **A220**, 77 (1953).

(3) E. Wigner, *Z. physik. Chem.*, **B23**, 28 (1933).

(4) K. F. Bonhoeffer and P. Harteck, *ibid.*, **B4**, 113 (1929).

(5) A. Farkas and K. F. Bonhoeffer, *ibid.*, Bodensteinband, 636 (1931).

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cules in a mobile physically adsorbed layer and paramagnetic sites. By using the transition probabilities given by Wigner[3] and by calculating the fraction of the time a molecule spends over a paramagnetic site while moving as a two-dimensional gas in the adsorbed layer, Harrison and McDowell developed an absolute rate expression. This expression predicts in agreement with experiment a negative temperature dependency of the rate constant and independence of the rate constant with pressure. Absolute rate calculations for the case of low surface coverage were in agreement with experiment when reasonable values were used for the various constants involved.

The present work is concerned with an experimental study of the variation of the rate constant with temperature, pressure and number of paramagnetic sites for the case of high surface coverages. The rate investigations were carried out by the static method on impregnation catalysts of several concentrations of Cr_2O_3–Al_2O_3 with most of the work being done on 0.05 and 0.24% chromia–alumina.

Theoretical Development

The conversion follows the usual unimolecular rate law

$$u_t = u_0 e^{-k_H t} \tag{1}$$

where $u_t = x_t - x_e$ and $u_0 = x_0 - x_e$ in which x_t, x_0 and x_e are the percentages of parahydrogen at time $t = t$, 0 and ∞, respectively; and k_H is the rate constant. In order to compare theoretical and experimental results the rate constant and the variables upon which it theoretically depends are given below; but no reproduction of the considerations leading to this rate expression is given here. The general expression Harrison and McDowell obtained for the rate constant for a parahydrogen conversion taking place in a physically adsorbed layer is given by

$$k_H = \frac{sK\rho a\,(RTM)^{1/2}\overline{l^2}G(T)}{\sqrt{2}r_s^2 N p v \beta_0 l_m}\left(\frac{\alpha_0\mu e^{Q/RT}}{1+\frac{\alpha_0\mu}{\beta_0\nu}e^{Q/RT}}\right) \tag{2}$$

where s is the total surface area in sq. cm.; ρ is the number of active sites per sq. cm.; a is the area per paramagnetic site in sq. cm.; ν is the number of hydrogen molecules per sq. cm. in a complete monolayer; r_s is the mean distance of a hydrogen molecule from the surface in a physically adsorbed layer; p is the pressure; v is the volume of the system; T is the absolute temperature; M is the molecular weight of hydrogen; R is the gas constant; N is Avogadro's number; $\overline{l^2}/l_m$ is the ratio of the mean square path to the mean path across an idealized circle of interaction for a molecule of hydrogen moving in the adsorbed layer. Also in equation 2, α_0 is the condensation coefficient, which is independent of temperature assuming no activation energy of adsorption; β_0 is a desorption coefficient, which is independent of temperature and $\mu = pN/(2\pi MRT)^{1/2}$ is the rate molecules of hydrogen strike one sq. cm. of surface per sec.; Q is the activation energy of desorption. Again, in equation 2, K is given by

$$K = \frac{24\mu_a^2\mu_p^2 I\pi^2}{h^2 m} \tag{3}$$

where μ_a is the magnetic moment of each paramagnetic surface site; μ_p is the proton magnetic moment; I is the moment of inertia of a hydrogen molecule of mass m; and h is Planck's constant. $G(T)$ in equation 2 is given by

$$G(T) = \left\{1 + \frac{n_p(T)}{n_0(T)}\right\}\left\{\frac{\sum_{J=0,1,2,\ldots} J\exp(-E_J/kT)}{\sum_{J=0,2,4,\ldots}(2J+1)\exp(-E_J/kT)}\right\} \tag{4}$$

where $n_p(T)$ and $n_0(T)$ are the equilibrium concentrations of para- and orthohydrogen, respectively, at the temperature T; J is the rotational quantum number and E_J is the rotational energy of the molecule in the state J given by

$$E_J = J(J+1)h^2/(8\pi^2 I) \tag{5}$$

Substitution of $\mu = pN/(2\pi MRT)^{1/2}$ in equation 2 yields

$$k_H = \frac{ACT^{1/2}G(T)}{T^{1/2}e^{-Q/RT} + Bp} \tag{6}$$

where

$$A = \frac{NKa\alpha_0\overline{l^2}}{2\pi^{1/2}\nu\beta_0 r_s^2 l_m} \text{ and } B = \frac{\alpha_0 N}{\beta_0\nu(2\pi MR)^{1/2}}$$

The total number of moles, C, of paramagnetic sites exposed on the surface to hydrogen conversion is given by $C = s\rho/N$.

Noting that the half-life $\tau_{1/2} = \ln 2/k_H$ and utilizing equation 6, the half-life time is given by

$$\tau_{1/2} = \frac{\ln 2}{AG(T)C}\left(\frac{Bp}{T^{1/2}} + e^{-Q/RT}\right) \tag{7}$$

As approximations, at sufficiently low pressures the first term in equation 7 can be neglected; at sufficiently high pressures the second term can be neglected. Thus for high pressures approximately

$$\tau_{1/2} = \frac{Bp\ln 2}{AT^{1/2}G(T)C} \tag{8}$$

These equations (particularly equation 7) will be examined subsequently in the light of the experimental determination of the pressure, concentration and temperature dependencies of the heterogeneous ortho–parahydrogen conversion at low temperatures under pressure in contact with chromia–alumina catalysts.

Experimental

Rate Apparatus.—The apparatus for the rate determinations consisted essentially of a stainless steel cylinder 1 in. i.d. of 200-cc. volume, suspended from a brass cover plate which closed the end of a standard brass cryostat typical of those used in this Laboratory. Unsilvered slit windows in the glass dewar were visible through opposing Lucite windows in the cryostat. In a run specially purified hydrogen under pressure could be expanded from a 1.5-l. calibrated cylinder on to the catalyst previously conditioned in the catalyst chamber. Liquid nitrogen was the cryostating bath in the majority of the runs. Samples of hydrogen were withdrawn through a 0.009 in. i.d. stainless steel capillary tube extending into the mid-region of the chamber. A capillary lock between two specially designed valves allowed eight locks of purge preceding each of twelve samples to be taken with a total hydrogen depletion of less than 0.1% of the total amount of hydrogen in the chamber. Pressures before and after expansion of the hydrogen were read by means of a Bourdon laboratory test gage which had been calibrated under dead weight gage.

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Analytical Apparatus.—Samples stored in a series of Pyrex bulbs over mercury were analyzed using the Farkas microthermal conductivity method, employing a pressure of 0.05 mm.[6,7] The cell was calibrated with mixtures prepared volumetrically from normal and 50% parahydrogen. The calibration curve showed a maximum deviation of 2% at a concentration corresponding to $u_t/u_0 = 0.5$. The precision of the cell was approximately 0.2% in u_t/u_0 at 0.5.

Surface Area Apparatus.—Surface areas were measured volumetrically at liquid nitrogen temperature using the BET[8] method in which the volume of nitrogen required to form a monolayer on the catalyst surface was estimated from the adsorption isotherms.

Hydrogen Purification.—Hydrogen obtained from the hydrogen liquefaction cycle of this Laboratory was initially purified by passage through a liquid nitrogen trap, over platinized asbestos at 400° and through another liquid nitrogen trap. This procedure removed the condensable impurities, converted oxygen to water and removed the water formed, respectively. The platinized asbestos also served to equilibrate the hydrogen to normal with respect to its ortho–parahydrogen composition. Final purification was effected by liquefaction, filtration through glass wool to remove any solid nitrogen present, gasification, second liquefaction and distillation. High pressure pure hydrogen was obtained by condensing this hydrogen into a heavy copper chamber immersed in liquid hydrogen with subsequent isolation and then by heating the copper chamber while it was connected to a storage cylinder at room temperature.

Catalyst Preparation.—Special Bayer-process alumina in the form of 1/8 in. pellets of low iron content was prepared in a 50 lb. lot by the Harshaw Chemical Company. The composition was stated by the manufacturer to be as follows: SiO_2, 0.03%; Fe_2O_3, 0.008%; TiO_2, 0.007%; Na_2O, 0.4%; and Al_2O_3, 99.+%. This carrier was heated to 600° for 16 hours, appeared snow white, and will be called the unleached carrier. Leached carrier was prepared by agitating 450 g. of the unleached carrier with 500 ml. of 1 N HNO_3 for 16 hours. This was followed by washing overnight with 7.5 gallons of double distilled water, drying and calcining at 600° for 16 hours. The surface area decreased from 94.9 to 87.4 sq. m./g. The loss in weight due only to acid action was not determined. Catalysts of various chromia concentrations in the range 0–2% were prepared by agitating 228.3 g. of the carrier with 200 ml. of chromic acid solution of the appropriate concentration. Reagent grade CrO_3 from Baker and Adamson Chemical Company was used. The stated maximum impurity of Fe, Al, Ba, etc., was 0.03%. The carrier and chromic acid were sealed in a liter glass-stoppered bottle and rolled slowly for 16 hours, then washed with 4 l. of double distilled water. The bright yellow pellets were dried at 110° for several hours and heated for 16 hours at 300°. The product at this point was bright with small dark patches which were thought due to partial reduction. Reduction to a uniform green chromic oxide was accomplished by passing hydrogen over the catalyst at 350° for 5 hours.

Chromium Analysis.—Solutions of chromic acid were analyzed by adding a known excess of ferrous ammonium sulfate and back titrating with standard potassium dichromate in a 1.5 M phosphoric–5 M sulfuric acid media with diphenylamine sulfonate indicator.[9] Chromia–alumina catalysts were analyzed by the same method after fusion with sodium peroxide followed by careful neutralization with 6 N sulfuric acid.

Pretreatment of Catalysts.—The usual pretreatment procedure was to pump at room temperature for 24 hours on approximately 175 g. of catalyst sealed in the high pressure chamber. This was followed by pumping 24 hours at 200°. Hydrogen from the purification train previously mentioned was passed slowly over the catalyst at 200° for 3 hours. Then the catalyst was pumped while cooling down to "run" temperature. At this temperature the catalyst was purged several times with some of the specially prepared high pressure hydrogen. The chamber was pumped after this treatment until the start of a catalytic run, which usually took place within a few hours after the final purge. The only treatment between runs on the same catalyst was to evacuate the chamber at low temperatures.

Catalytic Runs.—Specially purified hydrogen was expanded onto the evacuated catalyst from a calibrated cylinder. The drop in pressure and the cylinder temperature were used to calculate the amount of gas delivered to the catalyst chamber. Temperature was measured with a copper–constantan thermocouple.

Results

Catalysts.—Nitrogen surface areas on the catalysts prepared from the leached carrier were very nearly independent of chromia concentration. Surface areas for 0.00, 0.0486 and 1.08% chromia–alumina catalysts were 87.4, 87.6 and 86.7 sq. m./g., respectively. Adsorption isotherms for the up-take of chromic acid on the leached and unleached alumina carrier during the preparation of the chromia–alumina catalysts showed an increase of amount of chromic acid adsorbed with increasing final chromic acid concentration. Adsorption on the leached carrier was approximately five to ten times that on the unleached carrier for a given final concentration of chromic acid at lower (less than 0.05 mole/l.) concentrations. The isotherm for the unleached carrier leveled off at a chromic acid adsorption corresponding to a catalyst composition of 1.78% chromia–alumina by weight. It is assumed that essentially all chromic acid molecules or ions that are adsorbed on the alumina will do so in pores which are large enough for hydrogen to penetrate in the dried catalyst so that analysis of the finished catalyst for chromium is an effective measure of the number of paramagnetic sites available for reaction. Cunningham and Johnston[10] found that the rate constant in the heterogeneous liquid hydrogen conversion on several of the same catalysts used in this work varied linearly with the chromia concentration. This would seem to indicate that the chromic acid is adsorbed on the alumina in essentially a monolayer.

Rate Data.—Rate constants for the ortho–parahydrogen conversion on chromia–alumina catalysts were obtained from the slope of the line produced by plotting $\ln (u_0/u_t)$ *vs.* t (equation 1). Figs. 1, 2 and 3 show these plots for 0.0486 and 0.237% chromia–alumina under several conditions of temperature and pressure. In these plots time has been adjusted so as to give coincidence with the origin.

A summary of the rate data is given in Tables I and II. The first column gives the run designation. The 28 series runs were made on the unimpregnated leached alumina carrier which was used in the majority of the runs. The carrier and catalysts were in the form of 1/8 in. pellets. The 28 series blank runs were used to correct the low concentration runs for the catalytic activity of the carrier. Conditions of temperature and pressure for the runs within a series were changed in the order given by the second number in the first column. The total number of g.-atom of chromium in the catalyst chamber and assumed to be available for interaction with the hydrogen is given in the second

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(7) A. Farkas, "Orthohydrogen, Parahydrogen and Heavy Hydrogen," Cambridge University Press, 1935, p. 25.

(8) S. Brunauer, P. H. Emmett and E. Teller, THIS JOURNAL, **60**, 309 (1938).

(9) A. R. Olson, E. F. Orlemann and C. W. Koch, "Introductory Quantitative Analysis," W. H. Freeman and Company, San Francisco, Cal., 1948, p. 228.

(10) C. M. Cunningham and H. L. Johnston, to be published.

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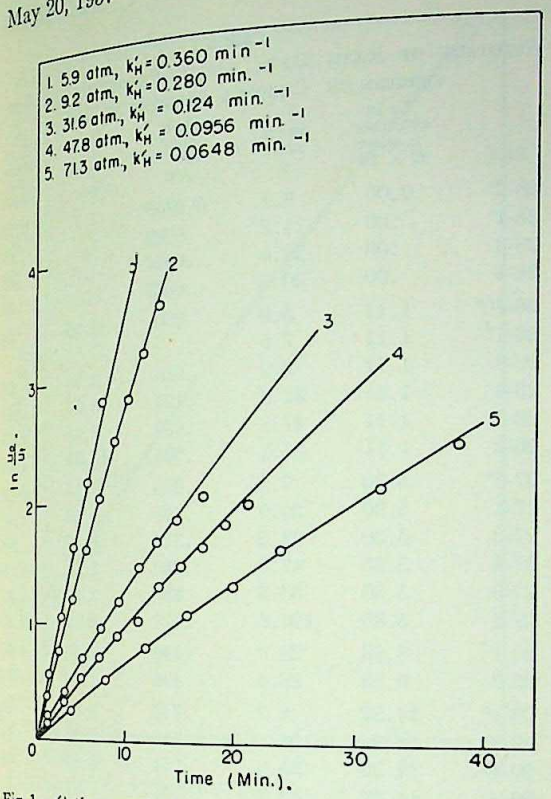

Fig. 1.—Ortho-para hydrogen conversion on 0.0486% Cr_2O_3–Al_2O_3 at 77°K. and various pressures.

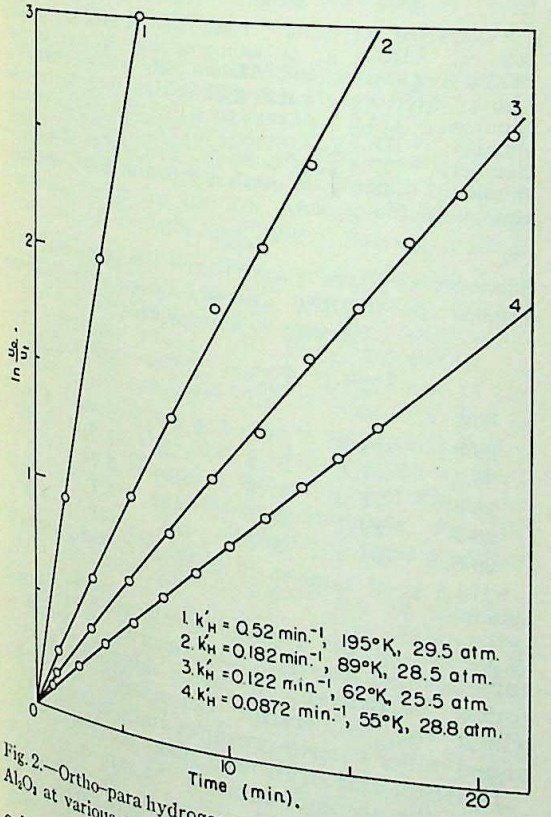

Fig. 2.—Ortho-para hydrogen conversion on 0.0486% Cr_2O_3–Al_2O_3 at various temperatures and approximately 28 atm.

column. The uncorrected rate constant k_H which was obtained from the slopes of the lines (Figs. 1, 2 and 3) are given in the fourth column. The half-

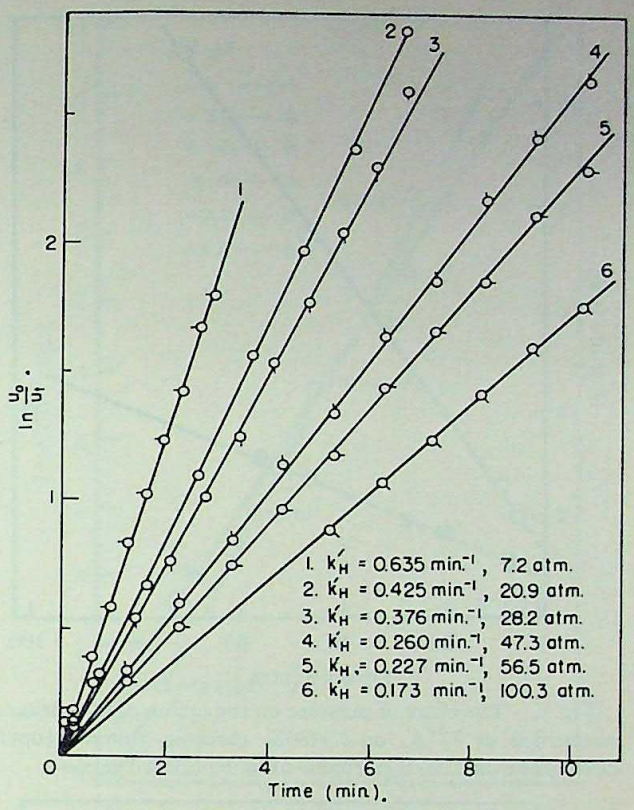

Fig. 3.—Ortho-para conversion in hydrogen on 0.237% Cr_2O_3–Al_2O_3 at 77°K. and various pressures.

lives calculated from rate constants corrected for the blank alumina runs (series 28) are shown in the fifth column. The number of moles of hydrogen delivered to the chamber is given in the sixth column.

Pressure Dependency.—The data for the 1.11×10^{-3} g.-atom chromium (0.0486% chromia–alumina) and 5.30×10^{-3} g.-atom chromium (0.237% chromia–alumina) at 77°K. plotted as half-life *vs.* pressure can be represented by two straight lines given approximately by the equations

$$\tau_{1/2} = 0.136p + 1.18 \text{ and } \tau_{1/2} = 0.0391p + 0.82 \quad (9)$$

respectively, as shown in Fig. 4.

Temperature Dependency.—For the 1.11×10^{-3} g.-atom chromium runs (Table II) a plot of half-life *vs.* $1/[T^{1/2}\,G(T)]$ as suggested by equation 8, shown in Fig. 5, at approximately 29.5 atm. can be represented by the solid straight line. The half-life values were corrected approximately to a pressure of 29.5 atm. by utilizing the first of equations 9.

Paramagnetic Site Dependency.—The rate data for runs (Table I) made at approximately 29 atm. and 77°K. are shown in Fig. 6 in which half-life is plotted against reciprocal site content C of the catalyst chamber.

Discussion of the Results

A summary of the rate data can be seen in Fig. 7 in which half-life *vs.* $p/[CT^{1/2}G(T)]$ is plotted. It is to be noted that while the plots of pressure and site content dependencies shown in Figs. 4 and 6 are made to test agreement with the general equation 7, the plot of the temperature dependency in Fig. 5 is not necessarily made to correspond to the

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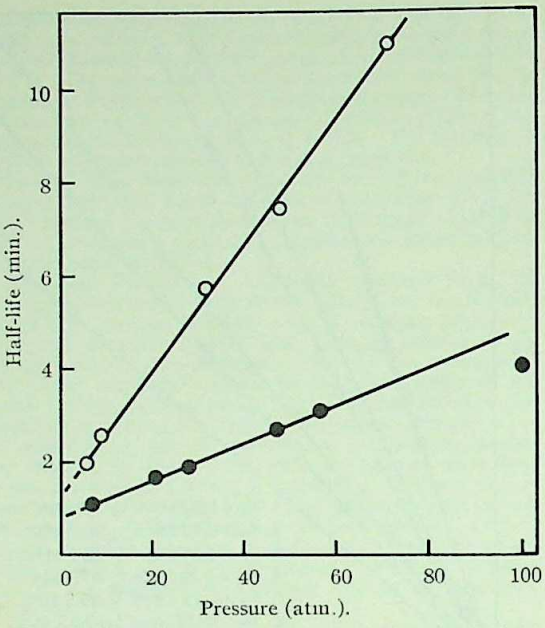

Fig. 4.—The effect of pressure on the ortho-parahydrogen conversion at 77°K. on 0.0486% chromia–alumina (open circles) and on 0.237% chromia–alumina (closed circles).

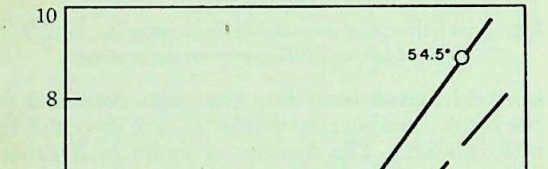

Fig. 5.—The effect of temperature on the ortho–parahydrogen conversion at approximately 29.5 atmospheres on 0.0486% chromia–alumina. The solid line represents the experimental data; the broken line was calculated from the absolute rate expression of Harrison and McDowell.[2]

high coverage case given by equation 8, since Q the activation energy of desorption is unknown.

The data in general support the theory of Harrison and McDowell; however it may be pointed out that the temperature dependency plot appears to intersect the origin (Fig. 5) while the plots of pressure and site content [illegible] (Fig. 4, 6) do not. This appears to indicate an inconsistency between the data and theory. It would, of course, be desirable to make additional runs in which the temperature dependency was determined under various pressures and site contents.

Harrison and McDowell make a rough calculation of the absolute value of the rate constant k_H by assigning reasonable values to the variables in equation 6 and neglecting the pressure term in the denominator valid for the case of low surface coverage. Their calculated value compares well with their experimental value (5.1×10^{-3} and $3.1 \times$ [illegible], respectively).

Table I

Summary of Rate Data, Ortho–Parahydrogen Conversion on Chromia–Alumina at 77°K.

Run	Cr in chamber, g.-atom $C \times 10^3$	Press. atm., p	Rate const., min.$^{-1}$ k'_H	Half-life,[a] min. $\tau_{1/2}$	H_2 in chamber, moles
28-2[b]	0.00	9.4	0.0106	..	0.27
28-1	.00	14.3	.0082	..	.40
28-3	.00	20.3	.0054	..	.56
28-4	.00	20.3	.0057	..	.52
26-10[c]	1.11	5.9	.360	1.99	.18
26-1[d]	1.11	7.9	...	..	..
26-9	1.11	9.2	.280	2.58	.28
26-4	1.11	31.6	.124	5.74	.81
26-3	1.11	47.8	.096	7.45	1.13
26-2	1.11	71.3	.065	10.94	1.66
27-5[e]	5.30	7.2	.635	1.11	0.20
27-1	5.30	20.9	.425	1.65	.50
27-2	5.30	28.2	.376	1.87	.68
27-4	5.30	47.3	.260	2.68	1.09
27-3	5.30	56.5	.227	3.08	1.27
27-6	5.30	100.3	.173	4.03	2.20
23-1[f]	6.93	28.0	.496	1.40	0.69
23-2	6.93	28.6	.496	1.40	.74
29-4[g]	14.32	9.2	.746	0.93	.28
29-3	14.32	14.4	.712	0.97	.43
29-1	14.32	25.0	.754	0.92	.63
29-2	14.32	30.3	.507	1.37	.79
24[h]	40.7	28.9	.604	1.15	.68
22[i]	46.7	30.6	1.05	0.66	.61

[a] Corrected for blank. Total catalyst chamber volume 202 cc. [b] 173.5 g. of unimpregnated leached carrier. [c] 173.5 g. of catalyst 19 CrAL of 0.0486% chromia–alumina. [d] Lost. [e] 170.0 g. of catalyst 21 CrAL of 0.237% chromia–alumina. [f] 174.5 g. of catalyst 4 CrA of 0.302% chromia–alumina. [g] 173.5 g. of catalyst 20 CrAL of 0.627% chromia–alumina. [h] 177.4 g. of catalyst 7 CrA of 1.74% chromia–alumina. [i] 143.6 g. of catalyst 2 CrA of 2.47% chromia–alumina in 163-cc. vol.

Table II

Summary of Rate Data, Ortho–Parahydrogen Conversion on 0.0486% Chromia–Alumina at Approximately 29 Atmospheres[a]

Run	Temp., °K. T	Press. atm., p	Rate const., min.$^{-1}$ k'_H	Half-life, min. $\tau_{1/2}$	H_2 in chamber, moles
26-8	54.5	28.8	0.087	8.49	1.05
26-5	61.6	25.5	.122	5.84	0.83
26-4	77.3	31.6	.124	5.74	.81
26-7	89.1	28.5	.182	3.91	.59
26-6	194.5	29.5	.52	1.39	.25

[a] 173.5 g. of catalyst 19 CrAL of 0.0486% chromia–alumina.

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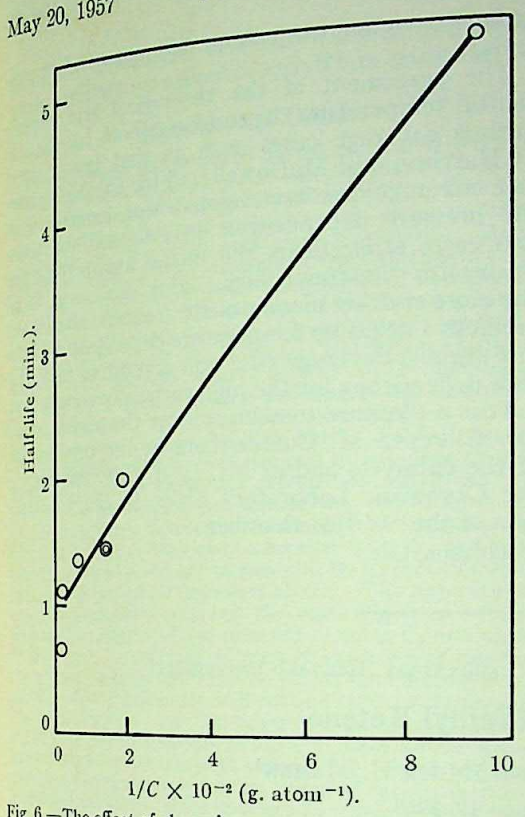

Fig. 6.—The effect of chromium content in chromia–alumina catalysts on the ortho–parahydrogen conversion at 77°K. and approximately 29 atmospheres.

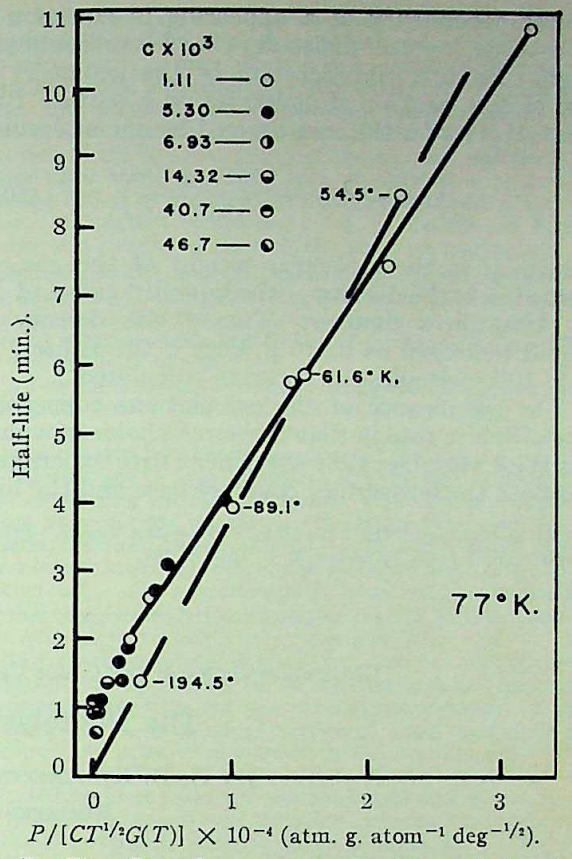

Fig. 7.—The effect of pressure, temperature and chromium content in chromia–alumina catalysts on the ortho-parahydrogen conversion.

While many of the variables appearing in equation 8 are not known with much accuracy, it was thought nevertheless of some value to make an absolute rate calculation using the same choice of the variables that Harrison and McDowell made in their calculation for the low coverage case. Harrison and McDowell used the following values: $\overline{l^2}/l_m$ was taken as 10^{-8} cm.; r_s was taken as 3 Å.; μ_a, the magnetic dipole equal to one Bohr magneton was 9.27×10^{-21} erg gauss^{-1}; μ_p, the proton magnetic moment, was 1/1840 Bohr magneton; s, the surface area, was 20 m.^{2}; v, the volume of the reaction vessel, was 200 ml.; T was 200°K.; a, the fraction of the surface active, was taken as 0.1; p was 10 cm.; θ, the fraction of the surface covered, was taken as 0.02; and ν, the number of molecules corresponding to a complete monolayer, was 10^{16} molecules cm.$^{-2}$. The calculated K from equation 3 was 3.3×10^{-48} c.g.s. units.[11]

The additional data necessary for an absolute rate calculation for the case of the ortho–parahydrogen conversion on 0.0486% chromia–alumina at 195°K. and 29.5 atmospheres are as follows: μ_{Cr}, the magnetic dipole moment for trivalent chromium using the spin only formula, is 3.87 Bohr magnetons[12]; $C = s\rho/N = 1.11 \times 10^{-3}$ moles trivalent chromium; v is taken as 120-cc. dead space volume; and the radius of an active center was taken as 2 Å. This last value was chosen by Harrison and McDowell for the radius of the paramagnetic site of a free radical and is adopted here for chromium for the purposes of this calculation. From the above the following is calculated: from equation 3, $K = 2.6 \times 10^{-48}$ c.g.s. units; using equations 4 and 5 together with the equilibrium para–ortho ratios[13] $T^{1/2}G(T) = 7.81$ deg.$^{1/2}$ and, finally, $\tau_{1/2} = 1.2$ min. The experimental half-life shown in Table II for run no. 26–6 is 1.4 min. The closeness of agreement is, of course, fortuitous in view of the accuracy with which the various values in the calculation are known.

For the case of 0.0486% chromia–alumina at 28.8 atmospheres and 55°K. the following is calculated: $T^{1/2}G(T) = 1.16$ deg.$^{1/2}$ and $\tau_{1/2} = 7.7$ min. The experimental half-life is shown in Table II for run no. 26–8: $\tau_1/_2 = 8.5$ min.

For the case of 0.0486% chromia–alumina at 71.3 atmospheres and 77°K., the following is calculated: $T^{1/2}G(T) = 2.00$ deg.$^{1/2}$, $s\rho/N = 1.11 \times 10^{-3}$ mole trivalent chromium in the chamber; $\tau_{1/2} = 11.5$ min. compared to an experimental value of 11.0 shown in Table I, run 26–2.

For 0.237% chromia–alumina at 100.3 atmospheres and 77°K., the following is calculated: $s\rho/N = 5.30 \times 10^{-3}$ g.-atom; $\tau_{1/2} = 3.5$ min. compared to an experimental value of 4.0 min. shown in Table I, run 27–6.

In Fig. 5 the dashed line represents the calculated half-life *vs.* $1/[T^{1/2}G(T)]$. It is seen that all the calculated half-lives are well within the variation which is possible in view of the eighth

(11) It appears that K should be one-half this value, making the calculated rate constant $k_H = 2.5 \times 10^{-3}$ min.$^{-1}$.

(12) J. H. Van Vleck, "The Theory of Electric and Magnetic Susceptibilities," Oxford at the Clarendon Press, 1932, p. 285.

(13) A. Farkas, ref. 7, p. 14.

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power dependency of r_s appearing in equation 8. The value $\nu = 10^{16}$ molecules cm.$^{-2}$ is undoubtedly high. From a consideration of the geometry of the closest packing of molecules on a surface Brunauer[14] gives for the area covered by one molecule

$$\text{Area} = (4)(0.866)\left(\frac{M}{4\sqrt{2}N_A\delta_l}\right) \qquad (10)$$

where M is the molecular weight of the gas adsorbed, δ_l is the density of the liquefied gas, and N_A is Avogadro's number. Taking the density of liquid hydrogen as 0.070 g. cm.$^{-3}$, the value $\nu = 7 \times 10^{14}$ molecules cm.$^{-2}$ can be calculated.

The significance of the calculations concerning the absolute rate is that the same choice of values for these variables gave agreement with experiment for both the low surface coverage case and the high surface coverage case, using different catalyst systems.

The agreement of the theoretical and experimental temperature dependencies both for the low surface coverage cases such as that investigated by Harrison and McDowell and for the higher surface coverage case investigated here, together with the pressure dependencies investigated for these two cases strengthens the model assumed in the theory for the conversion. This agreement is all the more striking in view of the fact that the theory predicts a negative temperature dependency for the low surface coverage case and a positive temperature dependency for the high surface coverage case.

It is a pleasure to acknowledge the assistance of Dr. Clarence M. Cunningham in the preparation of the catalysts and of Mr. L. E. Cox, foreman of the Cryogenic Laboratory Shop, in the construction of the catalyst chamber.

COLUMBUS, OHIO

(14) S. Brunauer, "The Adsorption of Gases and Vapors," Princeton University Press, Princeton, N. J., 1945, p. 287.

[CONTRIBUTION FROM THE GIBBS CHEMICAL LABORATORY, HARVARD UNIVERSITY]

The Photolysis of Methyl Ketene

BY G. B. KISTIAKOWSKY AND BRUCE H. MAHAN[1]

RECEIVED DECEMBER 19, 1956

The gas phase photolysis of methyl ketene was investigated using light of 3650, 3130 and 2400 Å. wave length. The principal photolytic products were found to be CO, C_2H_4 and C_4H_8. The experimentally determined effects of temperature, wave length of light, methyl ketene and inert gas concentrations are explained by a mechanism involving vibrationally excited ethylidene radicals rearranging at measurable rates into ethylene. The alternative mechanism involving only photo-excited methyl ketene molecules is shown to be inconsistent with observations.

Introduction

Extensive investigations of the photolysis of ketene[2-7] have demonstrated the formation of the methylene radical and have provided some information on its kinetic behavior. The photolysis of the next homolog, methyl ketene, has not been described in the literature. By analogy, it should result in the formation of the ethylidene radical, CH_3CH. Previous attempts to study the chemistry of this radical have involved the pyrolysis and photolysis of diazoethane, CH_3CHN_2, and acetaldazine, $CH_3CHNNCHCH_3$. The decomposition of the latter was found to be quite complicated[8] and apparently does not involve the ethylidene radical to any important extent. Investigations of the properties of the ethylidene radical produced from diazoethane have been hampered by the hazards involved in handling this material.

Rice and Glasebrook[9] observed no reaction of the ethylidene radical with antimony mirrors when pyrolyzing diazoethane at 650° and higher. The only decomposition products detected were ethylene and nitrogen. The authors concluded that if ethylidene was formed at all under their conditions, it isomerized to ethylene so fast as to exclude all other reactions.

Barrow, Pearson and Purcell[10] observed the removal of selenium and tellurium mirrors when pyrolyzing diazoethane at 400°. As the furnace temperature approached 600° the rate of mirror removal progressively decreased, thus confirming the speculation of Rice and Glasebrook on the thermal instability of the ethylidene radical. The products resulting from the reaction with selenium mirrors were shown by Barrow, *et al.*, to have the properties of selenoacetaldehyde. The same product was obtained when the authors decomposed diazoethane photochemically in the presence of selenium mirrors.

The ultraviolet photolysis of diazoethane was also studied by Brinton and Volman[11] who detected small amounts of butene-2, hydrogen and acetylene among the products, in addition to ethylene and nitrogen. The authors suggested that butene-2 originated from the reaction

$$CH_3CH + CH_3CH \longrightarrow CH_3CHCHCH_3$$

Repeated explosions of diazoethane led to the discontinuation of this work. As the following will

(1) General Electric Fellow, 1955–1956.

(2) (a) R. G. W. Norrish and G. Porter, *Disc. Faraday Soc.*, **2**, 97 (1947); (b) G. B. Kistiakowsky and N. W. Rosenberg, THIS JOURNAL, **72**, 321 (1950).

(3) M. Vanpee and F. Grard, *Bull. soc. chim. belg.*, **60**, 208 (1951).

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(6) H. Gesser and E. W. R. Steacie, *Can. J. Chem.*, **34**, 113 (1956).

(7) J. Chanmugam and M. Burton, THIS JOURNAL, **78**, 509 (1956).

(8) R. K. Brinton, *ibid.*, **77**, 842 (1955).

(9) F. O. Rice and A. L. Glasebrook, *ibid.*, **66**, 1354 (1944).

(10) R. F. Barrow, T. G. Pearson and R. H. Purcell, *Trans. Faraday Soc.*, **31**, 880 (1935).

(11) R. K. Brinton and D. H. Volman, *J. Chem. Phys.*, **19**, 1394 (1951).

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show, the photolysis of methyl ketene provides a more satisfactory source of ethylidene radicals.

Experimental Details

Methyl ketene was prepared by the method of Jenkins.[12] The vapor of propionic anhydride was pyrolyzed at low pressure in a quartz tube heated externally to 600°. The products passed through a trap cooled to −78° where unreacted anhydride and propionic acid were condensed. Methyl ketene was collected in a subsequent trap which was cooled to −161°, more volatile gases being removed continuously by a diffusion pump. The contents of the second trap were analyzed as 99% methyl ketene and were further purified by two slow bulb-to-bulb distillations. The delivery bulb was kept at −78° and the receiver bulb at −111°, continuous pumping by a diffusion pump assisting in the removal of non-condensables. The first and last quarters of each distillation were discarded. The freshly distilled product was 99.9% absorbed by Ascarite and no ethylene or other lower boiling gases were ever detected as impurities. Although the purified methyl ketene was stored in a trap cooled with liquid nitrogen, the amount of impurity non-absorbable in Ascarite slowly increased with the age of the preparation and could not be removed by a repetition of the purification procedure described above. The impurity was not identified chemically but the mass spectrum of older preparations suggested the presence of some C_3 and C_5 hydrocarbons. An attempt to remove these impurities by a low pressure column fractionation failed, since methyl ketene rapidly polymerized in the still pot and on the column packing. The presence of the impurities in methyl ketene, which may have amounted to 0.5% in some kinetic experiments, made it advisable to express the results of photochemical experiments mainly in terms of carbon monoxide and ethylene yields, since analyses for these products were not complicated by the above-mentioned impurities.

The ketene which was used as an internal actinometer for the quantum yield measurements was prepared by the pyrolysis of acetic anhydride and was purified and stored in an identical manner to methyl ketene.

Hydrogen used in the analytical procedure was Matheson Extra Dry grade (99.8%), which was passed over heated platinized silica gel and $Mg(ClO_4)_2$ to remove oxygen and water vapor.

Oxygen from an Airco tank was treated similarly before use in the combustion analyses.

The *n*-butane was Phillips Petroleum Company Research Grade material (99.9%) and was used after removing non-condensables at −161°.

Sulfur hexafluoride, Matheson C.P. Reagent grade, was distilled twice from −111 to −161°, the first and last quarters of each distillation being discarded.

Carbon dioxide, Matheson Bone Dry grade (99.8%), was used after the removal of non-condensables at −161°.

Diethyl ketone, used for actinic measurements, was Eastman White Label grade, subjected to two bulb-to-bulb vacuum distillations before use.

The photochemical experiments were carried out in a static system. This consisted of the usual pumping arrangement, cold traps and bulbs for the storage of the required chemicals, a gas mixing manifold, a reaction cell, a quartz spiral manometer and a semi-micro gas analytical system.

The light source for almost all the experiments was a low pressure mercury arc of the type described by Bates and Taylor.[13] Its high intensity made it especially suited for this research, since enough products could be obtained for analysis after only five minutes irradiation time. Methyl ketene dimerizes at a measurable rate in the vapor phase. By keeping the pressure of methyl ketene at 30 mm. and below and limiting the runs to five minutes, dimerization was kept to negligible proportions (considerably less than 0.5% in the reaction cell).

The lamp consisted essentially of three concentric quartz tubes. The discharge was maintained in the outermost annular space by a 20 Å. direct current, at a 47-volt potential drop. The light intensity was kept reasonably constant by a servo-mechanism controlled by an RCA 935 photoelectric cell.

A Pyrex reaction cell was axially located in the innermost space of the lamp. To maintain a constant temperature, either water or a filter solution was circulated through the annular space immediately surrounding the reaction cell. The other annular space of the lamp could be filled with a second filter solution, the thickness of each layer being 7 mm. To isolate the 3130 Å. group of the mercury spectrum the outer filter space was filled with an aqueous solution containing 300 g. of $NiSO_4 \cdot 6H_2O$ and 75 g. of $CoSO_4 \cdot 7H_2O$ per liter. A solution containing 0.5 g. of K_2CrO_4 per liter of water was circulated through the inner compartment. To isolate the 3650 Å. spectral region the circulated medium was an aqueous solution containing 0.02 g. of 2,7-dimethyl-3,6-diazacyclohepta-1,6-diene hydrochloride per liter while the second solution contained 500 g. of $CuSO_4 \cdot 5H_2O$ and 75 g. of $CoSO_4 \cdot 7H_2O$ per liter.

A few experiments were made using the strongly reversed resonance line of a British Thomson–Houston high pressure mercury lamp. The radiation from this almost point source was collimated by a quartz lens, passed through a 3 cm. filter of chlorine gas (1 atm. pressure) and through another filter cell containing nitrogen saturated with mercury vapor at room temperature. Following the filters were a cylindrical quartz reaction cell of 12 cm. length and a front surface aluminized mirror to reflect the radiation back into the reaction cell. The asymmetrically broadened resonance line of this lamp extended from approximately 2550 to 2300 Å., the average wave length being about 2400 Å.

The reaction mixtures were prepared by admitting the components successively into a one-liter flask and measuring their pressures with the quartz spiral manometer. A glass stirrer, driven magnetically, ensured rapid mixing of the components prior to admission to the reaction cell. Since the rate of thermal dimerization of methyl ketene was affected by inert gases and was subject to wall effects, it was impossible to prepare and keep inert gas–methyl ketene mixtures of accurately predetermined composition. This mixture was therefore made up to the approximate composition desired and a sample of it was analyzed while the irradiation was taking place.

The progress of the (dark) dimerization of methyl ketene and of the photochemical reaction were followed manometrically, using the quartz spiral manometer, but reliance was placed on the chemical analysis of the reaction mixtures. This was carried out in a system similar to that described by Nash.[14] The product gases were passed through a trap cooled by liquid nitrogen and the non-condensables separated, measured and analyzed by combustion over CuO. Methyl ketene was separated from the condensables by passing them through either Ascarite or anhydrous magnesium perchlorate. The latter agent proved to be an excellent absorber of methyl ketene and thus provided means for analyzing mixtures of methyl ketene and carbon dioxide. The condensable reaction products were then separated into two fractions, one volatile at −161°, and both fractions were analyzed by combustion with added oxygen on platinized silica gel, or catalytic hydrogenation. Samples could be withdrawn for infrared or mass spectrometric analysis. The performance of the entire analytical system was checked repeatedly with known gas mixtures.

Experimental Results

1. The Absorption Spectrum and the Nature of the Products.—The absorption spectrum of methyl ketene was compared with that of ketene using a Cary recording spectrophotometer. As Fig. 1 shows, the two spectra are very similar, except that the absorption of methyl ketene is slightly shifted to lower frequencies. The low resolution tracings showed no evidence of vibrational structure in either spectrum.

Figure 1 shows that with the radiation of a mercury arc filtered only by the Pyrex walls of the reaction cell, the effective radiation must consist of the 3130, 3440 and 3650 Å. line groups. Experiments designed to determine the nature of the reaction products were carried out with this polychromatic

(12) A. D. Jenkins, *J. Chem. Soc.*, 2563 (1952).
(13) J. R. Bates and H. S. Taylor, THIS JOURNAL, **49**, 2438 (1927).
(14) L. K. Nash, *Ind. Eng. Chem.*, **18**, 505 (1946).

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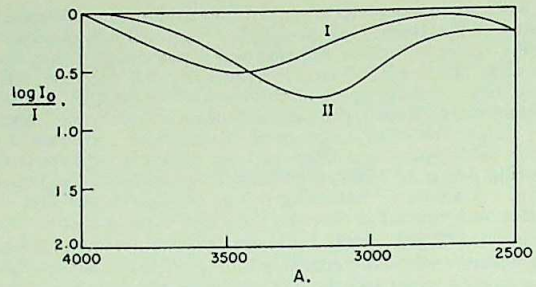

Fig. 1.—Absorption spectra of methyl ketene (I) and of ketene (II), both in a 10 cm. layer at 86 mm. pressure.

radiation. Followed manometrically, the reaction was observed to be accompanied by a pressure increase, the rate decreasing with irradiation time in a manner quite similar to that observed with ketene. This fact suggests that the intermediates formed in the photochemical decomposition of methyl ketene react with the stable products of the reaction just as methylene reacts with the ethylene formed in the decomposition of ketene. Subsequent experiments on the methyl ketene system showed that ethylene was one of the reaction products, and that the rate of pressure increase was lowered by adding ethylene to the reaction mixture.

Gaseous products which were not condensed in a trap at −196° were found analytically to be pure carbon monoxide. A mass spectrometric examination of this fraction indicated the presence of traces of methane.

The fraction non-condensable at −161° was shown by catalytic hydrogenation to be a pure mono-olefin or an equimolar mixture of acetylene and ethane. A mass spectrometric analysis showed it to be ethylene with at most 0.5% ethane and no higher hydrocarbons. The infrared spectrum of the sample showed the 10.52 μ band of ethylene and no other bands, because of the small size of the sample available.

The hydrogenation of the fraction non-volatile at −161° showed it to contain on the average one double bond per mole. Combustion with oxygen, the results of which are shown in Table I, identified

Table I

Two Combustion Analyses of the Product Fraction Condensable at −161°

All quantities are in micromoles

	I	II
Condensable at −161°	0.636	0.586
Mole no. change on combustion	−1.82	−1.70
Calcd. for C_4H_8	−1.91	−1.75
CO_2 in products	2.41	2.64
Calcd. for C_4H_8	2.54	2.34

the material as a C_4 hydrocarbon. A mass spectrometric analysis was consistent with the identification as a C_4 mono-olefin, but the size of the sample precluded the identification of the butene isomer present.

The results of these analyses were taken to mean that, within the accuracy of the measurements, methyl ketene is decomposed by ultraviolet light into a mixture of carbon monoxide, ethylene and butene

$$2CH_3CHCO + nh\nu \longrightarrow 2CO + (2 - x)C_2H_4 + \frac{x}{2}C_4H_8 \quad (1)$$

Table II shows that this is quantitatively correct and also demonstrates that the composition of the hydrocarbon fraction depends on the pressure of methyl ketene in the reaction cell. The higher the pressure the less ethylene and the more butene is obtained, but the sum of ethylene plus twice the amount of butene remains equal to carbon monoxide, as indicated by eq. 1.

Table II

The Composition of Products Formed by Polychromatic Radiation at 24° in 300 Seconds

—CH_3CHCO— Initial pressure mm.	μmoles	CO produced, μmoles	(CO)/(C_2H_4)	(C_4H_8)/(C_2H_4)	Total hydrocarbons as C_4, μmoles
2.6	5.8	1.01	1.22	0.13	1.04
4.6	10.2	1.12	1.39	.19	1.10
4.8	10.7	1.37	1.14	.10	1.42
6.9	15.3	1.34	1.61	.32	1.39
8.5	18.9	1.45	1.61	.37	1.55
9.0	20.0	1.63	1.60	.43	1.78
10.7	23.8	2.43	2.10	.53	2.38
11.6	25.9	2.51	2.32	.63	2.45
17.7	39.4	3.98	2.25	.68	4.17
19.3	42.9	3.97	2.41	.67	3.85
19.7	43.8	5.92	2.74	.60	4.76
25.6	56.9	3.46	1.98	.55	3.66

2. Quantum Yields.—Primary quantum yields of ketene and methyl ketene decompositions under exposure to 3130 Å. radiation at 24° were determined using diethyl ketone as the internal actinometer. The absorption coefficients of all three were determined with the Cary spectrophotometer. Only the ratios, of course, were required for the calculations. The quantum yield of diethyl ketone was found to be approximately unity[15] at room temperature and low radiation intensities. At higher intensities, comparable to those used here, the yield may be as low as 0.6.[16] The latter experiments were made with diethyl ketone concentrations one-half to one-third as great as those of Table III, thus favoring radical recombination processes. The value to be used in the calculations thus lies between 1.0 and 0.6 and Table III shows therefore that the primary quantum yield of ketene decomposition is between 1.12 and 0.67. Experiments were made with different pressures of ketene at this wave length and the ratio of carbon monoxide production to the pressure of ketene was found to be independent of pressure. Since the fraction of absorbed radiation was small, this shows the independence of the quantum yield of pressure and so suggests, but does not prove, that the quantum yield is unity. In any case, the uncertainty does not affect the validity of the conclusions to be made below.

To determine the primary quantum yield of methyl ketene decomposition some assumption

(15) W. Davis, This Journal, 70, 1868 (1948).

(16) K. O. Kutschke, M. H. J. Wijnen and E. W. R. Steacie, *ibid.*, 74, 714 (1952).

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TABLE III

THE PRIMARY QUANTUM YIELD OF KETENE DECOMPOSITION AT 3130 Å.[a]

p, mm.	Compound	CO, moles/sec. $\times 10^{-15}$	I_{abs}, quanta/sec. $\times 10^{-15}$	I_0, quanta/sec. $\times 10^{-16}$
37	$(C_2H_5)_2CO$	1.43	1.43	3.3
32	$(C_2H_5)_2CO$	1.28	1.28	3.4
			Av.	3.35×10^{16}
17	CH_2CO	3.6	1.6	

Ratio of primary quantum yield of ketene to quantum yield of diethyl ketone: 1.12.

[a] For these experiments the lamp was run at reduced intensity.

must be made regarding secondary reactions. Consideration of the data presented in Table II and analogy with the ketene mechanism suggest the set of reactions

$$CH_3CHCO + h\nu \longrightarrow CO + CH_3CH$$
$$CH_3CH \longrightarrow CH_2CH_2 \qquad (2)$$
$$CH_3CH + CH_3CHCO \longrightarrow C_4H_8 + CO$$

The amount of carbon monoxide directly resulting from the primary process is therefore

$$CO_{primary} = C_2H_4 + 1/2(CO_{obsd} - C_2H_4) \qquad (3)$$

Use of this equation in the quantum yield calculations avoids the least accurately determined quantity, the yield of butene. On this basis, the primary quantum yield of carbon monoxide, using 3130 Å. wave length radiation, is found to depend slightly on the pressure of methyl ketene and to tend to the same value as that of ketene (unity?) at low pressures, as shown in Fig. 2.

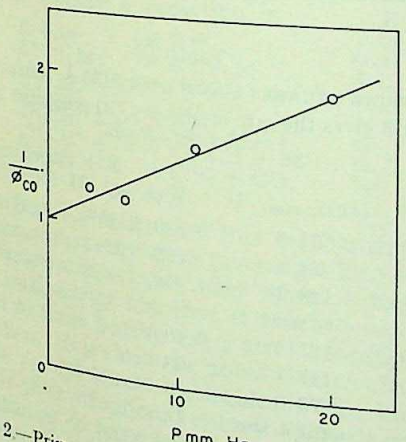

Fig. 2.—Primary quantum yields of methyl ketene decomposition by radiation of 3130 Å. wave length, calculated assuming that of ketene is unity.

The primary quantum yield of methyl ketene decomposition in the 3650 Å. wave length region was determined at 24° using ketene as the internal actinometer. The quantum yields for ketene at this wave length were interpolated from the graph given by Strachan and Noyes.[5] The results are shown in Fig. 3. The total light intensity entering the reaction cell at this wave length was 2×10^{18} quanta/second. The decrease of the quantum yield with increasing pressure of methyl ketene is seen to be more exaggerated than the corresponding behavior of ketene reported by Strachan and Noyes.

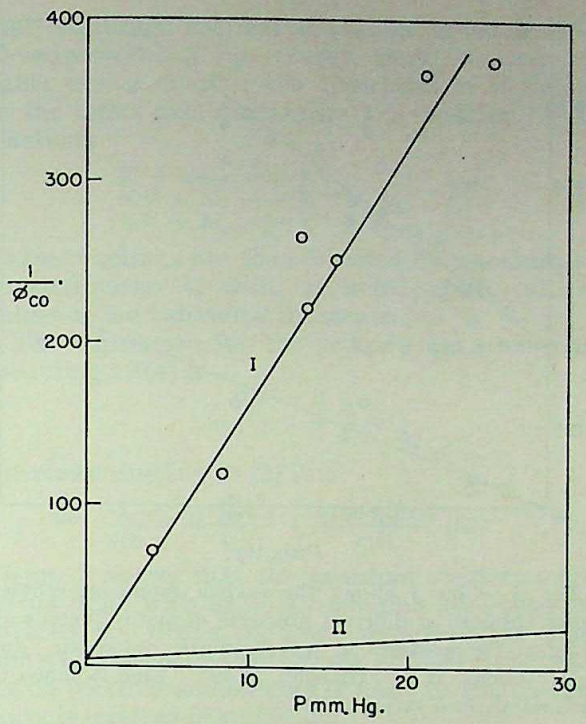

Fig. 3.—Primary quantum yields (I) of methyl ketene decomposition in radiation of 3650 Å. wave length. Line II shows data of Strachan and Noyes (ref. 5) obtained with ketene at this wave length.

3. Effects of Temperature.—The provisional reaction mechanism specified above suggests that if the unimolecular rearrangement of the ethylidene radical into ethylene and the competing step (attack on a methyl ketene molecule) have different activation energies, the carbon monoxide–ethylene ratio should change with temperature at constant methyl ketene concentration. Experiments were therefore carried out at 5 and 49° using polychromatic radiation. The results, together with those of Table II obtained at 24°, are plotted in Fig. 4. The carbon monoxide–ethylene ratio is seen to be a linear function of the concentration of methyl ketene. Temperature has no observable effects.

For purposes of comparison the butene–ethylene ratio is also plotted in this figure. The data are consistent with a straight line having zero intercept. As already noted in a preliminary publication,[17] the forms of the relations between the methyl ketene concentration and the carbon monoxide–ethylene and butene–ethylene ratios are consistent with the provisional mechanism proposed above.

4. The Effects of Radiation Frequency.—Separate measurements of the carbon monoxide–ethylene ratio in the initial stage of the reaction were made using spectrally isolated radiation of 3650, 3130 and 2400 Å. wave length. The results are presented graphically in Fig. 5. It is seen that while the behavior remains qualitatively the same over this entire spectral region, the probability of forming ethylene, rather than butene, at a

(17) G. B. Kistiakowsky and B. H. Mahan, *J. Chem. Phys.*, **24**, 922

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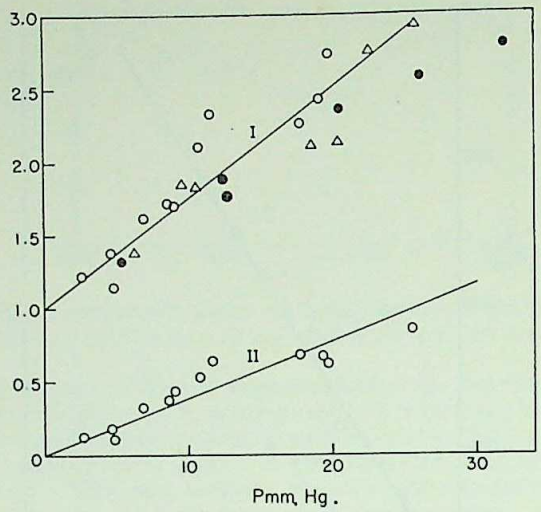

Fig. 4.—Line I shows the carbon monoxide:ethylene ratios obtained at different pressures of methyl ketene and different temperatures in polychromatic radiation: dots, at 5°; circles, at 24°; triangles, at 49°. Line II shows the butene:ethylene ratios at 24°.

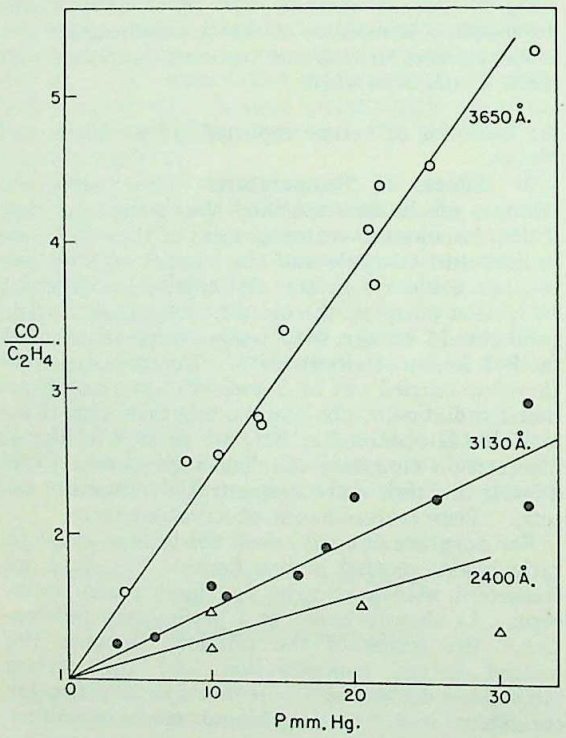

Fig. 5.—The carbon monoxide:ethylene ratios in monochromatic radiation of three wave lengths as functions of methyl ketene pressure.

given pressure of methyl ketene, increases rapidly with increasing energy of the light quanta used in the photolysis.

5. The Effects of Inert Gases.—The effects of some inert gases were studied using 3130 Å. radiation at 24°. The results in Table IV are shown graphically in Fig. 6, where the quantity $((CO)/(C_2H_4) - 1)/P_{CH_3CHCO}$ is plotted against the ratio

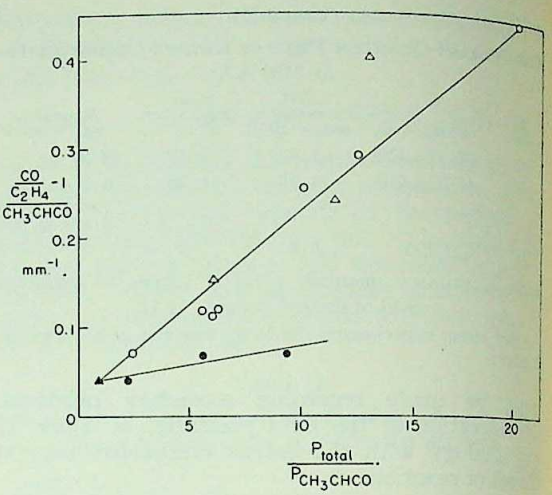

Fig. 6.—Effect of inert gases on a function of the carbon monoxide:ethylene ratio:solid triangle, no inert gas; dots, carbon dioxide; circles, *n*-butane; open triangles, sulfur hexafluoride; 3130 Å. radiation.

of the total pressure to the pressure of methyl ketene. While it seemed highly probable that sulfur hexafluoride and carbon dioxide would not participate chemically in the reaction, butane might be suspected of reacting with ethylidene radicals. A sample of the products non-condensable at −161° was therefore subjected to a mass spectrometric examination, which showed only a negligible amount of ethane to be present. This does not prove the absence of an addition reaction[18] but it does make more legitimate the inclusion of butane in Fig. 6.

TABLE IV

EFFECTS OF INERT GASES WITH 3130 Å. RADIATION

Column 3 gives the rate of primary CO production in molecules per second

CH_3CHCO, mm.	CO_2, mm.	(CO)/sec.	$\frac{(CO)/(C_2H_4) - 1}{(CH_3CHCO)}$
23.5	31.9	0.590×10^{15}	0.0396
5.4	24.4	.296	.068
18.9	149.4	.368	.68
	SF_6, mm.		
24.6	125.4	0.40	0.153
10.3	117.1	.20	.242
6.0	78.0	.19	.405
	n-C_4H_{10}, mm.		
18.5	98.5	0.544	0.120
24.2	125.1	.740	.110
4.2	81.6	.204	.443
30.2	40.2	.565	.070
22.3	102.2	.456	.119
7.3	66.7	.266	.245
5.8	67.4	.193	.292

An attempt was made to determine the effect of inert gas when the mixture was irradiated with 3650 Å. light. Preliminary runs indicated that the total yield of CO was decreased and the ratio of carbon monoxide to ethylene was increased by the addition of an inert gas (carbon dioxide and *n*-

(18) See for example, H. E. Buttery, R. G. Laughlin and N. Chakkiburi, THIS JOURNAL, 78, 3224 (1956).

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butane just as with 3130 Å. radiation). The amounts of products obtained under these conditions were so small that quantitative separation from the large excess of inert gas was extremely difficult. These experiments were not pursued further.

Discussion

The experimental data show that the products of the photochemical decomposition of methyl ketene are carbon monoxide and a mixture of ethylene and butene in varying proportions. An increase of collisional frequency, either through addition of an inert gas or through an increase of the methyl ketene concentration lowers the primary quantum yields, far more so with 3650 Å. radiation than at 3130 Å. The limiting (zero pressure) quantum yield is approximately unity for 3130 Å. radiation but may be less than unity with 3650 Å. radiation. The carbon monoxide–ethylene ratio is increased by increasing the wave length of absorbed radiation and by increasing the concentration of methyl ketene and inert gases, but is independent of temperature.

These observations are readily explained by a reaction mechanism which involves ethylidene radicals. It must be postulated that the ethylidene radicals are produced with excess vibrational and translational energies and have reactivities which depend on the wave length of radiation used to produce them. Denoting by K a molecule of methyl ketene, by M any molecule, including methyl ketene, by * the electronic excitation of methyl ketene, and by $'$, $''$, increasing amounts of vibrational energy, the mechanism applicable to 3130 Å., and undoubtedly to 2400 Å. radiation, is

$$\begin{array}{lll} K + h\nu = K^{*''} & & I_{abs} \\ K^{*''} + M = K^{*} + M & & k_2 \\ K^{*''} = CH_3CH'' + CO & & k_3 \\ CH_3CH'' = CH_2CH_2 & & k_4 \\ CH_3CH'' + K = C_4H_8 + CO & & k_5 \\ CH_3CH'' + M = CH_3CH + M & & k_6 \\ CH_3CH + K = C_4H_8 + CO & & k_7 \\ K^{*} + M = K + M & & k_8 \end{array} \qquad (4)$$

The essential feature of this mechanism is the assumption that ethylidene rearranges into ethylene with measurable velocity only when it has excess vibrational energy but that it reacts with methyl ketene to form butene even after vibrational deactivation. It is also to be noted that electronically excited methyl ketene molecules which have lost most of their vibrational energy through collisions are assumed to have only one possible fate: loss of electronic energy by some further collision process. This assumption recognizes the experimental fact that the quantum yields obtained with 3650 Å. radiation were two orders of magnitude lower than those obtained at 3130 Å., indicating that photo-excited molecules with small amounts of vibrational energy dissociate only rarely compared with molecules which have a large amount of excess vibrational energy.

If the uncertain limiting quantum yield with 3650 Å. radiation is actually unity, mechanism 4 applies here also, but with altered rate constants because of the lower excitation energy of the ethylidene radicals. If the limiting quantum yield at this wave length is below unity, it may be supposed that additional thermal activation[5] is required for decomposition. This energy may be acquired either before or after the absorption of radiation. In the latter case mechanism 4 is modified by the reactions

$$\begin{array}{lll} K + h\nu_{3650} \longrightarrow K^{*\prime} & & I_{abs} \\ K^{*\prime} + M \longrightarrow K^{''*} + M & & K_1 \\ K^{*\prime} + M \longrightarrow K^{*} + M & & k_{-1} \end{array} \qquad (5)$$

These reactions are then followed by reactions 2–8 of mechanism 4, with, as noted above, altered values of the individual constants.

The expression for the primary quantum yield according to (4) is

$$1/\phi_{CO} = 1 + \frac{k_1}{k_3}(M) \qquad (6)$$

whereas according to (5) it is

$$\frac{1}{\phi_{CO}} = \frac{k_1 + k_{-1}}{k_1} + \frac{k_2(k_1 + k_{-1})}{k_1 k_3}(M) \qquad (7)$$

Figure 2 shows that the quantum yield measurements done with 3130 Å. radiation are consistent with eq. 6. Either eq. 6 or 7 represents the quantum yield measurements made at 3650 Å. depending on whether an intercept of unity or greater than unity is inferred from Fig. 3.

The expressions for the ratios $(CO)/(C_2H_4)$ and $(C_4H_8)/(C_2H_4)$ given by mechanism 4 or 5 are

$$\frac{(CO)}{(C_2H_4)} = 1 + \frac{2k_5}{k_4}(K) + \frac{2k_6}{k_4}(M) \qquad (8)$$

$$\frac{(C_4H_8)}{(C_2H_4)} = \frac{k_5}{k_4}(K) + \frac{k_6}{k_4}(M) \qquad (9)$$

The data of Figs. 4 and 5 show that these ratios are linear functions of the methyl ketene pressure, and that the slopes of the two lines are in the ratio of two to one. Furthermore, the intercepts are one and zero, exactly as predicted by eqs. 8 and 9.

The proposed free radical mechanism is completely consistent with the experimental data but it is not unique in this respect. A mechanism based on photo-excited methyl ketene molecules leads to formally identical rate equations

$$\begin{array}{lll} CH_3CHCO + h\nu \longrightarrow CH_3CHCO^{*''} & & I_{abs} \\ CH_3CHCO^{*''} + M \longrightarrow CH_3CHCO + M & & Mk_2 \\ CH_3CHCO^{*''} \longrightarrow CH_2CH_2 + CO & & k_9 \\ CH_3CHCO^{*''} + CH_3CHCO \longrightarrow C_4H_8 + 2CO & & k_{10} \\ CH_3CHCO^{*} + CH_3CHCO \longrightarrow C_4H_8 + 2CO & & k_{11} \\ CH_3CHCO^{*} + M \longrightarrow CH_3CHCO + M & & Mk_8 \end{array} \qquad (10)$$

Aside from the fact that no free radicals are involved here, this mechanism differs from the mechanism 4 in an extremely important detail. The reactivity of a photo-excited molecule in a bimolecular step such as 10 cannot be expected to be overwhelmingly dependent on the amount of vibrational energy possessed by such a molecule. Therefore step 11, the reaction of a vibrationally deactivated but electronically excited molecule, must be included in the mechanism 10. However, to account for the decreased quantum yields found experimentally at 3650 Å., it must be concluded that k_{11} is much smaller than k_{10} in mechanism 10; that is, the bimolecular reactivity of the excited molecule must be strongly dependent on its vibrational excitation. Despite this inconsistency, let us examine the behavior predicted by the excited molecule mechanism when an inert gas is present

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in the reaction mixture. Mechanism 10 gives the expression

$$\frac{\frac{(CO)}{(C_2H_4)} - 1}{(K)} = 2\frac{k_{10}}{k_9} + 2\left(\frac{k_{11}}{k_9}\right)\left[\frac{k_2(M)}{k_{11}(K) + k_8(M)}\right] \quad (11)$$

Since the quantum yields obtained at 3650 Å. were generally less than 0.01, k_{11} is necessarily much smaller than k_8. In the presence of a large amount of inert gas, $k_8(M)$ is very much greater than $k_{11}(K)$, and so we may, to a very good approximation, eliminate the latter term from the denominator of the last term in eq. 11. The excited molecule mechanism is then seen to predict that the quantity $(CO)/(C_2H_4) - 1/(K)$ is independent of the pressure of inert gas. This prediction is to be contrasted to the expression obtained from the free radical mechanism

$$\frac{(CO)/(C_2H_4) - 1}{(K)} = 2\frac{k_5}{k_4} + 2\frac{k_6}{k_4}\frac{(M)}{(K)} \quad (12)$$

Reference to Fig. 6 shows that the quantity $[(CO)/(C_2H_4) - 1]/(K)$ is indeed a linear function of the ratio of total pressure to the pressure of methyl ketene, as predicted by the free radical mechanism 4 and eq. 12. The excited molecule mechanism, carried to its logical conclusion, predicts the effect of inert gases incorrectly.

Equations 8 and 12, and Figs. 5 and 6 give the ratio k_5/k_6 as 1.8 when the quenching gas is *n*-butane or sulfur hexafluoride and 7.5 for carbon dioxide. Varied information in the literature referring to rates of intermolecular energy exchange, suggests that a vibrationally excited ethylidene radical probably does not lose most of its excess energy in a single collision, but does so after a small number, when collisions are with a complex molecule. Hence a value of $10^{-1}Z_0$ for k_5 appears to be reasonable and therefore (see eq. 8 and Fig. 5) $k_4 \cong 10^8$ sec.$^{-1}$ when ethylidene radicals are produced by the 3130 Å. radiation.

If the quenching rate constant, k_6, is the same for radicals produced by the 3650, 3130 and 2400 Å. radiation, the isomerization rate constants, k_4, are in the ratio 1:2.9:4.7, as shown by Fig. 5. Qualitatively, this is readily understood because radicals produced by radiation of higher frequency undoubtedly acquire larger vibrational energy and the specific unimolecular rate constant of a molecule having energy E, when E_0 is the minimum energy required for the reaction, has been estimated[19] to be proportional to

$$\left(\frac{E - E_0}{E}\right)^{n-1} \quad (13)$$

Here n denotes the number of internal degrees of freedom among which the energy is randomly distributed. A quantitative application of the expression 13 to the two ratios of k_4 obtained above is questionable because it is not known what fraction of the total energy of the radiation is present as vibrational energy of the ethylidene radical. An extreme assumption can be made that this energy is equal to the energy of the light quanta less the dissociation energy of the C–C double bond in methyl ketene. A consistent answer can then be obtained only if the dissociation energy is taken to be about 68 kcal., which gives $E_0 \cong 3$ kcal. if $n = 6$. This value of the dissociation energy is probably too low because, assuming that the dissociation energies of ketene and methyl ketene are the same, it gives 79 kcal. for the heat of formation of the methylene radical. From this it follows that the energies of successive separation of hydrogen atoms from methane are: 102, 98, 118, 80 kcal., a rather improbable sequence. Undoubtedly some of the radiation energy is converted into translational energy of the two fragments resulting from the decomposition of methyl ketene. Qualitatively, these calculations are important because they show that the formation of vibrationally excited ethylidene radicals from methyl ketene molecules, which have absorbed 3650 Å. radiation, is consistent with the experimental data; this in turn shows that E_0, the minimum activation energy for rearrangement into ethylene, is quite small. The small value of E_0 suggests, according to mechanism 4, which neglects thermal activation, that the reaction of quenched ethylidene radicals with methyl ketene (reaction 7) is very fast. In this respect, ethylidene behaves very much like methylene.[20]

In conclusion a few comments should be made on the primary quantum yields. From the dependence of the quantum yield on pressure with 3130 Å. radiation, the lifetime before decomposition (the reciprocal of the specific dissociation probability) of an excited methyl ketene molecule can be estimated as 3×10^{-9} second if every collision results in deactivation. The specific dissociation probability after absorption of 3650 Å. radiation is 230 times smaller if quenching occurs on every collision. If the quantum yields extrapolated to zero pressure are less than unity, fluorescence or radiationless transitions to a long lived electronic state (which is quenched even at the lowest pressures investigated), as well as the previously mentioned possibility of thermal excitation (mechanism 5) might be responsible. One of the present authors (BHM) and Dr. R. Williams failed to observe any fluorescence from solutions of ketene in a rigid medium at −195° upon irradiation with 3650 Å. light. This suggests that if the limiting quantum yields for these molecules are indeed less than one at 3650 Å., internal conversion to the ground state is responsible.

It is interesting to note that comparison of the pressure dependence of the quantum yield of carbon monoxide from ketene irradiated with 3650 Å. light[5] with our similar data obtained with methyl ketene indicates that the dissociative lifetime of ketene is shorter than that of methyl ketene by a factor of 25. All these dissociative lifetimes are short compared with the radiative lifetimes, which may be estimated from the integrated absorption coefficients as 3×10^{-6} and 7×10^{-6} sec. for ketene and methyl ketene, respectively. The near ultraviolet absorption of ketene probably represents a singlet–singlet transition, and it has been recently demonstrated[20] that methylene radicals resulting from the photochemical decomposition of ketene are in a singlet state. Therefore the

(19) L. S. Kassel, "The Kinetics of Homogeneous Gas Reactions," (The Chemical Catalog Co.), Reinhold Publ. Co., New York, N. Y., 1932.

(20) G. B. Kistiakowsky and K. H. Sauer, THIS JOURNAL, 78, 3699 (1956).

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May 20, 1957

relatively long lifetimes to decomposition of ketene and methyl ketene molecules are not due to electronic multiplicity correlation rules. The lifetimes of these molecules can be likened to those of thermally activated molecules, the delay in both cases being due to migration of vibrational amplitude among several bonds of the molecule. On this basis, the lifetime of the photo-excited molecules behave as qualitatively predicted by eq. 13; the lifetimes decrease with total energy and increase with the complexity of the molecule.

CAMBRIDGE 38, MASS.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, HUMBLE OIL & REFINING COMPANY]

Reactions of Gaseous Ions. I. Methane and Ethylene

BY F. H. FIELD, J. L. FRANKLIN AND F. W. LAMPE

RECEIVED OCTOBER 1, 1956

At elevated pressures in a mass spectrometer ion source reactions occur between certain ions and the neutral species present. We have studied the various secondary ions formed in methane and ethylene at elevated pressures and have determined the reactions by which they are formed and the rates of these reactions. The rates are all extremely fast. The reaction rates have been treated by classical collision theory and it has been shown that to a fair approximation the cross-sections and reaction rate constants can be predicted from a simple balance of rotational and polarization forces.

Introduction

Secondary processes in mass spectrometers were first observed by early workers in the field[1] but were treated, for the most part, as nuisances due to experimental difficulties that had to be overcome in the development of analytical mass spectrometry. In recent years, however, a number of studies of secondary processes have been reported[2] which are of considerable interest because of the information afforded concerning the gaseous reactions of ions with molecules. Tal'roze and Lyubimova[3] reported the formation of CH_5^+ in methane. Stevenson and Schissler[4] published specific reaction rates for the formation of CD_5^+ in deuterated methane, D_3^+ in deuterium, and for the reactions of A^+ with H_2, D_2 and HD. In a recent note Schissler and Stevenson[5] have reported many more ion–molecule reactions included in which are reactions forming $C_2H_5^+$ and $C_2D_5^+$ in methane and deuterated methane, respectively, and $C_2H_5^+$, $C_3H_3^+$ and $C_3H_5^+$ in ethylene. These reactions were reported to exhibit cross-sections that decreased to zero at finite values of ion-energy and small negative temperature coefficients.

This paper comprises a detailed study of the ion–molecule reactions taking place in methane and ethylene when these compounds are subjected to ionization by electron impact in a mass spectrometer.

Theoretical

Consider the reaction of a primary ion with a neutral molecule to consist of the formation of a transition-state ion which then decomposes unimolecularly to various product ions and neutral fragments. That is

$$P^+ + M \xrightarrow{k_1} PM^+ \qquad \text{(R1)}$$

$$PM^+ \xrightarrow{k_{S_j^+}} S^+_j + F_j \qquad \text{(R2)}$$

where there will be a set of the above reactions for each primary ion that reacts with neutral molecules. If the time of decomposition of the transition-state ion is short compared with ionic residence times in the ionization chamber, the number of secondary ions of the jth type that are formed will be

$$n_{S_j^+} = \frac{k_{S_j^+}}{\sum_j k_{S_j^+}} n_{PM^+} \qquad (1)$$

where the n's are the number of ions of the various kinds formed per unit time. Since the primary ions are formed in the electron beam at a constant rate, in the following for the sake of simplicity we shall in general refer to the n's as the number of ions formed, the rate aspect of the process to be kept in mind at all times. The number of transition-state ions formed is equal to the product of the number of primary ions formed, the number of collisions made by one primary ion with neutral molecules during its ionization chamber residence time, and the collision efficiency or

$$n_{PM^+} = fQ[M]n^0_{P^+} \qquad (2)$$

where

$n^0_{P^+}$	=	number of primary ions formed
f	=	collision efficiency for the formation of PM^+
Q	=	total no. of collisions made by a single primary ion with neutral molecules at unit concn.
[M]	=	no. of molecules per unit volume

Combining (1) and (2) and introducing τ, the time in which the primary ion makes collisions with neutrals (the primary ion residence time), gives

$$n_{S_j^+} = \frac{k_{S_j^+}}{\sum_j k_{S_j^+}} n^0_{P^+} f \frac{Q}{\tau_{P^+}} [M]\tau_{P^+} \qquad (3)$$

Q/τ_{P^+} is the time-average collision rate, and the product of this quantity and the collision efficiency is the rate constant for the formation of the transition-state ion. Recognizing this and rearranging (3) gives

$$\frac{n_{S_j^+}}{n^0_{P^+}} = \frac{k_{S_j^+}}{\sum_j k_{S_j^+}} k_1 [M]\tau_{P^+} \qquad (4)$$

Thus the various types of primary ions formed will be propor-

(1) H. D. Smyth, *Rev. Mod. Phys.*, **3**, 347 (1931).
(2) For a complete review see F. H. Field and J. L. Franklin, "Electron Impact Phenomena and the Properties of Gaseous Ions," Academic Press, New York, N. Y., in press.
(3) V. L. Tal'roze and A. K. Lyubimova, *Doklady Akad. Nauk. S.S.S.R.*, **86**, 909 (1952).
(4) D. P. Stevenson and D. O. Schissler, *J. Chem. Phys.*, **23**, 1353 (1955).
(5) D. O. Schissler and D. P. Stevenson, *ibid.*, **24**, 926 (1956).

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tional to the number of primary ions collected plus the number of secondary ions (derived from the primary ions) collected. Thus, if we assume equal collection efficiencies for all ions we can write (remembering that the n's are really numbers of ions per unit time)

$$\frac{I_{S_j^+}}{I_{P^+} + \sum_j I_{S_j^+}} = \frac{k_{S_j^+}}{\sum_j k_{S_j^+}} k_1 [M] \tau_{P^+} \qquad (5)$$

where the I's are the observed ion-currents. In addition, it is easily shown that

$$\frac{I_{S_j^+}}{I_{S_k^+}} = \frac{k_{S_j^+}}{k_{S_k^+}} \qquad (5a)$$

To determine specific reaction rates from experimental measurements it is necessary to calculate the average residence time of the primary ions in the ionization chamber. In these calculations an idealized model of the ionization chamber is used, in that we ignore the effects of: (1) the magnetic field in the ionization chamber, (2) potential penetrations through the various ionization chamber orifices, (3) space charge effects, and (4) surface charge effects. The electron beam is assumed to be of infinitesimal thickness and the potential gradient in the ionization chamber (due to the ion-repeller) is taken as uniform.

Consider the primary ion to be formed in the electron beam at a distance d_0 from the ion-exit slit and at the moment of its formation to be moving with average thermal velocity in a direction making an angle ϕ with the perpendicular directed from the electron beam to the slit. It easily can be shown from the laws of motion that the residence time, τ, of an ion reaching the ion-exit slit is given by

$$\tau = \frac{1}{A}\sqrt{2Ad_0 + B^2\cos^2\phi} - \frac{B}{A}\cos\phi \qquad (6)$$

where

$A = eV/m$
$B = \sqrt{8kT/\pi m}$
e = electronic charge
V = voltage gradient in the ionization chamber
m = mass of the ion

Since all values of ϕ are equally probable, the average ion residence time is obtained by integration as

$$\bar{\tau} = \frac{1}{4\pi}\int_0^{\pi} \tau(2\pi \sin\phi)\, d\phi \qquad (7a)$$

or

$$\bar{\tau} = \frac{1}{2A}\sqrt{B^2 + 2Ad_0} + \frac{d_0}{2B}\ln\frac{\sqrt{B^2 + 2Ad_0} + B}{\sqrt{B^2 + 2Ad_0} - B} \qquad (7b)$$

This equation does not apply accurately at ionization chamber voltage gradients less than about 1 volt/cm. since at lower fields some of the ions will be lost by striking the ion repeller.

The reaction rate constant k_1 can be evaluated from the observed ion currents by the use of equations 5, 5a and 7b.

By means of the following analysis the observed ion currents can be used to determine the cross section for the reaction $P^+ + M \rightarrow PM^+$. By combining equations 1 and 2 and converting to currents we obtain

$$\frac{n_{S_j^+}}{n_{P^+}} = \frac{I_{S_j^+}}{I_{P^+} + \sum I_{S^+}} = \frac{k_{S_j^+}}{\sum k_{S^+}} fQ[M] \qquad (8a)$$

Q, the total number of collisions made by a single primary ion with neutral molecules at unit concentration can be written

$$Q = \sigma Q' \qquad (8b)$$

where

Q' = total no. of collisions made by a primary ion during its ionization chamber lifetime with neutral molecules at unit concn. taking the collision cross-section to be unity
σ = collision cross-section for a primary ion and neutral molecule

Substituting (8b) in (8a) gives

$$\frac{I_{S_j^+}}{I_{P^+} + \sum_j I_{S_j^+}} = \frac{k_{S_j^+}}{\sum_j \Sigma_{S_j^+}} k f\sigma Q'[M] \qquad (8c)$$

For a reaction with no activation energy, $f\sigma$ constitutes the reaction cross-section. Equation 8c permits the evaluation of this quantity from experimental measurements if Q' is known.

To obtain an expression for Q', we again consider the primary ion to be formed in the electron beam at a distance d_0 from the slit and at the moment of its formation to be moving with average thermal velocity in a direction making an angle ϕ with the perpendicular directed from the electron beam to the side of the chamber containing the slit. We assume that the number of ions of each type emerging from the slit is proportional to the number of that type in the ionization chamber. If this is true the position of the ion, at the instant of its formation, along an axis parallel to the electron beam is arbitrary and we take this coördinate to be zero. The velocity of any ion at time t after its formation can then be shown to be

$$v = \sqrt{B^2 + A^2t^2 + 2ABt\cos\phi} \qquad (9)$$

where the symbols are as defined previously. The average ion velocity is obtained by integration over all directions as before and is

$$\bar{v}_1 = \left(B + \frac{A^2t^2}{3B}\right) \qquad (10)$$

for the region in which $B > At$.

$$\bar{v}_2 = \left(At + \frac{B^2}{3At}\right) \qquad (11)$$

for the region in which $At > B$.

Similarly, the average relative velocity of two species α and β moving at different velocities is

$$\bar{\xi}_1 = \left(v_\alpha + \frac{v_\beta^2}{3v_\alpha}\right) \text{ for } v_\alpha > v_\beta \qquad (12)$$

$$\bar{\xi}_2 = \left(v_\beta = \frac{v_\alpha^2}{3v_\beta}\right) \text{ for } v_\beta > v_\alpha \qquad (13)$$

where ξ denotes relative velocity.

Substituting (10) and (11) for the ion velocity, v_β, and B for the average thermal velocity, v_α, of the neutral molecules into (12) and (13) results in

$$\xi_1 = \frac{1}{3}\left(4B + \frac{2A^2t^2}{3B} + \frac{A^4t^4}{9B^3}\right) \text{ for } At < B \qquad (14)$$

$$\xi_2 = \frac{1}{3}\left(3At + \frac{B^2}{At} + \frac{3AtB^2}{3A^2t^2 + B^2}\right) \text{ for } At > B \qquad (15)$$

Therefore, for unit cross-section, the total number of collisions made by one primary ion with neutral molecules at unit concentration during the time

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$$Q' = \int_0^{B/A} \xi_1\, dt + \int_{B/A}^{\tau} \xi_2\, dt \qquad (16)$$

where B/A is the time at which the ion and molecule velocities are equal. Integration of (16) gives

$$Q' = \frac{A\bar{\tau}^2}{2} + \frac{B^2}{A}\left[\frac{247}{382} + \frac{1}{3}\ln\frac{1A\bar{\tau}}{\sqrt{B^2+3A^2\bar{\tau}^2}}\right] \qquad (17)$$

where $\bar{\tau}$ is given by (7b).

In the above derivation it was assumed the neutral molecules were all moving with average thermal velocity. Actually there exists a distribution of velocities. However, it has been shown[6] that consideration of this distribution leads to a small difference in relative velocities that is well within our experimental error.

Experimental

Three types of measurements were made: (1) the variation of ion intensities with pressure (pressure studies), (2) the variation of ion intensities with ion repeller voltage (repeller studies), and (3) the appearance potentials of various ions. The first two types of measurements were made with a slightly modified Consolidated Electrodynamics Corp. (CEC) Model 21-620 cycloidal focussing mass spectrometer. The appearance potential measurements were made with a Westinghouse Type LV mass spectrometer.

The pertinent dimensions and operating characteristics of the CEC instrument are as follows. The distance between the ion repeller electrode and the ion exit slit is 1.0 mm., and the electron beam (thickness = 0.17 mm.) passes midway between the two. The length of the repeller electrode in the direction of the electron beam is 5.63 mm. The instrument as received from the manufacturer was modified by by-passing the pressure sensitive filament protection circuit and by altering the ion repeller circuit to permit the application of constant, predetermined repeller voltage. It is not provided with an adjustment for the electron accelerating voltage, and consequently all measurements were made at the manufacturer's pre-set value of about 75 volts. Similarly, no control over the ionization chamber temperature is provided (although the temperature can be measured), and temperature variations of 20–25° occurred from one experiment to another and even in the course of a single experiment. The actual value of the temperature may be taken as 150 ± 10°. The electron current was maintained at 2 μamp.

The methane and ethylene were of Phillips reagent grade, and they were condensed in liquid nitrogen and subjected to a bulb-to-bulb distillation. A middle fraction constituting about half the material condensed was collected for the measurements.

Pressure Studies.—The pressure studies involved the determination of the mass spectra of methane and ethylene at different values of the reservoir pressure. In the CEC mass spectrometer secondary ions begin to be formed in detectable amounts at a reservoir pressure of about 1 mm. In most of the experiments the reservoir pressure was varied between 1 and 30 mm. in steps of 2–5 mm. The reservoir pressure was determined by a small mercury manometer read with a cathetometer, and values obtained in this way were reproducible to 0.1 mm. In all pressure studies the repeller voltage was maintained at 1.0 volt, an arbitrarily selected value.

The quantitative interpretation of the results requires a knowledge of the pressure in the ionization chamber. To determine this quantity as a function of the more easily measured reservoir pressure, the ion repeller of the mass spectrometer was biased negatively with respect to the ionization chamber and the collected ion current measured with an RCA millimicroammeter. The repeller currents (I_i) for various reservoir pressures (p_r) were determined for argon and neon, and plots of I_i/p_r against p_r were constructed. For reservoir pressures up to about 4 mm. I_i/p_r remained constant with pressure and then increased. From this behavior and from a rough comparison of the atomic mean free paths with the known diameter of the gas leak into the ionization chamber (1 μ), we conclude that for relatively low molecular weight gases at reservoir pressures up to about 4 mm. the gas flow through the leak is molecular in character, but above this pressure mass flow occurs. In the region where molecular flow occurs, the ionization chamber atom concentration (N_i) can be expressed as $N_i = \gamma p_r$, and substituting in the relation $I_i/I_e = N_i Q_i l$ we get $\gamma = I_i/I_e Q_i l p_r$ (I_e = electron current, Q_i = total cross-section for ionization, and l = length of the repeller). From this equation, values of Q_i obtained from the data tabulated by Massey and Burhop,[7] and our experimental currents we find $\gamma_{Ne} = 7.7 \times 10^{12}$ and $\gamma_A = 7.3 \times 10^{12}$. These are equal to within experimental error, as is to be expected theoretically.

To establish the total cross-section for ionization for methane and ethylene it is assumed that in the molecular flow range of pressures the average of the values of γ for argon and neon can be applied to methane and ethylene. Then the Q_i values for these substances can be calculated from the observed currents in this pressure range. Knowing the Q_i values the ionization chamber concentration corresponding to any reservoir pressure can be calculated from the observed currents.

The Q_i values obtained are $Q_i(CH_4) = 4.8_3 \times 10^{-16}$ cm.² and $Q_i(C_2H_4) = 6.9_2 \times 10^{-16}$ cm.². Recently Otvos and Stevenson[8] have determined the relative total ionization cross-sections for a number of compounds, and from their data one calculates that $Q_i(C_2H_4)/Q_i(CH_4) = 1.55$. Our value for this ratio is 1.43, in satisfactory agreement. However, from Otvos and Stevenson, $Q_i(CH_4)/Q_i(Ne) = 4.28$, whereas our value is 7.75. Partially as a consequence of this discrepancy, we determined the total ionization cross-section of acetylene, obtaining the value $5.6_0 \times 10^{-16}$ cm². This agrees reasonably well with the value of 4.98×10^{-16} cm.² quoted by Massey and Burhop. Unfortunately, Otvos and Stevenson do not give a value for the total ionization cross-section for acetylene by low energy electrons. However, their relative value for ethylene can be converted to an absolute value of 4.13×10^{-16} cm.² using the Massey and Burhop value for $Q_i(Ne)$, and this ethylene value is appreciably lower than both our acetylene value and that given by Massey and Burhop. This seems quite suspicious, and consequently we have used our values of the methane and ethylene cross-sections in the determination of the ionization chamber concentrations.

An example of the variation of the intensities of primary and secondary ions as a function of the ionization chamber molecular concentrations, N_i, is given in Fig. 1. We think that the observed deviations from first- and second-order behavior are to be attributed to scattering of the ion beam in the analyzer and, if this be true, the intensity variation of CH_4^+, for example, should be represented by the relations

$$I_{CH_4^+} = aN_i e^{-\sigma_s L N_a} \qquad (18a)$$

$$\log (I_{CH_4^+}/N_i) = -\sigma_s L N_a/2.303 + \log a \qquad (18b)$$

where σ_s is the scattering cross-section, L is the path length in the analyzer (taken to be 8.0 cm. in our instrument), and N_i and N_a the molecular concentrations in the ionization chamber and the analyzer, respectively. Since the experimental plot of $\log (I_{CH_4^+}/N_i)$ against N_a is approximately a straight line (a small amount of curvature exists), we conclude that indeed the form of the CH_4^+ curve in Fig. 1 is for practical purposes completely accounted for by scattering in the analyzer, and we infer that all observed deviations from expected first- or second-order behavior can be attributed to this source. The values of N_a used in the plot of eq. 18b were calculated from pressures indicated by an ionization gage located on the envelope of the analyzer. The gage was not calibrated. From the mean slope of the plot we calculate that for the scattering of CH_4^+ in CH_4 in our instrument $\sigma_s = 4.0 \times 10^{-15}$ cm.².

To enable us to assess the extent to which scattering affects the values of the current ratios $I_s/(I_p + I_s)$ needed in the kinetic calculations, we have derived[9] an approximate expression for the scattering of an ion beam in the analyzer of a mass spectrometer. The scattering is assumed to re-

(6) L. B. Loeb, "The Kinetic Theory of Gases," McGraw-Hill Book Co., New York, N. Y., Ind. Ed. 1934, p. 96.

(7) H. S. W. Massey and E. H. S. Burhop, "Electronic and Ionic Impact Phenomena," Oxford Univ. Press, 1952, p. 38.

(8) J. W. Otvos and D. P. Stevenson, THIS JOURNAL, **78**, 546 (1956).

(9) Details of the derivation are available on request.

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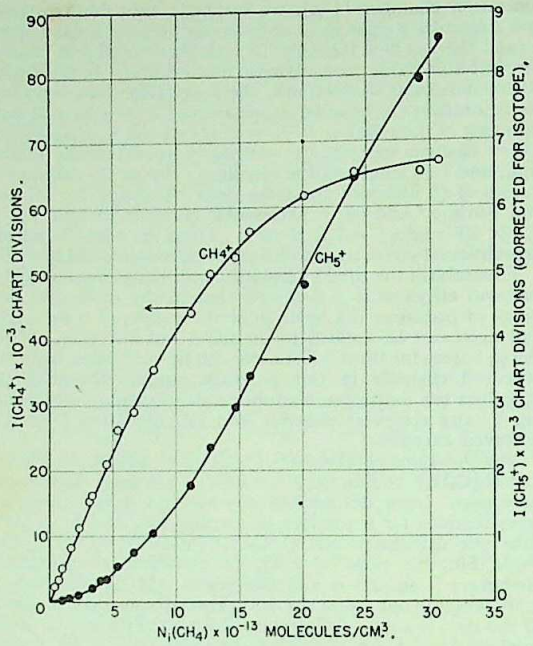

Fig. 1.—Primary and secondary ion currents against ion chamber concentration.

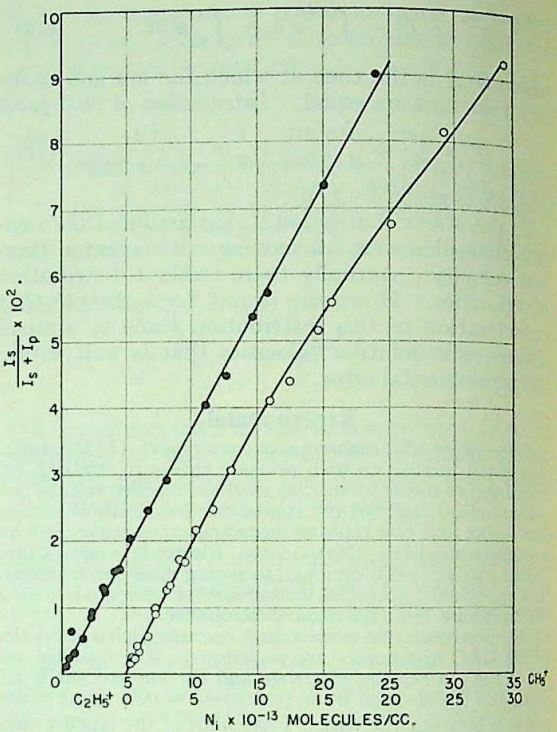

Fig. 2.—Typical curves of current ratios against ion chamber concentration.

sult solely from ion–molecule polarization interaction. The expression is

$$\sigma_s = \left(\frac{3\pi^3\alpha eL}{16 S_{eff}\, V_{esu}}\right)^{1/2} = 41.8\left(\frac{\alpha eL}{S_{eff}\, V_{pract.}}\right)^{1/2} \quad (19)$$

where

α = polarizability of the scattering gas
e = electronic charge
L = ion path length in analyzer in cm.
V = ion accelerating voltage
S_{eff} = av. distance from center of collector slit to edges of slit in cm.
$S_{eff} \cong \lambda/4$ where λ = length of collector slit in cm.

For the scattering of CH_4^+ in CH_4 in our mass spectrometer we calculate from equation 19 that $\sigma_s = 2.0 \times 10^{-15}$ cm.^{2}, to be compared with the experimental value of 4.0×10^{-15} cm.^{2}. The agreement is sufficiently satisfactory to lead us to believe that the theoretical dependence of σ_s on α and V is substantially correct, and thus we write $\sigma_s = b(\alpha/V)^{1/2}$. The constant b is evaluated from the experimental value of σ_s, and the semi-empirical expression $\sigma_s = 1.45 \times 10^{-2}(\alpha/V)^{1/2}$ results.

For the formation of the CH_5^+ ion from methane we have the relation

$$\frac{I_{CH_5}}{I_{CH_4^+} + I_{CH_5^+}} \approx \frac{I_{CH_5^+}}{I_{CH_4^+}} \alpha N_i e^{-N_a L(\sigma_{CH_5^+} + \sigma_{CH_4^+})} \quad (20)$$

and using scattering cross-section values calculated from our semi-empirical expression we calculate that a graph of $I_{CH_5^+}/(I_{CH_4^+} + I_{CH_5^+})$ *versus* N_i should not depart from linearity by as much as 10% until $N_a = 8.2 \times 10^{13}$ molecules/cc. Since the N_a value corresponding to the highest N_i value used in our experiments is 3.4×10^{13}, noticeable deviations of the current ratio from linearity should not be observed. As Fig. 2 shows, this prediction is correct. Similar calculations lead to the prediction that the graph of $I_{C_2H_5^+}/(I_{CH_5^+} + I_{C_2H_5^+})$ *vs.* N_i should depart from linearity by 10% at $N_i = 4 \times 10^{13}$ molecules/cc., which is in approximate agreement with the behavior of the experimental graph given in Fig. 2. From these and similar results we feel that differential scattering effects are not important at ion source concentrations below about $N_i = 5 \times 10^{13}$ molecules/cc. The rate constants reported in this paper are calculated only from current ratios at concentrations below this value. Two other factors which will affect the accuracy of $I_s/(I_s + I_p)$ are (1) mass discrimination in the analyzer and (2) primary and secondary ions are formed in different regions of the ionization chamber. From discrimination information reported by Robinson[10] we estimate that the largest discrimination effect occurring in our experiments is 12%. The second factor might give rise to a difference in collection efficiency for the two types of ions, but we do not know the magnitude of the resulting error, if any, in the current ratio value.

Repeller Studies.—The repeller studies involved the determination of primary and secondary ion mass spectra at different values of the ion repeller voltage (V_R) at a known, essentially constant value of the reservoir pressure (about 5 mm.). Three types of variation of ion intensities with increasing repeller voltage are to be observed (Fig. 3). That for primary ions is illustrated by the plot of $I_{CH_4^+}$, while the two types observed for secondary ions are illustrated by the plots of $I_{CH_5^+}$ and $I_{C_2H_5^+}$. We are unable to explain these differences in behavior.

None the less, the forms of the intensity variations with repeller voltage can be used in interpreting the observed secondary spectrum of methane. By comparing Figs. 3 and 4 we conclude that the mass 29 and 17 ions are formed by one type of process, namely, a bimolecular gas phase ionic reaction, but that the mass 26, 27, 28 and 16 ions are formed by another type of process, namely, ionization by electron impact in the electron beam. Since the intensity of the mass 28 ion shows a first-order pressure dependence, it seems likely that it results from a small amount of impurity, probably N_2. However, the mass 26 and 27 intensities are second order in methane pressure and must be formed from methane by some kind of secondary reaction. The appearance potential of the mass 26 ion is 11.5 e.v., which, within the limits of experimental error, is equal to the ionization potential of acetylene. This suggests that the methane undergoes a bimolecular reaction (probably on the filament) to produce acetylene, which diffuses into the ionization chamber and undergoes ionization in the electron beam. The mass 27 ion probably is formed in the same way, although the observed appearance potential (12.1 e.v.) is of no help in elucidating the nature of the ion or the reaction by which it is formed.

(10) C. S. Robinson and J. G. Hall, *Rev. Sci. Instruments*, **27**, 561 (1956).

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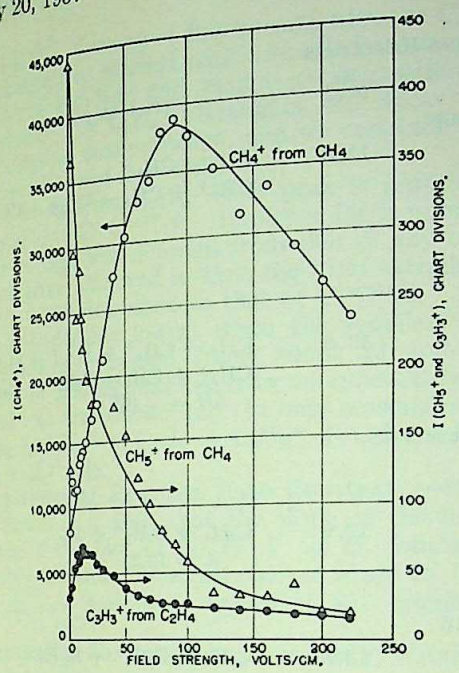

Fig. 3.—Primary and secondary ion currents against ionization chamber field strength.

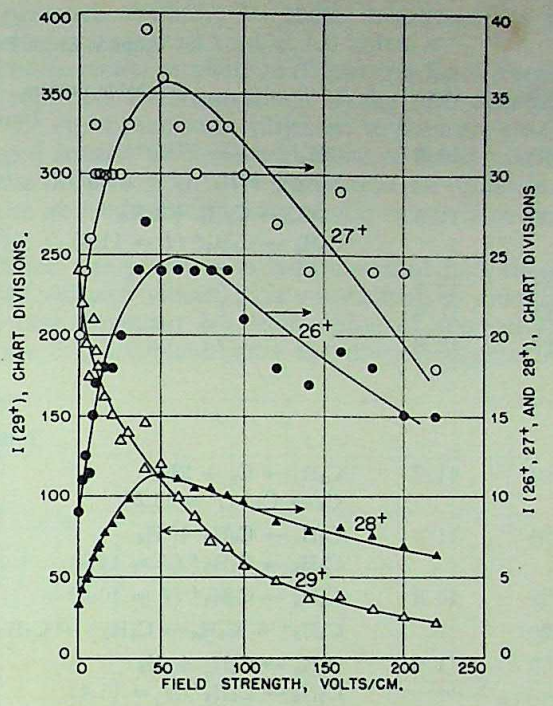

Fig. 4.—Plots of various ion currents from CH_4 against field strength.

Results obtained from repeller studies are subject to an uncertainty stemming from the possible variation in ion collection efficiency with repeller voltage. In addition, results at quite low values of V_R (less than 1 volt) are particularly suspect because the conditions in the ion source at these low voltages are probably ill-defined. Potential penetrations through the ion exit slit and the electron beam slits, the potential depression in the electron beam, surface charges, etc., could cause the actual potential in the ionization chamber to be several tenths of a volt different from that calculated on the basis of only the applied repeller voltage.

An observation which may be related to problems of ion collection efficiency is that at values of $V_R > 2.5$ volts the observed intensity of the mass 29 ion from ethylene becomes smaller than the intensity of the $C^{12}C^{13}H_4^+$ ion as calculated from the observed intensity of the mass 28 ion. On the surface this means that the secondary ion contribution to the mass 29 intensity vanishes above $V_R = 2.5$ volts and is probably erroneous even below this value. We can offer no explanation for this behavior.

Appearance Potential Measurements.—Measurements of appearance potential were made in a Westinghouse Type LV mass spectrometer using the vanishing current technique. For most of the measurements O_2 introduced along with the material under investigation was used to calibrate the electron energy scale, but in a few measurements CO_2 was used. The methane or ethylene pressure in the gas reservoir was kept at about 10 mm., which gave about maximum secondary ion currents. Experimental difficulties prevented the determination of the ionization chamber pressure to which this reservoir pressure corresponds. The electron current was maintained at 3.0 μamp. and the ion repeller at 1.9 volts.

The ionization efficiency curves sometimes show breaks (discontinuities) which are attributable to the high pressures. These arise from two sources: (1) contributions to the ion current at a given mass from ions one or two mass units different as a result of scattering and (2) pyrolysis of the sample yielding products which upon ionization contribute to the ion current at the mass being investigated. The difficulty stemming from the first process can be circumvented by obtaining the appearance potentials by repeatedly scanning across the mass spectral region of interest at small increments of the ionizing voltage. The ion intensities free from scattered contributions can then be obtained by reading the peak heights from the means of the adjacent valleys. The occurrence of pyrolysis can be inferred from the form of the ionization efficiency curve, from the value of the lowest appearance potential, and from some knowledge of the chemical properties of the substance under investigation.

From the observed agreement of replicate determinations we estimate the uncertainty in the appearance potential values to be about 0.3 volt except for the values for the mass 50 and 51 ions from ethylene, which are probably uncertain to about 1 volt.

Results[11]

Typical high pressure mass spectra (reservoir pressure = 10 mm.) of methane and ethylene are given in Table I. Table II contains the appearance potentials of the more important ions and the

TABLE I

HIGH PRESSURE MASS SPECTRA OF METHANE AND ETHYLENE (P_r = 10 MM., V_R = 1 V.)

CH_4		C_2H_4	
m/e	Intensity, chart div.	*m/e*	Intensity, chart div.
12	530	24	670
13	1500	25	2230
14	3580	26	17600
15	33700	27	22500
16	39400	28	37200
17	1780	29	1250
26	58	37	8
27	167	38	20
28	163	39	190
29	990	40	17
30	30	41	830
		42	24
		50	26
		51	33
		52	14
		53	102
		54	6
		55	72

(11) When discrepancies appear between this paper and a previous note (THIS JOURNAL, **78**, 5697 (1956)), the present results supersede those in the latter.

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TABLE II

APPEARANCE POTENTIALS AND REACTIONS

m/e	A_1 (e.v.)	Probable process	A_2 (e.v.)	Probable process
		Ions from methane		
17	10.9	$CH_4 + N_2 \rightarrow NH_3^+ \ldots$ $NH_3 \rightarrow NH_3^+ (I = 10.5^a)$?	12.8	$CH_4 \rightarrow CH_4^+$ $CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3$[b]
26	11.5	$2CH_4 \rightarrow C_2H_2 + 2H_2$ $C_2H_2 \rightarrow C_2H_2^+ (I = 11.4)$		
27	12.1	?		
28	11.4	?		
29	12.6	?	13.9	$CH_4 \rightarrow CH_3^+ + H$ ($A = 14.4$) $CH_3^+ + CH_4 \rightarrow C_2H_5^+ + H_2$,[c] $\Delta H = -19$[d]
		Ions from ethylene		
24	11.7	$C_2H_4 \rightarrow C_2 + 2H_2$ $C_2 \rightarrow C_2^+ (I = 11.5)$		
26	11.4	$C_2H_4 \rightarrow C_2H_2 + H_2$ $C_2H_2 \rightarrow C_2H_2^+ (I = 11.4)$	12.9	$C_2H_4 \rightarrow C_2H_2^+ + H_2$ ($A = 13.5$)
28	10.3	$C_2H_4 \rightarrow C_2H_4^+ (I = 10.6)$		
29	..	$C_2H_3^+ + C_2H_4 \rightarrow C_2H_5^+ + C_2H_2$,[c] $\Delta H = -16$		
39	11.8	$C_2H_4 \rightarrow C_2H_2 + H_2$ $C_2H_2 \rightarrow C_2H_2^+ (I = 11.4)$ $C_2H_2^+ + C_2H_4 \rightarrow C_3H_3^+ + CH_3$, $\Delta H = -15$	13.8	$C_2H_4 \rightarrow C_2H_2^+ + H_2$ ($A = 13.5$) $C_2H_2^+ + C_2H_4 \rightarrow C_3H_3^+ + CH_3$,[c] $\Delta H = -15$
41	10.1	$C_2H_4 \rightarrow C_2H_4^+ (I = 10.6)$ $C_2H_4^+ + C_2H_4 \rightarrow C_3H_5^+ + CH_3$,[c] $\Delta H = -17$		
50	24.5	$C_2H_4 \rightarrow C_2^+ + H_2 + H(?)$ ($A = 26.5$) $C_2^+ + C_2H_4 \rightarrow C_4H_2^+ + H_2$, ($\Delta H = -162$)		
51	19.5	$C_2H_4 \rightarrow C_2H^+ + H_2 + H$ ($A = 19.3$) $C_2H^+ + C_2H_4 \rightarrow C_4H_3^+ + H_2$, $\Delta H = -92$		
53	12.7	$C_2H_4 \rightarrow C_2H_2^+ + H_2$ ($A = 13.5$) $C_2H_2^+ + C_2H_4 \rightarrow C_4H_5^+ + H$, $\Delta H = -13(?)$		
55	10.8	$C_2H_4 \rightarrow C_2H_4^+ (I = 10.6)$ $C_2H_4^+ + C_2H_4 \rightarrow C_4H_7^+ + H$, $\Delta H = -15$		

[a] Ionization potentials (I) and appearance potentials (A) in e.v. Values taken from tabulation given in reference 2. [b] Reaction previously observed by Tal'roze and Lyubimova, reference 3. [c] Reaction previously observed by Schissler and Stevenson, reference 5. [d] Heats of reaction in kcal./mole. Values are calculated from ionic heats of formation tabulated in reference 2.

reactions by which they are formed. A_1 and A_2 refer to the lower and higher critical potentials found in a given ionization efficiency curve. The identification of the reactant ions has been made by considering the energetics of possible reactions, the appearance potentials of the various ions, and the dependence of the ion abundance upon pressure and repeller voltage. All the reactions involving the gas phase reactions of ions show second-order pressure dependence, and their repeller voltage dependence corresponds to that of a secondary ion. The accepted values of the primary ion ionization and appearance potentials with which the secondary ion appearance potentials are to be compared are given parenthetically in Table II. It is assumed that only exothermic secondary reactions will be observed, and this assumption can be justified by detailed considerations. The heats for the secondary reactions thought to occur are given in Table II.

Additional Comments on Table II: $m/e = 24$ and 26 from C_2H_4.—The appearance potentials of these ions were determined to learn the technique of making appearance potential measurements at high pressures. The ethylene mass 28 ion was used to calibrate the ionizing voltage scale. The two high pressure critical potentials observed for the mass 26 ion agree closely with the accepted values for the ionization potential of C_2H_2 and the appearance potential for the electron impact process $C_2H_4 \rightarrow C_2H_2^+ + H_2$, respectively; and this agreement indicates strongly that the lower high pressure value refers to acetylene molecules formed by pyrolysis from ethylene. Similarly, since the appearance potential for the formation of mass 24 ion from ethylene by fragmentation under electron impact is 26.5 volts,[2] the high pressure appearance potential for this ion refers to C_2 formed by pyrolysis and really constitutes a measure of the ionization potential of the C_2 molecule. As such it confirms the value of $I(C_2) = 11.5 \pm 1.0$ volts found by Chupka and Inghram.[12] By contrast, we found no evidence that products of mass 25 or 27 are produced in the pyrolysis of ethylene.

$m/e = 39$ from C_2H_4.—Two appearance potentials of $C_3H_3^+$ were found, the lower one corresponding to, although slightly greater than, $I(C_2H_2)$, and the upper falling midway between $A(C_2H_2^+)$ and

(12) W. A. Chupka and M. G. Inghram, *J. Chem. Phys.*, **21**, 371 (1953).

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$A(C_2H_3^+)$. Because of this uncertainty, the $C_3H_3^+$ abundance was studied with a small, fixed concentration of ethylene and various concentrations of acetylene. The $C_3H_3^+$ abundance was linear with the acetylene concentration, and we conclude that this ion is formed from $C_2H_2^+$.

m/e = 29 from C_2H_4.—This peak in part is attributable to $C^{12}C^{13}H_4^+$. Its dependence upon repeller voltage was different from that of any other ion we have observed in that the total abundance of m/e = 29 decreased to that of $C^{12}C^{13}H_4^+$ (and even considerably lower) when the repeller voltage gradient increased above about 25 volt/cm. In view of this peculiar behavior no appearance potential was determined, but the only reasonable reaction is $C_2H_3^+ + C_2H_4 \rightarrow C_2H_5^+ + C_2H_2$, $\Delta H = -16$ kcal./mole.

Experimental Reaction Rate Constants.—From equation 5 it is seen that the slope of the linear portion of the plot of $I_S/(I_P + I_S)$ *vs.* ionization chamber molecular concentration is equal to $(k_{s_j^+}/\sum_j k_{s_j^+})k_1 \tau_{P^+}$, and using values of τ_{P^+} calculated from equation 7b, $(k_{s_j^+}/\sum_j k_{s_j^+})\, k_1$ is readily obtained. When only one product ion is formed from a given transition state ion $(k_{s_j^+}/\sum_j k_{s_j^+})k_1$ reduces to k_1, the bimolecular rate constant. When several product ions are formed k_1 is obtained by taking $\sum_j (k_{s_j^+}/\sum_j k_{s_j^+})k_1$. Table III contains the rate constants for all the reactions of methane and ethylene subjected to pressure studies. In these measurements the repeller voltage was kept at 1.0 volts.

TABLE III

RATE CONSTANTS FROM PRESSURE STUDIES (V_R = 1.0 VOLT)

Reaction	$(k_{s_j^+}/\Sigma_j k_{s_j^+})k_1 \times 10^{10}$ (cc./molecule sec.)		$k_1 \times 10^{10}$ (cc./molecule sec.)
$CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3$	8.9		
	9.4	8.93	8.93
	8.5		
$CH_3^+ + CH_4 \rightarrow C_2H_5^+ + H_2$	10.2		
	9.9	9.67	9.67
	8.9		
$C_2H_3^+ + C_2H_4 \rightarrow C_2H_5^+ + C_2H_2$	3.6		
	3.8	3.82	3.82
	3.9		
	4.0		
$C_2H_2^+ + C_2H_4 \rightarrow C_3H_3^+ + CH_3$	2.6		
	2.4	2.50	
$C_2H_2^+ + C_2H_4 \rightarrow C_4H_5^+ + H$	1.6		
$C_2H_4^+ + C_2H_4 \rightarrow (C_4H_8^+)$	1.6	1.60	
$C_2H_4^+ + C_2H_4 \rightarrow C_3H_5^+ + CH_3$			4.10
$C_2H_4^+ + C_2H_4 \rightarrow C_4H_7^+ + H$	4.7	4.80	
	4.9		
$C_2H_4^+ + C_2H_4 \rightarrow (C_4H_8^+)$	0.54	0.495	
	0.45		
$C_2^+ + C_2H_4 \rightarrow C_4H_2^+ + H_2$			6.30
$C_2H^+ + C_2H_4 \rightarrow C_4H_3^+ + H_2$	10.5	10.2	10.2
	9.8		
	4.7	5.8	5.8
	6.9		

The percentage average deviations from average for replicate determinations of the rate constants for the eight reactions subjected to pressure studies ranged from 0 to 19%, with most of the deviations of the order 3–5%. We guess that an upper limit to the absolute uncertainty of the values is perhaps 15%.

When the pressure is held constant and the repeller voltage varied it is convenient to calculate the rate constant for each value of the voltage. Figure 5 is a typical curve showing the dependence

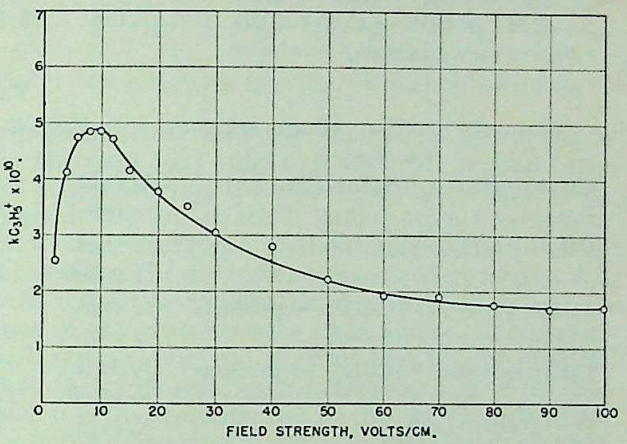

Fig. 5.—Rate constant for $C_2H_4^+ + C_2H_4 \longrightarrow C_3H_5^+ + CH_3$ against ion chamber field strength.

of the rate constant upon the ionization chamber electric field strength, and Table IV contains the rate constants at several field strengths, for all of the reactions subjected to repeller studies. The reservoir pressure was kept at 5 mm. The values tabulated are the averages of replicate measurements. As a matter of interest, measurements on the reaction $CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3$ were made at field strengths up to 220 volts/cm. The form of the curve up to a field strength of 100 volts/cm. was like that of Fig. 5, and above 100 volts/cm. the value of the rate constant remained essentially constant with a value of about 2.2×10^{-10} cc./molecule sec.

The agreement between replicate determinations of the rate constants from repeller voltage studies (making comparisons at 10 volts/cm.) is generally satisfactory, the percentage deviations from average ranging from 1 to 15% with most of the deviations of the order of 5–10%. The agreement between the rate constant values determined from repeller studies (Table IV, 10 volt/cm. values) and pressure studies (Table III) is acceptable, the percentage differences between average values ranging from 0 to 15% for all values but one (42%) with most of the values falling between 0 and 10%.

It is interesting to note from Tables III and IV that the values of k_1 of all of the reactions differ from each other by at most about a factor of 2.5. These rate constants correspond to extremely fast reactions, and such fast reactions cannot have any appreciable energy of activation. This is in accordance with observations of Stevenson and Schissler and of Schissler and Stevenson,[5] who measured

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TABLE IV

REACTION RATE CONSTANTS AT VARIOUS FIELD STRENGTHS ($P_R \approx 5$ MM.)

Reaction	$10^{10}(k_s^+ j/\Sigma j k_s^+ j)k_1$, cc./molecule sec. at indicated V/d 100	60	40	20	10	8	6	2
$CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3$	2.2	4.8	7.0	8.4	8.5	8.5	8.0	5.0
$CH_3^+ + CH_4 \rightarrow C_2H_5^+ + H_2$	3.4	5.4	7.4	8.8	8.4	7.8	7.0	4.8
$C_2H_3^+ + C_2H_4 \rightarrow C_2H_5^+ + C_2H_2$[a]				0.9	3.0	3.2	3.4	2.2
$C_2H_2^+ + C_2H_4 \rightarrow C_3H_3^+ + CH_3$	1.6	1.5	1.8	1.9	2.4	2.3	2.2	1.2
$C_2H_2^+ + C_2H_4 \rightarrow C_4H_5^+ + H$	0.44	0.46	0.72	1.2	1.6	1.6	1.6	0.70
$C_2H_2^+ + C_2H_4 \rightarrow (C_4H_6^+)$	2.0	2.0	2.5	3.1	4.0	3.9	3.8	1.9
$C_2H_4^+ + C_2H_4 \rightarrow C_3H_5^+ + CH_3$	1.5	1.8	2.5	3.3	4.6	4.6	4.4	2.4
$C_2H_4^+ + C_2H_4 \rightarrow C_4H_7^+ + H$	0.13	0.14	0.20	0.34	0.50	0.54	0.49	0.24
$C_2H_4^+ + C_2H_4 \rightarrow (C_4H_8^+)$	1.6	1.9	2.7	3.6	5.1	5.1	4.9	2.6
$C_2^+ + C_2H_4 \rightarrow C_4H_2^+ + H_2$	5.8	7.1	7.2	8.8	10.1	10.2	9.3	3.6
$C_2H^+ + C_2H_4 \rightarrow C_4H_3^+ + H_2$	1.6	2.5	2.4	2.9	3.8	3.7	3.0	1.5

[a] Values very uncertain.

TABLE V

CROSS-SECTIONS, σ, IN CM.^{2} $\times 10^{16}$ AT VARIOUS FIELD STRENGTHS

Reaction		100	60	40	20	10	8	6	4	2
$CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3$	$f\sigma$ expt.	5.6	15	27	45	61	66	68	71	55
	σ calcd.	10	13	15	20	26	27	29	32	36
$CH_3^+ + CH_4 \rightarrow C_2H_5^+ + H_2$	$f\sigma$ expt.	8.4	17	28	46	58	59	58	59	51
	σ calcd.	10	13	15	20	26	27	29	32	36
$C_2H_2^+ + C_2H_4 \rightarrow (C_4H_6^+) \rightarrow$ products	$f\sigma$ expt.	6.4	8.2	12	21	36	38	41	40	27
	σ calcd.	13	16	19	25	32	34	37	40	45
$C_2H_4^+ + C_2H_4 \rightarrow (C_4H_8^+) \rightarrow$ products	$f\sigma$ expt.	5.4	9.2	14	26	48	52	55	54	38
	σ calcd.	13	16	19	25	32	34	37	40	45
$C_2^+ + C_2H_4 \rightarrow C_4H_2^+ + H_2$	$f\sigma$ expt.	18	28	35	58	89	97	98	82	49
	σ calcd.	13	16	19	25	32	34	37	40	45
$C_2H^+ + C_2H_4 \rightarrow C_4H_3^+ + H_2$	$f\sigma$ expt.	5.1	10	12	19	34	36	32	29	21
	σ calcd.	13	16	19	25	32	34	37	40	45

the rates of several such reactions at various temperatures. Unfortunately, we were unable to vary the temperature in our reaction zone. Stevenson and Schissler[4] have reported a value of $1.3_8 \times 10^{-9}$ cc./molecule sec. for the rate constant for the reaction $CD_4^+ + CD_4 \rightarrow CD_5^+ + CD_3$. The ionization chamber field strength is not stated. The agreement with our value for the reaction of CH_4 is good.

Experimental Reaction Cross-sections.—The reaction rates can be expressed in terms of reaction cross-sections, $f\sigma$. Experimental values of $f\sigma$ have been calculated from the current ratios using equation 8c taking Q' values from equation 17, and these values (the averages of replicate determinations) are listed in Table V. Theoretical values of the cross-sections calculated from equation 29 described below are also listed in Table V. A graph of experimental and theoretical cross-sections against ionization chamber field strength is given in Fig. 6.

Schissler and Stevenson[5] report the following cross-sections

Reaction	Cross-sections ($\times 10^{16}$) in cm.^{2} at ion energy 0.10 e.v.	1.00 e.v.
$CH_3^+ + CH_4 \rightarrow C_2H_5^+ + H_2$	165 ± 5	39 ± 1
$C_2H_4^+ + C_2H_4 \rightarrow C_3H_5^+ + CH_3$	112 ± 3	21 ± 1
$C_2H_2^+ + C_2H_4 \rightarrow C_3H_3^+ + CH_3$	24 ± 3	6 ± 1

The agreement with our experimental results (comparing Schissler and Stevenson's 0.10 and 1.00 e.v. values with our values at 4 and 40 volts/cm.) is not bad, particularly when it is remembered that the reactions to be compared are slightly different. Here we consider the total reactions for $C_2H_4^+$ and $C_2H_2^+$. Schissler and Stevenson[5] report that for the reactions tabulated the cross-sections decrease to zero at finite values of the average speed of the ion. We cannot deduce exactly how they calculate their average speed, and so we cannot make a definite comparison of our results with theirs. However, within the voltage range that we investigated, the cross-sections for all reactions but one remained finite. The exception is the formation of $C_2H_5^+$ from ethylene. Its behavior was very strange, and although we do not understand it, we are inclined to attribute it to unknown instrumental effects.

Our reaction cross-sections are quite large and relatively invariant from one reaction to another. By comparison, the gas kinetic cross sections of CH_4 and C_2H_4 at 423°K. are[13] 47.8×10^{-16} cm.^{2} and 66.5×10^{-16} cm.^{2}, respectively.

Theoretical Reaction Cross-sections.—It is of interest to attempt to explain these large cross-sections theoretically. Following the general approach introduced by Eyring, Hirschfelder and Taylor,[14] we assume that the cross-section is determined by the distance, r, at which the centrifugal force tending to separate ion and molecule is exactly counterbalanced by the attractive force due

(13) Landolt-Börnstein Zahlenwerte and Functionen, 6 Auflage, "Atom und Molecularphysik," 1 Teil, Springer-Verlag, Berlin, 1950, p. 370.

(14) H. Eyring, J. O. Hirschfelder and H. S. Taylor, *J. Chem. Phys.*, **4**, 479 (1936). See also S. Glasstone, J. K. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., New York, N. Y., 1941, pp. 226 ff.

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to polarization of the molecule by the ion. In our calculation it is assumed that all of the initial energy of the system (KE of ion and molecule and potential energy of the polarization interaction) is converted into rotational energy of the ion–molecule complex; we neglect any translational energy of the center of gravity of the complex. Thus, the theory is approximate, and cross-sections obtained from it constitute lower limits to the true values.

The rotation is treated classically. The centrifugal force away from center of mass must be the same for both ion and molecule, so

$$\frac{m_1 v_1^2}{r_1} = \frac{m_2 v_2^2}{r_2} \qquad (21)$$

The center of mass of the system is defined by $m_1 r_1 = m_2 r_2$ with $r_1 + r_2 = r$, the distance between ion and molecule. From the definition of the center of mass, r, and equation 21

$$m_1 v_1 = m_2 v_2 \qquad (22)$$

that is, the linear momentum of the molecule and ion must be equal when rotating. The energy must be conserved so

$$\frac{\alpha e^2}{2r^4} + T_1^0 + T_2^0 = T_1^f + T_2^f \qquad (23)$$

where T_1^0 and T_2^0 are the initial average kinetic energy of the ion and molecule, respectively, T_1^f and T_2^f are the kinetic energies of the ionic and neutral components, respectively, of the transition state, and α is the polarizability of the molecule. From (22) and (23)

$$T_1^f = \frac{m_2}{m_1 + m_2}\left[\frac{\alpha e^2}{2r^4} + T_1^0 + T_2^0\right] \qquad (24)$$

The average initial kinetic energies are

$$\overline{T}_1^0 = \left[\frac{eVd_0}{3} + \frac{3kT}{2}\right] \qquad (25)$$

$$\overline{T}_2^0 = 3/2kT \qquad (26)$$

In (25) and (26) k is the Boltzmann constant, T is the temperature, and the other terms are as defined previously. Combining equations 24, 25 and 26

$$T_1^f = \frac{m_2}{m_1 + m_2}\left[\frac{\alpha e^2}{2r^4} + 3kT + \frac{eVd_0}{3}\right] \qquad (27)$$

The attractive force due to polarization is given by $2\alpha e^2/r^5$, and equating polarization force to centrifugal force

$$\frac{2\alpha e^2}{r^5} = \frac{2T_1^f}{r_1} \qquad (28)$$

Substituting for T_1^f and r_1 and taking $\sigma = \pi r^2$

$$\sigma = \frac{e\pi\sqrt{\alpha}}{\sqrt{6kT + \frac{2eVd_0}{3}}} \qquad (29)$$

Theoretical cross-section values calculated from equation 29 are given in Table V and a plot is given in Fig. 6. The polarizability values used for CH_4 and C_2H_4 are 2.55×10^{-24} cm.^{3} and 4.06×10^{-24} cm.^{3}, respectively, as calculated from molar polarization values given in Landolt–Börnstein.[15] The theoretical and experimental cross-sections disagree at worst by about a factor of two, which is satisfactory for calculations of this kind. We

(15) Ref. 13, 3 Teil, p. 515.

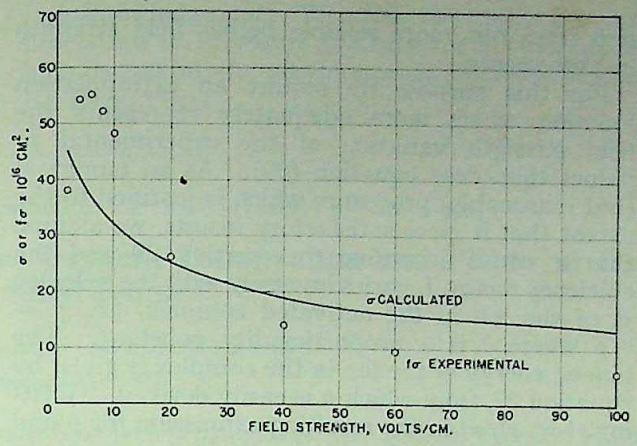

Fig. 6.—Cross-sections for $C_2H_4^+ + C_2H_4 \longrightarrow [C_4H_8^+]$.

conclude, then, that the theoretical treatment is for the most part valid and that the dominant factor in determining the cross-sections for these reactions is the ion–molecule polarization interaction. However, in addition to the disagreement in absolute values, theory and experiment do not agree well with respect to (1) the detailed functional dependence of the cross-sections upon ionization chamber field strength and (2) the fact that theory predicts that the cross-sections for the reactions of all ions with a given molecule will be the same, while in actuality some variation from one reaction to another does occur. While we are inclined to the belief that these disagreements result largely from inadequacies in the theory, some of the difficulty may result from experimental error and/or a variable experimental efficiency factor, f. In particular, we do not think that the maximum observed in the experimental $f\sigma$ *vs.* field strength relation at low field strengths is significant, but rather that it results from a lack of knowledge of the true conditions existing in the ionization chamber at low repeller voltages.

Stevenson and Schissler[4] and Schissler and Stevenson[5] find a small negative temperature coefficient (for the cross-section ?) for some reactions, while for others the rate constant is independent of the temperature. It may be seen from equation 29 that the cross-sections theoretically should depend inversely on the temperature, and at low ionization chamber field strengths the cross-sections are approximately proportional to $T^{-1/2}$. From equations 5, 7b, 8c, 17 and 29 it may be seen that the dependence of the rate constant, k_1, on temperature will be very complicated and cannot be predicted. However, the theory cannot account for the occurrence of temperature coefficients in some reactions but not in others.

Rate Constants for Thermal Speed Ions.—We are not aware of the existence of any values based on experiment of bimolecular rate constants of gaseous thermal speed ions, and it is of considerable interest to attempt to get such values. We do not think that the rate constants we have obtained at zero repeller voltage correspond to thermal speed ions because of the previously discussed lack of definition of the potentials in the ionization chamber at very low voltages. Consequently, we prefer to obtain the rates by extrapola-

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tion from our more reliable higher field strength measurements.

For this purpose we require an extrapolation function which more adequately represents the field strength variation of the experimental $f\sigma$ values than does equation (29). As an empirical (but reasonable) procedure which is justified to the extent that it gives satisfactory results, we assume that σ varies according to equation 29 and the efficiency factor, f, varies inversely with the velocity p, of the ion in the activated complex, *i.e.*, $f = \theta/p$ where θ is a proportionality constant. The kinetic energy of the ion in the complex is given by equation 27, from which p is easily derived. Writing $r^4 = \sigma^2/\pi^2$ in the resulting expression for p and taking σ from equation 29, we obtain

$$f = \frac{1}{2}\left(\frac{m_1(m_1 + m_2)}{m_2}\right)^{1/2} \frac{\theta}{(3kT + eVd_0/3)^{1/2}} \quad (30)$$

where the indices 1 and 2 refer to the ion and the molecule, respectively. Then $f\sigma$, the experimental cross-section, is

$$f\sigma = \frac{1}{2}\left(\frac{m_1(m_1 + m_2)}{m_2}\right)^{1/2} \frac{\theta e\pi\alpha^{1/2}}{(3kT + eVd_0/3)} \quad (31)$$

The proportionality constant θ can be evaluated from one experimental value of $f\sigma$ or preferably from the slope of a plot of $f\sigma$ *vs.* $1/(3kT + eVd_0/3)$. The resulting function represents nicely the field strength variation of $f\sigma$ except for the dubious points at low field strengths, as is illustrated by the typical plot given in Fig. 7.

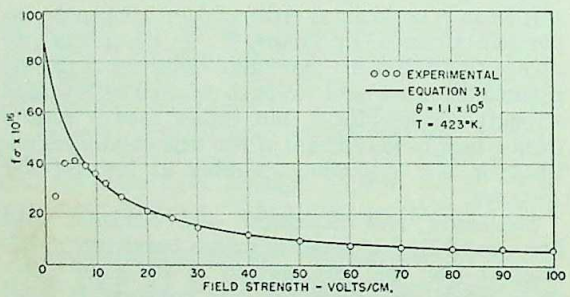

Fig. 7.—Typical plot of $f\sigma$ *vs.* field strength for $C_2H_2^+ + C_2H_4 \longrightarrow [C_4H_6^+]$.

The relationship between rate constant and cross-section is

$$k = f\sigma\bar{\xi} \quad (32)$$

where $\bar{\xi}$ is the relative velocity of the ion and molecule. Taking $f\sigma$ from equation 31 for $V = 0$ and $\bar{\xi}$ from equation 12 evaluated for thermal velocities, we obtain for the rate constant for thermal speed ions

$$k_{V=0} = \frac{\theta e}{6}\left(\frac{8\pi\alpha}{kT}\right)^{1/2}\left(\frac{m_\alpha + m_\beta}{m_\beta}\right)^{1/2} \quad (33)$$

The index α always refers to the lighter particle.

Eyring, Hirschfelder and Taylor[14] have developed an expression for the rate constant of thermal speed ions, namely

$$k = 2\pi\kappa e\alpha^{1/2}\left(\frac{m_\alpha + m_\beta}{m_\alpha m_\beta}\right) \quad (34)$$

where κ is the transmission coefficient. In Table VI we list thermal cross-sections and rate constants calculated by our extrapolation method and rate constants calculated from the Eyring, Hirschfelder and Taylor[14] expression taking $\kappa = 1$.

TABLE VI

CROSS-SECTIONS AND RATE CONSTANTS FOR THERMAL REACTIONS

Reaction	Extrl. experimental $f\sigma_{298°K.}$ (cm.² × 10¹⁶)	Extrl. experimental $k_{298°K.}$ (cc./mole sec. × 10⁹)	Theoretical (EH&T) k (cc./mole sec. × 10⁹)
$CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3$	221	2.8	1.3
$CH_3^+ + CH_4 \rightarrow C_2H_5^+ + H_2$	251	3.2	1.3
$C_2H_2^+ + C_2H_4 \rightarrow (C_4H_6^+)$	123	1.2	1.3
$C_2H_4^+ + C_2H_4 \rightarrow (C_4H_8^+)$	155	1.5	1.3
$C_2H^+ + C_2H_4 \rightarrow C_4H_3^+ + H_2$	131	1.2	1.3
$C_2^+ + C_2H_4 \rightarrow C_4H_2^+ + H_2$	284	3.5	1.3

TABLE VII

COMPARISON OF PRIMARY AND SECONDARY MASS SPECTRA (BASED ON LARGEST OF THE PEAKS COMPARED)

Ion	Primary 1-Butene	Primary *cis*-Butene-2	Primary Isobutene	Primary Cyclobutane	Secondary from $C_2H_4^+ + C_2H_4$
$C_3H_4^+$	6.5	7	11	6.5	1.5
$C_3H_5^+$	100	100	100	100	100
$C_4H_6^+$	2.5	4	2.5	3	0.2
$C_4H_7^+$	18	22	16	21	8.8
	1,2-Butadiene	1,3-Butadiene	1-Butyne	2-Butyne	From $C_2H_2^+ + C_2H_4$
$C_3H_3^+$	100	100	100	57	100
$C_4H_4^+$	28	11	10	23	7
$C_4H_6^+$	100	59	57	100	54

With thermal rate constants and cross-sections of this magnitude it is self-evident that the occurrence of ionic reactions must be seriously considered in any process in which the formation of ions is a possibility, *e.g.*, in radiation chemistry processes. The agreement between our rate constants and those from Eyring, Hirschfelder and Taylor[14] is satisfactory, but it should be noted that our treatment predicts a weak ($T^{-1/2}$) dependence of the rate constant on temperature, which is not found in the EH&T expression. We do not know which of these predictions is correct.

Comparison of Secondary and Primary Mass Spectra.—In those cases where a known intermediate such as $C_4H_8^+$ or $C_4H_6^+$ is formed it is interesting to compare the primary mass spectrum from various C_4H_8 and C_4H_6 compounds with our observed secondary spectrum. Thus the intensities of those peaks in the secondary mass spectrum of ethylene which might have resulted from the reaction of $C_2H_4^+$ and C_2H_4 are compared to those of the same peaks in the primary spectra of various C_4H_8 compounds. Similarly the secondary spectra that might have resulted from the reaction of $C_2H_2^+$ and ethylene are compared to those of several C_4H_6 compounds. Such comparisons are made in Table VII taking the primary spectra from the API tabulation. There is an approximate correspondence which indicates that the intermediate ions (activated complex) must be at least qualitatively similar to the respective parent ions in the

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primary spectra. In fact, it is tempting to decide that the $C_4H_6^+$ intermediate is more similar to the 1,3-butadiene or 1-butyne ions than to the other two primaries shown.

Acknowledgment.—We wish to express our appreciation to Mr. Burl L. Clark for his invaluable help in making the measurements and calculations.

BAYTOWN, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Effects of Structure, Product Concentration, Oxygen, Temperature and Phase on the Radiolysis of Alkyl Iodides

BY EVALYN O. HORNIG AND JOHN E. WILLARD

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The yields of elemental iodine as a function of radiation dosage have been determined for the radiolysis with Co^{60} γ-rays of seven purified degassed alkyl iodides. Doses $>16 \times 10^{20}$ e.v./ml. were used in some cases. Although six of the iodides show linear dependence of G_{I_2} on radiation dosage at low doses, all depart from linearity at higher doses, and the G_{I_2} for isobutyl iodide decreases with increasing dose even at the start of irradiation. The linear dependence is attributed to a balanced competition between HI and I_2 for thermal radicals and, consistent with this concept, the rate of exchange with radioiodine during radiolysis is found to be dependent on the concentration of added I_2 or O_2. The dependence of G_{I_2} on the β-hydrogen content of the alkyl iodides is confirmed and ascribed to increased probability of HI formation by decomposition of excited molecules as the number of β-hydrogens per molecule increases. Added O_2 increases the initial G_{I_2} for C_2H_5I by an amount independent of the O_2 pressure from 2 to 188 mm., but as the I_2 concentration increases with increased dosage G_{I_2} returns to its degassed level at a rate inversely dependent on the oxygen pressure. With added iodine present at a concentration elevenfold greater than the dissolved oxygen, the initial G_{I_2} was the same as that in the absence of additives. G_{I_2} for four iodides tested is essentially independent of temperature in the liquid phase from 20 to $-78°$ and for C_2H_5I from 108 to $-78°$, but the G_{I_2} values for both CH_3I and C_2H_5I have a positive temperature coefficient in the crystalline solid phase. G values for two iodides studied in both the glassy and crystalline states at $-190°$ were higher in the glassy state, a result which is tentatively ascribed to molecular orientation favoring a stereospecificity for hot radical reactions.

Introduction

The purpose of the work of this and the following paper[1] was to elucidate further[2] the mechanisms of radiolysis of the alkyl iodides. The investigations have included studies of: (1) the competitive reactions of O_2, I_2 and HI with thermal radicals produced in the radiolyses and (2) the effects of temperature, molecular structure and irradiation in the solid crystalline and glassy states on the yields of elemental iodine.

Experimental

The alkyl iodides, Eastman or Matheson best grade, were purified by passage through activated alumina, followed by distillation through a two-foot Vigreux column, the middle 50% being retained. Identical iodine yields were obtained from the irradiation of samples of ethyl iodide purified as above, and from those purified by shaking with concentrated H_2SO_4 and washing with Na_2SO_3 solution prior to distillation. The purified iodides were degassed by several cycles of freezing, pumping and thawing on a vacuum system, and then were vacuum-distilled through P_2O_5 into the irradiation vessels and sealed off.

During the irradiation, the samples (5 ml.) were contained in an annular vessel,[4] which surrounded a 40-curie Co^{60} γ-ray source.[4] The radiation intensity on the samples was 2×10^5 roentgens/hr., the absorption of energy in the alkyl iodides being at the rate of about 2×10^{19} e.v. per ml. per hr.

Iodine analyses were made with a Beckman DU spectrophotometer. A spectrophotometer cell made from square Pyrex tubing was attached to the annular vessel so that iodine analyses could be made between successive irradiations of the same sample without exposing it to the air. Concentrations were read at the absorption maximum at 478 mμ and for high concentrations at 550 and 625 mμ. The high concentration readings were checked at 478 mμ in methyl and ethyl iodide irradiations by using 0.98 and 0.95 cm. silica inserts in the analysis cells. Determinations of molar extinction coefficients were made at the three wave lengths for methyl, ethyl and *n*-propyl iodides, the values obtained being 1280, 356 and 72.8 l./mole cm., respectively. Since the extinction coefficients were the same for the three iodides, it was assumed that the same values would also be applicable to the other iodides.

To irradiate samples at -78, -123 and $-190°$, they were surrounded during the irradiation by baths of solid CO_2 and acetone, butyl chloride slush, and liquid air, respectively. A thermostatically controlled bath of mineral oil was used for the irradiations at 108°.

Oxygen of known pressure was admitted to degassed samples of ethyl iodide on a vacuum line, either from a cylinder or by heating $KClO_3$ containing MnO_2. The number of moles oxygen introduced to the sample vessel was determined from the pressure change in a known volume of the vacuum apparatus, measured with a phosphoric acid manometer. The solubility of oxygen in ethyl iodide was found to be 8×10^{-6} mole/l. per mm. pressure at 23°,[5] so that the concentration of dissolved oxygen in the samples could be determined from the gas pressure.

Iodine labeled with I^{131} was prepared from carrier-free iodine solutions by adding the desired amount of KI and oxidizing with acidified KIO_3. The iodine was transferred into the irradiation vessels by vacuum distillation through P_2O_5. A solution-type Geiger counter was used to measure

(1) R. J. Hanrahan and J. E. Willard, THIS JOURNAL, **79**, 2434 (1957).

(2) Previous investigators have determined the relative yields of I_2 from X-ray and α-particle irradiation of air-saturated ethyl iodide,[3a] from γ-irradiation of eight air-saturated alkyl iodide,[3b] from fast electron irradiation[3c] of degassed CH_3I, CH_3I_2, C_2H_5I and *n*-C_3H_7I, and from X-ray irradiation of degassed CH_3I,[3c,d] C_2H_5I,[3c,d,h] propyl[3d,h] and butyl iodides.[3d] The yields of various products from the X-ray irradiation[3e,h] and very low intensity Co^{60} γ-ray irradiation[3e] of degassed CH_3I have also been determined. Similarities and contrasts between the radiolysis and photolysis of the alkyl iodides have been considered.[3c,d,e,f] Distillation with added carriers following irradiation in the presence of radioiodine has been used to identify intermediate free radicals.[3g,h]

(3) (a) M. Lefort, P. Bonet-Maury and M. Frilley, *Compt. rend.*, **226**, 1904 (1948); (b) P. Sue and E. Saeland, *Bull. soc. chim. France*, 437 (1949); (c) R. H. Schuler and W. H. Hamill, THIS JOURNAL, **74**, 6171 (1952); (d) E. L. Cochran, W. H. Hamill and R. R. Williams, Jr., *ibid.*, **76**, 2145 (1954); (e) C. R. Petry and R. H. Schuler, *ibid.*, **75**, 3796 (1953); (f) W. H. Hamill and R. H. Schuler, *ibid.*, **73**, 3466 (1951); (g) L. H. Gevantman and R. R. Williams, Jr., *J. Phys. Chem.*, **56**, 569 (1952); (h) R. H. Schuler and R. C. Petry, THIS JOURNAL, **78**, 3957 (1956).

(4) R. F. Firestone and J. E. Willard, *Rev. Sci. Inst.*, **24**, 904 (1953).

(5) E. O. Hornig, Ph.D. thesis, University of Wisconsin, Feb. 1956, available from University Microfilms, Ann Arbor, Michigan.

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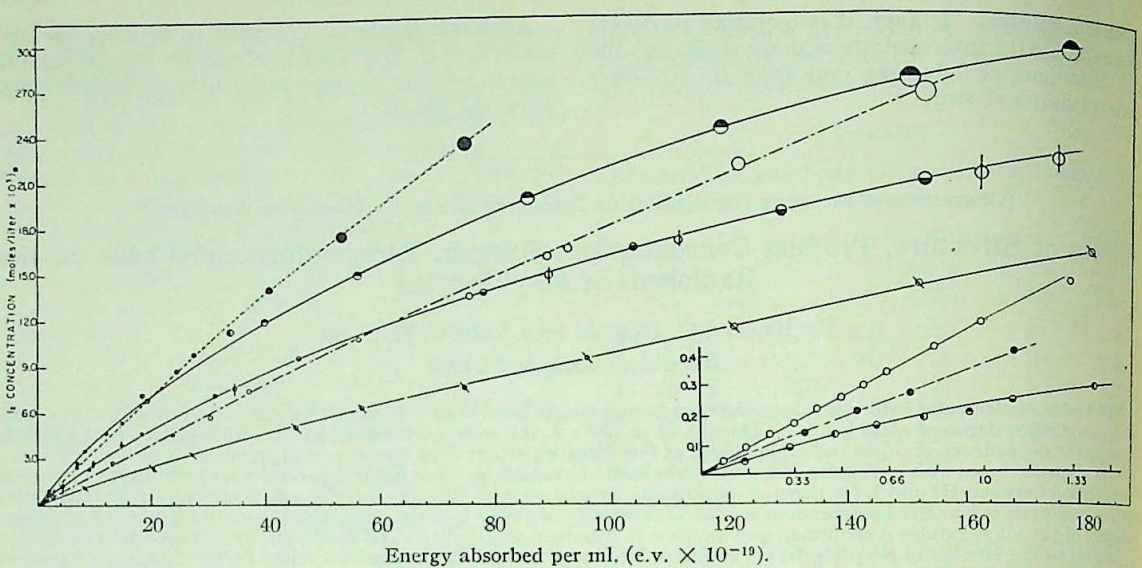

Fig. 1.—Iodine production in the radiolysis of degassed alkyl iodides as a function of energy absorbed: ○, methyl; ●, ethyl; ◒, *n*-propyl; ◓, isopropyl; ϕ, *n*-butyl; ◌, isobutyl; ◐, *s*-butyl.

the distribution of activity between organic and inorganic combination after radiolysis.

Results

Variation of Iodine Yields with Radiation Dosage.—Figure 1 shows the change of iodine concentration with time of irradiation for seven alkyl iodides. Six of these showed no change in slope up to radiation doses as high as 4.5×10^{19} e.v./ml.[6] The seventh, isobutyl iodide, gave yields which dropped from 3.36 I atoms (as $^1/_2$ I_2) produced per 100 e.v. absorbed initially to 1.89 after 0.64×10^{19} e.v./ml. was absorbed (see insert of Fig. 1). Identical results were obtained with each of three separately purified *i*-C_4H_9I samples. For the much higher radiation doses plotted in the main portion of Fig. 1, all of the iodides except methyl showed a region of decreasing rate of I_2 production. For those compounds which were subjected to the largest dosage (isobutyl, isopropyl, *n*-propyl) the values of G_{I_2} for increments of irradiation after the samples had been exposed to 16×10^{20} e.v./ml., all came to the same value of 0.95 ± 0.03. The curvature is of interest because it is indicative of competing reaction steps which change in importance with changing concentration of the radiolysis products, and because previous investigators[3c,d,e] of the radiolysis of alkyl iodides using X-rays or fast electrons and small total dosage (maximum I concentrations of about 10^{-3} mole/l.) have reported that the iodine production is linear or nearly linear[3h] with absorbed energy for all the iodides which they studied.

G Values.—Table I shows the values of *G* we have obtained for low radiation doses ($< 1.3 \times 10^{-3}$ mole/l. of I_2 produced), and also the literature values for similar systems. To determine the energy absorbed, $FeSO_4$ in 0.8 *N* H_2SO_4 was exposed to the source under conditions identical to those used for the alkyl iodide samples. A value of 15.6 Fe^{++} oxidized per 100 e.v. absorbed was assumed.[7] The absorption in the aqueous $FeSO_4$ solution (1.33×10^{19} e.v./ml. hr.) was multiplied by factors[5] to correct for the difference between its density and average atomic number and those of each of the iodides. The rates of energy absorption so obtained were 2.64×10^{19} e.v./ml. hr. for CH_3I, 2.26×10^{19} for C_2H_5I, 2.05×10^{19} for *n*-C_3H_7I, 2.02×10^{19} for *i*-C_3H_7I, 1.94×10^{19} for *n*-C_4H_9I, 1.92×10^{19} for *i*-C_4H_9I and 1.91×10^{19} for *s*-C_4H_9I. For four of the iodides, the *G* values for the liquids were determined on at least three separate samples from two different purifications, and several irradiations were made on each sample.[5] The results were usually reproducible to closer than ± 2%.

TABLE I

G VALUES[a] FOR IODINE PRODUCTION IN THE RADIOLYSIS OF LIQUID ALKYL IODIDES

	Present work, Temperatures, °C					Other work, room temp.
	Room	108	−78	−120	−190	
CH_3I	2.52			0.94[f]	0.64[f]	3.3,[b] 2.7,[c] 2.4[d]
C_2H_5I	4.25	4.05	4.34	2.05	0.95[f]	4.1,[b] 4.1,[c] 4.05[d]
					3.05[g]	
n-C_3H_7I	3.20					3.5,[c] 2.88[e]
i-C_3H_7I	5.36		5.26		0.65[f]	5.3[e]
n-C_4H_9I	3.38				3.38[g]	
i-C_4H_9I	1.89[h]		1.89	3.19[f]	2.60[f]	
s-C_4H_9I	5.04		4.80		4.43[g]	

[a] The radiation yields (*G* values) are expressed as equivalents of iodine ($^1/_2$ I_2) produced per 100 e.v. absorbed. They are for irradiations at iodine concentrations of $<1.3 \times 10^{-3}$ mole/l. [b] For *ca.* 1 mev. X-radiation.[3a] [c] For 1–2 mev. electron bombardment.[3c] [d] For very low intensity Co^{60} rays.[2e,3h] [e] For 120 kvp. X-radiation.[3h] [f] Crystalline solid. [g] Glassy solid. [h] Note first paragraph under Results.

The only absolute yield for I_2 production in the radiolysis of degassed alkyl iodides by γ-rays reported in the literature, of which we are aware, is that for a five-week irradiation of CH_3I with a very low intensity (300 mc.) Co^{60} source.[3e] The value

(6) To establish the initial linearity of the ethyl iodide plot, measurements were made at iodine concentrations as low as 10^{-6} mole/l. with the aid of a 10 cm. absorption cell.

(7) C. J. Hochanadel and J. A. Ghormley, *J. Chem. Phys.*, **21**, 880 (1953).

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obtained after correction[3h] for $G_{Fe^{+++}} = 15.6$ is in good agreement with our result of 2.5 obtained at 550-fold higher radiation intensity. Absolute yields of iodine production from the X-ray[3c,h] and electron irradiation[3e] of CH_3I, C_2H_5I and n-C_3H_7I are in good agreement with the γ-ray yields, considering differences in dosimetric methods used.

Structure Effects.—From Fig. 1 and Table I, it may be seen that the initial values of G for the radiolysis of the iodides are related as follows: i-C_3H_7I > s-C_4H_9I > C_2H_5I > n-C_3H_7I ≅ n-C_4H_9I > CH_2I > i-C_4H_9I. A similar sequence of relative yields has been observed by Cochran, Hamill and Williams[3d] for the radiolysis with low energy X-rays and for photolysis with ultraviolet light and they have suggested that the order may be correlated with the fraction of the hydrogen atoms in the molecule which is in the β position to the C–I bond. Our data plotted in Fig. 2 as a function of both the fraction of hydrogen atoms in the β-position and the number of hydrogen atoms per molecule in the β-position give a smoother correlation with the latter plot. CH_3I, which has no β-hydrogen atoms, does not fall in line on either plot.

Temperature and Phase Effects.—From Table I it may be seen that the G values for liquid C_2H_5I at 108, 20 and −78° are indistinguishable and that there is likewise little or no temperature effect on the radiolysis of liquid i-C_3H_7I, i-C_4H_9I or s-C_4H_9I in going from 20 to −78°. By contrast, the three iodides for which determinations were made at two temperatures in the crystalline state, all show a higher yield at −120° than −190° (Table I and Table II).

TABLE II

EFFECT OF TEMPERATURE AND STATE ON G VALUES

Cpd.	$G_{liquid}/G_{cryst.}$ Cryst. −120°	Cryst. −190°	$\frac{G_{cryst.}\ -120°}{G_{cryst.}\ -190°}$	$\frac{G_{liquid}}{G_{glass}\ -190°}$	$\frac{G_{glass}\ -190°}{G_{cryst.}\ -190°}$
CH_3I	2.7	3.9	1.5		
C_2H_5I	2.0	4.3	2.3	1.35[a]	3.3
i-C_3H_7I		9.0			
n-$C_4H_{10}I$				1.0	
i-$C_4H_{10}I$			1.3	0.4	1.6

[a] The C_2H_5I glass may have crystallized before the completion of the irradiation.

Iodine yields in the solid phase irradiations were determined by spectrophotometric measurements on the liquid after melting. Identical G values were obtained for long and short solid phase irradiations and for irradiations after melting and refreezing a previously irradiated solid.

Of special interest is the fact that in the two cases where determinations were made both on the glassy[8] state and the crystalline states of a compound at the same temperature, the yields in the glassy state were much higher (Table II). Isobutyl iodide in the crystalline state at −190° showed a lower initial G_{I_2} than the liquid but no curvature corresponding to that illustrated for the liquid in the insert on Fig. 1. After the absorption of about 8×10^{18} e.v./ml. the value for the crystals is higher than that for the liquid.

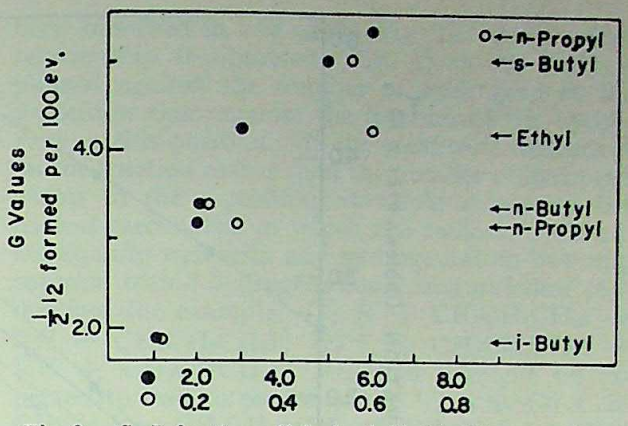

Fig. 2.—G_{I_2} for the radiolysis of alkyl iodides, as a function of the β-hydrogen content: ●, number of β-hydrogen atoms per molecule; ○, fraction of hydrogen atoms in the β-position.

Effect of Oxygen.—The fact that iodine tagged with I^{131} exchanges with alkyl iodides undergoing radiolysis,[3c,e,h] is strong evidence for the presence of thermal alkyl radicals which return iodine to organic combination by the $R + I_2 \rightarrow RI + I$ reaction. At sufficiently high concentration, oxygen would be expected to compete with the I_2 for these radicals and thus increase the net I_2 yield. Such an increase has been demonstrated by Schuler and Petry[3h] for air-saturated and oxygen-saturated CH_3I and C_2H_5I. We have also investigated this effect with ethyl iodide using a series of different oxygen pressures ranging from 2 to 188 mm. (a variation of dissolved oxygen concentration from 1.6×10^{-5} mole/l. to 1.5×10^{-3} mole/l.). In agreement with the observations of Schuler and Petry,[3h] the *initial* rate of iodine production at all of the oxygen pressures was about 2.3 times that for degassed samples and it decreased with increasing radiation dose (Fig. 3). The higher the initial oxygen concentration the greater was the dose required to bring about a given decrease in rate toward the degassed value. This is consistent with the conclusion[3h] that the initial rate in the presence of oxygen represents the case where all

(8) When degassed samples of the alkyl iodides are cooled rapidly in liquid air, they often form transparent, glassy solids instead of opaque crystals. The glassy form is least stable for the iodides with 1, 2 and 3-carbon atoms. It is relatively easily obtained and can be indefinitely maintained at low temperatures in the cases of n-C_4H_9I and i-C_4H_9I. Similar observations on the relative stability of glasses as a function of chain length have been reported for the alkyl bromides.[9] The glasses sometime crack without crystallizing. C_6H_5I glass has been found to crystallize always when raised above about −165°.[10] It can be obtained and maintained at lower temperatures only in very clean degassed vessels with freshly annealed surfaces.

In order to be sure that the visible differences between apparently crystalline and apparently glassy samples indicate a true difference in state, we have frozen samples of n-C_4H_9I and i-C_4H_9I to the glassy state at −190° with thermocouples imbedded in them. The samples were then placed in Dewar flasks and allowed to warm slowly (15 minutes) to room temperature. During this time, the temperature of the thermocouples was recorded on a chart recorder. For both compounds the gradual slope of the warming curve changed to a vertical rise at about −125° indicating a sudden evolution of heat as a result of the conversion of the glass to the crystalline form. If, following this transition, the solid was cooled to −190° and again allowed to warm, no such heat evolution was observed, but each time the solid was melted and refrozen to the glass, the warming curves showing the crystallization process could be reproduced.[8]

(9) F. S. Rowland and W. F. Libby, *J. Chem. Phys.*, **21**, 1495 (1953).

(10) T. O. Jones and J. E. Willard, Absts. of 128th meeting of Am. Chem. Soc., Minneapolis, Minnesota, Sept. 1955, p. 35-R.

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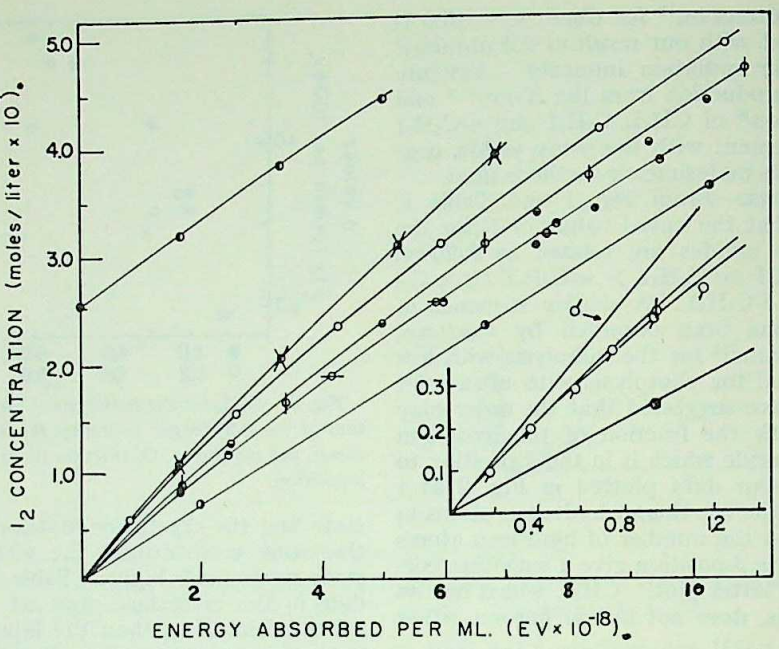

Fig. 3.—Iodine production in the radiolysis of ethyl iodide as a function of energy absorbed and of oxygen pressure. Initial oxygen pressures in mm.: ◑, degassed; ◓, 2.7; ◔, 4.7; ●, 5.6; ◒, 10.9; ◕, 10.5; ○, 18; ⊗, 42.8; σ, 188; ◐, 7.5 (I_2 present at the start of radiolysis); ρ, 5.8, using 10 cm. light path.

thermal radicals are scavenged by the dissolved gas and none have the opportunity to return iodine to organic combination by reaction with I_2. As the I_2 concentration builds up, this species competes more and more effectively for the radicals thus reducing the rate of iodine production. The HI formed probably is oxidized by the oxygen.

The above concept of the mechanism is substantiated by the fact that the accelerating effect of O_2 can be counteracted by adding I_2 prior to irradiation (Fig. 3). At an initial mole ratio of I_2 to dissolved O_2 of 11, the rate was equal to that of degassed samples with no additives.

Estimates of the consumption of O_2 during irradiation in the experiment of Fig. 3 indicate that the decrease in its accelerating effect with time of irradiation cannot be attributed to depletion of the O_2. If it is assumed that one molecule of O_2 was consumed for each $^1/_2$ I_2 formed in excess of that formed in degassed samples, the depletion of O_2 after the rates had returned essentially to the degassed value was less than 10%. It is probable that the ratio of O_2 consumed to I_2 formed is actually less than 1/0.5, as a result of reactions of peroxy radicals to liberate I_2 from HI.

Information from Irradiation in the Presence of Radioiodine.—When it was first observed that oxygen accelerated the production of iodine from C_2H_5I and that the maximum initial rate was independent of the O_2 concentration over a wide range, it was thought that the only important reaction steps governing I_2 production were: (1) a hot radical production of $^1/_2$ I_2, such as $C_2H_5 + C_2H_5I \rightarrow C_2H_4 + C_2H_6 + I$, which was not sensitive to additives, and (2) a thermal radical step of the type $C_2H_5 + I_2 \rightarrow C_2H_5I + I$ which returned $^1/_2$ I_2 to organic combination and was sensitive to radical scavengers. According to this mechanism, the rate of exchange of radioiodine during radiolysis in the absence of oxygen should be independent of iodine concentration and should equal the increase in rate of iodine formation caused by an excess of oxygen. Also, the ratio of the G value for exchange to that for I_2 production should be constant, in the absence of oxygen.

Experiments designed to test these predictions gave the data of Table III which indicate that there must be another species in addition to iodine which competes for the thermal radicals in degassed samples. It may be seen that (1) the G value for exchange with both C_2H_5I and i-C_3H_7I increases with increasing initial iodine concentration, (2) the G

TABLE III

EFFECT OF I_2 AND O_2 CONCENTRATIONS ON EXCHANGE[a] OF I^{131} BETWEEN I_2 AND RI DURING RADIOLYSIS

Cpd. irradiated	I_2 added, mole/l. $\times 10^3$	Time of irradn., min.	G of exchange	$\frac{G_{ex}}{(G^{I}/_{2I_2})}$[d]	$\frac{G_{ex}}{(G^{I}/_{2I_2})}$ pure
C_2H_5I	0.30	10	4	1.24	0.93
	0.51	10	4.3	1.36	1.02
	2.1	10	6.2	2.03	1.45
[b]	0.63	7.5	2.2	0.34	0.51
[c]	0.31	5	0.4	0.08	0.14
i-C_4H_9I	0.49	15	5.1	3.22	2.76
i-C_3H_7I	0.29	6	6.1	1.70	1.14
	0.11	5	4.2	1.00	0.79

[a] "Exchange" as used here includes transfer of iodine from I_2 or HI to all organic forms. It has been shown by Gevantman and Williams[2g] and Schuler and Petry[3b] that exchange occurs predominantly into the parent compound. [b] C_2H_5I + 1 atm. of O_2 to give a dissolved O_2 concn. of *ca.* 6×10^{-3} mole/l. [c] C_2H_5I + 550 mm. of O_2 to give a dissolved O_2 concn. of *ca.* 4×10^{-3} mole/l. [d] Comparison of G exchange with $G_{^1/_2I_2}$, in the same sample containing initially added I_2 at the concn. of column 2. [e] Comparison of exchange for the samples with added iodine, with $G_{^1/_2I_2}$ for degassed samples with no I_2 initially present.

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value for I_2 production decreases with increasing initial iodine concentration, and (3) the ratio of the G value for exchange to that for iodine production in degassed samples increases with increasing concentration of initially added iodine.

Below we report evidence that HI is a radiolysis product of the alkyl iodides. In the following paper it will be shown that the effect of initial I_2 concentration on the G values for iodine production and exchange may be quantitatively explained on the basis of a competition between HI and I_2 for alkyl radicals, similar to the competition which has been shown to occur in the photolysis[11] of ethyl iodide.

Evidence That HI is a Product.—In order to determine HI production, samples of alkyl halides which had been irradiated in the presence of radioiodine were frozen with liquid air before breaking the vacuum, and were then shaken with a mixture of CCl_4 and H_2O. The HI dissolved in the water while the I_2 stayed predominantly in the CCl_4. The water was washed three times with fresh aliquots of CCl_4 and counted, the ratio of its activity to the total inorganic activity indicating the fraction of the latter which was HI. Ratios of HI/I_2 formed ranging from less than unity for C_2H_5I and i-C_4H_9I to considerably higher for i-C_3H_7I were found. In view of present knowledge of the role of HI in the mechanism[1] these would be expected to vary with the initial iodine concentration and the duration of the irradiation.

Discussion

The evidence presented above advances our knowledge of the radiolysis of alkyl iodides in several respects.

1. **Competitive Radical Reactions.**—By showing (Fig. 3, Table III) that the rate of iodine production and the rate of exchange of radioiodine are dependent on the ratio of oxygen concentration to iodine concentration and also on the ratio of iodine concentration to some other product (shown later to be HI), the results indicate that the yields, both with and without oxygen present, are determined by competitive reactions which consume thermal radicals.

2. **Absence of Intensity Effect.**—The fact that the G values for iodine production (Table I) are the same for irradiation at 2×10^5 r./hr. with a 40 c. Co^{60} source as at 350 r./hr. with a 300 mc. source[3e] confirms the fact that the radiolysis is independent of the intensity of γ-radiation. This is consistent with the conclusion, which may be reached from a consideration[12] of relative concentrations of radicals and iodine scavenger molecules, that there is no interaction between radicals produced in different tracks.

3. **Structure Effects.**—The fact, reported by Cochran, Hamill and Williams,[3d] that $G_{1/2\ I_2}$ for the radiolysis of alkyl iodides increases as a function of the hydrogen atoms on the carbon atoms adjacent to the one containing the iodine has also been observed in our work (Fig. 1). A smoother relationship is obtained (Fig. 1) if the yield is plotted against the number of hydrogens in the β-position than against the fraction of the hydrogens in this position. If the yield were dependent on the fraction rather than the number of hydrogen atoms in the β-position, it would suggest a hot radical mechanism in which the radicals could react equally well with any hydrogen atom but only reaction with β hydrogens could lead to iodine production, for example: (1) $\underline{R} + CH_3CH_2CH_2I \rightarrow RH + CH_2CH_2CH_2I$; (2) $\underline{P} + CH_3CH_2CH_2I \rightarrow RH + CH_3CHCH_2I$. Reaction 2 might be expected to lead to production of $^1/_2$ I_2 by (3) $CH_3CHCH_2I \rightarrow CH_3CH{=}CH_2 + I$, but the product of (1) could not form a double bond by elimination of I and would probably react by (4) $CH_2CH_2CH_2I + I_2 \rightarrow CH_2ICH_2CH_2I + I$. Evidence from characterization experiments[3g,h] with radioiodine indicates little or no diiodide formation and so argues against the sequence of reactions 1 and 4 which would be expected to be prominent if the suggested hot radical hypothesis were responsible for the β-hydrogen effect.

In view of the evidence[1] that a large portion of the iodine produced in the radiolysis of ethyl iodide results from the step $C_2H_5 + HI \rightarrow C_2H_6 + I$ in competition with $C_2H_5 + I_2 \rightarrow C_2H_5I + I$, it may be speculated that the increase in rate of iodine production with increase in the number of β-hydrogen atoms is a result of an increase in the probability that *excited molecules* can eliminate HI and thus increase the ratio of HI to I_2 in the system. This could be a one-step process such as $CH_3CHICH_3 \rightarrow CH_2{=}CHCH_3 + HI$. As noted above, we have found that the yield of HI from i-C_3H_7I is considerably greater than from C_2H_5I and i-C_4H_9I.

4. **Non-linear Dependence of Yield on Energy Input.**—Figure 1 shows that all of the iodides except i-butyl show a linear increase in iodine concentration with absorbed energy up to about 10^{-3} M, in accordance with previous observations,[3] but that all of these show a curvature in the direction of lower G values if the irradiation is continued to 10^{-2} M I_2 or higher. It appears[1] that in the linear region, iodine production is the result of a hot reaction, plus a competition between I_2 and HI for thermal radicals, with the fraction of radicals which are used up by each path in the competition remaining constant because the ratio of HI produced to I_2 produced remains constant. It would appear that the most probable cause of deviation from linearity, at concentrations where direct energy absorption by the reaction products is negligible, is a reaction between HI and some other reaction product to decrease the rate of HI accumulation and hence favor the reaction $R + I_2 \rightarrow RI + I$ over that of $R + HI \rightarrow RH + I$. If olefins are produced which can react with HI ($C_2H_4 + HI \rightarrow C_2H_5I$) this process, being bimolecular, might become apparent only after these reactants had built up appreciably in concentration. Scavenging of radicals by a product other than I_2 or HI is not a satisfactory explanation of the curvature since such a species would be in constant ratio

(11) (a) D. Bunbury, R. R. Williams, Jr., and W. H. Hamill, Abstracts 125th Meeting, Am. Chem. Soc., Minneapolis, Sept. 1955, p. 26R; (b) D. L. Bunbury, R. R. Williams, Jr., and W. H. Hamill, This Journal, **78**, 6228 (1956).

(12) G. Levey and J. E. Willard, *ibid.*, **74**, 6161 (1952).

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to the HI and I_2 throughout an experiment. It is possible that electron attachment or charge transfer processes which can lead to the net removal of HI or increased return of I_2 to organic combination become more important as the I_2 and HI concentrations increase.

Temperature and Phase Effects.—The fact that samples of the same solid alkyl iodide at the same temperature give different G values for I_2 production when they are in the glassy state than when they are in the crystalline state seems to indicate that the orientation of the molecules with respect to each other at the time energy is absorbed is an important factor in determining the chemical consequences of the energy absorption. In the ordered arrangement of a crystal hot C_2H_5 radicals formed from C_2H_5I may preferentially attack certain parts of adjacent C_2H_5I molecules, while in the random arrangement of a glass there can be no such specificity. Such preferential attack or various other sterically sensitive hot reactions may account for the difference in the G_{I_2} values in the different states.

For reactions activated by radiative neutron capture[12-14] the "organic yield" has been observed to increase, decrease or remain essentially unchanged with change of phase, depending on the compound, but with no obvious correlation with the molecular structure or the density.[12-14] In view of the contrast between the iodine yields for the glass and the crystalline phases in the present work, it seems plausible that the primary factor in determining the effect of freezing on the organic yields of activation by nuclear processes may be the orientation of the molecules in the crystal lattice.

The absence of a temperature effect in the radiolysis of liquid C_2H_5I from -78 to 108° suggests that the pattern of radical recombination reactions which occurs is not governed by the ease of diffusion of the radicals. This behavior is in contrast to that of CCl_3Br where G_{Br_2} is temperature sensitive, the apparent activation energy being about 3 kcal./mole.[15]

Acknowledgment.—This work was supported in part by the United States Atomic Energy Commission and in part by the University Research Committee with funds made available by the Wisconsin Alumni Research Foundation.

(13) M. S. Fox and W. F. Libby, *J. Chem. Phys.*, **20**, 487 (1952).
(14) S. Goldhaber, R. S. H. Chiang and J. E. Willard, THIS JOURNAL, **73**, 2271 (1951).
(15) R. F. Firestone and J. E. Willard, Absts. of 127th meeting of the Am. Chem. Soc., Cincinnati, Ohio, April 1955, p. 23Q.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Quantitative Treatment of the Elementary Processes in the Radiolysis of Alkyl Iodides by γ-Rays

BY ROBERT J. HANRAHAN AND JOHN E. WILLARD

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The mechanism of radiolysis of alkyl iodides with Co^{60} γ-rays includes the production of HI, I_2, alkyl radicals and hydrocarbons within the "hot spots" of the radiation tracks, and reaction of the thermalized radicals outside the tracks with HI and I_2 to abstract H and I, respectively. From the effects of added HI and I_2 on the rates of I_2 production and radioiodine exchange, it is possible to deduce the rates of the elementary reactions. For ethyl iodide, integrated rate equations which predict the rates of I_2 and HI production and of exchange have been obtained. The predicted rates are in agreement with the experimental results.

Introduction

The yield of iodine per unit of energy absorbed in the radiolysis of degassed ethyl iodide[1] is independent of the concentration of iodine built up during the radiolysis[1,2] and is independent of the temperature from -78 to 108°.[2] It has been thought that the iodine yield is independent of initially added iodine[3,4] although the data presented might be interpreted to indicate a small decrease for such addition.[3] These facts have led to the assumption that iodine production does not occur by any reaction involving the thermalized radicals, *i.e.*, occurs only by hot processes.

In the present work a careful re-examination of the effect of I_2 added prior to radiolysis has shown that it reduces the initial rate of iodine production by nearly 50%. This, together with the observation that HI is a product of the radiolysis,[2] has indicated that an important part of the mechanism is a reaction in which thermal alkyl radicals abstract hydrogen from HI, as it is in the photolysis of ethyl iodide reported by Bunbury, Williams and Hamill.[5] A quantitative study has therefore been made of the role played by HI and I_2 in competing for thermalized radicals.

Experimental

The methods of purification and irradiation of alkyl iodides were similar to those described in the preceding paper.[2] Mallinckrodt reagent grade iodine was used without further purification. All reaction mixtures were degassed by vacuum line techniques.

Dry HI was prepared from a 55% aqueous solution of HI (Merck) from which the free iodine was removed with red phosphorus. The water was removed by covering the frozen solution with P_2O_5, and allowing it to melt after evacuation. The HI gas was then passed through more

(1) A review and bibliography of the subject is given in the preceding paper.[2]
(2) E. O. Hornig and J. E. Willard, THIS JOURNAL, **79**, 2429 (1957).
(3) R. H. Schuler and W. H. Hamill, *ibid.*, **74**, 6171 (1952).
(4) R. H. Schuler and R. C. Petry, *ibid.*, **78**, 3954 (1956).
(5) (a) D. L. Bunbury, R. R. Williams, Jr., and W. H. Hamill, abstracts of 128th meeting of the Am. Chem. Soc., Minneapolis, Minn., Sept. 1955, p. 26N; (b) D. L. Bunbury, R. R. Williams, Jr., and W. H. Hamill, THIS JOURNAL, **78**, 6228 (1956).

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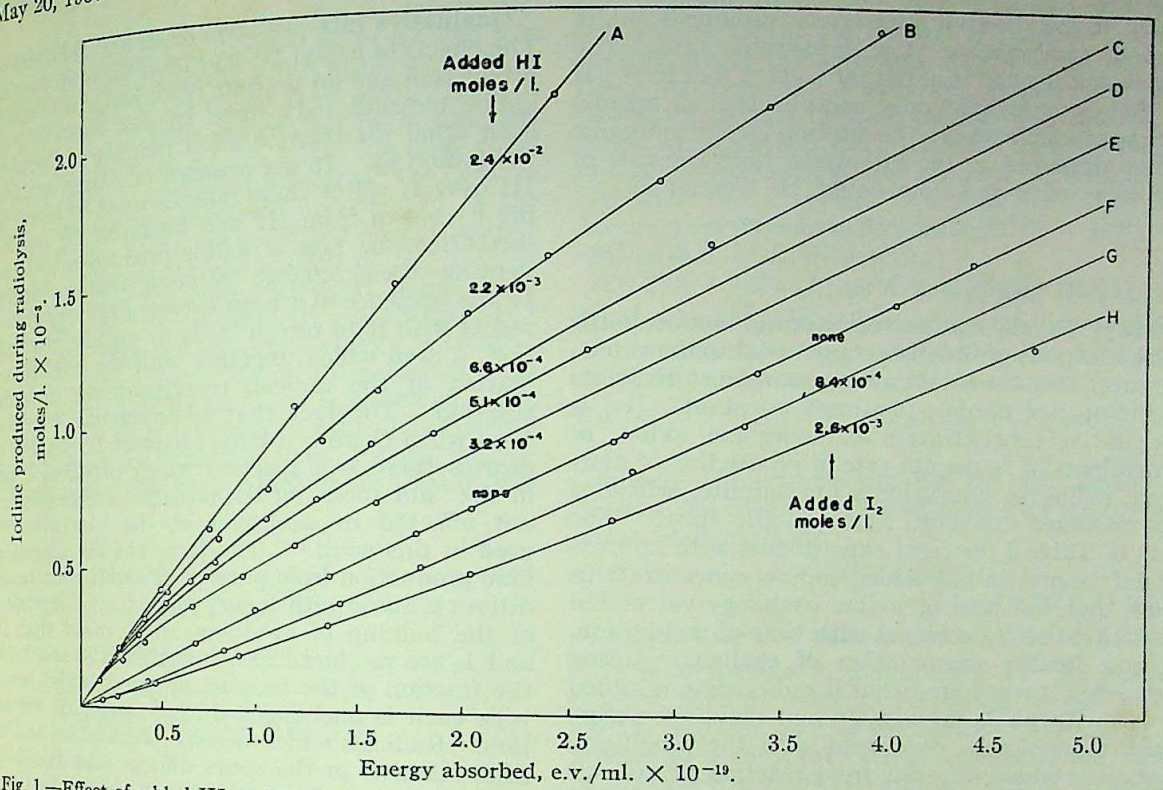

Fig. 1.—Effect of added HI and I_2 on the γ-radiolysis of ethyl iodide. Points are from experimental data[22]; curves are calculated by equation 27.

P_2O_5, supported on glass wool, on the vacuum line. Its pressure was measured with a mercury manometer, which reacted with it only slightly. Fluorocarbon grease was used on the stopcocks; silicone grease appeared to react to give volatile products. To tag the HI, carrier free I^{131} as aqueous iodide was added to the aqueous HI before the P_2O_5. To tag I_2 a similar iodide solution was added to I_2 and the latter distilled through P_2O_5.

Iodine concentrations were determined with a Beckman D.U. spectrophotometer provided with a photomultiplier tube as the detector to increase the sensitivity, and a Baird interference filter to cut out stray light coming through the monochromator. With this equipment it was possible to determine optical densities accurately up to a value of nearly 5 by taking readings against a set of standard solutions having optical densities of 1, 2 and 3. All readings were taken at 4780 Å. (visible absorption maximum; molar extinction coefficient 1280 l./mole cm.). Since the absorption spectrum of iodine in alkyl iodides is temperature sensitive,[6] rough thermostating was provided during later runs by controlling the room temperature at 24 ± 1°.

When it was desired to analyze for radioiodine in the forms of HI, I_2 and organic combination, the reaction cell was broken open while the contents were frozen at liquid air temperature and the reaction mixture was dissolved in CCl_4 and extracted with water to remove HI, and with aqueous sulfite to remove I_2. The water, sulfite and organic solutions were counted, and density corrections were applied when necessary. Solutions treated in this way which had not been irradiated showed about 1% exchange between organic and inorganic forms when opened the same day and 5% exchange when opened after two weeks. All samples were stored in the dark at all times.

Results and Discussion

Evidence for Competitive Reaction Steps.—Three lines of evidence establish the fact that organic radicals born during the radiolysis of degassed ethyl iodide do not all react with I_2 but may undergo a competing reaction which produces rather than consumes inorganic iodine. These are the decrease in iodine yield (G_{I_2}) caused by added iodine, the increase in G_{I_2} caused by added hydrogen iodide, and the increase in exchange yield ($G_{exch.}$) caused by added iodine.

Effect of Added I_2 on G_{I_2}.—The effect of added iodine on the initial rate[7] of iodine production in the radiolysis of ethyl iodide was determined in 14 experiments with initial iodine concentrations ranging from 2.6×10^{-3} to 4.3×10^{-4} M. In all cases the initial rate was, within experimental error, 54% of the rate in the absence of added iodine and increased toward the normal rate as the run continued. This is illustrated by typical results plotted as curves G and H of Fig. 1.

Effect of Added HI on G_{I_2}.—When HI is added to ethyl iodide prior to radiolysis, the effect on the rate of I_2 production is opposite to that produced by added I_2. This is illustrated by the curves above the straight line of Fig. 1. All the curves approach the same maximum rate at zero time and fall off toward the rate for ethyl iodide without additives at longer irradiation times, the falling off being slower the higher the concentration of HI. The initial rate with added HI was 2.55 times the rate without additive and 4.73 times the initial rate with added I_2. Solubility determinations for ethyl iodide solutions showed that about 95% of the HI present in a standard irradiation vessel was always in the liquid phase.

Effect of Added I_2 on Exchange Reaction.—It is known from previous work[1,2] that radioiodine

(6) D. E. Schuler and R. H. Schuler, This Journal, 76, 3092 (1954).

(7) Evaluated by plotting the average rate from time zero to time t *vs.* time of irradiation t and extrapolating to zero t. "Rate" as used in this paper is directly proportional to "G value," *i.e.*, number of molecules which react per 100 e.v. absorbed. For ethyl iodide a rate of 0.0312 μ equivalent per min. per 5-ml. sample equals a G value of 1.

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added to ethyl iodide undergoing radiolysis enters organic combination at a measurable rate. The compound formed is about 90% ethyl iodide.[4,8] If in this exchange the only complication of normal exchange kinetics were the dilution by the inorganic iodine produced in the radiolysis, then the rate of exchange of radioiodine could be treated as

$$-d[I^*]/dt = K([I^*]/([I_0] + [I] \text{ produced})) = K([I^*]/([I_0] + Rt)) \quad (1)$$

$$\log([I^*]/[I_0^*]) = K/R \log([I_0]/([I_0] + Rt)) \quad (2)$$

where $[I^*]$ is the concentration of radioiodine in the inorganic phase (directly proportional to the counting rate), K is the total exchange rate in equivalents of iodine per minute (assumed constant), $[I_0]$ is the initial concentration of inorganic iodine in equivalents, R is the net rate of production of inorganic iodine in equivalents per minute, which is also assumed constant, and t is the time.[9] The data of Table I for eight experiments with approximately equal initial added iodine concentrations show that the rate of iodine exchange calculated from equation 2 decreases with time of irradiation.

In a further examination of exchange during radiolysis, it was found that if radioiodine is added as HI with no I_2 initially present exchange occurs much more slowly, consistent with the conclusion that the exchange results from reaction of radicals with I_2 but not with HI. As I_2 is formed the radioiodine would be expected to equilibrate with it rapidly by HI–I_2 exchange.

TABLE I

RESULTS OF EXCHANGE EXPERIMENTS

Time of irrad., min.	Initial $[I_2]$, equiv. $\times 10^5$	$\frac{I^* \text{ not exchd.}}{I^*_{total}}$	Exchange rate, equiv./min.[b] From eq. 2	From Fig. 2 curve B
4.93[a]	9.46	0.915	0.176	0.148
9.66	8.25	.834	.166	.146
11.2	7.73	.803	.171	.145
22.3[a]	8.04	.712	.144	.140
38.7	8.92	.614	.142	.136
58.0	9.37	.522	.153	.133
74.4	8.45	.455	.141	.131
88.3	8.66	.411	.141	.130

[a] Based on two runs; all others based on one run. [b] Rates given in equivalents $\times 10^6$ per min. per 5-ml. sample volume, at an energy absorption rate of 3.77×10^{17} e.v./ml. min.

Absence of Effect by Added C_2H_4 and $C_2H_4I_2$.—Ethyl iodide containing 0.07 mole/l. of ethylene gave essentially the same G_{I_2} value as ethyl iodide with no additives and showed no back reaction with products to alter the HI/I_2 ratio during two days of standing after irradiation.

Ethylene iodide[10] at a concentration of about 10^{-3} M in ethyl iodide did not affect the rate of I_2 production in the radiolysis. In unirradiated samples of this type, slow decomposition of the $C_2H_4I_2$ occurred over a period of two months, producing iodine. No such build-up ever occurred in irradiated samples of pure C_2H_5I.

(8) L. H. Gevantman and R. R. Williams, Jr., *J. Phys. Chem.*, **56**, 569 (1952).

(9) A similar equation is given by W. H. Hamill and R. H. Schuler, THIS JOURNAL, **73**, 3466 (1951).

(10) Prepared by the method of Semonoff, "Jahresbericht über die Leistungen der reinen und technischen Chemie," *Fortschritte der Chemie*, 1864, p. 483.

Qualitative Interpretation of HI and I_2 Effects.—The effects of added HI and I_2 on the rate of iodine production and on the rate of exchange with radioiodine indicate that these species compete with each other for thermal alkyl radicals produced in the radiolysis. In the presence of a large excess of HI over I_2, all of these radicals react by abstracting hydrogen from HI and liberating $^1/_2$ I_2, thus increasing the rate of iodine production and preventing the exchange reaction from occurring. In the presence of a large excess of I_2 every radical reacts with it to return $^1/_2$ I_2 to organic combination, a step which, together with the original formation of the radical, constitutes the exchange reaction. The fact that I_2 production continues even when there is a large excess of I_2 over HI indicates there is a reaction which produces iodine in the "hot spots" of the radiation tracks which is not affected by additives at the concentrations used in this work.[11] The fact that the rate of iodine production from pure ethyl iodide without additives is linear with energy input (*i.e.*, independent of the buildup of products) must mean that HI and I_2 are produced in a constant ratio and hence the fraction of the radicals produced which reacts with each is unchanged during continued irradiation. Radicals which become thermalized and escape reaction in the spurs diffuse into the body of the solution where they must react with HI or I_2 rather than with other radicals. The concentrations of I_2 and HI produced by even very short irradiations of pure ethyl iodide are far greater than the steady-state radical concentration in the bulk of the solution.[16]

A set of reaction steps adequate to explain the observations discussed above is given below. Underlined formulas indicate excited molecules or radicals. It is assumed that the initial excitation and ionization produced by the high energy electrons resulting from the γ-ray absorption lead to

(11) The main mechanism of energy dissipation by Co^{60} γ-rays (1.1 and 1.3 mev.) is the ejection of Compton electrons (average energy *ca.* 440 kev.) which in turn eject electrons of low energies (*ca.* 100 e.v.) which loose their energy in small regions called "hot spots" or "spurs." These spurs are of the order of 1000 Å. apart. With scavenger concentrations of less than about 10^{-3} mole fraction, the only reactions which occur in the spurs are reactions of excited molecules or radicals or ions with the solvent, or reactions between radicals immediately after thermalization and before diffusion. At concentrations of the order of 10^{-3} mole fraction or somewhat higher, the probability of an additive molecule being in the solvent cage with an excited molecule or radical begins to be great enough so that alterations in hot processes may be observed. This has been illustrated by the effects of halogen scavengers on the organic yields of reactions activated by radiative neutron capture,[12,13] the probability for the case of two particle recombinations processes has been discussed and evaluated,[14,15] and observations of such effects have been made in the photolysis of liquid ethyl iodide.[5b]

(12) S. Goldhaber and J. E. Willard, THIS JOURNAL, **74**, 318 (1952).

(13) G. Levey and J. E. Willard, *ibid.*, **74**, 6161 (1952).

(14) (a) R. M. Noyes, *ibid.*, **77**, 2042 (1955); (b) **78**, 5486 (1956).

(15) J. C. Roy, R. R. Williams, Jr., and W. H. Hamill, *ibid.*, **76**, 3274 (1954).

(16) The fact that the initial increase in rate of I_2 production caused by added HI is independent of the concentration of added HI and that the initial decrease in rate of I_2 production caused by added I_2 is independent of the concentration of added I_2 over the range tested (Fig. 1) indicates that, within the sensitivity of the experiments, each of these additives affects the rate only by competition with the other for free radicals and not by interfering with some independent process such as the combination of radicals with other radicals or atoms. The latter process, which is a sensitive function of scavenger concentration, has been observed in other systems.[12,13]

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excited ethyl iodide molecules (step 3) which may decompose by step 4 to produce HI or by step 5 to produce hot ethyl radicals which either react by 6 to liberate $^1/_2$ I_2 or are thermalized by 7. Ionic or ion-molecule reactions which led to a constant rate of production of HI, $^1/_2$ I_2 and thermal ethyl radicals could account equally well for the data on the thermal radical reactions investigated in the present work. The reactions listed do not include C-C bond cleavage or elimination of H_2, both of which are minor processes.[4] If C–H bond cleavage occurs, the H atoms probably react with C_2H_5I to form HI, since the activation energy is small[17a] and they must undergo 10^3 or 10^4 collisions with solvent before meeting an HI or I_2 molecule. The recombination of ethyl radicals with iodine atoms in the spurs is not included, since it is not experimentally observable by the techniques used in this work.

Reactions in spurs

$$C_2H_5I \rightsquigarrow \underline{C_2H_5I} \quad (3)$$

$$\underline{C_2H_5I} \longrightarrow C_2H_4 + HI \quad (4)$$

$$\underline{C_2H_5I} \longrightarrow \underline{C_2H_5\cdot} + I\cdot \quad (5)$$

$$\underline{C_2H_5\cdot} + C_2H_5I \longrightarrow C_2H_4 + C_2H_6 + I\cdot \quad (6)$$

$$\underline{C_2H_5\cdot} + M \longrightarrow C_2H_5\cdot + M \quad (7)$$

Thermal radical reactions

$$I\cdot + I\cdot \longrightarrow I_2 \quad (8)$$

$$C_2H_5\cdot + I_2 \xrightarrow{k_{I_2}} C_2H_5I + I\cdot \quad (9)$$

$$C_2H_5\cdot + HI \xrightarrow{k_{HI}} C_2H_6 + I\cdot \quad (10)$$

Quantitative Interpretation of HI and I_2 Effects.—On the basis of the above data and reaction scheme, it is possible to derive equations which allow the prediction of the rates of I_2 production, HI production and exchange for any concentration of added HI or I_2. For this purpose we shall let A = rate of production of thermal alkyl radicals which escape from the spurs; B = total[18] rate of production of I_2 by hot processes (reactions 5 and 6); and C = the rate of HI production *via* reaction 4. A, B and C are constants if the energy absorbed per cc. per sec. is constant. Then setting the rate of thermal radical production equal to the rate of removal by reactions 9 and 10

$$A = k_{I_2}[I_2][C_2H_5] + k_{HI}[HI][C_2H_5] = [C_2H_5](k_{I_2}[I_2] + k_{HI}[HI]) \quad (11)$$

and

$$[C_2H_5] = A/(k_{I_2}[I_2] + k_{HI}[HI]) \quad (12)$$

The C_2H_5 radicals do not become homogeneously distributed through the solution but in general react with HI or I_2 before they have proceeded far from the radiation tracks.[13] Therefore, the $[C_2H_5]$ term does not represent a homogeneous steady-state concentration in the usual sense but nevertheless does represent the number of radicals per unit volume, when volumes large compared to the distance between the tracks are considered. The treatment is valid because the fate of a radical depends solely on the $[HI]/[I_2]$ ratio and not on the radical concentration, because radical–radical reactions are not involved.[13] The rate of iodine production may then be expressed as

$$d[I_2]/dt = B - (k_{I_2}/2)([I_2][C_2H_5]) + (k_{HI}/2)([HI][C_2H_5]) \quad (13)$$

The factor of $^1/_2$ is introduced by the use of molar concentrations. After substituting the expression for $[C_2H_5]$ and rearranging this becomes

$$d[I_2]/dt = B + (A/2) - A[[I_2]/([I_2] + (k_{HI}/k_{I_2})[HI])] \quad (14)$$

Similarly the expressions for the production of HI and the rate of return of iodine to the organic phase (exchange) are

$$d[HI]/dt = C - A + A[[I_2]/([I_2] + (k_{HI}/k_{I_2})[HI])] \quad (15)$$

$$d[C_2H_5I]_{exch}/dt = A[I_2]/([I_2] + (k_{HI}/k_{I_2})[HI]) \quad (16)$$

It is a necessary consequence of the stoichiometry of the system, according to our mechanism, that the sum of the moles of HI and I_2 increases at a constant rate regardless of the values of the rate constants k_{HI} and k_{I_2}. Thus, on adding equations 14 and 15 one obtains

$$d([HI] + [I_2])/dt = C + B - A/2 \quad (17)$$

or

$$([HI] + [I_2]) - ([HI] + [I_2])_0 = (C + B - A/2)t \quad (18)$$

The experimental data on the initial rates of I_2 production with added I_2 (minimum rate),[19] with added HI (maximum rate), and without additives may be used to evaluate A and B. These rates expressed as microequivalents of product per 5-ml. sample per min., at an energy absorption rate of 3.77×10^{17} e.v./ml. min., are: without additives, 0.0654; maximum, 0.1670; minimum, 0.0353. From equation 14 it may be seen that when HI is in large excess

$$d[I_2]/dt = B + {}^1/_2A = 0.1670 \quad (19)$$

and when I_2 is in large excess

$$d[I_2]/dt = B - {}^1/_2A = 0.0353 \quad (20)$$

These equations yield A = 0.1317 μequivalent/min. as the rate of thermal radical production and B = 0.1012 μequivalent/min. as the total rate of iodine production by hot processes, including that which normally back-reacts *via* reaction 9.

The constant C (*i.e.*, the total rate of HI formation including that which back reacts) can be evaluated if it is assumed that the rate constants

(17) E. W. R. Steacie, "Atomic and Free Radical Reactions," Reinhold Publ. Corp., New York, N. Y., 1954, (a) p. 733; (b) pp. 742-743.

(18) The *total* rate of I_2 production by hot processes is the rate of reaction 5 and any hot processes such as (6) which ensue. It includes the rate of production of I_2 which subsequently returns to organic combination by reaction with thermalized ethyl or other radicals. It does not include the formation of I_2 *via* reaction 10. The *net* rate of I_2 production by hot processes is the "total" rate minus that which back reacts with thermal radicals in the presence of excess I_2 scavenger.

(19) If the only possible steps in the radiolysis were those represented by equations 3 through 10, the minimum rate of iodine production observed with added I_2 would be the rate of the sequence of hot reactions 5, 6 since the sequence 5, 7, 9 does not affect I_2 concentration. If, however, any ethyl iodide molecules are dissociated by steps such as $C_2H_5I \rightarrow CH_3 + CH_2I$ or $C_2H_5I \rightarrow C_2H_4I + H$, rather by rupture of a C–I bond, and the fragments then react with I_2, the sequence will consume I_2. The minimum rate is therefore the rate of the sequence 5, 6 minus the rates of any sequences of the latter type. Such sequences do not alter the quantitative treatment presented unless the assumption made below that $k_{I_2} = k_{HI}$ is not valid for them; at most the effect will be small since about 90% of the radicals produced are ethyl radicals.

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for reactions 9 and 10 (*i.e.*, k_{I_2} and k_{HI}) are equal. This assumption is not unreasonable since the activation energy for each of these processes is near zero[17b] and there are many collisions per encounter in the liquid phase,[20] so that both HI and I_2 may react with ethyl radicals on nearly every encounter. Using this assumption, the following relation, derived from equations 14, 19 and 20, may be evaluated

$$\left(\frac{[HI]}{[I_2]}\right)_{Normal} = \frac{k_{I_2}(\text{norm. rate} - \text{min. rate})}{k_{HI}(\text{max. rate} - \text{min. rate})} = 0.296 \quad (21)$$

where the ratio applies to the radiolysis of initially pure ethyl iodide, and the normal, maximum, and minimum rates refer to the radiolysis with no additives, with excess HI, and with excess I_2, respectively. Multiplying this ratio by the iodine production rate for ethyl iodide with no additives gives

$$d[HI]/dt = ([HI]/[I_2])d[I_2]/dt = 0.296 \times 0.0654 = 0.0193\ \mu\text{mole/min.} \quad (22)$$

Substitution of the value for the HI production rate into equation 15 together with the value of the ratio $[I_2]/([I_2] + [HI])$ for a run with no additives yields the value of C as 0.0493 μmole/minute.

The differential equations for the various rates can now be written

$$d[I_2]/dt = 0.1671 + 0.1317\ [I_2]/([I_2] + [HI]) \quad (23)$$

$$d[HI]/dt = -0.0824 + 0.1317[I_2]/([I_2] + [HI]) \quad (24)$$

$$d[HI + I_2]/dt = 0.0847 \quad (25)$$

$$d[C_2H_5I]_{exch}/dt = 0.1317\ [I_2]/([I_2] + [HI]) \quad (26)$$

The approximation $k_{I_2}/k_{HI} = 1$ has been assumed in all the above equations except (25). The equations can be integrated only when this assumption is made; the resulting equations are[21]

$$[I_2] = 0.0654t + 0.772([HI]_0 + [I_2]_0) + (0.228[I_2]_0 - 0.772[HI]_0)\left(1 + \frac{0.0847t}{[HI]_0 + [I_2]_0}\right)^{-1.55} \quad (27)$$

$$[HI] = 0.0193t + 0.228([HI]_0 + [I_2]_0) + (0.772[HI]_0 - 0.228[I_2]_0)\left(1 + \frac{0.0847t}{[HI]_0 + [I_2]_0}\right)^{-1.55} \quad (28)$$

$$[HI] + [I_2] = 0.0847t + [HI]_0 + [I_2]_0 \quad (29)$$

$$[C_2H_5I]_{exch} = 0.1017t + (0.228[I_2]_0 - 0.772[HI]_0)\left(1 + \frac{0.0847t}{[HI]_0 + [I_2]_0}\right)^{-1.55} \quad (30)$$

The last equation refers to the quantity of ethyl iodide re-formed by the back reaction, a process which can be observed only when radioiodine is present.

Comparison of Predicted Rates of I_2 and HI Production with Experimental Results.—From Fig. 1 it can be seen that values for the iodine concentration as a function of time of irradiation calculated from equation 27 agree well with the experimentally determined values for all initial concentrations of HI and I_2 tested.[22]

The rate of production of HI during radiolysis is a good test of the assumptions in deriving equations 27–30 since experimental data on HI production were not used in the derivation. In two experiments on ethyl iodide without additives, the $[HI]/[I_2]$ ratio was determined after irradiation by adding radioiodine prior to extraction in the manner described above for the exchange experiments. The values obtained for the HI production rate were 0.018 and 0.019 μmole/min. which can be compared with the predicted value of 0.0193 μmole/min.

These experimental results can be used to solve equation 21 for k_{I_2}/k_{HI}; the values obtained are 0.94 and 0.99. The difference between these values and 0.34 recently reported by Bunbury, Williams and Hamill[5b] for the same radical reactions in the photolysis of C_2H_5I is probably greater than our experimental error. The agreement of the iodine production and exchange rates predicted by equation 27–30 with the experimental results also supports the validity of the conclusion that $k_{I_2}/k_{HI} \cong 1$.

Analysis for HI during the exchange experiments shown in Table I indicated an average HI production rate of 0.037 ± 0.009 μmole/min. Under the same conditions the predicted values range from 0.046 μmole/min. at 5 min. to 0.031 μmole/min. at 60 min., giving an average value of about 0.038. The experimental data do not show any clear trend, since the trend expected is of the same order of magnitude as the experimental error. The reliability of these latter experiments is not good enough to consider the results as proof of the assumption that $k_{I_2} = k_{HI}$, but the results are consistent with this conclusion.

Comparison of Predicted Rate of Exchange with Experimental Results.—The rate of transfer of initially added radioiodine from inorganic to organic form may be expressed as $-d[I^*]/dt = (d[C_2H_5I]_{exch}/dt)([I^*]/([HI] + 2[I_2]))$ where $d[I^*]/dt$ is the rate at which equivalents of radioiodine are removed from the inorganic phase, $[I^*]/([HI] + 2[I_2])$ is the ratio of equivalents of ratioiodine to total iodine in the inorganic phase (the probability that a given iodine atom encountered by an alkyl radical is radioactive) and $d[C_2H_5I]_{exch}/dt$ is the total rate of reaction of thermalized ethyl radicals with I_2 from the bulk of the medium. Since $[I^*]$ occurs on both sides of the equation the conversion factor from concentration to counting rate cancels, and $[I^*]$ may be taken as the counting rate of the inorganic phase. It is possible to substitute for these quantities using equation 26 for the total rate of re-formation of ethyl iodide and the integrated equations 27 and

(20) E. Rabinowitch, *Trans. Faraday Soc.*, **33**, 1225 (1932).

(21) Integrate eq. 25 first and substitute in 23 and 24 giving equations in the variables $[I_2]$ and t only; integrate 23 and 24. Substitute the expressions for $[I_2]$ and $[I_2] + [HI]$ from 23 and 25, respectively, into 26 and integrate.

(22) The values for the initial I_2 concentration used in the calculation of curves G and H of Fig. 1 were determined by spectrophotometric measurement. The value of the HI concentration used for curve D was accurately determined by using radioiodine of known specific activity. In the experiment shown by curve A, there was a sufficient excess of HI over I_2 to give the maximum rate for the entire experiment, hence knowledge of the exact concentration is not critical. The experimental values of HI added for runs B, C and E were less accurately known because they depended on measuring the PV product of about 10^{-5} mole of HI and transferring it quantitatively through the vacuum line. For these cases the values for the initial HI concentration used with equation 27 for the calculations were 10 to 30% different from the experimental values, a choice being made which gave a fit with the data for iodine production. As a result curves F, G and I are only a semi quantitative verification of the mechanism.

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TABLE II

G-VALUES FOR THE RADIOLYSIS OF ALKYL IODIDES WITH AND WITHOUT ADDED HI AND I_2

Iodide	No. of β-H atoms	G_I[a] for I atom production: Normal[b]	Max. (HI added)	Min.[c] (I_2 added)	½(max. − min.),[d] G for thermal free radical production	½(max. + min.), G for C–I bond cleavage[e]	Predicted ratio of [HI]/[I_2][f]	G_I for thermal contr. to normal rate[g]
Methyl	0	2.54	11.74	2.16	4.79	6.96	0.041	0.38
Ethyl	3	4.19	10.68	2.25	4.22	6.46	.296	1.94
n-Propyl	2	3.22	9.82	1.72	4.05	5.76	.227	1.50
Isopropyl	6	6.20	9.48	3.36	3.06	6.42	.866	2.84
n-Butyl	2	3.26	9.30	1.75	3.78	5.52	.250	1.51
Isobutyl	1	1.86	8.88	1.43	3.72	5.16	.061	0.43
sec-Butyl	5	5.00	9.34	2.28	3.53	5.80	.627	2.72

[a] ½ I_2 produced per 100 e.v. absorbed. [b] For alkyl iodides with no HI or I_2 added prior to irradiation. Some of these values are taken from reference 1. [c] Net rate of iodine production by hot processes.[18] [d] The factor ½ is required to convert from G_I to $G_{free\ radical}$ because in the presence of excess HI two iodine atoms are formed for each thermal radical, as indicated by equations 5 and 10 of the text. [e] Total rate of production of iodine by hot processes.[18] [f] Given by $(G_{norm} - G_{min})/(G_{max} - G_{min})$. [g] This column is the value of column 3 minus column 5 and represents the G value for the reaction of thermal radicals with HI in the absence of initially added scavengers.

28 for the concentrations of HI and I_2 as a function of the time of radiolysis, but the equation obtained cannot be integrated. (Iodine must be added initially to study the exchange, hence the HI, I_2 and total exchange rates will all vary with the time of irradiation.) By assuming that the various rates are constant over short periods of irradiation and using iterative calculations, the fractional exchange which will be observed over longer periods may be predicted. This calculation was performed using an initial iodine concentration of 8.4 μmoles for comparison with the data in Table I. The results of the calculation are shown by curve A of Fig. 2. The predicted exchange rate averaged over the first 5 minutes was 0.128 and over the first 60 minutes 0.113 μmole/min. The experimental points of curve B of Fig. 2 show that exchange occurred considerably faster than predicted.

The solid line of curve B, which fits the experimental data, was obtained in a semi-empirical manner as follows: the iterative calculations described above were repeated, assuming that there is a constant component to the exchange rate of 0.020 μequivalents/min. which is independent of HI or I_2 concentration, *i.e.*, which is the result of exchange by a "hot" process. Thus the rate over the first 5 minutes was taken to be 0.148 and over the first 60 minutes 0.133 μequivalent/min.; values are given in Table I for comparison with the earlier calculations. It is believed that these numbers represent better values for experimental exchange rates than those calculated from equation 2. The short irradiation values based on the latter are unduly influenced by exchange induced in preparing and analyzing the samples (about 0.5 to 1%) and the long irradiation values are subject to error because equation 2 does not take into account the competition of HI with I_2 for C_2H_5 radicals.

There is no obvious reason why the exchange rate predicted by equation 26 (curve A, Fig. 2) should be in error by as much as 20% unless some step which contributes to exchange but does not affect HI or I_2 concentrations has been omitted from the postulated mechanism. This point of view is strengthened by the fact that the derived equations predict the iodine production rate during the same set of exchange experiments within 1 or 2%. Various speculations as to the basis for the discrepancy are possible. For example, it might be explained if excited ethyl iodide molecules with too little energy to produce radicals have a much higher "rate constant" for undergoing exchange with I_2 than for degradation of the energy in non-reactive collisions with other ethyl iodide molecules.

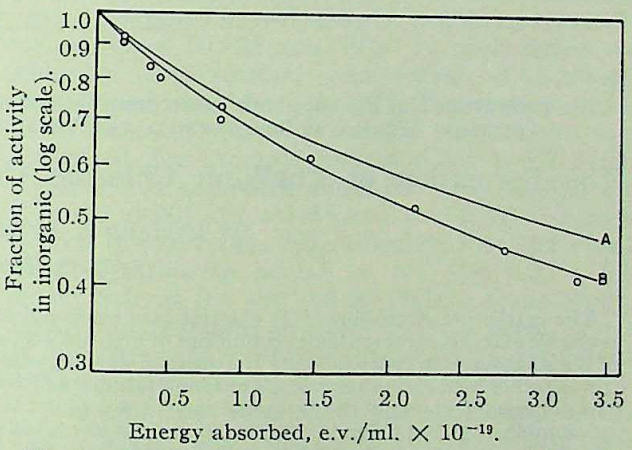

Fig. 2.—Exchange of radioiodine during the radiolysis of ethyl iodide solutions which initially contained about 8.4 × 10^{-4} molar iodine. Points are from experimental data. Curve A was calculated by equation 30; curve B was calculated by a semi-empirical method described in the text.

This hypothesis is attractive because the high energy electrons in the system undoubtedly dissipate much of their energy in producing low lying excited states of ethyl iodide. It might predict a concentration dependence but this would probably be difficult to observe because the excess exchange in only a small fraction of the total exchange yield. If thermal ethyl radicals can abstract I as well as H from HI, the rate of exchange in the presence of HI would be higher than predicted but the increase would be expected to be a function of the [HI]/[I_2] ratio.

Effect of Added HI and I_2 on the Radiolysis of Other Alkyl Iodides.—The data of Table II show that the influence of added HI and I_2 on the radiolysis of six additional alkyl iodides is qualitatively similar to the effect on ethyl iodide but quantitatively different.

Of particular interest is the fact that added iodine appears to reduce the iodine yield from methyl

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iodide, since this implies that HI is a product of the radiolysis. The effect seems to be greater than can be attributed to experimental error.

According to the discussions above the rate of iodine production in ethyl iodide and presumably in the other alkyl iodides must depend on: (1) the net rate of I_2 production in the spurs; (2) the rate of production of thermal radicals in the spurs; (3) the ratio of HI to I_2 production. The question may be raised as to which of these factors is responsible for the fact that G_{I_2} with no added scavengers increases with increasing number of β-hydrogens in the molecule.[2,23] From Table II it may be seen that the effect is not attributable to the rate of thermal radical production (columns 2 and 6), that the net rate of I_2 production in the spurs does increase with increase in the β-hydrogen content, except in going from C_2H_5I to *sec*-C_4H_9I, (column 5) and that the ratio of thermal radical reaction with HI to reaction with I_2 also increases (column 7). The G value for reaction of thermal radicals with HI shows the smoothest increase as a function of the number of β-hydrogens in the molecule (column 8). Column 7 gives the total rate at which iodine is produced in the spurs by reactions 5 and 6, including the iodine which back reacts via the exchange reaction 9. As the carbon chain length of the alkyl iodide increases the number of bonds in the molecule other than the C–I bond increases. As a result of this the rate for C–I bond rupture might be expected to decrease; this was found experimentally. It can also be seen that the secondary iodides (isopropyl and *sec*-butyl) show slightly higher rates of C–I bond rupture than the corresponding primary compounds, which might be expected on the basis of bond strengths.

Acknowledgment.—The work of this paper was supported in part by the University Research Committee with funds made available by the Wisconsin Alumni Research Foundation and in part by the United States Atomic Energy Commission. During part of the work one of the authors (R.J.H.) held a fellowship given by the Monsanto Chemical Company.

MADISON, WISCONSIN

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[CONTRIBUTION NO. 503 FROM THE INSTITUTE FOR ATOMIC RESEARCH AND DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE. WORK WAS PERFORMED IN THE AMES LABORATORY OF THE U. S. ATOMIC ENERGY COMMISSION]

The Formation of Thallium Chloride Complexes and their Extraction into Ether[1]

BY DONALD L. HORROCKS AND A. F. VOIGT

RECEIVED NOVEMBER 12, 1956

The extraction of thallium(III) chloride into isopropyl ether has been studied using tracer techniques with Tl^{204}. Appreciable extraction occurs under conditions of high acidity, and the extraction is markedly dependent upon the ionic strength of the solution. In order to study the effect of varying acidity and chloride concentration over a wide range, the study was run at rather high ionic strength. The temperature coefficient and heat of extraction were determined in the range of 20–30°. The empirical formula of the extracted species was found to be $HTlCl_4$ and a higher complex, H_2TlCl_5, was found not to be extractable. At low chloride concentrations and low acidity the extraction cannot be explained completely by this mechanism and it is postulated either that $TlCl_3$ extracts or that $HTlCl_4$ ionizes in ether under these conditions.

The extraction of thallium(III) from hydrohalic acids into ether has been reported by several investigators.[2–6] It has been developed into an analytical method for separating thallium from most elements, except iron(III), gallium(III), gold(III), and some others. Aside from noting the optimum conditions for complete extraction of the thallium, no investigations of the nature of the extraction process have been made. This research was undertaken to obtain information about the thallium compound present in the ether phase, the dependence of the extraction upon the concentrations of acid and chloride, the temperature coefficient of the extraction and the extraction equilibrium constant. These should be of interest in comparison with the analogous Fe(III) which has been shown to extract into ether as $HFeCl_4$.[7]

Preliminary investigations of the extraction of thallium(III) from $HClO_4$–LiCl–$LiClO_4$ solutions into isopropyl ether showed appreciable extraction only at relatively high acid and chloride concentrations and also showed that the extraction depends very markedly upon the ionic strength. It was thus necessary to perform the investigations in solutions of constant, high ionic strength. On the other hand the sensitivity of the tracer method made it possible to do the experiments at low concentration, about 10^{-3} M, of thallium.

The results of these conditions was that the determination of the activity coefficients of the various ionic species was difficult, but not as difficult as it would have been at higher thallium concentrations. In estimating activity coefficients it was necessary to make some assumptions which may not be completely valid.

The distribution of thallium between phases was measured by tracer techniques over a range of

(1) Based in part on a thesis presented by Donald L. Horrocks to Iowa State College in partial fulfillment of the requirements for the Ph.D. degree, November, 1955.

(2) Rothe, *Stahl und Eisen*, **12**, 1052 (1892); **13**, 333 (1893).

(3) (a) A. A. Noyes, W. C. Bray and E. B. Spear, THIS JOURNAL, **30**, 489, 515, 559 (1908); (b) E. H. Swift, *ibid.*, **46**, 2375 (1924).

(4) I. Wada and R. Ishii, *Bull. Inst. Phys. Chem. Res. Tokyo*, **13**, 264 (1934); [*C. A.*, **28**, 3334 (1934)].

(5) H. M. Irving, *Quart. Rev.*, **5**, 200 (1951).

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TABLE I

EMPIRICAL FORMULA OF SPECIES IN ETHER PHASE

Initial conditions	[Tl] × 10⁴, moles/l.	[Cl⁻] × 10³, moles/l.	[H⁺] × 10⁴, moles/l.	Cl⁻/Tl	H⁺/Tl
3.0 *M* total concn., 0.10 *M* LiCl, 0.4 *M* $HClO_4$	6.66	2.75	5.7	4.13	0.86
3.0 *M* total concn., 0.4 *M* LiCl, 1.6 *M* $HClO_4$	8.63	3.8	8.6	4.39	1.00
2.0 *M* total concn., 1.0 *M* LiCl, 1.0 *M* $HClO_4$	5.75	2.70	5.9	4.69	1.02

chloride ion, acid and total salt concentrations. In the interpretation of the data, it was found advantageous to use formation constants determined by Benoit[8] for the various thallium(III) chloride complexes up to $TlCl_4^-$. Experimentally, this species, in the form of the acid, was essentially the only thallium compound found in the ether phase. Hence the distribution could be represented by a constant

$$K = \frac{(HTlCl_4)_e}{(H^+)_w(TlCl_4^-)_w} = \frac{[Tl_e]\gamma^e HTlCl_4}{(H^+)(Tl^{+3})(Cl^-)^4 K_4} \quad (1)$$

in which ( ) represents activity, [ ] concentration, $K_4 = (TlCl_4^-)/(Tl^{+3})(Cl^-)^4$ and $\gamma^e HTlCl_4$ is the activity coefficient of $HTlCl_4$ in ether. This extraction coefficient, K, can be expressed in terms of the measured distribution ratio, $K_T = [Tl]_e/[Tl]_w$ by considering all of the aqueous chloride complexes of thallium, their formation constants of the form

$$K_n = \frac{(TlCl_n^{3-n})}{(Tl^{+3})(Cl^-)^n} \quad (2)$$

and the appropriate activity coefficients. The equation obtained is

$$K = K_T \frac{\gamma^e HTlCl_4}{(H^+)(Cl^-)^4 K_4}\left[\sum_{n=0}^{5} K_n \gamma^n_{Cl^-}[Cl^-]^n/\gamma TlCl_n^{3-n}\right] \quad (3)$$

in which K_0 is set equal to 1. Hydrolyzed forms of thallium(III) were assumed to be unimportant at the acid concentrations used. Several series of extractions were made, each one at constant acidity and ionic strength, but with varying chloride concentration. Since the concentration of the ethereal thallium species was always small its activity coefficient was assumed constant. Thus a new extraction constant could be defined, as

$$K' = \frac{K(H^+)}{\gamma^e HTlCl_4} = \frac{K_T}{(Cl^-)^4 K_4}\left[\sum_{n=0}^{5} K_n \gamma^n_{Cl^-}[Cl^-]^n/\gamma TlCl_n^{3-n}\right] \quad (4)$$

Materials.—Thallium(I) nitrate, obtained by dissolving thallium metal in HNO_3, was oxidized to thallium(III) by aqua regia. The thallium(III) chloride was extracted into ether from a 6 to 7 *N* HCl solution and precipitated as Tl-$(OH)_3$ by shaking with a dilute NaOH solution. The Tl-$(OH)_3$ was purified by repeated solution in 6 to 7 *N* HCl, extraction into ether and reprecipitation as $Tl(OH)_3$. The $Tl^{204}NO_3$ obtained from the Oak Ridge National Laboratory, Oak Ridge, Tennessee, was purified in this same manner. A desired amount of the purified active and inactive Tl_2O_3 was dissolved in excess $HClO_4$ and the resulting solution standardized, the thallium determined as Tl_2CrO_4 as reported by Kleinberg[9] and the excess $HClO_4$ by titration with standard base, allowing for the titration of the thallium. The solution was 0.0106 *M* $Tl(ClO_4)_3$ in 4.05 *M* $HClO_4$. The chloride and hydrogen ion concentrations were varied and the ionic strength was maintained constant by the use of standard solutions of LiCl, $HClO_4$ and $LiClO_4$.

(8) R. Benoit, *Bull. soc. chim. France*, 518 (1949).

(9) J. Kleinberg, "Collected Radiochemical Procedures," A.E.C. Document LA-1721, Los Alamos Scientific Laboratory, Public

Technique.—Aqueous solutions of the desired thallium(III), Cl^- and H^+ concentrations and ionic strength were extracted with equal volumes of isopropyl ether by mixing in a constant temperature bath with an automatic shaker. The temperature was 30° except for the study of temperature dependence. The solutions were shaken for 40 minutes and then allowed to separate for 30 minutes before the samples were removed with pipets. The ether samples were evaporated into 2 to 3 ml. of water. Analyses were made for acid, chloride and thallium. The acid and chloride analyses were done volumetrically, the thallium analyses radiochemically, with the addition of known amounts of carrier $Tl(NO_3)_3$ in HNO_3 to facilitate precipitation and filtration. The thallium, precipitated as Tl_2CrO_4, was filtered onto small paper discs, washed with alcohol and dried at 110°. The samples were covered with 3.3 mg./cm.² cellophane discs and mounted on cardboard backing for counting.

Discussion

The temperature dependence of the extraction was determined in two series of extractions at temperatures of 20, 25 and 30°. In each series the chloride concentration was varied at constant acidity and ionic strength. The distribution ratio, K_T, decreased markedly as the temperature was increased, for example from a solution 0.2 *M* in LiCl, 0.6 *M* in $HClO_4$ and 1.53 *M* in $LiClO_4$, K_T was 4.0 at 20°, 2.5 at 25° and 1.5 at 30°. Values of ΔH of extraction were calculated by the Van't Hoff equation to be 9.5 ± 0.7 and 9.9 ± 0.3 kcal./mole at 0.4 and 0.6 *M* $HClO_4$, respectively, at an ionic strength of 2.33. Each of these values is the average of six or more calculations at different chloride concentrations.

The empirical formula of the compound in the ether phase was determined by analyzing this phase for chloride, ionizable hydrogen and thallium. Results in Table I have been corrected for the extraction of chloride and acid under identical conditions except for the absence of thallium. The high values observed for the Cl^-/Tl ratios are due principally to the small amounts present. From these data, it was assumed that the empirical formula of the ethereal species was $HTlCl_4$.

The observed distribution ratio, K_T, decreased as the chloride concentration was increased. Data at an ionic strength of 3.0 are shown in Fig. 1. Similar results were obtained at an ionic strength of 2.0. A reasonable explanation of this effect is the formation of a non-extractable species, such as $TlCl_5^=$. Since it was not possible to obtain sufficient data at low chloride concentrations to evaluate the constants for the mono to tetra-chloro complexes independently, the values of Benoit[8] were used. His determinations of these constants, defined as in equation 2 are for K_1, 1.38 × 10⁸; K_2, 4 × 10¹³; K_3, 6 × 10¹⁵; and K_4, 10¹⁸. Equation 4 was used with these constants in successive approximations to determine a value of K_5 which would give the best evaluation of K'. This treatment gave 2.96 × 10¹⁷ for K_5. In the region of very high ionic strength, about 5, the formation of

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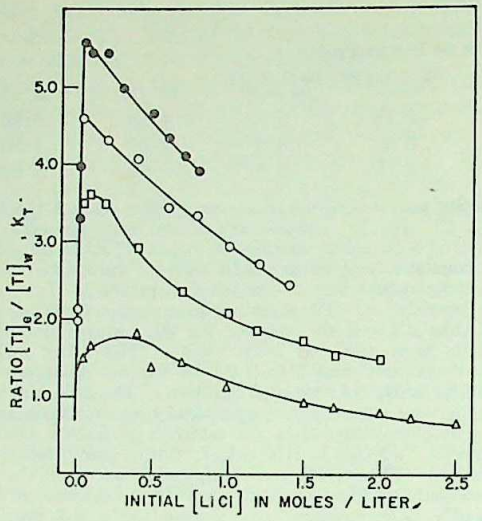

Fig. 1.—Extraction at total salt and acid concentration of 3.0 *M*: ●, 2.2 *M* $HClO_4$; ○, 1.6 *M* $HClO_4$; □, 1.0 *M* $HClO_4$; △, 0.4 *M* $HClO_4$.

three phases was observed which has been described in the cases of $FeCl_3$ and $GaCl_3$ extraction.[10-12] The three phases are a "light ether," a "heavy ether" and an aqueous phase with 90–96% of the thallium in the heavy ether phase. Repetition of these experiments in the absence of thallium gave rise to the same phenomenon so that under these conditions it is caused by the high salt and acid concentration and not by the heavy metal complexes. In the case of solutions 4 *M* in $HClO_4$ and 1 *M* in LiCl plus $LiClO_4$, large amounts of the acid were found in the heavy ether layer. The explanation by Nachtrieb and Fryxell for the similar phenomenon in $FeCl_3$ extraction was that the acid H_2FeCl_5 was forming ethereal polymers by multiple hydrogen bonds. In the present case $HClO_4$ may be replacing the H_2FeCl_5 in such a polymer with ether molecules.

The difficulties of interpretation which were brought about by the three phase behavior at very high ionic strength made it necessary to conduct the more detailed study of the extraction at lower ionic strength. The total salt plus acid concentrations were kept at 2.0 and 3.0 *M* while the chloride and acid concentrations were varied. Equation 4 was used to calculate K' using the Debye–Hückel equation[13] for the estimation of the activity co-

$$-\log \gamma_i = \frac{AZ_i^2\sqrt{\mu}}{1 + Ba_i\sqrt{\mu}}$$

efficients of the thallium species. As the various forms of thallium(III) are large ions, the product $B \times a_i$ was taken as 3 for all species. The activity coefficient of the chloride ion was assumed to be equal to the mean activity coefficient of HCl under the same conditions; values of 0.993 at 2.0 *M* HCl and 1.288 at 3.0 *M* HCl at 30° were used. The calculated values of K' are shown in Figs. 2 and 3.

The constant values of K' at all but the lowest chloride concentrations indicate that the description of the extraction in terms of extractable $HTlCl_4$ and non-extractable H_2TlCl_5 is valid. The sharp increase in the values of K' at low chloride

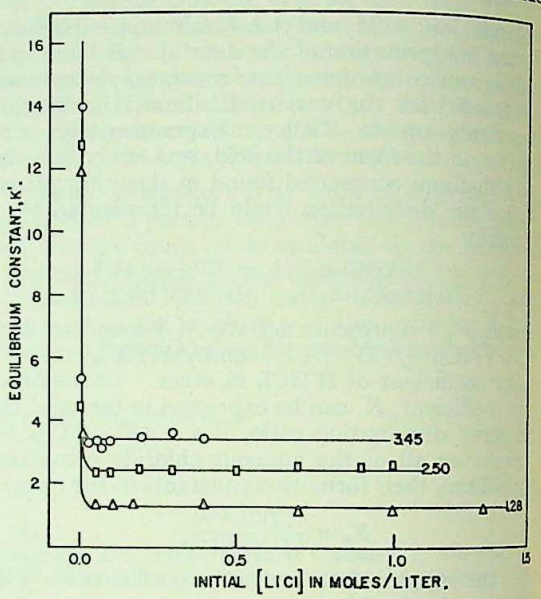

Fig. 2.—Dependence of K' upon [LiCl] at constant acid concentration for ionic strength equal to 2.0: ○, 1.6 *M* $HClO_4$; □, 1.0 *M* $HClO_4$; △, 0.4 *M* $HClO_4$.

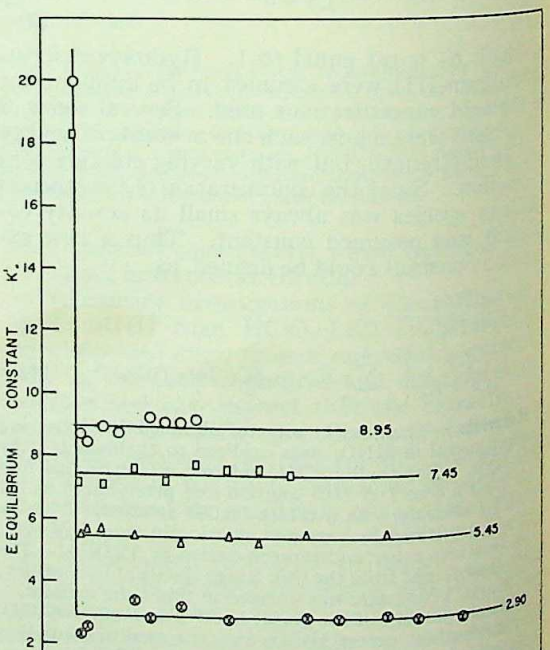

Fig. 3.—Dependence of K' upon [LiCl] at constant acid concentration for ionic strength equal to 3.0: ○, 2.2 *M* $HClO_4$; □, 1.6 *M* $HClO_4$; △, 1.0 *M* $HClO_4$; ⊘, 0.4 *M* $HClO_4$.

(10) R. W. Dodson, G. J. Forney and E. H. Swift, THIS JOURNAL, **58**, 2573 (1936).

(11) R. J. Myers and D. E. Metzler, *ibid.*, **72**, 3772 (1950).

(12) N. H. Nachtrieb and R. E. Fryxell, *ibid.*, **71**, 4035 (1949); **74**, 897 (1952).

(13) I. M. Klotz, "Chemical Thermodynamics," Prentice-Hall, New York, N. Y., 1950, p. 329.

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concentrations is attributed to one or both of two factors, the co-extraction of $TlCl_3$ or the ionization of $HTlCl_4$ in highly dilute ether solutions.

The directly measured extraction coefficient, K_T, showed a first-order dependence on the concentration of hydrogen ion. The quantity K', involving formation constants and activity coefficients, also showed such a relationship when plotted against the $HClO_4$ concentration as in Fig. 4. The linear acid dependence agrees with the idea that $HTlCl_4$ is the extracted species and in addition indicates that the activity coefficient of the hydrogen ion is constant at a given ionic strength.

The acid dependence is expressed in equations 1 and 4 and if these truly represent the data one would expect the curves of Fig. 4 to pass through the origin. The fact that they do not, indicates that at lower acid concentrations some other process is taking place which could be either the ionization of $HTlCl_4$ in ether or the co-extraction of $TlCl_3$.

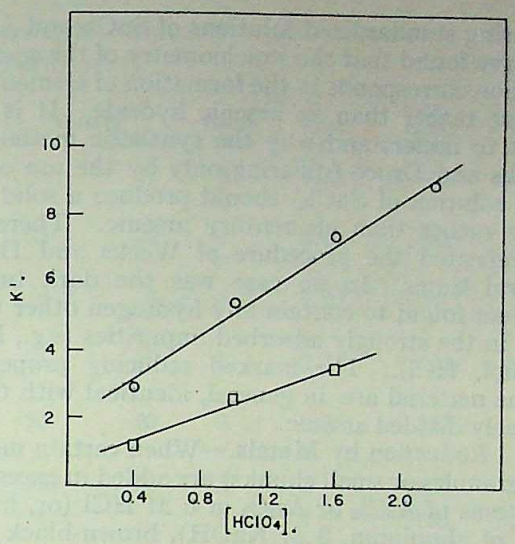

Fig. 4.—Dependence of K' upon $HClO_4$ concentration: O, 3.0 M total salt and acid concentration; □ 2.0 M total salt and acid concentration.

Conclusions

The following results and conclusions can be drawn from this study.

The extraction was found to have a negative temperature coefficient in the range of 20 to 30°. An average value of ΔH of 9.7 ± 0.5 kcal. per mole was found under the conditions of the experiments.

In order to explain the reduced extraction at high acidities a non-extractable species with formula H_2TlCl_5 was postulated. The data were used to calculate its formation constant as 3.0×10^{17}.

The empirical formula of the extracted species was found to be close to $HTlCl_4$.

At a given ionic strength and acid concentration the extraction equilibrium constant was found to be essentially constant, independent of the chloride concentration except when this was quite low. The lack of constancy was possibly due to ionization of $HTlCl_4$ in the ether phase or to coextraction of the $TlCl_3$ species.

The extraction was found to have a linear dependence on the hydrogen ion concentration in agreement with the supposition that $HTlCl_4$ was the species extracted. The fact that the extraction did not extrapolate to zero at low acidity agrees with the idea that $TlCl_3$ is extracting or that $HTlCl_4$ is ionizing in the ether phase. Values of the extraction coefficient at 30° are about 2.3 at an ionic strength of 2 and 4.3 at an ionic strength of 3 and relatively high acidities.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Solid Arsenic Hydrides

BY W. L. JOLLY, L. B. ANDERSON AND R. T. BELTRAMI

RECEIVED OCTOBER 3, 1956

Various methods for preparing solid arsenic hydrides have been evaluated as to yield and product composition. Atom ratios of hydrogen/arsenic as high as 0.52 have been observed for solid hydrides. A method has been developed for preparing an unstable, volatile arsenic hydride (probably biarsine, As_2H_4) from arsine by use of a silent electrical discharge.

I. Introduction

The literature contains many conflicting statements regarding the solid arsenic hydrides. Not only the compositions of these hydrides, but also their methods of preparation, have been the subject of dispute.[1] We have evaluated various preparative methods in terms of both yield and hydrogen content of the product. Several new preparative methods have been developed, including a method for the preparation of an unstable, volatile hydride (probably biarsine).

Some studies of the adsorption of arsine on arsenic have been made, in an attempt to elucidate the nature of the solid arsenic hydrides.

II. Results and Discussion

A. Reduction of Arsenic Solutions. 1. Reduction by $SnCl_2$.—Weeks and Druce[2] reported that a brown, amorphous arsenic hydride may be prepared by the action of an ether solution of stannous chloride on a solution of arsenic trichloride in aqueous hydrochloric acid

$$2AsCl_3 + 4SnCl_2 + 2H^+ + 2Cl^- = As_2H_2 + 4SnCl_4$$

(1) See, for example, "Gmelins Handbuch der Anorganischen Chemie," System-Nummer 17, Verlag Chemie, G. m. b. H., Weinheim/Bergstrasse, 1952, pp. 195–200.

(2) E. J. Weeks and J. G. F. Druce, *Chem. News*, **129**, 31 (1924).

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By using standardized solutions of $SnCl_2$ and $AsCl_3$ we have found that the stoichiometry of the *aqueous* reaction corresponds to the formation of elementary arsenic rather than an arsenic hydride. It is difficult to understand why the synthetic method of Weeks and Druce (differing only by the use of an *ether* solution of $SnCl_2$) should produce a solid hydride rather than elementary arsenic. Therefore we repeated the procedure of Weeks and Druce several times. In no case was the dark brown product found to contain any hydrogen other than that in the strongly adsorbed impurities (*e.g.*, H_2O, alcohol, HCl). The marked reducing properties of the material are, in general, identical with those of finely divided arsenic.

2. Reduction by Metals.—When certain metals (as granules or small chunks) are added in excess, to solutions of $AsCl_3$ or As_2O_3 in 6 *M* HCl (or, in the case of aluminum, 3 *M* NaOH), brown-black precipitates form, along with large amounts of hydrogen (and some arsine). The results of such experiments are summarized in Table I. The empirical formulas are the average values from several experiments. The best products were consistently obtained by the use of powdered magnesium, although the yields were never as great as those obtained by the use of granulated zinc. It is interesting that practically no solid product was obtained when calcium was the reducing agent. This may be caused by the extremely rapid reaction of calcium with water and by the fact that the calcium chunks floated on the surface of the solution.

TABLE I

REDUCTION OF 0.24 *M* As(III) SOLUTIONS BY METALS

Metal	Soln.	Yield, %	Empirical formula of solid product
Mg	HCl	~25	$AsH_{0.19}$
Zn	HCl	~85	$AsH_{0.04}$
Al	HCl	~18	$AsH_{0.025}$
Al	NaOH	~85	$AsH_{0.025}$
Ca	HCl	0	.....

An important method of isolating trace amounts of arsenic for subsequent analysis involves the quantitative reduction to arsine by zinc in hydrochloric or sulfuric acid solution.[3] Apparently little or no solid product is obtained when the arsenic concentration is very low.

3. Reduction by Miscellaneous Reducing Agents.—The reduction of $AsCl_3$ in 6 *M* HCl by chromous chloride gave a product of composition $AsH_{0.02}$ when the chromous chloride was in excess, and a product of composition $AsH_{0.002}$ when the $AsCl_3$ was in excess.

The addition of lithium hydride chunks to a solution of sodium arsenite gave no solid product. In this respect lithium hydride resembles calcium. Perhaps some reduction to arsine took place in the case of these powerful reducing agents.

B. Electrolytic Reduction of Arsenic Solutions.—Davy[4] was the first to report the formation of a brown precipitate when a solution of potassium hydroxide was electrolyzed using an arsenic cathode. Weeks[5] stated that the brown material obtained from a similar experiment was a solid arsenic hydride, but he gave no analytical data. Olszewsky[6] obtained a similar product by electrolyzing a solution of arsenious acid, using platinum electrodes.

We chose mercury as a cathode principally because of its high overvoltage for hydrogen evolution. Since hydrogen overvoltage increases with both increasing current density and decreasing temperature, we usually cooled the electrolytic cell as much as possible without unduly increasing the resistance. It is well known that arsine is liberated when an arsenic solution is reduced at a mercury cathode,[7,8] and we suspected that the presence of arsine was necessary for the formation of "solid arsenic hydrides."

The results are summarized in Table II. It will be noted that the ratio of hydrogen to arsenic in the product was high for those runs in which the electrolyte was acidic and cold. On the other hand, yields (based on electrical efficiency) were low under these conditions. It was observed that when the electrolytic experiments were started, the brown precipitate did not form at the surface of the mercury cathode, rather it formed homogeneously throughout the catholyte. We suspected that this phenomenon was caused by the reaction of dissolved arsine with the As(III) in the solution. It has been reported that arsine and arsenious acid react to give arsenic.[9]

We did not vary the concentration of As(III) in the electrolyte. It is known, however, that, as the concentration of As(III) decreases, the ratio of solid product to liberated arsine also decreases. In fact, when the concentration of As(III) is sufficiently small, quantitative yields of arsine gas are obtained.[3,8] It is probably significant that, in the reduction of As(III) solutions by sodium amalgam, the proportion of arsenic appearing as the metal (or solid hydride?) decreases with decreasing As(III) concentration.[10]

C. Oxidation of Arsine. 1. Oxidation by As(III).—Since our observations of the electrolysis of As(III) solutions led us to suspect that at least part of the solid product was formed by the reaction between arsine and As(III), we performed some experiments in which arsine was passed through As(III) solutions. The reaction of arsine with arsenious acid in sulfuric acid solution at room temperature was found to be so slow as to be an impractical synthetic method. We were unable to collect enough product to analyze. However, arsine reacts more rapidly with $AsCl_3$ in 6 *M* HCl. The product from such an experiment was found to have the empirical formula $AsH_{0.021}$. It thus seems likely that only a minor fraction of the product from the electrolytic preparations was formed by the reaction of arsine with arsenious acid.

(3) E. B. Sandell, "Colorimetric Determination of Traces of Metals," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1950, p. 150.
(4) H. Davy, *Phil. Trans. Royal Soc. (London)*, **100**, 31 (1810).
(5) E. J. Weeks, *Chem. News*, **128**, 54 (1924).
(6) K. Olszewsky, *Arch. Pharm.*, [3] **13**, 563 (1878).
(7) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, New York, N. Y., 1941, p. 261.
(8) F. S. Aumonier, *J. Soc. Chem. Ind.*, **46**, 341 (1927).
(9) J. N. Friend, "A Textbook of Inorganic Chemistry," Vol. VI, Part IV, Chas. Griffin and Co., Ltd., London, 1938, p. 91.
(10) M. Cichocki and K. Szlaczka, *Monatsh.*, **83**, 200 (1925); *C. A.*, **46**, 7413b (1952).

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TABLE II

ELECTROLYTIC REDUCTION OF ARSENIC(III) SOLUTIONS

(15 g. As_2O_3 per l. of catholyte)

Run	Av. temp., °C.	Supporting electrolyte	Anode type	Current density, amp./cm.² Initial	Current density, amp./cm.² Final	Voltage Initial	Voltage Final	Hours, run	Yield, g.	Atom ratio H/As	Mole ratio AsH_3/H_2[a]
1	46	0.18 M H_2SO_4 .063 M Na_2SO_4	C	0.052	0.052	25	17	3	4.51	0.056	0.0181
2	12	.18 M H_2SO_4 .063 M Na_2SO_4	C	.052	.052	22	22	3	0.35	.193	.0845
3	56	1.8 M H_2SO_4 0.063 M Na_2SO_4	C	.052	.052	6.2	6	4	4.23	.048	.0258
4	28	.18 M H_2SO_4 .063 M Na_2SO_4	C	.052	.052	21	18	3	3.10	.0034	.448
5	5	.18 M H_2SO_4 .063 M Na_2SO_4	C	.052	.052	25	23	8	0.81	.227	.0822
6	16	.5 M NaOH	C	.052	.0173	35	60	11	9	.029	.0435
7	7	1.8 M H_2SO_4 0.063 M Na_2SO_4	Pt	.052	..	8	..	9	2	.156	.091
8	10	.18 M H_2SO_4 .063 M Na_2SO_4	Pt	.052	.043	22	40	11.5	2.07	.072	.0793
9	7	None	Pt	8.6×10^{-4}	8.6×10^{-3}	120	120	2	1.27	.001	.367
10	10	.063 M Na_2SO_4 H_2 bubbled through soln.	Pt	0.016	0.028	62	20	6	0.5	.025	.0161
11	5	0.18 M H_2SO_4 .063 M Na_2SO_4	Pt	.052	.035	26	22	6	0.33	.258	.0771
12	8	.88 M H_3PO_4 .12 M NaH_2PO_4	Pt	.035	.035	30	30	9	0.74	.168	.0478

[a] Mole ratio AsH_3/H_2 in gas from vacuum thermal decomposition of vacuum heated product.

2. **Oxidation by $SnCl_4$.**—Moser and Brukl[11] reported the preparation of a hydride of the composition As_4H_2 by the oxidation of arsine by stannic chloride in aqueous hydrochloric acid. We repeated their experiments, but under conditions such that the $SnCl_4$ was always in excess. (Moser and Brukl kept the arsine in excess.) Our products had the average empirical formula $AsH_{0.18}$.

D. **Decomposition of Arsine by a Silent Electrical Discharge.**—Ogier[12] decomposed arsine in a discharge tube and obtained only 85.6% of the theoretical amount of hydrogen gas. This datum corresponds to a solid residue of the composition $AsH_{0.43}$. We repeated this experiment twice, using a closed discharge tube, and obtained solids with calculated compositions $AsH_{0.20}$ and $AsH_{0.23}$.

E. **Disproportionation of Biarsine (?).**—In preliminary experiments it was found that, when arsine was passed through a silent electrical discharge tube followed by a trap cooled to −196°, a yellow-brown solid formed in the trap.

Nast[13] has isolated small amounts of biarsine, As_2H_4, from the volatile products in the hydrolysis of magnesium aluminum arsenide. Pure biarsine was reported to be extremely unstable, decomposing to arsine and a solid red hydride of the approximate composition $AsH_{0.62}$. We suspected that, in our preliminary experiments with the discharge tube, the arsine had been decomposed to, among other things, hydrogen and biarsine. Presumably the biarsine, in turn, decomposed at the cold trap into arsine and the yellow-brown solid which we observed.

Further experiments indicated that we could, indeed, isolate a volatile material (not arsine) from the discharge tube products. This material (which may have been a mixture of biarsine and higher polymers such as As_3H_5 and As_3H_3) could be partially condensed in traps cooled to −80° and almost completely condensed in traps cooled to −120°. It partially decomposed to a bright yellow non-volatile hydride (and probably arsine and/or hydrogen) during the processes of condensation and vaporization. The yellow hydride, on warming to room temperature, turned red and finally brown. The volatile material was too unstable to analyze directly, but several samples of the solid hydride were analyzed. The average of several analyses corresponded to the empirical formula $AsH_{0.52 \pm 0.07}$.

F. **Ammonolysis of Sodium Arsenide.**—When ammonium chloride is added to a liquid ammonia solution of $NaAsH_2$, arsine is liberated and a finely divided brown precipitate of arsenic forms. This precipitated arsenic was found to contain only negligible amounts of hydrogen, in agreement with the findings of Johnson and Pechukas.[14]

G. **Adsorption of Arsine on Arsenic.**—The arsenic prepared by the method of Weeks and Druce ("As_2H_2") was found to be extremely finely divided. One sample had a surface area of 120 m.²/gram.

The adsorption of arsine on a similar sample of arsenic at −78.5° was found to show some hystere-

(11) L. Moser and A. Brukl, *Monatsh.*, **45**, 25 (1924).
(12) J. Ogier, *Ann. chim. phys.*, [5] **20**, 17 (1880).
(13) R. Nast, *Chem. Ber.*, **81**, 271 (1948).
(14) W. C. Johnson and A. Pechukas, THIS JOURNAL, **59**, 2065 (1937).

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sis in an adsorption–desorption cycle, but there was no strong bonding between the arsine molecules and the arsenic.

III. Experimental[15]

A. Analysis.—The solid arsenic hydrides were analyzed by thermal decomposition in a vacuum manifold. Weighed samples were heated *in vacuo* until the arsenic sublimed vigorously. The evolved gases were Toepler-pumped through, successively, a tube of Ascarite (to absorb CO_2, HCl and H_2O), a trap cooled to −78° (to trap H_2O, alcohol, etc.), and a trap cooled to −196° (to trap AsH_3). The non-condensable gas was usually assumed to be hydrogen; occasionally this was checked by a molecular weight determination or by mass-spectrometric analysis. Arsine was identified by its vapor pressure at the melting point of CS_2: lit.[14] 35 mm., found 34–36 mm. Usually the molar ratio AsH_3/H_2 in the gaseous decomposition products was approximately 0.05. The hydrogen contents of the solid hydrides were calculated from the molecular hydrogen and arsine evolved in the thermal decompositions.

B. Electrolytic Reduction of Arsenic Solutions. 1. Apparatus.—The anode compartment was a cylindrical tube 100 mm. long with a 40-mm. fritted disc at the lower end. Two types of anodes were used. One was a graphite rod 12 mm. in diameter. The other was a 1 × 10 cm. strip of platinum sheet. The cathode compartment was a one-liter "tall form" beaker, equipped with a stirrer. A pool of mercury (1/2 inch deep) in the bottom of the cathode compartment served as the cathode. Electrical contact was made to the mercury by a platinum-tipped wire passing through a tube. In some experiments, the cell was cooled externally with ice-water.

2. General Procedure.—Fifteen grams of arsenious oxide was dissolved in 25 ml. of 5 *M* sodium hydroxide. The solution was diluted with water and the appropriate amount of sulfuric acid to a volume of one liter.

In run no. 12, phosphoric acid was used instead of sulfuric acid. The catholyte for run no. 9 was prepared by dissolving arsenious oxide in hot water. The catholyte of run no. 6 was half-molar sodium hydroxide. The anolytes were the same as the catholytes in acid or base composition, but lacking in arsenious oxide. In run no. 6 the platinum anode was immersed directly in the catholyte.

At the end of each run, the mercury was removed with a separatory funnel, and the product was collected in a fritted funnel by vacuum filtration. The product was washed with water and dried for at least eight hours *in vacuo* over magnesium perchlorate.

Table II summarizes the data for each experiment.

C. Decomposition of Arsine by a Silent Electrical Discharge.—The discharge tube was similar to the usual ozone generator. It consisted of a glass cylindrical "finger" within and concentric with another glass cylinder. The discharge tube could be closed by means of stopcocks located at either end. The capacity of the tube was 63 cc.; the inner and outer cylinders were separated by about 0.5 cm. When in operation, 20,000 volts (60 cycles) were applied across the gap (one electrical contact was made to a salt solution in the inner "finger"; the other contact was made to aluminum foil wrapped around the outer cylinder). The results of two static experiments with AsH_3 are given in Table III.

TABLE III

S.E.D. DECOMPOSITION OF AsH_3 TO $AsH_x + (3/2 - x/2)H_2$

Voltage	Time (min.)	Initial mmoles AsH_3	Mmoles AsH_3 dec.	Moles H_2 formed per mole AsH_3 dec.	x (calcd.)
20,000	11	0.254	0.253	1.400	0.20
20,000	10	.696	.279	1.385	.23

In the first experiment, the discharge tube was flamed after pumping out the hydrogen and unreacted arsine in an attempt to decompose the residual brown solid hydride. Only 0.0050 mmole of H_2 and 0.0035 mmole of AsH_3 were obtained (corresponding to 0.010 mmole of H_2 total). One calculates that 0.016 mmole of H_2 were combined in the solid hydride; the deficiency was probably caused by incomplete thermal decomposition. (The peculiar shape of the discharge tube prevented efficient flaming.)

D. Disproportionation of "Biarsine."—The experiments may be divided in two classes: (1) those in which arsine was pumped through the discharge tube at low pressure (<1 mm.), and (2) those in which the arsine was carried through the discharge tube by a large excess of hydrogen gas (*ca.* 1 atm.). The former experiments were characterized by the formation of brown solid deposits in the tubing leading from the discharge tube. This phenomenon was probably caused by the glow discharge, which extended beyond the discharge tube itself. In the latter experiments, the brown deposit was limited to the interior of the discharge tube. In general, both methods involved the decomposition of about 5% of the arsine.

The gases leaving the discharge tube were usually first passed through a −120° trap and then through a −196° trap. After complete passage of the arsine through the discharge, the system was pumped down to about 10 μ pressure. The −120° trap was then closed off and *slowly* warmed to room temperature, thereby decomposing the "biarsine."

The trap was then evacuated. The red-brown solid residue was gently heated with a flame until it was black and the evolved arsine and hydrogen were measured. The remaining arsenic metal was dissolved in warm nitric acid and the solution was analyzed for arsenic by the molybdenum-blue colorimetric method.[3] For every 100 cc. of arsine passed through the discharge with one atmosphere of hydrogen, about 0.01 mmole of arsenic was obtained in the form of the solid hydride in the first trap (0.014 mmole in the low pressure experiments).

In Table IV, the results of five experiments are summarized.

TABLE IV

ANALYSIS OF SOLID DECOMPOSITION PRODUCT OF "BIARSINE"

Mmoles H_2 evolved during thermal decn.	Mmoles AsH_3 evolved during thermal decn.	Mmoles As remaining after thermal decn.	Calcd. empirical formula
0.0024	0.00261	0.0270	$AsH_{0.43}$
.00294	.00357	.0244	$AsH_{0.49}$
.0140	.0162	.119	$AsH_{0.57}$
.00157	.00367	.0210	$AsH_{0.37}$
.00354	.00327	.0356	$AsH_{0.43}$

In several qualitative experiments, the material in the −120° trap was not allowed to decompose completely, but was distilled to various places in the vacuum line. It was noted that, after distilling the material from a glass receptacle, a film of yellow solid remained which, when warmed to room temperature, turned red-brown. The material seemed to be relatively stable in the gaseous state, even at room temperature.

IV. Conclusions

The experimental data indicate that whenever one attempts to form elementary arsenic in the presence of arsine, the solid product contains not only arsenic, but also varying amounts of firmly held hydrogen. If we conclude that the presence of arsine is essential to the formation of these solid arsenic hydrides, then it is explained why a weak reducing agent like stannous chloride will only reduce As(III) to elementary arsenic. (Stannous chloride is thermodynamically incapable of reducing As(III) to arsine.)

It is very unlikely that the hydrogen of these solid hydrides exists as molecular hydrogen or arsine adsorbed on arsenic. Perhaps the solid hy-

(15) For detailed experimental data, the reader is referred to University of California Radiation Laboratory Report UCRL-4707, "Solid Arsenic Hydrides," June 7, 1956. The data on the preparation of arsine, the chemical reduction of As(III) solutions, the oxidation of arsine, the ammonolysis of sodium arsenide and the adsorption studies are presented in that report.

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drides prepared by certain methods consist of hydrogen and arsine occluded in cracks and holes in arsenic particles, but it is difficult to explain the very hydrogen-rich solids of composition $AsH_{0.5}$ in this manner. When macro amounts of these latter hydrides are available, various physical-chemical studies may elucidate their structure.

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BERKELEY, CAL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

The Reaction of Silylamines with Boron Trifluoride. Methyl- and Silylaminoboron Difluorides

BY SEI SUJISHI AND SAMUEL WITZ

RECEIVED DECEMBER 17, 1956

N-Silyldimethylamine, N-methyldisilylamine and trisilylamine react with boron trifluoride to yield dimethylaminoboron difluoride, N-methylsilylaminoboron difluoride and disilylaminoboron difluoride, respectively, and silyl fluoride. The variation in the physical properties of the aminoboron difluorides is discussed. Silylaminoboron difluorides decompose to form borazole derivatives and silyl fluoride. New vapor pressure data for silyl fluoride and N,N′,N″-trimethyl-B,B′,B″-trifluoroborazole were obtained.

With trimethylboron as the reference acid, the base strengths of silylamines show the following order: $(CH_3)_3N > (SiH_3)(CH_3)_2N > (CH_3)(SiH_3)_2N \sim (SiH_3)_3N$.[1] Neither methyldisilylamine nor trisilylamine forms an addition compound with trimethylboron and, therefore, their relative base strengths are not known.

With the object of completing this order, the reactions of the silylamines with boron trifluoride were investigated. Boron trifluoride appeared to be a suitable reference acid since Burg and Kuljian had reported that trisilylamine–boron trifluoride forms reversibly in the range −78 to −40° with a solid–gas equilibrium pressure of 3.7 mm. at −55°.[2] Although we found evidence for the formation of amine–boron trifluoride addition compounds, we could not measure the equilibrium pressures. This difficulty arose because secondary reactions, which yield aminoboron difluorides and silyl fluoride, occurred too rapidly. The nature of this secondary reaction is similar to that reported for the silylamine–boron trichloride system[2] and is the subject of the present paper.

Results and Discussion

Reaction of Silylamines with Boron Trifluoride.—Silyldimethylamine, methyldisilylamine and trisilylamine all absorbed an equimolar quantity of boron trifluoride at −80° to form white solids. Silyl fluoride was liberated slowly and at −80° less than an equivalent of it was formed in 16 hours.

When the amine–boron trifluoride mixtures were warmed to 25° about an equivalent of silyl fluoride was obtained. The formation of silyl fluoride was rapid in the methyldisilylamine and silyldimethylamine systems but was slow in the trisilylamine system. In the trisilylamine–boron trifluoride system, the total pressure indicated that trisilylamine–boron trifluoride was completely dissociated at partial pressures of 27 mm. of the components. After several days, however, almost an equivalent of silyl fluoride was obtained.

Along with silyl fluoride, substituted aminoboron difluorides were obtained. Dimethylaminoboron difluoride,[3] N-methylsilylaminoboron difluoride and disilylaminoboron difluoride were isolated from the silyldimethylamine, methyldisilylamine and trisilylamine systems, respectively. The silylaminoboron difluorides have not previously been reported in the literature.

The results suggest that the reactions of the silylamines with boron trifluoride proceed in two steps: (1) absorption of boron trifluoride to form an addition compound and (2) the elimination of silyl fluoride from the addition compound to form aminoboron difluoride.

$$(SiH_3)_2N: + BF_3 = (SiH_3)_3N:BF_3 \qquad (1)$$

$$(SiH_3)_3N:BF_3 = SiH_3F + (SiH_3)_2N{=}BF_2 \qquad (2)$$

The heats of formation of the addition compounds in the gas phase, from the amine and boron trifluoride, can be estimated and correlated with the results. According to Brown and Johannesen, the heat of formation of trimethylamine-boron trifluoride is −28 kcal./mole.[4] We have suggested that the substitution of a silyl group for a methyl group increases the heat of formation by about 9 kcal. for each successive substitution.[1] Hence, the approximate heat of formation of silyldimethylamine–boron trifluoride is −19 kcal., for methyldisilylamine–boron trifluoride −10 kcal., and for trisilylamine–boron trifluoride −1 kcal.

The last value is compatible with the observed gas phase non-association in the trisilylamine–boron trifluoride system.[5] The rapid formation of silyl fluoride in the methyldisilylamine–boron trifluoride and silyldimethylamine–boron trifluoride systems at 25° is compatible with heats of for-

(1) S. Sujishi and W. Witz, THIS JOURNAL, **76**, 4631 (1954).

(2) A. B. Burg and E. S. Kuljian, *ibid.*, **72**, 3103 (1950).

(3) (a) J. F. Brown, Jr., *ibid.*, **74**, 1219 (1952); (b) A. B. Burg and J. Banus, *ibid.*, **76**, 3903 (1954).

(4) H. C. Brown and R. B. Johannesen, *ibid.*, **75**, 16 (1953).

(5) The value of −1 kcal. for the heat of formation of trisilylamine–boron trifluoride appears on first consideration to be too small to account for the formation of the solid adduct at −80°. However, A. B. Burg and Sr. A. A. Green (*ibid.*, **65**, 1838 (1943)) report that trimethylamine–boron trifluoride molecules form associated aggregates even in the gas phase. In the solid state, therefore, strong dipole forces between the addition compound molecules could stabilize the adduct.

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mation of the addition compounds. Steps 1[6] and 2 both occur rapidly in these systems. The elimination of silyl fluoride may be comparably rapid from trisilylamine–boron trifluoride, but because of the low concentration of the addition compound the over-all rate is slow.

We conclude that, with boron trifluoride as the reference acid, methyldisilylamine is a stronger base than trisilylamine.

Aminoboron Difluorides.—The volatility of the substituted aminoboron difluorides increases in a striking manner with successive replacement of methyl groups by silyl groups. Thus, at 0° the vapor pressures are 0.2 mm. for solid dimethylaminoboron difluoride, 23 mm. for solid methylsilylaminoboron difluoride and 230 mm. for liquid disilylaminoboron difluoride. The high vapor pressure of disilylaminoboron difluoride is especially noteworthy. It is greater than that of either trisilylamine (110 mm.) or of methyldisilylamine (193 mm.) at 0°.[1]

The heats of vaporization and the melting points of dimethylaminoboron difluoride (19.1 kcal. and 160–164°) and disilylaminoboron difluoride (7.2 kcal. and $< -120°$) also show marked difference. Unfortunately corresponding values could not be determined for methylsilylaminoboron difluoride because of its instability toward decomposition. However, it was noted that methylsilylaminoboron difluoride was a solid at 25°.

The physical properties suggest that in the condensed state, dimethylaminoboron difluoride molecules are associated by strong intermolecular forces, while disilylaminoboron difluoride molecules are unassociated and held together by ordinary van der Waals forces. The interaction between methylsilylaminoboron difluoride molecules appears to be intermediate between these two extremes.

Previous workers have not agreed on the state of aggregation of dimethylaminoboron difluoride in the solid. Brown[3a] has assumed that dimethylaminoboron difluoride is dimeric while Burg and Banus[3b] have assumed that it is monomeric. Both of these conclusions were extrapolated from vapor density results. Brown's data were obtained at 155° and 747 mm. while Burg and Banus do not state the conditions of their experiments. Our data show that at low pressures (35 mm. at 96°), monomers are the chief species in the gas phase, while at moderate pressures (141 mm. at 136°) dimers occur to the extent of about 30%.

Convincing evidence for the association of dimethylaminoboron difluoride in the solid may be obtained by examination of the properties of aminoboron dichlorides. There is very little difference in the physical properties of monomeric dimethylaminoboron dichloride (m.p. −43°, v.p. 26 mm. at 25°)[7] and disilylaminoboron dichloride (m.p. $< -78°$, v.p. 22 mm. at 25°).[2] In contrast, dimeric dimethylaminoboron dichloride is much less volatile (v.p. 1 mm. at 90°)[7] and higher melting (m.p. 142°).[7] On the basis of these facts, it would be expected that the properties of monomeric dimethylaminoboron difluoride and disilylaminoboron difluoride should be similar. The enormous difference actually observed, therefore, indicates that dimethylaminoboron difluoride is associated in the solid state.

Wiberg and Schuster[8] and Brown and Osthoff[7] have suggested that the dimerization of dimethylaminoboron dichloride occurs through nitrogen–boron coördinate bond formation. We assume that the association of dimethylaminoboron difluoride also occurs through nitrogen–boron coördinate bonds. Without specifying the nature of the molecular unit in the solid, but assuming only that all possible coördinate bonds are formed, as for example in cyclic polymers or linear polymers, it is possible to estimate the heat of dissociation of such bonds between dimethylaminoboron difluoride molecules. The estimation is made in the same way as the value for the proposed nitrogen–silicon coördinate bond in silyldimethylamine was obtained.[1] For dimethylaminoboron difluoride, the heat of dissociation thus obtained is 10.5 kcal./mole of nitrogen–boron bond.

The estimated value of 10.5 kcal. for dimethylaminoboron difluoride can now be used to explain the variation in the physical properties of the silylaminoboron difluorides. In methylsilylaminoboron difluoride, the silyl group stabilizes the monomer by 9 kcal./mole and the nitrogen–boron coördinate bond energy decreases to 1.5 kcal. Similarly in disilylaminoboron difluoride, the two silyl groups reduce the heat of dissociation to −7.5 kcal. and, hence, disilylaminoboron difluoride shows no association.

Decomposition of Aminoboron Difluorides.—The silylaminoboron difluorides decomposed to form borazole derivatives and silyl fluoride. This reaction is similar to the decomposition of silylaminoboron dichlorides.[2] Thus, methylsilylaminoboron difluoride yielded N,N′,N″-trimethyl-B,B′,B″-trifluoroborazole, a compound previously reported by Wiberg and Horeld,[9] and disilylaminoboron difluoride yielded N,N′,N″-trisilyl-B,B′,B″-trifluoroborazole. The quantity of the last compound was too small to characterize the compound.

The rate of formation of silyl fluoride was rapid from methylsilylaminoboron difluoride and slow from disilylaminoboron difluoride. Burg and Kuljian[2] found that methylsilylaminoboron dichloride decomposed more rapidly than disilylaminoboron dichloride. These differences in rate may be rationalized by the mechanism suggested below.

Mechanism of Elimination of Silyl Fluoride.—When silylamines form addition compounds with boron trifluoride, the electron density on the fluorine atom should be relatively large and the electron density on the silicon atom relatively small. The fluorine atoms have three pairs of unshared electrons and, hence, may form coördinate bonds in the transition state with the silicon atom, using its 3d orbitals,[10] either in the same molecule or in a different molecule. The elimination of silyl fluoride is facilitated in this

(6) The rate of formation of trimethylamine–boron trifluoride has been found to be very rapid with only a small activation energy; G. B. Kistiakowsky and R. Williams, *J. Chem. Phys.*, **23**, 334 (1955).

(7) C. A. Brown and R. C. Osthoff, THIS JOURNAL, **74**, 2784 (1952).

(8) E. Wiberg and K. Schuster, *Z. anorg. Chem.*, **213**, 77 (1933).

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(10) C. G. Swain, R. M. Esteve, Jr., and R. H. Jones, THIS JOURNAL, **71**, 965 (1949).

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TABLE I

CONDITIONS FOR SEPARATION OF COMPOUNDS

System	$(SiH_3)_3N-BF_3$		$(CH_3)(SiH_3)_2N-BF_3$		$(SiH_3)(CH_3)_2N-BF_3$
Compd.	$(SiH_3)_2NBF_2$	$(SiH_3NBF)_3$	$(CH_3)(SiH_3)NBF_2$[a]	$(CH_3NBF)_3$	$(CH_3)_2NBF_2$
Dist. T, °C.	− 80	25	25	25	25
Cond. T, °C.	−126	−80	−126	−80	−80

[a] Methylsilylaminoboron difluoride was purified by distillation through a trap at −80° and condensation in a trap at −126°.

way. As indicated earlier the rate-determining step in the over-all reaction, of silylamines with boron trifluoride, is the formation of the addition compound.

The decomposition of silylaminoboron difluorides may be interpreted similarly. Silyl fluoride is eliminated from the dimer. This is followed by the association of the resultant boron–nitrogen derivative with another mole of silylaminoboron difluoride and the elimination of silyl fluoride from the adduct. The rate-determining step is the formation of the dimer. Since silylmethylaminoboron difluoride dimerizes more readily than disilylaminoboron difluoride, the rate of elimination of silyl fluoride from the former is greater than from the latter.

Experimental Part

A Stock type high vacuum line was employed. The silylamines were prepared and purified by methods described previously.[1] Boron trifluoride (Matheson Co., Inc.) was purified in the vacuum line and a tensiometrically homogeneous sample (v.p. obsvd. 300 mm. at −111.8°, lit.[11] 300 mm.) obtained.

The various products of the reactions were separated and purified by fractional distillation and condensation. Silyl fluoride, which was obtained in all of the reactions, was isolated by distillation at either −126 or −117°. The pertinent data for the separation of the other compounds are summarized in Table I.

Silyl fluoride was purified by the method described in the section on the vapor pressure of silyl fluoride. When the presence of boron trifluoride was suspected, the silyl fluoride fraction was treated with a measured quantity of ethyl ether. The ethyl ether combined with the boron trifluoride to form ethyl ether–boron trifluoride. The silyl fluoride, ethyl ether and ethyl ether–boron trifluoride were separated by distillation and the quantity of boron trifluoride originally present was calculated from the results of the separation. This method will be referred to as the ethyl ether test for boron trifluoride.

All quantities expressed in cc. are those for the gas at S.T.P. These volumes are accurate to ±0.2 cc.

Silyldimethylamine–Boron Trifluoride System.—Silyldimethylamine, 10.6 cc., and 10.6 cc. of boron trifluoride were combined and kept at −80°. A white solid was observed and the pressure remained constant at 98 mm. (6 cc.) for 15 hours. The pressure did not change significantly as the temperature was raised. Thus, at −55° it was 97 mm. and at −30° it was 109 mm. The mixture was warmed to 22°. The pressure rose to 198 mm. (11.9 cc.) and a white crystalline solid was observed.

The mixture was fractionated and 11.0 cc. of crude silyl fluoride and an unmeasured quantity of dimethylaminoboron difluoride were obtained. The crude silyl fluoride was found to contain 0.3 cc. of silane, 6.0 cc. of boron trifluoride (ethyl ether test), 1.3 cc. of pure silyl fluoride (v.p. 29 mm. at −126°) and 3.4 cc. of a mixture of silyl fluoride and polyfluorosilane (v.p. 23 mm. at −126.3°).

Dimethylaminoboron Difluoride.—The dimethylaminoboron difluoride was identified by its v.p. (obsd. 4.2 mm. at 55° and 20.0 mm. at 70° lit.[3b] 3.8 and 19.1 mm., respectively) and its m.p. (obsd. 146–149°, 160–165°, 164–165°, lit. 155° (Burg)[3b] and 167–169° (Brown)[3a]). The heat of sublimation may be calculated to be about 19 kcal./mole of monomer gas.

In a similar expt., 24.4 cc. of boron trifluoride and 24.4 cc. of silyldimethylamine reacted at 25° in 5 minutes to yield 0.9 cc. of silane, 23.3 cc. of silyl fluoride, 0.3 cc. of polyfluorosilane, and dimethylaminoboron difluoride. The dimethylaminoboron difluoride was tensiometrically homogeneous with a v.p. of 8.3 mm. at 65.1°. The vol. of the gas was 20.8 cc. at 136° and 141 mm. and 21.3 cc. at 161° and 154 mm. Using the initial quantities of boron trifluoride and silyldimethylamine as the base, it may be calculated that the dimethylaminoboron difluoride was about 30% dimerized.

Methyldisilylamine–Boron Trifluoride System.—Methyldisilylamine, 17.8 cc., and 17.8 cc. of boron trifluoride were kept at −80°. The pressure slowly rose to 32 mm. in 2 hours and to 49 mm. (10 cc.) in 16 hours. A white solid was observed. The mixture was distilled at −126° and 10.1 cc. of distillate which contained 0.3 cc. of silane, 9.7 cc. of silyl fluoride and 0.1 cc. of polyfluorosilane was obtained. All of the fractions were recombined and the mixture warmed to 27°. After 10 min., the pressure became constant at 174 mm. (35.2 cc.). A very small quantity of white solid failed to vaporize. After 45 min. at 27°, the mixture was fractionated. Silane, 0.2 cc., silyl fluoride, 23.8 cc., polyfluorosilane, 0.5 cc., and crude methylsilylaminoboron difluoride, 10.9 cc., were obtained.

Methylsilylaminoboron Difluoride.—The crude methylsilylaminoboron difluoride was purified by distillation at −80°. In 15 minutes, 1.7 cc. of distillate was obtained and in the next ½ hour no further quantity of volatile fraction was obtained. The residue, 7.8 cc., was pure methylsilylaminoboron difluoride. It was a white solid at 0° and was tensiometrically homogeneous with a v.p. of 23.0 mm. The mol. wt. by vapor density measurement at 27° and 106 mm., was 108 (calcd. for $(CH_3)(SiH_3)NBF_2$ 109.0).

Methylsilylaminoboron difluoride decomposed slowly even at 0°. All of the material present in the crude methylsilylaminoboron difluoride fraction were combined and the mixture allowed to stand at 27°. After 20 hours, white crystals were observed and by fractionation, 4.1 cc. of silyl fluoride was isolated. After 5 days a total of 10.7 cc. of silyl fluoride, 0.2 cc. of methylsilylaminoboron difluoride and 3.2 cc. of crude N,N′,N″-trimethyl-B,B′,B″-trifluoroborazole were obtained.

N,N′,N″-Trimethyl-B,B′,B″-trifluoroborazole.—The crude trimethyltrifluoroborazole, 3.2 cc., was purified by distillation at −23°. A tensiometrically homogeneous sample (v.p. 0.25 mm. at 0°) was obtained. The v.p. were measured at various temperatures. The results may be expressed by the equation $\log P_{mm} = -3165.2/T°_K + 10.8256$. The results are summarized in Table II. The

TABLE II

VAPOR PRESSURE OF $(CH_3NBF)_3$

T, °C.	0.0	25.1	34.8	44.6	54.7
P_{mm}, obsd.	.25	1.6	3.6	7.3	14.9
P_{mm}, calcd.	.17	1.6	3.5	7.4	14.9

mol. wt., by vapor density measurement at 64° and 15.6 mm., was 176 (calcd. for $(CH_3NBF)_3$, 176.6). The heat of vaporization is calculated to be 14.5 kcal. The m.p. in an evacuated and sealed capillary tube was 88–89° (lit. 85°).[12]

In a duplicate experiment, 12.5 cc. of methyldisilylamine and 12.5 cc. of boron trifluoride reacted to yield as the final products 22.8 cc. of silyl fluoride, 1.8 cc. of silylmethylaminoboron difluoride and 3.4 cc. of trimethyltrifluoroborazole.

(11) E. Pohland and W. Harlos, *Z. anorg. allgem. Chem.*, **207**, 242 (1932).

(12) The physical constants reported for N,N′,N″-trimethyl-B,B′,B″-trifluoroborazole (ref. 9) are m.p. 85°, v.p. 6 mm. at 69° and 320 mm. at 186°. Although the m.p. observed by us is in fair agreement with the value reported, the v.p. show very poor agreement.

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Trisilylamine–Boron Trifluoride System.—Boron trifluoride, 14.4 cc., and trisilylamine, 14.4 cc., were combined and kept at −80°. After 0.6 hour the pressure reached a minimum value of 22 mm. and a white solid formed. The pressure slowly increased and in 1.6 hours was 26 mm. (5 cc.). The mixture was distilled at −126° and 5.9 cc. of silyl fluoride was obtained (v.p. at −123.2°, obsd. 42.5 mm., SiH_3F 43.1 mm.). The absence of boron trifluoride was confirmed by the ethyl ether test.

The residue was a solid at −80° and exerted a pressure of 1.9 mm. This was examined for homogeneity by distilling small quantities away at −80° and measuring the pressure over the solid after each distillation at −53.7°. The pressure varied from 12.8 to 2.2 mm. and, hence, the solid was not homogeneous. All of the fractions were combined and the total gas volume was measured. At 27° and 113.5 mm. the volume was 22.8 cc. (This value combined with the volume of silyl fluoride recovered initially, 5.9 cc., yields a total of 28.7 cc. The sum indicates that there was no net change in the number of moles of gas in the system. As it will be shown below, silyl fluoride is produced by reaction 2. Since all of the components of reaction 1 are volatile at 27°, the fact that only a portion of the silyl fluoride expected for complete reaction was obtained shows that trisilylamine and boron trifluoride must coexist as gases without association. The partial pressure of the components may be calculated to be 27 mm.)

The mixture, 22.8 cc., was kept at 27° and periodically analyzed for silyl fluoride. The additional quantity of silyl fluoride obtained was 4.5 cc. after one hour and 7.2 cc. after 5 days. (The total quantity of silyl fluoride obtained thus far was 13.1 cc. or 0.93 equivalent of the starting components.)

Heating the residue after the separation of silyl fluoride did not appreciably effect the rate of formation of silyl fluoride. Thus, 4 hours at 55° gave 0.8 cc., 24 hours at 75° gave 2.2 cc., 24 hours at 85° gave 0.1 cc. and 18 hours, at 115° gave 0.5 cc. of silyl fluoride, respectively.

A total of 16.7 cc. of silyl fluoride and 12.5 cc. of other products was obtained. The 12.5-cc. fraction was separated into 11.9 cc. of disilylaminoboron difluoride and 0.6 cc. of borazole derivative.

Disilylaminoboron Difluoride.—The 11.9-cc. fraction was identified as disilylaminoboron difluoride by vapor density measurement. The mol. wt. was 124 at 23° and 144 mm. (calcd. for $(SiH_3)_2NBF_2$, 125.0). The vapor pressures of the compound, a liquid down to −120°, were measured. The results can be represented by the equation $\log P_{mm} = -1563/T°_K + 8.102$ and are given in Table III. The heat of vaporization is 7.2 kcal.

TABLE III

VAPOR PRESSURE OF $(SiH_3)_2NBF_2$ (LIQUID)

T, °C.	−52.5	−49.3	−30.9	−23.4
P_{mm}, obsd.	11.1	13.2	45.8	69.9
P_{mm}, calcd.	10.5	13.2	44.8	70.0

Disilylaminoboron difluoride decomposed very slowly when it was stored as a gas at room temperature. One of the products of the decomposition was silyl fluoride. The other product was undoubtedly N,N′,N″-trisilyl-B,B′,B″-trifluoroborazole, although the quantity obtained was too small to permit positive identification. The decomposition reaction may be written as

$$3(SiH_3)_2NBF_2 = 3SiH_3F + (SiH_3NBF)_3 \quad (3)$$

The quantities of products isolated may be accounted for by equations 2 and 3. Thus, assuming that reaction 2 proceeded to completion, the quantity of disilylaminoboron difluoride which decomposed according to equation 3 should be 14.4 − 11.9 = 2.5 cc. The total quantity of silyl fluoride recovered then should be 14.4 + 2.5 = 16.9 cc. (obsd., 16.7 cc.) and that of the borazole derivative 0.8 cc. (obsd., 0.5 cc. in the trap at −80°).

In a duplicate expt., 13.6 cc. of trisilylamine and 13.6 cc. of boron trifluoride reacted to yield 18.0 cc. of silyl fluoride, 9.8 cc. of disilylaminoboron difluoride and a small quantity of the borazole derivative (v.p. 2.5 mm. at 24°). The borazole derivative was hydrolyzed with aqueous ammonium hydroxide and 10.8 cc. of hydrogen was obtained. Using the quantity of disilylaminoboron difluoride isolated as the base, it may be calculated that 17.4 cc. of silyl fluoride (obsd., 18.0 cc.) and 1.27 cc. of the trisilyltrifluoroborazole should have been obtained. The last compound on hydrolysis should yield 11.4 cc. of hydrogen (obsd., 10.8 cc.).

Disilylaminoboron Difluoride–Boron Trifluoride System.—Disilylaminoboron difluoride did not react with boron trifluoride at moderate pressure at either 26 or −80°. Thus, when 9.8 cc. of disilylaminoboron difluoride and 9.8 cc. of boron trifluoride were combined at 26° the total pressure remained constant at 169 mm. (19.6 cc.) for 18 hours. By fractional condensation, 9.2 cc. of boron trifluoride was isolated from the mixture.

Similarly, when 9.8 cc. of disilylaminoboron difluoride and 9.5 cc. of boron trifluoride were kept at −80°, the total pressure of 48 mm. (9.8 cc.) indicated that the boron trifluoride was not soluble in liquid disilylaminoboron difluoride. After three days at −80°, 9.8 cc. of boron trifluoride was isolated from the mixture.

Disilylaminoboron difluoride and boron trifluoride did react, however, at −80° when the partial pressure of boron trifluoride was high. Disilylaminoboron difluoride, 9.8 cc., and 64.4 cc. of boron trifluoride were sealed in an ampoule of 6-cc. volume and kept at −80° for five days. (The v.p. of boron trifluoride is roughly 4.5 atm. at this temp.) After the first day white crystals and a colorless liquid phase were observed. On distillation at room temperature 73.2 cc. of gas was recovered from the ampoule. A small quantity of grayish white residue was left in the ampoule. Fractionation yielded 0.5 cc. of unidentified product (volatile at 25°, non-volatile at −80°), 3.4 cc. of disilylaminoboron difluoride (v.p. obsd. 15.5 mm. at −45.4°, calcd. 17 mm.), 57.4 cc. of boron trifluoride (ethyl ether test), 1.5 cc. of silane, 7.5 cc. of silyl fluoride (v.p. obsd., 28.9 mm. at −127.5°, calcd. 28 mm.), and 1.6 cc. of polyfluorosilane (v.p. obsd., 15 mm. at −127.2°).

The results of the experiment indicate that 7.0 cc. of boron trifluoride reacted with 6.4 cc. of disilylaminoboron difluoride to yield 7.5 cc. of silyl fluoride, and 3.1 cc. of silane and polyfluorosilane and other products.

Vapor Pressure of Silyl Fluoride.—The vapor pressures of silyl fluoride obtained in the present work differed considerably from those reported by Emeleus and Maddock.[13] Emeleus and Maddock obtained silyl fluoride from the reaction of silyl chloride with antimony trifluoride and state that the purity of the product did not exceed 98%.

The different fractions of silyl fluoride isolated from the experiments were combined and purified by distillation through a series of traps kept at −126, −160 and −196°. The major portion of the silyl fluoride condensed in the −160° trap along with some less volatile material. The silyl fluoride was recovered from this by slow distillation at −160°. A tensiometrically homogeneous sample was thus obtained. The purity was further established by mol. wt. determination and by hydrolysis. The mol. wt. at 24° and 80.6 mm. was 50.0 (calcd. for SiH_3F, 50.08). Hydrolysis with saturated aqueous sodium hydroxide at 30–40° for 45 min. of 8.84 cc. and 11.57 cc. samples gave 26.5 cc. (calcd., 26.5 cc.) and 34.4 cc. (calcd., 34.7 cc.) of hydrogen, respectively.

The vapor pressures of the liquid were measured and the results can be expressed by the equation $\log P_{mm} = -984.86/T°_K + 8.2001$. The results are summarized in Table IV. The extpd. b.p. is −88.1° and the heat of vaporization is 4.5 kcal./mole. Emeleus and Maddock reported −98.6° and 4.5 kcal., respectively, for these two values.[13]

TABLE IV

VAPOR PRESSURE OF SiH_3F (LIQUID)

T, °C.	−127.2	−119.8	−117.8	−112.3
P_{mm}, obsd.	28.5	60.3	72.2	120.0
P_{mm}, calcd.	28.5	60.3	72.2	120.0

Acknowledgment.—This work was made possible by a Frederick Gardner Cottrell grant from the Research Corporation.

CHICAGO 16, ILLINOIS

(13) H. J. Emeleus and A. G. Maddock, *J. Chem. Soc.*, 293 (1944).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

Inorganic Chemistry in Trifluoroacetic Acid[1]

BY GEORGE S. FUJIOKA AND GEORGE H. CADY

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In the investigation of inorganic reactions in anhydrous trifluoroacetic acid, the effects of anhydrous HCl, H_2S, $HClO_4$, H_2SO_4, SO_3, H_3PO_4, HPO_3, Cl_2, CrO_3, $KMnO_4$ and SO_2 upon 25 dissolved trifluoroacetates of metals were studied. The reactions obtained from H_2S closely paralleled those obtained in acidic aqueous systems. More chlorides, perchlorates and bisulfates were precipitated from trifluoroacetic acid than from water. The reactions with H_2SO_4 were in most cases rapid and complete. By contrast, the reactions with SO_3 were slow and only partially complete. Orthophosphoric acid produced precipitates slowly. Many of these precipitates were in the form of gels, suggesting polymer formation. The reagents CrO_3, Cl_2 and $KMnO_4$ acted as oxidizing agents, but more slowly than in water. Hydrogen peroxide decomposed in the presence of dissolved trifluoroacetates of metals to form water and oxygen. It also reduced Mn(VII) to Mn(II), and reacted with CrO_3 forming a blue-green solution of a peroxy–chromium compound. The slow reaction of $KMnO_4$ with trifluoroacetic acid produced the gases: CO_2, CF_3COF and COF_2, while Mn(VII) was reduced to Mn(III).

Trifluoroacetic acid is a good solvent for a wide variety of organic compounds, both aliphatic and aromatic.[2,3] Inorganic compounds also dissolve in trifluoroacetic acid[4] but in general to a lesser degree than in water. The solubility of inorganic salts in trifluoroacetic acid must be considered high, particularly when the low dielectric constant, 8.22 at 30°,[5] is taken into account. The low electrical conductivities[6] of salts when dissolved in trifluoroacetic acid illustrate that the acid is not a good ionizing solvent. Ionic type reactions do occur, however, and this study deals largely with such reactions.

Experimental

(I) Reactions Occurring in the Solvent Trifluoroacetic Acid.—The solvent, trifluoroacetic acid, as supplied by the manufacturer (Minnesota Mining and Manufacturing Co.) was used without further purification. The metal trifluoroacetate solutions were prepared from salts synthesized by Hara and Cady in their solubility studies.[4] Solutions of $AsOCF_3CO_2$ and the trifluoroacetates of NH_4^+, Sb(III), Bi(III), Cr(III), Fe(III), Pb(II), Li, Mn(II) and Hg(I) were prepared by the authors. Either the carbonates or oxides of the metals were caused to react with trifluoroacetic acid containing enough trifluoroacetic anhydride to combine with water formed by the reaction. The trifluoroacetates were then obtained as solids by evaporating away the solvent. With the exception of $AsOCF_3CO_2$ the products were crystalline solids. The arsenic compound formed a clear, colorless gel which took on a milky white appearance after standing for several weeks. When the temperature of the milky solid was raised to a few degrees above that of the room it again became colorless. No definite melting point could be observed. When possible, 0.1 *m* solutions were used. Saturated solutions were employed for substances of lower solubility than 0.1 *m*.

The reactants were either gases or compounds dissolved in trifluoroacetic acid. The gaseous reactants were HCl, H_2S, SO_2, Cl_2 and SO_2. Except for SO_2 the gases were dried by passage through concentrated sulfuric acid or by passage through a trap cooled with a Dry Ice–acetone bath. Sulfur trioxide was carried from a storage bulb to the reaction solution by dry N_2. The reactants which were dissolved in trifluoroacetic acid were reagent grade $HClO_4$, H_2SO_4, H_3PO_4, HPO_3, CrO_3, H_2O_2 and $KMnO_4$.

With H_2SO_4, H_3PO_4 or H_2O_2 an anhydrous solution was prepared by first dissolving an aqueous solution of known concentration in trifluoroacetic acid. A calculated amount of trifluoroacetic anhydride was then added to just react with the water present. A slight excess of trifluoroacetic anhydride was added to all solutions to maintain the anhydrous state. No anhydride was added to the perchloric acid solution. The anhydride was added, however, to the reaction mixtures either just before the addition of the perchloric acid solution or just after. The order of addition produced no observed effect upon the final results.

Table I lists the concentrations of the stock solutions of trifluoroacetates used for these studies. Table II lists the concentrations of solutions of the reactants. In the cases of HCl, H_2S, Cl_2 and SO_2 the concentrations were those reached by saturating trifluoroacetic acid with the gases at 26° under a total pressure of one atmosphere.

TABLE I

CONCENTRATIONS OF TRIFLUOROACETATES

Solute[a]	Molal concn. (mole/1000 g.)	Solute	Molal concn. (mole/1000 g.)
NH_4[a]	0.1	Mg	0.1
As(III)[a]	.015	Mn(II)	.025
Sb(III)	.015	Hg(II)	.1
Ba	.1	Hg(I)	.1
Bi(III)	.04	Ni(II)	.1
Cd	.1	K	.1
Ca	.09	Ag(I)	.1
Cr(III)	.06	Na	.1
Co(II)	.1	Sr	.1
Cu(II)	.1	Sn(IV)[a]	.1
Fe(III)	.03	Sn(II)	.06
Pb(II)	.1	Zn	.03
Li	.1		

[a] All the solutes are trifluoroacetates except As(III) and Sn(IV) which are $AsOCF_3CO_2$ and $SnCl_4$.

TABLE II

APPROXIMATE CONCENTRATION OF REACTANTS IN TRIFLUOROACETIC ACID

Reactants	Molal concn.	Reactants	Molal concn.
HCl	0.1	HPO_3	0.5
H_2S	0.2	Cl_2	.2
$HClO_4$	2	CrO_3	.008
H_2SO_4	15	H_2O_2	1.3
SO_3	?	$KMnO_4$	0.04
H_3PO_4	0.3	SO_2	0.6

The reactions were carried out at 25 to 26° in 10 × 75 mm. test-tubes using in each case between 0.5 to 1.5 ml. of a solution of a metal trifluoroacetate. The reactant solutions were added to the trifluoroacetate solutions dropwise until about a two-fold excess was present or until further addition ceased to yield an observable reaction. Gaseous reactants were bubbled through the trifluoroacetate solution until all observable reaction ceased. The reactions were carried out with solutions of trifluoroacetic anhydride

(1) Presented at Minneapolis meeting of the American Chemical Society, September 16, 1955. From the Ph.D. thesis of G. S. Fujioka, 1956.

(2) Booklet, "Trifluoroacetic Acid," Minnesota Mining and Manufacturing Co., Saint Paul, Minnesota, 1950.

(3) J. J. Katz, *Nature*, **174**, 509 (1954).

(4) R. Hara and G. H. Cady, THIS JOURNAL, **76**, 4285 (1954).

(5) W. Dannhauser and R. H. Cole, *ibid.*, **74**, 6105 (1952).

(6) J. H. Simons and K. E. Lorentzen, *ibid.*, **74**, 4746 (1952).

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(*ca.* 0.05 g.) added to the reaction vessel to ensure anhydrous conditions at all times.

Precipitates formed by the reactions were concentrated by centrifugation, washed with trifluoroacetic acid by decantation, and dried in an oven at 105°. The remaining solid was analyzed in most cases. The supernatant liquid was evaporated, and the residue, if any, was dissolved in water and qualitatively analyzed for both the anion and cation. A designation of "Complete," "Nearly Complete" or "Partial" was placed on the extent of a particular precipitation reaction depending upon whether the qualitative tests showed the metallic ion in question to be (a) absent, (b) present in trace quantity, (c) present in appreciable amount.

Table III lists the precipitates obtained in the reactions of hydrogen chloride, hydrogen sulfide and perchloric acid and the solutes listed in Table I. It is possible that some of the precipitates may have contained trifluoroacetic acid of solvation.

Many analyses of the precipitates resulting from reactions with anhydrous sulfuric acid indicated the presence of both acid and normal sulfates. It appears unlikely that two sulfate species were precipitated from the reaction mixture. It is more probable that some of the precipitated acid sulfates were partially converted to normal sulfates while being washed with pure trifluoroacetic acid. Table IV lists the solutes that gave a sulfate precipitate. The table also gives the mole percentages of acid and normal sulfate found by analysis.

TABLE III

REACTIONS OF TRIFLUOROACETATES IN TRIFLUOROACETIC ACID

Reactant	Product
HCl	Chloride ppt.:
	Reaction, complete: Cd(II), Cu(II), Pb(II), Hg(II), Hg(I), Ni(II), Zn(II). All the ppt. colors were white except for Ni(II) which was amber
	Reaction, nearly complete: Bi(III), Co(II), Mn(II), Sn(II). The Co(II) ppt. was light blue, but the others were white
	Reaction, partial: Fe(II), olive color
	Colloidal ppt.: Ag(I), white, orange CrO_2 soln. was converted to a red soln. probably CrO_2Cl_2
H_2S	Sulfide ppt.:
	Reaction, complete: Sb(III), Cd(II), Cu(II), Hg(II), Hg(II) and Hg from Hg(I), Ag(I)
	Reaction, nearly complete: Fe(II) soln. and S from Fe(III), Sn(II), Zn(II)
	Reaction, partial: Bi(III)
	Colloidal ppt.: As(III), orange CrO_3 soln. was converted to a green soln. of Cr(III) and H_2SO_4
	The colors of the sulfides were the same as the colors obtained from pptn. from aqueous media
$HClO_4$	Perchlorate ppt.:
	Reaction, complete: K(I)
	Reaction, nearly complete: NH_4^+, Cd(II), Hg(I), Ag(I), Na(I), Sr(II), Sn(II), Zn(II)
	Reaction, partial: Sb(III), Ba(II), Bi(III), Cr(III), Co(II), Cu(II), Fe(III), Pb(II), Mg(II), Mn(II), Hg(II), Ni(II)
	Colloidal ppt.: As(III) (solid not identified)
	Cobalt perchlorate was pink, copper perchlorate was light blue, nickel perchlorate was light green. All the other perchlorates were white

Sulfur trioxide precipitated most of the metals which reacted with dissolved sulfuric acid. A few sulfates were precipitated which were not brought down by sulfuric acid. Sulfur trioxide is very soluble in trifluoroacetic acid and is known to react with the acid to produce trifluoroacetic anhydride and sulfuric acid. With a high concentration of SO_3 some of the sulfuric acid may be converted to pyrosulfuric acid. Some of the precipitates were normal sulfates. Others were either acid sulfates or pyrosulfates or mixtures. As a sample was dried in the oven before analysis it had a chance to absorb water which would convert a pyrosulfate to an acid sulfate. On this account the analyses did not clearly characterize all of the precipitates. On the basis of the metal to sulfate ratio and on this alone the compositions of the precipitates are given in Table V in terms of the % of normal sulfate and the % of pyrosulfate. Table V lists: (1) the trifluoroacetates that gave precipitates with SO_3, (2) the weight per cent. of the cation and of the sulfate ion found in the precipitate, (3) the molar ratio of the cation to the sulfate, (4) the possible formula or formulas that could fit this molar ratio (assuming pyrosulfate and not acid sulfates to be present).

Table VI lists the reactions obtained with orthophosphoric acid and Table VII gives the reactions obtained with metaphosphoric acid. The high phosphate content of many of the precipitates suggests that in those cases polyphosphates were formed. The precipitates produced by orthophosphoric acid were generally slow in forming and often they were in the form of gels. The precipitate obtained from stannic chloride and orthophosphoric acid formed a foam and expanded to about 50 times its original volume when it was dried at 105°.

TABLE IV

REACTIONS OF TRIFLUOROACETATES WITH SULFURIC ACID

Trifluoroacetate	Ppt. formula[a]	Ppt. color	Extent of reaction
Sb(III)	$Sb_2(SO_4)_3$	White	Nearly complete
Ba	$BaSO_4$	White	Complete
Bi(III)	$Bi(HSO_4)_3$, 75%; $Bi_2(SO_4)_3$, 25%	White	Nearly complete
Cd	$CdSO_4$, 90%; $Cd(HSO_4)_2$, 10%	White	Complete
Ca	$CaSO_4$	White	Complete
Co(II)	$CoSO_4$	Pink	Complete
Cu(II)	$CuSO_4$, 84%; $Cu(HSO_4)_2$, 16%	White	Complete
Fe(III)	$Fe_2(SO_4)_3$	White	Complete
Pb(II)	$PbSO_4$, 57%; $Pb(HSO_4)_2$, 43%	White	Complete
Li	$LiHSO_4$	White	Partial
Mg	$Mg(HSO_4)_2$	White	Complete
Mn(II)	$MnSO_4$, 50%; $Mn(HSO_4)_2$, 50%	White	Complete
Hg(II)	$HgSO_4$	White	Nearly complete
Hg(I)	Hg_2SO_4	White	Nearly complete
Ni(II)	$NiSO_4$, 55%; $Ni(HSO_4)_2$, 45%	Pale green	Complete
Ag(I)	$AgHSO_4$, 70%; Ag_2SO_4, 30%	White	Partial
Sn(II)	$SnSO_4$	White	Nearly complete
Sr	$SrSO_4$	White	Complete
Zn	$ZnSO_4$	White	Complete

[a] Based on analysis of the precipitate after washing in trifluoroacetic acid and drying at 105°.

Chromium trioxide and potassium permanganate failed to precipitate dichromates or permanganates with the dissolved metal trifluoroacetates. They still retained their oxidizing activities but to somewhat lesser degree than in water. In the reactions with potassium permanganate, the manganese was reduced to the +3 state rather than the +4 or +2 state. The reactions of these substances are summarized in Tables VIII and IX. The oxidation reactions of chlorine are listed in Table X.

Besides the oxidation reactions with some trifluoroacetates, potassium permanganate also reacted slowly with the pure anhydrous solvent. After three hours, a solution of the salt had lost about 3% of its oxidizing power. Mass spectrum analyses of the gaseous products showed the presence of CO_2, CF_3COF and COF_2. In these analyses the major constituent found was carbon dioxide. The presence of some silicon tetrafluoride in the product indicated that part of the carbonyl fluoride reacted with the glass container. A solution of potassium permanganate in trifluoroacetic acid had a green color similar to that of a solution of potassium permanganate in concentrated sulfuric acid. The Mn(VII) was present as a volatile substance, probably Mn_2O_7, which distilled under vacuum with the trifluoroacetic acid. To avoid danger from possible explosions only small amounts of potassium permanganate were used.

(II) Solubilities of Gases in Trifluoroacetic Acid.—The concentrations given in Table II for gaseous reactants are those for saturated solutions at 26°. These quantities were

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TABLE V

REACTIONS OF TRIFLUOROACETATES WITH SULFUR TRIOXIDE

Trifluoroacetate	Color of ppt.	Extent of reaction	Ppt. analysis: % Cation	% SO_4^{-2}	Molar ratio Cation/SO_4^{-2}	Possible formula(s)
Sb(III)	White	(Colloidal)	43	53	1/1.56	$Sb_2(SO_4)_3$
Ba	White	Complete				$BaSO_4$
Bi(III)	White	Partial	64	30	1/1	?
Cd	White	Partial	52	45	1/1	$CdSO_4$
Ca	White	Complete	18	81	1/1.9	CaS_2O_7, 90% $CaSO_4$, 10%
Co(II)	Pink	Partial	39	60	1/0.9	$CoSO_4$
Cu(II)	White	Complete	35	66	1/1.25	$CuSO_4$, 75% CuS_2O_7, 25%
Pb(II)	White	Partial	56	50	1/1.9	PbS_2O_7, 90% $PbSO_4$, 10%
Mg	White	Complete	11	82	1/1.9	MgS_2O_7
Hg(II)	White	Partial	66	33	1/1	$HgSO_4$
Hg(I)	White	Nearly complete	69	29	1.14/1	HgS_2O_7, 75% Hg_2SO_4, 25%
Ni(II)	Pale green	Partial	23	74	1/2	NiS_2O_7
Ag(I)	White	Partial	67	33	1.8/1	Ag_2SO_4, 80% $Ag_2S_2O_7$, 20%
Sn(IV)[a]	White	Complete	40	32	1/1	?
Sn(II)	White	Partial	55	10% Cl^- 45	1/1	$SnSO_4$
Zn	White	Complete	40	59	1/1	$ZnSO_4$

[a] Sn(IV) is $SnCl_4$ and not a trifluoroacetate.

TABLE VI

REACTIONS OF TRIFLUOROACETATES WITH PHOSPHORIC ACID

Trifluoroacetate	Color of ppt.	Extent of reaction	Ppt. analysis: % Cation	% PO_4^{-3}	Molar ratio Cation PO_4^{---}	Possible formula(s)
Sb(III)	White	Partial	38	62	1/2.09	?
Bi(III)	White	Partial	53	48	1/2	?
Cd	White	Partial	28	71	1/3	?
Co(II)	Pink	Partial	38	62	1/1	$CoHPO_4$
Mn(II)	White	Partial	31	64	1/1.2	$MnHPO_4$, 80% $Mn(H_2PO_4)_2$, 20%
Hg(I)	White	Nearly complete	64	35	1/1.1	$Hg(H_2PO_4)_2$
Ag(I)	White	Partial	46	52	1/1.28	?
Sn(IV)[a]	White		43	38	1/1.1	?
Sn(II)	White	Nearly complete	36	60	1/2.08	$Sn(H_2PO_4)_2$
Zn	White		27	78	1/2.0	$Zn(H_2PO_4)_2$

[a] Sn(IV) is $SnCl_4$ rather than a trifluoroacetate.

TABLE VII

REACTIONS OF TRIFLUOROACETATES WITH METAPHOSPHORIC ACID

Trifluoroacetate	Color of ppt.	Extent of reaction	Ppt. analysis: % Cation	% PO_3^-	Molar ratio Cation PO_3^-	Possible formula(s)
Sb(III)	White	Nearly complete	52	34	1/1	$SbOPO_3$
Bi(III)	White	Nearly complete	48	52	1/3	$Bi(PO_3)_3$
Cd	White	Partial	42	53	1/1.8	$Cd(PO_3)_2$
Hg(I)	White	Partial	55	42	1/2	?
Ag(I)	White	Partial	46	53	1/1.55	?
Sn(II)	White	Nearly complete	57	39	1/1	?
Zn	White	Complete	29	66	1/2	$Zn(PO_3)_2$

TABLE VIII

REACTIONS OF SOLUTES WITH CHROMIC ACID ANHYDRIDE[a]

Solute[b]	Products: Oxidation	Reduction	Color of final soln.	Extent of reaction
Sb(III)	Sb(V)	Cr(III)	Light green	Partial
Mn(II)	Mn(III)	Cr(III)	Dark orange	?
Hg(I)	Hg(II)	Cr(III)	Light green	Complete
Sn(II)	Sn(IV)	Cr(III)	Light green	Complete
SO_2	H_2SO_4	Cr(III)	Light green	
H_2O_2	Peroxy–chromium soln.		Blue green	

[a] CrO_3 in trifluoroacetic acid is pale orange in color. [b] Except for SO_2 and H_2O_2 all the solutes were trifluoroacetates. All the solutes were colorless.

TABLE IX

REACTIONS OF TRIFLUOROACETATES WITH POTASSIUM PERMANGANATE

Solute	Product: Oxidation	Reduction	Color of final soln.	Extent of reaction
Sb(III)[a]	Sb(V)	Mn(III)	Brown-red	Complete
As(III)[b]	As(V)	Mn(III)	Brown-red	Partial
HCl	Cl_2(?)	Mn(III)	Brown-red	Partial
Mn(II)[a]	Mn(III)	Mn(III)	Brown-red	Partial
Hg(I)[a]	Hg(II)	Mn(III)	Brown-red	Partial
Sn(II)[a]	Sn(IV)	Mn(III)	Brown-red	Nearly complete
H_2S	S	Mn(II)	Colorless	
H_2S[c]	H_2SO_4	Mn(III)	Brown-red	
SO_2	H_2SO_4	Mn(III)	Brown-red	Complete

[a] These solutes are trifluoroacetates. [b] $AsOCF_3CO_2$. [c] Reaction with excess $KMnO_4$.

TABLE X

REACTIONS OF TRIFLUOROACETATES WITH CHLORINE

Trifluoroacetate	Product: Oxidation	Reduction	Color of product	Extent of reaction
Sb(III)	Sb(V)	Cl^-	Clear soln.	Partial
As(III)[a]	As(V)	Cl^-	White ppt.	Partial
Hg(I)	Hg(II)	Hg_2Cl_2	White ppt.	Nearly complete
Ag(I)[b]	AgCl, CO_2	CF_3Cl	White ppt. (colloidal)	
Sn(II)	Sn(IV)	Cl^-	Clear soln.	Nearly complete

[a] As(III) compound is $AsOCF_3CO_2$. [b] Reaction of $AgCF_3CO_2$ and Cl$_2$ was reported by Haszeldine.[7]

(7) R. N. Haszeldine, *J. Chem. Soc.*, 584 (1951).

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determined by using a gas measuring tube in such a way that the materials were confined over mercury. First, a sample of gas was placed in the tube and measured. Second, a measured sample of trifluoroacetic acid was added from a hypodermic syringe. The apparatus was then shaken mechanically for several hours until repeated measurements of the volume of gas in the tube indicated that the solution had become saturated. By using the measured changes in the volume of gas and by applying a correction for the partial pressure of trifluoroacetic acid vapor, it was possible to calculate the solubility coefficients given in Table XI. The coefficient given is that of Ostwald. It is the volume of gas (ml.) absorbed in unit volume of solvent (1 ml.), the pressure of the gas being that existing over the solution. The pressure given in the table is the difference between atmospheric pressure and the partial pressure of trifluoroacetic acid. To permit a comparison, the table also gives the corresponding solubility coefficients for aqueous solutions of the same gases as found in the literature[8,9] for a temperature of 25°, and partial pressures of 74 to 76 cm.

TABLE XI

SOLUBILITIES OF GASES IN TRIFLUOROACETIC ACID

Gas	Temp., °C.	Partial pressure of gas, cm.	Ml. of gas dissolved in one ml. of solvent In CF_3COOH	In H_2O[8,9]
CO_2	27	65.2	3.5	0.826
CO	26	64.6	0.0	0.0208
Cl_2	25.5	65.6	9.3	1.985
HBr	26	65.7	6.6	580
HCl	26	65.2	4.1	423
H_2S	26	65.7	8.6	2.46
N_2	26	63.6	0.1	0.0156
N_2O	24.5	66.5	4.3	0.65
O_2	27	64.2	0.2	0.0309
PH_3	26	65.3	15.9	?
SO_2	26	66.7	23.4	35.7

Discussion

Although trifluoroacetic acid is not a good ionizing solvent, rapid reactions resembling ionic reactions in water do occur. Many of these changes proceed to completion. The ease with which they occur suggests that the reactants exist as ion pairs. Many precipitation reactions which do not occur in water proceed in trifluoroacetic acid. Generally speaking, precipitation reactions of hydrogen sulfide which take place in acidic aqueous solutions also occur in anhydrous trifluoroacetic acid. An exception to this is the failure of lead sulfide to precipitate in trifluoroacetic acid. A large number of precipitates were obtained in trifluoroacetic acid which are not produced in water. This is especially true for the precipitation of the perchlorates.

The observed high solubilities of gases confirm other studies[2,4] which have indicated the excellence of trifluoroacetic acid as a solvent. Most of the gases tested are considerably more soluble in the acid than in water. The exceptions to this are the hydrogen halides and sulfur dioxide which are highly soluble in water, because they react with the solvent.

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(8) Seidell, "Solubilities of Inorganic and Metal Organic Compounds," Vol. 1, 3rd Ed., D. Van Nostrand Co., New York, N. Y., 1940.

(9) "International Critical Tables," Vol. III, McGraw-Hill Book Co., New York, N. Y., 1928, pp. 256–258.

[CONTRIBUTION FROM THE RICHARDSON CHEMISTRY LABORATORY OF TULANE UNIVERSITY]

Inorganic Complex Compounds Containing Polydentate Groups. XII. Cobalt(II) Complexes of Tetraethylenepentamine

BY HANS B. JONASSEN AND FRED W. FREY[1]

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The complexing tendency of tetraethylenepentamine (abbrev. tetren) with the cobalt(II) ion has been determined. The data indicates that all five amino groups of tetren coördinate. The sixth coördinating position can be occupied by H_2O, CH_3OH or the OH^- ion. The complexity constants of $[CotetrenH_2O]^{2+}$ have been determined at 25, 35 and 45°. The complex ion $[CoTetrenOH]^{1+}$ has been shown to oxygenate reversibly with only a slight amount of oxidation.

Introduction

The metal complexes of polyamines containing up to four amino groups have been investigated extensively.[2,3]

The purification of tetraethylenepentamine (abbrev. tetren) the next higher polyamine has only recently been accomplished.[4]

The present study was undertaken to investigate the type of complexes formed between the cobalt(II) ion and tetren.

(1) Abstracted in part from the Ph.D. dissertation of Fred W. Frey, Tulane University, 1954.

(2) G. Schwarzenbach, *Helv. Chim. Acta*, **33**, 974 (1950).

(3) H. B. Jonassen, G. G. Hurst, R. B. LeBlanc and W. Meibohm, THIS JOURNAL, **56**, 16 (1952).

(4) H. B. Jonassen, F. W. Frey and A. Schaffner, *ibid.*, **79**, 1950 (1957).

Experimental

A. Materials.—The tetren was obtained from the Carbide and Carbon Corporation and purified as described previously.[4] All other chemicals were C.P. materials.

B. Instruments.—The *p*H measurements were made with a Model G *p*H meter standardized with Beckman buffer solutions of *p*H 4, 7 and 10. The solutions were measured in constant temperature baths at 25 ± 0.2°, 35 ± 0.2°, and 45 ± 0.2°. The spectrophotometric measurements were made on a Beckman Model B spectrophotometer with matched Corex cells. The conductometric titrations were performed as described earlier.[5]

C. Determination of Log *K* Values of $[CotetrenH_2O](ClO_4)_2$.—The complexity constants of the cobalt tetren complex were determined by the method of Bjerrum[6] at 25,

(5) H. B. Jonassen, R. E. Reeves and L. Segal, *ibid.*, **77**, 2467 (1955).

(6) J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Sons, Copenhagen, 1941.

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35 and 45°; 100 ml. of a solution 0.001 *M* in tetren 0.5 *M* in HNO_3 and 0.0005 *M* in $Co(ClO_4)_2$ were titrated with 0.01 *M* NaOH. The values of log *K* are 15.07 at 25°, 14.97 at 35° and 14.87 at 45°.

D. **Conductometric Titrations. 1. Titration of Tetren with $CoCl_2$.**—In the titration of 2 ml. of 0.2134 *M* tetren in acetone with 0.051 *M* $CoCl_2$ in acetone breaks occur at mole ratios of about 0.98 cobalt to 1 tetren and 1.98 cobalt to 1 tetren (Fig. 1). A precipitate forms which initially is brown but becomes green as excess of $CoCl_2$ is added.

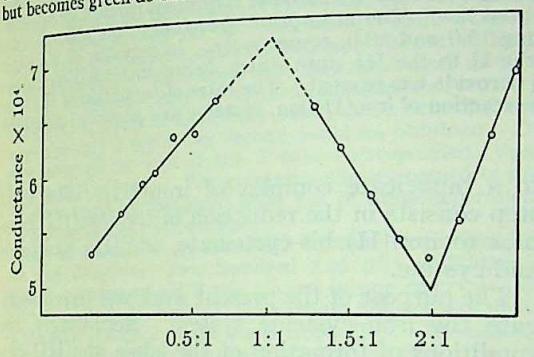

Fig. 1.—Ratio Co/amine.

2. **Titration of $CoCl_2$ with Tetren.**—Ten ml. of 0.051 *M* $CoCl_2$ in acetone was titrated with 0.2134 *M* tetren in acetone. A break occurs at a ratio of 2 moles Co to 1 of amine. The precipitate is initially green but turns brown as more tetren is added.

3. **Titration of Tetren with $Co(ClO_4)_2$.**—A methanol solution of tetren was titrated with $Co(ClO_4)_2$ in methanol, since the complex is insoluble in methanol. Two ml. of 0.599 *M* tetren was titrated with 0.559 *M* $Co(ClO_4)_2$ at 1 and 30°. A break in the curve occurs at a mole ratio of 1.08 moles tetren to 1 mole cobalt.

E. **Preparation of the Solid Complexes. 1. [Cotetren-CH_3OH]Cl_2.**—Since the conductometric titration curves indicated the brown species formed in excess tetren, this complex was precipitated from a solution containing an excess of tetren. Three hundred ml. of 0.041 *M* $CoCl_2$ in acetone was added to 100 ml. of 0.2134 *M* tetren in acetone. Acetone was added to complete precipitation. The precipitate was filtered by suction, recrystallized from methanol and acetone.

Anal. Calcd. for [CotetrenCH_3OH]Cl_2: Cl, 20.2; N, 19.9. Found: Cl, 19.76; N, 19.29.

2. [CotetrenCH_3OH]$CoCl_4$.—Seventy-five ml. of 0.234 *M* tetren in acetone was added to 400 ml. of 0.051 *M* $CoCl_2$ in acetone. The precipitate was filtered and recrystallized from methanol and acetone.

Anal. Calcd. for [CotetrenCH_3OH]$CoCl_4$: N, 14.5; Cl, 29.5. Found: N, 14.04; Cl, 29.90.

In order to establish the existence of the $CoCl_4^{2-}$ ion the precipitate was allowed to come to equilibrium with acetone at 25° and the spectra observed. A maximum is observed at about 695 mμ which has been described by Katzin[7] to the $CoCl_4^{2-}$ ion.

3. [CotetrenCH_3OH]$(ClO_4)_2$.—Twenty-two ml. of 0.56 *M* $Co(ClO_4)_2$ was added to 20 ml. of 0.6015 *M* tetren in methanol and precipitation completed by addition of 25 ml. of ether. The brown precipitate was filtered and washed with methanol and dried in an oven at 90°.

Anal. Calcd. for [CotetrenCH_3OH]$(ClO_4)_2$: Co, 12.2; N, 14.7. Found: Co, 12.2; N, 14.35.

4. [Cotetren$OH]_2PtCl_6$.—Although the perchlorate complex is only slightly soluble in CH_3OH, it dissolves very rapidly in methanolic NaOH or KOH. From this it was concluded that the methanol molecule was replaced by hydroxide ions. Chloroplatinic acid in methanol was added and a brown precipitate was formed.

Anal. Calcd. for [Cotetren$OH]_2[PtCl_6]$: Pt, 20.6; Co, 12.4. Found: Pt, 20.6; Co, 12.1.

F. **Oxygenation and Deoxygenation of** [CotetrenOH]ClO_4. **1. Oxygenation.**—Attempts to oxygenate [Cotetren$H_2O]^{2+}$ in water solution were unsuccessful in neutral or basic solution, oxidation to cobalt(III) occurs.

However, when 10 ml. of methanolic NaOH solution containing 0.0913 g. of the complex was placed in an oxygen atmosphere at 32° a rapid pickup of oxygen occurred during the first 10 minutes, as determined in a vapor pressure apparatus. After 15 minutes, further volume changes were very slight indicating that only extremely slow oxidation occurs.

Figure 2 shows the curve obtained when volume is plotted against time in minutes. A blank of 10 ml. of methanolic NaOH in the system produced a negligible volume decrease of 0.1 ml.

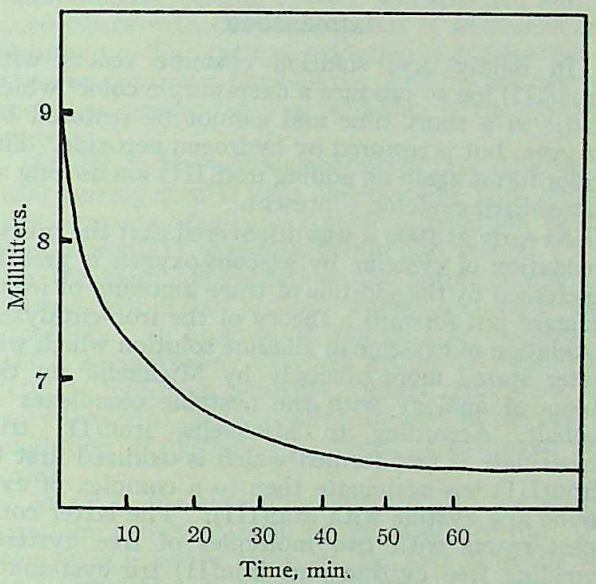

Fig. 2.—Rate of oxygenation.

2. **Deoxygenation of the Complex.**—Eighteen ml. of a methanolic NaOH solution containing 0.15 g. of the oxygenated complex were placed in a vapor pressure apparatus until equilibrium vapor pressure was obtained. Similarly the vapor pressure of a blank 18 ml. of methanolic NaOH solution was measured. The corrected volume of oxygen released by the oxygenated complex was 4.09 ml.

Discussion of Results

As expected, the log *K* values for the 1:1 complexes are greater for $[Cotetren]^{2+}$ (log *K* formation = 15.1) than for $[Cotrien]^{2+}$ (log *K* formation = 11.1). Analysis of the precipitates indicate that methanol and hydroxide ions seemingly can occupy the sixth position in this complex.

As the oxygenation and deoxygenation data show only in a methanolic NaOH solution can the complex become oxygenated; in water solution *oxidation* occurs immediately. If it is assumed that oxygenation occurs through an oxygen–oxygen bridge between two cobalt complexes the theoretical volume of oxygen recovered from the sample should have been 4.43 ml. whereas experimentally only 4.09 ml. was recovered, a decrease of about 8%. This seems to indicate some oxidation occurred for these complexes in line with the observation of the slight decrease in volume during the oxygenation studies.

Acknowledgment.—The financial support of the Office of Ordnance Research, U. S. Army, for this and continuing investigations is gratefully acknowledged.

New Orleans, La.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF OREGON]

The Oxidation of Cysteine by Iron and Hydrogen Peroxide

BY ROY G. NEVILLE[1,2]

RECEIVED DECEMBER 13, 1956

The conditions of formation of the labile purple iron(III) cysteine complex in oxygen-free acid and basic solution have been studied. In acid solution the complex decomposes in less than 0.5 sec., but under basic conditions persists for approximately 40 min., the color fading according to a roughly exponential law. The absorption spectrum of the residual color possesses maxima at 445 and 570 mμ, the extinction values being 15.0 and 19.0, respectively. In presence of hydrogen peroxide the cysteine complex of iron is rapidly oxidized from the II to the III state which, being unstable, decomposes yielding cystine and iron(II) ion, the process continuing until all peroxide has reacted. The rates of formation of the iron-(III) cysteine complex, its oxidation by peroxide at *p*H 8, and the reaction of iron(II) ion, cysteine and peroxide, have been studied using a rapid-flow technique.

Introduction

In mildly acid solution cysteine reacts with iron(III) ion to produce a deep-purple color[3] which fades in a short time and cannot be restored by oxygen, but is restored by hydrogen peroxide. The color forms again on adding iron(III) ion as long as unoxidized cysteine is present.

As early as 1909 it was discovered that the rate of oxidation of cysteine by gaseous oxygen is greatly increased by the addition of trace amounts of iron.[4] Harris[5] put forward a theory of the iron-catalyzed oxidation of cysteine in alkaline solution which was later stated more precisely by Michaelis[6] on the basis of analogy with the cysteine complexes of cobalt. According to Michaelis, iron(II) tris-cysteinate is first formed which is oxidized first to iron(III) tris-cysteinate then to a complex of cysteine and cystine with iron(III). The latter complex reacts with two molecules of free cysteine yielding free cystine and iron(II) tris-cysteinate. This cyclic process results in the oxidation of all cysteine present to cystine.

When gaseous oxygen is the oxidant it is reduced to water, hydrogen peroxide being an intermediate. Pirie[7] showed that addition of peroxide to an iron-containing cysteine solution increased the rate of oxidation, but no direct evidence for the existence of hydrogen peroxide in this reaction was available until Schales[8] carried out the reaction in presence of luminol (5-amino-2,3-dihydro-1,4-phthalazinedione), when a very pronounced chemiluminescence resulted. This luminescent reaction is known to occur only in presence of peroxide ion which may thus be detected in concentrations down to 1 part in 10^7.

Working in absence of oxygen, Schubert[9] isolated a number of complexes of iron with cysteine, and presented a theory similar to that of Michaelis but differing in the constitution of the complexes assumed as intermediates. According to Schubert, at *p*H 8–10, the first formed complex is iron (II) bis-cysteinate which is oxidized by oxygen to a binucleate complex of iron(III). The third step consists in the reduction of the iron(III) complex to iron(II) bis-cysteinate, iron(II) hydroxide and cystine.

The purpose of the present work was to reinvestigate the iron–cysteine system. Accordingly, the conditions of formation of the labile iron(III) cysteine complex have been studied in the presence and absence of peroxide ion, and the views of Michaelis and Schubert have been substantiated.

Experimental

Chemicals.—All reagents were of C.P. grade. Cysteine hydrochloride was supplied by Eastman Organic Chemicals, Rochester, New York, and was used without further purification. Assay of fresh samples by three independent methods showed it to contain about 94% –SH group.[10] A portion of cysteine oxidized with iron-free nitric acid gave no color with thiocyanate and thus may be considered free from iron.

Equipment.—Spectral determinations were carried out using a Beckman spectrophotometer, model DU, and 1 cm. quartz cells fitted with ground-glass stoppers.

Cysteine Complex of Iron(III). Formation in Acid Solution.—Experiments were conducted under nitrogen in which 0.1 ml. of 0.01 *M* iron(III) ammonium sulfate was added to eight oxygen-free solutions of 0.01 *M* hydrochloric acid (10 ml. each) containing cysteine ranging in concentration from 10^{-1} to 5×10^{-5} *M*. Water used to prepare solutions was freed from dissolved oxygen by boiling, sweeping out with oxygen-free nitrogen and storing under nitrogen. In all cases a transient purple coloration was produced which persisted for approximately 0.5 sec.

Cysteine Complex of Iron(III). Formation in Alkaline Solution.—Repeating the above experiments in 0.01 *M* ammonia solution the same purple color formed. This faded gradually on standing, usually persisting for about 20 to 40 minutes depending on the concentration of cysteine.

Cysteine Complex of Iron(III). From Iron(II) Cysteine and Hydrogen Peroxide.—To six oxygen-free solutions of 0.01 *M* hydrochloric acid, containing cysteine ranging in concentration from 10^{-1} to 5×10^{-4} *M*, was added 0.1 ml. of 0.01 *M* iron(II) ammonium sulfate, free from iron(III) ion. Reactions were conducted under nitrogen. To each solution 3.0 ml. of 3% hydrogen peroxide was added. No color was produced, but positive reaction with thiocyanate ion indicated the presence of iron(III). On standing cysteic acid precipitated.

A similar series of experiments at *p*H 8 likewise gave no coloration with peroxide, but within a few seconds cysteic acid precipitated. That all cysteine had reacted was shown by a negative reaction with sodium nitroprusside.

Spectrum of Iron(III) Cysteine Complex.—Absorption spectra of 9×10^{-3} *M* solutions of complex were determined between 400 and 600 mμ. Solutions were prepared by mixing 10.0 ml. of 0.01 *M* cysteine in ammonia at *p*H 9 with 1.0 ml. aliquots of either 0.01 *M* iron(II) ammonium sulfate or iron(III) ammonium sulfate. The initially intense purple of the iron(III) cysteine was allowed to fade until the intensity of color remained sensibly constant, as deter-

(1) Adapted in part from a portion of the Ph.D. thesis of Roy G. Neville placed in the Library, University of Oregon, Eugene, Oregon, September, 1954.

(2) For reprints: 3013 63rd Avenue S. W., Seattle 16, Washington.

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mined by plotting the optical density at a given wave length (445 mμ) *versus* time. The spectrum was then determined. Absorption maxima occur at 445 and 570 mμ, the extinction values being 15.0 and 19.0, respectively. The spectra obtained from either iron(II) or iron(III) ion were identical.

Apparatus for Determining Rates of Fast Reactions.—A simplified apparatus, based on the principle used by Roughton and Millikan,[11] was employed to obtain semi-quantitative measurements on the rates of reaction of cysteine with iron.

The apparatus consisted of two 250-ml. tap-funnels (serving as reservoirs for the reactants) which were connected to a T-tube, one arm of which was 150 cm. in length (internal diameter, 0.36 cm.) and was graduated in centimeters. Pressure could be applied simultaneously to both solutions by means of a mercury head, and a rate of flow of approximately 1 meter per second could be obtained. One centimeter on the arm of the T-tube corresponded, therefore, to 0.01 second. For greatest accuracy complete mixing must occur by turbulent flow, but in these experiments the flow was largely streamline.

Rate of Formation of Iron(III) Cysteine from Iron(III) Ion and Cysteine.—Two hundred and fifty milliliters of 0.01 *M* cysteine at *p*H 8 was placed in one reservoir, and 250 ml. of 0.01 *M* iron(III) ammonium sulfate was placed in the other reservoir of the above apparatus. By means of stopcocks, the iron solution was allowed to flow, then the cysteine was run in. The deep-purple iron(III) complex formed immediately, the maximum intensity of color being within 1 cm. of the mixing chamber.

Rate of Formation of Iron(III) Cysteine from Iron(II) Ion, Cysteine and Hydrogen Peroxide.—Two hundred and fifty milliliters of 0.01 *M* cysteine in dilute ammonia at *p*H 8 (containing 1.0 ml. of 0.01 *M* iron(II) ion per 100 ml. of cysteine solution) were allowed to react with 0.01 *M* hydrogen peroxide (iron-free) in the mixing chamber of the apparatus. The rates of flow of the two solutions were equal. The cysteine solution was purple due to iron(III) complex formed by oxidation of iron(II) ion by the oxygen in solution. This color served to show the course of the reaction. On mixing the two solutions the color faded within 1 cm. of the mixing chamber.

Rate of Oxidation of Cysteine by Hydrogen Peroxide.—Two hundred and fifty milliliters of 0.01 *M* cysteine (iron-free) in dilute ammonia at *p*H 8, containing a trace of nitroprusside ion, was allowed to react with 0.01 *M* hydrogen peroxide in the mixing chamber of the apparatus. Most of the sulfhydryl-nitroprusside color faded within 1 cm. of the mixing chamber, but a faint color persisted to a length of 60 cm.

Results and Discussion

Under oxygen-free conditions, addition of small amounts of iron(III) ion to acid solutions 10^{-1} to 5×10^{-5} *M* in cysteine produces a transient purple complex which persists for about 0.5 second or less. Similar experiments at *p*H 8–9 result in a purple complex which fades gradually but persists for 20–40 minutes depending on the cysteine concentration. Decomposition of this complex is thus strongly catalyzed by hydrogen ions. Addition of hydrogen peroxide to oxygen-free dilute acid or alkaline solutions of cysteine containing iron(II) ion produces no colored complex. That a very rapid oxidation occurs is demonstrated by the precipitation of crystalline cysteic acid a few seconds after peroxide addition.

These oxidation phenomena may be interpreted in the following manner. Hydrogen peroxide oxidizes the iron(II) cysteine complex to the iron(III) state which, being unstable, decomposes immediately yielding cystine and iron(II) ion, in accordance with the observations of Michaelis and Schubert. The cycle of oxidation and reduction of the iron continues until all the peroxide has reacted and then ceases, the iron returning to the divalent state.

At *p*H 8, the semi-quantitative rate data show that mixing iron(II) ion and cysteine with hydrogen peroxide results in complete oxidation of the purple iron(III) complex within 0.01 second. Under the same *p*H conditions the purple complex is formed within 0.01 second on mixing cysteine with iron(III). In absence of iron 0.01 *M* cysteine at *p*H 8 is completely oxidized within 0.6 second by 0.01 *M* hydrogen peroxide. These data show the very powerful catalytic effect of iron on the rate of oxidation of cysteine by oxygen or hydrogen peroxide.

At *p*H 9, the absorption spectrum of the purple complex shows maxima at 445 and 570 mμ. By comparison, at the same *p*H, the spectra of the bis- and green tris-complexes of cobalt(III) with cysteine and 2-mercaptoethylamine (in which amino and sulfhydryl coördination occur) possess maxima at 440 and 570–580 mμ.[12] Coördination in the iron(III) complex may also occur *via* the amino and sulfhydryl groups of cysteine, but at the present time there is no evidence to substantiate this hypothesis.

Acknowledgment.—The author wishes to express his thanks to the Research Corporation for financial assistance throughout this investigation.

EUGENE, OREGON

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[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

The Association of SCN^- with $Cr(H_2O)_6^{+3}$, $Cr(NH_3)_6^{+3}$, and $Cr(NH_3)_5Cl^{++}$ in Aqueous Solution[1]

BY ARTHUR L. PHIPPS[2] AND ROBERT A. PLANE

RECEIVED DECEMBER 3, 1956

Measurements of ultraviolet absorption spectra were made which indicate that there is slight association of SCN^- with $Cr(H_2O)_6^{+3}$, $Cr(NH_3)_6^{+3}$ and $Cr(NH_3)_5Cl^{+2}$ in aqueous solutions. Limits were assigned to equilibrium constants for the associations and for all three cases the constant lay between 10^{-1} and 10^{-3}. For the $Cr(H_2O)_6^{+3}$ and $Cr(NH_3)_6^{+3}$ measurements were made over the temperature range 3 to 26°. From such measurements the enthalpy change on association was found to be 0 ± 1 kcal. mole^{-1} and the entropy change at 25° was limited to the range -1.2 to -17 cal. deg.$^{-1}$ mole^{-1} for $Cr(H_2O)_6^{+3}$ and -1.2 to -14 cal. deg.$^{-1}$ mole^{-1} for $Cr(NH_3)_6^{+3}$. This entropy decrease is primarily responsible for the fact that SCN^- shows less tendency to associate with complex cations than do other anions (such as halides) which have previously been studied. The entropy decrease could arise from the loss of rotational entropy of SCN^- on association.

The association in solution of complex cations of the type $Co(NH_3)_6^{+3}$, $Cr(NH_3)_6^{+3}$, etc., with various anions has in recent years received considerable investigation.[3-13] For practically all of the systems studied association constants were found to lie between about ten and a thousand. Yet in most studies the total ionic strength was maintained constant by addition of sodium perchlorate, and it was assumed that there was no association of ClO_4^- with the highly charged cation. From the consistencies of the individual investigations this was apparently a valid conclusion, however a possibly surprising one in view of results that all other anions showed a marked tendency toward association. It seemed of interest to establish more directly the specificity of "outer sphere" association and if possible to determine factors which are responsible for specificity.

Of the methods used for detection and study of outer sphere complexes probably the most direct involves measurement of ultraviolet absorption spectra. It is generally found that in the ultraviolet region, ionic association is usually accompanied either by the appearance of a new absorption band, or by a shift of an existing band. These spectral changes can be attributed either to the introduction of a new electronic transition (for example the transfer of an electron from anion to cation), or to the perturbation of an existing electronic transition. The present authors found no spectral changes with changing concentration in solutions of $Cr(H_2O)_6^{+3}$ and ClO_4^-, even when ClO_4^- concentration was greater than 4 *M*. (The cation $Cr(H_2O)_6^{+3}$ was picked on solubility considerations and is suitable since it undergoes substitution reactions quite slowly.[14]) Such results do not necessarily indicate lack of association between these ions since the spectrum might remain unchanged by association, or accompanying changes might occur in the far ultraviolet. It was necessary therefore to pick a system in which a spectral change could be noted, but one in which association might be expected to be slight. From earlier work,[10,12] thiocyanate ion seemed to be suitable on both counts.

Experimental

The general experimental procedure involved rapidly mixing temperature equilibrated solutions to give a final solution of known composition. This solution was immediately placed in a thermostated cell of a Beckman DU quartz spectrophotometer and absorption measurements begun. The entire process, from mixing to measurement, required but 45 seconds. The time was kept short in order to minimize substitution reaction and other side reactions. The most serious such side reaction is a decomposition of thiocyanate in acidic solution to give an unknown species which is highly absorbing in the ultraviolet region. (Solutions containing $Cr(H_2O)_6^{+3}$ were made acidic, 0.05 or 0.10 *M* in order to suppress hydrolysis). At the wave lengths and temperatures used, the rate of change of the spectra amounted to several per cent. per minute, so that readings were taken periodically and extrapolated to time of mixing.

Absorption spectra of solutions of $Cr(H_2O)_6(ClO_4)_3$ plus $HClO_4$, of $Cr(NH_3)_6(ClO_4)_3$, and of $Cr(NH_3)_5Cl(ClO_4)_2$ were measured, individually and after being mixed with solutions containing NaSCN in the wave length region 2,600 to 2,900 Å. Every solution containing thiocyanate was also checked at 4750 Å., the wave length of maximum absorption of $FeSCN^{++}$, to ensure absence of ferric ion.

Materials.—Chromic perchlorate was made by reducing CrO_3 in $HClO_4$ with 30% H_2O_2. Excess H_2O_2 was destroyed by heating in the presence of platinized Pt. The solution was evaporated to crystals and these were recrystallized from 0.5 *M* $HClO_4$. Chromic analyses were performed spectrophotometrically following oxidation to chromate. Mallinckrodt AR 70% $HClO_4$ was used without purification. Reagent grade NaSCN was twice recrystallized from redistilled water. $NaClO_4$ was made by exactly neutralizing analytical reagent NaOH with analytical reagent $HClO_4$ and crystallizing. $Cr(NH_3)_6(ClO_4)_3$ was prepared by dissolving anhydrous $CrCl_3$ in liquid NH_3 in the presence of a bit of dissolved sodium.[15] The residue was dissolved in water, filtered, and $Cr(NH_3)_6(ClO_4)_3$ precipitated from the filtrate by addition of concentrated $HClO_4$. The product was washed with alcohol and ether and dried under vacuum in the dark. Chloropentamminechromium(III) chloride was obtained as a by-product and was purified by dissolving it in warm water, filtering and precipitating with concen-

(1) From the thesis submitted by Arthur L. Phipps to the Graduate School of Cornell University in partial fulfillment of the requirements for the degree of Master of Science.

(2) Westvaco Mineral Products Division, P. O. Box 920, Modesto, California.

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trated HCl. The salt was filtered, washed with alcohol and ether, and dried under vacuum. The water used in all experiments was redistilled in a Barnstead block tin still.

Results

$Cr(H_2O)_6^{+3}$ + SCN^-.—The results of a typical series of experiments are shown in Fig. 1, which gives the optical density ($\log I_0/I$) for one cm. light path lengths of 0.040 *M* $Cr(H_2O)_6(ClO_4)_3$, 0.40 *M*

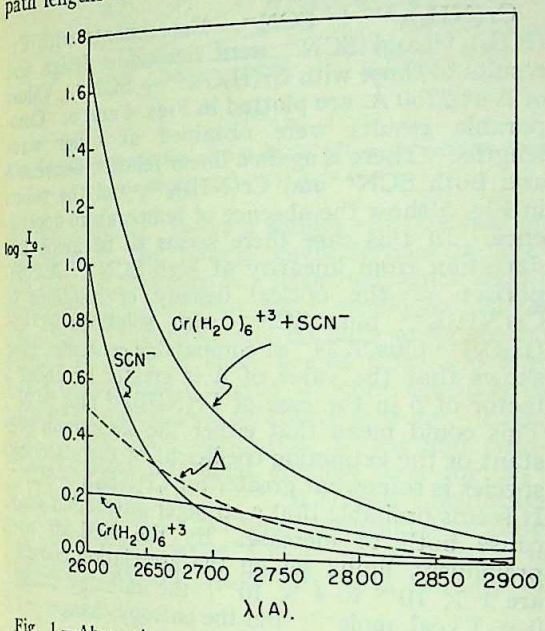

Fig. 1.—Absorption spectra of various ions in acidic solution at 3° for 0.04 *M* $Cr(H_2O)_6(ClO_4)_3$ and 1 *M* NaSCN in 0.1 *M* $HClO_4$.

though the chromic spectrum is *not* affected by change of acidity or temperature in the ranges covered by these experiments, the SCN^- spectrum was somewhat affected—increasing both with increasing acidity and with increasing temperature. In every case the Δs were obtained by subtracting the contribution of the $Cr(H_2O)_6^{+3}$ and that of a NaSCN solution identical with the final mixture except that $Cr(H_2O)_6(ClO_4)_3$ was absent.

Because of the decrease of Δ and of the optical density of SCN^- with increasing wave length, measurements at low SCN^- concentration were most precise at shorter wave length, and those at high SCN^-, at longer wave length. The shortest wave length at which the entire range of SCN^- concentration from 0.02 to 2.0 *M* could be precisely studied was 2750 Å. The results of experiments at this wave length are given in Fig. 2. Values of Δ are plotted *versus* formal concentration of SCN^-, and the plot shows that experiments at two acidities, three temperatures, with and without added $NaClO_4$ (to make total ionic strength 2 *M*) form a single curve, which is essentially a straight line. Experiments at other wave lengths give similar results.

If the association between SCN^- and $Cr(H_2O)_6^{+3}$ is governed by the equilibrium

$$Cr(H_2O)_6^{+3} + SCN^- \longrightarrow Cr(H_2O)_6SCN^{+2}$$

as seems to be true of all other cases studied,[3-13] then within the accessible range of SCN^- concentrations a significant fraction of the chromic ion is never converted to the associated species. Significant conversion would cause the plot of Δ *vs.* SCN^- concentration to approach zero slope; on the other hand only slight association requires the plot to approach a straight line of finite slope. From an assessment of errors and precision of the present experiments, it is found that an association equilibrium constant greater than 0.1 would cause detectable de-

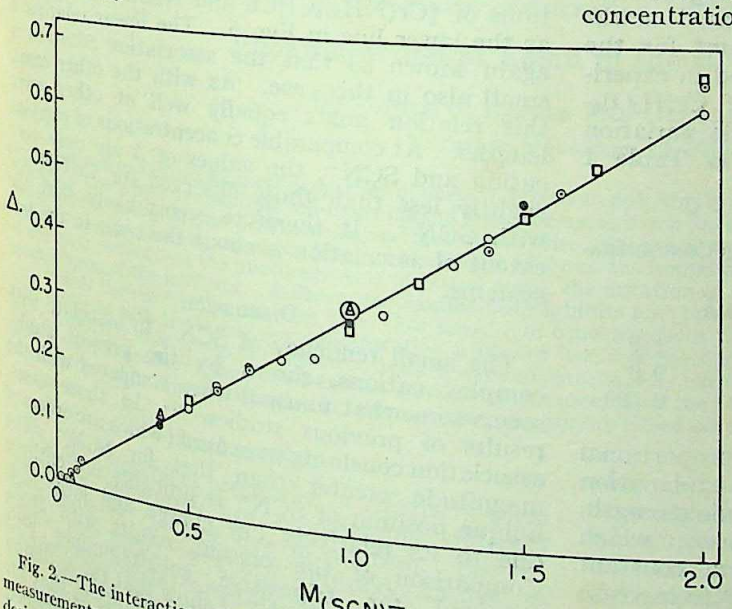

Fig. 2.—The interaction of 0.04 *M* $Cr(H_2O)_6^{+3}$ and various concentrations of SCN^-. Data obtained from optical density measurements at 2750 A. Circles represent points obtained at 3°; squares, at 15°; triangles, at 26°. Open symbols designate solutions containing 0.05 *M* $HClO_4$; symbols with dots, solutions containing 0.1 *M* $HClO_4$; blackened symbols, solutions containing sufficient $NaClO_4$ to make total ionic strength 2 *M*.

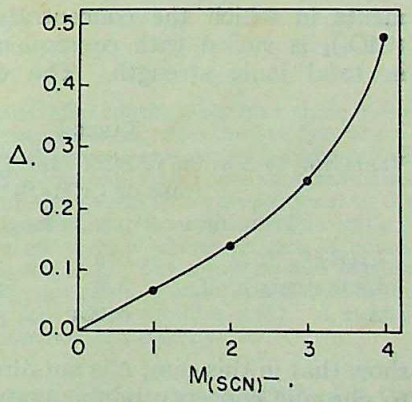

Fig. 3.—The interaction of 0.04 *M* $Cr(H_2O)_6^{+3}$ and SCN^-. Data obtained at 2900 Å., 3° and in solutions containing 0.05 *M* $HClO_4$.

NaSCN and a mixture of the two, all solutions 0.10 *M* in $HClO_4$, and at 3°. The dotted line in the figure represents the optical density of the mixture minus that of the separate chromic and thiocyanate solutions (hereafter called Δ). Al-

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viation from the straight line described by the points in Fig. 2. In addition to this upper limit placed on the value of K, a lower limit can be assigned by assuming a maximum value for the extinction coefficient of the associated species. If this coefficient is assumed to be 10^4 at 2750 Å., it follows from the data plotted in Fig. 2 that at 1.0 M SCN^-, the concentration of the ion pair would be 3.2×10^{-5} and K would be 8×10^{-4}.

It might seem somewhat curious that even if the association constant for this system is small, points at various ionic strengths (both those in which the total ionic strength was allowed to vary from 0.36 to 2.34 and those in which the total ionic strength was maintained constant at 2.00 by addition of $NaClO_4$) describe a straight line. This would seem to indicate that over the concentration range investigated, the pertinent activity coefficients ratios of individual species are nearly constant. It is perhaps significant that the activity coefficients ($\gamma_\pm$) for NaSCN which comprises the bulk concentration in most experiments vary by less than $\pm 5\%$ in the ionic strength range of these experiments, and those of $NaClO_4$, which comprises the bulk concentration in the remaining experiments are almost equally constant and differ from the NaSCN coefficients by about 10%.[16]

At higher SCN^- concentrations, a plot of Δ *vs.* concentration of SCN^- does not give a straight line. Data obtained at 2900 Å. are plotted in Fig. 3. The curvature is in the opposite direction demanded by that for the "saturation" of an association. In this concentration region the activity coefficients of NaSCN increased markedly,[16] and may quite possibly account for the deviation. Similar deviations are noted in experiments in which the concentration of $Cr(H_2O)_6(ClO_4)_3$ is varied with consequent wide variation in total ionic strength. The data in Table I

TABLE I

VARIATION OF Δ AT 0.5 M SCN^- AND VARIOUS CONCENTRATIONS OF $Cr(H_2O)_6^{+3}$

Temperature 3°; wave length 3090 Å.

$Cr(H_2O)_6^{+3}$, M	0.5	1.0	1.5
Ionic strength, M	3.6	6.6	9.6
Δ	0.054	0.196	0.509

show that in this case, Δ is not directly proportional to chromic concentration. Again the explanation could well lie in the fact that at high ionic strength, activity coefficients of SCN^- increase, which should cause the apparent association constant (based on concentrations not activities) to increase with increasing ionic strength.

It was noted earlier that the effect of temperature on observed values of Δ is quite small. If the assumption is made that the absorption process (*i.e.*, extinction coefficient of the associated species) is not affected by temperature, then any change in Δ with temperature is due to a change in the extent of association. From a comparison of duplicate points at the temperatures 3, 15 and 26° of Fig. 2, it is found that the change in equilibrium constant within this temperature range is less than 10% so that the enthalpy change for the association is within 1 kcal. $mole^{-1}$ of 0. With this value for ΔH and the two limits previously placed on the equilibrium constant, it is possible to place limits on the entropy change for the association. At 25°, the entropy change lies in the range -1.2 to -17 cal. deg^{-1} $mole^{-1}$.

$Cr(NH_3)_6^{+3}$ + SCN^-.—Experiments with $Cr(NH_3)_6^{+3}$ and SCN^- were similar in design and results to those with $Cr(H_2O)_6^{+3}$ + SCN^-. Values of Δ at 2750 Å. are plotted in Figs. 4 and 5. Comparable results were obtained at other wave lengths. There is again a linear relation between Δ and both SCN^- and $Cr(NH_3)_6^{+3}$, and the points in Fig. 5 show the absence of temperature dependence. In this case there seems to be much less deviation from linearity at high SCN^-. A comparison of the optical density of solutions of $Cr(NH_3)_6^{+3}$ plus SCN^- with solutions of $Cr(H_2O)_6^{+3}$ plus SCN^- at comparable concentrations, shows that the value of Δ is greater by about a factor of 5 in the case of $Cr(NH_3)_6^{+3}$ plus SCN^-. This could mean that either the association constant or the extinction coefficient of the associated species is somewhat greater for $Cr(NH_3)_6^{+3}$–SCN^-. It seems probable that a stronger interaction would cause both to increase. By the methods used previously, limits set on the association constant are 1×10^{-1} to 4×10^{-3}; the enthalpy change, 0 ± 1 kcal. $mole^{-1}$; and the entropy change, -1.2 to -14 cal. $deg.^{-1}$ $mole^{-1}$.

$Cr(NH_3)_5Cl^{++}$–SCN^-.—Experiments with solutions of $[Cr(NH_3)_5Cl]Cl_2$ and NaSCN are plotted as the lower line in Fig. 5. The linear relation is again shown so that the association constant is small also in this case. As with the other cases, this relation holds equally well at other wave lengths. At comparable concentrations of complex cation and SCN^-, the values of Δ are only very slightly less than those observed for $Cr(NH_3)_6^{+3}$ with SCN^-. It therefore seems likely that the extent of association is about the same in the two systems.

Discussion

The small tendency of SCN^- to associate with complex cations, shown by the present study, seems somewhat unusual when compared with the results of previous studies.[3-13] In those cases, association constants were found which are orders of magnitude greater than that for SCN^-. The unique position of SCN^- is probably not entirely due to its relatively low charge and large size. Comparison of the present results with those obtained for tripositive cobaltammines plus SO_4^{--},[13] Cl^-, Br^- and I^-,[8] show that the enthalpy of association for SCN^- is as favorable as that for any of the other cases. (The values of ΔH obtained in the previous studies range from 0 to +3.7 kcal./mole). The significant difference between SCN^- and other anions is the entropy change which accompanies association. Whereas the entropy term for the associations noted above are all positive by 10 or more calorie $mole^{-1}$ $degree^{-1}$, that for SCN^- is negative. Of the anions previously

(16) R. A. Robinson and R. H. Stokes, *Trans. Faraday Soc.*, 45, 612 (1949).

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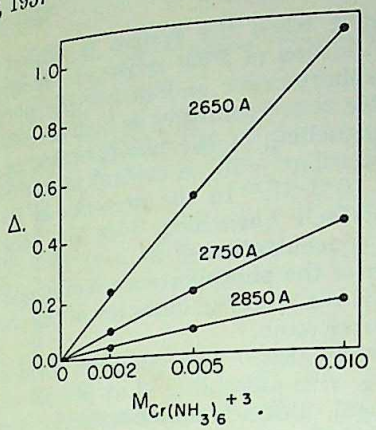

Fig. 4.—The interaction of 1.0 *M* SCN^- with various concentrations of $Cr(NH_3)_6^{+3}$ at 3°.

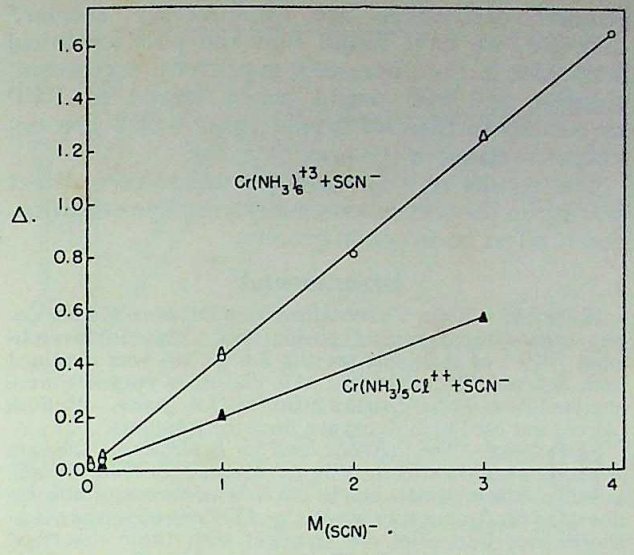

Fig. 5.—The interaction of 0.01 *M* $Cr(NH_3)_6^{+3}$ and 0.005 *M* $Cr(NH_3)_5Cl^{+2}$ with various concentrations of SCN^-. Data obtained from optical density measurements at 2750 Å. Circles represent points obtained at 3°; triangles, at 26°.

studied, only N_3^- shows a similar entropy loss on association.[8] The unique characteristic of N_3^- and SCN^- is that each is a linear ion which might possess rotational entropy which would be lost on association. Unfortunately, no data exist on the entropy of either of these anions from which it would be possible to decide whether the ions in aqueous solution possess rotational entropy. However, for gas phase association, Evans and Nancollas estimate rotational entropy loss for N_3^- of 11 cal. degree^{-1} mole^{-1}.[8] A similar calculation for SCN^- shows its gas phase rotational entropy loss to be 16 cal. degree^{-1} mole^{-1}. This value is sufficiently large to change the total entropy of association from a positive value, such as is found for other anions, to a negative value defined by the present experiments, and, hence, can account for the very slight tendency toward association noted for SCN^-.

ITHACA, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Photoreduction of Eosin in the Bound State[1a,b]

BY JUDITH S. BELLIN AND GERALD OSTER

RECEIVED NOVEMBER 30, 1956

The spectral and photochemical properties of eosin Y bound to polyvinylpyrrolidone differ considerably from those of the free dye. The bound dye exhibits self-quenching of fluorescence at much lower concentrations than does the free dye, whereas for self-quenching of phosphorescence (in rigid media) the opposite is true. Furthermore, *p*-phenylenediamine which quenches the phosphorescence of the free dye is without effect on the bound dye. Nitrobenzene retards the photoreduction of free eosin but inhibits the photoreduction of bound eosin, the duration of the inhibition period being proportional to the concentration of the inhibitor. *p*-Phenylenediamine both inhibits and retards the photoreduction of bound eosin while it only retards the reaction for the free dye. For small dye concentrations the quantum yield of photoreduction of bound eosin increases with increasing dye concentration while for free dye the opposite is the case. These rate studies suggest that a bound dye molecule in the first electronically excited state rapidly exchanges energy with a bound dye molecule in the ground state to produce a long-lived excited species which reacts with the reducing agent (here ascorbic acid). A mechanism is proposed for dye-sensitization in silver halide photography based on photoreduction of bound dye.

Introduction

The photochemical properties of dyestuffs when bound to substrates are considerably different from those of the free dye in solution. For example, rose bengal (2′,4′,5′,7′-tetraiodo-3,4,5,6-tetrachlorofluorescein) is readily photooxidized in solution whereas the dye when bound to polyvinylpyrrolidone (PVP) resists photooxidation even when exposed to sunlight for one month.[2] On the other hand, dyes which are bound to high polymeric substrates are more readily photoreduced than are the free dyes.[3–5]

The present paper is concerned with the photoreduction of eosin Y (2′,4′,5′,7′-tetrabromofluorescein) when bound to PVP in solution. The kinetics of photoreduction of free eosin Y have been studied.[6] It has been shown that the kinetics of photoreduction of free fluorescein and its halo-

(1) (a) This paper represents a part of the dissertation submitted by Judith S. Bellin to the faculty of the Graduate School of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under Contract No. AF18(600)1182.

(2) G. Oster, *J. Polymer Sci.*, **9**, 553 (1952).
(3) G. Oster, *Trans. Faraday Soc.*, **47**, 660 (1951).
(4) G. Oster, *J. Polymer Sci.*, **9**, 553 (1952).
(5) G. Oster and J. Bellin, THIS JOURNAL, **78**, 294 (1957).
(6) G. Oster and A. H. Adelman, *ibid.*, **78**, 913 (1956).

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genated derivatives are qualitatively similar.[7] Likewise, we have found that the photochemical properties of the fluorescein-type dyes, erythrosin, phloxine and rose bengal, when bound to PVP are similar to those of bound eosin which are described in detail in the present paper.

The results of the present studies have direct bearing on the phenomena underlying dye-sensitization in silver halide photography.

Experimental

Materials.—Eosin Y as obtained from Eastman Kodak Co. was used without further purification. Polyvinylpyrrolidone (PVP) of molecular weight 5.6×10^5 was obtained from Schenley Laboratories. All the other reagents were obtained from Fisher Scientific Co. as C.P. grade. Helium (Airco) was used to flush oxygen from the solutions.

Procedures.—The methods used for determining the rate of photoreduction of eosin Y in the presence of ascorbic acid as well as the methods used in the measurements of absorption spectra, fluorescence spectra and fluorescence and phosphorescence intensities are identical with those described in our previous paper.[5] The wave length of the actinic light employed was that maximally absorbed by eosin Y, namely, 518 mμ.

Precautions were necessary in measuring the fluorescence quenching by *p*-phenylenediamine (PPD) since the oxidation of this substance is sensitized by eosin.[8] Freshly prepared mixtures were used for each measurement. A buffered stock solution of PPD was kept under helium in order to prevent its oxidation by air.

Results

Spectra.—A dilute solution of eosin Y is orange (absorption maximum at 518 mμ) and exhibits a yellow-green fluorescence when excited by blue light. With excess PVP the color changes to red (absorption maximum at 528 mμ with excess PVP) and the fluorescence is yellow and is of greater intensity. In contrast to our observations with triphenylmethane dyes,[5] the shape of the absorption spectra of eosin Y is unchanged on binding to the high polymer and is merely shifted to longer wave lengths.

By following the change in optical density at the wave length where the spectral changes are the largest (518 mμ for eosin Y) as a function of the amount of PVP added, we obtained a binding curve.[9] Employing the customary analysis of the binding data, we find at *p*H 5.0 that one gram of PVP binds 1.0×10^{-5} mole of eosin (see Fig. 1).

Fluorescence and Phosphorescence.—Solutions of free eosin show evidence of self quenching of fluorescence at a dye concentration of about 10^{-4} *M* (Fig. 2). An actual decrease in fluorescence intensity occurs at concentrations exceeding 10^{-3} *M*. On the other hand, in presence of PVP self-quenching becomes evident at concentrations of dye as low as 10^{-6} *M* and the fluorescence intensity is a maximum at 10^{-5} *M* (Fig. 2).

PPD quenches the fluorescence of eosin Y in the bound as well as in the free state. In all cases the quenching obeys the Stern–Volmer equation. At *p*H 5.0 the quenching constants of PPD for the dye in the free and in the bound states are, respectively, 4.37 and 3.14 liters/mole.

Oxygen-free solutions of eosin Y in glycerol at temperatures below −90° exhibit a yellow phosphorescence when the system is excited by blue light. Addition of PVP enhances the intensity of the phosphorescence and makes the phenomenon observable at temperatures as high as −60°.

Self quenching of the phosphorescence of eosin Y in glycerol at −90° is evident at dye concentrations of 10^{-4} *M*. In the presence of PVP, however, this self quenching does not occur. PPD up to a concentration of at least 10^{-4} *M* is not a quencher of the phosphorescence of bound eosin Y, whereas it is a powerful quencher of the phosphorescence of free eosin.

Photoreduction.—The quantum yield of photobleaching with ascorbic acid at *p*H 5.0 of eosin Y, rose bengal, phloxine and fluorescein is greater in the bound than in the free state. The resulting colorless solutions exhibit a weak yellow fluorescence when excited by near ultraviolet light. Both bound and free fluorescein-type dyes reduce tetrazolium salts to insoluble formazans under the conditions of the photobleaching reaction, while in the dark no formazan is produced. This shows that in the photobleaching process a reduced form of the dye is produced which in turn is capable of reducing the tetrazolium salts. As is the case with free fluorescein-type dyes,[6] the quantum yield ϕ of the photoreduction of bound eosin Y as a function of reductant (A), here ascorbic acid, follows the relation $\phi = (A)/\alpha + \beta(A)$ where α and β are constants, independent of incident light intensity; there is, however, a striking difference between the free and the bound dye as regards their dependency of quantum yield on dye concentration. Whereas, with free dye the quantum yield of photoreduction decreases with increasing dye concentration, in the case of bound dye the quantum yield increases with increasing dye concentration up to about 6×10^{-4} *M* in eosin and a limiting value is attained at higher dye concentrations (Fig. 3). The photoreduction of bound triphenylmethane dyes[5] is similar in all these respects to those of bound eosin.

Photoreduction of bound eosin Y is inhibited by small amounts of nitrobenzene. For example, the addition of 10^{-6} *M* nitrobenzene causes an induction period of one minute during which the nitrobenzene is destroyed and after which the reaction proceeds at a rate equal to that of the inhibitor-free system. The induction period is directly proportional to the amount of nitrobenzene added. This phenomenon is similar to that observed for the case of bound triphenylmethane dyes.[5] In the case of free eosin, however, nitrobenzene acts as a retarder rather than as an inhibitor.

The effect of PPD on the rate of photoreduction of bound eosin Y is illustrated in Fig. 4. There is a period of inhibition, after which the photoreduction takes place at a reduced rate compared with that of the inhibitor-free system.

Discussion

The increased fluorescence yield of eosin on binding to PVP may be due to the increased planarity of the dye when bound.[10] The data of Fig. 1 show that the rate of photoreduction of bound eosin is not directly proportional to the degree of

(7) A. H. Adelman and G. Oster, THIS JOURNAL, **78**, 3977 (1956).
(8) G. Oster and M. Schrader, to be published.
(9) G. Oster, *J. Polymer Sci.*, **16**, 235 (1955).
(10) Compare G. Oster and Y. Nishijima, THIS JOURNAL, **78**, 1581 (1956).

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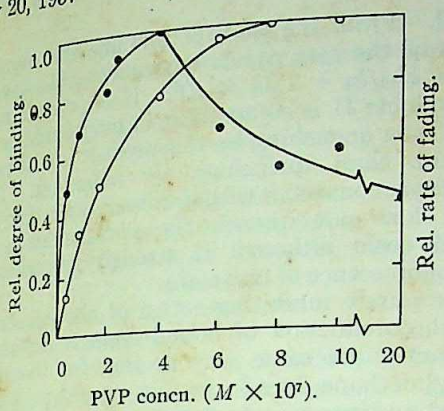

Fig. 1.—Open circles, degree of binding of eosin Y to polyvinylpyrrolidone (PVP) by changes in optical density at 518 mμ. Solid circles, rate of fading at *p*H 5.0 in the presence of 1.6×10^{-3} *M* ascorbic acid. Dye concentration 5×10^{-6} *M*.

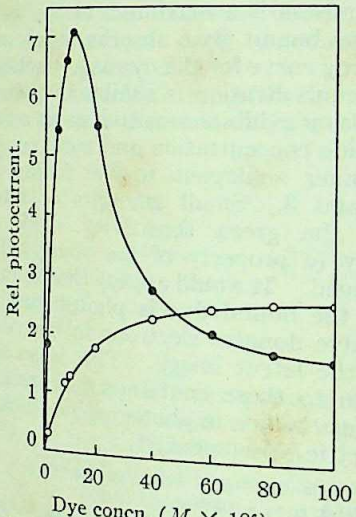

Fig. 2.—Fluorescence as a function of concentration of eosin Y for free dye (open circles) and for dye bound to 0.6% PVP (closed circles). A yellow Corning 7-30 filter was interposed between the sample and the phototube (RCA 931 A.).

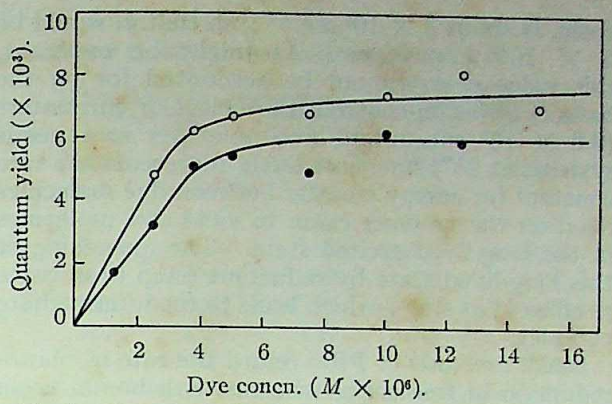

Fig. 3.—Quantum yield of fading of eosin Y as a function of dye concentration at *p*H 5.0. Throughout 1.1×10^5 g. of PVP per mole of dye. Open circles, 3.2×10^{-3} *M* ascorbic acid, filled circles, 1.6×10^{-3} *M* ascorbic acid.

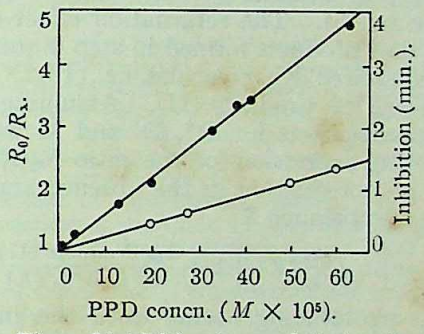

Fig. 4.—Time of inhibition (open circles) and retardation (closed circles) of fading of eosin Y as a function of concentration of paraphenylenediamine (PPD). Dye concentration, 5×10^{-6} *M*, PVP concentration, 0.06%, ascorbic acid concentration, 1.6×10^{-3} *M*, in acetate buffer at *p*H 5.0.

binding; a maximum rate of fading is attained at a ratio of dye to polymer at which not all the dye molecules are considered by the absorption criterion to be bound. This suggests a redistribution of dye molecules on the polymer chain resulting in further changes in optical density but with a decreased rate of fading due to decreased possibilities of dye–dye interaction (see below).

As in the case of the bound triphenylmethane dyes,[5] the following kinetic scheme is consistent with the fading data of bound eosin: (1) $D + h\nu \rightarrow D^*$, (2) $D^* \rightarrow D + \text{heat}$ (and/or $h\nu_f$), (3) $D^* \rightarrow D'$, (4) $D^* + D \rightarrow D' + D$, (5) $D' \rightarrow D + h\nu_p$, (6) $D' + A \rightarrow D + A$, (7) $D' + A \rightarrow M$, (8) $M \rightarrow$ colorless products (I), (9) $M + \times \rightarrow$ colorless products (II) + D. In our terminology, D, D* and D′ refer to bound dye molecules in the ground, first electronically excited, and long-lived electronically excited states, respectively, the unbound dye being photochemically inert under the conditions employed in these studies. The reductant A reacts only with D′ either to quench the phosphorescence (step 6) or to form an intermediate complex M (step 7). This complex in turn can decompose to give reduced dye products or, in the presence of inhibitor X, can cause the destruction of X with the regeneration of dye. The justification for this formulation is treated in detail in our previous paper.[5] Using steady-approximations for the transient species (D*, D′ and M) these reaction steps lead to the following equation for the quantum yield of photoreduction

$$\Phi = \left[\frac{k_8}{k_8 + k_9(\mathrm{X})}\right]\left[\frac{k_7(\mathrm{A})}{k_5 + (k_6 + k_7)(\mathrm{A})}\right]\left[\frac{k_3 + k_4(\mathrm{D})}{k_9 + k_3 + k_4(\mathrm{D})}\right]$$

where the *k*'s are the rate constants for the reactions indicated by the subscripts. Since the quantum yield is zero when extrapolated to zero dye concentration (Fig. 3), $k_4(\mathrm{D})$ is much larger than k_3 and hence, as with bound triphenylmethane dyes, step 3 is negligible compared with step 4. In contrast to the behavior of bound triphenylmethane dyes, however, $k_4(\mathrm{D})$ for bound eosin must be comparable to k_2, since a plateau in the rate of fading is reached at higher dye concentrations. As in the case of bound triphenylmethane dyes we evaluate the ratio of the constants[5] which for eosin are $k_4/k_2 = 2.24 \times 10^5$, $k_6/k_5 = 450$, $k_7/k_5 = 211$, liters per mole, respectively. We estimate that k_2, the reciprocal of the lifetime of bound

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eosin, is about 3×10^8 sec.$^{-1}$ [11] so that k_4 would be 6×10^{13} l./mole/sec. As might be expected, this value of k_4 cannot be accounted for on the basis of diffusion-controlled bimolecular encounters (6.6×10^9 encounters/sec./mole/liter in aqueous systems at 25°) but more likely represents the rate constant for energy transfer between dye molecules fixed on the polymer chain to yield dye molecules in the long-lived excited state. The quenching of this long-lived state by reductant (step 6) is twice as efficient as step 7 which leads to the intermediate complex.

Small amounts of PPD retard the rate of photoreduction of free eosin[6] whereas with bound eosin inhibition as well as retardation occurs (Fig. 4). Since there is no appreciable fluorescence quenching at these low PPD concentrations, the step $D^* + X \rightarrow D + X$ is unimportant but reaction occurs as in step 9 to account for the observed inhibition (compare ref. 5). The retardation effect of PPD requires that products formed in step 9 quench the long-lived excited dye molecules, *i.e.*, (10) D′+ products (II) → D + products (II). Assuming steady-state concentrations for D*, D′ and M we derive the following expression for the ratio R_0/R_x of the rates of photoreduction in the absence and in the presence of substance X

$$\frac{R_0}{R_x} = \left[1 + \frac{k_9}{k_8}(\mathrm{X})\right]\left[1 + \frac{k_{10}(\text{Products (II)})}{k_5(k_6 + k_7)(\mathrm{A})}\right]$$

Since no photofading occurs until the inhibition period is ended k_9 must be much larger than k_{10}. Step 9 requires that the concentration of Product II be proportional to the amount of PPD added (X_0). We may express the amount of retardation which occurs after the inhibition period is completed as

$$\frac{R_0}{R_x} = 1 + \frac{k_{10}'(X)_0}{k_5 + (k_6 + k_7)(\mathrm{A})}$$

Thus, as shown in Fig. 4, the retardation is directly proportional to the amount of PPD originally added. From the slope of this line and using the ratios of the rate constants enumerated above we obtain $k'_{10}/k_6 = 1.35 \times 10^6$. If the concentration of Products II is comparable in magnitude to that of X_0 then quenching by this product is much more efficient than quenching by reductant. These results are consistent with the observation that PPD itself does not quench the phosphorescence of bound eosin although it strongly quenches the phosphorescence of free eosin.

The purely inhibiting action of nitrobenzene on the photoreduction of bound eosin is explainable in exactly the same way as that for bound triphenylmethane dyes.[5] In this case, step 10 is not important since no retardation occurs.

It has been known for many years that eosin applied to silver halide photographic emulsions will render the emulsion sensitive to green light.[12] Silver bromide emulsions sensitized with eosin have been studied in our laboratory.[13] The sensitivity of the emulsion is a maximum at the wave length where the bound dye absorbs light maximally. The binding curve for the dye as a function of silver bromide concentration is similar to that of Fig. 1. The emulsion exhibits sensitivities as a function of silver halide concentration and eosin concentration in a manner analogous to the fading curves of Figs. 1 and 3. Small amounts of nitrobenzene suppress the green sensitivity while the blue sensitivity (a property of the silver halide itself) is unchanged. It would appear that in this system, at least, the bound dye is photoreduced and the reduced dye donates electrons to the silver halide to form the latent image. This is an alternative suggestion to those contained in current theories of dye-sensitization in photography which postulate photoelectric phenomena.[14]

(11) Compare, P. Pringsheim, "Fluorescence and Phosphorescence," Interscience Publishers, Inc., New York, N. Y., 1949, p. 316.

(12) J. Waterhouse, *Brit. J. Photo.*, **23**, 233 (1876).

(13) G. Oster, to be published.

(14) For review, see W. West and B. H. Carroll in "The Theory of the Photographic Process," Ed. by C. E. K. Mees, Revised Edition, The Macmillan Co., New York, N. Y., 1954.

BROOKLYN, N. C.

[CONTRIBUTION FROM THE QUARTERMASTER RESEARCH AND DEVELOPMENT CENTER]

Spectroscopic Studies on Dyes. IV. The Fluorescence Spectra of Thioindigo Dyes[1]

BY DELBERT A. ROGERS, J. DAVID MARGERUM AND GEORGE M. WYMAN[1a]

RECEIVED JANUARY 28, 1957

The fluorescence spectra of eight thioindigo dyes in benzene solution were determined, using the 546 mμ Hg-line for excitation. Each dye has a fluorescence band at a wave length somewhat longer (usually by *ca.* 35 mμ) than its first absorption maximum. Exposure of the dye solutions to yellow light prior to the measurement results in decreased fluorescence. The intensity of fluorescence was found to be proportional to the concentration of *trans* isomer present. This behavior, which is similar to that observed for stilbene,[2] indicates that *trans*-thioindigo possesses a tightly-held coplanar structure, while its *cis* isomer is non-coplanar. These conclusions are shown to be consistent with the visible and infrared absorption data. The addition of ethanol quenches the fluorescence of these dyes. The possible implications of this phenomenon with regard to the photochemistry of thioindigo-dyed cellulosic materials are discussed.

Introduction

In their study of the fluorescence spectra of *cis*- and *trans*-stilbene, Lewis and his co-workers have found that only the *trans* isomer exhibits fluorescence.[2] While a large number of articles dealing with fluorescence spectra have appeared in the lit-

(1) Presented before the Division of Physical and Inorganic Chemistry at the 130th Meeting of the American Chemical Society, Atlantic City, New Jersey, September 16–21, 1956. (1a) U. S. Army Res. and Dev. Liaison Group, (D671 DU), Rheingau Allee 2, Frankfurt-am-Main, Germany.

(2) G. N. Lewis, T. T. Magel and D. Lipkin, THIS JOURNAL, 62, 2973 (1940).

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TABLE I

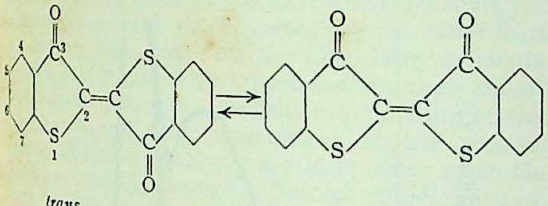
THE DEPENDENCE OF FLUORESCENCE INTENSITY ON THE *cis–trans* ISOMERIZATION OF THIOINDIGO DYES

Dye	Substituents on thioindigo	Concn. mole/l. × 10^5	From absorption measurements: λmax (mμ) *trans*	λmax (mμ) *cis*	[*trans*]yellow[a] / [*trans*]blue	From fluorescence measurements: λmax (mμ)	Iyellow[b] / Iblue
I	None	0.64	546	485	0.35	582	0.38
II	4,4′-Dimethyl-6,6′-dichloro-	1.1	538	483	.37	575	.36
III	4,4′-Dimethyl-5,6,7-trichloro-	0.5	551	493	.37	583	.36
IV	5,5′-Dichloro-4,4′,7,7′-tetramethyl	1.9	568	505	.51	602	.52
V	5,5′,7,7′-Tetramethyl-	3.4	564	491	.56	600	.62
VI	4,4′,5,5′,7,7′-Hexachloro-	1.5	564	493	.55	590	.59
VII	6,6′-Diethoxy	6.6	515	458	.25	553	[c]
VIII	"Vat Scarlet G" (a hemi-thioindigo)	4.1	514	465	.48	581	.46

[a] Ratio of concentrations of *trans* isomer present after pre-irradiations. [b] Ratio of intensities of fluorescence observed after pre-irradiations. [c] Fluorescence obscured by mercury emission line.

erature since that time, further mention of the fluorescence of *cis-trans* isomers has been limited to the derivatives[3a,3b] or the vinylogs[4a,4b] of stilbene. In harmony with the behavior of stilbene, in each of these instances the solutions containing the largest concentration of *trans* isomers showed greatest fluorescence intensity.

Brode and Wyman have reported the existence of an equilibrium between *cis* and *trans* isomers in



trans I *cis*

solutions of thioindigo (I) dyes in inert solvents.[5] They found that the position of the equilibrium was a function of the wave length range of the light to which the solution had been exposed. It was also possible to separate the two isomers by chromatographic adsorption in the dark. These findings made it appear desirable to undertake a study of the fluorescence of thioindigo dyes for the following reasons: (1) to find out whether the behavior of these dyes followed the pattern shown by the aromatic olefins; and (2) to see if an examination of their fluorescence spectra would yield additional information concerning the structure of dyes of this type.

Experimental

Preparation of Solutions.—Approximately 10 mg. of each dye was dissolved in *ca.* 300 ml. of benzene by heating near the boiling point for several hours. The solution was then cooled to room temperature and diluted to a suitable concentration. The concentrations were determined spectrophotometrically, using appropriate data from reference 3a and 3b.

Pre-irradiation of Solutions.—The dye solution contained in a 2-cm. or 5-cm. absorption cell was exposed for five minutes to filtered light from a Bausch and Lomb Microscope Illuminator (Catalog No. 31-35-85-11), using either a blue or a yellow filter. The blue filter used for all of the dyes was Corning No. 5543. Three yellow filters were used: Corning No. 3385 for dyes VII and VIII; No. 3484 for dye II and Filter No. 3482 for the five other dyes (*cf.* Table I). The cell length was selected to give an absorption measurement in the range of maximum sensitivity of the spectrophotometer.

Measurement of Absorption Spectra.—The absorption spectra of the pre-irradiated dye solutions were determined in the 400–650 mμ region by means of a Cary Recording Spectrophotometer (Model 11), against the solvent as the reference. The solutions resulting from the chromatographic separation described below were measured on a Beckman DU spectrophotometer.

Measurement of Fluorescence Spectra.—The Fluorescence Attachment of the Model 11 Cary Spectrophotometer was used to measure the fluorescence spectra. All measurements were made at a slit width of 0.5 mm., using the 546 mμ Hg-line for excitation. Whenever fluorescence measurements were desired, immediately upon completion of the pre-irradiation in the longer cell, the solution was transferred to a 1-cm. absorption cell and its fluorescence determined. This operation was necessary because, probably due to self-absorption, the amount of *trans* to *cis* conversion was found to be a function of cell length. In no instance was there evidence for a shift in the *cis–trans* equilibrium caused by the exciting light of the Hg-arc of the fluorescence attachment.

Chromatographic Separation of *cis*- and *trans*-Thioindigo.—The chromatographic separation of the two isomers of thioindigo was carried out as described in reference 3a. However, in view of the quenching action of ethanol on the fluorescence of thioindigo, it was necessary to evaporate the solution containing the *cis*-isomer to dryness and dissolve the residue in benzene before measuring its fluorescence spectrum.

Results

The behavior of 4,4′-dimethyl-6,6′-dichlorothioindigo, which is shown in Fig. 1, is characteristic of all the dyes studied in this investigation. Each dye has a band of fluorescent emission in the visible region at a wave length somewhat longer than its first absorption band. Thioindigo dyes enriched with respect to the *cis* isomers (by pre-irradiation with yellow light) show fluorescence at the same wave lengths but with diminished intensity. There was also no evidence for any new fluorescence bands that may be attributable to the *cis*-isomers when the 436 or 366 mμ Hg-lines were used for the excitation, even for dyes VII and VIII, the *cis* isomers of which absorb strongly near 450 mμ (*cf.* Table I). Consequently this suggests that only the *trans* isomers exhibit fluorescence.

Further confirmation of this conclusion was obtained from a comparison of the fluorescence intensity with the relative concentration of the *trans* isomer as shown in Table I. The last column in this table shows that the ratio of the fluorescence in-

(3) (a) A. J. Henry, *J. Chem. Soc.*, 1156 (1946); (b) Y. Hirshberg and F. Bergmann, THIS JOURNAL, **72**, 5118 (1950).

(4) (a) A. Sandoval and L. Zechmeister, *ibid.*, **69**, 553 (1947); (b) F. Bergmann, *ibid.*, **72**, 5117 (1950).

(5) (a) G. M. Wyman and W. R. Brode, *ibid.*, **73**, 1487 (1951); (b) W. R. Brode and G. M. Wyman, *J. Research Natl. Bur. Standards*, **47**, 170 (1951).

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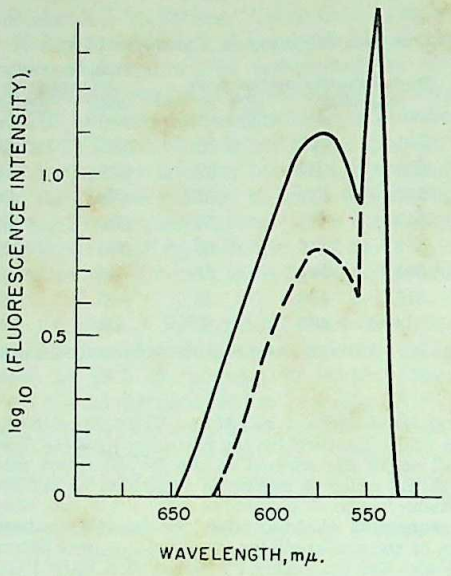

Fig. 1.—Fluorescence spectrum of 4,4′-dimethyl-6,6′-dichlorothioindigo in benzene: (———) pre-irradiated with blue light; (– – – –) pre-irradiated with yellow light. Concentration: 2.8 mg./l.; exciting light, 546 mμ.

tensity of each dye solution that had been preirradiated with yellow light (*i.e.*, enriched with respect to *cis*) to that of the same solution pre-irradiated with blue light (*i.e.*, essentially all-*trans*). Correspondingly, the fourth column in the table gives the ratio of the concentrations of the *trans* isomer present under these two sets of conditions, determined independently from absorption measurements. The good agreement between these two figures shown for each dye indicates that the fluorescence intensity is directly proportional to the concentration of *trans* isomer. It is then evident from these data that the *cis* isomers can possess little or no fluorescence in this region of the spectrum.

In order to obtain direct proof of this conclusion it was decided to measure the fluorescence of a solution of *cis*-thioindigo. Accordingly, the chromatographic separation of the isomers was carried out and the fluorescence and absorption spectra of the resulting solutions were measured, as shown in Fig. 2. While the solution contained mostly *cis*-thioindigo, the absorption at 550–570 mμ showed that there was also an appreciable amount (*ca.* 10%) of *trans* isomer present. (It is believed that the *trans* compound formed during the additional operations required for the removal of the ethanol.) However, a comparison of the fluorescence spectra obtained on this solution before and after irradiation with blue light (thus representing the two extremes with respect to the concentration of each isomer) disclosed that the fluorescence intensity was again proportional to the concentration of the *trans* form (*cf.* Fig. 2.) On the basis of all this evidence it is possible to conclude that only the *trans* isomers of thioindigo dyes exhibit fluorescence.

The quenching of fluorescence that is caused by the addition of a small amount of ethanol to a solution of a thioindigo dye in benzene is readily noticeable even to the naked eye. This interesting effect, which was inadvertently noticed during

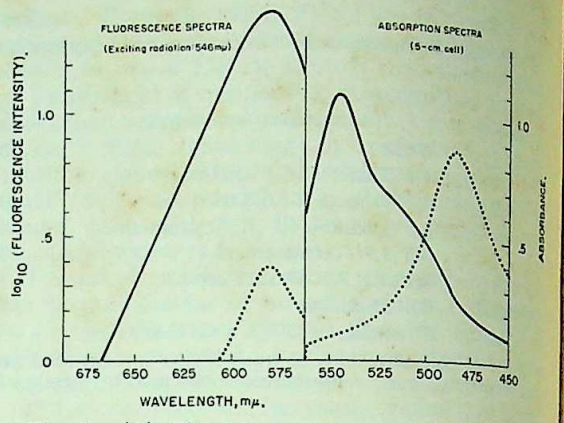

Fig. 2.—(A) Fluorescence spectrum of thioindigo in benzene: (. . . . . .) mainly *cis* form, from chromatographic separation; (———) the same solution, after irradiation with blue light. (B) Absorption spectra of the same two solutions; concentration, 4 mg./l.

the feasibility of using ethanol in the chromatographic separation of the two thioindigo isomers was explored, is shown in Fig. 3.

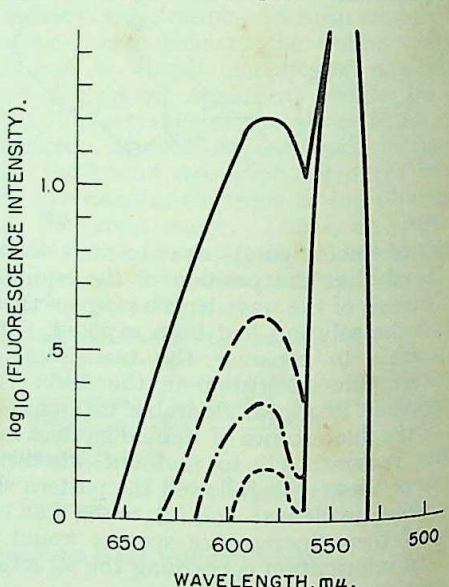

Fig. 3.—Effect of ethanol on the fluorescence spectrum of thioindigo in benzene. Concentration of dye, 2 mg./l.; concentration of ethanol, (———) 0%; (– – – –) 5%; (—·—·—) 10%; (·····) 20% by volume. Exciting light, 546 mμ.

In order to show that the fluorescence quenching by ethanol is not brought about by conversion of the *trans* isomer to the non-fluorescing *cis* form of thioindigo, the following experiment was carried out. Two solutions of equal thioindigo concentration were made up, one in benzene and the other in benzene containing 10% ethanol. The visible absorption spectra of these solutions were recorded after pre-irradiation with blue light and then after pre-irradiation with yellow light. The pre-irradiations were for five minute periods and were made under the same conditions for each solution. The results (cf. Table II) show that the presence of etha-

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nol does not favor the formation of the *cis* isomer, but on the contrary stabilizes *trans*-thioindigo.

TABLE II

EFFECT OF ETHANOL ON *trans–cis* PHOTOISOMERIZATION

Solvent	Fraction of *trans*-thioindigo present[a] Benzene	90% benzene–10% ethanol[b]
Blue light	1.00	1.00
Yellow light	0.38	0.72

[a] Calculated from absorbancies at 562 mμ, where the *cis*-thioindigo does not absorb appreciably. [b] In 10% ethanol the *trans* absorption band is shifted slightly (*ca.* 2 mμ) to longer wave length.

Discussion of Results

While at the present time our understanding of the relation between fluorescence spectra and chemical structure is not as thorough as it is with respect to electronic or vibrational spectra, nonetheless, it has been possible to arrive at certain correlations in this respect.[6] A molecule which has been raised to an electronically excited state by the absorption of a quantum of light of appropriate frequency, can lose this excess energy and return to the ground state by one of three processes: internal conversion, external conversion or fluorescent emission. *Internal conversion* occurs when the energy of electronic excitation is converted to some other form of energy (*e.g.*, heat) by the absorbing molecule. While it is believed that most radiationless transitions occur in this manner, the exact nature of this process is not fully understood at the present time. *External conversion* is said to occur when the excited molecule through collisions transfers its excess energy to one or more other molecules, *e.g.*, solvent molecules. *Fluorescent emission* occurs only when the excited molecule cannot readily lose its energy by either of these processes. The probability for *internal conversion* depends principally on the structure of the molecule, while the ease of external conversion is a function of the solvent and the temperature. Consequently, whether or not a given molecule will exhibit fluorescence under certain conditions will be determined by both structural and environmental factors. By studying the fluorescence of different compounds under comparable conditions, it is possible to cancel out the environmental variables and thus to correlate fluorescence with chemical structure.

The failure of *cis*-stilbene to exhibit fluorescence (in contrast with its *trans*-isomer) was attributed by Lewis, Magel and Lipkin to its non-coplanar structure, which results from the steric interference of the *ortho*-hydrogen atoms of the two benzene rings.[2] According to their views the coplanar *trans*-stilbene molecule is prevented from *internal conversion* of its electronic energy because of its rigidly-held compact structure. In the non-coplanar *cis* isomer, on the other hand, which is not constrained by nearly as much resonance energy, the energy of electronic excitation is relatively readily converted to vibrational energy and/or dissipated as heat. Studies of the fluorescence of 4,4′-stilbenedicarboxamidine,[3a] 9,9′-diphenanthrylethylene and 1,4-diphenylbutadiene[4a,4b] have indicated that this behavior was characteristic of aromatic olefins and have thus provided further support for this interpretation.

It is clear from the results of the present investigation that thioindigo derivatives also follow the pattern set by the aromatic olefins. This immediately suggests a compact, coplanar structure for the *trans* compounds and a less constrained non-coplanar configuration for the *cis* isomers. Recent X-ray diffraction studies on crystalline thioindigo indicated that in the solid phase the dye exists in a tightly-held, coplanar *trans* configuration.[7] The unusually short distance (2.82 Å.) between the sulfur and oxygen atoms of adjacent rings was considered to indicate the existence of secondary bonds (probably stemming from electrostatic attraction) between these atoms, thus resulting in further stabilization of the *trans* structure.

A scale drawing of the structure of the two thioindigo isomers is shown in Fig. 4. The *trans* isomer

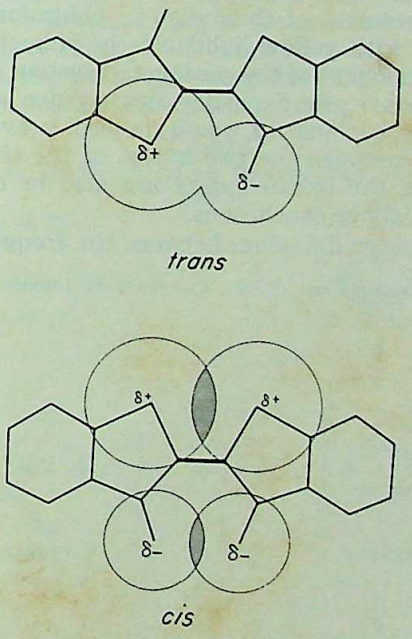

Fig. 4.—Diagram of the spatial arrangement of atoms in *cis*- and *trans*-thioindigo.

was drawn on the basis of Mme. v. Eller's data[7] while the structure of the *cis* isomer was constructed by rotating half of the *trans* molecule 180° about the central axis. The circles were drawn to scale using the van der Waals radii of 1.40 Å. for oxygen and 1.85 Å. for sulfur. It is readily apparent from Fig. 4 that the steric interference of the two carbonyl oxygen atoms and the two sulfur atoms would be expected to cause a departure from coplanarity in the *cis* isomers. Since oxygen atoms of carbonyl groups carry a partial negative charge[8] and the sulfur atoms in a resonating system of this type are probably carrying a slight positive charge, the steric

(6) The following references contain up-to-date discussions on this subject: (a) P. Pringsheim, "Fluorescence and Phosphorescence," Interscience Publishers, Inc., New York, N. Y., 1949; (b) T. Foerster, "Fluoreszenz Organischer Verbindungen," Vanden-Loek and Ruprecht, Goettingen, 1951; (c) W. West, "Fluorescence and Phosphorescence" (Chapter VI) in "Technique in Organic Chemistry," A. Weissberger, Editor, Vol. IX, Interscience Publishers, Inc., New York, N. Y., 1956.

(7) Helene v. Eller, *Bull. soc. chim. France*, 1444 (1955).

(8) *Cf.* L. Pauling, "The Nature of the Chemical Bond," 2nd Edition, Cornell University Press, Ithaca, N. Y., 1943, p. 75.

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effect will be further augmented by electrostatic repulsion. Since the hemithioindigoid dye Vat Scarlet G also behaves in a similar manner even though it only possesses one sulfur atom, it appears that the steric hindrance induced by the overlapping and the repulsion of the carbonyl groups alone is sufficient to induce non-coplanarity.

The departure from coplanarity brought about in the *cis*-thioindigo dyes by a combination of steric hindrance and electrostatic repulsion is further substantiated by the visible and infrared spectra of these compounds. In the visible region the *cis* isomers have been reported to show absorption of much shorter wave lengths (by *ca.* 60 mμ) than do their *trans* counterparts.[5a,5b] This hypsochromic shift has been attributed to the higher potential energy of the *cis* over the *trans* in their excited states, with these excited states pictured as having a central carbon–carbon single bond and charged oxygen and sulfur atoms. Electrostatic repulsion of the two oxygen atoms and of the two sulfur atoms in the excited *cis* form would give it a higher potential energy and would also force non-coplanarity. In the infrared spectrum the observed shift of the carbonyl stretching band from 6.04 to 5.90 μ when a solution of thioindigo in chloroform is irradiated with yellow light[9] clearly indicates a severe curtailment of the conjugated system in which the carbonyl group participates. Since a departure from coplanarity would, indeed, prevent conjugation between the two halves of the thioindigo molecule, the infrared data are also in harmony with the above conclusions.

The energy difference between the frequencies of the *trans* absorption maximum and that of the maximum fluorescence intensity is small for the thioindigo dyes I through VII. It varies between 2.1 kcal./mole for dye V and 3.8 kcal./mole for dye VII. These low energy differences indicate that *trans* to *cis* conversion probably cannot accompany fluorescence, but instead is a competitive photochemical process.

The observed effect of the addition of ethanol to a benzene solution of *trans*-thioindigo indicates that not only is the quantum yield of fluorescence decreased, but that the efficiency of the *trans* to *cis* photoisomerization is also diminished. This suggests that a third, competing photochemical reaction is involved. Perhaps this is due to the formation of a loosely held complex between the alcohol and the dye, or, alternatively, some other mechanism by which energy can be transferred from the dye to an ethanol molecule. While the carbonyl stretching frequency of thioindigo in chloroform is only slightly affected by the addition of ethanol,[10] the possibility of complex formation cannot be definitely ruled out. It is interesting to note in this connection that thioindigo dyes do not exhibit fluorescence when dyed on cellophane or on cellulosic fibers. Since these polysaccharides are chemically similar to ethanol, this suggests an analogy between the mechanism by which the fluorescence of these dyes is quenched by ethanol and their reported "tendering" effect on cotton.[11]

Acknowledgment.—The authors are indebted to Mr. John Sousa for his assistance with the experimental work.

NATICK, MASS.

(9) J. Weinstein and G. M. Wyman, THIS JOURNAL, **78**, 2387 (1956).

(10) J. Weinstein and G. M. Wyman, *ibid.*, **78**, 4009 (1956).

(11) A. Landolt, *J. Soc. Dyers Colourists*, **65**, 659 (1949).

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ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Relative Extents of Catalytic Hydrogen–Deuterium Exchange in the Nuclear Positions of Phenylacetamide[1,2]

BY WILLIAM A. BONNER

RECEIVED DECEMBER 19, 1956

When phenylacetamide was treated with deuterated Raney nickel in refluxing deuteroethanol, 49% of the α-hydrogens and 42% of the nuclear hydrogens underwent hydrogen–deuterium exchange. The product was degraded to aniline, and various nuclear positions of the aniline were selectively brominated. Deuterium assays of the brominated samples indicated the nuclear deuterium distribution as 26% *ortho*-, 46% *meta*- and 28% *para*-. Repetition of this deuteration in benzene solvent for thrice the reaction time led to H–D exchange at only 6.5% of the α-hydrogens and 2.6% of the nuclear hydrogens of phenylacetamide. These results are discussed briefly with regard to the mechanism of nuclear H–D exchange under these catalytic conditions.

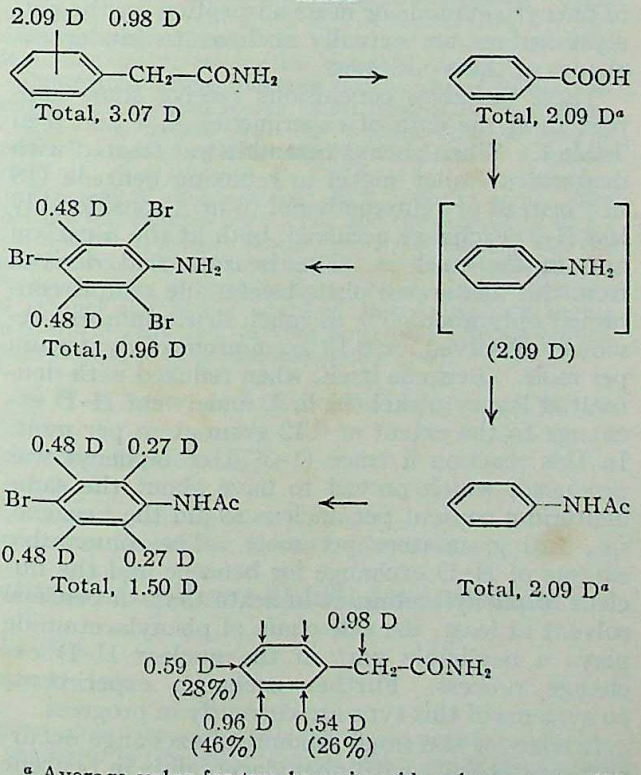
Recently we reported[3] that both α-hydrogen and nuclear hydrogen atoms in mandelamide and phenylacetamide undergo exchange with deuterium on treatment with deuterated Raney nickel catalyst in refluxing deuteroethanol. When these studies were extended to optically active 2-phenylpropionamide, it was found[4] that such exchange processes occurred more rapidly than did racemization, indicating a certain stereospecificity for such exchange reactions. This stereospecificity, as well as the occurrence of ring and methyl-group exchange, were tentatively rationalized[4] in terms of a stereospecifically adsorbed carbonium ion intermediate. Ethylbenzene was similarly shown[4] to undergo nuclear hydrogen–deuterium exchange under the same conditions.

If nuclear H–D exchange occurred as postulated[4] *via* a benzyl type carbonium ion intermediate and its nuclear canonical stabilizing structures, then nuclear H–D exchange ought to occur predominantly in the *o*- and *p*-positions of the aromatic ring. In order to test this hypothesis we have again engendered α-position and nuclear H–D exchange in phenylacetamide by the action of deuterated Raney nickel in refluxing deuteroethanol. The deuterated phenylacetamide product was oxidized to benzoic acid, and deuterium assays of the two substances provided an indication of nuclear *vs.* chain deuteration. The relative extents of ring deuteration at the *o*-, *m*- and *p*-positions of the benzoic acid product were determined by conversion of the latter to aniline, then by selective bromination of appropriate derivatives of the aniline, followed by deuterium assay of the bromination products. The results of these experiments are indicated in Table I, and the conclusions regarding relative positions of H–D exchange reached therefrom are summarized in Chart I.

Chart I indicates approximately 1:1.8:1.1 ratios, respectively, for the *o*, *m*- and *p*-distribution of deuterium atoms in the phenyl nucleus of phenylacetamide. Ratios for random nuclear exchange would be 2:2:1. It is interesting to compare these results with those of Lauer and Errede[5] who studied the action of Raney alloy in refluxing deuterium oxide with sodium deuteroxide on aniline. Using similar techniques, they found exchange ratios of about 6.5:1.0:1.2, respectively, for the *o*-, *m*- and *p*-positions of aniline under these conditions. The predominant exchange at the *o*-position was attributed to the anchoring of the aniline molecule to the catalyst through the electron pair of nitrogen, thus locating the *o*-hydrogens sterically in the most favorable position for exchange.

CHART I

DEUTERIUM DISTRIBUTION IN DEUTERATED PHENYLACETAMIDE



ᵃ Average value for two benzoic acid and one acetanilide assays.

From the data in Table I and Chart I it is clear that there is no marked selectivity for any specific nuclear position in the catalytic H–D exchange of phenylacetamide. This argues against such nu-

(1) This constitutes Communication IX in the series "The Stereochemistry of Raney Nickel Action."

(2) We are grateful to the Petroleum Research Fund Advisory Board of the American Chemical Society for its support of a portion of this research.

(3) W. A. Bonner, THIS JOURNAL, **76**, 6350 (1954).

(4) W. A. Bonner and J. A. Zderic, *ibid.*, **78**, 4389 (1956).

(5) W. M. Lauer and L. A. Errede, *ibid.*, **76**, 5162 (1954).

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TABLE I

DEUTERIUM CONTENTS OF PRODUCTS FROM EXPERIMENTS ON THE DEUTERATION OF PHENYLACETAMIDE

No.	Reactant	Product	Product combustion water % D_2O	Product combustion water % H_2O	Hydrogen-deuterium relationships D/H[c]	Hydrogen-deuterium relationships D + H[d]	Product, gram-atoms per mole D	Product, gram-atoms per mole H
1	Phenylacetamide[a]	Phenylacetamide-*d*	36.5	63.5	0.517	9	3.07	5.93
2	Phenylacetamide-*d*	Benzoic acid-*d*	35.1	64.9	.487	6	1.93	4.07
3	Benzoic acid-*d*	Acetanilide-*d*	26.0[e]	74.0[e]	.316[e]	9	2.16	6.84
4	Benzoic acid-*d*	2,4,6-Tribromoaniline-*d*	26.2	73.8	.320	4	0.96	3.04
5	Acetanilide-*d*	*p*-Bromoacetanilide-*d*	20.4	79.6	.231	8	1.50	6.50
6	Phenylacetamide[b]	Phenylacetamide-*d*	3.1	96.9	.0288	9	0.26	8.74
7	Phenylacetamide-*d*	Benzoic acid-*d*	2.5	97.5	.0230	6	.13	5.87
8	Benzene	Benzene-*d*	2.3	97.7	.0212	6	.12	5.88
		Diphenyl-*d*	2.3	97.7	.0212	10	.20	9.80

[a] Reaction employing deuterated Raney nickel in absolute C_2H_5OD. [b] Reaction employing deuterated Raney nickel in benzene. [c] Obtained from the relation $18 \times \% D_2O/20 \times \% H_2O = D/H$. [d] Total number of H-species atoms in the product molecule. [e] Average of two determinations.

clear exchange resulting as a consequence of resonance stabilization of a benzylcarbonium ion intermediate as previously hypothesized[4] and suggests rather that nuclear H–D exchange here is a more or less random process occurring *independently* of any additional exchange taking place at the α-carbon. Also, by Lauer's argument, our relatively low value for exchange at the *o*-positions indicates that the benzyl carbon was in all probability in no way involved in attaching the molecule to the catalyst surface. The lower than statistical exchange value at the *o*-positions, in fact, argues that steric factors in phenylacetamide or in its adsorption on the catalyst surface are actually such as to hinder exchange at these positions.

These tentative conclusions receive some support from the data of experiments, 6, 7 and 8 in Table I. When phenylacetamide was treated with deuterated Raney nickel in refluxing benzene (18 hr.) instead of deuteroethanol (6 hr.), considerably less H–D exchange occurred, both at the α-carbon and in the nucleus. The benzoic acid derived from this deuterated phenylacetamide sample contained only about 6% as much deuterium as previously observed, or 0.13 gram-atom of deuterium per mole. Benzene itself, when refluxed with deuterated Raney nickel (30 hr.), underwent H–D exchange to the extent of 0.12 gram-atom per mole. In this reaction a trace (1–3%) of biphenyl was produced, which proved to have about the same deuterium content per nucleus as did the benzene, *i.e.*, 0.20 gram-atom per mole. The comparable extents of H–D exchange for benzene and the nucleus of phenylacetamide indicate that, in benzene solvent at least, the side chain of phenylacetamide plays a negligible part in the nuclear H–D exchange process. Further exchange experiments on systems of this type are currently in progress.

In view of the small amount of exchange occurring catalytically with phenylacetamide in benzene solution, we have again[3] attempted the dehydroxylation of optically active mandelamide to produce optically active α-deuterophenylacetamide. When L(+)-mandelamide was treated with deuterated Raney nickel in refluxing benzene solution for 5 hr., the phenylacetamide recovered proved, however, to be optically inactive.

Experimental

Deuterated Raney Nickel. Sample A.—About 50 g. of Raney nickel[6] was equilibrated three times for 24-hr. periods with heavy water (30-ml. portions) (recovered from previous experiments[4]; distilled from a trace of sodium hydroxide; containing some dioxane), then for 2.5 days with 18 ml. of 99+% deuterium oxide. The catalyst so prepared was filtered damp-dry by suction immediately prior to its use.

Sample B.—Freshly prepared Raney nickel[6] was filtered damp-dry (55 g.) on a sintered funnel, then treated with thorough mixing with 8 ml. of 99+% deuterium oxide having d^{20} 1.077. After two days the mixture was sucked damp-dry at the aspirator, then treated with thorough mixing with an additional 8 ml. of 99+% D_2O. The filtrate had d^{20} 1.038. After a second 2-day period the mixture was again filtered damp-dry and treated with an additional 8 ml. of 99+% D_2O. The second filtrate had d^{20} 1.064. After seven days the mixture was again sucked damp-dry, and the filtrate was found to have d^{20} 1.077. The catalyst sample was assumed at this point to be completely deuterated and was used without further equilibration.

Deuterated Raney Nickel with Phenylacetamide.—Phenylacetamide (6.00 g.) was dissolved with heating in absolute deuteroethanol[3] (34 ml.), whereupon the entire sample of deuterated Raney nickel was added after sucking damp-dry from its final equilibration rinse. The mixture was heated under reflux (calcium chloride tube protection) with occasional swirling during an 8-hr. period, then filtered on a sintered funnel. The filter cake was rinsed thoroughly with ethanol and acetone, then sucked damp-dry (50 g.). The filtrate was evaporated to dryness, and the residue was dissolved in ethanol (100 ml.) to exchange $-ND_2$ for $-NH_2$. The solution was again evaporated, to yield 5.64 g. (94%) of deuterated phenylacetamide. A small portion of this product was recrystallized from a mixture of ethanol and ligroin to provide a sample for deuterium assay. The deuterium content was measured as previously[3] by combustion, collection of the combustion water and mass spectrographic assay of the latter[7]; combustion water, % D_2O, 36.5.

Hydrolysis and Oxidation of Deuterated Phenylacetamide.—The above deuterated phenylacetamide (5.57 g.) was stirred under reflux with 10% sodium hydroxide solution (100 ml.) and glass beads. After ten minutes, solution of the amide was complete, and potassium permanganate (10 g.) was gradually added to the reaction mixture. After initial foaming had subsided, an additional 10 g. of potassium permanganate was added, and the mixture was stirred under reflux during 2 hr. Excess sodium sulfite was added to destroy residual permanganate, and the mixture was filtered to remove MnO_2. The cake was rinsed well with water, and the filtrate was acidified. The precipitated benzoic acid was filtered, and the filtrate was extracted four

(6) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(7) Mass spectrographic analyses of the combustion water from this and the succeeding exchanges were conducted by Dr. H. Eding and Mr. C. Lanpher of Stanford Research Institute.

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times with C.P. ether. The extract was washed, dried and evaporated. The total crude benzoic acid weighed 4.78 g. (95%). A sample of this acid was recrystallized (Norit) from water, then sublimed *in vacuo* prior to assay, m.p. 121.5–122.5°; combustion water, % D_2O, 35.1.

Deuterated Benzamide.—The above deuterated benzoic acid (4.06 g.) was converted to benzamide by refluxing with thionyl chloride, followed by treatment of the residue therefrom with chilled ammonium hydroxide. The crude amide was recovered in 1.60 g. (40%) yield. It was recrystallized from a mixture of ethanol (1 ml./g.) and ligroin (3 ml./g.) to yield two crops: (1) 1.26 g., m.p. 126–127° and (2) 0.25 g., m.p. 121–123.5°.

Hofmann Degradation of Diluted Deuterated Benzamide.—1.487 g. of the above deuterated benzamide was diluted with 1.487 g. of recrystallized stock benzamide. The mixture was treated with a solution of potassium hydroxide (4.2 g.) and bromine (1.42 ml.) in water (38 ml.). The mixture was swirled thoroughly, then treated with a solution of potassium hydroxide (5.9 g.) in water (10 ml.). The temperature was maintained at 70–80° for 35 minutes, whereupon the mixture was steam distilled, collecting 75 ml. of distillate. The distillate was salted and extracted four times with ether. The extract was dried over potassium hydroxide, filtered and freed of solvent through a small column. The residue was 2.24 g. (98%) of crude aniline.

Deuterated Tribromoaniline.—Bromine (0.5 ml.) in acetic acid (3 ml.) and water (2 ml.) was added with stirring to 0.3 ml. of the above aniline dissolved in a mixture of acetic acid (2 ml.) and water (3 ml.). After five minutes the mixture was diluted with water, and the crude tribromoaniline (0.95 g., 89%) was collected. The latter was recrystallized twice (Norit) from dilute ethanol, to give 0.29 g. of a sample having m.p. 119.5–120°; combustion water, % D_2O, 13.1; corrected for dilution, 26.2%.

Deuterated Acetanilide.—One and nine-tenths grams of the above aniline was converted to acetanilide by the method described by Fieser.[8] The crude product was obtained in 1.13 g. (41%) yield. A sample was purified by vacuum sublimation prior to deuterium assay, m.p. 113.5–114.5°; combustion water, % D_2O, 13.5, 12.5; corrected for dilution, 26.0%.

Deuterated *p*-Bromoacetanilide.—One gram of the above acetanilide was brominated according to the procedure of Fieser,[9] using proportional reagent quantities. The crude product, 1.51 g. (95%), was recrystallized twice from dilute ethanol prior to deuterium assay, m.p. 167–167.5°; combustion water, % D_2O, 10.2; corrected for dilution, 20.4%.

Action of Deuterated Raney Nickel on Benzene.—About 4 g. of the above sample B deuterated Raney nickel was sucked damp-dry and treated with 40 ml. of azeotropically dried benzene. The mixture was distilled to a small volume, then treated with additional benzene and distilled to a residual volume of about 10 ml. At this point the clumped catalyst had become evenly dispersed through the solvent, no more D_2O was apparent in the distillate and the catalyst was quite pyrophoric. The mixture was refluxed during 30 hr., then filtered damp-dry. The residual catalyst was markedly pyrophoric. Odor and infrared examination of the filtrate suggested the presence of a product other than benzene. Evaporation of 5.38 g. of the filtrate left a pasty residue of 0.07 g. (1.3%). This smelled like biphenyl and was purified twice by sublimation at 70° (0.5 mm.). The white sublimate had m.p. 69–70° and showed no mixed m.p. depression with a sublimed sample of biphenyl (m.p. 69–70°). In another experiment 2.40 g. of the above filtrate left 0.08 g. (3.7%) of crude biphenyl. This was purified by sublimation and combusted for deuterium assay; combustion water, % D_2O, 2.3.

A 0.25-ml. sample of the above benzene filtrate was freed of its deuterated biphenyl by passage through a 4-foot Celite–Silicone vapor phase chromatographic column.[10] The benzene fraction was collected[10] and combusted for deuterium assay; combustion water, % D_2O, 2.3.

Deuterated Raney Nickel in Benzene on Phenylacetamide.—A portion of sample B deuterated Raney nickel above was sucked damp-dry (25 g.). The damp sample was added to azeotropically topped benzene (300 ml.), and the mixture was distilled down to 60 ml., driving off the majority of residual D_2O and giving a uniform suspension of catalyst. Phenylacetamide (6.00 g.) and dry benzene (10 ml.) were added, and the mixture was refluxed for 18 hr. under $CaCl_2$-tube protection. The hot mixture was filtered and the cake was rinsed twice with boiling benzene and five times with boiling acetone. Solvent evaporation left 5.40 g. (90%) of product. A portion thereof was recrystallized twice from an ethanol–ligroin mixture, m.p. 157–158°; combustion water, % D_2O, 3.1.

In a separate experiment it was found that ordinary Raney nickel in benzene had no readily detectable chemical action on phenylacetamide during 65 hr. of refluxing.

Hydrolysis and Oxidation of Deuterated Phenylacetamide.—A 5.20-g. portion of the above deuterated phenylacetamide was hydrolyzed as before with refluxing 10% sodium hydroxide solution (100 ml.), then oxidized by treatment with excess potassium permanganate. Usual processing led to 4.11 g. (87.5%) of benzoic acid. A portion was recrystallized from water and sublimed prior to deuterium assay; combustion water, % D_2O, 2.5.

Deuterated Raney Nickel in Benzene on L(+)-Mandelamide.—Deuterated Raney nickel (sample B, 23 g. damp weight) was treated with dry benzene (200 ml.). The mixture was azeotropically dried by distillation to a volume of 60 ml., then treated with 1.00 g. of L(+)-mandelamide ($[\alpha^{25}]D$ +69.0° (*c* 2, acetone), 96% optically pure). The mixture was refluxed for 5.2 hr., and the product (0.40 g.) was isolated as usual. It was dissolved in ethanol, and the solution was allowed to stand 18 hr., then evaporated to dryness. Two recrystallizations (Norit) from a mixture of ethanol and ligroin produced phenylacetamide having m.p. 157.5–158° and showing no optical activity beyond experimental error in acetone solution (*c* 3).

(8) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, p. 165.

(9) Reference 8, p. 167.

(10) W. A. Bonner and T. W. Greenlee, THIS JOURNAL, **79**, 1696 (1957).

STANFORD, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, KYOTO UNIVERSITY]

The Dipole Moments and Molecular Structures of *ac-trans*-Dihalogenotetralins[1]

BY TOSHIO FUJITA

RECEIVED SEPTEMBER 11, 1956

The dipole moments of 2,3-dihalogenotetralins and 1,2-dihalogenotetralins were measured in solution at various conditions, to show that each of these compounds has a half-chair ring and can occur in two conformations which are in equilibrium through ring conversion. Then, the energy difference ΔE between the two conformations of each compound is estimated. From comparison of the ΔE values, it is concluded that the properties of 2,3-dihalogeno compounds are very similar to those of corresponding dihalogenocyclohexenes, and the *aa* conformation of the 1,2-isomers is more stable than that of the 2,3-isomers.

The concept of "non-bonded energy"[2] in cyclohexane derivatives has given clear explanations to

(1) Presented at the monthly meeting of Kansai Branch of the Agricultural Chemical Society of Japan, Kyoto, June 23, 1956.

(2) W. Klyne, "Progress in Stereochemistry," Vol. I, W. Klyne, Ed., Butterworths Scientific Pub., London, 1954, p. 36.

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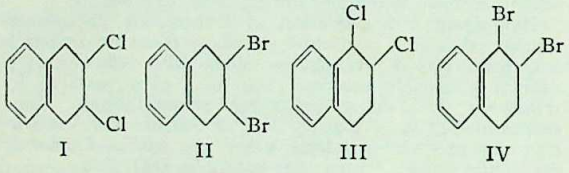
the stereostructures of polycyclic perhydro-systems, especially those of the steroids, and has been generally considered to be applicable to the partially unsaturated polycyclic compounds involving the cyclohexene or tetralin systems.[3] It has been concluded by several investigators[4–6] that, as in the case of cyclohexane derivatives, cyclohexene derivatives also are more stable in the half-chair form than in the half-boat form and can occur in two conformations which are in equilibrium through ring conversion, unless the energy difference between the two is too large.

If the small difference between the double bond lengths of cyclohexene and tetralin be neglected, quite similar arguments may be applied in these two systems. There has been, however, relatively little experimental evidence about the stereostructures of tetralin derivatives other than the X-ray analysis by Lasheen,[7] who has shown that naphthalene tetrachloride has a half-chair ring.

In the work herein reported, dipole moments of four dihalogenotetralins (I–IV) were measured at various conditions to shed more light on the stereostructures of tetralin derivatives, especially that of 1,2,3,4-tetrahydro-1-naphthoic acid, a synthetic plant growth substance,[8] which has been investigated in the author's laboratory.



I II III IV

Experimental

Preparation of Materials.[9] **2,3-Dihalogenotetralins (I) and (II).**—To a solution of 10 g. (0.077 mole) of 1,4-dihydronaphthalene,[10] b.p. 89–92° (20 mm.), in 50 ml. of carbon tetrachloride, 50 ml. of carbon tetrachloride containing 5.5 g. (0.078 mole) of chlorine or 12.5 g. (0.078 mole) of bromine was dropped slowly with stirring at 0°. The solvent was removed *in vacuo*, and the residue was recrystallized several times from ethanol to give 8 g. of I, m.p. 83.5–84° (reported[11] 84–85°), or 15 g. of II, m.p. 73–73.5° (reported 71.5–72°,[10] 73.5–74°),[12] respectively.

1,2-Dihalogenotetralins (III) and (IV) were prepared by halogen addition to 1,2-dihydronaphthalene,[10,13] b.p. 90° (20 mm.), in a procedure similar to that used in preparing the 2,3-isomers. From 3 g. of 1,2-dihydronaphthalene, there was obtained 2.5 g. of III, m.p. 40–41°. *Anal.* Calcd. for $C_{10}H_{10}Cl_2$: Cl, 35.28. Found: Cl, 35.43. Braun and Kirschbaum[13] prepared liquid 1,2-dichlorotetralin, b.p. 155–160° (20 mm.), by direct chlorination of tetralin at 100°, and reported that this substance did not crystallize on cooling. It seems likely that this liquid was a mixture of *cis*- and *trans*-isomers.

In a similar manner, 5 g. of IV was obtained, m.p. 71–72° (reported 70–71°,[10] 70°[13]).

Solvents.—Benzene, freed from thiophene by treatment with anhydrous aluminum chloride, was dried over metallic sodium and then distilled, and the fraction boiling at 80–80.5° was collected. *n*-Heptane was treated with coned. sulfuric acid, dried over metallic sodium and then distilled, and the fraction boiling at 95.5–98° was collected.

Measurement.—The dielectric constant ϵ of the solution was measured with the heterodyne beat apparatus as described by Morino and Miyagawa.[14] The density d was determined with a pycnometer similar to that designed by Lipkin, Davison, Harvey and Kurtz.[15] The total molar polarization $P_{2\infty}$ was calculated by a modified Hedestrand method similar to that introduced by Halverstadt and Kumler,[16] differing in that densities were used rather than specific volumes

$$P_{2\infty} = \frac{\epsilon_1 - 1}{\epsilon_1 + 2}\frac{M_2}{d_1}\left[1 + \frac{3a}{(\epsilon_1 - 1)(\epsilon_1 + 2)} - \frac{b}{d_1}\right]$$

where M_2 is molecular weight of solute, ϵ_1 and d_1 are, respectively, the dielectric constant and density of the solvent, and a and b are the coefficient of linear expansion of ϵ and d of solution with respect to the weight fraction of the solute w; $\epsilon = \epsilon_1 + aw$, $d = d_1 + bw$. The dipole moment μ is given by the equation

$$\mu = 0.0128[\{P_{2\infty} - (P_E + P_A)\}T]^{1/2}$$

where P_E and P_A are the electronic and atomic polarization of the solute, respectively, and T is the temperature in absolute scale. $P_E + P_A$ was taken to be equal to the molecular refraction calculated from the atomic refractions given in the Landolt–Börnstein table. The values thus obtained are listed in Table I. The experimental error in μ is ± 0.02 *D* in I and III and $\pm$ 0.03 *D* in II and IV.

TABLE I

RESULTS OF MEASUREMENTS

Solvent	T, °K.	ϵ_1	d_1	a	b	$P_{2\infty}$, cc.	μ, *D*
I, 2,3-Dichlorotetralin: $P_E + P_A = 52.23$ cc.							
Benzene	283	2.3037	0.8890	1.658	0.271	108.33	1.61
	298	2.2731	.8729	1.630	.271	108.97	1.63
	313	2.2435	.8571	1.602	.270	109.66	1.72
n-Heptane	274	1.9803	.7322	1.167	.321	98.63	1.44
	298	1.9457	.7117	1.178	.322	101.17	1.55
	323	1.9093	.6899	1.140	.321	101.43	1.61
II, 2,3-Dibromotetralin: $P_E + P_A = 58.03$ cc.							
Benzene	298	2.2730	0.8727	0.645	0.441	84.19	1.13
	313	2.2434	.8569	.661	.448	84.58	1.17
n-Heptane	274	1.9814	.7324	.533	.447	78.00	0.93
	298	1.9469	.7118	.540	.435	80.38	1.04
	323	1.9096	.6903	.550	.432	81.92	1.13
III, 1,2-Dichlorotetralin: $P_E + P_A = 52.23$ cc.							
Benzene	298	2.2730	0.8729	1.390	0.279	99.26	1.53
n-Heptane	274	1.9810	.7326	1.125	.324	96.13	1.40
	298	1.9464	.7121	1.097	.318	97.10	1.48
	323	1.9088	.6903	1.072	.320	97.60	1.55
IV, 1,2-Dibromotetralin: $P_E + P_A = 58.03$ cc.							
Benzene	298	2.2733	0.8726	0.847	0.443	95.00	1.34
n-Heptane	274	1.9801	.7325	.790	.442	97.76	1.54
	298	1.9455	.7120	.740	.442	95.10	1.55
	323	1.9091	.6903	.677	.433	92.51	1.59

Discussion

An appropriate model of the tetralin molecule is required for the analysis of the moment values obtained. First, the half-chair model will be discussed. It is assumed that unsaturated and allylic carbon atoms are coplanar, and the intramolecular distortions are minimum when the bond distances

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(15) M. R. Lipkin, J. A. Davison, W. T. Harvey and S. S. Kurtz, *Ind. Eng. Chem., Anal. Ed.*, **16**, 55 (1944).

(16) L. E. Halverstadt and W. D. Kumler, THIS JOURNAL, **64**, (1942).

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and bond angles in Fig. 1 are taken as follows: C=C, 1.38 Å.; C—C, 1.54 Å.; $\angle\theta = 122°$, $\angle\gamma = 111°04'$, $\angle\delta = 108°$, $\angle\beta = \angle\beta' = 109°28'$, $\angle\alpha = 109°50'$, $\angle\alpha' = 109°04'$. To calculate the dipole moments, (i) as the moment value of tetralin itself, 0.52 *D* in benzene obtained by Sidgwick and Springall[17] is used, and (ii) the empirical rule suggested by Morino, Miyagawa and Oiwa[18] is applied, which is as follows: (1) C → Cl, C → Br and C → H bond moments are assumed to be 1.86, 1.79[19] and 0.00 *D*, respectively. (2) In the C—C bond in which C atom locates in the α-position to the first halogen atom, a moment of 0.27 *D* (hal. = Cl) or 0.51 *D* (hal. = Br) is induced in the direction of C ← C. (3) In the C—C bond in which C atom locates in the β-position to the first halogen atom, a moment of 0.15 *D* is induced in the direction of C ← C. (4) In the C—halogen bond in which C atom locates in the β-position to the first halogen atom, a moment of 0.24 *D* (hal. = Cl) or 0.42 *D* (hal. = Br) is induced in the direction of C ← halogen.

The calculation by this rule, instead of using 1.91 *D* for C—halogen bond moment,[20] seems reasonably accurate because of the good agreement of observed and calculated moment values of a number of halogenated hydrocarbons, especially polyhalogenocyclohexanes.[18,21]

In III and IV, this rule cannot be directly applied; therefore, the double bond in the benzene ring is regarded to be a single bond. This assumption may be quite adequate, because the induction effect estimated from this assumption is nearly equivalent to that from the moment values of benzyl halide and methyl halide.

TABLE II

DIPOLE MOMENTS CALCULATED FROM MOLECULAR MODEL[a]

	cis		*trans*	
	ae	*ea*	*aa*	*ee*
I, 2,3-Dichloro-	2.70	2.70	0.09	3.15
II, 2,3-Dibromo-	2.57	2.57	.51	3.10
III, 1,2-Dichloro-	3.13	3.28	.96	3.24
IV, 1,2-Dibromo-	3.01	3.08	1.32	3.26

[a] Symbols *a* and *e* are used as in cyclohexane derivatives; *a*, nearer to the perpendicular of the benzene ring; *e*, nearer to the plane of the benzene ring than the other.

The moments thus calculated for different conformations of each geometrical isomer are shown in Table II. From this table it is clear that if these compounds are of *trans* configurations, the apparent average moment values should vary with the abundance ratio of two conformations at a given temperature unless the energy difference ΔE between them is too large, because the calculated moment values

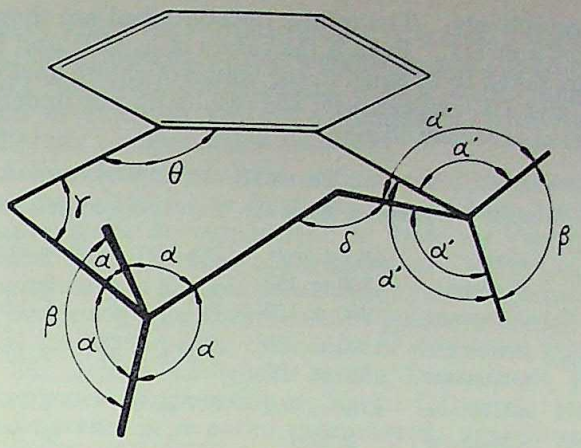

Fig. 1.

undergo appreciable change through ring conversion. On the other hand, if these are of *cis* configurations, their moment values should be observed in the neighborhood of 2.5–3.0 *D* relatively independent of the temperature. But actually, as shown in Table I, the observed values are found around 1.6 *D* (I), 1.1 *D* (II), 1.5 *D* (III) and 1.3 *D* (IV), and apparent moments of I, II and III increase with temperature. Therefore, it is concluded that these four compounds are of *trans* configurations and that the addition of halogen to dihydronaphthalene proceeds as a *trans* addition.

The more stable conformation of I, II or III is obviously *aa*. In IV, $d\mu/dT \fallingdotseq 0$. If the energy difference ΔE between two conformations were equal to zero, then the apparent moment value should become 1.8 *D* independently of temperature. Because the observed moment values 1.35 *D* are in good agreement with the calculated value for the *aa* conformation, 1.32 *D*, IV exists almost entirely as the *aa* conformation.

Let the number of the *aa* molecules be N_a and that of the *ee* molecules be N_e, then the following equation is obtained; $N_e/N_a = e^{-\Delta E/RT}$, and the apparent dipole moment $\bar{\mu}$ is calculated as

$$\bar{\mu}^2 = \frac{N_e\mu_e^2 + N_a\mu_a^2}{N_e + N_a} = \frac{\mu_a^2 + \mu_e^2 \exp(-\Delta E/RT)}{1 + \exp(-\Delta E/RT)}, \text{ or}$$

$$\bar{\mu}^2 - \mu_a^2 = \frac{\mu_e^2 - \mu_a^2}{1 + \exp(\Delta E/RT)}$$

where μ_a and μ_e are the theoretical moment values of *aa* and *ee* conformations, respectively. Using the apparent moment values $\bar{\mu}$ observed at different temperatures and the calculated moment values μ_a in Table II, the energy differences ΔE and the moments μ_e of the *ee* conformations are calculated for I, II and III, according to the method proposed by Lennard-Jones and Pike.[22] The lower limit of ΔE of IV is obtained from the equation[23]

$$4\Delta\mu\cdot\bar{\mu} \geqq (\mu_e^2 - \mu_a^2)[1/\{1 + \exp(\Delta E/RT)\} - 1/\{1 + \exp(\Delta E/RT')\}]$$

where $\Delta\mu$ is the experimental error, T and T' are the highest and lowest temperatures at which the moments are measured. In this equation, $\Delta\mu$, $\bar{\mu}$, μ_a and μ_e are taken to be 0.03, 1.35, 1.32 and 3.22 *D*,

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(19) These are the observed moment values for methyl chloride and methyl bromide in the gaseous state; *cf.* S. Sänger, O. Steiger and K. Gächter, *Helv. Phys. Acta*, **5**, 200 (1932); L. G. Groves and S. Sugden, *J. Chem. Soc.*, 158 (1937).

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(23) I. Miyagawa, *J. Chem. Soc. Japan* (*Pure Chem. Sect.*), **75**, [illegible] (1954).

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respectively. The results thus obtained are shown in Table III. Even if the values of μ_a of II and IV are taken to be equal to the values of chloro analogs I and III, respectively, the results do not undergo an appreciable change.

TABLE III

ENERGY DIFFERENCE BETWEEN TWO CONFORMATIONS

	Solvent	ΔE, cal./mole	μ_e, D	μ_a (D) calcd. from model
I	Benzene	800 ± 150	3.6 ± 0.3	3.15
	n-Heptane	900 ± 150		
II	Benzene	1400 ± 200	3.5 ± 0.3	3.10
	n-Heptane	1550 ± 200		
III	*n*-Heptane	1350 ± 150	3.7 ± 0.4	3.24
IV	*n*-Heptane	≧2000	.....	3.26

As discussed above, the half-chair model can well explain the observed moment values. On the other hand, the model of the half-boat form cannot, because the calculated moment values become considerably larger than the observed values, *e.g.*, in the compound I, *cis* form, *2e3e* (3.3 *D*) ⇄ *2a3a* (3.5 *D*); *trans* form, *2a3e* = *2e3a* (2.2 *D*). Recently, Kumler and Huitric[24] have demonstrated that "six-membered ring compounds with two or more atoms in the ring that do not have sp^3-binding, such as a bivalent atom or a carbonyl which has essentially sp^2-binding, are most likely to have flexible forms" from the study of the molecular structures of α-halocyclohexanones. These dihalogenotetralins are such a type of compound since the ring with halogens has two carbon atoms with sp^2-binding. Even if the observed facts can well be explained by the half-chair model, it is too much to decide only from dipole moment values that these dihalogenotetralins have the half-chair structure and have not any contributions from the half-boat or the other flexible structures. The fact that compounds I, II and III have different moments in benzene and *n*-heptane and that the moments in any one solvent vary with temperature, may be accounted for by the alternative hypothesis that a flexible form makes an appreciable contribution to the structure, according to Kumler and Huitric's idea.

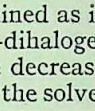
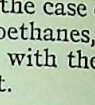
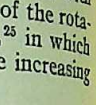
However, taking into consideration Sakashita's results,[6] from Raman spectra of *trans*-4,5-dichloro-1-cyclohexene, that this compound has only two possible structures in the liquid state or solution, and from the dipole moment values, that the observed facts can well be explained only when these two possible structures are the *aa* and *ee* conformations of the half-chair structure, it is quite reasonable to conclude that these tetralin derivatives, structurally very similar compounds to dichlorocyclohexene, are also of half-chair ring structure.

The fact that ΔE of II or IV is, respectively, larger than that of I or III in the same solvent, may be caused by the larger van der Waals radius of the bromine atom, as in the case of dihalogenocyclohexanes and -cyclohexenes.

The structural chemical properties of 2,3-dihalogenotetralins are very similar to those of the corresponding dihalogenocyclohexenes, as shown in Table IV. It seems that in these substances, where a condensed benzene ring is compared with a double bond, there are no remarkable differences in the properties, as the various interactions about halogen atoms opposite to a double bond or a benzene ring are nearly the same. The change of ΔE with solvent may be explained as in the case of the rotational isomers of 1,2-dihalogenoethanes,[25] in which the energy difference decreases with the increasing dielectric constant of the solvent.

TABLE IV

ΔE VALUES (CAL./MOLE) OF I AND II, AND THEIR RELATED COMPOUNDS IN VARIOUS SOLVENTS

X	Solvent			
Cl	C_6H_6	−400[a]	700[b]	800
	n-C_7H_{16}	..	...	900
	CCl_4	50[a]	800[b]	..
Br	C_6H_6	80[a]	1300[c]	1400
	n-C_7H_{16}	500[a]	...	1550
	CCl_4	500[a]	1400[c]	..

[a] K. Kozima, K. Sakashita and S. Maeda, THIS JOURNAL, 76, 1965 (1954). [b] Ref. 6. [c] K. Sakashita, private communication, April, 1956.

The increase of ΔE from dihalogenocyclohexanes to -cyclohexenes or -tetralins is supposed to be caused partly by the following factor. In these compounds, the *aa* conformation is subjected to the mutual repulsion between hydrogen and halogen atoms which are in so-called *meta-axial* relationship. In dihalogenocyclohexane, there are 4 *meta-axial* pairs in *aa* conformation, but in dihalogenocyclohexene and -tetralin, owing to the disappearance of two hydrogen atoms, there are only 2 *meta-axial* pairs. Therefore, it seems that *aa* forms of the latter two are less subjected to such repulsion than the former, so *aa* forms of dihalogenocyclohexene and -tetralin are more stable than that of dihalogenocyclohexane.

It is clear from Table III that ΔE values of 1,2-dihalogenotetralins are considerably larger than those of the corresponding 2,3-dihalogenotetralins. The bonds attached to C-1 are not truly equatorial or axial in character, and the directions of these bonds are less distinguishable than those attached to C-2, but the interactions of halogen atom at C-1 with C-8 and H at C-8 do not exist in the 2,3-isomers, and it is considered that these interactions play an important role in the increase of ΔE. Then it is reasonable to consider that in 1,2-dihalogenotetralin, both halogen–H at C-8 and halogen–C-8 distances are considerably shorter in *ee* than in *aa*, therefore, the steric repulsion in *ee* of 1,2-dihalogenotetralin becomes greater than in that of the 2,3-isomer, making the former considerably more unstable than the latter.

From the discussions above, the following conclusions are obtained: (1) Each of these *ac-trans*-dihalogenotetralins has a half-chair ring and can occur in two conformations through ring conversion, as in the case of dihalogeno-cyclohexane and -cyclohexene. (2) The structural chemical prop-

(24) W. D. Kumler and A. C. Huitric, THIS JOURNAL, 78, 3369 (1956).

(25) [illegible] *Phys.*, 22, 198 (1954).

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erties of *trans*-2,3-dihalogenotetralin are very similar to those of *trans*-4,5-dihalogeno-1-cyclohexene. (3) As to *trans*-1,2-dihalogenotetralin, probably because of the sterical repulsions of halogen at C-1 with C-8 and H at C-8, the *ee* conformation become more unstable than that of the 2,3-isomer, therefore, ΔE becomes larger than that of 2,3-dihalogenotetralin.

From these conclusions the following could be speculated: (1) In regard to *ac*-monosubstituted positional isomers, the abundance ratio of *axial* conformation to *equatorial* one may become larger in α-substituted tetralin than in the β-substituted one. (2) In 1,2-disubstituted tetralin, not only of *trans* configuration but of *cis* configuration, the more stable conformation may be generally the one in which the substituent at C-1 is *axial*. When two substituents are fused together to make another ring, the *trans* configuration cannot occur other than in *1e2e;* in the *cis* configuration, however, *1a2e* may be more stable than *1e2a*.

Acknowledgment.—The author wishes to express his sincere thanks to Professor Tetsuo Mitsui for his invaluable encouragement, to Professor Yonezo Morino and Dr. Ichiro Miyagawa of Tokyo University and Dr. Kiyoshi Sakashita of Tokyo Institute of Technology for their constant guidance and advice, rendered during the course of this work, and to Mr. Ichiro Taniguchi of the Department of Electronical Engineering of Kyoto University for his assistance in preparing the measuring apparatus.

KYOTO, JAPAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BOSTON UNIVERSITY]

Ionization and Dissociation Equilibria in Liquid Sulfur Dioxide. VI. Hexaphenylethane[1]

BY HARRY P. LEFTIN AND NORMAN N. LICHTIN

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The effects of solute purity, light and oxygen on the electrical conductivity of sulfur dioxide solutions of hexaphenylethane have been investigated. Contrary to previous reports, pure solutions of hexaphenylethane do not conduct significantly. Electrolytes are, however, generated by the action of light and of oxygen. Comparison of the data for oxygenated solutions of hexaphenylethane with the conductivity of tetramethylammonium sulfate in liquid sulfur dioxide at 0.1° over the dilution range 200 to 100,000 liters per mole suggests that a 2–1 electrolyte is present. These observations make possible simple explanation of earlier reports on the properties of solutions of hexaarylethanes in sulfur dioxide.

Introduction

The differences in behavior of solutions of hexaphenylethane[2] in sulfur dioxide and in organic solvents has been the subject of considerable discussion. Thus in so called "non-ionizing" solvents, molecular weight,[3] magnetic susceptibility[4] and spectral[5] data in conjunction with photochemical instability[6] and rapid reaction with oxygen[7] demonstrate conclusively the dissociation of hexaarylethanes into free radicals. In sulfur dioxide, however, the solutions have been reported to conduct the electric current,[8] to be photochemically stable[9] and to fail to react with oxygen.[10] Moreover, the observed color[11] and spectrum[12] in SO_2 have been described as differing markedly from those observed in many other solvents.[13]

This anomalous behavior has received several chemical interpretations[14] which differ in detail but which all assume an ionization mechanism involving only hexaphenylethane and sulfur dioxide. These proposed mechanisms can be divided into two general classes depending upon the valence type of the electrolyte produced and, therefore, in view of the recent demonstration[15] of the applicability of modern electrolyte theory to solutions of electrolytes in sulfur dioxide, would be distinguishable on the basis of conductivity data alone. Unfortunately the data of Walden[8a] and of Gomberg[8b] lack precision and do not extend over a sufficient concentration range to be useful for this purpose. Accordingly, attempts were made initially to obtain precise conductivity data employing crystalline samples of pure hexaphenylethane. These investigations revealed[16] that the observed conductivity is an artifact of interaction with light or oxygen and is not characteristic of pure solutions.

(1) Based on a dissertation submitted by H. P. Leftin in partial fulfillment of a requirement for the Ph.D. at Boston University, May, 1955.

(2) For general reviews of this subject see: (a) M. Gomberg, *Chem. Rev.*, **1**, 91 (1924); (b) G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 680–713.

(3) (a) M. Gomberg and L. H. Cone, *Ber.*, **37**, 2037 (1904); (b) M. Gomberg and C. S. Schoepfle, THIS JOURNAL, **39**, 1652 (1917).

(4) (a) N. W. Taylor, *ibid.*, **48**, 854 (1926); (b) E. Muller, I. Muller-Radloff and W. Bunge, *Ann.*, **520**, 235 (1935); (c) M. F. Roy and C. S. Marvel, THIS JOURNAL, **59**, 2622 (1937); (d) R. Preckel and P. W. Selwood, *ibid.*, **63**, 3397 (1941).

(5) (a) J. Piccard, *Ann.*, **381**, 347 (1911); (b) K. Ziegler and L. Ewald, *ibid.*, **473**, 163 (1929).

(6) S. T. Bowden and W. J. Jones, *J. Chem. Soc.*, 1149 (1928).

(7) (a) M. Gomberg, *Ber.*, **33**, 3150 (1900); THIS JOURNAL, **22**, 757 (1900); (b) J. Schmidlin, *Ber.*, **41**, 2471 (1908).

(8) (a) P. Walden, *Z. physik. Chem.*, **43**, 443 (1903); (b) M. Gomberg and L. H. Cone, *Ber.*, **37**, 2033 (1904); (c) M. Gomberg and F. W. Sullivan, Jr., THIS JOURNAL, **38**, 1342 (1905); (c) Reference 6, p. 1153.

(9) L. C. Anderson, THIS JOURNAL, **44**, 1810 (1922).

(10) M. Gomberg and F. W. Sullivan, THIS JOURNAL, **57**, 1673 (1935).

(11) (a) K. H. Meyer and H. Wieland, *Ber.*, **44**, 2557 (1911); (b) Reference 10.

(12) Reference 10.

(13) Ziegler and Ewald, reference 5b, reported that the spectra of hexaphenylethane solutions are identical in a series of solvents covering a wide range of dielectric constant, ion solvating power and structural properties.

(14) (a) Reference 2a, p. 102; (b) P. Walden, "Chemie der Freien Radicale," S. Hirzel, Leipzig, 1924, p 154; (c) W. A. Waters, "Chemistry of Free Radicals," Oxford Press, London, 1948, pp. 35–36; (d) Reference 2b, p. 712; (e) H. I. Cole, *Philippine J. Sci.*, **19**, 681 (1922); (f) G. Cilento and W. F. Walter, THIS JOURNAL, **76**, 4469 (1954).

(15) (a) N. N. Lichtin and P. D. Bartlett, *ibid.*, **73**, 5530 (1951); (b) N. N. Lichtin and H. P. Leftin, *J. Phys. Chem.*, **60**, 160, 164 (1956).

(16) H. P. Leftin and N. N. Lichtin, THIS JOURNAL, **76**, 2593 (1954).

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Experimental

Hexaphenylethane.—This was prepared in an all-glass apparatus by shaking a solution of 30 g. (0.108 mole) of triphenylchloromethane in 300 ml. of acetone with 80 g. (0.40 mole) of mercury. The reaction was carried out in a 580-ml. sealed flask, A, shielded from light by wrapping with aluminum foil and equipped with a side arm closed by a fragile glass membrane. Prior to sealing, the reaction flask and contents were cooled to −40° and evacuated to the autogenous pressure of the mixture. Shaking was provided at room temperature by a Burrell model CC shaker set at speed 10. After a 9-hour shaking period the side arm (containing a sealed in coarse sintered disk) of a receiving flask, B, was sealed onto the side arm of the reaction flask. The receiving flask was then dried by flaming and pumping and finally evacuated to a pressure of 10^{-4} mm. through a stopcock, C, sealed to its neck. With the stopcock closed, the apparatus was removed from the vacuum line and transferred to a darkened room where the synthesis was completed. The fragile glass membrane was smashed by means of a glass bead and the orange solution was filtered through the coarse sintered disk by rotating the apparatus. A small side bulb on flask A served to prevent plugging of the filter disk by trapping most of the mercury residue. This residue was washed free of product with solvent distilled back into A from B. During such distillations the solutions were never warmed above 30° and the process was speeded by cooling the receiving bulb to −78°. The product was crystallized by concentrating the solution to one-fourth of its original volume and cooling in an ice-bath for several hours. The mother liquors were decanted into vessel A, and the product then recrystallized from solvent freshly distilled from A into B. Usually three recrystallizations were executed prior to final product isolation. Following the removal of mother liquors from the final recrystallization the apparatus was dismembered by sealing off at the connecting arm.

The vessel containing the yellow or buff colored crystalline product was wrapped with aluminum foil and pumped through C for 24 hours at a pressure of 10^{-5} mm. It was next sealed off from the vacuum line directly below C and transferred to a vacuum dry-box.[17] The dry-box was evacuated overnight to a pressure of 10^{-3} mm. and filled with "Seaford"[18] nitrogen which had been passed over fine copper turnings at 800°, cooled to −78° and finally passed over Drierite. The dry-box atmosphere was further purified by exposure to sodium until a freshly cut surface of the metal showed no signs of tarnish after two hours. Light entering the dry-box was kept to a minimum with the aid of a red filter fashioned from a watch glass made of Corning L. A. glass.

After the flask was opened in the dry-box the yellow solid was transferred to a sintered glass funnel and washed rapidly with a small quantity of pure acetone. This simple washing procedure effectively removes all of the colored surface impurity[19] leaving pure white crystalline hexaphenylethane. The pure product was next distributed into glass bulbs for analysis, conductivity measurement (*vide infra*) and melting point determination. In this way several samples of identical history could be obtained.

Several batches of hexaphenylethane were prepared by this method and one batch was prepared by the method of Lichtin and Thomas.[20]

At least two samples or each lot of hexaphenylethane were transferred to bulbs and analyzed by quantitative oxygenation in the absence of pyrogallol according to the procedure of Lichtin and Thomas.[20] Melting point capillary tubes were filled in the dry-box, temporarily sealed with a plug of Apiezon "Q" putty, removed from the dry-box and immediately sealed with a needle point flame. Melting points were determined using an electrically heated stirred H type bath and were not corrected. Table I summarizes the relevant data for different batches.

TABLE I

PHYSICAL PROPERTIES OF HEXAPHENYLETHANE

Color	Melting range,[a] °C.	Oxygen absorption (% of theory)
White	153.5–154	99.5 ± 0.1
White	153–154	97.2 ± .1
Pale yellow	.....	95.8 ± .3
Pale yellow	146–148	94.0 ± .1
Yellow	144–146	90.4 ± .3

[a] Literature values: 145–147°, M. Gomberg, THIS JOURNAL, 36, 1144 (1914); 150–152° (cor.) ref. 20.

Reagents and Solvents.—Triphenylchloromethane was prepared from Eastman White Label triphenylcarbinol by reaction with acetyl chloride in dry ether. A pure white product was obtained by rapid crystallization from a hot saturated solution. Recrystallization from ether and vacuum drying at room temperature afforded 93 to 97% yields of pure white crystalline product, m.p. 112.5–113° (uncor.).

Mercury was triple distilled C.P. grade and was outgassed at 100° for several minutes before use. The following solvents were of C.P. grade: acetone was stored over Drierite for several weeks, filtered, refluxed over calcium hydride and distilled before use; ether was dried over calcium hydride and filtered.

Sampling Technique for Conductivity Runs.—Samples (50–200 mg.) for conductivity measurements were stored in sealed preweighed break-off type bulbs (equipped with female standard taper joints) which were filled in the vacuum dry-box. The filled bulbs were then attached to a manifold, which was then evacuated by means of an external pump connected through the base plate of the dry-box. The evacuated manifold and bulbs were transferred from the dry-box to a vacuum line and pumped at 10^{-5} mm. for several hours. The sample bulbs were then sealed off at their necks. During the sealing operation the lower portion of the bulb containing the sample was kept immersed in an ice-bath in order to prevent thermal decomposition.

Sample weights (usually 50–200 mg.) were determined by difference with an accuracy of better than ±1 mg. An appropriate vacuum correction, based on the measured bulb volume, was applied in each case and was usually of the order of 3–4 mg. with an uncertainty of about 0.5 mg. due to the volume occupied by the sample. The bulbs were wrapped in aluminum foil and stored in a light-proof box in the freezing compartment of a refrigerator. Samples stored in this manner showed no visible evidence of deterioration after 18 months.

Conductivity Measurements.—The conductivity cell, thermostat and bridge assembly employed in this work have been described previously.[21] The temperature of measurement was −8.93 ± 0.03°. The vacuum line was similar to that used in earlier work.[21] Procedures employed in preparing solutions in the cell differed from those previously reported in the following respects.

Hexaphenylethane was introduced into the conductivity cell by smashing the breakoff diaphragm of an evacuated sample bulb sealed to the inlet tube of the sealed, evacuated, sulfur dioxide-filled cell. A glass grid was installed in the inlet tube in order to support the glass-sheathed, gold-plated, solenoid-activated, iron rod used for this purpose. That this grid did not introduce significant drainage errors was established by measurements employing triphenylchloromethane as solute. The small quantity of glass fragments introduced into the electrode compartment by this procedure caused a negligible error in the measured volume of the solution. All conductivity measurements as well as the preparation of the solutions were carried out under dark-room conditions except where otherwise indicated. Only light provided by a Kodak ruby-red safelight was permitted.

(17) G. R. Thomas and N. N. Lichtin, *Rev. Sci. Inst.*, 23, 738 (1952).

(18) Containing 1% hydrogen, supplied by Air Reduction Co.

(19) Gomberg[2a] claimed that even in the solid state hexaphenylethane undergoes a slow photochemical transformation. Since light of the wave length most active in effecting this transformation[12] was rigorously excluded in the present procedures, it seems unlikely that the surface color is due to this cause. The ease with which the color can be removed suggests that it may be due to adsorption of a soluble colored impurity or of the monomeric radical from the mother liquors. In this respect it is interesting that color was not produced when white hexaphenylethane in an evacuated sealed tube was exposed either to sunlight or to ultraviolet light for several days at room temperature. In the absence of light, however, a yellow coloration developed when the ethane was exposed to the atmosphere.

(20) N. N. Lichtin and G. R. Thomas, THIS JOURNAL, 76, 3021 (1954).

(21) N. N. Lichtin and H. Glazer, *ibid.*, 73, 5537 (1951).

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to contact the solutions. Sulfur dioxide, Virginia Smelting Co., Extra-Dry Es-O-Too refrigeration grade, was dried in the gas phase over $Mg(ClO_4)_2$ and distilled into the cell from a helix-packed bulb. In about half of the runs the solvent was degassed prior to distillation into the cell by pumping at −78° for varying periods of time. In two runs the degassed solvent was further purified by distillation from about 2 g. of hexaphenylethane. Solvent conductivity determined at the end of each run was usually in the range 1.0×10^{-7} to 2.2×10^{-7} mho cm.$^{-1}$.

Sulfur dioxide solutions of the product formed by the reaction of hexaphenylethane with oxygen were prepared by the following procedure. A stopcock was added to the exit arm of the cell. The cell was filled with degassed sulfur dioxide, removed from the line and a solution of hexaphenylethane prepared in the usual way. The solution was then thermostated, its resistance measured, and dry tank oxygen admitted through the stopcock with the aid of the vacuum line. Equilibration with oxygen was considered complete when the conductivity of the solution remained unchanged for two hours. The cell was then evacuated to the autogenous pressure of the solution at −35°, sealed off at the stopcock and conductivity behavior measured at −8.9° in the usual way. After several dilutions these runs had to be terminated because the residue was so strongly solvated that a sufficient volume of solvent could not be recovered by distillation from the reservoir bulb.

Experiments in which the influence of light was examined were carried out at 0° using an unsilvered Dewar ice thermostat. Illumination of the electrode compartment of the cell was provided by a Burton long wave length ultraviolet lamp.

Recovery of Solutions.—The design of the conductivity cell did not permit recovery of solutes after a conductivity run without atmospheric contamination. Therefore, solutions for this purpose were prepared with the aid of the vacuum line in a separate reaction vessel. A solution of hexaphenylethane (99.5% purity by oxygenation) in degassed sulfur dioxide was maintained in the dark at about −10° for four hours. Removal of the solvent under reduced pressure left a bright yellow residue which was pumped at 10^{-5} mm. for 24 hours. This residue, dissolved in acetone, showed the presence of unchanged hexaphenylethane by a positive Schmidlin test[22] and by the formation of triphenylmethyl peroxide (m.p. 185–186°) on exposure to oxygen.

The addition of oxygen to a solution of the ethane in degassed sulfur dioxide in the dark afforded a blood-red residue which failed to satisfy Schmidlin's criterion and did not yield any dityrityl peroxide. The color of the residue changed to a dirty brown on exposure to atmospheric moisture. The residue was insoluble in hydrocarbon solvents, chloroform and carbontetrachloride. Yellow solutions were obtained in methanol, ethanol, acetone, ether and glacial acetic acid. However, attempted crystallization from these solvents afforded only intractable gums. Hydrolysis of an acetone solution gave an almost white, gummy precipitate which could not be crystallized. This hydrolysis product behaved like a triarylcarbinol in Bowden's[23] test. Its visible spectrum in 98% sulfuric acid solution was similar but not identical to that of triphenylcarbinol. An intense absorption band with its maximum at 440 mμ and a shoulder at 410 mμ was observed with the hydrolyzate, whereas triphenylcarbinol displays maximum absorption at 435 mμ with an only slightly less intense maximum at 410 mμ. Since the hydrolyzate was impure these data can only be regarded as suggestive. The aqueous filtrate from the hydrolysis did not show the presence of sulfate ion when tested with barium chloride.

Triphenylmethyl Peroxide.—This was prepared by oxygenation of hexaphenylethane in benzene solution in the dark. Recrystallization from chloroform afforded white crystals, m.p. 186–187°. This material (3.4 mg.) ground to a fine powder failed to dissolve completely in degassed liquid SO_2 (45 ml.) even after standing at 0° for three hours with occasional mixing. Contrary to Walden's[8a] observations, the solution remained colorless and its specific conductivity (3×10^{-7} mho cm.$^{-1}$ compared to 1×10^{-7} for the pure solvent) remained constant. These results establish that trityl peroxide, present as an impurity in hexaphenylethane, cannot account for the observed conductivity of sulfur dioxide solutions of the parent hydrocarbon.

Tetramethylammonium Sulfate.—This was prepared by shaking for 24 hours a solution of 19 g. (0.12 mole) of Eastman White Label tetramethylammonium bromide in 50 ml. of distilled water with 15 g. (0.06 mole) of C.P. silver sulfate at room temperature in the absence of light. The silver bromide was removed and the solution treated for three 10-hour periods with fresh batches (10 g.) of silver sulfate until no further reaction could be detected. The solution was carefully evaporated to dryness on a steam-bath and the residue was dissolved in 95% ethanol, filtered, and crystallized by adding acetone. The product, recrystallized three times from an acetone–alcohol mixture, washed with acetone, pulverized and dried over P_2O_5 for two weeks, was a white, hygroscopic powder. Its purity by gravimetric sulfate analysis was 99.4 ± 0.1%.

Results and Discussion

Data.—The conductivity of a solution of hexaphenylethane in liquid sulfur dioxide purified only by passage through $Mg(ClO_4)_2$ and distillation increases significantly under the influence of ordinary fluorescent tube room illumination or daylight. Under dark-room conditions the conductivity of such a solution does not change with time. Measurements performed in the dark are, however, not reproducible from sample to sample even when carried out on samples of high purity and identical history. Yet, though the Λ *vs.* v curves are quite different, they resemble each other in a way which suggests that the same electrolyte is present in all cases but at concentrations which deviate from the stoichiometric values by factors that differ from run to run. This is illustrated in Fig. 1. Included for comparison are plots of the data for typical 2:1 and 1:1 electrolytes, tetramethylammonium sulfate and bromide, respectively. The former, but not the latter, resembles the hexaphenylethane curves.

The data of Table II illustrate the effect on the conductivity of solutions of purification of the solvent. Evidently, conductivity is associated with the presence of a volatile impurity which can be removed efficiently by preliminary treatment with hexaphenylethane. These facts, combined

TABLE II

EFFECT OF SOLVENT PRETREATMENT ON CONDUCTIVITY AT −8.9° OF HEXAPHENYLETHANE SOLUTIONS PREPARED IN THE DARK

Solute purity,[a] %	Dilution, l./mole	$\kappa \times 10^8$,[b] mhos cm.$^{-1}$	Solvent pretreatment
95.8	208.1	70.4	No degassing
94	219.2	9.86	Pumped 1 hr.
94	236.3	2.67	Pumped 4 hr.
97	226.2	0.95	Pumped 3 hr., redistilled from Ph_6C_2
97	111.7	3.77	Pumped 2 hr.
97	111.7	362.1	Above soln. after treatment with O_2
97	250	206	Above soln., diluted

[a] By quantitative oxygenation. [b] Corrected for solvent conductance.

(22) A solution of hexaphenylethane in an organic solvent loses its yellow color instantly when agitated in the presence of air. The color returns slowly when the solution is then allowed to stand undisturbed. This phenomenon, first described by Schmidlin[7b], can be repeated several times until all of the hexaphenylethane has been converted to the peroxide.

(23) S. T. Bowden, *Analyst*, **59**, 618 (1934). An intense color characteristic of a triarylcarbonium ion is produced when a triarylcarbinol dissolved in ether is treated first with a drop of concentrated HCl and then with a saturated ether solution of cupric chloride.

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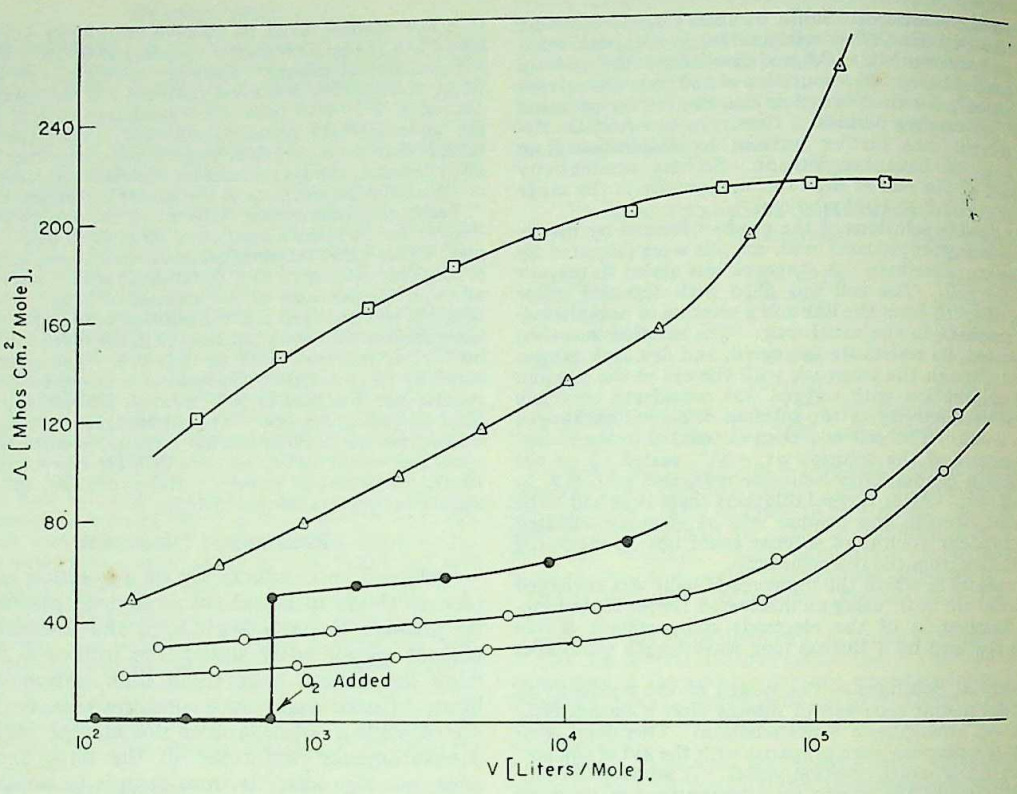

Fig. 1.—Conductivity data in sulfur dioxide solution: —O—, hexaphenylethane (99.5% by O_2 analysis) in ordinary SO_2 (containing O_2 as impurity) at −8.9°; —●—, hexaphenylethane (99.5% by O_2 analysis) in degassed SO_2 at −8.9°, data to the right of the arrow indicate behavior after the addition of O_2; —△—, tetramethylammonium sulfate at 0.1° (typical 1–2 electrolyte); —⊡—, tetramethylammonium bromide at −8.9° (typical 1–1 electrolyte).

with the very large increase in conductivity consequent upon addition of oxygen to a feebly conducting degassed solution, lead to the conclusion that this impurity is molecular oxygen. Other facts support this conclusion.

The conductivity achieved on saturating with oxygen is greater than that observed for solutions prepared without degassing (*cf.* Fig. 1) although of the same order of magnitude. As detailed in the Experimental section, hexaphenylethane can be recovered, apparently unchanged, from solution in degassed sulfur dioxide, but the residue remaining after removal of solvent from an oxygenated solution is neither hexaphenylethane nor its peroxide. Ditrityl peroxide is, in fact, only slightly soluble in sulfur dioxide and its saturated solutions do not conduct significantly. The oxygenation of hexaphenylethane in sulfur dioxide is irreversible, however, as demonstrated by the use of hexaphenylethane as a getter from which purified sulfur dioxide can be distilled and by the fact that thorough degassing of an oxygenated solution does not affect its conductivity materially. Solutions resulting from oxygenation are similar in appearance (blood-red) to these prepared in sulfur dioxide which has not been degassed. Solutions in degassed sulfur dioxide are yellow and visually appear to be identical with solutions of hexaphenylethane in common organic solvents.

The action of near ultraviolet light on the conductivity of a solution of hexaphenylethane in degassed sulfur dioxide and of an oxygenated solution is illustrated in Fig. 2. Degassed solutions are strongly and irreversibly affected while oxygenated solutions appear to be inert. Irradiation of solutions in degassed sulfur dioxide produces a change in color from yellow to brown. Removal of solvent from such irradiated solutions yields a dark red gum which responds negatively to tests for the presence of hexaphenylethane.

Information on the nature of the oxygenation product is, at present, fragmentary and inconclusive. Observations on the product of hydrolysis of the oxygenation product suggest the presence of impure triphenylcarbinol. This is supported by the spectroscopic observations reported for solutions in sulfur dioxide which very probably contained the oxygenation product as the principal solute. That the anion probably bears a charge of minus two is indicated by the comparisons of Fig. 1. The same conclusion follows from the application of Shedlovsky's procedure[24] for determining equilibrium constants to the data of a typical run with hexaphenylethane in ordinary sulfur dioxide and to the data for tetramethylammonium sulfate on the basis of the assumption that *both solutes are 1:1 electrolytes.* Relevant conductivity data are summarized in Table III. The resulting similar strongly inflected plots of $1/\Lambda S(z)$ *vs.* $c\Lambda f_{\pm}^{2}S(z)$[25] are

(24) T. Shedlovsky, *J. Franklin Inst.*, **225**, 739 (1938).

(25) $S(z)$ is Shedlovsky's function, c the concentration in moles per liter and $f_{\pm}$ the mean ionic activity coefficient.

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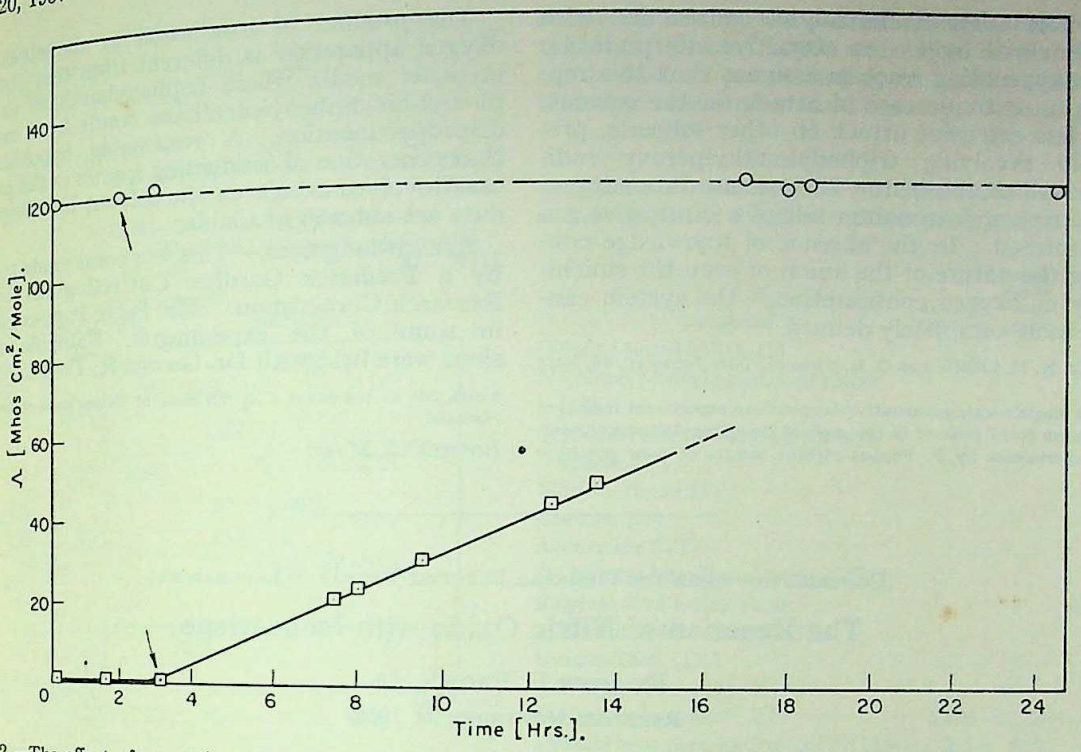

Fig. 2.—The effect of near ultraviolet light on the conductivity of hexaphenylethane solutions at 0°; arrow indicates the time at which illumination was started: —⊡—, degassed SO_2, 6750 liters/mole; —O—, oxygenated SO_2, 2600 liters/mole.

compared in Fig. 3 with the straight line Shedlovsky plot obtained from the data for a typical 1:1 electrolyte. There is, however, the possibility that the sulfur dioxide solution of the oxygenation product contains several electrolytes, and that the similarity to 2:1 electrolyte behavior is illusory. No evidence on the nature of the anion was obtained other than the failure to detect sulfate in the hydrolyzate.

TABLE III

CONDUCTIVITY OF TETRAMETHYLAMMONIUM SULFATE AND OXYGENATED HEXAPHENYLETHANE IN SULFUR DIOXIDE

$[(CH_3)_4N]_2SO_4$[a]			Ph_6C_2[b]		
v, l./mole	$\kappa \times 10^6$, mhos[c] cm.$^{-1}$	Λ, mhos-cm.^{2} mole^{-1}	v, l./mole	$\kappa \times 10^6$, mhos[c] cm.$^{-1}$	Λ, mhos-cm.^{2} mole^{-1}
170.0	292.4	49.71	218	133.3	29.1
387.2	164.2	63.58	499	66.0	32.9
882.7	90.69	80.05	1140	31.8	36.3
2013	49.21	99.06	2610	15.1	39.2
4590	25.72	118.0	5960	6.99	41.7
10470	13.02	136.3	13600	3.27	44.6
23870	6.547	156.3	31200	1.61	50.4
54450	3.511	191.2	71500	0.89	64.2
124100	2.102	260.8	164000	0.58	89.8

[a] 0.12 ± 0.03°. [b] Partially oxygenated solution, light excluded, −8.93°. [c] Corrected for solvent conductivity.

Discussion

It is now apparent that earlier work involved solutions in sulfur dioxide of hexaarylethanes that were either completely oxygenated or nearly so. Although spectroscopic and magnetic studies on oxygen-free solutions in sulfur dioxide are lacking, qualitative observations of color, oxygen absorption and sensitivity to irradiation as well as conductivity data make it seem highly probable that the usual triphenylmethyl–hexaphenylethane equilibrium mixture is present in such solutions.

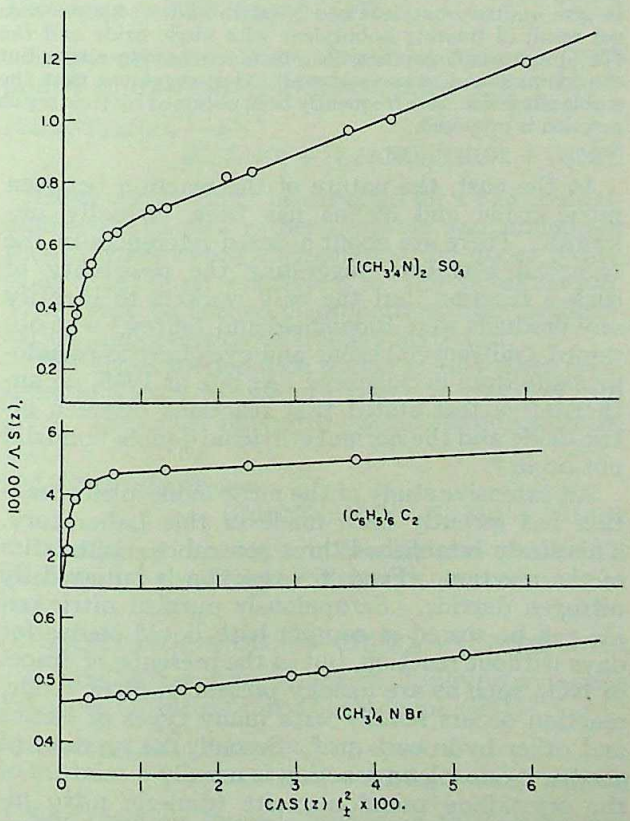

Fig. 3.—Shedlovsky plots for salts in sulfur dioxide solution.

The unusual character of these solutions relates

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to the formation of electrolytes on reaction with oxygen or with light. An attractive interpretation of the oxygenation reaction assumes that this represents an extreme case of attack on the solvent. Much less extensive attack on other solvents, presumably involving triphenylmethylperoxy radical[26] is well established. The present data suggest that a triphenylcarbonium salt of a dinegative anion is formed. In the absence of knowledge concerning the nature of the anion or even the stoichiometry of oxygen consumption,[27] the system cannot be more completely defined.

(26) *Cf.* N. N. Lichtin and G. R. Thomas, THIS JOURNAL, **76**, 3021 (1954).

(27) A single rough quantitative oxygenation experiment indicated consumption of 0.7 mole of O_2 per mole of hexaphenylethane. Additional experiments by P. Pappas yielded results of poor precision which fell in the range 1 ± 0.5 mole of O_2 per mole of hexaphenylethane.

The product of irradiation in the absence of oxygen apparently is different from that obtained in other media where triphenylmethane and diphenyl-bis-diphenyleneethane result from induced disproportionation. A reasonable hypothesis is that generation of conducting species in the present case involves attack on the solvent but diagnostic data are not now available.

Acknowledgment.—This work was made possible by a Frederick Gardner Cottrell grant by the Research Corporation. Mr. Peter Pappas assisted in some of the experiments. Valuable discussions were held with Dr. George R. Thomas.

BOSTON 15, MASS.

[CONTRIBUTION FROM THE GENERAL ELECTRIC RESEARCH LABORATORY]

The Reaction of Nitric Oxide with Isobutylene

BY JOHN F. BROWN, JR.

RECEIVED NOVEMBER 28, 1956

Nitric oxide containing traces of nitrogen dioxide reacts readily with liquid isobutylene to give nitrogen and a mixture of nitrated products. This mixture is believed to contain β-nitroisobutylene (22%); nitro-*t*-butanol (9%); traces of isobutylene pseudonitrosite, nitro-*t*-butyl nitrate and α-hydroxyisobutyraldoxime; and major amounts (66%) of a substance having the partial structure (nitro-*t*-butyl)$_4N_2O_2$. The latter is very unstable and decomposes on standing or gentle warming to give α-nitroisobutylene and N-(nitro-*t*-butyl)-hydroxylamine, which also decomposes on standing or heating. Thus, the net result of treating isobutylene with nitric oxide and then distilling the product is the formation of nitroisobutylene (74%) and small quantities of substances having nitro-*t*-butyl groups joined to nitro, nitroso, nitrate ester, hydroxyl, hydroxylamino and oximino groups. It is suggested that the (nitro-*t*-butyl)$_4N_2O_2$ is representative of the unidentified unstable oils which have frequently been obtained by treating olefins with N_2O_3 or N_2O_4. A mechanism for the NO–isobutylene reaction is proposed.

In the past, the nature of the reaction between nitric oxide and olefins has been virtually unknown. There are about a dozen references in the technical literature suggesting the possibility of such a reaction, but the only workers to identify any products were Bloomfield and Jeffrey,[1] who obtained 1-nitrocyclohexene and cyclohexene pseudonitrosite from cyclohexene. As late as 1949, an authoritative text stated that reactions between nitric oxide and the normal ethylenic double bond did not occur.[2]

An extensive study of the nitric oxide–olefin reaction has recently been made in this Laboratory. This study established three general characteristics of the reaction. First, the reaction is initiated by nitrogen dioxide. Scrupulously purified nitric oxide can be stored in contact with liquid olefins for days without reaction, but in the presence of traces of NO_2, such as are usually present in nitric oxide, reaction occurs readily with many types of olefins and other hydrocarbons.[3] Second, the product of a nitric oxide–olefin reaction is usually a mixture of the crystalline pseudonitrosite (dimeric nitro nitroso adduct) and an unstable liquid mixture which will undergo a "fume-off" or low-order explosion upon attempted distillation. It was found that the decomposition of these liquids could be controlled by steam distillation or passage through a falling film still, but no means of fractionating any significant quantity without decomposition was discovered. Third, the distilled liquid reaction products consist mainly of mixtures of nitroölefins. For example, 1-octene gives 1-nitro-1-octene and 1-nitro-2-octene.[3] In general, the linear olefins give fair yields of both nitroölefins and pseudonitrosites, while the branched olefins give good total yields of nitroölefins but little pseudonitrosite.

It was evident, however, that any detailed understanding of the nitric oxide–olefin reaction would require considerably more information about the nature of the reaction products. The present investigation of the products from the nitric oxide–isobutylene reaction was undertaken in order to obtain such information.

Basically, this objective required that a detailed analysis be made on a complex mixture which was changing composition continually during the course of the analysis. In order to accomplish this, a large batch of nitric oxide–isobutylene reaction product was prepared and the stoichiometry of the reaction determined. The product was fractionated, mainly by distillations under mild conditions, until a large number of fractions representing individual compounds or simple mixtures had been obtained. Analysis of these then permitted

(1) G. F. Bloomfield and G. A. Jeffrey, *J. Chem. Soc.*, 120 (1944).

(2) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," The Clarendon Press, Oxford, 1949, p. 213.

(3) C. A. Burkhard, J. F. Brown, Jr., C. S. Herrick, R. L. Myers and D. T. Hurd, Abstracts of Papers, 126th Meeting, American Chemical Society, September 12–17, 1954, p. 42-O.

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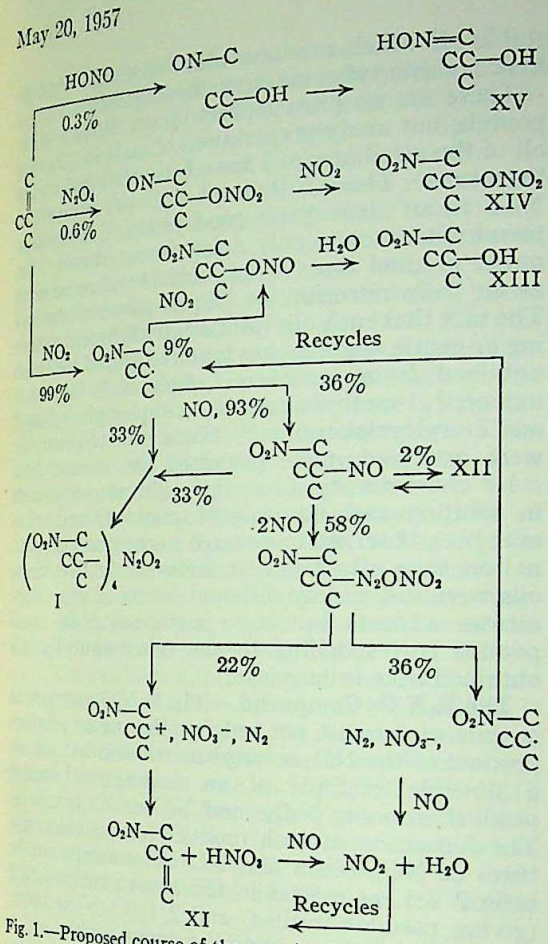

Fig. 1.—Proposed course of the reaction between nitric oxide and liquid isobutylene.

complete identification and estimation of the constituents of the separated fractions. During the fractionation, the refractive indices, infrared spectra and other properties of the mixtures were followed closely in order to detect changes in product composition as they occurred. The nature of the changes that the individual product constituents underwent under the conditions of the fractionation were then determined and used as the basis for estimates of the product composition at earlier stages. Finally, the resulting estimate of the initial product composition was checked by comparing the stoichiometric ratios which it predicted against those actually observed.

Results

The results of this investigation are summarized in Table I. The composition "after fractionation" shows corrected analytical values for the aggregate composition of 45 liquid and solid organic fractions separate from the crude product. The composition "initially present" represents these values adjusted for all the changes that were observed to be occurring during the fractionation, while that at the "intermediate stage" represents a somewhat hypothetical product in which the decomposition of I, the most sensitive constituent, has gone to completion, while that of II, the next most sensitive, has not yet begun.

The major primary product of the reaction between nitric oxide and isobutylene is a thick, unstable oil having the partial structure (nitro-*t*-butyl)$_4$N$_2$O$_2$ (I) and hence referred to as the R$_4$N$_2$O$_2$ compound. Upon standing or gentle warming it undergoes elimination and decomposition to give α-nitroisobutylene (1-nitro-2-methyl-1-propene, X) and N-(nitro-*t*-butyl)-hydroxylamine (II).

Table I

Estimated Composition of the Product from the Reaction of Nitric Oxide with Excess Liquid Isobutylene at 28°

Compound	Initially present	Intermediate stage	After fractionation
(Nitro-*t*-butyl)$_4$N$_2$O$_2$ (I)	66.4	..	..
N-(Nitro-*t*-butyl)-hydroxylamine (II)	..	15	1.0
O,N-Bis-(nitro-*t*-butyl)-hydroxylamine (III)	..	..	0.4
Nitromethane (IV)	..	..	1.8
Acetone (V)	..	..	0.8
Acetoxime (VI)	..	..	0.2
O-(Nitro-*t*-butyl)-acetoxime (VII)	..	..	2.3
Regenerated isobutylene	..	..	*ca.* 1
1,2-Dinitroisobutane (VIII)	..	..	0.8
Unidentified (IX)	..	2	..
α-Nitroisobutylene (X)	..	49	49.7
β-Nitroisobutylene (XI)	21.8	21.8	24.2
Isobutylene pseudonitrosite (XII)	2.1	2.1	2.7
Nitro-*t*-butanol (XIII)	8.8	8.8	8.8
Nitro-*t*-butyl nitrate (XIV)	0.6	0.6	0.6
α-Hydroxyisobutyraldoxime (XV)	0.3	0.3	0.3
Liquids b.p. > 100° (1 mm.) (XVI)	..	..	7.3

$$(C_4H_8NO_2)_4N_2O_2 \longrightarrow 3C_4H_7NO_2 + (C_4H_8NO_2)NHOH + (HNO)$$

However, as might be expected for a β-nitroalkylamine,[4] II is also rather unstable and undergoes three further types of decomposition under conditions like those employed in the fractionation. These may be termed disproportionation, dealdolization and reversion to starting materials.

The disproportionation occurs mainly when solutions of II are allowed to stand in the cold and gives the O,N-bis-(nitro-*t*-butyl)-hydroxylamine (III).

$$2(C_4H_8NO_2)NHOH \longrightarrow (C_4H_8NO_2)NHO(C_4H_8NO_2) + NH_2OH$$

Dealdolization occurs on heating and results in a cleavage of the II into nitromethane and acetoxime.

$$(CH_3)_2C(CH_2NO_2)NHOH \longrightarrow CH_3NO_2 + (CH_3)_2C{=}NOH$$

A similar reaction of the dialkylhydroxylamine III gives O-(nitro-*t*-butyl)-acetoxime (VII).

$$(CH_3)_2C(CH_2NO_2)NHO(C_4H_8NO_2) \longrightarrow CH_3NO_2 + (CH_3)_2C{=}NO(C_4H_8NO_2)$$

The reaction termed "reversion to starting materials" is a complex autocatalytic process which is induced by heating with nitrogen oxides. It appears to involve the steps

$$(CH_3)_2C(CH_2NO_2)NHOH + NO_2 \longrightarrow (CH_3)_2C(CH_2NO_2)NO \quad (XII)$$

(4) A. Lambert and J. D. Rose, *J. Chem. Soc.*, 1511 (1947).

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$$(CH_3)_2C(CH_2NO_2)NO \overset{\Delta}{\rightleftharpoons} (CH_3)_2C{=}CH_2 + NO + NO_2$$

$$(CH_3)_2C(CH_2NO_2)NO + NO_2 \longrightarrow NO + (CH_3)_2C(CH_2NO_2)NO_2 \quad \text{(VIII)}$$

$$(CH_3)_2C{=}CH_2 + NO \longrightarrow N_2, (CH_3)_2C{=}CHNO_2, \text{etc.}$$

The net result of this process is the formation of gaseous products such as isobutylene, nitrogen and nitric oxide, along with XII, VIII and considerable tar. The thermal dissociation and disproportionation of the pseudonitrosite, represented by the last three equations, was examined independently and found to give good yields of dinitroisobutane VIII, along with regenerated isobutylene, X, N_2 and NO.

Finally, it was noted that a little isomerization[5] of the α-nitroisobutylene (X) to the more volatile β-nitroisobutylene (XI) occurred during one distillation in which the base II was present.

By adjusting the values of the final composition listed in Table I for the observed conversions of II and IX into III–X and XVI, of X into XI and of I into II, X and probably IX, the composition listed in Table I as "initially present" was calculated. This composition predicts that the stoichiometric ratios of isobutylene consumed to nitric oxide consumed to nitrogen produced to water produced should be 1.00:2.54:0.58:0.063. The observed values, 1.00:2.50:0.60:0.064, are within experimental error of these and hence provide independent support for the estimated initial composition of the product.

Discussion

Relationship to Other Nitrations.—It would appear from Table I that the products of the nitric oxide–olefin reaction are qualitatively, though not quantitatively, the same as those obtained in other olefin nitrations. Except for the hydroxylamine derivatives, all of the NO–isobutylene reaction products are representative of those obtained by treating isobutylene or other olefins with N_2O_3, N_2O_4 or nitric acid. Thus, the reaction of N_2O_4 with isobutylene in ether gave 54.9% VIII, 36.5% XIII, 2.3% XIV and 8.0% 1,3-dinitro-2-methylpropanol-2, which was stated to have resulted from the further nitration of XI.[6] In addition, the formation of X and of substances giving gaseous decomposition products during distillation was noted. The reaction of N_2O_3 with isobutylene in ether gave 24% XII, 14% XIII, 4% of the dinitro alcohol, a little VIII, and a large quantity of an unidentified oil which gave X on treatment with alkali.[6] α-Hydroxyisobutyraldoxime has not been identified in such reaction products, but the corresponding compound, 3-hydroxy-3-methyl-2-butanoxime, has been obtained from 2-methyl-2-butene,[7] and the nitrate ester of α-hydroxyisobutyraldoxime, isobutylene nitrosate, has been obtained by treating isobutylene with N_2O_4 in the absence of a solvent.[8] The latter reaction also gave VIII, XII, nitroisobutylene and a very unstable oil which produced diisobutylamine and β-hydroxyisobutylamine upon hydrogenation.

There are no prior reports of any $R_4N_2O_2$ compounds, but many preparations of materials having all of the attributes of I have been described in the literature. The addition of "nitrous fumes" or N_2O_3 to an olefin gives good yields of crystalline pseudonitrosites in only a few cases; usually, the major product is a viscous, unstable oil referred to as an "oily nitrosite" or "liquid pseudonitrosite." The fact that such oils form α-nitroölefins on standing or gentle warming has been recognized for those obtained from camphene,[9] β-pinene,[10] styrene,[11] indene,[12] 1-methylindene,[12] 1,1-diphenylethylene[13] and 1-arylcyclohexenes.[14] Since none of these oils were analyzed, none possessed the intense blue color characteristic of tertiary nitroso compounds in solution and no isolated pseudonitrosite has ever been observed to undergo a spontaneous elimination to α-nitroölefin, it seems likely that these oils were not simply different forms of the nitro-nitroso adducts but were instead $R_4N_2O_2$ compounds corresponding to the (nitro-*t*-butyl)$_4N_2O_2$ obtained from isobutylene.

The $R_4N_2O_2$ Compound.—The $R_4N_2O_2$ compound is thus of interest not only as the major primary product of the NO–isobutylene reaction but also as a possible example of an unrecognized major product in many N_2O_3– and N_2O_4–olefin reactions. The formation of such products means that mixtures of NO_2, olefin and NO can combine in the ratio 2:2:1, as well as in the known ratios 1:1:1 (giving pseudonitrosites) and 2:1:0 (giving nitrosates, nitro nitrites and dinitro compounds).

The available data do not seem to permit an unambiguous structural assignment to our $R_4N_2O_2$ compound, but a fairly good case can be made for the structure $\begin{matrix} R \\ RO \end{matrix}\!\!>\!NN\!<\!\!\begin{matrix} R \\ OR' \end{matrix}$, which we prefer. It is believed that the compound is formed by a combination of nitro-*t*-butyl radicals and NO in a 2:1 ratio. This could occur by the steps

$$C_4H_8 + NO_2 \longrightarrow \cdot C_4H_8NO_2{\equiv}R\cdot$$

$$R\cdot + NO \longrightarrow RNO$$

$$RNO + R\cdot \longrightarrow R\dot{N}OR \longrightarrow (RNOR)_2$$

Several similar processes have been described in the literature. Gingras and Waters found that 2-cyano-2-propyl radicals could combine with NO in a 3:1 ratio to give the trialkylhydroxylamine and with aromatic nitroso compounds to give aryldialkylhydroxylamines.[15] On the other hand, the triarylmethyl radicals produced by reducing triphenylmethane dyes with zinc combined with NO in a 2:1 ratio, especially in the presence of excess reducing agent, giving bis-(triarylmethyl)-hydroxylamines.[16] A 2:1 adduct of triphenylmethyl radicals and NO was obtained once by Schlenk and

(5) H. Shechter and J. W. Shepherd, THIS JOURNAL, **76**, 3617 (1954).

(6) N. Levy, C. W. Scaife and A. E. Wilder-Smith, *J. Chem. Soc.*, 52 (1948).

(7) M. I. Konovalov, *J. Russ. Phys. Chem. Soc.*, **33**, 48 (1901); H. Weghofer, *Erdöl u. Kohle*, **4**, 105 (1951).

(8) A. Michael and G. H. Carlson, *J. Org. Chem.*, **5**, 1 (1940).

(9) W. Jagelki, *Ber.*, **32**, 1499 (1899).

(10) O. Wallach and E. Isaac, *Ann.*, **346**, 243 (1906).

(11) E. A. Sommer, *Ber.*, **28**, 1328 (1895).

(12) O. Wallach and E. Beschke, *Ann.*, **336**, 1 (1904).

(13) P. Lipp, W. Lüdicke, N. Kalinkoff and A. P. Petkoff, *Ann.*, **449**, 21 (1926).

(14) T. R. Govindachari, B. R. Pai, N. Arumugam and K. Nagarajan, *Chemistry & Industry*, 757 (1954).

(15) G. de B. Gingras and W. A. Waters, *J. Chem. Soc.*, 1920 (1954).

(16) E. Weitz, L. Müller and K. Dinges, *Ber.*, **85**, 878 (1952).

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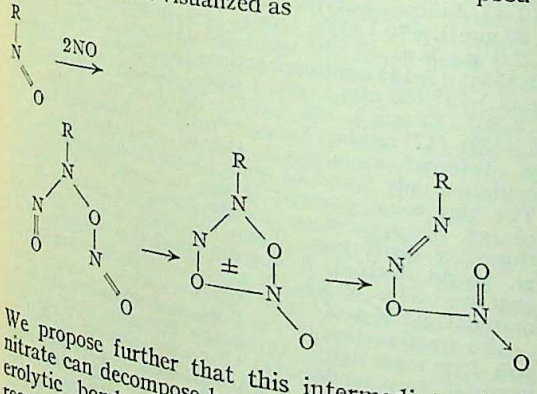
Mair.[17] The exact structure of none of these 2:1 adducts is known with certainty, but Schlenk and Mair's adduct is clearly different from the N,N(?)-bis-(triphenylmethyl)-hydroxylamine obtained from triphenylcarbinol and hydroxylamine.[18]

Mechanism.—The reaction between nitric oxide and isobutylene is remarkable in that under very mild conditions it gives a complex mixture of products, none of which bears much obvious structural relationship to the starting material, nitric oxide. In order to rationalize this fact, it seems desirable to set forth our conception of the mechanism of the reaction, even though much of the detailed evidence in its support must await the publication of our observations on other olefin nitrations. This mechanism, shown in Fig. 1, is based upon the following considerations.

First of all, the need for catalytic quantities of NO_2 in the reaction, the structures of the organic products and the similarity of those products to those obtained from N_2O_3– and N_2O_4–olefin reactions all suggest that these products must be formed *via* such species as NO_2, N_2O_3, N_2O_4, HNO_2, etc. The available information on the mechanisms of the reactions of these substances with olefins,[19] as well as our own studies of the stereochemistry of the nitric oxide–cyclohexene reaction products, indicates that products such as VIII, XII and XIII are mainly formed by free radical processes involving addition of NO_2 to the double bond, while products such as XIV and XV are formed by ionic processes involving attack of NO^+ on the double bond.

The central problem of the mechanism thus becomes that of accounting for the formation of NO_2 in the reaction medium. We have proposed[20] that this occurs *via* a diazo nitrate, as shown in Fig. 1. The formation of this diazo nitrate from the pseudonitrosite can be visualized as



We propose further that this intermediate diazo nitrate can decompose by either homolytic or heterolytic bond rupture. The homolytic process regenerates the original radical and hence accomplishes a simple disproportionation of the NO into N_2 and NO_2, which is a thermodynamically feasible reaction ($\Delta F = -59.6$ kcal.).

$$R\cdot + 3NO \longrightarrow RN_2ONO_2$$
$$RN_2ONO_2 \longrightarrow R\cdot + N_2 + NO_3\cdot$$
$$NO_3\cdot + NO \longrightarrow 2NO_2$$
$$\overline{4NO \longrightarrow N_2 + 2NO_2}$$

The heterolytic decomposition gives diazonium nitrate, thence carbonium nitrate, thence β-nitroisobutylene and nitric acid. It also accomplishes a conversion of NO to NO_2, but does so less efficiently than the homolytic route.

$$NO_2 + C_4H_8 \longrightarrow R\cdot$$
$$R\cdot + 3NO \longrightarrow RN_2ONO_2$$
$$RN_2ONO_2 \longrightarrow RN_2^+NO_3^- \longrightarrow R^+NO_3^- + N_2$$
$$R^+NO_3^- \longrightarrow C_4H_7NO_2 + HNO_3$$
$$HNO_3 + 0.5NO \longrightarrow 0.5H_2O + 1.5NO_2$$
$$\overline{C_4H_8 + 3.5NO \longrightarrow C_4H_7NO_2 + 0.5H_2O + 0.5NO_2 + N_2}$$

These proposals are based upon the known reactions of nitrosobenzene with 2NO to give benzenediazonium nitrate,[21] of certain triarylmethyl radicals with 3NO to give triarylcarbonium nitrates[16] and upon the formation of β-nitrocarbonium ion rearrangement products in some other nitric oxide–olefin reactions.[20] Similar mechanisms involving intermediate diazo nitrates have been proposed to account for other unexpected products from the reactions of NO, NOCl and N_2O_3 with organic compounds[20] and for the nitric oxide–benzaldehyde reaction.[22]

Experimental

All melting points are corrected, boiling points are uncorrected. Elementary analyses, done by Mrs. J. Northrop and Mrs. J. Martin, represent single determinations and are reliable to ±0.5%. The C.P. isobutylene and nitric oxide used were purchased from the Matheson Co. Analyses showed that the nitric oxide cylinders used contained 93.0–94.5% NO, 1.5–2.0% N_2O, 4–5% N_2 and traces of NO_2 while the isobutylene was free of non-olefinic constituents.

General Characteristics of the Reaction.—Preliminary experiments showed that the nitric oxide and isobutylene would react when the gases were mixed and held in a glass bulb at 24–35°, when the mixed gases were passed through an 18 × 1200 mm. glass tube at 30–60° or when gaseous nitric oxide was passed into liquid isobutylene under pressure. Induction periods were observed in the glass bulb runs unless the liquid products of a previous run were present; once started, the reactions proceeded with a reproducible velocity which was readily followed by the pressure drop. Starting with 200 mm. of isobutylene and 550 mm. of nitric oxide, the roughly third-order reactions had half-times of 5–11 minutes in the range 24–35°. In the 18 × 1200 mm. tube, with a 3:1 NO–isobutylene mixture flowing at 200 ml./min. at 50°, formation of liquid products occurred only in the last 200 mm. of the tube unless a few ml./min. of air were admitted along with the reactants to help catalyze the reaction. The product in each of these cases was a green oil which slowly evolved gas on standing at 0°. Attempts to fractionate these oils by distillation at 10 mm. or by chromatographing over alumina led to low-order explosions or "fume offs." The infrared spectra showed that the products from the reactions of isobutylene vapor contained oxidation products (formic acid, aldehydes and ketones) as well as nitration products (nitrate esters and nitro compounds), while the products from liquid isobutylene contained only nitration products. Effort was therefore concentrated on the latter reaction.

Liquid Phase Reaction.—The apparatus used was designed and operated by R. L. Myers and C. S. Herrick. It consisted of a one-liter stainless steel autoclave equipped

(17) W. Schlenk and L. Mair, *Ber.*, **44**, 1169 (1911).
(18) A. Mothwurf, *ibid.*, **37**, 3150 (1904).
(19) A. I. Titov, *Zhur. Obshchei Khim.*, **16**, 1896 (1946); A. N. Baryshnikova and A. I. Titov, *Doklady Akad. Nauk S.S.S.S R.*, **91**, 1059 (1953); H. Shechter and F. Conrad, THIS JOURNAL, **75**, 5610 (1953); J. C. D. Brand and I. D. R. Stevens, *Chemistry & Industry*, 469 (1956).
(20) J. F. Brown, Jr., Abstracts of Papers, 126th Meeting American Chemical Society, September 12–17, 1954, p. 43-O.

(21) E. Bamberger, *Ber.*, **30**, 506 (1897); F. H. Westheimer, E. Segel and R. Schramm, THIS JOURNAL, **69**, 776 (1947).
(22) L. F. Kuhn, Abstracts of Papers, 130th Meeting American Chemical Society, September 16–21, 1956, p. 16-O.

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with a stirrer, cooling coil, gas inlet tube, reflux condenser, pressure regulating valve set to hold the internal pressure at 150 p.s.i. and tanks for collecting and measuring the reactant and product gases. In operation, the system was flushed with nitrogen, a weighed quantity of isobutylene admitted to the autoclave and nitric oxide passed in at a rate of 4.8 moles/hr. The product gases passed through the Dry Ice cooled reflux condenser and pressure regulating valve into accumulator tanks. At the end of the run, the apparatus was flushed with a known quantity of nitrogen and the total gaseous product analyzed; except for small quantities of unreacted nitric oxide, nitrous oxide and isobutylene, nitrogen was the sole gaseous product. Next, the autoclave was cooled to −50°, most of the liquid product poured out and the remainder rinsed out with acetone. The liquid product was allowed to come to room temperature, and then finally degassed *in vacuo* by pumping through a −78° trap; the resulting weight loss was taken to represent unreacted isobutylene. In this way, 281 g. (5.01 moles) of isobutylene was treated with 217 g. (7.23 moles) of nitric oxide at 28° to give 121 g. (2.16 moles) of unreacted isobutylene, 3.0 g. (0.10 mole) of unreacted nitric oxide, 48.1 g. (1.72 moles) of nitrogen and 325.7 g. of deep blue-green liquid reaction product, which consisted of a 295.9 g. main portion and 29.8 g. recovered from the acetone rinsings. Thus, the reaction could be estimated to have been proceeding under an NO partial pressure of 0.4 atm. and to have consumed 160 g. (2.85 moles, 57% conversion) of isobutylene and 214 g. (7.13 moles, 99% conversion) of nitric oxide.

Distillation.—The conversion of the crude product to distillates suitable for fractionation was carried out only on the main portion of the crude liquid reaction product. This was passed twice through a falling film still[23] maintained at 60° under 5 mm. pressure and the volatiles collected in −78° traps. The two portions of the distillate, 63.5 and 36.7 g., n^{20}D 1.4450 and 1.4516 on oil phases, both separated aqueous layers on warming to 0° (3.0 ml., n^{20}D 1.3425, and 0.1 ml., respectively). The aqueous layers were combined, saturated with sodium sulfate, and the 0.1 ml. of oil which separated combined with the other oils to give a total first distillate, which was a blue oil, 97.2 g., n^{20}D 1.4475. The residue was a viscous green liquid, 195.7 g., n^{20}D 1.4850. It became somewhat more mobile after standing nine days at 5° and was then passed through the still at 100° under 1 mm. pressure to give a second distillate (blue-green oil, 116.7 g., n^{20}D 1.4624) and a viscous brown residue (79.0 g., n^{20}D 1.4838). The latter was extracted with two 350-ml. portions of water, and the aqueous extracts saturated with salt and extracted with ether. This gave 8.2 g. of recovered water-soluble liquid, 12.1 g. of unrecovered water-soluble products and 58.7 g. of water-insoluble residue. An attempt to crystallize the latter from an ether–hexane solution at −78° was unsuccessful, and 5.9 g. of the material was accidentally lost during the solvent removal. The remaining 52.8 g. was distilled in two portions from an oil-bath; gas evolution was noted, but no explosion occurred. This gave a third distillate (43.9 g., n^{20}D 1.4638, 1.4650 and 1.4492 on successive thirds), a residual tar (5.5 g., b.p. >100° (1 mm.)) and a 3.4-g. loss, presumably due mostly to the gaseous products evolved. In all of these operations, all apparatus used was rinsed with ether after use in order to minimize handling losses.

Fractionation Procedure.—In fractionating the first three mixtures obtained from the crude product, effort was made to separate the less stable higher boiling products first, meanwhile accumulating the stabler lower boiling materials (indicated by *) for a single fractional distillation later.

The recovered water-soluble products were distilled to give (a), 5 ml., b.p. <85° (2.5 mm.); (b), 2.7 g., b.p. 85–96° (2.5 mm.); and 0.5-g. residue. Redistillation of (b) in a small molecular still gave (c) 0.6 g., trap condensate; (d) 1.9 g., partially solid; and 0.2 g. of residue. Crystallization of (d) from cold ether gave 0.7 g. of II and mother liquors (d′), n^{20}D 1.4698.

The first distillate from the falling film still was allowed to stand five days at 0° and then 3.8 g. of crystalline XII removed. Distillation of the mother liquors from a flask held at 35–40° gave distillate (e)*, 49.2 g., very pale blue, n^{20}D 1.443; and a deep blue residue, 44.2 g., n^{20}D 1.4591, which deposited 2.2 g. more XII on standing. Another distillation under the same conditions gave (f)*, 27.5 g., n^{20}D 1.462, and another deep blue residue which deposited 0.7 g. XII on standing. The residual liquid was combined with fraction (a) and the second falling film still distillate and carefully distilled, giving (g)*, 4.5 ml. trap condensate; (h)*, 77.0 g., b.p. 35–40° (4 mm.), n^{20}D 1.4651; (i) 11.0 g., deep blue, b.p. 40 (4 mm.)–40° (1.5 mm.) n^{20}D 1.4567; and (j) 47 ml., pale blue residue, n^{20}D 1.4571. On standing at 5°, (i) deposited 0.3 g. of XII, leaving liquid (i′).

The fraction (j) at this point presumably consisted mainly of II and XIII; a small sample which was not distilled immediately was examined after two weeks storage at 0° and found to be mostly extractable with water. Infrared examination of the water-insoluble portion, (j′) indicated the presence of III, IX, and XIV; VIII could not be detected. The distillation of (j) was commenced under 2 mm. pressure, using a 110° oil-bath. At first, distillation proceeded normally, giving a light blue distillate (b.p. 55° (2 mm.), probably XIII). Then the contents of the pot turned a deep blue-green and a vigorous evolution of gases commenced. The heating bath was removed, but the evolution of gases (estimated at 10 g. from weight loss) continued for several minutes, the pressure remained at 30–60 mm. despite continued pumping, and about 10 ml. of deep blue liquid distilled into the receiver. At the completion of this gas evolution, normal distillation was continued, giving fractions (k)*, 4.5 ml., trap condensate; (l), 17 ml., b.p. 55–75° (2 mm.), but including the deep blue liquid which distilled during the gas evolution; (m), 1.5 g., b.p. 65–85° (1 mm.), n^{20}D 1.4511; (n), 3.0 g., b.p. *ca.* 85° (1 mm.), n^{20}D 1.4532; and a clear brown residue, 9.5 g., n^{20}D 1.4865. On standing at 5°, (*l*) deposited 2.0 g. XII, m.p. 81–82°, leaving mother liquors (l′), n^{20}D 1.4464. A solution of (n) in ether deposited 1.5 g. of VIII on cooling to −78°, leaving liquid (n′).

The fractions (i′) and (l′) were combined and redistilled, giving (o)*, 1.0 ml., in trap; (p)*, 8 ml., b.p. 40–50° (4 mm.), n^{20}D 1.4594; (q)*, 7.5 ml., b.p. 50–61° (4 mm.), deep blue, n^{20}D 1.4483; (r) 9.0 g., b.p. 61 (4 mm.)–50° (1 mm.) almost colorless, n^{20}D 1.4438; and 0.5 g. of yellow-brown residue. Fraction (r) largely solidified to crystalline XIII after long standing at 5°.

All of the fractions marked * were combined to give a single lot, 173.0 g., n^{20}D 1.4557, which was distilled through a six-plate column by Mr. E. M. Hadsell. This gave seventeen fractions: (1) trap condensate, 2.0 g., n^{20}D 1.4127; after removing 0.5 g. water by drying over sodium sulfate; (2) forerun, 1.3 g., b.p. 44.5–47.5° (20 mm.), n^{20}D 1.4243; (3–4) β-nitroisobutylene (XI), 37.6 g., b.p. 47.5–50.0° (20 mm.), n^{20}D 1.4326–1.4342; (5–6) intermediate fractions, 22.0 g., b.p. 49 (19 mm.)–55° (11 mm.), n^{20}D 1.4370–1.4556; (7–14) α-nitroisobutylene (X), 89.8 g., b.p. 55 (11 mm.)–73° (23 mm.), n^{20}D 1.4695–1.4702; (15) 5.3 g., b.p. 73–86° (23 mm.), n^{20}D 1.4647; (16) hold-up; 5.0 g., n^{20}D 1.4472; (17) residue, 7.0 g., n^{20}D 1.4501; handling loss, 3.0 g. Infrared examination showed that fractions 3–17 contained only X and XI, while 16 and 17 were largely XIII. The blue color, presumably due to traces of XII in the charge, disappeared completely during the course of the three-day distillation. From the plots of b.p. and n_D *vs.* weight distilled, it was concluded that fractions 1–17 contained 53 g. of XI, 101 g. of X, 2.0 g. of lower boiling material and 14 g. of higher boiling material.

The fractionation of the third crude distillate (43.9 g.) was done separately. Distillation through a short column gave (s), trap condensate, 3.2 g., two phases; (t) 3.8 g., b.p. 51–60° (19 mm.), n^{20}D 1.4514; (u), 8.4 g., b.p. 60–62° (19 mm.), n^{20}D 1.4590; (v), 8.2 g., b.p. 61.5° (18 mm.), n^{20}D 1.4615; (w), 7.9 g., b.p. 61.5–65° (18 mm.), n^{20}D 1.4614; and residue (x). Fractions (u), (v) and (w) consisted essentially entirely of X and XI. The constancy of their ratio through three successive fractions and the drop in refractive index during the fractionation were interpreted to mean that the known[6] base-catalyzed interconversion of X and XI was effecting a transformation of X to the more volatile XI during the distillation. Fraction (s) smelled distinctly of hydroxylamine, and its vapor gave a weakly alkaline reaction to test paper. It was neutralized with a little sulfuric acid and saturated with sodium sulfate to remove the water, giving (s′), 2.0 g., n^{20}D 1.3887. On cooling to −78°, a little VI, m.p. and mixed m.p. 59–61°, separated from fractions (t) and (u).

The distillation of (x) gave (y), trap condensate, 1.4 g., (z), 3.5 g., b.p. 50–65° (5 mm.), n^{20}D 1.4532; (aa), 3.5 g.

(23) N. Levy and C. W. Scaife, *J. Chem. Soc.*, 1094 (1946).

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b.p. 65–70° (5 mm.), $n^{20}D$ 1.4489; (bb), 3.5 g., b.p. 70 (5 mm.)–120° (1 mm.), $n^{20}D$ 1.4688; and 0.2 g. of residue. Drying (y) over sodium sulfate gave (y'), 1.0 g., $n^{20}D$ 1.4400. After removing analytical samples, fractions (z) and (aa) were first extracted with 6-ml. portions of water until no further volume change was notable, then shaken with sodium bisulfite solution to remove X and finally dried over sodium sulfate. The proportions of water-soluble, bisulfite-soluble and insoluble materials in (z) and (aa) were 34, 33 and 33%; and 27, 6 and 67%, respectively. About 60% of the water-soluble material was recovered by saturating the solutions with salt and extracting with ether, giving (cc), 1.2 g., $n^{20}D$ 1.4445, which was found to be >95% XIII. The combined insoluble oils, 2.9 g., were distilled through a Holzman column giving (dd), 0.18 g., b.p. 74.5–76° (5 mm.), $n^{20}D$ 1.4532; (ee), pure VII, 1.40 g., b.p. 77° (5 mm.), $n^{20}D$ 1.4460; (ff), 0.84 g., b.p. 77° (5 mm.), $n^{20}D$ 1.4465; and residue, 0.3 g. Finally, fraction (bb) was observed to have deposited some crystals after standing a month at 0°. These were extracted with aqueous sulfuric acid, the extracts made alkaline and extracted with ether to recover 0.4 g. of II, which was considerably less than the content indicated by the infrared spectrum to have been present originally. The acid-insoluble portion was distilled in a small molecular still to give (gg), 2.1 g.; this rapidly deposited crystals of III, 1.0 g., leaving (gg'), 1.0 g., yellowish oil, $n^{20}D$ 1.4655.

The net result of this fractionation was the isolation of all of the stable reaction products listed in Table I except for IV, V, XIV, and XV; and the separation of the crude reaction product into 50 organic fractions which represented either individual compounds or simple mixtures of substances having similar volatilities.

Analytical Procedures.—In general, qualitative analyses of the separate product fractions were based upon infrared spectra and the isolation of constituents, while the quantitative analyses were based upon the infrared spectra and other physical properties of the fractions.

First of all, the infrared spectra of authentic specimens of all of the stable product components were determined. The major features of most of these spectra have already been reported and discussed.[24] Next, qualitative analyses of the product fractions were made by comparing their spectra with those of the authentic materials. It was possible to identify all of the bands of the product spectra with bands of the appropriate intensity in the standards; thus the presence of appreciable amounts of stable products other than those listed in Table I could be eliminated.

In making quantitative estimates from the infrared spectra, use was made of the "internal standard" technique in most cases. This took advantage of the fact that most of the products were nitro-*t*-butyl derivatives and hence gave primary nitro NO_2 asymmetrical stretching bands near 6.42 μ which had molar extinction coefficients (in $CHCl_3$) near 550. Thus, the ratio of the intensity of any given band in the sample to that of the 6.42 μ band, divided by the corresponding ratio in the standard, gave the ratio of that constituent to the total primary nitro content of the sample. The relative content of α-nitroisobutylene (X), which was present to a greater or lesser extent in most of the samples analyzed, was estimated from the intensities of its 6.58 and 7.37 μ bands relative to the 6.42 μ band, adjusted for the lower extinction coefficients (380 and 280, respectively) of these bands. This method was checked where possible by a comparison of the refractive index of the sample with those of the components. The estimated compositions of fractions (z) and (aa) were checked by selective extraction, as already noted, and that of (d') was checked by an elementary analysis.

It was thus determined that the compositions of the various fractionated product mixtures were as follows: Fraction c, 0.6 g.: 0.1 X, 0.5 XIII. Fraction d', 1.2 g.: 0.7 II, 0.5 XV. Fraction m, 1.5 g.: 0.5 VIII, 0.2 X, 0.3 XIII, 0.5 XIV. Fraction n', 1.5 g.: 0.8 VIII, 0.2 XIII, 0.5 XIV. Fraction r, 9.0 g.: 0.7 VII, 7.0 XIII, 1.3 XIV. Low boilers from fractions 1–17, other than water, 1.5 g.: 0.6 IV, 0.6 V, 0.1 VI, 0.1 X, 0.1 XI. High boilers from fractions 1–17, 14 g.: 13.0 XIII, 1.0 XVI. Fraction s', 2.0 g.: 1.6 IV, 0.2 V, 0.1 X, 0.1 XI. Fraction t, 3.8 g., 0.3 IV, 0.3 V, 0.2 VI (by isolation), 2.2 X, 0.8 XI. Fractions u, v, w, 24.5 g.: 18.4 X, 6.1 XI. Fraction y', 1.0 g.: 0.3 IV, 0.5 X, 0.2 XI. Fraction z, 3.5 g.: 1.2 VII, 1.2 X, 1.1 XIII. Fraction aa, 3.5 g.: 2.4 VII, 0.2 X, 0.9 XIII. Fraction bb, 3.5 g.; 1.4 II, 1.2 III, 0.6 VII, 0.3 XVI.

The aggregate weights of the constituents of these mixtures, along with those of X and XI in fractions 1–17, of the II, VIII and XII separated in crystalline form during the fractionation, and of the residues and water obtained are listed in Table II as weights of compounds present "In Fractions."

Treatment of Losses.—The total weight of the water and the 45 liquid and solid organic fractions obtained up through fraction bb was 257.8 g. The remainder of the 295.9 g. of crude product taken for fractionation was accounted for by three types of losses. These were unrecovered water-soluble materials lost in the first extraction, 12.1 g.; gases evolved during degradative distillations, 13.4 g.; and mechanical losses due to handling, spillage, sampling, evaporation, etc., 12.6 g.

In order to obtain some understanding of the nature of the unrecovered water-soluble materials, known quantities of the water-soluble products II, XIII and XV were separately run through the water extraction and recovery procedure used. Each was recovered in about 65% yield, which was in line with a previous report of high losses during the extraction of isobutylene nitration products with water.[6] Since 8.2 g. of these products were recovered, this suggests that another 4.4 g. of the same materials were lost in the extraction. This 4.4 g. was assumed to represent 3.0 g. of XIII, 0.7 g. of II, 0.3 g. of XV and 0.4 g. of XVI, on the basis of the contents of these substances in the recovered water-soluble product after fractionation.

TABLE II

PRODUCTS OBTAINED BY FRACTIONATING 295.9 G. OF CRUDE REACTION PRODUCT

Compound	In fractions, g.	Corrected weight, g.	Mole C_4-units
II	2.8	3.6	0.0268
III	1.2	1.3	.0110
IV	2.8	2.9	(.0475)[c]
V	1.1	1.2	.0207
VI	0.3	0.3	.0041
VII	4.9	5.1	.0585
VIII	2.8	2.9	.0196
X	124.0	130.1	1.2869
XI	60.3	63.3	0.6261
XII	9.0	9.4	.0710
XIII	23.0	27.1	.2275
XIV	2.3	2.4	.0146
XV	0.5	0.8	.0078
XVI	17.7	19.0	.1880[d]
Inorg.[a]	5.1	25.0[b]	....
C_4H_8	...	1.5	.0274
	257.8	295.9	2.59
Losses			
H_2O sol.	12.1		
Gases	13.4		
Mechan.	12.6		
	295.9		

[a] Inorganic products: H_2O, NH_2OH, N_2, NO, etc. [b] Includes 5.4 g. corrected weight of recovered water, 7.7 g. H_2O water-soluble materials not otherwise accounted for and 11.9 g. of gases not accounted for as isobutylene. [c] In totaling the C_4-units, the C_3-units in V, VI and VII were counted as C_4, while the C_1 of IV, obtained in nearly equivalent amount, was not counted. [d] Assumed to have average composition of a nitroisobutylene polymer.

An attempt was made to divide up the 12.6 g. of mechanical losses on the basis of the estimated compositions of the various intermediate fractions on which they were incurred. This indicated that the losses were rather uniformly distributed among the product constituents and hence that the most satisfactory procedure would be to assume that these

(24) J. F. Brown, Jr., THIS JOURNAL, 77, 6341 (1955).

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losses were proportional to the quantities of constituents found present in the 257.8 g. of recovered product fractions. By adding these distributions of the 12.6 g. of mechanical losses and the 4.4 g. of unrecovered water-soluble products to the quantities of constituents present in the recovered fractions, the corrected yield figures shown in the third and fourth columns of Table II were determined.

It was noted that these corrected yields of organic products accounted for 2.56 moles of isobutylene. Since the 295.9 g. of product fractionated had originally come from 2.59 moles of isobutylene (*i.e.*, 2.85 × 295.9/325.7) this left 0.03 mole unaccounted for. This was assumed to represent regenerated isobutylene, lost during the fractionation along with the other gaseous products. However, this yield figure for regenerated isobutylene must be taken only as an order of magnitude, since it represents a small difference between large quantities. The percentage yields listed in the last column of Table I are calculated directly from the molar yields in Table II.

(Nitro-*t*-butyl)$_4$N$_2$O$_2$ (I).—The 29.8-g. portion of the crude reaction product which was not fractionated was kept at 0° for 4 weeks and 0.6 g. of crystalline XII removed. A 14.7-g. portion of the remaining liquid was extracted with four 100-ml. portions of cold water to remove II, XIII and XV, once with a disodium phosphate solution and twice more with water. The remaining oil was devolatilized by very brief stirring at 50° under 0.5 mm. pressure to give 4.0 g. of a concentrate of I. This was a viscous, yellow-brown oil, n^{20}D 1.4911, which was insoluble in solutions of sodium bisulfite or dilute acids. It was stored at −78° between analyses, the sequence of which was infrared spectrum, ultraviolet spectrum, elementary analyses and molecular weight; during this sequence sufficient decomposition occurred to lower the n^{20}D to 1.4904.

The usual infrared analysis indicated that the sample contained about 13% X, 12% III, 2% XIV, 2% of a hydroxylic impurity, later identified as XIII, and possibly a little IX. The remaining 65–70% of the sample, namely, I, gave an infrared spectrum which was very similar to those of the other nitro-*t*-butyl derivatives. It showed the strong bands of a primary nitro compound at 6.43, 7.00 and 7.27 μ, but no bands indicative of OH, NH, olefinic CH, C=C, C=N or C=O groups, nor were there any ultraviolet absorption bands above 230 μ. Prominent characterizing infrared bands lay at 7.95, 8.25, 8.70, 10.97 and 13.55 μ. In chloroform solution, the intensities of the 6.43 and 6.58 μ bands ($E^{1\%}_{1cm.}$) were 40 and 4.9, respectively; on the basis of the previously indicated molar extinction coefficients, this indicated that for each C$_4$-residue in the sample there were 0.85 primary nitro group and 0.15 conjugated nitro group, or a total of 1.00 nitro group per C$_4$-residue. Since each of the identified contaminants contained one nitro group per C$_4$-residue, it follows that Compound I must also have contained one nitro group per C$_4$-residue.

The analysis (found: C, 41.3; H, 6.5; N, 17.7; mol. wt., benzene cryoscopic, 232) corresponded almost exactly with the formula C$_8$H$_{15}$N$_3$O$_5$ for the over-all mixture. Fortuitously, this turned out to be very close to the aggregate elementary composition of the identified contaminants, so that the calculated elementary composition of I would be little affected by small errors in the estimates of the impurity content. At any rate, by allowing for the known contaminants and for the uncertainties resulting from decomposition during analysis and the standard error in the analyses, it was concluded that the analyses fixed the composition of the I contained in the sample within the limits (C$_8$H$_{15-16}$N$_3$O$_5$)$_{1-2}$.

Assuming that I is not a free radical, the three permissible formulas within these limits are C$_8$H$_{15}$N$_3$O$_5$, (C$_8$H$_{15}$N$_3$O$_5$)$_2$ and (C$_8$H$_{16}$N$_3$O$_5$)$_2$. The last formula was supported by three other facts. First, the compound was known to contain 1.0 primary nitro group per C$_4$-residue and to give entirely α-nitroisobutylene and nitro-*t*-butyl derivatives on decomposition. This indicated that all of the C$_4$-residues were present as nitro-*t*-butyl (C$_4$H$_8$NO$_2$) groups. Second, the high index and viscosity of the compound, despite the absence of conjugated structures or hydrogen bonding groups such as OH or NH, supported the formulas of higher molecular weight. Third, as already noted, the over-all stoichiometry of the reaction was in support of the conclusion that the major initial product was (C$_8$H$_{16}$N$_3$O$_5$)$_2$.

The I had a half-life of about three weeks at 0° and a similar stability in dilute chloroform solution at room temperature. Successive infrared spectra on the solution showed the 6.43 μ band of the I decreasing and the 6.58 μ (and other) bands of the X increasing steadily. Complete decomposition resulted when an attempt was made to distil 2.0 g. of the concentrate in a molecular still under a high vacuum at 50°. Infrared analyses indicated that the products had the following compositions: trap condensate (1.2 g., n^{20}D 1.4673), 1.1 g. of X, 0.1 g. of XI and XIII; liquid distillate (0.4 g.), 0.3 g. of II, 0.05 g. of X, 0.05 g. of XIV; residue, 0.3 g. The decomposition of the 1.3–1.4 g. of I contained in the sample thus gave 0.3 g. of II and 0.9 g. of X, in addition to that already present. The residue gave a little more X on further heating.

To confirm the identification of II in the liquid distillate, the portion remaining after analysis was divided into two 0.1–0.2-g. portions. Both were noted to become partly crystalline on standing a week at 0°. The solid from one was removed and recrystallized twice from chloroform–hexane to give 0.035 g. of II, m.p. and mixed m.p. 56.5–58°. The other was left at 0° for 6 months and then filtered. The solid, 0.11 g., was recrystallized from methanol and found to be III, m.p. 60–61.5°, mixed m.p. with II, 41–51°. The liquid contained VII; however, neither III nor VII could be detected in the original liquid distillate.

N-(Nitro-*t*-butyl)-hydroxylamine (II).—Recrystallization of the crude product from fractions (d) and (bb) from ether or methanol gave white crystals, m.p. and mixed m.p. 57–58°. The infrared spectrum showed the expected bands of primary nitro and hydroxylamino groups.[24]

Anal. Calcd. for C$_4$H$_{10}$N$_2$O$_3$: C, 35.8; H, 7.5; N, 20.9. Found: C, 35.9; H, 7.7; N, 21.1.

The compound was synthesized independently by shaking 2.0 g. of X with a solution of 2.0 g. of hydroxylamine hydrochloride and 0.8 g. of sodium hydroxide in 5 ml. of water for a few minutes. The odor of the X disappeared, and on cooling II crystallized out. Extraction of the mother liquors with ether and crystallization of the crude product from the extract at −78° gave 1.8 g. of crude II, m. 46–57°. After two recrystallization from methanol, 1.6 g. (60%) of pure II, m.p. 57–58.5°, was obtained.

The formulation of II as an N- rather than an O-alkyl hydroxylamine was based upon the infrared spectrum, which showed no NH$_2$ deformation band and upon its oxidation to the nitroso compound XII. One gram of II was dissolved in a solution of 2 ml. of concentrated sulfuric acid in 10 ml. of water at 0°, and a solution of 2 g. of sodium dichromate was added dropwise with stirring until the yellow color persisted. The mixture was allowed to stand an hour at 0° to permit the deep blue oil to dimerize and solidify. The crude solid, m. 74–78°, weighed 0.8 g. Recrystallization from carbon tetrachloride gave 0.7 g. (71%) of XII, m.p. 82.5–83.5°. The oxidation could also be effected by N$_2$O$_4$. When this was added to a solution of II in chloroform at 0°, the deep blue color of the nitroso compound XII appeared instantly. As more N$_2$O$_4$ was added, however, this pseudonitrosite was oxidized to the dinitro compound[25] and the color disappeared.

The pyrolysis of II was examined by a procedure which we have employed with a variety of unstable olefin nitration products. This consisted of heating 0.1–0.3 g. of the compound in a small test-tube whose bottom was in an oil-bath and whose sides were at room temperature. It was found that working with larger quantities frequently led to uncontrollable decomposition reactions. When 0.276 g. of II was thus heated an hour at 120°, there was a 15% weight loss, apparently due to the volatilization of IV and VI. The residual 0.234 g. of colorless liquid largely crystallized on cooling to give VI, m.p. and mixed m.p. 59–61°. This dealdolization of II to IV and VI appeared to be irreversible; when a mixture of IV, VI and piperidine was allowed to stand several days at room temperature, removal of the volatile reactants *in vacuo* left only a trace of residue, and this was completely unaffected by chromic acid.

The pyrolytic experiment was repeated using 0.148 g. of II, but this time several small (0.5–1.0-mg.) portions of fuming nitric acid were added as an NO$_2$ source. After each addition, a blue-green color appeared, and a steady evolution of gas began and continued for several minutes before subsiding. After an hour, further additions of the acid provoked no additional gas evolution; 3 mg. had been added in all. The tube then contained 0.047 of a brown oil;

[24] A. Hantzsch and O. W. Carlson, *J. Org. Chem.*, **4**, 169 (1939).

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i.e., 70% of the II had been converted to vapors and lost. The residual oil could not be crystallized from solution in a little methanol at −78°, even after seeding with VIII and II. Other strong acids produced no visible effects when added to hot II.

O,N-Bis-(nitro-*t*-butyl)-hydroxylamine (III).—The crude product from fraction (gg) was recrystallized from methanol to give large monoclinic tablets, m.p. 61–62.5°. The compound was insoluble in dilute acids, and the infrared spectrum indicated that the NH group was not hydrogen bonded (very sharp band of medium intensity at 3.07 μ). Otherwise, the infrared spectrum was quite similar to that of II.[14]

Anal. Calcd. for $C_8H_{17}N_3O_5$: C, 40.8; H, 7.2; N, 17.9. Found: C, 41.4, 40.4; H, 7.0, 6.9; N, 17.9.

The compound was synthesized independently by allowing a mixture of 0.37 g. of II, 2.0 g. of X and 0.01 ml. of triethylamine to stand overnight at room temperature. The amine and unreacted II were then extracted with dilute acid and the excess X evaporated *in vacuo*. Crystallization of the residue from methanol gave a 23% yield of III, m.p. and mixed m.p. 61–62°.

When 0.5 g. of III was heated in a bath at 180° for a few minutes (no discoloration), 0.2 ml. of distillate b. 103–130°, was obtained. This deposited some crystalline VI on cooling and left a liquid indicated by its infrared spectrum to be largely IV. The spectrum of the distillation residue indicated that it contained roughly equal amounts of VII and X.

Low Boiling Products.—Nitromethane (IV), acetone (V) and acetoxime (VI) were identified in the various cold trap condensates and fore-runs from their infrared spectra. Commercial samples were used for the infrared reference spectra and mixed m.p. determinations.

O-(Nitro-*t*-butyl)-acetoxime (VII).—The pure specimen obtained as fraction (ee) (b.p. 77° (5 mm.), $n^{20}D$ 1.4460) was a colorless liquid having a pleasant, somewhat camphoraceous odor, which showed the characteristic infrared bands of primary nitro and oxime ether groups.[24] The same material was synthesized independently by allowing a mixture of 3.65 g. (0.05 mole) of VI, 5.05 g. (0.05 mole) of X and 10 drops of triethylamine stand for three days at room temperature. The resulting mixture was extracted with dilute sulfuric acid and with strong sodium bisulfite solution, washed, dried and distilled to give 6.3 g. (72%) of VII, b.p. 77° (5 mm.), $n^{20}D$ 1.4460.

Anal. Calcd. for $C_7H_{14}N_2O_3$: C, 48.2; H, 8.1; N, 16.1. Found: C, 48.5, 49.0; H, 7.7, 8.1; N, 15.9.

1,2-Dinitroisobutane (VIII).—The solid obtained from fraction (n) was recrystallized from ether at −78° to give soft, waxy crystals, m.p. 53°, reported[6] m.p. 52–53°. The infrared spectrum[24] showed all the bands expected for this structure.

Unidentified Products.—Fraction (j′) showed a strong infrared band at 10.10 μ which was not present in the spectra of any of the redistilled product fractions or identified products. This band was presumed to indicate the presence of an unidentified unstable product component IX, which was probably another nitro-*t*-butyl derivative.

The portion of the crude reaction product which was allowed to stand four weeks at 0° contained some substance, possibly a nitrolic acid, which could be extracted with water or weakly alkaline buffers to give yellow or orange solutions. These solutions were reversibly decolorized by acidification with strong acids. The same behavior was shown by fractions (d′) and (s) (weak test), by specimens of X which had stood in glass bottles for several months (but not by fresh X) and by the crude products of the isobutylene vapor–nitric oxide and the isobutylene–N_2O_4 reactions (strong tests).

α-Nitroisobutylene (1-Nitro-2-methyl-1-propene, X).—The best specimen obtained, fraction 10, was a pale yellow oil, b.p. 64° (18 mm.), $n^{20}D$ 1.4702; reported[5] b.p. 72° (25 mm.), $n^{20}D$ 1.4710.

β-Nitroisobutylene (3-Nitro-2-methyl-1-propene, XI).—The best specimen obtained, fraction 3, was a colorless oil, b.p. 47.5–48.5° (20 mm.), $n^{20}D$ 1.4326; reported[5] b.p. 56° (25 mm.), $n^{20}D$ 1.4330.

Isobutylene Pseudonitrosite, Bis-(1-nitro-2-nitroso-2-methylpropane) (XII).—The five portions of XII recovered from the crude distillates (m.p. 81–82°) were recrystallized once from ether–acetone to give pure XII as large, orthorhombic tablets, m.p. 85–86°, to a deep blue liquid; reported, m.p. 80–82°,[8] 81°,[6] 87–88°.[26] When dissolved in solvents at room temperature, the solutions were initially colorless, but turned deep blue within a minute or two.

The pyrolysis of XII was conducted as described for II. When 0.200 g. was held at 120°, there was a gradual evolution of gas and fading of the blue color. After 25 minutes, 0.153 g. of light yellow liquid, $n^{20}D$ 1.4548, remained. The composition estimated from the infrared spectrum was 70% VIII, 20% X and 10% uncertain. Crystallization of a solution of this pyrolysate in methanol at −78° gave 0.080 g. of VIII, m.p. 47–50°. Other runs showed that the composition of the pyrolysate was very little affected by 10° variations in the temperature, by carrying out the pyrolysis under nitrogen or by operating in an evacuated sealed ampoule. In the last case, a mass spectrometric analysis (by F. J. Norton) on the gaseous product showed that it was mainly isobutylene and nitrogen, with lesser quantities of nitric oxide and traces of nitromethane, acetone, etc.

In looking for other possible transformations of XII under the conditions of the product fractionation, a novel reaction with nitric acid was discovered. When 0.2 g. of XII was dissolved in 3 ml. of cold absolute nitric acid, a reddish-brown solution was formed, which soon changed to light yellow. Dilution and washing with water gave an oil which distilled completely to give pure XIV (by infrared), $n^{20}D$ 1.4500. However, this reaction was markedly inhibited by traces of water and did not occur at all with 70% nitric acid, so that it probably could not have occurred during the product fractionation.

Nitro-*t*-butanol (XIII).—This was obtained in >80% purity in fractions (c), (r), 16, 17 and (cc). The sample used for the infrared standard (b.p. 55° (2 mm.), m.p. 24°, $n^{20}D$ 1.4435) was prepared by the condensation of nitromethane with acetone.[27]

Nitro-*t*-butyl Nitrate (XIV).—The isolation of this compound was not undertaken since the infrared identification (in fractions (m), (n′) and (r)) was particularly unambiguous. The strong bands of nitrate esters[24] are detected readily even in dilute solutions, and in XIV there also occurs a rare type of splitting of the nitrate NO_2 symmetrical stretching band into a pair of bands at 7.70 and 7.91 μ. The sample used for the infrared standard was prepared by nitrating 1.00 g. of XIII with 4 ml. of absolute nitric acid in 17 ml. of chloroform for 15 minutes at 0°. Extraction with water, solvent removal, further repeated extractions with water and distillation in a small molecular still gave 0.39 g. of XIV, $n^{20}D$ 1.4500, which solidified completely upon storage in a 5° refrigerator; reported[6] $n^{20}D$ 1.449, m.p. 6°.

α-Hydroxyisobutyraldoxime (XV).—This was detected only in fraction (d′), which was estimated from the infrared spectrum to be a roughly 2:1 mixture of II and XV. However, since the "internal standard" method was not applicable to such a mixture, an elementary analysis was made, which indicated that the actual proportions were about 62 and 38%.

Anal. Calcd. for 38% $C_4H_9NO_2$ + 62% $C_4H_9N_2O_3$: C, 40.1; H, 7.5; N, 18.2. Found: C, 40.1; H, 6.7; N, 17.8, 18.2, 18.4.

The specimen used for the infrared standard ($n^{20}D$ 1.4847) was prepared by the alkaline hydrolysis of the corresponding nitrate ester.[28]

Calculation of Initial Product Composition.—In calculating the initial product composition from that of the fractionated products, the major assumption made was that all of the products II through X, along with a little XII, the regenerated isobutylene, and XVI came from I, mostly *via* II, by the paths already indicated in the Results section. This assumption is based upon the observed behavior of compounds I, II, III and XII under conditions like those used in fractionating the product mixture and upon a number of observations made during the fractionation. Two of these seem particularly significant to the assumption in point. First, even though some decomposition of I must have occurred during the falling film distillation at 60°, the first crude distillate contained less than a third of the

(26) C. C. Price and C. A. Sears, THIS JOURNAL, **75**, 3275 (1953).
(27) A. Lambert and A. Lowe, *J. Chem. Soc.*, 1517 (1948).
(28) V. Meyer and C. Askenasy, *J. Russ. Phys. Chem. Soc.*, **33**, 496 (1901).

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X ultimately obtained. This is shown by its refractive index and the indices of the mixed nitroisobutylene fractions (e and f) obtained from it. Second, even though all of the intermediate fractions gave high boiling residues upon redistillation, the original distillations of the 295.9 g. of crude product converted all but 5.5 g. to materials b. <100° (1 mm.). This indicates that there was very little or no formation of stable telomeric or condensed products in the original reaction.

The one point left in doubt concerns the origin of the acetone (V) which could have come either from the dealdolization of XIII or the dealdolization of II, followed by reaction of the resulting acetoxime with water and/or nitrous acid. We have arbitrarily selected the latter route in our calculation because of the greater instability of II.

Thus, the initial contents of XIII, XIV and XV were assumed to be the same as the corrected values for those in the final products. The content of XII was taken as the final amount less that formed in the distillation of fraction (j) and the initial content of XI taken as the final content less the 10% formed during the distillation which gave fractions (u-w). The resulting estimate of the initial product composition is shown in Table I.

This estimate means that in our reaction, which consumed 2.85 moles of isobutylene, the initial product mixture should have contained (1/4 × 1.89) moles of I, 0.62 mole of XI, 0.06 mole of XII, 0.25 mole of XIII, 0.02 mole of XIV and 0.01 mole of XV. The formation of such a mixture would require the consumption of 7.195 moles of NO and would produce at the same time 1.66 moles of N_2 and 0.18 mole of water. These are within experimental error of the observed values, namely, 7.13 moles of NO consumed, 1.72 moles of N_2 produced and 0.183 mole of H_2O (3.0 g. × 325.7/295.9) removed from the first falling film distillate.

SCHENECTADY, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

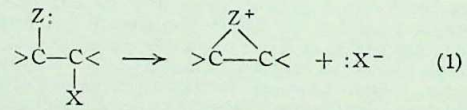
Rates of Acetolysis of *cis*- and *trans*-2-Nitroxycyclohexyl *p*-Bromobenzenesulfonates and *p*-Toluenesulfonates

BY STANLEY J. CRISTOL AND BORIS FRANZUS

RECEIVED NOVEMBER 6, 1956

The rates of solvolysis of *cis*- and *trans*-2-nitroxycyclohexyl *p*-bromobenzenesulfonates and *p*-toluenesulfonates in acetic acid at 87.9° have been measured. Solvolyses with the *trans* isomers proceed at a rate less than twice that of the *cis* isomers, indicating that the nitroxy group is not an effective anchimeric group. The preparations of these arenesulfonates and of *cis*- and *trans*-1,2-cyclohexanediol mononitrates are described.

Winstein and his co-workers[1] have shown that rate enhancement occurs when a group on a β-carbon atom participates in solvolysis of another group on the α-carbon atom, *viz.*



(1)

For example, the *p*-bromobenzenesulfonate (brosylate) of *trans*-2-acetoxycyclohexanol—where the acetoxy group is sterically situated so as to permit participation as in (1)—solvolyzes in acetic acid 630 times as rapidly as the *cis* isomer (where participation is sterically impossible). In similar fashion *trans*-2-bromocyclohexyl brosylate reacts 800 times as rapidly as the *cis* isomer. These groups therefore are effective participants. However, both *cis* and *trans*-cyclohexanediol dibrosylate react at about the same rate. Thus arenesulfonoxy groups are ineffective in this participation.

The rates of solvolysis of *cis*- and *trans*-2-nitroxycyclohexyl *p*-bromobenzenesulfonate and *p*-toluenesulfonate were determined in acetic acid at 87.9°, substantially as described by Winstein and co-workers.[1] The rate constants are given in Table I (average of two runs), along with data of Winstein for 2-acetoxycyclohexyl and 2-*p*-bromobenzenesulfonoxycyclohexyl brosylates and/or tosylates.

It will be noted that the *trans*-nitroxy compounds are less than twice as reactive as the corresponding *cis* compounds and that their rate constants for solvolysis are of the same order of magnitude as the *cis*-2-acetoxy compounds or the 2-arenesulfonoxy compounds. The results indicate clearly that effective participation of nitroxy does not obtain and that an intermediate such as I is not being formed in the rate-determining step in solvolysis. The effect of the nitroxy group appears limited to its inductive effect (similar to the *cis*-acetoxy and the arenesulfonoxy group), which thus slows down the rate significantly with respect to cyclohexyl

TABLE I

REACTION RATE CONSTANTS FOR ACETOLYSIS OF 2-SUBSTITUTED CYCLOHEXYL *p*-TOLUENESULFONATES AND *p*-BROMOBENZENESULFONATES

2-Substituent	Temp., °C.	10^5k, sec.$^{-1}$
p-Toluenesulfonates		
trans-Acetoxy	99.7	20,000[a]
cis-Acetoxy	99.7	53[a]
	88	*ca.* 18[b]
trans-Nitroxy[c]	87.88	5.6
cis-Nitroxy[c]	87.88	3.9
p-Bromobenzenesulfonates		
Hydrogen	74.95	15,000[d]
trans-Acetoxy	74.95	3750[d]
cis-Acetoxy	74.95	5.9[d]
trans-Bromobenzenesulfonoxy	74.95	8.5[d]
	88	*ca.* 30[e]
cis-Bromobenzenesulfonoxy	74.95	9.5[d]
	88	*ca.* 30[e]
trans-Nitroxy[c]	87.88	13
cis-Nitroxy[c]	87.88	7.1

[a] Data of Winstein, Grunwald, Buckles and Hansen.[1a] [b] Estimated from data at 100° by assuming rate constant is one-third of value at 100°. [c] Present work; solution contained 0.05*M* sodium acetate and 0.36*M* water. [d] Data of Winstein, Grunwald and Ingraham.[1b] [e] Estimated from data at 75° by assuming rate constant is thrice that at 75°.

(1) (a) S. Winstein, E. Grunwald, R. E. Buckles and C. Hanson, THIS JOURNAL, **70**, 816 (1948); (b) S. Winstein, E. Grunwald and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

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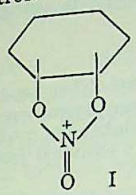
arenesulfonates, but it would be of interest to determine the stereochemistry of the solvolysis to see whether compound I may be still involved in stereochemical control.



I

Many of the compounds for this study were prepared for the first time. The *trans* compounds were prepared by the reaction sequence: cyclohexene oxide plus nitric acid to *trans*-1,2-cyclohexanediol mononitrate; mononitrate plus arenesulfonyl chloride to nitroxycyclohexyl arenesulfonate. The *cis* compounds were prepared from *cis*-1,2-cyclohexanediol monoacetate.[2] This was nitrated, and the nitroxy acetate was hydrolyzed selectively with dilute base to remove the acetoxy group and retain the nitrate group. The resulting *cis*-diol mononitrate was then arenesulfonated. The structure of each of the mononitrates was established by hydrogenolysis.

Acknowledgments.—The authors are indebted to the Office of Ordnance Research, U. S. Army, for support of this research under a contract between that Office and the University of Colorado. The analyses were performed by Galbraith Microanalytical Laboratories.

Experimental

Determination of Rate Constants.—The rate constants were determined substantially as described by Winstein, Hanson and Grunwald.[3] The solvent was acetic acid containing excess sodium acetate, 0.05 *M*, and water, 0.36 *M*, and the solutions were titrated with standard perchloric acid in acetic acid, using either brom phenol blue or methyl violet as indicator.

***trans*-2-Nitroxycyclohexyl *p*-Toluenesulfonate.**—A solution of 0.50 g. (3 mmoles) of *trans*-cyclohexanediol mononitrate[4] and 0.6 g. of *p*-toluenesulfonyl chloride in enough pyridine to dissolve the reagents was kept in a refrigerator for 3.5 days. The reaction mixture was poured into water, the solid removed by filtration and recrystallized once from benzene–petroleum ether and twice from cyclohexane. It then melted at 84.0–84.3°.

Anal. Calcd. for $C_{13}H_{17}O_6NS$: C, 49.51; H, 5.43. Found: C, 49.71; H, 5.57.

***trans*-2-Nitroxycyclohexyl *p*-bromobenzenesulfonate** was prepared in the same fashion (time 1.5 days) with *p*-bromobenzenesulfonyl chloride. After three recrystallizations, it melted at 89.6–90.3°.

Anal. Calcd. for $C_{12}H_{14}O_6BrNS$: C, 37.90; H, 3.71. Found: C, 37.81; H, 3.82.

***cis*-1,2-Cyclohexanediol Mononitrate.**—A solution containing[2] 13.0 g. (0.082 mole) of 1,2-cyclohexanediol monoacetate and 6.43 g. of diacetate (estimated by saponification equivalent) in 40 ml. of chloroform was added dropwise over a period of 2 hr. to a solution of 10.7 ml. of nitric acid (d. 1.50, 98% nitric acid) in 50 ml. of 96% sulfuric acid. A temperature between −25 and −7° was maintained during the addition. The reaction mixture was poured into ice-water, and the chloroform layer was separated. The water layer was extracted once with 50 ml. of chloroform. The combined chloroform extracts were washed with water, saturated sodium bicarbonate and water. The chloroform solution was dried over anhydrous magnesium sulfate, and the material was distilled. The product, which was a mixture of *cis*-2-acetoxycyclohexyl nitrate and *cis*-1,2-cyclohexanediol diacetate, boiled at 68–73° (0.5 mm.) and weighed 16.7 g. The product was estimated to contain 9.4 g. (58% of mixture, 56% yield) of 2-acetoxycyclohexyl nitrate by quantitative hydrogenolysis over platinum oxide catalyst.

Sixteen grams of this mixture was treated with 100 ml. of 1.4 *M* sodium hydroxide solution in 75 vol. % ethanol at room temperature for 50 minutes. The extent of reaction was followed by titration of aliquots with standard hydrochloric acid, and it was apparent that hydrolysis of the acetate ester groups from the diacetate and nitrate–acetate was substantially complete at the end of this time. This method takes advantage of the relative inertness of nitrate esters to hydrolysis with alkali.[5-7] The solution was then neutralized with dilute acid, saturated with sodium chloride and extracted with three 100-ml. portions of ether. The ether extracts were combined and washed with 400 ml. of saturated salt solution. The ethereal solution was dried overnight over anhydrous magnesium sulfate, and the ether was distilled. The product, *cis*-1,2-cyclohexanediol mononitrate, boiled at 63–63.2° (0.3 mm.), $n^{20}D$ 1.4787, and weighed 3.81 g. (54% yield).

Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.62; H, 6.72; N, 8.55.

Hydrogenolysis of this nitrate over platinum oxide at atmospheric pressure gave crude *cis*-diol, m.p. 89–96°, mixed m.p. with *cis*-diol,[2] 89–96°, mixed m.p. with *trans*-diol,[2] 66–80°.

cis-2-Nitroxycyclohexyl *p*-toluenesulfonate was prepared as described above for the *trans* isomer, m.p. after recrystallization from cyclohexane, 74.5–75.2°.

Anal. Calcd. for $C_{13}H_{17}O_6NS$: C, 49.51; H, 5.43. Found: C, 49.50; H, 5.52.

cis-2-Nitroxy *p*-bromobenzenesulfonate was prepared as described above for the *trans* isomer, m.p. after recrystallization from cyclohexane, 94–94.5°.

Anal. Calcd. for $C_{12}H_{14}O_6BrNS$: C, 37.90; H, 3.71. Found: C, 37.97; H, 3.72.

BOULDER, COLORADO

(2) S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2787 (1942); S. Winstein, H. V. Hess and R. E. Buckles, *ibid.*, **64**, 2796 (1942); D. Ginsberg, *ibid.*, **75**, 5746 (1953).
(3) S. Winstein, C. Hanson and E. Grunwald, *ibid.*, **70**, 812 (1948).
(4) A. G. Brook and G. F. Wright, *Can. J. Chem.*, **29**, 308 (1951).
(5) J. W. Baker and D. M. Easty, *Nature*, **166**, 156 (1950); *J. Chem. Soc.*, 1193, 1208 (1953).
(6) S. J. Cristol, B. Franzus and A. Shadan, THIS JOURNAL, **77**, 2512 (1955).
(7) B. Franzus, Ph.D. thesis, University of Colorado, 1954.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

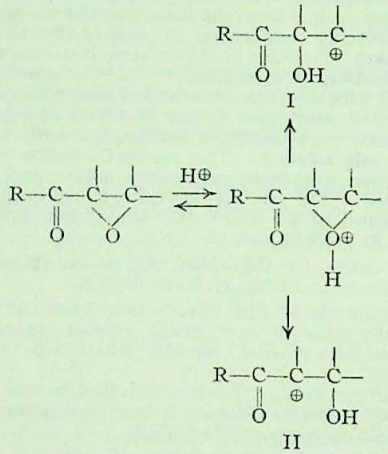
The Rearrangement of α,β-Epoxy Ketones. VI. 1,1-Disubstituted Ethylene Oxides

BY HERBERT O. HOUSE, DONALD J. REIF[1] AND RICHARD L. WASSON[1]

RECEIVED NOVEMBER 12, 1956

α,β-Epoxy-α-phenylpropiophenone, α,β-epoxy-α-ethylpropiophenone and 1,2-dimesityl-2,3-epoxy-1-propanone have been isomerized to α-formyldesoxybenzoin, α-formylbutyrophenone and the enol of α-formyldesoxymesitoin, respectively, by treatment with boron trifluoride. The analogous rearrangement of α,β-epoxypropiophenone produced 1,3,5-tribenzoylbenzene. The interpretation of the results suggests that a carbonium ion adjacent to a carbonyl group is either equivalent in stability or more stable than a primary carbonium ion.

The products derived from the acid-catalyzed isomerization of a variety of α,β-epoxy ketones have been rationalized by the assumption that the initial step in the isomerization involves cleavage of the oxirane ring to leave a positive charge on the carbon atom beta to the carbonyl group (I).[2,3] The fission of the oxirane ring to form the transient cation I rather than II appeared to be justified; the formation of structure II would be expected to be energetically unfavorable since this structure places partial positive charges on adjacent atoms.



Although a carbonyl group is usually considered to destabilize an adjacent carbonium ion (such as II),[4,5] there is little evidence bearing on the extent of this destabilization relative to the effect of other substituents. Since the mode of cleavage (*i.e.*, I or II) of the oxirane ring accompanying the acid-catalyzed rearrangement of α,β-epoxy ketones appeared to offer a measure of the relative stability of a carbonium ion (or a partial positive charge)[3] adjacent to a carbonyl group, we were led to study the isomerization of certain 1,1-disubstituted ethylene oxides III. The products formed by rearrangement of these oxides III would provide a measure of the relative stabilities of a primary carbonium ion (Fig. 1, reaction path A) and a carbonium ion adjacent to a carbonyl group (Fig. 1, reaction path B).

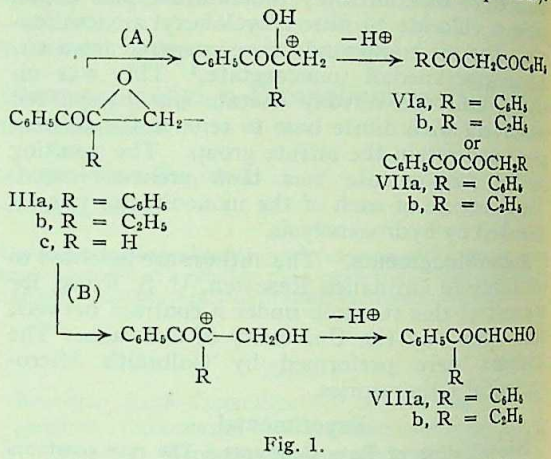
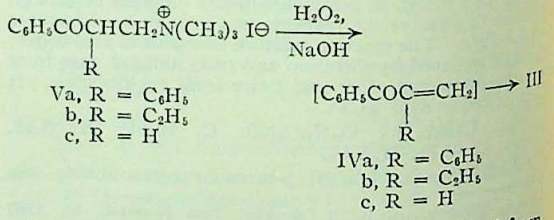


Fig. 1.

For the preparation of the keto oxides III, we investigated procedures which would avoid isolation of the unstable acrylophenone precursors IV. Direct reaction of the appropriate Mannich base methiodides V with alkaline hydrogen peroxide was found to produce the desired oxides.[6]



In a previous study[2b] the product derived from the isomerization of α-phenyl-*cis*-benzalacetophenone oxide appeared to be best explained by the assumption that the reaction proceeded *via* an ion of the type II. This observation suggested that the formation of a carbonium ion adjacent to a carbonyl group may occur without difficulty if the ion is stabilized by an adjoining aryl group.[7] We therefore chose α,β-epoxy-α-phenylpropiophenone (IIIa) for our initial studies in an effort to favor reaction path B (Fig. 1). The rearrangement of

(1) Alfred P. Sloan Research Assistant, 1956.

(2) For previous papers in this series see THIS JOURNAL, (a) **76**, 1235 (1954); (b) **77**, 6525 (1955); (c) **78**, 2298 (1956); (d) **78**, 4394 (1956); (e) **79**, 1488 (1957).

(3) The cleavage of the oxirane ring and the attendant rearrangement may well be concerted processes. If this is the case, the positive charge would not reside entirely on the β-carbon atom as depicted in I. Studies to determine the relative charge distribution in the transition state are currently in progress.

(4) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 150.

(5) The failure of certain α-halo ketones to react with silver nitrate has been attributed to such destabilization [for example, see R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 143].

(6) This reaction is analogous to the use of the quaternary salts of Mannich bases as precursors for unsaturated ketones in the Michael reaction [see J. H. Brewster and E. L. Eliel, *Org. Reactions*, **7**, 99 (1953)].

(7) The successful use of α-aryl α-halo ketones as alkylating agents in the Friedel–Crafts reaction [P. Ruggli, H. Dahn and J. Wegmann *Helv. Chim. Acta*, **29**, 113 (1946)] is in agreement with this idea.

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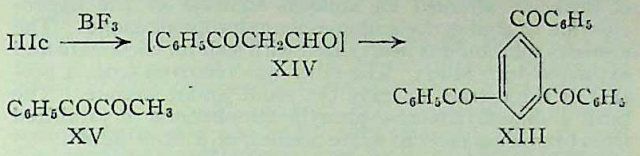
the oxide IIIa in the presence of boron trifluoride etherate yielded the keto aldehyde VIIIa, the product expected if the reaction followed path B (Fig. 1). We were unable to isolate either of the diketones VIa or VIIa.

A previous example of an acid-catalyzed isomerization of an oxide analogous to IIIa has been reported[8]; the reaction of 1,2-dimesityl-2,3-epoxy-1-propanone (IX) with a mixture of acetic and hydriodic acids was found to yield an unknown product isomeric with the starting ketone. We have effected the same reaction by treatment of the oxide IX with boron trifluoride etherate. The product is acidic and has an infrared spectrum which is suggestive of an enolized β-dicarbonyl compound. Since the product does not resemble either of the known, isomeric enolized diketones X[9] or XI,[10] the compound was assigned the enolized keto aldehyde structure XII, an analog of the keto aldehyde VIIIa derived from IIIa. This assignment was confirmed when compound XII was synthesized by the reaction of the bromomagnesium enolate of desoxymesitoin (XIII) with ethyl formate.

We next turned our attention to α,β-epoxy-α-ethylpropiophenone (IIIb). Rearrangement of the epoxide IIIb *via* reaction path B (Fig. 1) would involve a tertiary cation adjacent to a carbonyl group as was the case with IIIa; however, the formation of such an ion from IIIb would not be favored by an adjoining phenyl ring. The isomerization of the epoxide IIIb proceeded much more slowly than isomerizations previously studied as might be expected if the reaction involved the formation of a relatively unstable carbonium ion. Best results were obtained when the rearrangement was effected in the presence of a benzene solution of gaseous boron trifluoride rather than with boron trifluoride etherate.[11] The only products which could be isolated from the isomerization were the keto aldehyde VIIIb and its degradation product, butyrophenone; neither of the diketones VIb and VIIb or compounds derived from them, the products expected from rearrangement *via* path A (Fig. 1), could be isolated from the reaction mixture.

We therefore investigated the behavior of α,β-epoxypropiophenone (IIIc). Reaction of this oxide IIIc with boron trifluoride yielded the triketone XIII as the only isolable product. The triketone XIII was presumably derived from the intermediate keto aldehyde XIV; when an authentic sample of the keto aldehyde XIV was subjected to the conditions of the rearrangement, only the triketone XIII was produced. The alternative product, the diketone XV which might result from the isomerization of the oxide IIIc, has been found to be stable to acids[12] and, consequently, is not the precursor of the triketone XIII.



In order to determine which of the reaction paths C or D (Fig. 2) was operative in the conversion of the oxide IIIc to the triketone XIII, the isomerization of the partially deuterated oxide XVI was studied. The fate of the deuterium label in each reaction path is outlined in Fig. 2; 47% of the deuterium present in the oxide XVI was retained in the product XIII. Consequently, we are led to believe that approximately half of the isomerization of the oxide IIIc is proceeding *via* reaction path C (Fig. 2) and the remainder *via* path D (Fig. 2).

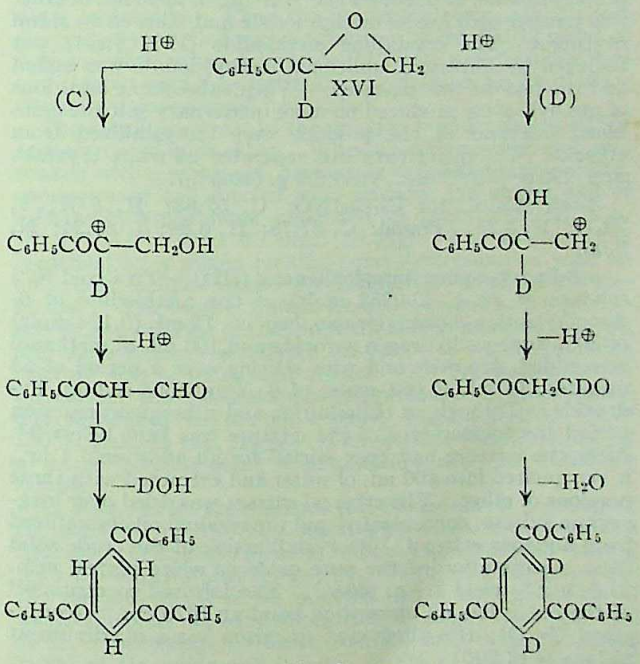
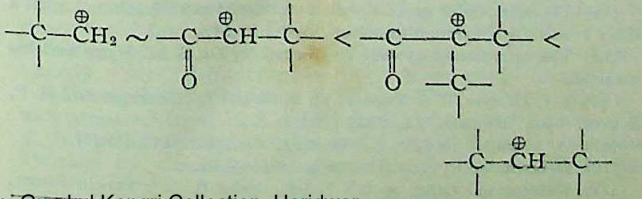


Fig. 2.

Our results suggest that the stability of a carbonium ion adjacent to a carbonyl group is approximately equivalent to the stability of a primary carbonium ion. The order of relative stabilities suggested by our present and previous[2] experiments is



(8) R. C. Fuson, D. J. Byers, C. A. Sperati, R. E. Foster and P. F. Warfield, *J. Org. Chem.*, **10**, 69 (1945).
(9) R. P. Barnes and A. E. Brandon, THIS JOURNAL, **65**, 2175 (1943).
(10) A. Behal and V. Auger, *Bull. soc. chim. France*, [3] **9**, 696 (1893).
(11) See ref. 2b, footnote 13.
(12) W. W. Hartman and L. J. Roll, *Org. Syntheses*, **23**, 1 (1943).

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The authors wish to acknowledge the assistance of Dr. R. C. Fuson who kindly supplied samples of desoxymesitoin and mesityl α-mesitylvinyl ketone for this study.

Experimental[13,14,15]

The Methiodide of β-Dimethylamino-α-phenylpropiophenone (Va).—The reaction of 25 g. (0.128 mole) of desoxybenzoin with a solution of 23 ml. of 25% aqueous dimethylamine and 11.1 ml. of 37% aqueous formaldehyde in 50 ml. of ethanol according to the directions of Denton and co-workers[16] afforded an aqueous solution of the hydrochloride of β-dimethylamino-α-phenylpropiophenone. The aqueous solution was neutralized with sodium carbonate and extracted with ether. The ether was removed from a portion of the extract to leave the crude amine ketone. The pure β-dimethylamino-α-phenylpropiophenone crystallized from petroleum ether as white needles, m.p. 82.0–82.8°.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.49; H, 7.47; N, 5.40.

The ether extract was dried over magnesium sulfate, treated with excess methyl iodide and allowed to stand at 15° for 12 hr. The crude product, collected on a filter, was recrystallized from aqueous ethanol. The methiodide separated as white crystals, m.p. 182.8–183.8° dec., yield 23.8 g. (48.5% based on desoxybenzoin).

Anal. Calcd. for $C_{18}H_{22}INO$: C, 54.71; H, 5.62; I, 32.11; N, 3.54. Found: C, 54.60; H, 5.56; I, 32.31; N, 3.76.

The Methiodide of β-Piperidino-α-phenylpropiophenone.—A solution of 10.5 g. (0.035 mole) of β-piperidino-α-phenylpropiophenone, m.p. 90.8–91.8° (lit.[17] 91°), in 40 ml. of ether was treated with excess methyl iodide and allowed to stand overnight. The crystalline methiodide (17% yield) was removed by filtration, additional methyl iodide was added and the process was repeated. When subsequent additions of methyl iodide produced no more quaternary salt the combined fractions of the product were recrystallized from ethanol. The quaternary salt separated as white crystals, m.p. 192.8–193.6° dec., yield 6.0 g. (40.5%).

Anal. Calcd. for $C_{21}H_{26}INO$: C, 57.88; H, 6.01; I, 29.11; N, 3.21. Found: C, 57.78; H, 6.24; I, 29.24; N, 3.05.

α,β-Epoxy-α-phenylpropiophenone (IIIa).—To a cold (0°) mixture of 10 g. (0.0253 mole) of the methiodide of β-dimethylamino-α-phenylpropiophenone, 12 ml. (0.124 mole) of 30% aqueous hydrogen peroxide and 100 ml. of methanol was added, dropwise and with stirring over a period of 25 minutes, 14 ml. (0.084 mole) of 6 *N* aqueous sodium hydroxide. Throughout the addition and subsequent reaction period the temperature of the mixture was kept below 2°. After the mixture had been stirred for an additional 1 hr., it was poured into 400 ml. of water and extracted with three portions of ether. The ethereal extract was dried over magnesium sulfate, concentrated and the residual oil crystallized from aqueous ethanol. Recrystallization of the crude solid from hexane afforded the pure oxide as white plates, m.p. 29.6–30.6°, yield 3.7 g. (66%). The infrared spectrum[15,19] of the oxide has an absorption band at 1670 cm.$^{-1}$ (conjugated C=O); the ultraviolet spectrum has a maximum at 252 mμ (ε 13,600).

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H, 5.39. Found: C, 80.18; H, 5.19.

Rearrangement of α,β-Epoxy-α-phenylpropiophenone (IIIa).—A solution of 260 mg. (0.00117 mole) of the oxide in 10 ml. of benzene was treated with 0.3 ml. (0.0024 mole) of boron trifluoride etherate and the resulting solution was allowed to stand at room temperature for 20 minutes. The reaction mixture was diluted with ether, washed with water and dried over magnesium sulfate. After the solvents had been removed, the residual oil was crystallized from hexane to give the **borofluoride complex of α-formyldesoxybenzoin** as yellow needles, m.p. 99.2–100° (lit.[20] 97–99°), yield 141 mg. (44%). In subsequent experiments the α-formyldesoxybenzoin was isolated as its copper complex, m.p. 223–224.5° (lit.[20] 220–221°), yield 65.3%, and, after treatment with phenylhydrazine as **1,4,5-triphenylpyrazole**, m.p. 211.2–212.2° (lit.[20] 210–211°), yield 75%. Each of the products was identified by a mixed melting-point determination with an authentic sample. As a control experiment a sample of the oxide IIIa was treated with phenylhydrazine under the same conditions which were employed to prepare 1,4,5-triphenylpyrazole from the crude isomerization product; none of the pyrazole could be isolated.

In an effort to isolate any benzyl phenyl diketone present as its quinoxaline, a crude rearrangement product was boiled with a solution of *o*-phenylenediamine dihydrochloride in ethanol. The only crystalline product which could be isolated was desoxybenzoin, m.p. 60–61° (lit.[21] 60°), yield 35%, which formed a 2,4-dinitrophenylhydrazone melting at 202–203.5° (lit.[22] 203°). All of our attempts to isolate dibenzoylmethane or one of its derivatives from the reaction mixture were unsuccessful.

Rearrangement of 1,2-Dimesityl-2,3-epoxy-1-propanone (IX).—Mesityl α-mesitylvinyl ketone [infrared absorption[19,23] 1665 cm.$^{-1}$ (conjugated C=O), 1625 cm.$^{-1}$ (conjugated C=C), 975 cm.$^{-1}$ (C=CH_2 adjacent to a carbonyl group)[23]] was converted to the epoxy ketone IX, m.p. 150.5–151.5° (lit.[8] 152–152.5°), by the procedure previously described.[8] The infrared spectrum[19,23] of the oxide has a band at 1700 cm.$^{-1}$ (C=O of a sterically hindered aryl ketone) but lacks the absorption at 975 cm.$^{-1}$ found in the corresponding unsaturated ketone. A mixture of 0.50 g. (0.0016 mole) of the oxide, 2 ml. (0.016 mole) of boron trifluoride etherate and 25 ml. of cyclohexane was stirred for 2 minutes, diluted with ether, washed with water and concentrated. The residual solid crystallized from ligroin (b.p. 90–120°) as white needles, m.p. 250–252°, yield 0.27 g. (54%). An additional crystallization sharpened the melting point of the keto aldehyde to 251–252°.

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84; mol. wt., 308. Found: C, 81.76; H, 7.96; mol. wt., 245 (Rast).

An attempt to effect the same rearrangement in ether solution with boron trifluoride etherate resulted in isolation of the unchanged oxide (75% recovery).[11]

The infrared spectrum[19,25] of the enolized keto aldehyde has a broad intense band in the 3 μ region with its center at 2950 cm.$^{-1}$ (associated O–H); in the 6 μ region a band of medium intensity is found at 1630 cm.$^{-1}$ accompanied by a broad, intense band with its center at 1565 cm.$^{-1}$ (C=O and/or C=C of an enolized β-dicarbonyl compound). The product was shown to be identical with the sample, m.p. 250–253°, prepared by Fuson and co-workers[8] by means of a mixed melting-point determination. Although the compound dissolved readily in aqueous alkali, it was remarkably stable to cleavage. After a solution of the compound in 10% aqueous sodium hydroxide had been heated on a steam-bath for 1 hr., 98% of the unchanged, enolized keto aldehyde was recovered when the reaction mixture was acidified. The behavior of the compound was also anomalous in that an ethanolic solution of the product gave no color with ferric chloride.

1,2-Dimesityl-2-propen-3-ol-1-one (XII).—A solution of 280 mg. (0.001 mole) of desoxymesitoin and 1 ml. (0.001 mole) of a standard solution of ethylmagnesium bromide in 25 ml. of benzene was refluxed for 40 minutes and then treated with 3 ml. (0.037 mole) of ethyl formate. The resulting mixture was refluxed for 19 hr., diluted with ether and washed with aqueous ammonium chloride. After the

(13) All melting points are corrected and all boiling points are uncorrected.

(14) The ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, model 11 MS.

(15) The microanalyses were performed by Dr. S. M. Nagy and his associates.

(16) J. J. Denton, R. J. Turner, W. B. Neier, V. A. Lawson and H. P. Schedl, THIS JOURNAL, **71**, 2048 (1949).

(17) C. Mannich and D. Lammering, *Ber.*, **55**, 3510 (1922).

(18) Determined in carbon tetrachloride solution.

(19) Determined either with a Baird, model B, or a Perkin-Elmer, model 21, double beam infrared recording spectrophotometer fitted with a sodium chloride prism.

(20) W. Wislicenus and A. Ruthing, *Ann.*, **379**, 229 (1911).

(21) C. Graebe and H. Bungener, *Ber.*, **12**, 1079 (1879).

(22) C. F. H. Allen and J. R. Richmond, *J. Org. Chem.*, **2**, 222 (1937).

(23) The abnormal location for the band attributable to the C-H bending vibration of a terminal methylene group of vinyl ketones has been reported previously by M. H. J. Davison and G. R. Bates.

(24) M. H. J. Davison and G. R. Bates, *J. Chem. Soc.*, 2607 (1953).

(25) Determined as a suspension in a potassium bromide pellet.

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solvents had been removed from the organic layer, the residue was taken up in boiling methanol and the solution was decolorized with Norit, diluted with water and cooled. After the unchanged desoxymesitoin, m.p. 90–93°, recovery 182 mg. or 65%, had been removed, concentration of the mother liquor afforded 26 mg. of the crude enolized keto aldehyde, melting over the range 220–245°. The pure enolized dicarbonyl compound crystallized as white needles, m.p. 251–253°, yield 12 mg. (11% based on the unrecovered desoxymesitoin). The melting point of a mixture of the product with a sample obtained by rearrangement of 1,2-dimesityl-2,3-epoxy-1-propanone was not depressed.

The Methiodide of β-Dimethylamino-α-ethylpropiophenone (Vb).—The Mannich base hydrochloride was prepared from 40 g. (0.27 mole) of butyrophenone, 16.8 g. (0.56 mole) of paraformaldehyde and 49 g. (0.6 mole) of dimethylamine hydrochloride according to the general directions of Burckhalter and Fuson.[26] The paraformaldehyde and dimethylamine hydrochloride were added in two equal portions, the second portion being added after 4 hr.; a total reaction time of 16 hr. was employed. An aqueous solution of the Mannich base hydrochloride was neutralized with sodium carbonate and the amine was taken up in ether. The ethereal solution was dried over magnesium sulfate, treated with excess methyl iodide and allowed to stand for 12 hr. The methiodide separated as fine, white crystals, m.p. 188.8–189.8°, yield 59.3 g. (63%). The melting point of the product was not altered by recrystallization from an ethanol-ether mixture.

Anal. Calcd. for $C_{14}H_{22}INO$: C, 48.43; H, 6.40; I, 36.56; N, 4.03. Found: C, 48.47; H, 6.22; I, 36.58; N, 4.03.

α,β-Epoxy-α-ethylpropiophenone (IIIb). A. From the Methiodide Vb.—To a cold (−4°) solution of 58.8 g. (0.17 mole) of the quaternary salt and 81 ml. (0.84 mole) of 30% aqueous hydrogen peroxide in 500 ml. of methanol was added, dropwise and with stirring over a period of 20 minutes, 94 ml. (0.56 mole) of 6 *N* aqueous sodium hydroxide. The resulting mixture was stirred for 2 hr.; throughout the addition and subsequent reaction period the temperature of the mixture was kept at −2°. The reaction mixture was poured into water and the resulting mixture was extracted with ether. The extract was dried over magnesium sulfate and concentrated. The components of the extract were separated by repeated fractional distillation through a Holtzmann column. The α,β-epoxy-α-ethylpropiophenone (IIIb), a colorless liquid boiling at 60–61° (0.15 mm.), $n^{25}D$ 1.5249, amounted to 3.35 g. (11.2%). The infrared spectrum[19,27] of the oxide has a band at 1675 cm.$^{-1}$ (conjugated C=O); the ultraviolet spectrum has a maximum at 246.5 mμ (ε 11,600) with a minimum at 220 mμ (ε 2,210). The nuclear magnetic resonance spectrum of the oxide, determined as a pure liquid with a Varian Associates high-resolution nuclear magnetic resonance spectrometer, model V4300B, has the following peaks (expressed as cycles per second relative to the proton resonance of water): a triplet with its center at −174 sec.$^{-1}$ (CH_3 adjacent to CH_2); a singlet at −135 sec.$^{-1}$ (CH_2 adjacent to CH_3); a quadruplet with its center at −96 sec.$^{-1}$ (CH_2 of an oxide ring); and two multiple peaks centered around +90 sec.$^{-1}$ and +108 sec.$^{-1}$ attributable to the nuclear resonance of protons bonded to an aromatic ring.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 75.05; H, 6.86.

The α-ethylacrylophenone (IVb), collected in the initial fractions of the distillation, amounted to 11.24 g. (41.5%), b.p. 49–50° (0.15 mm.), $n^{25}D$ 1.5300 [lit.[26] b.p. 85° (5 mm.), $n^{25}D$ 1.5267]. The infrared spectrum[19,27] of the unsaturated ketone has a band at 1645 cm.$^{-1}$ (conjugated C=O) with a shoulder at 1625 cm.$^{-1}$ (conjugated C=C). The spectrum also exhibits a band at 975 cm.$^{-1}$ (C=CH_2 adjacent to a carbonyl group)[24] which is not present in the spectrum of the oxide. The ultraviolet spectrum of the unsaturated ketone has a maximum at 246 mμ (ε 10,000) with a minimum at 220 mμ (ε 6,650).[25] The nuclear magnetic resonance spectrum of the unsaturated ketone, determined as previously described, has the following peaks (relative to the proton resonance of water): a triplet with its center at −170 sec.$^{-1}$ (CH_3 adjacent to CH_2); a quadruplet with its center at −115 sec.$^{-1}$ (CH_2 adjacent to CH_3); a doublet (+7 and +18 sec.$^{-1}$) attributable to the two non-equivalent hydrogen atoms of the terminal methylene group; and a series of peaks centered around +92 sec.$^{-1}$ attributable to the nuclear resonance of protons bonded to an aromatic ring. Because of the discrepancy in refractive index values the composition of the unsaturated ketone was also determined.

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.30; H, 7.52.

B. Epoxidation of α-Ethylacrylophenone (IVb).—A solution of 11.1 g. (0.069 mole) of the unsaturated ketone and 20 ml. of 30% aqueous hydrogen peroxide in 70 ml. of methanol was cooled to 0°, and 6 ml. (0.036 mole) of 6 *N* aqueous sodium hydroxide was added dropwise and with stirring. The resulting mixture was stirred for 3 hr. at room temperature, diluted with water and extracted with ether. After the extract had been dried and concentrated, distillation of the residue through a 30-cm. Podbielniak concentric tube fractionating column, model GE-117, afforded 6.91 g. (56.5%) of α,β-epoxy-α-ethylpropiophenone, b.p. 68.5° (0.4 mm.), $n^{25}D$ 1.5258. The infrared and ultraviolet spectra of the product are identical with the spectra of the oxide sample previously described.

Rearrangement of α,β-Epoxy-α-ethylpropiophenone (IIIb).—A solution of 309 mg. (0.00175 mole) of the oxide in 15 ml. of benzene was saturated with gaseous boron trifluoride and the resulting solution was allowed to stand for 3 hr. The reaction mixture was diluted with ether, washed with water and extracted with three portions of 5% aqueous sodium hydroxide. When the remaining ether solution was concentrated, boiled with a solution of 2 ml. (0.012 mole) of 6 *N* aqueous sodium hydroxide for 24 hr. and then acidified and treated with 2,4-dinitrophenylhydrazine, no 2,4-dinitrophenylhydrazone could be isolated.

The alkaline extract of the reaction mixture was acidified and extracted with ether. When the ethereal solution was shaken with a saturated, aqueous solution of cupric acetate, concentrated and diluted with pentane, the **copper salt of α-formylbutyrophenone** separated as green needles, m.p. 181.5–183.5°, yield 60 mg. (16.5%). The product was identified by a mixed melting-point determination with an authentic sample whose preparation is subsequently described. The mother liquors from the copper salt were dissolved in a solution of sodium hydroxide in aqueous ethanol, and the solution was refluxed for 1 hr. When the resulting mixture was acidified and treated with 2,4-dinitrophenylhydrazine, the **2,4-dinitrophenylhydrazone of butyrophenone** separated as orange needles, m.p. 190–191° (lit.[29] 190°), yield 64 mg. (14%). The product was identified by a mixed melting-point determination with an authentic sample.

In subsequent experiments the alkali-soluble fraction of the reaction mixture was boiled with a solution of sodium hydroxide in aqueous ethanol and then acidified and treated with 2,4-dinitrophenylhydrazine. With reaction times for the rearrangement of 20 minutes and 3 hr. the yields of butyrophenone 2,4-dinitrophenylhydrazone were 50 and 49%, respectively. When a solution of 270 mg. (0.00153 mole) of the oxide and 0.5 ml. (0.004 mole) of boron trifluoride etherate in 15 ml. of benzene was allowed to stand for 1.5 hr. and then worked up in the same manner, the yield of butyrophenone 2,4-dinitrophenylhydrazone was 40%. In no case could either acetophenone 2,4-dinitrophenylhydrazone or benzoic acid be isolated. Treatment of the reaction mixture from the rearrangement with either phenylhydrazine or *o*-phenylenediamine dihydrochloride failed to yield crystalline products.

As a control experiment, α,β-epoxy-α-ethylpropiophenone was treated first with a boiling solution of sodium hydroxide and then with 2,4-dinitrophenylhydrazine as described previously. No 2,4-dinitrophenylhydrazone could be isolated.

α-Formylbutyrophenone (VIIIb).—This β-keto aldehyde was prepared from 14.8 g. (0.1 mole) of butyrophenone, 7.5 g. (0.1 mole) of ethyl formate and 4.8 g. (0.2 mole) of sodium hydride by the standard procedure.[30] The product was

(26) J. H. Burckhalter and R. C. Fuson, THIS JOURNAL, **70**, 4184 (1948).

(27) Determined in a chloroform solution.

(25) The second band expected from the cross-conjugated system of the unsaturated ketone IVb is apparently masked by other absorption in the region 210–240 mμ. The oxide IIIb absorbs much less strongly in this region than does the unsaturated ketone IVb.

(29) D. P. Evans, *J. Chem. Soc.*, 785 (1936).

(30) C. R. Hauser, F. W. Swamer and J. T. Adams, *Org. Reactions*, **8**, 126 (1954).

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separated from an ether solution of the organic components of the reaction mixture by extraction with a saturated, aqueous solution of sodium carbonate. The alkaline solution was acidified and extracted with ether. Evaporation of the ether followed by recrystallization of the residue afforded the pure keto aldehyde as white needles, m.p. 96–97°, yield 3.5 g. (20%). The infrared spectrum[19,25] has a broad band in the 3 μ region (associated O–H) as well as strong bands in the 6 μ region at 1645 and 1505 cm.$^{-1}$ (C=O and/or C=C of an enolized β-dicarbonyl compound). When the spectrum[19] of the product was determined in chloroform solution, two additional bands appeared in the 6μ region at 1675 cm.$^{-1}$ (conjugated C=O) and 1710 cm.$^{-1}$ (unconjugated C=O). Our product is, therefore, the **enol form of α-formylbutyrophenone.**

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.95; H, 6.96.

The α-formylbutyrophenone sample, m.p. 86–87°, previously reported[31] is apparently the tautomer of the sample we have isolated.

A portion of the keto aldehyde was converted to its copper salt in the usual manner. **The copper salt of α-formylbutyrophenone** separated from an ether–pentane mixture as blue-green needles, m.p. 182.5–183.5°. The infrared spectrum[19,25] of the copper salt has broad absorption bands in the 6 μ region with their centers at 1585 and 1572 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{22}O_4Cu$: C, 63.86; H, 5.32. Found: C, 63.94; H, 5.36.

Alkaline Cleavage of α-Formylbutyrophenone (VIIIb).—A solution of 1.0 g. (0.0057 mole) of the keto aldehyde and 2 ml. (0.012 mole) of 6 *N* aqueous sodium hydroxide in 20 ml. of ethanol was boiled under reflux until an acidified sample of the reaction mixture no longer gave a color with ferric chloride (1 hr.). The mixture was diluted with water and extracted with ether. Treatment of the residue from the ether solution with 2,4-dinitrophenylhydrazine yielded 1.62 g. (95%) of butyrophenone 2,4-dinitrophenylhydrazone, m.p. 190–191°.

1-Phenyl-1,3-pentanedione (VIb).—The reaction of 13.7 g. (0.114 mole) of acetophenone with 5.5 g. (0.228 mole) of sodium hydride and 23.3 g. (0.228 mole) of ethyl propionate in the usual manner[30] produced the β-diketone, b.p. 131–135° (6 mm.), n^{25}D 1.5820 [lit.[32] b.p. 120–122° (5 mm.), n^{20}D 1.5837], yield 12.4 g. (62%). The infrared spectrum[19,27] of the product has a broad band in the 6 μ region with its center at 1625 cm.$^{-1}$ (enolized β-diketone).

Alkaline Cleavage of 1-Phenyl-1,3-pentanedione (VIb).—A solution of 1.0 g. (0.0057 mole) of the diketone and 1.5 ml. (0.009 mole) of 6 *N* aqueous sodium hydroxide in 20 ml. of ethanol was refluxed until an acidified sample from the reaction mixture gave no color with ferric chloride (24 hr.). The mixture was diluted with water and extracted with ether. Evaporation of the ether followed by treatment with 2,4-dinitrophenylhydrazine yielded acetophenone 2,4-dinitrophenylhydrazone, m.p. 249–250° (lit.[33] 249–250°), yield 1.10 g. (65%). Acidification of the aqueous solution from the reaction mixture followed by appropriate manipulations afforded 0.10 g. (14.4%) of benzoic acid, m.p. 120–121°. Both products were identified by mixed melting point determinations with authentic samples.

Reaction of 1-Phenyl-1,3-pentanedione (VIb) with Boron Trifluoride.—A solution of 1.0 g. (0.0057 mole) of the diketone in 20 ml. of benzene was saturated with gaseous boron trifluoride, and the solution was allowed to stand for 2 hr. The benzene was removed and the residue crystallized from a hexane–ether mixture. **The borofluoride complex of 1-phenyl-1,3-pentanedione** separated as white needles, m.p. 68.4–69.2°, yield 638 mg. (50%). The infrared spectrum[19,27] of the product has a broad absorption band in the 6 μ region with its center at 1552 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{11}BF_2O_2$: C, 59.00; H, 4.91; B, 4.82; F, 16.97. Found: C, 58.89; H, 5.09; B, 4.83; F, 16.76.

When a solution of 200 mg. (0.0009 mole) of the complex and 2.0 ml. (0.012 mole) of 6 *N* aqueous sodium hydroxide in 20 ml. of ethanol was refluxed for 24 hr. and the neutral fraction of the product treated with 2,4-dinitrophenylhydrazine as previously described, the yield of acetophenone 2,4-dinitrophenylhydrazone, m.p. 249–250°, was 180 mg. (67%). In a second control experiment a solution of 100 mg. of the borofluoride complex in 20 ml. of ether was extracted with three portions of 5% aqueous sodium hydroxide. Concentration of the ether solution left 60 mg. of the unchanged borofluoride complex, m.p. 67–69°. The alkaline extract was acidified and extracted with ether; treatment of the ethereal extract with saturated, aqueous cupric acetate yielded 33 mg. (28%) of the copper complex of 1-phenyl-1,3-pentanedione, m.p. 153–154° (lit.[32] 151°). The product was identified by a mixed melting-point determination with an authentic sample.

α,β-Epoxypropiophenone (IIIc).—A suspension of 3.0 g. (0.0094 mole) of the crude methiodide of β-dimethylaminopropiophenone,[34] m.p. 203–209°, and 5 ml. (0.052 mole) of aqueous 30% hydrogen peroxide in 55 ml. of methanol was cooled to 0°, and 6 ml. (0.036 mole) of 6 *N* aqueous sodium hydroxide was added dropwise and with stirring. The resulting mixture was stirred for 1 hr. at 0°, diluted with 150 ml. of water and extracted with 3 portions of ether. The ether extract was dried and concentrated to leave an oil which crystallized from an ether–petroleum ether mixture. The oxide separated as white plates, m.p. 52–53° (lit.[35] 53°), yield 0.78 g. (60.6%). The infrared spectrum[19,27] of the product has a band at 1675 cm.$^{-1}$ (conjugated C=O).

Rearrangement of α,β-Epoxypropiophenone (IIIc).—A solution of 0.1 g. (0.0007 mole) of the oxide in 25 ml. of benzene was saturated with gaseous boron trifluoride over a period of 2 minutes and then worked up in the usual manner. None of the copper salt of benzoylacetaldehyde could be isolated from the crude rearrangement product. The reaction product, **1,3,5-tribenzoylbenzene (XIII)**, crystallized from ethanol as white plates, m.p. 118–120° (lit.[36] 119°), yield 0.05 g. (56%). The infrared spectrum[19,25] of the compound has a band at 1685 cm.$^{-1}$ (conjugated C=O). When a benzene solution of the oxide was heated with 0.5 equivalent of boron trifluoride etherate for 15 minutes, the yield of the triketone XIII was 20%. As in the former case no benzoylacetaldehyde could be isolated.

Benzoylacetaldehyde (XIV).—The sodium salt of the keto aldehyde was prepared by the reaction of 60 g. (0.5 mole) of acetophenone with sodium hydride (12 g., 0.5 mole) and ethyl formate (45 g., 0.6 mole) in the usual manner.[30] Reaction of the crude sodium salt with cupric acetate afforded the **copper salt of benzoylacetaldehyde** which crystallized from an ether–pentane mixture as dark green needles, m.p. 212–213° dec., yield 110.7 g. (62%).

Anal. Calcd. for $C_{18}H_{14}O_4Cu$: C, 60.42; H, 3.92. Found: C, 60.61; H, 4.16.

A sample of benzoylacetaldehyde derived from 0.34 g. (0.0013 mole) of the copper salt was dissolved in ether and treated with 0.5 ml. (0.004 mole) of boron trifluoride etherate. The solution was refluxed for 15 minutes and then worked up in the usual way. None of the benzoylacetaldehyde could be recovered; instead 1,3,5-tribenzoylbenzene was isolated, m.p. 117–119°, yield 0.28 g. (80%). The compound was shown to be identical with the sample prepared by rearrangement of α,β-epoxypropiophenone both by a mixed melting-point determination and by comparison of the infrared spectra of the two samples.

Partially Deuterated α,β-Epoxypropiophenone (XVI).—A solution of 12 g. (0.1 mole) of acetophenone and 1 g. of sodium hydroxide in a mixture of 20 ml. of deuterium oxide and 20 ml. of ethanol was refluxed for 18 hr. The deuterium content of the recovered acetophenone was 21.92 atom per cent. deuterium or 1.75 gram atoms of deuterium per mole. The acetophenone was converted to the methiodide of β-dimethylaminopropiophenone and subsequently to α,β-epoxypropiophenone by the procedures described previously. The deuterium content of the epoxy ketone was 1.40 atom per cent. deuterium or 0.112 gram atom of deuterium per mole.

Rearrangement of Partially Deuterated α,β-Epoxypropiophenone (XVI).—A 1.0-g. (0.0067 mole) sample of the oxide was isomerized as previously described. The yield of par-

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May 20, 1957

tially deuterated 1,3,5-tribenzoylbenzene, m.p. 118–119.5°, was 0.30 g. (34%). The deuterium content or the triketone was 0.87 atom per cent. deuterium or 0.157 gram atom of deuterium per mole (47% retention of the deuterium present in the epoxy ketone).

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, STANDARD OIL CO.]

Reaction of Arenes with Silver Fluoride in Hydrogen Fluoride Solution

BY D. A. MCCAULAY AND A. P. LIEN

RECEIVED NOVEMBER 5, 1956

Silver fluoride, dissolved in anhydrous hydrogen fluoride, reacts with arenes to form a stable complex containing 3 moles of arene. The complex reverts to silver fluoride and arene as the hydrogen fluoride is removed by distillation. AgF–HF is therefore a useful solvent for separating arenes from other hydrocarbons. In contrast with other metal fluorides that complex with arenes, AgF in HF is a base; it inhibits rather than promotes such reactions as alkyl-group migration. The stability of the arene–silver fluoride complex is almost independent of the number and orientation of the alkyl groups on the ring. It differs from the σ-complexes formed by the action on arenes of HF plus other metal fluorides, such as BF_3, TiF_4, CbF_5, TaF_5, and acts more like a π-complex.

A few metal fluorides act as co-acids with liquid anhydrous hydrogen fluoride. A criterion used in previous work to establish such co-acid properties was whether the fluoride enabled a proton to add to a xylene molecule.[1] In the presence of a sufficiently strong co-acid, normally insoluble xylene accepts a proton and dissolves in the hydrogen fluoride. On the other hand, certain metal fluorides that are obviously bases in the hydrogen fluoride system also cause arenes to dissolve in this medium. Thus, Klatt[2] found that silver fluoride, which is soluble and ionizes in hydrogen fluoride probably according to the equation[3] can

$$AgF + HF \rightleftharpoons AgFH^+ + F^-$$

bring into solution up to four mole-equivalents of arene.

In the present study, batch extractions of hydrocarbon mixtures and petroleum fractions with AgF–HF have been used to elucidate the action of silver fluoride on arenes. Our objects were to determine how silver fluoride differs from the acidic fluorides and to learn whether it could be used to extract arenes from hydrocarbon mixtures, separate arenes from each other, or promote such reactions as alkylation and disproportionation.

Experimental

Silver fluoride, obtained from the Beta Research Laboratory, was dissolved in hydrogen fluoride and heated to 100° under vacuum to drive off any moisture present with the hydrogen fluoride. The hydrogen fluoride, a commercial grade of 99.6% purity supplied by the Matheson Co., was distilled before each experiment. The hydrocarbons, C.P. grades obtained from commercial suppliers, were used without further purification. The petroleum fractions used were typical straight-run and reformed West Texas naphthas.

The extraction runs were carried out in a 1.5-liter carbon–steel autoclave. Silver fluoride, hydrocarbon and a measured volume of hydrogen fluoride were added to the autoclave and stirred for 1 hr. After a settling period of 2 hr., the acid layer was withdrawn from the bottom of the autoclave into a polyethylene flask cooled in Dry Ice. In most cases, the extracted arenes were sprung by slowly adding water to the chilled acid phase. After a large excess of water had been added, the displaced arenes were decanted from the aqueous acid. The raffinate layer was drained from the autoclave. Both hydrocarbon products were then washed with ammonium hydroxide and were analyzed by appropriate means, such as refractive index measurement and infrared and ultraviolet absorption.

In a few experiments designed to show whether the silver fluoride could be regenerated and used again the technique differed. After the mixing step, the autoclave was heated to 50° and the hydrocarbon and hydrogen fluoride were distilled into an evacuated flask to recover the silver fluoride residue for re-use.

Extraction of Known Mixtures.—Four mixtures of known hydrocarbons were each extracted with an equal volume of hydrogen fluoride plus silver fluoride. The results are shown in Table I.

TABLE I

EXTRACTION OF ARENES FROM SYNTHETIC MIXTURES

Arene	Benzene	Xylene[a]	C_8-Alkylbenzenes[b]	
Moles AgF per mole arene	0.17	0.17	1.0	1.0
Feed, vol. %				
Arene	40	40	32	32
n-Heptane	60	60	60	66.5
Olefin	....	...	8[c]	....
Propyl sulfide	....	...	....	1.5
Raffinate, vol. %				
Arene	22.5	25	0	0.4
Olefin	....	...	0	....
Propyl sulfide	....	...	....	0
Extract, vol. %				
Arene	97	95	97	94.5
Olefin	....	...	0	....
Propyl sulfide	....	...	....	4.5
Arene removed				
%	56.5	50	100	99
Moles per mole AgF	3.3	3.0	1.0	1.0
Separation factor, β[d]	144	57	>1000	1220

[a] Equal parts of *m*- and *p*-xylene. [b] Equal parts of all four. [c] Equal parts of *n*-octene and cyclohexene. [d] Quotient of the arene-to-heptane ratio in the extract phase divided by the arene-to-heptane ratio in the raffinate.

The mixture of benzene and *n*-heptane was about 56% dearomatized to give an extract containing 97% benzene. The separation factor, β, which measures the relative distribution of benzene and *n*-heptane between the two phases, has a high value of 144. Conventional solvents, such as diethylene glycol or sulfur dioxide, give β's ranging from 5

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to 15. The exceptionally high selectivity of AgF–HF indicates that more than physical solution is involved; the amount extracted suggests that a coördination complex containing 3 moles of arene per mole of silver is formed. The excess 0.3 mole of benzene is probably extracted by physical solution. Xylene is known to be much less soluble in common solvents than benzene and, as expected, exactly 3 moles are extracted per mole of AgF. The excess one mole-equivalent observed by Klatt[3] could have resulted from working with pure arenes rather than with a heptane solution.

In the two runs with C_8-alkylbenzenes, two representative impurities were also present. One feed contained about 8% olefins, which alkylated the xylenes and were extracted as alkylbenzenes. The other feed contained about 1.5% propyl sulfide, which ended in the acid layer. In both these runs, excess AgF effected complete extraction. Also, the β-values jumped to well over 1000. Excess AgF changed the nature of the solvent and "salted out" the physically dissolved, uncombined hydrocarbon. The system AgF–HF is exceptional among solvents in that completeness and selectivity can be improved simultaneously.

The effect of hydrogen fluoride on extraction is summarized in Table II. Selectivity decreases as less hydrogen fluoride is used. Apparently, large amounts of arene–AgF complex change the nature of the solvent and increase the physical solubility of hydrocarbons in the acid phase. In the most concentrated solution, about 86 g. of AgF was present per 100 g. of hydrogen fluoride, whereas the measured solubility of AgF in hydrogen fluoride is only 33 g. per 100 g.[3] Because complexes form with arenes, much more than this amount of AgF goes into solution. Identical results were obtained when these runs were repeated after distilling off the HF and arenes under vacuum at 50°. Activity of the silver fluoride was unimpaired by the distillation step.

TABLE II
EFFECT OF HF CONCENTRATION

Extraction charge: 1 mole AgF, 6 moles arene, 7.5 moles *n*-heptane

HF, moles	111	18.5	7.4
Raffinate composition, moles			
Arene	2.97	2.93	2.77
n-Heptane	7.35	7.23	6.87
Acid-phase composition, moles			
HF	111.0	18.5	7.4
AgF	1.0	1.0	1.0
Arene	3.03	3.08	3.23
n-Heptane	0.17	0.27	0.63
Separation factor, β	50	28	13

Extraction of Petroleum Fractions.—Extraction experiments with one volume HF per volume of hydrocarbon and 1.0 mole of AgF per mole of arene were made also on two petroleum naphthas that contained a wide variety of arenes with boiling points up to 230°.

A high sulfur heavy naphtha, upon treatment with AgF–HF, formed a large amount of sludge, which interfered with phase separation. The sulfur compounds occurring in the naphtha—unlike propyl sulfide, which introduced no complication—evidently form an insoluble complex with silver fluoride. The naphtha was therefore desulfurized with HF alone before treatment with AgF–HF. No sludge formed and phase separation was good. As shown in Table III, all the arenes were extracted and the extract was almost 100% arene.

TABLE III
EXTRACTION OF LIGHT PETROLEUM STOCKS WITH HF–AgF

	Desulfurized heavy naphtha		Reformed light naphtha	
	Vol. % arene	$n^{20}D$	Vol. % arene	$n^{20}D$
Feed	23	1.4332	54.5	1.4477
Raffinate	0	1.4180	1.0	1.3873
Extract	99	1.4982	99.0	1.4968
% of aromatic removed	100		98	
Separation factor, β	>5000		4500	

A reformed naphtha was completely and selectively freed of arenes upon extraction with AgF–HF. All naturally occurring arenes boiling up to at least 230° can therefore be extracted from mixtures.

Separation of Arenes.—The possibility of separating close-boiling arenes from each other by extraction with AgF–HF was also investigated. Mixtures of two arenes in *n*-heptane solution were stirred with half a volume of hydrogen fluoride plus 1/6 mole AgF per mole of arene—enough to complex half of the arenes. The results are reported in Table IV. The separation factor, β, is equal to the equilibrium constant for the reaction in which both arenes compete for the silver ion

$$\text{Arene B}\cdot Ag^+ + \text{arene A} \rightleftarrows \text{arene A}\cdot Ag^+ + \text{arene B}$$

$$\beta = K_{eq} = [A\cdot Ag^+][B]/[B\cdot Ag^+][A]$$

It is therefore a measure of the relative stability of the two arene complexes with AgF–HF.

Complexes of AgF with *m*- and *p*-xylene are about equally stable, the *m*-xylene complex being slightly stronger. The difference in stability is too small to be used in a practical process for separating these two isomers.

TABLE IV
SEPARATION OF ARENES WITH AgF–HF

Feed				
Arene A	*p*-Xylene	*p*-Xylene		
Arene B	*m*-Xylene	Ethylbenzene		
Raffinate				
Vol. % A	13.5	5.5	12.1	17.4
Vol. % B	11.6	20.3	13.9	7.7
Ratio A to B	1.16	0.27	0.87	2.26
Extract				
Vol. % A	47.8	25.4	50.0	69.3
Vol. % B	47.2	69.5	41.3	22.8
Ratio A to B	1.01	0.37	1.21	3.04
Separation factor, β	0.87	1.35	1.39	1.35

The experiments comparing *p*-xylene and ethylbenzene at three different concentrations show, first, that the *p*-xylene complex is stronger by a factor of 1.35 and, second, that ethylbenzene itself is unreactive. The latter effect contrasts directly with the behavior of ethylbenzene in HF–BF_3, where extensive disproportionation occurs almost instantaneously, even at temperatures as low as 0°.[4] The difference in stability between the silver complexes of *p*-xylene and ethylbenzene can be made the basis of a process for separating ethylbenzene from the close-boiling xylenes. Separation by distillation, because of the low value of 1.05 for the relative volatility, requires about 150 stages; extraction with AgF–HF could give the same separation in about 20 stages.

Effect of AgF on Alkylation.—Because AgF can make arenes soluble in hydrogen fluoride, it should promote alkylation by providing intimate contact between catalyst and reactants. This supposition was tested by four experiments, reported in Table V, in which ethylene and an arene were stirred with 1.5 volumes of HF for 60 minutes at 15°. When added to a stirred mixture of *m*-xylene and hydrogen fluoride, ethylene alkylates *m*-xylene at a moderate rate. But, when enough AgF is present to bring the xylene into solution, the rate of alkylation decreases and only half as much ethylene reacts. Also, as demonstrated by the toluene runs, if the olefin instead of the arene is added to the AgF–HF first, alkylation stops completely. Therefore, despite providing a homogeneous reaction medium, AgF inhibits alkylation—probably by a combination of two effects: (a) lowering the acidity of the catalyst by raising fluoride concentration and (b) tying up both olefin and arene as unreactive complexes.

Conclusion

The differences between the behavior of AgF in hydrogen fluoride and that of other metal fluorides

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TABLE V

ALKYLATION OF ARENES WITH ETHYLENE

	m-Xylene	Toluene		
AgF, moles per mole arene	0	——0.33——		
Ethylene, moles per mole arene	——1.0——		——0.33——	
Order of addition	——Olefin to arene——		Arene to olefin	
Product distribution, mole %				
m-Xylene	62	77	..	..
Ethylxylene	20	16	..	..
Diethylxylene	6	2	..	..
Triethylxylene	2	1	..	..
Tetraethylxylene	10	4	..	..
Toluene	..	..	92	100
Ethyltoluene	..	..	7	0
Diethyltoluene	..	..	1	0
% of ethylene reacted[a]	78	39	27	0

[a] Unreacted ethylene appeared as ethyl fluoride.

(1) are summarized in Table VI. Silver fluoride acts as a base, decreases the acidity of the HF and inhibits acid-catalyzed reaction. The acidic fluorides markedly increase the hydrogen-ion concentration and thereby promote such acid-catalyzed reactions as alkylation and disproportionation. In forming complexes, the acidic fluoride coördinates with a fluoride ion and thereby assists a proton to add to the aromatic ring

$$\text{arene} + HF + BF_3 \longrightarrow \text{arene}\cdot H^+BF_4^-$$

Because the metal fluoride itself is not part of the arene cation, the tendencies of the various arenes to form a complex should be independent of the metal fluoride used. Such was actually observed with the acidic fluorides.

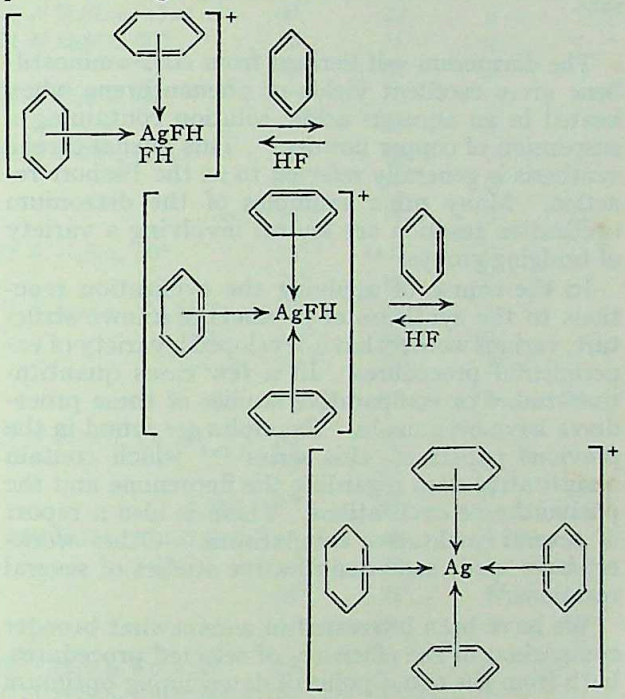
TABLE VI

BEHAVIOR OF METAL FLUORIDES IN HYDROGEN FLUORIDE

Property	AgF	BF_3, TiF_4, TaF_5, or CbF_5
Ionizes as	Base	Acid
Moles arene in complex	3	1
Benzene and toluene complexes	Stable	Unstable
Selectivity between *m*- and *p*-xylene	None	High
Catalytic activity		
Ethylbenzene disproportionation	Inactive	Promotes
Alkylation	Inhibits	Promotes

The arene cation is a σ-complex,[5] the stability of which is determined primarily by the number and orientation of alkyl groups on the ring.[6] The stability of the complex between arene and silver ion, however, is almost independent of the substituent groups. This cation therefore acts more like a π-complex; the silver ion combines loosely with the cloud of π-electrons around the ring.

Arenes and silver ion interact weakly[7] even in aqueous solution, but in anhydrous hydrogen fluoride the complex is many orders of magnitude more stable. Perhaps, because it is such a strong acid, hydrogen fluoride does not monopolize the vacant coördination positions around the silver ion but allows them to be filled by the arene to form complexes having the structures



The complex containing three molecules of arene is stable even at low arene concentrations, but it shows little tendency to take on an additional molecule. The reason for the sharp cut-off at three is not clear; perhaps steric requirements prevent more than three molecules from approaching within bonding distance.

The stability of the complex depends upon hydrogen fluoride concentration. As hydrogen fluoride is removed from solution, the complex dissociates and the arene separates as a distinct organic layer. Because a strong chemical bond is formed in solution, extraction with AgF–HF is highly selective, and because this bond is easily broken by removal of a low-boiling solvent, a separation process based upon this technique is practical.

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[Contribution from the Department of Chemistry of the University of South Carolina]

Intramolecular Reactions. V. Factors Affecting the Yield in Diazonium Cyclization Reactions[1]

By DeLos F. DeTar and Thomas E. Whiteley[2]

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A quantitative study of the effect of a series of reaction conditions on the product yields in the diazonium cyclization reaction shows that there is a great deal of individuality among the various diazonium salts. For the diazonium salts derived from *cis*-2-aminostilbene, from 2-amino-*sym*-diphenylethane and from 2-amino-3′-nitrobenzophenone, the best conditions are those of Pschorr, the use of a copper powder catalyst in dilute sulfuric acid. However, 2-(4′-methylbenzoyl)-benzenediazonium bisulfate and *o*-phenoxybenzenediazonium fluoborate gave a considerable amount of reduction product in the presence of copper powder. For these compounds the use of moderately concentrated sulfuric acid gave the best results.

The diazonium salt derived from *cis*-2-aminostilbene gives excellent yields of phenanthrene when heated in an aqueous acidic solution containing a suspension of copper powder.[3] This phenanthrene synthesis is generally referred to as the Pschorr reaction. Many other examples of the diazonium cyclization reaction are known involving a variety of bridging groups.[1,4,5]

In the course of applying the cyclization reactions to the synthesis of products of known structure, various workers have developed a variety of experimental procedures. In a few cases quantitative studies or comparative studies of these procedures have been made. Examples are found in the previous papers of this series[1,3b,6] which contain quantitative data regarding the fluorenone and the phenanthrene cyclizations. There is also a report of several qualitative comparisons.[7] Other workers have made semi-quantitative studies of several reactions.[8,9]

We have been interested in a somewhat broader comparison of the efficiency of selected procedures, both from the stand-point of determining optimum reaction conditions and from the standpoint of obtaining qualitative information about the mechanisms of the cyclization process. The purpose of the present work was to test out a series of typical cyclization procedures on a representative series of diazonium salts.

Among the large variety of cyclization procedures that have been described previously, the following general classes may be recognized: (1) The diazonium salt is heated in dilute acidic solution. Diazotized 2-aminobenzophenone gives a 65% yield of fluorenone under these conditions,[6] but diazotized *cis*-2-aminostilbene gives only about 30% of phenanthrene, due to a side reaction leading to indazole.[3b] (2) The diazonium salt is heated in dilute acidic solution in the presence of copper powder. These are the usual conditions for the Pschorr phenanthrene synthesis. (3) The diazonium salt is heated in alkaline solution. This procedure has given good results in the synthesis of 2-hydroxyphenanthrene-9-carboxylic acid[10] and with 2-methoxyphenanthrene-9-carboxylic acid[11] but gives low yields in the fluorenone series and in several other series.[6,7] (4) An aqueous ethanolic solution of the diazonium salt is treated with copper powder, or an aqueous solution is treated with hypophosphorous acid.[3a] The first variant gave an 85% yield of 2,3-methylenedioxyphenanthrene-9-carboxylic acid,[12a] and the second gave a 70% yield of 4,6-dimethylphenanthrene-9-carboxylic acid,[12b] but in other than the phenanthrene series such methods appear to lead to extensive replacement of the diazonium group with hydrogen with a serious diminution of the yield of cyclic product. (5) Miscellaneous methods have been reported such as treatment of an acetone suspension of the crystalline diazonium fluoborate with copper powder,[8] formation of the triazene by reaction of the diazonium salt with dimethylamine followed by treatment of a suspension of the triazene in an organic solvent with gaseous hydrogen chloride[8] and preparation of and decomposition of the N-nitrosoacetylamide.[8,13] In none of the reported examples were the yields by these miscellaneous methods any more attractive than those obtained by the first four procedures.

Since a considerable amount of information was already available regarding the fluorenone synthesis,[6-9] 2-(4′-methylbenzoyl)-benzenediazonium bisulfate was selected for a survey of the cyclization conditions. These included the use of a wide range of sulfuric acid concentrations, with and without copper catalysts, and a few examples of the use of other media such as sodium hydroxide, aqueous alcohol and glacial acetic acid. From this work six reaction conditions were selected for further investigation with four other diazonium salts, so chosen as to be representative of the various types used in the cyclization reaction. The results of this comparative study are summarized in Table I. The individual runs which have been averaged in Table I

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(12) (a) R. Konovalova, S. Yunussov, and A. Orekov, *Bull. Soc. Chim. France*, [5], **6**, 1479 (1939); (b) E. E. Lewis and R. C. [illegible], 1940).

(13) D. F. DeTar and C. S. Savat, This Journal, **75**, 5117 (1953).

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and a number of others which represent additional reaction conditions are given in Tables II and III.

TABLE I

EFFECT OF CONDITIONS ON YIELD IN THE DIAZONIUM CYCLIZATION REACTION[a]

Diazonium salt from	Reaction conditions: 1 *N* H_2SO_4	1 *N* H_2SO_4 + Cu	1 *N* H_2SO_4 + CuCl	21 *N* H_2SO_4	21 *N* H_2SO_4 + Cu	21 *N* H_2SO_4 + CuCl
cis-2-Aminostilbene	36	94	94	46	60[b]	42
2-Amino-*sym*-diphenylethane	45	74	68	58	49	49
2-Amino-3'-nitrobenzophenone	40[b]	90	74[c]	53[b]	51	67
2-Aminodiphenyl ether	14[c]	20[d]	20[d]	27[c]	10[c,d]	17[c,d]
2-Amino-4'-methylbenzophenone	60	45[d]	46	74[e]	67	73[b]

[a] Entries are average percentage yield of cyclic product from crystalline diazonium salt, based on two runs unless otherwise indicated. The individual runs are presented in Tables II and III. Reaction temperatures from 25–90° or more all give the same product yield in the fluorenone series as can be seen from the data in Table II and from previous work. The averages for the yield of 3-methylfluorenone from diazotized 2-amino-4'-methylbenzophenone are for all runs under a given set of conditions regardless of temperature. For the first four compounds all cyclizations were carried out at 80°. The std. deviations given in Tables II and III were pooled: these are 3.8% for a single entry, 2.7% for averages of 2 (37 D.F.). Two averages which differ by 6% are significantly different at the 95% level. [b] Average of three values. [c] Single value. [d] Extensive reduction occurred. See Tables II and III. [e] Average of six values.

The reasons for the choice of the six reaction conditions listed in Table I are as follows: The use of dilute sulfuric acid, both with and without copper powder was, of course, mandatory, since these are the most commonly used cyclization conditions. The use of cuprous chloride was suggested by previous work.[1] There were also indications that the yields might be improved in more concentrated acid since the lower water concentration might reduce the yield of phenol and increase that of cyclic product. The 21 *N* acid was chosen as a suitable compromise, since 36 *N* acid led to diminished yields (Table II), apparently due to sulfonation. It also seemed desirable to test the effect of copper and cuprous chloride in the more concentrated acid. The low yields obtained with alkali and in aqueous ethanol indicated that there was little point in testing these conditions except perhaps with the phenanthrene synthesis.

The diazonium salts listed in Table I are representative of those used in the various cyclization reactions in that the cyclization of diazotized *cis*-2-aminostilbene typifies the Pschorr phenanthrene synthesis, that of diazotized 2-amino-*sym*-diphenylethane is representative of the two-atom bridge series, including the aporphine types,[14] the two 2-aminobenzophenones represent respectively a type which gives good yields of fluorenone in acidic solution in the absence of catalysts and one which does not. The salt from 2-aminodiphenyl ether is intended as a representative of the ethers and possibly of the N-alkyldiphenylamines.

The most surprising feature of the results reported in Table I is the extreme individuality exhib-

(14) C. Barger and G. Weitnauer, *Helv. Chim. Acta*, **22**, 1036 (1939).

TABLE II

PRODUCTS FROM 2-(4'-METHYLBENZOYL)-BENZENEDIAZONIUM BISULFATE

Conditions		Fluorenone, %[a] Obsd.	2-Hydroxy-4'-methylbenzophenone, %[b] Obsd.	4-Methylbenzophenone, %[c] Obsd.	Av. total[d]
1 *N* H_2SO_4, reflux		59	32	0	
		62[e]	38	0	
		86[f,g,h]	14[g,h]	0	
	Av.	61	35	0	96
10 *N* H_2SO_4, reflux		69	29	0	
21 *N* H_2SO_4, 60°		65	14	0	
		80	19	0	
21 *N* H_2SO_4, 90°		80[i]	..	0	
		76	20	0	
21 *N* H_2SO_4, reflux		72	18	0	
		78	17	0	
	Av.	75[j]	18[j]	0	93
31 *N* H_2SO_4, 60°		25[h,k]	3	0	
		77[l]	12	0	
1 *N* H_2SO_4, Cu, R.T.		48	25	13	
	R.T.	43	38	10	
	reflux	79[g,h]	36[h]	3[h]	
	Av.	46	33	12	91
21 *N* H_2SO_4, Cu, 80°		66	22	0	
		70	21	0	
	Av.	68	22	0	88
1 *N* H_2SO_4, CuCl, R.T.		47	44	6	
		46	36	5	
		68[h]	21[h]	5[h]	
	Av.	46	40	6	92
10 *N* H_2SO_4, CuCl, 80°		62	27	0	
21 *N* H_2SO_4, CuCl, 60°		73	20	0	
	80°	72	13	0	
	90°	75	20	0	
	Av.	73	18	0	91
31 *N* H_2SO_4, CuCl, 60°		82	13	0	
		75	12	0	
	Av.	78	12	0	90
36 *N* H_2SO_4, CuCl, 60° (2.5 hours)		49[m]	2	0	
1 *N* H_2SO_4, Cu, 50–50 C_2H_5OH–H_2O, R.T.		7	5	91	
		4	10	88	
	Av.	6	8	90	104
Glacial AcOH, 90°		62	..	0	
2 *N*, NaOH, Cu, 35°		29	38	20	
2 *N*, NaOH, Cu, reflux		29[e]	30	17	
	Av.	29	34	18	81

[a] Std. dev. is 4.3 (absolute) (15 D.F.); based on deviations of yields of replicate runs from their average. All runs in the same medium are considered replicates, regardless of temp. Yields are based on crystalline diazonium salt. [b] Std. dev. 4.1 (14 D.F.). [c] Std. dev. 1.8 (4 D.F.). [d] Std. dev. 4.3% (14 D.F.). [e] Fluoborate salt used. [f] 1 g. run; others were 150–350 mg. [g] Separation incomplete. [h] Omitted in calcn. of std. dev. [i] Diazonium salt not isolated; diazotization mixture made up to indicated acid strength and heated. Yield is based on the amine. [j] Av. of preceding 6 runs (5 for hydroxy compound). [k] Run for several hours permitting loss by sulfonation. [l] Run for 2 hr. [m] Loss by sulfonation.

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TABLE III

PRODUCTS FROM THE DIAZONIUM FLUOBORATE OF *cis*-2-AMINOSTILBENE, FROM THE DIAZONIUM FLUOBORATE OF 2-AMINO-*sym*-DIPHENYLETHANE, FROM 2-PHENOXYBENZENEDIAZONIUM FLUOBORATE AND FROM 2-(3′-NITROBENZOYL)-BENZENEDIAZONIUM FLUOBORATE

	cis-2-Aminostilbene	2-Amino-*sym*-diphenylethane				2-Phenoxybenzenediazonium fluoborate		2-(3′-Nitrobenzoyl)-benzenediazonium fluoborate		
Conditions[a]	Phenanthrene[b]	9,10-Dihydrophenanthrene[c]	2-Hydroxy-*sym*-diphenylethane[d]	*sym*-Diphenylethane[e]	Phenanthrene[f]	Dibenzofuran[g]	Diphenyl ether[h]	Mixture of 2- and 4-nitrofluorenone[i]	2-Hydroxy-3′-nitrobenzophenone[j]	3-Nitrobenzophenone[k]
1 *N* H_2SO_4	37	44	45	0	0	14	0	37	56	0
	35	45	44	0	0			37	50	0
								47	54	0
1 *N* H_2SO_4, Cu	95	78	6	6	2.4	24	26	89	4	2
	93	70	10	5	2.2	15	34	90	4	0
1 *N* H_2SO_4, CuCl	92	71	7	4	1.7	17	26	74	2	19
	96	65	2	5	0.7	23	18			
1 *N* H_2SO_4, Cu, H_3PO_2	97	..	..	..	..	..	..	..	..	..
10 *N* H_2SO_4, Cu	97	..	..	..	..	25	23	..	..	..
10 *N* H_2SO_4, CuCl	..	..	..	..	..	..	..	61	4	30
21 *N* H_2SO_4	46	59	34	0	0	27	0	54	42	0
	45	57	32	0	0			52	39	0
								53	40	0
21 *N* H_2SO_4, Cu	62	52	29	5	2.0	10	52	46	8	0
	61	46	25	6	2.1			56	7	4
	56									
21 *N* H_2SO_4, CuCl	40	50	39	0	0	17	31	65	20	0
	45	48	28	0	0			69	20	0

[a] Carried out on 100–400 mg. of diazonium salt in 25 ml. of solution at 80° until spot test on β-naphthol paper was negative (1 to 4 hr. except for uncatalyzed reactions of 2-phenoxybenzenediazonium salts which required 20–30 hr.). All entries are per cent yields based on crystalline diazonium salt. [b] Std. dev. 2.6 (7 D.F.). [c] 3.6 (6). [d] 4.4 (5). [e] 0.6 (3). [f] 0.3 (3). [g] 5 (2). [h] 6 (2). [i] 4.1 (7). [j] 1.9 (7). [k] 3.4 (2).

ited by the various salts. In view of this characteristic there is indeed some question as to how typical any given reaction may be.

With the diazonium salts derived from *cis*-2-aminostilbene, 2-amino-*sym*-diphenylethane and 2-amino-3′-nitrobenzophenone, the best results were obtained under the Pschorr conditions, copper powder in the presence of dilute sulfuric acid. With 2-(4′-methylbenzoyl)-benzenediazonium salts and 2-phenoxybenzenediazonium salts, the Pschorr conditions lead to appreciable reduction giving by-products which are difficult to remove. For these latter two salts the use of 21 *N* sulfuric acid alone gave the best results. In none of the cyclizations did cuprous chloride offer any advantage over the above conditions.

The reaction of the diazonium salts in the absence of catalysts probably involves SN1 cleavage of the C–N bond,[6] and the higher yields of cyclic product at the higher acid concentrations can be explained on the basis that there are fewer water molecules to react to give the phenolic by-product.

The results in the presence of cuprous chloride and of copper powder are more difficult to explain in detail. There is a considerable variation in the effectiveness of these catalysts at the two acid levels. The high phenanthrene yield with copper powder, cuprous chloride or with hypophosphorous acid and copper powder does suggest that some sort of free radical process may be involved under these conditions.

Experimental

The preparation of the following compounds has already been described: 2-amino-4′-methylbenzophenone,[6,15] 2-amino-3′-nitrobenzophenone,[6] *cis*-2-nitrostilbene,[3b,16] 2-aminodiphenyl ether,[7,17] 2-(3′-nitrobenzoyl)-benzenediazonium fluoborate,[6,18] the diazonium fluoborate of *cis*-2-aminostilbene,[3b] 3-methylfluorenone,[6] 4-methylbenzophenone,[19] 2-hydroxy-4′-methylbenzophenone,[6] 2-chloro-4′-methylbenzophenone,[6] mixtures of 2- and 4-nitrofluorenone,[6] dibenzofuran,[7] diphenyl ether,[19] *sym*-diphenylethane.[19]

***cis*-2-Aminostilbene Hydrochloride.**—*cis*-2-Nitrostilbene was reduced with ferrous hydroxide,[3a,b] but the amine was converted to its hydrochloride with concd. aq. hydrochloric acid; m.p. 201–203°.

2-Amino-*sym*-diphenylethane Hydrochloride.—*cis*-2-Nitrostilbene (3.68 g.) was hydrogenated in methanolic solution (180 ml.) with 0.36 g. of 10% palladium-on-charcoal. Dry hydrogen chloride was passed through an ether solution of the amine to give 3.8 g. of 2-amino-*sym*-diphenylethane hydrochloride, m.p. 189–190°.[3a] The absence of the strong peak at 796 cm.$^{-1}$ characteristic of *cis*-2-aminostilbene shows that reduction was complete.

2-Phenoxybenzenediazonium Fluoborate.—2-Aminodiphenyl ether was diazotized in hydrochloric acid and the fluoborate salt precipitated with fluoboric acid (82% yield). **The diazonium fluoborate of 2-amino-*sym*-diphenylethane** was similarly prepared in 50% yield.

2-(4′-Methylbenzoyl)-benzenediazonium Bisulfate.—2-Amino-4′-methylbenzophenone (1.0 g.) was dissolved in 12 ml. of glacial acetic acid, 2 ml. of methanol and 1 ml. of concd.

(15) H. J. Scheifele and D. F. DeTar, *Org. Syntheses*, **32**, 8 (1952).

(16) Using the decarboxylation procedure of D. F. DeTar and L. A. Carpino, THIS JOURNAL, **78**, 475 (1956).

(17) F. Ullmann, *Ber.*, **29**, 1881 (1896).

(18) The salt was purified by solution in dimethylformamide and precipitation with ether.

(19) Commercial sample.

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sulfuric acid. It was diazotized at 0° with 0.6 ml. of freshly distilled *n*-butyl nitrite. Ether was added until the mixture became turbid and, on rubbing, the diazonium salt crystallized. It was purified by solution in glacial acetic acid and precipitation with ether; yield 80%.

3-Nitrobenzophenone.[20]—This was prepared by the Friedel-Crafts reaction from *m*-nitrobenzoyl chloride; colorless crystals, m.p. 93.5–94.0°, after vacuum sublimation and recrystallization from ethanol. The reported m.p. is 94–95°.

Phenanthrene.—This was a colorless sample, m.p. 96–97°, prepared by Mr. Julian Pruitt.[21]

2-Hydroxy-3′-nitrobenzophenone.—This compound was isolated from the decomposition of 2-(3′-nitrobenzoyl)-benzenediazonium salts; m.p. 95.5–96.5°, reported m.p. 96–97°.[4]

2-Hydroxy-*sym*-diphenylethane. This was isolated by chromatography from decomposition mixtures; m.p. 81–82°, reported m.p. 83.5°.[22]

Gattermann Copper Powder.[23]—Zinc dust was added to a saturated aqueous solution of copper sulfate until the blue color began to fade. The copper powder was washed by decantation and allowed to stand in dilute hydrochloric acid until hydrogen no longer was evolved. It was then washed until chloride ion was absent in the wash water, filtered, washed with ethanol, with ether and dried *in vacuo*. The catalyst was freshly prepared for each run.

Cuprous Chloride.[24]—This also was freshly prepared for each run in 2-g. quantities by heating 20 ml. of a solution containing 312 g. of copper sulfate pentahydrate and 81 g. of sodium chloride per liter while adding 8 ml. of a second solution containing 138 g. of sodium bisulfite and 88 g. of sodium hydroxide per liter. The precipitated cuprous chloride was washed by decantation using freshly boiled water, then centrifuged and used without drying.

Kochi Cuprous Chloride Solution.[25]—To 15 ml. of acetone (purified with permanganate) was added 5 ml. of water, 0.6 g. of lithium chloride and 1.2 g. of cupric chloride dihydrate. Nitrogen was bubbled through to remove oxygen, and the mixture was then refluxed for 24 hr. The small amount of solid material was disregarded.

Procedure for Decomposition of the Diazonium Salts.—The same general technique was followed with all the reactions. A 150–350 mg. sample of the diazonium salts was mixed with 25 ml. of the reaction medium in a 125-ml. Erlenmeyer flask and allowed to stand, or heated, with occasional shaking until the spot test on filter paper moistened with sodium β-naphthoxide solution was no longer red. In the runs with copper or cuprous chloride approximately 2-g. amounts of these catalysts were used.

Isolation and Identification of Reaction Products from 2-(4′-Methylbenzoyl)-benzenediazonium Salts.—The cooled reaction mixture was extracted with five 15-ml. portions of methylene chloride.[26] The solution was evaporated, the residue dissolved in 5 ml. of benzene and introduced onto a column of alumina, 19 × 100 mm., of approximately grade 4.[27] A 50–50 mixture of benzene and pentane was then passed through the column and the first 40 ml. of solvent collected in a tared beaker (fraction 1). A further 40 ml. was collected but usually contained only a few mg. of dissolved material. A solution of 13% methanol in chloroform was then passed through the column and 40 ml. collected (fraction 2). In some runs, especially those in the presence of copper or of cuprous chloride, there was a small dark yellow band which remained on the column after the methanol–chloroform treatment. Solvents were removed at room temperature by evaporation using a desiccator equipped for continuous passage of a slow stream of dry dust-free air. The recovery of material from the chromatographic separation was usually 90–100%.

The decompositions carried out in sulfuric acid of various concentrations and at various temperatures gave a chromatographic first fraction which was almost pure 3-methylfluorenone as determined by m.p. (typically 64–66° as compared with 66.0–66.5° for the pure 3-methylfluorenone) and by the identity of the infrared spectra with those of the pure material. The chromatographic second fraction was checked in a few cases and proved to be pure 2-hydroxy-4′-methylbenzophenone, m.p. 60.5–61.5°.

The decompositions carried out in the presence of copper or of cuprous chloride gave a first fraction which was an oil-coated solid. The infrared curve had all the peaks present in 3-methylfluorenone–4-methylbenzophenone mixtures and no others. Since both of these products are expected, no attempt was made to separate them for further identification. The absence of 2-chloro-4′-methylbenzophenone was shown by the infrared curves.

The runs in 85 and 96% sulfuric acid gave low yields of extractable material; the aqueous layer was yellow. These results suggest that sulfonation was occurring at these acid concentrations.

The identity of the products present in the first chromatographic fraction was checked for all runs except for a few replicate runs carried out in the absence of catalysts.

The results of the product studies are summarized in Table II. In addition to these results, it was found that the reaction of 2-(4′-methylbenzoyl)-benzenediazonium bisulfate with the Kochi cuprous chloride solution in acetone gave 98.3 and 99.0% of 2-chloro-4′-methylbenzophenone.

Reaction Products from 2-(3′-Nitrobenzoyl)-benzenediazonium Salts.—The procedure was the same as the above except for use of grade 2 alumina as adsorbent and methylene chloride as eluent. The mixture of 2- and 4-nitrofluorenones was identified on the basis of the identity of the infrared peaks with those present in samples previously obtained. The proportions of isomers varied somewhat from one set of reaction conditions to another, but this point was not investigated. The 2-hydroxy-3′-nitrobenzophenone was also identified on the basis of its infrared curve.

The spectra of the first chromatographic fraction derived from certain runs in the presence of copper or of cuprous chloride had the peaks characteristic of 3-nitrobenzophenone in addition to those of the nitrofluorenone mixture.

The results of these runs are summarized in Table III.

Reaction Products from *o*-Phenoxybenzenediazonium Salts.—The reaction product from this diazonium salt was a black tar, and a large portion of the reaction mixture consisted of unidentified highly colored products. The dibenzofuran and the diphenyl ether were obtained in the first 40 ml. of benzene eluent using grade 1 alumina. They were identified and determined quantitatively by means of their infrared spectra. The results are summarized in Table III.

Reaction Products from the Diazonium Fluoborate of *cis*-2-Aminostilbene.—Since benzaldehyde was present in some of the runs in the absence of catalysts, the reaction mixture was treated with a small amount of hydrogen peroxide or of potassium persulfate in order to oxidize it to benzoic acid. The chromatographic separation was carried out with grade 4 alumina using benzene as the eluent. The progress could be followed by observing the column with long wave length ultraviolet light; the phenanthrene, the indazole and an unidentified strongly adsorbed component were all fluorescent. The first fraction in all runs consisted of phenanthrene; *cis*-stilbene was absent, for there was no adsorption at 700 or at 780 cm.$^{-1}$ which are strong peaks for *cis*-stilbene. The results are summarized in Table III.

Reaction Products from the Diazonium Fluoborate of 2-Amino-*sym*-diphenylethane.—The extractions were carried out with ether. The chromatographic separation utilized grade 2 alumina with benzene as eluent. Since a reference sample of 9,10-dihydrophenanthrene was not available, the first chromatographic fractions from runs in sulfuric acid (in the absence of catalysts) were used. The infrared spectra of these fractions showed that *sym*-diphenylethane and phenanthrene were both absent. 9,10-Dihydrophenanthrene has been prepared previously by the diazonium cyclization reaction.[5]

(20) R. Geigy and W. Koenigs, *Ber.*, **18**, 2401 (1885).
(21) (a) W. E. Bachmann, THIS JOURNAL, **57**, 555 (1935); (b) A. Jeanes and R. Adams, *ibid.*, **59**, 2608 (1937).
(22) R. Stoermer, *Ber.*, **36**, 3982 (1903).
(23) C. Gattermann, *ibid.*, **23**, 1219 (1890).
(24) C. S. Marvel and S. M. McElvain, "Organic Syntheses," Coll. Vol. I, 2d Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 170.
(25) J. K. Kochi, THIS JOURNAL, **77**, 5274 (1955).
(26) In runs in which copper or cuprous chloride was present the procedure was somewhat different: the reaction mixture was stirred with 15 ml. of methylene chloride and filtered. The catalyst was rinsed with four 10-ml. portions of methylene chloride, and the filtrate was extracted with three 10-ml. portions.
(27) H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941); E. Lederer and M. Lederer, "Chromatography," Elsevier Publishing Co., New York, N. Y., 1954, p. 22.

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The infrared spectra of reactions run in the presence of copper had peaks at 810 and 733 cm.$^{-1}$ that were not accounted for by the 9,10-dihydrophenanthrene or by *sym*-diphenylethane. Phenanthrene has characteristic peaks at these positions. The presence of phenanthrene was verified by the appearance of characteristic ultraviolet peaks at 3295, 3375 and 3455 Å. The rather concentrated sample required cut off at 3200 Å. The phenanthrene concentration as estimated by the base-line technique agreed excellently with that estimated from the infrared curve. That the phenanthrene originated from the diazonium salt of 2-amino-*sym*-diphenylethane and not from that of *cis*-2-aminostilbene present as an impurity was established by the observation that phenanthrene was not produced in all runs.

Quantitative Spectrophotometric Analyses.—Infrared spectra were obtained in carbon disulfide solution in a fixed cell 0.106 mm. thick using a Perkin–Elmer model 21 spectrophotometer equipped with sodium chloride optics. For quantitative work, concentrations were adjusted to give peaks between 15 and 85% transmittance. The curve of the pure solvent was used to obtain the 100% transmission line, and a strong solvent absorption peak was used to give the 0% absorption value. Ultraviolet spectra were obtained with a Cary model 14 spectrophotometer using solvent in the reference beam. The absorbance curve of solvent *vs.* solvent was run after each solution.

A representative calibration analysis of known 3-methylfluorenone and 4-methylbenzophenone mixtures is given in Table IV. The results obtained with mixtures of the other compounds are comparable.

TABLE IV

INFRARED ANALYSIS OF KNOWN MIXTURES OF 3-METHYLFLUORENONE AND 4-METHYLBENZOPHENONE[a]

3-Methylfluorenone taken, %[b]	4-Methylbenzophenone taken, %	3-Methylfluorenone found, %[c]	4-Methylbenzophenone found, %[d]
1.001	0.428	0.939	0.432
1.014	1.044	.984	1.066
0.985	1.438	.989	1.422
.916	0.094	.993	0.086
.351	.356	.404	.351
1.777	.157	1.726	.156

[a] Using the 3-methylfluorenone peaks at 1723 and 765 cm.$^{-1}$ and the 4-methylbenzophenone peaks at 1668 and 1276 cm.$^{-1}$. [b] Concn. in wt. % in CS_2. [c] Std. dev. 0.063. [d] Std. dev. 0.015.

An ultraviolet spectrophotometric assay was made of several samples of 2-(4′-methylbenzoyl)-benzenediazonium bisulfate and showed that the preparation of pure samples of this diazonium salt was readily reproducible.

COLUMBIA, S. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

The Base-promoted Dehydrohalogenation of *cis*- and *trans*-2-Chlorocycloalkyl Aryl Sulfones[1]

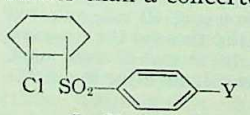
BY HARLAN L. GOERING, DOUGLAS I. RELYEA AND KING L. HOWE[2]

RECEIVED JUNE 29, 1956

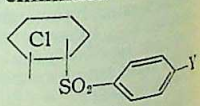
The base-promoted dehydrochlorination of *cis*-(I) and *trans*-2-chlorocyclohexyl aryl sulfones (II), and *cis*-(III) and *trans*-2-chlorocyclopentyl aryl sulfones (IV) in "80%" ethanol has been investigated. Rate constants and activation energies were determined for the least reactive of the four series of compounds, the *trans*-2-chlorocyclohexyl aryl sulfones. The other three series of compounds are too reactive to follow by the sampling technique used in the present work. For these compounds approximate relative reactivities were determined. In each of the four series of chlorocycloalkyl aryl sulfones I–IV, electron-withdrawing substituents in the aryl moiety increase the rate of dehydrochlorination. The following rate sequence for corresponding *p*-substituted 2-chlorocycloalkyl aryl sulfones was observed: *cis*-2-chlorocyclopentyl > *cis*-2-chlorocyclohexyl > *trans*-2-chlorocyclopentyl > *trans*-2-chlorocyclohexyl. The rate of elimination for *trans*-2-chlorocyclohexyl phenyl sulfone is essentially the same as that for *trans*-2-tosyloxycyclohexyl phenyl sulfone. The *trans*-2-chlorosulfones II and IV undergo *cis* elimination, evidently by a two-step process involving abstraction of the C_1-hydrogen followed by conversion of the resulting anion to the elimination product. The first step is rate determining and irreversible under the present conditions (*i.e.*, 80% ethanol containing 0.004 to 0.03 *M* sodium hydroxide). Presumably the *cis*-chlorosulfones I and III undergo a concerted *trans* dehydrohalogenation.

Introduction

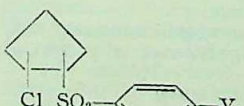
In connection with a study[3,4] of the stereochemistry of radical additions, several *cis*-(I) and *trans*-2-chlorocyclohexyl aryl sulfones (II) and *cis*-(III) and *trans*-2-chlorocyclopentyl aryl sulfones (IV) were prepared. This paper describes the base-promoted dehydrochlorination of these four series of compounds in "80%"[5] ethanol. The effect of the β-sulfone group on the rate of dehydrohalogenation was of interest for comparison with the effect of β-halogen atoms observed in an earlier study.[6] The behavior of the *trans*-2-chlorocycloalkyl aryl sulfones was also of particular interest because of the recent observation by Bordwell and co-workers[7] that in similar systems the β-sulfone group activates the β-hydrogen so that *cis* elimination occurs rather than a concerted *trans* elimination.



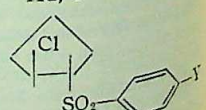
Ia, Y = H
Ib, Y = CH_3
Ic, Y = Cl



IIa, Y = H
IIb, Y = CH_3
IIc, Y = Cl
IId, Y = NO_2



IIIa, Y = H
IIIb, Y = CH_3
IIIc, Y = Cl



IVa, Y = H
IVb, Y = CH_3
IVc, Y = Cl
IVd, Y = NO_2

(1) This work was supported by the United States Air Force through the Office of Scientific Research of the Air Research and Development Command under contract No. AF 18(600) 1037.

(2) Socony–Mobil Fellow, 1955–1956.

(3) H. L. Goering, D. I. Relyea and D. W. Larsen, THIS JOURNAL, 78, 348 (1956).

(4) K. L. Howe and D. I. Relyea, unpublished results.

(5) The solvent was prepared by mixing four volumes of pure ethanol and one volume of water at 25°.

(6) H. L. Goering and H. H. Espy, THIS JOURNAL, 78, 1454 (1956).

(7) (a) J. Weinstock, R. G. Pearson and F. G. Bordwell, *ibid.*, 76, 4748 (1954); 78, 3468 (1956); (b) F. G. Bordwell and R. J.

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Results

The chlorosulfones I-IV were obtained by oxidation (hydrogen peroxide or perbenzoic acid) of the corresponding sulfides. *trans*-2-Chlorocycloalkyl aryl sulfides were prepared by the *trans* addition[3,8] of the appropriate benzenesulfenyl chloride to cyclohexene or cyclopentene. The *cis*-chlorosulfides were obtained by the radical addition of the appropriate thiophenol to 1-chlorocyclohexene or 1-chlorocyclopentene.[3,4] *trans*-2-Tosyloxycyclohexyl phenyl sulfone, which was of interest for comparison of the rate of elimination with that of *trans*-2-chlorocyclohexyl phenyl sulfone, was prepared from the corresponding alcohol which in turn was obtained by oxidation of *trans*-2-hydroxycyclohexyl phenyl sulfide.[3]

The 2-chlorocycloalkyl aryl sulfones I-IV dehydrochlorinate rapidly at 0 to 10° in "80%" ethanol containing 0.004 to 0.03 *M* sodium hydroxide. That the reactions are indeed base-promoted is clear from the fact that the chlorosulfones do not solvolyze to a detectable extent in 24 hours at 25°, whereas in the presence of 0.03 *M* sodium hydroxide the least reactive compounds IIa and IIb are about 50% reacted in 2 hours at 10°.

The chlorosulfones dehydrochlorinate so rapidly that only for the least reactive series of compounds, the *trans*-2-chlorocyclohexyl aryl sulfones (II), could accurate rate constants be determined. The specific second-order rate constants (k) for this series of compounds and for *trans*-2-tosyloxycyclohexyl phenyl sulfone are shown in Table I. The reactions were quenched by rapidly delivering aliquots of reaction mixture into excess acid. The extent of reaction at the time of quenching was determined by either (a) titration with base to determine the amount of base consumed during the reaction (method A) or (b) Volhard titration of chloride ion (method B). The values of k given in Table I are the averages and mean deviations of six to ten values calculated by use of the appropriate equation for a second-order reaction. The reactions were followed to about 80% completion and no trends in k were observed. As shown in Table I, values of k were found to be reproducible.

The remaining three series of compounds (I, III and IV) dehydrochlorinate too rapidly even at 0° to be followed by conventional sampling techniques. Approximate relative reactivities for these compounds at 0° were determined from the lengths of time required for solutions 0.02 *M* in substrate and 0.01 *M* in sodium hydroxide in "80%" ethanol containing brom thymol blue to reach the same color as that of a slightly alkaline buffered solution of the indicator. From the relative reactivities thus obtained, together with the approximate second-order rate constant of 0.35 l. mole^{-1} sec.$^{-1}$ for the dehydrochlorination of *trans*-2-chlorocyclopentyl *p*-chlorophenyl sulfone (IVc) at 0°,[9] the reactivities of I, III and IV relative to *trans*-2-chlorocyclohexyl phenyl sulfone (IIa) can be calculated. The results are presented in Table II. As indicated in Table II, the relative reactivities measured in this way are reproducible to within 10%.

TABLE I

RATES OF SECOND-ORDER ELIMINATION FOR *trans*-2-CHLOROCYCLOHEXYL ARYL SULFONES AND *trans*-2-TOSYLOXYCYCLOHEXYL PHENYL SULFONE IN "80%" ETHANOL

trans-2-Chlorocyclohexyl- sulfone	Method[a]	Temp. °C.	RX 10^3M	NaOH 10^3M	10^3k, l. mole^{-1} sec.$^{-1}$	E_a, kcal.
p-Tolyl		0.0			2.6[b]	16.6
(IIb)	B	8.36	9.8	19.8	6.44 ± 0.02	
	A	19.86	17	28	21.2 ± .3	
	B	20.05	9.9	9.4	21.0 ± .1	
Phenyl		0.0			4.5[b]	15.7
(IIa)	B	8.36	9.5	19.7	10.7 ± 0.2	
	A	9.95	11	13	11.5 ± .3	
	A	9.95	23	25	11.0 ± .2	
	A	19.86	16	27	34.3 ± 1.2	
	B	20.05	9.3	9.5	32.8 ± 0.1	
p-Chloro-		0.0			10.1[b]	16.5
phenyl	A	1.35	16	27	11.0 ± 0.1	
(IIc)	A	1.35	15	29	10.9 ± .2	
	B	8.36	9.5	9.6	24.7 ± .4	
	A	9.95	12	8.1	25.3 ± 1.2	
	A	9.95	11	24	25.8 ± 2.0	
	B	20.05	10	8.8	79.4 ± 0.8	
	B	20.05	6.3	9.4	81.0 ± 0.7	
p-Nitro-		0.0			57.7[b]	15.4
phenyl	B	8.36	4.5	4.6	134 ± 3	
(IId)	B	8.36	4.4	9.5	134 ± 2	
	B	20.05	3.0	3.6	401 ± 12	
	B	20.05	4.9	5.1	404 ± 10	
trans-2-		0.0			3.7[b]	
Tosyloxy-	A	1.35	7.5	18	4.5 ± 0.4	
cyclo-	A	1.35	4.3	18	5.0 ± .5	
hexyl	A	9.95	4.4	18	14.6 ± .3	
phenyl	A	9.95	5.5	18	14.7 ± .7	
sulfone						

[a] Method A, reaction followed by determination of amount of base consumed; method B, reaction followed by determination of amount of chloride ion produced. [b] Determined by extrapolation.

TABLE II

APPROXIMATE RELATIVE REACTIVITIES OF BASE-PROMOTED DEHYDROCHLORINATION OF *cis*-2-CHLOROCYCLOHEXYL ARYL SULFONES (I) AND *cis*- (III) AND *trans*-2-CHLOROCYCLOPENTYL ARYL SULFONES (IV) IN "80%" ETHANOL AT 0°

Compound	Rel. rate
trans-2-Chlorocyclohexyl phenyl sulfone (IIb)	1
cis-2-Chlorocyclohexyl aryl sulfones	
p-Tolyl (Ib)	280
Phenyl (Ia)	490[a]
p-Chlorophenyl (Ic)	1600
trans-2-Chlorocyclopentyl aryl sulfones	
p-Tolyl (IVb)	21
Phenyl (IVa)	31
p-Chlorophenyl (IVc)	78
p-Nitrophenyl (IVd)	550
cis-2-Chlorocyclopentyl aryl sulfones	
p-Tolyl (IIIb)	760
Phenyl (IIIa)	1200[a]
p-Chlorophenyl (IIIc)	3700[a]

[a] This value is the average of two independent experiments which differed by the following percentage: Ia, 4%; IIIa, 8%; IIIc, 8%.

Kern, THIS JOURNAL, **77**, 1141 (1955); (c) F. G. Bordwell and M. L. Peterson, *ibid.*, **77**, 1145 (1955).

(5) A. J. Havlik and N. Kharasch, *ibid.*, **78**, 1207 (1956).

(6) Dr. Robert Jagow, University of Wisconsin, unpublished results.

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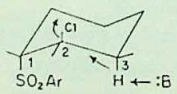
As shown in Table I electron-withdrawing substituents in the aryl moiety of *trans*-2-chlorocyclohexyl aryl sulfone (II) increase the rate of base-promoted dehydrochlorination. The kinetic data for the four members of this series give an excellent fit with the Hammett equation[10] and ρ at 0° is 1.42 ± 0.01. The data in Table II show that ρ is also positive for *cis*-2-chlorocyclohexyl aryl sulfone (I) and *cis*-(III) and *trans*-2-chlorocyclopentyl aryl sulfone (IV).

Discussion

In both the *cis* and *trans* isomers the β-sulfone group has a large accelerating effect on the rate of the base-promoted dehydrohalogenation. For example, *trans*-2-chlorocyclohexyl *p*-tolyl sulfone (IIb), the least reactive member of the least reactive series, is about 10^6 times as reactive as cyclohexyl chloride.[11] *cis*-2-Chlorocyclohexyl phenyl sulfone is about 10^9 times as reactive as cyclohexyl chloride.

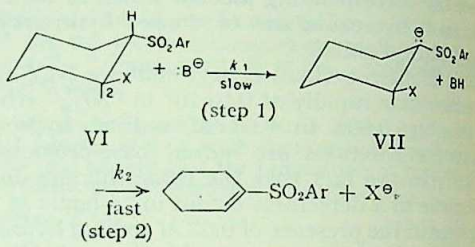
From the much greater reactivities of the *trans*-chlorosulfones than of cyclohexyl chloride it is apparent that a *cis* dehydrohalogenation is involved. Clearly the sulfone group in II could not accelerate a concerted *trans* elimination involving the C_3-hydrogen (V) or an S$_N$2 displacement (at C_2) by a factor of 10^6. In fact the sulfone group would be expected to retard the rates of these processes. The axial conformation (with chlorine in an axial position) is required for a concerted E2 elimination[6,12] and preferred for an S$_N$2 displacement.[13] Not only would the sulfone group tend to shift the conformational equilibrium toward the equatorial form (as compared to the conformational equilibrium for cyclohexyl chloride) which would retard the rate,[14] but in addition the axial sulfone group in the reactive conformation would retard both of these processes by shielding the C_3-axial hydrogen and the back side of C_2. The *cis* dehydrohalogenation of the *trans*-2-chlorocycloalkyl sulfones is not surprising and in fact would be expected in view of the observations by Bordwell, *et al.*,[7] that *cis* elimination is more rapid than *trans* if the *cis*-β-hydrogen is activated by a sulfone or similar group.



V

The most informative observation concerning the mechanism of the *cis* elimination is the nearly identical rates of elimination for *trans*-2-chlorocyclohexyl phenyl sulfone (IIa) and *trans*-2-tosyloxycyclohexyl phenyl sulfone (VI, X = $OSO_2C_6H_4CH_3$). Ordinarily, *p*-toluenesulfonates are much more reactive than the corresponding chlorides for second-order elimination reactions; *e.g.*, cyclohexyl *p*-toluenesulfonate[14] reacts with base—presumably the main reaction is an E2 elimination—more rapidly than cyclohexyl chloride[15] in absolute ethanol (75°) by a factor of 180.

The similar rates for IIa and the corresponding *p*-toluenesulfonate, the high reactivity of IIa and the effect of substituents on the rate are consistent with the two-step process illustrated below. This mechanism, which involves the removal of the β-proton by lyate ion ($:B^{\ominus}$) followed by conversion of the anion VII to product, has previously been suggested[16] for the dehydrohalogenation of β-benzene hexachloride.



Although certain details of this mechanism are not known, *e.g.*, the reactive conformation of the anion VII, etc., the present data show that step 1 is rate-determining and irreversible. Thus the second-order constants in Table I correspond to k_1 in step 1. Presumably the *trans*-2-chlorocyclopentyl aryl sulfones, which obviously undergo a *cis*-elimination, also react by this so-called E1cB[17] mechanism.

It is clear from the present and earlier[7] studies that in systems such as II, IV and VI, the β-sulfone group increases the acidity of the C_1-hydrogen (or in other words stabilizes the anion VII)[17] so that *trans* elimination does not compete with proton abstraction (step 1). It is interesting to note that a *trans*-β-halogen atom does not activate the *cis*-hydrogen atom sufficiently for *cis* elimination to be important as compared to *trans* elimination, *e.g.*, *trans*-1,2-dihalocyclohexanes give primarily 3-halocyclohexene as the initial product.[6] In systems where *trans* elimination is not possible (*e.g.*, β-benzene hexachloride) β-halogen atoms are sufficiently activating so that *cis* dehydrochlorination can be realized.[16] The latter observation, together with the fact that under certain conditions *trans*-1,2-dihalocyclohexanes give some 1-halocyclohexene[6,7] indicates that a *trans*-β-halogen is almost sufficiently activating for proton abstraction (*cis* elimination) to compete with the E2 reaction. This suggests that in the cyclohexyl system *cis* dehydrohalogenation will predominate if a *trans* substituent is present with a larger electron-withdrawing effect than that of a halogen atom.

The almost identical rates for IIa and the corresponding *p*-toluenesulfonate show that the leaving group is not involved in the rate-limiting step. This also shows that step 1 is irreversible. Undoubtedly k_2 in step 2 is larger for the *p*-toluene-

(10) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapt. VII.

(11) Extrapolation of the second-order rate constants for the dehydrohalogenation of cyclohexyl chloride in "80%" ethanol at 80 and 100° (ref. 6) gives a value of 5×10^{-9} *l. mole*$^{-1}$ sec.$^{-1}$ for 10°.

(12) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, Chapt. VIII.

(13) E. L. Eliel and R. S. Ro, *Chemistry & Industry*, 251 (1956).

(14) S. Winstein and N. J. Holness, THIS JOURNAL, 77, 5562 (1955).

(15) E. D. Hughes, C. K. Ingold and J. B. Rose, *J. Chem. Soc.*, 3839 (1953).

(16) S. J. Cristol, THIS JOURNAL, 69, 338 (1947); (b) S. J. Cristol, N. L. Hause and J. S. Meek, *ibid.*, 73, 674 (1951); (c) S. J. Cristol and D. D. Fix, *ibid.*, 75, 2647 (1953).

(17) C. K. Ingold, S. Weaver and L. K. Levy, *ibid.*, 77, 509 (1955).

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TABLE III

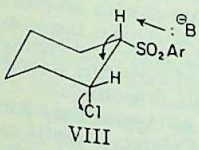
PHYSICAL PROPERTIES AND ANALYTICAL DATA FOR *trans*-2-CHLOROCYCLOPENTYL AND *trans*-2-CHLOROCYCLOHEXYL ARYL SULFIDES

2-Chlorocyclo sulfide	B.p. °C.	Mm.	$n^{25}D$	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Pentyl *p*-tolyl	122–123	0.1	1.5711	$C_{12}H_{15}ClS$	63.56	63.53	6.67	6.58
Pentyl phenyl	102–103	.5	1.5783	$C_{11}H_{13}ClS$	62.10	62.33	6.16	6.34
Pentyl *p*-chlorophenyl	125–126	.1	1.5894	$C_{11}H_{12}Cl_2S$	53.45	53.21	4.90	4.70
Pentyl *p*-nitrophenyl	51.8–52.8 (m.p.)			$C_{11}H_{12}ClNO_2S$	53.03	53.15	5.19	5.28
Hexyl *p*-tolyl	155–157	.3	1.5736	$C_{13}H_{17}ClS$	64.84	64.75	7.11	6.91
Hexyl *p*-chlorophenyl	160–162	.3	1.5890	$C_{12}H_{14}Cl_2S$	55.18	55.40	5.40	5.16
Hexyl *p*-nitrophenyl	64.4–65.6 (m.p.)			$C_{12}H_{14}ClNO_2S$	51.27	51.70	4.70	4.76

sulfonate than for the chloride by a factor of about 200. Thus if step 1 were reversible, step 2 would be in competition with this reverse reaction and the *p*-toluenesulfonate would undergo elimination faster than the chloride.

The observation that the first step in the *cis* elimination is irreversible in the present case suggests that the absence of deuterium exchange[18] does not necessarily rule out the possibility of a carbanion intermediate.[18] This observation also parallels that of Cristol and Fix[16c] that in the *cis* dehydrochlorination of benzene hexachloride, presumably by a two-step process similar to the one shown above, step 2 is 150 times as fast as the reverse of step 1.

Evidently the *cis*-chlorosulfones react by a concerted *trans* (E2) elimination (VIII). In the cyclohexyl system the *cis*-chlorosulfones are more reactive than the corresponding *trans* isomers by factors of 400 to 500. For the cyclopentyl system the factors are smaller, the *cis* isomers being more reactive than the corresponding *trans* isomers by factors of 40 to 50.



VIII

The large effect of the sulfone group in VIII on the rate of dehydrohalogenation is illustrated by comparing the rates for the *cis*-chlorosulfones I (Table II) with that for cyclohexyl chloride.[11] This comparison shows that the *trans* elimination in VIII is about 10^9 times faster than it would be if the sulfone group were replaced by hydrogen. The equatorial sulfone group in VIII has a considerably larger effect than a similarly located halogen atom; *cis*-1,2-dichlorocyclohexane dehydrohalogenates (to give 1-chlorocyclohexene) about 100 times faster than cyclohexyl chloride.[6] It is interesting to note that substituents in the aryl moiety have about the same effect in all four series of compounds.

Experimental

trans-2-Chlorocyclopentyl and *trans*-2-Chlorocyclohexyl Aryl Sulfides.—These series of compounds were prepared by the *trans* addition[3,5] of the corresponding sulfenyl chlorides to cyclopentene[19] and cyclohexene according to the general method of Lecher and Stocklin.[20] Benzene-, *p*-toluene- and *p*-chlorobenzenesulfenyl chloride were prepared by chlorinolysis of the corresponding thiophenols.[21] *p*-Nitrobenzenesulfenyl chloride was prepared by the chlorinolysis of 4,4′-dinitrodiphenyl disulfide.[22] The preparation of *trans*-2-chlorocyclohexyl phenyl sulfide was described in an earlier paper.[3] The properties of the *trans*-2-chlorocycloalkyl aryl sulfides prepared by this procedure are shown in Table III.

cis-2-Chlorocyclopentyl and *cis*-2-Chlorocyclohexyl Aryl Sulfides.—These series of compounds were prepared by the radical (photoinitiated) addition[3] of the corresponding thiophenol to 1-chlorocyclopentene[23] and 1-chlorocyclohexene,[3] according to the method described below for the preparation of *cis*-2-chlorocyclohexyl phenyl sulfide. A mixture of 77 g. (0.70 mole) of thiophenol (Eastman Kodak Co. White Label, redistilled) and 81.5 g. (0.70 mole) of 1-chlorocyclohexene in a Vycor flask was stirred for 10 days. During this period the solution was kept under nitrogen and irradiated with a Hanovia (type S100) mercury arc lamp placed 10 cm. from the reaction flask. Distillation of the reaction mixture gave 78 g. (49%) of crude ***cis*-2-chlorocyclohexyl phenyl sulfide**, b.p. 121–125° (0.5 mm.), $n^{25}D$ 1.5838, which solidified almost completely. After recrystallization from hexane the product melted at 38–39°.[24]

Anal. Calcd. for $C_{12}H_{15}ClS$: C, 63.56; H, 6.67. Found: C, 63.79; H, 6.78.

cis-2-Chlorocyclohexyl *p*-tolyl sulfide and *cis*-2-chlorocyclohexyl *p*-chlorophenyl sulfide were prepared in the same manner. In each case the crude reaction product, *i.e.*, product containing diaryl disulfide, was used for the preparation of the sulfones. The chlorosulfides were separated from the disulfide by chromatography using a column packed with Alcoa F-20 activated alumina. Pentane solutions of the crude products were passed through the column and the material was eluted with *n*-pentane. In each case the diaryl disulfide was eluted first and the disulfide was cleanly separated from the chlorosulfide.

The solid ***cis*-2-chlorocyclohexyl *p*-tolyl sulfide** remaining after evaporation of the pentane, melted at 34–35° (pentane).

Anal. Calcd. for $C_{13}H_{17}ClS$: C, 64.84; H, 7.11. Found: C, 65.23; H, 7.23.

Pure ***cis*-2-chlorocyclohexyl *p*-chlorophenyl sulfide**, m.p. 34.5–35.0° (pentane), was obtained in a similar manner.

Anal. Calcd. for $C_{12}H_{14}Cl_2S$: C, 55.18; H, 5.40. Found: C, 55.14; H, 5.62.

(15) See P. S. Skell and C. R. Hauser, THIS JOURNAL, **67**, 1661 (1945); D. G. Hill, B. Stewart, S. W. Kantor, W. A. Judge and C. R. Hauser, *ibid.*, **76**, 5129 (1954); see also ref. 16c.

(16) B. B. Corson and V. N. Ipatieff, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 157.

(20) H. Lecher and P. Stocklin, *Ber.*, **58**, 414 (1925).

(21) H. Lecher, *ibid.*, **58**, 409 (1925).

(22) M. T. Bogert and A. Stull, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1941, p. 220.

(23) 1-Chlorocyclopentene, b.p. 103.0–103.5°, $n^{25}D$ 1.4364, was prepared according to the method of E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 1755 (1951). Contrary to the report of these workers, this product was found to be unreactive toward aqueous alcoholic silver nitrate.

(24) The liquid sample of *cis*-2-chlorocyclohexyl phenyl sulfide described in reference 3, prepared by irradiation with a specially constructed high-intensity Hanovia lamp (type SC-2537) which was in contact with the reaction mixture, has been found to contain significant amounts of diphenyl disulfide. In the present work it has been found that less intense irradiation, *e.g.*, a Hanovia (type 30600) lamp placed 10 cm. or more from the reaction mixture, reduces considerably the formation of disulfide formed in the addition of thiophenol, *p*-thiocresol and *p*-chlorothiophenol.

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TABLE IV

PHYSICAL PROPERTIES AND ANALYTICAL DATA FOR 2-CHLOROCYCLOALKYL ARYL SULFONES

2-Chlorocyclosulfone	Method of prepn.[a]	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
			A. *Trans* series				
Pentyl *p*-tolyl	B	46.4–48.4	$C_{12}H_{15}O_2ClS$	55.70	55.68	5.84	5.71
Pentyl phenyl	B	84.2–84.8	$C_{11}H_{13}O_2ClS$	53.98	54.45	5.35	5.61
Pentyl *p*-chlorophenyl	B	59.0–59.8	$C_{11}H_{12}O_2Cl_2S$	47.33	47.48	4.33	4.12
Pentyl *p*-nitrophenyl	B	96.8–97.6	$C_{11}H_{12}O_4ClNS$	45.60	45.73	4.17	4.15
Hexyl *p*-tolyl	A	43.2–44.2	$C_{13}H_{17}O_2ClS$	57.23	57.24	6.28	6.21
Hexyl *p*-chlorophenyl	A	74.0–74.6	$C_{12}H_{14}O_2Cl_2S$	49.15	49.56	4.81	4.57
Hexyl *p*-nitrophenyl	A	142.0–142.8	$C_{12}H_{14}O_4NClS$	47.45	47.81	4.65	4.56
			B. *Cis* series				
Pentyl *p*-tolyl	A	95.9–96.5	$C_{12}H_{15}O_2ClS$	55.70	55.82	5.84	5.94
Pentyl phenyl	A	94.6–95.3	$C_{11}H_{13}O_2ClS$	53.98	53.88	5.35	5.24
Pentyl *p*-chlorophenyl	A	95.4–96.2	$C_{11}H_{12}O_2Cl_2S$	47.33	47.32	4.33	4.09
Hexyl *p*-tolyl	A	74.5–75.0	$C_{13}H_{17}O_2ClS$	57.23	56.79	6.28	6.03
Hexyl *p*-chlorophenyl	A	135.7–136.2	$C_{12}H_{14}O_2Cl_2S$	49.15	49.08	4.81	4.88

[a] A = oxidation of sulfide with 30% hydrogen peroxide in acetic acid; recrystallization from acetic acid–water (2:1). B = Oxidation of sulfide with perbenzoic acid in chloroform; recrystallization from chloroform–hexane (1:9).

The *cis*-2-chlorocyclopentyl aryl sulfides were prepared in the same way.[4] These samples, which contained about 10% of the corresponding diaryl disulfides, were not purified further but were converted directly to the corresponding sulfones.

Conversion of Sulfides to Sulfones.—The *cis*- and *trans*-2-chlorocycloalkyl aryl sulfides were converted to the corresponding sulfones by oxidation with hydrogen peroxide in acetic acid[25] or perbenzoic acid in chloroform.[26] The properties of the sulfones, with the exception of *cis*- and *trans*-2-chlorocyclohexyl phenyl sulfone which were reported previously,[3] are shown in Table IV together with the analytical data.

***trans*-2-Tosyloxycyclohexyl Phenyl Sulfone.**—*trans*-2-Hydroxycyclohexyl phenyl sulfide[3] was oxidized with hydrogen peroxide in acetic acid (see above) to ***trans*-2-hydroxycyclohexyl phenyl sulfone**, m.p. 102–103° (aqueous acetic acid).

Anal. Calcd. for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71. Found: C, 59.72; H, 6.86.

A solution of 14.40 g. (0.060 mole) of *trans*-2-hydroxycyclohexyl phenyl sulfone in 60 ml. of dry pyridine was treated with 19.06 g. (0.100 mole) of *p*-toluenesulfonyl chloride. After standing for one week at room temperature the reaction mixture was decanted from the pyridine hydrochloride and the excess *p*-toluenesulfonyl chloride was hydrolyzed by addition of 20 ml. of water in small portions. The solution was poured into cold water and the mixture extracted with chloroform. The combined chloroform extracts were washed with 20% sulfuric acid and dried over sodium sulfate. Evaporation of the chloroform left 15 g. (63%) of light yellow solid, m.p. 115–116°. Recrystallization from acetone–pentane (15:85) gave pure *trans*-2-tosyloxycyclohexyl phenyl sulfone as white needles, m.p. 119.0–119.5°.

Anal. Calcd. for $C_{19}H_{22}O_6S_2$: C, 57.85; H, 5.62. Found: C, 58.13; H, 5.65.

Kinetic Experiments. Method A.—This method was used for determining the rates of elimination of the *trans*-2-chlorocyclohexyl aryl sulfones and *trans*-2-tosyloxycyclohexyl phenyl sulfone. A typical experiment was carried out as follows. A solution of an accurately weighed 0.6-g. sample of IIa in 75 ml. of "80%" ethanol[5] was thermostated at 9.95°. At zero time 50 ml. of 0.07305 *M* sodium hydroxide in "80%" ethanol (previously thermostated at 9.95°) was added and the resulting solution was rapidly and thoroughly agitated by swirling the reaction vessel in the thermostat. At appropriate time intervals (*ca.* every 10% reaction to 80% completion) 10-ml. aliquots were withdrawn and rapidly delivered into 5 ml. of 0.06041 *M* hydrochloric acid to stop the reaction. The percentage reaction at the time of sampling was determined by titration of the excess acid to the brom thymol blue end-point with 0.05594 *M* sodium methoxide in methanol. Specific second-order rate constants were calculated by use of the appropriate equation. Seven to ten values were determined for each kinetic experiment and the averages of these, together with the mean deviations, are given in Table I.

Method B.—In this method, the reaction was followed by titration of chloride ion. In a typical experiment, 0.37 g. of IIb in 75 ml. of "80%" ethanol was thermostated at 8.36°; 50 ml. of 0.02535 *N* sodium hydroxide in "80%" ethanol was weighed and thermostated in a tared stoppered flask. At zero time, the sodium hydroxide solution was quickly poured (in 1–2 seconds) into the flask containing the solution of sulfone and mixed thoroughly by swirling. The exact amount of sodium hydroxide solution used was determined by weighing the empty flask after the transfer. At appropriate time intervals, 10-ml. aliquots were withdrawn and rapidly delivered into 5 ml. of 3 *M* nitric acid at 0° to quench the reaction. The automatic pipet used for this purpose was wrapped with asbestos and kept in a large test-tube immersed in the thermostat. The amount of chloride ion in the nitric acid solution was determined by the Volhard method using 0.02 *M* standard silver nitrate and potassium thiocyanate solutions.

Determination of Approximate Relative Reactivities of *cis*- and *trans*-2-Chlorocyclopentyl and *cis*-2-Chlorocyclohexyl Aryl Sulfone.—The dehydrochlorinations of these chlorosulfones were too fast to follow by the method described above. Approximate relative reactivities for these compounds at 0° were determined from the relative lengths of time required for solutions 0.02 *M* in substrate and 0.00845 *N* in sodium hydroxide in "80%" ethanol containing brom thymol blue to reach the same color as that of a slightly alkaline buffer solution containing the indicator. The buffer solution was prepared by mixing 9 ml. of 0.1 *N* sodium hydroxide, 10 ml. of 0.1 *M* potassium dihydrogen phosphate, 1 ml. of water and 20 ml. of absolute ethanol; 15 ml. was then placed in an 8″ × 1.25″ test-tube and 2 drops of 0.05% brom thymol blue indicator (in ethanol) was added to give a bluish-green reference color. In a typical experiment a solution of 0.0777 g. (0.300 mmole) of *cis*-2-chlorocyclohexyl phenyl sulfone in 10.00 ml. of "80%" ethanol was prepared in an 8″ × 1.25″ test-tube and 2 drops of 0.05% brom thymol blue indicator was added and the solution thermostated at 0°. At zero time, 5 ml. of 0.02535 *M* sodium hydroxide in "80%" ethanol, previously thermostated at 0°, was added with an automatic pipet. The automatic pipet used for this purpose was wrapped with asbestos and stored in a large test-tube immersed in ice. The test-tube was tightly stoppered and swirled. The color of the solution gradually changed from a rich blue to green, and finally to yellow. The time at which the color of the solution first became indistinguishable from the bluish-green color of the reference buffer solution was found to be 12±3 seconds.

(25) H. Gilman and H. S. Broadbent, THIS JOURNAL, **69**, 2056 (1947).

(26) L. N. Lewin, *J. prakt. Chem.*, [2] **71**, 494 (1905); Beilstein, **6**, 221.

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May 20, 1957

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

A New Synthesis of α-Nitroesters[1,2]

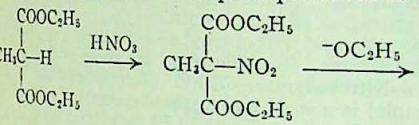
BY NATHAN KORNBLUM, ROBERT K. BLACKWOOD AND JACK W. POWERS

RECEIVED SEPTEMBER 17, 1956

A simple new synthesis of α-nitroesters which involves treating α-haloesters with sodium nitrite in the presence of phloroglucinol is described; 66 to 91% yields of pure α-nitroesters are obtained.

While α-nitroesters have been prepared on a number of occasions, none of the methods employed can be characterized as genuinely useful.[3] For example, while the reaction of α-iodoesters with silver nitrite gives 77–84% yields of α-nitroesters,[4] it suffers from important drawbacks. The readily available α-bromoesters react so slowly that they cannot be used and, so, must first be converted to α-iodoesters. Even with α-iodoesters the reaction is so slow, despite the use of a 100% excess of silver nitrite, as to be impractical for the preparation of any but low molecular weight, straight chain, α-nitroesters.[4]

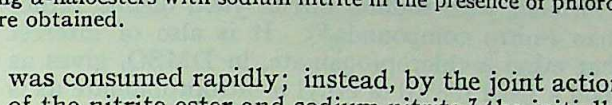
Nitration of malonic esters and subsequent alkaline degradation as, for example, in eq. 1 has been used, but the isolation of pure products is difficult



$$CH_3\overset{\displaystyle -}{C}(COOC_2H_5)_2\text{—}NO_2 + (C_2H_5O)_2CO \quad (1)$$

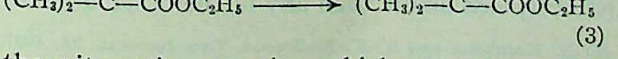
and the yields are low (15–22%).[5]

As pointed out previously[6] the reaction of organic halides with sodium nitrite requires a solvent which will dissolve both reactants; this immediately rules out most common solvents. Dimethylformamide (DMF) not only has the requisite solvent properties but, in addition, the reaction in this medium is very rapid so that processes which destroy the initially produced nitroparaffin and alkyl nitrite do not have a chance to intrude.[6,7] When, however, an attempt was made to carry out the reaction of equation 2, none of the α-nitroester could be isolated even though the α-bromoester was consumed rapidly; instead, by the joint action of the nitrite ester and sodium nitrite,[7] the initially produced α-nitroester was very quickly converted into the α-oximinoester.



$$RCHCOOC_2H_5 \xrightarrow[DMF]{NaNO_2} RCHCOOC_2H_5 + RCHCOOC_2H_5 \quad (2)$$
(Br) (NO₂) (ONO)

It transpires, however, that simply by adding phloroglucinol to the reaction mixture the formation of oximinoesters is prevented and pure α-nitroesters are obtained in excellent yields (Table I). The phloroglucinol functions as a scavenger for nitrite esters and is especially effective for this purpose. That this attribute of phloroglucinol is involved is shown by the production of ethyl α-nitroisobutyrate in 78–91% yields without phloroglucinol being present (eq. 3). Here the α-nitroester being devoid of α-hydrogen cannot undergo



$$(CH_3)_2\text{—}C(Br)\text{—}COOC_2H_5 \xrightarrow{NaNO_2} (CH_3)_2\text{—}C(NO_2)\text{—}COOC_2H_5 \quad (3)$$

the nitrosation reaction which converts α-nitroesters to α-oximinoesters.[7]

It also has been found that the reaction can be conducted in dimethyl sulfoxide (DMSO); in fact, DMSO is somewhat superior to DMF in the α-nitroester synthesis (*cf.* Table I). This superiority appears to derive principally from the distinctly greater solubility of sodium nitrite in DMSO; less solvent is needed and shorter reaction times are required.[8]

TABLE I

SYNTHESIS OF α-NITROESTERS FROM α-BROMOESTERS

Ethyl α-nitroester	Reaction time,[c] hr. In DMSO	Reaction time,[c] hr. In DMF	Yield, % In DMSO	Yield, % In DMF
Propionate[a]	1.5	2	66	62
Butyrate	1.5	2.5	83	70–75
Valerate	1.5	...	87	..
Caproate	1	5	76	74
Isobutyrate[b]	5	44	91	78
Isovalerate	75	150	75	67
α-Phenyl-α-nitroacetate	..	2.5	..	70

[a] From ethyl α-chloropropionate a 68% yield of ethyl α-nitropropionate was obtained (solvent DMSO; reaction time 48 hr.). A run employing ethyl α-iodopropionate in DMF gave a 62% yield of ethyl α-nitropropionate after 2 hr. [b] No phloroglucinol employed. [c] DMF solutions *ca.* 0.5 molar in RBr and *ca.* 0.8 molar in $NaNO_2$. DMSO solutions *ca.* 1.2 molar in RBr and *ca.* 2 molar in $NaNO_2$.

(1) Paper XVI in the Series "The Chemistry of Aliphatic and Alicyclic Nitro Compounds." A preliminary account of this work appeared in *Chemistry & Industry*, 443 (1955).

(2) This research was supported, in part, by grants from The Explosives Department of E. I. du Pont de Nemours and Co. and, in part, by the United States Air Force under Contract No. AF18(600)-310 monitored by the Office of Scientific Research, Air Research and Development Command.

(3) For a complete review see the Ph.D. thesis of J. H. Eicher, Purdue University, 1952.

(4) N. Kornblum, M. E. Chalmers and R. Daniels, THIS JOURNAL, **77**, 6654 (1955).

(5) C. Ulpiani, *Gazz. chim. ital.*, **35**, I, 273 (1905); W. Steinkopf and A. Supan, *Ber.*, **43**, 3246 (1910); A. K. MacBeth and D. Traill, *J. Chem. Soc.*, **127**, 892 (1925); N. Kornblum and J. H. Eicher, THIS JOURNAL, **78**, 1496 (1956). Subsequent to our preliminary communication,[1] W. D. Emmons and J. P. Freeman [THIS JOURNAL, **77**, 4291 (1955)] described a modification of the Ulpiani procedure which, while an improvement, remains much inferior to the synthesis of α-nitroesters from α-bromoesters and sodium nitrite.

(6) N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto and G. E. Graham, THIS JOURNAL, **78**, 1497 (1956).

(7) N. Kornblum, R. K. Blackwood and D. D. Mooberry, *ibid.*, **78**, 1501 (1956).

(8) A rough rate study made using ethyl α-bromobutyrate shows that the reaction with sodium nitrite occurs at essentially the same rate in DMSO and in DMF (25°); *cf.* Experimental.

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Irrespective of whether DMSO or DMF is used, the reaction of α-haloesters with sodium nitrite is carried out at room temperature and, as the data of Table I show, it makes readily available a wide variety of α-nitroesters. Especially noteworthy is the preparation, in excellent yield, of ethyl α-nitroisobutyrate (eq. 3), since *t*-alkyl halides on treatment with sodium nitrite yield olefins rather than *t*-nitro compounds.[6,9] It is also of interest that ethyl α-chloropropionate, in DMSO, gives as good a yield (68%) of ethyl α-nitropropionate as is obtained from the α-bromoester.[10]

In only one instance does the new α-nitroester synthesis fail. If ethyl bromoacetate is treated with sodium nitrite in the usual way, a very rapid reaction ensues, but no ethyl nitroacetate can be isolated.[11]

α-Nitroesters possessing an α-hydrogen are relatively strong acids. They dissolve slowly in aqueous sodium bicarbonate, the rate of solution being a function of the molecular weight of the ester; in aqueous sodium carbonate they dissolve after a few minutes and, with 10% aqueous sodium hydroxide, they go into solution almost instantaneously. From the salts the α-nitroesters are readily regenerated (at least from sodium carbonate solution) by aqueous acetic acid and urea.[12]

Table II shows the apparent pK_A values of several α-nitroesters and nitroparaffins in 50% aqueous ethanol.[13]

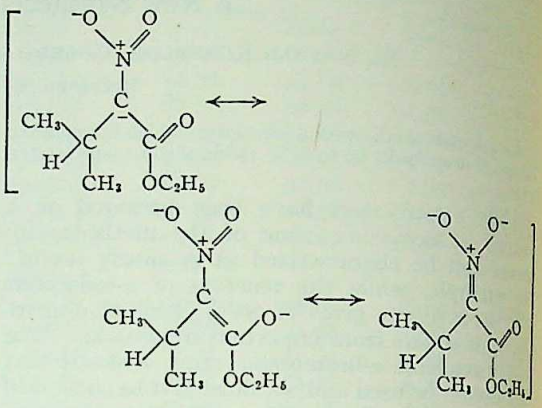
TABLE II

APPARENT pK_A VALUES IN 50% AQUEOUS ETHANOL

Compound	Apparent pK_A
Ethyl α-nitropropionate	7.5
Ethyl α-nitrobutyrate	7.6
Ethyl α-nitrocaproate	7.7
Ethyl α-nitroisovalerate	9.0
Ethyl α-nitro-α-phenylacetate	6.9
1-Nitrobutane	10
2-Nitrobutane	9.4
Phenylnitromethane	8.2
Benzoic acid	5.7[a]

[a] F. G. Bordwell and G. D. Cooper, THIS JOURNAL, 74, 1058 (1952), report an apparent pK_A of 5.73.

Straight chain, secondary α-nitroesters are about 100 times stronger acids than 2-nitrobutane. It is also noteworthy that ethyl α-nitroisovalerate is distinctly less acidic than any of the other α-nitroesters. This may well be a case of steric inhibition of resonance.



Experimental

Reagents.[14]—N,N-Dimethylformamide (DMF, du Pont technical grade), phloroglucinol dihydrate (Ringwood technical grade) and dimethyl sulfoxide (DMSO, Stepan Chemical Co.) were used as received.[15] The α-bromoesters were commercial products which were rectified and only material of constant b.p. and $n^{20}D$ was used. Ethyl α-bromo-α-phenylacetate ($n^{20}D$ 1.5360) was specially prepared by Fairfield Laboratories. Sodium nitrite was an analytical grade.

The preparation of ethyl α-nitrobutyrate exemplifies the DMF procedure and that of ethyl α-nitrovalerate typifies the DMSO procedure. Reaction times are given in Table I.

Ethyl α-Nitrobutyrate.—Ethyl α-bromobutyrate (58.5 g., 0.30 mole) is poured into a stirred mixture of 600 ml. of DMF, 36 g. of sodium nitrite (0.52 mole) and 40 g. (0.32 mole) of anhydrous phloroglucinol (or 52 g. of phloroglucinol dihydrate; *cf.* footnote 15) in a 1-l. three-necked flask equipped with a sealed stirrer. The flask is stoppered, immersed in a water-bath maintained at room temperature, and stirring is continued for 2.5 hr. The reaction mixture is then poured into 1.2 l. of ice-water layered over with 300 ml. of diethyl ether. After separation of the upper layer, the aqueous phase is extracted four more times with 100-ml. portions of ether. The combined extracts are washed with four 100-ml. portions of water and then dried over anhydrous magnesium sulfate. The mixture is filtered with suction, the magnesium sulfate is washed with four 25-ml. portions of ether and these are combined with the filtrate. Using a small column, the ether is removed under reduced pressure, heat being supplied by a bath whose temperature is gradually raised to *ca.* 60°. The residual yellow liquid is transferred to a 100-ml. flask, the column is attached and the remaining solvent is removed under reduced pressure. Rectification of the residue yields 2–3 g. of forerun in the range 33–71° (1 mm.) which is followed by 34–36 g. (70–75%) of colorless ethyl α-nitrobutyrate (b.p. 71° (1 mm.), $n^{20}D$ 1.4233).

In the preparation of ethyl α-nitro-α-phenylacetate, the procedure was modified in that the crude product was not rectified; instead it was dissolved in aqueous sodium carbonate, regenerated with aqueous acetic acid and urea[12] and, finally, distilled.

The reaction is not critically dependent on conditions. Thus, using ethyl α-bromopropionate, the same yield of ethyl α-nitropropionate was obtained at 0° and at 25°.

(9) N. Kornblum and R. K. Blackwood, THIS JOURNAL, 78, 4037 (1956).

(10) It is probable that α-chloroesters in DMF will also give excellent yields of α-nitroesters despite the somewhat longer reaction times which will be required.

(11) Precisely what happens has yet to be determined. Even lowering the reaction temp. to −20°, a device which is successful in the preparation of phenylnitromethane from benzyl bromide (ref. 6), fails to produce a trace of ethyl nitroacetate [W. M. Weaver, unpublished work].

(12) N. Kornblum and G. E. Graham, THIS JOURNAL, 73, 4041 (1951).

(13) The apparent pK_A values in Table II are *ca.* 1.5 units higher than pK_A's determined in water. Thus, in water, benzoic acid has pK_A 4.20 [R. A. Benkeser and H. R. Krysiak, THIS JOURNAL, 75, 2424 (1953)]; *cf.* also G. W. Wheland and J. Farr, *ibid.*, 65, 1433 (1943).

(14) We thank the du Pont Co., the Ringwood Chemical Corporation and the Stepan Chemical Co. for generous gifts of DMF, phloroglucinol and DMSO, respectively.

(15) With ethyl α-nitrobutyrate, ethyl α-nitrovalerate and ethyl α-nitrocaproate, the yields were not altered (*cf.* Table I) by using phloroglucinol rendered anhydrous by heating for 3 hr. at 110° and DMSO which had been dried by standing over calcium hydride for several days. As regards reactions conducted in DMF, while all but one of the preparations summarized in Table I were carried out with anhydrous phloroglucinol, it is extremely probable that phloroglucinol dihydrate is equally effective. In experiments using ethyl α-bromopropionate and ethyl α-iodopropionate, phloroglucinol dihydrate gave 60–62% yields of ethyl α-nitropropionate, whereas with anhydrous phloroglucinol the yields were 62%.

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May 20, 1957

Extension of the reaction time at 25° from 2 hr. to 17 hr. gave no loss in yield.

In reactions employing ethyl α-bromopropionate and ethyl α-iodopropionate, the use of half the amount of anhydrous phloroglucinol (20 g.) gave only 3 to 5% less ethyl α-nitropropionate. Other nitrate ester scavengers may be employed, but phloroglucinol seems to be far and away the most effective at destroying the nitrite ester formed along with the α-nitroester. Thus use of resorcinol (in the same molar concentration as an otherwise identical experiment using phloroglucinol) led to only a 25% yield of the α-nitropropionate along with an 8% yield of ethyl α-oximinopropionate. Furthermore, the rectified product, in spite of having correct refractive index, was highly colored.

In the conversion of ethyl α-bromoisobutyrate to the α-nitroester, the same yield (78%) was obtained in the presence and in the absence of phloroglucinol.

Ethyl α-Nitrovalerate.—Ethyl α-bromovalerate (60.9 g., 0.3 mole) is poured into a solution of 250 ml. of dimethyl sulfoxide (DMSO), 36 g. of sodium nitrite (0.52 mole) and 52 g. of phloroglucinol dihydrate (0.32 mole) in a 500-ml. three-necked flask equipped with a sealed stirrer. The flask is stoppered, immersed in a water-bath maintained at room temperature and stirring is continued for 1.5 hr. A slurry forms after *ca.* 0.5 hr., and, if necessary, a small amount of DMSO is added to facilitate stirring. The reaction mixture is then poured into 600 ml. of ice-water layered over with 200 ml. of diethyl ether. After separation of the upper layer, the aqueous phase is extracted four more times with 75-ml. portions of ether. The combined extracts are washed with four 100-ml. portions of water and then dried over anhydrous magnesium sulfate.

Using a small column the ether is removed at atmospheric pressure and the residual yellow liquid is rectified. This gives 44.2 g. (87% yield) of colorless ethyl α-nitrovalerate; b.p. 62° (1 mm.), $n^{20}D$ 1.4266.

TABLE III

PHYSICAL CONSTANTS OF α-NITROESTERS

Ethyl α-nitroester	B.p. °C.	B.p. Mm.	$n^{20}D$	Literature[a] B.p. °C.	Mm.	$n^{20}D$
Propionate	55	1	1.4209	75	9	1.4210
Butyrate	71	1	1.4233	82	8	1.4233
Valerate[b]	62	1	1.4266			
Caproate	68	0.5	1.4300	80	3	1.4302
Isobutyrate[c]	46	1	1.4197			
Isovalerate[d]	60	1	1.4269			
α-Phenylacetate[e]	92	0.15	1.5098			

[a] Ref. 4. [b] *Anal.* Calcd. for $C_7H_{13}O_4N$: C, 47.99; H, 7.48. Found: C, 48.22; H, 7.69. [c] *Anal.* Calcd. for $C_4H_9NO_4$: C, 44.8; H, 6.89; N, 8.71. Found: C, 44.8, 44.6; H, 7.01, 7.11; N, 8.72. [d] *Anal.* Calcd. for $C_7H_{13}NO_4$: C, 48.0; H, 7.50; N, 8.00. Found: C, 47.9; H, 7.51; N, 8.03. [e] *Anal.* Calcd. for $C_{10}H_{11}NO_4$: C, 57.5; H, 5.30; N, 6.70. Found: C, 57.5; H, 5.48; N, 6.79.

Relative Reaction Rates in DMF and in DMSO.—In one arm of a two-armed flask was placed 50 ml. of 0.05 *N* ethyl α-bromobutyrate solution (0.488 g.) and in the other was placed 50 ml. of a solution which was 0.05 *N* in $NaNO_2$ (0.173 g.) and 0.05 *N* in anhydrous phloroglucinol. The flask was immersed in a constant temperature bath (25°), and after the two solutions had come to temperature they were mixed. Aliquots (5 ml.) were withdrawn, run into dilute sulfuric acid and titrated for bromide ion with 0.05 *N* $AgNO_3$. The following is a typical result and shows that the reaction of α-bromoesters with sodium nitrite occurs at essentially the same rate in DMF and in DMSO.

Time, min.	0.05 *N* $AgNO_3$ ml. DMSO	DMF
1	0.25	0.31
5	0.80	0.90
10	1.18	1.38
20	1.58	1.73
35	1.87	1.91
50	2.00	2.02
∞	2.50	2.50

The Reaction of Ethyl α-Bromopropionate with Sodium Nitrite in DMF without Phloroglucinol.—Ethyl α-bromopropionate (0.3 mole) was treated with sodium nitrite in DMF as described above except that no phloroglucinol was present. After 5.5 hr. the reaction mixture was worked up in the usual way. After removal of the ether 24.4 g. of a pale green, partly crystalline, residue remained. This, when treated with petroleum ether, gave 9.2 g. (24% yield) of ethyl α-oximinopropionate, m.p. 93.5–94°, mixed m.p. with authentic ethyl α-oximinopropionate, 94–94.5°. Concentration of the petroleum ether mother liquors left a green oil which, when rectified at 1 mm., gave no ethyl α-nitropropionate; it was not investigated further.

The Reaction of Ethyl α-Bromobutyrate with Sodium Nitrite in DMSO without Phloroglucinol.—Ethyl α-bromobutyrate (0.14 mole) was treated with sodium nitrite in DMSO as described above, except that no phloroglucinol was present. After 15 minutes the reaction mixture was worked up in the usual way. Distillation gave a 65% yield of ethyl α-oximinobutyrate, m.p. 59°, lit.[16] m.p. 58–60°.

pK_A Determinations.—The apparent pK_A values given in Table II were determined at 25° by a procedure analogous to that of Bordwell and Cooper.[17] A Beckman *p*H meter equipped with calomel and glass (sodium) electrodes and calibrated with standard buffers at *p*H 9.16 and 7.00 was employed. Solutions of the various nitro compounds (*ca.* 0.01 *M*) in 50% (by volume) aqueous ethanol were titrated with aqueous sodium hydroxide (0.0967 *N*). An equal volume of absolute ethanol was added simultaneously from a second buret. The *p*H value at half-neutralization was taken as the pK_A value. With the weaker acids several minutes were required before a constant, equilibrium reading could be obtained. In no case was more than 5 min. required and, in general, the time interval was inversely proportional to the acid strength. Since no special potassium glass electrode was employed, apparent pK_A values above 9 must necessarily be only approximate, due to the electrode error above *p*H 9.

LAFAYETTE, INDIANA

(16) N. Kornblum and J. H. Eicher, THIS JOURNAL, **78**, 1494 (1956).

(17) F. G. Bordwell and G. D. Cooper, *ibid.*, **74**, 1058 (1952).

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[CONTRIBUTION FROM ROHM AND HAAS CO., REDSTONE ARSENAL RESEARCH DIVISION]

aci-Nitroalkanes. II. The Mechanism of the Nef Reaction[1]

BY M. FREDERICK HAWTHORNE

RECEIVED AUGUST 2, 1956

The kinetics of the acid-catalyzed solvolysis of seven *sec-aci*-nitroalkanes has been determined in a nitrogen atmosphere at 0° in 80% by volume methanol by the use of a newly developed spectrophotometric microanalytical method for *aci*-nitroalkanes. All kinetics were conducted with approximately 1×10^{-3} *M* *aci*-nitroalkane solutions. In each case the reaction was found to be first order in both *aci*-nitroalkane and hydrogen ion and reproducible to ±15%. Spectrophotometric product analyses for nitroalkanes indicated that, with the possible exception of nitrocyclobutane, no detectable amounts of nitroalkane were regenerated under kinetic conditions. Product isolation experiments indicated that each of the *aci*-nitroalkanes studied gave excellent yields of the corresponding ketones (isolated as 2,4-dinitrophenylhydrazones) on hydrolysis under conditions similar to those of the kinetic experiments and very little if any pseudonitrole. The *sec-aci*-nitroalkane reactivity sequence cyclohexyl > cyclobutyl > 2-propyl > 1-cyclopropylethyl > cyclopentyl > dicyclopropylmethyl > cycloheptyl was observed and when coupled with the first-order dependence of reaction rate on both hydrogen ion and *aci*-nitroalkane concentrations, leads to the conclusion that the rate-determining step of the Nef reaction is most probably the nucleophilic attack of solvent on the unsaturated carbon atom of the conjugate acid of the *sec-aci*-nitroalkane. The near average reactivity of the cyclopropyl-substituted nitroalkanes is discussed. The ultraviolet absorption spectra of the anions of these latter nitroalkanes show a marked shift of their absorption maxima to longer wave lengths when compared with the absorption spectra of anions of other representative *sec*-nitroalkanes.

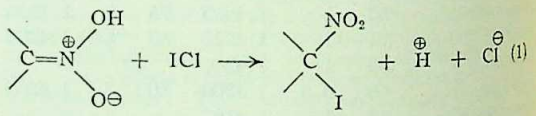
Although the hydrolysis of *aci*-nitroalkanes (Nef reaction) often has been utilized as a synthetic method for the preparation of carbonyl compounds[2] and a mechanism recently has been proposed,[3] no kinetic studies of this reaction have been reported. Because of this lack of quantitative information, the present investigation was initiated in an effort to bring the mechanism of this reaction more sharply into focus and to secure additional information with regard to the stereoelectronic requirements of *aci*-nitroalkanes.

Secondary nitroparaffins were chosen for study since diverse members of this series are easily prepared by the trifluoroperoxyacetic acid oxidation of the corresponding oximes[4] and the hydrolysis of their *aci*-isomerides has been shown[2,3] to produce the corresponding ketones in high yield. Nitrocycloalkanes received particular attention since their kinetic examination coupled with the recent generalizations of Brown, Brewster and Shechter[5] provided a tool which was used to specify the probable course of the reaction.

Kinetic Method

In order to examine the rates of the acid-catalyzed hydrolysis of *sec-aci*-nitroalkanes, certain experimental requirements were necessarily imposed on any method chosen. These include: (1) the use of low *aci*-nitroalkane concentrations which would minimize the importance of bimolecular side reactions which might occur between *aci*-nitroalkane molecules, (2) the generation of the anions of the nitroalkanes in an atmosphere containing no oxygen,[6] (3) a method for the instantaneous addition of strong acid to the nitroalkane anion solution with a minimum temperature increase and the ultimate production of a predetermined hydrogen ion concentration, (4) an analytical method for the determination of *aci*-nitroalkane at low concentrations and in the presence of a moderate concentration of strong acid.

These requirements were met and the rates of acid-catalyzed hydrolysis of seven *sec-aci*-nitroalkanes were determined at 0° in 80% by volume methanol using a spectrophotometric adaptation of the classical halometric determination of *aci*-nitroalkanes[7] described by equation (1).



(1)

Each rate run was carried out under nitrogen. Approximately 1×10^{-3} *M* concentrations of *aci*-nitroalkanes were generated in a stirred reactor in the presence of known hydrogen ion concentrations by the addition of a known and excess amount of concentrated hydrochloric or perchloric acid to a solution of nitroalkane anion.[8]

The nitroalkane anion was prepared under nitrogen in the reactor from a known volume of standardized dilute sodium hydroxide solution in 80% methanol and approximately 3 mg. of nitroalkane.

In essence, the analytical method consisted of the rapid addition of an aliquot of reaction mixture to a known and excess amount of iodine monochloride in aqueous methanol solution followed by the addition of a small portion of an intimate mixture of N,N,N′,N′-tetramethyl-*p*-phenylenediamine dihydrochloride and sodium acetate. The excess iodine monochloride rapidly and quantitatively reacted as

(1) This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

(2) See W. E. Noland, *Chem. Revs.*, **55**, 137 (1955), for a critical review and many examples of the synthetic applications of this reaction.

(3) E. E. van Tamelen and R. J. Thiede, THIS JOURNAL, **74**, 2615 (1952).

(4) W. D. Emmons and A. S. Pagano, *ibid.*, **77**, 4557 (1955).

(5) H. C. Brown, J. H. Brewster and H. Shechter, *ibid.*, **76**, 467 (1954), have successfully correlated the relative thermodynamic stabilities of cycloalkyl systems having *exo*-cyclic double bonds in terms of alkyl hydrogen eclipsing and I-strain; see also H. C. Brown and G. Ham, *ibid.*, **78**, 2735 (1956).

(6) G. A. Russell, *ibid.*, **76**, 1595 (1954), reported the facile oxygenation of the 2-nitropropane anion [illegible]

(7) K. H. Meyer and P. Wertheimer, *Ber.*, **47**, 2347 (1914).

(8) The temperature increase of reaction solution was minimized by the use of small quantities of base and acid and by operating in dilute solution. The hydrogen ion concentration was calculated on the assumption that all the *aci*-nitroalkanes employed were weak acids (*p*Ka 4–6) and that they were present in an undissociated state. In one run perchloric acid was substituted for hydrochloric acid without

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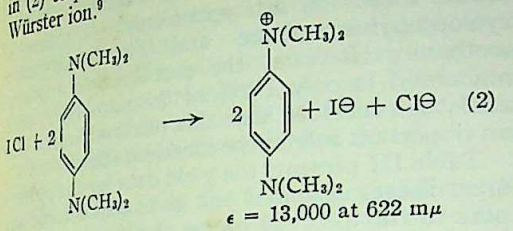
in (2) to produce an intensely blue solution of the Würster ion.[9]



(2)

ϵ = 13,000 at 622 mμ

The spectrophotometric determination of the amount of Würster ion produced allowed the calculation of the instantaneous concentration of *aci*-nitroalkane present in the aliquot taken. Since the stoichiometry of (1) is cleanly observed, each *aci*-nitroalkane examined was in this manner given an effective extinction coefficient of 2.6×10^4 at 622 mμ.

Results

Each *sec-aci*-nitroalkane examined in the manner described above gave acceptable first-order plots with the determined first-order rate constant reproducible to ±15% and proportional to the hydrogen ion concentration. The instantaneous rate expression is then defined by (3).

$$v = k[H^+]\ [aci\text{-nitroalkane}] \qquad (3)$$

Figure 1 is a typical first-order plot obtained with *aci*-nitrocyclohexane and Fig. 2 illustrates the

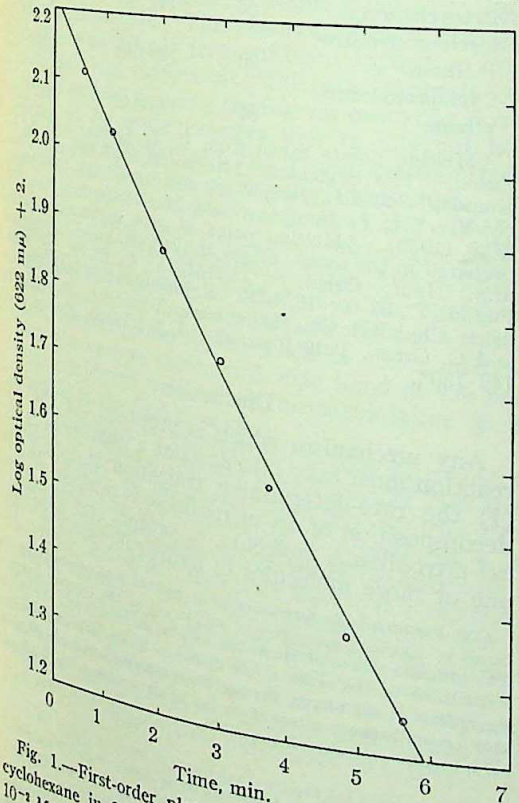


Fig. 1.—First-order plot of the solvolysis of *aci*-nitrocyclohexane in 80% methanol at 0.0° containing 4.4 × 10^{-1} *M* hydrochloric acid.

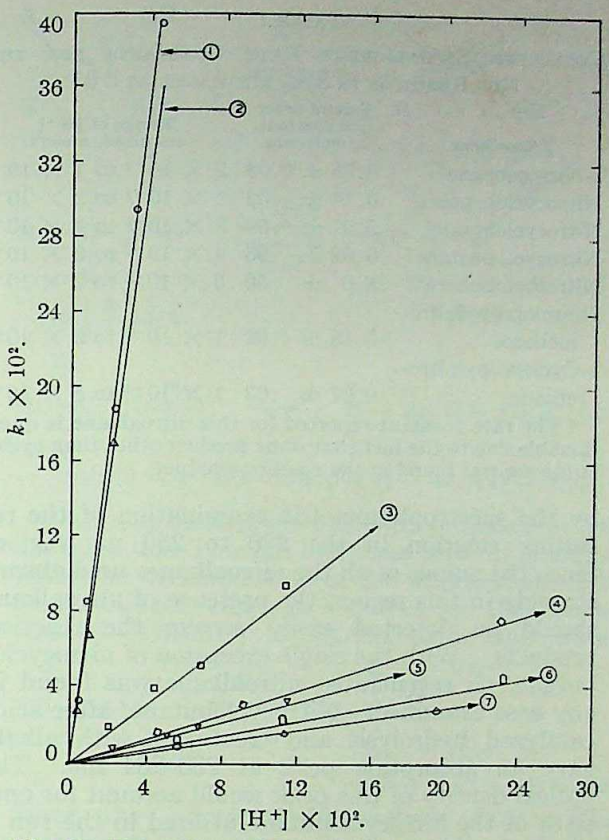


Fig. 2.—Dependence of pseudo first-order rate constant on hydrogen ion concentration for: nitrocyclohexane, 1; nitrocyclobutane, 2; 2-nitropropane, 3; nitrocyclopentane, 4; 1-cyclopropylnitroethane, 5; dicyclopropylnitromethane, 6; and nitrocycloheptane, 7.

fit of all the data obtained to equation 3. It should be noted that within experimental error all of the lines in Fig. 2 pass through the origin. This observation rules out the occurrence of a kinetic term of the form 4 which would result if *aci*-nitro-

$$v = k'[aci\text{-nitroalkane}] \qquad (4)$$

alkane were tautomerizing to the nitroalkane at a significant rate.[10]

Table I summarizes the second-order rate constants obtained in the hydrolysis of *aci*-nitrocyclobutane, -cyclopentane, -cyclohexane, -cycloheptane, 2-*aci*-nitropropane, *aci*-nitrocyclopropylethane and *aci*-nitrodicyclopropylmethane. With the exception of nitrocyclohexane and 2-nitropropane, all the parent nitroalkanes were prepared by the peroxytrifluoroacetic acid oxidation of the corresponding oximes.[4] The two cyclopropyl compounds reported here were each obtained in approximately 40% yield.

Product analyses were carried out in every case for both regenerated nitroalkane and for the ketone product of the Nef reaction. The analytical procedure applied to the former possible product was based on the treatment of the reaction mixture with strong base in a nitrogen atmosphere followed

(9) L. Michaelis, M. P. Schubert and S. Granick, THIS JOURNAL, 61, 1981 (1939).

(10) R. G. Pearson and R. L. Dillon, *ibid.*, 72, 3574 (1950), have shown that in the case of nitroethane this tautomerization reaction is observed kinetically as the reaction of nitroalkane anion with general acids, $RNO_2^- + HA \rightarrow RHNO_2 + A^-$. The kinetic isolation of the acid-catalyzed hydrolysis of *aci*-nitroalkane at relatively high acid concentrations is to be expected on the basis of the difference in transition state composition of the two competing processes.

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TABLE I

COLLECTED SECOND-ORDER RATE CONSTANTS FOR THE NEF REACTION IN 80% METHANOL AT 0.0°

Nitroalkane	Second-order rate constant, l./mole-min.	Range of $[H^+]$ examined, mole/l.
2-Nitropropane	0.78 ± 0.08	2×10^{-2} to 1×10^{-1}
Nitrocycloheptane	0.14 ± .02	5×10^{-2} to 2×10^{-1}
Nitrocyclohexane	8.9 ± .50	3×10^{-3} to 4×10^{-2}
Nitrocyclopentane	0.32 ± .05	4×10^{-2} to 2×10^{-1}
Nitrocyclobutane[a]	8.0 ± .50	3×10^{-3} to 2×10^{-2}
Dicyclopropylnitromethane	0.18 ± .02	1×10^{-1} to 3×10^{-1}
1-Cyclopropylnitroethane	0.27 ± .03	1×10^{-1} to 5×10^{-1}

[a] The rate constant reported for this nitroalkane is questionable due to the fact that some product other than cyclobutanone was found in the reaction product.

by the spectrophotometric examination of the resulting solution in the 220 to 250 mμ region. Since the anions of all the nitroalkanes used absorb strongly in this region, the presence of nitroalkane should be detected easily among the reaction products. With the single exception of nitrocyclobutane, no regenerated nitroalkane was found in any case examined. Nitrocyclobutane, after acid-catalyzed hydrolysis and treatment with alkali, gave an absorption peak at 230–234 mμ. The optical density of this peak would account for one-sixth of the nitrocyclobutane utilized in the run if the extinction coefficient of the product were the same as that of the nitrocyclobutane anion. It appears that nitrocyclobutane does not give the Nef reaction quantitatively under the conditions employed. That the material responsible for the 230–234 mμ peak in the products was not due to nitrocyclobutane, which escaped the initial treatment with hydroxide ion, was shown by the fact that this absorption was independent of the time allowed for the initial ionization reaction.

Table II summarizes the absorption maxima of the nitroalkane anions employed in this study. The striking bathochromic shift observed on the introduction of α-cyclopropyl rings into a *sec*-nitroalkane lends considerable support to the concept of the unsaturated character of cyclopropyl groups.[11]

TABLE II

THE ULTRAVIOLET ABSORPTION SPECTRA OF NITROALKANE ANIONS IN 80% METHANOL

Parent nitroalkane	λ_{max}, mμ	$\epsilon_{max} \times 10^{-4}$[a]
2-Nitropropane	227	1.06
Nitrocycloheptane	234	1.15
Nitrocyclohexane	237	1.20
Nitrocyclopentane	230	1.13
Nitrocyclobutane	234	1.17
Dicyclopropylnitromethane	248	1.17
1-Cyclopropylnitroethane	240	1.25

[a] Values dependable to only ±5%.

The second product analysis employed involved the execution of the rate experiments at somewhat higher (*ca.* 0.07 *M*) *aci*-nitroalkane concentrations and the isolation of the resulting ketone as its 2,4-dinitrophenylhydrazone. In these runs, a fleeting blue intermediate always was observed. Pseudonitrole formation was noted only in the cases of cyclopropylnitroethane and dicyclopropylnitromethane. However, the pseudonitrole produced amounted to only 1–2% of the nitroalkane used, and it is concluded that this reaction did not play an important role in the kinetic studies.[12]

Table III presents the yield data for the series of nitroalkanes examined and gives considerable support to the assumed course of the reaction. The somewhat lower yield of 2,4-dinitrophenylhydrazone obtained from nitrocyclobutane may be due to the incomplete separation of the ketone as the solid derivative. However, as stated above, spectrophotometric examination of an alkaline solution of the reaction products of nitrocyclobutane did show absorption in the 230 mμ region, and it is conceivable that the Nef reaction may here take another course and produce correspondingly less cyclobutanone.

TABLE III

COLLECTED PRODUCT ANALYSIS DATA FOR THE NEF REACTION IN 80% METHANOL AT 0.0°

Parent nitroalkane	Crude ketone 2,4-dinitrophenylhydrazone Yield, %	M.p., °C.	M.p. pure 2,4-dinitrophenylhydrazone, °C.
2-Nitropropane	76	124–126	126[a]
Nitrocycloheptane	94	145–146	148[a]
Nitrocyclohexane	97	158–159	162[a]
Nitrocyclopentane	89	136–138	142[a]
Nitrocyclobutane	56	142	146[b]
Dicyclopropylnitromethane	96	189–191	193[c]
1-Cyclopropylnitroethane	64	140–142	155[d]

[a] Melting points taken from R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y. [b] N. J. Demjanov and M. Dojarenko, *Ber.*, 55, 2739 (1932). [c] Melting point of pure authentic samples prepared in the usual fashion and recrystallized to constant m.p. *Anal.* Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.78; H, 4.86. Found: C, 53.50; H, 4.78. Ketone obtained from the Aldrich Chemical Co., Milwaukee, Wis. [d] J. D. Roberts and C. Green, THIS JOURNAL, 68, 214(1946), give m.p. of 149–150°.

Discussion

Any mechanism which is proposed for the Nef reaction must take into account a number of facts: (1) the rate-determining transition state for the decomposition of *aci*-nitroalkane is composed of an *aci*-nitroalkane molecule, a proton and probably one or more molecules of hydroxylic solvent. (2)

(12) Pseudonitrole formation is at present best accounted for in terms of spurious quantities of nitrite ion in the reaction mixture. The ultimate source of nitrite ion may be an impurity in the parent nitroalkane or the result of air oxidation of the nitroalkane anion. Regardless of the source, the reaction producing pseudonitrole probably occurs between nitrosonium ion or its precursor, $H_3{}^+ONO$ and *aci*-nitroalkane or nitroalkane anion.

$$RNO_2H + NO^{\oplus} \longrightarrow R(NO_2)(NO) + H^{\oplus}$$

Such a process would make a much smaller contribution to the over-all course of *aci*-nitroalkane decomposition in the low concentration kinetic experiments than the preparative experiments due to its second-order character.

(11) R. H. Eastman and S. K. Freeman, THIS JOURNAL, 77, 6642 (1955), and previous papers of this series.

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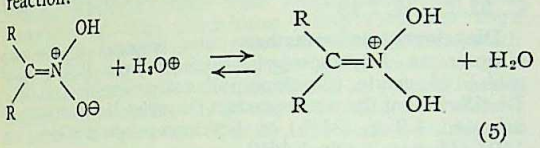
The reactivity sequence, *aci*-nitrocyclohexane > -nitrocyclobutane > -nitropropane > -nitrocyclopentane > -1-cyclopropylnitroethane > -dicyclopropylnitromethane > -nitrocycloheptane is observed. (3) A blue intermediate having an appreciable lifetime is produced. (4) *aci*-Nitroalkanes having enhanced resonance stabilization do not normally give the Nef reaction[3] or do so only very slowly.

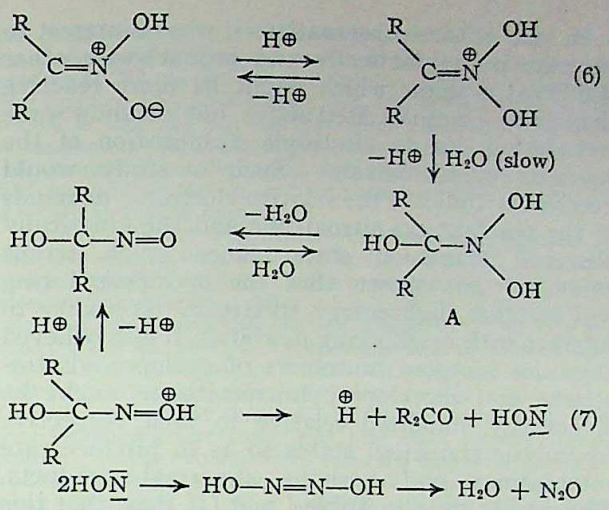
The bare fact that the first slow step of the Nef reaction involves a protonated *aci*-nitroalkane molecule immediately suggests the possibility that equilibrium (5) plays an important role in the reaction.



(5)

Thus, the conjugate acid of the *aci*-nitroalkane molecule which is produced in this equilibrium would have an electron-deficient carbon atom attached to nitrogen and would be labile to nucleophilic attack at this carbon atom. This tentative conclusion is further strengthened by the consideration of the relative rates of reaction found in the nitrocycloalkane series as follows: Brown, Brewster and Shechter[5] have recently summarized a great deal of reactivity data which leads to the postulate that a 5-ring having an exocyclic double bond is always extremely stable relative to its 6-ring counterpart. This observation is rationalized by these authors in terms of bond opposition interactions. On somewhat different grounds one would expect a 4-ring having an exocyclic double bond to be quite reactive due to internal bond angle deformation and the 7-ring system should appear much as the cyclopentyl derivative. The fact that at 0° *aci*-nitrocyclohexane is hydrolyzed 27 times faster than *aci*-nitrocyclopentane and 11 times faster than *aci*-nitropropane, and *aci*-nitrocyclobutane is nearly as reactive as the cyclohexyl compound (this latter result should be accepted with caution, *vide supra*) leads to the conclusion that the carbon–nitrogen double bond of the reactive conjugate acid of an *aci*-nitroalkane is destroyed in the first slow step.

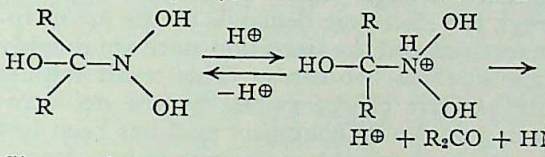
The question of the role of the blue intermediate which is observed during a preparative Nef reaction cannot be answered definitely at this time. However, the very fact that it persists at a detectable concentration level while *aci*-nitroalkane is being destroyed[13] indicates that it is a relatively stable species. Since the intense blue color of these intermediates strongly suggests the presence of a nitroso group, they may be tentatively formulated[2] as α-hydroxynitrosoalkanes which may arise as in (6) and decompose to ketone and nitrous oxide by one of many possible paths such as (7).[14]



(6)

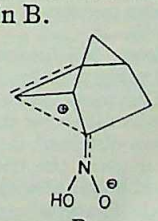
(7)

A similar mechanism has been proposed by van Tamelen and Thiede,[3] but these authors prefer to write the decomposition of the intermediate A by acid-catalyzed cleavage followed by the conversion of $HN(OH)_2$ to nitrous oxide and water.



Since the α-hydroxynitrosoalkane intermediate postulated above may be in mobile hydrolytic equilibrium with A, these paths are presently indistinguishable.[15]

The reluctance of highly resonance stabilized *aci*-nitroalkanes to undergo the Nef reaction has been discussed previously in terms of stabilization of the reactant. Notable examples of this class of nitroalkanes are α-phenylnitroethane[16] and phenylnitromethane which give hydrolytically stable *aci*-nitro tautomers on acidification of their anions with strong mineral acids.[17] Similarly, Wildman and Saunders[18] report that the 5-nitrobicyclo-[2,2,1]2-heptenes fail to undergo the Nef reaction and these authors attribute this inertness to the stabilization of the *aci*-nitrotautomer by the 1,3-interaction shown in B.



B

(13) In the preparative experiments carried out in this study the acid concentration was such as to give the calculated half life of the *aci*-nitroalkane a duration of only a few minutes in the slowest cases. The blue intermediate often was found to persist in these same experiments for as long as two to four minutes.

(14) D. C. Iffland and G. X. Criner, *Chemistry & Industry*, 176 (1956), has described compounds obtained by the reaction of lead tetraacetate with ketoximes and believed to be α-acetoxynitroso alkanes. Acid hydrolysis of these materials yields the corresponding ketone presumably *via* an α-hydroxynitroso intermediate. M. F. Hawthorne and R. D. Strahm have found that the second-order silver ion catalyzed solvolysis of 1-chloro-1-nitrosocyclohexane in aqueous acetonitrile produces cyclohexanone in 90% yield, nitrous oxide and no hydroxylamine. This reaction sequence most likely passes through 1-hydroxy-1-nitrosocyclohexane and will be described in detail in the following paper of this series.

(15) Additional processes may be proposed such as the acid-catalyzed dimerization of the α-hydroxynitrosoalkane followed by the elimination of HON=NOH and two molecules of ketone.

(16) E. Bamberger and R. Seligman, *Ber.*, **36**, 706 (1903).

(17) N. Kornblum and G. E. Graham, THIS JOURNAL, **73**, 4041 (1951).

(18) W. C. Wildman and D. R. Saunders, *J. Org. Chem.*, **19**, 381 (1954).

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In view of these observations it was of interest to examine both kinetically and product-wise other stabilized systems which might be more reactive than those examples cited above, but yet show some retardation due to electronic stabilization of the reactant *aci*-nitroalkane. Such a study would necessarily indicate the relative electronic demands of the reactant *aci*-nitroalkane and the kinetically observed transition state. Since much recent evidence[10] has shown that the cyclopropyl ring will stabilize high energy species by its ability to interact with neighboring *p*-orbitals, it was believed that the *aci*-nitro tautomers of cyclopropylnitroethane and dicyclopropylnitromethane might be sufficiently stabilized relative to their respective hydrolytic transition states so as to produce rate retardations and perhaps abnormal products. The results given in Table I and III show that this is not the case since the rates of hydrolysis of these two *aci*-nitroalkanes are no less than would be expected on the basis of steric hindrance to the attack of solvent and the corresponding ketones are obtained in high yield. It therefore appears as though the electronic demands of the *aci*-nitroalkane reactant and the transition state are roughly the same in these two cases. This result implies that the positive charge gained by the *aci*-nitroalkane in going to its conjugate acid has been lost to the attacking solvent in the succeeding transition state. In the cases of α-phenylnitroethane and phenylnitromethane the increased stability of the *aci*-nitrotautomers may shift the rate-determining transition state so far toward products that the positive charge of the reactant *aci*-nitrotautomers is almost wholly held by nucleophilic solvent in the transition state.[19] The unsaturation afforded the system by the phenyl group would thus stabilize the reactant species but would not appreciably stabilize the rate-determining transition state and a rate retardation would result.

Experimental[20]

2-Nitropropane was obtained from Mathieson, Coleman and Bell, Inc., and distilled through a 50–75 plate center-rod distillation column at atmospheric pressure. After a small forerun, the center portion of the material was taken; b.p. 119.5°, n^{20}D 1.3940.

Nitrocyclohexane from Mathieson, Coleman and Bell, Inc., was fractionated using a Helipak packed column of *ca.* 20 plates efficiency at 15 mm. A center portion boiling at 102° and n^{20}D 1.4619 was taken for use.

Nitrocyclobutane was obtained in 32% yield from 5.0 g. of cyclobutanone oxime using the trifluoroperoxyacetic acid method of Emmons and Pagano[4] with a disodium acid phosphate acid scavenger. The crude product was twice distilled through a Holzman column[21] at 40 mm.; b.p. 78–79°, n^{20}D 1.4429.[22]

Nitrocyclopentane,[23] b.p. 90° (40 mm.) and n^{20}D 1.4518, was prepared as previously described.[4]

Nitrocycloheptane,[23,24] b.p. 101° (15 mm.) and n^{20}D 1.4721, was prepared as previously described.[4]

1-Cyclopropylnitroethane.—To 7.4 g. (0.075 mole) of crude cyclopropylmethyl ketoxime was added 200 ml. of pure acetonitrile, 2.0 g. of dry urea and 78 g. of disodium acid phosphate. The mixture was brought to reflux with stirring, and a trifluoroperoxyacetic acid solution prepared from 5.5 ml. (0.20 mole) of 90% hydrogen peroxide and 34.0 ml. (0.24 mole) of trifluoroacetic anhydride in 50 ml. of acetonitrile was added slowly over a 1-hr. period. Stirring and refluxing was continued for one additional hour. The mixture was cooled, poured into one liter of water and extracted with ether three times. The combined ether extracts were washed three times with water, dried over magnesium sulfate and concentrated to an oil under a small column. The residual oil was fractionated with a Holzman column giving 3.5 g. (42%) of 1-cyclopropylnitroethane, b.p. 70° at 22 mm., n^{15}D 1.4338.

Anal. Calcd. for $C_5H_9NO_2$: C, 52.16; H, 7.88. Found: C, 52.30; H, 7.98.

Dicyclopropylnitromethane was prepared in the same manner as 1-cyclopropylnitroethane from 12.5 g. (0.10 mole) of crude dicyclopropylketoxime melting at 67°.[25] Distillation of the crude product through a Holzman column[21] afforded 4.9 g. (35%) of dicyclopropylnitromethane, b.p. 110° (15 mm.), n^{15}D 1.4619.

Anal. Calcd. for $C_7H_{11}NO_2$: C, 59.55; H, 7.85. Found: C, 59.87; H, 8.00.

Kinetic Procedure.—All kinetic measurements were made at 0° by the use of a 4-liter Dewar flask cryostat containing a well-stirred mixture of ice and water. The reaction vessel was a 150-ml. wide-neck test-tube shaped flask having a Tru-bore stirrer powered by a variable-speed direct current motor. A nitrogen inlet and outlet were attached to the apparatus as was a tightly-stoppered sampling port. "Prepurified" grade nitrogen was supplied directly from the tank through a pressure regulator. Stopcocks on the gas line were arranged in such a manner as to allow rapid sweeping of the system or maintenance of a few millimeters of positive pressure in the closed system. This nitrogen pressure was maintained during each run and prevented the admittance of air when aliquots of reaction mixture were removed through the open sampling port.

The procedure is as follows: The system was thoroughly flushed with nitrogen, and 200 ml. of 0.060 *N* sodium hydroxide in 80% methanol was introduced under nitrogen through the open sampling port. Exactly 0.003 ml. (essentially 3 mg. of each compound investigated) of nitroalkane was added to the sodium hydroxide solution in the same manner. The port was then closed with a rubber stopper and the solution briefly stirred with the attached stirrer. This reaction mixture was allowed to stand under nitrogen for 1 hr. to ensure complete conversion of the nitroalkane to its sodium salt. The reaction vessel was then immersed in the ice–water cryostat, 50 ml. of 80% methanol added and the solution brought to 0° during a 20-minute period. To initiate the Nef reaction, a small accurately measured volume (0.025 to 1.00 ml.) of 12.00 *N* hydrochloric acid was rapidly introduced beneath the surface of the reaction mixture while the solution was vigorously stirred. The use of extremely dilute solutions minimized the effect of heat of neutralization on the temperature of the reaction system. At intervals, 2.00-ml. aliquots of reaction solutions were removed through the sampling port by the use of an automatic pipet. The pipet previously had been cooled to 0° by immersion in a methanol-bath which in turn was cooled by ice and water. The contents of the pipet were discharged into a 10-ml. volumetric flask containing 3 ml. of *ca.* 4×10^{-4} *M* iodine monochloride in 80% methanol. The color of the iodine monochloride faded instantaneously, and the time of delivery was taken as the time of the point. About 20 mg. of an intimately ground mixture of equal weights of sodium acetate and N,N,N′,N′-tetramethyl-*p*-phenylenediamine was added to the flask, the flask shaken to effect conversion to Würster's blue, the solution made up to volume with 80% methanol and the optical density determined at 622 mμ with a Beckman model DK-1 recording spectrophotometer. Preliminary experiments with accurately titrated iodine monochloride solutions gave a value of 1.3×10^4 for the extinction coefficient of Würster's blue at that wave length. Optical density values were within 5% of the theoretical

(19) G. S. Hammond, THIS JOURNAL, **77**, 334 (1955).

(20) All melting and boiling points are uncorrected.

(21) C. W. Gould, G. Holzman and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

(22) D. C. Iffland, G. X. Criner, M. Koral, F. J. Lotspeich, Z. B. Papanastassiou and S. M. White, Jr., THIS JOURNAL, **75**, 4044 (1953). report b.p. of 77° (40 mm.) and n^{20}D 1.4432.

(23) D. C. Iffland, *et al.* (ref. 21), report n^{25}D 1.4518 for nitrocyclopentane and n^{20}D 1.4710 for nitrocycloheptane.

(24) W. D. Emmons and A. S. Pagano report n^{20}D 1.4720 for nitrocycloheptane (ref. 4).

(25) H. Hart and O. E. Curtis, THIS JOURNAL, **78**, 112 (1956), report

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values calculated on the basis of complete conversion of nitroalkane to anion and complete reaction of the resulting *aci*-nitro tautomer. Acid concentrations present in each run were calculated on the basis of negligible ionization of the *aci*-nitroalkane and by the relationship

$$[H^+] = \frac{N(\text{ml. } N \text{ normal acid used}) - 2.00\ (N \text{ of base used})}{52.0}$$

In each run an acceptable first-order constant was obtained from log (optical density) *vs.* time plots. Figures 1 and 2 present the data obtained from one nitrocyclohexane run and from all runs with all nitroalkanes, respectively. Table I summarizes all second-order rate constants.

Spectrophotometric Measurements.—The ultraviolet absorption spectra of the nitroalkane anions recorded in Table II were determined in 80% methanol using a model DK-1 Beckman spectrophotometer and 1-cm. stoppered silica absorption cells. The nitroalkane anion solutions were prepared under nitrogen as described above and diluted with 50 ml. of solvent at room temperature in the reactor. Aliquots of these solutions were further diluted and immediately examined. Since the density of each nitroalkane examined was within a few per cent. of unity, the concentrations of nitroalkanes employed were calculated on the assumption that the 0.003 ml. of nitroalkane introduced was equal to 3 mg. of material. For this reason the extinction coefficients may be accurate only to ±5%.

Reaction products were analyzed for regenerated nitroalkane by making a run as described above and withdrawing no aliquots. The reaction mixture was then warmed to room temperature, and 5 ml. of 19 *N* (saturated) sodium hydroxide solution was added under nitrogen. After 1 to 2 hr. the spectrum of the basic reaction mixture was scanned using suitably diluted 19 *N* sodium hydroxide in the solvent cell. Only nitrocyclobutane showed absorption in the 230 mμ region. In two such experiments with this compound, the concentration of nitroalkane present in the basic solution before acidification was such as to give an optical density reading at 234 mμ of 0.91 after suitable dilution. After the Nef reaction had been carried out, the optical density observed at 232–234 mμ was 0.16 when concentrations were normalized to that or the original nitroalkane anion solution. About one-sixth of the nitrocyclobutane either survived the Nef reaction or the reaction produced a small amount of strongly absorbing impurity.

Ketone Isolation Procedure.—One-half gram samples of each nitroalkane were dissolved in 4.0 ml. of 2.5 *N* sodium hydroxide in 80% methanol in the reactor under nitrogen and at room temperature. After 0.5 hr., 50 ml. of 80% methanol was added and the solution cooled to 0° for 0.5 hr. Exactly 3.0 ml. of 12 *N* hydrochloric acid was added and the solution was stirred for 0.5 hr. In every case examined, acidification led to the immediate formation of a blue color. In each case, except those of 1-cyclopropylnitroethane and dicyclopropylnitromethane, this blue color rapidly disappeared. In the two abnormal cases the blue color persisted and finally disappeared as pseudonitrole separated from solution. Filtration of these solutions afforded about 5–10 mg. of unstable white solid which turned blue on solution in warm methylene chloride. A control experiment showed that 1-nitrosonitrocyclohexane was stable under these reaction conditions and indicates that pseudonitroles would have been isolated if they had been produced in other cases.

In every case the reaction mixture was placed on the steam-bath and warmed to 60°. At this point a slurry of 1 g. of 2,4-dinitrophenylhydrazine in 100 ml. of 6 *N* hydrochloric acid was added and the solution stirred and heated for 20 minutes, cooled to room temperature and filtered. The crude crystalline derivatives were washed with warm water, dried, weighed and melting points determined. Table III summarizes the yield data.

HUNTSVILLE, ALABAMA

[CONTRIBUTION FROM ROHM AND HAAS CO., REDSTONE ARSENAL RESEARCH DIVISION]

aci-Nitroalkanes. III. The Solvolysis of α-Chloronitrosocycloalkanes in the Presence of Electrophilic Silver Ion

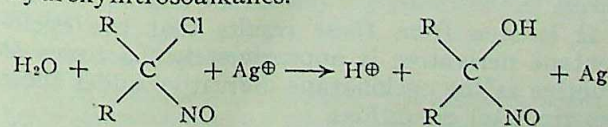
BY M. FREDERICK HAWTHORNE AND R. DONALD STRAHM

RECEIVED SEPTEMBER 4, 1956

1-Chloronitrosocyclohexane and 1-chloronitrosocyclopentane are rapidly converted to cyclohexanone and cyclopentanone, respectively, in essentially quantitative yields when treated with silver perchlorate in 20:30:50 (by volume) ethanol:water:acetonitrile at 50.0°. The rates of these reactions were determined under the above conditions by titration of liberated hydrogen ion. The rate equation in each case is of the form $d[H^+]/dt = k[Ag^+][\text{chloronitrosocycloalkane}]$ with the second-order rate constant, k, equal to 2.0 and 5.0 × 10^{-2} l. mole^{-1} min.^{-1} for 1-chloronitrosocyclohexane and 1-chloronitrosocyclopentane, respectively. No hydroxylamine, nitrogen, nitric oxide or nitrogen dioxide was produced and nitrous oxide was identified by gas chromatography. Silver chloride is produced in quantitative yield. It is suggested that these transformations probably proceed *via* the α-hydroxynitrosocycloalkanes which are in turn produced by the nucleophilic attack of water upon the α-carbon atom. This proposed path is in accord with recent proposals concerning the mechanism of the Nef reaction.

Because of our previous interest in the mechanism of the Nef reaction[1] and the probable relationship of the chemistry of α-hydroxynitrosoalkanes to that reaction, it was of interest to seek a more direct route to such materials and to determine their mode of decomposition in acidic aqueous media.

Piloty and Stock[2] long ago reported the synthesis of 2-nitro-2-nitrosopropane by the reaction of silver nitrite with 2-bromo-2-nitrosopropane in ethereal solution. This silver ion assisted displacement of bromide ion by nitrite ion probably proceeded by way of a concerted termolecular displacement reaction such as those recently characterized by Kornblum and Hardies[3] and by Hammond and Hawthorne.[4] It thus appeared probable that the similar treatment of 1-chloronitrosoalkanes with silver ion in the presence of water and in the absence of nucleophilic anions might yield α-hydroxynitrosoalkanes.



(1)

(1) M. F. Hawthorne, THIS JOURNAL, **79**, 2510 (1957).
(2) O. Piloty and A. Stock, *Ber.*, **35**, 3093 (1902).
(3) N. Kornblum and D. E. Hardies, Abstracts of the 130th Meeting of the American Chemical Society, September 16 to 21, 1956, Atlantic City, N. J., p. 2-O.
(4) G. S. Hammond and M. F. Hawthorne, Abstracts of the 126th Meeting of the American Chemical Society, New York, N. Y., September 12 to 17, 1954, p. 41-O.

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Two reactions of this type have been studied from the viewpoint of reaction kinetics and product analysis.

Results

In order to test this hypothesis 1-chloronitrosocyclopentane and 1-chloronitrosocyclohexane were prepared[5] as recently described. Both materials could be stored in the dark at Dry Ice temperatures for long periods of time without decomposition. Preliminary solubility measurements indicated that these materials would dissolve in quantity in aqueous solvent systems only if this solvent contained ethanol. For this reason a ternary solvent system prepared from 2 volumes of ethanol, 3 volumes of water and 5 volumes of acetonitrile was utilized in the kinetic and product experiments.

The kinetics of the reaction of each of the 1-chloronitrosocycloalkanes with silver perchlorate was determined in the dark at 50.0° by titration of the hydrogen ion produced during each run. In every case the kinetics were of the form (2) and each kinetic experiment was carried to about 50% reaction. Initial silver perchlorate concentrations

$$d[H^{\oplus}]/dt = k_2[Ag^{\oplus}][\text{1-chloronitrosocycloalkane}] \quad (2)$$

were varied four-fold (*ca.* 0.1 to 0.4 *M*) in each case while the initial 1-chloronitrosoalkane concentration was always near 0.2 *M*. Control experiments based on the spectrophotometric determination of the 1-chloronitrosoalkanes in the 620 mμ region proved that these materials were thermally and photochemically stable under the conditions of the kinetic experiments. Figure 1 gives a typical second-order plot obtained for both the cyclohexane and cyclopentane derivatives at the same initial concentration of reactants, and Table I records a summary of all the rate data obtained.

TABLE I

RATES OF SILVER ION ASSISTED SOLVOLYSES OF 1-CHLORONITROSOCYCLOHEXANE AND -PENTANE IN 50:30:20 ACETONITRILE, WATER, ETHANOL (VOLUME) AT 50.0

Initial concentrations, mole/l. [Chloronitrosoalkane]	[$AgClO_4$]	Second-order constant, l./mole-min. × 10^2
0.200[a]	0.099	2.06
.199[a]	.159	1.84
.200[a]	.300	2.03
.199[a]	.310	2.11
.199[a]	.416	2.30
.200[b]	.305	4.92
.200[b]	.149	4.97
.201[b]	.164	4.87
.201[b]	.100	4.97
.207[b]	.400	5.23

[a] 1-Chloronitrosocyclohexane, mean $k_2 = 2.07 \pm 0.23 \times 10^{-2}$ l./mole-min. [b] 1-Chloronitrosocyclopentane, mean $k_2 = 5.08 \pm 0.16 \times 10^{-2}$ l./mole-min.

It is seen from these results that the cyclopentane derivative is approximately 2.5 times as reactive as the cyclohexane derivative under these experimental conditions.

Several reactions were carried out under kinetic conditions and the products examined. It was found that both the cyclopentyl and cyclohexyl derivatives gave quantitative yields of silver chloride and 85 and 92% yields of the corresponding ketone (isolated as 2,4-dinitrophenylhydrazones), respectively. The reaction mixtures were found to evolve no gas during the reaction. Similarly, no nitrogen dioxide or nitric oxide was observed in either case as evidenced by the absence of brown fumes above the reaction mixture. Hydroxylamine was shown to be absent by treating a portion of the reaction mixtures with an acidic solution of ferric chloride[6] followed by titration of the resulting ferrous ion with standard potassium permanganate solution. In no case was more than a trace of ferrous ion produced. Vapor phase chromatography[7] of a portion of each reaction mixture at −78° gave a single large peak for a soluble gas present in high concentration and with the characteristic retention time of nitrous oxide. Although these latter experiments were not quantitative in nature, the complete absence of other nitrogen-containing compounds in the reaction mixture supports the view that nitrous oxide is the only nitrogenous product.

Discussion

The fact that the reaction of silver perchlorate with 1-chloronitrosocyclohexane and 1-chloronitrosocyclopentane in aqueous ethanolic acetonitrile obeys the kinetic equation 1 over a range of silver salt concentrations leads to the conclusion that silver ion functions as the electrophilic reagent, solvent as the nucleophile[8] and that perchlorate ion is not kinetically involved.[9] Furthermore, the fact that the cyclopentane derivative is 2.5 times as reactive as the cyclohexane derivative under the same conditions lends considerable support to the idea that a displacement reaction on carbon is the rate-determining process.[10]

Granted that an α-hydroxynitrosoalkane is formed *in situ* as the product of this rate-determining displacement reaction, the reaction products arising from the decomposition of this intermediate may be rationalized in terms of the reaction sequence 3 which was proposed as an integral portion of the Nef reaction sequence.

Further evidence for reaction sequence 3 is to be found in the recently reported work of Iffland and Criner.[11] These authors report that cyclohexanone oxime reacts readily with lead tetraacetate to produce a blue liquid which appears to be 1-acetoxnitrosocyclohexane. Hydrolysis of this ma-

(5) E. Muller, H. Metzger and D. Fries, *Ber.*, **87**, 1449 (1954); **88**, 1891 (1955).

(6) N. H. Furman, "Scott's Standard Methods of Chemical Analysis," 5th Ed., D. Van Nostrand Co., Inc., New York, N. Y., 1939, p. 647.

(7) We are indebted to Dr. Charles B. Colburn for performing these experiments.

(8) Although a mixed solvent was used in the kinetic and product experiments, the approximately 4:1 mole ratio of water to ethanol present in that solvent mixture would probably make water the dominant product-determining nucleophile in these reactions. It should be pointed out that if ethanol is the nucleophile which initially attacks the substrate, the product which seems likely to arise from this attack may revert, by acid-catalyzed hydrolysis, to the products formed by the direct attack of water.

(9) The observed kinetics do not distinguish between this situation and that situation which would exist if silver perchlorate were completely associated and both silver ion and perchlorate ion entered into the rate-determining transition state. This latter situation is most improbable due to the ionizing power of the solvent mixture.

(10) H. C. Brown and G. Ham, THIS JOURNAL, **78**, 2735 (1956).

(11) D. C. Iffland and G. X. Criner, *Chemistry & Industry*, 176 (1956).

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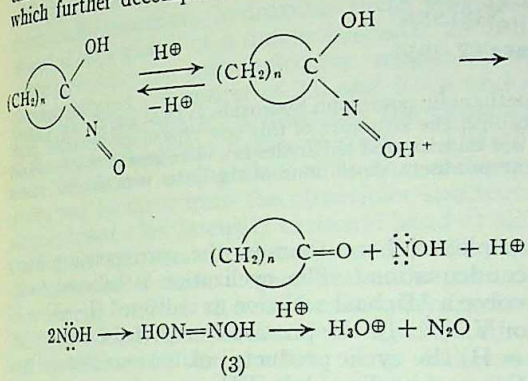
terial in aqueous acid media produces a quantitative yield of cyclohexanone. It seems reasonable to assume that the first step of this hydrolysis is the formation of 1-hydroxynitrosocyclohexane which further decomposes as in 3. Although the



(3)

authors did not isolate or identify nitrous oxide, its presence in the reaction products is indicated.

Experimental[12]

1-Chloronitrosocyclopentane was prepared in 75% yield by the method of Muller, Fries and Metzger[5] and fractionated with a 20-plate Heli-pak column at 15 mm., b.p. 42° and $n^{20}D$ 1.4570 (lit.[5] $n^{20}D$ 1.4570).

1-Chloronitrosocyclohexane was prepared and distilled in a like manner[5] at 15 mm., b.p. 55°, $n^{20}D$ 1.4630 (lit.[5] $n^{20}D$ 1.4629).

Acetonitrile was obtained from the Union Carbide and Carbon Co. and distilled from phosphorus pentoxide, b.p. 80°.

Ethanol was Union Carbide and Carbon C.P. absolute ethanol and the water used in the kinetic experiments was de-ionized conductivity water.

Silver perchlorate was chemically pure and obtained from the G. Frederick Smith Chemical Co. It was vacuum dried over phosphorus pentoxide before use.

Kinetic measurements were carried out in 10-ml. volumetric flasks which had been blackened with several coats of black paint. All kinetic measurements were carried out at 50.0 ± 0.01° in a solvent prepared by mixing 2 volumes of ethanol and 3 volumes of water with 5 volumes of acetonitrile. The following procedure was employed: an estimated amount of anhydrous silver perchlorate was placed in a 100-ml. volumetric flask and dissolved in *ca.* 100 ml. of solvent. Aliquots of this solution were taken and titrated for silver using standard ammonium thiocyanate and ferric alum indicator in dilute nitric acid. A predetermined weight of chloronitrosocycloalkane was weighed into a blackened 100-ml. volumetric flask and thermostated at 50.0°. The proper volume of standard silver perchlorate solution which had been previously thermostated was added and the reaction initiated by solution of the chloronitrosoalkane and the time noted. Several 10.0-ml. aliquots of reaction mixture were immediately transferred to thermostated 10-ml. volumetric flasks. At various time intervals a sample flask was withdrawn, its contents washed into 20 ml. of distilled water covered by 10–15 ml. of hexane. The hexane completely separated the blue nitroso compounds from the aqueous phase and allowed the produced acid to be titrated to the brom thymol blue end-point with standard, 0.10 *N* sodium hydroxide. The resulting acid titer was used in the calculation of the instantaneous concentrations of silver perchlorate and chloronitrosoalkanes, and these values were treated as in Fig. 1. In every case the reactions were carried to at least 50% completion. Spectrophotometric control experiments carried out at 620 mμ and in the reaction solvent at 50.0° showed that not more than 1–2% of chloronitrosoalkane decomposed during the course of the longest kinetic run. In one kinetic experiment it was found that the acid titer agreed with the quantity of silver chloride to within 2% at 50% reaction.

(12) All melting and boiling points are uncorrected.

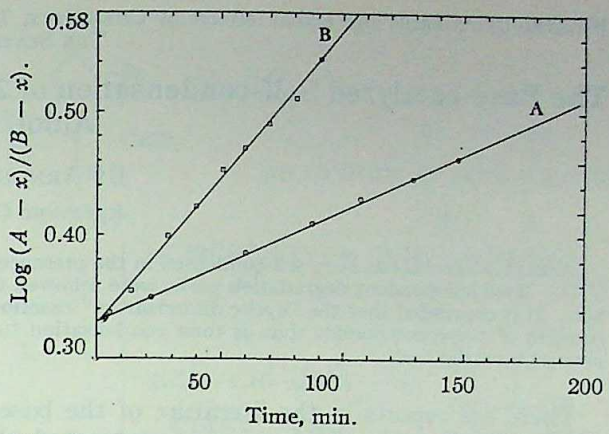


Fig. 1.—Second-order plot of the reaction of 0.100 *M* silver perchlorate with 0.20 *M* 1-chloronitrosocyclohexane, A, and 0.20 *M* 1-chloronitrosocyclopentane, B.

Product analyses were carried out for silver chloride, hydroxylamine, ketone and nitrous oxide in the following manner: after the disappearance of blue color a reaction mixture originally prepared from 70 ml. of 0.40 *M* silver perchlorate and made up to 0.20 *M* with chloronitrosoalkane was filtered with a tared sintered glass funnel of medium porosity. The silver chloride so collected was washed with ethanol and then ether and air-dried. In every case the yield of silver chloride was found to be quantitative to within 1–2%.

The filtrate and combined washings were treated with a slight excess of aqueous 5% sodium chloride solution, to precipitate excess silver ion and the solid separated by filtration. The volume of the final filtrate (*ca.* 150 ml.) was determined and the solution divided into two equal portions. The first portion was treated with 2.5 g. of 2,4-dinitrophenylhydrazine hydrochloride and 5 ml. of concentrated hydrochloric acid and then heated for 1 hr. on the steam-bath. The mixture was then cooled to room temperature and the precipitated 2,4-dinitrophenylhydrazone separated by filtration, washed copiously with warm 5% aqueous hydrochloric acid followed by water and then air-dried. In this manner crude cyclopentanone and cyclohexanone 2,4-dinitrophenylhydrazones melting at 138–142°[13] and 156–160°,[13] respectively, were obtained in 85 and 92% yields, respectively.

The remaining half of the filtrate was reduced to *ca.* 20 ml. by low pressure evaporation and 1 g. of ferric ammonium sulfate and 5 ml. of concentrated sulfuric acid added. The resulting solution was refluxed for 5 minutes and immediately titrated with standard 0.1 *N* potassium permanganate solution. A permanent pink color was obtained on the addition of only 0.20 ml. of 0.0832 *N* permanganate showing the absence of hydroxylamine.[6]

Nitrous oxide was found to be present in a reaction mixture before work-up by placing 0.10 ml. of the solution on an infusorial earth gas chromatographic column having ethanol as a liquid phase. A chromatogram was obtained on this column using helium carrier gas and at −78°. Only a single peak was obtained and this had the characteristic retention time of nitrous oxide.[7] The absence of brown fumes and the lack of pressure increase during every experiment show that nitrous oxide was the only nitrogen-containing gaseous product.

HUNTSVILLE, ALABAMA

(13) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1947, p. 221, report melting points of 142 and 166°, respectively.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, THE UNIVERSITY OF IDAHO, PURDUE UNIVERSITY AND RUTGERS, THE STATE UNIVERSITY]

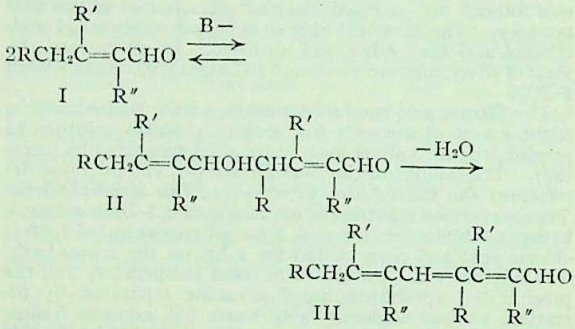
The Base-catalyzed Self-condensation of 2-Ethyl-2-hexenal. I. Formation of a Cyclic Aldol, $C_{16}H_{28}O_2$[1]

BY ARNOLD T. NIELSEN[2]

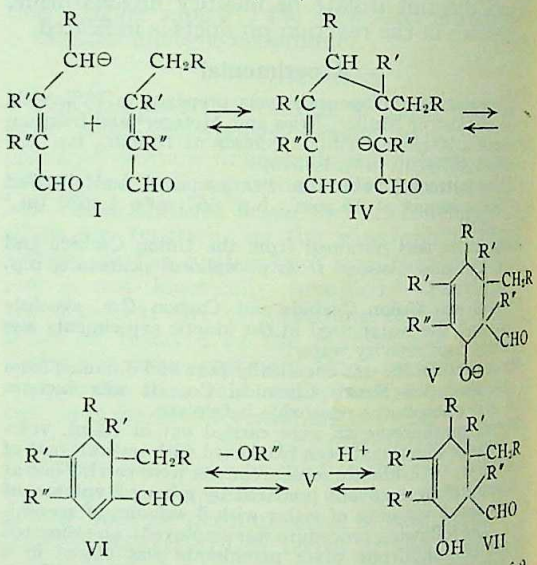
RECEIVED OCTOBER 22, 1956

2-Ethyl-2-hexenal has been self-condensed in the presence of methanolic potassium hydroxide to yield a cyclic aldol dimer VIII. Two independent degradation paths were followed to establish the structure of this new type of condensation product. It is concluded that the "cyclic dimerization" reaction of α,β-unsaturated aldehydes is a more general base-catalyzed reaction of these compounds than is their condensation to linear products, since none of the latter were obtained in the present investigation.

There are reports in the literature of the base-catalyzed self-condensation of α,β-unsaturated aldehydes to either cyclic or linear products. The latter compounds are believed to arise from an aldol condensation, involving carbonyl attack at the γ-carbon, which generally produces a conjugated trienal III.[3-5] A weakly basic catalyst (usually piperidine acetate) is employed in this reaction, the intermediate aldol II seldom being isolated because of its ease of dehydration. Mixed condensations of this type, employing two different aldehydes, also have been reported.[3,4b,6]



Cyclic condensation products have been obtained from crotonaldehyde,[3,4b,7] 3-methyl-2-butenal[3,8] and citral,[3] stronger basic catalysts being employed here than in the corresponding linear condensation. The cyclization is believed to involve a Michael addition as indicated (I → V → VI or VII).[8] In the previously reported examples (R′ = H) the cyclic products isolated were dienals (type VI), not cyclic aldols (VII).



In the present work the self-condensation of 2-ethyl-2-hexenal, in the presence of methanolic potassium hydroxide catalyst, has been investigated. Although no previous study of this condensation had been reported at the time this work was initiated, there appeared independently, subsequent to our first report,[9] patents disclosing some of these preliminary results.[10] The present paper presents a more detailed study of the reaction. The base-catalyzed self-condensation of 2-ethyl-2-hexenal was also studied recently by Häusermann.[11] However, with the elevated temperatures which he employed, the condensation products obtained were different from those reported herein.

On the basis of previously reported work one would expect 2-ethyl-2-hexenal to self-condense

(1) Presented at the 127th American Chemical Society Meeting, Cincinnati, Ohio, April, 1955.

(2) School of Chemistry, Rutgers, The State University, New Brunswick, N. J.

(3) 3-Methyl-2-butenal, for example, yields 3,7-dimethyl-2,4,6-octatrienal (III, R and R″ = H; R′, = CH_3); (a) F. G. Fischer and K. Löwenberg, *Ann.*, **494**, 263 (1932); (b) F. G. Fischer and K. Hultzsch, *Ber.*, **68**, 1726 (1935).

(4) (a) T. Reichstein, C. Ammann and G. Trivelli, *Helv. Chim. Acta*, **15**, 261 (1932); (b) K. Bernhauer, K. Irrgang, K. Adler, M. Mattauch, P. Miller and F. Neiser, *Ann.*, **525**, 43 (1936); (c) F. G. Fischer, K. Hultzsch and W. Flaig, *Ber.*, **70**, 370 (1937); (d) R. Kuhn and C. Grundmann, *ibid.*, **71**, 2274 (1938); (e) C. Grundmann, *Chem. Ber.*, **81**, 510 (1948).

(5) The self-condensation of 2-methyl-2-pentenal in the presence of ethanolic potassium hydroxide has been reported to yield a linear glycol, $C_{12}H_{22}O_2$, possibly derived from an aldol such as II; A. von Lenz, *Monatsh.*, **24**, 155 (1903). J. Ducasse (*Bull. soc. chim. France*, [5] **11**, 333 (1944)) obtained this same glycol from propanal using sodium ethoxide catalyst.

(6) Yields in these reactions range 10–50%; (a) E. Barraclough, J. W. Batty, I. M. Heilbron and W. E. Jones, *J. Chem. Soc.*, 1549 (1939); (b) R. Kuhn and C. J. O. Morris, *Ber.*, **70**, 853 (1937); P. Karrer and A. Rüegger, *Helv. Chim. Acta*, **23**, 284 (1940).

(7) K. Bernhauer and G. Neubauer, *Biochem. Z.*, **251**, 173 (1932).

(8) The cyclization of 3-methyl-2-butenal has previously been pictured as a diene addition (*cf.* refs. 3 and 7). E. A. Braude, B. F. Gofton, G. Lowe and E. S. Waight (*J. Chem. Soc.*, 4054 (1956)) concur with this mechanism in the cases of their reported lithium-catalyzed cyclization of 3-methyl-2-butenal. [illegible] (*cf.* refs. 3 and 4b), [illegible] *Helv. Chim. Acta*, **34**, 1482 (1951).

to the cyclic ketol, 2-acetyl-1,3,3,5-tetramethyl-5-cyclohexen-1-ol. On the other hand, the postulated mechanism for the self-condensation of 1-acetylcyclohexene is in agreement with the one shown here (*cf.* E. R. H. Jones and H. P. Koch, *J. Chem. Soc.*, 393 (1942)).

(9) A. T. Nielsen, Ph.D. Thesis, University of Washington, June, 1947.

(10) (a) R. H. Hall and K. H. W. Tuerck, British Patent 608,983, Sept. 23, 1948; *C. A.*, **44**, 4493 (1950); (b) R. H. Hall and K. H. W. Tuerck, U. S. Patent 2,528,592, Nov. 7, 1950; *C. A.*, **45**, 3686 (1951).

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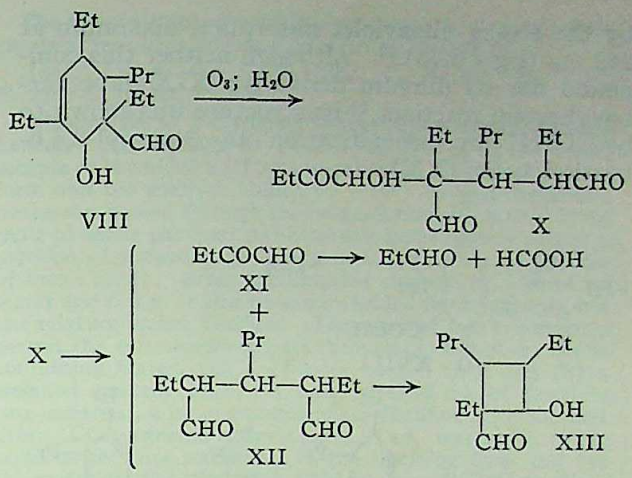
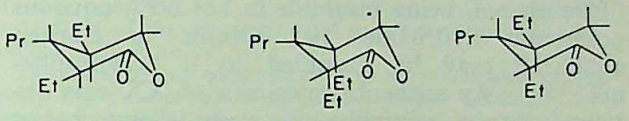
initially to either a linear or a cyclic aldol dimer (II or VII). It was found, however, that unlike other α,β-unsaturated aldehydes previously studied, it failed to react in the presence of weak bases. On the other hand, when treated with aqueous methanolic potassium hydroxide, there was produced a 40% yield[12] of a dimer, $C_{16}H_{28}O_2$, as indicated by analysis and molecular weight data. Strong infrared absorption at 3.0 and 5.9 μ and a Zerewitinoff determination indicated the presence of one hydroxyl and one carbonyl group. The absence of olefinic conjugation with the carbonyl group was apparent from the ultraviolet spectrum which showed a low intensity carbonyl band at 320 mμ but no maximum in the region 200–270 mμ. The compound formed a monoöxalomonophenylhydrazone and a 2,4-dinitrophenylhydrazone and gave a Schiff aldehyde reaction. Quantitative hydrogenation and bromination data indicated the presence of only one olefinic double bond. Reduction with lithium aluminum hydride gave a glycol, $C_{16}H_{30}O_2$ (IX), also having one double bond. The above data are in agreement with a cyclic aldol structure for the dimer (*i.e.*, VIII; VII, R′ = H, R = R″ = Et); such a compound cannot, of course, dehydrate to VI.

Since no cyclic aldol had been reported previously as a product of the self-condensation of an α,β-unsaturated aldehyde, it was felt that additional evidence in support of structure VIII was required, particularly in view of the limited number of examples of this cyclization reaction.[3,4b,7,14] Such evidence was first obtained by ozonolysis of the dimer to yield the following products[15]: formic acid (38%), propionic acid (30%), propionaldehyde (8%), carbon dioxide (3%) and a neutral, steam-volatile compound, $C_{12}H_{22}O_2$ (XIII), (*ca.* 30% yield, crude). The latter substance showed strong infrared absorption at 2.9 and 5.8 μ assigned to one hydroxyl and one carbonyl group, respectively; a Zerewitinoff determination supported this assignment. The ozonolysis products readily can be rationalized on the basis of structure VIII by the equations shown. Under the reaction conditions the intermediate X (not isolated) is cleaved, by dealdolization, to 2-ketobutanal (XI) and the dialdehyde XII which readily cyclizes to the aldol XIII.[16–18]



Aldol XIII when treated with methanolic potassium hydroxide led to the lactone XIV, a compound previously reported by Häusermann.[11,19,20]



XIV XIVa XIVb

By direct titration with 0.5 *N* sodium hydroxide XIV was easily saponified to regenerate its precursor, the anion of 2,4-diethyl-5-hydroxy-3-propylpentanoic acid (XV). Oxidation of XV with permanganate led to a high melting *meso* isomer of 2,4-diethyl-3-propylpentanedioic acid (XVI), m.p. 151–151.5°,[21] which was found, by mixture melting point determination, to be identical with an authentic sample of this acid kindly provided by Dr. Häusermann.[11]

Because the ozonolysis gave products somewhat indirectly derived from VIII, more direct evidence for the presence of a six-membered ring was sought by chromic acid oxidation. This reaction produced equal molar amounts of carbon dioxide and a neutral compound $C_{15}H_{26}O$. The same product was obtained by oxidizing VIII with permanganate and decarboxylating the crude acid (XVII) formed thereby. The presence of one double bond in the product was demonstrated by quantitative hydrogenation. That this bond was conjugated with a carbonyl group was indicated

(12) The maximum yield (40%) was obtained using 0.6 mole-equivalent of potassium hydroxide per mole of aldehyde (25°, 30 minutes reaction time); under these same conditions, shorter or longer reaction periods gave a lowered yield. At the longer reaction times (1–2 hr.) large amounts of an acidic compound, $C_{16}H_{30}O_3$, were produced (ref. 13). Increasing or decreasing the reaction temperature or alkali concentration did not increase the yield.

(13) A. T. Nielsen, THIS JOURNAL, **79**, 2524 (1957).

(14) The structure of the product has been established in two of the three reported cases of self-condensation to a cyclic dienal, *viz.*, 3-methyl-2-butenal[3a] and crotonaldehyde.[7] The reaction has perhaps not been recognized as a general one because of the paucity of examples (*cf.* ref. 8).

(15) Yields in parentheses are based on the assumption that one mole-equivalent of each compound is formed from VIII.

(16) The formation of a four-membered cyclic aldol is believed to be favored by the buttressing effect of adjacent alkyl substituents; (a) R. C. Fuson in H. Gilman, "Organic Chemistry," 2nd Ed., Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 81; (b) S. Winstein and E. Grunwald, THIS JOURNAL, **70**, 828 (1948).

(17) Under the conditions of the experiment, none of the 2-ketobutanal was isolated, since it decomposed, apparently completely, into formic acid and propionaldehyde. For similar cleavages of 2-hydroxy aldehydes *cf* (a) R. Pummerer, O. Guyot and L. Birkofer, *Ber.*, **68**, 480 (1935); (b) C. Harries and H. O. Türk, *Ann.*, **374**, 338 (1910) and (c) W. G. Young, A. C. McKinnis, I. D. Webb and J. D. Roberts, THIS JOURNAL, **68**, 293 (1946); refs. b and c refer to ozonolysis experiments.

(18) Only an 8% yield of propionaldehyde was obtained (as its 2,4-dinitrophenylhydrazone), since the major portion was oxidized to propionic acid (30% yield); T. E. Friedemann (*J. Biol. Chem.*, **73**, 331 (1927)) observed pyruvaldehyde to be very rapidly oxidized by hydrogen peroxide at *p*H 7 or less to formic and acetic acids.

(19) See H. Meerwein, *Ber.*, **53**, 1829 (1920), for other examples of disproportionation of 1,5-dialdehydes.

(20) The dialdehyde XII should readily equilibrate to the most stable conformation in the presence of base, thus leading to the equatorial form XIV. The alternate structure (XIVa) which could lead to a *meso*-acid may be considered unstable relative to XIV. The possibility of epimerization at the position alpha to the carbonyl group occurring readily as a result of the mild saponification conditions (direct titration with 9.5 *N* sodium hydroxide) appears unlikely; the lactone structure XIVb (which would lead to racemic XVI in the absence of epimerization) is therefore excluded.

(21) The racemic isomer melts at 98–99° (ref. 13).

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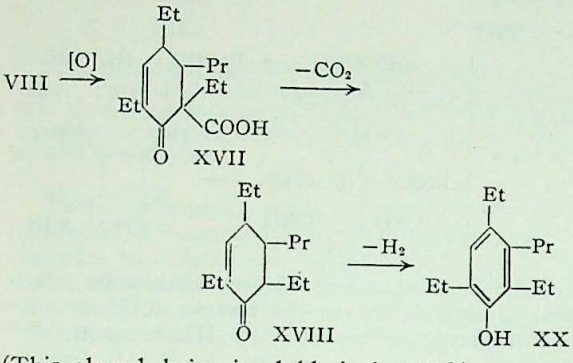
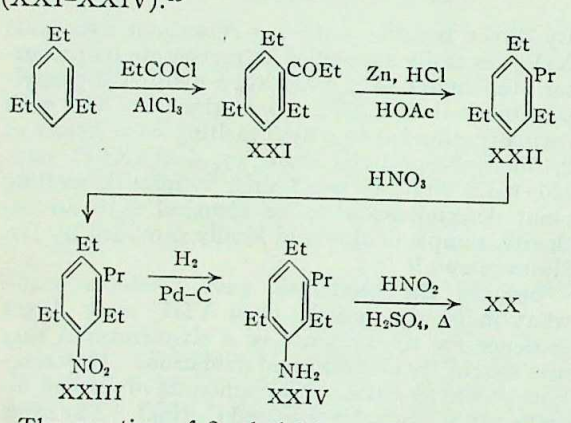
by the strong ultraviolet absorption maximum at 242 mμ (log ε 3.75).[22] Although neither this compound nor its dihydro derivative XIX gave carbonyl-group reactions,[23] its structure was shown to be XVIII by aromatization to 3-propyl-2,4,6-triethylphenol (XX).



(This phenol, being insoluble in hot 50% aqueous potassium hydroxide, but soluble in Claisen alkali,[24,25] may be classified as a "cryptophenol."[26,27]) An authentic specimen of XX was obtained by an unambiguous route shown below (XXI–XXIV).[28]



The reaction of 2-ethyl-2-hexenal to form VIII provides the first reported example of the dimerization of an α,β-unsaturated aldehyde to yield a cyclic aldol which is incapable of dehydration; in previously reported cases cyclization has always led to cyclic dienals.[8] It should be emphasized that 2-ethyl-2-hexenal, unlike its lower homologs, failed to yield any linear condensation product. Thus, it would appear that the "linear aldol condensation" discussed above is limited to suitably unhindered aldehydes (I, R, R′ and R″ no larger than methyl); also, it requires a milder basic catalyst than the corresponding condensation to cyclic products. The position of the equilibrium I ⇄ II evidently is determined to some extent by steric factors. In cases where the formation of II is unfavorable, the "cyclic dimerization" is realized (assisted by the formation of a six-membered ring) and would appear to be possible for all examples, including higher homologs of 2-ethyl-2-hexenal having γ-hydrogens, and to be a typical, general reaction of these compounds.

Experimental[29]

2-Ethyl-2-hexenal.—Preliminary experiments indicated that purified, freshly distilled, samples of 2-ethyl-2-hexenal were required for maximum yields of condensation products. Traces of peroxide or acidic impurities in the aldehyde had no effect on the reaction, but in larger amounts these substances caused much resin formation with resulting lowered yields of condensation products. Peroxide-free 2-ethyl-2-hexenal was prepared by the self-condensation,[30] in a nitrogen atmosphere, of peroxide-free butanal, b.p. 70–72° (690 mm.), $n^{25}D$ 1.3770.[31] The pure 2-ethyl-2-hexenal obtained (71% yield) was distilled under nitrogen; b.p. 81° (34 mm.), $n^{25}D$ 1.4504. It was found to contain no peroxide[32] and 0.1% of an acidic impurity[33] by direct titration with 0.1 *N* sodium hydroxide It was found unnecessary, however, to employ this highly purified material, since samples of aldehyde which had been purified by the following procedure gave equally good results. A 423-g. sample of Carbide 2-ethyl-2-hexenal[34] was washed successively with five 100-ml. portions of *N* sodium hydroxide solution and then with *N* hydrochloric acid and water. After drying over anhydrous magnesium sulfate in a nitrogen atmosphere, the aldehyde was distilled *in vacuo* under nitrogen; b.p. 67° (18 mm.), yield 368 g.; peroxide and acidic impurities were 0.6 and 0.3%, respectively.[32,33]

Self-condensation of 2-Ethyl-2-hexenal: Preparation of 2-Hydroxy-6-propyl-1,3,5-triethyl-3-cyclohexene-1-carboxaldehyde (VIII).—2-Ethyl-2-hexenal (160 g., 1.27 moles), purified by the alkali extraction procedure described above, was freshly distilled, under nitrogen, directly into the reaction flask. A solution of 48 g. of potassium hydroxide (85% assay, 0.73 mole) in 25 ml. of water and 65 ml. of methanol was then added during 1.5 minutes with vigorous stirring while a nitrogen atmosphere was maintained and the temperature held at 25° by ice-bath cooling. The color quickly changed to orange while the alkali was being added, and after a total reaction time of 30 minutes (temp. 25°), 500 ml. of water was added rapidly to the mixture with stirring. The oily layer which formed was separated, the aqueous layer extracted four times with ether and the extracts combined with the main portion. The ether solution was washed with water and dried over magnesium sulfate.

After distilling the ether on the steam-bath, the residue was distilled *in vacuo* to yield the following fractions: (1) 56 g., b.p. 60–61° (14 mm.), 2-ethyl-2-hexenal (35% recovery); (2) 72 g. (45%), b.p. 114–115° (0.12 mm.), $n^{25}D$ 1.4885, crude aldol VIII; (3) residue, 8 g. Redistillation of fraction 2 gave 63.5 g. (40% yield) of pure VIII, b.p. 114–116° (0.16 mm.), $n^{25}D$ 1.4893.

Anal. Calcd. for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18; mol. wt., 252.4. Found: C, 76.27; H, 11.39; mol. wt., 250, 253.[35]

(22) R. B. Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942).

(23) *Cf.* R. Cornubert, C. Borel, M. De Demo, J. Garnier, R. Humeau, H. Le Bihan and G. Sarkis, *Bull. soc. chim. France*, [5] **2**, 195 (1935).

(24) L. Claisen, *Ann.*, **418**, 69, 96 (1919); **442**, 210, 224 (1925).

(25) G. H. Stillson, THIS JOURNAL, **68**, 722 (1946).

(26) K. Auwers, *Ber.*, **39**, 3160, 3167 (1906).

(27) G. H. Stillson, D. W. Sawyer and C. K. Hunt, THIS JOURNAL, **67**, 303 (1945).

(28) When 2,4,6-triethylpropiophenone (XXI) was reduced to the hydrocarbon XXII (27% yield) by a forcing Clemmensen procedure, deacylation also occurred with the formation of 1,3,5-triethylbenzene in 24% yield. This appears to be the first reported case of deacylation accompanying a Clemmensen reduction.

(29) All melting points are corrected. Boiling points are uncorrected.

(30) C. Weizmann and S. F. Garrard, *J. Chem. Soc.*, **117**, 324 (1920).

(31) *Cf.* F. E. McKenna, E. C. Lingafelter and H. V. Tartar, THIS JOURNAL, **71**, 2263 (1949), on purification and peroxide formation of propanal.

(32) Procedure of K. Nozaki, *Ind. Eng. Chem., Anal. Ed.*, **18**, 583 (1946).

(33) Acidic and peroxide impurity each assumed to have a molecular weight of 142, for purposes of calculating percentage by weight present.

(34) A generous supply of 2-ethyl-2-hexenal was provided us by the Carbide and Carbon Chemicals Corp., South Charleston, West Va.

(35) The procedure of R. E. Kitson, A. N. Oemler and J. Mitchell (*Anal. Chem.*, **21**, 404 (1949)) was used, with slight modifications, for this molecular weight determination.

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The aqueous alkaline solution above, remaining after extraction with ether, was acidified with concd. hydrochloric acid. The oil which formed was separated and the aqueous part extracted three times with ether. The ether extracts and the oil were combined and dried over magnesium sulfate. After distilling the ether, the residue was distilled to give (1) 1.4 g., b.p. 85–142° (0.25 mm.); (2) 9.2 g., b.p. 142–155° (0.25 mm.), $n^{25}D$ 1.4764 and 1.0 g. of residue.

Attempts were made to increase the yield of VIII by varying the experimental conditions. It was found that, under the conditions of the above experiment, either longer or shorter reaction periods gave lower yields of VIII. At shorter reaction times than 30 minutes, larger amounts of unreacted 2-ethyl-2-hexenal were recovered; at longer reaction times (1–2 hr.) less unreacted aldehyde was recovered; but greater amounts of acidic material were obtained. Higher reaction temperatures or alkali concentrations produced a less pure aldol in lowered yield, whereas lower temperatures or alkali concentrations made necessary a prolonged reaction time without increasing the yield.[13]

Quantitative hydrogenation of a 0.5-millimole sample of the aldol VIII at 689 mm. and 23° (acetic acid solvent containing a few drops of concd. hydrochloric acid, 5% palladium–charcoal catalyst) resulted in absorption of 1.00 mole-equivalent of hydrogen in 300 minutes, after which time hydrogenation continued extremely slowly (*ca.* 0.065 mole-equivalent per hour). On quantitative bromination with a 5% solution of bromine in carbon tetrachloride, 1.07 mole-equivalents of bromine were absorbed, with some hydrogen bromide evolution. A Zerewitinoff determination showed 1.03 active hydrogens and 1.04 additional mole-equivalents of methylmagnesium iodide reacted. The compound gave a positive Schiff aldehyde test. A sample of the aldol, b.p. 132–135° (0.5 mm.), $n^{25}D$ 1.4894, showed a broad ultraviolet maximum at 320 mμ (log ε 2.1), a minimum at 270 mμ (log ε 1.85) (95% ethanol solvent). There was no maximum in the range 200–270 mμ. The infrared spectrum showed bands at 3.0m, 3.5, 3.6, 5.9, 6.9, 7.3m, 9.4m, 9.75 and 13.0 μ.

The oxalomonophenyldihydrazone[36] separated from dilute aqueous ethanol or from ligroin as a cream-colored amorphous powder, m.p. 95–97°. The derivative was contaminated with a small amount of less soluble impurity which could not be removed by crystallization.

Anal. Calcd. for $C_{24}H_{26}N_4O_3$: C, 67.26; H, 8.47. Found: C, 68.6; H, 8.9.

A 2,4-dinitrophenylhydrazone derivative was prepared, m.p. 40–62°. It could not be purified to constant melting point by recrystallization.

6-Hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ol (IX).—To a solution of 1.1 g. (0.029 mole) of lithium aluminum hydride in 80 ml. of ether was added, with stirring, a solution of 13.0 g. (0.0515 mole) of the aldol VIII dissolved in 35 ml. of dry ether, during 30 minutes[37]; stirring was continued for 10 minutes longer. The solution was then treated successively with 45 ml. of water and 50 ml. of 10% sulfuric acid. The ether layer was separated, washed with water and dried over magnesium sulfate. After distilling the ether there was obtained 9.7 g. (74% yield) of the extremely viscous glycol, b.p. 133–135° (0.36 mm.), $n^{25}D$ 1.4930[38]; infrared bands at 2.78m, 2.92m, 3.40, 3.48, 6.05w, 6.85, 7.26, 8.1w, 8.67w, 9.20w, 9.68, 10.02, 10.60w, 11.20w, 11.52w and 11.95w μ (chloroform solvent).

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.49; H, 12.12.

On quantitative hydrogenation of the glycol (under conditions identical with those employed with the above aldol VIII) 0.95-mole-equivalent of hydrogen was absorbed in 120 minutes, after which time hydrogenation ceased. A Zerewitinoff determination indicated 1.98 active hydrogens and an additional 0.1 mole-equivalent of methylmagnesium iodide reacted.

(36) P. P. T. Sah and H. Wang, *J. Chinese Chem. Soc.*, **14**, 39 (1946); *C. A.*, **43**, 6971 (1949).

(37) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947).

(38) Hall and Tuerck (ref. 10) reduced the aldol VIII to an unsaturated glycol, $C_{16}H_{30}O_2$, by hydrogenation with Raney nickel catalyst, 74% yield, b.p. 149–151° (2 mm.), $n^{20}D$ 1.4966, bis-3,5-dinitrobenzoate m.p. 178°. Attempts to prepare a 3,5-dinitrobenzoate of the above glycol resulted in the formation of a gum which failed to crystallize.

The bis-*p*-nitrophenylurethan was prepared as pale yellow crystals from high boiling ligroin, m.p. 76.5–78.5°.

Anal. Calcd. for $C_{30}H_{38}N_4O_8$: C, 61.84; H, 6.57. Found: C, 62.29; H, 6.9.

Ozonolysis of 2-Hydroxy-5-propyl-2,4,6-triethyl-3-cyclohexene-1-carboxaldehyde (VIII).—A 25.3-g. (0.10 mole) sample of the aldol VIII was dissolved in 100 ml. of chloroform and the solution chilled to −15°; oxygen containing ozone was passed through the cold solution at a rate of 0.014 mole of ozone per hour until the exit gases rapidly caused a solution of potassium iodide to turn red (8 hr.; 0.11 mole of ozone used). After distilling the chloroform, 150 ml. of water and 6.6 g. of zinc dust were added to the ozonide and the mixture steam distilled. The receiver was arranged to permit the exit vapors to pass through (1) a washing bottle containing water, (2) a Drierite packed tube and (3) a weighed Ascarite tube. A total of 4040 ml. of distillate was collected, a large amount of oil distilling with the first liter. Concentrated sulfuric acid, 10 ml., was added to the aqueous mixture remaining in the distilling flask and the steam distillation continued, 2350 ml. of additional distillate being collected; very little oil distilled with the last portion of water collected. Throughout the distillation, aliquot portions of the distillate, taken at intervals, were titrated with 0.1 *N* sodium hydroxide to determine the rate of distillation of water-soluble acid; of the total acid collected (0.068 mole) 65% of this amount (0.044 mole) distilled after adding the sulfuric acid.

The Ascarite tube gained 0.14 g. in weight, corresponding to a 3.2% yield of carbon dioxide. A blank determination showed such minute amounts of carbon dioxide in the steam which was used that no correction of this value was necessary.

The total combined aqueous steam distillate obtained was found to contain 0.068 mole of water-soluble acid; aliquot samples of the distillate were analyzed as follows: Formic acid was determined quantitatively by a modification of the procedure of Reid and Weihe.[39] The total amount obtained was found to be 0.038 mole (56% of the total water-soluble acid).

One aliquot portion of the distillate was neutralized with dilute sodium hydroxide solution, evaporated to dryness, diluted with water and acidified with sulfuric acid. In order to decompose the formic acid, the solution was refluxed with mercuric oxide until no more carbon dioxide was evolved. The acid which remained gave Duclaux numbers 12.2, 11.9, 11.5 on distillation (reported[40] for propionic acid, 11.9, 11.7, 11.3). The *p*-phenylphenacyl ester of this acid, m.p. 102.5°, showed no depression in melting point when mixed with an authentic sample of *p*-phenylphenacyl propionate, m.p. 102–103°.

The original distillate was found to contain 0.0079 mole of total carbonyl compounds. (Carbonyl analysis was made by reaction of an aliquot sample with hydroxylamine hydrochloride and titration of the liberated hydrochloric acid with 0.1 *N* sodium hydroxide.) An aliquot portion was neutralized with dilute sodium hydroxide and this solution refluxed gently while nitrogen was passed slowly through it. The exit gases when passed into a solution of 2,4-dinitrophenylhydrazine in dilute phosphoric acid formed an orange precipitate, m.p. 153–155°, after recrystallization from dilute ethanol. This compound showed no depression in melting point when mixed with an authentic sample of propionaldehyde 2,4-dinitrophenylhydrazone, m.p. 154–155°.

Thus from the ozonolysis of VIII there were produced a 38% yield of formic acid, 30% propionic acid, 8% propionaldehyde, 3% carbon dioxide and 30% (crude) of the aldol XIII (see below). The remainder of the ozonolysis products were 1.4 g. of steam-volatile oil produced after acidification of the zinc salts with sulfuric acid, 5.7 g. of neutral and 2.9 g. of acidic, non-steam-volatile, undistillable residue. The total weight of ozonolysis products obtained was 22.7 g. (from 25.3 g. of VIII).

1,3-Diethyl-2-hydroxy-4-propylcyclobutanecarboxaldehyde (XIII).—In the above ozonolysis experiment, the oil which distilled before adding the sulfuric acid was separated and the aqueous part extracted twice with ether, the ether

(39) J. D. Reid and H. D. Weihe, *Ind. Eng. Chem., Anal. Ed.*, **10**, 271 (1938).

(40) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 147.

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extracts being combined with the main portion. After drying and distilling the ether, there was obtained on distillation a forerun, 0.7 g., b.p. 72–78° (0.3 mm.); 6.3 g. of crude compound XIII, b.p. 78–113° (0.3 mm.); and 1.1 g. of residue. On redistillation 3.7 g. (19% yield) of the light yellow, nearly odorless aldol was produced, b.p. 84–92° (0.3 mm.), $n^{25}D$ 1.461–1.463.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; mol. wt., 198.3. Found: C, 72.46; H, 10.99; mol. wt. (Rast), 194, 195.

The infrared spectrum showed bands at 2.90m, 3.38, 3.45, 3.64w, 5.80, 6.85, 7.30, 7.90m, 8.05m, 9.1, 10.4 and 12.90m μ.

A Zerewitinoff determination showed 0.72 active hydrogen and 1.37 mole-equivalents additional methylmagnesium iodide reacted. Oxidation of the compound with alkaline or acid potassium permanganate under various conditions failed to yield a compound which could be isolated in pure form.

2,4-Diethyl-3-propyl-1,5-pentanolactone (XIV).—To a solution of 15.3 g. (0.077 mole) of XIII in 100 ml. of methanol was added, in small portions, a solution of 24 g. of potassium hydroxide (85%) in 60 ml. of methanol and 20 ml. of water (temperature, 10–15°). The orange solution which formed was allowed to stand 24 hr. at 3°, 24 hr. at room temperature (solution became dark red) and then refluxed gently for 1 hr. The methanol was then distilled and the residue diluted with 500 ml. of water. The resulting mixture was extracted five times with ether to remove neutral material. The aqueous solution remaining was acidified with hydrochloric acid and extracted three times with ether. The resulting ether solution of acidic material was extracted with saturated sodium bicarbonate solution, *N* hydrochloric acid and water and dried over magnesium sulfate. Distillation gave: (1) 1.9 g., b.p. 140–152° (10 mm.), $n^{25}D$ 1.4617; (2) 2.6 g. (17%) of XIV, b.p. 152–156° (10 mm.), $n^{25}D$ 1.4613; (3) 1.5 g., b.p. 161–164° (9 mm.), $n^{25}D$ 1.4636; and 2.0 g. of residue. (Häusermann[11] reported b.p. 147–149° (11 mm.), $n^{18}D$ 1.4660 for XIV.) The infrared spectrum of fraction 2, above, showed bands at 3.53, 3.60, 5.85, 6.90, 7.30, 7.95, 8.15m, 8.45, 8.75, 8.95, 9.50m, 10.60w and 13.0w μ.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; mol. wt., 198.3. Found: C, 72.77; H, 11.13; sapn. equiv., 199.

The dried ether solution above, containing neutral material, was distilled to yield the following fractions: 1.4 g., b.p. 120–135° (13 mm.), $n^{25}D$ 1.4702; 2.3 g., b.p. 135–145° (13 mm.), $n^{25}D$ 1.4808; and 1.5 g. of residue; these fractions were not investigated further.

2,4-Diethyl-3-propylpentanedioic Acid (XVI).[11]—A small sample of fraction 2 above (XIV) was saponified, by direct titration, with 0.5 *N* sodium hydroxide; the resulting solution was treated with potassium permanganate to yield the acid XVI, m.p. 151–151.5°, after one recrystallization from water (lit.[11] m.p. 149–150°).[21] When this material was mixed with an authentic sample (m.p. 151–151.5°), kindly provided by Dr. Häusermann, the melting point was not depressed.

5-Propyl-2,4,6-triethyl-2-cyclohexen-1-one (XVIII).—A solution of 33 g. (0.33 mole) of chromic anhydride in 40 ml. of water and 40 ml. of acetic acid was added during 1 hr., with stirring, to a solution of 61.3 g. (0.244 mole) of VIII. The temperature was maintained below 25° during the addition. After 3.5 hr., the solution was warmed to 70–80° and the stirring continued for 25 additional hr. A slow stream of nitrogen was continuously passed through the apparatus, the exit gases being conducted through a purifying train and finally through an Ascarite packed tube. The Ascarite tube gained in weight 2.21 g., corresponding to a 20.6% total yield of carbon dioxide; the yield was *ca.* 19% in 15 hr.

After adding 340 ml. of 6 *N* sodium hydroxide solution and extracting with ether, the ether extracts were washed with water, *N* sodium hydroxide solution, water and dried. After distilling the ether, the residue was fractionally distilled to yield 11.2 g. (20.7% yield) of the unsaturated ketone XVIII, having a faint fruity odor, b.p. 94–96° (0.2 mm.), $n^{25}D$ 1.4829; 29.0 g., b.p. 113–140° (0.20 mm.), partly oxidized and unchanged material; and 7.2 g. of residue. From the alkaline aqueous portion remaining after the ether extractions there was isolated, after acidification, 4.6 g. of a viscous oil which gave off carbon dioxide when heated strongly. The yield of crude ketone and of carbon dioxide could be increased to 50% by using a 75% excess of chromic anhydride; however, in this case, the ketone could not be obtained in a pure state by redistillation, and the use of a smaller excess of oxidizing agent was found to be more desirable.

A 12.5-g. sample of VIII, suspended in a solution of 100 ml. of 5 *N* sulfuric acid and 20 ml. of acetic acid was stirred with 11 g. of potassium permanganate for 2.5 hr. at 25°. After adding sodium bisulfite to dissolve the manganese dioxide, the oxidation product was separated into neutral and acidic portions in the usual manner. The acid product was a viscous oil, 3.7 g., containing crude 2-oxo-6-propyl-1,3,5-triethyl-3-cyclohexene-1-carboxylic acid (XVII). [No attempt was made to characterize this acid, since it decarboxylated so readily; on warming slightly on the steam-bath it rapidly evolved carbon dioxide.] Distillation of this material gave 1.0 g. of the neutral, unsaturated ketone XVIII, b.p. 120–127° (0.5 mm.), $n^{25}D$ 1.4807, and 1.6 g. of residue. The neutral fraction from the oxidation was distilled to yield 0.8 g., b.p. 60–130° (0.8 mm.); 3.6 g., b.p. 130–139° (1.0 mm.), $n^{25}D$ 1.4859; and 1.9 g. of residue.

The ketone XVIII was found to react with bromine in carbon tetrachloride solution very slowly without evolution of hydrogen bromide. Quantitative hydrogenation of a small sample in isoamyl alcohol solvent containing a few drops of hydrochloric acid (platinum catalyst, 25°, 690 mm.) showed 0.9 mole-equivalent of hydrogen absorbed in 1.5 hr., after which time hydrogenation continued very slowly (1.0 mole-equivalent total absorbed in 3 hr.). The ultraviolet spectrum showed maxima at 242 mμ (log ϵ 3.75) and 293 mμ (log ϵ 2.79) and a minimum at 281 mμ (log ϵ 2.76) (95% ethanol solvent). Attempts to prepare a carbonyl derivative of this ketone, using a variety of carbonyl reagents, failed, the original reactants being recovered in each case; infrared bands at 2.90w, 3.40, 3.50, 5.82m, 5.98, 6.85, 7.28m, 11.10w and 11.50 μ.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.02; H, 11.79; mol. wt., 222.4. Found: C, 80.26; H, 11.48; mol. wt., 227, 228.5.[25]

3-Propyl-2,4,6-triethylcyclohexanone (XIX).—An 11.6-g. sample of the above unsaturated ketone XVIII (0.052 mole) dissolved in a solution of 50 ml. of acetic acid, 10 ml. of water and 1 ml. of concd. hydrochloric acid was hydrogenated at 690 mm. (0.87 g. of platinum oxide and 4 g. of 5% palladium-on-charcoal catalysts) until one mole-equivalent of hydrogen was absorbed (64 hr.). After filtering the catalyst, the filtrate was diluted with 350 ml. of water and extracted with ether. The ether extracts were washed with *N* sodium hydroxide solution, then with water and dried. After distilling the ether, the residue was distilled to yield 0.7 g., b.p. 80–89° (0.6 mm.); 4.7 g. of crude XIX, b.p. 88–93° (0.35 mm.), $n^{25}D$ 1.4668; 2.8 g., b.p. 94–95° (0.2 mm.), $n^{25}D$ 1.4700; and 0.7 g. residue. Redistillation of the second fraction gave 2.6 g., b.p. 78–82° (0.17 mm.), $n^{25}D$ 1.466, having a faint sweet odor, which was used for elemental analysis; infrared bands at 3.0w, 3.40, 3.48, 5.83, 6.85, 7.27, 8.85w and 9.10w μ.

Anal. Calcd. for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 79.91; H, 12.39.

Attempts to prepare a carbonyl derivative of this ketone failed, the original reactants being recovered in each case.[23]

2,4,6-Triethyl-3-propylphenol (XX) from XVIII.—A 0.70-g. (3.16 millimoles) sample of 5-propyl-2,4,6-triethyl-2-cyclohexen-1-one (XVIII) was refluxed with 0.35 g. of 5% palladium–charcoal catalyst for 1 hr., during which time 0.71 mole-equivalent of hydrogen was collected. After filtering, the residue was distilled through a small Emich tube, to yield 0.32 g. (45%) of the yellow phenol, b.p. 262–266° (690 mm.), $n^{25}D$ 1.506–1.510. Redistillation gave a sample which was used for analysis, $n^{25}D$ 1.5086. The compound rapidly became dark orange in the presence of air, but could be stored under nitrogen without change. The ultraviolet spectrum showed a broad maximum at 281 mμ (log ϵ 3.22) (95% ethanol solvent); infrared bands at 2.87, 3.47, 3.53, 5.95w, 6.22w, 6.37w, 6.87, 7.30m, 7.70m, 7.93, 8.25, 8.45, 9.05 (shoulder), 9.15–9.20, 9.40m, 10.1w, 11.4m, 11.6m and 12.1m μ.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.69; H, 11.21.

The phenol was insoluble in 50% aqueous potassium hydroxide solution but soluble in Claisen alkali.[24,25] It re-

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acted with sodium metal but gave a negative ferric chloride test in alcohol. The infrared spectrum showed some absorption at 5.95 μ which was absent in the authentic sample of XX (see below) and which is believed to be due to the presence of a small amount of carbonyl compound (XIX or XVIII) which could not be removed by distillation; in all other respects the two samples were spectroscopically identical.

The phenylurethan derivative was prepared by refluxing a solution of 0.44 g. of the above phenol XX from the condensation, 4 ml. of phenyl isocyanate and 5 ml. of pure diethylene glycol dimethyl ether for 22 hr. After distilling the solvent and excess phenyl isocyanate, the residue was extracted with boiling hexane and filtered hot to remove insoluble material. From the filtrate, by fractional crystallization from hexane, there was obtained 0.14 g. of the crude crystalline derivative, m.p. 111–119°. Three recrystallizations from petroleum ether gave long white needles, m.p. 120–121°; when mixed with an authentic sample of 2,4,6-triethyl-3-propylphenol phenylurethan derivative, m.p. 122–122.5° (see below), the melting point was not depressed. When the ether solvent was omitted from the procedure, no derivative could be isolated.

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61. Found: C, 77.77; H, 8.59.

2,4,6-Triethylpropiophenone (XXI).—To a solution of 58.7 g. (0.362 mole) of purified 1,3,5-triethylbenzene (b.p. 101° (21 mm.), $n^{25}D$ 1.4934[41]) and 37.2 g. (0.40 mole) of freshly distilled propionyl chloride, b.p. 76–78°, in 50 ml. of dry tetrachloroethane was added, with stirring, during 1 hr., 66 g. (0.50 mole) of anhydrous aluminum chloride (temp. 26–35°). After addition of approximately one-third of the aluminum chloride, the solution became deep red in color. The solution was held at 40° with continuous stirring for 30 minutes after addition of the aluminum chloride. It was then poured into 400 g. of ice and stirred until all of the complex was dissolved. The oil was separated with the aid of ether and washed successively with *N* sodium hydroxide, *N* hydrochloric acid and water. After drying over magnesium sulfate and distilling the solvents, there was obtained 12 g., b.p. 80–109° (5 mm.), containing mainly unreacted 1,3,5-triethylbenzene (20% recovery) and 60 g. (77%) of colorless, odorless 2,4,6-triethylpropiophenone, b.p. 109–110° (4 mm.), $n^{25}D$ 1.5040, and 1.0 g. of residue; infrared bands at 3.42, 5.90, 6.20, 6.35, 6.90, 7.10, 7.28, 7.48, 7.57 (shoulder), 7.90m, 8.25, 8.68, 9.30, 9.47, 9.88, 10.56, 11.48, 12.40m, 12.69m, 13.15m and 13.84w μ.

The Perrier modification[42] gave a low yield of the propiophenone compound in addition to higher boiling material believed to contain much diacylated product.

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.27; H, 10.07.

The ketone failed to react with 2,4-dinitrophenylhydrazine under forcing conditions.

2-Propyl-1,3,5-triethylbenzene (XXII).[43]—A solution of 39.8 g. (0.182 mole) of the ketone XXI in 400 ml. of acetic acid was added dropwise, during 4.5 hr., to a refluxing mixture of 750 g. of amalgamated zinc and 150 g. of water, while, starting simultaneously, 2500 ml. of concd. hydrochloric acid was added during 7.5 hr.; refluxing was continued 14 hr. after addition of the hydrochloric acid was complete. The mixture was then steam distilled and 2 l. of distillate collected. The distillate was extracted three times with ether and the combined ether extracts washed with *N* sodium hydroxide solution and water and dried over magnesium sulfate. Distillation gave the following fractions: (1) 8.1 g., b.p. 78–85° (6 mm.), $n^{25}D$ 1.4931; (2) 3.6 g., b.p. 92–101° (4 mm.), $n^{25}D$ 1.4930; (3) 15.3 g., b.p. 101–108° (5 mm.), $n^{25}D$ 1.4976; (4) 2.2 g. residue.

Fractions 1 and 2 were combined, distilled from sodium at 760 mm. (b.p. 216–230°) and then *in vacuo* to yield 7.0 g., b.p. 101–102° (21 mm.), $n^{25}D$ 1.4932, of 1,3,5-triethylbenzene (24% yield). The infrared spectrum of this sample was identical with that of an authentic sample of 1,3,5-triethylbenzene; infrared bands at 3.47, 5.62w, 5.70w, 6.23, 6.88, 7.28, 7.58, 8.60w, 9.35, 9.45, 11.35, 11.6, 12.1w, 12.80w and 14.20 μ.

Fraction 3, distilled from sodium at 760 mm., b.p. 252–254°, and redistilled *in vacuo*, gave 10.0 g. (27% yield), b.p. 134–136° (21 mm.), $n^{25}D$ 1.4960, of 2-propyl-1,3,5-triethylbenzene; infrared bands at 3.48, 6.20m, 6.90, 7.28, 7.60w, 9.20w, 9.35m, 9.50, 11.10w, 11.30m, 11.50, 12.90w and 13.7w μ. (The strong band at 14.20 μ found in 1,3,5-triethylbenzene is absent.)

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.60; H, 11.96.

Nitration of 2-Propyl-1,3,5-triethylbenzene.—To 2-propyl-1,3,5-triethylbenzene (3.06 g., 0.015 mole) was added dropwise, with stirring, a mixture of 2 ml. of fuming nitric acid and 6 ml. of concd. nitric acid during 50 minutes (temperature 3–4°). Stirring was continued at 5° for 5 hr. and then at 24° for 30 minutes. The mixture was then poured into ice-water and extracted with ether. The ether extract was washed four times with water, dried over magnesium sulfate and the ether distilled. Distillation of the residue gave 1.8 g. of crude 1-nitro-3-propyl-2,4,6-triethylbenzene (XXIII), b.p. 117–120° (0.50 mm.), and 1.2 g. of residue. A redistilled sample which was used for analysis had b.p. 109–112° (0.25 mm.), $n^{25}D$ 1.5140; infrared bands at 3.48, 5.95, 6.25m, 6.58, 6.88, 7.30, 7.82, 8.30m, 8.60m, 9.23m, 9.50, 10.50w, 11.37, 12.27, 12.75m and 13.55w μ.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 74.97; H, 9.45; N, 4.15.

The poor elemental analysis suggests that the compound probably decomposed on distillation or on standing.

3-Propyl-2,4,6-triethylaniline (XXIV).—A 2.50-g. sample of the above crude nitro compound, dissolved in 100 ml. of acetic acid, was hydrogenated at 50 pounds pressure in the presence of 5.0 g. of 10% palladium–charcoal catalyst until the theoretical amount of hydrogen was absorbed (3 hr.). After filtering the catalyst, the acetic acid was evaporated *in vacuo* leaving a mass of brown crystals. These were suspended in benzene and dry hydrogen chloride gas was passed through the mixture; a few ml. of ethanol was then added and the volatile materials evaporated *in vacuo*. Trituration of the residue with petroleum ether gave 1.4 g. (26% from hydrocarbon XXII) of white crystalline 3-propyl-2,4,6-triethylaniline hydrochloride (neut. equiv. calcd. for $C_{15}H_{26}ClN$: 255.8; found, 255 (by direct titration with 0.1 *N* sodium hydroxide)). Reduction of the nitro compound with tin and hydrochloric acid also was successful and gave a 22% over-all yield of the hydrochloride (from XXII).

The above hydrochloride (1.4 g.) when treated with *N* sodium hydroxide gave an oil which was extracted with ether, dried and distilled under nitrogen to yield 0.5 g. (11% yield from XXII), b.p. 101–102° (0.35 mm.), $n^{25}D$ 1.5265, of 3-propyl-2,4,6-triethylaniline; infrared bands at 2.95w, 3.40, 3.47, 6.15, 6.86, 7.28m, 7.75m, 8.25w, 9.20w, 11.36 and 12.1w μ.

Anal. Calcd. for $C_{15}H_{25}N$: C, 82.13; H, 11.49. Found: C, 82.04; H, 11.49.

3-Propyl-2,4,6-triethylphenol (XX) from 3-Propyl-2,4,6-triethylaniline.—3-Propyl-2,4,6-triethylaniline (0.90 g., 4.1 mmoles) when treated with 10 ml. of 2 *N* sulfuric acid, formed a precipitate of the corresponding sulfate, soluble on warming. To a cold stirred suspension of the finely divided sulfate was added a solution of 0.28 g. (4.1 mmoles) of sodium nitrite in 2 ml. of water (temperature 5–10°). After 20 minutes a gummy solid had formed; 45 ml. of 12 *M* sulfuric acid was then added to the mixture, causing the temperature to rise to 90°. After warming on the steam-bath for a few minutes, the mixture was cooled and allowed to stand 2 hr. at room temperature. The red oil which formed was extracted three times with petroleum ether, the extracts washed with water and sodium bicarbonate solution and dried, under nitrogen, over magnesium sulfate. Dry hydrogen chloride was passed into the solution to precipitate a small amount of black material. The mixture was filtered and the filtrate distilled *in vacuo* under nitrogen through a short column to yield, in addition to 0.30 g. of residue and holdup, 0.24 g. (27%) of 3-propyl-2,4,6-triethylphenol, b.p. 96–98° (0.4 mm.), $n^{25}D$ 1.5181–1.5193; λ_{max} 282 mμ, (log ϵ 3.31); infrared bands at 2.87m, 3.47, 3.52, 6.10w, 6.25w, 6.37w, 6.85, 7.30m, 7.70m, 7.93, 8.25, 8.45, 9.05m (shoulder), 9.15–9.20, 9.40m, 10.1w, 11.41, 11.62m and 12.1m μ.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.80; H, 10.98.

(41) L. I. Smith and C. O. Guss, THIS JOURNAL, **62**, 2625 (1940).

(42) G. Perrier, *Ber.*, **33**, 815 (1900).

(43) This forcing procedure for the Clemmensen reduction of a hindered ketone was adapted from one by E. Philippi and G. Rie, *Monatsh.*, **42**, 5 (1921).

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The phenylurethan derivative was prepared as above, except that diethylene glycol diethyl ether was used as solvent (reaction temperature 165°); small colorless prisms from hexane, m.p. 122–122.5°.

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.74; H, 8.66; N, 4.27.

2,4,6-Triethylphenol was prepared in 86% yield from 2,4,6-triethylaniline[44]; b.p. 104–106° (3 mm.), m.p. 20–21°, $n^{25}D$ 1.5158; λ_{max} 279 mμ, log ε 3.28 (95% ethanol); infrared bands at 2.90, 3.50, 5.70w, 6.25m, 6.90, 7.30w, 7.66m, 7.87m, 8.45, 8.75, 9.40m, 10.0w, 11.5 and 12.5 μ.

The phenylurethan derivative was prepared using the procedure developed for XX, above; plates from hexane, m.p. 117–118°.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.60; H, 7.88; N, 5.00.

2,4,6-Triethylphenyl Propionate: Attempted Preparation of 3-Hydroxy-2,4,6-triethylpropiophenone.—To 2,4,6-triethylphenol (8.9 g., 0.05 mole) in 30 ml. of nitrobenzene was slowly added 20 g. (0.15 mole) of aluminum chloride, with stirring (temp. below 20°). After 10 minutes, 9.25 g. (0.10 mole) of propionyl chloride was added during 30 minutes (temp. 15–20°). The mixture was stirred 14 hr. at *ca.* 25°, 0.5 hr. at 90° and then poured into ice and hydrochloric acid. The mixture was worked up in the usual manner and twice distilled to yield 9.0 g. (77%) of 2,4,6-triethylphenyl propionate, b.p. 100° (1 mm.), $n^{25}D$ 1.4920; infrared bands at 3.48, 3.54, 5.72, 6.25m, 6.55w, 6.90, 7.40, 7.90, 8.50, 8.80, 9.48, 10.20, 11.30, 11.50 and 12.45m μ. The ultraviolet absorption was weak; λ_{max} 265 mμ, ε 500; 273 mμ, ε 380.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.93; H, 9.37.

Hydrolysis of the ester (2.32 g.) was effected by refluxing with concd. hydrochloric acid and zinc dust and gave 1.4 g. (78%) of 2,4,6-triethylphenol, b.p. 94–97° (1 mm.); λ_{max} 277 mμ, log ε 3.13.

Reaction of the ester with additional propionyl chloride and aluminum chloride in nitrobenzene gave recovered starting material and no acylated product.

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(44) 1-Nitro-2,4,6-triethylbenzene, b.p. 99° (1 mm.), $n^{22}D$ 1.510, prepared in 83% yield by nitration of 1,3,5-triethylbenzene, was reduced with iron and water to 2,4,6-triethylaniline in 81% yield, b.p. 106–112° (2 mm.), $n^{25}D$ 1.5330; *cf.* W. B. Dillingham and E. E. Reid, THIS JOURNAL, **60**, 2606 (1938).

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, THE UNIVERSITY OF IDAHO AND RUTGERS, THE STATE UNIVERSITY]

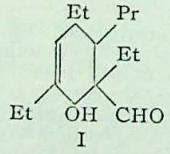
The Base-catalyzed Self-condensation of 2-Ethyl-2-hexenal. II. Formation of a Glycol, $C_{16}H_{30}O_2$, and a Lactone, $C_{16}H_{30}O_3$[1]

BY ARNOLD T. NIELSEN[2]

RECEIVED OCTOBER 22, 1956

The aldol dimer I of 2-ethyl-2-hexenal undergoes an intramolecular disproportionation in the presence of methanolic potassium hydroxide to form 5,7-dihydroxy-3-propyl-2,4,6-triethyl-1,5-heptanolactone (III). In the presence of 2-ethyl-2-hexenal, I also undergoes a Cannizzaro reaction leading to the glycol II, 2-ethyl-2-hexenoic acid and butyric acid. A mechanism for the formation of III in a preferred conformation is discussed.

2-Ethyl-2-hexenal has been shown to self-condense in the presence of aqueous methanolic potassium hydroxide to yield the cyclic dimer I.[3] It has been observed that the yield of I decreases rapidly as the reaction time is increased while, simultaneously, other products are formed, including a C_{16}-lactone III, a C_{16}-glycol II and 2-ethyl-2-hexenoic and butyric acids (Fig. 1).



I

The preparation of compounds I, II and III has been reported previously,[4,5] although no structures were suggested by Anseln and Nickl or Hall and Tuerck.[5] Häusermann[6] also has studied the self-condensation of 2-ethyl-2-hexenal but under more vigorous reaction conditions (25–50% aqueous sodium hydroxide, *ca.* 200°, 22 hr.) than those of the present investigation. He isolated, among other products, butyric and 2-ethyl-2-hexenoic acids, 2,4-diethyl-3-propyl-1,5-pentanolactone and a C_{16}-glycol, to which no structure was assigned. No C_{16}-lactone was reported by him. There are scattered reports in the literature of the formation of high molecular weight glycols and lactones from various saturated and unsaturated aliphatic aldehydes, in the presence of basic catalysts.[4-7] In most cases, however, the structures of these condensation products have not been established.

The glycol II, formed in 10–30% yields, was found to be identical with the lithium aluminum hydride reduction product of the aldol I.[3] It is believed to have been formed by a Cannizzaro reaction involving reduction of I and oxidation, principally of butanal[8] and 2-ethyl-2-hexenal to butanoic and 2-ethyl-2-hexenoic acids.[9] The linear

(1) Presented, in part, at the 130th American Chemical Society Meeting, Atlantic City, N. J., September, 1956.

(2) School of Chemistry, Rutgers, The State University, New Brunswick, N. J.

(3) A. T. Nielsen, THIS JOURNAL, **79**, 2518 (1957).

(4) A. T. Nielsen, Ph.D. thesis, University of Washington, 1947.

(5) R. H. Hall and K. H. W. Tuerck, (a) British Patent 608,985, Sept. 23, 1948; *C. A.*, **44**, 4493 (1950); (b) U. S. Patent 2,528,592, Nov. 7, 1950; *C. A.*, **45**, 3866 (1951); (c) H. Anseln and E. Nickl, German Patent 752,482, Feb. 23, 1953; *C. A.*, **50**, 2658 (1956).

(6) M. Häusermann, *Helv. Chim. Acta*, **31**, 1431 (1948).

(7) (a) A. Borodin, *Ber.*, **6**, 982 (1873); (b) A. v. Lenz, *Monatsh.*, **24**, 155 (1903); (c) H. Meerwein, *J. prakt. Chem.*, [2] **97**, 225, 257 (1918); (d) H. Meerwein, *Ber.*, **53**, 1829 (1920); (e) J. Ducasse, *Bull. soc. chim. France*, [5] **11**, 333 (1944); (f) W. Hunter, B. I. O. S. Report No. 1053, Item No. 22. German Acetylenic Chemical Industry, Miscellaneous Organic Compounds, October 13, 1947, pp. 239–241.

(8) Butanal must be formed mainly by hydration of 2-ethyl-2-hexenal to butyraldol, followed by dealdolization. Evidence for formation of butanal from 2-ethyl-2-hexenal (alkaline catalyst) has been reported previously; S. G. Powell and A. T. Nielsen, THIS JOURNAL, **70**, 3627 (1948); Y. Sprinzak, *ibid.*, **74**, 2116 (1952).

(9) The aldol I, itself, is apparently not an important oxidizing agent in this reaction since it was found to be converted solely into lactone III under the milder conditions of the reaction (Fig. 1). However, under more vigorous reaction conditions where the yield of II is higher, some I may be oxidized, leading to a larger amount of

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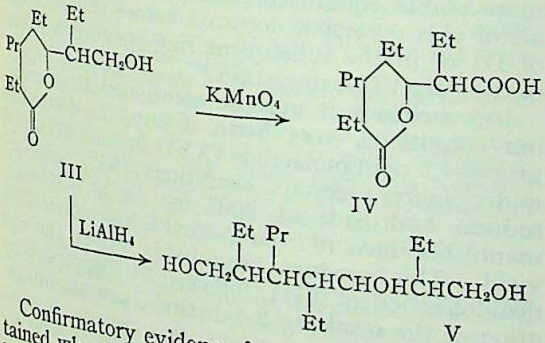
relationship between the mole-per cent. yield of II and these acids supports this view (Table I, Experimental part).

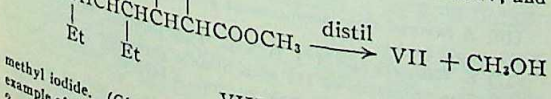
The third major product obtained from the reaction of 2-ethyl-2-hexenal with alkali was shown by elemental analysis, molecular weight and saponification equivalent determinations to be $C_{16}H_{30}O_3$ (40–56% yield). Strong infrared absorption at 2.98 μ, the formation of a monoacetate derivative and the Zerewitinoff determination indicated the presence of one free alcoholic hydroxyl group. Oxidation of III with permanganate led to a monocarboxylic acid lactone, $C_{16}H_{28}O_4$ (IV), in 75% yield, indicating the hydroxyl group to be primary. Compound III was insoluble in hot aqueous *N* sodium hydroxide solution but could be converted into its carboxylate anion with hot aqueous alcoholic *N* sodium hydroxide (saponification equivalent determination). This observation, and the presence of strong infrared absorption at 5.85 μ, support a six-membered lactone structure. Failure of III to react with bromine in carbon tetrachloride or potassium permanganate in acetone and, particularly, failure to absorb hydrogen under conditions favorable for facile hydrogenation of I and II, as well as the empirical formula and spectral data, suggest the absence of olefinic unsaturation in the molecule. Reduction of III with lithium aluminum hydride led to a crystalline triol V, $C_{16}H_{34}O_3$ (58%), m.p. 96.5–97.5°. A Zerewitinoff determination supports the triol assignment as does the intense infrared band at 2.97μ and the absence of carbonyl absorption in the 5.5–6.0μ region; compound V failed to react with lead tetraacetate or periodic acid. On the basis of the above preliminary evidence structure III was proposed for the lactone, IV for the corresponding acid and V for the triol.



Confirmatory evidence for structure III was obtained when VII, the methyl ester of IV (obtained by reaction of IV with diazomethane or of its monosilver salt VI with methyl iodide),[10] was

undistillable acid residue (*cf.* Table I) and proportionately less butyric and 2-ethyl-2-hexenoic acids.

(10) Ester VII was also obtained by demethanolation, during distillation, of the dimethyl ester VIII. The latter compound was obtained from the corresponding disilver salt, prepared from IV, and methyl iodide. (*Cf.* E. Oberreit, *Ber.*, **29**, 1998 (1896), for a similar example of thermal demethanolation in the case of methyl 4-hydroxy-2-propylpentanoate.)



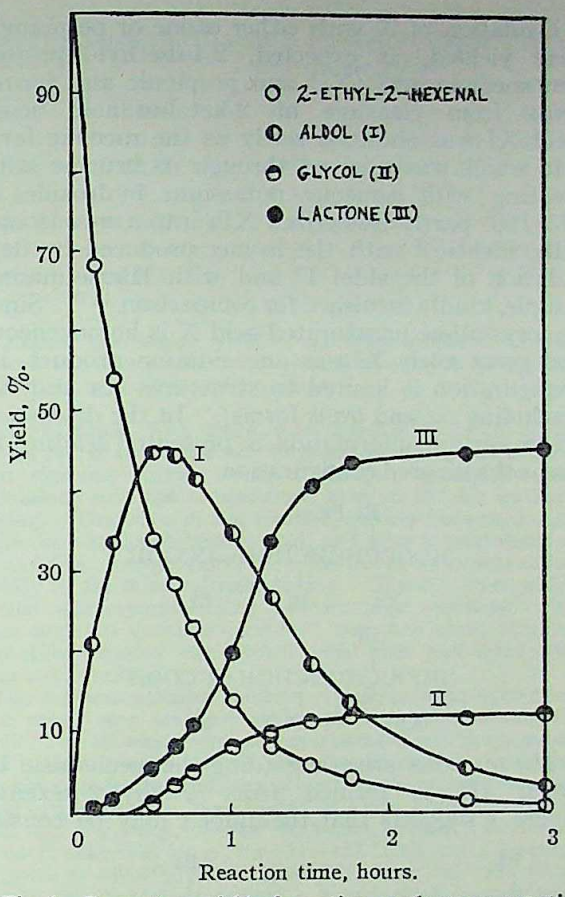
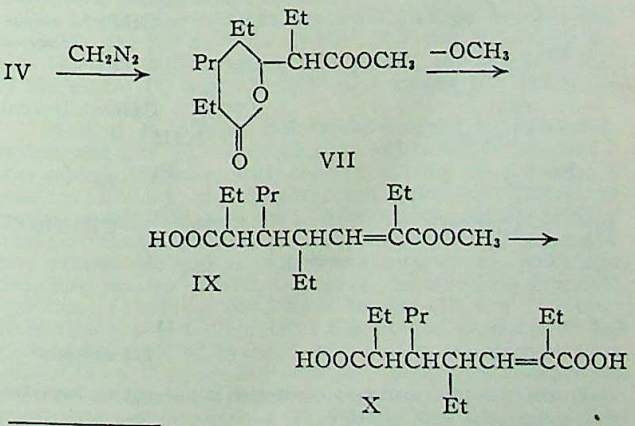


Fig. 1—Percentage yield of reaction products *vs.* reaction time for self-condensation of 2-ethyl-2-hexenal at 25°; for reaction conditions see Experimental part.

treated with one mole-equivalent of sodium methoxide to open the lactone ring and yield the unsaturated monoester IX.[11] Hydrolysis of IX gave the crystalline free acid X (83% yield from VII); α,β-unsaturation was demonstrated in the latter by its ultraviolet[12] (λ_{max} 218 mμ, ϵ 16,300) and infrared[13] (λ_{max} 5.85–5.95, 6.14μ) absorption characteristics.



(11) Examples of this reaction in five-membered ring systems have been reported; J. A. Elvidge, R. P. Linstead and P. Sims, *J. Chem. Soc.*, 1793 (1953), and earlier papers in this series.

(12) α,β-Dialkylacrylic acids exhibit a maximum absorption in the ultraviolet region at *ca.* 217 mμ, α- or β-monoalkyl substituted acrylic acids at *ca.* 208 mμ; J. Cason, N. L. Allinger and D. E. Williams, *J. Org. Chem.*, **18**, 842 (1953); J. Cason and L. L. Rinehart, *ibid.*, **20**, 1951 (1955).

(13) N. K. Freeman, THIS JOURNAL, **75**, 1859 (1953).

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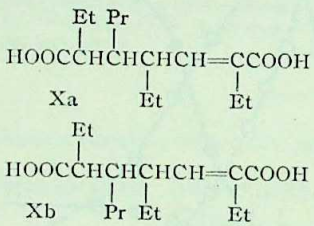
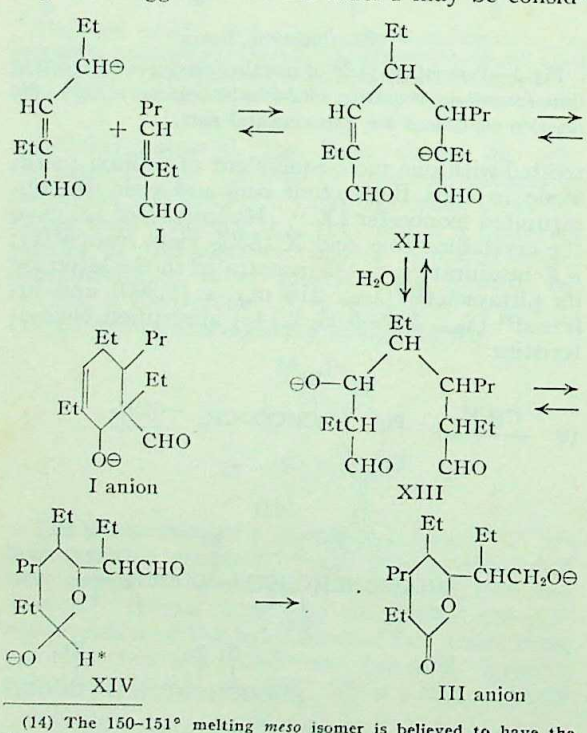
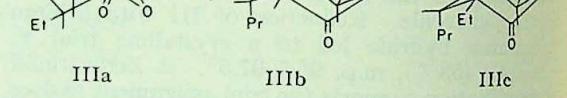
Oxidation of X with either ozone or permanganate yielded, as expected, 2,4-diethyl-3-propylpentanedioic acid (XI) and propionic and formic acids from cleavage of 2-ketobutanoic acid.[3] Acid XI was obtained solely as the racemic form XIa which was resolved through its brucine salts. Heating with aqueous potassium hydroxide at 175–180° partly isomerized XIa into a *meso* isomer XIb, identical with the isomer produced by degradation of the aldol I[3] and with Häusermann's sample, kindly furnished for comparison.[14,15] Since the crystalline unsaturated acid X is homogeneous and gives solely XIa as an oxidation product, its configuration is limited to structures Xa and Xb (excluding *cis* and *trans* forms). In the discussion below certain information is presented leading to Xa as the favored configuration.



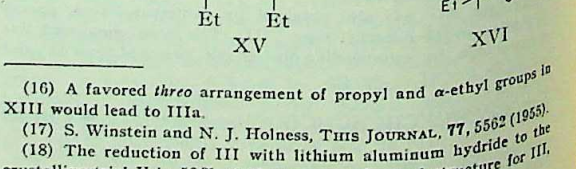
The question arises regarding the mechanism by which III is formed from 2-ethyl-2-hexenal. Figure 1 suggests that the aldol I may be considered as an intermediate, and this is confirmed by experiment, since under the same reaction conditions I is converted exclusively to III in good yield. The mechanism therefore appears to be intramolecular and may reasonably be formulated as shown. In this mechanism the common intermediate precursor of I and III is the anion XII. A hydrated dialdehyde, XIII, is presumed to be the precursor of the cyclic hemiacetal XIV, which undergoes internal disproportionation to III through hydride transfer.



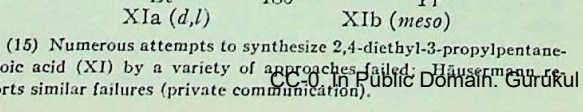
In order for this internal transfer to be sterically possible, both the starred hydrogen and formylpropyl group must be axially rather than equatorially directed; hence the hydroxybutyl group in lactone III must likewise be axial at the time of formation (IIIa). On the assumption that the other three alkyl groups originally occupied the energetically preferred equatorial positions, lactone III should have the conformation IIIa,[16] or more probably the equivalent form IIIb, in which the bulky hydroxybutyl group has become equatorial by a near-strainless ring inversion.[17] However, conformation IIIb would predict the formation of *meso*-XI on degradation of III, whereas the isomer actually isolated was *d,l*-XI. This discrepancy can be accounted for by assuming that the axial ethyl group alpha to the carbonyl of IIIb becomes inverted, in the presence of strong alkali, to the more stable equatorial position (IIIc). Whether all of this inversion occurred before the isolation of III or in the subsequent ring-opening reaction of the ester VII is uncertain.[18]



In conclusion it may be mentioned that under our conditions, very little, if any, 2,4-diethyl-3-propyl-1,5-pentanolactone (XVI) formed, although under more vigorous conditions (50% aqueous sodium hydroxide at 200° for 24 hr.) Häusermann[6] obtained it from 2-ethyl-2-hexenal in 36% yield. This product presumably arises through dealdolization of XIII, followed by disproportionation of the resulting 2,4-diethyl-3-propylpentanedial (XV).[19]



(14) The 150–151° melting *meso* isomer is believed to have the *threo* configuration XIb; *cf.* ref. 3.



(15) Numerous attempts to synthesize 2,4-diethyl-3-propylpentanedioic acid (XI) by a variety of approaches failed; Häusermann reports similar failures (private communication).

(16) A favored *threo* arrangement of propyl and α-ethyl groups in XIII would lead to IIIa.

(17) S. Winstein and N. J. Holness, THIS JOURNAL, 77, 5562 (1955).

(18) The reduction of III with lithium aluminum hydride to the crystalline triol V in 58% yield suggests a favored structure for III, to at least the extent of this yield.

(19) An alternate mechanism involving Michael addition of butanal to 2-ethyl-2-hexenal appears unlikely since this reaction fails in practice (unpublished work, this Laboratory; *cf.* ref. 6).

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Experimental[20]

6-Hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ol (II).—To purified 2-ethyl-2-hexenal[3] (113 g., 0.90 mole) was added dropwise, with stirring, during 1.5 hr., a solution of 50 g. (0.76 mole) of potassium hydroxide (86% assay) in 65 ml. of methanol and 16 ml. of water. A nitrogen atmosphere was maintained during the reaction but no external cooling was provided. The temperature gradually rose to 80° during 30 minutes, while one-sixth (17 ml.) of the potassium hydroxide solution was being added gradually. Within the next 60 minutes the addition of the alkali was complete and the temperature had dropped to 40°. Stirring was continued for 1.5 hr., water then added and the mixture separated into acid and neutral parts as described previously.[3]

Distillation of the neutral part gave the following main fractions: (1) 2 g., recovered 2-ethyl-2-hexenal; (2) 37 g. (32%) of the glycol II, b.p. 124–129° (0.25 mm.), $n^{25}D$ 1.4926; (3) 7.3 g. of residue. A redistilled sample of the glycol was obtained as a pale yellow, extremely viscous liquid, b.p. 135–138° (0.45 mm.), $n^{25}D$ 1.4935, d^{23}_4 0.921; infrared bands at 3.0, 3.45, 3.53, 5.85w, 6.1w, 6.87, 7.28 and 9.7 μ (chloroform).

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; mol. wt., 254.4. Found: C, 75.76; H, 11.48; mol. wt., 252, 256.[21]

Quantitative hydrogenation of a 5.56-millimole sample of the glycol (689 mm., 23°, acetic acid solvent, a few drops of concentrated hydrochloric acid promotor, 5% palladium–charcoal catalyst) resulted in absorption of 1.06 mole-equivalents of hydrogen in 270 minutes, after which time hydrogenation essentially ceased. On quantitative bromination of the glycol with a 5% solution of bromine in carbon tetrachloride, 0.91 mole-equivalent of bromine was absorbed. A Zerewitinoff determination showed 1.90 active hydrogens and no additional methylmagnesium iodide reacted.

The **bis-*p*-nitrophenylurethan** derivative was obtained as yellow microcrystals from high boiling ligroin, m.p. 74–78°. When mixed with a sample of the bis-*p*-nitrophenylurethan derivative of II obtained previously,[3] m.p. 76.5–78.5°, the melting point was not depressed.

Distillation of the acid part from the above reaction gave (1) *ca.* 3 g., b.p. 50–83° (0.4 mm.), mainly butyric acid; (2) 6.6 g., b.p. 83–138° (0.3 mm.), mainly 2-ethyl-2-hexenoic acid; (3) 37 g. (31%), b.p. 150–157° (0.35 mm.), lactone III, $n^{25}D$ 1.4740; (4) 13.0 g. of residue.

The **butyric acid** fraction was redistilled to yield a sample, b.p. 159–162° (760 mm.), $n^{20}D$ 1.3990, neut. equiv. 90; *p*-phenylphenacyl ester, m.p. 81.5–82.5°, alone and when mixed with an authentic sample.

The **2-ethyl-2-hexenoic acid** fraction was dissolved in ether and extracted with sodium hydroxide solution. Acidification of the alkaline extracts gave a sample, b.p. 98–99.5° (2.7 mm.), $n^{20}D$ 1.455,[22] neut. equiv. 145 (calcd. for $C_8H_{14}O_2$, 142.2). The amide derivative, prepared through the acid chloride, melted at 69–69.5°, alone, and when mixed with an authentic sample.[23] *Anal.* Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71. Found: C, 68.1; H, 10.7.

The total yield of acids and glycol produced in various runs was calculated by determining the number of moles of each product produced per 100 moles of 2-ethyl-2-hexenal employed (mole-per cent. yield); for purposes of calculation the acid residue was assigned an equivalent weight of 270. In these runs the potassium hydroxide concentration, rate of addition of the catalyst, reaction time and temperature were varied. The glycol yields were proportional to the total mole-per cent. yield of acids produced, as shown in Table I.

Preparation of 5,7-Dihydroxy-3-propyl-2,4,6-triethyl-1,5-heptanolactone (III). Method A. From 2-Ethyl-2-hexenal.—2-Ethyl-2-hexenal, purified as described previously,[3] was freshly distilled under nitrogen, directly into the reaction flask (128.4 g., 1.02 moles). A solution of 38 g. of potas-

Table I

Yields of Acids and Glycol II Formed in Various Runs

Run	II	Mole-per cent. yields[a] A	B	C
11	16.0	3.8	5.1	5.4
9	13.5	4.0	4.9	2.5
8	11.5	3.2	3.9	1.9
4	9.5	4.1	3.2	1.6
10	8.3	2.4	3.6	1.7
27	5.5	1.2	1.4	1.6
16	5.0	1.3	1.4	0.8
18	2.5	0.6	0.8	0.3

[a] Actual percentage yield of II from 2-ethyl-2-hexenal is twice the above value: A = butyric acid, B = 2-ethyl-2-hexenoic acid, C = acid residue.

sium hydroxide (85% assay, 0.58 mole) in 18 ml. of water and 64 ml. of methanol was then added during one minute with vigorous stirring while a nitrogen atmosphere was maintained and the temperature held at 25° by ice-bath cooling. The color of the solution quickly became orange while the alkali was being added, and after a total reaction time of 7 hr. (temperature, 25°), 500 ml. of water was added rapidly to the mixture with stirring. The oily layer which formed was separated, the aqueous layer extracted with ether and the extracts combined with the main portion. The ether solution was washed with water and dried over magnesium sulfate.

The aqueous alkaline solution remaining after extraction with ether was acidified with concentrated hydrochloric acid. The oil which formed was separated and the aqueous part extracted with ether. The oil and ether extracts were combined and after distilling the ether, the residue was distilled to give (1) 1 g., b.p. 35–55° (0.7 mm.), mainly butyric acid; (2) 3 g., b.p. 93–114° (0.4 mm.), mainly 2-ethyl-2-hexenoic acid; (3) 1.4 g., b.p. 114–151° (0.3 mm.), forerun; (4) 68.4 g. (49.6%)[4] of lactone III, b.p. 152–157° (0.25 mm.); (5) 10.5 g. of residue. A redistilled sample used for analysis was a colorless, slightly viscous liquid, b.p. 153–155° (0.3 mm.), $n^{25}D$ 1.4757; infrared bands at 2.98m, 3.46, 3.53, 5.80–5.85, 6.86m, 7.25m, 8.32, 9.05–9.10m and 9.6–9.65m μ.

Anal. Calcd. for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18; mol. wt., 270.4. Found: C, 70.93; H, 11.22; mol. wt., 274, 275[21]; sapn. equiv., 264.

The lactone was found not to decolorize bromine in carbon tetrachloride or dilute potassium permanganate in acetone. No hydrogen was absorbed by the compound in acetic acid in the presence of 5% palladium–charcoal catalyst (695 mm., 27°). A Zerewitinoff determination indicated 1.3 active hydrogens and 1.7 additional mole-equivalents of methylmagnesium iodide reacted.

The above ether solution of neutral material was distilled to yield: (1) 2.3 g., b.p. 40–100° (2.7 mm.); (2) 4.9 g., b.p. 100–135° (0.7 mm.), mainly aldol I; (3) 16.6 g. (14%) of the glycol II, b.p. 135–137° (0.5 mm.); (4) 15.4 g. of neutral residue.

Method B. From 6-Formyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ol (I).—To 36.9 g. (0.146 mole) of the aldol I was added dropwise, with stirring, during 30 minutes, a solution of 10.9 g. of 85% potassium hydroxide in 18 ml. of methanol and 6 ml. of water. After stirring for 2.5 hr., the mixture was treated with 160 ml. of water and separated into neutral and acid parts as in the condensation procedure described above. Distillation gave the following principal fractions: (1) 19.1 g. (46.8%) of lactone III, b.p. 154–160° (0.55 mm.), $n^{25}D$ 1.4755; (2) 1.5 g. of acid residue; (3) 6.5 g., b.p. 129–140° (0.56 mm.), $n^{25}D$ 1.4873, mainly recovered aldol; (4) 6.7 g. neutral residue. Hall and Tuerck[5] reported a similar experiment in which they employed sodium hydroxide and reported a 47.5% yield of III, b.p. 162–163° (3 mm.), $n^{20}D$ 1.4781.

Influence of Reaction Conditions on the Self-condensation of 2-Ethyl-2-hexenal.—A study was made of the effect of reaction conditions on the yields of the products I, II and III produced from the self-condensation of 2-ethyl-2-

(20) Melting points are corrected; boiling points are uncorrected.

(21) Procedure of R. B. Kitson, A. N. Oemler and J. Mitchell, *Anal. Chem.*, **21**, 404 (1949).

(22) Reported b.p. 107–108° (3 mm.), $n^{20.5}D$ 1.4590; J. Lichtenberger and M. Naftali, *Bull. soc. chim. France*, [5] **4**, 325 (1937).

(23) C. Mannich and E. Kniss, *Ber.*, **74**, 1637 (1941), report m.p. 67–68°.

(24) In another run in which 344.2 g. of 2-ethyl-2-hexenal was used (reaction time 16 hr.), the yield of III was 208.2 g., 56.4%, b. p. 172–176° (1 mm.).

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hexenal. Factors studied were reaction time, temperature, catalyst concentration and rate of addition of the catalyst. From these experiments optimum procedures were developed for the preparation of the products. Use of freshly purified and distilled 2-ethyl-2-hexenal, in a nitrogen atmosphere, gave the best yields.

The reaction time determined the yields of product obtained, as shown in Fig. 1 (temperature 25°; potassium hydroxide to aldehyde molar ratio, 0.57; catalyst addition time, *ca.* two minutes). Reaction times longer than 3 hr. gave only slightly increased yields of II and III under these conditions.[24]

A reaction temperature of *ca.* 25° was found to give less undistillable residue than did higher temperatures. Product yields also were higher, except in the case of glycol II, where maximum yield was obtained by permitting the reaction mixture to warm spontaneously to 80°. Using a reaction time of 1 hr., a potassium hydroxide–aldehyde molar ratio of 0.85 and a catalyst addition time of 12 minutes, the percentage yields of recovered 2-ethyl-2-hexenal, I, II and III, respectively, at three different temperatures were as follows: (13°) 37% 2-ethyl-2-hexenal, 42% I, 0% II, 3% III; (25°) 5% 2-ethyl-2-hexenal, 21% I, 13% II, 41% III; (40°) 1% 2-ethyl-2-hexenal, 3% I, 12% II, 46% III.

Employing a reaction time of 1 hr., temperature 25°, catalyst addition time 12 minutes, the yields of recovered 2-ethyl-2-hexenal, I, II and III, respectively, were found to vary with potassium hydroxide–aldehyde molar ratios as follows: ratio 0.85, 5% 2-ethyl-2-hexenal, 21% I, 13% II, 41% III; ratio 0.57, 13% 2-ethyl-2-hexenal, 33% I, 3% II, 22% III; ratio 0.29, 65% 2-ethyl-2-hexenal, 21% I, 0% II, 0.5% III.

The addition time of the catalyst when short (*ca.* 1–2 minutes) gave the maximum yields of I and III (see Fig. 1). A longer addition time was required for the best yields of II; in the optimum procedure described above the time was 1.5 hr. (total reaction time, 3 hr.).

5-Propyl-2,4,6-triethyl-1,3,7-heptanetriol (V).—A solution of 28.7 g. (0.106 mole) of the lactone III in 130 ml. of dry ether was added dropwise, with stirring, during 140 minutes to a solution of 4.9 g. (0.129 mole) of lithium aluminum hydride in 200 ml. of ether.[25] The rate of addition of the lactone was adjusted so as to produce gentle refluxing. After addition of the lactone was complete, refluxing by heating was continued for an additional 20 minutes; first 10 ml. of water and then 160 ml. of 10% sulfuric acid were added cautiously with stirring. The ether layer was separated and the aqueous part extracted twice with ether. The combined ether fractions were washed with water and dried. The ether was removed and the residue crystallized from 400 ml. of petroleum ether to yield 16.9 g. (58%) of V as white prisms, m.p. 96–97°; recrystallization did not raise the melting point; infrared bands at 2.77w, 2.97, 3.43, 6.85, 7.01m, 7.26m, 9.31, 9.87, 10.38m, 10.72w, 11.37w and 12.20w μ (chloroform). Repetition of the above experiment, using a 3-fold excess of lithium aluminum hydride and a reflux time of 22 hr., also gave a 58% yield of V.

Anal. Calcd. for $C_{16}H_{34}O_3$: C, 70.02; H, 12.49. Found: 70.22; H, 12.59.

The filtrate obtained above was distilled to yield 2.1 g., b.p. 123–166° (0.5 mm.); 5.7 g., b.p. 166–177° (0.4 mm.), (very viscous); and 1.1 g. of residue; these fractions were not further investigated.

The triol in a Zerewitinoff determination was found to have 3.1 active hydrogens and react with 0.1 mole-equivalent additional methylmagnesium iodide. It did not absorb hydrogen in acetic acid solvent at one atmosphere pressure in the presence of 5% palladium–charcoal catalyst.

3-Propyl-2,4,6-triethyl-5-hydroxy-1,7-heptanedioic Acid-1,5-lactone (IV).—To 37.9 g. (0.14 mole) of lactone III, suspended in a solution of 200 ml. of 10% sulfuric acid and 30 ml. of acetic acid, was added, with stirring during 30 minutes, 31.6 g. of powdered potassium permanganate, keeping the temperature at 25° by external cooling; stirring was then continued for 1.5 hr. Sufficient sodium bisulfite was added to dissolve the manganese dioxide and the mixture extracted with ether. The ether extracts were washed with water and 10% sodium hydroxide solution. The alkaline extracts were extracted several times with ether and then acidified with hydrochloric acid. The oil which separated was extracted with ether, the extract dried and the solution concentrated. All traces of volatile matter were finally removed by heating for 6 hr. at 100° (0.16 mm.) leaving 29.9 g. (75%) of very pure IV, an extremely viscous yellow liquid, $n^{25}D$ 1.4762; molecularly distilled at bath temperature, 135–139° (2–4 μ), $n^{25}D$ 1.4760. The acid could not be crystallized; infrared bands at 3.45, 5.77, 5.84, 6.85, 7.25, 7.9–9.1 and 9.83mμ (chloroform).

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93; mol. wt., 284.4. Found: C, 67.26; H, 10.20; neut. equiv., 282 (by direct titration); sapn. equiv., 144.

The *p*-**bromophenacyl ester** derivative was obtained as white platelets from ethanol, m.p. 114.5–115.5°.

Anal. Calcd. for $C_{24}H_{33}O_6$: C, 59.88; H, 6.91. Found: C, 59.78; H, 7.07.

Disilver 3-Propyl-2,4,6-triethyl-5-hydroxy-1,7-heptanedioate.—The lactone acid IV (31.4 g., 0.1104 mole) was dissolved in 400 ml. of 1.075 *N* sodium hydroxide, the solution heated on the steam-bath for 1 hr. and then allowed to stand overnight at room temperature. After extracting with ether, the aqueous solution was diluted with one l. of ethanol, then neutralized by slowly adding, with vigorous stirring, 176 ml. of 1.109 *N* nitric acid (faint pink color to phenolphthalein). A solution of 40 g. of silver nitrate in 550 ml. of water was then added dropwise with stirring. The precipitate was rapidly filtered, washed thoroughly with water and dried in a vacuum desiccator over calcium chloride, keeping light absent; the yield of white powder was 56 g. (98%), m.p. 134–136° dec. Slowly, on standing in the dark, or rapidly, on exposure to light, the salt darkened and became brown.

Anal. Calcd. for $C_{16}H_{28}O_6Ag_2$: Ag, 41.80. Found: Ag, 41.80.

Dimethyl 3-Propyl-2,4,6-triethyl-5-hydroxy-1,7-heptanedioate (VIII).—To the above disilver salt (28.2 g., 0.0545 mole), suspended in 200 ml. of dry ether and 100 ml. of dry benzene, was added, dropwise, 68 g. of methyl iodide during 30 minutes (temperature 23–25°). Stirring was continued for 40 hr., the mixture filtered and the silver iodide precipitate washed thoroughly with ether. The filtrate was dried over magnesium sulfate and the ether removed to leave a yellow oil (pumped at 1 mm., 24 hr., 25°). The crude diester (14.8 g., 82%, $n^{25}D$ 1.4572), could not be distilled without decomposition (see below); infrared bands at 2.93 m, 3.48, 5.83, 6.90, 7.0, 7.30m, 7.95, 8.45, 8.62, 10.5m, 10.65w and 12.6 m μ.

Anal. Calcd. for $C_{18}H_{34}O_5$: C, 65.42; H, 10.37; mol. wt., 330.45. Found: C, 65.31; H, 10.31; sapn. equiv., 164.

3-Propyl-2,4,6-triethyl-5-hydroxy-1,7-heptanedioic Acid-1,5-lactone Methyl Ester (VII). Method A. Demethanolation of Dimethyl 3-Propyl-2,4,6-triethyl-5-hydroxy-1,7-heptanedioate (VIII).—A 4.95-g. (0.015 mole) sample of the dimethyl ester VIII was heated in a small distilling flask at a bath temperature of 155–160° for 30 minutes. During this time 0.25 g. of methanol was collected, b.p. 65–67°; 3,5-dinitrobenzoate, m.p. 109–110°, alone and when mixed with an authentic sample. Distillation of the residue at 0.5 mm. gave fractions: (1) 0.3 g., b.p. 123–136°; (2) 3.2 g. (71% crude VII), b.p. 136–144°, $n^{25}D$ 1.462–1.465 (65% b.p. 138–142°); (3) 1.0 g. residue and holdup. Redistillation of fraction 2 gave 2.1 g., b.p. 136–144° (0.30 mm.), $n^{25}D$ 1.4640, used for analysis; infrared spectrum was identical with sample prepared by method B.

Anal. Calcd. for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13; mol. wt., 297.4. Found: C, 68.22; H, 9.98; sapn. equiv., 149.

Method B. From 5-Hydroxy-2,4,6-triethyl-1,7-heptanedioic Acid-1,5-lactone (IV) and Diazomethane.—A 13.4-g. (0.047 mole) sample of the lactone acid IV dissolved in 50 ml. of ether was treated with excess diazomethane for 1 hr. The volatile material was evaporated and the residue distilled at 1.5 mm. to yield (1) 1.0 g., b.p. 141–155° (1.5 mm.); (2) 9.8 g. (70%) of VII, b.p. 155–157° (1.5 mm.); and (3) 2.7 g. residue. Redistillation of fraction 2 gave an analytical sample, $n^{25}D$ 1.4643; infrared bands at 3.42, 3.50, 5.75, 6.85, 6.92, 7.25, 7.87, 8.12, 8.35, 9.80, 10.1, 10.45m and 12.55m μ.

Anal. Calcd. for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.31; H, 9.

(25) R. F. Nystrom and W. G. Brown, THIS JOURNAL, 69, 2548 (1947).

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Method C. From Monosilver Salt of 3-Propyl-2,4,6-triethyl-5-hydroxy-1,7-heptanedioic Acid-1,5-lactone and Methyl Iodide.—The acid lactone IV, 11.7 g. (0.0412 mole), in 50 ml. of ethanol was exactly neutralized with 0.1 *N* sodium hydroxide and diluted to 200 ml. with water. A solution of 8.0 g. of silver nitrate in 100 ml. of water was added slowly with vigorous stirring. The white precipitate was filtered, washed with water and dried *in vacuo* in the dark; yield 12.9 g. (80%) of white powder, m.p. 100–110° dec., with sintering at 90°.

Anal. Calcd. for $C_{16}H_{29}O_4Ag$: Ag, 27.6. Found: Ag, 28.2.

To the above silver salt, 12.3 g. (0.315 mole), dissolved in 100 ml. of dry ether was added slowly, with stirring, 22 g. of methyl iodide (temperature 20–25°); stirring was continued for 24 hr. The silver iodide was filtered and washed with ether (7.3 g., 99%). Evaporation of the ether left 8.2 g. of an oil which was distilled to yield the following fractions at 0.4 mm.: (1) 1.9 g., b.p. 83–136°; (2) 4.0 g. (43%) of VII, b.p. 136–146° (80% b.p. 136–144°), $n^{25}D$ 1.4628; (3) 1.7 g. residue; fraction 2 infrared spectrum identical with sample prepared by method B.

5-Propyl-2,4,6-triethyl-2-heptenedioic Acid (X).—A solution of 14.0 g. (0.0468 mole) of ester VII and 1.2 g. (0.052 mole) of sodium metal in 50 ml. of dry methanol was allowed to stand at room temperature for 45 minutes and then refluxed 17 hr. Sodium hydroxide, 15 g., and 20 ml. of water were then added, and refluxing continued for 23 hr. The solution was diluted with 1500 ml. of water and chilled to 4°. A solution of 30 ml. of acetic acid in 200 ml. of water was then added dropwise, slowly, with vigorous stirring during 30 minutes; after seeding with pure X, stirring was continued at 2° for 4.5 hr. and the mixture then placed in the refrigerator overnight. The precipitate which formed was filtered and washed thoroughly with water; 11.1 g. (83.3%), m.p. 87–95°, white, crystalline powder. In another, similar, run a 78% yield of product, m.p. 90–100°, was obtained. A sample recrystallized from dilute ethanol melted at 99.5–100.5°, small prisms; λ_{max} 218 mμ, ε 16,300 (95% ethanol solvent, 10^{-4} *M*); infrared bands at 3.50, 5.85–5.95, 6.14, 6.87, 7.10, 7.28m, 7.80, 8.65w, 9.35w, 10.75 (broad) and 7.8–8.35 μ (broad) (chloroform).

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93; mol. wt., 284.4. Found: C, 67.17; H, 9.92; neut. equiv., 141.5 (by direct titration).

The bis *p*-phenylphenacyl ester was prepared in the usual manner, recrystallized from ethanol, m.p. 114–115°.

Anal. Calcd. for $C_{44}H_{48}O_6$: C, 78.54; H, 7.19. Found: C, 78.3; H, 7.3.

The unsaturated acid X failed to react with bromine in carbon tetrachloride or with potassium permanganate in acetone. On quantitative hydrogenation of a small sample of the acid, however, 1.0 mole-equivalent of hydrogen was absorbed in 2 hr. (palladium–charcoal catalyst, one atmosphere, 25°, acetic acid solvent), after which time hydrogen uptake ceased. Removal of solvent and catalyst gave a gum which failed to crystallize. The dimethyl ester of X, prepared on a small scale from X and diazomethane, also absorbed one mole-equivalent of hydrogen under the above reaction conditions to yield a saturated dimethyl ester (carbonyl band at 5.81 μ; band at 6.1 μ absent); these esters, prepared on a micro scale, were not distilled. Treatment of the hydrogenated acid with aqueous potassium hydroxide at 160–175° or its dimethyl ester with sodium methoxide in refluxing methanol failed to lead to a crystalline product.

Ozonolysis of 5-Propyl-2,4,6-triethyl-2-heptenedioic Acid (X).—A 500-mg. (1.76 mmole) sample of the acid X in 15 ml. of carbon tetrachloride and 15 ml. of chloroform was ozonized at 0° using a 3-fold molar excess of ozone. The solution was then refluxed 24 hr. with a solution of 10 ml. of *N* sodium hydroxide and 10 ml. of 30% hydrogen peroxide. The solvent layer was separated; the aqueous layer was washed with chloroform and then distilled to remove neutral volatile material. The aqueous residue was acidified with *N* sulfuric acid and extracted with ether. The ether extracts were washed with water (washings added to aqueous part) and saturated sodium bicarbonate solution. The bicarbonate washings were washed with ether, acidified with sulfuric acid and the aqueous part extracted with ether. The ether extracts were washed with water (washings added to aqueous part) and dried. Evaporation of the ether gave 234.6 mg. of a viscous oil (neut. equiv. 130) which crystallized slowly from dilute alcohol to yield 73.5 mg. of crystals, m.p. 97–98°. Recrystallization gave short rectangular prisms, m.p. 98–99°, of racemic 2,4-diethyl-3-propylpentanedioic acid (XIa); when mixed with starting compound X, the melting point was 80–85°; infrared bands: 3.25–3.35 (shoulder), 3.46, 3.50, 3.80m, 5.85, 6.85, 7.10m, 7.25w, 7.85, 8.76w, 8.95w, 9.20w, 9.65, 10.75m (shoulder) and 11.10m μ; broad bands, 3–4, 7.5–8.5 and 10–12 μ (chloroform); this spectrum was practically identical with the uncrystallized oil, above.

Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63; mol. wt., 230.32. Found: C, 62.5; H, 9.5; neut. equiv., 114 (by direct titration).

The combined aqueous portions from the above ozonolysis were made alkaline with sodium hydroxide and distilled to remove volatile neutral material. The aqueous residue was acidified with sulfuric acid and steam distilled to yield 2.15 meq. (1.22 mole-equivalents) of steam volatile water-soluble acidic material. This solution was refluxed with 3 g. of mercuric oxide for 2.5 hr. and distilled to yield 1.50 meq. of acid (0.65 meq. (37%) destroyed formic acid by difference).[3] The remaining distilled water-soluble acid was identified as propionic (85%) by conversion to its *p*-phenylphenacyl ester, m.p. 102–102.5° (melting point not depressed by admixture with authentic sample, m.p. 102–103°).

A 55-mg. sample of the low melting acid, XIa, was dissolved in a solution of 6 g. of potassium hydroxide (85% assay) in 6 ml. of water and heated, with shaking, in a steel bomb at 175–180° for 16 hr. Recovery of the acid in the usual manner gave 45 mg. of an oil which was crystallized from water to yield the crude high melting *meso* isomer, XIb, m.p. 140–145°; one recrystallization raised the melting point to 150–150.5° (rectangular prisms). When mixed with an authentic sample of *meso*-2,4-diethyl-3-propylpentanedioic acid,[26] the melting point was not depressed.

Permanganate Oxidation of 5-Propyl-2,4,6-triethyl-2-heptenedioic Acid. Preparation of Racemic 2,4-Diethyl-3-Propylpentanedioic Acid (XIa).—Permanganate oxidation of X was found to be a more efficient method of securing the racemic dibasic acid, XIa. To a solution of 1.205 g. (4.23 mmoles) of acid X in 40 ml. of saturated sodium bicarbonate solution was added, dropwise, with stirring, during 4.5 hr., a solution of 2.2 g. of potassium permanganate in 100 ml. of water (temperature, 0–5°). Stirring was continued at 0–25° for 17.5 hr. and the mixture warmed on the steam-bath for 30 minutes to remove the pink color. The manganese dioxide was then filtered and washed and the filtrate acidified with dilute hydrochloric acid. The aqueous suspension of the crude acid which separated as an oil was heated to 90° and treated with sufficient ethanol to give a clear solution. The solution on standing several days deposited 521 mg. (51%) of product, m.p. 92–95°, and on further standing 265 mg. of additional crystalline material, m.p. 75–90°; total crude yield, 81%. The crude product could be purified easily by slow crystallization from water or dilute ethanol (seeding); long, needle-like prisms, m.p. 94–96°.

Resolution of Racemic 2,4-Diethyl-3-propylpentanedioic Acid.—A solution of 1.527 g. (6.63 mmoles) of the racemic acid XIa was dissolved in a solution of 40 ml. of ethanol and 150 ml. of water and heated on the steam-bath. A solution of 2.62 g. (6.63 mmoles) of anhydrous brucine in 50 ml. of ethanol was then added slowly to the hot solution. The cooled solution was allowed to evaporate slowly at room temperature and during several days seven successive crops of crystals were removed by alternate filtration and evaporation of the filtrate; 1.70 g. of the crude *l*-acid brucine salt, m.p. 135–144°, and 2.1 g. of the crude *d*-acid brucine salt, m.p. 110–120°, were recovered by this procedure.

Recrystallization of the first crop of crystals, 1.18 g., m.p. 142–144°, from dilute ethanol gave 800 mg. of purified *l*-2,4-diethyl-3-propylpentanedioic acid monobrucine salt, m.p. 142–143°. *Anal.* Calcd. for $C_{35}H_{48}N_2O_8 \cdot 2H_2O$: C, 63.61; H, 7.93; N, 4.24. Found: C, 63.80; H, 7.77; N, 3.94. To the salt, 800 mg., in 50 ml. of hot 10% ethanol, was added dilute ammonium hydroxide dropwise until a slight excess was present. The solution was chilled and the brucine filtered (450 mg.). The filtrate was acidified

(26) Authentic sample kindly supplied by Dr. Häusermann (ref. 6).

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with dilute hydrochloric acid and the oily acid crystallized on standing to yield 216 mg. of partly active *l*-2,4-diethyl-3-propylpentanedioic acid, m.p. 93–94°, $[\alpha]^{20}D$ −2.4° (*c* 10); 95% ethanol used as solvent for all rotations measured.

Fractional crystallization of the crude *d*-acid monobrucine salt gave 929 mg. of the purified salt as rectangular prisms, m.p. 114–121°. Regeneration of the *d*-acid from this sample in the manner used above for the *l*-acid gave 180 mg. of partly active *d*-2,4-diethyl-3-propylpentanedioic acid, m.p. 85–93°, $[\alpha]^{20}D$ 5.4° (*c* 11), and a second crop, 71 mg., m.p. 86–91°, somewhat more active, $[\alpha]^{20}D$ 11.0° (*c* 5).

Dehydration of 5,7-Dihydroxy-3-propyl-2,4,6-triethyl-1,5-heptanolactone.—A 41.9-g. (0.155 mole) sample of the lactone III was slowly distilled with a few crystals of iodine in a nitrogen atmosphere to yield 2.14 g. (0.119 mole) of water. The remaining residue was diluted with ether and washed with potassium hydroxide solution and water. After drying and distilling the ether, the following main fractions were obtained: (1) 3.5 g. of forerun, b.p. 60–134° (4.0 mm.); (2) 10.5 g. (27%) of crude C_{16}-unsaturated lactone mixture, b.p. 134–142° (4.0 mm.); (3) 1.0 g. of recovered III, b.p. 150–158° (1.3 mm.); and (4) 21 g. of residue. The crude lactone mixture was purified by extraction with *N* sodium hydroxide; b.p. 125–127° (0.5 mm.), $n^{25}D$ 1.4728; infrared bands at 3.37, 3.47, 5.64, 5.76, 6.84, 7.25m, 8.38, 8.85m, 9.25m, 10.40m and 11.1w μ.

Anal. Calcd. for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.03; H, 11.31.

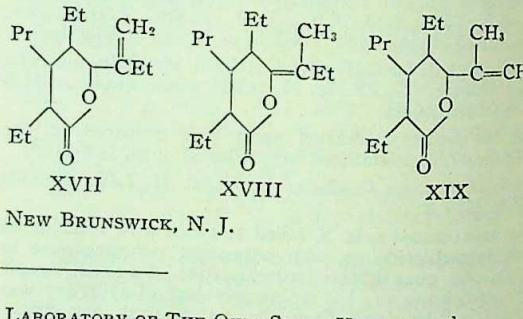
On quantitative hydrogenation the unsaturated lactone mixture absorbed 1.0 mole-equivalent of hydrogen (platinum catalyst, one atm., 25°). On quantitative bromination (bromine in acetic acid), 0.68 mole-equivalent of bromine was absorbed. A Zerewitinoff determination showed 0.19 active hydrogen and 1.92 additional moles of methylmagnesium iodide reacted. Other acidic catalysts (sulfuric and phosphoric acids, aluminum oxide at 400°) were used to dehydrate III, but iodine distillation gave the best results.

A 4.83 g. (0.0192 mole) sample of the lactones in chloroform was ozonized using a slight excess of ozone. After removing the chloroform, the ozonide solution was decomposed with water, first at room temperature, then at reflux temperature while air was aspirated through the mixture. The exit vapors were passed through 2,4-dinitrophenylhydrazine reagent to yield 1.26 g. of precipitate, m.p. 85–150°. Fractional crystallization of this material gave (1) 0.74 g., m.p. 112–125°, and (2) 0.28 g., m.p. 135–140°. Recrystallization of the first fraction gave orange needles, m.p. 116–117°; melting point not depressed when mixed with an authentic sample of 2-butanone 2,4-dinitrophenylhydrazone, m.p. 117°. Several recrystallizations of the smaller second fraction gave orange platelets, m.p. 155–157°, identified as acetaldehyde 2,4-dinitrophenylhydrazone (mixture melting point with authentic sample, m.p. 157°, undepressed). Water-soluble, steam-volatile acidic material was isolated; 0.0108 equivalent total. By refluxing with mercuric oxide, 0.0036 equivalent of this acid was destroyed (formic acid, 19%).[3] The remainder of the acid, 0.072 equivalent (37.5%), gave Duclaux numbers, 8.5, 7.5 and 6.8 and a *p*-phenylphenacyl ester derivative, m.p. 106–114°, which could not be recrystallized to constant melting point. Acetic acid is believed to be the main constituent of this portion, with a small amount of higher molecular weight acid(s). Of the 1.26 g. of 2,4-dinitrophenylhydrazone derivative which precipitated, it is estimated from the above fractionation data that 0.0034 equivalent (18%) of 2-butanone and 0.015 equivalent of acetaldehyde (7.5%) were formed. Other ozonolysis products isolated were water insoluble and included 1.1 g. of a steam-volatile neutral oil, 0.37 g. of a neutral non-steam-volatile gum and 0.41 g. of an oily non-steam-volatile acid; none of these fractions could be crystallized, and they were not investigated further.[27]

7-Acetoxy-5-hydroxy-3-propyl-2,4,6-triethyl-1,5-heptanolactone.—A solution of 70.7 g. (0.0262 mole) of the lactone III in 150 ml. of acetic anhydride was treated with one drop of concentrated sulfuric acid and allowed to stand 15 hr. at room temperature, then heated on the steam-bath for 8 hr. After standing overnight and then treating with 2 g. of barium hydroxide, the material was distilled *in vacuo* to remove acetic acid and acetic anhydride. The residue was then filtered and the filtrate distilled twice to yield 63 g. (77%) of the colorless acetate, b.p. 158–162° (0.5 mm.), $n^{25}D$ 1.4662. By slowly distilling the acetate through a glass tube packed with glass wool (450°), low yields (10–20%) of unsaturated lactone were obtained.

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.19; H, 10.33. Found: C, 69.57; H, 10.65.

(27) The above data suggest the unsaturated lactone mixture to consist mainly of the isomers



XVII XVIII XIX

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Steric Effects in Hydrolysis of Hindered Amides and Nitriles[1]

BY LIN TSAI,[2] T. MIWA[3] AND MELVIN S. NEWMAN[4]

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The relative extent of alkaline hydrolysis in ethylene glycol at 190–192° of seven hindered aliphatic amides has been determined. The results are reasonably well correlated by the Rule of Six. Alkaline hydrolysis of hindered aromatic amides leads to the formation of nitriles. The acidic hydrolysis of hindered aliphatic nitriles to amides and the conversion of these amides to acids by sulfuric acid–sodium nitrite treatment is described.

Perhaps the most inclusive study of steric hindrance to carbonyl addition reactions in the aliphatic series is that involving the acid-catalyzed esterification. In this work the effect of structure on the rate of esterification with methanol of 26 saturated aliphatic acids was reported and discussed in terms of the Rule of Six and other variables.[5] However, the rates of esterification of highly sterically hindered acids could not be measured because the side reaction between the catalyst, hydrogen chloride and methanol became too important a factor when longer times and higher temperatures were needed for esterification. For example, diisopropylacetic acid esterified too slowly to measure under the general conditions used for the other acids. Accord-

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(2) Post-doctoral fellow, 1954–1955.

(3) Research assistant, 1953–1954.

(4) To whom inquiries should be sent.

(5) K. L. Loening, A. B. Garrett and M. S. Newman, THIS JOURNAL,

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ingly, we became interested in other reactions which might be studied quantitatively to yield information on highly hindered acid derivatives. We here report our observations on hydrolysis of highly hindered amides, both aliphatic and aromatic, and of hindered nitriles.

Because of experimental difficulties we were unable to devise a simple accurate procedure to measure the rate constants of alkaline hydrolysis of hindered amides. Experiments in which reactants were sealed in small stainless steel bombs equipped with closures using lead or gold gaskets failed because of leaks which developed erratically at the 190–210° temperatures needed for hydrolysis.[6] Accordingly, we turned to hydrolysis in ethylene glycol–alkali mixtures at atmospheric pressure. The extent of hydrolysis was estimated by titration of the ammonia evolved. The results are listed in Table I.

TABLE I

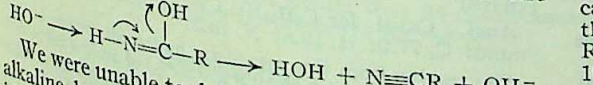
ALKALINE HYDROLYSIS OF HINDERED AMIDES IN ETHYLENE GLYCOL AT 190–192°

Amide	% NH_3 in 48 hr.	Six no.
1 $(C_2H_5)_4CCONH_2$	50.4	9
2 $(CH_3)_3CC(CH_2)_2CONH_2$	34.5	9
3 $[(CH_3)_2CH]_2CHCONH_2$	16.7	12
4 $[(CH_3)_3C](C_2H_5)CHCONH_2$	12.5	12
5 $[(CH_3)_3C][(CH_3)_2CH]CHCONH_2$	3.0	15
6 $[(CH_3)_2CH]_2(CH_3)CCONH_2$	2.4	12
7 $[(CH_3)_2CH]_2(C_2H_5)CCONH_2$	2.2	15

The over-all results are roughly what one would expect by application of the Rule of Six. In amides 6 and 7 we seem to be approaching a limit in steric hindrance, as the change from a methyl to an ethyl group in the α-position makes little difference, whereas in the acid series a similar change often makes a considerable difference (acids 12 and 24 in Table I).[5] We attach no significance to the small differences in ammonia obtained for amides 5, 6 and 7.

Turning to aromatic amides, we found that attempts to follow the alkaline hydrolysis in the ethylene glycol–alkali system used for the aliphatic mixtures revealed the presence of nitriles corresponding to the starting amides. Blank experiments in ethylene glycol alone (190–195°) showed that no nitrile was formed. Alkali is necessary for nitrile formation. We believe that this finding represents the first case of alkaline dehydration of an amide to a nitrile in solution.[7]

The transformation is pictured as a base-catalyzed elimination reaction of the enol form of the amide.



We were unable to detect a similar reaction in the alkaline hydrolyses of the hindered aliphatic amides mentioned above. Our results in the aromatic series are summarized in Table II.

TABLE II

ALKALINE TREATMENT OF HINDERED AROMATIC AMIDES IN ETHYLENE GLYCOL AT 195–197°

Amides	Moles of amide	NaOH–ethylene glycol (0.27 molal), g.	% nitrile (in 12 hr.)	% NH_3
Mesitamide	3.1×10^{-3}	100	56	0.6
2,3,5,6-Tetramethylbenzamide	2.9×10^{-3}	100	62	Trace
2,4,6-Triisopropylbenzamide	2.0×10^{-2}	650	58	0.7

In addition to the studies on alkaline hydrolysis of hindered amides, which was shown to be impractical on a kinetic basis, we have also studied the acid-catalyzed conversion of hindered amides to acids by nitrous acid.

In our study of acid hydrolysis of hindered aliphatic nitriles,[8] the nitrile was dissolved in an excess of strong sulfuric acid and held at specified temperatures for various times. The amide formed and nitrile unreacted were determined. The results of these experiments are summarized in Table III. Here again the increase in steric hindrance parallels the increase in six number. Since nitriles are in general somewhat less subject to steric hindrance than are amides, it is not surprising to find that nitriles of six number of 12 (nitriles 2 and 3, Table III) are hydrolyzed fairly well under rather drastic conditions. However, when the six number rises to 15 and 18 (nitriles 4 and 5, Table III), hydrolysis is extremely difficult and, from a practical point of view, unattainable under the prevailing conditions. Other attempts at higher and lower temperatures were even more unpromising.

In our study of the conversion of hindered amides to acids, we turned to treatment with nitrous acid in strong sulfuric acid solution, as previous work in the literature indicated that this procedure worked fairly well for moderately hindered amides.[9] Our results are summarized in Table IV. Although we did not include very highly hindered amides in this work (because we were unable to get sufficient quantities by hydrolysis of the required nitriles), we include the studies on the moderately hindered amides because this work shows that treatment with nitrous acid in strong sulfuric affords an excellent procedure for conversion to acids.

Experimental[10]

Mesitamide.—Mesitylene was brominated[11] to bromomesitylene which was converted to the Grignard reagent and carbonated to form the acid.[12] Treatment of the acid with thionyl chloride followed by ammonia furnished the amide. Recrystallization from benzene gave pure mesitamide, m.p. 192.0–193.5° (reported[13] m.p. 187–188°).

(6) Many of these experiments were performed by Dr. H. S. Eleuterio, post-doctoral fellow, 1953–1954.

(7) The conversion of benzamide to benzonitrile has previously been accomplished by fusion with lime. See (a) F. Wohler, *Ann.*, **192**, 362 (1878); (b) R. Anschütz and G. Schultz, *ibid.*, **196**, 48 (1879). We have checked this by converting mesitamide to mesitonitrile.

(8) The preparation of the hindered nitriles will be described in a forthcoming publication.

(9) (a) C. Schuerch, Jr., and E. Huntress, THIS JOURNAL, **70**, 2824 (1948); (b) N. Sperber, D. Papa and E. Schwenk, *ibid.*, 3091 and references contained therein.

(10) Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. All melting points are corrected.

(11) L. I. Smith, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 95.

(12) D. M. Bowen, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 553.

(13) K. Kangri Collection, Haridwar, *J.*, **23**, 468 (1900).

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TABLE III

ACIDIC HYDROLYSIS OF HINDERED NITRILES IN SULFURIC ACID

	Nitrile, $R_1R_2R_3CCN$ R_1	R_2	R_3	H_2SO_4 %	H_2SO_4 g./g. nitrile	Time, hr.	Temp., °C.	Amides Yield, %	Amides Pure sample m.p., °C.	Rec. nitriles, %
1	C_2H_5	C_2H_5	C_2H_5	75	1.7	0.5	140	93	110.6–111.4	..
2	$(CH_3)_2CH$	$(CH_3)_2CH$	H	75	1.7	0.5	140	83	147.2–149.4	..
3	$(CH_3)_2CH$	$(CH_3)_2CH$	CH_3	75	1.7	0.6	140	66[a]	57.8–58.8[b]	..
4	$(CH_3)_2CH$	$(CH_3)_2CH$	C_2H_5	85	5.4	18	100	25[a]	95.8–96.4[c]	..
				95	14	45	50	10[a]		32
				95	10	70	65	15[a]		75
5	$(CH_3)_2CH$	$(CH_3)_2CH$	$(CH_3)_2CH$	95	10	168	70	Trace		57
6	$(CH_3)_3C$	CH_3	CH_3	[d]	2.1	1	140	63[e]	203.5–204.5[f]	79

[a] Based on crude product. [b] *Anal.* Calcd. for $C_9H_{19}NO$: C, 68.3; H, 11.5; N, 8.9. Found: C, 68.5; H, 11.5; N, 8.9. [c] *Anal.* Calcd. for $C_{10}H_{21}NO$: C, 70.1; H, 12.4; N, 8.2. Found: C, 70.3; H, 12.3; N, 8.1. [d] In this experiment 23.9 g. of nitrile was heated in 30 ml. of 85% sulfuric acid and 10 ml. of acetic acid. [e] The corresponding acid, m.p. 195.0–196.0°, was also obtained in 20% yield. [f] *Anal.* Calcd. for $C_8H_{17}NO$: C, 67.1; H, 12.0; N, 9.8. Found: C, 66.8; H, 11.8; N, 9.6.

TABLE IV

CONVERSION OF HINDERED AMIDES TO ACIDS

	Amide, $R_1R_2R_3CCONH_2$ R_1	R_2	R_3	75% H_2SO_4 g./g. nitrile or amide	$NaNO_2$, mole/mole nitrile or amide	Yield, %	Acid Pure sample m.p., °C.
1	C_2H_5	C_2H_5	C_2H_5	3.2	1.4	90[a]	38.9–39.5[b]
2	$(CH_3)_2CH$	$(CH_3)_2CH$	H	1.7	1.5	93[a]	20.0[c]
3	$(CH_3)_2CH$	$(CH_3)_2CH$	CH_3	2.4	2.3	88	49.5–50.2[d]
4	$(CH_3)_2CH$	$(CH_3)_2CH$	C_2H_5	2.4	4.8	71	56.4–57.0[e]
5	$(CH_3)_3C$	CH_3	CH_3	[f]	1.9	63[a]	198.5–199.0[g]
6	$(CH_3)_3C$	$(CH_3)_2CH$	H	2.7	1.4	76	B.p. 224[h]

[a] Figures represent over-all yield from corresponding nitriles which were hydrolyzed by 75% H_2SO_4 to give the crude amides which were treated directly with specified amount of sodium nitrite. [b] C. Schuerch, Jr., and E. H. Huntress, THIS JOURNAL, **70**, 2824 (1948). [c] F. C. B. Marshall, *J. Chem. Soc.*, 2754 (1930). [d] *Anal.* Calcd. for $C_9H_{18}O_2$: C, 68.3; H, 11.5; neut. equiv., 158.2. Found: C, 68.5; H, 11.5; neut. equiv., 158.5. [e] *Anal.* Calcd. for $C_{10}H_{20}O_2$: C, 69.8; H, 11.7. Found: C, 69.7; H, 11.7. [f] In this experiment, 9.5 g. of the nitrile was heated at 150° in 20.1 g. of 75% sulfuric acid and 8.5 g. of acetic acid for 1.5 hr. After the reaction mixture was cooled, 10 g. of sodium nitrite was added. [g] A. Byers and W. S. Hickinbottom, *J. Chem. Soc.*, 1334 (1948). [h] A. A. Sacks and J. G. Aston, THIS JOURNAL, **73**, 3902 (1951), reported the following physical constants for this acid: b.p. 122.5–123.8° (22 mm.), $n^{20}D$ 1.4343.

2,3,5,6-Tetramethylbenzamide (m.p. 187–188°, reported[14] m.p. 178°) was obtained in a similar manner from durene.

Anal. Calcd. for $C_{11}H_{15}ON$: N, 7.9. Found: N, 7.9.

2,4,6-Triisopropylbenzamide (m.p. 216.5–219.5°, reported[15] m.p. 218.7–219.3°) was similarly prepared from 1,3,5-triisopropylbenzene.

***t*-Butylethylacetamide.**—A mixture of 50.4 g. of *t*-butylethylacetic acid[16] (m.p. 76–78°) and 50 g. of thionyl chloride was allowed to stand overnight at room temperature and then heated at 90° for 4 hr. The reaction mixture was distilled twice through a fractionation column to give 51.8 g. (91%) of pure *t*-butylethylacetyl chloride, b.p. 67–69° at 25 mm. The acid chloride was poured into an ethereal solution of ammonia to give the crude amide which was recrystallized from a mixture of benzene–Skellysolve B (petroleum ether, b.p. 65–69°) to furnish 44.8 g. (98%) of *t*-butylethylacetamide, m.p. 136.6–137.2°.[17]

Anal. Calcd. for $C_8H_{17}ON$: C, 67.1; H, 11.9; N, 9.8. Found: C, 67.2; H, 12.2; N, 9.8.

***t*-Butylisopropylacetonitrile and *t*-Butylisopropylacetamide.**—To a solution of sodium ethoxide (prepared from 23 g. of sodium in about 400 ml. of absolute ethanol) was introduced 169 g. of ethyl *t*-butylcyanoacetate[18] and 190 g. of isopropyl iodide. The mixture was heated under reflux for 15 hr. The solvent was removed by distillation under reduced pressure. The residue was taken up in 200 ml. of water and extracted several times with benzene–ether mixture. The combined extracts were successively washed with sodium hydrosulfite, sodium hydroxide and saturated sodium chloride solutions and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the residual liquid was fractionated at 18 mm. pressure to afford 64.5 g. (38%) of unchanged ethyl *t*-butylcyanoacetate, b.p. 110–113°, and 89.0 g. (42%) of ethyl *t*-butylisopropylcyanoacetate, b.p. 128–132°.

A mixture of ethyl *t*-butylisopropylcyanoacetate (75 g.) and 150 g. of potassium hydroxide was fused and distilled. The distillate was again fused with 100 g. of potassium hydroxide and distilled. Fractionation of the distillate afforded 22.2 g. (45%) of *t*-butylisopropylacetonitrile, b.p. 178–181°.

Anal. Calcd. for $C_9H_{17}N$: C, 77.6; H, 12.3; N, 10.1. Found: C, 77.0; H, 12.8; N, 10.2.

The residue from the potassium hydroxide fusion on taking up in water furnished 12.9 g. (23%) of an insoluble solid which was recrystallized from benzene–Skellysolve B to give pure *t*-butylisopropylacetamide, m.p. 124.8–125.6°.

Anal. Calcd. for $C_9H_{19}ON$: C, 68.7; H, 12.2; N, 8.9. Found: C, 68.8; H, 12.0; N, 8.9.

Alkaline Hydrolysis of Hindered Aliphatic Amides.—The solvent used in these experiments was ethylene glycol (b.p. 196–198°) which was purified by refluxing with 2 g. of sodium (per liter of solvent) for several hours and distilling.

(14) V. Meyer and L. Wohler, *Ber.*, **29**, 2571 (1896).

(15) A. Newton, THIS JOURNAL, **65**, 2441 (1943).

(16) We wish to thank Dow Chemical Co. for a generous gift of this acid.

(17) W. A. Mosher and J. C. Cox, Jr., THIS JOURNAL, **72**, 3701 (1950), reported this amide as melting at 115–116°. In order to check the identity of our amide, m. p. 137°, we alkylated 25 g. of *t*-butylacetonitrile with sodium amide (from 6 g. of sodium in 400 ml. of ammonia) and 29 g. of ethyl bromide for 20 hours, to yield 12.2 g. of *t*-butylethylacetonitrile, b. p. 170–175°, and 5.0 g. of *t*-butyldiethylacetonitrile, b. p. 198–200°. A redistilled sample of *t*-butylethylacetonitrile, b. p. 174–175°, was analyzed (Calcd. for $C_8H_{15}N$: C, 76.7; H, 12.1; N, 11.2. Found: C, 76.7; H, 12.2; N, 11.3) and hydrolyzed by heating 2 g. with 3.4 g. of 75% sulfuric acid for 1.5 hours, at 140–150° to yield 1.6 g. of amide, m. p. 135–136°, undepressed by mixing with a sample of the amide of *t*-butylethylacetic acid, m. p. 136–137°, made from the acid obtained from the Dow Co.

(18) C. R. Hauser and C. R. Hance, *Org. Reactions*, **2**, 322 (1950).

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A solution of sodium hydroxide in ethylene glycol was prepared by mixing an appropriate amount of carbonate-free 40% sodium hydroxide solution with ethylene glycol. The concentration of sodium hydroxide in the solution was determined by titration of weighed aliquots, after diluting 10-fold with distilled water, against standard sulfuric acid using phenolphthalein as indicator.

The hydrolysis of the amide was carried out in a 3-necked flask equipped with a reflux condenser, a thermometer and an inlet for nitrogen gas which was bubbled slowly through the reaction mixture. The outlet of the reflux condenser was led into a known volume of standard sulfuric acid solution which served as an absorption system for ammonia. The reaction flask was heated by a heating mantle and the temperature was controlled by a Thermocap relay.[19]

A weighed amount of a 0.5 molal solution of sodium hydroxide in ethylene glycol was placed in the reaction flask. The temperature of the system was brought rapidly to 190–192°, and a weighed amount of amide ($^1/_{20}$ of the molar concentration of sodium hydroxide in the solution) was introduced.

The condenser and the absorption system was immediately connected to the reaction flask. Ammonia evolved during the course of the reaction was entrained by the stream of nitrogen and absorbed in the standard sulfuric acid solution. After 48 hr. the reaction was stopped and the amount of ammonia from the hydrolysis was estimated by titration of the excess acid against standard sodium hydroxide solution using as indicator screened methylene blue–methyl red. The results are shown in Table I.

Reaction of Hindered Aromatic Amides with Sodium Hydroxide in Ethylene Glycol.—A procedure similar to that described for the hydrolysis of aliphatic amides was employed. After the formation of nitrile was observed in preliminary experiments, the apparatus was modified by replacing the reflux condenser by a distilling condenser. The nitrile formed during the course of the reaction was removed from the reaction mixture by co-distillation with ethylene glycol. The reaction was carried out for 12 hr. during which about 10% of the reaction mixture was distilled. The amount of ammonia evolved was determined by titration. The nitrile was isolated from the distillate.

Mesitonitrile (m.p. 50°, reported[20] m.p. 53°) was purified by sublimation at 40° and 0.1 mm. pressure. The infrared spectrum (chloroform solution) showed an intense band at 4.6 μ (2170 cm.$^{-1}$) due to the nitrile function.[21] In one experiment, an intimate mixture of 0.30 g. of mesitamide and 2.8 g. of powdered sodium hydroxide was heated at 290–310° under 20 mm. pressure for 0.5 hr. Mesitonitrile (m.p. 49°) was obtained in 86% yield.

2,3,5,6-Tetramethylbenzonitrile (m.p. 73–74°, reported[22] m.p. 76–77°) was purified by sublimation at 50° and 0.08 mm. pressure. The infrared spectrum (chloroform solution) showed an intense band at 4.6 μ (2170 cm.$^{-1}$).

2,4,6-Triisopropylbenzonitrile was purified by chromatography of the crude substance in redistilled Skellysolve F (petroleum ether, b.p. 35–55°) over activated alumina. The solvent was removed under reduced pressure at room temperature. The residue was distilled to afford a pure sample of the nitrile, b.p. 264–268° at 740 mm., n^{20}D 1.5089 (lit.[15] n^{20}D 1.5093). Physical properties and the infrared spectrum of this nitrile were identical with those of a sample of the nitrile obtained by the dehydration of 2,4,6-triisopropylbenzamide by means of thionyl chloride in benzene solution. The results are summarized in Table II.

Acidic Hydrolysis of Hindered Aliphatic Nitriles.—A mixture of the nitrile[8] and sulfuric acid of known concentrations was heated at a specific temperature. After a certain period of heating, the reaction mixture was poured into a large excess of ice-water, and the mixture was worked up by the usual method of extraction. The extent of hydrolysis of the nitrile was indicated by the yield of the amide and the amount of recovered nitrile. The conditions and results of these experiments are summarized in Table III.

Conversion of Aliphatic Amides to Acids.—The amides were treated with a mixture of sodium nitrite and sulfuric acid according to procedures described in the literature.[9] The conditions and results are shown in Table IV.

(19) Niagara Electronic Laboratories, Andover, N. Y. This instrument controlled the supply of electrical power to the heating system. The change of electric capacity necessary for the operation of this type of relay was effected by the movement of the mercury thread in the thermometer to which the relay lead was connected.

(20) R. Scholl and F. Kacer, *Ber.*, **36**, 331 (1903).

(21) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

(22) O. Jacobsen, *Ber.*, **22**, 1224 (1889).

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[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis and Solvolysis of the 2-Halo-1,4-endoxocyclohexanes[1]

BY JAMES C. MARTIN[2] AND PAUL D. BARTLETT

RECEIVED DECEMBER 17, 1956

A kinetic study of the hydrolysis of *exo*-2-chloro-1,4-endoxocyclohexane has shown it to be less reactive than *exo*-norbornyl chloride by a factor of approximately 2000. Its relative inertness is considered to result from the inductive effect of the oxygen bridge, enhanced by its geometric situation. Solvolysis of *endo*-2-chloro-1,4-endoxocyclohexane was slower than that of its *exo* isomer by a factor of 160 (at 140°). This factor is of the same order of magnitude as the corresponding factor in the solvolysis of norbornyl derivatives suggesting that the anchimeric acceleration of ionization of the *exo*-2 substituent is not greatly affected by substitution of an oxygen bridge for the methylene bridge of the norbornyl derivatives. In every case the solvolysis product was that expected to result from rearrangement, 3-formylcyclopentanol. The structures of these chloro ethers, which were obtained from the photochlorination of 1,4-endoxocyclohexane, were confirmed by dipole moment studies. *exo*-2-Bromo-1,4-endoxocyclohexane, isolated from the N-bromosuccinimide bromination of the parent ether, showed a reactivity 30-fold greater than its chloro analog. An interesting side product (16%) isolated from this bromination reaction was β-bromopropionyl isocyanate.

Introduction

A large amount of work of a quantitative nature has been performed on the solvolytic reactions of the various norbornyl derivatives.[3] In the frame of understanding created by this work we have examined the chemical consequences of the replace-

(1) Presented before the Organic Division of the American Chemical Society at its Atlantic City Meeting, September, 1956.

(2) National Science Foundation Fellow, 1953–1954.

(3) (a) J. D. Roberts, W. Bennett and R. Armstrong, THIS JOURNAL, **72**, 3329 (1950); (b) J. D. Roberts and W. Bennett, *ibid.*, **76**, 4623 (1954); (c) S. Winstein and D. Trifan, *ibid.*, **71**, 2953 (1949); (d) S. Winstein and D. Trifan, *ibid.*, **74**, 1147, 1154 (1952); (e) S. Winstein, B. Morse, E. Grunwald, H. Jones, J. Corse, D. Trifan and H. Marshall, *ibid.*, **74**, 1127 (1952); (f) S. Winstein, E. Clippinger, A. H. Fainberg and G. C. Robinson, *Chem. and Ind.*, 664 (1954); (g) J. D. Roberts and C. C. Lee, THIS JOURNAL, **73**, 5009 (1951); (h) J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *ibid.*, **76**, 4501 (1954); (i) P. D. Bartlett and L. H. Knox, *ibid.*, **61**, 3184 (1939); (j) W. von E. Doering and E. F. Schoenewaldt, *ibid.*, **73**, 2333 (1951); (k) S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, *ibid.*, **77**, 4183 (1955); (l) S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956).

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ment of the 1,4-endomethylene bridge of the norbornyl system by the oxygen bridge of the 1,4-endoxocyclohexane system.

Results and Discussion

The photochlorination of 1,4-endoxocyclohexane at −40° led to the isolation of a series of chloro ethers including *exo*-2-chloro-1,4-endoxocyclohexane and *endo*-2-chloro-1,4-endoxocyclohexane. Infrared analysis showed the *exo* isomer to be formed in amount 2.2 times that of the *endo* isomer. None of the α-chloro ether, 1-chloro-1,4-endoxocyclohexane, which would result from bridgehead chlorination, was isolated. This is in accord with previously reported[4] unsuccessful attempts to obtain bridgehead chlorination in other systems.

The bromination of the parent ether, 1,4-endoxocyclohexane, with N-bromosuccinimide yielded *exo*-2-bromo-1,4-endoxocyclohexane.

These monohalo ethers were separated and purified by fractional distillation. The more highly chlorinated ethers resulting from further treatment with chlorine were separated by means of chromatography on alumina. A summary of the pure compounds isolated is presented in Table I.

TABLE I

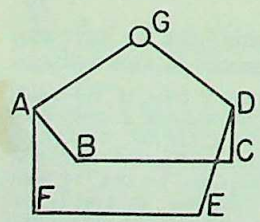
PRODUCTS OF THE HALOGENATION OF 1,4-ENDOXOCYCLOHEXANE

Ether	M.p. or b.p. °C.
endo-2-Chloro-1,4-endoxocyclohexane	68.0 (27)[a]
exo-2-Chloro-1,4-endoxocyclohexane	48.0 (4)[a]
exo-2-Bromo-1,4-endoxocyclohexane	68.2 (2)[a]
Dichloro ether	143.2–144.0
Trichloro ether	154.5–145.8
Tetrachloro ether	77.8–78.8
Hexachloro ether	108.6–109.0
Octachloro ether	158.8–159.4

[a] The value in parentheses refers to pressure (mm.).

The constraint afforded by the bicyclic structure of this series of halo ethers maintains quite constant the angles between the various bonds and, therefore, the angles between the bond moments. This greatly facilitates the interpretation of dipole moment data. If one considers the composite electric moment of the unsubstituted 1,4-endoxocyclohexane to be a vector directed toward the oxygen atom and perpendicular to the plane of carbon atoms 2, 3, 5 and 6, the effect of superposing moments arising from replacement of the various hydrogen atoms by halogen may be computed.

A geometric model for the bicyclic nucleus of this system was derived using vector analytical procedures.[5] The model chosen for these calculations used a value for the C–C bond length of 1.55 Å. and for the C–O bond length, 1.44 Å. The values of the angles in this model were: ∠ FAB = 101°, ∠ ABC = 103°, ∠ AGD = 102° 54′ and ∠ BAG = 101° 14′.



The theoretical dipole moments were calculated as the resultant of the ether dipole moment (the experimental moment of 1,4-endoxocyclohexane, 1.74 *D*) and the C–Cl bond moment (the experimental moment of cyclopentyl chloride, 2.08 *D*)[6].

TABLE II

RESULTS OF DIPOLE MOMENT STUDIES ON THE MONOHALO-1,4-ENDOXOCYCLOHEXANES

Compound	Solvent	Moment, *D* Calcd.	Found
1,4-Endoxocyclohexane	Benzene	..	1.70
	CCl_4	..	1.78
1-Chloro-1,4-endoxocyclohexane	.....	3.20	..
exo-2-Chloro-1,4-endoxocyclohexane	Benzene	3.17	3.07
	CCl_4	3.17	2.99
endo-2-Chloro-1,4-endoxocyclohexane	Benzene	0.82	1.08
exo-2-Bromo-1,4-endoxocyclohexane	CCl_4	3.17	3.03

These data make it clear that the assignment of structure for *endo*-2-chloro-1,4-endoxocyclohexane is the correct one. The data for the other chloro ether are compatible with either *exo*-2-chloro-1,4-endoxocyclohexane or 1-chloro-1,4-endoxocyclohexane. The isolation of 3-formylcyclopentanol (V) as the solvolysis product from both of the chloro ethers confirmed the assignment of the structure *exo*-2-chloro-1,4-endoxocyclohexane. The structure of the bromo ether was similarly shown to be *exo*-2-bromo-1,4-endoxocyclohexane. The hydroxyaldehyde was formed nearly quantitatively in the solvolyses of all three of these halo ethers. The structure 3-formylcyclopentanol was established by Wolff–Kishner reduction to the known[7] *trans*-3-methylcyclopentanol.

The assigned structures for these halo ethers were found to be compatible with the observed infrared spectra and proton nuclear magnetic resonance (NMR) spectra. The NMR spectra, obtained using a Varian Associates model V-4300B high resolution spectrograph, are schematically summarized in Fig. 1.

The parent ether, 1,4-endoxocyclohexane, shows two resonance peaks, of approximate relative intensities 4 and 1, at positions corresponding to Gutowsky δ-values[8] of approximately −0.43 and −0.10 (the methylene and the bridgehead hydrogens, respectively). No evidence of splitting, from spin-spin interaction, was observed for either of these peaks.

The spectra of the *exo*-2-halo-1,4-endoxocyclohexanes show a total of four main resonance peaks corresponding, presumably (in order of increasingly negative δ-values), to the bridgehead hydrogens (intensity 2), the halomethylene hydrogen (1), the methylene adjacent to halomethylene (2) and the other two methylene groups (4). The positions of these peaks are expressed as δ-values: *exo*-chloride, (−0.10, −0.15, −0.37, −0.43); *exo*-bromide (−0.10, −0.15, −0.35, −0.43). The peak at 0.10 is a poorly resolved doublet, as might be expected from the non-equivalence of the bridgehead hydro-

(4) See D. E. Applequist and J. D. Roberts, *Chem. Revs.*, **55**, 1065 (1954).

(5) E. J. Corey and R. A. Sneen, *ibid.*, [illegible] (1956).

(6) H. Rogers and J. D. Roberts, *ibid.*, **68**, 843 (1946).

(7) M. Godelot, G. Cauquil and R. Calas, *Bull. soc. chim.*, **6**, 1351 (1939).

(8) L. H. Meyer, A. Saika and H. S. Gutowsky, THIS JOURNAL, **75**, [illegible] (1953).

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TABLE III

ENTHALPIES AND ENTROPIES OF ACTIVATION FOR SOLVOLYSIS

Compound	Solvent	$\Delta H^{\ddagger}$, kcal.	$\Delta S^{\ddagger}$, e.u.
exo-2-Chloro-1,4-endoxocyclohexane	50% dioxane–H_2O	29.43 ± 0.12	− 7.47 ± 0.29
endo-2-Chloro-1,4-endoxocyclohexane	50% dioxane–H_2O	30.87 ± 0.15	−14.07 ± 0.34
exo-2-Bromo-1,4-endoxocyclohexane	50% dioxane–H_2O	24.6 ± 0.54	−15.00 ± 1.45
exo-2-Norbornyl *p*-bromobenzenesulfonate	Acetic acid	23.3[a]	7.7[a]
endo-2-Norbornyl *p*-bromobenzenesulfonate	Acetic acid	26.0[b]	− 1.5[b]

[a] This value, calculated from the data of Winstein,[3e] was from two runs at temperatures differing by 8.77°. [b] Calculated from the data of Winstein.[3e]

TABLE IV

SOLVOLYSES OF THE 2-HALO-1,4-ENDOXOCYCLOHEXANES

Run	Compound	Concentration halide, mole/l.	Temp., °C.	Reaction followed, %	Added salt	Salt concn., mole/l.	k, sec.$^{-1}$[a]
1	*exo*-Br	0.03967[b]	85.0	58.1			(8.58 ± 0.06) × 10^{-7}
2	*exo*-Br	.03988[c]	85.0	52.9			(4.64 ± .05) × 10^{-7}
3	*exo*-Br	.04028[d]	85.0	79.0			(8.24 ± .04) × 10^{-6}
4	*exo*-Br	.04020[d]	100.7	70.6			(3.77 ± .03) × 10^{-5}
5	*exo*-Br	.04344[d]	120.0	90.0			(1.85 ± .03) × 10^{-4}
6	*exo*-Br	.04026[d]	85.0	32.5	KCl	0.10	(8.41 ± .04) × 10^{-6}
7	*exo*-Br	.04193[d]	85.0	52.8	$NaClO_4$	.10	(9.07 ± .03) × 10^{-6}
8	*exo*-Cl	.04328[d]	100.7	32.8			(1.17 ± .03) × 10^{-6}
9	*exo*-Cl	.04069[d]	120.0	64.1			(8.81 ± .37) × 10^{-6}
10	*exo*-Cl	.04032[d]	140.0	79.1			(5.66 ± .04) × 10^{-5}
11	*endo*-Cl	.03969[d]	140.0	38.7	NaOAc	0.042	(3.47 ± .09) × 10^{-7}
12	*endo*-Cl	.03948[d]	160.0	66.4	NOaAc	.041	(2.08 ± .02) × 10^{-6}
13	*endo*-Cl	.03420[d]	175.0	71.4	NaOAc	.042	(7.10 ± .08) × 10^{-6}
14	*endo*-Cl	.03961[d]	140.0	84.6			Autocatalytic
15	*endo*-Cl	.03610[d]	140.0	44.2	HCl	.02	Autocatalytic
16	*endo*-Cl	.03312[d]	140.0	19.6	KCl	.02	Autocatalytic

[a] These first-order rate constants were determined by a least squares treatment of the data. The uncertainties which are indicated are standard deviations. [b] In 80% ethanol (vol.). [c] In 80% ethanol (wt.). [d] In 50% dioxane (wt.).

gens because of the halogen at position 2. The halomethylene hydrogen resonance at −0.15 is strongly split into a triplet, presumably from spin–spin interaction with the protons of the neighboring methylene. The resonance of this neighboring methylene, at −0.37 or −0.35, appears as a doublet, as expected from such an interaction.

The *endo*-chloride shows a similar spectrum with an additional poorly resolved peak, of intensity approximately 1, at −0.32, possibly to be attributed to a transannular interaction of an *endo*-hydrogen at position 6 with the *endo*-chlorine. In addition, there is some evidence of splitting in the methylene peak at −0.43. The positions of the resonance peaks for this compound are (−0.05, −0.12, −0.32, −0.37, −0.43).

Results of kinetic studies on the solvolytic reactions of these ethers are outlined in Tables III and IV. The reactions were followed by acidimetric titration of aliquots.

A direct comparison of the rate constants for the *exo*- and *endo*-2-chloro-1,4-endoxocyclohexanes at 140° in 50% dioxane–water gives a reactivity ratio of 163 for these isomers, the *exo* isomer being the more reactive. Table V gives calculated values for this ratio from the present work, the work of Roberts and the work of Winstein. It can be seen that this ratio is not changed greatly in the 1,4-endoxocyclohexane system from its value in the norbornyl system.

The calculated value (from ΔH^* and ΔS^*) of the rate constant for the solvolysis of *exo*-2-chloro-1,4-endoxocyclohexane in 50% aqueous dioxane at 85.0° is 1.88 × 10^{-7} sec.$^{-1}$. The value of the rate constant for the solvolysis of the corresponding bromo ether is decreased by a factor of 9.6 when the solvent is changed from 50% dioxane–water to 80% (by weight) dioxane–water. Assuming a parallel

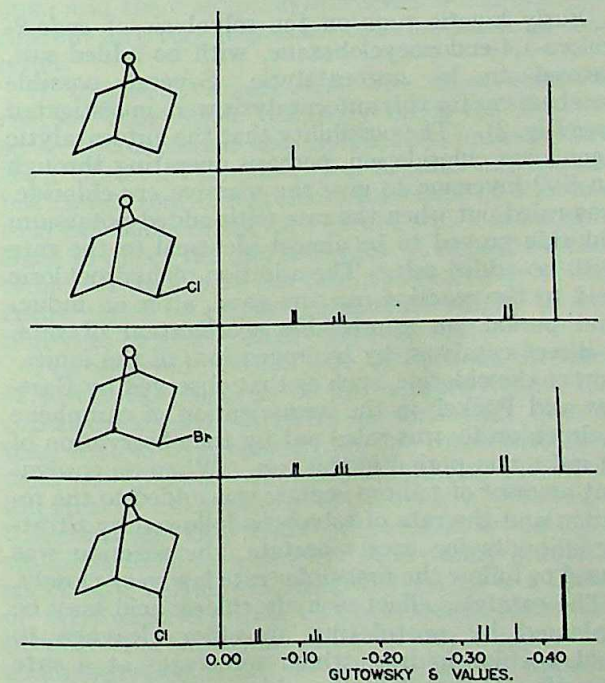

Fig. 1.—Proton nuclear magnetic resonance spectra of 1,4-endoxocyclohexane derivatives.

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change in the rate constant for the chloro ether in these two solvents, one calculates a rate constant for the *exo*-chloride at 85.0° in 80% (by vol.) ethanol of 1.96×10^{-8} sec.$^{-1}$. Under these same conditions Roberts[3b] found a rate constant of 3.89×10^{-5} sec.$^{-1}$ for *exo*-norbornyl chloride.

Comparison of these values for the two bicyclic systems shows the norbornyl chloride to be more reactive than its oxygen-bridged analog by a factor of 2.0×10^{3}. A similar calculation for the *endo* isomers gives a factor of 6.0×10^{3}.

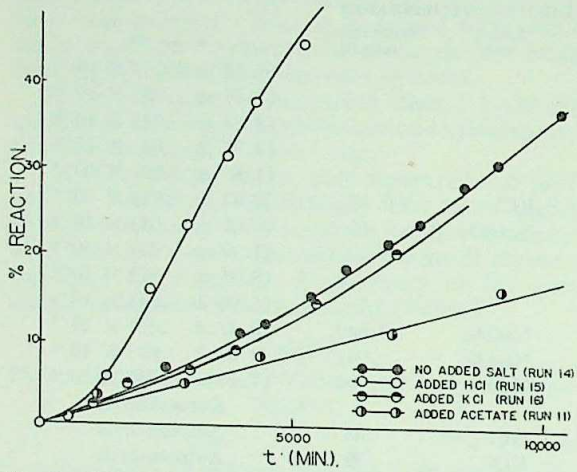
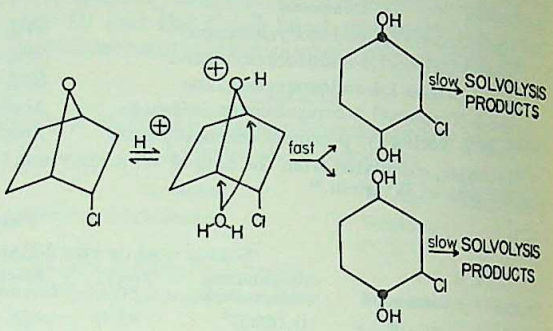


Fig. 2.—Solvolysis of *endo*-2-chloro-1,4-endoxocyclohexane in 50% dioxane–water (by weight) at 140°.

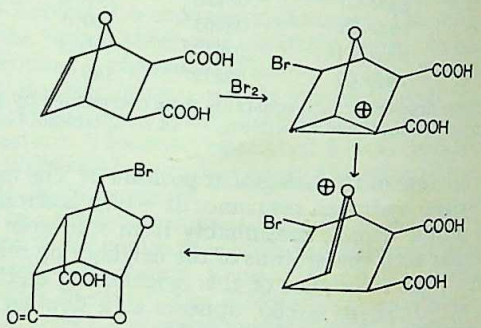
Early kinetic runs on the solvolysis of *endo*-2-chloro-1,4-endoxocyclohexane, with no added salt, proved to be autocatalytic. Several possible mechanisms for this autocatalysis were investigated (see Fig. 2). The possibility that the autocatalytic agent was chloride ion, perhaps operating through an SN2 inversion to give the reactive *exo*-chloride, was ruled out when the rate with added potassium chloride proved to be almost identical to the rate with no added salt. The addition of hydrochloric acid to the reaction mixture gave, after an induction period, an appreciable acceleration of rate. A direct catalysis, by hydrogen ion, of the ionization of the chloride, such as that observed by Bartlett and Pöckel[9] in the isomerization of camphene hydrochloride, was ruled out by the observation of an induction period in this run. When an equivalent amount of sodium acetate was added to the reaction and the rate of solvolysis followed by titrating aliquots for excess acetate, the reaction was found to follow the first-order rate law very closely.

The catalytic effect of hydrochloric acid may be explained by postulating an ether cleavage to yield a chlorohydrin, which solvolyzes at a rate somewhat faster than the chloro ether. In a related case[3a] the solvolysis of 2-chloro-2-methylpropanol-1 is slower than that of *t*-butyl chloride by a factor of 6.5×10^{-3}. Since *endo*-2-chloro-1,4-endoxocyclohexane is approximately 10^{-4} as reactive as cyclohexyl chloride in solvolytic reactions, we might expect the chlorohydrin from the ether cleavage to be about 60–70 times as reactive as the chloro ether itself. Such a ratio of reactivities could account for the observed behavior.

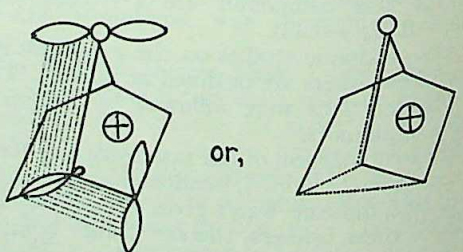


Two different interactions of the unshared electron pairs of the oxygen bridge might be expected to affect the *exo*/*endo* reactivity ratio in these solvolytic reactions.

With regard to the first of these effects, Woodward and Baer[10] postulated an important contribution from the oxonium form of the positively charged intermediate ion as a driving force in the rearrangement which accompanies the addition of bromine to *exo-cis*-3,6-endoxo-Δ^4-tetrahydrophthalic acid.



In the present work we must consider the possible stabilization, by such an oxonium form, of the transition state leading to the positive ion. Any such stabilization involves an interaction between a lone pair orbital of oxygen, the bonding orbital between C_1 and C_6 and the developing p-orbital at C_2, where the leaving group is *exo*.



Since the observed *exo*/*endo* ratio is of the same order of magnitude for the endoxo- and endomethylene series, it is unnecessary to postulate an important contribution of this oxonium form in the transition state. Once the ion is formed, however, slight changes in geometry, perhaps over a very small potential energy barrier, might be expected

(9) P. D. Bartlett and I. Pöckel, THIS JOURNAL, 60, 1585 (1938).

(10) R. B. Woodward and H. Baer, *ibid.*, 70, 1161 (1948).

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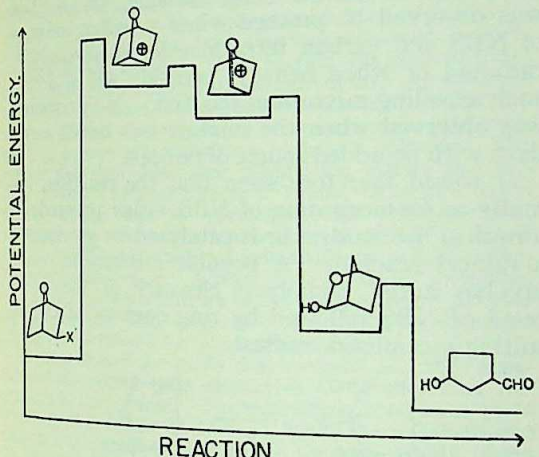
TABLE V

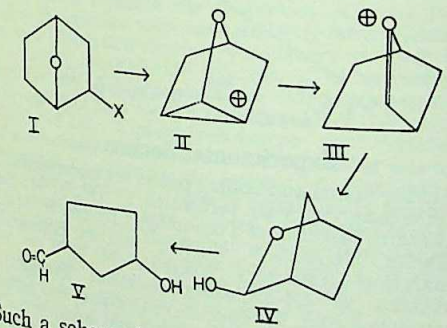
exo/endo REACTIVITY RATIOS IN SOLVOLYTIC REACTIONS

Series of compounds	Temp., °C.	k_{exo}/k_{endo}	k_{endo}, sec.$^{-1}$
Norbornyl chlorides[3b]	85	70	5.6×10^{-7}
Norbornyl brosylates[3f]	25	350	2.5×10^{-7}
	85	275	4.7×10^{-4}
2-Chloro-1,4-endoxocyclohexanes	140	163	3.5×10^{-7}
	85	211	8.9×10^{-10}
	25	318	1.2×10^{-13}

to twist the molecule into a form much more favorable to overlap between oxygen lone pair orbitals and a p-orbital on C_1. The large stabilization so attained would be similar to that in the transition states for the ionizations of α-halo ethers.

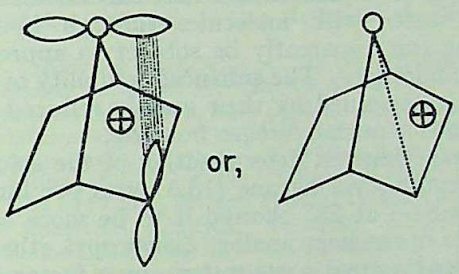


A POSSIBLE POTENTIAL ENERGY SCHEME.



Such a scheme is compatible, but of course not uniquely so, with the observed isolation of rearranged product (as aldehyde) in nearly quantitative yield. It is also compatible with results of experiments designed to intercept the cationic intermediate with azide ion. According to Swain[11] the azide ion is a more active nucleophile than water by a factor of 10^4 to 10^5. In his kinetic treatment of interception experiments using azide ion, Swain considered the alkyl azide to be formed irreversibly where the alkyl group was, for example, triphenylmethyl. In the present work solvolyses with 0.6 *N* added azide (sufficient, using Swain's competition factor, to capture more than 99% of the carbonium ions in competition with water), the product obtained was 3-formylcyclopentanol with less than 3% of an alkyl azide. A possible explanation for this unexpected behavior would involve an attack of azide ion either on II or on III, which is formed very rapidly from II, to give the α-azido ether which is then subject to hydrolysis to 3-formylcyclopentanol.

A second effect to be ascribed to the lone pair electrons might be classified as a homoallylic interaction—a direct interaction between the developing p-orbital at the ionizing center and a lone pair orbital. The situation is superficially similar to that which gave rise to a rate acceleration of 10^{11} in the solvolysis of *anti*-7-dehydronobornyl tosylate.[3k,1] In that system the interaction is between a developing p-orbital at C_7 and the π-electron system of C_2 and C_3. In the present system we might postulate a lesser, but perhaps still substantial, interaction between the developing p-orbital at C_2 and a lone pair orbital on oxygen. The result of such an interaction would be an acceleration of the rate of ionization of an *endo* substituent.



Again, the failure to observe any major difference in the *exo/endo* reactivity ratios for the endoxo and the endomethylene series would seem to rule out any very important contribution from this effect.

It might be argued that the observation of roughly comparable reactivity ratios for the two series of compounds does not, in fact, indicate that these effects are inoperative or of small importance but rather that it represents the result of a fortuitous cancelling of the two effects, which are postulated to affect the *exo/endo* ratio in opposite directions. If such were the case, the reactivity of the entire series of endoxo compounds might be expected to be greater than that observed.

The observed factor of 6×10^3 between the rates of solvolytic reactions of the norbornyl and 1,4-endoxocyclohexyl chlorides is somewhat greater than that to be expected from the consideration of model compounds[12] or that predicted by the dipole interaction calculations of Winstein.[13,14] Winstein concludes that the rate depression in acetolysis reactions to be expected from the purely inductive effect of a neighboring methoxy group is a factor of approximately 100. The observed difference between the solvolysis rates of the endoxo and endomethylene series of compounds is approximately 60 times greater than this.

In the 1,4-endoxo compounds the ether bridge corresponds not only to a β-alkoxy group but also to a γ-alkoxy group relative to substituents at the 2-position. This statement is equivalent to a

(11) C. G. Swain, C. B. Scott and K. H. Lohmann, THIS JOURNAL, **75**, 136 (1953); C. G. Swain and C. B. Scott, *ibid.*, **75**, 141 (1953).

(12) S. Winstein and E. Grunwald, *ibid.*, **70**, 828 (1948).

(13) S. Winstein, E. Grunwald and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

(14) S. Winstein, *ibid.*, **73**, 2700 (1951).

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recognition that the orientation of the over-all ether dipole is fixed in such a manner as to increase the effectiveness of its interaction with dipoles at the 2-position.

A somewhat similar situation is discernible in data on the acid dissociation constants of conjugate acids of amines.[15]

Amine	pK_{AH} (25°)
Ethylamine	10.81
β-Methoxyethylamine	9.45
Morpholine	8.70
Piperidine	11.28

The pK_{AH} for ethylamine exceeds that for β-methoxyethylamine by 1.36 units, whereas the difference in the corresponding constants for the two cyclic amines is 2.58.

Another possible explanation for the enhanced inductive effect of the oxygen bridge lies in a consideration of the solubilities of ethers in water. Ferguson[16] has pointed out that the association of liquid water with molecules through hydrogen bonding can apparently be subject to appreciable steric hindrance. The enhanced solubility of cyclic ethers is explained by their greatly reduced steric hindrance to such hydrogen bonding.

An experimental determination of the solubility of 1,4-endoxocyclohexane (10.5 parts per hundred parts water) at 25° showed it to be more soluble than its open-chain analog, diisopropyl ether (0.2 parts per hundred parts water), by a factor of approximately 50.

If this increased solubility may be attributed to increased effectiveness of hydrogen bonding of the ether with water, an individual molecule of the bicyclic ether, in aqueous solution, would be much more likely to be involved in a hydrogen bonded association than an acylic ether. In the rate studies of this work one might expect such hydrogen bonding to deactivate the molecule toward an ionization which would place a positive charge on the bicyclic nucleus.

The most straightforward interpretation of the present results, therefore, would postulate the principal effect of the oxygen bridge on solvolysis rates to be a simple inductive effect. Any resonance effects of this oxygen would seem to be relatively unimportant in the transition states of such reactions.

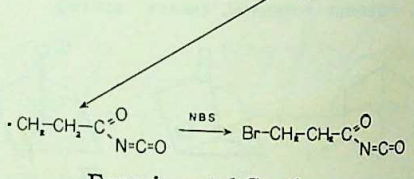
As a side-product in the photochemical bromination of 1,4-endoxocyclohexane with N-bromosuccinimide (NBS), an appreciable yield (*ca.* 15%) of β-bromopropionyl isocyanate was isolated. The material, isolated by distillation at reduced pressure (b.p. 53–56° (2 mm.)), showed an infrared absorption peak at 4.45 μ, an absorption characteristic of organic isocyanates. It reacted vigorously with water to evolve one mole of carbon dioxide and yield crystalline β-bromopropionamide. The identity of the material was further established by comparison of its infrared spectrum and reactivity toward water with that of a sample of β-bromopropionyl isocyanate prepared by the reaction of β-bromopropionyl chloride and silver cyanate.

$$AgCNO + RCOCl \longrightarrow RC(=O)-N=C=O + AgCl$$

The formation of isocyanate was also observed in the absence of 1,4-endoxocyclohexane when a boiling suspension of NBS in carbon tetrachloride was strongly irradiated. The yield, followed by observation of the infrared absorption at 4.45 μ, was small but definite, reaching a maximum after about 24 hr., then disappearing as heating and irradiation were continued. This is compatible with the observed instability of β-bromopropionyl isocyanate.

The reaction of N-bromosuccinimide to give the isocyanate was found to proceed only under those conditions generally conceded to be favorable to radical mechanisms. For example, the reaction was observed to proceed when a boiling mixture of NBS and carbon tetrachloride was strongly irradiated or when benzoyl peroxide was added to such a boiling mixture in the dark. No isocyanate was observed when the mixture was boiled in the dark with no added source of radicals.

It would therefore seem that the reaction, formally an isomerization of NBS, either proceeds by a radical mechanism or is catalyzed by products of a radical reaction. A possible mechanism would involve initial homolytic cleavage of the N-Br bond of NBS followed by ring opening of the resulting succinimide radical.



Experimental Section

All melting points and boiling points are uncorrected.

The microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology; by Dr. H. Manser, Eidg. Techn. Hochschule, Zurich; and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Chlorination of 1,4-Endoxocyclohexane: Procedure.—The starting material, 1,4-endoxocyclohexane, was prepared after the manner of Fehnel, Goodyear and Berkowitz.[17] It was purified by distillation through a 100-cm., vacuum jacketed column packed with glass helices. The product showed b.p. 119–119.5° (766 mm.), $n^{20}D$ 1.4480; infrared spectrum (letters refer to intensity—strong, medium or weak; wave length in μ): 3.39s, 3.45m, 3.50m, 6.81m, 6.90m, 7.59m, 7.69m, 7.94s, 8.39s, 8.77w, 9.11w, 9.31m, 10.01s, 10.27m, 10.72s, 11.05m, 11.40s, 12.18s, 12.71m, 13.12w.

The chlorinations were carried out in a reaction vessel fitted with a fritted-glass gas dispersion tube. The reaction vessel was immersed in a cooling bath of Dry Ice in acetone in an unsilvered Dewar flask. This permitted the irradiation of the reaction mixture with a sunlamp at a distance of about 4 in. The chlorine was measured by condensing it into a calibrated Pyrex trap and measuring its volume at the boiling point (where its density is 1.56 g./ml.). As the chlorine evaporated it was carried from this trap in a stream of dry nitrogen (Airco Prepurified Nitrogen), through a phosphorus pentoxide drying tower and into the reaction vessel through a gas dispersion tube. Any unreacted chlorine

(15) R. J. Bruehlman and F. H. Verhoek, THIS JOURNAL, **70**, 1401 (1948).

(16) L. N. Ferguson, *ibid.*, **77**, 5260 (1955).

(17) E. A. Fehnel, S. Goodyear and J. Berkowitz, *ibid.*, **73**, 4978

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which was carried through the reaction vessel was condensed in a trap at −78°. This chlorine was distilled back into the first trap in the system and recirculated until all of it was used. A loss of chlorine through the final trap became obvious in some of the longer experiments. Each section of this apparatus was suitably protected from suck-back of liquids by interposition of a reversed trap. All of the traps were of approximately 250-ml. capacity. All of the connections in this apparatus were either of Pyrex glass or Tygon tubing. The lamp was a General Electric sunlamp.

The Monochloro Isomers.—In a typical experiment, 1,4-endoxocyclohexane (190 g., 1.94 moles) was placed in a 250-ml. reaction tube in the chlorination system described above and cooled to −22° in a Dry Ice–carbon tetrachloride-bath. To this solution 137 g. (1.94 moles) of chlorine was added slowly, in a stream of nitrogen, through the gas dispersion tube. The mixture was irradiated during this addition by a sunlamp. The chlorine was added in about 1 hr., and the small amount of chlorine from the exit trap was passed again into the reaction vessel. A moderate flow of nitrogen was maintained throughout the reaction to promote stirring and to remove hydrogen chloride formed in the reaction. After 3 hr. all the chlorine was consumed, as indicated by the loss of color. The reaction was allowed to return to room temperature as the stream of nitrogen was continued for 2 hr. more. The crude reaction mixture (260 g.) was then allowed to stand over moist sodium carbonate overnight to destroy any remaining hydrogen chloride. The mixture was then dried over magnesium sulfate and distilled through a 19-plate column at 1 mm. A large fraction distilled at less than 30° (principally the starting ether, 108.0 g.). A second fraction boiling at 30–37° weighed 15.9 g. (6.2%) and consisted principally of *endo*-2-chloro-1,4-endoxocyclohexane. A fraction, b.p. 37–40°, weighing 9.29 g. (3.7%) was a mixture of the two isomers. Another fraction, b.p. 40–43°, weighing 73.0 g. (28.4%) was principally *exo*-2-chloro-1,4-endoxocyclohexane.

The two isomers are easily differentiated and their separation followed by their distinctive C–Cl stretching frequencies in the infrared. The *endo* isomer absorbs at 14.25 μ and the *exo* isomer at 14.5 μ. Since the unsubstituted ether is transparent to radiation in the wave length region 14–16 μ and each of the two monochloro isomers has a well-defined absorption peak in a different part of this region, it was possible to estimate the proportion of these isomers formed in the reaction more accurately by infrared analysis.

The two absorption maxima were shown to obey Beer's law in carbon tetrachloride solution. The extinction coefficient for the 14.25 μ peak of the *endo* isomer was found to be larger than that for the 14.50 μ peak of the *exo* isomer by a factor of 2.1. The analysis was run on the crude product of a chlorination reaction in which the ether was used in sixfold excess to minimize the amount of polychlorination. By comparison of the two (nearly equal) peaks representing the two monochloro ethers, the *exo* isomer was found to be present in quantity 2.2 times as great as the *endo* isomer.

The two monochloro isomers were purified by redistillation. The *endo* isomer boiled at 68° (27 mm.), $n^{25}D$ 1.4780, d_{25} 1.1833; Infrared spectrum (wave length in μ): 3.39s, 3.46w, 3.54w, 6.84m, 6.93m, 7.56w, 7.62m, 7.69m, 7.91m, 8.03s, 8.33w, 8.45s, 8.71m, 9.04m, 9.33w, 9.65m, 10.05s, 10.57s, 10.93w, 11.55m, 12.06m, 12.39s, 12.75s, 13.11s, 14.25s.

Anal. Calcd. for C_6H_9OCl: C, 54.32; H, 6.84; Cl, 26.74. Found: C, 54.51; H, 6.81; Cl, 27.4 (Stepanov determination).

The *exo* isomer boiled at 48.0° (4 mm.), $n^{25}D$ 1.4847, d_{25} 1.1927; infrared spectrum (wave length in μ): 3.39s, 3.52m, 6.84m, 6.95m, 7.61w, 7.75m, 7.81m, 7.91m, 7.97m, 8.04m, 8.24m, 8.33m, 8.40s, 8.70w, 8.86m, 9.30m, 9.55s, 9.76m, 10.00s, 10.18m, 10.63s, 10.95m, 11.03m, 11.29s, 11.84m, 12.25s, 12.53m, 13.03m, 14.50m.

Anal. Calcd. for C_6H_9OCl: C, 54.32; H, 6.84; Cl, 26.74. Found: C, 54.08; H, 6.62; Cl, 27.0 (Stepanov determination).

Dichloro-1,4-endoxocyclohexane.—*exo*-2-Chloro-1,4-endoxocyclohexane (10 g., 0.075 mole) in a small reaction tube equipped with a gas dispersion tube was placed in a chlorination train similar to the one described above except that smaller traps were used in order to reduce the volume of the system. The ether was treated with one equivalent of chlorine (5.4 g., 3.4 ml.) at −22°, with irradiation. After reaction was complete (1 hr.), the reaction was warmed to 30° with nitrogen scrubbing for 2 hr. The 11.32 g. of material yielded 2.4 g. (19%) of crystalline material on cooling in a refrigerator, which, after several recrystallizations from benzene and carbon tetrachloride gave small white needles m.p. 143.2–144.0°; infrared spectrum (wave length in μ): 3.32m, 3.38m, 6.90m, 6.95m, 7.59m, 7.80w, 7.90m, 8.05m, 8.16m, 8.27m, 8.40m, 8.55w, 9.80s, 9.95s, 10.20w, 10.55m, 10.85m, 11.03s, 11.40s, 12.42m, 12.51m, 14.02w, 14.81w.

Anal. Calcd. for $C_6H_8OCl_2$: C, 43.10; H, 4.85; Cl, 42.46. Found: C, 43.07, 42.79; H, 4.65, 4.98; Cl, 43.02, 42.28.

More Highly Chlorinated Ethers.—These ethers were formed from the treatment of pure 1,4-endoxocyclohexane with chlorine as described above. Adding more equivalents of chlorine over longer periods of time, it was necessary to raise the temperature of the reaction slowly to prevent formation of solid material. The various crude reaction mixtures were separated by chromatography into crystalline components which were further purified by recrystallization.

A trichloro ether crystallized from benzene as small white needles, m.p. 154.5–154.8°; infrared spectrum (wave length in μ): 3.35w, 6.95w, 7.02m, 7.58m, 7.80w, 7.91m. 8.06m, 8.13m, 8.25m. 8.38m, 8.63m, 9.50w, 9.95s, 10.18m, 10.30w, 10.60m, 10.82m, 11.11s, 11.42s, 12.45s, 14.22m, 14.90m.

Anal. Calcd. for $C_6H_9OCl_3$: C, 35.74; H, 3.50; Cl, 52.75. Found: C, 35.54; H, 3.28; Cl, 52.02.

A tetrachloro ether gave, from pentane solution, chunky rhomboidal crystals, m.p. 77.8–78.8° (softens 77.0°); infrared spectrum (wave length in μ): 3.42w, 6.99m, 7.63w, 7.98m, 8.10m, 8.50m, 8.57m, 8.98m, 9.36m, 9.90m, 10.00m, 10.21s, 10.31m, 10.46m, 10.99m, 12.47s, 13.48m.

Anal. Calcd. for $C_6H_6OCl_4$: C, 30.55; H, 2.57; Cl, 60.12. Found: C, 30.58; H, 2.69; Cl, 60.28.

A hexachloro ether was obtained as white prisms, m.p. 106.8–107.3°, from pentane; infrared spectrum (wave length in μ): 3.30w, 7.73m, 8.08m, 8.23m, 9.67m, 9.74m, 10.25s, 10.55m, 10.69s, 10.90s, 11.62s, 11.73s, 12.76m, 12.90s, 13.43w.

Anal. Calcd. for $C_6H_4OCl_6$: C, 23.65; H, 1.32; Cl, 69.80. Found: C, 23.83; H, 1.49; Cl, 68.78.

An octachloro-1,4-endoxocyclohexane was recrystallized from ligroin to yield long stave-like crystals, m.p. 158.4–159°; infrared spectrum (wave length in μ): 3.28w, 8.25m, 9.57w, 9.90m, 10.28s, 10.66s, 10.74m, 11.06w, 11.58s, 11.96m.

Anal. Calcd. for $C_6H_2OCl_8$: C, 19.28; H, 0.54; Cl, 75.90. Found: C, 19.30; H, 0.61; Cl, 75.83.

Bromination of 1,4-Endoxocyclohexane.—N-Bromosuccinimide (greater than 99% purity) from Arapahoe Chemicals, Inc., was freshly recrystallized from water before use in these experiments. The substitution of NBS from another source (Fisher Scientific Co.) made no apparent difference in the course of the reaction. Merck Reagent carbon tetrachloride was used as solvent.

In a typical experiment 1,4-endoxocyclohexane (196.0 g., 2.0 mole) was dissolved in 500 ml. of carbon tetrachloride in a 1-l. flask fitted with a reflux condenser and a calcium chloride drying tube. NBS (178 g., 1.0 mole) was added to this solution and the suspension heated to boiling while irradiating with a sunlamp. After about 2 hr. the mixture became homogeneous. The heating and irradiation were continued for 5 hr. altogether, and the resulting deep-red solution was cooled overnight in a refrigerator at 0°. The crystals of succinimide (42.0 g., 42.5%) which were deposited during this time were removed by filtration. The solvent and excess 1,4-endoxocyclohexane were removed by distillation at water-pump pressure. The liquid residue was then fractionally distilled through a 50-cm., vacuum-jacketed column packed with glass helices. The following fractions were taken:

Fraction	B.p., °C. (2 mm.)	Weight, g.
I	53.0–56.0	21.40
II	56.0–62.0	7.63
III	62.0–68.0	7.77
IV	68.0–68.5	20.85
V	68.5–75.0	22.30

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The various fractions were examined by infrared spectroscopy. The fore-run contained carbon tetrachloride and recovered 1,4-endoxocyclohexane. No part of the fore-run showed an absorption near 4.5 μ which could be attributed to an isocyanate.

Fraction I was essentially pure β-bromopropionyl isocyanate. Fraction II contained a small amount of higher boiling material but was mostly the isocyanate. These first two fractions constitute a yield of 16.3% of β-bromopropionyl isocyanate. Redistillation gave a colorless liquid, b.p. 54.0–55.0° (2 mm.), which had a sharp, characteristic odor and was mildly lachrymatory. A small sample of this material was distilled into a tube and sealed off under high vacuum. It began to acquire a yellow color after one day at room temperature and after two weeks was an extremely viscous, semi-solid material of deep orange color.

Fraction IV was essentially pure *exo*-2-bromo-1,4-endoxocyclohexane (11.8%). The distillation was discontinued during the collection of fraction V when a rapid decomposition occurred in the pot leaving a black tar and evolving much hydrogen bromide.

Reaction of the Isocyanate with Water.—To β-bromopropionyl isocyanate (0.50 g., 0.0028 mole) from the reaction described above, tetrahydrofuran containing 10% water was added dropwise until no further gas evolution was observed on adding another drop of the water solution. The evolved gas was carried in a stream of nitrogen through a trap containing aqueous barium hydroxide. The precipitated barium carbonate was filtered, washed with 100 ml. of water and dried at 100° (0.56 g., 1.13 moles per mole of isocyanate). The tetrahydrofuran and excess water were removed from the reaction mixture by distillation at reduced pressure leaving 0.40 g. of a white crystalline material, m.p. 109.5–111.7°. After two recrystallizations from benzene, the material melted 115.6–116.3°. This was mixed with authentic β-bromopropionamide (m.p. 115.3–116.3°) prepared from β-bromopropionyl chloride and ammonia[18] to give a mixed m.p. 115.3–116.3°.

β-Bromopropionyl Isocyanate from Silver Cyanate.—The method used is a rather general one for the preparation of acyl isocyanates.[19] In a 300-ml. round-bottomed flask fitted with a reflux condenser, addition funnel and calcium chloride drying tube, silver cyanate (Eastman Kodak Co., white label grade, 45.0 g., 0.30 mole) was suspended with magnetic stirring in 100 ml. of dry ether. To this suspension was added, over a 2-hr. period, 34.4 g. (0.20 mole) of β-bromopropionyl chloride in 50 ml. of dry ether. The suspension was then heated to boiling with continued stirring for 6 hr. The silver salts were then filtered from the solution, washed with ether and the washings combined with the reaction mixture. Solvent was removed at reduced pressure and the remaining liquid distilled through a 30-cm. Vigreux column at *ca.* 2 mm. The fraction boiling in the range 52–56° (4.4 g., 12%) exhibited an infrared spectrum identical with that of a sample of the isocyanate from the NBS reaction described above. Infrared spectrum (wave length in μ): 3.43w, 4.45s, 5.77s, 7.19m, 7.50w, 7.95w, 8.25w, 8.50m, 8.72m, 9.87m, 9.77m, 9.95m, 15.20m.

Anal. Calcd. for $C_4H_4O_2NBr$: C, 26.00; H, 2.27. Found: C, 26.35; H, 2.70.

This material also reacted vigorously with water to produce β-bromopropionamide.

N-Bromosuccinimide in Carbon Tetrachloride.—Observation of the very intense absorption of β-bromopropionyl isocyanate at 4.45 μ was used to follow its formation from NBS under a variety of conditions. In these experiments NBS (5.0 g.) was suspended in 50 ml. of carbon tetrachloride in a flask fitted with a reflux condenser and protected from atmospheric moisture by a calcium chloride drying tube. During the reaction 1-ml. aliquots were withdrawn at intervals of 6–8 hr. and examined for absorption at 4.45 μ. In parallel experiments, all conducted at the boiling point of carbon tetrachloride, the mixture was in one case irradiated with a sunlamp, shielded from all light in another case and, in a third case, protected from light after adding 0.10 g. of benzoyl peroxide. After 24 hr. spectra of the crude reaction mixtures taken in sodium chloride cells 0.016 in. in thickness against reference cells containing pure carbon tetrachloride showed 63% absorption at 4.45 μ for the irradiated reaction and 85% for the reaction with added benzoyl peroxide. The mixture which was heated in the dark with no added catalyst showed no absorption in this region even after 36 hr. Further heating of the two reaction mixtures which showed absorption at 4.45 μ brought about diminution and eventual loss of this absorption.

exo-2-Bromo-1,4-endoxocyclohexane.—Material from fraction IV of the distillation of the NBS bromination reaction was redistilled (b.p. 68.0–68.2° (2 mm.), $n^{25}D$ 1.5176, d_{25} 1.5410).

Anal. Calcd. for C_6H_9Br: C, 40.7; H, 5.12. Found: C, 40.88; H, 4.89.

This bromo ether (4.4866 g., 0.02534 mole) was dissolved in 20 ml. of 95% ethanol containing 4.748 g. (0.0279 mole) of silver nitrate. The mixture was then allowed to stand in a dark place at room temperature for 24 hr. The precipitated silver bromide was filtered, washed, dried at 95° and weighed (4.7477 g., 0.02528 mole). This corresponds to 45.03% Br in the sample; calcd. for C_6H_9Br, 45.14% Br.

Method of Determining Dielectric Constants.—The heterodyne beat frequency method[20] was used to determine the dielectric constants, at 25.0°, of dilute solutions of the materials being studied, in carbon tetrachloride or benzene. The apparatus used in these determinations is fully described by Osthoff.[21] It consists, in essence, of a fixed frequency crystal oscillator, at 100 kc., coupled with a vacuum-tube oscillator circuit containing the measurement cell and a calibrated precision variable condenser. The frequency of the latter circuit can be very accurately adjusted, by means of the precision condenser, until the beat frequency between the two circuits is zero.

Measurements of Densities.—Densities were measured to an accuracy estimated at one part in 20,000 by means of a single stem pycnometer of 20-ml. volume.

Treatment of Data.—The calculations of the molar polarization at infinite dilution were made by the method of Hedestrand[22] using the convenient notation of Bender, Flowers and Goering.[23] The dipole moments were then calculated from the Debye equation.[20]

Solvolysis of the 2-Halo-1,4-endoxocyclohexanes: Solvents.—Dioxane was purified by the procedure of Hess and Frahm.[24] After this treatment it was distilled through a 100-cm. column packed with glass helices (b.p. 100.6–100.8°). It was then stored under nitrogen in a dark place and used in not more than two weeks.

Absolute ethanol (2 l.) was added to 20 g. of sodium metal and the resulting solution boiled for two days to destroy aldehydes. The ethanol was then distilled and stored under nitrogen until used.

Distilled water from the laboratory source was redistilled from potassium permanganate and stored under nitrogen.

The solvent mixtures used in this work were made up by weighing the required amounts of the pure solvents. The solvent mixture which was made up to volume percentage specifications was weighed out in proportions calculated from the densities of the pure solvents at 25°.

Procedure for the *exo* Isomers.—The kinetic runs were followed by titrating samples individually sealed in glass tubes. These tubes were made by sealing one end of a 12 in. length of 12 mm. Pyrex tubing. Just before use they were carefully flushed with nitrogen and tightly stoppered with a plug of glass wool.

The solutions for kinetic analysis were made up by weighing the halo ether and the added salt into a 250-ml. volumetric flask and making the solution up to volume with the solvent being studied.

A hypodermic needle was used to introduce 16-ml. portions of the solution through the glass wool plugs into the freshly prepared glass tubes. The tubes were then quickly sealed off about 1.5–2 in. above the surface of the liquid, placed in a woven-wire basket and lowered into the constant temperature bath, maintained constant to within ±0.01°.

(18) C. Hamilton and C. Simpson, THIS JOURNAL, **51**, 3159 (1929).

(19) A. J. Hill and W. M. Degnan, U. S. Patent 2,378,486 (1945); cf. C. Paal and H. Pollak, *Ber.*, **71B**, 2627 (1938).

(20) See C. P. Smyth in A. Weissberger, "Physical Methods of Organic Chemistry," Vol. I, 2nd Ed., Part II, Interscience Publishers, Inc., New York, N. Y., 1949, pp. 1611, *et seq.*

(21) R. C. Osthoff, Ph.D. Thesis, Harvard University, 1951. We thank Professor E. G. Rochow for the loan of this apparatus.

(22) G. Hedestrand, *Z. physik. Chem.*, **B2**, 428 (1929).

(23) P. Bender, D. Flowers and H. Goering, THIS JOURNAL, **77**, 3463 (1955).

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At the desired intervals of time samples were withdrawn from the bath, quickly cooled in ice-water and then allowed to come to room temperature. Samples of 15 ml. were then accurately measured out, diluted with 45 ml. of distilled water and titrated with 0.1013 *N* aqueous sodium hydroxide. All titrations were performed using a Beckman Autotitrator with a 5-ml. microburet.

Procedure for Solvolysis of the *endo* Isomer.—The same procedure was used with *endo*-2-chloro-1,4-endoxocyclohexane as with the *exo* isomer with the exception that an amount of sodium acetate approximately equivalent to the halo ether was weighed into the sample. The reaction was then followed by titrating the excess sodium acetate in the aliquots to an end-point at *p*H 3.6 with 0.121 *N* hydrochloric acid.

Treatment of Data.—The first-order rate constants were obtained by a least squares treatment of the data as outlined by Youden.[25] The uncertainties are expressed as standard deviations. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated from the absolute rate equation with the uncertainties again expressed as standard deviations.

Product Studies.—*exo*-2-Bromo-1,4-endoxocyclohexane (17.7 g., 0.10 mole) was dissolved in 250 ml. of 50% dioxane–water in a 300-ml. flask equipped with openings for an amber-glass electrode, a calomel electrode, a reflux condenser and the addition tip from the Beckman Autotitrator. The mixture was magnetically stirred with a Teflon-covered bar. It was brought to the boiling point by an electric heating mantle and maintained at *p*H 6.5–7.5 by the Autotitrator for 2000 min. This required 14.55 ml. of 4.89 *N* sodium hydroxide solution (71% reaction).

The solvent was removed by distillation at water-pump pressure leaving a paste of organic matter and sodium bromide. To this was added 50 ml. of dioxane to dissolve the organic matter, and the inorganic bromide was removed by filtration. The filtrate was then made up to 200 ml. with 50% dioxane–water. Aliquots of 20 ml. were taken for analytical tests.

Using this procedure outlined by Wilds,[26] aldehyde was estimated by titration of the hydrochloric acid released by oximation with hydroxylamine hydrochloride. Two aliquots gave values for aldehyde equivalent to 81.1% and 80.2% of the solvolyzed material.

Other aliquots were used to prepare the 2,4-dinitrophenylhydrazone and the *bis*-dimedone condensation product by the directions of Shriner and Fuson.[27]

The solution in which the 2,4-dinitrophenylhydrazone was formed was diluted with 200 ml. of water to make the precipitation complete and then filtered through a sintered-glass crucible. The derivative was washed with 20 ml. of 0.1 *N* hydrochloric acid, then 200 ml. of water, dried at 100° and weighed. After repeated recrystallization from benzene–pentane mixtures, this derivative gave m.p. 118.6–119.8°. The same derivative was isolated from the sealed tube solvolysis of the *endo*- and *exo*-chlorides; infrared spectrum (wave length in μ): 3.41s, 3.52m, 6.85m, 6.92m, 6.98m, 7.60w, 7.68w, 7.79m, 7.94m, 8.17m, 8.40s, 8.75m, 8.89m, 9.60m, 9.80m, 9.98s, 10.21m, 10.41w, 10.68s, 11.00w, 11.10w, 11.35s, 11.90m, 15.15w, 15.39w.

Anal. Calcd. for $C_{12}H_{14}O_6N_4$: C, 48.98; H, 4.80; N, 19.04. Found: C, 49.15; H, 4.59; N, 18.74.

The dimedone derivative was recrystallized from benzene–pentane mixtures to a constant melting point of 163.3–164.2°; infrared spectrum (wave length in μ): 2.79m, 2.95m, 3.42s, 3.70m, 5.80s, 6.97m, 7.25m, 7.50m, 8.10m, 8.55m, 9.30m, 9.89s, 10.53m.

Anal. Calcd. for $C_{22}H_{32}O_6$: C, 70.18; H, 8.56. Found: C, 70.47; H, 8.61.

Runs protected from oxygen by the use of the sealed tube technique showed substantially higher yields of aldehyde. In these experiments two tubes from a kinetic run were opened simultaneously. One 15-ml. aliquot was titrated directly. The other was mixed with 15 ml. of 0.5 *N* hydroxylamine hydrochloride solution, allowed to stand overnight, then titrated to the same *p*H as shown by a parallel blank run. The difference in the two titers represents aldehyde present.

In run 1, in 80% (by vol.) ethanol at 85.0°, such duplicate points were taken at 5212, 12470 and 16820 min. The percentage of aldehyde in the solvolysis product at each of these points was determined by the above outlined method. These percentages were found to be 100.8, 98.2 and 103.2%, respectively, at these three times.

In a special run at 120.0°, the *exo*-chloride, in 50% dioxane, was shown to yield 97.3 and 99.6% aldehyde at 653 and 1213 min.

The solvolysis product of the *endo*-chloride was analyzed at 160°, using points of run 12, in 50% dioxane with added sodium acetate. In these analyses the customary 15-ml. aliquot was diluted with 30 ml. of water and titrated with standard acid to *p*H 3.4 to learn the extent of solvolysis. The 15 ml. of 0.5 *N* hydroxylamine hydrochloride was added and the solution allowed to stand at room temperature overnight. It was then titrated back to *p*H 3.4 with standard base. At 2245 min. this method indicated 91.7% of the solvolysis product to be aldehyde and at 5110 min., 85.4%. (In these runs at the higher temperature a considerable darkening of the solution was observed in samples withdrawn after about 3000 min.)

Identification of 3-Formylcyclopentanol.—A sample (1.5 g.) of the crude product from a solvolysis of *exo*-2-bromo-1,4-endoxocyclohexane in boiling 50% dioxane was dissolved in 10 ml. of hydrazine (Eastman Kodak Co., 95%) and heated on a steam-bath for 24 hr. The solution was then concentrated to 4–5 ml. by distilling excess hydrazine at reduced pressure. This solution was added to an ethanolic solution of sodium ethoxide prepared by dissolving 1.0 g. of sodium in 10 ml. of absolute ethanol. The solution was sealed in a Carius tube and heated at 190–200° for 36 hr. The resulting solution was acidified with concd. hydrochloric acid and distilled. After removal of the ethanol two colorless liquid phases co-distilled at 55° (60 mm.). The non-aqueous phase was taken up in ether and dried over magnesium sulfate. Removal of the solvent left a colorless oil (0.3 g.), $n^{28}D$ 1.4446; *trans*-3-methylcyclopentanol,[7] $n^{28}D$ 1.4450. To this was added 0.24 g. of phenyl isocyanate, the mixture heated on a steam-bath for 10 min. and then diluted with 30 ml. of pentane. On chilling the material the phenylurethan (0.26 g.) was deposited from the solution as white needles (after recrystallization from pentane, m.p. 81.4–82.0°; phenylurethan derivative of *trans*-3-methylcyclopentanol,[7] m.p. 82°).

Solvolysis with Added Azide.—*exo*-2-Bromo-1,4-endoxocyclohexane (15.0 g., 0.0847 mole) was dissolved in a solution of 250 ml. of 50% dioxane containing 20 g. of sodium azide (0.308 mole, 1.23 molar). The solution was treated as in the previously described product studies, being boiled for 1600 min. at *p*H 6.0–7.0. Removal of the solvent and inorganic bromide left 8.45 g. of a viscous oil which showed an infrared spectrum nearly identical with that of 3-formylcyclopentanol with an added absorption peak of medium intensity at 4.74 μ. Chromatography on alumina of 1.60 g. of the crude product gave 29 mg. of an oil (eluted with 100% ether) which showed a very intense absorption at 4.74 μ. This was dissolved in 5 ml. of methanol and 10 mg. of platinum oxide added. The suspension was stirred under one atm. of hydrogen for 12 hr. The supernatant liquid was then saturated with hydrogen chloride and the crystalline amine hydrochloride (18 mg.) collected and dried, m.p. *ca.* 240°.

Acknowledgment.—The expenses of this research were met in part by a grant from the Mallinckrodt Chemical Works.

CAMBRIDGE, MASSACHUSETTS

(25) W. J. Youden, "Statistical Methods for Chemists," John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 40–44.

(26) R. Wilds, "Estimation of Organic Compounds," University Press, Cambridge, 1953, pp. 144–150.

(27) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," by John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 171–172.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PENNSYLVANIA STATE UNIVERSITY]

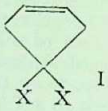
The Reactions of Bivalent Carbon Species. Addition of Dihalocarbenes to 1,3-Butadiene

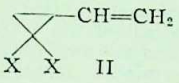
BY ROBERT C. WOODWORTH AND PHILIP S. SKELL

RECEIVED NOVEMBER 21, 1956

The reactions of dibromo- and dichlorocarbenes $:CBr_2$ and $:CCl_2$ to 1,3-butadiene are three center types of addition reactions producing 1,1-dihalo-2-vinylcyclopropanes. The structures of these products were demonstrated by conversion to the 2,2-dihalocyclopropanecarboxylic acids. The similarity of this addition reaction to heterolytic halogenation of 1,3-butadiene is discussed.

The reaction of 1,3-butadiene with dihalocarbenes $:CCl_2$ and $:CBr_2$ would be expected to produce 4,4-dihalocyclopentenes (I) by 1,4-addition or 1,1-dihalo-2-vinylcyclopropanes (II) by 1,2-addition.


I

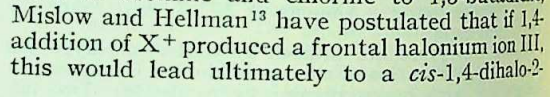

II

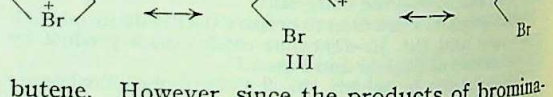
Dichloro- or dibromocarbene was generated in the presence of 1,3-butadiene by the action of base on chloroform or bromoform, respectively.[1,2] The major product from the reaction of 1,3-butadiene, bromoform and potassium *t*-butoxide is a heavy, sweet smelling, colorless liquid obtained in 70% yield. It rapidly discolors in air. The major product from the reaction of 1,3-butadiene, chloroform and potassium *t*-butoxide is a volatile, sweet smelling colorless liquid obtained in 50% yield. Since neither I nor II have been described previously, it was desirable that the homogeneity of the reaction products be established. Infrared spectra of fractions distilled from the reaction mixtures indicated that the dibromo product was contaminated only with unreacted bromoform. The dichloro product, however, contained an unknown contaminant boiling a few degrees lower than the main product. Careful fractional distillation of the contaminated material separated a small amount of the pure contaminant which proved to be 1,1-dichloro-2,2-dimethylcyclopropane, on comparison with the boiling point, refractive index and infrared spectrum reported for this compound.[2] This substance is formed in low yield in the reaction of chloroform with potassium *t*-butoxide in the presence of *t*-butyl alcohol,[2] probably by the addition of dichlorocarbene to isobutylene obtained by the dehydrating action of the dihalocarbenes on alcohols.[3] The bands observed in the infrared spectra of the successive fractions from the chloroform–1,3-butadiene reaction mixture can be explained by the major product and a single contaminant, 1,1-dichloro-2,2-dimethylcyclopropane.

Cleavage of the unsaturated bond with ozone was employed to prove the structures of the addition products. Ozonolysis of I should yield a dicarboxylic acid, and ozonolysis of II should yield a monocarboxylic acid. Ozonolysis of the dibromo- and dichloro-products yielded monocarboxylic acids with the correct analyses and neutral equivalents, respectively, for 2,2-dibromocyclopropanecarboxylic acid and 2,2-dichlorocyclopropanecarboxylic acid. The conclusion from these results is that both dibromo- and dichlorocarbene exhibit 1,2-addition to 1,3-butadiene and the products produced in this reaction have structure II.

Other instances of 1,2-additions to conjugated diolefins have been reported for the reactions of these olefins with diazoacetic esters in the presence of a copper catalyst to produce vinylcyclopropanecarboxylic esters.[4–8] Evidence which strongly suggests the intermediacy of a carbene in copper-catalyzed decompositions of diazo compounds has been presented.[9–12]

In the consideration of the heterolytic 1,4-additions of bromine and chlorine to 1,3-butadiene, Mislow and Hellman[13] have postulated that if 1,4-addition of X^+ produced a frontal halonium ion III, this would lead ultimately to a *cis*-1,4-dihalo-2-butene. However, since the products of bromination and chlorination of 1,3-butadiene were the *trans*-1,4-dihalo-2-butenes, these authors concluded that the intermediate halonium ion probably has structure IV.


III


IV

The affinity of the dihalocarbenes for olefins with electron-releasing substituents[14] and the stereochemical evidence for a singlet state (no unpaired electrons) for carbenes[12] led to the postulate

(1) J. Hine, THIS JOURNAL, **72**, 2438 (1950); J. Hine and A. M. Dowell, *ibid.*, **76**, 2688 (1954); J. Hine, A. M. Dowell and J. E. Singley, *ibid.*, **78**, 479 (1956).

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(5) H. Staudinger, O. Muntwyler, L. Ruzicka and S. Seibt, *Helv. Chim. Acta*, **7**, 390 (1924).

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(7) (a) I. G. M. Campbell and S. H. Harper, *J. Chem. Soc.*, 283 (1945); (b) S. H. Harper and H. W. B. Reed, *ibid.*, 779 (1955).

(8) M. Matsui, Japanese Patent, 1769 (1952); *C. A.*, **48**, 2093 (1954).

(9) I. A. D'yakonov, *Zhur. Obshchei Khim.*, **19**, 1734 (1949).

(10) P. Yates, THIS JOURNAL, **74**, 5376 (1952).

(11) M. S. Kharasch, T. Rudy, W. Nudenberg and G. Büchi, *J. Org. Chem.*, **18**, 1030 (1953).

(12) P. S. Skell and R. C. Woodworth, THIS JOURNAL, **78**, 4496 (1956).

(13) K. Mislow and H. M. Hellman, *ibid.*, **73**, 244 (1951); K. Mislow, *ibid.*, **75**, 2512 (1953); H. M. Hellman, J. W. Hellman and K. Mislow, *ibid.*, **76**, 3574 (1954).

(14) P. S. Skell and A. Y. Garner, *ibid.*, **78**, 5430 (1956).

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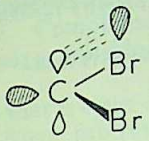
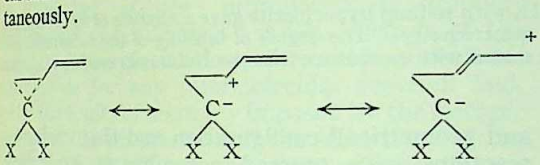
that carbenes may be considered as sp^2-hybridized species, which by virtue of their vacant *p*-orbital exhibit electrophilic behavior predominantly.



IV

From this point of view one might have anticipated that the 2-electron deficient species $:CX_2$ and Br^+ would show similar behavior toward 1,3-butadiene. The intermediate complex in the reactions of dihalocarbenes with 1,3-butadiene may be described by V, in which bonding to both carbons of the double bond is developed simultaneously.



V

The electron-seeking character of the carbenes leads to the suggestion that electron-withdrawing (halogen) substituents on the 1,3-butadiene system will result in cyclopropane formation at the unsubstituted double bond, while electron-donating (alkyl) substituents will direct this addition to the substituted double bond. In partial confirmation of this prediction can be cited the failure to obtain an adduct when dichlorocarbene is generated in the presence of hexachloro-1,3-butadiene. Also it has been reported that carbethoxycarbene adds to the terminal double bond of 1-phenyl-1,3-butadiene[4] and the γ,δ-olefinic linkage of sorbate and α-methylsorbate esters.[7] In contradiction of an earlier report[5] the major product obtained from the reaction of carbethoxycarbene with isoprene is the ethyl ester of 2-methyl-2-vinylcyclopropanecarboxylic acid.[15]

Experimental

Procedure.—Solvent-free potassium *t*-butoxide was prepared by dissolving potassium metal in anhydrous *t*-butyl alcohol (dried by distillation from potassium *t*-butoxide). The excess alcohol was removed by distillation and then by pumping to an ultimate pressure of 2 mm. at a temperature of 95°. The dry cake was pulverized mechanically and the flask fitted with a stirrer, thermocouple and dropping funnel. The flask was cooled in a freezing carbon tetrachloride–Dry Ice-bath. The haloform was added to a slurry of the potassium *t*-butoxide in liquid 1,3-butadiene at such a rate that the reaction temperature never exceeded −10°. The haloform was added at a rate of approximately 0.5 mole per hour to avoid excessive temperature rise as a result of the rapid exothermic reaction. The reactants were stirred for an additional hour after the haloform addition was complete and then diluted with pentane and water. The organic layer was separated, washed with cold water, dried over anhydrous sodium sulfate, the solvent removed by distillation and the residue distilled to obtain the reaction products.

Ozonolyses were carried out in pentane solution, the viscous ozonide separating from the solution as it formed. The ozonides were decomposed in the presence of hydrogen peroxide and sulfuric acid and then refluxed to ensure complete oxidation of the aldehydes.

Reaction of 1,3-Butadiene with Chloroform and Potassium *t*-Butoxide.—The quantities of reactants were 239 g. (4.4 moles) of 1,3-butadiene, 170 g. (1.42 moles) of chloroform and 1.6 moles of potassium *t*-butoxide (from 62 g. of potassium metal). The products were distilled at atmospheric pressure to obtain 103 g. of material boiling at 115–123°, $n^{25}D$ 1.4662–1.4720. These fractions were combined and redistilled through a 50–100 plate column (24 in. × 8 mm. Podbielniak Mini-cal column packed with Hastelloy Heli-grid). The major portion of the product was separated as a fraction boiling constant at 122.5° (730 mm.), $n^{25}D$ 1.4720–1.4722. This product was identified as 1,1-dichloro-2-vinylcyclopropane. The foreruns were recombined and distilled through the same column to separate approximately 3 g. of 1,1-dichloro-2,2-dimethylcyclopropane, a middle fraction boiling at 115.8–116.7° (729 mm.), $n^{25}D$ 1.4450. These physical properties compare favorably with those reported by Doering and Hoffmann[2] (b. 118–120°, $n^{20}D$ 1.4461). The infrared spectrum of this substance appeared to be identical with that reported.[2] All of the fractions obtained between the 1,1-dichloro-2,2-dimethylcyclopropane and the 1,1-dichloro-2-vinylcyclopropane were examined by obtaining their infrared spectra on the neat liquid. All of the bands in the spectra were attributable to these two products, no other bands being evident. The total weight of 1,1-dichloro-2-vinylcyclopropane obtained was 98.5 g. (51%).

Anal. Calcd. for $C_5H_6Cl_2$: C, 43.83; H, 4.42. Found: C, 44.28; H, 4.41.

Ozonolysis of 1,1-Dichloro-2-vinylcyclopropane to 2,2-Dichlorocyclopropanecarboxylic Acid.—From the ozonolysis of 10.0 g. of 1,1-dichloro-2-vinylcyclopropane, there was obtained 8.0 g. of a crude viscous liquid monobasic acid (neutral equivalent 196 and pK_a 3.47) which crystallized from heptane. Recrystallization from hexane raised the melting point to 75–76°. Titrations of the pure acid indicated a monobasic acid, pK_a 3.50, 3.51 (23°, 0.01, 0.005 *M*).

Anal. Calcd. for $C_4H_4Cl_2O_2$: C, 30.86; H, 2.59; neut. equiv., 155. Found: C, 31.16; H, 2.55; neut. equiv., 151, 159, 155.

The *p*-bromophenacyl ester of this acid (recrystallized from ethanol) melted at 122–123°.

Anal. Calcd. for $C_{12}H_9BrCl_2O_3$: C, 40.92; H, 2.58. Found: C, 41.11; H, 2.63.

Reaction of 1,3-Butadiene with Bromoform and Potassium *t*-Butoxide.—The reactants were 152 g. (2.81 moles) of 1,3-butadiene, 125 g. (0.495 mole) of bromoform and 0.51 mole of potassium *t*-butoxide (from 20 g. of potassium metal). The products from this reaction were distilled in vacuum through a Vigreux column to separate a forerun of bromoform (identified through its infrared spectrum) and a fraction boiling 69.5–70.0° (26 mm.), $n^{25}D$ 1.4520, which was identified as 1,1-dibromo-2-vinylcyclopropane. A total of 67 g. of product was obtained (64% of theory, taking into account the recovered bromoform). This product darkens rapidly on contact with air.

Anal. Calcd. for $C_5H_6Br_2$: C, 26.58; H, 2.68. Found: C, 26.61; H, 2.52.

Ozonolysis of 1,1-Dibromo-2-vinylcyclopropane to 2,2-Dibromocyclopropanecarboxylic Acid.—From the ozonolysis of 19.4 g. of 1,1-dibromo-2-vinylcyclopropane, 10.0 g. of crude acid was obtained. Recrystallization of this acid from hexane gave a product whose melting point was 94–95°. Titration curves indicated this acid was a monobasic acid, pK_a 3.48, 3.57 (24°, 0.01, 0.005 *M*).

Anal. Calcd. for $C_4H_4Br_2O_2$: neut. equiv., 244. Found: neut. equiv., 242, 240.

The Reaction of Hexachloro-1,3-butadiene with Chloroform and Potassium *t*-Butoxide.—To a suspension of 0.43 mole of potassium *t*-butoxide in 133 g. of hexachloro-1,3-butadiene and 250 ml. of *n*-pentane, 40 g. of chloroform was added. Unreacted hexachloro-1,3-butadiene was recovered. The same result was obtained when potassium *t*-butoxide was added to a chloroform–hexachlorobutadiene mixture.

Infrared Spectra.—The following infrared spectra were obtained for the neat liquids in a 0.0235-mm. cell using NaCl optics, recording wave length in microns. 1,1-Dichloro-2-vinylcyclopropane: 3.27(m) 3.37(mw) 4.80(vw) 4.92(vw) 5.45(w) 5.56(w) 5.78(mw) 6.11(ms) 6.31(vw) 6.99(m) 7.03(ms) 7.57(mw) 7.73(mw) 8.20(s) 8.36(m) 8.97(vs)

(15) I. A. Dyakonov and V. F. Myznikova, *C. A.*, **47**, 4295e (1953).

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9.32(m) 9.55(ms) 9.82(s) 10.15(s) 10.90(vs) 11.38(m) 13.00–13.10(vs) 14.86(s) 15.02(ms).

1,1-Dibromo-2-vinylcyclopropane: 3.27(m) 3.37(mw) 3.43(m) 3.52(mw) 4.80(vw) 4.93(vw) 5.45(w) 5.81(vw) 6.13(m) 6.99(m) 7.05(m) 7.58(w) 7.73(mw) 8.24(m) 8.41(m) 9.03(vs) 9.55(ms) 9.89(s) 10.16(vs) 10.85–10.90(vs) 11.56(mw) 12.73(w) 13.93(vs).

1,1-Dichloro-2,2-dimethylcyclopropane: 3.37(ms) 3.40(s) 3.45(s) 3.50(m) 3.68(w) 6.30(w) 6.85(s) 6.92(ms) 6.97(s) 7.21(m) 7.27(ms) 7.52(vw) 7.62(w) 7.80(w) 7.94(mw) 8.22(w) 8.94(s) 9.06(s) 9.40(vs) 9.62(s) 9.96(ms) 10.34(m) 11.00(w) 11.20(w) 11.64(ms) 12.25(w) 12.70(m) 13.19(vs) 14.12(vw) 14.95(vw).

UNIVERSITY PARK, PENNSYLVANIA

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Confirmation of the Intramolecular Nature of the Hofmann "Haloamide" Reaction by Double Labeling

BY THOMAS J. PROSSER AND ERNEST L. ELIEL

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Treatment of a mixture of *m*-$DC_6H_4CONH_2$ and $C_6H_5CON^{15}H_2$ with sodium hypochlorite gave a mixture of *m*-$DC_6H_4NH_2$ and $C_6H_5N^{15}H_2$ free of *m*-$DC_6H_4N^{15}H_2$ as established by mass spectrometry. The degree of labeling of the substrates and the sensitivity of the analytical method are such that it can be stated with confidence that the Hofmann reaction is at least 96% intramolecular.

The reaction of an amide with hypohalite to give an amine or derivative thereof, *e.g.*, $RCONH_2 + NaOBr \rightarrow RNH_2 + CO_2 + NaBr$, is known as the Hofmann haloamide reaction.[1,2] This reaction, as well as several other related ones,[3] has long been considered to be intramolecular. Evidence for this is entirely stereochemical and comes from the fact that amides in which the R-group is asymmetric at the point of attachment—such as $C_6H_5CH(CH_3)CONH_2$—yield amines in which configuration is retained and optical activity almost completely preserved,[4] even where activity is due to restricted rotation in a biphenyl system,[5] and that geometric configuration of the R-group is also preserved[6] in the rearrangement of R from carbon to nitrogen which must occur in the Hofmann haloamide reaction. Moreover, the reaction proceeds normally at bridgehead carbon atoms.[7]

While the stereochemical evidence for retention of configuration is thus overwhelming, it is not so convincing that this constitutes proof for the intramolecular nature of the rearrangement, especially in view of the fact that certain intermolecular reactions involving carbanion intermediates have recently been shown to involve retention of optical[8] and geometrical[9] configuration and that carbanion reactions may proceed normally at bridgehead carbon atoms.[10] An independent proof of the intramolecular nature of the Hofmann haloamide reaction thus seemed desirable.

The most convincing evidence for the intramolecular nature of any reaction comes from study of the products obtained in the reaction when carried out on a mixture of two substrates A–B and A′–B′. If only products corresponding to A–B and A′–B′ are obtained in a reaction involving rupture of the A–B bond, then the reaction is intramolecular; but if products corresponding to A–B′ and A′–B are also obtained, then the reaction is at least in part intermolecular. In fact this criterion may well be considered an operational definition of the terms "intramolecular" and "intermolecular." In the case of the Hofmann haloamide reaction, an appropriate experiment would be to rearrange a mixture of $RCONH_2$ and $R'CON^{15}H_2$, cleanly separate the two chemically distinct products RNH_2 and $R'NH_2$ (labeled or unlabeled), and demonstrate by conventional degradation to nitrogen gas and isotope ratio measurements of the latter[11] that RNH_2 contains no excess of the N^{15} isotope. There are, however, two difficulties with such a procedure. One is the need for rigorous purification of RNH_2, to eliminate the possibility of contamination with $R'N^{15}H_2$. This difficulty can be obviated by carrying out the N^{15} analysis by direct mass spectrometry[12] of RNH_2 at reduced ionizing voltage[13]—provided RNH_2 and $R'NH_2$ are not isomeric. The second difficulty is concerned with the need of choosing $RCONH_2$ and $R'CONH_2$ so

(1) A. W. Hofmann, *Ber.*, **14**, 2725 (1881). We prefer to include the word "haloamide" since at least two other reactions—the alkylation of amines and the degradation of quaternary ammonium salts—are commonly associated with Hofmann's name.

(2) For a review see E. S. Wallis and J. F. Lane in R. Adams, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1946, pp. 267–306.

(3) *Cf.* D. J. Cram in M. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 251–253.

(4) E. S. Wallis and S. C. Nagel, THIS JOURNAL, **53**, 2787 (1931); C. L. Arcus and J. Kenyon, *J. Chem. Soc.*, 916 (1939).

(5) F. Bell, *ibid.*, 835 (1934); E. S. Wallis and W. W. Moyer, THIS JOURNAL, **55**, 2598 (1933).

(6) W. A. Noyes, *et al.*, *Am. Chem. J.*, **16**, 503 (1894); **24**, 290 (1900); **27**, 425 (1902); THIS JOURNAL, **32**, 1669 (1910); **36**, 118 (1914); **39**, 2692 (1917); J. Weir, *J. Chem. Soc.*, **99**, 1270 (1911).

(7) P. D. Bartlett and L. H. Knox, THIS JOURNAL, **61**, 3184 (1939).

(8) R. L. Letsinger, *ibid.*, **72**, 4842 (1950); D. J. Cram, J. Allinger and L. Langemann, *Chemistry & Industry*, 919 (1955). The cases cited by A. N. Nesmeyanov, O. A. Reutov and S. S. Poddubnaya, *Doklady Akad. Nauk S.S.S.R.*, **88**, 479 (1953), *C. A.*, **48**, 2632b (1954), and S. Winstein, T. G. Traylor and C. S. Garner, THIS JOURNAL, **77**, 3741 (1955), may or may not be pertinent here.

(9) *Cf.* E. Eliel in M. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 154–155.

(10) W. v. E. Doering and L. K. Levy, THIS JOURNAL, **77**, 509 (1955).

(11) D. W. Wilson, A. O. C. Nier and S. P. Reimann, "Preparation and Measurement of Isotopic Tracers," J. W. Edwards, Ann Arbor, Mich., 1946, pp. 20–22, 31–39.

(12) *Cf.* H. W. Washburn in W. G. Berl's "Physical Methods of Chemical Analysis," Vol. I, Academic Press, Inc., New York, N. Y., 1950, pp. 618–620; E. L. Eliel, T. J. Prosser and G. W. Young, *J. Chem. Ed.*, **34**, 72 (1957).

(13) D. P. Stevenson and C. D. Wagner, THIS JOURNAL, **72**, 5612 (1950).

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that their rates of rearrangement are approximately the same; otherwise one might be completely rearranged before the other begins to react and no crossed products would result *even if* the reaction were intermolecular. Compliance with this condition usually requires considerable preliminary experimentation.

It occurred to us that a clear-cut experiment to distinguish intra- from intermolecular reaction paths would be to rearrange benzamide-*m*-*d* in the presence of benzamide-N^{15}. These compounds must rearrange at approximately the same rate (except for the small isotope effect of the N^{15}) so that, if the reaction is to any extent intermolecular, the product should contain some aniline-*m*-*d*-N^{15}. This species can be easily detected mass spectrometrically, since its mass number is 95 whereas the mass-number of the intramolecular products aniline-*m*-*d* and aniline-N^{15} is 94. Details of the calculations are given below; they show no evidence whatsoever for any intermolecular reaction and, given the limits of accuracy imposed by the isotopic purity of the substrates and the sensitivity of the analytical method, it can be stated with confidence that the Hofmann haloamide reaction is at least 96% intramolecular.[14]

The method used here to demonstrate the intramolecular nature of the Hofmann haloamide reaction commends itself to application in a wide variety of other reactions whose intra- or intermolecular nature is in doubt. The method should frequently be easy to apply, especially in view of the fact that the nature (C^{13}, N^{15} or D, but not O^{18} whose degree of enrichment is insufficient for the purpose at hand) as well as the position of the tracer can be adapted, to a considerable extent, to the experimenter's convenience.[15]

A double-labeling method of the above type has apparently been used only once before[16] in a demonstration of the intermolecular nature of hydride exchange between $(CH_3)_3CD$ and $(CH_3)_2CHC^{13}H_3$. Double-labeling with a somewhat different purpose has been used in biochemical studies.[17]

Experimental[18]

Benzamide-N^{15}.—Labeled ammonia was generated[19] from ammonium-N^{15} nitrate[20] containing 33.4 atom % N^{15} and converted to benzamide-N^{15} by treatment with benzoyl chloride in ether.[21] Recrystallized from water the product was obtained in well-formed crystals (79%) which, however, melted over a range[22] 124–129°.

Toluene-*m*-*d* was prepared from *m*-tolylmagnesium bromide and deuterium oxide (99.5+ %) as previously described.[23] Preliminary experiments indicated that removal of the bulk of the ether prior to addition of the deuterium oxide[24] was necessary to ensure adequate isotopic purity of the product.[25] When DCl and CH_3COOD (used in preference to heavy water alone in view of the difficulties reported in ref. 25) was added to *ethereal* *m*-tolylmagnesium bromide, isotopic purity of the resulting toluene-*m*-*d* was about 10% less than when the method of Weldon and Wilson[25] was used, even though the product was removed from the reaction vessel by vacuum distillation without ever coming in contact with ordinary water or acid. Toluene-*m*-*d* boiled at 106–108°, $n^{20}D$ 1.4960, and was obtained in 69% yield (lit.[26] for toluene, b.p. 110.6° (760 mm.), $n^{20}D$ 1.4968).

Anal.[29] toluene-*d*, 96.0%; unlabeled toluene, 4.0%.

Benzamide-*m*-*d*.—Toluene-*m*-*d* was converted to benzoic-*m*-*d* acid in 73% yield by oxidation with alkaline permanganate essentially as described for the *o*-*d* compound.[27] Treatment of the acid, m.p. 121–125°, with thionyl chloride[27] gave benzoyl-*m*-*d* chloride, b.p. 79–83.5° (16 mm.), in 90% yield. This chloride with concentrated aqueous ammonia yielded benzamide-*m*-*d*, m.p. 125–129°, in 81% yield.

Anal. Calcd. for C_7H_6DNO: D, 14.28 atom %. Found: D, 13.55 atom % corresponding to an isotopic purity of 94.9%.

Anilines.—The Hofmann haloamide reaction of the benzamides was carried out by means of freshly prepared sodium hypochlorite as described before.[21] Benzamide-*m*-*d* gave aniline-*m*-*d*, b.p. 82–82.5° (20 mm.), $n^{20}D$ 1.5858 (lit.[28] b.p. 85.8° (24.1 mm.), $n^{20}D$ 1.5863 for aniline) in 70% yield.

Anal.[29] aniline-*d*, 95.8%; unlabeled aniline, 4.2%.

Benzamide-N^{15} similarly yielded aniline-N^{15}, b.p. 84–85° (24 mm.), $n^{20}D$ 1.5841, in 72% yield. *Anal.*[29] labeled, 31.9%; unlabeled, 68.1%.

A mixture of 2.02 g. of benzamide-*m*-*d* and 1.98 g. of benzamide-N^{15} similarly yielded 2.16 g. (70.1%) of mixed aniline, b.p. 83.5–84.0° (22–23 mm.), $n^{20}D$ 1.5845. The composition of this mixture is discussed below.

Mass Spectra and Calculations.—The mass spectra were recorded on a Consolidated 21-103A instrument at reduced ionizing voltage. Each spectrum was recorded three times. Below are shown the individual and average patterns for aniline, the peak heights and patterns for aniline-*m*-*d* and aniline-N^{15} and the peak heights and treatment of same for the three spectra of the mixture. The spectra of aniline-*m*-*d* and aniline-N^{15} were handled as follows: The 93-peak was assumed to be due entirely to light aniline (since the aniline spectrum showed no 92-peak). The contribution of light aniline to 94 and 95 was then calculated from the aniline pattern and deducted from the 94- and 95-peaks in the spectra of the labeled compounds.[30] The remaining 94- and

(14) If 95+% N^{15} had been used in this investigation, this limit could have been as high as 99%. High-purity nitrogen-15 is now available: *Chem. Eng. News*, **34**, 5324 (1956).

(15) The nature and position of the tracer must be such that it is not subject to exchange in the course of the reaction studied and preparation of the substrates. This is why benzamide-*m*-*d* was chosen in this work in preference to the *o*-*d* or *p*-*d* isomer: Aniline is known to undergo exchange of ring-hydrogen atoms in the *ortho* and *para* positions in acid media: M. Harada and T. Titani, *Bull. Chem. Soc. Japan*, **11**, 554 (1936).

(16) O. Beeck, J. W. Otvos, D. P. Stevenson and C. D. Wagner, *J. Chem. Phys.*, **17**, 418, 419 (1949).

(17) E.g., V. du Vigneaud, J. R. Rachele and A. M. White, THIS JOURNAL, **78**, 5131 (1956).

(18) Mass spectra by Mr. George W. Young with the exception of those used in the analyses of aniline-*m*-*d* and aniline-N^{15} which were performed by Mr. Seymour Meyerson of the Standard Oil Company (Indiana). Deuterium analysis by combustion and falling drop method by Mr. Jozsef Nemeth, University of Illinois.

(19) R. Schoenheimer and S. Ratner, *J. Biol. Chem.*, **127**, 301 (1939).

(20) Purchased from Eastman Kodak Co., Rochester, N. Y.

(21) W. S. Fones and J. White, *Arch. Biochem.*, **20**, 118 (1949).

(22) V. Grignard, *Traité de Chimie Organique*, **13**, 438 (1941), reports that benzamide is dimorphic, the labile form melting at 128° and the stable at 115°.

(23) J. Turkevich, H. A. McKenzie, L. Friedman and R. Spurr, THIS JOURNAL, **71**, 4045 (1949).

(24) From Stuart Oxygen Co., San Francisco, Calif.

(25) *Cf.* L. H. P. Weldon and C. L. Wilson, *J. Chem. Soc.*, 235 (1946).

(26) A. F. Forziati, A. R. Glasgow, C. B. Willingham and F. D. Rossini, *J. Research Natl. Bur. Standards*, **36**, 129 (1946).

(27) C. D. Hurd and J. Azorlosa, THIS JOURNAL, **73**, 37 (1951).

(28) W. Ramsay and S. Young, *J. Chem. Soc.*, **47**, 648 (1885); R. Weegmann, *Z. physik. Chem.*, **2**, 229 (1888).

(29) By mass spectrometry at reduced ionizing voltage.

(30) This procedure is not entirely justified theoretically, since in deducting the 94 contribution of aniline, one deducts not only the contribution due to 6 × 1.1% C^{13} but also that due to 0.38% N^{15} and 7 × 0.02% D caused by naturally occurring heavy isotopes. The error is insignificant in the case of aniline-*d* but affects the 95-pattern of aniline-N^{15} to the extent of about 6%. However, even if this error carried entirely into the mixture spectrum, it would affect the 95 residual only to the extent of 0.25 scale division. Actually the effect tends to cancel altogether, since the mixture spectrum is treated in the same way as the aniline-N^{15} spectrum.

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ANILINE PATTERN

m/e	1	2	3	Average
92	0	0	0	0
93	100	100	100	100
94	7.50	7.51	7.43	7.48
95	0.24	0.24	0.24	0.24

ANILINE-*m*-*d* (THREE SPECTRA)

m/e	Peak height	Contribution: Aniline	Contribution: Aniline-*m*-*d*	Pattern
93	30.0; 30.5; 30.3	30.0; 30.5; 30.3	0	0
94	377.0; 368.0; 358.0	2.24; 2.28; 2.27	374.8; 365.7; 355.7	100
95	27.3; 25.5; 26.1	0.1; 0.1; 0.1	27.2; 25.4; 26.0	7.28; 6.97; 7.34 (7.31)[c]

ANILINE-N^{15} (THREE SPECTRA)

m/e	Peak height	Contribution: Aniline	Contribution: Aniline-N^{15}	Pattern
93	173.7; 168.6; 163.8	173.7; 168.6; 163.8	0	
94	94.8; 92.4; 88.5	13.0; 12.6; 12.3	81.8; 79.8; 76.2	100
95	6.0; 6.0; 5.8	0.4; 0.4; 0.4	5.6; 5.6; 5.4	6.85; 7.01; 7.09 (6.98)[d]

MIXTURE (THREE SPECTRA)

	m/e	Peak height	Contribution: Aniline	Contribution: Labeled[a]	Contribution: Aniline-*m*-*d*[b]	Contribution: Aniline-N^{15}[b]	Residue
1st	93	123.3	123.3	0	0	0	0
	94	248.4	9.2	239.2(100)	184.0	55.2	0
	95	17.4	0.3	17.1(7.15)	13.45	3.85	−0.2
2nd	93	120.3	120.3	0	0	0	0
	94	242.4	9.0	233.4(100)	179.5	53.9	0
	95	17.0	0.3	16.7(7.16)	13.12	3.76	−0.2
3rd	93	117.9	117.9	0	0	0	0
	94	237.3	8.8	228.5(100)	175.8	52.7	0
	95	16.7	0.3	16.4(7.18)	12.85	3.68	−0.1

[a] Total labeled material (pattern in parentheses). [b] Contribution to 94-peak calculated on the assumption that $^{12}/_{13}$ of this peak is due to aniline-*m*-*d* and $^{1}/_{13}$ to aniline-N^{15}. Contribution to 95-peak calculated from assumed 94-peak and appropriate pattern. [c] Average of first and third values. [d] Average.

95-peaks were used to calculate patterns for aniline-*m*-*d* and aniline-N^{15} and the three patterns for each compound were averaged.

The mixture spectrum was handled as follows: The 93-peak was again taken to be due to aniline and the contribution of aniline to the 94- and 95-peaks was deducted.[30] The residual 94-peaks are due to aniline-*m*-*d* and aniline-N^{15}. Since the patterns at 95 of these two species are very similar, only a rough apportionment between the two species is necessary and this was obtained by assuming that *ca.* $^{3}/_{13}$ of the labeled material bore the N^{15}-label and $^{10}/_{13}$ the D-label.[31] The residual 95 peak was then calculated and found insignificant in all three spectra.

Sensitivity of Method.—In setting an upper limit to the amount of intermolecular reaction giving rise to aniline-N^{15}-*m*-*d* which might escape detection, one has to make an assumption on the minimum height of the 95 residual which can be clearly detected. Since the total height of the 95-peak is only about 17 divisions, the assumption that a residual of at least one scale division can be clearly detected is certainly a most conservative one. Since the sum of the peak heights at the parent peaks due to aniline (at 93) and the labeled anilines (at 94) is about 350 scale divisions, one division at 95 would correspond to about 1 part doubly labeled aniline in 350 or about 0.3% (making the reasonable assumption that the sensitivities for unlabeled, singly labeled and doubly labeled species at the parent peak are roughly equal).

It can be calculated that about 4% intermolecular reaction suffices to produce 0.3% doubly labeled material; thus 4% is the maximum of intermolecular reaction that might have escaped detection. The 4% figure is arrived at as follows: Out of 200 parts of a 50–50 mixture of aniline-N^{15} and aniline-*m*-*d*, according to the above analyses 95.8 parts will be deuterated, 31.9 parts will contain N^{15} (neglecting natural deuterium and N^{15}) and the rest will be unlabeled. If there is 4% of intermolecular reaction, then 8 parts of the above mixture, containing 3.83 parts deuterium and 1.28 parts N^{15} will be subject to random recombination (neglecting any isotope effects), giving rise to 0.61 part in 200 or *ca.* 0.3% of doubly labeled material.

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(31) Making the rough assumption that *all* of the 50% deuterated material was labeled but only 30% of the 50% N^{15} material was labeled. The calculations are in no way sensitive to this assumption. For example, in the first mixture spectrum, if all the labeled material was assumed to be aniline-*m*-*d*, the residue would be −0.4 and if all labeled material was assumed to be aniline N^{15}, the residue at 95 would be +0.4.

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[CONTRIBUTION FROM JOHN HARRISON LABORATORY OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

A Further Study of the Dissociation and Association of Furoic and Thenoic Acids and of the Rates of Saponification of Their Ethyl Esters

BY SHIGERU OAE AND CHARLES C. PRICE

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Additional data on the pK_a's for furoic and thenoic acids and on the rates of saponification of their ethyl esters indicate that the latter are not accurately predicted from the former by the Hammett equation. The difference is not due to differing degrees of association of the acids and, unlike the case of α-naphthoic acid, does not appear to be steric.

We have reported[1] that the saponification of ethyl 2-furoate proceeded at a rate considerably slower than predicted from the pK_a for 2-furoic acid.

In seeking additional evidence for the nature of this alleged effect, we have discovered a regrettable error of a factor of ten in the calculation of the rate constant for ethyl 2-furoate, which largely eliminates the discrepancy. We do, however, wish to report additional data on the pK_a's for furoic and thenoic acids, on the rates of saponification of their ethyl esters over a wider range in temperature and on the degree of their association.

Experimental

2-Furoic, benzoic, 1- and 2-naphthoic acids were commercial products (Eastman Kodak Co.), while the preparation and properties of 2-thenoic acid were described in the previous paper.[2] 3-Thenoic acid was kindly supplied by Dr. E. E. Campaigne of Indiana University. All these acids were recrystallized at least twice. The preparations of ethyl thenoates were also described elsewhere,[2] while the ethyl 2-furoate was obtained from Norwich Pharmacal Co. The esters were redistilled just before use. Dioxane was purified as before.[2] Benzene was purified by repeated crystallization after fractional distillation through an efficient column.

The saponification rate constants were determined as previously.[2] All the volumetric apparatus used was calibrated at each temperature under which kinetic measurements were made, while the thermostat used was maintained within the range of ±0.02°. Typical data are shown in Table I and all of the data are summarized in Table II.

TABLE I

ALKALINE SAPONIFICATION OF ETHYL 2-THENOATE IN 70% DIOXANE AT 45.00 ± 0.02°

(Ethyl 2-thenoate) = (NaOH) = 0.02500N = a

t, sec.	x	$a(a-x)t$	k_2, mole^{-1}, sec.$^{-1}$, l.
191	0.001850	0.110541	0.01673
505	.004325	.261022	.01656
853	.006550	.393446	.01664
1170	.008355	.489791	.01685
1549	.009758	.590246	.01653
1881	.011003	.658209	.01671
2255	.012050	.730056	.01650
2698	.013175	.797596	.01651
		Mean	0.0166 ± 0.0001

TABLE II

RATE CONSTANTS FOR THE ALKALINE HYDROLYSIS OF ETHYL ESTERS OF AROMATIC AND HETEROCYCLIC ACIDS IN 70% DIOXANE

Compound	$10^3 \times k_2$, mole^{-1}, sec.$^{-1}$, l. 7.5°	20.0°	25.0°	32.5°	40.0°	45.0°	E[d]	log PZ	$\Delta H\ddagger$[d,e]	$\Delta S,\ddagger$[e] e.u.
2-Thenoate		2.36 ± 0.03	3.51[a] (3.00[b])	6.51 ± 0.05	8.38[b]	16.6 ± 0.1	14.69	8.31	14.11	−22.45
3-Thenoate		2.20 ± .04	3.33[a] (3.17[b])	6.21 ± .06	11.2[b]	15.3 ± .1	14.42	8.09	13.84	−23.46
2-Furoate	4.17 ± 0.05	11.2 ± .1	15.9[a] (22.7[b])	31.1 ± .4			13.74	8.29	13.16	−22.54
Benzoate[c]			3.42		10.7		14.0	7.82		
1-Naphthoate[c]			1.28		3.77		13.4	6.9		
2-Naphthoate[c]			3.46		11.3		14.7	8.38		

[a] These kinetic values were calculated by interpolating from the values of E and log PZ. [b] Taken from the data in ref. 2. [c] Taken from the data by C. C. Price and R. H. Michel, THIS JOURNAL, 74, 3652 (1952). [d] Kcal./mole. [e] Calculated from the equation, $k = \frac{kT}{h} e^{-\Delta H\ddagger/RT} e^{\Delta S\ddagger/R}$ and $\Delta H\ddagger = E - RT$, see Glasstone, Laidler and Eyring "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.

TABLE III

HAMMETT σ-CONSTANTS FOR THE ACID DISSOCIATION CONSTANTS IN 78.1% ETHANOL AND THE RATES OF ALKALINE SAPONIFICATION OF THE ESTERS, IN 70% DIOXANE

Acid	pK_a	$k_2$sapn. × 10^3 at 25°	σ_a[a]	σ_s[b]	$\Delta\sigma$
Benzoic	6.70 (6.37[c])	(3.42[c])	(0.00)	(0.00)	(0.00)
2-Thenoic	5.95 (5.72[c])	3.51 (3.00[c])	0.36 (.31[c])	0.005 (−0.02)[c]	.35
3-Thenoic	(6.23[c])	3.33 (3.17[c])	(.07[c])	− .005 (− .01[c])	.08
2-Furoic	5.43 (5.37)[d]	15.9 (22.7[d])	0.61 (.47[d])	.29 (.36[d])	.32
1-Naphthoic	6.25 (6.13[c])	(1.28[c])	.22 (.12[c])	(− .18[c])	.40
2-Naphthoic	6.30	(3.46[c])	.03	(0.00[c])	.03

[a] $\sigma_a = (pK_a \text{ for benzoic} - pK_a)/2.07$. [b] $\sigma_s = \log (k_{sap.}/3.42)/2.31$. [c] Taken from the data in ref. 2. [d] Taken from the data in ref. 1. [e] C. C. Price and R. H. Michel, THIS JOURNAL, 74, 3652 (1952).

New measurements of the acid strengths of benzoic, 2-thenoic, 2-furoic, 1- and 2-naphthoic acids at 25° in 78.1% ethanol by volume were made as before,[2] using a Beckman glass electrode pH meter model H2. The values obtained are listed in Table III.

Freezing point determinations were made for each acid using 43.60 g. (50.0 ml. at 25°) of pure benzene. Benzoic acid is quite soluble in benzene, but 2-thenoic acid is not very soluble (less than 2.3 g. in 100 ml. of benzene at 5°),

(1) C. C. Price and E. A. Dudley, THIS JOURNAL, 78, 68 (1956).
(2) C. C. Price, E. C. Mertz and J. Wilson, *ibid.*, 76, 5131 (1956).

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while 2-furoic acid is still much less soluble (less than 0.6 g. in 100 ml. of benzene at 5°). Therefore, the freezing point determination of 2-furoic acid was made only in a rather lower concentration. The determined values are listed in Table IV.

Discussion

The data on rates of saponification, outlined in Tables II and III, show clearly that the rates of saponification of ethyl benzoate, 2-naphthoate and 3-thenoate are in reasonable agreement with values predictable from pK_a (indicated by reasonable agreement between σ_a and σ_s in Table III). The earlier discrepancy[1,2] between σ_a and σ_s for 1-naphthoate, 2-furoate and 2-thenoate persists. However, as judged from energy and entropy of activation, the reasons for these discrepancies are dissimilar. For example, the 1-naphthoate has very much the lowest temperature independent factor (log PZ = 6.9), whereas the 2-furoate and 2-thenoate have the largest (log PZ = 8.29 and 8.31, respectively).

A redetermination of pK_a values for benzoic, 2-furoic, 2-thenoic, 1- and 2-naphthoic acids (Table

TABLE IV

THE VALUES OF OBSERVED MOLECULAR WEIGHTS AND DEGREE OF ASSOCIATION OF 2-FUROIC, 2-THENOIC AND BENZOIC ACIDS IN BENZENE SOLUTION

Acid	Mol. wt.	Weight of sample, g.	ΔT, °C.	Mol. wt. (obsd.)	Degree of association, %
2-Furoic	112	0.2343	0.150	183	82
		.2011	.127	186	83
		.2128	.144	174	78
2-Thenoic	128	0.2131	.130	192	75
		.3268	.205	190	74
		.7018	.370	223	87
		.7551	.420	211	82
		1.0186	.520	230	90
		1.2553	.670	220	86
Benzoic	226	0.3268	.205	190	78
		.7551	.420	211	87
		.7393	.390	226	93
		1.2553	.670	220	90

Infrared spectra of benzoic, 2-thenoic, 2-furoic, 1- and 2-naphthoic acids were obtained in potassium bromide disks, using a Perkin–Elmer, model 21, autorecording spectrophotometer, as shown in Table V.

TABLE V

INFRARED SPECTRA OF BENZOIC, 2-THENOIC, 2-FUROIC, 1- AND 2-NAPHTHOIC ACIDS (IN POTASSIUM BROMIDE)

Benzoic		2-Thenoic		2-Furoic		1-Naphthoic		2-Naphthoic	
ν	Rel. % abs.	ν	Rel. % abs.	ν	Rel. % abs.	ν	Rel. % abs.	ν	Rel. % abs.
3400	35	3400	42	3400	52	3450	59	3450	53
3100–2800*	57	3100–2800*	79	3150–2800*	77	3100–2800*	73	3080–2750*	64
2670*	55	2620*	78	2650*	78	2620*	68	2640*	63
2550*	55	2530*	78	2560*	78	2520*	65	2560*	64
						1950	48	1960	45
						1820	42	1810	43
1690*	83	1680*	95	1685*	93	1680*	90	1680*	83
1605	46					1625	72	1635	69
1585	47			1585	89	1595	77	1595	56
						1575	66	1575	57
1500	35	1525	92			1515	75	1510	52
				1476	91	1465	57	1475	61
1450	65					1450	63	1445	52
1425*	66	1433*	95	1428*	86	1420*	69	1425*	69
		1405	82	1387	73	1395	54		
1330	75	1355	89			1350	54	1360	66
1285*	79	1283*	97	1300*	91	1300*	83	1305*	82
								1265	62
		1230	82	1240	83	1250	74	1240	74
1180	55			1180	87	1205	72	1200	68
						1145	68	1155	57
1130	50			1125	88			1130	66
1100	37	1107	84					1100	50
1075	47	1078	66	1078	68	1082	58	1080	49
1028	50	1045	85	1020	88	1028	50	1015	43
1000	37					998	54	985	47
						945	48		
933*	63	930*	71	933*	86	928*	47	945–925*	64
		910	84	926–913	80	890–880	64	905	65
		866	72	887	86			864	69
		858	88	851	60	855	57	832	60
						808	61		
						794	49		
		761	76			772	89	778	84
707	84	748	87	770–755	90	755–745	66	755	80
683	56	735	92					732	56
665	64	722	95			720	56	728	56

* Bands so marked are characteristic for the associated form of the acid.

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III) leads to values of σ_a in reasonable agreement with those from earlier data.[1,2]

Recently there have appeared two papers which are related to our study, the one dealing with the alkaline hydrolysis of ethyl 2-thenoate and 2-furoate[3] and the other of ethyl 1- and 2-naphthoate,[4] both in 85% ethanol. Using these data[3,4] together with the rates of saponification and ρ in the same solvent,[5] we can calculate the Hammett σ-constants for the saponification rates of ethyl benzoate, 2-furoate, 2-thenoate, 1- and 2-naphthoate, as shown in Table VI.

Although the temperature-independent factors in these two separate experiments[3,4] are quite far apart, the over-all picture thus calculated is in fairly reasonable agreement with our data.

To test the hypothesis that the heterocyclic acids might have intra- rather than intermolecular hydrogen bonding, the degree of association of benzoic, 2-thenoic and 2-furoic acids were determined cryoscopically in benzene. These data, summarized in Table IV, indicate that all three acids have almost the same degree of association, and our data do not support the earlier claim that 2-furoic acid is largely monomeric in benzene.[6]

(3) E. Imoto, Y. Otsuji, T. Hirai and H. Inoue, *J. Chem. Soc. Japan* (Pure Chem. Section), **77**, 804, 809 (1956).

(4) P. Fitzgerald, J. Parker, J. Vaughan and A. F. Wilson, *J. Chem. Soc.*, 170 (1956).

(5) (a) D. P. Evans, J. J. Gordon and H. B. Watson, *ibid.*, 1430 (1937); (b) C. K. Ingold and W. S. Nathan, *ibid.*, 222 (1936); (c) H. H. Jaffe, *Chem. Revs.*, **53**, 191 (1953).

(6) L. M. Nazarova and Y. K. Syrkin, *Izvest. Akad. Nauk. S. S. R., Oddl. Khim. Nauk.*, **35** (1949) (*C. A.*, **43**, 4913 (1949)).

For the solid acids, infrared spectra in potassium bromide disks, as shown in Table V, reveal no significant changes in position or relative intensity of the bands associated with the carboxyl group, in support of the conclusion that all the acids are associated in the crystalline state, as was already pointed out previously by X-ray study,[7] in the case of 2-furoic acid.

TABLE VI

HAMMETT σ-CONSTANTS FOR THE ACID DISSOCIATION CONSTANTS AND THE RATES OF ALKALINE SAPONIFICATION OF THE ESTERS IN 85% ETHANOL

Acid	pK_a[a]	$k_2$sapn. $\times 10^4$ at 25°	σ_a[a]	σ_s[f]	$\Delta\sigma$
Benzoic	6.70	6.07[a]	0.00	0.00	0.00
2-Thenoic	5.95	5.63[b]	.36	− .01	.37
2-Furoic	5.43	24.5[c]	.61	.24	.37
1-Naphthoic	6.25	4.79[d]	.22	− .04	.26
2-Naphthoic	6.30	10.0[d]	.03	.08	.05

[a] Taken from ref. 5. [b] Extrapolated from the value of ΔE (18.9 kcal./mole) and log PZ (10.6) in ref. 3. [c] Directly taken from ref. 3. [d] Extrapolated from the values of ΔE (14.5 kcal./mole for 1-naphthoate and 16.1 kcal./mole for 2-naphthoate) and log PZ (7.3 for 1-naphthoate and 8.8 for 2-naphthoate, respectively) in ref. 4. [e] Taken from our measurement—see Table III. [f] $\sigma_s = \log (k_{sap}/6.07 \times 10^4)/2.54$.

(7) T. Goodwin and C. M. Thomson, *Acta Cryst.*, **7**, 166 (1954) (*C. A.*, **48**, 7385 (1956)).

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[CONTRIBUTION FROM THE ORGANIC RESEARCH DEPARTMENT, PENNSYLVANIA SALT MANUFACTURING CO.]

Thermal Syntheses of Telomers of Fluorinated Olefins. I. Perfluoropropene[1]

BY MURRAY HAUPTSCHEIN, MILTON BRAID AND FRANCIS E. LAWLOR

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A novel method of producing addition-type polymers by a process which does not proceed by chain propagation is described. The formation of telomers of perfluoropropene of formula $R[CF_2CF(CF_3)]_nI$ where R = CF_3, C_3F_7, $C_4F_9CF(CF_3)$, $C_4F_9CF(CF_3)CF_2CF(CF_3)$ and $CF_2ClCFCl$ and n = 1 to 15 has been accomplished by purely thermal means. The unique advantages of this simple process as a method of producing telomers of certain types of relatively non-polymerizable olefins are expounded.

This is the first paper in a series dealing with the syntheses of telomers of fluorinated olefins by purely thermal means.

Considerable work from both academic and industrial laboratories has been described on photochemical and peroxide-induced telomerizations of fluoroölefins which are readily polymerized by free radical initiators. Little information has been reported, however, on (1) thermally induced telomerizations and (2) telomerizations of olefins which do not readily homopolymerize in the presence of free radical initiators.[2]

Although perfluoropropene has been copolymerized with fluorinated[3,4] and unfluorinated[3,5] olefins as well as with ethylene oxide,[6] there is no literature reference to the homopolymerization of perfluoropropene to $[-CF_2CF(CF_3)-]_n$, in spite of considerable study.[5] We have now found that polyperfluoropropenes of molecular weights to 2500 may be synthesized by reaction of perfluoropropene with perfluoroalkyl iodides at about 200°. Moreover, the reaction may be controlled to give products of any desired narrow molecular weight range from n = 1 to 15.

Replacement of the iodine atom by fluorine or

(1) The work herein reported was carried out under contract between the Office of Naval Research and the Pennsylvania Salt Manufacturing Co. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) See R. N. Haszeldine, *J. Chem. Soc.*, 4291 (1955), for an excellent review of many of the factors affecting telomerization.

(3) J. C. Sauer, U. S. Patent 2,549,935 (1951).

(4) W. T. Miller, U. S. Patent 2,598,283 (1952).

(5) R. M. Adams and F. A. Bovey, *J. Polymer Sci.*, **9**, 481 (1952).

(6) M. Hauptschein and J. M. Lesser, THIS JOURNAL, **78**, 676

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chlorine, or its removal by a coupling reaction converts the telomer

$R_f[-CF_2CF(CF_3)-]_nI$ into $R_f[-CF_2CF(CF_3)-]_nF$, $R_f[-CF_2CF(CF_3)-]_nCl$

or $R_f[-CF_2CF(CF_3)-]_n[(CF_3)CFCF_2-]_nR_f$ where R_f is a perfluoroalkyl group.[7] These fluorocarbon materials are useful as heat transfer fluids, hydraulic fluids, oils, greases, waxes, insulators, dielectrics, plasticizers and modifiers of certain fluorocarbon plastics.

The photochemical reaction of perfluoropropene with trifluoroiodomethane was first described by Haszeldine.[8] Under conditions similar to those used in the rapid reaction of tetrafluoroethylene with trifluoroiodomethane[9] (*i.e., vapor phase* irradiation in a silica tube), which gave mainly solid products, $CF_3(CF_2CF_2)_nI$ where $n = 4$ to >20, the slow perfluoropropene–trifluoroiodomethane reaction gave 2-iodoperfluorobutane. A small amount of $CF_3[CF_2CF(CF_3)]_nI$ where $n = 2$ also was formed but no material where the value of n exceeded 2 was reported. It was similarly shown that 2-iodoperfluorobutane reacted very slowly with perfluoropropene to give only $CF_3[CF_2CF(CF_3)]_2I$.

Heretofore, in addition to $CF_3CF=CF_2$, certain unsaturated compounds including C_2H_4, C_2H_2, $CH_2=CHCF_3$, $CH_2=C=CH_2$, $CH_3CH=CH_2$ and $CFCl=CFCl$ have been shown to "telomerize" with great difficulty by ultraviolet or peroxide initiation. The products obtained in these cases were almost entirely the 1:1 adducts. Previous efforts to force olefins such as ethylene, propene, 3,3,3-trifluoropropene or hexafluoropropene to give a polymer $RCFX[olefin]_nY$ with $n > 4$ or 5, by cutting down the proportion of chain-transfer agent RCFXY,[10] merely caused the intermediate radical to undergo reactions other than by addition with a second molecule of olefin, *e.g.*, disproportionation, dimerization or internal expulsion of halogen to give an olefin.[2]

The results of the present investigation (see Tables I and II) demonstrate that perfluoropropene can give telomers such as $C_2F_7[CF_2CF(CF_3)]_nI$ where $n = 10$ and higher.

This simple thermal method of producing telomers of perfluoropropene is applicable to other relatively non-polymerizable or poorly polymerizable olefins (*vide infra*). It is proposed that this method proceeds by "successive addition steps" (probably involving transient radical formation and a single transition state for each addition) with little contribution from a chain mechanism including a propagation step, *i.e.* $RCFX[olefin]\cdot + (n-1)$ olefin $\rightarrow$ $RCFX[olefin]\cdot_n$, etc. For example, in the case of the perfluoropropene reaction with perfluoropropyl iodide, the formation of telomers may be regarded as occurring in discrete steps.[11]

$$C_3F_7I + CF_2{=}CFCF_3 \longrightarrow C_3F_7CF_2CF(CF_3)I$$

$$C_3F_7CF_2CF(CF_3)I + CF_2{=}CFCF_3 \longrightarrow C_3F_7[CF_2CF(CF_3)]_2I, \text{ etc.}$$

$$C_3F_7[CF_2CF(CF_3)]_nI + CF_2{=}CFCF_3 \longrightarrow C_3F_7[CF_2CF(CF_3)]_{n+1}I$$

Thermal syntheses of perfluoropropene with CF_3I, C_3F_7I, $C_4F_9CFICF_3$, $C_4F_9CF(CF_3)CF_2CF(CF_3)I$ and $CF_2ClCFCII$[12] have been successfully carried out. $R[CF_2CF(CF_3)]_nI$ where R = CF_3, C_3F_7, $C_4F_9CF(CF_3)$, $C_4F_9CF(CF_3)CF_2CF(CF_3)$ and $CF_2ClCFCl$ and $n = 1$ to >10 have been obtained. Thus any reactant containing the moieties: $-CF_2I$, $-CF(C_nF_{2n+1})I$ and $-CFXI$ (where X = polyhalogenoalkyl) can be used. In addition, modified reactions of perfluoropropene have been effected simply by heating the olefin in the presence of iodine monochloride.[7] A new reactant, CF_3CFICF_2Cl, is formed *in situ* to begin the formation of telomers. Likewise, iodine has been made to react with perfluoropropene to form modified telomers. At somewhat higher temperatures CF_2Br_2 and fluoroalkyl bromides containing the groups $-CF(C_nF_{2n+1})Br$ and $-CFClBr$ may be used as reactants.[7]

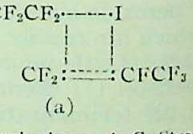
Although the full scope of this method of producing telomers has not been determined, certain conclusions with regard to the types of unreactive (relatively non-polymerizable) olefins to which it is applicable may be drawn. 1. An olefin which on addition of R_fI would form a $-CF_2I$, $-CF(C_nF_{2n+1})I$ or similar linkage, *e.g.*, $R_fI + CF_2{=}CHCF_3 \rightarrow R_fCH(CF_3)CF_2I$,[13] $R_fI + CH_2{=}CFCF_3 \rightarrow R_fCH_2CF(CF_3)I$, would be expected to produce a telomer.

2. Olefins such as ethylene and propene would form on addition of R_fI the linkages $-CH_2CH_2I$ and $-CH_2CHICH_3$. Such C–I bonds do not undergo facile homolytic fission[8] and the temperatures required for telomer formation would probably exceed those necessary for competing size reactions or decomposition. Thus, successful thermal synthesis of telomers of these olefins is improbable.

The maintenance of a sufficiently high energy level to overcome the energies of activation required to promote and sustain the reaction is undoubtedly one of the principal reasons why telomers of unreactive olefins can be produced at appreciable rates by thermal synthesis but not by photochemical or peroxide-induced initiation.

The data in Tables I and II present the important conditions, results and product characterizations of the reactions of perfluoropropene with *n*-C_3F_7I, CF_3I, $C_4F_9CFICF_3$ and $C_4F_9CF(CF_3)CF_2CFICF_3$.

as shown schematically by the transition complex (a) without primary



(a)

(7) M. Hauptschein, M. Braid and F. E. Lawlor, forthcoming publication.

(8) R. N. Haszeldine, *J. Chem. Soc.*, 3559 (1953).

(9) R. N. Haszeldine, *ibid.*, 3761 (1953).

(10) C–Y in RCFXY is weak, yet RCFX is sufficientiy reactive to attack the olefin, *e.g.*, when RCFXY = CF_2I, $CF_2ClCFCII$ or $CF_2ClCFClBr$.

(11) It is proposed that in these addition steps the $C_3F_7\cdot$ and the I· from the same molecule add simultaneously to the double bond, *i.e.*, chain transfer with the solvent (C_3F_7I) is a minor effect. It is likely that the thermally activated molecule [illegible]

dissociation. See A. D. Kirschenbaum, A. G. Streng and M. Hauptschein, THIS JOURNAL, **75**, 3141 (1953).

(12) P. Tarrant and M. R. Lilyquist, *ibid.*, **77**, 3640 (1955), attempted the reaction of perfluoropropene with 1,2-dichloro-2-iodo-1,1,2-trifluoroethane in the presence of benzoyl peroxide as the catalyst at 100°. No addition products or simple telomers were obtained.

(13) The direction of the photochemical addition of CF_2I to $CF_2{=}CHCF_3$ has been established by R. N. Haszeldine and B. R. Steele, *J. Chem. Soc.*, 2685 (1953).

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TABLE I

NEW COMPOUNDS

CF_3 | $C_3F_7(CF_2CF)_nI$ n	B.p. °C.	Mm.	n^tD	t, °C.	Mol. wt. Calcd.	Mol. wt. Found	λmax,[a] mμ	ε[b]	Analyses, %[m] Carbon Calcd.	Carbon Found	Fluorine Calcd.	Fluorine Found
1	62	95	1.3284	24	446	..	282	210	16.2	..	55.4	55.4
2	110	760										
3	62	10	1.3310	24	596	..	282	210	18.1	18.0	60.6	60.5[c]
4	104	100										
3.7 (av.)[d,e]	101	10	1.3340	24	746	..	282	200	19.3	19.4	63.7	63.6
7 (av.)[f,h]	83	*ca.* 0.1	1.3395	19	896	..	282	190	20.1	20.3	65.7	66.0
10 (av.)[f,i]			1.337	24								
		ca 0.1	1.336	24	..	854[e]	282	..	..	..	..	..
	73–94	<0.1			1346	1300[e]	282	..	21.4	21.4	69.2	69.4
	125–135	<0.1			1786	1700[e]	282	..	22.1	22.2	70.9	70.7
	135–160											
CF_3 | $CF_3(CF_2CF)_nI$ n												
1[g]	64	760	1.3282	25	346	..	280	205	13.9	13.8	49.4	49.6
2[g]	64	71	1.3322	26	496	..	282	210	17.0	17.1	57.5	57.3
3	73	10	1.3350	25.5	646	..	282	205	18.6	18.8	61.8	61.8
4	105	10	1.3368	25	796	..	282	210	19.6	19.8	64.4	64.4
9 (av.)[j]	130–150	*ca.* 0.1	1.3358	32	1546	..	282	245	21.8	21.7	70.0	70.0
11 (av.)[k,l]	150–170	*ca.* 0.1	1.3357	35	1846	1800[e]	282	..	22.1	22.2	71.0	..

[a] Ultraviolet spectrum maxima in isooctane, 2,3,3-trichloroheptafluorobutane and 1,1,2-trichlorotrifluoroethane. [b] Molar extinction coefficient in isooctane. [c] *Anal.* Calcd. for $C_9F_{19}I$: I, 21.29. Found: I, 21.1. [d] Kinematic viscosities in centistokes: 199.5 (78.4°F.), 11.7 (141.4°F.), 4.04 (197.8°F.). [e] Molecular weight calculated in the usual way from the absorbancy (at 282 mμ) of a known concentration in isooctane, 2,3,3-trichloroheptafluorobutane or 1,1,2-trichlorotrifluoroethane. [f] Solids at room temperature. [g] R. N. Haszeldine, *J. Chem. Soc.*, 3559 (1953), reported for n = 1, b.p. 65.5°, n^{25}D 1.340. The latter value is apparently in error. For n = 2, the reported boiling point is 136–138°. [h,i,j,k,l] Melting point ranges of these clear glass-like solids, respectivley, are: 55–58°, 74–80°, 35–42°, 47–56°, 68–76° (l is the m.p. range of $CF_3[CF_2CF(CF_3)]_{ca.15}I$). [m] Most of the microanalyses were done by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. In all cases percentage hydrogen was zero.

TABLE II

THERMAL TELOMERIZATIONS AT 200° IN SHAKING AUTOCLAVE

Mole ratio C_3F_7:C_3F_7I	Time, hr.	Pressure, p.s.i. Initial	Pressure, p.s.i. Terminal	Conversion,[a] %	Yield, % n = 1	n = 2	n = 3	n = 4	$n > 4$ [%, (av. n-value)]
1.32[b]	41(220°)	2100	800	37	72	22	5	1	
1.39[b]	88	2000	1000	37	84	14	2	..	
1.51	64	2800	1200	50	68	22	10	[c]	
2.63	22	3600	2300	41	75	18	7	[c]	
2.75	42	5000	2900	57	63	22	15	[c]	
4.07	63	4700	2300	73	56	24	16	4	
4.26	112	3000	1300	84	65	21	13	1	
4.83	98[f]	4600	2100	88	44	28	16	8	4 (5)
4.89	20	4600	3500	52	66	19	16	[c]	
10.4	336	4700	1900	94	7	11	41	30	3 (5), 7 (7), 2 (10)
C_3F_6:$C_3F_5CFICF_3$									
2.97	21.5	2400	1950	23	..	79	21	..	
9.2	137	9000	4800	*ca.* 70	..	*ca.* 10		*ca.* 50[g]	*ca.* 40 (7)[h]
C_3F_6:$C_3F_7(CF_2CF)_3I$ CF_3									
7.47	144	3400	1700	*ca.* 80					*ca.* 50% by wt. $n < 4$
12.8	137	10,700	5950	*ca.* 90	..	..		*ca.* 60[g]	*ca.* 50% by wt. $n \geqslant 4$
C_3F_6:CF_3I									*ca.* 40 (10)[i]
4.64	113	3500	1800	68	48	22	17	[d]	13 (5)
5.43	122(194°)	4150	2800	51(?)	47	23	19	8	4 (8)[e]

[a] Conversion of iodide to telomer $C_3F_7[CF_2CF(CF_3)]_nI$. [b] No shaking. [c] Small amounts of n = 4 included in n = 3. [d] Some n = 4 included in n = 5. [e] Some n = 11 and n = *ca.* 15 in residue. [f] This run was repeated but was repressured with perfluoropropene to 4700 p.s.i. after one day. Comparable conversions were obtained in only 2 days. [g] n = 3–5. [h] n = 5–10 (a balsam-like solid.). [i] n = 6–15 (estd.). The residue (n = *ca.* 13–15) was a transparent, friable solid boiling above 190° at <0.1 mm.

In agreement with the findings of Haszeldine[8] for the photochemical addition of trifluoroiodomethane to perfluoropropene, the direction of radical attack of CF_3·, C_3F_7·, $C_4F_9CF(CF_3)$, $C_4F_9CF(CF_3)CF_2CF(CF_3)$ and $CF_2ClCFCl$· under thermal conditions is exclusively on the CF_2 group of perfluoropropene. The ultraviolet spectra maxima shown in Table I are at 280–282 mμ in agreement with the value for the $-CF_2CFICF_2-$ chromophore which is *ca.* 10 mμ further to the red than that for the $-CF_2-$

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CF_2I chromophore (271 mμ).[8] Thus, in the addition of 1-iodoperfluoropropane to perfluoropropene, the adduct is I and not II. Fluorination of this adduct with cobalt trifluoride gave only perfluoro-*n*-hexane as the product, which confirms the structure I.

$CF_3CF_2CF_2CF_2CFICF_3$ (I) $\qquad$ $CF_3CF_2CF_2CF(CF_3)CF_2I$ (II)

Thermal reactions (telomerizations) in autoclaves of reactive olefins such as chlorotrifluoroethylene and tetrafluoroethylene in contrast to the unreactive perfluoropropene are much more difficult to control to give well defined products of narrow molecular weight ranges. Using reaction times of 1–5 hr. in contrast to several days for the photochemical liquid phase reaction[2] and under otherwise comparable conditions, the $CF_2ClCFClI + CF_2{=}CFCl$ thermal reaction gave products of much wider molecular weight ranges. Under certain thermal conditions $CF_2ClCFClI$ and $CF_2ClCFCl(CF_2CFCl)_nI$ can react with comparable facility with additional olefin. Thus it is difficult even in the presence of an excess of this very efficient chain transfer agent and very short reaction times in autoclaves, to conveniently limit the spread of molecular weights.

The best control of a thermal reaction of chlorotrifluoroethylene was carried out in the liquid phase using a short contact time in a spiral tube reactor at a 5.8:1 mole ratio of $CF_2ClCFClI$ to $CF_2{=}CFCl$. The product composition was *ca.* 22% each of n = 1, 2 and 3 and *ca.* 33% of $n = 4$ to > 10.

In an autoclave reaction, $CF_2ClCFClI + CF_2{=}CF_2$ gave predominantly very high molecular weight telomers of formula $CF_2ClCFCl(CF_2CF_2)_nI$. A liquid-phase reaction in the tube reactor, however, should provide more effective control of the reaction (especially since the C–I bond in a $-CF_2I$ group is stronger than in a $-CFClI$ group) but is potentially extremely hazardous.

In contrast, control of the thermal reaction of perfluoropropene with 1-iodoperfluoropropane is simple. High or even equal ratios of iodide to olefin are not necessary to realize high yields of $n = 1$ and $n = 2$, since a chain transfer step is not necessary. The reaction time is the important variable in controlling the process, and high yields of $n = 1$ may be achieved with iodide-to-olefin ratios varying from 1:1 to <1:5 by terminating the reaction after a suitable time interval and pressure drop. Thus, since perfluoropropene does not telomerize significantly by chain propagation, it is always advantageous to use reasonably high proportions of olefin regardless of the ultimate chain length desired and obtain particular ranges of n by limiting the reaction time. A high initial pressure (olefin concentration) and good agitation enhance olefin–iodide contact and increase the reaction rate.

The rate of reaction of C_3F_7I with perfluoropropene to give $n = 1$ is somewhat more rapid than the reaction of the products $C_3F_7[CF_2CF(CF_3)]_nI$ with the same olefin. This may be attributed to the greater reactivity of the primary $CF_3CF_2CF_2$· radical relative to the secondary $-CF(CF_3)$ radical.

An examination of Table II will reveal that when the mole ratio of $C_3F_6:C_3F_7I$ was 4.3:1 and the initial pressure was 4600 p.s.i. an increase in time of approximately fivefold raised the conversion from 52 to 88%. The product distribution (% yields) for 20 and 98 hr., respectively, were for n = 1, 66, 44; n = 2, 19, 28; n = 3, 16, 16; n = 4, —, 8; n = 5, 0, 4.

When the mole ratio of $C_3F_6:C_3F_7I$ was 10.4 and the time was 336 hr., the total yield of product for n = 3–10 was 83%; n = 3, 41%; n = 4, 30%.

At an initial pressure of 10,700 p.s.i. and at a mole ratio of $C_3F_6:C_3F_7[CF_2CF(CF_3)]_2I = 12.8$ the yield of product after 137 hr. reaction time was *ca.* 60% for n = 3–5 and *ca.* 40% for n = 6–15.

It has been demonstrated that reaction times (for a given conversion) can be shortened greatly by the periodic addition of olefin to maintain a high pressure or concentration.

Experimental

General Procedure.—A 300-ml. Monel autoclave was charged with the fluoroalkyl iodide. The autoclave was cooled in Dry Ice or liquid nitrogen and the olefin was introduced by vacuum transfer. The autoclave was closed and heated to about 200°, usually in a shaker. After the reaction period, the olefin was recovered by condensation in appropriately refrigerated traps. Rectification of the remaining reaction products in a Vigreux unit effected the separation of the individual telomer fractions. Table I lists the physical constants and the analytical data for the new compounds. The conditions and results of the various runs are summarized in Table II. In most cases two-thirds of the autoclave volume was occupied by liquid phase.

In a typical run, 98.0 g. (0.331 mole) of 1-iodoperfluoropropane and 240 g. (1.60 moles) of perfluoropropene (4.83 mole ratio of olefin:iodide) were used. The pressure dropped from 4600 to 2100 p.s.i. in 4 days, most of the drop occurring during the first day. [If after one day the autoclave was repressured with sufficient perfluoropropene (20–40 g.) to raise the pressure to 4500–5500 p.s.i., the rate of reaction as indicated by the pressure drop was increased markedly. Thus, the maintenance of a high olefin concentration by periodic addition of more olefin, would have greatly shortened the times given in Table II.] There were recovered 157 g. of perfluoropropene and 6.7 g. of 1-iodoperfluoropropane. A total of 176 g. of product was collected and characterized as summarized in the tables.

In all of these experiments no more than a few tenths of a gram of free iodine was collected from the autoclave, indicating the absence of significant side reactions at the temperatures used. The perfluoropropene telomers are considerably more stable during distillation than the $CF_2ClCFCl(CF_2CFCl)_nI$ telomers.

During these procedures precautions were taken to exclude oxygen to prevent reactions with the iodides. The $C_3F_7[CF_2CF(CF_3)]_nI$ telomers where n = 1 to 5 are clear fluids varying in viscosity range from a light to a barely flowing liquid. The solids of $n > 5$ are transparent waxes and glasses.

Fluorination of 2-Iodoperfluorohexane.—Cobalt trifluoride (60 g.) supported on copper shot was placed in a vertical copper tube, which was surrounded by a tube furnace. 2-Iodoperfluorohexane (20 g., 0.0448 mole) was added drop by drop on top of the cobalt trifluoride under a dry nitrogen atmosphere at 260–290°. The exit gases were condensed in a Dry Ice-cooled trap, washed with 5% sodium hydroxide (some handling losses occurred), dried with Drierite and distilled to give only *n*-perfluorohexane (75%), b.p. 54°, as shown by its infrared spectrum.[14]

The Thermal Reaction of 1,2-Dichloro-2-iodo-1,1,2-trifluoroethane with Perfluoropropene.—A 300-ml. Monel autoclave filled with Monel balls to reduce the effective volume to 150 ml. was charged with 50 g. of $CF_2ClCFClI$ and 75 g. of perfluoropropene and heated for 112 hr. at 172–197° in a molten salt-bath and then for 15.5 hr. in a shaker at 201°. During this period the pressure dropped from 950 p.s.i. at 172° to 750 p.s.i. at 201°. At this time

(14) A. D. Kirshenbaum, A. G. Streng and M. Hauptschein, THIS JOURNAL, 75, 3141 (1953).

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an additional 20 g. of perfluoropropene was charged into the autoclave which was heated for 40 hours more at 201°. Seventy grams of olefin and 15 g. of $CF_2ClCFClI$ were recovered. Rectification of the remaining product *in vacuo* gave $CF_2ClCFCl[CF_2CF(CF_3)]_nI$ where n = 1 (25 g.), b.p. mostly 58.5–60.5° at 20 mm., $n^{25}D$ 1.3908, λ_{max} 282 mμ, ε 203. *Anal.* Calcd. for $C_5Cl_2F_9I$: C, 14.0. Found: C, 14.4, 14.5. Where n = 2 (15 g.), b.p. mostly 97.5–104° at 20 mm., $n^{25}D$ 1.3760, λ_{max} 282 mμ, ε 205. *Anal.* Calcd. for $C_7Cl_2F_{13}I$: C, 16.6. Found: C, 16.6, 16.9. Where $n = 3_{av.}$ (7 g.), b.p. mostly 77–87° at *ca.* 0.1 mm., $n^{27}D$ 1.3706, (not analyzed). Where $n = 4_{av.}$ (4 g.), b.p. 87–138° at *ca.* 0.1 mm., $n^{27}D$ 1.3691, λ_{max} 282 mμ. *Anal.* Calcd. for $C_{14}Cl_2F_{27}I$: C, 19.1; mol. wt., 879. Found: C, 19.0; mol. wt. (from absorbancy at 282 mμ of a known concentration in 2,3,3-trichloroheptafluorobutane using an ε value of 205), 850.

The Thermal Reaction of 1,2-Dichloro-2-iodo-1,1,2-trifluoroethane with Chlorotrifluoroethylene. (a) **In Autoclaves.**—A 1-l. stainless steel autoclave was charged with 650 g. (2.33 moles) of 1,2-dichloro-2-iodo-1,1,2-trifluoroethane and 248 g. (2.13 moles) of chlorotrifluoroethylene (1.1:1 mole ratio of iodide to olefin) and heated for 5 hr. at 180° in a molten salt-bath. During this time a pressure drop from 500 to 300 p.s.i. was observed with the major portion of the reaction occurring in the first hour (ΔP = 125 p.s.i.).

Forty-five grams of olefin was recovered from the autoclave by gaseous transfer to a Dry Ice-cooled trap, and the remaining products were distilled through a short Vigreux column. A total of 581 g. of $CF_2ClCFClI$ was recovered, b.p. 99–102°, and telomer fractions, $CF_2ClCFCl(CF_2CFCl)_nI$, were taken as follows: n = 1–2, b.p. 45–93° at 1 mm. (36 g.); n = 3–4, b.p. to 150° at <0.1 mm. (80 g.). When the vapor temperature of 150° was reached, the temperature of the still-pot was sufficiently elevated due to the presence of very high molecular weight telomers to cause extensive liberation of iodine and the distillation had to be stopped. The distilled fractions were identified and the composition of the hard waxy residue (127 g.) was estimated to be n = 4 to >20 (mostly n > 10) by reference to published physical data[3] and ultraviolet molar extinction determinations.

Another experiment was carried out using a molar ratio of $CF_2ClCFClI:CF_2{=}CFCl$ of 15:1 at 160–170° for 5.7 hr. The yield of n = 1 and 2 was <20%, whereas under liquid phase photochemical conditions (5 days) a 75% yield of n = 1 was obtained by Haszeldine.[2]

(b) **In Hot Tubes.**—An attempt to prepare n = 1 by passing $CF_2{=}CFCl$ through a large excess of refluxing $CF_2ClCFClI$ in a vertical column heated to 180° failed to give any significant reaction. Therefore, an alternative reaction system allowing higher pressures and temperatures as well as short contact time was designed.

At an average rate of 9.6 g./min., a mixture of 2230 g. (8.0 moles) of 1,2-dichloro-2-iodo-1,1,2-trifluoroethane and 160 g. (1.37 moles) of chlorotrifluoroethylene was pumped by means of a Lapp Pulsafeeder micropump from a charge cylinder through a stainless steel coil immersed in a molten salt-bath at 200°. Practically all of the coil volume was occupied by liquid phase, and the contact time in this hot zone was calculated as <10 min. During the reaction, the pressure was maintained at 750 p.s.i. by adjusting the rate at which products were vented from the coil to a Dry Ice-cooled receiving gas cylinder. Twelve grams of chlorotrifluoroethylene and 2150 g. of $CF_2ClCFClI$ were recovered. The product distribution of the remaining 211 g. of crude telomer was n = 1 (22%), n = 2 (22%), n = 3 (22%) and n = 4 to >10 (33%).

In the above apparatus at a rate of 17 g./min. at 195–200° and at pressures of 600–650 p.s.i. only slight reaction occurred.

The Thermal Reaction of 1,2-Dichloro-2-iodo-1,1,2-trifluoroethane with Tetrafluoroethylene.—1,2-Dichloro-2-iodo-1,1,2-trifluoroethane (200 g., 0.716 mole) and 30 g. (0.316 mole) of tetrafluoroethylene (2.4 mole ratio of iodide to olefin) were charged into a 300-ml. nickel autoclave and heated in a molten salt-bath for 2.75 hr. at 171°. After the reaction period, during which the pressure fell from 600 to 450 p.s.i., 15 g. of tetrafluoroethylene was recovered. From the remaining products 170 g. of $CF_2ClCFClI$ was recovered (some handling losses), and 16 g. of a white crumbly solid was the only other product. This solid contained only very small amounts of iodine and its ultraviolet spectrum showed a very faint maximum at *ca.* 270 mμ. Its infrared spectrum closely resembled that of polytetrafluoroethylene.

Ultraviolet Spectra.—A Beckman ratio recording spectrophotometer, model DK-2, was used.

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PHILADELPHIA 18, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Studies in Organic Sulfur Compounds. IX.[1] Preparation and Desulfurization of Optically Active 1,1-Diphenyl-3-mercaptopropan-2-ol[2]

BY CARL DJERASSI AND J. GROSSMAN

RECEIVED DECEMBER 12, 1956

Acid cleavage of spiro-(5-diphenylmethyl-1,3-oxathiolane-2,3′-cholestane) (I) followed by lithium aluminum hydride reduction of the resulting disulfide VII led to optically pure 1,1-diphenyl-3-mercaptopropan-2-ol (IV). Raney nickel desulfurization of this β-mercaptoethanol or of its O,S-dibenzoate (VI) furnished 1,1-diphenylpropan-2-ol or its benzoate, respectively. The rotations of this alcohol (IIIa) and its derivatives were identical with those of the earlier prepared desulfurization product of the hemithioketal I. These results show that no racemization occurs in the formation of alcohols by Raney nickel desulfurization of hemithioketals (*e.g.*, I) or of β-mercaptoethanols (*e.g.*, IV).

The observation[1] that Raney nickel desulfurization of hemithioketals (1,3-oxathiolanes) results in introduction of oxygen has led to an investigation of the scope of this reaction, and the appropriate experiments will be reported at a future time. We have also been concerned with the mechanism of this reaction and certain observations bearing on this aspect form the subject of the present paper.

The desulfurization of spiro-(5-diphenylmethyl-1,3-oxathiolane-2,3′-cholestane) (I) led[1] to over 50% each of cholestan-3-one (II) and 1,1-diphenylpropan-2-ol (III). This alcohol (III) was optically active ($[\alpha]D$ +5.8°, 3,5-dinitrobenzoate $[\alpha]D$ −46.8°), and since an antipode with the same optical properties (but opposite in sign) was isolated by desulfurization of a diastereoisomer of the hemithioketal I, it was assumed that complete re-

(1) Paper VIII, C. Djerassi, M. Gorman and J. A. Henry, THIS JOURNAL, 77, 4647 (1955).

(2) This work was carried out under contract No. DA-20-018-ORD-13474 with the Office of Ordnance Research, U. S. Army.

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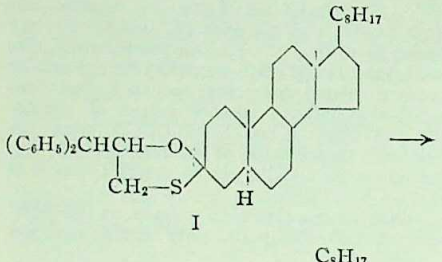
tention of optical activity is observed in this reaction. This leads to the mechanistically important conclusion that the oxygen present in the original hemithioketal I is the one eventually found in 1,1-diphenylpropan-2-ol (III) and that rupture of the C–O bond during the desulfurization occurred only at the position indicated by the dotted line[3] in structure I.

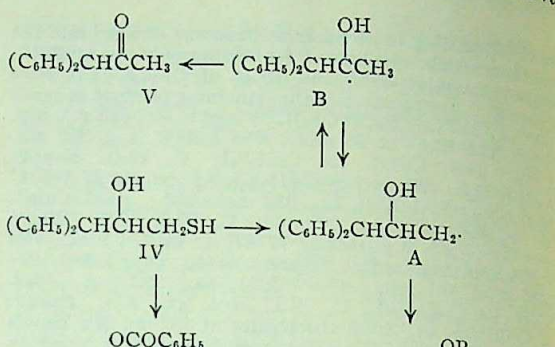


I

II III

The fact that both antipodes of 1,1-diphenylpropan-2-ol (III) were obtained does not exclude rigorously the possibility that partial racemization to *exactly the same extent* may have occurred in the desulfurization of the two diastereoisomeric hemithioketals (I), and independent confirmation was considered necessary since optically pure 1,1-diphenylpropan-2-ol (III) has not been described in the literature.[3a] The approach used in the present investigation also has a bearing on the mechanism of the desulfurization of β-mercaptoethanols, since it has been observed earlier[1] that desulfurization will yield a mixture of alcohol (predominant) and ketone. In the case of 1,1-diphenyl-3-mercaptopropan-2-ol (IV), both 1,1-diphenylpropan-2-ol (IIIa) and 1,1-diphenylacetone (V) were produced, and it could be demonstrated that they were not formed from each other by reduction or oxidation. Mechanistically, two simple paths can be suggested for the formation of the alcohol and these are not mutually exclusive: (a) the initially formed free radical A may pick up hydrogen to lead directly to the alcohol IIIa or (b) there may occur a 1,2-shift to the radical B which could either lose a hydrogen atom to give the ketone V or accept one, thus providing an alternate route to the alcohol IIIa.

Experimentally, these two mechanisms should be differentiable by studying the desulfurization of an optically active β-mercaptoethanol since only intermediate B would involve racemization. It was felt that by preparing optically active 1,1-diphenyl-3-mercaptopropan-2-ol (IV) both questions posed above could be answered in a satisfactory manner.



Since hemithioketals can be cleaved by means of acid,[4] the three diastereoisomeric hemithioketals I[1] constituted an ideal starting material for the preparation of an optically pure β-mercaptoethanol, which had the additional advantage of being crystalline. Treatment of any one of the three diastereoisomeric hemithioketals I[1] with hydrochloric acid in boiling *unpurified* dioxane yielded the same crystalline product, m.p. 140–142°, which was shown to be bis-(1,1-diphenyl-2-hydroxy-3-propyl) disulfide (VII).[5] Diastereoisomers B and C[1] yielded levorotatory material ([α]D − 168°) while diastereoisomer A[1] furnished the dextrorotatory antipode ([α]D +170°). Reduction of the appropriate disulfide VII with lithium aluminum hydride afforded the two optically pure antipodes of crystalline 1,1-diphenyl-3-mercaptopropan-2-ol (IV),[6] further characterized as the O,S-dibenzoate VI. The alcohol IV could be obtained directly from the hemithioketal I when the acid cleavage was conducted in *freshly purified* dioxane, suggesting that peroxides in the unpurified solvent were responsible for disulfide formation.

Raney nickel desulfurization of (+)-1,1-diphenyl-3-mercaptopropan-2-ol (IV) yielded 1,1-diphenylacetone (V) and 1,1-diphenylpropan-2-ol (IIIa) identical in all respects including rotation of the alcohol and its 3,5-dinitrobenzoate (IIIc) with specimens obtained earlier[1] by desulfurization of diastereoisomer A of the hemithioketal I. Furthermore, desulfurization of the O,S-dibenzoate VI[7] led to an optically active benzoate IIIb which had the same rotation as the benzoylation product of 1,1-diphenylpropan-2-ol obtained by desul-

(3) This is based on the assumption that complete retention of configuration rather than complete inversion of configuration is involved in the desulfurization of the hemithioketal.

(3a) NOTE ADDED IN PROOF.—It has been called to our attention that both antipodes of this alcohol and certain of its derivatives have been described already by D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **76**, 28 (1954).

(4) J. Romo, G. Rosenkranz and C. Djerassi, *ibid*, **73**, 4961 (1951).

(5) A control experiment with *dl*-1,1-diphenyl-3-mercaptopropan-2-ol (IV) demonstrated that it was converted into the disulfide VII when subjected to the same treatment as the hemithioketal I.

(6) The racemic substance already has been prepared by another procedure by C. Djerassi, M. Gorman, F. X. Markley and E. B. Oldenburg, THIS JOURNAL, **77**, 568 (1955).

(7) It is pertinent to note that no diphenylacetone (V) was encountered in this experiment.

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furization of either I or IV. On the basis of these results, we feel confident that the earlier assumed[1] retention of optical activity in the desulfurization of hemithioketals (such as I) is indeed justified and that the desulfurization of β-mercaptoethanols (such as IV) to the corresponding alcohol (such as III) does not involve the carbon atom bearing the alcoholic function.

Experimental[8]

Bis-(1,1-diphenyl-2-hydroxy-3-propyl) Disulfide (VII).—A mixture of 1.5 g. of isomer C (m.p. 153°) of spiro-(5-diphenylmethyl-1,3-oxathiolane-2,3′-cholestane) (I),[1] 100 cc. of *unpurified* dioxane, 8 cc. of concd. hydrochloric acid and 20 cc. of water was heated under reflux for 18 hr., cooled, diluted with water and extracted with ether. The washed and dried ethereal solution was evaporated to dryness and the residue was chromatographed on 50 g. of Fisher alumina deactivated in hexane solution with 5 cc. of 10% acetic acid. Elution with hexane gave 210 mg. of recovered hemithioketal I while 620 mg. of cholestan-3-one (II) (m.p. 127–129°) was eluted with 8:2 hexane–benzene. The desired disulfide (380 mg.) was eluted with 1:1 hexane–benzene and after two recrystallizations from hexane–ether yielded 320 mg. of colorless crystals, m.p. 140–142°, $[\alpha]_D$ −163° (*c* 0.55).

Anal. Calcd. for $C_{30}H_{30}O_2S_2$: C, 74.05; H, 6.22; S, 13.16; mol. wt., 486. Found: C, 74.40; H, 6.20; S, 13.26; Rast mol. wt., 438.

Similar cleavage of 2.0 g. of isomer A (m.p. 194°) yielded 0.42 g. of (+)-bis-(1,1-diphenyl-2-hydroxy-3-propyl) disulfide, m.p. 140–142°, $[\alpha]_D$ +170° (*c* 0.6), while 1.1 g. of isomer B (m.p. 175°) gave 0.2 g. of the (−)-disulfide VII.

The *dl*-disulfide, m.p. 110–112°, was prepared by boiling *dl*-1,1-diphenyl-3-mercaptopropan-2-ol (IV)[6] with unpurified dioxane–hydrochloric acid for 24 hr.

1,1-Diphenyl-3-mercaptopropan-2-ol (IV). (a) By Acid Cleavage in Purified Dioxane of Spiro-(5-diphenylmethyl-1,3-oxathiolane-2,3′-cholestane) (I).—A solution of 4.0 g. of isomer A[1] of the hemithioketal I was heated under reflux for 24 hr. in 200 cc. of freshly purified (distilled from sodium) dioxane with 16 cc. of concd. hydrochloric acid and 40 cc. of water. The mixture was processed as above and after separating much unreacted hemithioketal and some cholestan-3-one, 280 mg. of the desired (+)-1,1-diphenyl-3-mercaptopropan-2-ol (IV) was obtained from the hexane–benzene (1:1) eluates; m.p. 69–72°, raised after recrystallization from hexane–ether to m.p. 74–75°, $[\alpha]_D$ +38° (*c* 1.05). The antipode ($[\alpha]_D$ −36°) was obtained in the same manner from isomer C.

Anal. Calcd. for $C_{15}H_{16}OS$: C, 73.75; H, 6.60. Found: C, 73.29; H, 6.88.

(b) By Lithium Aluminum Hydride Reduction of Bis-(1,1-diphenyl-2-hydroxy-3-propyl) Disulfide (VII).—A solution of 300 mg. of the (−)-disulfide VII in 50 cc. of tetrahydrofuran was heated under reflux for 24 hr. with a large excess of lithium aluminum hydride. Decomposition of the reagent with ethyl acetate followed by addition of 10% hydrochloric acid and isolation with ether yielded 280 mg. of the above described (−)-1,1-diphenyl-3-mercaptopropanol, m.p. 70–74°, which was raised to 74–75° after one recrystallization. Similar treatment of 100 mg. of the (+)-disulfide VII gave 80 mg. of (+)-1,1-diphenyl-3-mercaptopropan-2-ol (IV).

1,1-Diphenyl-3-mercaptopropan-2-ol O,S-Dibenzoate (VI).—A mixture of 200 mg. of (+)-1,1-diphenyl-3-mercaptopropan-2-ol (IV), 1 cc. of benzoyl chloride and 5 cc. of pyridine was allowed to stand at room temperature for 24 hr., diluted with water, and the product was extracted with ether. After appropriate washing and drying, the residue was recrystallized from methanol to furnish 230 mg. of the (+)-dibenzoate, m.p. 129–131°, $[\alpha]_D$ +69° (*c* 0.70); $\lambda_{max}^{CHCl_3}$: 5.76, 5.93, 7.82, 8.43 and 8.95 μ.

Anal. Calcd. for $C_{29}H_{24}O_3S$: C, 76.97; H, 5.35; S, 7.07. Found: C, 76.91; H, 5.45; S, 6.80.

Similar treatment of the *dl*-mercaptopropanol[6] yielded ***dl*-1,1-diphenyl-3-mercaptopropan-2-ol dibenzoate** (VI), m.p. 146–147°, the infrared spectrum (chloroform solution) of which was identical with that of the (+)-isomer.

Anal. Found: C, 77.45; H, 5.44; S, 6.81.

Desulfurization of 1,1-Diphenyl-3-mercaptopropan-2-ol (IV).—A 350-mg. sample of (+)-1,1-diphenyl-3-mercaptopropan-2-ol in 100 cc. of ethyl methyl ketone was heated with stirring under reflux with 6 g. of 3 day old W-2 Raney nickel catalyst (deactivated by heating for 1 hr. in ethyl methyl ketone solution). The reaction mixture was processed in the previously described manner[1] including chromatography. Elution with hexane gave 65 mg. of diphenylacetone (V), m.p. 55–58° (identified by infrared spectrum), while the desired diphenylpropanol (IIIa)[1] (150 mg., m.p. 56–58°, $[\alpha]_D$ +6°) was removed with 1:1 hexane–benzene. The alcohol was converted into (+)-1,1-diphenylpropan-2-ol 3,5-dinitrobenzoate (IIIc)[1] which exhibited m.p. 154–155°, $[\alpha]_D$ −44.4° (*c* 0.95) after recrystallization from methanol, and into (+)-1,1-diphenylpropan-2-ol benzoate, m.p. 78–79°, $[\alpha]_D$ +18° (*c* 2.03).

Desulfurization of 1,1-Diphenyl-3-mercaptopropan-2-ol O,S-Dibenzoate (VI).—The desulfurization of 300 mg. of *dl*-1,1-diphenyl-3-mercaptopropan-2-ol O,S-dibenzoate was carried out in the above described manner with 6 g. of 4 day old W-2 Raney nickel catalyst in 100 cc. of ethyl methyl ketone for 2 days. Recrystallization of the crude reaction product yielded 120 mg. of *dl*-1,1-diphenylpropan-2-ol benzoate (m.p. 90–92°). In order to ensure[7] the absence of 1,1-diphenylacetone in the mother liquors, these were saponified with 10% methanolic potassium hydroxide solution, and the total product was found not to possess any carbonyl band in the infrared. Chromatography yielded 55 mg. of 1,1-diphenylpropan-2-ol, m.p. 59–61°.

When the desulfurization was carried out with (−)-1,1-diphenyl-3-mercaptopropan-2-ol O,S-dibenzoate, there was obtained after recrystallization from methanol (−)-1,1-diphenylpropan-2-ol benzoate (IIIb), m.p. 77–79°, $[\alpha]_D$ −17° (*c* 0.43), the infrared spectrum of which was identical with that of the *dl*-benzoate.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.52; H, 6.54.

DETROIT, MICHIGAN

(8) All melting points were determined on the Kofler block. We are indebted to Mrs. Dolores Phillips for the infrared spectral measurements and to Dr. A. Bernhardt (Mülheim, Germany) for the microanalyses. All rotations were measured in chloroform solution in 1-dcm. tubes.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthesis of the Thieno[3,2-b]pyrrole System

BY H. R. SNYDER, L. A. CARPINO,[1] J. F. ZACK, JR.,[2] AND J. F. MILLS[3]

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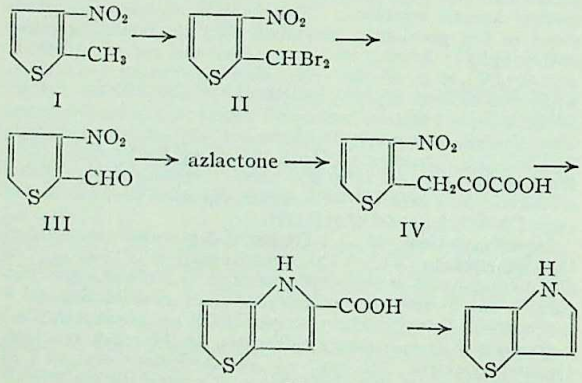
The synthesis of thieno[3,2-b]pyrrole (VI) was carried out by conversion of 3-nitro-2-methylthiophene to 3-nitro-2-thenaldehyde followed by application of the azlactone synthesis to give 3-nitro-2-thienylpyruvic acid, which was reduced to the thienopyrrolecarboxylic acid (V). Decarboxylation of V to thieno[3,2-b]pyrrole (VI) was effected by heat in an evacuated sealed tube. A similar reaction scheme proceeding from 2-nitro-3-methylthiophene was examined in order to obtain the isomeric thienopyrrole, but the final step, reduction of the pyruvic acid, was unsuccessful.

A number of thiophene analogs of physiologically active compounds have been found to be active as anti-metabolites. For example, β-3-thienylalanine inhibits the growth of the microorganisms, *S. cervisiae* and *E. coli*.[4] Attention was directed toward the preparation of a thiophene analog of indole with the hope of converting it to the corresponding tryptophan by one of the well-known methods.

The synthesis of thieno[3,2,-b]pyrrole (VI) was carried out by the modified Reissert method[5] as indicated (I → VI).

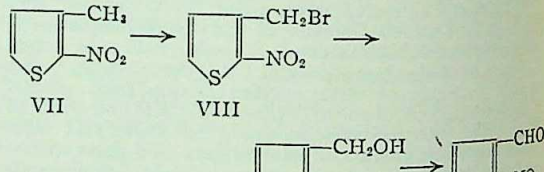


For the preparation of 3-nitro-2-methylthiophene (I) a modification of the method of Rinkes was used.[6] 2-Methylthiophene was converted to 5-methyl-2-acetylthiophene by the method of Hartough and Kosak.[7] The ketone was oxidized to 2-methyl-5-thenoic acid with alkaline hypochlorite.[8] Nitration and subsequent decarboxylation gave I.

One or two moles of N-bromosuccinimide in boiling carbon tetrachloride converted I to the mono- or dibromide II, and the latter was transformed to 3-nitro-2-thenaldehyde (III) *via* the diacetate. The pyruvic acid (IV), which was prepared by hydrolysis of the azlactone of III, was reduced to the thienopyrrolecarboxylic acid (V) by means of aqueous ammonia and ferrous sulfate.[9] This acid (V) is similar in physical appearance and melting point to indole-2-carboxylic acid, and like the latter it imparts a red-brown coloration[10] to a ferric chloride solution. It differs from indole-2-carboxylic acid in that it chars on melting rather than undergoing smooth decarboxylation. Attempted decarboxylation with mercuric acetate also failed. Decarboxylation of V was effected by heating the acid in an evacuated tube.

Thieno[3,2,-b]pyrrole is a white crystalline substance, melting at about 30°, that has an odor very similar to that of indole. When exposed to air at room temperature, it decomposes. It forms a red picrate that decomposes on standing in alcohol. The infrared spectrum (Fig. 1) is similar to that of indole in many respects.

A similar method was examined for the preparation of the isomeric acid. The key steps leading to the aldehyde X are



In contrast to the reactivity of 3-nitro-2-methylthiophene with N-bromosuccinimide, the isomeric compound VII is unaffected by this reagent in boiling carbon tetrachloride.[11] However, it was found that reaction could be made to occur by substituting ethylene dibromide for the lower-boiling solvent.

It was possible to convert the bromide VIII directly to the aldehyde X by oxidation with selenium dioxide, but the results were not consistent.[12] A more reliable method involved oxidation of the alcohol IX by N-bromosuccinimide in a method similar to that of Grob and Schmid.[13]

Conversion of the aldehyde X to the corresponding pyruvic acid was carried out by the method outlined above. Reduction of the pyruvic acid gave a non-crystalline product which underwent decomposition on attempted purification.

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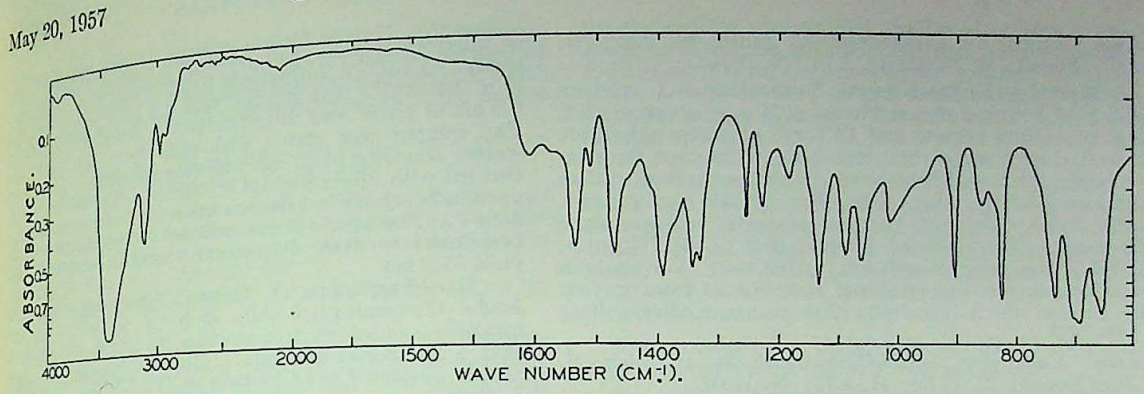

Fig. 1.

Experimental

2-Methyl-5-thenoic Acid.—This acid was prepared by acylation of 2-methylthiophene followed by a haloform reaction according to the procedures described by Hartough, *et al.*[7,8]

2-Methyl-3-nitro-5-thenoic Acid.—The following procedure is a convenient modification of the method of Rinkes.[6] Fuming nitric acid (300 g., sp. gr. 1.5) was added slowly to 700 ml. of acetic anhydride contained in a 2-l. round-bottomed flask fitted with a Hershberg stirrer and cooled by means of a Dry Ice–acetone mixture. The resulting solution was cooled to −12°, and 210 g. of finely powdered 2-methyl-5-thenoic acid was added, with stirring, in portions of 1–2 g., during the course of 45 minutes. A pale pink solid separated; after addition of the acid, the mixture was stirred for ten minutes, during which time the temperature fell to −20°. The crystalline solid was filtered and triturated with 400 ml. of water and 100 g. of ice. When the ice had melted, the pink solid was collected and washed three times with water; the wet product was recrystallized from 95% ethanol. Large orange-pink crystals (126.5 g., 45.7%), m.p., 178–180°, separated on standing. A sample was sublimed at 160° (0.8 mm.) to yield white crystals, m.p. 180–181° (lit.[6] 181°).

A by-product, 2-methyl-3,5-dinitrothiophene, can be isolated by pouring the acetic anhydride filtrate onto 2 kg. of ice and 2 l. of water, filtering the sticky red solid which precipitates and recrystallizing it from ethanol and then from high-boiling petroleum ether to give tan colored crystals (8–15 g.) melting at 97–99° (lit.[6] 99–100°).

3-Nitro-2-methylthiophene.—The following is a necessary modification of Rinkes' procedure.[6] A 1-l. round-bottomed flask containing a mixture of 163 g. of the nitro acid, 290 g. of quinoline and 6 g. of copper powder was fitted with a thermometer suspended into the mixture. A length of rubber tubing leading to an aspirator was loosely inserted into one of the necks of the flask to draw off vapors of water and quinoline. The flask was heated slowly with an electrical heating mantle at such a rate that the internal temperature rose approximately ten degrees every five minutes. The mass became fluid at about 85–95° and, after 55 minutes, the temperature had risen to 210°. At this point the mixture was cooled under tap water, and a solution of 600 ml. of water and 250 ml. of 85% phosphoric acid was added. The mixture was steam distilled; the distillate (5 l.) was acidified with a little dilute hydrochloric acid (1:1), cooled in an ice-bath, and the crude nitro compound (74.5 g., 59.7%) was collected. Recrystallization from low-boiling petroleum ether gave 64 g. of nearly white crystals, m.p. 44–46°. From the filtrate there was obtained an additional 5.5 g. of pure product making the total yield 69.5 g. (55.5%). It was possible to decarboxylate the acid by the mercuric acetate method, but the yield was lower (46%).[14]

3-Nitro-2-thenyl Bromide.—A solution of 14 g. of 3-nitro-2-methylthiophene (m.p. 44–46°) dissolved in 100 ml. of carbon tetrachloride was dried by distillation of a little of the solvent. There was then added, all at once, 17.3 g. of N-bromosuccinimide (recrystallized from water, dried over sulfuric acid) and 0.05 g. of benzoyl peroxide, and the mixture was refluxed for 24 hr. The mixture was cooled in an ice-bath and the crystalline succinimide was separated. The filtrate was evaporated on the steam-bath to an orange, slightly lachrymatory, thick liquid which solidified on cooling in an ice-bath. This was triturated with low-boiling petroleum ether and washed out of the flask with the aid of this solvent to give 20 g. (92%) of sticky orange solid. The crude bromide was recrystallized from about 400 ml. of low-boiling petroleum ether, which deposited 10 g. (m.p. 57–60°) of light yellow needles. An additional 1.1 g. of pure product was obtained from the filtrate so that the total yield was 11.1 g. (51.2%). The analytical sample melted at 60–62°.

Anal. Calcd. for $C_5H_4O_2NSBr$: C, 27.04; H, 1.82; N, 6.31. Found: C, 27.20; H, 2.08; N, 6.39.

3-Nitro-2-thenyl Acetate.—The acetolysis of 3-nitro-2-thenyl bromide was carried out by the method of Shriner, Fuson and Curtin.[15] For analysis the ester was recrystallized once from ethanol and twice from low-boiling petroleum ether, from which it separated in the form of slender white needles melting at 58.5–60.5°.

Anal. Calcd. for $C_7H_7O_4NS$: C, 41.80; H, 3.51; N, 6.96. Found: C, 42.08; H, 3.58; N, 6.92.

3-Nitro-2-thenal Bromide.—A mixture of 1.1 g. of 3-nitro-2-methylthiophene, 2.8 g. of N-bromosuccinimide, 0.01 g. of benzoyl peroxide and 25 ml. of dry carbon tetrachloride was refluxed for 20 hr. The solution was cooled in an ice-bath, the succinimide removed by filtration and the filtrate evaporated on the steam-bath to a thick reddish liquid (1.8 g., 75.8%) which solidified on cooling. For analysis it was recrystallized three times from low-boiling petroleum ether, which deposited the dibromide in the form of faintly yellow triangular plates melting at 72.8–74°.

Anal. Calcd. for $C_5H_3NO_2Br_2S$: C, 19.95; H, 1.01; N, 4.65. Found: C, 19.77; H, 1.20; N, 4.42.

3-Nitro-2-thenaldehyde.—A mixture of 16.5 g. of 3-nitro-2-methylthiophene, 42 g. of N-bromosuccinimide (recrystallized from water, dried over sulfuric acid), 0.15 g. of benzoyl peroxide and 200 ml. of dry carbon tetrachloride was refluxed for 66 hr., cooled in an ice-bath and filtered to remove the succinimide along with some unreacted N-bromosuccinimide.

The filtrate was evaporated on the steam-bath *in vacuo*, and to the remaining oil were added 120 ml. of ethanol, 150 ml. of water and 25 g. of sodium acetate. The resulting mixture was refluxed for 1.5 hr., 50 ml. of hydrochloric acid (sp. gr. 1.18) was added, and the refluxing was continued for 0.75 hr. The solution was then treated with Darco, the filtrate diluted with 1 l. of saturated sodium chloride solution and the resulting mixture extracted with four 50-ml. portions of ether. The ether solution was dried over magnesium sulfate and the solvent removed by distillation. The residue was distilled from a Claisen flask and 6.3 g. (34.8%) of yellow liquid, which partially solidified in the receiver, was collected at 113–127° (2–3 mm.). The aldehyde became reddish brown on standing and therefore was analyzed as the semicarbazone which forms, on recrystallization from dimethylformamide, small yellow crystals melting at 247–248° dec.

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Anal. Calcd. for $C_6H_6O_3N_4S$: C, 33.64; H, 2.82; N, 26.16. Found: C, 33.92; H, 2.70; N, 26.40.

2-Methyl-4-(3-nitro-2-thenal)-5-oxazolone.—A mixture of 6.3 g. of 3-nitro-2-thenaldehyde, 4.74 g. of acenturic acid, 0.2 g. of sodium acetate and 13.7 ml. of acetic anhydride was heated for 1 hr. on the steam-bath, whereupon the mixture became red, and bright red crystals separated. After cooling at 5–10° for about 5 hr., the crystals were filtered, washed twice with small portions of acetic acid and once with water. The air-dried product (6.2 g., 64.7%, m.p. 182–185°) was pure enough for further use. For analysis the azlactone was recrystallized three times from methyl ethyl ketone, which deposited yellow-orange needles melting at 185–186°.

Anal. Calcd. for $C_9H_6N_2O_4S$: C, 45.38; H, 2.54; N, 11.76. Found: C, 45.80; H, 2.73; N, 11.67.

When an attempt was made to recrystallize the azlactone (2 g.) from 95% ethanol the solid went into the boiling solution slowly but did not separate on cooling. After evaporation of the alcohol at room temperature, 1.3 g. of reddish brown crystals were deposited, m.p. 147–150°. This compound, in contrast to the azlactone, is easily soluble in hot ethanol and was recrystallized for analysis from this solvent, which deposited a mass of lemon-yellow needles melting at 150.5–152°. Presumably this is ethyl α-acetamino-β-(2-nitro-3-thienyl)-acrylate, which was formed by opening of the azlactone ring by ethanol.

Anal. Calcd. for $C_{11}H_{12}O_5N_2S$: C, 46.48; H, 4.26; N, 9.86. Found: C, 46,81; H, 4.16; N, 10.00.

3-Nitro-2-thienylpyruvic Acid.—A mixture of 6.1 g. of 2-methyl-4-(3-nitro-2-thenal)-5-oxazolone (m.p. 182–185°) and 170 ml. of 1 *N* hydrochloric acid was refluxed for 2 hr. The yellow-orange solution was treated with Darco, filtered and allowed to cool in the ice-chest overnight. The yellow solid which separated (4.5 g., 82.1%) was recrystallized from acetic acid, which deposited 3.5 g. of tiny yellow crystals, m.p. 195–197° dec. From the filtrates, diluted with water, there was obtained an additional 0.3 g. of the pure acid. The total yield was 3.8 g. (69%). The analytical sample, prepared exactly as described above from a different batch of the azlactone, was recrystallized twice from acetic acid, which deposited tiny yellow needles, m.p. 191.5° dec. It is not known why the product obtained above (m.p. 195–197°) melted at a higher temperature than the analytical sample.

Anal. Calcd. for $C_7H_5O_6NS$: C, 39.07; H, 2.34; N, 6.51. Found: C, 39.43; H, 2.14; N, 6.62.

Thieno(3,2-b)pyrrole-2-carboxylic Acid (V).—A solution of 30 g. of ferrous sulfate heptahydrate in 33.5 ml. of warm water was added in one portion to the deep violet-red solution of 3.5 g. of 3-nitro-2-thienylpyruvic acid (m.p. 195–197°) in 33.5 ml. of water and 23.5 ml. of concentrated aqueous ammonia (sp. gr. 0.90). The black mixture was warmed on the steam-bath for 0.5 hr. with occasional shaking. The mixture was filtered and the residue on the filter extracted with 20 ml. of hot dilute aqueous ammonia. The resulting brown solution was treated with Darco and evaporated on the steam-bath *in vacuo* until the ammonium salt began to separate. The mixture was cooled, acidified with hydrochloric acid (sp. gr. 1.18) and the brownish powdery solid collected (1.3 g., m.p. 193–195° dec., yield 48%). Recrystallization from ethanol–water (1:1) gave 0.9 g. (33.3%) of brown needles, m.p. 197–198° dec. After three recrystallizations from ethanol–water (1:1), the acid separated in the form of small white needles, m.p. 193–194° dec., which darkened slightly on standing.

Anal. Calcd. for $C_7H_5O_2NS$: C, 50.31; H, 3.02; N, 8.38. Found: C, 50.58; H, 3.18; N, 8.85, 8.52.

Since thieno(3,2-b)pyrrole-2-carboxylic acid undergoes extensive charring on melting, it could not be decarboxylated by heating above the melting point. On heating at 155–160° (0.5–1.5 mm.), the acid merely sublimes. On shaking with a mixture of 10% ferric chloride solution and ethanol (1:1), the acid develops a reddish brown color. The acid dissolves in concentrated sulfuric acid to give a bright yellow-orange solution which develops a red color on standing.

Chromatography of Thieno(3,2-b)pyrrole-2-carboxylic Acid.—Silicic acid (9.0 g.) was ground with 5 ml. of water in a mortar, slurried with 40 ml. of chloroform and packed in a 50-ml. buret. The column was washed with 200 ml. of chloroform that had been previously saturated with water. Thieno(3,2-b)pyrrole-2-carboxylic acid (32.3 mg., m.p. 193–194°) was ground with 0.5 g. of silicic acid and 0.5 ml. of water, and this material was added to the column. The column was eluted with chloroform saturated with water; fractions of 10 ml. size were collected. These were titrated with dilute sodium hydroxide. The thieno(3,2-b)-pyrrole-2-carboxylic acid was collected in fractions number 3 to 7. The product was isolated by acidification of the basic extracts of the chloroform fractions; m p. 203–204°, yield 31.2 mg.

Decarboxylation of Thieno(3,2-b)pyrrole-2-carboxylic Acid.—Chromatographically pure V (178.2 mg., 1.07 mmoles) was sealed in a reaction tube that was equipped with a break-seal side arm. The reaction tube was completely immersed in an oil-bath at 210–220° for 30 minutes. A clear liquid condensed on the walls of the tube when it cooled. The break-seal side arm was attached to a high vacuum line and the carbon dioxide was distilled to a calibrated manometer from a −90° trap. The amount of carbon dioxide found was 1.07 mmoles (100%). The vapor pressure was measured at −110° and found to be 29 mm. (carbon dioxide has a vapor pressure of 26 mm. at −110°). The reaction tube was washed out with carbon disulfide, and the extracted material was sublimed at 10^{-3} mm. onto a cold finger cooled with a Dry Ice–acetone mixture. A total of 45.0 mg. (36.6%) of a white product was obtained. The material had an odor very similar to that of indole and melted between 30 and 35°. The infrared spectrum (Fig. 1), determined as a smear, was consistent with the proposed structure (VI). The product decomposes at room temperature when exposed to the air for a few minutes. A solution of picric acid in ethanol was added to the material and a red precipitate resulted. The picrate decomposes to an amorphous black powder on standing overnight in ethanol.

A control experiment was carried out with 1 mmole of indole-2-carboxylic acid. A 100% yield of carbon dioxide and a 60% yield of indole were realized.

Attempted Mannich Reaction with Thieno(3,2-b)pyrrole.—Glacial acetic acid (60 mg., 1.0 mmole) was added to 46 mg. (0.5 mmole) of piperidine followed by 50 mg. of formalin. Thieno(3,2-b)pyrrole (45 mg., 0.366 mmole) was added, and the solution was allowed to stand for 5 hr. The solution was washed into a centrifuge tube, and 2 ml. of 2.0 *N* sodium hydroxide was added. A very small amount of oil resulted. No crystalline product could be isolated.

A control reaction was carried out with 1 mmole of indole. A 75% yield of the piperidine Mannich base of indole resulted.

2-Nitro-3-methylthiophene.—To prepare this compound (46% yield) the method of Rinkes[16] was used with certain modifications. In a typical run 100 g. of 3-methylthiophene dissolved in 200 ml. of acetic acid was added during 15–20 minutes to a nitrating mixture of 200 ml. of acetic acid and 100 g. of fuming nitric acid (sp. gr. 1.5) at −15 to −12°. If the addition was not carried out rapidly, much tar was formed.

2-Nitro-3-thenyl Bromide.—A mixture of 132 g. of 2-nitro-3-methylthiophene, 200 ml. of dry ethylene dibromide, 206 g. of N-bromosuccinimide (recrystallized from hot water and dried over sulfuric acid) and 0.8 g. of benzoyl peroxide was refluxed gently for 3 hr. During the first hour the solution had a red-brown color, and vapors of bromine escaped at the top of the condenser. The color abruptly became dark brown and bromine vapors were no longer evolved. The solution was cooled in an ice-bath, 100 ml. of carbon tetrachloride was added and the dark brown succinimide was filtered and washed with three 50-ml. portions of carbon tetrachloride. The filtrate was washed with four 200-ml. portions of water, dried over magnesium sulfate, and the solvent was distilled from a steam-bath with the aid of a water aspirator. The residue was distilled under vacuum from a 1-l. flask (a large flask was required because of excessive frothing during the later stages of the distillation) fitted with a 6-in. Vigreux column. Two fractions were collected: fraction I, 29 g., b.p. 88–110° (1.1–1.3 mm.); fraction II, 123 g., b.p. 110–147° (1.2–3.0 mm.).

Both fractions solidified on standing. The lower-boiling material was mainly unreacted 2-nitro-3-methylthiophene. The higher boiling fraction was mainly 2-nitro-3-thenyl

(16) I. Rinkes, *Rec. trav. chim.*, **52**, 1052 (1933).

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bromide and corresponded to a yield of 60%. It was pure enough for further use, but if desired it could be purified by recrystallization from low-boiling petroleum ether from which it separated in the form of long white needles which melted at 63–65°.

Anal. Calcd. for $C_5H_4NO_2SBr$: C, 27.04; H, 1.82; N, 6.31. Found: C, 27.48; H, 1.80; N, 6.31.

The bromide was characterized as the pyridinium salt which was prepared by allowing the components to stand in dry ether. The salt separated from ethanol in the form of shiny leaflets, m.p. 232–233° dec.

Anal. Calcd. for $C_{10}H_9N_2O_2BrS$: C, 39.87; H, 3.00. Found: C, 40.07; H, 2.89.

2-Nitro-3-thenyl Alcohol (XXXI).—A mixture containing 161.5 g. of 2-nitro-3-thenyl bromide (crude, as prepared above), 161.5 g. of sodium formate and 1700 ml. of 50% ethanol was refluxed for a period of 2 hr., and then 200 ml. of hydrochloric acid (sp. gr. 1.18) was added and the solution refluxed for 1.5 hr. longer. The hot solution was treated with Darco and diluted with 2 l. of water. The aqueous solution was saturated with sodium chloride, and the oil was extracted with ether. The ether solution was dried over magnesium sulfate, and after removal of the solvent by distillation from a steam-bath, the residue was distilled under vacuum. Two fractions were collected: fraction I, 15 g. (12.8%), b.p. 98–114° (0.2–0.55 mm.); fraction II, 63.7 g. (55%), b.p. 129–146° (0.6–0.8 mm.).

Both fractions solidified during collection. The second fraction was sufficiently pure for conversion directly to the aldehyde in the next step, while the first fraction was purified by crystallization from methanol or 70% ethanol, from which the alcohol separated in the form of yellowish crystals, m.p. 90–92°.

Anal. Calcd. for $C_5H_5O_3NS$: C, 37.73; H, 3.17; N, 8.80. Found: C, 38.32; H, 3.12; N, 8.71.

2-Nitro-3-thenaldehyde.—In a 1-l. round-bottomed flask fitted with a reflux condenser and Hershberg stirrer were mixed 76.7 g. of crude 2-nitro-3-thenyl alcohol (prepared as given above), 48 g. of finely powdered calcium carbonate, 85.2 g. of N-bromosuccinimide (recrystallized from water, dried over sulfuric acid) and 500 ml. of carbon tetrachloride (dried by distillation). The mixture was refluxed gently with stirring. During the first hour of heating, the mixture was watched carefully, because the refluxing became vigorous enough to require removal of the source of heat momentarily. The solution became brown in color, and some bromine vapor escaped from the top of the condenser. After a total of 3.5 hr. of refluxing, the reaction flask was cooled in an ice-bath and the orange solid filtered off. The orange residue was washed on the filter with three small portions of carbon tetrachloride, and the combined yellow filtrates were dried over magnesium sulfate. After removal of the solvent *in vacuo* on the steam-bath, the residue was distilled under vacuum. Two fractions were collected: fraction I, 10.1 g. (13.4%), b.p. 84–87° (0.3 mm.); fraction II, 35.1 g. (46.5%), b.p. 91–112° (0.3–0.9 mm.).

Both fractions partially crystallized on standing. Fraction I was less pure than fraction II, although it could be used in the next step without difficulty. For analysis, a small amount of fraction II was recrystallized twice from a mixture of low-boiling petroleum ether and absolute ether (1:1), which deposited the aldehyde in the form of short yellow needles, m.p. 55.5–56.5°.

Anal. Calcd. for $C_5H_3O_3NS$: C, 38.21; H, 1.92; N, 8.91. Found: C, 38.59; H, 2.09; N, 8.92.

The semicarbazone was prepared in the usual manner. For analysis it was recrystallized from dimethylformamide, from which it separated in the form of small bright yellow needles, m.p. 265–266° dec.

Anal. Calcd. for $C_6H_6O_3N_4S$: C, 33.64; H, 2.82; N, 26.16. Found: C, 34.02; H, 2.98; N, 26.02.

2-Methyl-4-(2-nitro-3-thenal)-5-oxazolone.—This azlactone was prepared in 55.8% yield from X exactly as given for the isomeric compound except that nitromethane was used to recrystallize the product for analysis. The oxazolone separated in the form of orange plates, m.p. 196–198° dec.

Anal. Calcd. for $C_9H_6N_2O_4S$: C, 45.38; H, 2.54; N, 11.76. Found: C, 45.58; H, 2.56; N, 11.87.

2-Nitro-3-thienylpyruvic Acid.—This acid was prepared in 51.3% yield as given for the isomeric compound IV except that the heating was continued for 3 hr., since this isomer proved to be more stable toward hydrolysis. The compound separated from acetic acid in the form of bright yellow needles, m.p. 186° dec.

Anal. Calcd. for $C_7H_5O_5NS$: C, 39.07; H, 2.34; N, 6.51. Found: C, 39.36; H, 2.42; N, 6.45.

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URBANA, ILLINOIS

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Phosphopeptides Obtained by Partial Acid Hydrolysis of α-Casein[2]

BY N. J. HIPP, M. L. GROVES AND T. L. MCMEEKIN

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A partial acid hydrolysis of α-casein was resolved into fractions containing phosphopeptides by chromatography on Dowex 50. The impure fractions were further purified by chromatography and the electrophoretically pure subfractions were analyzed for their amino acid composition on Dowex 50. In addition to phosphoserine the following dipeptides were found: phosphoserylglutamic acid, phosphoserylalanine and phosphoserylphosphoserine. The extensive destruction of serine on complete hydrolysis of the peptides is discussed.

The physiological significance of phosphorus in casein and other phosphoproteins has been the subject of a number of recent investigations.[3] The presence of phosphorus is also advantageous in structural studies on casein since partial hydrolysis with enzymes and acid produces phosphopeptides which can be uniquely separated from the non-phosphopeptides. Numerous phosphopeptide fractions have been prepared from casein, particularly by enzymic digestion.[4] Lipmann[5] has shown that at least 50% of the casein phosphorus is present as ser-

(1) A laboratory of the Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture.

(2) Presented in part before the Division of Biological Chemistry, 128th Meeting of the American Chemical Society, Minneapolis, Minnesota, September 11–16, 1955.

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ine phosphate after partial acid hydrolysis. de Verdier[6] has isolated small amounts of phosphothreonine from casein. Methods have been described by de Verdier[6] and Ågren and Glomset[7] for the fractionation of phosphopeptides from partial hydrolysates of casein.

The present study describes the separation and composition of some of the phosphopeptides produced by partial acid hydrolysis of α-casein

Experimental

Partial Acid Hydrolysis of Casein.—Exploratory experiments established that heating at 80° for 10 hours in 2.2 *N* hydrochloric acid was to be preferred for preparing phosphopeptides with minimum formation of inorganic phosphorus. These conditions were observed, using a 3-g. sample of finely divided α-casein prepared by the urea method[8] suspended in 360 ml. of hydrochloric acid. At the end of hydrolysis the solution was light brown and contained a small amount of insoluble material. Hydrochloric acid was removed at 25–30° with the Craig rotary evaporator.[9] Evaporation was repeated three times after the addition of water. The residue was then extracted with 0.05 *N* hydrochloric acid and the insoluble material removed by centrifugation. The soluble portion was made to 100-ml. volume. Under these conditions of hydrolysis, 40% of the peptide bonds of α-casein were broken as was shown by Van Slyke amino nitrogen analyses. The insoluble material accounted for 10% of the original nitrogen or phosphorus and was probably essentially unchanged α-casein.

Phosphoserine and phosphotyrosine used for identity purposes, were made by the method of Levene and Schormüller[10] as modified by Plimmer.[11] The analysis and properties of the phosphoserine have previously been reported.[12] The sample of synthetic phosphothreonine was kindly furnished by Dr. Bernard J. Jandorf of the Army Chemical Center, Maryland.

Color values for the phospho-amino acids on a molar basis relative to leucine using the photometric ninhydrin method of Moore and Stein[13] were as follows: phosphoserine 1.03, phosphotyrosine and phosphothreonine 0.94. With a Dowex 50-X8,[14] 120 mesh (see below), 0.9 × 100 cm. resin column using 0.05 *N* hydrochloric acid as influent as used by Schaffer, *et al.*,[15] phosphoserine and phosphothreoine are resolved into sharp peaks at 92 and 163 ml., respectively, and phosphotyrosine is resolved into a broader peak at 460 ml.

Ion-exchange Chromatography.—Dowex 50-X8 resin, 200–400 mesh, was treated with hydrochloric acid and 1 *N* sodium hydroxide as described by Moore and Stein.[16] The resin used for the separation of the phosphopeptides was passed through a 120-mesh screen and that used for the determination of amino acids through a 200-mesh screen. The hydrogen form of the resin that was used for the separation of phosphopeptides was obtained by washing the sodium form in a column with 1 *N* hydrochloric acid until the effluent was free of salt as determined by evaporation of 200-ml. aliquots. It was found that the completeness of the removal of sodium ion from the resin had a pronounced effect on the resolution of the phosphopeptides on elution with dilute hydrochloric acid. All of the resin columns were poured in at least five sections with a slurry of the resin in the first influent solvent and at least five hold-up volumes were run through the column before it was charged. A column 0.9 × 100 cm. was used for the exploratory runs of acid hydrolysates and a column 3.8 × 100 cm. for the 3-g. hydrolysate. Sufficient pressure was applied to the column to give a flow rate of 4 ml. per hour with the smaller columns and 50 ml. per hour for the large columns. Fractions of 1 ml. were collected from the small column and 8.5 ml. from the large column with an automatic fraction collector. The location of the phosphopeptides was determined by the photometric ninhydrin method of Moore and Stein[13] using 0.5-ml. aliquots from the large columns. The location of the inorganic phosphorus was determined by spot tests[17] and estimated by the method of Sumner.[18]

The Dowex 1-X10 resin, 200–400 mesh, was washed on a fritted glass Buchner funnel with 500 ml. of 2 *N* sodium hydroxide using slight suction. After washing with water followed by 1 *N* hydrochloric acid and then water, the resin was suspended in about 5 times its volume of water and after standing 2 hours the supernatant was decanted. The last step was repeated about 5 times until the final wash was almost clear. The resin was then passed through a 120-mesh screen.

Paper Chromatography.—Two-dimensional paper chromatograms for the qualitative determination of amino acids were prepared by the descending method as described by Levy and Chung[19] using butanol–acetic acid–water (4:1:5) and buffered phenol.

For the determination of the homogeneity of phosphopeptide fractions one-dimensional chromatograms using the butanol–acetic acid–water solvent system has been found to be useful. For the slow-moving acidic phosphopeptides the best results are obtained by running the chromatogram for more than 24 hours and allowing the solvent to drip from the serrations at the end of the paper.

Paper Electrophoresis.—The method described by Kunkel and Tiselius[20] with Whatman 3-MM paper between glass plates was used. The best results were obtained by performing the experiments in a cold room at 4°. A potential of 400 volts was applied to the paper between glass plates 15 × 45.5 cm. using 0.1*N* acetic acid as the buffer. For paper electrophoresis of the phosphopeptides the use of acetic or formic acid as buffer gave satisfactory results. No satisfactory resolution of phosphopeptides was obtained when Veronal was used as the buffer at *p*H 8.6.

N-Terminal Group Analysis.—The peptides were treated with the Sanger reagent,[21] 1-fluoro-2,4-dinitrobenzene (DNFB), as described by Davie and Neurath.[22] The DNP peptides were hydrolyzed with constant boiling hydrochloric acid in sealed tubes for 8 hours at 105° since Levy and Li[23] have found that 90% of the DNP terminal serine is destroyed when DNP-ACTH is hydrolyzed for 24 hours at 110° with constant boiling hydrochloric acid. The ether-soluble extracts of the hydrolyzed DNP peptides were then chromatographed on paper with 1.5 *M* phosphate buffer at *p*H 6.0 as described by Levy.[24] The colorless water-soluble fractions were chromatographed on paper with butanol–acetic acid–water.[19] The DNP amino acids used for control substances were prepared and described by Mellon, *et al.*[25]

Amino Acid Content of Phosphopeptides.—The amino acid composition of the phosphopeptides was determined by the Moore and Stein method[16] using Dowex 50-X8 resin. The peptides were hydrolyzed with 6 *N* hydrochloric acid at 120° for 20, 70 and 140 hours. The values for the serine content of the 70- and 140-hour hydrolysates were extrapolated to zero time to determine the initial serine content. A chromatogram of a 20-hour hydrolysate of phosphopeptide 4-C, which are the conditions frequently used for complete hydrolysis of protein, clearly showed incomplete hydrolysis

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of the organic phosphorus as well as of the peptide. This was confirmed by the chromatogram of the 70-hour hydrolysate where the peak due to phosphoserine could not be detected and the serine and glutamic acid content increased. Differences in the rate of destruction of serine in the hydrolysis of various proteins are discussed by Smith and Stockell.[25] They predict, on the basis of the reports by Sanger[27] and Leach,[28] that serine, threonine and aspartic acid will be liberated completely from peptides after 20 hours of hydrolysis. It is apparent, however, that complete hydrolysis of phosphoserine and its peptides is not obtained in 20 hours. Rees[29] has shown that the destruction of serine on hydrolysis is accompanied by the formation of ammonia. Smith and Stockell[26] have shown that for the hydrolysis of papain and carboxypeptidase the increase in ammonia parallels the destruction of serine, but that the percentage loss of serine at a given time depends on the initial amino acid content of the protein, as well as on unknown factors. For the determination of the destruction of serine on hydrolysis of phosphoseryl peptides, ammonia was determined with a short column (0.9 × 15 cm.) of Dowex 50-X8 as described by Moore and Stein[16] using only the *p*H 5.0 and *p*H 6.5 citrate buffers, since basic amino acids were not present.

Results

Chromatography of Phosphopeptides on Dowex 50-X8.—The partial acid hydrolysate from 3 g. of α-casein was made to 100 ml. as previously described. Seventy-five milliliters, amounting to 2.25 g. of protein, was chromatographed on a 3.8 × 100 cm. column of Dowex 50-X8. The results for two hydrolysates are shown in Fig. 1. The chromatograms show that the hydrolysis and resolution into phosphopeptide fractions are highly reproducible. The nitrogen and phosphorus content of these fractions are given in Table I. Under the conditions employed the non-phosphorus portion of the hydrolysate is retained by the resin. Of the total phosphorus put on the column 90.7% was eluted and is associated with only 8.9% of the nitrogen. The relatively high amount of nitrogen and phosphorus in the base-line fractions is due in part to the large number of tubes with low optical density that were not satisfactorily resolved, and possibly in part to the low color values of the components. All of the inorganic phosphorus that was formed on hydrolysis, equivalent to only 9.35% of the phosphorus of α-casein subjected to hydrolysis, is eluted in fraction 2, near the front of the chromatogram, together with peptides containing organic phosphorus. It is of interest to note that the phosphopeptides in fraction 1 have less affinity for the resin than does inorganic phosphorus. The total organic phosphorus in the six fractions, equivalent to 56% of the phosphorus put on the column, is associated with 5.1% of the nitrogen put on the column. The atomic ratios of N–P of the fractions reported in the last column of Fig. 1 are higher than they should be since they contain free ammonia; the uptake of ammonia by the acid solution during the concentration and handling of the fractions is difficult to prevent. The low ratios of nitrogen to phosphorus, however, reflect the concentration of phosphorus when compared to α-casein with a ratio of 34.4.

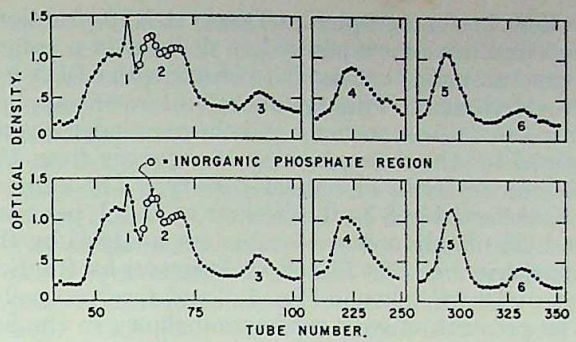

Fig. 1.—Chromatogram of the phosphopeptides in a partial hydrolysate of α-casein. Chromatography was carried out on a 3.8 × 100 cm. column of Dowex 50-X8 at 37.5° using 0.05 *N* hydrochloric acid as influent. The effluent was collected in 8-ml. fractions. Aliquots (0.5 ml.) were removed for analysis by the ninhydrin method. Each chromatogram was run on separate hydrolysates. The graph is corrected to an equivalent basis for variations in volume due to changes in the weight of drops during a run.

Paper electrophoresis showed only one of these fractions to be homogeneous. The other fractions contained up to four or more components. Fraction 5, which appeared to be homogeneous, had the same mobility as phosphoserine, but on complete hydrolysis it was found to contain aspartic acid and glutamic acid in addition to serine.

TABLE I

NITROGEN AND PHOSPHORUS COMPOSITION[a] OF PHOSPHOPEPTIDE FRACTIONS OBTAINED FROM PARTIAL ACID HYDROLYSIS OF α-CASEIN

(Fractions are numbered as in Fig. 1. The Dowex 50 column was charged with 286.0 mg. of nitrogen and 20.63 mg. of phosphorus.)

Fraction	Nitrogen, mg.	Organic phosphorus, mg.	Atomic ratio,[e] N/P
1	4.74	3.96	2.7
2	2.94	2.39[c]	2.7
3	0.96	0.73	2.9
4	2.74	1.70	3.6
5	2.43	2.26	2.4
6	0.85	0.50	3.8
Base line[b]	10.76	5.04	4.7
Total	25.42	16.58	
Recovery, %	8.9	90.7[d]	

[a] Values are corrected for aliquots taken from fractions for ninhydrin analysis based on average weight of fraction. [b] Includes all tubes of the chromatogram not taken for the fractions. [c] In addition this fraction contains 2.14 mg. of inorganic phosphorus which is equivalent to a conversion of 9.35% of the phosphorus of α-casein to inorganic phosphorus. [d] Includes the inorganic phosphorus in fraction 2. [e] The calculated atomic N/P ratio of α-casein is 34.4.

Rechromatography of Fractions.—Exploratory experiments with an anion-exchange column of Dowex 1-X10 in the hydrogen form, using dilute hydrochloric acid as influent, showed that only the last three fractions from the Dowex 50 column could be resolved into several subfractions. Attempts to resolve the first three fractions with various forms of Dowex 50 or Dowex 1 and 2 using a number of volatile influent solvents have not been successful.

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For chromatography on Dowex 1-X10, fractions 4, 5 and 6 were evaporated to dryness in a rotary evaporator and then made to 25 ml. with 0.01 *N* hydrochloric acid. Twenty-four milliliters was applied to a 1.9 × 20 cm. column and the remainder was retained for the determination of recovery from the column in terms of optical density. The effluent was collected in 8.5-ml. fractions at 25 ml. per hour and 0.5-ml. aliquots were taken for analysis by the ninhydrin method. The chromatograms for fraction 4, 5 and 6 are shown in Figs. 2, 3 and 4, respectively. The per cent. of each subfraction shown in the figures is in terms of total optical density units eluted from the column. The average recovery from the column for each of the three fractions in these terms exceeded 96%.

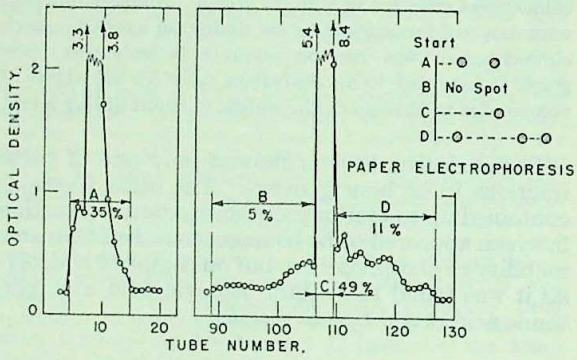

Fig. 2.—Chromatogram of fraction 4 obtained as shown in Fig. 1. Chromatography was carried out on a 1.9 × 20 cm. column of Dowex 1-X10 using 0.01 *N* hydrochloric acid as influent to tube 92 where a gradient with 0.1 *N* hydrochloric acid was used. The normality at subfraction C was 0.015. The effluent was collected in 8.5-ml. fractions and 0.50-ml. aliquots were removed for analysis by the ninhydrin method. Paper electrophoresis was performed as described in the text.

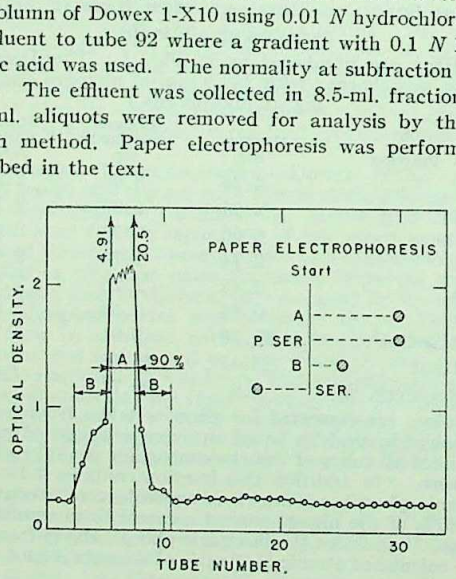

Fig. 3.—Chromatogram of fraction 5 obtained as shown in Fig. 1. Chromatography was carried out on 1.9 × 20 cm. column of Dowex 1-X10 using 0.01 *N* hydrochloric acid as influent. The effluent was collected in 8.5-ml. fractions and 0.50-ml. aliquots were removed for analysis by the ninhydrin method. Paper electrophoresis was performed as described in the text.

For paper electrophoresis, the subfractions were combined and concentrated *in vacuo* and made to the same optical density in order to obtain comparable concentrations. The electrophoretic results are also shown in Figs. 2, 3 and 4. The influent for the chromatography of fraction 4 shown in Fig. 2 was 0.01 *N* hydrochloric acid to tube No. 92 where a 500-ml. ground joint wash bottle was used as a mixing chamber for gradually increasing normality by addition of 0.1 *N* hydrochloric acid. The acidity of the effluent at subfraction C (Fig. 2) was 0.015 *N* as shown by titration. The results obtained by paper electrophoresis showed that only subfraction C was homogeneous; subfractions A and D contained a total of five components, and B was insensitive to the ninhydrin spray.[19]

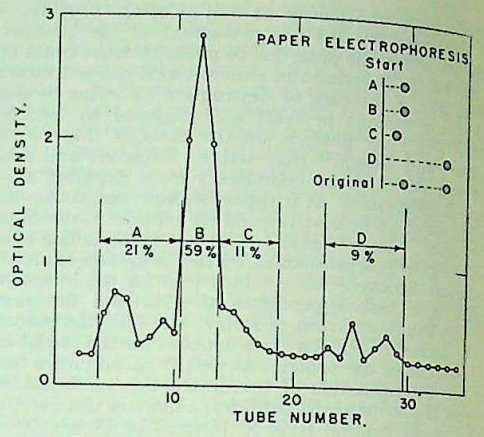

Fig. 4.—Chromatogram of fraction 6 obtained as shown in Fig. 1. Chromatography was carried out on 1.9 × 20 cm. column of Dowex 1-X10 using 0.01 *N* hydrochloric acid as influent. The effluent was collected in 8.5-ml. fractions and 0.50-ml. aliquots were removed for analysis by the ninhydrin method. Paper electrophoresis was performed as described in the text.

Fraction 5, which appeared to be homogeneous by paper electrophoresis, having the same electrophoretic mobility and behavior on Dowex 50-X8 as phosphoserine, was rechromatographed on Dowex 1-X10 with 0.01 *N* hydrochloric acid as influent solvent. The chromatogram of fraction 5 (Fig. 3) shows that 90% of the fraction is now concentrated in two tubes and that the fraction contained two electrophoretic components. The nature of the chromatogram indicates that complete resolution was not obtained. This was later confirmed when subfraction A was resolved on the Dowex 50-X8 column of Moore and Stein[16] for the determination of amino acids. Phosphoserine emerged without holdup at the front as reported by Moore and Stein,[30] followed by another peak separated by one tube having a low optical density. This was considered to be a satisfactory resolution in view of the high proportion of one component. On the basis of optical density and without correction for the color factor, which is unknown for the minor component, subfraction A contains 96.3% phosphoserine.

Chromatography of fraction 6 on Dowex 1-X10 with 0.01 *N* hydrochloric acid as influent solvent is shown in Fig. 4. The four subfractions as shown by paper electrophoresis contained three components. As judged by the nature of the

(30) S. Moore and W. H. Stein, *J. Biol. Chem.*, **211**, 893 (1954).

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chromatogram, subfraction D should contain two components one of which may be insensitive to the ninhydrin spray; in subfraction A the chief component has apparently the same electrophoretic mobility as the component in subfraction B which contained 59% of the total material. Fraction 6, therefore, contains at least five components as determined by an analysis of its subfractions compared with only two components that were found by paper electrophoresis of the original material.

The character of the three chromatograms suggests that each of the main subfractions contained some impurity. This could not be established by either paper electrophoresis or paper chromatography, even when large amounts of samples were used for analysis. That the subfractions did contain up to about 10% of impurity was later confirmed when the amino acid compositions were determined.

The main subfraction of each fraction shown to be homogeneous by electrophoresis (4-C, Fig. 2; 5-A, Fig. 3; and 6-B, Fig. 4) was analyzed qualitatively for amino acid composition after complete hydrolysis. Each of the subfractions was found to contain glutamic acid, aspartic acid and serine, and subfraction 6-B also contained alanine. The only N-terminal amino acid that was found by paper chromatography studies on the hydrolyzed DNP subfractions was serine.

The resolution of fractions 1 and 2 (Fig. 1) into several subfractions with paper chromatography using butanol–acetic acid–water (5:4:1) suggested that chromatography on a cellulose column under similar conditions might be successful. Experiments with a 1 × 25 cm. cellulose column resolved each fraction into several ninhydrin-positive peaks. The first influent solvent was a butanol–acetic acid–water (10:1:2) system, which did not interfere with the ninhydrin determination, followed by 50% ethanol–water gradient and then by an aqueous hydrochloric acid gradient. Analysis of the subfractions obtained in large scale experiments with 3.8 × 25 cm. columns showed that only one of them (from fraction 2, designated 2-C) was electrophoretically homogeneous. This was eluted at the change-over to 50% ethanol–water and contained serine and glutamic acid.

Amino Acid Analyses of Subfractions.—The amino acid analyses of the main subfractions which were electrophoretically homogeneous are shown in Table II. The results are expressed in terms of the molar ratios of the constituent amino acids. Except as noted, the values in the table for 4-C were calculated from the data on the 140-hour hydrolysate since the 70-hour hydrolysis was not complete. For 5-A and 6-B the values are the average of the 70- and 140-hour hydrolysate values which agreed within experimental error. The values reported for subfraction 2-C were obtained on an hydrolysate which was complete after only 20 hours.

The amino acid chromatograms of some of the subfractions showed several ninhydrin peaks for which the amino acids could not be found or established by paper chromatography and are not included in Table II. For subfractions 4-C, 5-A and 6-B one of these peaks, less than 0.02 of a residue, appeared at the front of the chromatogram where phosphoserine is eluted. In control experiments, however, with a mixture of the amino acids and phosphoserine subjected to the same hydrolytic conditions, no new peaks appeared and the phosphoserine was hydrolyzed completely. The first peak, therefore, is due to an impurity which on hydrolysis yields an acid compound; the second peak, equivalent to less than 0.03 of a residue, appeared just before the serine peak with good resolution. This peak may well be due to threonine, although it could not be detected by paper chromatography presumably because of its low concentration. It is possible, therefore, that a peptide containing threonine constitutes a minor impurity in the subfractions.

TABLE II

AMINO ACID COMPOSITION OF ELECTROPHORETICALLY HOMOGENEOUS PHOSPHOPEPTIDE SUBFRACTIONS OBTAINED FROM PARTIAL ACID HYDROLYSIS OF α-CASEIN

(Results are expressed in terms of the molar ratios of the constituent amino acids.[a])

	Subfractions			
	4-C	5-A	6-B	2-C
Aspartic acid	**0.11**	0.03	0.06	..
Glutamic acid	**0.92**	0.07	0.12	0.14
Alanine	..	..	**1.08**	..
Serine (extrapolated[b])	0.73	0.86	0.93	0.96[e]
Serine (min.[c])	1.00	1.00	1.00	1.00
Phosphoserine[d]	..	1.02	..	..

[a] Based on the minimum serine content taken as unity. [b] Value obtained by straight-line extrapolation of data from 70- and 140-hour hydrolysis to zero time. [c] Calculated from the phosphorus content and based on the assumption that the phosphorus is present as the mono-ester of serine. [d] Determined on unhydrolyzed subfraction by chromatography on Dowex 50-X8 resin of Moore and Stein.[16] [e] Value is the sum of the serine and the ammonia formed by destruction of serine determined on a single hydrolysis with 6 *N* hydrochloric acid at 120° for 6 hours by chromatography on the Dowex 50-X8 resin.

The chromatogram of the hydrolysate of subfraction 4-C contained additional components eluted as an unresolved double peak in the region where glycine and alanine appear. This double peak, present to the extent of 0.38 of a residue in the 20-hour hydrolysate, was reduced to 0.14 of a residue in the 70-hour hydrolysate; no further reduction was obtained in the 140-hour hydrolysate. This is a sufficient quantity to be detected by paper chromatography, but the presence of glycine or alanine could not be established. The double peak, therefore, contains a peptide which is apparently resistant to 140-hour hydrolysis. That this peptide might contain valine is suggested by the appearance of a peak in the chromatogram of 0.08 of a residue where valine is expected to be eluted and by the known resistance to acid hydrolysis of peptides containing valine.[26,31]

The compositions of the individual subfractions in terms of integral number of amino acid residues per mole are given in boldface type in Table II. The method of analysis, however, is capable of revealing the presence of impurities in the subfractions at levels which are not detectable by paper

(31) E. L. Smith, A. Stockell and J. R. Kimmel, *J. Biol. Chem.*, **207**, 551 (1954).

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electrophoresis or by paper chromatography of the hydrolyzed amino acids.

From an analysis of the data in Table II the composition of the subfraction as given in Table III can be calculated based on the following additional experimental evidence: (1) serine was the only amino acid that was found to be N-terminal in each of the subfractions (not determined for 2-C) by paper chromatography of the hydrolyzed DNP subfractions. Since the DNP phosphopeptides are resistant to hydrolysis, the long periods of heating required for complete hydrolysis cause an excessive destruction of serine, making the quantitative determination of N-terminal serine difficult. (2) The chain length of the main constituent of the subfractions was estimated by a determination of the ratio of the ninhydrin color value of the hydrolyzed as compared to the unhydrolyzed material. The ratio is of significant value when the chain length is small, and the amount of impurity of unknown chain length is low. Furthermore, this ratio can be used only for the estimation of short chain lengths with any degree of certainty, because the relative color value of serine and other dipeptides varies considerably as shown by Harris, *et al.*,[32] and Dowmont and Fruton.[33] These variations may lead to false conclusions, particularly for longer chain peptides. For the first three subfractions in Table III the experimentally determined ninhydrin ratio of the 70-hour hydrolysate to the unhydrolyzed is 2.0, 1.2 and 2.0, respectively. For subfraction 2-C using a 20-hour hydrolysate, the experimentally determined ratio is 1.8; however, due to the uncertainty of the relative color value of the unhydrolyzed peptide, this ratio is taken as 2. The value of 1.2 for subfraction 5-A can be accounted for by the presence of 10% of a tripeptide as an impurity which is consistent with the Van Slyke amino-nitrogen values.

The Van Slyke analysis on subfraction 4-C is of particular interest. This subfraction reacted with nitrous acid to yield all of its nitrogen as α-amino nitrogen under the usual conditions. The liberation of 2 moles of nitrogen with nitrous acid from γ-dipeptides of glutamic acid and other γ-glutamyl dipeptides was shown to occur by Sachs and Brand.[35,36] Since serine, however, was found to be the N-terminal amino acid of the dipeptide, a γ-glutamyl structure for the dipeptide is not possible. A mechanism for the liberation of peptide nitrogen from γ-glutamyl-peptides with nitrous acid was shown to parallel the formation of reaction products with a lactone structure by Sachs and Brand.[35] The same mechanism may be applicable for the phosphoserylglutamic acid dipeptide where the elements of water necessary for lactone formation are present in the phosphate radical.

TABLE III

COMPOSITION OF SUBFRACTIONS[a]

	% of constituents on mole basis			
	4-C	5-A	6-B	2-C
Pser. Glu	90			
Pser. Asp	10			
Pser.		90[c]		
Pser. (Asp, Glu)		10		
Pser. Ala			90	
Pser. (Ala, Glu, Asp)			10	
Pser. Pser.				75[d]
Glu. Pser.[b]				25[e]

[a] The abbreviations for amino acids and conventions for indicating their sequence are those of Sanger and Tuppy[34]; when the sequence of amino acids in a peptide is known, they are separated by periods, and when not known they are enclosed in parentheses and separated by commas. Additional abbreviations: Pser = O-phosphoserine. [b] This structure is assigned because the peptide Pser.Glu is resolved in another fraction from Dowex 50 (4-C). [c] On the basis of ninhydrin optical density, 96% of this subfraction is phosphoserine. [d] This value is 87% if the impurity in this subfraction is a tripeptide, such as (Glu, Pser.Glu) instead of a dipeptide. [e] Equivalent to 12% on molar basis and 10% on weight basis of glutamic acid as impurity in subfraction.

Discussion

The amount of destruction of serine found on hydrolyzing serine phosphopeptides as shown in Table IV is greater than has been reported for the destruction of serine in proteins. The values usually taken for the destruction of the hydroxy amino acids were established in the careful study by Rees[29] averaging 10% for serine and 5% for threonine after 24 hours in boiling 6 *N* hydrochloric acid. In the experiments by Hirs, *et al.*,[37] the loss of serine was 16% and that of threonine was 8% when either ribonuclease or a synthetic mixture of amino acids corresponding to an hydrolysate of serum albumin was heated for 20 hours with 6 *N* hydrochloric acid in sealed tubes at 110°. Good recoveries, however, were obtained by extrapolation of the analytical results to zero time. Gordon and Ziegler[38] found that serine and threonine were completely stable in the hydrolysis of α-lactalbumin at 120° even when the protein was hydrolyzed for 140 hours. The results in Table IV show that the lability of serine is apparently dependent in some degree on the amino acid with which it is associated. The value of 64.6% recovery for the 70-hour hydrolysate of subfraction 5-A, which is essentially phosphoserine, is comparable to the value of 61.0 obtained by Hirs and associates[37] for the recovery of serine from a 70-hour hydrolysate at 110° of a synthetic mixture

TABLE IV

RECOVERY OF SERINE FROM SUBFRACTIONS HEATED WITH 6 *N* HCl AT 120°

Subfraction	% Recovery[a] Time of hydrolysis 70 hr.	140 hr.	By extrapolation to zero time
4-C[b]	55.5	38.3	73
5-A	64.6	42.0	87
6-B	75.2	54.5	93

[a] Calculated from the phosphorus content and based on the assumption that all of the serine is phosphorylated and is present as the monoester. [b] A 20-hour hydrolysate contained phosphoserine.

(32) J. I. Harris, R. D. Cole and N. G. Pon, *Biochem. J.*, **62**, 154 (1956).

(33) Y. P. Dowmont and J. S. Fruton, *J. Biol. Chem.*, **197**, 271 (1952).

(34) F. Sanger and H. Tuppy, *Biochem. J.*, **49**, 463 (1951).

(35) H. Sachs and E. Brand, THIS JOURNAL, **75**, 4608 (1953).

(36) H. Sachs and E. Brand, *ibid.*, **76**, 3601 (1954).

(37) C. H. W. Hirs, W. H. Stein and S. Moore, *J. Biol. Chem.*, **211**, 941 (1954).

(38) W. G. Gordon and J. Ziegler, *Arch. Biochem. Biophys.*, **67**, 80 (1956).

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corresponding in composition to a hydrolysate of bovine serum albumin. This suggests that the phosphate itself has no appreciable effect on the hydrolytic destruction of serine. It is apparent from the last column of Table IV that a correction for losses of serine by extrapolation of the results to zero time, assuming first-order kinetics for the decomposition, would lead to considerable error.

Phosphoserylglutamic acid was first isolated by Levene and Hill[40] from an enzymatic digest of casein. de Verdier[39] has reported the presence of phosphoserylglutamic and phosphoserylalanine and several other peptides of phosphoserine from acid digests of casein but was not able to establish that serine was N-terminal.

(39) C. H. de Verdier, *Acta Chem. Scand.*, **8**, 1302 (1954).

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE SECTION ON ENZYMES OF THE LABORATORY OF CELLULAR PHYSIOLOGY, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Synthesis of Some Model Pyrimidine Nucleosides

BY H. TODD MILES

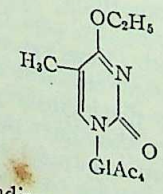
RECEIVED NOVEMBER 23, 1956

Methods of preparing some N-alkyl and O-alkyl pyrimidine nucleosides are described.

In order to study the tautomeric forms of certain nucleosides and nucleotides in solution[1] by their infrared spectra it was desirable to have derivatives of the possible tautomeric forms in which the labile hydrogen is replaced by methyl or ethyl groups. The present article describes the synthetic methods used for the compounds not previously reported.

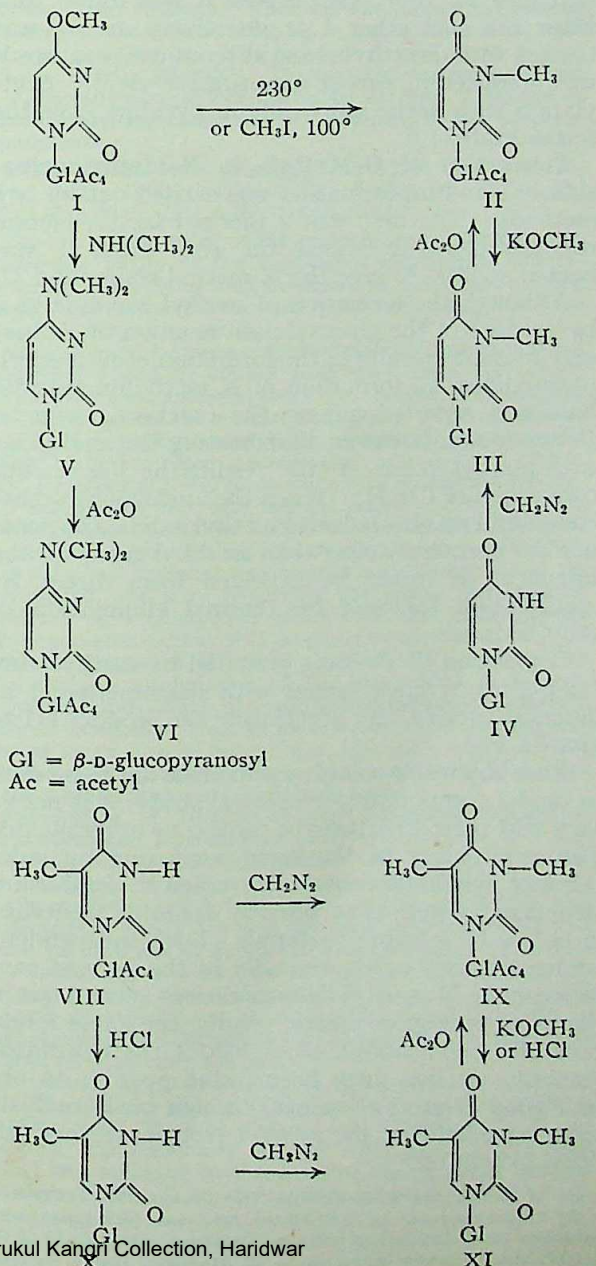
Direct N-Methylation of Nucleosides.—Levene and Tipson[2] reported the preparation of 3-methyluridine by use of diazomethane on 2′,3′-di-O-acetyl-5′-O-triphenylmethyluridine in ether solution. It was found recently[1] that 3-methyluridine could be prepared much more conveniently by direct treatment of the nucleoside in methanol with diazomethane, thus obviating the introduction and subsequent removal of acetyl or trityl groups. By this method 3-methylthymidine, 1-β-D-glucopyranosyl-3-methyluracil and 1-β-D-glucopyranosyl-3-methylthymine have been prepared for the first time. In each case only the product of N-methylation was isolated.

Preparation of the O-Alkyl Nucleosides.—The 1-(2′,3′,4′,6′-tetra-O-acetyl)-β-D-glucopyranosyl-4-alkoxypyrimidines (I and VII) were prepared by the method of Hilbert and Johnson.[3] Compound I has been reported before[3] and readily can be isolated from the reaction mixture in crystalline form.



VII

The corresponding thymine compound VII, however, has not been isolated by previous workers[4,5] though it obviously has been present in reac-



(1) H. T. Miles, *Biochim. Biophys. Acta*, **22**, 247 (1956).
(2) P. A. S. Levene and R. S. Tipson, *J. Biol. Chem.*, **104**, 385 (1934).
(3) G. E. Hilbert and T. B. Johnson, THIS JOURNAL, **52**, 4489 (1930).
(4) W. Schmidt-Nickles and T. B. Johnson, *ibid.*, **52**, 4511 (1930).
(5) D. W. Visser, I. Goodman and K. Dittmer, *ibid.*, **70**, 1926 (1948).

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tion mixtures. Since the O-ether was required as such and not merely as an intermediate, attempts were made to prepare it by varying the pyrimidine and the glucosyl halide reactants, the temperature and the pressure; but from none of the reactions could the desired product be isolated. Finally a chromatographic method was found which permitted isolation of the pure material from the reaction mixture.

Deacetylation of I and VII was accomplished by treatment with a catalytic amount of potassium methoxide, followed by removal of the potassium ion by titration with 60% perchloric acid to a *p*H meter reading of 8.1.[6] In each case the product was a glass, which could be reacetylated to the original O-alkyl material.

Synthesis of 1-Glucosyl-4-dimethylamino-2-pyrimidone (V).—In order to have a model compound for cytidine which would be incapable of tautomerizing, it was desired to prepare a compound of structure V. For this purpose it was found that when the enol ether I or its ethoxy analog was treated with dimethylamine at room temperature V was produced in almost quantitative yield. Acetylation with acetic anhydride in pyridine gave the tetraacetate of V.

Conversion of O-Methyl- to N-Methylnucleoside.—This transformation was carried out by two methods. The first was a thermal lactim–lactam rearrangement in which the enol ether I was heated at 230° to give the N-methyl compound II.

Although the formation of methyl bromide as a by-product of the glycosylation reaction of Hilbert and Johnson[3] results in the formation of N-methylpyrimidines, no formation of N-methylnucleosides has been reported among the reaction products. It was found, however, that heating the enol ether with methyl iodide at 100° resulted in the smooth conversion of I to II. When the analogous O-ethyl compound was heated with methyl iodide, the product has a methyl rather than an ethyl group on the nitrogen, as would be expected from direct N-methylation followed by thermal elimination of ethyl iodide.

Compound II also was prepared by methylating 1-β-D-glucopyranosyluracil with diazomethane, as described above, and acetylating the product III to give II.

Since the water-soluble compounds are to be used as model compounds for spectral study, it is necessary that their structures be proved by other means. The availability of the same compound by independent synthetic routes does much to establish a structure as well as to provide desirable flexibility in choice of starting materials. Such independent evidence was sought originally in the present case because the N-methyl determinations carried out in the usual way gave erratic results, the value found generally being about an eighth of the calculated amount. It has since been found possible to obtain good N-methyl values, though both analysts have reported that the methyl groups are very difficult to split off.[7]

Paper Chromatography.—The R_f values of the water-soluble members of the present series as well as some of the natural nucleosides were determined in two solvents and are presented in Table I. While these values are not precise physical constants they are reasonably reproducible even when no elaborate precautions are taken; they indicate the relative mobilities of the compounds and show which separations can be achieved readily. The compounds were detected by quenching of the fluorescence caused in the paper by a Mineralite ultraviolet lamp. Ascending chromatograms were used.

In all cases the 3-N-methyl compound had a higher R_f than the parent nucleoside, presumably because of its greater relative solubility in the nonaqueous phase. Comparison of IV with X, of IV with uridine, and of uridine with thymidine suggest that with analogous compounds the R_f generally decreases with the number of hydroxyl groups on the sugar and increases with the number of methyl groups on the ring, especially if a labile hydrogen has been replaced by methyl.

A useful application of paper chromatography of these compounds is in following the diazomethane methylation. It is easy to tell whether the reaction has gone to completion or not and even, roughly, the ratio of reactant to product.

A Convenient Micro Method for Distinguishing O-Methyl from N-Methyl.—The greatest usefulness of paper chromatograms in the present study was in demonstrating with a few micrograms of material whether a methyl or ethyl group was attached to oxygen or nitrogen. When little material is available it is often impractical to carry out an acid hydrolysis of the enol ether and isolate the crystalline nucleoside.

A few micrograms of the methyl nucleoside were added to concentrated hydrochloric acid. After the solution had stood overnight the acid was evaporated and the reaction product was chromatographed. The compounds which were derived from acetates of nucleoside enol ethers (the structures of the acetates have been demonstrated by acid hydrolysis of larger quantities to known nucleosides[3,5]) by potassium methoxide deacetylation gave products which had the same R_f values as the corresponding nucleosides.

N-Methyluridine, whose structure was proved by Levene and Tipson,[2] and the other compounds prepared by diazomethane methylation in this study were unaffected by acid treatment. Since both N-methyl and O-methyl compounds move well above the parent nucleoside in all solvents, there is no difficulty distinguishing the two by acid treatment even when they have the same R_f.

The R_f's after acid treatment of the seven compounds tested are given for two solvents in Table I.

Experimental[7,8]

3-Methylthymidine.—To a solution of 800 mg. of thymi-

(6) W. Bonner and W. L. Koehler, THIS JOURNAL, **70**, 314 (1948).

(7) "Microanalyses," by J. F. Alicino, Metuchen, New Jersey, with exception of O-CH_3 and N-CH_3 determinations of compounds II, IX(M) and XI, which were done by W. Manser, Zürich.

land. The second N-CH_3 determination of IX(A) was done by Alicino by running the same sample through the procedure four times and using longer heating periods. The first three titrations gave roughly a third each of the theoretical value, and the fourth titration a negligible amount. A repeated N-CH_3 analysis of 3-methylthymidine has not yet been obtained.

(8) Melting points were measured on a Kofler apparatus and are cor-

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TABLE I

Schleicher & Schuell no. 598 paper was used for the chromatograms.

Compound	Solvent A[a]	Solvent A[a] After acid treatment	Solvent B[b]	Solvent B[b] After acid treatment
Uridine	0.29	..	0.26	..
3-Methyluridine	.69	0.68	.44	0.42
Thymidine	.62	..	.47	..
3-Methylthymidine	.84	.83	.72	.74
Cytidine	.28	..	.20	..
1-β-D-Glucopyranosyluracil	.19	..	.15	..
1-β-D-Glucopyranosyl-3-methyluracil (III)	.60	.60	.31	.30
1-β-D-Glucopyranosylthymine	.34	..	.24	..
1-β-D-Glucopyranosyl-3-methylthymine (XI)	.68	.70	.40	.39
1-β-D-Glucopyranosyl-4-ethoxy-2-pyrimidone[c]	.63	.20	.43	.13
1-β-D-Glucopyranosyl-4-methoxy-2-pyrimidone[c]	.50	.20	.28	.14
1-β-D-Glucopyranosyl-4-ethoxy-5-methyl-2-pyrimidone[c]	.70	.33	.40	.21
1-β-D-Glucopyranosyl-4-dimethylamino-2-pyrimidone (V)	.29	..	.17	..

[a] Solvent A: triethylamine, *t*-butyl alcohol, water (2:10:3). [b] Solvent B: 88% formic acid, *n*-butyl alcohol, water (10:10:3); let stand 24 hr. and use upper layer. Fresh solvent was not used because of the rapid esterification, which caused a marked change in composition and deposition of an aqueous layer during the running of the chromatogram. A 24-hour period of storage was chosen for convenience, though it does not represent equilibrium. [c] The values are reported for compounds from which the potassium ion has been removed. When this has not been done, the R_f values are lower though still reproducible for a given sample.

dine (Schwarz) in 70 ml. of methanol was added 80 ml. of a solution of diazomethane[9] in ether. The loss of color and evolution of nitrogen were rapid during the early part of the reaction. After the addition the solution was allowed to stand several hours in an ice-bath. The product after evaporation of solvent was a sirup which could not be induced to crystallize.

The reaction mixture was then chromatographed on 100 g. of potato starch in butanol saturated with water. The progress of the chromatogram was followed by the optical density at 260 mμ. The peak of optical density came at about 80 ml. of effluent, and the fractions from 60 to 120 ml. of effluent, representing 540 mg., were combined and crystallized from a mixture of methanol, ethyl acetate and ether.[10]

Further crystallizations were from methanol and ether and gave a material melting at 132.5–134° (unless the material had been thoroughly dried, it melted at about 72°, then resolidified and melted at 130–131°).

Anal. Calcd. for $C_{11}H_{16}N_2O_8$: C, 51.56; H, 6.29; N, 10.93; OCH_3, 0.00; NCH_3, 5.85. Found: C, 51.51; H, 6.34; N, 10.46; OCH_3, 0.00; NCH_3, 0.89.[7]

1-Glucosyl-3-methyluracil (III).—To a suspension of 170 mg. of IV (prepared by the Hilbert and Johnson[3] method) in 15 ml. of methanol was added 8 ml. of ether solution of diazomethane.[9] The reaction was slower than the first one, so 1 ml. of water was added and the suspension refluxed to bring most of the material in solution and then cooled before the slow addition of another 7 ml. of diazomethane solution. The product was treated with charcoal, filtered, and most of the solvent evaporated.

The initial sirup was finally induced to crystallize from a mixture of methanol, ethyl acetate and ether.[10] After four more crystallizations and drying under vacuum, the m.p. was 247–248.5°.

Anal. Calcd. for $C_{11}H_{16}N_2O_7$: C, 45.83; H, 5.60; N, 9.72; NCH_3, 5.20. Found: C, 45.79; H, 5.56; N, 9.93; NCH_3, 5.09.

The same compound was prepared from a sample of II by deacetylation with potassium methoxide. After crystallization from methanol and ether the latter material had an infrared spectrum identical with III prepared by the diazomethane reaction, and a mixture of the two showed no melting point depression.

1-(Tetra-O-acetyl-β-D-glucopyranosyl)-3-methyluracil (II). A. Reaction with Methyl Iodide.—To a mixture of 7 ml. of methyl iodide and 4 ml. of acetone was added 400 mg. of I (in other preparations the ethoxy analog was used with equal success). The reaction tube was sealed and heated at 100° for about 60 hours. The tube was opened, the solvent evaporated, the residue taken up in methanol, treated with charcoal and filtered. The compound crystallized to give 320 mg. of m.p. 99–103°. The material was recrystallized to a constant m.p. of 105–108° after drying. A sample of narrower melting range was not obtained in any of these experiments.

Anal. Calcd. for $C_{19}H_{24}N_2O_{11}$: C, 50.00; H, 5.30; N, 6.14; OCH_3, 0.00; NCH_3, 3.29. Found: C, 49.09; H, 5.02; N, 5.98; OCH_3, 0.00; NCH_3, 2.98.

The low carbon value of the analysis can be attributed to inadequate purity of the compound, although it was recrystallized five times from methanol to a constant melting range. For some reason the compound appears to be unusually difficult to purify.

Since II could be formed by two methods from the known compound I and by simple acetylation from III (which gave a very good analysis) there is no reason to doubt that the compound has the indicated structure. The conversion of II back to III by deacetylation confirms that no unusual change had taken place on acetylation.

B. Pyrolysis of I.—A combustion tube containing 300 mg. of I was flushed out with helium, sealed and heated in a Carius furnace at 230° for 24 hr. A solution of the material in methanol deposited 200 mg. of crystals, m.p. 104–107°. The light tan material was treated with charcoal and recrystallized, the m.p. remaining the same. An infrared spectrum of a chloroform solution of this material was superimposable on that of II prepared by method A.

C. Acetylation of III.—Fifty mg. of III (prepared by diazomethane methylation of IV) was added to 1.5 ml. of pyridine and 1.5 ml. of acetic anhydride and the mixture allowed to stand in the cold for a week. The solution was worked up to give 30 mg. of m.p. 100–105°, which had an infrared spectrum in chloroform solution identical with those of the samples prepared by methods A and B.

Preparation of 1-(Tetra-O-acetyl-β-D-glucopyranosyl)-4-ethoxy-5-methyl-2-pyrimidone (VII).—A mixture of 8.5 g. of 2,4-diethoxy-5-methylpyrimidine and 13.4 g. of freshly recrystallized tetra-O-acetyl-α-D-glucopyranosyl bromide was heated in a 50-ml. flask at 60°. Through a side arm protected by a Dry Ice trap the flask was connected to a house vacuum line of about 100 mm. pressure. The flask was heated for a week, the last day at 75°. From the reaction mixture there was obtained 19 g. of sirup which resisted all attempts at crystallization (small amounts of methylpyrimidines formed in this and similar reactions were filtered off from ether solution).

A successful chromatographic method was found and applied as follows to 14 g. of the sirup. A column of 350 g. of Magnesol[11] (Food Machinery and Chemical Co.; the material was previously washed with acetone and then dried) was prepared from a benzene slurry and a benzene solution of the 14 g. of reaction mixture poured on it.

(9) The diazomethane solutions used in these reactions were prepared by covering solid N-methyl-N-nitroso-N′-nitroguanidine with 10 ml. of ether per g. of solid and adding 40% potassium hydroxide solution slowly to the chilled mixture. At the completion of the reaction the diazomethane solution was decanted.

(10) In recrystallizing this and other water soluble members of the present series the compound was dissolved in a minimum quantity of methanol at the boiling point and either ethyl acetate (in which most of the compounds are only slightly soluble) or ether (in which they are insoluble) or both were added slowly to the point of cloudiness. Chilling at −10 to 0° then generally caused crystal formation.

(11) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, THIS JOURNAL, 67, 527 (1945).

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The eluting solution was ethanol in benzene, the volume used at each concentration being as follows: 500 ml., 100:1 benzene–ethanol (even with concentrated solutions there is very little volume change on mixing benzene and ethanol); 700 ml., 50:1; 700 ml., 20:1; 1000 ml., 10:1; 200 ml., 5:1; 300 ml., 2:1.

The effluent was tested for the desired material by placing a drop on filter paper and looking for quenching of fluorescence. As long as no quenching material came off, large fractions of 500–1000 ml. were collected and evaporated to confirm the absence of material; 100-ml. fractions were evaporated and weighed as the solute came off the column. The fractions from 1970 to 2000 ml. effluent were combined to give 4.2 g. of sirup, which crystallized spontaneously on standing two days. The fractions from 2000 to 2200 ml. effluent gave an additional 1.3 g. of sirup, which crystallized on seeding. The remainder of the effluent provided no crystalline material.

The substance obtained from the column was recrystallized to a m.p. of 132–133°.

Anal. Calcd. for $C_{21}H_{28}N_2O_{11}$: C, 52.07; H, 5.83; N, 5.97. Found: C, 52.00; H, 5.91; N, 5.87.

The enol ether obtained in this manner was deacetylated with potassium methoxide as described above to give a glass, which could be reacetylated to the original tetraacetate.

More careful chromatography of 5 g. of reaction sirup on 90 g. of Magnesol, using an automatic fraction collector and taking 7-ml. cuts, gave a 1.6-g. fraction which provided 1.3 g. of material melting at 131.5–133°. If the same per cent. yield of crystalline product had been obtained in the larger chromatogram, the yield of crystalline material for the reaction would have been about 31% instead of the observed 19%.

Although previous workers[5] failed to isolate the present compound they obtained its acid hydrolysis product, β-D-glucopyranosylthymine, in 43% yield.

1-β-D-Glucopyranosyl-3-methylthymine (XI).—The most convenient preparation of 1-tetra-O-acetyl-β-D-glucopyranosylthymine (VIII) proved to be the method of condensing dithyminylmercury with tetra-O-acetyl-α-D-glucopyranosyl bromide reported recently by Fox, Yung, Davoll and Brown.[12]

Six g. of VIII was dissolved in 40 ml. of chloroform and 10 ml. of methanol. On chilling VIII came out of solution, but as the material reacted with the first 15 ml. of diazomethane solution (a total volume of 40 ml. was eventually used) it all went into solution. The solvent was evaporated, more chloroform added, the solution treated with charcoal and again evaporated. The sirupy product could not be induced to crystallize; after standing several days without solvent, it crystallized spontaneously. The yield of IX was 5 g., m.p. 112–116°. A mixture of ethanol, ether and a little hexane was found to give the best results of the solvents tried. The m.p. of the purified material was 120–122°.

Anal. Calcd. for $C_{20}H_{26}N_2O_{11}$: C, 51.06; H, 5.57; N, 5.96; OCH_3, 0.00; NCH_3, 3.19. Found: C, 51.23; H, 5.46; N, 5.89; OCH_3, 0.00; NCH_3, 3.13 (M); 3.57 (A).[7]

The above tetraacetate IX was converted to XI by treating a solution of 500 mg. of pure tetraacetate in 18 ml. of absolute methanol with several mg. of potassium, warming for 10 min. and leaving overnight. When ether was added to the solution, the product came out as a sirup. The potassium ion was then removed by titration with perchloric acid followed by centrifugation.[6] This time when ether was added to the point of turbidity and the solution cooled, crystals separated. The yield was 250 mg. of m.p. 197–200°. This material was treated with alumina and charcoal in methanol and crystallized 5 times to a constant melting range of 196–202°. (The upper limit is the point at which the last crystals visible under the polarizer disappear.) Despite the broad range, the analysis indicated that the material was pure and had the expected constitution.

Anal. Calcd. for $C_{12}H_{18}N_2O_7$: C, 47.68; H, 6.00; N, 9.27; OCH_3, 0.00; NCH_3, 4.96. Found: C, 47.79; H, 5.90; N, 9.33; OCH_3, 0.00; NCH_3, 3.85.

Alternate Preparation of IX.—In view of the originally poor NCH_3 analyses it was considered desirable to carry out the reverse of the above transformation, that is, the methylation of 1-β-D-glucopyranosylthymine, a known compound,[5] to give IX.

Accordingly, dry hydrogen chloride was passed into a cold solution of VIII in 200 ml. of methanol for 15 minutes and the stoppered solution allowed to stand a day. The solution was evaporated under vacuum and the sirup crystallized from methanol and ether. After one recrystallization the m.p. was 272–274.5°, in agreement with the reported value[5] of 271°.

The glucosylthymine was then treated in aqueous methanol (10% water to increase solubility) with ethereal diazomethane, as described above for IV. The product was a sirup that crystallized on seeding with a crystal of IX obtained by the potassium methoxide deacetylation described above. After recrystallization the present material, when mixed with XI, showed no melting point depression and had an identical infrared spectrum.

1-β-D-Glucopyranosyl-4-dimethylamino-2-pyrimidone (V).—To a mixture of 30 ml. of dimethylamine and 15 ml. of methanol in a pressure bottle was added 1.5 g. of the 4-ethoxy analog of I. The bottle was closed and allowed to stand at room temperature for two days. Most of the solvent was evaporated under air stream on the steam-bath and ethyl acetate and ether[10] then added to cause crystallization. The yield was 0.95 g. (99%). The material even after several crystallizations and drying for analysis exhibited a double melting point, the first at about 170–180°, with subsequent crystallization of the melt, the second at 271–273°.

In an earlier experiment the same reaction was carried out with I at 60° and the same product obtained in 82% yield.

Anal. Calcd. for $C_{12}H_{19}N_3O_6$: C, 47.83; H, 6.36; N, 13.95; NCH_3, 9.96. Found: C, 47.53; H, 6.59; N, 13.96; NCH_3, 6.75.

The tetraacetate of V was prepared by reaction with acetic anhydride in pyridine in the cold. The m.p. of the pure material was 281–282°.

Anal. Calcd. for $C_{20}H_{27}N_3O_{10}$: C, 51.17; H, 5.80; N, 8.95; NCH_3, 6.40. Found: C, 51.21; H, 5.87; N, 9.04; NCH_3, 6.74.

BETHESDA, MD.

(12) J. J. Fox, N. Yung, J. Davoll and G. B. Brown, THIS JOURNAL, 78, 2117 (1956).

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May 20, 1957

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Structure of Flavothebaone[1]

BY J. MEINWALD AND G. A. WILEY[2]

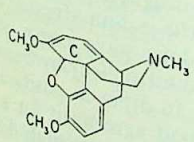
RECEIVED JANUARY 8, 1957

Structure V is deduced for flavothebaone, a rearranged derivative of the alkaloid thebaine, on the basis of a probable mechanism for its formation from thebainehydroquinone (IIIa). This structure differs from part-structure IV originally proposed by Schöpf, in 1938, and from VI and VII put forward, in 1954, by Bentley. New experimental evidence provides strong support for this formulation. Thus, the discovery that dihydrothebainehydroquinone (VIII) undergoes a parallel transformation proves that the C_7–C_8 unsaturation is not essential for the flavothebaone rearrangement. Spectral as well as chemical evidence corroborates the presence of an *isolated* α,β-unsaturated carbonyl system. This new feature is reconciled with the red color developed by flavothebaone in base. The ultraviolet spectrum of flavothebaone, not directly predictable from V, is discussed briefly.

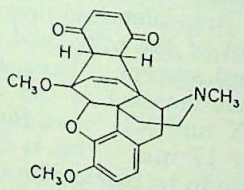
Introduction and Theoretical Discussion

The reaction of *p*-benzoquinone with the alkaloid thebaine (I), described for the first time by Sandermann[3] and by Schöpf,[4] in 1938, gives the expected Diels-Alder adduct thebainequinone (II). This adduct may be regarded as the diketo form of a hydroquinone, and in accord with the generally observed behavior of this type of compound it may be doubly enolized under a variety of conditions to thebainehydroquinone (IIIa). IIIa suffers a deep-seated change on strong acid treatment, losing one methylene group and giving rise to the rearrangement product flavothebaone, $C_{24}H_{23}O_5N$.

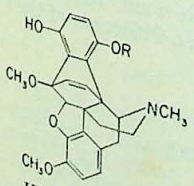
Extensive studies by Schöpf revealed that flavothebaone contained one new phenolic hydroxyl group, an intact tertiary nitrogen, and an α,β-unsaturated ketone system.[4] When flavothebaone is dissolved in base, a striking red coloration develops. This phenomenon led Schöpf to the conclusion that the unsaturated ketonic chromophore *must be conjugated with the hydroquinone ring.* Since methylation of the hydroquinone hydroxyls or saturation of the double bond produced derivatives which were not red in base, this relationship seemed entirely reasonable. On the basis of these early studies, Schöpf tentatively advanced part structure IV for flavothebaone, but was unable to arrive at a complete structure.



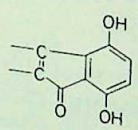
I



II



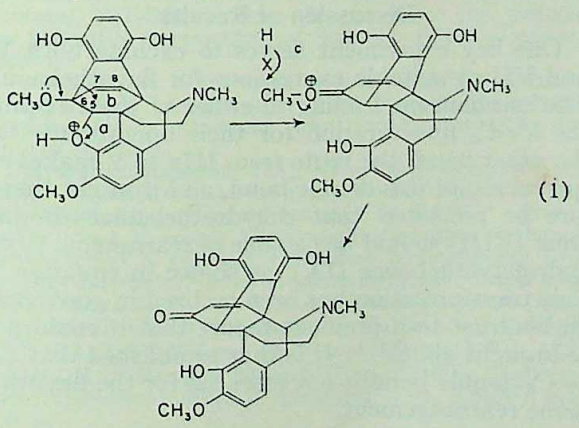
IIIa, R = H
IIIb, R = CH_3



IV

The work of Schöpf incorporated a large number of carefully performed transformations, including a successful Hofmann degradation and Beckmann rearrangement. Oxidative degradations were less fruitful. In view of the complexity of the flavothebaone molecule, it seemed that little progress could be hoped for until a plausible structure could be derived which would serve as a sound working hypothesis. Toward this end, it was of interest to speculate on what acid-catalyzed reactions IIIa might be expected to undergo.

Of the many rearrangement pathways open to the substrate IIIa, one reaction sequence appeared to be so compelling as to eliminate from detailed consideration all other possibilities until the favored scheme could be tested. The postulated sequence, as shown in equation 1, is initiated by protonation of the cyclic ethereal oxygen, and proceeds *via* (a) cleavage of the C_5–O bond, (b) migration of the hydroquinone moiety from C_6 to C_5, and finally (c) attack of the resultant hybrid by any nucleophilic species to give V. This simple mechanism



(1)

V

seemed particularly attractive in view of the high yield and lack of side products obtained in the reaction. It involves only a single 1,2-shift of an electronically excellent migrating group which furthermore is almost exactly *trans* to the vanishing C_5–O bond. Since the easily derived structure V possesses a new phenolic hydroxyl group, an intact tertiary nitrogen and an α,β-unsaturated ketone system, this formula was tentatively assigned to flavothebaone.

That the application of theoretical considerations to the evidence discussed above does not necessarily lead to this conclusion was dramatically demonstrated by the publication of a highly imagi-

(1) A preliminary Communication of some of the results reported in this paper has appeared in *Chemistry & Industry*, 957 (1956).
(2) Opportunity Fellow, John Hay Whitney Foundation, 1955–1956; Allied Chemical and Dye Corp. Fellow, 1956–1957.
(3) W. Sandermann, *Ber.*, **71**, 648 (1938).
(4) C. Schöpf, K. von Gottberg and W. Petri, *Ann.*, **536**, 216 (1938).

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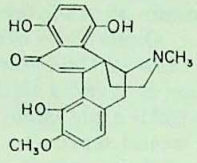
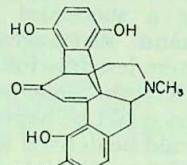
native discussion of the flavothebaone problem by Bentley in 1954.[5] This discussion appeared well after work aimed at testing the validity of structure V had begun in these laboratories, and served to stimulate interest in this research by offering alternate flavothebaone structures. A complete review of this significant discussion is beyond the scope of the present paper, but the key points may be readily summarized. Rather complex mechanistic considerations led to structures VI ($C_{22}H_{21}O_6N$) *or* VII for flavothebaone. Bentley was able to exclude VI by confirming Schöpf's molecular formula and by an analysis of ultraviolet data. With some reservations he was thus led to VII as the correct flavothebaone structure. Brief



VI



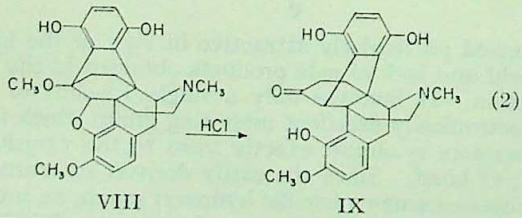
VII

consideration was also given to V, but this possibility was quickly dismissed, largely because of its failure to incorporate extended conjugation.[6]

After a preliminary account of the results of our flavothebaone researches had appeared,[1] Bentley and co-workers published a brief note in which "flavothebaone is allotted structure V."[7] Although they did not present the reason(s) for abandoning their earlier assignment or the evidence supporting V, it is apparent that these workers have deduced structure V independently.

Discussion of Results

One key experiment serves to exclude both VI and VII as suitable expressions for flavothebaone. The mechanisms leading to either of these require the C_7–C_8 unsaturation for their operation.[5] On the other hand, the route from IIIa to V makes no special use of this double bond, and it might therefore be predicted that dihydrothebainehydroquinone (VIII) should be capable of rearranging to dihydroflavothebaone (IX), as shown in equation 2. This transformation has been realized in good yield (in contrast to a previous report that it could not be brought about[5]). It is thus established that the C_7–C_8 double bond is not essential for the flavothebaone rearrangement.



VIII IX (2)

Three types of evidence indicate the presence of an *isolated* α,β-unsaturated ketone system in flavothebaone. The first of these is outlined on Chart 1, and provides information on the point of attachment of the carbonyl group. Lithium aluminum hydride reduction of flavothebaone trimethyl ether (X) gives rise to flavothebaol trimethyl ether (XI). XI is readily reoxidized to X by manganese dioxide, indicating its allyl or benzyl nature.[8] In sharp contrast, dihydroflavothebaol trimethyl ether (XIII), prepared by lithium aluminum hydride reduction of dihydroflavothebaone trimethyl ether (XII) or by catalytic reduction of XI, is resistant to manganese dioxide oxidation even under more drastic conditions. These observations indicate that the carbonyl group of flavothebaone must be insulated from both aromatic rings.

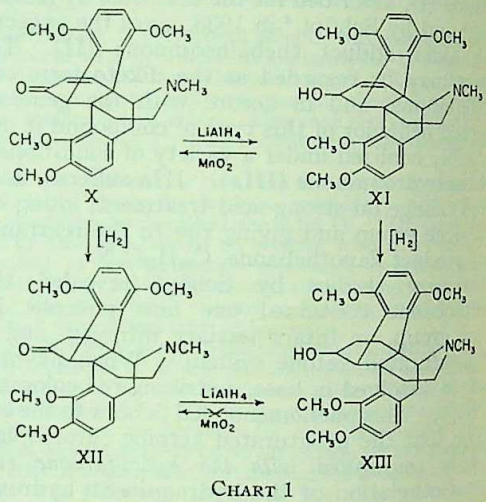
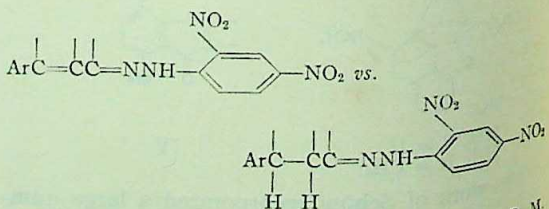


CHART 1

Infrared data support this conclusion. XII shows a single carbonyl absorption band at 5.82 μ (in $CHCl_3$ solution), as would be expected for an isolated carbonyl chromophore. X, on the other hand, shows carbonyl absorption at 5.97 μ (in $CHCl_3$ solution), in accord with expectation.

Ultraviolet data provide insight into the environment of the other end of the α,β-unsaturated carbonyl system. Thus, the long wave length ultraviolet maxima of the 2,4-dinitrophenylhydrazones of X and XII were found to *differ* in position by only 17 mμ. This is in good agreement for a $\Delta\lambda$ value to be expected for a pair of compounds differing by one conjugated double bond,[9] but is much too small to be compatible with a difference of the type shown below.



(5) K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Clarendon Press, Oxford, 1954, pp. 293–301.

(6) It should be pointed out that VII has the conjugation extending to the catechol rather than to the hydroquinone ring. As a result of this, it becomes impossible to use VII to rationalize Schöpf's findings with respect to the color reaction as discussed above.

(7) K. W. Bentley, J. Dominguez and J. P. Ringe, *Chemistry & Industry*, 1353 (1956).

(8) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(9) A typical $\Delta\lambda$ value of 20 mμ is given by A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold Ltd., London, 1954, p. 111.

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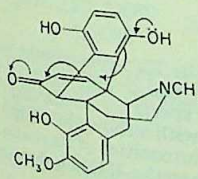
All these observations support V to the exclusion of all other structures so far considered. There are two objections that must be overcome, however, before this formulation can be accepted without reservation. The first of these is the necessity of rationalizing the red color of flavothebaone in base. Re-examination of this phenomenon reveals that the coloration is not due to the development of an intense, long wave length absorption maximum, as had been generally assumed, but rather to the appearance of a long, low-intensity tail in the visible. In fact, the actual spectral change accompanying anion formation is to *shorter* wave lengths (from λ_{max} 280 mμ (3.50), 345 mμ (3.55) to λ_{max} 257 (4.04), 298 mμ (3.84)). Furthermore, the reversibility of this color formation never has been demonstrated. When this point was investigated, it was found that although on a preparative scale flavothebaone can be recovered from basic solutions, *in very dilute solutions* (such as those used for determining ultraviolet spectra) *the reaction is not reversible.* This result takes on increased significance when compared with the behavior of flavothebaone monomethyl ether (XIV). This derivative undergoes a spectral shift to longer wave lengths in base (from λ_{max} 280 mμ (3.49), 344 mμ (3.53) to λ_{max} 293 mμ (3.78) and 404 mμ (3.32)) and the change is reversed by addition of acid, even in very dilute solutions. Finally it should be mentioned that even dihydroflavothebaone (IX), in which no extended conjugated system can exist, develops a brownish color irreversibly in base. From all this it seems clear that the appearance of a color in base is associated with a *reaction* of the unprotected hydroquinone ring which is more complex than simple anion formation.[10] One objection to structure V for flavothebaone is thus overcome.

The remaining difficulty is the unexpected 345 mμ maximum in the flavothebaone spectrum, which could not have been predicted on the basis of structure V. In view of the weight of the evidence presented thus far, it seems best to regard this spectrum as a problem *per se*. It is nevertheless a problem that must be resolved before V can be accepted unconditionally. A number of "abnormal" ultraviolet spectra have come to light recently,[11]



and it is tempting to ascribe this long wave length absorption to "homoconjugation" interaction, perhaps of the sort shown in formula XV. In the absence of any direct analogy for this particular system, however, it is necessary to put this speculation on firm ground by examination of a suitable model system. A synthesis of an appropriate model is now underway. The results of this study as well as of some confirmatory degradations which are now in progress will be presented in a subsequent publication.

Acknowledgments.—This problem was first brought to the attention of one of the authors by Dr. Bernhard Witkop in 1948. We are indebted to Professor Gilbert Stork for valuable discussions and encouragement, and to Dr. Max Tishler, Merck and Co., for a generous supply of thebaine.

Experimental[12]

Dihydrothebainehydroquinone (VIII).—Thebainehydroquinone (IIIa) was hydrogenated in glacial acetic acid over PtO_2 according to the procedure of Schöpf.[4] The H_2 uptake was 1.12 moles and a crude product was obtained in 94% yield. After recrystallization from absolute methanol the m.p. was 281–282° (lit.[4] 273°); infrared spectrum (KBr): 2.98, 3.78 and 3.99 μ (diffuse); ultraviolet spectrum: λ_{max}^{EtOH} 299 mμ (3.79).

Flavothebaone (V).—Compound V was prepared according to the method of Schöpf.[4] Best yields were obtained (in excess of 90%) when thebainehydroquinone (IIIa) was heated at 100° with concentrated HCl for 6 rather than 3 hours. The phenolic base was isolated most conveniently as the bright yellow acid hydrochloride trihydrate ($C_{24}H_{23}O_5N\cdot 2HCl\cdot 3H_2O$). Recrystallization from water gave the hydrochloride trihydrate ($C_{24}H_{23}O_5N\cdot HCl\cdot 3H_2O$). Further drying in a vacuum desiccator gave pale yellow needles of a hydrochloride monohydrate ($C_{24}H_{23}O_5N\cdot HCl\cdot H_2O$)[4]; infrared spectrum (KBr): 2.99, 3.17, 3.72, 5.98, 6.18, 6.32 μ; ultraviolet spectra (taken on $C_{24}H_{23}O_5N\cdot HCl\cdot 3H_2O$): λ_{max}^{EtOH} (0.1 *N* H^+) 279 mμ (3.51) and 346 mμ (3.56); λ_{max}^{EtOH} (0.1 *N* OH^-) 257 mμ (4.04) and 298 mμ (3.84).

Anal. Calcd. for $C_{24}H_{23}O_5N\cdot HCl\cdot H_2O$: C, 62.65; H, 5.65. Found: C, 62.82; H, 5.80.

An additional amount of V, as the free base, could be precipitated from the aqueous recrystallization liquors with saturated $NaHCO_3$ solution. In our hands this material was difficult to recrystallize and further purification was not achieved.

Flavothebaone dissolves in sodium hydroxide solution to give a deep red solution. Acidification of this solution reprecipitates flavothebaone (identified by ultraviolet and infrared spectra).

Dihydroflavothebaone (IX).—The hydrogenation was carried out on flavothebaone hydrochloride trihydrate using 10% Pd:$BaSO_4$ catalyst as described by Schöpf.[4] The H_2 uptake was 1.16 moles. Recrystallization from methanol–water yielded a colorless crystalline hydrochloride (presumably dihydrate); infrared spectrum (KBr): broad 2.98–3.25, 3.74(w), 5.85, 6.20, 6.32 μ; ultraviolet spectra (intensities calculated on the basis of $C_{23}H_{25}O_5N\cdot HCl\cdot 2H_2O$): λ_{max}^{EtOH} (0.1 *N* H^+) 291 mμ (3.73) and 309 mμ (3.70); λ_{max}^{EtOH} (0.1 *N* OH^-) 259 mμ (3.89) and 303 mμ (3.84); 2,4-dinitrophenylhydrazone: infrared spectrum: 2.94, 5.84(w), 6.17, 6.28 μ.

Anal. Calcd. for $C_{30}H_{29}O_8N\cdot HCl\cdot H_2O$: C, 56.10; H, 5.02; N, 10.90. Found: C, 56.33; H, 4.97; N, 10.55.

Rearrangement of Dihydrothebainehydroquinone (VIII) to Dihydroflavothebaone (IX).—Dihydrothebainehydroquinone (4.70 g.) was dissolved in 25 ml. of glacial acetic acid. This solution was added to a concentrated HCl solution held at 95–100° on a water-bath. White crystals soon began to appear. After 9 hours the solution was cooled and the crystals filtered, washed and dried (2.77 g.). Additional material was obtained by diluting the filtrate with water and cooling to 5° (1.84 g.). The total yield was 86% (based on the dihydrate formulation). Recrystallization from water yielded colorless crystalline hydrochloride. The infrared spectrum (KBr) was indistinguishable from that of the authentic sample of IX; ultraviolet spectra (in-

(10) A very careful attempt to make the formation of an anion from flavothebaone reversible in dilute solution by operating under an atmosphere of nitrogen is described in the Experimental section.

(11) Some early cases are cited by J. Meinwald, S. L. Emerman, N. C. Yang and G. Büchi, THIS JOURNAL, **77**, 4401 (1955). Two excellent recent papers dealing with this general problem have been published by R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302 (1956), and by R. R. H. Jones, G. H. Mansfield and M. C. Whiting, *ibid.*, 4073 (1956).

(12) All melting points were taken on a calibrated Fisher–Johns hot-stage. Ultraviolet spectra were recorded using a Beckman ultraviolet spectrophotometer, model DK.

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tensities calculated on the basis of $C_{23}H_{25}O_5N \cdot HCl \cdot 2H_2O$): λ_{max}^{EtOH} (0.1 *N* H^+) 291.5 mμ (3.70) and 309 mμ (3.71); λ_{max}^{EtOH} (0.1 *N* OH^-) 257 mμ (3.99) and 302 mμ (3.78).

A 2,4-dinitrophenylhydrazone was prepared and found to have an infrared spectrum (KBr) indistinguishable from that of authentic dihydroflavothebaone 2,4-dinitrophenylhydrazone.

Flavothebaone Trimethyl Ether (X).—Methylation of flavothebaone was carried out as prescribed by Schöpf employing sodium ethoxide and phenyltrimethylammonium chloride.[4,13] The free base was obtained in 72% yield and gave a m.p. of 252.5–253.0° with sintering below 240° (lit.[4] 253°) after recrystallization from absolute methanol; infrared spectrum ($CHCl_3$ soln.): 5.97, 6.25, 6.34 μ; ultraviolet spectrum: λ_{max}^{EtOH} 266–290 mμ (3.43) and 337 mμ (3.49); 2,4-dinitrophenylhydrazone: m.p. 298–299° (browns after melting) ultraviolet spectrum: λ_{EtOH}^{max} 3.94 mμ (4.35).

Anal. Calcd. for $C_{33}H_{33}O_8N_5$: C, 63.15; H, 5.30. Found: C, 63.29; H, 5.40.

Flavothebaol Trimethyl Ether (XI).—To an agitated suspension of flavothebaone trimethyl ether (5.0 g.) in 250 ml. of absolute ether which had previously been cooled to 0–5°, was added a 2-fold amount of ethereal $LiAlH_4$ solution over a 2-hour period. After stirring 24 hr. at 0–5°, saturated Na_2SO_4 solution and then solid anhydrous Na_2SO_4 were added. After several hours the mixture was filtered and the solid washed thoroughly with ether. The ether was evaporated to leave a white solid (4.57 g., 91%). Several recrystallizations from absolute ethanol gave white feathery crystals, m.p. 267.5–268°, with browning after melting; infrared spectrum ($CHCl_3$ solution): 2.91, 6.23, 6.36 μ; ultraviolet spectrum: λ_{max}^{EtOH} 291 mμ (3.70), shoulder around 300 mμ.

Anal. Calcd. for $C_{27}H_{31}O_6N$: C, 72.14; H, 6.95; N, 3.12. Found: C, 72.17; H, 7.10; N, 3.39.

MnO_2 Oxidation of Flavothebaol Trimethyl Ether (XI).—Active MnO_2 (500 mg.), prepared after the method of Attenburrow, *et al.*,[8] was ground to a fine powder and suspended in 150 ml. of absolute benzene. Flavothebaol trimethyl ether (50 mg.) was added and the mixture agitated for 4 hours. After filtration and evaporation of the benzene a yellowish residue was left which had an ultraviolet spectrum identical with that of flavothebaone trimethyl ether. After recrystallization from absolute methanol its melting point was 252.5–254° and not depressed when mixed with an authentic specimen.

Dihydroflavothebaone Trimethyl Ether (XII).—Flavothebaone trimethyl ether was hydrogenated over PtO_2 in glacial acetic acid as described by Schöpf.[4] Colorless needles were obtained on recrystallization from absolute methanol, m.p. 242–244° with browning after melting (lit.[4] 219–20°, clear at 238°); infrared spectrum ($CHCl_3$ solution): 5.82, 6.21, 6.31 μ; ultraviolet spectrum: λ_{max}^{EtOH} 291–300 mμ (3.66); 2,4-dinitrophenylhydrazone: m.p. 251–252°. ultraviolet spectrum: λ_{max}^{EtOH} 377 mμ (4.4).

Anal. Calcd. for $C_{33}H_{35}O_8N_5$: C, 62.94; H, 5.60; N, 11.12. Found: C, 62.82; H, 5.64; N, 11.18.

Dihydroflavothebaol Trimethyl Ether (XIII). A. From Flavothebaol Trimethyl Ether (XI).—Flavothebaol trimethyl ether (250 mg.) was hydrogenated over PtO_2 in 40 ml. of glacial acetic acid. After 70 minutes H_2 uptake had stopped at 0.91 mole. After filtration and evaporation of most of the acetic acid, the free base was precipitated with aqueous ammonia. Recrystallization from absolute ethanol gave colorless clusters of needles, m.p. 193–194°.

B. From Dihydroflavothebaone Trimethyl Ether (XII).—Dihydroflavothebaone trimethyl ether (500 mg.) was slurried in 50 ml. of absolute ether and reduced with $LiAlH_4$. The product was worked up in the usual way and after several recrystallizations from absolute ethanol, gave colorless needle clusters, m.p. 193–194°, with no depression on mixing with a specimen prepared by method A; infrared spectrum (KBr): 2.80, 6.25, 6.37 μ; ultraviolet spectrum: λ_{max}^{EtOH} 288.5 mμ (3.74), shoulder *ca.* 300 mμ.

Anal. Calcd. for $C_{27}H_{33}O_5N$: C, 71.81; H, 7.37; N, 3.10. Found: C, 71.62; H, 7.11; N, 3.37.

Treatment of Dihydroflavothebaol Trimethyl Ether (XIII) with MnO_2.—Agitation of dihydroflavothebaol trimethyl ether with active MnO_2 in absolute benzene for 24 hr. gave back only unchanged starting material, identified by m.p., mixture m.p. and ultraviolet spectrum.

Thebainehydroquinone Monomethyl Ether[14] (IIIb).—IIIb was prepared from thebainehydroquinone (IIIa) as described by Schöpf, by heating with methyl *p*-toluenesulfonate in the absence of base.[4] After recrystallization from absolute methanol, off-white rectangular plates were obtained, m.p. 238–240° (lit.[4] 238°); infrared spectrum (KBr): 3.01, 6.13, 6.25 μ; ultraviolet spectra: λ_{max}^{EtOH} (0.1 *N* H^+) 310 mμ (3.83) and shoulder *ca.* 290 mμ; λ_{max}^{EtOH} (0.1 *N* OH^-) 320 mμ (3.63) and shoulder *ca.* 294 mμ.

Flavothebaone Monomethyl Ether (XIV).—XIV was prepared by rearrangement of thebainehydroquinone monomethyl ether (IIIb) as described by Schöpf.[4] Isolated as the hydrochloride and crystallized from water, it formed light yellow cubes (presumably a dihydrate); infrared spectrum (KBr): 2.94, 3.13, 3.27, 3.69(w), 5.85, 5.95, 6.20, 6.30 μ; ultraviolet spectra (intensities calculated on basis of the dihydrate formula): λ_{max}^{EtOH} (0.1 *N* H^+) 280 mμ (3.49), 344 mμ (3.53) and shoulder *ca.* 320 mμ; λ_{max}^{EtOH} (0.1 *N* OH^-) *ca.* 240 mμ shoulder on intense end-absorption, 293 mμ (3.78) and 404 mμ (3.32).

Ultraviolet Spectral Studies.—The spectra presented in Table I were taken as described below.

TABLE I

Compound and medium	λ_{max}^{EtOH} mμ (log ε)	Color of solution
Flavothebaone		
Acidic	279(3.51), 346(3.56)	Yellow
Basic	257(4.04), 298(3.84)	Red-brown
Reverse (acidic)[a]	285(3.54), 315sh.	.....
Reverse after 20 hr.[a]	283(3.62), 315sh.	.....
Double reverse (basic)[a]	257(3.46), 298(3.50)	.....
Dihydroflavothebaone		
Acidic	291(3.73), 309(3.70)	Colorless
Basic	259(3.89), 303(3.84)	Pale pink
Reverse (acidic)[b]	285(3.71), 310(3.33)	.....
Flavothebaone monomethyl ether		
Acidic	280(3.49), 344(3.53), 320sh.	Yellow
Basic	293(3.78), 404(3.32)	Bright yell.
Reverse (acidic)[b]	280(3.52), 344(3.54), 320sh.	Yellow

[a] It appears that the KCl precipitate adsorbs some of the alkaloid. Note that the double reverse has lower intensities than the original spectrum in alkaline solution. [b] These reverses were done with ethanolic H_2SO_4 in place of HCl. It appears from the intensities of flavothebaone monomethyl ether after reverse that the $KHSO_4$ does not adsorb appreciable quantities of alkaloid.

A. Acidic.—Ten-ml. aliquots of ethanolic solution of alkaloid were acidified with 2.5 ml. of 1.0 *N* ethanolic HCl and diluted to 25.0 ml. with ethanol. These solutions were run against a similarly prepared solvent blank.

B. Basic.—Ten-ml. aliquots were prepared and run as A substituting 1.0 *N* ethanolic KOH for the HCl.

C. Reverse.—These experiments were run by taking 10.0-ml. aliquots of alkaloid stock solutions and adding

(13) Poor results were obtained when this reagent was contaminated with the iodide from which it is prepared. A good grade of this reagent is readily prepared by agitating a solution of phenyltrimethylammonium iodide with excess AgCl for 48 hr. After filtering and stripping the water, a crude product is obtained which gives a negative test for I^- (no iodine color in organic layer on shaking a sample with "Clorox" and CCl_4). It is conveniently crystallized from acetone–ether.

(14) The position of the new methyl group in IIIb had originally been assigned as shown by Schöpf. A series of experiments, involving chiefly a spectral study of IIIb and many related compounds, has tended to confirm this structure. A full discussion of this point would be out of place here, however, and should appear in a separate publication.

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2.5 ml. of 1.0 *N* ethanolic KOH solution. After brief shaking 5.0-ml. portions of 1.0 *N* ethanolic HCl were added and the solutions diluted to 25.0 ml. Portions of the solutions were centrifuged and the spectra run against similarly prepared blanks.

D.—The double reverse was achieved by treating a 5.0-ml. aliquot of the reverse (acidic) solution with 5.0 ml. of 1.0 *N* ethanolic KOH, diluting to 25.0 ml., centrifuging and running against a similarly prepared blank.

Anaerobic Attempt to Recover Flavothebaone from Dilute Base.—A stock solution of flavothebaone was de-oxygenated with N_2 for 0.5 hour as was an ethanolic KOH solution. Some of the stock solution was pipetted into the KOH solution while continuing to sweep with N_2. The solution turned orange-yellow but became light yellow after a few minutes. An evacuated gas cell was attached to the system and a portion of the solution was thereby withdrawn. The ultraviolet spectrum of this yellow sample was the same as those of the red-brown solutions obtained without the above precautions. A portion of the alkaline solution was poured into ethanolic H_2SO_4, centrifuged and the spectrum taken. It was the same as the spectrum given by flavothebaone after acidification of the basic solution as listed in Table I.

ITHACA, N. Y.

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

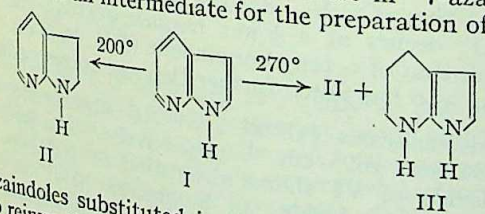
7-Azaindole. IV. The Hydrogenation of 7-Azaindole and Related Compounds[1,2]

BY MICHAEL M. ROBISON, FLORENCE P. BUTLER AND BONNIE L. ROBISON

RECEIVED DECEMBER 12, 1956

High-pressure hydrogenation of 7-azaindole (I) in neutral medium at 200° produces 2,3-dihydro-7-azaindole (II), while at higher temperatures the pyrroline ring is cleaved to yield 2-amino-3-ethylpyridine (IV). In acid medium, however, the ring is hydrogenated at atmospheric temperature and pressure to form 2,3,3a,4,5,6-hexahydro-1H-pyrrolo[2,3-b]pyridine (VI). The structure of this product was demonstrated by comparison with the corresponding hexahydro compounds obtained from the reductions of 1-methyl-7-azaindole (VII) and 7-methyl-7H-pyrrolo[2,3-b]pyridine (IX). 1,7-Dimethyl-1H-pyrrolo[2,3-b]pyridinium iodide (XV), on the other hand, reacts with five moles of hydrogen under similar conditions and 1-methyl-3-(2-methylaminoethyl)-piperidine hydroiodide (XVI) is formed. Miscellaneous derivatives of 7-azaindole including a number resulting from ring closure across the 1- and 7-positions are also described.

In 1943, Kruber[3] attempted to cleave the pyrrole ring of 7-azaindole (I) by high-pressure hydrogenolysis with a nickel catalyst in decalin solution. He reported that the pyrrolopyridine, unlike indole which can be cleaved to form *o*-ethylaniline,[4] reacts with one mole of hydrogen at 200° to form 2,3-dihydro-7-azaindole (II), and that at 250–270° a tetrahydroazaindole is produced as well. On the basis of its formation of a dibenzoyl derivative, Kruber proposed the structure 4,5,6,7-tetrahydro-7-azaindole (III) for the latter, but no conclusive evidence was offered for the structure of either hydrogenation product. An interest in "7-azaindoline" as an intermediate for the preparation of 7-azaindoles substituted in the pyridine ring led us to reinvestigate the course of these hydrogenations and to extend the investigation to related reductions.



Hydrogenation of 7-azaindole at the prescribed[3] temperature and pressure with an aged W-4 Raney nickel catalyst[5] afforded a dihydro compound apparently identical with that described by Kruber. Evidence in support of the azaindoline structure was obtained from the ultraviolet spectrum of the compound (Fig. 1). The absorption maxima in the

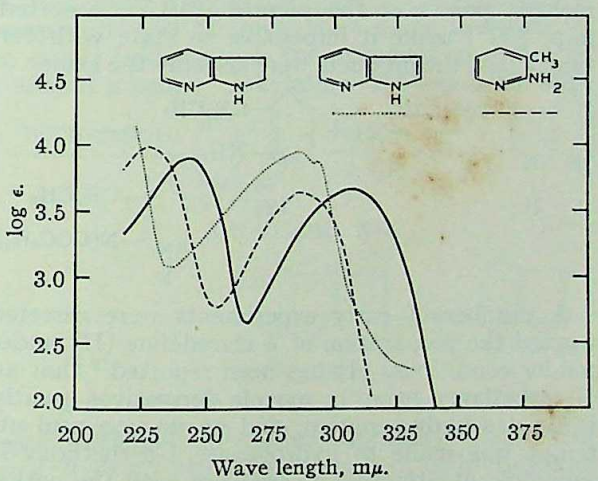


Fig. 1.

spectrum of the dihydro derivative show a bathochromic shift relative to the 7-azaindole absorption and the spectrum of II is more comparable to that of 2-amino-3-picoline, although the peaks in the latter spectrum also occur at a shorter wave length. Similar relationships are noted between the spectra of 2-methylindole,[6] 2-methylindoline[6] and *o*-toluidine[7] and between those of indene and hydrindene.[8] Although such a comparison does not provide conclusive evidence for the 2,3-dihydro structure, it does lend strong support to such a formulation. Attempts at substitution reactions in the pyridine ring of the dihydro compound are anticipated and these, if successful, will serve to confirm the structure.

In this Laboratory it was found that hydrogena-

(1) This investigation was supported by a research grant, number C-2574, from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) Preceding paper, M. M. Robison and B. L. Robison, THIS JOURNAL, **78**, 1247 (1956).

(3) O. Kruber, *Ber.*, **76**, 128 (1943).

(4) J. Von Braun, O. Bayer and G. Blessing, *ibid.*, **57**, 392 (1924).

(5) A. A. Pavlic and H. Adkins, THIS JOURNAL, **68**, 1471 (1946).

(6) H. Kondo and H. Katsura, *Ber.*, **73**, 1424 (1940).

(7) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951.

(8) R. A. Morton and A. J. A. De Couveia, *J. Chem. Soc.*, 911 (1934).

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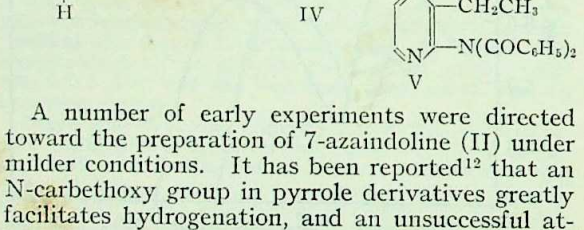
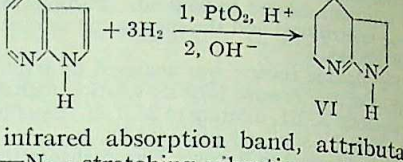
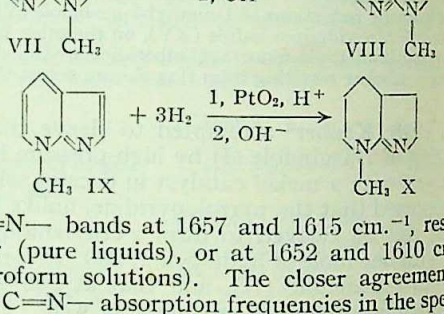
tion of azaindole at 250–270° afforded a mixture of the dihydro compound and a slightly more volatile material, as reported by Kruber.[3] Although distillation equipment capable of effecting a completely clean separation was not available, the ultraviolet spectra of the lower-boiling fractions were measured. These spectra were inconsistent with the pyrrole structure but corresponded very closely to the spectrum of 2-amino-3-picoline (see Fig. 1 and Experimental). The aminopyridine derivative likely to be formed in the reaction would be the known[9] 2-amino-3-ethylpyridine (IV) resulting from hydrogenolysis of the pyrrole ring and it was found that the low-boiling fractions did consist mainly of this "tetrahydro compound" contaminated by the 7-azaindoline. The identity of the purified crystalline material was demonstrated by mixture melting point of the amine and of its picrate with authentic samples of these compounds. Further, since 2-amino-3-picoline[10] and 2-aminopyridine[11] readily form dibenzoyl derivatives, it seemed possible that the "tetrahydro derivative" of Kruber was actually the hydrogenolysis product. The dibenzoyl derivative V melted at 166°, in fair agreement with the melting point (168°) reported by Kruber, but the discrepancies in the physical constants of the amine itself and in the melting points of the picrate (210.5°, reported[3] m.p. 200°) make it impossible to state with certainty that the products were actually the same.



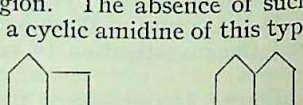
A number of early experiments were directed toward the preparation of 7-azaindoline (II) under milder conditions. It has been reported[12] that an N-carbethoxy group in pyrrole derivatives greatly facilitates hydrogenation, and an unsuccessful attempt was made to hydrogenate 1-carbethoxy-7-azaindole at atmospheric pressure with the active W-4 Raney nickel.[5] 7-Azaindole also was recovered unchanged after prolonged treatment with refluxing ethereal lithium aluminum hydride, in agreement with results observed with indole itself.[13] In a further search for mild reduction conditions hydrogenation in acid medium was tried, since the pyridine ring undergoes facile reduction in such circumstances.[14] It was found that 7-azaindole reacts with 3 moles of hydrogen at atmospheric temperature and pressure when stirred with Adams catalyst in aqueous ethanolic hydrochloric acid. The product, which is considered to be 2,3,3a,4,5,6 - hexahydro - 1H - pyrrolo[2,3 - b]pyridine (VI), is a strong base ($pK_b \sim 2.3$) and has an



intense infrared absorption band, attributable to the >C=N— stretching vibration, at 1652 cm.$^{-1}$ (KBr disk) or 1635 cm.$^{-1}$ ($CHCl_3$ solution). In an effort to provide closely-related spectral models to ascertain the position of the >C=N— bond, 1-methyl-7-azaindole (VII) and 7-methyl-7H-pyrrolo[2,3-b]pyridine (IX)[15] were also hydrogenated. The products were assigned the structures 1-methyl-2,3,3a,4,5,6-hexahydro-1H-pyrrolo[2,3-b]-pyridine (VIII) and 7-methyl-2,3,3a,4,5,6-hexahydro-7H-pyrrolo[2,3-b]pyridine (X) on the bases of the absence of >NH stretching absorptions in their infrared spectra and the occurrence of



>C=N— bands at 1657 and 1615 cm.$^{-1}$, respectively (pure liquids), or at 1652 and 1610 cm.$^{-1}$ (chloroform solutions). The closer agreement of the >C=N— absorption frequencies in the spectra of VI and VIII is at least strongly suggestive of the $\Delta^{7(7a)}$-structure, rather than the $\Delta^{1(7a)}$-structure corresponding to X. Further support for this formulation is to be found in a thorough-going series of investigations by Witkop,[16] who has found that the >C=N— absorption of hexahydroindole (XI) occurs at a lower frequency (1647 cm.$^{-1}$) than that of octahydroquinoline (XII, 1658 cm.$^{-1}$) and who has noted further that the corresponding hydrochlorides exhibit $>C{=}\overset{+}{N}H$ absorptions at 1684 and 1695 cm.$^{-1}$, respectively. The hydrochloride of VI shows absorption at 1684 cm.$^{-1}$ (KBr) and is lacking an "immonium band" in the 4.5–5.5 μ region. The absence of such a band is expected for a cyclic amidine of this type.[16c]



Further investigations of VI included dehydrogenation with palladium-on-charcoal. That the ring system had not been ruptured in the reduction was demonstrated by the formation of 7-azaindole. Early experiments also included benzoylation by several methods. From all of these a product was isolated whose analysis corresponded to the di-

(9) M. M. Robison and B. L. Robison, This Journal, **77**, 457 (1955).

(10) O. Seide, *Ber.*, **57**, 1802 (1924).

(11) E. H. Huntress and H. C. Walter, *J. Org. Chem.*, **13**, 735 (1948).

(12) H. Adkins and H. L. Coonradt, This Journal, **63**, 1563 (1941).

(13) P. L. Julian and H. C. Printy, *ibid.*, **71**, 3206 (1949).

(14) H. S. Mosher in Elderfield's "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, Vol. I, p. 623.

(15) M. M. Robison and B. L. Robison, This Journal, **77**, 6554 (1955).

(16) (a) B. Witkop, *ibid.*, **78**, 2873 (1956); (b) **76**, 5597 (1954); (c) *Experientia*, **10**, 420 (1954).

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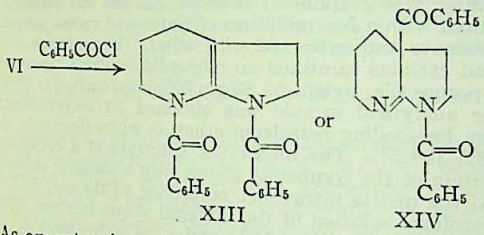
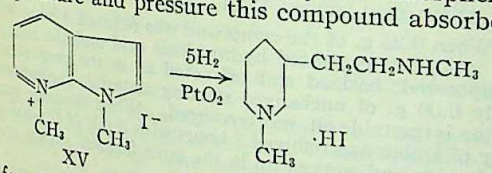
benzoyl derivative of VI. In contrast to these results neither VIII nor X would form benzoyl derivatives under similar conditions. The structure of the acylation product is not clear. On the basis of structure VI, possibilities include either XIII or XIV for the derivative. On hydrolysis in concentrated hydrochloric acid an 87% yield of benzoic acid was obtained from the material, though the amine itself could not be isolated. Further experiments, however, demonstrated that the amine is relatively unstable to aqueous acid or base. The infrared spectrum of the dibenzoyl derivative provides no conclusive evidence for either structure, though it seems to favor structure XIV, since in the double-bond stretching region two strong absorptions are noted at 1635 and 1677 cm.$^{-1}$ as well as a shoulder at 1650 cm.$^{-1}$. On the basis of the available evidence, however, the exact structure must remain in doubt. In conjunction with the benzoylation studies, it may be noted that the amine was found to react in a 1:1 molar ratio with phenyl isocyanate. This result is in agreement with the proposed structure.

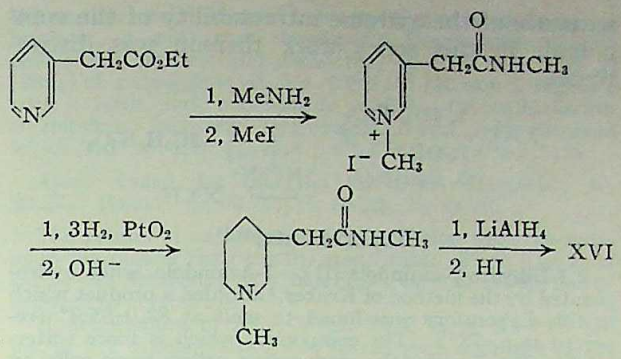


As an extension of the above reductions it was of interest to investigate the course of hydrogenation of 1,7-dimethyl-1H-pyrrolo[2,3-b]pyridinium iodide (XV). Rather surprisingly, at atmospheric temperature and pressure this compound absorbed

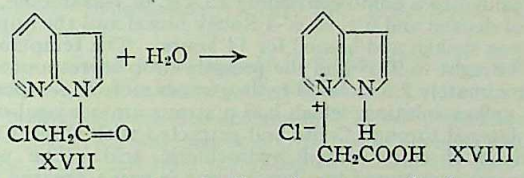


a fourth mole of hydrogen as rapidly as the first three and a fifth mole somewhat more slowly. Further, addition of hydriodic acid to the aqueous ethanol solutions completely prevented hydrogen uptake. The reaction of five moles of hydrogen indicated that one of the rings had been opened, and by analogy to the course of hydrogenation of compound IX in *neutral* medium,[15] it was expected that this would be the pyrrolidine ring. That the compound isolated was indeed the piperidine derivative XVI was demonstrated by comparison with an authentic sample, prepared by an unequivocal synthesis as shown below.

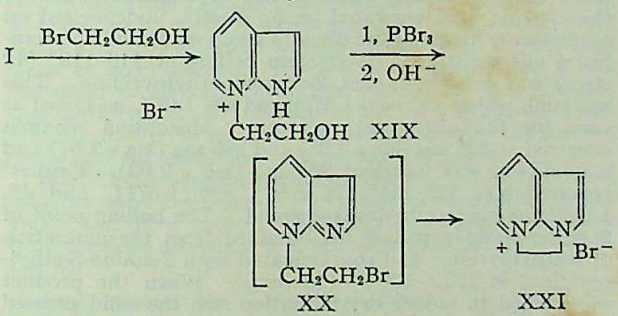
Some earlier experiments were directed to the preparation of tricyclic derivatives of azaindole by ring closure across the two nitrogen atoms, with the expectation of studying hydrogenations and other reactions in this series. Thus 1-chloroacetyl-7-azaindole (XVII) was prepared to attempt to form by intramolecular alkylation at the 7-position a product analogous to the imidazo[1,2-a]pyridine derivative obtained[17] on similar treatment of 2-



aminopyridine. On standing exposed to the atmosphere, or more readily on heating in water, the compound did undergo alkylation, but only with concomitant hydrolysis of the amide linkage to form the 7-carboxymethyl-1H-pyrrolo[2,3,-b]pyridinium chloride (XVIII).



Because of the facile cleavage of the amide linkage, work was discontinued on the chloroacetyl compounds and attempts were made to construct an *ethano* bridge across the nitrogens according to a second scheme. Alkylation of 7-azaindole with



2-bromoethanol proceeded normally[15] to form 7-(2-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridinium bromide (XIX). Treatment of this salt with phosphorus tribromide apparently replaced the alcohol function by bromine to form the corresponding 2-bromoethyl salt and on basification a yellow color developed, indicating the formation of a 7-alkyl-7H-pyrrolo[2,3-b]pyridine.[15] When this was immediately extracted into ether and the solution warmed the color was largely discharged and a white salt, apparently impure XXI, was formed. Numerous attempts to purify this quaternary bromide were unsuccessful, however. Some analyses indicated the possibility of solvates, but the only satisfactory result obtained was that for the picrate corresponding to XXI. Several experiments were carried out on the hydrogenation of the crude bromide, with an apparent reaction of approximately four molar equivalents of hydrogen. From the reduction mixture a distyphnate was prepared whose analysis was satisfactory for XXII, but because of the large percentage of styphnic acid in the adduct these analytical data provided no conclusive information about the hydrogenation state. As a con-

(17) A. E. Chichibabin, *Ber.*, **57**, 2092 (1924).

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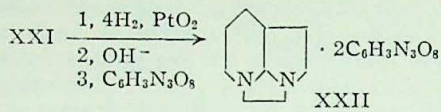
sequence of the extreme intractability of the compounds in this series work thereon was discontinued.



XXII

Experimental[18,19]

2,3-Dihydro-7-azaindole (II).—7-Azaindole, when hydrogenated by the method of Kruber,[3] afforded a product which in this Laboratory was found to melt at 83.0–85.0° (reported m.p. 78°). The compound, which is more water-soluble than 7-azaindole, gives only a yellow-green color on treatment with aqueous sodium nitroprusside and sodium hydroxide and the color changes to a pale green on acidification. These results are in contrast to the exceptionally strong blue-green → blue color reaction with azaindole.[9] The benzoyl derivative, prepared by the method of Kruber, melted at 119.5–121.5° (reported m.p. 120°).

2-Amino-3-ethylpyridine (IV).—Hydrogen at 78 atmos. was added to a bomb containing 22.4 g. of 7-azaindole, 100 ml. of decalin and 5 g. of W-4 Raney nickel and the apparatus was shaken and heated for 14 hours. The temperature was brought to 270° and the pressure-drop corresponded to approximately 2.5 moles of hydrogen per mole of compound. The yellow solution, which had a strong ammoniacal odor, was filtered through Celite and extracted with three 10-ml. portions of concentrated hydrochloric acid. The water layer was evaporated to a low volume *in vacuo*, treated with excess potassium carbonate and extracted with chloroform. The chloroform solution was dried over potassium carbonate and distilled. The product, together with some dihydro compound, was collected in four fractions (total 4.67 g.) boiling over the range 114° (12 mm.) to 135° (10 mm.). After the high-boiling fractions had crystallized partially, the crystals were separated (m.p. 78–82°, undepressed on admixture with authentic dihydro compound) and the combined oils redistilled. A fraction boiling at 116–118° (12 mm.) was relatively pure 2-amino-3-ethylpyridine. This material, which had $n^{24}D$ 1.5728 and d^{20}_4 1.047, was used as such for the ultraviolet spectrum. Absorption maxima occurred at 230 mμ (log ε 3.95) and 290 mμ (log ε 3.67) and a minimum was found at 258 mμ (log ε 2.93). Kruber[3] reported b.p. 133–134° (15 mm.), $n^{20}D$ 1.57117 and d^{20}_4 1.0891 for his tetrahydro compound. The boiling point of 2-amino-3-ethylpyridine[9] (as obtained from the amination of 3-ethylpyridine and contaminated with 2-amino-5-ethylpyridine) is 122.5–128.5° (18 mm.). When the product was chilled to induce crystallization and the solid pressed on porous tile and recrystallized from low-boiling petroleum ether, white plates were obtained, m.p. 41.0–41.5° alone and m.p. 41.5–43.5° on admixture with authentic 2-amino-3-ethylpyridine (reported[9] m.p. 43–45°).

2-Amino-3-ethylpyridine Picrate.—This adduct was prepared by reaction of the recrystallized amine with picric acid in 95% ethanol and recrystallization from the same solvent. There were obtained yellow needles, m.p. 210.0–211.0° dec. On admixture with picrate prepared from authentic amine (m.p. 209.0–210.5° dec.) these melted at 208.5–210.5° dec.

Anal. Calcd. for $C_7H_{10}N_2 \cdot C_6H_3N_3O_7$: C, 44.45; H, 3.73. Found: C, 44.61; H, 3.62.

2-(Dibenzoylamino)-3-ethylpyridine (V).—This derivative was prepared by the method of Huntress and Walter[11] for 2-(dibenzoylamino)-pyridine except that the crude product was washed with ethanol, with 5% hydrochloric acid and with 5% sodium bicarbonate to remove monobenzoyl compound and colored impurities. The yield of washed product, which had m.p. 159.5–162.5°, was 53%. It was found that recrystallization from ethanol[11] resulted in a material with a wide melting range, but recrystallization from 1:3 benzene–cyclohexane afforded white prisms, m.p. 165.5–166.5°.

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: N, 8.48. Found: N, 8.40.

(18) Melting points are corrected, boiling points uncorrected.

(19) Analyses by Drs. Weiler and Strauss, Oxford, England, except for some nitrogen determinations carried out by a semimicro Kjeldahl technique in this Laboratory.

1-Carbethoxy-7-azaindole.—To a stirred solution of 5.90 g. of 7-azaindole and 3.95 g. of dry pyridine in 50 ml. of anhydrous ether a solution of 5.40 g. of ethyl chloroformate in 50 ml. of dry ether was added over a period of one hour. The mixture was refluxed for 3.5 hours, cooled and filtered from the precipitate of pyridine hydrochloride, which was washed with four 25-ml. portions of ether. The combined ether solutions were dried over sodium sulfate, the solvent was removed and the residue was chilled to form oily crystals which, after pressing on filter paper and washing with low-boiling petroleum ether, weighed 7.61 g. (80%), m.p. 42.0–48.5°. The analytical sample was recrystallized from the same solvent as long white filaments, m.p. 47.0–49.5°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.31; N, 14.73. Found: C, 63.28; H, 5.28; N, 15.1.

Treatment of 7-Azaindole with Lithium Aluminum Hydride.—To a stirred solution of 145 mg. of lithium aluminum hydride in 15 ml. of dry ether was added a solution of 236 mg. of 7-azaindole in the same quantity of solvent. The mixture was refluxed 11 hours, the hydride decomposed and the ether dried and evaporated. Light-tan azaindole (0.21 g.) was recovered, m.p. 107.0–108.0°.

2,3,3a,4,5,6-Hexahydro-1H-pyrrolo[2,3-b]pyridine (VI).—A mixture of 2.36 g. of 7-azaindole, 50 ml. of 95% ethanol, 10 ml. of concentrated hydrochloric acid and approximately 0.5 g. of pre-reduced Adams catalyst was stirred with hydrogen for 12 hours, during which time about 103% of the theoretical hydrogen was absorbed. The colorless solution was evaporated *in vacuo* and the oily residue was treated with a few milliliters of water and excess potassium carbonate and extracted with ether. Evaporation of the dried extracts furnished an oily solid, which after pressing on porous tile, weighed 1.88 g. (76%) and melted at 88–96°. The analytical sample was obtained on recrystallization from low-boiling petroleum ether as white filaments, m.p. 103.5–104.5°. The ultraviolet spectrum of a cyclohexane solution of the compound shows only a shoulder extending into the quartz ultraviolet range, log ε (214 mμ) 3.72. A chloroform solution of the material shows infrared absorption at 3420 cm.$^{-1}$ (>NH) and a >C=N— band at 1635 cm.$^{-1}$ with a slight shoulder at 1665 cm.$^{-1}$ The pK_b, taken as equal to pOH at half-neutralization, is 2.3.

Anal. Calcd. for $C_7H_{12}N_2$: C, 67.68; H, 9.76; N, 22.56; neut. equiv., 124.2. Found: C, 67.70; H, 9.67; N, 22.52; neut. equiv., 125.1, 124.5.

When 0.25 g. of the compound was refluxed 4 hours with 10 ml. of concentrated hydrochloric acid and the solution evaporated, basified and extracted as in the preparation, only 0.06 g. of unchanged starting material, accompanied by an intractable oil, was recovered. When the same quantity of amine was refluxed 3 hours with 5 ml. of 5% sodium hydroxide and worked up in the same fashion, only a small quantity of oil was isolated.

Hydrochloride of Hexahydroazaindole.—After several unsuccessful attempts to precipitate this salt from anhydrous ether, the amine was treated with excess concentrated hydrochloric acid and the solution evaporated to dryness. The semi-liquid residue was dried at 60° (1 mm.) for 6 hours, during which period it became fairly hard. The exceptionally hygroscopic solid was quite soluble in most organic solvents. It could be recrystallized, albeit not satisfactorily, from dry benzene. The shiny white plates had m.p. 143.5–147.0°.

Anal. Calcd. for $C_7H_{13}N_2Cl$: C, 52.33; H, 8.15; N, 17.44. Found: C, 51.66; H, 8.10; N, 16.20.

Dehydrogenation of Hexahydroazaindole.—A mixture of 0.25 g. of the amine and 0.12 g. of 5% palladium-on-charcoal was heated at 250° for 3 hours in a nitrogen atmosphere. The mixture was extracted with hot cyclohexane and the extract was filtered through a bed of Darco and evaporated to yield 68 mg. of oily, yellow solid. This was pressed on porous tile and washed with cyclohexane, then dissolved in a few milliliters of 5% hydrochloric acid and treated with Darco. Precipitation with sodium bicarbonate afforded white solid, m.p. 105.0–106.0° both alone and on admixture with 7-azaindole. The product gave a positive sodium nitroprusside test.[9]

Dibenzoyl Derivative of VI.—Benzoyl chloride (1.12 g.) was added rapidly to a stirred mixture of 0.50 g. of amine, 10 ml. of anhydrous pyridine and 20 ml. of dry benzene and the solution was heated at 65° for 0.5 hour, during which

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time a heavy oil layer separated. The mixture was then poured into 200 ml. of water and extracted as directed in Shriner, Fuson and Curtin.[20] Evaporation of the benzene layer left a residue which was dried *in vacuo* and washed with cold ethyl acetate. The resulting 0.79 g. (59%) of cream-colored solid had m.p. 140–144°, and was insoluble in dilute acid. The analytical sample was obtained on recrystallization from 1:3 ethanol–water as large leaves, m.p. 143.5–147.5°. No means of narrowing the melting range was found.

Anal. Calcd. for $C_{21}H_{20}N_2O_2$: C, 75.87; H, 6.08; N, 8.43. Found: C, 75.62; H, 5.93; N, 8.63.

When the reaction was carried out with equimolar quantities of benzoyl chloride and amine, only the dibenzoyl product was isolated, but in greatly reduced yield. Benzoylation in sodium hydroxide or in an ethereal suspension of potassium carbonate gave the same results.

When 664 mg. of the derivative was refluxed 5 hours with 5 ml. of concentrated hydrochloric acid and the cooled solution extracted with ether, 426 mg. (87%) of benzoic acid, m.p. 122.0–123.0° (undepressed on admixture with authentic acid), was obtained. Evaporation, basification and extraction of the water layer afforded only 23 mg. of oil.

1-Phenylcarbamyl-2,3,3a,4,5,6-hexahydro-1H-pyrrolo-[2,3-b]pyridine.—Equimolar quantities of the hydrogenation product and phenyl isocyanate were mixed and the solid product was dissolved in 5% hydrochloric acid and filtered to remove traces of diphenylurea. The amide was precipitated by base in 93% yield and recrystallized from *n*-hexane for analysis. The resulting fine, white needles had m.p. 86.5–89.0° (cloudy melt). A narrower melting range could not be attained.

Anal. Calcd. for $C_{14}H_{17}N_3O$: N, 17.27. Found: N, 17.20.

7-Methyl-2,3,3a,4,5,6-hexahydro-7H-pyrrolo[2,3-b]pyridine (X).—A solution of 3.085 g. of IX[15] in 50 ml. of 95% ethanol and 10 ml. of concentrated hydrochloric acid reacted with 105% of the theoretical volume of hydrogen when reduced under the conditions employed for 7-azaindole. The hydrogenation mixture was worked up by the usual method except that the base was extracted into chloroform and distilled. There was thus obtained a 68% yield of hygroscopic, colorless oil, b.p. 108° (22 mm.) to 109° (18 mm.). The redistilled analytical sample had b.p. 105–106° (18 mm.), $n^{25}D$ 1.5077 and $d^{23.5}{}_4$ 0.996. The pK_b, determined by titration, was found to be 2.5.

Anal. Calcd. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27; neut. equiv., 138.2. Found: C, 69.42; H, 10.08; N, 20.80; neut. equiv., 139.1.

An attempt to benzoylate this amine by the pyridine method using a 1.5:1 molar excess of benzoyl chloride was unsuccessful. No oil layer separated during the reaction period and the product from the extracts consisted of a very small quantity of dark oil from which crystals of benzoic acid separated on standing.

1-Methyl-7-azaindole (VII).—It was found that this compound can be prepared in greatly improved yield by a modification of the method previously described.[15] 7-Azaindole (5.90 g.) was dissolved in 100 ml. of dry xylene and refluxed and stirred in a nitrogen atmosphere with 2.40 g. of sodium hydride for 3 hours. The suspension was cooled, 14.20 g. of methyl iodide in 25 ml. of xylene was added and the mixture was refluxed again for 1.5 hours. Excess hydride was then decomposed by the addition of ethanol after which the xylene layer was extracted with a mixture of 100 ml. of water and 25 ml. of concentrated hydrochloric acid in three portions. The acid solution was then made basic and steam distilled directly after which the procedure was as previously described.[15] The faintly-yellow product from one distillation had b.p. 114–122° (25 mm.) and $n^{19}D$ 1.5978, and weighed 4.10 g. (62%). Use of a still larger molar ratio of sodium hydride and methyl iodide was not tried, but it seems probable that such a procedure might further improve the yield.

1-Methyl-2,3,3a,4,5,6-hexahydro-1H-pyrrolo[2,3-b]pyridine (VIII).—When 5.766 g. of VII was hydrogenated in the same quantity of solvent and under the conditions described above, the theoretical quantity of hydrogen reacted. When the residue from the evaporation was made basic, however, a red color developed. Evaporation of the chloroform extracts and distillation afforded only 1.68 g. (28%) of pale-yellow oil, b.p. 108–113° (16 mm.), together with a large, red, non-volatile residue. On redistillation a colorless, intensely hygroscopic liquid was obtained which had b.p. 106° (15 mm.), $d^{26}{}_4$ 0.995 and $n^{24}D$ 1.5158.

Anal. Calcd. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.76; H, 10.32; N, 19.70.

The results of an attempted benzoylation were the same as in the case of the 7-methyl compound. From 0.55 g. of amine was obtained 0.31 g. of a brown oil which could not be induced to crystallize.

Hydrogenation of XV.—When 2.756 g. of XV[15] in 120 ml. of 5:1 ethanol–water was stirred with hydrogen in the presence of pre-reduced Adams catalyst from 0.5 g. of platinum oxide, four moles of hydrogen was taken up in 12 hours and a fifth mole reacted in another 15 hours. Filtration, evaporation and drying *in vacuo* left 2.7 g. of sticky, yellow solid which was recrystallized from acetonitrile under nitrogen. The recovery of white, crystalline material from the first recrystallization was typically only about 50%. The analytical sample of 1-methyl-3-(2-methylaminoethyl)-piperidine hydroiodide (XVI) had m.p. 140.0–142.0° (cloudy melt).

Anal. Calcd. for $C_9H_{21}N_2I$: C, 38.03; H, 7.45; N, 9.86. Found: C, 38.07; H, 7.51; N, 9.99.

N-Methyl-3-pyridineacetamide.—Ethyl 3-pyridineacetate[21] (24.78 g.) was dissolved in 50 ml. of aqueous methylamine which had been saturated at 0°, and the flask was stoppered tightly and allowed to stand for 71 hours. The solution was filtered to remove a small amount of insoluble impurity and evaporated to dryness *in vacuo*. On chilling, the residue crystallized affording a hygroscopic, slightly oily solid. This was boiled with cyclohexane and chilled to cause resolidification after which the hydrocarbon was decanted and the residue dried thoroughly *in vacuo*. The product (m.p. 56–64°) weighed 22.89 g. (theoretical yield 22.53 g.). No solvent was found from which the material could be recrystallized. For attempted purification it was subjected to several evaporative distillations in a sublimation apparatus at 140° (0.5 mm.), but the white product had m.p. 61–65°. No method was found to narrow the melting range and the analytical results were 1–3% low.

N-Methyl-3-pyridineacetamide Picrate.—This derivative was prepared by reaction of equimolar quantities of the amide and picric acid in 95% ethanol and recrystallization from the same solvent. The yellow needles had m.p. 177.5–178.5°.

Anal. Calcd. for $C_8H_{10}N_2O \cdot C_6H_3N_3O_7$: C, 44.33; H, 3.45; N, 18.47. Found: C, 44.49; H, 3.11; N, 18.40.

1-Methyl-3-(N-methylcarbamylmethyl)-pyridinium Iodide.—To 0.30 g. of amide was added 1.42 g. of methyl iodide and the mixture was allowed to stand overnight. The excess methylating agent was decanted and the crystalline product dried *in vacuo* to yield 0.59 g. (100%) of light-yellow solid, m.p. 117–125°. The analytical sample was obtained as pale-yellow needles from acetonitrile, m.p. 127.0–128.0°.

Anal. Calcd. for $C_9H_{13}N_2OI$: C, 37.00; H, 4.49; N, 9.59. Found: C, 37.44; H, 4.48; N, 9.66.

The reaction also was run on a 0.15 molar scale using only 0.5 mole of methyl iodide. With such quantities, however, efficient cooling is necessary to avoid overheating and loss of product.

N,N′-Dimethyl-3-piperidineacetamide.—The methiodide (30.73 g.) and approximately 1.5 g. of reduced Adams catalyst were added to 135 ml. of 80% ethanol and hydrogenated at an initial pressure of 3 atmospheres. After 34 hours, reaction had ceased and the pale-gold solution was filtered through Celite and evaporated to dryness. Water (25 ml.) and a small quantity of sodium bisulfite were added and the mixture was made strongly basic with potassium carbonate and extracted with chloroform. The extracts were dried over potassium carbonate and evaporated. The residue crystallized readily on drying *in vacuo* to yield 16.01 g. (89%) of a white solid, m.p. 76–79°. The

(20) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 226.

(21) R. L. Maland and P. M. Dehn, THIS JOURNAL, 69, 1797 (1947).

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analytical sample was recrystallized from cyclohexane as white filaments, m.p. 82.0–83.0°.

Anal. Calcd. for $C_9H_{18}N_2O$: C, 63.47; H, 10.68; N, 16.45. Found: C, 63.33; H, 10.48; N, 16.10.

1-Methyl-3-(2-methylaminoethyl)-piperidine Hydroiodide (XVI).—To a stirred suspension of 1.5 g. of lithium aluminum hydride in 75 ml. of dry tetrahydrofuran, a solution of 3.41 g. of the piperidine amide in 25 ml. of tetrahydrofuran was added over a 20-minute period. The mixture was refluxed with stirring for 8 hours, 0.75 g. more hydride being added after 2 hours. The excess reducing agent was decomposed with ethanol, approximately 50 ml. of saturated aqueous potassium hydroxide was added and the layers were separated. The aqueous layer was washed with additional ether and the combined organic solutions were dried over potassium hydroxide. The solvent was evaporated and the product distilled, during which process an appreciable quantity of water-soluble solid residue separated. The distillation product weighed only 0.49 g. (16%) and had b.p. 68–74° (15 mm.). The amine was not investigated further as such but was converted directly to the hydroiodide XVI by addition of the theoretical quantity of aqueous hydriodic acid. Evaporation of the solution *in vacuo* afforded a white solid which after washing with acetonitrile weighed 0.83 g. and had m.p. 139.5–141.5°. Recrystallizations from this solvent in a nitrogen atmosphere produced the analytical sample, m.p. 141.5–143.0° (cloudy melt). On admixture with the hydrogenation product this melted at 142.0–143.5°.

Anal. Calcd. for $C_9H_{21}N_2I$: N, 9.86. Found: N, 9.87.

1-Chloroacetyl-7-azaindole (XVII).—To a stirred solution of 5.90 g. of 7-azaindole and 3.96 g. of anhydrous pyridine in 100 ml. of dry ether a solution of 5.55 g. of chloroacetyl chloride in 50 ml. of ether was added over a period of 35 minutes. During the addition the temperature was kept below −10°. Water (50 ml.) was then added to dissolve the yellow precipitate of pyridine hydrochloride, the layers were separated, the water layer was extracted with three 60-ml. portions of ether and the combined ether solutions were dried over magnesium sulfate. Evaporation of the solvent in a nitrogen stream at room temperature left a residue which crystallized partially on chilling. The crystals were separated from the oil by filtration and the latter was caused to deposit a small amount of additional solid on further cooling. The combined greenish-yellow crystals, after thorough pressing on filter paper, weighed 5.93 g. (61%) and melted at 102–105°. The analytical sample was obtained in the form of long, white needles from cyclohexane, m.p. 107.5–109.0.

Anal. Calcd. for $C_9H_7N_2OCl$: C, 55.53; H, 3.63; N, 14.40. Found: C, 55.91; H, 3.69; N, 14.52.

Attempted Cyclization of XVII.—When the chloroacetyl compound was allowed to stand exposed to the air for a month, it gradually liquefied, then resolidified. The resulting solid decomposed at about 212°. When 1.94 g. of the amide was heated 4 hours with 25 ml. of boiling water, the solid gradually dissolved and the solution became acidic. Evaporation of the colorless liquid *in vacuo* afforded an oil which, after drying over phosphorus pentoxide, was triturated with acetone to produce 1.02 g. (48%) of white solid, m.p. 216–218°. For analysis the strongly acidic compound was recrystallized from absolute ethanol through which gaseous hydrogen chloride was bubbled. The white 7-carboxymethyl-1H-pyrrolo[2,3-b]pyridinium chloride (XVIII) darkens at 190° and has m.p. 218.0–218.5° dec. The ultraviolet spectrum of a water solution has maxima at 224 mμ (log ε 4.30) and at 295 mμ (log ε 3.95) and a minimum at 252 mμ (log ε 2.70).

Anal. Calcd. for $C_9H_9N_2O_2Cl$: C, 50.83; H, 4.27; N, 13.18. Found: C, 51.28, 51.14; H, 4.40, 4.18; N, 12.99.

An attempt also was made to cyclize the amide in the absence of water. When the material was heated in refluxing xylene for 1.5 hours much decomposition ensued and no salt-like material separated from the solution. The polymeric products were not investigated further.

7-(2-Hydroxyethyl)-1H-pyrrolo[2,3-b]pyridinium Bromide (XIX).—A mixture of 5.90 g. of 7-azaindole and 31.2 g. of 2-bromoethanol was heated 1.5 hours on the steam-bath in a nitrogen atmosphere. The cooled mixture was poured into 300 ml. of ether and the white product was separated by filtration and dried *in vacuo*. There was thus obtained 10.69 g. (88%) of product with m.p. 161–168°. The analytical sample was prepared by recrystallization from *n*-propyl alcohol, m.p. 174.5–175.0°.

Anal. Calcd. for $C_9H_{11}N_2OBr$: C, 44.46; H, 4.57; N, 11.52. Found: C, 44.11; H, 4.84; N, 11.41.

Cyclizations of XIX.—To a stirred suspension of 2.43 g. of XIX in 50 ml. of dry toluene, which was maintained at 0°, a solution of 2.70 g. of phosphorus tribromide in 75 ml. of dry toluene was added over a period of 3 hours. Stirring was continued as the mixture was allowed to warm slowly to room temperature, after which it was allowed to stand overnight. The slurry was then refluxed gently for 2 hours, the toluene was decanted and the residue was covered with ether. Ice, followed by dilute sodium hydroxide solution, was added to the well-cooled mixture and the yellow ether layer was separated. The aqueous phase was then saturated with potassium carbonate and extracted with additional ether until the yellow color was removed completely. The extracts were dried briefly over magnesium sulfate and evaporated on the steam-bath to yield a yellow, oily solid. This was triturated with acetone and separated by filtration. The acetone solution was again evaporated to dryness to produce additional white solid which was separated in the same manner, the washings and evaporations being repeated until no additional product was obtained. The total yield of white solid, after one recrystallization from 1:4 absolute ethanol–carbon tetrachloride, was 0.82 g., m.p. 148.5–149.5° dec. Analytical results corresponding to a simple empirical formula were not obtained on recrystallization from this or other solvents. It was noted that after recrystallization the product *lost* weight on exposure to air while the weight remained *constant* on storing over phosphorus pentoxide. It was eventually determined that the material was a solvate containing carbon tetrachloride, for the desiccator-dried material gave a positive test for chlorine, on sodium fusion, as well as bromine. On exposure to air the carbon tetrachloride was lost, but was apparently replaced to some degree by water. Neither by this treatment nor on drying at elevated temperatures could a satisfactory sample be prepared. The ultraviolet spectrum of a water solution of a sample dried at 60° exhibits maxima at 230 mμ (log ε 4.20) and 292 mμ (log ε 3.94) and a minimum at 248 mμ (log ε (2.08), if the ε values are calculated on the basis of pure XXI.

From the supposed XXI, which can be named most simply as 1,7-ethano-1H-pyrrolo[2,3-b]pyridinium bromide, a picrate was prepared by reaction of 0.5 g. of the salt, 0.32 g. of sodium acetate trihydrate and 1.02 g. of picric acid in 30 ml. of water. Recrystallizations of the product from 95% ethanol produced the analytical sample, m.p. 146.0–147.0°.

Anal. Calcd. for $C_9H_9N_2 \cdot C_6H_2N_3O_7$: C, 48.26; H, 2.98; N, 18.76. Found: C, 48.42; H, 3.33; N, 18.3.

Hydrogenation of XXI.—A solution of 503 mg. of XXI in 25 ml. of 95% ethanol with Adams catalyst reacted with 3.64 molar equivalents of hydrogen in approximately 11 hours. The solution was filtered and evaporated to dryness and about one-third of the residue was treated with a solution of 0.49 g. of 2,4,6-trinitroresorcinol and 0.14 g. of hydrated sodium acetate in water. The resulting yellow precipitate was recrystallized from water and from methanol to produce the analytical sample of XXII, m.p. 195.5–196.0° dec.

Anal. Calcd. for $C_9H_{16}N_2 \cdot 2C_6H_3N_3O_8$: C, 39.26; H, 3.45; N, 17.44. Found: C, 39.14; H, 3.35; N, 17.7.

Absorption Spectra.—All ultraviolet spectra were measured on a Beckman model DU quartz spectrophotometer at concentrations varying from 10^{-4} to 5×10^{-5} *M*. The solvent was cyclohexane, unless otherwise specified. Infrared spectra were determined on either a Perkin–Elmer spectrophotometer or a Baird instrument by Dr. S. M. Nagy and associates at the Microchemical Laboratory, Massachusetts Institute of Technology.

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[CONTRIBUTION FROM THE ROBERT W. LOVETT MEMORIAL LABORATORIES FOR THE STUDY OF CRIPPLING DISEASES, MASSACHUSETTS GENERAL HOSPITAL AND THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

Partial Esterification of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside in Pyridine Solution[1]

BY ROGER W. JEANLOZ AND DOROTHY A. JEANLOZ

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Partial esterification of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside in pyridine solution with chlorides of carboxylic and sulfonic acids gave the monoester in position 2 in preponderant yield. When anhydrides were used for partial esterification, the carboxylic anhydrides gave the monoester in position 3 in preponderant yield, whereas the sulfonic anhydrides gave the monoester in position 2.

In order to study the influence of neighboring groups on the solvolysis of sulfonyl esters of glucose,[2] it has been necessary to prepare the various acetyl, benzoyl, methylsulfonyl and *p*-tolylsulfonyl derivatives of methyl 4,6-*O*-benzylidene-α-D-glucoside (I) reported in Fig. 1.

While this work was being completed, the preparation of some of the derivatives described here was reported either by different methods, or with quite different yields. Bourne, *et al.*,[3,4] have described the preparation of the partially substituted acetates III and IV and benzoates VI and VII using trifluoroacetyl intermediates. Since the preparation of the intermediates makes this method quite lengthy, the reagent is expensive and the yields starting from I are not excellent (III, 41%; IV, 38%; VI, 26%; VII, 41%), it seemed of interest to investigate the direct partial acetylation and benzoylation of I.

Monobenzoylation and mono-*p*-toluenesulfonylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (I) using the acid chlorides in pyridine solution have been described previously. Although Ohle and Spencker[5] reported that the hydroxyls in position 2 and 3 reacted at the same speed, and that they could not obtain a monoderivative, Robertson and Griffith[6] obtained the 2-*O*-*p*-tolylsulfonyl derivative, isolated as derivative XIX, in a 20% yield. Bolliger and Prins,[7] using a chromatographic separation, were able to increase the yield of XVII to 60 to 70%. Robertson and Griffith[6] reported that monobenzoylation was difficult to control and gave poor and not reproducible yields. The 2-*O*-benzoyl derivative VI was obtained in a 9% yield, after isolation as 2-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl derivative XXI. In both esterifications the reaction in position 2 was preponderant. After completion of the work described here, the preparation of the 2-*O*-methylsulfonyl derivative XI from I using two intermediate steps was reported.[8]

Repetition of Robertson and Griffith's procedure,[6] consisting of a partial benzoylation of I followed by a *p*-toluenesulfonylation, gave a mixture of products quite complex, as the known methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucoside (V) and methyl 2,3-di-*O*-*p*-tolylsulfonyl-4,6-*O*-benzylidene-α-D-glucoside (XVI) were isolated in addition to the 2-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl derivative XXI already described by Robertson and Griffith. Consequently it was thought of interest to study separately each step of the reaction. The results of the monoesterification of I by various reagents under various conditions of temperature are reported in Table I.

When methyl 4,6-*O*-benzylidene-α-D-glucoside (I) was treated with acetic anhydride, most of the substitution took place in position 3 intead of position 2, as expected. From the 3-*O*-acetyl derivative IV, almost quantitative yields of the 2-*O*-methylsulfonyl XII and 2-*O*-*p*-tolylsulfonyl XVIII derivatives were obtained.

The preferential reaction of the carboxylic anhydride with position 3 as observed with acetic anhydride, was confirmed using benzoic anhydride, and from the 3-*O*-benzoyl derivative VII the 2-*O*-acetyl derivative VIII was obtained. However, all attempts at obtaining a 3-*O*-*p*-tolylsulfonyl derivative, using *p*-toluenesulfonic anhydride alone or in presence of bases like dimethylamine, were unsuccessful. Likewise, only the 2-*O*-methylsulfonyl derivative XI could be isolated, besides the dimesyl derivative X from the reaction of I with methanesulfonyl anhydride. In the latter case, the yields in crystalline material were much lower than when using methanesulfonyl chloride and in this case substitution of the anhydride for the chloride had not the advantage found by Linstead, Owen and Webb.[9]

Esterification with acid chlorides took place in position 2, as reported previously. However, acetylation with acetyl chloride did not afford a good yield in crystalline material and the best yield of 2-*O*-acetyl derivative III was obtained when the reaction was carried out at room temperature with acetic anhydride in presence of pyridinium chloride. From III, the 3-*O*-benzoyl VIII, the 3-*O*-methylsulfonyl XIV and 3-*O*-*p*-tolysulfonyl XX derivatives were obtained.

The best yield in 2-*O*-benzoyl derivative VI was

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(2) R. W. Jeanloz and D. A. Jeanloz, manuscript in preparation.

(3) E. J. Bourne, M. Stacey, C. E. M. Tatlow and J. C. Tatlow, *J. Chem. Soc.*, 826 (1951).

(4) E. J. Bourne, A. J. Huggard and J. C. Tatlow, *ibid.*, 735 (1953).

(5) H. Ohle and K. Spencker, *Ber.*, **61**, 2387 (1928).

(6) C. J. Robertson and C. F. Griffith, *J. Chem. Soc.*, 1193 (1955).

(7) H. R. Bolliger and D. A. Prins, *Helv. Chim. Acta*, **28**, 465 (1945).

(8) J. Honeyman and J. W. W. Morgan, *J. Chem. Soc.*, 3660 (1955).

(9) R. P. Linstead, L. N. Owen and R. F. Webb, *ibid.*, 1225 (1953).

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TABLE I

ESTERIFICATION OF METHYL 4,6-*O*-BENZYLIDENE-α-D-GLUCOPYRANOSIDE IN PYRIDINE SOLUTION

Reagent	Amount of reagent, moles	Temp., °C. Initial	Final	Crystalline derivatives isolated in % 2,3-Diester	2-Ester	3-Ester	Starting material
$(CH_3CO)_2O$	1.25	20–30	20–30	26	3[b]	42	7
$(C_6H_5CO)_2O$	1.10	20–30	20–30	9	13	25	23
	1.10[a]	50	50	22	12	22	15
$(CH_3SO_2)O$	1.1	0	0	6	40		3
		0	20–30	8	34		4
		−20	0	5	36		22
$(CH_3C_6H_4SO_2)O$	1.1	20–30	20–30	15[b]	80–85[b]		
$(CH_3CO_2)O + C_6H_5N{\cdot}HCl$	1.05	0	20–30	21	30	5	16
CH_3COCl	1.25	0	0	23	16		3
C_6H_5COCl	1.25[a]	0	0	35	24	6	12
CH_3SO_2Cl	1.1	0	20–30	16	68		

Reaction time one day, except for experiments marked [a] five days. [b] Crude material.

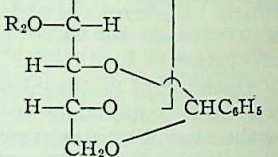
obtained when the reaction was started at −10°, carried out for some time at 0°, and finally at room temperature. Starting from VI, the 3-*O*-acetyl IX, 3-*O*-methylsulfonyl XV and 3-*O*-*p*-tolysulfonyl XXXI derivatives were prepared in an almost quantitative yield.

Methanesulfonylation was carried out with methanesulfonyl chloride added at 0° and the reaction left to proceed at room temperature. The results were very similar to the ones obtained by Bolliger and Prins[7] in the *p*-toluenesulfonylation procedure. Starting from the 2-*O*-methylsulfonyl derivatives XI, the 3-*O*-acetyl XIII and 3-*O*-benzoyl XIII derivatives were prepared in almost theoretical yield.

Bourne and co-workers[3,4] concluded that the 3-*O*-acetyl, 3-*O*-benzoyl and 3-*O*-trifluoroacetyl derivatives of I were stable, though the 2-*O*-*p*-tolylsulfonyl ester is formed preferentially. However, this finding was based on a reaction carried out in strongly alkaline aqueous solution. In dry or wet pyridine, the 2-benzoyl derivative was stable.

The experiments described here show that the relative reactivity of the positions 2 and 3 of I greatly depends on the number of protons present in the reaction medium, either by external addition, or by release during the reaction. When formed, the esters are stable under the conditions of the reaction, as no migrations of the 2-benzoyl under the action of pyridine,[4] or of the 3-acetyl under the action of pyridinium chloride are observed. However, displacement of the less stable ester by a competing grouping was observed in the isolation of some methyl 2-*O*-*p*-tolylsulfonyl-3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucoside (XX) after reaction of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucoside (III), with *p*-toluenesulfonyl chloride. This result does not support Bourne's suggestion that acetic anhydride in presence of pyridine causes migration of ester whereas *p*-toluenesulfonyl chloride in the same medium is without effect. While displacement was observed with the latter reagent, as described above, no migration was ever seen during acetylation of the 2-*O*-benzoyl VI and 3-*O*-benzoyl VII derivatives.

While the influence of the other groupings (methyl and benzylidene) on the difference in reactivity of positions 2 and 3 cannot be estimated alone, conformation plays certainly a role. This is shown by the isolation in preponderant yield of the 3-*O*-*p*-tolylsulfonyl and 3-*O*-benzoyl esters after reaction of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside with *p*-toluenesulfonyl chloride and benzoyl chloride respectively,[10] whereas benzoylation of methyl 4,6-*O*-benzylidene-α-D-altropyranoside with benzoic anhydride[2] gave only the 2-*O*-benzoyl derivative.



	R_1	R_2
I	H	H
II	CH_3CO	CH_3CO
III	CH_3CO	H
IV	H	CH_3CO
V	C_6H_5CO	C_6H_5CO
VI	C_6H_5CO	H
VII	H	C_6H_5CO
VIII	CH_3CO	C_6H_5CO
IX	C_6H_5CO	CH_3CO
X	CH_3SO_2	CH_3SO_2
XI	CH_3SO_2	H
XII	CH_3SO_2	CH_3CO
XIII	CH_3SO_2	C_6H_5CO
XIV	CH_3CO	CH_3SO_2
XV	C_6H_5CO	CH_3SO_2
XVI	$CH_3C_6H_4SO_2$	$CH_3C_6H_4SO_2$
XVII	$CH_3C_6H_4SO_2$	H
XVIII	$CH_3C_6H_4SO_2$	CH_3CO
XIX	$CH_3C_6H_4SO_2$	C_6H_5CO
XX	CH_3CO	$CH_3C_6H_4SO_2$
XXI	C_6H_5CO	$CH_3C_6H_4SO_2$

FIG. 1.

These results are not in agreement with the generalization that 2-hydroxyl groups of carbohydrates are more reactive than other secondary hydroxyl groups, especially in alkaline media.[11]

(10) E. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 1 (1945); M. Gyr and T. Reichstein, *ibid.*, **28**, 226 (1945).

(11) J. M. Sugihara, *Advances in Carbohydrate Chem.*, **8**, 1 (1953).

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Studies on a number of different carbohydrates besides glucose, using a variety of conditions, should be undertaken before general concepts are evolved.

Experimental[12]

Acetylation of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside (I) with Acetic Anhydride.—To a solution of 10.0 g. of I in 20 ml. of anhydrous pyridine was added 4.2 ml. (1.25 moles) of acetic anhydride. After standing at room temperature for 24 hours, ice was added and the mixture extracted with chloroform. The organic phase was washed five times with ice-cold 2 *N* sulfuric acid, three times with saturated sodium bicarbonate and then water, and dried over sodium sulfate. After evaporation *in vacuo*, the resulting partially crystalline sirup (12.2 g.) was dissolved in benzene, an equal volume of hexane added, and chromatographed on 250 g. of silicic acid. A mixture of benzene and ether 19:1 eluted methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (II). After recrystallization, it melted at 109–110°, showing a rotation of $[\alpha]^{24}D$ +72 ± 1° (in chloroform, *c* 1.04)[13] and weighed 3.36 g. (26%).

A mixture of benzene and ether 9:1 eluted 0.30 g. (3%) of a crystalline mixture in which methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (III) (see below) was predominant. Mixtures of benzene and ether 4:1, 2:1, 1:1 and pure ether, eluted **methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (IV).** Crystallization from a mixture of acetone, ether and pentane gave 4.78 g. (42%) of silk-like needles, m.p. 176–177°, $[\alpha]^{23}D$ +114 ± 1° (in chloroform, *c* 0.57).[15] *Anal.* Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 58.95; H, 5.94.

Mixtures of methanol and ether eluted the starting material. After recrystallization, 0.71 g. (7%) was obtained, m.p. 163–165°, showing no depression in admixture with authentic material.

Acetylation of I with Acetyl Chloride.—To a solution of 2.0 g. of I in 5 ml. of anhydrous pyridine was added at 0° 0.63 ml. (1.25 moles) of acetyl chloride. After standing overnight at 0°, the mixture was extracted and purified as described above. After chromatography and crystallization, 0.73 g. (23%) of diacetyl derivative II was obtained and 0.06 g. (3%) of starting material. Elution with mixtures of ether and benzene 4:1 and 2:1 gave crystalline fractions of **methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (III).** After crystallization from a mixture of ether and pentane, 0.37 g. (16%) of prismatic needles were obtained, m.p. 133–134°, $[\alpha]^{26}D$ +106 ± 2° (in chloroform, *c* 1.27).[15] *Anal.* Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.17; H, 6.22.

Acetylation of I with Acetic Anhydride in Presence of Pyridinium Chloride.—To a solution of 1 ml. of anhydrous pyridine in 20 ml. of dry ether was added dry hydrochloric acid to saturation. After removal of the ether and excess hydrochloric acid, 20 ml. of anhydrous pyridine and 2.0 g. of I were added. After dissolution and cooling at 0°, 0.70 ml. (1.05 moles) of acetic anhydride was added and the solution left at room temperature overnight. After addition of ice, the reaction was worked as described above. The recrystallized 2,3-diacetyl II, 2-acetyl III, 3-acetyl IV derivatives and starting material I were recovered in 21, 30, 5 and 16% yields, respectively.

Benzoylation of I with Benzoyl Chloride.—To a solution of 5.0 g. of I in 5 ml. of anhydrous pyridine cooled at 0° was added slowly 2.0 ml. (1.25 moles) of cooled benzoyl chloride. The solution was left at 0° overnight, and, after addition of ice, was extracted as described above. The residual sirup (7.0 g.) was dissolved in benzene, four volumes of hexane were added, and the solution chromatographed on 200 g. of alumina. Pure benzene and mixtures of benzene and ether, 99:1, 49:1, 19:1 and 9:1, eluted crystalline fractions, which gave after crystallization from a mixture of acetone, ether and pentane 3.00 g. (35%) of methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (V), m.p. 154°, $[\alpha]^{26}D$ +94 ± 2° (in chloroform, *c* 1.51),[17] and showing no depression in admixture with authentic material.

Mixtures of benzene and ether 4:1, 2:1, 1:1 and pure ether eluted crystalline fractions; crystallization from a mixture of acetone, ether and pentane gave 1.63 g. (24%) of prismatic needles of **methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (VI)**, m.p. 169–170° (moistening at 165°), $[\alpha]^{26}D$ +111 ± 2° (in chloroform, *c* 1.64).[18] *Anal.* Calcd. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.22; H, 5.79. Pure ether, mixtures of ether and ethyl acetate and pure ethyl acetate eluted 3-*O*-benzoyl derivative VII. After crystallization from a mixture of acetone, ether and pentane, 0.42 g. (6%) was isolated, melting at 218–219° and showing no depression with the product isolated below.

Mixtures of ethyl acetate and methanol eluted 0.60 g. (12%) of crude crystalline starting material.

The same reaction was carried out in mixing a solution of 10.0 g. of I in 10 ml. of anhydrous pyridine with a solution of 4.1 ml. of benzoyl chloride (1.0 moles) in 10 ml. of anhydrous pyridine, both previously cooled to −10°. After a few hours at 0°, and overnight at room temperature, the mixture was worked out as described above: 2.15 g. (12%) of crystalline V, 5.90 g. (43%) of crystalline VI, 1.70 g. (8%) of crystalline VII and 2.20 g. (22%) of crystalline starting material was obtained.

Benzoylation of I with Benzoic Anhydride.—A solution of 2.0 g. of I and 1.80 g. (1.1 moles) of benzoic anhydride in 10 ml. of anhydrous pyridine was heated at 50° for 24 hours under moisture protection. After cooling, the mixture was purified by extraction and chromatography, as previously described. After elution of 0.76 g. (22%) of crystallized dibenzoate V and 0.34 g. (12%) of crystallized 2-*O*-benzoyl derivative VI, crystalline fractions were eluted and gave, after crystallization from a mixture of acetone, ether and pentane, 0.61 g. (22%) of **methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (VII)** as long needles, m.p. 219–220°, $[\alpha]^{26}D$ + 34 ± 1° (in chloroform, *c* 1.10).[19] *Anal.* Calcd. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.13; H, 5.60. In addition, 0.30 g. (15%) of crude starting material was recovered.

When the reaction was carried out at 70°, the yields obtained were approximately the same, whereas at room temperature (25–30°), 9% of V, 13% of VI, 25% of VII and 23% of I were obtained after crystallization.

Methanesulfonylation of I with Methanesulfonyl Chloride.—To a solution of 5.0 g. of I in 15 ml. of anhydrous pyridine, was added a solution of 1.75 ml. (1.3 moles) of methanesulfonyl chloride in 15 ml. of anhydrous pyridine. Both solutions had been previously cooled at 0°. After standing at room temperature for 24 hours, a small amount of ice was added and after 2 hours the solution was extracted with chloroform as described above. The residual sirup (7.15 g.) gave, after crystallization from a mixture of acetone, ether and pentane, 1.75 g. of **methyl 4,6-*O*-benzylidene-2-*O*-methylsulfonyl-α-D-glucopyranoside (XI)**, as prismatic needles, m.p. 135–136°, $[\alpha]^{24}D$ +73 ± 1° (in chloroform, *c* 2.22).[20] *Anal.* Calcd. for $C_{15}H_{20}O_8S$: C, 49.99; H, 5.59; S, 8.90. Found: C, 49.91; H, 5.67; S, 8.92.

The mother liquors dissolved in a 1:1 mixture of hexane and benzene were chromatographed on silicic acid. A 1:1 mixture of benzene and ether eluted 1.50 g. of sirupy **methyl 4,6-*O*-benzylidene-2,3-di-*O*-methylsulfonyl-α-D-glucopy-**

(12) R. W. Jeanloz, THIS JOURNAL, **76**, 555 (1954). "Silica Gel Davison" grade 923; 100–200 mesh was replaced by the less expensive grade 950; 60–200 mesh, without noticeable change in adsorption. In order to obtain good separations, a fully activated silicic acid was found necessary. When deactivation by contact with moist air occurred, reactivation was obtained by heating to 170–200° (Manufacturer's instructions). The proportion of weight of substance to be adsorbed to weight of adsorbent was 1 to 20–30 for alumina, and 1 to 50–100 for silicic acid. The proportion of weight of substance in g. to volume of fraction of eluent in ml. was 1 to 100. The ratio of diameter to length of the column was 1 to 5 for alumina and 1 to 20 for silicic acid.

(13) Mathers and Robertson[14] reported m.p. 108–109°, $[\alpha]D$ +75.5° (in chloroform).

(14) D. S. Mathers and G. J. Robertson, *J. Chem. Soc.*, 696 (1933).

(15) Bourne, *et al.*,[4] reported m.p. 174°, $[\alpha]^{14}D$ +110° (in chloroform).

(16) Bourne, *et al.*,[4] reported m.p. 133–134°, $[\alpha]^{19}D$ +112° (in chloroform, *c*, 0.86).

(17) Bourne, *et al.*,[4] reported m.p. 151–152°; Ohle and Spencker[6] m.p. 148°, $[\alpha]^{19}D$ +96.81° (in chloroform, *c*, 2.828).

(18) Bourne, *et al.*,[4] reported m.p. 165–166°, $[\alpha]^{21}D$ +109.5° (in chloroform, *c* 2.09).

(19) Bourne, *et al.*,[4] reported m.p. 217–218°, $[\alpha]^{19}D$ +33.5° (in chloroform, *c* 2.55).

(20) Hanagan Collection, Harid reported m.p. 132–133°, $[\alpha]^{23}D$ +72° (in chloroform, *c* 1.2).

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ranoside (X), which crystallized after a few days. Crystallization from a mixture of acetone, ether and pentane gave 1.22 g. (16%) of stout prisms, m.p. 188–190°, $[\alpha]^{26}D$ +49 ± 1° (in chloroform, *c* 1.46).[21] *Anal.* Calcd. for $C_{16}H_{22}O_{16}S_2$: C, 43.83; H, 5.02; S, 14.63. Found: C, 43.97; H, 5.18; S, 14.54.

Elution with a mixture of benzene and ether gave, after recrystallization, an additional crop of methyl 4,6-*O*-benzylidene-2-*O*-methylsulfonyl-α-D-glucopyranoside, 2.63 g., total yield 4.38 g. (68%).

Methanesulfonylation of I with Methanesulfonyl Anhydride.—To a solution of 500 mg. of I in 15 ml. of anhydrous dichloroethane was added 340 mg. (1.1 moles) of methanesulfonyl anhydride.[22] After cooling at 0°, 3 ml. of anhydrous pyridine was added and the mixture was left standing at 0° overnight. Ice was added and the solution was extracted with chloroform and purified by chromatography on silicic acid as previously described. Elution with 9:1 mixtures of benzene and ether gave methyl 4,6-*O*-benzylidene-2,3-di-*O*-methylsulfonyl-α-D-glucopyranoside (X), which after recrystallization from a mixture of acetone, ether and pentane weighed 45 mg. (6%), m.p. 186–188°, $[\alpha]^{24}D$ +51 ± 2° (in chloroform, *c* 1.33), and showed no depression in admixture with the product described above. Elution with mixtures of benzene and ether 4:1 gave 280 mg. of methyl 4,6-*O*-Benzylidene-2-*O*-methylsulfonyl-α-D-glucopyranoside (XI). After recrystallization from a mixture of acetone, ether and pentane, 255 mg. (40%) was obtained, m.p. 133–134°, $[\alpha]^{26}D$ +73 ± 2° (in chloroform, *c* 1.38). It showed no depression with the product described above. Elution with a mixture of ether and methanol 19:1 gave the starting material (15 mg., 3%, after recrystallization).

When mixing took place at 0°, and the reaction carried out at room temperature for 5 days, the yields were 8% for X, 34% for XI and 4% for the starting material. When the reaction was carried out in an excess of pyridine as solvent, extensive decomposition occurred at room temperature; when the mixture was made at −20° and the reaction carried out at 0° for 4 days, only slight decomposition occurred and the yields were 36% for X, 5% for XI and 22% for the starting material.

***p*-Toluenesulfonylation of I with *p*-Toluenesulfonic Anhydride.**—To a solution of 200 mg. of I in 2 ml. of anhydrous pyridine was added 280 mg. of *p*-toluenesulfonic anhydride (1.1 moles).[23] After standing at room temperature overnight and after addition of ice, the mixture was handled as previously described. Besides the 2,3-ditosyl derivative XVI isolated in a 15% crude yield, only methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (XVII) (crude yield 80–85%) could be obtained after recrystallization, melting at 151–153°[24] and not showing a depression in admixture with authentic material.

Attempts at *p*-toluenesulfonylation with *p*-toluenesulfonic anhydride in the presence of ethylamine, in pyridine or dichloroethane solution, were unsuccessful.

Methyl 2-*O*-Acetyl-3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (VIII) from III.—To a solution of 105 mg. of III in 2 ml. of anhydrous pyridine cooled at −20° was added 0.055 ml. (1.5 moles) of benzoyl chloride. After standing overnight at 0° and 2 hours at room temperature, ice was added and the mixture handled as previously described. The crystalline residue was crystallized from a mixture of ether and pentane to give 133 mg. (95%) of typical rectangular or hexagonal prisms, m.p. 154–155°, $[\alpha]^{25}D$ +24 ± 2° (in chloroform, *c* 1.39). *Anal.* Calcd. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.33; H, 5.79.

From VII.—To a solution of 100 mg. of VII in 1 ml. of pyridine was added 0.5 ml. of acetic anhydride. After standing overnight at room temperature, the mixture was worked up as usual and gave 106 mg. (95%) of prisms, m.p. 153–154°, showing no depression with the compound described above.

Methyl 3-*O*-Acetyl-2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (IX).—A solution of 100 mg. of VI in 1 ml. of anhydrous pyridine was treated with 0.05 ml. of acetic anhydride overnight at room temperature. After the usual work-up, crystallization from a mixture of ether and pentane gave 106 mg. (95%) of needles, m.p. 110–112°, $[\alpha]^{21}D$ +118 ± 2° (in chloroform, *c* 0.69). *Anal.* Calcd. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.44; H, 5.71.

Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-*O*-methylsulfonyl-α-D-glucopyranoside (XII) from XI.—A solution of 0.75 g. of XI in 2.5 ml. of anhydrous pyridine was treated for one day at room temperature with 1.0 ml. of acetic anhydride. After the usual work-up, crystallization from a mixture of ether and pentane gave 0.79 g. (94%) of prismatic needles, m.p. 125–126°, $[\alpha]^{21}D$ +59 ± 1° (in chloroform, *c* 3.32). *Anal.* Calcd. for $C_{17}H_{22}O_9S$: C, 50.74; H, 5.51. Found: C, 50.29; H, 5.81.

From IV.—To a solution of 1.5 g. of IV in 5 ml. of anhydrous pyridine was added a solution of 0.5 ml. (1.4 moles) of methanesulfonyl chloride in 5 ml. of pyridine, both solutions previously having been cooled at 0°. After standing at room temperature overnight, the mixture was handled as previously described. Crystallization from a mixture of ether and pentane gave 1.82 g. (98%) of needles, m.p. 125–126°, showing no depression in admixture with the material described above.

Methyl 3-*O*-Benzoyl-4,6-*O*-benzylidene-2-*O*-methylsulfonyl-α-D-glucopyranoside (XIII).—To a solution of 0.94 g. of XI in 3 ml. of anhydrous pyridine cooled at 0° was added 0.45 ml. (1.5 moles) of benzoyl chloride. After standing for one day at 0°, the mixture treated as usual, gave after crystallization from a mixture of acetone, ether and pentane, 1.14 g. (94%) of prismatic needles, m.p. 174–175°, $[\alpha]^{21}D$ +39 ± 2° (in chloroform, *c* 2.13). *Anal.* Calcd. for $C_{22}H_{24}O_9S$: C, 56.89; H, 5.21. Found: C, 56.75; H, 5.09.

Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-3-*O*-methylsulfonyl-α-D-glucopyranoside (XIV).—To a solution of 0.50 g. of III in 5 ml. of anhydrous pyridine cooled at 0° was added 0.2 ml. (1.4 moles) of methanesulfonyl chloride. After standing at room temperature for a day, the mixture was treated as usual. Crystallization from a mixture of ether and pentane gave 0.59 g. (95%) of elongated prisms, m.p. 150–151°, $[\alpha]^{24}D$ +71 ± 2° (in chloroform, *c* 1.15). *Anal.* Calcd. for $C_{17}H_{22}O_9S$: C, 50.74; H, 5.51; S, 7.97. Found: C, 50.90; H, 5.67; S, 7.80.

Methyl 2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-methylsulfonyl-α-D-glucopyranoside (XV).—To a solution of 825 mg. of VI in 3 ml. of anhydrous pyridine previously cooled to 0° was added 0.23 ml. (1.4 moles) of methanesulfonyl chloride. After standing overnight at room temperature, the mixture was worked up as usual. Crystallization from a mixture of acetone, ether and pentane gave 930 mg. (94%) of prismatic needles, m.p. 169–171°, $[\alpha]^{26}D$ +123 ± 2° (in chloroform, *c* 1.06). *Anal.* Calcd. for $C_{22}H_{24}O_9S$: C, 56.89; H, 5.21; S, 6.90. Found: C, 56.93; H, 5.35; S, 6.97.

Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (XVIII) from XVII.—A solution of 1.0 g. of XVII in 2.5 ml. of anhydrous pyridine was treated overnight at room temperature with 1.0 ml. of acetic anhydride. After addition of ice and extraction with chloroform, as previously described, crystallization from a mixture of acetone, ether and pentane gave 1.03 g. (95%) of shiny platelets, m.p. 161–162° (moistening at 158°), $[\alpha]^{26}D$ +50 ± 1° (in chloroform, *c* 2.20).[25]

From IV.—To a solution of 1.5 g. of IV in 5 ml. of anhydrous pyridine was added a solution of 1.25 g. of *p*-toluenesulfonyl chloride in 5 ml. of pyridine, both solutions having previously been cooled to 0°. After standing one day at room temperature, ice was added and the product isolated as previously described. Crystallization from a mixture of acetone, ether and pentane gave 2.17 g. (97%) of shiny platelets, m.p. 160–161°, and not showing a depression in admixture with the product described above.

***p*-Toluenesulfonylation of Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (III).**—To a solution of 500 mg. of III in 5 ml. of anhydrous pyridine previously cooled at 0° was added 400 mg. (1.3 moles) of *p*-toluenesulfonyl chloride. After standing at room temperature for one week, the mixture was worked up as usual. The residual sirup was dissolved in benzene, an equal volume of hexane was added, and the solution was chromatographed on 20 g. of

(21) Honeyman and Morgan[3] reported m.p. 188–189°, $[\alpha]^{20}D$ +49° (in chloroform, *c* 1.4).

(22) L. Field and P. H. Settlage, THIS JOURNAL, **76**, 1222 (1954).

(23) L. Field, *ibid.*, **74**, 394 (1952).

(24) Ohle and Spencker[5] reported m.p. 149°, Robertson and Griffith[6] reported m.p. 153–154°.

(25) Bourne, *et al.*,[3] reported for an almost identical procedure 69% yield, m.p. 160–162°, $[\alpha]^{21}D$ +51.2° (in chloroform, *c* 0.76).

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May 20, 1957

alumina. Mixtures of benzene and ether 19:1 and 9:1 eluted crystalline fractions. Crystallization from a mixture of acetone, ether and pentane gave 485 mg. (66%) of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (XX), as stout prisms, m.p. 124–125°, $[\alpha]^{24}D$ +26 ± 2° (in chloroform, *c* 0.51).[26] *Anal.* Calcd. for $C_{28}H_{28}O_8S$: C, 57.73; H, 5.48; S, 6.70. Found: C, 57.93; H, 5.58; S, 6.53. From the mother liquors, 8 mg. (1%) of shiny platelets, m.p. 157–159°, were obtained. In admixture with methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (XVIII) described above no depression of the m.p. was observed.

Elution with 4:1, 2:1 and 1:1 mixtures of ether and benzene gave crystalline fractions. After crystallization from a mixture of acetone, ether and pentane, 125 mg. (25%) was obtained, melting at 133–134° and showing no depression in admixture with the starting material.

Action of Pyridinium Chloride on Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (IV).—A solution of 0.1 ml. of anhydrous pyridine in 5 ml. of dry ether was saturated with dry hydrogen chloride. After removal of the ether and excess hydrogen chloride, 5 ml. of anhydrous pyridine and 200 mg. of IV were added. After one day at room temperature, ice was added and the product was isolated as described above. Recrystallization from a mixture of ether and pentane gave 190 mg. (95%) of starting material, m.p. 176–177°.

Acknowledgments.—The authors wish to thank Mrs. Shirley Butterworth and Miss Anne Foley, for technical assistance.

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(26) Bourne, *et al.*,[3] reported a yield of 49%, m.p. 120–121°, $\alpha^{23}D$ +23.1° (in chloroform, *c* 0.78).

[CONTRIBUTION FROM THE ROBERT W. LOVETT MEMORIAL LABORATORIES FOR THE STUDY OF CRIPPLING DISEASES, MASSACHUSETTS GENERAL HOSPITAL, AND THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

4-*O*-Methyl-D-glucosamine Hydrochloride (2-Amino-2-deoxy-4-*O*-methyl-D-glucose Hydrochloride)[1]

BY ROGER W. JEANLOZ AND CHARLES GANSSER[2]

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The synthesis of 4-*O*-methyl-D-glucosamine hydrochloride (2-amino-2-deoxy-4-*O*-methyl-D-glucose hydrochloride), a reference substance for structural studies of glucosamine-containing substances, is described. It was obtained in a sirupy state, starting from methyl 2-acetamido-2-deoxy-6-*O*-triphenylmethyl-α-D-glucopyranoside and from methyl 2-acetamido-3-*O*-tolylsulfonyl-α-D-glucopyranoside. It was transformed into the crystalline *N*-acetyl and *N*-(2′-hydroxynaphthylidene) derivatives.

In a previous paper[3] describing the methylation of methyl 2-acetamido-2-deoxy-6-*O*-triphenylmethyl-α-D-glucopyranoside (IV), a crystalline compound was isolated in addition to the known methyl 2-acetamido-2-deoxy-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside and methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside. The structure of a methyl 2-acetamido-2-deoxy-4-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (III) was ascribed to this product on the basis of its elementary analysis, of its mode of preparation, and because it was possible to prepare a monoacetyl derivative. It was of interest to ascertain this structure by an independent synthesis and at the same time synthesize the still unknown 4-*O*-methyl-D-glucosamine hydrochloride (VII), to complete the series of the known monomethyl derivatives of 2-amino-2-deoxy-D-glucopyranose.

The first attempt to obtain a 4-*O*-methyl-derivative, using as starting material a compound in which positions 3 and 6 were protected during methylation by methylsulfonyl groups, was unsuccessful, because such groupings could not be removed subsequently by reductive splitting.[4]

Another experiment in which the methylation of the methyl 2-acetamido-2-deoxy-3-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl derivative was attempted did not give conclusive results (see Experimental part).

Finally, the following route as shown in the accompanying diagram was successful: Controlled *p*-toluenesulfonylation of methyl 2-acetamido-2-deoxy-3-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (I)[5] gave, in excellent yield, the sirupy 3,6-di-*O*-*p*-tolylsulfonyl derivative II, characterized by a crystalline 4-*O*-acetyl derivative. Methylation with methyl iodide and silver oxide produced the sirupy 4-*O*-methyl derivative V. It was purified from the starting material by acetylation followed by chromatography. Although this product could not be obtained in crystalline form, and showed a rotation slightly different from the rotation of the product prepared by *p*-toluenesulfonylation of methyl 2-acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranoside (VI), it analyzed correctly and was used as such. Splitting of the *p*-tolylsulfonyl groups was accomplished by reduction and afforded in a 73% yield a crystalline methyl 2-acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranoside (VI) identical in all respects with the crystalline product obtained by weak acid hydrolysis of methyl 2-acetamido-2-deoxy-4-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (III). Additional evidence for the identity of both compounds was obtained

(1) Studies on hyaluronic acid and related substances, XIV. This is publication No. 205 of the Robert W. Lovett Memorial Laboratories for the Study of Crippling Diseases, Department of Medicine, Harvard Medical School, Boston, and the Massachusetts General Hospital. This investigation has been supported by research grants from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service (Grant A-148-C2), and from Eli Lilly and Co. It was presented before the Division of Carbohydrate Chemistry at the 129th Meeting of the American Chemical Society, Dallas, Texas, April, 1956.

(2) Fellow of the Swiss Foundation "Stiftung für Stipendien auf dem Gebiete der Chemie."

(3) R. W. Jeanloz, THIS JOURNAL, **74**, 4597 (1952).

(4) R. W. Jeanloz and C. G. Buchner-By, unpublished.

(5) R. W. Jeanloz, THIS JOURNAL, **76**, 555 (1954).

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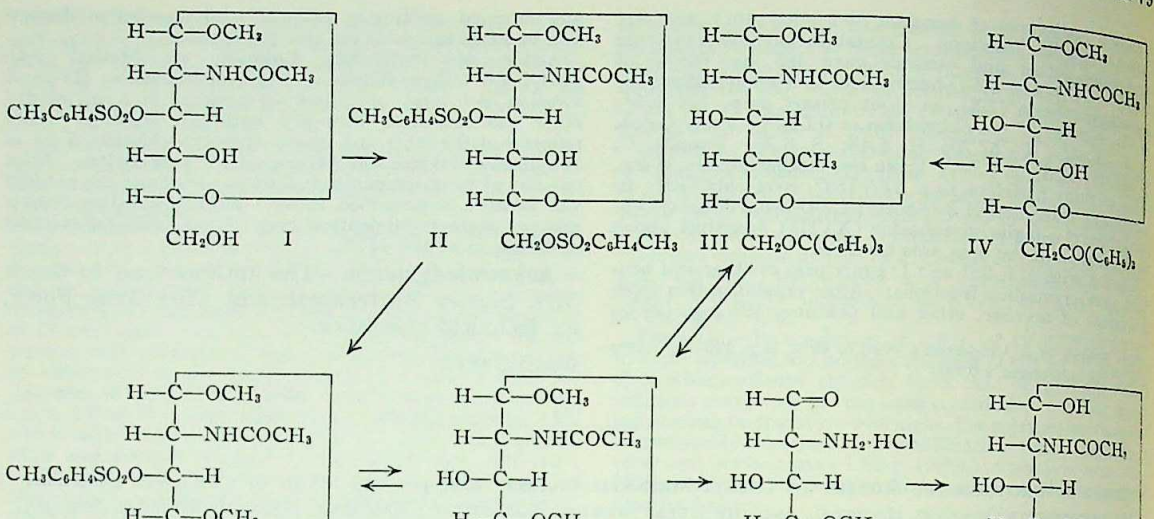

by preparing III using as starting material the glycoside VI obtained through the route of the *p*-tolylsulfonyl derivatives. Attempts to characterize VI in preparing a crystalline 3,6-*O*-diacetyl derivative, were unsuccessful. Two different methods of preparation gave sirupy products, showing an identical rotation but with quite incorrect elementary analysis. The synthesis of methyl 2-acetamido-2-deoxy-3,4-6-tri-*O*-methyl-α-D-glucopyranoside[3,6] starting from VI showed that no shifting of the ring had occurred during methylation. Hydrolysis of VI gave the sirupy 2-amino-2-deoxy-4-*O*-methyl-D-glucosamine hydrochloride (VII), which was transformed into the crystalline N-acetyl (VIII) and N-(2′-hydroxynaphthylidene) (IX) derivatives.

Experimental[7]

Methyl 2-Acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranoside (VI) from III.—A solution of 105 mg. of methyl 2-acetamido-2-deoxy-4-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (III)[3] in 4 ml. of glacial acetic acid was heated on the water-bath and 3 ml. of water was added dropwise. After one hour, the solution was cooled and diluted with 15 ml. of water. The triphenylcarbinol (47 mg.) was filtered off and the solution evaporated to dryness *in vacuo*. The crystalline residue, recrystallized from cold ethanol and from a mixture of ethanol and ether gave 43 mg. (85%) of elongated needles, m.p. 232–233°, $[\alpha]^{24}D$ +158 ± 5° (in methanol, *c* 0.58). *Anal.* Calcd. for $C_{10}H_{19}O_6N$: C, 48.18; H, 7.68. Found: C, 48.06; H, 7.84.

Methyl 2-Acetamido-2-deoxy-3,6-di-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (II).—To a solution of 500 mg. of methyl 2-acetamido-2-deoxy-3-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside[5] (I), in 1.5 ml. of dry pyridine was added 280 mg. (1.15 moles) of *p*-toluenesulfonyl chloride dissolved in 2.5 ml. of dry pyridine, both solutions having previously been cooled at −20°. The solution was kept at 0° overnight and at room temperature for one day; then the excess chloride was decomposed by addition of ice and the solution extracted with chloroform. The chloroform layer was washed three times each with ice-cold water, ice-cold 2 *N* sulfuric acid, saturated sodium bicarbonate solution, and water, dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silicic acid. Elution with mixtures of ether and ethyl acetate afforded a quantitative yield of II as a colorless sirup; $[\alpha]^{24}D$ +62 ± 2° (in chloroform, *c* 1.30). *Anal.* Calcd. for $C_{23}H_{29}O_{10}NS_2$: C, 50.82; H, 5.38; S, 11.80. Found: C, 50.98; H, 5.50; S, 11.66.

Acetylation of 82 mg. of II with acetic anhydride and pyridine in the usual manner gave the 4-*O*-acetyl derivative which was purified by chromatography on silicic acid. Elution with pure ether and mixtures of ether and ethyl acetate gave crystalline fractions which after recrystallization from a mixture of acetone, ether and pentane afforded 62 mg. (80%) of prisms, m.p. 142°, $[\alpha]^{21}D$ +78 ± 2° (in chloroform, *c* 0.96). *Anal.* Calcd. for $C_{25}H_{31}O_{11}NS_2$: C, 51.27; H, 5.34. Found: C, 51.41; H, 5.47.

Methyl 2-Acetamido-2-deoxy-4-*O*-methyl-3,6-di-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (V) from II.—Five hundred and five milligrams of II was refluxed for one day with 10 ml. of methyl iodide and 300 mg. of silver oxide; after another addition of 200 mg. of silver oxide, reflux was continued for another day. The silver residue was filtered and washed exhaustively with acetone, and the filtrate, evaporated *in vacuo*, was dissolved in benzene and chromatographed on silicic acid. Elution with mixtures of ether and ethyl acetate gave 430 mg. of a hygroscopic sirup. It was acetylated with acetic anhydride and pyridine in the usual manner to transform the unreacted II into its crystalline 4-*O*-acetyl derivative. After repeated evaporation *in vacuo* with toluene the remaining sirup was chromatographed on silicic acid. Elution with mixtures of ether and ethyl acetate (9:1 and 4:1) gave 412 mg. (80%) of V, as a colorless glass, $[\alpha]^{24}D$ +75 ± 2° (in chloroform, *c* 1.10). *Anal.* Calcd. for $C_{24}H_{31}O_{10}NS_2$: C, 51.69; H, 5.60; OCH_3, 11.13. Found: C, 51.60; H, 5.77; OCH_3, 11.04. The crystalline acetyl derivative of II was eluted with a mixture of ether and ethyl acetate 2:1.

From VI.—To a solution of 48 mg. of VI in 0.5 ml. of anhydrous pyridine was added 120 mg. of *p*-toluenesulfonyl chloride. After standing one day at 0° and another day at room temperature, ice was added and the solution was extracted with chloroform. The extract was washed with 2 *N* sulfuric acid, then with saturated sodium bicarbonate, and water and was dried over sodium sulfate. After removal of the solvent by distillation *in vacuo*, the sirupy residue was chromatographed on silicic acid. Elution with mixtures of benzene and ether afforded a first peak of substance, weighing 21 mg. (19%) which could not be induced to crystallize; $[\alpha]^{26}D$ +68 ± 2° (in chloroform, *c* 2.09). *Anal.* Calcd. for $C_{24}H_{31}O_{10}NS_2$: C, 51.69; H, 5.60; S, 11.33. Found: C, 51.99; H. 5.44; S, 11.33. The more polar fractions, some being partially crystalline, were not further investigated.

Methyl 2-Acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranoside (VI) from V.—To a solution of 275 mg. of V in 10 ml. of 0.05% methanolic sodium amalgam was added 4 g. of 2.5% sodium amalgam was

(6) W. O. Cutler, W. N. Haworth and S. Peat, *J. Chem. Soc.*, 1979 (1937).

(7) See ref. 5 and R. W. Jeanloz and D. A. Jeanloz, THIS JOURNAL, **79**, 2579 (1957).

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added and the mixture was shaken overnight. After addition of water, the solution was saturated with carbon dioxide, the mercury was filtered off through a layer of Celite and Darco G-60, and washed with methanol. The filtrate was evaporated to dryness *in vacuo*, dried by co-distillation with dry toluene, and the residue was extracted with acetone. After evaporation *in vacuo*, the crystalline residue was recrystallized from a mixture of methanol and ether, affording 90 mg. (73%) of prismatic needles, m.p. 232–233°, $[\alpha]^{22}D$ +157 ± 2° (in methanol, *c* 1.16). *Anal.* Calcd. for $C_{10}H_{19}O_6N$: C, 48.18; H, 7.68; OCH_3, 24.90. Found: C, 48.05; H, 7.60; OCH_3, 24.69. In admixture with the material described above, the m.p. was not depressed.

Acetylation of 50 mg. of VI with acetic anhydride and pyridine in the usual manner, gave, after chromatography on silicic acid, 58 mg. (87%) of the **3,6-di-*O*-acetyl** derivative as a homogeneous peak, eluted with mixtures of chloroform and ether. It failed to crystallize and showed $[\alpha]^{25}D$ +79 ± 2° (in chloroform, *c* 2.93). *Anal.* Calcd. for $C_{14}H_{21}O_8N$: C, 50.44; H, 6.96. Found: C, 51.27; H, 6.85.

Acetylation of 50 mg. of VI was carried out by heating with 2 ml. of acetic anhydride and 100 mg. of fused sodium acetate for 4 hours on the water-bath. After dilution with water, the solution was extracted with chloroform. After washing with water, the extract was dried over sodium sulfate, the solvent was removed by distillation *in vacuo* and the residue chromatographed on silicic acid, as described above. A quantitative yield of the sirupy **3,6-di-*O*-acetyl** derivative was obtained, $[\alpha]^{25}D$ +77 ± 2° (in chloroform, *c* 2.22). *Anal.* Calcd. for $C_{14}H_{23}O_8N$: C, 50.44; H, 6.96. Found: C, 51.43; H, 7.20.

Methylation of VI with dimethyl sulfate and sodium hydroxide[8] in the usual manner gave the methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-glucopyranoside. Purification was obtained by chromatography on silicic acid. Elution with mixtures of acetone and methanol (19:1) afforded a crystalline material. On recrystallization from a mixture of chloroform and pentane, long prismatic needles were obtained (yield about 40%), m.p. 166–168° (sublimation at 150°) $[\alpha]^{20}D$ +122 ± 4° (in chloroform, *c* 2.23). In admixture with authentic material,[3,6] the m.p. was not depressed.

Methyl 2-Acetamido-2-deoxy-4-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (III) from VI.—A solution of 50 mg. of VI obtained from V and 115 mg. of triphenylchloromethane (2.0 equivalents) in 4.5 ml. of dry pyridine was left at 47° for 6 days. The pyridine was evaporated *in vacuo* at room temperature and the residue dried in a desiccator over calcium chloride and potassium hydroxide. After a new addition of 57 mg. of triphenylchloromethane (1.0 equivalent) and of 3.0 ml. of dry pyridine, the solution was left at 100° for four hours, the excess chloride decomposed by addition of ice and the solution extracted with chloroform. The chloroform layer was washed three times each with ice-cold saturated potassium bisulfate solution, sodium bicarbonate and water, dried over sodium sulfate and evaporated *in vacuo*. The residue was dissolved in benzene and chromatographed on silicic acid. Elution with mixtures of ethyl acetate and acetone afforded 36 mg. (36%) of crystalline fractions. Recrystallization from a mixture of acetone and ether gave 22 mg. (22%) of prisms (III), m.p. 210–212°, $[\alpha]^{24}D$ +59 ± 2° (in chloroform, *c* 0.81). In admixture with the material previously described[3] the m.p. was not depressed.

4-O-Methyl-D-glucosamine Hydrochloride (2-Amino-2-deoxy-4-O-methyl-D-glucose Hydrochloride) (VII).—A solution of 200 mg. of VI in 5 ml. of 3 *N* hydrochloric acid was heated for three hours on the steam-bath. After cooling it was diluted with 15 ml. of water, and the solution was evaporated *in vacuo*. The residue was dissolved in methanol, the solution was filtered through Celite and Darco G-60, and evaporated *in vacuo*. The colorless hygroscopic sirup (VII) was kept in a desiccator for several days over soda lime and obtained in a quantitative yield: $[\alpha]^{24}D$ +90 ± 2° (in water, *c* 1.70), $[\alpha]^{26}D$ + 108 ± 2° (in methanol, *c* 1.19). *Anal.* Calcd. for $C_7H_{16}O_5NCl$: C, 36.61; H, 7.02; Cl, 15.44; OCH_3, 13.51. Found: C, 36.43; H, 7.16; Cl, 15.30; OCH_3, 13.40.

2-Acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranose (VIII).—To a solution of 72 mg. of VII in 1 ml. of absolute methanol was added 58 mg. of silver acetate and 0.7 ml. of acetic anhydride. The mixture was left at 0° overnight, at room temperature for three hours, refluxed for five minutes, and filtered through Celite. The silver residue was washed with methanol and then with 1 ml. of hot water, and one drop of 0.1 *N* hydrochloric acid was added to the filtrate. After two hours the solution was filtered through Celite and Darco G-60 and the filtrate evaporated *in vacuo*. The residue was crystallized from a mixture of methanol and ether, and gave 41 mg. (56%) of prisms, m.p. 211–215° dec. The compound showed mutarotation from $[\alpha]^{24}D$ +79° (after 16 minutes) to $[\alpha]^{22}D$ +69 ± 2° (after 24 hours, in water, *c* 1.02). *Anal.* Calcd. for $C_9H_{17}O_6N$: C, 45.95; H, 7.28. Found: C, 45.77; H, 7.39.

2-Deoxy-2-(2′-hydroxynaphthylidenamino)-4-*O*-methyl-D-glucopyranose (IX).—A solution of 60 mg. of VII in 3 ml. of water was treated as previously described[3] with 110 mg. of 2-hydroxynaphthaldehyde and 30 mg. of sodium acetate trihydrate. The product was purified by chromatography on silicic acid. Elution with mixtures of ethyl acetate and acetone gave crystalline fractions. Recrystallization from a mixture of monomethyl glycol, methanol and ether gave 46 mg. (53%) of yellow, prismatic needles, m.p. 218–219° dec., $[\alpha]^{22}_{5461}$ +305 ± 10° (in methanol, at equilibrium, *c* 0.14). *Anal.* Calcd. for $C_{18}H_{21}O_6N$: C, 62.24; H, 6.09. Found: C, 62.28; H, 6.18.

Methyl 2-Acetamido-2-deoxy-3-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside.—To a solution of 550 mg. of methyl 2-acetamido-2-deoxy-3-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside[5] (I) in 5 ml. of dry pyridine was added 400 mg. (1.05 moles) of triphenylchloromethane. After standing overnight at room temperature, the solution was heated at 100° for 2 hours. After cooling, ice was added, and the solution was extracted with chloroform. The organic phase was washed three times each, at 0° with a saturated solution of potassium bisulfate, at room temperature with a saturated solution of sodium bicarbonate and with water, then dried over sodium sulfate. After evaporation *in vacuo*, the residue was dissolved in benzene and chromatographed on silicic acid. Elution with mixtures of benzene and ether 2:1 and 1:1 and with pure benzene gave 600 mg. (67%) of a colorless sirup; $[\alpha]^{28}D$ +42 ± 2° (in chloroform, *c* 1.46). *Anal.* Calcd. for $C_{35}H_{37}O_8NS$: C, 66.54; H, 5.90; S, 5.08. Found: C, 66.43; H, 5.94; S, 5.24.

Acetylation of 43 mg. of the above sirup with acetic anhydride and pyridine in the usual manner gave, after purification by chromatography and recrystallization from a mixture of ether and pentane, 36 mg. (80%) of the **4-*O*-acetyl derivative**, as prismatic needles, m.p. 145–148°, $[\alpha]^{24}D$ +75 ± 3° (in chloroform, *c* 1.26). *Anal.* Calcd. for $C_{37}H_{39}O_9NS$: C, 65.95; H, 5.83; S, 4.76. Found: C, 66.04; H, 5.82; S, 4.92.

Attempts to methylate methyl 2-acetamido-2-deoxy-3-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside with methyl iodide and silver oxide gave only the starting material, identified by its crystalline 4-*O*-acetyl derivative.

Acknowledgment.—The authors wish to thank Mrs. Shirley Butterworth for her technical assistance.

BOSTON, MASS.

(8) Attempts with methyl iodide and silver oxide alone or in presence of dimethylformamide[9] gave unsatisfactory results.

(9) R. Kuhn, *Angew. Chem.*, **67**, 32 (1955).

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[CONTRIBUTION FROM THE ROBERT W. LOVETT MEMORIAL LABORATORIES FOR THE STUDY OF CRIPPLING DISEASES, MASSACHUSETTS GENERAL HOSPITAL, AND THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

3,4-Di-*O*-methyl-D-galactosamine Hydrochloride (2-Amino-2-deoxy-3,4-di-*O*-methyl-D-galactose Hydrochloride)[1,2]

BY ROGER W. JEANLOZ, DIETER M. SCHMID AND PIERRE J. STOFFYN

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The synthesis of 3,4-di-*O*-methyl-D-galactosamine hydrochloride (2-amino-2-deoxy-3,4-di-*O*-methyl-D-galactose hydrochloride), a reference substance for structural studies of galactosamine-containing substances, is described. It was prepared from 1,6:2,3-dianhydro-β-D-talopyranose, and was transformed into the crystalline *N*-acetyl and *N*-(2'-hydroxynaphthylidene) derivatives and into methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranoside. The latter compound was found identical to a similar product synthesized from the known methyl 2-acetamido-2-deoxy-α-D-galactopyranoside, prepared from D-galactosamine, obtained from a natural source.

Dimethyl derivatives of D-galactosamine are of special importance in the elucidation of the structure of derivatives of galactosamine isolated from natural sources, such as chondrosine,[3] and uridine diphosphate–acetylgalactosamine sulfate.[4] The synthesis of 4,6-di-*O*-methyl-D-galactosamine hydrochloride has been reported previously.[5,6] In this paper, the synthesis of a second dimethylgalactosamine, 3,4-di-*O*-methyl-D-galactosamine hydrochloride (XV), is described. Although the synthesis of 3,4-di-*O*-methyl-D-glucosamine hydrochloride successfully has been reported,[7] starting from D-glucosamine and using a 6-*O*-trityl derivative as an intermediate, an analogous synthesis in the galactosamine series was at first not considered, because of the unavailability of large amounts of D-galactosamine as starting material. Instead, the synthesis was started with a material obtained from lactose, which had been used for the preparation of 4-*O*-methyl-D-galactosamine hydrochloride, namely, 1,6:2,3-dianhydro-β-D-talose (II).[8]

The synthesis of the key compound, 2-acetamido-1,6-anhydro-2-deoxy-3,4-di-*O*-methyl-β-D-galactopyranose (VII), was investigated, using various intermediates and methylation procedures. In a first pathway, catalytic deacetylation of 2-acetamido-3,4-di-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-galactopyranose[9] (VI) with barium methoxide gave 2-acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose (V). The same compound was obtained in acetylating 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose (I), with acetic anhydride in methanol. Consideration of the spatial structure of 2-acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose shows that the hydroxyl in position 3 is in axial position and is considerably shielded by the 1,6-anhydro ring. Consequently, its reactivity is expected to be much lower than the reactivity of the vicinal equatorial group in position 4. This was indeed the case and methylation of the hydroxyl in position 3 was very slow.[10] From the treatment of V with methyl iodide and silver oxide, only the starting material could be recovered in crystalline form. Methylation in dimethylformamide solution[11] was not successful, no crystalline product being isolated. Methylation with methyl sulfate and sodium hydroxide afforded the best way to obtain, in a 35% yield, the dimethyl derivative VII, whereas the 4-*O*-methyl derivative VIII was isolated in a 40% yield. Direct methylation of the 3,4-di-*O*-acetyl derivative VI with methyl sulfate and sodium hydroxide did not proceed successfully and only 11% of the dimethyl derivative was obtained.

In the second pathway, methylation of 2-acetamido-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactose (VIII) and its 3-*O*-acetyl derivative IX[8] was studied. The starting material VIII was obtained either by catalytic deacetylation of IX or by acetylation of 2-amino-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactopyranose (III)[8] with acetic anhydride in methanol. Methylation of VIII with methyl iodide and silver oxide afforded the crystalline dimethyl derivative in a low yield of 15%, whereas reaction with methyl iodide after treatment with potassium in absolute ether or liquid ammonia did not lead to crystalline compounds. Methylation with methyl sulfate and sodium hydroxide was again the best method and dimethyl derivative VII and starting material VIII were isolated in yields of 35 and 45%, respectively.

The lack of reactivity of the hydroxyl in position 3 was also reflected in its very small contribution to the polarity of the molecule. Whereas in adsorption chromatography on silicic acid mono- and dimethyl ethers are generally eluted into two very distinct peaks, VIII and VII were eluted in a continuous peak, in which the middle fractions always contained a mixture of both.

Hydrolysis of VII with 2 *N* hydrochloric acid for 24 hours was carried out as described for the 4-*O*-methyl compounds.[8] From the resulting mixture, the crystalline 2-amino-1,6-anhydro-2-deoxy-3,4-di-*O*-methyl-β-D-galactose hydrochloride (XIV) was

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(2) Presented before the Division of Carbohydrate Chemistry at the 129th Meeting of the American Chemical Society, Dallas, Texas, April, 1956.

(3) J. Hebting, *Biochem. Z.*, **63**, 353 (1914).

(4) J. L. Strominger, *Biochim. Biophys. Acta*, **17**, 283 (1955).

(5) P. J. Stoffyn and R. W. Jeanloz, THIS JOURNAL, **76**, 563 (1954).

(6) For an addendum, see Experimental part.

(7) R. W. Jeanloz, THIS JOURNAL, **74**, 4597 (1952).

(8) R. W. Jeanloz and P. J. Stoffyn, *ibid.*, **76**, 5682 (1954).

(9) S. P. James, F. Smith, M. Stacey and L. F. Wiggins, *J. Chem. Soc.*, 625 (1946).

(10) A similar observation has been made in the methylation of 1,6-anhydro-β-D-galactopyranose, which afforded mostly the 2,4-di-*O*-methyl derivative (private communication of Dr. J. Fellig, Massachusetts Institute of Technology).

(11) N. Kuhn, *Angew. Chem.*, **67**, 32 (1955).

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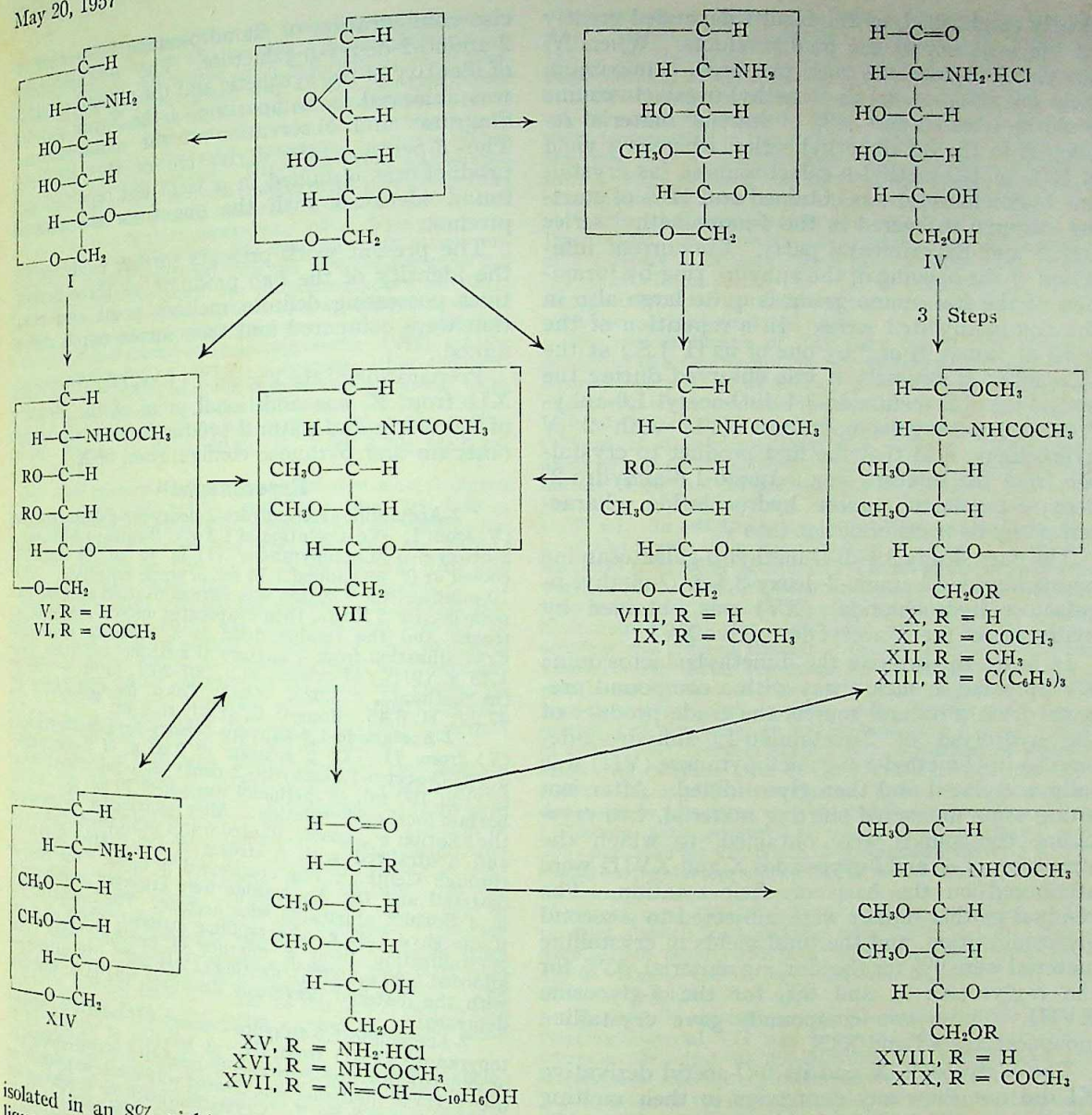

isolated in an 8% yield. The remaining mother liquors were *N*-acetylated and after chromatography 22% of starting material was recovered, whereas the 3,4-di-*O*-methyl-D-galactosamine (XV) was isolated as its crystalline *N*-acetyl derivative XVI in a 23% yield. When XV was isolated as the crystalline *N*-(2′-hydroxynaphthylidenamino) derivative XVII, yields up to 41% were obtained. When the hydrolysis was followed by two methanolyses, a yield of up to 59% of crystalline α- and β-methyl glycosides X and XVIII was obtained, whereas only 9% of starting material was recovered.

The relatively low yields of free amino sugar hydrochloride XV obtained and the large amount of starting material recovered, compared to the nearly quantitative yield obtained in hydrolysis of methyl *N*-acetylglycoside derivatives, are easily explained on the basis of the relative speed of scission of the *N*-acetyl groups, and of the internal (1,6-anhydro) and external (methyl) glycosidic bonds. In the cases of 2-acetamido-1,6-anhydro-compounds and methyl 2-acetamidoglycosides, hydrolysis of the acetyl radical linked to the amino group proceeds concurrently with the hydrolysis of the glycosidic linkages. Studies in the glucose, galactose and mannose series have shown, however, the 1,6-anhydro internal glycosidic bond to be more resistant to hydrolysis than the glycosidically linked methoxyl. Consequently, the amount of free amino groups produced during hydrolysis of the internal glycosidic bond is much greater than that produced during the hydrolysis of the methoxyl glycosidic linkage. It has also been demonstrated a number of times that the presence of a vicinal free amino group inhibits completely the hydrolysis of a methoxyl bond by dilute acid and it is probable that a similar inhibition takes place in 1,6-internal glycosidic bond. The formation of free amino groups will thus control the degree of opening of the ring. The influence of the substitution at position 3 or 4 on the splitting of the acetyl group and consequently on the formation of substituted galactosamine with free aldehyde groups could not be

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clearly established, as the results depended greatly on the isolation of the final products. When *N*-acetylated derivatives were prepared, a maximum yield of 23% of 3,4-di-*O*-methyl-D-galactosamine could be isolated and 30% of starting material recovered in the 3,4-dimethyl series, whereas a yield of 53% of 4-*O*-methyl-D-galactosamine (as crystalline hydrochloride) was obtained and 17% of starting material recovered in the 4-monomethyl series (ref. 8 and Experimental part). Concurrent inhibition of the opening of the anhydro ring by formation of the free amino group is quite large also in the non-methylated series. In a repetition of the work of James, *et al.*,[9] by one of us (P.J.S.) at the University of Brussels, it was observed during the hydrolysis of 2-acetamido-3,4-di-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-galactopyranose (VI) with 2 *N* hydrochloric acid that the first product to crystallize from the mixture was 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose hydrochloride, characterized by its transformation into V.[12]

The pure sirupy 3,4-di-*O*-methyl-D-galactosamine hydrochloride (2-amino-2-deoxy-3,4-di-*O*-methyl-D-galactose hydrochloride) (XV) was obtained by hydrolysis of the *N*-acetyl derivative XVI.

In order to correlate the dimethylgalactosamine XV prepared in such a way with a compound prepared from a natural source, the crude product of the hydrolysis of 2-acetamido-1,6-anhydro-2-deoxy-3,4-di-*O*-methyl-β-D-galactopyranose (VII) was fully acetylated and then glycosidified. After isolating some unreacted starting material, two crystalline compounds were obtained, to which the structures of α- and β-glycosides X and XVIII were attributed on the basis of their rotation. The residual mother liquors were subjected to a second glycosidification, and the total yields in crystalline material were 9% for the starting material, 53% for the α-glycoside X and 6% for the β-glycoside XVIII. These two compounds gave crystalline monoacetates XI and XIX.

The α-glycoside X and its 6-*O*-acetyl derivative XI did not show any depression in their melting points in admixture with identical products obtained by methylation of methyl 2-acetamido-2-deoxy-6-*O*-triphenylmethyl-α-D-galactopyranoside. This compound had been synthesized from methyl 2-acetamido-2-deoxy-α-D-galactopyranoside prepared from D-galactosamine (IV) which was isolated from a natural source.[13] In addition, the trityl derivative XIII was prepared from the α-glycoside X obtained *via* the route of the 1,6-anhydro derivatives and found to be identical with the same derivative synthesized from natural D-galactosamine. Such identity is not only evidence that galactosamine prepared from lactose and natural galactosamine are identical, but it also proves that X is really the α-anomer and possesses the pyranose configuration.

James, *et al.*, have proved in their work[9] the precise configuration of chondrosamine to be that of 2-amino-2-deoxy-D-galactose. The establishment of identity of the synthetic and the natural product was achieved by comparison of the X-ray powder diagrams and observation of the mutarotations. The β-pentaacetate derivative of the synthetic product was obtained in a yield not reported and found identical with the one from the natural product.

The present work presents further evidence for the identity of the two products, as three derivatives possessing definite melting point and rotation were compared and their mixed m.p.'s determined.

Preparation of the known 3,4,6-tri-*O*-methyl ether XII from X was additional proof of the identity of synthetic and natural product and of the α-anomerism and pyranose configuration of X.

Experimental[14]

2-Acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose (V) from I.—To a solution of 1.3 g. of 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose[9] (I) in 40 ml. of methanol cooled at 0° was added 1.75 ml. of acetic anhydride. After 10 minutes, the solution was allowed to stand at room temperature for 3 hours, then evaporated under a stream of nitrogen and the residue dried in a desiccator overnight. Crystallization from a mixture of methanol and ether gave 1.48 g. (91%) of prisms, m.p. 207–208°, $[\alpha]^{25}D$ −5 ± 1° (in methanol, *c* 1.02). *Anal.* Calcd. for $C_8H_{13}O_5N$: C, 47.29; H, 6.45. Found: C, 47.20; H, 6.49.

2-Acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose (V) from VI.—To a solution of 2.90 g. of 2-acetamido-3,4-di-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-galactopyranose[9] (VI) in 100 ml. of methanol was added 10 ml. of a 1.6 *N* barium methoxide solution. After refluxing for 10 minutes, the solution was cooled, diluted with a small amount of water and neutralized with a stream of CO_2. After filtration through Celite, it was evaporated *in vacuo*. The filtered material and the dry residue were extracted exhaustively in a Soxhlet apparatus with acetone. The combined extracts gave 1.92 g. of crystalline material, which after recrystallization from a mixture of methanol and ether afforded 1.89 g. (92%), melting at 204–207°. In admixture with the material previously described, the m.p. was not depressed.

2-Acetamido-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactopyranose (VIII) from III.—A solution of 95 mg. of 2-amino-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactopyranose[8] (III) in methanol was treated with acetic anhydride as described above for I. Crystallization from a mixture of acetone and ether gave 103 mg. (87%) of prismatic needles, m.p. 122–123°. When the melt was seeded with the material described below, crystallization in stout prisms occurred and a m.p. of 152–153° was observed, $[\alpha]^{24}D$ −53 ± 2° (in chloroform, *c* 0.98). *Anal.* Calcd. for $C_9H_{15}O_5N$: C, 49.76; H, 6.96. Found: C, 49.78; H, 6.84.

2-Acetamido-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactopyranose (VIII) from IX.—To a solution of 1.53 g. of 2-acetamido-3-*O*-acetyl-1,6-anhydro-4-*O*-methyl-β-D-galactopyranose[8] (IX) in 50 ml. of methanol was added 5 ml. of a 1.6 *N* barium methoxide solution. After refluxing for 10 minutes, the cooled solution was diluted with water, neutralized with a stream of CO_2 and filtered through Celite and charcoal. The filter was washed with water, the combined filtrates evaporated *in vacuo*, and the residue was extracted with boiling acetone. After evaporation, 1.30 g. of crude product was obtained; crystallization from a mixture of acetone and ether gave 1.16 g. (90%) of VIII, m.p. 120–122°. In admixture with the material described above, the m.p. was not depressed.

Methylation of V with Methyl Sulfate and Sodium Hydroxide.—To a solution of 2.21 g. of V in a minimum amount of water was added, with vigorous stirring and at room temperature, 33.3 ml. of methyl sulfate and 102.4 ml. of a 30% sodium hydroxide solution, in 20 portions each

(12) Using concentrated hydrochloric acid for 30 hours (2.2 *N* in the text of the Experimental part!) James, *et al.*,[9] were able to split the 1,6-anhydro ring in presence of a free amino group and obtain a yield of D-galactosamine hydrochloride greater than 50%. So great a concentration of acid was avoided in the treatment of methylated sugars in order to avoid demethylation.

(13) R. W. Jeanloz and R. G. Naves, unpublished.

(14) R. W. Jeanloz, THIS JOURNAL, **76**, 555 (1954); R. W. Jeanloz and D. A. Jeanloz, *ibid.*, **79**, 2579 (1957).

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at 15-minute intervals. The *p*H was checked frequently and always kept on the alkaline side. After the last addition, the mixture was stirred for a half-hour at room temperature, and then neutralized with CO_2. The precipitate was filtered off, and the filtrate was extracted several times with chloroform. The combined chloroform extracts were dried over sodium sulfate and evaporated *in vacuo*, giving 1.6 g. of crystalline residue. The water layer was evaporated *in vacuo* at 40°, and the residue dried in a desiccator. Combined with the filtered material, it was extracted with chloroform, in a Soxhlet apparatus. After drying over sodium sulfate, the chloroform was evaporated *in vacuo*, and the sirupy residue combined with the first residue gave 2.5 g. of crude product, which was chromatographed on silicic acid. Mixtures of ethyl acetate and acetone 4:1 eluted 940 mg. of crystalline fractions of **2-acetamido-1,6-anhydro-2-deoxy-3,4-di-*O*-methyl-β-D-galactopyranose (VII)**. After recrystallization from a mixture of acetone, ether and pentane, 880 mg. (35%) of stout prisms was obtained, m.p. 109–111°, $[\alpha]^{27}D$ −87 ± 2° (in chloroform, *c* 1.14). *Anal.* Calcd. for $C_{10}H_{17}O_5N$: C, 51.94; H, 7.41; N, 6.06; OCH_3, 26.84. Found: C, 52.04, 51.83; H. 7.56, 7.50; N, 6.18; OCH_3, 26.82.

The same mixture of ethyl acetate and acetone 4:1 eluted 300 mg., which could not be crystallized, and then 1.49 g. of partially crystalline fractions, which after recrystallization from a mixture of acetone and ether gave 935 mg. (40%) of VIII, melting at 119–121°. In admixture with the material described above, the m.p. was not depressed.

Methylation of VI with Methyl Sulfate and Sodium Hydroxide.—The methylation was carried out on 350 mg. of VI at 55° and 2.4 ml. of methyl sulfate and 7.1 ml. of a 30% solution of sodium hydroxide were introduced in 10 portions for two hours. After purification as described above, 32 mg. (11%) of VII was obtained, m.p. 108–110°, showing no depression in admixture with the compound described above; $[\alpha]^{25}D$ −82 ± 4° (in chloroform, *c* 0.60).

Methylation of VIII with Methyl Sulfate and Sodium Hydroxide.—A solution of 200 mg. of VIII in the minimum amount of water was methylated at room temperature with 1.3 ml. of methyl sulfate and 4.0 ml. of a 30% solution of sodium hydroxide, as described for V. After chromatography, 72 mg. (34%) of VII was obtained, melting at 108–110°, and showing no depression in admixture with the compound obtained above. In addition, 64 mg. (32%) of starting material, m.p. 120–121°, was obtained. In other experiments on a larger scale, the yield of VII varied from 25 to 37% and the yield in starting material was such as to give a total yield of crystalline products of 65 to 70%. The recovered starting material added to the non-crystallizable mother liquors gave again, after methylation, the same yield in VII.

Methylation of VIII with Methyl Iodide and Silver Oxide.—Five hundred mg. of VIII was methylated under reflux with 20 ml. of methyl iodide and four times 500 mg. of silver oxide, added over a 36-hour period. After 48 hours, the silver salts were filtered off and washed with acetone. The solution was evaporated *in vacuo*, and the residue chromatographed on silicic acid to give VII in a 15% yield, m.p. 103–105°, showing no depression with the material described above. No crystalline starting material could be recovered.

Methylation of IX with Methyl Sulfate and Sodium Hydroxide.—Two hundred mg. of IX was methylated at 55° with 1.4 ml. of methyl sulfate and 4.1 ml. of a 30% solution of sodium hydroxide as described for VI; 26 mg. (12%) of VII was obtained, m.p. 108–110°, showing no depression with the material described above.

3,4-Di-*O*-methyl-D-galactosamine Hydrochloride (2-Amino-2-deoxy-3,4-di-*O*-methyl-D-galactose Hydrochloride (XV) and 2-Acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranose (XVI).—A solution of 0.70 g. of VII in 50 ml. of 2 *N* hydrochloric acid in a sealed tube was heated for 24 hours in a boiling water-bath. After filtration through a layer of Darco G-60, the solution was evaporated *in vacuo* at 50° and the last traces of water and hydrochloric acid were removed by co-distillation with absolute ethanol. After a few weeks, the colorless sirup crystallized spontaneously, and was filtered after dilution with a mixture of methanol and acetone. Recrystallization from a mixture of methanol and acetone gave 55 mg. (8%) of **2-amino-1,6-anhydro-2-deoxy-3,4-di-*O*-methyl-β-D-galactose hydrochloride (XIV)**, as needles, subliming above 230° and decomposing above 250°, $[\alpha]^{27}D$ −26 ± 2° (in water, *c* 0.85). *Anal.* Calcd. for $C_8H_{16}O_4NCl$: C, 42.56; H, 7.15; Cl, 15.71; OCH_3, 27.50. Found: C, 42.48; H, 7.07; Cl, 15.68; OCH_3, 27.55. To a solution of 18 mg. of XIV in 1 ml. of methanol was added 14 mg. of silver acetate and 0.2 ml. of acetic anhydride. After standing a few hours at room temperature in the dark, the solution was filtered and one drop of 0.01 *N* hydrochloric acid was added to the filtrate. After one hour, the solution was filtered and evaporated *in vacuo* to dryness. The residue was dissolved in acetone, and filtered through a double layer of Celite and Darco G-60. Evaporation and crystallization of the residue in a mixture of acetone, ether and pentane gave 18 mg. (95%) of VII, m.p. 110–111°, $[\alpha]^{24}D$ −88 ± 2° (in chloroform, *c* 0.97); the m.p. showed no depression in admixture with the material described above.

The mother liquors of XIV (dry weight 0.72 g.) were subjected to a new hydrolysis by refluxing with 20 ml. of 3 *N* hydrochloric acid for 24 hours. After evaporation *in vacuo*, dissolution of the residue in water, filtration through a double layer of Celite and Darco G-60, and evaporation to dryness, 0.72 g. of a colorless sirup was obtained. Elementary analysis and rotation showed that it was composed approximately of 60% of XV and 40% of XIV, $[\alpha]^{27}D$ +62 ± 2° (in water, *c* 3.93). *Anal.* Found: C, 41.14; H, 8.18; O, 31.89. In order to separate those two components, 0.60 g. of the above sirup was dissolved in 10 ml. of methanol and 0.46 g. of silver acetate and 0.5 ml. of acetic anhydride were added. After standing for 2 days at room temperature in the dark, the solution was filtered, one drop of 0.1 *N* hydrochloric acid was added, and after a few hours the solution was filtered through a double layer of Celite and Darco G-60. After concentration *in vacuo*, 0.59 g. of a colorless sirup was obtained. Dissolved in chloroform, it was chromatographed on silicic acid. Elution with various mixtures of ethyl acetate and acetone gave 152 mg. (26%) of crude VII; recrystallization from a mixture of acetone, ether and pentane gave 134 mg. (22%), m.p. 110–112°, $[\alpha]^{25}D$ −86 ± 1° (in chloroform, *c* 1.18); the m.p. was not depressed in admixture with the compound described above.

Elution with mixtures of acetone and methanol gave 235 mg. (38%) of crude **2-acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranose (XVI)**; recrystallization from a mixture of methanol, ether and pentane gave 150 mg. (23%) of prisms, m.p. 199–200° (with slight decomposition). The product showed mutarotation from $[\alpha]^{27}D$ +114° (after 4 minutes) to $[\alpha]^{26}D$ +92 ± 2° (after 24 hours, in water, *c* 1.07). *Anal.* Calcd. for $C_{10}H_{19}O_6N$: C, 48.18; H, 7.68. Found: C, 48.07; H, 7.64.

The yields in crystalline materials showed that 30% of the starting material VII was recovered after *N*-acetylation, whereas 23% had its 1,6-anhydro ring opened and was transformed into the crystalline derivative XVI.

A solution of 110 mg. of XVI in 2 ml. of 2 *N* hydrochloric acid was heated on the steam-bath for 2 hours. After distillation *in vacuo* and co-distillation with absolute ethanol, the sirupy residue was left overnight in a desiccator over soda lime. It was dissolved in methanol, filtered through a double layer of Celite and Darco G-60 and evaporated to give 127 mg. (100%) of a colorless sirup, **3,4-di-*O*-methyl-D-galactosamine hydrochloride (XV)**, $[\alpha]^{24}D$ +108 ± 2° (in water, *c* 1.77). *Anal.* Calcd. for $C_8H_{18}O_5NCl$: C, 39.43; H, 7.44; Cl, 14.55; OCH_3, 25.47. Found: C, 39.27; H, 7.59; Cl, 14.51; OCH_3, 25.67.

2-Deoxy-2-(2′-hydroxynaphthylidenamino)-3,4-di-*O*-methyl-β-D-galactopyranose (XVII).—Hydrolysis of 200 mg. of VII gave 200 mg. of crude sirup. Dissolved in 2 ml. of water, it was treated as previously described[7] with 290 mg. of sodium acetate trihydrate and 440 mg. of 2-hydroxynaphthaldehyde dissolved in 20 ml. of methanol. On purification by chromatography, mixtures of ethyl acetate and acetone 4:1, 2:1, 1:1 and pure acetone eluted crystalline fractions. Crystallization from methanol and ether gave 130 mg. (41%) of yellow crystals, m.p. 203–204° (with slight decomposition). The product showed mutarotation from $[\alpha]^{26}_{5461}$ +107° (after 8 minutes) to $[\alpha]^{27}_{5461}$ +332 ± 5° (after 5 days, in methanol, *c* 0.15). *Anal.* Calcd. for $C_{19}H_{23}O_6N$: C, 63.15; H, 6.41. Found: 63.08; H, 6.52.

Methyl 2-Acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranoside (X) and Methyl 2-Acetamido-2-deoxy-3,4-di-*O*-methyl-β-D-galactopyranoside (XVIII) from VII.—The crude product of hydrolysis (534 mg.) of 475 mg. of VII was shaken for 60 hours with 15 ml. of acetic anhydride and

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15 ml. of dry pyridine. After evaporation *in vacuo*, the last traces of reagents were removed by co-distillation with dry toluene. The amorphous residue was refluxed for two hours with 40 ml. of 2% hydrochloric acid in methanol. After cooling, the chloride ion was removed with silver carbonate, and the last traces of silver with hydrogen sulfide. After filtration through a double layer of Darco G-60 and Celite, the solvent was evaporated *in vacuo* and the crude crystalline residue, dissolved in chloroform, was chromatographed on silicic acid. Elution with ethyl acetate gave after recrystallization 37 mg. of starting material VII, m.p. 108–110°. Elution with a mixture of ethyl acetate and acetone 2:1 gave crystalline fractions, which after recrystallization from a mixture of methanol and ether afforded 185 mg. of **methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranoside (X)**, as prismatic needles, m.p. 219–220°, $[\alpha]^{25}D$ +146 ± 1° (in methanol, *c* 1.50). *Anal.* Calcd. for $C_{11}H_{21}O_6N$: C, 50.18; H, 8.04; OCH_3, 35.36. Found: C, 50.35; H, 8.17; OCH_3, 35.18. In admixture with material obtained by hydrolysis of methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside, synthesized from natural D-galactosamine,[13] the m.p. was not depressed. Acetylation of 51 mg. of X with acetic anhydride and pyridine in the usual manner gave, after recrystallization from a mixture of acetone and ether, 51 mg. (90%) of the **6-*O*-acetyl derivative XI**, as fine needles, m.p. 203–204°, $[\alpha]^{27}D$ +123 ± 2° (in chloroform, *c* 0.70). *Anal.* Calcd. for $C_{13}H_{23}O_7N$: C, 51.14; H, 7.59. Found: C, 51.10; H, 7.71. In admixture with material prepared from natural D-galactosamine,[13] the m.p. was not depressed.

Elution with a mixture of ethyl acetate and acetone 1:1 gave a crystalline fraction. After recrystallization from a mixture of methanol and ether, 30 mg. (6%) of **methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-β-D-galactopyranoside (XVIII)** was obtained as needles, m.p. 247–249°, $[\alpha]^{25}D$ −18 ± 3° (in methanol, *c* 0.76). *Anal.* Calcd. for $C_{11}H_{21}O_6N$: C, 50.18; H, 8.04. Found: C, 50.05; H, 8.09. Acetylation of 16 mg. of XVIII with acetic anhydride and pyridine in the usual manner gave, after recrystallization from a mixture of methanol and ether, 16 mg. (85%) of the **6-*O*-acetyl derivative (XIX)**, as prismatic needles, m.p. 247–248°, $[\alpha]^{26}D$ 0 ± 4° (in chloroform, *c* 0.63). In admixture with the starting material, the m.p. was depressed at 215–235°. *Anal.* Calcd. for $C_{13}H_{23}O_7N$: C, 51.14; H, 7.59. Found: C, 51.21; H, 7.73.

The residual mother liquors and non-crystalline fractions were refluxed with 25 ml. of 2% hydrochloric acid in methanol for 2 hours and the solution was treated as described above, but using lead carbonate instead of silver carbonate to remove the chloride ion. After chromatography, 40 mg. of crude starting material VII was recovered, from which only 6 mg. of crystalline product was obtained, giving a total yield of 43 mg. (9%). An additional yield of 84 mg. of crude crystalline α-glycoside X was isolated from which 50 mg. of pure compound was crystallized, to give a total yield of 285 mg. (53%).

In another experiment, in which a smaller amount of starting material was subjected to only one hydrolysis and one methanolysis, the yield in crystalline starting material VII recovered was 20%, whereas 24% of pure crystalline α-glycoside X and 3% of pure crystalline β-glycoside XVIII were isolated.

Fifty mg. of X was methylated under reflux for 48 hours with 10 ml. of methyl iodide and two additions of 100 mg. of silver oxide. After filtration of the silver salts and evaporation, the crystalline residue was crystallized from a mixture of acetone and ether to give 47 mg. (90%) of methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-galactopyranoside (XII), m.p. 189–192°, after a second recrystallization. In admixture with authentic material,[15] the m.p. was not depressed; $[\alpha]^{27}D$ +143 ± 2° (in methanol, *c* 0.79).

Methyl 2-Acetamido-2-deoxy-3,4-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (XIII).—A solution of 36 mg. of X and 56 mg. (1.5 moles) of triphenylchloromethane in 0.5 ml. of anhydrous pyridine was heated at 55° for three days. After dilution with 10 ml. of ice-cold water, the precipitate was filtered off, dried in a desiccator and dissolved in a mixture of benzene and hexane 1:1. Chromatography on alumina afforded a large amount of triphenylcarbinol, eluted with pure benzene. A mixture of ether and methanol 9:1 eluted 40 mg. of crystalline XIII. Recrystallization from a mixture of acetone, ether and pentane gave 30 mg. (43%) of prismatic needles, m.p. 222–224°, $[\alpha]^{27}D$ +66 ± 4° (in chloroform, *c* 0.52). *Anal.* Calcd. for $C_{30}H_{35}O_6N$: C, 71.26; H, 6.98. Found: C, 71.29; H, 7.09. In admixture with material obtained by methylation of methyl 2-acetamido-2-deoxy-6-*O*-triphenylmethyl-α-D-galactopyranoside, synthesized from natural D-galactosamine (IV),[13] the m.p. was not depressed.

Hydrolysis of 2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-4-*O*-methyl-α-D-galactopyranose (IX).—In a preceding paper,[8] the hydrolysis of 300 mg. of IX with 2.5 *N* hydrochloric acid has been reported and 140 mg. of 4-*O*-methyl-α-D-galactosamine hydrochloride was isolated. The residual mother liquors were dissolved in 5 ml. of methanol and 165 mg. of silver acetate and 0.2 ml. of acetic anhydride were added. After standing at room temperature for 48 hours, in the dark, the solution was filtered and one drop of 0.1 *N* hydrochloric acid was added. After a few hours, the solution was filtered through Darco G-60 and Celite, evaporated *in vacuo* and the residue, dissolved in chloroform, was chromatographed on silicic acid. Mixtures of ethyl acetate and acetone eluted 50 mg. of crystalline fractions, 2-acetamido-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactopyranose (VIII). Recrystallization from a mixture of acetone and ether gave 43 mg. (17%) of stout prisms, m.p. 153–154°, $[\alpha]^{25}D$ −51 ± 2° (in chloroform, *c* 0.95). In admixture with the material described above (m.p. 122–123°) the m.p. was not depressed.

Elution with a mixture of acetone and methanol 49:1 gave 24 mg. of crystalline fractions, behaving like authentic 2-acetamido-2-deoxy-4-*O*-methyl-D-galactose.[16] However, recrystallization from a mixture of methanol and acetone afforded only 4 mg. of impure crystals. The remaining mother liquors were not further investigated.

Methyl 2-Acetamido-2-deoxy-4,6-di-*O*-methyl-3-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside.—This compound had been previously obtained only in sirupy form.[5] After standing one year, it crystallized spontaneously. It was recrystallized from a mixture of ether and pentane to give prisms melting at 106–108°, $[\alpha]^{21}D$ +94 ± 2° (in chloroform, *c* 1.17). *Anal.* Calcd. for $C_{18}H_{27}O_8NS$: C, 51.78; H, 6.52. Found: C, 51.82; H, 6.53.

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BOSTON, MASS.

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May 20, 1957

[CONTRIBUTION FROM THE ROBERT W. LOVETT MEMORIAL LABORATORIES FOR THE STUDY OF CRIPPLING DISEASES, MASSACHUSETTS GENERAL HOSPITAL, AND THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

The Synthesis of D-Allosamine Hydrochloride[1]

BY ROGER W. JEANLOZ

RECEIVED DECEMBER 17, 1956

Sirupy D-allosamine hydrochloride has been synthesized from methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranose and transformed into the crystalline N-acetyl and N-(2′-hydroxynaphthylidene) derivatives.

The increasing importance of glucosamine and galactosamine as components of biological systems and the recent isolations of new amino sugars from microorganisms[2] makes desirable the synthesis of 2-aminohexoses, to be used for reference or as biological substrates.

Fifty years ago, Fischer and Leuchs,[3] applied to D-arabinosimine the cyanohydrin method of lengthening the carbon chain and obtained impure D-glucosamine. In a series of papers, Levene later extended Fischer's work and prepared the eight possible 2-aminohexonic acids, but the yield was sometimes small and inconsistent.[4] Reduction of the aminohexonic acid generally gave poor yields and impure products. Only syntheses of D-glucosamine,[5] D-galactosamine[6] and D-mannosamine[7] were reported. A contaminated amino sugar was obtained from xylose. After treatment with phenylhydrazine it gave gulosazone, whereas benzoylation produced a crystalline pentabenzoate in small yield, not further identified.[5,8]

Recently catalytic hydrogenation of lactosazone led to the isolation of a 2-amino sugar in very minute amounts.[9]

The synthesis of 2-aminohexoses with the best yield takes place by addition of ammonia to 2,3-epoxy derivatives of hexoses.[10] However, only amino sugars with the 2,3-*trans* configuration are obtained and the final yield of the 2-amino isomer is controlled by the conformation of the molecule. Baker, *et al.*,[11] extending Winstein's work[12] on the influence of neighboring groups on the solvolysis of sulfonyl esters, have greatly increased the usefulness of the above described method. They were able to show, in the pentose series, that sulfonyl ester groups in transvicinal position to an acetylamino group can be split with concurrent Walden inversion, thus synthesizing 3-aminoribose from 3-aminoxylose. Application of the same method in the hexoses series to natural or synthetic 2-aminohexoses possessing *trans* configuration in positions 2,3 would make possible the preparation of the 2-aminohexoses possessing the 2,3-*cis* configuration. It is the aim of the present paper to describe this application to the naturally occurring D-glucosamine to obtain the new 2-amino-sugar, D-allosamine.

Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[13] treated with methanesulfonyl chloride in the presence of pyridine gave the 3-*O*-methylsulfonyl derivative II. When II was heated in the presence of sodium acetate in methyl Cellosolve solution, it yielded a small amount of I, and the crystalline methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside (III) characterized as its crystalline 3-monoacetate IV. Hydrolysis of III with 60% acetic acid afforded a crystalline methyl 2-acetamido-2-deoxy-α-D-allopyranoside (V), from which a crystalline 3,4,6-triacetate VI could be prepared. 2-Amino-2-deoxy-D-allose hydrochloride (D-allosamine hydrochloride) (IX) was obtained as a sirup by treatment of IV with hydrochloric acid. IX was characterized as two crystalline compounds, the 2-acetamido VII and the 2-(2′-hydroxynaphthylideneamino) (VIII) derivatives. Degradation with ninhydrin in presence of pyridine[14] gave rise to D-ribose (X). The latter compound, owing to lack of material, was identified by paper chromatography only. However, this additional evidence and the mode of preparation leaves little doubt as to the structure of the amino sugar.

Experimental[15]

Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-α-D-glucopyranoside (II).—To a solution of 11.5 g. of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[13] (I) in 50 ml. of anhydrous pyridine was added a solution of 6 ml. of methanesulfonyl chloride in 50 ml. of anhydrous pyridine, both solutions being previously cooled to 0°. After standing 8 days at 0°, ice was added, and after a few hr. the mixture was diluted with 2 l. of ice-cold water and left overnight in the refrigerator. The precipitate was filtered, washed well with ice-cold water and dried in a desiccator. After recrystallization from acetone, it yielded 13.0 g. (90%) of needles, m.p. 213–214°, with slight decomposition. The m.p. varied with the speed of heating. Very slow heating gave m.p. as low as 199–200°;

(1) Studies on hydaluronic acid and related substances, XVI. This is publication No. 207 of the Robert W. Lovett Memorial Laboratories for the Study of Crippling Diseases, Department of Medicine, Harvard Medical School, Boston, and the Massachusetts General Hospital. This investigation has been supported by a research grant from The National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service (Grant A-148-C2). Presented at the XIVth International Congress of Pure and Applied Chemistry, Zurich, Switzerland, July 1955.

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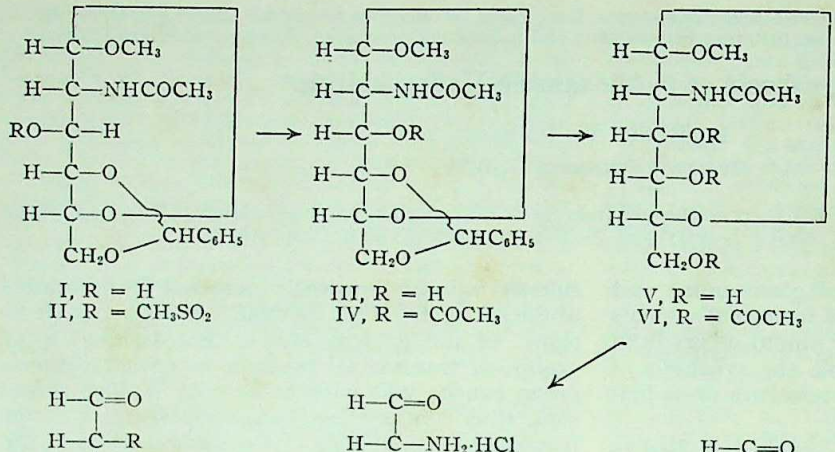
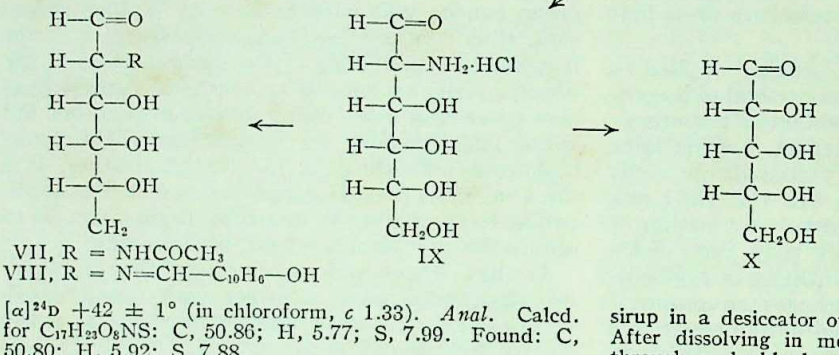


I, R = H
II, R = CH_3SO_2

III, R = H
IV, R = $COCH_3$

V, R = H
VI, R = $COCH_3$



VII, R = $NHCOCH_3$
VIII, R = N=CH—$C_{10}H_6$—OH

IX

X

$[\alpha]^{24}D$ +42 ± 1° (in chloroform, *c* 1.33). *Anal.* Calcd. for $C_{17}H_{23}O_8NS$: C, 50.86; H, 5.77; S, 7.99. Found: C, 50.80; H, 5.92; S, 7.88.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside (III).—A solution of 450 mg. of II and 400 mg. of sodium acetate trihydrate in 10 ml. of 95% methyl cellosolve was heated under reflux for 40 hr. After cooling, the solution was extracted with 150 ml. of chloroform. The chloroform layer was washed three times with water and dried over sodium sulfate. After evaporation *in vacuo*, the residual crystalline mixture was dissolved in chloroform and chromatographed on 20 g. of silicic acid. Mixtures of chloroform and ether 4:1, 2:1, 1:1 and pure ether eluted fractions, which after crystallization from a mixture of acetone, ether and pentane gave 42 mg. (10%), m.p. 202–206° (with decomposition), which showed no depression in admixture with the starting material (II).

Mixtures of ether and ethyl acetate varying from 19:1 to 1:1 eluted fractions, which were crystallized from a mixture of acetone and pentane to give 236 mg. (66%) of fine needles III, m.p. 214–215°; $[\alpha]^{24}D$ +64 ± 2° (in chloroform, *c* 0.95). *Anal.* Calcd. for $C_{16}H_{21}O_6N$: C, 59.43; H, 6.55. Found: C, 59.31; H, 6.55. The test for S was negative.

Ethyl acetate eluted fractions weighing 50 mg. (14%) with a m.p. of 259–261° after crystallization from a mixture of chloroform, ether and pentane. When mixed with methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside,[13] the m.p. was not depressed.

The same reaction carried out with a tenfold amount gave an identical yield.

Acetylation of 35 mg. of III with acetic anhydride and pyridine in the usual manner gave, after crystallization from a mixture of acetone, ether and pentane, 28 mg. (70%) of the 3-*O*-acetyl derivative IV, as elongated prisms, m.p. 213–214°; $[\alpha]^{25}D$ +17 ± 3° (in chloroform, *c* 0.71). *Anal.* Calcd. for $C_{18}H_{23}O_7N$: C, 59.17; H, 6.34. Found: C, 59.13; H, 6.29. In admixture with methyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (m.p. 203–205°),[16] the m.p. was depressed to 175–205°. In admixture with III, the m.p. was depressed to 180–195°.

Methyl 2-Acetamido-2-deoxy-α-D-allopyranoside (V).—A solution of 1.0 g. of III in 50 ml. of 60% acetic acid was heated for 1 hr. on a water-bath. The benzaldehyde and the water were removed by distillation *in vacuo*, followed by codistillation with water, then with absolute toluene. After standing overnight in a desiccator, the residual sirup was crystallized from a mixture of ethanol and ether to give 0.71 g. (96%) of stout prisms, m.p. 155–156°; $[\alpha]^{23}D$ +92 ± 1° (in methanol, *c* 1.25). *Anal.* Calcd. for $C_9H_{17}O_6N$: C, 45.95; H, 7.29. Found: C, 45.98; H, 7.14.

Acetylation of 0.36 g. of V with acetic anhydride and pyridine in the usual manner gave, after recrystallization from a mixture of acetone, ether and pentane 0.51 g. (92%) of the 3,4,6-tri-*O*-acetyl derivative VI as stout, hexagonal prisms, m.p. 107–109°; $[\alpha]^{24}D$ +68 ± 1° (in chloroform, *c* 2.21). *Anal.* Calcd. for $C_{15}H_{21}O_9N$: C, 49.86; H, 6.42. Found: C, 49.76; H, 6.35.

D-Allosamine Hydrochloride (2-Amino-2-deoxy-D-allose Hydrochloride (IX)).—A solution of 1.0 g. of V in 5 ml. of 2 *N* hydrochloric acid was heated on the water-bath for 2 hr. After evaporation *in vacuo*, the last traces of hydrochloric acid, water and acetic acid were removed by codistillation *in vacuo* with absolute ethanol and benzene and storage of the residual sirup in a desiccator over soda lime and calcium chloride. After dissolving in methanol, the solution was filtered through a double layer of Darco-G-60 and Celite and evaporated *in vacuo*. A colorless sirup (yield 100%) was obtained which did not crystallize after three years; $[\alpha]^{25}D$ +29 ± 2° (in water, *c* 1.35). *Anal.* Calcd. for $C_6H_{14}O_5NCl$: C, 33.26; H, 6.48; N, 6.50; Cl, 16.44. Found: C, 33.42; H, 6.67; N, 6.43; Cl, 16.48. A small amount, deposited on paper and treated with ninhydrin and pyridine as previously described,[14] gave a spot with an R_f identical to that of D-ribose (X).

2-Acetamido-2-deoxy-β-D-allose (VII).—To a solution of 110 mg. of IX in 1 ml. of methanol was added 83 mg. of silver acetate and 0.1 ml. of acetic anhydride. After standing one day at 0° and 5 hr. at room temperature, the mixture was heated to boiling, filtered through Celite, and the precipitate was washed with 1 ml. of hot water. One drop of 0.1 *N* hydrochloric acid was added to the filtrate. After 2 hr., the solution was filtered through a double layer of Darco G-60 and Celite and concentrated. Crystallization from a mixture of ethanol, acetone and ether gave 87 mg. (77%) of VII, m.p. 205–207° (starting at 190°) with slight decomposition. Starting from room temperature the m.p. was 201–203°. The compound showed mutarotation, from $[\alpha]^{24}D$ −57 (after 6 minutes) to −48 ± 2° (after 16 hr., in water, *c* 0.51). *Anal.* Calcd. for $C_8H_{15}O_6N$: C, 43.44; H, 6.83. Found: C, 43.57; H, 6.85.

2-Deoxy-2-(2′-hydroxynaphthylidenamino)-D-allose (VIII).—A solution of 55 mg. of IX and 30 mg. of sodium acetate trihydrate in 1 ml. of water was treated as previously described[17] with 110 mg. of 2-hydroxynaphthaldehyde in 10 ml. of methanol. Purification was effected by chromatography; the substance was eluted by a mixture of acetone and methanol 49:1. Crystallization from a mixture of pyridine, methanol and acetone gave 32 mg. (38%) of small yellow prisms, m.p. 199–200° (with decomposition above 185°); $[\alpha]^{25}_{5461}$ −80 ± 5° (at equilibrium, in methanol, *c* 0.17). *Anal.* Calcd. for $C_{17}H_{19}O_6N$: C, 61.25; H, 5.75. Found: C, 61.09; H, 5.88.

Acknowledgments.—The author wishes to thank Miss Ann Foley and Mrs. Shirley Butterworth for technical assistance.

BOSTON, MASS.

(16) L. F. Wiggins, *J. Chem. Soc.*, 18 (1947).

(17) R. W. Jeanloz, THIS JOURNAL, **74**, 4597 (1952).

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

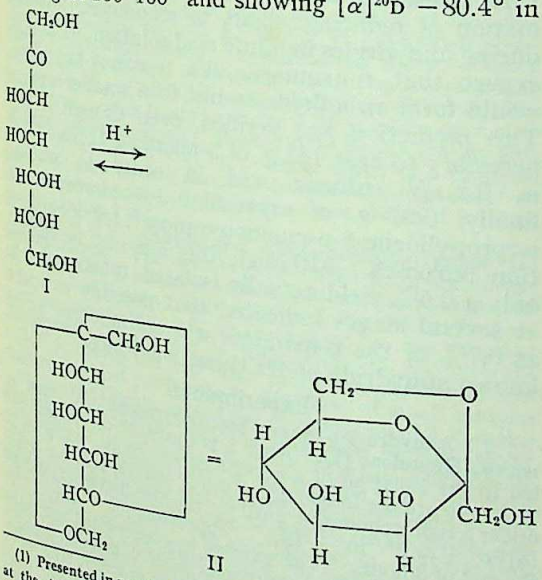
The Formation of 2,7-Anhydro-β-D-*manno*-heptulopyranose by the Action of Acid on D-*manno*-Heptulose and of Alkali on Phenyl α-D-*manno*-Heptulopyranoside; also 1,6-Anhydro-β-D-mannopyranose from D-Mannose in Acid Solution[1-3]

BY EMMANUEL ZISSIS, LAURA C. STEWART AND NELSON K. RICHTMYER

RECEIVED DECEMBER 14, 1956

D-*manno*-Heptulose has been converted by hot dilute acid in about 8% yield to 2,7-anhydro-β-D-*manno*-heptulopyranose, whose structure has been established through periodate oxidation methods. D-Mannose has been transformed similarly in about 0.6% yield to 1,6-anhydro-β-D-mannopyranose. Acetylation of D-*manno*-heptulose with acetic anhydride and pyridine forms first the 1,3,4,5,7-pentaacetate (described earlier as the α-hexaacetate) and then, much more slowly, the true α-D-*manno*-heptulopyranose hexaacetate (melting point 86–89°, $[\alpha]^{20}D$ +41.5° in chloroform). Condensation of both the penta-acetate and the hexaacetate with phenol in the presence of *p*-toluenesulfonic acid as catalyst yielded phenyl α-D-*manno*-heptulopyranoside pentaacetate. Deacetylation, and subsequent degradation of the phenyl α-D-*manno*-heptulopyranoside with hot aqueous alkali gave about a 15% yield of the same 2,7-anhydro-β-D-*manno*-heptulopyranose that was formed by the action of acid on D-*manno*-heptulose.

The conversion of aldohexoses, aldoheptoses and heptuloses in dilute acid solution to equilibrium mixtures containing one or more monomeric, non-reducing anhydrides has been studied extensively in this Laboratory. In general, heptuloses are transformed to a significantly greater extent than are the corresponding aldoses, and production of the 2,7-anhydroheptulopyranoses has been reported to occur to the following extents: *altro*, 91; *ido*, 85; *gulo*, 80; *allo*, 50; *talo*, 32; *gluco*, 2.[4] In extending these studies to the *manno* configuration we now find that D-*manno*-heptulose (I) is converted by dilute acids to an equilibrium mixture from which we could isolate a crystalline anhydride melting at 159–160° and showing $[\alpha]^{20}D$ −80.4° in water. Its structure was proved by periodate oxidation methods to be 2,7-anhydro-β-D-*manno*-heptulopyranose (II). No trace of other anhydrides, such as the 2,7-anhydro-β-D-*altro*-heptulofuranose derived from sedoheptulose[2] or the dimolecular dianhydride derived from D-*gluco*-heptulose,[3] was found.



In the equilibrium mixture of sedoheptulose (= D-*altro*-heptulose) and sedoheptulosan, the amount of anhydride varies with the temperature,[2] being 91% at 20° and only 84.5% at 80°. With D-*manno*-heptulose the equilibrium is shifted in the opposite direction with a change in temperature so that at 40° there is only 3% anhydride while at 80° there is about 7% anhydride (Table I). According to the principle of LeChatelier and Braun these results might not be unexpected, because the effect of heat is to displace the equilibrium in the direction of the thermodynamically less-favored component.

TABLE I

THE EFFECT OF TEMPERATURE ON THE AMOUNTS OF D-*manno*-HEPTULOSE (I) AND ITS ANHYDRIDE (II·H_2O) IN THE EQUILIBRIUM MIXTURE IN 0.2 *N* HYDROCHLORIC ACID

Time, hr.	Temp., °C.	$[\alpha]^{20}D$	% II·H_2O[a]	% I[b]	Mole % DHEF[c]
119	40	+25.9°	2.8	94.9	..
237	40	+25.9	2.8	94.6	0.11
16	60	+23.5	5.2	93.0	.26
40	60	+23.6	5.1	93.3	..
3	80	+21.2	7.4	89.8	.55
5	80	+21.3	7.3	89.8	.88

[a] Calculated from the specific rotation on the assumption that the solution contained only D-*manno*-heptulose (I) and 2,7-anhydro-β-D-*manno*-heptulopyranose (II) as its monohydrate of $[\alpha]^{20}D$ −73.5°; total concentration, 0.1 molar. [b] Determined by a ferricyanide titration method. [c] Calculated from the ultraviolet spectra on the assumption that the molecular absorption coefficient of DHEF [= 5-(1,2-dihydroxyethyl)-2-furaldehyde] is about the same as that of HMF [= 5-(hydroxymethyl)-2-furaldehyde]. For further details of the methods, see reference 2.

The acetylation of D-*manno*-heptulose by acetic anhydride and pyridine for 48 hours at 0° was reported by Montgomery and Hudson[5] to produce large prisms melting at 110° and showing $[\alpha]^{20}D$ +39.0° in chloroform. Carbon, hydrogen and acetyl analyses of their compound, as well as its

(1) Presented in part before the Division of Carbohydrate Chemistry at the Atlantic City Meeting of the American Chemical Society, September 18, 1956.

(2) For the preceding paper on anhydro sugars, see N. K. Richtmyer and J. W. Pratt, THIS JOURNAL, **78**, 4717 (1956).

(3) For a recent paper on anhydro sugars that includes pertinent references to their preparation by both these methods, see L. C. Stewart, E. Zissis and N. K. Richtmyer, *Chem. Ber.*, **89**, 535 (1956).

(4) Although D-*altro*-heptulose appears to give the highest yield of anhydride yet reported, it should be noted that the 91% represents the amount as determined at the very favorable temperature of 20° whereas the values for the other sugars were obtained at 95–100°. It is expected that *ido*-heptulose and perhaps *gulo*-heptulose will generate more than 91% anhydride when they are allowed to stand in dilute acid solution at 20°.

(5) E. M. Montgomery and C. S. Hudson, THIS JOURNAL, **61**, 1654 (1939).

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transformation to an "acetobromo" compound and subsequent reaction of the latter to form the methyl glycoside pentaacetate, led them to designate it the α-hexaacetate. We find, however, that their product was actually a pentaacetate: it showed clearly a hydroxyl band in its infrared spectrum and upon further reaction with acetic anhydride and pyridine it yielded the true α-D-*manno*-heptulopyranose hexaacetate as small prismatic needles melting at 86–89° and showing $[\alpha]^{20}D$ +41.5° in chloroform. Our further studies have shown that acetic anhydride and pyridine at 25° convert D-*manno*-heptulose rapidly to the pentaacetate stage (65% yield isolated after one hour), whereas complete acetylation is achieved only after about 5 days. Comparable results with D-*gluco*-heptulose had been reported earlier by Wolfrom and Thompson[6] and by Frush and Isbell.[7] The first-named pair of investigators found that their "acetobromo" compound, with silver carbonate and aqueous acetone, yielded α-D-*gluco*-heptulose pentaacetate, and they thus established that the free hydroxyl group was at C2 in the pentaacetate. We have found, similarly, that penta-*O*-acetyl-α-D-*manno*-heptulopyranosyl bromide[5] is converted by gentle hydrolysis to the pentaacetate, which must, therefore, also be designated the 1,3,4,5,7-pentaacetate.

Acetylated glycosyl bromides are usually prepared from the fully acetylated sugars. We have found, in agreement with the experiment described by Montgomery and Hudson,[5] that the α-D-*manno*-heptulopyranose pentaacetate, in which the hydroxyl group at C2 is unsubstituted, is converted, readily and in high yield, by hydrogen bromide in glacial acetic acid to penta-*O*-acetyl-α-D-*manno*-heptulopyranosyl bromide. Likewise, the reaction of Helferich and Schmitz-Hillebrecht[8] is usually carried out with the fully acetylated sugar. We have found that the condensation of α-D-*manno*-heptulopyranose 1,3,4,5,7-pentaacetate with phenol, in the presence of *p*-toluenesulfonic acid as catalyst, can be effected although the yield in our only experiment was not so good as when we used the hexaacetate later. The product of these reactions was phenyl α-D-*manno*-heptulopyranoside pentaacetate, melting at 103–104° and showing $[\alpha]^{20}D$ +35.9° in chloroform; upon catalytic deacetylation it yielded phenyl α-D-*manno*-heptulopyranoside, melting at 181–183° and showing $[\alpha]^{20}D$ +89.6° in water.

In a recent paper[3] we reported that the reaction of phenyl α-D-*gluco*-heptulopyranoside with hot aqueous potassium hydroxide produced at least a 34% yield of 2,7-anhydro-β-D-*gluco*-heptulopyranose. Phenyl α-D-*manno*-heptulopyranoside appears to be degraded similarly to the extent of about 15%, and 8.4% of crystalline 2,7-anhydro-β-D-*manno*-heptulopyranose was isolated from the reaction mixture. In both cases there was extensive destruction of the remainder of the material. Earlier studies had shown that phenyl β-D-glucopyranoside is converted practically quantitatively to 1,6-anhydro-β-D-glucopyranose, and the reaction mechanism has been established satisfactorily.[9] Phenyl heptulosides, however, have a CH_2OH group attached to the glycosidic carbon atom (C2), and this situation tends to complicate the picture. Thus, we have suggested two possible, simple mechanisms for the degradation of phenyl α-D-*gluco*-heptulopyranoside to the anhydro sugar,[3] postulating inversion of configuration at the glycosidic carbon atom at each step. With phenyl α-D-*manno*-heptulopyranoside also, we may write similar one- and three-step reaction mechanisms. The first, delineated in the simplest manner, represents the reaction as involving elimination of the elements of phenol between C2 and C7, with inversion of configuraton at C2 (III → II). The alternate mechanism involves elimination of the elements of phenol between C2 and C3 and the formation of the 2,3-epoxide IV; this may be followed by rearrangement (reversible) to the 1,2-epoxide V, and a final rearrangement to the anhydro sugar II, which is stable to hot alkali. Other pathways may lead through the epoxide IV or through the isomeric 1,2-epoxide VI to free D-*manno*-heptulose (I), which is not stable to alkali and forms tarry decomposition products.

We hope that additional experiments now in progress on appropriately substituted heptuloses will contribute further to the study of these reaction mechanisms.

As a result of our earlier studies on the transformation of reducing sugars to monomeric, non-reducing anhydrides in dilute acid solution, we should expect that D-mannose, like D-*manno*-heptulose, would form an anhydride but to a smaller extent. This prediction was verified, even though it was necessary to heat 144 g. of D-mannose at about 83° in 0.2 *N* sulfuric acid in order to obtain, finally, 0.87 g. of crystalline 1,6-anhydro-2,3-*O*-isopropylidene-β-D-mannopyranose[10] for identification purposes. Although this amount represents only a 0.5% yield actually isolated, rotational data at several stages indicated that possibly as much as 0.7% of the D-mannose was transformed to its known anhydride under those conditions.

Experimental

2,7-Anhydro-β-D-*manno*-heptulopyranose (II) from D-*manno*-Heptulose (I).—After a preliminary experiment had led to the isolation of a crystalline anhydride, 100 g. of D-*manno*-heptulose in 800 ml. of 0.5 *N* sulfuric acid was boiled under a reflux condenser until the rotation had dropped from $[\alpha]^{20}D$ +29.2° to +18.5° (approximately constant) at the end of 3 hours. The solution was neutralized cautiously with aqueous barium hydroxide, filtered through carbon, and concentrated *in vacuo* to a sirup from which 60 g. of D-*manno*-heptulose was recovered by crystallization from ethanol. The remaining sugar was removed by heating its aqueous solution with excess barium hydroxide, neutralizing with sulfuric acid, filtering through carbon, and deionizing with Amberlite IR-120 and Duolite A-4 ion-exchange resins. The solution, upon concentration to a small volume, was levorotatory; it was concentrated further to a sirup that was crystallized from ethanol to yield a total of 3.3 g. of the anhydride. The 2,7-anhydro-β-D-*manno*-heptulopyranose separated as clusters of prisms from aqueous ethanol,

(6) M. L. Wolfrom and A. Thompson, This Journal, **56**, 1804 (1934).

(7) H. L. Frush and H. S. Isbell, *J. Research Natl. Bur. Standards*, **34**, 111 (1945).

(8) B. Helferich and E. Schmitz-Hillebrecht, *Ber.*, **66**, 378 (1933).

(9) See, for example, C. E. Ballou, *Advances in Carbohydrate Chem.*, **9**, 59 (1954).

(10) A. E. Knauf, R. M. Hann and C. S. Hudson, This Journal, **63**, [illegible]

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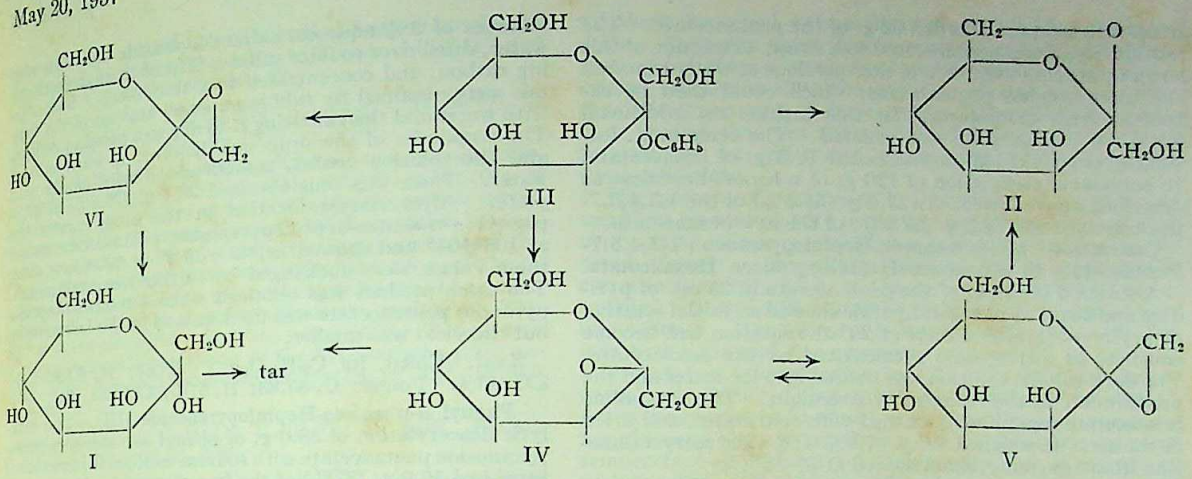

and after several recrystallizations melted at 159–160° and showed $[\alpha]^{20}D$ −80.4° in water (*c* 2.0).

Anal. Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.30. Found: C, 43.54; H, 6.38.

After the experiments at 40, 60 and 80°, summarized in Table I, had been completed, a final run was made in which 21.02 g. of D-*manno*-heptulose in 1 liter of 0.2 *N* sulfuric acid was heated for 3 hours at 90°. The rotation $[\alpha]^{20}D$ +19.6° indicated the formation of 9.0% of 2,7-anhydro-β-D-*manno*-heptulopyranose, while an estimation of reducing sugar by the ferricyanide method indicated that 87.6% of the D-*manno*-heptulose remained. From an ultraviolet absorption spectrum of the very slightly colored solution we could estimate the presence of about 1.6 mole % of DHEF. The mixture was heated with excess barium hydroxide for 20 hours on the steam-bath, neutralized with carbon dioxide until the solution was no longer alkaline to phenolphthalein, filtered, deionized, and concentrated *in vacuo* to a small volume. At that point, the rotation of the solution corresponded to 1.73 g. (9.0%) of 1,6-anhydro-β-D-*manno*-heptulopyranose; crystallization from ethanol yielded 1.54 g. (8.0%) of material that upon recrystallization gave 1.38 g. (7.2%) of pure anhydride melting at 159–160°. The mother liquor from the 1.54 g., when examined by paper chromatography, showed only the anhydride and a trace of heptulose, with no evidence either of a furanose anhydride such as was obtained from D-*altro*-heptulose[2] or of a dimolecular dianhydride such as was obtained from D-*gluco*-heptulose.[3]

Oxidation of 2,7-Anhydro-β-D-*manno*-heptulopyranose (II) with Periodate.—The oxidation of 0.3865 g. of the anhydride with a 20% excess of sodium metaperiodate appeared to be complete within 1 hour at 20° as indicated by the constant rotation $[\alpha]^{20}D$ −17.3° (calculated as the expected dialdehyde). This value is comparable to the average −17.2° found for the four other anhydroheptuloses of this structure reported previously.[3] Titration of small samples at the end of 24 hours showed the consumption of 2.10 molar equivalents of oxidant and the liberation of 0.98 molar equivalent of formic acid. No formaldehyde could be detected. The remaining 90% of the solution was neutralized with barium hydroxide and enough additional barium ions were added as barium chloride to precipitate the iodate and periodate ions present. The solution (*p*H *ca.* 6.6) was concentrated *in vacuo* to dryness, and the dialdehyde extracted with 40 ml. of warm methanol. To the filtered solution was added 0.8 g. of 2,5-dichlorophenylhydrazine, and the mixture concentrated and heated on the steam-bath for 1 hour. Because inorganic material crystallized during this process, and especially when pentane was added to the methanol solution, it was necessary to concentrate finally on the steam-bath to a sirup and then extract the sirup with ether. Upon the addition of pentane to the clear ether solution, the product crystallized readily; wt. 0.6 g., m.p. 154–156°. After two recrystallizations, the m.p. was 157–158° and showed no depression when the material was mixed with an equal amount of 4-D-*glycero*-2-hydroxymethyl-1,3-dioxolane-2,4-*cis*-dicarboxaldehyde bis-2,5-dichlorophenylhydrazone derived in similar fashion from sedoheptulosan.[3] The rotation, $[\alpha]^{20}D$ +40.0° in chloroform (*c* 0.5), was in good agreement with the value +40.6° reported previously.

α-D-*manno*-Heptulopyranose 1,3,4,5,7-Pentaacetate and α-D-*manno*-Heptulopyranose Hexaacetate from the Acetylation of D-*manno*-Heptulose in Pyridine at 5°.—A suspension of 120 g. of D-*manno*-heptulose (powdered to pass through an 80-mesh sieve) in 600 ml. of dry pyridine was cooled in ice-water and to it was added 600 ml. of acetic anhydride. The mixture was shaken overnight at 5° and the resulting solution kept an additional 4 days at that temperature. The reaction mixture was then poured into 4 liters of cracked ice and water and left overnight in the refrigerator. The acetylated material was divided between the aqueous pyridine solution and the precipitated gum. The latter was dissolved in chloroform and the chloroform solution washed with ice-cold, dilute sulfuric acid and then with water, dried over sodium sulfate, filtered through a small amount of carbon, and concentrated *in vacuo* to a thin sirup. This was diluted with pentane and inoculated with seed crystals of "D-mannoheptulose α-hexaacetate" remaining from the earlier researches of Montgomery and Hudson.[5] The crystals grew slowly at room temperature into large prisms and after repeated additions of pentane during the next two weeks there was obtained 52.3 g. of product originally designated as the hexaacetate but now identified as α-D-*manno*-heptulopyranose 1,3,4,5,7-pentaacetate. After recrystallization from ether–pentane the pentaacetate melted at 105–106° and showed $[\alpha]^{20}D$ +39.4° in chloroform (*c* 2). Montgomery and Hudson[5] reported m.p. 110° and $[\alpha]^{20}D$ +39.0° in chloroform (*c* 2) for their "hexaacetate"; their original sample, now about 20 years old, melted at 99–103° and in admixture with our pentaacetate melted at 100–105°. After one recrystallization from ether, their sample melted at 104–106° with no depression of melting point when mixed with our pentaacetate. The infrared spectrum of their original sample in chloroform solution was practically identical with that of our pentaacetate, with both showing clearly a hydroxyl band at 3570 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{24}O_{12}$: C, 48.57; H, 5.75; CH_3CO, 51.2. Found: C, 48.61, 48.49; H, 6.11, 5.93; CH_3CO, 52.6.

The chloroform–pentane mother liquor from the 52.3 g. of pentaacetate was concentrated to a sirup that was covered with about a liter of water and left at room temperature for two weeks with occasional stirring. At that time, small prismatic needles had begun to appear in the sirup and upon refrigeration for a week the sirup crystallized completely. The product was filtered, washed with water, and dried in the air; wt. 61.3 g. After recrystallization from 90 ml. of warm ethanol by the cautious addition of 90 ml. of water, the new, authentic α-D-*manno*-heptulopyranose hexaacetate melted at 85–88°, a value that was raised to 86–89° by additional recrystallizations in the same manner. The hexaacetate showed $[\alpha]^{20}D$ +41.5° in chloroform (*c* 1). Its ultraviolet absorption spectrum showed no absorption in the region of 280 mμ, indicating no ketone group and thus verifying the cyclic structure of the hexaacetate.

Anal. Calcd. for $C_{19}H_{26}O_{13}$: C, 49.35; H, 5.67; CH_3CO, 55.9. Found: C, 49.17; H, 5.51; CH_3CO, 56.1.

The original aqueous pyridine solution was extracted with chloroform, and the extract washed, dried and concentrated in the usual manner. Dilution of the residual thin

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sirup with pentane afforded 62 g. of the pentaacetate. The mother liquor was concentrated to a sirup; extraction of this sirup by stirring with several liter portions of water removed the more soluble pentaacetate, which could then be extracted with chloroform. In this fashion an additional 9.3 g. of pentaacetate was isolated. The remaining, less soluble sirup yielded an additional 10.5 g. of hexaacetate. In summary, acetylation of 120 g. of D-*manno*-heptulose as described above furnished 123.6 g. (51.5%) of the 1,3,4,5,7-pentaacetate and 71.8 g. (27.2%) of the new hexaacetate.

Conversion of α-D-*manno*-Heptulopyranose 1,3,4,5,7-Pentaacetate to α-D-*manno*-Heptulopyranose Hexaacetate.—A solution of 5.4 g. of the pentaacetate in 25 ml. of pyridine and 25 ml. of acetic anhydride showed an initial rotation of $[\alpha]^{20}D$ +7°; after 5 days at 20° the rotation had become constant at $[\alpha]^{20}D$ +35°, calculated as the hexaacetate. The dark-colored solution was poured into ice-water and the mixture left in the refrigerator overnight. The crystalline hexaacetate was filtered, washed with cold water, and dried in the air. It weighed 4.7 g. (79%) and after recrystallization from aqueous ethanol melted at 85–88°.

Preparation of α-D-*manno*-Heptulopyranose Hexaacetate and of α-D-*manno*-Heptulopyranose 1,3,4,5,7-Pentaacetate at 20–25°.—When 21 g. of D-*manno*-heptulose was dissolved in 250 ml. of pyridine and 100 ml. of acetic anhydride added, the observed rotation at 20° in a 1-dm. tube dropped rapidly from +2.84 to +0.59° within an hour and then began to rise, with values of +1.97, +2.56, +2.98, +3.25 and +3.98° being observed at the end of 1, 2, 3, 4 and 7 days, respectively. The dark-colored reaction mixture was poured onto cracked ice and left at 5° overnight to crystallize. The resulting hexaacetate was filtered, washed with water, and dried; it weighed 21.2 g.; and an additional 17.4 g. was isolated by extraction of the aqueous pyridine solution with chloroform in the usual manner, giving a total yield of 38.6 g. (83.6%).

When the acetylation of D-*manno*-heptulose was interrupted near the point of minimum rotation, good yields of the 1,3,4,5,7-pentaacetate could be obtained. Preliminary experiments on 5-g. batches were run for 30, 45, 60, 75 and 90 minutes, and when these were poured onto cracked ice and left at 5° overnight, the portions of crystalline pentaacetate weighed 4.3, 5.3, 7.0, 6.6 and 5.5 g., respectively. The product thus obtained was a fairly unstable, pyridine-solvated form melting at 73–75°; it could be converted to the solvent-free modification by heating overnight at 55°, by longer standing at room temperature in the air or in an evacuated desiccator over concentrated sulfuric acid, or by recrystallization. In a final experiment, 10 g. of D-*manno*-heptulose was dissolved in 130 ml. of warm pyridine, the solution was cooled and to it was added 50 ml. of acetic anhydride. The reaction generated a small amount of heat. The solution was kept at 25° for 1 hour, poured into 500 ml. of ice-water, and the mixture allowed to stand for several hours at room temperature. Upon extracting with chloroform and washing the solution with cold acid in the usual manner, the resulting sirup weighed 18.7 g. Crystallization from ether–pentane afforded a total of 13.1 g. (65.5%) of D-*manno*-heptulose 1,3,4,5,7-pentaacetate

Penta-*O*-acetyl-α-D-*manno*-heptulopyranosyl Bromide from α-D-*manno*-Heptulopyranose 1,3,4,5,7-Pentaacetate.—Five grams of the pentaacetate was dissolved in 25 ml. of glacial acetic acid saturated with hydrogen bromide at 0°, the mixture left at room temperature for 2 hours, diluted with 60 ml. of chloroform, poured into ice-water, and the product isolated in the usual manner. The resulting sirup crystallized readily from ether, depositing 5.2 g. (90%) of prisms melting at 84–90°. After recrystallization from ether–pentane the bromide melted at 87–92° and showed $[\alpha]^{20}D$ +106° in chloroform (*c* 1), in good agreement with the values 92 and +104.0°, respectively, reported by Montgomery and Hudson.[5] In an unsuccessful attempt to condense 2.3 g. of the penta-*O*-acetyl-α-D-*manno*-heptulopyranosyl bromide with *p*-toluenethiol, 0.6 g. (30%) of D-*manno*-heptulopyranose 1,3,4,5,7-pentaacetate was recovered; it was undoubtedly formed as a result of hydrolysis of a portion of the bromide by the sodium salt of the thiol.

Phenyl α-D-*manno*-Heptulopyranoside Pentaacetate.—A fused mixture of 30 g. of α-D-*manno*-heptulopyranose hexaacetate, 27 g. of phenol and 1.5 g. of *p*-toluenesulfonic acid monohydrate was heated for 1 hour at 65–75° and 15 mm. pressure. The dark reaction mixture was dissolved in 450 ml. of chloroform and the solution washed twice with equal volumes of 3% aqueous sodium hydroxide and then with water, dried over sodium sulfate, filtered through decolorizing carbon, and concentrated to a thick sirup. Seed crystals were obtained by rubbing a small amount of the sirup with water and then allowing it to dry to a powdery residue. The remainder of the sirup was dissolved in warm ethanol and the solution cooled, seeded and diluted slowly with water. There was thus obtained 22.7 g. (70.5%) of shiny plates. After recrystallization in the same manner the phenyl α-D-*manno*-heptulopyranoside pentaacetate melted at 103–104° and showed $[\alpha]^{20}D$ +35.9° in chloroform (*c* 1); these values were unchanged by further recrystallizations. The same product was obtained when α-D-*manno*-heptulopyranose pentaacetate was used instead of the hexaacetate, but the yield was smaller.

Anal. Calcd. for $C_{23}H_{28}O_{12}$: C, 55.64; H, 5.69; CH_3CO, 43.4. Found: C, 55.83; H, 5.75; CH_3CO, 43.1.

Phenyl α-D-*manno*-Heptulopyranoside (III).—The catalytic deacetylation of 20.0 g. of phenyl α-D-*manno*-heptulopyranoside pentaacetate with sodium methoxide in methanol furnished 10.0 g. (87%) of the free glycoside. It separated as flat prisms from 3 parts of absolute ethanol and after two recrystallizations it melted at 181–183° and showed $[\alpha]^{20}D$ +89.6° in water (*c* 0.6).

Anal. Calcd. for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.63; H, 6.09.

2,7-Anhydro-β-D-*manno*-heptulopyranose (II) from Phenyl α-D-*manno*-Heptulopyranoside (III).—A solution of 9.9 g. of the phenyl glycoside in 250 ml. of *N* aqueous potassium hydroxide was boiled under a reflux condenser until the rotation became constant, after 3.5 hours, at $[\alpha]^{20}D$ −12° calculated as anhydroheptulose. On the assumption that the only optically active material present was the anhydro-*manno*-heptulose of $[\alpha]^{20}D$ −80.4°, the value $[\alpha]^{20}D$ −12° would correspond to a 15% yield. The dark-brown reaction mixture was made slightly acid with sulfuric acid to facilitate its decolorization with activated carbon; after that step the solution was neutralized to phenolphthalein with potassium hydroxide and concentrated *in vacuo*. The dry residue was extracted thrice by boiling with 100-ml. portions of absolute ethanol. The combined extracts were concentrated and an aqueous solution of the residual material was deionized by passage through Amberlite IR-120 and Duolite A-4 ion-exchange resins. The solution was concentrated *in vacuo* to a sirup whose solution in absolute ethanol deposited a total of 0.56 g. (8.4%) of chunky prisms. After one recrystallization from absolute ethanol the product melted at 156–159°, showed $[\alpha]^{20}D$ −77.9° in water, and suffered no depression of melting point when mixed with an equal amount of 2,7-anhydro-β-D-*manno*-heptulopyranose prepared by the action of acid on the sugar as described earlier in this paper.

2,7-Anhydro-β-D-*manno*-heptulopyranose Tetrabenzoate.—Benzoylation of 0.5 g. of the anhydride II in the usual manner yielded a sirup. This was dissolved in warm ethanol and left at 5° overnight. The gum that deposited was dissolved in chloroform and the solution clouded with pentane and left at −5° for several days. The thick prisms that separated were filtered and washed with pentane; wt. 1.0 g. The product appeared to melt at 38–39° to a viscous sirup, and the same melting point was observed after recrystallization from chloroform–pentane. However, attempts to obtain an analytical sample by drying in the air at 20–25° resulted in liquefaction and either chloroform or pentane of crystallization was suspected. The product showed no tendency to crystallize from ethanol. For analysis and rotation the sample was heated to constant weight at 77° in a high vacuum; $[\alpha]^{20}D$ −67° in chloroform (*c* 1.5).

Anal. Calcd. for $C_{35}H_{28}O_{10}$: C, 69.07; H, 4.64. Found: C, 68.94; H, 4.64.

2,7-Anhydro-β-D-*manno*-heptulopyranose Tetratosylate.—A mixture of 0.5 g. of the anhydride II and 4 g. of *p*-toluenesulfonyl chloride in 8 ml. of pyridine was kept at room temperature for 3 days and then poured onto cracked ice. A quantitative yield of the crystalline tosylate resulted. The product was recrystallized from 50 parts of absolute ethanol; it separated as fine needles that weighed 2.1 g. and melted at 145–147°. Recrystallization from chloroform–pentane then produced needles that melted at 85–100°, even after drying at 60° overnight, and the product may have

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been solvated. A final recrystallization from ethanol gave the original, higher-melting form with m.p. 145–147° and $[\alpha]^{20}D$ +29.4° in chloroform (*c* 1.2).

Anal. Calcd. for $C_{35}H_{36}O_{14}S_4$: C, 51.97; H, 4.49; S, 15.85. Found: C, 52.24; H, 4.55; S, 15.65.

2,7-Anhydro-3,4-*O*-isopropylidene-β-D-*manno*-heptulopyranose.—A mixture of 1.0 g. of the anhydride II, 10 g. of anhydrous copper sulfate and 100 ml. of acetone was stirred mechanically for 48 hours, filtered and the solution concentrated to a sirup (1.26 g.) that crystallized spontaneously. From acetone–pentane there was obtained 0.85 g. of the *O*-isopropylidene derivative; it separated as clusters of acicular prisms and, after three recrystallizations, melted at 106–107° and showed $[\alpha]^{20}D$ −21.8° in water (*c* 2). Assignment of the *O*-isopropylidene group to the 3,4-positions is by analogy with 1,6-anhydro-β-D-mannopyranose and similar compounds.

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.95. Found: C, 51.70, 51.91; H, 6.91, 6.95.

1,6-Anhydro-β-D-mannopyranose from D-Mannose in Acid Solution and Isolation as Its 2,3-*O*-Isopropylidene Derivative.—Preliminary experiments showed that D-mannose suffered only negligible loss of rotatory power when a 0.1 *M* solution in 0.2 *N* hydrochloric acid was heated at 40° and at 60°. When a 0.2 *M* solution in 0.2 *N* hydrochloric acid was equilibrated overnight at 20° it showed $[\alpha]^{20}D$ +13.99°; after the solution had been heated at 80° for 3 and 6 hours, the rotations were +13.82 and +13.70°, respectively. For the attempted isolation of the expected very small amount of anhydride, three portions of D-mannose, totaling 144.13 g. and made to 4 liters at 20° in volumetric flasks with 0.2 *N* sulfuric acid, were allowed to stand overnight at that temperature. The rotations were $[\alpha]^{20}D$ +13.98, +13.96 and +14.06°. The first liter portion was heated 24 hours at about 70° and then showed $[\alpha]^{20}D$ +13.38°. The second liter portion was heated 32 hours at about 83° and then showed $[\alpha]^{20}D$ +13.24°. The third, 2-liter portion was heated 24 hours at about 83° and then showed $[\alpha]^{20}D$ +13.17°. These final values correspond to the presence of 0.5, 0.6 and 0.7%, respectively, of 1,6-anhydro-β-D-mannopyranose, calculated on the assumption that the solutions contained only D-mannose and its known anhydride. Reducing sugar determinations by the ferricyanide method indicated a small loss but the values were not considered reliable because the apparent change was less than the limit of accuracy of the method. Ultraviolet absorption data showed that less than 0.2% of 5-(hydroxymethyl)-2-furaldehyde was generated by heating D-mannose under these conditions.

The unchanged D-mannose in the 4 liters of solution was sacrificed by heating with excess barium hydroxide, and then neutralizing, filtering, deionizing and concentrating in the usual manner. The sirupy residue had a levorotation corresponding to 0.62 g. of the expected anhydride, but it weighed 9 g. and still contained material that reduced Fehling solution. Accordingly, it was treated again with barium hydroxide and the new sirup weighed 3.1 g. and had a levorotation corresponding to 0.91 g. (0.70%) of the expected anhydride. When an attempt to isolate 1,6-anhydro-β-D-mannopyranose by direct crystallization was unsuccessful, the sirup was extracted with 300 ml. of acetone at room temperature and the extract shaken with 10 g. of anhydrous copper sulfate for 42 hours. The filtered and concentrated solution crystallized readily. The product, isolated in two batches with the aid of 2-propanol and 1-butanol, weighed 0.87 g. (0.54%) and after one recrystallization from 1-butanol was identified as 1,6-anhydro-2,3-*O*-isopropylidene-β-D-mannopyranose[10] by melting point and mixed melting point of 160–161° and specific rotation $[\alpha]^{20}D$ −57.5° in water (*c* 1.8). Knauf, Hann and Hudson[10] reported m.p. 161–162° and $[\alpha]^{20}D$ −58.8° in water (*c* 2.08).

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BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

Crystalline 3-Deoxy-α-D-*ribo*-hexose. Preparation and Properties of 1,6-Anhydro-3-deoxy-β-D-*arabino*-hexopyranose, 1,6-Anhydro-3-deoxy-β-D-*ribo*-hexopyranose and Related Compounds[1,2]

BY JAMES W. PRATT AND NELSON K. RICHTMYER

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3-Deoxy-D-*arabino*-hexose and 3-deoxy-D-*ribo*-hexose have been shown to form their 1,6-anhydrides in aqueous acid to the extent of 29 and 10%, respectively. The 1,6-anhydrides were characterized as their di-*O*-acetyl derivatives. 3-Deoxy-α-D-*ribo*-hexopyranose and the phenyl 3-deoxy-α- and β-D-*ribo*-hexopyranosides have been obtained crystalline.

When LaForge and Hudson[3] established that hot aqueous acid acts on sedoheptulose (= D-*altro*-heptulose) to form a non-reducing anhydride, they were led to assume that this sugar is unique in this respect since their observation had no precedent, and, of course, many sugars had previously been subjected to such conditions on many occasions. An extension of this idea to include all sugars possessing the *altro* configuration was strongly suggested by the fact that D-altrose exhibits the same property.[4] Subsequently, the results of a number of investigations in this Laboratory have shown that although the amount of anhydride at equilibrium varies from more than 90% to less than 1%, the reaction is quite general among the aldohexoses, aldoheptoses and heptuloses.

Reeves[5] has sought to explain the ease of formation of the altrose[4] and idose[6] anhydrides in dilute aqueous acid in terms of the ring conformation of the parent aldohexose. His suggestion that the conformation of the β-D-pyranose ring exerts a con-

(1) Presented in part before the Division of Carbohydrate Chemistry at the Atlantic City Meeting of the American Chemical Society, September 18, 1956.

(2) For the preceding paper on anhydro sugars see E. Zissis, L. C. Stewart and N. K. Richtmyer, THIS JOURNAL, **79**, 2593 (1957).

(3) F. B. LaForge and C. S. Hudson, *J. Biol. Chem.*, **30**, 61 (1917).

(4) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **57**, 1716 (1935).

(5) (a) R. E. Reeves, *ibid.*, **72**, 1499 (1950); (b) *Advances in Carbohydrate Chem.*, **6**, 107 (1951).

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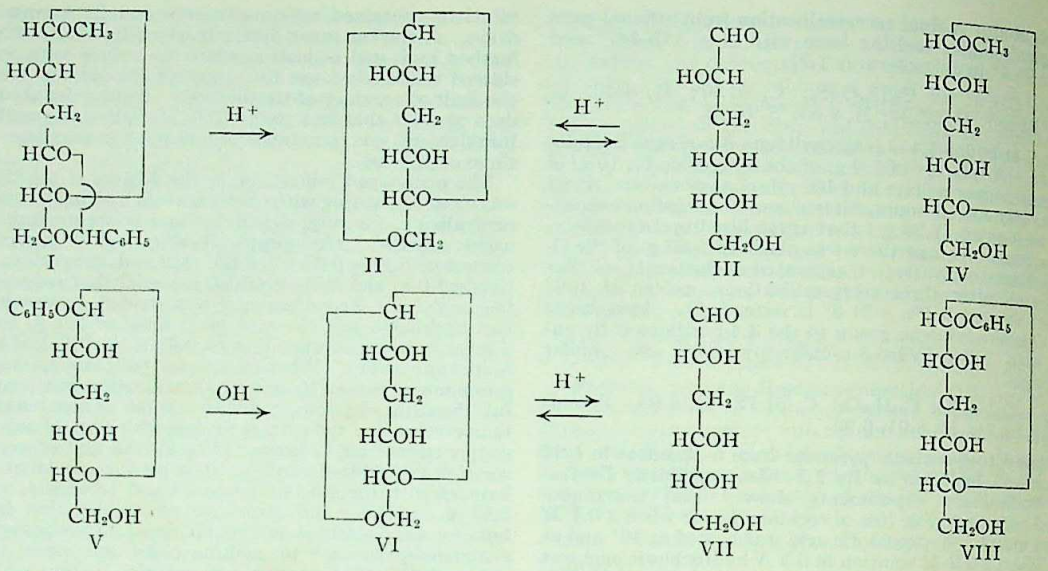

trolling influence should, perhaps, be broadened to include the α-D-pyranose ring as well, since we are dealing with a complex equilibrium and thus are concerned mainly with the question of thermodynamic stability. The stability of the anhydride itself is perhaps the most important factor; next in importance is the question of the relative stabilities of any and all of the tautomers, anomers and conformational isomers of the free sugar.

Since the generality of the reaction has been established, we are faced with the modified problem of evaluating the several steric factors which influence the extent to which the "forward" reaction proceeds (sugar ⇄ anhydride). Reeves' "instability factors"[7] serve as a useful guide in this area, but in the light of recent data they are somewhat inadequate except for idose and altrose at one end of the scale and glucose and mannose at the other.

From some recent data, particularly the amount of 1,6-anhydroallose[8] which resulted from this reaction, we have been led to the idea that the hydroxyl group on C3 plays a very prominent role in controlling the point of equilibrium. If this is true, a 3-deoxy sugar should react much more readily than the less reactive member of a 3-epimeric pair. A diminished reactivity compared with the more reactive epimer would be expected since a favorably situated hydroxyl not only would not interfere with bridge formation but, by introducing an "instability factor" in the opposite chair conformation, would increase the probability of the favorable orientation. In order to test this hypothesis we have prepared 3-deoxy-D-*arabino*-hexose, which is related to D-mannose and D-altrose, and 3-deoxy-D-*ribo*-hexose, related to D-glucose and D-allose. Our hypothesis is supported by the observations that at equilibrium in aqueous acid the amount of anhydride (molar basis) formed from 3-deoxy-D-*arabino*-hexose is 29% (*cf.* from D-mannose <1%[2]; from D-altrose 57%[4]); and from 3-deoxy-D-*ribo*-hexose 10% (*cf.* from D-glucose 2% or less[9]; from D-allose 14%[8]). We are at present engaged in extending this study to the remaining 3-deoxy-D-hexoses, and for this reason prefer not to argue too strongly for the hypothesis until the remaining data are available.

3-Deoxy-D-*arabino*-hexose (III), as its methyl 4,6-*O*-benzylidene-α-pyranoside derivative (I), was prepared uneventfully from methyl α-D-glucoside by the multistep method of Prins,[10] which employs as intermediates methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, the corresponding 2-*p*-tolylsulfonyl ester, and the 2,3-anhydro-D-mannose derivative.[11] Hot, aqueous acid effected the hydrolytic removal of benzaldehyde and the aglycon, and continued heating resulted in the formation of an appreciable amount of the 1,6-anhydro sugar. The remaining free sugar was removed by heating the solution with excess barium hydroxide and subsequent deionization. Although the anhydride failed to crystallize, it was characterized through its crystalline dibenzoate and diacetate. The rotation ($[\alpha]^{20}D$ −156°) of the 1,6-anhydro-3-deoxy-β-D-*arabino*-hexopyranose (II) and the point of equilibrium between sugar and anhydride in the presence of acid were determined in solutions obtained by careful saponification of the pure diacetate. The free anhydride was not oxidized by periodate.

3-Deoxy-D-*ribo*-hexose (VII) was prepared, as its methyl 4,6-*O*-benzylidene-α-pyranoside derivative, from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside also, but *via* the 2,3-di-*p*-tolylsulfonyl ester and the 2,3-anhydro-D-allose derivative.[11] Catalytic hydrogenolysis of the 2,3-anhydro compound[10,12] yielded methyl 3-deoxy-α-D-*ribo*-hexopyranoside as a sirup which was identified by the preparation of the crystalline 4,6-*O*-benzylidene derivative.

Acetylation of methyl 3-deoxy-α-D-*ribo*-hexo-

(7) Reference 5b, p. 124.

(8) J. W. Pratt and N. K. Richtmyer, THIS JOURNAL, **77**, 1906 (1955).

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(12) D. A. Prins, *Helv. Chim. Acta*, **29**, 1 (1946).

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pyranoside followed by acetolysis produced a sirupy mixture of acetates (presumably tetraacetates). This mixture was heated with phenol in the presence of *p*-toluenesulfonic acid,[13] the product deacetylated, and phenyl 3-deoxy-β-D-*ribo*-hexopyranoside (V) obtained crystalline. Treatment of the phenyl glycoside with hot, strong caustic followed by appropriate purification afforded the desired 1,6-anhydride as a sirup which could not be induced to crystallize. A crystalline diacetate was readily obtained, however, and this derivative was used for subsequent studies in the manner outlined for the epimer. The rotation of the 1,6-anhydro-3-deoxy-β-D-*ribo*-hexopyranose (VI) is $[\alpha]^{20}D$ −79.9°. The anhydride was not oxidized by periodate.

We desired to obtain the sugar VII in as pure a form as possible, and so prepared the crystalline tetra-*O*-acetyl derivative first reported by Černý and Pacák.[14] Catalytic deacetylation of this material yielded the sugar as small needles melting at 105.5–107° and mutarotating in water from +102° (initial, extrapolated) to +32.2° (final, 3 hours); the rotatory data indicate that the 3-deoxy-*ribo*-hexose is the α-D-pyranose form. It is of interest to note that the equilibrium rotation of the sugar is in excellent agreement with the value +31.8° calculated from the data obtained by the equilibration of the anhydride in aqueous acid.

Experimental

Methyl 4,6-*O*-Benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside (I).—Lithium aluminum hydride reduction of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside in the manner reported by Prins[10] led smoothly and in good yield to a product which after recrystallization, first from ether–pentane and then from aqueous methanol, melted at 111.5–113° and showed $[\alpha]^{20}D$ +95.5° in chloroform (*c* 2.2). Prins reports m.p. 111–112° and $[\alpha]^{20}D$ +107.3 ±2° in chloroform (*c* 0.941); Bolliger and Prins previously reported +95.0° (*c* 2.904) in chloroform.[15]

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.22; H, 6.70.

Action of Dilute Aqueous Acid on Methyl 4,6-*O*-Benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside (I).—A sample of I weighing 1.0163 g. was suspended in 0.2 *N* hydrochloric acid and allowed to stand at room temperature to effect solution. After 18 hours the volume was made to 50.0 ml. with water and the optical activity observed as $\alpha^{20}D$ +6.53° in a 4-dm. tube. The solution was heated to 100° and the rotation was observed to change in 3 hours to −0.72°, unchanged by heating an additional seven hours. This treatment was repeated with 5 g. of I. After a 3.5-hour heating period the solution was transferred to a silver flask, made strongly alkaline with barium hydroxide, and heated 2 hours to destroy the remaining sugar. The solution was neutralized with solid carbon dioxide, filtered, deionized by passage through Amberlite IR-120 and Duolite A-4, and concentrated *in vacuo* to a thick sirup of 1,6-anhydro-3-deoxy-β-D-*arabino*-hexopyranose (II) which weighed 1.2 g. The material has not as yet crystallized.

1,6-Anhydro-2,4-di-*O*-benzoyl-3-deoxy-β-D-*arabino*-hexopyranose.—The sirupy anhydride (II, 1.2 g.) was dissolved in 10 ml. of dry pyridine and 2.5 ml. of benzoyl chloride added. The mixture was allowed to stand four hours at room temperature and was then poured over a mixture of ice and solid sodium bicarbonate, and worked up in the usual manner. A few crystals were obtained from a chloroform solution of the benzoate by the addition of pentane, and these were used successfully to seed the ethanol solution of the sirup which yielded 1.5 g. of water-white, prismatic needles which on further recrystallization melted at 120–121.5° and showed a rotation $[\alpha]^{20}D$ −203.7° in chloroform (*c* 1.6).

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.13. Found: C, 67.88; H, 5.21.

1,6-Anhydro-2,4-di-*O*-acetyl-3-deoxy-β-D-*arabino*-hexopyranose.—The anhydride dibenzoate (18 g.) was debenzoylated catalytically and freed from methanol by evaporation in a stream of air and from methyl benzoate by extraction with ether. The sirupy anhydride was acetylated by the acetic anhydride–fused sodium acetate procedure and the resulting product (virtually quantitative) worked up in the usual way. Recrystallized first from ether–pentane and then from 10 parts of absolute ethanol, and dried overnight at 65° the white, prismatic needles melted at 99.5–101° and showed $[\alpha]^{20}D$ −139.2° in chloroform (*c* 0.37).

Anal. Calcd. for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13; CH_3CO, 37.4. Found: C, 51.88; H, 6.30; CH_3CO, 37.1.

Optical Activity of 1,6-Anhydro-3-deoxy-β-D-*arabino*-hexopyranose (II).—The anhydride diacetate (0.4260 g.) was saponified at room temperature with 5 ml. of *N* sodium hydroxide solution. After five hours, 5 ml. of *N* hydrochloric acid was added, the volume made to 25.0 ml. with water, and the rotation observed in a 4-dm. tube: $\alpha^{20}D$ −6.76°. From this value the specific rotation of the anhydride is calculated to be $[\alpha]^{20}D$ −156°.

Equilibrium in Acid Solution between 3-Deoxy-D-*arabino*-hexose (III) and its 1,6-Anhydride (II).—The anhydride diacetate (2.3092 g.) was saponified as before. After saponification, sufficient 5 *N* hydrochloric acid was added to make the final solution (50.0 ml.) 0.6 *N* in hydrochloric acid. The solution was allowed to stand 40 days at 41° during which time the observed rotation in a 4-dm. tube changed from −18.35° (extrapolated to zero time) to −0.94°; this value did not change during an additional 20 days. An estimation of aldose sugar by the iodine–alkali method[16] gave a value of 7.12 mmoles of aldose or 71.0% on a molar basis. It is assumed that the remaining 29.0% is the anhydride II. From these data the rotation of the 3-deoxy-D-*arabino*-hexose can be calculated as $[\alpha]^{20}D$ +46.8°. This is considerably higher than the value +17.7 ±2° reported by Bolliger and Prins[15] for their sirup. However, their material had been heated 3 hours at 100° in 0.75 *N* sulfuric acid and undoubtedly contained considerable levorotatory anhydride II.

Attempted Oxidation of 1,6-Anhydro-3-deoxy-β-D-*arabino*-hexopyranose (II) with Sodium Metaperiodate.—Di-*O*-acetyl-1,6-anhydro-3-deoxy-β-D-*arabino*-hexopyranose (0.2470 g.) was saponified by treatment with 5 ml. of *N* sodium hydroxide solution at room temperature for five hours. The alkali was neutralized by the addition of *N* sulfuric acid, 5 ml. of a 0.45 *M* solution of sodium metaperiodate added, and the volume made to about 20 ml. with water. After being allowed to stand in the dark at room temperature overnight, the solution was further diluted to a volume of 25.0 ml. and 5-ml. aliquots were tested for periodate consumption. The titration difference (0.08 ml.) was of the order of the limit of experimental error.

Phenyl 3-Deoxy-β-D-*ribo*-hexopyranoside (V).—Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside was hydrogenolyzed at 110° under a hydrogen pressure of 2000 p.s.i. in the presence of Raney nickel. Rebenzylidenation of the sirupy methyl 3-deoxy-D-*ribo*-hexoside (IV) yielded methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside which showed a specific rotation in chloroform $[\alpha]^{20}D$ +121.5° (*c* 2), which is considered to be not significantly different from the reported value +115.8°.[12] In subsequent runs, the purified sirupy methyl glycoside was acetylated with acetic anhydride and sodium acetate and then acetolyzed with acetic anhydride containing 2% sulfuric acid by volume. The sirupy mixture of acetates was worked up in the usual way. To 100 g. of mixed acetates were added 100 g. of phenol and 2 g. of *p*-toluenesulfonic acid monohydrate and the fused mass was heated under reduced pressure at 65–75° for 1.5 hr.[13] The resulting product, isolated in the usual manner, failed to crystallize and so was deacetylated catalytically. On removal of solvents the mixture crystallized in part to yield 10.8 g. of material

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which on recrystallization from 15 parts of hot water melted at 183–185° and showed $[\alpha]^{20}D$ −94.0° in water (*c* 0.27).

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 60.00; H, 6.71. Found: C, 60.07; H, 6.84.

1,6-Anhydro-3-deoxy-di-*O*-acetyl-β-D-*ribo*-hexopyranose.—A suspension of 6.9 g. of phenyl 3-deoxy-β-D-*ribo*-hexopyranoside (V) in 200 ml. of 2.6 *N* aqueous sodium hydroxide was heated for 19 hours at 100° in a silver flask. The clear, pale-yellow solution was neutralized with 3 *N* sulfuric acid, concentrated *in vacuo* to a paste of sirup and crystals, and the slurry extracted thrice with 150-ml. portions of absolute ethanol. The extract was filtered, and the solvent removed *in vacuo* leaving 4.3 g. of sirup which failed to crystallize. Acetylation with acetic anhydride and sodium acetate resulted in the production of 4 g. (45% based on the phenyl glycoside) of crystalline material which on recrystallization from absolute ethanol melted at 114–116° and showed $[\alpha]^{20}D$ −74.0° in chloroform (*c* 0.7).

Anal. Calcd. for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13; CH_3CO, 37.4. Found: C, 52.00; H, 6.13; CH_3CO, 37.0.

Optical Activity of 1,6-Anhydro-3-deoxy-β-D-*ribo*-hexopyranose (VI).—The anhydride diacetate (0.2475 g.) was saponified in *N* sodium hydroxide at room temperature. After 3 hours an equivalent amount of *N* sulfuric acid was added, the volume made to 25.0 ml., and the rotation observed. By this procedure the anhydride VI was found to show $[\alpha]^{20}D$ −79.9°.

Attempted Periodate Oxidation of 1,6-Anhydro-3-deoxy-β-D-*ribo*-hexopyranose (VI).—To 20.0 ml. of the solution referred to in the paragraph above was added 5 ml. of a 0.45 *M* solution of sodium metaperiodate and the volume was made to 50.0 ml. After 20 hours in the dark at 20°, the solution was found to show $[\alpha]^{20}D$ −83.4°; after 9 days the specific rotation was −78.5°. These values do not differ significantly from that established for the anhydride. Periodate consumption in 20 hours was found to be 0.1 mole/mole.

Equilibrium in Acid Solution between 3-Deoxy-D-*ribo*-hexose (VII) and its 1,6-Anhydride (VI).—To 1.3953 g. of anhydride diacetate in a 50.0-ml. volumetric flask was added 6 ml. of 5 *N* sodium hydroxide solution. After 2 hours at room temperature, 10 ml. of 5 *N* hydrochloric acid was added, the volume made to the mark with water, and the solution placed in an oven at 60–62°. In five days the rotation became constant. The aldose content of the equilibrated solution, estimated by the alkali-iodine method,[16] was found to be 89.8% (molar basis). By the method given above for the epimeric system it can be shown that the specific rotation of 3-deoxy-D-*ribo*-hexose (VII) is $[\alpha]^{20}D$ +31.8°.

3-Deoxy-D-*ribo*-hexose.—Tetra-*O*-acetyl-3-deoxy-D-*ribo*-hexose was prepared from the sirupy product of the hydrolysis of methyl 3-deoxy-α-D-*ribo*-hexopyranoside (IV) using the sodium acetate in hot acetic anhydride procedure employed by Černý and Pacák.[14] After recrystallization from absolute ethanol our product melted at 129–130° in agreement with the literature value but showed $[\alpha]^{20}D$ −14° in chloroform (*c* 1) in contrast with the value −20° reported by the earlier authors.

Anal. Calcd. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.45; H, 6.06.

The acetate (1.0 g.) under 10 ml. of methanol was cooled to 3° and 0.2 ml. of *N* sodium methoxide in methanol was added. Solution was effected in four hours at that temperature. After two additional hours the base was destroyed by the addition of 2 drops of glacial acetic acid and the solvents were removed *in vacuo*. The sirupy product, taken up in absolute ethanol, was induced to crystallize and yielded 0.36 g. of material in the form of clusters of very small needles. Deposition of material was remarkably slow. On recrystallization from absolute ethanol the 3-deoxy-D-*ribo*-hexose melted at 105.5–107° and showed in water (*c* 1) $[\alpha]^{20}D$ +102° (initial, extrapolated) → +97.0° (2.5 min.) → +32.2° (3 hours; constant).

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.79; H, 7.24.

Phenyl 3-Deoxy-α-D-*ribo*-hexopyranoside (VIII).—An attempt was made to prepare the 1,6-anhydro-3-deoxy-β-D-*ribo*-hexopyranose by the alkaline hydrolysis of a mixture of the anomeric phenyl glycopyranosides. A crystalline product was obtained which on recrystallization from ethanol-ether melted at 136–138° and showed $[\alpha]^{20}D$ +172° in water. Rotational and analytical data as well as the method of preparation indicate that the compound is phenyl 3-deoxy-α-D-*ribo*-hexopyranoside which, as might be expected, was not affected by hot, aqueous alkali. The substance, unlike its anomer, is very soluble in water and alcohol.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 60.00; H, 6.71. Found: C, 60.33; H, 6.88.

Acknowledgment.—The authors wish to thank Mr. John T. Sipes for the preparation of both of the 2,3-anhydro intermediates, Mr. Edward W. Tracy for assistance with several steps of the procedures, and Dr. William C. Alford and his associates of the Institutes' Microanalytical Laboratory for the elemental analyses.

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, ARGONNE NATIONAL LABORATORY]

The Absence of an Amadori Rearrangement in Glucosazone Formation[1]

BY FELIX FRIEDBERG[2] AND LOUIS KAPLAN

RECEIVED JANUARY 21, 1957

Glucose-1-*t* is converted to its phenylosazone without loss of tritium. This observation invalidates any mechanism of osazone formation requiring an intermediate with two hydrogen atoms on carbon-1, including the Amadori rearrangement proposed by Weygand.

The classical scheme of Emil Fischer for osazone formation suffers from the difficulty of accounting for the oxidizing action of phenylhydrazine. In order to overcome this difficulty, Weygand[3] has proposed that the phenylhydrazone first formed rearranges, producing a carbonyl group at an adjacent carbon which then condenses with more phenylhydrazine. He has suggested two paths for the reaction, as shown by (A) and (B) in the chart. Path B, which involves an Amadori rearrangement,[4]

(1) Work performed under the auspices of the U. S. Atomic Energy Commission.

(2) College of Medicine, Howard University. Resident Research Associate, Argonne National Laboratory, 1956.

(3) F. Weygand, *Ber.*, **73**, 1284 (1940).

(4) Although the enolization involved in path A is sometimes referred to as an Amadori rearrangement (W. W. Pigman and R. M. Goepp, Jr., "Chemistry of the Carbohydrates," Academic Press, Inc., New York, N. Y., 1948, p. 405), J. E. Hodge (*Advances in Carbohydrate Chem.*, **10**, 169 (1955)) recommends that this designation be reserved for the complete conversion of a N-substituted aldosylamine to a 1-amino-1-deoxy-2-ketose.

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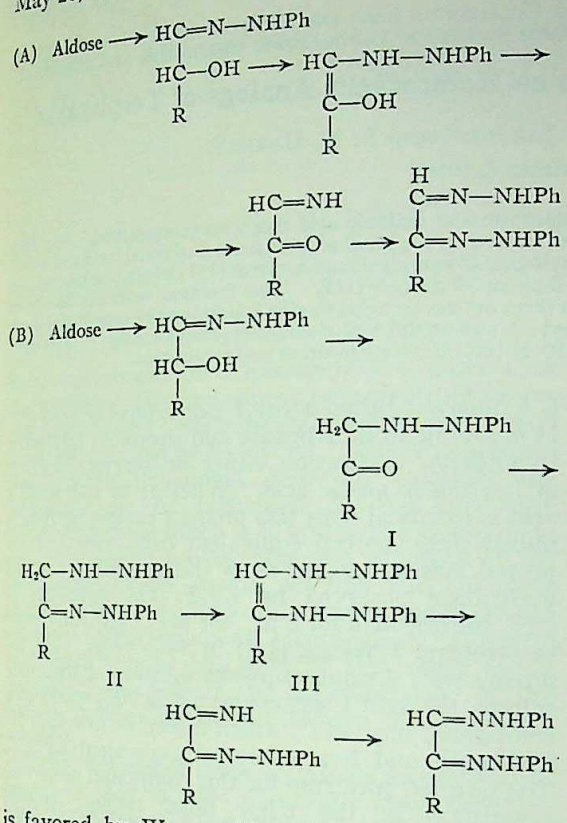

is favored by Weygand,[5] and this mechanism is cited by several reviewers.[6,7]

The preparation of glucose-1-*t* in connection with another problem[8] has permitted a test of Weygand's mechanism B. In this scheme the hypothetical isoglucosamine intermediate I contains two hydrogen atoms on carbon atom 1, one of which is subsequently lost. Any osazone formed by way of this intermediate from glucose-1-*t* would therefore contain less tritium than the original glucose. Since, in fact, the phenylosazone had a molar activity identical with that of the glucose, it must be concluded that I is not an intermediate in glucosazone formation.

Experimental

D-Glucose-1-*t* was prepared by reduction[9] of δ-gluconolactone with sodium borohydride-*t*.[10] The details of the preparation and purification will be described elsewhere.[8] After crystallization in the α-form,[11] the material melted at 146° and had an initial specific rotation of +103°. A portion of the glucose was converted[12] to the β-pentaacetate, m.p. 129–131°. Another portion was heated with phenylhydrazine, acetic acid and sodium acetate to form[13] the phenylosazone, m.p. 202° dec., some of which was oxidized[13] with copper sulfate to the osotriazole, m.p. 195°. The derivatives were recrystallized to constant specific activity as listed in Table I. More than 99% of the tritium in the glucose was shown, by oxidation to calcium gluconate, to be on carbon atom 1.

Tritium assays were performed by ion-current measurement[14] on the gas obtained by the zinc fusion procedure.[15] Replicate determinations on each compound had an average deviation of less than 1%.

Discussion

The results in Table I show that, within an uncertainty of about 1%, there is no loss of tritium during the formation of the phenylosazone from glucose-1-*t*.[16] In the absence of an isotope effect, one-half of the tritium should have been lost if the phenylosazone had been formed from the isoglucosamine derivative I. It is extremely unlikely that the practically quantitative retention of tritium can be explained on the basis of an isotope effect, since an isotopic rate ratio, k_H/k_T, of at least fifty would have to be postulated for the hydrogen migration II → III. It must, therefore, be concluded that Weygand's path B cannot be the principal mechanism of osazone formation, at least in the case of glucose.

TABLE I

Compound	Activity μc./g.	Activity μc./mmole
α-D-Glucose	39.7	7.15
β-D-Glucose pentaacetate	18.0	7.03
Phenyl-D-glucosazone	19.9	7.13
Phenyl-D-glucosotriazole	26.7	7.08

Of the other mechanisms which have been proposed for osazone formation, Weygand's path A is not affected by the isotopic results reported here. It has, however, been challenged[17] (along with path B) on the ground that it does not explain why osazone formation is favored by an electron-attracting group on the phenylhydrazine. The mechanism of Braude and Forbes,[18] patterned after that of Kenner and Knight,[19] overcomes this objection and is consistent with the isotopic results. The alternative proposed[17] by Bloink and Pausacker for osazone formation from benzoin would, if applied to glucose, involve as an intermediate the isoglucosamine derivative I of Weygand's path B and cannot, therefore, be correct for this case.

LEMONT, ILLINOIS

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE, AND THE BIOMEDICAL RESEARCH GROUP, LOS ALAMOS SCIENTIFIC LABORATORY, UNIVERSITY OF CALIFORNIA]

2-Pyrones. XXV. 3,6-Diaryl-2-pyrones as Heterocyclic Analogs of Terphenyl

BY RICHARD H. WILEY,[1a] C. H. JARBOE[1b] AND F. N. HAYES[1c]

RECEIVED NOVEMBER 3, 1956

The synthesis of 6-phenyl-2-pyrone from phenylpropargyl aldehyde and malonic acid has been re-examined. Previous structural assignments for the products of the reaction have been revised on the basis of additional analytical data and infrared absorption characteristics. The principal product is 4-phenylbuten-3-yne-1,1-dicarboxylic acid (I) which can be cyclized to 3-carboxy-6-phenyl-2-pyrone (II). Decarboxylation gives 6-phenyl-2-pyrone (III). This reaction sequence has been extended to the condensation of phenylpropargyl aldehyde with three arylacetic acids to give 2,5-diphenylpenten-2-yne-4-oic acid (V), 3,6-diphenyl-2-pyrone (VI) and the related β-naphthyl-, *p*-biphenylyl and *p*-methoxyphenyl analogs. Introduction of the electron donor methoxy group results in lowered yields in both the condensation and cyclization.

The use of some of their heterocyclic analogs as replacements for *p*-terphenyl and *p*-quaterphenyl solutes in liquid scintillation counters has been sufficiently successful[2] to justify the continued exploration of related structural types. Such an effort is complicated by the fact that the *p*-polyphenyl structure, which is desired because the maximum scintillation response appears to be associated with the maximum resonance stabilization of the *para* structure, corresponds to a 1,4-diaryl heterocyclic structural type which is comparatively unknown. This study was undertaken to develop syntheses for a variety of 1,4-(*p*-)diaryl heterocycles to be examined in terms of their effectiveness as scintillators relative to *p*-terphenyl as a standard. In the present paper we wish to describe the preparation and characterization of a series of 3,6-diaryl-2-pyrones.

The possibility of preparing a 3,6-diaryl-2-pyrone by a modification of the synthesis originally described by Kalff[3] for the synthesis of 6-phenyl-2-pyrone was selected as the most attractive route to these structures. This synthesis as originally described involved the condensation of phenylpropargyl aldehyde with malonic acid to form an unstable compound, m.p. 208–218°, assigned the structure 6-phenyl-2-pyrone-3-carboxylic acid (II). This was reported to undergo decarboxylation in acetic acid at room temperature to give 6-phenyl-2-pyrone (III), m.p. 68°, and at steam-bath temperatures to give a compound, m.p. 218°, assigned the structure of a dilactone (IV) on the basis of its insolubility in bicarbonate, solubility in sodium hydroxide and stability toward decarboxylation.

On repeating the condensation we obtained only one product, m.p. 214–218°, regardless of the temperatures used, which could not possibly be II or IV on the basis of its characteristics. These include the presence of a strong maximum at 2210 cm.$^{-1}$ in the infrared absorption spectrum, which establishes that it is a disubstituted acetylene,[4] and a neutral equivalent of 108. Together these data indicate that the structure of this compound is 4-phenyl-1-buten-3-yne-1,1-dicarboxylic acid (I). It is soluble in bicarbonate and shows no tendency to undergo cyclization either on recrystallization or heating in acetic acid. Whether or not Kalff's acid is identical with this product cannot be determined since neutral equivalent data were not reported, but it does not show the instability toward cyclization observed by Kalff. On refluxing in 50% sulfuric acid for 3 hr., the acid I was converted to 6-phenyl-2-pyrone (III) in 54% yield. On refluxing with a dilute aqueous solution of mercuric sulfate, the acid I was converted in 80% yield to a compound, m.p. 214°, which is soluble in warm bicarbonate and has a neutral equivalent of 216. The infrared spectrum for this compound shows no absorption in the triple bond region, typical 2-pyrone carbonyl absorption at 1735 cm.$^{-1}$ and associated carboxyl carbonyl absorption at 1775 cm.$^{-1}$.[5] It shows absorption maxima in the ultraviolet at 240 mμ (log ε 3.73) and 345 mμ (log ε 4.17) as does also 6-phenyl-2-pyrone (235 mμ, log ε 3.92 and 330 mμ, log ε 4.12). It is readily converted in 67.5% yield to 6-phenyl-2-pyrone on refluxing with 50% sulfuric acid. On the basis of these data we believe this product to be 6-phenyl-2-pyrone-3-carboxylic acid (II). Again absence of a neutral equivalent for the compound obtained by Kalff makes it impossible to say definitely that the material he had is identical with ours.

In extending this reaction to the condensation of acrylacetic acids with phenylpropargyl aldehyde, it was found that this modification of the reaction proceeds best as a Perkin reaction. In acetic anhydride solution with sodium acetate as a catalyst 30–90% yields of the acetylenic acid V were obtained. Table I summarizes the yields obtained and the data characterizing the products from phenylacetic acid and the four substituted phenylacetic acids used. It can be seen that electron donor substituents in the aryl nucleus of the arylacetic acid decrease the yield significantly. The best yields and an increased reaction rate resulted using the *p*-biphenyl and α-naphthyl derivatives in which the *p*-biphenyl and α-naphthyl groups presumably are more effective electron-attracting groups than is the unsubstituted phenyl group. What little information is available[6] indicates that this is contrary to the effect usually produced by electron-attracting substituents in the aryl nucleus of the arylacetic acid in Perkin reactions.

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(2) F. N. Hayes, D. G. Ott and V. N. Kerr, *Nucleonics*, **14**, No. 1, 44 (1956); F. N. Hayes, D. G. Ott, V. N. Kerr and Betty S. Rogers, *ibid.*, **13**, No. 12, 38 (1955).

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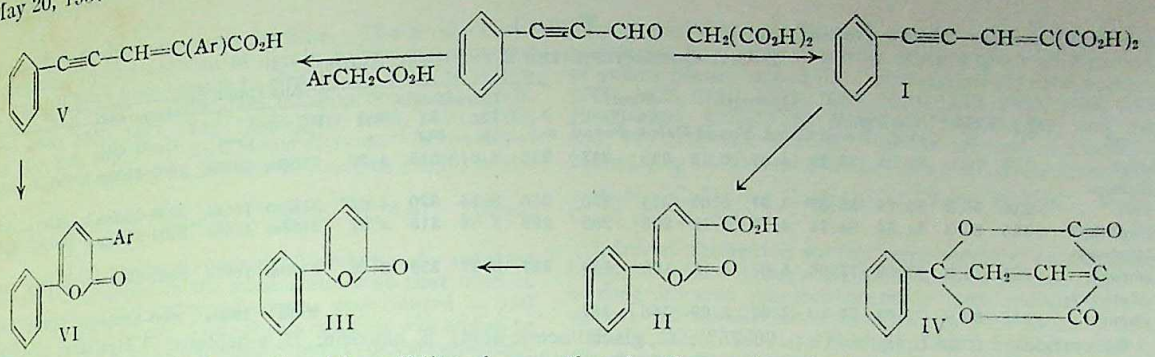


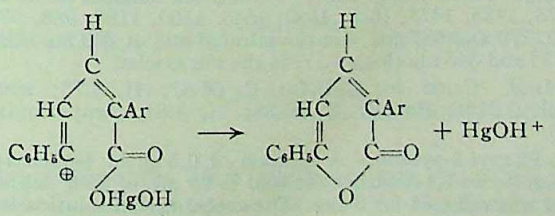
Such comparisons are of questionable validity since the available data are almost exclusively those for reactions using *o*-nitrobenzaldehydes in which steric effects must be important. Electron-attracting substituents should, however, facilitate the formation of the carbanion derived from the mixed anhydride which is to add to the aldehyde in accordance with usually accepted concepts of the mechanism of the Perkin reaction and therefore should, if this is an important factor, facilitate the reaction. This apparent inconsistency indicates that more precise data defining this effect would provide a more adequate understanding of the factors involved in the mechanism of the Perkin reaction.

The structures of these acetylenic acids are confirmed by their infrared absorption characteristics. They show typical disubstituted acetylene stretching absorptions of medium intensity between 2188 and 2205 cm.$^{-1}$, bonded hydroxyl stretching vibrations of medium intensity and very broad at 2800–3200 cm.$^{-1}$, C—O stretching or O—H deformation vibrations at 1412 and 1430 cm.$^{-1}$, and very strong carbonyl stretching vibrations at 1660–1680 cm.$^{-1}$, and the characteristic acid bands in the 1250–1268 cm.$^{-1}$ region.

Cyclization of the 2-aryl-5-phenylpenten-2-yne-4-oic acids (V) to the corresponding 3-aryl-6-phenyl-2-pyrones (V) takes place in aqueous organic solvents with mercuric sulfate catalyst. The choice of solvent and temperature and the role of the substituents in the aryl group are all important factors in the reaction. The phenyl analog is formed in 40–60% yields in 2.5 hr. in aqueous acetone or dioxane. Under otherwise similar conditions, 12.5-hr. reaction times are required to obtain similar yields of the β-naphthyl compound. A reaction time of 24 hr. and a much higher catalyst concentration are required to obtain at best 20% yields of the *p*-biphenyl derivative, and it is necessary to use aqueous methanol as the solvent for the cyclization of the *p*-methoxyphenyl derivative since only resins were obtained using dioxane or acetone. No satisfactory conditions could be found for the cyclization of the *m*-methoxyphenyl compound. A crystalline mercuric salt of the acid precipitated from all reaction media tried and could not itself be successfully cyclized. Because these conditions are obviously highly critical, the details of each reaction are given in the Experimental section. Data upon which the selection of these conditions was based will not be recorded here.

The pyrones isolated from these reactions are all yellow, crystalline materials with infrared absorption in the carbonyl stretching range at 1695 to 1712 cm.$^{-1}$. This displacement to frequencies below the 1720 cm.$^{-1}$ carbonyl frequency usually associated with the carbonyl stretching vibration in 2-pyrones[7] has been observed in other 3-substituted 2-pyrones.[8] This carbonyl absorption is displaced much too far toward higher frequencies to be confused with the β-substituted-5-membered lactone carbonyl absorptions.[9] This eliminates the possibility that cyclization has given a γ-lactone. In contrast to the acetylenic acids, absorption in the conjugated carbon–carbon unsaturation region is noted at 1620–1650 cm.$^{-1}$ as a band of medium intensity. The ultraviolet spectra of the 3-aryl-6-phenyl-2-pyrones show two maxima, as do other 2-pyrones,[10] but the frequencies are displaced to 245–265 mμ (log ϵ 4.00–4.27) and 360–370 mμ (log ϵ 4.10–4.56). This shift to longer wave lengths presumably is due to the additional conjugation.

The cyclization of these acids may be visualized as proceeding through initial hydration of the triple bond followed by lactonization or through cyclic addition of the carboxylic acid to the triple bond. The fact that the reactions require aqueous media suggests that hydration may be involved. In the addition of acetic acid to acetylene, traces of water result in acetaldehyde formation indicating a more rapid rate for the hydration reaction than for the addition of the acid. Initial attack by a proton at the γ-carbon atom followed by cyclization through displacement of the oxymercuri group offers a more direct mechanism, but this simplicity is perhaps misleading.



These compounds were examined by the Biomedical Research Group of the Los Alamos Laboratories of the University of California for activity as solutes in standard liquid scintillation counting systems. The results of this testing indicate that even though these materials are strongly fluorescent, they are not effective as scintillators. None

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TABLE I

2-ARYL-5-PHENYLPENTEN-2-YNE-4-OIC ACIDS

Aryl	M.p., °C.	Yield,[a] %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Neut. equiv. Calcd.	Neut. equiv. Found	Absorption data: Ultraviolet[b] λ, mμ	Ultraviolet[b] log ε	Ultraviolet[b] λ, mμ	Ultraviolet[b] log ε	Infrared[d] RC≡CR	Infrared[d] C=O	Infrared[d] C=O, OH		
Phenyl	159	79,L	82.24	82.12	4.87	5.18	248	247	225	3.34	315	4.20	2200m	1680s	3000–2500m,b	1415s	1268s
p-Biphenylyl	218	90,G	85.16	85.07	4.97	5.03	324	320	250	3.35	370	3.60[c]	2180m	1665s	3000–2500m,b	1425m	1620s
β-Naphthyl	195	85,G	84.54	84.74	4.73	5.12	298	295	290	3.08	315	3.07	2188m	1665s	3000–2500m,b	1412s	1255s
p-Methoxyphenyl	185	44,B	77.68	77.66	5.07	5.15	166	163	287	3.32	320	3.29	2190m	1665s	3000–2500m,b	1412m	1250s
m-Methoxyphenyl	138	30,H	77.68	77.70	5.07	5.09	166	162	..	..	..	..	2205	1660s	3000–2500m,b	1430m	1260s

[a] Recrystallized from L, ligroin (b.p. 66–75°); G, glacial acetic acid; B, benzene; H, *n*-heptane. [b] Methanol solutions. [c] Chloroform solution. [d] vs, very strong; s, strong; m, medium; w, weak; b, broad. Frequencies given in cm.$^{-1}$.

show relative pulse height values, determined as previously described,[2] over 0.12.

Acknowledgment.—This research was supported in part under Contract AT-(40-1)-2162 between the University of Louisville and the Atomic Energy Commission. The authors acknowledge this support with appreciation.

Experimental[11]

The phenylpropargyl aldehyde, malonic acid and arylacetic acids used in the following experiments were obtained from commercial sources. The *p*-biphenylacetic acid was prepared by a previously described procedure.[12]

4-Phenyl-1-buten-3-yne-1,1-dicarboxylic Acid (I).—A solution of 2.6 g. of phenylpropargyl aldehyde and 2.1 g. of malonic acid in 20 ml. of glacial acetic acid was allowed to stand for 48 hr. The entire reaction mass was poured into 200 ml. of ice-water. The solid precipitate was filtered, dissolved in bicarbonate solution and decolorized two times with activated charcoal. The solution was acidified with dilute hydrochloric acid to precipitate 2.8 g., 65.2%, of yellow 4-phenyl-1-buten-3-yne-1,1-dicarboxylic acid. m.p. 214–218°. Similar yields were obtained when the reaction mixture was refluxed for 4 hr. Infrared absorption maxima occur at 2210, 1730, 1645, 1580, 1485, 1450, 1250, 764 and 685 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.67; H, 3.73; neut. equiv., 108. Found: C, 66.66; H, 3.69; neut. equiv., 108.

3-Carboxy-6-phenyl-2-pyrone.—A catalyst prepared by heating 0.5 g. of yellow mercuric oxide in 4 ml. of concd. sulfuric acid until the color was discharged was dissolved in 50 ml. of distilled water and added to 1 g. of 4-phenyl-1-buten-3-yne-1,1-dicarboxylic acid in a 125-ml. round-bottom flask. This mixture was refluxed for 4 hr., cooled to room temperature and filtered. The crude 3-carboxy-6-phenyl-2-pyrone thus obtained is soluble in bicarbonate solution on gentle warming. On recrystallization from glacial acetic acid there was obtained 0.8 g., 80%, of yellow-orange product, m.p. 218°. Absorption maxima occur at: 1775, 1735, 1675, 1630, 1580, 1545, 1500, 1180, 988, 934, 840, 770 and 687 cm.$^{-1}$ in the infrared and at 240 mμ (log ε 3.73) and 345 mμ (log ε 4.17) in the ultraviolet.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.67; H, 3.73; neut. equiv., 216. Found: C, 66.88; H, 3.84; neut. equiv., 216.

6-Phenyl-2-pyrone.—A solution of 0.5 g. of 4-phenyl-1-buten-3-yne-1,1-dicarboxylic acid in 20 ml. of 50% sulfuric acid was refluxed for 3 hr. The cooled turbid solution was poured into 200 g. of cracked ice to precipitate the crude 6-phenyl-2-pyrone. Recrystallization from petroleum ether gave 0.2 g., 54%, of light yellow plates, m.p. 68°. Absorption maxima occur at: 1725, 1635, 1580, 1545, 1506, 1460, 1410, 1343, 1118, 1076, 1009, 957, 844, 800, 768 and 687 cm.$^{-1}$ in the infrared and at 235 mμ (log ε 3.92) and 330 mμ (log ε 4.12) in the ultraviolet.

From 3-Carboxy-6-phenyl-2-pyrone.—A solution of 1 g. of 3-carboxy-6-phenyl-2-pyrone in 10 ml. of 50% sulfuric acid was refluxed for 1.5 hr. The cooled reaction mixture was poured into 100 ml. of ice-water to precipitate 0.5 g., 67.5%, of 6-phenyl-2-pyrone.

2,5-Diphenylpenten-2-yne-4-oic Acid.—A solution of 6.0 g. of phenylpropargylaldehyde and 6.0 g. of phenylacetic acid in 25 ml. of acetic anhydride was heated on a boiling water-bath. When temperature equilibrium was attained 3.0 g. of sodium acetate was stirred into the reaction mixture. The reaction was kept at water-bath temperature for 48 hr. The cooled solution was poured onto 300 g. of chipped ice and neutralized with bicarbonate to precipitate the crude product as a yellow brown solid. Recrystallization from ligroin (b.p. 66–75°) gave 9.0 g., 79%, of the product as yellow needles, m.p. 159°. Infrared absorption maxima occur at: 2900, 2200, 1680, 1600, 1580, 1562, 1490, 1440, 1415, 1300, 1280, 1268, 1180, 1070, 1038, 1006, 998, 918, 911, 887, 783, 773, 755, 699 and 687 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87; neut. equiv., 248. Found: C, 82.22, 82.22; H, 5.26, 5.38; neut. equiv., 247.

In the case of *p*-biphenylacetic acid and *β*-naphthylacetic acid the condensation was complete in 6 hr. Further details of the reaction with other arylacetic acids are given in Table I.

3,6-Diphenyl-2-pyrone.—A catalyst prepared by heating 0.1 g. of yellow mercuric oxide in 5 ml. of concd. sulfuric acid for 15 min. was dissolved in 20 ml. of distilled water. This solution was warmed on a water-bath and 20 ml. of *p*-dioxane containing 1.0 g. of 2-phenyl-5-phenylpenten-2-yne-4-oic acid gradually stirred in. The mixture was heated with agitation for 2.5 hr. The cooled reaction mass was poured onto 200 g. of cracked ice to precipitate the crude yellow product which on recrystallization from ethanol gave 0.4 g., 40%, of yellow needles, m.p. 161° (mixed m.p. with the starting acetylenic acid is 120°). The use of acetone in place of *p*-dioxane in this procedure results in yields of 60%. Absorption maxima occur at: 1712, 1625, 1600, 1575, 1550, 1490, 1450, 1355, 1258, 1110, 1085, 1078, 1046, 1023, 1002, 967, 944, 915, 901, 814, 784, 767, 754, 719, 691 and 685 cm.$^{-1}$ in the infrared and at 245 mμ (log ε 4.25) and 360 mμ (log ε 4.46) in the ultraviolet.

Anal. Calcd. for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 82.12; H, 5.03.

3-(ε-Naphthyl)-6-phenyl-2-pyrone.—A catalyst prepared by heating 0.2 g. of yellow mercuric oxide in 10 ml. of concd. sulfuric acid for 15 minutes was dissolved in 20 ml. of distilled water and brought to 60°. To the hot mixture 0.5 g. of 2-(*β*-naphthyl)-5-phenylpenten-2-yne-4-oic acid in 75 ml. of acetone was added in a dropwise manner. Refluxing commenced immediately and was continued for 12 hr. The brown reaction mixture was filtered and upon cooling precipitated the crudely crystalline pyrone. Crystallization two times from benzene gave 0.2 g., 40%, of yellow plates, m.p. 197°. Absorption maxima occur at: 1695, 1620, 1598, 1540, 1490, 1450, 1363, 1325, 1273, 1117, 1145, 1023, 986, 917, 896, 863, 847, 824, 767, 750, 646 and 685 cm.$^{-1}$ in the infrared and at 250 mμ (log ε 4.24) and 365 mμ (log ε 4.31) in the ultraviolet.

Anal. Calcd. for $C_{21}H_{14}O_2$: C, 84.54; H, 4.73. Found: C, 84.54; H, 4.85.

3-(*p*-Biphenylyl)-6-phenyl-2-pyrone.—A catalyst prepared by heating 1.0 g. of yellow mercuric oxide with 10 ml. of concd. sulfuric acid for 0.5 hr. was dissolved in 20 ml. of distilled water. To this was added 0.5 g. of 2-(*p*-biphenylyl)-5-phenylpenten-2-yne-4-oic acid in 50 ml. of acetone. The mixture was refluxed for 24 hr., cooled to room temperature and the precipitate was extracted with

(11) Analyses by Micro Tech Laboratories, Skokie, Ill.

(12) E. Schwenk and D. Papa, *J. Org. Chem.*, **11**, 798 (1946).

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May 20, 1957

toluene in a Soxhlet apparatus for 2 hr. The product was precipitated by the addition of ligroin to the extracts and crystallized twice from toluene to give 0.1 g., 20%, of yellow needles, m.p. 268°. Absorption maxima occur at: 1705, 1650, 1600, 1550, 1487, 1448, 1355, 1110, 1142, 1120, 1103, 963, 890, 838, 813, 778, 753, 724 and 683 cm.$^{-1}$ in the infrared and at 265 mμ (log ε 4.27) and 365 mμ (log ε 4.56) in the ultraviolet.

Anal. Calcd. for $C_{23}H_{16}O_2$: C, 85.16; H, 4.97. Found: C, 85.46; H, 4.96.

3-(*p*-Methoxyphenyl)-6-phenyl-2-pyrone.—A catalyst mixture was prepared in the same manner as that used in the synthesis of 3,6-diphenyl-2-pyrone and diluted to 100 ml. with distilled water; 5 ml. of this catalyst was added to a solution of 0.5 g. of 2-(*p*-methoxyphenyl)-5-phenylpenten-2-yne-4-oic acid in 50 ml. of methanol. The reaction was kept at 45–50° for 48 hr. and the methanol evaporated. The precipitate was filtered, washed with distilled water and crystallized two times from ethanol to give 0.1 g., 20%, of yellow plates, m.p. 170°. Absorption maxima occur at: 1700, 1625, 1610, 1575, 1550, 1510, 1490, 1450, 1358, 1305, 1290, 1250, 1175, 1110, 1083, 1047, 1027, 965, 900, 840, 806, 777, 763 and 683 cm.$^{-1}$ in the infrared and occur at 250 mμ (log ε 4.00) and 370 mμ (log ε 4.10) in the ultraviolet.

Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.50; H, 5.10.

Infrared absorption spectra were obtained on potassium bromide pellets using a Baird Associates double beam recording infrared spectrophotometer with sodium chloride optics. Ultraviolet absorption spectra were obtained using 1.00-cm. silica cells in a Beckman DU spectrophotometer. Absolute methanol was used as solvent except as noted.

LOUISVILLE 8, KENTUCKY

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Pyrolysis of Alkyl Phosphates

BY HENRY E. BAUMGARTEN AND ROBERT A. SETTERQUIST[1]

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The preparation of amyl dimethyl, dimethyl hexyl, dimethyl octyl, dioctyl methyl and cyclohexyl dimethyl phosphates is described. These five alkyl phosphates and three others have been pyrolyzed to give olefins in high yield. The pyrolyses were accompanied by extensive rearrangement of the olefinic double bond.

In the preparation of olefins by the pyrolysis of esters, it is becoming increasingly apparent that a considerable variation in the nature of the acid moiety is allowable. A recent review[2] has cited numerous examples of olefin formation by pyrolysis in the liquid and vapor phases of esters of many different organic acids, and to these examples may be added the pyrolyses of esters of the inorganic acids, boric acid[3] and sulfurous acid.[4–6] Although no systematic study of the pyrolysis of the esters of phosphorus acids has been reported, isolated examples of the thermal decomposition of such substances to olefins have been described. For example, Gerrard[7] reported that *n*-octyl phosphorodichloridite decomposed to give octylene at 150°. Arbuzov and Valitova[8] obtained olefinic products by heating tertiary alkyl phosphites with methyl iodide in a sealed tube at 200°. Cronje[9] reported that the pyrolysis of dihydrogen dialkyl pyrophosphates at 180° yielded olefins. Other workers have reported obtaining olefinic by-products during the preparation or reaction of various organophosphorus esters but, in most instances, the immediate precursor of the olefin has not been identified and in many may not have been an organophosphorus compound. The present communication describes the preparation and pyrolysis of a number of alkyl phosphates and is the first of a series to be devoted to the pyrolysis of various phosphorus derivatives. From the many possible simple and mixed alkyl and aryl phosphates three types were selected for study: alkyl dimethyl phosphates (I), dialkyl methyl phosphates (II) and trialkyl phosphates (III).

$$\underset{\text{I}}{RCH_2CH_2OP(O)(OCH_3)_2} \longrightarrow RCH{=}CH_2 + HOP(O)(OCH_3)_2$$

$$\underset{\text{II}}{(RCH_2CH_2O)_2P(O)OCH_3} \longrightarrow 2RCH{=}CH_2 + (HO)_2P(O)OCH_3$$

$$\underset{\text{III}}{(RCH_2CH_2O)_3PO} \longrightarrow 3RCH{=}CH_2 + (HO)_3PO$$

Preparation of the mixed phosphates (I) was effected by treatment of the appropriate alcohol (IV) with phosphorus oxychloride in the presence of dimethylaniline followed by reaction of the intermediate alkyl phosphorodichloridate (V) with sodium methoxide.

$$\underset{\text{IV}}{RCH_2CH_2OH} + POCl_3 \xrightarrow{C_6H_5NMe_2} \underset{\text{V}}{RCH_2CH_2OP(O)Cl_2} \xrightarrow{CH_3ONa} \underset{\text{I}}{RCH_2CH_2OP(O)(OCH_3)_2}$$

The phosphates thus prepared are described in Table I. This procedure was more effective in our hands than the alternative treatment of dimethyl phosphorochloridate with the alkoxide of IV or with IV and a tertiary amine.[10]

Dioctyl methyl phosphate (II, R = C_6H_{13}) was prepared by treating the commercially available dioctyl phosphorochloridate with sodium methoxide in ether or, preferably, with methanol and tri-

(1) Minnesota Mining and Manufacturing Co. Fellow, 1955–1956.
(2) W. J. Bailey and J. J. Hewitt, *J. Org. Chem.*, **21**, 543 (1956).
(3) G. L. O'Connor and H. R. Nace, THIS JOURNAL, **77**, 1578 (1955).
(4) D. Libermann and A. Rouiax, *Compt. rend.*, **226**, 2151 (1948).
(5) C. C. Price and G. Berti, THIS JOURNAL, **76**, 1207 (1954).
(6) G. Berti, *ibid.*, **76**, 1213 (1954).
(7) W. Gerrard, *J. Chem. Soc.*, 84 (1944).
(8) A. E. Arbuzov and F. G. Valitova, *Izvest. Akad. Nauk, U.S.S.R. Otdel. Khim. Nauk*, 801 (1952); *C. A.*, **47**, 10462 (1953).
(9) J. H. Cronje, *J. S. African Chem. Inst.* [N.S.], **2**, 1 (1949).

(10) The choice of the procedure selected was based on a relatively small number of orienting experiments. In view of the results of G. M. Steinburg (*J. Org. Chem.*, **15**, 637 (1950)) the reaction of IV with dimethyl phosphorochloridate (or its precursors, dimethyl phosphite and triethylamine) could prove to be superior to the method chosen.

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TABLE I

ALKYL PHOSPHATES

Phosphate	Method[a]	Yield, %	B.p., °C.	Mm.	$n^{25}D$	Composition	Phosphorus, % Calcd.	Phosphorus, % Found	Infrared spectrum,[b] cm.$^{-1}$ P → O stretch	P–O–Me stretch	P–O–C stretch
Amyl dimethyl	B	66	72–74	0.4	1.4127	$C_7H_{17}O_4P$	15.81	15.59	1283(s)	1190(w)	1135(vs)
Cyclohexyl dimethyl	A	41	106	1.5	1.4417	$C_8H_{17}O_4P$	14.88	14.72	1280(s)	1188(w)	1015(vs) 1035(vs)
Dimethyl hexyl	B	70	100	1.7	1.4180	$C_8H_{19}O_4P$	14.75	14.63	1280(s)	1187(w)	1035(vs)
Dimethyl octyl	A	70	130	1.7	1.4236	$C_{10}H_{23}O_4P$	13.00	12.53	1286(s)	1192(w)	1040(vs)
Dioctyl methyl	[c]	58	162–164	1	1.4362	$C_{17}H_{37}O_4P$	9.21	9.20	1286(s)	1188(w)	1035(vs)

[a] Method A = solid sodium methoxide in ether; method B = methanolic sodium methoxide. [b] L. J. Bellamy ("The Infrared Spectra of Complex Molecules," Methuen and Co., London, 1954, Chap. 18) quotes for the P → O stretching vibration, 1250–1300 cm.$^{-1}$, for the P–O–CH_3 stretching vibration, 1190 ± 3 cm.$^{-1}$, for the P–O–C(aliphatic) stretching vibration, 1000–1500 cm.$^{-1}$. [c] See Experimental section.

TABLE II

OLEFINS FROM THE PYROLYSIS OF ALKYL PHOSPHATES

Phosphate	Amount pyrolyzed, g.	Time, of addn., min.	Temp., °C.	B.p. range, °C.	Yield[a] of olefin, %	Infrared spectrum[b] C=C stretching, cm.$^{-1}$
Amyl dimethyl	10.0	180	500	25–35	85	1638, ~1650
Cyclohexyl dimethyl	14.2	45	350	78–83	66	1648
Dimethyl *n*-hexyl	8.0	120	420	63–70	88	1643, ~1656, ~1667
	14.3	120	350	64–68[1]	97	1642, ~1652, 1667
	11.2	120	300	63–68	90	1643, ~1654, ~1667
	12.6	45	300	60–67	87	
	11.4	120	250	.....	0[c]	
Dimethyl octyl	14.5	60	300	120–125	75	1643, 1666
Dioctyl methyl	12.0	120	300	120–125	99	1645, 1668
Tributyl	10.0	180	500	.....	75	1635
Triisoamyl	17.4	60	350	20–38	67	
Tri-(2-ethyl) hexyl	25.0	93	350	117–121	90	1646, 1670

[a] Based on total possible olefin obtainable. [b] L. J. Bellamy "(The Infrared Spectra of Complex Molecules," Methuen and Co., London, 1954, Chap. 3) quotes the average values for the C=C stretching vibration as, for $CHR{=}CH_2$ 1643 cm.$^{-1}$, for $CHR_1{=}CHR_2$ (*trans*) 1673 cm.$^{-1}$, for $CHR_1{=}CHR_2$ (*cis*) 1657 cm.$^{-1}$. [c] 9.8 g. (86%) of dimethyl *n*-hexyl phosphate recovered.

ethylamine in carbon tetrachloride. All of the simple trialkyl phosphates (III) used in this study were available from other sources.

The phosphates were pyrolyzed by dropping them through a 1-in. Pyrex or Vycor glass tube packed with 1/16-in. glass helices and heated to various temperatures by a tube furnace. The results of several typical pyrolyses are given in Table II. Inasmuch as a strong acid (phosphoric acid, its methyl or dimethyl ester or polymeric acids derived from these) should be formed in the elimination reaction, extensive isomerization of the double bond was expected in the olefin formed. Therefore, that part of the pyrolysate which boiled within the temperature range dictated by the boiling points of the expected olefins was collected as product.

In every run some darkening of the pyrolysis tube indicated that carbonization occurred in varying amounts, perhaps adding to the extent of isomerization.[11] As the temperature was increased the extent of the darkened area also increased.

The results of Table II indicate that alkyl phosphates pyrolyze readily at temperatures of 300° and above to give excellent yields of olefin. From many experiments the optimum temperature appeared to be around 350°, although occasionally good yields were obtained at 300°. It is interesting to note that in the attempted pyrolysis of dimethyl *n*-hexyl phosphate at 250°, no olefin was obtained and 85.5% of the starting material was recovered. Thus, the pyrolysis temperature of the phosphates is intermediate between those of the sulfites (170–260°) and of the acetates (400–550°).[6]

Essentially the stoichiometric amounts of olefin were obtained from II and III, two and three moles of olefin per mole of phosphate, respectively.

Although no attempt was made to determine quantitatively the composition of the olefinic products, the infrared spectra of all olefin fractions were examined for evidence of double bond migration. In all instances in which such migration would be expected, the infrared spectra indicated that migration had occurred. To illustrate, the frequencies of selected bands occurring in the spectrum of the product obtained from dimethyl *n*-hexyl phosphate at 350° are given in Table III together with the characteristic frequencies reported[12] for 1-hexene and *cis*- and *trans*-2-hexene. Comparison of these values indicates that a mixture of olefins was present in the pyrolysate. Inasmuch as the spectrum of the product obtained at 350° differed little from those of olefins formed at various temperatures from 300 to 400°, small variation in temperature apparently had little

(11) W. J. Bailey and L. Nicholas, *J. Org. Chem.*, **21**, 854 (1956).

(12) N. Sheppard and D. M. Simpson, *Quart. Rev.*, **6**, 1 (1952).

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TABLE III

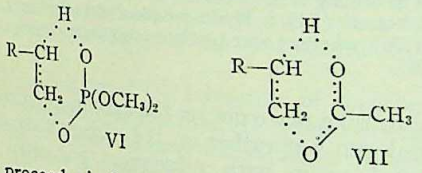
INFRARED SPECTRUM OF HEXENE PYROLYSATE[a]

Mode	1-Hexene	*cis*-2-Hexene	*trans*-2-Hexene	Pyrolysate
CH stretching	3083	3010	3026	3080
				3010
C=C stretching	1656	1656	(1670)	1667
				~1652
				1642
				1408
CH bending (in plane)	1416	1408	1299	1408
	1297			1297
	993	694	966	993
CH bending (out of plane)	910			966
	632			907
	1820[b]			690
				1820

[a] Values for 1-hexene, *cis*-2-hexene, *trans*-2-hexene from ref. 12. [b] Overtone.

effect on the extent of isomerization, although the isomerization may have been in part thermal in origin. Of the other phosphates pyrolyzed, only cyclohexyl dimethyl phosphate appeared to give a single olefin, substantially free from rearrangement products.

Although a cyclic transition state (VI) can be written for the pyrolysis of alkyl phosphates which resembles that (VII) now commonly accepted for the pyrolysis of acetates and other esters of organic acids,[13] it seems more likely that the reaction



VI

VII

may proceed *via* ionic intermediates either to the exclusion of or in competition with the cyclic mechanism. Much of the argument offered by Berti[6] in support of an ionic type of cleavage for alkyl sulfites appears to be applicable to the cleavage of phosphates as well.

Experimental[14]

Alkyl Dimethyl Phosphates.—Equimolar amounts of the alcohol, phosphorus oxychloride and dimethylaniline and twice the molar amount of sodium methoxide were used. Special care was taken to maintain anhydrous conditions throughout each preparation.

A mixture of dry ethyl ether (100 ml. for each 10 g. of alcohol used), the alcohol and dimethylaniline was treated dropwise with stirring with phosphorus oxychloride in dry ether (100 ml. for each 20 g. of phosphorus oxychloride) while the temperature was maintained below −15°. After the addition was completed the mixture was allowed to stand and come to room temperature. The resulting ethereal solution of alkyl phosphorodichloridate was transferred from the precipitated dimethylaniline hydrochloride through a filter stick into another large, 3-necked, round-bottomed flask. The solid amine hydrochloride was washed with dry ether and the ethereal solution was added to the filtrate. Solid sodium methoxide (method A) or a 10% solution of sodium methoxide in methanol (method B) was added slowly while the cooled (in ice) ether solution was stirred rapidly. The reaction mixture was allowed to stand overnight at room temperature. The precipitated sodium chloride was separated by filtration and the ethereal solution was washed with 100 ml. of 5% aqueous sodium bicarbonate and then dried over anhydrous magnesium sulfate. The product was distilled under reduced pressure through an 18-in. by 0.5-in. Vigreux column.

Dioctyl Methyl Phosphate. (a) **From Sodium Methoxide.**—To a solution of 170.5 g. (0.5 mole) of dioctyl phosphorochloridate in 200 ml. of ether cooled in ice was added 27 g. (0.5 mole) of sodium methoxide in small portions. The reaction mixture was allowed to stand overnight and the sodium chloride was separated by filtration. The filtrate was washed with 5% aqueous sodium bicarbonate, then several portions of water and dried over magnesium sulfate. The ether was distilled from the product, giving 146 g. (87%) of crude dioctyl methyl phosphate, $n^{25}D$ 1.4400. Although purification by distillation was possible, in the presence of traces of acid, decomposition took place (even at 0.25 mm.) giving octene, which contaminated the distilled ester (*vide infra*).

(b) **From Methanol and Triethylamine.**—To a stirred solution of 10 g. (0.10 mole) of triethylamine and 3.5 g. (0.11 mole) of methanol in 200 ml. of dry carbon tetrachloride held at 0° in an ice-bath was added over a period of 1 hr. a solution of 33 g. (0.097 mole) of dioctyl phosphorochloridate in 50 ml. of carbon tetrachloride. The mixture was removed from the cold bath and allowed to stand at room temperature protected from moisture until no further precipitate of triethylamine hydrochloride formed.[15] The filtered carbon tetrachloride solution was washed successively with 5% hydrochloric acid, water, 5% aqueous sodium bicarbonate (twice) and water. The solution was dried over magnesium sulfate and then divided into two equal portions. The first half of the solution was distilled through a 24-in. column of the Podbielniak type.[16] Small fractions were collected at frequent intervals, a total of 9.5 g. (58%) of dioctyl methyl phosphate, b.p. 162–164° (1 mm.), $n^{25}D$ 1.4361–1.4362, being collected before the temperature at the take-off fell (to about 150°). On raising the bath temperature from about 210 to 230°, the remainder of the liquid in the still-pot suddenly and almost instantly decomposed forming octene, 2.5 g. (23%) (which was caught in the cold trap protecting the pump).

The second half of the solution was evaporated on the steam-bath under reduced pressure (down to 0.5 mm.), giving 14.2 g. (87%) of crude dioctyl methyl phosphate, $n^{25}D$ 1.4378. The infrared spectra of the crude product and of the distillate described above were not perceptibly different, indicating that for most practical purposes the crude material should suffice.

Pyrolysis Procedure.—The apparatus consisted of either a thick walled Pyrex or a Vycor glass tube, 25-mm. o.d. and 24 in. long, inserted in a vertically disposed FD303 Hoskins electric furnace. The tube was packed for 12 in. of its depth with 1/16-in. Pyrex glass helices (which were cleaned after each run with a solution of hot concentrated nitric and sulfuric acids and rinsed thoroughly with distilled water). A Hershberg-type dropping funnel,[17] modified to permit the pressure-equalized introduction of nitrogen into the system, was used to introduce the sample. The pyrolysate was collected in a large (50-mm. o.d.) side-arm test-tube immersed in a Dry Ice–methanol-bath. In some experiments the side-arm of the test-tube was connected to a U-tube immersed in Dry Ice–methanol as a precautionary measure, but normally this precaution was not necessary. A slow flow of nitrogen (about 1–2 l. per hour) was introduced into the tube during pyrolysis to sweep the vapors into the receiver and maintain a non-oxidizing atmosphere within the apparatus. All gases not condensed in the cold bath(s) were collected in a gas buret over water.

The temperature of the tube was determined using a Leeds and Northrup Model 8667 pyrometer and an iron–constantan thermocouple, the thermocouple leads being inserted in a

(13) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 462.

(14) Boiling points are uncorrected. The alcohols used in this work were obtained from the Matheson Co., Inc. We are indebted to Dr. H. A. Pagel for gifts of tributyl and trikosoamyl phosphate, to the Victor Chemical Works for dioctyl phosphorochloridate and to the Carbide and Carbon Chemicals Co. for tri-(2-ethylhexyl) phosphate.

(15) The quantity of triethylamine hydrochloride precipitated after 4 hr. was 48%, after 16 hr., 79%, after 40 hr., 95%, after 64 hr., 100%.

(16) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1950, p. 237.

(17) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 129.

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well extending about half-way into the packed section of the tube.[18] The temperature was controlled to ±6°.

The optimum rate of addition of phosphate during pyrolysis appeared to be about 0.3 g. of ester per minute, although little change in the yield of olefin occurred when the rate was varied from 0.06 to 0.3 g. per minute. The crude pyrolysate was purified by distillation through an 8-in. Vigreux column. The olefin fraction boiling in the range of temperatures given in the literature[19] for the expected olefin and isomerization products was collected for infrared analysis.[20] No attempt was made to identify other by-products. After a run the tube was usually clean throughout except for an approximately 2-in. area about 1 in. from the top of the packing, which was black. Etching of the tube in this area took place.

(18) A number of tube designs, including all-glass construction, have been employed to permit insertion of the thermocouple well and the dropping funnel into the relatively small tube opening. The simplest of these (and the easiest to disassemble and clean) was a tube terminating in an open cup of about 35-mm. o.d. The dropping funnel and thermocouple well were fitted into the cup with a clean rubber stopper. This device was very satisfactory provided that in inserting the pyrolysis tube into the apparatus it was first fitted with a 1.25-in. sleeve of 1-in. copper tubing and a fairly tight-fitting shield formed from a 2-in. square of asbestos cement board (Transite) (to conduct away the heat and to seal off the opening of the furnace, respectively). Otherwise, the rubber stopper charred badly at the higher temperatures.

(19) S. W. Ferris, "Handbook of Hydrocarbons," Academic Press, Inc., New York, N. Y., 1955.

(20) Infrared determinations were made by Mr. E. R. Magnuson with a Perkin–Elmer recording instrument, model 21, employing sodium chloride optics and the neat liquid or gas.

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[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH AND THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CHICAGO]

Phosphonic Acids. IV.[1] Preparation and Reactions of β-Ketophosphonate and Enol Phosphate Esters[2]

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In contrast to α-chlorinated ketones which react with triethyl phosphite to form enol phosphate esters, α-iodoketones react "normally" with triethyl phosphite to yield β-ketophosphonate esters. Thus iodoacetone reacts with triethyl phosphite at room temperature to form diethyl β-ketopropylphosphonate (II). Diethyl β-ketopropylphosphonate also may be prepared by the acid-catalyzed ethanolysis of diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb), a substance which is obtained by the smooth reaction of two moles of triethyl phosphite with α,α′-dichloroacetone. Treatment of diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb) with sodium ethoxide in boiling ethanol results in the elimination of the elements of diethyl hydrogen phosphate to form diethyl propynylphosphonate (VI). Hydrogenation of diethyl isopropenyl phosphate (VIII) over palladium yields diethyl isopropyl phosphate (IX), whereas over platinum reductive cleavage of the enol ester linkage takes place to form diethyl hydrogen phosphate (X).

It has long been recognized that the reaction of α-chloroketones with sodium diethyl phosphonate[3] and with triethyl phosphite[4] gives rise to unusual products which, although originally formulated as β-ketophosphonates, do not react with the usual carbonyl reagents and which, on acid hydrolysis, undergo cleavage to produce a ketone and inorganic phosphate. The reason for this behavior became clear when it was demonstrated that the reaction of triethyl phosphite with α-chlorinated aldehydes[5] and ketones[6,7] takes place in a manner different from that of simple alkyl halides to yield predominantly enol phosphate esters rather than β-ketophosphonate esters. The most reasonable explanation proposed for this phenomenon is that the polarization induced by the electronegative halogen atoms causes the attack of triethyl phosphite to take place not on the carbon atom bearing the halogen but rather on the carbon atom of the carbonyl group with subsequent concerted rearrangement.[8]

In connection with the synthesis of phosphonate analogs of certain phosphorylated intermediates of metabolism,[1] a method was desired for the preparation of authentic β-ketophosphonate esters. If it is assumed that chloro and polyhaloketones react abnormally in the Arbuzov reaction because of the polarization induced on the carbonyl group by the electronegative halogen atoms, it was considered that an iodoketone might react normally since the less electronegative iodine atom would exert a smaller polarization effect as well as being more reactive toward simple displacement. Accordingly, the reaction of iodoacetone (I) with triethyl phosphite was investigated and found to proceed exothermically at room temperature to produce diethyl β-ketopropylphosphonate (II), with only a small amount of diethyl isopropenyl phosphate being formed.[9] This β-ketophosphonate (II) forms the expected 2,4-dinitrophenylhydrazone derivative, and its infrared spectrum shows strong carbonyl absorption at 1717 cm.$^{-1}$ and

(1) Paper III, S. Preis, T. C. Myers and E. V. Jensen, THIS JOURNAL, **77**, 6225 (1955).

(2) This investigation was supported in part by a grant from the National Institutes of Health, Public Health Service (RG-3053).

(3) P. Nylen, Dissertation, Uppsala, 1930, p. 59; I. S. Bengelsdorf, Ph.D. Dissertation, University of Chicago, 1951, p. 18.

(4) B. A. Arbuzov, B. P. Lugovkin and N. P. Bogonostseva, *Zhur. Obshchei Khim.*, **20**, 1468 (1950); *C. A.*, **45**, 1506 (1951).

(5) (a) W. Perkow, *Ber.*, **87**, 755 (1954); (b) W. Perkow, E. W. Krockow and K. Knoevenagel, *ibid.*, **88**, 662 (1955).

(6) (a) J. F. Allen and O. H. Johnson, THIS JOURNAL, **77**, 2871 (1955); (b) J. F. Allen, S. K. Reed, O. H. Johnson and N. J. Brunsvold *ibid.*, **78**, 3715 (1956).

(7) (a) A. N. Pudovik and N. M. Lebedeva, *Doklady Akad. Nauk S.S.S.R.*, **101**, 889 (1955); *C. A.*, **50**, 3219 (1956); (b) A. N. Pudovik, *Zhur. Obshchei Khim.*, **25**, 2173 (1955); *C. A.*, **50**, 8486 (1956); (c) A. N. Pudovik, *Doklady Akad. Nauk S.S.S.R.*, **105**, 735 (1955); *C. A.*, **50**, 11230 (1956).

(8) M. S. Kharasch and I. S. Bengelsdorf, *J. Org. Chem.*, **20**, 1356 (1955).

(9) Since the completion of this work, Pudovik[7b,c] has reported the reaction of iodoacetone with triethyl phosphite in boiling diethyl ether to produce diethyl β-ketopropylphosphonate (II) accompanied by small amounts of diethyl isopropenyl phosphate. No mention is made of the formation of the higher boiling phosphate-phosphonate ester III.

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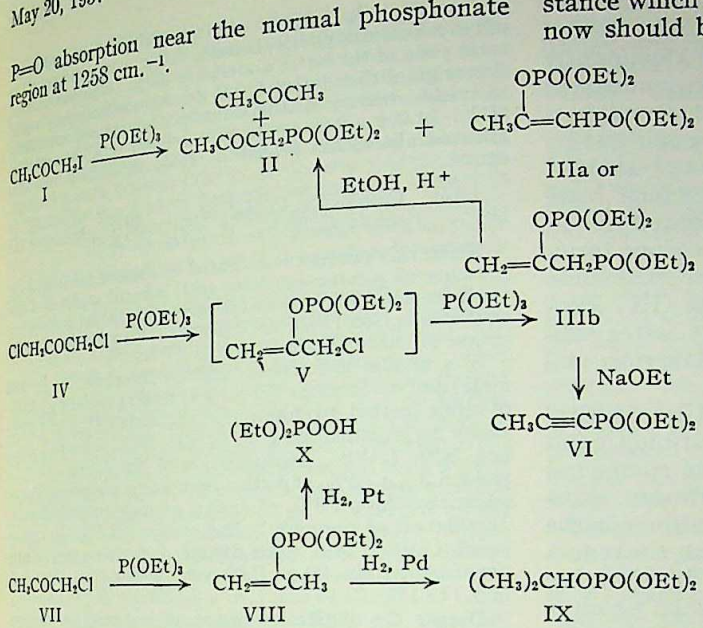

From the reaction of iodoacetone with triethyl phosphite, there was also isolated, besides ethyl iodide and a small amount of diethyl ethylphosphonate, significant amounts of acetone and of a higher boiling material which was shown to be a diethyl diethylphosphonoisopropenyl phosphate[10] (III). As described below, the latter substance can be transformed into diethyl β-ketopropylphosphonate by ethanolysis of the enol phosphate linkage.

The mechanism of the formation of acetone and the phosphate-phosphonate III presents an interesting problem. Inasmuch as the presence of a small amount of hydrogen iodide was noted during the distillation of the reaction product, it was considered that this material may act catalytically to reduce iodoacetone to acetone liberating iodine which then reacts either with iodoacetone or with the activated methylene group of the β-ketophosphonate II to regenerate hydrogen iodide and form either α,α′-diiodoacetone or diethyl α-iodo-β-ketopropylphosphonate. Either of these substances conceivably could react with triethyl phosphite to form III. However, in an experiment designed to eliminate the presence of hydrogen iodide by carrying out all steps under anaerobic conditions in the dark in the presence of solid potassium carbonate, substantial amounts of III again were produced, although in this case no hydrogen iodide was detectable. Therefore, the mechanism of the formation of the phosphate-phosphonate III remains uncertain.

Since an enol phosphate ester linkage represents a potential carbonyl group, an alternative route to diethyl β-ketopropylphosphonate was suggested. It has been reported[6a] that α,α′-dichloroacetone reacts with one mole of triethyl phosphite to form diethyl 3-chloroisopropenyl phosphate, a substance which still contains one chlorine atom which now should be capable of replacement by a phosphonate group in the normal Arbuzov reaction. Accordingly, the reaction of α,α′-dichloroacetone with excess triethyl phosphite was investigated and found to proceed smoothly with the evolution of two moles of ethyl chloride to produce diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb).[11] In contrast to its reaction with chloroacetone which requires a temperature of at least 150°, it is noteworthy that the reaction of the first mole of triethyl phosphite with α,α′-dichloroacetone took place at room temperature.

On prolonged heating with absolute ethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid, ethanolysis of the enol phosphate linkage of IIIb took place affording a 63% yield of diethyl β-ketopropylphosphonate (II) accompanied by triethyl phosphate.

When an ethanolic solution of the phosphate-phosphonate IIIb was treated with one mole of sodium ethoxide at room temperature, the enol phosphate linkage was destroyed rapidly as indicated by the disappearance of the characteristic enol absorption band at 1640 cm.$^{-1}$. However, this base-induced cleavage gave not only triethyl phosphate and diethyl β-ketopropylphosphonate, but also substantial amounts of diethyl propynylphosphonate (VI) and, after acidification, diethyl hydrogen phosphate. When the reaction of IIIb with sodium ethoxide was carried out at elevated temperature, the elimination of the elements of diethyl hydrogen phosphate took place to the exclusion of the ethanolysis reaction affording diethyl propynylphosphonate (VI) in 69% yield.

The product from the reaction of sodium ethoxide with IIIb is assigned the structure of diethyl propynylphosphonate (VI) rather than the isomeric diethyl propargylphosphonate on the basis of its infrared spectrum (triple bond stretching at 2210 cm.$^{-1}$ typical of disubstituted acetylenes rather than 2100–2140 as in monosubstituted acetylenes as well as the absence of the characteristic ≡CH stretching absorption at 3300 cm.$^{-1}$) and the fact that it does not react with ammoniacal silver nitrate. The formation of VI from IIIb may involve the allene, $H_2C{=}C{=}CHPO(OEt)_2$, as an intermediate; investigations of this possibility are in progress and will be reported separately. An attempt was made to prepare authentic diethyl propargylphosphonate for comparison by the reaction of triethyl phosphite with propargyl bromide. This reaction did not proceed in a straightforward manner, but yielded chiefly a mixture of high boiling unstable products accompanied by a very small amount of a material apparently identical with VI.

(10) Inasmuch as there were minor differences between the infrared spectrum of this substance and that of the product obtained from dichloroacetone which undoubtedly possesses the structure IIIb, it is not yet certain whether structure IIIa or IIIb is the correct one in this case.

(11) Since the completion of this work, a similar preparation of diethyl 3-diethylphosphonoisopropenyl phosphate from dichloroacetone has been reported.[7b]

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In confirmation of the observations of others,[6a,7] the reaction of chloroacetone (VII) with triethyl phosphite was found to produce predominantly diethyl isopropenyl phosphate (VIII) accompanied by small amounts of diethyl β-ketopropylphosphonate. The structure of VIII was confirmed by its unique infrared spectrum (enol band at 1646 cm.$^{-1}$ and phosphate-type P=O stretching band at 1270 cm.$^{-1}$ rather than phosphonate-type at 1240–1250 cm.$^{-1}$), by ozonolysis to produce formaldehyde and by hydrogenation over palladium to produce diethyl isopropyl phosphate (IX) identical with an authentic sample of the latter substance prepared by the method of Atherton and Todd.[12]

When the hydrogenation of diethyl isopropenyl phosphate was carried out using a platinum catalyst, two moles of hydrogen per mole of compound were absorbed to produce diethyl hydrogen phosphate (X) and presumably propane, although the latter substance was not isolated. Thus, the reductive cleavage of an enol phosphate bond under these conditions is similar to the cleavage which is known to take place when enol esters of carboxylic acids are hydrogenated with a platinum catalyst.[13]

An attempt was made to prepare diethyl β-ketopropylphosphonate from chloroacetone by blocking the carbonyl group as the ethylene ketal. It was found that the dioxolane of chloroacetone, prepared according to Kühn,[14] did not react with triethyl phosphite at 160° nor with sodium diethylphosphonate in boiling tetrahydrofuran.

Experimental[15]

Diethyl β-Ketopropylphosphonate (II) from Iodoacetone (I).—Freshly distilled iodoacetone (52.2 g., 0.28 mole), b.p. 68–69° (24 mm.), prepared by the reaction of potassium iodide with chloroacetone in aqueous ethanol,[16] was added[17] slowly with stirring to triethyl phosphite (47.3 g., 0.29 mole) held at 0–5°. After the addition was complete, the cold bath was removed, whereupon the reaction mixture warmed spontaneously to about 35° and remained at this temperature for 2 hr. when the temperature began to fall. Distillation of the reaction mixture at reduced pressure yielded, in addition to a forerun (13.6 g.) and a high boiling residue (15.0 g.), diethyl β-ketopropylphosphonate (II), 15.5 g., 30%, b.p. 83–84° (0.4 mm.), n^{25}D 1.4310, reported[7b] b.p. 126° (9 mm.), n^{20}D 1.4350, with characteristic infrared absorption peaks at 1165, 1258 and 1717 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{15}O_4P$: C, 43.30; H, 7.79; P, 15.99. Found: C, 43.00; H, 7.94; P, 16.12.

Treatment of this product with 2,4-dinitrophenylhydrazine in methanol–sulfuric acid solution gave the 2,4-dinitrophenylhydrazone derivative, m.p. 104.9–105.5°.

Anal. Calcd. for $C_{13}H_{19}O_7N_4P$: N, 14.96. Found: N, 15.11.

Redistillation of the 13.6 g. of forerun yielded crude diethyl isopropenyl phosphate, 7.2 g., 14%, b.p. 60–68° (1.5 mm.), n^{25}D 1.4136, plus an additional amount of diethyl β-ketopropylphosphonate, 6.2 g., 12%, bringing the total yield of the latter material to 42%. The residue from the original distillation (15.0 g.) was molecularly distilled to yield diethyl diethylphosphonoisopropenyl phosphate (III), 14.0 g., 0.04 mole, n^{25}D 1.4469, with characteristic infrared absorption peaks[18] at 1149, 1252, 1290 and 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{24}O_7P_2$: C, 40.00; H, 7.32; P, 18.77. Found: C, 39.93; H, 7.41; P, 18.50.

When this product was heated in absolute ethanol in the presence of *p*-toluenesulfonic acid, infrared analyses of test portions showed a progressive decrease in the intensity of the enol absorption (1648 cm.$^{-1}$) with the appearance and increase of carbonyl absorption (1717 cm.$^{-1}$).

In a similar experiment, triethyl phosphite (74 g., 0.45 mole) and iodoacetone (77 g., 0.42 mole) gave 29.2 g., 38%, of crude diethyl β-ketopropylphosphonate (II), n^{25}D 1.4300, which on redistillation gave 21.9 g., 28%, of purified product, n^{25}D 1.4340. Redistillation of the forerun (7.1 g.) yielded 3.7 g., 5%, of diethyl isopropenyl phosphate plus an additional 2.0 g., 3%, of diethyl β-ketopropylphosphonate. Distillation of the high boiling residue (32.5 g.) through a small Claisen flask gave diethyl diethylphosphonoisopropenyl phosphate, 30 g., 0.09 mole, boiling from 125° (0.10 mm.) to 136° (0.14 mm.), n^{25}D 1.4465.

During the distillation of the original reaction mixture, 86.5 g. of volatile material collected in the −80° trap, and one gram of a fuming substance which appeared to be hydrogen iodide collected in a subsequent trap cooled in liquid nitrogen. Redistillation of the volatile product through a Fenske column yielded acetone, 6.4 g., 0.11 mole, b.p. 55–56°, n^{25}D 1.3850, m.p. of dinitrophenylhydrazone derivative, 123.5–124.5°; ethyl iodide, 40.7 g., 0.26 mole, b.p. 71–72°, n^{25}D 1.5074; and a third product which appeared to be diethyl ethylphosphonate, 5.2 g., 0.03 mole, b.p. 78–88° (16 mm.), n^{25}D 1.4120.

In an attempt to prevent the formation of the high boiling product (III) by eliminating the presence of hydrogen iodide in the reaction system, iodoacetone (26.5 g., 0.14 mole), freshly distilled in subdued light into a receiver containing a small amount of solid potassium carbonate, and triethyl phosphite (22.8 g., 0.14 mole) were allowed to react in the dark in an atmosphere of nitrogen in the presence of a little potassium carbonate. As before, the mixture warmed spontaneously to 35° for about 2 hr. On distillation of the reaction mixture in subdued light, no trace of hydrogen iodide was noticeable in the liquid nitrogen-cooled trap, but the yield of diethyl β-ketopropylphosphonate, 7.8 g., 33%, was approximately the same as in previous experiments, and 7.0 g., 0.021 mole, of the high boiling product (III) was obtained.

Diethyl 3-Diethylphosphonoisopropenyl Phosphate (IIIb) from α,α′-Dichloroacetone.—To recrystallized α,α′-dichloroacetone (10.0 g., 0.079 mole) one molar equivalent of triethyl phosphite (13.1 g., 0.079 mole) was added at such a rate that the temperature of the stirred reaction mixture which warmed spontaneously, and evolved ethyl chloride was maintained at about 50°. When the addition was complete and the temperature began to drop, an additional equivalent of triethyl phosphite (13.1 g., 0.079 mole) was added in one portion and the reaction mixture heated at 160° for 2 hr. After the evolution of ethyl chloride (8.3 g., 82%) had ceased, the mixture was cooled, and the small amount of unreacted triethyl phosphite was removed at reduced pressure. The residue (14 g.) was molecularly distilled to yield diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb), 12.9 g., 50%, n^{25}D 1.4429, reported[7c] n^{20}D 1.4435, with characteristic infrared absorption peaks at 1164, 1272 and 1650 cm.$^{-1}$.

(12) F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 674 (1947).

(13) H. H. Inhoffen, G. Stoeck, C. Kölling and V. Stoeck, *Ann.*, **568**, 52 (1950).

(14) M. Kühn, *J. prakt. Chem.*, [2] **156**, 103 (1940).

(15) Microanalyses were carried out by Mr. William Saschek, by Micro-Tech Laboratories, Skokie, Ill., and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were determined as liquid films unless otherwise specified. The authors are grateful to Dr. Marcel Harnik for carrying out many of the infrared determinations involved in this study.

(16) R. Scholl and G. Mattaiopoulos, *Ber.*, **29**, 1550 (1896).

(17) If the triethyl phosphite is added to excess iodoacetone, the reaction mixture turns dark.

(18) The infrared spectrum of this substance was identical with that of diethyl diethylphosphonoisopropenyl phosphate (IIIb) obtained from the reaction of triethyl phosphite with α,α′-dichloroacetone except for a slight modification and broadening of the P=O bands at 1252 and 1290 cm.$^{-1}$ and the presence of an additional moderately strong band at 1149 cm.$^{-1}$ which obscures partially the POEt band at 1165 cm.$^{-1}$.

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Anal. Calcd. for $C_{11}H_{24}O_7P_2$: C, 40.00; H, 7.32; P, 18.77; neut. equiv., 165. Found: C, 39.73; H, 7.27; P, 18.20; neut. equiv., 169.[19]

A subsequent experiment was carried out in a similar fashion except that a 50% excess of triethyl phosphite was employed. Thus, from α,α′-dichloroacetone (97 g., 0.76 mole) and triethyl phosphite (378 g., 2.28 moles) there was obtained a crude product (238 g., 95%, $n^{25}D$ 1.4432) which on distillation in a Claisen flask yielded purified diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb), 210 g., 84%, b.p. 118–120° (0.05 mm.), $n^{25}D$ 1.4459, with an infrared spectrum identical with that of the analyzed sample of this substance.

Diethyl β-Ketopropylphosphonate (II) from IIIb.—A solution of diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb, 25.4 g.; 0.077 mole) and *p*-toluenesulfonic acid (250 mg.) in 100 ml. of absolute ethanol was heated under reflux for 24 days until infrared analysis of test portions showed complete disappearance of enol absorption and no further increase in the carbonyl absorption. The reaction mixture was deacidified by passage through a column containing 100 g. of Amberlite IRA-410 (OH) resin which had been washed thoroughly with ethanol. The eluate was stirred with 2.0 g. of barium hydroxide whereupon 4.8 g. of a solid precipitate slowly formed and was removed by filtration. Recrystallization of this solid from 80% alcohol gave barium diethyl phosphate derived from the triethyl phosphate produced in the ethanolysis reaction.

Anal. Calcd. for $C_8H_{20}P_2Ba$: C, 21.66; H, 4.54; P, 13.97. Found: C, 21.69; H, 4.73; P, 14.31.

The alcohol was evaporated from the above filtrate, and the residue (16.8 g.) was distilled at reduced pressure to yield, after a small forerun, diethyl β-ketopropylphosphonate (II), 9.4 g., 63%, b.p. 80–89° (1.0 mm.), $n^{25}D$ 1.4300, with an infrared spectrum identical with that of the analyzed sample of this material prepared from iodoacetone. The 2,4-dinitrophenylhydrazone of this product melted at 105.0–105.7°, not depressed by admixture with the derivative of the authentic diethyl β-ketophosphonate, m.p. 104.9–105.2°.

Reaction of IIIb with Sodium Ethoxide at Room Temperature.—A solution of crude diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb, 66 g., 0.20 mole) in 80 ml. of absolute ethanol was added to 200 ml. of absolute ethanol in which metallic sodium (4.6 g., 0.20 mole) had been dissolved. After standing 1 hr. at room temperature, infrared analysis of a neutralized test portion indicated complete disappearance of enol absorption (1640 cm.$^{-1}$) with the appearance of strong carbonyl absorption (1717 cm.$^{-1}$), was well as a sharp, fairly strong peak at 2222 cm.$^{-1}$ typical of acetylenic compounds. After 2 hr., the reaction mixture was freed of alkali by passage through a column of Amberlite IR-120 resin which had been washed with ethanol. The alcohol was evaporated from the eluate at reduced pressure, and the residual oil was distilled through a small Vigreux column to yield triethyl phosphate, 16.7 g., b.p. 56.5–59° (0.5 mm.), $n^{25}D$ 1.4060, reported[20] $n^{25}D$ 1.4039.

Anal. Calcd. for $C_6H_{15}O_4P$: C, 39.62; H, 8.24; P, 17.00. Found: C, 39.62; H, 8.09; P, 16.86.

This was followed by a series of fractions (total wt. 24.9 g.) boiling from 63 to 86° (0.5 mm.), $n^{25}D$ 1.4200 to 1.4350, which, from their infrared spectra, appeared to be mixtures of diethyl alkylphosphonates possessing both carbonyl and alkyne absorption. There remained a high boiling, acidic residue, 16.1 g., the infrared spectrum of which was practically identical with that of the analyzed sample of diethyl hydrogen phosphate (X) described below.

Fractionation of a portion of the combined mixture of the phosphonate esters through a Podbielniak Heliband column yielded a small amount of diethyl β-ketopropylphosphonate (II), b.p. 65° (0.8 mm.), $n^{25}D$ 1.4307, several larger fractions showing progressively less carbonyl and more alkyne absorption and, finally, a small fraction of apparently pure diethyl propynylphosphonate (VI), b.p. 73° (0.8 mm.), $n^{25}D$ 1.4432.

Anal. Calcd. for $C_7H_{13}O_3P$: C, 47.73; H, 7.44. Found: C, 47.34; H, 7.56.

Diethyl Propynylphosphonate (VI) from IIIb.—Diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb, 33 g., 0.10 mole) was added over a 0.5-hr. period to a refluxing solution of sodium (2.28 g., 0.099 mole) in 70 ml. of absolute ethanol with stirring in an atmosphere of dry nitrogen. The cooled orange-colored reaction mixture was then both neutralized and freed of diethyl hydrogen phosphate by passage through a column of 750 ml. of Amberlite MB-1 resin which had been previously washed with 750 ml. of 95% ethanol followed by 300 ml. of absolute ethanol. The ethanol was evaporated from the eluate and the residue (21.6 g.) distilled at reduced pressure. After a 6-g. forerun, there was obtained diethyl propynylphosphonate (VI), 12.0 g., 69%, b.p. 108–110° (2.1 mm.), $n^{25}D$ 1.4449, with characteristic infrared absorption peaks at 1168, 1270 and 2210 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{13}O_3P$: C, 47.73; H, 7.44; P, 17.59. Found: C, 47.73; H, 7.59; P, 17.36.

Reaction of Triethyl Phosphite with Propargyl Bromide.—A mixture of propargyl bromide (31.7 g., 0.266 mole) and triethyl phosphite (43.2 g., 0.26 mole) was heated to 90° whereupon a vigorous exothermic reaction took place. After this reaction had subsided (30 minutes) the mixture was heated under reflux for 1 hr. An additional amount of triethyl phosphite (21.6 g., 0.13 mole) was added and heating continued for another hour. Ethyl bromide (17.9 g., 0.16 mole) was collected in a cold trap. Distillation of the red-brown residue under reduced pressure yielded, after a forerun of triethyl phosphite, a substance apparently identical in its properties and infrared spectrum with diethyl propynylphosphonate (VI), 2.3 g., 5%, b.p. 98–103° (2 mm.), $n^{25}D$ 1.4453.

Anal. Calcd. for $C_7H_{13}O_3P$: C, 47.73; H, 7.44; P, 17.59. Found: C, 47.65; H, 7.59; P, 17.33.

The major distillable product (13 g.) was a higher boiling material, b.p. 150–152° (0.2 mm.), $n^{25}D$ 1.4756, which was unstable on storage. The structure of this material has not as yet been determined.

Anal. Found: C, 45.24; H, 7.61; P, 16.45.

A non-volatile residue (27 g.) remained in the still-pot.

Diethyl Isopropenyl Phosphate (VIII).—A mixture of redistilled chloroacetone (25 g., 0.27 mole) and triethyl phosphite (50 g., 0.30 mole) was heated for 4 hr. at 165°. During this time ethyl chloride (17.1 g., 0.26 mole) and 1 g. of higher boiling material were evolved and collected in a cold trap. The reaction mixture was cooled and distilled at reduced pressure. Crude diethyl isopropenyl phosphate (45 g.) was collected at 56–65° (0.1 mm.). A portion of this product was redistilled through a Podbielniak Heliband micro-column to yield pure VIII, b.p. 57° (0.6 mm.), $n^{25}D$ 1.4158; reported b.p. 72–73° (1 mm.),[6a] 96° (12 mm.),[7b] $n^{35}D$ 1.4135,[6a] $n^{20}D$ 1.4190,[7b] with characteristic infrared absorption peaks at 1165, 1270 and 1646 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{15}O_4P$: C, 43.30; H, 7.79; P, 15.96. Found: C, 42.55; H, 7.93; P, 16.13.

In a similar experiment, the reaction product of chloroacetone (50 g., 0.54 mole) and triethyl phosphite (100 g., 0.60 mole) gave, on distillation through a Vigreux column, diethyl isopropenyl phosphate (VIII), 84 g., 80%, b.p. 98–101° (11 mm.), $n^{25}D$ 1.4187, and diethyl β-ketopropylphosphonate, 9.5 g., 9%, b.p. 87–97° (1.5 mm.), $n^{25}D$ 1.4324, with an infrared spectrum similar to that of the product (II) obtained from the reaction of triethyl phosphite and iodoacetone.

Treatment of diethyl isopropenyl phosphate with 2,4-dinitrophenylhydrazine in ethanol or in ethanol–acetic acid solution did not yield any derivative. When this reaction was carried out in methanol–sulfuric acid solution, yellow needles were obtained which, after two recrystallizations from ethanol, melted at 123–124.5° and did not depress the melting point of the 2,4-dinitrophenylhydrazone prepared from acetone.

Anal. Calcd. for $C_9H_{10}O_4N_4$: N, 23.5. Found: N, 23.3.

Ozonolysis of Diethyl Isopropenyl Phosphate.—A solution of VIII (508 mg., 2.62 mmoles) in 500 ml. of ethyl ace-

(19) For the determination of the neutral equivalent, a weighed sample of the ester was hydrolyzed by refluxing overnight with 6 *N* hydrochloric acid, and most of the hydrogen chloride was removed by azeotropic distillation with two portions of benzene. The residue was diluted with water and titrated electrometrically. The titration curve found was that of phosphoric acid; the neutral equivalent was calculated on the basis of the alkali required to raise the *p*H from the first inflection point at 4.2 to the second inflection point at 8.5.

(20) D. P. Evans, W. C. Davies and W. J. Jones, *J. Chem. Soc.*, 1310 (1930).

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tate was treated with ozone at −80° at the rate of 0.5 mmole per minute. After five minutes, unreacted ozone was present in the effluent gases whereupon ozonization was halted and the mixture concentrated to 20 ml. under reduced pressure. This residue was diluted to 250 ml. with water, and after standing for several days aliquot samples were removed and analyzed for formaldehyde. Colorimetric determination with chromotropic acid indicated a 14.6% yield of formaldehyde whereas gravimetric determination as the methone derivative gave a 12.2% recovery.

Diethyl Isopropyl Phosphate (IX) from VIII.—A solution of VIII (1.54 g., 7.9 mmoles) in 20 ml. of ethyl acetate was hydrogenated in the presence of 210 mg. of 10% palladium-on-charcoal. At the end of 42 minutes, 8.4 mmoles of hydrogen had been absorbed and further uptake ceased. After removal of the catalyst and the solvent, the residue was distilled to yield diethyl isopropyl phosphate (IX), 1.1 g., 70%, b.p. 84–86° (20 mm.), $n^{25}D$ 1.4038. This material is quite hygroscopic; a hydroxyl peak was observed in the infrared absorption spectrum unless determined in carbon tetrachloride solution immediately after drying over magnesium sulfate, in which case the infrared spectrum (characteristic peaks at 1167 and 1262 cm.$^{-1}$) was identical with that of a similarly dried solution of authentic diethyl isopropyl phosphate. Analytical results on a sample of the pure liquid IX dried with magnesium sulfate were not quite correct, but they were similar to those found with the authentic material (see below). Phosphorus analyses were low and varied widely on duplicate samples of this substance.

Anal. Calcd. for $C_7H_{17}O_4P$: C, 42.86; H, 8.67; neut. equiv., 196. Found: C, 41.50; H, 8.78; neut. equiv., 200.[19]

Diethyl Isopropyl Phosphate (IX) from Diethyl Phosphonate.[12]—A solution of diethyl phosphonate (13.8 g., 0.10 mole), dry isopropyl alcohol (20 ml.), bromotrichloromethane (20 ml.) and 2,6-lutidine (20 ml.) in 100 ml. of dry ether was allowed to stand overnight at room temperature whereupon a copious precipitate of amine hydrobromide was formed. This was removed by filtration, and the filtrate was washed with 15 ml. of water, dried and evaporated under reduced pressure. Distillation of the residue yielded diethyl isopropyl phosphate, 3.9 g., 24%, b.p. 101–103° (20 mm.), $n^{25}D$ 1.4042. The infrared spectrum of this compound (in CCl_4) showed characteristic peaks at 1167 and 1262 cm.$^{-1}$. As mentioned previously, because of the hygroscopic nature of this substance, it was necessary to dry the solution before determination of the spectrum, and the results obtained on microanalysis were not quite correct even after drying the sample with magnesium sulfate.

Anal. Calcd. for $C_7H_{17}O_4P$: C, 42.86; H, 8.67; P, 15.76; neut. equiv., 196. Found: C, 41.65; H, 8.92; P, 13.26; neut. equiv., 207.[19]

Diethyl Hydrogen Phosphate (X) from VIII.—Preliminary investigations of the hydrogenation of diethyl isopropenyl phosphate (VIII) using reduced platinum oxide in ethyl acetate indicated that two moles of hydrogen were absorbed to form a strongly acidic product. In one experiment VIII (186 mg., 0.96 mmole) in 15 ml. of ethyl acetate was hydrogenated using 45 mg. of platinum oxide, whereupon 1.69 mmoles of hydrogen were absorbed in 15 minutes. After filtration, the entire reduction mixture was titrated electrometrically with standard alkali to *p*H 7.9. In this way an equivalent weight of 202 was obtained for VIII as compared to the calculated value of 194.

To isolate the reduction product, a solution of VIII (3.5 g., 0.018 mole) in 35 ml. of absolute ethanol was hydrogenated in a Parr apparatus with 400 mg. of platinum oxide for 90 minutes. After filtration and evaporation of the solvent, the residue was distilled in a molecular still to yield diethyl hydrogen phosphate (X), 1.66 g., 60%, $n^{25}D$ 1.4170, reported[21] $n^{25}D$ 1.4152.

Anal. Calcd. for $C_4H_{11}O_4P$: C, 31.20; H, 7.14; P, 20.15. Found: C, 31.30; H, 7.37; P, 20.20.

(21) A. D. F. Toy, THIS JOURNAL, **70**, 3882 (1948).

CHICAGO 37, ILLINOIS

[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH AND THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CHICAGO]

Phosphonic Acids. V.[1] An Improved Method for the Preparation of Sodium Diethyl Phosphonate and a Study of its Comparative Reactivity with Alkyl Halides and *p*-Toluenesulfonates[2]

BY RONALD G. HARVEY, TERRELL C. MYERS, HERBERT I. JACOBSON AND ELWOOD V. JENSEN

RECEIVED JUNE 18, 1956

Sodium diethyl phosphonate is prepared rapidly and conveniently by treatment of a solution of diethyl phosphonate with an excess of sodium hydride. In tetrahydrofuran solution, the relative reaction rates of primary alkyl halides and *p*-toluenesulfonates with sodium diethyl phosphonate are RBr > ROTs > RCl. The reaction of sodium diethyl phosphonate with trimethylene chlorobromide gives diethyl γ-chloropropylphosphonate, which on hydrolysis yields γ-chloropropylphosphonic acid.

Sodium diethyl phosphonate, or sodium diethyl phosphite, a reagent commonly used for the preparation of phosphonic acid esters, generally has been prepared[3] by treatment of a solution of diethyl phosphonate with either an equivalent amount of sodium ethoxide (or methoxide) or else with metallic sodium which dissolves with the evolution of hydrogen. Since alcohol and diethyl phosphonate probably do not differ greatly in their acid strengths the former method has the disadvantage that some sodium ethoxide may remain in the mixture either to compete with sodium diethyl phosphonate in its nucleophilic reactions or to react with the products formed. The latter procedure has the disadvantage that metallic sodium dissolves rather slowly in solutions of diethyl phosphonate so that many hours or even days may be required for completion of the reaction. Moreover, the dissolving metal acts as a reducing agent, and solutions of sodium diethyl phosphonate prepared in this way invariably are contaminated with phosphine compounds as indicated by the characteristic odor.[4]

It was found that the undesirable features of either procedure could be avoided by the use of sodium hydride as the basic reagent according to the equation

$$HPO(OEt)_2 + NaH \longrightarrow NaPO(OEt)_2 + {}^1/_2H_2$$

(1) Paper IV, H. I. Jacobson, M. J. Griffin, S. Preis and E. V. Jensen, THIS JOURNAL, **79**, 2608 (1957).

(2) This investigation was supported in part by a grant from the National Institutes of Health, Public Health Service (RG-3053).

(3) G. M. Kosolapoff, "The Organic Chemistry of Phosphorus," John Wiley and Sons, Inc., New York, 1950, p. 202.

(4) P. Nylen, Dissertation, Uppsala, 1930, p. 32.

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May 20, 1957

A suspension of this substance reacts rapidly with a tetrahydrofuran solution of diethyl phosphonate with the evolution of hydrogen to produce a solution of sodium diethyl phosphonate free from phosphine odors.

Recently it was observed that primary and secondary alkyl esters of *p*-toluenesulfonic and methanesulfonic acids react with sodium diethyl phosphonate in a manner similar to that of alkyl halides to produce the corresponding diethyl alkylphosphonate esters.[5] In order to evaluate the potential usefulness of this reaction, a comparison was made of the relative reactivity of alkyl chlorides, bromides and tosylates toward sodium diethyl phosphonate. In this study, freshly prepared sodium diethyl phosphonate[6] was allowed to react at 20° in tetrahydrofuran solution with a threefold excess of *n*-butyl bromide, *n*-butyl chloride and *n*-butyl tosylate, respectively. The progress of these reactions was followed by measurement of the bromide, chloride or tosylate ions produced at various time intervals. As indicated by the data of Fig. 1, the relative reactivities are in the order Br > OTs > Cl with the initial rates in the approximate order of 280:70:1.

$$ROTs + NaPO(OEt)_2 \longrightarrow RPO(OEt)_2 + NaOTs$$

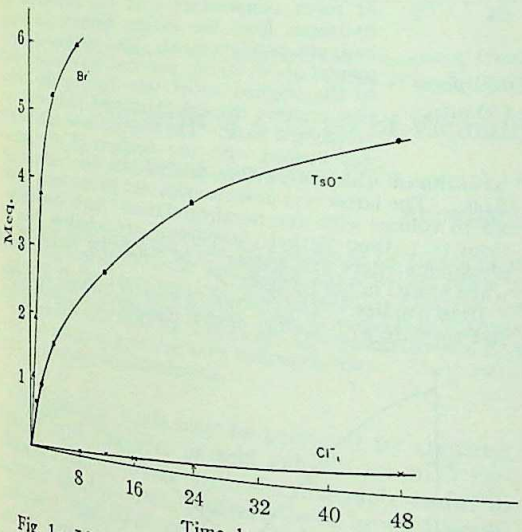

Fig. 1.—Liberation of ions from the reaction of sodium diethyl phosphonate (10 meq. from Na) with either *n*-butyl bromide, *n*-butyl tosylate or *n*-butyl chloride (30 meq.) at 20°.

When sodium diethyl phosphonate is allowed to react with a mixture of excess *n*-butyl bromide and *n*-butyl tosylate at 30°, bromide ion is liberated at about 4 times the rate of tosylate (Fig. 2). The concentration of bromide ion reaches a maximum in about 2 hr., whereupon it begins to disappear rapidly with an accompanying increase in the rate of appearance of tosylate ion. Similarly, when sodium diethyl phosphonate is allowed to react with a mixture of butyl chloride and butyl tosylate, chloride ion reaches a maximum concentration and then disappears (Fig. 3).

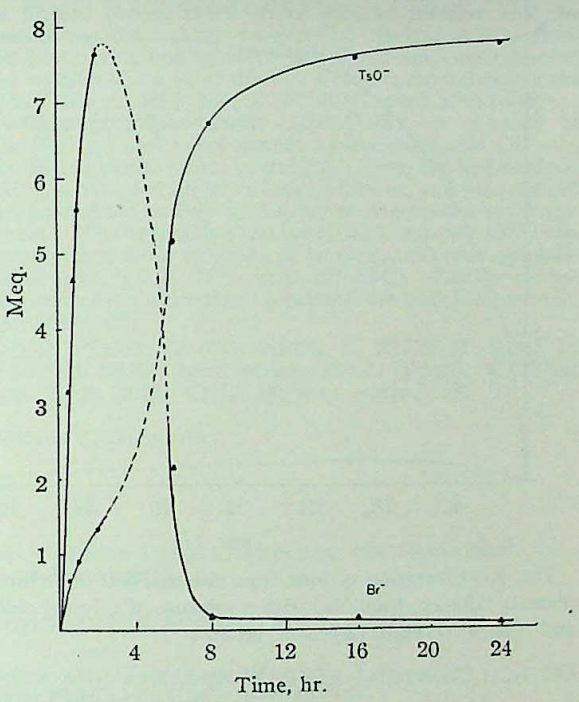

Fig. 2.—Liberation of ions from the reaction of sodium diethyl phosphonate (10 meq. from NaH) with a mixture of *n*-butyl bromide (30 meq.) and *n*-butyl tosylate (30 meq.) at 30°.

The disappearance of bromide (and chloride) ion probably results from a reaction with butyl tosylate in the following manner

$$ROTs + Br^- \longrightarrow RBr + TsO^-$$

However, a suspension of finely pulverized sodium bromide in tetrahydrofuran shows little tendency to react with butyl tosylate. It would appear that the sodium bromide produced from the reaction of sodium diethyl phosphonate with alkyl bromides may be in an extremely finely divided or otherwise reactive form. That this reactivity is gradually lost is indicated by an experiment in which sodium diethyl phosphonate was allowed to react with butyl bromide for 15 hr. at 30° and then butyl tosylate added. As is shown in Fig. 4, again there is a disappearance of bromide ion accompanied by an appearance of tosylate ion, but in this case it is much less rapid or complete than when the butyl tosylate is present during the liberation of the sodium bromide.

In all the reactions studied, using sodium diethyl phosphonate prepared both from sodium and from sodium hydride, the amount of halide or tosylate ions liberated was never greater than 70 to 80% of that calculated on the basis of the diethyl phosphonate employed, even after very long reaction

(5) T. C. Myers, S. Preis and E. V. Jensen, THIS JOURNAL, **76**, 4172 (1954).

(6) A number of these experiments were carried out previous to the development of the sodium hydride method for the preparation of sodium diethyl phosphonate, and in these studies metallic sodium was employed for the preparation of this reagent. However, the rates of liberation of sodium bromide from *n*-butyl bromide at 30° with sodium diethyl phosphonate prepared by either method were found to be similar. The results obtained with a mixture of butyl bromide and butyl tosylate illustrated in Fig. 2 for sodium diethyl phosphonate prepared with sodium hydride are entirely analogous to those obtained with the reagent prepared from metallic sodium.

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periods. These results indicate either that excess sodium or sodium hydride does not convert diethyl phosphonate completely to the sodium derivative or, more probably, that sodium diethyl phosphonate does not react completely with excess alkyl halide or tosylate. Evidence suggesting the latter possibility has been obtained by other investigators.[7]

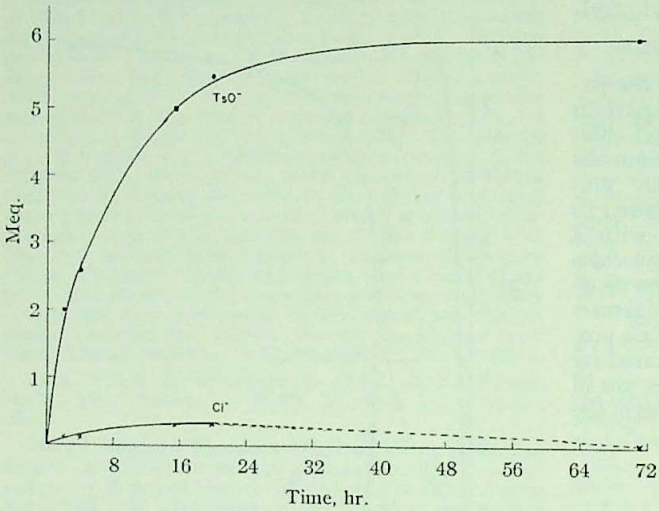

Fig. 3.—Liberation of ions from the reaction of sodium diethyl phosphonate (10 meq. from Na) with a mixture of *n*-butyl chloride (30 meq.) and *n*-butyl tosylate (30 meq.) at 30°.

$$\left.\begin{array}{l}\mathrm{ClCH_2CH_2CH_2OTs}\ \text{(I)}\\ \mathrm{ClCH_2CH_2CH_2Br}\ \text{(II)}\end{array}\right\} \xrightarrow{\mathrm{NaPO(OEt)_2}} \mathrm{ClCH_2CH_2CH_2PO(OR)_2}$$
IIIa, R = Et
b, R = H

When sodium diethyl phosphonate was allowed to react in tetrahydrofuran with an equimolar amount of trimethylene chlorohydrin tosylate (I), diethyl γ-chloropropylphosphonate (IIIa) was isolated in 22% yield; with two molar proportions of trimethylene chlorobromide (II) the yield of IIIa was 54% based on sodium diethyl phosphonate. Hydrolysis of IIIa with concentrated hydrochloric acid gave crystalline γ-chloropropylphosphonic acid (IIIb).

Experimental

Reagents.—Commercial diethyl phosphonate, *n*-butyl chloride, *n*-butyl bromide and *n*-butyl tosylate[8] were redistilled before use. Tetrahydrofuran was dried by distillation from calcium hydride and stored over sodium. The sodium hydride used was a bluish material obtained from the du Pont Co.; the gray product obtained from Metal Hydrides, Inc., was found unsatisfactory in that it produced brown solutions and formed gelatinous material which prevented filtration of the final solution. It was found convenient to weigh out several 4-g. portions of du Pont sodium hydride in a dry-box and store these in stoppered bottles in a desiccator. The entire contents of one bottle then was used for an individual preparation of sodium diethyl phosphonate as described below without further need for the dry-box.

In the competition experiments which were carried out previous to the development of the sodium hydride method for the preparation of sodium diethyl phosphonate, this reagent was prepared in the conventional manner[3] by dissolving metallic sodium in a tetrahydrofuran solution of diethyl phosphonate. The method of preparation of sodium diethyl phosphonate is specified for each experiment.

Preparation of Sodium Diethyl Phosphonate with Sodium Hydride.—The reaction of diethyl phosphonate with sodium hydride was carried out conveniently in a dry 300-ml. 2- or 3-necked flask equipped with a dropping funnel with pressure equalizer and an outlet protected by a drying tube. In the bottom of the flask was sealed a medium porosity fritted glass disk[9] through which the final solution could be filtered through an all-glass connection into a 250-ml. volumetric flask. A continuous stream of dry helium or nitrogen at about 5 cm. pressure was introduced through this disk both to flush out the system and to stir the contents of the flask during the reaction.

Approximately 100 ml. of dry tetrahydrofuran was placed in the flask and a bottle of sodium hydride containing a 10% molar excess over the diethyl phosphonate to be used was opened and quickly emptied into the tetrahydrofuran. This mixture was cooled to −12° by immersion in a Dry Ice–chloroform–carbon tetrachloride mixture, and then diethyl phosphonate was added from the dropping funnel at such a rate that the evolution of hydrogen did not become too vigorous. After addition was complete the mixture was allowed to stand at room temperature until the evolution of hydrogen from the sodium hydride particles had practically ceased. The helium stream, now at about 20 cm. pressure, was transferred to the original outlet tube forcing the reaction mixture through the fritted disk into the volumetric flask. The residual sodium hydride was washed with two portions of dry tetrahydrofuran which were then filtered into the volumetric flask. The latter was now removed and its contents made up to volume with dry tetrahydrofuran. Such stock solutions of sodium diethyl phosphonate are colorless, free of phosphine odors and appear to be stable for several days when stored in the refrigerator.

Rate Studies.—The reaction of *n*-butyl chloride, bromide and tosylate with sodium diethyl phosphonate were carried

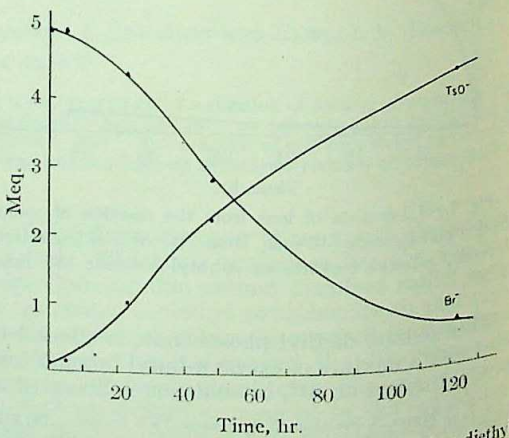

Fig. 4.—Ionic composition of a mixture of sodium diethyl phosphonate (10 meq. from NaH) and *n*-butyl bromide allowed to react for 15 hr. at 30° and then treated (at 0 time) with *n*-butyl tosylate (30 meq.) at 30°.

(7) D. H. Chadwick and S. Kaufman, private communication; A. F. Isbell, Abstracts of the 129th Meeting of the American Chemical Society, Dallas, Texas, April, 1956, p. 2 Q.

(8) Addition of a small amount of solid sodium carbonate prevents darkening of butyl tosylate during distillation.

(9) This flask was similar to that obtainable from the Scientific Glass Apparatus Co. (#J-1779) or the H. S. Martin Co. (#M-21180) except that the connection to the fritted disk was of capillary tubing without a stopcock, terminating with a vapor outlet and standard taper connector for the volumetric flask.

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out in 250-ml. volumetric flasks agitated on an Eberbach shaking machine. Reactions at 20 ± 1° were carried out in air conditioned room; reactions at 30 ± 0.2° were immersed in a constant temperature water-bath. In each flask there was placed 30 millimoles of the butyl halide or tosylate dissolved in 10 ml. of dry tetrahydrofuran. At zero time there was added 10 ml. of a tetrahydrofuran solution containing sodium diethyl phosphonate (prepared from 10 millimoles of diethyl phosphonate). After shaking for the appropriate time period, the reaction was stopped by the addition of 150 ml. of water and 60 ml. of pentane. After thorough mixing, the pentane layer was removed; the aqueous layer was diluted to volume and aliquot portions were analyzed for halide ion by the Volhard titration and for tosylate ion by comparison of the ultraviolet absorption at 261 mμ with that of a standard solution of sodium tosylate.

Diethyl γ-Chloropropylphosphonate (IIIa) from Trimethylene Chlorohydrin Tosylate (I).—A solution of I (14.9 g., 0.06 mole) and sodium diethyl phosphonate, prepared by the action of excess sodium on diethyl phosphonate (8.57 g., 0.06 mole), in tetrahydrofuran (50 ml.) was stirred at room temperature for 72 hr. Then dry pentane (70 ml.) was added and the mixture filtered. The solid residue (9.41 g.) contained chlorine (6.0%), sulfur (13.1%) and phosphorus (2.6%). The filtrate was concentrated under reduced pressure and the residue (14.2 g.) distilled. The fraction (4.3 g.) boiling at 59–78° (0.04 mm.) was redistilled to yield diethyl γ-chloropropylphosphonate (IIIa), 2.1 g., 16%, b.p. 68–70° (0.05 mm.), n^{25}D 1.4423.

Anal. Calcd. for $C_7H_{16}O_3PCl$: C, 39.16; H, 7.51; P, 14.44. Found: C, 38.53; H, 7.80; P, 14.10.

The higher boiling fraction (6.7 g.) appeared to be a mixture from which no pure substances could be isolated.

Repetition of the above reaction on a 0.4 molar scale yielded similar results with diethyl γ-chloropropylphosphonate isolated in 22% yield.

From Trimethylene Chlorobromide (II).—To a stirred solution of sodium diethyl phosphonate, prepared by the action of excess sodium on diethyl phosphonate (27.6 g., 0.20 mole) in tetrahydrofuran (400 ml.), trimethylene chlorobromide (63.0 g., 0.40 mole) was added. After 15 minutes a white solid began to separate. After stirring at room temperature for 4 hr. the reaction mixture was filtered, the filtrate concentrated under reduced pressure and the residue distilled. After recovery of the excess chlorobromide, a fraction boiling at 85–100° (0.32 mm.) was collected and redistilled to yield diethyl γ-chloropropylphosphonate (IIIa), 23.2 g., 54%, b.p. 97–99° (0.25 mm.), n^{25}D 1.4429.

γ-Chloropropylphosphonic Acid (IIIb).—A mixture of IIIa (3.0 g.) and concentrated hydrochloric acid (30 ml.) was heated under reflux overnight. Then the hydrochloric acid was removed under reduced pressure, and benzene (10 ml.) was added and distilled away to remove the last traces of acid. The crystalline residue (2.0 g., m.p. 95–102°) was recrystallized from chloroform to give γ-chloropropylphosphonic acid, 1.7 g., 76%, m.p. 101–104°. Further recrystallization from chloroform furnished the analytical sample, m.p. 104–105°.

Anal. Calcd. for $C_3H_8O_3PCl$: C, 22.72; H, 5.08; P, 19.55; Cl, 22.37; neut. equiv., 158.6. Found: C, 23.12; H, 5.12; P, 19.60; Cl, 22.14; neut. equiv., 158.

CHICAGO 37, ILLINOIS

[CONTRIBUTION FROM THE CHEMOTHERAPY BRANCH, CHEMICAL WARFARE LABORATORIES AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Synthesis of a Series of Vicinally Substituted Hydroxamic Acids[1]

BY MARVIN A. STOLBERG,[2] WILLIAM A. MOSHER AND THEODOR WAGNER-JAUREGG

RECEIVED JULY 17, 1956

A series of hydroxamic acids were prepared by standard procedures from the corresponding esters with the exception of *o*-methoxybenzohydroxamic acid which was obtained from the acid chloride. Compounds which have not been previously reported in the literature are: *o*-nitrobenzohydroxamic, *o*-methoxybenzohydroxamic, *o*-dimethylaminobenzohydroxamic, *cis*-hexahydrophthalohydroxamic and *exo-cis*-3,6-endoxohexahydrophthalohydroxamic acids. *cis*-N-Hydroxyhexahydrophthalamide and *endo-cis*-N-hydroxy-3,6-endomethylene-Δ⁴-tetrahydrophthalimide were obtained from the reaction of the corresponding anhydrides with hydroxylamine. Their infrared spectra were compared to that of N-hydroxyphthalimide and N-hydroxyisophthalimide.

Hydroxamic acids may be prepared by treating esters, acid chlorides or acid anhydrides with hydroxylamine.[3] Other methods, although useful in certain specific cases, generally have limited application. The hydroxamic acids described in this paper were prepared from the corresponding esters with the exception of *o*-methoxybenzohydroxamic acid which was obtained from the acid chloride. Since difficulties were encountered in the isolation and purification of the hydroxamic acids and prime attention was paid to the purity of the products, the yields reported do not necessarily reflect efforts to reach a maximum. A good general method for the separation of certain hydroxamic acids from the corresponding carboxylic acids which are frequent impurities is by treatment of an alkaline aqueous solution with carbon dioxide, which results in precipitation of the hydroxamic acid. This method is applicable to water-insoluble hydroxamic acids that have a pK_a above 9.0.

Compounds prepared for this investigation which have not been previously reported in the literature are: *o*-nitrobenzohydroxamic,[4] *o*-methoxybenzohydroxamic,[4] *o*-dimethylaminobenzohydroxamic, *cis*-hexahydrophthalohydroxamic and *exo-cis*-3,6-endoxohexahydrophthalohydroxamic acids. The latter compound proved to be a powerful vesicant and contact with the skin should be avoided. This compound has a basic structure similar to cantharidine, which is a well known vesicant.

An attempt was made to prepare *o*-hydroxymethylbenzohydroxamic acid from phthalide and hydroxylamine. A small portion of the crude sodium salt of the product obtained produced a deep wine color when treated with ferric chloride in 0.1 *N* HCl which is typical of hydroxamic acids. However, treatment of an aqueous solution of the salt with carbon dioxide or hydrochloric acid

(1) Abstracted from the dissertation submitted by M. A. Stolberg to the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1956.

(2) To whom inquiries should be forwarded: Tracerlab, Inc., 1601 Trapelo Rd., Waltham, Mass.

(3) H. L. Yale, *Chem. Revs.*, **33**, 209 (1943); F. Mathis, *Bull. soc. chim., France*, **5**, D9 (1953).

(4) These compounds were reported as the barium salts by R. D. Closson, C. W. Hauser, THIS JOURNAL, **61**, 618 (1939).

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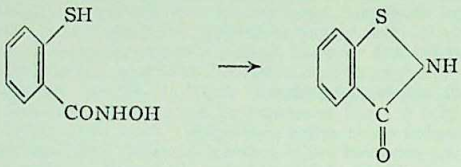
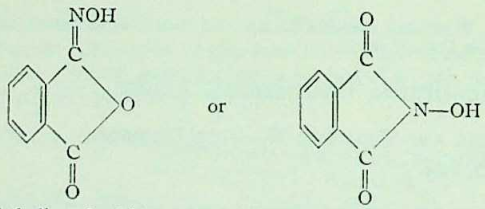
yielded phthalide instead of the hydroxamic acid. Similarly, phthalide was obtained from a methanolic solution of the salt when treated with a carboxylic acid resin (IRC-50). The reaction of methyl *o*-mercaptobenzoate and hydroxylamine produced benzisothiazol-3-one (I) instead of the desired *o*-mercaptobenzohydroxamic acid. The formation of I from the ester and hydroxylamine could occur by the elimination of water from *o*-mercaptobenzohydroxamic acid formed as an intermediate.



I does not produce a color with ferric chloride in anhydrous alcohol, in contrast to hydroxamic acids, but when a drop of water was added to the light orange solution, a deep wine color was produced. This indicated that compound I may hydrolyze in water to form the desired hydroxamic acid. However, all attempts to isolate the hydroxamic acid from aqueous solution were unsuccessful.

The disodium salt of phthalohydroxamic acid when acidified yields "phthaloxime" (II) instead of the hydroxamic acid.[5]

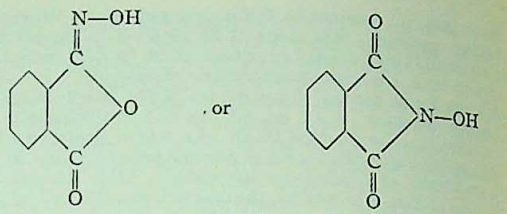


Phthalic anhydride mono-oxime (IIa)

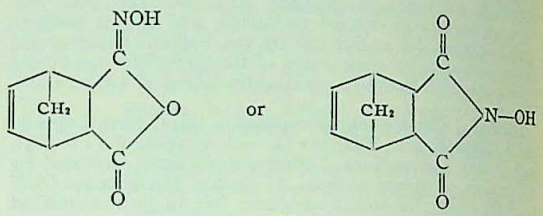
N-hydroxyphthalimide (IIb)

Since *cis*-hexahydrophthalohydroxamic acid is stable, an attempt was made to prepare the corresponding half-hydroxamic acids from the reactions of *cis*-hexahydrophthalic anhydride and *endo-cis*-3,6-endomethylene-Δ^4-tetrahydrophthalic anhydride with hydroxylamine. The products isolated, III and IV, respectively, had analyses which corresponded to the "phthaloxime" structure instead of the desired half-hydroxamic acids. The titration of these compounds with alkali gave no indication of the formation of the corresponding half-hydroxamic acids.

Brady and associates[6] formulated the structure of "phthaloxime" (II) as phthalic anhydride mono-oxime (IIa). Ames and Grey[7] reported the preparation of N-hydroxyphthalimide (IIb) by the reaction of phthalic anhydride with O-benzylhydroxylamine followed by hydrogenolysis, and this product was found to be identical with "phthaloxime." Ames and Grey believe that the correct structure is N-hydroxyphthalimide (IIb) based upon the following observations: 1. N-benzyloxy- and N-hydroxy-phthalimide show infrared



III



IV

imide absorption bands (1700–1800 cm.$^{-1}$) similar to those of N-ethylphthalimide. 2. The ultraviolet absorption spectra are also similar to those of phthalimide. 3. The pK_a value (7.0) is well outside the normal range of oximes (pK_a *ca.* 10–12).

The infrared spectra of IIb, III and IV indicated that they are structurally similar. The carbonyl absorption bands around 1700 cm.$^{-1}$ (see Table I) are clearly different from those of N-hydroxyisophthalimide (phthalic anhydride monoöxime, IIa) obtained by Carpino[8] which has the characteristic doublet at 1810 and 1825 cm.$^{-1}$. Carpino also noted that the iso derivatives lack the very broad carbonyl bands of normal phthalimides which are present in II, III and IV. III and IV have therefore been assigned the structures *cis*-N-hydroxyhexahydrophthalimide and *endo-cis*-N-hydroxy-3,6-endomethylene-Δ^4-tetrahydrophthalimide.

TABLE I

INFRARED CARBONYL ABSORPTIONS AND pK_a VALUES

	Carbonyl absorptions[a]			
	a	b	c	pK_a
IIa	..	1825, 1810 s	..	..
	..	1690m, 1610w	..	..
IIb	1708, 1745 s	1705, 1745 s	1745	7.0
	1795s	1787s	1795	..
III	1690, 1710 s	..	..	6.0
	1790s			
IV	1695, 1710 s	..	..	5.9
	1770s			

[a] a, present investigation; b, Carpino[8]; c, Ames and Grey.[7]

Experimental

o-Methoxybenzohydroxamic Acid.—A chloroform solution of 8.5 g. (0.5 mole) of *o*-methoxybenzoyl chloride was added dropwise, with stirring, to 100 ml. of a chloroform solution containing 3.8 g. (0.055 mole) of hydroxylamine hydrochloride and 10.6 g. (0.105 mole) of triethylamine. The solution was stirred for an hour to ensure complete reaction after which the solvent was vacuum distilled. The solid residue was dissolved in water and hydrochloric acid

(5) C. D. Hurd, C. M. Buess and L. Bauer, *J. Org. Chem.*, **19**, 1140 (1954).

(6) O. L. Brady, L. C. Baker, R. F. Goldstein and S. Harris, *J. Chem. Soc.*, 529 (1938).

(7) D. E. Ames and T. F. Grey, *ibid.*, 3518 (1955).

(8) Prepared by a method obtained from Dr. L. A. Carpino.

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was added with cooling to *p*H *ca.* 2, yielding a precipitate which was filtered, washed with cold water and dissolved in dilute alkali. Small pieces of Dry Ice were added to the alkaline solution and a precipitate was obtained which was recrystallized from acetone–ether, m.p. 129–131°, yield 6.4 g. (77%).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.5; H, 5.5; N, 8.4. Found: C, 58.2; H, 5.8; N, 8.2.

o-Aminobenzohydroxamic Acid.—The procedure used for the preparation of the other hydroxamic acids was very similar, differing only in the quantities employed and methods of isolation. The general procedure was as follows, using *o*-aminobenzohydroxamic acid as an example. To a solution of 5.0 g. (0.03 mole) of sodium in 150 ml. of absolute methanol there was added a solution of 7.0 g. (0.1 mole) of hydroxylamine hydrochloride in 100 ml. of absolute methanol. The sodium chloride which precipitated was removed by filtration, and 15.1 g. (0.1 mole) of methyl anthranilate was added to the filtrate. The resulting solution was heated on a steam-bath for 30 minutes. Upon cooling, the sodium *o*-aminobenzohydroxamate which precipitated was filtered, dissolved in a minimum quantity of water and the solution acidified to *p*H 4 with acetic acid. The resultant precipitate was recrystallized twice from water to yield a colorless product, m.p. 142–143°, yield 3.2 g. (71%). The melting point reported in the literature is 149°.[9]

Anal. Calcd. for $C_7H_8O_2N_2$: C, 55.5; H, 5.3; N, 18.6. Found: C, 55.3; H, 5.3; N, 18.4.

o-Nitrobenzohydroxamic Acid.—When 20.0 g. (0.11 mole) of methyl *o*-nitrobenzoate was added to the alcoholic hydroxylamine solution, an orange color developed. Only a small quantity of the sodium salt precipitated using conditions described above. The solvent was removed under reduced pressure and the resulting crude solid was dissolved in water. Upon acidification a yellow precipitate was obtained which was recrystallized from hot water. The yellow needles melted at 131–133°, yield 10.0 g. (50%).

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.2; H, 3.3; N, 15.4. Found: C, 46.3; H, 3.6; N, 15.2.

o-Dimethylaminobenzohydroxamic Acid.—Only a small quantity of hydroxamic acid formed during the first hour based upon the test with ferric chloride. Heating the solution yielded products which were difficult to separate and isolate. The best procedure was to stir the ester and hydroxylamine at room temperature for 24 hr. The solvent was vacuum evaporated and the solid residue stirred with ether to remove any unreacted ester. The precipitate was filtered, dissolved in a small quantity of water and carbon dioxide bubbled into the aqueous solution. The hydroxamic acid precipitated and was recrystallized from ether, m.p. 129–131°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.1; H, 6.7; N, 15.6. Found: C, 59.5; H, 6.7; N, 15.3.

(9) A. W. Scott and B. L. Wood, *J. Org. Chem.*, **7**, 508 (1942).

***cis*-Hexahydrophthalohydroxamic Acid.**—This hydroxamic acid obtained from 10.0 g. (0.05 mole) of methyl *cis*-hexahydrophthalate was prepared and isolated exactly as above, m.p. 191–193°, yield 6.0 g. (60%).

Anal. Calcd. for $C_8H_{14}O_4N_2$: C, 47.5; H, 7.0; N, 13.9. Found: C, 47.9; H, 7.1; N, 13.3.

***exo-cis*-3,6-Endoxohexahydrophthalohydroxamic Acid.**—Treatment of the aqueous solution of the disodium salt of *exo-cis*-3,6-endoxohexahydrophthalohydroxamic acid (obtained as above) with carbon dioxide or hydrochloric acid did not produce a precipitate. The aqueous solution, after treatment with hydrochloric acid, was evaporated to dryness. The mixture was extracted with acetone in a Soxhlet extractor 4 hr., and a white crystalline product was obtained on evaporation of the acetone, m.p. 186° dec. *Care* should be exercised when handling this compound because it is a vesicant.

Anal. Calcd. for $C_8H_{12}O_5N_2$: C, 44.5; H, 5.7; N, 13.0. Found: C, 44.8; H, 5.8; N, 12.8.

N-Hydroxyhexahydrophthalimide.—A solution of 7.7 g. (0.05 mole) of *cis*-hexahydrophthalic anhydride[10] in 50 ml. of methyl alcohol was added to a solution containing 1.82 g. (0.05 mole) of hydroxylamine in 10 ml. of methyl alcohol. A red color was obtained with ferric chloride immediately. The reaction mixture was stirred for several hours at room temperature after which the solvent was vacuum removed. A colorless viscous oil was obtained which crystallized by scratching with a glass rod. The water-soluble, white crystalline product was recrystallized from chloroform–ligroin (60–90), m.p. 110–112°, yield 7.0 g. (83%).

Anal. Calcd. for $C_8H_{11}O_3N$: C, 56.7; H, 6.6; N, 8.3. Found: C, 56.7; H, 6.6; N, 8.4.

N-Hydroxy-3,6-endomethylene-Δ^4-tetrahydrophthalimide.—To a solution of 9.85 g. (0.06 mole) of *endo-cis*-3,6-endomethylene-Δ^4-tetrahydrophthalic anhydride[10] in 50 ml. of methyl alcohol there was added an equimolar mixture of hydroxylamine and sodium methoxide in methanol. A small quantity of precipitate was observed after 24 hr. at room temperature. The solvent was removed under reduced pressure after which the salt was dissolved in a minimum quantity of water and precipitated with acid. The white crystalline product was recrystallized from chloroform–ligroin (60–90) and produced a red color with ferric chloride, m.p. 165–166°, yield 8.6 g. (80%).

Anal. Calcd. for $C_9H_9O_3N$: C, 60.3; H, 5.1; N, 7.8. Found: C, 60.1; H, 5.0; N, 7.6.

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(10) Samples were kindly supplied by the National Aniline Division of the Allied Chemical and Dye Corporation, 40 Rector Street, New York 6, N. Y.

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[CONTRIBUTION FROM THE CHEMOTHERAPY BRANCH, CHEMICAL WARFARE LABORATORIES, AND THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

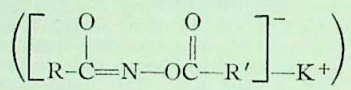
Rates of Reaction of Vicinally Substituted Hydroxamic Acids with Isopropyl Methylphosphonofluoridate (Sarin)[1]

BY MARVIN A. STOLBERG[2] AND WILLIAM A. MOSHER

RECEIVED JULY 17, 1956

The half-time of hydrolysis, pseudo-monomolecular rate constants and the specific rate constants for the reaction of certain *o*-substituted benzohydroxamic and vicinal dihydroxamic acids with isopropyl methylphosphonofluoridate (Sarin) are reported. A plot of the $\log_{10}$ of the specific rate constants *versus* the pK_a's of the hydroxamic acids coincided with the line previously established for the *p*-substituted benzohydroxamic acids. Thus, there is no marked change of the rates of reaction of hydroxamic acids with Sarin due to vicinal substitution and no alteration in the nature of the reacting group by these substituents. The most probable reactive form of the hydroxamate ion is postulated.

An exhaustive investigation of the Lossen rearrangement of acylated hydroxamic acids has been reported by Hauser and associates.[3] It was shown that the rates of decomposition of the potassium salts of a series of dibenzohydroxamates



in which R is phenyl and R′ is phenyl, containing certain *o*-, *m*- and *p*-substituents, are, with the exception of the *o*-methoxy derivative, directly related to the ionization constants of the acids corresponding to R′COOH. In a series of dibenzohydroxamates studied, where R′ is phenyl and R is phenyl, containing certain *m*- and *p*-substituents, an inverse relationship exists between the rate constants and the ionization constants. However, the rate constants of the *o*-substituted phenyl derivatives are more than 100 times greater than would be predicted.

The peculiar effects of a substituent in the *o*-position have been attributed to an *ortho* or proximity effect[4]; however, it has not been possible to estimate the relative importance of electrical effects and specific *ortho* effects for a strongly polar substituent. Generally, these effects have been attributed to steric inhibition of resonance, F strain and hydrogen bonding. The enhancement in rates of reactions by vicinal groups has been reported frequently in the literature.[5]

In the investigation of candidate drugs for the destruction of the "nerve gas" isopropyl methylphosphonofluoridate (Sarin), Hackley, *et al.*,[6] and Swidler, *et al.*,[7] have observed the rapid reaction rates of certain *p*-substituted benzohydroxamic acids with this compound. In a search for more efficacious prophylactic compounds, it was important to determine whether these reactions could be markedly accelerated by placing substituents in the *o*-position. In the accompanying paper[8] the synthesis of certain *o*-substituted benzohydroxamic and vicinal dihydroxamic acids is described.

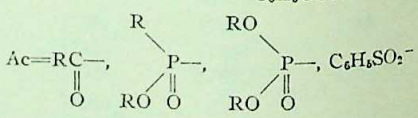
The half-times of hydrolysis of Sarin in the presence of various hydroxamic acids are reported in Table I. To assure first-order kinetics the reactions were carried out with a tenfold molar excess of hydroxamic acid over Sarin. The values were obtained by measuring the rate of addition of standard alkali consumed by the reaction mixture when maintained at a fixed *p*H by a Beckman autotitrator. A detailed discussion of the use of this instrument for studying the kinetics of the reaction of benzohydroxamic acid with Sarin was reported by Swidler and Steinberg.[9] They confirmed the validity of the use of acid production as a measure of the destruction of Sarin as well as the mechanism postulated for the reaction between hydroxamic acids and phosphoryl halides,[6] sulfonyl halides[10] or acyl halides[10a] in alkaline aqueous or inert solvents. These reactions proceed by the initial acylation of the hydroxamate ion followed by a Lossen rearrangement according to the scheme

$$(C_6H_5CONHO)^- + AcX \longrightarrow C_6H_5CONHOAc + X^-$$

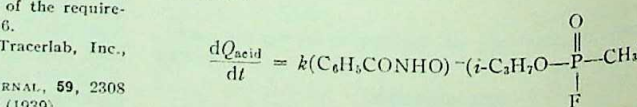
$$C_6H_5CONHOAc + OH^- \longrightarrow (C_6H_5CONOAc)^- + H_2O$$

$$(C_6H_5CONOAc)^- \longrightarrow C_6H_5NCO + Ac^-$$

$$C_6H_5NCO + (C_6H_5CONHO)^- \longrightarrow C_6H_5CONHOCONHC_6H_5$$



The rate of the reaction was found to be dependent on the concentration of the hydroxamate ion and the rate equation for the reaction was established as



Since the amount of hydroxamate ion used up in the course of the reaction is negligible in comparison

(1) Abstracted from the dissertation submitted by M. A. Stolberg to the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1956.

(2) To whom inquiries should be forwarded: Tracerlab, Inc., 130 Trapelo Road, Waltham, Mass.

(3) C. R. Hauser and W. B. Renfrow, THIS JOURNAL, **59**, 2308 (1937); R. D. Bright and C. R. Hauser, *ibid.*, **61**, 618 (1939).

(4) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 204.

(5) *Cf.* (a) C. G. Swain and J. F. Brown, Jr., THIS JOURNAL, **74**, 2538 (1952); (b) D. E. Pearson and W. E. Cole, *J. Org. Chem.*, **20**, 488 (1955).

(6) B. E. Hackley, Jr., R. Plapinger, M. A. Stolberg and T. Wagner-Jauregg, THIS JOURNAL, **77**, 3651 (1955).

(7) R. Swidler, R. Plapinger and G. M. Steinberg, to be published shortly.

(8) M. A. Stolberg, W. A. Mosher and T. Wagner-Jauregg, THIS JOURNAL, **79**, 2615 (1957).

(9) R. Swidler and G. M. Steinberg, *ibid.*, **78**, 3594 (1956).

(10) (a) M. A. Stolberg, R. C. Tweit, G. M. Steinberg and T. Wagner-Jauregg, *ibid.*, **77**, 765 (1955); (b) C. D. Hurd and L. Bauer, *ibid.*, **76**, 3781 (1954).

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TABLE I

RATES OF REACTION OF SARIN (1×10^{-4} *M*) WITH *o*-SUBSTITUTED BENZOHYDROXAMIC AND VICINAL DIHYDROXAMIC ACIDS (1×10^{-3} *M*) AT *p*H 7.6 AND 30.5 ± 0.20°

Hydroxamic acid	pK_a	Anion $\times 10^4$ *M*	Half-time of hydrolysis, min.	$k^a_{obs} \times 10^3$, sec.$^{-1}$	k,[b] l. mole^{-1} sec.$^{-1}$
C_6H_5–	8.8	0.592	7.5	1.54	26.1
o-HOC_6H_4–	7.8	3.86	6.5	1.78	4.6
o-$NO_2C_6H_4$–	8.2	2.04	7.8	1.45	7.4
o-$CH_3OC_6H_4$–	8.9	0.476	11.5	1.00	21.1
o-$NH_2C_6H_4$–	9.0	0.382	8.8	1.32	35.3
o-$(CH_3)_2NC_6H_4$–	9.05	0.342	9.0	1.28	37.5
$C_8H_{12}O_5N_2$[c]	9.3	0.200	14.0	0.83	41.7
$C_8H_{14}O_4N_2$[d]	9.75	0.070	9.8	1.17	168

[a] k_{obs} = pseudomonomolecular rate constant = k-(RCONHO)$^-$. [b] k = specific rate constant. [c] *exo-cis*-3,6-Endoxohexahydrophthalohydroxamic acid. [d] *cis*-Hexahydrophthalohydroxamic acid.

with the total, the velocity equation takes the form

$$\frac{dQ_{acid}}{dt} = k_{obs}(i\text{-}C_3H_7O\text{—}\underset{\underset{F}{|}}{\overset{\overset{O}{\|}}{P}}\text{—}CH_3)$$

where $k_{obs} = k(C_6H_5CONHO^-)$.

Swidler, Plapinger and Steinberg[7] have studied the reactions of *p*-substituted benzohydroxamic acids with Sarin and have come to the following conclusions: 1. A conventional Hammett plot of log k/k_0 *vs.* σ established a ρ of -0.77 ± 0.05. This value was reported to be consistent with a gross mechanism involving the attack of an anion upon a neutral molecule and inconsistent with a rate step involving Lossen rearrangement which yielded larger negative ρ-values (ρ *ca.* -2.6).[11] The excellence of the fit of compounds over a rather wide range of σ-values attested to the apparent mechanistic unity throughout the series and the practical utility of determining the comparative reactivities of the hydroxamic acids toward Sarin by following the rate of acid production.

2. A conventional Brönsted plot of log k *vs.* pK_a of *para* substituted benzohydroxamic acids yielded a β of $+0.78$, whereas the comparable value for the line upon which the hydroxide ion lies was *ca.* $+0.5$. It was therefore postulated that the inordinate reactivity of the hydroxamic acids most probably is due to a stereospecific attack upon the Sarin molecule.

3. The hydroxamic acids could be considered as polyfunctional catalysts and react with Sarin in a manner similar to catechol.[12]

The pseudo-monomolecular rate constant (k_{obs}) and specific rate constant (k) for the reaction of Sarin with each of the *o*-substituted benzohydroxamic and vicinal dihydroxamic acids are reported in Table I. Values of log k *versus* pK_a for these compounds fell, within experimental error, on the line established for *p*-substituted benzohydroxamic acids (Fig. 1). It is obvious that a vicinal group

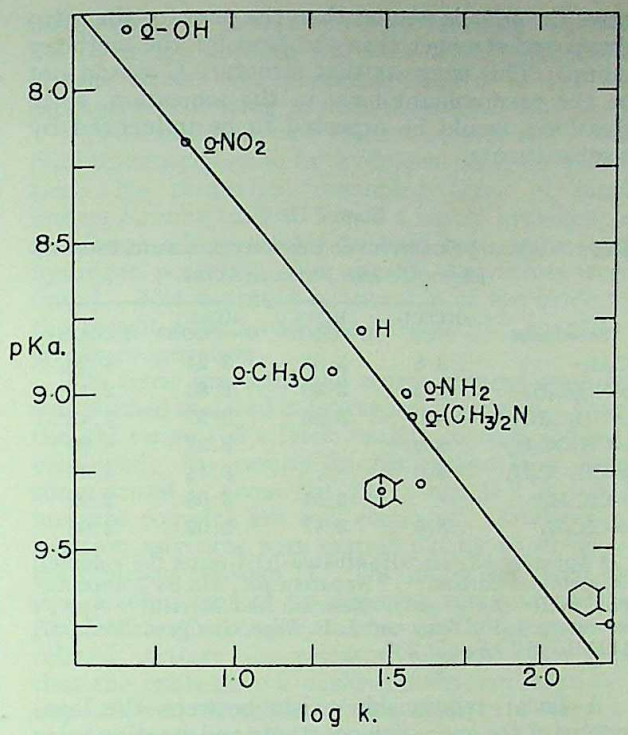

Fig. 1.—Relationship between pK_a values of certain *o*-substituted benzohydroxamic and vicinal dihydroxamic acids and log k for their reaction with Sarin. The equation for the line was obtained from a least squares plot of *p*-substituted benzohydroxamic acids.

produces no marked acceleration in the rate of reaction of a hydroxamic acid with Sarin. Changes in the rate of reaction were dependent only on the ionization constant of the hydroxamic acid. Since these derivatives adhere to a Brönsted relationship, it follows that there is no alteration of the reacting group by vicinal substituents.

The tautomeric structures of hydroxamic acids are

$$R\text{—}\underset{\underset{OH}{|}}{\overset{\overset{}{|}}{C}}\!=\!N\text{—}OH \rightleftharpoons R\text{—}\underset{\underset{O}{\|}}{\overset{\overset{H}{|}}{C}}\text{—}N\text{—}OH$$

The abstraction of a proton with base could thus provide

$$R\text{—}\underset{\underset{A}{}}{\overset{\overset{OH}{|}}{C}}\!=\!N\text{—}O^- \qquad R\text{—}\underset{\underset{B}{}}{\overset{\overset{O\ H}{\|\ |}}{C}}\text{—}N\text{—}O^-$$

$$R\text{—}\underset{\underset{}{}}{\overset{\overset{O^-}{|}}{C}}\!=\!N\text{—}OH \leftrightarrow R\text{—}\underset{\underset{C}{}}{\overset{\overset{O}{\|}}{C}}\text{—}\bar{N}\text{—}OH$$

Although absolute evidence as to which anion (A, B or C) is the reactive species cannot be provided, the *o*-derivatives yield information that enables one to postulate the most probable reactive form.

Examination of data in Table II reveals that a comparable relationship exists between the acidities of the benzohydroxamic acid and phenylpropiolic acid series, but they are quite different from the benzoic acid series. In the benzoic acid series the *ortho* isomer is markedly stronger than the *para* regardless of substituent, whereas in the former

(11) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(12) (a) W. A. Mosher and R. Denison, Annual Progress Report of Research for Chem. Corps, June 15, 1952; (b) J. Esptein, D. H. Rosenblatt and M. M. Demek, THIS JOURNAL, **78**, 341 (1956); (c) T. Wagner-Jauregg, *Arzneimittel-Forsch.*, **6**, 194 (1956).

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cases the *ortho* is weaker than the *para* for the nitro group and stronger than the *para* for the methoxy group. This suggests that structure C would not be the predominant form in the ionization, since this form would be expected to be influenced by *o*-substituents.

TABLE II

pK_a'S OF *o*- AND *p*-SUBSTITUTED BENZOHYDROXAMIC, PHENYLPROPIOLIC AND BENZOIC ACIDS

Substituent	pK_a RCON-HOH	pK_a RC≡C—COOH[a]	pK_a RC≡C—COOH[b]	pK_a RCOOH[c]
C_6H_5–	8.8	3.58	3.24	4.20
o-$NO_2C_6H_4$–	8.2	3.39	2.83	2.17
p-$NO_2C_6H_4$–	8.0	3.26	2.57	3.42
o-$CH_3OC_6H_4$–	8.9	..	3.37	4.09
p-$CH_3OC_6H_4$–	9.0	..	3.44	4.47
o-ClC_6H_4–	..	3.51	3.08	2.92
p-ClC_6H_4–	8.6	3.47	3.07	3.98

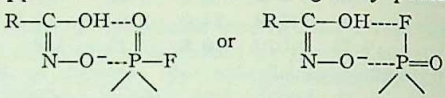
[a] Apparent pK_a's in 50% ethanol–50% water (by volume); Roberts and Carboni.[13] [b] Apparent pK_a's in 35% dioxane–65% water (by weight); Newman and Merrill.[14] [c] pK_a's in water; J. F. Dippy and J. E. Page, *J. Chem. Soc.*, 357, (1938). All pK_a's at 25°.

A linear relationship exists between the logarithms of the ionization constants and reaction rates of *o*-, *m*- and *p*-substituted phenylpropiolic acids with diphenyldiazomethane,[13] whereas ester saponification[13] and acid-catalyzed esterification[14] of *o*-substituted phenylpropiolic acids were faster than would be expected from the relationship between the rates and ionization of the *m*,*p*-substituted acids. This effect was ascribed to a decrease in the reaction site–ring distance, since both esterification and hydrolysis of esters involve attack of a nucleophilic agent at the carbonyl carbon.[13]

Since a linear relationship does exist between the logarithms of the ionization constants and the reaction rates of *o*-, *m*- and *p*-substituted benzohydroxamic acids with Sarin, it seems improbable that structure C is the reactive form because the *o*-substituents do not produce a deviation from linearity that would be expected if reaction occurred close to the ring.

Thus, tautomers A and/or B would appear to be the reactive forms of the anion in both ionization and reaction with electrophilic reagents, since both would take place at a site which is at a maximum distance from the *o*-substituent. However, if the inordinate reactivity of the hydroxamate ion (when compared to simple bases, *i.e.*, OH^-) is due to a concerted attack upon the Sarin molecule in a manner similar to catechol, the most probable reactive form is tautomer A.

Thus the interpretations presented above offer support to the mechanism originally postulated.[12c]



Experimental

Ionization Constants.—The pK_a's reported in Table I were obtained from conventional potentiometric titrations in the presence of 0.1 *M* potassium nitrate. All compounds reported except for *o*-hydroxybenzohydroxamic acid were either sufficiently soluble in water to titrate directly with standard base or stable in alkali so that excess standard base could be added and back titrated with standard acid. Due to the slight decomposition of *o*-hydroxybenzohydroxamic acid in alkali, the value reported is uncertain.

Kinetic Method.—The half-times of hydrolysis of Sarin in the presence of various hydroxamic acids are reported in Table I. The values were obtained by measuring the rate of addition of standard alkali taken up by the reaction mixture when maintained at a fixed *p*H by a Beckman autotitrator. The reaction was carried out as follows: a quantity of the hydroxamic acid was dissolved in 0.1 *M* potassium nitrate solution contained in a jacketed beaker through which water of 30.5 ± 0.2° was circulated from a thermostatically controlled bath. The final concentration of the hydroxamic acid in these experiments was 10^{-3} *M*. The solution was adjusted to *p*H 7.6 and the volume to 245 ml.

A stock solution of 0.65 ml. of Sarin (99% pure) in 100 ml. of water was prepared fresh daily. *Caution* should be exercised since Sarin is *extremely toxic* in both the liquid and vapor phase and must be handled in a hood of large capacity. In the *p*H range of 4 to 6, which the solution assumed, Sarin is resistant to hydrolysis. A 5-ml. aliquot was then added to the hydroxamic acid solution. The final concentration of the solution with respect to Sarin was 10^{-4} *M*. The quantity of standard 0.01 *N* sodium hydroxide delivered by the autotitrator *vs.* time was recorded.

ARMY CHEMICAL CENTER, MD.
NEWARK, DEL.

(13) J. D. Roberts and R. A. Carboni, THIS JOURNAL, **77**, 5554 (1955).

(14) M. S. Newman and S. H. Merrill, *ibid.*, **77**, 5552 (1955).

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Rearrangement and Decarboxylation Reactions of N,N-Dimethylglycine Oxide

BY C. C. SWEELEY AND E. C. HORNING

RECEIVED APRIL 9, 1956

Ferric ion-catalyzed reactions of dimethylglycine oxide were studied in aqueous solution over the *p*H range 2–9. It was found that two modes of N-oxide rearrangement occurred; the products were formaldehyde and sarcosine, and dimethylamine and glyoxylic acid. In addition to these rearrangement reactions, a decarboxylation reaction also occurred, with a maximum rate near *p*H 8. The products of this reaction were carbon dioxide, formaldehyde and dimethylamine; these correspond to the products of oxidative decarboxylation of an α-amino acid.

A preliminary report from this Laboratory described a ferric ion-catalyzed rearrangement reaction of *t*-amine oxides.[1] This rearrangement (reaction A) was presumed to give a carbinolamine (II); the observed reaction products were a secondary amine (through reaction B) and formaldehyde or formic acid and the *t*-amine (reaction C). The products are equivalent to those ex-

(1) M. S. Fish, C. C. Sweeley and E. C. Horning, *Chemistry and Industry*, R. 24 (1956).

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pected from a Polonovski reaction,[2] but the conditions are quite different. The Polonovski reaction is conducted in boiling acetic anhydride and is reported to occur by way of a free-radical mechanism[3]; the mechanism of the ferric ion induced reaction, which occurs in aqueous solution, is unknown.

$$\underset{\text{I}}{RCH_2N(CH_3)_2O} \xrightarrow[H_2O]{Fe^{+++}} \underset{\text{II}}{RCH_2N\begin{matrix}CH_3\\CH_2OH\end{matrix}} \quad (A)$$

$$\text{II} \longrightarrow \underset{\text{III}}{RCH_2NHCH_3} + HCHO \quad (B)$$

$$HCHO + \text{I} \longrightarrow RCH_2N(CH_3)_2 + HCOOH \quad (C)$$

The significance of reaction A lies in its relationship to what is known about biological methylation and demethylation reactions. It is known that the demethylation of drugs,[4] of N-methyltryptophan,[5] and of sarcosine and N,N-dimethylglycine[6] involves an oxidative sequence in which a methyl group is removed as formaldehyde or its cellular equivalent. It is also known that the *de novo* synthesis of the N-methyl groups of N,N-dimethylethanolamine is mediated by a folic acid derivative, in distinction from the methylation reaction which converts dimethylaminoethanol to choline and which requires methionine.[7] The methylation reactions leading to a secondary amine (N-methylethanolamine) and a tertiary amine (N,N-dimethylethanolamine) may require 5-hydroxymethyltetrahydrofolic acid.[8]

The successive steps of oxide formation, oxide rearrangement (reaction A) and hydrolytic cleavage of a methylol intermediate (reaction B) constitute a chemical model for demethylation, and methylation to a secondary or tertiary amine may be represented by the same sequence operating in a reverse direction. An enzyme-catalyzed amino acid oxide rearrangement corresponding to the transformation I → III has been observed[9] with a mouse liver homogenate for *l*-N,N-dimethyltyrosine oxide and *dl*-N,N-dimethyltryptophan oxide. These observations provide evidence that reaction A can occur as a cellular reaction in mammalian tissue, and it therefore seems likely that N-oxides are intermediates in biological methylation–demethylation reactions.

The enzymatic demethylation of N,N-dimethylglycine[6] to sarcosine and the cellular equivalent of formaldehyde is an oxidative sequence in which the amino acid is a normal component of mammalian metabolism.[10] It was therefore desirable to study the ferric ion induced reactions of N,N-dimethylglycine oxide with particular regard to the rearrangement leading to demethylation.

N,N-Dimethylglycine oxide was prepared from N,N-dimethylglycine by hydrogen peroxide oxidation. Its properties resembled those of most known *t*-amine oxides; it was a highly hygroscopic substance which tended to hold both water and hydrogen peroxide. No suitable derivatives were found. The expected relationship of the oxide to the parent amino acid was indicated by quantitative hydrogenation.

The ferric ion-catalyzed rearrangement reaction was studied in detail in two types of systems. Over the *p*H range 1–5 a ferric oxalate complex ion was employed; the results in this system have been summarized.[1] Over the *p*H range 2–9 a ferric tartrato complex ion was employed. Analyses of reaction mixtures were carried out by paper chromatography (system I). This work was aided by the development of an excellent spray procedure for detecting secondary amines in the presence of related tertiary (or primary) amines. The fact that the oxide gave a positive ninhydrin reaction[11] also allowed detection of the oxide in chromatographic analyses. Densitometer graph (B) in Fig. 1 shows a typical result obtained at *p*H 1.5, and this may be compared with (C) and (D) which represent reactions carried out at *p*H 6 and 4, respectively. The secondary amine in zone 1 was eluted from the appropriate zone in preparative runs and was identified as sarcosine by conventional biochemical procedures. Formaldehyde was detected in a usual way.[12] The secondary amine in zone 2 was found to be a volatile organic base whose concentration could be determined by a standard Kjeldahl distillation and titration procedure. The R_f value corresponded to that found for dimethylamine, but it was considered possible that this fraction might include some trimethylamine (arising by decarboxylation of the amino acid oxide to trimethylamine oxide); in separate experiments it was found that trimethylamine and/or trimethylamine oxide were not reaction products, and that therefore a direct decarboxylation to trimethylamine oxide was not occurring. A specific test procedure for glyoxylic acid[13] was applied to reaction mixtures containing the secondary amine of zone 2, and a spray procedure (adapted from the test) was used in chromatographic analyses to detect glyoxylic acid. Both sets of results indicated that glyoxylic acid and dimethylamine appeared simultaneously as reaction products when the rearrangement was carried out at *p*H 4–6; these data indicate that the ferric ion catalyzed reaction for N,N-dimethylglycine oxide occurred along both possible routes.

(2) M. Polonovski and M. Polonovski, *Bull. soc. chim. France*, 1190 (1927), and earlier papers.

(3) V. Boekelheide and D. L. Harrington, *Chemistry and Industry*, 1423 (1955).

(4) B. B. Brodie, J. Axelrod, J. R. Cooper, L. Gaudette, B. N. LaDu, C. Mitoma and S. Udenfriend, *Science*, **121**, 603 (1955).

(5) T. Yoshida and S. Fukuyama, *J. Biochem.* (*Japan*), **34**, 429 (1941).

(6) C. Mackenzie, in "Amino Acid Metabolism," Johns Hopkins University Press, Baltimore, Md., 1955, p. 684.

(7) J. A. Stekol, S. Weiss and E. I. Anderson, THIS JOURNAL, **77**, 5192 (1955).

(8) This tetrahydrofolic acid derivative was proposed as a cellular equivalent for formaldehyde by A. D. Welch and C. A. Nichol (*Ann. Rev. Biochem.*, **21**, 633 (1952)).

(9) M. S. Fish, C. C. Sweeley, N. M. Johnson, E. P. Lawrence and E. C. Horning, *Biochim. Biophys. Acta*, **21**, 196 (1956).

(10) The amino acids of ref. 9 are not known to be cellular components.

(11) *t*-Amine oxides give positive ninhydrin reactions. The nature of the reaction is unknown.

(12) M. S. Fish, N. M. Johnson and E. C. Horning, THIS JOURNAL, **78**, 3668 (1956).

(13) S. Udenfriend, in "Methods of Biochemical Analysis," Vol. II, Elsevier Publishing Co., New York, N. Y., 1954, p. 255.

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$$ON(CH_3)_2CH_2COOH \xrightarrow[pH\ 4\text{–}6]{Fe^{+++}} \begin{cases} \longrightarrow HOCH_2N(CH_3)CH_2COOH \longrightarrow CH_3NHCHCOOH + HCHO \\ \longrightarrow (CH_3)_2NCHOHCOOH \longrightarrow (CH_3)_2NH + \begin{matrix} CHO \\ | \\ COOH \end{matrix} \end{cases}$$

Separate experiments have provided evidence for the enzymatic formation of *t*-amine oxides[14] and for the rearrangement of N,N-dimethyltyrosine oxide and N,N-dimethyltryptophan oxide by an amino acid oxide hydroxytransferase in mouse liver.[10] From these observations, we suggest that the enzymatic demethylation of dimethylglycine described by Mackenzie[6] involves the intermediate steps of N-oxide formation and N-oxide rearrangement. This view is supported by the results presented in this paper for the non-enzymatic demethylation of dimethylglycine oxide, under conditions which approximate those of the cell.

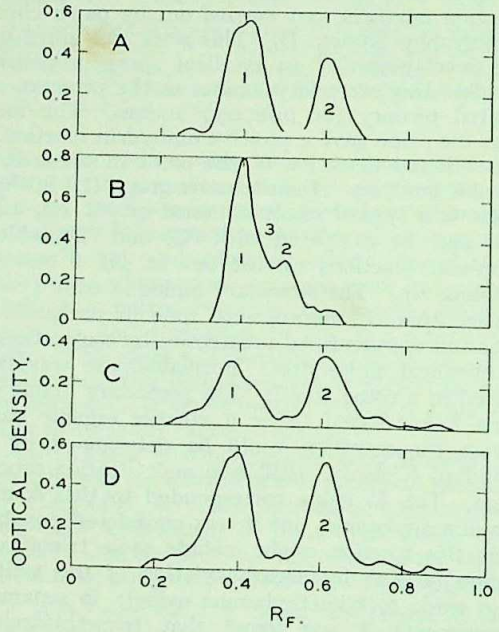

Fig. 1.—Densitometer data: A, reference compounds sarcosine (1), dimethylamine (2); B, sarcosine (1) and N,N-dimethylglycine oxide (2) in rearrangement with oxalic acid (*p*H 1.5), N,N-dimethylglycine-1-C^{14} (3) detected on radioautographs; C, sarcosine (1) and dimethylamine (2) in rearrangement reaction with tartaric acid (*p*H 6); D, sarcosine (1) and dimethylamine (2) in rearrangement reaction with tartaric acid (*p*H 4). The paper chromatograms were developed in *t*-butyl alcohol–acetic acid–water (3:1:1) and sprayed with ninhydrin reagent.

Data relating to a novel decarboxylation reaction of the oxide are in Fig. 2. This reaction was discovered when the possibility of a direct decarboxylation of the oxide to trimethylamine oxide and carbon dioxide was considered. Carbon dioxide was found as a reaction product when the oxide was subjected to ferric ion catalysis above about *p*H 5, but trimethylamine and trimethylamine oxide were found to be absent. A quantitative study of the yields of key reaction products (formaldehyde, dimethylamine and radioactive carbon dioxide) as a function of *p*H was carried out with N,N-dimethylglycine-1-C^{14} oxide. The observation that the increase in carbon dioxide yield, which rose to a maximum near *p*H 8, was paralleled by increasing yields of formaldehyde and dimethylamine, suggests strongly that the decarboxylation may be represented by

$$HO-\overset{\oplus}{N}(CH_3)_2-CH_2-C(=O)-O^{\ominus} \xrightarrow[pH\ 8]{Fe^{+++}} HO^{\ominus} + (CH_3)_2\overset{\oplus}{N}{=}CH_2 + CO_2$$

$$(CH_3)_2\overset{\oplus}{N}{=}CH_2 \xrightarrow{H_2O} (CH_3)_2NH + HCHO$$

The reaction may be represented as a β-elimination in which the concerted separation of carbon dioxide and hydroxide ion is facilitated by formation of a ferric ion–amino acid oxide complex.

In this connection, recent work on the oxidative decarboxylation of amino acids should be mentioned. Spenser, Crawhall and Smyth[15] recently proposed a new reaction pathway to explain the known effects of oxidizing agents on α-amino acids.[16]

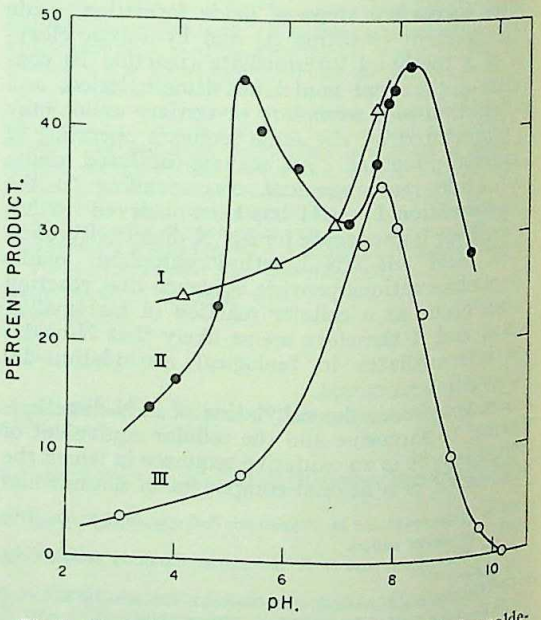

Fig. 2—Variations in yield of dimethylamine (I), formaldehyde (II) and carbon dioxide (III) with *p*H for reactions with ferric-tartrato complex ion at 22–23° for 90 minutes.

(14) M. S. Fish, N. M. Johnson, E. P. Lawrence and E. C. Horning, *Biochim. et Biophys. Acta*, **18**, 564 (1955).

(15) I. D. Spenser, J. C. Crawhall and D. G. Smyth, *Chemistry and Industry*, 796 (1956).

(16) Hypotheses under consideration up to 1934 (including the Wieland–Bergel, the Bergel–Bolz and the Haber–Willstätter proposals) were reviewed by Bergel (*Hoppe-Seyler's Z. physiol. Chem.*, **223**, 66 (1934)). The Herbst–Clarke mechanism is described in *J. Biol. Chem.*, **64**, 93 (1925).

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The new experimental data leading to this proposal included isotope tracer studies which showed that the hydrogen on the α-carbon atom was not involved in the reaction, and oxidation experiments with α-N-diphenylglycine in which a Schiff base was found as the reaction product. The results were interpreted in terms of an oxidative ($OH^{\oplus}$) attack on the α-carbon atom, with concurrent loss of carbon dioxide. The immediate product, a carbinolamine, would then be expected to hydrolyze to an amine and an aldehyde or ketone (the normal products of oxidative decarboxylation of an α-amino acid) or to yield a Schiff base (as found for α,N-diphenylglycine). Data cited by Spenser, Crawhall and Smyth included the fact that the reaction fails for trialkyl (betaine) structures, and that it is successively more effective with substitution on the amino group (through mono and dimethyl stages). The critical point of this hypothesis lies in the assumption that a carbinolamine must be postulated as an intermediate product. The isolation of a Schiff base supports this view only indirectly. Our experimental observations with N,N-dimethylglycine oxide suggest that an alternate explanation should be considered. The reaction may involve oxidative ($OH^{\oplus}$) attack on the amino group, followed by concurrent β-elimination and loss of carbon dioxide, and leading to hydroxide ion, carbon dioxide and a Schiff base as the products. It is not necessary to assume that carbinolamine formation is a prerequisite for Schiff base formation. This explanation is supported by the data of Spenser, Crawhall and Smyth and by the observations in this paper.

The place of oxidative decarboxylation in plant biosynthesis has been reserved by Spenser, Crawhall and Smyth for future discussion. If both oxidative decarboxylation and oxidative demethylation occur as cellular reactions *via* amino acid oxides, it may be possible to demonstrate an enzyme-catalyzed rearrangement reaction for N-oxides. This possibility is under study.

Experimental

N,N-Dimethylglycine hydrochloride was prepared in 84% yield by reductive methylation of glycine with formaldehyde,[17] using Adams platinum catalyst in a low pressure apparatus.

N,N-Dimethylglycine Oxide.—A solution of 0.80 g. of N,N-dimethylglycine hydrochloride in 15 ml. of water was adjusted to *p*H 6 with Amberlite resin (IR-45, hydroxyl phase). The resin was removed by filtration, and 14 ml. of 0.2 *M* barium hydroxide solution and 10 ml. of 15% hydrogen peroxide were added. The solution (*p*H 12) was allowed to stand at room temperature for 1.5 hours (the *p*H dropped to 8). Barium ion was removed as barium sulfate and the filtrate was concentrated under reduced pressure to 5 ml. Ethanol (20 ml.) was added and the solution was again reduced in volume to 2 ml. After the addition of 5 ml. of ethanol, 100 ml. of acetone and 100 ml. of ether, the product was allowed to crystallize. The yield (after washing with ether and drying) was 0.35 g. (40%) of the amino acid oxide.

Anal. Calcd. for $C_4H_9NO_3.0.5H_2O.0.5H_2O_2$: C, 33.10; H, 7.63; N, 9.65. Found: C, 32.95; H, 7.36; N, 9.43.

The oxide was a colorless, highly hygroscopic substance. Repeated preparative runs gave material whose melting points were identical but not sharp (68–73° dec., Kofler).

(17) D. E. Pearson and J. D. Bruton, THIS JOURNAL, **73**, 864 (1951).

The infrared spectra of these samples were identical and different from that of N,N-dimethylglycine (specific bands due to the N-oxide functional group have not been located in N-oxides under study in this Laboratory.[1,9,12] The oxide gave a positive ninhydrin reaction[11] and it was detected in chromatographic analyses in this way. All systems (Table I) gave single, well-defined areas for the oxide. The ionophoresis data (Table II) indicated that the amino acid oxide was a stronger acid than glycine or sarcosine.

TABLE I

PAPER CHROMATOGRAPHIC DATA (R_f VALUES)

Compound	Solvent systems[b] I	II	III	IV
Glycine	0.29	0.49	0.30	..
Sarcosine	.40	.58	.74	0.13
N,N-Dimethylglycine oxide	.52	.70	.95	..
Glyoxylic acid	.25	..	..	..

TABLE II

PAPER IONOPHORETIC DATA[a]

Compound	R_g[b]	Distance (cm.)
Urea	0.10	0.8
N,N-Dimethylglycine oxide	.13	1.0
Sarcosine	.76	6.2
Glycine	1.00	7.9

[a] Conditions: 300 v., 3.5 ma., 4 hours at 22–23°, with 25% aqueous acetic acid as electrolyte. [b] Ratio calculated for distance from origin.

No satisfactory derivatives were found. The chloroaurate, chloroplatinate, picrate and flavianate were not suitable derivatives. The thiouronium salt from *p*-bromobenzylthiouronium bromide retained the generally unsatisfactory physical properties of the oxide.

The formulation of the oxide as a solvate with both water and hydrogen peroxide is in accord with current knowledge of *t*-amine oxide properties. Aliphatic *t*-amine oxides often crystallize with water and/or hydrogen peroxide,[18] and one-half mole equivalent of hydrogen peroxide is not uncommon.[19] In accordance with Bodendorf and Binder,[19] the material was found to liberate iodine from potassium iodide solution. The structure of the oxide was verified by quantitative reduction to N,N-dimethylglycine. A 10-mg. quantity of Pd-C (10%) catalyst in 5 ml. of ethanol was saturated with hydrogen in a micro apparatus for quantitative hydrogenations. A solution of 70 mg. of the oxide in 30 ml. of ethanol was added, and the subsequent hydrogenation required 15.7 ml. (97% of the requirement for reduction of the oxide and peroxide of solvation) of hydrogen. This method is preferred over that of Bodendorf and Binder.[19] The product was isolated as the hydrochloride and it was found to be authentic N,N-dimethylglycine hydrochloride (infrared and m.p. data).

N,N-Dimethylglycine-1-C^{14} oxide was required for decarboxylation studies. It was prepared from N,N-dimethylglycine-1-C^{14} by the usual procedure. The infrared spectrum (Nujol) showed no changes from non-radioactive preparations, and the paper chromatographic and paper ionophoretic behavior showed no changes. The specific activity of the preparation was compared with that of the parent compound, and this was used as an experimental determination of the molecular weight of the solvated oxide: calcd. for formula above, mol. wt., 146; found 146.

Mild heating (to obtain a non-solvated product) resulted in decomposition of the oxide.

Paper Chromatographic Systems and Sprays.—Systems used for the examination of reaction mixtures and for identification of products were: (I) *t*-butyl alcohol–acetic acid–water (3:1:1); (II) propanol–acetic acid–water (10:1:9); (III) phenol–water (4:1);[20] (IV) propanol–1 *N* ammonium hydroxide (5:1). System I gave excellent results in qualitative analyses of reaction mixtures. The time required for separations was usually 16 hours at room temperature (22–23°). The papers were washed Whatman 1 and washed Whatman 3 MM.

(18) C. C. J. Culvenor, *Rev. Pure appl. Chem.*, **3**, 83 (1953).
(19) K. Bodendorf and H. Binder, *Arch. pharm.*, **287**, 326 (1954).
(20) H. K. Berry and L. Cain, *Arch. Biochem.*, **24**, 179 (1949).

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The ninhydrin spray was a 0.2% solution in 50% aqueous pyridine. The strips were heated to develop the colored areas, and the chromatograms were preserved by spraying with a dilute cupric nitrate solution,[21] followed by exposure to ammonia to remove the excess nitric acid.

For secondary amines, the chromatogram was sprayed with a freshly prepared 1% sodium nitroprusside solution containing 10% (v./v.) of acetaldehyde. This was followed immediately by a spray with 2% sodium carbonate solution. A slowly developing deep blue spot on a light pink or colorless background constituted a positive test for secondary amines. This method was a modification of a spot test procedure for detecting secondary amines.[22] It gave no reaction with components of the reaction mixtures other than sarcosine and dimethylamine.

A spray to detect glyoxylic acid was developed from a qualitative test procedure.[13] The paper chromatogram was sprayed with a freshly prepared solution of 1% phenylhydrazine hydrochloride in 0.5 *N* hydrochloric acid. After drying (heat), the paper was sprayed with 3% hydrogen peroxide in 0.5 *N* hydrochloric acid. A red color was formed with glyoxylic acid.

Rearrangement of N,N-Dimethylglycine Oxide. A. Oxalate System.—In a typical experiment, a solution containing 3.0 mg. (20 μmoles) of N,N-dimethylglycine oxide, 200 μmoles of oxalic acid and 60 μmoles of ferric nitrate nonahydrate, in a total volume of 1.3 ml. (*p*H 1.5–2.0), was kept at 60° for 30 minutes. Paper chromatography of 50–100 μg. of organic constituents with system I, followed by a ninhydrin spray, gave a pattern as shown in the densitometer (Photovolt Model 520, 545 mμ filter) graph of Fig. 1B. Similar experiments were run at five intervals in the *p*H range 1–5; above *p*H 2 the yield of sarcosine decreased slowly.

In these experiments, the ferric ion was presumably present as an oxalato complex ion.[23] Above *p*H 5 a slow precipitation of ferric hydroxide interfered with the experiments.

B. Tartrate System.—A solution containing 1.0 mg. (6.9 μmoles) of N,N-dimethylglycine oxide, 40 μmoles of tartaric acid and 2.0 μmoles of ferric nitrate nonahydrate was adjusted to the appropriate *p*H with 10% sodium carbonate solution (final volume of 1.0 ml.). It was heated at 60° for 15 minutes. Paper chromatography, using system I with a ninhydrin spray or a secondary amine spray, was used for qualitative analysis of the reaction mixture. The densitometer records in Fig. 1C-1D were obtained with a ferric ion:oxide ratio of 0.3:1 at *p*H 6.0 and 3.0:1 at *p*H 4.0, respectively. A ninhydrin spray was used for both records.

A series of experiments were run at *p*H 2–11, with heating for 15 minutes at 60°. Visual examination of the chromatograms indicated that for runs in the *p*H range 4–8, all of the oxide was consumed, and approximately the same yield of the two secondary amines was obtained. Below *p*H 4 the yield fell, and unreacted oxide was present. At *p*H 8–9 the yield also fell, and at *p*H 10–11 there was no rearrangement.

The ferric ion was present in these solutions as a tartrato complex ion. When iron tartrate solutions of the concentrations used here were irradiated in the absence of air, an oxidation–reduction reaction occurred, and all of the iron was reduced to the ferrous state (as judged by the complete disappearance of the characteristic yellow color of ferric ion). This reaction may occur during the rearrangement, but its effect was kept at a minimum by using freshly prepared solutions for each experiment. The ferrous–tartrato complex seems to be of no great significance in these reactions. Some oxidation of the tartrate ion (by air or the amine oxide) may also occur.

Identification of Sarcosine and Dimethylamine.—A preparative run was carried through chromatography on Whatman 3MM paper. Zone 1 was eluted (water) and the amine was compared with an authentic sample of sarcosine in four solvent systems. The eluted material, sarcosine, and a mixture were run concurrently; the R_f values are in Table I, together with data for glycine and N,N-dimethylglycine oxide. Chromatographic identity was observed.

A comparison of the reaction product with sarcosine was also carried out by paper ionophoresis on washed Whatman 1 paper with 25% acetic acid as the electrolyte. The data are in Table II, with comparative values for glycine. Ionophoretic identity was observed for the authentic and eluted samples.

The reaction product gave a positive test (blue color) with a secondary amine spray; the test result was identical with that produced by authentic sarcosine.

Dimethylamine was recognized by chromatographic separation (zone 2) in system I, followed by spraying with ninhydrin or the secondary amine reagent (in alkaline systems, the amine is lost by evaporation). With system I, the R_f of dimethylamine was 0.61; chromatograms were run with the reaction mixture, an authentic sample at approximately the same concentration, and a mixture. In all cases the R_f values and the colors with both sprays were identical for these comparative runs. Quantitative determinations were also made as described.

Identification of Glyoxylic Acid.—Reaction mixtures were tested for the presence of glyoxylic acid by a spot test procedure.[13] One drop each of the mixture, 12 *N* hydrochloric acid and a freshly prepared 1% solution of phenylhydrazine hydrochloride were mixed and heated at 80° for 5 minutes. The mixture was chilled and treated with one drop each of 12 *N* hydrochloric acid and 3% hydrogen peroxide. An intense red color constituted a positive test. Blank runs, omitting the oxide, gave faint pink colors.

This procedure was modified for use as a spray, and in system I it was found that authentic glyoxylic acid (prepared from dichloroacetic acid)[24] and the reaction mixture gave corresponding colored areas (R_f 0.25).

Formaldehyde and Formic Acid Tests.—These were carried out as described in a previous study of the rearrangement of N,N-dimethyltryptamine oxide.[12] With a Fe^{+++} to oxide ratio of 0.03:1, it was found possible to detect formaldehyde directly in the reaction mixture by a chromotropic acid color test.

Metal Ions.—With two sets of standard conditions (a) an oxalate system at *p*H 2 with a metal ion to oxide ratio of 3:1, and (b) a tartrate system at *p*H 5–6 with a metal ion to oxide ratio of 0.3:1, it was found that Co^{++}, Ni^{++}, Cu^{++}, Mg^{++} and Cr^{+++} were without catalytic effect. No reaction was observed in a tartrate system at *p*H 4–6 with $[Fe(CN)_6]^{---}$ or an 8-hydroxyquinoline-5-sulfonic acid complex with ferric ion. With Fe^{++} in a 3:1 ratio, and with a tartrate system at *p*H 5, the oxide reacted as usual and the two amine products were observed in normal yield.

Quantitative Determination of Products.—In a series of experiments, conducted at 23° for 90 minutes with a 0.6:1 mole ratio of ferric ion to oxide, the *p*H of the reaction was varied. Formaldehyde, dimethylamine and carbon dioxide were determined quantitatively. The results are shown in Fig. 2.

A. Determination of Formaldehyde.—In a typical experiment, 1.0 mg. (6.9 μmoles) of N,N-dimethylglycine oxide in 1.0 ml. of water was adjusted to *p*H 5.0 with 0.1 *N* sodium hydroxide solution. A solution (1.0 ml.) of tartaric acid (50 μmoles) and ferric nitrate nonahydrate (4 μmoles) was adjusted to *p*H 5.0 with 0.1 *N* sodium hydroxide and was added to the solution of the oxide. After 90 minutes at 23° the reaction mixture was pipetted into a 50-ml. flask fitted with a distilling head and condenser. The solution was acidified with 2.0 ml. of 8.5% phosphoric acid and the mixture was distilled at atmospheric pressure into 1.0 ml. of ice-water. The tip of the condenser was immersed in the ice-water. An additional 3.0 ml. of water was added to the residue and distillation was repeated, collecting 7.0 ml. of distillate in all. Formaldehyde was determined on an aliquot of the distillate by a modified Hantzsch reaction with acetylacetone and ammonium acetate.[25] Optical density measurements were made with a Beckman DU spectrophotometer.

B. Determination of Dimethylamine.—A solution of oxide (13.7 μmoles), tartaric acid (100 μmoles) and ferric nitrate nonahydrate (8.0 μmoles), adjusted to *p*H 4.5 as described in the previous section for formaldehyde determination, was allowed to stand at 23° for 90 minutes. The solution was pipetted into a Kjeldahl still with 8.0 ml. of 20% sodium hydroxide solution. The volatile base was steam distilled for 4 minutes into 5.0 ml. of 5% boric acid

(21) R. J. Block, E. L. Durrum and G. Zweig, "A Manual of Paper Chromatography and Paper Electrophoresis," Academic Press, New York, N. Y., 1955, p. 90.

(22) Ref. 13, p. 191.

(23) N. V. Sidgwick, "Chemical Elements and their Compounds," Oxford University Press, 1951, p. 1260.

(24) O. Doebner, *Ann.*, 311, 129 (1900).

(25) T. Nash, *Biochem. J.*, 55, 416 (1953).

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May 20, 1957

containing 3 drops of methyl red (0.1%)–brom cresol green (0.1%) indicator. The dimethylamine was determined by titration of the boric acid solution with 0.01 *N* hydrochloric acid.

In separate experiments, the volatile organic base fraction was examined for the presence of trimethylamine by the sensitive quantitative procedure of Cromwell.[26] Trimethylamine was not present. The oxide of trimethylamine was prepared; it gave a positive ninhydrin reaction[11] and it was found to be absent in chromatographic analyses of reaction mixtures at *p*H 4–8.

C. Determination of Carbon Dioxide.—A reaction mixture (*p*H 7.0), containing N,N-dimethylglycine oxide-1-C^{14} (6.9 μmoles), tartaric acid (50 μmoles) and ferric nitrate nonahydrate (4 μmoles), was prepared in the usual way and allowed to react for 90 minutes at 23° in a flask connected to a sodium hydroxide trap. The solution was acidified with 1.0 ml. of 8.5% phosphoric acid and the system was flushed with nitrogen for 15 minutes. The carbon dioxide collected in the sodium hydroxide trap was counted[27] as barium carbonate. Runs at other *p*H values were made in the same way.

N,N-Dimethylglycine hydrochloride-1-C^{14} (7.1 μmoles) and glyoxylic acid (400 μmoles) gave no carbon dioxide under similar conditions (catalyst, tartrate, 23°, 90 minutes).

D. *p*H Effects.—Over the *p*H region where decarboxylation was the primary reaction it was observed that the *p*H rose as the reaction proceeded. Initial and final *p*H values were averaged to locate the points near *p*H 8 in Fig. 2.

(26) B. T. Cromwell, *Biochem. J.*, **46**, 578 (1950).

(27) C. V. Robinson, *Science*, **112**, 198 (1950).

BETHESDA, MD.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF IOWA STATE COLLEGE]

Some Reactions of *o*-Halophenyllithium Compounds

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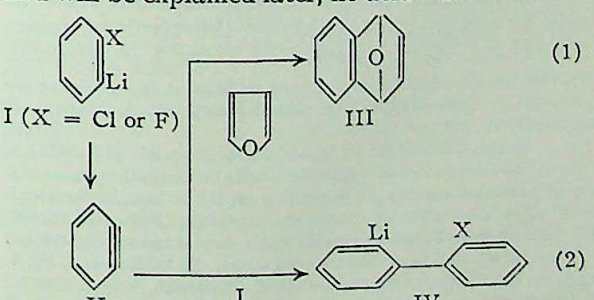
When *o*-chloro- and *o*-fluorophenyllithium are prepared at −90 and −60°, respectively, in the presence of furan and then carbonated, the main product is 1,4-dihydronaphthalene-1,4-endoxide (III) while the corresponding 2-carboxy-2′-halobiphenyl (IV) is obtained in small yields. *o*-Dibromobenzene and *n*-butyllithium in the presence of furan also give III under modified conditions. Only III is obtained when an RLi is added to a mixture of the *o*-bromohalobenzene and furan at a temperature above that at which the *o*-halophenyllithium compound is stable. Methyllithium and phenyllithium are equally effective in reacting with an *o*-halobromobenzene in the presence of furan to give excellent yields of III. 2-Chloro-2′-(triphenylsilyl)-biphenyl has been synthesized and compared with the bromo-isomer prepared by a less ambiguous method. The results are discussed and correlated.

As a continuation of some of our earlier studies concerned with *o*-halophenyllithium compounds,[1] we have investigated further some of their reactions and possible routes by which these organometallic compounds couple to form new organolithium compounds. In order to obtain a better understanding of the various transformations, the elegant procedure of Wittig and Pohmer[2] was employed in this present work. These workers successfully interacted *o*-bromofluorobenzene with lithium amalgam in furan to obtain 1,4-dihydronaphthalene-1,4-endoxide (III), a strained molecule which has been formulated as arising *via* a Diels–Alder reaction between furan and the benzyne intermediate (II). Furthermore, the reactive species II has been postulated as being formed from *o*-fluorophenyllithium after the latter has been generated by the interaction of *o*-bromofluorobenzene and lithium amalgam.[3] In view of these results it was hoped that furan could be used in a similar fashion to trap any intermediate which might arise during the break-down of *o*-halophenyllithium compounds (I). *o*-Fluoro- and *o*-chlorophenyllithium were prepared at −60 and −90°, respectively. A relatively large excess of furan was added in each case and then the mixtures were allowed to warm to −50° for the chloro-isomer and −10° for the fluoro-isomer. Since Color Test I[4] was positive in both cases at these temperatures, the mixtures were carbonated. The run involving *o*-bromochlorobenzene afforded 41% of III and 11% of 2-carboxy-2′-chlorobiphenyl; with *o*-bromofluorobenzene the yield of III was 67% while 4% of 2-carboxy-2′-fluorobiphenyl was isolated.

A modified procedure was used with *o*-dibromobenzene since it was found in previous studies that *o*-bromophenyllithium is a short-lived intermediate.[1] Consequently, *o*-dibromobenzene was added to a mixture of furan and butyllithium. The yield of III was 68%; however, as might be expected and will be explained later, no acid was isolated.



From the foregoing results it is clear that in the case of *o*-chloro- and *o*-fluorophenyllithium some reactive intermediate is competitively reacting with furan and with I. Furthermore, evidence substantiates that such a competitive reaction occurs only when the organolithium compound is formed first independently of the other reactants. In order to ascertain that no metalation reaction

(1) H. Gilman and R. D. Gorsich, THIS JOURNAL, **78**, 2217 (1956); this reference contains a general survey of relevant literature citations.

(2) G. Wittig and L. Pohmer, *Angew. Chem.*, **67**, 348 (1955). See also G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1950), for details about which we have just learned, after returning proof, of study mentioned in their prior communication.

(3) It is interesting to note that the same reaction in the absence of furan gives diphenylene and triphenylene; G. Wittig and W. Herwig, *Ber.*, **87**, 1511 (1954).

(4) H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).

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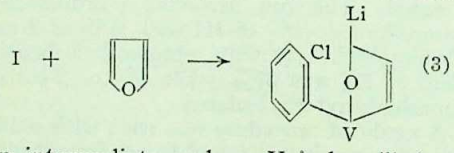
ensued between furan and I followed by another similar metalation between the halobenzene and 2-furyllithium at a warmer temperature, an attempt was made to metalate chlorobenzene under conditions used for the competitive reactions. No acid was detected after carbonation; most of the chlorobenzene was recovered.

At this time the most plausible explanation for the presence of coupling product in the competitive reaction is one involving II, although an alternate explanation has been proposed recently for a related reaction.[5] Intuitively the halide in I would not be expected to be displaced by a nucleophile because the high electron density in the position adjacent to the chlorine atom should hinder such an approach. Also, nucleophilic aromatic substitution reactions are facilitated by electron-withdrawing groups and not electron-donating substituents.[6] It is conceivable the anion of I may displace the halogen in another molecule of I either just before or during the formation of the reactive intermediate II.[7]

The rapid conversion of *o*-bromophenyllithium to II did not allow its preparation prior to the addition of furan, and, as a result, the concentration of *o*-bromophenyllithium probably was so slight that the main reaction was between II and furan.

The reaction path leading to III might involve a nucleophilic attack of I on furan or the more likely reaction of II with furan. Of the two possibilities, it appears better to rationalize on the basis of II being the key intermediate. If I is considered as being the attacking species, a reaction path (3) might be expected. Evidence indicates



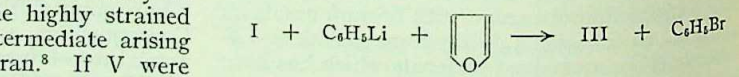
(3)

that an intermediate such as V is less likely to undergo ring closure to give the highly strained molecule III than would an intermediate arising from interaction of II with furan.[8] If V were formed as an intermediate, ring closure at such a low temperature would be doubtful in view of polar effects and formation of the strained molecule III.[6,9] The formation of V *via* I is unprecedented since there is no known instance wherein furan is attacked in such a manner. In fact under these conditions furan is inert to such an attack, and at warmer temperatures the only product formed is 2-furyllithium.[10]

On the basis of the aforementioned discussion wherein II has been visualized as the intermediate in the various reactions, it would be expected that if compound I were generated at a temperature above that at which it is stable, the concentration of I would be negligible and no coupling product (IV) should be detected. This has been verified by adding butyllithium to a mixture of furan and an *o*-bromohalobenzene at temperatures considerably higher than those at which the stability of I has been well-established. For example, when butyllithium is added to a mixture of *o*-bromochlorobenzene and a large excess of furan, only III has been isolated. No acids were found to be present. The same was found to be true for the fluoro- and bromo-isomers, although in the latter case the results are not as significant as for the former two.

Organolithium compounds other than butyllithium have been found equally suitable if not somewhat superior for generating the reactive species II at moderate temperatures. A 75% yield of III has been obtained with phenyllithium while with methyllithium yields up to 84% of III have been isolated. This is surprising because, in the past, methyllithium has been found to be very ineffective in halogen–metal interconversion reactions.[11] The unusual effectiveness in this case may be attributed to the formation of the highly reactive intermediate II.

In order to substantiate that a halogen–metal interconversion reaction was the initial step in the reaction between *o*-bromochlorobenzene and phenyllithium, the latter compound was synthesized from iodobenzene and lithium. Recovery of



bromobenzene in a good yield supports the above proposal. No attempt was made to recover methyl bromide when methyllithium was used.

A reaction between *o*-dichlorobenzene and butyllithium in the presence of furan was unsuccessful. Carbonation, after stirring at room temperature for 1 hr., afforded only 2-furoic acid. It is conceivable that conditions might be varied so as to effect a reaction since there is evidence that a reaction occurs between butyllithium and *o*-dichlorobenzene in the absence of furan.[13]

Recent related work can be correlated with the results in this communication together with pre-

(5) An ion-pair mechanism has been formulated in explaining the interaction of chlorobenzene with sodium amide; A. A. Morton, *J. Org. Chem.*, **21**, 593 (1956).

(6) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 273 (1951).

(7) It has been shown that benzyne can be formed either *via* a stepwise or concerted mechanism depending on the halogen being eliminated when metalation reactions are involved. However, in this case these findings do not necessarily apply since it cannot be assumed that the initial step is similar in both cases; J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, THIS JOURNAL, **78**, 601 (1956); see also, J. D. Roberts, C. W. Vaughan, L. A. Carlsmith and D. A. Semenow, *ibid.*, **78**, 611 (1956).

(8) In distinguishing between the two paths, it is not pertinent whether the interaction of benzyne with furan is a polar reaction or a four-center-type reaction. Since there is no sharp line between the latter two types of reaction mechanisms, it is difficult to rationalize by which one the benzyne interacts with furan; J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp. 450–461.

(9) Previous studies (ref. 1) showed that an intermediate such as 2-(*o*-chlorophenyl)-2′-lithiobiphenyl does not undergo ring closure below approximately −50° to give the planar, non-strained system, triphenylene.

(10) In general, metalation reactions proceed smoothly only at room temperature or higher when diethyl ether is the solvent; H. Gilman and J. W. Morton, Jr., "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, Chap. 6.

(11) Methyllithium interconverts only with very reactive halides such as *o*-bromoanisole. Phenyllithium is generally more effective but has the disadvantage of occasionally participating in side-reactions (ref. 12).

(12) R. G. Jones and H. Gilman, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 343.

(13) R. D. Gorsich, unpublished studies.

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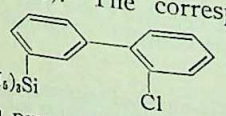
vious findings.[1] In the related work, 2,2′-diiodobiphenyl has been postulated as an intermediate in the reaction of *o*-diiodobenzene with butyllithium and lithium in non-polar solvents.[14] It is unlikely that *o*-iodophenyllithium would be present as such in any appreciable concentration in view of the instability of *o*-bromophenyllithium at −110°, and, especially since a refluxing mixture of benzene and petroleum ether (b.p. 40–60°) was employed. Since the *o*-diiodobenzene was added to butyllithium, an intermediate such as 2-iodo-2′-lithiobiphenyl (formed according to scheme 2) would be expected to react further with butyllithium to give 2,2′-dilithiobiphenyl.[15] The latter, in turn, could interact with two equivalents of II to give 2,2′-bis-(*o*-lithiophenyl)-biphenyl. This compound could partially couple with butyl iodide, formed during the interconversion reaction, to give 2,2′-bis-(*o*-*n*-butylphenyl)-biphenyl.[16] The remaining organodilithium compound would give the corresponding acid after carbonation. When lithium interacted with *o*-diiodobenzene, the major product was triphenylene. This is not too surprising since it is quite possible that in this case the intermediate, 2-iodo-2′-lithiobiphenyl, would tend to react preferentially with II instead of with lithium, and as a result one would get 2-(*o*-iodophenyl)-2′-lithiobiphenyl, a type of molecule which has been shown to undergo readily ring closure to yield triphenylene.[10]

Caution should be exercised in interpreting all reactions of *o*-bromohalobenzenes with RLi compounds as proceeding *via* the benzyne intermediate. Recent investigations infer that the solvent plays an important role in the reaction of a bromohalobenzene with an RLi compound. For example, it has been found in this Laboratory that two equivalents of *o*-dibromobenzene in tetrahydrofuran interact with one equivalent of butyllithium to give good yields of 2,2′-dibromobiphenyl. Apparently, *o*-bromophenyllithium couples with *o*-dibromobenzene rather than pass through the benzyne intermediate.[17]

2-Chloro-2′-(triphenylsilyl)-biphenyl has been prepared by allowing an ethereal solution of *o*-chlorophenyllithium to warm in the presence of triphenylchlorosilane. A small amount of triphenylene was isolated also. The former compound probably is formed *via* the organolithium compound (IV, X = Cl). The corresponding



bromo-isomer has been prepared in a less ambiguous manner by means of a monohalogen–metal interconversion reaction between 2,2′-dibromobiphenyl and butyllithium followed by reaction with triphenylchlorosilane. The infrared spectra of the two compounds compared favorably.

Experimental[18]

Reactions of *o*-Halophenyllithium Compounds in the Presence of Furan. (a) ***o*-Chlorophenyllithium.**—The *o*-chlorophenyllithium was prepared at −90° by adding a pre-cooled solution of 19.16 g. (0.10 mole) of *o*-bromochlorobenzene in 25 ml. of dry diethyl ether, during 17 min., to 80 ml. of a stirred ethereal solution containing 0.10 mole of *n*-butyllithium[19] and cooled to −100° by means of an ethanol–ether–liquid nitrogen slurry.[1] The temperature was not allowed to rise above −90° during the addition. After stirring the reaction mixture at −90° for 45 min., 48 g. of redistilled furan (Eastman) was added, and then the resulting solution was stirred between −75 and −70° for 10 min. The mixture was allowed to warm further to −50°, becoming quite milky at −65°. The reaction mixture then was stirred for 2.5 hr. at the minimum temperature afforded by a Dry Ice–acetone-bath. Subsequently the mixture was cooled to −95° and carbonated by adding powdered Dry Ice. The reaction mixture was allowed to warm to room temperature, whereupon, hydrolysis was effected with water. The aqueous layer was separated from the organic layer and was warmed to expel dissolved ether, cooled and then acidified with sulfuric acid. A brown precipitate was filtered, dissolved in ethanol, decolorized with Norit-A and then water was added slowly until the solution was slightly cloudy. On cooling, there crystallized 0.53 g. of acid melting at 139–140°. A mixed melting point with an authentic sample of 2-carboxy-2′-chlorobiphenyl obtained previously[1] showed no depression.

The organic layer was extracted with three 50-ml. portions of 5% sodium hydroxide. Acidification of the basic extract and subsequent work-up left an oil which crystallized after standing for 2 weeks. This material then was extracted with 5% sodium bicarbonate and after acidification with concentrated hydrochloric acid, there was deposited 0.72 g. of acid melting at 137–139°. The total yield of 2-carboxy-2′-chlorobiphenyl was 1.25 g. (10.7%).

The neutral organic layer was dried over anhydrous sodium sulfate, and the solvent was allowed to slowly evaporate. The resulting crystalline material was sublimed at room temperature (*ca.* 25°) and 0.005 mm. to yield 5.84 g. (40.6%) of product melting at 54–55°. The reported melting point of 1,4-dihydronaphthalene-1,4-endoxide is 55–56°.[2]

The adduct was cleaved by passing hydrogen chloride into a methanolic solution containing 2.0 g. (0.0139 mole) of 1,4-dihydronaphthalene-1,4-endoxide (III) and refluxing for about 3 hr.[2] The yield of α-naphthol melting at 94–95° was 1.61 g. (80%). A mixed melting point with an authentic specimen showed no depression.

(b) ***o*-Fluorophenyllithium.**—The *o*-fluorophenyllithium was prepared in accordance with a procedure described previously[1] from 10.0 g. (0.057 mole) of *o*-bromofluorobenzene in 30 ml. of ether and 40.5 ml. of an ethereal solution containing 0.057 mole of *n*-butyllithium at approximately −60°. To the organolithium solution cooled to about −70° was added 49 g. of redistilled furan. The temperature was not allowed to rise above −60° during the furan addition. The reaction mixture was allowed to warm slowly to −50° and was maintained between −50 and −45° for 10 min.; between −45 and −40° for 10 min.; between −35 and −30° for 10 min.; between −30 and −25° for 10 min.; and, between −15 and −10° for 25 min. Since Color Test I was positive, the reaction mixture was cooled to −65° and then poured jet-wise into a slurry of Dry Ice and ether. The carbonated mixture was worked up as described in the preceding experiment. Acidification of

(14) H. Heaney, F. G. Mann and I. T. Millar, *J. Chem. Soc.*, 1 (1956).

(15) Iodides are very reactive in interconversion reactions; see ref. 7.

(16) Alkyl iodides are more prone to be involved in coupling reactions than are other halides. For example, methyl iodide couples with 1-naphthyllithium to give a good yield of 1-methylnapthalene; H. Gilman and F. W. Moore, THIS JOURNAL, **62**, 1843 (1940); see, also, H. Gilman, C. G. Brannen and R. K. Ingham, *J. Org. Chem.*, **22**, in press (1957).

(17) This same type of reaction can be applied also to other bromohalobenzene isomers, *e.g.*, *p*-bromochlorobenzene yields 4,4′-dichlorobiphenyl. The latter reaction excludes the possibility of II being an intermediate in reactions carried out in tetrahydrofuran; H. Gilman and B. Gaj, *J. Org. Chem.*, **22**, in press (1957).

(18) All reactions involving organometallic compounds were carried out in a dry, oxygen-free nitrogen atmosphere and all melting points are uncorrected. The infrared spectra were run on a Baird Associates double beam infrared spectrometer in the sodium chloride region.

(19) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, THIS JOURNAL, **71**, 1499 (1949). The yield of butyllithium was determined according to a procedure described by H. Gilman and A. H. Haubein, *ibid.*, **66**, 1515 (1944).

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the aqueous layer left needle-like crystals. These were combined with similar crystals obtained by acidification of the basic solution obtained after extracting the organic layer with 5% sodium hydroxide. Recrystallization of the 2-carboxy-2′-fluorobiphenyl from a mixture of ethanol and water yielded 0.23 g. (3.7%) of product melting at 138–140°. A mixed melting point with an authentic sample[1] of the acid showed no depression.

The organic layer on work-up as described above yielded a crystalline material which was sublimed at room temperature and 0.003 mm. to yield 5.49 g. (67%) of III melting at 54–55°.

(c) **o-Bromophenyllithium.**—A solution of 13.5 g. (0.057 mole) of *o*-dibromobenzene in 20 ml. of ether was added dropwise, during 15 min., to 70 ml. of an ethereal solution containing 0.057 mole of *n*-butyllithium and 61.5 g. of furan cooled to −110° by means of an ethanol–ether–liquid nitrogen slurry. The temperature remained between −110 and −100° during the addition. The reaction mixture was stirred at −65° for 1 hr., and, although Color Test I was negative, carbonation was effected in the same manner as described for *o*-chlorophenyllithium. Following the usual work-up no acid was isolated from the aqueous layer.

The crude adduct obtained from the organic layer was purified by sublimation at 45° and 0.005 mm. to yield 5.60 g. (68%) of pure III melting at 54.5–55.5°.

Addition of RLi to a Mixture of Furan and *o*-Bromohalobenzene. (a) ***n*-Butyllithium and *o*-Bromofluorobenzene.**—To a rapidly stirred solution of 7.00 g. (0.04 mole) of *o*-bromofluorobenzene in 15 ml. of ether and 41 g. of furan was added 30 ml. of an ethereal solution containing 0.042 mole of *n*-butyllithium. The addition funnel containing the *n*-butyllithium was jacketed and cooled by means of Dry Ice and acetone. The temperature of the reaction mixture was maintained between −30 and −25° during the addition which required 15 min. Color Test I was negative on completion of the addition. The mixture was warmed to −20° and poured into water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and finally the ether and excess furan were distilled on a steam-bath. A small amount of *n*-butyl bromide was distilled under reduced pressure, and the remaining material was sublimed at room temperature and 0.003 mm. to yield 3.90 g. (68%) of III.

The results of the interaction of *n*-butyllithium with the *o*-chloro- and *o*-bromo-isomers are given in Table I.

(c) **Phenyllithium and *o*-Bromochlorobenzene.**—The phenyllithium was prepared by adding a solution of 11.3 g. (0.055 mole) of iodobenzene in 60 ml. of ether to a suspension of 12.1 g. of lithium wire cut into small pieces and contained in 100 ml. of ether. The mixture was cooled with an ice-bath during the addition which required 2.5 hr. The mixture was stirred in the ice-bath for 2 hr. after the addition was complete and at room temperature for another 2 hr. After concentrating the mixture to 45 ml., a single acid titration indicated the yield to be 0.053 mole; 25 ml. of this solution was added, during 7 minutes, to a stirred solution of 5.75 g. (0.03 mole) of *o*-bromochlorobenzene in 10 ml. of diethyl ether and 31 g. of furan, while maintaining the temperature between −25 and −30°. The mixture was stirred at −30° for 25 min. and then was hydrolyzed with water. The two layers were separated and the organic layer was worked up in the usual manner. After distilling the ether and excess furan, the remaining material was distilled at 155–160° (745 mm.) to give 3.33 g. (71%) of bromobenzene, n^{20}D 1.5585. The infrared spectrum was identical with that of a pure sample of bromobenzene.

Because of the high bath temperature (230°) encountered during the distillation, the adduct was converted to a dark brown material from which a trace of α-naphthol was sublimed. No other material was identified.

Three grams of III was refluxed under nitrogen for 4 hr. No adduct was recovered and the resulting product was a brown material very similar to the above material.

Attempted Metalation of Chlorobenzene in Furan with Butyllithium.—Twenty-two milliliters of an ethereal solution containing 0.03 mole of butyllithium was added, during 5 min., to a stirred solution of 3.48 g. (0.03 mole) of chlorobenzene in 15 ml. of diethyl ether and 30 g. of furan. The addition was carried out between −35 and −40° and was stirred at −30° for an additional 30 min. on completion of the addition. The mixture was cooled to −60° and carbonated in the usual manner. The aqueous layer on acidification, extraction with ether, and sublimation of the resulting solid gave 0.33 g. of 2-furoic acid, m.p. 130–132°. After distillation of solvent from the organic layer, there was obtained 2.06 g. (60%) of unreacted chlorobenzene. No Diels–Alder adduct was isolated.

2-Chloro-2′-(triphenylsilyl)-biphenyl.—An ethereal solution containing 0.10 mole of *o*-chlorophenyllithium was prepared at −70° in accordance with an earlier procedure. After stirring the organolithium solution at −70° for 1 hr., 10 g. (0.034-mole) of triphenylchlorosilane in 90 ml. of ether was added, and the reaction mixture was allowed to slowly warm to room temperature. Three hours after completion of the addition Color Test I was positive. Subsequently an additional 4.73 g. of triphenylchlorosilane in 25 ml. of ether was added, and then the mixture was allowed to stir at room temperature for 10 hr. The mixture was hydrolyzed with 5% hydrochloric acid. The ethereal layer was separated, dried over anhydrous sodium sulfate and the ether was distilled. The residue was suspended in warm petroleum ether (b.p. 60–70°) and the white solid (mostly triphenylsilanol) was filtered off. The filtrate was chromatographed on a column of alumina. Elution was effected with 100 ml. of petroleum ether followed by 400 ml. of a 1:1 mixture of petroleum ether and benzene. The white solid was then chromatographed on the same column and was eluted with a 1:1 mixture of petroleum ether and benzene. A total of

TABLE I

REACTIONS OF *o*-XC_6H_4Br WITH RLi IN THE PRESENCE OF FURAN

Run	Halide[a]	Halide, mole	RLi[b]	Temp., °C.[c]	Furan, g.[d]	Addn. time, min.	Yield of 1,4-dihydronaphthalene-1,4-endoxide, %
1	*o*-ClC_6H_4Br	0.042	*n*-C_4H_9Li	−40[e]	41	15[f]	64
2	*o*-BrC_6H_4Br	.042	*n*-C_4H_9Li	−50[e]	41	12[f]	80
3	*o*-ClC_6H_4Br	.026	CH_3Li	−20	30	10[g]	84
4	*o*-BrC_6H_4Br	.032	CH_3Li	−35	35	10[h]	77
5	*o*-FC_6H_4Br	.026	C_6H_5Li[i]	−30[j]	29	10	74[k]

[a] RLi was added to the halide in every run. [b] Equivalent amount of RLi was used in all runs. [c] Temperature during the addition of the RLi. [d] In all runs 15 ml. of dry diethyl ether was admixed with the furan. [e] Mixture warmed to −10° before hydrolyzing with water. [f] Negative Color Test I after addition. [g] Mixture warmed to −10° and carbonated after 10 min. [h] Color Test I was positive on completion of the addition. A negative Color Test I resulted after warming to −10°. The mixture was hydrolyzed with water. [i] C_6H_5Li prepared from C_6H_5Br. [j] Warmed to −20° before hydrolysis. [k] Recovered 1.18 g. (30%) of C_6H_5Br, n^{20}D 1.5578.

(b) **Methyllithium and *o*-Bromofluorobenzene.**—Nineteen milliliters of an ethereal solution containing 0.026 mole of methyllithium[20] was added during 7 min. to a rapidly stirred solution of 4.38 g. (0.025 mole) of *o*-bromofluorobenzene in 15 ml. of ether and 29 g. of furan. The temperature of the reaction mixture during the addition was maintained between −10 and −12°. The reaction mixture was carbonated and worked up as described previously. No acid was found in the acidified aqueous layer. The organic layer was worked up as usual, and the crude adduct was sublimed at room temperature and 0.003 mm. to yield 3.01 g. (84%) of III.

The results of the interaction of methyllithium with the *o*-chloro- and *o*-bromo- isomers are summarized in Table I.

(20) W. J. Hickinbottom, A. A. Hyatt and M. B. Sparke, *J. Chem. Soc.*, 2533 (1954).

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9 fractions was collected. The oil from the second fraction when washed with ethanol gave a white solid which was crystallized from ethyl acetate to give 0.15 g. of tetraphenylsilane, identified by means of a mixed melting point with an authentic sample. Removal of the solvent from the third fraction left a yellow paste which was refluxed in petroleum ether. There was isolated 1.4 g. (13%) of product melting at 149–152°. Two additional crystallizations gave an analytical sample of 2-chloro-2′-(triphenylsilyl)-biphenyl melting at 157.5–158.5°.

Anal. Calcd. for $C_{30}H_{23}ClSi$: Si, 6.28. Found: Si, 6.23, 6.27.

Fraction four gave 0.25 g. of pale yellow plates melting at 194–196°. A mixed melting point with an authentic sample of triphenylene showed no depression.

2-Bromo-2′-(triphenylsilyl)-biphenyl.—A solution of 25 ml. (0.032 mole) of butyllithium was added over a period of 6 min. to a rapidly stirred solution of 10 g. (0.032 mole) of 2,2′-dibromobiphenyl in 100 ml. of dry ether. A temperature of −20° was maintained during the addition. After completing the addition, the mixture was stirred at −15° for 45 min. Subsequently 9.44 g. (0.032 mole) of triphenylchlorosilane dissolved in 85 ml. of ether was added at −15°, and the mixture was allowed to warm to room temperature. The mixture was stirred overnight at room temperature and then was refluxed for 7 hr. after which time Color Test I was positive. After adding 100 ml. of *n*-heptane, the resulting mixture was distilled until an internal temperature of 70° was reached, whereupon a negative color test was obtained after 20 min. The mixture was hydrolyzed with water. An insoluble material was filtered and crystallized from ethanol to give colorless needles, 1.92 g., m.p. 152–153°. Work-up of the filtrate as described in the preceding experiment yielded an additional 1.81 g. of product, m.p. 147–149°. The total yield of 2-bromo-2′-(triphenylsilyl)-biphenyl was 3.73 g. (24%). The analytical sample melted at 152.5–154°.

Anal. Calcd. for $C_{30}H_{23}BrSi$: Si, 5.71. Found: Si, 5.63, 5.45.

The infrared spectrum of the bromo-isomer as a carbon disulfide solution was very similar to that of the chloro-isomer, thus indirectly confirming the structure of the latter.

Acknowledgments.—The authors wish to express their appreciation to the Materials Laboratory, Wright Air Development Center, Wright–Patterson Air Force Base, Ohio, for financial assistance. They also are grateful to the Institute for Atomic Research, Iowa State College, and Mr. E. Miller Layton for assistance in the infrared determinations.

AMES, IOWA

[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Reactions of Trichloromethyl-1,3,5-triazine Derivatives with Amines[1]

BY ALFRED KREUTZBERGER

RECEIVED SEPTEMBER 19, 1956

A method has been found which, by means of amines, permits the replacement by NHR-groups of all trichloromethyl groups attached to a 1,3,5-triazine ring. Use of diamines leads to longer chains of higher molecular 1,3,5-triazine compounds. In 1,3,5-triazine derivatives bearing both trichloromethyl and carbethoxy groupings, ammonia reacts first of all with one trichloromethyl group.

As is well known, the trichloromethyl groups of several organic compounds like chloral, trichloroacetic acid, trichloroacetone and others are split off upon reaction with alkali to form anions[2] which then, by combining with a proton, form chloroform. In connection with investigations on trichloromethyl-1,3,5-triazines,[3,4] especially 2-methyl-4,6-bis-trichloromethyl-1,3,5-triazine (I) and 2-phenyl-4,6-bis-trichloromethyl-1,3,5-triazine (II),[5] it was desirable to know whether these compounds reacted with bases analogously. The various replacement reactions of trichloromethyl groups attached to the 1,3,5-triazine ring by NHR-groups are described in the present article, along with some comparable observations on carbethoxytrichloro-1,3,5-triazines.

In the reaction of I or II with concentrated aqueous ammonia, only one of the two trichloromethyl groups turned out to be replaceable by the NH_2-group under very mild conditions, thus yielding 2-methyl-4-amino-6-trichloromethyl-1,3,5-triazine (III) and 2-phenyl-4-amino-6-trichloromethyl-1,3,5-triazine (IV), respectively. An attempt to replace the last trichloromethyl group by increasing the reaction temperature failed. Instead, at higher temperatures compound I yielded quantitatively 2-methyl-4-amino-6-hydroxy-1,3,5-triazine (V) upon reaction with aqueous ammonia and a mixture of III and V upon reaction with ethanolic ammonia solution.[6]

It was, however, desired to find a method by which all trichloromethyl groups attached to a triazine ring could be replaced by NHR-groups, because application of diamines would then lead to higher molecular compounds containing two or more 1,3,5-triazine rings linearly connected. This objective was achieved through working in OH-free media, like dioxane, chloroform and N,N-dimethylformamide.

Thus, by bubbling ammonia into a solution of I in N,N-dimethylformamide, 2-methyl-4,6-diamino-1,3,5-triazine (XI) was obtained. By the same

(1) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation sponsored by the Ohio Mathieson Chemical Corporation, Baltimore, Md.

(2) F. Arndt and B. Eistert, *Ber.*, **68**, 196 (1935).

(3) Ch. Grundmann and G. Weisse, *Chem. Ber.*, **84**, 684 (1951).

(4) Ch. Grundmann, H. Ulrich and A. Kreutzberger, *ibid.*, **86**, 181 (1953).

(5) K. Dachlauer, German Patent 682,391, Oct., 1939 (to I. G. Farbenindustrie A.-G.).

(6) These findings are in conformity with the results obtained from the action of concd. aqueous ammonia on 2,4,6-tris-trichloromethyl-1,3,5-triazine (VI) as reported by A. Weddige, *J. prakt. Chem.*, [2] **33**, 81 (1886). Only the first two trichloromethyl groups in VI could be replaced by the amino group with formation of 2-amino-4,6-bis-trichloromethyl-1,3,5-triazine (VII) and 2,4-diamino-6-trichloromethyl-1,3,5-triazine (VIII). Similar results were obtained when methylamine was used in place of concd. aqueous ammonia. The substitution by the NHR-group of the last trichloromethyl group in VI, however, could not even be forced under more severe conditions, and as end product only 2,4-diamino-6-hydroxy-1,3,5-triazine (IX) and 2,4-bis-methylamino-6-hydroxy-1,3,5-triazine (X), respectively, could be obtained.

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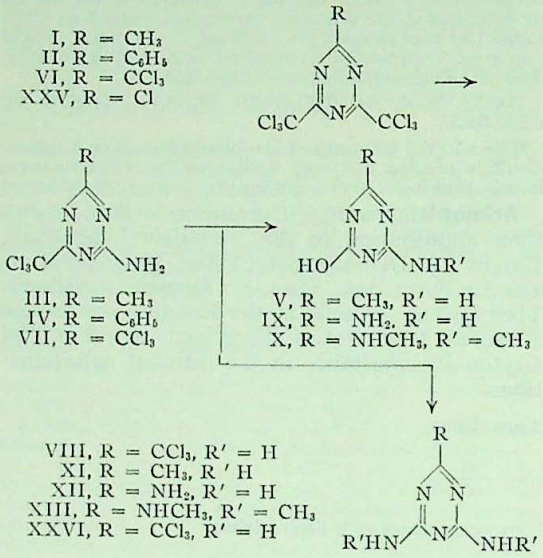
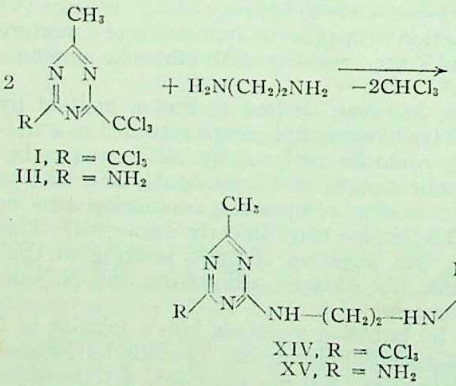
procedure, the conversion of VI with ammonia into 2,4,6-triamino-1,3,5-triazine (XII) and with methylamine into 2,4,6-tris-methylamino-1,3,5-triazine (XIII) was successful.

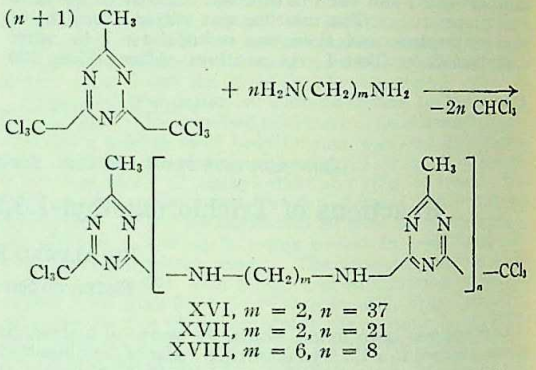


Furthermore, by the above procedure but using diamines, the linkage of two triazine rings was achieved. Thus the reaction of two molecules of I with one molecule of ethylenediamine in chloroform led to N,N′-bis-[2-methyl-4-trichloromethyl-1,3,5-triazinyl-(6)]-ethylenediamine (XIV). In addition, by the above method, the reaction of the last trichloromethyl group of the triazine ring with diamine could be brought about. Two molecules of III on reaction with one molecule of ethylenediamine in dioxane yielded N,N′-bis-[2-methyl-4-amino-1,3,5-triazinyl-(6)]-ethylenediamine (XV).



In principle by the same method, the linkage of more than two triazine rings with each other into longer chains could be brought about. In this case the molar ratio between I and the diamine had to be about 1:1 and a longer reacting time had to be allowed. At first, for the purpose of the determination of the molecular weight of these polymers, some measurements of specific viscosity were made which showed, upon comparison with the analytically found chlorine values, that the chain ends of the polymers consisted of trichloromethyl groups. That, in turn, meant that in subsequent experiments the molecular weight could be calculated simply from the analytical chlorine values. The accuracy of the chlorine analyses limits the accuracy of the calculation of the n-values for formulas XVI and XVII to ± 3.

Generally the chain length proved to be essentially dependent on the kind of diamine and the solvent used. Thus the reaction of I with ethylenediamine in m-cresol yielded a polymer XVI having a molecular weight of 5920, while the same starting materials in N,N-dimethylformamide gave the polymer XVII with a molecular weight of 3500. Using the latter solvent for the reaction between I and hexamethylenediamine, the polymer XVIII with the somewhat lower molecular weight of 1990 was obtained. All these polymers, particularly XVIII, exhibit molding properties in the molten state.



In these studies on the behavior of trichloromethyl groups attached to the 1,3,5-triazine ring, these groups were compared with carbethoxy groups as to their reactivity toward ammonia. As suitable compounds for these investigations, 2,4-bis-trichloromethyl-6-carbethoxy-1,3,5-triazine (XIX)[7] and 2-trichloromethyl-4,6-bis-carbethoxy-1,3,5-triazine (XX)[7] were chosen. Subjecting these two compounds to conditions under which in the aforementioned cases only one CCl_3 group was replaced by an NH_2 group, not only one CCl_3 group, but also one (in XIX) or two (in XX) carbethoxy groups reacted. Thus XIX was converted to 2-amino-4-trichloromethyl-6-carbamyl-1,3,5-triazine (XXI). The reaction product of XX was assigned the constitution of 2-hydroxy-4,6-bis-carbamyl-1,3,5-triazine (XXII) on the basis of the fact that it is insoluble in $NaHCO_3$, Na_2CO_3 and diluted NaOH solutions, but soluble in concd. NaOH solution. Thus, the question as to whether the CCl_3 group in XX acts toward ammonia as a "first" or "last" CCl_3 group, is to be answered in favor of the latter possibility on account of the OH-substitution.

Since under these conditions the two different functional groups of both XIX and XX reacted simultaneously, no conclusions as to their relative reactivities could be drawn. Thus milder conditions of reaction seemed indicated. It was found that when exactly equimolar amounts of ammonia and the triazine derivative were caused to react in absolute ethereal solution at 0°, only one functional

(7) H. Bosshard, H. Bohni, H. R. Mathys, R. Mitsche, E. Tschudi, H. Isler and S. Seide, *Ann.*, **577**, 84 (1952).

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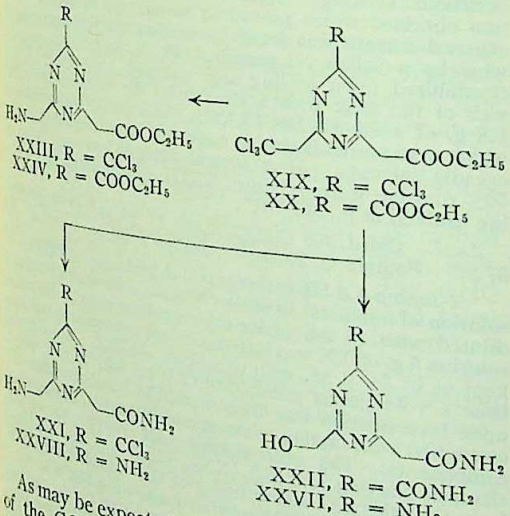
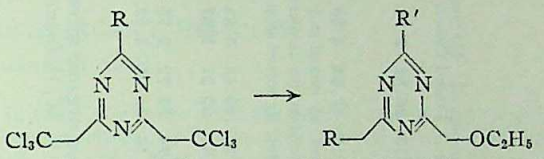
group, *viz.*, the CCl_3 group, was replaced. Thus, XIX furnished 2-amino-4-carbethoxy-6-trichloromethyl-1,3,5-triazine (XXIII) while XX yielded 2-amino-4,6-bis-carbethoxy-1,3,5-triazine (XXIV). Summarizing, it can be said that in 1,3,5-triazine derivatives containing both CCl_3 and $COOC_2H_5$ groups, the first CCl_3 is the most reactive of these functional groups toward ammonia. Second in order of activity, however, is not the second CCl_3 group but the $COOC_2H_5$ group as is evidenced by the formation of XXI.

In this connection it may be worthwhile to notice that when both CCl_3 and Cl groups are attached to the 1,3,5-triazine nucleus, the first CCl_3 group reacts most easily with ammonia. Thus 2,4-bis-trichloromethyl-6-chloro-1,3,5-triazine (XXV) reacts with ammonia to give 2-trichloromethyl-4,6-diamino-1,3,5-triazine (XXVI).[8] In this reaction no formation of the intermediate 2,4-bis-trichloromethyl-6-amino-1,3,5-triazine, which is stable under the conditions employed, was observed.

In analogy with the formation of V, the action of concentrated aqueous ammonia on XIX or XXI at elevated temperatures yielded 2-amino-4-hydroxy-6-carbamyl-1,3,5-triazine (XXVII), thus replacing the last CCl_3 group by a hydroxy rather than by an amino group. In this reaction, in addition to XXVII, only minor amounts of 2,4-diamino-6-carbamyl-1,3,5-triazine (XXVIII) were obtained. As in preceding cases, the replacement of the last CCl_3 group in XXI by NH_2 was attained by means of gaseous ammonia and N,N-dimethylformamide as solvent. In this manner, XXVIII was the sole reaction product.



As may be expected, the nucleophilic replacement of the CCl_3 group attached to the 1,3,5-triazine ring also proceeds with other suitable agents, *e.g.*, ethanol. The latter, upon reaction with trichloromethyl-1,3,5-triazine derivatives, gives principally the analogous results as ammonia. The only difference appears to be one of degree in that ethanol reacts more powerfully. Thus VI reacts with ethanol in the presence of a base to give directly 2,4,6-tris-ethoxy-1,3,5-triazine (XXIX), intermediates analogous to VII and VIII not being isolable.[9] XXIX also was obtained by the action of ethanol on XXV in the presence of sodium ethoxide, in this case the expected intermediates being isolable.[10] Another case of nucleophilic substitution of the CCl_3 group in the 1,3,5-triazine series was observed when it was attempted to dehalogenate XIX by hydrogen using ethanol as solvent, palladium-on-charcoal as catalyst and triethylamine as scavenger to bind HCl. In this reaction 2-ethoxy-4-methyl-6-carbethoxy-1,3,5-triazine (XXX) was obtained as one of the products.[11]



Acknowledgment.—The author is very much indebted to the Olin Mathieson Chemical Corporation for their generous support of this work. Furthermore he wishes to thank Dr. C. J. Grundmann of this Laboratory for his interest in the work and for stimulating discussions.

Experimental[12]

General Procedure Used for the Reaction of Trichloromethyl-1,3,5-triazine Derivatives. (A) With Concentrated Aqueous Ammonia (28%) at Room Temperature.—A suspension of 5 to 10 g. of the particular trichloromethyl-1,3,5-triazine derivative in 20 to 40 ml. of 28% aqueous ammonia was shaken for 2 to 3 hr. at room temperature, with an additional 15 to 25 ml. of the aqueous ammonia being added from time to time in smaller portions. Chloroform was evolved thereby. In some cases also heat was evolved so that cooling was necessary to maintain the suspension at room temperature. In other cases a somewhat elevated temperature (up to 50°) was necessary. The reaction product was vacuum-filtered, dried and recrystallized. Compounds III, IV, XXI and XXII in Table I were prepared by this procedure.

(B) With Aqueous Ammonia (28%) at 100°.—Batches of the type and size described under (A) were heated on a water-bath for 4 hr. Thereafter they were evaporated to dryness and the residues were recrystallized. Compounds V, IX and XXVII were produced by this procedure.

(C) With Amines in OH-free Solvents.—An amount of 5 to 10 g. of the requisite trichloromethyl-1,3,5-triazine derivative was, respectively, dissolved or suspended in N,N-dimethylformamide, chloroform or dioxane. If the amine was gaseous, it was bubbled into the reaction mixture, the temperature varying between room temperature and 165° according to the ease of the reaction. The liquid amines were added to the reaction mixture which was then shaken at a temperature chosen as explained above. The end-point of the reaction was evidenced by cessation of chloroform evolution and was usually reached after a total reaction time of 2 to 4 hours. If the reaction product remained in solution, the reaction mixture was evaporated to dryness, but if the reaction product precipitated, it was vacuum-filtered and dried. The solids were then either recrystallized or, if a suitable solvent could not be found, they were purified by extracting the impurities with ethanol, acetone and ether. Examples are listed in Table I as XI, XII, XIII, XIV, XV and XXVIII.

Polymer XVI.—Ethylenediamine (2.0 g.) was added to a solution of I (10.0 g.) in *m*-cresol (25.0 g.) and the mixture heated for 4 hr. at 205–210°. From the resulting reddish brown oil the solvent was distilled off *in vacuo* and the crude

(8) H. Schroeder and Ch. Grundmann, THIS JOURNAL, **78**, 2447 (1956).

(9) Ch. Grundmann and E. Kober, unpublished results.

(10) H. Schroeder and Ch. Grundmann, unpublished results.

(11) Ch. Grundmann and G. Weisse, unpublished results.

(12) All melting points are corrected.

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TABLE I

SUBSTITUTION OF CCl_3 GROUPS ATTACHED TO A 1,3,5-TRIAZINE RING

Starting compound	Amine	Solvent	Temp., °C.	Reacn. time, hr.	Resulting compound	Yield, %	Recrystn. solvent	Solubility	M.p., °C. cor.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
I	NH_3	Water[a]	25	2	III	79	Methanol–H_2O 55:45	Ins. petr. ether, sl. sol. CS_2, sol. Y[b]	158–159	$C_3H_3N_4Cl_3$								
II	NH_3	Water	40–50	2	IV	90	Acetone–H_2O 1:1	Ins. water, petr. ether; sl. sol. CS_2; sol. Y[b]	175–170	$C_9H_7N_7Cl_3$								
V	NH_3	Water	100	4	V	100	Water	Ins. benzene, sol. water	>400	$C_6H_6N_6O$	38.10	37.84	4.80	4.86	44.43	44.52		
VI	NH_3	DMF[c]	165	3.5	XI	51	Water	Sol. water, ethanol	278–279	$C_3H_3N_3$		Ident. by mixed m.p. with authentic sample[d]						
VI	NH_3	DMF	165	4	XII	48	Water	Sol. water, insol. Z[e]		$C_3H_6N_6$		Identification as picrate[f]						
V	CH_3NH_2	DMF	165	2.5	XIII	44	Water	Sol. water, ethanol	115	$C_4H_{10}N_6$		Ident. by mixed m.p. with authentic sample[g]						
V	$CH_2(NH_2)_2$	$CHCl_3$	25	2	XIV	14	Ethanol–H_2O 7:3	Ins. water, sl. sol. ether, sol. Y[b]	221–222	$C_4H_{12}N_8Cl_6$		23.29	22.89	44.23	44.01			
III	$CH_2(NH_2)_2$	Dioxane	130	2	XV	42		Ins. water and Z[e]	328–330	$C_6H_6N_{10}$	43.46	43.43	5.84	6.11				
XIX	NH_3	Water	25	3	XXI	80	Gl. HAc	Sol. pyridine, nitrobenzene, gl. acetic acid, ethyl malonate	315–316	$C_6H_6Cl_3N_7O$	23.41	23.21	1.87	1.75				
XX	NH_3	Water	25	2	XXII	89		Ins. water and Z[e]	>400	$C_7H_6N_8O_2$	32.79	32.72	2.75	2.62	38.25	38.41		
XIX	NH_3	DMF	25	3.5	XXVIII	100	Water	Sol. water, glacial acetic acid, tetrahydrofurfuryl alcohol; ins. Y[b]	>400	$C_7H_8N_8O$	31.16	31.03	3.92	4.20	54.53	54.50		

[a] With ethanol as solvent at 100°, a mixture of III and V was obtained; yields: 58% of III and 13% of V. [b] Y = all other common organic solvents. [c] DMF = N,N-dimethylformamide. [d] M. Nencki, *Ber.*, 7, 776 (1874). [e] Z = all common organic solvents. [f] A. Werner, *J. Chem. Soc.*, 107, 721 (1915). [g] A. W. Hofmann, *Ber.*, 18, 2763 (1885).

brown remainder best purified by successive boiling out with alcohol and acetone. Thus a faintly yellow powder was obtained which was insoluble in all usual organic solvents; m.p. about 370°, yield 3.0 g. (64%).

Anal. Calcd. for $C_{223}H_{336}N_{183}Cl_6$: C, 46.24; H, 5.72; Cl, 3.59. Found: C, 46.56; H, 5.79; Cl, 3.59, 3.58.

Polymer XVII.—Ten parts by weight of I and two parts by weight of ethylenediamine were dissolved in 25 parts by weight of N,N-dimethylformamide and heated for 3 hr. at 170–180°, thereby precipitating a yellowish brown mass, the amount of which could be increased by adding acetone to the cooled suspension. Since the product obtained could not be recrystallized, the best way to purify it was by separate extractions with boiling acetone and alcohol. The yellowish powder so obtained amounted to 3.5 g. (73%) and melted at about 250°.

Anal. Calcd. for $C_{132}H_{192}N_{108}Cl_6$: C, 45.25; H, 5.52; Cl, 6.07. Found: C, 45.23; H, 5.97; Cl, 6.06, 6.21.

Polymer XVIII.—A mixture of 10.0 g. of I, 3.5 g. of hexamethylenediamine and 25 ml. of N,N-dimethylformamide was heated for 3 hr. at 160–170°. During this time the crude condensation product precipitated. After cooling, the reaction mixture was diluted with acetone, boiled for a short time and filtered. Since the solid was insoluble in lower boiling solvents like carbon tetrachloride or acetone and soluble in higher boiling ones like nitrobenzene but could not, however, be recrystallized from the latter ones, it could be purified best by successive extractions with boiling acetone, alcohol and carbon tetrachloride. The yellow powder so obtained melted at 200–201°, yield 2.5 g. (37%). Soluble also in mineral acids, XVIII could be reprecipitated from such a solution by neutralization with dilute alkali.

Anal. Calcd. for $C_{86}H_{139}N_{43}Cl_6$: C, 51.93; H, 7.05; Cl, 10.69. Found: C, 51.96, 51.76; H, 7.34, 7.42; Cl, 10.42, 10.40.

2-Amino-4-carbethoxy-6-trichloromethyl-1,3,5-triazine (XXIII).—Of a saturated solution of ammonia in ether (at 0°), 16 ml. was diluted with 15 ml. of ice-cold absolute ether. To this solution 5 g. of XIX was added in small portions and the whole reaction contents kept at 0° for 2 hr. with occasional shaking. Upon filtration, 0.3 g. of a white solid was obtained which proved to be starting material. The ethereal filtrate was freed from ether on the steam-bath whereby a yellow oil remained which, to a large extent, crystallized upon cooling and repeated scratching of the wall of the flask with a glass rod. By vacuum-filtration 1.8 g. of white needles (XXIII, yield 54%) was obtained which were insoluble only in water but soluble in all common organic solvents. After several recrystallizations from a 50% dioxane–water mixture, XXIII was obtained as glittering leaflets, m.p. 130–131°.

Anal. Calcd. for $C_7H_7Cl_3N_4O_2$: C, 29.44; H, 2.47; Cl, 37.26. Found: C, 29.39; H, 2.56; Cl, 37.40.

2-Amino-4,6-bis-carbethoxy-1,3,5-triazine (XXIV).—A solution of ammonia in ether (19 ml.), saturated at 0°, was diluted with 15 ml. of ice-cold absolute ether. Into this solution 5 g. of XX was introduced and the reaction contents kept at 0° for 3 hr. with occasional shaking. During this time a voluminous precipitate (2.9 g.) had formed which upon investigation was found not to be homogeneous. By extraction with boiling ether, it could be separated into two components. The ether-soluble part proved to be unchanged starting material (XX), which was also obtained from the ethereal mother liquor of the original precipitate. The total amount of XX recovered was 4.0 g. (80%).

The ether-insoluble portion amounted to 0.4 g., melted at 179–180° and could be obtained by recrystallization from acetone–water (1:5) as white, small leaflets melting at 182–183°.

Anal. Calcd. for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04; N, 23.23. Found: C, 44.74, 44.94; H, 5.09, 5.33; N, 23.15, 23.14.

2-Amino-4-hydroxy-6-carbamyl-1,3,5-triazine (XXVII).—Five grams of XIX was added slowly with stirring to 40 ml. of concd. aqueous ammonia at room temperature and then kept for 6 hr. on the steam-bath. The somewhat cloudy hot solution was vacuum filtered and the filtrate allowed to cool down, whereby 0.3 g. (16.9% yield) of glittering crystals came off which had no melting point up to 400° and were

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Upon evaporation of the aqueous filtrate to dryness, 1.8 g. of a white substance was obtained. This substance, being insoluble in all common organic solvents and being soluble in hot water only, proved to be a hydrate of XXVII. Attempts to remove the hydrate water by heating the substance *in vacuo* resulted in partial decomposition of the material. Therefore for analysis the product was dried *in vacuo* for 1 hr. at 56°. It decomposed then in the melting point tube at 168–173°. The analysis of this sample indicated the presence of 2.5 moles of water.

Anal. Calcd. for $C_4H_5N_5O_2 \cdot 2.5H_2O$: C, 24.01; H, 5.04; N, 35.00. Found: C, 24.03; H, 5.51; N, 35.65.

COLUMBUS, OHIO

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

1,4-Addition of Grignard Reagents to 9-Phenanthryl Ketones[1]

BY REYNOLD C. FUSON AND STANLEY J. STRYCKER

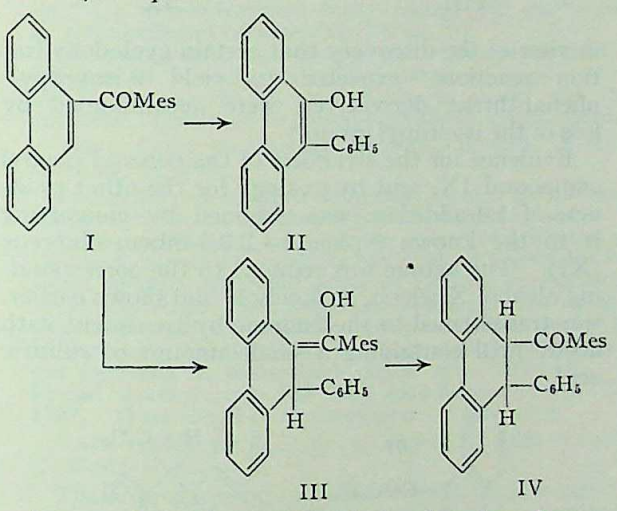
RECEIVED DECEMBER 20, 1956

It has been shown that 9-phenanthryl mesityl ketone reacts in the 1,4-manner with the methyl and phenyl Grignard reagents to give the corresponding 10-substituted 9,10-dihydrophenanthrenes. 9-Phenanthryl phenyl ketone and phenyl 9-phenanthrenecarboxylate react with phenylmagnesium bromide to yield phenyl 10-phenyl-9,10-dihydro-9-phenanthryl ketone.

The 1,4-addition of Grignard reagents to conjugated systems involving benzene rings, discovered 27 years ago by Gilman, Kirby and Kinney,[2] and almost at the same time by Kohler and Nygaard,[3] takes place more readily in the naphthalene series.[4] The difference, ascribed to the greater degree of double bond quality of the 1,2-bond in naphthalene, would be expected to be even more pronounced in suitably constituted phenanthrene derivatives; the 9,10-double bond of phenanthrene is known to have a higher order of reactivity than the bonds in naphthalene. To test this idea, we have prepared certain 9-phenanthryl ketones and subjected them to the action of Grignard reagents.

Our experiments have shown that mesityl 9-phenanthryl ketone (I) does react in the conjugate manner with the phenyl and methyl reagents. The first experiment with phenylmagnesium bromide gave an intractable oil. Chromatographic separation on an alumina-packed column yielded a small amount of the original ketone and a new compound which proved to be a phenol. It melted at 143–144° and formed an acetate (m.p. 153–155°) and benzoate (m.p. 179–180°). The melting points of the three compounds checked those given by Koelsch[5] for 9-phenyl-10-phenanthrol (II), its acetate and its benzoate. The formation of the phenanthrol is reminiscent of the production of 2-phenyl-1-naphthol in the naphthalene series[4] and similarly may be ascribed to the air oxidation of the enol III. In a subsequent experiment the expected dihydro ketones IV were isolated.

Methylmagnesium iodide behaved in a similar manner, the dihydro compound V likewise being obtained in two forms. Our belief that the methylated ketones are the expected diastereoisomers is strengthened by the observation that, when heated with a palladium-on-charcoal catalyst, the isomer having the lower melting point (109–110°) was changed to the higher-melting (154.5–155.5°) compound.



In search of a less highly hindered carbonyl compound we tried phenyl 9-phenanthroate (VI). With phenylmagnesium bromide it gave 9-benzoyl-10-phenyl-9,10-dihydrophenanthrene (VIII), presumably by way of 9-phenanthryl phenyl ketone (VII). This idea was supported by the results of experiments with the benzoyl compound VII. With the phenyl reagent it yielded the same dihydro ketone VIII obtained from the ester. We were satisfied with the structure VIII for this ketone, isolated in only one form, when we found that it could be dehydrogenated. The aromatized ketone, 9-benzoyl-10-phenylphenanthrene (IX), was obtained in small amount directly from the reaction mixture produced by the treatment of the phenyl ketone VII with phenylmagnesium bromide.

The aromatization could be effected in 76% yield by treatment of the dihydro ketone with bromine. This method was successful also in the aromatization of the methyl ketone V and the phenyl ketone IV. In the latter case, however, the dehydrogenation was accompanied by an unexpected cleavage. The cleavage product that was isolated proved to be 9-phenylphenanthrene. If mesitoic

(1) This investigation was supported in part by a grant from the Office of Ordnance Research, U.S. Army (Contract No. DA-11-022-ORD-874).

(2) H. Gilman, J. E. Kirby and C. R. Kinney, THIS JOURNAL, **51**, 2252 (1929).

(3) E. P. Kohler and E. M. Nygaard, *ibid.*, **52**, 4128 (1930).

(4) R. C. Fuson, B. C. McKusick and F. W. Spangler, *ibid.*, **67**, 257 (1945).

(5) C. F. Koelsch, *ibid.*, **56**, 480 (1934).

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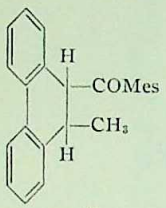
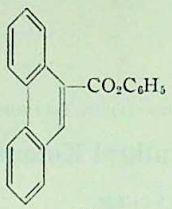
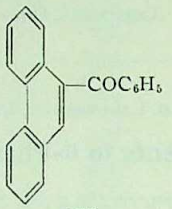
acid was formed also, as seems probable, it must have been retained by the alumina of the column employed in the chromatographic separation of the reaction mixture. This cleavage seems less strange



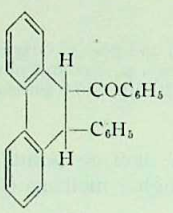
V



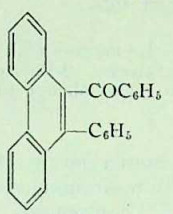
VI



VII



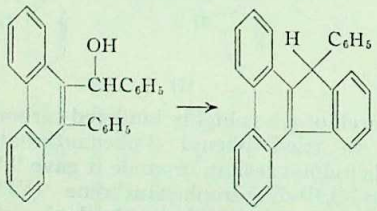
VIII



IX

in view of the discovery that certain cyclodehydration reactions, expected to yield 9-isopropylphenanthrene derivatives, were accompanied by loss of the isopropyl group.[6]

Evidence for the structure of the benzoyl phenyl compound IX, and by analogy for the other products of 1,4-addition, was obtained by converting it to the known 9-phenyl-1,2,3,4-dibenzofluorene (XI). The ketone was reduced to the corresponding alcohol X which, as Koelsch[7] had shown earlier, was transformed to the fluorene by treatment with acetic acid containing a small amount of sulfuric acid.



X XI

9-Phenanthryl mesityl ketone was made by condensing 9-phenanthrylmagnesium bromide with mesitoyl chloride and also by the action of 9-phenanthroyl chloride on mesitylene in the presence of aluminum chloride. The preparation of 9-phenanthryl phenyl ketone from 9-cyanophenanthrene and the phenyl Grignard reagent was of especial interest since the nitrile itself might have reacted in the conjugate manner. However, chromatographic separation of the reaction mixture, after hydrolysis, gave no other phenanthrene derivative.

Experimental[8]

Phenyl 9-Phenanthroate (VI).—The procedure was similar to that employed earlier for the synthesis of phenyl 1-naphthoate.[9] A mixture of 12.9 g. of 9-phenanthroyl chloride and 5.1 g. of phenol was warmed to initiate the reaction. The evolution of hydrogen chloride continued for about 1 hr.; 60 ml. of methylcyclohexane was added and the mixture heated under reflux for 45 minutes. The hot mixture was filtered and the filtrate allowed to cool. The phenyl phenanthroate separated in the form of large clumps of colorless needles, m.p. 113.5–115.5°, yield 13.8 g. (85%). Recrystallization of the ester from ethanol raised the melting point to 115.5–116.5°.

Anal.[10] Calcd. for $C_{21}H_{14}O_2$: C, 84.54; H, 4.73. Found: C, 84.46; H, 5.01.

The infrared spectrum[11] contains absorption bands assignable to an ester function (1737 and 1200 cm.$^{-1}$) and a monosubstituted phenyl group (683 cm.$^{-1}$).

9-Benzoylphenanthrene (VII).—The procedure was patterned after that described for the preparation of 9-acetylphenanthrene.[12] A solution of 5.0 g. of 9-cyanophenanthrene in 50 ml. of dry benzene was added quickly to a Grignard reagent prepared from 19.3 g. of bromobenzene, 2.99 g. of magnesium and 200 ml. of ether. The dark, clear reaction mixture turned green and became opaque. During a 7-hr. period of reflux the color changed to a deep amber. The reaction mixture was cooled by means of an ice-bath, and an excess of dilute hydrochloric acid was added, with stirring. The initially formed yellow, fluffy precipitate changed suddenly to a milky white crystalline substance during the acidification. The precipitate was removed by filtration and warmed on a steam-bath for 4 hr. with distilled water. The crystalline material gradually changed to a clear oil, which settled to the bottom of the container. The oil, which was extracted with a mixture of ether and benzene, was subjected to chromatography. The 9-benzoylphenanthrene crystallized from high-boiling petroleum ether as colorless needles, m.p. 90–91°,[13] yield 5.3 g. (76%).

In the infrared spectrum a strongly conjugated carbonyl band appears at 1665 cm.$^{-1}$, a sharp peak at 701 cm.$^{-1}$ suggests the monosubstituted phenyl radical, and *o*-disubstitution of the phenanthrene nucleus is indicated by a sharp peak at 725 cm.$^{-1}$. A medium peak at 885 cm.$^{-1}$ may be assigned to the isolated hydrogen atom at the 10-position of phenanthrene.

9-Mesitoylphenanthrene (I). The Grignard Method.—The procedure described by Miller and Bachmann[14] for 9-acetylphenanthrene was used as a pattern. The 9-phenanthrylmagnesium bromide, prepared from 71.0 g. of 9-bromophenanthrene, was added slowly to a solution of mesitoyl chloride in 250 ml. of anhydrous benzene. An immediate precipitate appeared and the mixture became warm. After completion of the addition, which required 30 minutes, the mixture was stirred at room temperature for an additional 3 hr. The 9-mesitoylphenanthrene, isolated by usual procedures, crystallized from benzene–ethanol, yield 71 g. (80%). It was purified by sublimation at 160° (1.5 mm.), m.p. 193.0–193.5°.

Anal. Calcd. for $C_{24}H_{20}O$: C, 88.85; H, 6.21. Found: C, 88.55; H, 6.18.

The infrared spectrum has bands attributable to a conjugated carbonyl group (1662 cm.$^{-1}$) and the mesityl radical (843 cm.$^{-1}$).

9-Mesitoylphenanthrene (I). The Friedel–Crafts Method.—The procedure was similar to that described for the preparation of 2-mesitoylnaphthalene.[4] One gram of anhydrous aluminum chloride was added to a mixture of 1.0 g. of 9-phenanthroyl chloride, 1.0 g. of mesitylene and 25 ml. of pure symmetrical tetrachloroethane, and the mixture was heated gently on a steam-bath for 2 hr. The dark solution was poured carefully into dilute hydrochloric acid, and

(6) C. K. Bradsher and D. J. Beavers, THIS JOURNAL, **78**, 3193 (1956).

(7) C. F. Koelsch, *ibid.*, **56**, 480 (1934).

(8) All melting points are corrected and boiling points are uncorrected.

(9) R. C. Fuson and F. W. Wassmundt, THIS JOURNAL, **78**, 5409 (1956).

(10) The microanalyses were performed by Mr. Joseph Nemeth, Mrs. R. Maria Benassi, Mrs. Lucy Chang, Mrs. Esther Fett, Mrs. Ruby Ju and Mr. Rollo Nesset.

(11) The infrared spectra were determined by Mr. James Brader, Mrs. Louise Griffing and Mrs. Beverly Thomas.

(12) J. E. Callen, C. A. Dornfeld and G. H. Coleman, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 26.

(13) W. E. Bachmann, THIS JOURNAL, **56**, 1363 (1934).

(14) H. J. Miller and G. B. Bachman, *ibid.*, **57**, 766 (1935).

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the solvent and unchanged mesitylene were removed by steam distillation. The crude product was boiled with methanol to which decolorizing carbon had been added and the mixture filtered. The ketone separated from the filtrate in beautiful, thin plates which had a yellow tinge, m.p. 187.5–189.5°, yield 0.96 g. (71%). It melted at 193.0–193.5° after sublimation. A mixture melting point with the product from the Grignard method showed no depression.

Condensation of Phenylmagnesium Bromide with Phenyl 9-Phenanthroate.—A solution of 5 g. of the ester in 75 ml. of dry benzene was added, over a period of 40 minutes, to a Grignard reagent made from 13.1 g. of bromobenzene, 2.02 g. of magnesium and 100 ml. of anhydrous ether. The reaction did not seem to be highly exothermic, and the solution slowly developed a green color. After being heated, under reflux and with stirring, for 17 hr., the mixture was treated with a saturated solution of ammonium chloride. The two-phase system, which had a marked odor of phenol, was stirred for 3 hr. The aqueous layer was extracted once with 150 ml. of ether and the ether solution added to the original organic layer.

Extraction of the organic layer with 10% sodium hydroxide removed phenol, which was isolated as 2,4,6-tribromophenol, m.p. 94–95°.[15] Steam distillation of the organic layer served to remove solvent and biphenyl. By recourse to chromatography 9-benzoyl-10-phenyl-9,10-dihydrophenanthrene was isolated which, after recrystallization from absolute ethanol, melted at 151.5–152.5°, yield 4.35 g. (72%).

Anal. Calcd. for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found: C, 89.78; H, 5.41.

The infrared spectrum contains significant bands at 2900, 1690, 747 and 695 cm.$^{-1}$ which are consistent with the structure assigned.

9-Benzoyl-10-phenylphenanthrene.—A solution of 0.45 g. of bromine in 50 ml. of carbon tetrachloride was added to a solution of 1.0 g. of the dihydro compound VIII in 50 ml. of carbon tetrachloride. The solution was maintained at reflux for 3 hr. at the end of which time the evolution of hydrogen bromide seemed to be complete. After being washed with a 10% solution of sodium bisulfite, the solution was freed of solvent by evaporation at reduced pressure. The clear colorless oil, left as a residue, was heated for 2 hr. with 150 ml. of dimethylaniline. The crude 9-benzoyl-10-phenylphenanthrene, isolated by pouring the previously cooled reaction mixture into dilute sulfuric acid, was recrystallized from 95% ethanol, m.p. 176–177°, yield 0.76 g. (76%).

Anal. Calcd. for $C_{27}H_{18}O$: C, 90.47; H, 5.06. Found: C, 90.38; H, 5.04.

The infrared spectrum contains bands attributable to a strongly conjugated carbonyl group (1670 cm.$^{-1}$), a monosubstituted phenyl radical (698 and 759 cm.$^{-1}$) and an *o*-disubstituted phenyl segment (724 cm.$^{-1}$). Moreover, aliphatic carbon–hydrogen bonds were indicated to be absent.

9-Phenyl-1,2,3,4-dibenzofluorene (XI).—A mixture of 0.19 g. of 9-benzoyl-10-phenylphenanthrene in 25 ml. of dry ether was warmed to effect solution, and to the solution was added slowly a slurry of 0.020 g. of lithium aluminum hydride in 10 ml. of ether. The mixture was heated on a steam-bath for 2 hr. and then treated successively with wet ether, aqueous ethanol and water. The gummy, viscous oil left by removal of solvent from the organic layer did not crystallize and was dissolved in 10 ml. of glacial acetic acid by warming. To the resulting solution were added 2 drops of concentrated sulfuric acid.[5] When the mixture was heated on the steam-bath, colorless crystals began to form immediately and the mixture soon appeared to be solid. The fluorene (0.14 g., 77% yield) crystallized from ethanol–toluene in the form of colorless, fluffy needles, m.p. 212–213°. The melting point given by Koelsch is 210–211°.

Anal. Calcd. for $C_{27}H_{18}$: C, 94.70; H, 5.30. Found: C, 94.48; H, 5.38.

The infrared spectrum has peaks suggesting the presence of an aliphatic hydrogen atom (2850 cm.$^{-1}$), monosubstituted benzene ring (698, 750 cm.$^{-1}$) and *o*-disubstitution (725 cm.$^{-1}$). The ultraviolet spectrum shows maxima at 247 mμ (log ε 4.92) and 322 mμ (log ε 4.48) with shoulders at 263 and 278 mμ.

Condensation of Phenylmagnesium Bromide with 9-Mesitoylphenanthrene.—Forcing conditions were employed and the entire experiment including the hydrolysis step was conducted in an atmosphere of nitrogen. A solution of 6.48 g. of the ketone in 75 ml. of dry benzene was added slowly to a Grignard reagent made from 6.28 g. of bromobenzene, 0.96 g. of magnesium and 50 ml. of anhydrous ether. The initial deep amber color changed to a deep green and, after the mixture had been heated for 6 hr. under reflux, was a milky yellow. At the end of a total reflux period of 8 hr., 80 ml. of 3 *N* hydrochloric acid was added and the two-phase system stirred overnight at reflux to effect ketonization. The organic layer, after being washed successively with water, 10% sodium bicarbonate solution and water, was dried over sodium sulfate. Removal of the solvent at reduced pressure left a yellow, viscous oil which crystallized slowly while being allowed to cool. Methanol removed the color, leaving the 9-mesitoyl-10-phenyl-9,10-dihydrophenanthrene as colorless crystals, m.p. 196–199°, yield 4.5 g. The compound was purified by recrystallization from chloroform–methanol, m.p. 202–203°.

Anal. Calcd. for $C_{30}H_{26}O$: C, 89.51; H, 6.51. Found: C, 89.51; H, 6.69.

Infrared analysis of the compound indicates the presence of a ketone function (1703 cm.$^{-1}$), the mesityl nucleus (852 cm.$^{-1}$), a monosubstituted phenyl radical (702 cm.$^{-1}$) and an *o*-disubstituted benzene ring (739 cm.$^{-1}$).

Chromatographic separation of the residue permitted the isolation of a white crystalline substance, m.p. 140.5–141.5°, the analysis of which is also in accord with the structure, 9-mesitoyl-10-phenyl-9,10-dihydrophenanthrene.

Anal. Calcd. for $C_{30}H_{26}O$: C, 89.51; H, 6.51. Found: C, 89.84; H, 6.71.

Except for minor shifts of certain bands, the infrared spectrum is the same as that of the higher-melting isomer.

In one experiment, in which two instead of five moles of Grignard reagent were used for each mole of ketone, the reaction product underwent oxidative cleavage—presumably at the enol stage. By chromatographic separation on alumina it was possible to isolate a compound which proved to be 9-phenyl-10-phenanthrol, which crystallized from aqueous methanol as transparent plates, m.p. 143–144°. It formed an acetate, m.p. 153–155°, and a benzoate, m.p. 177–179°. These values check those given by Koelsch.[5]

Anal. Calcd. for $C_{20}H_{14}O$: C, 88.86; H, 5.22. Found: C, 88.67; H, 5.13.

The infrared spectrum indicates not only the presence of a tertiary hydroxyl group (3530 cm.$^{-1}$) and of a monosubstituted phenyl ring (700 cm.$^{-1}$) but also the absence of aliphatic hydrogen atoms, of a carbonyl group and of a mesityl nucleus.

Condensation of Methylmagnesium Iodide with 9-Mesitoylphenanthrene.—A solution of 3.0 g. of the ketone in 75 ml. of dry benzene was added to a Grignard reagent made from 4.10 g. of methyl iodide, 0.70 g. of magnesium and 75 ml. of anhydrous ether. The reaction mixture immediately became dark green, but the color was gradually discharged during the subsequent 6-hr. period of heating the mixture under reflux. The two-layer system, produced by the addition of 75 ml. of 2 *N* hydrochloric acid, was heated under reflux for 13 hr. to ensure ketonization. An atmosphere of nitrogen was maintained throughout the experiment.

The organic layer was washed with water, with 10% sodium bicarbonate solution and again with water. The clear solution, after being dried overnight with anhydrous sodium sulfate, had a magenta color. Removal of the solvent left a pale yellow, viscous material which solidified when allowed to stand, m.p. 105–135°. Trituration of this solid with ether yielded a yellow oil and 1.4 g. of a white powdery solid, m.p. 152–155°, which proved to be the high-melting form of 9-mesitoyl-10-methyl-9,10-dihydrophenanthrene (V). It was purified by recrystallization from aqueous methanol, m.p. 154.5–155.5°.

Anal. Calcd. for $C_{25}H_{24}O$: C, 88.19; H, 7.11. Found: C, 88.11; H, 7.23.

The infrared spectrum shows bands attributable to a ketone group (1700 cm.$^{-1}$), the mesityl nucleus (853 cm.$^{-1}$) and an *o*-disubstituted benzene ring (740 and 760 cm.$^{-1}$).

(15) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systemic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 264 and 326.

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The low-melting form of 9-mesitoyl-10-methyl-9,10-dihydrophenanthrene was obtained by submitting the ether-soluble portion of the product to a chromatographic separation on alumina. The major part of the material was eluted with a 10:1 ratio of cyclohexane to ether. Large needles, m.p. 109–110°, separated from a cooled aqueous ethanolic solution in a yield of 1.1 g.

Anal. Calcd. for $C_{25}H_{24}O$: C, 88.19; H, 7.11. Found: C, 87.83; H, 7.39.

The infrared spectrum of this compound is nearly superimposable on that of the higher-melting isomer.

Aromatization of 9-Mesitoyl-10-methyl-9,10-dihydrophenanthrene.—A solution of 0.24 g. of bromine in 10 ml. of carbon tetrachloride was added to 0.50 g. of 9-mesitoyl-10-methyl-9,10-dihydrophenanthrene dissolved in 25 ml. of carbon tetrachloride. The evolution of hydrogen bromide continued over a period of 5 hr. The reaction mixture was washed with sodium bisulfite and with water, and the solvent was removed. Chromatography of the pale yellow oil yielded a substance, m.p. 111–112°, which crystallized from ethanol. The combustion analysis agrees with that calculated for 9-mesitoyl-10-methylphenanthrene.

Anal. Calcd. for $C_{25}H_{22}O$: C, 88.72; H, 6.55. Found: C, 88.33; H, 6.64.

The infrared analysis of this compound is consistent with this structure. A conjugated carbonyl group (1658 cm.$^{-1}$), the mesityl nucleus (854 cm.$^{-1}$) and characteristic aromatic peaks (757, 726 cm.$^{-1}$) are found in the spectrum.

Aromatization of 9-Mesitoyl-10-phenyl-9,10-dihydrophenanthrene.—A solution of 3.0 g. of 9-mesitoyl-10-phenyl-9,10-dihydrophenanthrene in 60 ml. of carbon tetrachloride was treated with 1.19 g. of bromine. The solution was heated gently until the evolution of hydrogen bromide was complete. Removal of the solvent left a dark oil, which was triturated with ethanol. Crystals separated from the cooled solution in the form of hexagonal plates, m.p. 160–161°, yield 1.7 g. This compound proved to be 9-mesitoyl-10-phenylphenanthrene.

Anal. Calcd. for $C_{30}H_{24}O$: C, 89.96; H, 6.04. Found: C, 89.67; H, 6.13.

The infrared spectrum of this compound contains peaks characteristic of a conjugated carbonyl group (1660 cm.$^{-1}$), the mesitylene radical (850 cm.$^{-1}$), *o*-disubstituted (725 cm.$^{-1}$) and monosubstituted benzene (699, 761 cm.$^{-1}$).

The ethanol filtrate yielded an oil which was subjected to chromatography. A hydrocarbon was isolated from the cyclohexane eluent. An aqueous acetic acid solution of this substance deposited a white crystalline material in the form of rosettes, m.p. 104–105°, yield 0.5 g. Its picrate melts at 113–114°. Koelsch[5] reports a melting point of 105–106° for 9-phenylphenanthrene and a melting point of 115° for its picrate.

Anal. Calcd. for $C_{20}H_{14}$: C, 94.45; H, 5.55. Found: C, 94.51; H, 5.53.

The infrared spectrum is consistent with a hydrocarbon structure. The only significant peaks of absorption which occur indicate monosubstituted benzene (700 cm.$^{-1}$) and aromatic vibrations (745, 725 cm.$^{-1}$). The ultraviolet spectrum exhibits a maximum at 254 mμ (log ϵ 4.95) which is characteristic of the phenanthrene nucleus.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES, UNIVERSAL OIL PRODUCTS CO.]

Alkylation of Benzene with Polyhalides in the Presence of Saturated Hydrocarbons and Aluminum Chloride[1]

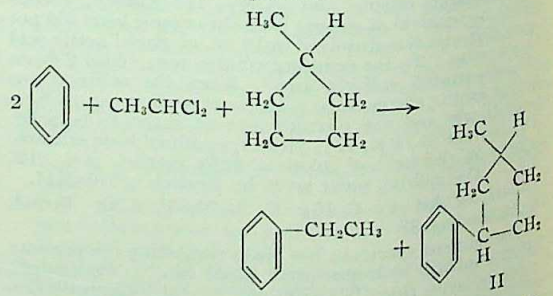
BY LOUIS SCHMERLING, ROBERT W. WELCH AND J. P. LUVISI

RECEIVED NOVEMBER 3, 1956

The aluminum chloride catalyzed condensation of a 1,1-dihaloalkane with benzene results in the formation of a primary alkylbenzene when the reaction is carried out in the presence of a hydrogen donor, namely a saturated hydrocarbon containing a tertiary carbon atom. Thus, for example, *n*-butylbenzene and (x-methylcyclohexyl)-benzene are produced in good yield by the reaction of benzene with 1,1-dichlorobutane in the presence of methylcyclohexane. Large amounts of hydrogen transfer products are also obtained with 2,3-dibromobutane and with 1,2-dichloro-2-methylpropane but not with 1,2-dichlorobutane. The mechanisms of these reactions and of the isomerization of tertiary alkylbenzenes is discussed.

In previous papers it was shown that excellent yields of primary monoalkylbenzenes (for example, isobutylbenzene[2] and 1-phenyl-3,3-dimethylbutane)[3] are obtained by the aluminum chloride catalyzed reaction of benzene with dichloroalkanes (1,2-dichloro-2-methylpropane and 1,1-dichloro-3,3-dimethylbutane, respectively) in the presence of a saturated hydrocarbon containing a tertiary carbon atom. The present paper describes the results of an investigation of the scope of this hydrogen transfer reaction, various polyhalides and saturated hydrocarbons being studied.

1,1-Dichloroethane.—The chief product obtained by the reaction of 1,1-dichloroethane with excess benzene in the presence of aluminum chloride at 3–4° was 1,1-diphenylethane (33% yield). Ethylbenzene was obtained in no more than 2% yield.[4] When the experiment was repeated, but with the addition of methylcyclopentane, practically no diphenylethane was produced. Instead, the chief reaction products were ethylbenzene and (methylcyclopentyl)-benzene isolated in approximately equal yields (42 and 38%, respectively) in accordance with the equation



(1) Presented before the Division of Organic Chemistry of the American Chemical Society at the Atlantic City Meeting, September, 1956.

(2) L. Schmerling, R. W. Welch and J. P. West, THIS JOURNAL, **78**, 5406 (1956).

(3) L. Schmerling, J. P. Luvisi and R. W. Welch, *ibid.*, **77**, 1774 (1955).

(4) Another product, 9,10-dimethyl-9,10-dihydroanthracene, isolated by previous workers was not obtained, presumably because of the large excess of benzene (6.2:1) over dichloroethane; *cf.* A. Angelbis and C. Anschütz, *Ber.*, **17**, 165 (1884).

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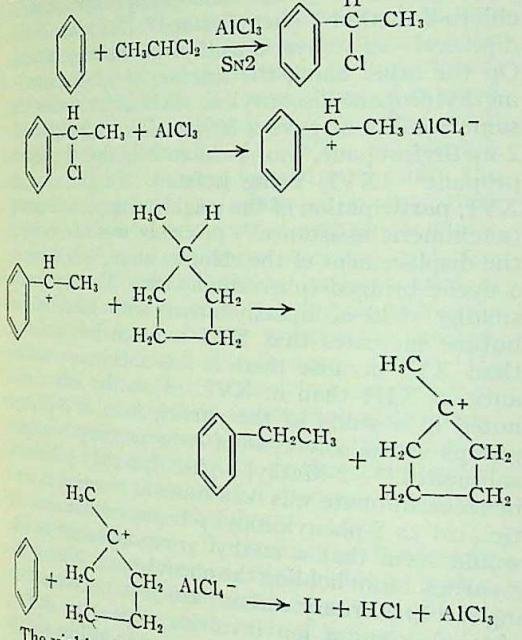
May 20, 1957

Infrared analysis showed that II contained little, if any, of the tertiary cycloalkylbenzene, (1-methylcyclopentyl)-benzene, further evidence that alkylation and cycloalkylation in the presence of aluminum chloride tends to yield secondary, rather than tertiary, alkyl and cycloalkylbenzenes.[5]

The reaction mechanism apparently involves the intermediate formation of the carbonium ion corresponding to (1-chloroethyl)-benzene, followed by the abstraction of the hydride ion attached to the tertiary carbon atom of methylcyclopentane to form ethylbenzene and the tertiary methylcyclopentyl cation, which reacts with benzene to yield II as final product.

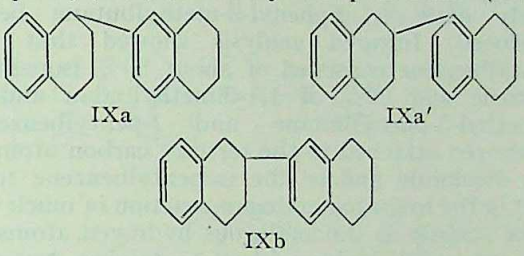


The yields of ethylbenzene and II were increased to about 60% each by carrying out the reaction at higher temperatures, 39–41°.

Use of a smaller ratio of benzene to dichloroethane (2:1 instead of 5.2:1) and of hydrogen donor (methylcyclohexane) to dichloroethane (1.6:1 instead of 4:1) resulted in the further reaction of the primary products with the formation of disubstituted benzenes. Besides ethylbenzene (42%) and methylcyclohexylbenzene (III, 31%), there was obtained diethylbenzene (9%) and (x-methylcyclohexyl)-ethylbenzene (IV, 9%).

Decahydronaphthalene was a more active hydrogen donor than methylcyclopentane. When it was used at 2–4°, phenyldecahydronaphthalene (V, chiefly the 2-phenyl isomer) was obtained in 70% yield. Ethylbenzene and a small amount (0.5%) of bis-(decahydronaphthyl)-benzene (VI) also were isolated.

1,2,3,4-Tetrahydronaphthalene served as both the aromatic hydrocarbon and the hydrogen donor when treated with 1,1-dichloroethane and aluminum chloride at 26–96°. "Self-alkylation" of the tetrahydronaphthalene occurred; tetrahydronaphthyltetrahydronaphthalene (IX) and ethyltetrahydronaphthalene (VII) were obtained in 40–45% yield. Dehydrogenation of a lower boiling fraction of IX gave 1,2′-binaphthyl, indicating that it was either or both 6-(1,2,3,4-tetrahydro-1-naphthyl)- and 5-(1,2,3,4-tetrahydro-2-naphthyl)-1,2,3,4-tetrahydronaphthalene (IXa and IXa′). The fact that alkylation of 1,2,3,4-tetrahydronaphthalene with alkyl chlorides in the presence of aluminum chloride gives 6-alkyl derivatives exclusively[6] indicates that the compound was IXa. Dehydrogenation of the higher boiling fraction, which was present in somewhat larger amount, to 2,2′-binaphthyl showed that it was 6-(1,2,3,4-tetrahydro-2-naphthyl)-1,2,3,4-tetrahydronaphthalene (IXb).



Schroeter[7] obtained a 0.5–1.0% yield of a crystalline compound (m.p. 53–54°), to which he assigned the structure IXb, by the action of 1–2% aluminum chloride on tetrahydronaphthalene at 50–70° for 6–10 hr. Attempts to crystallize the product of the present investigation were unsuccessful.

A crystalline by-product (VIII, m.p. 71–72°) of lower boiling point than IX was isolated in 0.5% yield. Analysis and dehydrogenation indicated that it was an octahydroanthracene. Schroeter[7] found that 1,2,3,4,5,6,7,8-octahydroanthracene is a major product (obtained in about 2% yield) of the action of aluminum chloride on tetrahydronaphthalene. It is apparently formed *via* ring opening of the tetrahydronaphthalene to produce 4-phenylbutyl cation which condenses with tetrahydronaphthalene forming 6-(4-phenylbutyl)-1,2,3,4-tetrahydronaphthalene which undergoes dephenylation to 4-(1,2,3,4-tetrahydro-2-naphthyl)-butyl cation, ring closure of which yields *sym*-octahydroanthracene.[8]

1,1-Dibromoethane.—When 2,3-dimethylbutane was used as hydrogen transfer agent for the alkylation of benzene with 1,1-dibromoethane, the hexylbenzene, which was isolated in 21% yield together with a 34% yield of ethylbenzene, consisted chiefly of 3-phenyl-2,2-dimethylbutane, the isomer which is also the chief product of the alkylation of benzene with either 2-chloro-2,3-dimethylbutane or 1-chloro-3,3-dimethylbutane.[5]

Dichloromethane.—Bicyclohexyl produced an 18% yield of a mixture of 3- and 4-phenylbicyclohexyl (Xa and Xb, respectively) when present in a reacting mixture of methylene chloride and benzene in the presence of aluminum chloride. Toluene was obtained in 15% yield.

1,1-Dichlorobutane.—The behavior of 1,1-dichlorobutane was similar to that of 1,1-dichloroethane. In the absence of hydrogen donor, 1,1-diphenylbutane (36%) was the principal product; butylbenzene was obtained in no more than 3%

(5) L. Schmerling and J. P. West, THIS JOURNAL, **76**, 1917 (1954).
(6) A. Barbot, *Bull. soc. chim.*, [4] **47**, 1314 (1930).
(7) G. Schroeter, *Ber.*, **57**, 1990 (1924).
(8) *Cf.* references 6 and 7.

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yield. In the presence of methylcyclohexane, *n*-butylbenzene and (methylcyclohexyl)-benzene were obtained in about 63–64% yield. On the other hand, the presence of cyclohexane had no effect on the reaction; the yields of products were identical to those obtained in the absence of donor. It is obvious that cyclohexane which does not contain a tertiary carbon atom was not a hydrogen donor under the reaction conditions (2–4°).

1,1-Dichloro-3-methylbutane.—Hydrogen transfer occurred with 1,1-dichloro-3-methylbutane, even in the absence of a saturated hydrocarbon; the product consisted of pentylbenzenes (27%), relatively little 1,1-diphenyl-3-methylbutane being produced. Infrared analysis showed that the pentylbenzene consisted of about 80% isopentylbenzene and 20% of 1,1-dimethylindan and/or 2-methyl-3-phenylbutane and *t*-pentylbenzene. Hydrogen attached to the tertiary carbon atom in the dichloride and/or the isopentylbenzene took part in the hydrogen exchange reaction in much the same manner as the analogous hydrogen atoms in the saturated hydrocarbons containing tertiary carbon atoms, yielding intermediates which reacted to yield the pentylbenzene isomers and/or the dimethylindan. It was not possible to distinguish between these hydrocarbons by means of infrared. The nature of the reaction, however, makes it seem most plausible that the by-product was the indan formed by ring closure at the tertiary carbon atom of isopentylbenzene. The dichloride which lost the hydride ion attached to the tertiary carbon atom was presumably converted to unsaturated product, making up the so-called "lower layer" catalyst complex, and to high boiling by-product.

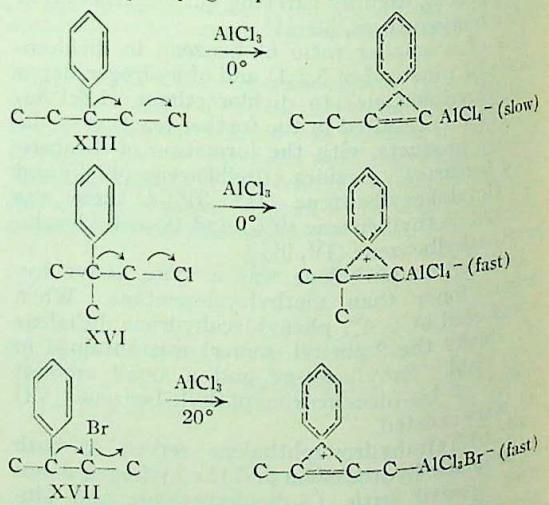
In the presence of methylcyclohexane, a higher yield (49%) of pentylbenzene (approximately 85–90% isopentylbenzene and 10–15% of other pentylbenzenes or dimethylindan) was obtained together with a 42% yield of (methylcyclohexyl)-benzene (III).

(2,2-Dibromoethyl)-cyclohexane.—Further evidence that the presence of a tertiary carbon atom in a dihalide results in comparatively high yields of monoalkylbenzene even in the absence of a saturated hydrocarbon was obtained by carrying out the reaction of 2,2-dibromoethyl)-cyclohexane with benzene in the presence of aluminum chloride. When no saturated hydrocarbon was used as a donor, 1-cyclohexyl-2-phenylethane (XII) was obtained in 37% yield. When isopentane was used, the yield of XII was 40%; there was a relatively low yield (12%) of pentylbenzene (85–90% 2-methyl-3-phenylbutane and 10–15% *t*-pentylbenzene) indicating that the hydrogen atom attached to the tertiary carbon atom in the dibromoethylcyclohexane is more readily abstracted than is that in isopentane.

1,2-Dichlorobutane.—The dihalides in the above-described experiments were those in which both halogen atoms are attached to the same carbon atom. Some dihalides in which the halogens are on adjacent carbon atoms were also tested: 1,2-dichlorobutane and 2,3-dibromobutane.

The reaction of 1,2-dichlorobutane with benzene in the presence of aluminum chloride at 4–6° resulted in a 37% yield of 1-chloro-2-phenylbutane[9] (XIII) and only 8% of diphenylbutane consisting of about 85% 1,2-diphenylbutane (XIV) and 15% of crystalline *meso*-2,3-diphenylbutane; formation of the crystalline isomer presumably involved rearrangement of XIII or XIV.

Formation of only 8% of the diphenylbutane was due apparently to the comparative inactivity of the chlorine atom attached to the primary carbon atom under the reaction conditions. This is somewhat analogous to the previously described[2] observation that the reaction of 1,3-dichloro-3-methylbutane with benzene in the presence of aluminum chloride at 2–4° produces as high a yield (28–29%) of the monophenyl compound 1-chloro-3-methyl-3-phenylbutane[10] (XV) as of the diphenyl derivative 2-methyl-2,3-diphenylbutane. On the other hand, the reaction of 1,2-dichloro-2-methylpropane (isobutylene dichloride) under the same conditions gave a 50% yield of 1,2-diphenyl-2-methylpropane, no 1-chloro-2-methyl-2-phenylpropane[11] (XVI) being isolated. In the case of XVI, participation of the neighboring phenyl group (anchimeric assistance[12]) probably was involved in the displacement of the chlorine atom,[2] resulting in a cyclic bridged (phenonium) ion. The markedly smaller yield of diphenylbutane with 1,2-dichlorobutane indicates that XIII is much less reactive than XVI because there is less anchimeric assistance in XIII than in XVI. A similar effect was noted in a study of the participation of β-phenyl groups in the solvolysis of some primary benzenesulfonates.[12] 2-Methyl-2-phenylpropyl *p*-bromobenzenesulfonate was 6.25 times as reactive in acetic acid as 2-phenylpropyl *p*-benzenesulfonate. It would seem that a methyl group attached to the β-carbon atom holding the phenyl group (thus making it a quaternary carbon) assists in the formation of a phenonium ion involving a primary carbon atom more than does hydrogen. As will be shown below, a β-phenyl group attached to a carbon atom



(9) Also named [1-(chloromethyl)-propyl]-benzene (*C. A.*).
(10) Also named (3-chloro-1,1-dimethylpropyl)-benzene (*C. A.*).
(11) Also named (2-chloro-1,1-dimethylethyl)-benzene (*C. A.*) and (chloro-*t*-butyl)-benzene.
(12) S. Winstein, C. R. Lindgren, H. Marshall and L. L. Ingraham, [illegible]

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holding hydrogen does seem to participate in the reaction when the halogen is on a secondary carbon atom as in 2-bromo-3-phenylbutane.

The effect of saturated hydrocarbons on the reactions of these dihalides may be explained similarly. When the reaction of 1,2-dichlorobutane with benzene was carried out in the presence of methylcyclohexane, the hydrogen transfer reaction occurred to a relatively small extent, yielding 7% each of *sec*-butylbenzene and the cycloalkylbenzene (III). Diphenylbutane (about 93% 1,2- and 7% 2,3-isomer) and the chlorobutylbenzene XIII were obtained in approximately the same yields (7 and 50%, respectively) as in the absence of the saturated hydrocarbon. Formation of the phenonium ion from XIII was slow. The reaction was similar to that of 1,3-dichloro-3-methylbutane with benzene and methylcyclopentane or isobutane[2]; the chloropentylbenzene XV was obtained in good yields (44 and 33%, respectively) together with methylcyclopentylbenzene (II, 38%) or *t*-butylbenzene (48%) which were formed in part by the hydrogen transfer of the saturated hydrocarbon with the dihalide *before* it reacted with the benzene. On the other hand, hydrogen transfer with the intermediate chlorobutylbenzene (or ionic analog) was the chief reaction when isobutylene dichloride reacted with benzene in the presence of methylcyclohexane, yielding isobutylbenzene (57%), III (70%) and 1-(methylcyclohexyl)-4-isobutyl-benzene (14%).[2] Anchimeric assistance by the phenyl group occurred readily only with the latter chloride, there being little participation by the phenyl group in the chloropentylbenzene XV because it and the chlorine atom are not "neighbors."

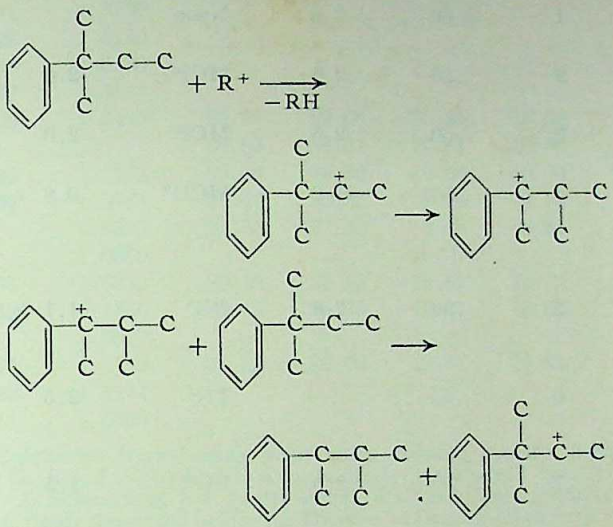
2,3-Dibromobutane.—In contrast to the results with the 1,2-dichlorobutane, high yields of hydrogen transfer product were obtained with a dihalide in which the halogen atoms were attached to adjacent secondary carbon atoms, namely 2,3-dibromobutane. In the presence of methylcyclopentane at room temperature, butylbenzene (95–96% *sec*-butylbenzene and 4–5% isobutylbenzene) and methylcyclopentylbenzene II were obtained in 68 and in 60% yield, respectively. In the absence of a saturated hydrocarbon, the chief product was *meso*-2,3-diphenylbutane (50%) together with a small amount of butylbenzene (6%).

The reaction may have involved the intermediate formation of 2-bromo-3-phenylbutane (XVII, not isolated) which under the influence of aluminum chloride and the neighboring group was converted to the cyclic bridged ion, reaction of which with benzene yielded diphenylbutane and with methylcyclopentane yielded *sec*-butylbenzene and methylcyclopentylbenzene II. The phenonium ion which is formed has been discussed in detail by Cram.[13] The small amount of isobutylbenzene which was formed can be explained by assuming a bridged ion involving the methyl group instead of the phenyl group.

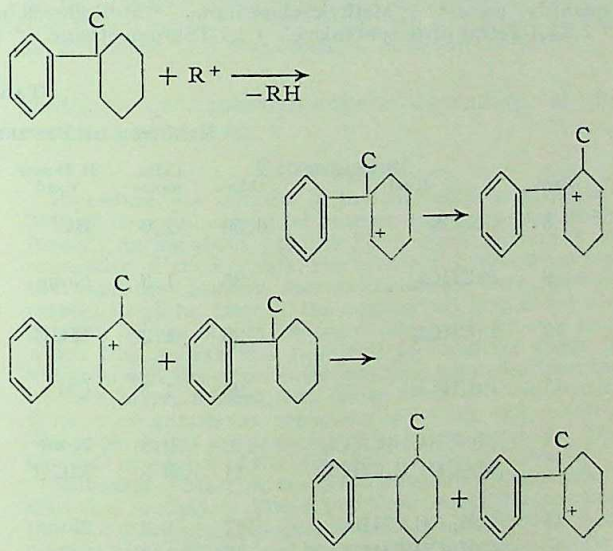
Anchimeric assistance also explains the fact that secondary, rather than tertiary, alkylbenzenes are produced in the presence of aluminum chloride.[5]

(13) D. J. Cram, THIS JOURNAL, **71**, 3863 (1949); **74**, 2129, 2137, 2139 (1952); and **75**, 332 (1953).

It has been postulated[5] that the primary product is a tertiary alkylbenzene which is isomerized to the secondary alkylbenzene by way of a chain reaction involving the formation of a resonance stabilized benzyl cation



Similarly



An objection to this type of mechanism is that hydrogen atoms attached to secondary carbon atoms are not abstracted readily under the reaction conditions. For example, cyclohexane is not a hydrogen donor in the reaction of benzene with 1,1-dichlorobutane (expt. 11). However, the objection is plausibly overcome by postulating that the neighboring phenyl group participates in the displacement of the hydride ion.

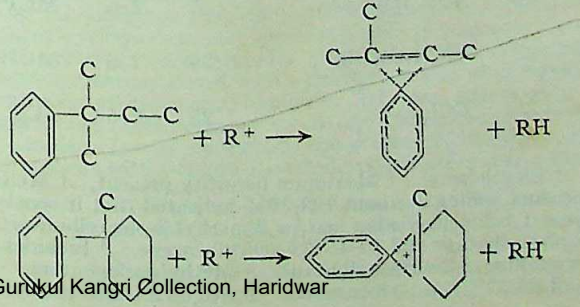


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TABLE I

REACTION OF BENZENE WITH 1,1-DICHLOROETHANE

Expt.	Reactants, moles $MeCHCl_2$	C_6H_6	H donor	$AlCl_3$, Moles	$AlCl_3$, g.	Temp., °C.	Chief products, Compound	%
1	0.50	2.6	None	..	5	3–4	PhEt	2[b]
							$MeCHPh_2$ (I)	33
2	.50	2.6	MCP[c]	2.0	5	3–4	PhEt	42
							MeC_6H_8Ph (II)	38
3	.50	2.6	MCP[c]	2.0	5	39–41	PhEt	62
							MeC_6H_8Ph (II)	60
4	.50	1.0	MCH[d]	0.8	5	38–51	PhEt	42
							$PhEt_2$	9
							$MeC_6H_{10}Ph$ (III)	31
							$MeC_6H_{10}PhEt$ (IV)	9
5	.50	2.6	DN[e]	1.1	5	2–4	PhEt	43
							$C_{10}H_{17}Ph$ (V)	70
							$(C_{10}H_{17})_2Ph$ (VI)	0.5
6	.45	..	TN[f]	2.5	5	26–96	$C_{10}H_{11}Et$ (VII)	44
							$C_{14}H_{18}$ (VIII)	0.5
							$(C_{10}H_{11})_2$ (IX)	41
7	.50[g]	2.6	BIP[h]	1.5	5	2–32	PhEt	34
							$PhCHMeCMe_3$	21

[a] Based on the equation: $MeCHCl_2 + 2C_6H_6 + RH \rightarrow PhEt + PhR + 2HCl$, where RH is the diluent. [b] Maximum quantity present. [c] Methylcyclopentane. [d] Methylcyclohexane. [e] Decahydronaphthalene (67% *cis*-, 33% *trans*-). [f] 1,2,3,4-Tetrahydronaphthalene. [g] 1,1-Dibromoethane. [h] Biisopropyl (*i.e.*, 2,3-dimethylbutane).

TABLE II

REACTION OF BENZENE WITH POLYHALIDES

Expt.	Polyhalide, Kind	Mole	C_6H_6, moles	H Donor, Kind	Moles	$AlCl_3$, g.	Temp., °C.	Chief products, Compound	%
8	CH_2Cl_2	0.50	2.6	BC[a]	2.0	5	25–27	PhMe	15
								$C_6H_{11}C_6H_{10}Ph$ (X)	18
9	$PrCHCl_2$	.25	1.3	None	..	3	2–3	PhBu	3[b]
								$PrCHPh_2$ (XI)	36
10	$PrCHCl_2$	.25	1.3	MCH[c]	1.0	3	2–4	PhBu	63
								$MeC_6H_{10}Ph$ (III)	64
11	$PrCHCl_2$	.25	1.3	CH[d]	1.0	3	2–4	PhBu	3[b]
								$PrCHPh_2$ (XI)	36
12	$Me_2CHCH_2CHCl_2$	.10	0.8	None	..	3	3–5	$PhCH_2CH_2CHMe_2$[e]	27
13	$Me_2CHCH_2CHCl_2$	.11	0.8	MCH[c]	0.6	3	3–3	$PhCH_2CH_2CHMe_2$[e]	49
								$MeC_6H_{10}Ph$ (III)	42
14	$C_6H_{11}CH_2CHBr_2$	.17	1.3	None	..	5	5–25	$PhCH_2CH_2C_6H_{11}$ (XII)	37
15	$C_6H_{11}CH_2CHBr_2$	.17	1.3	*i*-C_5[f]	1.0	5	0–26	$PhCH_2CH_2C_6H_{11}$ (XII)	40
								PhC_5H_{11}[g]	12
16	$EtCHClCH_2Cl$	.50	2.6	None	..	5	4–6	PhCHEtCH$_2$Cl (XIII)	37
								$EtCHPhCH_2Ph$ (XIV)	8[h]
17	$EtCHClCH_2Cl$	.50	2.6	MCH[c]	2.0	5	3–3	PhCHEtMe	7
								PhCHEtCH$_2$Cl (XIII)	50
								$MeC_6H_{10}Ph$ (III)	7
								$EtCHPhCH_2Ph$ (XIV)	7[i]
18	$Me(CHBr)_2Me$	.25	2.6	None	..	5	28–29	PhBu	6
								$(MeCHPh)_2$	50
19	$Me(CHBr)_2Me$	.25	2.6	MCP[j]	1.5	5	28–29	PhCHEtMe	68
								MeC_5H_8Ph (II)	60
20	$ClCH_2CHCl_2$	.26	2.6	MCH[c]	1.5	5	33–53	$PhCH_2CH_2Ph$	58
								$MeC_6H_{10}Ph$ (III)	60
21	CCl_4	.25	2.5	*i*-C_5[c]	2.0	5	24–28	CH_2Ph_2	24
								PhC_5H_{11}[k]	30[l]

[a] Bicyclohexyl. [b] Maximum quantity present. [c] Methylcyclohexane. [d] Cyclohexane. [e] The infrared spectrum of the product boiling at about 190–195° indicated that it consisted of about 80% isopentylbenzene and 20% of what might have been 1,1-dimethylindan and/or 2-methyl-3-phenylbutane. [f] Isopentane. [g] Infrared analysis indicates 85–90% 2-methyl-3-phenylbutane and 10–15% *t*-pentylbenzene. [h] Includes about 15% crystalline 2,3-diphenylbutane. [i] Includes about 7% crystalline 2,3-diphenylbutane. [j] Methylcyclopentane. [k] Infrared analysis indicates 65–70% 2-methyl-3-phenylbutane and 30–35% *t*-pentylbenzene. [l] Based on a theoretical yield of 2 moles of CH_2Ph_2 from 1 mole of carbon tetrachloride.

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TABLE III

PHYSICAL PROPERTIES OF THE REACTION PRODUCTS

	Compound	B.p., °C.	Mm.	B.p. at 760 mm., °C.[b]	$n^{20}D$	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	$MeCHPh_2$[c]	123–124	10	260–261	1.5730				
II	MeC_5H_8Ph[d]	77–79	4	225–228	1.5190				
III	$MeC_6H_{10}Ph$[e]	95–99	7	235–240	1.5180				
IV	$MeC_6H_{10}PhEt$	110–115	4	270–277	1.5174				
V	$C_{10}H_{17}Ph$	134–135	4	300–302	1.5360[f]	89.65	89.66	10.35	10.36
VI	$(C_{10}H_{17})_2Ph$	.....[g]				89.07	88.91	10.93	10.81
VII	$C_{10}H_{11}Et$	76–78	4	223–225	1.5373	89.94	90.20	10.06	10.05
VIII	$C_{11}H_{18}$[h]	113–126	3	283–299[i]	1.5664	90.46	90.32	9.54	9.78
IXa	$(C_{10}H_{11})_2$	176	3	370	1.5898	91.55	91.45	8.45	8.61
IXb	$(C_{10}H_{11})_2$	180	1	385	1.5960				
Xa	$C_6H_{11}C_6H_{10}Ph$	132–135	1	336–337	1.5310	89.19	89.16	10.81	10.77
Xb	$C_6H_{11}C_6H_{10}Ph$	173–174	4	350–352[j]	1.5350	89.19	89.33	10.81	10.66
XI	$PrCHPh_2$[k]	132	7	284	1.5570				
XII	$PhCH_2CH_2C_6H_{11}$	89–90	1	274–275	1.5183	89.29	89.09	10.71	10.82
XIII	$PhCHEtCH_2Cl$[l]	86–88	8	220–222	1.5174				
XIV	$EtCHPhCH_2Ph$[k]	124–128	8	270–275	1.5565				

[a] Analyses by Micro-Tech Laboratories, Skokie, Ill. [b] Calculated from boiling point under reduced pressure using Lippincott nomograph, *Ind. Eng. Chem.*, **38**, 320 (1946). [c] G. Egloff, "Physical Constants of Hydrocarbons," Vol. III, Reinhold Publishing Corp., New York, N. Y., 1946, p. 347. [d] L. Schmerling, J. P. Luvisi and R. W. Welch, THIS JOURNAL, 77, 1774 (1955). [e] L. Schmerling, R. W. Welch and J. P. West, paper presented before the Division of Organic Chemistry of the American Chemical Society at the Dallas Meeting, April 1956. [f] d^{20}_4 0.9729; mol. ref. calcd. 68.26, obsd. 68.69. [g] M.p. 158–160°. [h] An octahydroanthracene, *cf.* G. Egloff, ref. *c*, Vol. IV, p. 62. [i] Becomes partially crystalline on standing; m.p. 71–72°. [j] Crystallizes on standing; m.p. 83° (recrystallized from ethanol). [k] C. Egloff, ref. *c*, Vol. III, p. 358. [l] P. A. Levene, L. A. Mikeska and K. Passoth, *J. Biol. Chem.*, **88**, 27 (1930); G. J. VanZoeren, U. S. Patent 2,349,779.

When the phenonium ion abstracts a hydride ion from the tertiary alkyl- or cycloalkylbenzene, the reaction occurs at the tertiary carbon atom of the bridged ion, yielding secondary alkyl- or cycloalkylbenzene as the final product.

1,1,2-Trichloroethane.—Good yields (58–60% each) of bibenzyl and methylcyclohexylbenzene III were obtained by the reaction of 1,1,2-trichloroethane and benzene in the presence of methylcyclohexane and aluminum chloride at 33–53°. Bimolecular nucleophilic displacement of a chlorine on each carbon atom by benzene with the resultant formation of α-chlorobibenzyl occurred, followed by hydrogen-chlorine exchange involving the active benzylic chlorine atom. Alternatively, (2-chloroethyl)-benzene may have been formed first.

Bibenzyl was also a major product of the reaction in the absence of a saturated hydrocarbon.[14] Other products included diphenylmethane and anthracene. Hydrogen transfer reactions involving intermediate products, *e.g.*, 9,10-dihydroanthracene, apparently occurred.

Carbon Tetrachloride.—Hydrogen transfer occurred when carbon tetrachloride was contacted with benzene and isopentane in the presence of aluminum chloride at room temperature. Diphenylmethane was obtained in 24% yield and pentylbenzene (65–70% 2-methyl-3-phenylbutane and 30–35% *t*-pentylbenzene) in 30% yield, based on the theoretical yield of 2 moles of pentylbenzene per mole of carbon tetrachloride.

$$CCl_4 + 4C_6H_6 + 2C_5H_{12} \longrightarrow CH_2(C_6H_5)_2 + 2C_6H_5C_5H_{11} + 4HCl$$

In the absence of saturated hydrocarbon, the principal product of the reaction of carbon tetrachloride with benzene is either triphenylchloromethane or triphenylmethane depending on the reaction conditions.[15]

Experimental

Procedure.—A solution of the polyhalide in about 20–35% of the total amount of benzene used was added slowly (usually during about 1 to 2 hr.) to a stirred mixture of the remainder of the benzene, the saturated hydrocarbon and the catalyst. Stirring was continued for from approximately 1 to 3 hr. after all the mixture had been added (depending on the rate of hydrogen chloride evolution), after which the product was permitted to stand for about 10 minutes, and the upper layer was then separated from the catalyst layer, washed with dilute alkali and with water, dried over anhydrous potassium carbonate and distilled. The experiments are summarized in Tables I and II. The physical properties of the products are given in Table III.

Materials.—Most of the polyhalides were commercially available products. The 1,1-dichloro-3-methylbutane and the (2,2-dibromoethyl)-cyclohexane were prepared by condensing vinyl chloride and bromide with isopropyl chloride[16] and cyclohexyl bromide,[17] respectively.

Identification of Products.—The well-known alkylbenzenes were identified by their physical properties and by comparison of their infrared spectra with those of the authentic compounds. These included toluene, ethylbenzene, diethylbenzene, *n*- and *sec*-butylbenzene, isopentylbenzene, *t*-pentylbenzene, 2-methyl-3-phenylbutane and 2,2-dimethyl-3-phenylbutane.[5] Diphenylmethane was similarly identified. Bibenzyl (m.p. 52–53°) and 2,3-diphenylbutane (m.p. 123–125°) were characterized by melting point and by "mixed melting point" with authentic samples.

The infrared spectra of the methylcycloalkylbenzenes II and III indicated that the tertiary compounds 1-methyl-1-phenylcyclopentane and 1-methyl-1-phenylcyclohexane were not present. It is probable that II was (3-methylcyclopentyl)-benzene mixed with a smaller amount of (2-methylcyclopentyl)-benzene. Similarly, III was presumably a mixture of (3-methylcyclohexyl)- and (4-methylcyclohexyl)-benzene. It was identical to the product of the alkylation of benzene with 1-chloro-1-methylcyclohexane or with 3- or 4-

(14) A. Gardeur, *Bull. acad. roy. Belg.*, [3] **34**, 920 (1898).

(15) C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941, pp. 116–118.

(16) L. Schmerling, THIS JOURNAL, **68**, 1650 (1946).

(17) L. Schmerling, *ibid.*, **71**, 698 (1949).

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methylcyclohexanol in the presence of aluminum chloride.[18]

The structures of several of the remaining polynuclear compounds were determined by dehydrogenation to known crystalline aromatic hydrocarbons using a platinum–alumina catalyst at 250–350°.

The **phenyldecahydronaphthalene V** yielded product, m.p. 92–95°, which on recrystallization from alcohol melted at 100–101°. 2-Phenylnaphthalene is reported to melt at 100–102°, 1-phenylnaphthalene at 84–86°.[19] Attempts to isolate product melting at about 85° by fractional crystallization were unsuccessful. Hence, V was apparently principally 2-phenyldecahydronaphthalene.

Compound VIII yielded yellow needles melting at 205–207° which did not depress the melting point of anthracene. Since analysis indicated that the formula of VIII was $C_{14}H_{18}$, it may be concluded that it was an octahydroanthracene.

The lower boiling **tetrahydronaphthyltetrahydronaphthalene (IXa)** gave yellow crystals, m.p. 73–74°. The higher boiling material (IXb) yielded product of m.p. 180–181°. The approximate melting points reported in the literature[20] for the binaphthyls are: 1,1′-, 156°; 1,2′-, 76°; and 2,2′-, 187°. Fractional crystallization of the products failed to yield any material melting near 156°. It may be concluded that IX consists of 6-(1,2,3,4-tetrahydro-2-naphthyl)-1,2,3,4-tetrahydronaphthalene and either or both 6-(1,2,3,4-tetrahydro-1-naphthyl)- and 5-(1,2,3,4-tetrahydro-2-naphthyl)-1,2,3,4-tetrahydronaphthalene. While the relative amounts of these isomers were not determined, it appeared from the fractionation data that the 6-(1,2,3,4-tetrahydro-2-naphthyl)- isomer was present in largest amount.

The phenylbicyclohexyl (Xa) liquid fraction yielded a crystalline product which on fractional crystallization gave 2 parts of white flakes, m.p. 205–206°, and 8 parts of white needles, m.p. 83–85°. Dehydrogenation of the crystalline phenylbicyclohexyl Xb yielded product, m.p. 204–205°. The literature[21] values for the melting points of 1,2-, 1,3- and 1,4-diphenylbenzene are, respectively, 55–58°, 84–89° and 205–214°. Hence, X was a mixture of 3- and 4-phenylbicyclohexyl, the latter being a crystalline compound, Xb.

(18) L. Schmerling, unpublished results.

(19) G. Egloff, "Physical Constants of Hydrocarbons," Vol. IV, Reinhold Publishing Corp., New York, N. Y., 1947, p. 226.

(20) G. Egloff, ref. 19, Vol. IV, p. 317.

(21) G. Egloff, ref. 19, Vol. III, p. 473.

DES PLAINES, ILLINOIS

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

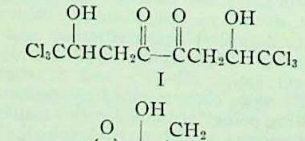
The Structure of Chloretyl, the Product of the Reaction between Chloral and Biacetyl

BY NELSON J. LEONARD, JOHN C. LITTLE[1] AND A. JERRY KRESGE[2]

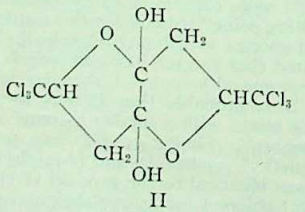
RECEIVED DECEMBER 12, 1956

Spectral and chemical evidence has been presented to establish the structure of chloretyl, the product of the reaction between chloral and biacetyl, as 3,7-di-(trichloromethyl)-2,6-dioxabicyclo[3.3.0]octane-1,5-diol (II). The stereochemical structures of the α- and β-isomers of chloretyl (racemates) have been tentatively assigned as *cis–cis–cis* (VI) and *cis–cis–trans* (VII).

In 1952, a product of molecular formula $C_8H_8Cl_6O_4$ was obtained by Schlenk[3] from the reaction of chloral with biacetyl, in 2:1 molar proportion, in the presence of piperidinium acetate. The structure of the colorless solid, m.p. 199–201° dec., was not established, and the suggested formulations of the compound as a diketone dihydrate or a monohydrate of a hydroxyketone were not fully satisfactory. The property of the compound that was difficult to accommodate in postulated structures was the absence of absorption in the ultraviolet and visible regions. We reasoned that if the initial reaction product were conceived as normal (I), simple conversion to a bis-hemiketal would provide a structural expression II, 3,7-di-(trichloromethyl) - 2,6 - dioxabicyclo[3.3.0]octane - 1,5 - diol, which would satisfy the data presented by Schlenk for the $C_8H_8Cl_6O_4$ compound. Our postulate has been confirmed by infrared absorption and nuclear magnetic resonance studies and by additional chemical evidence. Moreover, we are in a position to consider the stereochemistry of the predominant product and its isomers.



I



II

We used conditions for the reaction between chloral and biacetyl similar to those of Schlenk. However, we were able to isolate two isomeric compounds, $C_8H_8Cl_6O_4$: an α-isomer capable of existing in readily interconvertible dimorphic forms, m.p. *ca.* 206° dec. and *ca.* 175° dec., and a β-isomer, m.p. 175–177°, in lower yield. As a convenience, we wish to use the name "chloretyl" (klôrĕtĕl) for these products, or specifically, "α-chloretyl" and "β-chloretyl."

The infrared absorption spectra of the dimorphic forms of α-chloretyl were virtually identical as Nujol mulls and identical as 1% solutions in benzene. The spectrum of the β-isomer was similar but not identical to the α-chloretyl spectrum. The spectra of both isomers confirmed the absence of olefinic and carbonyl unsaturation and indicated the presence of hydroxyl. The spectrum of solid α-chloretyl showed a sharp hydroxyl band at 3480 cm.$^{-1}$ and that of β-chloretyl at 3450 cm.$^{-1}$ (Nujol mull). There were also present in the 9–11 μ region absorption bands resembling those exhibited by tetrahydrofuran. The most logical structure for chloretyl, consistent with the precursors in synthesis and the ana-

(1) National Science Foundation Fellow, 1954–1957.

(2) Eli Lilly and Co. Fellow, 1952–1953.

(3) H. Schlenk, *Ber.*, **85**, 901 (1952). We wish to record our appreciation for recent conversations with Dr. Schlenk concerning the structure and chemistry of this product.

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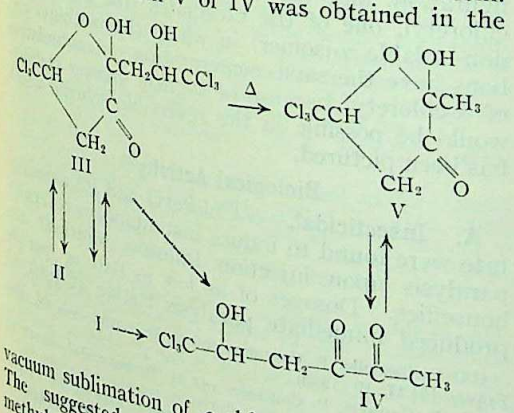
lytical and spectral data, is given by II. As further physical confirmation of this structure, the NMR spectrum, determined in dioxane solution,[4] showed clearly (Fig. 1) the ratio of 1:1:2 for the different types of hydrogen in α-chloretyl, *i.e.*, 2 hydroxyl hydrogens: 2 $CH-CCl_3$ hydrogens: 4 methylene hydrogens.

Chemical confirmation of structure II was found in the positive identification of the hemiketal hydroxyl function. Although the usual acetylation methods failed,[3] it was possible to obtain the monoacetate by prolonged heating of α-chloretyl with isopropenyl acetate in benzene solution in the presence of *p*-toluenesulfonic acid. The high frequency of the C=O stretching band (1765 cm.$^{-1}$ in the infrared spectrum of α-chloretyl monoacetate was indicative of the $-O-\overset{|}{\underset{|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_3$ system. This argument is based upon the general finding that an electronegative substituent on the α-carbon of the alcohol portion of an ester increases the carbonyl absorption frequency and the specific observation that the model compound 1,1-diacetoxypropane has a carbonyl absorption maximum at 1761 cm.$^{-1}$.[5] The mono-3,5-dinitrobenzoate of α-chloretyl also exhibited ester carbonyl absorption in this region, at 1764 cm.$^{-1}$. Attempts to combine both hemiketal hydroxyls of II in ketal formation with methanol, ethylene glycol, acetone or cyclopentanone were not successful.

The presence of an easily accessible α-diketone grouping in α-chloretyl was demonstrated in the reactions with *o*-phenylenediamine, hydroxylamine and phenylhydrazine. The quinoxaline, dioxime and osazone formed were derivatives of 6,6,6-trichlorohexan-5-ol-2,3-dione (IV). Under the usual reaction conditions chloretyl apparently reverts to the intermediate IV by losing the chloral moiety from either the acyclic I or monocyclic III form. The hemiketal form V of IV was obtained in the vacuum sublimation of α-chloretyl or β-chloretyl. The suggested structure, 2-methyl-5-trichloromethyl-1-oxacyclopentan-2-ol-3-one (V), is based mainly on analysis and spectrum. Oxidation of



chloretyl with hydrogen peroxide in acetic acid has been found to give 4,4,4-trichloro-3-hydroxybutyric acid in low yield,[3] consistent with any sequence leading to III, I or IV, followed by oxidation. The isomeric relation of α-chloretyl and β-chloretyl was shown by the production of the same quinoxaline (of IV) and the same monocyclic compound (V) from either precursor.

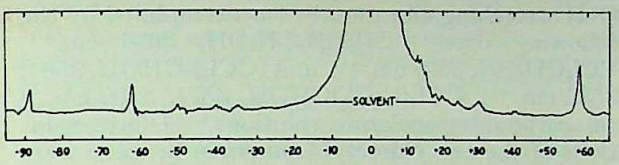
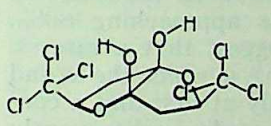
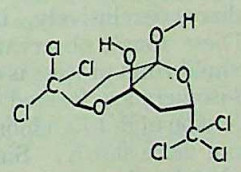


Fig. 1.—Nuclear magnetic resonance shift relative to reference (parts per million): $(H - H_r/H_r)$; frequency 30 mc.; zero of reference, dioxane.

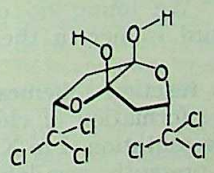
In considering the possible stereochemical structural assignments of α- and β-chloretyl, if it is recognized that in the synthetic procedure an energetically favorable ring closure completes the formation of the bicyclic system (*e.g.*, I or III → II), it follows that forms of II having a *trans* ring juncture can be excluded on the basis of analogy with the greater stability of *cis*-bicyclo[3.3.0]octane over the *trans* isomer.[6,7] Among the possible representations of chloretyl having a *cis* ring juncture (VI, VII, VIII; one form used to designate each racemate), the *trans*–*cis*–*trans* structure VIII is the least favored, since it is the only one in which the trichloromethyl groups are in steric apposition. Moreover,



VI
CIS-CIS-CIS



VII
CIS-CIS-TRANS



VIII
TRANS-CIS-TRANS

the infrared O–H stretching frequency exhibited by a structure like VIII should be in the normal free hydroxyl range, whereas both isomers of chloretyl which have been isolated had infrared hydroxyl bands at lower than normal frequency, suggestive of the proximity of chlorine to hydroxyl hydrogen,

(4) By Dr. James N. Shoolery and staff of Varian Associates, Palo Alto, Calif., on the commercial Varian instrument. We are grateful to Dr. Shoolery for his interest and his help. It is possible that disease might conceal some peaks of the compound, so that reliance must be placed on other information available as well.

(5) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).

(6) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 611 (1936).

(7) For a discussion of the relatively greater stability of the *cis* form in another model ring system, 3,7-dioxabicyclo[3.3.0]octane, a moiety of sesamin and asarinin, see M. Beroza and M. S. Schechter, THIS JOURNAL, **78**, 1242 (1956); *cf.* A. Michael and J. Ross, *ibid.*, **55**, 3684 (1933). A. C. Cope and T. Y. Shen, *ibid.*, **78**, 5916 (1956), have recently demonstrated highly stereospecific ring closures to *cis*-2,6-dioxabicyclo[3.3.0]octanes.

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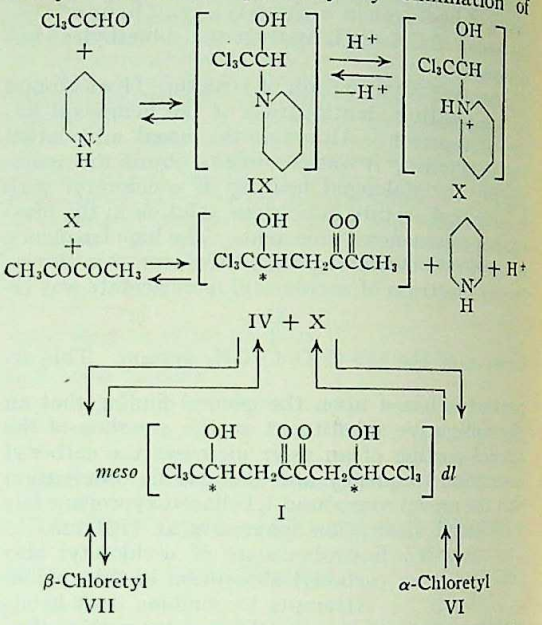
as in the examples of the chloroalcohols[8-10] and chlorophenols.[11,12]

On the basis of the foregoing arguments, the remaining problem lies in the assignment of the proper geometrically-isomeric structures, VI and VII, to α- and β-chloretyl. In our tentative assignment, reliance has been placed again upon the infrared spectral effect of an adjacent chlorine atom, which is to lower the frequency of the free hydroxyl O–H stretching vibration,[10,12] as exemplified by the following series: $CH_3CH_2CH_2OH$, 3636 cm.$^{-1}$; CCl_3CH_2OH, 3597 cm.$^{-1}$; and $(CCl_3)_2CHOH$, 3584, 3534 cm.$^{-1}$; $CCl_3(C_2Cl_5)CHOH$, 3571, 3509 cm.$^{-1}$ (in carbon tetrachloride solution).[8] Dilute solutions of the two chloretyl isomers in benzene were examined in the 3 μ region, and maxima were observed at 3550 cm.$^{-1}$ for β-chloretyl and 3510 cm.$^{-1}$ for α-chloretyl. No splitting of either band was observed. The difference is considered real and suggests that in α-chloretyl the equivalent hydroxyls are in a more electronegative environment than they are in β-chloretyl. This situation would be satisfied if α-chloretyl were assigned the *cis–cis–cis* structure (VI), with effectively two chlorines adjacent to the hydroxyls, and β-chloretyl, the *cis–cis–trans* structure (VII), with one chlorine exerting attraction for the hydroxylic hydrogens. Consistent with the infrared findings is the qualitative observation that α-chloretyl appears to be the thermodynamically more stable isomer. Thus, reactions of chloral with biacetyl which were allowed to run for 36 hr. gave approximately equal quantities, although in low yield, of α- and β-chloretyl, while reactions which were allowed to proceed to near completion (11 days) produced the α-isomer almost exclusively, in yields approaching 80%. These rough observations suggest that a rate *vs.* equilibrium process is occurring, in which the α- and β-isomers are formed randomly at first and a conversion of β- to α-chloretyl takes place subsequently and more slowly. Since a reversible process exists whereby the γ-isomer VIII could revert to VI, it is logical that VIII would not survive even if it were formed initially. We found no evidence of the presence of a third isomer in the crude reaction products.

Of the several reaction schemes which can be postulated for the formation of chloretyl, the formula diagram representation (I to X) accounts satisfactorily for the presently available facts. The intermediate IX is similar to the benzylidene-bis-piperidine intermediate proposed in condensations involving benzaldehyde and a piperidine catalyst.[13] The equilibrium between the hydroxyamine IX and the corresponding bis-amine probably lies predominantly on the side of the hydroxyamine because of the great stability of the hydroxyl group in this system, as in chloral hydrate, chloral hemiacetals and other examples.[14-20] The reaction of chloral with piperidine (or morpholine) at about 50° is vigorous and leads to the formation of the N-formyl derivative,[21] probably by elimination of



chloroform from IX. This possible side reaction in the chloretyl preparation was repressed by chilling the reaction mixture prior to the addition of piperidine. Participation of the protonated intermediate X in the aldol condensation with biacetyl is envisaged with the loss of piperidine and the formation of IV. The key step in the reaction sequence then becomes the condensation of IV with a second chloral intermediate to form either *dl*- or *meso*-I. The *meso* form is a precursor of β-chloretyl, the racemate in which the methinyl carbons are of opposite configuration, and the *dl* form is a precursor of α-chloretyl, one of the racemates (the other is the non-isolable γ-isomer) in which the methinyl carbons have the same configuration. Accumulation of α-chloretyl because of slightly greater stability would be possible in the reversible scheme which has been pictured.

Biological Activity[22]

A. Insecticidal.—α-Chloretyl and its monoacetate were found to induce instantaneous reversible paralysis upon injection (dioxane solution) into houseflies. Dosages of as low as 0.01 μg. per fly produced immediate paralysis lasting at least 45

(8) R. N. Haszeldine, *J. Chem. Soc.*, 1757 (1953).

(9) O. Bastiansen, *Acta Chim. Scand.*, **3**, 415 (1949).

(10) L. R. Zumwalt and R. M. Badger, THIS JOURNAL, **62**, 305 (1940).

(11) O. R. Wulf, U. Liddel and S. B. Hendricks, *ibid.*, **58**, 2287 (1936).

(12) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, pp. 300 ff.

(13) W. Dilthey and B. Stallmann, *Ber.*, **62**, 1603 (1929), and work in progress in this Laboratory.

(14) F. Caujolle, P. Couturier and C. Dulaurens, *Bull. soc. chim. France*, [5] **17**, 19 (1950).

(15) F. Caujolle, P. Couturier and M. Doumerc, *ibid.*, [5] **17**, 22 (1950).

(16) P. Couturier, *ibid.*, [5] **17**, 25 (1950).

(17) M. Ikawa and K. P. Link, THIS JOURNAL, **72**, 4373 (1950).

(18) H. Gault and G. Mennicken, *Compt. rend.*, **229**, 1239 (1949).

(19) K. Matsumura and M. Ito, THIS JOURNAL, **77**, 6671 (1955).

(20) J. Décombe, *Compt. rend.*, **237**, 336 (1953).

(21) G. B. L. Smith, M. Silver and E. I. Becker, THIS JOURNAL, **70**, 4254 (1948); E. Merck, German Patent 334,555.

(22) We wish to thank Professor C. W. Kearns, Department of Entomology, University of Illinois, for making the results of the entomological tests available to us, and Dr. K. K. Chen, The Lilly Research Laboratories, Eli Lilly and Co., for the pharmacological results.

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May 20, 1957

minutes. By contrast, α-chloretyl mono-3,5-dinitrobenzoate and β-chloretyl were inactive.

B. Pharmacological. Anticonvulsant.—α-Chloretyl showed 40% protection at 400 mg./kg. by the Electroshock method and 25% protection by the Metrazol method (same dosage) upon oral administration to rats. **Hypnotic.**—Oral administration of from 400 to 900 mg./kg. to rats produced no hypnosis.

Experimental[23]

Condensation of Chloral with Biacetyl.[24]—To a chilled solution of 20.0 g. (0.233 mole) of biacetyl, 70 g. (0.48 mole) of chloral and 9.0 g. (0.15 mole) of glacial acetic acid in 70 ml. of anhydrous benzene, 8.4 g. (0.10 mole) of piperidine was added dropwise. The system was swept with nitrogen and stirred at 25° for 10 days. The precipitate was collected by filtration and washed with hexane. The crude chloretyl (37.2 g.) was dissolved in 120 ml. of warm dioxane, and the solution was diluted with water. The mixture was chilled with vigorous shaking until the chloretyl crystallized. The solid was broken into fine particles, and the mixture was filtered. After washing with cold 50% aqueous methanol and drying, the **α-chloretyl** weighed 36.5 g. (41%), m.p. *ca.* 203° dec. An analytical sample was prepared by recrystallization from benzene–hexane as colorless needles, m.p. *ca.* 206° dec. from a hot or acidic (with a trace of acetic acid) solution or m.p. *ca.* 175° dec. from a cool basic (a trace of pyridine) solution.

Anal. Calcd. for $C_5H_8Cl_6O_4$: C, 25.23; H, 2.12. Found: C, 25.24; H, 2.14.

The infrared absorption spectrum showed maxima (Nujol mull) at 3480 (OH); 1292, 1149, 1095, 1080, 1048, 1013; 814, 790 cm.$^{-1}$ (CCl_3); (1% solution in benzene) at 3510 (OH); 1392, 1294, 1250, 1135, 1106, 950, 910, 836; 812, 801 cm.$^{-1}$ (CCl_3). The compound in cyclohexane solution was transparent in the ultraviolet region, 215–400 mμ.

The mother liquor and washings from the α-chloretyl isolation were diluted with benzene. The combined liquid was washed thoroughly with water, followed by a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and treated with decolorizing carbon. Filtration yielded a light yellow-orange solution from which the solvent was removed in vacuum to yield an orange solid. The solid was suspended in boiling hexane, and the mixture was filtered. After washing and drying, the solid obtained (14.6 g., 17%) was found to be a mixture of approximately 90% α- and 10% β-chloretyl. The latter was separated and purified by fractional crystallization from benzene–hexane, with treatment with decolorizing carbon. An analytical sample of β-chloretyl was prepared by recrystallization from benzene–hexane as colorless needles, m.p. 175–177°, different from the isomorphic form of α-chloretyl, m.p. 175° dec.

Anal. Calcd. for $C_5H_8Cl_6O_4$: C, 25.23; H, 2.12. Found: C, 25.39; H, 2.18.

The infrared absorption spectrum showed maxima (Nujol mull) at 3450 (OH); 1288, 1264, 1192, 1173, 1142, 1130, 1110–1085, 1044, 1018, 925, 903, 864, 840; 810–790 cm.$^{-1}$ (CCl_3); (1% solution in benzene) at 3550 (OH); 1395, 1368, 1320, 1270, 1205, 1145, 935, 903, 868, 837; 809 cm.$^{-1}$ (CCl_3).

Both isomers of chloretyl were instantly soluble in cold, dilute sodium hydroxide,[25] soluble in cold methanol and ethanol, somewhat soluble in benzene and insoluble in hexane and water. Chloretyl decomposed upon prolonged heating in hydroxylic solvents but appeared to be stable in crystalline form when pure.

Quinoxaline Formation.—A mixture of 0.50 g. (1.31 mmoles) of α-chloretyl and 0.16 g. (1.48 mmoles) of *o*-phenylenediamine in 15 ml. of absolute ethanol was heated under reflux for 8 hr. and then allowed to stand overnight. Dilution with water yielded 0.39 g. (97%) of red-brown platelets, m.p. 147–148°. Sublimation or recrystallization from aqueous ethanol gave ivory platelets, m.p. 148–149°.

Anal. Calcd. for $C_{12}H_{11}Cl_3N_2O$: C, 47.16; H, 3.63; N, 9.17; Cl, 34.80. Found: C, 47.22; H, 3.61; N, 9.10; Cl, 34.72.

The analysis and infrared spectrum (including maxima at 3200, 1104 and 794–810 cm.$^{-1}$) were consistent with the formulation of this product as **2-[1′-(2′-hydroxy-3′,3′,3′-trichloropropyl)]-3-methylquinoxaline.**

β-Chloretyl was converted to the quinoxaline by heating 85 mg. (2.24 mmoles) of this isomer with 27 mg. (2.5 mmoles) of *o*-phenylenediamine in 4 ml. of absolute ethanol for 6 hr. Dilution with 4 ml. of water and cooling caused the separation of 47 mg. (69%) of ivory platelets, which were recrystallized from aqueous ethanol, m.p. 147–148°, identical by the usual criteria with the product described above.

Oxime Formation.—A mixture of 1.00 g. (2.63 mmoles) of α-chloretyl, 0.42 g. (6.0 mmoles) of hydroxylamine hydrochloride, 5 ml. of absolute ethanol and 5 ml. of pyridine was heated under reflux for 12 hr. Evaporation of solvent yielded a brown residue which upon trituration with water formed heavy granular crystals, m.p. 186–187° dec. Sublimation yielded colorless crystals, m.p. 188–189° dec.

Anal. Calcd. for $C_6H_9Cl_3N_2O_3$: C, 27.35; H, 3.44; N, 10.63. Found: C, 27.93; H, 3.57; N, 10.38.

The analysis and infrared spectrum (including maxima at 3560, 3210, 3070 and 1090 cm.$^{-1}$) were consistent with the formulation of the product as **6,6,6-trichlorohexan-5-ol-2,3-dione dioxime.**

Osazone Formation.—A mixture of 0.50 g. (1.31 mmoles) of α-chloretyl, 0.35 g. (3.24 mmoles) of phenylhydrazine and a few crystals of sodium acetate in 15 ml. of 95% ethanol was heated under reflux for 3 hr., diluted with water and allowed to stand at 5° overnight. The solid which separated was recrystallized from aqueous ethanol as small orange needles, m.p. 164–165°. The infrared absorption spectrum (Nujol mull) exhibited maxima at 3300, 1608, 1575 and 1100 cm.$^{-1}$ among others.

Anal. Calcd. for $C_{18}H_{19}Cl_3N_4O$: C, 52.25; H, 4.63; N, 13.56. Found: C, 52.26; H, 4.59; N, 13.30.

On the basis of analysis and infrared spectrum, this product can be assigned the structure **6,6,6-trichlorohexan-5-ol-2,3-dione bis-phenylhydrazone.**

α-Chloretyl Monoacetate.—A mixture of 8.05 g. (21.1 mmoles) of α-chloretyl, 5.00 g. (50.0 mmoles) of isopropenyl acetate and a few crystals of *p*-toluenesulfonic acid in 50 ml. of benzene was heated under reflux for 20 hr. The solvent was removed *in vacuo*, and the residue was dissolved in 95% ethanol. The solution was treated with decolorizing carbon, filtered, and the filtrate was diluted with water. The solid α-chloretyl monoacetate was collected and dried, m.p. 91–94°, yield 6.19 g. (73%). Purification by sublimation or recrystallization from aqueous ethanol resulted in colorless crystals, m.p. 93–94°.

Anal. Calcd. for $C_{10}H_{10}Cl_6O_5$: C, 28.40; H, 2.38; Cl, 50.30; mol. wt., 422.9. Found: C, 28.55; H, 2.56; Cl, 50.88; mol. wt., 423, 444 (Rast, camphor).

The infrared absorption spectrum showed maxima (Nujol mull) at 3040 (OH); 1765 (C=O); 1255, 1210, 1184, 1125, 1085, 1053, 1016, 965, 935, 912, 897, 871, 840; 814, 805 cm.$^{-1}$ (CCl_3).

α-Chloretyl Mono-3,5-dinitrobenzoate.[26]—To 4 ml. of pyridine was added 0.22 g. (1.04 mmoles) of 3,5-dinitrobenzoic acid and 0.41 g. (2.16 mmoles) of *p*-toluenesulfonyl chloride. The mixture was cooled to 0°, and 0.20 g. (0.53 mmole) of α-chloretyl was added. The mixture was kept at 0° for 8 hr. and was then diluted with ice-water. The solid which separated was recrystallized from aqueous ethanol as a light tan powder, m.p. *ca.* 208° dec., yield 0.12 g. (30%). Repeated recrystallization from dioxane–ethanol–water yielded nearly colorless platelets, m.p. 215° dec.

(23) Melting points are corrected and boiling points are uncorrected. We are indebted to Mrs. Lucy Chang, Mrs. Ruby Ju, Mrs. R. Maria Benassi, Miss Claire Higham and Mr. Joseph Nemeth for the microanalyses and to Mrs. Louise Griffing, Mr. James Brader and Mr. Cy Portnow for determination of the infrared spectra, using a Perkin-Elmer automatic recording infrared spectrometer, model 21.

(24) All reagents were purified.

(25) Equilibration with the open form(s), I and/or III, would liberate the trichloromethylcarbinol group, which is acidic. A pK'_a value of 11.8 has been reported for trichloroethanol.[8] The cause of the solubility may also reside in a hydrolysis reaction of the trichloromethyl group, since Schlenk found chloride ion to be liberated when α-chloretyl was treated with aqueous sodium carbonate.[3]

(26) J. H. Brewster and C. J. Ciotti, Jr., This Journal, **77**, 6214 (1955).

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Anal. Calcd. for $C_{15}H_{10}Cl_6N_2O_9$: C, 31.33; H, 1.75; N, 4.87; Cl, 37.00. Found: C, 31.92; H, 1.83; N, 4.68; Cl, 36.40.

The infrared spectrum showed maxima (5% in chloroform) at 1764 (C=O); 1560, 1351 (NO_2); 1274, 1161, 1130, 1082, 1020, 966; 815 cm.$^{-1}$ (CCl_3).

Decomposition of Chloretyl on Heating in Vacuum.—When either α- or β-chloretyl was sublimed at 135–140° (0.2 mm.), a small amount of unstable colorless compound, m.p. 102° dec., was obtained as the more volatile fraction. This substance was tentatively assigned the structure V, **2-methyl-5-trichloromethyl-1-oxacyclopentan-2-ol-3-one**, on the basis of analysis and infrared absorption spectrum: ν_{max}^{Nujol} 3355 (OH); 1751 (C=O); 1185, 1156, 1139, 1099, 995, 936, 911, 869; 799 cm.$^{-1}$ (CCl_3).

Anal. Calcd. for $C_6H_7Cl_3O_3$: C, 30.86; H, 3.02. Found: C, 30.89; H, 2.82.

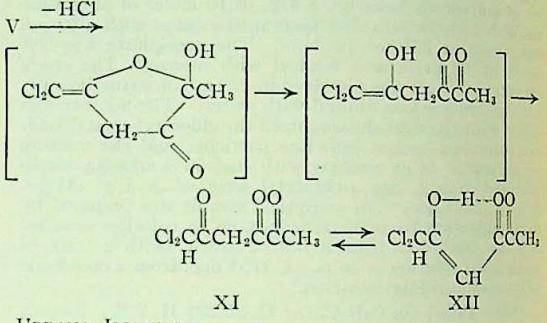
This material soon decomposed on standing at 25° to a yellow oil, with apparent loss of HCl. The infrared spectrum of the oil is consistent with the structure XI, **6,6-dichlorohexane-2,3,5-trione**, which probably exists largely as the enol XII.[27] The infrared spectrum showed maxima (5% in chloroform) at 3600–3000 (broad absorption with much fine structure, characteristic of bonded OH); 1720 (C=O); 1642 (conj. C=O); 1602 (C=C); 1423–1416, 1365, 1320, 1240–1213, 1115, 1098, 977, 840 cm.$^{-1}$.

Preparation of 2,2,2-Trichloroethyl 3,5-Dinitrobenzoate.[26]—To a cold solution of 1.42 g. (6.7 mmoles) of 3,5-dinitrobenzoic acid and 2.54 g. (13.6 mmoles) of *p*-toluenesulfonyl chloride in 20 ml. of cold dry pyridine was added 1.0 g. (6.7 mmoles) of 2,2,2-trichloroethanol. The mixture was allowed to stand at 0° for 1.5 hr. and was poured into 300 ml. of ice-water with vigorous stirring. The resultant peach-colored solid was collected by filtration and recrystallized from 95% ethanol to yield 1.55 g. (68%) of ivory platelets, m.p. 128–131°. Treatment with decolorizing carbon and repeated recrystallization from ethanol yielded an analytical sample of white platelets, m.p. 140–141°.

Anal. Calcd. for $C_9H_5Cl_3N_2O_6$: C, 31.45; H, 1.48; N, 8.15. Found: C, 31.70; H, 1.58; N, 8.33.

The infrared spectrum (5% in chloroform) showed maxima at 1755 (C=O); 1634, 1603 (aromatic); 1554, 1351 (NO_2); 1274, 1163 (C–O); 835 cm.$^{-1}$ (non-enhanced CCl_3). It will be noted that the position of the C=O maximum is at lower frequency than that exhibited by α-chloretyl mono-3,5-dinitrobenzoate.

(27) The formation of XI may be conceived as



URBANA, ILLINOIS

COMMUNICATIONS TO THE EDITOR

THE ENZYMATIC CONVERSION OF MEVALONIC ACID TO SQUALENE

Sir:

The recent isolation and identification of mevalonic acid (DL-β,δ-dihydroxy-β-methylvaleric acid, MVA) a new precursor of cholesterol[1–3] constitute an important advance in the understanding of terpene and steroid biogenesis. In this communication, we wish to report the transformation of mevalonic acid to squalene by soluble yeast enzymes and to describe experiments bearing on the mechanism of MVA utilization. Particle-free extracts of dried baker's yeast have been prepared which catalyze the conversion of DL-2-C^{14}-MVA to a radioactive lipid, shown to be squalene by alumina chromatography and by preparation of the thiourea adduct[4] and of the crystalline hexahydrochloride.[5] No sterols are synthesized from MVA under these conditions. Dialysis and treatment with charcoal to remove cofactors render the yeast extract completely inactive. Activity is restored by addition of Mn^{++}, ATP[6] and pyridine nucleotide (Table I). The reaction proceeds anaerobically as well as in air. Experiments bearing on the mechanism of the condensation process have been carried out with 2-C^{14},5-di-T-mevalonic acid. Tritium was introduced by partial reduction of β-hydroxy-β-methylglutaric acid with $LiAlT_4$. The purified product, when combined with authentic DL-2-C^{14}-MVA and recrystallized several times as the dibenzylethylenediamine salt or chromatographed on paper, showed no change in the T:C^{14} ratio. Squalene synthesized by yeast extracts from the doubly labeled MVA contained T and C^{14} in the same ratio as the precursor (Table II). From the work of Tavormina and Gibbs,[7] it is known that C_1 of mevalonic acid is lost during the conversion to cholesterol and hence the isoprenoid chain must be formed by condensations linking C_5 of one MVA residue (or a derivative thereof) to C_2 of another. The retention of T during squalene formation clearly rules out a preliminary oxidation of mevalonic acid to β-hydroxy-β-methylglutaric acid (or a derivative). Though the unchanged T:C^{14} ratio suggests that both hydrogen atoms at C_5 (δ-carbon) of MVA are

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(2) P. A. Tavormina, M. H. Gibbs and J. W. Huff, *ibid.*, **78**, 4498 (1956).

(3) L. D. Wright, *Federation Proc.*, **16**, 274 (1957).

(4) N. Nicolaides and F. Laves, THIS JOURNAL, **76**, 2596 (1954).

(5) I. M. Heilbron, E. D. Kamn and W. M. Owens, *J. Chem. Soc.*, 1630 (1926).

(6) The following abbreviations are used: DPN and TPN, di- and tri-phosphopyridine nucleotide; ATP, adenosine triphosphate.

(7) P. A. Tavormina and M. H. Gibbs, THIS JOURNAL, **78**, 6210 (1956).

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May 20, 1957

TABLE I

CONVERSION OF DL-2-C^{14}-MVA TO SQUALENE IN YEAST EXTRACTS

Each experimental flask contained 1 ml. of yeast extract, 1 mg. of nucleotide as indicated, Mn^{++} or Mg^{++} 10^{-3} *M*, 8 μg. of DL-2-C^{14}-MVA (2500 c.p.m.). Incubation in air at 30° for 3 hr.

Additions						c.p.m. in squalene formed by extract	
DPN	DPNH	TPN	TPNH	ATP[a]	Mn^{++}	Mg^{++}	A[b]	B[c,d]
				+	+		277	192
+				+	+		407	178
	+			+	+		93	108
		+		+	+		364	308
			+	+	+			
				+		+	169	24
+					+		59	18
+				+			4	12
+				+	+		36	36

[a] Cryst. ATP-Na salt (Pabst & Co.); the same activity was obtained by preparations of 95% purity. [b] Dried baker's yeast was extracted by incubation with 3 vol. of 0.066 *M* $(NH_4)_2HPO_4$ for 3 hr. at 37°, the mixture kept at 4° for 16 hr. and centrifuged at 25,000 × *g* for 30 min. The supernatant was recentrifuged at 105,000 × g for 2 hr., dialyzed for 12 hr. against 4 changes of 0.005 *M* phosphate buffer *p*H 7.0, and finally treated with acid-washed Norite-A. [c] The material precipitating from extract A with $(NH_4)_2SO_4$ at 30% saturation was dialyzed for 12 hr. against 0.03 *M* phosphate buffer, *p*H 7.0 and centrifuged for 2 hr. at 105,000 × *g*. This supernatant (prep. B) contained 1.5 mg. of protein per ml. as compared to 12 mg. protein per ml. in prep. A. [d] Experiments carried out by Dr. H. Danielsson.

TABLE II[a]

CONVERSION OF DL-2-C^{14},5-DI-T-MVA TO SQUALENE

	C^{14}, d.p.m.	T, d.p.m.	T/C^{14}
(1) C^{14}, T analyses of MVA[b]			
Preparation IA	2440	7300	3.00
IB	2220	6600	2.97
(2) Incubation experiments[c]			
Squalene formed from IA	450	1400	3.10
IA	560	1520	2.71[d]
IB	360	1040	2.90
IB	1140	3380	2.97

[a] The T and C^{14} analyses were performed with a Packard Liquid Scintillation Counter by the New England Nuclear Corporation, Boston, Massachusetts. [b] The product obtained on treatment of β-hydroxy-β-methylglutaric acid with $LiAlT_4$ in dioxane was adsorbed on Dowex-1-formate and eluted with 0.1 *N* formic acid. Authentic 2-C^{14}-MVA was added and the mixture crystallized several times as the dibenzylethylenediamine salt.[1] This, after removal of the amine, was chromatographed on paper in an ethanol–ammonia system. Strips were cut separately from the slower moving section (IA) and the middle portion (IB) of the radioactive peak (R_f = 0.57), the MVA eluted with water and aliquots assayed for T and C^{14}. [c] For each experiment aliquots of the 2 fractions (IA and IB) containing 120 μg. of MVA were incubated with 15 ml. of a crude yeast extract (supernatant from 25,000 × *g* centrifugation, Table I, footnote *b*) in the presence of 9 mg. DPN, Mn^{++} 10^{-3} *M*, and 30 mg. of hexose diphosphate, for 3 hr. at 30° in air. In all expts. approximately 30% of the radioactivity was recovered in the hydrocarbon fraction. [d] Isolated and analyzed as the crystalline squalene hexahydrochloride.

retained, the possibility that the R·CH_2O–group is oxidized to R·CHO cannot be ruled out because large rate differences are known to exist for the breaking of C–H and C–T bonds.[8] In any event, these results eliminate a Claisen-type condensation mechanism and raise the distinct possibility that the condensing unit is MVA itself or a derivative of the same oxidation level. The data of Table I indicate that the reduced forms of the pyridine nucleotides are the more efficient cofactors, as would be expected from the reductive nature of the over-all transformation: 6MVA + 2H → squalene + $6H_2O$ + $6CO_2$. The concurrent participation of the oxidized nucleotides nevertheless cannot be excluded at this time. The participation of Mn^{++} is of interest since Mn^{++} is known to accelerate both enzymatic[9] and non-enzymatic[10] decarboxylations. A stimulation of cholesterol synthesis from acetate by Mn^{++} previously has been reported.[11] The dependence of the process on ATP suggests that a phosphorylation step is involved in the formation of squalene from mevalonic acid. This phosphorylation probably is not associated with the activation of carboxyl groups, since no requirement for Coenzyme A could be demonstrated.

Acknowledgments.—This work was supported by grants-in-aid from the National Science Foundation, the U. S. Public Health Service and the Life Insurance Medical Research Fund. The authors are greatly indebted to Drs. P. A. Tavormina and J. M. Sprague of the Merck, Sharp and Dohme Research Laboratories for a generous gift of DL-2-C^{11}-mevalonic acid.

(5) K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955). The isotope effect may come into play because the reducing agent in the preparation of MVA was a mixture of $LiAlH_4$ and $LiAlT_4$.

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(10) R. Steinberger and F. H. Westheimer, THIS JOURNAL, **71**, 4158 (1949).

(11) G. L. Curran and O. L. Clute, *J. Biol. Chem.*, **204**, 715 (1953).

(12) Holder of a Union Carbide and Carbon Fellowship in Biochemistry.

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H. RILLING[12]
K. BLOCH

RECEIVED APRIL 11, 1957

PREPARATION OF A SOLUBLE MAMMALIAN TYROSINASE[1]

Sir:

Mammalian tyrosinase, unlike the soluble, highly purified,[2] well characterized[3] plant product, has been reported to be firmly bound to melanized cellular particles.[4] In view of the emphasis which has been placed on the difficulty of removing this enzyme from particulate matter,[4,5] we would like to report a relatively simple technique for the preparation of a soluble, melanin-free mammalian tyrosinase.

(1) This work was supported by the National Cancer Institute, grant C-2620.

(2) H. R. Dalton and J. M. Nelson, THIS JOURNAL, **61**, 2946 (1939).

(3) M. F. Mallette and C. R. Dawson, *Arch. Biochem.*, **23**, 29 (1948).

(4) (a) A. B. Lerner, T. B. Fitzpatrick, Evan Calkins and W. H. Summerson, *J. Biol. Chem.*, **178**, 185 (1948); (b) Denis Kertész, *J. Nat. Can. Inst.*, **14**, 1081 (1954); (c) H. G. Dubuy, M. W. Woods, Dean Burk and M. D. Lackey, *ibid.*, **9**, 325 (1948); (d) H. S. Mason, *Advances in Enzymology*, **16**, 105 (1955).

(5) A. B. Lerner and T. B. Fitzpatrick, *Physiol. Rev.*, **30**, 91 (1950); A. B. Lerner, *Advances in Enzymology*, **14**, 73 (1953); I. W. Sizer, *ibid.*, **14**, 129 (1953).

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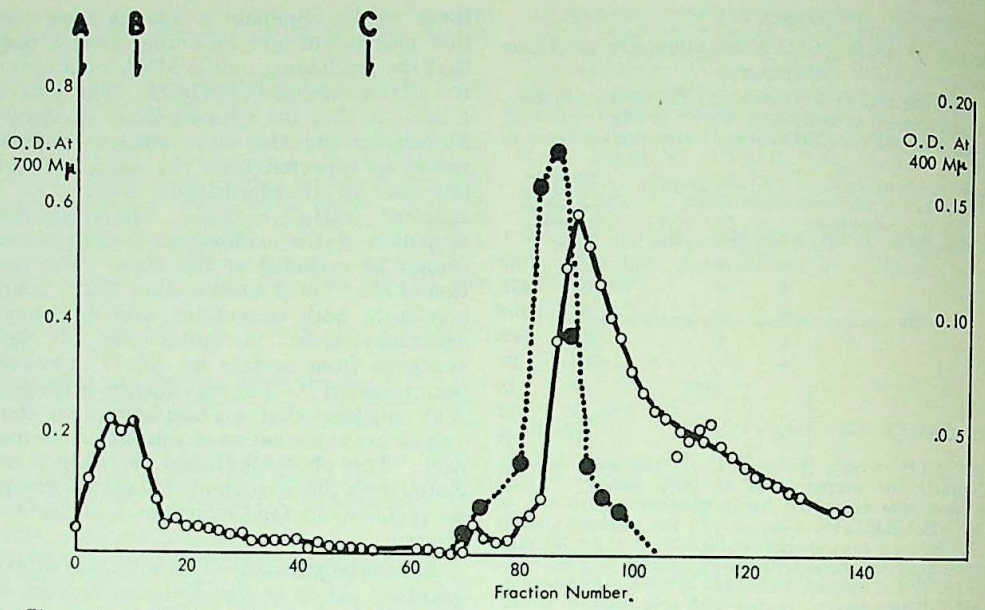

Fig. 1.—Chromatography of tyrosinase on DEAE-cellulose ion exchanger, using 3.0 g. of exchanger (capacity 0.59 meq./g.) in a column 26 × 1.2 cm. Collection after 1 hold-up volume (16 ml.), 2.1-ml. fractions. 0—0—0—0, Folin-Lowry[10] reaction with 0.1-ml. aliquots measured at 700 mμ, Coleman spectrophotometer; ●·····●·····●, tyrosinase activity of 0.1-ml. aliquots in terms of melanin produced after incubation with tyrosine in 2.7 ml., *p*H 6.8 phosphate buffer for 3 hours. O.D. measured at 400 mμ. A, 0.005 *M* phosphate buffer, *p*H 6.0, plus 0.05 *M* NaCl. B, 0.005 *M* phosphate buffer, *p*H 7.0, plus 0.05 *M* NaCl with gradient change to 0.05 *M* phosphate buffer, *p*H 8.0, through 50 ml. mixing chamber. C, Gradient change to 0.15 *M* phosphate buffer, *p*H 8.0.

Harding-Passey melanoma (415 g.) was homogenized with 2100 ml. of cold distilled H_2O in a Waring Blendor and centrifuged for one hour at 600 × *g*, and the extraction repeated. The supernatant fractions (*p*H 6.9) were combined and made 0.1 satd. with $(NH_4)_2SO_4$. An equal volume of cold acetone was added and the black precipitate was removed on a buchner funnel. These steps are critical to tyrosinase solubility which appears to depend on the ammonium sulfate salting the enzyme into the 50% acetone–water solution. Another volume of acetone was added to the clear filtrate and the precipitate was removed on a buchner, washed with acetone, and dried over P_2O_5 to yield 4.8 g. of a white powder.

The product (3.65 g.) was dissolved in 200 ml. of H_2O, the *p*H was kept at 6–7 with a few drops of 1 *N* NaOH, and was dialyzed for 24 hours against 2 liters of cold distilled H_2O. Lyophilization gave 0.96 g. of active material or 1.2% of the original dry weight of tumor. To establish the absence of cellular particles, a 1% solution of this material was subjected to centrifugation in the ultracentrifuge (Spinco model E). After 1 hour at 260,000 × *g*, the activity remained in the upper part of the cell and the fastest boundary indicated had a sedimentation constant of 3.4, although the material was not homogeneous.[6]

Tyrosinase activity was assayed manometrically against L-tyrosine plus small amounts of dopa.[4a] For the calculation of activity, the unit of Hogeboom and Adams[7] has been used but referred to the protein nitrogen content to obtain specific activity as units per mg. The original homogenate had a specific activity of 2.6 units/mg. N. The product had a specific activity of 25 units/mg. N and contained 18% of the starting activity.

Further purification was attempted by chromatography on a DEAE cellulose[8] column using differential elution.[9] The results are shown in Fig. 1.

The most highly purified fraction (S2) from the chromatogram gave a positive biuret test. The remainder of the activity peak was pooled and was shown to catalyze the oxidation of both L-dopa and L-tyrosine through some pink intermediate, presumably dopachrome, to black melanin. Heating at 100° for 30 minutes completely destroyed the activity.

Although preparations having 500 units/mg. N have been obtained, Figure 1 indicates that optimum conditions for complete chromatographic separation were not established. Experiments to improve these conditions are being carried out as rapidly as starting material becomes available.[10]

(6) We are indebted to John A. Cooper for the ultracentrifuge study.

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RECEIVED JANUARY 16, 1957

BIOSYNTHESIS OF SPHINGOSINE IN VITRO

Sir:

We wish to report the preparation of an enzyme system obtained from rat brain tissue which cata-

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May 20, 1957

lyzes the incorporation of serine-C^{14} into sphingosine and to identify some of the cofactors required for this conversion. The incorporation of radioactivity from acetate-1-C^{14} and L-serine-3-C^{14} into sphingosine has been observed *in vivo*.[1,2]

Brain tissue obtained from 10–14 day old rats was homogenized with 3 volumes of isotonic sucrose or 0.1 *M* potassium phosphate buffer (*p*H 7.8), and differential centrifugation was accomplished according to Brody and Bain.[3] The enzymes required for the conversion of L-serine to sphingosine were found in the supernatant solution obtained after sedimenting the particulate matter by centrifuging at 25,000 × *g* for 30 minutes. The enzyme preparation was dialyzed for 4 hours against 100 volumes of a solution containing 0.01 *M* potassium phosphate buffer (*p*H 7.0), 0.001 *M* cysteine hydrochloride and 0.001 *M* disodium ethylenediaminetetraacetic acid.

Following incubation, the lipids were quantitatively extracted with *n*-butanol and 18 μmoles of sphingosine sulfate were added to each sample as carrier. The mixtures were refluxed for 6 hours in 85% methanol made 1.2 *M* with respect to H_2SO_4, and subsequently extracted with petroleum ether which was back-washed two times with dilute acid. The methanolic solution containing the sphingosine sulfate was concentrated under vacuum, and the sphingosine base was recovered from salt-saturated alkaline aqueous phase by extracting with 2% isoamyl alcohol in heptane.[4] The solvents were evaporated under reduced pressure and the sphingosine was recrystallized two times from petroleum ether. Approximately 80% of the carrier sphingosine was recovered with the use of this procedure. The twice recrystallized sphingosine was found to have constant specific radioactivity.

TABLE I

ENZYMATIC CONVERSION OF SERINE-3-C^{14} TO SPHINGOSINE

Except as noted, the incubation mixtures contained 1.5 ml. of dialyzed supernatant solution obtained by centrifuging a 1:3 (w./v.) cell-free preparation of rat brain tissue at 25,000 × *g* for 30 minutes, 150 μmoles of potassium phosphate buffer (*p*H 7.8), 4 μmoles of DL-serine-3-C^{14} (4 μC.), 1 μmole of pyridoxal phosphate, 5 μmoles of $MgCl_2$, 0.3 μmole of triphosphopyridine nucleotide (TPN), 20 μmoles of nicotinamide, 2 μmoles of uridine triphosphate (UTP), 0.4 μmole of cytidine triphosphate (CTP), 5 μmoles of adenosine triphosphate (ATP), and 0.1 ml. of liver kochsaft in a total volume of 2.0 ml. Incubation time, 3 hours at 38° in air.

Reactant omitted	Distribution of radioactivity in recovered sphingosine: Sphingosine, c./m./μmole	Residue after periodate degradation, c./m./μmole
None	155	26
None, heated at 100° for 10 min.	3	..
Kochsaft	11	..
Pyridoxal phosphate	35	23
$MgCl_2$	71	20
TPN	90	20
DPN	93	22
Nicotinamide	110	25
UTP	140	26
CTP	165	25
ATP	170	28

As shown in the table, the conversion of serine-3-C^{14} to sphingosine requires the presence of pyridoxal phosphate, magnesium chloride, triphosphopyridine nucleotide, diphosphopyridine nucleotide, and an as yet unidentified substance present in a kochsaft obtained from rat liver tissue. The recovered sphingosine was degraded with sodium periodate,[4,5] and the radioactivity of the residual aliphatic aldehyde was determined. It is apparent from these data that the radioactivity from the serine-C^{14} is preferentially localized in positions 1 and 2 of sphingosine and that the reaction does not represent random incorporation of radioactivity via an active one or two carbon fragment. These findings have been confirmed with the use of L-serine-U-C^{14} as substrate in this system.

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NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS
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BETHESDA, MARYLAND — GEORGE J. KOVAL

RECEIVED APRIL 1, 1957

A NOVEL ORGANO-CHROMIUM COMPOUND

Sir:

The known organo-chromium compounds, apart from the anionic cyanide and ethynyl complexes[1] of chromium(III) are compounds of chromium(0), chromium(I) or chromium(II)[2] which generally do not contain simple carbon–chromium bonds. We wish to report the first preparation (in solution) of a simple organo-chromium compound of the type $Cr(H_2O)_5R^{++}$ where R is benzyl. The compound has not yet been obtained crystalline, but solutions of the pure perchlorate in dilute perchloric acid solution have been obtained and are fairly stable (half-life in absence of oxygen at room temperature of about 1.5 days). The structure of the compound, benzylpentaaquochromium(III) perchlorate, can be regarded as analogous to that of the chloride complex, $Cr(H_2O)_5Cl^{++}$, of chromium(III); *i.e.*, the compound is a complex of Cr(III) with the *benzyl anion*. The remarkable stability of this organo-metallic compound in acid solution is undoubtedly related to the inertness of Cr(III) complexes to substitution.[3]

The benzylchromium compound was prepared by reducing benzyl chloride (or bromide or iodide) with aqueous 1 *M* chromous perchlorate in 1 *M* perchloric acid, either heterogeneously or in presence of alcohol or other suitable organic solvents. Countercurrent distribution of the product at 5° with the solvent system 0.01 *M* perchloric acid–butanol gave, after 70 transfers, a separation of the organo-chromium compound (partition coefficient

(1) R. Nast and E. Sirtl, *Chem. Ber.*, **11**, 1723 (1955).
(2) F. A. Cotton, *Chem. Revs.*, **55**, 551 (1955); H. H. Zeiss and W. Herwig, THIS JOURNAL, **78**, 5959 (1956); E. O. Fischer and W. Hafner, *Z. anorg. Chem.*, **286**, 146 (1956); G. Wilkinson, THIS JOURNAL, **76**, 209 (1954); T. S. Piper and G. Wilkinson, *J. Inorg. Nuclear Chem.*, **3**, 104 (1956).
(3) H. Taube, *Chem. Revs.*, **50**, 69 (1952).

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0.35) from $Cr(H_2O)_6^{+++}$ (mainly) and $Cr(H_2O)_5Cl^{++}$ (partition coefficient 0.13). Separation was also effected by ion-exchange chromatography on Dowex 50-X4 resin and elution with 1 *M* perchloric acid. The ion $Cr(H_2O)_5Cl^{++}$ (green) was eluted first, followed by $Cr(H_2O)_5CH_2Ph^{++}$ (yellow to orange-yellow) whilst $Cr(H_2O)_6^{+++}$ remained on the column. All the above operations were carried out in an atmosphere of oxygen-free nitrogen and as rapidly as possible.

Solutions of the benzylchromium compound were yellow to brownish-red depending on the concentration, and the spectrum of the solution had a low intensity maximum at 540 mμ and a high intensity maximum at 358 mμ. Decomposition of the complex in the absence of oxygen by heating or by keeping for several days gave bibenzyl; in the presence of oxygen benzaldehyde was the main product. The compound was decomposed very rapidly by sulfur dioxide but was stable to carbon dioxide. Hydrogenation in presence of a palladium catalyst gave toluene. Solutions of the compound reacted very quickly with aqueous mercuric chloride with *no change in pH of the solution* to give benzylmercuric chloride and $Cr(H_2O)_6^{+++}$ (not $Cr(H_2O)_5Cl^{++}$) in equimolecular amounts. Therefore the compound must contain one benzyl group per chromium atom and two positive charges. Hence it is a Cr(III) complex and its stability is best rationalized by the normal octahedral complex structure mentioned before. It differs, as might be expected, from the chloride complex in having a tendency to dissociate in a homolytic fashion to give benzyl radicals and chromous ion. An alternate structure which can be considered for the compound is a complex of the tropylium ion and Cr(I) in the manner[2] of dibenzene–Cr(I) but with only one ring involved per chromium atom, although this is somewhat unlikely on the above evidence. However, such a structure can be excluded because all the carbon atoms would then become equivalent and it was found that α-methyl, *o*-methyl- and *p*-methylbenzyl halides gave different compounds on reduction with chromous perchlorate.

Reduction of benzyl chloride with chromous chloride in hydrochloric acid gave toluene rather than an organo-metallic compound. This can be understood from the work of Taube[4] as the initially formed complex, $Cr(H_2O)_4Cl{\cdot}CH_2Ph^+$, will have chloride ion as well as water molecules in the coördination sphere and such a chlorine atom favors reduction by bridging[4] with the reducing agent. The resultant Cr(II) complex is then no longer substitution-inert and dissociates to benzyl anions which react with the solvent to give toluene. Therefore, the isolation of $Cr(H_2O)_4CH_2Ph^{++}$ in the chromous perchlorate reduction is due to the fact that this compound (like $Cr(H_2O)_6^{+++}$ but unlike $Cr(H_2O)_5Cl^{++}$ and $Cr(H_2O)_4Cl_2^+$) is reduced by Cr^{++} extremely slowly, as well as to the substitution-inertness of dipositive complexes of Cr-(III).

Allyl chloride and phenacyl chloride were readily reduced by chromous perchlorate, but without observable formation of organo-metallic compounds. Work on the reduction of halogen compounds by chromous salts is continuing.[5]

(5) This work was supported by a grant from the National Research Council of Canada.

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(4) H. Taube and E. L. King, This Journal, **76**, 4053 (1954); H. Taube and H. Myers, *ibid.*, **76**, 2103 (1954).

THE BIOSYNTHESIS OF SQUALENE FROM MEVALONIC ACID

Sir:

Tavormina, *et al.*,[1] have reported the incorporation of 2-C^{14}-labeled mevalonic acid (3,5-dihydroxy-3-methylvaleric acid) into cholesterol by homogenates of rat liver. These investigators have also provided evidence that the carboxyl carbon of the substrate is almost completely converted to carbon dioxide, and therefore not incorporated into cholesterol.[2]

We have confirmed the finding that 2-C^{14}-mevalonic acid[3] is converted to cholesterol, and in addition have demonstrated that it is rapidly converted to squalene by homogenates as well as by the supernatant fluid obtained from such preparations following high speed centrifugation.[4]

Employing homogenates of rat liver and 2-C^{14}-mevalonic acid, we have repeatedly isolated C^{14}-squalene into which has been incorporated 10 to 20% of the substrate. Squalene recovered from several of the experiments was combined and purified by chromatography on alumina.[4] It was subsequently chromatographed on silicic acid, eluting with an increasing gradient of benzene in petroleum ether. The latter process yields squalene as a single radioactive peak.[5]

In contrast to cruder preparations of squalene, this product is completely degraded by ozonolysis to acetone, levulinic acid and succinic acid. These substances were separated and further degraded. Acetone was converted to iodoform and acetic acid, and the acetic acid degraded by the Schmidt method.[6] The levulinic acid was converted to iodoform and succinic acid. The succinic acid was degraded by the Schmidt technique to carbon dioxide and ethylenediamine. All of the degradation products were converted to carbon dioxide and counted as barium carbonate.

The radio-analyses (Table I) demonstrated that approximately 80% of the isotopic carbon of the squalene is present in the methyl carbons of acetone and in carbon 3 of levulinic acid. The succinic acid sample, representing the central four carbons of squalene, contained only a small amount of isotope. It is clear that only one of the methylene groups of the levulinic acid was appreciably labeled.

(1) P. A. Tavormina, M. H. Gibbs and J. W. Huff, This Journal, **78**, 4498 (1956).

(2) P. A. Tavormina and M. H. Gibbs, *ibid.*, **78**, 6210 (1956).

(3) The authors express their appreciation to Merck Sharp and Dohme for a generous supply of labeled mevalonic acid used in these experiments.

(4) F. Dituri, F. A. Cobey, J. V. B. Warms and S. Gurin, *J. Biol. Chem.*, **221**, 181 (1956).

(5) [illegible] Horowitz and S. Gurin, in preparation.

(6) E. F. Phares and M. V. Long, This Journal, **77**, 2556 (1955).

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TABLE I

SPECIFIC ACTIVITY OF THE DEGRADATION PRODUCTS OF C^{14}-SQUALENE

Degradation product	Specific activity, c.p.m. per mg. C
Acetone	306
Carbonyl carbon	10
CH_3	360
Succinic acid	70
-COOH	30
$-CH_2-$	80
Levulinic acid	150
CH_3 (carbon 5)	17
-COOH (carbons 1 and 4)	28
$-CH_2-$ (carbons 2 and 3)	310

and it is probable from the data that only one of the methyl carbons of the acetone fragment contained C^{14} (Fig. 1).

$$\left[C^*H_2C{=}CHCH_2C^*H_2C{=}CHCH_2C^*H_2C{=}CHCH_2{-}\right]$$
$$\qquad\qquad CH_3 \qquad\qquad CH_3 \qquad\qquad CH_3$$

Fig. 1.—Principal distribution of isotopic carbon in biosynthetic squalene.

The distribution of isotope in the squalene suggests that the mevalonic acid was not decarboxylated to yield a five carbon intermediate prior to condensation. If a five carbon intermediate is first produced, the compound would have to react asymmetrically to give the observed isotope distribution. This possibility has not been excluded by the data presented here. Whether mevalonic acid is or is not the biological precursor of squalene and cholesterol, there appears to be little breakdown and re-condensation prior to polymerization. It is likely that decarboxylation occurs during or after polymerization.

Complete details will be presented in a subsequent publication.

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RECEIVED MARCH 16, 1957

SOME ENZYMATIC REACTIONS OF 6,8-DITHIOLOCTANOIC (DIHYDROLIPOIC) ACID AND ITS ACETOACETIC THIOESTER[1]

Sir:

Evidence has been presented that AcAc[2] synthesis in soluble liver fractions from a source of Ac-S-CoA involves the intermediate formation of AcAc-S-CoA by thiolase, which catalyzes reaction 1, followed by deacylation of AcAc-S-CoA to AcAc.[3-5] However, a direct deacylation of synthetic AcAc-S-CoA is not catalyzed by these enzyme fractions.

$$2\text{Ac-S-CoA} \rightleftharpoons \text{AcAc-S-CoA} + \text{HS-CoA} \qquad (1)$$

We find that AcAc synthesis by partly purified ox or chicken liver enzyme preparations from Ac-S-CoA (generated by phosphotransacetylase from acetyl phosphate and CoA-SH[3]) requires the addition of a mono- or dithiol compound. Among active thiols, (±)-DTO[6] has the greatest activity, half maximum activation of AcAc synthesis occurring with 1×10^{-4} M (±)-DTO compared to 3.5×10^{-4} M BAL and 2×10^{-3} M GSH. These liver fractions also catalyze the reactions (2), (3)

$$(\pm)\text{-S-AcAc-DTO} + H_2O \longrightarrow \text{AcAc} + (\pm)\text{-DTO} \qquad (2)$$

$$\text{AcAc-S-Pn (or CoA)} + (\pm)\text{-DTO} \rightleftharpoons \text{Ac-S-Pn (or CoA)} + (\pm)\text{-S-Ac-DTO} \qquad (3)$$

Mono-(±)-S-AcAc-DTO was synthesized by reacting one equivalent of diketene with (±)-DTO. Presumably it is the 8-ester, since acetic anhydride and DTO have been shown to give 8-S-Ac-DTO.[7] While DTO does not give a positive nitroprusside assay for sulfhydryl,[8,9] we find the monothiol, monothioester form does. Thus, monoacylation of DTO results in the appearance of one sulfhydryl equivalent (by nitroprusside assay), as well as one thioester equivalent (measured with hydroxylamine or optically at 240 mμ). The synthesis and breakdown of mono-S-acyl-DTO compounds can therefore be measured by nitroprusside assay.

The thioesterase catalyzing reaction 2 is assayed optically by following the decrease in light absorption at λ 310 mμ or λ 240 mμ, since (±)-S-AcAc-DTO has an absorption spectrum characteristic of acetoacetyl thioesters.[10,11] It is present in liver but apparently not in other tissues. The enzyme has been purified 40-fold from chicken liver and shown to be different from AcAc-SG thioesterase.[12] It hydrolyzes S-AcAc and S-Ac esters of DTO, MTO and BAL (Table I).

As measured optically at λ 310 mμ, liver and heart enzyme fractions catalyze a disappearance of AcAc-S-Pn and AcAc-S-CoA, provided DTO (or certain mono- or dithiols) is added. With DTO, the decrease in E_{310} due to disappearance of AcAc-SR is accompanied by a simultaneous increase in E_{240}, signifying an increase in total thioester concentration. Balance studies (Table II) show that for each mole of AcAc-S-Pn disappearing, *two* moles of

(1) Supported by grants from the U. S. Public Health Service (No. A-739) and the Williams–Waterman Fund of the Research Corporation.

(2) Abbreviations: 6,8-dithioloctanoic (dihydrolipoic) acid, DTO; monothioloctanoic acid, MTO; coenzyme A (reduced), CoA-SH; pantetheine, Pn-SH; glutathione, GSH, dimercaptopropanol, BAL; thioesters, acyl-S-R; acids: acetic, Ac; acetoacetic, AcAc; *tris*-(hydroxymethyl)-aminomethane, Tris; E, optical density; all reference is to sign of rotation (*cf.* footnote 7).

(3) E. R. Stadtman, M. Doudoroff and F. Lipmann, *J. Biol. Chem.*, **191**, 377 (1951).

(4) J. R. Stern, M. J. Coon and A. del Campillo, *Nature*, **171**, 28 (1953).

(5) J. R. Stern, M. J. Coon and A. del Campillo, *J. Biol. Chem.*, **221**, 1 (1956).

(6) DTO, MTO and 6-thioldecanoate were kindly supplied by Dr. J. A. Brockman of Lederle Laboratories.

(7) I. C. Gunsalus, L. S. Barton and W. Gruber, THIS JOURNAL, **78**, 1763 (1956).

(8) I. C. Gunsalus in "The Mechanism of Enzyme Action," the Johns Hopkins Press, Baltimore, Md., 1954, p. 545.

(9) I. Fridovitch and P. Handler, *J. Biol. Chem.*, **223**, 321 (1956).

(10) F. Lynen, *Federation Proc.*, **12**, 683 (1953).

(11) J. R. Stern, *J. Biol. Chem.*, **221**, 33 (1956).

(12) J. R. Stern, S. Grisolia and J. Hammond, *Federation Proc.*, **15**, 363 (1956).

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TABLE I

SUBSTRATES FOR THIOESTERASE

15-fold purified chicken liver thioesterase. ~0.5 μM thioester in 0.067 M Tris–HCl buffer pH 7.0. Specific activity = $-\Delta E_{240}$ per minute per mg. protein. Values in parentheses refer to synthetic S-acetyl ester.

	Specific activity
8-S-AcAc-MTO	82
(±)-8-S-AcAc,6-ethyl-MTO	69
(±)-S-AcAc-DTO	56 (60)[a]
(±)-6-S-AcAc-MTO	17
(±)-6-S-AcAc-Decanoate	7.5
S-AcAc-BAL	310 (30)

[a] (+)-6-S-Ac-DTO was hydrolyzed at same rate as the synthetic ester.

thioester and *one* mole of thiol are formed. This stoichiometry is consistent with reaction 3 and follows from the fact that AcAc-SR does not assay as thioester by the hydroxylamine method[5] while S-Ac-DTO assays as both thiol and thioester. The Ac-S-Pn and Ac-S-DTO formed were further identified by paper chromatography. It is not yet determined whether 6- or 8-S-Ac-DTO is formed. This mixed thiolysis reaction represents a novel enzymatic synthesis of S-Ac-DTO. It differs from the synthesis of (+)-6-S-Ac-DTO from Ac-S-CoA and (−)-DTO catalyzed by DTO transacetylase[7,8] in that it involves transacetylation with a 4-carbon fragment and utilizes both (−)-DTO and (+)-DTO.[13] The enzyme(s) catalyzing reaction 3 differs from the thiolase[14,15] of the fatty acid cycle (reaction 1) in that (a) AcAc-S-Pn is more reactive than AcAc-S-CoA, (b) it is less sensitive to iodoacetamide, and (c) it is not readily reversible, if at all. Interestingly, other thiol compounds which activate AcAc synthesis (*e.g.*, BAL, GSH, cysteine) can substitute for DTO in reaction 3, yielding the corresponding S-Ac ester.

TABLE II

THIOLYSIS OF AcAc-S-Pn BY DTO

1.50 μM AcAc-S-Pn, 4.0 μM DTO, 150 μM Tris–HCl buffer pH 8.1 and 0.9 mg. ox liver protein. Incubated 13 minutes at 25°. Values in μM.

	Acetyl acceptor		
	(±)-DTO	(+)-DTO	(−)-DTO
Δ AcAc-S-Pn[a]	−1.50	−1.50	−1.50
Δ Sulfhydryl[b]	+1.43	+1.44	+1.71
Δ Hydroxamic acid	+2.99	+2.98	+2.88

[a] Measured optically at 310 mμ. [b] Nitroprusside assay.

(±)-S-AcAc-DTO is reduced by DPNH in the presence of crystalline heart β-hydroxybutyryl-S-CoA dehydrogenase.[16] Liver fractions do not catalyze a thiolysis of (±)-S-AcAc-DTO by DTO, CoA-SH, Pn-SH or GSH. Nor do they convert (+)-6-S-Ac-DTO[7] or (±)-8-S-Ac-DTO to AcAc.

Since thioesterases exist in liver for S-AcAc-DTO and AcAc-SG, the latter are possible intermediates in AcAc synthesis. However, experiments so far have failed to demonstrate their enzymatic formation, *e.g.*, by AcAc transfer from AcAc-S-CoA (or Pn). The precise role of DTO and other thiols in activating AcAc synthesis is being investigated further.

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(13) We are indebted to Dr. K. Folkers of Merck–Sharp and Dohme Research Laboratories for (+) and (−) lipoic acids.

(14) J. R. Stern and S. Ochoa, in "Biochemical Problems of Lipids," Butterworths Publications, London, 1956, p. 162.

(15) F. Lynen, K. Decker, O. Wieland and D. Reinwein, ref. 14, p. 142.

(16) J. R. Stern, unpublished experiments.

A NEW PATHWAY FOR PROPIONATE OXIDATION

Sir:

Oxidation of propionate in animal tissues occurs by a carboxylation pathway through methyl malonate to succinate.[1] Stadtman[2] has observed the formation of β-alanyl-CoA from acryl-CoA extracts of *Clostridium propionicum*. Mahler and Huennekens suggest an α-oxidative pathway.[3] In this communication evidence is presented in support of a β-oxidative pathway in peanut mitochondria.[4]

The oxidation of sodium propionate-1-C^{14} to $C^{14}O_2$ by mitochondria isolated from cotyledons of germinated peanuts[4a] is dependent upon ATP,[5] CoA, DPN, GSH and αKG; TPN and Mn^{++} stimulate the oxidation.

TABLE I

COFACTOR REQUIREMENTS FOR OXIDATION OF PROPIONATE-1-C^{14} TO $C^{14}O_2$

The complete reaction mixture contained 0.1 μmole propionate-1-C^{14} (5500 c.p.m.); 0.5 ml. mitochondria (approximately 20 mg. protein) in 0.2 M Tris- 0.5 M sucrose, pH 7.2, containing about 5×10^{-3} % BAL; 10 μmoles phosphate buffer, pH 7.1; 50 μmoles KCl; 1 μmole ATP; 0.3 μmole CoA; 0.2 μmole DPN; 0.1 μmole TPN; 5 μmoles GSH; 1 μmole αKG; 0.2 ml. 20% KOH in the center well; 0.3 ml. 10 M H_2SO_4 in the sidearm, final volume 1.7 ml. Time of incubation, 2 hr., temperature 25°. % oxidation = $BaC^{14}O_3$ (c.p.m.) × 100/substrate (c.p.m.).

Components	% Oxidation	Components	% Oxidation
Complete	24	−TPN	21
−ATP	1	−GSH	17
−CoA	2	$-MnSO_4$	20
−DPN	14	−αKG	5

Since pools of pyruvate, lactate, succinate and methyl malonate added during propionate-1-C^{14} oxidation do not acquire any label, these compounds do not appear to participate as intermediates. Furthermore, no propionate-dependent fixation of $C^{14}O_2$ can be demonstrated.

To examine the course of oxidation, propionate-1-C^{14}, -2-C^{14} and -3-C^{14}[6] were incubated with a complete reaction mixture for different periods of time and ether-extractable reaction products separated by paper chromatography. In each case a new radioactive spot (R_f 0.25 in ethanol ammonia; propionate R_f 0.42) appeared, which decreased

(1) M. Flavin, P. J. Ortiz and S. Ochoa, *Nature*, **176**, 823 (1955).

(2) E. R. Stadtman, *Federation Proc.*, **15**, 360 (1956).

(3) H. R. Mahler and F. M. Huennekens, *Biochim. et Biophys. Acta*, **11**, 575 (1953).

(4) In a recent personal communication, Dr. M. J. Coon describes a propionate → βHP → β-alanine pathway in animal tissues. In peanut mitochondria no β-alanine accumulates.

(4a) P. K. Stumpf, *Plant Physiology*, **30**, 55 (1955).

(5) Abbreviations: ATP, adenosine triphosphate; CoA, coenzyme A; DPN, diphosphopyridine nucleotide; GSH, glutathione; Mn^{++}, manganese; αKG, α-ketoglutarate; βHP, β-hydroxypropionate.

(6) Kindly donated by Dr. Harland G. Wood.

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May 20, 1957

with time. This spot, identified as βHP, was characterized by (a) two dimensional co-chromatography with authentic βHP, (b) dichromate oxidation[7] of βHP derived from propionate-2-C^{14}, to a dicarboxylic acid which co-chromatographed with malonic acid. The dicarboxylic acid was degraded by pyrolysis[8] to radioactive acetate and CO_2 and (c) esterification of the acid with diazomethane and conversion to a hydroxamic acid (with hydroxylamine) which co-chromatographed with authentic βHP hydroxamate.

Both propionate-1-C^{14} and βHP-1-C^{14}[9] rapidly release the carboxyl-C^{14} as $C^{14}O_2$. No radioactive Krebs cycle acids are produced. The cofactor required for the oxidation of βHP-1-C^{14} to $C^{14}O_2$ is ATP.

Under the same conditions, propionate-2-C^{14} and βHP-2-C^{14}[9] slowly release C^{14} as $C^{14}O_2$, only after the appearance of radioactive citric, succinic, malic and fumaric acids. With propionate-3-C^{14} a rate of $C^{14}O_2$ release between that of propionate-1-C^{14} and of -2-C^{14} is observed with the formation of labeled Krebs cycle acids. Succinate derived from propionate-1-C^{14} is not labeled. Succinate derived from propionate-2-C^{14} is labeled exclusively in the methylene groups and succinate derived from propionate-3-C^{14} is labeled exclusively in the carboxyl groups.

The conversion of propionate-C^{14} to βHP-C^{14} is dependent on oxygen, ATP and CoA. Other cofactors were not tested.

The pathway may be formulated as[10]

$$CH_3{\cdot}CH_2\,COOH \xrightarrow{ATP,\ CoA} CH_3{\cdot}CH_2{\cdot}CO{\cdot}CoA \longrightarrow$$

$$CH_2{=}CH{\cdot}CO,\ CoA \xrightarrow{H_2O} CH_2OHCH_2{\cdot}CO{\cdot}CoA$$

$$\boxed{CH_2OH{\cdot}CH_2{\cdot}COOH}$$

$$HOOC{\cdot}CH_3 \qquad ATP$$

$$\boxed{\text{Krebs Cycle Acid}} \longrightarrow \boxed{CO_2}$$

(7) By the method used for lactate oxidation in S. Aronoff, "Techniques of Radiobiochemistry," The Iowa State College Press, Ames, Iowa, 1956, p. 141.

(8) S. Aronoff, ref. 7, p. 140.

(9) Radioactive βHP, presumably labeled as shown, was isolated by paper chromatography of the reaction product of propionate-1-C^{14} or -2-C^{14} oxidation.

(10) Compounds in blocks were isolated and characterized.

(11) This work was supported in part by a grant from the National Science Foundation.

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RECEIVED MARCH 27, 1957

THE STEREOSPECIFIC RADICAL ADDITION OF HYDROGEN BROMIDE TO *cis*- AND *trans*-2-BROMO-2-BUTENE[1]

Sir:

In previous work it was found that a high degree of stereospecificity is observed in the radical addition of hydrogen bromide to cyclohexene[2,3] and cyclopentene[4] derivatives. From this and other considerations it appeared possible that under favorable conditions stereospecificity might be observed with this addendum in acyclic systems. We wish to report that the radical addition of hydrogen bromide to the isomeric 2-bromo-2-butenes in liquid hydrogen bromide at −80° is indeed stereospecific and results in almost complete *trans* addition. Other radical additions which have been investigated have been found to be non-stereospecific[5] and apparently this is the first report of a stereospecific radical addition in an acyclic system.

The additions were promoted by irradiation with a quartz-jacketed Hanovia type SC-2537 lamp which fit into the reaction vessel so that the reaction mixture occupied the annular space between the walls of the lamp and reaction vessel. During the reaction the vessel was immersed in a Dry Ice–acetone bath. Mixtures of approximately 20 ml. of anhydrous liquid hydrogen bromide and 5 g. of *cis*- or *trans*-2-bromo-2-butene (shown to be homogeneous by gas chromatographic analysis[6] and physical properties) were irradiated after which the hydrogen bromide was allowed to evaporate and the composition of the residual reaction mixture determined by gas chromatographic[6] and infrared analysis.

In a typical experiment pure *cis*-2-bromo-2-butene in liquid hydrogen bromide was irradiated for 7.5 minutes. The composition of the product (gas chromatographic analysis[6]) was found to be < 0.5% 2-bromo-2-butene (largely isomerized to the *trans* isomer), 3% 2,2-dibromobutane (presumably formed by ionic addition), 92% *meso*-2,3-dibromobutane, 5% *dl*-2,3-dibromobutane and < 0.5% 1,2-dibromobutane.

Irradiation of *trans*-2-bromo-2-butene for 15 minutes under similar conditions gave a mixture consisting of 5% of unreacted *trans*-2-bromo-2-butene, 83% *dl*-2,3-dibromobutane, 8.5% *meso*-2,3-dibromobutane and 3.5% 1,2-dibromobutane. The analytical method was calibrated and confirmed using pure authentic samples of all of the components and synthetic mixtures of these. Infrared spectroscopic examination of the reaction products also showed that the *cis*-bromobutene is converted primarily to *meso*-dibromide and the

(1) This work was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. AF 18(600)1037.

(2) H. L. Goering, P. I. Abell and B. F. Aycock, Jr., THIS JOURNAL, **74**, 3588 (1952).

(3) H. L. Goering and L. L. Sims, *ibid.*, **77**, 3465 (1955).

(4) K. L. Howe, unpublished work.

(5) P. S. Skell and R. C. Woodworth, THIS JOURNAL, **77**, 4638 (1955); P. S. Skell, R. C. Woodworth and J. H. McNamara, *ibid.*, **79**, 1253 (1957).

(6) Excellent separation was obtained with a 10 ft. column packed with the commercial detergent, Tide. An operating temperature of 70° and flow rate of 40 ml. helium per minute were used to check for purity and analyze the 2-bromo-2-butenes. An operating temperature 120° was used for analysis of the reaction mixtures.

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trans-bromobutene gives primarily *dl*-dibromide. These experiments were repeated several times and found to be reproducible. Increasing the reaction (irradiation) time to one hour did not result in any significant changes.

That the above additions are radical rather than ionic is clear from the orientation. When a mixture of *cis*-2-bromo-2-butene and liquid hydrogen bromide was allowed to stand in the dark at −80° for one hour the reaction mixture was found to contain 8.5% of bromobutene (mostly *trans* isomer) and 91.5% 2,2-dibromobutane. Under similar conditions using *trans*-2-bromo-2-butene the reaction mixture consisted of 10% of unreacted bromobutene, 87% 2,2-dibromobutane and 3% *dl*-2,3-dibromobutane (presumably formed by radical addition). These experiments also were found to be reproducible.

The present work demonstrates clearly that under the present conditions the radical addition involves a stereospecific *trans* addition. Assuming that the chain process involves two steps, (1) addition of a bromine atom to form an intermediate radical followed by (2) transfer with the addendum,[3,7] it is clear that different intermediate radicals are formed from the isomeric bromobutenes which undergo the transfer step faster than they are interconverted. Clearly the time interval between the two steps must be very short. A concerted process involving attack of a bromine atom on a substrate molecule complexed with hydrogen bromide has been suggested previously[3] and may be involved in the present case.

(7) M. S. Kharasch, J. V. Mansfield and F. R. Mayo, THIS JOURNAL, **59**, 1155 (1937).

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RECEIVED APRIL 8, 1957

ISOPROPOXYFLUOROMETHYLENE[1]

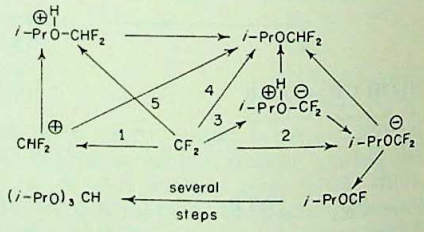
Sir:

Methylene is formed in such homolytic reactions as the decomposition of diazomethane and the photolysis of ketene,[2] and some of its derivatives apparently are formed in analogous reactions. Many of the polar reactions claimed to involve methylenes have been shown not to,[3] but the basic hydrolysis of chloroform, the reaction for which such a mechanism was first suggested,[4] does proceed through dichloromethylene.[5] The *dihalomethylenes*[6] appear to be the only ones that have been established as intermediates in polar reactions, since it is not clear just how concerted the observed α-eliminations with rearrangement are.[7] We now present evidence for the intermediate, isopropoxyfluoromethylene.

Chlorodifluoromethane reacted rapidly (k = 8×10^{-3} l. mole^{-1} sec.$^{-1}$) with potassium isopropoxide in dry isopropyl alcohol at 0° to give isopropyl difluoromethyl ether (b.p. 44.2–44.5°, d^{25}_4 0.97604, n^{25}D 1.3204, molecular refraction calcd. 22.115, found 22.404), triisopropyl orthoformate and about 1% fluoroform as the only detected organic products (no carbon monoxide or propylene[8]). The yields of the two major products were calculated from the base and chloride concentrations by stoichiometric considerations. The fraction of isopropyl orthoformate produced increased from 0.15 with 0.02 M isopropoxide to 0.30 with 0.10 M isopropoxide. The isopropyl difluoromethyl ether was inert under the reaction conditions and reacted very slowly even at 50°.

The basic decomposition of chlorodifluoromethane in methanol must involve difluoromethylene since with sodium thiophenolate the formation of phenyl difluoromethyl sulfide is powerfully catalyzed by sodium methoxide.[9] Under the more strongly basic conditions of the present case the α-dehydrochlorination is even better facilitated. The competing initial removal of hydrogen fluoride must be a negligible side reaction. While fluorine atoms increase the reactivity of haloforms from which other halogens may be removed to give fluoromethylenes, the initial removal of fluoride ions is very difficult, fluoroform being inert even to potassium *t*-amyl oxide at 50°.[10] This rules out the possibility that the orthoester is produced from chlorofluoromethylene, a hypothesis that is also incompatible with the change in orthoester yield with changing isopropoxide concentration.

The only subsequent reactions of the difluoromethylene that seem plausible are



protonation (1), coördination with isopropoxide ion (2) or isopropyl alcohol (3), or simultaneous protonation and coördination with isopropoxide (4) or alcohol (5). Reactions 1, 4 and 5 can lead reasonably only to i-PrOCHF$_2$, as do 2 and 3 if the carbanions formed thereby are protonated. Hence the isopropyl orthoformate must be formed through reaction 2 and/or 3 followed (or accompanied) by loss of a fluoride ion.[11] Reaction through the i-PrOCF$_2^-$ anion seems more reason-

(1) This investigation was supported in part by the Office of Naval Research.

(2) F. O. Rice and A. L. Glasebrook, THIS JOURNAL, **56**, 2381 (1934); T. G. Pearson, R. H. Purcell and G. S. Saigh, *J. Chem. Soc.*, 409 (1938).

(3) F. Adickes, *Ber.*, **60**, 272 (1927); **63**, 3012 (1930); C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor and A. E. Brodhag, THIS JOURNAL, **78**, 1653 (1956).

(4) A. Geuther, *Ann.*, **123**, 121 (1862).

(5) J. Hine, THIS JOURNAL, **72**, 2438 (1950); J. Hine and A. M. Dowell, Jr., *ibid.*, **76**, 2688 (1954).

(6) We use the term to include only species in which carbon is attached to two other atoms, neglecting isocyanides, for example.

(7) D. G. Hill, W. A. Judge, P. S. Skell, S. W. Kantor and C. R. Hauser, THIS JOURNAL, **74**, 5599 (1952).

(8) *Cf.* J. Hine, E. L. Pollitzer and H. Wagner, *ibid.*, **75**, 5607 (1953).

(9) J. J. Porter, unpublished experiments from this Laboratory. *Cf.* ref. 5.

(10) J. Hine, A. M. Dowell, Jr., and J. E. Singley, Jr., THIS JOURNAL, **78**, 479 (1956); and N. W. Burske, unpublished experiments from this Laboratory.

(11) Sn2 attack on the intermediate i-PrOCF$_2^-$ anion seems improbable for the same reasons that have been applied in the case of the trichloromethyl anion.[5]

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May 20, 1957

able since the loss of fluoride ion should be facilitated by the unshared electron pairs of the isopropoxy group. Since isopropoxyfluoromethylene is the only intermediate in the scheme in which the inert end-product, i-PrOCHF$_2$, has been bypassed, it must be an intermediate in the formation of the isopropyl orthoformate.

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Kozo Tanabe

Received March 23, 1957

GLUTAMIC ASPARTIC TRANSAMINASE

Sir:

Glutamic aspartic transaminase of pig heart has been highly purified and the presence of firmly bound pyridoxal phosphate has been confirmed. The enzyme was purified by heat denaturation (75° for 20 minutes in maleate buffer pH 6.0), ammonium sulfate fractionation (50–67%), adsorption of impurities onto calcium phosphate followed by chromatography on a calcium phosphate column[1] and a repetition of the ammonium sulfate fractionation to give an over-all yield of 30%. Sedimentation and electrophoresis studies indicate that the enzyme is 70% pure; it has an activity of 380 μM glutamate/min./mg. protein using a modification of the assay of Nisonoff, *et al.*,[2] at 37° and pH 8.5. The preparation contains one mole of pyridoxal phosphate per 67,000 grams of protein.

Figure 1 shows that the enzyme is colorless at pH 8.5 (λ_{max} 362 mμ) but turns yellow at pH 4.8 (λ_{max} 430 mμ) and in 0.1 N NaOH (λ_{max} 388 mμ). In the latter solution the prosthetic group is split off and could be isolated by use of a Dowex 1-Cl column. In 0.1 N HCl the chromophore absorbs strongly at 295 mμ. Its 2,4-dinitrophenylhydrazone, which is not extracted from acidic solution by ethyl acetate, absorbs at 478 mμ in alkali and at 415 mμ in acid. These spectra confirm the fact that the prosthetic group is a derivative of pyridoxal phosphate. It should be noted, however, that the pyridoxal phosphate has characteristically different spectra when bound to the enzyme. We believe that these spectra may be due to a pyridoxal phosphate imine, since Metzler[3] has shown that these imines absorb at 360 mμ at high pH and above 410 mμ at lower values. Matsuo and Greenberg[4] have shown that the crystallized cystathionase/homoserine dehydrase has a similar absorption band at 427 mμ.

Carbonyl reagents react with the transaminase to yield the enzyme oxime, hydrazones, cyanhydrin and complexes with thiols and bisulfite, all of which have characteristic spectra.

The addition of glutamate to the enzyme at pH 8.5 causes the absorption peak to shift to 332 mμ (see Fig. 1) a peak which is characteristic of all pyridoxine compounds including the zwitterion form of pyridoxamine. Isolation of the prosthetic group on Dowex 1-Cl, after the addition of excess glutamate, yielded pyridoxamine phosphate characterized by its absorption bands in acid (λ_{max} 293) alkali (λ_{max} 306) and at pH 5.2 (λ_{max} 326). The addition of less glutamate causes partial disappearance of the pyridoxal phosphate (measured as its 2,4-dinitrophenylhydrazone after cleavage from the enzyme by 0.1 N alkali) and the formation of an equivalent amount of α-ketoglutarate.

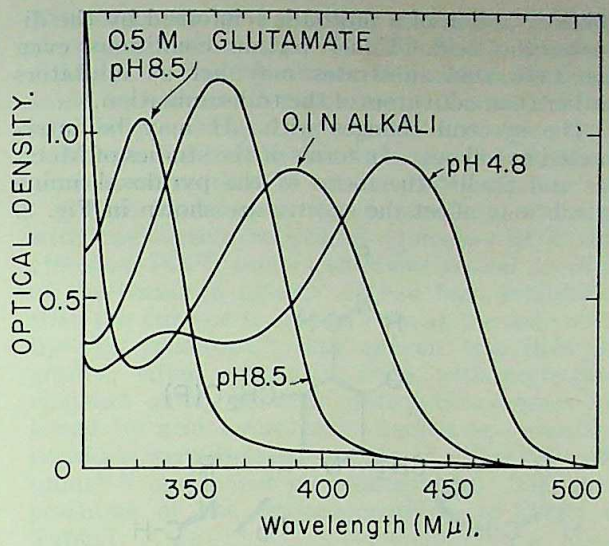

Fig. 1.—Spectra of the enzyme in 0.1 M Tris buffer pH 8.5 alone and with 0.5 M glutamate, in 0.1 N NaOH and in 0.15 M acetate buffer pH 4.8. Each cuvette contained 0.863% protein.

The reaction is reversed by increasing concentrations of ketoglutarate added to the enzyme in the presence of a constant amount of glutamate, as shown by an increase in the band at 362 mμ characteristic of the free enzyme and an increase in the band at 435 mμ ascribed to a complex of ketoglutarate with the protonated enzyme. By the use of C^{14}-glutamate rapid transamination has been confirmed in this steady-state system in which the concentrations of glutamate and ketoglutarate do not change. We believe that these experiments essentially confirm the pyridoxal-pyridoxamine hypothesis suggested on structural grounds by Snell.[5]

Dicarboxylic acids combine with the protonated form of the enzyme to produce an absorption maximum at about 435 mμ. The order of effectiveness is: glutarate > maleate > adipate > malate > ketoglutarate > oxalacetate > succinate. The fact that oxalate, malonate, pimelate, suberate, glycolate and fumarate do not interact suggests that a specific orientation of both carboxyl groups is required and that this specificity may be related to the substrate specificity of the enzyme.

These complexes may explain the apparent stabilizing effect of maleate in this purification and that of ketoglutarate in the purification of kynurenine transaminase.[6] This type of complex formation results in a new type of inhibition,[7] in which the in-

(1) V. E. Price and R. E. Greenfield, *J. Biol. Chem.*, **209**, 363 (1954).
(2) A. Nisonoff, S. S. Henry and F. W. Barnes, Jr., *ibid.*, **199**, 699 (1952).
(3) D. E. Metzler, This Journal, **79**, 485 (1957).
(4) Y. Matsuo and D. M. Greenberg, *Federation Proc.*, **16**, 218 (1957).
(5) E. E. Snell, *J. Biol. Chem.*, **154**, 313 (1944).
(6) M. Mason, *Federation Proc.*, **15**, 310 (1956).
(7) A. E. Braunstein, *Nature*, **143**, 609 (1939).

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hibitory action of a proton is reinforced by the dicarboxylic acid. Under certain conditions even the keto acid substrates may act as inhibitors rather than activators of the transamination.[8]

The spectral changes with *p*H may be interpreted as follows. In terms of the studies of Metzler and Snell[3,9] the forms of the pyridoxal imine which may affect the spectra are shown in Fig. 2.

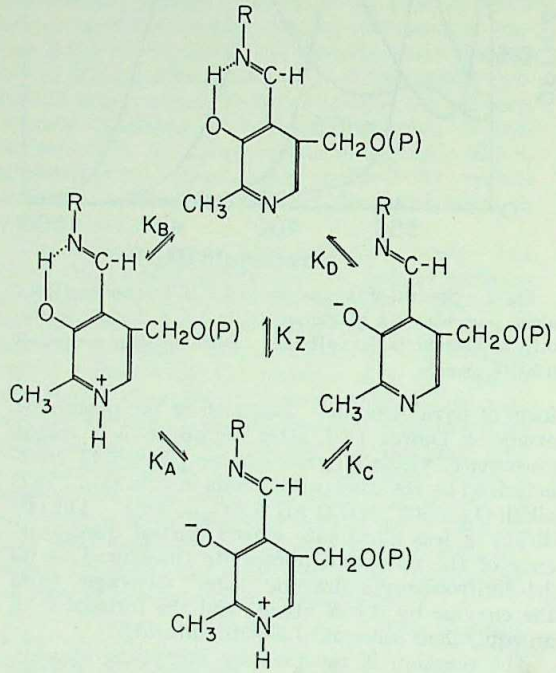

Fig. 2.—The ionization of pyridoxal phosphate imines.

These equations are based on the assumption that the yellow color may be ascribed to the hydrogen chelate ring. Rupture of this ring by a change in *p*H results in loss of color. A pK_A of 6.2 for this color change for the transaminase suggests that it is the dipolar form of the imine which occurs at neutrality, in contrast to the non-polar forms of the imines studied by Metzler[3] (pK_B = 5.9, pK_D = 10.5).

The implications of these findings with reference to the mechanism of enzymatic transamination will be discussed elsewhere.

Acknowledgment.—We are happy to acknowledge financial support from Ethicon, Inc.

(8) *Cf.* P. Peyser, Doctoral Dissertation, Columbia University, New York, N. Y., 1954.

(9) D. E. Metzler and E. E. Snell, THIS JOURNAL, **77**, 2431 (1955).

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RECEIVED MARCH 21, 1957

A STABLE EQUIMOLAR COPPER(II)–ALBUMIN COMPLEX

Sir:

A simple and rapid amperometric titration technique has been developed for the determination of bovine serum albumin (BSA) with [illegible]

ammoniacal buffer at *p*H 9.2. Figure 1 shows current voltage curves of copper(II) at the rotated platinum electrode (RPE) in a buffer 0.1 *M* in ammonia and 0.1 *M* in ammonium nitrate (curve B). The first wave corresponds to the reduction of copper(II) to copper(I). No copper waves are observed when albumin is present in a molar concentration greater than that of copper (curve D). Curve E illustrates the reappearance of the copper waves when an excess of copper is present.

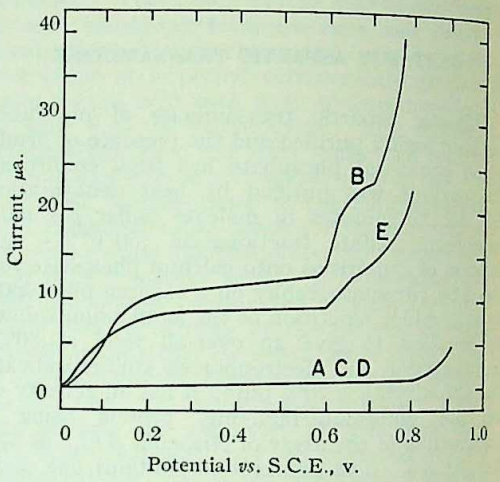

Fig. 1.—Current voltage curves at rotated platinum electrode; buffer, 0.1 *M* NH_3 + 0.1 *M* NH_4NO_3; *p*H 9.2; speed of rotation, 900 r.p.m.: A, residual; B, 4.0 × 10^{-5} *M* Cu(II); C, 7.3 × 10^{-5} *M* BSA; D, 7.3 × 10^{-5} *M* BSA + 6.5 × 10^{-5} *M* Cu(II); E, 7.3 × 10^{-5} *M* BSA + 13.0 × 10^{-5} *M* Cu(II).

By amperometric titration at the RPE in ammonia buffer at −0.4 volt, we have found that copper(II) reacts rapidly with native BSA in a mole ratio of one to one. Similar results have been obtained under proper conditions at *p*H 8 and 10. The rapid reaction is followed by a slower reaction of additional amounts of copper(II); this does not interfere with the titration. The sulfhydryl group is not involved in the reaction with copper(II). After addition of one or two moles of copper(II) per mole BSA, 0.68 mole sulfhydryl per mole BSA[1] was found by subsequent amperometric titration with mercuric chloride and/or silver nitrate.[2] Also, addition of 0.68 mole of silver nitrate or mercuric chloride per mole BSA prior to titration with copper(II) did not affect the results of this titration.

Titrations of BSA have also been carried out in a denaturing mixture which was 4 *M* in guanidine hydrochloride, 0.1 *M* in ammonia and 0.1 *M* in ammonium nitrate. A reaction ratio of copper(II) to BSA somewhat greater than unity (about 1.3) was found. This higher reaction ratio is ascribed to oxidation by copper(II)[3] of the sulfhydryl group which is oxidizable to disulfide in denatured al-

(1) W. L. Hughes, Jr., THIS JOURNAL, **69**, 1836 (1947); *Cold Spring Harbor Symposium Quant. Biol.*, **14**, 79 (1949).

(2) I. M. Kolthoff, W. Stricks and L. Morren, *Anal. Chem.*, **26**, 366 (1954); I. M. Kolthoff and W. Stricks, THIS JOURNAL, **72**, 1952 (1950).

(3) I. M. Kolthoff and W. Stricks, *Anal. Chem.*, **23**, 763 (1951).

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bumin. When the sulfhydryl group in denaturing medium is inactivated by addition of 0.68 mole of silver nitrate or potassium ferricyanide, the reaction ratio of copper(II) to BSA was again found to be unity.

Our experiments have been carried out under conditions quite different from those of Klotz, *et al.*,[4] and no comparison with their results is made here. Our results show that in the *p*H range 8–10, one copper(II) is bound to the BSA molecule extremely tightly, and that the sulfhydryl group is not the reactive group. It is of interest to note that nickel(II), even in very small concentrations, and also, to a lesser extent, cobalt(II) greatly interfere with the copper(II) BSA reaction while even large amounts of zinc(II) have very little effect. Thus, the group in the BSA molecule responsible for the binding of copper(II), the nature of which is at present unknown, apparently also forms stable complexes with nickel(II) and cobalt(II) but not with zinc(II). One unique site in the BSA molecule is the N-terminal aspartyl group, and further work may show whether this group is the site of copper(II) binding.

There is very little (if any) reaction between copper(II) and human γ-globulin under our conditions. The method has been applied to the determination of albumin in blood serum, and preliminary results are promising.

Acknowledgment.—This work was supported by grants from the U. S. Public Health Service and from the Louis and Maud Hill Family Foundation.

(4) I. M. Klotz and H. G. Curme, THIS JOURNAL, **70**, 939 (1948); H. A. Fiess and I. M. Klotz, *ibid.*, **74**, 887 (1952); I. M. Klotz, J. M. Urquhart and H. A. Fiess, *ibid.*, **74**, 5537 (1952); I. M. Klotz, J. M. Urquhart, T. A. Klotz and J. Ayers, *ibid.*, **77**, 1919 (1955); I. M. Klotz, I. L. Faller and J. M. Urquhart, *J. Phys. Colloid Chem.*, **54**, 18 (1950); I. M. Klotz and H. A. Fiess, *ibid.*, **55**, 101 (1951).

(5) On leave of absence from Bucknell University, Lewisburg, Pa.

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RECEIVED MARCH 25, 1957

ENZYME CATALYSIS AND ENZYME SPECIFICITY—COMBINATION OF AMINO ACIDS AT THE ACTIVE SITE OF PHOSPHOGLUCOMUTASE[1]

Sir:

In the classical template model for enzyme action the substrate is assumed to be absorbed with a precise fit into an area called the "active site" of the protein.[2] Presumably the amino acids at this site provide not only the catalytic action but also the specificity of the enzyme. From the widely varying specificity patterns of enzymes it would be anticipated that the amino acid composition at the active site would vary to fit the particular substrate. On the other hand, stereochemical and other evidence had led to the hypothesis that a few bond-breaking mechanisms might be common to reactions of widely different specificities[3] and hence there might be some common amino acid sequences. The sequence of a portion of the active site of chymotrypsin has been established[4–6] and hence a comparison could be made if similar information could be obtained for an enzyme of very different specificity. Such an opportunity arose when it was demonstrated that the active site of phosphoglucomutase was marked by a serine phosphate.[7,8]

P^{32}-labeled enzyme was prepared by exchange with radioactive substrates (glucose-1-PO_4^{32} and glucose-6-PO_4^{32}) under conditions similar to those of the standard assay.[9] It had been established that the enzyme is labeled only at the active site by this procedure.[8] The enzyme was then degraded, either with acid alone, with proteolytic enzymes alone, or with proteolytic enzymes followed by acid hydrolysis. Radioactive phosphopeptides were isolated by use of Dowex 50 columns[10,11] and paper chromatography. The compositions of the phosphopeptides are shown in Table I.

TABLE I

P^{32}-PHOSPHOPEPTIDES ISOLATED FROM PHOSPHOGLUCOMUTASE

Peptide	Phosphopeptide obtained by treatment with	Amino acid compn.
1	Proteolytic + acid	(Asp,Ser,Gly,Glu)
2	Proteolytic + acid	(Asp,Ser,Gly,Glu,Ala)
3	Proteolytic + acid	(Asp,Ser,Gly,Glu,Ala,Val,Thr)
4	Proteolytic only	(Asp,Ser,Gly,Glu)
5	Proteolytic only	(Asp,Ser,Gly,Glu Ala,Val,Thr, Leu)
6	Acid only	(Asp,Ser,Gly,Glu,Ala)
7	Acid only	(Asp,Ser,Gly,Glu,Ala,Val Thr, Leu)

While the detailed sequence has not been completely established, it is to be noted that the composition of each peptide and the order from comparison of lower and higher peptides is in perfect agreement with the sequence for chymotrypsin which is Asp Ser Gly Glu Ala Val.[4–6] The probability that the 7 peptides isolated from phosphoglucomutase would agree with this sequence by chance alone is very small. Moreover the concordance of the acid derived and proteolytic enzyme plus acid derived peptides is strong evidence against the sequence being an artifact of the separation procedure. The data therefore indicate that the amino acid sequence of the active site for at least 6 amino acids is the same for an enzyme which specifically hydrolyzes peptide bonds and an enzyme that specifically transfers phosphate between carbohydrate molecules.

This apparently surprising result is good support for the above mentioned hypothesis that common bond-breaking mechanisms exist despite vary-

(1) Research carried out at Brookhaven National Laboratory under the auspices of the U. S. Atomic Energy Commission.

(2) E. Fischer, *Ber.*, **27**, 2985 (1894).

(3) D. E. Koshland, Jr., "Mechanism of Enzyme Action," edited by McElroy and Glass, Johns Hopkins Press, Baltimore, Md., 1954, p. 608.

(4) J. A. Cohen, R. A. Oosterbann, M. G. Warringa and H. S. Jansz, *Disc. Faraday Soc.*, **20**, 114 (1955).

(5) N. K. Schaffer, S. Harshman, R. R. Engle and R. W. Drisko, *Federation Proc.*, **14**, 275 (1955).

(6) F. Turba and G. Gundlach, *Biol. Z.*, **327**, 186 (1955).

(7) G. R. Jolles and L. Anderson, Am. Chem. Soc. Abstracts, Sept. 1955, p. 23c.

(8) E. P. Kennedy and D. E. Koshland, Jr., *J. Biol. Chem.*, in press.

(9) V. A. Najjar, *ibid.*, **175**, 280 (1948).

(10) M. Flavin, *ibid.*, **210**, 771 (1954).

(11) N. K. Schaffer, S. Harshman and R. R. Engle, *ibid.*, **214**, 799 (1955).

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ing specificity type. It suggests further that (a) the common sequence around serine is involved in making the otherwise inert CH_2OH side chain reactive and (b) the amino acids responsible for the specificity lie further from the reactive serine, perhaps in adjacent coils. While there must be an intimate steric relation between the amino acids responsible for the catalytic action and those responsible for the specificity, these results indicate that the two may be separable. In this case common sequences related to specificity as well as to the bond-breaking action might be expected, a result which would be of enormous value in relating enzyme structure to function.

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BROOKHAVEN NATIONAL LABORATORY D. E. KOSHLAND, JR.
UPTON, L. I., NEW YORK MARY JANE ERWIN

RECEIVED APRIL 15, 1957

ENZYMATIC INTRODUCTION OF DOUBLE BONDS INTO STEROID RING A

Sir:

The introduction of unsaturation into ring A of steroids is of interest in connection with the aromatization involved in biosynthesis of estrogens,[1] and in the microbiological formation of Δ^1-dehydrosteroids,[2] some of which possess interesting physiological properties. *Pseudomonas testosteroni* (A.T.C.C. No. 11996)[3] can utilize certain steroids as a sole source of carbon and degrade these compounds to CO_2 and H_2O by a series of reactions catalyzed by adaptive enzymes. During the course of a study of the pathway involved in the oxidative degradation of steroids by this microörganism, it was found that early steps were the interconversion of 17β-hydroxyl and 17-ketone functions and the introduction of Δ^1-double bonds and Δ^4-double bonds into steroids of both the 5α-H and 5β-H series. Such reactions have been reported in a variety of microbiological systems.[1,2] The enzymatic interconversion of 17β-hydroxy- and 17-ketosteroids is catalyzed by the diphosphopyridine nucleotide-linked enzyme β-hydroxysteroid dehydrogenase and has been analyzed in detail.[4] The purpose of the present communication is to report on the enzymatic mechanism of the introduction of double bonds into steroids. This constitutes, to our knowledge, the first demonstration of these reactions by means of soluble enzymes.

Under suitable conditions *Ps. testosteroni* carries out efficient conversions of androstane-3,17-dione (I), testosterone, Δ^4-androstene-3,17-dione (II), Δ^1-androstene-3,17-dione (III) and etiocholan-17β-ol-3-one to principally $\Delta^{1,4}$-androstadiene-3,17-dione (IV) and to a lesser extent to $\Delta^{1,4}$-androstadien-17β-ol-3-one (V). In a typical conversion, this microörganism was grown in 450 ml. of a medium containing 0.5% sodium lactate in a mineral base, at 30° and an initial *p*H of 7.0, and at the end of 24 hours 45 mg. of II was added in 2 ml. of acetone and the incubation continued for 24 hours longer. Extraction of the culture with ethyl acetate, followed by chromatography on silicic acid, crystallization from hexane–acetone, and sublimation at 90–115° (0.0005 mm.) afforded 20.5 mg. of IV, m.p. 140.5–141° (no depression on admixture with an authentic sample); $[\alpha]^{25}D$ +123° (*c* 1.04, in $CHCl_3$); λ_{max}^{alc} 243 mμ (ϵ 16,200); sulfuric acid chromogens[5] were identical with a known sample (peaks at 265, 305 and 390 (broad) and a minimum at 288 mμ); (*Anal.* Found: C, 80.08; H, 8.46. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51); infrared analysis showed λ_{max}^{KBr} 5.77 μ (17-ketone), 6.04, 6.17 and 6.25 μ ($\Delta^{1,4}$-3-ketone), identical with an authentic sample. Mixed paper chromatography showed no separation from authentic IV.

In similar experiments, conversions in good yield of I and III to IV were demonstrated and the products rigorously identified by comparison paper chromatography, m.p. and infrared spectra. Evidence for the presence of small amounts of V in each case was obtained. Conversion of 19-*nor*-testosterone by the same system in 72 hours gave a 67% yield of estrone m.p. 253–256°; $[\alpha]^{25}D$ +154° (*c* 0.644, in dioxane); λ_{max}^{alc} 282 mμ (ϵ 1960); on addition of NaOH, λ_{max}^{alc} 243 mμ (ϵ 8000) and 300 mμ (ϵ 2500). The infrared spectrum showed peaks at 5.83 μ (17-ketone), 6.32, 6.18 μ (—C=C—) and 3.06 μ(OH group), and was identical with that of authentic estrone. On paper chromatography the substance migrated as estrone and gave the phenolic reaction with the Turnbull reagent.[6] Estradiol-3,17β was also found in smaller amounts.

Cell-free extracts of *Ps. testosteroni* were prepared from cultures grown on 0.5% sodium lactate as described above. After 24 hours growth, II was added to give a final concentration of 0.01% and incubation continued for 24 hours longer. Cells were harvested and washed by centrifugation. The washed cells efficiently converted I to IV. After rupture by sonic oscillation in a 9 KC Raytheon oscillator for 20 minutes, the sonicate also converted I to IV vigorously.

The unwashed residue from centrifugation of the sonicate for 20 minutes at 10,000 × *g* was also active in this conversion. The supernatant alone was inactive and its activity could be restored by adding phenazine methosulfate (PMS), an oxidation reduction dye which reacts with certain flavoprotein enzymes[7] but not by the addition of di- and triphosphopyridine nucleotides. The supernatant upon the addition of PMS still introduced Δ^1- and Δ^4-double bonds after centrifuging for 30 minutes at 105,000 × *g*. The enzymatic activities were demonstrated in a variety of ways including paper chromatographic analysis of products and ultraviolet spectrophotometry of products formed from I.

A convenient and specific assay of the Δ^1-dehydrogenase activity was the measurement of estrone formation from Δ^4-estrene-3,17-dione with the Folin

(1) P. Talalay, *Physiol. Revs.*, in press.

(2) S. H. Eppstein, P. D. Meister, H. C. Murray and D. H. Peterson, *Vitamins and Hormones*, **14**, 359 (1956).

(3) P. Talalay, M. M. Dobson and D. F. Tapley, *Nature*, **170**, 620 (1952).

(4) (a) P. Talalay and M. M. Dobson, *J. Biol. Chem.*, **205**, 828 (1953); (b) P. Talalay and P. I. [illegible] (1956).

(5) A. Zaffaroni, *Rec. Prog. in Hormone Research*, **8**, 51 (1953).

(6) G. M. Barton, R. S. Evans and J. A. F. Gardner, *Nature*, **170**, 249 (1952).

(7) T. P. Singer, E. B. Kearney and V. Massey, in O. H. Gaebler, "Enzymes: Units of Biological Structure and Function," Academic [illegible] p. 417.

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May 20, 1957

reagent.[8] Table I demonstrates the progression of this reaction with time and demonstrates the requirement for PMS.

TABLE I

CONVERSION OF Δ^4-ESTRENE-3,17-DIONE TO ESTRONE BY Δ^1-DEHYDROGENASE

	μM Phenol (as estrone) Incubation time, min. 0	45	60	90
(1) Complete system[a]	0.10	0.42	0.48	0.63
(2) Enzyme omitted[b]	.11	.10	.09	.09
(3) Estrone synthesized, (1) minus (2)	..	.32	.39	.54
(4) PMS omitted[c]	.03	.05	.04	.05
(5) Steroid omitted	.01	.02	.01	.02

[a] The reactions were carried out in air with agitation at 30° in 4 ml. systems containing 115 μM phosphate buffer, pH 7.2, and the following additions in the complete system. 0.2 ml. enzyme (supernatant from 105,000 × *g* centrifugation, see text) containing 4.3 mg. protein; 1.84 μM Δ^4-estrene-3,17-dione in 0.1 ml. acetone (or 0.1 ml. acetone only when steroid was omitted); and 3.1 μM phenazine methosulfate (added last). At the end of the reaction the mixture was acidified with 0.3 ml. of concd. HCl, extracted three times with a total of 12 ml. of CH_2Cl_2, the extract dried over Na_2SO_4, and a 5-ml. aliquot evaporated to dryness and analyzed by the Folin reaction.[8] A standard curve was prepared using estrone. [b] A small blank which did not increase on incubation was always found when PMS and steroid were mixed either in the absence of enzyme or in the presence of acid-inactivated enzyme. [c] The sample of Δ^4-estrene-3,17-dione was found to be contaminated with about 1–2% phenol, presumably estrone.

It is believed that at least two and probably three separate enzymes are involved in these dehydrogenating reactions (Δ^1-, Δ^4-5α- and Δ^4-5β-dehydrogenases), and that probably these enzymes are flavoproteins.

This work has been supported by a grant from the American Cancer Society. We are indebted to the U. S. Public Health Service for a fellowship (H.R.L.) and to the American Cancer Society for a Scholarship (P.T.).[9]

(8) O. H. Lowry, N. J. Rosebrough, A. L. Farr and R. J. Randall, *J. Biol. Chem.*, **193**, 265 (1951).

(9) Dr. D. H. Peterson and colleagues have observed the transformation of 19-*nor*-testosterone to estrone and estradiol-3,17β by *Septomyxa affinis* (personal communication).

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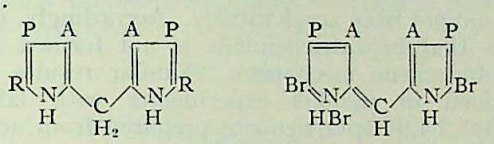
RECEIVED MARCH 18, 1957

DIPYRRYLMETHANES

Sir:

Although dipyrrylmethane itself and nuclear carboxy, acyl, and hydroxy derivatives are known, those without such groups or their vinylogs are not, being presumed to be very unstable.[1] It now appears that some dipyrrylmethanes of the latter type, which may be intermediates in the biosynthesis of porphyrins, may be obtained by and undergo conventional pyrrole reactions without fission or oxidation at the bridge.

For example, I (R = H) forms nearly colorless micro-prisms without visible absorption, m.p. 199° dec., Ehrlich's reaction strongly positive cold. (Calcd. for $C_{19}H_{22}N_2O_8$: C, 56.15; H, 5.46; N, 6.89; eq. wt., 101.6. Found: C, 56.35; H, 5.57; N, 6.80; eq. wt., 103.2.) It was obtained in 80% yield from I (R = COOH)[2] with 10% sodium hydroxide for four hours at 170°, and also from II[2] with sodium amalgam. Diazomethane converted I (R = H) into its tetramethyl ester III, m.p. 105°, (Calcd. for $C_{23}H_{30}N_2O_8$: C, 59.73; H, 6.54; N, 6.06. Found: C, 59.58; H, 6.59; N, 6.10) which gave IV (80%), the ester of I (R = CHO), m.p. 203°, with hydrogen cyanide and hydrogen chloride (Calcd. for $C_{25}H_{30}N_2O_{10}$: C, 57.91; H, 5.83; N, 5.40. Found: C, 57.85; H, 5.73; N, 5.34).



I II

A = CH_2·COOH; P = CH_2CH_2·COOH

Uroporphyrin II[2] was obtained from I (R = H) with formic acid and hydrogen bromide–acetic acid at 100° (∼ 20%, methyl ester, m.p. *ca.* 310°, degraded to coproporphyrin II methyl ester, m.p. 284–286°) and also from III with IV in methanolic hydrogen bromide at 20° followed by warming with aqueous sodium hydroxide (∼ 25%, methyl ester, m.p. *ca.* 313–315°, degraded to coproporphyrin II methyl ester, m.p. 285–286°). Under these last conditions neither III nor IV separately gave any porphyrin.

(2) S. F. MacDonald and K. H. Michl, *Canad. J. Chem.*, **34**, 1768 (1956).

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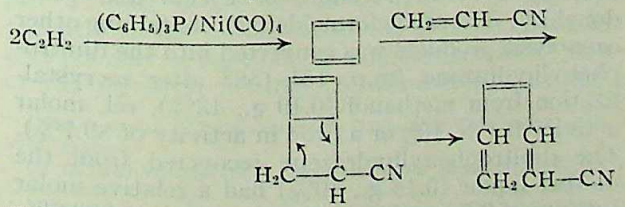
RECEIVED MARCH 18, 1957

A MECHANISM STUDY OF THE 2,4,6-HEPTATRIENENITRILE SYNTHESIS FROM ACRYLONITRILE AND ACETYLENE

Sir:

The existence of transition-metal complexes of cyclobutadiene as intermediates in reactions of acetylene has been suggested recently.[1] For example, it was proposed that the cycloöctatetraene synthesis from acetylene in the presence of nickel cyanide catalyst involves the intermediate complex $Ni(CN)_2 \cdot C_4H_4$. As an extension of this concept, it seemed reasonable to postulate that the heptatrienenitrile synthesis from acrylonitrile and acetylene[2] could be pictured as



(1) H. C. Longuet-Higgins and L. E. Orgel, *J. Chem. Soc.*, 1969 (1956); private communication with one of the authors.

(2) T. L. Cairns, A. C. England, H. L. Jackson, G. H. Kalb and J. C. Sauer, THIS JOURNAL, **74**, 5636 (1952).

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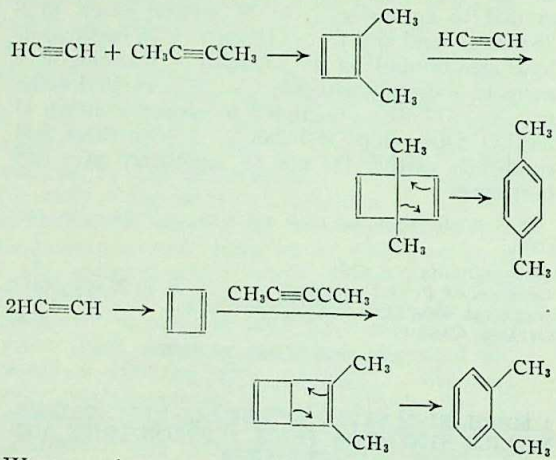
This reaction sequence necessitates having the terminal methylene group of the heptatrienenitrile derived from the acrylonitrile rather than from the acetylene. A tracer study was carried out to test this hypothesis.

For this purpose, C^{14}-labeled 2,4,6-heptatrienenitrile was prepared by the reaction of labeled acrylonitrile ($\overset{*}{C}H_2=\overset{*}{C}H$-CN) with acetylene in the presence of a nickel carbonyl/triphenylphosphine catalyst. The terminal methylene group in the heptatrienenitrile was then removed by ozonolysis and found to contain virtually no C^{14}. This result affords strong evidence that the terminal methylene group in heptatrienenitrile is derived from acetylene and not from acrylonitrile. Accordingly, it appears that heptatrienenitrile is not formed by a cyclobutadiene mechanism. Similar results were obtained in parallel experiments with labeled methyl 2,4,6-heptatrienoate prepared from acetylene and labeled methyl acrylate.

Another extension of the cyclobutadiene mechanism would suggest that some *p*-xylene, as well as *o*-xylene, should be formed in the cotrimerization of dimethylacetylene with acetylene.



We were, however, unable to detect any *p*-xylene by ultraviolet or infrared analyses.

The labeled acrylonitrile (rel. molar activity 3.8 × 10^5 dis./min.) was prepared by pyrolysis of labeled lactonitrile acetate at 555–560°. The acetate was made by heating labeled vinyl acetate, hydrogen cyanide and potassium cyanide catalyst.[3] Labeled 2,4,6-heptatrienenitrile (rel. molar activity 3.9 × 10^5 dis./min.) was prepared by injecting acetylene into the labeled acrylonitrile.[2] The heptatrienenitrile was ozonized in methylene chloride by the procedure of Clemo and Macdonald.[4] The crude formaldehyde containing other ozonolysis products was converted into the dinitrophenylhydrazone (m.p. 151–158° after recrystallization from methanol (0.19 g., 13%), rel. molar activity 0.4 × 10^5, or a drop in activity of 89.7%). The dinitrophenylhydrazone recovered from the mother liquor (0.14 g., 10%) had a relative molar activity of 0.3 × 10^5, or a drop in activity of 92.3%. The derivative appeared to be essentially pure dinitrophenylhydrazone of formaldehyde based on infrared analysis.

Tagged methyl heptatrienoate (rel. molar activity 60 × 10^4 dis./min.) was prepared from tagged methyl acrylate and acetylene.[2] Ozonolysis gave formaldehyde whose dinitrophenylhydrazone showed a drop in relative molar activity of 98%.

In the dimethylacetylene/acetylene cotrimerization, the reactants were heated with a $Ni(CO)_2[(C_6H_5)_3P]_2$ catalyst in tetrahydrofuran at 80–165° under a bomb gage pressure of 5–15 atm. for 3 hr. Benzene, styrene and *o*-xylene were identified as products. There was no indication of the presence of even small amounts of *p*-xylene (based largely on infrared and ultraviolet spectral data).

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RECEIVED APRIL 4, 1957

(3) E. L. Carpenter, British Patent 591,489 (1947).

(4) G. R. Clemo and J. McL. Macdonald, *J. Chem. Soc.*, 1294 (1935).

THE SYNTHESIS OF D-GULOSAMINE

Sir:

A new aminosugar has been isolated recently from streptothricin and streptolin B and the structure of a 2-aminosugar, D-gulosamine, has been proposed for it.[1] This appears to be the first reported isolation of a naturally occurring 2-aminohexose other than the well known D-glucosamine and D-galactosamine. It is also the first isolation of a naturally occurring sugar with the gulose configuration.

We wish to report the synthesis of a 2-aminohexose, possessing the D-gulosamine configuration and also having identical properties to the naturally isolated compound described above. Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside[2] treated with methanesulfonyl chloride in pyridine solution gave an 86% yield of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-α-D-galactopyranoside (I), m.p. 219–220°, $[\alpha]^{24}D$ +169° (*c* 1.12, $CHCl_3$). *Anal.* Calcd. for $C_{17}H_{23}O_8NS$: C, 50.86; H, 5.77; S, 7.99. Found: C, 50.93; H, 5.86; S, 7.90. Hydrolysis of I with 60% acetic acid afforded a quantitative yield of methyl 2-acetamido-2-deoxy-3-*O*-methylsulfonyl-α-D-galactopyranoside (II), m.p. 179–180°, $[\alpha]^{22}D$ +132° (*c* 0.88, CH_3OH). *Anal.* Calcd. for $C_{10}H_{19}O_8NS$: C, 38.33; H, 6.11. Found: C, 38.48; H, 6.22. It was characterized by the 4,6-di-*O*-acetyl derivative, m.p. 163–164°, $[\alpha]^{24}D$ +96° (*c* 0.83, $CHCl_3$). *Anal.* Calcd. for $C_{14}H_{23}O_{10}NS$: C, 42.31; H, 5.83. Found: C, 42.22; H, 5.79. A solution of II in methyl cellosolve heated in the presence of sodium acetate[3] gave a product, subsequently acetylated with pyridine and acetic anhydride. After purification by chromatography, a 56% yield of methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-gulopyranoside (III) was obtained;

(1) E. E. Van Tamelen, J. R. Dyer, H. E. Carter, J. V. Pierce and E. E. Daniels, THIS JOURNAL, **78**, 4817 (1956).

(2) P. J. Stoffyn and R. W. Jeanloz, *ibid.*, **76**, 561 (1954).

(3) R. R. Baker, R. F. Schaub, J. P. Joseph and J. H. Williams, *ibid.*, **76**, 4014 (1954).

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May 20, 1957

m.p. 123–124°, $[\alpha]^{21}D$ +76° (*c* 0.91, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{23}O_9N$: C, 49.86; H, 6.42. Found: C, 49.71; H, 6.45. Catalytic deacetylation of III with barium methylate afforded methyl 2-acetamido-2-deoxy-α-D-gulopyranoside (yield 72%) (IV), m.p. 79–82°, $[\alpha]^{25}D$ +72° (*c* 0.74, CH_3OH). *Anal.* Calcd. for $C_9H_{17}O_6N$: C, 45.95; H, 7.29. Found: C, 45.80; H, 7.22. A crystalline *O*-benzylidene derivative was prepared, m.p. 111–114°, $[\alpha]^{25}D$ +71° (*c* 0.90, CH_3OH). *Anal.* Calcd. for $C_{16}H_{21}O_6N$: C, 59.43; H, 6.55. Found: C, 59.08; H, 7.07. 2-Amino-2-deoxy-D-gulose hydrochloride (D-gulosamine hydrochloride) (V) was obtained in a 66% yield by treatment of IV with hydrochloric acid, 150–170° dec., $[\alpha]^{22}D$ +6.1° (10 min.) → −17.9° (36 hr.) (*c* 0.90, H_2O). *Anal.* Calcd. for $C_6H_{14}O_5NCl$: C, 33.26; H, 6.48; N, 6.50; Cl, 16.44. Found: C, 33.47; H, 6.56; N, 6.32; Cl, 16.52. A crystalline derivative was prepared, 2-deoxy-2-(2′-hydroxynaphthylidenamino)-D-gulose, m.p. 186–188° dec., $[\alpha]^{22}_{5461}$ − 150° (at equilibrium, *c* 0.60, methyl cellosolve). *Anal.* Calcd. for $C_{17}H_{19}O_6N$: C, 61.26; H, 5.75. Found: C, 61.16; H, 5.86. The structure of V was ascertained by degradation with ninhydrin in presence of pyridine[4] to D-xylose, identified by paper chromatography. Chromatographed on paper in the mixture *n*-propanol–ammonia 1% 70:30, V migrated 1.18, compared to D-glucosamine 1.00, D-galactosamine 0.91, and D-allosamine[5] 1.03. Treatment of V with pyridine and acetic anhydride, followed by reflux with methanolic hydrochloric acid and subsequent reacetylation of the crude product with pyridine and acetic anhydride, gave a compound, m.p. 116–119°, $[\alpha]^{23}D$ −54° ($CHCl_3$) to which the structure of a methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-gulopyranoside (VI) was attributed on the basis of the sequence of reactions, rotation and analysis. Found: C, 49.69; H, 6.58.

A sample of natural gulosamine,[6] chromatographed on paper had the same R_f value as V. Submitted to the above described treatment, it gave a compound, m.p. 116–119°, $[\alpha]^{23}D$ −53°, showing no depression of the m.p. in admixture with VI.

(4) P. J. Stoffyn and R. W. Jeanloz, *Arch. Biochem. Biophys.*, **52**, 373 (1954).

(5) R. W. Jeanloz, THIS JOURNAL, **79**, 2591 (1957).

(6) We are very grateful to Dr. John R. Dyer, Georgia Institute of Technology, Atlanta, Georgia, for providing a sample of natural D-gulosamine hydrochloride.

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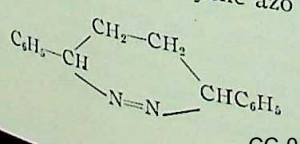
RECEIVED FEBRUARY 21, 1957

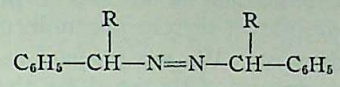
A CYCLIC AZO COMPOUND, 3,6-DIPHENYL-3,4,5,6-TETRAHYDROPYRIDAZINE (I)

Sir:

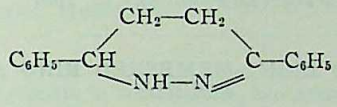
We wish to report the preparation and decomposition of the six-membered cyclic azo compound (I)



a potential source of the biradical 1,4-diphenyl-1,4-butadiyl (II) $C_6H_5\dot{C}HCH_2C\dot{C}H_2HC_6H_5$ which is of interest as possibly being formed by interaction of two molecules of styrene monomer during thermal polymerization. Compound I is analogous to the acyclic azo compounds[1] (III) R = CH_3 or



C_2H_5, which lead to styrene-type radicals. Attempts to prepare a six-membered cyclic azo compound analogous to azo-bis-iso-butyronitrile[2] failed, apparently because of thermal instability. A previously reported[3] synthesis of I had in fact led to the hydrazone-type tautomer[4] (IV)



λ_{max} 292 mμ, log ε 4.19.

Compound I was prepared by (1) addition of diethyl azo-dicarboxylate to 1,4-diphenylbutadiene-1,3, forming the adduct, 1,2-dicarboethoxy-3,6-diphenyl-1,2,3,6-tetrahydropyridazine, 95% yield, m.p. 134–136°, reported[5] 132°; (2) hydrogenation of the adduct to the hexahydro derivative, 70% yield, m.p. 85–87°, reported[5] 87°; (3) saponification with potassium hydroxide and decarboxylation in boiling methanol under nitrogen, and autoxidation during concentration of the dried ether extract, 22% yield, decomposing with vigorous gas evolution when placed in a bath at 120°, λ_{max} 287 mμ, log ε 3.49, λ_{max} 387 mμ, log ε 2.89. *Anal.* Calcd. for $C_{16}H_{16}N_2$: C, 81.30; H, 6.82; N, 11.85. Found: C, 81.48; H, 6.92; N, 11.75. The absorption due to the azo linkage is displaced from its normal position at about 350 to 387 mμ, apparently because of the *cis* configuration of I, acyclic aliphatic azo compounds normally having the *trans* configuration about the azo-linkage. Compound I is tautomerized readily to IV, by heat or by polar solvents.

Thermal decomposition of I in dilute solution in decalin at 135 and 100°, in ethylbenzene at 100°, and in 3.46 moles/l. styrene in ethylbenzene at 100° and at 80° leads to essentially quantitative evolution of nitrogen. Thermal decomposition of solid I leads to partial isomerization to IV; styrene is formed as one of the products of decomposition of solid I, identified as the dibromide, m.p. and mixed m.p. 68–70°, reported[6] 72–73°. The decomposition in solution at 80° had a half-life of about 20 minutes and appeared about 100 times as fast as that of the acyclic analog[1] III, due apparently to the *cis* nature of the cyclic compound and possibly in part due to concomitant formation of the styrene. A large (24-membered) ring bis-

(1) S. G. Cohen, S. J. Groszos and D. B. Sparrow, THIS JOURNAL, **72**, 3947 (1950).

(2) C. G. Overberger, N. R. Byrd and R. R. Mesrobian, *ibid.*, **78**, 1961 (1956).

(3) A. P. J. Hoogeveen and C. V. van Hoogstraten, *Rec. trav. chim.*, **52**, 378 (1933).

(4) S. G. Cohen and C. H. Wang, THIS JOURNAL, **77**, 2457 (1955).

(5) K. Alder and H. Rickert, *Ann.*, **585**, 81 (1954).

(6) R. Fittig and E. Erdmann, *ibid.*, **216**, 194 (1883).

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azo compound[7] has been reported, with ultraviolet absorption maximum and rate of decomposition quite similar to those of the acyclic analogs,[1] the size of the ring apparently allowing the azo linkages to assume the *trans* configuration. Decomposition of 0.036 mole/l. of I in 3.46 moles/l. styrene in ethylbenzene at 80° led to polymerization of 8.5 molecules of styrene per molecule of I.

Acknowledgment.—We are pleased to acknowledge generous support of this work by the National Science Foundation (NSFG575).

(7) C. Overberger and M. Lapkin, THIS JOURNAL, **77**, 4651 (1955).

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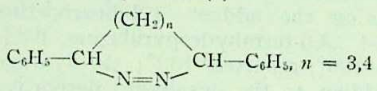
RECEIVED FEBRUARY 12, 1957

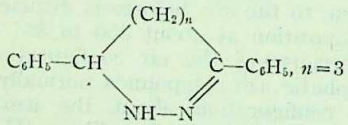
SEVEN- AND EIGHT-MEMBERED RING AZO COMPOUNDS

Sir:

We wish to report the synthesis and decomposition of the azo compounds (I)



Decomposition of these cyclic azo compounds should provide biradicals of the benzyl type. The preparation of the six-membered ring analog is also described in this issue.[1] A method for the preparation of the hydrazine precursor of I, $n = 3$, by reduction of the azine with lithium aluminum hydride has been reported previously.[2] As a preparative method, this procedure is unsatisfactory owing to the formation of the hydrazone (II)



λ_{max} 290 mμ, log ϵ 3.73, from incomplete reduction of the azine and from isomerization of the azo compound obtained by autoxidation of the hydrazine under the conditions of isolation. Quantitative reduction of the cyclic azine[2] with hydrogen over 10% palladium-on-charcoal followed by immediate oxidation of the crude hydrazine with mercuric oxide gives 29.4% of I, $n = 3$, m.p. 115°, with gas evolution, λ_{max} 290 mμ, log ϵ 2.21, λ_{max} 389 mμ, log ϵ 2.03. *Anal.* Calcd. for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.51; H, 7.01; N, 11.23. Air oxidation of the crude hydrazine has also yielded the azo compound. The normal azo absorption found in acyclic azo compounds at approximately 350 mμ,[3] has been displaced to 389 mμ, presumably due to the *cis* configuration forced on the azo link in I, $n = 3$. Thermal decomposition of I, $n = 3$, in xylene solution at 100.2° gives first-order kinetics, half-life 2.9 minutes, with a 94% evolution of nitrogen after 31 minutes. Decomposition of I in xylene at 80° gave a half-life of 27.1 minutes with only a 71.5% evolution of nitrogen. These decomposition rates are over 100 times faster than the corresponding linear *trans*[3] azo compounds. Analysis of products of the decomposition at 80° indicates the presence of the hydrazone II, $n = 3$, λ_{max} 290 mμ, log ϵ 3.60. Analysis of the ultraviolet spectrum of I, $n = 3$, has shown that I slowly isomerizes to the hydrazone II, $n = 3$, in ethanol at room temperature.

The synthesis of the eight-membered ring azo compound I, $n = 4$, was carried out by preparing the appropriate cyclic azine by a modification of the method of Overberger and Lapkin,[4] m.p. 136–137°, λ_{max} 268 mμ, log ϵ 4.45. *Anal.* Calcd. for $C_{18}H_{18}N_2$: C, 82.42; H, 6.92; N, 10.68; mol. wt., 262. Found: C, 82.64; H, 6.90; N, 10.43; mol. wt. 281 (ebullioscopic in butanol). Quantitative reduction of the azine followed by immediate oxidation with mercuric oxide yielded 57% of I, $n = 4$, m.p. 88–90°, λ_{max} 368 mμ, log ϵ 1.65. *Anal.* Calcd. for $C_{18}H_{20}N_2$: C, 81.77; H, 7.63; N, 10.60; mol. wt., 264. Found: C, 81.60; H, 7.47; N, 10.73; mol. wt., 297 (ebullioscopic in butanol).[5] The infrared absorption for both I, $n = 3,4$, are almost identical, show no hydrazone absorptions and confirm the conclusions made from ultraviolet data.

Acknowledgment.—We wish to thank the National Science Foundation for the support of a portion of this work, Grant NSF-1453.

(3) S. G. Cohen, S. J. Groszos and D. B. Sparrow, *ibid.*, **72**, 3947 (1950).

(4) C. G. Overberger and M. Lapkin, *ibid.*, **77**, 4651 (1955).

(5) J. M. Zanden and G. DeVries, *Rec. trav. chim.*, **75**, 1159 (1956) have reported the preparation of the 3,8-di-(*p*-anisyl) derivative of I, $n = 4$.

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BOOK REVIEWS

Magnetochemistry. Second Edition. Completely Revised and Rewritten. By PIERCE W. SELWOOD, Professor of Chemistry, Northwestern University. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1956. xii + 435 pp. 16 × 23.5 cm. Price, $11.50.

The subject of magnetochemistry has proliferated in the thirteen years since the first edition of this monograph appeared and the second edition, which has been revised, expanded and brought up-to-date, is a most welcome addition to the literature. The author states that about one-half of the available references, covering the literature through 1955 *Chemical Abstracts*, have been included in this edition. The present volume is unique in providing a modern survey of the applications of magnetic measurements to chemical problems since the treatises by Klemm and by Bhatnagar and Mathur are now quite out-of-date. The author has largely avoided repetition of material adequately covered elsewhere and his treatment complements those in other books on magnetism by Van Vleck, Stoner, Bates and Bozoroth, all of which represent the viewpoint of the physicist.

The first three chapters of the new edition are devoted to experimental methods of measuring average susceptibilities, principal susceptibilities and specific magnetization; these provide a practical guide to current practice which should be studied by anyone contemplating experimental work of this type. A nine-page chapter on resonance methods and a chapter on diamagnetic anisotropy are new. The chapters covering diamagnetism of molecules, diamagnetism of atoms, paramagnetism of atoms, paramagnetism of molecules and ferromagnetism have been partly rewritten, numerous references added and many helpful tables of data inserted. A new chapter reviews applications of atomic paramagnetism, particularly to glasses, irradiated solids and luminescent solids. Antiferromagnetism not even listed in the index to the first edition, now receives a separate chapter. The applications of ferromagnetism and antiferromagnetism to structural inorganic chemistry are stressed rather than the technological applications. The chapter on metallic diamagnetism and paramagnetism has been completely rewritten and the book concludes with an interesting account of magnetochemistry and heterogeneous catalysis, a subject to which Selwood and his students have made extensive contributions.

The most disappointing features of the new edition to this reviewer are the scanty treatment accorded to resonance methods and to theoretical developments. Nuclear magnetic resonance and paramagnetic resonance are already important tools for investigating chemical problems and each already has an extensive literature. Although many references to specific applications have been inserted through the text, in addition to the brief chapter introducing the methods, the reader must turn elsewhere for an adequate review of experimental methods or of results. Important theoretical developments often receive no attention. Thus Pauling's theory of the magnetic properties of metals and the band theory each receive only a reference. Since readable introductions to many of these topics are rare the casual reader will no doubt often fail to gain an understanding of the physical bases of the phenomena. However, by exclusion of such material it has undoubtedly been possible to keep down the size and cost of the book.

Although emphasis throughout is on experimental methods and results it avoids being a mere compendium of references. Brief summaries of pertinent theoretical work provide, in many cases, the background for understanding and interpreting the data. References have been chosen which for the most part offer either a theoretical or practical advance with the result that nearly every application of magnetism to chemistry is at least mentioned. The treatment of experimental articles is critical and, reflecting the wide experience of the author, many doubtful results are questioned (such as the "superparamagnetism" of Kobozev, *et al.*). Direct or implied suggestions for research abound and should stimulate workers in a variety of fields to apply magnetochemical methods to their problems.

The new edition will be indispensable to workers in the field particularly in view of the fact that the two-thousand listed references come largely from journals not usually read by the chemist and often not available. The volume is highly recommended as a comprehensive guide to "classical" magnetochemistry to anyone interested in structural chemistry, solid state physics or the application of magnetic measurements in chemistry. The style is clear and readable, the organization good and the background required of the reader very modest.

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Die Polarographie in der Medizin, Biochemie und Pharmazie. By M. BŘEZINA and P. ZUMAN, Polarographisches Institut der Tschechoslowakischen Akademie der Wissenschaften, Prag. Akademische Verlagsgesellschaft, Geest und Portig K.-G., Sternwartenstrasse 8, Leipzig C 1, Germany. 1956. 800 pp. 17.5 x 25 cm. Price, DM 48.

This monograph, which is a "revised and enlarged translation" of the first (1952) Czech edition, deals with the use of the polarograph in analyzing not only biological, clinical and pharmaceutical materials, but virtually every other kind of organic sample as well. Most of its pages are devoted to the determination of organic substances, but there is also a quite comprehensive treatment of the determination of inorganic constituents. Its subject is thus both important and broad, and one cannot but welcome this extensive treatment by two well-known contributors to the polarographic literature.

The nature and scope of the treatment may be illustrated by the contents of the section dealing with the determination of lead. Here, within twenty pages, are given descriptions of methods for dealing with thirty different kinds of samples, including, for example, blood, fingernails, tin cans, cadavers and port wine. Most of the procedures are given in enough detail to permit their practical execution without the necessity of consulting the original literature: this should be especially valuable to the busy clinical analyst. Where two or more procedures for analyzing similar samples have been proposed, all are usually described in about equal detail. This has the advantage of placing at the reader's disposal an extensive summary of the work in this field up to about 1954, and especially of that portion of it which is due to the authors and their Czech colleagues. However, it will be regretted that room could not be found for a critical evaluation of the merits of the various procedures or for some description of the chemical and electrochemical processes on which they are based.

Though the authors have succeeded in giving an admirably thorough presentation of their own country's achievements in polarographic analysis, there are some noteworthy gaps in their coverage of the remainder of the literature. Derivative polarography (attributed to Vogel and Říha alone) is discussed at some length, though without reference either to an important paper by Lingane and Williams or to the related and no less meritorious technique of polarography with superimposed a.-c. On the other hand, rotating solid metal electrodes are dismissed very briefly, and such other techniques as electro-separations at controlled potential and coulometry at controlled current are not even mentioned. Nor is any reference made to the fundamental work of Elving, *et al.*, on the influence of ionic strength in organic polarography.

Although the extensive table of "the most important" half-wave potentials of inorganic and organic substances will be gladly received by those concerned with descriptive polarography, it is marred by a number of errors and other defects. The errors may be typified by two examples. The value given (+0.67 for the half-wave potentials of the "copper(I)–copper(II)" couple in sulfate and citrate media are

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evidently derived from the work of Kalousek, which actually involved mixed potentials and had nothing to do with copper(I). On p. 665 $E_{1/2}$ is given as − 0.54 v. *vs.* N.C.E. for the process Re(I)→Re(II) in 1 *M* perchloric acid: though no reference is given, the only possible source known to this reviewer is a paper by Lingane which gives a different half-wave potential, a different oxidation state of the starting material, and a different concentration of the supporting electrolyte, and also describes three additional waves of which no mention is made in the table. In the organic section of the table, the consistent use of trivial rather than systematic names of organic compounds is regrettable, as is the frequent failure to give full details concerning supporting electrolyte composition. As in the remainder of the book, American sources are poorly represented in this table—the reviewer sought in vain for any mention of a long and important series of papers by Elving, *et al.*—and over half of those which are listed are over ten years old.

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Fortschritte der Chemie Organischer Naturstoffe (Progress in the Chemistry of Organic Natural Products). Volume XIII. Edited by L. ZECHMEISTER, California Institute of Technology, Pasadena. Springer-Verlag, Mölkerbastei 5, Wien 1, Austria. 1956. xii + 624 pp. 16.5 × 23.5 cm. Price, $24.75; Ganzleinen, $25.60.

Earlier volumes in this series have presented comprehensive reviews by leading workers on topics which, while of current interest, have not become hackneyed by repeated reviewing. The present volume continues this valuable tradition, although some of the chapters have been anticipated to a greater or less degree by reviews published elsewhere.

The chapter on infrared spectra of natural products by A. R. H. Cole discusses instrumentation, and then considers numerous applications to problems in the structure of natural products, principally of steroids and terpenoids. Cole wisely does not attempt to duplicate the comprehensive collections of information about infrared spectra of organic compounds which are available in the writings of Bellamy and of Norman Jones, but his chapter is interesting and useful.

O.Th. Schmidt's review of gallotannins and related compounds gives a good summary of a field with which most organic chemists are probably not very familiar; the reader should note that "genetisch" in this chapter is apparently synonymous with the word "biogenetic" in English.

The cardiac drugs have offered one of the most complex structural problems in the whole steroid field, and in spite of many outstanding researches, particularly the classical studies of W. L. Jacobs, the structural problems are not all solved. Ch. Tamm gives a comprehensive and timely review of the chemistry of the glycosides and the aglycones.

Tropolone chemistry is reviewed by one of its most active exponents, Nozoe; the coverage is not as comprehensive as that in the recent review article by Pauson, but Nozoe's paper contains some new material and is a readable summary.

J. R. Price contributes an interesting and well-written chapter on alkaloids which can be considered to be related to anthranilic acid; the alkaloids considered include those of the quinoline, acridine, furoquinoline and quinazoline types.

The chemistry and pharmacology of the Rauwolfia alkaloids are discussed by Chatterjee, Pakrashi and Werner; this paper is comprehensive, is admirably up to date (Woodward's total synthesis of reserpine is included) and will undoubtedly be very useful to the many workers in this field. The section on pharmacology is particularly well done.

The great advances made in method of polypeptide synthesis in the last decade, and the large amount of work currently going on in the field of protein structure, make the last chapter, by Grassmann and Wünsch, particularly timely. They present a comprehensive and valuable, although occasionally rather uncritical, survey of methods of synthesis of the peptide bond; the chapter is, as far as the reviewer knows, the most complete and up to date discussion available.

In summary, all of the chapters will be useful to the specialist, and they all make instructive and broadening reading to the organic chemist who is interested in structural and theoretical problems. The emphasis of the whole book is on structural organic chemistry; possibly a chapter or two of more biological and biochemical nature, such as have appeared in earlier volumes of the series, would have provided some welcome variety.

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PHYSICAL AND INORGANIC CHEMISTRY

[CONTRIBUTION FROM THE REFINING TECHNICAL & RESEARCH DIVISIONS, HUMBLE OIL & REFINING COMPANY]

Reactions of Gaseous Ions. II. Acetylene

BY F. H. FIELD, J. L. FRANKLIN AND F. W. LAMPE

RECEIVED JANUARY 23, 1957

The gas phase reactions of several organic positive ions with acetylene have been identified and their rates measured. The rates are in approximate agreement with values calculated theoretically. Appearance potentials of several primary ions have been measured to provide energy data necessary for interpretation of certain secondary reactions.

In a recent paper[1] we reported on studies of the reactions of ions from methane and ethylene in a mass spectrometer ion source. The present paper reports the results of studies of the reactions of ions from acetylene. Hinkle, Roberts and Hamner[2] have reported secondary ions from several acetylenes but did not identify the reactions or measure the reaction rates. In this paper we describe experiments by which the reactions leading to the formation of several secondary ions from acetylene were determined and their rates measured.

Results and Discussions

A typical mass spectrum of acetylene at a reservoir pressure of 10.3 mm. is given in Table I. The important secondary peaks are those having m/e ratios of 51, 50, 49, 37 and 38. All of these peaks exhibited an approximately second-order pressure dependence and so could not be attributed to impurities. Further, their variation in intensity with repeller voltage clearly showed them to be secondary ions.

TABLE I

MASS SPECTRUM OF ACETYLENE AT 10.3 MM. RESERVOIR PRESSURE ($N = 11 \times 10^{13}$ MOLECULES/CC.) ($V_R = 1$ V.)

m/e	Intensity, arbitrary units	m/e	Intensity, arbitrary units
12	510	37	44
13	1590	38	21
14	70	39	4
24	1530	49	55
25	5800	50	750
26	38000	51	930
27	750	52	≈12

In order to identify the reactions by which these secondary products were formed, their appearance potentials were measured in the Westinghouse Type LV mass spectrometer using the techniques described in the previous paper. Firm data have not previously been obtained for the appearance potentials and heats of formation of certain of these ions. In order to interpret the results of our secondary reactions, it was necessary to determine the heats of formation of these ions by measuring their appearance potentials as primary decomposition products. Accordingly, we determined the appearance potentials of the C_3H^+ and C_4H^+ ions from 1,3-butadiene, 1-butyne and vinylacetylene and of the $C_4H_2^+$ and $C_4H_3^+$ ions from vinylacetylene. In addition, for purposes of calibration we measured the appearance potential of the CH^+, C_2^+ and C_2H^+ ions from acetylene. The appearance potentials of these primary ions and the corresponding heats of formation are given in Table II.

Our value for C_2H^+ is in sufficiently good agreement with the value of 17.8 v. reported by Coats and Anderson[3] and Kusch, Hustrulid and Tate.[4] Also, our appearance potential for CH^+ agrees within the accuracy of the measurements with the value of 22.3 v. reported by the latter workers.

We found three values for the appearance potential of the C_2^+ ion from acetylene. The low value of about 13 v., which is quite approximate, is probably attributable to a small amount of pyrolysis on the filament. There were also two quite definite

(1) F. H. Field, J. L. Franklin and F. W. Lampe, THIS JOURNAL, **79**, 2419 (1957).

(2) Hinkle, Roberts and Hamner, paper presented at meeting of ASTM Committee E-14, Cincinnati, Ohio, May 28–June 1, 1956.

(3) F. H. Coats and R. C. Anderson, THIS JOURNAL, **77**, 895 (1955).

(4) P. Kusch, A. Hustrulid and J. T. Tate, *Phys. Rev.*, **52**, 843 (1937).

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Table II

Appearance Potentials of Primary Ions

m/e	Ions from acetylene	Ap, v.	ΔHf (ion),[a] kcal./mole
13	$C_2H_2 \rightarrow CH^+ + CH$	21.68	
24	$C_2 \rightarrow C_2^+$	≈13	
	$C_2H_2 \rightarrow C_2^+ + H_2$	18.2	474
	$C_2H_2 \rightarrow C_2^+ + 2H$	22.7	472
25	$C_2H_2 \rightarrow C_2H^+ + H$	17.3	401
	Ions from 1,3-butadiene		
37	$C_4H_6 \rightarrow C_3H^+ + CH_3 + H_2$	12.44	282
	$\rightarrow C_3H^+ + CH_3 + 2H$	18.96	328
49	$C_4H_6 \rightarrow C_4H^+ + 2H_2 + H$	15.75	336
	$\rightarrow C_4H^+ + 5H$	25.30	349
	Ions from 1-butyne		
37	$C_4H_6 \rightarrow C_3H^+ + CH_3 + H_2$	12.59	299
	$\rightarrow C_3H^+ + CH_3 + 2H$	17.62	312
49	$C_4H_6 \rightarrow C_4H^+ + 2H_2 + H$	13.20	292
	$\rightarrow C_4H^+ + 5H$	22.68	303
	Ions from vinylacetylene		
37	$C_4H_4 \rightarrow C_3H^+ + ?$	18.71	?
49	$C_4H_4 \rightarrow C_4H^+ + H_2 + H$	12.13	293
	$\rightarrow C_4H^+ + 3H$	17.02	301
50	$C_4H_4 \rightarrow C_4H_2^+ + H_2$	12.84	361
51	$C_4H_4 \rightarrow C_4H_3^+ + H$	12.59	303

[a] Calculated using heats of formation taken from the API tables.[5] The heat of formation of vinylacetylene was estimated by the method of group equivalents[6] assuming a resonance energy of 4 kcal/mole.

discontinuities in the ion intensity curves, one at 18.2 v. and the other at 22.7 v. The higher value corresponds within experimental accuracy to the 23.3 and 23.9 v. values of Coats and Anderson and Kusch, Hustrulid and Tate. This we attribute to the reaction

$$C_2H_2 \longrightarrow C_2^+ + 2H$$

The lower appearance potential 18.2 v. differs from the higher by almost exactly $D(H_2)$ and accordingly it is reasonable to attribute it to the reaction

$$C_2H_2 \longrightarrow C_2^+ + H_2$$

We are concerned that other investigators have not observed this appearance potential, but in our instrument it was definite and we think the interpretation is a reasonable one.

It was surprising to find the lower appearance potentials for the C_3H^+ ion from 1,3-butadiene and 1-butyne so small. The values appear real, however, and we have no choice but to accept them. In each case we have interpreted the appearance potential as corresponding to the reaction giving the highest heat of formation for C_3H^+. Although there is a discrepancy of 17 kcal./mole between the results from the two sources, the heat of formation nevertheless appears to be in the neighborhood of 290 kcal./mole. Further, the higher appearance potentials, if interpreted as corresponding to the formation of hydrogen atoms instead of H_2, give approximate agreement with this heat of formation of C_3H^+. The literature gives very few measurements of the appearance potential of C_3H^+. The only one capable of unequivocal interpretation is that of Field[7] from cyclopropane. His value of 15.0 v. leads to a heat of formation of C_3H^+ of 307 kcal./mole if one assumes the reaction

$$\text{Cyclo-}C_3H_6 \longrightarrow C_3H^+ + 2H_2 + H$$

More extensive atomization of hydrogen would give unreasonably low heats of formation of C_3H^+. Coats and Anderson[3] obtained a value of 18.4 v. from propyne which would lead to a heat of formation of 416 or 312 kcal./mole depending upon whether the decomposition reaction involved the formation of $H_2 + H$ or 3H. Hissel[8] measured the appearance potential of C_3H^+ from pyrrole, furan and thiophene. The results can be interpreted as corresponding to a heat of formation of C_3H^+ in the neighborhood of 300 kcal./mole, but since the reactions are complicated, any interpretation would be equivocal. It appears then, from all of the available measurements, that a value for the heat of formation of C_3H^+ in the neighborhood of 300 kcal./mole is correct although it is indeed lower than would have been anticipated.

The appearance potentials of the C_4H^+ ion similarly lead to surprisingly low values for the ion's heat of formation. Although again close agreement is not obtained amongst the heats of formation from various sources, we must conclude that the heat of formation of C_4H^+ is in the neighborhood of 300 kcal./mole. Unfortunately, we know of no reliable measurement for the appearance potential from other sources.

In an earlier paper, Franklin and Field[9] reported the appearance potential of $C_4H_2^+$ from vinylacetylene as 12.88 v. Partly for purposes of calibration we remeasured this appearance potential and found excellent agreement with the previous value. This leads to a heat of formation of 361 kcal./mole which is in fair agreement with that which one calculates from ionization potentials reported by Price and Walsh.[10]

Our value for the heat of formation of the $C_4H_3^+$ ion is appreciably lower than that obtained from Coats and Anderson's[3] value as determined from butyne-2. We are inclined to prefer our value since it corresponds to a simpler decomposition.

In Table III, we compare the appearance potentials of ions formed in acetylene by secondary processes with that of the primary ion formed from acetylene by a primary process. From this, it is evident that $C_4H_3^+$ and $C_4H_2^+$ are formed by reaction of $C_2H_2^+$ with acetylene. Further, these two peaks are by far the most intense in the secondary spectrum and undoubtedly correspond to reaction of a very abundant primary ion.

It is of interest that two appearance potentials for the C_4H^+ ion were found. These correspond approximately to the two appearance potentials of C_2^+ from acetylene at 18.2 and 22.7 v. We did not observe a C_4H^+ appearance potential at around 13 v., but this is not surprising since the amount of

(5) Rossini, Pitzer, Arnett, Braun and Pimentel, "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons," Carnegie Institute of Technology Press, Pittsburgh, Pennsylvania, 1953.

(6) J. L. Franklin, *Ind. Eng. Chem.*, **41**, 1070 (1949).

(7) F. H. Field, *J. Chem. Phys.*, **20**, 1734 (1952).

(8) J. Hissel, *Bull. Soc. Roy. Sci. Liège*, **21**, 457 (1952).

(9) J. L. Franklin and F. H. Field, This Journal, **76**, 1994 (1954).

(10) W. C. Price and A. D. Walsh, *Trans. Faraday Soc.*, **41**, 381 (1945).

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TABLE III

IDENTIFICATION OF SECONDARY REACTIONS

m/e	Ap secondary ion, v.	Ap of nearest primary ion from C_2H_2, v.	Probable reaction	ΔH_r,[a] kcal./mole
51	11.07	11.4	$C_2H_2^+ + C_2H_2 \rightarrow C_4H_3^+ + H$	− 16
50	11.38	11.4	$C_2H_2^+ + C_2H_2 \rightarrow C_4H_2^+ + H_2$	− 10
49	19.2	18.2	$C_2^+ + C_2H_2 \rightarrow C_4H^+ + H$	−181
49	22.5	22.7	$C_2^+ + C_2H_2 \rightarrow C_4H^+ + H$	
38	21.3	21.68	$CH^+ + C_2H_2 \rightarrow C_3H_2^+ + H$	−2 to −30
38	21.3	21.68	$CH^+ + C_2H_2 \rightarrow C_3H^+ + H_2$	−109
37	22.9	21.68	$CH^+ + C_2H_2 \rightarrow C_3H^+ + 2H$ or $CH^+ + C_2H_2 \rightarrow C_3H^+ + H_2$	− 5

[a] Calculated using heats of formation of ions taken from the compilation of Field and Franklin[11] and heats of formation of neutral molecules taken from the API tables.[3]

pyrolysis was so small that even the primary C_2^+ peak corresponding to it was very difficult to measure.

The appearance potentials of both the 37 and 38 peaks in the secondary spectrum agree most closely with that of CH^+ and we conclude, therefore, that both of these ions are formed by the reaction of CH^+ with acetylene. Both processes would be exothermic. Further, these secondary peaks are comparatively small and would be expected to arise from a comparatively weak precursor.

In the previous paper,[1] we showed that where two secondary ions arise from a common primary, the reaction can be best interpreted as involving the decomposition of a common activated complex. This is also true of the ions from acetylene. Thus, comparison in Table IV of the relative intensities of $C_4H_3^+$ and $C_4H_2^+$ ions formed as primary decomposition products of C_4H_4 and as secondary products from the reaction of $C_2H_2^+$ and C_2H_2, shows very close agreement. The C_4H^+ is also formed as a primary product from C_4H_4, but appearance potentials indicate that it is not formed in appreciable amounts from the reaction of $C_2H_2^+$. Since this reaction is slightly exothermic, the absence of C_4H^+ as a secondary product of the reaction of $C_2H_2^+$ suggests that some activation energy is involved.

TABLE IV

COMPARISON OF PRIMARY AND SECONDARY MASS SPECTRA (BASED ON LARGEST OF PEAKS COMPARED)

Ion	Relative intensities Primary from C_4H_4	Sec. from $C_3H_3^+ + C_2H_2$	Ion	Relative intensities Primary from C_4H_2	Sec. from $C_2^+ + C_2H_2$
$C_4H_3^+$	100	100	C_4H^+	100	100
$C_4H_2^+$	83	81	C_4^+	24	45 ?
C_4H^+	13	6			

It is interesting also that the primary mass spectrum of C_4H_2 and the secondary spectrum of $C_2^+ + C_2H_2$ show approximate agreement for the C_4H^+ and C_4^+ ion intensities. The C_4^+ ion intensity was too small to permit a detailed study, but it seems reasonable that it might be formed from the reaction of C_2^+ ions.

As in the previous paper,[1] we measured the variation in ion intensities at a series of pressures while holding the repeller voltage constant and from this the rate constants for the various reactions at fixed voltage have been calculated by means of the equations (see ref. 1).

$$\frac{I_{S_j^+}}{I_{P^+} + \sum_j I_{S_j^+}} = \frac{k_{S_j^+}}{\sum_j k_{S_j^+}} k_1 [M] \tau_{P^+} \quad (1)$$

$$\tau_{P^+} = \frac{1}{2A}\sqrt{B^2 + 2Ad_0} + \frac{d_0}{2B} \ln \frac{\sqrt{B^2 + 2Ad_0} + B}{\sqrt{B^2 + 2Ad_0} - B} \quad (2)$$

$A = ev/m$

$B = \sqrt{8kT/\pi m}$

d_0 = distance from electron beam to the ion exit slit

v = ionization chamber field strength

In Table V, the rate constants are given at a field strength of 10 volts/cm. It is of interest that, as in the previous studies, the rate constants for the various reactions differ by a comparatively small amount.

TABLE V

RATE CONSTANTS FROM PRESSURE STUDIES (FIELD STRENGTH = 10 VOLTS/CM.)

	$\left(\frac{k_{S_j^+}}{\Sigma k_{S_j^+}}\right) k_1 \times 10^{10}$ (cc./molecule sec.)	$k_1 \times 10^{10}$ (cc./molecule sec.)
$C_2H_2^+ + C_2H_2 \rightarrow C_4H_3^+ + H$	5.0	
$C_2H_2^+ + C_2H_2 \rightarrow C_4H_2^+ + H_2$	3.9	
$C_2H_2^+ + C_2H_2 \rightarrow (C_4H_4^+)$		8.9
$C_2^+ + C_2H_2 \rightarrow C_4H^+ + H$	7.3	7.3
$CH^+ + C_2H_2 \rightarrow C_3H_2^+ + H$	3.5	
$CH^+ + C_2H_2 \rightarrow C_3H^+ + H_2$	6.9	
$CH^+ + C_2H_2 \rightarrow (C_3H_3^+)$		10.4

The rate constants were also measured at different field strengths while holding the pressure constant. Table VI gives the average rate constants for the various reactions at several field strengths. In accordance with previous experience, all of these values tend to go through a maximum in the neighborhood of 8 to 20 volts per cm. Such discrepancies as are to be found between Tables V and VI are to be attributed to experimental error.

Equation (3) relates rate constant to reaction cross section, σ

$$k = f\sigma Q'/\bar{\tau} \quad (3)$$

where

$$Q'/\bar{\tau} = \frac{A\bar{\tau}}{2} + \frac{B^2}{A\bar{\tau}}\left[\frac{247}{382} + \frac{1}{3}\ln\frac{2A\bar{\tau}}{\sqrt{B^2 + 3A^2\bar{\tau}^2}}\right] \quad (4)$$

f is an efficiency factor, and other terms are defined above. Values of $f\sigma$ have been calculated from the measured rate constants and the results are given in Table VII.

In the previous paper we have shown that σ can be calculated from the equation

$$\sigma = \frac{e\pi\sqrt{\alpha}}{\sqrt{6kT + 2/3eVd_0}} \quad (5)$$

where α is the polarizability. Values of σ have been calculated from equation 4 using $\alpha = 3.88 \times 10^{-24}$ from Landolt-Börnstein[12] and the results are given

(11) F. H. Field and J. L. Franklin, "Electron Impact Phenomena and the Properties of Gaseous Ions," Academic Press, New York, N. Y., in press.

(12) Landolt-Börnstein, "Zahlenwerte und Functionen, 6 Auflage, Atom und Molecular Physik," 3 Teil, Springer-Verlag, Berlin, 1950, p. 515.

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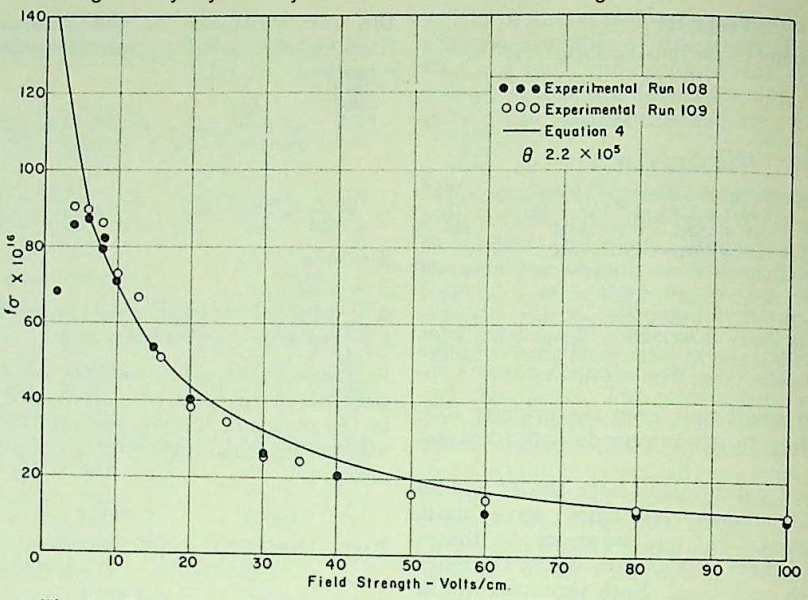

Fig. 1.—Typical plot of $f\sigma$ *vs.* field strength for $C_2H_2^+ + C_2H_2 \rightarrow [C_4H_4^+]$.

in Table VII. The agreement amongst the experimental cross sections for the various reactions is rather close as would be expected from theory.

As in the previous paper[1] rate constants and reaction cross sections for thermal speed ions were obtained by extrapolation from the more reliable higher field strength measurements. It was shown that the reaction cross section could be represented by

$$f\sigma = {}^1/_2\left(\frac{m_1(m_1+m_2)}{m_2}\right)^{1/2}\frac{\theta e\pi\alpha^{1/2}}{\left(3kT+\frac{eVd_0}{3}\right)} \quad (6)$$

where the indices 1 and 2 refer to the ion and molecule, respectively, and with θ determined from the slope of a plot of $f\sigma$ *vs.* $1/(3kT + eVd_0/3)$. That equation 4 represents quite nicely the variation of $f\sigma$ with field strength is shown in Fig. 1. The rate constant for thermal speed ions was shown to be

$$k_{v=0} = \frac{\theta e}{6}\left(\frac{8\pi\alpha}{kT}\right)^{1/2}\left(\frac{m_\alpha + m_\beta}{m_\beta}\right)^{1/2} \quad (7)$$

where the index α always refers to the lighter reactant.

Table VI

Reaction Rate Constants at Various Field Strengths ($P_R \approx 5$ Mm.)

Reaction	$10^{10}\left(\frac{k_{ej}^+}{\Sigma k_{ej}^+}\right) k_1$, cc./molecule sec. at indicated V/d							
	100	60	40	20	10	8	6	2
$C_2H_2^+ + C_2H_2 \rightarrow C_4H_3^+ + H$	1.5	1.7	2.1	3.2	4.5	4.8	4.5	2.7
$C_2H_2^+ + C_2H_2 \rightarrow C_4H_2^+ + H_2$	1.7	1.7	2.0	2.7	3.7	3.9	3.6	2.2
$C_2H_2^+ + C_2H_2 \rightarrow (C_4H_4^+)$	3.2	3.4	4.1	5.9	8.2	8.7	8.1	4.9
$C_2^+ + C_2H_2 \rightarrow C_4H^+ + H$	5.5	5.4	5.8	6.6	8.5	9.2	7.4	4.3
$CH^+ + C_2H_2 \rightarrow C_3H_2^+ + H$	1.8	2.1	2.4	3.2	3.0	2.6	2.0	1.1
$CH^+ + C_2H_2 \rightarrow C_3H^+ + H_2$	4.1	4.3	5.5	7.1	6.0	5.4	4.3	2.3
$CH^+ + C_2H_2 \rightarrow (C_3H_3^+)$	5.9	6.4	7.9	10.3	9.0	8.0	6.3	3.4

Table VII

Cross Section, σ, in Cm.^{2} × 10^{16} at Indicated Field Strength

Reaction		Field strength							
		100	60	40	20	10	8	6	2
$C_2H_2^+ + C_2H_2 \rightarrow C_4H_4^+ \rightarrow$ Products	$f\sigma$	11	15	21	41	77	87	90	68
$C_2^+ + C_2H_2 \rightarrow C_4H^+ + H$	$f\sigma$	18	22	29	45	68	85	84	55
$CH^+ + C_2H_2 \rightarrow C_3H_3^+ \rightarrow$ Products	$f\sigma$	14	19	28	50	58	55	49	34
Theoretical	σ	13	20	24	31	39	42	45	55

In Table VIII we list thermal reaction cross sections and rate constants calculated by our extrapolation method and rate constants calculated from the Eyring, Hirschfelder and Taylor[13] expression taking $\kappa = 1$.

Experimental

The experimental methods employed have been described

(13) H. Eyring, J. O. Hirschfelder and H. S. Taylor, *J. Chem. Phys.*, **4**, 479 (1936). See also Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., New York, N. Y., 1941, pp. 220 ff.

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TABLE VIII

CROSS-SECTIONS AND RATE CONSTANTS FOR THERMAL REACTIONS

Reaction	Extrapolated experimental $f\sigma$ (298°K.) cm.² × 10¹⁶	Extrapolated experimental $k_{298\,°K.}$ (cm.³/molecule-sec.) × 10⁹	Theoretical (ref. 13) k (cm.³/molecule-sec.) × 10⁹
$C_2H_2^+ + C_2H_2 \rightarrow (C_4H_4^+)$	251	2.1	1.3
$C_2^+ + C_2H_2 \rightarrow C_4H^+ + H$	256	2.1	1.3
$CH^+ + C_2H_2 \rightarrow (C_3H_3^+)$	282	2.5	1.6

previously.[1] In studying reaction rates a Consolidated Electrodynamics Corporation (CEC) Model 21-620 cycloidal focusing mass spectrometer was used. In calibrating the ion source for pressure, the ionization cross section of acetylene was determined as $5.6_0 \times 10^{-16}$ cm.² in reasonably good agreement with the value of 4.98×10^{-16} cm.,² reported by Massey and Burhop.[14] Appearance potentials were measured on a Westinghouse Type LV mass spectrometer. The acetylene used in these studies was commercial tank material obtained from Matheson Chemical Company and purified by repeated condensation at liquid nitrogen temperatures. The 1,3-butadiene was Phillips research grade having a stated purity of 99.51% and the 1-butyne was an API standard sample of 99.87% purity. Both were used without further purification. The vinylacetylene was obtained from the du Pont Company and was used without treatment since a mass spectrum indicated it to be of satisfactory purity.

Acknowledgment.—We wish to express our appreciation to Mr. B. L. Clark for his help in making the measurements and calculations.

(14) H. S. W. Massey and E. H. S. Burhop, "Electronic and Ionic Impact Phenomena," Oxford University Press, London, 1952, p. 265.

BAYTOWN, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF ROCHESTER]

Electronic and Vibrational States of the Nitrite Ion. I. Electronic States[1]

BY JEROME W. SIDMAN[2]

RECEIVED AUGUST 16, 1956

The lowest absorption transition of the nitrite ion has been studied in the crystalline state at 77°K. and at 4°K., using single crystals of $NaN^{14}O_2$ and $NaN^{15}O_2$ in polarized light. The corresponding fluorescence transition also has been studied. The spectra are sharp, and can be analyzed in considerable detail to yield vibrational and lattice frequencies for both the ground and excited electronic states. From the intensity dichroism and vibrational structure, it is concluded that the weak absorption transition of $NaN^{14}O_2$ with origin at 25977 cm.$^{-1}$ at 4°K. (25977 cm.$^{-1}$ for $NaN^{15}O_2$ at 4°K.) is allowed by symmetry and is polarized perpendicular to the plane of the NO_2^- ion ($^1B_2 \leftarrow {}^1A_1$). Comparisons with theory and with previous work are made wherever possible. The effect of environment on the electronic spectrum of NO_2^- is discussed. The NO_2^- spectra also are compared with the spectra of other 18-valence electron molecules, such as O_3, SO_2, HCO_2^-, ONCl, etc. The simplest LCAO–MO treatment appears to give a qualitatively correct description of the excited electronic states of NO_2^-.

Introduction

Within the last few years, considerable progress has been made toward understanding the electronic spectra of polyatomic molecules. Although much attention has been given to large aromatic hydrocarbons, a survey of the literature reveals that relatively few triatomic molecular electronic spectra have been completely analyzed. The vapor spectra of triatomic molecules are sometimes sharp enough to permit analysis of the rotational fine structure, from which the transition moment direction and the geometry change can be deduced. However, even in such cases, there may be so many closely spaced bands present in the spectrum that the vibrational analysis is made difficult. Furthermore, if the molecule is very different from a symmetric top, the rotational analysis becomes quite difficult. In the cases in which the bands are broadened by predissociation, less information can be obtained.

The study of crystal and mixed crystal spectra has provided exact information about symmetry properties and vibrational structure of the electronic transitions of large, complex molecules. In this paper and in the following one, the results of such a study are reported for the lowest singlet-singlet electronic transition of the NO_2^- molecule-ion. Although it has been known since 1934 that the spectra of crystalline $NaNO_2$ and KNO_2 are sharp at low temperatures,[3] a complete analysis has not yet been given. The recent polarization studies of Trawick and Eberhardt[4] have provided additional information, which, together with the vibrational analysis presented in this work, lead to conclusions about the nature of the ground and lowest excited electronic states of this molecule. These results should also be applicable to other related molecules which possess the same number of valence electrons and similar geometry, and comparisons and predictions will therefore be made where possible.

Experimental

Mallinckrodt Analytical Reagent Grade $NaNO_2$ was further purified by recrystallization from water. Single crystals of suitable thickness were prepared readily by crystallization from molten $NaNO_2$ between quartz disks. The experimental arrangement used to record the absorption and fluorescence spectra of single crystals at low temperature has been described in a previous publication.[5] In this work, a tungsten filament lamp was the source for the absorption experiments, and a medium-pressure Hg arc with a Corning 5860 filter was used to excite the fluorescence of $NaNO_2$. All spectra were recorded on Kodak

(1) This research was generously supported by the Office of Ordnance Research of the United States Army, under Contract DA-30-115 ORD-728 with the University of Rochester.

(2) Department of Theoretical Chemistry, Cambridge University, England. Post-doctoral fellow, 1955 to 1956, under a grant by the Shell Fellowship Committee to the Department of Chemistry of the University of Rochester.

(3) G. Rodloff, *Z. Physik*, **91**, 511 (1934).

(4) W. G. Trawick and W. H. Eberhardt, *J. Chem. Phys.*, **22**, 1462 (1954).

(5) J. W. Sidman, *ibid.*, **78**, 4217 (1956).

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103-0 or 103-a-F plates. Fe arc spectra were used to calibrate the wave lengths.

The $NaN^{15}O_2$ was prepared by reducing fused $NaN^{15}O_3$ with powdered Pb.[6,7]

Results

The polarized absorption and fluoresence spectra of crystalline $NaNO_2$ at 77°K. and at 4°K. are shown in Figs. 1 and 2. A summary of the results of the vibrational analyses, which are further discussed in section (B), is given in Table I.

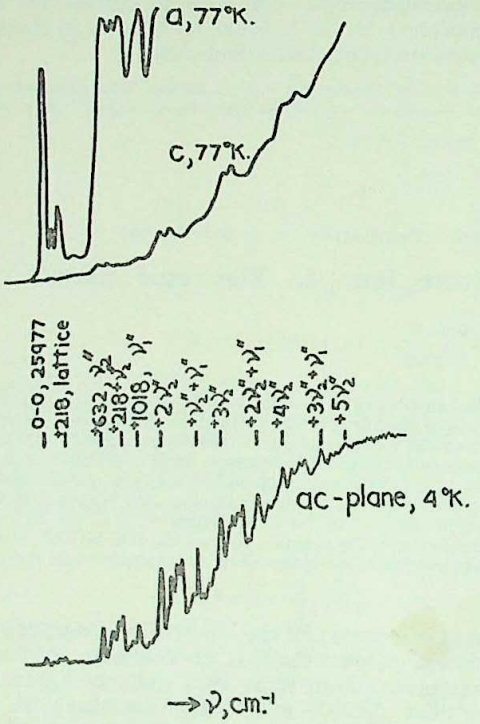

Fig. 1.—Microphotometer tracing of the absorption spectrum of $NaN^{14}O_2$, tungsten strip filament lamp source: top, polarized spectrum of single crystal, 77°K., *ac*-plane; bottom, *ac*-plane, 4°K.

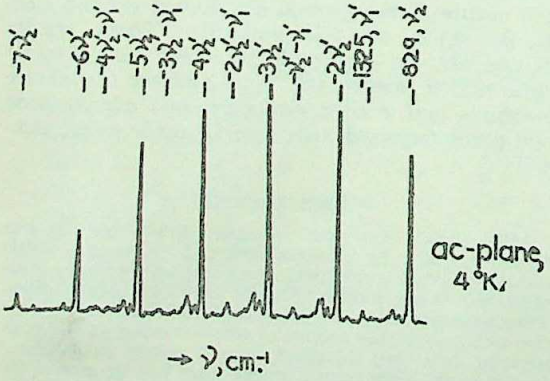

Fig. 2.—Microphotometer tracing of the fluorescence spectrum of $NaN^{14}O_2$, *ac*-plane, 4°K. Lines in the source obscure the 0-0 band.

(6) J. Turner, *J. Soc. Chem. Ind.*, **34**, 585 (1915).

(7) $HN^{15}O_3$ was obtained from the Isomet Corporation, 118 Union Street, Palisades Park, N. J. The isotopic concentration of N^{15} was 99.5%.

TABLE I

SUMMARY OF THE RESULTS OF THE VIBRATIONAL ANALYSES OF THE $^1B_2 \leftarrow {}^1A_1$ ABSORPTION AND FLUORESCENCE TRANSITIONS OF $NaN^{14}O_2$ AND $NaN^{15}O_2$ AT 77 AND AT 4°K.

Frequencies are in cm.$^{-1}$.

	$NaN^{14}O_2$	$NaN^{15}O_2$
0–0, $^1B_2 \leftarrow {}^1A_1$, 77°K.	25960 ± 8	25960 ± 8
0–0, $^1B_2 \leftarrow {}^1A_1$, 4°K.	25977 ± 3	25977 ± 3
Vibrational frequencies in $^1A_1$, 4°K.	$\nu_1 = 1325 \pm 4$ $\nu_2 = 829 \pm 2$	$\nu_1 = 1306 \pm 4$ $\nu_2 = 824 \pm 2$
Vibrational frequencies in $^1B_2$, 4°K.	$\nu_1 = 1018 \pm 4$ $\nu_2 = 632 \pm 4$	$\nu_1 = 1006 \pm 4$ $\nu_2 = 621 \pm 4$
Lattice frequencies in $^1A_1$, 4°K. (±15 cm.$^{-1}$)	45, 105, 165, 205, 270	45, 80(?), 105, 165, 205, 270
Lattice frequencies in $^1B_2$, 4°K. (±15 cm.$^{-1}$)	65, 110, 155, 180, 218	65, 110, 155, 180, 218

Discussion and Interpretation

(A) **Assignment of the Electronic Transitions.**—The determination of the symmetry properties of the combining states in an electronic transition of a polyatomic molecule is as important as the determination of the energy and transition probability. Until recently, the direct determination of this property has been quite difficult. It has often been difficult or impossible to determine correctly the electronic symmetry properties from polarized spectra of single crystals, due to intermolecular coupling between identical molecules in the crystal.[8,9] Such effects are absent in the polarized absorption spectra of dilute mixed crystals, and considerable data are now available for the electronic assignments of the aromatic hydrocarbons from mixed crystal studies.[10]

The crystals which have been studied previously are molecular crystals, in which the molecule and its nearest neighbors are identical. $NaNO_2$ is an ionic crystal, and the nearest neighbors of the NO_2^- ions are Na^+ ions, which shield the NO_2^- ions from each other. Consequently, effects due to intermolecular coupling, such as dichroic splitting of the 0–0 band and/or formation of trapped excitons,[9,11] should be much less prominent in $NaNO_2$, which may be regarded as a concentrated (50%) mixed crystal in which there is order with respect to the position and orientation of both the solute (NO_2^-) and solvent (Na^+).

Trawick and Eberhardt[4] have studied the polarization properties of the electronic transitions of single crystals of $NaNO_2$ at 77°K. They have found that the origin of the lowest absorption band at λ 3851.4 Å. is polarized perpendicular to the plane of the NO_2^- ion. The results of this investigation are in agreement with Trawick and Eberhardt's work. However, thicker crystals at wave lengths shorter than λ 3851.4 Å. show that there is weak but definite absorption for light polarized in the plane of the NO_2^- ion (Fig. 1). This will be discussed in further detail in section (C).

(8) D. S. McClure and O. Schnepp, *J. Chem. Phys.*, **23**, 1575 (1955).

(9) J. W. Sidman, *Phys. Rev.*, **102**, 96 (1956).

(10) J. W. Sidman and D. S. McClure, *J. Chem. Phys.*, **24**, 757 (1956); J. W. Sidman, *ibid.*, **25**, 115, 122 (1956).

(11) J. W. Sidman, THIS JOURNAL, **79**, 305 (1957).

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The polarization of the crystal absorption spectrum does not in itself lead to an unambiguous electronic assignment, since it is possible that the electronic transition might be forbidden by symmetry and that its appearance might be due to a vibrational or to a lattice perturbation, or both. However, an unambiguous determination often can be made if the same electronic transition appears in fluorescence. Excitation of crystalline $NaNO_2$ with the λ 3660 Å. Hg group produces a weak but detectable fluorescence spectrum, which nearly is the mirror image of the absorption spectrum.[12] Although lines from the Hg arc interfere in the region near λ 3851.4 Å., the vibrational analyses of the absorption and the fluorescence spectra leave no doubt that the lowest absorption band at λ 3851.4 Å. is the 0–0 band of an electronic transition which is allowed by symmetry and which is polarized perpendicular to the plane of the NO_2^- ion. Since the molecular point group, molecular site group in the crystal, and crystallographic space group are all C_{2v}, the polarization results of the crystal spectra should be directly applicable to the free ion.

The crystal structure of $NaNO_2$ has been extensively and carefully investigated.[13–15] A diagram of the crystal and molecular structure is shown in Fig. 3. The crystallographic axes are labeled according to Ziegler's notation.[13]

If a totally-symmetric electronic ground state is assumed, ($^1A_1$), the polarization results lead to the $^1B_1 \leftarrow {}^1A_1$ electronic assignment for the lowest absorption transition of NO_2^-.[16] The orbital assignment proposed by Trawick and Eberhardt is $n_N \rightarrow \pi_3$, which is in agreement with the fact that the transition is allowed by symmetry but is nevertheless weak ($\epsilon_{max} \cong 25$, $\lambda_{max} \cong 3550$ Å.[17]). The $n_O \rightarrow \pi^*$ transitions of carbonyl compounds are also weak, even though the transition may be formally allowed by symmetry, as in glyoxal[18] and biacetyl.[19] This is to be expected, since the n- and π-orbitals do not simultaneously possess large amplitude in the same regions of space, so that the integrand in the transition moment integral $\int (n)^* R (\pi) d\tau$ is everywhere small, and consequently leads to low intensity for $n \rightarrow \pi^*$ transitions. Furthermore, $n \rightarrow \pi^*$ transitions which are allowed by symmetry possess a transition moment which is necessarily perpendicular to the nodal plane of the π-orbitals, since the n-orbitals and the π-orbitals are, respectively, symmetric and antisymmetric with respect to reflection in the plane of the molecule. This has been verified experimentally in glyoxal from the analysis of the rotational structure.[18] Thus, the $^1B_2 \leftarrow {}^1A_1$, $n_N \rightarrow \pi_3$ assignment for the lowest transition of NO_2^- appears to be reasonable.

A qualitative orbital energy level diagram for

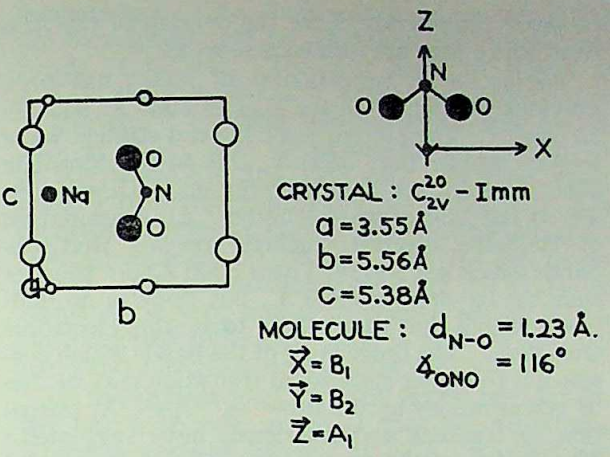

Fig. 3.—Crystal structure of $NaNO_2$ and molecular structure of NO_2^-. The clear circles are at $a = 0$, whereas the dark circles are displaced by $a/2$. The crystallographic axes are labelled according to Ziegler's notation.[13] The bond distance and bond angle of NO_2^- are from Carpenter's work.[14]

the n- and π-orbitals of the NO_2^- molecule is shown in Fig. 4, and orbital assignments of the three electronic transitions which are observed at wave lengths longer than 2000 Å. are also shown in the diagram.[17] It is assumed that the σ-bonding orbi-

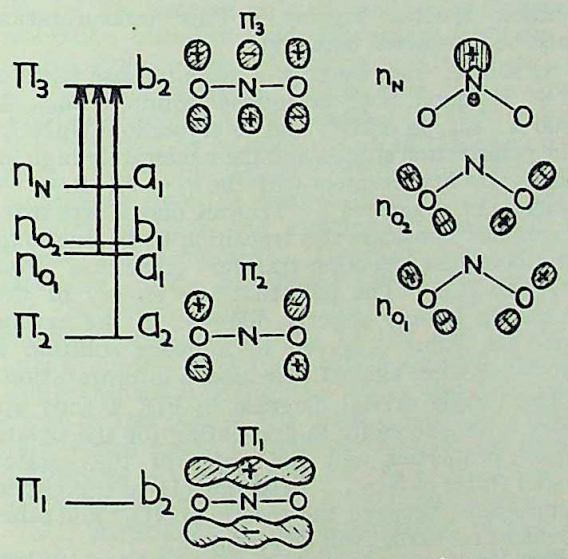

Fig. 4.—Schematic diagram of the one-electron n- and π-molecular orbitals of NO_2^-. The orbital transitions which may correspond to the observed electronic transitions of NO_2^- are shown in the diagram.

tals are lower than π_1, and the σ*-antibonding orbitals are higher than π_3. This is reasonable, since the hybridized AOs which form the σ-MOs overlap with each other more than the p-AOs which form the π-MOs, so that the energy difference between the σ- and σ*-MOs is greater than the energy difference between the π- and π*-MOs. The n-MOs are essentially AOs (which may be hybridized), since they are formed from orbitals which overlap very little with the σ-orbitals. Since O is more electronegative than N, the n_O orbitals are placed slightly below the n_N orbital.[4] The two n_O orbitals should

(12) J. W. Sidman, This Journal, **78**, 2911 (1956).
(13) G. E. Ziegler, *Phys. Rev.*, **38**, 1040 (1931).
(14) G. B. Carpenter, *Acta Cryst.*, **5**, 132 (1952).
(15) M. R. Truter, *ibid.*, **7**, 73 (1954).
(16) The group-theoretical notation is that of H. Eyring, J. Walter and G. E. Kimball, "Quantum Chemistry," John Wiley and Sons, New York, N. Y., 1943.
(17) H. L. Friedman, *J. Chem. Phys.*, **21**, 319 (1953).
(18) J. C. D. Brand, *Trans. Faraday Soc.*, **50**, 431 (1954).
(19) J. W. Sidman and D. S. McClure, This Journal, **77**, 6461, 6471 (1955).

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be nearly degenerate, since the overlap of the AOs from which they are formed is so small.

The $n_O \rightarrow \pi_3$ transition(s) of NO_2^- has been previously assigned[4] to the $\lambda_{max} \cong 3000$ Å., $\epsilon_{max} \cong 15$ band.[17] The present work has not studied wave lengths shorter than 3300 Å., due to the complete absorption by the double Pyrex glass Dewar vessels at the shorter wave lengths. An examination of Rodloff's spectral tracings[3] reveals that the bands which are observed near 3200 Å. are broader than the bands near 3800 Å., but there is no definite evidence that they belong to another electronic transition. The broadening of the bands which correspond to higher vibrational transition may be due to perturbations by the $n_O \rightarrow \pi_3$, $^1B_2 \leftarrow {}^1A_1$ transition, as Trawick and Eberhardt have suggested.[4] The absence of the $n_O \rightarrow \pi_3$ transition in the crystal spectrum is difficult to understand, but possibly it could be explained if the upper state were unstable. Absorption due to this transition would then be nearly continuous, and would not appear unless the crystal thickness were much greater than that which is necessary for detecting the very sharp $n_N \rightarrow \pi_3$ transition. The intensity due to a very diffuse transition at any individual wave length would thus be very much less than the intensity due to a sharp transition in the same region, even though the integrated intensities over the corresponding regions of absorption are similar, as the solution spectra suggest.[17] This interpretation must be considered tentative.

At shorter wave lengths, a more intense band of NO_2^- is found, both in aqueous solution ($\lambda_{max} \cong 2100$ Å., $\epsilon_{max} \cong 5500$[17]) and in crystalline $NaNO_2$[4]. The polarization studies and the moderately high intensity are in agreement with the $\pi_2 \rightarrow \pi_3$, $^1B_1 \leftarrow {}^1A_1$ assignment suggested by Trawick and Eberhardt.[4] Friedman[17] considers this transition to be due to an intermolecular electron-transfer transition from NO_2^- to H_2O. The fact that the energy of this transition is only slightly different in the crystal from the value observed in aqueous solution is strong evidence against Friedman's interpretation.

The simple orbital diagram in Fig. 4 thus appears to be successful in accounting for the polarization properties and the order of the excited singlet states of NO_2^-. In section (D) of this paper, comparisons between the spectra of NO_2^- and other isovalent molecules will be given.

(B) Analysis of the Vibrational and Lattice Structure.—In an electronic transition of a polyatomic molecule in the crystalline state, fine structure due to transitions involving simultaneous changes in the vibrational and lattice states usually appears in the spectrum. In order to resolve this structure, it is desirable to study the spectra at very low temperatures. If the vibrational fine structure can be analyzed, it is sometimes possible to determine how the arrangement of the nuclei and the bonding between them differs in the upper and lower electronic states. This leads to an understanding of valence and molecular structure which is deeper than that obtained either from the study of the vibrational spectrum of the ground electronic state alone or from the study of an electronic spectrum which is broad because of perturbations by the environment. The full power of the vibrational fine structure analysis in elucidating the molecular and electronic structure can be felt if the molecule is small and if isotopically substituted species are available. The recent availability[20] of isotopically pure N^{15} has enabled such a study to be performed for NO_2^-.

The lattice fine structure which appears in the electronic transitions of molecules in crystals and mixed crystals provides information about lattice oscillations, and should be valuable in understanding intermolecular forces in the solid state. So far, extensive interpretation of the lattice structure has not been made, although lattice frequencies in many molecular crystals and mixed crystals have been determined from the analysis of the electronic transitions.[10]

The analysis of the fine structure of the $n_N \rightarrow \pi_3$, $^1B_2 \leftarrow {}^1A_1$ absorption transition of NO_2^- in crystalline $NaN^{14}O_2$ and $NaN^{15}O_2$ at 4°K. is quite straightforward. At 77°K., the 0–0 band in both $NaN^{14}O_2$ and $NaN^{15}O_2$ is 25960 ± 8 cm.$^{-1}$, whereas at 4°K. the 0–0 band has shifted slightly to 25977 ± 3 cm.$^{-1}$ in both cases. It is possible that there is a calibration error in Rodloff's work,[3] since the work of Trawick and Eberhardt and of the present author are in agreement with respect to the 0–0 frequency at 77°K. The most prominent feature of the absorption transition in $NaN^{14}O_2$ is the progression of a single frequency of 632 ± 4 cm.$^{-1}$ (621 ± 4 cm.$^{-1}$ in $NaN^{15}O_2$) in which the intensity maximum is in the fourth band of the progression. This is seen most readily in the microphotometer tracings in Figs. 2 and 5 of ref. 3, in which the source is a hydrogen discharge tube, which provides a more uniform background than the tungsten filament lamp employed in this research. Besides the main progression, additions of a frequency of 1018 ± 4 cm.$^{-1}$ (1006 ± 4 cm.$^{-1}$ in $NaN^{15}O_2$) to each of the bands in the main progression are also seen in the spectrum. Rodloff has previously identified the main progression (A_1, B_1, C_1, D_1, etc., in Fig. 2, ref. 3), but he has not identified the 1018 cm.$^{-1}$ interval. It is clearly seen in his tracing, however (A_1, B_5; B_1, C_5; C_1, D_5; etc., in Fig. 2 of ref. 3). It is clear that this identification is correct, and that B_5 represents a vibrational addition to A_1 and not to B_1, since there is no band between A_1 and B_1 which corresponds to band B_5 between B_1 and C_1.

The analysis of the lattice structure in the absorption spectrum yields the values 65, 110, 155, 180 and 218 cm.$^{-1}$ for the lattice frequencies of $NaNO_2$ in $^1B_2$ at 4°K. Due to the greater diffuseness of the lattice additions, the lattice frequencies may be uncertain by ±15 cm.$^{-1}$. Within this limit of error, the lattice frequencies are indistinguishable in $NaN^{14}O_2$ and in $NaN^{15}O_2$.

The analysis of the fluorescence transition is also quite straightforward. The main progression in $NaN^{14}O_2$ is 829 ± 2 cm.$^{-1}$ (823 ± 2 cm.$^{-1}$ in $NaN^{15}O_2$). The 1325 ± 4 cm.$^{-1}$ frequency in $^1A_1$ of $NaN^{14}O_2$ corresponds to 1018 ± 4 cm.$^{-1}$ in $^1B_2$. Virtually all of the intensity in the fluorescence transition is contained in the bands of the 829

(20) W. Spindel and T. I. Taylor, *J. Chem. Phys.*, **24**, 626 (1956).

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cm.$^{-1}$ progression, in which the intensity maximum is in the fourth band. The bands corresponding to the 1325 cm.$^{-1}$ frequency and the lattice additions appear only very weakly in fluorescence. A correspondence between lattice frequencies in $^1A_1$ and $^1B_2$ is also found. The lattice frequencies (±15 cm.$^{-1}$) in $^1A_1$ of $NaN^{14}O_2$ and $NaN^{15}O_2$ at 4°K. are 45, 105, 165, 205 and 270 cm.$^{-1}$. In addition, a lattice frequency of 80 cm.$^{-1}$ possibly appears in $NaN^{15}O_2$. It is interesting to observe that the highest frequency lattice mode in $^1B_2$ and in $^1A_1$ is different by an amount which far exceeds the experimental error.

The absorption and fluorescence spectra, although very similar, do show some differences, so that they are not quite "mirror images" of each other. The lattice structure is much more prominent in absorption than in fluorescence, as can be seen from an examination of Figs. 1 and 2. It is interesting to note that the bands of the 632 cm.$^{-1}$ progression (in absorption) are accompanied by very pronounced lattice structure, but that the lattice structure is far less pronounced, or is even absent, in the 1018 cm.$^{-1}$ additions to the bands of the 632 cm.$^{-1}$ progression.

The detailed assignments of the vibrational states of $NaNO_2$ and the calculation of the force constants of NO_2^- are discussed in detail in the following paper.[21] A summary of the analyses of the absorption and fluorescence spectra is given in Table I. Anharmonic corrections in the ν_2 progression are negligible (<3 cm.$^{-1}$) for the first few members of the progression. In fluorescence, the anharmonic correction to $6\nu_2$ is approximately 20 cm.$^{-1}$.

(C) **The Effect of the Environment on the Electronic Transition.**—Since the lowest absorption transition of NO_2^- can be studied under a variety of conditions, it is possible to determine the relationship between the environment and the nature of the spectrum.

(1) **The Effect of Temperature.**—The increase in sharpness of the spectrum with decrease in temperature is seen in Fig. 1 of ref. 3. This is due to a decrease in the population of the excited lattice states. Even at 77°K., absorption due to molecules in the first excited state of the 110 cm.$^{-1}$ lattice mode can be detected in the spectrum. With the same crystal at 4°K., the bands corresponding to the "hot" lattice transition of the 110 cm.$^{-1}$ frequency are absent. The small shift of the bands when the temperature is decreased from 77 to 4°K. probably is due to further contraction of the lattice.

(2) **The Effect of Other Ions.**—The environment of the NO_2^- ion can be altered by changing the positive ion in the lattice or by dissolving it in the lattice of another crystal. In KNO_2, the bands at 77°K. are much broader than the bands in $NaNO_2$ at the same temperature. Even at 4°K., the KNO_2 bands are more diffuse than the $NaNO_2$ bands. The results found in this research for KNO_2 are in good agreement with the results of Rodloff,[3] who has given photographs and tracings of the KNO_2 absorption spectrum at low temperature. The fluorescence bands of KNO_2 are correspondingly broader than the fluorescence bands of $NaNO_2$. The 0–0 band in KNO_2 at 4°K. is 25412 ± 10 cm.$^{-1}$, which constitutes a shift of 565 cm.$^{-1}$ to lower frequencies relative to $NaNO_2$ at 4°K. The vibrational frequencies in $^1B_2$ of KNO_2 are 616 and 1015 cm.$^{-1}$, in good agreement with the frequencies in $^1B_2$ of $NaNO_2$. The lattice structure is partially resolved at 4°K., and a lattice frequency of 120 cm.$^{-1}$ (in $^1B_2$) can be detected. The vibrational envelope of the $^1B_2 \leftarrow {}^1A_1$ transition is very similar in $NaNO_2$ and in KNO_2, the principal difference being a shift of the 0–0 band and a decrease in sharpness in KNO_2.

In the environment of a still larger positive ion, the bands become so broad that the vibrational structure appears diffuse. At 77°K., it is not possible to resolve any vibrational structure in the $^1B_2 \leftarrow {}^1A_1$ transition in $CsNO_2$. Rodloff found no structure in the corresponding absorption transition of barium nitrite at 20°K.[3] In dilute mixed crystals of NO_2^- in KBr or in KCl,[22] the $^1B_2 \leftarrow {}^1A_1$ transition is shifted to lower frequencies (0–0 band = 25100 ± 100 cm.$^{-1}$ at 77°K.), and the bands are broader than in crystalline $NaNO_2$ at the same temperature.

The red shift and increase in diffuseness in the case of the larger positive ions can be understood on the basis of the MO description of the $n_N \rightarrow \pi_3$, $^1B_2 \leftarrow {}^1A_1$ transition. The $n_N \rightarrow \pi_3$ electronic transition transfers electronic charge from the nitrogen atom to the N–O bonds, and therefore leads to increased electronic charge near the O atoms. The dipole moment in the excited $^1B_2$ state is therefore expected to be higher than in the ground $^1A_1$ state. Since the larger positive ions are more polarizable than the smaller ones, they will preferentially stabilize the electronic state with the higher dipole moment. Therefore, the more polarizable positive ions should decrease the energy of the $^1B_2$ state relative to the $^1A_1$ state, as is observed. Greater coupling of the low frequency lattice vibrations of the positive ion with the electronic transition of the NO_2^- ion is also expected to occur in the case of the more polarizable positive ions, which might possibly account for the greater diffuseness of the bands of the $^1B_2 \leftarrow {}^1A_1$ transition in lattices containing K^+, Cs^+ and Ba^{++} ions.

(3) **Anomalies in the Polarization of the Absorption and Fluorescence Bands.**—An examination of Fig. 1 reveals that the vibrational and lattice structure of the $^1B_2 \leftarrow {}^1A_1$ transition shows a weak but definite intensity in the *c*-axis component of the crystal spectrum. A careful examination of the plate revealed that the 0–0 band appeared to be completely *a*-axis polarized, but that the lattice additions to the 0–0 band, which are weaker than the 0–0 band in the *a*-axis spectrum, did appear weakly in the *c*-axis spectrum. The lattice additions to the 0–0 band therefore lead to a partial depolarization of the absorption spectrum. Some of the intensity of the higher, more intense vibrational bands in the *c*-axis spectrum may be due to unavoidable errors involved in the optical

(21) J. W. Sidman, THIS JOURNAL, **79**, 2675 (1957).

(22) E. Hutchinson and P. Pringsheim, *J. Chem. Phys.*, **23**, 1113 (1955).

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arrangement. However, in the regoin near the 0–0 band, the *c*-axis component of the lattice structure cannot be due to experimental error. Since the *c*-axis corresponds to a direction in the plane of the NO_2^- molecule, the excitation of lattice quanta in the electronic transition must therefore be accompanied by oscillations of the NO_2^- molecule about the molecular symmetry axis. Hexter and Dows[23] have discussed the effect upon the dichroic ratios, in the vibrational spectra of molecular crystals, of libration of molecules about axes perpendicular to that of the transition moment of the molecular vibration. These results are in qualitative agreement with Hexter and Dows' explanation.

The fluorescence spectrum of single crystals of $NaNO_2$ also shows anomalous polarization. Both spectroscopic examination and direct visual observation indicate that the fluorescence spectrum at 77°K. is strongly depolarized relative to the absorption spectrum. (The 0–0 band itself could not be observed in fluorescence, due to the presence of source lines in the same region of the spectrum.) The *c*-axis fluorescence is approximately 50% as intense as the *a*-axis fluorescence. The degree of depolarization of the fluorescence spectrum is so much greater than the degree of depolarization of the absorption spectrum that it appears necessary to explain it in a different way. In previous studies of the polarized absorption and fluorescence spectra of crystals and mixed crystals, it has been found that the fluorescence spectrum at low temperatures may be partially or completely depolarized with respect to the corresponding absorption spectrum.[9,24] The detailed explanation of this puzzling phenomenon has not yet been proposed, and additional work appears necessary.

(D) Comparison with the Electronic Spectra of Other Molecules.—Mulliken[25] and, more recently, Walsh[26] have discussed the orbitals and spectra of AB_2-type molecules. The results of this work on NO_2^- are in agreement with Walsh's $^1B_2 \leftarrow {}^1A_1$ assignment[27] for the lowest electronic absorption transition of other isovalent molecules, such as SO_2. However, the higher excited singlet states do not appear to correspond in all cases. In section (A), reasons were given for assigning the second transition of NO_2^- as $n_O \rightarrow \pi_3$, $^1B_2 \leftarrow {}^1A_1$. In SO_2, there is strong evidence, based on the appearance of both a_1 and b_1 vibrations in the electronic transition, that the second transition is of the $\pi \rightarrow \pi^*$ (or $n \rightarrow \sigma^*$ or $\sigma \rightarrow \sigma^*$) type, and that the upper state is either $^1A_1$ or $^1B_1$.[23]

The qualitative orbital energy level diagram for NO_2^- which is shown in Fig. 4 gives a reasonable description of the NO_2^- spectrum, although it differs in several respects from the diagram given by Walsh.[26] It is likely that the relative orbital energies will vary from one molecule to another, and

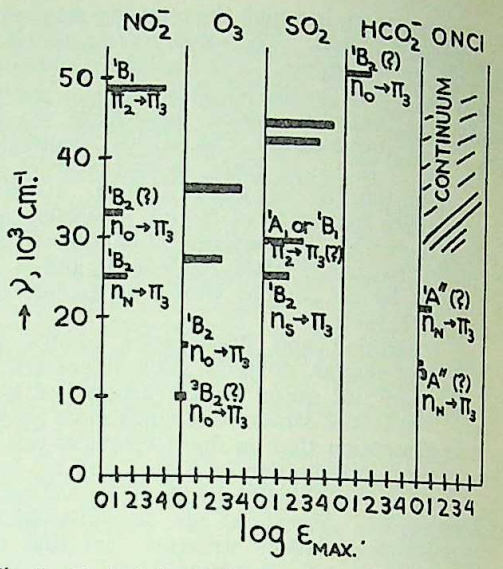

Fig. 5.—Excited electronic states of molecules which are isovalent with NO_2^-. References to the experimental data for O_3, SO_2 and ONCl are to be found in Walsh's paper.[26] The data for HCO_2^- are from Bielecki and Henri.[30] Some of the more certain assignments are shown, and others are given by Walsh.[26]

that appreciable differences may occur within this isovalent series. In the sequence HCO_2^-, NO_2^-, O_3, it is seen that the corresponding excited electronic states are lowered as the central atom becomes more electronegative. It is quite reasonable to expect that excited states derived from the $\pi_2 \rightarrow \pi_3$ configuration should decrease in energy when the central atom is more highly electronegative, since this will decrease the orbital energy of π_3 but will not affect the orbital energy of π_2. The $\pi_2 \rightarrow \pi_3$ transition has not been observed below 50000 cm.$^{-1}$ in HCO_2^-. In HCOOH[29] the strong absorption in the vicinity of 64500 cm.$^{-1}$ may be due to the $\pi \rightarrow \pi$ transition. The $\pi_2 \rightarrow \pi_3$ transition moves down to 49000 cm.$^{-1}$ in NO_2^- and moves down still further to either 27000 cm.$^{-1}$ or to 36000 cm.$^{-1}$, more probably the latter, in O_3. It is more difficult to predict the behavior of the $n \rightarrow \pi$ transitions, since the non-bonding orbital of the central atom and the antibonding π_3 orbital are both lowered in energy by an increase in the electronegativity of the central atom. However, the $n_O \rightarrow \pi_3$ transition involving the non-bonding orbitals of the end oxygen atoms should decrease in energy in the sequence HCO_2^-, NO_2^-, O_3. These simple considerations appear to be qualitatively capable of accounting for many of the spectral differences in Fig. 5. The molecules SO_2 and ONCl are included for completeness, but the bonding in these molecules is considerably different than in HCO_2^-, NO_2^- and O_3, inasmuch as S can employ 3d AOs whereas ONCl is asymmetric.

It should be emphasized that the simple one-electron LCAO-MO description of the electronic transitions is at best rather crude. In particular, it

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(25) R. S. Mulliken, *Rev. Mod. Phys.*, **14**, 204 (1942).
(26) A. D. Walsh, *J. Chem. Soc.*, 2266 (1953).
(27) Since Walsh and the present author have employed different labelling schemes for the axes in NO_2^-, it is necessary to interchange B_1 and B_2 when comparing results.
(28) N. Metropolis, *Phys. Rev.*, **60**, 295 (1941).
(29) W. C. Price and W. M. Evans, *Proc. Roy. Soc.* (*London*), **A162**, 110 (1937).
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June 5, 1957

is necessary to explicitly consider configurational interaction (CI) in treating the $n \rightarrow \pi$ transitions, since in NO_2^- both the $n_N \rightarrow \pi_3$ configuration and one of the $n_O \rightarrow \pi_3$ configurations belong to the B_2 representation of C_{2v}. The extent of CI will in general vary from molecule to molecule, and it is possible that this may be a prime consideration in determining the energies of the $n \rightarrow \pi$ transitions in these molecules.

Acknowledgments.—The continued interest of Professor A. B. F. Duncan is gratefully acknowledged. I am very grateful to Professor J. R. Platt for many helpful criticisms.

ROCHESTER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF ROCHESTER]

Electronic and Vibrational States of the Nitrite Ion. II. Vibrational States[1]

BY JEROME W. SIDMAN[2]

RECEIVED AUGUST 16, 1956

The infrared absorption spectra of $NaN^{14}O_2$ and $NaN^{15}O_2$ have been examined. The vibrational frequencies and assignments deduced from the infrared absorption spectrum agree with the results of the fluorescence and Raman spectra. The vibrational assignments for the lowest ($^1A_1$) state are, for $NaN^{14}O_2$, $\nu_1 = 1325$ cm.$^{-1}$, $\nu_2 = 829$ cm.$^{-1}$, $\nu_3 = 1270$ cm.$^{-1}$, and, for $NaN^{15}O_2$, $\nu_1 = 1306$ cm.$^{-1}$, $\nu_2 = 824$ cm.$^{-1}$, $\nu_3 = 1243$ cm.$^{-1}$. A complete force constant calculation has been performed for NO_2^-, with the results, $f_d = 8.1_0$, $f_{dd} = 2.3_5$, $f_{d\alpha}/d^2 = 2.5$, $f_{d\alpha}/d = 0.9$, in units of 10^5 dyne cm.$^{-1}$. The partial vibrational assignments in the first excited singlet electronic state ($^1B_2$) are, for $NaN^{14}O_2$, $\nu_1 = 1018$ cm.$^{-1}$, $\nu_2 = 632$ cm.$^{-1}$, and, for $NaN^{15}O_2$, $\nu_1 = 1006$ cm.$^{-1}$, $\nu_2 = 621$ cm.$^{-1}$. From a quantitative application of the Franck–Condon principle, the bond angle in the excited state is calculated to change by approximately 9° for the 0–0 transition. The bond distance in the excited state changes little, if at all. The geometry and bonding are discussed. The vibrational frequencies and force constants are compared with the values in related molecules, such as O_3, HCO_2^- and SO_2. Some of the similarities and differences can be explained in terms of valence theory. However, the large value of f_{dd} in O_3 and in NO_2^-, but not in SO_2 or, presumably, in HCO_2^-, cannot be explained completely at the present time.

Introduction

The vibrational spectra of triatomic molecules have received considerable study during recent years. Although it might at first sight appear to be simple to identify and to assign the three fundamental vibrational frequencies of a triatomic molecule, a few molecules, of which O_3 is possibly the best known example, have tenaciously resisted analysis until very recently. A survey of the literature reveals that NO_2^-, which is iso-electronic with O_3 and geometrically very similar to it, is another triatomic molecule for which the vibrational assignment is uncertain.

In the previous paper,[3] the analysis of the vibrational fine structure of the $^1B_2$—$^1A_1$ electronic transition has been given for the absorption and fluorescence spectra of crystalline $NaN^{14}O_2$ and $NaN^{15}O_2$ at 4°K. In this paper, the infrared spectra, vibrational assignments and force constants of NO_2^- will be discussed.

Experimental

The preparation of $NaN^{15}O_2$ has been described in the previous paper.[3] Infrared absorption spectra were recorded on a Perkin–Elmer Double Beam Recording Spectrophotometer, Model 21, using a NaCl prism. Atmospheric H_2O and CO_2 absorption bands were used to calibrate the wave lengths.

The most convenient method for studying the infrared spectra was the KBr-pressed pellet. The $NaNO_2$ was ground in an agate mortar with Harshaw Chemical Company's Spectroscopic Grade KBr. Pressed pellets of 1 mm. thickness which contained 0.3% $NaNO_2$ were suitable. Comparison of the spectrum of the pressed pellet with the spectrum of the dilute mixed crystal of NO_2^- in KBr showed numerous differences between the spectra, indicating that the pressed pellet spectrum is due to $NaNO_2$ dispersed in KBr, and not to a solid solution of NO_2^- in KBr.[4] Furthermore, the infrared spectra of pressed KBr pellets of other nitrite salts showed differences between themselves, which is additional evidence that the spectra are not due to a solid solution of the nitrite salt in KBr, but are due to physically dispersed microcrystals.

A single recrystallization from H_2O yielded a sample of $NaNO_2$ which showed no trace of the intense NO_3^- band at 1300 cm.$^{-1}$.

Results

The infrared spectra of $NaN^{14}O_2$ and $NaN^{15}O_2$ are shown in Fig. 1. The assignments of the bands are given in Table I.

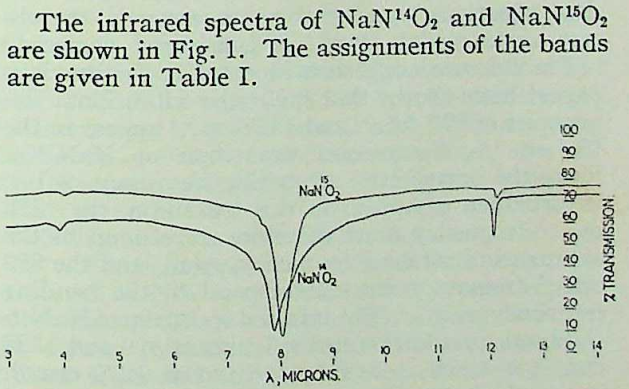

Fig. 1.—Infrared absorption spectra of $NaN^{14}O_2$ and $NaN^{15}O_2$ in KBr pressed pellets. The pure KBr pellet was used as a blank, and absorption due to traces of adsorbed H_2O have been subtracted out of the spectrum. Perkin–Elmer Model 21 Recording Infra-Red Spectrophotometer, NaCl prism, linear wave length scale. The spectra were calibrated against atmospheric H_2O and CO_2 absorption bands.

(1) This research was generously sponsored by the U. S. Army, Office of Ordnance Research, under Contract DA-30-115 ORD-728 with the University of Rochester.

(2) Department of Theoretical Chemistry, Cambridge University, England. Post-doctoral fellow, 1955–1956, under a grant by the Shell Fellowship Committee to the Department of Chemistry of the University of Rochester.

(3) J. W. Sidman, THIS JOURNAL, 79, 2669 (1957).

(4) I am grateful to Dr. P. Yuster of the Argonne National Laboratory for a gift of the mixed crystals of NO_2^- with KBr. Since the infrared spectrum of the mixed crystal is currently under investigation in the Argonne laboratory, further data will not be reported here.

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TABLE I

ASSIGNMENT OF THE VIBRATIONAL STATES OF NO_2^- [a]

Raman spectrum, $NaN^{14}O_2$ in H_2O [b]				Infrared spectrum, single crystal of $NaN^{14}O_2$ [c]				Infrared spectrum, $NaN^{14}O_2$ and $NaN^{15}O_2$ dispersed in KBr pellet (this work)			
ν, cm.$^{-1}$	Rel. int.	ρ	Assnt.	ν, cm.$^{-1}$	Pol.	Rel. int.	Assnt.[c]	ν, cm.$^{-1}$ $NaN^{14}O_2$	ν, cm.$^{-1}$ $NaN^{15}O_2$	Rel. int.	Assnt.
813	1.0	0.21	ν_2	831	b	s	ν_2	829	824	m	$\nu_2(a_1)$
1240	2.4	.84	ν_3	970	c	w		1270	1243	vs	$\nu_3(b_1)$
1331	12.9	.43	ν_1	1130	a, b	w	(NO_2^-) + (lattice)	1325	1306	m	$\nu_1(a_1)$
				1170–1300	c	ms	(NO_2^-) + (lattice)	2550	2485	w	$2\nu_2$
				1230	a, b	ms					
				1325	b	s	ν_1				
				1360	c	vs	ν_3				
				2120	c	w	$(\nu_2 + \nu_3)$?				
				2670	c	s	$\nu_1 + \nu_2$				

[a] It is suggested that the assignments based on the infrared spectrum of the single crystal are incorrect.

Discussion and Interpretation

(A) Assignment of the Vibrational Frequencies.—The previous data on the vibrational spectrum of NO_2^- are given in Table I, together with results which have been obtained in this work. Literature sources which report more bands than can be attributed to NO_2^- are not included in Table I. A unique vibrational assignment can be proposed from the very careful Raman data due to Langseth and Walles,[5] who have studied the Raman spectra of aqueous $NaN^{14}O_2$. The depolarization ratios of the Raman bands lead to the unexpected conclusion that ν_3, the asymmetric stretching frequency, which is broad and depolarized in the Raman spectrum, is lower than ν_1, the symmetric stretching frequency, which is sharp and polarized in the Raman spectrum. This led Langseth and Walles to propose a structure in which the bond angle was assumed to be nearly 90° and in which a formal bond between the O atoms was assumed. However, such a structure did not agree with the X-ray crystallographic results which were available at that time.[6] Although the more recent structure determinations have led to some revisions, the obtuse-angle model (116°) is considered correct.[7,8]

The fluorescence results reported in the previous paper[3] have shown that molecular vibrational frequencies of 829 cm.$^{-1}$ and 1325 cm.$^{-1}$ appear in the $^1B_2 \rightarrow {}^1A_1$ fluorescence transition of $NaN^{14}O_2$. Since the asymmetric stretching frequency, $\nu_3(b_1)$, is forbidden to appear in this transition, the 1325 cm.$^{-1}$ frequency must therefore correspond to the symmetric stretching frequency, $\nu_1(a_1)$, and the 829 cm.$^{-1}$ frequency must correspond to the bending frequency, $\nu_2(a_1)$. The infrared spectrum of $NaN^{14}O_2$ shows, in addition to the bands at 829 and 1325 cm.$^{-1}$, a much more intense band at 1270 cm.$^{-1}$, upon which the 1325 cm.$^{-1}$ band is superimposed (Fig. 1). The fluorescence, infrared and Raman data are in good agreement, and lead to the assignments shown in Table I. The intensity of ν_3 in infrared absorption is greater than that of ν_1, as is usually the case in triatomic molecules.

The numerical value of ν_3 given in this work does not agree with the work of Newman,[9] who has studied the polarized infrared spectrum of single crystals of $NaN^{14}O_2$ at 77°K. For radiation polarized along the *c*-axis in the *ac*-plane, Newman's spectra show total absorption from 1100 to 1400 cm.$^{-1}$, due to the insurmountable difficulties in preparing thin single crystals. Newman has chosen the high frequency peak at 1360 cm.$^{-1}$ as ν_3, but the low frequency peak at 1170 cm.$^{-1}$ has not been satisfactorily assigned. The *center* of the broad band is in the vicinity of 1270 cm.$^{-1}$, which agrees with the single peak observed in this work. The assignment ν_3 = 1270 cm.$^{-1}$ compares more favorably with the Raman spectrum of an aqueous solution of $NaNO_2$ (ν_3 = 1240 cm.$^{-1}$)[5] than does Newman's assignment ν_3 = 1360 cm.$^{-1}$

The polarized infrared crystal spectrum[9] shows incomplete dichroism for the 831 cm.$^{-1}$ band, even when parallel light is used. The appearance of the 831 cm.$^{-1}$ band in the *a*- and *c*-axis spectra may be induced by librations of the NO_2^- ion in the crystal,[10] since otherwise only the *b*-axis spectrum would be expected to show this band.

The assignments of the a_1 vibrational frequencies in the $^1B_2$ electronic state can be made readily, using the results of the previous paper.[3] The assignments are ν_1 = 1018 cm.$^{-1}$, ν_2 = 632 cm.$^{-1}$, for $NaN^{14}O_2$, and ν_1 = 1006 cm.$^{-1}$, ν_2 = 621 cm.$^{-1}$, for $NaN^{15}O_2$.

(B) Calculation of the Force Constants and Normal Coördinates of NO_2^- in the $^1A_1$ (Ground) Electronic State.—The observation that $\nu_3 < \nu_1$ indicates that the interaction constants are not negligible in NO_2^-. Earlier attempts to account for the vibrational potential energy on the basis of the simple valence or central force fields were not successful.[11] Using the observed frequencies for both $N^{14}O_2^-$ and $N^{15}O_2^-$ in $^1A_1$, it is possible to calculate the force constants for the most general potential function. The procedure for doing this has been described in detail by Polo and Wilson in connection with their calculations for SO_2.[12] The vibrational assignments in cm.$^{-1}$ for $N^{14}O_2^-$ are (without anharmonic corrections) ν_1 = 1325 ± 4, ν_2 = 829 ± 2, ν_3 = 1270 ± 4, and the geometrical data are α = 116 ± 3°, d = 1.23 ± 0.03 Å. Using these data, various sets of force constants which reproduce the frequencies of $N^{14}O_2^-$ can be calculated. The best set of force constants is determined by requiring

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that the force constants reproduce the observed frequencies for $N^{15}O_2^-$: $\nu_1 = 1306 \pm 4$, $\nu_2 = 824 \pm 2$, $\nu_3 = 1243 \pm 4$. The experimental frequencies are in satisfactory agreement with the Teller–Redlich product rule. The best set of force constants, in units of 10^5 dyne/cm., is $f_d = 8.1_0$, $f_{dd} = 2.3_5$, $f_\alpha/d^2 = 2.5$, $f_{d\alpha}/d = 0.9$.

The normal coördinates readily can be determined, and will be important in connection with the calculations described in the next section. The internal coördinates of the A_1 class which have been used in this calculation are S_1, the symmetric stretching of the two N–O bonds, and S_2, the deformation of the O–N–O angle. The normal coördinates Q_1 and Q_2, which are associated, respectively, with the vibrations ν_1 and ν_2, are related to the symmetry coördinates S_1 and S_2 through the transformation $S_t = L_{kt}Q_k$. The results are $S_1 = 0.3_1Q_1 + 0.0_4Q_2$, $S_2 = -0.2_8Q_1 + 0.3_7Q_2$. The relative contribution of each symmetry coördinate S_t to a given normal coördinate Q_k is given by the ratio of the coefficients in the t column of the matrix whose elements are L_{kt}, inasmuch as $(\partial S_t/\partial Q_k)_{Q_{k'}} = L_{kt}$, where all other normal coördinates $Q_k'(k' \neq k)$ are held constant in the partial differentiation. It is thus seen that the normal coördinate Q_1 contains nearly equal amounts of the symmetric stretching of the N–O bonds (S_1) and the angle deformation (S_2). In Q_1, the stretching of the N–O bonds is accompanied by a decrease in the O–N–O angle. The normal coördinate Q_2 contains very little S_1, and may be described adequately as a deformation of the O–N–O angle (S_2).

(C) The Geometry and Bonding of NO_2^- in the $^1B_2$ (Excited) Electronic State.—Craig[13] has shown that it is possible to calculate the dimensions of the excited state of a polyatomic molecule if the intensity distribution in the vibrational structure of the electronic transition is known. The intensity distribution is very sensitive to the change of the molecular dimensions when the molecule undergoes an electronic transition, but it is much less sensitive to changes in the force constants.

In the case of NO_2^-, long progressions of ν_2 appear both in absorption and in fluorescence in the $^1B_2$–$^1A_1$ transition. The intensity maximum is in the 0-3 (and 3-0) band in the ν_2 progression. The ν_1 frequency does not form long progressions, and only a single quantum of it can be detected. In the $^1A_1$ state, the normal coördinate analysis described in the previous section indicates that the normal coördinate Q_2 is composed almost entirely of bending (S_2). Assuming[13] that k_α/ν_2 is approximately the same in $^1B_2$ and in $^1A_1$, the quantitative application of the Franck–Condon principle leads to the result that the bond angle has changed by about $9 \pm 4°$ in the $^1B_2$–$^1A_1$ transition. Lacking rotational structure, it is not possible to directly determine the sign of the change. Excitation of an electron from the n_N orbital to the π_3 orbital leads to an increase of electronic charge in the vicinity of the O atoms. This should cause an increase in the bond angle, due to increased electronic repulsion between the O atoms. If a 9° increase in the bond angle is accepted, then the results of this work tend to confirm many of Walsh's predictions for the lowest electronic transition in this class of molecules.[14] The appearance of ν_1 in the electronic–vibrational transition is attributed to the fact that Q_1 contains an appreciable fraction of S_2. It is thus reasonable to conclude that the principal geometry change in $^1B_2$ is a small increase of the bond angle, and that the bond distance changes slightly, if at all.

(D) The Bonding in the A_1 (Ground) Electronic State of NO_2^-; Comparison with Other Molecules.—The interpretation of the vibrational frequencies and force constants can provide useful information about the nature of the bonding in a molecule.[15] Such data are especially valuable if comparisons can be made with other molecules. Fortunately, accurate vibrational assignments have been proposed for O_3,[16,17] SO_2[12,18] and HCO_2^-.[19] Since these molecules are isovalent with respect to NO_2^-, a comparison can be of value. The pertinent data are shown in Table II.

TABLE II

VIBRATIONAL FREQUENCIES AND FORCE CONSTANTS OF MOLECULES RELATED TO NO_2^-

	$N^{14}O_2^-$	O_3	SO_2	HCO_2^-
d, Å.	1.23	1.276	1.432	d_{C-O} = 1.27
α, °	116	117	119.5	α(OCO) = 124°
ν_1, cm.$^{-1}$	1325	1110	1122	symm. C–O stretch = 1377
ν_2, cm.$^{-1}$	829	705	507	O–C–O bend = 784
ν_3, cm.$^{-1}$	1270	1043	1341	asymm. C–O stretch = 1584
$fd \times 10^5$, dyne/cm.	8.10	5.70	10.02	.....
$fdd \times 10^5$, dyne/cm.	2.35	1.52	0.03	.....
$f\alpha/d^2 \times 10^5$, dyne/cm.	2.5	1.28	0.793	.....
$fd\alpha/d \times 10^5$, dyne/cm.	0.9	0.332	0.20	.....

The molecules which are most similar are O_3 and NO_2^-. It is possible to relate the differences in their force constants to their molecular structure. The stretching and bending force constants are appreciably higher in NO_2^- than in O_3. This is related to the fact that the bond distance is shorter in NO_2^- (1.23 Å.) than in O_3 (1.276 Å.). The difference in electronegativity between O and N would give the bonds in NO_2^- higher ionic character, shorter bond distance, and higher stretching and bending force constants than the bonds in O_3, due to the possibility of increased ionic-covalent resonance in NO_2^-. The higher positive values of the interaction constants in NO_2^- are attributed to greater repulsion between the end oxygen atoms,[20] due both to the shorter distance between them and to the greater electronic charge on them relative to the end oxygen atoms in O_3.

Although the bond angle is very similar in all four molecules, it is seen that O_3 and NO_2^- differ

(12) D. P. Craig, *J. Chem. Soc.*, 2146 (1950).

(14) A. D. Walsh, *ibid.*, 2266 (1953).

(15) See, for example, G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., New York, N. Y., 1945.

(16) R. M. Badger and M. K. Wilson, *J. Chem. Phys.*, **18**, 998 (1950).

(17) L. Pierce, *ibid.*, **24**, 139 (1956).

(18) D. Kivelson, *ibid.*, **22**, 904 (1954).

(19) R. Newman, *ibid.*, **20**, 1663 (1952).

(20) C. A. Coulson, J. Duchesne and C. Manneback, *Nature*, **160**, 793 (1947). See also "Vol. Comm. Victor Henri, Contribution à l'Etude de la Structure Moleculaire," Desoer, Liege, 1948, p. 33.

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markedly from SO_2 and from HCO_2^- in one important respect. The asymmetric stretching frequency (ν_3) in O_3 and in NO_2^- is lower than the symmetric stretching frequency (ν_1), whereas in SO_2 and in HCO_2^- the reverse is true. As Bernstein and Powling have shown,[21] the ratio $(\nu_1/\nu_3)^2$ depends approximately on the relative magnitudes of the stretching force constant and the bond–bond interaction constant, and also on a term which involves the atomic masses and the bond angle. In the molecules NO_2^-, O_3, SO_2 and HCO_2^-, the latter term which involves the molecular geometry is less than unity. The geometrical term becomes close to unity only when the bond angle is nearly 90°. For obtuse angle AB_2 molecules in which the bond–bond interaction constant is negligible in comparison with the stretching force constant, the value of ν_1 is then lower than the value of ν_3. This is the usual case in most AB_2 molecules.[22] Although the data are not sufficiently complete to permit a force constant calculation for HCO_2^-, it is reasonable to expect that the bond–bond interaction constant for the C–O bonds will not be as large relative to the C–O stretching force constant as the corresponding interaction constant in NO_2^- and in O_3. The cases in which $\nu_3 < \nu_1$ are relatively few in number. Thus far, NO_2^-, O_3 and OF_2[21] appear to be definitely established cases of this sort. In NO_2^- and in O_3, the complete force constant analyses have indeed verified that the bond–bond interaction constant is large and positive, and presumably the same would be true for OF_2.

The origin of the interaction terms in the vibrational potential function has been discussed by Coulson, Duchesne and Manneback.[20] According to these authors, the resonance effect is expected to lead to a positive value of the bond–bond interaction constant in AB_2 molecules. However, it appears to be necessary to consider other features of the electronic structure in order to explain why NO_2^- and O_3 should behave differently from HCO_2^- and SO_2. One feature in which NO_2^- and O_3 differ from HCO_2^- is in the nature of the orbitals on the central atom. Whereas the central atom in NO_2^- and in O_3 possesses a non-bonding orbital, the carbon atom in HCO_2^- does not have such a non-bonding orbital. In addition, the C–H bending mode (b_1) could influence the frequency of the asymmetric C–O stretching mode (b_1). In SO_2, Moffitt[23] has shown that the sulfur atom employs the 3d atomic orbitals in building the molecular orbitals, so that the sulfur atom can form a full double bond with each oxygen atom. The observed force constants (Table II) are in agreement with this. A full double bond between the central atom and both end atoms cannot occur in O_3 or in NO_2^-, since the oxygen and nitrogen atoms can employ only the 2s and the three 2p AOs in building the MOs. The bonding in SO_2 may therefore be quite different from the other molecules in which the central atom is C, O or N. It is possible that the electrons in the non-bonding orbital on the central atom in O_3 and in NO_2^- may actually make some contribution to the bonding. SCF–MO calculations would be needed to test this hypothesis. In OF_2, an additional important effect contributing to f_{dd} may be the repulsion of the non-bonding electrons on the F atoms. Electrostatic repulsions between non-bonded atoms should lead to a positive contribution to f_{dd}.[20]

In conclusion, it does not appear possible at the present time to explain the wide variation of f_{dd} in NO_2^- and O_3 relative to SO_2 and, presumably, HCO_2^-. Other similarities and differences can be reasonably well accounted for in terms of valence theory. As additional complete force constant data for simple molecules become available, through the use of isotopes of C, N and O and through analysis of the centrifugal distortion coefficients from microwave spectroscopy, it is hoped that a clearer account of the details of the bonding in simple molecules and the relation of the force constants and interaction constants to the molecular structure will eventually emerge.

Acknowledgments.—The continued interest of Professor A. B. F. Duncan is gratefully acknowledged. I am grateful to Dr. I. M. Mills for several clarifying discussions.

(21) H. J. Bernstein and J. Powling, *J. Chem. Phys.*, **18**, 685 (1950).
(22) W. G. Penney and G. B. B. M. Sutherland, *Proc. Roy. Soc. (London)*, **A156**, 654 (1936).
(23) W. Moffitt, *ibid*, **A200**, 409 (1950).

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June 5, 1957

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE CATHOLIC UNIVERSITY OF AMERICA]

The Dimethylamino Radical[1]

BY FRANCIS OWEN RICE AND CHESTER J. GRELECKI

RECEIVED DECEMBER 26, 1956

A paramagnetic violet solid is obtained by passing dilute vapors of tetramethyltetrazene ($(CH_3)_2N—N=N—N(CH_3)_2$) over a tungsten filament heated to about 1300° and then quickly condensing the products onto a liquid nitrogen-cooled surface. This material changes suddenly and irreversibly to a white solid when warmed to about −160°. The resulting mixture contains substantial quantities of tetramethylhydrazine which presumably results from the condensation of two dimethylamino radicals, $2\,(CH_3)_2N\cdot \longrightarrow (CH_3)_2N—N(CH_3)_2$. These results strongly suggest that the violet material is the dimethylamino radical. The violet material also was prepared by irradiating the vapors of tetramethyltetrazene with intense ultraviolet light and quickly freezing the products with liquid nitrogen.

Audrieth and Ogg[2] have reviewed the chemistry of hydrazine and point out that tetra-substituted tetrazenes exhibit thermal instability and when heated yield nitrogen gas and tetra-substituted hydrazines. For example, azyl radicals have been postulated[3] as the intermediate which condenses to form the substituted hydrazine as

$$R_2N—N=N—NR_2 \longrightarrow 2R_2N\cdot + N_2$$

$$2R_2N\cdot \longrightarrow R_2N—NR_2$$

Our experiments were designed to stabilize the intermediates formed during the vapor phase decomposition of tetramethyltetrazene by quickly freezing the products of the reaction with liquid nitrogen. Under the proper conditions we found that it was possible to stabilize a very reactive violet material which appeared to be stable indefinitely at −196° but which changed suddenly to a white solid when allowed to warm up to about −160°.

Experimental

In preparing tetramethyltetrazene the method of Renouf[4] was modified slightly. An ethereal solution of unsymmetrical dimethylhydrazine was oxidized with silver oxide. The powdered silver oxide was added at a rate such that the solution refluxed gently. After the required amount of oxidizing agent had been added, the mixture was cooled and the crude product was obtained by filtering the solution, drying it over anhydrous potassium carbonate and then removing the ether under reduced pressure. The product was distilled *in vacuo* and the fraction boiling at 25° at 12 mm. was collected.

The Thermal Reaction.—Tetramethyltetrazene vapors at low pressure (~0.1 mm.) were passed over a tungsten filament heated to between 1200 and 1300° as determined by an optical pyrometer. The rate of flow was about 10^{-4} moles per minute and after a few minutes, a violet deposit collected on a liquid nitrogen-cooled finger which was about 3 cm. from the hot filament. If the finger was brought closer to the wire, adverse radiation effects were encountered and no violet material was obtained. Preliminary experiments had shown that the violet material is not formed when tetramethyltetrazene is passed through a quartz furnace in the usual way. Indeed, even with a tungsten filament, the geometry of the apparatus is important in obtaining the violet deposit.

The permanent gases formed during this phase of the reaction were removed from the system by means of a high speed diffusion pump and were collected in a gas buret. A sample of these gases was analyzed on the mass spectrometer and the following results were obtained: % N_2, 70.5, 71.5; % H_2, 24.8, 23.6; % CH_4, 4.5, 4.7. In a typical experiment 1.16×10^{-3} moles of tetramethyltetrazene produced 0.74×10^{-3} moles of permanent gas. Thus each mole of tetramethyltetrazene used produced 0.45 mole of N_2. If one makes the reasonable assumption that the nitrogen is produced mainly by the reaction $(CH_3)_2N—N=N—N(CH_3)_2 \rightarrow 2(CH_3)_2N\cdot + N_2$, then under the conditions of this experiment about half of the tetramethyltetrazene escapes decomposition.

The deposit which collected on the filter was a violet, paramagnetic solid and its appearance did not change after standing for several hours at −196°. The liquid nitrogen was removed from the finger and liquid propane at −190° was added and allowed to warm up slowly. When the temperature reached −160° the violet color disappeared quite suddenly and a white deposit resulted. No permanent gas was evolved during this transition.

The deposit was then warmed to −78° and by means of a mass spectrometric analysis, it was found that traces of all three methylamines vaporized at this temperature. When the deposit was finally warmed to room temperature all of the material was in the vapor phase and a representative sample of the vapors was analyzed on the mass spectrometer. The mass spectrum of the products contained a peak at $m/e = 88$ which is characteristic of tetramethylhydrazine. The products also contained a substantial amount of undecomposed tetramethyltetrazene, and the ratio of the peak at $m/e = 116$, which is characteristic of the tetramethyltetrazene, to the peak at $m/e = 88$ was 1.14. The exact concentrations of these two substances cannot be obtained simply by a comparison of these peaks, since the ratio of the ion concentrations need not be the same as the ratio of the concentrations of the two materials present. It can, however, be concluded that both tetramethyltetrazene and tetramethylhydrazine were present in comparable concentrations.

The Photolytic Reaction.—The vapors of tetramethyltetrazene were passed through a quartz tube which was irradiated with a low pressure mercury lamp. The mercury lamp consisted of a quartz tube 12 mm. in diameter and six feet long (the tube was coiled spherically in six coils and was placed concentrically about the reaction chamber which also consisted of a quartz tube 12 mm. in diameter). The two electrodes consisted of tungsten to quartz seals and were sealed to the ends of the spiral. The lamp contained a few drops of mercury and a few mm. of an inert starter gas. The cold finger was located at the exit end of the reaction tube about 2.5 cm. from the last coil of the lamp.

The flow characteristics of the system were the same as in the experiments where the hot tungsten filament was employed, but in the photolytic case a much larger amount of material had to be used before a good colored deposit was obtained. This was because, in the photolytic reaction, only 2–3% of the tetramethyltetrazene, as determined by the amount of nitrogen formed during the reaction, was decomposed.

The deposit appeared to be identical with the product formed during the thermal decomposition on the tungsten filament. The transition to a white solid took place at −160° when the violet deposit was warmed slowly. In a blank experiment where all conditions were the same except that the lamp was not on, the deposit which collected was

(1) This work was supported in part by Atomic Energy Commission contract No. AT-(40-1)-1305.

(2) L. F. Audrieth and R. A. Ogg, "The Chemistry of Hydrazine," John Wiley and Sons, New York, N. Y., 1951.

(3) Wieland and Fressel, *Ann.*, **392**, 133 (1912).

(4) E. Renouf, *Ber.*, **13**, 2173 (1880).

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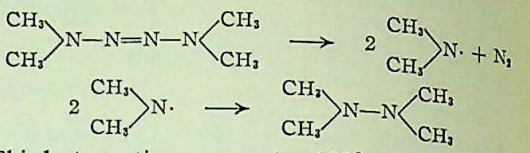
white and no transition could be observed when it was warmed to −160°.

The mass spectrum of the residue at room temperature indicated that a small but definite amount of tetramethylhydrazine was present in the products. The only other material which could be identified definitely was the undecomposed tetramethyltetrazene.

Discussion

The main products of the reaction were found to be nitrogen and tetramethylhydrazine and so it seems reasonable to assume that the following mechanism accounts for the main part of the reaction.



This last reaction occurs at −160° when the transition from violet to white is observed.

WASHINGTON, D. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Rate Constants for the Recombination of Iodine Atoms in Liquid Hexane and Decane; Temperature Coefficient for the Recombination in Carbon Tetrachloride

BY SUKUMAR ADITYA[1] AND JOHN E. WILLARD

RECEIVED JANUARY 7, 1957

The rate constants for the combination of iodine atoms in CCl_4, n-C_6H_{12} and n-$C_{10}H_{22}$ at room temperature and in CCl_4 at 50° have been determined using flash photolysis techniques. The value of the constant is not greatly influenced by the chain length of the hydrocarbon solvent. The activation energy of the reaction in CCl_4 is about 3 kcal./mole.

By the methods of flash photolysis it is possible to measure directly the rates of atom recombination reactions. This has been done for iodine atoms[2] and bromine atoms[2c,2e] in the gas phase, as a function of temperature,[2b,2c] and for iodine atoms in carbon tetrachloride[2c,3,4] and heptane[3] solutions at room temperature. Values for the recombination rate of iodine atoms in carbon tetrachloride and in hexane have also been calculated[5] by combining photostationary state data[6] with quantum yield data,[5] and with lifetime measurements[7] made by the rotating sector technique. Values for the quantum yields for escape of iodine atoms from their parent molecular partnership have been determined both directly by flash photolysis[3,4] and by the use of a scavenger for iodine atoms.[5] Such data are gradually providing a more quantitative knowledge of the life history of atoms and radicals in solution.

In the present work the rate constants for the recombination of iodine atoms in hexane, decane and carbon tetrachloride at room temperature and in carbon tetrachloride at 50° have been determined by the flash photolysis method, using equipment and techniques similar to those reported elsewhere.[2c,4]

The solvents used were Mallinckrodt "AR low sulfur" carbon tetrachloride, Phillips "pure" grade hexane and Matheson decane. The hydrocarbons were further purified by fractional distillation and prolonged mechanical stirring with concentrated H_2SO_4, followed by washing and drying. They were degassed and transferred to the reaction cell under vacuum, the hexane being distilled through phosphorus pentoxide in the process.[8]

TABLE I

COMPILATION OF RATE CONSTANTS FOR IODINE ATOM COMBINATION IN SOLUTION

Solvent[a]	k, l. moles^{-1} sec.$^{-1}$ × 10^{-10} This work[b]	Marshall and Davidson[3]	Rabinowitch and Wood and Noyes and co-workers[5]	Strong and Willard[4]
CCl_4	0.69 ± 0.06	0.72 ± 0.01	0.84	0.57 ± 0.05[c]
CCl_4(50°)	1.03 ± 0.15			
n-C_6H_{12}	1.8 ± 0.6		1.56	
n-C_7H_{16}		2.2 ± 0.4	1.02	
n-$C_{10}H_{22}$	1.6 ± 0.4			

[a] All at room temperature except for the CCl_4 experiments at 50°. [b] The data are the average of 11 experiments for CCl_4 at 23°, 8 for CCl_4 at 50°, 32 for n-C_6H_{14} and 26 for n-$C_{10}H_{22}$. The limits given are the standard deviation. [c] The difference between this value and that obtained in the present work on the same instrument is of the order of the discontinuous instrumental variations previously described.[2e]

The results of this work and previous determinations of the rate constants (defined as k in $d[I_2]/dt = k[I]^2$) of atom recombinations in solution are given in Table I. Considering the difficulties of such experiments the degree of agreement between different workers and different methods for the carbon tetrachloride solutions and for similar hydrocarbons is gratifying.

(1) Ravensham College, Cuttack, India. Fulbright Smith-Mundt Scholar (1953–1954), Project Associate (1954–1955), University of Wisconsin.

(2) (a) M. L. Christie, R. G. W. Norrish and G. Porter, *Proc. Roy. Soc.* (*London*), **A216**, 152 (1952); (b) K. E. Russell and J. Simons, *ibid.*, **A217**, 271 (1953); (c) R. L. Strong and J. E. Willard, Abst. of the New York Meeting of the Am. Chem. Soc., Sept., 1954, p. 26R; (d) M. L. Christie, A. J. Harrison, R. G. W. Norrish and G. Porter, *Proc. Roy. Soc.* (*London*), **A231**, 446 (1955); (e) R. L. Strong, J. C. W. Chien, P. E. Graf and J. E. Willard, *J. Chem. Phys.*, in press.

(3) R. Marshall and N. Davidson, *ibid.*, **21**, 659 (1953).

(4) R. L. Strong and J. E. Willard, THIS JOURNAL, **79**, 2098 (1957).

(5) F. W. Lampe and R. M. Noyes, *ibid.*, **76**, 2140 (1954).

(6) E. Rabinowitch and W. C. Wood, *Trans. Faraday Soc.*, **32**, 547 (1936).

(7) J. Zimmerman and R. M. Noyes, *J. Chem. Phys.*, **18**, 658 (1950).

(8) To prevent pyrolysis of the hydrocarbon vapor while the reaction cell was being sealed off a plug of the solid was frozen in the side arm with the aid of liquid air on glass wool. This device was necessary to avoid the danger of cracking the optical cell if the bulk of the liquid was frozen in it.

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June 5, 1957

Comparison of the rate constants which we have obtained in hexane and decane with each other and with the value of Marshall and Davidson[3] for heptane indicates that there is no large effect of chain length on the rate constant over this range. A small effect may exist within the error limits of these determinations.

Calculation of the apparent activation energy from the rate constants in CCl_4 at 23 and 50° gives a value of 3.2 kcal./mole. This is in the range which would be expected for a diffusion controlled process such as this. The activation energy for the diffusion of iodine molecules in CCl_4 has been found to be 3.3 kcal./mole.[9]

(9) E. W. Haycock, B. J. Alder and J. H. Hildebrand, *J. Chem. Phys.*, 21, 1601 (1953).

The activation energy found for the gas phase recombination of iodine atoms in the presence of argon is −1.4 kcal./mole,[2e] the negative value being ascribed to the decreasing stability of the two-body complex which is believed to play a role in the "three body" recombination process. In solution "third body" solvent molecules are always present so the rate of diffusion rather than the stability of the two body complex is rate controlling.

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MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Kinetic Studies of Thiourea Derivatives. I. Methylthiourea

BY WILLIAM H. R. SHAW AND DAVID G. WALKER

RECEIVED DECEMBER 19, 1956

The decomposition of methylthiourea in aqueous media has been studied over a wide *p*H range. In acid solutions two parallel first-order reactions were observed and corresponding rate constants evaluated at several temperatures. Above *p*H 7 additional complicating reactions were encountered. The experimental results are compared with those previously reported for urea and thiourea. A possible mechanism is discussed.

Introduction

The isomerization of urea to ammonium cyanate has been investigated previously in this Laboratory.[1] Recently, analogous results were also reported for thiourea,[2] and the marked similarity of the two reaction systems noted. Since both reactions were found to be strictly first-order, presumably unimolecular, decompositions, it seemed desirable to obtain comparable data with related compounds. The present paper is the first in a series to be devoted to the kinetic study of urea and thiourea derivatives.

Although the fundamental organic chemistry of methylthiourea recently has been thoroughly discussed and reviewed by Sahasrabudhey and Singh,[3] no kinetic data on the decomposition of this compound could be found in the literature. Moreover, reasoning based on the mechanism previously postulated for the isomerization of thiourea indicated that the decomposition of the 1-methyl derivative should exhibit several novel features.

Experimental

Methylthiourea was prepared by the addition of ammonia to methyl isothiocyanate.[4] The crude product was recrystallized twice from water, m.p. 118.7–120.4° (lit.[4] m.p. 119–120.5°). Titration of weighed amounts of the purified material with standard mercuric nitrate[5] indicated that the compound was at least 99% pure.

Anal. Calcd. for $C_2H_6N_2S$: C, 26.60; H, 6.70; N, 31.07. Found: C, 26.65; H, 6.69; N, 30.82.

(1) W. H. R. Shaw and J. J. Bordeaux, THIS JOURNAL, **77**, 4729 (1955).
(2) W. H. R. Shaw and D. G. Walker, *ibid.*, **78**, 5769 (1956).
(3) R. H. Sahasrabudhey and R. Singh, *J. Indian Chem. Soc.*, **30**, 459 (1953).
(4) E. C. Horning, Ed., "Organic Syntheses," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1955, pp. 617–618.
(5) R. H. Sahasrabudhey and R. Singh, *J. Indian Chem. Soc.*, **30**, 223 (1953).

The apparatus and techniques utilized in this investigation were those employed in earlier work[1,2] except as noted below.

Reaction mixtures were analyzed for ammonia and methylamine by the following modification of the ion-exchange method previously described.[1,2,6] Samples of the reacted solutions were adjusted to *p*H 6–7 and passed through ion-exchange columns containing Dowex 50. After careful washing the adsorbed ammonium and methylammonium ions were eluted from the resin with dilute sodium hydroxide. After suitable *p*H adjustment separate aliquots were used to determine ammonia by nesslerization, and methylamine by a colorimetric analysis described in detail elsewhere.[7] The methylamine analysis was not affected by the amounts of ammonia present in the reaction mixtures. In the ammonia analysis, on the other hand, a moderate interference by methylamine was encountered. Suitable corrections could, however, be made by appropriate calibration of the Nessler reagent in the presence of the interfering substance. The average deviation of a set of 8 independent analyses of a 1.11 m*M* methylamine hydrochloride solution was 3.0%. Whereas the average deviation of a set of 8 analyses of 0.148 m*M* ammonium chloride that was also 0.286 m*M* in methylamine sulfate was found to be 4.4%.

Results

As in previous papers the reactions were studied by the method of initial rates. The equation

$$p_1/t = k_1\bar{u} \qquad (1)$$

was used in the analysis of experimental data. In this equation $\bar{u}$ is the average methylthiourea concentration; p_1 denotes the concentration of a particular product, P_1, formed in the reaction time, t; and k_1 is an empirical rate constant based on the rate of formation of P_1. Since very little reactant was consumed during the reaction period, $\bar{u}$ differed from the initial reactant concentration by less than 2%. The rates of formation of three reaction prod-

(6) W. H. R. Shaw and J. J. Bordeaux, *Anal. Chem.*, **27**, 138 (1955).
(7) F. D. Snell and C. T. Snell, "Colorimetric Methods of Analysis," 3rd Edition, Vol. 4, D. Van Nostrand Co., Inc., New York, N. Y., 1954, p. 338.

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ucts: (1) thiocyanate ion, (2) ammonia and (3) methylamine were followed and corresponding empirical rate constants k_1, k_2 and k_3 were calculated by means of equation 1.

In acid solution all the k's were independent of reactant concentration and reaction time, establishing that the rates of formation of all products were first order with respect to methylthiourea. Measurements conducted with solutions varying in average methylthiourea ($\bar{u}$) from 44.5 to 444 mM, for reaction times from 11.8 to 24.8 hr. gave the following best values for the empirical first-order constants at 100.0 ±0.1°: k_1 = 0.57 ±0.07 × 10^{-7} sec.$^{-1}$, k_2 = 1.84 ±0.15 × 10^{-7} sec.$^{-1}$, k_3 = 2.49 ±0.25 × 10^{-7} sec.$^{-1}$. All of the experimental solutions used to obtain the above values were 0.01 M in H_2SO_4. The behavior of these constants with changing acidity of the media is displayed in Fig. 1. The constant based on the rate of thiocyanate production (k_1) was found to be independent of $\bar{u}$ and t in both acidic and basic solutions, nor was the magnitude of this parameter affected by pH changes over a very wide range. The behavior of the other two constants was considerably more complex. Above pH 7 these parameters were strongly dependent on pH, $\bar{u}$ and t. As indicated in the legend, the results plotted in Fig. 1 were obtained with a reactant concentration of 0.050 M and a reaction time of 36 hours.

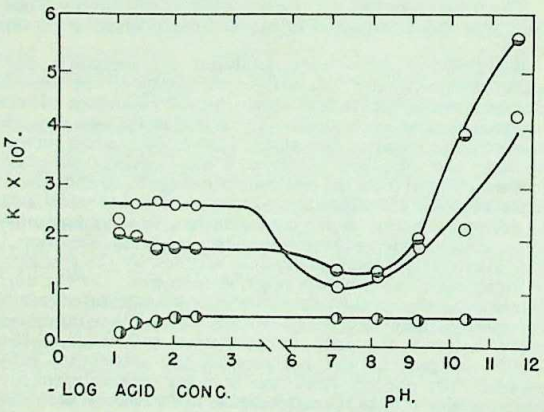

Fig. 1.—Empirical first-order rate constants as a function of acid concentration. The constants: k_1, k_2 and k_3 are based on the rate of formation of thiocyanate (◑), ammonia (◒), and methylamine (○), respectively. Runs above pH 7 were made in buffered 0.01 M borax solutions. Results recorded below pH 7 were based on data collected for HCl. All runs were made at 100.0 ± 0.1° at an initial methylthiourea concentration of 0.050 M and a reaction time of 36.0 hr.

The temperature dependencies of the constants based on thiocyanate production (k_1) and ammonia production (k_2) were also measured (Table I). These runs were made in acid media to eliminate the complexities mentioned in the preceding paragraph. The effect of ionic strength was likewise studied in media of low pH. Experiments were performed with solutions containing added sodium sulfate varying in concentration from 0.00 to 0.50 M at 100°. These solutions were also 0.01 M in H_2SO_4. A reaction time of 88.7 hr. was employed with an average methylthiourea concentration of 38 mM. No salt effects were observed.

As in the case of thiourea the reaction mixtures were subjected to a qualitative test for sulfide ion. Reacted samples obtained at all pH's studied were acidified (unless already acidic) and treated with mercuric nitrate solution. No precipitate was obtained with solutions that had reacted at pH's below 7, but those above pH 7 yielded a faint precipitate that became increasingly pronounced with increasing pH of reaction.

The rate constants recorded in Table I are reported to one more significant figure than is justified by the experimental data. The over-all average percentage deviations for k_1, k_2 and k_3 were approximately 10, 5 and 9%, respectively. Within a given run, however, much smaller deviations were encountered. In the extended reaction periods employed (as long as 89 hours) it was somewhat difficult to maintain precise temperature control, and, consequently, part of the lack of reproducibility from run to run could be attributed to this source of error. For these long reaction periods the temperature was controlled only to approximately ±0.1°.

TABLE I

RATE CONSTANTS OBTAINED AT VARIOUS TEMPERATURES IN ACID SOLUTIONS

Temp., °C. ±0.1	$\bar{u}$[a]	t[b]	First-order rate constants,[c] sec.$^{-1}$ × 10^7 k_1	k_2
	A. Medium, 0.01 M HCl			
100.0	49.3	29.5	0.65[d]	2.09[d]
110.1	49.2	9.82	2.40	7.55
120.2	48.8	4.00	8.13	24.8
130.0	48.3	1.90	24.7	68.8
140.0	46.7	1.40	86.0	197
	B. Medium, 0.015 M HNO_3			
100.0	100	6.55	0.62[d]	1.93[d]
110.0	49.5	6.17	2.30	7.02
120.0	24.4	4.58	8.20	25.1
130.0	9.43	3.62	28.1	74.0
140.0	8.96	2.78	78.9	169

[a] $\bar{u}$ is the average concentration of methylthiourea (millimoles/liter). [b] t is reaction time in hours. [c] The constants k_1 and k_2 are based on the rate of production of thiocyanate and ammonia, respectively. [d] For the least squares arrhenius analysis a value of 0.57 was used for k_1 and 1.84 for k_2 at this temperature. These values represent the average of all experimental data obtained at 100° whereas the values presented in Table I are based on 4 runs.

Discussion

The mechanism previously postulated for the thiourea decomposition assumed intramolecular hydrogen transfer and dissociation of the activated complex to form ammonia and thiocyanic acid. In this case hydrogen transfers from N to N′ and from N′ to N cannot be distinguished experimentally since the reaction products formed by both processes are identical. This degeneracy should, however, be removed in the decomposition of methylthiourea and different reaction products should result from these two different modes of hydrogen

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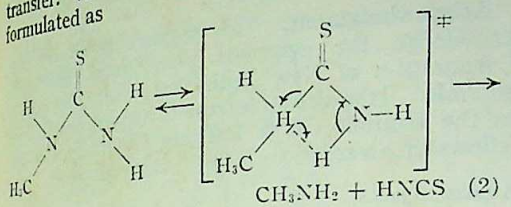
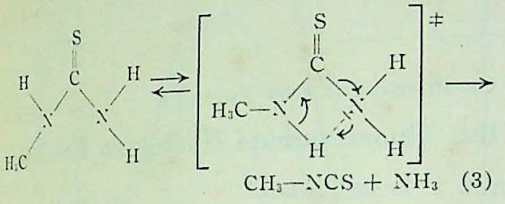
transfer. A tentative reaction scheme might be formulated as



$$CH_3NH_2 + HNCS \quad (2)$$



$$CH_3{-}NCS + NH_3 \quad (3)$$

Additional reaction by the products must also be considered.

$$HNCS \longrightarrow H^+ + NCS^- \quad (4)$$

$$CH_3 - NCS + H_2O \longrightarrow CH_3NH_2 + COS\uparrow \quad (5)$$

$$NH_3 + H^+ \rightleftharpoons NH_4^+ \quad (6)$$

$$CH_3NH_2 + H^+ \rightleftharpoons CH_3NH_3^+ \quad (7)$$

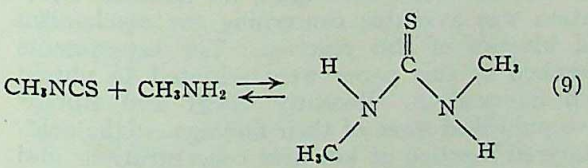
Since isothiocyanic acid is a strong acid,[8] equation 4 is written as an irreversible process. In acid, methyl isothiocyanate is converted[9] rapidly into methylamine and carbon oxysulfide (eq. 5). It follows, therefore, that the final products of reaction 2 in acid solution will be methylammonium ions and thiocyanate ions. From stoichiometric considerations the thiocyanate concentration produced by this reaction should be equal to the methylammonium ion simultaneously generated. Reaction 3 will yield ammonium and methylammonium ions in equimolar amounts. It becomes apparent, therefore, that the empirical first-order rate constant based on the production of thiocyanate, k_1, is the true rate constant for reaction 2. Similarly, k_3, based on ammonia production should be assigned to reaction 3. k_3, on the other hand, must be regarded as a composite constant; and, if the preceding reasoning is correct, it follows from the stoichiometry of reactions 2–7 that

$$k_3 = k_1 + k_2 \quad (8)$$

As previously mentioned (Results) the best values for the various constants at 100° are as follows: $k_1 = 0.57 \pm 0.07 \times 10^{-7}$ sec.$^{-1}$, $k_2 = 1.84 \pm 0.15 \times 10^{-7}$ sec.$^{-1}$, $k_3 = 2.49 \pm 0.25 \times 10^{-7}$ sec.$^{-1}$. It becomes apparent, therefore, that equation 8 correctly represents the experimental data. The decomposition of methylthiourea in acid solution must, consequently, be regarded as two parallel first-order reactions producing methylamine as a common product. The rate constant for these reactions can, however, be unambiguously assigned from experimental data on the rate of formation of other products (*e.g.*, SCN^- and NH_4^+).

A further examination of these results and those displayed in Table I reveals several points of interest. The rate constant (k_1) for reaction 2 is less than the constant (k_2) characterizing reaction 3. This generalization is true at all temperatures studied. Moreover, both of these constants differ significantly from the corresponding values reported for urea and thiourea particularly when statistical factors are also considered. In the most concentrated acid solutions studied (Fig. 1), k_1 falls off slightly and k_2 shows a corresponding increase. This same phenomenon was observed with thiourea and was attributed[2] to the conversion of thiocyanate to ammonium ion. With the addition of this known reaction, therefore, all the data obtained in acid solutions can be rationalized by the reaction scheme presented (equations 2–7). A least squares Arrhenius analysis of the data in Table I gave the following parameters describing the temperature dependence of k_1: $A = 9.87 \times 10^{14}$ sec.$^{-1}$, $E = 37.9$ kcal. Analogous parameters for k_2 are: $A = 3.37 \times 10^{13}$ sec.$^{-1}$, $E = 34.5$ kcal. The frequency factors and activation energies are reported to three figures solely for purposes of calculation of rate constants at various temperatures from the A and corresponding E. Because of the limited temperature range studied and experimental error (see Results) it is possible to select a wide variety of A's and corresponding E's that will give an adequate fit.

In solutions above *p*H 7 the empirical constants show a more complex behavior. As the hydrogen ion concentration is reduced, the equilibria described by eq. 6 and 7 will lie farther toward the left. The rate of conversion of methyl isothiocyanate to methylamine should also be diminished since this reaction is presumably acid catalyzed. Thus in media of slightly alkaline *p*H an increased ratio of methylamine to methylammonium ion should be encountered and methyl isothiocyanate should enjoy a longer lifetime than in solutions of greater acidity. Consequently, since the reverse of reaction 3 is a well known comparatively fast reaction, the decrease in k_2 and k_3 readily can be understood. The reaction



$$CH_3NCS + CH_3NH_2 \rightleftharpoons \quad (9)$$

is also most probably involved. Other evidence substantiates the existence of such complicating reactions. Thus, in alkaline media, the observed dependence of k_2 and k_3 on $\bar{n}$ and t can be interpreted on this same basis. In analogy to the thiourea case[2] the subsequent increase in these two empirical constants with increasing *p*H can be ascribed to the onset of a parallel base-catalyzed reaction that does not produce thiocyanate. The production of increasing amounts of sulfide precipitate (see Results) indicates, as before,[2] the onset of this reaction.

One rather striking aspect of the kinetic behavior of methylthiourea remains to be discussed—the remarkable *p*H independence of k_1. Since thiocyanic acid (unlike cyanic) is strong, the only species to be considered in water solutions in the *p*H range studied is the thiocyanate ion. However, according

(8) H. E. Williams, "Cyanogen Compounds," 2nd ed., Edward Arnold & Co., London, England, 1948, pp. 307–309.
(9) A. W. Hofmann, *Ber.*, **1**, 169 (1868).

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to the mechanism presented, complicating reverse reactions occur through the un-ionized acid (see eq. 2 for example). Since no significant concentration of un-ionized thiocyanic acid is present in the solutions studied, the rate of thiocyanate production is independent of hydrogen ion concentration over a 10^9-fold change in this variable.

A more detailed theoretical account of the effect of methyl substitution on the rate of decomposition will be presented in the last paper of this series when additional data on other methylated thioureas has accumulated.

Acknowledgment.—The authors gratefully acknowledge the generous grant from Research Corporation of New York that made this study possible. It is also a pleasure to express our thanks to the Humble Oil & Refining Company for the fellowship awarded to D.G.W. this past year.

AUSTIN, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

A Study of the Mechanism and Kinetics of the Thioacetamide Hydrolysis Reaction[1]

BY DONALD ROSENTHAL[2] AND T. IVAN TAYLOR

RECEIVED OCTOBER 3, 1956

The hydrolysis of thioacetamide to acetic acid, ammonia and hydrogen sulfide is catalyzed by both acids and bases. The base-catalyzed reaction was found to be the more rapid. Thioacetic acid was detected as an intermediate in both reactions. The relative importance of thioacetic acid and acetamide as intermediates is not known. A spectrophotometric investigation of the hydrolysis showed the rate of disappearance of thioacetamide to be first order with respect to thioacetamide concentration. The acid-catalyzed reaction was investigated in HCl and $HClO_4$ solutions at concentrations from 0.3 to 6 M at 35°. A maximum was observed in the first-order thioacetamide rate constant at an HCl concentration of about 4.5 M, and at an $HClO_4$ concentration of about 4 M. A mechanism involving the rapid and reversible addition of a proton followed by the rate-determining addition of water is consistent with the observed kinetics. The presence of a protonated thioacetamide ion in acid solution was detected spectrophotometrically. The observed first-order rate constants were not significantly different from those calculated using a rate expression $\log k = \log k_2K_1 + \log [H_3O^+] - \log(1 + K_1h_0) + BC$ derivable from the proposed detailed mechanism. In the above equation k is the first-order thioacetamide rate constant, h_0 is the antilog of minus the acidity function, C is the molar concentration of electrolyte, and K_1 and k_2 are simple or complex constants depending upon the detailed nature of the reaction. The BC term is presumably equal to the logarithm of an activity coefficients quotient. The maximum and observed rate constants for acetamide hydrolysis at 50° can also be explained in terms of a similar mechanism and rate expression.

Thioacetamide has been found useful in qualitative analysis[3] as a substitute for hydrogen sulfide gas.

The stoichiometric equation for the complete hydrolysis of thioacetamide is[4]

$$CH_3{-}\overset{\overset{S}{\|}}{C}{-}NH_2 + 2H_2O \longrightarrow CH_3{-}\overset{\overset{O}{\|}}{C}{-}OH + NH_3 + H_2S$$

When this study was begun, no detailed information was available concerning the mechanism and kinetics of this reaction. The experiments described in this paper were initiated to obtain such information. Recently, Swift and Butler[5] have published some of their findings on the acid-catalyzed reaction at low acid concentrations and elevated temperatures.

Intermediates in the Hydrolysis Reactions.—In the course of the hydrolysis reaction two chemical bonds must be broken, *viz.*, the carbon–nitrogen and carbon–sulfur bonds. Depending upon which bond is first broken, there are two possible intermediates in the reaction, thioacetic acid and acetamide. In both the base- and acid-catalyzed reactions thioacetic acid was found to be an intermediate. In the base-catalyzed reaction there was a gradual shift in the absorption maximum with time toward the wave length at which the thioacetate ion absorbs, 2450 Å. (see Fig. 1). In the acid-catalyzed reaction a substance was extracted which gave an identical spectrum to that of thioacetic acid when treated in the same manner (see Fig. 2). Acetamide has no characteristic absorption maximum above 2150 Å. and consequently could not be detected by these measurements.

The fact that thioacetic acid is an intermediate does not preclude the possibility that acetamide is also an intermediate, and that two competitive reactions are occurring. Indeed, Swift and Butler[5] were able to explain the observed change in pH upon the hydrolysis of thioacetamide at low acid concentrations and elevated temperatures by postulating acetamide as an intermediate. From the available evidence, it is not possible to evaluate the relative importance of acetamide and thioacetic acid as intermediates in the hydrolysis under the conditions of the experiments described herein.

Kinetics and Mechanism

Dependence of Rate upon Thioacetamide Concentration.—Preliminary experiments indicated that thioacetamide conforms to Beer's law for the range of concentration employed in these experiments, *ca.* 2×10^{-4} to 10^{-6} M, the absorption maximum at 2615 Å. being employed.

A plot of log absorbancy at 2615 A. *versus* time revealed the rate of the acid- and base-catalyzed

(1) Taken in part from a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science of Columbia University. Presented at the meeting of the American Chemical Society, Minneapolis, Minnesota, September 16, 1955.

(2) Department of Chemistry, The University of Chicago, Chicago, Illinois.

(3) H. H. Barber and T. I. Taylor, "Semimicro Qualitative Analysis," Harper and Bros., New York, N. Y., 1953.

(4) A. W. Hofmann, *Ber.*, **11**, 340 (1878); C. V. Jorgensen, *J. prakt. Chem.*, **66**, 33 (1902).

(5) E. H. Swift and E. A. Butler, *Anal. Chem.*, **28**, 146 (1956).

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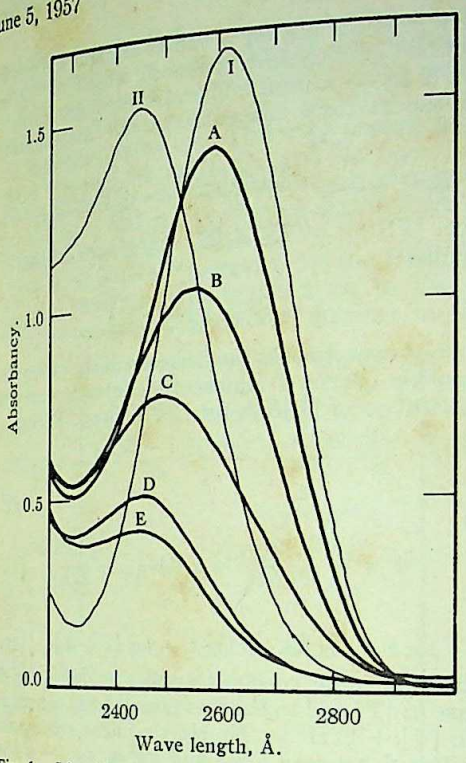

Fig. 1.—Identification of the intermediate in the base-catalyzed hydrolysis of thioacetamide; thioacetamide in 0.10 *N* NaOH: A, after 2.2 minutes; B, after 111 minutes; C, after 273 minutes; D, after 1521 minutes; E, after 7520 minutes; I, thioacetamide in water; II, thioacetic acid in water.

reactions to be first order with respect to thioacetamide concentration, *i.e.*

$$-d[T]/dt = k[T] \qquad (1)$$

where T = $CH_3-\overset{S}{\overset{\|}{C}}-NH_2$ (see Fig. 3).

The base-catalyzed reaction is much more rapid than the acid-catalyzed reaction (at 25° in 0.11 *M* NaOH k is 7×10^{-5} sec.$^{-1}$, in 0.1 *M* HCl k is 7×10^{-7} sec.$^{-1}$, and in distilled water $k < 4 \times 10^{-8}$ sec.$^{-1}$).

Dependence of Rate upon Hydrogen Ion Concentration.—A detailed investigation of the acid-catalyzed reaction at 35° revealed a non-linear increase of rate with increasing hydrogen ion concentration to a maximum at about 4.5 *M* HCl, or about 4 *M* $HClO_4$, and a subsequent decrease in rate (Tables I and III, column 2). Similar maxima have been found in the hydrolysis of amides[6] and in other cases.[7]

The cause and explanation of the amide maxima are not well understood.[6,8] Initially, the dependence of rate upon acid concentration at rates up to but not beyond the maximum will be considered. The maximum will be discussed in a later section of the paper.

If the rate-determining step in the hydrolysis

(6) V. K. Krieble and K. A. Holst, THIS JOURNAL, **60**, 2976 (1938).
(7) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, chapter XI.
(8) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 586–587.

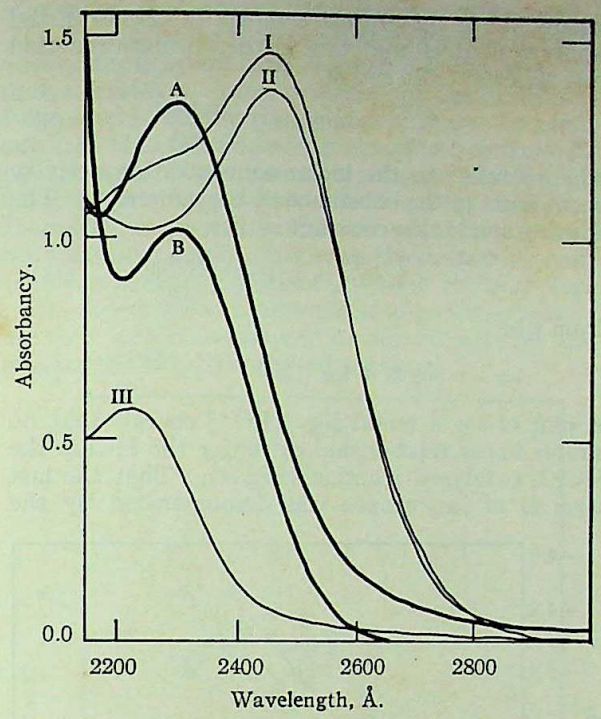

Fig. 2.—Identification of the intermediate in the acid-catalyzed hydrolysis of thioacetamide: A, extracted intermediate in 0.01 *N* NaOH; B, thioacetic acid extract in 0.04 *N* NaOH; I, thioacetic acid in water; II, thioacetic acid in 0.0001 *N* NaOH; III, thioacetic acid in 1.3 *N* HCl.

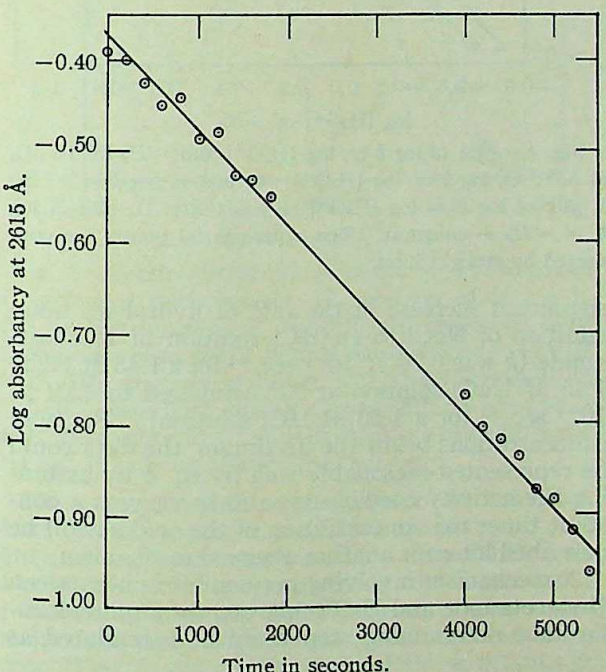

Fig. 3.—First-order plot of thioacetamide hydrolysis in 4.50 *M* HCl at 35°; initial thioacetamide concentration 1.43×10^{-5} *M*; $k = 23.9 \times 10^{-5}$ sec.$^{-1}$, S.D.$_k$ = 0.35×10^{-5} sec.$^{-1}$

were the initial reaction between thioacetamide (T) and H_3O^+, the reaction could be represented as

$$T + H_3O^+ \rightleftharpoons (M^*) \xrightarrow{k_2} TH^+ + H_2O \quad \text{(slow)} \quad (I)$$
$$TH^+ + H_2O \longrightarrow \text{products} \quad \text{(fast)}$$

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where M* is the critical complex in the Brønsted sense or a transition state in the absolute reaction rate theory. The rate is

$$-\frac{d[T]}{dt} = k_2[T][H_3O^+]\frac{f_T f_{H_3O^+}}{f_{M^*}} \quad (2)$$

where f refers to the molar concentration activity coefficients of the substance of the subscript. The thioacetamide rate constant is then

$$k = -\frac{1}{T}\frac{d[T]}{dt} = k_2[H_3O^+]\frac{f_T f_{H_3O^+}}{f_{M^*}} \quad (3)$$

from which

$$\log k = \log k_2 + \log [H_3O^+] + \log\frac{f_T f_{H_3O^+}}{f_{M^*}} \quad (4)$$

A plot of log k *versus* log $[H_3O^+]$ reveals that no simple linear relationship exists for the HCl or the $HClO_4$ catalyzed reaction (Fig. 4). That the last term is of importance was demonstrated by the

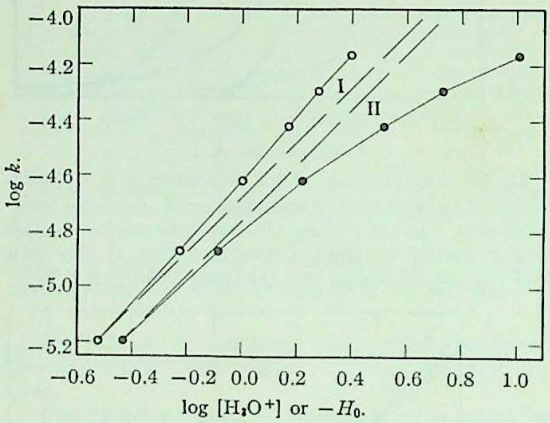

Fig. 4.—Plot of log k *vs.* log $[H_3O^+]$ and $-H_0$ for $HClO_4$ at 35°: ○, log k *vs.* log $[H_3O^+]$; ●, plot of log k *vs.* $-H_0$; I, plot of log k = log $[H_3O^+]$ + constant; II, plot of log $k = -H_0$ + constant. The experimental points are connected by straight lines.

significant increase in the rate of hydrolysis upon addition of NaCl to an HCl solution of thioacetamide (k was 6.79×10^{-5} sec.$^{-1}$ for a 1.45 M HCl–1.45 M NaCl solution at 35° compared to 4.29×10^{-5} sec.$^{-1}$ for a 1.50 M HCl solution). For acid concentrations below the maximum, the data could be represented reasonably well by eq. 4 by assuming the activity coefficients ratio to vary as a constant times the concentration of the acid as will be described later for another assumed mechanism.

A mechanism involving pre-equilibrium between thioacetamide and H_3O^+ followed by a unimolecular rate-determining step could be formulated as

$$T + H_3O^+ \overset{K_1}{\rightleftharpoons} TH^+ + H_2O \quad \text{(fast)}$$

$$TH^+ \rightleftharpoons (M^*) \xrightarrow{k_2} X^+ \quad \text{(slow)} \quad \text{(II)}$$

$$X^+ + H_2O \longrightarrow \text{products} \quad \text{(fast)}$$

The rate is

$$\frac{d(\text{products})}{dt} = -\frac{d([T] + [TH^+])}{dt} = k_2[TH^+]\frac{f_{TH^+}}{f_{M^*}} \quad (5)$$

$$= k_2K_1[T][H_3O^+]\frac{f_T f_{H_3O^+}}{f_{M^*}} = k_2K_1[T]h_0 \quad (6)$$

where h_0 is the antilog of minus Hammett's acidity function[9] applicable to cases in which M* differs from T by a proton. The rate constant k for the decrease in total concentration of thioacetamide, $[T] + [TH^+]$, is

$$k = \frac{1}{[T] + [TH^+]}\frac{d([T] + [TH^+])}{dt} = \frac{k_2K_1[T]h_0}{[T] + [TH^+]} \quad (7)$$

Since $[TH^+] = K_1[T][H_3O^+]f_T f_{H_3O^+}/f_{TH^+}a_{H_2O} = K_1[T]h_0$

$$k = k_2K_1h_0\left(\frac{1}{1 + K_1h_0}\right) \quad (8)$$

In our experiments the decrease in the concentration of the species T (thioacetamide) was measured. Substitution of $[T]K_1h_0$ for $[TH^+]$ in eq. 5 gives

$$-\frac{d([T] + [T]K_1h_0)}{dt} = -\frac{d[T](1 + K_1h_0)}{dt} = k_2K_1[T]h_0 \quad (9)$$

and

$$k = -\frac{1}{[T]}\frac{d[T]}{dt} = k_2K_1h_0\left(\frac{1}{1 + K_1h_0}\right) \quad (10)$$

or

$$\log k = \log k_2K_1 + \log h_0 - \log (1 + K_1h_0) \quad (11)$$

Thus, the same constant applies to both the decrease in [T] and to the decrease in total concentration, $[T] + [TH^+]$. No simple linear relationship was found between log k and log h_0, *i.e.*, $-H_0$ (see Fig. 4). If K_1 is sufficiently large, the inclusion of the last term in eq. 11 would result in a better fit than is obtained in Fig. 4, but this expression could only result in a limiting value of k equal to k_2 at large values of h_0 and would not explain the observed maximum.

Perhaps a more reasonable mechanism is one similar to that for the hydrolysis of the amides[10] in which the slow step is a bimolecular reaction between the protonated thioacetamide and water

$$T + H_3O^+ \overset{K_1}{\rightleftharpoons} TH^+ + H_2O \quad \text{(fast)}$$

$$TH^+ + H_2O \rightleftharpoons (M^*) \xrightarrow{k_2} \text{products} \quad \text{(slow)} \quad \text{(III)}$$

In this formulation, the transition state is one which differs from T, not only by a proton, but also by a water molecule. The rate is

$$\frac{d(\text{products})}{dt} = -\frac{d([T] + [TH^+])}{dt} = k_2[TH^+]\frac{a_{H_2O}f_{TH^+}}{f_{M^*}}$$

$$= k_2K_1[T][H_3O^+]\frac{f_T f_{H_3O^+}}{f_{M^*}} \quad (12)$$

and

$$-\frac{d[T]}{dt} = \frac{k_2K_1[T][H_3O^+]}{(1 + K_1h_0)}\frac{f_T f_{H_3O^+}}{f_{M^*}} \quad (13)$$

As shown previously, the rate constant determined from the decrease in total thioacetamide concentration ($[T] + [TH^+]$) or from the decrease in thioacetamide concentration is

$$k = k_2K_1[H_3O^+]\frac{1}{(1 + K_1h_0)} \times \frac{f_T f_{H_3O^+}}{f_{M^*}} \quad (14)$$

or

$$\log k = \log k_2K_1 + \log[H_3O^+] - \log (1 + K_1h_0) + BC \quad (15)$$

(9) L. P. Hammett and A. J. Deyrup, THIS JOURNAL, 54, 2721 (1932).

(10) C. A. Bunton, *et al.*, *J. Chem. Soc.*, p. 784–787.

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In eq. 15, $BC = \log f_T f_{H_3O^+}/f_{M^*}$, where B is a constant depending upon the nature of the non-electrolyte (thioacetamide) and the electrolyte (acid) present, and C is the "molar ionic strength" (acid concentration in moles/l.). This expression results from the fact that $\log f_T = B'C$ and $\log f_{H_3O^+}/f_{M^*}$ is relatively smaller in magnitude than the non-electrolyte term and can be written approximately equal to $B''C$ so that $B = B' + B''$.[11]

A plot of $\log k/[H_3O^+]$ *versus* C for the HCl and $HClO_4$ catalyzed reactions is presented in Fig. 5 for acid concentrations below the maxima in the rate of hydrolysis. In this plot, the data for each acid can be represented adequately by a straight line given by

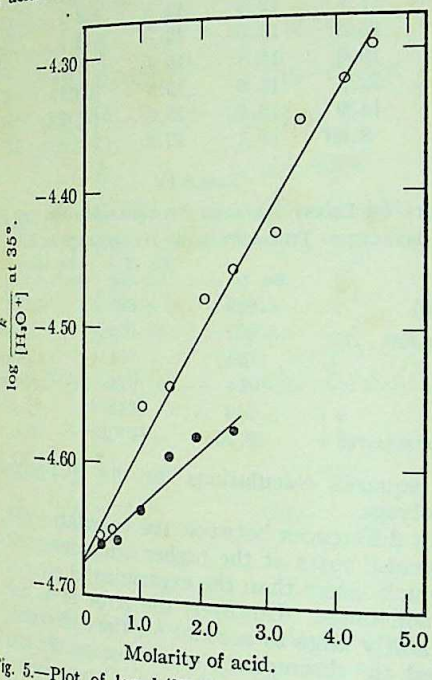

Fig. 5.—Plot of $\log k/[H_3O^+]$ *vs.* molarity of acid at 35°: k is the first-order thioacetamide rate constant in sec.$^{-1}$; O, HCl; ●, $HClO_4$.

$$\log k = \log k_2K_1 + \log[H_3O^+] + BC \qquad (16)$$

which is similar to eq. 4 except for the pre-equilibrium constant. The least squares values of the constants in eq. 16 were calculated and are given in the last columns of Tables II and IV. The experimental rate constants did not differ significantly from the values calculated using the least squares constants and eq. 16 as shown by the values in the next to the last columns in Tables I and III.

The least squares values of $\log k_2K_1$ are not significantly different for the HCl and $HClO_4$ data, while the B values are significantly different. This is expected since k_2 and K_1 should be independent of the acid used while the values of f_T and $f_{H_3O^+}/f_{M^*}$ may be different for acids with different anions. As the concentration of the acid approaches that for the maximum in the rate, this simplified eq. 16 does not satisfactorily represent the results.

(11) F. A. Long, F. B. Dunkel and W. F. McDevit, *J. Phys. Colloid Chem.*, **55**, 824 (1951).

Consideration of the Maximum.—Mechanism (III), usually referred to as A-2,[10] involves a pre-equilibrium in which TH^+ is in equilibrium with T (thioacetamide). Some evidence for the existence of the species TH^+ is presented in Fig. 6. In concentrated HCl solution a new absorption maximum appears at 2370 Å., presumably due to protonated thioacetamide (spectrum II, Fig. 6). Spectra III and IV demonstrate that this maximum is due to a species in equilibrium with thioacetamide and not to an irreversible intermediate in the reaction. A pK_1 of −1.76 was determined at room temperature (see Experimental section for details and assumptions involved in the calculations).

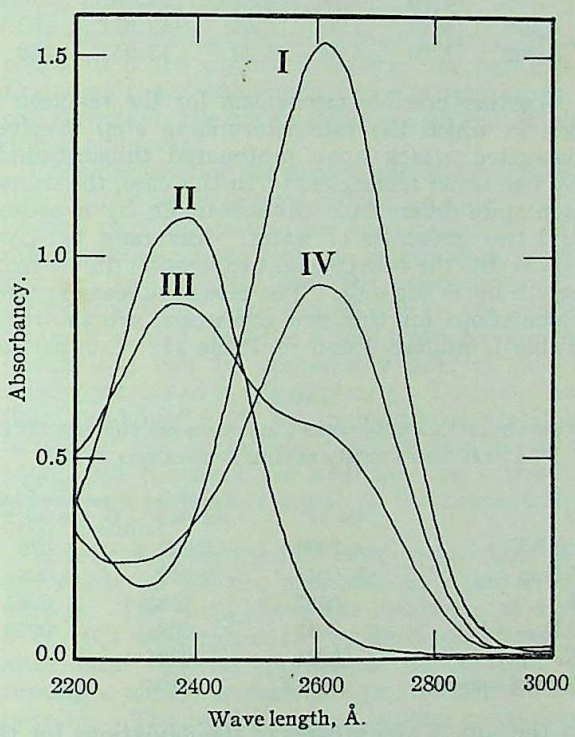

Fig. 6.—Spectrophotometric evidence for the existence of protonated thioacetamide: I, spectrum of *ca.* 6.4 × 10^{-5} *M* thioacetamide in water (2 cm. absorption cell); II, spectrum of *ca.* 6.4 × 10^{-5} *M* thioacetamide in 11.9 *M* HCl; III, spectrum of 1.6 × 10^{-4} *M* thioacetamide in 6 *M* HCl about 5 minutes after mixing (10 cm. absorption cell); IV, solution in III, diluted about one-half with water and run 16 minutes after original mixing.

The more complete expression for the rate constant for this mechanism (III) is given by eq. 15. Since h_0 increases more rapidly than $[H_3O^+]$ at the higher acid concentrations, the term $\log(1 + K_1h_0)$ becomes increasingly larger causing a decrease in k thus accounting for the observed maxima. The least squares values of the constants in eq. 15 were calculated for the $HClO_4$ data, including the data beyond the maximum. There are no significant differences between the experimental and the calculated rates employing the least squares values of the constants (Table I, column 3). The fact that the least squares value of K_1 of 0.028 is of the same relative order of magnitude as the value obtained at room temperature, 0.017, further supports the validity of the postulated rate eq. 15.

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TABLE I

COMPARISON OF THE OBSERVED AND CALCULATED RATES FOR THE $HClO_4$ CATALYZED HYDROLYSIS OF THIOACETAMIDE AT 35°

Concn. $HClO_4$, moles/l.	Expt. $k \times 10^{-5}$ sec.$^{-1}$	Least squares calcd. $k \times 10^{-5}$, sec.$^{-1}$ Eq. 15	Eq. 15 + log a_{H_2O}	Eq. 15 log $(1 + K_1h_0) = 0$	h_0
0.301	0.66	0.64	0.65	0.65	0.37
0.600	1.32	1.34	1.37	1.35	.83
1.008	2.34	2.41	2.49	2.36	1.68
1.486	3.79	3.80	3.95	3.67	3.31
1.908	5.04	5.09	5.31	4.92	5.41
2.500	6.68	6.83	7.09	*6.87*	10.2
2.936	8.55	7.85	8.10	(8.45)	16.1
2.958	7.63	7.89	8.12	(8.53)	16.5
3.983	8.16	7.97	7.97	(12.81)	52.0
5.007	5.30	5.44	5.31	(17.95)	168

Another possible mechanism for the reaction is one in which the rate-determining step involves concerted attack upon protonated thioacetamide by two water molecules.[12] In this case, the transition state differs from thioacetamide by a proton and two molecules of water. Assuming $f_T f_{H_3O^+}/f_{M^*} = BC$ the rate constant expression differs from eq. 15 by + log a_{H_2O}. The results of least squares calculations for this new expression are shown in Table I, column 4 and in Table II. Comparison

TABLE II

RESULTS OF LEAST SQUARES CALCULATIONS FOR THE $HClO_4$ CATALYZED THIOACETAMIDE HYDROLYSIS AT 35°

	Eq. 15	Eq. 15 + log a_{H_2O}	Eq. 15 assuming log $(1 + K_1h_0) = 0$
log k_2K_1	−4.7006	−4.697	−4.676
S.D.$_{\log k_2K_1}$	<0.0058	<0.012	0.004
B	.0987	.1283	.0461
S.D.$_B$	< .0041	< .0086	.0053
K_1	.0281	.0335	....
Sum of squares	.00238	.0105	....

of the sum of the squares of the deviations for the bimolecular and termolecular expressions gives a ratio of 4.4 to 1. Assuming an F test can be applied to the results, it can be stated with 95% certainty that the bimolecular expression is significantly better than the termolecular expression in accounting for the observed results (F at the 95% level is 3.8).

Equation 15 is identical with eq. 16 when $K_1h_0 << 1$; *i.e.*, when the concentration of protonated thioacetamide is negligible compared to the concentration of thioacetamide. This was the assumption which was implicitly made in some of the earlier calculations. Comparison of the constants in Table II, columns 1 and 3 reveals that significantly different values of the least squares constants are obtained. Thus, despite the fact that the rates calculated assuming $K_1h_0 << 1$ are in good agreement with the experimental rates at hydrogen ion concentrations up to but not beyond the maximum, the constants so calculated are not in good agreement with the constants obtained from the more complete equation 15, nor is the assumption that $K_1h_0 << 1$ apparently valid.

Tables III and IV present the results of the

TABLE III

COMPARISON OF THE OBSERVED AND CALCULATED RATES FOR THE HCl-CATALYZED HYDROLYSIS OF THIOACETAMIDE AT 35°

Concn. HCl, moles/l.	Expt. $k \times 10^{-5}$, sec.$^{-1}$	Least squares calcd. $k \times 10^{-5}$, sec.$^{-1}$ Eq. 15	Eq. 15 + log a_{H_2O}	Eq. 15 log $(1 + K_1h_0) = 0$	h_0
0.299	0.66	0.70	0.68	0.68	0.37
.506	1.13	1.24	1.22	1.19	0.68
1.032	2.86	2.88	2.87	2.69	1.65
1.497	4.29	4.63	4.64	4.28	2.87
2.05	6.82	6.99	7.03	6.52	5.10
2.49	8.69	9.09	9.18	8.63	7.31
3.12	11.6	12.0	12.2	12.2	12.2
3.49	15.6	13.5	13.7	14.7	16.6
4.11	19.6	15.3	15.4	*19.6*	27.5
4.50	22.7	15.8	15.8	(23.1)	37.8
5.25	14.9	15.5	15.3	(31.2)	69.8
6.24	8.69	13.1	12.8	(45.0)	157

TABLE IV

RESULTS OF LEAST SQUARES CALCULATIONS FOR THE HCl-CATALYZED THIOACETAMIDE HYDROLYSIS AT 35°

	Eq. 15	Eq. 15 + log a_{H_2O}	Eq. 15 assuming log $(1 + K_1h_0) = 0$
log k_2K_1	−4.669	−4.680	−4.671
S.D.$_{\log k_2K_1}$	<0.027	<0.025	0.0056
B	.139	.164	.0849
S.D.$_B$	< .014	< .013	.0038
K_1	.042	.041	....
Sum of squares	.0756	.0703	....

least squares calculations for the HCl-catalyzed hydrolysis.

The differences between the calculated and experimental rates at the higher acid concentrations are much larger than the experimental error of the rate constants. However, the error in h_0 may be sufficiently large to account for the differences,[13,14] so that the discrepancy is not necessarily attributable to the inadequacy of eq. 15. Comparison of the results of the least squares calculations reveals no significant difference between the results obtained assuming the bimolecular or termolecular expressions (ratio of sum of squares 1.1, F at 95% level is 3.2). While there was no significant difference between the log k_2K_1 calculated using eq. 15 and 16, there was, as in the $HClO_4$ calculations, a significant difference between the B values calculated from these two equations.

Summarizing the results for the $HClO_4$ and HCl hydrolysis reactions, the observed rates are consistent with the rates calculated assuming the mechanism (III) and rate expression 15. Further, the values of log k_2K_1 calculated from the $HClO_4$ and HCl catalyzed reactions are identical within experimental error; and the value of B for HCl is significantly different from the value for $HClO_4$. These results are what would be anticipated for the detailed reaction postulated. The values of K_1 calculated for the HCl and $HClO_4$ reactions are probably not significantly different, although it is difficult to obtain a good estimate of S.D.$_{K_1}$, and the values of K_1 are relatively of the same order of magnitude as the value calculated at room temperature.

(12) C. G. Swain, THIS JOURNAL, 70, 1119 (1948).

(13) M. A. Paul and F. A. Long, "H_0 and Related Indicator Acidity Functions," to be published in *Chem. Revs.*

(14) E. A. Braude, *J. Chem. Soc.*, 1871 (1948).

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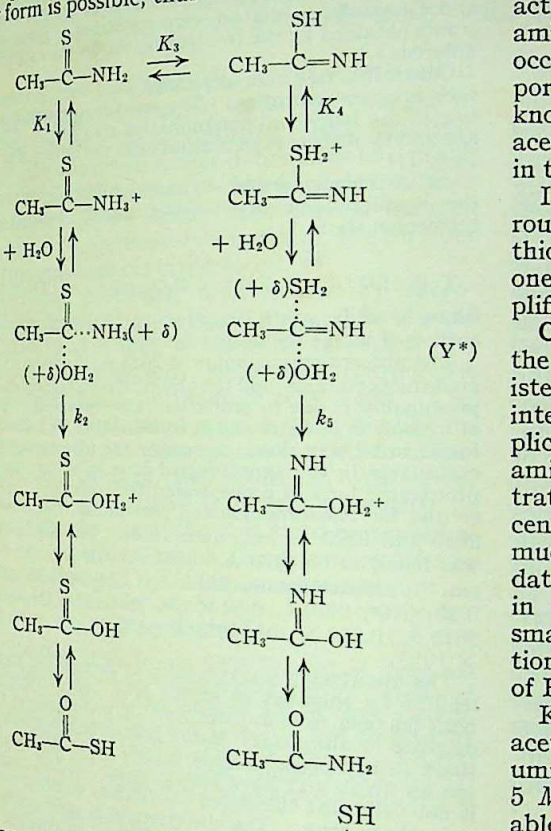
June 5, 1957

Consideration of Tautomerism, the Detailed Mechanism of Thioacetamide Hydrolysis.—One complication, which was neglected in the previous kinetic treatment, is that thioacetamide can be written in two tautomeric forms. The available evidence[15] seems to indicate that both forms are actually present in aqueous solution. Reaction *via* either form is possible, thus



It is assumed that species such as $CH_3\text{-}\overset{SH}{\overset{|}{C}}(OH)NH_2$ are present in negligibly small concentrations and do not affect the rate expression.

In terms of this mechanism the following rate expression (17) can be obtained

$$-\frac{dc}{dt} = k_2K_1\,[T][H_3O^+]\frac{f_T f_{H_3O^+}}{f_{M^*}} + k_5K_3K_4\,[T][H_3O^+]\frac{f_T f_{H_3O^+}}{f_{Y^*}} \quad (17)$$

where c is the sum of the concentrations of the two protonated and the two unprotonated species. Thus

$$c = [T] + K_3[T]\frac{f_T}{f_{TSH}} + K_1[T]h_0 + K_3K_4[T]h_0$$

where TSH is the thiolimido form of thioacetamide. Assuming the two activity quotients are equal, the expression is obtained

$$-\frac{d[T]}{dt} = \frac{(k_2K_1 + k_5K_3K_4)[T][H_3O^+]}{1 + K_3\frac{f_T}{f_{TSH}} + (K_1 + K_3K_4)h_0}\frac{f_T f_{H_3O^+}}{f_{M^*}} \quad (18)$$

Equation 18 is similar to eq. 13 except that the constants are now sums of products of more constants and the second term in the denominator is new. This expression can be written in a form identical with eq. 13, if $1 + K_3f_T/f_{TSH}$ is relatively constant under the conditions of the experiments, either because $K_3f_T/f_{TSH} << 1$ or because f_T/f_{TSH} is relatively constant. Further study is necessary before any detailed conclusions concerning eq. 17 and 18 can be drawn.

The detailed mechanism postulated leads to thioacetic acid as an intermediate product when reaction occurs *via* the thionamide form, and to acetamide as an intermediate product when reaction occurs *via* the thiolimido form. The relative importance of reaction *via* these two routes is not known and thus the relative importance of thioacetic acid and acetamide as intermediate products in the hydrolysis cannot be evaluated.

If the reaction proceeds predominantly by one route, or if the equilibria between the protonated thionamide and thiolimido forms is very much in one direction, the constants in eq. 18 can be simplified somewhat.

Consideration of the Hydrolysis of Amides.—In the hydrolysis of several different amides the existence of a maximum has been reported.[6] The interpretation of most of the kinetic data is complicated by the fact that the concentrations of amide employed were comparable to the concentrations of acid, and the actual hydrogen ion concentrations can be appreciably affected if very much protonated amide is formed. There are some data available[16,17] for the hydrolysis of acetamide in which the acetamide concentration is rather small and therefore the hydrogen ion concentration is approximately equal to the concentration of HCl added.

Kinetic data for the HCl-catalyzed hydrolysis of acetamide at 50° are presented in Table V, column 2. The rates above the maximum at 4 and 5 *M* HCl were calculated by extrapolating available data[17] to the appropriate temperature, assuming a simple Arrhenius type function was applicable. The results of least squares calculations are summarized in Tables V and VI.

TABLE V

COMPARISON OF THE OBSERVED AND CALCULATED RATES FOR THE HCl-CATALYZED HYDROLYSIS OF ACETAMIDE AT 50°

Concn. HCl, moles/l.	Expt. $k \times 10^{-5}$, sec.$^{-1}$	Least squares calcd. $k \times 10^{-5}$, sec.$^{-1}$ Eq. 15	Eq. 15 + log a_{H_2O}	Eq. 15 + log $(1 + K_1h_0) = 0$	h_0
0.100	1.13	1.06	1.05	1.07	0.11
.200	2.07	2.06	2.06	2.08	.24
.300	3.00	3.01	3.01	3.03	.37
.600	5.14	5.59	5.60	5.57	.83
1.00	8.19	8.41	8.43	8.31	1.58
1.50	11.3	11.0	11.1	10.9	2.88
2.00	12.9	12.8	12.8	12.6	4.79
2.60	13.9	13.9	13.9	13.9	8.00
3.12	14.2	14.0	14.0	14.4	12.2
4.00	12.7[a]	12.7	12.6	(14.5)	25.1
5.00	9.30[a]	9.35	9.35	(13.7)	57.5

[a] Rate calculated from the data[17] assuming an Arrhenius type function.

The experimental rates and the rates calculated using the least squares values of the constants in

(15) A. Hantzsch, *Ber.*, **64B**, 664 (1931).

(16) H. v. Euler and A. Olander, *Z. physik. Chem.*, **131**, 111 (1928).

(17) J. Taylor, *J. Chem. Soc.*, 2743 (1930).

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TABLE VI

RESULTS OF LEAST SQUARES CALCULATIONS FOR THE HCl-CATALYZED ACETAMIDE HYDROLYSIS AT 50°

	Eq. 15	Eq. 15 + log a_{H_2O}	Eq. 15 assuming log $(1 + K_1h_0) = 0$
log k_2K_1	−3.966	−3.967	−3.960
S.D.$_{\log k_2K_1}$	<0.017	<0.005	0.006
B	− .0994	− .0832	− .1206
S.D.$_B$	< .0034	< .0034	.0059
K_1	.0147	.0121	....
Sum of squares	.00250	.00254	....

eq. 15 are in good agreement with each other (Table V, columns 2 and 3). The results assuming the bimolecular expression are not significantly better than those assuming the termolecular expression (ratio of sum of squares in Table VI is 1.02, F at the 95% level is 3.4). The B values calculated from eq. 16 using data only up to the maximum and from eq. 15 are significantly different from each other, but there is no significant difference between the log k_2K_1 values. Here, as before, the assumption which is implicitly made in using eq. 16 to describe the rate data up to the maximum, *i.e.*, $K_1h_0 << 1$, is not valid. The importance of looking for the presence of a maximum and considering the concentration of protonated species which may be present, whenever a mechanism such as (III) is proposed, is readily apparent from the present studies. Such considerations may be useful in distinguishing between mechanisms (I), (II) and (III). The presence of a maximum is not consistent with mechanism (II) and is only consistent with (I) if B is negative. A careful consideration of eq. 15 and 4 may be necessary to distinguish between mechanisms (I) and (III) unless the protonated species can be detected in substantial concentration.

Experimental Details and Calculations

Reagents.—Eastman Kodak Co. white label brand thioacetamide was purified by recrystallization from benzene. The resulting material was white in color and had a melting point range of 109.8 to 111.9°.

Reagent grade HCl and $HClO_4$ were employed.

Rate Measurements.—The following general procedure was employed in all the rate determinations at 35° with only minor modifications in specific instances. The reaction was initiated by bringing both reactants to 35° in a thermostated water-bath, mixing them together and then transferring the reaction mixture to a 10-cm. quartz cell in a specially designed thermistor controlled thermostated Beckman spectrophotometer compartment (to be described elsewhere). The temperature in this compartment was controlled at 35 ± 0.1°. Sufficient time (*ca.* 45 minutes) was allowed for the reaction solution to return to 35° before readings were taken.

The initial concentration of thioacetamide employed in these experiments was about 1×10^{-5} M. Absorbancy readings at 2615 Å. were taken five at a time, 200 seconds apart, at selected time intervals during the course of the reaction with a Beckman D.U. spectrophotometer. The time intervals were selected so that readings could be taken over a time period of several half-lives.

Upon completion of the experiment, a known volume of the reaction mixture was titrated with a standardized solution of sodium hydroxide to a methyl red–brom cresol green end-point, and the concentration of acid computed.

In some instances the absorbancy readings were corrected by determining the correction due to solvent or cell differences between the reaction and reference cells. In other instances the Guggenheim method[18] was employed to eliminate this source of error. The first-order rate constants were determined in each case by the method of least squares. At two different acid concentrations both the cell correction and Guggenheim method were employed. The rate constants obtained by the two techniques were not significantly different.

Generally, two rate determinations were performed at each acid concentration. The standard percentage deviation of the individual determination was 2.9%. The average values of these experimental rates are reported in Tables I and III.

pK of Thioacetamide.—The stoichiometric equation for the equilibrium between thioacetamide and protonated thioacetamide is

$$T + H_3O^+ \underset{}{\overset{K_1}{\rightleftharpoons}} TH^+ + H_2O \text{ and } K_1 = [TH^+]/[T]h_0$$

where $h_0 = f_T a_{H_3O^+}/f_{TH^+} a_{H_2O} = [a_{H^+}(f_T/f_{TH^+})]$ and h_0 is the antilog of minus the acidity function.

The absorption maximum at 2615 Å. is due to unprotonated thioacetamide, and the absorption maximum at 2370 Å. presumably is due to protonated thioacetamide. The rate of hydrolysis in water and in concentrated HCl solution was found to be very slow. Assuming the thioacetamide exists exclusively in the unprotonated form in water, and in the protonated form in concentrated HCl solution, the absorptivities for thioacetamide and protonated thioacetamide at 2615 and 2370 Å. were determined. The isosbestic point was found to be 2470 Å. (Absorptivities in liters mole^{-1} cm.$^{-1}$: thioacetamide, 2615 Å., 1.17×10^4; 2370 Å., 0.22×10^4; 2470 Å., 0.62×10^4; protonated thioacetamide, 2615 Å., 0.080×10^4; 2370 Å., 0.88×10^4; 2470 Å., 0.62×10^4.)

The absorbancy was measured at each of the three wave lengths for solutions of known HCl concentration where both maxima were in evidence. It was assumed that the decrease in absorbancy at the isosbestic point was due entirely to hydrolysis and not in any way due to tautomeric species which may have been present. If this assumption is not valid, the calculated equilibrium constants could be seriously in error. The absorbancies in each solution were multiplied by the appropriate factors to correct for hydrolysis. In 4.30 M HCl log $[TH^+]/[T]$ was −0.49 (2615 Å.), −0.25 (2370 Å.); log K_1 was −2.00 and −1.76, respectively. In 5.52 M HCl log $[TH^+]/[T]$ was 0.15 and 0.438; log K_1 was −1.79 and −1.50. $\overline{\log K_1} = -1.76$ and S.D.$_{\overline{\log K_1}} = 0.10$.

Calculation of the Least Squares Constants for Equation 15.—Since eq. 15 contains the non-linear term log $(1 + K_1h_0)$, simple linear regression methods cannot be employed. What was done was to assume a value for K_1, to evaluate log $(1 + K_1h_0)$ and then to calculate the least squares value of B and log k_2K_1 for the linear expression

$$(\log k + \log (1 + K_1h_0) - \log [H_3O^+]) = \log k_2K_1 + BC$$

The sum of the squares of the deviations of the experimental log k minus the calculated log k was computed. This operation was repeated for various values of K_1 and in this way those values of the constants K_1, B and log k_2K_1 for which the sum of the squares of the deviations was a minimum were computed. An estimate of S.D. of log k_2K_1 and B was calculated from the linear expression, in which it is assumed there is no error in K_1. The "true" S.D. is presumably less than these estimated values.

CHICAGO 37, ILLINOIS

(18) E. A. Guggenheim, *Phil. Mag.*, [7] **2**, 538 (1926).

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June 5, 1957

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Microwave Spectra and Structure of CF_2=CH_2, CF_2=CHD and CF_2=CD_2

BY WALTER F. EDGELL, PHILIP A. KINSEY[1] AND JONATHAN W. AMY

RECEIVED OCTOBER 27, 1956

The K-band microwave spectra of CF_2CH_2, CF_2CHD and CF_2CD_2 have been recorded and analyzed. With the assumptions that $\angle HCH=DCD = 120°$ and $r_{CD} = r_{CH} = 0.009$ Å., the following structural parameters have been calculated: $r_{CF} = 1.321 \pm 0.005$ Å., $r_{CC} = 1.311 \pm 0.005$ Å., $\angle FCF = 109° 15' \pm 25'$, $r_{CH} = 1.10 \pm 0.05$ Å.

The structure of CF_2CH_2 is of interest since it provides further information as to the changes in molecular configuration resulting from multiple fluorine substitution in simple hydrocarbons. Such information for the series of fluorinated methanes was summarized by Lide[1]; the carbon–halogen bonds become progressively shorter as the number of fluorine substituents is increased.

CF_2CH_2 has previously been studied by microwave spectroscopy[2] and by electron diffraction.[3] It was felt that it was worthwhile to repeat the microwave investigation, since the frequencies were measured to an accuracy of only 3 mc. The spectra of the deuterated species were studied to reduce the number of assumptions needed to calculate the structure of the molecule. However, with the data given here it is still necessary to assume a value for one of the structural parameters, and for the extent to which the geometry of the molecule is changed by isotopic substitution.

Experimental

The CF_2CH_2, CF_2CHD and CF_2CD_2 used in these experiments were part of the samples prepared by Edgell and Ultee[4] for the study of the infrared and Raman spectra. The purity of the CF_2CD_2 and CF_2CHD was checked by mass spectrographic analysis. The per cent. of CF_2CHD in CF_2CD_2 was 5.3%. The main impurity in CF_2CHD was 2% of CF_2CH_2. There was also evidence of about 0.4% of CF_2CD_2.

Observations were made with a Stark-effect sweep spectrometer of the Hughes–Wilson type[5] using a 100 kc. square wave for modulation.

	CF_2CH_2 Obsd.	CF_2CH_2 Calcd.
A	11,000.8	11,000.8
B	10,428.8	10,429.5
C	5,345.6	.....
$\Delta = I_C - (I_A - I_B)$	0.234	
$\kappa =$	0.79771	

The modulating voltages ranged up to about 800 practical volts. All measurements were made in a 10 ft. K-band wave guide absorption cell at Dry Ice temperature. 1N26 crystal detectors were used and a Bendix radio range compass (ARN-7) was modified for use as a receiver. The sensitivity of the system was sufficient to detect NH_3 lines with an intensity of 1×10^{-7} cm.$^{-1}$.

Frequency measurements were made using harmonics from a UHF signal source[6] which was calibrated by comparison with the standard frequencies broadcast by station WWV. It is felt that the frequencies given are accurate to ±0.3 mc., unless otherwise noted.

(1) D. R. Lide, Jr., THIS JOURNAL, **74**, 3548 (1952).
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Analysis of the Spectra; CF_2CH_2.—As pointed out by Roberts and Edgell,[2] CF_2CH_2 is an oblate slightly asymmetric rotor, and to account for the microwave spectrum the dipole must be along the axis of the least moment of inertia. The two Q branch transitions which would be observed for the limiting symmetric rotor each split into a series of lines as a result of the asymmetry. The band heads of these two sub-branches are near 26,700 mc., and one series extends to higher, one to lower frequencies. In addition two R transitions should be found in the region near these Q sub-branch band heads. The whole region should also be covered with lines originating from high J transitions, or from other Q sub-branches whose origins are outside the region of observation.

An initial search of the region from 17,000 to 30,000 mc. yielded approximately 80 lines. Stark patterns indicated that most of these lines had fairly high J-values. Analysis of the spectrum essentially confirmed the assignments previously made.[2] In addition the $2_{02} \rightarrow 3_{03}$ and $2_{12} \rightarrow 3_{13}$ lines were found at the frequencies predicted on the basis of these assignments, and displayed the expected resolved Stark patterns. Table I gives the calculated and observed frequencies of all identified transitions. The observed but unidentified lines for CF_2CH_2 are listed in Table II. The rotational constants are (in mc./sec.) (table).

CF_2CD_2.—More than 50 lines were found in the spectrum of CF_2CD_2 in the region from 19,000 to 35,000 mc. Although it was possible to calculate the general pattern of the spectrum from the assumed model, the great density of lines in the spectrum made an unambiguous assignment of individual transitions difficult. The analysis was greatly facilitated by the fact that the $1_{01} \rightarrow 2_{02}$ and $1_{11} \rightarrow 2_{12}$ lines could be identified on the basis of their Stark patterns. Table I shows the observed and calculated frequencies based on the rotational constants given above.

CF_2CHD Obsd.	CF_2CHD Calcd.	CF_2CD_2 Obsd.	CF_2CD_2 Calcd.
10,926.9	10,931.6	10,590.5	10,590.5
9,545.5	9,541.6	8,994.1	8,986.7
5,086.7	.....	4,855.9	.....
0.262		0.235	
0.52692		0.44326	

CF_2CHD.—About 80 lines were seen in the spectrum of CF_2CHD in the region from 18,000 to 36,000 mc. After identifying the $1_{01} \rightarrow 2_{02}$ transition on the basis of its Stark pattern, the analysis was completed by assignment of Q branch transitions. The observed and calculated frequencies

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TABLE I

THE ROTATIONAL TRANSITIONS OBSERVED AND IDENTIFIED OF CF_2CH_2, CF_2CHD AND CF_2CD_2 IN MC./SEC.

Transition	CF_2CH_2	CF_2CHD	CF_2CD_2
$1_{11} \rightarrow 2_{12}$	26,465.6(26,465.6)[a]	24,805.5(24,805.5)	23,561.7(23,561.7)
$1_{01} \rightarrow 2_{02}$	26,991.7(26,991.9)	25,912.7(25,912.7)	24,778.2(24,778.2)
$1_{10} \rightarrow 2_{11}$	36,633[b] (36,632.0)	33,723.1(33,723.1)	.....
$2_{02} \rightarrow 3_{03}$	37,461[b] (37,459.0)	35,751.8(35,751.8)	34,178.2(34,178.2)
$2_{12} \rightarrow 3_{13}$	37,417 (37,415.9)	35,512.2(35,512.4)	33,857.0(33,856.8)
$3_{13} \rightarrow 3_{12}$	26,646.2(26,646.2)	24,595.1(24,598.0)	23,114.4(23,120.8)
$3_{03} \rightarrow 3_{22}$	26,881.2(26,876.2)	25,937.9(25,939.7)	24,950.7(24,955.4)
$3_{12} \rightarrow 3_{31}$	18,075.0(18,078.6)	21,056.0(21,057.1)	21,587.7(21,589.2)
$4_{22} \rightarrow 4_{41}$	19,710.9(19,713.6)	26,327.3(26,329.5)	.....
$4_{13} \rightarrow 4_{32}$	27,014.7(27,010.8)	26,815.7(26,818.4)	.....
$4_{23} \rightarrow 4_{22}$	26,627.6(26,625.4)	23,004.8(23,007.9)	21,084.9(21,093.0)
$4_{24} \rightarrow 4_{32}$	.....	.....	26,203.4(26,208.0)
$4_{14} \rightarrow 4_{24}$	.....	.....	33,619.5(33,628.4)
$4_{04} \rightarrow 4_{23}$	.....	35,643.3(35,648.7)	.....
$5_{33} \rightarrow 5_{32}$	25,725.2(25,724.3)	20,529.2(20,529.4)	.....
$5_{23} \rightarrow 5_{42}$	27,297.0(27,295.7)	28,728.4(28,732.4)	28,933.9(28,938.0)
$5_{24} \rightarrow 5_{23}$	.....	34,704.2(37,707.7)	32,567.8(32,578.5)
$5_{32} \rightarrow 5_{51}$	.....	33,792.5(33,795.8)	.....
$5_{14} \rightarrow 5_{33}$	.....	35,643.3(35,648.8)	.....
$6_{42} \rightarrow 6_{41}$	25,245.7(25,245.9)	.....	.....
$6_{43} \rightarrow 6_{41}$	24,771.0(24,771.3)	.....	.....
$6_{33} \rightarrow 6_{52}$	27,821.2(27,819.9)	32,264.5(32,259.6)	.....
$6_{24} \rightarrow 6_{43}$	.....	35,922.1(35,924.4)	.....
$7_{53} \rightarrow 7_{52}$	23,435.7(23,440.2)	.....	.....
$7_{43} \rightarrow 7_{62}$	28,696[b] (28,699.3)	.....	.....
$7_{44} \rightarrow 7_{43}$	.....	30,804.8(30,812.0)	.....
$8_{63} \rightarrow 8_{62}$	21,745.2(21,749.2)	.....	.....

[a] Calculated frequencies are in parentheses. [b] These lines are measured with an accuracy of ±1 mc.

TABLE II

OBSERVED BUT UNIDENTIFIED LINES OF CF_3CH_2

17,008[a]	20,957.1	23,270[a]	24,357.4	26,329.0
17,229.3	21,484.0	23,323.0	24,449.6	26,335.6
17,843.8	21,572.6	23,360.4	24,543.3	26,726[a]
17,892.1	21,689.0	23,647.1	24,581.4	26,832.0
18,907.5	22,236.3	23,770.5	24,639.8	27,112.0
19,098.9	22,273.4	23,814.4	24,729.2	27,218.6
19,254[a]	22,386.2	23,994.7	24,809.7	27,680.4
19,660.9	22,394.8	24,020.5	25,352.1	28,177.7
19,723.3	22,744.7	24,149.3	25,448.9	28,414.2
19,726.5	23,180.0	24,293.6	25,516.3	28,438.1
20,038.2	23,208.1	24,323.2	25,742.0	28,455.1
20,345.0	23,215.3	24,353.3	26,116.4	28,945.3

[a] These lines were measured with an accuracy of ±1 mc.

based on the rotational constants above are given in Table I.

Structural Parameters.—For a planar molecule, the moment of inertia about the axis perpendicular to the plane should equal the sum of the other two moments. As a result of zero-point vibrations, this holds only approximately for actual molecules; the small value of the "defect" $\Delta = I_C - (I_A - I_B)$ given above confirms the assumed planarity of CF_2CH_2.

The moment of inertia around the C–C bond in CF_2CH_2 is a function of only two parameters: r_{FF}, the distance between fluorine atoms and r_{HH}, the distance between hydrogen atoms. With the assumption that the geometry of the molecule is unchanged by isotopic substitution one can calculate r_{FF} and r_{HH} directly from the A moments of inertia for CF_2CH_2 and CF_2CD_2. Since this assumption can only be approximately true, it seemed preferable to assume instead a value for δ, the shortening of the C–H distance with deuterium substitution. The value chosen was 0.009 Å., in agreement with the results of Miller, *et al.*,[7] for the methyl halides; it seems unlikely that δ would differ from this value by more than a few thousandths of an ångström. In these calculations it is assumed that the HCH angle is near 120°; the results are almost independent of the precise value.

r_{FF} proves to be very insensitive to δ, changing by only 0.002 Å. if δ is changed from 0 to 0.009 Å. The best value of r_{FF} is 2.154 Å.

The r_{HH} and r_{DD} distances, of course, are more sensitive to δ: for $\delta = 0$, $r_{HH} = r_{DD} = 1.881$ Å.; for $\delta = 0.009$ Å., $r_{HH} = 1.912$ Å., $r_{DD} = 1.897$ Å.

The B moment of inertia of CF_2CH_2 depends on three parameters which may be taken as the projection of the CF distance on the CC axis, the C–C distance and the HCH angle. Although three isotopic species were available, the equation relating the observed moment to these parameters for CF_2CHD is nearly a linear combination of the corresponding equations for CF_2CH_2 and CF_2CD_2, and gives no additional information. It is therefore necessary to assume a value for one parameter in order to determine a structure.

As a result of the small mass of the H atom, the moment depends only slightly on any assumption made about the configuration of the CH_2 group. If the HCH angle is chosen as 120° for all isotopic species, and the isotope effect on the CH distance

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is the same as assumed above, the resulting parameters are those given below along with the results of the electron diffraction study.[3]

	This research	Electron diffraction[3]
∠FCF	109° 15′ ± 25′	110°
C-F	1.321 ± 0.005 Å.	1.321
C-C	1.311 ± 0.005 Å.	1.311 ± 0.035 Å.
∠HCH	120° (assumed)	117° ± 7°
C-H	1.10 ± 0.05 Å.	1.07 ± 0.02 Å.

The CH distance corresponding to our choice of the HCH angle is 1.10 Å. A change in the angle of 9° changes the CH distance by 0.05 Å., but only changes the other parameters by less than 0.005 Å. Thus the microwave data still leave the geometry of the CH_2 group somewhat uncertain, but defines the remaining parameters quite precisely, since the actual HCH angle can hardly be expected to differ so greatly from 120°.

The measured FCF angle is nearer to the tetrahedral value than to that of 120° expected on the usual assumption that the σ-bonds are formed with sp^2 hybrids. It is interesting to note that near-tetrahedral values of the corresponding angle are not unusual in the substituted ethylenes, though the angle reported for ethylene itself[8] is 119° 55′. The particularly small value of the FCF angle is also in line with that reported[1] for CH_2F_2.

Comparison of the C–C distance with that found for ethylene[8] indicates that there is appreciable triple-bond character in the bond, an effect that may be associated with the closing of the FCF angle.

Acknowledgment.—The authors would like to thank Dr. Norbert Muller for many helpful discussions and the Purdue Research Foundation, acting under Contract No. AT(11-1)-164 of the Atomic Energy Commission, who supported this research.

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LAFAYETTE, INDIANA

[CONTRIBUTION FROM SOUTHERN METHODIST UNIVERSITY]

Experimental Investigation of the Distribution of Salicylic Acid between Cyclohexane and Water

BY JOHN J. BANEWICZ, CHARLES W. REED AND MARK E. LEVITCH

RECEIVED JANUARY 10, 1957

The distribution of salicylic acid between water and cyclohexane was investigated at various temperatures from 24.00 to 55.00° and at concentrations from 10^{-4} to 10^{-2} mole per liter in water and cyclohexane. The concentrations were determined spectrophotometrically. In the more dilute concentrations, the dimerization of salicylic acid in cyclohexane was found to be negligible; and from the data in this region the ionization and distribution constants were obtained. In the more concentrated regions the dimerization became appreciable; and from the data in this region the dimerization constant was calculated. With these constants known as a function of temperature, the heats, entropies and free energies of dimerization, distribution and ionization were calculated.

In spite of the numerous references to salicylic acid in the literature there are very few data on the dimerization of salicylic acid in non-polar solvents. By studying the distribution of salicylic acid between cyclohexane and water not only can the distribution coefficient be obtained, but also the ionization constant of the salicylic acid in water and the dimerization constant in cyclohexane. Furthermore if determinations are made at different temperatures the various enthalpy, free energy and entropy changes can be calculated.

Experimental

Materials.—Matheson practical grade cyclohexane was used. The cyclohexane was purified by passage through a column of activated silica gel in accordance with the procedure of Graff, O'Conner and Skau.[1] Salicylic acid was recrystallized from cyclohexane and then sublimed.

Spectrophotometric Measurements.—The concentrations of salicylic acid in both the cyclohexane and water layers were determined spectrophotometrically using a Beckman DU spectrophotometer. For each solvent, solutions of known concentration were prepared ranging from 10^{-4} to 10^{-2} mole per liter. The standard solutions in each solvent were saturated with respect to each other. Salicylic acid has absorption maxima in water at 231 and 296 mμ and in cyclohexane at 240 and 310 mμ. Beer's law was obeyed at all four peaks.

The following equations were found to relate A, the absorbance, to C_g, the concentration of salicylic acid in grams of acid per gram of solvent

Water	231 mμ	$C_g = 2.09 \times 10^{-5} A$
Cyclohexane	240 mμ	$C_g = 2.08 \times 10^{-5} A$
Water	296 mμ	$C_g = 3.96 \times 10^{-5} A$
Cyclohexane	310 mμ	$C_g = 4.32 \times 10^{-5} A$

All readings were taken in triplicate with an average variation of 0.002 absorbance units.

Distribution Method.—Preliminary measurements were made to determine the approximate relation between equilibrium concentrations of the aqueous and cyclohexane solutions of salicylic acid. With this information seven different mixtures were made up with concentrations varying from about 10^{-2} to 10^{-4} mole per liter. The mixtures were placed in glass-stoppered Pyrex bottles in a constant temperature bath and allowed to equilibrate for three days with occasional shaking. At the end of this time samples were withdrawn from each layer, diluted by weight if necessary to bring the concentration into the spectrophotometric range, and the absorbance determined.

This procedure was repeated daily until constant concentration values were obtained. Almost always equilibrium was obtained within a three-day period. Using the known dilution factor, the concentrations of salicylic acid in the water and cyclohexane layers were calculated. The concentrations were converted to moles per liter, assuming the solutions to be so dilute that the solvent and solution densities could be considered identical.

This procedure was repeated for all the solutions at seven different temperatures, 24.00, 29.50, 32.00, 36.00, 40.05, 47.13 and 55.00°. The temperature was controlled to within 0.01° by a Sargent Thermonitor unit.

(1) M. M. Graff, R. T. O'Conner, and E. L. Skau, *Ind. Eng. Chem. Anal. Ed.*, **16**, 556 (1944).

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Results

Representative data obtained for the 24.00° run are shown in Table I. Calculations of the

TABLE I

DATA OBTAINED CORRELATING CONCENTRATION OF SALICYLIC ACID IN WATER AND IN CYCLOHEXANE FOR TEMPERATURE OF 24.00°

Mixture	Molar concn. (moles/l.) C_w	C_c	C_w/C_c	$\sqrt{1/C_c}$
I	0.000650	0.0000261	35.3	183
II	.00135	.0000443	30.4	147
III	.00197	.0000758	26.0	115
IV	.00328	.000218	15.0	67.7
V	.00648	.000753	8.61	36.5
VI	.00777	.00106	7.33	30.7
VII	.00857	.00129	6.63	27.8
VIII	.0152	.00601	3.80	15.9

various equilibrium constants from these data were considerably simplified when it was found that at the most dilute concentrations the dimerization of salicylic acid in cyclohexane was negligibly small.

The three equilibria involved are, first the ionization of salicylic acid in water, second the dimerization of salicylic acid in cyclohexane, and last the distribution of the undimerized and undissociated salicylic acid between the water and the cyclohexane layers. If C_w is the spectrophotometric value obtained for the total concentration in moles per liter of the salicylic acid in water and a represents the moles per liter of the acid which have ionized, then the ionization constant, K_i, may be written as

$$K_i = \frac{a^2}{C_w - a} \qquad (1)$$

In the cyclohexane layer, if C_c represents the total concentration of acid and b the concentration of single molecules which have associated in moles per liter then the dimerization constant, K_{dim}, is

$$K_{dim} = \frac{1/2\, b}{(C_c - b)^2} \qquad (2)$$

The distribution constant, K_d, which involves undissociated and undimerized salicylic acid then becomes

$$K_d = \frac{C_w - a}{C_c - b} \qquad (3)$$

When the concentration of acid in cyclohexane is so low that b may be assumed to be negligibly small compared to C_c then (3) becomes

$$K_d = \frac{C_w - a}{C_c} \qquad (4)$$

Under these conditions equations 1, 2 and 4 may be combined to give

$$\frac{C_w}{C_c} = K_d + \sqrt{\frac{K_i K_d}{C_c}}$$

Hence, if dimerization can be neglected in the regions of extreme dilution a plot of C_w/C_c *vs.* $\sqrt{1/C_c}$ should be linear with a slope of $\sqrt{K_i K_d}$ and an intercept of K_d.

In Fig. 1 the curves obtained at the various temperatures are shown. Values of K_d and K_i were calculated from the linear portion of each plot; and then with these values, from the data in the curved region, the K_{dim}' s were calculated. These are shown in Table II.

TABLE II

EQUILIBRIUM CONSTANTS INVOLVED IN THE DISTRIBUTION OF SALICYLIC ACID BETWEEN CYCLOHEXANE AND WATER

Temp., °C.	Ionization constant $K_i \times 10^{-3}$	Distribution coefficient K_d	Dimerization constant K_{dim}
24.00	1.78	10.4	1393
29.50	2.32	7.25	619
32.00	2.68	6.42	446
36.00	3.18	5.05	243
40.05	3.91	3.98	143
47.13	5.18	2.80	61.0
55.00	6.88	1.83	23.7

The plots of log K *vs.* $1/T$ for each of the equilibrium constants gave good straight lines. The average deviation of the points from a straight line in each case was less than five parts per thousand. From the slopes of these lines, the corresponding values of $\Delta H°$ were calculated in accordance with the van't Hoff equation. These are listed in Table III. Values of $\Delta F°$ and $\Delta S°$ were also calculated and are included in Table III.

Discussion

Most of the previous determinations of the ionization constant of salicylic acid in water have been made at 25°.[2,3,4,5,6] All of the values noted by different investigators lie close to 1.0×10^{-3} at this temperature, while in this investigation 1.9×10^{-3} was observed. The reason for this difference is not known. It does not seem likely that the small amount of cyclohexane dissolved in the water would be enough to give rise to appreciable error. Also, since the value of K_i was obtained in the extremely dilute solution region, any discrepancy cannot be attributed to the deviation of the activity coefficients from unity. The heat of ionization is also much greater than that reported by Bradley and Lewis.[4] There are several excellent review articles concerned with the hydrogen bond and dimerization in which thermodynamic con-

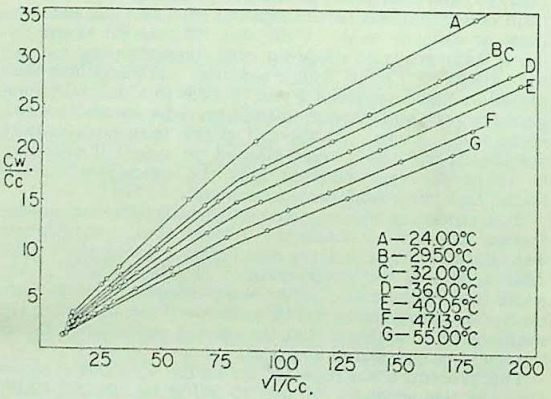

Fig. 1.—Graphical data from which ionization, distribution, dimerization constants can be calculated.

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TABLE III

THERMODYNAMIC VALUES OBTAINED IN SALICYLIC ACID–CYCLOHEXANE–WATER SYSTEM

Heat of ionization, 8150 cal./mole; heat of distribution, −10500 cal./mole; heat of dimerization, −24500 cal./mole.

	Free energy change (cal./mole)			Entropy Change (cal./mole degree)		
Temp., °C.	Ionization	Distribution	Dimerization	Ionization	Distribution	Dimerization
24.00	3738	−1383	−4268	14.9	−30.7	−68.1
29.50	3652	−1190	−4170	14.9	−30.7	−67.2
32.00	3595	−1128	−3705	14.9	−30.7	−68.1
36.00	3528	−996	−3370	15.0	−30.7	−68.3
40.05	3452	−859	−3082	15.0	−30.7	−68.4
47.13	3330	−655	−2611	15.1	−30.7	−68.3
55.00	3250	−395	−2068	14.9	−30.8	−68.4

stants are calculated and experimental methods discussed.[7-9] One objection to the distribution method is the possibility that the small amount of water present in the organic layer will form a hydrate with the acid being studied, increasing the solubility of the acid appreciably over that in the anhydrous organic solvent (see Lassettre[7]). Consequently, the solubility of salicylic acid in both anhydrous and water-saturated cyclohexane was investigated, but no significant difference found. Another objection is that the solvent in which the dimerization is taking place will influence the dimerization to some extent, and therefore the values obtained from solution studies will not necessarily agree with those from vapor studies. Indeed, the fact that the acid dissolves in the solvent indicates that some interaction between the two must take place and that the acid molecules will be partially solvated. Moelwyn-Hughes, Davies and their colleagues[10,11] have found that the magnitude of this effect is a function of the dielectric constant of the solvent, with the values of the heat and entropy of dimerization obtained by distribution methods approaching the vapor method values as the dielectric constant of the solvent decreases. In this respect cyclohexane should give better values than benzene or carbon tetrachloride.

Allen and Caldin have compiled values for the entropy and enthalpy changes involved in the dimerization of many different acids. For aliphatic acids, vapor phase measurements give values of $\Delta S°$ of about −36 e.u., and for $\Delta H°$ about −14 kcal./mole. They found that the value of $\Delta S°$ was in good agreement with the value based on the change in translational and rotational degrees of freedom in dimerization. In solution, as expected, the values are higher, $\Delta H°$ being about −8 kcal./mole and $\Delta S°$ ranging from −15 to −22 e.u. with concentrations expressed in moles/l. units or −21 to −28 in atmospheres. This variation in the entropy change then gives a measure of the increase in order of the monomers due to partial solvation.

Relatively little work has been done on aromatic acid. Many years ago Hendrixson[12] measured the $\Delta H°$ for both benzoic acid and salicylic acid by the investigation of the distribution of these acids between water and benzene, and water and chloroform. The values of $\Delta H°$ obtained for benzoic acid were −8.35 kcal./mole for the chloroform and −8.71 kcal./mole for the benzene systems. These values are in good agreement with those determined later by other investigators using different methods.[13,14]

The values of $\Delta H°$ for salicylic acid obtained by Hendrixson were −5.63 kcal./mole for benzene and −7.68 kcal./mole for chloroform.

The values obtained for $\Delta S°$ and $\Delta H°$ in this investigation of salicylic acid not only are considerably different from those obtained by Hendrixson, but they are also much different from the general values obtained for other acids. In the general reaction 2 monomer → dimer, the total entropy change can be considered to be made up of two parts.[15] The first is the change due to the translational and rotational degrees of freedom, and the second is the change due to the vibrational degrees. The first term must be negative since three translational and three rotational degrees of freedom are lost on association. The vibrational contribution, on the other hand, is positive since new vibrational degrees result from the association process. The value of the total entropy change on association for salicylic acid is about equal to the translational and vibrational contribution expected. The vibrational term, then, must be quite small indicating that the dimer bonds are very strong. This is consistent with the high value of the heat of dimerization observed.

DALLAS, TEXAS

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[Contribution from the Division of Chemical Development, Tennessee Valley Authority[1]]

Heat of Solution of Monocalcium Phosphate Monohydrate

By Edward P. Egan, Jr., Basil B. Luff and Zachary T. Wakefield

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The heat of solution of monocalcium phosphate monohydrate(c) in phosphoric and hydrochloric acids was measured as a function of acid concentration at 25°. The hypothetical heat of solution at infinite dilution could not be fixed closer than within the range −3 to −4 kcal. mole^{-1}.

As part of a long-range study of the thermodynamic properties of the calcium phosphates, the heat of solution of monocalcium phosphate monohydrate in acid was measured as a function of the concentration of the solvent. The final value sought was the heat of solution at infinite dilution.

Two solvents, solutions of hydrochloric acid and of phosphoric acid, were used on the naive assumption that two independent extrapolations to zero concentration of acid thus could be obtained.

Materials and Apparatus.—The solution calorimeter and the method of preparing the monocalcium phosphate monohydrate have been described.[2]

The volume of acid solution was 850 ml. in each measurement. The acid was weighed from a special volumetric flask.

The samples of monocalcium phosphate monohydrate, 4 to 8 g., were suspended below the stirrer in thin-walled glass bulbs about 3.5 cm. in diameter that were sealed to a glass rod extending through the hollow stirrer shaft. The bulbs were broken against the bottom of the calorimeter flask at the beginning of the dissolution period. The calorimeter system was calibrated electrically immediately before and after the dissolution. The initial temperature was adjusted so that the dissolution ended within a few hundredths of a degree of 25°, and no temperature corrections were necessary. The ice point was taken as 273.16°K., and one defined calorie as 4.1840 abs. j. No trend of ΔH with change in weight of salt was observed.

Observations.—The observed heats of solution are listed in Table I, and the average values at each concentration of acid are plotted in Fig. 1. The curves in Fig. 1 do not follow the theoretical linear relation for low-valent electrolytes at high dilutions.[3] Some of the necessary information is lacking for an extended Debye–Hückel extrapolation at low concentrations of solvent acid.

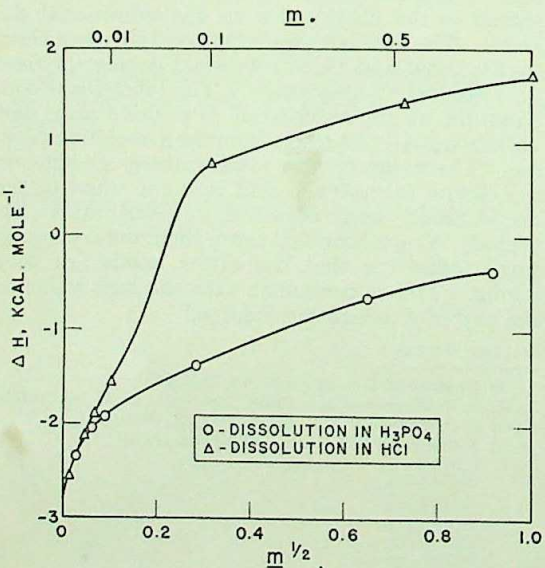

Fig. 1.—Heat of solution of $Ca(H_2PO_4)_2 \cdot H_2O$(c).

Table I

Heat of Solution of Monocalcium Phosphate Monohydrate in Phosphoric and Hydrochloric Acids

Dissolution in H_3PO_4			Dissolution in HCl		
Molality of acid	ΔH, cal. mole^{-1} Obsd.	Av.	Molality of acid	ΔH, cal. mole^{-1} Obsd.	Av.
0.0008	−2338	−2338	0.0002	−2543	−2543
.0040	−2033	−2035	.0022	−2121	−2121
	−2030				
	−2042		.0054	−1888	−1894
				−1899	
.0083	−1899	−1908			
	−1904		.0109	−1563	−1542
	−1921			−1521	
.079	−1391	−1387	.101	765	767
	−1398			769	
	−1372				
			.534	1410	1411
.429	−611	−665		1412	
	−678				
	−705		1.038	1718	1708
				1711	
.843	−351	−357		1696	
	−362				

A power series equation expressing ΔH as a function of $m^{1/2}$ extrapolates to a value of −2750 cal. mole^{-1} for ΔH at zero m. A plot of ΔH as a function of $m^{1/3}$ decreases the curvature of the lines, and a linear extrapolation through the ΔH values at the four lowest concentrations yields −2850 cal. mole^{-1} for ΔH at zero m. The observed ΔH, extrapolated to infinite dilution, is taken as −2800 cal. mole^{-1}. Since the curves in Fig. 1 approach the axis rather steeply, an extrapolation to zero m probably represents a lower limit in absolute magnitude for the heat of solution at infinite dilution.

The difference between the heats of solution in the two acids at the same molality is approximately constant at 2000 cal. mole^{-1} when the molality is greater than 0.1. The ΔH in solutions of hydrochloric acid is driven in the endothermic direction by an amount that apparently is equivalent to the endothermic heat of solution of calcium chloride. At molalities of less than 0.1, there is insufficient chloride ion in the solution of hydrochloric acid to

(1) Article not copyrighted.

(2) E. P. Egan, Jr., Z. T. Wakefield and K. L. Elmore, This Journal, 78, 1811 (1956).

(3) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, N. Y., 1943.

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form calcium chloride with all the calcium, and the heats of solution approach those in solutions of phosphoric acid.

Substitution of the heats of formation, $Ca(H_2PO_4)_2 \cdot H_2O(c)$, $-816{,}820$; $Ca^{++}(aq)$,[4] $-129{,}770$; $H_2O(liq)$,[4] $-68{,}317$; $H_2PO_4^-(aq)$,[5] $-311{,}320$ cal. mole^{-1} in the equation

$$Ca(H_2PO_4)_2 \cdot H_2O(c) + (aq) = Ca(H_2PO_4)_2 \cdot H_2O(aq) = Ca^{++}(aq) + 2H_2PO_4^-(aq) + H_2O(liq)$$

yields a value of -3910 cal. mole^{-1} for the heat of solution of $Ca(H_2PO_4)_2 \cdot H_2O(c)$ at infinite dilution. This value represents the difference between large numbers; also, one of the values used in its derivation—the heat of formation of $H_2PO_4^-(aq)$—is uncertain. With the uncertainty involved in the extrapolation of the observed heats of solution to infinite dilution, the hypothetical heat of solution of $Ca(H_2PO_4)_2 \cdot H_2O(c)$ at infinite dilution can be fixed no closer than within the range -3 to -4 kcal. mole^{-1}.

WILSON DAM, ALA.

(4) F. D. Rossini, D. D. Wagman, W. H. Evans, S. Levine and I. Jaffe, "Selected Values of Chemical Thermodynamic Properties," National Bureau of Standards Circular 500, U. S. Govt. Printing Office, Washington, D. C., 1952.

(5) Derived from the heat of formation of H_3PO_4 (aq), $-309{,}440$ cal. mole^{-1}, and the heat of the first ionization of H_3PO_4, -1880 cal. mole^{-1}, as reported by T. D. Farr, Tennessee Valley Authority, *Chem. Eng. Rept.* No. 8 (1950).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

Electrochemical Behavior of Aromatic N-Nitrosohydroxylamines

BY PHILIP J. ELVING AND EDWARD C. OLSON

RECEIVED JANUARY 9, 1957

The electrochemical behavior of three aromatic N-nitrosohydroxylamines was studied: N-nitrosophenylhydroxylamine N-nitroso-α-naphthylhydroxylamine and N-nitroso-*p*-xenylhydroxylamine, whose ammonium salts are known as cupferron, neocupferron and *p*-phenylcupferron, respectively; the last is a new compound. Three well-defined polarographic waves can occur in the *p*H region from −0.4 to 12. The first wave split (change from wave I to II) results from a tautomeric equilibrium between the nitroso hydroxy and amine oxide forms; the second wave split (change from wave II to III) is due to a typical acid–anion equilibrium. Coulometric studies, and isolation and identification of major reduction products by macroscale electrolysis at controlled potential indicate that the reduction in acidic solution (waves I and II) proceeds by a process, or processes, involving a total of 6 electrons to the aromatic hydrazine. In alkaline solution (wave III) only 4 electrons are involved with the final product being the aromatic hydrocarbon; the mechanism proposed has been substantiated by following the change in *p*H of the solution with electrolysis of the nitrosohydroxylamine. The apparent discrepancies in previous work have been elucidated.

A systematic study of the polarographic and coulometric behavior of N-nitrosophenylhydroxylamine,[1] N-nitroso-α-naphthylhydroxylamine (neocupferron) and a new compound, N-nitroso-*p*-xenylhydroxylamine (*p*-phenylcupferron), usually added as the ammonium salts, was undertaken to elucidate the reduction pattern and to resolve apparent differences in the literature.[2,3] Such an investigation also served as background for the development of analytical methods including amperometric titration methods employing cupferron as titrant.

Previous polarographic study[2] of N-nitrosophenylhydroxylamine indicated two waves in the *p*H range from 1.1 to 12.5. A similar study[3] of N-nitroso-α-naphthylhydroxylamine, the abstract of which appeared after the present investigation was underway, described four polarographic waves in the same *p*H region; the apparent differences in behavior between the two closely related structures was not too convincingly explained; even so, the explanations involved selective emphasis. Attempted coulometric studies were unsatisfactory and the results were not given.[3]

(1) The ammonium salt which is the form in which the compound is usually used, is called cupferron; for convenience, this name will hereafter be used to designate both the compound and its ammonium salt. The names, neocupferron and *p*-phenylcupferron, apply and will be used in the same sense.

(2) I. M. Kolthoff and A. Liberti, THIS JOURNAL, **70**, 1885 (1948).

(3) C. Calzolari and A. Donda, *Ann. Chim. (Rome)*, **43**, 753 (1953).

Polarographic Behavior[4]

Figures 1 and 2 and Table I summarize the variations of half-wave potential, $E_{1/2}$, and of limiting

TABLE I

DIFFUSION CURRENT CONSTANTS OF AROMATIC N-NITROSOHYDROXYLAMINES[a]

	$I = i_d/Cm^{2/3}t^{1/6}$		
*p*H	Cupferron	Neocupferron	*p*-Phenylcupferron
10% H_2SO_4	10.5	9.38	6.47
1.02	10.8	8.84	6.71
1.99	10.2	9.10	6.19
2.80	10.1	9.39	6.19
3.78	10.1	9.56	5.66

[a] These were measured on oxygen-free solutions, about 10 min. after mixing. The values, although reproducible, may be in slight error due to acid decomposition.

TABLE II

COMPOSITION OF MACILVAINE BUFFERS, IONIC STRENGTH = 1

$Na_2HPO_4.12H_2O$, g./l.	$H_3Cit.H_2O$, g./l.	KCl, g./l.	*p*H
1.4	20.6	74.5	1.99
14.7	16.7	68.7	2.80
27.6	12.9	62.8	3.78
36.9	10.2	55.5	4.72
45.2	7.7	48.9	5.69
58.9	3.7	40.4	6.76
69.6	0.6	32.9	7.58

(4) Detailed tables of experimental data can be secured from the author.

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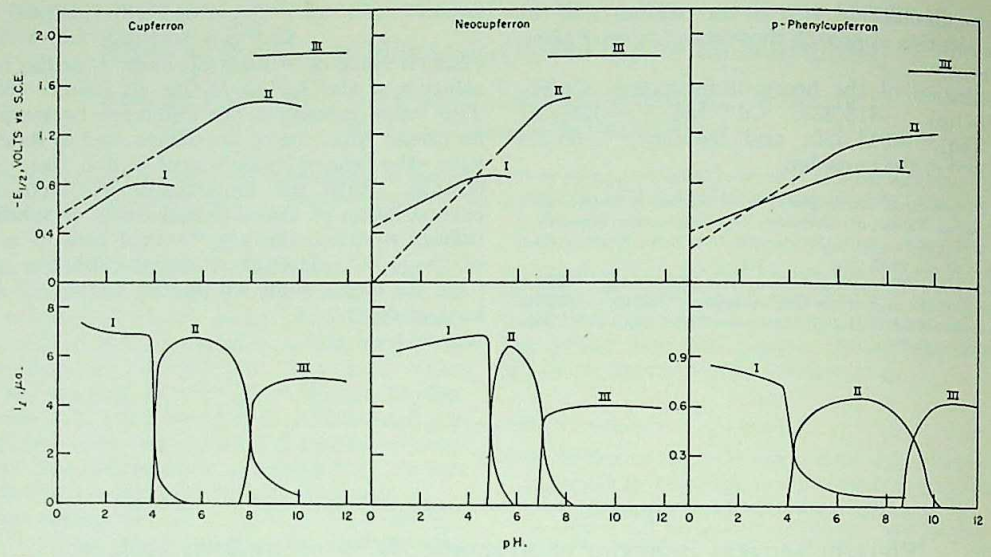

Fig. 1.—Variation with pH of half-wave potential and wave height of aromatic N-nitrosohydroxylamines. In each case curve I refers to wave I, II to wave II and III to Wave III. The concentrations are cupferron, 0.33 mM; neocupferron 0.32 mM; and phenylcupferron, 0.0062 mM.

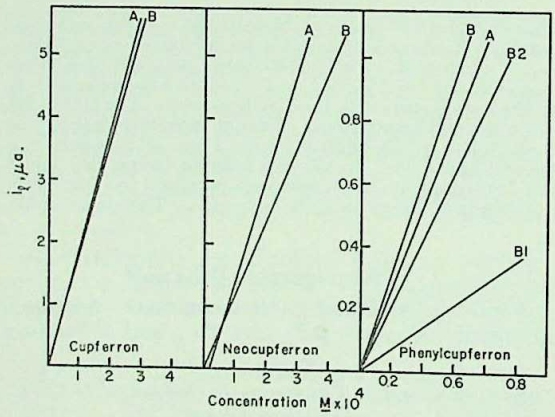

Fig. 2.—Variation of wave height with concentration for aromatic N-nitrosohydroxylamines. Cupferron: A, pH 2.80; B, pH 5.80. Neocupferron: A, pH 2.80; B, pH 5.69. Phenylcupferron: A, wave I at pH 2.80; B, sum of waves I and II at pH 6.76; B1, wave I at pH 6.76; B2, wave II at pH 6.76.

current, i_1, for each of the waves of the three cupferrons in solutions ranging in acidity from 10% sulfuric acid to pH 12. All three cupferrons give a single well-defined wave in strongly acidic solution. As the pH is increased, the wave splits into two at about pH 4 to 5. A second wave split occurs at somewhat higher pH. Extrapolation of the straight line portions of the plots of $E_{1/2}$ *vs.* pH to pH 0.00 for the first two waves of each compound leads to the expressions

Cupferron:

$$I^{E_{1/2}} = -0.42 - 0.132pH,\ II^{E_{1/2}} = -0.53 - 0.120pH$$
$$III^{E_{1/2}} = -1.85$$

Neocupferron:

$$I^{E_{1/2}} = -0.44 - 0.100pH,\ II^{E_{1/2}} = +0.03 - 0.201pH$$
$$III^{E_{1/2}} = -1.82$$

Phenylcupferron:

$$I^{E_{1/2}} = -0.40 - 0.081pH,\ II^{E_{1/2}} = -0.26 - 0.130pH$$
$$III^{E_{1/2}} = -1.75$$

The significance of the coefficient of the pH is not clear. A coefficient of about 0.12 indicates that $E_{1/2}$ varies with the square of the hydrogen ion concentration; for a reversible reaction, this might be interpreted to mean that two hydrogen ions are involved per electron transferred. $E_{1/2}$ for the third wave is pH-independent in all three cases. Kolthoff and Liberti[2] give for the similar equation for their first cupferron wave, $_IE_{1/2} = -0.58 - 0.128\ pH$; this would tend to indicate that their first wave and the present second wave are identical.

Wave height is directly proportional to concentration (Fig. 2); $E_{1/2}$ is unaffected by change in concentration. Increasing the ionic strength at pH 1.08 from 0.1 to 1.0 shifts $E_{1/2}$ about 0.02 v. in a more positive direction for each compound.

Current-controlling Processes.—Because of the importance of the nature of the current-controlling process (diffusion, rate or adsorption) relative to the possible origins and reduction mechanisms of the waves, the variations of i_1 with both drop-time and temperature were determined in pH regions where wave I alone, both waves I and II, wave II alone, and waves II and III were present.

The proportionality of i_1 of the first two waves for all three compounds to the square root of the height of the mercury column and the magnitudes of the temperature coefficients of i_1 for the same waves indicate that the processes resulting in these waves are diffusion controlled, with the following exceptions: wave II in the region where waves II and III coexist is at least partially kinetic in nature; lack of indication of any kinetic character for wave I may be due to inability to resolve that wave more clearly in the presence of wave II.

Calzolari and Donda[3] found their first, second and [illegible] neocupferron waves to be diffusion-

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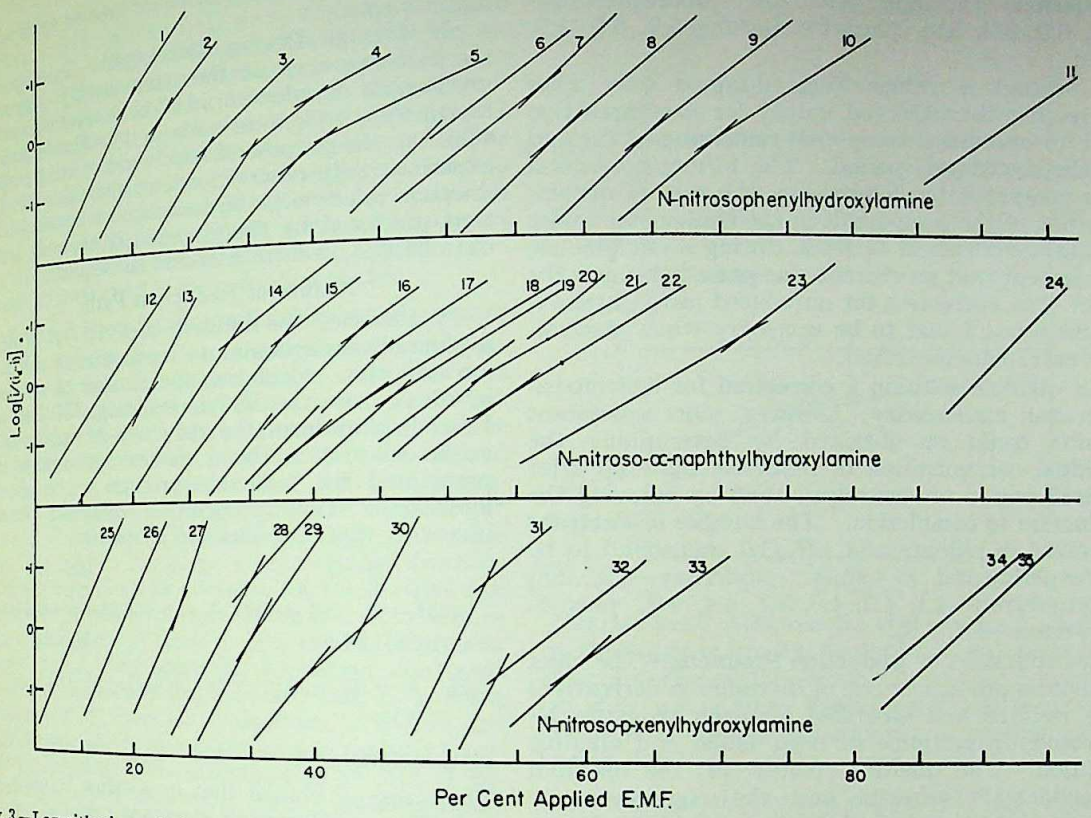

Fig. 3.—Logarithmic analysis of the polarographic waves of aromatic N-nitrosohydroxylamines over *p*H range −0.4 to 12.

Cupferron		Neocupferron		Phenylcupferron	
Curve	*p*H 10% H_2SO_4	Curve	*p*H 10% H_2SO_4	Curve	*p*H 10% H_2SO_4
1	1.02	12	1.02	25	1.02
2	1.99	13	1.99	26	1.99
3	2.80	14	2.80	27	2.80
4	3.78	15	3.78	28	3.78
5	4.10	16	4.10	29	4.72
6	4.72	17	4.72	30	5.69
7	5.69	18	4.98	31	6.76
8	6.76	19	5.20	32	7.58
9	7.58	20	5.38	33	9.81
10	11.73	21	5.69	34	11.73
11		22	6.76	35	
		23	11.78		
		24			

controlled at *p*H values where only a single wave was observed, *e.g.*, *p*H 1.9, 6.7 and 9.2; measurements made in regions of multiple waves did not yield interpretable results. Kolthoff and Liberti[2] found their first cupferron wave (already identified with the present wave II) to be kinetic controlled at *p*H 8.25 and the second wave to be diffusion controlled; they used the Brdicka–Wiesner equation[5] to calculate the kinetic current and found reasonable agreement between experimental and calculated values.

Logarithmic Analysis of the Waves.—Logarithmic analysis of the polarograms shows a multiplicity of processes to be occurring at the electrode (Fig. 3). Even in strongly acidic solution, the plot of log $[i/(i_d - i)]$ *vs.* E for each wave shows more than one straight-line segment.

The irreversible nature of the electrochemical reduction of aromatic N-nitrosohydroxylamines at the D.M.E. is shown by the values of the reciprocal slopes of the various straight-line segments; in no case does α, calculated from the slope as being equal at 25° to $0.059/\alpha$, have a value approaching 2. Likewise, the sum of the α values, when more than one process is involved, is never much greater than 2, although coulometric reduction (*cf.* next section) shows 6 electrons to be involved in the reduction in acidic solution and 4 in alkaline solution.

Coulometric and Other Macroscale Reductions

Coulometric *n* Values.—Coulometry at *p*H 3.50 show 6 electrons to be involved in the reduc-

(5) R. Brdicka and K. Wiesner, *Collection Czechoslov. Chem. Communs.*, **12**, 138 (1947).

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tion in acidic solution (experimental n values: cupferron—6.1, 5.9, 5.9, 5.9; neocupferron—5.8, 6.0, 5.9, 5.9; phenylcupferron—5.9, 6.0, 5.9, 5.9).

Constant n values were obtained only after correcting the observed values for decomposition and for unreduced compound remaining at the end of the electrolysis period. The former correction was computed by determining the rate of decomposition of the compounds in the coulometer under conditions identical to those during a coulometric run except that no current was passed through the cell. The correction for unreduced nitrosohydroxylamine was found to be necessary when electrolysis rates were measured.

In alkaline solution a correction for decomposition was unnecessary; however, more consistent results could be obtained by determining the residual concentration of reducible material after a fixed period of electrolysis than by carrying the reduction to completion. The number of electrons involved in reduction at pH 11.7 was found to be 4 (experimental n values: cupferron—4.2, 3.8; neocupferron—4.1, 4.3, 4.0, 3.7, 4.4, 4.2; phenylcupferron—4.1, 3.8).

Identification of Reduction Products.—The chief reduction product or one of its common derivatives was isolated and identified for each aromatic N-nitrosohydroxylamine in both acidic and alkaline solution. The melting points of the isolated benzaldehyde adducts and the coulometric n values show conclusively that in acidic solution aromatic N-nitrosohydroxylamines are reduced by a process or combination of processes involving a total of 6 electrons to the corresponding aromatic hydrazine.

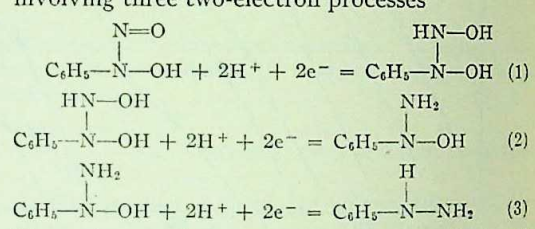
In alkaline solution the results indicate a four-electron reduction to the hydrocarbon. In all runs a strong odor of the aromatic hydrocarbon became apparent shortly after electrolysis began. In the cases of neo- and p-phenylcupferron, the naphthalene and biphenyl formed were filtered and recrystallized, and a melting point taken. In several runs the crude product was isolated, dried and weighed; between 40 and 60% of the weight of hydrocarbon anticipated was isolated. Low results could result from a number of factors, *e.g.*, the difficulties inherent in handling such small quantities of precipitate in the large apparatus required for electrolysis, the high vapor pressure of naphthalene and biphenyl coupled with the fact that a rapid stream of nitrogen was passed through the solution during the entire electrolysis period, and the possible reduction of the cupferrons by more than one mechanism resulting in the formation of some soluble reduction product; loss due to entrainment in the nitrogen stream would seem to be the major factor.

Several of the coulometer solutions after electrolysis under alkaline conditions were made strongly acidic and were then extracted several times with ether and chloroform to remove hydrocarbon and unreduced starting material. The resultant aqueous solution failed to give a test for an aromatic amine when tested with bromine water after neutralization, thus eliminating the possibility of reduction by a four-electron or other process to an aromatic amine.

pH Change During Electrolysis.—To examine the consequences of the subsequently proposed mechanism of reduction in alkaline solution, coulometric type runs were made in unbuffered alkaline solution, the purpose of which was to compare the experimentally observed rate of hydroxide ion production relative to hydroxylamine consumed to that predicted by the proposed mechanism. The data (Fig. 4) will be discussed subsequently.

Nature of Reduction Path

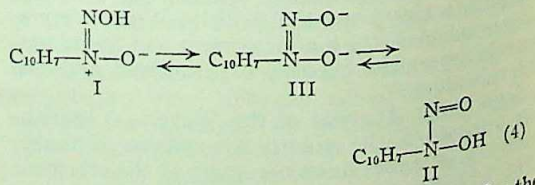
By assuming the diffusion coefficient of N-nitrosophenylhydroxylamine to equal that of benzoate ion and then calculating the number of electrons involved from the Ilkovic equation, Kolthoff and Liberti[2] considered the reduction of cupferron in acidic solution to be a six-electron process and postulated the reduction product to be phenylhydrazine. They proposed a reduction scheme involving three two-electron processes



They also concluded that in alkaline solution the reduction involves four electrons inasmuch as the polarographic wave height is two-thirds of that in acidic medium and suggested that the reduction product is an N-aminohydroxylamine.

Calzolari and Donda[3] in their similar neocupferron study suggested that the reduction proceeds in only two stages: a $4e^-$ reduction of the amine oxide or nitrosohydroxy forms to the aminohydroxylamine (combination of equations 1 and 2) and then a $2e^-$ reduction to the hydrazine (equation 3). The results of the present investigation, as subsequently discussed, indicate that both mechanisms may be operative in different restricted pH regions, but that a third mechanism is operative in the alkaline region.

Kolthoff and Liberti ascribed the first of the two cupferron waves they observed to reduction of the undissociated form of nitrosohydroxylamine and the second wave to reduction of its anion. Calzolari and Donda explain their four waves on the basis of a more complicated picture. The substitution of phenyl by naphthyl is assumed to facilitate the possibility of occurrence of both the amine oxide (I) and nitroso hydroxy (II) forms of neocupferron



They also assume the dissociation constant for the equilibrium I $\rightleftarrows$ III + H^+, to be greater than that

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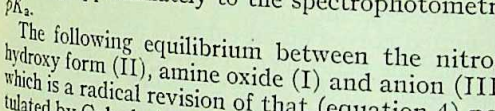
for II ⇌ III + H$^+$, I to be more readily reducible than II, and the anion III to be common for both equilibria. Their first wave, assumed due to 4e$^-$ reduction of I, decreases with increasing *p*H due to formation of anion III. The latter then recombines with H$^+$ to form the less highly dissociated II whose 4e$^-$ reduction results in the second wave. The third wave, which is very ill-defined, is ascribed to the further 2e$^-$ reduction of the 4e$^-$ reduction products of I and II. The fourth wave which occurs in the alkaline region and is more or less *p*H-independent is assigned to the reduction of III.

Relation of Wave Pattern to Equilibrium Processes

Since the aromatic N-nitrosohydroxylamines are weak acids, a double polarographic wave observed in the *p*H region corresponding to or somewhat greater than the pK_a of the nitrosohydroxylamine in question may be due to the fact that an acid and its anion are usually reduced at different potentials.[6] The pK_a of cupferron has been estimated[2,7a] as 4.28 in solution of low ionic strength; it is also given as 5.3.[7b] The large extent of acid dissociation has been cited as evidence for the existence of cupferron largely in the amine oxide rather than in the nitroso hydroxy form.[7b] For use in the present investigation, the apparent ionization constants were determined spectrophotometrically at an ionic strength of 1; these pK_a values are 4.11, 3.92 and 3.97 for cupferron, neocupferron and *p*-phenyl cupferron, respectively.[8] Examination of Fig. 1 reveals the appearance of a second polarographic wave for each compound in the *p*H region corresponding approximately to the spectrophotometric pK_a.

The following equilibrium between the nitroso hydroxy form (II), amine oxide (I) and anion (III), which is a radical revision of that (equation 4) postulated by Calzolari and Donda,[3] is, as subsequently discussed, in harmony with the data of Figs. 1 and 3, and furnishes a basis for the formulation of the reduction mechanism



II I III (5)

Waves I and II.—Since no decrease in diffusion current accompanies the first wave split, the latter would seem to result from the two acid forms of the cupferron which can exist in tautomeric equilibrium. Additional support for this postulate comes from the *p*H dependence of waves I and II, and the expected relative ease of reduction and the acidic strengths of the two forms. The apparently diffusion controlled nature of wave I may result from a relatively slow rate of interconversion of the two forms, as well as from failure to resolve waves I and II clearly. The present authors tend, in common with others, to favor the amine oxide being the predominant form in solutions varying

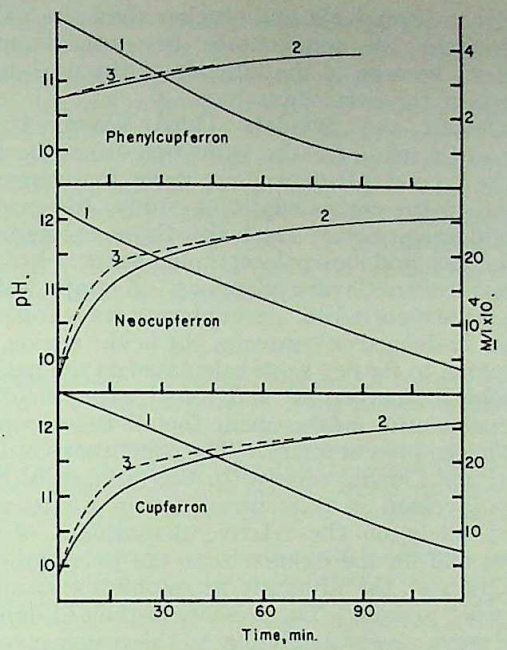
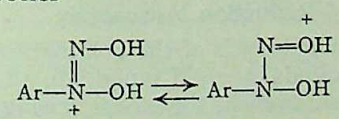


Fig. 4.—Rates of electrolysis and of increase in *p*H during the electrolysis of aromatic N-nitrosohydroxylamines in unbuffered alkaline solution: 1, rate of electrolysis; 2, calculated rate of increase in *p*H for liberation of 5 moles of hydroxide ion per mole of compound reduced; 3, measured rate of increase in *p*H.

from neutral to slightly acidic (*p*H 4); in more strongly acidic solution (*p*H 1–2) the nitroso hydroxy form appears to predominate.

The present assignment of wave I to the nitroso hydroxy form and of wave II to the amine oxide form is contrary to that of Calzolari and Donda, but is in harmony with the facts cited. The mechanism for the interconversion of I and II in acidic solution rather than proceeding through a common anion as postulated by Calzolari and Donda more likely occurs through the cyclic form resulting from hydrogen bonding or through a protonated species



(6)

The polarographic waves of the two tautomeric forms of cupferron coexist over a very narrow *p*H region; the height of the wave is the same before and after the first wave split (Fig. 1). For these reasons, an unfortunate choice of a buffer interval from *p*H 3.1 to 4.4 (at which the first wave has virtually disappeared) resulted in the failure of the previous investigators[2] to find an equilibrium corresponding to I ⇌ II. They postulated, and quite correctly for their data, a very large kinetic current for cupferron in the *p*H range of 4 to 8. However, on the basis of the present investigation it appears that their second wave actually corresponds to the third cupferron wave and that the *p*H of 7.2 reported by them as that where the two cupferron waves are equal, actually refers to the second and third waves. Quite commonly the apparent polarographic $\frac{1}{2}K$ of an acid is found to lie from a few

(6) I. M. Kolthoff and J. J. Lingane, "Polarography," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1952.
(7) (a) I. V. Pyatnitokii, *Zhur. Anal. Khim.*, 1, No. 2, 135–139 (1946); C. A., 41, 725 (1947); (b) L. F. and M. Fieser, "Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., 1956, pp. 605–607.
(8) P. J. Elving and E. C. Olson, THIS JOURNAL, 78, 4206 (1956).

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tenths to several *p*H units higher than the values determined by conductance or potentiometric methods because of the kinetics of the acid-anion process at the electrode surface.

Calzolari and Donda's Third Wave.—If allowance is made for the transition from the first to the second *p*H-dependent wave inadvertently missed in the earlier cupferron study, the present general wave picture reconciles those encountered in the two previous polarographic studies[2,3] of the aromatic nitrosohydroxylamines. A major difference is the reported $4e^-$ neocupferron wave followed by an ill-defined $2e^-$ wave in the acidic region,[3] as compared to the $6e^-$ wave calculated on the basis of analogy for cupferron[2] and found experimentally by coulometric measurement for all three cupferrons in the present study. The conclusions of Calzolari and Donda[3] relative to the number of electrons involved in their neocupferron waves were based solely on the relative magnitudes of the waves and on the opinion that the polarographic reduction of the aromatic nitrosohydroxylamines was a $6e^-$ process. The presence of their ill-defined third wave was probably due to the rather complicated buffer systems employed which resulted, as *p*H was changed, in considerable variation not only in ionic strength but also in the relative amounts of the various phosphate, citrate and borate species, many of which may interact with the reducible organic functional grouping to alter its ease of reduction and perhaps even to affect its polarographic wave pattern by separating the potentials required for the various steps in the over-all reduction process, *e.g.*, the sequence of three steps described in equations 1 to 3.

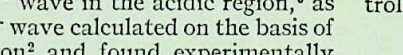
On the basis of the preceding discussion, it is interesting to compare the wave patterns found by Calzolari and Donda with the logarithmic analysis of the waves (Fig. 3); within the *p*H region in which they observed the appearance and disappearance of their third wave, the slope analyses show a change from three to two straight-line segments.

Reduction Mechanism

Logarithmic analysis of the polarographic waves of the compounds over *p*H range 1 to 12.5 (Fig. 3) indicates that, even in the steeply rising region of the polarographic wave which was the region analyzed, marked changes occur. Neo- and *p*-phenylcupferron show a single straight line in very strongly acidic media, but at *p*H 2 there are in all cases two distinct straight-line segments to the log plot. As the *p*H is increased, three straight-line segments appear in every case in the *p*H region immediately preceding the first wave split. After appearance of the second wave, analysis of the first wave gives only a single straight line, but analysis of the second wave again produces two straight lines. Only two straight lines are formed after the disappearance of the first wave.

Therefore, there seems to exist a *p*H region, *ca.* 2 to 7, in which the reduction proceeds *via* three $2e^-$ steps, as suggested for cupferron by Kolthoff and Liberti,[2] and *p*H regions, *ca.* 0 to 2 and *ca.* 7 to 10, in which a $4e^-$ reduction is probably followed by a $2e^-$ reduction, as suggested for neocupferron by Calzolari and Donda.[3] In very strongly acidic solution the reduction of the α-naphthyl and *p*-xenyl derivatives appears to take place in a single $6e^-$ step; no such region was found for the phenyl compound.

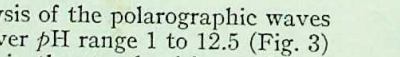
Wave in Alkaline Solution.—The third wave at higher *p*H represents the $4e^-$ reduction of the anion to the aromatic hydrocarbon. Inasmuch as logarithmic analysis of the polarographic waves after the second wave split gives only a single straight line, reduction in alkaline solution occurs in an effectively single $4e^-$ step, *i.e.*, the processes involving the transfer of all four electrons are controlled by a single step



(7)

If equation 7 is correct, 5 moles of hydroxide ion should be produced for each mole of aromatic N-nitrosohydroxylamine reduced. By carrying out the reduction at controlled potential in unbuffered alkaline solution, it was possible to follow both the increase in *p*H of the solution and the decrease in concentration of N-nitrosohydroxylamine. On comparing the measured *p*H as a function of time with that calculated from the measured decrease in concentration of reducible compound on the basis of 5 moles of hydroxide ion produced per mole of N-nitrosohydroxylamine consumed (Fig. 4), good agreement is found except in the region corresponding to the beginning of the electrolysis. Furthermore, by calculating the *p*H assuming production of 4 and 6 moles of hydroxide ion per molecule reduced and plotting the experimental and calculated curves on an enlarged scale, it is apparent that the experimental curve corresponds much more closely to the curve calculated for 5 hydroxyl ions per mole of reduced N-nitrosohydroxylamine than to either of the other curves.

It is possible to postulate a stepwise reduction to an aromatic hydroxyhydrazine followed by rearrangement in alkaline solution to the hydrocarbon, nitrogen and water since this rearrangement is known to occur in the presence of alkali[9]



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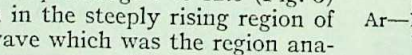

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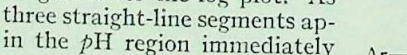

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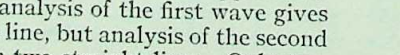

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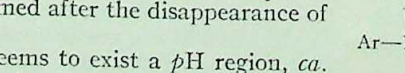

(12)

The over-all reaction (equation 12) is obviously identical with that previously proposed (equation 7).

(9) F. O. Rice and K. K. Rice, *J. Am. Chem. Soc.*, **93**, 270 (1908).

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Relative Ease of Reduction.—The general pattern for the waves of all three compounds is that of phenylcupferron being the most easily reducible and neocupferron the most difficultly reducible. This pattern correlates with the *p*-xenyl group being the most electron-withdrawing and the naphthyl group the least.

Possible Analytical Applications

Determination of an Individual Cupferron.—Since single well-defined polarographic waves are obtained for the aromatic N-nitrosohydroxylamines only below about *p*H 3.5 (Fig. 1), only the diffusion current constant values below *p*H 4 are pertinent for their polarographic determinations (Table I). The direct proportionality of diffusion current to concentration permits the ready determination of the individual compounds. The analytical precision ranges from about ±2 for cupferron to ±4 for neocupferron. The rapid decomposition of neocupferron in acidic solution is probably the major cause of the lack of precision in its polarographic determination.

The potential regions subtended by the polarographic waves of these compounds in acidic solution below *p*H 4 are so low, *i.e.*, −0.4 to −0.8 v. *vs.* S.C.E., that there should be few interferences among the organic compounds usually associated with the aromatic N-nitrosohydroxylamines.

$E_{1/2}$ values for the various cupferrons are sufficiently close to one another at a given *p*H to make the individual determination of any one cupferron in the presence of any other impossible, except perhaps by derivative polarography.

Basis for Amperometric Titration.—The previous discussion indicates use of aromatic N-nitrosohydroxylamines as reagents for titrations employing amperometric detection of the equivalence point to be practical. Kolthoff and Liberti[10] described the use of cupferron in the amperometric titration of Fe(III) and Cu(II), although the titration was preferably performed at potentials at which only the reduction current due to the metal ion was measured.

Use of neocupferron as a titrant is somewhat limited by its extremely rapid rate of decomposition in strongly acidic solution, as indicated by failure of the straight-line relation between concentration and i_l at *p*H 2.80 to pass through zero current at zero concentration (Fig. 2). Use of neocupferron is also limited by the fact that oxygen-free aqueous solutions of neocupferron decompose much more rapidly than do similar solutions of cupferron or phenylcupferron.

The use of *p*-phenylcupferron is restricted to the titration of minute amounts of metals since the solubility of the reagent is much less than that of either cupferron or neocupferron. An aqueous solution of the ammonium salt of N-nitroso-*p*-xenylhydroxylamine, saturated at 25°, contains only about 0.65 mg./ml. (approximately 3.1×10^{-3} *M*). The solubility of the free acid is, however, much less, being about one-fiftieth of this value. Oxygen-free aqueous solutions of this compound are considerably more stable than those of either cupferron or neocupferron. This increase in stability would be advantageous for the titration of very low concentrations of metals as would the lower solubility of the metal salts of *p*-phenylcupferron.[8]

Because of the low solubility of *p*-phenylcupferron and the instability of neocupferron, cupferron is considered best suited of the three N-nitrosohydroxylamines for the development of general titration procedures in spite of the somewhat greater solubility of its metallic salts. Procedures for amperometric titration of Group IVB metal ions with cupferron have been published.[11]

Experimental

Cupferrons.—G. F. Smith Chemical Co. reagent grade cupferron (ammonium salt of N-nitrosophenylhydroxylamine) was recrystallized twice from ethanol after treatment with Norit and finally once more from ethanol; the dried crystals (m.p. 162.5–163.5°) so purified are essentially 100.0% pure.[11a] Neocupferron (ammonium salt of N-nitroso-α-naphthylhydroxylamine) was prepared essentially by Smith's method[12] (m.p. 124–126°).

p-Phenylcupferron (ammonium salt of N-nitroso-*p*-xenylhydroxylamine) is a new compound which was prepared as follows: 10 g. of *p*-nitrobiphenyl was dissolved in a mixture of 500 ml. of 95% ethanol, 60 ml. of water and 6 g. of NH_4Cl; 10 g. of zinc dust was then added in one-gram portions with vigorous mechanical stirring and continuous cooling with tap water. After the reaction was complete, as indicated by a decrease in temperature of the reaction mixture, stirring was continued at room temperature for 30 min. The solution was then filtered into 30 ml. of glacial acetic acid, which appears to stabilize the hydroxylamine[13]; the resulting solution was then poured into a liter of cold water. The *p*-xenylhydroxylamine was filtered by suction and dissolved at once in 300 ml. of ether. After being dried over anhydrous sodium sulfate, the ether layer was filtered, cooled to 0° and saturated with ammonia gas. Freshly prepared *n*-butyl nitrite[14] was rapidly added dropwise, with vigorous mechanical stirring and passage of a rapid stream of ammonia, until 0.56 g. of butyl nitrite had been added for each gram of *p*-xenylhydroxylamine. The amonium salt of N-nitroso-*p*-xenylhydroxylamine which precipitated as very pale yellow platelets was filtered, washed with several portions of ether, and dried (m.p. 177–179°); yield was 64% of theory.

Anal. Calcd.: C, 62.13; H, 5.41; N, 18.23. Found: C, 62.33; H, 5.63; N, 18.23.

All three cupferrons were stored in the dark over ammonium carbonate; solutions of desired concentrations were prepared immediately before use by dissolving weighed portions of the crystalline salts in oxygen-free water.

Other Reagents.—Eastman Kodak white label grade tetramethylammonium bromide was purified by recrystallization. The salt was dissolved in the minimum amount of boiling reagent grade methanol and filtered, while hot, into an equal volume of reagent grade acetone. The mixture was then cooled to 0°; the crystals which formed were filtered, washed with cold 1:1 methanol–acetone and dried. This procedure gave a salt of sufficient purity to be used as a polarographic background electrolyte for potentials as negative as −2.2 v. *vs.* S.C.E.

A stock solution of tetramethylammonium hydroxide was prepared from purified bromide and freshly precipitated silver hydroxide.[15]

Nitrogen used for purging solutions of oxygen was first passed through chromous sulfate solutions to remove residual oxygen, then through distilled water to remove spray and finally through a portion of the solution to be purged

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(11) (a) E. C. Olson and P. J. Elving, *Anal. Chem.*, **26**, 1747 (1954); (b) P. J. Elving and E. C. Olson, *ibid.*, **27**, 1817 (1955); **28**, 251, 338 (1956).

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(13) H. Gilman and J. E. Kirby, THIS JOURNAL, **48**, 2190 (1926).

(14) A. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943.

(15) E. S. Peracchio and V. W. Meloche, THIS JOURNAL, **60**, 1770 (1938).

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in order to obtain vapor pressure equilibration. All other chemicals, including those used in buffer preparation, were of reagent or C.P. grade and were used without further purification; they were "polarographically pure."

Apparatus.—A Sargent Model XXI Polarograph, a Leeds & Northrup Model E Electro-Chemograph and a Fisher Elecdropode were used; potentials were checked with a Leeds & Northrup Type K potentiometer. A thermostated, jacketed H-type polarographic cell[16] containing a saturated calomel reference electrode was used. When changing from one temperature to another (20, 25 or 30 ± 0.1°), at least 24 hr. was allowed for the S.C.E. to reach thermal equilibrium. Capillaries, prepared from Corning marine barometer tubing, had $m^{2/3}t^{1/6}$ values at open circuit in water at 25° at 68 cm. mercury head of (1) 2.06, (2) 2.17 and (3) 2.04 mg.$^{2/3}$ sec.$^{-1/2}$; one capillary used only in drop-time studies had $m^{2/3}t^{1/6} = 1.75$ at 81 cm.

The coulometric apparatus was a modification of that of Lingane,[17] employing a water-jacketed (25 ± 0.1°) electrolysis cell, a stirred massive mercury electrode, a large external silver anode and an oxygen–hydrogen coulometer. The cathode potential was measured against S.C.E. with the Type K potentiometer.

A Beckman Model G *p*H meter was used to measure *p*H; in the alkaline region a Type E electrode was employed.

Polarographic Procedure.—A weighed portion of the reducible compound was dissolved in oxygen-free water and then diluted to the desired concentration with a stock solution of background electrolyte which had also been purged with nitrogen. The polarographic cell was rinsed twice with the test solution and then filled; the capillary was introduced and a rapid stream of nitrogen passed through the cell for 2 to 3 min., during which time the initial potential was set at the desired value. Nitrogen was passed over the solution during the polarographic run. All test solutions contained from 0.01 to 0.02% gelatin as a maximum suppressor. Potentials are reported *vs.* S.C.E. and at 25° unless otherwise noted; cell iR drops were negligible.

Constant ionic strength MacIlvaine buffers (Table II) were used between *p*H 2 and 7.6. Buffers of ionic strength 0.2 and 0.3 for use between *p*H 7 and 12 were prepared by titrating a solution of 0.05 M H_3PO_4 with 0.1 M tetramethylammonium hydroxide to the desired *p*H; both the acid and hydroxide solutions were approximately 0.1 M in tetramethylammonium bromide.

Coulometric and Macroscale Electrolysis Procedures.—The background electrolyte was deoxygenated in the electrolysis cell with a rapid nitrogen stream which was maintained throughout the experiment. The cathode mercury was then added; the bridge from the reference S.C.E. was adjusted so that it just touched the vigorously stirred mercury surface; the gas coulometer, in which the solution had just been saturated with hydrogen and oxygen,[17] was connected in series with the cell. The potential of the mercury cathode was made several tenths of a volt more negative than that at which the run was to be made; electrolysis was continued until the last traces of reducible impurities had been removed as indicated by the decrease in current.

Without breaking the circuit, the applied potential was reduced until the cathode potential attained the desired value; the coulometer buret was read; the deoxygenated sample solution was added to the cell and the potential readjusted to the desired value which was maintained during electrolysis.

After electrolysis had proceeded for 2.0 to 2.5 hr., the circuit was opened, a sample of the cell solution withdrawn and the residual aromatic N-nitrosohydroxylamine concentration determined polarographically. From the decrease in concentration and the volume of gas evolved, the number of electrons involved in the electrode reaction was calculated after making the necessary corrections,[17] including, if required, those for the homogeneous decomposition of the cupferron. In addition, the main product of the electrolytic reduction was isolated and identified as follows.

In the case of an acidic solution, the solution was drained from the cell and 2 or 3 drops of benzaldehyde was added followed by sufficient ethanol to take the benzaldehyde into solution; the mixture was then set aside. In all cases a precipitate appeared within 15 or 20 min.; however, additional time was allowed for the reaction to proceed to completion. After about 2 hr., an equal volume of water was added and the mixture cooled to 0° in an ice-bath. The precipitate was isolated and recrystallized at least twice from ethanol-water mixture; after drying, its melting point was determined. The benzaldehyde adducts isolated from the solutions of the products formed by electrolysis in acidic solution had the following melting points (literature values in parentheses for the RHN–NH_2–benzaldehyde condensation products where R is phenyl, α-naphthyl or *p*-xenyl): cupferron, 156–158° (155–156°); neocupferron, 143–144° (144–145°); *p*-phenylcupferron, 151–152° (153°).

In alkaline solution, the reduction product precipitated from the electrolysis solution and could be isolated by filtration. The product precipitated from neocupferron solution melted at 78–79° (m.p. of naphthalene, 80.2°) and the product from *p*-phenylcupferron solution at 68–69° (m.p. of biphenyl, 69–70°).

Acknowledgment.—The authors wish to thank the Atomic Energy Commission which helped support the work described.

ANN ARBOR, MICHIGAN

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND LABORATORY FOR NUCLEAR SCIENCE OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

A Spectrophotometric Study of the Indium–Bromide Complex Ions[1]

BY EUGENE A. BURNS AND DAVID N. HUME

RECEIVED JULY 9, 1956

The aqueous bromide complexes of indium have been investigated by means of ultraviolet spectrophotometry. The spectra obtained can best be interpreted by terms of the mono-, di-, tri- and tetrabromoindium ions whose stepwise formation constants have been evaluated at an ionic strength of 4.00 M. Analysis of the data by five distinct methods gives average values for the stepwise formation of $InBr^{++}$, $InBr_2^+$, $InBr_3$ and $InBr_4^-$ of 120, 19, 4 and 7, respectively.

In the past three years, fourteen articles have appeared in the literature concerning the nature of indium(III) in halide media, twelve specifically dealing with the bromide system. Table I lists the values of the consecutive formation constants of the indium bromide system observed by these workers, together with the values obtained in this investigation. The considerable lack of agreement among previous workers prompted the present investigation using spectrophotometric methods which are not subject to some of the difficulties in other methods.

(1) Abstracted from a thesis submitted by Eugene A. Burns in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Massachusetts Institute of Technology, May 4, 1956.

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TABLE I

COMPARISON OF REPORTED SUCCESSIVE FORMATION CONSTANTS OF THE INDIUM–BROMIDE SYSTEM

Investigator	Method	Ionic strength	k_1	k_2	k_3	k_4
Hepler and Hugus[2]	*p*H	Vary	159			
Schufle and Eiland[3]	Ion exchange	1.00	16	3.8	5.0	
DeSesa[4]	Potentiometric	Vary	65			
Sunden[5]	Potentiometric	2.00	95	3.8		
Sunden[6]	Extraction		85	4.7		
Cozzi and Vivarelli[7]	Polarography	2.00	6300	10		
Carleson and Irving[8]	Ion exchange	0.691	103	12.1	1.5	
Irving and Rossotti[9]	Extraction	1.00	114	19.1	2.3	0.2
This investigation	Spectrophotometric	4.00	120	19	4	7

Experimental

Metallic indium was obtained both from the Indium Corporation of America, Utica, N. Y. (99.97% pure) and from Fisher Scientific Company, N. Y. (99.9+% pure). The metal was dissolved in concentrated nitric acid and fumed down to near dryness with perchloric acid five times. The resulting solutions were tested for the presence of chloride and nitrate ions. It was observed that every attempt to dissolve indium metal in perchloric acid (which proceeded slowly) caused the reduction of some perchlorate to chloride. The dissolving of indium in 70% perchloric acid proceeded fairly rapidly if it was performed in a platinum dish, but still there was a detectable amount of chloride formed. The molarity of the indium was checked gravimetrically by precipitation with ammonium hydroxide followed by ignition at 1000°. The perchloric acid concentration was calculated by titration with standard sodium hydroxide to a phenolphthalein end-point and subtraction of the known equivalents of indium that were present.

Fisher C.P. sodium perchlorate (once recrystallized) and Mallinckrodt analytical reagent sodium bromide and perchloric acid were the chemicals employed.

All absorbance measurements were made using a Beckman model DU quartz photoelectric spectrophotometer with an ultraviolet attachment in a room whose temperature was controlled at 21.7 ± 0.6°. Matched silica cells of 0.100, 1.000 and 10.00 cm. lengths were employed. The corrections for scattered light were determined by observing the differences in absorbance of water when present in each of the cells and then applied to the appropriate observed absorbance in each cell.

Results

The solutions of indium perchlorate, and varying amounts of an excess of sodium bromide, gave spectra with maxima between 220 and 235 mμ, depending on the concentration of the two reactants. The initial studies showed that the absorption of the solutions changed with time, and on standing overnight the solutions became yellow in color. Chemical tests proved this to be due to free bromine being formed.

Several factors in the production of bromine were examined qualitatively. It became evident that: (1) indium was not necessary; (2) the solution had to be acidic, for concentrated solutions of sodium perchlorate and sodium bromide were relatively stable and (3) sodium perchlorate had to be present. Air was shown not to be the cause of the difficulty and the possibility of chlorate impurity in the sodium perchlorate was eliminated. Indium appeared to catalyze the oxidation, since when the spectra of indium solutions containing excess bromide at high ionic strength were examined with reference to identical solutions, not containing indium perchlorate, it was observed that the peak at 270–280 mμ grew as a function of time and in 90 minutes completely obliterated the peak at 235 mμ.

The addition of small amounts of sodium sulfite (to give about 5×10^{-4} *M* sulfurous acid) eliminated the bromine absorption peak, and the solutions remained colorless for 12 to 24 hours. No evidence for complex formation between sulfite and indium was found under these conditions: the weak absorption spectrum of sulfite was unaffected by the presence of indium.

The complexing of indium with sulfate that is formed as the sulfite is oxidized by the bromine was also considered. Assuming all of the sulfite (10^{-4} *M* in the experiments described below) to be converted to sulfate, and taking Sunden's[5,6] values for the formation constants of the indium sulfate and bromide complexes, it was found that the ratio of $InBr^{++}$ to $InSO_4^+$ was over 3000. Thus, since it was observed that indium in sulfate media does not absorb in the regions examined, the amount complexed as the sulfate is negligible and will not affect the spectra of indium in bromide media.

In the initial exploratory work it was observed that, as would be expected from the plus three oxidation state of indium, the ionic strength of the solutions examined was quite an important factor. This pronounced effect is illustrated in Fig. 1, which shows the effect of ionic strength on the absorption spectra of indium in the presence of a large excess of bromide.

Continuous Variations.—To get a general idea of what complexes might be seen by their absorption, continuous variations experiments were done over a range of concentration, wave length and ionic strength. The results are shown in Fig. 2. It is known[10,11] that the method of continuous variations may not be valid if more than one absorbing complex is present or if the complex being studied is not fairly stable in comparison with the others. Inasmuch as it was shown later that more than one complex showed absorption in this region, and that the formation constants were not greatly different from each other, the system is not ideally suited to study by this method. The work is, however, sug-

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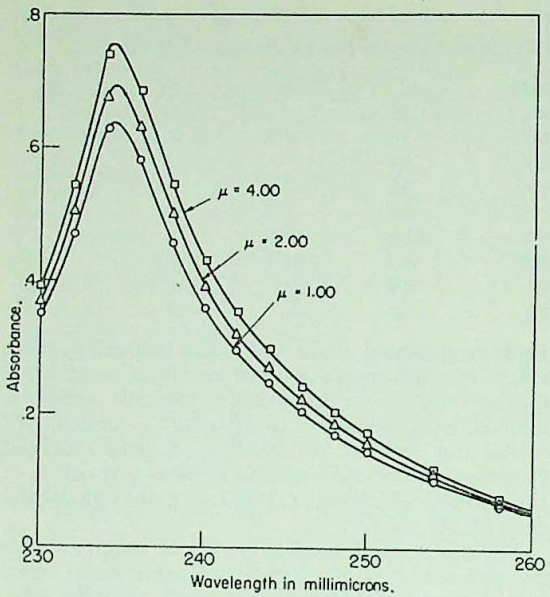

Fig. 1.—Spectra of indium in an excess of bromide as a function of ionic strength. Conditions: 2.50×10^{-4} *M* $In(ClO_4)_3$, 0.500 *M* NaBr, 0.100 *M* $HClO_4$, 1.00×10^{-4} *M* Na_2SO_3, 1.000 cm. silica cells.

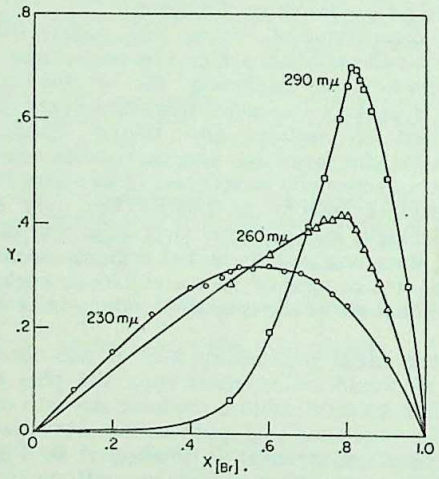

Fig. 2.—Typical continuous variations curves at varying concentrations, ionic strengths, acidities and wave lengths. 230 mμ: $(1 - x)(0.200)$ *M* $In(ClO_4)_3$, $(x)(0.0200)$ *M* NaBr, 0.197 *M* $HClO_4$, $\mu = 0.697$ *M*, and 1.000 cm. silica cells. 260 mμ: $(1 - x)(0.100)$ *M* $In(ClO_4)_3$, $(x)(0.100)$ *M* NaBr, 0.500 *M* $HClO_4$, 5.00×10^{-4} Na_2SO_3, $\mu = 2.100$ *M*, and 10.00 cm. silica cells. 290 mμ: $(1 - x)(1.00)$ *M* $In(ClO_4)_3$, $(x)(1.00)$ *M* NaBr, 0.796 *M* $HClO_4$, 0.00100 *M* Na_2SO_3, $\mu = 6.80$ *M*, and 1.00 cm. silica cells.

gestive that the mono- and tetrabromo complexes, and possibly others, are formed in solutions containing both indium and bromide ions.

Spectra of Indium in Excess Bromide.—Using the results of the experiments in the previous sections as a guide, the determination of the successive formation constants of the indium bromide complexes at an ionic strength of 4.00 *M* was attempted. An ionic strength of 4.00 *M* was chosen, since it would therefore be possible to have a maximum bromide concentration of 3.90 *M*, (all solutions were 0.100 *M* in perchloric acid). Higher bromide concentrations had been observed to lead to no significant further increase in the absorbance of the 235 mμ peak. The concentration of indium perchlorate was 2.5×10^{-4} *M*; sodium sulfite, 1.0×10^{-4} *M*; perchloric acid, 0.100 *M*; and the ionic strength was maintained with sodium perchlorate. The location of the peak was constant at 235 ± 1 mμ for the range of bromide concentration of 0.200 to 3.900 *M*. Approximately 15 minutes were required to obtain the spectrum of one of these solutions, beginning at higher and moving toward lower wave lengths. Absorption by bromide ion places a lower limit on the wave length at which the spectra can be measured. The slit width, which was often as wide as 1.2 mm., was always kept constant in the region of the maximum.

In order to obtain better resolution at shorter wave lengths, the indium concentration was increased ten-fold in some experiments and 0.100 cm. cells used. Figure 3 shows how the resulting decrease in background bromide absorption allows the spectra to be taken to shorter wave lengths and a wider range of concentrations to be studied. Good agreement between molar absorptiv-

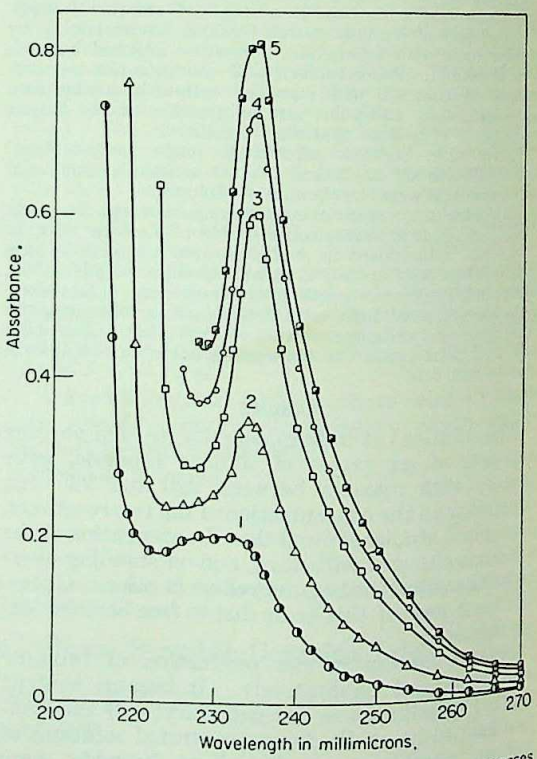

Fig. 3.—Spectra of indium in the presence of large excesses of bromide using 0.100 cm. silica cells. Conditions: 2.00×10^{-3} *M* $In(ClO_4)_3$, 0.100 *M* $HClO_4$, 5.00×10^{-4} *M* Na_2SO_3, $\mu = 4.00$ *M*. Curve 1, 0.100 *M* NaBr; curve 2, 0.200 *M* NaBr; curve 3, 0.500 *M* NaBr; curve 4, 1.000 *M* NaBr; curve 5, 3.90 *M* NaBr. When 1.00 cm. cells are used, the spectra have cutoffs between 225–234 mμ, depending on the concentration of bromide in the blank.

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ities (extinction coefficients) measured under the two sets of conditions.

Determination of the First Stability Constant.—Modified McConnell–Davidson[12] techniques were employed to evaluate the first two stability constants. In order to determine the first formation constant, an excess of indium was added to ensure that only three absorbing species were present: *i.e.*, In^{+++}, $InBr^{++}$ and Br^-. Assuming that all three species absorb, and incorporating the mass-action expression, $k_1 = (InBr^{++})/(In^{+++})(Br^-)$, the resulting expression can be derived for a specific wave length

$$\frac{ab}{A_0 - A_a - A_b} = \frac{1}{(\epsilon_\alpha - \epsilon_a - \epsilon_b)k_1} + \frac{a}{(\epsilon_\alpha - \epsilon_a - \epsilon_b)} \quad (1)$$

where ϵ_α, ϵ_a, and ϵ_b are the molar absorptivities of the complex, indic and bromide ions, respectively; a and b are the analytical concentrations of indic and bromide ions, respectively; A_0 is the observed absorbance of the solution containing the mixture of indium and bromide ions; and A_a and A_b are the absorbances of solution containing only a concentration of indium perchlorate and b concentration of sodium bromide, respectively. When $ab/(A_0 - A_a - A_b)$ is plotted *vs.* a, a straight line results, and the ratio of the slope to the intercept of the line is equal to the formation constant.

In the work performed in this section, each solution was 0.00200 M in sodium bromide, 0.100 M in perchloric acid, the concentration of indium perchlorate was varied from 0.006 to 0.100 M, and the ionic strength was maintained at 4.00 M by use of sodium perchlorate. The use of sodium sulfite was found to be unnecessary; bromide at these low concentrations was not appreciably oxidized. Table II shows the results of the McConnell–Davidson plots, all of which gave good straight lines.

TABLE II

McCONNELL–DAVIDSON DETERMINATION OF THE FIRST FORMATION CONSTANT

Wave length, mμ	$\epsilon_{InBr^{++}}$	ϵ_{Br^-}	$\epsilon_{In^{+++}}$	k_1
225.0	199.4	56.5	13.5	121
226.0	177.1	49.5	11.3	121
227.0	154.1	44.0	9.4	119
228.0	135.0	40.0	8.0	119
229.0	116.2	37.0	6.8	124
230.0	99.6	33.5	5.8	128
231.0	86.1	30.5	5.0	122
232.0	73.0	29.0	4.3	133
	Av. $k_1 = 123$		Std. dev. = 4.9	

Determination of the Second Stability Constant.—If the experimental conditions are altered slightly to give a small excess of bromide, the species $InBr_2^+$ will also be present. It is then possible to evaluate the second "stepwise" formation constant. If the second stepwise equilibrium is considered, the exact eq. 2 results

$$\frac{a}{D} = \frac{1}{(\epsilon_\beta - \epsilon_a - 2\epsilon_b)k_2} G + \frac{1}{(\epsilon_\beta - \epsilon_a - 2\epsilon_D)} \quad (2)$$

where $D = A_0 - A_a - A_b$, $k_2 = (InBr_2^+)/(InBr^{++})\cdot(Br^-)$, ϵ_β = molar absorptivity of the $InBr_2^+$ ion, and G is a function of the ligand concentration

$$G = \frac{1}{k_1 X^2} + \frac{1}{X} + \frac{(\epsilon_\alpha - \epsilon_a - \epsilon_b)a}{DX}$$

where X represents the equilibrium concentration of bromide. All that is needed is to plot a/D *vs.* G and k_2 can be determined from the resulting curve, for k_2 is equal to the intercept divided by the slope.

The spectra for indium in the presence of a slight excess of bromide (with water as the reference solution), for wave lengths 226–240 mμ at an ionic strength of 4.00 M were determined. The concentration of indium perchlorate was 2.00 mM, perchloric acid concentration was 0.100 M, and the bromide was varied at concentrations of 5.00, 10.00, 15.00, 20.00, 25.00 and 30.00 mM. It is obvious that the equilibrium concentration of halide and thus the values of G must be estimated from the six different estimated values of X. It was found that after the third approximation of X, a 10% difference in the estimated k_2 gave rise to less than half of 1% change in G, and less than 0.3% difference in the value of X. The equilibrium concentrations of bromide under the above conditions were calculated to be 4.24, 8.74, 13.37, 18.12, 22.92 and 27.73 mM, respectively. The approximation was performed only at 230 mμ; and since the resulting values of k_2 all differed by less than 10%, the above values of X were used at all wave lengths considered to calculate the function G. The results of the good straight lines that were obtained using this interpretation for the wave lengths 226–240 mμ are shown in Table III. The values of the molar absorptivities of the first complex at these wave lengths found in the determination of the first stability constant were used.

TABLE III

McCONNELL–DAVIDSON DETERMINATION OF THE SECOND FORMATION CONSTANT

Wave length, mμ	$\epsilon_{InBr^{++}}$	k_2
226.0[a]	1460	18.3
228.0[a]	1370	19.5
230.0	1310	18.6
232.0	1040	19.0
234.0	839	18.2
236.0	595	18.5
238.0	401	18.2
240.0	260	19.3

Av. $k_2 = 18.7$ $s = 0.51$

[a] Only 3 points determined this line.

Determination of Higher Complexes.—Further work was performed on solutions containing large excesses of bromide, in an effort to evaluate the stability constants of the higher complexes whose existence was suggested by the method of continuous variations. The data obtained were interpreted in a manner similar to that of Kingery and Hume[13]. At high halide concentrations, the stability constant for the highest complex can be determined on the basis of the reaction

$$InBr_r^{+3-r} + n Br^- = InBr_{r+n}^{+3-r-n} \quad (4)$$

(12) H. McConnell and N. Davidson, THIS JOURNAL, **72**, 3164 (1956).

(13) W. D. Kingery and D. N. Hume, *ibid.*, **71**, 2393 (1949).

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and

$$k_{r+n} = \frac{(InBr_{r+n}^{+3-r-n}}{(InBr_r^{+3-r})(Br^-)^n} \qquad (5)$$

If the higher complex is the only absorbing species, and the next lower complex is the only other species of indium present in appreciable amounts, an equation results

$$\log \frac{A_i}{A_L - A_i} = n(\log X_i) + \log k_{r+n} \qquad (6)$$

where A_i is the observed absorbance for a concentration X_i of bromide and A_L is the asymptotic limit of absorbance of A_i as X_i approaches infinity. By plotting $\log A_i/(A_L - A_i)$ *vs.* $\log X_i$, it is seen that the slope reveals the value of n, and the intercept, when $\log X_i$ is zero, is the formation constant, k_{r+n}. In this work, the bromide absorbs quite strongly due to its high concentration, and its absorbance was compensated for in the reference cell.

Figure 4 shows three typical curves in the determination of A_L. The plot of $\log A_i/(A_L - A_i)$ *vs.*

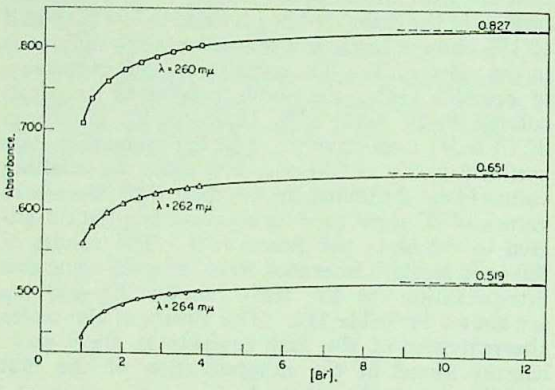

Fig. 4.—Typical determinations of the molar absorptivity. Conditions: 2.50×10^{-4} *M* $In(ClO_4)_3$, 0.100 *M* $HClO_4$, 1.00×10^{-4} *M* Na_2SO_3, $\mu = 4.00$ *M*, and 10.00 cm. cells.

$\log X_i$ was linear for 20 wave lengths between 235 and 270 mμ. All of these data were obtained using 2.50×10^{-4} *M* indium perchlorate, 0.100 *M* perchloric acid, 1.00×10^{-4} *M* sodium sulfite, and the bromide concentration was varied at 1.00, 1.20, 1.60, 2.00, 2.40, 2.80, 3.20, 3.60 and 3.90 *M*. Ten-centimeter cells enabled readings to be taken at wave lengths from 260 to 270 mμ, where it is felt the lower complex would not be absorbing, and readings were taken between 235 and 250 mμ with one-centimeter cells. Since the ratio $A_i/(A_L - A_i)$ was relatively constant in the two ranges for a particular bromide concentration, it can be concluded that the lower complex is not absorbing in the 235–250 range.

The formation constant for the addition of the last ligand was evaluated to be 6.1. The slope, 1.19, indicated that only one bromide was added.

The fact that the ratio $A_i/(A_L - A_i)$ at a particular value of X_i was relatively constant over the whole wave length range that was examined shows that the same species is absorbing throughout the range. The fact that the same method yielded a straight line shows that the method is valid, and hence the lower species does not absorb throughout the wave length range.

Since the continuous variation work suggested an $InBr_4^-$ species, it is reasonable to interpret the preceding work on the assumption that $k_{r+n} = k_4$. If this is the case, since $n = 1$, the lower species—*i.e.*, $InBr_3$—must exist in solution, and the third formation constant, k_3, can be determined by a difference technique. The fraction of the indium in the form of the fourth complex is

$$\frac{(InBr_4^-)}{(\Sigma In^{+++})} = \frac{k_1k_2k_3k_4X^4}{1 + k_1X + k_1k_2X^2 + k_1k_2k_3X^3 + k_1k_2k_4X^4} \qquad (7)$$

If $InBr_4^-$ is the only absorbing species, then the ratio $(InBr_4^-)/(\Sigma In^{+++})$ will equal A_i/A_L, where A_i and A_L have the same meaning as before. If the equilibrium concentration of bromide is large with respect to the equilibrium concentrations of the complexed indium, then the equilibrium concentration approximates the analytical concentration of bromide.

Absorbance measurements were taken as previously, with an ionic strength of 4.00 *M*, 2.50×10^{-4} *M* indium perchlorate, 1.00×10^{-4} *M* sodium sulfite, 0.100 *M* perchloric acid, and varying the sodium bromide concentration at 0.050, 0.100, 0.150, 0.200, 0.300, 0.400, 0.500, 0.600, 0.700 and 1.000 *M*. At these concentrations it was felt that the missing complex could be detected using the 1.000 and 10.00 cm. silica cells in the wave length ranges 240–250 and 260–270 mμ, respectively. Utilizing the limiting absorbances that had been determined before, the ratio A_i/A_L was determined for a particular bromide ion concentration as a function of wave length. With the exception of wave lengths below 244 mμ (particularly at low bromide concentrations), this ratio was constant.

Table IV lists the average values of the ratio A_i/A_L over the wave length regions examined as a function of the bromide concentration and cells employed. Since the values are in reasonably good agreement, it can be concluded that only one species is present and absorbing in these regions. The fact that the data obtained with the 10.00 cm. cells show a lower standard deviation—and give lower values for each respective bromide ion concentration, indicates that lower complexes are absorbing in the 240–250 mμ range, although not enough to change the ratio appreciably.

TABLE IV

FRACTION OF INDIUM COMPLEXED IN THE HIGHEST FORM

	1.000 cm. cells			10.00 cm. cells			
Br^-	n	f	s	n	f	s	k_1
1.000	5	0.858	0.013	10	0.854	0.003	23.0
0.700	7	.791	.004	6	.789	.004	10.0
.600	7	.755	.008	6	.749	.005	7.9
.500	5	.703	.004	6	.699	.004	7.0
.400	5	.629	.006	6	.624	.003	6.0
.300	4	.520	.005	6	.512	.003	5.3
.200	4	.351	.003	6	.341	.002	4.7
.150	4	.245	.004	6	.230	.003	4.4
.100	4	.126	.006	6	.115	.002	4.3
.050	4	.039	.006	6	.025	.002	4.1
Pooled std. dev. =			0.007			= 0.003	

Knowing k_1, k_2, k_4 and A_i/A_L as a function of the bromide concentration, it is possible to solve for k_3 (Table IV shows the resulting values of

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k_3. The diminishing trend with decreasing bromide concentration is believed to be caused by (1) errors in the "known" (k_1, k_2 and k_4) formation constants, and (2) amplification of a small effect by taking the difference of two large numbers. To avoid the latter effect only the results in the range 0.05 to 0.4 M bromide were averaged to give the most probable value of 4.8 for k_3.

Alternative Treatments of the Data.—The data of this investigation have been treated by several alternative methods described in a recent publication by Rossotti and Rossotti,[14] in order to compare the efficacy of the various methods used and to establish the best possible values of formation constants from the experimental results at hand.

In the first of these, by defining f_c as the fraction of the metal complexed as MX_c, we have

$$f_c = \frac{MX_c}{\Sigma M} = \frac{K_c X^c}{1 + \Sigma K_n X^n} \qquad (8)$$

where K_n is the over-all formation constant $k_1 \cdot k_2 k_3 \ldots k_n$. Taking logarithms, differentiating and substituting Bjerrum's $\bar{n}$ expression for the average number of ligands attached to the metal ion[15] we obtain

$$\frac{d(\log f_c)}{d(\log X)} = c - \bar{n} \qquad (9)$$

The continuous variations experiments indicate that the maximum value of c is probably 4; however, it is seen that this method just described will in turn evaluate c when data obtained during the determination of the second formation constant are employed in conjunction with the data of Table IV. Log f_c was plotted *vs.* log Br^- for bromide concentrations 0.050–1.000 M, as is shown in Fig. 5, and the slopes were determined as a function of the bromide ion concentration. The values of $c - \bar{n}$ are given in Table V, together with values of $\bar{n}$ (calculated assuming c to be 3, 4 and 5).

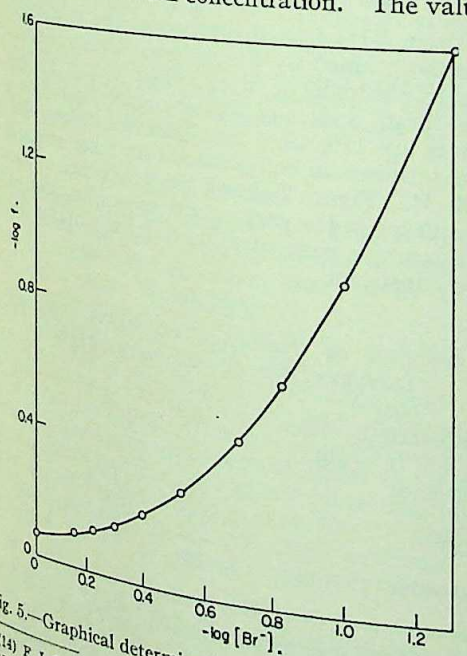

Fig. 5.—Graphical determination of the ligand number, $\bar{n}$.

(14) F. J. C. Rossotti and H. S. Rossotti, *Acta Chem. Scand.*, **9**, 1166 (1955).

(15) J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, 1941.

TABLE V

EVALUATION OF $\bar{n}$ VALUES

(Br^-)	$-\log f$	$-\log Br^-$	Slope	3-Slope	4-Slope	5-Slope
1.000	0.069	0.000	0.18	2.82	3.82	4.82
0.700	0.103	.155	.26	2.72	3.74	4.74
.600	.125	.222	.32	2.68	3.68	4.68
.500	.155	.301	.44	2.56	3.56	4.56
.400	.205	.398	.59	2.41	3.41	4.41
.300	.291	.523	.80	2.20	3.20	4.20
.200	.467	.699	1.24	1.76	2.76	3.76
.150	.638	.824	1.42	1.58	2.58	3.58
.100	.939	1.000	1.88	1.12	2.12	3.12
.050	1.602	1.301	2.34	0.66	1.66	2.66

$\bar{n}$ VALUES EVALUATED FROM DATA OBTAINED IN DETERMINATION OF SECOND CONSTANT

Indium $\times 10^3$	Total Bromide $\times 10^3$	Equilibrium bromide $\times 10^3$	$-\log Br^-$	$\bar{n}$
2.00	5.00	4.24	2.301	0.38
2.00	10.00	8.74	2.000	.63
2.00	15.00	13.37	1.824	.82
2.00	20.00	18.12	1.699	.94
2.00	25.00	22.92	1.602	1.05
2.00	30.00	27.73	1.523	1.14

Using the data obtained in the McConnell–Davidson determination of the second stability constant, $\bar{n}$ was calculated for a bromide range of 0.005–0.030 M.

Figure 6 shows the formation curve of indium in bromide medium: that is, $\bar{n}$ as a function of log Br^-.

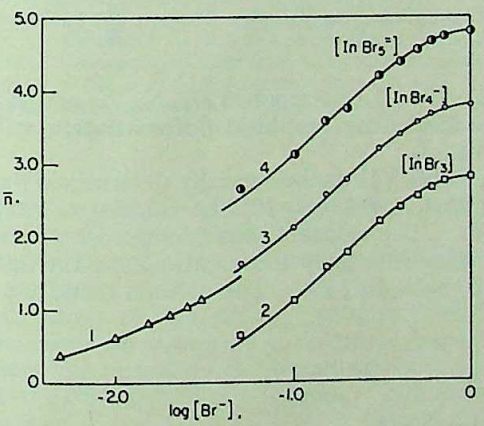

Fig. 6.—Formation curve of indium in a bromide medium. Curves 1, $\bar{n}$ calculated from data obtained in the determination of the second constant; 2, $\bar{n}$ calculated on the assumption that $InBr_3$ is absorbing species; 3, $\bar{n}$ calculated on the assumption that $InBr_4^-$ is absorbing species; 4, $\bar{n}$ calculated on the assumption that $InBr_5^=$ is absorbing species.

It is seen from this figure that assuming the absorbing species to be $InBr_3$ or $InBr_5^=$ leads to inconsistent results. A smooth curve can be drawn connecting the two sets of data only if $InBr_4^-$ is the species absorbing.

Using the values of $\bar{n}$ as a function of the bromide concentration, it is also possible to evaluate

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the formation constants by a graphical method outlined by Rossotti and Rossotti.[14]

$$J_1(X) = K_1 + \left(\frac{2-\bar{n}}{1-\bar{n}}\right) K_2X + \left(\frac{3-\bar{n}}{1-\bar{n}}\right) K_3X^2 + \left(\frac{4-\bar{n}}{1-\bar{n}}\right) K_4X^3 \ldots \quad (10)$$

The value of $J_1(X)$ when extrapolated to $X = 0$ is equal to k_1. In a similar manner, defining

$$J_2(X) = [J_1(X) - K_1]\left(\frac{1-\bar{n}}{2-\bar{n}}\right)\frac{1}{X}$$

it is seen that the value of $J_2(X)$ when extrapolated to $X = 0$ is equal to K_2, and so on for higher orders of $J(X)$.

Table VI lists the values of the $J(X)$ functions. When $J_3(X)$ was plotted *vs.* X, a very low value for K_3 was obtained which was felt to be in error. Only the values of $J_3(X)$ at low bromide concentrations were used in evaluating the intercept, at which concentrations very little $InBr_3$ exists, and they had twice been differentiated graphically. To obviate this problem, it was seen that all the values of $J_3(X)$ could be used if $J_3(X)$ were plotted *vs.* $[(4 - \bar{n})/(3 - \bar{n})](Br^-)$, and therefore the intercept would still equal K_3; but now K_4 could be evaluated, since it was equal to the slope of the resulting straight line. The fact that a relatively good straight line was obtained substantiates the fact that $InBr_4^-$ is the highest species existing in this system. The stepwise constants for the first four complexes were calculated to be 120, 19.0, 2.9 and 8.5, respectively.

The data obtained showing the fraction of indium complexed as $InBr_4^-$ can be used to evaluate the formation constants in yet a different manner. Rossotti and Rossotti[14] have derived the expression

$$H_0(X) = \frac{X^4}{f} = \frac{1}{K_4} + \frac{K_1}{K_4}X + \frac{K_2}{K_4}X^2 + \frac{K_3}{K_4}X^3 + X^4 \quad (11)$$

from which the parameters K_1, K_2, K_3 and K_4 may be evaluated by graphical differentiation with respect to X.

In Table VII experimentally determined f values are given, together with the calculated values of $H_J(X)$. The values obtained for the "stepwise" formation constants by this treatment of the data are ~110, ~18, 3.7, 7.4. The method turns out to be not very good for k_1 or k_2 since the intercepts of $H_0(X)$ and $H_1(X)$ are very small and not very accurately known.

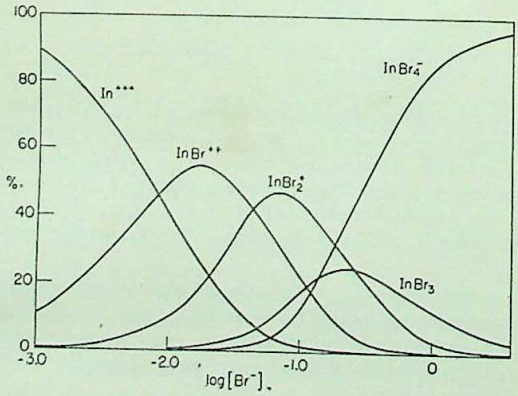

Fig. 7.—Percentage of indium in its various forms as a function of the free bromide concentration at $\mu = 4.00$.

TABLE VI

ANALYSIS OF SPECTROPHOTOMETRIC DATA USING $\bar{n}$ VALUES BY ROSSOTTI–ROSSOTTI $J(X)$ FUNCTIONS

Br^-	$\bar{n}$	$J_1(X)$	$J_2(X) \times 10^{-3}$	$J_3(X) \times 10^{-1}$	$\frac{4-\bar{n}}{3-\bar{n}}(Br^-)$
(0.00000)	(0.00)	(120)	(2.30)		
0.00424	0.38	+144	+2.21	(6.7)	
.00874	.63	+194	+2.31	0.6	+0.0124
.01337	.82	+340	+2.51	+ 8.5	+ .0195
.0181	.94	+869	+2.34	+ 1.1	+ .0269
.0229	1.05	−917	+2.38	+ 1.7	+ .0347
.0277	1.14	−293	+2.43	+ 1.7	+ .0426
.0496	1.50	− 60.4	+3.64	+ 9.0	+ .0827
.0995	2.12	− 19.0	−13.05	+21.0	+ .2127
.1494	2.58	− 10.9	− 2.39	+43.3	+ .506
.200	2.76	− 7.8	− 1.48	+59.7	+1.033
.300	3.20	− 4.8	−0.763	−61.2	−0.200
.400	3.41	− 3.5	− .528	−24.3	− .576
.500	3.56	− 2.8	− .403	−15.1	− .393
.600	3.68	− 2.3	− .325	−10.7	− .282
.700	3.74	− 1.9	− .274	− 8.6	− .246
1.000	3.82	− 1.4	− .188	− 5.5	− .220

TABLE VII

ANALYSIS OF SPECTROPHOTOMETRIC DATA OF FRACTION OF $InBr_4^-$ BY ROSSOTTI–ROSSOTTI $H(X)$ FUNCTIONS

Br^-	f	$H_0(X)$	$H_1(X)$	$H_2(X)$	$H_3(X)$	$H_4(X)$
0.0000		(0.000020)	(0.0022)	(0.037)	(0.0135)	1.00
.0496	0.025	.000242	.00448	.0460	.182	0.95
.0995	.115	.00852	.00837	.0620	.251	1.17
.1494	.230	.00216	.0143	.0810	.294	1.06
.200	.341	.00469	.0234	.106	.345	1.05
.300	.512	.01573	.0524	.167	.434	1.00
.400	.624	.0410	.1025	.251	.535	1.00
.500	.699	.0890	.178	.352	.630	0.99
.600	.749	.173	.288	.477	.733	1.00
.700	.789	.304	.434	.617	.829	0.99
1.000	.854	1.171	1.171	1.169	1.132	1.00

Table VIII lists the values of the stability constants obtained by the different treatments of the spectrophotometric data. The values chosen as the "best" values of the successive formation constants are 120, 19, 4 and 7 for the mono-, di-, tri- and tetrabromo complexes at an ionic strength of 4.00 *M*. Figure 7 shows the percentage of indium complexed in the various species as a function of the free bromide concentration using the above formation constants.

TABLE VIII

COMPARISON OF FORMATION CONSTANTS OBTAINED BY DIFFERENT SPECTROPHOTOMETRIC METHODS

Method	k_1	k_2	k_3	k_4
McConnell–Davidson	123	18.7	..	..
$\log A_i/(A_L - A_i)$	..	..	..	6.1
Difference	..	..	4.8	..
$J(X)$	120	19.2	2.9	8.5
$H(X)$	~110	~18	3.7	7.4
Best value	120	19	4	7

Discussion

From the spectrophotometric study, it is definite that four species, $InBr^{++}$, $InBr_2^+$, $InBr_3$ and $InBr_4^-$ are present in aqueous solutions under the conditions examined: *i.e.*, ionic strength of 4.00 *M*, 0.100 *M* perchloric acid, and 5×10^{-4} *M* sodium sulfite. The fact that the fourth complex is

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present in appreciable amounts is contrary to the findings of Irving and Rosotti[9] who were the only other workers to observe the existence of the fourth complex. In all previous studies, any small error in the determination of the equilibrium concentration of indium and/or a graphically determined quantity might be amplified on successive graphical treatment with the result that the information on the highest complexes would be least accurate. The spectrophotometric method, however, is unique in that a direct measure of the fourth complex in aqueous solution is possible. The formation constants for the first three complexes obtained in this investigation agree reasonably well with those of previous authors.

The evidence was so clear-cut for the four monomeric species that it was not necessary to consider the possibility of dimerization. The dimeric species observed by Irving and Rossotti were found only for "macro" amounts of indium in high hydrobromic acid concentrations, conditions not strictly comparable to ours.

The fact that Woodward and Bill,[16] from a study of the Raman spectra of indium salts in the presence of a large excess of bromide, concluded no tetrahedral $InBr_4^-$ ion to be present in aqueous solution, does not necessarily contradict the present findings. Indium frequently shows hexacoördination, and one would expect to find $[In(H_2O)_2Br_4]^-$ ions in solutions such as ours. The case of iron is a pertinent analogy. It is extracted from hydrochloric acid solutions by ether and other solvents in the form of $HFeCl_4$, which is described as tetracoördination,[17] although some water is also extracted. The stoichiometric solubility of KCl in anhydrous ethyl acetate solutions of $FeCl_3$ to form the compound $KFeCl_4$ appears to be a clean-cut example of tetracoördination of iron[18]; yet in aqueous media, the octahedral character of ferric complexes is beyond question.[19]

Acknowledgment.—This work was supported in part by the United States Atomic Energy Commission.

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CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF MINING AND METALLURGICAL ENGINEERING, UNIVERSITY OF ILLINOIS]

Electrode Potential Studies of Liquid–Solid Equilibrium in Zn–Cd and Zn–In Alloys

BY R. W. BOHL[1] AND V. D. HILDEBRANDT

RECEIVED DECEMBER 14, 1956

Thermodynamic properties of liquid alloys were determined in binary Zn–Cd and Zn–In alloys by the measurement of electrode potentials of galvanic cells of the type: Zn(liq)/$ZnCl_2$(in KCl–LiCl liq)/Zn(in liq soln.). Measurements were carried out over a range of temperatures from 420 to 530°. Liquid–solid phase equilibrium was calculated by finding the temperature at which activities of zinc in the solid state and in liquid alloys were equal. The activity of zinc in the solid was calculated from heat of fusion and heat capacity data for pure zinc. The e.m.f. data were used in turn to calculate the heat of fusion of pure zinc, based on published values of liquidus point. Values thus determined showed much less scatter than published values based on calorimetric techniques. The properties of the liquid alloys were examined with regard to solution theory, and Zn–Cd alloys were shown to closely approach regular behavior, while Zn–In alloys showed some deviation from this behavior. Both systems showed positive deviations from Raoult's Law, and positive heats of solution over the entire composition range.

Introduction

Electrode potential studies have long been used to evaluate thermodynamic properties of solutions, but this technique has seldom been applied to the study of phase equilibrium in metal systems. Early applications of electrode potential studies to metal systems by Lindeck[2] and Richards[3] were limited to the study of thermodynamic properties of amalgams. Later, Taylor[4] and Hildebrand[5] used the principles of e.m.f. measurements in studying the thermodynamics of liquid metal solutions. Seltz and his co-workers[6] were among the first to apply the technique to the problem of phase equilibrium in binary metal systems. An excellent review of recent experimental results, techniques, and methods of calculation in this field is given by Dunkerley and Mills.[7]

In this investigation, accurate and precise e.m.f. measurements were made on galvanic cells of liquid alloys of the binary systems Zn–Cd and Zn–In, and the data used to calculate the thermodynamic properties of the liquid alloys and determine the liquid–solid equilibrium. The cells were of the type

$$\text{Zn(liq)}/Zn^{++}/\text{Zn(in liq soln.)} \qquad (1)$$

If the cell reaction, Zn(liq) → Zn(in liq soln.), is reversible and unique, and only Zn^{++} ions carry the current, the following relation applies to the reaction

$$\Delta\bar{F}_{Zn} = -2E\mathfrak{F} \qquad (2)$$

where $\mathfrak{F}$ is the Faraday constant and E is the e.m.f. in volts. If pure liquid zinc is taken as the standard state, the activity of Zn, the more electropositive component of the cell, can be calculated

(1) Abstracted from a thesis submitted to the Graduate College of the University of Illinois, June, 1956, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Table I

Electromotive Force Data

T, °C.	N_n	E.m.f. (mv.)	N_{Zn}	E.m.f. (mv.)	N_{Zn}	E.m.f. (mv.)	N_{Zn}	E.m.f. (mv.)	N_{Zn}	E.m.f. (mv.)
					Zinc–cadmium system					
422	0.970	0.797	0.939	1.57	0.906	2.31	0.873	2.89	0.837	3.69
435		.830		1.62		2.38		3.01		3.83
457		.863		1.69		2.49		3.16		4.03
468		.874		1.73		2.54		3.24		4.09
483		.896		1.77		2.62		3.33		4.27
490		.914		1.79		2.63		3.39		4.29
513		.939		1.85		2.73		3.53		4.58
Curve	$E = 0.0016T + 0.14$		$E = 0.0032T + 0.22$		$E = 0.0049T + 0.26$		$E = 0.0069T - 0.01$		$E = 0.0084T + 0.21$	
dE/dT	1.6×10^{-3} mv./°		3.2×10^{-3}		4.9×10^{-3}		6.9×10^{-3}		8.4×10^{-3}	
424	0.760	5.06	0.679	6.12	0.584	7.37	0.482	9.37		
442		5.14		6.40		7.77		9.90		
462		5.43		6.68		8.22		10.51		
473		5.55		6.89		8.51		10.91		
486		5.63		7.02		8.70		11.18		
513		5.89		7.42		9.27		11.96		
Curve	$E = 0.0097T - 0.92$		$E = 0.0145T - 0.02$		$E = 0.0214T - 1.68$		$E = 0.0293T - 3.04$			
dE/dT	9.7×10^{-3}		14.5×10^{-3}		21.4×10^{-3}		29.3×10^{-3}			
421	0.365	12.70	0.301	15.13	0.233	19.02	0.161	25.75	0.084	39.08
432		13.15		15.68		19.68		26.59		41.19
450		13.83		16.54		20.78		28.00		43.15
464		14.45		17.24		21.60		29.04		44.58
477		15.01		17.91		22.43		30.09		45.96
498		15.83		18.93		23.69		31.70		48.15
515		16.56		19.82		24.81		33.13		50.07
529		17.20		20.61		25.78		34.38		51.69
Curve	$E = 0.0414T - 4.76$		$E = 0.0512T - 6.93$		$E = 0.0621T - 7.17$		$E = 0.0791T - 8.60$		$E = 0.1067T - 4.91$	
dE/dT	41.4×10^{-3}		52.1×10^{-3}		62.1×10^{-3}		79.1×10^{-3}		106.7×10^{-3}	
					Zinc–indium system					
423	0.971	0.69	0.940	1.26	0.909	1.76	0.875	2.24	0.841	2.51
434		.70		1.30		1.80		2.30		2.61
448		.72		1.37		1.84		2.38		2.70
467		.75		1.41		1.90		2.49		2.85
478		.76		1.43		1.99		2.56		2.97
494		.79		1.47		2.02		2.65		3.09
508		.80		1.51		2.13		2.76		3.24
517		.82		1.51		2.11		2.78		3.32
Curve	$E = 0.0013T + 0.14$		$E = 0.0028T + 0.09$		$E = 0.0043T - 0.10$		$E = 0.0057T - 0.17$		$E = 0.0085T - 1.10$	
dE/dT	1.3×10^{-3} mv./°		2.8×10^{-3}		4.3×10^{-3}		5.7×10^{-3}		8.5×10^{-3}	
424	0.803	3.10	0.725	3.81	0.638	4.31	0.540	5.42	0.430	7.25
441		3.27		4.05		4.67		5.93		7.96
456		3.44		4.28		4.97		6.42		8.63
471		3.50		4.47		5.28		6.80		9.18
491		3.72		4.77		5.66		7.38		10.02
505		3.88		5.00		5.99		7.83		10.65
511		3.98		5.14		6.18		8.07		10.90
524		4.05		5.27		6.38		8.38		11.44
Curve	$E = 0.0096T - 0.98$		$E = 0.0151T - 2.62$		$E = 0.0211T - 4.65$		$E = 0.0299T - 7.25$		$E = 0.0420T - 10.56$	
dE/dT	9.6×10^{-3}		15.1×10^{-3}		21.1×10^{-3}		29.9×10^{-3}		42.0×10^{-3}	
424	0.370	8.96	0.304	11.47	0.238	15.33	0.165	22.30	0.086	36.75
434		9.47		12.08		16.06		23.21		38.52
446		10.07		12.79		16.92		24.24		39.83
458		10.56		13.36		17.62		25.25		41.25
474		11.46		14.41		18.90		26.76		43.29
493		12.37		15.51		20.30		28.50		45.58
513		13.39		16.79		21.72		30.23		47.84
526		14.13		17.65		22.76		31.53		49.50
Curve	$E = 0.0513T - 12.82$		$E = 0.0607T - 14.30$		$E = 0.0739T - 16.05$		$E = 0.0914T - 16.48$		$E = 0.1201T - 13.62$	
dE/dT	51.3×10^{-3}		60.7×10^{-3}		73.9×10^{-3}		91.4×10^{-3}		120.1×10^{-3}	

for the entire composition range from the relation

$$\ln a_{Zn} = \Delta\bar{F}_{Zn}/RT \qquad (3)$$

The activity of the second component of the system can then be determined by graphical integration of the Gibbs–Duhem equation

$$\log(a_2/N_2) = -\int_{N_{Zn}=0}^{N_{Zn}} (N_{Zn}/N_2)\log(a_{Zn}/N_{Zn}) \qquad (4)$$

If measurements are carried out over a sufficient temperature range, the slope of the e.m.f. *vs.* temperature curve can be established, and the enthalpy of the cell reaction can be calculated by the Gibbs–Helmholtz equation

$$T(dE/dT) = E - \Delta H/2\mathfrak{F} \qquad (5)$$

where $H = \bar{H}_{Zn} - H_{Zn}°$, and is usually designated as $\bar{L}_{Zn}$.

Graphical integration again facilitates calculation of the partial molar enthalpy of the second component of the cell, $\bar{L}_2$

$$L_2 = -\int_{N_{Zn}=0}^{N_{Zn}} (N_{Zn}/N_2)d\bar{L}_{Zn} \qquad (6)$$

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TABLE II

THERMODYNAMIC PROPERTIES AT 470°

N_{Zn}	$\overline{\Delta F}_{Zn}$	$\overline{\Delta F}_{Cd}$	$\overline{L}_{Zn}$	$\overline{L}_{Cd}$	ΔH^M	$\overline{\Delta S}_{Zn}$	$\overline{\Delta S}_{Cd}$	$\overline{S}^{xs}_{Zn}$	$\overline{S}^{xs}_{Cd}$	$\overline{F}^{xs}_{Zn}$	$\overline{F}^{xs}_{Cd}$	F^{xs}
Zinc–cadmium system												
0.084	−2087	− 117	1578	10	141	4.93	0.17	0.01	0.00	1572	13	144
.161	−1364	− 213	1313	43	247	3.60	.34	− .03	− .01	1337	45	253
.233	−1016	− 297	1095	98	330	2.84	.53	− .05	.00	1136	95	337
.301	− 810	− 366	906	171	392	2.31	.72	− .08	.01	964	162	404
.365	− 678	− 435	741	257	433	1.91	.93	− .09	.03	812	234	445
.482	− 495	− 568	501	442	470	1.34	1.36	− .09	.05	583	403	490
.584	− 386	− 694	340	628	460	0.98	1.78	− .09	.04	408	601	488
.679	− 315	− 816	220	826	414	.72	2.21	− .05	− .05	257	862	451
.760	− 253	−1010	144	1005	351	.53	2.72	− .02	− .12	152	1131	387
.837	− 191	−1236	82	1210	271	.37	3.29	.02	− .31	72	1442	295
.873	− 149	−1473	61	1341	224	.28	3.79	.01	− .16	52	1572	245
.906	− 117	−1747	43	1518	182	.22	4.39	.02	− .31	29	1744	190
.939	− 80	−2212	27	1800	135	.14	5.40	.01	− .15	13	1917	129
.970	− 40	−3068	14	2165	79	.07	7.05	.01	.08	5	2109	68
Zinc–indium system												
N_{Zn}	$\overline{\Delta F}_{Zn}$	$\overline{\Delta F}_{In}$	$\overline{L}_{Zn}$	$\overline{L}_{In}$	ΔH^M	$\overline{\Delta S}_{Zn}$	$\overline{\Delta S}_{In}$	$\overline{S}^{xs}_{Zn}$	$\overline{S}^{xs}_{In}$	$\overline{F}^{xs}_{Zn}$	$\overline{F}^{xs}_{In}$	F^{xs}
0.086	−1973	− 122	2142	11	193	5.54	0.18	0.67	0.00	1657	10	151
.165	−1221	− 225	1911	47	355	4.21	.37	.63	.01	1437	41	272
.238	− 862	− 317	1670	108	480	3.41	.57	.56	.03	1256	85	364
.304	− 656	− 390	1424	190	565	2.80	.78	.43	.06	1101	144	435
.370	− 521	− 460	1237	305	649	2.37	1.03	.39	.11	948	221	490
.430	− 423	− 525	1016	437	686	1.94	1.29	.26	.17	823	305	531
.540	− 314	− 629	711	723	722	1.38	1.82	.16	.28	596	518	560
.638	− 243	− 728	483	1047	688	0.98	2.39	.09	.37	422	773	549
.725	− 207	− 799	311	1426	618	.70	2.99	.06	.42	268	1109	499
.803	− 164	− 947	165	1892	505	.44	3.82	.00	.59	161	1449	415
.841	− 134	−1085	158	2116	471	.39	4.31	.05	.66	123	1626	362
.875	− 116	−1192	79	2338	360	.26	4.75	− .01	.62	80	1883	305
.909	− 89	−1417	58	2570	287	.20	5.37	.01	.61	52	2119	240
.940	− 65	−1718	31	2827	197	.13	6.12	.01	.53	25	2445	170
.971	− 35	−2382	10	3339	108	.06	7.70	.00	.67	9	2825	92

The partial molar entropies of the reactions can be calculated from the relationship

$$\Delta \bar{F}_i = \Delta \bar{H}_i - T\Delta S_i \qquad (7)$$

The integral molar quantities can be calculated from the partial molar functions by means of the general relation

$$G = N_1 G_1 + N_2 G_2 \qquad (8)$$

Experimental

The alloys studied were prepared from high purity metal obtained from commercial sources. The electrolyte, consisting of an eutectic mixture of potassium and lithium chlorides to which was added about 5% zinc chloride, was prepared from reagent grade chemicals.

The cell consisted of a water-cooled brass top sealed with black wax to an outer 64 mm. Pyrex tube. The top brass fitting was provided with openings through which seven electrodes could be placed in addition to a thermocouple well and an opening to a vacuum system. The alloy electrodes were contained in bulbs prepared from 13 mm. Pyrex tubing with tungsten wire leads sealed in 3 mm. tubing. The cell was assembled so that the electrode containers could be moved from the water-cooled section of the cell into the electrolyte without breaking the vacuum on the cell.

The cell was heated in a furnace consisting of a 5-in. i.d. Alundum core non-inductively wound with Kanthal, and surrounded by 3 inches of Sil-o-cel insulation.

A steel pot containing a low melting nitrate–nitrite salt bath was placed inside the Alundum core, and the cell was immerserd in this bath to a depth near the water-cooled section. This arrangement provided very uniform heating of the cell, and the large thermal mass of the furnace protected against temperature fluctuations. The temperature of the furnace was controlled by a variable transformer. The water cooled top of the cell which projected out of the furnace was maintained at ambient temperatures. Thermocouples in the cell and at various positions in the furnace salt bath checked within 1°, ensuring against the presence of thermal gradients.

With seven electrodes, e.m.f. measurements between five alloys and a pure zinc electrode could be taken simultaneously; the seventh was a pure zinc electrode permitting measurement of the e.m.f. between two pure zinc electrodes. This measurement provided a check against spurious readings due to changes in electrolyte composition, thermal gradients, etc.

Tungsten leads from the electrodes were connected through a selector switch to a L and N Type K-2 potentiometer. The vacuum was provided by a mechanical pump operating through a pressure regulator. The system contained a three-way valve for admitting helium to the system.

The procedure followed in preparing the alloys consisted first of melting the as received metals under vacuum and casting them into sticks. The alloys were then weighed out, sealed under vacuum in Pyrex tubes, and again melted. The alloys thus prepared were cut into pieces for charging into the electrode containers described above. Weight checks made after alloying and after the experimental runs were completed showed a negligible change, and the analyses given are the as weighed analyses.

The electrolyte was melted in an open beaker to which a small pellet of zinc was added, and then cast into a 57 mm. Pyrex tube which fit inside the cell. The use of this inner cell was a precaution taken to avoid the danger of cracking the outer cell.

The cell was assembled with the electrode bulbs positioned in the water-cooled section of the cell. This assembly was placed in the salt pot furnace at a temperature just under the melting point of the electrolyte under a vacuum of 20 μ for a period of ten days prior to the actual experimental run in order to out-gas and desiccate the electrolyte and break up any complex chlorate ions which may have been present.

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When the period of electrolyte desiccation was complete, the temperature of the furnace was raised to about 450° and the electrodes lowered from the cold zone into the molten electrolyte without breaking the vacuum on the system. The pressure regulator was set at about 8 mm. and retained for one hour after the alloys were melted to remove any dissolved gases. Helium was then flushed through the cell several times before the cell, containing about one-half atmosphere of helium, was sealed from the vacuum system. The cell was held overnight at constant temperature to attain equilibrium before readings were begun. Readings were repeated at each temperature at 10 minute intervals until a constant e.m.f. was obtained for each alloy. The temperature of the cell was then changed and the process repeated. Readings were made over a temperature range of 420 to 530°.

As a test of reversibility of the cell reaction, data were taken on both heating and cooling cycles. Readings on heating and cooling were as reproducible as were the readings at constant temperature; *i.e.*, within 0.02 mv. This reproducibility is taken as an excellent criterion of reversibility. The e.m.f. measured between the two pure zinc electrodes was 0.00 ± 0.03 mv. for all runs.

Discussion of Results

The e.m.f. measured between pure zinc and a series of Zn–Cd and Zn–In alloys as a function of temperature is given in Table I. These data lay on straight lines within the experimental accuracy of the readings. The equations of the lines were calculated by the method of least squares, and from the equations dE/dT and the e.m.f. at particular temperatures were determined. Subsequent calculations of thermodynamic properties were based on these values. Figures 1 and 2 show the activities of the components as a function of composition, while Table II gives the values of selected thermodynamic properties calculated at 470° about midway in the temperature range investigated. Both systems studied show positive deviation from Raoult's law, and positive heats of mixing.

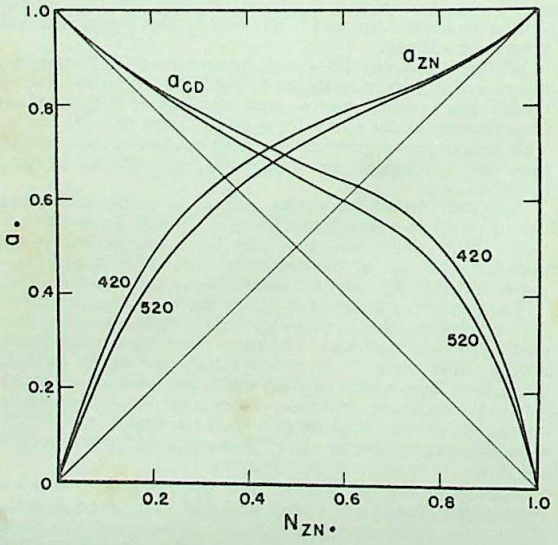

Fig. 1.—Activity *vs.* atom fraction for Zn–Cd alloys at 420 and 520°.

The liquid–solid equilibrium was determined by finding the temperature at which the activity of zinc in the liquid phase equalled that in the solid. A graphical solution was obtained by plotting

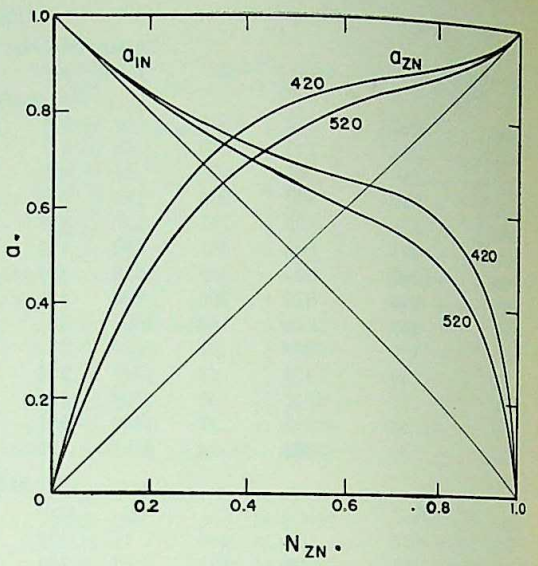

Fig. 2.—Activity *vs.* atom fraction for Zn–In alloys at 420 and 520°.

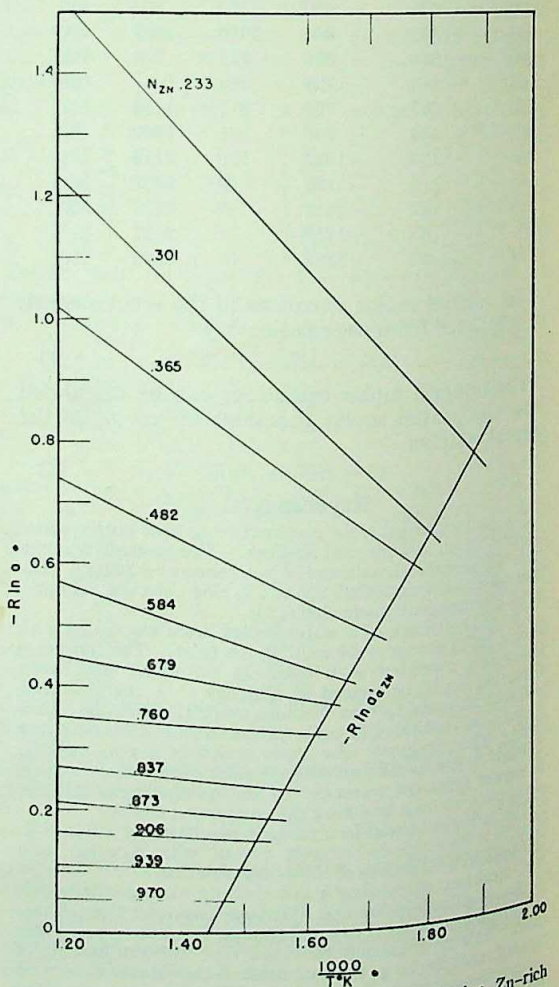

Fig. 3.—Plot of $-R \ln a$ *vs.* $1/T$ to determine Zn-rich liquidus points in Zn–Cd system.

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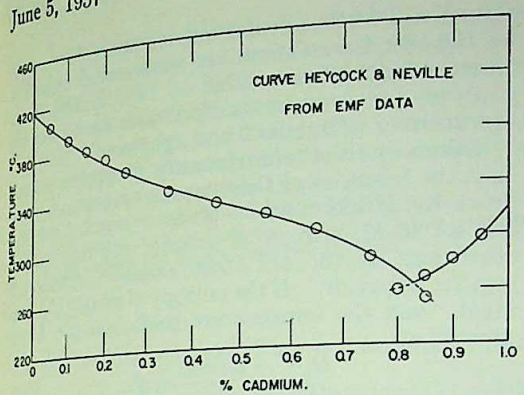

Fig. 4.—Comparison of calculated liquidus points in Zn–Cd system with data of Heycock and Neville.

$-R \ln a_{Zn}$ against $1/T$. Since, according to the Gibbs-Helmholtz equation

$$\frac{d(\Delta F/T)}{d(1/T)} = -\Delta H \text{ and } \Delta F/T = -R \ln a_{Zn} \quad (9)$$

such a plot should yield a straight line if ΔH is constant over the temperature range considered.

Values of $-R \ln a_{Zn}$ for the liquid alloys are readily calculated from the e.m.f. data. The value of $-R \ln a'_{Zn}$ (the prime indicates the solid phase) can be calculated from available thermodynamic data by application of another form of the Gibbs-Helmholtz equation to the reaction Zn(liq) → Zn(solid)

$$d(\Delta F/T) = -(\Delta H/T^2)\, dT \quad (10)$$

Using specific heat and heat of fusion data for pure zinc, this expression can be evaluated as

$$\Delta F/T = -7.6551 \log T + 0.2256 \times 10^{-2} T - 0.0023 \times 10^{-4} T^2 + 287.1/T + 19.8781 \quad (11)$$

The activity calculated by this expression must be multiplied by the composition of the α-solid–solution zinc phase to correct for the small amount of solubility which zinc has for the solute element. This correction assumes that Raoult's law is obeyed in the solid phase—a reasonable assumption in such a dilute solution. The solid solubility data for the Zn–Cd system were taken from the work of Stockdale,[8] and for the Zn–In system from Rhines and Grobe.[9]

The method is illustrated in Fig. 3 for the determination of the Zn-rich liquidus in the Zn–Cd system. Curves of $-R \ln a$ for the liquid alloys were extrapolated until they intersect the curve for the solid phase, the points of intersection giving the temperatures of the liquidus points.

Good agreement has been obtained with the generally accepted Zn–Cd liquidus of Heycock and Neville[10] as determined by thermal analysis. Figure 4 shows their curve, and the liquidus points calculated from the e.m.f. data are shown as experimental points. The comparative eutectic temperatures and compositions are 266° and 82.5% Zn by Heycock and Neville, and 265° and 82.5% calculated from these data as the intersection of the Zn-rich and Cd-rich liquidus curves.

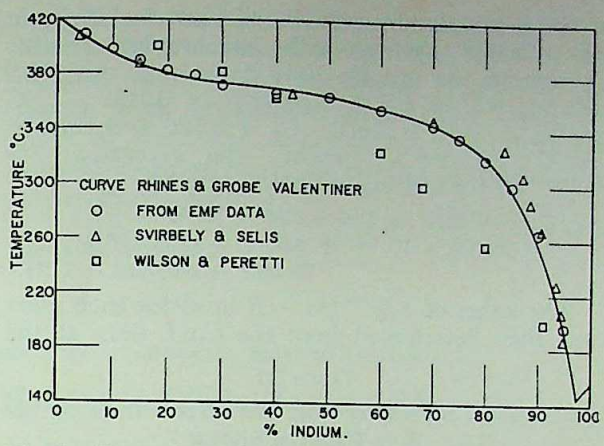

Fig. 5.—Comparison of calculated liquidus points in Zn–In system with data from other investigators.

The In–Zn phase diagram has been determined by Rhines and Grobe,[9] Valentiner,[11] Wilson and Peretti,[12] and Svirbely and Selis.[13] The curve shown in Fig. 5 is drawn from the data of the first two references, and represents the most widely accepted values. Values from the latter two investigations as well as from this study are shown as plotted points in the figure. Again the liquidus determined from these data agrees very well with the published values of the other investigators.

The results of Svirbely and Selis were also based on e.m.f. studies. In their work, e.m.f. data were taken below the melting point of Zn, with pure solid Zn as one electrode (Type II cells) as well as above the melting point (Type I cells) as in this study. The results of their work agree quite well with this study, although a different procedure requiring a more complicated graphical analysis was followed in the liquidus determinations. In their work the a_{Zn} in pure solid zinc and in liquid alloys was calculated with pure liquid Zn as the standard state. Phase equilibrium was then determined by simultaneous solution of plots of a_{Zn} *vs.* temperature for solid Zn and a_{Zn} *vs.* N_{Zn} at various temperatures for the liquid alloys.

Determination of liquidus points by either method depends on accurate values of specific heat and heat of fusion for pure Zn. Values of heat of fusion quoted in the literature, however, are widely scattered as might be expected in view of the experimental difficulties of high temperature calorimetry. The value chosen to calculate the activity of supercooled liquid Zn in this research is the result of a recent evaluation by the National Bureau of Standards.[14] Other sources quote values from 1504[15] to 1765[16] cal./mole. These discrepancies suggest the application of the e.m.f. data to evaluate the heat of fusion. The evaluation can be made by essentially the same method as the determination of the liquidus, but with ΔH_f of Zn as the unknown, and using reliable values of liquidus temperatures.

(5) D. Stockdale, *J. Inst. Metals*, **44**, 75 (1930).
(6) P. Rhines and A. Grobe, *Trans. Am. Inst. Mining Met. Eng.*, **156**, 253 (1944).
(10) C. T. Heycock and F. H. Neville, *J. Chem. Soc.*, **71**, 383 (1897).
(11) S. Valentiner, *Z. Metallkunde*, **35**, 250 (1943).
(12) C. Wilson and E. A. Peretti, *Ind. Eng. Chem.*, **28**, 204 (1936).
(13) W. J. Svirbely and S. M. Selis, THIS JOURNAL, **75**, 1532 (1953).
(14) D. D. Wagman, private communication.
(15) F. Wust, A. Meuthen and R. Durrer, *Forsch. Gebiete Ingenierw.*, No. 204 (1918).
(16) K. K. Kelley, U. S. Bur. Mines Bull. 476, 1949.

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Such calculations were carried out for alloys in the Zn–Cd system with encouraging results. Accepting the specific heat data from the NBS (Zn(c): $C_p = 5.202 + 0.3238 \times 10^{-2}T - 0.01038 \times 10^{-4}T^2$: Zn(l): $C_p = 8.526 - 0.1274 \times 10^{-2}T$ cal./deg. g. atom), the expression for $\Delta F/T$ for the melting of Zn was derived

$$\Delta F/T = -7.6552 \log T + 0.2256 \times 10^{-2}T - 0.0023 \times 10^{-4}T^2 + \Delta H_f/T - 1362.9/T + 22.2601 - \Delta H_f/692.7 \quad (12)$$

The value of $\Delta F/T$ ($= -R \ln a$) for each alloy was then determined from the e.m.f. data at the liquidus temperature given by the phase diagram and corrected for the solubility of Cd in solid Zn. With this value, ΔH_f was evaluated from the above equation. Such calculations made for four alloys in the Zn–Cd system are given in Table III. These results give a value of 1.64 ± 0.03 kcal./g. atom compared to the best evaluation from the literature of 1.66 ± 0.10 kcal./g. atom.

Table III

Calculation of ΔH_f of Zinc from E.m.f. Data on the Zinc–Cadmium System

Alloy, wt. % Cd	ΔH_f, cal./g. atom
45	1672
55	1604
65	1616
75	1676

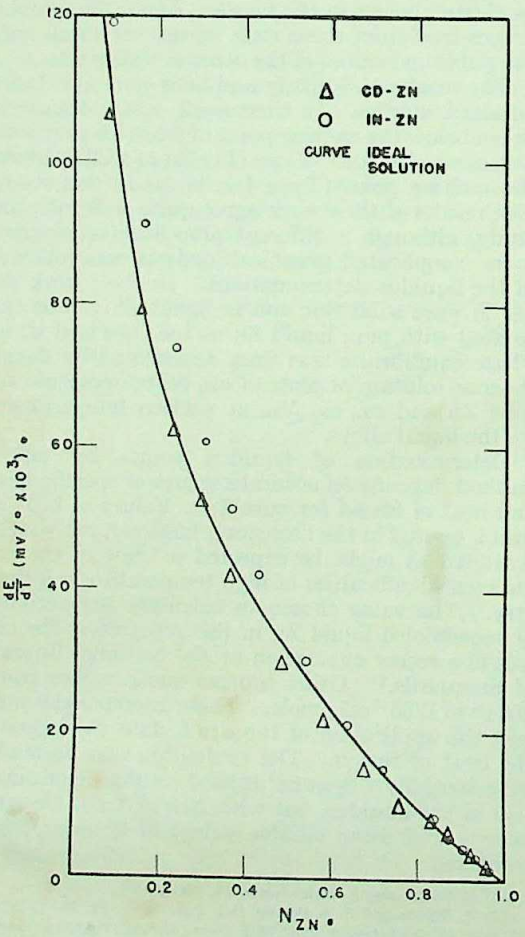

Fig. 6.—Curve shows dE/dT for cell whose components have ideal entropy of mixing. Experimental data shown as plotted points.

Values of the thermodynamic properties suggest that the behavior of these systems is regular, as defined by Hildebrand.[17] Since a regular solution has an ideal entropy of mixing, the temperature coefficient of the cell is an excellent criterion of regular behavior. If the entropy of mixing is indeed ideal, then the temperature coefficient can be expressed as

$$\frac{dE}{dT} = \frac{-2.303R}{n\mathfrak{F}} \log N_{Zn} \quad (13)$$

This curve is plotted in Fig. 6 along with experimental values measured for the cells studied. The data for the Zn–Cd system are seen to approach regular behavior closely, while the agreement is not as good for the Zn–In alloys.

A regular solution also can be shown to follow the relation

$$RT \ln \gamma_2 = BN_1^2 \quad (14)$$

Some departure from this relation is seen in Fig. 7, as the experimental points deviate from linearity.

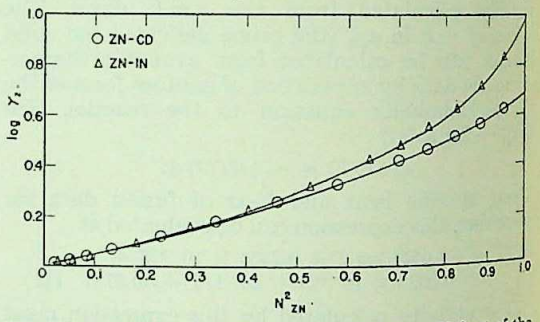

Fig. 7.—Variation of the log of the activity coefficient of the solute with the square of the atom fraction of Zn.

When the volume fraction rather than atom fraction is used, as Hildebrand has suggested, the agreement with the theoretical curve is much improved, as shown in Fig. 8. It is not unexpected that the volume fraction is of considerable importance in the properties of solutions, since the relative volumes greatly affect the degree of packing and the action of interatomic forces. Data for the molar volumes of the pure metals were taken from the density

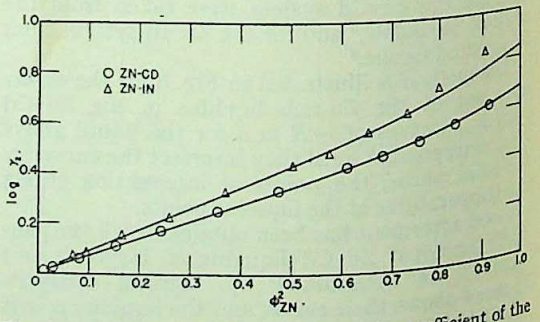

Fig. 8.—Variation of the log of the activity coefficient of the solute with the square of the volume fraction of Zn.

(17) J. H. Hildebrand and R. L. Scott, "Solubility of Non-electrolytes," Chem. Catalog Co., Inc., Monograph #17, 1950.

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data of Hogness[18] and Williams and Miller.[19] The value of the constant in the volume expression was evaluated at 470° as 2290 and 2810 cal./g. atom for the Zn–Cd and Zn–In systems, resp.

It might be argued that the regular solution concept is unrealistic (Lumsdem[20]), but an alternative approach to solution behavior based on a statistical model is so empirical at present that it is impossible to make any predictions of solution behavior from constituent properties. Until the state of statistical theory advances beyond the present empirical state, the concept of regular solutions appears justified.

URBANA, ILLINOIS

(18) T. R. Hogness, THIS JOURNAL, **43**, 1621 (1921).
(19) D. D. Williams and R. R. Miller, *ibid.*, **72**, 3821 (1950).
(20) J. Lumsdem, "Thermodynamics of Alloys," Inst. Metals (London), Monograph and Report Series No. 11, 1950.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND BIOLOGY, FRIENDS UNIVERSITY]

Reaction of Mercury(II) with Halides in Glacial Acetic Acid

BY ORLAND W. KOLLING

RECEIVED JANUARY 28, 1957

The reaction between mercury(II) acetate and potassium halides in glacial acetic acid yields HgX_2 as the predominant species. The stoichiometry of the reaction was determined by potentiometric titrations with the glass and calomel electrodes, in which the glass electrode responds to changing acetate concentration. Potential difference measurements as a function of concentration of solution were made for reactants and products, and demonstrated the order of increasing acidity to be $Hg(OAc)_2 < KCl < KBr < KI$ for these weak acids in glacial acetic acid.

As a result of covalent bonding, mercury(II) chloride, bromide and iodide are soluble in a number of organic solvents, and form non-ionic aqueous solutions. In aqueous solutions containing excess halide, mercury(II) forms tetrahedral complexes of the type $HgX_4^=$, through (sp^3) hybridization. Analogous molecular and ionic species might be expected for glacial acetic acid solutions of mercury(II) halides, for it has been demonstrated that mercury(II) acetate reacts with amine hydrohalides, liberating the amine, quantitatively.[1] The present study confirms that the predominant species present in glacial acetic acid solutions of mercury(II) chloride, bromide and iodide is HgX_2, and that such solutions are essentially non-ionic.

The stoichiometry of the reaction between mercury(II) acetate and the potassium halides was established by potentiometric titrations. The covalent nature of the mercury–halide bond in glacial acetic acid solution was shown by potentiometric measurements, using the method of Higuchi, Danguilan and Cooper.[2] Curves representing the potential difference between the glass and calomel electrodes as a function of solution concentration were determined for the reactants and products, as well as for reference salts.

Experimental Details

All chemicals in these experiments were analytical reagent grade and were used without additional purification. Solution concentrations were restricted to the hundredth formal level by the limited solubility of alkali halide salts in glacial acetic acid.

Preparation of Standard Solutions.—Standard solutions of perchloric acid and hydrochloric acid were prepared by adding suitable amounts of the concentrated aqueous acids to glacial acetic acid and adding sufficient acetic anhydride to consume the water present from the concentrated acids. Each acid solution was allowed to stand for one week, then standardized potentiometrically against potassium acid phthalate (primary standard grade, dried two hours at 120°). The glacial acetic acid solution of hydrochloric acid was 0.00343 *F* and the perchloric acid was 0.0414 *F*, with an uncertainty of ±2 p.p.t.

The 0.0100 *F* solutions of potassium chloride, bromide, iodide, acetate and acid phthalate, and mercury(II) acetate and chloride, in glacial acetic acid were prepared from accurately weighed portions of finely ground and dried samples of the salts. All stock solutions and dilutions from these were carefully thermostated at 25.0 ± 0.1°. The somewhat rapid release of triiodide from glacial acetic acid solutions of potassium iodide necessitated immediate measurements on freshly prepared solutions for this salt.

Malachite green indicator solution was 0.001 *F* prepared by dissolving the solid (as the hydrochloride) in glacial acetic acid.

Volumetric Methods.—Indirect titrations of mercury(II) acetate were made by adding to aliquots of the mercury(II) solution known excesses of the potassium halide salt solution, and the equivalent potassium acetate released was titrated with standard perchloric acid. The end-points in these acid–base titrations were determined both potentiometrically with the glass–calomel electrode pair and with malachite green as a visual indicator, using 0.20 ml. of the latter solution per 30-ml. sample solution being titrated.

Direct titrations of 2.00-ml. aliquots of mercury(II) acetate solution with hydrochloric acid and the potassium halide solutions were made in a total solution volume of 15 ml., and the titration curves were determined from potentiometric measurements.

Potential Difference. Dilution Measurements.—The method employed for the determination of the potential difference as a function of concentration was that of Higuchi, Danguilan and Cooper.[2] In all potentiometric measurements a Beckman Model H-2 *p*H meter, equipped with the usual glass and calomel electrodes, was used. The reference solution was 0.100 *F* sodium salicylate in glacial acetic acid, and the reported values are differences in absolute magnitude between the e.m.f. for the sodium salicylate solution and that for the unknown solution. The e.m.f. for the reference solution was checked before and after each unknown solution. The experimental uncertainty in these potential measurements is ±1 millivolt.

Results

Titrations.—To establish the mole ratio in which the halide reacts with mercury(II) acetate, a number of direct and indirect titrations were performed.

First, to a fixed amount of mercury(II) acetate, known amounts of potassium halide were added, and in accordance with equation 1 the released

(1) C. Pifer and E. Wollish, *Anal. Chem.*, **24**, 300 (1952).
(2) T. Higuchi, M. Danguilan and A. Cooper, *J. Phys. Chem.*, **58**, 1167 (1954).

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potassium acetate was titrated with perchloric acid.

$$Hg(OAc)_2 + yKX = HgX_y + yK(OAc) \quad (1)$$

The ratio of $Hg(OAc)_2$:KX was varied in the range 4:1 to 1:10, and for all ratios it was observed that the potassium acetate released was equivalent to the amount of halide consumed. These results, as shown in Fig. 1, indicate the ratio of X:Hg(II) to be 2:1 in the product.

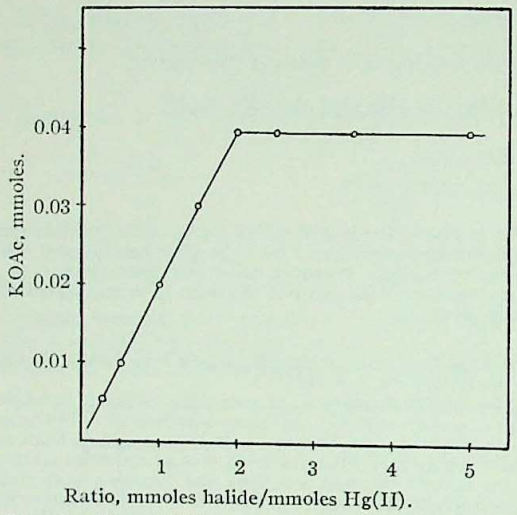

Fig. 1.—The stoichiometry of the reaction between Hg(II) acetate and chloride, bromide and iodide in glacial acetic acid.

Secondly, direct titrations of known amounts of mercury(II) acetate were made, using hydrochloric acid as titrant. The potentiometric titration curve in Fig. 2 may be compared with the compar-

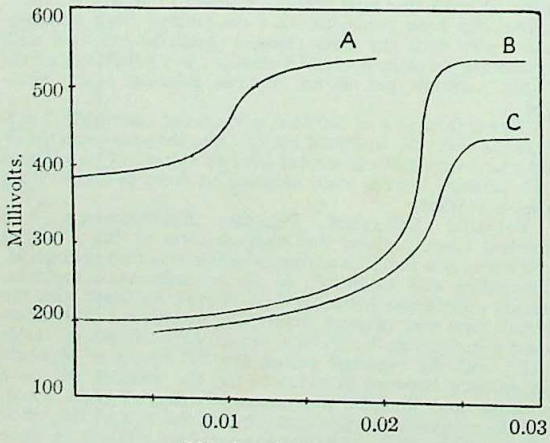

Fig. 2.—Potentiometric titration curves for: (A) potassium acid phthalate with HCl; (B) mercury(II) acetate with HCl; and (C) mercury(II) acetate with KBr.

able curve for the neutralization of hydrochloric acid (a moderately strong acid) with potassium acid phthalate (a moderately strong base). Also, it was observed that mercury(II) acetate could be titrated directly with potassium chloride, bromide and iodide. A typical curve for this direct titration is plotted in Fig. 2. For all direct titrations, the reaction is that given in equation 1, and the product is HgX_2, as was noted above. It is interesting that the curves are not symmetrical in shape, but beyond the break in the curve a nearly constant e.m.f. is obtained (except for the iodide where the magnitude of the e.m.f. becomes greater as triiodide is released from the excess titrant).

Potential Difference *vs.* Concentration.—In Fig. 3 the potential difference between the glass–calomel electrode pair is plotted as a function of concentration of solution in glacial acetic acid for potassium acetate, potassium acid phthalate, the

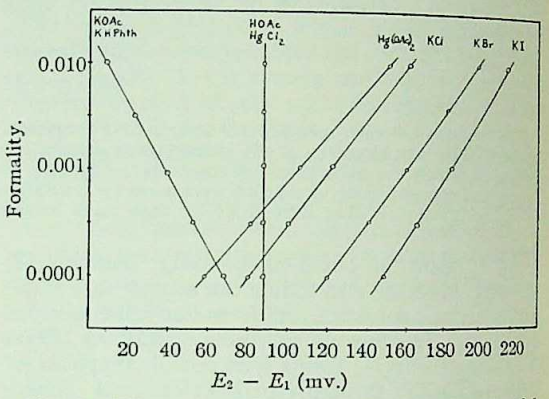

Fig. 3.—Effect of solution concentration on potential difference between the glass–calomel electrode pair in glacial acetic acid. E_1 is the e.m.f. for the reference solution and E_2 is that for the unknown solution.

potassium halides, mercury(II) acetate and mercury(II) chloride. For all compounds, a linear plot is obtained, and, with the exception of the plot for mercury(II) chloride, the slopes correspond closely to 0.0591/2 volts per tenfold change in concentration. The dilution curves for potassium acetate and potassium acid phthalate are coincident, and that for mercury(II) chloride is indistinguishable from that for the solvent alone.

The dilution curves indicate that the order of decreasing acidity is $I^- > Br^- > Cl^-$ for the potassium salts. This is consistent with the results of Kolthoff and Willman.[3] Mercury(II) acetate is more weakly acidic than the potassium halide salts, sufficiently so that a considerable excess of the former may be present with amines without competing in the quantitative reaction between the bases and perchloric acid. The very weak basicity assigned to mercury(II) acetate by Kolthoff and Willman[3] would suggest that this compound is among the most nearly "neutral salts" in glacial acetic acid. The dilution curve for mercury(II) chloride shows the compound to be a complete non-electrolyte in glacial acetic acid. Potassium acetate and potassium acid phthalate appear to be bases of equal strength.

Discussion and Conclusions

It is apparent that the reaction between mercury(II) acetate and the potassium halides is one between moderately strong electrolytes to produce

[3] Kolthoff and Willman, THIS JOURNAL, 56, 1014 (1934).

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one non-ionized product and a strong base. In the unsymmetrical titration curves for this reaction it is significant that beyond the break in the curve the e.m.f. increases much less than would be expected from the dilution curves on the potassium halides. This would suggest that the excess titrant undergoes interaction with mercury(II) chloride, probably through ion-pair or ion-multiple formation, or through coördination of halide by mercury(II) to give products of the type K_nHgX_{2+n} (where n = 1, 2, . . .). However, the nature of the product of this interaction cannot be determined by the present experimental approach. It appears certain that the predominant product of the reaction between mercury(II) and halide in glacial acetic acid is molecular HgX_2.

Although it would be expected that the course of the reaction between mercury(II) acetate and a halogen acid could be followed with the glass electrode, it was not anticipated that this indicator electrode would be suitable for the titrations with the potassium halides. Experimentally, it is easily demonstrated that mercury(II) acetate undergoes no detectable neutralization reaction with perchloric acid nor with potassium acid phthalate, when titrated potentiometrically with the glass–calomel electrode pair. Likewise, it is notable that the magnitude of the break in the titration curve for potassium acid phthalate (a strong base) with hydrochloric acid (a moderately strong acid) is significantly smaller than that for the reaction between mercury(II) acetate and the same acid or the potassium halide. It is evident that the mercury(II) acetate–potassium halide reaction cannot be considered as a neutralization reaction involving a direct or indirect proton transfer mechanism. The glass electrode appears to respond as the indicator electrode toward changes in acetate concentration during the titration involving a nearly neutral acetate and the release of a strongly basic acetate. It has been suggested by Higuchi, Feldman and Rehm,[4] that measurements of acidity and basicity in glacial acetic acid with the glass electrode may be expressed in terms of acetate concentrations. Such an interpretation appears to be experimentally valid.

(4) T. Higuchi, J. Feldman and C. Rehm, *Anal. Chem.*, **28**, 1120 (1956).

WICHITA 13, KANSAS

[CONTRIBUTION FROM THE MONSANTO CHEMICAL COMPANY, RESEARCH DEPARTMENT, INORGANIC CHEMICALS DIVISION]

Principles of Phosphorus Chemistry. III. Structure Proofs by Nuclear Magnetic Resonance[1]

BY C. F. CALLIS, J. R. VAN WAZER, J. N. SHOOLERY[2] AND W. A. ANDERSON[2]

RECEIVED NOVEMBER 12, 1956

Structure proofs based on nuclear magnetic resonance measurements are given for some oxyacids of phosphorus and several other phosphorus compounds. Indirect spin–spin coupling shows that essentially all of the primary and secondary phosphite esters, as well as the free acid and its salts, are present in the form in which one hydrogen is attached directly to the phosphorus. Structure proofs are given for the hypophosphate, isohypophosphate and diphosphite molecule-anions, as well as for P_2S_3 and $P_4O_6S_4$. Indirect spin–spin splitting in the tripoly- and tetrapolyphosphate anions shows that the P-O-P linkages are basically covalent; and all of the data indicate that the often postulated P^{+5} ion does not exist in the phosphates and related compounds.

Gutowsky, McCall and Slichter[3] have already shown that indirect spin–spin splitting of nuclear magnetic resonance peaks is a powerful tool for proving structures in the chemistry of phosphorus. Thus, these authors were able to demonstrate that the hydrogen and fluorine atoms are attached directly to the phosphorus by primarily covalent bonds in the following structures: PH_3, PF_3, $(CH_3O)PF_2$, $OPClF_2$, $OPCl_2F$ and the $F_2PO_2^-$, $H_2PO_2^-$, $HPO_3^=$ and PF_6^- ions. In this paper, structure proofs based on both indirect spin–spin splitting and chemical shifts will be presented along with a discussion of bonding in phosphorus compounds. The experimental procedure and the raw data are given in Paper II of this series. Unless otherwise designated, the data are P^{31} spectra. The majority of the measurements were made at 7140 gauss and 12.3 Mc. The chemical shifts relative to 85% orthophosphoric acid are defined as

$$\delta = \frac{H_{\text{sample}} - H_{H_3PO_4}}{H_{H_3PO_4}} \times 10^6$$

where H is the resonance field strength. The splittings given in cycles per second (c.p.s.) can be converted to parts per million (p.p.m.) of the applied field by dividing by the frequency of the rf probe in Mc., or to field units in gauss by multiplying the p.p.m. value by the field strength (times 10^{-6}) in gauss.

The simplest method of differentiating between chemical shifts and indirect spin–spin splittings is to make measurements at different field strengths. Thus, the separation between resonance peaks attributable to differently situated phosphorus atoms in a molecule or molecule-ion (the chemical shift) is found to be invariant with field strength when measured in p.p m. of the field. In other words, the separation divided by the field strength is a constant. On the other hand, the separation between multiplet peaks due to indirect spin–spin

(1) Presented in part by C. F. Callis at the Phosphorus Symposium held on April 9, 1956, at the American Chemical Society Meeting in Dallas, Texas. Papers I and II in this series are published in THIS JOURNAL, **78**, 5709, 5715 (1956).

(2) Varian Associates, Palo Alto, California.

(3) H. S. Gutowsky, D. W. McCall and C. P. Slichter, *J. Chem. Phys.*, **21**, 279 (1953); H. S. Gutowsky and D. W. McCall, *ibid.*, **22**, 162 (1954).

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coupling between a specific phosphorus atom and some other atom having nuclear spin is the same value in gauss or frequency units at any field. This method of determining whether a given set of lines is due to chemical shifts or spin–spin coupling was used in this study whenever there was some doubt in the matter.

Splitting by Directly Attached Atoms

Organic Phosphites.—Tertiary esters of phosphorous acid are quite universally represented with three atoms attached to the phosphorus, as shown by the formula $(RO)_3P$. However, the primary and secondary esters are depicted with either three or four atoms attached directly to the phosphorus.[4] This comes about by a shift of the hydrogen atom, as shown below for the secondary ester.

$$(RO)_2P(OH) = (RO)_2P(H)O \qquad (1)$$

The question of which of these two forms predominates has been argued for many years in the literature. However, Kosolapoff[4] and others have indicated recently that, because of hydrogen bonding between the phosphorus of one anion and the oxygen of another, both forms are simultaneously present, and the old question of which form predominates is simply semantics.

Nuclear magnetic resonance has shown that the question is not a semantic one. Indirect spin–spin splitting by the hydrogen attached directly to the phosphorus and the absence of other detectable peaks at field strengths where resonance is observed for the trisubstituted phosphites proves that approximately 95% or more of the primary and secondary esters, as well as the free acid, are present in the form in which one hydrogen is attached directly to the phosphorus. In other words, equation 1 is shifted far to the right. This means that the primary and secondary phosphites are more closely related[5] in structure to the phosphonates than they are to the tertiary esters, which can be considered as completely substituted phosphine derivatives. Whatever hydrogen bonding is present probably consists of a strong bond between the phosphorus and the hydrogen and a much weaker, secondary bond between the hydrogen and the oxygen atoms of neighboring molecules. The nuclear magnetic resonance data show that the hydrogen on the phosphorus atom is not readily exchanged whereas other experience[1,6] has shown that there should be considerable exchange of hydrogens on a given oxygen atom.

Substituted Phosphines.—Gutowsky has shown that phosphine, PH_3, gives the expected four peaks of relative areas 1–3–3–1, with a splitting between adjacent peaks of 170 c.p.s. Monomethyl- and dimethylphosphine give 1–2–1 and 1–1 patterns, respectively, with splittings of 205 c.p.s. Trimethylphosphine, as expected, gives only one peak (no splitting). In measuring these substituted phosphines, a relatively large field gradient of 0.05 gauss per cm. was used so that spin–spin splitting due to interaction of the phosphorus with the hydrogens on the methyl groups was not visible.

Ethyldifluorophosphine, $(C_2H_5)PF_2$, ethylchlorofluorophosphine, $(C_2H_5)(Cl)PF$, and ethylisopropoxyfluorophosphine, $(C_2H_5)(F)P(OC_3H_7)$ gave three, two and two peaks, respectively, with splitting in satisfactory agreement with that previously reported[3] for fluorine.

Splitting by Atoms Attached Directly and through an Intermediate Atom

Oxyacids Containing Two P Atoms.—The historically known salts of the oxyacids of phosphorus containing two phosphorus atoms per anion are the (1) pyrophosphate, (2) hypophosphate and (3) pyrophosphite. Blaser[7] has described two more anions which he has called (4) "isohypophosphate" and (5) "diphosphite." The structures of the anions of these five acids—as determined from chemical evidence—are

(1) $\left[\begin{smallmatrix} O & O \\ OPOPO \\ O & O \end{smallmatrix}\right]^{=}$ (2) $\left[\begin{smallmatrix} O & O \\ OP—PO \\ O & O \end{smallmatrix}\right]^{=}$

(3) $\left[\begin{smallmatrix} O & O \\ OPOPO \\ H & H \end{smallmatrix}\right]^{-}$ (4) $\left[\begin{smallmatrix} O & O \\ OPOPO \\ O & H \end{smallmatrix}\right]^{=}$ (5) $\left[\begin{smallmatrix} O & O \\ OP—PO \\ O & H \end{smallmatrix}\right]^{-}$

The P^{31} magnetic resonance spectra of the pyrophosphate (1) and hypophosphate (2) anions each show only one resonance peak. This proves that the structures, assuming two phosphorus atoms, are symmetrical and that no hydrogens are attached directly to the phosphorus. Up to now, the proof that the hypophosphate ion is symmetrical was weak, being based on crystal symmetry[8] from X-ray diffraction without assignment of atom positions. Interpretation of chemical data both for and against the symmetrical structure has appeared in the literature over the past century; of these, the most convincing[9] supports the incorrect isohypophosphate formula for the hypophosphate ion.

The chemical shift of the pyrophosphate anion, obtained from measurements on a solution of tetrasodium pyrophosphate in water, is +6 p.p.m. of the applied field (7140 gauss) relative to 85% orthophosphoric acid. The chemical shift of the hypophosphate anion obtained in the same way from an aqueous solution of disodium dihydrogen hypophosphate, is −9 p.p.m.

The pyrophosphite (3) anion exhibits two equal peaks, with the center of the two peaks shifted +5 p.p.m. of the applied field relative to 85% orthophosphoric acid. The separation of these peaks was found to be 630 c.p.s. at a field of 7140 gauss and 685 c.p.s. at a field of 9850 gauss. Since the difference between these two values is of the order of the experimental error involved, the two peaks undoubtedly arise from indirect spin–spin

(4) *E.g.*, G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, New York, N. Y., 1950, pp. 192–199.

(5) G. M. Kosolapoff, also J. R. Van Wazer, "Encyclopedia of Chemical Technology," Vol. X, (Edited by Kirk and Othmer), Interscience Publishers, New York, N. Y., 1953, pp. 498 and 466.

(6) J. T. Arnold, *Phys. Rev.*, **102**, 136 (1956).

(7) B. Blaser, *Ber.*, **68**, 1670 (1935); **86**, 563 (1953). Also paper given at the Phosphorus Symposium held on April 9, 1956, at the American Chemical Society Meeting in Dallas, Texas.

(8) B. Raistrick, *Sci. J. Roy Coll. Sci.*, **19**, 9 (1949); B. Raistrick and E. Hobbs, *Nature*, **164**, 113 (1949); R. Brooks and T. C. Alcock, *ibid.*, **166**, 435 (1950).

(9) B. Blaser and P. Halpern, *Z. anorg. Chem.*, **215**, 33 (1933). [The interpretation given in this paper does not represent Dr. Blaser's present views. He now supports the symmetric formula (no. 2 in the

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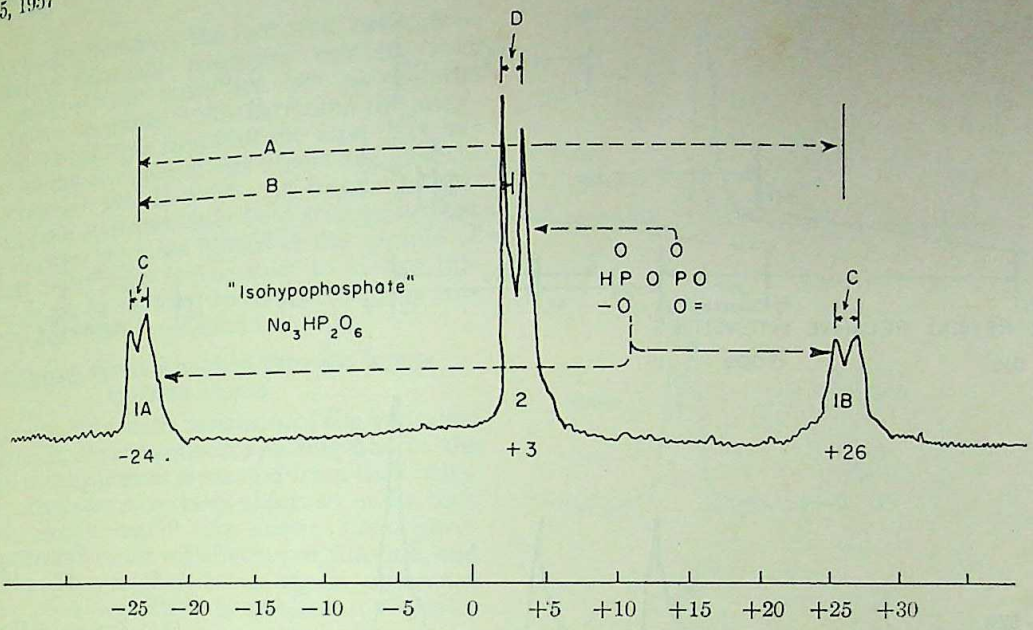

Fig. 1.—P^{31} magnetic resonance spectrum of the isohypophosphate anion at 7140 gauss and 12.3 Mc.: A = 620 c.p.s.; B = 27 p.p.m. or 328 c.p.s.; C = 17 c.p.s.; D = 17 c.p.s.

coupling. This means that the structure is symmetrical, with one hydrogen attached to each phosphorus atom.

The spectrum of the isohypophosphate (4) anion is shown in Fig. 1. This anion gives a splitting of 620 c.p.s. for the hydrogen attached directly to one of the phosphorus atoms. The magnitude of this splitting (to give Peaks 1A and 1B) is approximately equal to that of the phosphite anion (590–690 c.p.s.), and of the dialkyl phosphites (670–700 c.p.s.). The area of peak 2 equals the area of Peaks 1A plus 1B as would be expected for the assignment of peak 2 to the phosphorus atom to which no hydrogen is attached. All three peaks show a splitting of 17 c.p.s. due to interaction of the two chemically different phosphorus atoms through the bridging oxygen. This amount of splitting is approximately equal to the splitting found for the interaction of end and middle groups in the phosphates (see Fig. 3). The observed spectrum is in agreement with the theoretical treatment of the system containing three coupled nuclei discussed in the following paragraph, if the reasonable assumptions are made that the coupling of the hydrogen to the adjacent phosphorus is much greater than the coupling of the hydrogen to the other phosphorus and also much greater than the coupling of the two phosphorus atoms. Thus, the structure proposed by Blaser on the basis of chemical evidence has been proven correct by this physical method.

The phosphorus spectrum of the diphosphite (5) anion is shown in Fig. 2b. This spectrum corroborates the mathematical treatment of a system consisting of three coupled nuclei of spin $1/2$. The Zeeman levels shown in the schematic diagram, Fig. 2a, were calculated from the following Hamiltonian[10] representing the total energy of the system, assuming that the spin-coupling of the hydrogen and either phosphorus is small compared to the chemical shift between the hydrogen and either phosphorus

$$\mathcal{H} = -\hbar\{\omega_H I_H^0 + \omega_{P1} I_{P1}^0 + \omega_{P2} I_{P2}^0 + J_{HP1} I_H^0 I_{P1}^0 + J_{HP2} I_H^0 I_{P2}^0 + J_{P1P2}[I_{P1}^0 I_{P2}^0 + 1/2(I_{P1}^+ I_{P2}^- + I_{P1}^- I_{P2}^+)]\} \quad (2)$$

where $\mathcal{H}$ is the Hamiltonian operator, $\hbar$ the quantum of action divided by 2π, ω the unperturbed resonance frequency, I^0 the z-component of the spin operator chosen in the direction of the applied magnetic field, J the spin-coupling constant, and $I^{\pm}$ the complex spin operator in the plane perpendicular to the field. The subscripts H, P1 and P2 refer to the hydrogen nucleus, the phosphorus adjacent to the hydrogen, and the other phosphorus, nucleus respectively. The resonance frequencies of the phosphorus nuclei derived from equation 2 are

$$\omega_1 = \omega_{P2} + 1/2\delta + 1/2(J' + J_{P1P2}) + 1/2\sqrt{(\delta + J'')^2 + J_{P1P2}^2} \quad (3)$$

$$\omega_2 = \omega_{P2} + 1/2\delta + 1/2(J' - J_{P1P2}) + 1/2\sqrt{(\delta + J'')^2 + J_{P1P2}^2} \quad (4)$$

$$\omega_5 = \omega_{P2} + 1/2\delta - 1/2(J' - J_{P1P2}) + 1/2\sqrt{(\delta - J'')^2 + J_{P1P2}^2} \quad (5)$$

$$\omega_6 = \omega_{P2} + 1/2\delta - 1/2(J' + J_{P1P2}) + 1/2\sqrt{(\delta - J'')^2 + J_{P1P2}^2} \quad (6)$$

$$\omega_3 = \omega_{P2} + 1/2\delta + 1/2(J' + J_{P1P2}) - 1/2\sqrt{(\delta + J'')^2 + J_{P1P2}^2} \quad (7)$$

$$\omega_4 = \omega_{P2} + 1/2\delta + 1/2(J' - J_{P1P2}) - 1/2\sqrt{(\delta + J'')^2 + J_{P1P2}^2} \quad (8)$$

$$\omega_7 = \omega_{P2} + 1/2\delta - 1/2(J' - J_{P1P2}) - 1/2\sqrt{(\delta - J'')^2 + J_{P1P2}^2} \quad (9)$$

$$\omega_8 = \omega_{P2} + 1/2\delta - 1/2(J' + J_{P1P2}) - 1/2\sqrt{(\delta - J'')^2 + J_{P1P2}^2} \quad (10)$$

(10) W. A. Anderson, *Phys. Rev.*, **102**, 151 (1956).

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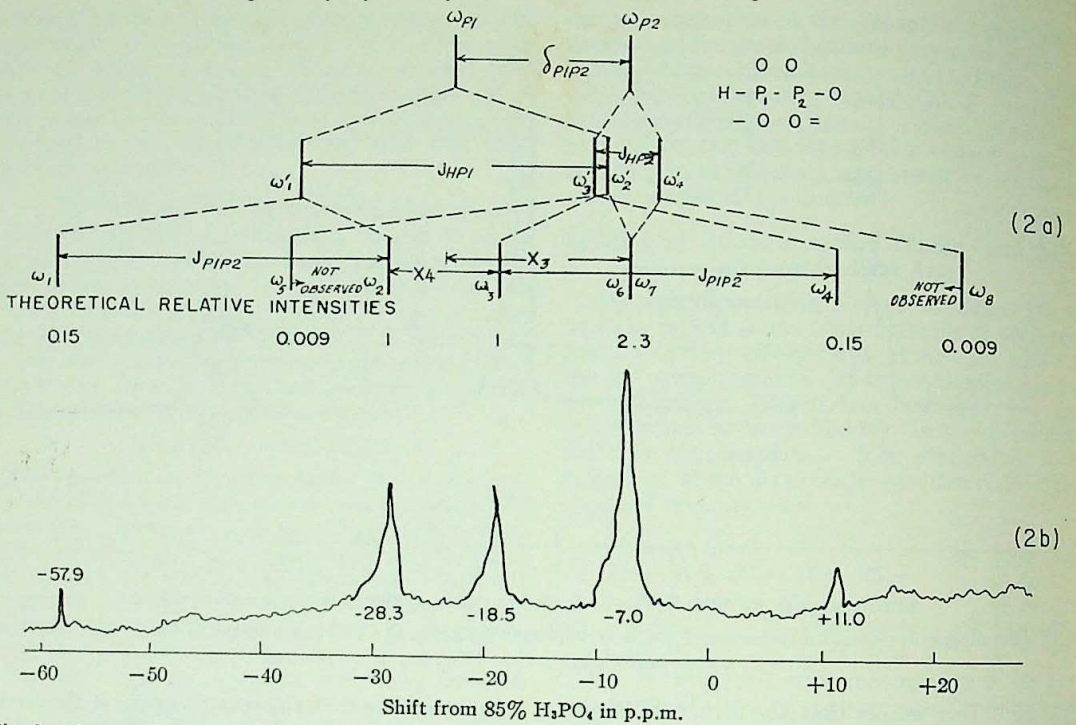

Fig. 2.—Zeeman levels and observed phosphorus spectrum for the diphosphite anion at a field of 9440 gauss. Because of saturation effects at the high rf field used to show up the small peaks, the peak areas are not strictly proportional to their predicted values. The measured values of X_3 and X_4 are 16.4 and 9.8 p.p.m. of the applied field as compared to the calculated values of 16.2 and 9.6 p.p.m., respectively. At the 7140 gauss field, the observed values of X_3 and X_4 are 21.9 and 9.5 p.p.m. compared to the calculated values of 21.6 and 10 p.p.m., respectively.

where δ is the chemical shift between the phosphorus nuclei, and

$$J' = {}^1/_2(J_{HP1} + J_{HP2}) \quad (11)$$

$$J'' = {}^1/_2(J_{HP1} - J_{HP2}) \quad (12)$$

Examination of the phosphorus spectrum does not yield sufficient information to compute the chemical shift of the phosphorus nuclei and all of the spin-coupling constants. Consequently, it was necessary to examine the hydrogen spectrum of the diphosphite anion dissolved in D_2O in order to obtain the phosphorus–hydrogen spin-coupling constants. Four lines were observed in the hydrogen spectrum (one masked by HDO resonance), which means that the hydrogen is strongly coupled to both of the phosphorus nuclei. Measurements of line spacings on these hydrogen spectra, and on the phosphorus spectra reproduced in Fig. 2b at two different fields permit the calculation of the quantities summarized in Table I. In these computations it was assumed that the resonance frequencies, ω_6 and ω_7, form an unresolved doublet.

The line intensities of the satellite lines, ω_1, ω_5, ω_4, and ω_8, relative to the parent line intensities are given by the ratios $[\sqrt{(\delta \pm J'')^2 + J^2_{P1P2}} - J_{P1P2}]/[\sqrt{(\delta \pm J'')^2 + J^2_{P1P2}} + J_{P1P2}]$. These relative values are included in Fig. 2a just below the schematic diagram. Two of the satellite lines, ω_1 and ω_4, were observed only under conditions of high rf power (some saturation) and their resonance frequencies are in agreement with those predicted from the mathematical treatment.

The theoretical splitting of the phosphorus lines resulting in resonance frequencies ω_1', ω_2', ω_3' and ω_4' can be obtained from equations 3–10 inclusive by setting J_{P1P2} equal to zero. It is interesting to note that the observed splitting of these lines is not symmetrical, and that the more asymmetric the split of the line, the greater the difference in relative line intensities—with the more intense line near the center of the pattern.

TABLE I

NUCLEAR MAGNETIC RESONANCE CONSTANTS OF THE DIPHOSPHITE ANION

Notation	Spin-spin couplings: Cycles[a] per sec.	Value: Gauss (spectrum)	P,P-Chemical shift in P spectrum: Value (p.p.m.) Between nuclei	Shift of P2 relative to 85% H_3PO_4	Field (gauss)
J_{P1P2}	480 ± 10	0.28 (phosphorus)	15.4	−7.0	7140
J_{HP1}	444	.26 (phosphorus)	15.8		9440
		.10 (hydrogen)			
J_{HP2}	94	.054 (phosphorus)			
		.022 (hydrogen)			

[a] $\frac{\text{Spin–spin coupling in gauss}}{\text{Field strength in gauss}} \times$ frequency of probe.

The explanation for the observed spectra is in accord with the structure for the diphosphite anion given by Blaser. Other authors[11] have suggested that the substance called a "diphosphite" by Blaser is simply a tautomeric form of phos-

(11) A. D. Mitchell, *J. Chem. Soc.*, **127**, 336 (1925); J. H. Kolitow-

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phorous acid. However, the fact that the hydrogen nuclear resonance spectrum exhibits four peaks indicates that there are two phosphorus atoms in the structure. Furthermore, the magnitude of the splitting supports the idea that hydrogen and the two phosphorus atoms are directly bonded together, *viz.*, H–P–P. All in all, the nuclear magnetic resonance data lend strong support to the structure given by Blaser[7] if the sample of trisodium diphosphite (amorphous to X-ray diffraction) which he supplied to us represents a reasonably pure (> 95%) compound.

Splitting by Atoms Attached through Intermediate Atoms

In the case of magnetic resonance of the hydrogen nucleus in organic compounds, splitting due to the interaction of hydrogens separated from each other by two carbon atoms has been observed under high resolution conditions.[10,12] As shown here, phosphorus also can interact with hydrogen, fluorine, and chemically different phosphorus atoms separated from the phosphorus atom in question by one or two other atoms.

Polyphosphates.—The spectra of the pyro-, tripoly- and tetrapolyphosphate[13] anions are shown in Fig. 3. As previously described,[14] isolated (orthophosphate), end, and middle PO_4-groups resonate at measurably different external fields, with the end- and middle-group shifts being 5–10 and 18–21 p.p.m. with respect to 85% H_3PO_4, which contains the isolated PO_4-groups. In Fig. 3, the end-group resonance peaks are denoted by E, and the middle-group resonance peaks by M. Since the two phosphorus nuclei in the pyrophosphate ion are indistinguishable, internally and externally, *i.e.*, they are chemically equivalent, the indirect spin–spin coupling does not show up as observable splitting, although this coupling ought to be approximately equal to the coupling of the end and middle phosphorus atoms in the tripolyphosphate anion (J_{P1P2} in the pyrophosphate $\approx J_{P1P2} = J_{P2P3}$ in the tripolyphosphate). For the tripolyphosphate anion, the area under peak M is half the area under peak E, and the M peak is split into three parts, of approximate relative areas 1–2–1, whereas the E peak is split into two parts of equal area. Since the middle-group phosphorus is attached to two chemically different phosphorus atoms (in the two end groups), spin–spin splitting into a 1–2–1 triplet is to be expected. Likewise, attachment of the two end-group phosphorus atoms to the lone middle group gives spin–spin splitting into a 1–1 doublet. Measurements of the spectrum of tripolyphosphate at a higher field (9,850 gauss) offer additional verification of the accepted structure. The ratio of the separations, ($\delta_1/\delta_2 = 1.3$), of the pairs of multiplets at the two fields is in acceptable agreement with the ratio of the two fields ($H^6/H_2 = 9850/7140 = 1.4$), as expected for non-equivalent nuclei. The splitting

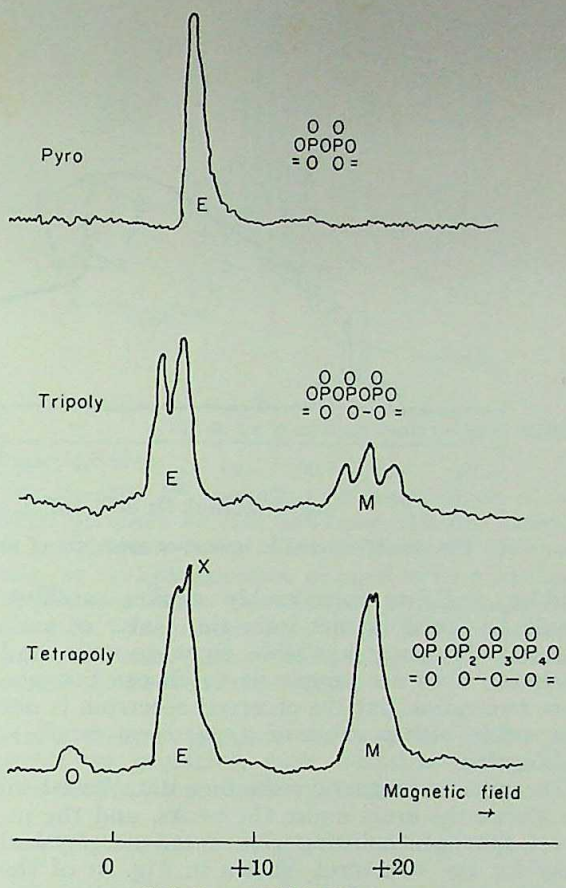

Fig. 3.—P^{31} magnetic resonance spectra of chain-phosphate anions at 7140 gauss and 12.3 Mc. as adjusted to the same scale. The end-group peaks are denoted by E, and the middle-group peaks by M. Orthophosphate impurity is denoted by O, and the extra height of the peak marked "X" is due to some pyrophosphate impurity.

in the multiplets (17 c.p.s.) is independent of field strength as was confirmed earlier[3] for several cases of multiplet splittings.

For the tetrapolyphosphate anion, the E and M peaks are of approximately equal area (after correction for pyrophosphate, a known impurity), and are both split into doublets of intensity 1–1. Such a picture is in accord with the published analysis[15] for the case of four coupled nuclei in a molecule with a plane of symmetry and two pairs of non-equivalent nuclei.[16] If we let $J_{P1P2} = J_{P3P4}$ be the spin coupling between adjacent end and middle phosphorus nuclei, and J_{P2P3} be the spin coupling between the central nuclei, a similar analysis can be made for various values of the ratio of $J_{P2P3}/J_{P1P2} = J_{P3P4}$. For this ratio equal to zero, a simple doublet with spacing $J_{P1P2} = J_{P3P4}$ is predicted for each phosphorus group. For the above ratio equal to one, two lines with spacing $J_{P1P2} = J_{P3P4}$ are still predicted for each phosphorus group, but in addition two slightly weaker lines are predicted closer to the center of each

(12) *E.g.*, see the spectrum shown by B. P. Dailey and J. N. Shoolery, This Journal, **77**, 3977 (1955).

(13) See O. T. Quimby, *J. Phys. Chem.*, **58**, 603 (1954); R. K. Osterfeld and R. P. Langguth, *ibid.*, **59**, 76 (1955), for information about the tetrapolyphosphate.

(14) J. R. Van Wazer, C. F. Callis and J. N. Shoolery, This Journal, **77**, 4945 (1955).

(15) H. H. McConnell, A. D. McLean and C. A. Reilly, *J. Chem. Phys.*, **23**, 1152 (1955).

(16) J. R. Van Wazer, M. Goldstein and E. Farber, This Journal, **75**, 1563 (1953); C. F. Callis, J. R. Van Wazer and P. G. Arvan, *Chem. Rev.*, **54**, 777 (1954).

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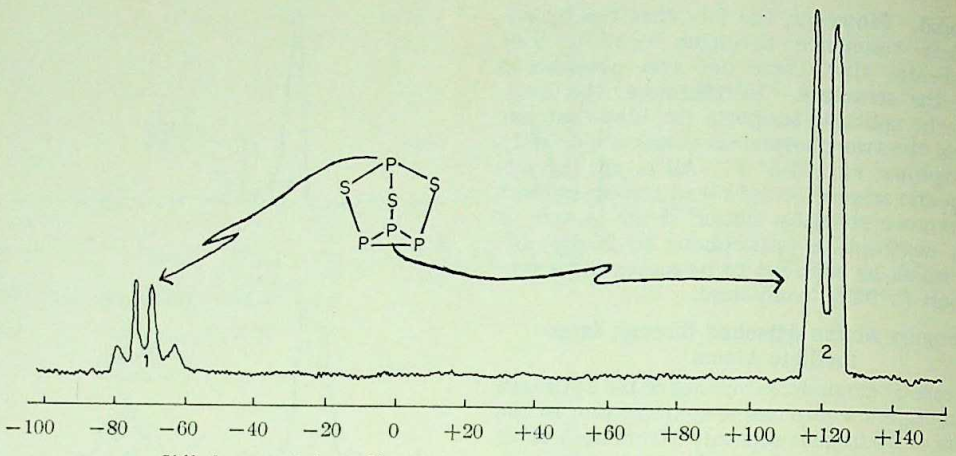

Fig. 4.—P^{31} magnetic resonance spectrum of phosphorus sesquisulfide at 7140 gauss and 12.3 Mc.

doublet, and two considerably weaker satellites should be found farther from the center of each doublet. Presently available signal-to-noise and resolution does not permit us to choose between these two ratios, but the observed spectrum is not compatible with a value of $J_{P2P3}/J_{P1P2} = J_{P3P4}$ greater than *ca.* 1.2.

The nuclear magnetic resonance data based on the shifts, the areas under the peaks, and the indirect spin–spin splitting give a unique physical proof for the structures (shown in Fig. 3) of the tripoly- and tetrapolyphosphates, for which only chemical structure proofs have heretofore been available.[17]

Phosphorus Sulfides.—The most interesting member of this class of compounds which we have studied is phosphorus sesquisulfide, P_4S_3, the nuclear magnetic spectrum of which is shown in Fig. 4. In accord with the structure of this compound as determined by X-ray diffraction[18] and shown in Fig. 4, there are two major peaks. Peak 1, which is a 1–3–3–1 quadruplet, corresponds to the phosphorus atom connected through three sulfur atoms to the other three, chemically different phosphorus atoms. Peak 2, a 1–1 doublet exhibiting a total area which is three times that of peak 1, is attributable to the three phosphorus atoms in a ring. Splitting of this peak is due to interaction with the lone phosphorus atom. Presumably, the relatively large splitting (86 c.p.s.) in the case of this sulfide as compared to the splitting (17 c.p.s.) in compounds in which the chemically different phosphorus atoms are separated by oxygens is attributable to the fact that the phosphorus atoms are triply connected[19] in the sulfide (also bent bonds) and is not due to a difference between oxygen and sulfur in transmitting the interaction between the phosphorus atoms.

The existence of one peak in the spectrum of phosphorus sulfoxide, $P_4O_6S_4$, is in agreement with a symmetrical structure[20] in which the four phosphorus atoms are identical.

Splitting by Hydrogen and Fluorine Atoms.—Hydrogen and fluorine interacting with phosphorus through an intermediate atom or atoms cause spin–spin splitting as well as do phosphorus atoms which are chemically different. An example of such behavior is found in dichlorofluoromethyl-tris-(dimethylamido)-phosphonium chloride, $[Cl_2FCP(N(CH_3)_2)_3]^+ Cl^-$, in which the fluorine attached to the carbon atom causes a splitting of 85 c.p.s. of the phosphorus peak.

Splitting is not recorded in the Appendix of Paper II for the compounds containing P–C linkages (such as the phosphonates) because the spectra of these compounds were observed with insufficient resolution to show up splitting of the order of magnitude of *ca.* 20 c.p.s. However, a recent spectrum of trimethylphosphite, $P(OCH_3)_3$, has been taken under conditions of extremely high resolution and shows spin–spin splitting due to the hydrogens acting on the phosphorus through the carbon *and* oxygen atoms. This spectrum, shown in Fig. 5, clearly exhibits eight of the ten peaks (two of which are too small to show over the background) for the 1–9–36–84–126–126–84–36–9–1 splitting expected for coupling with nine other atoms—the nine hydrogens in the molecule. In comparison, it was found that at the same resolution no fine structure showed up in the peak observed for triphenyl phosphite. Presumably this lack of fine structure is due to the fact that in the triphenyl phosphite the nearest hydrogen is separated from the phosphorus by three intermediate atoms (–C–C–O–) as compared to the two intermediate atoms (–C–O–) in the trimethyl compound.

Dimethyl phosphite shows two major peaks, with a splitting of 710 c.p.s., because of the hydrogen atom directly attached to the phosphorus. Under super high resolution conditions, both of these

(17) The previously available structure proofs for these two anions have been (1) proximate analysis, (2) *p*H titration, (3) cryoscopy in $Na_2SO_4 \cdot 10H_2O$, (4) paper chromatography, and (5) interpretation of hydrolysis data.

(18) O. Hassel and A. Pettersen, *Tid. Kem. Berg. Met.*, **1**, 57 (1941).

(19) J. R. Parks, This Journal, **79**, 757 (1957), has shown that the chemical shift of triply connected phosphorus compounds can be related to the electronegativity of the ligands and the bond angles. This reference gives a more quantitative picture of the idea presented here.

(20) A. Stock, *Ber.*, **72**, 1130 (1939).

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major peaks are split into seven subpeaks of relative heights 1–6–15–20–15–6–1 by the six hydrogens attached to the carbon atoms. This secondary splitting corresponds to *ca.* 14 c.p.s.

When the spectrum of orthophosphoric acid was run at the same resolution as was used in showing the fine structure of trimethyl phosphite in Fig. 5, there was no sign of fine structure due to interaction of the weakly acidic hydrogens through the oxygen atoms on the phosphorus. This means that the average frequency of the exchange process of the weakly acidic hydrogen from one phosphate to another or from phosphate to water and *vice versa* must exceed the splitting frequency, and thus collapse the spin–spin coupling to a single resonance line. As was noted in Paper II of this series, removal of the third, extremely weakly acidic hydrogen from the orthophosphate ion causes a slight negative shift which probably indicates covalent bonding of this hydrogen, with concomitant rapid exchange.

Structures from Chemical Shifts

By utilizing shift contributions, as described in Paper II, an approximation can be made to the positions of resonance peaks to be found for phosphorus atoms attached to various given atoms. Likewise, a good estimation can be made of the amount of spin–spin splitting to be observed. Examples of this type of structure analysis are found for the isohypophosphate anion and phosphorus sesquisulfide in this paper and for ethyl "metaphosphate" in Paper II.

Estimation of the average number of phosphorus atoms in a mixture of chain phosphates also exemplifies the use of chemical shifts to determine structures. It is found that the relative areas of the end-group (A_E) and middle-group (A_M) peaks for a solution of a vitreous sodium phosphate gives the number average chain length, $\bar{n}$, as expected from the equation $\bar{n} = 2(A_E + A_M)/A_E$.

As shown in Fig. 2 of Paper II in this series, attachment of phenyl groups to a phosphate moiety causes a significant positive shift—with a shift of +5 p.p.m. (with respect to 85% H_3PO_4) for one phenyl group and +12 p.p.m. for two phenyl groups in a 7140 gauss field. Therefore, if pentaphenyl bis-(diethylene glycol) triorthophosphate and hexaphenyl tris-(diethylene glycol) tetraorthophosphate exhibit structures in which isolated PO_4-groups are separated by organic radicals so that two phenyl groups are attached to the PO_4-groups at the end of the resulting chains and one phenyl group is attached to the PO_4-group(s) away from the ends, they will have peaks at the positions found for the corresponding monomers. Moreover, the hexaphenyl compound should exhibit two peaks of equal area and the pentaphenyl compound a peak at +5 p.p.m., which is half the size of the peak at +12 p.p.m. The observed spectra showed two equal sized peaks at +7.5 and +12.5 p.p.m. for the hexaphenyl compound and one peak at +7.0 p.p.m. and another twice as large at +13 p.p.m. for the pentaphenyl compound. These results demonstrate that the organic chemist who synthesized these compounds most probably attributed the proper structure to them. At least

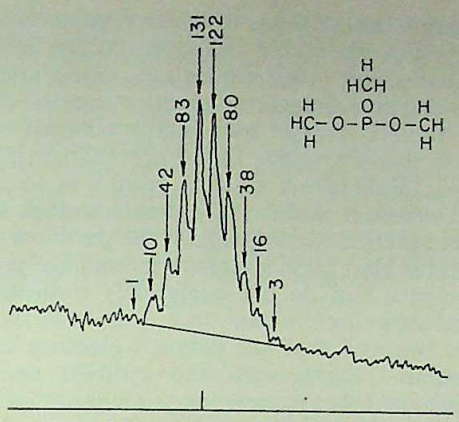

Fig. 5.—The P^{31} magnetic resonance spectrum of trimethyl phosphite at 7140 gauss and 12.3 Mc. showing the fine structure due to spin–spin splitting of the phosphorus by the hydrogen atoms on the three methyl groups. The measured heights are listed (on a relative basis) over each peak. The random-noise height is somewhat less than *ca.* ±4 units. Theoretical splitting for nine attached atoms is 1-9-36-84-126-126-84-36-9-1.

the compounds give nuclear magnetic resonance spectra as predicted from his structures. The structure for the pentaphenyl compound is thus

$$\begin{array}{ccccc} & O & & O & \\ C_6H_5OPOC_2H_4OC_2H_4OPOC_2H_4OC_2H_4OPOC_6H_5 & & & & \\ & O & & O & \\ & C_6H_5 & & C_6H_5 & \end{array}$$

Discussion

During the first half of the Twentieth Century, much of the discussion of the structure of oxyacids in the chemical and mineralogical literature was in terms of completely ionized atoms. According to this picture, a solid sodium phosphate would be made up of P^{+5}, $O^{=}$ and Na^{+} ions, so arranged as to give close packing of spheres (the ions) with alternation of positive and negative charges in such a manner as to result in electroneutrality over even relatively short distances within the array. Application of this idea was usually confined to solids, although one would have to infer that, for example, condensed phosphate molecule-ions in solution were merely aggregates of P^{+5} and $O^{=}$ ions. The existence of spin–spin splitting in the tripoly- and tetrapolyphosphates indicates that this ionic picture is false and that a better picture consists of covalently bonded phosphorus and oxygen atoms making up the phosphate molecule-anions, the negative charges of which are balanced by the counter ions, *e.g.*, Na^{+}, some of which may be tightly affixed to the oxygens of the molecule-anions. If these condensed phosphate anions were merely a collection of ionized atoms, the rate of exchange (say, between the oxygens of the P–O–P linkages and the water) would be so rapid that no indirect spin–spin coupling could be observed.

Although complete X-ray structure analyses[21]

(21) *E.g.*, see C. Romers, J. A. A. Ketelaar and C. H. MacGillavry, *Acta Cryst.*, **4**, 114 (1951); S. Furberg, *Acta Chem. Scand.*, **9**, 1557 (1955).

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in which detailed electron density projections are employed do show that the atoms in the anions of phosphates and other similar oxyacids share electrons, occasional reports[22] purporting to demonstrate the existence of such highly charged ions as P^{+5} occasionally appear in the crystallographic literature. Publication of such results is to be deplored unless it is definitely demonstrated that a covalent picture cannot explain the data[23] or unless it is stated that ionic structure factors are used for convenience and do not necessarily indicate that the real structure is ionic.

It is believed that the detailed electron density projections[21] along with the indirect spin–spin splitting and other nuclear magnetic resonance data reported here and in Paper II of this series demonstrate that an ionic representation[24] of phosphorus in its compounds must be considered absurd unless one is equally ready to represent carbon in organic compounds as being ionized, *e.g.*, C^{+4} in CCl_4 or C^{-4} in CH_4.

Acknowledgment.—The authors wish to thank Dr. Bruno Blaser of Henkel und Cie. for donation of the samples of disodium pyrophosphite, tetrasodium isohypophosphate tetrahydrate and trisodium diphosphite; and B. M. Zeffert, Norbert Muller and H. Finegold of the Chemical Warfare Laboratories, Army Chemical Center, for the spectra of sodium tripolyphosphate, disodium pyrophosphite and trisodium diphosphite at the higher field. The assistance of R. C. Jones of Varian in obtaining the data and of J. R. Parks of Monsanto in interpreting it is greatly appreciated.

(22) *E.g.*, see R. Brill and A. P. de Bretteville, *Acta Cryst.*, **8**, 567 (1955). In recent private communication, Dr. R. Brill made the following statement concerning this reference: "The results primarily indicate only that the scattering powers of Al and P are equal at the third order of the basis reflections. This would be expected for the ions Al^{+3} and P^{+5}. However, this would also be the case if Al and P contain the same number of electrons and the distribution of electrons around both atoms would not differ too much."

(23) We believe this to be impossible for the phosphates, at least.

(24) For recent extreme ionic views, see W. A. Weyl, "The Screening of Cations as a Basic Principle of Inorganic Chemistry," Office of Naval Research, Technical Report No. 52, Contract No. N6onr 269 Task Order 8, Pennsylvania State College, July, 1952.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

The Molecular Structure of $B_{10}H_{12}I_2$[1]

BY RILEY SCHAEFFER

RECEIVED FEBRUARY 4, 1957

The structure of $B_{10}H_{12}I_2$, obtained from $B_{10}H_{14}$ by treatment with I_2, has been determined by X-ray diffraction techniques. The unique space group D_{2h}^{10}Pccn and the presence of four molecules per unit cell requires the molecule to possess a twofold axis and makes possible the unambiguous determination of the intramolecular iodine–iodine distance. This observed distance is in agreement with that expected if substitution has occurred at the apices of the two pentagonal pyramids which share a common edge in the $B_{10}H_{14}$ structure.

Introduction

Although substituted diboranes ($B_2H_2R_4$) and borines (HBR_2) have been known for many years and present few structural problems, only two substitution derivatives of higher boranes have been described. Both $B_{10}H_{12}I_2$ and $B_{10}H_{12}Br_2$ were prepared by Stock by direct action of the halogen on $B_{10}H_{14}$.[2] Although many isomeric dihalides of decaborane are possible, the nature of the products obtained by Stock indicates that a single isomer was obtained at least in large part. Apparently, effects are operative in determining the mechanism of substitution which have not as yet been adequately assessed and it was consequently of considerable interest to determine which of the isomers was formed.

Experimental

A sample of $B_{10}H_{12}I_2$ crystallized from benzene as flat plates was available. Several crystals were selected, mounted, coated with Krylon and examined by X-ray diffraction. The crystals were not well formed but one showed only a small amount of extraneous scattering, which did not interfere with indexing, and was used for further study. Weissenberg and rotation photographs taken with filtered Cu radiation and precession photographs taken with filtered Mo radiation showed orthorhombic symmetry and gave the following unit cell dimensions: $a = 13.13$, $b = 7.26$, $c = 12.00$ Å.

Comparison of the unit cell dimensions with those of the disordered unit of $B_{10}H_{14}$ strongly suggested that only four molecules were present per unit cell. Indexing of the reflections on the basis of this unit cell led to the criteria for systematic extinction

$$hkl \text{ present in all orders} \quad (1)$$

$$0kl \text{ present only for } l = 2n \quad (2)$$

$$hk0 \text{ present only for } h + k = 2n \quad (3)$$

$$h0l \text{ present only for } l = 2n \quad (4)$$

The space group was thus uniquely established as D_{2h}^{10}-Pccn.

Sets of precession pictures of varying intensity were obtained by timed exposures of the $h0l$ and $hk0$ zones and the intensities of individual spots estimated visually with the aid of a standard scale prepared from the same crystal. Values of F_{hkl}^2 (on an arbitrary scale) were calculated from the observed intensities by application of the Lorentz and polarization factors.

Iodine positions were located readily by analytical interpretation of the Patterson function. Since the general positions of the space group are eightfold and only four molecules are present, the molecules must possess a center of symmetry or lie on a twofold axis. If the molecule is structurally derived from $B_{10}H_{14}$ it cannot possess a center of symmetry and must consequently have iodines substituted in one of the five sets of positions equivalent under twofold rotation (see Fig. 1). The intramolecular iodine–iodine distance could then be determined readily from the $hk0$ projection of the iodine

(1) Presented at the American Chemical Society Meeting in Cincinnati, Ohio, in April, 1955. This work was supported in part by a Summer Research Grant to Iowa State College in 1954 by E. I. du Pont de Nemours and Company which is gratefully acknowledged.

(2) A. Stock, "Hydrides of Boron and Silicon," Cornell University Press, Ithaca, N. Y., 1933, pp. 120–122.

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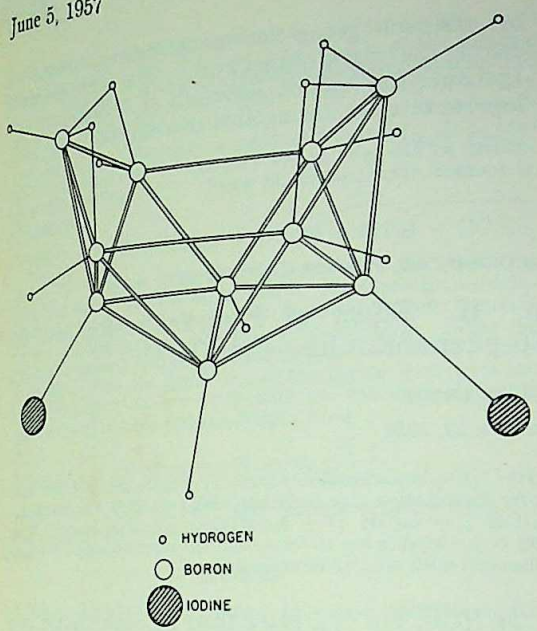

Fig. 1.—The molecular structure of $B_{10}H_{12}I_2$.

positions since they were required by the space group to lie in a plane perpendicular to the *C*-axis; this distance was found to be 6.25 Å. Using 2.20 Å. as a close approximation to the expected B–I bond distance (the sum of the covalent radii of the atoms), the iodine–iodine distance was calculated for each of the pairs of positions related by the twofold axis by an analytical extension of the B–H bond in the decaborane unit cell using the coördinates of Kasper, Lucht and Harker.[3] It was immediately apparent that position 5 need not be considered since the sum of the bond distances is only 6.12 Å. and the B–H angle is about 120°. It was also necessary to consider only one of the sets 1 and 4 since they would lead to identical I–I distances. Iodine–iodine distances calculated for substitution on positions 1, 2 and 3 were 7.28, 5.92 and 7.56 Å., respectively.[4] In view of the fact that Kasper, *et al.*, were not able to determine the hydrogen positions with high precision, agreement between the observed value (6.25 Å.) and that calculated for position 2 (5.92 Å.) may be considered good. A further refinement of the $B_{10}H_{14}$ structure by Moore and Lipscomb leads to the following somewhat different parameters of interest[5]

	x	$y - 1/4$	z
B_1	0.034	0.080	0.000
B_2	.100	.023	.168
B_3	.116	.028	− .131
H_1	.041	.138	.000
H_2	.164	.026	.320
H_3	.195	.042	− .220

Recalculation of the expected I–I distances for substitution on position 1, 2 and 3 leads to values of 7.88, 6.21 and 7.60, respectively. The agreement between the calculated distance for position 2 and the observed is now better than one has any right to expect when one considers the accuracy with which the hydrogen positions in $B_{10}H_{14}$ are known and possible variation in the B–I bond distance from that assumed.

Structure factors calculated for the crystal based on the assumption that only iodine was present in the cell were in moderately good agreement with the observed values; the usual index of reliability $R = ||F_{obsd}| - |F_{calcd}^{1}|/|F_{obsd}|$ was 0.18 for the $hk0$ zone and 0.20 for the $h0l$ zone after application of a temperature factor correction of the usual form with $B = 4.42$ and adjustment of the scale of F_{obsd} to provide the best fit to F_{calcd}. Fourier syntheses were calculated for both $hk0$ and $h0l$ zones using the largest observed structure factors and assigning to them the signs calculated from the iodine positions. No direct indication of molecular shape was present in the $hk0$ projection since two molecules overlap. However the $h0l$ projection shown in Fig. 2 distinctly suggests a cup shaped boron arrangement with the iodine near the closed surface and thus bonded to either position 2 or 5. As noted above, the latter position is not suitable on the basis of I–I distance.

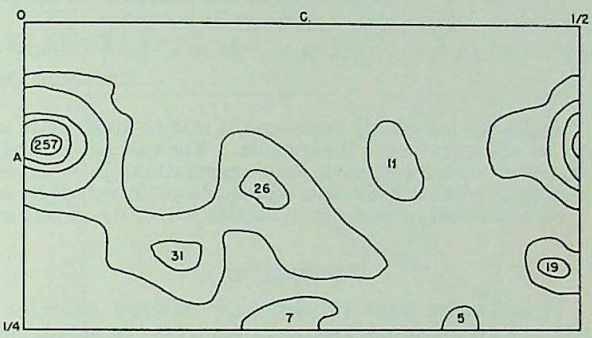

Fig. 2.—$h0l$ Fourier projection of $B_{10}H_{12}I_2$.

Both the $hk0$ and $h0l$ projections suggested parameters for two of the borons (well defined election density maxima) and corrections of structure factors were made for these. A difference synthesis for each zone suggested positions for the remaining boron atoms and second difference syntheses, which included contributions of these borons in F_{calcd}, suggested only slight shifts in parameters for all atoms in the cell. On the basis of the final positions located by the difference synthesis, R values of 0.103 were calculated for both the $hk0$ and $h0l$ zones. The low R values obtained make it apparent that further refinement will be difficult since agreement already is nearly as good as expected experimental error in estimating intensities will permit. Although the R values for each zone are surprisingly sensitive to the boron locations, values of the parameters common to both zones differ by as much as 0.020. Furthermore, attempts to obtain boron positions in the $0kl$ projection (where only data obtained with Cu radiation were available) were unsuccessful. Since the isomer problem had already been adequately resolved, further refinement with the diiodide seemed unprofitable. The partial refinement that was possible with the iodine compound makes it seem quite likely that accurate boron positions could be obtained for $B_{10}H_{12}Br_2$ and study of this compound has been initiated.

Discussion

The dipole moment of $B_{10}H_{14}$ is 3.52 ± 0.02 debye units according to Laubengayer and Bottei.[6] Calculations of Eberhardt, Crawford and Lipscomb[7] show that considerable negative charge should be located on the borons at positions 2. The fact that these atoms are the site of the iodines in $B_{10}H_{12}I_2$ strongly suggests that the mechanism of iodination of the borane is similar to that of an aromatic hydrocarbon in which attack of a positive halogen species occurs at the site of localized negative charge within the substrate molecule. Experiments carried out in this Laboratory by Mr. Gerald Brennan using ICl and N-bromosuccinimide tend to support this mechanism for halogenation and will

(3) J. S. Kasper, C. M. Lucht and D. Harker, *Acta Cryst.*, **3**, 436 (1950). The numbering system used in this paper has been adopted for the present work.

(4) Recalculation of the B–H bond distances using the data of Kasper, Lucht and Harker leads to values somewhat different from those reported by them. The recalculated bond lengths were used in calculating the expected I–I distances.

(5) E. B. Moore, Jr., and W. N. Lipscomb, unpublished results. The author wishes to thank Professor Lipscomb for permission to quote a portion of his results.

(6) A. W. Laubengayer and R. Bottei, THIS JOURNAL, **24**, 1618 (1952).

(7) W. H. Eberhardt, B. L. Crawford and W. N. Lipscomb, *J. Chem. Phys.*, **22**, 989 (1954).

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be reported in detail at a later date. Other substitution reactions which might proceed by similar mechanisms will warrant investigation.

Acknowledgments.—The author is greatly indebted to Professor R. E. Rundle and members of his research group for many helpful discussions during the course of this work. The facilities of the Institute for Atomic Research of Iowa State College were used during this investigation.

AMES, IOWA

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Kinetics of 1,10-Phenanthroline Chelation. II. Effect of Hydroxide Ion on the Dissociation Rate of Tris-(1,10-phenanthroline)-iron(II)[1,2]

BY D. W. MARGERUM

RECEIVED DECEMBER 10, 1956

Hydroxide ion greatly increases the rate of dissociation of tris-(1,10-phenanthroline)-iron(II) despite the fact that there are no acidic protons in the complex. The value of k_0, first-order dissociation rate constant with respect to the complex, is dependent on the hydroxide ion concentration: $k_0 = k_d + k_1[OH^-] + k_2[OH^-]^2 + k_3[OH^-]^3$. The kinetics may be explained by an SN2 mechanism with nucleophilic attack by water or hydroxide ion to form reaction intermediates, which are in turn attacked by water or hydroxide ion, or by an SN1 mechanism with similar intermediates.

Introduction

It is known that the brightly colored complex, tris-(1,10-phenanthroline)-iron(II), is stable in aqueous solution in the pH range 2–9.[3] Outside this pH range there is noticeable dissociation of the complex. Although the rate of dissociation of tris-(1,10-phenanthroline)-iron(II) (hereafter abbreviated $FePh_3^{++}$) has been studied by a number of workers,[4–6] all of these studies have been performed in acidic solutions. Under the conditions of these studies, the rate of dissociation of the complex is first order with respect to the concentration of $FePh_3^{++}$ and independent of acidity. The acidities examined were from 0.005 to 0.50 M H_2SO_4. The kinetics of the over-all iron(II)-1,10-phenanthroline system are summarized as follows,[4] omitting the coördinated water molecules

$$\left.\begin{aligned} Fe^{++} + Ph &\rightleftharpoons FePh^{++} \\ FePh^{++} + Ph &\rightleftharpoons FePh_2^{++} \end{aligned}\right\} \text{Fast}$$

$$FePh_2^{++} + Ph \underset{k_d}{\rightleftharpoons} FePh_3^{++} \quad \text{Slow}$$

where $k_d = 0.0045$ min.$^{-1}$. Only the addition or removal of the third 1,10-phenanthroline molecule to iron(II) proceeds at a measurable rate. Because of the stability of the mono and tris complexes, the bis-(1,10-phenanthroline)-iron(II) ion, $FePh_2^{++}$, does not exist in any appreciable concentration in solutions of varying iron(II) and 1,10-phenanthroline concentration.[7]

Tris-(1,10-phenanthroline)-iron(II) has been resolved into its optical isomers and the rate of its racemization has been studied.[6] The racemization rate is also independent of acidity (from 0.1 to 1.0 M HCl), but is greater than the dissociation rate. It has been suggested that racemization of $FePh_3^{++}$ proceeds both by a dissociation mechanism and by an intramolecular racemization mechanism.

Much more work has been done on the mechanism of substitution reactions with cobalt(III) complexes than with other coördination compounds. When weak nucleophilic groups react with cobalt(III) complexes, the reactions proceed by SN1 kinetics. More powerful nucleophilic substitutions may be interpreted as SN2[8] or SN1CB[9,10] reactions. The SN1CB reaction is one where the conjugate base of the complex is formed prior to a slow first-order step in the reaction mechanism. In support of the SN1CB kinetics it has been pointed out that "complexes containing no acidic protons release their replaceable ligands at a rate independent of the pH of the solution."[10] This generalization may be applicable to the cobalt(III) complexes but it does not fit all complexes. Tris-(1,10-phenanthroline)-iron(II) contains no acidic protons but its dissociation rate in basic solution is highly dependent upon the pH of the solution. This paper is concerned with the nature and significance of the hydroxide ion effect on the rate of dissociation of $FePh_3^{++}$.

Experimental

A stock solution of $FePh_3^{++}$ was prepared using a slight excess of 1,10-phenanthroline so that the concentration of $FePh_3^{++}$ was 4.87×10^{-4} M and the excess 1,10-phenanthroline was 2.55×10^{-4} M. Ten-ml. aliquots of this solution were diluted to 100 ml. volumes in solutions containing KCl, NaOH and slight amounts of ethylenediaminetetraacetic acid. The latter was added to help displace the equilibrium by reacting with Fe(II) and to prevent the precipitation of iron hydroxides. The KCl was used to maintain constant ionic strength. The dissociation rates were followed at 510 mμ with a thermostated (25.0°) Beckman DU spectrophotometer. All measurements were started 1 to 3 minutes after mixing the reagents and readings were taken every 30 or 60 seconds for 10 to 20 minutes.

(1) Presented at the Atlantic City Meeting of the American Chemical Society, September, 1956.

(2) For paper I in this series see THIS JOURNAL, **78**, 4211 (1956).

(3) W. B. Fortune and M. G. Mellon, *Ind. Eng. Chem., Anal. Ed.*, **10**, 60 (1938).

(4) T. S. Lee, I. M. Kolthoff and D. L. Leussing, THIS JOURNAL, **70**, 3596 (1948).

(5) W. W. Brandt and D. K. Gullstrom, *ibid.*, **74**, 3532 (1952).

(6) F. Basolo, J. C. Hayes and H. M. Neuman, *ibid.*, **76**, 3807 (1954).

(7) I. M. Kolthoff, D. L. Leussing and T. S. Lee, *ibid.*, **72**, 2173 (1950).

(8) D. D. Brown, C. K. Ingold and R. S. Nyholm, *J. Chem. Soc.*, 2678 (1953).

(9) J. S. Anderson, H. V. A. Briscoe and N. F. Spoor, *ibid.*, 361 (1943).

(10) R. G. Pearson, R. E. Meeker and F. Basolo, THIS JOURNAL, **78**, 709 (1956).

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Hydroxide ion concentrations were calculated either from the amount of NaOH added or from the pH of the solution using a Beckman Model G pH meter equipped with an E-2 (high alkalinity) electrode. Since some NaOH will react with the added ethylenediaminetetraacetic acid (abbreviated H_4Y), the following calculation was used. It is possible to assume that all the H_4Y added, Y_T, will be present as either HY^{-3} or Y^{-4}. Then from the charge balance in the solution

$$[OH^-] = [\text{NaOH added}] + [Na^+]_0 - 3[Y_T] - [Y^{-4}]$$

where $[Na^+]_0$ is the original concentration of Na^+ resulting from the use of the disodium salt of ethylenediaminetetraacetic acid. The $[Y^{-4}]$ can be estimated from titration curves and the approximate pH of the solution. Since the $[Y_T]$ was maintained between 0.002 and 0.010 M, these corrections were not significant at the higher hydroxide ion concentrations. At low hydroxide ion concentrations pH was also used to calculate the $[OH^-]$ from

$$\log m_{OH} = p\text{H} + \log \frac{K_w}{f_{NaOH}}$$

where $K_w = 1.008 \times 10^{-14}$ and f_{NaOH} was taken from the ionic strength of the solution.[11]

Results

When $FePh_3^{++}$ is placed in basic solutions, its rate of dissociation is much faster than when it is in acidic solutions. The half-life of the bright red complex in sulfuric acid solutions is 2.5 hours while in strong base the colored complex may completely disappear in only ten minutes. Spectrophotometric evidence indicates none of the blue, oxidized state of the complex $FePh_3^{+++}$ is formed during the disappearance of $FePh_3^{++}$. Two additional tests show that oxidation is not responsible for the rapid disappearance of the red complex in strong base. First, the reaction is just as fast in the presence of a reducing agent such as sodium hydrosulfite ($Na_2S_2O_4$). Second, when the solid blue iron(III) complex, $FePh_3(ClO_4)_3$, is dissolved in water and strong base is added, the blue solution immediately turns red due to the formation of the iron(II) complex. Although the 1,10-phenanthroline molecule does not decompose readily, it is also conceivable that hydroxide ion could attack the 1,10-phenanthroline molecule in the iron(II) complex. In order to test for decomposition of 1,10-phenanthroline, a solution of $FePh_3^{++}$ was allowed to dissociate completely in 0.72 M NaOH in the absence of ethylenediaminetetraacetic acid. On neutralization of the solution, the bright red complex, identical with the original solution, re-formed. (It was necessary to add more Fe(II) or else hydroxylamine to re-form all the complex, as the original Fe(II) released from the $FePh_3^{++}$ rapidly formed iron(III) hydroxide in the strong base.) From these tests it is apparent that the 1,10-phenanthroline itself is not decomposed and it can be assumed that the disappearance of the red color is, in fact, due only to the dissociation of the original complex.

The hydroxide ion concentration is either in large excess of the $[FePh_3^{++}]$ or else it is well buffered by the ethylenediaminetetraacetic acid. Hence, during any given kinetic run the $[OH^-]$ is a constant. The presence of excess hydroxide ion and of ethylenediaminetetraacetic acid also displaces the equilibrium so far that the reverse reaction, *i.e.*, the formation of $FePh_3^{++}$, is in all cases negligible over the time the reaction was followed kinetically. Therefore, the dissociation of $FePh_3^{++}$ appears to be first order

$$\frac{-\,d[FePh_3^{++}]}{dt} = k_0[FePh_3^{++}] \qquad (1)$$

where k_0 is a function of $[OH^-]$, ionic strength and temperature. A variation in the $[Y^{-4}]$ from 0.001 to 0.010 M at constant $[OH^-]$ and constant ionic strength indicated that for the concentration range used in these experiments Y^{-4} had no appreciable effect on the dissociation rate.

The rates of dissociation are highly dependent on the $[OH^-]$ as shown in Fig. 1, where three typical first-order plots are given. As the hydroxide ion concentration is increased, the value of k_0 becomes larger and larger. Figures 2 and 3 illustrate the effect of $[OH^-]$ on k_0 with three different series of constant ionic strength runs. Increased ionic strength decreases the effect of $[OH^-]$ on k_0, but k_0 still increases rapidly with $[OH^-]$ even at $\mu = 4.5$. The experimental data are summarized in Table I.

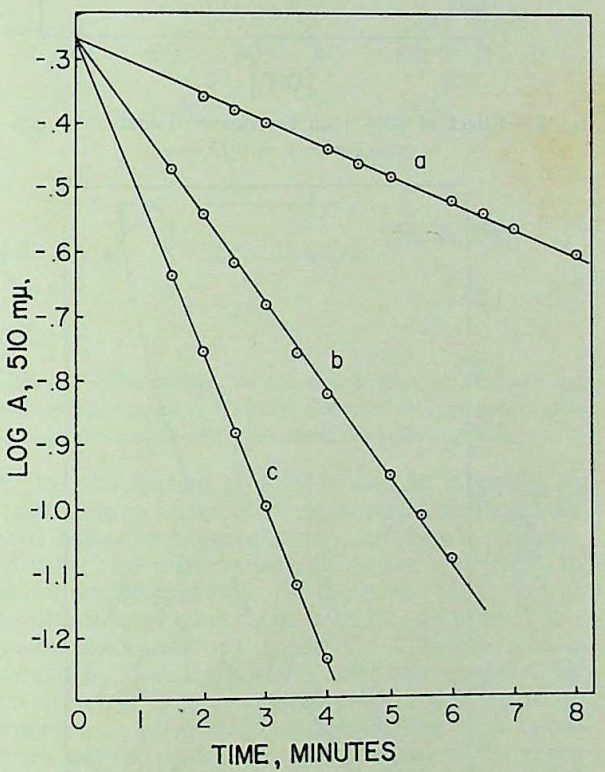

Fig. 1.—First-order plot of dissociation of $FePh_3^{++}$ at various $[OH^-]$: a is 0.098 M $[OH^-]$; b is 0.496 M $[OH^-]$; and c is 0.997 M $[OH^-]$.

At low $[OH^-]$, k_0 can be expressed as $k_d + k_1[OH^-]$, where k_d is the intercept in Figs. 2 and 3 and k_1 is the slope of the straight line near the intercept. The constant, k_d, is merely k_0 in neutral (or acid) solutions and experimental values for k_d at various ionic strengths are summarized in Table II. These values are in agreement with the previously determined values in acidic solutions except that previously the effect of ionic strength was not taken into account.

(11) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, N. Y., 1950, p. 560.

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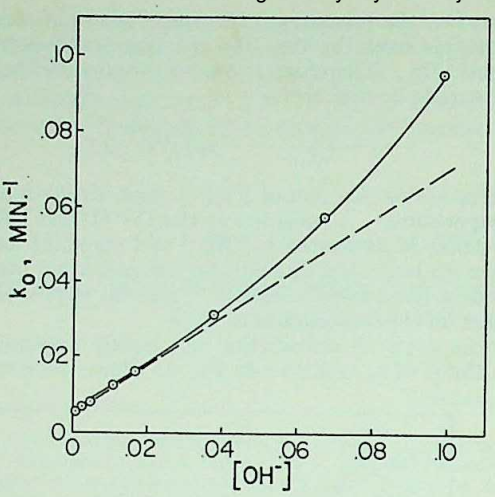

Fig. 2.—Effect of [OH$^-$] on the observed first-order constant with $\mu = 0.15$.

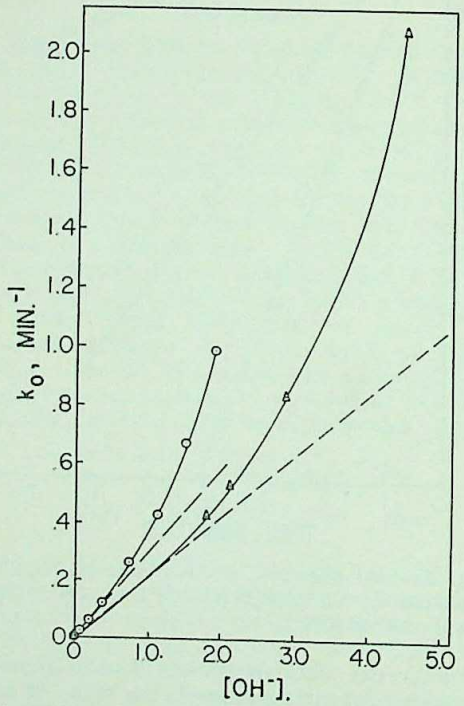

Fig. 3.—Effect of [OH$^-$] on the observed first-order constant: O, for $\mu = 2.01$; △, for $\mu = 4.55$.

As the [OH$^-$] increases, k_0 becomes more dependent on [OH$^-$] and can be expressed as

$$k_0 = k_d + k_1[OH^-] + k_2[OH^-]^2 \quad (2)$$

so that

$$\frac{k_0 - k_d}{[OH^-]} = k_1 + k_2[OH^-] \quad (3)$$

From eq. 3, a plot of $(k_0 - k_2)/[OH^-]$ against [OH$^-$] should give a straight line of intercept k_1 and slope k_2. Figure 4 indicates that eq. 2 adequately fits the behavior of k_0 up to about 1 M hydroxide ion. Despite the inherent errors from small differences between k_0 and k_d at low [OH$^-$], the

TABLE I

EFFECT OF HYDROXIDE ION AND IONIC STRENGTH ON THE OBSERVED DISSOCIATION RATE CONSTANT OF $FePh_3^{++}$

Ionic strength μ	[OH$^-$]	k_0 (min.$^{-1}$)	Ionic strength μ	[OH$^-$]	k_0 (min.$^{-1}$)
0.150	0.000470	0.00524	1.047	0.0653	0.0286
.150	.00210	.00656	1.047	.137	.0571
.154	.00460	.00800	1.047	.352	.151
.149	.0103	.0125	1.049	.495	.226
.151	.0163	.0157	1.049	.710	.349
.151	.0374	.0311	1.048	.854	.450
.152	.0665	.0571	1.050	.997	.559
.153	.0982	.0946	2.01	.0635	.0237
.556	.000421	.00478	2.01	.178	.0596
.551	.00595	.00672	2.01	.369	.1203
.556	.0143	.0113	2.02	.752	.260
.552	.0453	.0244	2.01	1.134	.427
.553	.0608	.0336	2.00	1.517	.670
.551	.1373	.0743	2.00	1.897	.990
.549	.281	.161	4.56	1.79	.425
.549	.353	.206	4.55	2.15	.526
.550	.496	.310	4.56	2.87	.838
1.045	.00790	.00832	4.56	4.46	2.07

TABLE II

EFFECT OF IONIC STRENGTH ON THE INDIVIDUAL DISSOCIATION RATE CONSTANTS OF $FePh_3^{++}$

Ionic strength μ	Dissociation constants, min.$^{-1}$			
	k_d	k_1	k_2	k_3
0.15	4.96×10^{-3}	0.64	2.5	0.3
.55	4.54×10^{-3}	.45	0.33	.06
1.05	4.27×10^{-3}	.36	.17	.03
2.01	3.86×10^{-3}	.29	.06	.02
4.56	3.25×10^{-3}	.21	.014	.006

intercepts correspond to k_1 and straight line plots are obtained. However, Fig. 5 indicates that at still higher [OH$^-$] k_0 increases even more rapidly with [OH$^-$] than by eq. 2. It is possible to fit all the values of k_0 up to 4.5 M NaOH by assuming the expression

$$k_0 = k_d + k_1[OH^-] + k_2[OH^-]^2 + k_3[OH^-]^3 \quad (4)$$

The values of k_d, k_1, k_2 and k_3, which become increasingly dependent on the ionic strength of the solution, are given in Table II for various ionic strengths. In the evaluation of all these constants,

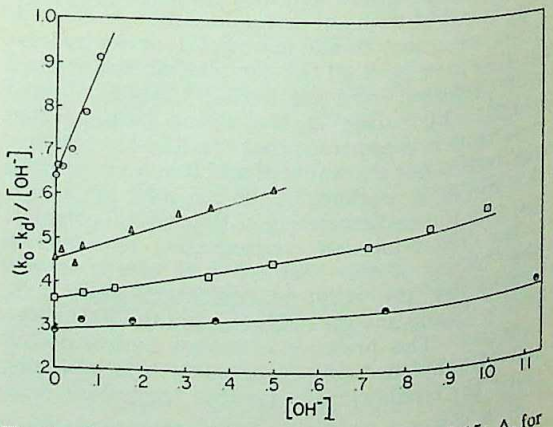

Fig. 4.—Dependence of k_0 on eq. 3: O, for $\mu = 0.15$; △, for $\mu = 0.55$; □, for $\mu = 1.05$; ●, for $\mu = 2.01$.

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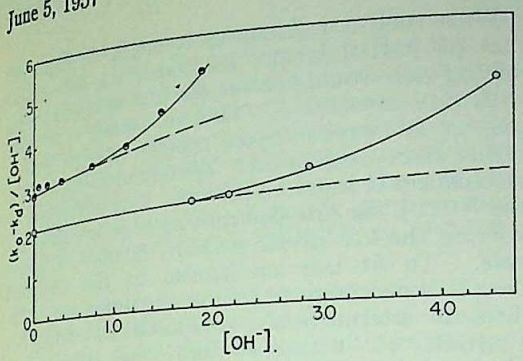

Fig. 5.—Dependence of k_0 on eq. 3: ⊖, for $\mu = 2.01$; O, for $\mu = 4.56$.

it was useful to assume that their logarithms *versus* $\sqrt{\mu}$ would appear as smooth curves. The values of k_3 are only estimates, especially at low ionic strengths. Increased ionic strength consistently suppresses the size of the rate constants even at very high ionic strengths. There is no apparent inversion of the k_1 or k_2 values above one molar KCl that can account for the rapid increase in k_1 at high $[OH^-]$. Equation 4 and the k values in Table II can be used to accurately predict the dissociation rate of $FePh_3^{++}$ at any concentration of hydroxide ion.

Discussion

It has previously been shown that only the loss of the first Ph molecule from $FePh_3^{++}$ is a kinetically important step in the dissociation of the complex. The present study has borne this out as in all cases the kinetics appear first order with respect to $FePh_3^{++}$ and independent of Ph concentration. Therefore, any mechanism involving the formation of kinetically significant bis-(1,10-phenanthroline)-iron(II) complexes, such as that below, would be ruled out.

$$FePh_3^{++} \rightleftharpoons \left\{ \begin{matrix} FePh_2(H_2O)_2^{++} + Ph \\ FePh_2(OH)(H_2O)^{+} + Ph \\ FePh_2(OH)_2 + Ph \end{matrix} \right\} \longrightarrow \text{Products}$$

This mechanism is not possible because the varying concentration of Ph during a reaction would alter the kinetics from those observed.

If the $FePh_3^{++}$ complex is compared to the cobalt(III) complexes, the question arises whether or not the iron(II) complex is subject to nucleophilic attack by water or hydroxide ion. Two sets of mechanisms can be considered, one assuming water and hydroxide ion attack and the other assuming hydroxide ion catalysis. The nucleophilic mechanism is discussed first.

1. **Nucleophilic Attack.**—If it is assumed that hydroxide ion is capable of nucleophilic attack on $FePh_3^{++}$, it would be consistent to assume that the water molecule behaves similarly so that in neutral solutions the dissociation of $FePh_3^{++}$ proceeds by attack of water. The observed kinetics show that k_0 has greater than a first-order dependence on hydroxide ion. Since a combination of attack by water and hydroxide ions to give bi-, tri- and tetramolecular reactions is unreasonable, it is necessary to assume some type of unstable reaction intermediate where H_2O or OH^- is associated with $FePh_3^{++}$. Although this intermediate might be pictured as some type of complex with a coördination number of seven, it is more convenient to represent it as having one singly-bonded 1,10-phenanthroline molecule. The latter is assumed in Fig. 6. Since two nitrogen–iron bonds must be broken

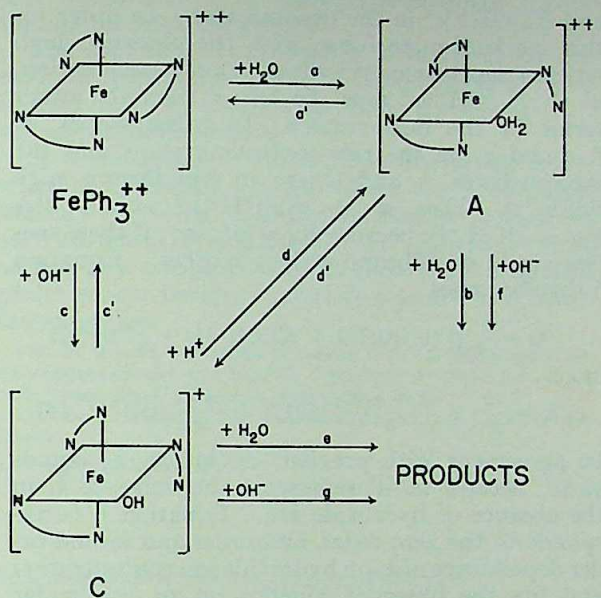

Fig. 6.—Mechanism for the dissociation of $FePh_3^{++}$ by nucleophilic attack of H_2O and OH^-: N–N represents 1,10-phenanthroline; A and C are unstable intermediates.

in the dissociation of a Ph molecule, it would be reasonable to expect that under nucleophilic attack both bonds would not react and break simultaneously. In other words, a four centered reaction would not be expected. If the bonds do not break simultaneously then there must be an intermediate species such as A or C in Fig. 6. The species A is formed by the attack of H_2O and the species C by the attack of OH^-. Once A is formed it would be expected to come to rapid equilibrium with C because only a proton transfer is involved in going from one intermediate to the other. The intermediates, A or C, may revert back to $FePh_3^{++}$ by unimolecular reactions or they may lose the activated Ph molecule by subsequent nucleophilic attack by another H_2O or OH^-.

Let

$$K_d = \frac{d'}{dK_w} = \frac{[C]}{[OH^-][A]}$$

and use the steady-state approximations to assume that $d[A]/dt + d[C]dt = 0$. From Fig. 6

$$\frac{-d[FePh_3^{++}]}{dt} = k_0[FePh_3^{++}] = (a + c[OH^-])\,[FePh_3^{++}] - a'[A] - c'[C]$$

and assuming no reversible reaction from the products

$$[A] = \frac{a + c[OH^-]}{a' + b + f[OH^-] + K_d[OH^-](c' + e + g[OH^-])}\,[FePh_3^{++}]$$

and

$$[C] = K_d[OH^-][A]$$

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Therefore, the rate constant[12] is

$$k_0 = (a + c[OH^-]) \frac{b + f[OH^-] + K_d[OH^-](e + g[OH^-])}{a' + b + f[OH^-] + K_d[OH^-](c' + e + g[OH^-])} \quad (5)$$

In eq. 5, the numerator and denominator of the part in the brackets are identical except for a' and $K_d[OH^-]c'$ in the denominator. In order for this mechanism to agree with the observed high order of dependence of hydroxide ion concentration, $a' + K_d[OH^-]c'$ must be larger than the other terms in the denominator. In other words, b, f, e and g are the rate-controlling steps and the intermediates A and C are in equilibrium with $FePh_3^{++}$. Then $a' + K_d[OH^-]c'$ equals $a'/a(a + c[OH^-])$, because $K_d = a'c/ac'$, if these species are in equilibrium with each other. Equation 5 then becomes

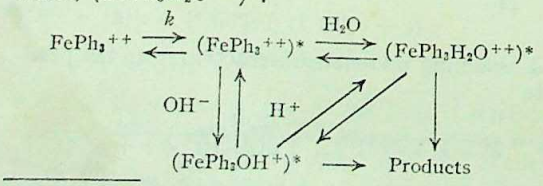
$$k_0 = \frac{a}{a'} \{b + f[OH^-] + K_d[OH^-](e + g[OH^-])\}$$

or

$$k_0 = \frac{ab}{a'} + \frac{af + aeK_d}{a'}[OH^-] + \frac{agK_d}{a'}[OH^-]^2 \quad (6)$$

In agreement with previous definition, k_d equals ab/a', because ab/a' represents the value of k_0 in the absence of hydroxide ion. Equation 6 corresponds to the zero-order, first-order and second-order dependence of k_0 on hydroxide ion concentration and fits the observed kinetics up to one molar $[OH^-]$. The introduction of a $[OH^-]^3$ term above one molar hydroxide ion concentration may be due to several factors. At such high ionic strengths it is possible that specific salt effects, characteristic of NaOH as opposed to KCl, might change the activity coefficients. This would be equivalent to having a high concentration of NaOH cause an increase in the values of k_d, k_1 and k_2, something which is not observed with KCl. Another explanation of the $[OH^-]^3$ term can be derived by extending the kinetic picture of Fig. 6. A second Ph molecule in intermediate C can be activated to form another intermediate, D, with two singly bonded phenanthroline molecules. If D then goes to product by OH^- attack, the system would have a $[OH^-]^3$ term.

2. Hydroxide Ion Catalysis.—An alternative explanation to nucleophilic attack may be postulated by assuming that $FePh_3^{++}$ spontaneously forms an intermediate, $(FePh_3^{++})^*$, where one Ph molecule is only partially bonded to Fe(III). This intermediate might rapidly accept a water molecule or hydroxide ion prior to the complete dissociation of the Ph molecule from the Fe(II). The intermediate with a hydroxide ion, $(FePh_3OH^+)^*$, would lose the partially bonded Ph molecule more readily than the intermediate formed with water, $(FePh_3H_2O^{++})^*$.



With such a mechanism it might be expected that as $[OH^-]$ greatly increased, the rate-determining step would become the first activation step with rate constant k. This, of course, is not the case as k_0 increases more rapidly at high $[OH^-]$ rather than leveling off. Therefore, to apply this mechanism it must be assumed that regardless of the $[OH^-]$, the rate-determining steps are those involving the loss of the partially bonded Ph molecule. To fit this mechanism to the observed data it is necessary to assume the formation of additional intermediates, $(FePh_3(OH)_2^0)^*$ and $(FePh_3(OH)_3^-)^*$, with two and three one-bonded phenanthroline molecules, respectively. If nucleophilic attack is not allowed, then each of these intermediates must be preceded by their corresponding activated species with which OH^- equilibrates.

Another mechanism should be mentioned in addition to the two already considered, both of which change the bonding to Fe(II). Ion pair formation between $FePh_3^{++}$ and OH^- could conceivably lead to intermediates with one or more OH^-, which would dissociate at different rates. However, other ions such as Cl^-, F^-, NO_3^- and ClO_4^- might be expected to form ion pairs as readily as OH^-, but none of these ions increase the dissociation rate. In fact, as noted earlier, increased ionic strength decreases the dissociation rate rather than increasing it. Hence, an ion pair type mechanism is not possible unless OH^- forms some unique species with $FePh_3^{++}$, in which case it would essentially be bonded to Fe(II) and no longer a mere ion pair.

The dissociation of $FePh_3^{++}$ is not the only phenanthroline reaction where it has been necessary to postulate reaction intermediates to explain the kinetics. The dissociation and formation rates of mono-(1,10-phenanthroline)-nickel(II) are affected by acidity in such a way as to necessitate the assumption of a partially bonded intermediate.[2] Other studies on the racemization of $FePh_3^{++}$ have shown an intramolecular racemization in addition to the dissociation racemization.[6] The intramolecular racemization can be explained readily from the point of view of a partially bonded intermediate. It is possible to predict that the racemization reaction should proceed faster in basic solutions.

The exact nature of the reaction intermediates with 1,10-phenanthroline complexes is not clear. The intermediate might be considered as having opened a chelate ring and coördinated another nucleophilic group to the central ion shown in Fig. 6. However, the fact that the nitrogen atoms in 1,10-phenanthroline are only 2.5 Å. apart and that the 1,10-phenanthroline molecule is a fixed planar structure has been used as steric arguments against any tendency for 1,10-phenanthroline to behave as a monodentate group.[6] On the other hand, optical isomers of 4,5-disubstituted phenanthrenes have been obtained.[13] These compounds have a structure similar to 1,10-phenanthroline and optical isomers can exist only by steric repulsion causing nonplanarity of the molecule. Hence, it is not impos-

(12) Equation 5 may also be derived by first assuming only that $d[A]/dt = 0$, and $d[C]/dt = 0$ and then simplifying the resulting expression by assuming that d' and c' are very small.

(13) M. S. Newman and A. S. Hussey, THIS JOURNAL, 69, 3023

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sible to have a reaction intermediate with a broken chelate ring. The alternative explanation is a reaction intermediate with a seven coördinated iron(II) ion. Such a coördination intermediate would presumably necessitate changes in electron configuration of the complex, which would account for the slowness of its formation. Somewhere in the dissociation reaction the electronic configuration for iron(II) changes from $d^2d^2d^2D^2SP^3$ to $d^2d^1d^1d^1d^1SP^2D^2$.

It is not possible from this work to definitely establish whether the hydroxide ion effect on $FePh_3^{++}$ is due to an SN1 or an SN2 mechanism. Both mechanisms involve partially dissociated species and neither mechanism accounts for the observed $[OH^-]^3$ term without the introduction of several intermediates. However, the SN2 mechanism is the simpler of the two. It has fewer intermediates and gives a $[OH^-]^2$ dependence at low hydroxide ion concentrations without the necessity of assuming an intermediate with two activated Ph molecules. The hydroxide ion is not the only nucleophilic ion which can accelerate the dissociation of $FePh_3^{++}$. Cyanide ion and thiocyanate ion both cause faster dissociation of $FePh_3^{++}$.[14] The cyanide ion kinetics with $FePh_3^{++}$ resemble the hydroxide ion kinetics, with a reaction intermediate likely. The aqueous cyanide ion causes faster dissociation than the hydroxide ion. All of these factors contribute to the feasibility of an SN2 mechanism with reaction intermediates containing nucleophilic groups.

The fact that it is possible to bring about the rapid dissociation of $FePh_3^{++}$ should prove of value in analytical separations involving the use of 1,10-phenanthroline kinetics.[15]

It is naturally of considerable interest to know whether hydroxide ion will affect the dissociation kinetics of other 1,10-phenanthroline complexes such as nickel(II) and cobalt(III). These systems, as well as a comparison of the effect of other nucleophilic groups besides hydroxide ion, are now under investigation.

(14) P. Grimes, "Reactions of Anions with 2,2′-Bipyridine, 1,10-Phenanthroline and the Iron(II) Complexes of These Reagents," M.S. Thesis, Ames, Iowa, Iowa State College, 1956.

(15) D. W. Margerum and Charles V. Banks, *Anal. Chem.*, **26**, 200 (1954).

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SYDNEY]

Tridentate Chelate Compounds. I

BY FRANCIS LIONS AND KENNETH V. MARTIN[1]

RECEIVED DECEMBER 10, 1956

New tridentate chelate compounds containing three donor nitrogen atoms and possessing structural features resembling those of terpyridine have been prepared and shown to form coördination compounds readily. Some polymers possessing recurring tridentate chelate groups also have been prepared and their capacity to combine with metal salts demonstrated. Some of the iron containing polymers have unusual magnetic properties.

2,6-Bis-(α-pyridyl)-pyridine (I), better known by its trivial name "terpyridine," is a most important tridentate chelate compound which has been extensively studied. However, it is relatively inaccessible. In 1953 one of the authors and his co-workers[2] reported briefly on the preparation and use of 8-(α-pyridylmethyleneamino)-quinoline (II) as a tridentate chelate compound with constitutional features similar to those of I and showed that it coördinated with iron(II) salts similarly to I. The present paper describes a number of new tridentate chelate compounds, each containing three donor nitrogen atoms and some possessing details of molecular structure similar to I.

2-Aminomethylpyridine (III) is available from the reduction with zinc dust and acetic acid of pyridine-2-aldoxime.[3] We have also found that it can be synthesized from the 2-chloromethylpyridine of Matsumura[4] by condensation with potassium phthalimide using Bolhofer and Shea-han's[5] modification of the Gabriel reaction, and hydrolysis of the 2-phthalimidomethylpyridine so obtained. However, the over-all yield is small and the method of Craig and Hixon is preferable.

III reacts readily with pyridine-2-aldehyde to give the Schiff base 2-(α-pyridylmethyleneaminomethyl)-pyridine (IV) as a pale yellow oil. IV might well be expected to function as a tridentate chelate compound with all three nitrogen atoms acting as donors and attaching the tridentate residue to a metal atom in two coplanar 5-membered ring "chelate loops."[6] The molecules of both I and IV possess the same sequence of atoms and bonds, *viz.*, –N=C–C=N–C–C=N–, in the donor chain, so that at least some of the possibilities which exist for double bonding and resonance must be similar for the molecules of both substances.

Addition of iron(II) sulfate to an aqueous suspension of II results in formation of an intensely red-colored solution from which bis-(2-(α-pyridylmethyleneaminomethyl) - pyridine) - iron(II) perchlorate (V) can be precipitated. This salt is diamagnetic and must apparently be an octahedral iron(II) complex salt with lower level ($3d^24s4p^3$) covalent bonds. Its complex cation must be very similar structurally to that of the bis-terpyridine iron(II) salts, each tridentate residue lying in one

(1) University Research Fund Student of the University of Sydney.

(2) F. P. Dwyer, N. S. Gill, E. C. Gyarfas and F. Lions, THIS JOURNAL, **75**, 3834 (1953).

(3) L. C. Craig and R. M. Hixon, *ibid.*, **53**, 4367 (1931).

(4) E. Matsumura, *J. Chem. Soc. Japan*, **74**, 363 (1953); *cf.* C.A. **48**, 6442b (1954).

(5) J. C. Bolhofer and W. A. Shehan, THIS JOURNAL, **72**, 2786 (1950).

(6) *Cf.* F. P. Dwyer, N. S. Gill, E. C. Gyarfas and F. Lions, *ibid.*, **74**, 4188 (1952).

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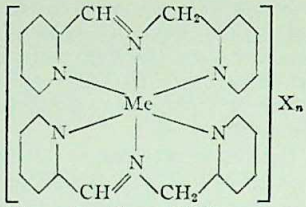
or other of two equatorial planes at right angles to each other, the metal atom being in both planes



V, Me = Fe, X = (ClO_4), $n = 2$
VI, Me = Co, X = (ClO_4), $n = 2$
VII, Me = Co, X = I, $n = 3$.

(Fig. 1). The complex cation of V should thus exist in enantiomorphous forms.

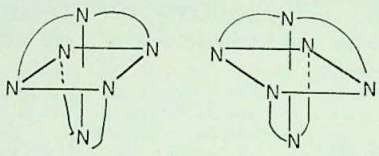
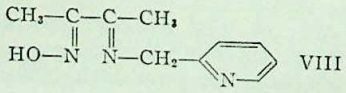


Fig. 1.

Addition of cobalt(II) chloride to an ethanolic solution of IV leads to development of a deep-blue color and blue bis-(2-(α-pyridylmethyleneaminomethyl)-pyridine)-cobalt(II) perchlorate (VI) can be precipitated. Its magnetic moment of 4·3 Bohr magnetons indicates the use of upper level ($4s4p^34d^2$) covalent bonds. Treatment of the blue ethanolic solution of the complex cobalt(II) chloride corresponding to VI with a mild oxidising agent, such as aqueous hydrogen peroxide, changes the color to brown. After destruction of excess peroxide by boiling, addition of potassium iodide to the cooled solution leads to precipitation of diamagnetic bis-(2-(α-pyridylmethyleneaminomethyl)-pyridine)-cobalt(III) iodide (VII). Structurally, the complex cations of VI and VII must be constituted similarly to those of V.

Interaction of III and diacetyl monoxime in hot ethanol leads to formation of colorless crystalline 2-oximino-3-methyl-4-aza-5-α-pyridyl-Δ^3-pentene (VIII). VIII coördinates readily with iron(II) and cobalt salts. Thus, solid VIII readily dissolves in aqueous iron(II) sulfate solutions with development of an intense red color and diamagnetic bis-(2-oximino-3-methyl-4-aza-5-α-pyridyl-Δ^3-pentene)-iron(II) iodide (IX) readily can be precipitated by addition of a soluble iodide.

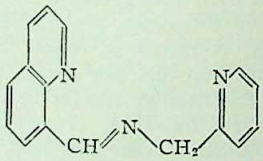


VIII

Interaction of VIII with cobalt(II) chloride in aqueous ethanol followed by oxidation with cerium(IV) nitrate leads to formation of the complex bis-(2-oximino-3-methyl-4-aza-5-α-pyridyl-Δ^3-pentene) cobalt(III) salt and the diamagnetic iodide X can be precipitated. Heating of the reaction mixture during the preparation leads to decomposition and liberation of diacetyl. In each of the complex salts IX and X the two residues of VIII function as tridentates without proton loss from the oximino group, each tridentate residue forming two coplanar 5-membered ring chelate loops with the metal atom, the structural pattern being similar to that of Fig. 1.

We have again prepared 8-(α-pyridylmethyleneamino)-quinoline[2] (II) and have found that it combines readily with cobalt(II) salts to give complex cobalt(II) salts which can be oxidized to the cobalt(III) state. Thus, bis-(8-(α-pyridylmethyleneamino)-quinoline)-cobalt(III) perchlorate can be obtained as a diamagnetic crystalline solid. The relative ease of synthesis of II and similar compounds suggests commencement of a study of the coördinating capacity of substituted derivatives of XI. It has already been amply demonstrated that substituents in the 2,2′-bipyridine or the 1,10-phenanthroline molecule can affect the chelating power, whether because of steric or electron-attracting or -repelling effects.[7] We have condensed pyridine-2-aldehyde with 8-aminoquinaldine[8] to obtain the Schiff base 8-(α-pyridylmethyleneamino)-2-methylquinoline (XII) and have found that XII coördinates readily with iron(II) salts to give diamagnetic intensely-green bis-(8-(α-pyridylmethyleneamino)-2-methylquinoline)-iron(II) salts. The intensity of the color is indistinguishable from that obtained with XI and it seems reasonable to infer that the single substituent methyl group in the quinoline nucleus does not materially affect the chelating capacity, despite its proximity to one of the donor nitrogen atoms. This is in marked contrast to the effect on the chelating power of 2,2′-bipyridine or of 1,10-phenanthroline of methyl groups similarly introduced into positions adjacent to the donor nitrogen atoms.

Quinoline-8-aldehyde[9] condenses readily with 2-aminomethylpyridine (III) to give 2-(8′-quinolylmethyleneaminomethyl)-pyridine (XVI), which coördinates readily as a tridentate chelate compound with iron(II) sulfate in aqueous solution. From the resulting intensely-green solution can be isolated green crystalline diamagnetic bis-(2-(8′-quinolylmethyleneaminomethyl) - pyridine) - iron(II) iodide (XVII). It is worth noting that of the two chelate loops formed by a molecule of XVI when it coördinates with a metal atom, one is a five-membered ring whilst the other is six-membered.



XVI

In any consideration of design of new tridentate chelate compounds related to I cognizance must be taken of the recent availability of pyridine-2,6-dialdehyde (XVIII). XVIII will condense with primary amines (2 mols.) to give Schiff bases of the general formula XIX in which there is the same sequence of donor atoms and bonds as

(7) *Cf. e.g.*, W. W. Brandt, F. P. Dwyer and E. C. Gyarfas, *Chem. Revs.*, **54**, 991 (1954).
(8) D. L. Hammick, *J. Chem. Soc.*, 1302 (1926).
(9) R. C. Elderfield and M. Siegel, THIS JOURNAL, **73**, 5622

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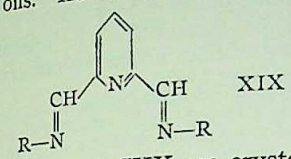
in I. When R is methyl or ethyl in XIX these bases are oils. However, when R is phenyl or



XIX

benzyl the compounds XIX are crystalline solids. These coördinate readily with metal salts as tridentate chelates. Thus, it is quite easy to prepare the red diamagnetic bis-(2,6-pyridylene-dimethyleneaniline)-iron(II)[10] perchlorate (XX) and bis-(2,6-pyridylene-dimethylenebenzylamine)-iron(II) bromide (XXI), typical octahedral iron(II) complex salts with lower level ($3d^2 4s 4p^3$) covalent bonding. Structurally, the planar tridentate residues in a molecule of one of them must be situated in two planes at right angles, and since these residues are symmetrical, the complex ion must be identical with its mirror image so that the salts are not resolvable (Fig. 2).

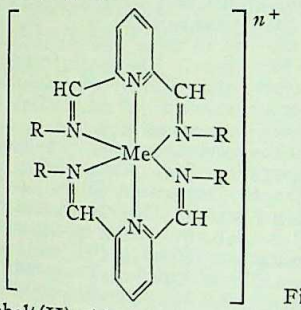


Fig. 2.

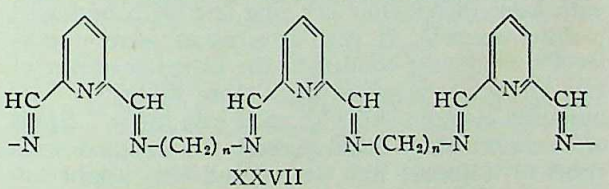
From cobalt(II) chloride and XIX (R = $-CH_2C_6H_5$) in aqueous ethanol can be obtained in solution bis-(2,6-pyridylene-dimethylenebenzylamine)-cobalt(II) chloride. The corresponding iodide XXII, which crystallizes in dark brown needles, is paramagnetic with a magnetic moment of 3.8 Bohr magnetons. The chloride can be oxidized in solution with chlorine and, eventually, diamagnetic bis-(2,6-pyridylene-dimethylenebenzylamine)-cobalt(III) iodide can be isolated. This oxidation cannot be effected with any rapidity with cerium(IV) nitrate in nitric acid solution, almost pure complex cobalt(II) salt being recoverable.

When copper(II) chloride is allowed to react with XIX (R = $-CH_2C_6H_5$) in ethanol a bright green color develops and a solid separates. Addition of more base results in re-solution of the solid and change of color to grey-green. From this solution perchloric acid precipitates bis-(2,6-pyridylene-dimethylenebenzylamine)-copper(II) perchlorate (XXIII). We consider this salt to be an octahedral copper(II) complex salt with $4s 4p^3 4d^2$ upper level covalent bonds. Six-covalent copper(II) complexes are not novel.[11]

Pyridine-2,6-dialdoxime (XXIV) appears to function as a tridentate chelate compound. Thus, when it is treated in aqueous ethanol solution with iron(II) sulfate and then sodium acetate, a deep-red crystalline solid $C_{14}H_{11}N_6O_4FeNa$ (XXV) is obtained. This is a binary electrolyte with the coördinated iron atom in the anion. However, further consideration of its structure is reserved for a later paper.

Reduction of XXIV with zinc dust and acetic acid leads to formation in good yield of 2,6-bis-aminomethylpyridine (XXVI), a colorless oil which absorbs carbon dioxide from the air but which can be characterized by its crystalline bis-salicylidene or its bis-piperonylidene derivative. XXVI reacts readily with iron(II) sulfate in aqueous solution to give deep green bis-(2,6-di-(aminomethyl)-pyridine)-iron(II) sulfate, and then addition of potassium iodide causes precipitation of the corresponding iodide, a paramagnetic salt with a magnetic moment of 5.2 Bohr magnetons, indicative of upper level covalent bonding. Exposure of this salt to moisture and air leads to breakdown and liberation of iron(III) hydroxide. XXVI also reacts readily with nickel(II) salts and bis-[2,6-di-(aminomethyl)-pyridine]-nickel(II) bromide was isolated as deep mauve-colored needles.

Among the condensation products obtainable from XVIII and primary amines are the linear polymers derivable from diamines. We have condensed XVIII with ethylenediamine, 1,6-diaminohexane and benzidine and have obtained solid infusible polymers from each condensation. The molecules of each of them contain potential tridentate chelate groups, a section of the polymer chain occurring in the molecules of each of the former two being capable of formulation as in XXVII. It would therefore seem reasonable to ex-



XXVII

pect them to be able to absorb certain kinds of metal salt from solution through the ability of the recurring tridentate groups to coördinate with the metal atoms. The polymer derived from benzidine apparently possesses very little capacity for coördination with ions such as iron(II) which favor an octahedral environment. However it will combine with salts such as copper(II) chloride. The polymers from ethylenediamine and hexamethylenediamine do readily combine with salts such as iron(II) sulfate, rapidly acquiring a purplish-blue color when suspended in aqueous solutions of it.

Consideration of the spatial requirements of the various atoms in the molecule of the polymer derived from hexamethylenediamine shows that it should be possible for two successive tridentate residues in the chain to coördinate with the same six-covalent metal atom, the two planar tridentate residues becoming disposed in two planes at right angles to each other. If this process were to occur regularly along the chain the resulting giant molecule might be looked on as containing a series of sexadentate chelate residues regularly spaced along a linear molecule and each coördinated through six nitrogen atoms to a metal atom. However, it

(10) The bivalent radical C_5H_4N is named pyridylene by analogy with phenylene.

(11) *Cf. e.g.*, G. Peyronel, *Gazz. chim. ital.*, **71**, 363 (1951); E. I. Ottstott and H. A. Laitinen, THIS JOURNAL, **72**, 4724 (1950); S. Kirschner, *ibid.*, **78**, 2372 (1956).

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is quite unlikely that such regularity could occur. Thus, if in a series of five successive three-nitrogen-atom groups along the chain the first and second became bonded to a metal atom (as a sexadentate) and the fourth and fifth did also, then the third group—now an isolated tridentate group—might function by bonding to a metal atom to produce cross-linking of neighboring polymer chains. It might also remain unattached. Such a process of forming recurring sexadentate coördinated ions along the chain of the polymer would involve very complicated twining and twisting and it hardly seems probable that a polymer molecule, once formed, could undergo this process.

In fact, suspension of the powdered water-insoluble 1:1 polymer obtained by condensing XVIII with hexamethylenediamine in an aqueous solution containing excess iron(II) sulfate, followed by boiling, leads to the taking up of one molecule of iron(II) sulfate for each two residues of XVIII. The suspended solid acquires a deep reddish-blue color. This iron-containing solid is insoluble in any of the common solvents and does not melt below 300°. The analytical results suggest that in its molecules each iron atom is probably bonded to the six nitrogen atoms from two tridentate residues, the results agreeing with an empirical formula $C_{26}H_{34}N_6FeSO_4 \cdot 6H_2O$. The magnetic behavior was quite unusual, the solid being ferromagnetic with a molar susceptibility (ψ_m) of $155{,}000 \times 10^{-6}$ c.g.s. unit. It is difficult, without much more evidence, to draw conclusions concerning the molecular structure. Ferromagnetism is usually observed in lattices of magnetic particles with loose interatomic bonding and with unpaired parallel spins.[12] If each iron atom were upper-level convalently bonded to the nitrogen atoms of two tridentate residues then there would be four unpaired electron spins for each iron atom. Spins of one iron atom could possibly be coupled with spins of adjacent iron atoms and this might account for the observed ferromagnetism.

When an ethanolic solution of XVIII is added to a solution of hexamethylenediamine and iron(II) sulfate in aqueous ethanol (polymer preparation in the presence of iron(II) sulfate) a small amount of an insoluble solid separates from the solution. Addition of a soluble perchlorate to the red filtrate then causes precipitation of a diamagnetic red complex iron(II) perchlorate. From its elementary composition it would appear that in this salt two iron(II) atoms are bound for every seven tridentate residues in the polymer molecule. Since the material is diamagnetic it seems probable that the immediate environment of each iron atom contains six bound nitrogen atoms (from two tridentate residues), and the solubility of the sulfate in water suggests that these are derived from successive residues in the same polymer chain and that there is no cross-linking.

Suspension of the finely ground pre-formed 1:1 polymer in an alcoholic solution of cobalt(II) chloride followed by boiling, leads to the taking up of one molecule of cobalt(II) chloride for each residue of XVIII, the polymer being converted into a brown solid. This was found to be paramagnetic (3.7 Bohr magnetons). Without further prolonged studies it is only possible to guess at its structure, but it could be that there are present chlorine bridges linking cobalt atoms in structures of the type shown in Fig. 3.

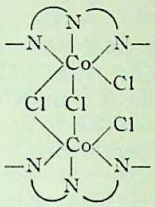

Fig. 3.

These preliminary studies with polymers are being continued.

Experimental

2-Aminomethylpyridine.—The base, best prepared by the method of Craig and Hixon,[3] was a colorless oil, b.p. 104° (20 mm.). It also was prepared as follows. 2-Picoline-N-oxide (4 g.) was added to a solution of *p*-toluenesulfonyl chloride (7 g.) in dry benzene (20 ml.). After 4 hours the benzene was removed *in vacuo* and the residue heated at 170° (oil-bath) for 1 hour. The residual thick dark oil was washed with ether, then treated with saturated aqueous sodium bicarbonate solution (20 ml.). Three extractions with ether (50 ml.) were then made and the combined extracts dried and the solvent removed. The remaining crude 2-chloromethylpyridine (3 g., picrate had m.p. 144°) was dissolved in dimethylformamide (20 ml.) and potassium phthalimide (5 g.) added. The stirred mixture was then heated at 100° for 6 hours. After cooling, aqueous potassium hydroxide solution (50 ml. of 10%) was added and two ether extractions (25 ml.) made. The combined ether extracts were washed with 5% potassium hydroxide solution, dried over solid potassium hydroxide and then the ether removed. After many recrystallizations from ethanol **2-phthalimidomethylpyridine** (0.5 g.) was obtained in colorless plates, m.p. 125°.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.6; H, 4.2; Found: C, 70.5; H, 4.4.

Hydrolysis of this compound to 2-aminomethylpyridine was effected by the method of Ing and Manske.

Bis-[2-(α-pyridylmethyleneaminomethyl)-pyridine]-iron(II) Perchlorate Monohydrate (V).—Admixture of equimolecular proportions of freshly distilled pyridine-2-aldehyde and III caused immediate reaction and rise of temperature to about 60°. The condensation was completed by warming at 100° for 15 min. The yellow oily Schiff base IV could not be induced to crystallize. Addition of aqueous iron(II) sulfate (0.7 g. of the heptahydrate) to IV (1 g., 2 moles) led to formation of an intensely red solution from which saturated aqueous sodium perchlorate solution precipitated a red salt. Recrystallized from water this formed dark red plates which decomposed at 193°. The salt was diamagnetic.

Anal. Calcd. for $C_{24}H_{22}N_6FeCl_2O_8 \cdot H_2O$: C, 4.38; H, 3.7; Fe, 8.4; Found: C, 44.0; H, 4.0; Fe, 8.3.

Bis-[2-(α-pyridylmethyleneaminomethyl)-pyridine]-cobalt(II) Perchlorate Monohydrate (VI).—A solution of cobalt(II) chloride hexahydrate (0.7 g.) in water (10 ml.) was added to IV (1 g.). An immediate blue color developed and a small amount of solid separated. This was filtered off and saturated aqueous sodium perchlorate solution (5 ml.) added to the filtrate. A deep blue precipitate formed. It was collected, well washed with water and dried *in vacuo*. On exposure to air it gradually changed to a red gum.

Anal. Calcd. for $C_{24}H_{22}N_6CoCl_2O_8 \cdot H_2O$: C, 43.0; H, 3.6; Co, 8.8; Found: C, 43.1; H, 3.9; Co, 8.9.

This complex cobalt(II) salt had a magnetic moment of 4.2 Bohr magnetons at 23°.

2-Oximino-3-methyl-4-aza-5-α-pyridyl-Δ³-pentene(VIII).—2-Aminomethylpyridine (5 g.) was added to a solution of

(12) R. S. Nyholm, *Quart. Revs.*, 7, 377 (1953).

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diacetylmonoxime (5 g.) in ethanol (20 ml.) and the mixture refluxed for 5 minutes. The product (3.5 g., 40%) crystallized on cooling, and was recrystallized from ethanol and thus obtained in colorless needles, m.p. 157°.

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.8; H, 6.8; Found: C, 62.6; H, 6.7.

Bis-(2-oximino-3-methyl-4-aza-5-α-pyridyl-3-pentene)-iron(II) Iodide Dihydrate (IX).—Iron(II) sulfate heptahydrate crystals (0.23 g.) were added to a stirred suspension of VIII (0.45 g.) in water (5 ml.). The solids soon dissolved to a deep red solution. Saturated aqueous potassium iodide solution (5 ml.) was then added. The complex iodide which crystallized was collected and recrystallized from an ethanol–ether mixture, being thus obtained as a diamagnetic micro-crystalline red solid which did not melt below 300°.

Anal. Calcd. for $C_{20}H_{26}N_6O_2FeI_2 \cdot 2H_2O$: C, 33.0; H, 4.1; Fe, 7.7. Found: C, 32.5; H, 4.2; Fe, 7.5.

Bis-(2-oximino-3-methyl-4-aza-5-α-pyridyl-Δ³-pentene)-cobalt(III) Iodide (X).—A solution of cobalt(II) chloride hexahydrate (0.2 g.) in water (5 ml.) was added to a solution of VIII (0.3 g.) in ethanol (10 ml.). A solution of cerium(IV) ammonium nitrate (0.2 g.) in nitric acid (10 ml. of *N*) was then added to the brown solution, followed eventually by saturated aqueous potassium iodide solution (3 ml.). The diamagnetic complex cobalt(III) iodide crystallized and was collected and dried *in vacuo*. Heating of the reaction mixture during the preparation led to liberation of diacetyl.

Anal. Calcd. for $C_{20}H_{26}N_6O_2CoI_3$: C, 29.2; H, 3.2; Co, 7.2. Found: C, 28.7; H, 3.1; Co, 7.0.

Bis-[8-(α-pyridylmethyleneamino)-quinoline]-cobalt(III) Perchlorate.—8-(α-Pyridylmethyleneamino)-quinoline[2] (XI) was prepared precisely as follows. Freshly redistilled pyridine-2-aldehyde (5.35 g.) was added to a solution of recrystallized 8-aminoquinoline (7 g.) in ethanol (6 ml.) and the mixture warmed at 100° for 1 minute. It was then cooled and dry ether (15 ml.) added. Vigorous scratching induced crystallization of the Schiff base in yellow needles which were collected and washed with dry ether, m.p. 139–140°. Recrystallization from ethanol, as previously reported, leads to some decomposition.

Anal. Calcd. for $C_{15}H_{11}N_3$: C, 77.2; H, 4.8; Found: C, 76.2; H, 5.1.

A solution of cobalt(II) acetate tetrahydrate (0.55 g.) in methanol (15 ml.) was added to a solution of XI (0.95 g.) in ethanol (5 ml.). Hydrogen peroxide solution (5 ml. of 3%) was then added and the solution evaporated to a volume of approximately 5 ml. Addition of saturated aqueous sodium perchlorate solution (5 ml.) caused precipitation of the diamagnetic brown cobalt(III) perchlorate which was collected, washed and dried *in vacuo*. It decomposed above 265°.

Anal. Calcd. for $C_{30}H_{22}N_6CoCl_3O_{12}$: C, 43.7; H, 2.7; Co, 7.2. Found: C, 43.5; H, 2.8; Co, 7.2.

Bis-[8-(α-pyridylmethyleneamino)-quinaldine]-iron(II) Iodide Dihydrate.—Solutions of 8-aminoquinaldine (3.06 g.) in ethanol (5 ml.) and pyridine-2-aldehyde (2.14 g.) in ethanol (5 ml.) were mixed and gently refluxed for 5 min. After cooling, a solution of iron(II) sulfate heptahydrate (2.4 g.) in water (10 ml.) was added. An intense green color developed. Saturated aqueous potassium iodide solution (5 ml.) was added. The complex iron(II) salt which separated was collected and recrystallized from aqueous ethanol. It was obtained in black prisms which decomposed above 250°.

Anal. Calcd. for $C_{32}H_{26}N_6FeI_2 \cdot 2H_2O$: C, 46.7; H, 3.7; Fe, 6.8. Found: C, 46.3; H, 3.4; Fe, 6.6.

Bis-(8-quinolylmethylene-α-aminomethylpyridine)-iron(II) Iodide Trihydrate (XVII).—Admixture of hot solutions of quinoline-8-aldehyde[9] (0.8 g.) in ethanol (3 ml.) and 2-aminomethylpyridine (0.55 g.) in ethanol (2 ml.) gave an orange solution. Addition of a solution of iron(II) sulfate heptahydrate (0.6 g.) in water (5 ml.) gave an intense green solution from which saturated aqueous potassium iodide solution precipitated the dimagnetic complex iron(II) salt.

Anal. Calcd. for $C_{32}H_{26}N_6FeI_2 \cdot 3H_2O$: C, 44.6; H, 3.7; Fe, 6.5. Found: C, 44.5; H, 3.5; Fe, 6.5.

2,6-Pyridylene-bis-methyleneaniline (XIX, R = C_6H_5).—Freshly distilled aniline (8 g.) was added to a solution of pyridine-2,6-dialdehyde (5.8 g.) in ethanol (30 ml.) and the solution boiled under reflux for 30 minutes. On cooling, the Schiff base crystallized. Recrystallized from ethanol it formed colorless needles, m.p. 98°.

Anal. Calcd. for $C_{19}H_{15}N_3$: C, 80.0; H, 5.3; Found: C, 79.6; H, 5.5.

Bis-[2,6-pyridylene-bis-methyleneaniline]-iron(II) Perchlorate Dihydrate.—A solution of iron(II) sulfate heptahydrate (1 g.) in water (10 ml.) was added to a solution of XIX (R = C_6H_5) (2 g.) in ethanol (10 ml.). An intensely red solution resulted. Ethanol was removed by evaporation from a water-bath and perchloric acid solution (5 ml. of 5%) added. The complex iron(II) perchlorate which precipitated was collected and recrystallized from ethanol and obtained in red plates which decompose violently at 215°.

Anal. Calcd. for $C_{38}H_{30}N_6FeCl_2O_8 \cdot 2H_2O$: C, 52.4; H, 3.9; Fe, 6.5; Found: C, 52.7; H, 4.0; Fe, 6.3.

Boiling of aqueous solutions of this salt caused some decomposition.

2,6-Pyridylene-bis-(methylenebenzylamine) (XIX, R = $-CH_2C_6H_5$).—A solution of benzylamine (4.36 g.) and pyridine-2,6-dialdehyde (2.7 g.) in ethanol (20 ml.) was heated under reflux for 40 minutes. After concentration and cooling a colorless solid (6.2 g.) was deposited. Recrystallized from ethanol it formed colorless tablets, m.p. 80°.

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.5; H, 6.1. Found: C, 80.3; H, 6.3.

Bis-(2,6-pyridylene-bis-methylenebenzylamine)-iron(II) Bromide Bi-sesquihydrate (XXI).—Saturated aqueous potassium bromide solution (10 ml.) was added to the intensely red solution obtained by mixing solutions of XIX (R = $CH_2C_6H_5$) (1.25 g.) in ethanol (10 ml.) and iron(II) sulfate heptahydrate (0.55 g.) in water (10 ml.). The precipitate was collected and recrystallized from water. Dark red diamagnetic needles, m.p. 265° (with previous softening at 165°), were thus obtained.

Anal. Calcd. for $C_{42}H_{38}N_6FeBr_2 \cdot 2.5H_2O$: C, 56.9; H, 4.9; Fe, 6.3. Found: C, 56.7; H, 4.8; Fe, 6.2.

Bis-(2,5-pyridylene-bis-methylenebenzylamine)-cobalt(II) Iodide.—Addition of a solution of cobalt(II) chloride tetrahydrate (0.7 g.) in water (10 ml.) to a solution of XIX (R = $CH_2C_6H_5$) (2 g.) in ethanol (10 ml.) caused a yellow solid to separate from the solution. It redissolved on addition of water (10 ml.). Addition of saturated aqueous potassium iodide solution then caused the complex cobalt(II) iodide to separate. It was collected and recrystallized from ethanol, and was thus obtained in dark brown needles, m.p. 251°.

Anal. Calcd. for $C_{42}H_{38}N_6CoI_2$: C, 53.7; H, 4.0; Co, 6.3. Found: C, 53.6; H, 4.0; Co, 6.1.

The molar conductance of this salt in 10 *M* aqueous solution was 255 ohms^{-1}. The salt was paramagnetic with a moment of 3.8 Bohr magnetons.

Bis-(2,6-pyridylene-bis-methylenebenzylamine)-cobalt(III) Iodide Dihydrate.—A solution of cobalt(II) chloride hexahydrate (0.6 g.) in water (20 ml.) was added to a solution of XIX (R = $CH_2C_6H_5$) (1.5 g.) in ethanol (10 ml.). Chlorine was then bubbled through the solution for 10 minutes, the intense red-brown color changing to brown. Eventually, saturated aqueous potassium iodide solution (10 ml.) was added. The solid salt which separated was collected, washed well with water and ethanol and dried *in vacuo*. It was a micro-crystalline, relatively insoluble diamagnetic solid, m.p. 212°.

Anal. Calcd. for $C_{42}H_{38}N_6CoI_3 \cdot 2H_2O$: C, 45.7; H, 3.8; Co, 5.4. Found: C, 45.8; H, 3.7; Co, 5.1.

Bis-(2,6-pyridylene-bis-methylenebenzylamine)-copper(II) Perchlorate.—A solution of the base XIX (R = $CH_2C_6H_5$) (0.63 g.) in ethanol (10 ml.) was added to a solution of copper(II) chloride dihydrate (0.17 g.) in ethanol (10 ml.). A bright green solid separated at once. On warming it dissolved and the color changed to gray-green. Perchloric acid (5 ml. of 5%) was added. The complex copper(II) perchlorate crystallized in grey-green plates which were collected, washed and dried *in vacuo*.

Anal. Calcd. for $C_{42}H_{38}N_6CuCl_2O_8$: C, 86.7; H, 4.3; N, 9.5; Cu, 7.2. Found: C, 56.3; H, 4.4; N, 9.3; Cu,

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Pyridine-2,6-dialdoxime was obtained in colorless needles, m.p. 216° (from ethanol).

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.9; H, 4.2. Found: C, 50.9; H, 4.5.

Addition of an aqueous solution of iron(II) sulfate heptahydrate (0.59 g.) to a solution of this pyridine-2,6-dialdoxime (0.7 g.) in ethanol (10 ml.) caused development of an intense red color. Addition of sodium acetate solution caused a deep red solid to crystallize. It was recrystallized several times from hot water.

Anal. Calcd. for $C_{14}H_{11}N_6O_4FeNa$: C, 41.4; H, 2.7; Fe, 13.8; Found: C, 41.5; H, 3.2; Fe 13.1.

The equivalent conductivity at 23° was 124 ohms^{-1} indicating the salt to be a binary electrolyte.

2,6-Bis-(aminomethyl)-pyridine.—Glacial acetic acid (500 ml.) and zinc dust (400 g.) were added over a period of 2 hours to a stirred solution of pyridine-2,6-dialdoxime (25 g.) in ethanol (100 ml.). After standing overnight the solids were separated by filtration and well washed with ethanol and these washings added to the filtrate which was then evaporated almost to dryness *in vacuo*. A considerable excess of strong potassium hydroxide solution was then added and the oil which separated was taken up in ether (4 lots of 500 ml.). After removal of the ether the residual oil was distilled *in vacuo* and obtained colorless, b.p. 112° (1.2 mm.), (13 g., 63%). It solidified on standing but was difficult to handle because of its tendency to carbonate.

Anal. Calcd. for $C_7H_{11}N_3$: C, 61.3; H, 8.0; Found: C, 60.0; H, 7.9.

For analysis it was much better to prepare derivatives such as 2,6-bis-(piperonylideneaminomethyl)-pyridine colorless needles, from pyridine–ethyl acetate, m.p. 179°.

Anal. Calcd. for $C_{23}H_{19}N_3O_4$: C, 68.8; H, 4.8; Found: C, 68.7; H, 4.9.

2,6-Bis-(salicylideneaminomethyl)-pyridine, almost colorless needles (from ethanol), had m.p. 120°.

Anal. Calcd. for $C_{21}H_{19}N_3O_2$: C, 73.1; H, 5.5; Found: C, 72.9; H, 5.5.

Bis-[2,6-di-(aminomethyl)-pyridine] iron(II) Iodide.—The base XXVI (0.9 g.) was added to a solution of iron(II) sulfate heptahydrate (0.7 g.) in water (10 ml.). After filtration the resulting deep green solution was treated with saturated aqueous potassium iodide solution (5 ml.). The green complex iodide which separated was collected, washed and dried *in vacuo*. It did not melt below 300°.

Anal. Calcd. for $C_{14}H_{22}N_6FeI_2$; C, 28.8; H, 3.8; Fe, 9.6. Found: C, 28.6; H, 3.8; Fe, 9.6.

Allowing aqueous solutions of this salt to stand in air leads to decomposition and iron(III) hydroxide is deposited. The salt has a magnetic moment of 5.24 Bohr magnetons (23°).

Bis-(2,6-(diaminomethyl)-pyridine)-nickel(II) Bromide. (XXVI).—(0.6 g.) was added to a solution of nickel(II) sulfate sexahydrate (0.5 g.) in water (10 ml.). Addition of saturated aqueous potassium bromide solution (5 ml.) to the resulting deep mauve solution caused the complex nickel(II) bromide to separate. It crystallized from hot water in mauve needles which did not melt below 300°.

Anal. Calcd. for $C_{14}H_{22}N_6NiBr_2$: C, 34.1; H, 4.5; Ni, 12.0; Found: C, 33.8; H, 4.6; Ni, 11.7.

Condensation of Pyridine-2,6-dialdehyde with 1,6-Diaminohexane.—The following experiment was typical. A hot solution of pyridine-2,6-dialdehyde (3.5 g., 1 mole) in ethanol (20 ml.) was added to a hot solution of 1,6-diaminohexane (3 g., 1 mole) in ethanol (20 ml.) and the mixture boiled. Within 20 sec. a white solid had separated from the hot solution. It was collected and washed with hot ethanol. It was insoluble in most solvents but did dissolve on warming in dimethylformamide. However, this solution soon redeposited solid, probably because of molecular weight increase due to further condensation. The solid did not melt but decomposed when very strongly heated.

Anal. Calcd. for $(C_{13}H_{17}N_3)_n$: C, 72.6; H, 7.9; Found: C, 72.0; H, 7.9.

Addition of this dried, finely ground white polymer (0.65 g.) to a boiling solution of iron(II) sulfate heptahydrate (1.8 g., excess) in water (25 ml.) caused its transformation to a deep red powder. This was collected and well washed with water. It was insoluble in any of the common solvents.

Anal. Calcd. for $(C_{13}H_{17}N_3)_2 \cdot FeSO_4 \cdot 6H_2O$; C, 45.2; H, 6.7; Fe, 8.1. Found: C, 45.6; H, 6.5; Fe, 8.1.

This solid was found to be ferromagnetic with a molar susceptibility at 24° of 155,000 × 10^{-6} c.g.s. unit.

The finely ground polymer (0.5 g.) was suspended in ethanol (15 ml.) and a solution of cobalt(II) chloride sexahydrate in ethanol (50 ml.) added. The liquid was then gently refluxed. The white polymer gradually changed in color to deep brown but the solution was still a blue color after one hour. The solid polymer was again ground and reheated with the solution which eventually became colorless. The solid was then collected, well washed with ethanol and dried *in vacuo*.

Anal. Calcd. for $C_{13}H_{17}N_3CoCl_2$; C, 45.2; H, 5.0; Co, 14.2. Found: C, 44.9; H, 5.4; Co, 13.8.

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SYDNEY, AUSTRALIA

[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY AT HARVARD UNIVERSITY]

Vinyl Derivatives of the Metals. IV. The Preparation of Vinylgermanium Compounds by the Grignard Method[1]

BY DIETMAR SEYFERTH

RECEIVED JANUARY 17, 1957

The addition of germanium(IV) chloride to vinylmagnesium bromide in tetrahydrofuran solution results in moderate yields of hexavinyldigermane in addition to tetravinylgermane. Diethyldivinylgermane and ethyltrivinylgermane have also been prepared. Hexavinyldigermane is cleaved by bromine and by iodine to give trivinylgermanium bromide and iodide, respectively.

The use of the vinyl Grignard reagent in tetrahydrofuran solution for the preparation of vinyltin compounds[2] and vinylsilanes[3] has been reported recently. In the examples where tin(IV) chloride and tetrachlorosilane were vinylated only tetravinyltin and tetravinylsilane, respectively, were isolated.

We have now investigated the reaction of vinylmagnesium bromide[4] in tetrahydrofuran solution

(1) Part III, D. Seyferth, *J. Org. Chem.*, **22**, in press (1957).

(2) D. Seyferth and F. G. A. Stone, THIS JOURNAL, **79**, 515 (1957).

(3) S. D. Rosenberg, *et al.*, Abstracts of Papers Presented at the 130th Meeting of the American Chemical Society, Atlantic City, September 1956, p. 81-O.

(4) H. Normant, *Compt. rend.*, **239**, 1510 (1954).

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with germanium(IV) chloride and some ethylgermanium chlorides. Addition of germanium(IV) chloride to a slight excess of this Grignard reagent gave a 26% yield of hexavinyldigermane in addition to a 35% yield of the expected tetravinylgermane. Identification of the former compound was made on the basis of analysis, determination of molecular weight, molar refraction and its conversion to trivinylgermanium iodide by iodine cleavage and trivinylgermanium bromide by means of bromine cleavage

$$(CH_2{=}CH)_3GeGe(CH{=}CH_2)_3 + X_2 \longrightarrow 2(CH_2{=}CH)_3GeX$$

Johnson and Harris[5] have reported that hexaphenyldigermane is similarly obtained in the reaction of an excess of phenylmagnesium bromide with germanium(IV) chloride is an ether–toluene solvent system. No such reductive alkylation of germanium(IV) chloride has been observed with aliphatic Grignard reagents. Johnson and Harris made no attempt to explain their observed reaction, but it is noteworthy that they demonstrated that the phenylation of germanium(IV) chloride can be forced to give tetraphenylgermane exclusively by completely removing the ether and operating at the temperature of the refluxing toluene solution.

In the few years that have elapsed since the work of Johnson and Harris it has become increasingly apparent that the chemistry of germanium presents some anomalies, and that in some cases the reactions of certain germanium compounds do not parallel those of the corresponding silicon and tin compounds. For example, organogermanium halides can be reduced to the hydrides by zinc and hydrochloric acid[6]; this reaction is not observed with the corresponding chlorides of silicon and tin. Also, as Gilman and his co-workers have shown, the reaction of triphenylgermane with alkyllithium compounds results in the formation of triphenylgermyllithium,[7] while triphenylsilane[8] and triphenyltin hydride[9] are alkylated by alkyllithium compounds. These and other differences in the reactions of germanium compounds on one hand, and of silicon and tin compounds on the other, were explained by these and other workers[10] on the basis of a higher electronegativity of germanium, new experimental verification of which has now been provided in this Laboratory by Allred and Rochow.[11] It is interesting to note that such "reductive coupling" as described by Johnson and Harris and by the author of the present study has not been observed in the Grignard alkylation of tetrachlorosilane and tin(IV) chloride with phenylmagnesium and vinylmagnesium bromides, and it is possible that these results similarly could be a direct consequence of the high electronegativity of germanium, and that the reaction proceeds *via* an unstable or poorly stable intermediate containing a Ge–Mg bond. Work in this Laboratory[12] has shown that a germanium Grignard reagent of the type $(CH_3)_3GeMgCl$ does not form when trimethylgermanium chloride is treated with magnesium in diethyl or dibutyl ether in the presence or absence of a catalyst. Other workers[7] have shown that triphenylgermane does not exchange with a Grignard reagent. However, these observations do not preclude the possibility of an unstable $(CH_2{=}CH)_3GeMgBr$ or $(C_6H_5)_3GeMgBr$ intermediate in the "reductive coupling" reaction. Such an intermediate could possibly be formed in an exchange reaction between trivinylgermanium halide and vinylmagnesium bromide, but we consider it more likely that formation of such an intermediate would occur *via* primary reduction of $GeCl_4$ to $GeCl_2$ by the Grignard reagent, followed by vinylation to give divinylgermane(II). The latter could then add vinylmagnesium bromide

$$GeCl_4 + 2CH_2{=}CHMgBr \longrightarrow GeCl_2 + CH_2{=}CH{-}CH{=}CH_2 + MgCl_2 + MgBr_2$$

$$GeCl_2 + 2CH_2{=}CHMgBr \longrightarrow (CH_2{=}CH)_2Ge + MgCl_2 + MgBr_2$$

$$(CH_2{=}CH)_2Ge + CH_2{=}CHMgBr \longrightarrow (CH_2{=}CH)_3GeMgBr$$

$$(CH_2{=}CH)_3GeMgBr + (CH_2{=}CH)_3GeCl \longrightarrow (CH_2{=}CH)_3GeGe(CH{=}CH_2)_3 + {}^1/_2MgCl_2 + {}^1/_2MgBr_2$$

Both the reduction of metal halides to a lower oxidation state by Grignard reagents[13] and the addition of active organometallic reagents to diorganogermane(II) compounds[14] have been reported previously.

The vinylmonogermanes prepared in this study are much more stable with respect to cleavage reactions than are the corresponding vinyltin compounds.[1,15] Thus mercuric chloride in refluxing ether solution caused no cleavage of the vinylgermanium bond and no redistribution reaction was observed on refluxing a mixture of tetravinylgermane and germanium(IV) chloride. These indications that the Ge–C mean bond energy is considerably greater than that of the Sn–C bond in analogous organotin compounds are further borne out by the recently described successful side-chain chlorination of ethylgermanium trichloride.[16] Attempted side-chain chlorination of ethyltin trichloride resulted in Sn–C bond cleavage.[17] Hexavinyldigermane appears to be moderately stable in air, turning from colorless to light yellow in color over a period of several weeks.

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(17) C. R. Dillard, Final Report, U. S. Office of Naval Research Contract N9 onr-95700, August 31, 1952.

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Experimental

1. **Diethyldivinylgermane.**—To 0.5 mole of vinylmagnesium bromide in 200 ml. of tetrahydrofuran[18] was added 18 g. (0.089 mole) of diethylgermanium dichloride, dissolved in an equal volume of tetrahydrofuran, at such a rate that a gentle reflux was maintained. The reaction mixture was refluxed for about 20 hours, then was cooled and hydrolyzed with 75 ml. of a saturated aqueous solution of ammonium chloride. The organic layer was decanted and the residual salts were washed with diethyl ether, the washings being added to the decanted liquid. Distillation of the solvents followed by fractional distillation of the residue gave 11.5 g. (70%) of diethyldivinylgermane, b.p. 59–60° at 28.5 mm., $n^{25}D$ 1.4540.

Anal. Calcd. for $C_8H_{16}Ge$: C, 51.99; H, 8.73. Found: C, 52.16; H, 8.80.

2. **Ethyltrivinylgermane.**—A similar procedure was followed in the reaction of 1.0 mole of vinylmagnesium bromide in 300 ml. of tetrahydrofuran with 35.3 g. (0.17 mole) of ethylgermanium trichloride. A 50% yield (15.5 g.) of ethyltrivinylgermane, b.p. 55–57° at 28 mm., $n^{25}D$ 1.4605, was obtained.

Anal. Calcd. for $C_8H_{14}Ge$: C, 52.56; H, 7.72. Found: C, 52.55; H, 7.62.

3. **Tetravinylgermane and Hexavinyldigermane.**—To a solution of 2.0 mole of vinylmagnesium bromide in 800 ml. of tetrahydrofuran was added 95.5 g. (0.445 mole) of germanium(IV) chloride at such a rate that a gentle reflux was maintained. The reaction mixture was then refluxed for about 20 hours. After it had cooled to room temperature the mixture was hydrolyzed with 300 ml. of a saturated aqueous solution of ammonium chloride. The orange organic layer was decanted and the residual salts were washed with ether, the washings being combined with the organic layer. After the solvents had been removed by distillation the brownish liquid residue was fractionally distilled to give: (a) **tetravinylgermane**, b.p. 52–54° at 27 mm., $n^{25}D$ 1.4676, d^{25}_4 1.040; 28.5 g., a yield of 35.4%. *Anal.* Calcd. for $C_8H_{12}Ge$: C, 53.15; H, 6.69. Found: C, 53.00; H, 6.96; (b) a small middle run, boiling from 65° at 23 mm. to 89° at 4.2 mm., which turned grape red on standing in air; (c) **hexavinyldigermane**, b.p. 55° at 0.35 to 0.25 mm., $n^{25}D$ 1.5217, d^{25}_4 1.171; 17.8 g., a yield of 26.1%. *Anal.* Calcd. for $C_{12}H_{18}Ge_2$: Ge, 47.23; C, 46.87; H, 5.90; mol. wt., 307.5. Found: Ge, 47.02; C, 47.00; H, 6.19; mol. wt. (Rast), 318.

The product from another run gave: C, 47.06; H, 6.14. The molar refractions calculated from the data did not check those calculated for any of the other possible higher boiling products such as $(Vi_3Ge)_2O$, Vi_3GeBr, Vi_3GeOH, Vi_3GeBr_3, Vi_2GeCl_2, $(Vi_2GeO)_n$ and others. No direct check was possible since the bond refraction of the Ge–Ge bond is not known. Using the refractive index and density listed above we calculate a value of 6.6 for the Ge–Ge bond refraction, which as expected, lies between the values of the Si–Si and Sn–Sn bond refractions.

4. **Trivinylgermanium Iodide.**—To a solution of 7.2 g. (0.023 mole) of hexavinyldigermane in 30 ml. of diethyl ether were added a few crystals of iodine. The iodine color was not discharged on refluxing the solution for one hour. When most of the ether had been replaced by chloroform the iodine was used up slowly on further heating. The rest of the iodine (5.94 g. total, 0.023 mole) was then added and the solution was refluxed for four hours. The solution at the end of this time was dark in color, but this did not appear to be due to free iodine. The chloroform was boiled off at atmospheric pressure and the dark residue was fractionally distilled to give 6 g. (45.6%) of trivinylgermanium iodide, b.p. 71–74° at 12 mm., and about 1 g. of unreacted digermane. Trivinylgermanium iodide is extremely sensitive to light; the initially colorless distillate rapidly turned reddish pink and darkened further on standing.

Anal. Calcd. for C_6H_9IGe: C, 25.68; H, 3.23; I, 45.22. Found: C, 26.20; H, 3.46; I, 44.84.

5. **Trivinylgermanium Bromide.**—To 10 g. (0.0325 mole) of hexavinyldigermane in chloroform solution was added dropwise a solution of 5.2 g. (0.0325 mole) of bromine in chloroform. The bromine was decolorized immediately in a very vigorous reaction and the solution soon began to reflux. After the addition was completed the solvent was boiled off and the residue was fractionally distilled to give 3.5 g. (23%) of trivinylgermanium bromide, b.p. 58° at 10 mm., $n^{25}D$ 1.5057.

Anal. Calcd. for C_6H_9BrGe: C, 30.84; H, 3.88; Br, 34.21. Found: C, 30.79; H, 3.99; Br, 34.23.

In addition, an unidentified high-boiling fraction distilled continuously from 75° at 6.0 mm. to 93° at 1.4 mm.

Trivinylgermanium bromide had the sharp smell and lachrymatory action normally associated with trialkyltin halides.

6. Analyses were performed by the Schwarzkopf Microanalytical Laboratories, Woodside 77, New York.

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(18) Tetrahydrofuran was obtained from the Electrochemicals Department, E. I. du Pont de Nemours & Co., and was purified by distillation from lithium aluminum hydride.

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ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY (No. 2117) AND THE DEPARTMENT OF CHEMISTRY AND LABORATORY FOR NUCLEAR SCIENCE AND ENGINEERING, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

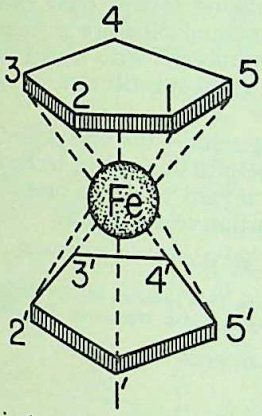
The Dipole Moment of Bis-(*p*-chlorophenylcyclopentadienyl)-iron

BY DOROTHY A. SEMENOW AND JOHN D. ROBERTS[1]

RECEIVED JULY 23, 1956

The dipole moment (3.12 *D*) found for bis-(*p*-chlorophenylcyclopentadienyl)-iron indicates a molecular configuration having the *p*-chlorophenyl groups in rather close proximity to one another.

The sandwich structure[2] for ferrocene[3] is supported by X-ray[3,4-7] and electron[3,8] diffraction, diamagnetic moment,[2] infrared absorption spectrum,[2] dipole moment[2] and chemical properties.[2] In the crystal, the rings occupy fairly fixed positions best described by the antiprismatic sandwich structure (I).[3,4-7] The apparent spreading of the carbon atoms along the circumference of the rings is regarded as being due to a fairly large amplitude of thermal vibration and hindered rotation.[3]



Free rotation is, however, suggested by electron diffraction patterns for ferrocene vapor,[3,8] as well as chemical[2,3] and dipole moment studies[9] of bis-(acetylcyclopentadienyl)-iron and molecular orbital treatments of the ferrocene molecule.[10,11] The dipole moment of a bis-(*p*-chlorophenylcyclopentadienyl)-iron measured in the present investigation provides evidence that, even though the rings may rotate freely, not all possible orientations of a bis-substituted ferrocene are equally probable.

Experimental and Results

The bis-(*p*-chlorophenylcyclopentadienyl)-iron, kindly supplied by Dr. V. Weinmayr of the Jackson Laboratory, E. I. du Pont de Nemours and Co., was prepared by treatment of the ferricinium ion $[Fe(C_5H_5)_2]^{\oplus}$ with *p*-chlorophenyldiazonium ion.[12] The purity of the compound was established by analysis.[12] Assignment of the *p*-chlorophenyl substituents to different rings is supported by the infrared spectrum (of carbon tetrachloride and carbon disulfide solutions) which showed no bands at 9.0 and 9.95 μ characteristic of unsubstituted ferrocenylcyclopentadienyl rings.[3,13,14]

The dipole moment of bis-(*p*-chlorophenylcyclopentadienyl)-iron was measured in benzene solution as described previously[15,16] and evaluated by linear extrapolation of the dielectric constant to zero concentration[17,18] (method I) to be 3.12 ± 0.03 *D*. A value of 2.96 ± 0.13 *D* was obtained by linear extrapolation of molar polarization to zero concentration[19] (method II). Method I is considered to be more reliable because the extrapolated function is linear at low concentrations whereas this is not true for method II.[17,18] The data used for method I are summarized in Table I.

TABLE I

DIPOLE MOMENT DATA FOR BIS-(*p*-CHLOROPHENYLCYCLOPENTADIENYL)-IRON IN BENZENE AT 24.90°

Wt. fract. (w_2)	Sp. vol. (V)	ϵ	$n^{24.9}D$
0.000000	1.14564	(2.26992)	1.49701
.010957	1.14073	2.30198	1.49835
.016409	1.13817	2.32112	1.49897
.022337	1.13555	2.32997	1.49960
.030856	1.13171	2.36243	1.50052

$\alpha = \Delta\epsilon/\Delta w_2 = 2.92727$ $\beta = \Delta V/\Delta w_2 = -0.45203$

$MR_D = 109.5 \pm 0.7$ $\mu = 3.12 \pm 0.03$ D.

Discussion of Results

The dipole moments expected for non-freely rotating bis-(*p*-chlorophenyl)-ferrocene structures (see I) and for a freely rotating model were calculated using the following assumptions. (1) Only the C–Cl moments make important contributions to the dipole moment of the molecule—*i.e.*, phenylferrocene would have a very low or zero dipole moment. This assumption is supported by the close agreement between the dipole moments of acetophenone (2.97 *D*)[20] and monoacetylferrocene (3.02 *D*)[9] and the near identity of the first acid ionization constant of ferrocenedicarboxylic acid with that of benzoic acid.[21] These data indicate that the ferro-

(1) Gates and Crellin Laboratories of Chemistry, California Institute of Technology.

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cenyl and phenyl groups have comparable electronegativities. (2) The C–Cl axes lie in the planes of the cyclopentadienyl rings to which the *p*-chlorophenyl groups are attached. This orientation of the C–Cl bond is expected if the cyclopentadienyl carbon atoms form the usual aromatic-type sp^2-bonds to substituents. The calculated distance between the cyclopentadienyl rings, 3.6 Å.,[22] is probably large enough to preclude distortion by steric repulsions between substituents on different rings. The vector moment of each C–Cl bond was taken as 1.56 *D*.[23]

The dipole moment for the freely rotating model was calculated using the equation for freely rotating angular groups[9,24] where α and β are the angles ($\alpha = \beta = 90°$) which the moment vectors of the *p*-chlorophenyl groups make with the axes about which they rotate and θ (180°) is the angle between these axes; a and b ($a = b = 1.56$) are the electric moment vectors.

$$\mu = \sqrt{a^2 + b^2 + 2ab \cos \alpha \cos \beta \cos \theta}$$

The dipole moments calculated for the various possible structures of the bis-(*p*-chlorophenyl)-ferrocene are summarized in Table II.

The experimental moment of 3.12 ± 0.03 *D* eliminates a freely rotating model (calculated $\mu = 2.20$ *D*) and is in closest agreement with the moment expected for the 1,1′, prismatic (method I) or 1,1′-antiprismatic (method II) structure. Configurations like these with angles of only 0–36° between the two C–Cl dipole vectors would not be expected to be favored on the basis of dipole–dipole repulsions. However, the tendency for molecules to exist in "*cis*-like" configurations irrespective of such repulsions has been noted in other cases. Thus, the *cis*-configuration of disalicylide is apparently most stable and this has been attributed to resonance involving the lactone bridge.[25] An analogous preference for a *cis*-like "boat" configuration as the most stable form of 1,6-dichloro-1,5-cycloöctadiene has been explained by operation of secondary valence forces,[26] possibly dispersion forces. Such valence forces may also account for why bis-di-(*p*-chlorophenyl)-ferrocene appears to exist in a configuration with the *p*-chlorophenyl groups quite close to one another. A similar conclusion was reached by Hampson and Weissburger[27] with regard to the orientations of the *ortho*-substituents in *o,o*′-dichlorobiphenyl.

TABLE II

DIPOLE MOMENTS CALCULATED FOR DI-(*p*-CHLOROPHENYL)-FERROCENE STRUCTURES

Structure (see I)	Dipole moment, *D*
1,1′, prismatic	3.12
1,1′, antiprismatic	2.97
1,2′, antiprismatic	1.83
1,3′, antiprismatic	0
Freely rotating cyclopentadienyl rings	2.20

Acknowledgment.—We are pleased to acknowledge several helpful suggestions by Prof. Myron Rosenblum with regard to dipole moment calculations and interpretation of the results.

(22) The value of 3.6 Å. is obtained using a value of 1.4 Å. for the C–C ring distance and 2.0 Å. for the C–Fe distance.[5,6,7]

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PASADENA, CALIFORNIA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Studies in the Ferrocene Series. I. Some Reactions of Compounds Related to Monobenzoylferrocene[1]

BY NORMAN WELIKY AND EDWIN S. GOULD

RECEIVED OCTOBER 24, 1956

The ketones benzoylferrocene (I) and anisoylferrocene and several diketones have been made from ferrocene (dicyclopentadienyliron) by Friedel–Crafts acylations. Benzoylferrocene is reduced to the pinacol, 1,2-diphenyl,1,2-diferrocenylethanediol (IV), with methylmagnesium bromide in the presence of cobalt chloride; the same ketone is reduced to phenylferrocenylmethanol (II) with lithium aluminum hydride, to phenylferrocenylmethane (X) with zinc, sodium or aluminum and to still another carbinol, probably phenyldiferrocenylmethanol (IX), with sodium amalgam in benzene. The pinacol rearranges with extraordinary ease, with migration of the ferrocene moiety, and is surprisingly easily oxidized to the parent ketone by atmospheric oxygen. The secondary alcohol, phenylferrocenylmethanol, forms ethers under exceptionally mild conditions and behaves somewhat like a tertiary alcohol. These reactions suggest that a carbonium ion obtained by removal of an –OH group alpha to the ferrocene system is subject to special stabilization, possibly by dispersal of the positive charge through partial shift of *d*-electron density from the iron atom into the ring. The oxime of benzoylferrocene (VII) rearranges, through its tosylate, to the anilide of ferrocenecarboxylic acid (VIII).

The easy preparation and purification of benzoylferrocene allows the synthesis and study of a number of relatively simple compounds in which the benzene ring and the ferrocene system are attached to a common carbon atom. Chart I summarizes the transformations which we have carried out.

Acylations.—By suitable variations of reaction conditions, the Friedel–Crafts acylation of ferro-

(1) Based on research carried out under Contract No. DA 30-069-ORD-1137, Project No. TB2-0001 (836), between the U. S. Army, Ordnance Department, and the Polytechnic Institute of Brooklyn.

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cene may be made to yield either mono- or diketones as major products.[2] Benzoylferrocene (but no appreciable quantity of dibenzoylferrocene) is obtained from the acylation of ferrocene if equivalent quantities of ferrocene and aluminum halides are used. Since ferrocene reacts with aluminum halides (in a manner which is not yet clear), to form colored products, our most successful preparations of benzoylferrocene (I) and anisoylferrocene were carried out by slow addition of a "Perrier complex"[3] of the acid chloride and aluminum halide to ferrocene solutions.

Reductions of Benzoylferrocene.—Six different products resulting from the reduction of benzoylferrocene with various reagents have been characterized; in addition to these, several reduction products remain unidentified. Reduction with lithium aluminum hydride yields the expected secondary alcohol, phenylferrocenylmethanol (II), which is also formed in small yield from reduction with sodium. This carbinol has an unusually labile hydroxyl group since it is converted to its methyl ether (III, R = CH_3) merely on boiling with aqueous methanol. Similarly, the isopropyl ether results from the reduction of benzoylferrocene with aluminum isopropoxide in isopropyl alcohol, a situation bringing to mind the similar behavior of certain α,β-unsaturated ketones.[4]

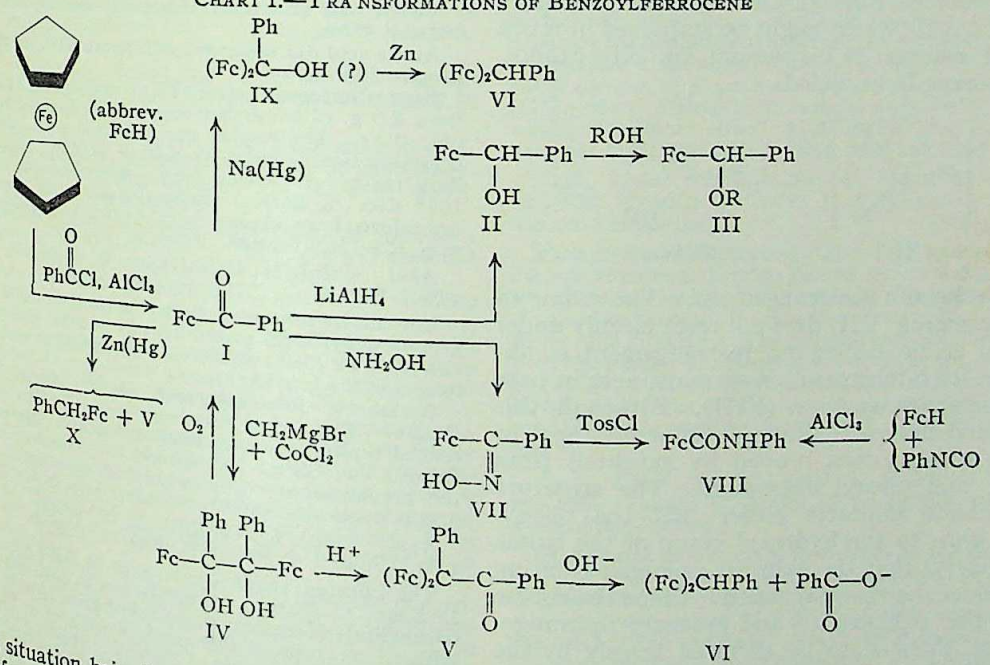
The usual methods for bimolecular reduction of ketones to pinacols did not work when applied to benzoylferrocene. No reaction occurred when a solution of the ketone in isopropyl alcohol was irradiated in sunlight for a month,[5] whereas reduction with magnesium–magnesium iodide[6] yielded unidentified products. Among the less conventional bimolecular reduction methods attempted, the most successful was that of Kharasch and Lambert[7] using methylmagnesium bromide and cobalt(II) chloride. The pinacol IV thus obtained rearranged with remarkable ease (merely upon passing gaseous HCl over its solution in benzene) to the pinacolone V. The structure of the latter is indicated by its degradation in base to phenyldiferrocenylmethane (VI) and benzoate.

The pinacolone V is also formed as a minor product in the Clemmensen reduction of benzoylferrocene; the pinacol, which would be expected to rearrange immediately under Clemmensen conditions, is probably an intermediate here. The chief product from the Clemmensen reduction is the expected desoxo compound, phenylferrocenylmethane (X).

Reduction with sodium amalgam yields an additional alcohol which may be reduced further with zinc to VI. This evidence, together with its analysis, suggests that the alcohol is phenyldiferrocenylmethanol (IX), although it is difficult to see how such a product would arise from reduction of benzoylferrocene. This alcohol, like phenylferrocenylmethanol (II), is converted to its methyl ether merely on heating with methanol.

The exceptional ease with which carbinols II and IX are converted to their ethers and the very mild conditions under which the pinacol IV rearranges suggest that the presence of the ferrocene system in the position alpha to a hydroxyl group lowers the energy barrier to conversion of the carbinol to the corresponding carbonium ion. It does

CHART I.—TRANSFORMATIONS OF BENZOYLFERROCENE



(2) (a) The behavior of ferrocene in the Friedel–Crafts reaction has been summarized by P. L. Pauson, *Quart. Revs.*, **9**, 409 (1955). See also: (b) R. B. Woodward, M. Rosenblum and M. C. Whiting, THIS JOURNAL, **74**, 3459 (1952); (c) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and O. A. Nesmeyanova, *Doklady Akad. Nauk S.S.S.R.*, **97**, 459 (1954); (d) V. Weinmayr, THIS JOURNAL, **77**, 3009 (1955).

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(5) W. E. Bachmann and J. W. Ferguson, THIS JOURNAL, **56**, 208 (1934).

(6) W. E. Bachmann and F. H. Moser, *ibid.*, **54**, 1124 (1932).

(7) M. S. Kharasch and F. L. Lambert, *ibid.*, **63**, 2315 (1941).

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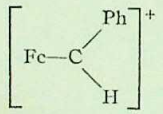
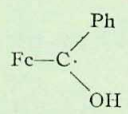
not seem probable that the presence of a single phenyl group and a single ferrocenyl group on a carbon atom would result in enough steric crowding to account for this effect. We suggest rather that a carbonium ion such as XI is stabilized by an unusual ability of the ferrocene system to delocalize the positive charge, possibly through a partial shift of *d*-electron density from the iron atom into the ring.

Equally remarkable is the ease with which the pinacol IV is converted back to benzoylferrocene upon exposure to air. This conversion takes place in polar solvents and in the presence of alumina or silica gel. The pinacol is most stable in the solid state (if protected from air) or in solutions of carbon disulfide or benzene. Very dilute solutions in the latter solvent show a drift in spectra; for a 0.0003 *M* solution, conversion to benzoylferrocene is over 80% complete after 4 days standing. Disproportionation, as is sometimes observed for basic solutions of pinacols,[8] evidently does not occur, for no phenylferrocenylmethanol (II) could be detected in solutions in which the pinacol had been converted to the ketone, even under conditions where the carbinol should survive. Little more can be said about this oxidation[9] on the basis of the present observations, but the possibility that it proceeds through small concentrations of the radical XII (which might be stabilized in much the same manner as carbonium ion XI) cannot, in our opinion, be excluded.



XI



XII

The Beckmann Rearrangement.—The oxime of benzoylferrocene (VII) does not react cleanly under the usual acidic Beckmann rearrangement conditions, but its *p*-toluenesulfonate rearranges in base to ferrocenecarboxanilide (VIII). Although this amide could not be hydrolyzed, either by acid or base, its identity was proved by synthesis from ferrocene and phenyl isocyanate. The structure of the amide indicates either that the phenyl group is *anti*- to the hydroxyl group of the oxime or (less likely) that the oxime is isomerized during the course of the rearrangement. Since the course of both the Beckmann[10] and pinacol[11] rearrangements are thought to be dictated largely by the configurations of the reactants, conclusions about the relative "migratory aptitudes" of the ferrocene system and the benzene ring cannot be drawn.

(8) W. Thorner and T. Zincke, *Ber.*, **10**, 1473 (1877); **11**, 65 (1878).

(9) Similar oxidations of fluorenopinacol and xanthopinacol to the corresponding ketones have been reported by C. R. Masson, V. Boekelheide and W. A. Noyes, Jr., "The Technique of Organic Chemistry," Vol. II, Arnold Weissberger, Editor, Interscience Publishers, Inc., New York, N. Y., 1956, p. 316.

(10) J. Meisenheimer, P. Zimmermann and U. v. Kummer, *Ann.*, **446**, 205 (1926).

(11) The conclusions of Curtin and co-workers, THIS JOURNAL, **73**, 3453 (1951), **74**, 5905 (1952), with regard to pinacolic deaminations and rearrangements of aryl-substituted bromohydrins probably may be applied also to the pinacol rearrangement since the three types of rearrangements are thought to proceed through similar transition states.

Experimental

Benzoylferrocene (I).—A Perrier complex[8] was prepared from 42 g. of benzoyl chloride and 42 g. of anhydrous aluminum chloride. This was dissolved in carbon disulfide and added, over a period of 0.5 hr., to a warm solution of 55 g. of ferrocene in 180 ml. of carbon disulfide. After 20 hr., the mixture was hydrolyzed, worked up in the usual manner and chromatographed on alumina. Red crystals (56 g., 67%) were obtained by crystallization from hexane; m.p. 108–109° (reported[12] 111.5–112.0°).

Anal. Calcd. for $C_{17}H_{14}OFe$: C, 70.35; H, 4.83; Fe, 19.3. Found: C, 70.38; H, 4.92; Fe, 19.0.

The infrared carbonyl band was at 1634 and phenyl absorption at 1458, 1588 and 1605 cm.$^{-1}$. Absorption of an unsubstituted ferrocene ring was at 1108 cm.$^{-1}$. Visible and ultraviolet peaks in alcohol were at 245 (ϵ 14,900), 274 (shoulder, ϵ 7,930), 362 (ϵ 1,230) and 478 mμ (ϵ 696).

Anisoylferrocene.—To 15 g. of anhydrous aluminum bromide in 70 ml. of carbon disulfide at 0° was added slowly 9.3 g. of anisoyl chloride. The resulting mixture was added slowly, with cooling, to 10 g. of ferrocene in 50 ml. of carbon disulfide. After 4 hr., the mixture was hydrolyzed and worked up in the usual manner. Chromatography on alumina yielded 4.5 g. (26%) of blood-red crystals. The product was purified further by sublimation at reduced pressure, a second chromatographic separation and, finally, crystallization from methanol–water. The yield of pure product (m.p. 82–83°) was 4.0 g. (23%).

Anal. Calcd. for $C_{18}H_{16}O_2Fe$: C, 67.50; H, 5.00. Found: C, 67.48; H, 4.97.

The infrared spectrum showed carbonyl absorption at 1612, phenyl absorption at 1515 and 1578 and absorption of unsubstituted ferrocene rings at 1110 cm.$^{-1}$.

Visible and ultraviolet absorption maxima were at 223, 284 and 477 mμ.

Anisic acid did not react with ferrocene in anhydrous hydrogen fluoride.

Benzoylferrocene oxime (VII) was prepared in pyridine[13] from 2.0 g. of benzoylferrocene. The heating period was only 2 hr. The residue was extracted with benzene and crystallization induced by adding hexane. One gram of dark red-brown crystals (48%) was obtained, m.p. 164–169° dec. A portion chromatographed on alumina and crystallized from benzene–hexane yielded orange-red needles, m.p. 158–159° (foamed), reported[12] 160° dec.

Anal. Calcd. for $C_{17}H_{15}ONFe$: C, 66.89; H, 4.91; N, 4.59. Found: C, 67.13; H, 4.82; N, 4.57.

The infrared spectrum indicated the absence of carbonyl groups. Hydroxyl absorption was at 3190, phenyl absorption at 1498, 1580 and 1600 and absorption of unsubstituted ferrocene rings at 1106 cm.$^{-1}$.

Beckmann Rearrangement of Monobenzoylferrocene Oxime.—Monobenzoylferrocene oxime (1 g.) was rearranged through its benzenesulfonyl ester by the method of Brown, Van Gulick and Schmid.[14] A benzene solution of the products was chromatographed on alumina, yielding 0.23 g. of cotton-like yellow needles, m.p. 208–210°.

Anal. Calcd. for $C_{17}H_{15}ONFe$: C, 66.89; H, 4.91; N, 4.59. Found: C, 67.81; H, 4.88; N, 4.58.[15]

The infrared amide bands were at 3280 (N–H), 1643, 1526 cm.$^{-1}$. Phenyl absorption was at 1500 and 1600 and unsubstituted ferrocene ring absorption at 1106 cm.$^{-1}$. The infrared spectrum of this amide was found to be identical to the infrared spectrum of the amide obtained from the reaction of phenyl isocyanate with ferrocene. Visible and ultraviolet maxima were at 245, 271 and 447 mμ in alcohol and chloroform.

Anilide of Ferrocenecarboxylic Acid.—To 5.0 g. of ferrocene and 2.9 g. of phenyl isocyanate in 100 ml. of carbon di-

(12) E. Csendes, reported by M. Rosenblum, Ph.D. Thesis, Harvard University, August, 1953, p. 85.

(13) W. E. Bachmann and M. Barton, *J. Org. Chem.*, **3**, 303 (1938).

(14) R. F. Brown, H. M. Van Gulick and G. H. Schmid, THIS JOURNAL, **77**, 1094 (1955).

(15) The analyses for carbon in this compound and in a number of additional ferrocene derivatives reported here are not fully satisfactory, although there seems little doubt as to the identity of the compounds. Some difficulty is encountered in obtaining very precise combustion analyses for certain substituted ferrocenes by conventional

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sulfide, 3.7 g. of anhydrous aluminum chloride was added in portions, while agitating the solution. The mixture was stirred 1 hr., refluxed 1 hr., then left overnight. The carbon disulfide was decanted. The oily residue and the carbon disulfide solution were hydrolyzed and acidified separately and the carbon disulfide removed by evaporation. The solid residues were washed with water and extracted with hexane to remove unreacted ferrocene. The residues were then extracted, first with benzene, then with chloroform. A yield of 2.1 g. (25% over-all, 60% based on ferrocene not recovered) of yellow-brown needles was obtained by crystallization of the extracted material from benzene. By repeated crystallization from isopropyl alcohol, cotton-like yellow needles were obtained, m.p. 205–207°.

The infrared spectrum of this substance was identical to the spectrum of the Beckmann rearrangement product of benzoylferrocene oxime. Evaporation of the hexane left 2.8 g. (57%) of ferrocene.

1,2-Diphenyl-1,2-diferrocenyl-ethanediol.[7]—Methylmagnesium bromide was prepared by passing methyl bromide through a mixture of 0.65 g. of magnesium and 10 ml. of anhydrous ether. Under an atmosphere of nitrogen, 70 mg. of anhydrous powdered cobalt(II) chloride was added to the solution at 0°. Then 2 g. of monobenzoylferrocene in 15 ml. of benzene was added dropwise. The mixture was stirred for 1.5 hr., refluxed 2.5 hr. and stirred 0.75 hr. While a nitrogen atmosphere was maintained, 30 ml. of a saturated aqueous solution of ammonium chloride was added dropwise. The mixture was transferred to a separatory funnel, washing the reaction flask with water and a minimum of ether. The remaining solid and organic layer were extracted with portions of ammonium chloride solution till almost all the dark suspended material changed to a pale yellow solid floating at the lower interface of the organic layer. The yellow solid was washed with water, dried in the air and recrystallized from benzene under nitrogen; yield 0.76 g. (38%), m.p. 125–145° dec.

Anal. Calcd. for $C_{34}H_{30}O_2Fe_2$: C, 70.10; H, 5.15; active H, 0.34. Found: C, 69.61; H, 5.15; active H, 0.36 (lithium aluminum hydride).

The infrared spectrum showed hydroxyl absorption at 3510, phenyl absorption at 1492, 1585 and 1620 and absorption due to unsubstituted ferrocene rings at 1106 cm.$^{-1}$. Carbonyl absorption was absent.

The visible absorption spectrum in benzene showed a maximum near 445 mμ (ε 281). The compound does not dissolve in alcohols or paraffinic solvents.

Solutions of the compound in benzene and carbon disulfide were yellow. In chloroform, dioxane or alcohol–benzene, the solutions rapidly turned red. Chromatography on alumina converted the pinacol to red crystals whose infrared spectrum showed bands characteristic of both the pinacol and benzoylferrocene. Recrystallization yielded a product whose infrared spectrum was identical to that of benzoylferrocene. The same conversion took place very slowly in benzene solution and was studied by measuring the increase in absorption at 362 mμ, the wave length at which benzoylferrocene shows a maximum but the pinacol shows a minimum. At the end of 4 days, a dilute solution of the pinacol in benzene (0.150 g./liter) was 80% converted to benzoylferrocene.

A sample of 20 mg. of the pinacol was dissolved in 5 ml. of benzene. Hydrogen chloride gas was led over the surface for 2 min. The test-tube was stoppered and allowed to stand three days. The benzene was decanted from a green oil and chromatographed on alumina. Development of the chromatogram with hexane yielded 5 mg. of benzoylferrocene and about 4 mg. of orange crystals, m.p. 211° dec. The infrared spectrum of the latter was identical to that of phenylbenzoyldiferrocenylmethane (V).

Phenylbenzoyldiferrocenylmethane (V).—Benzoylferrocene (0.3 g.) was reduced in 1 ml. of absolute alcohol with 0.6 g. of amalgamated zinc.[16] Alcoholic hydrogen chloride (2 ml.) was added over 30 minutes. The solution was heated for 1 hr. at 100° and allowed to stand overnight. The solution was diluted with benzene. Chromatography with benzene–hexane on alumina yielded two solids, the first an unidentified orange substance, m.p. 211° dec., the second the pinacolone V. Of the latter, 100 mg. (33%) was obtained, m.p. 195–198° dec. Infrared carbonyl absorption was at 1680, phenyl absorption at 1492, 1586 and 1600 and absorption of unsubstituted ferrocene rings at 1108 cm.$^{-1}$.

Anal. Calcd. for $C_{34}H_{28}OFe_2$: C, 72.34; H, 4.97. Found: C, 72.16; H, 5.26.

Phenyldiferrocenylmethane (VI).—A 20-mg. sample of the pinacolone V was heated at 100° for 24 hr. in 5% alcoholic potassium hydroxide. The solvent was evaporated to a low volume, extracted with water and filtered. The filtrate was extracted with ether and the ether extracts, in turn, extracted with $NaHCO_3$ solution. The bicarbonate solution was then acidified and re-extracted with ether and the ether then evaporated off. The gray-white solid which remained was sublimed to give a product, m.p. 110–115°. The X-ray powder photograph of this material was identical to that of benzoic acid. The residue from the original basic mixture was dissolved in hexane and chromatographed. In addition to a small amount of the original pinacolone, there was obtained about 10 mg. of phenyldiferrocenylmethane, m.p. 123–124° (from ethanol–water); infrared peaks were at 1106, 1492, 1586 and 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{24}Fe_2$: C, 7035; H, 5.22. Found: C, 70.14; H, 5.28.

Phenylferrocenylmethane (X).—To a solution of 0.5 g. of benzoylferrocene in 5 ml. of acetic acid was added 5 g. of zinc dust. The mixture was swirled and became viscous. Three 5-ml. portions of acetic acid were added, and the mixture was allowed to stand. After 3 hr., an additional 17 ml. of acetic acid and 1 ml. of concentrated hydrochloric acid were added. After 18 hr., an additional 5 g. of zinc dust was added, then 10 ml. more of concentrated hydrochloric acid. The red color disappeared from solution. The mixture was diluted with water and filtered, whereupon the major part of the colored material was precipitated on the surface of the zinc dust. The solid was extracted with benzene and the benzene extracts chromatographed on alumina. In addition to an unidentified solid, m.p. 218° dec., and a small amount of pinacolone V, there was obtained 0.13 g. (27%) of the desired hydrocarbon, m.p. 70–74° (from low boiling petroleum ether), λ_{max} at 440 mμ, and infrared peaks at 1105, 1497, 1560, 1588, 2920 and 2980 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{16}Fe$: C, 73.91; H, 5.79; mol. wt., 276. Found: C, 74.07; H, 5.36; mol. wt., 277 (isothermal distillation).

Phenylferrocenylmethanol (II).—To a solution of 6 g. of lithium aluminum hydride in 150 ml. of anhydrous ether was added a solution of 10 g. of benzoylferrocene in 600 ml. of anhydrous ether. Stirring was continued for 2 hr. After 20 hr., the mixture was hydrolyzed and the ether decanted from the solids. On evaporation of the ether, a yield of 9.6 g. (96%) of phenylferrocenylcarbinol was obtained, m.p. 81–82° (from low boiling petroleum ether); infrared absorption peaks were at 3470 (OH), 1500, 1560 and 1106 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{16}OFe$: C, 69.86; H, 5.48; mol. wt., 291. Found: C, 69.82; H, 5.32; mol. wt., 253 (isothermal distillation).

An attempt to convert this carbinol to the corresponding bromide with PBr_3 led instead to a product believed to be **di-(phenylferrocenylmethyl) ether** (which could be made also by treatment of the carbinol with *p*-toluenesulfonyl chloride). The carbinol (0.7 g.) was dissolved in 2 ml. of dry pyridine, the solution cooled to 0°, 0.2 g. of phosphorus tribromide added dropwise and cooling continued for 1.5 hr. After two days, the solvent was evaporated off and the oil dissolved in chloroform. The white solid was removed by adding benzene, then boiling to a low volume and adding hexane. Chromatography of the filtrate yielded a very small quantity of an unidentified substance, m.p. 110–112°, and about 20 mg. of the *sym*-ether, m.p. 52–56°.

Anal. Calcd. for $C_{34}H_{30}OFe_2$: C, 72.09; H, 5.29; mol. wt., 566. Found: C, 71.72; H, 6.21; mol. wt., (Rast), 508.

The infrared spectrum showed phenyl absorption at 1492, 1588 and 1610, absorption of unsubstituted ferrocene rings at 1104 and a strong ether absorption at 1097 cm.$^{-1}$.

On boiling phenylferrocenylcarbinol in a solution of methanol and water, and crystallization from these solvents, yellow crystals were obtained, m.p. 104–108°. After rechromatographing on alumina in hexane and recrystallizing the first yellow band eluted from methanol–water, the

(16) W. Steinkopf and A. Wolfram, *Ann.*, **430**, 115, 135 (1923).

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methyl ether of phenylferrocenylmethanol (III, R = CH_3) was obtained, m.p. 111–112°.

Anal. Calcd. for $C_{18}H_{18}OFe$: C, 70.59; H, 5.88; active H, 0.0. Found: C, 70.26; H, 5.20; active H, 0.0.

The infrared spectrum showed absorption of aliphatic C–H at 2880, 2930 and 2970, phenyl absorption at 1492 and 1559, absorption of unsubstituted ferrocene rings at 1104 and very strong ether absorption at 1063 cm.$^{-1}$.

Isopropyl Ether of Phenylferrocenylmethanol (III, R = *i*-Pr–).—Benzoylferrocene (1 g.) was reduced by the method of Meerwein–Ponndorf–Verley.[17] The hydrolyzed reaction mixture was extracted with benzene, the solvent removed and the mixture extracted with Skellysolve B and chromatographed on alumina with methanol. In addition to a small amount of the methyl ether of phenylferrocenylmethanol, there was isolated 0.35 g. (33%) of yellow crystals of the isopropyl ether, m.p. 74–75°.

Anal. Calcd. for $C_{20}H_{21}OFe$: C, 72.07; H, 6.31. Found: C, 71.24; H, 6.81.

The infrared spectrum showed absorption in the aliphatic C–H region at 2880, 2930 and 2970, phenyl absorption at 1492, 1540 and 1559, absorption of unsubstituted ferrocene rings at 1104 and very strong ether absorption at 1063 cm.$^{-1}$.

Like the carbinol and the methyl ether, the isopropyl ether is soluble in concentrated hydrochloric acid.

Reduction of Monobenzoylferrocene by Sodium.—To 0.25 g. of monobenzoylferrocene in 3 ml. of benzene was added 2.5 g. of 5% sodium amalgam. The mixture was refluxed 2 hr., poured into water and filtered. The organic layer was washed, dried and chromatographed on alumina. Evaporation of solvent from the eluted yellow band, just preceding the large red band of unreacted monobenzoylferrocene, left 35 mg. of orange yellow powder, 150–170° dec. (180–185° red droplets). This substance is believed to be phenyldiferrocenylmethanol (IX). Infrared absorption was found at 3520 (OH), 1492 and 1600 (phenyl) and 1107 cm.$^{-1}$ (ferrocenyl).

Anal. Calcd. for $C_{27}H_{24}OFe_2$: C, 68.05; H, 5.04; active H, 0.21. Found: C, 68.44; H, 5.11; active H, 0.36.

This compound was dissolved in 95% ethanol by refluxing for 15 min. Excess zinc dust was added, then alternately, small amounts of hydrochloric acid and zinc dust till most of the color was gone from the solution. The mixture was filtered, washed, dried, extracted with benzene and the solvent evaporated. The residue was extracted with hexane and chromatographed on alumina in that solvent, yielding a yellow solid with an infrared spectrum identical to that of phenyldiferrocenylmethane (VI).

A 30-mg. sample of the hydroxy compound was refluxed with methanol for 7.5 hr. Evaporation of the methanol yielded crystals which were purified by chromatography on alumina. The resulting product 28 mg., m.p. 158° dec., is presumably the methyl ether of IX. Its infrared spectra showed peaks at 2920, 2820, 1554, 1494, 1106 and a high absorption, indicative of ethers, at 1076 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{26}OFe_2$: C, 68.55; H, 5.31. Found: C, 69.41; H, 5.59.

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(17) A. L. Wilds, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 178.

[CONTRIBUTION FROM THE PLASTICS LABORATORY, PRINCETON UNIVERSITY]

Reductive Cleavage of Ferrocene[1]

BY DANIEL S. TRIFAN AND LOUIS NICHOLAS

RECEIVED JULY 25, 1956

In contrast to the extreme resistance of ferrocene to catalytic reduction, this aromatic ring system is reduced readily by lithium in ethylamine with cleavage of the molecule to metallic iron and cyclopentadiene. The reaction of lithium with ferrocene in ethylamine is very rapid and may be stopped after several minutes with good conversion. Qualitative experiments have ascertained that other metal-amine, ammonia combinations also similarly reduce ferrocene.

No method has yet been described for a mild controlled degradation of the ferrocene ring system (bis-cyclopentadienyl iron, $Fe(C_5H_5)_2$) suitable for structure assignments for isomeric substituted ferrocenes. In this investigation a convenient degradation procedure was sought which would effect cleavage of the ferrocene molecule into its component parts and permit separate examination of each of the resulting 5-carbon rings.

The catalytic hydrogenation route to dearomatization and collapse of the ferrocene molecule appears to be unsuccessful. The resistance of ferrocene to catalytic hydrogenation over platinum has been reported by Woodward, Rosenblum and Whiting.[2] Our own attempts to hydrogenate ferrocene using the more active 5% rhodium-on-alumina in acetic acid for periods up to several weeks have given similar negative results. Under these same conditions benzene is completely hydrogenated in 5 minutes. Fischer[3] also has reported failure to hydrogenate ferrocene with Raney nickel in alcohol at 150° and 150 atmospheres.[4]

As a means of transferring an electron to the ferrocene nucleus to dearomatize the molecule, the use of alkali metals was investigated. Lithium does not attack ferrocene in refluxing ether, benzene or toluene, although attack does occur at *ca.* 200° in mineral oil with formation of metallic iron. In contrast to these slow heterogeneous reactions, however, rapid cleavage of the ferrocene molecule into metallic iron and cyclopentadiene is obtained by use of lithium in ethylamine, the amine functioning as solvent for lithium atoms. This reducing system has been investigated by Benkeser and co-workers in connection with benzenoid aromatic compounds.[5]

(1) This research was supported jointly by the Army, Navy and Air Force under Signal Corps Contract No. DA-36-039SC-42633. Most of this material was submitted in preliminary form in August, 1955, and presented before the Division of Organic Chemistry, 130th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956.

(2) R. B. Woodward, M. Rosenblum and M. C. Whiting, THIS JOURNAL, 74, 3458 (1952).

(3) E. O. Fischer, *Angew. Chem.*, 67, 475 (1955).

(4) ADDED IN PROOF.—We have recently noted the interesting publication of A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, T. V. Nikitina and N. A. Simukova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 749 (1956), in which these investigators report the first successful catalytic hydrogenation of ferrocene and several of its derivatives using Raney nickel at 265–345° and 200–280 atmospheres.

(5) (a) R. A. Benkeser, R. E. Robinson, D. A. Sauve and O. H. Thomas, THIS JOURNAL, 76, 631 (1954); 77, 3230 (1955); (b) R. A. Benkeser, C. Arnold, R. F. Lambert and O. H. Thomas, *ibid.*, 77, 6042 (1955).

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June 5, 1957

A series of qualitative experiments summarized in Table I has been carried out to indicate the generality of ferrocene reduction by other alkali and alkaline earth metal-amine, ammonia combinations. The progress of the reaction was followed by the rate of reflux and the appearance of black metallic iron. Rates are substantially lower with sodium than with lithium, and lower in *n*-hexylamine than in ethylamine. Calcium–amine combinations give no reaction. In liquid ammonia, however, reductions with calcium, lithium and sodium are all vigorous. The lithium–ethylamine combination appears to be the most convenient and has therefore been selected for use in quantitative studies.

TABLE I

QUALITATIVE RATES OF REDUCTION OF FERROCENE

Metal	Amine	Description of initial reaction
Li	Ethylamine	Vigorous reaction, black iron
Na	Ethylamine	Gradual appearance of black iron; much slower than Li
Ca	Ethylamine	No reaction
Mg	Ethylamine	No reaction
Li	*n*-Hexylamine	Gradual appearance of black iron; slower than Na–ethylamine
Na	*n*-Hexylamine	Some darkening only after *ca.* 0.5 hr.
Ca	*n*-Hexylamine	No reaction even at b.p.
Li	Liq. NH_3	Vigorous reaction, black iron
Na	Liq. NH_3	Vigorous reaction, black iron
Ca	Liq. NH_3	Very vigorous reaction, black iron
Mg	Liq. NH_3	No reaction

When these results are compared with data on the reaction of sodium with various aromatic hydrocarbons, it may be estimated that in the series of aromatic compounds of increasing electron affinity: benzene << phenanthrene < naphthalene < anthracene, etc.,[6] ferrocene is closer to benzene than to other members of this series, although in view of the very much more rapid reaction of lithium–ethylamine with ferrocene than with benzene it would seem to be higher. Reaction periods of 8–10 hours are employed for the latter[4] while reductions of ferrocene give good conversions in a few minutes.

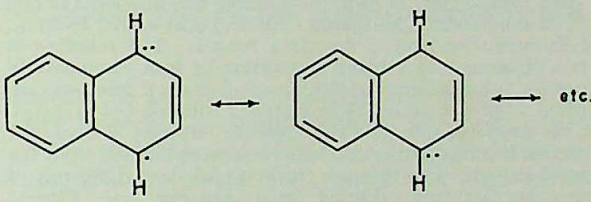
A typical ferrocene reduction using lithium in ethylamine for a period of 4–6 minutes resulted in reduction of 73% of the initial ferrocene. The cyclopentadiene was isolated both by distillation (53%) and by its adduct with maleic anhydride (71%).

A reductive cleavage of ferrocene using the calcium–ammonia reducing system[7] in ether was also carried out for comparison purposes and a 30% yield of cyclopentadiene, corrected for recovered ferrocene, was obtained as the maleic anhydride adduct. This procedure is much less convenient than that using lithium–ethylamine and no attempt was made to improve this yield.

The elemental iron produced in these ferrocene reduction reactions is very finely divided and when allowed to dry in air spontaneously oxidizes to a mixture of oxides. The yield of iron (98%) was therefore determined by solution in dilute sulfuric acid and titration of ferrous ion. In a semi-quantitative run designed to verify the elemental state of the initial iron product, the volume of hydrogen produced from the acidification of the reaction mixture corresponded roughly to that calculated from the amount of ferrocene reduced.[8]

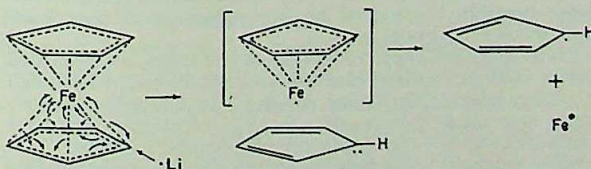
The finely divided iron obtained from a single run with sodium–ethylamine was pyrophoric and more reactive than that from lithium–ethylamine, probably because of a larger amount of adsorbed hydrogen in the former case due to the more rapid rate of hydrogen evolution.

The cleavage reaction proceeds by attack of lithium on carbon with transfer of an electron. Attack on the ferrocene aromatic system has different consequences from the parallel attack on benzenoid aromatic systems. In the latter case the π-electrons are displaced to give resonance-stabilized negative ion free radicals,[5] *e.g.*, I, with no consequent molecular rupture.



I

Similarly, it seems reasonable to suggest that in the analogous instance of the attack of lithium on one of the 5-carbon rings of ferrocene, the π-electrons are displaced to the conjugated double bond orbitals, or more precisely directly to the resonance hybrid orbitals, of the cyclopentadienide ion with resulting detachment from the iron atom. The remaining radical fragment presumably separates into free iron and cyclopentadienyl radical, which in turn may abstract hydrogen from solvent or an electron from lithium.



It is interesting to note that the mass spectrograms of ferrocene[9] and ferrocene derivatives[10] exhibit a very strong peak at mass number 121, corresponding to the C_5H_5Fe fragment, which may be interpreted as evidence of some appreciable degree of stability of this cyclopentadienyl–iron entity.

The instability of the $[(C_5H_5)Fe(C_5H_5)]^-$ anion may be contrasted with the stability of the $[(C_5H_5)Fe(C_5H_5)R]^+$ cation which presumably is an intermediate in the Friedel–Crafts acylation reac-

(6) D. E. Paul, D. Lipkin and S. I. Wiseman, THIS JOURNAL, 78, 116 (1956).

(7) B. A. Kazanskii and N. F. Glushnev, *J. Gen. Chem.* (*U.S.S.R.*), 8, 642 (1938); *C. A.*, 33, 1260 (1939).

(8) We are indebted to Alan R. Glueck of this Laboratory for these results.

(9) L. Friedman, A. P. Irsa and G. Wilkinson, THIS JOURNAL, 77 3689 (1955).

(10) Unpublished results from this Laboratory.

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tion. It may also be mentioned that the $[(C_5H_5)Fe(C_5H_4)]^-$ anion, which readily is obtained[11,12] by exchange reaction with, *e.g.*, *n*-butyllithium, is an obviously stable system since the π-electrons are not involved, and may be utilized in synthesis of corresponding ferrocene derivatives.

This reductive cleavage reaction should prove general for analogous metallocene systems. In addition to degradative structure applications, the reaction also provides a novel approach to the preparation of certain substituted cyclopentadienes from the correspondingly substituted ferrocene derivatives. Some experiments directed toward this end are currently in progress.

Experimental

Ferrocene Reduction with Lithium in Ethylamine.—Ferrocene cleavage runs were conducted in flasks with an 8 mm. bore stopcock at the bottom. Lithium wire (2 mm. diam.) was freshly extruded into the flask containing anhydrous ether which was drained through the stopcock just before the reaction was started. The flask was fitted with stirrer and a large capacity Dry Ice reflux condenser.

In a typical run, 29.39 g. of ferrocene was dissolved in 500 ml. of ethylamine (Matheson cylinder) and added to 21 g. of lithium wire from a dropping funnel. The reaction is very vigorous and a black suspension of iron immediately appears. A minimum addition period of *ca.* 2 min. was required to prevent flooding and after a total of 4–6 minutes, at the end of which time the vigorous refluxing abates, the reaction mixture and ethylamine rinse were drained from the excess lithium wire through the stopcock into 1500 ml. of ice–water mixture, diluted with benzene and filtered through Celite to remove iron. The aqueous phase was separated and extracted with numerous portions of benzene, followed by thorough washing of the benzene phase with water to remove ethylamine. The benzene solution was dried with magnesium sulfate and refluxed with 26.3 g. of maleic anhydride overnight. After the solution was concentrated and evaporated to dryness, the Diels–Alder adduct and excess maleic anhydride were hydrolyzed and extracted from unreduced ferrocene by treatment with portions of hot water. Fractional crystallization of the adduct acid, *endo-cis*-bicyclo[2,2,1]-5-heptene-2,3-dicarboxylic acid, from water yielded 25.78 g. (71% based on ferrocene reduced), m.p. 177.5–179°, lit.[13] 177–179°, mixed m.p. undepressed. A control run using cyclopentadiene and the same extraction and work-up procedure gave no better recovery.

A similar reduction was carried out using a reaction period of 6.5 hours during which time almost all of the lithium wire dissolved. However, only 32.8% (12.19 g.) of the theoretical amount of adduct acid was obtained under these conditions, possibly because of further reduction of the cyclopentadiene initial product.[4]

From a typical rapid reduction of ferrocene, as described above, cyclopentadiene also was isolated directly, although in poorer yield. Ferrocene (37.2 g.) in 300 ml. of ethylamine was allowed to react with 18 g. of lithium strips for 3 minutes and the black mixture was poured into ice. The volatile material was condensed into receivers cooled in Dry Ice at aspirator pressure and distilled. A hydrocarbon layer was separated from ethylamine by addition of water to several combined fractions and dried over $CaSO_4$ (11.2 g. of cyclopentadiene, 53% corrected for 7.4 g. of recovered ferrocene). The cyclopentadiene was identified as the maleic anhydride adduct, a 1.0-g. sample yielding 1.8 g. (72%) of the crude adduct, m.p. 161–163.5° unrecrystallized, lit.[11] 164–165°.

Delayed addition of the ferrocene after the lithium has entirely reacted with the ethylamine results in complete recovery of the ferrocene.

Characterization of Iron from Ferrocene Reductions.—Because of the spontaneous oxidation of the finely divided iron when dry, the yield of iron obtained from a ferrocene reduction was determined by adding the product of a reaction to a mixture of dilute sulfuric acid and ice. Titration of the aqueous phase with 0.1 *N* $KMnO_4$, after extraction with CCl_4 to remove cyclopentadiene, indicated 98% of the theoretical amount of ferrous ion.

The elementary state of the iron was verified by a semi-quantitative determination of hydrogen evolved from acidification of a reaction mixture.[7] The product from a typical reduction was transferred to an empty flask and most of the ethylamine swept out in a stream of helium. Dilute sulfuric acid was then added through a dropping funnel and the hydrogen collected in an inverted graduate, the estimated corrected volume corresponding to *ca.* 90% of the calculated amount.

The finely divided iron can be collected and rinsed with solvent but it immediately begins to oxidize to FeO, Fe_3O_4 and Fe_2O_3, turning from black to brown. Both the moist black and brown materials are characteristically magnetic.

In a single ferrocene cleavage (15 g.) the sodium–ethylamine combination was employed and the slower reaction allowed to continue for 50 minutes. The cyclopentadiene was not isolated, but the iron produced under these conditions was more reactive upon drying and oxidized in air with incandescence. Extreme precautions were required to avoid explosion.

X-Ray diffraction using a North American Philips Geiger-counter spectrometer was employed in the characterization of the iron and iron oxides obtained from this reaction. Freshly prepared iron samples were protected as well as possible from oxygen with either mineral oil (Nujol) or 2% Duco cement in acetone during filtration and measurement but it was still not possible because of the highly active surface to avoid the appearance of peaks corresponding to FeO, Fe_3O_4 and Fe_2O_3, *e.g.*, using Fe K_α radiation, 2θ = 45.9°, 53.5°; 38.1°, 54.9°, 73.6°; 45.2°, 52.2°, respectively. Of those samples most carefully protected the FeO peak at 45.9° was the most prominent oxide peak, while a sample which had been allowed to oxidize as completely as possible in air had its strongest peak at 45.2° (Fe_2O_3).

Although very weak Fe peaks at 57.0°, 85.4° and 102.2° could sometimes be detected with carefully protected samples, the results were not analytically satisfactory and the weak peaks may be due either to amorphous structure or particle size of the iron, where the oxides are either less critically dependent on particle size or have aggregated during oxidation. Finely divided iron similarly prepared by ferric chloride reduction with lithium in ethylamine showed the same weak Fe and various oxide peaks.

Ferrocene Reduction with Calcium in Ammonia.—Several preliminary qualitative tests showed that the reaction of ferrocene with calcium in ammonia was very vigorous and required caution. Ferrocene (30 g.) was dissolved in 500 ml. of anhydrous ether in a flask fitted with a large Dry Ice condenser. Calcium turnings (50 g.) were added and anhydrous ammonia was introduced very slowly with stirring until *ca.* 200–300 ml. of ammonia had been condensed, the addition being interrupted several times when the reaction appeared to increase in rate. Evidence of reaction appeared shortly after introduction of ammonia by the darkening of the calcium and appearance of black iron particles. Additional ether (200 ml.) was added to the cold reaction flask to further dissolve some of the precipitated ferrocene. After 5 hours, during which time a considerable increase in the amount of black suspension had developed, the condenser was filled with ice and the flask was warmed with tap water to allow escape of ammonia.

When the contents were at room temperature, 150 ml. of water was added cautiously from a dropping funnel. The ether phase was decanted from the calcium hydroxide–iron residue and the latter was extracted with numerous portions of benzene until colorless. The combined ether–benzene layer was washed with water to remove ammonia, dried with magnesium sulfate and refluxed with 26.3 g. of maleic anhydride overnight. After the solution was concentrated and evaporated to dryness, the adduct acid was separated from unreduced ferrocene (22.17 g.) by crystallization from water to yield 4.79 g. (30.3%) of recrystallized adduct acid. The presence of iron in the extracted residue was confirmed with a magnet test.

Ferrocene Reduction with Lithium in Mineral Oil.—Lithium sand was prepared by melting 10 g. of lithium in 150 ml. of mineral oil (Nujol) and cooling below the melting

(11) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and O. A. Nesmeyanova, *Doklady Akad. Nauk S.S.S.R.*, **97**, 459 (1954).

(12) R. A. Benkeser, D. Goggin and G. Schroll, THIS JOURNAL, **76**, 4025 (1954).

(13) O. Diels and K. Alder, *Ann.*, **460**, 113 (1928).

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point while stirring at high speed. When the contents were at 100°, 3.0 g. of ferrocene was added and gradual heating resumed, using a protective helium atmosphere. Careful visual examination indicated no appreciable reaction until the temperature had reached *ca.* 190° at which time the lithium surface appeared to darken slightly and the presence of iron particles could be discerned by testing with a magnet. Heating was resumed and the temperature raised to 220° over a 10-minute period and then the mixture was allowed to cool. By this time the lithium particles were very much darker and *ca.* 0.1 g. of magnetic black precipitate had settled to the bottom of the flask. After rinsing with solvent, the Fe-coated lithium sand adhered readily to the magnet. In the absence of lithium at these temperatures and in contact with air, no evidence of degradation could be observed.

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Organic Chemistry of Ferrocene. I. The Acetylation of Dialkylferrocenes[1]

BY KENNETH L. RINEHART, JR., KAYE L. MOTZ AND SUNG MOON

RECEIVED DECEMBER 3, 1956

Acetylation of 1,1′-dimethylferrocene gives a 7 to 3 ratio of the 3- or β-acetyldialkylferrocene to the 2- or α-acetyl isomer, while the ratio of the corresponding acetyldiisopropyl isomers obtained from acetylation of 1,1′-diisopropylferrocene is 9 to 2. The isomeric acetyldialkylferrocenes have been isolated, characterized by infrared and ultraviolet spectra and converted by oxidation to the corresponding carboxylic acids and by reduction to the corresponding alkyl derivatives. Dissociation constants of the isomeric dimethylferrocenecarboxylic acids and infrared spectra of the isomeric ethyldimethylferrocenes have been presented and discussed.

Since the initial report in 1951 of the isolation of ferrocene[2,3] and the discovery that the compound is, in many respects, an aromatic system,[4] there have been numerous chemical confirmations of the similarity of its chemistry to that of the classical benzenoid compounds and, indeed, the name ferrocene was chosen to indicate the compound's aromatic character.[4] Thus, for example, ferrocene may be acylated,[4,5] sulfonated,[5,6] metalated[7,8] and arylated by other aromatic nuclei.[7,9–12] On the other hand, in its resistance to alkylation[5,13] and its behavior toward oxidizing media[14] ferrocene shows marked differences from benzene. The present study has been undertaken as part of a general investigation of substituted ferrocenes and to investigate to what extent the normal directive effects of alkyl groups[15] are observed in the ferrocene system.

For this purpose the acylation reaction is particularly well adapted since it has been studied extensively in benzenoid systems and found to be highly selective in substitution at ring positions.[16] Further, acylation of ferrocenes leads to little or no degradation of the ring system and often gives products in high yields.[5,17] Previous investigations of acylations have shown similarities between ferrocene and benzene in that acylation may be accomplished under conditions employed for benzene[4,5] and also in that the presence of one acyl group on the ferrocene nucleus strongly deactivates the substituted ring toward further acylation[4,18] and to a certain extent deactivates the other ring as well.[5,13,18] By contrast, the presence of an alkyl group might be expected to activate somewhat the substituted ring toward acylation.[19]

In the present study the compounds investigated have been the 1,1′-dialkylferrocenes,[20] in which each ring bears a substituent alkyl group. Both 1,1′-dimethyl- (Ia) and 1,1′-diisopropyl-ferrocene (Ib) have been examined in order to observe the differing effects of the methyl and isopropyl substituents and the response of acylation of the system toward increasing steric bulk on the rings.

Acetylation of either of these compounds can give substitution in the 2- or 3- (α- or β-)[21] positions. If care is taken to prevent disubstitution, only two isomers are formed, 2-acetyl- (IIa,b) and 3-acetyl-1,1′-dialkylferrocenes (IIIa,b); measurement of the proportion of the two isomers leads to

(1) Presented in part at the 129th Meeting of the American Chemical Society, Dallas, Texas, April 8 to 13, 1956; see Abstracts of Papers, p. 12-N.

(2) T. J. Kealy and P. L. Pauson, *Nature*, **168**, 1039 (1951).

(3) S. A. Miller, J. A. Tebboth and J. F. Tremaine, *J. Chem. Soc.*, 632 (1952).

(4) R. B. Woodward, M. Rosenblum and M. C. Whiting, THIS JOURNAL, **74**, 3458 (1952).

(5) V. Weinmayr, *ibid.*, **77**, 3009 (1955).

(6) A. N. Nesmeyanov, XIVth International Congress of Pure and Applied Chemistry, Zurich, July 21–27, 1955; *cf.* Abstracts of Papers, p. 193.

(7) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and O. A. Nesmeyanova, *Doklady Akad. Nauk SSSR*, **97**, 459 (1954).

(8) R. A. Benkeser, D. Goggin and G. Schroll, THIS JOURNAL, **76**, 4025 (1954).

(9) A. N. Nesmeyanov, E. G. Perevalova and R. V. Golovnya, *Doklady Akad. Nauk SSSR*, **99**, 539 (1954).

(10) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and L. S. Shilovtseva, *ibid.*, **102**, 535 (1955).

(11) G. D. Broadhead and P. L. Pauson, *J. Chem. Soc.*, 367 (1955).

(12) V. Weinmayr, THIS JOURNAL, **77**, 3012 (1955).

(13) P. L. Pauson, *Quart. Revs.*, **9**, 391 (1955).

(14) G. Wilkinson, M. Rosenblum, M. C. Whiting and R. B. Woodward, THIS JOURNAL, **74**, 2125 (1952).

(15) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 236.

(16) R. C. Fuson, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 333; H. C. Brown and W. H. Bonner, THIS JOURNAL, **76**, 605 (1954); R. Pajeau, *Bull. soc. chim. France*, 544 (1946).

(17) R. Riemschneider and D. Helm, *Chem. Ber.*, **89**, 155 (1956).

(18) M. Rosenblum, Ph.D. Thesis, Harvard University, August, 1953.

(19) Reference 15, pp. 245–256.

(20) K. L. Rinehart, Jr., Sung Moon and K. L. Motz, in preparation.

(21) The α–β nomenclature commonly employed in heterocyclic and condensed ring aromatic compounds seems preferable to any system based on an *ortho–meta–para* scheme. Confusion arises in the five-membered ring series since electronically there are probably two "para" positions (1 and 4) and one "meta" position (*cf.* below).[14]

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an indication of directive influences in the ring.[22]

Influences favoring one or the other of the two isomers may be described as steric or electronic in nature. On purely steric grounds formation of the 3- or β-acetyl isomer is favored, especially from the acetylation of diisopropylferrocene. Electronic effects are more difficultly predictable. The inductive effect of an alkyl substituent should favor the formation of the 2- or α-acetyl isomer since this effect diminishes with increasing distance from the substituent. Hyperconjugative interaction of the alkyl group with the ring might be expected to enhance the reactivity of both positions, however, since acylation transition states of the usual type[23] in which the positive charge is delocalized about the ring may be pictured for substitution at either ring position.[24]

A greater number of such hypothetical delocalized forms may be drawn for hyperconjugation of the acylation transition state at a position alpha to the alkyl group, but, of course, the number of such forms says nothing for the stability or relative contribution of each.[25] From the above discussion no predictions may be made with certainty, but since the various electronic and steric influences are complex and to an extent oppose one another, it might be expected that a mixture of the two isomeric products should be formed in which neither isomer strongly predominates.

Both diisopropyl- and dimethyl-ferrocene were acetylated with acetic anhydride employing an aluminum chloride catalyst. To inhibit the formation of diacetyl products, only one-half mole of anhydride was employed per mole of ferrocene and the anhydride was added slowly to the ferrocene solution. The mixture of products was separated chromatographically, whereby the dialkylferrocene was recovered readily, while the two isomeric acetyldialkylferrocenes were separated with greater difficulty. The relative proportions of the two isomers formed from dimethyl- and diisopropylferrocene are summarized in Table I. These proportions were calculated from the ultraviolet spectra of mixtures of the two compounds and, as a check, for the diisopropylferrocene acetylation, also from the weights of the two isomers obtained from chromatographic fractions; agreement between the two methods is good.

TABLE I

PROPORTIONS OF ISOMERIC ACETYLDIALKYLFERROCENES FORMED

Dialkylferrocene acetylated[a]	Proportion of isomers, % α-[a]	β-[a]
1,1′-Dimethyl-	30[b]	70[b]
1,1′-Diisopropyl-	19[b]	81[b]
1,1′-Diisopropyl-	17[c]	83[c]

[a] α = 2-acetyldialkylferrocene (IIa,b). β- = 3-acetyldialkylferrocene (IIIa,b). [b] Composition estimated from ultraviolet spectra. [c] Composition estimated from weights of chromatographed isomers.

In the acetylation of dimethylferrocene there is little selectivity between the two positions and, while 3-acetyl-1,1′-dimethylferrocene is formed in somewhat greater amount, it nevertheless accounts for only 70% of the product and the 2-acetyl isomer for 30%. There is somewhat greater selectivity in the acetylation of diisopropylferrocene; here the β-isomer is formed in larger amount (82%) than with the methyl analog, while substitution of the α-position, hindered sterically, occurs to the extent only of 18%.

(22) It may be noted that Rosenblum[18] earlier acetylated monoethylferrocene and obtained the expected three isomers, although he did not assign definite structures to the two homoannular compounds. The present 1,1′-dialkyl system has the virtue of simplicity in that it allows the isolation and study of directive effects on substitution in the same ring uncomplicated by those exerted on substitution in the other ring.

(23) J. W. Baker, "Hyperconjugation," Oxford University Press, London, 1952, p. 48.

(24) It is on this basis that the α- and β-positions seem to resemble more closely the *o*- and *p*-positions of benzene, while no true *m*-position exists.

(25) On the basis of an approximate molecular orbital treatment of substituted ferrocenes, Richards has predicted the formation of a somewhat higher proportion of the α-isomer for both electron-donating and electron-withdrawing substituents [J. H. Richards, private com-

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tent of only 18%. This is rather a surprisingly small difference in light of the considerably greater bulk of the isopropyl group.[26] However, the bond angles of the 5-membered ring are much less conducive to steric crowding than those of benzene, as may be seen from Fig. 1, where van der Waals radii[25] have been drawn. Thus there is less interaction between adjacent substituents on the ring. This conclusion is supported by the ultraviolet spectra of the acetyl isomers and the dissociation constants of the corresponding isomeric acids presented below. The formation of the two isomers in similar amounts is consistent with the treatment of competing electronic effects outlined above. In summary, it may be stated that there is little selectivity between acylation at one or the other position of the ferrocene ring and that steric effects are not as important as in the benzene analogs, where acetylation of toluene gives nearly exclusively *p*-substitution,[29] although electronic factors presumably favor *o*-substitution also.[19]

As a further comparison between the ferrocene and benzene systems the physical properties of substituted ferrocenes are of interest. In Table II

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA OF FERROCENYL AND PHENYL KETONES

Ketone	λ_{max}, mμ[a]	ϵ_{max}[a]
Acetylferrocene	226	16,500 (14,600)[b]
	269	6,500 (5,400)[b]
2-Acetyl-1,1′-dimethylferrocene	227	18,600
	271	6,800
3-Acetyl-1,1′-dimethylferrocene	232	15,800
	274	6,600
2-Acetyl-1,1′-diisopropylferrocene	226	18,200
	271	6,700
3-Acetyl-1,1′-diisopropylferrocene	231	15,600
	273	6,700
Acetophenone	242	12,000 (12,800)[c]
o-Methylacetophenone	243	9,500 (8,850)[c]
m-Methylacetophenone	247	11,300
p-Methylacetophenone	252	15,800 (15,100)[c]

[a] Spectra determined in 95% ethanol. [b] Ref. 18. [c] Ref. 30.

are presented maxima from the ultraviolet spectra of the isomeric acetyl-dialkylferrocenes, together with those of the isomeric methylacetophenones for comparison. Both series of compounds have strong conjugated ketonic absorption; for phenyl ketones this is near 245 mμ, while for ferrocenyl ketones there are two bands, near 230 and 270 mμ. Of particular interest is the striking difference between the effect of alkyl substituents on the spectra of the two systems. Methyl substitution in the *p*-position of acetophenone increases both the wave length of maximum absorption and the

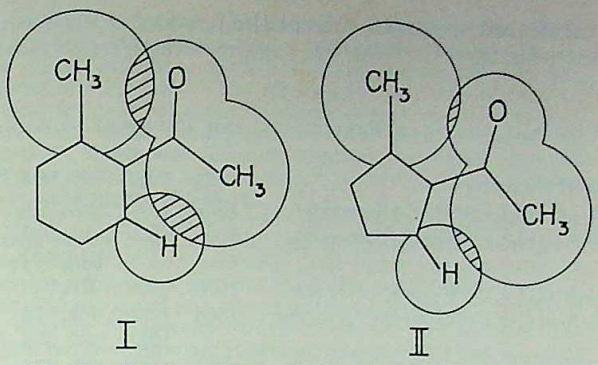

Fig. 1.—Overlap of van der Waals radii between acetyl and adjacent groups in substituted aromatic ketones: I, *o*-methylacetophenone; II, 2-acetyl-1,1′-dimethylferrocene.

extinction coefficient. A *m*-methyl substituent shifts the maximum to somewhat longer wave lengths but has little effect on the extinction coefficient. An *o*-substituent, on the other hand, does not shift the wave length of the peak at all from that of acetophenone but leads to a sharp decrease in the extinction coefficient. This behavior of *o*-methylacetophenone generally has been considered to be due to steric interaction between the acetyl group and the adjacent methyl and hydrogen,[28,30] and Braude has interpreted the effect more specifically as due to a decrease in the population of rotational conformations suitable for transition to the excited state responsible for the 245 mμ maximum.[31]

In the dialkylferrocenyl ketones the β-isomer shows a slight bathochromic shift and an extinction coefficient little different from that of acetylferrocene. In these properties it resembles *m*-methylacetophenone. However, the α-isomer shows strikingly different behavior from that of *o*-methylacetophenone. Although the peak wave length remains the same as that of acetylferrocene, the coefficient is higher than that of the unsubstituted ketone, rather than lower. Thus in these ultraviolet spectra, as in the acylation isomer ratios, steric effects are not so important as in the corresponding benzene compounds (*cf.* Fig. 1). This is further confirmed by the spectra of the diisopropyl ketones, which are nearly identical to those of the corresponding dimethyl isomers.[32]

Stronger absorption by the α-isomer must be due to electronic influences and may be attributed either to a strong inductive effect or to better hyperconjugative stabilization of the excited state in the α-isomer than in the β-analog (*cf.* above). The longer wave length absorption by the β-isomer is due probably to the greater length of the chromophoric system.

(26) An attempt was made to direct acetylation more stereospecifically by employing nitrobenzene as a solvent[27]; however, oxidation to the blue-green, water-soluble ferricinium cation was the predominant reaction under these conditions.

(27) G. Baddeley, *J. Chem. Soc.*, S99 (1949).

(28) M. T. O'Shaughnessy and W. H. Rodebush, THIS JOURNAL, **62**, 2906 (1940).

(29) R. Adams and C. R. Noller, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 111.

(30) R. B. Turner and D. M. Voitle, THIS JOURNAL, **73**, 1403 (1951).

(31) For reviews, *cf.* (a) E. A. Braude in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, eds., Academic Press, Inc., New York, N. Y., 1955, pp. 172–174; (b) E. A. Braude, *Experientia*, **11**, 457 (1955); E. A. Braude and E. S. Waight in "Progress in Stereochemistry," Vol. I, W. Klyne, ed., Academic Press, Inc., New York, N. Y., pp. 144–148.

(32) Although the ultraviolet spectrum of *o*-isopropylacetophenone appears not to have been recorded, it should have a lower extinction coefficient than that of *o*-methylacetophenone since 2,4,6-triisopropylacetophenone has λ_{max} (shoulder) 244 mμ, ϵ_{max} 2,000, while 2,4,6-trimethylacetophenone has λ_{max} 247 mμ, ϵ_{max} 3,500 (ref. 28).

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Infrared spectral bands of the ferrocenyl ketones are presented in Table III, again with those of the

TABLE III

INFRARED BANDS OF FERROCENYL AND PHENYL KETONES

Ketone	ν, cm.$^{-1}$[a]		
Acetylferrocene	1661	1285	896, 965
2-Acetyl-1,1′-dimethylferrocene	1667	1275	925, 930
3-Acetyl-1,1′-dimethylferrocene	1666	1299	901, 924
			940, 966
2-Acetyl-1,1′-diisopropylferrocene	1666	1269	925, 930
3-Acetyl-1,1′-diisopropylferrocene	1666	1280	905, 924
		1285	937, 969
Acetophenone	1683	1269	690, 761
o-Methylacetophenone	1682	1254	721, 759
m-Methylacetophenone	1684	1279	690, 786
p-Methylacetophenone	1681	1271	816

[a] Determined as liquid smears or mulls.

methyl acetophenones for comparison. From this Table it may be seen that the carbonyl stretching band of the ferrocenyl compounds falls near 1665 cm.$^{-1}$ for all isomers, at a somewhat longer wave length than that of the phenyl analogs. However, there are other characteristic bands which differ for α- and β-isomers but which for each positional isomer occur near the same position for both the dimethyl and diisopropyl compounds. Thus, the aromatic ketone band in the 1300–1250 cm.$^{-1}$ region occurs at lower frequency for the α-substituted compounds than for acetylferrocene itself but at higher frequency for the β-isomer. The spectra of corresponding alkyl acetophenones show a similar shift to higher frequencies for *m*- and *p*-substitution, lower for *o*-. In addition to the ketonic bands there are also bands in the 1000–900 cm.$^{-1}$ region, which has been shown to be highly useful for the characterization of isomeric polyalkylferrocenes.[20] In this region, too, both the dimethyl and diisopropyl compounds show similar bands for each of the positional isomers.

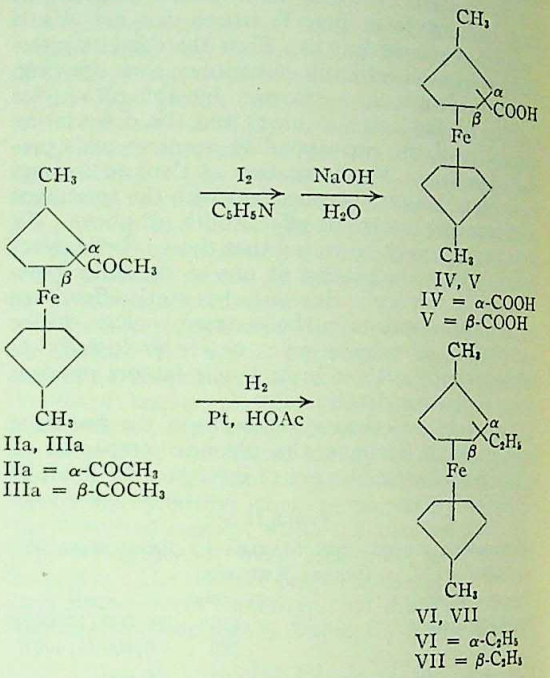
Each of the isomeric acetyldimethylferrocenes (IIa, IIIa) was oxidized by the modified iodoform procedure of Weinmayr[5] to the corresponding carboxylic acid (IV, V). Dissociation constants of the two acids and that of ferrocenecarboxylic acid are presented in Table IV, with those of benzoic and the toluic acids for comparison.

TABLE IV

DISSOCIATION CONSTANTS OF FERROCENE AND BENZENE CARBOXYLIC ACIDS

Acid	pK_a'	Solvent
Ferrocenecarboxylic acid	4.4[a]	Water
	7.3[a]	66% DMF
	7.26[b]	66% ethanol
1,1′-Dimethyl-2-ferrocenecarboxylic acid	5.4[a]	Water
	8.15[a]	66% DMF
1,1′-Dimethyl-3-ferrocenecarboxylic acid	4.7[a]	Water
	7.5[a]	66% DMF
Benzoic acid	4.20[c]	Water
	7.38[b]	66% ethanol
o-Toluic acid	3.91[c]	Water
m-Toluic acid	4.24[d]	Water
p-Toluic acid	4.34[d]	Water

[a] Determined in *ca.* 3×10^{-3} *M* solution. No correction has been applied for the small effect of ionic strength at this low concentration. Aqueous determinations were effected by back-titration of the potassium salts. [b] Ref. 18. [c] J. F. J. Dippy, *Chem. Revs.*, 25, 151 (1939). [d] G. Briegleb and A. Bieber, *Z. Elektrochem.*, 55, 250 (1951).



Here, as in the ultraviolet spectra of the ketones, the behavior of substituted ferrocenes is considerably different from that of the benzene analogs. While both *m*- and *p*-toluic acids are somewhat weaker acids than benzoic, *o*-toluic acid is stronger than the parent acid (*cf.* Table IV). The anomalous behavior of the *o*-isomer has been attributed by Brown[33] to steric interference toward conjugation between the carboxyl and ring.[34] However, *both* the 2- and 3-methyl-substituted ferrocene acids have lower dissociation constants than the unsubstituted acid, and the α-acid is the weakest of the three. The dissociation constants, then, as the ultraviolet spectra and isomer distribution ratios, support a view of the ferrocene system as being less affected (or at least affected differently) by steric factors than benzene. Electronic factors, either inductive or hyperconjugative, favoring greater electron release by the α-methyl, are probably responsible for the considerably lower dissociation constant of 1,1′-dimethyl-2-ferrocenecarboxylic acid, although an alternative explanation attributing the differences in dissociation constants to decreased solvation of the carboxylate anion[34,35] cannot be ruled out.

(33) H. C. Brown, D. H. McDaniel and O. Häfliger in ref. 31a, p. 603.

(34) Steric interference toward solvation of the carboxylate ion has been discussed by Newman[35] as an opposing effect which serves to lower the dissociation constants of *o*-substituted acids. No attempt is made in the present work to distinguish between the two effects. The principal point to be made is that the ferrocene and the benzene systems sometimes behave differently and that in the present case, the difference is probably due to the steric requirements of the two systems.

(35) H. L. Goering, T. Rubin and M. S. Newman, THIS JOURNAL, 76,

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The decreased proportion of one isomer formed on acetylation of diisopropylferrocene (as compared to the amount formed on acetylation of dimethylferrocene) argues strongly for the formulation of that as the sterically less favored isomer and thus the α-compound. In addition, the structures assigned to the two isomers have been confirmed by hydrogenation of both acetyldimethylferrocenes (IIa, IIIa) to the corresponding ethyldimethylferrocenes (VI and VII) and comparison of the infrared spectra of the two compounds to those of independently synthesized alkylferrocenes.[20]

The 1000–900 cm.$^{-1}$ region has been shown to contain characteristic bands for the identification of alkyl-substituted ferrocenes.[20] In Table V are

TABLE V

INFRARED BANDS OF ALKYL FERROCENES

Substituted ferrocene	ν cm.$^{-1}$[a]								
1,1′-Dimethyl-[b]		812	836	854		923			
						929			
2,2′-Diethyl-1,1′-dimethyl[b]	694	790	809	823		870		952	1207
								967	
2-Ethyl-1,1′-dimethyl-	693	790	807	823	850	870	926	949	1205
								969	
3-Ethyl-1,1′-dimethyl-		790	805	840	850		917	944	
			815				926		

[a] Determined as liquid smears. [b] Ref. 20.

presented bands from that region found in the spectra of the present hydrogenation products and those of two previously known polyalkyl ferrocenes, together with other significant bands useful in distinguishing between the two ethyldimethyl isomers.

Thus, 1,1′-dimethylferrocene has a single band in the 1000–900 cm.$^{-1}$ region, near 925 cm.$^{-1}$, while 2,2′-diethyl-1,1′-dimethylferrocene has two bands, at 965 and 950 cm.$^{-1}$. The 2-ethyl-1,1′-dimethylferrocene obtained on reduction of 2-acetyl-1,1′-dimethylferrocene should, then, have a band near 925 cm.$^{-1}$ characteristic of the monosubstituted ring and bands at 965 and 950 cm.$^{-1}$ characteristic of the α-disubstituted ring. As may be seen from Table V, this is indeed the case. The isomeric 3-ethyl compound has no bands at 965 and 950 cm.$^{-1}$, though it has one at 926 cm.$^{-1}$ for the methyl-substituted ring and bands at 917 and 944 cm.$^{-1}$, apparently characteristic of a 1,3-methylethyl disubstituted ring. Similarly, other bands present in the spectrum of 2-ethyl-1,1′-dimethylferrocene (*e.g.*, at 693, 870 and 1205 cm.$^{-1}$), and absent from that of the 3-ethyl- analog are found in the spectrum of 2,2′-diethyl-1,1′-dimethylferrocene.

Experimental[36]

Acetylation of dimethylferrocene was effected with acetic anhydride and aluminum chloride in the usual Friedel–Crafts manner. A mixture of 20.4 g. of 1,1′-dimethylferrocene[20] and 14.6 g. of aluminum chloride in 300 ml. of methylene chloride was cooled in an ice-bath, and 4.72 ml. of acetic anhydride in 25 ml. of methylene chloride was added during 3 hr. The reaction mixture was allowed to stand for 1 hr. at room temperature and was then poured over ice. After the organic phase had been separated and washed, methylene chloride was removed under reduced pressure and the residue was transferred to an alumina column 25-mm. × 120-cm.

After the column had been developed with benzene, the lower yellow band, containing recovered dimethylferrocene, was eluted with *n*-pentane. The upper orange band of acetylated isomers was eluted rapidly with hexane containing 5% methanol and concentrated to give 9.3 g. (72%) of a mixture of acetyldimethylferrocenes. The oil was distilled rapidly under high vacuum; the distillate had λ_{max} 229 mμ, ϵ_{max} 16,400, ϵ_{227} 16,300. From this spectrum and those of the two pure isomers given below the mixture may be estimated to consist of approximately 70% of the 3-acetyl isomer and 30% of the corresponding 2-acetyl isomer. The infrared spectrum of the distilled mixture was identical with that of the oil before distillation.

The orange oil was re-chromatographed in benzene on the same column to give two major fractions and an intermediate portion. The first fraction was concentrated to a red oil, which could be crystallized from *n*-pentane at Dry Ice–acetone temperatures to red crystals of **2-acetyl-1,1′-dimethylferrocene**, m.p. 15–16°. The ultraviolet spectrum of a distilled sample had λ_{max} 227 mμ, ϵ_{max} 17,600.

Anal. Calcd. for $C_{14}H_{16}FeO$: C, 65.65; H, 6.30; Fe, 21.80.[37] Found: C, 66.30; H, 6.65; Fe, 22.01.

The second fraction on concentration also yielded a red oil, which crystallized on standing to orange needles of **3-acetyl-1,1′-dimethylferrocene**, m.p. 48.4–48.6°. The ultraviolet spectrum had λ_{max} 232 mμ, ϵ_{max} 15,800, ϵ_{227} 15,300.

Anal. Calcd. for $C_{14}H_{16}FeO$: C, 65.65; H, 6.30; Fe, 21.80. Found: C, 65.33; H, 6.35; Fe, 22.13.

1,1′-Dimethylferrocene-2-carboxylic acid was prepared by a modification of the procedure of Weinmayr.[5,38] A mixture of 1.0 g. of 2-acetyl-1,1′-dimethylferrocene, 2 ml. of pyridine and 1.1 g. of iodine was agitated for 12 hr. at room temperature, then for 90 min. in a boiling water-bath. The mixture was diluted with aqueous 0.6 *N* sodium hydroxide and stirred for 24 hr. at room temperature, then for 1 hr. on the steam-bath. The mixture was filtered and acidified with glacial acetic acid to precipitate 185 mg. (18%) of 1,1′-dimethylferrocene-2-carboxylic acid. The crude material was dissolved in ether, filtered free of insoluble impurities, extracted into sodium carbonate solution, reprecipitated with hydrochloric acid and finally recrystallized from ether; m.p. 118–118.5° dec.

Anal. Calcd. for $C_{13}H_{14}FeO_2$: C, 60.49; H, 5.43; Fe, 21.64. Found: C, 60.34; H, 5.39; Fe, 21.68.

Potentiometric titration of the acid showed the apparent molecular weight[39] to be 256 ± 5 (theoretical is 260) and yielded the following dissociation constants: pK_a' 8.15 ± 0.05 (66% dimethylformamide, 34% water), pK_a' 5.4 ± 0.1 (water).

1,1′-Dimethylferrocene-3-carboxylic acid was prepared by the same procedure employed for the corresponding 2-carboxylic acid. The yield of crude acid was 373 mg. (37%), and the recrystallized acid had m.p. 106–106.5° dec., apparent molecular weight 258 ± 15, pK_a' 7.5 ± 0.1 (66% DMF), pK_a' 4.7 ± 0.1 (water).

Anal. Calcd. for $C_{13}H_{14}FeO_2$: C, 60.49; H, 5.43; Fe, 21.64. Found: C, 60.44; H, 5.55; Fe, 21.70.

2-Ethyl-1,1′-dimethylferrocene was prepared by reduction of 2-acetyl-1,1′-dimethylferrocene over platinum oxide

(36) Melting points and boiling points are uncorrected. Fractional distillations were through a 3-ft. Nester whirling band column. Ultraviolet spectra were determined in 95% ethanol in a Beckman model DU spectrophotometer, employing calibrated quartz cells. We are indebted to Mr. Jozsef Nemeth, Mrs. Maria Benassi and Mrs. Ruby Ju for microanalyses and to Mr. James Brader and Mrs. Louise Griffing for infrared spectra. The spectra were obtained for solids in Nujol mulls, for liquids as smears, with a recording Perkin–Elmer infrared spectrophotometer, model 21.

(37) Iron was determined (by J. Nemeth) by the general ashing technique (A. Steyermark, "Quantitative Organic Microanalysis," The Blakiston Co., New York, N. Y., 1951, p. 47), employing sulfuric acid and micro-size samples, ignited to 950°. The ferric oxide residue was weighed to constancy and corrected for surface moisture (previously established for a reliable sample) by deducting 1.5% of its weight.

(38) V. Weinmayr, U. S. Patent 2,683,157 (1954); *C. A.*, **49**, 10364a (1955).

(39) Uncertainty in values of the neutralization equivalents is due to the very small samples available for titration (*e.g.*, sample weight, 2.58 ± 0.05 mg.; volume of titrant, 0.0050 ± 0.0002 ml.).

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in a Parr bomb. Hydrogenation, effected in glacial acetic acid under 3.5 atm. pressure, was essentially complete after 24 hr. at room temperature. The product was dissolved in pentane, washed with sodium bicarbonate and separated from ketonic and alcoholic material by chromatography on an alumina column. Concentration of the pentane eluates gave the yellow-brown, liquid 2-ethyl-1,1′-dimethylferrocene.

Anal. Calcd. for $C_{14}H_{18}Fe$: C, 69.44; H, 7.49. Found: C, 69.78; H, 7.79.

3-Ethyl-1,1′-dimethylferrocene was prepared and purified by the procedure described above for the corresponding 2-ethyl isomer.

Anal. Calcd. for $C_{14}H_{18}Fe$: C, 69.44; H, 7.49. Found: C, 69.57; H, 7.76.

Acetylation of 1,1′-diisopropylferrocene was effected by the method described above for acetylation of the corresponding dimethylferrocene. To an ice-cold mixture of 8.75 g. of diisopropylferrocene[39] and 4.86 g. of aluminum chloride in 100 ml. of methylene chloride was added during 1 hr. 1.65 g. of acetic anhydride in 25 ml. of methylene chloride. The resulting mixture was stirred overnight at room temperature and poured over ice. After work-up the concentrated dark brown organic liquid was chromatographed on a 25-mm. × 120-cm. alumina column to give 3.6 g. (41%) of recovered diisopropylferrocene and a total of 4.54 g. (45%) of the isomeric acetyldiisopropylferrocenes, contained in seven fractions. From the weights of the individual fractions it was estimated that the monoacetyl compounds consisted of 17% of the 2-acetyl isomer and 83% of the 3-acetyl analog.

2-Acetyl-1,1′-diisopropylferrocene, obtained from an early chromatography fraction, was purified by distillation and had b.p. 120–125° (0.4 mm.), λ_{max} 226 mμ, ϵ_{max} 18,200, ϵ_{325} 18,000.

Anal. Calcd. for $C_{15}H_{24}FeO$: C, 69.21; H, 7.75. Found: C, 69.53; H, 7.73.

3-Acetyl-1,1′-diisopropylferrocene, obtained from a later chromatographic fraction and purified by distillation, had b.p. 150–155° (1.3 mm.), λ_{max} 231 mμ, ϵ_{max} 15,600, ϵ_{325} 14,300.

Anal. Calcd. for $C_{15}H_{24}FeO$: C, 69.21; H, 7.75. Found: C, 67.58; H, 7.78.

In a second run the above procedure was followed except that the aluminum chloride (1.63 g.) and acetic anhydride (0.572 g.) were added together in 10 ml. of methylene chloride to the diisopropylferrocene (3.0 g.) in 30 ml. of methylene chloride. From the chromatogram 0.65 g. (23%) of diisopropylferrocene was recovered. The acetylated material was removed in one band and distilled to give 0.85 g. (25%) of mixed isomers, b.p. 120–133° (0.8 mm.), λ_{max} 232 mμ, ϵ_{max} 15,500, ϵ_{325} 15,000. From these spectral data and those above for the two pure isomers the proportion of the 2-acetyl compound may be estimated to be 19%, that of the 3-acetyl compound 81%.

Acetylferrocene[40] was prepared by the procedure described above for the acetylation of dimethylferrocene. From 18.6 g. of ferrocene, 14.7 g. of aluminum chloride and 4.73 ml. acetic anhydride there was obtained after chromatography 7.4 g. (65%) of crude acetylferrocene. This material was recrystallized from benzene to give long red needles, m.p. 86–87°, λ_{max} 226 mμ, ϵ_{max} 16,500 (lit. m.p. 85–86°,[5] λ_{max} 225 mμ,[18] ϵ_{max} 14,600[18]).

Ferrocenecarboxylic acid was prepared by the procedure described above for the dimethylferrocenecarboxylic acids, except that the terminal heating of the aqueous sodium hydroxide solution was omitted.[5,38] From 1.0 g. of acetylferrocene there was obtained 0.35 g. (35%) of ferrocenecarboxylic acid, which was recrystallized from chloroform to give crystals which decomposed at 208.5°.[41] Potentiometric titration gave the apparent molecular weight as 250 ± 15 (theoretical is 232) and pK_a' 7.3 ± 0.1 (66% DMF), pK_a' 4.4 ± 0.1 (water) [lit.[18] pK_a' 7.26 (66% ethanol)].

Acetophenone was fractionally distilled; a center cut had b.p. 97–97.5° (14 mm.), $n^{25}D$ 1.5314, λ_{max} 242 mμ, ϵ_{max} 12,000 [lit. b.p. 85.5–86.5° (16 mm.),[30] $n^{20}D$ 1.5338,[41] λ_{max} 242 mμ[30], ϵ_{max} 12,800[30]].

o-**Methylacetophenone**[40] was prepared in 60% yield from the cadmium alkyl reaction from *o*-bromotoluene and acetyl chloride by the method of Cason.[43,44] The fractionally distilled product had b.p. 87–88° (11 mm.), $n^{25}D$ 1.5299, λ_{max} 243 mμ, ϵ_{max} 9,500 [lit. b.p. 93–94° (16 mm.),[30] $n^{20}D$ 1.5320,[42] λ_{max} 243 mμ,[30] ϵ_{max} 8,850[30]].

m-**Methylacetophenone**[40] was prepared from *m*-bromotoluene and acetyl chloride in 45% yield by the same procedure employed for the preparation of *o*-methylacetophenone. The twice fractionally distilled product had b.p. 97–98° (15 mm.), $n^{25}D$ 1.5285, λ_{max} 247 mμ, ϵ_{max} 11,300 [lit.[41] b.p. 109° (12 mm.), $n^{20}D$ 1.5306].

p-**Methylacetophenone** was fractionally redistilled; a center cut had b.p. 99–100° (12 mm.), $n^{25}D$ 1.5317, λ_{max} 252 mμ, ϵ_{max} 15,800 [lit. b.p. 94–95° (12 mm.)[30], $n^{25}D$ 1.5342,[42] λ_{max} 252 mμ[30], ϵ_{max} 15,100[30]].

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(40) We are indebted to Messrs. P. E. Sokol, K. D. Berlin and J. R. Larson for the preparation of these compounds.

(41) Further purification, either by recrystallization from ether or by dissolving in base and reprecipitating with acid, did not alter the melting point behavior, as the pale orange needles still decomposed below 210° and the decomposition point depended upon the rate of heating. Rosenblum[18] has reported decomposition at 210° and Nesmeyanov[7] over the range 195–205°, while Weinmayr[4] gave m.p. 225–230° for this compound.

(42) K. von Auwers, *Ann.*, **408**, 212 (1915).

(43) J. Cason, THIS JOURNAL, **68**, 2078 (1946).

(44) J. Cason and F. S. Prout, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 601.

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[CONTRIBUTION FROM THE DOW CHEMICAL CO., EASTERN RESEARCH LABORATORY]

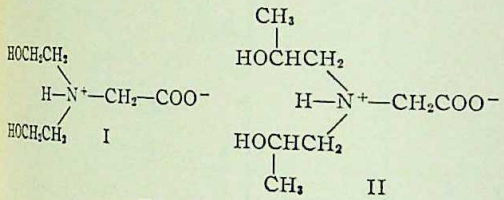
The Preparation and Chelating Properties of N,N-Bis-(2-hydroxypropyl)-glycine

BY ALBERT E. FROST, STANLEY CHABEREK AND NEWELL J. BICKNELL

RECEIVED NOVEMBER 29, 1956

N,N-Bis-(2-hydroxypropyl)-glycine has been synthesized and its acid dissociation constant and metal chelate stability constants with a number of metals determined. Present data indicate that this agent behaves as a tetradentate agent with all metals except copper. Comparison with the corresponding constants of N,N-bis-(2-hydroxyethyl)-glycine indicates a comparable affinity for hydrogen ion and divalent metal ions. However, the behavior with trivalent iron differs considerably from that of N,N-bis-(2-hydroxyethyl)-glycine.

Introduction.—A recent report on the chelating tendencies of the hydroxyethyl substituted glycine derivative N,N-bis-(2-hydroxyethyl)-glycine[1] (I) indicates (1) the association of hydroxyl groups with the metal ions and (2) the appreciable affinity of this derivative for transition metal ions. It, therefore, became of interest to investigate the chelating tendencies of the structurally similar N,N-bis-(2-hydroxypropyl)-glycine (DPG) (II), its homolog.



Experimental

Preparation.—N,N-Bis-(2-hydroxypropyl)-glycine was synthesized by the reaction of N,N-bis-(2-hydroxypropyl)-amine with potassium cyanide and formaldehyde in the molar ratios of 1:1.06:1.05 according to the procedure outlined by Bersworth.[2] The free acid was isolated from the straw-colored aqueous solution of the monopotassium salt by means of the hydrogen form of Dowex-50 on a column process. Elution of the column with distilled water followed by decolorization of the eluate with activated charcoal and concentration to small volume gave a gummy tan solid. Purification was accomplished by dissolution of this solid in a minimum volume of water and precipitation by the addition of a large volume (20 times) of acetone. Two such treatments produced a fine white powder melting at 129–131° (uncor.).

Anal.[3] Calcd. for $C_8H_{17}NO_4$: N, 7.3. Found: N, 7.0.

Method and Apparatus.—The experimental method employed in the study of the acid dissociation and metal chelate stability constants of N,N-bis-(2-hydroxypropyl)-glycine is essentially the same as that described by Chaberek and Martell.[4] The deviations from this procedure were the calibration of the glass electrode against a series of standard buffer solutions and the fact that all runs were made at a temperature of 29.6°. The amino acid concentration used in the several runs ranged from 3.5 to 3.8 × 10^{-3} *M*.

Calculations.—The calculations were carried out in the same manner as described in the above reference.[3] The metal chelate stability constants were calculated by both the algebraic and modified Bjerrum methods. Appreciable overlapping of the successive constants log K_1 and log K_2 made it necessary to correct log *K* values by successive approximations according to the procedure described by Carlson, McReynolds and Verhoek.[5] In the case of copper, the calculation of K_2 from the 1:1 and 2:1 titration data required a modification of the method cited above.[3] The copper–ligand interaction was sufficiently strong to lower the *p*H of the first buffer region to values considerably lower than four. A portion of the unbound ligand would, under these conditions, be converted to the positively charged species through association of a hydrogen ion with the dipolar ion (HA represents N,N-bis-(2-hydroxypropyl)-glycine)

$$HA + H^+ \longrightarrow H_2A^+ \qquad (1)$$

Formation of the positively charged species would decrease appreciably the concentration of (A^-) in this *p*H range. In order to account for the formation of H_2A^+, therefore, it was assumed that this positive ion had the same acid strength as glycine,[6] and the value of the dissociation constant for reaction 2 was taken as 4.5 × 10^{-3}.

$$H_2A^+ \overset{k^1}{\rightleftharpoons} HA + H^+;\ k^1 = (HA)(H^+)/(H_2A^+) \qquad (2)$$

Discussion of Results

1:1 Titration Curves.—The free acid curve of Fig. 1 has one inflection point at "*a*" value of 1 corresponding to formation of the monoalkali metal salt. The curve is typical of a weak monobasic

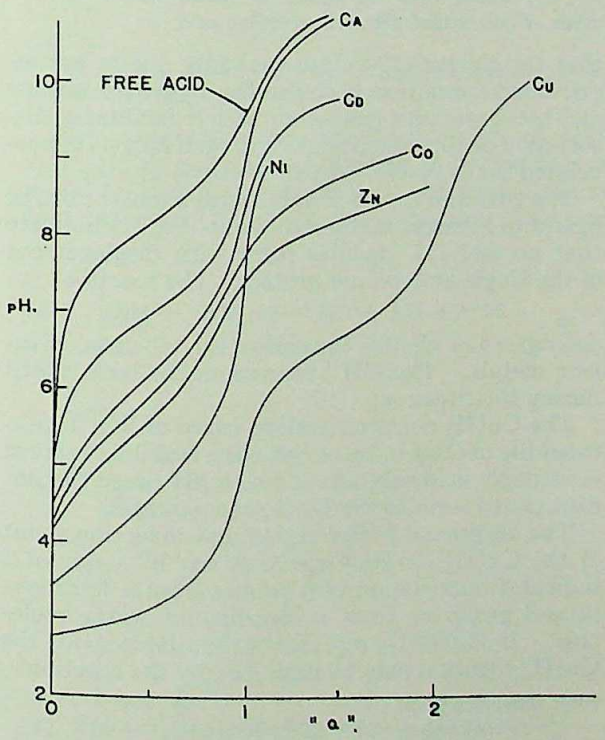


Fig. 1.—Titration of N,N-bis-(2-hydroxypropyl)-glycine (DPG): molar ratio of ligand to metal ion = 1:1; *a* = moles of base added per mole of acid.

(1) S. Chaberek, Jr., R. C. Courtney and A. E. Martell, THIS JOURNAL, **75**, 2185 (1953).
(2) P. C. Bersworth, U. S. Patent 2,407,645, Sept. 17, 1946.
(3) Analysis by Carol K. Fitz, 115 Lexington Avenue, Needham Heights 94, Mass.
(4) S. Chaberek, Jr., and A. E. Martell, THIS JOURNAL, **74**, 5052 (1952).
(5) G. A. Carlson, J. P. McReynolds and F. H. Verhoek, *ibid.*, **67**, 1334 (1945).
(6) H. S. Harned and B. B. Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, N. Y., 1950, p. 580.

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acid and exhibits a buffer region about *p*H 8.5. The calculated value of the acid dissociation constant is $10^{-8.13}$. In this respect it is similar to the homologous N,N-bis-(2-hydroxyethyl)-glycine. The greater acidity of the ammonium proton over

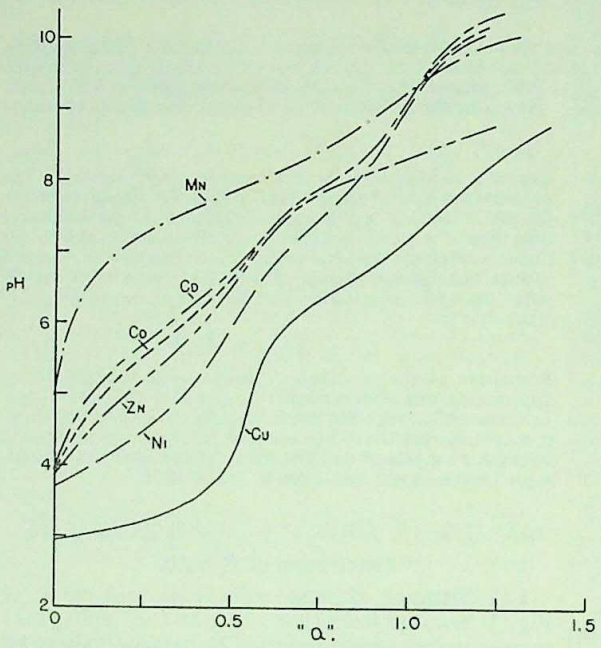


Fig. 2.—Titration of N,N-bis-(2-hydroxypropyl)-glycine (DPG): molar ratio of ligand to metal ion = 2:1; *a* = moles of base added per mole of amino acid.

that for glycine ($10^{-9.78}$) is probably due to hydrogen bond formation between the hydroxyl groups and the basic nitrogen atom which facilitates dissociation of the ammonium hydrogen ions as is postulated for N,N-bis-(2-hydroxyethyl)-glycine.[1]

The titration curves of DPG with a molar ratio of ligand to bivalent metal ion of one (Fig. 1) indicate that normal 1:1 chelates form with displacement of the single ammonium proton. The reaction

$$M^{+2} + HA + OH^- \longrightarrow MA^+ + H_2O \quad (3)$$

describes 1:1 chelate formation for all these bivalent metals. The OH^- represents the base added during the titration.

The Cu(II) chelate titration curve of Fig. 1 indicates the chelate to be of sufficient stability to form in strongly acid solution at which *p*H range the undissociated form of the DPG predominates.

The additional buffer region and inflection point of the Cu(II) titration curve at an "*a*" value of 2 indicates dissociation of a proton from a hydroxypropyl group or from a coördinated water molecule. If $HA(OH)_2$ represents the amino acid, the Cu(II) titration may be described by the reactions

First inflection point

$$HA(OH)_2 + Cu^{+2} \rightleftharpoons CuA(OH)_2^+ + H^+ \quad (4)$$

Second inflection point

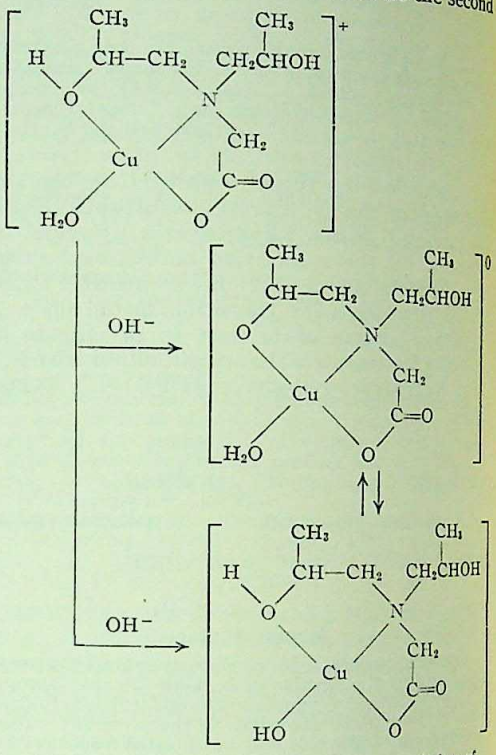
$$CuA(OH)_2(H_2O)^+ + OH^- \rightleftharpoons CuAO(OH)(H_2O) + H_2O \quad (5)$$

or

$$CuA(OH)_2(H_2O)^+ + OH^- \rightleftharpoons CuA(OH)(OH)_2 + H_2O \quad (6)$$

The two possible hydrolysis products bear a tautomeric relationship to each other, and it is likely that an equilibrium exists between these structures.

That proton dissociation as indicated above and not higher complex formation occurs at the second



Possible hydrolysis products of the 1:1 copper chelate of DPG

inflection point is evident from the fact that disproportionation to a higher chelate would result in precipitation of an equivalent amount of cupric hydroxide according to the reaction

$$2CuA(OH)^+_2 + 2OH^- \rightleftharpoons Cu(A)(OH)_2)_2 + Cu(OH)_2\downarrow \quad (7)$$

No precipitation was observed in this titration.

2:1 Titration Curves.—Titration curves for solutions containing ligand/metal ratios of two are shown in Fig. 2. All curves, with the exception of Mn(II)–DPG, have an inflection at an "*a*" value of 0.5 corresponding to the formation of the 1:1 metal chelate

$$M^{+2} + 2HA + OH^- \longrightarrow MA^+ + HA + H_2O \quad (8)$$

The excess DPG is present in essentially the dipolar acid species in the *p*H range of the inflections. Subsequent consumption of a second half mole of hydroxide per mole of amino acid and the presence of a second inflection at $a = 1$ for all systems except Zn(II) results from further interaction of excess ligand and the 1:1 metal chelate according to eq. 9

$$MA^+ + HA + OH^- \longrightarrow MA_2 + H_2O \quad (9)$$

In the case of the Mn(II) system, the absence of an inflection at $a = 0.5$ indicates a strong overlapping tendency involving the MA^+ and MA_2 species.

The Fe(III)–DPG System.—Titrations of Fe-

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(III)-DPG mixtures with ligand/Fe(III) ratios of 1 and 2 are plotted in Fig. 3.

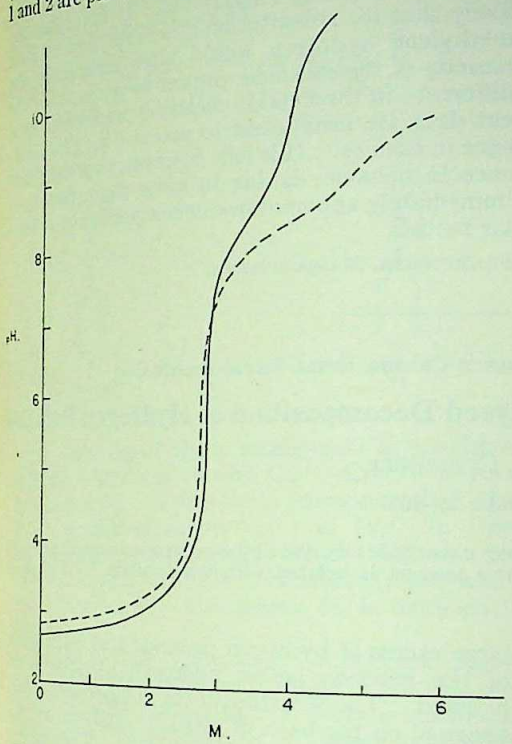

Fig. 3.—Titration of N,N-bis-(2-hydroxypropyl)-glycine in the presence of Fe(III) ions; —, Fe(III)/acid = 1:1; ---, Fe(III)/acid = 1:2; m = moles of base added per mole of metal ion.

The abscissa "m" of Fig. 3 denotes the number of moles of base added per mole of metal ion. The first inflection of both curves occurs at "m" $\approx$ 3, and a second weaker break is observed at "m" values of 4 and 5 for the 1:1 and 2:1 systems, respectively. Although the shapes and equivalence points for the Fe(III)–DPG system are strikingly similar to properties of the Fe(III)–bis-(2-hydroxyethyl)-glycine system for comparable ligand/metal ratios, the nature of the interactions are entirely different for these systems. Both 2:1 and 1:1 Fe(III)-DPG systems are characterized by the formation of ferric hydroxide at pH values of 2.75–3.0. Subsequent addition of standard base results in an extremely slow attainment of equilibrium and the precipitation of further amounts of the metal hydroxide. Consequently, the titration curves of Fig. 3 represent the stepwise formation of the ferric hydroxide and neutralization of DPG according to the reactions

1:1 titration curve

$$Fe^{+3} + 3OH^- \longrightarrow Fe(OH)_3\downarrow \quad \frac{3(OH^-)}{Fe} \qquad (10)$$

$$HA + OH^- \longrightarrow A^- + H_2O \quad \frac{1(OH^-)}{Fe} \qquad (11)$$

$\therefore$ inflections at $m = 3$ and $m = 4$

2:1 titration curve

$$Fe^{+3} + 3OH^- \longrightarrow Fe(OH)_3 \quad \frac{3(OH^-)}{Fe} \qquad (12)$$

$$2HA + 2OH^- \longrightarrow 2A^- + 2H_2O \quad \frac{2(OH^-)}{Fe} \qquad (13)$$

$\therefore$ inflections at $m = 3$ and $m = 5$

In spite of the behavior of this chelating agent in the acid and neutral pH range, it has been shown qualitatively that DPG chelates Fe(III) in alkaline solutions. Present data suggest, therefore, the formation of a ferric chelate which is considerably weaker than the corresponding Fe(III)–bis(2-hydroxyethyl)-glycinate. Experimental observations are consistent with the anticipated behavior of a weak ferric chelate which is extensively dissociated in acid solution.

Metal Chelate Formation Constants.—The first and second consecutive formation constants for the metal–DPG chelates are listed in Table I along with the corresponding values of the N,N-bis-(2-hydroxyethyl)-glycinate chelates (2-HxG).[1] The comparable affinities of both ligands for these metal ions are clearly evident from the corresponding log K data.

TABLE I

EQUILIBRIUM CONSTANTS

$T = 29.6°$, $\mu = 0.1$, $\gamma(H^+) = 0.78$

	DPG			2-HxG	
	log K_1			log K_1	
Metal	1:1	2:1	log K_2		log K_2
H^+	8.13(pk_2)			8.08(pk_1)	
Cu(II)	8.0	..	4.90	8.15	5.20
Ni(II)	6.33	6.44	3.82	6.37	4.40
Co(II)	5.16	5.48	3.35	5.25	3.52
Zn(II)	5.20	5.56	3.42	5.38	3.26
Cd(II)	4.72	5.06	3.18	4.81	3.37
Mn(II)	..	3.02	2.44	3.27	2.33
Ca(II)	..	2.65[a]	..	..	..

[a] Calculated algebraically from titration data of a solution containing a ligand/metal ratio of 10.

The comparable chelating tendencies of DPG and 2-HxG are further illustrated by comparing metal formation constants with the second ionization potential (Fig. 4) of the metal ion. Compari-

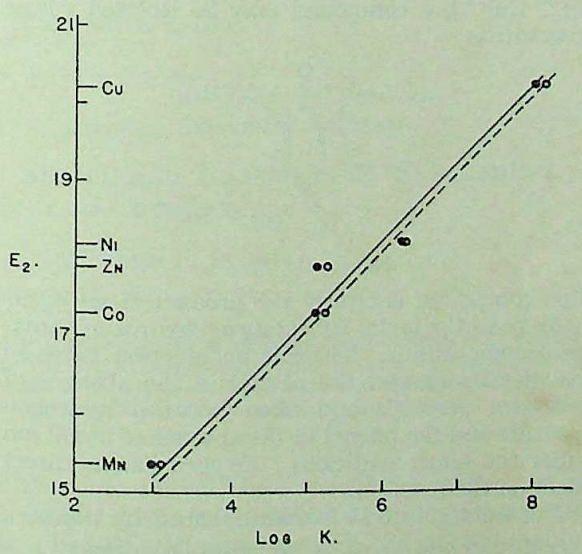

Fig. 4.—Correlation of metal chelate stability constant with second ionization potential; ●, K_{mk_2} for N,N-bis-(2-hydroxypropyl)-glycine; O, K_{mk_2} for N,N-bis-(2-hydroxyethyl)-glycine.

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son of DPG and 2-HxG of Table I indicates little or no difference in the chelating tendencies of 2-hydroxypropyl relative to 2-hydroxyethyl groups.

That N,N-bis-(2-hydroxypropyl)-glycine and the corresponding N,N-bis-(2-hydroxyethyl) derivative exhibit comparable chelating affinities for the divalent metal ions is clearly evident from the results of this investigation. This behavior is certainly predictable on the basis of the close structural similarities and the comparable basicities of these two compounds. The differences between DPG and 2-HxG with respect to the chelation of Fe(III) is, however, unexpected. A comparison of molecular models of both ligands shows no apparent steric effect with relation to the orientation of the electron donor groups around the Fe(III) ion. It is further unlikely that the substitution of a methyl group for a methylene hydrogen would alter sufficiently the basicity of the ethanolic proton to account for the difference in the Fe(III) chelating properties. Present data are insufficient to account for this difference in affinity. It is felt, however, that the difference in behavior is due to some steric factor not immediately apparent from a comparison of molecular models.

FRAMINGHAM, MASSACHUSETTS

[CONTRIBUTION FROM THE EMERYVILLE RESEARCH CENTER, SHELL DEVELOPMENT CO.]

Detection of $HO_2\cdot$ Radical in Metal Ion Catalyzed Decomposition of Hydrogen Peroxide

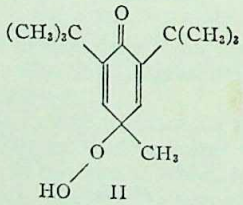
BY GALVIN M. COPPINGER

RECEIVED JANUARY 23, 1957

The appearance of $HO_2\cdot$ radical in the decomposition of hydrogen peroxide catalyzed by copper, iron or cobalt ions is detected by means of 2,6-di-*t*-butyl-4-methylphenol. A crystalline product is isolated with the structure 2,6-di-*t*-butyl-4-methyl-4-hydroperoxy-2,5-cyclohexadienone.

The radical $HO_2\cdot$ has been postulated as an intermediate in the decomposition of hydrogen peroxide in solution in the presence of a variety of metal ions.[1] Evidence for the existence of this radical is limited to inference drawn from final products of the decomposition and from the catalytic activity of the metal ion.

It has been possible to confirm the existence of the $HO_2\cdot$ radical in hydrogen peroxide decomposition by reaction of the radical with an antioxidant, utilizing a technique which has demonstrated the existence of other reactive radical intermediates.[2,3] When 2,6-di-*t*-butyl-4-methylphenol (I) is included in the system *t*-butyl alcohol, hydrogen peroxide, metal ion [Co^{++}, Fe^{++}, Fe^{+++}, Cu^{+}, Cu^{++}], a compound may be isolated whose structure is

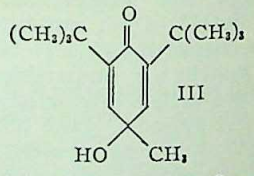


II

This compound is clearly the product of an intermediate in the metal ion catalyzed hydrogen peroxide decomposition. There is no reaction between the metal ions and the phenol in the absence of hydrogen peroxide and none between hydrogen peroxide and the phenol in the absence of metal ion under the same conditions. Oxygen has no direct effect on the reaction.

The isolation of II is accomplished by use of a large excess of hydrogen peroxide and interruption of the reaction before hydrogen peroxide is exhausted. The structure of the compound has been assigned on the basis of ultimate analysis, infrared spectrum and chemical reactivity. The infrared spectrum is the most distinctive characteristic of the cyclohexadienone structure, displaying a striking doublet at 6 μ.[4] Compound II also exhibits OH stretching bands with hydrogen bonding.

Compound II is reduced with Pt and H_2 to III. This compound (III) is also obtained from the air oxidation of 2,6-di-*t*-butyl-4-methylphenol in the presence of alkali.[5] The structure of III is assigned on the basis of analysis and infrared spectrum, OH stretching and doublet at 6 μ associated



III

with the cyclohexadienone configuration. It is transformed into 3,5-di-*t*-butyl-4-hydroxybenzyl acetate in acetic acid in the presence of a trace of strong acid.[6]

The hydroperoxide II is subject to metal ion catalyzed decomposition. The system II, Co^{++} and (I) in *t*-butyl alcohol, permits the isolation of three compounds: III, 1,2-bis-3,5-di-*t*-butyl-4-hydroxyphenylethane (IV) and 3,3′,5,5′-tetra-*t*-butyl-stilbene-4,4′-quinone (V). There is some

(1) Metal ion catalysis of H_2O_2 decomposition is reviewed by J. H. Baxendale, "Advances in Catalysis," Vol. IV, Academic Press, Inc., New York, N. Y., 1952, p. 31; J. Weiss, p. 343.

(2) T. W. Campbell and G. M. Coppinger, THIS JOURNAL, 74, 1469 (1952).

(3) A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.*, 3211 (1953).

(4) In addition to a limited number of examples available elsewhere, (E. Müller, K. Ley and W. Schmidhuber, *Ber.*, 89, 1738 (1956), see also reference 3) the author has examined the spectra of 15 compounds with the 2,5-cyclohexadienone structure with various substituents in the 2-, 4- and 6-positions. The very strong doublet about 6μ is always present and variation in wave length has not exceeded 0.03μ.

(5) F. C. Davis and G. M. Coppinger, unpublished.

(6) G. M. Coppinger and T. W. Campbell, THIS JOURNAL, 75, 734 (1953).

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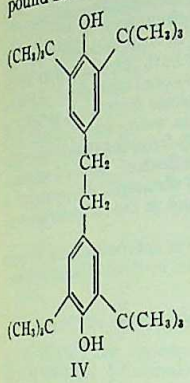
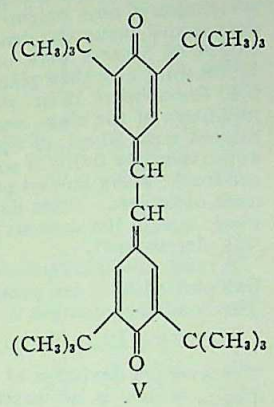
spectral evidence for the existence of a peroxy derivative of a dicyclohexadienone, but the compound has not been isolated.



IV



V

The isolation of these compounds is consistent with the reaction of II with Co^{++}–Co^{+++} to form RO· and RO_2·. It has been demonstrated that RO· is capable of converting I to IV.[7] In these reactions RO· is converted to ROH (III) with the apparent formation of a benzyl radical from I which then dimerizes IV. Compound IV is oxidized to V by RO·.[7]

The fate of RO_2· is not clear. Bickel and Kooyman[3] report that whereas a number of different peroxy radicals react with I to form peroxides of structures corresponding to II, triphenylmethylperoxy radical converts I in part to IV and V. It thus seems possible that a steric effect exists which depends upon the size of the R group in RO_2·, which determines whether RO_2· adds to the phenol or abstracts hydrogen from the phenol which results in the formation of a benzyl radical.

Experimental

4-Methyl-4-hydroperoxy-2,6-di-*t*-butyl-2,5-cyclohexadienone (II).—A solution of 0.1 mole of 2,6-di-*t*-butyl-*p*-cresol, 10 mg. of an appropriate metal salt and 1 mole of hydrogen peroxide (50w.%) in 250 ml. of *t*-butyl alcohol was allowed to stand at room temperature for 6 hr.; the metal salts used were cobalt naphthenate, cuprous chloride, cupric acetate, ferrous chloride and ferric chloride. The reaction is mildly exothermic. The copper salts occasionally produced a highly exothermic reaction. The decomposition is always accompanied by evolution of oxygen.

At the end of 6 hr. the solution is extracted with an equal volume of isoöctane and washed with water to remove the *t*-butyl alcohol. The isoöctane was removed at reduced pressure and the crystalline material was recrystallized from isooctane, m.p. 115°.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.5; H, 9.5. Found: C, 71.8; H, 9.4.

The yield of II varied from experiment to experiment. Calculations from the infrared spectra of the isoöctane extracts indicate the average yield of I was 25–30% of the parent phenol. The doublet at 6 μ was used for these estimations.

4-Methyl-4-hydroxy-2,6-di-*t*-butyl-3,5-cyclohexadienone (III).—Compound II was reduced in isoöctane solution with platinum-on-charcoal as catalyst, m.p. 112–113°. A mixed melting point with a sample of III obtained from air oxidation of 2,6-di-*t*-butyl-*p*-cresol in the presence of alkali was 112–113°.

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.4; H, 9.7. Found: C, 76.7; H, 9.6.

3,5-Di-*t*-butyl-4-hydroxybenzyl Acetate.—A solution of 1 g. of III and 10 mg. of *p*-toluenesulfonic acid in 10 cc. of acetic acid was allowed to stand at room temperature for 24 hr. At the end of this time the acetate had partially crystallized. Additional acetate was obtained on dilution with water; total yield 1 g., m.p. 105–106°, mixed m.p. with a sample prepared by the method of Coppinger and Campbell,[6] 102–104°. The infrared spectra of the two samples were identical. Coppinger and Campbell report 98° as the m.p. for the acetate. Compound II does not undergo this rearrangement in acetic acid.

Reaction of I, II and Co^{++}.—A solution of 2 g. of II, 1 g. of I and 10 mg. of cobalt naphthenate in 25 cc. of *t*-butyl alcohol was allowed to stand at room temperature for 24 hr. The reaction mixture was extracted with 50 cc. of ether and washed free of *t*-butyl alcohol with water. The ether was removed and the residue was fractionally crystallized from methanol. The stilbene quinone V was isolated first, m.p. 293–295°, mixed m.p. 293–296°. Compound IV was obtained as the second fraction, m.p. 173–175°, mixed m.p. 173–175°. The third fraction obtained by removal of the methanol was recrystallized from isoöctane to obtain III, m.p. 110–112°, mixed m.p. 111–113°.

EMERYVILLE, CALIF.

(7) RO· as $C_4H_9C(=O)O$·, S. C. Cosgrove and W. A. Waters, THIS JOURNAL, 388 (1951); RO· as $(CH_3)_3CO$·, G. M. Coppinger, unpublished.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

Substituent Effects on Naphthalene. Association Constants of Substituted Naphthalene–Picric Acid Complexes

BY PETE D. GARDNER AND WARREN E. STUMP

RECEIVED NOVEMBER 23, 1956

Association constants of the complexes formed by twenty-five systematically substituted naphthalenes with picric acid (picric acid) are equilibrated between chloroform and water and the extent to which the donor is capable of retaining the have been determined. The partition method was chosen for the study, wherein the donor compound and the acceptor acceptor in the chloroform phase is determined. It was found that complex stability is dictated by steric factors, inductive effects and resonance effects in the various series.

Molecular complexes formed by aromatic substances appear to be of two distinct types,[1,2] the type being determined largely by the nature of the acceptor. Those of the σ-type, exemplified by the aromatic–$HAlCl_4$[2] and aromatic–HBF_4[3] complexes, exhibit a very great stability dependence upon substituents, electron-donating substituents in the donor imparting increased strength to the complex. Complexation of the π-type,[2,4] on the other

(1) L. J. Andrews, *Chem. Revs.*, **54**, 713 (1954). This review describes current theories concerning complexation of this type and defines terms used here.

(2) H. C. Brown and J. D. Brady, THIS JOURNAL, **74**, 3570 (1952).

(3) D. A. McCaulay and A. P. Lien, *ibid.*, **73**, 2013 (1951).

(4) R. S. Mulliken, *ibid.*, **74**, 811 (1952).

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hand, is not as easily defined, as it appears that the effect of substituents varies somewhat unpredictably with the nature of the acceptor.[2,5] It has been shown, for example, that stability in the benzene–silver ion complex is determined by substituents in the donor molecule so as to permit a correlation with Hammett's σ-values.[5] Such a correlation is not possible with complexes formed by substituted benzenes with picryl chloride and picric acid. The stability of the latter type of π-complex appears to reflect, among other things, the steric requirement[6] and the electron-withdrawing properties of the substituent.[7,8]

This paper is the first of several concerned with general substituent effects in naphthalene[9] and with those factors influencing π-complex formation by this compound. The method chosen for the present work is the partition method. Association constants determined in this way are invariably higher than those measured by the spectrophotometric method. There can be little doubt that complexation as measured by the partition method is more extensive than simple π-complex formation. The spectrophotometric method, on the other hand, appears to measure only π-complexation[10] involving the ring, and thus the two data correspond to two different processes. Whatever the differences are, they should not vary appreciably within a given class of substituents, and the series-correlations described below should be a reasonable measure of substituent effects. Apparent anomalies peculiar to the method include donors containing the nitro group and, as will be seen later, probably acetyl and alkoxy donors as well. For this reason caution must be exercised in the interpretation of data in these series. They are not without value, however, since one of the objectives of the study, which will include a later examination of the spectrophotometric method,[11] is an evaluation of those additional forces (dispersion, etc.) superimposed upon charge-transfer complexation and contributing to the higher association constants observed here.

Experimental

Partition Procedure.—The method used was a modification of that used by Moore, Shepherd and Goodall[12] and improved by Anderson and Hammick[6] in which the donor compound and the acceptor (picric acid) are equilibrated between chloroform and water, and the extent to which the donor is capable of retaining the acceptor in the chloroform phase is determined. Modifications incorporated are apparent from the description given below. This procedure proved to be less cumbersome than those previously used, and the precision and accuracy did not seem to be impaired.

Picric acid in the amount of 0.85–1.05 g. was weighed into each of four equilibration vessels by means of a weighing stick. Fifty milliliters of water was delivered into each vessel from a calibrated pipet, followed by the similar addition of 50.00 ml. of a chloroform solution of the compound (0.083–0.174 M) under investigation. The latter solution was prepared on a weight–weight basis and its concentration determined using the density of chloroform at 27°.[13] The stoppered vessels were tumbled at approximately 26° for 10–30 min. and then placed in a bath maintained at 27 ± 0.1° for at least 12 hr. with occasional agitation. Twenty milliliters of the clear, aqueous phase from each vessel was diluted with 50 ml. of equilibrium water and titrated with approximately 0.016 N sodium hydroxide solution (carbonate-free)[14] using methyl purple indicator[15] to the disappearance of brown. From data thus obtained, the quantity of picric acid in the aqueous phase and in the chloroform phase was determined.

A reference distribution curve was determined as a straight line plotted from ten points by the method of least squares. The resulting equation is

$$\log C_{CHCl_3} = 1.11564 \log C_{H_2O} + 1.27563$$

The average deviation of the ten points was 0.00270 in log C_{CHCl_3} which is an average deviation of 0.00066 in the "average" point. The probable deviation was 0.00021.

The change in picric acid content of the chloroform phase due to the presence of a donor compound was used to calculate the association constant for the interaction by eq. 1[6]

$$K_1 = \frac{Y - P}{Pz} \qquad (1)$$

where K_1 is the apparent stability constant, Y is the experimentally determined concentration of picric acid, P is the concentration of picric acid in the absence of donor compound and z is the concentration of donor compound. The "salting-out" effect of the donor substance on the solubility of picric acid in the chloroform phase was taken into account.[16,17] The association constant K_s is the sum of K_1 and the solubility-depression constant k.[6] It was found that, due to the considerably larger values of K_1 obtained in this work, one of the simplifying assumptions made in the original derivation of eq. 1[6] was not valid. Calculation of K_s values was therefore made using eq. 2.

$$K_s = \frac{1 - \sqrt{1 - 4P(K_1 + k)}}{2P} \qquad (2)$$

Confidence limits of the mean of K_s values were based on the "t" test of significance using the 90% confidence level. Rejection of individual determinations was decided upon after K_1 values were calculated, discarding any single value of the four which differed greatly from the remaining three, or upon comparing K_s values, again using the "t" test at the 90% confidence level. Eight determinations were used with many of the compounds.

Materials.—Chloroform was stored over calcium chloride and fractionally distilled before use. All reagents used were purchased or prepared by routine procedures except where noted. Solids were recrystallized to constant m.p. and liquids were fractionally distilled or, in many cases, purified by crystallization of the picric acid complex followed by decomposition of the complex and fractional distillation of the donor. No significant discrepancies with literature values of physical constants were found; consequently, references to these are not included. The preparation of compounds followed procedures abstracted in Beilstein's "Handbuch" or *Chemical Abstracts*.

Experimental Results and Discussion

Association constants for all naphthalene derivatives studied are given in Table I along with mean K_1 and k values. Some of these data are represented graphically in Fig. 1.

A few of the complexes described below have been studied in other laboratories. Unfortunately, the various temperatures used render impossible

(5) L. J. Andrews and R. M. Keefer, THIS JOURNAL, **72**, 3113 (1950).

(6) H. D. Anderson and D. L. Hammick, *J. Chem. Soc.*, 1089 (1950).

(7) C. B. Coleman, Abstracts of Papers presented at the Meeting of the Am. Chem. Soc., Sept., 1955, p. 4-O.

(8) C. E. Castrow and L. J. Andrews, THIS JOURNAL, **77**, 5189 (1955).

(9) A study of the problem of substituent effects on naphthalene was initiated by C. C. Price and R. H. Michel, *ibid.*, **74**, 3652 (1952).

(10) S. D. Ross, M. Bassin, M. Finkelstein and W. A. Leach, *ibid.*, **76**, 69 (1954).

(11) See for, example, R. M. Keefer and L. J. Andrews, *ibid.*, **74**, 1891 (1952).

(12) T. S. Moore, G. Shepherd and E. Goodall, *J. Chem. Soc.*, 1447 (1931).

(13) "International Critical Tables," Vol. III, McGraw-Hill Book Co., Inc., New York, N. Y., pp. 27–28.

(14) Standardized against picric acid using methyl purple indicator

(15) Fleisher Chemical Co., Washington, D. C.

(16) R. Behrend, *Z. physik. Chem.*, **9**, 405 (1892).

(17) R. Behrend, *ibid.*, **10**, 265 (1892).

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TABLE I

ASSOCIATION CONSTANTS FOR INTERACTIONS OF SUBSTITUTED NAPHTHALENES WITH PICRIC ACID IN SOLUTION AT 27°

Donor	Source[c]	K_1 (mean)	k	K_s, l. mole^{-1}
Naphthalene	P	1.60	0.47	2.31 ± 0.03
1-Methyl-	P	2.24	.53	3.16 ± .04
1-Ethyl-	L	1.72	.59	2.61 ± .04
1-Isopropyl-	L	1.06	.65	1.87 ± .02
2-Methyl-	P	2.49	.54	3.50 ± .05
2-Ethyl-	L	1.87	.60	2.77 ± .02
2-Isopropyl-	L	1.57	.66	2.51 ± .09
1-Fluoro-	P	0.90	.49	1.49 ± .02
1-Chloro-	P	1.19	.52	1.87 ± .03
1-Bromo-	P	1.31[b]	.53	2.06 ± .05
1-Iodo-	P	1.38	.55	2.13 ± .02
2-Fluoro-	[a]	0.71	.49	1.28 ± .05
2-Chloro-	P	.87	.52	1.50 ± .03
2-Bromo-	L	.92	.53	1.57 ± .03
2-Iodo-	P	.93	.55	1.62 ± .02
1-Methoxy-	P	3.45	.56	4.89 ± .05
1-Ethoxy-	L	3.90	.62	5.78 ± .09
1-Isopropoxy-	P	3.22	.68	4.81 ± .16
2-Methoxy-	P	2.33	.56	3.30 ± .08
2-Ethoxy-	P	1.99	.62	3.01 ± .09
2-Isopropoxy-	L	1.98	.68	3.09 ± .09
1-Acetyl-	P	1.84	.59	2.76 ± .01
2-Acetyl-	P	1.60	.60	2.47 ± .03
1-Nitro-	P	0.80		
Acenaphthene	P	2.55	0.58	3.59 ± 0.16

[a] Kindly supplied in a good state of purity by Dr. R. R. Twelves, Department of Chemistry, University of Minnesota. [b] The significant discrepancy between this value and that previously reported[12] (0.17) cannot be explained. [c] P, purchased. L, prepared as described in the literature.

any correlations within series. The temperature-dependence of complexation is illustrated in thermodynamic functions calculated from association constants determined in this study of the naphthalene complex at 27° (K_s = 2.31) and 8° (K_s = 3.31). An Arrhenius plot of log K_s *vs.* T^{-1} gives ΔH −3.1 kcal. mole^{-1} and from this and the ΔF values, $\Delta F_{27°}$ = −670 and $\Delta F_{8°}$ = −500 cal. mole^{-1}, there is obtained ΔS = −8.7 cal. deg.$^{-1}$. These values differ significantly from those reported for this complex as determined by the spectrophotometric method.[18] This general phenomenon is discussed above and by Ross, *et al.*[10]

Alkylnaphthalenes.–It is apparent that complex stability in both series of alkylnaphthalenes is determined by the steric requirement of the substituent. The order is also that expected of hypercongugative participation of substituents. In view of the nature of the π-complex,[1] of which these are examples, there is little reason to suspect that hyperconjugation can contribute significantly to the π-electron density on the ring even under the demand of complexation.[19] The relative decrease in complex stability with increasing size of substituent in the 2-alkyl series parallels rather closely that observed in the alkylbenzene series, $CH_3 > C_2H_5 >$ iso-C_3H_7.[6] The relative decrease is even greater in the 1-series, a trend reported previously in the pair $CH_3 > C_2H_5$.

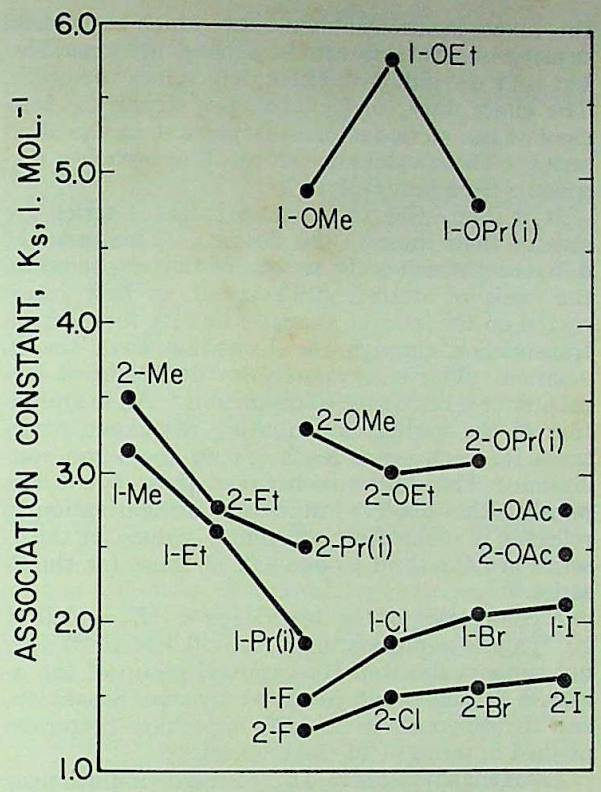

Fig. 1.

Halogenonaphthalenes.–As might be anticipated, association constants in these two series are much lower than those in the alkylnaphthalenes. The trend in both series is that dictated by the inductive effect of the substituent, constants in these series being in the order I > Br > Cl > F. It will be noted that this order is the reverse of that expected on the basis of steric requirement as well as that expected on the basis of the capacity for double bond formation by the substituent.[23] Values in these series parallel the order of substituent electronegativity.[24] Certainly it can be said that all of

(15) S. D. Ross and I. Kuntz, THIS JOURNAL, **76**, 74 (1954).

(19) See, for example, G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955.

(20) M. Orchin, *J. Org. Chem.*, **16**, 1165 (1951).

(21) The value for 2-*t*-butylnaphthalene is not included as this hydrocarbon preparation was found to be impure. The value does, however, fall in line with those of other 2-alkylnaphthalenes reported here. A sufficient quantity of the 1-*t*-butyl isomer could not be obtained by the only method[22] reported to give an unequivocally pure substance.

(22) E. Illingworth and A. T. Peters, *J. Chem. Soc.*, 1602 (1951).

(23) A. E. Remick, "Electronic Interpretations of Organic Chemistry," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1949, p. 103.

(24) L. Pauling, "The Nature of the Chemical Bond," 2nd Ed. Cornell University Press, Ithaca, N. Y., 1948, p. 64.

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the above-mentioned modes by which π-electron density on the ring can be altered are operative but that the inductive effect determines the order. The effect must, in fact, be very strong to overshadow the steric factor so important in the alkyl series. These values do not at all approach a reasonable Hammett σ-plot.[25]

It is interesting that values in the 1-series are greater than those in the 2-series. This order of difference, which is the reverse of that expected on the basis of steric considerations, is best interpreted on the basis of a greater facility for electron transmission through the 1-position than the 2-position. This is a capacity for double bond formation or a resonance phenomenon. An examination of the various contributing resonance structures for each series leads one to the same conclusion. The difference between these two series parallels that observed in molecular polarization as reflected in molar Kerr constants; values for the 1-series are one-third to one-half of those for the 2-series.[26]

A comparison of the acidities of α- ($K_a = 2.0 \times 10^{-4}$) and β-naphthoic acid ($K_a = 6.9 \times 10^{-5}$) does not support this, but the carboxyl group of the α-isomer is somewhat hindered by the 8-position, and the difference in acidities is perhaps better explained in terms of an "*ortho* effect."[27]

Alkoxynaphthalenes.–The 1-alkoxynaphthalene complexes are significantly more stable than those of the 2-series. Here again it is apparent that the difference between the two series is best explained in terms of a greater facility for double bond formation at the 1-position; resonance effects here, as in the halogenonaphthalenes, dictate the relative series difference. Values within each series, however, do not follow any reasonable order and as yet are unexplained.

Acetonaphthones.–The association constant for the 1-acetonaphthone complex is seen to be greater than that of the 2-isomer, but both values are significantly higher than might be anticipated. The presence of the acetyl group in either position should effectively diminish the π-electron density on the ring and thereby weaken the complex binding. The fact that these values are comparable with those of the ethylnaphthalenes, which have a similar steric requirement in the substituent, suggests that other factors are involved in the acetonaphthones. It is possible, for example, that the carbonyl group behaves as a "localized" donor as appears to be the case with aryl amines,[1] and possibly with the alkoxynaphthalenes considered above and the association constants reflect both types of complexation. This explanation is supported by the higher value for the 1-isomer; resonance effects, transmitted through the 1-position more readily than the 2-position, should permit greater polarization of the carbonyl group in the 1-isomer. In this regard, it should be noted that even 1-nitronaphthalene has an appreciable tendency to complex with picric acid.

AUSTIN, TEXAS

(25) This is perhaps apparent from a cursory inspection of the σ-values (*meta* or *para*) in the halogen series. The order of electron-withdrawing power is the reverse of that observed here.

(26) C. H. LeFevre and R. J. W. LeFevre, *J. Chem. Soc.*, 1641 (1955).

(27) J. F. J. ippy, *Chem. Revs.*, **25**, 151 (1939).

[CONTRIBUTION NO. 752 FROM THE DEPARTMENT OF CHEMISTRY, INDIANA UNIVERSITY]

Formation of the Silicon–Hydrogen Bond by the Reducing Action of Certain Sterically Hindered Grignard Reagents on Phenyltrichlorosilane

BY MACK C. HARVEY, WILLIAM H. NEBERGALL AND JOHN S. PEAKE

RECEIVED DECEMBER 10, 1956

Certain sterically hindered Grignard reagents have been found to react with phenyltrichlorosilane, $C_6H_5SiCl_3$, to form dialkylphenylsilanes, $R_2C_6H_5SiH$, and unsaturated hydrocarbons. By such reactions dicyclohexylphenylsilane and cyclohexene, dicyclopentylphenylsilane and cyclopentene, diisopropylphenylsilane and propene and di-*t*-butylphenylsilane and isobutylene have been obtained. Attempts to prepare di-*o*-tolylphenylsilane by this method were unsuccessful.

In 1933, Cusa and Kipping[1] reported that when no precautions were taken to exclude atmospheric oxygen, cyclohexoxydicyclohexylphenylsilane, $(C_6H_{11})_2C_6H_5SiOC_6H_{11}$, was formed when the product of the reaction of phenyltrichlorosilane with an excess of cyclohexylmagnesium bromide was hydrolyzed. When the reaction was carried out under nitrogen, however, the principal reaction product was found to be dicyclohexylphenylsilane, $(C_6H_{11})_2C_6H_5SiH$. These investigators suggested that $(C_6H_{11})_2C_6H_5SiMgBr$ was formed as an intermediate, which upon hydrolysis gave $(C_6H_{11})_2C_6H_5SiH$.

$$C_6H_5SiCl_3 + 2C_6H_{11}MgBr \longrightarrow (C_6H_{11})_2C_6H_5SiCl + 2MgBrCl$$

$$(C_6H_{11})_2C_6H_5SiCl + C_6H_{11}MgBr \longrightarrow (C_6H_{11})_2C_6H_5SiMgBr + C_6H_{11}Cl$$

$$(C_6H_{11})_2C_6H_5SiMgBr + H_2O \longrightarrow (C_6H_{11})_2C_6H_5SiH + Mg(OH)Br$$

It should be noted that tricyclohexylphenylsilane is not formed here due to the steric effects of the cyclohexyl group.[1,2]

Because various workers[3,4] have been unsuccessful in attempts to prepare stable Grignard type silicon–magnesium compounds, it was decided to repeat the work of Cusa and Kipping in an effort to determine the mechanism of the formation of

(1) N. W. Cusa and F. C. Kipping, *J. Chem. Soc.*, 1686 (1933).

(2) W. H. Nebergall and O. H. Johnson, THIS JOURNAL, **71**, 4022 (1949).

(3) F. R. Van Artsdalen and J. Gavis, *ibid.*, **74**, 3196 (1952).

(4) R. A. Benkeser and R. G. Severson, *ibid.*, **73**, 1424 (1951).

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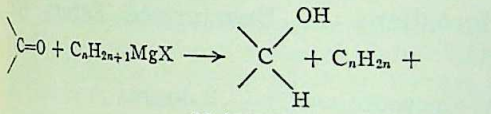
the silicon–hydrogen bond in dicyclohexylphenylsilane.

In the present investigation it was found that dicyclohexylphenylsilane is formed prior to the hydrolysis of the reaction mixture, which shows that the mechanism proposed by Cusa and Kipping[1] cannot be correct. It was also found that cyclohexene is a reaction product, an important fact that apparently was overlooked by the previous workers.

Because the steric effect of the cyclohexyl group is important in determining the course of the reaction, it was decided to try the action of other sterically hindered Grignard reagents upon phenyltrichlorosilane. Thus, it has been found that Grignard reagents containing the cyclopentyl, isopropyl and *t*-butyl groups react with phenyltrichlorosilane to form dicyclopentyl-, diisopropyl- and di-*t*-butyl-phenylsilane, respectively. The corresponding unsaturated hydrocarbons cyclopentene, propene and isobutylene were also identified as reaction products.

There are many reports in the literature concerning the reducing action of Grignard reagents toward carbonyl compounds. In these reactions the carbonyl compound is reduced to an alcohol and the alkyl group of the Grignard reagent is changed to an alkene.



$Mg(OH)X$ (after hydrolysis)

Generally, the reduction of carbonyl compounds by Grignard reagents has been observed in instances in which the normal addition reaction may be hindered sterically. Furthermore, reduction is observed usually with Grignard reagents which possess a hydrogen atom beta to the magnesium atom. According to mechanisms proposed by Whitmore[5] and by Wiberg and Bauer[6] for reactions of this type, the β-hydrogen shifts to the carbon atom of the carbonyl group and an alkene is formed.

The reduction of the silicon–chlorine bond by sterically hindered Grignard reagents appears to be similar to that observed for the carbonyl group. Thus we may write the following equations for the reaction of phenyltrichlorosilane with an excess of cyclohexylmagnesium bromide

$$C_6H_5SiCl_3 + 2C_6H_{11}MgBr \longrightarrow (C_6H_{11})_2C_6H_5SiCl + 2MgBrCl$$

$$(C_6H_{11})_2C_6H_5SiCl + C_6H_{11}MgBr \longrightarrow (C_6H_{11})_2C_6H_5SiH + C_6H_{10} + MgBrCl$$

Similar equations can be written for the reactions involved when cyclopentyl-, isopropyl- and *t*-butylmagnesium halides were employed. Additional evidence that a β-hydrogen atom is involved in the mechanism is provided by the fact that *o*-tolylmagnesium bromide, which does not contain an easily removable β-hydrogen atom, failed to reduce the silicon–chlorine bond of phenyltrichlorosilane.

(5) F. Whitmore and R. George, THIS JOURNAL, **64**, 1239 (1942).
(6) E. Wiberg and R. Bauer, *Z. Naturforsch.*, **76**, 129 (1952).

Experimental

All reactions involving a Grignard reagent were carried out in an atmosphere of oxygen-free, dry nitrogen. The ether used as a solvent was previously dried over sodium. All melting points and boiling points are uncorrected.

Dicyclohexylphenylsilane.—Magnesium turnings (37 g., 1.53 g. atoms) were placed in a one-liter, three-necked flask fitted with a motor-driven stirrer, reflux condenser, dropping funnel and nitrogen inlet. The magnesium was covered with anhydrous ethyl ether and nitrogen passed through the system to remove all air. The Grignard reagent was prepared by adding slowly a 30% solution of cyclohexyl bromide (253 g., 1.53 moles) in ether. After the addition of the cyclohexyl bromide was completed, the reaction mixture was refluxed for 2 hr. Phenyltrichlorosilane (25 g., 0.118 mole) in an equal volume of ether was added slowly to the Grignard reagent. The reaction mixture was then heated to 160–170° with all the volatile material being condensed and collected. Redistillation of the distillate gave 21 g. (0.25 mole) of cyclohexene, boiling at 81–82° (747 mm.). This compound was identified by its boiling point, unsaturation and infrared spectrum. A small portion of the residue in the distillation flask was extracted with ethyl ether and the ether removed by distillation. An infrared spectrum recorded for the residual liquid showed a strong Si–H bond.[7] This showed that dicyclohexylphenylsilane was produced prior to hydrolysis. The remainder of the residue in the distillation flask was hydrolyzed by a mixture of ice and dilute hydrochloric acid. The organic layer was extracted with ethyl ether, the ether solution dried over Drierite and the ether removed by distillation. Distillation of the residual liquid under reduced pressure gave 8.0 g. of dicyclohexyl (100–140° at 2.5 mm., and 236° at 737 mm.), 21 g. (0.078 mole) of dicyclohexylphenylsilane (124° at 0.03 mm.) and a small quantity of high-boiling polymeric material. The yield of $C_6H_5(C_6H_{11})_2SiH$ was 66%, $n^{25}D$ 1.538.

Anal. Calcd. for $C_{18}H_{28}Si$: C, 79.3; H, 10.3. Found: C, 79.3; H, 10.3.

Another experiment was conducted in which the above procedure was modified by holding the reaction mixture at the reflux temperature of the solvent for 30 hr. before hydrolysis. The yield of dicyclohexylphenylsilane in this experiment was only 2.0 g. (6%). This shows that the reduction of the silicon–chloride bond by the Grignard reagent is favored by higher temperatures.

Diisopropylphenylsilane.—Isopropylmagnesium chloride was prepared using 188 g. (1.53 moles) of isopropyl chloride and 37 g. (1.53 g. atoms) of magnesium. To the Grignard reagent was added 25 g. (0.118 mole) of phenyltrichlorosilane in an equal volume of ether. After the addition was completed, all volatile material was distilled into an ice-cooled chloroform solution of bromine, with the distillation flask being heated to 160–170°. The chloroform solution was then washed with a saturated aqueous solution of sodium sulfite to remove excess bromine, and, after drying the chloroform layer over Drierite, the chloroform was removed by distillation. The residual 1,2-dibromopropane distilled at 139–141° (747 mm.). This compound was identified by its boiling point and infrared spectrum; yield 61 g. (0.32 mole).

The residue in the distillation flask was worked up as described in the above experiment. The product obtained was diisopropylphenylsilane, which distilled at 58–60° (1.2 mm.), $n^{25}D$ 1.495, yield 24 g. (50%).

Anal. Calcd. for $C_{12}H_{20}Si$: C, 75.0; H, 10.4. Found: C, 74.8; H, 10.5.

Dicyclopentylphenylsilane.—The procedure described above was repeated using the Grignard reagent prepared from 238 g. (1.53 moles) of cyclopentyl bromide and 25 g. (0.118 mole) of phenyltrichlorosilane. The volatile material produced by heating the reaction mixture to 160–170° was condensed and redistilled. The cyclopentene formed as a reaction product distilled at 43–44° (747 mm.), yield 8 g. (0.12 mole). This compound was identified by its boiling point, unsaturation and infrared spectrum.

The dicyclopentylphenylsilane, which was obtained upon working up the residue in the distillation flask, distilled at 100° (0.03 mm.), $n^{25}D$ 1.529, yield 14.3 g. (49%).

(7) M. C. Harvey, W. H. Nebergall and John S. Peake, THIS JOURNAL, **76**, 4553 (1954).

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Anal. Calcd. for $C_{16}H_{24}Si$: C, 78.6; H, 9.90. Found: C, 78.8; H, 9.96.

Di-*t*-butylphenylsilane.—The procedure described above was repeated using the *t*-butylmagnesium bromide prepared from 279 g. (1.53 moles) of *t*-butyl bromide and 25 g. (0.118 mole) of phenyltrichlorosilane. The volatile material produced by heating the reaction mixture to 160–170° was passed into an ice-cooled chloroform solution of bromine. The chloroform solution was washed with an aqueous saturated solution of sodium sulfite to remove the excess bromine. The chloroform layer was dried over Drierite and the chloroform removed by distillation. The residual isobutylene bromide distilled at 149° (747 mm.), yield 27 g. (0.128 mole). This compound was identified by its boiling point and infrared spectrum.

The di-*t*-butylphenylsilane, which was obtained upon working up the residue in the distillation flask, distilled at 46° (0.4 mm.), yield 5.5 g. (10%), $n^{25}D$ 1.489.

Anal. Calcd. for $C_{14}H_{24}Si$: C, 76.4; H, 10.96. Found: C, 76.6; H, 10.90.

Attempted Preparation of Di-*o*-tolylphenylsilane.—The procedure described above was repeated using the Grignard reagent prepared from 190 g. (1.1 moles) of *o*-tolyl bromide and 11 g. (0.077 mole) of phenyltrichlorosilane. Ether was the only volatile compound recovered when the reaction mixture was heated to 160–170°. Upon working up the residue in the distillation flask and distilling the organic layer, toluene and a high-boiling, semi-crystalline material were obtained. An infrared spectrum of this material did not show the Si–H bond. This material was dissolved in a hot solution of alcoholic sodium hydroxide, from which 4 g. of a white crystalline solid precipitated upon cooling. Recrystallization from absolute alcohol gave a product which melted at 87–89°. Infrared spectral analysis showed the solid to contain the following groups: C_6H_5–Si, *o*-$CH_3C_6H_4$–Si–OH and Si–O. This compound may be di-*o*-tolylphenylsilanol, $(o\text{-}CH_3C_6H_4)_2C_6H_5SiOH$.

Anal. Calcd. for $C_{20}H_{20}OSi$: C, 78.9; H, 6.60. Found: C, 79.0; H, 7.2.

Another experiment was conducted in which the above procedure was modified by holding the reaction mixture at the reflux temperature for 4 hr. Upon hydrolysis of the reaction mixture a white solid was precipitated. This solid was recrystallized from hot toluene, giving 1.6 g. (0.07 mole) of product, m.p. 103°; identified as being *o*-tolylphenylsilanediol, $(o\text{-}CH_3C_6H_4)C_6H_5Si(OH)_2$.

Anal. Calcd. for $C_{13}H_{14}O_2Si$: C, 67.8; H, 6.10. Found: C, 67.8; H, 6.3.

Acknowledgments.—Analyses were by Miss J. Dickey of the Indiana University Microanalytical Laboratory. This paper is based upon work performed under contract Nonr-90802-Task NR 356-321 (Office of Naval Research).

BLOOMINGTON, IND.

[CONTRIBUTION FROM THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Aliphatic Organo-functional Siloxanes. V. Synthesis of Monomers by Platinum-catalyzed Addition of Methyldichlorosilane to Unsaturated Esters and Nitriles[1]

BY L. H. SOMMER, F. P. MACKAY, O. W. STEWARD AND P. G. CAMPBELL

RECEIVED NOVEMBER 23, 1956

Extension of an important synthesis discovered by G. H. Wagner, which involves platinum-catalyzed addition of silicon hydrides to olefins, has resulted in simple synthetic routes to nine monomers for organo-functional siloxanes. The nitriles and esters being reported have a functionality of 2 at the silicon atom. Reaction of methyldichlorosilane with acrylate esters results in addition of the silyl group to the non-terminal olefinic carbon and thus gives products in which the ester group is readily cleaved from silicon. In important contrast, methacrylate esters give addition of the silyl group to the terminal olefinic carbon and yield adducts which are stable toward cleavage of the ester group from silicon. Olefins in which the functional group is not conjugated with the double bond give products resulting from addition of the silyl group to the terminal olefinic carbon.

Introduction.—If organosilicon chemistry is to progress appreciably beyond the point represented in organic chemistry by monomers and polymers in which the basic chain of atoms (C–C–C bonds in organic chemistry and Si–O–Si groupings in organosilicon chemistry) bears unsubstituted hydrocarbon substituents, it seems essential that simple synthetic procedures be developed for the preparation of monomers which can easily be converted to aliphatic organo-functional siloxanes.

Previous publications from this Laboratory have reported synthetic approaches to aliphatic organo-functional siloxanes involving selective cleavage of one methyl group from trimethylsilyl, Me_3Si, in a variety of organo-functional silanes through reaction with concd. sulfuric acid.[2a,b,c]

More recently, the direct synthesis of organosiloxane esters and acids from halomethylsiloxanes and halomethylethoxysilanes has been reported. These latter syntheses represented a definite improvement over the former method and involved reaction, in suitable solvents, of the halomethylsilanes with anions derived from ethyl malonate and ethyl cyanoacetate. Organofunctional monomers in which the silicon is mono- as well as difunctional can be made by this synthesis.[2d]

However, an even simpler and more direct synthetic route obviously was desirable. In the present paper we wish to record such a synthesis which leads easily to aliphatic organo-functional monomers in which the functionality at the silicon atom is 2.

The addition of trichlorosilane to simple olefins proceeds smoothly and in excellent yield in the presence of diacetyl peroxide or ultraviolet light.[3] Addition of compounds containing the Si–H bond

$$R{-}CH{=}CH_2 + HSiCl_3 \xrightarrow[\text{or u.v. light}]{(CH_3COO)_2} RCH_2CH_2SiCl_3$$

(1) Paper 52 in a series on organosilicon chemistry. For Paper 51, see L. H. Sommer and O. F. Bennett, THIS JOURNAL, **79**, 1008 (1957).

(2) (a) L. H. Sommer, R. P. Pioch, N. S. Marans, G. M. Goldberg, J. Rockett and J. Kerlin, THIS JOURNAL, **75**, 2932 (1953); (b) L. H. Sommer, W. D. English, G. R. Ansul and D. N. Vivona, *ibid.*, **77**, 2485 (1955); (c) L. H. Sommer, G. M. Goldberg, G. H. Barnes and L. S. Stone, Jr., *ibid.*, **76**, 1609 (1954); (d) L. H. Sommer, J. M. Masterson, O. W. Steward and R. C. Leitheiser, *ibid.*, **78**, 4013 (1956).

(3) L. H. Sommer, E. W. Pietrusza and F. C. Whitmore, *ibid.*, **69**, 188 (1947); **70**, 484 (1948); C. A. Burkhard and R. H. Krieble, *ibid.*, **69**, 2687 (1947).

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to olefins also takes place in the absence of a catalyst at elevated temperatures (about 300°).[4]

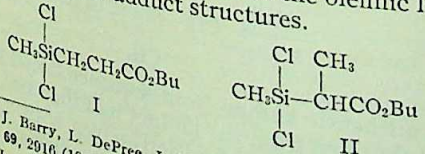
More recently, the addition of phenylsilane, diphenylsilane, phenylmethylsilane, amylsilane and tribromosilane to olefins in the presence of *t*-butyl perbenzoate has been reported.[5] However, attempts to extend this procedure to readily available olefins such as methyl acrylate or acrylonitrile resulted in rapid polymerization of the olefin. Thus, peroxide-catalyzed additions of silanes to olefins containing functional groups suffer from the limitations placed on this procedure by the polymerization of the readily available "vinyl monomers." A further limitation is provided by the greatly decreased reactivity of the Si–H bond in alkyldichlorosilanes as compared to trichlorosilane when a peroxide catalyst is used.[3]

In 1953, G. H. Wagner reported the use of platinum supported on finely divided charcoal as a catalyst for the addition of silicon hydrides to a number of olefins and to acetylene.[6] The addition reactions were performed at pressures of 45 to 115 p.s.i. and reaction temperatures of 100 to 300°. The olefins used were ethylene, allyl chloride, trichloroethylene, vinylidene fluoride and butadiene. Trichlorosilane was the silicon hydride most generally used. However, examples of addition reactions of triethoxysilane, ethyldichlorosilane and dichlorosilane also were reported.

In another publication Wagner and co-workers[7] reported the preparation of β-phenylethyltrichlorosilane by addition of trichlorosilane to styrene at 200° (20 hr. in a stainless steel pressure reactor) in the presence of *t*-butylcatechol (inhibitor) using 5% platinum on powdered charcoal. The yield of product was excellent.

In view of the above good results obtained with platinized charcoal catalyst using an easily polymerizable olefin such as styrene, it seemed that this catalyst might also be effective for the addition of silicon hydrides to other readily available "vinyl monomers." Application of this procedure to olefinic esters would provide a simple and direct route to the intermediates for organopolysiloxane ester systems.

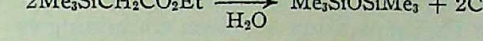
Platinum-catalyzed Addition of Methyldichlorosilane to Acrylates and Methacrylates.—In the present work reaction of *n*-butyl acrylate with methyldichlorosilane (2% Pt–C catalyst) in an all-glass apparatus at atmospheric pressure proceeded slowly. During 16 hr. the boiling point of the reaction mixture increased from 67 to 145°. Fractionation gave a 42% yield of adduct which analyzed correctly for *n*-butyl methyldichlorosilylpropionate. Addition of Si–H to the olefinic linkage can lead to two adduct structures.



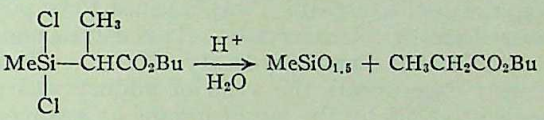
I

II

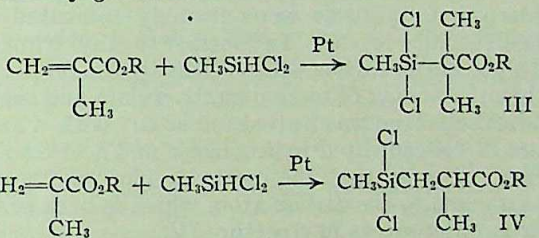
Structure II contains the Si—C—C=O grouping which is known to give carbon–silicon cleavage with acids and bases. For example, ethyl trimethylsilylacetate gives ethyl acetate when treated with dilute acid.[8] In contrast, structure I contains the



Si—C—C—C=O system which is stable toward cleavage of its C–Si bond with most reagents. When the adduct obtained from *n*-butyl acrylate was treated with water, a resinous solid separated and an oily upper layer formed. The organic layer upon distillation gave a 75% yield of *n*-butyl propionate. This result indicates structure II for the adduct.[9]



As another possible means of synthesizing the Si—C—C—C=O system through the platinum-catalyzed addition of silicon hydrides to olefins, the use of methacrylate esters was investigated next. The basis for this study was the possibility that the α-methyl group in methacrylate esters would lead to the desired mode of addition because of the steric requirements of that methyl group and/or its hyperconjugation with the olefinic double bond.



III

IV

The latter reaction was in fact realized with *n*-butyl methacrylate and compound IV (R = *n*-Bu) was obtained.

When methyldichlorosilane and *n*-butyl methacrylate were heated in the presence of 2% Pt–C, the boiling point of the reaction mixture increased to a maximum of 120° after 3 hr. Fractionation gave a 32% yield of *n*-butyl α-methyl-β-methyldichlorosilylpropionate, IV (R = *n*-Bu). This product when poured into water gave an oil but no solid. Treatment of this oil with hot acetic–hydrochloric acid mixture gave a stiff, acidic, silicon-containing polymer. If addition had given a product containing the silicon atom linked to the α-carbon of the methacrylate ester, the expected hydrolysis products would be methylpolysiloxane and *n*-butyl iso-

(4) A. J. Barry, L. DePree, J. W. Gilkey and D. E. Hook, THIS JOURNAL, **69**, 2916 (1947).

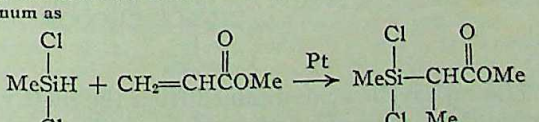
(5) J. L. Speier, R. Zimmerman and J. Webster, *ibid.*, **78**, 2278 (1956).

(6) G. H. Wagner, U. S. Patent 2,637,738, May 5 (1953).

(7) G. H. Wagner, D. L. Bailey, A. N. Pines, M. L. Dunham and D. B. McIntire, *Ind. Eng. Chem.*, **45**, 367 (1953).

(8) J. R. Gold, L. H. Sommer and F. C. Whitmore, THIS JOURNAL, **70**, 2874 (1948).

(9) Subsequent to the completion of our work, L. Goodman, R. M. Silverstein and J. N. Shoolery, *ibid.*, **78**, 4493 (1956), reported that methyldichlorosilane adds to methyl acrylate in the presence of platinum as



The product was characterized through use of nuclear magnetic reso-

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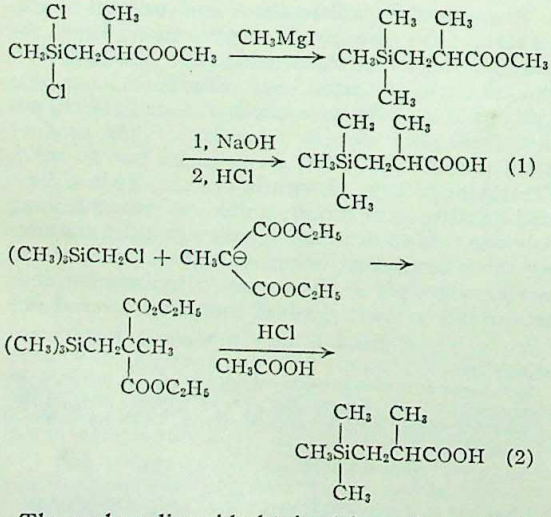
butyrate. Neither of these substances was formed on treatment of the adduct with water. (A definitive proof of the structures of the adducts obtained from methyl and ethyl methacrylates with methyldichlorosilane is given below.)

The addition of silicon hydrides to *methyl* methacrylate would provide an exceedingly convenient method for the preparation of silicon-containing esters since methyl methacrylate is more readily available than other methacrylate esters. Methyl methacrylate and methyldichlorosilane were heated together in the presence of 2% Pt–C. Within 3 hr. the boiling point of the reaction mixture increased from 54 to 142°. Fractionation gave a 58% yield of methyl α-methyl-β-methyldichlorosilylpropionate, IV (R = Me). There remained a large residue from the distillation which was believed to be polymerized methyl methacrylate. This corresponded to 24.5% of the starting quantity of ester. In subsequent experiments the yield of adduct was increased to 86% by the use of hexane as a solvent. An excess of methyldichlorosilane (100%) also increased the yield to 70%. Both of these procedures lowered the reaction temperature and greatly decreased the amount of polymerization of the methyl methacrylate. Similar results were obtained with ethyl methacrylate giving ethyl α-methyl-β-methyldichlorosilylpropionate, IV (R = Et) in 74% yield.

The structures of the methylacrylate methyldichlorosilane adducts were strongly indicated by their stability to acid. In contrast to ethyl trimethylsilylacetate, carbon–silicon cleavage did not occur when the adduct of methyl methacrylate and methyldichlorosilane was heated for 12 hr. with a mixture of concentrated hydrochloric and acetic acids. This indicates that the methyldichlorosilyl group is attached to the carbon atom which is beta to the carbonyl group as in structure IV.

A more definitive proof of structure for the methyldichlorosilane–methacrylate adducts was provided by the syntheses



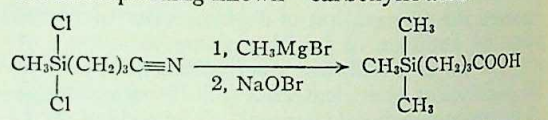
The carboxylic acid obtained from the methyldichlorosilane–methyl methacrylate adduct in sequence 1 was identical in physical properties with the acid obtained from the independent synthesis in sequence 2. The *p*-bromoanilide derivatives had the same m.p. and mixed m.p. Thus structure IV is shown to be the correct one.

Platinum-catalyzed Addition of Methyldichlorosilane to Unconjugated Olefinic Esters and Nitriles.—Table I gives data on the addition of methyldichlorosilane to nine olefinic esters and nitriles. Methyldichlorosilane reacts very readily with all of the unconjugated olefinic esters and nitriles in Table I. For the addition reactions of these olefins with methyldichlorosilane, it is usually advisable to add the silane slowly to the olefin and catalyst maintained at a temperature of 70–100°. The reaction is generally quite exothermic and may become very vigorous if all of the reactants are mixed and then heated. Platinum-on-charcoal catalyst (2% Pt) in the amount of 1 g. per mole of olefin is usually sufficient.

The methacrylates are far less reactive than the other olefins listed in Table I and hence can be mixed with catalyst and methyldichlorosilane and then heated.

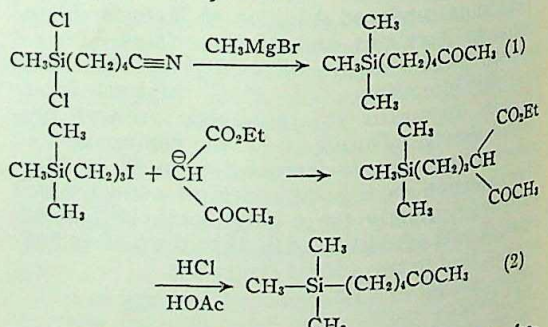
Evidence for addition of the silyl group to the terminal carbon of the unconjugated olefinic esters and nitriles of Table I was obtained by means of proofs of structure for three of the adducts.

The adduct from allyl cyanide was treated with methylmagnesium bromide to give 5-trimethylsilyl-2-pentanone and the ketone was then converted to the corresponding known[2a] carboxylic acid.



The authentic γ-trimethylsilylbutyric acid[2a] and the acid derived from the adduct had the same physical properties and gave derivatives with *p*-bromophenacyl bromide having the same melting point. A mixed m.p. showed no depression.

The adduct from 4-pentenonitrile was treated with methylmagnesium bromide to give 6-trimethylsilyl-2-hexanone. The same ketone was obtained from an acetoacetic ester synthesis using 3-iodopropyltrimethylsilane.



The authentic ketone from sequence 2 and the ketone obtained from the adduct had the same physical properties and gave derivatives with 2,4-dinitrophenylhydrazine having the same melting points. A mixed m.p. showed no depression.

The adduct from ethyl 4-pentenoate was treated with methylmagnesium bromide to give 6-trimethylsilyl-2-hexanol. The same alcohol, as

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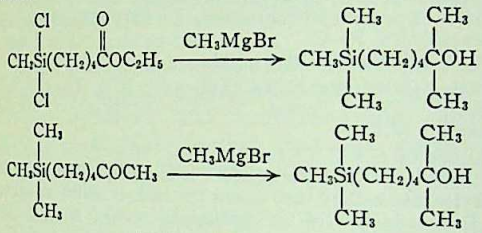
TABLE I

ADDITION OF METHYLDICHLOROSILANE TO UNSATURATED ESTERS AND NITRILES

Olefin	Product	Yield,[b] %	B.p. °C.	B.p. Mm.	Silicon, % Calcd.	Silicon, % Found	Chlorine, % Calcd.	Chlorine, % Found
$CH_2=C(CH_3)CO_2CH_3$	$CH_3(Cl_2)SiCH_2CH(CH_3)CO_2CH_3$	86	79	10	13.1	12.8	33.0	32.7
$CH_2=C(CH_3)CO_2C_2H_5$	$CH_3(Cl_2)SiCH_2CH(CH_3)CO_2C_2H_5$	74	105	17	12.2	12.0	30.9	31.0
$CH_2=C(CH_3)CO_2\text{-}n\text{-}C_4H_9$	$CH_3(Cl_2)SiCH_2CH(CH_3)CO_2\text{-}n\text{-}C_4H_9$	32	78	3	10.9	10.8	27.6	27.3
$CH_2=CHCH_2CO_2C_2H_5$	$CH_3(Cl_2)SiCH_2CH_2CH_2CO_2C_2H_5$[a]	81	108	12	12.2	12.6	30.9	31.2
$CH_2=CHCH_2CH_2CO_2C_2H_5$	$CH_3(Cl_2)SiCH_2CH_2CH_2CH_2CO_2C_2H_5$	85	118	8	11.5	11.7	29.2	29.2
$CH_2=CHCH_2CH(CO_2C_2H_5)_2$	$CH_3(Cl_2)SiCH_2CH_2CH_2CH(CO_2C_2H_5)_2$[a]	74	154	5	8.9	9.2	22.5	22.4
$CH_2=CHCH_2C\equiv N$	$CH_3(Cl_2)SiCH_2CH_2CH_2C\equiv N$	73	122	17	15.4	15.8	38.9	39.1
$CH_2=C(CH_3)CH_2C\equiv N$	$CH_3(Cl_2)SiCH_2CH(CH_3)CH_2C\equiv N$[a]	43	116	12	14.3	14.4	36.1	36.0
$CH_2=CHCH_2CH_2C\equiv N$	$CH_3(Cl_2)SiCH_2CH_2CH_2CH_2C\equiv N$	66	137	12	14.3	14.3	36.1	36.1

[a] Proposed structure for the adduct but definitive proof not obtained. [b] Yields are based on amount of olefin since an excess (about 10–20%) of methyldichlorosilane generally was used.

shown by physical properties and identical infrared spectrum, was obtained from reaction of 6-trimethylsilyl-2-hexanone with methylmagnesium bromide.



Experimental

Starting Materials.—Methyldichlorosilane, b.p. 41°, was obtained from Dow Corning Corp. and fractionally distilled before being used. Methyl methacrylate was used directly as obtained from Rohm and Haas Co. Ethyl methacrylate was the commercial grade supplied by Monomer–Polymer Inc. *n*-Butyl methacrylate was prepared by the reaction of methacrylic acid with *n*-butyl alcohol in the presence of sulfuric acid and hydroquinone. *n*-Butyl acrylate was supplied by Union Carbide and Carbon Corp. Ethyl vinylacetate was prepared from vinylacetyl chloride by the method of Jeffery and Vogel.[10] Dehydrochlorination of 4-chlorovaleronitrile, supplied by the du Pont Co., was effected in 50% yield by the use of quinoline, giving 4-pentenonitrile, b.p. 143° (730 mm.), $n^{20}D$ 1.4206.[11] 4-Pentenoic acid[12] was prepared by hydrolysis of 4-pentenonitrile. Ethyl 4-pentenoate was prepared from the acid by the method of Paul.[13]

The 2% Pt–C catalyst was supplied by Baker and Co.

Reaction of *n*-Butyl Acrylate and Methyldichlorosilane.—In an all-glass apparatus consisting of a 500-cc. flask and a glass-jointed condenser were placed 90 g., 0.7 mole, of *n*-butyl acrylate, 82 g., 0.71 mole, of methyldichlorosilane and 1 g. of 2% platinum-on-charcoal. After heating at reflux temperature for 16 hr., the temperature of the boiling reaction products was 145° as compared to an initial temperature of 67°. The reaction mixture was cooled, filtered to remove the catalyst and fractionated. There was obtained 71.7 g., 0.29 mole, of *n*-butyl methyldichlorosilylpropionate, b.p. 76° (3 mm.), 42% yield.

Anal. Calcd. for $C_8H_{16}SiO_2Cl_2$: Si, 11.5; Cl, 29.2. Found: Si, 11.7; Cl, 28.4.

When 20 g., 0.08 mole, of the adduct was poured into water, a solid and two liquid layers were formed. The solid was removed by filtration and the liquid layers were separated. Fractionation of the dried upper layer gave *n*-butyl propionate, b.p. 145°, 8 g., 0.06 mole, 75% yield, sapn. equiv. 131 (calcd. 130). This experiment clearly shows rapid C–Si cleavage and thus strongly indicates that the adduct is *n*-butyl α-methyldichlorosilylpropionate (II).

Reaction of *n*-Butyl Methacrylate and Methyldichlorosilane.—In an all glass apparatus consisting of a 500-cc. flask and a condenser were placed 72 g., 0.5 mole, of methyldichlorosilane, 1 g. of 2% Pt–C and 2 g. of hydroquinone (inhibitor). After heating for 3 hr. at reflux, the temperature of the reaction products in the flask had reached 120°. Heating at reflux was continued for 10 additional hr., but there was no further temperature rise. At this point the reaction mixture was cooled and 27 g., 0.23 mole, of additional methyldichlorosilane and 0.25 g. of Pt–C were added. Heating was then resumed, but the temperature fell to 87° where it remained during 12 more hr. of heating. Fractional distillation of the product gave *n*-butyl α-methyl-β-methyldichlorosilylpropionate (IV), 42.8 g., 0.16 mole, 32% of theoretical. When the product was treated with water, an oil was formed which contained no *n*-butyl isobutyrate. Further treatment of the oil with hot concd. hydrochloric–glacial acetic acid mixture gave no C–Si cleavage. A polysiloxane–polycarboxylic acid was obtained as a stiff polymer with considerable affinity for glass surfaces.

Reaction of Methyl Methacrylate and Methyldichlorosilane.—(a) In an all-glass apparatus consisting of a 500-cc. flask and a condenser were placed 110 g., 1.1 moles, of methyl methacrylate; 138 g., 1.2 moles, of methyldichlorosilane; 1.5 g., of 2% Pt–C and 1 g. of hydroquinone. This mixture was heated to the boiling point, 54°. The temperature rose steadily. After 3 hr. of heating, it had reached 142°. There was no additional temperature rise in 24 more hr. of heating. Fractionation gave methyl α-methyl-β-methyldichlorosilylpropionate, compound IV (R = CH_3), in 58% yield.

(b) The reaction was carried out in the same apparatus as above with the following quantities of materials: 50 g., 0.5 mole, of methyl methacrylate; 115 g., 1 mole, of methyldichlorosilane; 1 g. of 2% Pt–C; 1 g. of hydroquinone. These materials were heated from 60 to 87° (excess CH_3SiHCl_2 kept the temperature down) for 24 hr. The yield of product was 70% of the theoretical.

(c) The reaction was carried out with the following quantities of materials: 50 g., 0.5 mole, methyl methacrylate; 65 g., 0.56 mole, of methyldichlorosilane; 0.5 g. of 2% Pt–C; 1 g. of hydroquinone; 200 cc. of hexane as a solvent. These materials were heated from 64 to 75° for 16 hr. The yield of product was 86%.

(d) The reaction was attempted with the following materials: 100 g., 1 mole, of methyl methacrylate; 200 g., 1.8 moles, of methyldichlorosilane; 0.5 g. of *rhodium*-on-charcoal (Baker and Co.). When the rhodium catalyst was added to the methyldichlorosilane, there was a small flash of flame which immediately stopped. The reaction mixture was then heated at 56° for three days. No adduct was obtained.

Use of 5% palladium-on-charcoal and of Raney nickel as catalysts also gave *no* Si–H addition.

Additions of Methyldichlorosilane to Unconjugated Olefinic Esters and Nitriles.—A detailed description of the general procedure used in a typical reaction is as follows: Allyl cyanide, 101 g., 1.5 moles, and 0.75 g. of 2% Pt–C catalyst were placed in an all-glass apparatus equipped with a thermometer well, separatory funnel and condenser. (Rubber stoppers were *not* used in these preparations to avoid the possibility of sulfur poisoning of the catalyst.) The apparatus was vented through a concd. sulfuric acid Gilman trap. Allyl cyanide was then heated to reflux temperature

(10) G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 658 (1948).
(11) R. Paul and H. Cottin, *Bull. soc. chim.*, [5] **4**, 933 (1937).
(12) R. Linstead and H. Rydon, *J. Chem. Soc.*, 580 (1933).
(13) R. Paul, *Ann. chim.*, [10] **18**, 332 (1932).

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and methyldichlorosilane, 195 g., 1.7 moles, was added dropwise over a period of 2 hr. The reaction mixture was then heated overnight to ensure complete reaction. Fractionation of the filtered reaction product by means of a column packed with glass helices gave the product in 73% yield.

Proof of the Structure of the Methacrylate–Methyldichlorosilane Adducts. A. Reaction of Methylmagnesium Iodide with the Adduct, Methyl α-Methyl-β-methyldichlorosilylpropionate.—Addition of methylmagnesium iodide, 1 mole in 300 cc. of ether, to 108 g., 0.5 mole, of the adduct during 5 hr. was followed by stirring at room temperature for 20 hr. Treatment with water and dilute hydrochloric acid followed by fractionation gave methyl α-methyl-β-trimethylsilylpropionate, 22.4 g., 0.16 mole, b.p. 78° (28 mm.), $n^{20}D$ 1.4202, 32% yield.

Anal. Calcd. for $C_8H_{18}SiO_2$: Si, 16.1; sapn. equiv., 174; MR_D, 50.57. Found: Si, 15.8; sapn. equiv., 173; MR_D, 50.50.

B. Saponification of Methyl α-Methyl-β-trimethylsilylpropionate.—A mixture of 19.3 g., 0.11 mole, of methyl α-methyl-β-trimethylsilylpropionate, 5 g., 0.12 mole, of sodium hydroxide, 10 cc. of ethyl alcohol and 10 cc. of water was refluxed on the steam-bath for 14 hr. It was then cooled and acidified with hydrochloric acid. The layers were separated and the water layer was extracted with ether. The ether extracts were combined with the main organic layer and the combined layers were dried over anhydrous magnesium sulfate. Fractional distillation gave 10.9 g., 0.068 mole, 62% yield, of α-methyl-β-trimethylsilylpropionic acid, b.p. 90° (3 mm.), $n^{20}D$ 1.4309.[14]

Anal. Calcd. for $C_7H_{16}SiO_2$: Si, 17.5; neut. equiv., 160. Found: Si, 17.6; neut. equiv., 159.

In a 50-cc. flask were placed 1 g. of α-methyl-β-trimethylsilylpropionic acid, 40 cc. of benzene and 0.5 g. of thionyl chloride. These materials were allowed to react at room temperature with shaking. After 2 hr., 1.2 g. of *p*-bromoaniline was added, and the reaction mixture was heated on the steam-bath for 2 minutes. The reaction mixture was then filtered. The filtrate was extracted with 5% hydrochloric acid and then evaporated to dryness. Recrystallization from hexane gave shiny white plates, m.p. 117.2–117.5°.

Anal. Calcd. for $C_{13}H_{20}O_2SiBrN$: Si, 8.50. Found: Si, 8.70.

C. Preparation of Authentic α-Methyl-β-trimethylsilylpropionic Acid.—This acid was prepared again by reaction in ethanol of sodiomethylmalonic ester with chloromethyltriethylsilane, followed by treatment of the resulting diethyl (trimethylsilylmethyl)-methylmalonate with concd. hydrochloric–glacial acetic acid mixture. Fractionation gave the acid having b.p. 90° (3 mm.), $n^{20}D$ 1.4311.

The *p*-bromoanilide prepared by the procedure described above had m.p. 117–117.5°. A mixed melting point of the derivatives gave no depression.

Proof of the Structure of the Allyl Cyanide–Methyldichlorosilane Adduct.—A solution of the adduct (γ-cyanopropyl)-methyldichlorosilane, 136 g., 0.75 mole, in 200 cc. of ether was added to 2.7 moles of methylmagnesium bromide in 700 cc. of ether. After stirring and refluxing for 12 hr., the reaction mixture was hydrolyzed and treated with hydrochloric acid. Fractionation gave 5-trimethylsilyl-2-pentanone, 33.6 g., 0.21 mole, b.p. 71° (13 mm.), $n^{20}D$ 1.4231, d^{20} 0.8279, 30% yield.

Anal. Calcd. for $C_8H_{18}SiO$: Si, 17.7; MR_D, 48.80. Found: Si, 17.3; MR_D, 48.90.

Oxidation of 5-trimethylsilyl-2-pentanone with sodium hypobromite gave γ-trimethylsilylbutyric acid in 41% yield, b.p. 123° (16 mm.), $n^{25}D$ 1.4308.[15]

The *p*-bromophenacyl bromide derivative of the acid obtained from the adduct had m.p. 61–62°. *Anal.* Calcd. for $C_{15}H_{21}O_3SiBr$: Si, 7.85. Found: Si, 7.89.

The *p*-bromophenacyl bromide derivative from authentic acid[15] also had m.p. 61–62° and gave no depression in a mixed melting point determination.

Proof of the Structure of the Adduct from 4-Pentenonitrile and Methyldichlorosilane.—The adduct, 98.1 g., 0.5 mole, dissolved in 200 cc. of ether was stirred with methylmagnesium bromide, 1.75 moles, for 2 days and the reaction mixture was then hydrolyzed with water followed by dilute hydrochloric acid. The water layer was extracted three times with ether and the combined ether layers dried over magnesium sulfate. Fractional distillation gave 6-trimethylsilyl-2-hexanone, b.p. 85° (10 mm.), $n^{20}D$ 1.4289, d^{20} 0.8281.

Anal. Calcd. for $C_9H_{20}OSi$: Si, 16.3; MR_D, 53.43. Found: Si, 16.6; MR_D, 53.62.

The 2,4-dinitrophenylhydrazone was prepared and had m.p. 92.4–93°.

Anal. Calcd. for $C_{15}H_{24}O_4SiN_4$: Si, 7.97. Found: Si, 8.14.

The following comprises a description of the synthesis of authentic 6-trimethylsilyl-2-hexanone.

(γ-Chloropropyl)-methyldichlorosilane was prepared by addition of methyldichlorosilane to allyl chloride in the presence of 2% Pt–C. The product had b.p. 80° (18 mm.) and was obtained in 59% yield.

Anal. Calcd. for $C_4H_9ClSiCl_2$: Si, 14.7; Cl (attached to silicon), 37.0. Found: Si, 15.0; Cl (titration with 0.1 *N* alkali), 37.2.

Failure of the C–Cl bond to react with dilute alkali on titration shows that the product is indeed (γ-chloropropyl)-methyldichlorosilane and is not the adduct which would result from addition of the methyldichlorosilyl group to the non-terminal olefinic carbon. The latter would contain a C–Cl bond beta to silicon and should react quantitatively with alkali giving β-elimination.[16]

Treatment of (γ-chloropropyl)-methyldichlorosilane with excess methylmagnesium iodide gave γ-chloropropyltrimethylsilane, b.p. 148° (733 mm.), $n^{20}D$ 1.4310, d^{20} 0.8825, in 80% yield.

Anal. Calcd. for $C_6H_{15}SiCl$: Si, 18.6; MR_D, 44.38. Found: Si, 18.8; MR_D, 44.19.

Reaction of γ-chloropropyltrimethylsilane with sodium iodide in dry acetone gave γ-iodopropyltrimethylsilane, b.p. 103° (47 mm.), $n^{20}D$ 1.4910, d^{20} 1.3334, in 63% yield.

Anal. Calcd. for $C_6H_{15}SiI$: Si, 11.6; MR_D, 52.40. Found: Si, 11.9; MR_D, 52.59.

A solution of 133 g., 0.55 mole, of γ-iodopropyltrimethylsilane in 100 cc. of absolute alcohol was heated to reflux, and ethyl sodioacetoacetate, 0.55 mole, dissolved in 250 cc. of ethanol, was added *to* the iodide during 2.5 hr. The reaction mixture was then brought to the neutral point with hydrochloric acid. After distillation of the ethanol, removal of sodium iodide by washing with water, and drying, fractionation gave ethyl (γ-trimethylsilylpropyl)-acetoacetate, 92.2 g., 0.38 mole, b.p. 132° (9 mm.), $n^{20}D$ 1.4389, d^{20} 0.9269, a 68% yield.

Anal. Calcd. for $C_{12}H_{24}O_3Si$: Si, 11.5; MR_D, 69.09. Found: Si, 11.6; MR_D, 69.30.

The above substituted acetoacetate on heating with concd. hydrochloric acid gave authentic 6-trimethylsilyl-2-hexanone, b.p. 85° (10 mm.), $n^{20}D$ 1.4289, in 82% yield.

The 2,4-dinitrophenylhydrazone derivative of the authentic ketone had m.p. 92.5–93°. A mixed melting point with the derivative obtained above from the ketone derived from the adduct gave no depression.

Proof of the Structure of the Adduct from Ethyl 4-Pentenoate and Methyldichlorosilane.—The adduct, 60.8 g., 0.25 mole, was treated with 1.4 moles of methylmagnesium bromide. Fractionation of the product gave 6-trimethylsilyl-2-methylhexan-2-ol, 35.7 g., 0.19 mole, b.p. 93° (8 mm.), $n^{20}D$ 1.4377, d^{20} 0.8294, a 76% yield.

Anal. Calcd. for $C_{10}H_{24}OSi$: Si, 14.9; MR_D, 59.61. Found: Si, 15.0; MR_D, 59.53.

Authentic 6-trimethylsilyl-2-methylhexan-2-ol was pre-

(14) α-Methyl-β-trimethylsilylpropionic acid was prepared previously by reaction of ethyl α-methyl-α-trimethylsilylmethylacetoacetate with sodium ethylate in ethanol followed by treatment with hydrochloric acid. This gave the carboxylic acid having b.p. 92° (4 mm.), $n^{20}D$ 1.4310; L. H. Sommer and N. S. Marans, THIS JOURNAL, **72**, 1935 (1950).

(15) γ-Trimethylsilylbutyric acid was prepared previously by carbonation of the Grignard reagent derived from γ-bromopropyltrimethylsilane and had b.p. 118° (10 mm.), $n^{25}D$ 1.4320 [L. H. Sommer, E. Dorfman, G. M. Goldberg and F. C. Whitmore, THIS JOURNAL, **68**, 488 (1946)].

(16) L. H. Sommer, E. Dorfman, G. M. Goldberg and F. C. Whit-

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pared from 6-trimethylsilyl-2-hexanone by treatment with methylmagnesium bromide in the usual manner. The authentic alcohol had b.p. 93° (8 mm.), $n^{20}D$ 1.4376, d^{20} 0.8290.

Infrared spectra of the authentic alcohol and the alcohol derived from the adduct were identical.

UNIVERSITY PARK, PENNA.

[CONTRIBUTION NO. 2148 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

The Chromatographic Separation and Identification of Some Peptides in Partial Hydrolysates of White Turkey Feather Calamus

BY W. A. SCHROEDER, LOIS M. KAY, NANCY MUNGER, NANCY MARTIN AND JOAN BALOG

RECEIVED DECEMBER 11, 1956

Chromatographic investigations of partial acidic hydrolysates of unoxidized and oxidized white turkey feather calamus have resulted in the isolation and identification of 59 peptides. The sequences which have been observed suggest that unusual sequences do not occur in feather keratin. The possible relation of some of the more prominent sequences to the spatial structure of the proteins is discussed. The isolation and identification of cysteic acid peptides by means of ion-exchange chromatography are described.

Many published investigations treat the feather as a more or less homogeneous unit despite its visually apparent and morphologically distinct parts and despite the fact that the parts of a feather are known to develop from specific portions of the papilla.[1] Recent analyses[2,3] have shown that the amino acid composition is not identical in all parts of a feather, so that a distinct and properly characterized part only should be utilized for chemical investigations. The relatively good orientation which is observed in certain feather parts by X-ray diffraction might lead one to conclude that they are composed of a reasonably homogeneous protein, but cell walls and cell debris from the original growing feather certainly are not absent. Purification of the protein without alteration unfortunately is impossible because of its insolubility, so one is forced to use the material as it is obtained. Woodin[4] has obtained soluble keratin from whole feathers in an apparently homogeneous state with a molecular weight of about 10,000. This material is not unaltered protein inasmuch as it has been isolated after either oxidation or reduction. In the present paper, we describe the isolation and identification of peptides from partial hydrolysates of unaltered protein and of oxidized protein from white turkey feather calamus. Although the rachis has usually been used when well-oriented feather protein is desired, we have chosen the calamus for four reasons: (1) rachis and calamus develop from the same portion of the papilla, (2) the amino acid compositions are essentially identical, (3) the X-ray diffraction patterns for most of the calamus and for the rachis are identical,[5] and (4) necessary amounts of calamus are easy to obtain whereas the separation of the rachis from the medulla is laborious.

Experimental

Source of Calamus and Preparation of Oxidized Calamus.—The sample of white turkey feather calamus was prepared in the way previously described.[2]

Oxidized calamus for the investigation of cysteic acid peptides was prepared in the following manner which combines features of the methods of Schram, Moore and Bigwood[6] and of Hirs.[7] Preformed performic acid was prepared by mixing 9 volumes of 90% formic acid and one volume of 30% hydrogen peroxide. After an hour at room temperature, the mixture was cooled to 0° in an ice-bath and 25 ml. was added to 500 mg. of calamus in the form of pieces about 1 mm. square and 0.1 mm. thick. The reaction mixture was maintained at 0° for 16 hr. during which time the pieces of calamus became swollen but did not dissolve to any obvious extent. The reaction mixture was transferred with 50 ml. of ice-cold water to 350 ml. of ice-cold water in a lyophilizing bulb. The solution was then frozen and the solvents were removed by lyophilization. The process was repeated after the addition of 80 ml. of water. The residue contained pieces in the form of original calamus as well as the usual voluminous residue which soluble substances form on lyophilizing and it was evident that considerable solution had occurred during some part of the procedure.

Partial Hydrolysis of Calamus and Oxidized Calamus.—A 300-mg. sample of calamus and 3 ml. of concd. hydrochloric acid (Baker's Analyzed Reagent Grade) were placed in a 5-ml. volumetric flask. The stem of the flask was attached parallel to a shaft which was inclined at 45° and rotated at 25 r.p.m. In this way, the reaction mixture was constantly agitated for 48 hr. at 37°. Within a few minutes after hydrolysis was begun, the pieces of calamus began to swell and continued to do so until the liquid was almost filled. Gradual dissolving took place and was complete in 3 to 3.5 hr. to give a light brown solution which darkened somewhat during the remainder of the hydrolysis. After about 24 hr., a very small amount of dark insoluble material had become attached to the flask at the surface of the liquid; it was somewhat greasy and had a density less than that of water. It may be composed of sterols or fatty acids.

A 240-mg. sample of oxidized calamus in 2.5 ml. of concd. hydrochloric acid was hydrolyzed at 37° for 48 hr. with constant agitation as above. Most of the material dissolved almost immediately and the remainder within an hour to give a light brown solution. The same type of insoluble residue appeared after about 24 hr. At the end of the partial hydrolysis, the reaction mixture was transferred with 100 ml. of water to a lyophilizing bulb, the solution was frozen, and

(1) F. R. Lillie, *Biol. Rev.*, **17**, 247 (1942).

(2) W. A. Schroeder and L. M. Kay, THIS JOURNAL, **77**, 3901 (1955). A definition of terms relating to feathers is presented in this reference.

(3) W. H. Ward, C. H. Binkley and N. S. Snell, *Textile Res. J.*, **25**, 314 (1955).

(4) A. M. Woodin, *Biochem. J.*, **57**, 99 (1954).

(5) S. Krimm, private communication. Krimm has observed with turkey feathers that the proximal tip of the calamus is unoriented, that good orientation is present but changes in direction within the first 6 mm. from the tip and then is unchanged in direction and character throughout the remainder of the calamus and rachis.

(6) E. Schram, S. Moore and E. J. Bigwood, *Biochem. J.*, **57**, 33 (1954).

(7) C. H. W. Hirs, *J. Biol. Chem.*, **219**, 611 (1956).

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the solvent was removed. The residue was then taken up in 10 ml. of water which was again removed by lyophilizing.

Ion-exchange Chromatography of the Partial Hydrolysate of Calamus.—The partial hydrolysate of calamus was chromatographed on a column of Dowex 50-X4 that was 2.2 × 100 cm. in dimension. The resin (200–400 mesh, high porosity, Lot No. 3198-42) was purified in the manner that Moore and Stein[8] describe for Dowex 50-X8 and the column was packed as they suggest. The proportion of mesh sizes in the resin for this column was 4 parts of through-200-mesh resin and one part of 120–200 mesh resin. The detergent BRIJ35 and thiodiglycol were omitted from the buffers which otherwise were prepared as prescribed.[8]

The partial hydrolysate of calamus prepared as above was made up for chromatography by diluting with 42 ml. of *p*H 6.7 buffer after which the *p*H was brought to 2.1 with 3.8 ml. of 6 *N* sodium hydroxide. The 48 ml. of solution that was placed on the column contained the equivalent of 268 mg. of moisture- and ash-free calamus.

Development was begun with *p*H 3.42 buffer at a temperature of 55°. This temperature was maintained through the *p*H 4.25 buffer, but was reduced to 37° during the *p*H 6.7 and *p*H 8.3 buffers, and finally to room temperature when 0.2 *N* sodium hydroxide was used (see Fig. 1). Deaerated buffers were required at 55°. The flow rate of developer was 50 ml. per hr. and the fraction size was 5 ml. The ninhydrin procedure[9] was applied to 0.5-ml. portions of alternate fractions in order to determine the progress of the chromatogram.

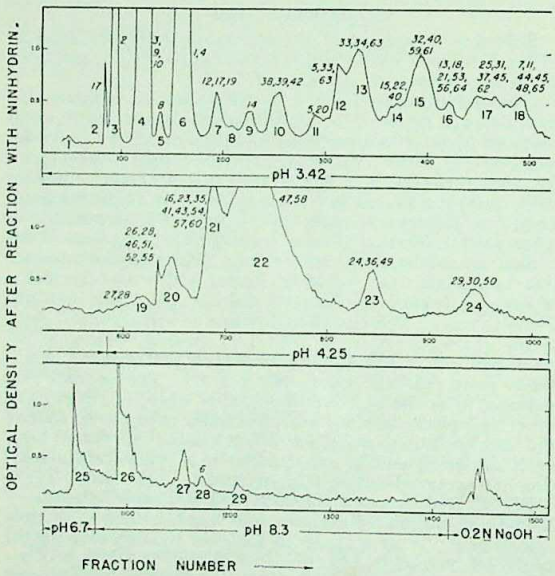

Fig. 1.—Chromatogram of a partial hydrolysate of unoxidized white turkey feather calamus on Dowex 50-X4. Zones are numbered consecutively. Italicized numerals identify compounds in each zone (see Table I).

Fractions containing a zone were pooled, neutralized to *p*H 6.5–7.5, evaporated at 35° to one-tenth their volume on a rotary evaporator,[10] finally evaporated to dryness in a vacuum desiccator over concd. sulfuric acid, and stored at −10° until investigated

Ion-exchange Chromatography of the Partial Hydrolysate of Oxidized Calamus.—The partial hydrolysate of oxidized calamus was chromatographed on a column of Dowex 1-X8 that was 1.6 × 100 cm. in dimension. The resin (200–400 mesh; Lot No. 3589-27; chloride form; medium porosity) was purified in the following way. A volume of about 300 ml. of resin was suspended in 750 ml. of water, the resin was allowed to settle for an hour, and the cloudy supernatant liquid was decanted; the process was repeated 4 times. The resin was then filtered, suspended in 200 ml. of 2 *N* hydrochloric acid, filtered and washed on the filter with 800 ml. of 2 *N* hydrochloric acid; this treatment was repeated once and the filter cake was finally washed with 500 ml. of water. The Dowex 1 was now passed wet through a 120-mesh sieve.[11] Fine particles were further removed at this point by seven suspensions and settlings in 500 ml. of water. The resin was converted to the chloroacetate form by suspending it in 600 ml. of *N* sodium chloroacetate, filtering, repeating this procedure twice and then washing on the filter with 1200 ml. of *N* sodium chloroacetate. This process was repeated with *N* chloroacetic acid and with 0.1 *N* chloroacetic acid and the resin was finally suspended in 600 ml. of the latter. The column was packed in the usual way and conditioned with 675 ml. of 0.1 *N* chloroacetic acid.

For chromatography, the residue that remained after the lyophilization of the partial hydrolysate was dissolved in 7 ml. of 0.01 *N* chloroacetic acid and placed on the column. Inasmuch as the moisture and ash content of the oxidized calamus was not determined, the amount of material that was placed on the column can only be estimated to be equivalent to 200–220 mg. of moisture- and ash-free protein.

The chromatogram was developed throughout with 0.1 *N* chloroacetic acid at room temperature (approximately 22°). The fraction size was 3 ml. and the flow rate of developer was 12 ml. per hr. to fraction no. 150, 18 ml. per hr. from there to fraction no. 400, and 24 ml. per hr. thereafter. The progress of the chromatogram was assessed by applying the ninhydrin procedure[9] to 0.5-ml. portions of alternate fractions.

Pooled fractions that contained a given zone were frozen and stored at −10°. For further investigation, the frozen solution was thawed and the chloroacetic acid was extracted with 2 × 25 ml. and 7 × 10 ml. of ether. Finally, aliquot portions of the extracted solution were removed and individually taken to dryness at 40° on a rotary evaporator.[10]

Further Separation and Identification of the Peptides.—The simpler mixtures of peptides which were obtained from the complex partial hydrolysate by means of the ion-exchange chromatography on Dowex 50-X4 were separated and identified by methods which did not differ appreciably from those previously utilized[12]; that is, the peptides in the pooled fractions were dinitrophenylated, separated by chromatography on silicic acid–Celite, estimated spectrophotometrically, and identified after complete hydrolysis. For peptides longer than dipeptides, the complete sequence was usually not determined; where the complete sequence is known it usually was obvious from the composition (thus, thr-val-val) or the peptide was difficult to hydrolyse and smaller peptides were isolated and identified.

Dinitrophenylation according to Levy and Chung[13] in aqueous solution is more satisfactory than in the aqueous alcoholic medium which was used heretofore.[12] Specifically, the procedure now used is this. The residue of buffer salts and peptides from the evaporation of the pooled fractions was dissolved in 10 to 15 ml. of water and the *p*H was adjusted to 8.5 to 9.5. A 20-mg. portion of sodium carbonate and 0.05 ml. of 2,4-dinitrofluorobenzene (DNFB) were then added and the reaction mixture was vigorously stirred at 40° for 3 hr. Extraction then followed the scheme previously used.[14] This method has the advantage that the buffer salts remain in solution but, what is more important, extraction of soln. 7[14] may not be necessary. Because of the absence of alcohol, the miscibility of phases during the extraction of excess DNFB from the basic reaction mixture (soln. 1[14]) is decreased and DNP-compounds are less likely to be carried over into soln. 7. If a yellow color is present in soln. 7 but disappears on acidification, it is caused by dinitrophenol and the solution may be discarded. Comparison of the two methods with test substances showed that the dinitrophenylation was equally quantitative in both.

Attempts to Separate DNP-Cysteic Acid Peptides Chromatographically.—Although definite separation of cysteic acid peptides was achieved by the use of Dowex 1, it is

(8) S. Moore and W. H. Stein, *J. Biol. Chem.*, **192**, 663 (1951).

(9) S. Moore and W. H. Stein, *ibid.*, **176**, 367 (1948).

(10) L. C. Craig, J. D. Gregory and W. Hausmann, *Anal. Chem.*, **22**, 1462 (1950).

(11) Only about one-fourth of this lot of Dowex 1 would pass a 200-mesh sieve.

(12) W. A. Schroeder, L. M. Kay, J. LeGette, L. Honnen and F. C. Green, THIS JOURNAL, **76**, 3556 (1954).

(13) A. L. Levy and D. Chung, *ibid.*, **77**, 2898 (1955).

(14) See Fig. 1 of ref. 12.

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hardly to be expected that the separation would be complete. Because DNP-peptides of other kinds can be so readily separated by chromatography on silicic acid–Celite, experiments with DNP-cysteic acid as test substance were begun in an attempt to find chromatographic conditions which might apply to DNP-cysteic acid peptides.

DNP-Cysteic acid itself can be prepared by dinitrophenylation in aqueous alcohol or in purely aqueous solution as above and can be extracted from the acidified reaction mixture with *n*-butanol. The product, however, is oily and less homogeneous than when the following procedure is used. To a solution of 10 mg. of cysteic acid (Nutritional Biochemicals Corpn.) in 5 ml. of water was added 0.25 ml. of 25% aqueous reagent trimethylamine (Matheson, Coleman and Bell). The *p*H was about 10. Then 0.05 ml. of DNFB (Eastman) was added and the reaction mixture was stirred vigorously at 40° for 3 hr. The reaction mixture was extracted with 4 × 25 ml. of ether to remove excess DNFB, then evaporated to dryness at 40° on a rotary evaporator, and finally evaporated twice to dryness after the addition of 5 ml. of water.

Unsatisfactory chromatograms resulted when DNP-cysteic acid was chromatographed on silicic acid–Celite by methods similar to those of Green and Kay.[15] DNP-Cysteic acid is very strongly adsorbed so that strong developers such as 7AA-35A-B and 8AA-40A-B are necessary. However, two zones are present on the chromatogram; the more strongly adsorbed when rechromatographed again produces two zones whereas the less strongly adsorbed is unchanged in its behavior on rechromatography. Apparently, the adsorbent forces a conversion to the less strongly adsorbed form.

Inasmuch as DNP-cysteic acid is highly polar and easily soluble in water, chromatography in systems in which the developer contained water were studied. These efforts for the most part have been fruitless. The separation of DNP-cysteic acid from DNP-cysteic acid peptides could be achieved (a separation was actually already accomplished with the undinitrophenylated compounds on Dowex 1) but the DNP-peptides did not separate from each other. The results of the experiments will be described briefly. Chromatography on Dowex 2-X10 in a manner similar to that for cysteic acid itself[6] apparently resulted in much destruction of the very strongly adsorbed DNP-cysteic acid. On Dowex 50,[8] the DNP-cysteic acid moved with the front of *p*H 3.42 buffer and although the DNP-peptides were retarded there was little evidence of separation. DNP-Cysteic acid is rather strongly adsorbed on starch when the developer is *n*-butanol–benzyl alcohol–water.[16] DNP-Cysteic acid peptides are less strongly adsorbed and some separation occurred but the procedure was not pursued further because of the apparent deleterious effect of butanol which has been mentioned above.

Many experiments were made to try to chromatograph DNP-cysteic acid on cellulose columns with developers patterned after those which are used in the paper chromatography of DNP-compounds. For this purpose, the following general procedure was used. Ten grams of Solka-Floc BW-200 (Brown Company, New York) was suspended in 50 ml. of developer, stirred vigorously for 30 min., filtered, and the process repeated. Finally, the Solka-Floc was suspended in 50 ml. of developer, the column was poured in the manner of starch columns[18] and then 25 ml. of developer was passed through. In a tube of 10 mm. inner diameter, most columns were about 30 cm. in length. The flow rate under identical conditions was dependent on the developer and was adjusted by positive or negative pressure to 5 to 10 ml. per hr. The following are typical of the developers which were studied: (1) 1:2:1 acetic acid–*n*-butanol–water,[17] (2) 1.5 *M* phosphate buffer at *p*H 6.0,[18] (3) *M* citrate buffer at *p*H 6.2,[19] (4) *t*-amyl alcohol saturated with 3% aqueous ammonia,[20] and (5) *t*-amyl alcohol saturated with 0.1 *M* phthalate buffer at *p*H 6.0.[21] With these developers in the order given, DNP-cysteic acid moves through the column with increasing slowness; thus, about 30 ml. of citrate buffer moves DNP-cysteic acid through a column of the above size whereas about 300 ml. are required with *t*-amyl alcohol–phthalate buffer. These experiments showed that several of these systems would separate DNP-cysteic acid from its DNP-peptides. However, there was no evidence that mixtures of DNP-peptides would separate. Development with citrate buffer is generally suitable for the identification of DNP-cysteic acid. Our experience has been that DNP-cysteic acid and its DNP-peptides tend to decompose rather readily.

Other Methods for Identifying the Cysteic Acid Peptides.—The degree of heterogeneity of the residue from particular pooled fractions of the Dowex 1 chromatogram was assessed by hydrolyzing a portion of the residue completely, dinitrophenylating the products of hydrolysis, extracting other DNP-amino acids from DNP-cysteic acid with ethyl acetate, and identifying the DNP-amino acids. When this procedure was applied to zones 0–4, 0–5 and 0–7, it was apparentt hat zones 0–4 and 0–5 contained mixtures of several peptides whereas zone 0–7 contained mostly (ser, cya[22]). For further investigation, another portion of zone 0–7 was dinitrophenylated prior to hydrolysis. From this hydrolysate, DNP-serine equivalent to about 20% of the quantity of peptide was isolated.[23] Although this result could be interpreted to mean that a mixture of ser-cya and cya-ser was present, this possibility was excluded by dinitrophenylating the amino acids in the extracted hydrolysate of the peptide: no DNP-serine was detected and it was concluded that ser-cya is the main constituent. Inasmuch as similar difficulty might be anticipated in the hydrolysis of other zones after dinitrophenylation, the final investigation of the cysteic acid peptides was made by hydrolyzing the undinitrophenylated residues from the pooled fractions, and identifying the constituent amino acids and estimating the amounts by chromatography on 100-cm. columns of Dowex 50.[8] In this way, if the several peptides in the mixture were present in sufficiently disparate amounts, the composition could be deduced by comparing the molar amounts of the constituents.

Results

The separations which were achieved by chromatographing the partial hydrolysate of unoxidized calamus on Dowex 50-X4 are depicted in Fig. 1. Although more satisfactory separations were obtained in preliminary small-scale experiments especially in the region of zones 11 to 18, there is relatively minor overlapping of the peptides from zone to zone.

All zones have been investigated and some compound has been identified in each with the exception of zones 1, 8, 25, 26, 27 and 29. The qualitative and quantitative results are presented in Table I. Minor components, identification of which was not attempted, were also present in most of the zones.

The anomalous behavior of asp-gly was again observed in this chromatogram: it was present in the non-adjacent zones 2 and 7. A similar unexplained behavior was observed in partial hydrolysates of Tussah silk fibroin.[24]

(15) F. C. Green and L. M. Kay, *Anal. Chem.*, **24**, 726 (1952).
(16) W. H. Stein and S. Moore, *J. Biol. Chem.*, **176**, 337 (1948).
(17) D. H. Peterson and L. M. Reineke, *ibid.*, **181**, 95 (1949).
(18) A. L. Levy, *Nature*, **174**, 126 (1954).
(19) M. Rovery and C. Fabre, *Bull. soc. chim. biol.*, **35**, 541 (1953).
(20) H. Fraenkel-Conrat, J. I. Harris and A. L. Levy in "Methods of Biochemical Analysis," Vol. 2, edited by D. Glick, p. 375.
(21) S. Blackburn and A. L. Lowther, *Biochem. J.*, **48**, 126 (1951).

(22) The commonly accepted abbreviations for the amino acids use the first three letters of the name but because of obvious duplication with cystine and cysteine, cysteic acid is usually abbreviated cySO₃H. Further difficulty arises with glutamic acid and glutamine and with aspartic acid and asparagine. In the interest of simplicity, we would like to suggest the following usages: cysteic acid, cya; cysteine, cye; glutamine, glm; and asparagine, asg.

(23) Our experience has been that greater destruction of DNP-serine compared to other DNP-amino acids is common during the hydrolysis of DNP-peptides although the destruction usually is not as great as observed here. A. L. Levy and C. H. Li (*J. Biol. Chem.*, **213**, 487 (1955)) recovered only 10 to 20% of the expected N-terminal DNP-serine from ACTH.

(24) L. M. Kay, W. A. Schroeder, N. Munger and N. Burt, THIS JOURNAL, **78**, 2180 (1956).

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TABLE I

PEPTIDES AND FREE AMINO ACIDS ISOLATED FROM A PARTIAL ACIDIC HYDROLYSATE OF UNOXIDIZED WHITE TURKEY FEATHER CALAMUS

Designation in Fig. 1	Amino acid or peptide	Isolated from zone no.	Amt. isold. μmoles/g.[a]	Designation in Fig. 1	Amino acid or peptide	Isolated from zone no.	Amt. isold. μmoles/g.[a]
1	alanine	6	77	*35*	ser-(i)leu	21	26.0
2	aspartic acid	3	118	*36*	ser-phe	23	4.3
3	glutamic acid	4	25	*37*	ser-pro	17	2.4
4	glycine	6	346	*38*	ser-ser	10	36.2
5	(iso)leucine[c]	11, *12*[b]	49	*39*	ser-thr[d]	10	1.2
6	lysine	28	1.2	*40*	thr-ala	14, *15*	48.9
7	phenylalanine	18	34	*41*	thr-(i)leu	21	10.6
8	proline	5	20	*42*	thr-ser[d]	10	2.0
9	serine	4	350	*43*	tyr-gly[d]	21	3.5
10	threonine	4	18	*44*	val-gly	18	49.3
11	tyrosine	18	11				
12	valine	7	8	*45*	ala-(gly,val)	*17*, 18	38.2
				46	gly-(gly,(i)leu)	20	7.5
13	ala-ala	16	5.1	*47*	gly-((i)leu,pro)	22	7.8
14	ala-asp	9	14.2	*48*	(i)leu-(ala,ser)[d]	18	3.1
15	ala-gly	14	7.5	*49*	phe-(glu,pro)	23	2.0
16	ala-(i)leu[c]	21	7.1	*50*	pro-(i)leu-(i)leu	24	18.9
17	asp-gly	2, *7*	7.1	*51*	ser-(ala,(i)leu)	20	11.0
18	asp-(i)leu	16	1.2	*52*	ser-(gly,(i)leu)	20	5.5
19	glu-asp	7	9.9	*53*	thr-(ala,val)	16	9.5
20	glu-gly	11	3.9	*54*	thr-pro-(i)leu[e]	21	14.2
21	glu-pro	16	3.9	*55*	thr-((i)leu,pro)[e]	20	6.3
22	gly-gly	14	17.3	*56*	thr-val-val	16	8.7
23	gly-(i)leu	21	30.3	*57*	val-ala-(i)leu	21	13.8
24	gly-phe	23	35.4	*58*	val-((i)leu,val)	22	5.5
25	gly-pro	17	41.0				
26	(i)leu-ala	20	4.7	*59*	ser-(ala,gly,val)[d]	15	5.1
27	(i)leu-glu	19	3.1	*60*	ser-(glu,phe,pro)	21	11.0
28	(i)leu-gly	*19*, 20	29.1	*61*	ser-(gly,(i)leu,pro)[d]	15	4.3
29	(i)leu-(i)leu	24	2.4	*62*	thr-(ala,(i)leu,pro)	17	13.8
30	phe-gly	24	34.6	*63*	thr-(ala,gly,val)	12, *13*	22.4
31	pro-glu	17	3.2	*64*	thr-(gly,(i)leu,pro)	16	10.2
32	ser-ala	15	50.8				
33	ser-glu	*12*, 13	15.4	*65*	ser-(asp,glu,phe,pro)	18	3.1
34	ser-gly	13	55.0				

[a] Recalculated to one g. of moisture- and ash-free calamus. The quantities of the DNP-peptides were determined spectrophotometrically. [b] The number of the zone which contained the major portion is italicized. [c] Inasmuch as the procedures did not distinguish between leucine and isoleucine, the designations "(iso)leucine" and "(i)leu" indicate that either or both may be present. [d] The presence of these peptides though probable is not definitely established. [e] Sequence may be identical; they were isolated from adjacent zones and in only one was the actual sequence identified.

Although zone 22 is the largest zone on the chromatogram, the quantity of peptides is insignificant and the main component is ammonia. Ammonia was not identified as such in this zone because much was inadvertently lost during the isolative procedures before it was realized that a volatile component was present. However, under these same conditions of chromatography, ammonia in a control chromatogram emerged in the same region. The exact point of emergence of this zone is somewhat dependent upon uncontrolled chromatographic conditions: in some chromatograms it has been well separated from a zone equivalent to zone 21 and has partially overlapped zone 23. It is rather surprising that ammonia emerges from the column so early in the chromatogram because Moore and Stein[16] report that it emerges near arginine with *p*H 11.0 buffer after several intermediate increases in the *p*H of the buffer. In the present experiments, ammonia emerged soon after the change to *p*H 4.25 buffer and the conditions differed from those of Moore and Stein essentially only in the use of about twice the volume of *p*H 3.42 buffer and a temperature of 55° instead of 37°.

Figure 2 shows the chromatogram which resulted when the partial hydrolysate of oxidized calamus was chromatographed on Dowex 1-X8. Most of the material in the hydrolysate emerges almost immediately from the column as would be expected; three poorly separated peaks can be detected in this region of the chromatogram. This chromatogram was continued only until shortly after the appearance of cysteic acid (zone 0–12). Preliminary chromatograms on 0.9 × 100-cm. columns failed to reveal any substances which were more strongly adsorbed than cysteic acid. Thus, in these chromatograms, development with 0.1 *N* chloroacetic acid was continued to about fraction no. 800 and was then changed to a linear gradient between 0.1 *N* and *N* chloroacetic acid. The apparatus described by Bock and Ling[25] in their Fig. 6 was used. By the use of 300 ml. in each reser-

(25) R. M. Bock and N. Ling, *Anal. Chem.*, **26**, 1543 (1954).

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voir of equal cross-sectional area, the influent concentration would be N chloroacetic acid when all had been used. The equilibrium is established somewhat less rapidly on Dowex 1 than on Dowex 50. Actually, the gradient was not apparent in the effluent until 200 fractions more had been collected. The concentration of chloroacetic acid in the effluent was about 0.5 N and in the mixer was about 0.75 N when the chromatogram was stopped 450 fractions after the change to gradient elution.

The peptides of cysteic acid which were tentatively identified are listed in Table II. As an example of the interpretation required to come to the conclusions given there, consider zone 0–5. Ion-exchange chromatography showed the presence of 6.5 μmoles of cysteic acid, 3.6 μmoles of serine, 4.0 μmoles of proline, 1.5 μmoles each of aspartic acid, glutamic acid and glycine, 1.2 μmoles of alanine, 0.8 μmole of (iso)leucine, and a trace of valine. Serine and proline are present in essentially equivalent amount (there is some destruction of serine during hydrolysis) and in more than twice the amount of any other amino acid except cysteic acid. If we assume that zone 0–5 must contain cysteic acid peptides, then it is reasonable to conclude that (cya, pro, ser) is present. If this is accepted, then about 2.5 μmoles of cysteic acid peptide are not accounted for and we have about 1.5 μmoles each of aspartic acid, glutamic acid, glycine and alanine unaccounted for. Hence, two other cysteic acid tripeptides may be present but it is futile to suggest their composition because so many possibilities arise. In this way, the peptides listed in Table II have been identified with reasonable certainty.

Table II

Tentative Identification of Cysteic Acid Peptides from a Partial Acidic Hydrolysate of Oxidized White Turkey Feather Calamus

Zone no. in Fig. 2	Compound	Approx. amt., μmoles/g.
0–1, 0–2, 0–3	Contain cysteic acid peptides in mixture with other peptides of hydrolysate	
0–4	Much overlap from zone 0–3. Possibly contains (phe, cya)	9
0–5	(cya, pro, ser)	18
0–6	(cya, glu, pro)	19
0–7	(cya, ser) probably ser, cya	50
0–8	(cya, glu, pro)	12
0–9	(cya, glu)	10
0–10	(cya, glu)	7
0–11	(cya, ser, glu?)[a]	..
0–12	cya	80

[a] Cysteic acid and serine are definitely present but the identification of glutamic acid is uncertain. A zone was present which emerged in the region where glutamic acid is expected but more rapidly than observed in other chromatograms.

Table III presents an accounting of the percentages of the amino acids in free and peptide form in these hydrolysates. If we calculate the amount of material in each of the zones on the basis of the ninhydrin color and compare this with the amount actually isolated and identified, a wide variety of values results. In some zones, nothing additional

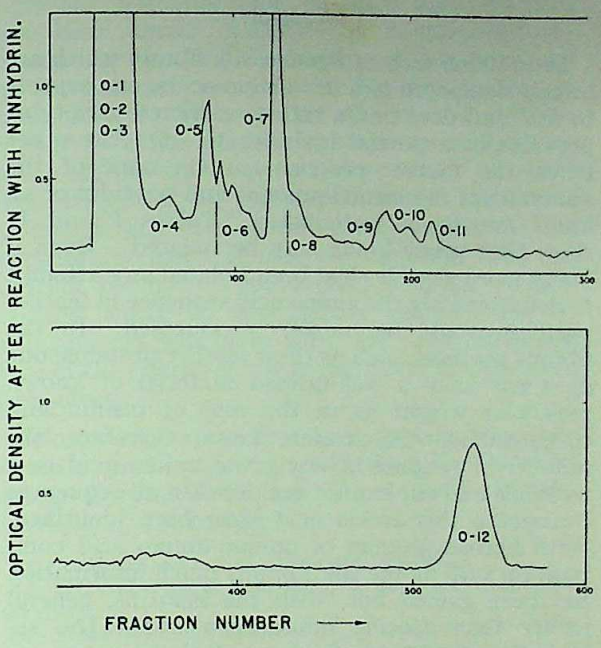

Fig. 2.—Chromatogram of a partial hydrolysate of oxidized white turkey feather calamus on Dowex 1-X8.

fied whereas in others the amount approaches or slightly exceeds 100%. In most of the major zones in Fig. 1, the amount accounted for on this basis was usually between 50 and 75%. These data must be treated with considerable reserve because the color yields of the peptides which constitute the zones are unknown. Approximately 10% of the protein has been accounted for in the form of free amino acids and about 20% in the form of peptides.

Table III

Percentage of Amino Acids in White Turkey Feather Calamus Accounted for by Peptides and Amino Acids of Tables I and II[a]

Amino acid	% accounted for by Free amino acids	Peptides	Total % accounted for
Ala	10	33	43
Asp	22	7	29
Glu	4	9	13
Gly	27	34	61
(I)leu	5	26	31
Lys	2	0	2
Phe	10	26	36
Pro	2	15	17
Ser	24	19	43
Thr	5	37	42
Tyr	5	2	7
Val	1	23	24
Cya	12	44[b]	56
Arg			0
Cys			0
Hist			0
Met			0

[a] Of the data from Table II, only cysteic acid is included here. If other amino acids from the cysteic acid peptides were added, possible double accounting might result because two hydrolysates are involved. [b] This amount was detected in peptide form, but the peptides themselves were not all identified.

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Discussion

In proteins such as *Bombyx* silk fibroin which are largely composed of a few amino acids, one expects to find and does find a rather restricted variety of peptides in a partial hydrolysate. On the other hand, the feather proteins contain none of the amino acids in unusual amount and peptides of all kinds are to be anticipated. Tables I and II show that many kinds may be isolated. Even if many more peptides had been isolated any attempt to define exactly the amino acid sequence in feather proteins would be unlikely to succeed. In the fibrous proteins, such as these feather proteins, one does not have a well-defined material of known molecular weight as in the case of insulin and corticotropin. One cannot know, therefore, the number of residues of any given amino acid in a molecule and one cannot decide when all sequences containing this amino acid have been identified. With fibrous proteins of unique amino acid composition such as the silk fibroins much information has been gained but, with the keratins, general rather than specific information about the sequences and structure is about all that one can expect to obtain.

In a preliminary experiment with oxidized calamus, a 48-hr. hydrolysate was chromatographed on a smaller scale on Dowex 50 under the conditions of Fig. 1 and the results were compared with those obtained from a 48-hr. hydrolysate of unoxidized calamus. As would be anticipated, cysteic acid and its peptides were essentially unretarded under these conditions and emerged almost with the front of the developer. Throughout the remainder of the chromatograms, the shapes and sizes of the peaks were almost identical and one may conclude that the presence of cysteic acid rather than cystine in the protein has had little influence on the course of the acidic hydrolysis. This type of comparison, admittedly, is not very exact because the components of the individual zones may not be identical. On the other hand, when hydrolysates of separate individual feather parts were compared, there were slight differences in the chromatograms which could be correlated with differences in the amino acid composition. Thus, 48-hr. hydrolysates of turkey feather barbs, calamus, medulla and rachis were made as described in the experimental part of this paper and were chromatographed under the conditions of Fig. 1. The barbs, in contrast to the other parts, required about 12 hr. instead of about 3 hr. for complete solution. The calamus and rachis are essentially identical in amino acid composition[2] and X-ray pattern[5] and the chromatograms of their partial hydrolysates were not significantly different. On the other hand, the chromatogram of the barb hydrolysate showed much smaller amounts of the zones equivalent to zones 9, 15 and 21 of Fig. 1 and two zones were present in the position of zone 23; the medulla hydrolysate showed these same differences to a lesser extent. It may be that the slower rate of solution of the barbs is responsible for these differences. However, zones 9 and 15 contain alanyl peptides and the alanine content of barbs is much greater than that of calamus while that of medulla is intermediate. Likewise, zone 21 contains peptides of leucine and/or isoleucine and the feather parts differ in their content of these amino acids. The possible relation is less obvious in this case because leucine and isoleucine were not distinguished from each other in the identification of the peptides.

The 32 dipeptides which have been isolated from the hydrolysate of unoxidized calamus are an appreciable fraction of the total number of dipeptides which are possible from combinations of the 11 amino acids in peptide form. The quantities are very dissimilar and this fact is probably partly a reflection of the ease or difficulty of hydrolysis of the particular bonds which must be hydrolyzed to give the peptide. It is unprofitable to speculate upon the sequences in the tri-, tetra- and pentapeptides as the following examples will show. The sequence in the peptide, thr-pro-(i)leu, was definitely established but the isolation of thr-(i)leu and not thr-pro would have led to the suggestion that the more probable sequence was thr-(i)leu-pro. Likewise, the sequence in gly-(gly,(i)leu) might equally well be either gly-(i)leu-gly or gly-gly-(i)leu on the basis of the amounts of gly-(i)leu, (i)leu-gly and gly-gly which were isolated.

The chromatographic separation of the cysteic acid peptides is not entirely satisfactory because zones 0–1 to 0–3 which contain the main bulk of the other peptides also contain cysteic acid peptides in about half the amount to be found in zones 0–4 to 0–11. Probably the chromatogram should be started with a developer such as 0.5 *M* acetic acid[26] in order to separate the neutral and weakly acidic compounds and then changed to 0.1 *N* chloroacetic acid in order to remove the more strongly acidic ones. On Dowex 1, the cysteic acid peptides are all appreciably less strongly adsorbed than cysteic acid itself. In contrast, on Dowex 50 peptides generally tend to emerge after any of the constituent amino acids.

Six cysteic acid peptides have been identified with some certainty. In zones 0–6 and 0–8, the main peptide has the composition (cya, glu, pro) and in zones 0–9 and 0–10, the composition is (cya, glu). Inasmuch as the separation of peptides of identical composition but different sequence is frequently observed on Dowex 50 chromatograms, it is safe to assume that in these instances also the peptides differ in sequence. It is interesting to observe that in these peptides cysteic acid and hence cystine has glutamic acid, serine and proline as close neighbors. Likewise, in the A chain of insulin,[27] glutamic acid and serine are adjacent to cystine. In feather keratin, proline also seems to be closely associated with cystine; possibly the close proximity of a cross-link between chains and of an amino acid of restricted structure such as a proline plays an important role in the structure.

When a protein contains as much proline as does feather keratin in which about one residue in ten is proline, it seems probable that this amino acid, by virtue of its definite spatial state, must play an important role in determining the spatial arrange-

(26) C. H. W. Hirs, S. Moore and W. H. Stein, THIS JOURNAL, 76, 6063 (1954).

(27) F. Sanger and E. O. P. Thompson, *Biochem. J.*, 53, 366 (1953).

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ment of the amino acids in the polypeptide chains. Because the ring system imposes such restrictions on proline, this amino acid will have a profound effect on the direction of the polypeptide chain whenever a prolyl residue is present in the sequence. Indeed, it is unlikely that the polypeptide chains in feather keratin would assume any of the pleated sheet or simple helical configurations[28,29] which have been suggested thus far. Is there any evidence from the present data or from other data that the amino acids adjacent to proline are restricted in any way? In the present investigation, 15 prolyl peptides have been identified. Of those peptides of determined sequence, gly-pro, and thr-pro-(i)leu are the most predominant. One may conclude tentatively that, in a sequence such as -X-pro-, X tends to be an amino acid with a relatively short side chain, for example, glycine, serine and threonine and that amino acids with longer side chains such as glutamic acid are less likely to be found in this sequence. This suggestion receives some support from the literature. Thus, in gelatin[12] and collagen,[30] -gly-pro- is an important sequence and -ala-pro- and -ser-pro- have been found. Likewise, in a melanophore-stimulating peptide, the sequences -gly-pro- and -ser-pro-pro- are present.[31,32] By comparison, a much different situation obtains in the corticotropins[33,34] which contain the sequences -lys-pro-val-, -arg-pro-val-, -tyr-pro-asp-, and -phe-pro-leu-. If, indeed, the proline residues are important in determining the spatial configuration of the polypeptide chains, it may be suggested that the adjacent residues in conjunction with the proline residues assist in maintaining certain specific arrangements which, in turn, are responsible for some of the characteristic properties of the proteins themselves.

Acknowledgments.—This investigation was supported in part by a contract between the Quartermaster Corps., U. S. Army, and the California Institute of Technology.

(28) L. Pauling, R. B. Corey and H. R. Branson, *Proc. Nat. Acad Sci.*, **37**, 205 (1951).

(29) L. Pauling and R. B. Corey, *ibid.*, **37**, 251 (1951).

(30) T. D. Kroner, W. Tabroff and J. J. McGarr, THIS JOURNAL, **77**, 3356 (1955).

(31) J. I. Harris and P. Roos, *Nature*, **178**, 90 (1956).

(32) I. I. Geschwind, C. H. Li and L. Barnafi, THIS JOURNAL, **78**, 4494 (1956).

(33) P. Bell, *ibid.*, **76**, 5565 (1954).

(34) W. F. White and W. A. Landmann, *ibid.*, **77**, 1711 (1955).

PASADENA, CALIFORNIA

[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING DIVISION OF CORNELL UNIVERSITY MEDICAL COLLEGE]

Pyrimidine Nucleosides. II. The Synthesis of 1-β-D-Arabinofuranosylthymine ("Spongothymidine")[1]

BY JACK J. FOX, NAISHUN YUNG AND AARON BENDICH

RECEIVED DECEMBER 19, 1956

1-D-Ribofuranosylthymine (I) was converted by a series of reactions to 1-β-D-arabinofuranosylthymine. Since this epimerization can occur only with nucleosides containing the β-D-glycosyl structure, the configuration at the glycosyl center of I and of other thymine nucleosides was firmly established as beta. 1-β-D-Arabinofuranosylthymine was shown to be identical with the naturally occurring nucleoside, "spongothymidine."

In Part I of this series[2] a method was described for the facile synthesis of thymine nucleosides by the condensation of poly-O-acylglycosyl halides with dithyminylmercury followed by removal of the protecting acetyl or benzoyl groups. In this manner 1-D-ribofuranosylthymine (I) and 1-D-xylofuranosylthymine (II) were prepared. The former was identical with a product prepared enzymically by Lampen[3] and also was shown to be similar to a compound isolated recently by Fink and co-workers[4] from rat liver slices incubated with radiothymine.

Spectral and metaperiodate-oxidation studies[2] with I and II showed that the sugar–pyrimidine linkage was at position 1 of thymine and, further, that the lactol ring structures were of the furanose type. It was demonstrated that I, II and 1-D-glucopyranosylthymine gave the same dialdehyde upon oxidation with metaperiodate. On the basis of the reasonable assumption that 1-D-glucopyranosylthymine (III) is a β-nucleoside,[5] it was tentatively concluded that I and II are nucleosides of the β-configuration.

An unequivocal determination of the structure at the glycosyl center of I would serve not only for the assignment of configuration to the biochemically produced materials of Lampen[3] and Fink,[4] but it would also help to provide a basis for future generalizations about the structure of nucleosides obtained by this new synthetic procedure with other pyrimidines. In this paper, a proof is given for the structure of 1-D-ribofuranosylthymine. As a corollary to this proof, a first synthesis and unequivocal proof of structure of "spongothymidine" are presented. A preliminary report on this study has appeared.[6]

A rigorous method for the determination of the

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, Public Health Service (Grant No. C-2329 and C-471), and from the Ann Dickler League.

(2) J. J. Fox, N. Yung, J. Davoll and G. B. Brown, THIS JOURNAL, **78**, 2117 (1956).

(3) J. O. Lampen, in W. D. McElroy and B. Glass, "Phosphorus Metabolism," Vol. II, The Johns Hopkins Press, Baltimore, Md., 1952, p. 368.

(4) K. Fink, R. R. Cline, R. B. Henderson and R. M. Fink, *J. Biol. Chem.*, **221**, 425 (1956).

(5) See discussion in footnote 12 of Part I of this series.

(6) J. J. Fox, N. Yung, *Federation Proc.*, **15**, 254 (1956).

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glycosylic configuration of certain nucleosides has been reported[7] which involves the formation of *cyclo*-nucleosides by intramolecular alkylation when 5′-tosyl derivatives of adenosine or cytidine are heated in inert solvents. An examination of molecular models shows that, for the formation of these *cyclo*-nucleosides to occur, the configuration at the glycosyl center must be beta. Michelson and Todd[8] have prepared O²,3′-*cyclo*thymidine and converted it to a 2′-deoxynucleoside (almost certainly the "deoxyxylosyl" analog) indicating that for the formation of this *cyclo*-nucleoside Walden inversion occurred at C³′.

An examination of molecular models shows that if, indeed, ribofuranosylthymine is a β-D-nucleoside, then the carbonyl oxygen atom at C² of the pyrimidine is favorably located for a rearward, nucleophilic attack upon either C², C³ or C⁵ of the sugar moiety. It should be possible, therefore, to isomerize I at C²′ or at C³′ *via* a *cyclo*-nucleoside intermediate starting from the appropriate sulfonic ester derivative of I.

1-D-Ribofuranosylthymine was converted into its 5′-trityl derivative IV by reaction with trityl chloride in pyridine.[9] Treatment of IV with methanesulfonyl chloride gave a sirup which resisted attempts at crystallization. This sirup should contain a 2′-O-mesyl derivative (V) and/or a 3′-O-mesyl isomer (VI). A 2′,3′-di-O-mesyl derivative also may be postulated as one of the reaction products along with some unreacted IV.

It should be noted that with structures V and VI (see Fig. 1) the vicinal hydroxyl functions are *cis* and the 5′-position is blocked by a trityl group so that elimination of the mesyloxy group with inversion at C²′ or at C³′ by a rearward attack by a sugar hydroxyl group is excluded. Treatment of this sirup with ammonia in aqueous methanol should effect *cyclo*-nucleoside formation with Walden inversion as a result of nucleophilic attack of O² of the pyrimidine upon either C²′ (in the case of V) or C³′ (from VI) to give VII or VIII, respectively (or both). Subsequent hydrolysis of the anhydro nucleoside(s) with acid (*cyclo*-ring opening) should also result in detritylation and give rise either to 1-β-D-arabinofuranosylthymine (IX) from VII or of 1-β-*D*-xylofuranosylthymine (X) from VIII (or both).[10] The latter nucleoside should be identical with II previously prepared directly *via* the mercuri procedure[2]; whereas IX would be 1-β-D-arabinofuranosylthymine, a new synthetic aldopentofuranosylthymine. It is clear from the foregoing discussion that (aside possibly from the recovery of starting material I) the only nucleosides which will be formed from this reaction sequence will possess a *trans* relationship between the 2′- and 3′-hydroxyl groups. Thus 1-β-D-lyxofuranosylthymine[11] cannot arise as a product of these reactions.

The experimental facts are that a product was isolated in crystalline form which was neither I nor X (II). The elemental analyses agreed with that for a pentosylthymine. This product was cleaved slowly by metaperiodate[12] with an uptake of one mole of oxidant per mole and without the liberation of formic acid in accord with a pentofuranosyl structure. The specific rotation of the dialdehyde solution resulting from this oxidation was identical with that obtained by similar treatment of I, II and III[2] demonstrating quite conclusively that the configuration at the glycosyl centers of all four compounds was similar (see Fig. 2).

On the basis of the non-identity of this nucleoside with I or X (or II), and since a lyxofuranosylthymine cannot arise from this synthesis, it is therefore obvious that the product obtained from these reactions is 1-β-D-arabinofuranosylthymine (IX). Consequently, the β-formulation must also be assigned to the glycosyl centers of I, II and III.

By virtue of the epimerization of I to IX, it is reasonable to assume that structures V and VII (not isolated) were intermediates in the synthesis of IX. Indeed, Brown and co-workers[13] have very recently reported the conversion of uridine to 1-β-D-arabinofuranosyluracil and have isolated a *cyclo*-uridine intermediate in crystalline form from a 2′-*O*-tosyl derivative of 5′-O-acetyluridine.

Bergmann and Feeney[14] have isolated a pentofuranosylthymine from certain Caribbean sponges. Spectral studies[15] as well as optical rotational data[14] indicated strongly that the sugar moiety was not D-ribose. On the basis of chemical and physicochemical studies, Bergmann and Burke[16] have assigned the 1-β-D-arabinofuranosyl structure to this thymine nucleoside.

We have compared IX with a sample of spongothymidine (kindly furnished by Drs. Bergmann and Burke) with regard to melting points, mixed melting points, optical rotation and detailed spectrophotometric behavior as a function of *p*H (including the high alkaline range[15]) and find them to be

(7) V. M. Clark, A. R. Todd and J. Zussman, *J. Chem. Soc.*, 2952 (1951); W. Anderson, D. H. Hayes, A. M. Michelson and A. R. Todd, *ibid.*, 1882 (1954).

(8) A. M. Michelson and A. R. Todd, *ibid.*, 816 (1955).

(9) IV gave a positive spray test for vicinal hydroxyls (J. G. Buchanan, C. A. Dekker and A. G. Long, *ibid.*, 3162 (1950)) thus confirming that tritylation had occurred at the 5′-position.

(10) This statement rests on the assumption that opening of the *cyclo*-nucleoside involves cleavage of the linkage between the oxygen atom of the *cyclo*-bridge and C² of the pyrimidine ring. Cleavage could occur also at the glycosyl linkage (≥C—N<) which, as pointed out by Michelson, *et al.*,[8] would give rise to glycosides. The latter type of compound would be unstable to the acidic conditions of the hydrolysis, and, indeed, in one of our experiments small amounts of thymine were isolated.

If a 2′,3′-di-O-mesyl derivative of IV had been formed and converted into a 3′- or 2′-mesylated derivative of VII or VIII, respectively, it may be postulated that in the course of these reactions a second rearward attack could occur with the formation of a 2′,3′-epoxide. The argument for the formation of IX or X is not altered since only *trans* isomers of I could arise from epoxide ring opening.

(11) Reference 30 in Part I of this series[2] contains these typographical errors; it should refer to 1-β-D-lyxofuranosylthymine instead of 1-β-D-xylofuranosylthymine. Reference 30 itself should read: "The synthesis of 1-β-D-lyxofuranosylthymine from 1-β-D-xylofuranosylthymine is underway in these laboratories."

(12) The slow uptake of metaperiodate is consistent with the presence of a *trans*-glycol system (C. C. Price and M. Knell, THIS JOURNAL, **64**, 552 (1942)). II and III also consume metaperiodate slowly, whereas with I the uptake is completed within a few minutes.[2]

(13) D. M. Brown, A. R. Todd and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

(14) W. Bergmann and R. J. Feeney, *J. Org. Chem.*, **16**, 981 (1951).

(15) J. J. Fox and D. Shugar, *Biochim. et Biophys. Acta*, **9**, 369 (1952).

(16) W. Bergmann and D. F. Burke, *Angew. Chem.*, **67**, 127 (1955), *J. Org. Chem.*, **20**, 1501 (1955).

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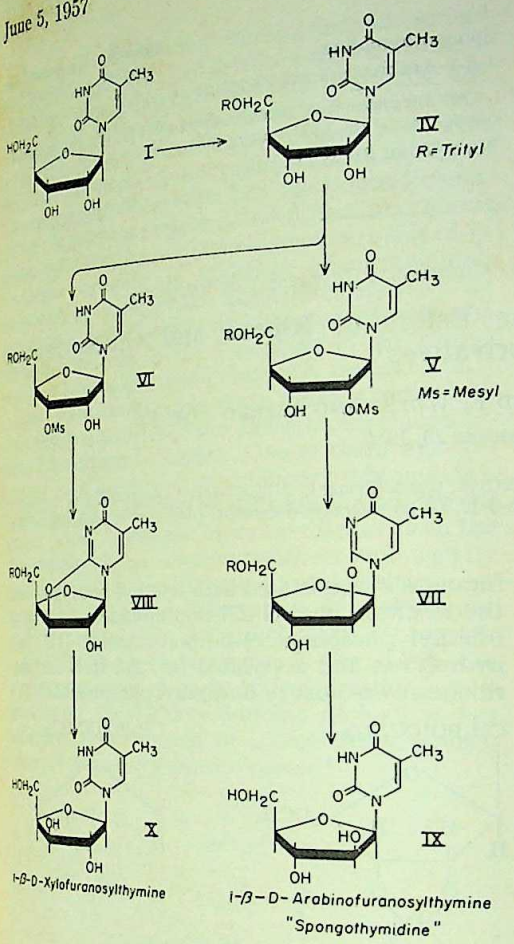

Fig. 1.

identical. Thus the epimerization sequence of I → IX constitutes a synthesis and, concomitantly, an independent proof of structure of this naturally occurring sponge nucleoside.

Acknowledgment.—The authors are indebted to Dr. George Bosworth Brown for helpful discussions and continued interest.

Experimental[17]

1-(5′-Trityl-β-D-ribofuranosyl)-thymine (IV).—The procedure of Levene and Tipson[18] for the tritylation of uridine was employed with modifications. A solution containing 6.0 g. (0.023 mole) of 1-β-D-ribofuranosylthymine (I) in 100 ml. of anhydrous pyridine was treated with 7.0 g. (0.025 mole) of triphenylchloromethane. After one day at 10°, the reaction mixture was warmed on a steam-bath for 2 hr., cooled and poured into ice-water. Upon vigorous stirring, a yellow, viscous sirup formed. The water was decanted and the sirup taken up in warm acetone. After filtration from a small residue, the filtrate was concentrated to a solid *in vacuo*. This residue was heated with 500 ml. of boiling water for 30 minutes, filtered and the precipitate taken up in hot ethanol from which it crystallized as knobby clusters. The precipitate was filtered, washed with benzene and dried (6.2 g.), m.p. 153–160°. Elemental analyses indicated a contamination of this product with approximately 20% of triphenylcarbinol. Purification was accomplished by two recrystallizations from benzene–alcohol followed, finally, by recrystallization from absolute alcohol to give needles, m.p. 155° (to a viscous sirup which clears at 165°). Triphenylcarbinol was isolated from the mother liquors.

Anal. Calcd. for $C_{29}H_{28}N_2O_6$: C, 69.60; H, 5.60; N, 5.60. Found: C, 69.46; H, 5.74; N, 5.52.

Conversion of IV to 1-β-D-Arabinofuranosylthymine (Spongothymidine).—Unrecrystallized IV (2.0 g.) in 35 ml. of cold, anhydrous pyridine was treated with methanesulfonyl chloride (0.8 ml.) and kept at 10° for 24 hr. One milliliter

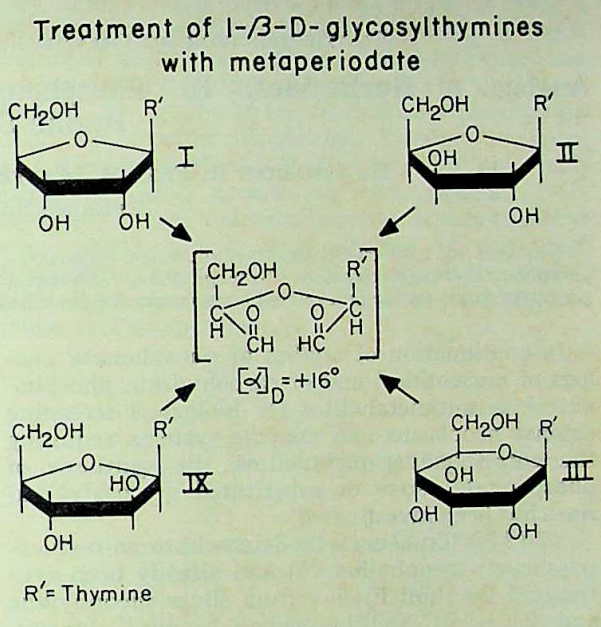

Fig. 2.

of water was then added to the cold mixture, and after 1 hr. the reaction mixture was poured into stirred ice-water. A precipitate formed which was washed well with water and dried.[19] This solid was added to 50 ml. of 95% methanol saturated with ammonia and let stand overnight at room temperature.

The solution was concentrated under vacuum, treated with water and acidified with sulfuric acid to *p*H 1 and refluxed for 2 hr. Upon cooling, triphenylcarbinol was removed by filtration and the filtrate made alkaline with barium hydroxide. The precipitated barium sulfate was removed and the filtrate treated with carbon dioxide (to *p*H 5). After filtration from barium salts, the filtrate was concentrated to approximately 10 ml. whereupon more inorganic salts precipitated. The filtrate obtained by separation from inorganic material was concentrated to 3 ml. Upon cooling, the nucleoside IX precipitated as clusters of needles, 0.15 g., m.p. 238–242° (undepressed by admixture with authentic spongothymidine). An additional 0.06 g. was obtained from the mother liquor. Recrystallization from 25% ethanol did not alter the melting point.

Anal. Calcd. for $C_{10}H_{14}N_2O_6$: C, 46.50; H, 5.46; N, 10.85. Found: C, 46.54; H, 5.62; N, 10.80.

The ultraviolet absorption spectrum of this product in aqueous solutions of various *p*H values (including the high alkaline range[15,20] was identical to that previously reported for spongothymidine.[15] As with spongothymidine,[14] IX consumed one mole of metaperiodate per mole without the liberation of formic acid. When IX was treated with metaperiodate in the same manner as were I, II and III,[2] a similar rotation ([α]D +16°) was obtained for the dialdehyde solution produced (see Fig. 2). The optical rotational prop-

(17) All melting points are uncorrected. Analyses performed by Dr. J. F. Alicino, Metuchen, N. J.

(18) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **104**, 385 (1934); **108**, 419 (1934).

(19) This precipitate melts at approximately 100° and gives a low sulfur analysis (theory, 5.54: found, 1.48) indicating, at best, only 25% of mesylated product. A larger excess of methanesulfonyl chloride does not seem to improve the sulfur content of the crude product.

(20) The spectrum of spongothymidine in the high alkaline range (*p*H 12–14) shows large shifts,[15] far greater than those noted for I or

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erties of the natural and the synthetic nucleoside were also similar[21]:

	$[\alpha]_{3350}$ Å.	$[\alpha]_{5461}$ Å.
Spongothymidine	+94°[22]	+111°
1-β-D-Arabinofuranosylthymine	+93°	+110°

(21) As in Part I of this series, optical rotations were determined with a polarimetric unit model D attachment to a Beckman model DU spectrophotometer. Concentrations were 0.5 g./100 ml. of aqueous solution, temperature 24°.

(22) Bergmann and Feeney[14] give $[\alpha]_D$ +80° (in 8% sodium hydroxide) and $[\alpha]_D$ +92° (in pyridine).

NEW YORK 21, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

Analogs of Nucleotides. II. Phosphonate Esters of Ribose and Glucopyranosyl Purine Derivatives[1]

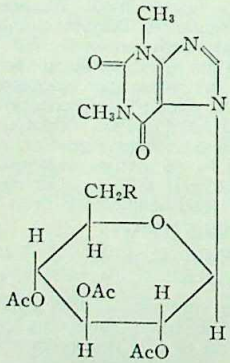
BY JEKISHAN R. PARIKH, MANFRED E. WOLFF AND ALFRED BURGER

RECEIVED NOVEMBER 29, 1956

Syntheses of 1,2,3-tri-*O*-acetyl-D-ribofuranose-5-deoxy-5-(diethyl phosphonate), 7-[2,3,4-tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-theophylline, 6-benzamido-9-[2,3,4-tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-purine and related compounds are described.

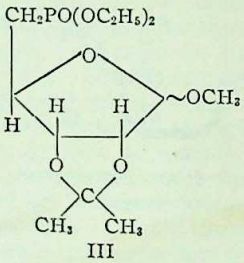
In continuation of studies of phosphonate analogs of nucleotides[2] and of carbohydrate phosphonates[3] as antimetabolites for biological screening against neoplasms and enzyme systems requiring the corresponding metabolites, the synthesis of phosphonate esters of substituted glycosidyl purines has been investigated.

7-(2,3,4-Tri-*O*-acetyl-6-deoxy-6-bromo-D-glucopyranosyl)-theophylline (I) had already been synthesized by Emil Fischer from silver theophylline and 2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-D-glucopyranosyl bromide.[4] It has now been found to undergo a Michaelis–Arbuzov reaction with triethyl phosphite, 7-[2,3,4-tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-theophylline (II) being formed in 40% yield. In attempts to introduce a 2,3-di-*O*-acetyl-5-deoxy-5-(diethyl phosphonate)-D-ribofuranosyl group into the 7-position of theophylline

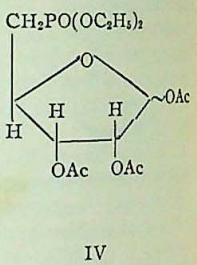


I, R = Br
II, R = $PO(OC_2H_5)_2$

methyl 2,3-isopropylidene-5-deoxy-5-iodo-D-ribofuranoside[5] was heated with triethyl phosphite, and the resulting methyl 2,3-isopropylidene-5-deoxy-5-(diethyl phosphonate)-D-ribofuranoside (III) was hydrolyzed and acetylated to 1,2,3-tri-*O*-acetyl-D-ribofuranose-5-deoxy-5-(diethyl phosphonate) (IV).

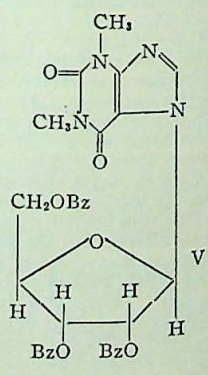


III



IV

The amorphous 1-chloro derivative obtained by treating IV with ethereal hydrogen chloride at 0° could not be condensed with either silver theophylline, or with 6-chloropurine mercuri chloride, although the reactivity of the 1-chlorine atom in a highly substituted ribose derivative was demonstrated by condensing 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[6] with silver theophylline to yield 7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-theophylline (V).



V

Following the model experiment leading to II,

(1) This work was supported by a grant-in-aid from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

(2) J. R. Parikh and A. Burger, THIS JOURNAL, **77**, 2386 (1955).

(3) B. S. Griffin and A. Burger, *ibid.*, **78**, 2336 (1956).

(4) E. Fischer, B. Helferich and P. Ostmann, *Ber.*, **53**, 873 (1920). The body of evidence in the literature suggests that the products from the condensation of purine metal adducts with 1-halogenoglucose and -ribose derivatives assume the β-configuration. It is likely, therefore, that I as well as other glycosidyl purines so designated in this article are β.

(5) P. A. Levene and E. T. Stiller, *J. Biol. Chem.*, **104**, 299 (1934).

(6) H. M. Kissman, C. Pidaks and B. R. Baker, THIS JOURNAL, **77**, 18 (1955).

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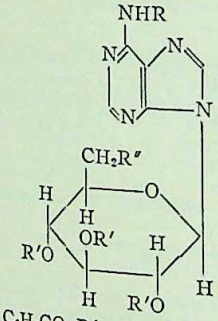
the mercuri chloride salt of 6-benzamidopurine[7] was condensed with 2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-α-D-glucopyranosyl bromide in xylene medium, and 24% of 6-benzamido-9-(2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VI) was obtained as the main reaction product. The assignment of position 9 to the glucosidic moiety in the adenine system is based on observations about glycosidation of the chloromercuri salt of 6-benzamidopurine[7,8]; in addition, 6-benzamidopurine exhibits characteristic absorption bands at 287 and 230 mμ, and VI at 281 and 235 mμ, respectively, while substitution in the 7-position of the purine system is known to cause a change in this pattern.

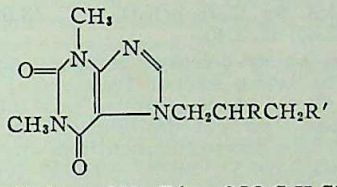
Two other compounds were also elaborated in appreciable quantities from the 6-bromoglucosidation of 6-benzamidopurine. One of them was recognized as 2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl chloride presumably formed by exchange of the 1-bromine atom by chlorine from the mercuri chloride salt, and probably accompanied by inversion at C-1.[9] Although its physical appearance, solubility and melting point were extremely similar to those of the isomeric 2,3,4-tri-*O*-acetyl-6-deoxy-6-chloro-α-D-glucopyranosyl bromide[10] the two isomers differ in their optical rotation. The structure of the 1-chloro-6-bromo derivative was confirmed by conversion to 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranose.[4]



VI, R = C_6H_5CO, R′ = Ac, R″ = Br
VII, R = H, R′ = Ac, R″ = Br
VIII, R = R′ = H, R″ = Br
IX, R = C_6H_5CO, R′ = Ac, R″ = $PO(OC_2H_5)_2$

The benzamido group of VI was unusually labile. When the compound was heated with ethanolic picric acid solution, 6-amino-9-(2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VII) picrate was formed. Treatment of this salt with Dowex No. 1 anion-exchange resin[7] followed by alkalinization removed both the picrate ion and the acetyl groups and led to crystalline 6-amino-9-(6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VIII). Heating of VI with triethyl phosphite furnished 6-benzamido-9-[2,3,4-tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-purine (IX). Experiments to hydrolyze its amide and ester groups with dilute ammonium hydroxide or methanolic sodium methoxide did not give the expected product. When VI was heated with ethyl diphenyl phosphite,[3,11] a material which contained neither phosphorus nor halogen was obtained.

Another phase of this problem concerned the preparation of starting materials for the synthesis of purinylalkanolphosphonate esters. In one series of experiments, 1-(7-theophyllinyl)-2,3-propanediol[12] was tosylated selectively to give 1-(7-theophyllinyl)-2-hydroxypropyl-3-(*p*-toluenesulfonate) (X). The 3-iodide derivative XI prepared from X failed to enter a Michaelis–Arbuzov reaction which confirms the findings of Preis, *et al.*,[13] who could not prepare alkyl β-hydroxyphosphonates by analogous routes. Protection of the alcoholic hydroxyl group in XI did not alter this picture. Attempts to secure 1-(7-theophyllinyl)-2-acetoxypropanol-3 by tritylating the diol, acetylating the resulting 1-(7-theophyllinyl)-2-hydroxy-3-propyl triphenylmethyl ether (XII), and hydrogenolyzing off the trityl group failed because the protecting acetyl group of XIII was lost under the conditions required for the removal of the trityl group.



X, R = OH, R′ = $OSO_2C_6H_4CH_3$
XI, R = OH, R′ = I
XII, R = OH, R′ = $OC(C_6H_5)_3$
XIII, R = OAc, R′ = $OC(C_6H_5)_3$

Condensation of adenine with 1-chloro-2,3-propanediol in alkaline solution furnished an amorphous product which was identified as 1-(6-amino-*x*-purinyl)-2,3-propanediol by analysis of its dipicrate. Since the compound did not yield a satisfactory product on tosylation it was not investigated further.

Experimental[14]

7-[2,3,4-Tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-theophylline (II).—A mixture of 5.31 g. (0.01 mole) of 7-(2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-D-glucopyranosyl)-theophylline (I)[4] and 6.64 g. (0.04 mole) of triethyl phosphite was heated at 165° for 4.5 hours, the yellow product was freed of excess triethyl phosphite under reduced pressure at 95°, and the oily residue washed with petroleum ether. It was triturated with 30 ml. of ether, and 2.35 g. (40%) of long colorless needles was filtered. After recrystallization from benzene–isoöctane, they exhibited m.p. 167–168°, $[\alpha]^{27}D$ −10.40° (chloroform, *c* 1.942).

Anal. Calcd. for $C_{23}H_{33}N_4O_{12}P$: C, 46.93; H, 5.65. Found: C, 47.30; H, 5.66.

7-(2,3,4-Tri-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranosyl)-theophylline.—A solution of 1.35 g. (2.5 mmoles) of I, 0.75 g. (5 mmoles) of sodium iodide and 0.2 g. of cuprous iodide in 30 ml. of anhydrous acetone was refluxed for 24 hours, and the solvent was removed under reduced pressure. The resinous residue was dissolved in 25 ml. of chloroform, filtered and washed with 5-ml. portions of water, 5% sodium thiosulfate solution and water. The solution was dried over sodium sulfate and the solvent evaporated under reduced

(7) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 1650 (1951).
(8) B. R. Baker R. E. Schaub and H. M. Kissman, *ibid.*, **77**, 5911 (1955).
(9) H. H. Schlubach, *Ber.*, **59**, 840 (1926), observed that α-bromoacetoglucose reacts with silver chloride to give β-chloroacetoglucose.
(10) B. Helferich and H. Bredereck, *ibid.*, **60**, 2000 (1927).
(11) A. E. Arbuzov and L. V. Nesterov, *Doklady Akad. Nauk, S.S.S.R.*, **92**, 57 (1953).
(12) P. V. Maney, J. W. Jones, E. G. Gross and H. M. Korns, *J. Am. Pharm. Assoc.*, **35**, 266 (1946).
(13) S. Preis, T. C. Myers and E. V. Jensen, THIS JOURNAL, **77**, 6225 (1955).
(14) All melting points are corrected. Microanalyses by the Misses

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pressure. The colorless crude residue weighed 1.5 g. and crystallized from 20 ml. of absolute ethanol, m.p. 197° after softening at 125° and partially melting at 135–137°.

Anal. Calcd. for $C_{19}H_{23}IN_4O_9$: C, 39.45; H, 4.00. Found: C, 39.50; H, 4.21.

6-Benzamido-9-(2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VI).—A mixture of 15.0 g. (31.6 mmoles) of chloromercuri 6-benzamidopurine,[7,15] 18.0 g. (41.7 mmoles) of I, 12 g. of Celite and 500 ml. of dry xylene was stirred and refluxed for 1 hour, filtered and the solid washed with hot xylene. The filtrate on cooling deposited 14.5 g. of colorless crystals, m.p. 100–135°. Three recrystallizations from 40 ml. of absolute ethanol yielded 4.45 g. (24%) of material, m.p. 213–214°; $[\alpha]^{27}D$ −23.64° (chloroform, *c* 1.903); λ_{max} 0.01 *N* HCl 281 mμ (ε 22,699.6), λ_{min} 0.01 *N* HCl 235 mμ (ε 10,303.6).

Anal. Calcd. for $C_{24}H_{24}BrN_5O_8 \cdot H_2O$: C, 47.37; H, 4.30. Found: C, 47.74; H, 4.34.

Water of hydration was removed by drying at 139° (1 mm.) for 24 hours. The anhydrous material melted at 214–215°.

Anal. Calcd. for $C_{24}H_{24}BrN_5O_8$: C, 48.82; H, 4.09; N, 11.86. Found: C, 48.85; H, 4.18; N, 12.08.

The yellow picrate crystallized from ice-cold ethanol, m.p. 185–186° dec.

Anal. Calcd. for $C_{30}H_{27}BrN_8O_{15}$: C, 43.96; H, 3.32. Found: C, 43.85; H, 3.40.

2,3,4-Tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl Chloride.—The xylene solution (*vide supra*) from which VI had been filtered was concentrated to 30 ml. and diluted with petroleum ether. It deposited 1.1 g. of colorless needles which after recrystallization from absolute ethanol melted at 165.5–166.5°, $[\alpha]^{28}D$ +170.1° (chloroform, *c* 1.19).

Anal. Calcd. for $C_{12}H_{16}BrClO_7$: C, 37.18; H, 4.16; halogen, 25.89. Found: C, 37.36; H, 4.20; halogen, 24.35.

Treatment of 0.3 g. of this substance with a mixture of 0.16 g. of silver acetate and 5 ml. of glacial acetic acid at 95° for 30 minutes, filtration from silver chloride, evaporation of the solvent and dilution with 30 ml. of water yielded 0.26 g. of colorless needles which after recrystallization from ethanol melted at 126–126.5°. A mixture melting point with an authentic sample[4] of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranose showed no depression.

The ethanolic mother liquors from the recrystallization of the 14.5 g. of crude VI described above gave on concentration and cooling 1.6 g. of buff-colored crystals which were recrystallized from absolute ethanol, m.p. 203–204°. The compound contained halogen, reacted rapidly with silver nitrate, and showed *p*H 5.

Anal. Found: C, 24.6; H, 3.1.

6-Amino-9-(2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VII).—When VI was treated with a hot ethanolic solution of picric acid, the picrate of VII crystallized out, m.p. 231–232° dec.

Anal. Calcd. for $C_{23}H_{23}BrN_8O_{14}$: C, 38.61; H, 3.24. Found: C, 38.65; H, 3.26.

6-Amino-9-(6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VIII).—Removal of picrate ion from the picrate of VII with Dowex No. 1 anion-exchange resin (in the chloride form) in 50% aqueous acetone[7] followed by alkalinization with 10% ammonium hydroxide yielded colorless crystals which melted at 214–216° dec. after sintering at 200°.

Anal. Calcd. for $C_{11}H_{14}BrN_5O_4$: C, 36.67; H, 3.91. Found: C, 36.28; H, 4.10.

The yellow picrate crystallized from ethanol, m.p. 204–205° dec.

Anal. Calcd. for $C_{17}H_{17}BrN_8O_{11}$: C, 34.64; H, 2.90. Found: C, 34.27; H, 3.00.

6-Benzamido-9-[2,3,4-tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-purine (IX).—A mixture of 1.9 g. (3.2 mmoles) of VI and 2.65 g. (16 mmoles) of triethyl phosphite was heated at 160–165° for five hours and excess triethyl phosphite was distilled from the orange-red solution under vacuum. The oily residue was washed with petroleum ether, dissolved in 15 ml. of absolute ethanol, cleared with Norite and allowed to crystallize after addition of ether. The mother liquor was evaporated, and the residue crystallized from water. A total of 0.8 g. (45%) of material of m.p. 200–201° was obtained. In another run, the product was isolated in comparable yield by chromatography of the oily material over activated alumina.

Anal. Calcd. for $C_{28}H_{34}N_5O_{11}P \cdot H_2O$: C, 50.52; H, 5.45; N, 10.52; P, 4.65. Found: C, 50.05; H, 5.58; N, 10.28; P, 5.29.

A solution of 0.8 g. of IX in 15 ml. of 1:1 aqueous acetone was treated with ammonium hydroxide to *p*H 9 and allowed to stand at 6° for 16 hours. The solvents were evaporated *in vacuo* and the resinous residue dissolved in chloroform. The chloroform solution was washed with water, dried and evaporated. The residue crystallized from water as shiny plates, m.p. 112–113°.

Anal. Found: C, 50.47; H, 5.31; N, 9.85; P, 5.08.

Action of Ethyl Diphenyl Phosphite on VI.—When VI was heated with a fourfold excess of ethyl diphenyl phosphite[4,11] at 165°, the reaction mixture turned dark within 2.5 hours and decomposed on further heating. Since warming at 100° did not furnish a homogeneous solution even after 190 hours, the reactants were heated at 155° for 3 hours, in another run. The resulting dark yellow solution was heated at 131° for another 48 hours, and now the clear brown mixture no longer contained bromine. It was taken up in isopropyl ether, and a residual insoluble gum was triturated with ether until it became an amorphous solid. This material was chromatographed over alumina in benzene–chloroform. The main oily fraction became amorphous on treatment with isopropyl ether and ether. It contained neither halogen nor phosphorus and decomposed at 70°.

Anal. Found: C, 52.07; H, 4.78.

Methyl 2,3-Isopropylidene-5-deoxy-5-(diethyl phosphonate-D-ribofuranoside (III).—A mixture of 41.1 g. (0.131 mole) of methyl 2,3-isopropylidene-5-deoxy-5-iodo-D-ribofuranoside[5] and 120 g. of triethyl phosphite was heated at 160–170° for ten hours and fractionated. After a forerun consisting essentially of diethyl ethylphosphonate, the product distilled as a pale yellow sirup, b.p. 128° (0.05 mm.), $n^{30}D$ 1.451; $[\alpha]^{30}D$ −48.6° (*c* 2.984, in acetone). The yield was 31%.

Anal. Calcd. for $C_{13}H_{25}O_7P$: C, 48.14; H, 7.77. Found: C, 47.42; H, 7.81.

When, instead of triethyl phosphite, ethyl diphenyl phosphite[3,11] was used and the reaction mixture was heated as above but for 120 hours, distillation furnished an oil, b.p. 159–160° (0.07 mm.), as the main product while the ribosidic material decomposed. The composition of the oily distillate corresponds to that of diphenyl ethylphosphonate.[11]

Anal. Calcd. for $C_{14}H_{15}O_3P$: C, 64.12; H, 5.78. Found: C, 63.88; H, 5.97.

1,2,3-Tri-*O*-acetyl-D-ribofuranose-5-deoxy-5-(diethyl phosphonate) (IV).—A solution of 5.0 g. (0.0154 mole) of methyl 2,3-isopropylidene-5-deoxy-5-(diethyl phosphonate)-D-ribofuranoside in 100 ml. of 0.05 *N* aqueous ethanolic (1:1) hydrochloric acid was refluxed for three hours, 3 ml. of pyridine was added, and the solvents were removed by co-distillation with benzene under reduced pressure. The residual oil strongly reduced Fehling solution and formed a sirupy diethyl mercaptal.[16] It was dissolved in 100 ml. of dry pyridine, cooled to 0°, and allowed to stand with 40 ml. of acetic anhydride for 24 hours. Excess acetic anhydride was decomposed carefully with water, the solution was diluted to 500 ml. and extracted repeatedly with chloroform. The chloroform extract was washed with 20% sulfuric acid, sodium carbonate solution and water, dried and distilled.

(15) 6-Benzamidopurine was prepared by a modification of the directions of A. Kossel, *Z. physiol. Chem.*, **12**, 241 (1888), by heating adenine with benzoic anhydride at 180° for 30 minutes. The yield was 83%, m.p. 242–244° dec.; λ_{max} 0.01 *N* HCl 287 mμ (ε 12,429), λ_{min} 0.01 *N* HCl 230 mμ (ε 5812).

(16) Additional evidence for the hydrolysis of the methyl ribofuranoside linkage of III may be gathered from the fact that G. W. Kenner, C. W. Taylor and A. R. Todd, *J. Chem. Soc.*, 1620 (1949), had hydrolyzed methyl 2,3-isopropylidene-5-benzyl-D-ribofuranoside under the same conditions. Again, a selective hydrolysis of the isopropylidene group in methyl 2,3-isopropylidene-5-deoxy-D-ribofuranoside could be achieved only in 70% methanolic dilute sulfuric acid [C. H. Shunk, R. Spoerri, J. Haldar Folkers, THIS JOURNAL, **77**, 2210 (1955)].

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The product (3.8 g., 62%) was a pale yellow oil, b.p. 165–168° (0.08 mm.).

Anal. Calcd. for $C_{15}H_{25}O_{10}P$: C, 45.48; H, 6.36. Found: C, 44.49; H, 6.29.

Treatment of IV with ethereal hydrogen chloride at 0° for 48 hours and thorough removal of the volatile reagents yielded a colorless amorphous product which gave a strong test for halogen and readily precipitated ethanolic silver nitrate solution.

7-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-theophylline (V).—A solution of 0.02 mole of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[6] in 35 ml. of anhydrous benzene was added to a stirred suspension of 6.98 g. (0.0242 mole) of silver theophylline in 50 ml. of dry xylene, the benzene was distilled off and the mixture stirred and refluxed for 3 hours. Silver chloride was filtered and the filtrate diluted with 500 ml. of low-boiling petroleum ether. The precipitated colorless soft needles (yield 25%) were recrystallized from isopropyl ether, m.p. 75° dec.; $[\alpha]^{22}D$ −22.1° (*c* 3.63, acetone).

Anal. Calcd. for $C_{33}H_{28}N_4O_9$: C, 63.45; H, 4.52. Found: C, 63.72; H, 4.35.

1-(7-Theophyllinyl)-2-hydroxypropyl-3-*p*-toluenesulfonate (X).—A solution of 85.0 g. (0.45 mole) of *p*-toluenesulfonyl chloride in 200 ml. of dry pyridine was added, over a period of 6 hours, to a stirred, ice-cold solution of 113.5 g. (0.45 mole) of 1-(7-theophyllinyl)-2,3-propanediol[12] in 300 ml. of dry pyridine and 250 ml. of dry ethylene dichloride. After stirring another 90 minutes at 0° and standing overnight, the mixture was treated carefully with 50 ml. of water, extracted with 200 ml. of water, and distilled under reduced pressure, moisture and some pyridine being removed by co-distillation with toluene. The semi-solid residue was taken up in 300 ml. of ethanol, 100 ml. of water was added, and the resulting colorless crystals (83.5 g., 45%) were collected. Recrystallization from ethanol gave a sample, m.p. 134–135°.

Anal. Calcd. for $C_{17}H_{20}N_4O_6S$: C, 49.99; H, 4.93. Found: C, 49.95; H, 5.17.

1-(7-Theophyllinyl)-3-iodo-2-propanol (XI).—This compound was prepared from X by heating with sodium iodide in acetone solution at 100° for 2 hours, and working up the mixture. It crystallized from absolute ethanol, m.p. 165–166°. The yield was 73%.

Anal. Calcd. for $C_{10}H_{13}IN_4O_3$: C, 32.98; H, 3.60. Found: C, 33.13; H, 3.67.

1-(7-Theophyllinyl)-2-acetoxypropyl-3-*p*-toluenesulfonate.—Acetylation of XI with acetic anhydride in excess dry pyridine at 0°, standing at 30° for 24 hours and decomposition with water, yielded 75% of a colorless product which was recrystallized from ethanol, m.p. 173–175°.

Anal. Calcd. for $C_{19}H_{22}N_4O_7S$: C, 50.63; H, 4.92. Found: C, 50.32; H, 5.11.

1-(7-Theophyllinyl)-2-acetoxy-3-iodopropane.—This compound was prepared in 54% yield from 1-(7-theophyllinyl)-2-acetoxypropyl-3-*p*-toluenesulfonate as described for XI above. The colorless plates (from ethanol) melted at 177–179° dec.

Anal. Calcd. for $C_{12}H_{15}IN_4O_4$: C, 35.48; H, 3.72. Found: C, 35.30; H, 3.68.

1-(7-Theophyllinyl)-2-hydroxy-3-propyl Triphenylmethyl Ether (XII).—A solution of 2.09 g. (0.01 mole) of 1-(7-theophyllinyl)-2,3-propanediol[12] and 2.79 g. (0.01 mole) of triphenylchloromethane in 20 ml. of dry pyridine was refluxed for 30 minutes, cooled and diluted with water. The gummy precipitate was washed with water, dried azeotropically with benzene, and crystallized from ethanol–pentane. The shiny plates melted at 174–176°.

Anal. Calcd. for $C_{29}H_{28}N_4O_4$: C, 70.14; H, 5.68. Found: C, 70.30; H, 5.86.

Acetylation with acetic anhydride in hot pyridine solution for 30 minutes gave **1-(7-theophyllinyl)-2-acetoxy-3-propyl triphenylmethyl ether** (XIII) which crystallized from ethanol, m.p. 169–171°.

Anal. Calcd. for $C_{31}H_{30}N_4O_5$: C, 69.13; H, 5.97. Found: C, 69.19; H, 5.85.

1-(6-Amino-x-purinyl)-2,3-propanediol Dipicrate.—A solution of 5.40 g. (0.04 mole) of adenine in 200 ml. of 0.2 *N* sodium hydroxide was treated with 4.42 g. (0.04 mole) of 1-chloro-2,3-propanediol, and the mixture was refluxed for five hours. The solvent was removed *in vacuo*, the residue was taken up in boiling methanol and filtered from sodium chloride. An amorphous precipitate was obtained by adding ether to the filtrate. It was converted to the yellow dipicrate which was recrystallized from a large volume of ethanol and did not melt below 300°.

Anal. Calcd. for $C_{20}H_{17}N_{11}O_{16}$: C, 35.99; H, 2.57. Found: C, 35.96; H, 2.42.

1,3-Bis-(7-theophyllinyl)-propanol-2.—To a suspension of 14.35 g. (0.05 mole) of dry silver theophylline in 350 ml. of dry dimethylformamide was added 6.85 g. (0.05 mole) of epibromohydrin. The mixture was stirred and heated at 130° but stirring had to be interrupted when a thick yellow precipitate separated. After standing for one hour, stirring and heating were resumed and continued for 4 hours. The granular precipitate was filtered, the solvent removed under reduced pressure, and the tan solid residue washed with cold acetone and ethanol. It was dissolved in dilute acid, reprecipitated with ammonium hydroxide, and weighed 4.5 g. (42%). Recrystallization from water with the aid of Norite gave colorless needles, m.p. 273–274°.

Anal. Calcd. for $C_{17}H_{20}N_8O_5$: C, 49.03; H, 4.84. Found: C, 49.09; H, 5.04.

(7-Theophyllinylmethyl)-oxirane.—When the reaction between silver theophylline and epibromohydrin described above was conducted in boiling xylene for 24 hours and the solvent was evaporated, a small amount of a solid could be extracted from the residue with boiling ligroin. The colorless product from the ligroin extract was recrystallized from ligroin–ethanol, m.p. 160–162°.

Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12. Found: C, 50.33; H, 5.00.

CHARLOTTESVILLE, VIRGINIA

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[CONTRIBUTION FROM THE MCCOLLUM-PRATT INSTITUTE, THE JOHNS HOPKINS UNIVERSITY]

Yeast Alcohol Dehydrogenase. III. Relation of Alcohol Structure to Activity[1]

BY JAN VAN EYS AND NATHAN O. KAPLAN

RECEIVED NOVEMBER 2, 1956

The specificity of yeast alcohol dehydrogenase toward alcohols has been investigated. It was concluded that three factors determine specificity: (1) nucleophilic character of the alcohol, (2) molecular dimensions of the alcohol, and (3) orientation of the alcohol molecule. The known stereospecificity of the enzyme is also apparent in the oxidation of truly asymmetric substrates. The absolute configuration of the suitable substrates is that of the L-series. The enzyme will serve as a lactic dehydrogenase, with ADP as an activator; this oxidation is specific for D(−)-lactic acid. The steric limitations of the alcohol oxidation are at least partially determined by the coenzyme used. The implications of these findings are discussed.

Introduction

The alcohol specificity of yeast ADH[2] has been studied by previous investigators.[3,4] However, no general conclusion was drawn from the structure of those alcohols which would function as a substrate for the enzyme. The only conclusion reached was that the enzyme is not specific for ethanol, but rather that many primary and secondary alcohols will be oxidized. It has recently been demonstrated that the oxidation of alcohol by yeast ADH is stereospecific with regard to ethanol.[5,6]

Previous work in this laboratory has shown that only one ethanol appears to be oxidized at a time,[7] even though four coenzyme molecules are bound.[7,8] In a search for explanations of this lack of stoichiometry an attempt was made to correlate the structure of the alcohol with its ability to serve as a substrate for yeast ADH. It was found that three factors govern the effectiveness of a given substrate: (1) the molecular dimensions of the substrate in the vicinity of the carbinol grouping; (2) the nucleophilic character of the alcohol; and (3) the orientation of the substrate with respect to the enzyme. In addition, data will be presented which indicate that the absolute configuration of the alcohol as oxidized is of the L-series.

Experimental

Enzymes.—Twice recrystallized yeast ADH was obtained commercially.[9] Crystalline beef heart LDH[9] was used as the L(+)-lactic acid specific lactic dehydrogenase; an ammonium sulfate cut between 50 and 75% saturation from a sonicate of *Leuconostoc mesenteroides* cells served as a source of D(−)-lactic acid specific LDH.[10]

Coenzymes.—DPN and ADP were obtained from the Pabst Laboratories. The coenzyme analogs were obtained by the action of pig brain DPNase on DPN in the presence of the appropriate pyridine base as described for the isonicotinic acid hydrazide[11] and acetylpyridine[12] analogs of DPN. DPNH was prepared enzymatically from DPN as described[11] previously.

Substrates.—All alcohols, when obtained as reagent grade, were used without prior purification. Those which were obtained in practical grade were purified by fractional distillation. Calcium D(−)-lactate and calcium L(+)-lactate were obtained from the California Foundation for Biochemical Research. Their purity was checked with the appropriate LDH, using acetylpyridine-DPN as coenzyme.[12] D(−)-Lactate contained less than 0.1% of the other isomer, but L(+)-lactic acid was contaminated with at least 5% of its enantiomorph. 2-Octanol was resolved *via* the brucine salt of the monohydrogenphthalates.[14]

Rate Determinations.—Rates were determined in a Beckman spectrophotometer, model DU, at the appropriate absorption maximum of the coenzyme used.[12,15] Rates were defined as the increase in optical density at the absorption maximum between the 15 and 30 second interval after starting the reaction with enzyme.

Results

Substrate Specificity

The Effect of Increasing Chain Length.—All primary alcohols tested will serve as a substrate for yeast ADH. In the straight chain homologous series, the reactivity decreases with increasing chain length. The only exception is methanol, which will be discussed below. The decrease in activity is not greater than can be expected from the decreased electronegativity of the carbinol grouping. Hine and Hine[16] have determined that the "acidity" of alcohols in a homologous series is approximately linearly related to the pK_a of the corresponding fatty acids. Thus, if one plots the logarithm of the relative rate of the straight chain alcohols *versus* the chain length, a straight line relationship should be obtained if the relative activity is due solely to the apparent dissociation ability of the alcohol. This indeed appears to be the case (Fig. 1). Variations of the concentration of the alcohols did not change the order of activity of the substrates.

(1) Contribution no. 172 of the McCollum-Pratt Institute. Supported in parts by grants from the American Cancer Society as recommended by the Committee on Growth of the National Research Council, and the National Cancer Institute of the National Institutes of Health (Grant No. 2347-C).

(2) Abbreviations used in this paper are: ADH, alcohol dehydrogenase; D-LDH, D(−)-lactic acid specific lactic dehydrogenase; L-LDH, L(+)-lactic acid specific lactic dehydrogenase; ADP, adenosine 5′-pyrophosphate; DPN and DPNH, oxidized and reduced diphosphopyridine dinucleotide, resp.; acetylpyridine-DPN and pyridine-3-aldehyde-DPN, the 3-acetylpyridine and pyridine-3-aldehyde analogs of DPN, resp.; and tris, trihydroxymethylaminomethane.

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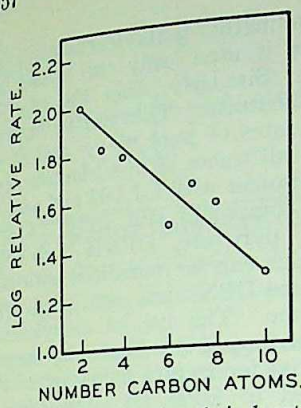

Fig. 1.—The effect of increasing chain length on the rate of oxidation: alcohol concentration 2.5×10^{-3} *M*, tris buffer, 0.05 *M*, *p*H 9.3, DPN 3.5×10^{-4} *M*. The value for amyl alcohol is not given, since the alcohol contained an inhibitor, which even on repeated fractional distillation could not be removed completely.

Effect of Steric Hindrance.—If the dissociation ability of the alcohol were the only determining step, compounds like chloroethanol or other alcohols with an electron attracting group should be better substrates than the corresponding primary alcohols. But this is not the case, chloroethanol is a poorer substrate than ethanol. The influence of substitution is indicated in Table I. It is clear that any substituent regardless of its electron donating or attracting ability, decreases the rate. That this effect is due to steric hindrance is best illustrated by the phenyl-substituted alcohols. This is shown in Fig. 2. Whereas benzyl alcohol and 2-phenylethanol are relatively poor substrates, 3-phenyl-1-propanol is oxidized at a quite rapid rate.

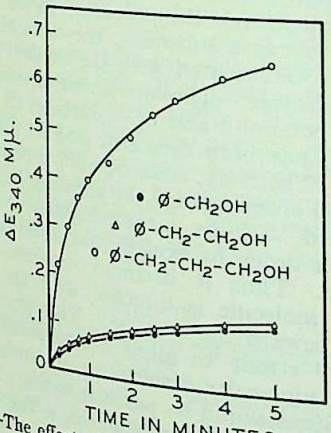

Fig. 2.—The effect of phenyl substitution on the rate of alcohol oxidation: substrate concentration 5×10^{-3} *M*, in tris buffer, *p*H 9.3, 0.05 *M*, DPN concentration 1.5×10^{-4} *M*, yeast ADH 250 mcg.

Effect of Orientation.—A third factor was found to play a role in the alcohol specificity. If steric hindrance were, together with nucleophilic character, the solely decisive factor, a large molecule would at all times be oxidized more slowly than a small molecule. However, *n*-decanol is not slower, relative to ethanol, than can be expected from the inductive effect of the sidechain. Therefore the

Table I

The Influence of Substitution on the Ability of Alcohols to Serve as Substrate for Yeast Alcohol Dehydrogenase

Alcohol[a]	Relative rate	Alcohol[a]	Relative rate
Methanol	8	Diethylamino-ethanol	0
Ethanol[b]	1000	2-Chloroethanol	8
n-Alkylcarbinols	[c]	Isobutyl alcohol	4
Methyl-*n*-alkyl carbinols	[d]	Isoamyl alcohol	4
Ethylene glycol	1.2	3-Hexanol	0
Glycerol	7	*t*-Butyl alcohol	0
Erythritol	2	D(−)-Lactic acid	3
L-Arabitol	1.5	Glycolic acid	17
2-Aminoethanol	22	DL-β-Hydroxy-butyric acid[e]	1
Dimethylamino-ethanol	0		

[a] The alcohols were tested at a concentration of 5.0×10^{-3} *M*, in tris buffer, 0.05 *M*, *p*H 9.3, DPN 1.5×10^{-4} *M*. Slow rates were checked with ADP as cofactor at a concentration of 7.0×10^{-3} *M*. [b] Arbitrarily assigned 1000. [c] See Fig. 1. [d] See Fig. 3. [e] Tested at double concentration.

"size" of ethanol and *n*-decanol appears to be the same for the enzyme. This can only be the case if both are oriented in such a way that only the carbinol moiety will attack the enzyme. This is even more clearly illustrated in the methyl-*n*-alkylcarbinol series. Even though isopropyl alcohol is relatively slowly oxidized, methylpropylcarbinol reacts faster although the dimensions of the latter are greater and the acidity of the carbinol is less. If one plots the logarithm of the relative rate of these secondary carbinols *versus* the chain length, a maximum is observed at 5 carbons (Fig. 3). The expected rate, assuming no

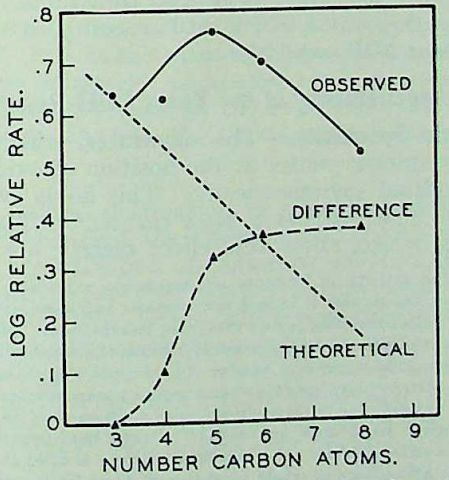

Fig. 3.—The effect of increasing chain length on the rate of oxidation of methyl-*n*-alkyl-carbinols: the concentration of alcohols was 2.5×10^{-3} *M* of the active isomer. The DL-isomers were employed for the alcohols of chain length of four carbons or more. Tris buffer, *p*H 9.3, 0.05 *M*, DPN 3.5×10^{-4} *M*. The theoretical rate was determined from the equation

$$\log \text{relative rate} = -0.09 (\text{no. carbon atoms}) + 0.88$$

This relationship was derived from the data in Fig. 1. The difference curve describes the deviation of the observed values from the theoretical relationship, and is proposed to

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steric hindrance and a decrease in nucleophilic character similar to the *n*-alkylcarbinols, would give a decrease of the rate with increasing chain length. The difference between expected and observed rates shows that an increase occurs up to about six carbon chain length (Fig. 3). This can be interpreted as an indication of orientation of the molecule. Similarly, lactic acid is oxidized stereospecifically.[17] Yet, if steric hindrance is taken into account, both the carboxy group and the methyl group could attack the enzyme. It may be mentioned here, that even though compounds like lactic acid are very poor substrates, significant and even rapid rates can be observed using about 7×10^{-3} *M* ADP as an activator[18] (Fig. 4).

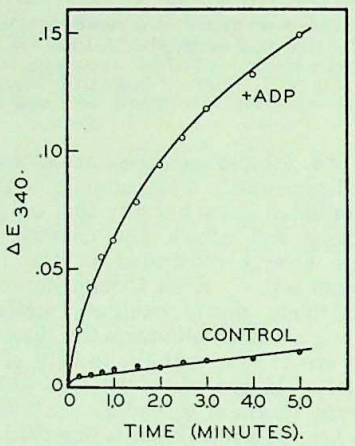

Fig. 4.—The effect of ADP on the rate of lactate oxidation: D(−)-lactic acid 7×10^{-3} *M*, DPN 1.5×10^{-4} *M*, in tris buffer, *p*H 9.3, 0.05 *M*, ADP concentration 8×10^{-4} *M*. Yeast ADH added 25 mcg.

Stereochemistry of the Yeast ADH Reaction

Steric Specificity.—The substrates, which have an asymmetric center at the position of oxidation, are oxidized asymmetrically. This holds even for ethanol,[5,6] which has a *meso* carbon.[19] The substrates which show this effect clearly are lactic acid and the methyl-*n*-alkylcarbinols. If the racemic mixture is used, only one isomer is oxidized (Table II). Similarly, only the D(−)-lactate is used as a substrate. This can be shown by comparing the rates of pure D(−)- and L(+)-lactate. Even when all traces of L(+)-lactate are removed from the D-isomer with L-LDH and acetylpyridine-DPN, the compound still serves as a substrate. Conversely, pyruvate, DPNH and ADH give a product which can be reoxidized with D-LDH and acetylpyridine-DPN, but not with L-LDH and the coenzyme. The use of acetylpyridine-DPN in these experiments is indicated by the more favorable potential for lactate oxidation of this analog as compared to DPN.[12,20] The effectiveness of the analog with many dehydrogenases recently has been demonstrated.[20]

TABLE II

THE STEREOSPECIFICITY OF YEAST ALCOHOL DEHYDROGENASE FOR SECONDARY ALCOHOLS

Alcohol oxidized[a]	μ Moles added	μ Moles DPN[b] reduced
Isopropyl alcohol	0.25	0.22
DL-2-Butanol	.25	.11
DL-2-Octanol	.25	.12
L(+)-Octanol-2[c]	.25	.25

[a] The substrates were tested in tris buffer, *p*H 9.3, 0.05 *M*, containing DPN 1.8×10^{-3} *M*, in a final volume of 3 ml. [b] Molar extinction coefficient of DPNH used: 6.22×10^3. [c] Monohydrogenphthalate $[\alpha]^{21}D$ +47.2° (*c* 0.65, ethanol); reported[14] +48.4°.

Influence of Orientation on Stereospecificity.—When 2-octanol was resolved, it became apparent that the isomer utilized was L(+)-octanol-2.

It was made likely above that *n*-alkyl carbinols are oriented in such a way that only the carbinol moiety will attack the enzyme. Since 3-hexanol cannot serve as a substrate, the octanol molecule appears to be oriented with the methyl group toward the enzyme. The correlation of configuration of L-(+)-octanol-2 and D(−)-lactate, as indicated in Fig. 5, has been demonstrated by Levene and Haller.[21] Therefore, since octanol is oriented with the methyl group toward the enzyme, lactate must be oriented with its carboxyl group toward the enzyme in order to explain the observed stereospecificity. Thus it becomes evident that the substrate molecule is directed with the negative grouping toward the enzyme. This orientation is sufficiently strong to allow stereospecificity even when the molecular dimensions are such that another position would be possible within the limitations imposed by the enzyme, as is the case with lactic acid.

Since the orientation of lactate and octanol appears to be strong, it is highly likely that ethanol will be similarly oriented. If we assume ethanol labeled with deuterium as in Fig. 5, the action of yeast ADH on this molecule would give rise to labeled acetaldehyde. The enantiomorph of the ethanol-*d* represented would give rise to deutero-labeled DPN.

(17) The activity of enzymes on uncommon substrates requires proof that the enzyme is indeed homogeneous and does not contain traces of a contaminating protein catalyzing this reaction. Yeast ADH as used is homogeneous by the physical criterion of ultracentrifugation, and the chemical criterion of number of coenzymes bound per mole of enzyme, both by ultracentrifugational separation techniques (ref. 8), and spectral shift due to the hydroxylamine addition reaction (ref. 7). Furthermore, yeast does not contain a lactic dehydrogenase, but rather a lactic acid oxidase. This latter enzyme is L(+)-lactic acid specific. All activity of whole yeast toward D(−)-lactic acid can be accounted for as due to ADH. This was shown by following the purification procedure of yeast ADH as described by Racker (E. Racker, *J. Biol. Chem.*, **194**, 313 (1950)), and measuring activity toward ethanol and D(−)-lactic acid thoughout the purification. The ratio of activity toward both substrates remained constant. The activity toward D(−)-lactic acid was also not due to trace contaminations with alcohols. This was shown by the following points: first, crystalline horse liver alcohol dehydrogenase failed to attack our D(−)-lactic acid preparation; secondly, D(−)-lactic acid can be oxidized stoichiometrically by the action of DPN and yeast ADH, and thirdly, pyruvate will serve as a substrate for yeast ADH. The product of this reaction will serve as a substrate for D-LDH.

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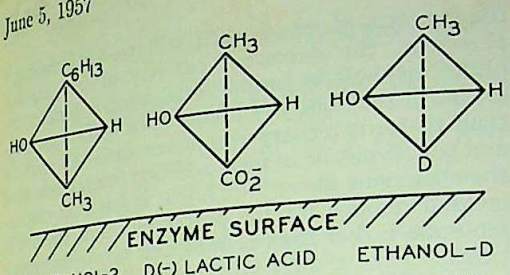

Fig. 5.—The configuration of substrates for yeast ADH.

Influence of Coenzyme on Magnitude of Steric Hindrance.—The enzyme appears to operate according to the reaction sequence[7,22]

Enzyme ⟶ enzyme–coenzyme ⟶
enzyme–coenzyme–substrate

The specificity of the reaction is therefore determined by the enzyme–coenzyme complex, and not by the enzyme alone. The steric limitations are largely governed by the coenzyme used. This can be shown by several lines of evidence. Previously described observations[15] show that some analogs of DPN will not catalyze ethanol oxidation even though the reduced form will reduce acetaldehyde.

Methanol is a poor substrate, since it is not oriented, and since it is too small to afford a fit on the enzyme. However, if one compares the rate of methanol oxidation relative to that of ethanol using different coenzyme analogs, a great variation in methanol effectiveness can be observed (Table III). It is seen that pyridine-3-aldehyde-DPN makes methanol become a reasonable substrate, while with acetylpyridine-DPN the rate with methanol is negligible. For isopropyl alcohol as substrate similar relationships hold. Thus one can assume that the "fit" of the substrate is afforded by the coenzymes and that relatively speaking pyridine-3-aldehyde-DPN gives a better "fit" for methanol than does DPN. The slow rates with acetylpyridine-DPN are not the result of its potential, since there seems to be very little potential difference between acetylpyridine-DPN and pyridine-3-aldehyde-DPN.[20] Furthermore the affinity of the enzyme for the three coenzymes is similar.[7]

TABLE III

THE INFLUENCE OF COENZYME ON THE SPECIFICITY OF YEAST ADH

Coenzyme	Relative rate of coenzyme reduction[a]	
DPN	Ethanol	Methanol
Acetylpyridine-DPN	100	0.8
Pyridine-3-aldehyde-DPN	22.3	.017
	7.3	.86

[a] All rates were performed in tris buffer, 0.05 *M*, *p*H 9.3. Coenzyme concentration, 1.5×10^{-4} *M*, substrate concentration, 5.0×10^{-3} *M*. Rate with DPN and ethanol assigned arbitrarily 100.

The Effect of Reduced DPN on the Rate of a Sterically Hindered Substrate.—The geometry of reduced DPN is markedly different from that of the oxidized form.[15] If the four DPN molecules on the enzyme are responsible for the magnitude of steric hindrance, the enzyme can be made less specific by keeping one of the coenzymes in the reduced state. Thus it can be shown that the rate with D(−)-lactic acid in the presence of ethanol is greater than the sum of the rates of the two substrates tested separately (Fig. 6A). One can postulate the following sequence to be operative

Enzyme-DPN_4 + ethanol ⟶
Enzyme-DPN_3–DPNH + acetaldehyde + H^+

Enzyme-DPN_3–DPNH + lactate ⟶
Enzyme-DPN_2–$DPNH_2$ + pyruvate + H^+

The same phenomenon is also observed with isopropyl alcohol, though the magnitude of the stimulation is not as marked as it is for lactate.

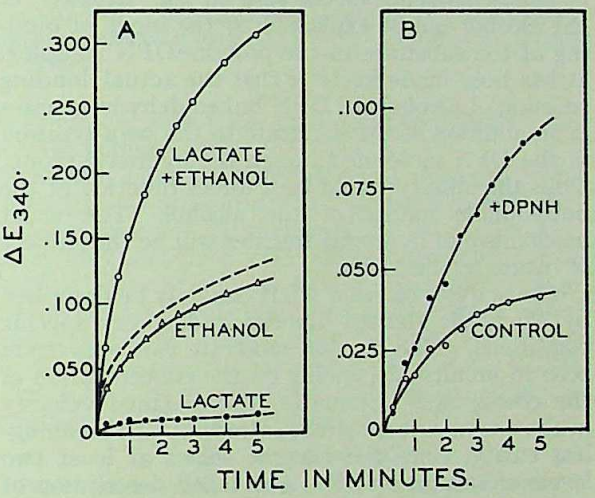

Fig. 6.—The effect of reduced coenzyme on the rate of lactate oxidation: A: Ethanol 5×10^{-3} *M*, D(−)-lactate 7×10^{-3} *M*, DPN 1.5×10^{-4} *M*, in tris buffer, *p*H 9.3, 0.05 *M*. The dashed curve represents the summation of the rates of lactate and ethanol taken separately. B: D(−)-lactate 7×10^{-3} *M*, DPN 1.5×10^{-4} *M*, in tris buffer, *p*H 9.3, 0.05 *M*; DPNH concentration 1.3×10^{-5} *M*.

The above postulation is strengthened by the observation that the addition of DPNH will activate the oxidation of lactate by DPN. This addition can be expected to yield the enzymatic species enzyme–DHN_3–DPNH, which is more efficient as a lactic dehydrogenase than is the species enzyme–DPN_4 (Fig. 6B). The effect is optimal by adding DPN and DPNH in a ratio of about 40 to 1. This is in accord with the stronger binding of DPNH by yeast ADH.[8] The addition of DPNH to a mixture oxidizing ethanol decreases the rate of ethanol oxidation as expected.

Discussion

The picture for alcohol specificity thus requires a model where the enzyme truly gives a place for the substrate to fit in. The easiest picture to explain this phenomenon is given by postulating the four DPN molecules close together and but one substrate molecule fitting in between. The size of the "hole" would be determined by the height of the DPN molecule and the distance between the four coenzyme molecules. A rigid geometry between

(22) J. van Eys and N. O. Kaplan, *Biochim. Biophys. Acta*, **23**, 574 (1957).

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the enzyme–coenzyme complex and substrate is adequate to explain stereospecificity toward the substrate, even when no formal bond between enzyme and substrate exists. Similarly a rigid geometry implies equally a stereospecificity toward the coenzyme. These forms of stereospecificity indeed do exist.[5,6,23]

This picture of enzyme–coenzyme–substrate complex is supported by the fact that the enzyme binds four moles of coenzyme,[7,8] but appears to bind only one substrate molecule at a time.[7] Additional evidence is given by the fact that modification of the structure of the DPN-tetrad changes the specificity of the enzyme. This can be done both by changing from DPN to a DPN analog in the reaction, or by converting one DPN to DPNH.

The dependence of the rate on the "acidity" of the alcohol can be explained by the mode of binding of the substrate to the protein–DPN complex. It has been made likely[7,24] that the actual binding reaction of alcohols to DPN linked dehydrogenases is an addition of the substrate to the *para*-position of the DPN molecule through the hydroxyl group. Thus the affinity would be a direct function of the nucleophilic nature of the alcohol. The exact mechanism of hydrogen transfer will be the subject of future publications.

The activity of yeast ADH can only be described by Michaelis-Menten kinetics under very specific conditions. The K_m for substrate can vary from zero to infinity, depending on the concentration of the coenzyme.[25] Similarly, the maximal velocity of the enzyme at substrate saturation is a meaningless entity, since the enzyme shows at least two levels of saturation.[25,26] A detailed description of the kinetics of yeast ADH will be forthcoming.[27] However, the decreased activity of less nucleophilic alcohols is proportional with a similar decrease in the ability of homologous *n*-alkyl mercaptans to form ternary complexes with the enzyme and coenzyme, or to form addition compounds with the coenzyme alone.[27] Thus it is felt that the decreased affinity for the *para*-position of the DPN molecule rather than a decreased rate of hydrogen transfer (*i.e.*, a lower k_3) is responsible for the lower rates with unnatural substrates.

It is not possible to translate the stereospecificity of yeast ADH to lactate and LDH. It is necessary for the assignment of absolute configurational specificity to know both specificity and orientation. There is also no *a priori* indication so far which side of the DPN molecule is reduced. In general, it is necessary to point out that the data solely apply to yeast ADH and are not be generalized to other dehydrogenases until further information is available.

The configuration of the secondary alcohols which are substrates is in agreement with the old observations of Neuberg and Nord[28] that fermenting yeast acts upon 2-octanone, yielding dextrorotatory 2-octanol. It is highly probable that the present studies relate to the ADH inside the yeast cell. Thus it appears that the stereospecificity observed is not an artifact, but truly a property of the enzyme *in vivo*. The significance of activation by nucleoside-polyphosphates[18] within the intact cell remains to be seen. However, since the activation by ADP is quite large, the yeast ADH in the presence of this nucleotide becomes a very unspecific enzyme. It must be pointed out again, however, that no substrate becomes oxidized because of the presence of ADP; the nucleotide merely serves as a tool to give rates rapid enough for convenient comparison with other substrates.

BALTIMORE, MD.

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June 5, 1957

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, QUEEN'S UNIVERSITY]

The Structure of the Type VIII Pneumococcus Specific Polysaccharide[1a,b]

BY J. K. N. JONES AND M. B. PERRY

RECEIVED OCTOBER 30, 1956

Acid hydrolysis of the specific polysaccharide of the Type VIII pneumococcus (S VIII) gave D-glucouronic acid (1 part), D-glucose (2 parts) and D-galactose (1 part). Partial acid hydrolysis afforded three acidic oligosaccharides: (a) an aldobiouronic acid, 4-*O*-(β-D-glucopyranosyluronic acid)-D-glucopyranose; (b) an aldotriouronic acid, *O*-β-D-glucopyranosyluronic acid-(1 → 4)-*O*-β-D-glucopyranosyl-(1 → 4)-D-glucopyranose; (c) an aldotetraouronic acid, *O*-β-D-glucopyranosyluronic acid-(1 → 4)-*O*-β-D-glucopyranosyl-(1 → 4)-*O*-α-D-glucopyranosyl-(1 → 4)-D-galactopyranose; and (d) a neutral disaccharide, 4-*O*-α-D-glucopyranosyl-(1 → 4)-D-galactopyranose. Hydrolysis of the methylated S VIII polysaccharide gave 2,3-di-*O*-methyl-D-glucuronic acid (1 part), 2,3,6-tri-*O*-methyl-D-glucose (2 parts) and 2,3,6-tri-*O*-methyl-D-galactose (1 part). Esterification of the S VIII acidic polysaccharide with diazomethane followed by reduction of the product with sodium borohydride in aqueous solution yielded a neutral polysaccharide which on hydrolysis gave D-glucose (3 parts) and D-galactose (1 part). Methylation and hydrolysis of this latter polysaccharide gave 2,3,6-tri-*O*-methyl-D-glucose (3 parts) and 2,3,6-tri-*O*-methyl-D-galactose (1 part). Periodate oxidation of the S VIII polysaccharide showed a consumption of 1.03 moles of metaperiodate per hexose unit. It is considered that the S VIII polysaccharide is essentially a linear chain, high molecular weight polymer with the repeating unit -*O*-β-D-glucopyranosyluronic acid-(1 → 4)-*O*-β-D-glucopyranosyl-(1 → 4)-*O*-α-D-glucopyranosyl-(1 → 4)-*O*-α-D-galactopyranosyl-(1 → 4)-.

I. Introduction

The cross precipitin reactions observed between the S III and the S VIII polysaccharides and their corresponding antisera[2-4] can be related to the occurrence in these two polysaccharides of a common structural unit of 4-*O*-(β-D-glucopyranosyluronic acid)-D-glucopyranose.[5] Similarly the cross reactions observed between the S III antiserum and the polysaccharides from *Azotobacter chroococcum*,[6] *Rhizobium radicicolum*,[7] gum arabic,[8,9] Friedlander's bacillus[10] and oxidized cotton cellulose,[5] all of which possess closely related aldobiouronic acid units, illustrates the remarkable correlation which exists between the fine structure of the carbohydrate and its serological specificity.

The structure of the S III polysaccharide is known to be that of a linear chain of 4-*O*-(β-D-glucopyranosyluronic acid)-D-glucopyranose units joined together by 1 → 3 linkages having the β-configuration.[10-12] The aldobiouronic acids isolated from the partial acid hydrolysis of both the S III and S VIII polysaccharides proved to be identical, both being convertible to the one crystalline hepta-*O*-acetyl methyl ester derivative.[13] The physical and chemical properties of the purified polysaccharide used in this investigation agree very closely with those previously recorded for the S VIII polysaccharide.[2,3,13]

On the basis of immunological evidence using quantitative precipitin and quantitative agglutination techniques, Heidelberger, Kabat and Mayer[4] concluded that the S VIII polysaccharide was probably a linear polymer having 4-*O*-(β-D-glucopyranosyluronic acid)-D-glucopyranose units interposed between other anhydrohexose units and that it had a minimum molecular weight of 140,000. This theory is in agreement with the experimental findings described in this paper.

II. Experimental

Paper chromatography was performed by the descending method[14] on Whatman No. 1 filter paper using several solvent systems: (a) ethyl acetate–acetic acid–water (9:2:2 v./v.); (b) ethyl acetate–acetic acid–formic acid–water (18:8:3:6 v./v.); (c) butan-1-ol–ethanol–water (4:1:2 v./v.); (d) butan-1-ol–pyridine–water (10:3:3 v./v.). Sugars were detected on the chromatogram by spraying with a solution of *p*-anisidine hydrochloride[15] or with a solution of silver nitrate in acetone followed by ethanolic sodium hydroxide solution.[16]

The rate of movement of the sugars on the chromatogram is quoted relative to that of tetra-*O*-methylglucopyranose (R_G), to galactose (R_{Gal}) or to rhamnose (R_{Rh}).

Solutions were concentrated under reduced pressure. Melting points are uncorrected. Optical rotations were determined at 20° in water, unless otherwise stated.

Isolation and Purification of the S VIII Polysaccharide.—The polysaccharide, which had been prepared by a method specifically designed to cause as little breakdown of the molecule as possible during its isolation,[17] was supplied in the form of a white fibrous solid which dissolved in water to give a highly viscous acidic solution, $[\alpha]_D$ +115° (*c* 0.4). The polysaccharide (7 g.) was dissolved in Fehling solution A (alkaline tartrate) (*ca.* 150 ml.), and Fehling solution B ($CuSO_4$) was added dropwise to the stirred solution until no more precipitation of the polysaccharide complex was obtained. The complex was removed by filtration under gravity on a sintered glass filter and washed well with cold water. The copper was removed from the complex by the addition of *N* hydrochloric acid (*ca.* 60 ml.) to the material suspended in water (1 l.) kept at 0°. The viscous solution was centrifuged, and the clear solution was poured into ethanol (4 vols.) with vigorous stirring. The precipitated polysaccharide was collected on the filter, washed with

(1) (a) A resume of this paper was presented at the 130th Meeting of the American Chemical Society in Atlantic City, N. J., September 16–21, 1956. (b) This work was made possible by the award of a grant from the Banting Research Foundation, Toronto, Canada.

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ethanol and dried *in vacuo* to give a fine white powder (6.2 g.).

The sodium salt of the S VIII polysaccharide was examined by electrophoresis using Whatman fiber-glass as the support and an electrolyte of crystalline borax (38 g.) in 0.12 *N* sodium hydroxide solution (1 l.). The paper was uniformly wetted with the electrolyte, and a 10% solution of the polysaccharide dissolved in the prepared electrolyte, was spotted on the base line.[18] After electrophoresis the carbohydrates were located by first spraying the paper with a 3% (w./v.) solution of α-naphthol in methanol followed by spraying it with concentrated sulfuric acid. The S VIII polysaccharide was thus located as a single discrete spot.

Electrophoresis of the S VIII polysaccharide (400 mg.) as described above, followed by extraction of the appropriate part of the paper with water, and deionization (resins), afforded the electrophoretically pure polysaccharide which had $[\alpha]_D$ +124° and equivalent weight 692. Hydrolysis of this polysaccharide with formic acid, followed by paper chromatographic examination of the hydrolyzate, showed it to be composed of glucuronic acid (1 part), galactose (1 part) and glucose (2 parts). The electrophoretically pure polysaccharide is chemically and physically indistinguishable from the starting material.

The polysaccharide could not be further fractionated by precipitation of its cetyltrimethylammonium salt and subsequent regeneration of the free polysaccharide.[19,20a,b] The S VIII polysaccharide obtained *via* its copper complex was deionized by passing its solution first through a bed of Amberlite ion-exchange resin IR 120(H) and then through a bed of IR 4B(OH).[21] The eluate was freeze-dried to give the ash-free polysaccharide which had $[\alpha]_D$ +121° (*c* 0.4) and equivalent weight of 703 (≡25.2% hexuronic anhydride), found by titration with standard alkali.

Anal. Calcd. for $[(C_6H_{10}O_5)_3.(C_6H_8O_6)]_x$ (polymer with a repeating unit of 3 hexose units and 1 hexuronic acid unit): C, 43.5; H, 5.72. Found: C, 43.6; H, 5.56; N, nil; P, nil.

The polysaccharide gave no color with iodine but gave a strong positive test for hexuronic acid with the naphthoresorcinol reagent.[22] Attempted autohydrolysis and attempted hydrolysis with 0.01 *N* sulfuric acid of 1% solutions of the polysaccharide at 100° for 8 hr. failed to liberate any sugars detectable on the chromatogram.

Component Sugars of the S VIII Polysaccharide.—The polysaccharide (1 g.) was heated with 90% formic acid (100 ml.) at 100° for 22 hr. The formic acid was removed by distillation and the residue further hydrolyzed by heating it with *N* sulfuric acid (15 ml.) for 2 hr. at 100°. After neutralization ($BaCO_3$) and filtration, a portion of the hydrolyzate was concentrated and examined on paper chromatograms. In solvent system d, detection with *p*-anisidine revealed two spots corresponding in position and color to galactose and glucose (visual ratio 1:2), and a component giving a red colored spot remained near the base line. In solvent system a, spots corresponding to galactose and glucose were again obtained together with a red spot (R_{Gal} 0.96) corresponding in position to a hexuronic acid. The main bulk of the hydrolyzate was passed first through a column of IR 120(H) resin (1.5 × 6 cm.) and then through a column of IR 4B(OH) resin (1.5 × 5 cm.). Concentration of the eluate gave the neutral sugars as a sirup (560 mg.) which was fractionated by partition chromatography on large sheets of filter paper using solvent system d as the mobile phase. Development was allowed to proceed for 5 days with intermediate drying of the papers at 24-hr. intervals. Extraction of appropriate sections of the paper afforded crystalline D-galactose, m.p. 165°, $[\alpha]_D$ +80° (*c* 1.1), which gave a 1-methyl-1-phenylhydrazone derivative, m.p. 186°, and D-glucose, m.p. 145°, $[\alpha]_D$ +50° (*c* 0.9) (mixed m.p.'s showed no depression).

The IR 4B column above was eluted with 10% formic acid and the formic acid then removed from the aqueous eluate by continuous extraction with ether. Examination of this latter eluate on paper chromatograms in solvent system a and detection with *p*-anisidine revealed one main spot (R_{Rh} 1.33) corresponding in position to authentic glucurono-6 → 3-lactone, and a faint spot (R_{Gal} 0.96) corresponding to glucuronic acid (galacturonic acid does not form a lactone and mannuronolactone has R_{Rh} 0.95). Concentration of this aqueous eluate to dryness and dissolution of the residue in glacial acetic acid on cooling afforded D-glucurono-6 → 3-lactone, m.p. and mixed m.p. 178°, $[\alpha]_D$ +18° (*c* 0.8).

Quantitative Estimation of the Component Sugars of S VIII.—Samples of the polysaccharide (*ca.* 30–40 mg.) were hydrolyzed for 20 hr. with 96% formic acid (3 ml.) in sealed tubes placed in a boiling water-bath. A weighed amount of L-rhamnose (*ca.* 15 mg.) was added and the formic acid removed by distillation. The residue was then hydrolyzed with *N* sulfuric acid (2 ml.) for a further 2 hr. at 100°. The acid was neutralized ($BaCO_3$), filtered, the filtrate concentrated to about 2 ml. and ethanol (6 ml.) was added. After standing at 5° for 8 hr. the precipitated barium D-glucuronate was removed on the centrifuge and the supernatant solution was concentrated to a small bulk and applied evenly to the base line of a paper chromatogram. The chromatogram was developed in solvent system d during 6 days with intermediate drying. The separated sugars were quantitatively extracted,[23] and the amounts of the sugars present were estimated colorimetrically by the benzidine method.[24] The results indicate that the galactose and the glucose are present in the ratio 1:2. Found: D-galactose, 21.4, 20.0, 24.0; D-glucose, 40.5, 42.1, 40.3 (based on the recovery of L-rhamnose).

The uronic anhydride content of the polysaccharide was determined by quantitative decarboxylation with 12% hydrochloric acid, and determination of the carbon dioxide produced, by an iodometric procedure.[25] Found: hexuronic anhydride, 27.8%, 26.8%, 27.8%.

Reduction of the S VIII Polysaccharide.—The freeze-dried ash-free S VIII polysaccharide (4 g.) was moistened with methanol and a solution of diazomethane in ether was added. When the initial vigorous liberation of nitrogen was over (10 min.) the excess diazomethane together with the solvents were removed by distillation. The residue was dissolved in water (150 ml.) to give a mobile solution which was added over 1 hr. to a solution of sodium borohydride (2 g.) in water (50 ml.) with vigorous stirring.[26] Stirring was continued overnight, and the excess borohydride was destroyed by acidification with 2 *N* sulfuric acid. The reaction mixture was poured with stirring into ethanol (4 vol.) and the precipitated polysaccharide was collected on the centrifuge. The above operations were repeated on this material after it had been deionized (resins) and freeze-dried again, to give a final product (3.2 g.) which was readily soluble in water to give a neutral mobile solution, $[\alpha]_D$ +130° (*c* 0.5). Attempted decarboxylation[25] yielded negligible amounts of carbon dioxide, and the naphthoresorcinol test[22] for uronic acid was negative.

The neutral polysaccharide (40 mg.) was hydrolyzed with 96% formic acid (4 ml.) in a sealed tube at 100° for 10 hr. and, after removal of the formic acid, hydrolysis was continued with *N* sulfuric acid (2 ml.) for 2 hr. at 100°. Examination of the neutralized ($BaCO_3$) hydrolyzate by paper chromatography in solvent system a revealed spots due to galactose and glucose, but no spot corresponding to glucuronic acid or its lactone could be detected. Prolonged development in solvent system d separated the two component sugars. Measurement of the intensities of the two spots produced with *p*-anisidine, using a photoelectric transmission densitometer,[27,28] indicated the galactose and the glucose to be present in the ratio 1:3.

Methylation of the S VIII Acidic Polysaccharide.—In order to prevent possible alkaline breakdown of the polysaccharide[29,30] during its methylation, the reducing end group was reduced to hexitol end group before methylation.

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To the sodium salt of the S VIII polysaccharide (2.1 g.) in water (50 ml.) was added a solution of sodium borohydride (15 mg.) in water (10 ml.) and the mixture was stirred for 1 hr. The excess sodium borohydride was destroyed by acidification of the reaction mixture with acetic acid. To the above solution of the polysaccharide was added, simultaneously and dropwise, sodium hydroxide (14 ml., 30% w./v.) and methyl sulfate (10 ml.) with vigorous stirring and ice-cooling, at a rate such that the mixture remained slightly alkaline. After 5 hr., the reaction mixture was allowed to warm to room temperature and sodium hydroxide (280 ml., 30% w./v.) and methyl sulfate (95 ml.) were added dropwise over 6 hr. and the stirring continued overnight. The same quantities of reagents were added over 5 hr., and the stirring was continued for a further 40 hr. The reaction mixture was heated on a boiling water-bath for 30 min. to destroy the excess methyl sulfate, and the volatile products were removed by distillation. The ice-cooled reaction mixture was brought to *p*H 2 by the cautious addition of 2 *N* sulfuric acid; the partially methylated polysaccharide was precipitated and was removed on a sintered glass filter. The product thus separated was methylated again using the above conditions, sufficient acetone being added to keep the polysaccharide in solution. The product isolated on acidification of the reaction mixture was further methylated by refluxing it with methyl iodide (40 ml.) containing methanol (1 ml.), while silver oxide (6 g.) was added portionwise over 6 hr. The final product obtained on chloroform extraction (1.71 g.) had $[\alpha]_D$ +68° (*c* 0.98 in acetone).

Anal. Calcd. for $(C_{36}H_{62}O_{21})_x$: OMe, 44.8. Found: OMe, 44.1.

Fission of the Methylated S VIII Polysaccharide.—A portion of the methylated S VIII polysaccharide (0.691 g.) was hydrolyzed by heating with 90% formic acid (100 ml.) for 10 hr. at 100°, and after removal of the formic acid by distillation, hydrolysis was continued by heating with *N* sulfuric acid (15 ml.) for a further 4 hr. After neutralization ($BaCO_3$) the hydrolyzate was filtered, and the filtrate was passed first down a column of IR 120(H) ion-exchange resin followed by IR 4B(OH) to give an eluate which on concentration gave the neutral methylated sugars as a sirup (A, 0.498 g.). The IR 4B resin above was eluted with *N* sulfuric acid, the eluate was neutralized ($Ba(OH)_2$) and the filtered solution was passed through a small bed of IR 120(H) resin to give an acid eluate, which on concentration, afforded the acidic methylated sugar (B, 0.123 g.).

Examination of the Neutral Methylated Sugars (A).—Paper chromatographic examination of this fraction in the solvent system d revealed two spots, having R_G 0.83 and 0.91 in the visual ratio 1:2. The mobility of the two components and the colors they gave with *p*-anisidine corresponded to those of 2,3,6-tri-*O*-methyl-D-galactose and 2,2,6-tri-*O*-methyl-D-glucose. Spraying with a 2% solution of dimethylaniline in glacial acetic acid containing 5% trichloroacetic acid[18] gave two purple spots corresponding to those revealed with the *p*-anisidine spray. No spots corresponding to tetra-*O*- or di-*O*-methyl sugars were detected. The sirup was moistened with a little methanol and set aside. The crystals which formed slowly were collected and recrystallized from ethanol (A1, 0.201 g.). The residual sirup when examined on paper chromatograms showed an increased intensity of the slow moving component (R_G 0.83). This sirup was fractionated on a cellulose column (3 × 24 cm.)[31] using light petroleum (b.p. 100–120°): butan-1-ol (7:3 v./v.) as the mobile phase. Evaporation of appropriate parts of the eluate gave two sirupy fractions which were purified by dissolution in water, acetone and then ether and on seeding from ethanol–ether mixture, the crystals were proved identical with (A1) causing no depression of m.p. and the two lots were combined.

Fraction 1 was chromatographically identical with (A1), with intermediate filtration and evaporation, and dried. crystallization of the whole fraction crystallized. After re-

Fraction 2 had R_G 0.83 in solvent system d, and was chromatographically pure (A2, 0.135 g.).

Characterization of (A1) as 2,3,6-Tri-*O*-methyl-D-glucose.—The crystals had m.p. 122°, undepressed on admixture with authentic 2,3,6-tri-*O*-methyl-D-glucose and $[\alpha]_D$ +73° (*c* 1.0).

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Anal. Calcd. for $C_9H_{18}O_6$: OMe, 41.9. Found: OMe, 40.2.

The bis-*p*-nitrobenzoate,[32] prepared in the usual way, had m.p. and mixed m.p. 188°, $[\alpha]_D$ −34° (*c* 0.8 in chloroform).

Characterization of (A2) as 2,3,6-Tri-*O*-methyl-D-galactose.—The sirup failed to crystallize. It had $[\alpha]_D$ +85° (*c* 0.9).

Anal. Calcd. for $C_9H_{18}O_6$: OMe, 41.9. Found: OMe, 40.6.

The sirup was dissolved in 1% methanolic hydrogen chloride (*c* 1.0) at 20° and the change in the specific optical rotation followed: $[\alpha]_D$ +46° (initial value), +20° (3 hr.), +2° (6 hr.), −10° (11 hr.), −28° (24 hr. constant value). This change in the specific optical rotation is that expected of 2,3,6-tri-*O*-methyl-D-galactose. The original sirup (A2, 50 mg.) was oxidized with bromine in the usual manner to give 2,3,6-tri-*O*-methyl-D-galactono-γ-lactone, 38 mg., m.p. and mixed m.p. 97°, $[\alpha]_D$ −37° (*c* 0.5).

Anal. Calcd. for $C_6H_{16}O_6$: OMe, 42.4. Found: OMe, 41.7.

Characterization of (B) as 2,3-Di-*O*-methyl-D-glucuronic Acid.—The sirup had $[\alpha]_D$ +36° (*c* 1.0).

Anal. Calcd. for $C_8H_{14}O_7$: OMe, 28.0. Found: OMe, 27.1.

Paper chromatographic examination of the sirup B in solvent system a revealed a single red spot with the *p*-anisidine spray R_G 0.64 which had the same rate of movement as authentic 2,3-di-*O*-methyl-D-glucuronic acid.

The sirup B (60 mg.) was refluxed with 1% methanolic hydrogen chloride (15 ml.) for 6 hr. and was neutralized (Ag_2CO_3). The methanolic solution was concentrated to dryness and the solution of the residue in dioxane–ether mixture (1:1 v./v., 8 ml.) was added dropwise with stirring to a solution of lithium aluminum hydride (0.1 g.)[33] in dioxane–ether mixture (1:1 v./v., 8 ml.). After stirring overnight, the excess lithium aluminum hydride was destroyed by the addition of ethyl acetate followed by water. The reaction mixture was brought to *p*H 8 by the addition of *N* sulfuric acid and the mixture filtered. The methyl-2,3-di-*O*-methyl-D-glucoside was extracted from the filtrate with chloroform. The concentrated chloroform extract was hydrolyzed by heating with 2 *N* hydrochloric acid (10 ml.) for 4 hr., neutralized (Ag_2CO_3), filtered and the filtrate evaporated to dryness. Extraction of the residue with hot ethyl acetate and concentration of the extract to a small bulk gave crystals of 2,3-di-*O*-methyl-D-glucose which had m.p. and mixed m.p. 109°, $[\alpha]_D$ +48° (*c* 0.7 in acetone).

Anal. Calcd. for $C_8H_{16}O_6$: OMe, 29.8. Found: OMe, 29.2.

Paper chromatographic examination of the above chloroform extract showed a single spot (R_G 0.73 in solvent system d, and R_G 0.71 in c), which had the same mobility as authentic 2,3-di-*O*-methyl-D-glucose.

Methylation of the Reduced S VIII Polysaccharide.—The neutral, reduced polysaccharide (3.4 g.) was methylated using sodium hydroxide and methyl sulfate as in the case of the acidic S VIII polysaccharide. The partially methylated product separated out during the final heating of the reaction mixture and the material was collected at this point. A product having OMe 36.6% was thus obtained, and its methoxyl content was raised[34] by dissolving the material (3.9 g.) in anisole (150 ml.) and freezing the solution using a Dry Ice-bath. Sodium (2 g.) in liquid ammonia (80 ml.) was added and the mixture allowed to warm to room temperature with frequent shaking. The ammonia was removed by distillation and the residue was refluxed with methyl iodide (48 ml.) for 8 hr. The reaction mixture was freed from excess methyl iodide and the distillation continued until about 10 ml. of anisole had been collected. The anisole solution of the polysaccharide remaining was again frozen, and lithium (2 g.) in liquid ammonia (100 ml.) was added and the above operations repeated. The reaction mixture was concentrated to near dryness, water being added at intervals during the distillation, until no more anisole

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remained in the flask. The aqueous solution was extracted continuously with chloroform, and the extract in 50% ethanol was passed down a small bed of ion-exchange resin MB 3 (Rohm & Haas Co., Philadelphia 5, Pa.) and concentrated to a light golden sirup (3.9 g.), $[\alpha]_D$ +63° (*c* 1.2 in chloroform).

Anal. Calcd. for $(C_9H_{16}O_5)_x$: OMe, 45.6. Found: OMe, 44.1.

Fractionation and Fission of the Methylated Reduced (Neutral) S VIII Polysaccharide.—The methylated polysaccharide (3.8 g.) was dissolved in chloroform (25 ml.), and petroleum ether (b.p. 100–120°) was added portionwise, the precipitated fractions being removed before carrying out further precipitation.

FRACTIONATION OF THE METHYLATED REDUCED S VIII POLYSACCHARIDE

Fraction	Petroleum ether added, ml.	Weight, g.	$[\alpha]_D$ (in $CHCl_3$)
1	50	0.102	+69°
2	70	0.010	+66
3	100	2.10	+65
4	140	1.34	+65
5	Residue	0.280	+59

Fractions 1, 2, 3 and 4 were combined and hydrolyzed as described for the methylated acidic S VIII polysaccharide. On paper chromatographic examination of the hydrolyzate in solvent system d, spots corresponding to 2,3,6-tri-*O*-methylgalactose and 2,3,6-tri-*O*-methylglucose in the visual ratio 1:3 were detected. No spots due to tetra-*O*, di-*O*- or mono-*O*-methylhexoses could be detected. On standing, the concentrated hydrolyzate gave crystals of 2,3,6-tri-*O*-methyl-D-glucose which were removed and characterized as described previously. Fractionation of the residual sirup upon a cellulose column gave more 2,3,6-tri-*O*-methyl-D-glucose which was combined with the first crop of crystals (2.3 g.) and 2,3,6-tri-*O*-methyl-D-galactose (0.785 g.) which was characterized as its crystalline aldono-γ-lactone, m.p. and mixed m.p. 97°, $[\alpha]_D$ −37° (*c* 0.8).

Periodate Oxidation of the Reduced Mixture of Tri-*O*-methylhexoses.—A portion (10 mg.) of the mixed tri-*O*-methylhexoses, obtained on hydrolysis of the fully methylated reduced S VIII polysaccharide, in water (2 ml.) contained in a 5-ml. volumetric flask, was reduced by the addition of sodium borohydride (8 mg.). After standing at room temperature for 2 hr., the excess borohydride was destroyed by the dropwise addition of 3 *N* sulfuric acid, and the acid solution was allowed to stand for 1 hr. to ensure complete removal of the reagent. Saturated *p*-hydroxybenzaldehyde solution (1 ml.)[35] and 0.3 *M* sodium metaperiodate solution (1 ml.) were added to the contents of the flask and the volume adjusted with water, to 5 ml. The reaction mixture was kept in the dark at 20°, and 1-ml. samples were withdrawn at intervals and pipetted into centrifuge tubes containing 20% lead dithionite solution (1 ml.)[36] to precipitate the periodate as insoluble lead periodate which was removed on the centrifuge. One ml. of the clear supernatant liquid was added to a 0.2% solution of chromotropic acid (1,8-dihydroxynaphthalene-3,6-disulfonic acid) (10 ml.) in sulfuric acid (60% v./v.) and the mixed reagents were allowed to stand for 30 min. The lead sulfate was removed by centrifugation and the supernatant liquid was transferred to glass stoppered tubes and heated on a vigorously boiling water-bath for 40 min. The absorption of the solution at 570 mμ was read on a Hilger spectrophotometer. A standard graph of absorption at 570 mμ against formaldehyde concentration was prepared using erythritol as a standard. No formaldehyde was liberated during the periodate oxidation of the above mixed tri-*O*-methylhexitols.

Periodate oxidation of 2,3,4-tri-*O*- and 1,3,4-tri-*O*-methylhexitols prepared by the borohydride reduction of the corresponding 2,3,4-tri-*O*- and 3,4,6-tri-*O*-methylhexoses under the conditions described above were found to liberate exactly 1 mole of HCHO per mole of tri-*O*-methylhexitol (complete after 8 min.). Periodate oxidation of the 1,4,5-tri-*O*- and 1,3,5-tri-*O*-methylhexitols prepared by reduction of the 2,3,6-tri-*O*- and 2,4,6-tri-*O*-methylhexoses failed to liberate any formaldehyde.

The reduced mixed tri-*O*-methylhexoses obtained from the polysaccharide were examined on paper chromatograms in solvent system d. Detection with a spray reagent of 1% aqueous sodium metaperiodate (4 parts), mixed prior to use with a 1% solution of potassium permanganate in 2% aqueous sodium carbonate solution (1 part),[37] revealed the sugars initially as a single pink spot against a white background (R_G 0.69) later observed as a white spot against a brown background. The *p*-anisidine spray failed to detect any sugars.

Partial Hydrolysis of the S VIII Acidic Polysaccharide.—The polysaccharide (6 g.) dissolved in 0.15 *N* sulfuric acid (300 ml.) was kept at 95° for 10 hr., neutralized ($BaCO_3$), filtered and the filtrate passed down columns of ion-exchange resins IR 120(H) (3 × 10 cm.) followed by IR 4B(OH) (3 × 14 cm.). The acid effluent was neutralized ($Ba(OH)_2$), concentrated to about 30 ml. and ethanol (70 ml.) was added to precipitate the barium uronates which were collected on the centrifuge (C, 2.4 g.). The ethanol supernatant was passed through a small bed of ion-exchange resin MB 3 and the neutral eluate concentrated to a sirup (D, 1.08 g.). The IR 4B resin above, which retained the low molecular weight acid oligosaccharides, was eluted[38–40] with 0.3 *N* formic acid at the rate of 0.5 ml. per min., and the eluate was collected on a fraction cutter. Appropriate fractions were combined; tubes containing two components owing to slight overlap were combined and further fractionated on sheets of Whatman 3MM filter paper in solvent system b. Formic acid was removed from the fractions by continuous extraction with ether. The following fractions were obtained: U1, hexuronic acid, 0.084 g., R_{Gal} 0.96 (in solvent b); U2, aldobiouronic acid, 0.650 g., R_{Gal} 0.46; U_3, aldotriouronic acid, 0.255 g., R_{Gal} 0.10; and U4, aldotetraouronic acid, 0.030 g., R_{Gal} 0.05.

Characterization of U1 as D-Glucuronic Acid.—The acid was converted to crystalline D-glucurono-6 → 3-lactone, m.p. and mixed m.p. 178°, $[\alpha]_D$ +18° (*c* 0.5).

Characterization of U2 as 4-*O*-(β-D-Glucopyranosyluronic Acid)-D-glucopyranose.—The chromatographically pure acid had $[\alpha]_D$ +7° (*c* 2.0) and equivalent weight 359 by titration with standard alkali ($C_{12}H_{20}O_{12}$ requires equiv. wt. 356). Hydrolysis with formic acid followed by paper chromatographic examination of the hydrolyzate showed the presence of glucuronic acid and glucose.

Conversion of U2 to its Hepta-*O*-acetyl-methyl Ester.[41]—The acid (150 mg.) in methanol (9 ml.) was esterified by the addition of a solution of diazomethane in ether. After removal of the solvents the residue was dissolved in acetic anhydride containing 5% anhydrous zinc chloride (12 ml.), and the reaction mixture was kept at 60° for 90 min. The residue remaining after removal of the acetic anhydride was extracted with warm methanol (2 × 10 ml.). Water (20 ml.) was added to the extract and, after standing for 6 min. at 0°, the precipitated derivative was collected. Recrystallization from ethanol afforded a product (130 mg.) which had m.p. 251° and $[\alpha]_D$ +42° (*c* 0.7 in chloroform) (literature[13] m.p. 250°, $[\alpha]_D$ +41.7°).

Anal. Calcd. for $C_{27}H_{36}O_{19}$: C, 48.7; H, 5.55; OMe, 4.7. Found: C, 48.64; H, 5.31; OMe, 4.94.

Reduction of U2 to Cellobiitol.[41]—The aldobiouronic acid (150 mg.) was esterified with diazomethane, and the ester dissolved in water (10 ml.) was added dropwise with stirring to a solution of sodium borohydride (50 mg.) in water (6 ml.). Reaction was allowed to proceed at room temperature for 5 hr., and acetic acid was added to destroy the excess borohydride. Removal of the ionic material on ion-exchange resins gave a non-reducing eluate which was concentrated to dryness, extracted with hot methanol (3 × 8 ml.) and the extract concentrated to about 0.5 ml. On keeping, crystals of cellobiitol were obtained (120 mg.) which after three recrystallizations from methanol had $[\alpha]_D$ −7.8° (*c* 5.0) and m.p. 143°, undepressed on admixture with au-

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thentic cellobiitol prepared by the borohydride reduction of cellobiose.

Characterization of U3 as *O*-β-D-Glucopyranosyluronic Acid-(1→4)-*O*-β-D-glucopyranosyl-(1→4)-D-glucopyranose.—The acid had $[\alpha]_D$ +12° (*c* 2.0) and equivalent weight 522 (calcd. for $C_{18}H_{30}O_{17}$: equiv. wt., 518). The acid was chromatographically pure, and determination of its reducing power by the alkaline hypoiodite method[42,43] gave a molecular weight of 528. Hydrolysis of the aldotrioruonic acid with formic acid followed by paper chromatographic examination showed it to contain glucuronic acid and glucose.

Methylation of U3.—The aldotrioruonic acid (100 mg.) was methylated using sodium hydroxide (105 ml., 30 w./v.) and methyl sulfate (24 ml.) in the usual way. The product was extracted with chloroform and further methylated using methyl iodide (8 ml.) and silver oxide (1 g.) to give a final product (92 mg.) which had $[\alpha]_D$ +11.5° (*c* 1.0 in $CHCl_3$).

Anal. Calcd. for $C_{29}H_{52}O_{17}$: OMe, 50.8. Found: OMe, 49.1.

The methylated aldotrioruonic acid (80 mg.) was hydrolyzed with formic acid (as for the S VIII polysaccharide) and the hydrolysate fractionated on a sheet of filter paper in solvent system d. The acidic component remained near the base line and after elution from the paper was passed through a little IR 120(H) resin and concentrated to dryness (19 mg.). This acid sugar was chromatographically pure giving a single red spot with the *p*-anisidine spray having R_G 0.84 in solvent system a and moved to the same position as authentic 2,3,4-tri-*O*-methylglucuronic acid. It had $[\alpha]_D$ +40° (*c* 0.5). The neutral methylated sugar gave a single spot R_G 0.91 in solvent system d and on keeping gave crystals of 2,3,6-tri-*O*-methyl-D-glucose (41 mg.) which had $[\alpha]_D$ +72° (*c* 0.8), m.p. and mixed m.p. 122°.

Reduction of U3 to Cellotriitol.—The aldotrioruonic acid (60 mg.) was converted to its methyl ester and reduced with aqueous sodium borohydride (as described for the conversion of U2 to cellotriitol), to give crystalline cellotriitol (48 mg.) which had $[\alpha]_D$ −5.5° (*c* 0.5) and m.p. 160° undepressed on admixture with authentic cellotriitol prepared by the borohydride reduction of cellotriose. The derivative co-chromatographed with authentic cellotriitol[44] having R_{Gal} 0.16 in solvent system a.

Characterization of U4 as *O*-β-D-Glucopyranosyluronic Acid-(1→4)-*O*-β-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-galactopyranose.—The barium uronates (C), obtained on the addition of ethanol to the acidic solution passing through the ion-exchange resins after partial hydrolysis of the S VIII polysaccharide, were examined on paper chromatograms in solvent system b. A component (R_{Gal} 0.05) corresponding in position to an aldotetraouronic acid was observed to be present. Separation of the uronates on sheets of Whatman 3MM filter paper in solvent system b during 5 days gave the chromatographically pure tetraouronic acid (280 mg.). It was identical in physical and chemical properties with U4 and the two parts were combined and examined together. No spot due to an aldopentaouronic acid could be detected on the chromatograms of the partially hydrolyzed S VIII polysaccharide.

The aldotetraouronic acid had $[\alpha]_D$ +65° (*c* 1.0), and equivalent weight 675 (required for an aldotetraouronic acid: equiv. wt., 670); hypoiodite oxidation[42,43] gave a molecular weight 698. Hydrolysis of U4 (8 mg.) with formic acid followed by paper chromatographic examination of the mixture of sugars showed it to contain glucuronic acid, galactose and glucose. Measurement of the spot intensities[27,28] indicated the galactose and glucose to be present in the ratio 1:2. The aldotetraouronic acid (10 mg.) was reduced directly with sodium borohydride (3 mg.) in water (5 ml.), and after deionization (resins) the reduced product was hydrolyzed with formic acid. Paper chromatographic examination of the hydrolyzate in solvent system d followed by detection with the *p*-anisidine spray revealed only glucose and a spot remaining near the base line (glucuronic acid). Detection with the silver nitrate spray showed in addition to glucose a spot on the chromatogram behaving in a manner similar to authentic dulcitol. The aldotetraouronic acid (U4, 120 mg.) was methylated as described for U3 to give a product (110 mg.) which had $[\alpha]_D$ +15° (*c* 1 in chloroform).

Anal. Calcd. for $C_{38}H_{67}O_{22}$: OMe, 49.7. Found: OMe, 48.8.

Hydrolysis of the methylated aldotetraouronic acid with formic acid and examination of the hydrolyzate on paper chromatograms in solvent d showed two spots with the *p*-anisidine spray, R_G 0.83 and 0.91 in the visual ratio 1:2, together with a third component which remained near the base line (tri-*O*-methylglucuronic acid). The components were separated on a sheet of Whatman 3MM filter paper in solvent system d to give: 1. 2,3,4-Tri-*O*-methyl-D-glucuronic acid, chromatographically pure. It gave a single red spot with the *p*-anisidine spray, had R_G 0.84 in solvent system a moving to the same position as an authentic specimen and had $[\alpha]_D$ +40° (*c* 0.4). The acid (19 mg.) in methanol (2 ml.) was neutralized with diazomethane and concentrated to dryness. The residue in water (8 ml.) was reduced by the addition of sodium borohydride (10 mg.), and the excess reagent was destroyed by the addition of *N* sulfuric acid. 0.3 *M* sodium metaperiodate (0.3 ml.) was added and the mixture kept at 40° for 4 hr. The reaction mixture was extracted with chloroform (4 × 8 ml.), the extract dried (anhyd. Na_2SO_4) and allowed to evaporate on a watch glass. Crystals of 2,3,4-tri-*O*-methyl-L-xylose, m.p. 89°, were obtained, which on examination on paper chromatograms in solvent system d gave a single red spot with the *p*-anisidine spray, R_G 0.96 corresponding in position with authentic 2,3,4-tri-*O*-methylxylose.

2. 2,3,6-Tri-*O*-methyl-D-galactose whose specific optical rotation in 1% methanolic hydrogen chloride fell from $[\alpha]_D$ +40° to −27° (28 hr.). The sugar (19 mg.) did not crystallize. It had R_G 0.83 in solvent system d and moved to the same position as authentic 2,3,6-tri-*O*-methylgalactose.

3. 2,3,6-Tri-*O*-methyl-D-glucose (32 mg.) which on keeping gave crystals, m.p. and mixed m.p. 121°, $[\alpha]_D$ +72°.

Partial Hydrolysis of the Aldotetraouronic Acid U4.—The acid (95 mg.) was partially hydrolyzed by heating it with 0.1 *N* sulfuric acid (10 ml.) for 4 hr. at 95°. Neutralization ($BaCO_3$) and examination of the filtered hydrolyzate on paper chromatograms in solvent system d showed the presence of a small amount of the aldotrioruonic acid (U3) (R_{Gal} 0.10), a neutral disaccharide, R_{Gal} 0.61 ($[\alpha]_D$ +140), a large proportion of an aldobiouronic acid (U2) (R_{Gal} 0.46) and galactose and glucose in the visual ratio 3:1. The component (17 mg.) with R_{Gal} 0.46 was separated on a paper chromatogram and on reduction of its methyl ester with sodium borohydride gave crystals of cellobiitol, m.p. and mixed m.p. 143°.

Examination of the Neutral Sugars (D) Obtained from the Partial Acid Hydrolysis of the S VIII Polysaccharide.—The sirup D was examined on paper chromatograms in solvent system d, and detection with the *p*-anisidine spray showed galactose and glucose in the visual ratio 2:1 together with a disaccharide, R_{Gal} 0.62, and a trace amount of a spot corresponding in position with a trisaccharide, R_{Gal} 0.33 (trace). The sirup (D, 980 mg.) dissolved in water (50 ml.) was passed down a column of charcoal–Celite (1:1 w./w.; 3 × 28 cm.)[45] and the column eluted with water until all the monosaccharides had been removed, whereupon the column was eluted with 5% ethanol solution in water. Appropriate portions of the eluate were combined and concentrated to give the disaccharide (121 mg.) and a trisaccharide (8 mg.).

Characterization of the Neutral Disaccharide as 4-*O*-(α-D-Glucopyranosyl)-D-galactopyranose.—The disaccharide was chromatographically pure and had $[\alpha]_D$ +140° (*c* 1.1). Determination of its reducing power by alkaline hypoiodite gave a molecular weight of 349 (required 342). Hydrolysis with 2 *N* sulfuric acid for 8 hr. at 100° and paper chromatographic analysis of the hydrolysate showed the disaccharide to be composed of glucose and galactose in the ratio of 1:1. The disaccharide (5 mg.) was reduced with sodium borohydride (3 mg.) in water (2 ml.) at room temperature for 6 hr.; after removal of the ionic material (resins) the solution was hydrolyzed with sulfuric acid and examined on paper chromatograms in solvent system d. Detection with the *p*-anisidine spray showed only glucose, while detection with the silver nitrate spray showed glucose to be present together with a second component which corresponded in position to dulcitol and which produced a dark spot on the

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chromatogram at a rate corresponding to the authentic hexitol.

The disaccharide (78 mg.) was methylated with sodium hydroxide (15 ml., 30% w./w.) and methyl sulfate (5 ml.) followed by a second methylation using sodium hydroxide (10 ml., 30% w./w.) and methyl sulfate (4 ml.). The product, which was extracted with chloroform, was further methylated with Purdie reagents to give a sirup (70 mg.) having $[\alpha]_D$ +52° (*c* 1.0 in chloroform).

Anal. Calcd. for $C_{20}H_{38}O_{11}$: OMe, 54.6. Found: OMe, 54.2.

The methylated disaccharide (60 mg.) was hydrolyzed with 90% formic acid and the hydrolyzate examined chromatographically. In solvent system d *p*-anisidine revealed two spots, R_G 1.00 and R_G 0.83. The sugars were fractionated on a sheet of filter paper in solvent d and the sugars eluted from appropriate sections of the chromatogram. The fast moving component (R_G 1.00, 20 mg.) had $[\alpha]_D$ +80° (*c* 0.5) and gave an anilide which crystallized from light petroleum in the form of white needles, m.p. 132°. The slower moving component (R_G 0.83, 16 mg.) showed a change in its specific optical rotation from $[\alpha]_D$ +44° → −28° (28 hr.) when it was dissolved at 20° in 1% methanolic hydrogen chloride. The resultant glycoside was hydrolyzed, and the reducing sugar so obtained was oxidized with bromine water to give its aldono-γ-lactone, m.p. and mixed m.p. with authentic 2,3,6-tri-*O*-methyl-D-galactono-γ-lactone, 96°.

Periodate Oxidation of the S VIII Acidic Polysaccharide.—The polysaccharide (*ca.* 100 mg. accurately weighed) was dissolved in water (80 ml.), and the solution was adjusted to *p*H 2.2 by the addition of sulfuric acid; 0.3 *M* sodium metaperiodate solution (5 ml.) was added and the volume made up to 100 ml. A blank solution containing no polysaccharide was prepared similarly. Oxidation was allowed to proceed in the dark at 20°. At intervals, the periodate uptake was estimated by transferring samples (10 ml.), from the oxidation mixture and the blank, to a solution of 2 *N* sulfuric acid (15 ml.) containing 20% potassium iodide solution (4 ml.). The liberated iodine was titrated with 0.02 *N* sodium thiosulfate solution, using starch as an indicator. The molar periodate consumption per mole of anhydrohexose unit was as follows: 0.67 (after 8 hr.), 0.94 (20 hr.), 1.18 (48 hr.), 1.25 (72 hr.), 1.32 (96 hr.), 1.39 (120 hr.) and 1.44 (144 hr.). Extrapolation of the over oxidation part of the curve to zero time gave a value corresponding to a periodate uptake of 1.03 moles per anhydrohexose unit (*i.e.*, 165 g. for a polymer containing 1 hexuronic acid unit per 3 hexose units).

Hydrolysis of the Periodate Oxidized S VIII Polysaccharide.—The S VIII polysaccharide (110 mg.) was oxidized with periodate as described above. After 80 hr., ethylene glycol (5 ml.) was added to destroy the excess periodate, and the reaction mixture was dialyzed against water employing a cellulosic membrane. The concentrated non-dialyzable material was hydrolyzed with 90% formic acid (20 ml.) for 8 hr. at 100°. After removal of the formic acid, hydrolysis was continued with *N* sulfuric acid (8 ml.) for 2 hr. at 100°. Examination of the neutralized ($BaCO_3$) hydrolyzate on paper chromatograms failed to indicate the presence of hexose or hexuronic acid.

III. Discussion

The S VIII polysaccharide used in this investigation was prepared by E. R. Squibb and Sons, New Brunswick, N. J., and was supplied to us through the kindness of Professor M. Heidelberger. The polysaccharide which was free from protein and glucosan was first purified *via* its copper complex to give a material which is considered to be essentially homogeneous. It could not be further fractionated *via* its cetyltrimethylammonium salt, and on electophoresis using a glass fiber support and an electrolyte of borax and sodium hydroxide, the polysaccharide moved as a single sharp band. The polysaccharide recovered in both cases was chemically and physically indistinguishable from the original polysaccharide.

The polysaccharide had a high positive specific optical rotation $[\alpha]_D$ +121°, and its equivalent weight (703) is that expected of a hexose polymer having one hexuronic acid unit in four. The polysaccharide contained no nitrogen, phosphorus or ash and gave no color with iodine. Attempted autohydrolysis and attempted hydrolysis with 0.01 *N* sulfuric acid failed to liberate any reducing sugars, indicating the absence of furanose sugars. Total acid hydrolysis followed by paper chromatographic examination of the hydrolyzate showed the polysaccharide to be composed of galactose, glucose and glucuronic acid. The component sugars were separated chromatographically and identified as D-galactose, D-glucose and D-glucuronic acid. Quantitative estimation of the component sugars showed them to be present in the ratio D-galactose:D-glucose:D-glucuronic acid 1:2:1.

The S VIII acidic polysaccharide was reduced to the corresponding neutral hexose polymer by borohydride reduction of the esterified carboxyl group of the glucuronic acid. The original polysaccharide was freeze-dried in order to produce the largest possible surface area and was treated with a solution of diazomethane in ether. In the short contact time required to neutralize the polysaccharide, no secondary methylation occurred. Reduction of the aqueous solution of the esterified material with sodium borohydride effected an almost quantitative conversion of the glucuronic acid in the polymer to glucose. Acid hydrolysis of this new polysaccharide showed it to contain D-galactose (1 part) and D-glucose (3 parts).

Hydrolysis of the methylated S VIII polysaccharide afforded 2,3-di-*O*-methyl-D-glucuronic acid (1 part), 2,3,6-tri-*O*-methyl-D-galactose (1 part) and 2,3,6-tri-*O*-methyl-D-glucose (2 parts), each identified by the preparation of crystalline derivatives. As no other methyl sugars were detected, the above evidence indicates that the polysaccharide is a high molecular weight, straight chain polymer containing 1 → 4 links only.

The methylated, borohydride reduced S VIII polysaccharide appeared to be homogeneous and on hydrolysis afforded 2,3,6-tri-*O*-methyl-D-galactose (1 part) and 2,3,6-tri-*O*-methyl-D-glucose (3 parts). The absence of any 3,4,6-tri-*O*- or 2,3,4-tri-*O*-methylhexose, and hence the absence of any small proportion of any 1 → 2 or 1 → 6 links in the original polysaccharide, was shown by the fact that no formaldehyde was produced on the periodate oxidation of the reduced ($NaBH_4$) mixture of tri-*O*-methylhexoses.

In a subsidiary experiment it was found that the periodate oxidation of the tri-*O*-methylhexitols obtained on the borohydride reduction of 3,4,6-tri-*O*- and 2,3,4-tri-*O*-methylhexoses produced 1 mole of formaldehyde per mole of tri-*O*-methylhexitol. Periodate oxidation of the reduced 2,3,6-tri-*O*-2,4,6-tri-*O*-methylhexoses failed to liberate any formaldehyde. The proportions of 3,4,6-tri-*O*-methylaldohexose and 2,3,6-tri-*O*-methylaldohexose in a synthetic mixture were determined in this way with an error of less than 1%. The procedure has proved of use in the determination of the proportions of tri-*O*-methylhexoses in the hydroly-

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zates of methylated polysaccharides especially when only micro amounts were available.

The evidence obtained from an examination of the hydrolysis products of the methylated neutral polysaccharide above again indicates that the original polysaccharide is a long straight-chain polymer joined throughout by 1 → 4 links.

Partial acid hydrolysis of the S VIII polysaccharide was effected with dilute sulfuric acid. The acid oligosaccharides were absorbed on ion-exchange resins and fractionally eluted with dilute formic acid. The neutral sugars were separated chromatographically to give the monosaccharides glucose and galactose, a disaccharide and a trisaccharide (trace, not examined). One aldobiouronic acid was obtained which was identical with that previously obtained and characterized by Goebel[13] as 4-*O*-(β-D-glucopyranosyluronic acid)-D-glucopyranose. The β-linkage originally assigned to the acid was confirmed by reduction of the methyl ester of the acid with sodium borohydride to give crystalline cellobiitol.

One aldotriouronic acid was obtained which on hydrolysis gave D-glucuronic acid (1 part) and D-glucose (2 parts). Hydrolysis of the methylated acid gave 2,3,4-tri-*O*-methyl-D-glucuronic acid and 2,3,6-tri-*O*-methyl-D-glucose. The low positive specific optical rotation, $[\alpha]_D$ +12°, indicated that both links had the β-configuration, a conclusion which was borne out by the reduction of the methyl ester of the acid with sodium borohydride, to give crystalline cellotriitol. The experimental evidence indicates the aldotriouronic acid to be *O*-β-D-glucopyranosyluronic acid-(1 → 4)-*O*-β-D-glucopyranosyl-(1 → 4)-D-glucopyranose. One aldotetraouronic acid was obtained which on hydrolysis gave D-glucuronic acid (1 part), D-galactose (1 part) and D-glucose (2 parts). Hydrolysis of a small amount of the directly reduced ($NaBH_4$) acid, followed by paper chromatographic examination of the hydrolyzate, showed the presence of glucuronic acid, glucose and dulcitol. Since no galactose or sorbitol could be detected in the hydrolyzate, the galactose must form the reducing end group of the molecule. Hydrolysis of the methylated acid gave 2,3,4-tri-*O*-methyl-D-glucuronic acid (1 part), 2,3,6-tri-*O*-methyl-D-galactose (1 part) and 2,3,6-tri-*O*-methyl-D-glucose (2 parts). Partial acid hydrolysis of the aldotetraouronic acid gave a small amount of the aldotriouronic acid previously characterized, a small amount of a neutral disaccharide, chromatographically identical with the disaccharide obtained from the partial hydrolysis of the original polysaccharide, and a large proportion of an aldobiouronic acid identified as 4-*O*-(β-D-glucopyranosyluronic acid)-D-glucopyranose. The experimental evidence indicates the structure of the aldotetraouronic acid to be *O*-β-D-glucopyranosyluronic acid-(1 → 4)-*O*-β-D-glucopyranosyl-(1 → 4)-*O*-α-D-glucopyranosyl-(1 → 4)-D-galactopyranose. The linkage between the glucose and galactose residue is assigned the α-configuration to account for the increase of the specific optical rotation from $[\alpha]_D$ +12° for the aldotriouronic acid to $[\alpha]_D$ +65° for the aldotetrauronic acid. The α-configuration assigned to this terminal link is also supported by the isolation of the neutral disaccharide 4-*O*-(α D-glucopyranosyl)-D-galactopyranose with the high optical rotation of $[\alpha]_D$ +140°, after hydrolysis of the tetrasaccharide. The neutral disaccharide which also was obtained from partial hydrolysis of the S VIII polysaccharide gave, on hydrolysis, glucose and galactose. Hydrolysis of a small amount of the reduced ($NaBH_4$) disaccharide followed by paper chromatographic examination of the hydrolyzate indicated the presence of glucose and dulcitol. This observation shows that galactose forms the reducing part of the molecule. Hydrolysis of the methylated disaccharide gave 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,6-tri-*O*-methyl-D-galactose. The high specific optical rotation ($[\alpha]_D$ +140°) of the disaccharide, considered in conjunction with the above evidence, leads to the sugar being assigned the structure 4-*O*-α-D-glucopyranosyl-D-galactopyranose. No pentaouronic acid could be detected chromatographically, and since the composition of the original polysaccharide would not allow for one if the polymer is to be composed of a single structural repeating unit, the S VIII polysaccharide is believed to be composed of a four-unit repeating block with the structure of the tetraouronic acid. The nature of the link joining the galactose to the glucuronic acid unit in the polymer has not been decided, but the high positive specific rotation of the original polysaccharide indicates that it may be of the α-type. Partial hydrolysis of the neutral ($NaBH_4$ reduced uronic acid free) polysaccharide is at present being carried out in an attempt to isolate the 4-*O*-D-galactopyranosyl-D-glucopyranose disaccharide and to determine its mode of linkage.

The S VIII acidic polysaccharide was oxidized with metaperiodate in a solution adjusted to *p*H 2.2, a *p*H at which hydrolysis of the intermediate formyl esters is a minimum[46,47] and hence "over oxidation" is also at a minimum. Extrapolation of the "over oxidation" part of the periodate curve to zero time gave a value for the periodate uptake corresponding to 1.03 mole of periodate per anhydrohexose unit. An entirely 1 → 4 linked hexapyranose linear polymer should show an uptake of 1.0 mole of periodate per anhydrohexose unit. The experimental result is therefore in agreement with the structure of the polymer put forward as a result of methylation and partial hydrolysis studies. Hydrolysis of the periodate-oxidized S VIII polysaccharide followed by paper chromatographic examination of the hydrolyzate failed to reveal the presence of any sugars. This latter evidence indicates the absence of any 1 → 3 links in the polymer structure.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Amino Acid Sequence of Glucagon. I. Amino Acid Composition and Terminal Amino Acid Analyses

BY W. W. BROMER, A. STAUB, E. R. DILLER, H. L. BIRD, L. G. SINN AND OTTO K. BEHRENS

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Evidence is presented that glucagon is a small protein, consisting of a single chain of 29 amino acid residues. The N-terminal amino acid is histidine as determined by the dinitrophenylation method; the C-terminal residue is threonine on the basis of evidence obtained from hydrazinolysis and carboxypeptidase treatment. Glucagon contains single residues of 7 amino acids; among them, methionine, tryptophan, valine and alanine are liberated from the C-terminus of the molecule by carboxypeptidase.

Introduction

The preparation[1] in this Laboratory of a crystalline material of pancreatic origin, glucagon, has made available a model protein for fundamental biological and structural studies. This series of papers will present evidence leading to the elucidation of the complete amino acid sequence of glucagon. The present paper describes the quantitative amino acid analysis and other fundamental studies of primary importance to the sequence determination.

Experimental

Materials and Procedures.—The glucagon used throughout the structure work was a twice-recrystallized lot (#208-158B-292A) prepared from hog pancreas that was homogeneous according to end group analysis and zone electrophoresis on starch.[1] The high purity of the sample is also demonstrated by the analyses reported below which show good over-all recovery, a complete absence of isoleucine, proline and cystine, and, in general, good stoichiometric relationships of the amino acid residues.

Moisture content of the preparation was 10.9% as determined by drying for 24 hr. at 100° *in vacuo* over P_2O_5. The nitrogen content was 17.45% (Kjeldahl).

For the study of amino acid composition, accurately weighed samples of crystalline glucagon were hydrolyzed for 20 or 72 hr. in the absence of air at 107 to 109° in about 200 volumes of 5.7 *N* HCl redistilled three times in glass. The hydrolyzates were processed in a manner similar to that described by Smith and Stockell.[2] The hydrolyzates often contained traces of humin and had a faint blue-gray hue. The presence of trace metals in the crystalline preparation may have catalyzed the destruction of tryptophan since later crystalline preparations isolated in the presence of Versene produced light straw-colored hydrolyzates. Humin formation did not hamper the handling of the sample and probably did not affect the results.

Amino Acid Determination.—The comparatively rapid Levy[3] method, based on the paper chromatographic separation of the dinitrophenyl- (DNP-) amino acids, was employed initially in the work and was followed by the more rigorous Dowex 50 column chromatographic method of Moore and Stein.[4] The dinitrophenylation method furnished adequate preliminary data to support the structure work and, as will be reported, the two methods gave similar results.

The Dinitrophenylation Method.—Throughout this work dinitrophenylations were performed for 90 min. at 40°, *p*H 9.0, essentially following the Levy modification[3] of the method of Sanger.[5] Prior to the paper chromatographic separation of the DNP-amino acids, dinitrophenol was removed by sublimation according to the method described by Mills.[6] DNP-derivatives were identified by comparison with known DNP-amino acids.[7]

Only 20 hr. hydrolyzates were used with the Levy method since no DNP-peptides were observed. Recognizing that the correction factors published by Levy for the destruction of the amino acids in insulin may not be completely applicable to another protein handled under different conditions, new factors were determined for glucagon. This was accomplished by utilizing the insulin factors as a first approximation. From these data a synthetic amino acid mixture resembling glucagon was prepared, hydrolyzed and treated identically to a protein hydrolyzate. In this manner new destruction factors were calculated. This process was repeated, giving a more precise set of correction factors which were used in the calculation of the number of amino acid residues in glucagon. The correction factors are as follows: aspartic acid, 1.10; threonine, 1.22; serine, 1.32; glutamic acid, 1.20; glycine, 1.33; alanine, 1.28; valine, 1.20; methionine, 2.12; tyrosine, 1.60; phenylalanine, 1.20; histidine, 2.19; lysine, 0.70; and arginine, 1.38. Of interest is the finding that, in every instance, the factors are higher than those reported by Levy, averaging about 17% greater. Histidine and methionine particularly appear to be subject to greater losses than previously reported.[3]

Table I indicates the results of the preliminary amino acid analysis by the Levy method. With the relatively few analyses it is not surprising that the tyrosine and arginine values do not fall near whole-residue figures. Di-DNP-tyrosine analyses at best are quite variable,[3] and DNP-arginine, being water-soluble, is rather difficult to desalt completely prior to paper chromatography. Indeed, the water-soluble DNP-derivatives of histidine, lysine and arginine have generally proved to be difficult to handle. Ex-

TABLE I

AMINO ACID ANALYSIS OF GLUCAGON

Amino acid	Av. quantity found,[a] μM	Calcd. no. of amino acid residues[b]	No. of amino acid residues to nearest integer
Aspartic acid	0.34	4.0	4
Threonine	.24	2.8	3
Serine	.30	3.5	4[c]
Glutamic acid	.24	2.8	3
Glycine	.09	1.1	1
Alanine	.09	1.1	1
Valine	.08	0.9	1
Methionine	.06	.7	1
Leucine	.18	2.1	2
Tyrosine	.13	1.5	1 or 2
Phenylalanine	.17	2.0	2
Histidine	.11	1.3	1
Lysine	.08	0.9	1
Arginine	.22	2.6	2 or 3
Tryptophan[d]	.085	1.0	1
			28–30

[a] Average of 2 or 3 analyses with exception of single glycine determination. [b] On basis of 7 amino acids being present as single residues. (0.085 μM is average of 7.) [c] Since serine is subjected to approximately 10% destruction during acid hydrolysis (*cf.* Table II), 4 is a more reasonable figure than 3. [d] Chemical analysis.[8]

(1) A. Staub, L. Sinn and Otto K. Behrens, *J. Biol. Chem.*, **214**, 619 (1955).

(2) E. L. Smith and A. Stockell, *ibid.*, **207**, 501 (1954).

(3) A. L. Levy, *Nature*, **174**, 126 (1954).

(4) S. Moore and W. H. Stein, *J. Biol. Chem.*, **192**, 663 (1951).

(5) F. Sanger, *Biochem. J.*, **39**, 507 (1945).

(6) G. L. Mills, *ibid.*, **50**, 707 (1952).

(7) Authentic DNP-amino acids were kindly supplied by Dr. Hans Neurath, Univ. of Washington, Seattle, Wash.

(8) J. C. Reid and D. C. Chambers, *Anal. Chem.*, **20**, 30 (1948).

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TABLE II

Gram amino acid residue per 100 g. protein

Amino acid	Time of hydrolysis: 20 hr. Hydrolyzate A	20 hr. Hydrolyzate B	20 hr. Av.	72 hr. Hydrolyzate A	72 hr. Hydrolyzate B	72 hr. Av.	Av. or extrap.*
Aspartic acid	13.3	13.1	13.1	12.8	12.8	12.6	13.3*
Threonine	8.17	8.16	8.20	7.74	(6.77)[a]	7.64	8.43*
Serine	8.63	8.93	8.72	6.75	6.64	6.76	9.62*
Glutamic acid	10.6	11.8	11.1	10.5	10.3	10.7	10.9
Glycine	1.82	1.61	1.60	1.93	1.44	1.56	1.58
Alanine	2.47	2.18	2.12	2.44	2.00	2.17	2.14
Valine	2.54	3.74	2.88	2.48	2.62	2.56	2.72
Methionine	3.33	3.99	3.51	3.22	2.83	3.14	3.32
Leucine	6.71	(8.05)	6.52	6.19	6.18	6.31	6.40
Tyrosine	9.09	8.99	9.20	(9.47)	8.34	8.27	9.59*
Phenylalanine	8.38	8.82	8.25	8.58	7.97	8.56	8.40
Histidine	3.85	3.28	3.51	3.25	2.98	3.22	3.37
Lysine	3.69	3.61	3.68	3.21	3.61	3.33	3.56
Ammonia ($-NH_2$)	3.02	2.65	2.85	3.80	3.78	3.54	2.62*
Arginine	8.75	(9.60)	8.87	7.88	8.40	8.38	8.54
Tryptophan[b]							5.20

[a] Values in parentheses not included in averages. [b] Average of 3 chemical analyses.[8]

traction from dilute acid solution into redistilled *n*-butanol provided a convenient method of preparing these derivatives for chromatography.

The values found for the other amino acids were reasonably close to whole residue units. The Levy method, used in this fashion, quickly and conveniently provided data on the amino acid composition of glucagon. These data provided an adequate working hypothesis during most of the structure determination.

Dowex 50 Method.—The elution curves in Fig. 1 illustrate the separation of amino acids achieved with the column chromatographic method of Moore and Stein.[4] The data of duplicate runs with two different hydrolyzates each at 20 and 72 hr. are given in Table II.

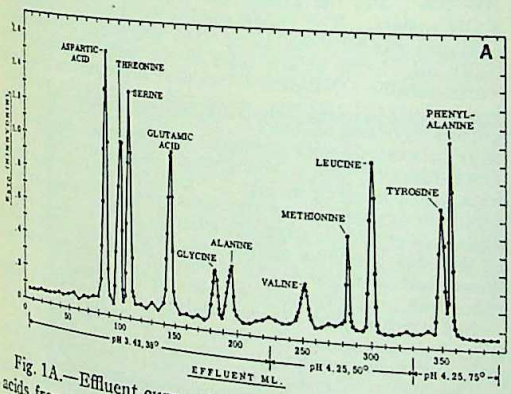

Fig. 1A.—Effluent curve of the neutral and acidic amino acids from a 72 hr. hydrolyzate of glucagon separated by chromatography on a 0.9 × 100 cm. column of Dowex 50-X8 resin. The quantity of hydrolyzate employed was 1.77 mg. The intensity of the color produced by reaction of the one ml. effluent fractions with ninhydrin was determined at 570 mμ in a Model B Beckman spectrophotometer. The elution curve obtained from these data is shown, with no corrections for base-line color or the various amino acid color yields.

In spite of the excellent repeatable separation of the amino acids, some variability in results was experienced. This was shown to be due to contamination with atmospheric ammonia. Because of these variations the data were subjected to the "t" test to determine whether or not the mean values found for 20 and 72 hr. differed significantly. It was found that the recoveries of aspartic acid, threonine, serine and tyrosine decreased with longer times of hydrolysis. Glutamic acid, methionine, histidine and arginine values appeared to decrease slightly; however, the difference between the 20 and 72 hr. values was not statistically significant.

The approximate percentage of destruction of these amino acids after 24 hr. of hydrolysis is: aspartic acid, 2%; threonine, 3.5%; serine, 11%; tyrosine, 5%. This rate of destruction is in reasonable accord with data published by Hirs, Stein and Moore,[9] Smith and associates,[2,10] and Rees[11] for other proteins and amino acid mixtures. Corrections for the losses of these acid-labile amino acids were calculated by extrapolation of the analytical data to zero time, assuming first-order kinetics for the decomposition (*cf.* 2, 9, 10). The method of calculation of Hirs, Stein and Moore[9] was employed.

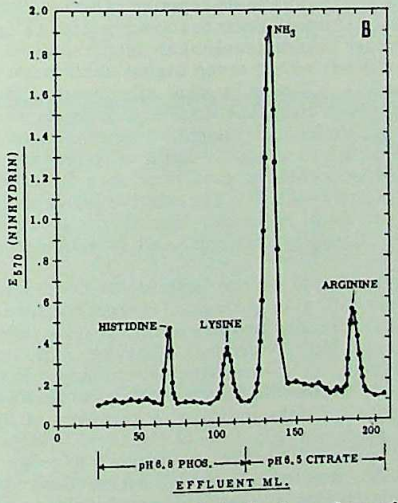

Fig. 1B.—Effluent curve of the basic amino acids from a 72 hr. hydrolyzate of glucagon separated by chromatography on a 0.9 × 15 cm. column of Dowex 50-X8 resin. The quantity of hydrolyzate analyzed was 1.77 mg. No corrections were applied for the base-line color or for the color yields of the various amino acids.

The amino acid composition and minimal molecular weight of glucagon calculated from these data are summarized in Table III.

(9) C. H. W. Hirs, W. H. Stein and S. Moore, *J. Biol. Chem.*, **211**, 941 (1954).

(10) E. L. Smith, A. Stockell and J. R. Kimmel, *ibid.*, **207**, 551 (1954).

(11) M. W. Rees, *Biochem. J.*, **40**, 632 (1946).

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TABLE III

AMINO ACID COMPOSITION AND MOLECULAR WEIGHT OF GLUCAGON

Amino acid	G. amino acid residue/100 g. protein	G. amino acid/100 g. protein	N as % total N	Minimal mol. wt.	Assumed no. of residues	Calcd. mol. wt.	Calcd. no. of residues/mol. wt. 3550
Aspartic acid	13.3	15.4	9.29	864	4	3460	4.11
Threonine	8.43	9.93	6.69	1200	3	3600	2.96
Serine	9.62	11.6	8.86	909	4	3640	3.91
Glutamic acid	10.9	12.4	6.22	1190	3	3570	2.98
Glycine	1.58	2.08	2.23	3610	1	3610	0.98
Alanine	2.14	2.68	2.42	3320	1	3320	1.07
Valine	2.72	3.22	2.21	3640	1	3640	0.97
Methionine	3.32	3.77	2.03	3960	1	3960	.90
Leucine	6.40	7.42	4.54	1770	2	3540	2.01
Tyrosine	9.59	10.6	4.70	1710	2	3420	2.08
Phenylalanine	8.40	9.42	4.58	1750	2	3500	2.03
Histidine	3.37	3.81	5.92	4070	1	4070	0.87
Lysine	3.56	4.06	4.46	3600	1	3600	.99
Ammonia	1.83[a,b]	1.94	9.16	876	4[a]	3500	4.05[a]
Arginine	8.54	9.52	17.6	1830	2	3660	1.94
Tryptophan	5.20	5.71	4.49	3580	1	3580	0.99
Totals	97.07	113.56	95.4		29	3550[c]	28.79
						3600[d]	

[a] Not included in totals or averages. [b] Direct chemical analysis.[11] [c] Average molecular weight from all residues except methionine and histidine, whose recoveries appeared to be low. [d] Average molecular weight for all residues.

The values for the stable amino acids represent averages of at least seven determinations. For most of the labile amino acids each point on the extrapolation curve was an average of four analyses. The amide NH_3 value listed was obtained by direct chemical analysis[11] and is an average of four determinations. Extrapolation of the chromatographic data yielded a significantly higher result. It is likely that this discrepancy may be attributed to the accumulation of NH_3 from air and the buffers. That this was indeed the case was verified by direct NH_3 analyses of the hydrolyzates prior to chromatography. The values obtained after correction for NH_3 from the destruction of serine and threonine (*cf.* 2, 9, 10, 11) were similar to those reported in Table III.

The average minimal molecular weight of 3550 was calculated on the basis that seven amino acids were present as single residues. This is in good agreement with the value of 3485 derived from the empirical formula of glucagon. Preliminary molecular weight determinations in 2 *M* guanidine solutions using the artificial boundary cell in the ultracentrifuge provided evidence for a molecular weight of approximately 4000.[12] The relative insolubility of glucagon and the small molecular size of the molecule render such physical studies difficult, and further determinations are planned.

An average yield of one mole of di-DNP-histidine was obtained per 3500 g. of glucagon. Direct chemical analysis[13] provided evidence for two free amino groups; these may be attributed to the N-terminal histidine and the ϵ-amino group of lysine. The small quantity of sulfur in the protein is completely accounted for by a single methionine residue.

The analytical data indicated a recovery of 97% of the weight of glucagon and 95% of the total nitrogen. These losses are reflected in the determined average molecular weight, 3550, which is about 2% higher than the value of 3485 calculated from the resulting empirical formula.

The data obtained from the two methods of amino acid analysis (*cf.* Tables I and III) is in good over-all agreement. In our hands, the data obtained from the Dowex 50 column method was more precise than that obtained from the dinitrophenylation technique. As previously discussed, the latter method utilizes inherently large correction factors. In addition, uncertainty exists in the analysis for certain DNP-amino acids. Advantages of the Levy method appear to be speed, ease of operation, use of a small sample, and the ability to simultaneously analyze a number of samples. The method was of particular value in this work as a rapid means of determining the approximate amino acid composition of glucagon, and later as a convenient method of analysis for certain of the smaller degradation peptides of glucagon.

N-Terminal Analysis.—Seven mg. ($^2\mu$moles) of glucagon was dinitrophenylated for 90 min. according to the method of Levy.[3] Excess reagent was removed by extraction of the basic reaction mixture with ether. Upon acidification (*p*H 1.0) of the aqueous solution the yellow DNP-protein derivative precipitated. After washing with cold dilute acid, the precipitate was hydrolyzed in 5.7 *N* HCl for 24 hr. at 107–109°, and the excess HCl was removed *in vacuo* over KOH pellets. The yellow residue was redissolved in dilute acid and was extracted three times with ether, leaving essentially all of the yellow color in the aqueous phase. The water-soluble DNP-derivatives were subsequently extracted into *n*-butanol and were separated by the paper chromatographic system of Levy.[3] Two yellow DNP-amino acids were observed with properties indistinguishable from di-DNP-histidine and ϵ-DNP-lysine. A photograph of a chromatogram is given in Fig. 2. Calculations from the ultraviolet determination of the eluted spots indicated an average recovery from triplicate analyses of 0.49 mg. (1 μmole) of di-DNP-histidine per 3.5 mg. of glucagon. These data show that histidine is the N-terminal amino acid, and also corroborate that lysine is located within the chain.

C-Terminal End Group Analysis.—Two methods were used to examine the C-terminus of glucagon, hydrazinolysis[14] and carboxypeptidase treatment.

The hydrazinolysis of glucagon was carried out in a manner similar to that originally described by Akabori and coworkers.[14] Heating the dry protein with hydrazine caused a splitting of peptide bonds, with formation of the hydrazides of all amino acids except the C-terminal one. The hydrazides were removed, in this case by condensation with benzaldehyde to form dibenzals, and the free C-terminal amino acid was identified. Care must be exercised to exclude water from the reaction since hydrolysis of the peptide bonds may then occur. Glucagon was dried *in vacuo* for 24 hr. at 100° over P_2O_5. In a typical experiment 24.4 mg. (7 μM) of the dried preparation was dissolved in 3 ml. of fresh anhydrous hydrazine. The reaction mixture was quickly sealed under N_2 and was incubated at 125 ± 3° for 7.5 hr. The excess reagent was removed *in vacuo* over H_2SO_4. The dried, white residue was redissolved in 3 ml. of H_2O, and 0.3 ml. of benzaldehyde was added. The mixture was shaken for about 5 min., was centrifuged, and the light orange benzaldehyde phase was washed once with 1 ml. of water. The benzaldehyde layer was discarded, and the

(12) Value determined by E. O. Davisson and H. W. Fisher, Physicochemical Research Division, Lilly Research Laboratories.

(13) Determined using a time study with the method of D. D. Van Slyke, *J. Biol. Chem.*, **12**, 275 (1912).

(14) S. Akabori, K. Ohno and K. Narita, *Bull. Chem. Soc. Japan*,

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process was repeated 3 times with the combined aqueous phase and wash.

At the end of the treatment both the aqueous and organic phases were water-clear. The resulting aqueous phase, about 7 ml., was evaporated under a stream of nitrogen and finally was washed into a 1-ml. volumetric flask. Aliquots were removed for one-dimensional paper chromatography in *n*-butanol–acetic acid–water (4:1:1), and for two-dimensional chromatography according to the method of Redfield.[15]

These paper chromatographic systems provided fast, qualitative identification of amino acids and, in addition, each was adapted for use in quantitative amino acid analysis. The analytical method of Connell, Dixon and Hanes[16] was used in conjunction with the chromatographic system using the solvent butanol:acetic acid:water. In the two-dimensional system of Redfield the chromatograms were developed by use of 0.2% ninhydrin in acetone. The ninhydrin-reacted amino acid spots were excised and were eluted with 75% acetone. The solutions were subjected to spectrophotometric analysis at 570 mμ. In both methods standard recovery curves of all the amino acids in glucagon were employed for quantitative analysis. Both methods were found to be useful in the analysis of hydrolyzates of small peptides as well as in the determination of the hydrazinolysis product.

In both chromatographic systems one major hydrazinolysis product was observed, indistinguishable from threonine. A photograph of such a chromatogram after the method of Redfield is given in Fig. 3. Traces of methionine were also found in some experiments. In these analyses 0.7–0.9 mole of threonine was found per mole of glucagon. Since the hydrazinolysis reaction clearly released only threonine in good yield, this amino acid must be the C-terminal residue of glucagon.

Carboxypeptidase Method.—To confirm the hydrazinolysis result, and to obtain additional data concerning the amino acids near the C-terminal end, glucagon was incubated with carboxypeptidase; the amino acids which were liberated were determined at various intervals during the incubation. The method of amino acid analysis employed in this work was essentially that of Levy[3] and was first used in this manner by Harris, Li, Condliffe and Pon.[17]

Crystalline carboxypeptidase[18] was washed three times with cold distilled water. The concentration of the enzyme was determined prior to each experiment by removing an aliquot of the suspension, dissolving the enzyme in dilute alkali, and determining the absorption at 280 mμ. The crystalline enzyme (0.6 μ*M*) was suspended in 1 ml. of 0.02 *N* $NaHCO_3$ and was dissolved by the dropwise addition of 0.1 *N* NaOH. The solution was immediately adjusted to pH 8.5 to 9 by the addition of 0.1 *N* HCl, and a 50-fold molar excess of diisopropylfluorophosphate (DFP) (0.1 *M* in isopropyl alcohol) was added. Upon the addition of DFP a sharp drop in *p*H occurred. The solution was quickly readjusted to *p*H 8.5 to 9 with 0.1 *N* NaOH, and was allowed to incubate at room temperature for 15 to 20 min.

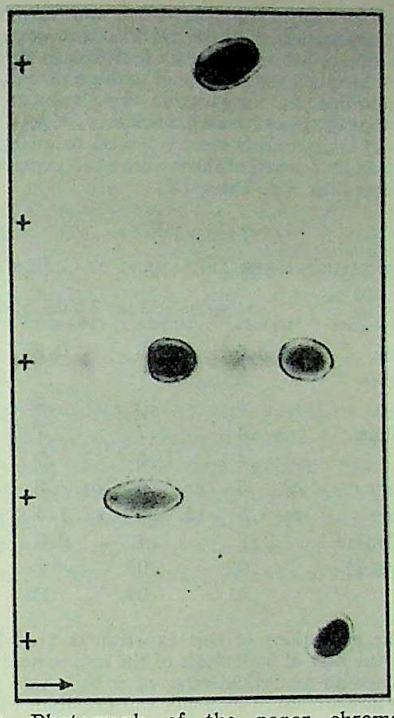

Fig. 2.—Photograph of the paper chromatographic separation of the DNP-derivatives resulting from the hydrolysis of DNP-glucagon. Reference lanes of authentic DNP-amino acids were run simultaneously. Spots were outlined in pencil for subsequent excision, elution and analysis.

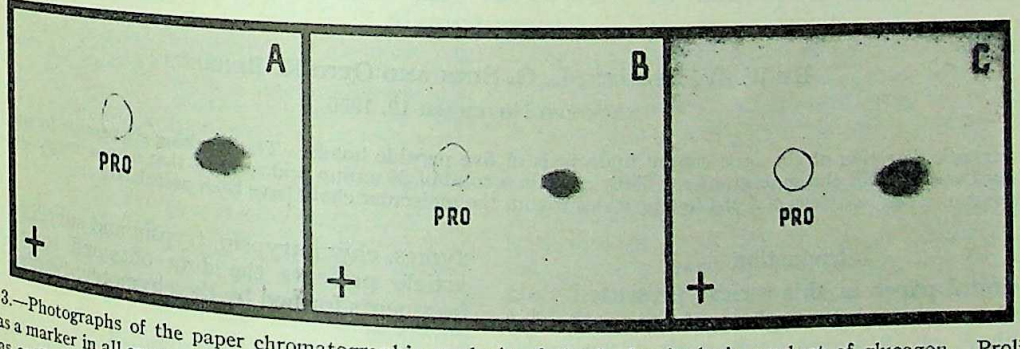

Fig. 3.—Photographs of the paper chromatographic analysis of the hydrazinolysis product of glucagon. Proline was added as a marker in all cases. Since ninhydrin reagent was used to visualize the amino acid spots, the faint yellow proline spot was outlined for purposes of identification: A, product of the hydrazinolysis of 0.04 μ*M* of glucagon; B, threonine (0.03 μ*M*); C, hydrazinolysis product plus 0.03 μ*M* of threonine.

The enzyme solution was added to 14 mg. (4 μmoles) of crystalline glucagon dissolved in 5 ml. of dilute NaOH (*p*H 9.0). The enzyme:substrate molar ratio was approximately 1:65. The volume was adjusted to 7.5 ml., the solution was incubated at room temperature (34°), and appropriate aliquots were removed at 20, 50 and 180 min., as well as at 24 hr. The aliquots were pipetted directly into 15-ml. beakers containing HCl sufficient to adjust the *p*H to approximately 2.5. Those aliquots which were not immediately dinitrophenylated were kept frozen until they could be reacted. In each instance dinitrofluorobenzene was added prior to raising the *p*H to 9.0. The DNP-amino acids were separated by paper chromatography as discussed previously. Since DNP-asparagine and DNP-glutamine do not separate under these conditions, this single spot was eluted and rerun

(15) R. R. Redfield, *Biochim. et Biophys. Acta*, **10**, 344 (1953).
(16) G. E. Connell, G. H. Dixon and C. S. Hanes, *Canad. J. Biochem. and Physiol.*, **33**, 416 (1955).
(17) J. I. Harris, C. H. Li, P. G. Coudliffe and N. G. Pon, *J. Biol. Chem.*, **209**, 133 (1954).
(18) Kindly supplied by Dr. Hans Neurath, Univ. Washington School of Medicine.

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on a system described by Blackburn and Lawther[19] that gives good separation of these DNP-amino acids. DNP-aspartic acid was also positively identified in this manner. Because of the increased number of manipulations, the analysis of glutamine and asparagine was subject to more error than that of the other amino acids.

At least 11 amino acids were released to an appreciable extent after 24 hr.; seven of these were nearly quantitatively liberated after 3 hr. (*cf.* Table IV).

TABLE IV

CARBOXYPEPTIDASE TREATMENT OF GLUCAGON

Amino acid liberated by carboxypeptidase	μM amino acid per 3.5 mg. glucagon 20 min.	50 min.	180 min.	24 hr.
Threonine	0.6	0.8	0.8	1.1
Methionine	.5	.7	.7	0.9
Valine	.5	.6	.8	.9
Tryptophan	.4	.7	.7	.9
Leucine	.4	.6	.7	.9
Asparagine	*ca.* .5	*ca.* .6	*ca.* .8	*ca.* 1.0
Glutamine	*ca.* .5	*ca.* .6	*ca.* 1.4	*ca.* 1.6
Phenylalanine	.2	.4	0.6	0.6
Aspartic acid	.02	.05	.2	.5
Alanine	.01	.02	.06	.3

Under the conditions of this experiment very little differential in the rate of hydrolysis of the amino acids was observed. Since an analytical error of ±10% was expected, no absolute assignment of sequence was possible. However, the data in Table IV indicate that threonine was probably liberated most rapidly by carboxypeptidase. These data, in conjunction with the clear-cut hydrazinolysis result showed that threonine is the carboxyl-terminal amino acid. The enzymatic release of methionine, tryptophan, valine and alanine is of considerable importance since these amino acids occur only once in the molecule. Obviously these amino acids can serve as markers for orientation of peptide fragments near the C-terminus of the molecule. Since a small amount of alanine and somewhat greater amounts of phenylalanine and aspartic acid were liberated, these amino acids are probably located at a position further removed from the C-terminus. Similarly, the gradual increase in the glutamine analysis to a value greater than one may be interpreted in terms of release of a second residue nearer the center of the molecule.

If optimum conditions had been found for the enzymatic reaction, additional sequential information could be obtained. Such experiments were planned, but before they had been conducted other data became available[20] that obviated the need for further carboxypeptidase experiments.

The evidence indicated that glucagon is a single chain polypeptide. The data make possible formulation of the following partial structure for glucagon.

$$\text{His(ser}_4\text{,glu,gly,thr}_2\text{,phe,asp}_2\text{,tyr}_2\text{,lys,leu,arg}_2\text{)ala(asp,phe,}\underset{\text{glu}_2\text{,asp,leu,try,val,met)thr}}{\overset{\text{NH}_2\text{NH}_2}{|\quad|}}$$

Acknowledgment.—The authors gratefully acknowledge the expert technical assistance of R. G. Scheib, C. T. Pugh and E. E. Logsdon.

(19) S. Blackburn and A. G. Lawther, *Biochem. J.*, **48**, 126 (1951).

(20) Papers II, III, IV and V in this series, THIS JOURNAL, **79**, 2798, 2801, 2805, 2807, (1957).

(21) The abbreviations for the amino acid residues used in these papers are those of E. Brand and J. T. Edsall, *Ann. Rev. Biochem.*, **16**, 224 (1947).

(22) Throughout this series of papers the arrangement of peptides is patterned after that suggested by F. Sanger, *Advances in Protein Chemistry*, **7**, 1 (1952).

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Amino Acid Sequence of Glucagon. II. The Hydrolysis of Glucagon with Chymotrypsin

BY W. W. BROMER, L. G. SINN AND OTTO K. BEHRENS

RECEIVED NOVEMBER 19, 1956

Chymotryptic digestion of glucagon caused hydrolysis of five peptide bonds. The resulting six peptide fragments were isolated by Dowex 50-X2 chromatography. They contain a total of 29 amino acid residues that have a composition identical to glucagon. The locations of 4 of these peptides within the molecular chain have been postulated.

Introduction

The inital paper in this series[1] presented data which demonstrated that glucagon consists of a single chain of 29 amino acids with a molecular weight of 3485. Single residues of methionine, tryptophan, valine, alanine, lysine, glycine and histidine were found. Histidine and threonine were determined as the N- and C-terminal residues, respectively. Furthermore, incubation with carboxypeptidase showed that methionine, tryptophan, valine and a small quantity of alanine, were liberated from the C-terminal portion of the molecule. To determine the sequence of the 29 amino acids in this polypeptide, an enzymatic degradative approach[2] was followed using the proteolytic enzymes, chymotrypsin, trypsin and subtilisin. This article presents the data obtained from peptide fragments formed by the chymotryptic digestion of glucagon.

Experimental

Materials.—Twice-recrystallized glucagon (Lot 208-158B-292A) was employed for all experiments.

Crystalline chymotrypsin (Lot CD 521) was obtained from Worthington Biochemical Corporation, Freehold, New Jersey.

Incubation of Glucagon with Chymotrypsin.—Glucagon (0.085%) was incubated with chymotrypsin (0.005%) at 37° in a dilute sodium acetate solution at *p*H 7.8 (enzyme: substrate molar ratio, about 1:120). Solution of the substrate was routinely accomplished by adjustment of the *p*H to 10 with 0.1 *N* NaOH. The reaction mixture was adjusted to *p*H 7.8 with 0.8 *N* HOAc and it remained essentially at this *p*H throughout the incubation.

In the preparative experiments the digests were acidified to *p*H 2.0, heated to 90° for 3 min., frozen and lyophilized.

(1) Reference to Paper I in this series, THIS JOURNAL, **79**, 2794 (1957).

(2) Consideration has been given to the possibility of enzyme-catalyzed rearrangements as first suggested by the work of M. Bergmann and O. K. Behrens, *J. Biol. Chem.*, **124**, 7 (1938); O. K. Behrens and M. Bergmann, *ibid.*, **129**, 587 (1939). Data obtained from a single enzyme should be interpreted with caution, and the examination of the degradation products from the action of more than one proteolytic enzyme is desirable.

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The rate, nature and extent of hydrolysis was investigated by dinitrophenylation[3] of aliquots of the reaction mixture removed at various time intervals. Samples that were not immediately reacted were treated as described above in the preparative experiments. The DNP-peptides were hydrolyzed for 20 hr. at 107° in 5.7 *N* HCl; the DNP-amino acids were separated by paper chromatography and were determined by the Levy[3] method. Corrections for the destruction of DNP-amino acids during acid hydrolysis were made using the data of Porter.[4]

This method not only provides an excellent means of determining the rate of the reaction, and thus the optimum time of digestion, but also provides evidence for the degree of splitting of the bonds, and gives information on the nature of the N-terminal residue of the newly formed peptides. The measurement of the DNP-amino acids provides reasonable indication of the quantity and the number of peptides actually liberated under the given hydrolytic conditions.

Dowex 50-X2 Separation of the Peptides.—The peptides in the enzymatic digests were resolved by column chromatography at room temperature with Dowex 50-X2, Lot 3328-12, 200 to 400 mesh, obtained from the Dow Chemical Company, Midland, Michigan. The resin and columns were prepared in a manner similar to that described by Moore and Stein.[5] For the purpose of packing the column, 0.1 *N* sodium citrate buffer at *p*H 3.0 was employed. The lyophilized digests were brought into solution using a minimum volume of this buffer, and were applied to the columns.

Columns 50 × 1.5 cm. were used in the isolation experiments, with a flow rate of about 7.5 ml. per hr. Fractions of 5 ml. were collected automatically, and 0.15 or 0.25-ml. aliquots were removed and analyzed by the quantitative ninhydrin method of Moore and Stein.[6] A gradient elution technique was employed using citrate buffers ranging (in 0.5 *p*H unit intervals) from *p*H 3 to 6.5, with the Na^+ concentration varying from 0.1 to 0.58 *N*. At appropriate intervals a higher *p*H, higher ionic strength buffer was applied, producing a reasonably smooth increase in both *p*H and ionic strength in the effluent. Volumes of about 300 ml. of buffer were used. All buffers contained 0.5% each of BRIJ 35, thiodiglycol and benzyl alcohol.

Preliminary Desalting of the Peptides.—After the peptides had been located in the effluent fractions by use of ninhydrin reagent, appropriate fractions were combined so as to include, in most instances, 95% of the peptide material. The combined fractions were swirled one hr. on a rotary shaker with 5 to 10 equivalents of Dowex 50-X4, Lot 707, 20 to 50 mesh, in the hydrogen form. The supernatant was removed by decanting and then drawing off the remaining solution with a small pipet. In most instances the supernatant gave no test with ninhydrin reagent and was discarded. In the event of a positive test, additional resin was added and the shaking was repeated. The resin beads were washed three times with 2 volumes of water, once with EtOH, and finally twice with water. They were then eluted by swirling with about 3 volumes of 5 *N* NH_4OH at 20 to 25° for 30 min. The beads were washed twice with NH_4OH and the combined eluates were evaporated *in vacuo* over P_2O_5 and concentrated H_2SO_4. The dry white residue was dissolved in dilute HCl (*p*H 3 to 4) and was washed into a volumetric flask. Small amounts of thymol and a broad spectrum antibiotic were added, and the solution was refrigerated to minimize growth of microörganisms. Sufficient salt and buffer-additives were removed by this method to permit direct paper chromatography of the peptides, or paper chromatographic separation of the peptide hydrolyzates. Pilot experiments indicated that significant quantities of peptide material were lost during the desalting procedure, depending upon the nature of the peptide. Despite such losses the desalting method was used routinely, since the presence of salts interferes markedly with the resolution of amino acids and proteins in paper chromatography. Paper chromatography was used extensively throughout the structure investigation because of the relative ease and speed of the method.

Analysis of Peptide Fragments.—An aliquot from each combined group of fractions from the Dowex 50 effluent was dinitrophenylated as previously described to ascertain the nature of the N-terminal residue and to provide additional evidence regarding the purity of the peptide itself. Certain peptides were subjected to 2-dimensional paper chromatography to provide additional information on homogeneity. Arbitrary corrections for destruction during acid hydrolysis were made for serine (10%), threonine (3.5%) and tyrosine (5%) (*cf.* 1). Yields of the peptides were based on both the DNP-end group and amino acid analyses, with the assumption that a given peptide occurred only once in the protein molecule. Hydrolyzates of the larger peptides were generally analyzed by the column method of Moore and Stein,[5] and/or by the dinitrophenylation method of Levy.[3] The hydrolyzates of the smaller peptides were analyzed by the two paper chromatographic methods reported in the preceding paper[1] in the section describing the C-terminal analysis.

Results

Rate of Hydrolysis.—A study of the rate of glucagon hydrolysis by chymotrypsin is presented in Fig. 1. If chymotrypsin follows the generally accepted specificity pattern, 5 bonds should be split adjacent to the 5 aromatic residues. The data presented in Fig. 1 are consistent with this expectation. Four different amino acids were found

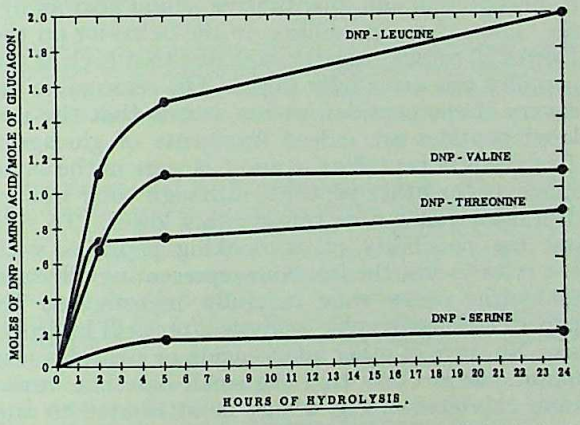

Fig. 1.—A study of the rate of the chymotryptic hydrolysis of the peptide bonds of glucagon, as followed by the dinitrophenylation method. Glucagon (0.085%) was digested with chymotrypsin (0.005%) at 37° in *p*H 7.8 buffer.

by the dinitrophenylation method as N-terminal residues of peptides newly formed by the chymotryptic rupture of peptide bonds Nearly quantitative splits were observed involving two leucine bonds, one valine bond and one threonine bond. In addition, a small yield of DNP-serine was obtained; data will be presented which indicate that the low recovery in the experiment is anomalous. In all likelihood a nearly quantitative split of the serine bond also was obtained. During the structure determination of corticotropin[7] similar difficulties with the dinitrophenylation method were experienced in determining serine as an N-terminal residue.

Separation of the Peptides.—In Fig. 2 is presented the Dowex 50-X2 effluent curve from the 8 hr. chymotrypsin digestion of 127 mg. (36.3 μmoles) of glucagon. Six major ninhydrin-positive peaks were detected, each of which represented a unique peptide fragment. Data on the analysis and recovery of each peptide are presented in Table I. No trace of peptide or amino acid impurities was

(3) A. L. Levy, *Nature*, **174**, 126 (1954).
(4) R. R. Porter, *Methods in Med. Res.*, **3**, 256 (1950).
(5) S. Moore and W. H. Stein *J. Biol. Chem.*, **192**, 663 (1951).
(6) S. Moore and W. H. Stein, *ibid.*, **211**, 907 (1954).
(7) A. L. Levy and C. H. Li, *ibid.*, **213**, 487 (1955).

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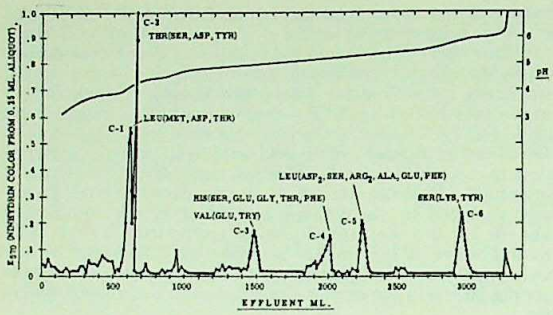

Fig. 2.—Separation of the peptides resulting from the 8 hr. chymotryptic hydrolysis of 127 mg. of glucagon. Chromatography was performed on a 1.5 × 50 cm. column of Dowex-X2 resin. The effluent was collected in 5-ml. fractions. The base-line variations were found to be caused by contamination with ammonia. A 0.2 *N* NaOH solution was used to clean the column, producing the final sharp rise in effluent *p*H.

detected in any of the 6 peptides by means of dinitrophenylation and quantitative amino acid analysis. These data, in addition to the behavior on the Dowex 50 column, clearly indicated that each of the peptides was essentially pure. The reasonable recovery of the peptides further attests that the isolated peptides are indeed fragments of glucagon. The yields of peptides C-3 and C-4 were in the same range as the other peptides, although their ninhydrin color yields were considerably lower. To rule out the possibility of overlooking peptides with low color yields, the fractions representing all small ninhydrin peaks were carefully investigated by paper chromatographic analysis after acid hydrolysis. No trace of other amino acids or peptides was found. It is likely that the small base-line variations exhibited in Fig. 2 may be attributed to ammonia contamination (*cf.* 1).

Table I

Peptides from the Chymotryptic Digestion of Glucagon

Peptide no.	Peptide compn. and anal.[a]	Yield, %
C-1	leu(met,asp,thr)	
	moles 1.0 0.8 1.2 1.0	40
C-2	thr(ser,asp,tyr)	
	moles 1.0 1.0 1.1 1.0	70
C-3	val(glu,try[b])	
	moles 1.3 0.6 1.0	60
C-4	his(ser,glu,gly,thr,phe)	
	moles 0.8 1.0 1.1 1.1 1.1 1.0	50
C-5	leu(asp_2,ser,arg_2,ala,glu,phe)	
	moles 0.9 1.9 1.0 1.8 1.0 1.0 0.8	50
C-6	ser(lys,tyr)	
	moles 0.9 1.3 1.0	50

[a] Hydrolyzates of the peptides were analyzed by the Moore and Stein[5] method, with the exceptions of C-3 and C-6 which were analyzed by paper chromatographic methods. [b] Chemical analysis.[8]

Twice as much C-6 peptide, containing N-terminal serine, was recovered as was expected from the rate study data. In view of this fact as well as the previously mentioned difficulty in the corticotropin structure work, it is likely that about the same degree of chymotryptic hydrolysis occurred in the case of the serine bond as was found with the other 4 bonds. If this hypothesis is correct the recovery of peptide C-6 was similar to that of the other peptides. The yields of the peptides are conservatively based on the assumption of 100% splitting, although the rate of hydrolysis data indicate that only 80 to 90% of the bonds were split after 8 hr. The shortest possible incubation time was chosen to minimize possible transpeptidation. The sum of the amino acid residues in all 6 peptides is 29, with a distribution of individual amino acids identical to that described for glucagon in the first paper of this series.[1] All evidence indicates that these peptides are fragments of glucagon produced by the specific hydrolytic action of chymotrypsin, and are not artifacts.

Discussion

It is appropriate at this point to consider the probable location of these peptides in the glucagon chain. Since only one histidine residue occurs in the molecule and it has been located in the N-terminal position, peptide C-4, His(ser,glu,gly,thr,phe), must be the N-terminus of glucagon. Threonine was shown to be the C-terminal amino acid; but, since there are three threonine residues in the protein, each in a different chymotryptic peptide, the establishment of the C-terminal peptide would seem to be more difficult. However the C-4 threonine-containing peptide already has been designated as the N-terminal peptide. Similarly, the threonine residue in peptide C-2, thr(ser,asp,tyr), cannot be C-terminal in glucagon since it already has been shown to be the N-terminus of peptide C-2. By process of elimination, peptide C-1, Leu(met,asp, thr) must be the C-terminal peptide in glucagon. Other evidence also supports this conclusion; the single residue of methionine, that has been located near the C-terminus because of rapid release by carboxypeptidase, is found in this peptide. Similarly, the absence of an aromatic residue from C-1 is consistent with this interpretation; the usual specificity of chymotrypsin requires that the rupture involves the carboxyl group of an aromatic amino acid. Only the C-terminal fragment should be devoid of such a residue. Additionally, the location of aspartic acid and leucine in the C-terminal peptide do not in any way disagree with the data obtained from carboxypeptidase.

Carboxypeptidase also liberated tryptophan, valine and a small quantity of alanine. Since these three amino acids occur only once in glucagon, they should be found in peptides adjacent to peptide C-1, the C-terminal peptide. On this basis, peptide C-3, val(glu,try), containing both valine and tryptophan, may be placed adjacent to the C-terminal peptide, C-1. Seven of the 11 amino acids liberated by carboxypeptidase now have been placed in relative position near the C-terminus of the molecule. The four remaining amino acids include the single alanine residue, phenylalanine, glutamine and aspartic acid. Of the 3 unplaced peptides only C-5 contains the combination of aspartic acid, glutamic acid, phenylalanine and, of course, the single alanine residue. Hence it would appear that peptide C-5 is adjacent to peptide C-3 which

(8) J. R. Spies and D. C. Chambers, *Anal. Chem.*, 20, 30 (1948).

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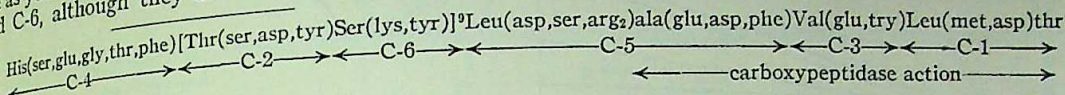
in turn is next to the C-terminal peptide. No clues are as yet available for the location of peptides C-2 and C-6, although they are obviously within the protein chain and must be adjacent to each other. Additional information is needed to determine which is adjacent to peptide C-4 and which to peptide C-5.

(9) Brackets indicate that the sequence of peptides C-2 and C-6 has not yet been determined.

The evidence available to this point may be summarized in the following partial structure of glucagon



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INDIANAPOLIS 6, INDIANA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Amino Acid Sequence of Glucagon. III. The Hydrolysis of Glucagon by Trypsin

BY W. W. BROMER, A. STAUB, L. G. SINN AND OTTO K. BEHRENS

RECEIVED NOVEMBER 19, 1956

Tryptic digestion of glucagon caused rapid hydrolysis of two peptide bonds and slower splitting of three additional bonds. The peptide fragments resulting from both a 2.25 and a 50 hr. digestion were isolated by use of resin chromatography and electrophoresis. The unique composition of the peptide fragments permitted the correlation of existing evidence into the following partial amino acid sequence of glucagon: His(ser,glu,gly,thr,phe)thr(ser,asp,tyr)ser.lys.tyr(leu,asp,ser,arg)-arg ala(glu,asp,phe)val(glu,try)leu(met,asp)thr.

Introduction

The first two papers of this series[1,2] have described the amino acid composition of glucagon, the end group analysis and the characterization of products of degradation by carboxypeptidase and chymotrypsin. Relative positions within the glucagon chain were assigned to 4 of the 6 peptides isolated from the chymotryptic digestion. To provide additional information useful for structural analysis glucagon has been hydrolyzed with another proteolytic enzyme, trypsin. The products of both 2.25 and 50 hr. tryptic hydrolyses of glucagon have been isolated and characterized.

Experimental

Materials.—Crystalline glucagon, lot 208-158B-292A, was used throughout this enzymatic study. Twice-recrystallized trypsin, lot T320, was obtained from the Worthington Biochemical Corporation, Freehold, New Jersey. The chymotrypsin content of this trypsin preparation was less than 0.2% according to analyses by the method of Ravin, *et al.*,[3] using N-benzoyl-DL-phenylalanine β-naphthyl ester as the substrate.

Hydrolysis of Glucagon by Trypsin.—An 0.085% solution of glucagon was incubated with 0.005% trypsin in a 0.05 *M* sodium citrate solution containing 1 mg. per ml. of $CaCl_2$. The enzyme:substrate mole ratio was approximately 1:100. The digestion was performed at 25°, *p*H 7.8, for as long as 50 hr. Excessive stirring of the incubate was avoided since trypsin was found to be inactivated under this condition. Aliquots were removed at various intervals for dinitrophenylation and for determination of the rate of appearance of the N-terminal residues of newly-formed peptides. Preliminary studies of the rate of hydrolysis provided evidence that certain bonds were split very rapidly, while others were ruptured quite slowly. Hence, in the preparative experiments aliquots were removed at both 2.25 and 50 hr.; these solutions were adjusted to *p*H 3 with HCl, were heated to 90° for 2 min., and were lyophilized.

Fractionation of the Trypsin Hydrolyzate.—The lyophilized digests were not completely soluble in the sodium citrate buffer (*p*H 3.0, 0.1 *N*) used in the Dowex 50-X2 chromatographic separation. The precipitate in each digest was peptide in nature, somewhat soluble in dilute alkali, but insoluble in the *p*H range 2.5 to 6.5. Because of the insolubility in the *p*H range of the buffers used in the Dowex 50 chromatography, the precipitate was removed by centrifugation, washed with cold dilute acid, redissolved in dilute alkali (*p*H 8.5 to 9.5) and frozen. The combined washes and supernatant were subjected directly to Dowex 50-X2 chromatography on 1.5 × 50 cm. columns as described in a previous report.[2]

End group analysis[4] of the acid-insoluble materials showed that the 2.25 hr. precipitate was not homogeneous, but the 50 hr. precipitate, isolated in small quantity, appeared to represent a single component. Because of the relatively high purity and small yield of the 50 hr. precipitate no further fractionation was attempted. However, the material which precipitated from the 2.25 hr. digest was subjected to electrophoresis on both starch and paper in 0.1 *N* sodium acetate (*p*H about 7.2) at a milliamperage and voltage of 15 and 300, respectively. The peptide material was eluted from the paper with 1% NH_4OH, and from one-half or one cm. sections of the starch with 5 ml. of water. The peptide material was located in both cases by use of the ninhydrin reagent.[5]

Results

Rate of Hydrolysis.—Glucagon was previously shown to contain one lysine and two arginine residues.[1] Because of the well-accepted specificity behavior of trypsin[6-10] in splitting only those bonds involving the carboxyl groups of these residues, it was expected that 3 bonds in glucagon would be split and 4 hydrolytic products would be formed. The rate of hydrolysis data presented in Fig. 1 show clearly that the tryptic hydrolysis of glucagon did

(1) Reference to Paper I in this series, THIS JOURNAL, **79**, 2794 (1957).
(2) Reference to Paper II in this series, *ibid.*, **79**, 2798 (1957).
(3) H. A. Ravin, P. Bernstein and A. M. Seligman, *J. Biol. Chem.*, **209**, 1 (1954).
(4) A. L. Levy, *Nature*, **174**, 126 (1954).
(5) S. Moore and W. H. Stein, *J. Biol. Chem.*, **211**, 907 (1954).
(6) C. H. W. Hirs, S. Moore and W. H. Stein, *ibid.*, **219**, 623 (1956).
(7) F. Sanger and H. Tuppy, *Biochem. J.*, **49**, 463, 481 (1951).
(8) F. Sanger and E. O. P. Thompson, *ibid.*, **53**, 353, 366 (1953).
(9) P. H. Bell, THIS JOURNAL, **76**, 5565 (1954).
(10) W. E. White and W. A. Landmann, *ibid.*, **77**, 1711 (1955).

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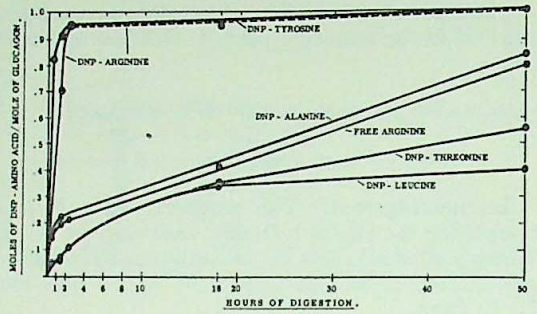

Fig. 1.—A study of the rate of the tryptic hydrolysis of the peptide bonds of glucagon, as determined by the dinitrophenylation method. An 0.085% solution of glucagon was digested with trypsin (0.005%) at *p*H 7.8 and 25°. Free arginine was determined by chromatography on Dowex 50-X8 resin.

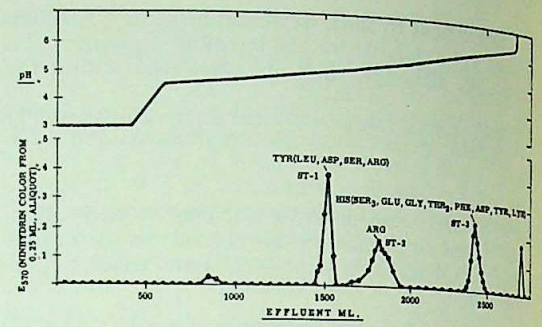

Fig. 2.—Separation of the acid-soluble peptides resulting from the 2.25 hr. tryptic hydrolysis of 146 mg. of glucagon. Chromatography was performed on a 1.5 × 50 cm. column of Dowex 50-X2 resin. Five-ml. effluent fractions were collected. A 0.2 *N* NaOH solution was used to clean the resin column, producing the final sharp rise in *p*H of the effluent.

not proceed in the expected manner. Within 2 hr. nearly complete hydrolysis of 2 peptide bonds occurred, since both di-DNP-tyrosine and DNP-arginine were obtained in high yield. With longer incubation, increasing quantities of DNP-alanine, DNP-threonine, DNP-leucine and free arginine were observed. None of these amino acids appeared to be quantitatively released even after 50 hr. digestion. The free arginine was determined by the analysis of aliquots of the digest on Dowex 50 columns according to the method of Moore and Stein.[11]

It is apparent that two peptide bonds were hydrolyzed rapidly during the trypsin digestion. At least some of these primary peptides must have been further degraded to yield 4 or more additional components.

Peptides from the 2.25 Hour Tryptic Digestion.—The effluent curve presented in Fig. 2 was obtained from the Dowex 50-X2 chromatography of the supernatant from 146 mg. (41.7 μmoles) of glucagon after digestion with trypsin for 2.25 hr. Separation of the components of the precipitate by paper electrophoresis is represented in Fig. 3 by the photograph of a paper strip developed with ninhydrin reagent. The quantitative amino acid analyses and recoveries of all the hydrolytic fragments are summarized in Table I.

TABLE I

PEPTIDES FROM THE 2.25 HOUR TRYPTIC HYDROLYSIS OF GLUCAGON

Peptide number	Peptide compn. and anal.[a]	Yield, %
ST-1	tyr(leu,asp,ser,arg)	
	moles 1.0 1.0 1.0 1.0 1.0	
ST-2	arg	70
ST-3	his(ser$_1$,glu,gly,thr$_1$,phe,asp,tyr,lys)	20
	moles 0.8 3.2 1.2 1.0 2.1 1.0 1.0 1.0 1.1	
ST-PA	arg(ala,glu$_1$,asp$_1$,phe,val,try,[b]leu,met,thr)	30
	moles 1.0 1.0 2.0 1.8 0.9 1.1 1.0 0.9 0.7 1.2	
ST-PB	ala(glu$_2$,asp$_1$,phe,val,try,[b]leu,met,thr)	~50
	moles 1.0 2.1 2.1 0.7 1.0 1.0 1.3 0.5 1.3	~25

[a] All peptides analyzed by Moore and Stein method.[11] Small amounts of peptides ST–PA and ST–PB available for analysis. [b] Chemical analysis.[12]

DNP-end group analysis of the acid-insoluble material provided evidence for two major components, one containing alanine as the N-terminus and the other arginine as the end group. No other DNP-amino acids were observed. Traces of ninhydrin-positive material other than peptides ST-PA and ST-PB were found by paper and starch electrophoresis; however, the quantity of material was not sufficient for identification. The yields of fragments ST-PA and ST-PB were estimated on the basis of amino acid and end group analyses prior to electrophoretic separation. The amino acid analyses were performed on small quantities of peptides isolated after electrophoretic separation.

The three fragments represented by the effluent curve in Fig. 2 were isolated, desalted and analyzed as described in a previous report.[2] No other peptide material was detected. DNP-end group and quantitative amino acid analyses, along with the Dowex 50 data, demonstrated the high purity of the fragments. The yield of arginine (ST-2) was calculated from the direct analysis of aliquots of the reaction mixture according to the method of Moore and Stein[11] for basic amino acids. Chromatography before and after hydrolysis provided additional evidence for free arginine.

These 5 isolated fragments may be considered in light of the splits predictable from the data on the rate of hydrolysis. Three major degradation products were anticipated after 2.25 hr. digestion. These products should contain histidine, tyrosine and arginine as N-terminal residues (*cf.* Fig. 1). The data in Table I indicate that those three peptides isolated in the highest yield, ST-1, ST-3 and ST-PA, contain these amino end groups. Furthermore, the sum of the amino acids in these three degradation products is identical to the amino acid composition of the entire glucagon molecule. The relatively low yield of ST-3 is perhaps understandable when the large size and amino acid composition of the peptide are considered. The presence of two basic residues and two aromatic residues probably tended to retard elution of the peptide from the Dowex 50 column and from the resin during the desalting step.

In addition to the two major splits during the first 2.25 hr. of separate study data indicated that

(11) S. Moore and W. H. Stein, THIS JOURNAL, 192, 663 (1951).
(12) J. R. Spies and D. C. Chambers, *Anal. Chem.*, 21, 30 (1949).

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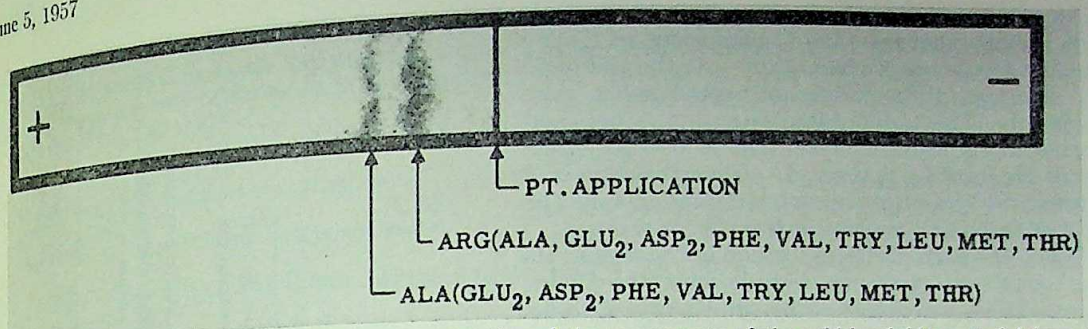

Fig. 3.—Photograph of the paper electrophoretic separation of the components of the acid-insoluble material from the 2.25 hr. tryptic digestion of glucagon. Electrophoresis was performed for 4 hr. at 5° in 0.1 *N* sodium acetate solution (*p*H 7.2), with a milliamperage and voltage of 15 and 300, respectively.

lesser splits had occurred which involved free arginine and N-terminal alanine. The two remaining fragments which were isolated, ST-2 and ST-PB, are in complete agreement with this prediction. On the basis of the yields and the composition of the fragments, it is probable that ST-2 and ST-PB arose from the degradation of ST-PA. The tryptic liberation of N-terminal arginine is somewhat unexpected in view of the resistance to tryptic hydrolysis of amino-terminal lysine in ribonuclease, as found by Hirs, Moore and Stein.[6]

Small yields (10%) of DNP-leucine and DNP-threonine were also detected in the rate study; no corresponding peptides were detected, possibly because the quantities were too small.

Peptides from the 50 Hour Tryptic Digestion.—Separation of the acid-soluble degradation products from 165.2 mg. (47.2 μmoles) of glucagon formed by a 50 hr. tryptic digestion is represented by the Dowex 50-X2 effluent curve in Fig. 4. Peak LT-5

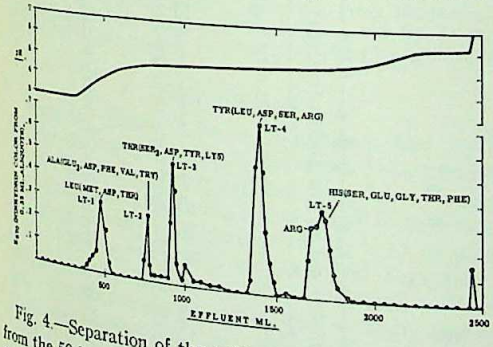

Fig. 4.—Separation of the acid-soluble peptides resulting from the 50 hr. tryptic hydrolysis of 165.2 mg. of glucagon. Chromatography was performed on a 1.5 × 50 cm. column of Dowex 50-X2 resin. Five-ml. effluent fractions were collected. A 0.2 *N* NaOH solution was used to clean the resin column, producing the final sharp rise in *p*H of the effluent.

was found by end group analysis to represent two components, one with arginine as the N-terminus and the other containing N-terminal histidine. Rechromatography of this mixture on Dowex 50-X8 columns described by Moore and Stein[11] for basic amino acids resulted in the separation of the two components, as demonstrated by the elution curve in Fig. 5. The elution pattern of peak LT-5B indicated that this component was identical with free arginine. Rechromatography after acid hydrolysis provided further evidence that a single arginine residue had been liberated. The analysis and recovery of the various isolated fragments is presented in Table II. End group and quantitative amino acid analysis provided evidence

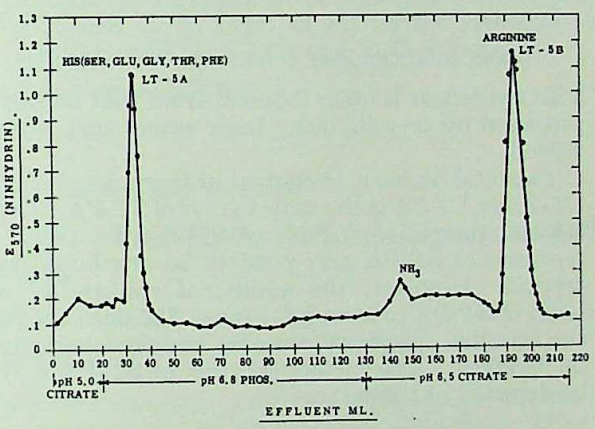

Fig. 5.—Rechromatography of the material represented by peak LT-5. Separation into two components was accomplished on a 0.9 × 15 cm. column of Dowex 50-X8 resin.

that LT-1 represented more than 80% of a single component. No evidence of amino acid or peptide impurities in the other peptides was observed, except that the acid-insoluble material contained a small amount of peptide probably identical to ST-PA.

TABLE II

PEPTIDES FROM THE 50 HOUR TRYPTIC DIGESTION OF GLUCAGON

Peptide no.	Peptide compn. and anal.[a]	Yield, %
LT-1	leu(met,asp,thr)	35
	moles 1.0 0.7 1.0 1.0	
LT-2	ala(glu$_2$,asp,phe,val,try[b])	30
	moles 1.0 2.1 1.1 0.9 1.1 1.0	
LT-3	thr(ser$_2$,asp,tyr,lys)	55
	moles 1.0 1.9 1.1 0.5 1.0	
LT-4	tyr(leu,asp,ser,arg)	95
	moles 0.8 1.0 1.2 1.0 0.6	
LT-5A	his(ser,glu,gly,thr,phe)	30
	moles 0.5 1.0 1.0 0.9 1.0 1.2	
LT-5B	arg	80
LT-PB	ala(glu$_2$,asp$_2$,phe,val,try,[b] leu,met,thr)	
	moles 1.2 2.1 1.9 1.1 1.0 1.0 1.1 0.6 0.9	~30

[a] The amino acids in all the peptides were analyzed as DNP-derivatives,[4] with the exception of LT-PB, which were determined by resin chromatography.[6] [b] Chemical analysis.[12]

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As previously discussed, the rate of hydrolysis data indicate that two major splits occurred during the first few hours of incubation. At the end of 50 hr. digestion, three additional partial splits were observed. This complicated situation is not conducive to the clear analysis that is possible when bonds are completely cleaved. Nevertheless it is of interest to consider the isolated products in the light of the splits predictable from the rate study.

When the yield and composition of the fragments are considered, only one peptide from the 50 hr. digest, LT-4, was found to be similar to a 2.25 hr. digestion product. Presumably the other major fragments isolated from the 2.25 hr. incubate, ST-3 and ST-PA, must have been further degraded.

The sum of the amino acids in peptides LT-5A and LT-3 is identical to the amino acid composition of ST-3. Apparently the trypsin preparation split ST-3 in the following manner

his(ser,glu,gly,thr,phe,thr,ser,asp,tyr,ser,lys)

↓

his(ser,glu,gly,thr,phe) + thr(ser,asp,tyr,ser,lys)

This hydrolysis is quite different from that usually produced by trypsin, as no basic amino acid is involved.

The total amino acid content of fragments LT-1, LT-2 and LT-5A is the same as that of ST-PA. The release of arginine (LT-5B or ST-2) from the N-terminus of ST-PA may possibly be attributed to trypsin. However, the additional rupture of a bond in ST-PA to form LT-1 and LT-2 does not fit the accepted specificity, since no basic residues can be involved. The further splitting of ST-PA may be depicted as follows:

arg(ala,glu,asp,phe,val,glu,try,leu,met,asp,thr)

↓

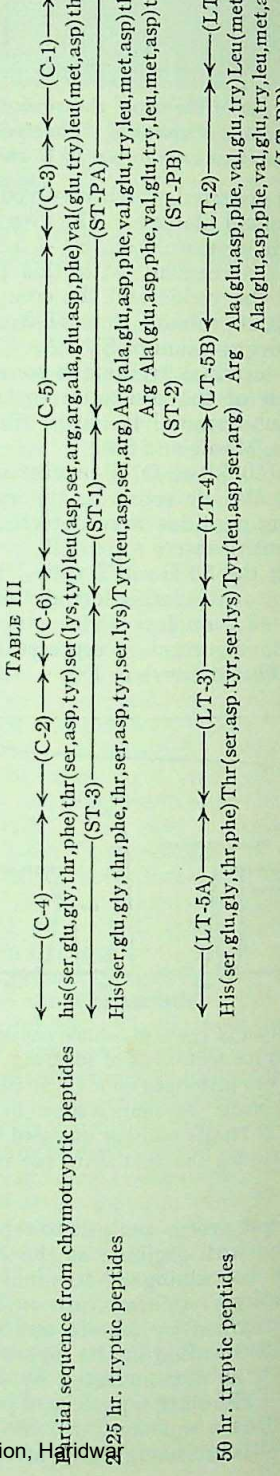
arg + ala(glu,asp,phe,val,glu,try) + leu(met,asp,thr)

Thus, a trypsin preparation has split two bonds in glucagon in addition to those predicted from the known specificity of trypsin. These observations are only incidental to the determination of the structure; nevertheless they are of considerable interest since nearly all other reports have confirmed the accepted specificity of trypsin. Two alternatives are possible; the activity is inherent in the trypsin, or it is caused by a proteolytic impurity such as chymotrypsin. The specificity of the hydrolysis is consistent with the latter interpretation; however, there is virtually no chymotrypsin in the trypsin preparation, only 2 of the known 5 chymotryptic splits were found, and the addition of β-phenyl propionate, a chymotrypsin inhibitor, to the incubate did not prevent the two splits in question.

Discussion

The information obtained from the tryptic digestion studies may be considered with respect to the structure of glucagon. Earlier work has shown that histidine and threonine are the N- and C-terminal residues of this chain, and that single residues of histidine, glycine, lysine, alanine, valine, tryptophan and methionine are present.

TABLE III



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June 5, 1957

The unique amino acid composition of peptide ST-3 may be utilized to locate the position in the glucagon chain of two peptides from the chymotrypsin digestion, C-2 and C-6.

(ST-3)
his(ser,glu,gly,thr,phe,thr,ser,asp,tyr,ser,lys)
(C-4) (C-2) (C-6)
his(ser,glu,gly,thr,phe)thr(ser,asp,tyr)ser(lys,tyr)

All other evidence is consistent with this interpretation (*cf.* Table III).

The three major fragments of glucagon formed after 2.25 hr. of trypsin digestion, ST-3, ST-1 and ST-PA, may be readily placed in position within the glucagon molecule. Peptide ST-3 contains N-terminal histidine, and ST-PA contains all of the amino acids liberated by carboxypeptidase, including potential C-terminal threonine which is not found in ST-1. Hence, ST-3 and ST-PA must be the N- and C-terminal peptides, respectively. This leaves only a position between these fragments for ST-1, producing a sequence of (ST-3)(ST-1)(ST-PA). As previously discussed, these three peptides account for the entire amino acid composition of glucagon. Since ST-2 (arginine) and ST-PB were, in all likelihood, formed by the degradation of ST-PA, the sequence involving these minor products can only be written as (ST-3)(ST-1)(ST-2)(ST-PB), again accounting for the amino acid composition of glucagon.

Extending these considerations to the peptides isolated from the 50 hr. trypsin digest, it may be recalled that LT-5A and LT-3 were formed from ST-3, and LT-5B, LT-2 and LT-1 were formed from ST-PA. Peptide LT-4 is identical to ST-1, hence the sequence of peptides can only be written (LT-5A)(LT-3)(LT-4)(LT-5B)(LT-2)(LT-1). LT-PB, isolated in small yield and identical in composition to ST-PB from the 2.25 hr. digestion, can be located in a similar position.

The evidence for the sequence of the peptides within the glucagon chain is summarized in Table III.

Acknowledgment.—The authors gratefully acknowledge the paper chromatographic work of H. L. Bird and C. T. Pugh as well as the technical assistance of W. A. Tandy and R. G. Scheib.

INDIANAPOLIS 6, INDIANA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Amino Acid Sequence of Glucagon. IV. The Hydrolysis of Glucagon with Subtilisin

BY L. G. SINN, OTTO K. BEHRENS AND W. W. BROMER

RECEIVED NOVEMBER 19, 1956

Ten of the peptide bonds of glucagon were ruptured by the proteolytic attack of subtilisin. The resulting mixture of eleven degradation products was fractionated by Dowex 50 chromatography and countercurrent distribution. The arrangement of the peptide fragments in the glucagon chain is correlated with existing information.

Introduction

Previous reports[1,2] have described the hydrolytic breakdown products of glucagon obtained from the action of chymotrypsin and trypsin. Each set of peptides isolated from an enzymatic digest has an amino acid composition identical to that of glucagon. The peptides can be arranged logically in only one manner. Since some areas of unknown sequence remained, glucagon was split by use of a third proteolytic enzyme, subtilisin. The eleven peptides formed by this digestion are characterized in this report.

Experimental

Materials.—Twice-recrystallized glucagon, Lot 208-158B-292A, and crystalline subtilisin[3] (preparation F, containing 20% Na_2SO_4) were used for all experiments.

Hydrolysis of Glucagon by Subtilisin.—Glucagon (0.09%) was incubated with subtilisin (0.003%) at 37° in 0.05 *M* sodium acetate solution at *p*H 7.5 for 24 hr. During the first few hours of the digestion the *p*H drifted slowly to 7, and required occasional readjustment.

The rate and nature of the hydrolysis was studied by dinitrophenylating aliquots of the digest that were removed at various time intervals. The DNP-peptides were hydrolyzed, and the DNP-amino end groups of each new peptide were determined quantitatively.[4] In the preparative experiments the reaction mixture was immediately subjected to Dowex 50-X2 chromatography as described in a previous report.[1]

Results

Rate of Hydrolysis.—The rate of hydrolysis of glucagon by subtilisin is represented by the curves in Fig. 1. The amount of the N-terminal amino acid of each newly formed peptide is plotted *versus* time. The specificity of subtilisin has not been rigidly established[5]; however, it is certain that the enzyme ruptures a rather wide variety of peptide linkages, forming small peptide fragments. According to the data in Fig. 1 subtilisin almost completely split three bonds involving aspartic acid, two involving leucine, and one each involving glycine, valine and threonine. In addition, sizable amounts of DNP-arginine and di-DNP-lysine were detected, but were not determined quantitatively. Bonds involving these residues were ruptured to a significant extent. A logical interpretation of these data was that glucagon was split by subtilisin in 10 places, giving rise to 11 peptide fragments.

The splitting of most of the bonds was essentially complete within 5 to 6 hr.; however, some of the

(1) Reference to Paper II of this series, THIS JOURNAL, **79**, 2798 (1957).

(2) Reference to Paper III of this series, *ibid.*, **79**, 2801 (1957).

(3) We gratefully acknowledge receipt of subtilisin from Dr. M. Ottesen, Carlsberg Laboratories, Copenhagen, Denmark.

(4) Dinitrophenylations and quantitative analyses were performed according to the method of A. L. Levy, *Nature*, **174**, 126 (1954).

(5) H. Tuppy, *Monatsh.*, **84**, 936 (1953).

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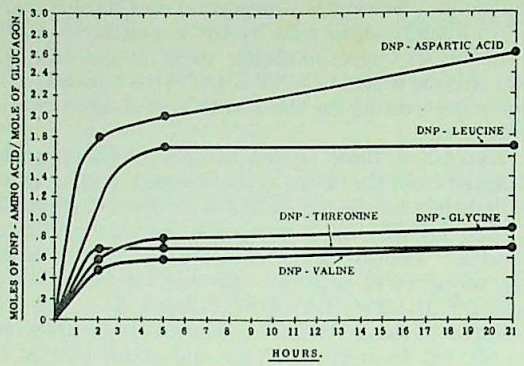

Fig. 1.—A study of the rate of the subtilisin hydrolysis of the peptide bonds of glucagon, as determined by the dinitrophenylation method. An 0.09% solution of glucagon was digested with subtilisin (0.003%) at *p*H 7.5 and 37°.

bonds required as long as 24 hr. for complete hydrolysis. Furthermore, since an uncertainty existed regarding the rate of splitting of arginine and lysine bonds, the incubation was continued for 24 hr. in the preparative experiments.

Separation and Analysis of the Peptides.—The Dowex 50-X2 effluent curve from the 24 hr. subtilisin digestion of 176.2 mg. (50.3 μmoles) of glucagon is presented in Fig. 2. The analysis and recovery of the peptide fragments is given in Table I.

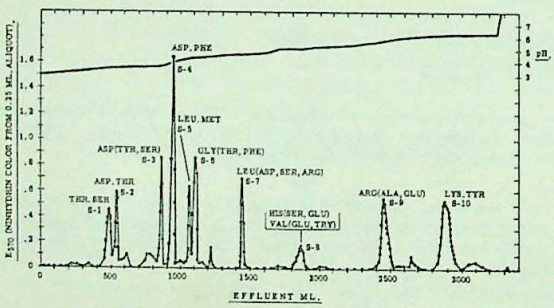

Fig. 2.—Separation of the degradation products resulting from the 24 hr. subtilisin digestion of 176.2 mg. of glucagon. Chromatography was performed on a 1.5 × 50 cm. column of Dowex 50-X2 resin. Five-ml. effluent fractions were collected. A 0.2 *N* NaOH solution was used to clean the resin column, producing the final sharp rise in *p*H of the effluent.

Peak no. 8 in the effluent curve in Fig. 2 was found to represent a mixture of two peptides. Upon application of the dinitrophenylation method both histidine and valine were identified as N-terminal residues. The DNP-derivatives of these peptides were separated by a 10 tube countercurrent distribution in 0.1 *N* HCl and ethyl acetate. The recovery of these two peptides was calculated after complete separation; the low yields were due, at least in part, to the increased number of manipulations. Both peptides, S-8A and S-8B, produced low color yields when reacting with ninhydrin, emphasizing the necessity for careful examination of all fractions which reacted with ninhydrin.

TABLE I

PEPTIDES FROM THE SUBTILISIN DIGESTION OF GLUCAGON

Peptide no.	Peptide Compn. and anal.[a]	Yield, %	Peptide no.	Peptide Compn. and anal.[a]	Yield, %	Peptide no.	Peptide Compn. and anal.[a]	Yield, %
S-1	thr.ser		S-5	leu met		S-8B	val(glu try[b])	15
	moles 0.8 1.2	55		moles 1.1 0.9	60		moles 1.0 1.0 1.0	
S-2	asp.thr		S-6	gly(thr,phe)		S-9	arg(ala,glu)	60
	moles 1.1 1.0	80		moles 1.1 0.9 1.0	85		moles 1.2 0.9 1.0	
S-3	asp(tyr,ser)		S-7	leu(asp,ser,arg)		S-10	lys.tyr	75
	moles 1.0 1.0 1.1	50		moles 1.0 0.9 1.0 1.0	80		moles 1.0 1.0	
S-4	asp.phe		S-8A	his(ser,glu)				
	moles 1.1 1.0	70		moles 0.8 1.0 1.3	25			

[a] All peptides analyzed by paper chromatographic means. Results given are the averages of at least three analyses. [b] Chemical analysis.[6]

TABLE II

Proposed partial sequence	His(ser,glu,gly,thr,phe)thr(ser,asp,tyr)ser.lys.tyr(leu,asp,ser,arg)arg.ala(glu,asp,phe)val(glu,try)leu(met,asp)thr						
Peptides from subtilisin digest	S-8A	S-6	S-1	S-3	S-10	S-7	S-9	S-4	S-8B	S-5	S-2
	His(ser.glu)	Gly(thr,phe)	Thr.ser	Asp(tyr,ser)	Lys.tyr	Leu(asp,ser,arg)	Arg(ala,glu)	Asp.phe	Val(glu,try)	Leu.met	Asp.thr
Summary	His(ser,glu)gly(thr,phe)thr.ser.asp.tyr.ser.lys.tyr.leu(asp,ser.arg)arg.ala.glu.asp.phe.val(glu try)leu.met.asp.thr										

(6) J. R. Spies and D. C. Chambers, *Anal. Chem.*, **20**, 30 (1948).

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June 5, 1957

Paper chromatographic analyses of acid hydrolyzates of such fractions gave no evidence for peptide material other than the 11 peptides indicated in Table I.

With the methods used in this structure study, peptides might be overlooked that did not produce color with ninhydrin reagent. This possibility in itself is rather improbable. Furthermore, from the data on the rate of hydrolysis it has been possible to rather accurately predict the number of peptides formed in each incubation and the N-terminus of each peptide.

Discussion

Assuming that each peptide occurs only once in the chain, the distribution of the amino acids in the 11 peptides was identical to the amino acid composition of glucagon. Only peptide S-3, asp(tyr,leu), contained a measurable amount of impurity, having about 0.2 mole of threonine per mole of peptide. Dinitrophenylation and quantitative amino acid data, along with the behavior of the peptides on Dowex 50 columns and their generally good recovery, all pointed to the conclusion that these peptides were genuine fragments of glucagon arising from the hydrolytic action of subtilisin.

Integration of the 11 peptides from the subtilisin digestion into the glucagon chain is represented in Table II.

Acknowledgment.—The authors are indebted to H. L. Bird and C. T. Pugh for the paper chromatography, and to W. A. Tandy and R. G. Scheib for their technical assistance.

INDIANAPOLIS 6, INDIANA

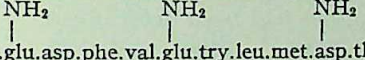
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Amino Acid Sequence of Glucagon. V. Location of Amide Groups, Acid Degradation Studies and Summary of Sequential Evidence

BY W. W. BROMER, L. G. SINN AND OTTO K. BEHRENS

RECEIVED NOVEMBER 19, 1956

Data is presented that elucidates the remaining unknown amino acid sequences in the glucagon chain, and that establishes the locations of the four amide groups. The following complete amino acid sequence of glucagon is proposed: His.ser.glu.-gly.thr.phe.thr.ser.asp.tyr.ser.lys.tyr.leu.asp.ser.arg.arg.ala.glu.asp.phe.val.glu.try.leu.met.asp.thr



Introduction

In preceding papers of this series[1–3] the degradation products of glucagon formed by the action of three different proteolytic enzymes have been described. These fragments of the glucagon chain can be arranged to fit together logically in only one manner; all of the data obtained are consistent with the proposed arrangement. However, the sequence of all the amino acids within the chain is not determined, and the location of the four amide groups can only be postulated from the behavior of the peptides on resin columns and from the carboxypeptidase data. This paper describes the elucidation of the unknown sequences, largely through partial acid degradation, and the final location of the amide linkages by means of chemical analysis.

Experimental

Partial Acid Degradation.—Peptides from enzymatic degradation of glucagon were dissolved in 11.7 *N* HCl at a concentration of about one μmole per ml., and the reaction mixture was incubated at 37° for 3 days. The excess acid was removed *in vacuo* over KOH pellets. The white residue was dissolved in water, and aliquots were subjected to paper chromatography in the solvent *n*-butanol:acetic acid:water, 4:1:1. The peptide degradation products were located by spraying an identification lane with ninhydrin reagent (*cf.* Fig. 1). Areas in the unreacted lanes corresponding to the ninhydrin-positive areas were excised, were eluted with 0.02 *N* HOAc, and were dinitrophenylated. The DNP-derivatives were hydrolyzed in acid, and the N-terminal residue and the amino acid composition were determined by paper chromatography.

Amide Analysis.—Two to 5 μmoles of a selected peptide was dissolved in dilute alkali at *p*H 8.5 to 9, and the solution was evaporated to dryness *in vacuo* over H_2SO_4. A solution of approximately 2 μmoles of peptide per ml. of 11.7 *N* HCl was prepared and was incubated at 37° for as long as 144 hr. At appropriate intervals, aliquots corresponding to 0.2 to 1 μmole of peptide were removed for ammonia analysis conducted either according to the method of Rees[4] or the procedure of Russell.[5] Each of the 7 peptides which were studied contained only one potential amide linkage.

In all cases a mixture of amino acids devoid of amide groups but otherwise simulating the peptide was treated similarly. Such control hydrolyses provided evidence for the amount of interfering substances or non-amide ammonia liberated.

Hydrolysis of Peptide C-3 with Carboxypeptidase.—A solution containing 0.02% peptide C-3, val(glu,try), and 0.024% carboxypeptidase was incubated under conditions identical to those employed in a previous report[6] enzyme:substrate mole ratio, about 1:65. Aliquots of the incubate were removed at various time intervals for dinitrophenylation and subsequent paper chromatography.[7]

Results

Partial Acid Degradation.—Three of the four remaining sequences were determined by characterizing the partial degradation products of the two enzymatically obtained peptides C-4, his(ser,glu)-

(1) Reference to Paper II of this series, THIS JOURNAL, **79**, 2798 (1957).
(2) Reference to Paper III of this series, *ibid.*, **79**, 2801 (1957).
(3) Reference to Paper IV of this series, *ibid.*, **79**, 2805 (1957).
(4) M. W. Rees, *Biochem. J.*, **40**, 632 (1946).
(5) J. A. Russell, *J. Biol. Chem.*, **166**, 457 (1944).
(6) Reference to Paper I of this series, THIS JOURNAL, **79**, 2794 (1957).
(7) A. L. Levy, *Nature*, **174**, 126 (1954).

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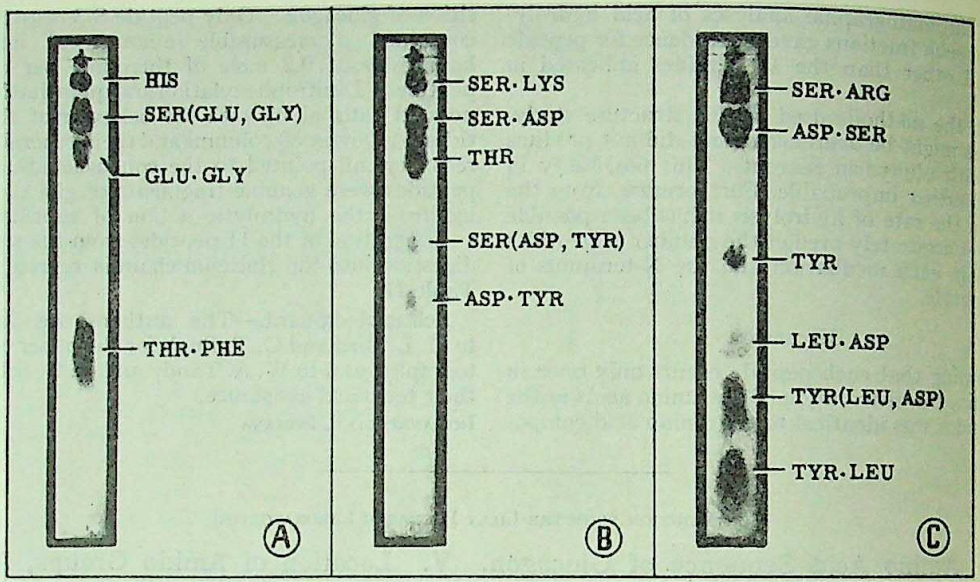

Fig. 1.—Photographs of the paper chromatographic separation of the acid hydrolysis products from peptides C-4, LT-3 and LT-4. The chromatograms were developed with *n*-butanol:acetic acid:water (4:1:1), and were treated with ninhydrin reagent: A, hydrolysis products of peptide C-4, His(ser,glu,gly,thr,phe); B, hydrolysis products of peptide LT-3, Thr(ser,asp,tyr,ser,lys); C, hydrolysis products of peptide LT-4, Tyr(leu,asp,ser,arg).

gly(thr,phe), and LT-4, tyr.leu(asp,ser,arg). In addition, peptide LT-3, thr.ser.asp.tyr,ser.lys, was similarly degraded. The quantitative amino acid composition of these peptides had been determined in the earlier described work.[1,2] Since acid degradation is not considered to promote rearrangements, such data elucidated the unknown sequences and also provided additional evidence for certain sequences which were proposed largely on the basis of data obtained from enzyme degradation.

Presented in Fig. 1 are photographs of the paper chromatographic separation of the acid hydrolysis products of the above three peptides.

The chromatograms were treated with ninhydrin reagent. In cases where overlapping of the spots occurred, the chromatograms were carefully excised to exclude the overlapping area. The analysis and recovery of the degradation products are presented in Table I. The figures on amino acid analysis are based on single or duplicate paper chromatographic analyses. Precise analytical data were not required to ascertain the amino acid composition of the degradation products since the parent peptides had been carefully analyzed and only one, LT-3, contained more than one residue of a given amino acid.

Small quantities of impurities were present in some of the hydrolytic products; this observation had been expected because of the non-specific degradative approach. Estimation of the purity of the fragments was based on end group analysis using the dinitrophenylation method. In the majority of cases at least 0.4 mole of a given amino acid residue was recovered per mole of starting peptide.

This recovery was considered acceptable since large losses had been expected due to the lengthy manipulation consisting of partial acid hydrolysis, paper chromatography, elution from the paper, dinitrophenylation, complete acid hydrolysis and

TABLE I

PAPER CHROMATOGRAPHIC ANALYSIS OF THE ACID DEGRADATION PRODUCTS

No. of parent peptide	Compn. and analysis of acid degrad. products	*Rf*	Estimated purity %	Major impurity
C-4	his	0.04	90	his(ser,glu)?
C-4	ser(glu,gly) moles 1.2 1.3 0.6	.12	80	gly
C-4	glu.gly moles 1.2 0.8	.20	100	...
C-4	thr.phe moles 1.1 0.9	.60	100	...
LT-3	ser.lys moles 1.0 1.0	.05	80	lys
LT-3	ser.asp moles 1.1 0.9	.14	80	asp
LT-3	thr	.21	100	...
LT-3	ser(asp,tyr) qual.	.37	65	asp(tyr.?)
LT-3	asp.tyr moles 1.2 0.8	.50	100	...
LT-4	ser.arg moles 0.9 1.1	.07	90	arg
LT-4	asp.ser qual.	.15	100	...
LT-4	tyr	.41	100	...
LT-4	leu.asp moles 0.8 1.2	.60	100	...
LT-4	tyr(leu,asp) moles 1.0 0.6 1.4	.72	100	...
LT-4	tyr.leu moles 1.0 1.0	.86	100	...

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paper chromatographic analysis of both the free and the DNP-amino acids. The degradation of the parent peptides into relatively few fragments may be attributed at least in part to the high content of serine and threonine in the peptides. Bonds involving the amino groups of the hydroxy amino acids are known[8] to be particularly labile in concentrated acids at rather low temperatures.

Sequence of Peptide C-3.—Paper chromatography[7] of the dinitrophenylated aliquots from the carboxypeptidase time study of peptide C-3 revealed the presence of two major DNP-derivatives in approximately equal amount. DNP-tryptophan was recognized readily; however, the second derivative did not correspond to any known DNP-amino acid. Quantitative analysis[9] demonstrated the complete absence of tryptophan in the unknown DNP-derivative. After hydrolysis, followed by paper chromatographic separation, the unknown spot was identified as DNP-val.glu. The course of the hydrolysis is represented by the curves in Fig. 2, with the DNP-peptide calculated as if it

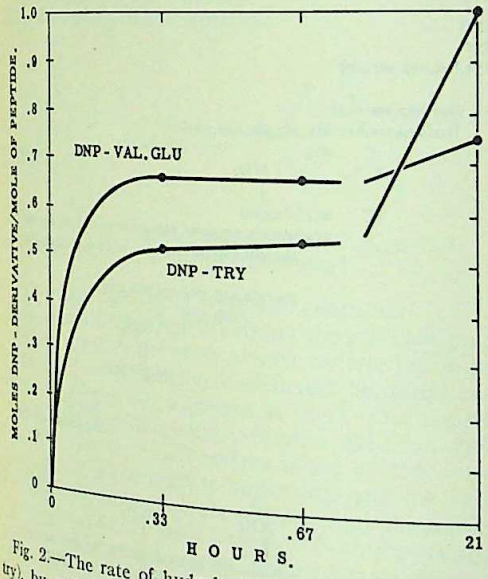

Fig. 2.—The rate of hydrolysis of peptide C-3, val(glu, try), by carboxypeptidase as determined by the dinitrophenylation method.

were DNP-valine. While the quantitative aspects of this experiment leave something to be desired, there can be little doubt that the sequence in peptide C-3 is val.glu.try. Both products of hydrolysis point to this conclusion; furthermore, this conclusion is in agreement with the usual specificity of chymotrypsin.

Location of the Amide Linkages.—The curves presented in Fig. 3 are representative of the results obtained from the amide analysis of peptides C-3, C-4, S-2, S-3, S-4, S-7 and S-9. In some cases the zero-time values for ammonia were abnormally high despite efforts to remove extraneous ammonia by concentration to dryness *in vacuo* from a weakly basic solution. Because of this difficulty it is possible that the quantitative recovery of the ammo-

(8) F. Sanger, *Advances in Protein Chem.*, **7**, 1 (1952).
(9) J. R. Spies and D. C. Chambers, *Anal. Chem.*, **20**, 30 (1948).

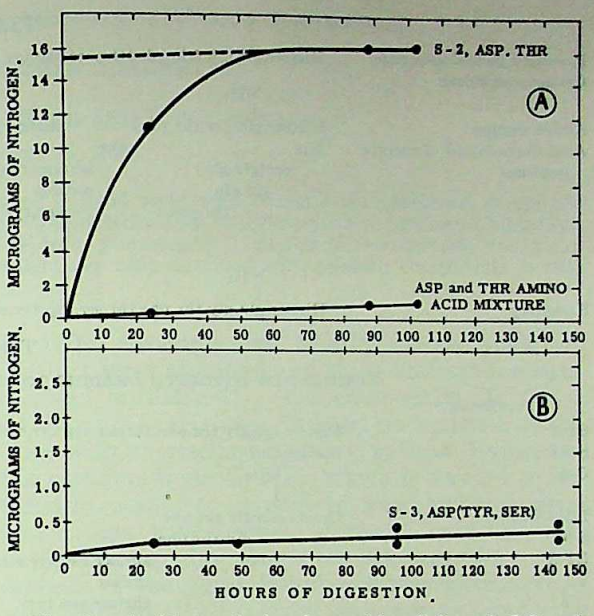

Fig. 3.—Amide analysis of peptides S-2 and S-3: A, ammonia nitrogen liberated from 1.2-μM aliquots of peptide S-2, and from equal quantities of a mixture of aspartic acid and threonine. Extrapolation to zero time provides a value of approximately one μM of NH_3 formed per μM of peptide S-2. B, Ammonia nitrogen liberated from 0.2 μM-aliquots of peptide S-3. Less than 0.1 μM of NH_3 was formed per μM of peptide S-3.

nia was masked by the initial high value, particularly in the cases of peptides C-4 and S-9

Despite this factor, the gradual release of ammonia during the digestion clearly showed which peptides contained the amide linkages. The quantitative data are presented in Table II. Of the 7

TABLE II

AMIDE ANALYSIS OF PEPTIDES FROM GLUCAGON DEGRADATION

Peptide no.	Peptide compn.	Moles of amide per mole of peptide
C-3	NH_2 | Val(glu,try)	1.1
C-4	NH_2 | His(ser,glu,gly,thr,phe)	0.6
S-2	NH_2 | Asp.thr	.9
S-3	Asp(tyr,ser)	.03
S-4	Asp,phe	.03
S-7	Leu(asp,ser,arg)	.0
S-9	NH_2 | Arg(ala,glu)	.5

peptides tested, only C-3, C-4, S-9 and S-2 yielded significant quantities of ammonia when incubated with strong acid. This is in agreement with the number of amide linkages found by chemical analysis of glucagon, and with the behavior of the peptides on resin columns. The data presented earlier on the release of amino acids from glucagon by the action of carboxypeptidase are also consistent with the conclusions that have been presented. Three amide-containing residues were liberated.

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TABLE III

Proposed partial sequence	His(ser,glu)gly(thr,phe)thr.ser.asp.tyr.ser.lys.tyr.leu(asp,ser,arg)arg.ala.glu.asp.phe.val(glu,try)leu.met.asp.thr
Carboxypeptidase	val.glu.try
	NH_2 NH_2 NH_2 NH_2
Amide groups	His(ser,glu,gly,thr,phe) asp(tyr,ser) leu(asp,ser,arg)arg (ala,glu)asp.phe val (glu,try) asp.thr
Acid degradation of certain peptides	His thr tyr.
	ser(glu.gly) ser(asp,tyr) tyr.leu
	glu.gly ser.asp tyr(leu,asp)
	thr.phe asp,tyr leu.asp
	ser.lys asp.ser
	ser.arg
	NH_2 NH_2 NH_2 NH_2
Summary	His.ser.glu.gly.thr.phe.thr.ser.asp.tyr.ser.lys.tyr.leu.asp.ser.arg.arg.ala.glu.asp.phe.val.glu.try.leu.met.asp.thr

TABLE IV

SUMMARY OF EVIDENCE LEADING TO THE AMINO ACID SEQUENCE OF GLUCAGON

Peptide no.[a]	Degradation products
ST-3	His(ser,glu,gly,thr,phe,thr,ser,asp,tyr,ser,lys)
S-8A	His(ser,glu)
C-4	NH_2
LT-5A	His.ser.glu.gly.thr.phe
S-6	gly(thr,phe)
LT-3	thr.ser.asp.tyr.ser.lys
S-1	thr.ser
C-2	thr(ser,asp,tyr)
S-3	asp(tyr,ser)
C-6	ser(lys,tyr)
S-10	lys,tyr
ST-1	tyr.leu.asp.ser.arg
LT-4	
S-7	leu(asp,ser,arg)
C-5	leu(asp,ser,arg,arg,ala,glu,asp,phe)
ST-2	arg
LT-5B	NH_2
S-9	arg(ala,glu)
ST-PA	arg(ala,glu,asp,phe,val,glu,try,leu,met,asp)thr
ST-PB	ala(glu,asp,phe,val,glu,try,leu,met,asp)thr
LT-PB	
LT-2	ala(glu,asp,phe,val,glu,try)
S-4	asp.phe
	NH_2
C-3	val.glu.try
S-8B	
S-5	leu.met
C-1	leu(met,asp)thr
LT-1	NH_2
S-2	asp.thr
Amino acids liberated by carboxypeptidase	NH_2 NH_2 NH_2
	ala(glu,asp,phe,val,glu,try,leu,met,asp)thr
	NH_2 NH_2 NH_2
Proposed sequence	NH_2 His.ser.glu.gly.thr.phe.thr.ser.asp.tyr.ser.lys.tyr.leu.asp.ser.arg.arg.ala.glu.asp.phe.val.glu.try.leu.met.asp.thr

[a] Prefix of the peptide number indicates the hydrolytic agent: ST = trypsin (2.25 hr.), S = subtilisin, C = chymotrypsin, LT = trypsin (50 hr.).

Two, as glutamine, occur in peptides C-3 and S-9. One, as asparagine, has been found in the terminal peptide, S-2. Finally, a residue of aspartic acid was released slowly by carboxypeptidase; the identification of this residue with the aspartic acid occurring in peptide S-4 is a logical interpretation.

Discussion

The results obtained by degradation of certain peptides with acid and with carboxypeptidase have been integrated into existing knowledge of the glucagon structure as shown in Table III. At least one line of evidence is available for each sequence in the chain, and in many cases more than one proof has been presented. In no case was it necessary to rely on the specificity of a proteolytic enzyme for a structure proof; however, with the exception of 2 or 3 minor splits caused by trypsin, the accepted specificity patterns of trypsin and chymotrypsin were confirmed. Of critical importance is the fact that all data, with no exceptions, are consistent with the final structure as proposed in Table III. A summary of all the evidence described in this series of reports is presented in Table IV.

Acknowledgment.—The authors gratefully acknowledge the assistance of E. R. Diller, E. E. Logsdon, H. L. Bird and C. T. Pugh. The authors also wish to thank C. W. Pettinga for the many helpful discussions and encouragement throughout this work.

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June 5, 1957

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF U. S. VITAMIN CORPORATION]

Pyridylethylated Benzoxazinediones[1]

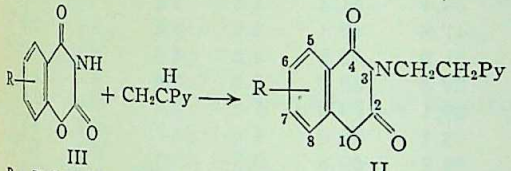
BY SEYMOUR L. SHAPIRO, IRA M. ROSE AND LOUIS FREEDMAN

RECEIVED DECEMBER 13, 1956

Pyridylethylation of 1,3-benzoxazine-2,4-diones has been effected in good yield with 2- and 4-vinylpyridines in the absence of a catalyst. Hydrolysis of some of these products to the N-pyridylethylated salicylamides and further to 2-pyridylethylamines has been demonstrated. Pyridylethylated products from phenobarbital, saccharin, succinimide and theophylline are also described. Interesting pharmacological responses have been obtained with selected compounds in this series.

The reported analgesic activity[2] of N-(2-(2-pyridyl)-ethyl)-phthalamide (I) suggested investigation of the corresponding 3-pyridylethylated 1,3-benzoxazine-2,4-diones (II) which embrace the structural elements of I as well as the analgetically active salicylamide structure. Recognition of enhancement of salicylate activity[3,4] by ring substituents indicated similar exploratory requirements for II.

Pyridylethylation of the 1,3-benzoxazine-2,4-diones (III) proceeded readily without catalyst and without solvent other than an excess of the vinylpyridine according to the equation



III II

R = H, 6-Cl, 6-Br, 8-CH_3, 6-OH, 7-OH, 6-C_6H_5, 8-C_6H_5
Py = 2-pyridyl, 4-pyridyl, 2-pyridyl-5-ethyl

The methiodides of II were also prepared.

The reaction apparently follows the reaction path suggested by Levine[5] with attack by the imide nitrogen of III on the electron-deficient terminal carbon atom of the vinyl groups in the 2- and 4-positions of the pyridine ring. Similar electron deficiency of the terminal carbon atom of the vinyl group in the 3-position[6] is impossible and no pyridylethylated products were obtained on attempted condensation of III with 2-methyl-5-vinylpyridine.

Yields of II ranged from 75% to quantitative as crude product and from 45–87% after recrystallization. The compounds prepared are described in Table I.

Two compounds related to type II were also prepared. In both of these, R = H. In one, the pyridyl group was replaced by the phenyl radical and in the other it was replaced by the 3,4-dimethoxyphenyl radical.

The required III was prepared by the sequence of reactions: substituted salicylic acid → methyl ester → amide. Reaction of the salicylamide with ethyl chlorocarbonate in pyridine–acetonitrile resulted in cyclization of the initially formed carbonic esters directly to III. Yields ranging from 84–100% as crude and 63–91% as recrystallized product were obtained and these findings are summarized in Table II. The compounds III (R = 6-OH, and 7-OH) were isolated under these conditions with unesterified hydroxyl groups. Evidently, the pyridine hydrochloride which is formed is sufficiently acidic to hydrolyze any carbonic ester which may have formed at the 6- or 7-hydroxyl group during the course of the reaction. Hydrolysis of the pyridylethylated benzoxazinediones with aqueous alkali at room temperature provided a convenient synthesis for the N-pyridylethylated salicylamides. The amides prepared are described in Table III.

The salicylamides (R = H, X = 2-pyridyl) upon hydrolysis with hydrochloric acid afforded 2-(2-aminoethyl)-pyridine (IV) as the dihydrochloride confirming the site of attack of III on the 2-carbon of the vinyl side chain of the pyridine.

Hot aqueous alkaline hydrolysis of II also afforded IV.

While these hydrolyses are synthetic pathways to these hitherto difficultly accessible amines, the reported synthesis[7] of IV and allied amines affords a much more convenient route.

Pyridylethylation also was studied and effected with theophylline and the imides, succinimide, saccharin and phenobarbital, and the results are described in Table IV.

Broad spectrum pharmacology did not show any regular structure–activity trends, although a variety of interesting responses were obtained in individual compounds for anticonvulsant, analgesic and anti-inflammatory effects in animal experiments. Thus the compounds (Table I) where R = H, Py = X and R = H, Py = Z showed anticonvulsant activity comparable to tridione. Analgesic activity two to three times that of salicylamide was noted with the compounds where R = 8-CH_3, Py = Y and R = 8-CH_3, Py = Z. The methiodides of the structures where R = 6-OH, Py = Y and R = 7-OH, Py = Y yielded anti-inflammatory activity superior to but were more toxic than butazolidin.

Experimental[8]

6-Bromo-1,3-benzoxazine-2,4-dione.—A suspension of 43.2 g. (0.2 mole) of 5-bromosalicylamide in 100 ml. of pyridine and 60 ml. of acetonitrile was maintained at 5° during addition of 22 ml. (0.22 mole) of ethyl chlorocarbonate over 20 minutes. The solution so obtained was concentrated until the internal temperature reached 122° (120 ml. of distillate collected) and then refluxed for 1 hr. Cooling and treating with 300 ml. of water and 10 ml. of concentrated hydrochloric acid yielded 46.2 g. (95.3%) of product.

(1) Presented at the 130th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956.
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(8) Descriptive data shown in the tables are not reproduced in the Experimental section.

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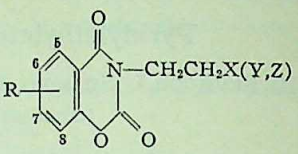
TABLE I

PYRIDYLETHYLATED BENZOXAZINEDIONES



X = 2-pyridyl, Y = 2-pyridyl-5-ethyl, Z = 4-pyridyl

R	XYZ	Yield, %[a]	M.p.,[a] °C.	Formula	Carbon, %[r] Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
H	X	64[e]	122	$C_{15}H_{12}N_2O_3$	67.2	66.8	4.5	4.4	10.4	9.9
HCl			202–205	$C_{15}H_{13}ClN_2O_3$	59.1	59.5	4.3	4.3		
CH_3I		53[e,l]	215–218	$C_{16}H_{15}IN_2O_3$	46.9	46.8	3.7	3.6	6.8	7.2
H	Y	75[b]	130–132	$C_{17}H_{16}N_2O_3$	68.9	69.1	5.4	5.4	9.5	9.3
CH_3I		58[d]	217–220	$C_{18}H_{19}IN_2O_3$	49.3	49.3	4.3	4.4		
H	Z	68[a]	155–156	$C_{15}H_{12}N_2O_3$	67.2	67.8	4.5	4.6		
CH_3I		60[d]	192–194	$C_{16}H_{15}IN_2O_3$	46.9	46.7	3.7	3.8	6.8	6.8
6-Cl	X	58[l]	154–155	$C_{15}H_{11}ClN_2O_3$	59.5	59.4	3.7	3.5	9.3	9.4
CH_3I		74[k]	212–218	$C_{16}H_{14}ClIN_2O_3$	43.2	42.8	3.2	3.0		
6-Cl	Y	39[b]	154	$C_{17}H_{15}ClN_2O_3$	61.7	62.1	4.6	4.8	8.5	8.3
6-Cl	Z	87[f]	215–216	$C_{15}H_{11}ClN_2O_3$	59.5	59.7	3.7	3.8	9.3	9.3
CH_3I		67[k]	183–185	$C_{16}H_{14}ClIN_2O_3$	43.2	43.2	3.2	3.2	6.3	5.9
6-Br	X	29[l]	161–165	$C_{15}H_{11}BrN_2O_3$	51.9	51.7	3.2	3.0	8.1	8.0
CH_3I		85[k]	218–221	$C_{16}H_{14}BrIN_2O_3$	39.3	39.0	2.9	2.9		
6-Br	Y	48[l]	155–157	$C_{17}H_{15}BrN_2O_3$	54.4	54.4	4.0	3.8		
CH_3I		52[k]	190–192	$C_{18}H_{18}BrIN_2O_3$	41.8	42.1	3.5	3.8	5.4	5.3
6-Br	Z	69[f]	229–230	$C_{15}H_{11}BrN_2O_3$	51.9	52.3	3.2	3.4	8.1	8.2
CH_3I		56[k]	190–193	$C_{16}H_{14}BrIN_2O_3$	39.3	39.0	2.9	2.6	5.7	5.8
8-CH_3	X	45[b]	132–133	$C_{16}H_{14}N_2O_3$	68.1	68.3	5.0	5.0	9.9	9.6
CH_3I		92[k]	230–235	$C_{17}H_{17}IN_2O_3$	48.1	48.0	4.0	3.7	6.6	6.8
8-CH_3	Y	57[b]	97–98	$C_{18}H_{18}N_2O_3$	69.7	69.8	5.9	5.8	9.0	9.2
CH_3I		88[k]	224–228	$C_{19}H_{21}IN_2O_3$	50.5	50.3	4.7	4.5	6.2	6.2
8-CH_3	Z	76[g]	181–183	$C_{16}H_{14}N_2O_3$	68.1	68.1	5.0	4.8	9.9	10.3
CH_3I		82[k]	190–200	$C_{17}H_{17}IN_2O_3$	48.1	48.2	4.0	3.9	6.6	6.7
6-C_6H_5	Y	63[l]	163–164	$C_{23}H_{20}N_2O_3$	74.2	74.4	5.4	5.6	7.5	7.7
CH_3I		87[m]	178–181	$C_{24}H_{23}IN_2O_3$	56.0	56.3	4.5	4.3	5.5	5.3
6-C_6H_5	Z	73[g]	170–171	$C_{21}H_{16}N_2O_3$	73.2	73.5	4.7	4.8	8.1	8.2
CH_3I		95[k]	214–215	$C_{22}H_{19}IN_2O_3$	54.3	54.2	3.9	4.0	5.8	6.1
8-C_6H_5	X	75[g]	166–168	$C_{21}H_{16}N_2O_3$	73.2	72.9	4.7	4.4	8.1	7.9
CH_3I		89[m]	194–198	$C_{22}H_{19}IN_2O_3$	54.3	54.4	3.9	4.0		
8-C_6H_5	Y	68[g]	139–142	$C_{23}H_{20}N_2O_3$	74.2	74.0	5.4	5.4	7.5	7.8
CH_3I		83[m]	211–213	$C_{24}H_{23}IN_2O_3$	56.0	55.9	4.5	4.5	5.5	5.3
8-OH	Z	57[g]	158–160	$C_{21}H_{16}N_2O_3$	73.2	73.4	4.7	4.8	8.1	8.3
CH_3I		89[m]	191–192	$C_{22}H_{19}IN_2O_3$	54.3	54.4	3.9	3.8	5.8	6.0
6-OH	X	32[g]	202–205	$C_{15}H_{12}N_2O_4$	63.4	63.6	4.3	4.1	9.9	9.7
CH_3I		96[p]	231–233	$C_{16}H_{15}IN_2O_4$	45.1	44.8	3.6	3.6	6.6	6.7
6-OH	Y	55[g]	192–194	$C_{17}H_{16}N_2O_4$	65.4	65.4	5.2	5.1	9.0	9.4
CH_3I		72[p]	210–213	$C_{18}H_{15}IN_2O_4$	47.6	48.0	4.2	4.2	6.2	5.8
6-OH	Z	73[j]	260	$C_{15}H_{12}N_2O_4$	63.4	63.0	4.3	4.4	9.9	10.1
CH_3I		81[p]	210–212	$C_{16}H_{15}IN_2O_4$	45.1	45.3	3.6	3.9		
7-OH	X	74[g]	217–219	$C_{15}H_{12}N_2O_4$	63.4	63.5	4.3	4.0	9.9	10.3
CH_3I		75[j]	243–245	$C_{16}H_{15}IN_2O_4$	45.1	44.9	3.6	3.5	6.6	6.9
7-OH	Y	57[g]	186–188	$C_{17}H_{16}N_2O_4$	65.4	65.2	5.2	4.8	9.0	8.8
CH_3I		76[p]	200–204	$C_{18}H_{19}IN_2O_4$	47.6	47.8	4.2	3.8	6.2	6.4
7-OH	Z	67[j]	260	$C_{15}H_{12}N_2O_4$	63.4	63.5	4.3	4.6	9.9	10.2
CH_3I		79[p]	208–210	$C_{16}H_{15}IN_2O_4$	45.1	44.7	3.6	3.0		
H	X[s]	59[b]	163–165	$C_{16}H_{13}NO_2$	71.9	71.6	4.9	4.9	5.2	5.5
H	X[t]	52[g]	173–175	$C_{18}H_{17}NO_5$	66.1	66.3	5.2	5.1	4.3	4.0

[a] Recrystallizing solvents. [b] Ethylacetate–hexane. [c] Methanol. [d] Ethanol. [e] Precipitated from acid solution with sodium hydroxide. [f] Methyl Cellosolve. [g] Butanol. [h] Chloroform. [i] Water. [j] Dimethylformamide. [k] Acetonitrile. [l] Ethyl acetate. [m] Acetonitrile–ethyl acetate. [n] Pyridine–hexane. [o] Acetonitrile–ether. [p] Dimethylformamide–ethyl acetate. [q] Melting points on Fisher–Johns apparatus, not corrected. [r] Analyses by Weiler and Strauss, Oxford, England. [s] X = phenyl. [t] X = 3,4-dimethoxyphenyl.

6-Chloro-3-(2-(4-pyridyl)-ethyl)-1,3-benzoxazine-2,4-dione.—To 6.59 g. (0.033 mole) of 6-chloro-1,3-benzoxazine-2,4-dione was added 25 ml. of 4-vinylpyridine and the reaction mixture heated under a nitrogen atmosphere for 2 hr. at 100° and then for 2 additional hr. at 150°. On cooling, the product separated, the excess 4-vinylpyridine was decanted and the crystalline mat of product ground under hexane and separated, giving 9.79 g. (97%).

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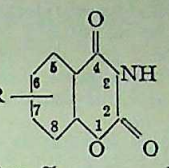
TABLE II

1,3-BENZOXAZINE-2,4-DIONES R

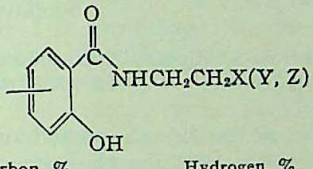


R	Yield, %[a]	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	82[g]	229–230[aa]							
6-Cl	64[f]	280[ab]	$C_8H_4ClNO_3$	48.6	48.8	2.0	2.2	7.1	6.9
6-Br	63[f]	286[ac]	$C_8H_4BrNO_3$	39.7	40.1	1.7	1.9	5.8	5.9
8-CH_3	81[g]	210–212[ad]	$C_9H_7NO_3$	61.0	61.2	4.0	4.2	7.9	7.8
6-C_6H_5	75[j]	258–259[ae]	$C_{14}H_9NO_3$	70.3	70.2	3.8	4.0	5.9	6.0
8-C_6H_5	91[g]	232–234[af]	$C_{14}H_9NO_3$	70.3	70.5	3.8	3.9	5.9	5.9
6-OH	88[n]	303–305[ag]	$C_8H_5NO_4$	53.6	53.8	2.8	2.9	7.8	7.9
7-OH	91[g]	310[ah]	$C_8H_5NO_4$	53.6	53.7	2.8	2.8	7.8	8.1

[a] Recrystallizing solvents are same as shown for Table I. [aa] Reported, E. Comanducci (*Rend. accad. sci. (Napoli)*, **27**, 48 (1921)); *C. A.*, 18, 1658$_2$ (1924), m.p. 221°. [ab] From 5-chlorosalicylamide, m.p. 223–224°; C. L. Arcus and D. B. Greenwood (*J. Chem. Soc.*, 1937 (1953)), m.p. 227–228°. [ac] From 5-bromosalicylamide, m.p. 233–238°; P. Kauschke (*J. prakt. Chem.*, [2] 51, 211 (1895)), m.p. 238°. [ad] From 3-methylsalicylamide, m.p. 107–109°; R. Anschütz, *et al.* (*Ann.*, **346**, 343 (1906)), m.p. 112°. [ae] From 5-phenylsalicylamide, m.p. 173–176°. *Anal.* Calcd. for $C_{13}H_{11}NO_2$: C, 73.2; H, 5.2; N, 6.6. Found: C, 73.2; H, 5.7; N, 6.9. [af] From 3-phenylsalicylamide, m.p. 144–145°. *Anal.* Calcd. for $C_{13}H_{11}NO_2$: C, 73.2; H, 5.2. Found: C, 73.5; H, 5.3. [ag] From 5-hydroxysalicylamide, m.p. 218–220°; P. Rayet (*Industrie chim. belge*, **17**, 478 (1952)); *C. A.*, **46**, 10445e (1952)), m.p. 218–218.5°. [ah] From 4-hydroxysalicylamide, m.p. 234–235° (*C. A.*, **46**, 10445e (1952), m.p. 234°).

TABLE III

N-PYRIDYLETHYLATED SALICYLAMIDES R

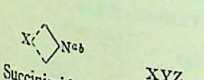


R	XYZ	Yield, %[a]	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	X	43	114–115	$C_{14}H_{14}N_2O_2$	69.4	69.7	5.8	6.2	11.6	11.8
H	Y	49	107–108	$C_{16}H_{18}N_2O_2$	71.1	71.3	6.7	7.1	10.4	9.8
H	Z	53	105–106	$C_{14}H_{14}N_2O_2$	69.4	69.4	5.8	5.8	11.6	11.8
3-C_6H_5	X	63	140	$C_{20}H_{18}N_2O_2$	75.5	75.2	5.7	6.1	8.8	9.1
3-C_6H_5	Y	58	113–114	$C_{22}H_{22}N_2O_2$	76.3	76.0	6.4	6.6	8.1	8.1
3-C_6H_5	Z	66	180–182	$C_{20}H_{18}N_2O_2$	75.5	75.2	5.7	5.6	8.8	8.6

[a] All compounds were recrystallized from ethyl acetate–hexane.

TABLE IV

PYRIDYLETHYLATED IMIDES[aa]



	XYZ	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Succinimide	X	71[b]	109–111	$C_{11}H_{12}N_2O_2$	64.7	64.2	5.9	5.5		
CH_3I		91[k]	212–218	$C_{12}H_{15}IN_2O_2$	41.6	41.9	4.4	4.0	8.1	7.9
Succinimide	Y	43[b]	101–102	$C_{13}H_{16}N_2O_2$	67.2	66.8	6.9	7.0	12.1	12.4
Theophylline[ac]	Z	16[l]	124–126	$C_{11}H_{12}N_2O_2$	64.7	65.4	5.9	6.1	13.7	13.8
CH_3I	X	57[c]	122–124	$C_{14}H_{15}N_5O_2$	58.9	59.0	5.3	5.2	24.6	24.9
Theophylline[ac]		60[c]	212–214	$C_{15}H_{18}IN_5O_2$	42.2	41.8	4.2	4.4		
Phenobarbital[ac]	Z	65[d]	175–177	$C_{14}H_{15}N_5O_2$	58.9	59.0	5.3	5.3	24.6	24.6
Saccharin[ac]	X	10[b]	143–146	$C_{19}H_{19}N_3O_3$	67.6	67.7	5.7	5.7	12.5	12.0
	X	38[c]	145–148	$C_{14}H_{12}N_2O_3S$	58.3	58.6	4.2	4.1	9.7	9.8

[a] The symbols have the same significance as shown in Table I. [ab] The compound used for pyridylethylation less its acidic hydrogen. [ac] These compounds were prepared by Mr. Harold Soloway of these laboratories using basic catalysis and the method of F. K. Kirchner and C. J. Cavallito, U. S. Patent 2,498,497, Feb. 21, 1950.

N-(β-Phenethyl)-salicylamide.—A solution of 15.2 g. (0.1 mole) of methyl salicylate and 20 ml. (excess) of β-phenethylamine was refluxed until a minimum internal temperature (104°) was reached. Volatiles were removed and 22.3 g. (92.5%) of product crystallized on cooling. Recrystallization from ether (51%) gave a product which melted at 94–95°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.3. Found: C, 75.1; H, 6.3.

This product was cyclized with ethyl chlorocarbonate as described above to yield the 3-(β-phenethyl)-1,3-benzoxazine-2,4-dione.

N-(β-[3,4-Dimethoxyphenyl]-ethyl)-salicylamide.—This was prepared from methyl salicylate and β-(3,4-dimethoxyphenyl)-ethylamine as described above in 19% yield; m.p. 110–111° (acetonitrile–ether).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.8; H, 6.4; N, 4.7. Found: C, 67.6; H, 6.2; N, 4.8.

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N-2-(4-Pyridylethyl)-3-phenylsalicylamide.—A suspension of 1.8 g. (0.0053 mole) of 3-(2-[4-pyridylethyl])-8-phenyl-1,3-benzoxazine-2,4-dione in 50 ml. of 5% sodium hydroxide dissolved after stirring for 2 hr. Acidification with hydrochloric acid, followed by addition of excess sodium bicarbonate, gave 1.55 g. (93.2%) of crude amide, m.p. 174–179°.

2-(2-Aminoethyl)-pyridine (from Acid Hydrolysis of Pyridylethylsalicylamide).—A solution of 2.92 g. (0.012 mole) of N-(2-[2-pyridyl]-ethyl)-salicylamide in 11 ml. of 20% hydrochloric acid was refluxed for 8 hr. The formed salicylic acid was removed, the filtrate refluxed an additional 8 hr. and salicylic acid again removed, total 1.01 g. After washing with ether, the filtrate was evaporated and the residue recrystallized from ethanol. There was obtained 1.25 g. (56%) of 2-(2-aminoethyl)-pyridine dihydrochloride, m.p. 182–188°.

Anal. Calcd. for $C_{17}H_{12}Cl_2N_2$: N, 14.4. Found: N, 14.3.

The dipicrate melted at 227–228° (ethanol) and when mixed with the dipicrate prepared from authentic 2-(2-aminoethyl)-pyridine,[7] m.p. 224–225°, showed no depression, mixed m.p. 225–226°.

2-(2-Aminoethyl)-pyridine (from Basic Hydrolysis of Pyridylethylated Oxazinedione).—A solution of 6.0 g. of II, R = H, Py = X (0.0223 mole) and 65 ml. of 8% sodium hydroxide was refluxed for 12 hr. Sodium hydroxide (30 g.) was added and the reaction mixture steam distilled.

Acidification of the pot residue with hydrochloric acid and addition of excess sodium bicarbonate yielded 2.92 g. (53.3%) of the product of incomplete hydrolysis, N-(2-[2-pyridyl]-ethyl)-salicylamide, m.p. 102–104°.

Acidification of the distillate with hydrochloric acid, evaporation to dryness and recrystallization from ethanol yielded 1.07 g. (24.5%) of 2-(2-aminoethyl)-pyridine dihydrochloride, m.p. 182–189°.

Acknowledgment.—The authors are indebted to Dr. G. Ungar and his staff for the physiological screening of the compounds and to Mr. J. Hinchen for his technical assistance.

YONKERS, NEW YORK

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY, THE OHIO STATE UNIVERSITY]

Pyrolysis of 3-Nitroso-5,5-disubstituted-2-oxazolidones

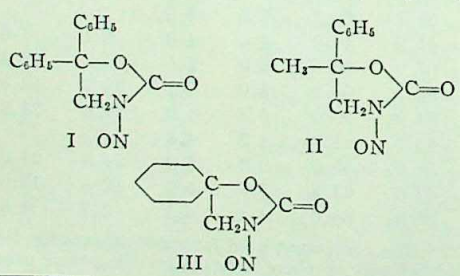
BY MELVIN S. NEWMAN AND ALAN E. WEINBERG[1]

RECEIVED DECEMBER 12, 1956

The pyrolyses of 3-nitroso-5,5-diphenyl-2-oxazolidone (I), 3-nitroso-5-methyl-5-phenyl-2-oxazolidone (II) and 3-nitroso-1-oxaazaspiro[4,5]decane-2-one (III) in the presence and absence of solvents is described.

Relatively little work has been reported on the pyrolysis of compounds containing the nitrosoamide group. Perhaps the earliest example is the pyrolysis of nitrosoacetanilide to yield biphenyl.[2] Recently, the pyrolysis of nitrosoamides has been used as an effective step in the series of reactions by which a primary aliphatic amine may be converted into the corresponding alcohol.[3] The mechanism of this reaction has been studied by Huisgen[4] and by White.[5]

We have been interested in the reactions which occur when nitrosoöxazolidones are treated with alkali.[6] Because of the thermal instability of certain of these nitrosoöxazolidones, we decided to study the pyrolysis of selected nitrosoöxazolidones. For this purpose we chose 3-nitroso-5,5-diphenyl-2-oxazolidone (I), 3-nitroso-5-methyl-5-phenyl-2-oxazolidone (II) and 3-nitroso-1-oxaazaspiro[4,5]decane-2-one (III), all of which had been prepared previously.[6b]



I II III

The pyrolysis of I in the absence of solvent yielded the parent oxazolidone, diphenylacetylene, 1,1-diphenylethylene and benzophenone in proportions which changed as the pyrolysis temperature was varied. The results are summarized in Table I.

TABLE I

PYROLYSIS OF 3-NITROSO-5,5-DIPHENYL-2-OXAZOLIDONE (I) AT VARIOUS TEMPERATURES

Yields[a] of	Temperature 120°	153°	168°	185°
Parent oxazolidone	57	51	40	18
$C_6H_5C{\equiv}CC_6H_5$[b,c]	16	20	23	32
$(C_6H_5)_2C{=}CH_2$[c,d]	15	21	26	40
$C_6H_5COC_6H_5$[e]	5	5	6	6
Residues[f]	7	3	5	4
Av. time of pyrolysis	13.5 hr.	2 hr.	2 hr.	40 min.

[a] % yield based on I originally decomposed. [b] Estimated as 2,4-dinitrophenylhydrazone of benzyl phenyl ketone after hydration of hydrocarbon fraction of products with sulfuric acid and mercuric sulfate. [c] Estimated by ultraviolet spectrophotometric analysis. [d] Estimated as 2,4-dinitrophenylhydrazone of benzophenone after ozonolysis. [e] Estimated as 2,4-dinitrophenylhydrazone. [f] The difference between products accounted for and 100% recovery was tarry residue.

Since the formation of parent oxazolidone in high yield in the absence of solvent and, hence, of any hydrogen donor other than the reacting molecule was surprising,[7] we also carried out the pyrolysis of I in eight solvents at the same tempera-

(1) Union Carbide and Carbon Fellow, 1955–1956. The material herein presented is taken from the Ph.D. thesis of A.E.W., O.S.U., 1956.

(2) E. Bamberger, *Ber.*, **30**, 366 (1897).

(3) See E. H. White, THIS JOURNAL, **77**, 6011 (1955), and references therein to other work in this field.

(4) R. Huisgen and J. Reinertshofer, *Ann.*, **575**, 197 (1952), and previous papers.

(5) E. H. White, THIS JOURNAL, **77**, 6014 (1955).

(6) (a) M. S. Newman and W. N. Edwards, *ibid.*, **76**, 1840 (1954); (b) M. S. Newman and A. Kutner, *ibid.*, **73**, 4199 (1951); (c) M. S. Newman, *ibid.*, **71**, 378 (1949).

(7) This finding had been foreshadowed by pyrolysis studies previously carried out, but not studied in detail; see ref. 6a.

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ture (153°). The results are summarized in Table II.

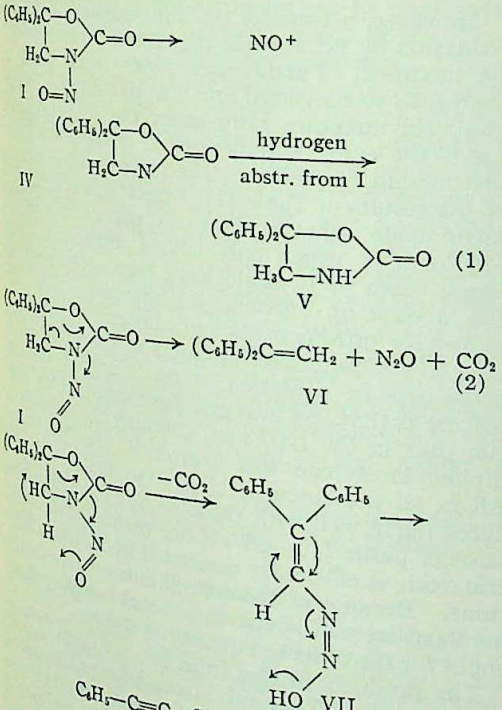
TABLE II

PYROLYSIS OF 3-NITROSO-5,5-DIPHENYL-2-OXAZOLIDONE (I) IN SOLVENTS AT 153°

Solvent	Products	Yield,[a] %
None, *t*-butylbenzene, Nitrobenzene, naphthalene, Methyl benzoate, Perchloropropylene, Bromobenzene	Oxazolidone	48–54
	$C_6H_5C{\equiv}CC_6H_5$	18–20[b,c]
	$(C_6H_5)_2C{=}CH_2$	21–22[c]
	$C_6H_5COC_6H_5$	5–6[d]
p-Xylene	Oxazolidone	80
	p-Toluic acid	18
Cumene	Oxazolidone	80
	$C_6H_5COCH_3$	22[d,e]
$(C_6H_5)_2C{=}CH_2$[f]	Oxazolidone	87
	$C_6H_5COC_6H_5$	10[d]

[a] Based on I originally decomposed. [b] Estimated as 2,4-dinitrophenylhydrazone of benzyl phenyl ketone after hydration of hydrocarbon fraction of products with sulfuric acid and mercuric sulfate. [c] Estimated by ultraviolet spectrophotometric analysis. [d] Estimated as 2,4-dinitrophenylhydrazone. [e] Average of five determinations. [f] This experiment was run at 185° for 40 minutes. No diphenylacetylene was found.

We believe that the results summarized in Table I may be explained by the following three decomposition paths.[8]



I IV V VI VII VIII

Decomposition by path 1 is favored (competitively) by a low temperature. The oxazolidyl free radical IV abstracts a hydrogen atom from some substrate to yield oxazolidone V. In the pyrolyses in the absence of added solvent the only sources of hydrogen atoms are starting compound I and the products VI and VIII, arising from decomposition by paths 2 and 3. From the results of pyrolyses in solvents (see Table II), it seemed unlikely that diphenylacetylene would act as a hydrogen-providing substrate and hence no separate run was made in diphenylacetylene as a solvent to check this point. However, diphenylethylene VI proved a ready source for hydrogen (see last experiment, Table II). Therefore, the amount of VI isolated in various runs undoubtedly is not a true measure of the amount of decomposition occurring *via* path 2 because some of the VI provides hydrogen to the free radical IV. The fate of the diphenylethylene which provides the hydrogen to the radical IV is unknown. However, since no diphenylacetylene VIII is formed in the pyrolysis of I in diphenylethylene VI it is obvious that VI cannot be the precursor of VIII.

Decomposition by path 2 involves a single concerted electron shift as shown. The same result might be pictured in other multistage ways, but the single process illustrated has the advantage of simplicity.

Decomposition by path 3 involves two concerted steps as shown. The same result might also be pictured in multistage processes, but the steps illustrated seem logical. Interestingly the hypothetical azo intermediate VII has a *cis* structure since the nitroso group in I undoubtedly is oriented as shown because of the dipole interactions of the carbonyl and nitroso groups.[9] As a general rule, *cis*-azo compounds are more labile than *trans*-azo compounds.[10]

As will be shown below, however, the results obtained from pyrolyses in cumene, *p*-xylene and 1,1-diphenylethylene, show that there is undoubtedly attack on the starting nitroso compound I by free radicals (either IV or nitric oxide) when the pyrolyses are carried out in the absence of these solvents (*e.g.*, alone or in the other solvents).

In all of the pyrolyses of I, alone and in most of the solvents used, there are formed small amounts of benzophenone and tar. The benzophenone undoubtedly arises mainly from oxidation of diphenylethylene by the nitric oxide formed in decomposition *via* path 1. This hypothesis is strengthened by the fact that the amount of benzophenone formed, although constant in many experiments (see Table II), was significantly increased when diphenylethylene was present in excess (last experiment, Table II). The oxidizing action of nitric oxide on organic substrates has been observed previously.[11] In a recent study of the oxidizing action of nitric oxide at 80° and 250 p.s.i. on cumene and other substrates, the phenyl ring was generally stable but alkyl substituents, particularly the iso-

(8) Decomposition by a path involving ring expansion to a seven-membered diazo carbonate structure was considered as a possibility. However, in view of the work of Huisgen and Reinertshofer[4] with nitrosopyrrolidone this mode of decomposition is estimated to occur to a very minor extent.

(9) The situation is analogous to that in the case of nitrosopyrrolidone, see ref. 4.

(10) See E. E. Turner and M. M. Harris, "Organic Chemistry," Longmans Green and Co., London, 1952, pp. 440, for a discussion of the evidence.

(11) T. Panzer, *Z. physiol. Chem.*, **93**, 378 (1925); A. Gorgas, *Ber.*, **63**, 2700 (1930); W. H. Fulweiler, *Am. Gas. J.*, **142**, 27 (1935); G. F. Bloomfield and G. A. Jeffrey, *J. Chem. Soc.*, 120 (1944); W. B. Biggs, *Gas. J.*, **235**, 213 (1941); J. C. Devins and C. A. Winkler, *Can. J. Research*, **26B**, 356 (1948); F. S. Bridson-Jones, G. D. Buckley, L. H. Cretcher and A. H. Gilbert, *J. Chem. Soc.*, 2099, 3009, 3016 (1951).

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propyl groups, were attacked.[12] Before our knowledge of this work,[12] we had shown that the oxidation of cumene at 153° by nitric oxide at atmospheric pressure yielded acetophenone and small amounts of methanol and acetone.

The pyrolyses in solvents are interesting in that the products in the first six solvents noted in Table II are the same as those formed when the pyrolysis is performed in the absence of solvent. However, when a solvent which has a hydrogen particularly easily attacked by the free radical IV is used, markedly different results are obtained. For example, at 153° in the absence of solvent, or in the presence of the first six solvents mentioned, about 50% of oxazolidone V is formed, whereas in *p*-xylene and cumene 80% of V is formed. In diphenylethylene VIII at 185°, 87% of V is formed. Two explanations for these facts seem possible.

A. *p*-Xylene, cumene and 1,1-diphenylethylene assist decomposition by path 1 rather than hinder decompositions by paths 2 and 3. This explanation implies that the activation energy of decomposition by path 1 is lowered by a solvent which can lose a hydrogen atom easily, probably by incorporation of a suitably oriented solvent molecule in the transition state.

B. Decompositions by paths 2 and 3 do not occur as shown but rather by attack of a free radical produced by path 1 on unchanged starting material I. Thus, in solvents which are more easily attacked by the free radicals than I, the free radical IV formed by path 1 attacks solvents (rather than I) to form oxazolidone. However, if explanation B were correct, it is difficult to see how diphenylethylene could arise from attack of the free radical IV on I since both hydrogens in the heterocyclic ring are needed if diphenylethylene is to be the end product of reaction.

In the pyrolysis run in cymene, a careful search for 2,3-dimethyl-2,3-diphenylbutane was made, as this compound would result from dimerization of the radical formed from cymene. However, no trace of this dimer was found. Probably this radical is attacked readily by nitric oxide or actually is not formed in a free condition. The cumene may solvate the N–NO bond prior to rupture in such a way that $C_6H_5C(CH_3)_2NO$ and oxazolidone V are formed directly. Such a four-center reaction would account for the solvent effect above noted for cumene, *p*-xylene and diphenylethylene.

The behavior of the oxazolidyl free radical IV stands in marked contrast to the pyrrolidyl radical, formed on pyrolysis from nitrosopyrrolidone, which attacks the benzene ring to give N-substituted pyrrolidones.[4] We found no N-substituted oxazolidones in all of the experiments summarized in Table II.

The pyrolysis of I in α-methylstyrene was carried out at 100° for 24 hr. in order to see if polymerization would be enhanced by any of the radicals formed. However, less polymer was obtained than in the blank run for control. Probably the nitric oxide formed acted as an inhibitor.

In order to obtain a more nearly complete picture of the pyrolysis of I alone, gas analyses were run at 120 and 185° on the products. The results are listed in Table III. According to the three paths pictured the following results should be observed: A. The amount of nitric oxide should correspond to the yield of oxazolidone V. B. The amount of nitrous oxide should correspond to the yield of diphenylethylene VI. C. The amount of nitrogen should correspond to the yield of diphenylacetylene VIII. D. The amount of carbon dioxide should correspond to the sum of the yields of VI and VIII.

TABLE III

GASEOUS AND OTHER DECOMPOSITION PRODUCTS FROM PYROLYSIS OF 3-NITROSO-5,5-DIPHENYL-2-OXAZOLIDONE (I)

Product	Mole prod./mole I at 120°	Mole prod./mole I at 185°
H_2O	0.08	0.25
N_2	.40	.35
NO	.04	.05
N_2O	.31	.53
CO_2	.53	.87
Oxazolidone	.57	.18
$(C_6H_5)_2C{=}CH_2$	.15	.40
$C_6H_5C{\equiv}CC_6H_5$	.16	.30
$C_6H_5COC_6H_5$	.05	.06
Tar	.07	.04

However, because of the side reactions involving oxidation by nitric oxide the expected results must be modified. Furthermore, since nitric oxide is known to be converted into nitrous oxide and nitrogen[13] (in unknown ratio under the conditions we used) the expected amounts of nitrogenous gases are difficult to predict. The most striking feature of the results in Table III is the low percentage of nitric oxide found in the gases, particularly in the 120° run in which only 4% of nitric oxide was found when 57% would have been expected from the amount of oxazolidone I obtained. The high values for nitrous oxide and nitrogen are attributable to the reduction products of the nitric oxide consumed in oxidation steps. Another striking feature is that less nitrogen was formed in the 185° run than in the 120° run, although the amount of diphenylacetylene was greater in the 185° run. All in all the amounts of gaseous products found agree fairly well with those to be expected on the basis of paths 1, 2 and 3 if one realizes that the nitric oxide is efficiently consumed in oxidation reactions. Because of the several unknown quantities involved we will not go into detail in trying to account for the observed quantities of gases.

The products arising from the pyrolyses of 3-nitroso-5-methyl-5-phenyl-2-oxazolidone (II) and of 3-nitroso-1-oxaazaspiro[4,5]decane-2-one (III) are listed in Table IV. In the case of II, more tar was formed than during comparable pyrolyses of I, whereas when III was pyrolyzed the only substance that could be identified was the parent oxazolidone.

The formation of parent oxazolidone, α-methylstyrene, acetophenone and methylphenylacetylene from pyrolysis of II may be explained by the decomposition paths 1, 2 and 3 previously discussed.

(12) Private communication from J. F. Brown, Jr., and C. A. Burkhard, General Electric Co., Schenectady, N. Y.

(13) J. W. Mellor, "Treatise on Inorganic and Theoretical Chemistry," Vol. VIII, Longmans, Green and Co., London, England, 1928, p.

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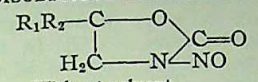
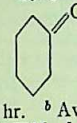
TABLE IV

PYROLYSES OF 3-NITROSO-5,5-DISUBSTITUTED-2-OXAZOLIDONES ALONE AND IN SOLVENTS



R₁	R₂	Products	Without solvent 153°[a]	Without solvent 185°[b]	$C_6H_5NO_2$	Solvent at 153° $C_6H_5COOCH_3$	$C_6H_5CH(CH_3)_2$
C_6H_5	CH_3	Parent oxazolidone[c]	64	50	61		88
II		$C_6H_5COCH_3$[d]	7	8	7		28
		$C_6H_5C{\equiv}CCH_3$[e]	6	7	7		
		$C_6H_5C(CH_3){=}CH_2$[f]	5	10			
		$C_6H_5CH{=}C{=}CH_2$[g]	6	8	6		
$-(CH_2)_5-$		Parent oxazolidone	70	57	66	67	90
III		$C_6H_5COCH_3$[d]					41
					2.1	1.4	

[a] Average time, 2 hr. [b] Average time, 35 min. [c] Isolated as crystalline solid. [d] Estimated as 2,4-DNPH derivative. [e] Estimated as 2,4-DNPH of propiophenone. [f] Estimated as 2,4-DNPH of acetophenone after ozonization. [g] Estimated as 2,4-dinitrophenylosazone of 1-phenyl-1,2-propanedione. [h] Estimated as 2,4-DNPH derivative.

However, the formation of phenylallene is difficult to explain. Actually phenylallene was not isolated as such. Its presence was deduced from the fact that the 2,4-dinitrophenylosazone of 1-phenyl-1,2-propanedione was obtained from the hydrocarbon fraction remaining after removal of acetophenone as its 2,4-dinitrophenylhydrazone by treatment with sulfuric acid and mercuric sulfate in the presence of excess 2,4-dinitrophenylhydrazine. Other possible precursors of the osazone were examined but were ruled out as follows: 2-phenyl-1,2-propanediol yielded 2-phenylpropanal[14]; propiophenone gave too small a yield of osazone to account for the amount obtained and furthermore would have been removed by the treatment with 2,4-dinitrophenylhydrazine prior to the mercuric sulfate catalyzed reaction; 1-phenyl-2-propanone afforded a good yield of 1-phenyl-1,2-propanedione on treatment with mercuric sulfate and sulfuric acid but would have been removed along with acetophenone in the original treatment with 2,4-dinitrophenylhydrazine; and methylphenylacetylene gave too small a yield of diketone on treatment with mercuric sulfate and sulfuric acid to account for the amount of osazone formed.

The phenylallene formed is probably the result of a free radical attack on II prior to its thermal decomposition by path 1.

Experimental

General Procedures.—All melting points up to 200° are corrected. The petroleum ethers used were Skellysolve F (b.p. 30–60°) and Skellysolve B (b.p. 55–70°). For chromatographic procedures, silicic acid (Mallinckrodt chromatographic grade) and alumina (Fisher chromatographic grade) were used after previous heating to 200° for 12 hr. The analysis was run by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Freshly prepared 2,4-dinitrophenylhydrazine solution[15] (DNPH) was used to analyze for aldehydes and ketones. A small excess of this reagent was refluxed for a few minutes with an ethanolic solution of the carbonyl compound and the mixture cooled for at least 4 hr. The precipitate was chromatographed on a short column packed with alumina and developed with benzene.

All solid compounds were compared to an authentic sample by mixed melting point and by infrared spectra of the Nujol mulls. Unless otherwise stated, all percentage yields are based on the nitroso compound used.

Pyrolysis of 3-Nitroso-5,5-diphenyl-2-oxazolidone (I) in the Absence of a Solvent at 185°.—In a dried flask connected to a gas collecting device, 10.33 g. of I was decomposed at 185°, this temperature being maintained with a salt-bath or by the immersion of the reaction flask in refluxing *p*-bromotoluene. The decomposition was active but never violent. Gas evolution ceased after 40 minutes; the dry gas collected (1559 ml., S.T.P.) represented 1.80 moles per mole of I. A sample of this gas when shaken with ammoniacal silver hydroxide gave no metallic silver,[16] denoting the absence of carbon monoxide.

After cooling, 12 ml. of Skellysolve F and 2.5 ml. of ethanol were added. The solid obtained was recrystallized from ethanol to yield 0.89 g. of 5,5-diphenyl-2-oxazolidone (V), m.p. 199–201° (reported[6b] m.p. 199.6–200.4°). The filtrate was evaporated to give 6.38 g. of a yellow oil, A. To 0.52 g. of A was added excess DNPH reagent. There was obtained 0.069 g. (6.1%) of the 2,4-dinitrophenylhydrazone of benzophenone, m.p. 238–239°.[17] The filtrate when refluxed for 1 hr. with 2 g. of mercuric sulfate and 5 ml. of sulfuric acid and cooled, afforded 0.331 g. (28.1%) of desoxybenzoin 2,4-dinitrophenylhydrazone,[18] m.p. 202–203°. Analogously, pure diphenylacetylene was converted to the same derivative in 85% yield.

A solution of 5.38 g. of oil A in 3 ml. of chloroform and 3 ml. of Skellysolve B was chromatographed on a 5.6 × 19 cm. column packed with silicic acid and developed with 5% ether in Skellysolve B. The first fraction eluted, oil B (4.66 g.), was shown by infrared spectrum to be a mixture of hydrocarbons and benzophenone. The second fraction, 0.64 g., was found to be V; when this was combined with the oxazolidone V obtained from the original reaction mixture, the total yield was 1.65 g. (17.9%). The third fraction (0.06 g.) was a black tar. Oil B was rechromatographed to yield 4.30 g. of a colorless oil C, whose infrared spectrum showed it to be solely hydrocarbon, and 0.35 g. of a pale yellow oil D, whose infrared spectrum was identical with that of an authentic sample of benzophenone. From D was obtained 0.69 g. (5.9%) of benzophenone 2,4-dinitrophenylhydrazone, m.p. 238–239°.

Oil C was treated in four ways: (a) No derivatives were obtained when 0.482 g. of C was treated with excess DNPH; however, when this solution was refluxed with 2 g. of mercuric sulfate and 5 ml. of sulfuric acid and cooled, 0.377 g. (27.5%) of desoxybenzoin 2,4-dinitrophenylhydrazone, m.p. 202–203°, was obtained. (b) During the early stages of

(14) M. Tiffeneau, *Ann. chim.*, [8] **10**, 343 (1907).

(15) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

(16) G. Lunge and H. R. Ambler, "Technical Gas Analysis," Curmey and Jackson, London, 1934, p. 228.

(17) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 363, report m.p. 238–239°.

(18) Reference 17, p. 365, reports m.p. 204°.

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the ozonolysis[19a,b] of 0.632 g. of oil C, 0.0216 g. of formaldehyde 2,4-dinitrophenylhydrazone, m.p. 164–165° (reported[20] m.p. 166°), was obtained by passing the exit gases through DNPH reagent. When the ozonized material was treated with zinc and acetic acid and worked up in the usual manner, benzophenone and 0.107 g. of benzoic acid, m.p. 120–121° (reported[21] m.p. 121.4°), were obtained. The benzophenone was converted to 0.547 g. of its 2,4-dinitrophenylhydrazone, m.p. 239–240°. This showed that at least 43% of the hydrocarbon mixture was unsymmetrically substituted. (c) Treatment of 0.263 g. of oil C with excess 2,4-dinitrobenzenesulfenyl chloride yielded 0.179 g., 15% based on I, of 1,1-diphenyl-2-(2,4-dinitrobenzenesulfenyl)-ethylene, m.p. 135.5–136.5° (reported[22] m.p. 135.5–136.5°). No acetylenic derivative was obtained.[23] (d) Oil C was submitted to multicomponent ultraviolet spectrophotometric analysis similar to that used by Tunnicliff, *et al.*[24] Pure samples of diphenylacetylene[25] ($c = 7.00 \times 10^{-4}$ g./100 ml. ethanol, 250 mμ, $E^{1\%}_{1cm.}$ 634; 270 mμ, $E^{1\%}_{1cm.}$ 1225) and 1,1-diphenylethylene[26] ($c = 7.00 \times 10^{-4}$ g./100 ml. ethanol, 250 mμ, $E^{1\%}_{1cm.}$ 808; 270 mμ, $E^{1\%}_{1cm.}$ 336) were used as reference compounds. The equations were

$$\text{absorbance}_{250m\mu} = 634X + 808Y$$
$$\text{absorbance}_{270m\mu} = 1225X + 336Y$$

where

X = concn. of diphenylacetylene
Y = concn. of 1,1-diphenylethylene
$A_{250m\mu} = 0.766$
$A_{270m\mu} = 0.765$

The solution of these equations showed that 2.23 g. (32.4%) of diphenylacetylene and 2.81 g. (40.3%) of 1,1-diphenylethylene were obtained from nitroso compound I.

Pyrolysis of I in Absence of Solvent at 120, 153 and 168°.—Decomposition and recovery of the decomposition products were described above. The temperature was maintained at 120° by immersing the reaction flask in refluxing 2-pentanol. This decomposition required 13.5 hr. Refluxing cumene was used at 153° and refluxing *t*-butylbenzene was used at 168°. Decomposition at these temperatures required 2 hr. The results are listed in Table I.

Pyrolysis of 3-Nitroso-5,5-diphenyl-2-oxazolidone (I) in Cumene. (A) **In Air.**—In a 250-ml. flask connected through a condenser to a cold trap were placed 4.08 g. of I and 52.0 g. of peroxide-free cumene. After 2 hr. at 153°, the mixture was cooled. Filtration yielded 2.69 g. (74.1%) of 5,5-diphenyl-2-oxazolidone (V) and 59 ml. of solution E.

A portion of E (44 ml.) was carefully fractionated to remove solvent to give oil F. A small forerun (0.68 g.) was found to contain methanol and acetone. The methanol was characterized as methyl 3,5-dinitrobenzoate (1.3%), m.p. 107.7–108.2° (reported[27] m.p. 108°). Oil F was chromatographed to yield four fractions: (1) cumene, (2) acetophenone, (3) V (0.129 g., 4.4%) and (4) 0.353 g. of tar.

When 5 ml. of solution E was treated with DNPH reagent, the resulting derivatives (0.169 g.) melted over a range, 227–249°. The solids were separated by chromatography on silicic acid using 10% ether in Skellysolve B as the developer. Two 2,4-dinitrophenylhydrazones were obtained, the acetophenone derivative (0.165 g., 42.7%), m.p. 249–250° (reported[28] m.p. 249–250°), and the acetone derivative (0.0033 g., 1.1%), m.p. 127.9–128.6° (reported[29] m.p. 128°). When a similar decomposition of nitroso compound I was run in the presence of 2,3-dimethyl-2,3-diphenylbutane (the cumene dimer), 91% of the dimer was recovered in addition to the other products of the decomposition.

(B) **In the Absence of Air.**—The experiment was repeated in a nitrogen atmosphere. Oxygen-free, water-free nitrogen was prepared from oil-pumped nitrogen using a Fieser type[30] absorption train modified by using cumene instead of xylene as the solvent for the metal ketyl. Nitrogen was pumped into the system for 4 hr. before the decomposition was begun. The products were isolated as described above: V (79%), acetophenone (30%), acetone (1%) and methanol (1%).

Pyrolysis of I in the Presence of α-Methylstyrene.—The polymerization of 50 ml. of freshly distilled α-methylstyrene was inhibited at 100° when 0.692 g. of I was added. The pyrolysis products were recovered as previously described: V, 84%; acetophenone, 42%; and 2.86 g. of polymer. The blank yielded 7.70 g. of polymer. The infrared spectra of the two polymers were identical.

Pyrolysis of I in the Presence of 1,1-Diphenylethylene.—The pyrolysis products obtained at 185° from 2.78 g. of I and 5.42 g. of 1,1-diphenylethylene were worked up as previously described. The products were 1.72 g. (87%) of V, 10.1% of benzophenone and unreacted 1,1-diphenylethylene. No diphenylacetylene was found.

Stability of 5,5-Diphenyl-2-oxazolidone (V) to Heat.—When 7.47 g. of V was heated in a salt-bath at 220–225° for 26 hr., 7.37 g. of V was recovered unchanged.

Gas Analyses of Decomposition Products from the Pyrolysis of I.[31]—A General Electrical analytical mass spectrometer was used for the analyses which employed the pressure sensitivity technique.[32] The sampling device was an all-glass system employing a 50-ml. decomposition bulb, a 50-ml. gas sample bulb adapted for direct attachment to the mass spectrometer. The decompositions were run under a low helium pressure (1 mm.) since helium is inert and has a mass number low enough not to interfere with the analysis. Carbon dioxide was the only carbon containing gas present since carbon monoxide was previously shown to be absent. The pressure sensitivities of pure gas samples and distilled water were run. It was found necessary to use an Ascarite[33] tube in order to separate carbon dioxide from nitrous oxide since the two gases had the same mass numbers (44). It was shown experimentally that this treatment had no effect on any of the gases except carbon dioxide and water, both of which were removed.

Decompositions of nitroso compound I were carried out at both 120 and 185°. Duplicate samples showed a 3% variation. The average results are found in Table III.

Pyrolysis of 3-Nitroso-5-methyl-5-phenyl-2-oxazolidone (II).—In a dried flask connected to a gas collecting device, 22.10 g. of III was decomposed at 185° in the manner previously described. The decomposition was vigorous but never violent. Gas evolution ceased after 40 minutes; the dry gas collected (2615 ml. S.T.P) represented 1.09 moles per mole of II. As in the case of the pyrolysis of I, no carbon monoxide was detected.

After cooling, the brown, mushy solid was mixed with four portions of Skellysolve F and filtered. The filtrate was concentrated to give 6.67 g. of oil G. Recrystallization of the 8.75 g. of solid from 15 ml. of toluene yielded 7.16 g. (37.7%) of 5-methyl-5-phenyl-2-oxazolidone (IX), m.p. 146–147° (reported[6b] m.p. 146.2–147.2°). The filtrate was chromatographed on alumina and developed with benzene to yield 0.11 g. (0.6%) of additional IX and 1.49 g. of tar.

When 0.46 g. of oil G was treated with DNPH reagent and the derivative worked up, 0.180 g. (8.1%) of the acetophenone derivative, m.p. 248–249°, was obtained. This filtrate was refluxed with 2 g. of mercuric sulfate and 5 ml. of sulfuric acid and then cooled. Workup as usual yielded two derivatives: 0.171 g. (7.4%) of propiophenone 2,4-dinitrophenylhydrazone, m.p. 190–191° (reported[34] m.p.

(19) (a) J. Doeuvre, *Bull. soc. chim.*, [5] **3**, 612 (1936); (b) E. Briner and D. Frank, *Helv. Chim. Acta*, **22**, 591 (1939).

(20) Reference 17, p. 50.

(21) Reference 17, p. 146.

(22) N. Kharasch and C. M. Buess, THIS JOURNAL, **71**, 2724 (1949).

(23) No adduct was formed with diphenylacetylene unless a catalytic amount of anhydrous aluminum chloride was present: *cf.* N. Kharasch and S. J. Assony, THIS JOURNAL, **75**, 1081 (1953).

(24) D. D. Tunnicliff, R. R. Brattain and L. R. Zumwalt, *Anal. Chem.*, **21**, 890 (1949).

(25) L. I. Smith and M. M. Falkof, *Org. Syntheses*, **22**, 50 (1942).

(26) C. F. H. Allen and S. Converse, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 226.

(27) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Thomas Y. Crowell Co., New York, N. Y., 1947, p. 370.

(28) Reference 17, p. 388.

(29) Reference 17, p. 374.

(30) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., p. 299.

(31) We wish to thank Mr. John W. Kraus who performed these analyses.

(32) *E.g.*, R. A. Friedel, A. G. Sharkey, Jr., J. L. Shultz and C. R. Humbert, *Anal. Chem.*, **25**, 1312 (1953).

(33) A form of soda lime, Arthur H. Thomas Co., Philadelphia, Pa.

(34) Reference 17, p. 390.

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190–191°), and 0.282 g. (7.5%) of 1-phenylpropane-1,2-dione 2,4-dinitrophenylosazone,[35] m.p. 263–264°.

Anal. Calcd. for $C_{21}H_{16}N_8O_8$: C, 49.6; H, 3.2; N, 22.0 Found: C, 49.4; H, 3.1; N, 21.9.

Propiophenone, when treated with mercuric sulfate and sulfuric acid in the presence of excess DNPH reagent, yielded 81% of the normal derivative and 12% of the osazone. After similar treatment, 1-phenyl-2-propanone yielded 89% of the osazone and none of the normal derivative, while 1-phenylpropyne yielded 74% of propiophenone 2,4-dinitrophenylhydrazone and 11% of the osazone.

When 1.54 g. of oil G was chromatographed on silicic acid and developed with Skellysolve B, four fractions were obtained: the first fraction, H (0.521 g.), was shown by infrared spectrum to be solely hydrocarbon. The second fraction was treated with DNPH reagent to yield 0.579 g. (7.8%) of the acetophenone derivative, m.p. 248–249°. The third fraction was 0.525 g. (12.8%) of additional IX. The fourth fraction was 0.211 g. of tar.

When 0.403 g. of H was ozonized[19a,b] and worked up as previously described, 0.606 g. (10.5%) of the acetophenone 2,4-dinitrophenylhydrazone, m.p. 248–249°, was obtained. When a portion of H was treated with DNPH reagent before ozonolysis, no carbonyl derivative was obtained.

Pyrolysis of 3-Nitroso-1-oxa-3-azaspiro[4.5]decan-2-one (III).—In a dried flask connected to a gas collecting device, 8.20 g. of III was decomposed at 185° in the manner previously described. The decomposition was moderate initially but became violent as the reaction proceeded. Gas evolution ceased after 40 minutes: the dry gas collected (963 ml., S.T.P.) represented 0.965 mole per mole of III. As in the case of the pyrolysis of I, no carbon monoxide was detected.

After cooling, the brown-black, tarry mass was made up to 10 ml. with chloroform to give solution J. When 5 ml. of J was treated with excess DNPH reagent, no derivative was obtained. When 5 ml. of J was chromatographed on a column packed with alumina and developed with 10% ether in Skellysolve B, two fractions were obtained. One fraction, a tar, remained on the column. The other fraction, concentrated and cooled, yielded 1.96 g. (56.8%) of 1-oxa-3-azaspiro[4.5]decan-2-one (X), m.p. 101–102° (reported[6a] m.p. 101.0–102.4°).

Pyrolyses of Nitroso Compounds I, II and III in the Presence of Solvents.—A typical reaction is described: a 25 × 200 mm. test-tube, which contained the nitroso compound (3.5–5.0 g.) and redistilled solvent (15–25 g.), was provided with an air condenser and maintained at 153 or 168° for 2 hr. or at 185° for 40 minutes.

Recovery of Decomposition Products. A. Nitroso Compound I.—After cooling, solid oxazolidone V was removed by filtration and the solvent carefully removed by distillation to yield an oil. Benzophenone was determined as the 2,4-dinitrophenylhydrazone and diphenylacetylene as desoxybenzoin 2,4-dinitrophenylhydrazone. When the solvent was adsorbed strongly enough on alumina so that the diphenylacetylene-1,1-diphenylethylene mixture could be selectively removed, multicomponent ultraviolet spectrophotometric analysis was used. The results are listed in Table II.

B. Nitroso Compounds II and III.—The recovery of the decomposition products was carried out as was previously described for II and III at 185°. In some cases in the decomposition of nitroso compound III, treatment of an aliquot of the reaction mixture with DNPH reagent yielded the cyclohexanone derivative, m.p. 161–162° (reported[36] m.p. 162°).

(35) 1-Phenylpropane-1,2-dione was prepared according to J. Wegmann and H. Dann, *Helv. Chim. Acta*, **29**, 1248 (1946).

(36) Reference 15, p. 262.

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

The Reaction of Substituted Indoles with Methyl Vinyl Ketone. New Synthesis of 2-Methylcarbazole

BY J. SZMUSZKOVICZ

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The reactions of indole, 2-methylindole and skatole with methyl vinyl ketone were investigated and the products characterized.

There are a number of examples in the literature which illustrate the behavior of the indole nucleus toward electrophilic components in the Michael-type reaction.

In the case of C_3-unsubstituted indoles, *under acidic conditions*, the negatively polarized C_3 undergoes reaction, *e.g.*, with acetamidoacrylic acid in acetic acid solution containing acetic anhydride,[1] with nitroethylene in benzene solution,[2] with propiolactone in the absence of solvent,[3] with diketene in the absence of solvent[4] and with acrylonitrile in acetic acid solution in the presence of copper borate.[5]

On the other hand, *the base-catalyzed* Michael-type reaction occurs at the 1-position. Thus, in a benzene solution containing potassium hydroxide, indole and acrylonitrile react to give 1-(β-cyano)-ethylindole,[6] 2-phenylindole reacts with acrylonitrile in the presence of trimethylbenzylammonium hydroxide to give 1-(β-cyano)-ethyl-2-phenylindole,[7] indole and methacrylonitrile in ethanolic sodium ethoxide solution gives rise to 1-(β-cyano-β-methyl)-ethylindole,[8] ethyl α-(3-indolyl)-isobutyrate afforded 1-(β-carboxypropyl)-3-indoleisobutyric acid on reaction with methacrylonitrile in ethanolic sodium methoxide and subsequent hydrolysis,[8] 2,3-dimethylindole reacts with acrylonitrile and sodium methoxide to give 1-(β-cyano)-ethyl-2,3-dimethylindole[9]; in some cases 1,3-dicyanoethylindoles are obtained as by-products

(1) H. R. Snyder and J. A. MacDonald, THIS JOURNAL, **77**, 1257 (1955).
(2) W. E. Noland and P. J. Hartmann, *ibid.*, **76**, 3227 (1954).
(3) J. Harley-Mason, *J. Chem. Soc.*, 2433 (1952).
(4) J. Harley-Mason, *Chemistry & Industry*, 886 (1951).
(5) W. Reppe and H. Ufer, German Patent 698,273 [*Frdl.*, **25**, 173 (1939)].
(6) A. P. Terentyev, A. N. Kost and V. A. Smit, *J. Gen. Chem. (USSR)* in English translation, **25**, 1905 (1955).
(7) R. C. Blume and H. G. Lindwall, *J. Org. Chem.*, **10**, 255 (1945).
(8) H. Erdtmann and Å. Jörnson, *Acta Chem. Scand.*, **8**, 119 (1954).
(9) C. F. Allen and T. G. Mann, *J. Chem. Soc.*, 1870 (1952).

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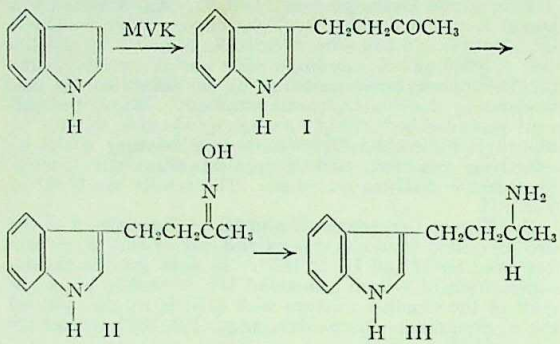
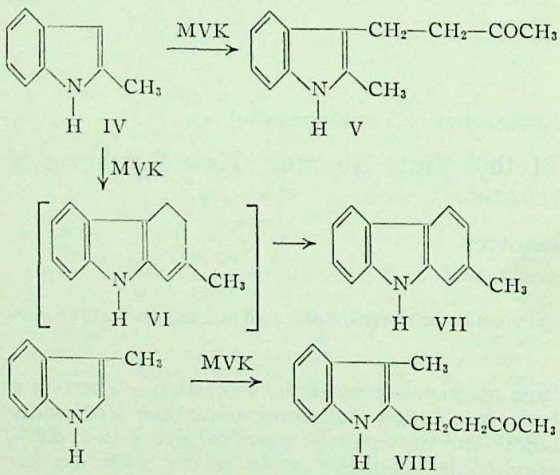
from the reaction of 2-substituted indoles with acrylonitrile.[10,11]

It has now been found that indole reacts with methyl vinyl ketone (MVK) in acetic acid medium with or without anhydride to give 75 and 69% yield, respectively, of 1-(3′-indolyl)-butanone-3 (I). The reaction also proceeds in the absence of solvent to give I in 22% yield.

Compound I was converted in a quantitative yield to a mixture of isomeric oximes (II) which was reduced with lithium aluminum hydride to 3-(3′-indolyl)-1-methylpropylamine (III), characterized as the creatinine sulfate complex.



Holland and Nayler[12] prepared I by treatment of gramine methosulfate with ethyl sodioacetoacetate in ethanol, the product subsequently being hydrolyzed with sodium hydroxide.



2-Methylindole (IV) reacted with MVK at 160° (5 hr. reaction time) in the absence of solvent to give a 28.6% yield of 1-[3′-(2′-methyl)-indolyl)]-butanone-3 (V). In acetic acid solution containing acetic anhydride the yield advanced to 84%. When hydroquinone was added to the two reactants and the temperature raised to 280°, 2-methylcarbazole (VII)[13] was isolated in 10% yield.[14] The reaction probably proceeded through an intermediate (VI) which was not isolated.

Skatole did not react with MVK in the absence of solvent even on prolonged heating (19 hr.). On the other hand, in acetic acid solution containing *acetic anhydride*[15,16] a moderate yield of 1-[2′-(3′-methyl)-indolyl]-butanone-3 (VIII) was obtained. When the reaction was conducted in acetic acid alone, the product VIII could not be isolated.

Experimental[17,18]

Preparation of 1-(3′-Indolyl)-butanone-3 (I).—Indole (2.34 g., 0.02 mole) was dissolved in glacial acetic acid (12 ml.), 4 ml. of acetic anhydride was added, then 4.2 g. (0.06 mole) of commercial methyl vinyl ketone. The solution was allowed to stand at room temperature for 5 minutes and then heated on the steam-bath (condenser, Drierite tube) for 25 minutes. The initial yellow solution turned dark brown. It was cooled in ice, 100 ml. of water was added and, after standing for a few minutes, the precipitate was filtered and washed with water. The crude product was recrystallized from benzene–petroleum ether (30–60°) as pale yellow needles, m.p. 93–94°, yield 2.8 g. (75%).

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.25; H, 7.13; N, 7.43.

Infrared spectrum: NH (3305 cm.$^{-1}$), C=O (1699), C=C (1621, 1572, 1555, 1492), *o*-disubstituted benzene (734, 725). **Ultraviolet spectrum:** λ_{max} 223 mμ (36,675), 275 (5,475), 283 (5,900), 291.5 (5,050).

When acetic anhydride was omitted[15] from the above procedure, the product I was obtained in 69.6% yield (m.p. 93–94°).

Preparation of the Oxime II.—One gram of I was dissolved in 10 ml. of 95% ethanol by warming. A solution of 2 g. of hydroxylamine hydrochloride and 3 g. of anhydrous sodium acetate in 10 ml. of water was added and the resulting solution refluxed for 15 minutes. It was then allowed to stand at room temperature for 45 hr., diluted with water and induced to crystallize by scratching. After cooling in ice for 1 hr., the crystals were filtered and washed with water; m.p. 89–115° (97% yield). Recrystallization from benzene–petroleum ether (30–60°) gave clusters, m.p. 89–111°.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.34; H, 7.14; N, 13.58.

Lithium Aluminum Hydride Reduction of the Oxime II. Synthesis of III.—A solution of II (0.9 g.) in 10 ml. of anhydrous ether was added dropwise with ice-cooling and swirling to a solution of 1.2 g. of lithium aluminum hydride in 70 ml. of ether. The resulting mixture was refluxed for 2 hr. and then allowed to stand overnight at room tempera-

(10) N. Roh and W. Wolff, German Patent 641,597 [*Frdl.*, **23**, 152 (1936)]; *C. A.*, **32**, 4602 (1938).

(11) The more drastic conditions used in these base-catalyzed Michael-type reactions suggest that thermodynamic control of products applies and that the 1-substituted product is the more thermodynamically stable isomer under the conditions of its formation. The milder acid conditions might favor kinetic control of products which result in 3-substitution. A test of this idea would involve submitting the adduct to the conditions under which the 1-adduct is prepared to see if 3-adduct yields 1-adduct [see also I. M. Bassett, R. D. Brown and A. Penfold in *Chemistry & Industry*, 892 (1956)].

(12) D. O. Holland and J. C. Nayler, J. Chem. Soc., 1461 (1955).

(13) For a review of carbazole syntheses see R. C. Elderfield, "Heterocyclic Compounds," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 296.

(14) This yield very likely could be improved on further experimentation.

(15) It is interesting that acetic anhydride seems to be essential for the reaction of skatole with MVK, especially in view of a similar observation of Snyder and MacDonald[1] in the case of indole and α-acetamidoacrylic acid.

(16) The crude product showed a weak band in the infrared at 1747 cm.$^{-1}$ and a strong band at 1662 cm.$^{-1}$. The 1747 cm.$^{-1}$ band could be eliminated by mild alkaline treatment (see Experimental). The 1662 cm.$^{-1}$ band persisted after this alkaline treatment and may be due to either the N-acetyl compound being present or, less likely, to the amidic character of the carbonyl imposed by interaction with the indolic nitrogen.

(17) All melting points are uncorrected. Ultraviolet spectra were determined in 95% ethanol using Cary spectrophotometers, models 11 and 14. Infrared spectra were determined in Nujol (except when otherwise specified) using a Perkin–Elmer recording infrared spectrophotometer, model 21.

(18) The author is indebted to Prof. D. J. Cram for an interesting discussion, to Dr. J. L. Johnson and his staff for spectral data, to Mr. W. A. Struck and his associates for microanalyses, and to Mr. L. G. [illegible] for faithful assistance.

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ture. Water was added, cautiously at first, then excess of 10% potassium hydroxide solution, and the mixture was extracted four times with ether. The ethereal extracts were washed once with water and then extracted three times with 10% hydrochloric acid. The acidic solution was reëxtracted with ether and then basified with excess potassium hydroxide. The resulting oily mixture was extracted three times with ether, washed twice with saturated salt solution, dried over sodium sulfate and evaporated to give 0.8 g. (95% yield) of pale yellow oil which could not be crystallized.

The amine (0.253 g.) was dissolved in 1.45 ml. of 1 *N* sulfuric acid and 4 cc. of water by gentle warming, the solution was filtered and 0.210 g. of creatinine sulfate was added. The solution was warmed to *ca.* 60° and 45 ml. of acetone was added. After 2 hr., the crystalline precipitate was filtered and washed with acetone–water (6:1); yield 0.436 g. (80%), m.p. 150–153°. The complex was recrystallized by dissolving in 4 ml. of warm water and adding 50 ml. of acetone. The needles were filtered, washed with cold acetone–water solution (4:1), then acetone and finally ether; m.p. 153–156° (completely clear at 160°).

Anal. Calcd. for $C_{16}H_{25}N_5O_5S + 1.5H_2O$: C, 45.06; H, 6.77; N, 16.42; S, 7.52. Found: C, 44.90; H, 6.73; N, 16.16; S, 8.26.

Synthesis of 2-Methylcarbazole (VII).—A mixture of 2-methylindole (6.6 g., 0.05 mole), MVK (4.2 g., 0.06 mole) and 0.3 g. of hydroquinone was heated for 1.5 hr. (outside bath temperature 155–160°). The temperature was then raised to 280–290° and maintained for 20.5 hr. The resulting reaction mixture crystallized within 1 hr. on standing at room temperature. On treatment with 20 ml. of benzene a slightly oily material was obtained which was recrystallized from the same volume of benzene to give 0.6 g. of plates melting at 261.5–262.5°.[19]

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.33; H, 6.20; N, 7.66.

Infrared spectrum: NH (3400), C=C (1627, 1608, 1486), *o*-disubstituted and trisubstituted benzene (806, 763, 744, 725). **Ultraviolet spectrum**: flex. 230 mμ, λ_{max} 235.5 (48,270), flex. 246, λ_{max} 259.5 (19,225), flex. 286, λ_{max} 297.5 (17,200), 323 (3,900), 335 (2,900).

The second crop amounted to 0.140 g. (m.p. 261–262°). The combined filtrates and washings were evaporated to dryness and the residual dark oil was distilled from an oil-jacketed flask at 0.1 mm. The first fraction, b.p. 120–160° (3.46 g.), was discarded. The second fraction, b.p. 180–270° (3.26 g.), solidified overnight and was crystallized from 5 ml. of benzene and 9 ml. of petroleum ether (30–60°) with seeding to give a third crop of VII (0.2 g., m.p. 252–255°). The fourth crop amounted to 14 mg. (m.p. 237–242°). The total yield of VII was 10.5% (0.954 g.). The picrate was formed in ethanol as orange-red needles, m.p. 168° (lit.[19] m.p. 168°).

Synthesis of 1-[3′-(2′-Methyl)-indolyl]-butanone-3 (V).—A mixture of 2-methylindole (13.1 g., 0.1 mole) and MVK (8.4 g., 0.12 mole) was heated under nitrogen at 155–162° for 5 hr. The resulting oil was allowed to stand overnight at room temperature. It was then distilled from an oil-jacketed flask at 0.05 mm. to give: (1) 5.97 g. of unchanged 2-methylindole, b.p. 120–160° (mainly 135–140°); (2) 10.82 g. of viscous yellow oil, b.p. 160–190°.

Fraction 2 was redistilled carefully at 0.05 mm. and material boiling at 180–190° was collected; 5.76 g. (28.6% yield), $n^{27.5}$D 1.5833. The analytical sample showed b.p. 185°, $n^{27.5}$D 1.5835.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.74; H, 7.59; N, 6.70.

Infrared spectrum: NH (3340), C=O (1698), C=C (1617, 1582, 1565, 1487), *o*-disubstituted benzene (740). Quantitative infrared comparison with I in the NH region indicated the presence of 92.9% of NH absorption.

The trinitrofluorenone derivative was formed in acetic acid–ethanol as black plates, m.p. 139–142°.

Anal. Calcd. for $C_{26}H_{40}N_4O_8$: C, 60.46; H, 3.90; N, 10.85. Found: C, 60.11; H, 3.98; N, 10.87.

When the reaction was run in acetic acid containing acetic anhydride (as described above) and the product extracted with ether, washed and distilled, an 84.6% yield of a yellow oil was obtained, b.p. 170–195° (0.05 mm.).

Infrared spectrum: NH (3400), C=O (1710), extraneous band at 1676 (probably due to N-acetyl impurity), C=C (1636, 1607, 1593, 1571, 1561, 1536, 1480), *o*-disubstituted benzene (746).

Synthesis of 1-[2′-(3-Methyl)-indolyl]-butanone-3 (VIII).—A solution of skatole (10 g., 0.0765 mole), MVK (16.2 g., 0.232 mole), 46 ml. of acetic acid and 15.5 ml. of acetic anhydride was heated on the steam-bath for 25 minutes. The resulting dark green solution was cooled to room temperature, 400 ml. of water was added and the heating continued on the steam-bath for 2 hr. The cooled mixture was extracted with ether (4 × 150 ml.). The ethereal extracts were washed once with water, twice with saturated salt solution and dried over sodium sulfate. The product (brown oil, 12.52 g.) was distilled from an oil-jacketed flask to give: (1) 4.12 g. of recovered skatole, b.p. 120–135° (0.1 mm.); and (2) 4.72 g. of an oil boiling at 170–210° (0.1 mm.). Redistillation of fraction 2 afforded 2.76 g. of material which was collected at 170–190° (0.05 mm.), n^{25}D 1.5835.

Infrared spectrum: NH (3380), weak band at 1747, C=O (1702), strong band at 1662, C=C (1600, 1537, 1477), *o*-disubstituted benzene (757).

The product (0.641 g.) was dissolved in 10 ml. of methanol, a solution of 1.0 g. of potassium hydroxide in 10 ml. of water was added and the solution heated on the steam-bath for 5 minutes. It was then cooled and extracted with ether (4 × 30 ml.). The ethereal extracts were washed twice with saturated salt solution, dried over sodium sulfate and evaporated. The resulting oil (0.4868 g.) was distilled from an oil-jacketed flask; b.p. 170–175° (0.05 mm.), 0.3296 g.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 76.81; H, 7.49; N, 5.98.

Infrared spectrum: essentially the same as above, but the band at 1747 no longer was present.

Apparently this product represents a mixture of the desired material VIII and the corresponding N-acetyl derivative. Quantitative infrared comparison with I in the NH region indicated 21.5% NH absorption.

KALAMAZOO, MICHIGAN

(19) G. R. Clemo and D. G. I. Felton, *J. Chem. Soc.*, 700 (1951); B. M. Barclay and N. Campbell, *ibid.*, 530 (1951); W. Borsche, A. Witte and W. Bothe, *Ann.*, **359**, 52 (1908).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

The Mechanisms of Permanganate Oxidation. IV. Hydroxylation of Olefins and Related Reactions

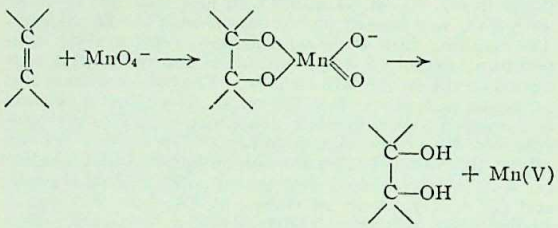
BY KENNETH B. WIBERG AND KLAUS A. SAEGEBARTH

RECEIVED OCTOBER 27, 1956

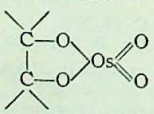
The oxygen introduced into oleic acid in its conversion to 9,10-dihydroxystearic acid by permanganate has been found to arise from the oxidizing agent. The reaction of bicyclo[2.2.1]-2-heptene with permanganate in neutral solution led to a new type of reaction, cleavage to a dialdehyde. The mechanisms for the formation of the diol, ketol and dialdehyde from a common intermediate are discussed.

Introduction

The hydroxylation of olefins by potassium permanganate has been known for many years and has proved a useful method for this conversion. Wagner, who did much of the early work on this reaction, proposed that it involved the formation of a cyclic ester between the permanganate ion and the olefin.[1] Decomposition of the intermediate with cleavage of the manganese–oxygen bonds would lead to the formation of the glycol.



This hypothesis received strong support from the careful stereochemical investigations of Böeseken and his co-workers[2] who determined that the reaction invariably gave the glycol formed by *cis*-addition of the hydroxyl groups. The formation of a cyclic ester intermediate has been well accepted, particularly since osmium tetroxide, which also gives *cis*-hydroxylation, has been shown by Criegee[3] to give an isolable intermediate which almost certainly has the structure



The most important evidence which now could be obtained would be a demonstration that the oxygens introduced into the olefin did arise from the permanganate. Since an excellent method for analyzing for O^{18} in organic molecules is now available,[4] we have studied the oxidation of an olefin with O^{18}-labeled permanganate. The olefin chosen was oleic acid since it gives an excellent yield of the diol and since the product is easily isolated.[5]

It was also of interest to study the effect of reaction conditions on the oxidation of other olefins, since whereas oleic acid gives quantitatively 9,10-dihydroxystearic acid in alkaline solution, the main product in a neutral solution is a mixture of 9,10- and 10,9-ketohydroxystearic acids.[6]

Results and Discussion

In studying the oxygen transfer from permanganate to oleic acid, it is desirable to effect the reaction under conditions which will minimize oxidation of the double bond by manganate, since it is known that manganate will exchange oxygens with water whereas permanganate will not,[7] and since the rate of oxidation by manganate is considerably lower than that for permanganate. Thus, if a large part of the oxidation were effected by manganate, the extent of oxygen transfer would be quite low Even with a large excess of permanganate, incomplete oxygen transfer would be expected since it is known that the rate of electron transfer between manganate and permanganate is very rapid,[8] permitting some exchange of O^{18} with the solvent to occur as the reaction proceeds.

The oxidation of oleic acid was effected at about *p*H 12 using the conditions of Lapworth and Mottram[5] (1.45 $KMnO_4$:1 oleic acid) and also using a larger excess of permanganate (2 $KMnO_4$:1 oleic acid). The large excess of permanganate is permissible since it is known that the oxidation of the diol under these conditions is very slow relative to the rate of oxidation[6] and since a nearly quantitative yield of diol was obtained in each case. The results are shown in Table I.

TABLE I

OXYGEN TRANSFER IN THE OXIDATION OF OLEIC ACID

Excess atom % O^{18} in $KMnO_4$[a]	[$KMnO_4$]/[oleic acid]	Excess atom % O^{18} in CO_2[a,b]	No. of oxygens from $KMnO_4$
0.910	1.45:1	0.117	1.03
.910	2.00:1	.176	1.55

[a] Excess over normal abundance, 0.204%. The precision of the results is ±0.002%. [b] Carbon dioxide from the oxygen analysis. In calculating the oxygen transfer, a dilution factor of four is used, two for the conversion of carbon monoxide to carbon dioxide and two for the oxygens in the carboxylate group of the acid.

It is clear from these results that over 1.5 atoms of oxygen are transferred from the oxidizing agent to the oleic acid in the course of the hydroxylation. A consideration of the effect of the permanganate–oleic acid ratio on the extent of oxygen transfer leads to the conclusion that the true extent of trans-

(1) G. Wagner, *J. Russ. Phys.-Chem. Soc.*, **27**, 219 (1895).

(2) J. Böeseken, *Rec. trav. chim.*, **40**, 553 (1921); J. Böeseken and M. C. de Graaff, *ibid.*, **41**, 199 (1922); J. Böeseken, *ibid.*, **47**, 683 (1928).

(3) R. Criegee, *Ann.*, **522**, 75 (1936); *Angew. Chem.*, **51**, 519 (1938); R. Criegee, B. Marchand and H. Wannowius, *Ann.*, **550**, 99 (1938).

(4) W. v. E. Doering and E. Dorfman, THIS JOURNAL, **75**, 5595 (1953).

(5) A. Lapworth and E. N. Mottram, *J. Chem. Soc.*, **127**, 1628 (1925).

(6) G. King, *ibid.*, 1788 (1936); J. E. Coleman, C. Ricciuti and D. Swern, THIS JOURNAL, **78**, 5342 (1956).

(7) M. C. R. Symons, *J. Chem. Soc.*, 3676 (1954).

(8) J. C. Sheppard and A. C. Wahl, THIS JOURNAL, **75**, 5133 (1953).

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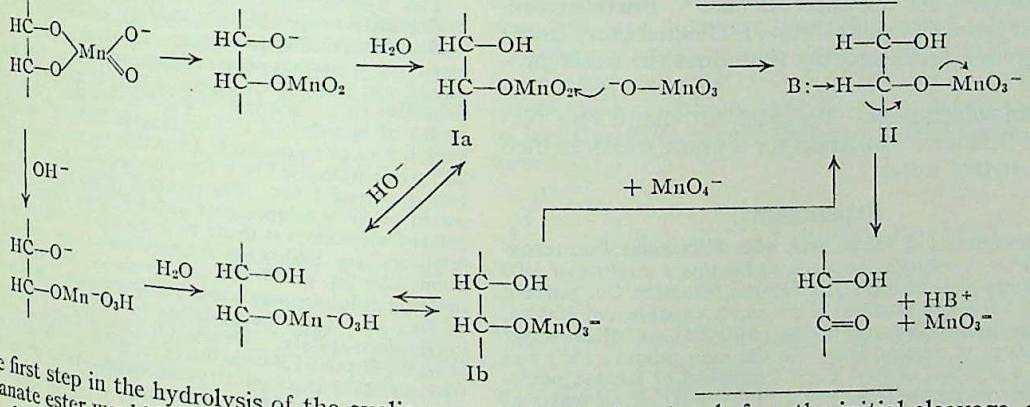
fer is close to 2. These results are then a confirmation of the proposal of Wagner and Böeseken.

As was mentioned previously, the high yield of diol from oleic acid is obtained only in basic solution, and a mixture of 9,10- and 10,9-ketohydroxystearic acids is obtained in neutral solution. That oleic acid is not an isolated case is shown by the observations of Lemieux and von Rudloff[9] that other olefins probably give ketols as intermediates in the permanganate–periodate oxidation at *p*H 7–8. It may also be noted that the hydroxylation of 2,3-dimethylbicyclo[2.2.2]-5-octene-2,3-dicarboxylic anhydride was best effected in 2 *N* sodium hydroxide (80% yield)[10] and that the hydroxylation of oleyl and elaidyl hydrogen phthalates were also best effected in basic solution.[11]

Since it is known that the ketol is not formed from the diol, it is reasonable to believe that the ketol and the diol are formed from a common intermediate which has two modes of reaction.[6] The formation of the ketol requires a four-electron oxidation. Since permanganate usually undergoes only a three electron change under the conditions used, two molecules of permanganate probably are involved in the formation of the ketol. Ketol formation is favored by low base concentration and relatively high permanganate concentration, and diol formation is favored by low permanganate and relatively high base concentration. Thus it appears that permanganate and hydroxyl ions compete for reaction with a common intermediate. A reasonable scheme for the reactions is

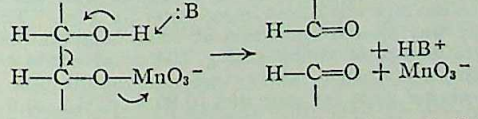


The first step in the hydrolysis of the cyclic permanganate ester would lead to the intermediates Ia or Ib depending on how the manganese–oxygen bond was broken. If both intermediates could be formed, one would expect that they could be interconverted, depending on reaction conditions. The intermediate (Ia or Ib) could be converted to the diol by reaction with hydroxyl ion and to the ketol by oxidation of the Mn(V) in the intermediate to Mn(VI) by permanganate, followed by cleavage of the remaining manganese–oxygen bond in such a way as to produce a carbonyl group. The oxidation would involve the transfer of either an electron or an oxygen ion-radical depending on which intermediate was involved.

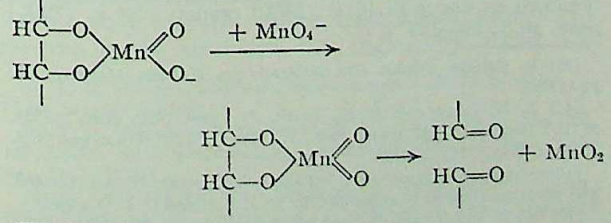
The conclusions reached above apply only to oxidations carried out in aqueous solution. In no case has the isolation of a ketol been reported when a mixture of an organic solvent and water was employed as the reaction medium, and in no case has base been added when these conditions were used. In fact, the recent procedures usually employ a neutral medium.

Straus and Rohrbacher[12] appear to have been the first to use a neutral solution for the hydroxylation reaction. They added magnesium sulfate to precipitate hydroxyl ions as magnesium hydroxide, presumably to avoid oxidation of the ethanol they used as the solvent, for the permanganate oxidation of ethanol is strongly base catalyzed. Subsequent workers have for the most part continued to use this procedure with either ethanol or acetone as the solvent. It is interesting to note that Straus and Rohrbacher reported the hydroxylation of 1,2-dihydronaphthalene to give, in addition to the diol, an unidentified non-crystalline neutral compound, which may have been a ketol.

In order to see whether a ketol might be obtained in a neutral permanganate oxidation, the reaction of bicyclo[2.2.1]-2-heptene was studied and was found to give a small amount of diol and cyclopentane-1,3-dicarboxaldehyde in 54–66% of the theoretical amount. There are two paths which might lead to this product. First, the intermediate II which led to the ketol could also give the dialdehyde by attack of base on a different position (reaction (A)). Second, further oxidation of the original cyclic permanganate ester, before the initial cleavage, might occur. This would lead to an intermediate similar



to that in the periodic acid oxidation of diols to carbonyl compounds.



(9) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

(10) K. Ziegler, G. Schenk, E. W. Krockow, A. Siebert, A. Wenz and H. Weber, *Ann.*, **551**, 1 (1942).

(11) G. Collin and T. P. Hilditch, *J. Chem. Soc.*, 246 (1932).

(12) K. Straus and A. Rohrbacher, *Ber.*, **54**, 69 (1921).

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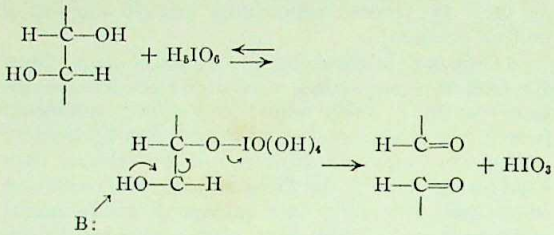
If the first of these possibilities were correct, one might expect that the first-formed intermediate in the periodate cleavage of diols (the periodate ester of one of the hydroxyl groups) should also be able to undergo this type of reaction, in which case the *trans*-glycol should react as fast or faster than the



cis-glycol. However, the opposite order of reactivity is found[13] and thus the cleavage cannot occur in this manner. The possible similarity between the permanganate and periodate reactions therefore leads us to favor the second path at this time. Further work on the effect of solvent and structure on this reaction is now in progress.

It was also of interest to determine whether alkaline permanganate would have any advantages over neutral permanganate for the hydroxylation reaction in mixed solvents. The oxidations of cyclopentene, cyclohexene and cycloheptene were effected in *t*-butyl alcohol–water solution at about *p*H 13 giving 55, 38 and 38% of the theoretical amounts of diol, respectively. The maximum yields reported for the oxidation in neutral solution are 34, 33 and 35% for the three olefins.[14] Furthermore, the oxidation in basic solution is effected more easily and gives a purer product than does the other procedure.

Acknowledgment.—We wish to thank the National Science Foundation for a grant which helped support this work.

Experimental[15]

Hydroxylation of Oleic Acid with Potassium Permanganate O^{18}.—A solution prepared by heating a mixture of 1.00 g. (3.5 mmoles) of oleic acid (Fisher Scientific Co. purified grade), 1.0 g. (25 mmoles) of sodium hydroxide and 100 ml. of water was cooled and diluted with 800 ml. of ice-water and 100 g. of crushed ice. To the cold mixture (5°) was added a solution of 0.80 g. (5.1 mmoles) of labeled potassium permanganate ($\%O^{18} = 1.114$)[16] in 80 ml. of water as rapidly as possible with vigorous stirring. After five minutes, the reaction mixture was decolorized with sulfur dioxide, 30 ml. of concentrated hydrochloric acid was added and the mixture was cooled in ice-water for 1 hr. The precipitate was filtered and dried at room temperature in a vacuum desiccator giving 1.05 g. (94%) of crude *erythro*-9,10-dihydroxystearic acid. One recrystallization from 95% ethanol gave the pure diol (0.90 g. 81%), m.p. 130–131°.[17]

The reaction was repeated using 1.10 g. (7 mmoles) of labeled potassium permanganate in 110 ml. of water. The solution was decolorized after one minute, and the diol was obtained as above (1.10 g. (98%) crude; 0.88 g. (79%) pure, m.p. 130–131°).

Oxygen-18 Analysis.—The apparatus and procedure was essentially that described by Doering and Dorfman,[4] except that the bubbler containing 2–3% bromine in 1:1 chloroform–carbon tetrachloride was not used. The high temperature furnace (1120°) consisted of a heating coil enclosed in a cylindrical sheet nickel housing which was constructed in two halves which were hinged together. The coil was approximately 15 mm. i.d. and 280 mm. long (73 turns spaced 2 mm. apart) of 12 gage Kanthal A-1 wire, having a resistance of 1.5 ohms. The electrical connections were made using pure nickel machine screws and nuts. The heating current was supplied from an 18 amp. Powerstat followed by a 2:1 stepdown transformer. At 1120°, the coil draws approximately 27 amp. at 50 volts.

The analyses were conducted in quadruplicate, and in each case the third and fourth analyses agreed to ±0.002%.

Oxidation of Bicyclo[2.2.1]-2-heptene with Potassium Permanganate. A. Dilute Basic Permanganate.—A solution of 23.4 g. (0.148 mole) of potassium permanganate and 5 g. (0.125 mole) of sodium hydroxide in 800 ml. of water, cooled to 0°, was added quickly with vigorous stirring to a cold mixture (−10°) of 1 l. of *t*-butyl alcohol, 200 ml. of water and 500 g. of cracked ice containing 9.42 g. (0.1 mole) of bicyclo[2.2.1]-2-heptene.[18] After 3–5 min., most of the permanganate color had been discharged, and sulfur dioxide was added to ensure complete reduction of the permanganate. The precipitate of manganese dioxide was filtered through a layer of Filter-Aid, most of the *t*-butyl alcohol was removed by distillation at atmospheric pressure, and the resultant solution was concentrated to about 250 ml. under reduced pressure with steam-bath heating. The solution was continuously extracted with ether for 48 hr., and the ether solution was dried over anhydrous sodium sulfate. Evaporation of the solvent gave 5.77 g. (45%) of a white crystalline solid which was purified by sublimation at 105–110° at 18 mm. giving 5.38 g. (40%) of *exo-cis*-bicyclo[2.2.1]heptane-2,3-diol, m.p. 139.5–140.5°.[19] The infrared spectrum (carbon tetrachloride solution) of the crude reaction product and of the purified material were identical and showed no absorption in the 6 μ region.

The hydroxylations of cyclopentene, cyclohexene and cycloheptene were effected using this procedure.

B. Neutral Permanganate.—A solution of 12.6 g. (0.08 mole) of potassium permanganate and 9.6 g. (0.08 mole) of anhydrous magnesium sulfate in 300 ml. of water was added dropwise to a vigorously stirred suspension of 9.42 g. (0.1 mole) of bicyclo[2.2.1]-2-heptene in 200 ml. of acetone at such a rate as to maintain a reaction temperature of −15 to 20° while immersed in a Dry Ice–acetone-bath. The addition required 1 hr. The reaction mixture was allowed to warm to room temperature and was then filtered. The resultant solution was made basic by the addition of 5 ml. of 40% sodium hydroxide solution and then evaporated to about 250 ml. at 60–70° under reduced pressure. The remaining solution was continuously extracted with ether for 48 hr., and the ether solution was dried over anhydrous magnesium sulfate. Distillation gave 4.1–5.0 g. (54–66%) of cyclopentane-1,3-dicarboxaldehyde, b.p. 80–87° at 2 mm. Redistillation through a 15-inch twisted wire gauze column gave the pure dialdehyde, b.p. 74–75° at 1.5 mm., $n^{25}D$ 1.4759, with good recovery.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0. Found: C, 66.2; H, 8.3.

The phenylhydrazone (m.p. 121–122°), dinitrophenylhydrazone (m.p. 225.5–226°) and the semicarbazone (m.p. 203–203.5°) were prepared.

Anal. Calcd. for $C_{19}H_{18}N_8O_8$ (2,4-dinitrophenylhydrazone): C, 46.9; H, 3.7. Found: C, 46.7; H, 3.8. Calcd. for $C_9H_{16}N_6O_2$ (semicarbazone): C, 45.0; H, 6.7. Found: C, 45.1; H, 6.8.

The above 2,4-dinitrophenylhydrazone did not on admixture depress the m.p. of the dinitrophenylhydrazone of cyclopentane-1,3-dicarboxaldehyde prepared by the lead tetraacetate cleavage of *exo-cis*-bicyclo[2.2.1]heptane-2,3-diol.

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(13) R. Criegee, *Sitzber. Ges. Beförder. ges. Naturw. Marburg*, **69**, 25 (1934).

(14) L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4026 (1952); M. F. Clarke and L. N. Owen, *ibid.*, 315 (1949); L. N. Owen and G. S. Saharia, *ibid.*, 2582 (1953).

(15) Melting points are corrected and boiling points are uncorrected. The microanalyses were performed by B. J. Nist and C. L. Ludwig.

(16) K. B. Wiberg and R. Stewart, THIS JOURNAL, **77**, 1786 (1955).

(17) Reference 5 reported m.p. 130.5–131.5°.

(18) Obtained through the courtesy of the Universal Oil Products Co.

(19) H. Kwart and W. G. Vosburgh, THIS JOURNAL, **76**, 5400 (1954), reported m.p. 140.5–140.6°.

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June 5, 1957

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ROHM & HAAS CO.]

The Preparation of 2-Methyloxazolidines and 2-Methyltetrahydro-1,3-oxazines from Acetylene and Aminoalcohols

BY WARREN H. WATANABE AND LAWRENCE E. CONLON

RECEIVED NOVEMBER 2, 1956

In the absence of any added catalyst acetylene reacts with aminoalcohols, $RNH(CR_2)_nOH$, where R is H or an alkyl group and n is 2 or 3, at pressures of 400–500 p.s.i. and temperatures of 100 to 200°, to form 2-methyloxazolidines (I, $n = 2$) and 2-methyltetrahydro-1,3-oxazines (I, $n = 3$). No vinyl ether is formed in this reaction. Owing to the instability of these products at reaction temperatures, the reactions are best carried out to 10–30% conversions. Yields based on unrecovered aminoalcohol then range from 30 to 75%. The theoretical implications of this new reaction are discussed and a possible mechanism proposed.

When acetylene is treated with an alcohol in the presence of a strong base, there is formed in good yield a vinyl ether. As one example, aminoalcohols are thus readily converted to aminoalkyl vinyl ethers.[1] Reppe has reported, moreover, that when N-phenylethanolamine is treated with acetylene, with zinc and cadmium acetates as catalyst, the isolated product is N-phenyloxazolidine[2] (whether exclusively or in mixture with the vinyl ether is not stated)

$$C_6H_5NHCH_2CH_2OH + HC{\equiv}CH \xrightarrow{Zn(OAc)_2\text{-}Cd(OAc)_2} \text{2-phenyloxazolidine} \quad (1)$$

We now have found that even in the absence of any added catalyst, aminoalcohols containing primary or secondary amino groups beta or gamma to the hydroxyl group are converted by acetylene exclusively to 2-methyloxazolidines and 2-methyltetrahydro-1,3-oxazines

$$R'NH(CR_2)_nOH + HC{\equiv}CH \longrightarrow \text{2-methyl-3-R'-tetrahydro-1,3-oxazine} \quad (2)$$

I, $n = 2,3$

Under these new conditions, aminoalcohols in which R′ is H, alkyl or substituted alkyl, but not aryl (N-phenyl ethanolamine does not undergo this reaction), are transformed to compounds I in yields ranging from about 5 to 75%, with conversions on the order of 13–30%.

A short study of reaction variables showed that yields were determined by a balance of reaction conditions, the major factors being the opposing ones of stability of the products and the reactivity of the aminoalcohols in the acetylene–aminoalcohol reaction. Calculations of very crude rate "constants" from weight gain and time of reaction data, assuming a first-order consumption of aminoalcohol, showed that the highest rate was obtained with N-methylethanolamine. Less rapid were the reactions of ethanolamine and 3-aminopropanol-1, both aminoalcohols with primary amino groups but with no substituents on the carbon chain, and least reactive were the aminoalcohols containing primary amino groups and alkyl substituents alpha or beta to the amino group.

Identification and Stability of Products.—Boiling points, physical constants, analyses and chemical reactions were not sufficient to provide clear-cut characterizations of the products. It was particularly desirable to show that these were actually the cyclic compounds and not the isomeric vinyl ethers. Fortunately there is in the infrared spectra of vinyl ethers a multiplicity of quite characteristic bands (1637, 1615, 960 and 810 $cm.^{-1}$)[3] which makes it possible to determine with certainty the presence or absence of vinyl ether. In none of the compounds prepared was any vinyl ether detected. Positive identification of the ring structure was, however, less satisfactory, although a pattern of peaks at longer wave lengths is claimed to be associated with O–C–N of the ring.[4] In those compounds (I) which have R′ = H, a further aid to identification is provided in the ring-chain tautomerism

$$\text{2-methyl-tetrahydro-1,3-oxazine} \rightleftharpoons HO(CR_2)_nN{=}CHCH_3 \quad (3)$$

$n = 2,3$

The Schiff base form could be characterized by —C=N— absorption at 1650–1680 $cm.^{-1}$ and, after dilution with a non-polar solvent, non-bonded –OH at 3570 $cm.^{-1}$.[5] All compounds prepared in this work capable of existing in the Schiff base form, except one, showed —C=N— absorption, indicating that at least some Schiff base was present. The exception was 2,4,4-trimethyloxazolidine, which had no absorption at all in the double bond region, thus unambiguously eliminating the vinyl ether form as well as the Schiff base.

The products, immediately after purification by fractional distillation, gave molecular refraction values only slightly lower than those calculated for the cyclic structure but higher by about 1.8

(1) (a) W. Reppe, U. S. Patent 1,959,927 (May 22, 1934); (b) W. Reppe and O. Hecht, U. S. Patent 2,157,347 (May 9, 1939); (c) M. F. Shostakovskii, I. A. Chekulaeva and N. A. Gershtein, *Izvest. Akad. Nauk. S.S.S.R., Otdel Khim. Nauk*, 328 (1951); *C. A.*, **46**, 897i (1952).

(2) Quoted in J. W. Copenhaver and M. H. Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold Publishing Corp., New York, N. Y., 1949, p. 36.

(3) J. D. Stroupe, personal communication; G. D. Meakins, *J. Chem. Soc.*, 4170 (1953).

(4) E. D. Bergmann, E. Zimkin and S. Pinchas, *Rec. trav. chim.*, **71**, 168 (1952); E. D. Bergmann, E. Gil-Av and S. Pinchas, THIS JOURNAL, **75**, 358 (1953).

(5) L. Kahovec, *Acta Phys. Austriaca*, **1**, 307 (1948); *C. A.* **42**, 6665c (1948); L. W. Daasch and U. E. Hanninen, THIS JOURNAL, **73**, 1873 (1950); L. W. Daasch, *ibid.*, **73**, 4523 (1951).

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units than values calculated for the Schiff base form. In the case of 2,4,4,-trimethyloxazolidine, which is, from infrared measurements, entirely in the cyclic form, the difference [M_D (theor. cyclic) $-M_D$ (exptl.)] was 0.27. This difference for three of the other four products ranged from 0.21 to 0.31. Thus if there is any validity to the claim that the proportion of the two forms in equilibrium 3 can be determined from the M_D value of the mixture, it must be concluded that these three products initially contained very little, if any, Schiff base. On subsequent warming of these compounds to room temperature there were rapid but measurable increases in both refractive index and density, which may have reflected the approach to an equilibrium state. Infrared curves were taken at least a day after the compounds were prepared, and it is thus not surprising that absorption bands for the Schiff base forms were found in these measurements.

There was also observed a non-reversible condensation of all our products to higher-boiling materials upon standing at room temperature, or upon short heating at higher temperatures. For those compounds (I) with R′ = H, Nace and Goldberg[6] have suggested that this conversion is most probably an aldol condensation proceeding through the Schiff base form

$$2CH_3CH{=}NR \longrightarrow CH_3CHCH_2CH{=}NR \longrightarrow \underset{\text{NHR}}{|}$$

$$CH_3CH{=}CHCH{=}NR + RNH_2 \quad (4)$$

$$R = (CR_2)_nOH,\ n = 2 \text{ or } 3$$

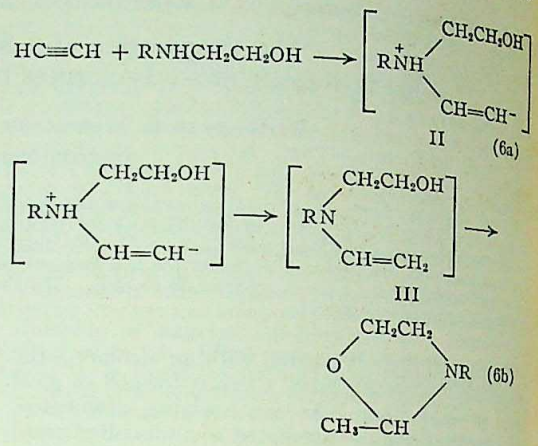
This condensation also contributes to changes in refractive index, density and infrared spectrum, measurements of which therefore must be used with caution if it is intended to draw conclusions as to proportions of oxazolidine and Schiff base. Since 2,3-dimethyloxazolidine cannot exist in Schiff base form, its mode of conversion to higher-boiling compounds is considerably more obscure.

Possible Mechanism.—It is probable that the present reaction is a special instance of vinylation, in which the reaction of acetylene is on the amine nitrogen rather than on the oxygen. It would then be analogous to the reaction of tertiary amines in aqueous solution with acetylene to form vinyl trialkylammonium hydroxide.[7] The general mechanism for such nucleophilic reactions on acetylene has been written as[8]

$$HC{\equiv}CH + N{:}^- \longrightarrow [HC{=}CHN]^- \text{ rate determining} \quad (5a)$$

$$[HC{=}CHN]^- + HN \longrightarrow CH_2{=}CHN + N{:}^- \text{ fast} \quad (5b)$$

where N:$^-$ is a nucleophilic species. The present reaction could then proceed in the steps



The intermediate II may go directly to product or proceed through a transitory N-vinylamine III, which then cyclizes. We have no positive proof of the existence of III, and since there are a number of other likely paths through which II may cyclize, we wish only to emphasize the probability of (6a) as the first step in the mechanism of reaction 2. Evidence supporting (6a) is our observation that acid reduces the rate of reaction 2.[9]

The possibility that (2) proceeds by O-vinylation to a vinyl ether, followed by cyclization, is excluded since O-vinylation requires a strongly basic catalyst. Moreover, it was not found possible to cyclize a representative aminoalkyl vinyl ether, obtained by base-catalyzed O-vinylation, to an oxazolidine under conditions in which reaction 2 occurs readily. A further possibility is that water acts as a catalyst, generating OH$^-$ by hydrolysis of the amine, which reacts with acetylene to form acetaldehyde. The acetaldehyde would then form the oxazolidine from the aminoalcohol, regenerating water. However, deliberately added water neither increased the rate of reaction nor improved the conversion to product; the reverse was rather the case.

Since reaction 1 is catalyzed by metal salts, it might be conceived that the apparently uncatalyzed reaction 2 was actually catalyzed by trace amounts of metal salts dissolved from the metal reactor. We do not believe this to be the case since sulfur, a mercaptan and a sequestering agent, all effective poisons for metal-catalyzed reactions, do not inhibit reaction 2. If, however, reaction 2 is indeed catalyzed by metal salts, then it no longer becomes possible to eliminate a two-step mechanism in which a vinyl ether is first formed, then cyclized. This is so since each step is independently known. Zinc and cadmium salts are stated to be catalysts for the vinylation of alcohols,[10] and we have shown that these same salts will catalyze

(6) H. R. Nace and E. P. Goldberg, THIS JOURNAL, **75**, 3646 (1953); the adlol condensation of an aldimine has been demonstrated by W. S. Emerson, S. H. Hess and F. G. Uhle, *ibid.*, **63**, 872 (1941).

(7) (a) W. Reppe, German Patent Appln. I-37, 024 (IVe/12o); B.I.O.S. Final Report No. 359, Item No. 22; (b) C. Gardner, V. Kerrigan, J. D. Rose and B. C. L. Weedon, *J. Chem. Soc.*, 789 (1949).

(8) R. Rigamonti and L. Bernardi, *Chimica e industria*, **34**, 561 (1952); S. I. Miller and G. Shkapenko, THIS JOURNAL, **77**, 5038 (1955).

(9) *Cf.* W. H. Watanabe and L. R. DeFonso, *ibid.*, **78**, 4542 (1956), in which it is shown that acid sharply reduces the rate of an aminolysis reaction. The aminolysis is therefore proposed to proceed largely through the amine anion, RNH$^-$. Since aminolysis and reaction 6a are both nucleophilic reactions of amines, it could be considered that the retarding action of acid on (6a) argues for HOCH$_2$CH$_2$NR as the actual reacting species.

(10) W. Reppe and O. Hecht, U. S. Patent 2,157,348 (May 9, 1939); C. E. Thalner, British Patent 656,556 (August 29, 1951).

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the cyclization of aminoalkyl vinyl ethers to 2-methyloxazolidines.[11]

Acknowledgments.—We thank Mr. O. H. Loeffler for his constant advice and encouragement during the course of this work and acknowledge with pleasure many stimulating discussions held with Dr. H. J. Schneider. Mr. Benjamin C. Wilbur provided technical assistance in a portion of this work.

Experimental

Materials, Apparatus and General Procedure.—The aminoalcohols were all commercially available compounds and were redistilled before use. As reactors there were used a 250-ml. magnetically-stirred stainless steel autoclave, heated with high-pressure steam, and a 300-ml. stainless steel rocking bomb, heated with a liquid heat transfer agent. The general procedure for all runs was as follows: The aminoalcohol was charged to the reactor, the reactor then sealed and pressure-tested, swept twice with nitrogen and twice with acetylene and finally cut off under about 50 p.s.i. acetylene. Heat was then applied to bring the reactor up to reaction temperature and the temperature maintained by suitable controls. Temperatures were in the range 100–180°. Acetylene was then pressed in to 400–600 p.s.i. and this pressure maintained by replenishing the acetylene as required. At the end of the reaction period the reactor was cooled, vented and drained. The raw product was in most instances directly fractionated under nitrogen to obtain the pure material. The product fractions were collected in receivers cooled with ice-water and every attempt was made to measure the density and refractive index of these materials within 5 min. of the time when the product was removed from the distilling column. It should nevertheless again be emphasized that some of the products, notably those with R′ = H in I, increased rapidly in these constants as the compounds aged, and our values may therefore not be entirely reliable. The neutralization equivalents of the products, as reported below, were obtained from potentiometric titration of the compounds in water with standard hydrochloric acid. Yield and conversion data for the reactions studied are given in Table I.

Preparation of 2-Methyloxazolidine.—About 175 g. of ethanolamine was dissolved in 60 g. of benzene and the solution distilled to remove any benzene–water azeotrope. Most of the benzene was then boiled off and the residue (169.0 g.) was charged to the magnetically-stirred autoclave. Since 10 g. of benzene was recovered later from the products, the charge therefore consisted of 159 g. (2.60 moles) of ethanolamine. Reaction with acetylene was then carried out according to the above general procedure at 145–150° for 2.5 hr. The material drained from the reactor weighed 180 g., the gain in weight of 11 g. corresponding to an acetylene uptake of 0.42 mole. Fractionation of this reaction mixture gave 26.0 g. of crude 2-methyloxazolidine, b.p. 50–56° (60 mm.), and 107.0 g. of recovered ethanolamine, b.p. 100° (90 mm.) –92° (40 mm.). The crude oxazolidine was therefore obtained in 12% conversion and 36% yield, based on unrecovered aminoalcohol. This material was sealed in an ampoule under nitrogen and immediately stored in the refrigerator. After storage for 13 days, it was found to have yellowed and become quite viscous. It was, however, combined with the crude product from another preparation of 2-methyloxazolidine and refractionated. Since the residue from this distillation amounted to 17.2 g. (largely column hold-up), it was clear that a large proportion of the 26 g. of apparently polymerized 2-methyloxazolidine had been regenerated in the distillation. The pure compound had b.p. 51–52° (60 mm.), $n^{25}D$ 1.4338, d^{25}_4 0.9651, M_D 23.50 (theor. 23.71), neut. equiv. 90.13 (theor. 87.12). These constants do not agree with those reported by Knorr and Matthes[12] and Doughty, *et al.*[13]

Anal.[14] Calcd. for C_4H_9ON: C, 55.14; H, 10.41; N, 16.08. Found: C, 55.29; H, 10.38; N, 15.92.

(11) This work will be described in a later communication.
(12) L. Knorr and H. Matthes, *Ber.*, **34**, 3484 (1901).
(13) J. B. Doughty, C. L. Lazzell and A. R. Collett, THIS JOURNAL, **72**, 2868 (1950).
(14) All microanalyses by Mr. C. W. Nash and associates.

TABLE I

THE EFFECT OF TEMPERATURE AND REACTION TIME ON YIELDS

Temp., °C.	Reacn. time, hr.	Conversion[a] %	Yield,[b] %
N-Methylethanolamine to 2,3-dimethyloxazolidine			
112	0.6	25	54
149	1.5	42	..
144	2.5	35	57
1-Aminopropanol-2 to 2,5-dimethyloxazolidine			
151	2.6	14	50
147	5.1	13	39
150	6.3	10	35
Ethanolamine to 2-methyloxazolidine			
111	5.0	8	..
147	2.5	12	36
151	4.2	18	..
180	3.2	3	5
2-Amino-2-methylpropanol-1 to 2,4,4-trimethyloxazolidine			
148	1.8	4	..
145	2.6	6	30
150	5.7	10	72
175	10.5	31	73
2-Aminobutanol-1 to 2-methyl-4-ethyloxazolidine			
180	2.3	23	56
3-Aminopropanol-1 to 2-methyltetrahydro-1,3-oxazine			
152	3.9	12	31

[a] Per cent. (by mole) of total aminoalcohol converted to pure product. [b] Per cent. (by mole) of unrecovered aminoalcohol converted to pure product.

Preparation of 2,5-Dimethyloxazolidine.—A charge of 141.0 g. (1.88 moles) of 1-aminopropanol-1 was treated with acetylene in the magnetically-stirred autoclave for 2.6 hr. at 136–152°. Fractionation of the reaction mixture gave 27.5 g. of 2,5-dimethyloxazolidine (14% conversion, 50% yield) b.p. 68–69° (120 mm.), $n^{25}D$ 1.4304, d^{25}_4 0.9246, M_D 28.28 (theor. 28.33), neut. equiv. 101.3 (theor. 101.15), and 100 g. of recovered 1-aminopropanol-2, b.p. 97–100° (80 mm.).

Anal. Calcd. for $C_5H_{11}ON$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.63; H, 10.99; N, 13.90.

Preparation of 2-Methyl-4-ethyloxazolidine.—2-Aminobutanol-1 (139.0 g., 1.56 moles) was treated in a similar fashion with acetylene. Fractional distillation of the product gave 41.5 g. of 2-methyl-4-ethyloxazolidine, b.p. 83° (105 mm.) to 81° (86 mm.) (mainly at 81.5° (86 mm.)), and 82.0 g. of recovered 2-aminobutanol-1, b.p. 113–115° (76–72 mm.) (23% conversion, 56% yield). Redistillation of this product gave pure 2-methyl-4-ethyloxazolidine, b.p. 84° (100 mm.), $n^{25}D$ 1.4302, d^{25}_4 0.9119, M_D 32.64 (theor. 32.95), neut. equiv. 115.7 (theor. 115.17).

Anal. Calcd. for $C_6H_{13}ON$: C, 62.57; N, 12.16; H, 11.38. Found: C, 62.80; N, 11.94; H, 11.22.

Preparation of 2,4,4-Trimethyloxazolidine.—2-Amino-2-methylpropanol-1 was dried by azeotropic distillation with benzene, and 122 g. of a mixture consisting of 114 g. (1.28 moles) of the aminoalcohol and 8 g. of benzene was allowed to react at 175° for 10.5 hr. The reaction mixture was fractionated into 46.0 g. of crude 2,4,4-trimethyloxazolidine, b.p. 62–75° (120 mm.), and 66.0 g. of recovered 2-amino-2-methylpropanol-1, b.p. 102° (120 mm.) to 97° (55 mm.) (31% conversion, 73% yield). This product was redistilled to give the pure oxazolidine, b.p. 72° (125 mm.), $n^{25}D$ 1.4215, d^{25}_4 0.8946, M_D 32.68 (theor. 32.95), neut. equiv., 118.6 (theor. 115.2).

Anal. Calcd. for $C_6H_{13}ON$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.59; H, 11.20; N, 11.91.

Another reaction carried out at 150° for 5.7 hr. gave a 10% conversion and 72% yield. When 3% by weight of water was added to the aminoalcohol before reaction, the conversion dropped to 4% and the yield to 22%.

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Preparation of 2,3-Dimethyloxazolidine.—A solution of 93 g. (1.24 moles) of N-methylethanolamine in 50 g. of benzene was distilled to remove the benzene–water azeotrope, most of the excess benzene distilled off and the residue (101.5 g.) charged to a 250-ml. magnetically-stirred autoclave. Reaction with acetylene was carried out at an average temperature of 144° for 2.5 hr. Fractional distillation of the reaction product yielded 43.5 g. of 2,3-dimethyloxazolidine, b.p. 50–58° (120 mm.), and 36.0 g. of recovered N-methylethanolamine, b.p. 100–102° (100 mm.) (35% conversion, 57% yield). The pure oxazolidine was obtained by redistillation, b.p. 54.5–55° (120 mm.), 109–110° (760 mm.) (lit.[12] 109° (758 mm.)), $n^{25}D$ 1.4200, d^{25}_4 0.8991, M_D 28.47 (theor. 28.67), neut. equiv. 100.9 (theor. 101.2).

Anal. Calcd. for $C_5H_{11}ON$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.46; H, 10.73; N, 13.48.

Preparation of 2-Methyltetrahydro-1,3-oxazine.—3-Aminopropanol-1 (161 g., 2.14 moles) was treated with acetylene at an average temperature of 152° for 3.9 hr. to give a product which, after fractionation, yielded 27.0 g. of 2-methyltetrahydro-1,3-oxazine, b.p. 68–70° (100 mm.), $n^{25}D$ 1.4382, d^{25}_4 0.9480, M_D 28.02 (theor. 28.33), neut. eqiv. 101.3 (theor. 101.2).

Anal. Calcd. for $C_5H_{11}ON$: N, 13.85. Found: N, 13.60.

Recovered 3-aminopropanol-1, b.p. 95° (25 mm.), amounted to 97.0 g. The conversion to product was therefore 12% and the yield 31%.

Preparation of 2-Methyltetrahydro-1,3-oxazine from Acetaldehyde.—A mixture of 75 g. (1.0 mole) of 3-aminopropanol-1 and 30 g. of anhydrous sodium carbonate in 200 ml. of anhydrous ether was placed in a three-neck flask equipped with a stirrer, reflux condenser and dropping funnel. The flask was cooled to 0° and 52 g. (1.2 moles) of acetaldehyde added slowly to the cooled (0–5°) and stirred mixture. After addition was complete, the reaction mixture was allowed to warm to room temperature during an additional 2 hr. of stirring. It was then filtered, most of the low-boiling material distilled from the filtrate under mild water-aspirator vacuum and the residue fractionally distilled. Product cuts were obtained as follows: 3.5 g., b.p. 63–65° (100 mm.), $n^{25}D$ 1.4390; 9.5 g., b.p. 65–68° (100 mm.), $n^{25}D$ 1.4389; 55.0 g., b.p. 68–70° (100 mm.), $n^{25}D$ 1.4389. The yield was therefore 67%. This product was identical in its physical constants with the product from the acetylene–aminoalcohol reaction.

Attempted Cyclization of N-Methylaminoethyl Vinyl Ether under Vinylation Conditions.—When N-methylethanolamine is treated, using strong base catalysis, with acetylene under 400–500 p.s.i. at 140–150° until reaction ceases, there is obtained a mixture containing approximately 25% 2,3-dimethyloxazolidine, b.p. 55–56° (120 mm.), and 50% N-methylaminoethyl vinyl ether, b.p. 65–67° (120 mm.). In order to test whether, under these conditions, the vinyl ether is first formed, then cyclizes to the oxazolidine, the following experiment was performed. A solution of 4.6 g. (0.2 mole) of sodium in 100 g. (1.33 moles) of N-methylethanolamine was mixed with 50 g. (0.49 mole) of N-methylaminoethyl vinyl ether and the resulting solution charged to a 300-ml. stainless steel rocking microbomb. The bomb was pressured to 195 p.s.i. with nitrogen at 23°, heated to 154°, with a resultant increase in pressure to 345–355 p.s.i., and kept at that temperature for 2.5 hr. The mixture was then fractionally distilled. There resulted a 92% recovery of the vinyl ether; no material identifiable as 2,3-dimethyloxazolidine was isolated.

Preparation of 2,3-Dimethyloxazolidine in the Presence of Metal Catalyst Poisons and Acid.—A mixture of 0.5 g. of powdered sulfur and 77.0 g. (1.0 mole) of N-methylethanolamine was treated with acetylene at an average temperature of 140° for 0.5 hr. Uptake of acetylene started immediately and continued vigorously. The crude product, which was homogeneous, had gained 16 g. in weight, corresponding to an acetylene uptake of 0.58 mole. Fractionation of this material gave 25.0 g. of 2,3-dimethyloxazolidine, b.p. 52–54° (120 mm.), and 39.9 g. of recovered N-methylethanolamine, b.p. 55–57° (10 mm.). The conversion to product was therefore 25% and the yield based on unrecovered aminoalcohol, 50%.

The reaction of 89.6 g. (1.2 moles) of N-methylethanolamine with acetylene, within the pressure range 470–460 p.s.i.g. at 117 ± 1° for 0.5 hr. was repeated four times. The first reaction charge (1) contained only the aminoalcohol, the second (2) contained in addition 7.5 g. of the dihydrate of ethylenediaminetetraacetic acid disodium salt, the third (3) contained in addition 2.4 g. of 1,5-pentanedithiol and the fourth (4) contained in addition 5.0 g. of 85% phosphoric acid. Crude rate measurements gave the following rates of absorption of acetylene in the first minute of reaction (in moles per minute): (1) 0.11, (2) 0.10, (3) 0.14, (4) 0.04. The rates during the next 10–20 minutes were: (1) 0.02, (2) 0.01, (3) 0.008, (4) 0.003. The experimental error was such that the rates of (1), (2) and (3) may be considered the same, but the rates in (4) were decidedly lower. Work-up of the reaction products resulted in 14.6 g. of 2,3-dimethyloxazolidine from (1) and 13.7 g. from (3). Most of the product obtained in (2) and (4) polymerized during reaction.

PHILADELPHIA 37, PENNA.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ROHM & HAAS CO.]

Homogeneous Metal Salt Catalysis in Organic Reactions. I. The Preparation of Vinyl Ethers by Vinyl Transetherification

BY WARREN H. WATANABE AND LAWRENCE E. CONLON

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The interchange reaction $ROCH{=}CH_2 + R'OH \rightleftarrows ROH + R'OCH{=}CH_2$, which is catalyzed by mercuric salts of weak acids, has been studied and found to be of wide scope and utility. It has been found that mercuric salts are specific catalysts for this reaction. A large number of other metal salts, as well as acid and base, were found to be without catalytic activity under conditions in which catalysis by mercuric salts of weak acids was rapid and efficient. As presently developed, the reaction gives yields ranging from relatively poor to excellent, but is nevertheless advantageous in that it provides a simple one-step synthesis of vinyl ethers from alcohols. Some attention has been given to the mechanism of this and related catalytic reactions, and a scheme involving acetoxymercuriacetals as intermediates is proposed.

Among the number of reactions which are specifically catalyzed by mercuric salts, there is an important group in which an olefinic function bonded to oxygen in an ester or ether is transferred to another oxygen atom in another ester or ether. For example, mercuric salts of strong acids catalyze the transfer to carboxylic acids of vinyl[1] or isopropenyl groups[2] from vinyl or isopropenyl esters to form new vinyl or isopropenyl esters. The same type of catalyst has been shown to cause transfer of vinyl groups from vinyl esters to alcohols to form, at low temperatures, vinyl ethers,[3] and to effect transfer of vinyl groups from vinyl ethers to alcohols to give new vinyl ethers, again at low

(1) W. O. Herrmann, U. S. Patent 2,079,068 (May 4, 1937); W. T. Toussaint and L. G. MacDowell, U. S. Patent 2,299,862 (October 27, 1942); R. L. Adelman, *J. Org. Chem.*, 14, 1057 (1949).

(2) J. B. Dickey and T. E. Stanin, U. S. Patent 2,646,437 (July 21, 1953).

(3) C. E. Schildknecht, THIS JOURNAL, 75, 2678 (1953).

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TABLE I

PREPARATION OF VINYL ETHERS BY VINYL TRANSETHERIFICATION

Alcohol vinylated	Vinylating agent	Method	Yield, %	B.p., °C.	Mm.	$n^{25}D$
Ethyl alcohol	*n*-Butyl vinyl ether	A	98	36–37		1.3768
Ethyl alcohol	*n*-Octyl vinyl ether	A	81			
n-Octyl alcohol	Ethyl vinyl ether	B	30	63–64	5	1.4268
Isopropyl alcohol	*n*-Butyl vinyl ether	A	66	54–56		1.3850
t-Butyl alcohol	2-Butoxyethyl vinyl ether	A	43	77–78		1.3987
2-Methoxyethanol	2-Butoxyethyl vinyl ether	A	62	106–108		1.4105
Cyclohexanol	2-Ethylhexyl vinyl ether	A	60	82–83	80	1.4547[6]
Dicyclopentenyl alcohol	*n*-Butyl vinyl ether	B	44	89–91	5	1.5068
Allyl alcohol	*n*-Butyl vinyl ether	A	75	66–67		1.4109
2-Methallyl alcohol	2-Ethoxyethyl vinyl ether	A	75	87–88		1.4204
2-Chloroallyl alcohol	Ethyl vinyl ether	B	18	107–110		1.4502
Benzyl alcohol	*n*-Butyl vinyl ether	B	15	103–104	25	1.5185[6]
Ethylene chlorohydrin	2-Ethylhexyl vinyl ether	A	52	58–59	120	1.4378
Ethylene chlorohydrin	Ethyl vinyl ether	B	37			
Ethylene cyanohydrin	1,2-Divinoxyethane	B	40	79–80	20	1.4335
1-Methyl-1-hydroxy-3-butanone	Ethyl vinyl ether	B	30	55–56	8	1.4316
2-Methyl-2-nitro-1-propanol	Ethyl vinyl ether	B	32	77–78	10	1.4400
2-Nitro-1-butanol	Ethyl vinyl ether	B	27	72–73	5	1.4402
Furfuryl alcohol	Ethyl vinyl ether	B	28	70–71	40	1.4740
N,N-Dimethylaminoethanol	2-Butoxyethyl vinyl ether	A	36	69–71	120	1.4259
2-(β-Hydroxyethyl)-pyridine	Ethyl vinyl ether	B	32	87–90	10	1.5118

temperatures.[4] More recently mercuric salts of weak carboxylic acids have been reported to be particularly effective in catalyzing the transfer of vinyl groups from vinyl ethers to alcohols.[5]

This last reaction, in which weak acid salts of mercury are used to effect vinyl transetherification

$$ROCH{=}CH_2 + R'OH \rightleftarrows ROH + R'OCH{=}CH_2 \quad (1)$$

also was encountered independently in these laboratories several years ago, and it is the purpose of this report to describe our development of this reaction, as well as to suggest a general mechanism for this and the other transfer reactions mentioned above.

Reaction Procedures.—Equation 1 states that vinyl transetherification is reversible, and we have demonstrated that reactions may be made to proceed in either direction by appropriate choice of method. Thus we have prepared *n*-octyl vinyl ether from ethyl vinyl ether and *n*-octyl alcohol, and ethyl vinyl ether from *n*-octyl vinyl ether and ethyl alcohol. The procedure used throughout by the British workers in their disclosure of this new reaction[5] was one in which the desired vinyl ether is directly fractionated out of a solution of catalyst, a high-boiling vinyl ether, and a lower-boiling alcohol which it is desired to vinylate. This is feasible since vinyl ethers generally have boiling points about 10 to 30° below those of the alcohols from which they are derived.[7] We have found this method (method A in Table I) to lead to uniformly good yields of product since the equilibrium in (1) is shifted continuously toward the products, and the newly-formed vinyl ether remains only for a short time in contact with the reaction mixture, thereby minimizing side reactions. Nine examples utilizing this procedure are listed in Table I.

A more general and flexible method, but one in which lower yields are obtained, is the equilibration of a mixture of a vinyl ether, in excess, catalyst and an alcohol which it is desired to vinylate (method B in Table I). The equilibrium is then frozen by flash-stripping the volatile components from the catalyst or by inactivating the catalyst, and the mixture separated. Special advantages of this method are that no restrictions as to boiling point are placed on the vinyl ether serving as vinylating agent (except, of course, that it must ultimately be separable from the product vinyl ether) and that low reaction temperatures may be used, allowing the reaction of thermally-labile materials. The major disadvantage is that low yields (20–40%) are obtained, owing to the occurrence of a side reaction in which acetals are formed by acid-catalyzed addition of alcohol to vinyl ether.[8]

$$ROCH{=}CH_2 + R'OH \xrightarrow{H^+} \begin{matrix} RO \\ \diagdown \\ CHCH_3 \\ \diagup \\ R'O \end{matrix} \quad (2)$$

This side reaction reduces yields to less than half the amount of product to be expected on the basis of an equilibrium constant of one for reaction 1. Table I lists eleven vinyl ethers prepared by method B.

It should be noted that vinyl transetherification provides a one-step synthesis of vinyl ethers directly from alcohols and, thus, in spite of the low yields obtained in reactions carried out by method B, is generally preferable to the common

(4) R. L. Adelman, THIS JOURNAL, **77**, 1669 (1955).

(5) G. A. Weeks and W. J. Grant, British Patent 709,106 (May 19, 1954).

(6) M. F. Shostakovskii and N. A. Gershtein, *Akad. Nauk S.S.S.R., Inst. Org. Khim., Sintezy Org. Soedinenii, Sbornik*, **2**, 35 (1952); *C. A.*, **48**, 633f (1954).

(7) The boiling points of vinyl ethers are usually almost identical with the boiling points of the corresponding ethyl ethers; *cf.* C. E. Schildknecht, A. O. Zoss and C. McKinley, *Ind. Eng. Chem.*, **39**, 180 (1947).

(8) H. S. Hill, THIS JOURNAL, **50**, 2725 (1928); W. Reppe and K. Baur, U. S. Patent 2,000,252 (May 7, 1935). See also more recent papers by M. F. Shostakovskii, *et al.*[9]

(9) M. F. Shostakovskii and E. N. Prilezhaeva, *J. Gen. Chem. (U.S.S.R.)*, **17**, 1129 (1947); *C. A.*, **42**, 3633d (1948).

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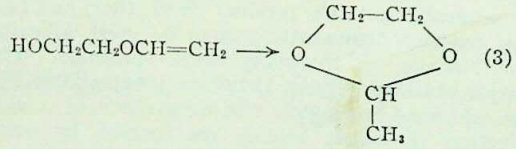
multi-step procedures (*e.g.*, by cracking of acetals,[10] by dehydrohalogenation of β-haloethyl ethers[11] or by reduction of haloacetals[12]). Base-catalyzed vinylation of alcohols by high pressure acetylene is an alternative one-step method,[13] but vinyl transetherification is of wider application in that it may be used with base-sensitive alcohols which cannot be vinylated with acetylene. Examples of such alcohols which have been converted to vinyl ethers in this work are ethylene chlorohydrin, ethylene cyanohydrin, 1-methyl-1-hydroxy-3-butanone, 2-nitro-1-butanol, 2-methyl-2-nitro-1-propanol, 2-chloroallyl alcohol and 2-(β-hydroxyethyl)-pyridine. Allyl and methallyl alcohols, which are vinylated with difficulty by acetylene,[14] are vinylated by the present method in good yield.

The alcohols listed in Table I indicate a reasonably broad scope for this reaction. Most of these compounds reacted smoothly, but several presented some special aspects which should be mentioned here. Acetal formation was marked in the reaction of ethylene chlorohydrin, even in method A, possibly due to splitting off of HCl with consequent strong acid catalysis of the acetal-forming reaction (2). Some improvement was observed when a salt of a weak acid was added to reduce acidity during the reaction. *t*-Butyl alcohol, ethylene cyanohydrin and N,N-dimethylaminoethanol all reacted very slowly, requiring long reaction times, with resulting losses in yield.[15] A number of other vinyl ethers were tried as vinylating agents for ethylene cyanohydrin, but only with the difunctional 1,2-divinoxyethane was it possible to obtain as high as 40% yield. The vinylation of ethylene glycol also was attempted, but while small amounts of both the monovinyl and divinyl ethers were isolated, the yields were in general low and variable. This is due to the competitive cyclization of 2-hydroxyethyl vinyl ether to 2-methyl-1,3-dioxolane,[12b] which also was isolated from among the



(3)

reaction products. When amino-alcohols containing primary and secondary amino groups were tried, the reaction was found not to proceed as in (1) but in another direction, which is described in the second paper of this series.[16]

(10) K. Baur, U. S. Patent 1,931,858 (October 24, 1933); F. Sigmund and R. Uchann, *Monatsh.*, **51**, 234 (1929).

(11) W. Chalmers, *Can. J. Research*, **7B**, 464 (1932); S. G. Powell and R. Adams, THIS JOURNAL, **42**, 646 (1920).

(12) (a) J. Wislicenus, *Ann.*, **192**, 106 (1878); (b) H. S. Hill and L. M. Pidgeon, THIS JOURNAL, **50**, 2718 (1928).

(13) For references to this work see J. W. Copenhaver and M. H. Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold Publishing Corp., New York, N. Y., 1949, p. 32, *et seq.*; W. E. Hanford and D. E. Sargent in H. Gilman, ed., "Organic Chemistry," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 1087–1093.

(14) R. Paul, G. Roy, M. Fluchaire and G. Collardeau, *Bull. soc. chim. France*, 121 (1950).

(15) Adelman has reported also that ethylene cyanohydrin reacts very slowly in vinyl acetate–alcohol interchange.[3]

(16) W. H. Watanabe, THIS JOURNAL, **79**, 2833 (1957).

Catalysts and Catalyst Systems.—Tests made on a variety of metal salts showed that mercuric salts are highly specific catalysts for reaction 1. Inactive salts included those of cobalt, cadmium, copper (cuprous and cupric), iron (ferrous and ferric), lead, silver, nickel and zinc. Of these inactive materials, a number effected the formation of high-boiling products (probably acetals); these salts were mainly halides, although several nitrates also led to this type of reaction.[17]

Adelman already has shown that strong acid salts of mercury will catalyze (1), although vinyl ethers can be isolated only when the reaction is carried out at low temperatures (−10° or lower).[4] We postulate that in the course of the catalysis the acid derived from the anion of the mercuric salt is set free, and it is therefore probable that the strength of this acid will determine the extent of side reaction 2. Our finding that mercuric salts of weak acids, particularly mercuric acetate and mercuric benzoate, are effective catalysts which can be used advantageously at higher temperatures supports this aspect of the catalysis. Thus the specific activity resides in the cation; the acid derived from the anion must take part in some later step of the catalysis but may also be the agent promoting side reactions.

Exceptions to our general observation that strong acid salts of mercury gave acetals at room temperature and above were found in mercuric iodide, mercuric fluoride and chloromercuriacetaldehyde, all of which gave vinyl ether products. These results imply that the extent of dissociation of the mercury salts is also a determining factor in establishing the balance of reactions 1 and 2.

Mechanism of the Reaction.—For those reactions catalyzed by strong acid salts of mercury (*e.g.*, mercuric sulfate), Adelman has postulated a mechanism wherein the vinyl compound first dissociates into an acetylene–mercuric salt complex, which then reacts with alcohol or carboxylic acid to form the product.[3] This mechanism requires that the catalyst for vinyl interchange also be a catalyst for the reaction of acetylene with alcohol or carboxylic acid to give vinyl ether or vinyl ester, and while this is true with mercuric salts of strong acids, it is not the case with mercuric salts of weak acids.[18] We agree with Adelman's proposal that the several mercuric salt-catalyzed vinyl interchange reactions probably proceed through the same general type of mechanism. We consider it more probable, however, that the actual reaction path will more closely correspond to the following scheme, which is written for vinyl transetherification. This mechanism is, in essence, a reversible alkoxymercuration. One of its important aspects is the formation of an intermediate or intermediates which are essentially symmetrical, so that the reverse reactions can lead either to the starting reactants or to the desired products. The anal-

(17) M. F. Shostakovskii and N. A. Gershtein, *J. Gen. Chem. (U.S.S.R.)*, **16**, 937 (1946); *C. A.*, **41**, 1999c (1947), report the use of metal chlorides to catalzye the addition of alcohols to vinyl ethers, forming acetals; see also H. T. Neher and L. N. Bauer, U. S. Patent 2,633,460 (March 31, 1953).

(18) R. R. Vogt and J. A. Nieuwland, THIS JOURNAL, **48**, 2071 (1931).

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$$Hg(OAc)_2 \rightleftharpoons HgOAc^+ + AcO^- \quad (4a)$$

$$HgOAc^+ + ROCH{=}CH_2 + R'OH \rightleftharpoons$$

$$\begin{matrix} RO \\ \diagdown \\ CHCH_2HgOAc \\ \diagup \\ R'O \end{matrix} + H^+ \quad (4b)$$

I

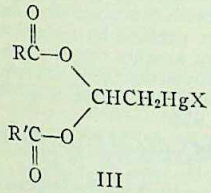
$$\begin{matrix} RO \\ \diagdown \\ CHCH_2HgOAc \\ \diagup \\ R'O \end{matrix} + ROCH{=}CH_2 + R'OH$$

$$\left[\begin{matrix} RO \\ \diagdown \\ CHCH_2- \\ \diagup \\ R'O \end{matrix}\right]_2 Hg + HOAc \quad (4c)$$

II

$$\begin{matrix} RO \\ \diagdown \\ CHCH_2HgOAc \\ \diagup \\ R'O \end{matrix} + R'OCH{=}CH_2 + ROH$$

ogous intermediate for vinyl transesterification (III) should also possess the property of reverting either to starting reactants or products, thus explaining the equilibrium character of this reaction.



III

The possibility that intermediates of the structure (I) may in fact be involved in the over-all path of vinyl transetherification is lent some credence by our finding that compounds of structure I readily can be prepared and isolated. Slow addition of sodium ethoxide in ethyl alcohol to mercuric acetate dissolved in ethyl vinyl ether gives a good yield of 2-acetoxymercuri-1,1-diethoxyethane (IV), which can be recrystallized and stored unchanged in the cold for at least several weeks.[19] 2-Acetoxymercuri-1-methoxy-1-ethoxyethane (V) was prepared similarly from sodium methoxide, mercuric acetate and ethyl vinyl ether.

$$R'O^- + ROCH{=}CH_2 + Hg(OAc)_2 \longrightarrow$$

$$\begin{matrix} R'O \\ \diagdown \\ CHCH_2HgOAc \\ \diagup \\ RO \end{matrix} + AcO^- \quad (5)$$

IV, $R = R' = C_2H_5$
V, $R' = CH_3$ $R = C_2H_5$

Compound V was kept refrigerated for several months and after this period was found to have decomposed largely into metallic mercury, ethyl vinyl ether and some acetaldehyde.

(19) A. N. Nesmeyanov, I. F. Lutsenko and N. I. Vereschagina, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 63 (1947); *C. A.*, **41**, 4148i (1948), have prepared chloro- and bromomercuriacetaldehyde in good yield by reaction of an alkyl vinyl ether and mercuric acetate in aqueous solution, followed by addition of KCl or KBr.

The 2-acetoxymercuri-1,1-diethoxyethane was found to be decomposed readily by acetic acid to ethyl vinyl ether and ethyl alcohol, thus establishing that such a structure is indeed labile to weak acid. This demonstration is a necessary although not a sufficient condition that structure I be an intermediate in vinyl transetherification. We are led to the proposal of step 4c, in which I reacts further with vinyl ether to give the diacetal II, by our observation that the 2-acetoxymercuriacetals in the absence of added acetic acid (as well as phenyl mercuric acetate, both mercury compounds with a single acid anion) are quite efficient catalysts for vinyl transetherification. This implies that structures $RHgCH_2CH(OR)_2$, where R is phenyl or $(RO)_2CHCH_2-$, may be formed, liberating acetic acid, and may subsequently be decomposed by this acid. As expected, di-*p*-tolylmercury, which is relatively stable to cleavage at the C–Hg bond, has no catalytic activity.

Acknowledgment.—We wish to thank Mr. O. H. Loeffler for much helpful advice and encouragement during the course of this work.

Experimental

Materials.—All vinyl ethers used as vinylating agents, except ethyl vinyl ether and 2-ethylhexyl vinyl ether, which were commercially available, were prepared by base-catalyzed high-pressure vinylation of the alcohols with acetylene[13] and were used either pure or as azeotropes with their precursor alcohols. The commercially obtained vinyl ethers were fractionated before use to remove polymerization inhibitors, which, being amines, inactivate the mercuric salt catalysts. No special effort was made to remove peroxides from the vinyl ethers, other than by distillation; however, these materials were never distilled to less than one-fifth the original pot charge. The alcohols were also purified by distillation. Dr. P. L. deBenneville and his associates kindly supplied the 1-methyl-1-hydroxy-3-butanone; all other alcohols were commercially available. All mercuric salts used were the best grade obtainable.

Analytical Methods.—A qualitative test for vinyl ethers which we found most useful in assessing the results of our experiments was as follows: several drops of the compound are placed on a spot plate and a drop of boron trifluoride etherate added with care. If the compound is a vinyl ether, there is an immediate, often violent, reaction with formation of black viscous or solid tars and evolution of fumes. Certain alcohols which are themselves polymerized by acid, such as furfuryl alcohol, also react in this manner to boron trifluoride. Azeotropes of vinyl ethers and alcohols react less violently but still rapidly. Acetals react very slowly, but do darken on standing for several minutes.

Quantitative analyses for the vinyl group were carried out by the method of Siggia, in which the vinyl ether is hydrolyzed in aqueous hydroxylamine hydrochloride, the acetaldehyde thereupon forming the oxime and liberating HCl, and the free HCl then determined by titration.[20]

Catalyst Testing.—The possible catalytic activity of metal salts in effecting reaction 1 was tested by determining whether these salts would convert a solution of ethyl alcohol and *n*-butyl vinyl ether to ethyl vinyl ether and *n*-butyl alcohol, under reflux. By this test the following compounds were found to be active catalysts: mercuric acetate, mercuric benzoate, phenyl mercuric acetate, mercuric citrate, mercuric chromate, mercuric oxalate, mercuric linoleate, mercuric fluoride, mercuric iodide, mercuric lactate, 2-acetoxymercuri-1,1-diethoxyethane, 2-acetoxymercuri-1-ethoxy-1-methoxyethane and chloromercuriacetaldehyde. The fluoride, iodide and lactate were relatively poor catalysts, giving acetals as well as transetherification product. The following compounds led to the formation of high-boiling products, presumably acetals: mercuric sulfate, mercuric nitrate, mercuric chloride, mercuric thiocyanate, mer-

(20) S. Siggia, "Quantitative Organic Analysis Via Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 63.

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curous sulfate, cuprous chloride, nickel bromide, nickel nitrate, nickel iodide, cobalt chloride, antimony trichloride, ferric chloride, bismuth nitrate, arsenic trichloride and sodium bisulfate. Compounds which gave no apparent reaction were mercuric cyanide, mercuric oxide, mercuric sulfide, mercurous chloride, cobalt acetate, cobalt carbonate, cadmium acetate, cadmium carbonate, cadmium oxide, cuprous thiocyanate, cuprous cyanide, cupric carbonate, ferrous sulfate, lead acetate, nickel acetate, nickel cyanide, nickel carbonate, nickel formate, nickel sulfate, thallous bromide, thallous malonate, zinc acetate, zinc bromide, zinc oxide, silver nitrate, silver acetate, ammonium chloride, sodium ethoxide and sodium hydroxide.

Preparation of Ethyl Vinyl Ether. Method A.—This and the following procedure are representative examples of method A. Mercuric acetate (5 g., 0.016 mole) was dissolved in a mixture of dry ethyl alcohol (50 g., 1.08 moles) and *n*-butyl vinyl ether (100 g., 1.0 mole) and the resulting solution placed on a short distilling column fitted with a total condensation partial take-off head. The distillation was first kept at total reflux until the vapor temperature settled at 36–37°, and the rate of distillation was thereafter adjusted so as to keep the boiling point within this range. There was distilled off 71 g. (0.98 mole) pure ethyl vinyl ether, b.p. 36–37°, a yield on the vinyl ether of 98%. Water was then added to the distilling flask, and an azeotrope of *n*-butyl alcohol and water, b.p. 93°, was distilled off and separated to give 71.2 g. (0.97 mole) of *n*-butyl alcohol.

Preparation of Allyl Vinyl Ether. Method A.—A solution of 5 g. of mercuric acetate in 602 g. of *n*-butyl alcohol–*n*-butyl vinyl ether azeotrope (90% vinyl ether, 5.4 moles) and 231 g. (3.98 moles) of dry allyl alcohol was distilled slowly through an efficient distilling column. The reflux ratio was so controlled as to remove distillate at 66–68°. After 6 hr., an additional 5 g. of mercuric acetate was added and distillation continued. An additional 14 hr. of distillation was required to carry the reaction to completion. The pot residue was distilled to recover excess *n*-butyl vinyl ether and the *n*-butyl alcohol formed. The product, 282.5 g., b.p. 66–68°, was an azeotrope of allyl alcohol with allyl vinyl ether, containing about 90% by weight of allyl vinyl ether. This azeotrope was stripped of allyl alcohol by washing with water and redistilling, giving allyl vinyl ether of greater than 98% purity, b.p. 67.5°, $n^{20}D$ 1.4109. *n*-Butyl vinyl ether (azeotrope with *n*-butyl alcohol) recovered amounted to 125 g.; *n*-butyl alcohol formed amounted to 339.5 g. The yield of pure allyl vinyl ether based on total alcohol was therefore 75%.

Removal of the last traces of allyl alcohol should not be attempted by distillation out of sodium since allyl vinyl ether reacts with sodium and, to an appreciable degree, rearranges to propenyl vinyl ether, $CH_3CH{=}CHOCH{=}CH_2$, b.p. 61–62°, which is very difficult to remove from allyl vinyl ether.[14]

Preparation of *n*-Octyl Vinyl Ether. Method B.—This and the following three procedures are representative of method B. A solution of 3 g. of mercuric acetate in 65 g. (0.5 mole) of *n*-octyl alcohol and 216 g. (3.0 moles) of ethyl vinyl ether was refluxed for 6 hr. During this period, the liquid temperature of the refluxing solution rose from 39.5 to 42°. Several grams of anhydrous potassium carbonate were then added to the cooled reaction mixture and excess ethyl vinyl ether and ethyl alcohol formed in the reaction were removed at reduced pressure. Distillation of this residue directly out of the carbonate gave 28 g. of crude product, b.p. 64–65° (5 mm.), and 30 g. of recovered *n*-octyl alcohol, b.p. 75–77° (5 mm.). The product, which by analysis was shown to contain 83% by weight of *n*-octyl vinyl ether, was distilled out of sodium to give the pure vinyl ether, b.p. 63–64° (5 mm.), $n^{20}D$ 1.4268. The yield based on total alcohol was 30%, the yield on unrecovered alcohol, 64%.

Preparation of 2-Nitro-2-methylpropyl Vinyl Ether. Method B.—A solution of 5 g. of mercuric acetate and 59.6 g. (0.5 mole) of 2-methyl-2-nitro-1-propanol in 146.2 g. (2.0 moles) of ethyl vinyl ether was heated under reflux for 6 hr. The reaction mixture was then cooled and washed with five 100-cc. portions of water, dried over anhydrous sodium sulfate and flash-distilled at less than 1 mm. pressure into a receiver chilled with Dry Ice until the distillate began to crystallize on the sides of the distilling apparatus. This distillate was fractionated and three cuts totaling 24.9 g., boiling over the range 71–80° (10 mm.), $n^{20}D$ 1.4404–1.4403, were obtained. These cuts were combined and by analysis found to contain 91.4% 2-nitro-2-methylpropyl vinyl ether. The yield was therefore 32%. Purification of the crude product was carried out by heating it with 50% aqueous sodium hydroxide on the steam-bath, diluting with ether, separating and redistilling to give 99.7% pure vinyl ether, b.p. 77–78° (10 mm.), $n^{20}D$ 1.4400.

Anal.[21] Calcd. for $C_6H_{11}O_3N$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.85; H, 7.55; N, 9.52.

Preparation of 2-(β-Vinoxyethyl)-pyridine. Method B.—A solution of 5 g. of mercuric acetate in 61.5 g. (0.5 mole) of 2-(β-hydroxyethyl)-pyridine (redistilled, b.p. 72° (0.35 mm.)) and 288 g. (4.0 moles) of ethyl vinyl ether was refluxed for 7 hr. The reaction mixture was freed of volatile material at 1 mm. pressure at room temperature and the residue from this process then fractionated to give 29.5 g. of crude product, b.p. 98–110° (22 mm.), active to boron trifluoride. Analysis showed this fraction to contain 80% by weight of 2-(β-vinoxyethyl)-pyridine, representing a 32% yield. This material was dissolved in 50 cc. of ether, washed with seven 10-cc. portions of water, dried and redistilled. The pure vinyl ether distilled at 87–89.5° (10 mm.), $n^{25}D$ 1.5118, d^{25}_4 1.0035, and was 98.4% pure by analysis.

Anal. Calcd. for $C_9H_{11}ON$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.84; H, 7.44; N, 9.25.

Preparation of 2-Cyanoethyl Vinyl Ether. Method B.—A mixture of 114.1 g. (1.0 mole) of 1,2-divinoxyethane, 35.5 g. (0.5 mole) of ethylene cyanohydrin, 2.0 g. of sodium acetate and 5.0 g. of mercuric acetate was heated under reflux for 2.5 hr. The reaction mixture was cooled and flash-distilled and the distillate fractionated to give several major fractions: 2-methyl-1,3-dioxolane, b.p. 43–44° (18 mm.), 15 g.; recovered 1,2-divinoxyethane, b.p. 71–85° (120 mm.), 42.5 g.; 2-cyanoethyl vinyl ether (95% pure), b.p. 75–85° (20 mm.), 20.5 g. (40% yield). There is no azeotrope formed with this vinyl ether and the alcohol, and it can therefore be purified by refractionation. The 95% crude product from another run in which ethyl vinyl ether was used as the vinylating agent was refractionated to give 100% 2-cyanoethyl vinyl ether, b.p. 79–80° (20 mm.), $n^{20}D$ 1.4335, d^{22}_4 0.9540.

Anal. Calcd. for C_5H_7ON: C, 61.83; H, 7.27; N, 14.44. Found: C, 61.75; H, 7.23; N, 14.37.

A sample of this product was hydrogenated in heptane with Raney nickel catalyst for 3 hr. under 1500 p.s.i. hydrogen at 100–105°.[22] Approximately three moles of hydrogen was absorbed per mole of compound. Fractionation gave material, b.p. 79° (120 mm.), neutralization equivalent by potentiometric titration with standard base, 103.4 (calculated as 3-ethoxypropylamine, 103.2). To purify this product, it was dissolved in 5% hydrochloric acid, extracted with ether, the acid solution made basic with 5% sodium hydroxide and again extracted with ether. The ether extract of the basic solution was dried over anhydrous sodium sulfate, calcium hydride and calcium oxide added and ether distilled off. The residue was put over fresh calcium hydride and fractionated, yielding material, b.p. 74–75° (120 mm.), $n^{20}D$ 1.4186, $n^{25}D$ 1.4166, d^{25}_4 0.8516 (lit.[23] for 3-ethoxypropylamine, $n^{20}D$ 1.4201, d^{20}_{20} 0.8613).

Anal. Calcd. for $C_5H_{13}ON$: C, 58.21; H, 12.70; N, 13.58. Found: C, 58.11; H, 12.65; N, 13.45.

Preparation of 2-Acetoxymercuri-1,1-diethoxyethane.—A slurry of 180 g. (0.565 mole) of mercuric acetate in 550 cc. of absolute ethyl alcohol was prepared, and to this was added 40 g. (0.538 mole) of ethyl vinyl ether with vigorous stirring. The mercuric acetate dissolved immediately, with an accompanying temperature rise to 40°. The solution was cooled to 20°, and a solution of 0.565 mole of sodium ethoxide in 200 cc. of absolute ethyl alcohol was added at such a rate as to keep the reaction temperature below 21°. The reaction mixture was stirred for 1 hr. and filtered and evaporated to dryness under a nitrogen atmosphere. The residue was then taken up in chloroform, filtered and again evaporated, leaving a mass of white fibrous crystals. Recrystallization from hot 30–60° petroleum ether gave 130 g. of product, m.p. 151–154° dec., a yield of 64% based on ethyl vinyl ether and 61% based on mercuric acetate. This

(21) Microanalyses by Mr. C. W. Nash and associates.

(22) We thank Dr. J. LoCicero for performing this hydrogenation.

(23) Wirth, This Journal, 67, 1505 (1945).

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material was stored in a vacuum desiccator over potassium hydroxide pellets.

Anal. Calcd. for $C_5H_{10}O_4Hg$: C, 25.50; H, 4.28; Hg, 53.24. Found: C, 25.3; H, 4.5; Hg, 54.0.

Preparation of 2-Acetoxymercuri-1-methoxy-1-ethoxyethane.—A solution of 4 g. (0.174 mole) of sodium in 100 cc. of dry methyl alcohol was added dropwise to a solution of 20 g. (0.063 mole) of mercuric acetate in 250 cc. of dry methyl alcohol until a reddish-orange precipitate of the basic salt began to appear. Ethyl vinyl ether was then added dropwise until this precipitate just dissolved. Alternate additions of sodium methoxide and ethyl vinyl ether were made in this manner until further addition of sodium methoxide failed to precipitate the basic salt. The solution was then evaporated to dryness under vacuum. The residue was taken up in chloroform, filtered to remove sodium acetate and the chloroform solution again evaporated under vacuum. The crystalline residue was recrystallized from 30–60° petroleum ether. About 0.5 g. of this product was tested for catalytic activity, and another small portion was dried in vacuum over phosphoric anhydride, m.p. 56–57°.

Anal. Calcd. for $C_7H_{14}O_4Hg$: Hg, 55.30. Found: Hg, 55.97.

The remainder of the product was stored in a tightly-capped bottle in the refrigerator. Examination of this material after about 7 months showed that it had decomposed largely into free mercury and a colorless two-phase liquid. Fractionation of the liquid gave 2 g., b.p. 31–36°, which had a slight odor of acetaldehyde but was mostly wet ethyl vinyl ether, and 6 g., b.p. 46.5–62°, which probably contained dimethyl acetal.

Decomposition of 2-Acetoxymercuri-1,1-diethoxyethane.—A slurry of 60 g. (0.16 mole) of this compound in 300 cc. of *n*-heptane was brought to gentle reflux on an efficient distilling column. An equimolar amount of glacial acetic acid was then added dropwise to this refluxing slurry over a 45-minute period. The solids in the pot turned from a white to a cream color after this addition, and after 1.5 hr. of reflux, the vapor temperature settled at 36°. Slow fractionation gave 3 g. of 94% pure ethyl vinyl ether. Further fractionation gave 22 g. over the range 40–98°, containing 16.5% ethyl vinyl ether and including a large amount of distillate, b.p. 69–70°, which was the azeotrope of ethyl alcohol with *n*-heptane. The total yield of ethyl vinyl ether was therefore 56%. No free mercury appeared during this distillation until the vapor temperature had reached 70°. All attempts to determine the form in which mercury was present in the distillation residue were unsuccessful, but it appeared that no simple salts of mercury were formed.

PHILADELPHIA 37, PENNA.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ROHM & HAAS CO.]

Homogeneous Metal Salt Catalysis in Organic Reactions. II. The Reaction of Vinyl Ethers with Aminoalcohols and 1,2-Diamines

BY WARREN H. WATANABE

RECEIVED NOVEMBER 2, 1956

When aminoalcohols, $RNH(CR_2)_nOH$, in which R is H, alkyl or aryl and n is 2 or 3, are treated with alkyl vinyl ethers in the presence of mercuric salts of weak acids or silver salts such as silver nitrate or silver acetate, there are formed in good yield 2-methyloxazolidines (I, n = 2) or 2-methyltetrahydro-1,3-oxazines (I, n = 3). Similarly, 1,2-diamines, treated with alkyl vinyl ethers with the same catalysts, give 2-methylimidazolidines (II). These new reactions are improved methods of preparation of these relatively unstable compounds. The relation of these reactions to vinyl transetherification[1] is discussed and a mechanism is proposed.

In a previous publication we have described a method of preparation of vinyl ethers by the reaction

$$ROCH{=}CH_2 + R'OH \rightleftarrows ROH + R'OCH{=}CH_2 \quad (1)$$

which is catalyzed by mercuric salts of weak acids.[1] We have now found that when the alcohol R′OH is an aminoalcohol, $RNH(CR_2)_nOH$, in which R is H, alkyl or aryl group and n is 2 or 3, reaction 1 takes a quite different course. The products in these instances are 2-methyloxazolidines (I, n = 2) or 2-methyltetrahydro-1,3-oxazines (I, n = 3) rather than the vinyl ethers

$$ROCH{=}CH_2 + R'NH(CR_2)_nOH \;(n = 2,3) \longrightarrow \text{I} + ROH \quad (2)$$

We have been able also to extend this reaction to 1,2-diamines, whereby 2-methylimidazolidines are formed

$$ROCH{=}CH_2 + R'NHCH_2CH_2NHR'' \longrightarrow \text{II} + ROH \quad (3)$$

The yields of the cyclic compounds prepared by this method range from about 40 to greater than 80% and are limited largely by the stability of these compounds. This new reaction thus is a simple, useful and generally preferable alternative to the standard method of preparation of I and II, which is by reaction of the aminoalcohols[2] or diamines[3] with acetaldehyde.

Catalysts.—The same catalysts found to be effective in our previous study of vinyl transetherification (*i.e.*, mercuric salts of carboxylic acids[1]) were also the most efficient catalysts for the present reaction. It was of interest that mercuric sulfate, which is a very active catalyst for vinyl transetherification at very low temperatures,[4] had no activity for reaction 2 and, probably due to the strongly basic nature of the reaction mixture, had no effect at all on the vinyl ether. Moreover, in contrast to the vinyl transfer reaction 1, for which mercuric salts are highly specific catalysts, the present reaction also was found to be catalyzed by silver nitrate and silver acetate. Zinc acetate,

(1) W. H. Watanabe and L. E. Conlon, THIS JOURNAL, **79**, 2828 (1957).

(2) (a) E. D. Bergmann, *Chem. Revs.*, **53**, 309 (1953); (b) L. Knorr and H. Matthes, *Ber.*, **34**, 3484 (1901); (c) A. I. Kiprianov and B. A. Rashkovan, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 1026 (1937); *C. A.*, **31**, 5356 (1937); (d) N. K. Ushenko, *C. A.*, **37**, 4395 (1943); (e) E. Zimkin and E. D. Bergmann, *Rec. trav. chim.*, **71**, 229 (1952).

(3) (a) J. Th. L. B. Rameau, *ibid.*, **57**, 192 (1938); (b) G. Lob, *ibid.*, **55**, 859 (1936); (c) V. S. Salvin and J. R. Adams, U. S. Patent 2,546,169 (March 27, 1951).

(4) R. L. Adelman, THIS JOURNAL, **77**, 1669 (1955).

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TABLE I

PRODUCTS PREPARED BY REACTIONS 2 AND 3

Aminoalcohol or diamine	R in ROCH=CH$_2$	Product[a]	B.p. or m.p. product °C.	Mm.	Method	Catalyst	Crude yield, %	Pure yield, %
Ethanolamine	2-Butoxyethyl	2-Methyl-ox.	50–55	60	A	$Hg(OBz)_2$	55	..
1-Aminopropanol-2	2-Butoxyethyl	2,5-Dimethyl-ox.	62.5–64.5	100	A	$Hg(OBz)_2$	53	40
2-Aminobutanol-1	2-Butoxyethyl	2-Methyl-4-ethyl-ox.	63–66	40	A	$Hg(OBz)_2$	64	55
2-Amino-2-methyl-propanol-1	Ethyl	2,4,4-Trimethyl-ox.	70.5–71	120	A	$Hg(OBz)_2$	83	72
		2,4,4-Trimethyl-ox.	70.5–71	120	B	$Hg(OAc)_2$	..	14
N-Methylethanolamine	Vinoxyethyl	2,3-Dimethyl-ox.	54–55	120	A	$Hg(OAc)_2$	..	68
N-Methylethanolamine	Vinoxyethyl	2,3-Dimethyl-ox.	54–55	120	A	$AgNO_3$	..	22
N-Methylethanolamine	Vinoxyethyl	2,3-Dimethyl-ox.	54–55	120	A	AgOAc	..	32
N-Phenylethanolamine	Ethyl	2-Methyl-3-phenyl-ox.	M. 58.5–59		B	$Hg(OAc)_2$	85	64
3-Amino-1-propanol	2-Butoxyethyl	2-Methyl-tet.	68.5–69	100	A	$Hg(OBz)_2$	..	65
3-Amino-1-propanol	Ethyl	2-Methyl-tet.	68.5–69	100	B	$Hg(OAc)_2$	..	60
Ethylenediamine	Ethyl	2-Methyl-imid.	M. 47.5–48.5		B	$Hg(OBz)_2$	41	..
N,N'-Diphenylethylene-diamine	Ethyl	2-Methyl-1,3-diphenyl-imid.	M. 92–93.5		B	$Hg(OAc)_2$	82	66

[a] For ox. read oxazolidine; for tet. read tetrahydro-1,3-oxazine; for imid., read imidazolidine.

cadmium acetate, cuprous chloride and ammonium chloride were found, under our testing conditions, to be without activity. The mercury salts were, however, preferable to the silver salts, because the latter underwent more extensive decomposition, accompanied by rapid loss in catalyst activity.

Reaction Procedures.—In Table I there are listed the compounds which have been prepared by reactions 2 and 3. The alkyl vinyl ethers used were those conveniently available and readily separable from the products of reaction. Catalysts generally used were mercuric acetate or mercuric benzoate; silver acetate and silver nitrate were tested in single reactions solely to demonstrate their activity.

Of the two methods used to carry out reaction 2, the more useful was the one in which the product was removed by distillation from the reaction mixture as rapidly as it was formed. Continuous removal was of particular advantage in that 2-methyloxazolidines (or the tautomeric Schiff bases, in the case of compounds I where R′ = H) are rapidly converted to condensation products at elevated temperatures.[5] This procedure (method A in Table I) is possible since 2-methyloxazolidines and 2-methyltetrahydro-1,3-oxazines have boiling points lower than their parent aminoalcohols. By choice of a high-boiling vinyl ether as the vinyl ether component, a system usually can be devised such that the lowest-boiling component will be the product, which can then be removed rapidly by distillation. Yields by this method are indeed to a large extent determined by the efficiency and speed at which this separation can be effected. It is certainly this possibility of continuous rapid removal of product which results in higher yields by this reaction than from the alternative method of preparation from acetaldehyde, in which the product cannot be removed until reaction is complete.

This distillation method loses its utility, however, when the product is very high-boiling (*e.g.*, 2-methyl-3-phenyloxazolidine), since an even higher-boiling vinyl ether would have to be employed. Fortunately, the phenyl compound proved to be relatively stable and could thus be obtained in good yield by heating the reactants under reflux (method B in Table I). The reflux procedure also was used in the preparation of 2-methylimidazolidines since the boiling points of these compounds are almost identical with those of the starting diamines, and the products cannot therefore be separated by distillation. Separation by crystallization could, however, be effected, since the imidazolidines had melting points higher than those of the starting diamines.

Discussion

A point of particular interest in the present work is the problem of whether reactions 2 and 3 proceed in a single step, or in two discrete steps, with a vinyl compound as an intermediate. There are substantial arguments for both hypotheses, but we believe that the preponderance of present evidence is in favor of a single-step mechanism. In support of a two-step mechanism are these points: (1) It already has been shown that mercuric salts of weak acids will catalyze vinyl transetherification.[1] It also has been found that aminoalkyl vinyl ethers can be cyclized by both mercuric and silver salts to oxazolidines and tetrahydro-1,3-oxazines.[6] Thus the two possible separate steps of a two-step mechanism (vinyl transetherification, followed by cyclization) are known reactions. (2) We moreover estimate, from the relative amounts of catalyst required for a sensible rate of reaction at room temperature, that cyclization proceeds much more rapidly than vinyl transetherification. Thus the exclusive isolation of the cyclic product is consistent with the probable relative rates of the presumed two steps.

Arguing against a two-step mechanism, however, are the following points: (1) the rate of the over-all reaction 2 or 3 is estimated, again purely on the basis of relative amounts of catalyst required for reasonable rates at room temperature, to be greater by at least a factor of five than vinyl trans-

(5) W. S. Emerson, S. M. Hess and F. C. Uhle, THIS JOURNAL, **63**, 872 (1941), have shown that aliphatic Schiff bases undergo aldol-type condensations, splitting off amine. H. R. Nace and E. P. Goldberg, *ibid.*, **75**, 3646 (1953), conclude from infrared evidence that 2-propyl-4-ethyloxazolidine, which polymerizes and changes rapidly in refractive index on standing, does so through an aldol-type condensation.

(6) Watanabe, unpublished work.

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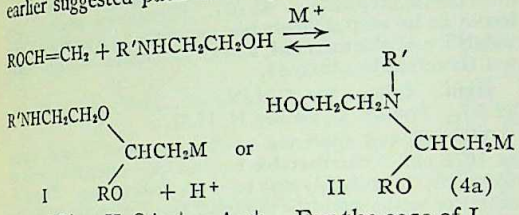
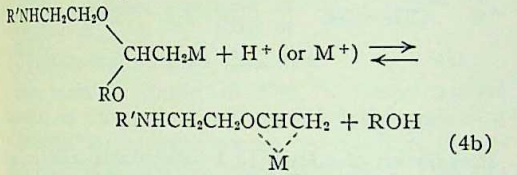
etherification. If this is the case, the transetherification cannot then be an intermediate step. (2) The two-step mechanism does not accommodate the 1,2-diamine reaction (3), unless an –O–vinyl to –NH transfer can occur. There is no reported reaction of such a type. (3) The two-step mechanism does not accommodate silver salt catalysis, since it has been found that silver salts do not catalyze vinyl transetherification.[1]

A possible one-step mechanism would be the following, which is patterned closely after our earlier suggested path for vinyl transetherification

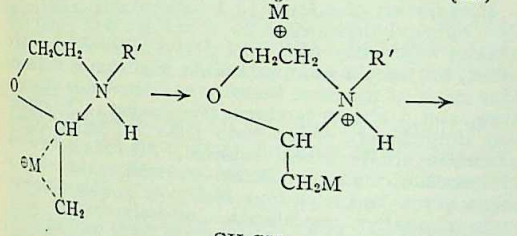


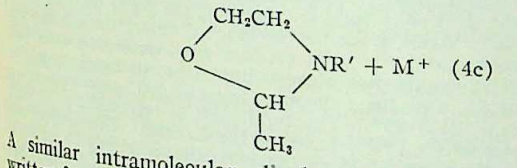
(4a)

where $M^+ = HgOAc^+$ or Ag^+. For the case of I



(4b)





(4c)

A similar intramolecular displacement can be written for II. We are, however, much less satisfied with the above postulate of a stable intermediate I or II in this reaction than in the case of vinyl transetherification where a similar intermediate was proposed, since essentially all of the metal salt should be complexed with the amine, leaving little available for covalent metal–carbon bond formation. It is nevertheless necessary that the metal salt in some manner activate the formation of a new O–C bond and, in lieu of a more sturdy alternative, we suggest reaction through such intermediates as I or II. It is, of course, possible that the steps (4a-c) take place simultaneously, in a single concerted process, obviating the necessity for the formation of any long-lived intermediates.

Experimental

Materials.—The aminoalcohols and diamines used were commercially available materials and were redistilled or recrystallized before use. 1,2-Divinoxyethane was prepared by the base-catalyzed reaction of acetylene with ethylene glycol.[7] The other vinyl ethers were commercially available and were purified by distillation. The metal salts were reagent grade chemicals, used as received.

General Comments.—Those compounds prepared where R = H and $n = 2$ in I (no substitution on the nitrogen of the 2-methyloxazolidines) were, with the exception of 2,4,4-trimethyloxazolidine, relatively unstable substances which became viscous upon standing, even in the cold.[5,8] There was thus an unavoidable loss upon the redistillation of the first crude product, and yields are therefore given for both the crude and redistilled product. As one consequence of the instability of these compounds, both $n^{25}D$ and d^{25}_4 values changed rapidly with time, and while every attempt was made to measure these values as quickly as possible, not too much reliance should be placed on these constants. Those compounds with N-substitution, or when $n = 3$, were much more stable, and the constants reported for them are more reliable. However, these substances will also darken and decompose slowly if left at room temperature.

Catalyst Testing.—The reaction of N-methylethanolamine and 1,2-divinoxyethane, which with mercuric acetate as catalyst gives about a 70% yield of 2,3-dimethyloxazolidine, was used as the standard reaction for the testing of various metal salts for catalytic activity. By this test mercuric acetate, mercuric benzoate, silver nitrate and silver acetate were found to be active, and mercuric sulfate, cuprous chloride, zinc acetate, cadmium acetate and ammonium chloride were found to be inactive. Recoveries of 1,2-divinoxyethane from tests on inactive substances ranged from 89 to 99% (recovery from the mercuric sulfate run, 99%).

Preparation of 2,5-Dimethyloxazolidine.—A cloudy, two-phase mixture resulted when 1-aminopropanol-2 (77.1 g., 1.03 moles) was mixed with 2-butoxyethyl vinyl ether (171.9 g., 1.19 moles). When 1 g. of mercuric benzoate was added, however, and dissolved by vigorous shaking, the mixture became homogeneous and an exotherm resulted which quickly brought the temperature of the solution to about 50°. The solution was therefore cooled and placed on a distillation column. An initial product cut, b.p. 55–68.5° (100 mm.), was taken, the distilling flask cooled and 1 g. of mercuric benzoate added to the reaction mixture; a second product cut taken at 65.5–70° (100 mm.) and the flask again cooled and another 1 g. of mercuric benzoate added; and a final product cut taken at 66–67°/100 mm. The weight of combined crude product was 55.1 g., a crude yield of 53%. Continued distillation of the reaction mixture yielded 117.6 g. of 2-butoxyethanol, b.p. 72–75° (20 mm.), 61–61.5° (10 mm.), a yield based on the aminoalcohol of 97%. The crude product was redistilled, giving 34.0 g. of pure 2,5-dimethyloxazolidine, b.p. 62.5–64.5° (100 mm.), $n^{25}D$ 1.4366, d^{25}_4 0.9371, which was thus obtained in 33% yield.

Anal. Calcd. for $C_5H_{11}ON$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.94; H, 11.36; N, 13.75.

2-Methyl-4-ethyloxazolidine was prepared by essentially the same method: $n^{25}D$ 1.4407, d^{25}_4 0.9219. *Anal.* Calcd. for $C_6H_{13}ON$: C, 62.57; H, 11.37; N, 12.16. Found: C, 62.70; H, 11.28; N, 11.85.

2,3-Dimethyloxazolidine was also prepared in a similar manner: $n^{25}D$ 1.4200, d^{25}_4 0.9001. *Anal.* Calcd. for $C_5H_{11}ON$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.38; H, 10.74; N, 13.77.

2,4,4-Trimethyloxazolidine.—This was prepared by both methods A and B: $n^{25}D$ 1.4240, d^{25}_4 0.8904. *Anal.* Calcd. for $C_6H_{13}ON$: C, 62.57; H, 11.37; N, 12.16. Found: C, 62.82; H, 11.49; N, 12.04.

The infrared spectrum of the product was determined and showed that this material was identical with 2,4,4-trimethyloxazolidine, prepared otherwise by the reaction of acetylene with 2-amino-2-methylpropanol-1.[9] There was no absorption in the double bond region, indicating first, that there was less than 0.5% of a vinyl ether present and, second, that this compound must exist entirely in the cyclic form and not as a Schiff base. This lack of any appreciable amount of a Schiff base tautomer is probably the reason why this compound is so much more stable than the other oxazolidines (I), with R = H, which we have prepared, and which all show evidence of existing at least partially in the Schiff base form.[9] The lack of vinyl ether is particularly signifi-

(7) W. Reppe, U. S. Patent 1,959,927 (May 22, 1934); A. E. Favorskii and M. F. Shostakovskii, *J. Gen. Chem.* (*U.S.S.R.*), **13**, 1 (1943); *C. A.*, **38**, 330 (1944).

(8) *Cf.* A. M. Paquin, *Ber.*, **82**, 316 (1949).

(9) W. H. Watanabe and L. E. Conlon, THIS JOURNAL, **79**, 2825 (1957).

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cant, since both the oxazolidine and the isomeric vinyl ether have identical boiling points[9] and no fractionation could have occurred by distillation if both these compounds had been formed in the reaction. Moreover, if the reaction proceeds in two steps, then the presumed first step (vinyl transetherification) would not be appreciably hindered sterically, whereas the presumed second step (cyclization) should be seriously hindered. Thus, this example is a particularly favorable case for isolation of the vinyl ether if any had formed.

2-Methyltetrahydro-1,3-oxazine was prepared by both methods A and B: $n^{25}D$ 1.4407, d^{25}_4 0.9459. *Anal.* Calcd. for $C_5H_{11}ON$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.57; H, 11.00; N, 13.59.

Preparation of 2-Methyl-3-phenyloxazolidine.—N-Phenylethanolamine (141.5 g., 1.03 moles) was dissolved in 86.3 g. (1.20 moles) of ethyl vinyl ether and 1 g. of mercuric acetate added to this solution. The solution warmed spontaneously and began to boil before all the mercuric salt had gone into solution. It was immediately placed under a reflux condenser and heated under reflux for 2 hr. During this period, the reaction temperature rose from 45 to 78°. The reaction mixture was then poured into a beaker and chilled in ice, whereupon it set to a crystalline mass. The solid was removed by filtration and recrystallized from ethyl alcohol, giving 143.8 g. of 2-methyl-3-phenyloxazolidine, m.p. 58–59°, a yield of 85.5%. This product was recrystallized again from 30–60° petroleum ether, resulting in 107.5 g. of pure product (64% yield), m.p. 58.5–59°. A final recrystallization from 85–100° petroleum ether gave an analytical sample, m.p. 59–59.5° (lit.[20] 60.5–61°).

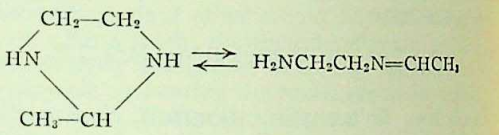
Anal. Calcd. for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.62; H, 7.89; N, 8.54.

Preparation of 2-Methylimidazolidine.—Ethylenediamine (65.5 g., 1.09 moles) was dissolved in 133.5 g. (1.85 moles) of ethyl vinyl ether and 1 g. of mercuric benzoate added to this solution. The mercuric salt dissolved only partially even with vigorous shaking; there was no immediate exotherm. The mixture was then heated under reflux for 8 hr. During this period the pot temperature rose from 42 to 51°, and almost all of the mercuric salt went into solution, accompanied by the formation of some globules of mercury. The solution was cooled and left overnight at room temperature. On the following day another 1 g. of mercuric benzoate was added. This time the mercuric salt went rapidly and completely into solution. Reflux was resumed, and over a 1-hr. period the pot temperature rose from 51.5 to 60°. The solution was then cooled and flash-distilled at about 0.5 mm. pressure into a receiver cooled with Dry Ice–acetone. The first cut of this flash-distillation, 66.9 g., was obtained without heating the distilling flask; this cut was terminated when a solid material started to plug the outlet of the take-off tube. A wide-bore outlet was then utilized, and a second cut was taken by heating the distilling flask to a maximum liquid temperature of 73°. This second fraction, 107.7 g., was partly solid at room temperature, but the solid soon dissolved in the liquid portion. The residue weighed 18.1 g.

The second fraction was overlaid with about twice its volume of 100–140° petroleum ether, well shaken, and chilled in Dry Ice–acetone to induce crystallization. The crystals were filtered under nitrogen from the resultant two-phase liquid mixture. The filtrate was again chilled, and the solid which formed again filtered off under nitrogen. This procedure was repeated about six times until no further crystallization occurred. The combined solid product was dried under vacuum at room temperature. The yield of this once-crystallized product, m.p. 46–49°, was 38.4 g., 41% based on the diamine. This material was recrystallized out of 30–60° petroleum ether to obtain an analytical sample, which was a white, very volatile, hygroscopic solid, m.p. 47.5–48.5°. Potentiometric titration of this sample with standard 0.1 *N* HCl gave replicate values of 43.39 and 42.91 for the neutralization equivalent (theor. for 2-methylimidazolidine, 43.07). Elementary analysis was found to be very difficult because of the hygroscopicity and volatility of the material, and an analysis for nitrogen could not therefore be obtained.

Anal. Calcd. for $C_4H_{10}N_2$: C, 55.77; H, 11.70; N, 32.53. Found: C, 56.36; H, 11.57.

The infrared spectrum of this compound showed bands at 1670 cm.$^{-1}$ attributable to —C=N— stretching, and at 1595 cm.$^{-1}$, probably due to $-NH_2$ deformation. These results are consistent with the Schiff base form of the imidazolidine



Preparation of 2-Methyl-1,3-diphenylimidazolidine.—N,N′-Diphenylethylenediamine (100.9 g., 0.48 mole) was shaken vigorously with 72.0 g. (1.0 mole) of ethyl vinyl ether, but only a small part of the solid diamine dissolved. One gram of mercuric benzoate was dissolved in this mixture, and a strong exotherm then resulted. The mixture was immediately placed under reflux and heating applied when the initial exotherm subsided. After 21 min. of reflux almost all of the solid had gone into solution and the liquid temperature had risen from 35.5 to 49°. Almost immediately thereafter crystallization suddenly occurred, filling the flask with solid and lowering the liquid temperature to 42°. After a further 40 min. of reflux, the mixture was cooled and the solid product dried under vacuum. Part of this solid was recrystallized from methanol, m.p. 90–91.5°, and the remainder from 85–100° petroleum ether, m.p. 91.5–95°. The total yield of recrystallized product was 93.4 g., 82% based on the diamine. This product was further recrystallized out of methanol, giving 75 g. (66% yield) of pure 2-methyl-1,3-diphenylimidazolidine, m.p. 92–93.5° (lit.[20] 98–100°), ebulliometric molecular weight, 226 (theor. 238).

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.40; H, 7.47; N, 11.76.

PHILADELPHIA 37, PENNA.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Hypotensive Agents. V. 4-(2′-Aminoethyl)-piperidine Derivatives

BY ARTHUR P. PHILLIPS

RECEIVED DECEMBER 19, 1956

A series of 4-(2′-aminoethyl)-piperidines has been prepared for testing for hypotensive ganglionic blocking activity. The most active compound in the series was comparable in activity to hexamethonium.

Following the discovery[1,2] of ganglionic blocking activity in 1-methyl-3-(4′-dimethylaminobutyl)-piperidine (I) and its bis-quaternary ammonium salts, several series of compounds[3] modelled after I have been prepared and tested for this kind of activity. The present paper reports the preparation and properties of another series of compounds structurally related to I. These are some 4-(2′-aminoethyl)-piperidine derivatives which can be represented by the general formula II. The products were made by the sequence of reactions shown

(1) S. Norton and A. P. Phillips, *Nature*, **172**, 867 (1953).
(2) A. P. Phillips, THIS JOURNAL, **76**, 2211 (1954).
(3) Paper IV of this series, A. P. Phillips, *ibid.*, 78, [illegible] (1956).

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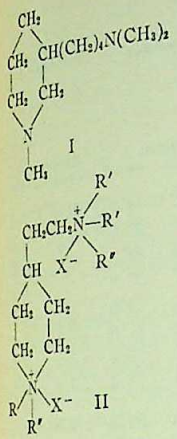

I

II

R = H or CH_3; N(R′)(R′) = $(CH_3)_2N$, $(C_4H_9)_2N$, pyrrolidine, piperidine or morpholine; R″X = HCl, CH_3I or C_2H_5I, etc.

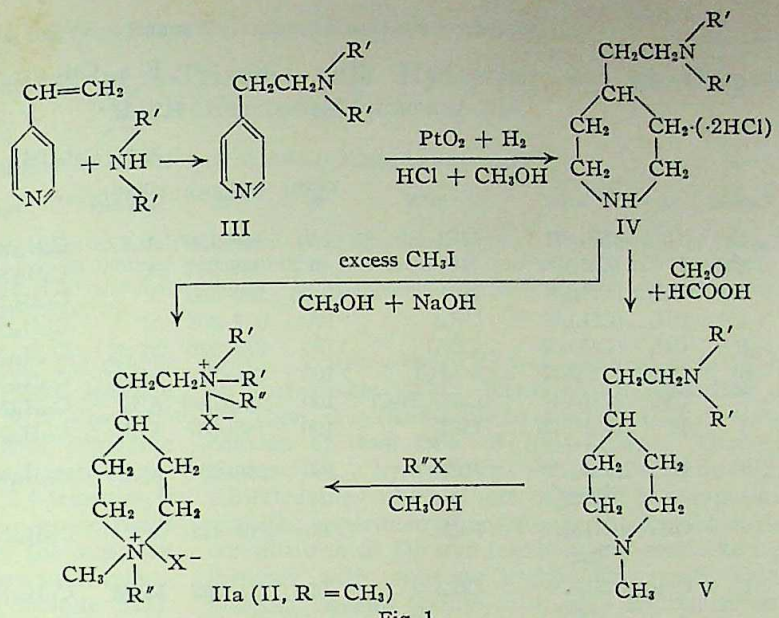

Fig. 1.

The reactions shown in Fig. 1 were carried through on the products obtained by the addition of dimethylamine, diethylamine, pyrrolidine, piperidine and morpholine to 4-vinylpyridine. The addition of amines to 4-vinylpyridine has been described in some detail earlier[4] and needs no further comment here.

The dihydrochlorides of the 4-(2′-aminoethyl)-pyridines (III) were hydrogenated in methanol solution using Adams catalyst, at about three to four atmospheres of hydrogen pressure and room temperature. Hydrogen uptake was usually slow, but high yields of the 4-(2′-aminoethyl)-piperidines (IV) were obtained.

Methylation of the 4-(2′-aminoethyl)-piperidines (IV) by the well-known Eschweiler[5]–Clarke[6] procedure gave the N-methyl-bis-tertiary amines V. The latter, V, were quaternized by refluxing with excess of the appropriate alkyl halide in methanol solution and gave the products IIa. When the products IIa were to be quaternized with methyl iodide, they could be obtained by an alternative route, the direct methylation of the compounds IV using excess methyl iodide in methanol in the presence of at least one equivalent of alkali.

The physical and analytical data for all the compounds are listed in Table I.

Pharmacology.—These 4-(2′-aminoethyl)-piperidines resemble the 3-(4′-dimethylaminobutyl)-piperidines (such as I) structurally. The new compounds differ in the point of attachment and the length of the side chain on the piperidine ring. With an inter-nitrogen chain of five carbons they are pentamethonium rather than hexamethonium analogs. Both the bis-tertiary amines and the derived bis-quaternary salts showed ganglionic blocking activity in cats; usually, however, the hypotensive effects were of a low order and of brief duration. Only the diethiodide and dimethiodide of the 4-(2′-pyrrolidinoethyl)-piperidine (compounds 12 and 11 of Table I) approached I and hexamethonium in potency. Thus the diethiodide (compound 12) at 2 mg./kg. gave a 50% lowering of blood pressure lasting for 1 hr.

The best of the bis-tertiary amines, 1-methyl-4-(2′-pyrrolidinoethyl)-piperidine (compound 10, Table I) gave a comparable blood pressure lowering but of shorter duration only at 8 mg./kg.

A more detailed report on the pharmacology of these compounds will appear elsewhere.

Acknowledgment.—The author is indebted to S. W. Blackman for the microanalyses included.

Experimental

Typical procedures for each of the general types of reactions are described below.

The addition of amines to 4-vinylpyridine proceeded very well in most cases and the details of these reactions have been described fully elsewhere.[4]

Catalytic Hydrogenation of 4-(2′-Pyrrolidinoethyl)-pyridine Dihydrochloride (Compound 9, Table I).—A solution containing 5 g. (0.02 mole) of 4-(2′-pyrrolidinoethyl)-pyridine dihydrochloride (m.p. 214–216°) in 150 cc. of methanol and 0.2 g. of Adams catalyst was shaken in a Burgess–Parr type machine at 3–4 atmospheres of hydrogen pressure and room temperature. The theoretical amount of hydrogen (0.06 mole) was absorbed over 5 hr. After removal of the platinum the filtrate was concentrated by evaporation and the product was crystallized by the addition of ethyl acetate. After several recrystallizations from ethanol–ethyl acetate mixtures, 5 g. (>95%) of white crystalline product was obtained, m.p. 266–267°.

Eschweiler–Clarke Methylation of 4-(2′-Dimethylaminoethyl)-piperidine (Compound 3, Table I).—After liberation of the oily base from its dihydrochloride, 8 g. (0.05 mole) of 4-(2′-dimethylaminoethyl)-piperidine was carefully neutralized by and dissolved in 10 cc. of 98–100% formic acid with cooling. About 10 cc. of 35–37% formalin was added at once and the mixture was heated for 2 hr. on a steam-bath. Another 5 cc. each of formic acid and formaldehyde solution was added and heating was continued for 2 hr. longer. An excess (15 cc.) of concentrated hydrochloric acid was added and the solution was evaporated to dryness. The residual solid was purified by several recrystallizations from hot ethanol and then gave 10 g. (85%) of white crystals, m.p. 299–300°. This was the dihydrochloride of 1-methyl-4-(2′-dimethylaminoethyl)-piperidine.

(4) A. P. Phillips, This Journal, **78**, 4441 (1956).
(5) W. Eschweiler, *Ber.*, **38**, 880 (1905).
(6) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, This Journal, **55**, 4571 (1933).

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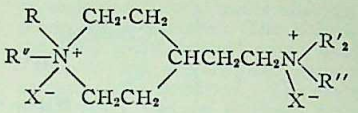
TABLE I

4-(2′-AMINOETHYL)-PIPERIDINES



Compd.	R	R′₂N	R″X	Yield, %	M.p., °C.	Crystn. solvent[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1[b]	H	CH_3NH	HCl	100	185-186	A·Æ	$C_8H_{20}N_2Cl_2$	44.6	44.2	9.4	9.1
2[b]	H	$(CH_3)_2N$	HCl	95	240–241	A	$C_9H_{22}N_2Cl_2$	47.1	47.0	9.7	9.6
3[c]	CH_3	$(CH_3)_2N$	HCl	85–90	299–300	A	$C_{10}H_{24}N_2Cl_2$	49.4	49.8	10.0	10.3
4[d,e]	CH_3	$(CH_3)_2N$	CH_3I	100	307–308	M	$C_{12}H_{28}N_2I_2$	31.7	32.0	6.2	5.9
5[c]	CH_3	$(CH_3)_2N$	C_2H_5I	100	275–276	M·Æ	$C_{14}H_{32}N_2I_2$	34.8	35.0	6.7	6.7
6[c]	CH_3	$(CH_3)_2N$	nC_3H_7I	100	214–215	M·Æ	$C_{16}H_{36}N_2I_2$	37.6	37.6	7.1	7.4
7[a]	CH_3	$(CH_3)_2N$	$C_6H_5CH_2Cl$	100	Hygr. oil	A·E	$C_{24}H_{36}N_2Cl_2\cdot 4H_2O$	58.1	59.0	8.9	8.7
8[b]	H	$(C_2H_5)_2N$	HCl	100	186–187	A·Æ	$C_{11}H_{26}N_2Cl_2$	51.4	51.4	10.2	10.2
9[b]	H	$(CH_2)_4N$[f]	HCl	100	266–267	A·Æ	$C_{11}H_{24}N_2Cl_2$	51.8	51.5	9.5	9.1
10[c]	CH_3	$(CH_2)_4N$[f]	HCl	95	310–312	A	$C_{12}H_{26}N_2Cl_2$	53.5	53.8	9.7	9.8
11[d]	CH_3	$(CH_2)_4N$[f]	CH_3I	95	291–292	M·Æ	$C_{14}H_{30}N_2I_2$	35.0	35.0	6.3	6.2
12[e]	CH_3	$(CH_2)_4N$[f]	C_2H_5I	100	264–265	M·E	$C_{16}H_{34}N_2I_2$	37.8	37.6	6.8	7.0
13[b]	H	$(CH_2)_5N$[g]	HCl	95	301-302	A	$C_{12}H_{26}N_2Cl_2$	53.5	53.5	9.7	9.7
14[c]	CH_3	$(CH_2)_5N$[g]	HCl	90	>334	M·Æ	$C_{13}H_{28}N_2Cl_2$	55.1	55.4	10.0	9.7
15[d]	CH_3	$(CH_2)_6N$[g]	CH_3I	100	290–291	M	$C_{15}H_{32}N_2I_2$	36.4	36.4	6.5	6.3
16[b]	H	$O(C_2H_4)_2N$[h]	HCl	80	290–293	M·A	$C_{11}H_{24}N_2OCl_2$	48.7	48.6	8.9	8.5
17[c]	CH_3	$O(C_2H_4)_2N$[h]	HCl	100	>330	M	$C_{12}H_{26}N_2OCl_2$	50.6	50.7	9.2	8.8
18[d]	CH_3	$O(C_2H_4)_2N$[h]	CH_3I	80	298–300	Aq·Ac	$C_{14}H_{30}N_2OI_2$	33.9	33.9	6.1	6.1

[a] A = ethanol; Ac = acetone; Aq = water; Æ = ethyl acetate; E = ether; M = methanol. [b] Made by catalytic hydrogenation of the 4-(2′-aminoethyl)-pyridine dihydrochloride. [c] From the secondary amine with formic acid and formalin. [d] From the secondary amine, excess methyl iodide and sodium hydroxide. [e] From the ditertiary amine and alkyl halide. [f] $(CH_2)_4N$ is the pyrrolidino group. [g] $(CH_2)_5N$ is the piperidino group. [h] $O(C_2H_4)_2N$ is the morpholino group.

1-Methyl-4-(2′-dimethylaminoethyl)-piperidine Bis-*n*-propiodide (Compound 6, Table I).—The oily base was liberated from the dihydrochloride described above. A solution of 1.7 g. (0.01 mole) of this base was refluxed with 5 cc. of *n*-propyl iodide in 50 cc. of methanol for 18 hr. (overnight). Evaporation of part of the methanol and addition of acetone gave 5.1 g. (100%) of white crystalline product. After recrystallization from ethanol the purified product melted at 214–215°.

1-Methyl-4-(2′-piperidinoethyl)-piperidine Bis-methiodide (Compound 15, Table I). By Alkylation of the Secondary Amine with Excess Methyl Iodide.—A solution of 2 g. (0.01 mole) of the base, 4-(2′-piperidinoethyl)-piperidine, in 50 cc. of methanol with 5 cc. of methyl iodide was refluxed for 2 hr. Another 5 cc. of methyl iodide and a solution of 1 g. of sodium hydroxide in 50 cc. of methanol were added and refluxing was continued for 3 hr. The reaction mixture was evaporated to dryness *in vacuo* and sodium iodide was removed by washing the solid residue with several 25-cc. portions of acetone. This procedure left 5 g. (100%) of white crystals. These were purified by crystallization from methanol and melted at 290–291°.

TUCKAHOE 7, N. Y.

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June 5, 1957

[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Triazines. XIX. Some Reactions of s-Triazine with Hydrazine and its Organic Derivatives

BY CHRISTOPH GRUNDMANN AND ALFRED KREUTZBERGER[1,2]

RECEIVED JANUARY 7, 1957

s-Triazine (I) is cleaved by anhydrous hydrazine to 1,2-diformylhydrazine dihydrazone (IV). The reactions of IV with carbonyl compounds and acetic anhydride, and its thermal decomposition to 4-amino-1,2,4-triazole and 1,2,4-triazole are described. I and aromatic hydrazines yield N,N′-diaryl-formazans. Semicarbazide, thio-semicarbazide and aminoguanidine lead to the corresponding 1,2,4-triazole derivatives.

We recently reported that *s*-triazine (I) reacts easily with primary amines with complete cleavage of the ring forming ammonia and N,N′-disubstituted formamidines.[3a] The reaction of *s*-triazine with the hydrohalides of hydrazine and monoalkyl- or monoaryl hydrazines leads to 1,2,4-triazoles.[3b] It was anticipated that free hydrazine would react like primary amines. In this case, the reaction product should be the as yet unknown formhydrazide hydrazone (II) or formamide hydrazone (III). In fact, a mixture of *s*-triazine and anhydrous hydrazine reacts even at room temperature. The reaction becomes very vigorous on gentle heating and consequently is better performed in an inert diluent. The product, m.p. 122–123° dec., is formed in good yield and has been shown to be identical with a compound obtained long ago from hydrocyanic acid and hydrazine,[4] and not the expected II or III. The earlier procedure gave only very small yields, our reaction makes this interesting compound readily accessible. On the basis of their degradation experiments, Müller and Herrdegen assigned to this product the formula 1,2-diformylhydrazine dihydrazone (IV). Their findings, however, would also be compatible with the structures II and III. Since IV is, by elementary analysis, almost indistinguishable from III and since molecular weight determinations gave somewhat erratic results because of the instability of this compound, much effort was spent on proving its constitution. With picric acid under various conditions, only hydrazine picrate was isolated. Ethereal hydrogen chloride formed a dihydrochloride which was stable on storage in contrast to the parent compound IV. In water, however, the dihydrochloride was easily hydrolyzed and underwent extensive decomposition. Benzoylation of IV yielded only N,N′-dibenzoylhydrazine. The compound IV condensed readily with carbonyl compounds. The dibenzal derivative V already has been described,[4] but is not very suitable for the characterization of IV because of its instability. The product from acetone appears to be the best. The 1,2-diformylhydrazine bis-(isopropylidenehydrazone) (VI) is a fairly stable and recrystallizable compound which, however, is difficult to obtain analytically pure as is the dibenzal derivative. Contrary to V, VI was obtained from IV in an appreciable yield. Based on the formation of VI, then, it is reasonable to conclude that IV must contain at least two $-N-NH_2$ groups. This excludes IVa, a hydrazinium salt of 1,2-dihydro-1,2,-4,5-tetrazine,[5] which otherwise would be compatible with the experimental findings.[6] Final proof of the constitution of IV was found in the complete hydrolysis with aqueous hydrochloric acid which yielded, besides formic acid, only hydrazine and no ammonia. This result definitely excludes formula III for the primary reaction product from hydrazine and *s*-triazine.

The formation of 1,2-diformylhydrazine dihydrazone (IV) from *s*-triazine and hydrazine could be explained by the assumption that, at first, in a normal cleavage of the *s*-triazine ring, three moles of formhydrazide hydrazone (II) are formed

$$C_3H_3N_3\,(I) + 6N_2H_4 = 3C_6H_2H_4\,(II) + 3NH_3$$
$$2CH_6H_4\,(II) = C_2H_8N_6\,(IV) + N_2H_4$$

and then two moles of the unstable intermediate II condense with loss of hydrazine to IV.

The 1,2-diformylhydrazine dihydrazone (IV) is light sensitive , turning pink, especially in the presence of air. This color is due apparently to the formation of 1,2,4,5-tetrazine (VIII), since the coloring matter is readily soluble in ether and volatile with the vapors of this solvent.[5,7] The first stage of this light-induced decomposition of IV is presumably the formation of 1,2-dihydro-1,2,4,5-tetrazine (VII)—or an isomer thereof—which then suffers dehydrogenation either spontaneously or by air oxidation. That, in fact, VII can easily be formed from IV is demonstrated by the reaction of IV with acetic anhydride. This leads to a product to which we have assigned the structure 1,2-diacetyl-1,2-dihydro-1,2,4,5-tetrazine (IX). The other possible constitution, 4-diacetylamino-1,2,4-triazole (X), is excluded by the synthesis of X from 4-amino-1,2,4-triazole (XII) and acetic anhydride, which yields a compound quite different from IX. Furthermore, IX is hydrolyzed readily by methanolic potassium hydroxide and the resulting intense red-colored solution presents, by its reactions, strong evidence for the presence of 1,2,4,5-tetrazine. 1,2,4,5-Tetrazine has not yet been isolated from the light-induced degradation products of IV, however. This failure stems partly from the in-

(1) This article is based on work performed under project 116-B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corporation, New York, N. Y.

(2) Preceding communication: Ch. Grundmann and E. Kober, THIS JOURNAL, **79**, 944 (1957).

(3) (a) Ch. Grundmann and R. Rätz, *J. Org. Chem.*, **21**, 1037 (1956). (b) Ch. Grundmann and A. Kreutzberger, *ibid.*, **77**, 6559 (1955); [2] **102**, 113

(4) E. Müller and L. Herrdegen, *J. prakt. Chem.*, (1921).

(5) 1,2-Dihydro-1,2,4,5-tetrazine is weakly acidic, Th. Curtius, A. Darapsky and E. Müller, *Ber.*, **40**, 837 (1907).

(6) Müller and Herrdegen, ref. 4, have already discussed this possibility.

(7) Th. Curtius, A. Darapsky and E. Müller, *Ber.*, **40**, 84 (1907); D. Wood, Jr., and F. W. Bergstrom, THIS JOURNAL, **55**, 3648 (1933).

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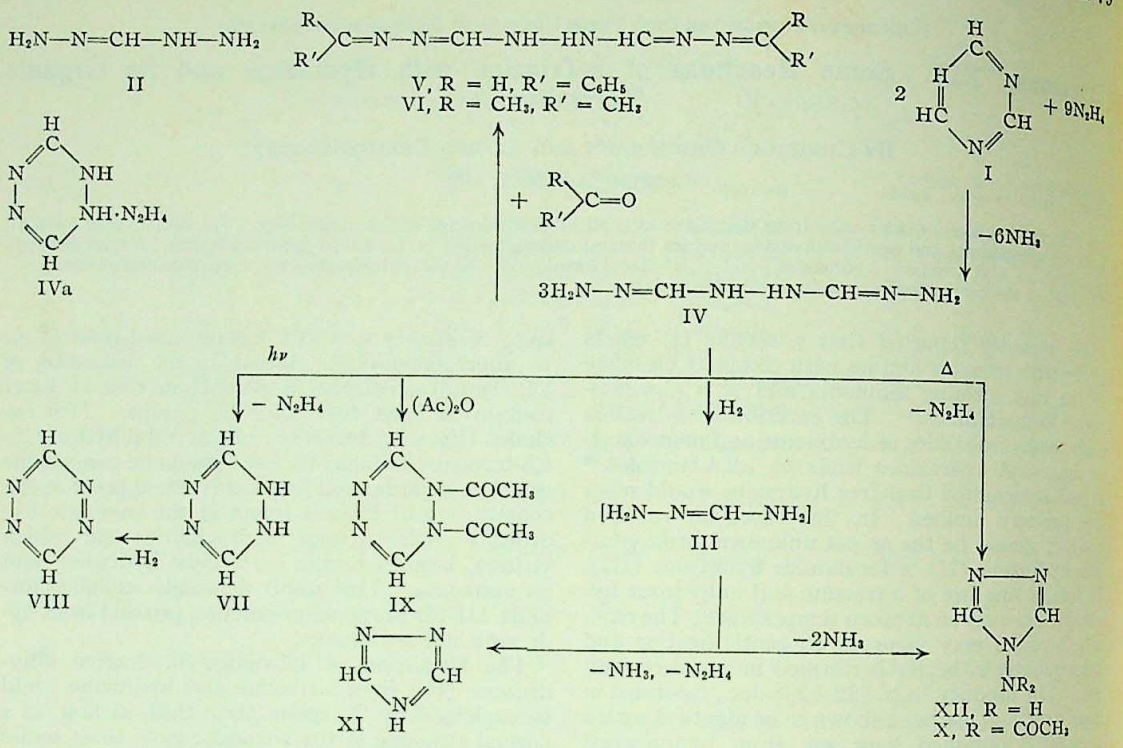

herent difficulty in isolating small quantities of such a volatile and sensitive substance as VIII, and also from the presence of another route of spontaneous decomposition of IV.

This second route of decomposition proceeds even in the dark and in a vacuum. It converts the hydrazoformaldehyde dihydrazone within several days at room temperature into a brownish, viscous oil. By fractional vacuum sublimation, we were able to isolate hydrazine, 1,2,4-triazole (XI, 38%), and 4-amino-1,2,4-triazole (XII, 15%) from this oil. The latter compound already has been noticed by Müller and Herrdegen among the thermal degradation products of IV.

While the formation of XII is easily understandable as the result of a ring closure of IV with the loss of one molecule of hydrazine, an explanation of the formation of XI seems much more difficult because it demands a reductive step in one or another phase of the self-decomposition of IV. At first, we made certain that 1,2,4-triazole is not an artificial product resulting from our mode of isolating the reaction product. 4-Amino-1,2,4-triazole is not converted into 1,2,4-triazole under the conditions of our experiments, either thermally or by the reductive action of hydrazine. The assumption that IV itself is reduced to formamide hydrazone (III), either by hydrazine, always present in the decomposing mixture, or by an internal oxidation–reduction process,[8] seems to be the only way to explain our results. That such a process may occur during the spontaneous decomposition of IV is indicated by a constant evolution of ammonia from the decomposing mixture. This ammonia can only stem from the reaction $2N_2H_4 = 2NH_3 + N_2 + H_2$, which yields the necessary reductive equivalent for the conversion of IV into III. Two molecules of this hypothetical intermediate III could then decompose to 1,2,4-triazole (XI) by loss of one molecule of ammonia and one molecule of hydrazine. By loss of two molecules of ammonia III could also yield 4-amino-1,2,4-triazole (XII).

Substituted hydrazines, as the free bases, react quite differently from the parent compound. In the first step aromatic hydrazines, like phenylhydrazine, apparently form diaryl-formhydrazide hydrazones (XV), which are not isolable but undergo spontaneous oxidation, either by air or by excess arylhydrazine, to the stable, intensively colored N,N′-diphenylformazans (phenylazo-formaldehyde phenylhydrazones). This reaction was successfully carried out with phenylhydrazine, *p*-bromophenylhydrazine and *p*-nitrophenylhydrazine, to yield the formazans XVIa, XVIb and XVIc. While the cleavage of *s*-triazines by primary amines is restricted to the parent compound, aromatic hydrazines cleave besides the parent compound I also trialkyl- and triaryl-*s*-triazines in the same way. From 2,4,6-trimethyl-*s*-triazine (Ia) we obtained the N,N′-diphenyl-C-methyl-formazan (XVId) and from 2,4,6-triphenyl-*s*-triazine (Ib) the N,N′-diphenyl-C-phenylformazan (XVIe).

With disubstituted hydrazines, less clear results were obtained. *asym*-Dimethylhydrazine reacts with *s*-triazine in a manner strictly analogous to a primary amine, yielding in this case the 1-formyl-2,2-dimethylhydrazine 2,2-dimethylhydrazone (XIII), the parent compound of which II is not known. With 1-methyl-1-phenylhydrazine, how-

(8) Reduction of hydrazo compounds by hydrazine derivatives to the corresponding amino compounds has been observed on different occasions, *cf.* R. Walther, *J. prakt. Chem.*, [2] **52**, 141 (1895); H. Beyer and G. Wolter, *Chem. Ber.*, **85**, 1075 (1952).

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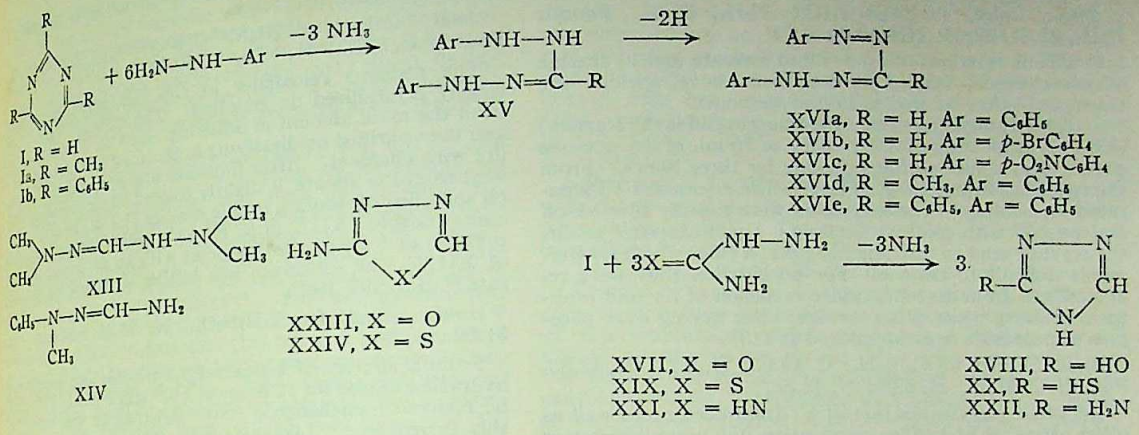

ever, the reaction proceeds only half-way. Without elimination of ammonia, but with breakdown of the *s*-triazine ring the N^3-methylphenylformamidrazone (XIV) is formed as the sole product. Even with a large excess of 1-methyl-1-phenylhydrazine and elevated temperatures, it was impossible to force the reaction to the tetra-substituted hydrazine derivative analogous to XIII. No explanation can be given at present for this striking difference in reactivity between the *asym*-dimethyl- and the 1-methyl-1-phenylhydrazine. As expected, symmetrically disubstituted hydrazines which do not contain an NH_2 group do not react with *s*-triazine under these conditions.

Among other hydrazine derivatives we have investigated the reaction of semicarbazide (XVII), thiosemicarbazide (XIX) and aminoguanidine (XXI) with *s*-triazine. In all cases these derivatives react as described previously for *o*-substituted diamines,[3a] forming, with cleavage of the triazine ring and liberation of ammonia, the corresponding 3-substituted-1,2,4-triazoles, 3-hydroxy-1,2,4-triazole (XVIII), 3-mercapto-1,2,4-triazole (XX) and 3-amino-1,2,4-triazole (XXII). It is interesting to note that in the case of XVII and XIX no formation of other possible products of ring closure, namely, 2-amino-1,3,4-oxadiazole (XXIII) and 2-amino-1,3,4-thiadiazole (XXIV) could be detected.[9]

Acknowledgment.—We are very much indebted to the Olin Mathieson Chemical Corporation for their generous support of this work. Furthermore, we wish to thank Mr. A. C. Schulz for his valuable assistance in the experimental work.

Experimental[10]

1,2-Diformylhydrazine Dihydrazone (IV).—With exclusion of direct light 8 g. of anhydrous hydrazine was added dropwise to a solution of 4.5 g. of *s*-triazine in 50 ml. of anhydrous ether. After standing overnight at room temperature, the almost colorless solid was collected under nitrogen and washed with small amounts of ice-cold anhydrous ether and then dried in a vacuum desiccator in the dark for two hours over phosphorus pentoxide; yield 80%. This crude product was best purified by digesting the finely powdered material with 5 ml. of cold absolute alcohol for 30 minutes followed by rapid filtration under nitrogen. A repetition of this procedure yielded 4.8 g. of pure IV as a micro-crystalline yellowish powder melting at 122–123° dec. No solvent could be found for IV in which this compound is soluble without decomposition.

Anal. Calcd. for $C_2H_8N_6$: C, 20.68; H, 6.95; N, 72.37. Found: C, 21.00; H, 7.09; N, 72.20.

Within a few seconds of exposure to the atmosphere IV turned pink, later red, but such samples kept *in vacuo* over concentrated sulfuric acid soon regained their original color (evaporation of the formed 1,2,4,5-tetrazine). The coloring matter could also be extracted with ether. After evaporation of such extracts, practically nothing remained, the red substance being entrained with the ether vapors.

The dihydrochloride of 1,2-diformylhydrazine dihydrazone was formed from a suspension of 5.8 g. of IV in 100 ml. of dry carbon tetrachloride by passing through a stream of dry hydrogen chloride for 24 hours, followed by vacuum filtration of the suspension. The filter cake was washed with dry carbon tetrachloride and dried on a porous plate in a desiccator over calcium chloride and paraffin chips for three days; m.p. 74–76° dec. All the above operations should be carried out with exclusion of moisture. The hydrochloride is extremely hygroscopic and is easily decomposed by water, the only isolable product in such cases being hydrazine hydrochloride.

Anal. Calcd. for $C_2H_8N_6 \cdot 2HCl$: C, 12.71; H, 5.33; Cl, 37.51. Found: C, 12.72; H, 6.12; Cl, 37.00.

The dihydrochloride apparently is stable for an unlimited time sealed in a glass tube.

With picric acid in aqueous solution or in alcoholic suspension, IV yielded a yellow crystalline picrate which was identified by analysis and mixed melting point (187–188°) with **hydrazine picrate.**[11]

Anal. Calcd. for $C_6H_7N_9O_7$: N, 26.82. Found: N, 26.62, 26.40.

Benzoylation of IV was carried out with benzoyl chloride in anhydrous quinoline and also by Pinner's procedure for the benzoylation of amidrazones,[12] but the only isolable product proved to be **N,N′-dibenzoylhydrazine,** according to analysis and a mixed melting point (245–246°) with an authentic sample.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.04; N, 11.66. Found: C, 70.01; H, 5.07; N, 11.71.

Acid Hydrolysis of IV.—Upon addition of 15 ml. of concentrated hydrochloric acid to 1.5 g. of freshly prepared pure IV the mixture became hot and foamed. When the initial reaction had subsided, the solution was evaporated on the steam-bath to dryness. The residue was dissolved in 30 ml. of water and again evaporated to dryness. This procedure was repeated twice more in order to remove all formic acid. The remaining white crystalline salt was dried in a desiccator over calcium chloride and analyzed for hy-

(9) Compare in this respect the formation of benzoxazole and benzthiazole from *s*-triazine and *o*-aminophenol, resp., *o*-aminothiophenol, Ch. Grundmann and A. Kreutzberger.[3a]

(10) All melting points are corrected, microanalyses are from Galbraith Laboratories, Knoxville, Tenn., and Spang Microanalytical Laboratory, Ann Arbor, Michigan.

(11) R. von Rothenburg, *Ber.*, **27**, 690 (1894).

(12) A. Pinner, *Ber.*, **27**, 984 (1894).

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drazine and ammonia by the method of the Mathieson Chemical Corporation.[13]

Anal. Calcd. for $N_2H_4 \cdot 2HCl$: N_2H_4, 30.53. Found: N_2H_4, 32.34, 32.69; NH_3, 0.00, 0.00.

Synthetic mixtures of ammonium formate and hydrazine dihydrochloride, treated as described above, yielded the calculated values for hydrazine and ammonia.

1,2-Diformylhydrazine Bis-(isopropylidenehydrazone) (VI).—A suspension of 3.2 g. of IV in 70 ml. of dry acetone gave a clear solution after refluxing for three hours. From the reddish solution 2.4 g. of large white crystals of VI separated on cooling. These crystals were rapidly filtered off and washed with cold dry acetone. Upon exposure to air, the crystals tend to turn slightly pink, a color which is afterwards difficult to remove. For purification they were recrystallized from acetone, under exclusion of air and moisture, yielding white prisms which, after drying over phosphorus pentoxide *in vacuo*, melted at 113°.

Anal. Calcd. for $C_8H_{16}N_6$: C, 48.95; H, 8.22; N, 42.83. Found: C, 47.78; H, 8.07; N, 42.32.

Repeated recrystallization of VI from acetone as well as other attempts at further purification did not yield better analytical values.

Condensation of IV was also attempted with benzaldehyde,[14] anisaldehyde, *o*-nitrobenzaldehyde, methyl ethyl ketone and acetophenone, but this resulted only in the isolation of the corresponding azines, while diethyl ketone and phenylacetone yielded only resins, and benzophenone and phenanthrenequinone did not react at all.

1,2-Diacetyl-1,2-dihydro-1,2,4,5-tetrazine (IX).—An amount of 10.5 g. of IV was added portionwise to 40 ml. of acetic anhydride. Dissolution occurred immediately with evolution of heat, while the color of the solution changed to orange. The reaction mixture was heated for two hours on the steam-bath and then the excess acetic anhydride distilled off *in vacuo*. The distillate was colored red by a volatile by-product, probably 1,2,4,5-tetrazine. In the distillation flask there remained a yellowish transparent sirup which slowly crystallized upon standing. The crude product was freed from adhering resinous material by dissolving in 17 ml. of hot acetone and decolorizing with charcoal. After cooling and filtration, 3.9 g. of a yellowish micro-crystalline substance was obtained. Upon repeated vacuum sublimation of this crude material, pure IX was obtained as faintly yellowish needles melting at 149–150°.

Anal. Calcd. for $C_6H_8N_4O_2$: C, 42.86; H, 4.80; N, 33.32; mol. wt., 168. Found: C, 42.57; H, 4.84; N, 33.07; mol. wt. (Rast), 168, 174.

IX has neither basic nor acidic properties. When a small sample was heated with an excess of 10% methanolic potassium hydroxide for a half-minute on the water-bath, the solution became intensively red. The colored matter could be extracted with ether and was volatile with the vapors of that solvent.

4-Diacetylamino-1,2,4-triazole (X).—When 10 g. of 4-amino-1,2,4-triazole (XII) was added portionwise to 100 ml. of acetic anhydride, a colorless solution resulted with evolution of heat. After heating for two hours on the steam-bath, the excess of acetic anhydride was removed by vacuum distillation. The remaining faintly brownish sirup crystallized slowly upon standing in a refrigerator for two weeks. The crude material was recrystallized with addition of charcoal from 30 ml. of boiling acetone, yielding 9.2 g. of white sturdy prisms, m.p. 129–131°.

Anal. Calcd. for $C_6H_8N_4O_2$: C, 42.86; H, 4.80; N, 33.32. Found: C, 42.75; H, 5.13; N, 33.22.

1,2,4-Triazole (XI) and 4-Amino-1,2,4-triazole (XII) from 1,2-Diformylhydrazine Dihydrazone (IV).—After 10.5 g. of IV had undergone spontaneous decomposition by storage in a vacuum desiccator in the dark for five days at room temperature, the resulting transparent brownish viscous oil was subjected to a slow fractional vacuum sublimation in a cold finger apparatus. After 12 hours at 140° bath temperature and 1 mm. 2.4 g. (38.4%) of white sturdy needles of 1,2,4-triazole (XI) was obtained. After one recrystallization from ethanol, the product was analytically pure, m.p. 120–121°. A mixed melting point with an authentic sample of XI[15] was without depression.

Anal. Calcd. for $C_2H_3N_3$: C, 34.78; H, 4.37; N, 60.85. Found: C, 35.11; H, 4.75; N, 60.80.

The resinous remainder in the distillation apparatus largely crystallized on standing. The crystals were freed from the main amount of adhering resins on a porous plate and then purified by dissolving in 30 ml. of ethanol and boiling with charcoal. After filtration and removal of the solvent from the filtrate, a slightly colored oil remained. This oil solidified on cooling to fine needles (1.1 g., 14.5%) of 4-aminotriazole (XII), m.p. 82–83°, which showed no depression in a mixed melting point with an authentic sample of XII.[16] The substance was further identified by its picrate,[17] m.p. 197–198°.

Anal. Calcd. for $C_8H_7N_7O_7$: N, 31.31. Found: N, 31.60.

From a mixture of 4-amino-1,2,4-triazole and anhydrous hydrazine heated for 12 hours at 140° and 1 mm., XII could be recovered unchanged. No 1,2,4-triazole was found in this experiment. Likewise, XII, heated alone to 180°, yielded no triazole.

1-Formyl-2,2-dimethylhydrazine 2′,2′-Dimethylhydrazone (XIII).—A mixture of *s*-triazine and *asym*-dimethylhydrazine (mole ratio 1:6) reacted slowly at room temperature under evolution of ammonia. The reaction was completed by heating for one hour at 100–115°. Subsequent vacuum distillation gave an 85% yield of XIII as a colorless mobile oil with an unpleasant odor, b.p. 73° (9 mm.); $n^{21}D$ 1.4664.

Anal. Calcd. for $C_5H_{14}N_4$: C, 46.13; H, 10.83; N, 43.04. Found: C, 45.92; H, 11.02; N, 43.02.

In an analogous manner, from 1-methyl-1-phenylhydrazine and *s*-triazine there was obtained the **N³-methylphenylformamidrazone (XIV)**. In this case, the remaining solid reaction product (72%) was purified by repeated recrystallization from ethyl acetate, yielding beige-colored needles, m.p. 103–104°.

Anal. Calcd. for $C_8H_{11}N_3$: C, 64.40; H, 7.43; N, 28.17. Found: C, 64.55; H, 7.31; N, 28.12.

No definite product other than XIV could be obtained from a mixture of an excess of *asym*-methylphenylhydrazine and *s*-triazine at temperatures up to 190°.

Phenylazoformaldehyde Phenylhydrazone (XVIa).—Phenylhydrazine, either in alcoholic solution or undiluted, reacted slowly with *s*-triazine with evolution of ammonia at room temperature. The initial reaction product, presumably XV, was a viscous oil which could not be obtained crystalline by any means, and which very soon turned red, even in an atmosphere of nitrogen. Heating the mixture decomposed the primary product into unidentifiable resinous matters, but, when the primary product was poured in thin layers on flat disks and kept there for about 14 days in contact with the air, the color increased to deep red and gradually the mass crystallized to red needles of XVIa, yield 83.6%. XVIa was purified by several recrystallizations, first from aqueous and then from absolute methanol, m.p. 119–120°.

Anal. Calcd. for $C_{13}H_{12}N_4$: C, 69.63; H, 5.39; N, 24.98. Found: C, 69.60; H, 5.33; N, 24.69.

XVIa was identified by a mixed melting point with an authentic sample[18] and by conversion into the acetyl phenylazo-formaldehyde phenylhydrazone, m.p. 189°.[19]

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.64; H, 5.30; N, 21.04. Found: C, 67.84; H, 5.39; N, 20.85.

***p*-Bromophenylazo-formaldehyde *p*-bromophenylhydrazone (XIVb)** was obtained from *s*-triazine and freshly prepared free *p*-bromophenylhydrazine in 81% yield. In this case oxidation of the intermediate hydrazidine XV occurred spontaneously during the reaction. The remaining dark red microcrystalline mass yielded XIVb after recrystallization from glacial acetic acid as small reddish brown needles, m.p. 114–115°. These were identified by mixed melting

(13) Ch. C. Clark, "Hydrazine," Mathieson Chemical Corporation, Baltimore, Md., 1953.

(14) Contrary to Müller and Herrdegen, ref. 4, we were not able to isolate their dibenzal derivative (V) by [illegible]

(15) G. Pellizari, *Gazz. chim. ital.*, **24**, [II] 222 (1894).

(16) C. F. H. Allen and A. Bell, *Org. Syntheses*, **24**, 12 (1944).

(17) S. Ruhemann and H. E. Stapleton, *J. Chem. Soc.*, **75**, 1133 (1899).

(18) H. v. Pechmann, *Ber.*, **25**, 3186 (1892).

(19) H. [illegible] and H. E. Wheelwright, *ibid.*, **25**, 3204 (1892).

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point with an authentic specimen.[20] In an analogous manner, the reaction of *s*-triazine with *p*-nitrophenylhydrazine resulted in *p*-nitrophenylazo-formaldehyde *p*-nitrophenylhydrazone (XIVc); yield 67%. After one recrystallization from benzene, reddish brown crystals, sintering at 94–95° and melting then slowly up to 104–105°, were obtained. They were identical with a sample prepared according to literature.[20]

A mixture of 2,4,6-trimethyl-*s*-triazine (Ia, 1.0 g.) and phenylhydrazine (5.3 g.) after heating for 30 minutes at 150–190° evolved ammonia and then turned deep red. From this crude product isolation of the N,N′-diphenyl-C-methylformazan, XVId (phenylazo-acetaldehyde phenylhydrazone) proceeded as described for XVIa. After recrystallization from ethanol the red, glittering needles of XVId (2.3 g.) melted at 122–123°. This melting point was not depressed upon mixing with an authentic sample.[21] With 2,4,6-triphenyl-*s*-triazine (Ib, 5.0 g.) and phenylhydrazine (10.5 g.) the reaction did not proceed to completion, even after two hours at 190°. After cooling the deep red solid obtained could be separated by extraction with boiling ethanol. The insoluble part (4.0 g.) was unreacted Ib, while the desired N,N′-diphenyl-C-methylformazan, XVIe, (phenylazo-benzaldehyde phenylhydrazone) crystallized from the concentrated alcoholic extracts (1.4 g.), m.p. 174–175°. The identity of XVIe was established by a mixed melting point with an authentic sample.[22]

(20) M. Busch and W. Wolbring, *J. prakt. Chem.*, [2] **71**, 374 (1905).
(21) E. Bamberger and W. Pemsel, *Ber.*, **36**, 87 (1903).
(22) H. v. Pechmann, *ibid.*, **27**, 1690 (1894).

3-Hydroxy-1,2,4-triazole (XVIII).—A vigorous reaction with evolution of ammonia occurred when a mixture of *s*-triazine (2.9 g.) and semicarbazide (XVII) (8 g.) in a flask was immersed into an oil-bath preheated to 100°. The mixture thereafter was heated for five minutes more at 120° and then allowed to cool. The resulting yellowish resin was extracted with hot ethanol and decolorized with charcoal. After evaporation to dryness the remaining crystalline XVIII (1.7 g., 18.7%) was recrystallized from alcohol, m.p. 234–235°.

3-Mercapto-1,2,4-triazole (XX) was obtained analogously from thio-semicarbazide (XIX) and *s*-triazine at a reaction temperature of 190°. The crude material (63.4%) was recrystallized from water, m.p. 215–216°.

3-Amino-1,2,4-triazole (XXII).—Free aminoguanidine (XXI) was prepared from the sulfate with an equivalent amount of barium hydroxide in aqueous solution, filtering off the precipitated barium sulfate and evaporating the filtrate to dryness *in vacuo*. The remaining crystalline free base is not stable. It soon turned red and must be used immediately. Its reaction with *s*-triazine at 210° as described above yielded 3-amino-1,2,4-triazole (47.4%), m.p. 158–159°, after recrystallization from ethyl acetate.

The compounds XVIII, XX and XXII were identified by mixed melting points with authentic samples prepared according to the literature.[23]

(23) O. Widmann and A. Cleve, *ibid.*, **31**, 379 (1898); M. Freund and C. Meinecke, *ibid.*, **29**, 2484 (1896); J. Thiele and W. Manchot, *Ann.*, **303**, 45 (1898).

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[CONTRIBUTION FROM THE CLAYTON FOUNDATION FOR RESEARCH, THE BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis and Biological Activity of Some 6-(Substituted)-aminopurines

BY CHARLES G. SKINNER, PETE D. GARDNER AND WILLIAM SHIVE

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Thirteen new 6-(substituted)-aminopurines have been synthesized and tested for biological activity in two assay systems. Some compounds which possessed the greatest activity in inhibition of hydra regeneration (*e.g.*, 6-(4-cyclohexylbutylaminopurine)) had relatively little effect on the rate of germination of lettuce seed (Early Curled Simpson); and those compounds (*e.g.*, 6-(α-naphthylmethyl)-aminopurine)) which possessed the greatest seed germination effect had relatively little activity in the hydra regeneration study.

The synthesis, and some biological activities, of several 6-(substituted)-purines has recently been reported from these laboratories.[1–4] In an effort to examine the relationship between biological activity and structure of the substituent group in the 6-positions of the purine nucleus, additional compounds have been prepared and are reported in this paper in conjunction with their biological activity in two assay systems.

6-(2-Furfuryl)-aminopurine (kinetin) has received considerable attention since it was reported by Miller, *et al.*,[5,6] to be a cell division factor in tobacco "wound" callus tissue. More recently, Miller has reported a stimulation of lettuce seed germination with kinetin, 6-benzylaminopurine and 6-hexylaminopurine,[7] and we have also observed such effects with various 6-(substituted)-thiopurine derivatives.[8] Liverman has observed an effect with both kinetin and several other adenine analogs in a leaf disk expansion type assay,[9] and the effects of some fifty 6-(substituted)-purines have been studied by Eakin, *et al.*, in these laboratories for their effect upon moss budding[10] and hydra tentacle regeneration.[2–4] More recently, a bacteriological assay for these purine analogs has been developed.[11] While it appears that no overall statement may be made with respect to most active compound(s) in the separate assay systems, a particular homolog is frequently the most active in more than one of the biological assays.

In the present study, differences in activity of some new 6-(substituted)aminopurines (Table I) in two different assay systems have been observed.

(1) C. G. Skinner and William Shive, THIS JOURNAL, **77**, 6692 (1955).
(2) R. G. Ham, R. E. Eakin, C. G. Skinner and W. Shive, *ibid.*, **78**, 264 (1956).
(3) C. G. Skinner, R. G. Ham, D. C. Fitzgerald, R. E. Eakin and W. Shive, *ibid.*, **78**, 5097 (1956).
(4) C. G. Skinner, R. G. Ham, D. C. Fitzgerald, R. E. Eakin and W. Shive, *J. Org. Chem.*, **21**, 1330 (1956).
(5) C. O. Miller, F. Skoog, M. H. von Saltza and F. M. Strong, THIS JOURNAL, **77**, 1392 (1955).
(6) C. O. Miller, F. Skoog, F. S. Okumura, M. H. Von Saltza and F. M. Strong, *ibid.*, **77**, 2662 (1955).
(7) C. O. Miller, *Plant Phys.*, **31**, 318 (1956).
(8) C. G. Skinner, J. R. Claybrook, F. D. Talbert and W. Shive, *Arch. Biochem. and Biophys.*, **65**, 567 (1956).
(9) R. A. Scott, Jr., and J. L. Liverman, *Plant Phys.*, **31**, 321 (1956).
(10) B. S. Gorton, C. G. Skinner and R. E. Eakin, *Arch. Biochem. and Biophys.*, **66**, 493 (1957).
(11) E. M. Lansford, Jr., C. G. Skinner and W. Shive, *Arch. Biochem. and Biophys.*, accepted for publication, 1957.

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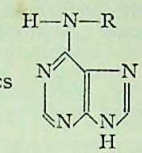
TABLE I

6-(SUBSTITUTED)-AMINOPURINES



R	Reaction conditions: Time, hr.	Temp., °C.	Solvent of recrystn.	Yield, %	M.p., °C. dec.	Empirical formula	Analyses, %: Calculated Carbon	Calculated Hydrogen	Found Carbon	Found Hydrogen
$C_6H_5(CH_2)_7-$	16	140	H_2O (H^+)	54	112–113	$C_{18}H_{23}N_5$	69.87	7.49	69.99	7.56
$C_6H_5(CH_2)_{11}-$	15	130	EtOH–H_2O	33	[a]	$C_{22}H_{31}N_5$	72.29	8.55	72.34	8.51
α-$C_{10}H_7(CH_2)-$	18	130	EtOH	48	258–259	$C_{16}H_{13}N_5$	69.80	4.76	70.02	4.61
α-$C_{10}H_7(CH_2)_5-$	19	130	EtOH	56	158–160	$C_{20}H_{21}N_5$	72.48	6.39	72.70	6.46
$C_6H_5O(CH_2)_2-$	18	140	EtOH	50	246–248	$C_{13}H_{13}N_5O$	61.16	5.13	60.86	5.23
$C_6H_5O(CH_2)_4-$	16	130	EtOH	35	156–158	$C_{15}H_{17}N_5O$	63.58	6.05	63.75	5.96
$C_6H_5OCHCH_2-$ (CH$_3$)	19	140	EtOH–ether	35	172–173	$C_{14}H_{15}N_5O$	62.43	5.61	62.79	5.57
$C_6H_{11}CH_2-$	18	140	Ether	75	219–222	$C_{12}H_{17}N_5$	62.31	7.41	62.74	7.71
$C_6H_{11}(CH_2)_2-$	19	140	Ether	90	243	$C_{13}H_{19}N_5$	63.64	7.81	63.36	7.48
$C_6H_{11}(CH_2)_3-$	17	140	EtOH	42	189–190	$C_{14}H_{21}N_5$	64.83	8.16	65.02	8.23
$C_6H_{11}(CH_2)_4-$	18	130	EtOH–H_2O	63	187–188	$C_{15}H_{23}N_5$	65.90	8.47	65.62	8.14
$C_6H_{11}(CH_2)_5-$	17	130	EtOH–H_2O (H^+)	65	163–164	$C_{16}H_{25}N_5$	66.86	8.77	66.92	8.50
$C_6H_{11}(CH_2)_6-$	16	130	EtOH–H_2O (H^+)	60	140–141	$C_{17}H_{27}N_5$	67.73	9.03	67.26	9.26

[a] This compound was a wax-like solid.

It is apparent from Table II that some compounds which possessed the greatest activity in inhibition of hydra regeneration (*e.g.*, 6-(4-cyclohexylbutyl)-aminopurine) had relatively little effect on the rate of germination of lettuce seed. Also, those compounds which possessed the greater seed germination effect (*e.g.*, 6-(α-naphthylmethyl)-aminopurine) had relatively little effect in the hydra regeneration study.

The preparations of these purine derivatives were accomplished through the general procedure of Elion, Burgi and Hitchings[12] which involves a thermal reaction between an amine and 6-methylthiopurine. Data concerning these compounds are reported in Table I. The intermediate amines usually were obtained through the corresponding nitrile by catalytic reduction. In an alternate procedure, the corresponding acid amide was reduced with lithium aluminum hydride.

In several instances, the acid required to prepare the desired amine was not available. These acids were prepared through the condensation of the appropriate aldehyde with ethyl ethylidenemalonate followed by reduction, hydrolysis and decarboxylation. Certain of the later condensation procedures did not yield the desired product. For example, the attempted condensation of 2-hydroxyl-1-naphthaldehyde with ethyl ethylidenemalonate failed, and an 81% recovery of starting material was obtained.

Experimental[13,14]

Starting Materials.—6-Methylthiopurine was prepared by the method of Elion, Burgi and Hitchings[12] from 6-mercaptopurine. The previously reported amines were synthesized by the catalytic reduction of the corresponding nitrile over Raney nickel in an alcohol–ammonium hydroxide solution: α-naphthylmethylamine, b.p. 153° (11 mm.)[15]; 2-phenoxyethylamine, b.p. 127° (27 mm.)[16]; 4-phenoxybutylamine, b.p. 145° (17 mm.), $n^{25}D$ 1.5235.[17]

Biological Testing.—The biological technique used to obtain the hydra regeneration data has been reported by Ham, Fitzgerald and Eakin.[18] The stimulation of lettuce seed germination was determined on a field variety of seed, Early Curled Simpson. The seeds were pre-soaked in the purine solutions for eight hours and then allowed to germinate in the dark at 30° on wet filter paper in covered Petri dishes. The percentage germination data recorded in Table II is based on 100 or more seeds per assay and the experimental technique will be presented elsewhere.[19]

7-Phenylheptylamine.—The amide of 7-phenylenanthic acid was prepared by a previously reported method[20] and used as the crude material, m.p. 82–85°.

A slurry of 10.0 g. of the amide in 150 ml. of anhydrous ether was added slowly with stirring to a suspension of 5.0 g. of lithium aluminum hydride in 100 ml. of ether. After addition was complete the mixture was stirred for an additional 10 hours. Upon the addition of dilute hydrochloric acid three layers resulted. The center one, presumably containing the hydrated amine-salt, was separated and made basic by the addition of dilute sodium hydroxide. The free amine was isolated by ether extraction and distilled to give 6.17 g. of colorless liquid, b.p. 157–160° (740 mm.). This amine did not form a solid picrate; however, a solid hydrochloride salt formed readily but was extremely hygroscopic. A sample of the amine which was redistilled for analysis boiled entirely at 157° (740 mm.).

Anal. Calcd. for $C_{13}H_2N$: N, 7.32. Found: N, 7.45.

11-Phenylundecylamine.—A sample of 50 g. of 11-phenylundecanoic acid (Eastman Organic Chemicals) was converted to the acid chloride *via* thionyl chloride, without purification, and transformed to 11-phenylundecylamide with concen-

(12) G. B. Elion, E. Burgi and G. H. Hitchings, THIS JOURNAL, **74**, 411 (1952).

(13) All melting points were made on a Fisher–Johns melting point block and are uncorrected.

(14) The analyses were done by Mr. J. R. Claybrook of the Biochemical Institute, The University of Texas, Austin, Texas, and by Drs. Weiler and Strauss, 164 Banbury Road, Oxford, England.

(15) Reported b.p. 155° (12 mm.); J. v. Braun, G. Blessing and F. Zobul, *Ber.*, **56**, 1996 (1923).

(16) Reported b.p. 115° (12 mm.); J. v. Braun, *Ber.*, **70**, 979 (1937).

(17) Reported b.p. 146–148° (17 mm.); C. S. Marvel and A. L. Tanenbaum, THIS JOURNAL, **44**, 2649 (1922).

(18) R. G. Ham, D. C. Fitzgerald, Jr., and R. E. Eakin, *J. Exp. Zool.*, **133**, 559 (1956). We are indebted to them for the data presented in Table II on the hydra tentacle regeneration effects of these compounds.

(19) C. G. Skinner, J. R. Claybrook, F. D. Talbert and W. Shive, *Plant Phys.*, 1957, accepted for publication.

(20) P. D. Gardner, W. J. Horton, G. Thompson and R. R. Twelves THIS JOURNAL, **74**, 6127 (1952) (m.p. 87–89°).

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TABLE II

BIOLOGICAL ACTIVITY OF SOME 6-(SUBSTITUTED)-AMINOPURINES

6-(Substituted)-aminopurine	Lettuce seeds germinated after 48 hr., %[a] 1 γ/ml.	10 γ/ml.	Inhibition of hydra-regeneration[b] Minimum concn. for full inhibition, μ-mole/ml.	Activity in terms of adenine equal to 1
Water blank control	.. (7.4) ..		...	..
7-Phenylheptyl-	5.6	1.4	0.001	5000
11-Phenylundecyl-	11.0	19.2	.008	625
α-Naphthylmethyl-	68.6	67.8	.04	125
2-α-Naphthylethyl-	9.0	2.7	.003	1700
5-α-Naphthylpentyl-	9.0	8.7	.004	1250
2-Phenoxyethyl-	59.0	63.8	.08	60
4-Phenoxybutyl-	7.9	6.3	.009	550
2-Phenoxypropyl-	30.6	65.2	.07	70
Cyclohexylmethyl-	74.4	57.9	.05	100
2-Cyclohexylethyl-	47.9	57.2	.02	250
3-Cyclohexylpropyl-	10.6	13.7	.004	1250
4-Cyclohexylbutyl-	9.6	11.5	.0009	5500
5-Cyclohexylpentyl-	10.0	16.2	.002	2500
6-Cyclohexylhexyl-	10.5	16.0	.002	2500

[a] The seeds were pre-soaked in purine solutions of the noted concentrations for 8 hours, drained, and allowed to germinate on wet filter paper in the dark at 30°. [b] These data were furnished by Mr. R. G. Ham and Dr. R. E. Eakin of the Biochemical Institute, The University of Texas, by a previously reported technique, ref. 18.

trated ammonium hydroxide. The reaction mixture tended to gel and only 16 g. of crystalline material was easily obtained. This product was dried over phosphorus pentoxide under vacuum, m.p. 42–44°.

Anal. Calcd. for $C_{17}H_{27}NO$: N, 5.36. Found: N, 5.64.

A suspension of 12.0 g. of 11-phenylundecylamide in 250 ml. of ether was added, with efficient stirring, to a suspension of 5.0 g. of lithium aluminum hydride in 200 ml. of dry ether at such a rate that reflux was not too vigorous. After standing overnight, ethyl acetate was added dropwise to the well-stirred mixture until the vigorous reaction subsided. A few milliliters of water was then added dropwise, followed by enough 10% hydrochloric acid solution to break the emulsion. The ether phase was separated, and was found to contain the amine hydrochloride which was converted to the free amine by drying over sodium hydroxide for several days. After removal of the solvent, the residue was distilled under reduced pressure, b.p. 145–149° (2 mm.), to yield 10.0 g. of product, $n^{25}D$ 1.4970.

Anal. Calcd. for $C_{17}H_{29}N$: N, 5.66. Found: N, 5.59.

ω-Cyclohexylalkylamines.—Methyl-(I), ethyl-(II), propyl-(III), butyl-(IV), pentyl-(V) and hexyl-(VI): Compounds I, II, III, IV and VI were prepared by hydrogenation, under 50 lb./sq. in. pressure of hydrogen, of a mixture containing 1 part of the corresponding nitrile,[21] 1 part of ammonium hydroxide and 3 parts of 95% ethyl alcohol in the presence of Raney nickel catalyst. After the theoretical amount of hydrogen had been consumed, the reaction mixture was filtered and the catalyst washed with alcohol. The solvent was then removed, and the residue was distilled under reduced pressure.

Compound V was prepared by the interaction of 5-cyclohexylvaleramide (18.3 g.) and lithium aluminum hydride (11.1 g.) in the presence of ether (500 ml.); and the reaction product was isolated in the same manner as that previously described for this reduction technique.

I, b.p. 37° (4 mm.), $n^{25}D$ 1.4645[23]; III, b.p. 60–26° (1.2 mm.), $n^{25}D$ 1.4640, 44% yield. *Anal.* Calcd. for $C_9H_{19}N$: N, 9.92. Found: N, 9.97. IV, b.p. 73° (1 mm.); $n^{25}D$ 1.4651, 75% yield. *Anal.* Calcd. for $C_{10}H_{21}N$: N, 9.02. Found: N, 9.12. V, b.p. 108–113° (6 mm.), $n^{25}D$ 1.4659, 60% yield. *Anal.* Calcd. for $C_{11}H_{23}N$: N, 8.27. Found: N, 8.17. VI, 104–112° (3 mm.), $n^{25}D$ 1.4641, 69% yield. *Anal.* Calcd. for $C_{12}H_{25}N$: N, 7.64. Found: N, 7.99.

2-Carboxyl-5-(1-naphthyl)-2,4-pentadienoic Acid.—A solution was prepared comprised of 15.6 g. of 1-naphthaldehyde and 27.9 g. of ethyl ethylidenemalonate[24] and treated with a solution prepared from 21.7 g. of potassium hydroxide (85%) and 150 ml. of methanol. The flask and contents were cooled as required to maintain the temperature below 30°. After 20 hr. at 30° the solution was acidified by the addition of 100 ml. of concd. hydrochloric acid in 150 ml. of water (with cooling). The resulting semi-solid precipitate was collected by suction filtration and triturated with hot methanol. The suspension was cooled to 0° and filtered to give 13.4 g. of yellow solid, m.p. 224–226° dec. A sample repeatedly recrystallized from butyrolactone–water or from acetic acid gave m.p. 232–233° dec.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.60; H, 4.53.

2-Carboxyl-5-(1-naphthyl)-valeric Acid.—A solution of 16.3 g. of the above acid was slurried with 200 ml. of glacial acetic acid. One-half gram of 5% palladium–charcoal was added and the mixture was shaken under 2 atm. pressure of hydrogen until the theoretical absorption of gas occurred. Isolation of the product in the usual manner and recrystallization from ethyl acetate–petroleum ether (60–68°) gave 13.95 g. of colorless solid (2 crops), m.p. 153–155° dec.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.51; H, 6.07.

5-(1-Naphthyl)-valeric Acid.—An 11.50-g. sample of the above dicarboxylic acid was heated at 190–200° (1 atm. pressure) until CO_2 evolution ceased. The cooled liquid crystallized upon trituration with petroleum ether and was recrystallized from ethyl–petroleum ether (60–68°) to give 8.50 g. of nearly colorless solid, m.p. 88–89°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.91; H, 7.07. Found: C, 78.65; H, 7.12.

The amide of the above substituted valeric acid was prepared by treating 7.57 g. with 20 ml. of thionyl chloride at 45° for 30 minutes (until gas evolution ceased). Excess thionyl chloride was removed using a water aspirator and warming on a steam-cone. The residue was poured slowly, with stirring, into 60 ml. of cold concentrated ammonium hydroxide. The solid thus formed was recrystallized from aqueous methanol or an ethyl acetate–petroleum ether mixture, to give 6.52 g. of colorless amide, m.p. 127–128°.

Anal. Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54. Found: C, 79.50; H, 7.36.

5-(1-Naphthyl)-pentylamine.—The amine was prepared by slowly adding a solution of 5.27 g. of the amide described above, dissolved in 100 ml. of dry ether, to a suspension of 2.28 g. of lithium aluminum hydride in 50 ml. of ether. The mixture was stirred for 20 hr. at room temperature and processed as before. Upon acidification three layers resulted, the amine salt being in the middle one. It was separated, made basic with dilute sodium hydroxide and extracted with ether. Distillation of the residue gave 3.40 g. of the amine as colorless liquid, b.p. 151–153° (1.0 mm.), $n^{25}D$ 1.5857.

Anal. Calcd. for $C_{15}H_{19}N$: N, 6.57. Found: N, 6.87.

2-Phenoxypropylamine.—This compound was prepared by reduction of the corresponding nitrile over Raney nickel catalyst and 50 lb./sq. in. hydrogen gas pressure, using the procedure previously described; b.p. 125–126° (22 mm.), $n^{20}D$ 1.5207.

Anal. Calcd. for $C_9H_{13}NO$: N, 9.27. Found: N, 9.29.

Attempted Condensation of 2-Hydroxy-1-naphthaldehyde with Ethyl Ethylidenemalonate.—Treatment of 20.0 g. of 2-hydroxyl-1-naphthaldehyde with 35.7 g. of ethyl ethylidenemalonate and 27.8 g. of 85% potassium hydroxide for a 20-hour period at 30° followed by the processing technique described above for 2-carboxyl-5-(1-naphthyl)-2,4-pentadienoic acid gave 16.3 g. (81%) of recovered starting material.

(21) The intermediates to form the various nitriles have previously been reported by P. L. Pickard and C. W. Young, THIS JOURNAL, 73, 42 (1951).

(22) Reported values, b.p. 163.5°, $n^{18}D$ 1.4646; O. Wallach, *Ann.*, 353, 297 (1907).

(23) Reported values, b.p. 85° (25 mm.), $n^{20}D$ 1.4656; B. L. Zenitz, E. B. Macks and M. L. Moore, THIS JOURNAL, 69, 1117 (1947).

(24) F. R. Goss, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, **123**, 3342 (1923).

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2-Carboxyl-5-(2-thenyl)-penta-2,4-dienoic Acid.—This substance was prepared by the procedure described above in which 19.5 g. of 2-thiophenaldehyde, 48.5 g. of the ester, 37.8 g. of potassium hydroxide and 200 ml. of methanol was used. Acidification gave the product as a yellow solid which, after recrystallization from acetic acid, melted at 211–212° dec. and weighed 11.1 g.

Anal. Calcd. for $C_{10}H_8O_4S$: C, 53.56; H, 3.60. Found: C, 53.91; H, 3.60.

Reduction of this substance to the corresponding saturated derivative could not be effected under 2 atmospheres of hydrogen pressure using platinum as a catalyst.

2-Carboxyl-5-(2-furyl)-penta-2,4-dienoic Acid.—Application of the above-described reaction conditions to a mixture of 43.0 g. of potassium hydroxide, 250 ml. of methanol, 19.2 g. of furfural, and 55.8 g. of the ester gave 9.53 g. of red-brown solid, m.p. 197–198° dec. Further purification afforded a tan sample having the same melting point. This substance absorbed four mole-equivalents of hydrogen (platinum, ethanol) at 30° and 2 atmospheres pressure.

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.69; H, 3.87. Found: C, 58.29; H, 4.00.

Subsequent reactions with this material proceeded anomalously in several respects and will be described in a later report.

6-(Substituted)-aminopurines.—The appropriate amines were condensed by the same general procedure whereby one part of 6-methylthiopurine was mixed with 2 to 5 parts of the corresponding amine, and the reaction mixture was sealed in a micro Carius tube and heated at 130 to 140° for 15 to 18 hours. At the conclusion of the heating period, the cooled bomb was opened carefully with an oxygen torch. The liberated methylmercaptan was immediately evident as a foul smelling by-product. In several instances a precipitate was present at this stage which could be washed with cold alcohol, dried, and analyzed directly. In other experiments the solvent had first to be removed under reduced pressure to yield a mass of crystals which, after treating with charcoal, and cooling, yielded the desired product. The yields varied considerably among the different amines; however, this may have been due more to solubility factors than to extent of the reaction, since the more soluble products were difficult to isolate in the small scale experiments that were conducted. Specific reaction conditions are itemized in Table I for each of the amines studied. The extent of purity of the reaction product could be ascertained readily by determining its ultraviolet absorption spectrum. 6-Methylthiopurine has a characteristic double peak at about 283 and 290 mμ (10 γ/ml. in 95% ethanol), which is absent in the 6-(substituted)-aminopurines. The 6-(substituted)-aminopurine spectra were almost identical in possessing a λ_{max} from about 267–271 mμ when examined at concentrations of 10 γ/ml. in 95% ethyl alcohol.

Austin, Texas

[Contribution from the Chemical Laboratory of Iowa State College and the Chemistry Department and the Oceanographic Institute of The Florida State University]

Recoverability of Phenylthiohydantoins from Amino Acids[1]

By Sidney W. Fox,[2] William Serat,[3] Thomas L. Hurst, Onnolee Underwood Trapp and Donna Lutjens

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Factors in the reaction of phenyl isothiocyanate with amino acids and amino acid residues in the analysis of peptides have been studied. Some of the same phenomena which interfere with quantitation of the extractive procedure contribute to the validity of the subtractive procedure. Use of an excess of phenyl isothiocyanate enhances the decomposition of amino acids to other substances.

In the development of methods of peptide analysis the need for convenient determinations of residue sequence and of characterization has been apparent for well over a decade.[4] The characteristics of an ideal N-terminal reagent for sequence assignment were prescribed in 1945.[4] Many of the attributes of such a reagent were found in fluorodinitrobenzene (FDNB) which has been successfully used by Sanger,[5] du Vigneaud,[6] Craig[7] and others.

In the development of more highly quantitative methods, of stepwise methods, and of procedures for characterization, a reagent of choice,[8] however, appears to be phenyl isothiocyanate[9] (PTC). Direct identification of the extracted phenylthiohydantoin (PTH) formed by fission of the reaction product of phenyl isothiocyanate with protein or peptide nevertheless poses procedural difficulties. Recoveries are usually low[10] (typically 20–40%), although higher recoveries have been attained.[11]

Probably the greatest error in the direct extraction procedure is introduced by destruction of the phenylthiohydantoin by the same mineral acid used for its formation. Such an effect was evident in the earliest experiments with phenyl isothiocyanate in this Laboratory.[12] This picture of simultaneous formation and destruction of PTH has been mentioned,[8] confirmed in detail[10,11] and is in accord with the known behavior of hydantoins.[13] The probability that destruction of PTH was occurring in the presence of mineral acid first led, indeed, to use of a subtractive method. The subtractive method consists of amino acid assays of an hydrolyzate followed by subsequent hydrolyses and assays after the terminal residues are successively removed. If the PTH formed decom-

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(2) Chemistry Department and Oceanographic Institute, The Florida State University, Tallahassee.

(3) In part from the M. S. thesis of William Serat, 1953.

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(5) F. Sanger, *ibid.*, **7**, 1 (1952).

(6) C. Ressler, S. Trippett and V. du Vigneaud, *J. Biol. Chem.*, **204**, 861 (1953).

(7) L. C. Craig, W. Hausmann and J. R. Weisiger, This Journal, **76**, 2839 (1954).

(8) D. De Fontaine and S. W. Fox, *ibid.*, **76**, 3701 (1954).

(9) P. Edman, *Acta Chem. Scand.*, **4**, 277, 283 (1950).

(10) P. H. Bell and R. G. Shepherd, "Conferences et Rapports, 5me Congrès International de Biochimie," 1956, p. 15.

(11) H. Fraenkel-Conrat and J. I. Harris, This Journal, **76**, 6058 (1954).

(12) S. W. Fox, T. L. Hurst and K. F. Itschner, *ibid.*, **73**, 3573 (1951).

(13) E. Wars, *Chem. Revs.*, **46**, 444 (1950).

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poses substantially to substances other than the original amino acid, the subtractive method would nevertheless yield the desired quantitative result. Experiments with synthetic peptides therefore emphasized finding conditions which would completely destroy N-terminal residues. The results indicated especially a need for a relatively high PTC/peptide ratio for quantitative loss of the N-terminal residue.[12]

These considerations emphasized the desirability of obtaining an evaluation of the extent of utilization of the PTHs following typical hydrolytic treatment and of the survival of the amino acids after the full analytical treatment with excess PTC.[12] Data on recovery from peptides have been provided for some of the amino acid residues.[12] In the absence of a roster of peptides representing all types of N-termini, free amino acids were carried through the treatment (Table IV).

Experimental and Results

The utilization of the PTHs from each of thirteen amino acids is reported in Table I. The PTHs were prepared as described by Edman.[9] In order to bring these into solution it was necessary to dissolve the compounds in ethanol and in some cases to autoclave promptly the resultant 5% ethanolic solution containing PTH and basal medium. The control and assay solutions contained the same proportion of ethanol.

TABLE I

UTILIZATION OF THIRTEEN PHENYLTHIOHYDANTOINS FROM AMINO ACIDS IN MICROBIAL ASSAY OF THE CORRESPONDING AMINO ACID

Amino acid as PTH	Assay organism	Assay titration values in ml. 0.05 *N* NaOH: Blank	PTH	Amino acid
Alanine	*L. citrovorum*	4.64	4.63	5.76
Arginine	*S. faecalis*	1.92	1.97	5.28
Aspartic acid	*L. mesenteroides*	1.56	1.59	3.16
Glutamic acid	*L. arabinosus*	5.42	5.52	6.51
Glycine	*L. brevis*	4.97	4.28	7.71
Isoleucine	*L. arabinosus*	1.02	3.00	5.56
Leucine	*L. arabinosus*	3.73	4.80	8.15
Lysine	*L. mesenteroides*	0.70	0.72	2.36
Methionine	*S. faecalis*	0.12	0.04	4.25
Phenylalanine	*L. brevis*	2.38	2.23	7.98
Proline	*L. brevis*	0.70	0.65	5.28
Tyrosine	*L. brevis*	1.13	1.17	6.40
Valine	*S. faecalis*	0.94	1.00	2.80

For the tests, 2.50 ml. of basal medium[14] lacking only the amino acid under study and including 0.25 ml. of the corresponding PTH in ethanol and 2.25 ml. of distilled water were combined in a culture tube. The amount of PTH chosen was that equivalent to 10 μg. of the amino acid in the final solution. In one set of control tubes, no PTH was included. In another set of tubes, 10 μg. of the amino acid was present. All tubes were prepared in triplicate; the figures given in Tables II–IV are averages. Except for glycine assays, individual values seldom exceeded ±5% variation from the average of triplicates. The tubes were covered with a towel, autoclaved for 15 minutes under 15 lb. of steam pressure, inoculated after cooling and incubated at 37° for 72 hr. The organisms used are given in Table I. It may be seen that the assay values in the use of PTH were almost the same as in the absence of the PTH except for three cases. These were glycine, isoleucine and leucine. Glycine–PTH appeared to be inhibitory. Although the individual assay values for glycine were the most variable, repetition of the experiment confirmed the finding that the derivative was truly inhibitory. The PTHs utilized were those of isoleucine and leucine.

(14) K. A. Kuiken, W. H. Norman, C. M. Lyman, F. Hale and L. Bletter, *J. Biol. Chem.*, **151**, 615 (1943).

TABLE II

UTILIZATION OF ISOLEUCINE-PTH AND OF LEUCINE-PTH AT VARIOUS CONCENTRATIONS OF THE DERIVATIVES

PTH as molar equiv. of L-amino acid Per tube, γ	Utilization, %: Isoleucine	Leucine
10	75	45
15	63	43
25	48	36

TABLE III

RECOVERY OF ISOLEUCINE AND LEUCINE FROM THE CORRESPONDING PTH AFTER HYDROLYTIC TREATMENT

Molar equiv. of L-amino acid Per tube, γ	Recovery, %: Isoleucine	Leucine
10	28	15
15	27	13
25	26	13

TABLE IV

RECOVERY OF AMINO ACIDS FOLLOWING N-TERMINAL ANALYTICAL TREATMENT WITH EXCESS PHENYL ISOTHIOCYANATE AND HYDROLYSIS

Amino acid	Recovery, %
Alanine (cx)	4.4, 9.7
Arginine (fr)	5.5, 2.0
Aspartic acid (mq)	6.8, 12
Cystine (aq)	6.8, 2.0
Glutamic acid (aVI)[a]	10.3, 12
Glycine (bt)	2.8, 5.5, 5.7
Histidine (mr)	5.4, 5.7
Isoleucine (aq, fq, fq)	4.4, 1.7, 1.4
Leucine (aq, fq, aq, fq)	4.1, 2.2, 5.7, 4.4
Lysine (mq)	2.6, 2.5
Methionine (fq, fq)	11.6, 5.3
Phenylalanine (bt)	1.5, 2.6
Proline (bt)	21, 20, 20
Serine (my)	2.4, 1.2
Threonine (fz)	1.8, 1.4
Tryptophan (aq)	4.5, 1.6
Tyrosine (bq)	3.5, 3.3
Valine (fq)	1.1, 0.0

[a] VI in B. F. Steele, H. E. Sauberlich, M. S. Reynolds and C. A. Baumann, *J. Biol. Chem.*, 177, 533 (1949). Letter combinations of organism and medium are given in S. W. Fox, T. L. Hurst and C. Warner, THIS JOURNAL, 76, 1154 (1954). Multiple symbols correspond to each determination; a single pair of symbols indicates the combination was used in all tests.

Accordingly, the PTHs were tested in a range of concentrations against standard curves for isoleucine and leucine. The results are presented in Table II.

In order to test the effect of the hydrolytic treatment on the PTH, samples of the leucine-PTH and isoleucine-PTH equivalent to 100 μg. of the L-amino acid per ml. of ethanol were each added to an equal volume of 12 *N* hydrochloric acid and autoclaved at 15 lb. steam pressure for 16 hr. These solutions were concentrated to dryness and dissolved in ethanol and prepared for assay as before. Results are given in Table III.

The recoveries of amino acids following full treatment of the type employed in analyses on peptides and proteins are given in Table IV. The procedure employed in these tests was to pipet 2.0 ml. of solution containing 2.00 mg. of standard L-amino acid into a 50-ml. beaker, to add 2.5 ml. of pyridine and 0.025 ml. of phenyl isothiocyanate and to add a small amount of brom thymol blue powder. To this was added sufficient 0.2 *N* sodium hydroxide to give an emerald green color. The beaker was covered and set in a 37° incubator for 6 hr., with maintenance of the original alkalinity by frequent additions of sodium hydroxide. The beakers were evaporated to dryness in evacuated desiccators containing sulfuric acid. When dry, 5.0 ml. of 3 *N* hydro-

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claved at 15 lb. pressure for 16 hr. The hydrochloric acid was driven off over steam, and the beaker was set in a desiccator containing also a beaker of ammonium hydroxide to neutralize any free acid. The contents were then diluted to volume for assay.

The results in Table V were obtained in the same way as for Table IV, except for the quantities used. To 50 mg. of each amino acid were added 1.0 ml. of water, 2.0 ml. of pyridine and the designated volume of PTC.

TABLE V

RECOVERY FROM 50 MG. OF LEUCINE OR LYSINE AFTER TREATMENT WITH VARIOUS AMOUNTS OF PHENYL ISOTHIOCYANATE (PTC)

Amino acid	Amount of PTC 0.1 ml., %	0.5 ml., %	1.0 ml., %	Lysozyme standard assay L-amino acid
DL-Leucine	6.6 ± 0.4	3.5 ± 0.3	2.1 ± 0.2	6.5 ± 0.3
	6.3 ± .1	3.2 ± .2	2.0 ± .2	6.3 ± .3
L-Lysine	1.9 ± .1		1.0 ± .1	5.9 ± .1
	1.6 ± .1		1.2 ± .1	5.8 ± .2
	2.0 ± .1		1.3 ± .1	5.9 ± .2

Discussion

The results of Table I show that direct utilization does not occur for most amino acid PTHs. A more extensive study with benzoylamino acids[15] revealed a similarly highly selective pattern for an acylamino acid series. These results are of interest for comparison in that *L. arabinosus* was able to use benzoylleucine but no other benzoylamino acid in substantial proportion, with the partial exception of cystine. The study with benzoylamino acids showed also that *S. faecalis* could not make use of benzoylleucine. In any analytical situation in which it might be significant, utilizability of leucine-PTH or isoleucine-PTH might thus be circumvented by employing another assay microbe. As will be seen, this need probably does not exist in the present type of application (Table IV).

The results of Table II reveal a commonly observed phenomenon, that of decreasing utilization with increasing concentration of a limiting nutrient. Tables II and III taken together demonstrate that in those few cases in which a derivative is utilizable most of this is lost by hydrolytic treatment. These results also help to explain low recoveries recorded in the literature for the extractive Edman procedure.

In evaluating effects in the steps of the subtractive procedure, it should be emphasized that this differs particularly in employing a large excess of PTC. The fact that higher ratios of PTC to glycylvaline result in more complete subtraction of N-terminal glycine[12] demonstrates that these considerations apply to peptides as well as to unsubstituted amino acids (Table IV). In addition such results support the conclusion that excess PTC contributes to destruction of terminal residue.

The ideal type of experiment in which to estimate the quantitative non-recoverability of an N-terminal amino acid residue would involve reaction with PTC of a variety of peptides for each of the residues in the N-terminal position. Some such experiments have been performed,[11,12] but the comprehensive completion of such a study is at present infeasible. Accordingly, each of the amino acids has been carried through such a process, as has been done for the companion C-terminal method,[16] to gain further insight into the reliability of the method. In addition, extended studies comparing concordance of C-terminal exposures and N-terminal exposures during proteolysis provide an independent type of check.[17] When the values of Table II are compared with the low recovery of valine following treatment with *excess* PTC and then hydrolysis as in Table V, it becomes evident that the treatment itself can lead to degradation of the N-terminal residue. Although the mechanism is not understood, this difference in behavior can explain how recoveries of extracted PTH can be incomplete whereas the subtractive method can yield quantitative results within the limits of error of assay.

With the partial exception of proline all of the recoveries in Table IV are essentially negligible within the limits of error of microbial assay. The loss of amino acid is more nearly complete in the N-terminal method than in the companion C-terminal procedure.[16] (In addition, the large difficulties encountered with glutamic acid, aspartic acid and proline at the C-terminus are not observed with the PTC procedure.) The destruction of N-proline in a peptide is more complete than in the amino acid.[12] The greater destructibility in a peptide, when superposed on incomplete utilizability of whatever PTH is formed (Table I) imparts to the subtractive method maximum validity.

The effect of varying ratio of PTC/amino acid also has been studied for lysine and leucine. The results of Table V show a trend similar to that observed with peptides.[12] The results in this table were controlled by simultaneous assay of lysozyme. The ± figures are standard deviations calculated from quadruplicate determinations at each of five levels of assay.

Among principal advantages of the subtractive PTC method are (1) that it functions by virtue of some factors which incidentally interfere with the quantitation of the extractive method and (2) the applicability to studying unfractionated mixtures of peptides[17] in a stepwise manner.[18] The stepwise nature of the method permitted distinguishing unfractionated and unfragmented cereal proteins containing a dominant lysine–arginine sequence[19] from lysozyme containing a lysylvalyl sequence.[8] This quality is particularly needed in a method employed for characterization of unfractionated proteins. A number of such applications have been reported[17–21] as have other advantages and limitations of the method.[17,22]

TALLAHASSEE, FLA.

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June 5, 1957

[CONTRIBUTION FROM THE CHEMICAL PROCESS IMPROVEMENT DEPARTMENT, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Studies of the Reversible Epimerization Occurring in the Tetracycline Family. The Preparation, Properties and Proof of Structure of Some 4-*epi*-Tetracyclines

BY J. R. D. MCCORMICK, SIDNEY M. FOX, LELAND L. SMITH, BARBARA A. BITLER, JULES REICHENTHAL, VICTOR E. ORIGONI, WALTER H. MULLER, ROBERT WINTERBOTTOM AND ALBERT P. DOERSCHUK

RECEIVED SEPTEMBER 19, 1956

The four known members of the tetracycline family of broad-spectrum antibiotics (tetracycline, 7-chlorotetracycline, 7-bromotetracycline and 5-hydroxytetracycline) can undergo a reversible epimerization at carbon four to form a new series of compounds, the 4-*epi*-tetracyclines. For each of the four epimeric pairs, the equilibrium mixture in a variety of solvents is composed of approximately equal amounts of the tetracycline and the 4-*epi*-tetracycline. The 4-*epi*-tetracyclines have been isolated from the equilibrium mixtures, crystallized, and characterized. The epimerization occurs in the *p*H range of approximately two to six and is aided by the presence of buffers; it becomes unmeasurably slow under more strongly acidic conditions or more strongly basic conditions. The proof that the new materials are carbon four epimers of the tetracyclines depends on consideration of (1) the conditions permitting and preventing epimerization, (2) the reversible nature of the epimerization, (3) the nature of the ultraviolet spectral differences between epimeric pair members and (4) the nature of the chemical transformations required to convert both members of an epimeric parent pair to a single substance.

The tetracycline family (I) consists of a small group of closely related hydronaphthacenes that are of interest because of their broad-spectrum antibiotic activity. The known members of this family are tetracycline,[1] 7-chlorotetracycline,[1] 7-bromotetracycline and 5-hydroxytetracycline.[2] The reactions of these compounds under strongly acidic conditions and under strongly alkaline conditions have been studied extensively in connection with the determinations of their structures.[3-5] It recently has been found that these substances, and certain of their derivatives, undergo a reversible isomerization under *p*H conditions in the range of two to six.[6] This reversible isomerization has been shown to be an epimerization occurring at carbon four, giving rise to a new series of compounds, the 4-*epi*-tetracyclines (II).[7,8] These new substances have been called the quatrimycins.[6] This paper describes conditions permitting and preventing the epimerization, methods of preparation and characteristics of some 4-*epi*-tetracyclines and evidence for the conclusion that the reaction leading to the new compounds is a reversible epimerization at carbon four.

The epimerization occurs in a variety of solvent systems within the *p*H range of approximately two to six; its rate is increased by the presence of certain anions, such as phosphate, citrate or acetate. Saturated solutions of tetracyclines or 4-*epi*-tetracyclines in glacial acetic acid (25°) or in 2:1 dimethylformamide–1 *M* aqueous phosphate (*p*H 3.5, 25°) are equilibrated within 24 hours. The mole fraction of 4-*epi*-tetracycline in a given equilibrium mixture varies from 0.4 to 0.6. Tables I and II present examples of conditions allowing epimerization. Epimerization rates are unmeasurably small in solutions more acidic than *p*H 2. For tetracycline in 0.03 *N* HCl, the epimerization rate is unmeasurably small and acid-catalyzed dehydration to anhydrotetracycline (III)[9,10] does not occur; tetracycline in such solutions is chemically stable over long periods of time. Further increases in acid strength bring about dehydration and aromatization to anhydrotetracycline; in 1.0 *N* HCl, 4-*epi*-tetracycline yields, without measurable isomerization, anhydro-4-*epi*-tetracycline (IV) (Table III, Fig. 1). Anhydro-4-*epi*-tetracycline is isomeric with, distinguishable from and reversibly convertible to anhydrotetracycline under conditions epimerizing the tetracyclines. Epimerization rates of the tetracyclines and their epimers are unmeasurably small in solutions more basic than

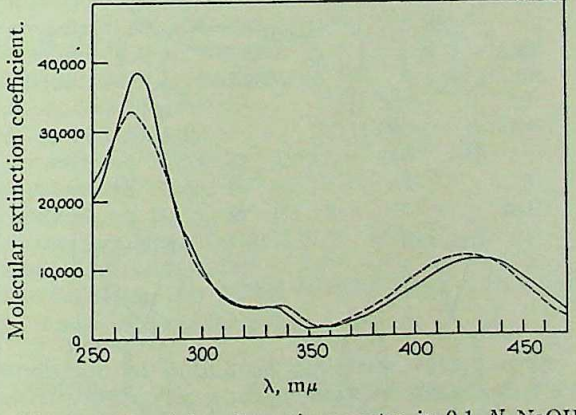

Fig. 1.—Ultraviolet absorption spectra in 0.1 *N* NaOH (aq.): – – –, anhydro-4-*epi*-tetracycline hydrochloride; ——, anhydrotetracycline hydrochloride.

(1) The trademarks of the American Cyanamid Co. for tetracycline and 7-chlorotetracycline are Achromycin and Aureomycin, respectively.

(2) The trademarks of Chas. Pfizer and Co., Inc., for tetracycline and 5-hydroxytetracycline are Tetracyn and Terramycin, respectively.

(3) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **74**, 3708 (1952).

(4) C. R. Stephens, L. H. Conover, F. A. Hochstein, P. P. Regna, P. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **74**, 4976 (1952).

(5) C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, W. J. Stein, C. F. Wolf and J. H. Williams, *ibid.*, **74**, 4981 (1952).

(6) A. P. Doerschuk, B. A. Bitler and J. R. D. McCormick, *ibid.*, **77**, 4687 (1955).

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(8) J. R. D. McCormick, S. M. Fox, L. L. Smith, B. A. Bitler, J. Reichenthal, V. E. Origoni, W. H. Muller, R. Winterbottom and A. P. Doerschuk, *ibid.*, **78**, 3547 (1956). Although ref. 7 and 8 represent independent work, much of the discussion in ref. 8 and also in this paper applies to ref. 7.

(9) C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, W. J. Stein, C. F. Wolf and J. H. Williams, *ibid.*, **74**, 4981 (1952).

(10) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **76**, 3568 (1954).

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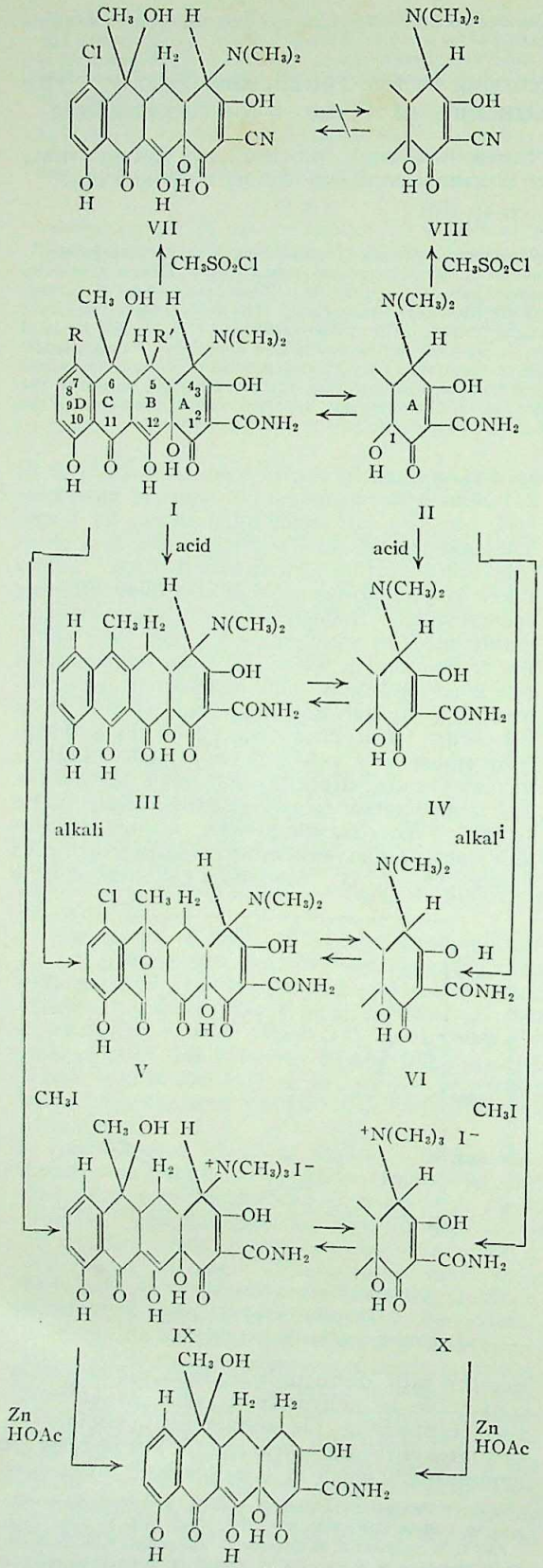

	R	R′
Tetracycline	H	H
7-Chlorotetracycline	Cl	H
7-Bromotetracycline	Br	H
5-Hydroxytetracycline	H	OH

*p*H 9. In 0.1 *N* NaOH, 7-chloro-4-*epi*-tetracycline yields, without measurable epimerization, iso-7-chloro-4-*epi*-tetracycline (VI) (Table III, Fig. 2). Iso-7-chloro-4-*epi*-tetracycline is isomeric with, distinguishable from and reversibly convertible to iso-7-chlorotetracycline (V)[10,11] (Fig. 3) under conditions epimerizing the tetracyclines.

Separation of the 4-*epi*-tetracyclines from the equilibrium mixtures has been accomplished by partition chromatographic methods and also by differential crystallization methods convenient for the preparation of large quantities of materials. A tabulation of the properties of the 4-*epi*-tetracyclines and the corresponding tetracyclines is presented in Tables III and IV and Fig. 2. In general, the 4-*epi*-tetracycline member of each pair has the lesser ultraviolet absorbency in the 250–300 mμ region, the greater alkali stability, the greater acid stability, the more negative optical rotatory power, the greater water solubility, the greater tendency to be associated with the aqueous phase of partition separation systems and the lower *in vitro* antibacterial activity against *Staphylococcus aureus*. All these differences in properties have been used for analyzing mixtures of epimeric pair members. However, the most useful properties were the antibacterial activity against *S. aureus* and the shapes of the ultraviolet curves, expressed as ratios of the absorbencies at different wave lengths. Of the several absorbancy ratios possible, the most useful for analytical purposes was the ratio between the absorbencies at 254 and at 267 mμ; this method is called the Absorbency Ratio (AR) Assay. Where 220–300 mμ ultraviolet interference was present, use was made of the ratio of *S. aureus* antibacterial activity to ultraviolet absorbency at the long wave length ultraviolet absorption maximum (~360 mμ); this method is called the Biological-Spectrophotometric Ratio (BSR) Assay. Ultraviolet interference in the 220–300 mμ region was more commonly encountered than was interference in the 360 mμ region, and the BSR assay was the more generally applicable of the two. Table V presents values of these properties for the pure compounds of the two series.

The constant nature throughout all pairs of the differences in properties between pair members, the fact that a single set of conditions can accomplish the epimerization of all members of the two series, and the fact that the limitations on the conditions allowing the epimerization are, insofar as they have been studied, similar for all members of the two series, indicate that the structural relationships between members of the pairs are the same for all pairs and that only a single process, common to all the cases, is involved in the conversions. Some confirmation of this comes from the fact that catalytic hydrogenation (palladium-on-carbon, 1.1 atmosphere) of 7-chloro-4-*epi*-tetracycline yields 4-*epi*-tetracycline.

(11) C. W. Waller, B. L. Hutchings, C. F. Wolf, A. A. Goldman, W. Bohonos and J. H. Williams, This Journal, 74, 4981 (1952).

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TABLE I

EXAMPLES OF CONDITIONS EPIMERIZING THE TETRACYCLINES, THE 4-*epi*-TETRACYCLINES AND SOME OF THEIR DERIVATIVES

Starting material concn., % (w./v.)	Solvent	Reaction time, hr.	Extent of epimerization, %
20% Tetracycline	2:1 MeOH/1 *M* aq. NaH_2PO_4, 25°, *p*H 3.5	4	47
20% Tetracycline	2:1 MeOH/1 *M* aq. NaH_2PO_4, 25°, *p*H 3.5	24	51[a]
20% Tetracycline	2:1 MeOH/1 *M* aq. NaH_2PO_4, 25°, *p*H 3.5	72	51[a]
20% Tetracycline	12:1 MeOH/4 *M* aq. NaH_2PO_4, *p*H 3.5	24	36
20% Tetracycline	1:0.05 H_2O/88% HCOOH, 25°	5	45[a]
10% 4-*epi*-Tetracycline	1:0.05 H_2O/88% HCOOH, 43°	2	50[a]
10% 4-*epi*-Tetracycline	1:0.05 H_2O/88% HCOOH, 77°	0.083	60[a]
10% 4-*epi*-Tetracycline	1:0.05 H_2O/88% HCOOH, 77°	.083	33[a]
10% Tetracycline	4.8% $Zn(OAc)_2$ dihydrate (4 equiv.) in gl. HOAc, 25°	.33	13
5% Tetracycline	4.8% $Zn(OAc)_2$ dihydrate (4 equiv.) in gl. HOAc, 25°	2.33	35
5% Tetracycline	4.8% $Zn(OAc)_2$ dihydrate (4 equiv.) in gl. HOAc, 25°	0.33	13
5% 4-*epi*-Tetracycline	4.8% $Zn(OAc)_2$ dihydrate (4 equiv.) in gl. HOAc, 25°	2.33	50
5% 4-*epi*-Tetracycline	4.8% $Zn(OAc)_2$ dihydrate (4 equiv.) in 1:1 HOAc–H_2O, 25°	2.0	~3
5% Tetracycline	4.8% $Zn(OAc)_2$ dihydrate (4 equiv.) in 1:1 HOAc–H_2O, 25°	4.0	~6
5% 4-*epi*-Tetracycline	4.8% $Zn(OAc)_2$ dihydrate (4 equiv.) in 1:1 HOAc–H_2O, 25°	2.0	18
5% 4-*epi*-Tetracycline	4.8% $Zn(OAc)_2$ dihydrate (4 equiv.) in 1:1 HOAc–H_2O, 25°	4.0	28
0.2 mg./ml. Tetracycline hydrochloride	Water, *p*H 3.5	48	7
1% 7-Chlorotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°, *p*H 3.5	24	44
0.4% 7-Chlorotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	0.17	9
0.4% 7-Chlorotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	0.50	17
0.4% 7-Chlorotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	1.0	24
0.4% 7-Chlorotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	3.0	35
0.4% 7-Chlorotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	4.0	40[a]
0.4% 7-Chlorotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	24	41[a]
1.2% 7-Chloro-4-*epi*-tetracycline ammonium salt	2:1 MeOH/1 *M* aq. NaH_2PO_4, 25°, *p*H 3.5	24	59[a]
20% 7-Chlorotetracycline	Glacial acetic acid	3	32
12% 7-Bromotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°, *p*H 4.3	16	48
12% 7-Bromotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°, *p*H 4.3	24	51
7% 5-Hydroxytetracycline	1:1:1 tetrahydrofuran/dimethylformamide/1 *M* aq. NaH_2PO_4, 25°, *p*H 5.3	20	38
16% 5-Hydroxytetracycline	Glacial acetic acid, 25°	20	27
40 μg./ml. Iso-7-chlorotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	0.083	12
40 μg./ml. Iso-7-chlorotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	2.5	67[a]
40 μg./ml. Iso-7-chlorotetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	3.5	68[a]
40 μg./ml. Iso-7-chloro-4-*epi*-tetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	0.083	5
40 μg./ml. Iso-7-chloro-4-*epi*-tetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	2.0	32[a]
40 μg./ml. Iso-7-chloro-4-*epi*-tetracycline	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	3.5	32[a]
0.32% Anhydrotetracycline hydrochloride	2:1 MeOH/1 *M* aq. NaH_2PO_4, 25°	20	37[a]
0.32% Anhydro-4-*epi*-tetracycline hydrochloride	2:1 MeOH/1 *M* aq. NaH_2PO_4, 25°	20	63[a]
0.1% Benzenesulfonyl-4-*epi*-tetracyclinonitrile	4:1 dimethylformamide/aq. H_3PO_4, 25°, *p*H 3.5	114	0
0.1% 7-Chloro-4-*epi*-tetracyclinonitrile	4:1 dimethylformamide/aq. H_3PO_4, 40°, *p*H 1	44	0
0.1% 7-Chlorotetracyclinonitrile	4:1 dimethylformamide/aq. H_3PO_4, 85°, *p*H 3.3	3	0
4.9% 4-*epi* Tetracycline methiodide	2:1 dimethylformamide/1 *M* aq. NaH_2PO_4, 25°	16.5	65
5.5% Tetracycline methiodide	3.6% $Zn(OAc)_2$ in 1:1 HOAc–H_2O, 25°	4.3	0
5.5% 4-*epi*-Tetracycline methiodide	3.6% $Zn(OAc)_2$ in 1:1 HOAc–H_2O, 25°	4.3	~9

[a] The attainment of equilibrium was demonstrated by no further change with additional time.

TABLE II

EFFECT OF BUFFER CONCENTRATION ON THE EPIMERIZATION RATE OF A 20% TETRACYCLINE HYDROCHLORIDE SOLUTION IN 2:1 METHANOL/AQUEOUS BUFFER AT *p*H 4 AND 25°

Buffer concn.	Extent of epimerization, %				
	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.
0.1 *M* NaH_2PO_4	4	12	35	40	49
1.0 *M* NaH_2PO_4	13	26	44	47	52

That the members of the pairs are not related as keto–enol tautomers is indicated by the facts that strong acid or strong base acts to prevent interconversion, rather than having a catalytic effect. The isomerization rate–*p*H value relationships and the effect of buffer anions suggest a mechanism of interaction of both acid and base with the isoelectric form; an analogy may be drawn to the mutarotation of glucose.[12] It follows from the equilibrium mixture composition that the free energy change accompanying epimerization is small; therefore the structures of pair members are probably not greatly different. From the essential ultraviolet absorption similarity between pair members it follows that epimerization does not involve any extensive change in the chromophores. It is, however, significant that, in all cases, the pair members differ only slightly in ultraviolet absorption characteristics in the 340–380 mμ region

(12) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 221, 338.

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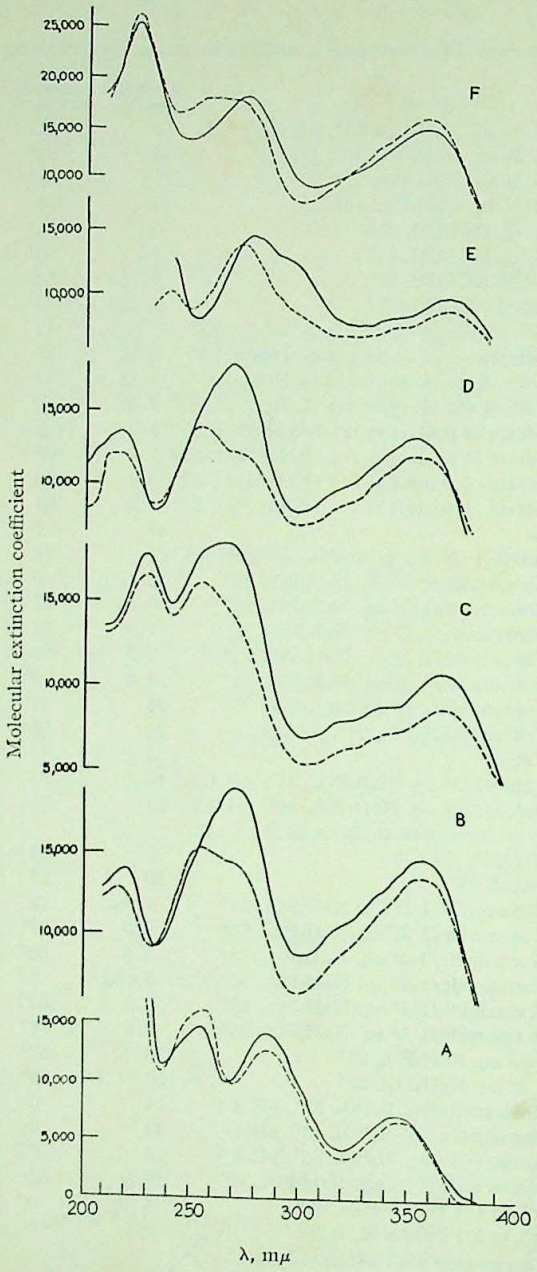

Fig. 2.—Ultraviolet absorption spectra: A, – – –, iso-7-chloro-4-*epi*-tetracycline; ———, iso-7-chlorotetracycline hydrochloride; both in 0.1 *N* NaOH (aq.); B, – – –, 4-*epi*-tetracycline ammonium salt monohydrate; ———, tetracycline hydrochloride; both in 0.1 *N* H_2SO_4 (aq.); C, – – –, 7-chloro-4-*epi*-tetracycline ammonium salt monohydrate; ———, 7-chlorotetracycline hydrochloride; both in 0.1 *N* H_2SO_4 (aq.) after 30 min.; D, – – –, 5-hydroxy-4-*epi*-tetracycline; ———, 5-hydroxytetracycline; both in 0.1 *N* H_2SO_4 (aq.); E, – – –, 7-chloro-4-*epi*-tetracyclinonitrile monohydrate; ———, 7-chlorotetracyclinonitrile; both in 0.1 *N* H_2SO_4 (aq.) containing 1% by volume of dimethylformamide; F, – – –, 4-*epi*-tetracycline methiodide; ———, tetracycline methiodide; both in 0.1 *N* H_2SO_4 (aq.).

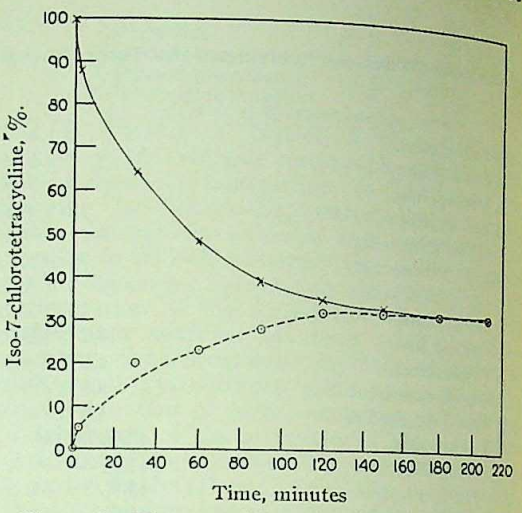

Figure 3.—The reversible epimerizations of (–o–o–) iso-7-chloro-4-*epi*-tetracycline and of (–x–x–x–) iso-7-chlorotetracyline in 2:1 dimethylformamide-1 *M* NaH_2PO_4 (aq.) at 25°.

but substantially in the 250–300 mμ region, the difference being consistent in character and direction for all pairs. It has been shown that the

Table III

A Comparison of the Properties of the Members of Epimeric Pairs Derived from the Tetracyclines[a] and Some of Their Degradation Products

Compound	$[\alpha]^{25}D$	M.p., °C. (dec.)
4-*epi*-Tetracycline (II)	−348°[b]	180–182
Tetracycline (I)	−235[b]	162–164
7-Chloro-4-*epi*-tetracycline (II)	−350[b]	209–213
7-Chlorotetracycline (I)	−245[b]	168–169
5-Hydroxy-4-*epi*-tetracycline (II)	−253[b]	163–164
5-Hydroxytetracycline (I)	−199[b]	183–185
Anhydro-4-*epi*-tetracycline hydrochloride (IV)	−265[b]	210–212
Anhydrotetracycline hydrochloride (III)	−210[b]	204–206
Iso-7-chloro-4-*epi*-tetracycline monohydrate (VI)	−160[b]	235–237
Iso-7-chlorotetracycline monohydrate (V)	− 97[b]	213–224
Benzenesulfonyl-4-*epi*-tetracyclinonitrile monohydrate	−336[c]	Dec. starting 200
Benzenesulfonyltetracyclinonitrile dimethylformamide solvate	−416[c]	Dec. starting 210
7-Chloro-4-*epi*-tetracyclinonitrile monohydrate (VIII)	−300[c]	Dec. starting 200
7-Chlorotetracyclinonitrile (VII)	−338[c]	Dec. starting 220
4-*epi*-Tetracycline methiodide (X)	−265[b]	161–162
Tetracycline methiodide (IX)	−198[b]	178–180
"Desdimethylamino-4 *epi*-tetracycline" (XI)	−251[d]	195
Desdimethylaminotetracycline (XI)	−250[d]	195

[a] Solutions of 7-bromotetracycline in solvents equilibrating the other tetracyclines changed in their ultraviolet absorption spectra and in their antibacterial activity toward *S. aureus* in directions and at rates completely comparable to those of the other tetracyclines, particularly to those of 7-chlorotetracycline. 7-Bromo-4-*epi*-tetracycline was isolated from these equilibrium mixtures as a crystalline solid having an ultraviolet absorption spectrum analogous to that of 7-chloro-4-*epi*-tetracycline and an antibacterial activity toward *S. aureus* of 5% that of 7-bromotetracycline. However, only small quantities were prepared from the available 7-bromotetracycline and recrystallized analytical material was not prepared. [b] Determined in 0.5% solution in 0.03 *N* HCl. [c] Determined in 0.5% solution in dimethylformamide. [d] Determined in 0.5% solution in Methyl Cellosolve.

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TABLE IV

ALKALINE AND ACID DESTRUCTION RATES OF THE MEMBERS OF EPIMERIC PAIRS DERIVED FROM THE TETRACYCLINES

Compound	Half reaction times in alkali	Half reaction times in 1.0 *N* H_2SO_4 (aq.), hr.	°C.
4-*epi*-Tetracycline	225 min. in 0.1 *N* NaOH (aq.) at 60°	24.0	24
Tetracycline	101 min. in 0.1 *N* NaOH (aq.) at 60°	15.5	24
7-Chloro-4-*epi* tetracycline	154 min. in *p*H 8.8 carbonate buffer (aq.) at 29°	12.8	50
7-Chlorotetracycline	53 min. in *p*H 8.8 carbonate buffer (aq.) at 29°	7.3	50
5-Hydroxy-4-*epi*-tetracycline	21.8 hr. in 0.1 *N* NaOH (aq.) at 23°	6.0	50[a]
5-Hydroxytetracycline	10.9 hr. in 0.1 *N* NaOH (aq.) at 23°	6.3	50[a]

[a] For these cases, the product of the acid-catalyzed reaction is of the apoterramycin type[13] rather than of the anhydrotetracycline type.

tetracycline structure as a whole acts as two essentially independent chromophores.[10] The ring A chromophore contributes only to the 250–300 mμ absorption, while the rings B-C-D chromophore contributes to both the 250–300 mμ absorption and the 340–380 mμ absorption. The fact that epimerization changes principally the 250–300 mμ absorption indicates that a change in the ring A chromophore is involved. A partial confirmation of this is found in the fact that the anhydro compounds arising from the acid-catalyzed dehydration of tetracycline and of 4-*epi*-tetracycline retain the isomeric, distinguishable and reversibly interconvertible characteristics of the parent pair. Formation of these anhydro compounds involves aromatization of ring C, eliminating, as possible sites for the reversible change, all asymmetric carbon atoms except those of ring A. Inversion of configuration at C.4a or C.12a was ruled out because of the very mild nature of the conditions allowing the change and the lack of side reactions.

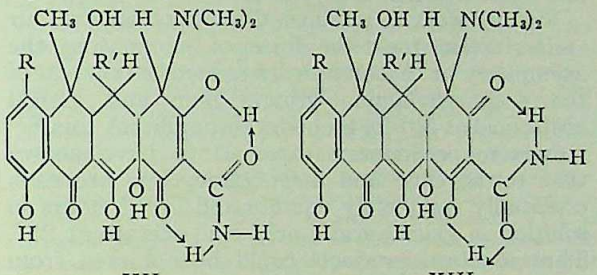
TABLE V

ULTRAVIOLET ABSORBENCY RATIOS AND BIOLOGICAL TO SPECTROPHOTOMETRIC ACTIVITY RATIOS USED FOR ASSAY OF EPIMERIC PAIR MIXTURES

Compound	Ratio of absorbency[a] at 254 mμ to absorbency at 267 mμ (AR)	Biological[b] to spectrophotometric activity[a] ratio (BSR) Value	Wave length used, mμ
Tetracycline hydrochloride	0.855	1.0	355
4-*epi*-Tetracycline hydrochloride	1.07	0.052	355
7-Chlorotetracycline hydrochloride	0.974	1.0	368
7-Chloro-4-*epi*-tetracycline hydrochloride	1.11	0.060	368
5-Hydroxytetracycline	0.836	1.0	352
5-Hydroxy-4-*epi*-tetracycline	1.13	0.032	352

[a] In 0.1 *N* H_2SO_4. [b] Turbidimetric assay against *S. aureus*.

The foregoing makes it most likely that the epimerization involves only a change in the configuration of C.4. The other possibility suggested by the published structures of the tetracyclines involves changes in the orientation of the 2-carboxamide group, whose free rotation might be prevented by strong hydrogen bonding with the two adjacent oxygen functions. The two interconvertible, isomeric possibilities resulting are represented by XII and XIII.



XII

XIII

This relationship has been suggested earlier to explain the existence of the two isomeric, distinguishable and interconvertible apoterramycins.[13] However, the interconversion of the apoterramycins is catalyzed by either acid or base. An attempt to exclude the carboxamide orientation possibility took the form of dehydrating the non-symmetric carboxamide group to the linear nitrile group. Treatment of tetracycline and 4-*epi*-tetracycline with benzenesulfonyl chloride in pyridine[13] resulted in carboxamide dehydration accompanied by esterification to form benzenesulfonylnitriles.[7,14] The benzenesulfonyltetracyclinonitrile and the benzenesulfonyl-4-*epi*-tetracyclinonitrile were isomeric and distinguishable (Table III), but neither could be reversibly interconverted under conditions equilibrating the tetracyclines in four minutes nor under a variety of other conditions, including a series of *p*H values suggested by the gain in acid strength occurring on nitrile formation. To exclude the possibility that benzenesulfonyl substitution was preventing epimerization and the possibility that the two benzenesulfonylnitriles were distinguishable because of differences in position of benzenesulfonyl substitution, 7-chlorotetracycline and 7-chloro-4-*epi*-tetracycline were treated with methanesulfonyl chloride in pyridine to form the unsubstituted nitriles VII and VIII (Table III, Fig. 2).[10,15] The two unsubstituted nitriles were likewise isomeric and distinguishable, but could not be reversibly interconverted under the conditions described for the substituted nitriles. The experiment demonstrates that the intact carboxamide group, although it may be involved in the ready interconversion of the parent compounds, is not essential to the existence of isomeric pairs. Interconversion of the nitrile pair members under conditions equilibrating the tetracyclines, had it been possible as it was with other derivatives,

(13) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **75**, 5455 (1953).

(14) The product of the corresponding reaction of 5-hydroxytetracycline has been described as being the 10-benzenesulfonylnitrile.[13]

(15) The method is that of R. Wilkinson, Research Division, American Cyanamid Company, who had previously prepared the nitrile of 7-chlorotetracycline by this method (unpublished).

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would have provided a simple, certain proof that the nitriles were indeed related as were the parent compounds and therefore that the sulfonyl chloride reagents had acted in completely parallel ways on all four compounds. The lack of this proof, taken with the lack of any other independent proof of the relationship between the nitrile pair members, such as independent synthesis, weakens the argument that distinguishable sulfonyl chloride reaction products have eliminated the carboxamide orientation possibility and have proved the carbon four epimerization alternative.[16]

Further work to establish the fact of carbon four epimerization took the form of eliminating the asymmetry at carbon four by reductive removal of the 4-dimethylamino group. Zinc and glacial acetic acid at 30° for six hours accomplishes this.[10,13] However, preliminary experiments have shown that tetracycline and 4-*epi*-tetracycline are each essentially completely equilibrated in 2.5 hours in solution in glacial acetic acid–zinc acetate at 25°. Thus identical products could be obtained from both members of an epimeric pair by reduction under these conditions either through the elimination of the asymmetry at carbon four or through the epimerization to a common product during the reaction. The problem of distinguishing between these two alternatives was resolved by the finding that the methiodides could be reduced under non-epimerizing conditions. Tetracycline methiodide (IX) and 4-*epi*-tetracycline methiodide (X) (Table III, Fig. 2) were prepared[17] and found to be isomeric, distinguishable and reversibly interconvertible. Neither methiodide was measurably epimerized after remaining four hours in a simulated reduction solvent consisting of 1:1 acetic acid–water with four equivalents of zinc acetate. In 1:1 acetic acid–water, reduction with zinc for 30 minutes was sufficient for reductive cleavage of the trimethylammonium group from both methiodides. The two resulting desdimethylamino compounds were identical (XI, Table III). Criteria of identity included elemental analysis, optical rotation, mixed melting point, ultraviolet spectra, infrared spectra, counter-current distribution and solubility. This represents sufficient proof that the quatrimycins are the 4-*epi*-tetracyclines.

Acknowledgment.—The authors wish to acknowledge, with appreciation, the work of Neva-Tay Smith on the catalytic hydrogenation of 7-chloro-4-*epi*-tetracycline to 4-*epi*-tetracycline and the work of A. G. Mistretta on the counter-current distribution of desdimethylaminotetracycline. The antibacterial activity determinations and many of the instrumental assays, the elemental analyses and the optical rotation determinations were done under the direction of H. S. Kelsey, L. Brancone and W. Fulmor, respectively.

Experimental

4-*epi*-Tetracycline Ammonium Salt Monohydrate.—A solution of 200 g. of tetracycline hydrochloride in 1 liter of 2:1 methanol–1 *M* aqueous NaH_2PO_4 was allowed to remain 20 hr. at 25°; epimerization occurred to the extent of 58%, as judged by the AR assay. Acetone (1500 ml.) was added and the mixture allowed to remain for 2 hr. at 4°. The resulting precipitate (primarily inorganic salts) was filtered out and the filtrate concentrated *in vacuo* to 400 ml. Saturation of the solution with gaseous ammonia resulted in the formation of a crystaline product which was filtered out and washed twice with 100-ml. portions of concentrated ammonia water and twice with 200-ml. portions of acetone. After drying *in vacuo* the product weighed 166 g. and represented a recovery of 93% of the 4-*epi*-tetracycline formed by the epimerization, as judged by the AR assay. One kilogram of material prepared in this way (~70% 4-*epi*-tetracycline) was dissolved in 3 liters of water by adjusting the *p*H to 8 with 400 ml. of concentrated hydrochloric acid. After being clarified by filtration, the solution was adjusted to *p*H 8.8 with 100 ml. of concentrated ammonia water. Scratching induced the formation of a crystalline product which was filtered out, slurry-washed with one liter of an 80:15:5 mixture of acetone, water and concentrated ammonia water, and washed on the filter with two liters of acetone and then with one liter of acetone. After drying *in vacuo*, the product, a crystalline ammonium salt, weighed 373 g. and assayed 96% total tetracyclines and 95% 4-*epi*-tetracycline by the AR assay.[18] Reprocessing the product through the procedure described above yielded 213 g. of crystalline 4-*epi*-tetracycline ammonium salt monohydrate which assayed 100% 4-*epi*-tetracycline ammonium salt monohydrate by both the AR and BSR assays. The antibacterial activity (turbidimetric) against *S. aureus* was 6.4% that of tetracycline hydrochloride; $[\alpha]^{25}D$ −321° (0.5% in 0.03 *N* HCl), m.p. 170° dec. The ultraviolet absorption spectrum in 0.1 *N* H_2SO_4 (aq.) showed λ_{max} in mμ (ε): 216 (14,100), 255 (16,700), 270 (15,600, shoulder), 355 (14,800).

Anal. Calcd. for $C_{22}H_{27}N_3O_8 \cdot H_2O$: C, 55.11; H, 6.11; N, 8.76; H_2O, 3.76. Found: C, 55.68; H, 6.08; N, 8.82; H_2O, 4.14.

4-*epi*-Tetracycline Monohydrate.—To a filtered solution of 390 g. of 4-*epi*-tetracycline ammonium salt in 2.5 liters of water and 60 ml. of concentrated hydrochloric acid (solution *p*H, 5.3) was added concentrated ammonia water to a final *p*H of 6.8. Scratching induced the formation of crystals which, after being washed twice with 1-liter portions of water and dried *in vacuo*, weighed 200 g. An analytical sample was prepared by dissolving 2 g. of this material in 25 ml. of water adjusted to *p*H 1.2 with concentrated hydrochloric acid, filtering, and adjusting the filtrate *p*H to 5.8 with concentrated ammonia water. The resulting crystalline product, after being washed with 10 ml. of water and 25 ml. of acetone and dried *in vacuo*, weighed 1.3 g. and assayed 100% 4-*epi*-tetracycline monohydrate by the AR and BSR assays. The antibacterial activity (turbidimetric) against *S. aureus* was 6.4% that of tetracycline hydrochloride; $[\alpha]^{25}D$ −335° (0.5% in 0.03 *N* HCl), m.p. 178° dec. The ultraviolet absorption spectrum in 0.01 *N* H_2SO_4 (aq.) showed λ_{max} in mμ (ε): 216 (13,900), 255 (16,400), 270 (15,200, shoulder), 355 (14,700).

Anal. Calcd. for $C_{22}H_{24}N_2O_8 \cdot H_2O$: C, 57.12; H, 5.68; N, 6.06; H_2O, 3.89. Found: C, 57.41; H, 5.62; N, 6.00; H_2O, 3.90.

(16) A related experiment has shown that N-mono-*t*-butylanhydrotetracycline (J. E. Lynch and C. R. Stephens, "Antibiotics Annual," Medical Encyclopedia, Inc., 1955–1956, p. 466), when allowed to remain in solution in 2:1 dimethylformamide/1 *M* aqueous NaH_2PO_4, undergoes a change in ultraviolet absorption spectrum comparable in rate, direction and magnitude to that undergone by anhydrotetracycline under the same conditions. Although the experiment does not clarify the nature of the epimerization, it does provide an example of a change in the carboxamide group that does not interfere with easy epimerization. The N-mono-*t*-butylanhydrotetracycline was prepared by J. Boothe, Research Division, American Cyanamid Co.

(17) The methods of methiodide preparation and reduction and an authentic sample of tetracycline methiodide for comparison purposes were obtained from J. Boothe, Research Division, American Cyanamid Co.

(18) Diluting the mother liquor with an equal volume of acetone and adjusting the *p*H to 9.0 with concentrated ammonia water yielded a second crop of crystals which, after washing and drying as before, weighed 444 g. and assayed 96% total tetracyclines and 70% 4-*epi*-tetracycline by the AR assay. The operations of this preparative process bring about little change in tetracycline or 4-*epi*-tetracycline except epimerization, so that recycle of second crystal crops, solvent-free mother liquors, etc., through re-equilibration and re-isolation is a feasible method of increasing the over-all yield.

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June 5, 1957

Tetracycline from 4-*epi*-Tetracycline.—A solution of 5 g. of 4-*epi*-tetracycline ammonium salt monohydrate in 100 ml. of glacial acetic acid was allowed to remain 24 hr. at 25° and was then mixed with 400 ml. of water and seeded with a small quantity of tetracycline neutral. The crystals which formed on aging were collected, washed, dried and dissolved in 5 volumes of 4:1 Ethyl Cellosolve–*n*-butyl alcohol. The *p*H of the solution was adjusted to 1.5 with concentrated hydrochloric acid. The crystals which formed on aging were collected, washed, dried and identified as tetracycline hydrochloride (with possible trace amounts of 4-*epi*-tetracycline hydrochloride) by ultraviolet and infrared spectra, antibacterial activity (turbidimetric) against *S. aureus* and paper chromatography.

7-Chloro-4-*epi*-tetracycline Ammonium Salt Monohydrate.—A solution of 100 g. of 7-chlorotetracycline in 500 ml. of 2:1 dimethylformamide–1 *M* aqueous NaH_2PO_4 was allowed to remain 20 hr. at 25°; epimerization occurred to the extent of 45%, as judged by the AR assay. Acetone (1 liter) was added and the resulting precipitate (primarily inorganic salts) filtered out. Adjustment of the filtrate to *p*H 8 with concentrated ammonia water yielded a crystalline product which, after being washed once with 25 ml. of a 2:1 acetone–dimethylformamide mixture and twice with 100-ml. portions of acetone and dried *in vacuo*, weighed 53.1 g. and represented a recovery of 78% of the 7-chloro-4-*epi*-tetracycline formed by the epimerization. To a filtered solution of 10 g. of this material in 25 ml. of water was added sufficient concentrated ammonia water to give a *p*H of 9.5. Aging for one hour yielded a crystalline product which, after being washed once with 10 ml. of 4:1 acetone–water and once with 20 ml. of acetone and dried *in vacuo*, weighed 4.2 g. and assayed 96% 7-chloro-4-*epi*-tetracycline ammonium salt by BSR assay. An analytical sample was prepared by dissolving 1.0 g. of this material in 10 ml. of water, filtering, adding 10 ml. of acetone to the filtrate, and adjusting the *p*H to 9.0 with concentrated ammonia water. The resulting crystalline product, after being washed with 3 ml. of 4:1 acetone–water and 10 ml. of acetone and dried *in vacuo*, weighed 0.64 g. and assayed 100% 7-chloro-4-*epi*-tetracycline ammonium salt monohydrate as judged by the AR and BSR assays. The antibacterial activity (turbidimetric) against *S. aureus* was 4.2% that of 7-chlorotetracycline hydrochloride; $[\alpha]^{25}D$ −321° (0.5% in 0.03 *N* HCl), m.p. 163–164° dec. The ultraviolet absorption spectrum in 0.1 *N* H_2SO_4 (aq.) showed λ_{max} in mμ (ε): 230 (18,300), 255 (17,700), 368 (9,400).

Anal. Calcd. for $C_{22}H_{26}N_3ClO_8 \cdot H_2O$: C, 51.40; H, 5.49; N, 8.18; Cl, 6.90; H_2O, 3.50. Found: C, 51.88; H, 5.63; N, 8.58; Cl, 7.02; H_2O, 2.88.

7-Chloro-4-*epi*-tetracycline.—To a filtered solution of 49.7 g. of 7-chloro-4-*epi*-tetracycline ammonium salt monohydrate in 400 ml. of water was added 9.2 ml. of concentrated hydrochloric acid. The resulting crystalline product, after being washed with water and with acetone and dried *in vacuo*, weighed 22.7 g. An analytical sample was prepared by dissolving 1 g. of this material in 30 ml. of methanol and filtering. On standing, crystals appeared which, after being washed with water and with methanol and dried *in vacuo*, weighed 0.64 g. and assayed 100% 7-chloro-4-*epi*-tetracycline by AR and BSR assay. The antibacterial activity (turbidimetric) against *S. aureus* was 4.0% that of 7-chlorotetracycline hydrochloride; $[\alpha]^{25}D$ −350° (0.5% in 0.03 *N* HCl), m.p. 209–213° dec. The ultraviolet absorption spectrum in 0.1 *N* H_2SO_4 (aq.) showed λ_{max} in mμ (ε): 230 (18,400), 255 (17,700), 368 (9,300).

Anal. Calcd. for $C_{22}H_{23}N_2ClO_8$: C, 55.18; H, 4.84; N, 5.84; Cl, 7.41. Found: C, 55.03; H, 4.90; N, 5.83; Cl, 7.56.

7-Chloro-4-*epi*-tetracycline Hydrochloride.—A solution of 40 g. of 7-chloro-4-*epi*-tetracycline ammonium salt monohydrate in 400 ml. of water was adjusted to *p*H 1 with 20 ml. of concentrated hydrochloric acid and aged for 30 min. The resulting crystalline product, after being washed with 25 ml. of cold water and dried *in vacuo*, weighed 19.3 g. and assayed 100% 7-chloro-4-*epi*-tetracycline hydrochloride by the AR and BSR assays. An analytical sample was prepared by dissolving 2.0 g. of this material in 75 ml. of 2-propanol and filtering, and aging. The resulting crystalline product, after being washed with 5 ml. of 2-propanol and dried *in vacuo*, weighed 1.7 g. and assayed 100% 7-chloro-4-*epi*-tetracycline hydrochloride by AR and BSR assay. The antibacterial activity (turbidimetric) against *S. aureus* was 4.7% that of 7-chlorotetracycline hydrochloride; $[\alpha]^{25}D$ −312° (0.5% in 0.03 *N* HCl), m.p. 211–214° dec. The ultraviolet absorption spectrum in 0.1 *N* H_2SO_4 (aq.) showed λ_{max} in mμ (ε): 230 (17,900), 255 (17,400), 368 (9,300).

Anal. Calcd. for $C_{22}H_{24}N_2Cl_2O_8$: C, 51.30; H, 4.69; N, 5.44; Cl, 13.77. Found: C, 51.80; H, 4.90; N, 5.26; Cl, 13.45.

5-Hydroxy-4-*epi*-tetracycline.—A solution of 100 g. of 5-hydroxytetracycline in 500 ml. of glacial acetic acid was allowed to remain 21 hr. at 25°; epimerization occurred to the extent of 29% as judged by the AR assay. Vacuum distillation to a volume of 200 ml., followed by the addition of 1500 ml. of water and vacuum distillation to 250 ml., resulted in the precipitation of unepimerized 5-hydroxytetracycline which, after being removed by filtration and dried *in vacuo*, weighed 61.7 g. and assayed 95% 5-hydroxytetracycline by microbiological assay (*S. aureus*) and 0% 5-hydroxy-4-*epi*-tetracycline by AR and BSR assay. The filtrate was adjusted to *p*H 7.7 with 70 ml. of concentrated ammonia water. The resulting crystalline product, after being washed twice with 50-ml. portions of water and dried *in vacuo*, weighed 14.9 g. and assayed 96% 5-hydroxy-4-*epi*-tetracycline by BSR assay. A filtered solution of 16.0 g. of material prepared in this way in 300 ml. of methanol and 1.5 ml. of concentrated hydrochloric acid was adjusted with concentrated ammonia water to *p*H 7 and aged for 2 hr. The resulting crystalline product was washed twice with 250-ml. portions of methanol, three times with 60-ml. portions of water, and twice with 50-ml. portions of acetone. After drying *in vacuo*, the product weighed 7.2 g. and assayed 100% 5-hydroxy-4-*epi*-tetracycline by AR assay and 98% by BSR assay. The antibacterial activity (turbidimetric) against *S. aureus* was 4.5% that of 5-hydroxytetracycline; $[\alpha]^{25}D$ −253° (0.5% in 0.03 *N* HCl), m.p. 163–164° dec. The ultraviolet absorption spectrum in 0.1 *N* H_2SO_4 (aq.) showed λ_{max} in mμ (ε): 215 (12,200), 253 (14,200), 275 (12,000), 355 (12,100).

Anal. Calcd. for $C_{22}H_{24}N_2O_9$: C, 57.34; H, 5.30; N, 6.08. Found: C, 57.68; H, 5.34; N, 6.42.

Anhydro-4-*epi*-tetracycline Hydrochloride.—A solution of 10 g. of 4-*epi*-tetracycline in a mixture of 75 ml. of butanol, 19 ml. of water and 31 ml. of concentrated hydrochloric acid was heated to 70° for one hour, cooled and diluted with 40 ml. of water. The *p*H was adjusted to 5.5 with 5 *N* sodium hydroxide and the resulting precipitate washed with water and dried (6.5 g.). One gram of this precipitate was slurried in 30 ml. of methanol containing 1 ml. of concentrated hydrochloric acid and the mixture filtered. One ml. of concentrated hydrochloric acid was added to the filtrate. The crystalline product that resulted after two hours aging was washed with cold methanol and cold water and dried (0.45 g.); $[\alpha]^{25}D$ −265° (0.5% in 0.03 *N* HCl), m.p. 210–212 dec. The ultraviolet absorption spectrum in 0.1 *N* NaOH (aq.) showed λ_{max} in mμ (ε): 225 (22,200), 268 (29,600), 320–340 (4,200, shoulder), 425 (9,300).

Anal. Calcd. for $C_{22}H_{23}N_2ClO_7$: C, 57.08; H, 5.01; N, 6.05; Cl, 7.66. Found: C, 56.84; H, 5.34; N, 5.86; Cl, 7.59.

Reversible Epimerization of Anhydrotetracycline Hydrochloride and Anhydro-4-*epi*-tetracycline Hydrochloride.—A solution of 0.032 g. of anhydrotetracycline hydrochloride[9,10] in 10 ml. of 2:1 methanol/1 *M* aqueous NaH_2PO_4 was allowed to remain at 25° for 20 hr. The same operation was carried out starting with anhydro-4-*epi*-tetracycline hydrochloride. The ultraviolet absorption spectra in 0.1 *N* sodium hydroxide were determined for both solutions before and after equilibration. At the end of 20 hr. the two solutions had identical ultraviolet absorption spectra which did not change further on additional standing. The ultraviolet absorption spectra of the equilibrium solutions corresponded to an equilibrium composition of 63% anhydrotetracycline and 37% anhydro-*epi*-tetracycline. The experiment demonstrates the approach to the same equilibrium composition starting from each of the two pure components.

Iso-7-chloro-4-*epi*-tetracycline Monohydrate.—A solution of 20 g. of 7-chloro-4-*epi*-tetracycline ammonium salt in 180 ml. of 0.5 *N* aqueous sodium hydroxide (*p*H of solution was

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9.4) was allowed to remain 24 hr. at 25°. The ultraviolet absorption spectrum of the solution indicated that the rearrangement to iso-7-chloro-4-*epi*-tetracycline had occurred without epimerization and in 86% yield. Adjustment of the *p*H of the solution to 7.0 yielded a gelatinous precipitate which, after being slurry-washed with water and dried over phosphorus pentoxide *in vacuo*, weighed 12.4 g. (64% yield). The ultraviolet absorption spectrum of this crude iso-7-chloro-4-*epi*-tetracycline indicated that epimerization had occurred during work-up to the extent of about 30%. The contaminating iso-7-chlorotetracycline was removed by successive extractions with hot methanol to yield crystalline iso-7-chloro-4-*epi*-tetracycline monohydrate, $[\alpha]^{25}D$ −160° (0.5% in 0.03 *N* HCl), m.p. 235–237° dec. The ultraviolet absorption spectrum in 0.1 *N* sodium hydroxide (aq.) showed λ_{max} in mμ (ε): 255 (15,400), 285 (12,300), 345 (7,100). The infrared spectrum indicated diketone bands in the 6–7 μ region and a phthalide band at 5.75–5.80 μ. A single pK_a of 8.3 was found in 1:1 water–methanol. The material migrated as a single component (R_f 0.80) in a 3% sodium arsenite paper chromatographic system[19] and also in a 1:1 water–methanol system (R_f 0.60).

Anal. Calcd. for $C_{22}H_{23}N_2ClO_8 \cdot H_2O$: C, 53.17; H, 5.07; N, 5.64; Cl, 7.14; H_2O, 3.63. Found: C, 52.98; H, 5.00; N, 5.33; Cl, 7.41; H_2O, 4.19.

Iso-7-chlorotetracycline.—7-Chlorotetracycline hydrochloride was dissolved in 0.1 *N* aqueous sodium hydroxide and processed as was the 7-chloro-4-*epi*-tetracycline above, to yield iso-7-chlorotetracycline monohydrate in 68% yield, $[\alpha]^{25}D$ −97° (0.5% in 0.03 *N* HCl), m.p. 213–224° dec. A single pK_a of 7.80 was found in 1:1 water–methanol.

Anal. Calcd. for $C_{22}H_{23}N_2ClO_8 \cdot H_2O$: C, 53.17; H, 5.07; N, 5.64; Cl, 7.14; water, 3.63. Found: C, 52.70; H, 5.20; N, 5.32; Cl, 7.14; water, 2.43.

Addition of concentrated hydrochloric acid to an acetone solution of the monohydrate yielded iso-7-chlorotetracycline hydrochloride,[11] $[\alpha]^{25}D$ −94.5° (0.5% in 0.03 *N* HCl), m.p. 255–258° dec. A single pK_a of 7.80 was found in 1:1 water–methanol. The ultraviolet absorption spectrum in 0.1 *N* sodium hydroxide (aq.) (Fig. 2) showed λ_{max} in mμ (ε): 255 (14,800), 285 (14,700), 345 (7,300). The ultraviolet and infrared spectra were identical with those of an authentic preparation.[11] The substance migrated as a single component (R_f 0.80) in a 3% sodium arsenite paper chromatographic system[19] and also in a 1:1 water–methanol system (R_f 0.60).

Reversible Epimerization of Iso-7-chlorotetracycline and of Iso-7-chloro-4-*epi*-tetracycline.—Repeated determinations of the ultraviolet absorption spectrum (in 0.1 *N* sodium hydroxide) of a 40 μg./ml. solution of iso-7-chlorotetracycline in 2:1 dimethyl formamide–1 *M* aqueous NaH_2PO_4 at 25° showed systematic changes occurring during the first 180 min. after preparation of the solution, with no additional changes occurring with further time. The ultraviolet absorption spectrum at equilibrium corresponded to a mixture of 32% iso-7-chlorotetracycline and 68% iso-7-chloro-4-*epi*-tetracycline.

The same sequence with iso-7-chloro-4-*epi*-tetracycline as the starting material yielded, after 120 min., a stable ultraviolet absorption spectrum corresponding to a mixture of 32% iso-7-chlorotetracycline and 68% iso-7-chloro-4-*epi*-tetracycline.

Figure 3 illustrates this approach to a common equilibrium mixture from both pure components.

4-*epi*-Tetracycline from 7-Chloro-4-*epi*-tetracycline.—A solution of 5 g. of 7-chloro-4-*epi*-tetracycline ammonium salt in 45 ml. of water containing 1.4 g. of 5% palladium-on-carbon was contacted with hydrogen on a Parr shaker. A rapid uptake of hydrogen ensued until, after 25 minutes, one equivalent of hydrogen was absorbed, at which time the rate decreased sharply. After filtration, the solution was diluted with 100 ml. of acetone, and the *p*H was adjusted to 9.0 with 1.0 ml. of concentrated ammonia water. Seeding induced the formation of crystalline ammonium salt which, after washing with acetone and drying *in vacuo* at 25°, weighed 2.60 g. The product had the ultraviolet absorption spectrum and microbiological assay of the ammonium salt of 4-*epi*-tetracycline.

(19) T. Berti and L. Cima, *Boll. Ist. Sieroterap. Milan.*, **33**, 643 (1954).

Benzenesulfonyl-4-*epi*-tetracyclinonitrile Monohydrate.—Twelve milliliters of benzenesulfonyl chloride was added dropwise with stirring to a mixture of 10 g. of 4-*epi*-tetracycline and 20 ml. of pyridine at 10° (ice-bath); the rate of addition was controlled so that the temperature did not exceed 40°. When the temperature began to fall, the reaction was continued for 30 min. without the ice-bath. One hundred ml. of ether was added with stirring, followed by settling and decantation of the supernatant. The thick, gummy residue was stirred with 500 ml. of water to yield an amorphous solid which was air-dried and slurried with 250 ml. of acetone to yield a yellow, crystalline, product which was filtered off, washed with acetone, and dried *in vacuo*. The product was dissolved in 15 ml. of dimethylformamide and 50 ml. of acetone was added. The resulting yellow, crystalline product, after drying *in vacuo*, weighed 5.2 g., $[\alpha]^{25}D$ −336° (0.5% in dimethylformamide), dec. at 200°. The ultraviolet absorption spectrum in 0.1 *N* H_2SO_4 (aq.) containing 1% by volume of dimethylformamide showed λ_{max} in mμ (ε): 270 (14,200), 347 (9,900) and λ_{min} in mμ (ε): 310 (7,650). The infrared spectrum showed a nitrile band at 4.56 μ.

Anal. Calcd. for $C_{28}H_{29}N_2SO_{10}$: C, 57.40; H, 4.96; N, 4.78; S, 5.47. Found: C, 57.51; H, 5.29; N, 4.74; S, 4.97.

Benzenesulfonyltetracyclinonitrile Dimethylformamide Solvate.—Twenty-four milliliters of benzenesulfonyl chloride was added dropwise with stirring to a mixture of 20 g. of tetracycline and 40 ml. of pyridine at 10° (ice-bath); the rate of addition was controlled so that the temperature did not exceed 50°. When the temperature began to fall, the reaction was continued for 30 min. without the ice-bath; 75 ml. of ether was added with stirring, followed by settling and decantation of the supernatant. To the thick, gummy residue was added 500 ml. of water; on stirring, the mixture was partly converted to a crystalline solid. The residue remaining after filtration was dried *in vacuo* and dissolved in 10 ml. of Ethyl Cellosolve containing 4.4 ml. of triethylamine (*p*H 9.5). After filtration, the solution was adjusted to *p*H 2.5 with concentrated HCl and allowed to remain on the rotary shaker overnight. The resulting crystalline product, after being washed with 10 ml. of Ethyl Cellosolve containing 1 ml. of 2 *N* HCl and being dried *in vacuo*, weighed 6.3 g. The product was recrystallized from 1:4 dimethylformamide–acetone, $[\alpha]^{25}D$ −416° (0.5% in dimethylformamide), dec. at 210°. The ultraviolet absorption spectrum in 0.1 *N* H_2SO_4 (aq.) containing 1% by volume of dimethylformamide showed λ_{max} in mμ (ε): 275 (15,250), 348 (11,350) and λ_{min} in mμ (ε): 319 (9,650). The infrared spectrum showed a nitrile band at 4.55 μ.

Anal. Calcd. for $C_{31}H_{34}N_3SO_{10}$: C, 58.20; H, 5.31; N, 6.56; S, 5.00. Found: C, 58.25; H, 5.24; N, 5.93; S, 4.93.

7-Chloro-4-*epi*-tetracyclinonitrile Monohydrate.—Four milliliters of methanesulfonyl chloride was added dropwise with stirring to a mixture of 5.0 g. of 7-chloro-4-*epi*-tetracycline and 20 ml. of pyridine at −5° (ice-bath); the addition rate was controlled so that the temperature did not exceed 5°. The mixture was stirred 1 hr., and 150 ml. of ether was then added, followed by stirring, settling, and decantation of the supernatant. The solids were leached with 75 ml. of water at *p*H 1. The wet residue remaining after filtration was dissolved in 10 ml. of dimethylformamide, after which was added 30 ml. of chloroform. Crystalline nitrile precipitated which, after being washed with acetone, washed with ether, and dried *in vacuo*, weighed 1.5 g., $[\alpha]^{25}D$ −300° (0.5% in dimethylformamide), dec. at 200°. The ultraviolet absorption spectrum in 0.1 *N* H_2SO_4 (aq.) containing 1% by volume of dimethylformamide showed λ_{max} in mμ (ε): 272 (14,100), 366 (8,750) and λ_{min} in mμ (ε): 320 (6,750). The infrared spectrum showed a nitrile band at 4.57 μ.

Anal. Calcd. for $C_{22}H_{23}N_2O_8Cl$: C, 55.10; H, 4.80; N, 5.85; Cl, 7.40. Found: C, 54.91; H, 4.76; N, 5.72; Cl, 7.89.

7-Chlorotetracyclonitrile.—Four milliliters of methanesulfonyl chloride was added dropwise with stirring to a mixture of 5.0 g. of 7-chlorotetracycline and 20 ml. of pyridine at −5° (ice-bath); the addition rate was controlled so that the temperature did not exceed 5°. The mixture was stirred 45 minutes and 100 ml. of water was then added with stirring. The yellow residue remaining after filtration was dissolved in dimethylformamide. Five volumes of acetone

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were added; the resulting crystalline product, after being washed with acetone and dried *in vacuo*, weighed 2.6 g., $[\alpha]^{25}D$ −338° (0.5% in dimethylformamide), dec. at 220°. The ultraviolet absorption spectrum in 0.1 *N* H_2SO_4 (aq.) containing 1% by volume of dimethylformamide showed λ_{min} in mμ (ε): 276 (14,100), 365 (9,350) and λ_{max} in mμ (ε): 325 (7,250). The infrared spectrum showed a nitrile band at 4.54 μ

Anal. Calcd. for $C_{22}H_{21}N_2O_7Cl$: C, 57.30; H, 4.56; N, 6.07; Cl, 7.69. Found: C, 56.99; H, 5.01; N, 6.37; Cl, 7.37.

Attempted Epimerization of the Nitriles. A. Benzenesulfonyl-4-*epi*-tetracyclinonitrile.—To a series of solutions of benzenesulfonyl-4-*epi*-tetracyclinonitrile in 4:1 dimethylformamide–water was added enough 85% orthophosphoric acid to give the following *p*H values: 0.3, 2.2, 2.6, 3.1, 3.5. In no case did aging for 114 hr. at 25° bring about any epimerization detectable by ultraviolet absorption spectrum changes. Both 4-*epi*-tetracycline and 7-chloro-4-*epi*-tetracycline were completely equilibrated in 24 hr. under the conditions of the *p*H 3.5 experiment above.

B. 7-Chloro-4-*epi*-tetracyclinonitrile.—A solution of 7-chloro-4-*epi*-tetracyclinonitrile (1 mg./ml.) in 4:1 dimethylformamide–water, brought to a *p*H of 1 with 85% orthophosphoric acid, was allowed to remain at 25° for 2 hr. and also at 40° for 44 hr. A solution of 7-chloro-4-*epi*-tetracyclinonitrile (1 mg./ml.) in 1:4 dimethylformamide–*p*H 7.0 phosphate buffer was allowed to remain at 25° for 22 hr. In no case could any epimerization be detected by ultraviolet absorption spectrum changes.

C. 7-Chlorotetracyclinonitrile.—To a series of solutions (1 mg./ml.) of 7-chlorotetracyclinonitrile in 4:1 dimethylformamide–water was added enough 85% orthophosphoric acid to give the following *p*H values: 0.3, 2.2, 2.6, 3.3. All solutions were aged at 25° for 22 hr. The *p*H 0.3 solution was heated to 40° for 22 hr. The *p*H 3.3 solution was heated to 85° for 3 hr. A solution of 7-chlorotetracyclinonitrile (1 mg./ml.) in 1:4 dimethylformamide—*p*H 7.0 phosphate buffer was allowed to remain at 25° for 22 hr. In no case could any epimerization be detected by ultraviolet absorption spectrum changes. Both 4-*epi*-tetracycline and 7-chloro-4-*epi*-tetracycline were completely equilibrated in 24 hr. under the conditions of the *p*H 3.5, 25° experiment above.

In the cases of all attempted nitrile equilibrations, the limits on the severity of the conditions tried were set by the appearance of other types of chemical changes.

4-*epi*-Tetracycline Methiodide.—A solution of 10 g. of 4-*epi*-tetracycline and 35 ml. of methyl iodide in 100 ml. of tetrahydrofuran was stirred for 24 hr. at room temperature. The resulting crystalline product was washed with 20 ml. of tetrahydrofuran and dried *in vacuo* at 40° to give a yield of 10.1 g. This was dissolved in 250 ml. of ethanol at 50°. Aging the solution with stirring at room temperature for 2 hr. gave a crop of crystalline methiodide contaminated with substantial amounts of unreacted 4-*epi*-tetracycline. The mother liquor was warmed to 40° and mixed with an equal volume of petroleum ether. On cooling, additional crystalline product precipitated which, after being washed with petroleum ether and dried, weighed 4.42 g., $[\alpha]^{25}D$ −265° (0.5% in 0.03 *N* HCl), m.p. 161–162° dec. The ultraviolet absorption spectrum in 0.1 *N* H_2SO_4 (aq.) showed λ_{max} in mμ (ε): 223 (21,900), 250 (15,100), 270 (15,000, shoulder), 355 (13,500).

Anal. Calcd. for $C_{23}H_{27}N_2O_8I$: C, 47.11; H, 4.64; N, 4.71; I, 21.64. Found: C, 47.32; H, 4.74; N, 4.64; I, 21.29.

Tetracycline Methiodide.—A solution of 30 g. of tetracycline and 105 ml. of methyl iodide in 450 ml. of tetrahydrofuran was stirred for 24 hr. at room temperature. The resulting crystalline product was washed with 50 ml. of tetrahydrofuran and dried *in vacuo* at 40° to give a yield of 34.5 g. Recrystallization from 750 ml. of ethanol (50°), washing with cold ethanol, and drying *in vacuo* yielded 19.3 g. of product, $[\alpha]^{25}D$ −198° (0.5% in 0.03 *N* HCl), m.p. 178–180° dec. The ultraviolet absorption spectrum in 0.1 *N* H_2SO_4 (aq.) showed λ_{max} in mμ (ε): 223 (25,400), 274 (18,000), 355 (14,600).

Anal. Calcd. for $C_{23}H_{27}N_2O_8I$: C, 47.11; H, 4.64; N, 4.71; I, 21.64. Found: C, 47.38; H, 4.58; N, 4.91; I, 22.15.

Reversible Epimerization of Tetracycline Methiodide and 4-*epi*-Tetracycline Methiodide.—A solution of 40 mg. of 4-*epi*-tetracycline methiodide in 1 ml. of 2:1 dimethylformamide–1 *M* aqueous NaH_2PO_4 was allowed to remain 16.5 hr. at 25°. At the end of that time a crystalline solid had formed whose ultraviolet absorption spectrum showed it to be pure tetracycline methiodide. An AR assay of the mother liquor indicated a composition of 65% tetracycline methiodide and 35% 4-*epi*-tetracycline methiodide.

Rapid Reversible Epimerization of Tetracycline and 4-*epi*-Tetracycline in Glacial Acetic Acid with Four Equivalents of Zinc Acetate (Simulated Reduction Solvent).—A solution of 50 mg. of tetracycline and 50 mg. of zinc acetate dihydrate (4 equivalents) in 1 ml. of glacial acetic acid was allowed to remain at 25° while its ultraviolet absorption spectrum was determined repeatedly. After 20 min., the tetracycline was approximately 13% epimerized; after 140 min., approximately 35% epimerized. The same sequence starting with 4-*epi*-tetracycline showed 13% tetracycline after 20 min., 50% after 140 min.

Slow Reversible Epimerization of Tetracycline Methiodide and 4-*epi*-Tetracycline Methiodide in 1:1 Acetic Acid–Water with Four Equivalents of Zinc Acetate (Simulated Reduction Solvent).—A solution of 55 mg. of tetracycline methiodide and 38 mg. of zinc acetate dihydrate (4 equivalents) in 1.0 ml. of 1:1 acetic acid–water was allowed to remain at 25° while its ultraviolet absorption was repeatedly determined. After 260 min., essentially no change (~3% epimerization) had occurred. The same sequence starting with 4-*epi*-tetracycline methiodide yielded essentially no change after 120 min. and approximately 9% change in the direction of tetracycline methiodide after 260 min. Under these conditions the epimerization rates for the methiodides are measurably slower than those for the parent compounds (Table I).

Desdimethylaminotetracycline. A. From Tetracycline Methiodide.—A solution of 1.0 g. of tetracycline methiodide in 30 ml. of 1:1 acetic acid–water was purged with nitrogen; 1.5 g. of zinc dust was added and the mixture shaken under nitrogen for 30 min. and filtered. The filtrate was diluted with an equal volume of water and freeze-dried. The resulting solid was slurried 30 min. with 80 ml. of water containing 0.8 ml. of concentrated hydrochloric acid. The residue was washed with water, dried *in vacuo* (354 mg.), and dissolved in 3 ml. of methanol. Fifty milliliters of ether was added and the resulting precipitate removed by filtration. The filtrate was evaporated to about 1 ml. and triturated with 3 ml. of water. Crystals formed which after water washing and drying weighed 270 mg. Recrystallization from warm methanol yielded desdimethylaminotetracycline, $[\alpha]^{25}D$ −250° (0.5% in Methyl Cellosolve), m.p. 195° dec. The ultraviolet absorption spectrum in 0.1 *N* methanolic sulfuric acid showed λ_{max} in mμ (ε): 221 (23,100), 263 (24,700), 360 (21,400).

Anal. Calcd. for $C_{20}H_{19}NO_8$: C, 59.75; H, 4.77; N, 3.49. Found: C, 59.80; H, 4.72; N, 3.30.

B. From 4-*epi*-Tetracycline Methiodide.—Three grams of 4-*epi*-tetracycline methiodide was reduced, freeze-dried, leached with hydrochloric acid and dried *in vacuo*, using the conditions described above for tetracycline methiodide, to yield 2.4 g. of product. Two grams of this material was extracted with 100 ml. of hot ethyl acetate, leaving 0.76 g. of unextractables consisting largely of unreacted methiodide. Dilution of the extract with four volumes of petroleum ether yielded a precipitate which on drying weighed 0.9 g. A solution of this precipitate in 5 ml. of warm methanol gave, after one hour aging at room temperature, a crystalline product which, after being washed with methanol and dried, weighed 0.23 g., $[\alpha]^{25}D$ −251° (0.5% in Methyl Cellosolve), m.p. 195° dec. Mixed melting point with the product from tetracycline methiodide showed no depression. The ultraviolet absorption spectrum in 0.1 *N* methanolic sulfuric acid showed λ_{max} in mμ (ε): 221 (22,200), 263 (24,300), 360 (21,300).

Anal. Calcd. for $C_{20}H_{19}NO_8$: C, 59.75; H, 4.77; N, 3.49. Found: C, 59.40; H, 4.88; N, 3.42.

Identity and Homogeneity of Desdimethylaminotetracycline from Tetracycline Methiodide and from 4-*epi*-Tetracycline Methiodide.—The samples of desdimethylaminotetracycline prepared from the two sources were judged identical on the basis of optical rotation, melting point, ultraviolet absorption spectrum and the elemental analysis data presented above. In addition, infrared spectra were identical.

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Countercurrent distribution in a 50-tube Craig machine, using the system chloroform against 0.2 *M* aqueous phosphate buffer (*p*H 7.53), gave, for each sample, a single peak at tube 34. The shape of the peak for each sample corresponded with the theoretical curve for a single component peaking at tube 34. The ultraviolet absorption spectra of both peak tube contents were identical with each other and with those of the two starting materials.

PEARL RIVER, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

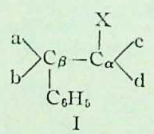
Studies in Stereochemistry. XXVI. Solvolytic Rearrangements in the 1,2-Diphenyl-2-methyl-1-butanol System[1]

BY DONALD J. CRAM AND JANET ALLINGER

RECEIVED OCTOBER 1, 1956

The tosylates of the optically pure diastereomers of the 1,2-diphenyl-2-methyl-1-butanol system have been solvolyzed in dry acetic and formic acids, respectively. Phenyl migration from C$_\beta$ dominates the reaction course, at the most only a trace of alkyl migration being observed. In the more nucleophilic and poorer ionizing solvent (acetic acid), a larger amount of unrearranged product was observed, the simple substitution reaction being somewhat stereospecific in the *direction of inversion*. In the less nucleophilic and better ionizing solvent (formic acid), a smaller amount of unrearranged product was observed, the simple substitution reaction being somewhat stereospecific in the *direction of retention*. The results indicate that three stereochemically discrete processes compete with one another, all three leading to simple substitution product: (1) a simple solvolytic inversion mechanism; (2) a simple solvolytic mechanism whose specificity is sterically induced by the asymmetry at C$_\beta$; (3) a phenonium ion mechanism which can lead to simple substitution product with retention of configuration. That rearranged products arise from both bridged and rearranged open carboniun ions is indicated.

In previous investigations of this series, the solvolytic behavior of systems I have been studied in which a = c = alkyl and b = d = hydrogen[2]; a = b = c = d = alkyl[3]; a = alkyl, b = c = hydrogen and d = phenyl[4]; and a = phenyl, b = c = hydrogen and d = alkyl.[5] Others have studied systems I in which a = alkyl, b = c = d = hydrogen[6]; a = b = c = hydrogen and d = alkyl[7]; a = c = phenyl, b = d = hydrogen.[8] The tendency for phenyl to participate in ionization was found to vary markedly with the electrical nature of substituents at C$_\alpha$ and C$_\beta$, as well as the character of the solvent, and the steric situation within the molecule. The 1,2-diphenyl-2-methyl-1-butanol



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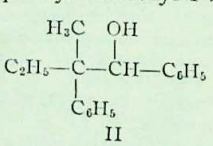


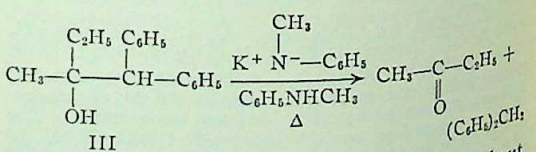
II

system (II) belongs in a borderline category with respect to phenyl involvement in ionization, and this paper reports the results of an investigation of the acetolysis and formolysis of its diastereomeric tosylates.

Methods

The four stereoisomers of II were isolated in a pure state and their configurations assigned in a previous investigation.[9] The four tosylate derivatives were prepared from the corresponding potassium alcoholates and tosyl chloride, the derivatives possessing the *threo* configuration being particularly unstable. The products were isolated in the usual way, the olefin–ester mixtures being converted (LiAlH$_4$) to alcohol–olefin mixtures which were separated into olefin and alcohol components. In runs involving *erythro* materials and *threo* materials, 73 and 87%, respectively, of the starting materials were accountable.

Analysis of Alcohol Fractions.—Comparison of the infrared spectra of the alcohol components obtained from the solvolyses with those of *threo*- and *erythro*-II and of III (product of phenyl migration) suggested the bulk of the material to consist of these components. Accordingly, infrared analytical procedures were developed based on these three components utilizing the six most advantageous wave lengths in the infrared for analysis. Two independent sets of three simultaneous equations when solved provided estimates of percentage composition. Known mixtures of the three components indicated the deviations from Beer's law to be small. The analyses for the acetolysis runs (runs 1 and 2 of Table I) for the total secondary alcohol (diastereomers of II) and tertiary alcohol III have a probable error of about 2% since the optical densities differ by factors from 1 to 4. The analyses for the individual diastereomers of II are grossly inaccurate because the optical densities of these components are rather close together, the biggest factor being 1.6. To improve the accuracy of this analysis and to examine the optical character of the diastereomeric components (II), the alcohol mixtures were heated with strong



III

(1) This work was sponsored by the Office of Ordnance Research, U. S. Army.

(2) (a) D. J. Cram, THIS JOURNAL, **71**, 3863 (1949); (b) **71**, 3875 (1949); (c) **74**, 2129 (1952); (d) **74**, 2159 (1952); (e) D. J. Cram and F. A. Abd Elhafez, *ibid.*, **75**, 3189 (1953); (f) D. J. Cram, *ibid.*, **75**, 332 (1953).

(3) D. J. Cram and J. D. Knight, *ibid.*, **74**, 5839 (1952).

(4) D. J. Cram and F. A. Abd Elhafez, *ibid.*, **75**, 339 (1953).

(5) D. J. Cram and F. A. Abd Elhafez, *ibid.*, **76**, 28 (1954).

(6) S. Winstein and K. C. Schreiber, *ibid.*, **74**, 2171 (1952).

(7) S. Winstein, M. Brown, K. C. Schreiber and A. H. Schlesinger, *ibid.*, **74**, 1140 (1952).

(8) C. J. Collins and W. A. Bonner, *ibid.*, **77**, 92 (1955).

(9) D. J. Cram and J. Allinger, *ibid.*, **76**, 4516 (1954). The meaning of the configurational terms *threo* and *erythro* as applied to system II are defined in this reference.

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TABLE I

ESTIMATED %-COMPOSITION OF ALCOHOL PRODUCTS FROM THE SOLVOLYSES OF TOSYLATE ESTERS OF 1,2-DIPHENYL-2-METHYL-2-BUTANOL (II)

Run	Solvent	Config. st. mat.	Infrared analysis[a] At 1355, 1054 and 895 cm.$^{-1}$ % III	% *threo*-II	% *erythro*-II	At 1245, 1145 and 885 cm.$^{-1}$ % III	% *threo*-II	% *erythro*-II
1	AcOH	(+)-*threo*-II	19	22	64	21	17	63
2	AcOH	(+)-*erythro*-II	24	32	45	29	25	46
3	HCOOH	(−)-*threo*-II	65	15	23	..	..	..
4	HCOOH	(−)-*erythro*-II	70	6	26	..	..	..
	Known mixture[b]		29	32	39	32	34	37
	Known mixture[c]		45	24	35	51	17	36
			At 1054 and 895 cm.$^{-1}$ % *threo*	% *erythro*	At 916 and 885 cm.$^{-1}$ % *threo*	% *erythro*	Polarimetric analysis % *threo*-II	% *erythro*-II
	II from run 1		30	73	28	75	30	70
	II from run 2		47	55	43	62	44	56
	II from run 3		58	45	57	47	54	46
	II from run 4		26	76	27	74	25	75
	Known mixture[d]		58	48	57	50		
	Known mixture[e]		28	75	32	73		

[a] Details of the method are in Experimental. [b] 30% III, 36% *threo*-II, 33% *erythro*-II. [c] 46% III, 23% *threo*-II, 31% *erythro*-II. [d] 54% *threo*-II, 46% *erythro*-II. [e] 32% *threo*-II, 68% *erythro*-II.

base under conditions that destroyed III and left II.[10] The isolation of diphenylmethane from the reaction provides qualitative evidence for III in the starting material. The diastereomeric mixtures of II thus obtained were submitted to a two-component infrared analysis utilizing four wave lengths in the infrared and appropriate known mixtures. A polarimetric analysis was also used (a plot of rotation *vs.* % composition is linear)[9] based on the assumption that the diastereomers were optically pure. The agreement between the two methods indicates this assumption to be valid. Independent evidence for their optical purity was found in the coincidence of rotations of IV obtained from known mixtures of optically pure diastereomers and from these mixtures obtained from the acetolyses. Table I records the results of these analyses, a sample of raw data being recorded in the Experimental.

$$\text{II} \xrightarrow[2,\ LiAlH_4]{1,\ CH_3C_6H_4SO_2Cl} C_6H_5{-}\underset{\displaystyle C_2H_5}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}{-}CH_2{-}C_6H_5 \qquad \text{IV}$$

The rotations of alcohols obtained from the acetolysis containing tertiary alcohol III were of course different from the corresponding alcohols after III had been removed. To see if III was active or inactive, synthetic mixtures of optically pure *threo*- and *erythro*-II and racemic III were prepared in the same proportions as the mixtures obtained from the solvolysis reactions. The rotations of these mixtures demonstrated that the rotational contributions of the three components were virtually additive. The differences in rotation between the synthetic mixtures and those obtained from the solvolyses suggest that the tertiary alcohol III in the solvolysis mixtures possesses a specific rotation of about 5° in the presence of *threo*- and *erythro*-II. The large number of analytical values utilized in the calculation makes this conclusion tentative. Since optically pure III was not prepared, the *degree* of optical purity of the III produced from the solvolyses cannot be estimated.

Similar analytical procedures were applied to the formolysis products (runs 3 and 4, Table I). Although the analysis at the first set of wave numbers gave internally consistent data (the sum of the components came to 100%), some of the values at the other set were not real. After being submitted to the treatment with base, the polarimetric and infrared analysis of the alcohol product pointed to the presence of only *threo*- and *erythro*-II in this final mixture. These facts suggest that small amounts of other components were present in the initial alcohol mixtures obtained from solvolysis, which were destroyed by the treatment with base. The ketone fragments obtained from the basic treatment were converted to their 2,4-dinitrophenylhydrazones. Although crystalline derivatives were obtained, pure compounds could not be isolated. The color of the solid material was characteristic of derivatives of ketones conjugated with benzene rings. The data taken as a whole suggest the contaminants to be products of either methyl or ethyl migration (V to VI) or both, which upon treatment with strong base would give acetophenone and propiophenone, respectively.[10] Unfortunately, the trace amounts involved did not permit definitive identification.

$$C_6H_5{-}\underset{\displaystyle OH}{\overset{\displaystyle C_2H_5}{\overset{|}{\underset{|}{C}}}}{-}\underset{\displaystyle C_6H_5}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{CH}}}}{-}C_6H_5 \qquad \text{V}$$

$$\xrightarrow[CH_3NHC_6H_5]{K^+N^-{-}C_6H_5} C_6H_5{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}C_2H_5 + C_2H_5{-}C_6H_5$$

$$C_6H_5{-}\underset{\displaystyle OH}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}{-}\underset{\displaystyle C_6H_5}{\overset{\displaystyle C_2H_5}{\overset{|}{\underset{|}{CH}}}}{-}C_6H_5 \qquad \text{VI}$$

$$\xrightarrow[CH_3NHC_6H_5]{K^+N^-{-}C_6H_5} C_6H_5{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}CH_3 + C_3H_7{-}C_6H_5$$

Analysis of Olefin Fractions.—Since the starting material (tosylate of II) is incapable of going directly to olefin, only rearranged olefins were

(16) D. J. Cram, J. Allinger and A. Langemann, *Chemistry & Industry*, 919 (1955).

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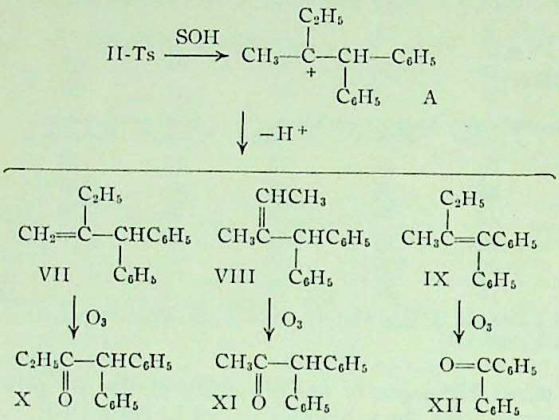
possible products of the reaction. Three olefins VII, VIII and IX could arise from the carbonium ion A produced by phenyl migration during the solvolysis of II-Ts. The analysis problem was simplified by converting the mixture of olefins obtained to their ketones (X, XI and XII) through ozonolysis, the ketonic mixtures being analyzed



through infrared techniques for these three components (see Experimental for details). The 2,4-dinitrophenylhydrazone of XI was isolated from the ketonic mixture obtained in run 2 and was compared with an authentic sample. These analyses provided only estimates of the amounts of the three components, since small amounts of unidentified components (~10%) interfered. Table II records these estimates as well as the yields of olefin and ketone obtained.

TABLE II

ESTIMATED % COMPOSITION OF KETONE DERIVED FROM OLEFINS ARISING IN SOLVOLYSIS OF II-Ts

Run[a]	Yield olefin,[c] %	Compn. ketone mixture,[b] % X	XI	XII
1	67	14	67	11
2	55	11	69	11
3	49	3	68	9
4	42	8	72	16

[a] Run numbers same as in Table I. [b] Details of method are in Experimental. [c] Based on tosylate.

Control Experiments.—Control experiments demonstrated that the acetates of II and III once formed were stable. The formates of II and III could not be prepared. The stabilities of the diastereomeric 1,2-diphenyl-1-propyl formates in formic acid at 25° have been examined previously[4] and were found to have been formed decidedly faster than they were interconverted. The similarity between this system and II taken in conjunction with the balance between the diastereomeric formates obtained from formolysis of II-tosylate (see Table I) indicates that the formates are formed somewhat faster than they react. The olefinic products in both the formolysis and acetolysis were demonstrated not to change upon further submission to solvolysis conditions. Earlier results[11] suggest that the balance of olefins is kinetically controlled in the acetolysis reaction, but might be thermodynamically controlled in the formolysis. The effectiveness of the removal of III from mixtures of II and III by treatment with strong base was demonstrated with experiments utilizing synthetic mixtures.

(11) D. J. Cram, THIS JOURNAL, 74, 5828 (1952).

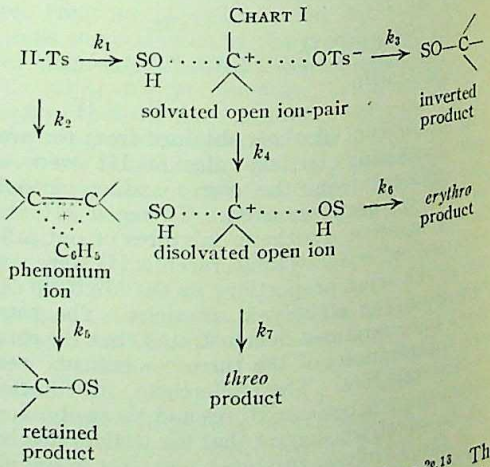
Discussion

The Products of Simple Substitution.—The results indicate that in the solvolysis of the 1,2-diphenyl-2-methyl-1-butyl system, a number of primary processes compete with one another, each of which leads to intermediates that partition between several different products. Phenyl and solvent participation in ionization are the likely primary processes, the first leading to phenonium ion,[2] the second to solvated open ion. Evidence for these two primary processes is found in the stereochemical course of substitution that occurs *without rearrangement*. In acetolysis the ratios of

Starting material	*erythro*-II-Ac / *threo*-II-Ac	*erythro*-II-Fm / *threo*-II-Fm
threo-II-Ts	2.3	0.85
erythro-II-Ts	1.3	3.0

erythro to *threo* acetates are different from the diastereomeric starting materials, predominating inversion occurring with *threo* and predominating retention with *erythro* material. These results can be most simply interpreted without assuming a phenonium ion intermediate. In Chart I, the starting material (II-Ts) can ionize with either phenyl or solvent participation, depending on the values of k_1 and k_2. If $k_1 >> k_2$, then the balance between product of retained and inverted configuration is controlled by the relative values of k_3 and k_4 on the one hand and k_6 and k_7 on the other. For the acetolysis of *threo*-II-Ts, k_3 being greater than k_4 explains the results. With *erythro*-II-Ts $k_4 > k_3$ and $k_6 > k_7$. Since the disolvated open ion is the same for each diastereomer,[12] k_6 and k_7 should be independent of starting configuration. This predisposition of the system to give *erythro* material is

CHART I



consistent with previous generalizations.[2c,13] The over-all process described by k_1-k_3 is similar in its

(12) Implicit in this statement is the assumption that the disolvated ion has a half-life longer than that of the rotations which lead to equilibration between the various conformations.

(13) D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, 74, 5851 (1952).

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steric requirements to SN2 processes, which is visualized in Chart II as occurring with the displacing group (X^-) coming across the smallest group (S) attached to the adjacent asymmetric carbon atom. The transition state for isomer A which is a model for *threo*-II-Ts should be more stable than that for B which is a model for *erythro*-II-Ts. Thus $k_3 > k_4$ for *threo*-II-Ts and $k_4 > k_3$ for *erythro*-II-Ts. Of the three conformations of the disolvated open ion in Chart III, only C allows the incoming solvent to come in across the smallest

CHART II

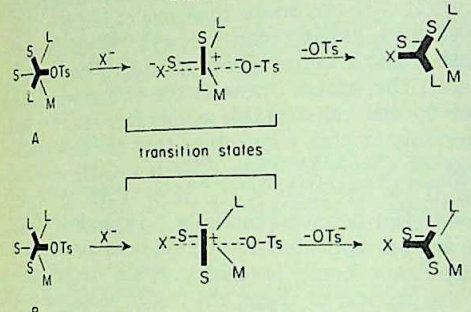
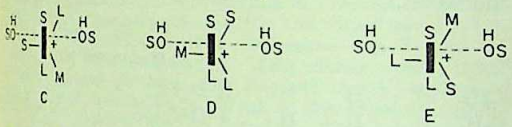
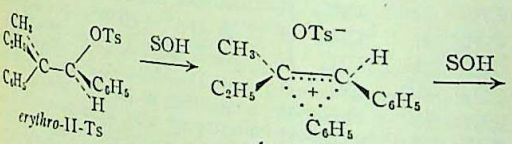
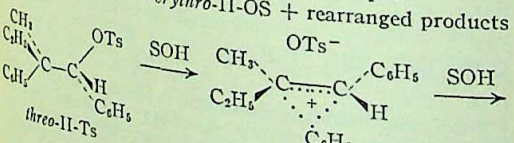


CHART III



group (S) attached to the adjacent carbon, and at the same time allows the two large groups (L) to be as far away from each other as possible. Thus *erythro* product should dominate, and $k_6 > k_7$, as is indeed observed.



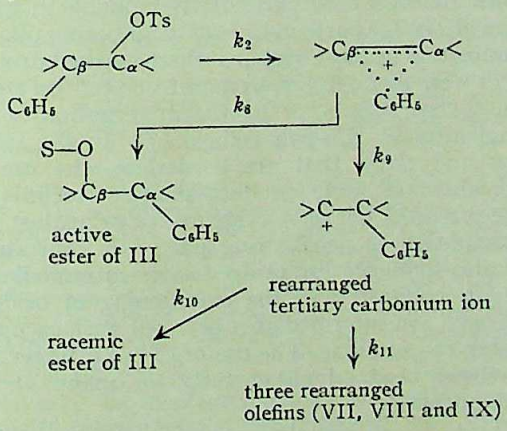


In the formolysis, on the other hand, with both starting materials the simple substitution reactions occurred with predominating retention of configuration. The stereospecificity was more marked with *erythro* isomer as the starting material. In this more ionizing and less nucleophilic solvent, the results cannot be explained only on the basis of the primary process described by k_1. In view of the facts that much of the product has undergone phenyl rearrangement and that in other systems a phenonium ion intermediate has been demonstrated,[2] it seems likely that the process described by k_2 leading to a phenonium ion is responsible for the dominating retention process. That the retention is more marked with *erythro* starting material is probably due to $k_4 > k_3$ in formic acid, and $k_6 > k_7$ (the relative values of these rates should be much more insensitive to solvent).

Although other processes such as the formation of phenonium ions from open ions or *vice versa* or ion-pair collapse might also play a role in the solvolyses, they are not demanded by the data.

The Products of Rearrangement.—Although the migration of methyl or ethyl groups probably occurred to a small extent particularly in the formolysis, the reaction products were largely those in which a phenyl migration had occurred. In the acetolysis the ratios of rearranged to unrearranged product were 4.6 and 4.0 for *erythro* and *threo* materials, respectively, while the corresponding values in the formolysis were 6.1 and 5.2. In each solvent, the amount of starting material accounted for was higher (85–88%) with *threo* than with *erythro* starting material (75–71%), and the absolute yields of both rearranged and simple substitution products were greater for the *threo* than for the *erythro* materials. It is clear that neither the slightly more important eclipsing effects expected from the phenonium bridge from *erythro* material nor the greater ease with which *threo* material enters into simple substitution play anything more than minor roles in directing the reaction courses.

The question of the optical purity of the tertiary alcohol III ultimately obtained in these experiments unfortunately was not settled. What few data are available suggest that it was at least partially active, which in turn points to the process de-



scribed by k_2–k_8. That most of the tertiary ester came from rearranged open ion (k_2–k_9) in the acetolysis is suggested by the fact that the ratios of yields of olefin (rearranged) to rearranged tertiary alcohol are about the same from both *threo* and *erythro* starting materials (15.2 and 14.1, respectively). The absolute yields of rearranged alcohol III were much higher (factor of 6) in the formolysis, and the ratios of yields of olefin to alcohol III were 1.71 and 1.61 from *threo* and *erythro* materials. In this solvent probably a lower proportion of III-ester came from rearranged open ion and a higher proportion directly from the phenonium bridge. That bridged ion-pairs go directly to ester product in the more dissociating formic acid solvent (as contrasted to acetic acid) has been demonstrated in other sys-

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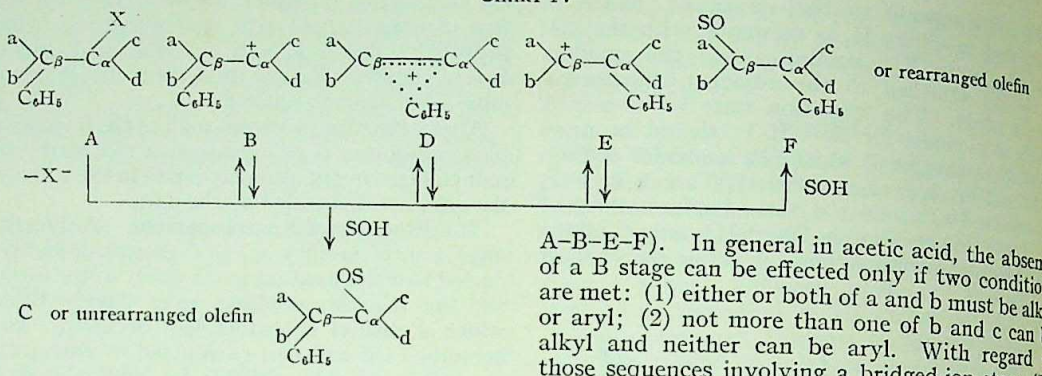
CHART IV



tems.[2c,e,14] That essentially all of the olefin came through the rearranged open ion (process k_9–k_{11}) in acetic acid is indicated by the fact that their ratios are independent of the starting configuration (see Table II). The same thing also probably is true in formic acid, although the analyses were so poor due to contaminants that this has not been demonstrated (Table II). It is interesting that in both solvents only small amounts of the most conjugated olefin (IX) were formed, presumably because of eclipsing effects.

The Variation in Mechanism of the Wagner–Meerwein Rearrangement (Phenyl the Migrating Group) as a Function of the Substituents at C_α and C_β.—Enough systems have now been studied in detail so that the dependency of the mechanism on the non-migrating substituents at C_α and C_β can be examined from a general standpoint. The kinetic tool has been particularly valuable in gaining evidence for participation of neighboring phenyl in ionization in those systems where marked driving forces were evident and were not masked by steric or inductive effects, or by the intervention of internal return[14] (ion-pair collapse).[2c] In the latter cases and those that are borderline, the use of stereochemical and product-analysis techniques have provided not only evidence for or against the participation of neighboring phenyl in ionization, but also evidence for bridged ionic intermediates, ion-pair collapse, and the partitioning of bridged and open ion intermediates between various paths leading to product. The use of C^{14} as a tracer has also been used advantageously for many of the same purposes.

Chart IV represents a general and simplified mechanistic scheme, reference to which permits the classification of systems according to what stereochemically differentiated gross mechanism for solvolysis applies. The capital letters refer to discrete species and the dashes to transition states separating these species. These data show that by appropriately substituting C_α and C_β and by utilizing the proper solvents, many combinations of intermediates can be detected. The following sequences have not been demonstrated: A–F, A–E–F (as distinct from a possible A–D–E–F), A–B–E–F (as distinct from a possible A–B–D–E–F) A–B–D–F (as distinct from a possible A–B–D–E–F), A–B–D–E–F (as distinct from a possible A–B–E–F). In general in acetic acid, the absence of a B stage can be effected only if two conditions are met: (1) either or both of a and b must be alkyl or aryl; (2) not more than one of b and c can be alkyl and neither can be aryl. With regard to those sequences involving a bridged-ion stage (D-stage), the bridge opens at the carbon which could lead to the most stable carbonium ion. It is interesting in this connection that the last two systems of Chart IV (a = CH_3, b = C_2H_5, c = C_6H_5, and d = H; a = CH_3, b = C_2H_5, c = CH_3, d = C_2H_5) behaved similarly. In the first of these, the bridge appeared to open in both directions, the quaternary being favored over the benzyl carbon. In the second of these, the bridge of course opened in both directions. In both systems open carbonium ions (B and E stages) appeared to be intermediates.

C_β a	C_β b	C_α c	C_α d	Mechanisms[a]
CH_3	H	H	H	A–D–F[b]
C_6H_5	H	H	H	A–D–?–F[c,d]
CH_3	CH_3	H	H	A–D–?[c,d]
C_6H_5	C_6H_5	H	H	A–D–?[c,d]
H	H	CH_3	H	A–B–C, A–D–C[*e]
CH_3	H	CH_3	H	A–D–C, A–D–F[f]
C_2H_5	H	CH_3	H	A–D–C, A–D–F, A–D–E–F[g]
CH_3	H	C_2H_5	H	A–D–C, A–D–F, A–D–E–F[g]
C_2H_5	H	C_2H_5	H	A–D–C, A–D–F[h]
C_6H_5	H	CH_3	H	A–D–E–F, A–D–F[i]
CH_3	CH_3	CH_3	H	A–D–?[c,d]
CH_3	H	C_6H_5	H	A–B–C, A–D–C[*j]
C_6H_5	H	C_6H_5	H	A–B–C, A–B–E–F or A–B–D–E–F[k]
CH_3	C_2H_5	C_6H_5	H	A–B–C, A–D–C,* A–B–D–E–F,[l] A–D–F[*m]
CH_3	C_2H_5	CH_3	C_2H_5	A–B–C, A–D–C, A–B–D–E–F[l,n]

[a] Only the dominant mechanism is put down except where small amounts of processes involving a D stage were detected. The solvent is acetic acid except those marked with an asterisk, where formic acid was employed. X is tosylate or brosylate, except where indicated differently. [b] S. Winstein and K. C. Schreiber, THIS JOURNAL, 74, 2171 (1952). [c] S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse, *ibid.*, 74, 1116 (1952). [d] Kinetic techniques indicated rate enhancements due to phenyl participation in ionization; products were not examined. [e] S. Winstein, M. Brown, K. F. Schreiber and A. H. Schlesinger, *ibid.*, 74, 1140 (1952). [f] Ref. 2a, 2c. [g] Ref. 2b, 2d. [h] Ref. 2e. [i] D. J. Cram and F. A. Abd Elhafez, *ibid.*, 76, 28 (1954). [j] Ref. 4. [k] Ref. 8. [l] Only probable. [m] Present study. [n] Ref. 3. X was a *p*-bromobenzoate group.

Experimental Part

Tosylates of the Four Stereoisomers of 1,2-Diphenyl-2-methyl-1-butanol (II).—The procedure is illustrated with the preparation of the derivative of (+)-*erythro*-II. A mixture of 100 ml. of dry benzene, 8.95 g. of (+)-*erythro*-II

(14) S. Winstein and K. C. Schreiber, THIS JOURNAL, 74, 2165 (1952).

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$[\alpha]^{25}D$ +1.86° (benzene, *c* 10.1)[9] and 1.5 g. of potassium metal were held at reflux under anhydrous conditions under nitrogen for 4 hours. The mixture was cooled to 0°, 7.16 g. of freshly crystallized tosyl chloride was added under nitrogen and the resulting mixture was stirred for 30 minutes. The mixture was filtered always keeping the cake wet with benzene (metallic potassium). The filtrates were washed with water, twice with dilute sodium carbonate solution, again with water and dried. The solvent was evaporated at 25°, and the residue was crystallized from pentane at 0° to give a 6.5-g. 1st crop and a 1.46-g. 2nd crop. Recrystallization of this material from an ether–pentane mixture at 0° afforded 6.4 g. (43% yield) of white needles, m.p. 52° dec., $[\alpha]^{26}D$ +60.2° (benzene, *c* 3.91).

Anal. Calcd. for $C_{24}H_{26}SO_3$: C, 73.06; H, 6.64. Found: C, 73.08; H, 6.60.

In a similar manner, 8.7 g. of (−)-*erythro*-II $[\alpha]^{25}D$ −1.91°, (benzene, *c* 10.5)[9] was converted to 9.8 g. (69% yield) of tosylate ester, m.p. 54° dec., $[\alpha]^{25}D$ −59.8° (benzene, *c* 3.70).

Anal. Calcd. for $C_{24}H_{26}SO_3$: C, 73.06; H, 6.64. Found: C, 73.23; H, 6.51.

Similarly, from (+)-*threo*-II $[\alpha]^{25}D$ +59.4° (benzene, *c* 10.4)[9] was obtained a 74% yield of tosylate (white needles), m.p. 54° dec. This ester was so unstable it decomposed before rotations and analysis could be obtained. From (−)-*threo*-II $[\alpha]^{2}D$ −59.3° (benzene, *c* 10.4)[9] was obtained a 53% yield of tosylate (white needles), m.p. 56° dec. The sample decomposed before rotation could be recorded.

Anal. Caled. for $C_{24}H_{26}SO_3$: C, 73.06; H, 6.64. Found: C, 73.19; H, 6.90.

Acetolysis of the Tosylates of the Isomeric 1,2-Diphenyl-2-methyl-1-butanols (II).—A solution of 1722 ml. of freshly distilled acetic acid, 64 ml. of acetic anhydride and 12.5 g. of C.P. anhydrous potassium carbonate was heated at reflux for 24 hours and cooled. This solution was 0.1002 *M* in potassium acetate. The tosylate of (+)-*erythro*-II (6.4 g., run 2) was added to 180 ml. of this solution. Solution of the ester required 20 minutes. This solution protected from moisture was allowed to stand at 25° for 83 hours, and then poured into 600 ml. of water containing 10 ml. of a saturated sodium chloride solution. The resulting mixture was extracted with pure pentane, the pentane solution was washed with water, sodium bicarbonate solution and again with water. The organic layer was dried, evaporated, and the residual oil was distilled at 2 mm. with a final bath temperature of 135° to give 4.21 g. of colorless oil. The small amount of residue (<0.05 g.) when triturated with water gave an acidic solution. The distillate was added to a stirred mixture of 0.4 g. of lithium aluminum hydride and 100 ml. of anhydrous ether and, after stirring for 50 minutes at 25°, the mixture was diluted first with wet ether and then with ice-cold water. The layers were separated, the organic layer was washed with water, dried and evaporated to an oil. This oil was dissolved in 5 ml. of pure pentane and chromatographed on a column of 120 g. of neutral Activity III alumina[15] made up in pentane. The olefin was washed from the column with pentane, 1.98 g. of distilled eluate being obtained, $n^{25}D$ 1.5690, $\alpha^{25}D$ +0.09° (1 dm., neat). The alcoholic fraction was eluted with 250 ml. of C.P. methanol to give 0.59 g. of viscous oil (distilled material), $n^{25}D$ 1.5689, $[\alpha]^{24}D$ +24.1° (benzene, *c* 10.0). These two fractions (olefin and alcohol) were used in the subsequent infrared and polarimetric analyses.

A similar acetolysis and isolation procedure (run 1) as applied to the tosylate of (+)-*threo*-II (6.10 g.) gave 3.5 g. of distilled alcohol–olefin product (residue 0.03 g.). Chromatographic separation of these fractions gave 2.33 g. of olefin, $n^{25}D$ 1.5711, $\alpha^{27}D$ +0.07° (1 dm., neat) and 0.79 g. of alcohol, $n^{25}D$ 1.5687, $[\alpha]^{25}D$+18.3° (benzene, *c* 10.2), which were submitted to infrared and polarimetric analysis.

Formolysis of the Tosylates of the Isomeric 1,2-Diphenyl-2-methyl-1-butanols (II).—A solution of 1.0 liter, 25% C.P. alcohol-free chloroform–75% anhydrous formic acid (% by volume) and 3.7 g. of anhydrous sodium formate was titrated[16] and found to be 0.0538 *M* in sodium formate. Kinetic measurements[16] indicated the rates of formolysis of a mixture of the diastereomeric tosylates to be too fast to measure, the reaction being over in less than 2 minutes at 25°. The tosylate ester of (−)-*erythro*-II (6.9 g., run 4) was dissolved in 360 ml. of the above solution (immediate solution was observed), allowed to stand at 25° for two minutes, and was poured onto one l. of crushed ice–water mixture containing 10 ml. of saturated sodium chloride solution. The isolation procedure was the same as in the acetolysis, 4.05 g. of distilled olefin–alcohol being obtained (no residue from the olefin–formate distillation was observed). The olefin fraction amounted to 1.60 g., $n^{25}D$ 1.5714, $\alpha^{25}D$ −0.26° (1 dm., neat), and the alcohol, 1.42 g., $n^{25}D$ 1.5686, $[\alpha]^{24}D$ −13.0° (benzene, *c* 10.2).

Similar treatment (run 3) of 7.0 g. of (−)-*threo*-II gave 4.22 g. of olefin–alcohol mixture (distilled). No residue was obtained from the olefin–formate distillation. The olefin fraction amounted to 1.91 g., $n^{25}D$ 1.5710, $\alpha^{25}D$ −1.71° (1 dm., neat), and the alcohol fraction was 1.59 g., $n^{25}D$ 1.5683, $[\alpha]^{24}D$ −17.7° (benzene, *c* 10.1).

The olefin fractions from both solvolyses appeared to be unstable to air and could not be allowed to stand.

Ozonolysis of Olefins Obtained from Solvolyses.—The procedure is illustrated as applied to olefin from run 2. To olefin (1.0 g.) dissolved in 40 ml. of C.P. methylene chloride at 0° was added (bubbled through) ozone for one hour. After this time a rubber tube fitted to the exit tube showed signs of decomposition. The mixture was then added dropwise to a refluxing mixture of 1.0 g. of zinc dust, a crystal of silver nitrate and 50 ml. of distilled water. The resulting mixture was refluxed for 15 minutes, cooled and extracted with pentane. The pentane layer was washed, dried, evaporated, and the residue was distilled at 2 mm. (bath temperature 135°) to give 0.92 g. of a ketonic mixture, $n^{25}D$ 1.5703, $\alpha^{25}D$ −0.11° (1 dm., neat). A small amount of this material when treated with 2,4-dinitrophenylhydrazine reagent afforded after two recrystallizations of the product yellow needles, m.p. 137.8–139.2°, undepressed by admixture with an authentic sample of the 2,4-dinitrophenylhydrazone of 1,1-diphenyl-2-propanone (m.p. 140°, see below for preparation).

The aqueous phase from the above ozonolysis decomposition reaction was filtered and was qualitatively tested for formaldehyde (Deniges method)[17a] and acetaldehyde, (Ley reagent).[17b] Both tests were positive, and appropriate controls established that the aldehydes did not come from solvent impurities.

Olefin (1.0 g.) from run 1 gave upon ozonolysis 1.0 g. of ketone, $n^{25}D$ 1.5760, $\alpha^{25}D$ −0.22° (1 dm., neat). Positive tests for acetaldehyde and formaldehyde were obtained.

Olefin (1.0 g.) from run 3 gave 0.88 g. of ketonic mixture, $n^{25}D$ 1.5722, $\alpha^{26}D$ −1.60° (1 dm., neat), whereas olefin (1.0 g.) from run 4 gave 0.95 g. of ketone, $n^{25}D$ 1.5730, $\alpha^{26}D$ −0.39° (1 dm., neat).

Reverse Condensation Reactions Run on Alcohol Fractions.—The procedure is illustrated as applied to a synthetic mixture of alcohols II and III. A mixture of potassium metal (0.111 g.) and 2 ml. of anhydrous N-methylaniline (distilled from potassium) was heated at 200° under nitrogen for two hours, cooled to 72°, and a solution of 0.214 g. of racemic 1,1-diphenyl-2-methyl-2-butanol (III, see below) and 0.451 g. of (+)-II (mixture of optically pure diastereomers, $[\alpha]^{25}D$ +20.33° (benzene, *c* 9.99) in 1 ml. of anhydrous N-methylaniline was added. The reaction mixture was stirred at 72° for 30 minutes, cooled to 0°, and the trace of unreacted potassium metal was decomposed with ethanolic N-methylaniline. The resulting mixture was shaken with 4 ml. of concentrated hydrochloric acid in 40 ml. of water, 20 g. of ice and pentane. The pentane extract was washed with acid, water, was dried and the solvent was evaporated. The resulting oil was chromatographed on 30 g. of Activity III neutral alumina[15] made up in pentane. Development of the column with pentane gave eluent which upon distillation gave 0.106 g. (71%) of hydrocarbon which possessed an infrared spectrum identical to that of diphenylmethane. The alcohol was washed from the column with 100 ml. of C.P. methanol. The solvent was evaporated, the residue was taken up in pentane, and this solution was washed with water, dried and evaporated. Distillation of the residue (2 mm. and 145° bath temperature) gave 0.35 g. (77% recovery) of the same mixture of diastereomers of II that was used as starting material, $[\alpha]^{24}D$ +20.1° (benzene,

(15) H. Brockmann and H. Schodder, *Ber.*, **74B**, 73 (1941).

(16) S. Winstein and H. Marshall, THIS JOURNAL, **74**, 1120 (1952).

(17) (a) J. F. Walker, Am. Chem. Soc. Monograph Series, Reinhold Publishing Corp., New York, N. Y., Vol. 98, 1944, p. 244; (b) p. 259.

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c 9.32), $n^{25}D$ 1.5692. Utilizing a similar procedure, alcohol from run 1 (0.70 g.) gave 0.08 g. of hydrocarbon and 0.48 g. of II, $[\alpha]^{25}D$ +19.3° (benzene, *c* 10.1). Likewise alcohol from run 2 (0.76 g.) gave 0.11 g. of hydrocarbon and 0.55 g. of II, $[\alpha]^{25}D$ +27.1° (benzene, *c* 10.1). Alcohol from run 4 (1.42 g.) gave 0.59 g. of hydrocarbon and 0.21 g. of alcohol, $n^{25}D$ 1.5685, $[\alpha]^{27}D$ −16.8° (benzene, *c* 5.23). Alcohol from run 3 (1.59 g.) gave 0.74 g. of hydrocarbon and 0.28 g. of II, $n^{25}D$ 1.5685, $[\alpha]^{25}D$ −32.9° (benzene, *c* 9.2). In all four of these runs, the infrared spectra of the hydrocarbon fractions were virtually identical to that of diphenylmethane. The chromatographs in runs 3 and 4 were run slightly differently than in the same procedure. Hydrocarbon was eluted with pentane, a ketonic contaminant was eluted with 20% ether in pentane, and the alcohol was eluted with methanol. The ketonic fraction in each case formed a *red* 2,4-dinitrophenylhydrazone which after two recrystallizations from ethanol gave *ca.* 2 mg. of red crystals which melted over a range and lower than 100°.

Conversion of 1,2-Diphenyl-2-methyl-1-butanol (II) to 1,2-Diphenyl-2-methylbutane (IV).—The procedure is illustrated as applied to a mixture of optically pure diastereomers of II. Alcohol (1.0 g.), $[\alpha]^{25}D$ +20.3° (benzene, *c* 9.91) was dissolved in 10 ml. of C.P. anhydrous benzene, and treated with 0.168 g. of potassium metal and 0.79 g. of tosyl chloride as in the procedure recorded above for the preparation of the tosylates of II. The crude tosylate ester thus obtained was added to a slurry (stirred) of 1.32 g. of lithium aluminum hydride and 100 ml. of anhydrous ether. The resulting mixture was stirred for two hours and allowed to stand at room temperature for 12 hours. Wet ether now was added and then finally a cold solution of aqueous ammonium chloride. The organic layer was washed with water, dried and evaporated. The residue was chromatographed on 30 g. of Activity I neutral alumina[16] made up in pure pentane. The desired product was eluted with 100 ml. of pure pentane, the solvent was evaporated, and the residual oil was distilled at 3 mm. and a bath temperature of 125°, wt. 0.55 g. This impure material was dissolved in 5 ml. of glacial acetic acid, 0.6 g. of 2,4-dinitrobenzenesulfenyl chloride was added and the resulting solution was heated at 100° for one hour. The reaction mixture was cooled and placed directly on a chromatographic column of 40 g. of activity III neutral alumina[15] made up in pure pentane. The desired hydrocarbon was eluted with 100 ml. of pure pentane, the solvent was evaporated, and the residue was distilled to give 0.55 g. (59% yield) of (+)-1,2-diphenyl-2-methylbutane (IV), $n^{25}D$ 1.5550, $\alpha^{25}D$ +66.3° (1 dm., neat), d^{25}_4 0.9718, $[\alpha]^{25}D$ +67.4° (neat).

Anal. Calcd. for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 90.95; H, 8.98.

Application of this procedure to 0.48 g. of the alcohol II obtained from run 1 gave 0.27 g. (60% yield) of optically pure hydrocarbon (IV), $n^{25}D$ 1.5542, $\alpha^{26}D$ +66.40 (1 dm., neat). From 0.55 g. of alcohol from run 2 was obtained 0.31 g. (60% yield) of optically pure IV, $n^{25}D$ 1.5547, $\alpha^{25}D$ +66.5° (1 dm., neat).

1,1-Diphenyl-2-propanone (XI).—This material was obtained in 55% yield[18] (two recrystallizations from pentane), m.p. 59–60.2° (reported[18] m.p. 60–61°). The 2,4-dinitrophenylhydrazone was prepared as yellow needles (absolute ethanol), m.p. 138–139.6° (reported[19] m.p. 140°).

Anal. Calcd. for $C_{21}H_{18}N_4O_4$: C, 64.61; H, 4.65. Found: C, 64.66; H, 4.81.

1,1-Diphenyl-2-butanone (X).—Application of a reported procedure[20] to the preparation of 1,1-diphenyl-1-hydroxy-2-butanol gave material, m.p. 114–115.1° (reported[20] m.p. 92°).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.33; H, 7.60.

Conversion of 5 g. of this glycol to X[20] gave 4.3 g. (97% yield) of product, $n^{25}D$ 1.5678. This material was converted to its semicarbazone, five recrystallizations of which (benzene) gave soft needles (50% yield), m.p. 187.6–189.8°, reported m.p. 194–195°[21] and 185°.[22] Regeneration of the ketone X[23] (85% yield) gave X as a colorless liquid, $n^{25}D$ 1.5668. A 2,4-dinitrophenylhydrazone derivative was prepared, yellow needles (absolute ethanol), m.p. 118.2–119.8°.

Anal. Calcd. for $C_{22}H_{20}N_4O_4$: C, 65.33; H, 4.98. Found: C, 65.22; H, 5.06.

(+)-1,2-Diphenyl-1-butanone.—Since this compound was a potential product of the rearrangement, it was prepared in optically pure form. Resolution of 2-phenylbutanoic acid[24] gave material, b.p. 130–132° (4 mm.), $n^{25}D$ 1.5128, $[\alpha]^{25}D$ +90.3°(1 dm., neat), reported[24] $[\alpha]^{25}D$ +89.9° (1 dm., neat). The acid chloride was obtained from 9 g. of the acid and 16.5 ml. of thionyl chloride, and was allowed to react with diphenylcadmium prepared from 18.5 g. of bromobenzene, 2.83 g. of magnesium and 11.3 g. of anhydrous cadmium chloride in the usual manner.[25] The product was distilled through a 2.5-foot Podbielniak type of column to give 10.2 g. (83% yield) of ketone, b.p. 150–151° (5 mm.), m.p. 54.2–57.8°. Recrystallization of this material (three times) from ethanol–pentane gave 4.3 g. of ketone, m.p. 57–58°, $[\alpha]^{25}D$ +230.2° (benzene, *c* 4.99).

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.67; H, 7.14; Found: C, 85.48; H, 7.17.

Racemic 1,1-Diphenyl-2-methyl-2-butanol (III).—Ethyllithium was prepared from 5.29 g. of lithium metal, 41.6 g. of ethyl bromide and 300 ml. of anhydrous ether. The reagent was filtered through a cotton plug, cooled under nitrogen to 0°, and mixed with 16 g. of 1,1-diphenyl-2-propanone in 50 ml. of dry ether. The solution (yellow) was stirred at 0° for one hour, and ammonium chloride solution was added. The organic layer was washed with water, dried and evaporated. The residual oil was treated with 27.8 g. of Girard T reagent[26] dissolved in 278 ml. of 10% (by volume) glacial acetic acid–absolute ethanol solution for 45 minutes. The mixture was then shaken with water and pure pentane, the pentane was washed with water, dried and evaporated. The residue was chromatographed on 320 g. of neutral ActivityIII alumina[15] made up in pure pentane. The column was washed with pentane, and developed with ether–pentane mixtures to give a number of fractions, each of which contained oil whose refractive indices and boiling points were virtually identical. This material was distilled (bath temperature 130–135° at 1 mm.) to give 12.4 g. of alcohol, $n^{25}D$ 1.5687. The infrared spectrum of this material contained a carbonyl band of weak intensity at 1705 cm.$^{-1}$.

When 5 g. of this material was treated with excess ethyllithium (6 mole ethyllithium to 1 mole "alcohol") at 25° for 4 hours there was obtained upon distillation of the crude reaction product 4.8 g. of the desired alcohol, $n^{25}D$ 1.5678. This material had no carbonyl absorption at 1705 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 84.74; H, 8.33.

The acetate of this tertiary alcohol III was prepared as follows: Alcohol III (2.9 g.) was treated at 135–140° for 68 hours with 12.3 g. of distilled acetic anhydride and 9.55 g. of pure pyridine. The black reaction mixture was shaken with pure pentane and dilute acid, the pentane layer was washed with acid solution, water, was dried and evaporated. The residue was chromatographed on 120 g. of Activity III neutral alumina[15] made up in pure pentane. From the eluent obtained with 5% ether–pentane was obtained 2.08 g. of a colorless oil, $n^{25}D$ 1.5473 (after distillation at 2 mm., 135° bath temperature). Crystallization of this material from methanol at −80° gave white tablets, m.p. 42.3–43.8°.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.80; H, 7.86. Found: C, 80.89; H, 7.87.

Both olefin and starting alcohol were isolated from the other chromatographic fractions.

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June 5, 1957

(+)-*erythro*-1,2-Diphenyl-2-methyl-1-acetoxybutane.—From 2.25 g. of optically pure (+)-*erythro*-II, 9.48 g. of C.P. distilled acetic anhydride and 7.34 g. of pure pyridine (reaction at 135–140° for 10 hours) the product was obtained by the usual method. The crude acetate was dissolved in 10 ml. of pentane. After standing at −10°, the material crystallized as dense white tablets, m.p. 40–44°, 1.62 g. Recrystallization of the solid from pentane gave 1.5 g., m.p. 42.4–44°. Additional material (0.5 g.) was obtained by chromatography of the filtrates, m.p. 42.4–44°, total yield 75%, $[\alpha]^{25}D$ +8.93° (benzene, *c* 4.71).

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.80; H, 7.86. Found: C, 80.98; H, 7.91.

(+)-*threo*-1,2-Diphenyl-2-methyl-1-acetoxybutane.—By a similar procedure except that a chromatographic purification was involved, 1.25 g. of (+)-*threo*-II gave 1.26 g. of its acetate as a colorless viscous oil, $n^{25}D$ 1.5476, $[\alpha]^{25}D$ +7.72° (benzene, *c* 4.72).

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.80; H, 7.86. Found: C, 80.82; H, 7.75.

Other Materials for Infrared Analyses.—Benzophenone (commercial material) was recrystallized from ether–pentane to constant melting point, m.p. 52–54°. An analytical specimen of (−)-1,2-diphenyl-1-propanone was available from other studies,[27] m.p. 34–35°, $[\alpha]^{25}D$ −206° (chloroform, *c* 4.2).

Control Experiments.—The olefin mixture (0.6 g., $n^{25}D$ 1.5706) obtained from run 2 was resubmitted to the whole acetolysis and isolation procedure to give 0.51 g. of recovered material (85%), $n^{25}D$ 1.5708. Ozonolysis of this olefin gave 0.51 g. of ketonic mixture, $n^{25}D$ 1.5752, $\alpha^{25.5}D$ −0.05° (1 dm., neat). Similar ozonolysis of the original olefin gave ketone, $n^{25}D$ 1.5756, $\alpha^{25}D$ −0.05° (1 dm., neat). The infrared spectra of the two ketone mixtures were identical.

An olefin mixture was obtained by chromatography of (−)-*threo*-II-tosylate on alumina, $n^{25}D$ 1.5750, $\alpha^{25}D$ −0.06° (1 dm., neat). This material (0.35 g.) was also subjected to the acetolysis procedure and recovered, $n^{25}D$ 1.5750, $\alpha^{26}D$ −0.06° (1 dm., neat). Both the original olefin and that subjected to the acetolysis procedure were converted to their ketones. The infrared spectra, indices of refraction and rotations of these two samples were essentially identical ($n^{25}D$ 1.5709 and $\alpha^{25}D$ +0.40°, 1 dm., neat).

An olefin mixture obtained from the acetolysis of the tosylate of *rac-erythro*-II (0.50 g., $n^{25}D$ 1.5692) was submitted to the conditions of formolysis and recovered, wt. 0.45 g., $n^{25}D$ 1.5692.

A mixture of optically pure diastereomeric acetates of (+)-*threo*-II and (+)-*erythro*-II (1.0 g., $n^{25}D$ 1.5478, $[\alpha]^{25}D$ +8.31° (benzene *c* 7.33) was subjected to the acetolysis conditions, and 0.90 g. of acetate was recovered, $n^{25}D$ 1.5482, $[\alpha]^{25}D$ +8.35° (benzene, *c* 7.33). Reduction of this material with lithium aluminum hydride gave 0.70 g. of (+)-*threo* and (+)-*erythro*-II, $n^{25}D$ 1.5694, $[\alpha]^{25}D$ +35.4° (benzene, *c* 10.06). This rotation corresponds to a composition of 58% (+)-*threo*-II and 42% (+)-*erythro*-II which corresponds to the composition of the original acetate mixture.

The tertiary acetate of III (0.50 g., $n^{25}D$ 1.5475) was submitted to the acetolysis procedure to give 0.42 g. of recovered acetate, $n^{25}D$ 1.5476, whose infrared spectrum was identical to that of the starting material. Submission of this acetate to the lithium aluminum hydride reduction procedure gave 0.30 g. of tertiary alcohol III, $n^{25}D$ 1.5680 (as compared to $n^{25}D$ 1.5678 of an authentic sample). The infrared spectrum of this material was the same as that of III.

Attempts to prepare the formates of II and III failed, so analogous controls could not be applied to the formolyses.

Infrared Analyses of the Alcohol Fractions.—These analyses were performed with a Perkin–Elmer recording spectrophotometer, model 21. The samples were run in a 0.027-mm. cell (sodium chloride) as liquid films with a solid salt block of identical thickness to the cell windows as a blank. The instrument was balanced at 1355.5 cm.$^{-1}$ with response 1:1, gain 4.5, supression 5, speed 0 and resolution 940. Table III records the optical densities of *threo*- and *erythro*-II and III at those wave lengths most advantageous for analysis, a synthetic mixture of the three components, and the alcohol fractions from the acetolyses. A similar type of data was obtained for the alcohol fractions from the formolysis which contain these three components, as well as for the alcohol fractions from the formolyses and acetolyses from which tertiary alcohol III had been removed.

Infrared Analysis of the Ketone Fractions from Olefin.—The same instrument and cells were employed, except the instrument was balanced at 1423.5 cm.$^{-1}$. The total spectra of the ketonic mixtures from the acetolysis (runs 1 and 2) were nearly identical to one another, differing only slightly in the intensity of some peaks. The carbonyl region exhibited only two absorption maxima at 1705 and 1655 cm.$^{-1}$, which correspond to unconjugated carbonyl and doubly conjugated carbonyl absorptions, respectively.[28] There was no absorption maximum that corresponded to singly conjugated carbonyl absorption[28] at 1680 cm.$^{-1}$, and the sensitivity of the instrument to this type of compound was demonstrated with a synthetic mixture of ketones X, XI and XII to which only 8% of 1,2-diphenyl-1-propanone was added. This mixture exhibited significant optical density (0.75) at this wave length. Two absorption maxima at 1580 (conjugated phenyl absorption)[28] and 1355 cm.$^{-1}$ (acetyl group absorption)[28] further identified the components of the unknown mixtures as probably containing 1,1-diphenyl-2-propanone (XI) and benzophenone (XII). The amounts of X, XI and XII in these mixtures were estimated utilizing the "base line density" method[29] and synthetic mixtures and the optical densities at the following most advantageous wave numbers, X at 1105 cm.$^{-1}$, XI at 1355 cm.$^{-1}$ and XII at 809 and 920 cm.$^{-1}$.

TABLE III

DATA FOR INFRARED ANALYSIS OF ALCOHOL FRACTIONS OBTAINED FROM ACETOLYSIS (RUNS 1 AND 2)[a]

	Optical densities at cm.$^{-1}$					
Compound	885.0	895.0	1054.0	1145.0	1245.0	1355.5
(+)-*threo*-II	0.129	0.281	0.569	0.200	0.269	0.204
(+)-*erythro*-II	.214	.207	.880	.207	.252	.217
III	.066	.117	.278	.565	.223	.379
Alcohol run 1[a]	.169	.212	.730	.281	.248	.244
Alcohol run 2[a]	.150	.213	.650	.308	.248	.256
Synthetic mixt.[b]	.143	.216	.633	.323	.254	.261

[a] Run numbers defined in Table I. [b] Footnote *b*, Table I.

The ketones from the formolyses (runs 3 and 4) were analyzed by the same methods, again no maximum at 1680 cm.$^{-1}$ being observed. The estimates of the three ketones in the four runs are recorded in Table II.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Studies in Stereochemistry. XXVII. Conformational Control of the Migrating Group in the Deamination of 3-Phenyl-2-butylamine[1]

BY DONALD J. CRAM AND JOHN E. MCCARTY

RECEIVED OCTOBER 1, 1956

The optically pure stereoisomers of 3-phenyl-2-butylamine have been deaminated in acetic acid and the products examined. With the *threo* isomer, methyl migration from Cβ dominated over phenyl migration by a factor of 1.5 to 1, whereas with the *erythro* isomer, phenyl migration from Cβ exceeded methyl migration by a factor of about 8 to 1. Methyl migration could not be detected when the stereoisomeric 3-phenyl-2-butyl tosylates were acetolyzed. These results coupled with those of others support the following hypothesis. Neither solvent nor neighboring group participation play much role in the breaking of the C–N_2^+ bond, and the fate of the *high energy open carbonium ion* thus created is determined by the relative proximity of the various neighboring groups and of solvent molecules. The relative positions of these species are therefore determined by the conformational populations of the starting diazotized amine. The products of methyl migration were partially optically active at the migration origin, this benzyl carbon atom having been partially inverted during the methyl migration. This result provides some evidence for the intervention of a *bridged methyl carbonium ion* intermediate in the rearrangement.

The propensity of the deamination reaction of aliphatic amines for initiating molecular rearrangements has been established by a large number of investigations. A number of recent mechanistic studies and observations have a direct bearing on the present research. Bernstein and Whitmore[2] demonstrated that the highly stereospecific rearrangement of (−)-1,1-diphenyl-2-amino-1-propanol to (+)-1,2-diphenyl-1-propanone observed much earlier by McKenzie, *et al.*,[3] occurred with inversion at the migration terminus. Roberts and co-workers[4c] found both methyl and hydrogen migration in the deamination of *n*-propylamine, but in this and other systems could find no evidence for the intervention of either hydrogen-[4a] or methyl-bridged carbonium ions.[4c,d] In the deamination of various *p*-substituted β-phenylethylamines, these authors[4b] observed a much smaller difference between the migratory aptitudes of *p*-nitrophenyl, phenyl and *p*-methoxyphenyl than had been observed in studies involving leaving groups other than N_2^+. Burr and Ciereszko[5] found in parallel studies of β-aryl-β-phenylethyl systems that with OH as a leaving group much greater differences in migratory aptitudes of phenyl and substituted phenyl were observed than when the leaving group was N_2^+. Curtin and co-workers[6] in an elegant study of the semipinacolic deamination reaction of various diastereomeric 2-phenyl-2-aryl-1-phenyl (or methyl)-1-ethylamines demonstrated that that aromatic nucleous migrated which gave a transition state where the bulky (non-migrating) groups attached to the two asymmetric carbon atoms were distributed *trans* to one another.

The present study describes the deaminative acetolysis of the optically pure diastereomers of 3-phenyl-2-butylamine (I). This system possesses certain peculiar advantages for mechanistic studies. (1) The acetolysis of 3-phenyl-2-butyl tosylate has been thoroughly studied,[7] and the effects of differences between tosylate and N_2 as leaving group can be assessed. (2) The intervention of "ethylene-phenonium ions" as intermediates in the migration of phenyl from Cβ to Cα can be detected making use of the symmetry properties of this system. (3) The three groups on Cβ, phenyl, methyl and hydrogen, all compete with one another in undergoing Wagner–Meerwein rearrangements, and in this system a correlation between the amounts of each group which migrate and the known configurations of the starting material is possible. (4) The system allows the stereochemistry of methyl migration to be examined at the migration origin (Cβ).

Three of the four optically pure stereomers of the 3-phenyl-2-butylamine system were prepared and their configurations determined in a previous study.[8] All four of the optically pure benzamide derivatives were reported.[8] In the current investigation the fourth isomeric amine possessing the D(−)-*erythro* configuration was prepared by the simple inversion in dioxane of the tosylate of optically pure D(−)-*threo*-3-phenyl-2-butanol. The rotation of this amine (α^{25}D −9.20°, *l* 1 dm., neat) compares favorably with that of its enantiomer prepared by direct resolution (α^{25}D +9.01°, *l* 1 dm., neat).

The methods of analysis and separation of the products of the deamination of the active isomers of 3-phenyl-2-butylamine are recorded in the Experimental, along with a number of control experiments on the solvolyses, the separations and the analyses.

Discussion

Table I records the yields of the various alcohol components obtained from the deaminative acetolysis of the stereomers of 3-phenyl-2-butylamine, as well as those obtained in previous studies[7] of the acetolyses under similar conditions of the tosylates

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(7) (a) D. J. Cram, *ibid.*, **71**, 3863 (1949); (b) **74**, 2129 (1952); (c) **74**, 2137 (1952); (d) D. J. Cram and J. E. McCarty, *ibid.*, **76**, 5740 (1954).

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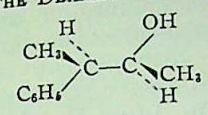
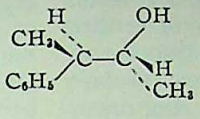
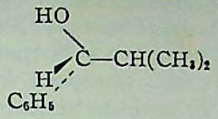
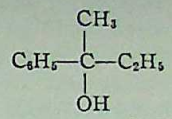
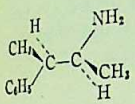
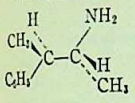
TABLE I

ALCOHOLIC PRODUCTS OF THE DEAMINATIVE AND TOSYLATE ACETOLYSIS OF THE 3-PHENYL-2-BUTYL SYSTEMS[a,b]

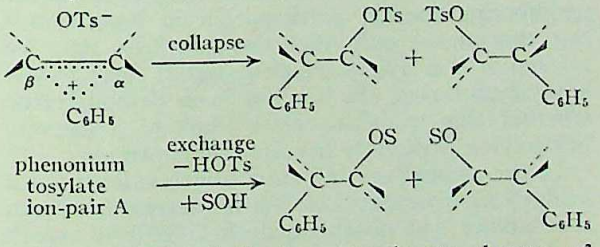
	Yield[b] *threo*, % Active	Racemic	Yield[b] *erythro*, % Active	Racemic	Yield,[b] % Active	Racemic	Yield,[b] %	Yield alcohol fraction,[c] %
 1, HNO_2, AcOH → 2, $LiAlH_4$	6	19	14	5	5	27	24[d]	50
[d(+)-*threo*-I] d(+)-*threo*-3-phenyl-2-butyl tosylate → 1, AcOH → 2, $LiAlH_4$	0.5	85	1	2.5	0	0	11	70
 1, HNO_2, AcOH → 2, $LiAlH_4$	6	0	68	0	0.2	6	20[d]	50
[d(+)-*erythro*-I] d(+)-*erythro*-3-Phenyl-2-butyl tosylate → 1, AcOH → 2, $LiAlH_4$	5	0	89	0	0	0	6	74

[a] The deaminative and tosylate acetolysis (ref. 7c) were both run at room temperature. However, a complete analysis of the secondary alcohol components of tosylate acetolysis was made only on product obtained from runs at 75° (ref. 11b). Enough data were obtained at both temperatures to indicate the patterns of results to be almost identical. The ratios of the various secondary alcohols to one another were taken from the runs at 75°. [b] Total alcohol fraction = 100%. [c] Starting amine or tosylate = 100%. [d] These are maximum values. Actual values are probably lower (see Experimental).

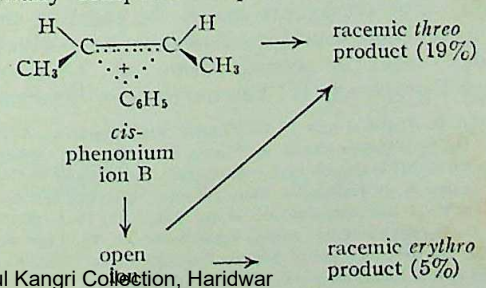
of the stereomers of 3-phenyl-2-butanol (III). In the deamination reaction each diastereomer gave appreciable but different amounts of products resulting from simple solvolysis (no rearrangement), from phenyl migration, from hydrogen and from *methyl migration*. In the tosylate solvolysis, the products of phenyl migration (3-phenyl-2-butanol) clearly dominated in both diastereomeric series, with small amounts of hydrogen migration, very small amounts of simple solvolysis product, and *no detectable product* from *methyl migration*.

Phenonium Ions as Intermediates in the Deamination Reaction.—In the tosylate solvolyses, both the high stereospecificity[7] and the enhancement of the rate of ionization[9] point to predominant phenyl participation in ionization. A complete analysis of the data for the *threo*-3-phenyl-2-butyl tosylate acetolysis[7c] provided the ratio 66/1 for phenyl over solvent participation in ionization and the ratio of 8/1 for hydrogen over solvent participation. Although a detailed calculation could not be carried out for the *erythro* isomer, it is clear that similar factors apply.[7b] In this and in similarly constituted systems,[10] phenonium tosylate ion-pairs (A) have been demonstrated to result from phenyl participation in ionization. These intermediates can collapse in either direction to give tosylate or can undergo anion exchange to give solvolyzed product. In acetic acid for the *threo*-3-phenyl-2-butyl system, collapse occurs four times as frequently as exchange.[7b]

A very different pattern of products arises in the deaminative acetolysis. That phenyl migrates from C_α to C_β is clear from the fact that in the *threo* series 24% of the alcoholic product is racemic 3-phenyl-2-butanol (III), 19% *threo* and 5% *erythro*. That simple substitution occurs to almost the same extent is indicated by the 20% of active 3-phenyl-2-butanol (6% *threo* and 14% *erythro*) obtained. With the *erythro* isomer, the high yield of product (68%) of configuration identical to that of starting material (substitution with retention) indicates that here as well phenyl migration occurred, although the symmetry properties of the system prevent its direct detection. The 6% of *threo* product indicates a somewhat lower degree of simple solvolysis in this as compared to the *threo* series.



These results indicate a moderate degree of stereospecificity for the process involving phenyl migration but of a much lower order than was observed in tosylate solvolysis. Of the 25% of *threo* product from *threo* starting material, 19% was racemic, pointing to the intervention of the internally compensated phenonium ion (B) as an



[9] S. Winstein and K. C. Schreiber, THIS JOURNAL, 74, 2165 (1952).
[10] (a) D. J. Cram, *ibid.*, 71, 3883 (1949); (b) 74, 2159 (1952).

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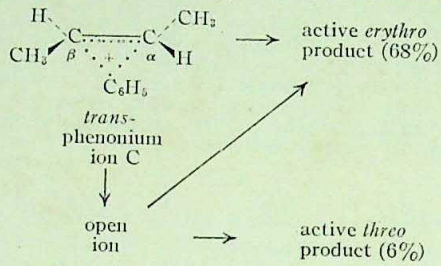
intermediate. This intermediate appears to have been disposed of both by direct ring opening to give *threo* product and by giving racemic open ion which in turn could go to either racemic *threo* or *erythro* material. This phenonium ion is then different in some respect from that produced from tosylate solvolysis, which only underwent direct ring opening to give racemic *threo* product. This point will be discussed later. In the *erythro* series, the phenonium ion produced is asymmetric, and direct ring



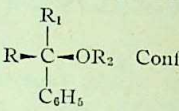
opening at either Cα or Cβ would give active material of the same configuration as the starting material. If this bridged ion gave open ion, this intermediate would be optically active and would give a mixture of active *threo* and *erythro* product. The results suggest that *direct ring opening* predominated in both series, but some rearranged, racemic, open ion is needed to explain the production of 5% racemic *erythro* product obtained from active *threo* starting material.

The Question of Bridged Methylcarbonium Ions as Intermediates in the Wagner–Meerwein Rearrangement.—Although bridged methylcarbonium ions frequently have been discussed[11] and deliberately sought for, not a shred of evidence for their intervention as reaction intermediates has been forthcoming. Some evidence has been obtained from rate comparisons in the solvolysis of neopentyl and more ramified tertiary systems for neighboring methyl participation in ionization,[12] but this means only that the *transition state for ionization is a hybrid* which *possesses some methyl bridged character*. It has not been demonstrated whether this transition state leads to a discrete bridged ion or directly to rearranged open ion.

In the present investigation some evidence for a bridged methylcarbonium ion is presented. From *threo*-amine was obtained alcohol, 32% of which was the product of methyl migration (1-phenyl-2-methyl-1-propanol or II) and from *erythro*-amine 6% was similarly rearranged. Of this rearranged material, 16% was optically active in the *threo* and 3% in the *erythro* runs. The stereochemistry of this rearrangement can be determined only if the relative configurations of reactant and product are known. The configurations of the starting materials have been established relative to D-glyceraldehyde,[8] but the configuration of 1-phenyl-2-methyl-1-propanol (II) has never been determined by chemical interconversions. However, the configuration of this compound can be assigned with a high probability of correctness relative to that of D-glyceraldehyde through the use of Freudenberg's displacement rule.[13,14] Levene, Mikeska and Marker[15] gathered the rotational data set forth in Table II, which when coupled with the known[16] configuration of 1-phenyl-1-ethanol allows the configurations of the other alcohols of Table II to be assigned the structures there set forth. The stereochemistry of the methyl migration thus becomes known and is formulated in Chart I.[17]

TABLE II

CONFIGURATIONS AND MOLECULAR ROTATIONS OF ALKYL SUBSTITUTED BENZYL ALCOHOLS AND DERIVATIVES



Configurational assignment

	Molecular rotations		
	R_2		
R_1	H[a]	Ac[a]	APTH[b,c]
CH_3	−52.5°	−194°	+32.0°
C_2H_5	−39.4°	−186°	−10.6°
$(CH_3)_2CH$	−34.9°	−178°	−21.0°
$CH(CH_3)_2$	−31.4°	−199°[d]	−62.6°
$(CH_3)_3CH_2$	−28.2°	−163°	−36.1°

[a] $M^{25}D$ (l 1 dm., neat). [b] Acid phthalate. [c] $M^{25}D$ (l 1 dm., c 0.01 M, ethanol). [d] From the present investigation.

Any mechanism used to explain this methyl migration must satisfy three main facts. (1) Both racemic and active product were obtained from both diastereomers. (2) The ratios of racemic to active product differ widely for the two diastereomers (*threo*, 5/1; *erythro*, 30/1). (3) In the production of optically active II, the migration origin was inverted. A completely concerted mechanism[18] by which all of the product was produced is thus eliminated, although the very remote possibility remains that the active portion of product arose by a completely concerted process, and the racemic material by a multistage course involving carbonium ions devoid of asymmetry. A mechanism in which *all of the product* arose from such a carbonium ion is also eliminated.

The data support the mechanistic scheme set forth in Chart I.[19] Here the *threo*-amine goes to a methyl bridged asymmetric carbonium ion with inversion of the migration terminus, the phenyl and methyl groups being *trans* to one another. Similarly the *erythro*-amine goes to a methyl bridge, also asymmetric, in which the methyl and

(11) (a) D. J. Cram and J. D. Knight, THIS JOURNAL, **74**, 5831 (1952); (b) S. Winstein and B. K. Morse, *ibid.*, **74**, 1133 (1952); (c) J. D. Roberts, M. Halmann and J. A. Yancey, ref. 8c and 8d; (d) H. C. Brown and R. B. Kornblum, THIS JOURNAL, **76**, 4510 (1954).

(12) (a) P. D. Bartlett, *Bull. soc. chim. France*, [5] **18**, C100 (1949); (b) P. D. Bartlett and M. Stiles, THIS JOURNAL, **77**, 2806 (1955); (c) P. D. Bartlett and M. S. Swain, *ibid.*, **77**, 2801 (1955); (d) S. Winstein and H. Marshall, *ibid.*, **77**, 6021 (1955).

(13) K. Freudenberg, W. Kuhn and I. Bumann, *Ber.*, **63B**, 2380 (1930).

(14) The authors are indebted to Professor H. S. Mosher for bringing this to our attention and wish to express their appreciation.

(15) (a) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **70**, 355 (1926); (b) P. A. Levene and R. E. Marker, *ibid.*, **97**, 381 (1932).

(16) K. Mislow, THIS JOURNAL, **73**, 3954 (1954).

(17) In the configurational formulations of this paper, that enantiomer which is convenient for portrayal is depicted. The fact that in some cases the other enantiomer was actually used in no way affects the principles involved.

(18) A completely concerted Wagner–Meerwein rearrangement (all bonds made and broken in the same transition state) has never been demonstrated and is very improbable.

(19) The stages intervening between starting material and the bridged ion are discussed in a later section.

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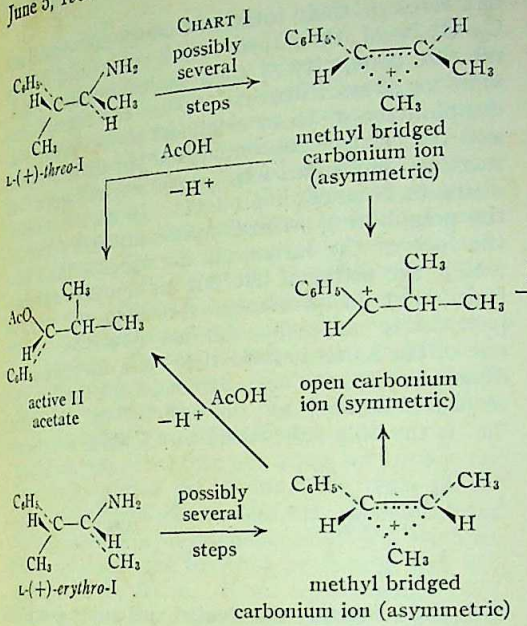
CHART I

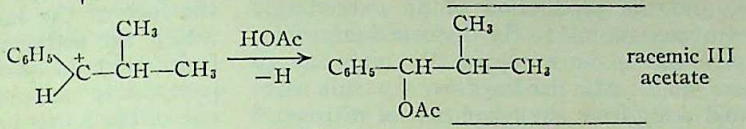


phenyl groups are *cis* to one another. Each of these bridged ions partition between two processes, one involving ring opening at the benzyl carbon to give directly (one transition state) optically active rearranged acetate with the migration origin inverted, the other involving ring opening to give the symmetrical phenyl isopropylcarbonium ion which goes to racemic rearranged acetate. Since the two bridges are diastereomerically related, they would partition differently between these two processes. The *trans* bridge from *threo* material might be expected to be the more stable of the two, and therefore to be the species more favorably disposed to undergo ring opening by solvent to give active product, as is indeed observed.

A second mechanistic scheme should also be considered (Chart II), in which the methyl bridges are transition states, not discrete intermediates. Thus *threo* material passing through a *trans* bridged transition state might give a rearranged disolvated open ion (D) which differs from that from *erythro* material (E) in rotational conformation. Should k_c be the same order of magnitude as k_e, optically active acetate with the migration origin inverted could arise. That D or E collapse *directly* from both sides with equal probability to give racemic material is unlikely, since the steric situation distinctly favors entrance from the top. The ratio of k_c/k_e should differ for D and E, and the greater stability of D should favor a higher value for this ratio, leading to a higher degree of optical activity for rearranged acetate, as was observed.

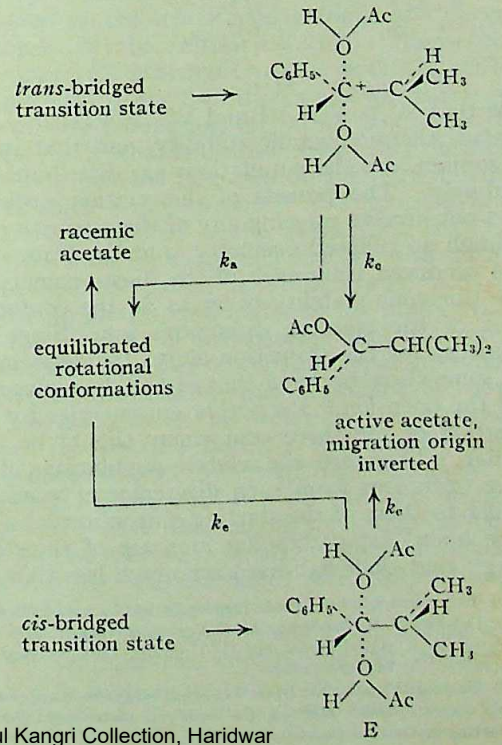
Of these two explanations, that involving the methyl bridge as a discrete intermediate is preferred on both the basis of simplicity and analogy. Since the leaving group in this deamination reaction is a nitrogen molecule, mechanisms involving rearranged ion-pairs or open carbonium ions solvated by nitrogen on one side and solvent on the other are highly unlikely.

The Hydrogen Migration in the Deamination Reaction.—In the acetolysis of the active diastereomers of 3-phenyl-2-butyl tosylate, evidence[7c] was obtained that hydrogen participated in the ionization stage to give both stereospecifically produced olefin as well as the rearranged methylethylphenylcarbonium ion, which reacted with solvent to give racemic tertiary acetate. In the present study, both diastereomers gave this same acetate in considerably higher yields. Unfortunately the methods of analysis prevented the optical character



of this tertiary acetate from being examined (see Experimental). A second difference between the tosylate acetolysis and the deaminative acetolysis is that nearly all of the *conjugated* olefin produced was destroyed by the nitrous acid, and therefore the stereospecificity of this elimination could not be studied. A peculiar consequence of this destruction of *conjugated* olefin was that the olefin isolated was largely 3-phenyl-1-butene. The total olefin fraction from *threo*-amine (11% yield) was reduced to 2-phenylbutane whose rotation indicated the olefin to be free of conjugated material and to have arisen by a completely stereospecific process. This fact prohibits the intervention of phenonium ions in the production of this unconjugated olefin, a point also demonstrated for the tosylate solvolyses. The olefin from *erythro*-amine (4%) reduced to 2-phenylbutene whose activity was only about 80% of what was to be expected from the completely unconjugated olefin which had arisen by a completely stereospecific path. Apparently a small amount of conjugated olefin survived the nitrous acid in this particular run.

CHART II



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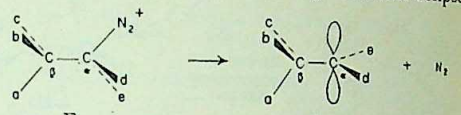
The Differences in Mechanism Between N_2 and OTs^- as Leaving Groups in Solvolyses.—The above results clearly demonstrate rather gross differences in the mechanisms for the deaminative and tosylate solvolyses. In the deaminative reaction the first stage is very probably the formation of a diazonium ion, which dissociates to a nitrogen molecule and a carbonium ion of some kind. The diazonium ion for aliphatic systems is unstable, and the production of an exceedingly stable nitrogen molecule in the dissociation process should give rise to an exceptionally high energy carbonium ion.[20] The driving force for this reaction should come from the formation of nitrogen[20] and not from neighboring group or solvent participation. Thus neighboring group or solvent probably become involved to an appreciable extent only at a later stage, that is, only after the production of a little-solvated, high energy, very short lived, *open* carbonium ion. The stereochemical consequences of this latter possibility will be examined as applied to the system at hand.

Chart III formulates the three conformations for each of the diastereomeric diazonium ions. Utilizing the principles developed earlier,[21] it seems probable that IV > V > VI and VII > VIII > IX in relative thermodynamic stability, and that in the diazonium ions the populations are distributed accordingly. The process of dissociation probably does not involve rotating any of these substituents through an eclipsed geometry, and the three open ions produced from each of the diastereomers fall into the same stability order as do the conformations of the starting diazonium ion. Since the geometry for the transition states for dissociation lies somewhere between that of the diazonium ion and the open ion,[22] the activation energies for dissociation of the three conformers should be very similar. Therefore, the relative populations of the three open ions from each diastereomer would be similar to those of the starting diazonium ions. If these open, flat carbonium ions are of such high energy that their half-lives are much less than the half-lives of their rotation through 60° about the C_β–C_α bond, then their fate is determined by the relative proximity of their nearest neighbors (solvent or β-substituents). Thus the relative nucleophilicity of these neighbors plays a minor role and the relative conformational populations of the starting diazonium ion become controlling in the ultimate balance of products. In such a scheme, the neighboring β-substituents must still approach the face of the carbonium ion opposite from that which the nitrogen left but for a reason different from that in which the β-substituents actually participate in carbonium ion formation. If F, one of the three conformations of a diazonium ion, dissociates to give open carbonium ion G, then "a" on C_β is flanked by "d" and "e" on C_α. Thus "a" is the only substituent on C_β which is eclipsed



F G

with the relatively unsolvated and empty p-orbital of the short lived "hot" carbonium ion. Other groups (b and c) could become involved only if rotation about C_β–C_α occurred to the extent of either 60 or 120°.

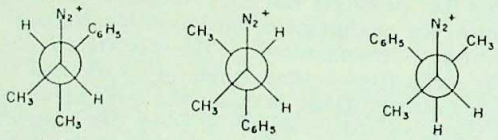
This hypothesis suggests that in the deamination of *threo*-3-phenyl-2-butylamine, methyl migration should exceed phenyl which should exceed hydrogen migration. The data (Table I) show that methyl accounted for 32%, phenyl for 24% and hydrogen migration for a maximum of 24% of the acetate produced.[23] For the *erythro* series, the hypothesis would predict that phenyl would predominate over hydrogen, which would exceed methyl migration. Of the acetate produced by this diastereomer (Table I), up to 68% could have involved phenyl[24] migration, a maximum of 20% hydrogen and only 6% methyl migration.

Two features make it unlikely that eclipsing effects in the formation of bridged transition states control the migrating group in these diastereomeric series. (1) These eclipsing effects played little or no role in either selecting the migrating group or effecting the rates of ionization for the acetolysis of the diastereomers of 3-phenyl-2-butyl tosylate. If eclipsing effects were important in this system, they certainly would be more likely to assert themselves in tosylate solvolysis where driving forces due to neighboring group participation are present. (2) The groups that are being eclipsed are rather small (*e.g.*, two methyl groups during phenyl migration in the *threo* series). In other reactions in other systems, the "*cis* effect" becomes important only when a medium and large or two large groups become involved.[25]

Tosylate and halide solvolyses differ in a second important respect from deaminative solvolyses.

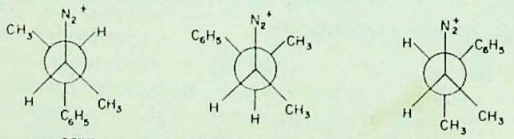
CHART III

Conformations of the L(+)-*threo*-diazonium ion



IV V VI

Conformations of the L(+)-*erythro*-diazonium ion



VII VIII IX

(20) This point has been made previously by Burr and Ciereszko (ref. 9b) and by D. Y. Curtin and M. C. Crew (ref. 10f).

(21) (a) F. A. Abd Elhafez and D. J. Cram, THIS JOURNAL, **74**, 5846 (1952); (b) **74**, 5851 (1952).

(22) Hammond's postulate [*ibid.*, **77**, 334 (1955)] would suggest that for this very exothermic reaction, the transition state would resemble the starting material in geometry.

(23) These values could be slightly in error as measures of the extent of each substituent migration since rearranged open carbonium ions could also give small amounts of conjugated olefin which was then destroyed by nitrous acid.

(24) A small part of this 68% undoubtedly arose by simple solvolysis with retention of configuration.

(25) D. Y. Curtin, *Record Chem. Progress* (*Kresge–Hooker Sci. Lab.*), **15**, 111 (1954).

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Although ion-pair intermediates have been demonstrated[7b,26] in a number of halide and tosylate solvolyses, no such species can intervene in the deamination reaction with N_2 as the leaving group. Such a molecule would not even be expected to solvate the carbonium ion it was leaving, as is probable with the conjugate acid of an ester, ether or alcohol dissociates. Unlike the phenonium tosylate produced in tosylate solvolysis of the 3-phenyl-2-butyl system,[7b] a phenonium ion produced from a high energy, open ion would be relatively naked and reactive. Unlike the phenonium tosylate ion-pair, this bridged ion might not only capture solvent, but also give rearranged open ion which in turn could capture solvent. Such a process might explain the production of the 5% of racemic *erythro*-acetate produced from active *threo*-amine.

This amount of acetate produced by *simple solvolysis* is greater in the deaminative than in the tosylate solvolysis. In the former, *threo* material gave 6% acetate with retention and 14% with inversion as compared to 0.6% retention and 4% inversion in the latter. From *erythro*-amine, 6% acetate resulted from simple acetolysis with inversion, whereas with tosylate, 4% acetate. The amount of acetate resulting from simple acetolysis with retention could not be measured. The relatively higher amount of simple solvolysis in the deamination reaction probably reflects the ability of solvent to compete better with neighboring groups for a less hindered open carbonium ion than for either the back side of a saturated carbon atom or either side of an ion-pair. Again it would appear that in passing from tosylate solvolysis to the deamination reaction selectivity based on steric effects becomes more important at the expense of electronic effects.

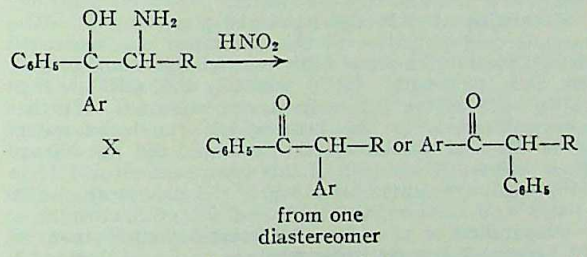
Other Solvolytic Deamination Reactions.—The general interpretation of the course of the deamination reaction in the present study is consistent with the results obtained in a wide variety of systems. Bartlett and Knox[27] observed that although the deamination of 1-apocamphylamine to give 1-apocamphanol or 1-chloroapocamphane occurred readily, attempts at substitution at this bridge-head carbon utilizing other leaving groups (H_2O^+ or Cl) failed even under brutal conditions. Thus participation by solvent or neighboring groups does not seem to be a necessary condition for dissociation in this deaminative substitution.

The demonstration by Bernstein and Whitmore[2] that the migration terminus is inverted in the deaminative rearrangement of 1,1-diphenyl-2-amino-1-propanol does not necessarily mean that phenyl participated in the dissociation of the diazonium ion. The most stable rotational conformation of the diazonium ion places one phenyl oriented 180° from the N_2 leaving group and a short lived, high energy, open carbonium ion produced by dissociation is sterically oriented to best attack this phenyl group, thus giving the observed stereochemical result.

The numerous observations[4b,5,6f] that the difference in migratory aptitude of various *p*-substituted phenyls became diminishingly small in the deamination reaction as compared to other carbonium ion-forming reactions are consistent with the concept of dissociation of the diazonium ion without neighboring group participation in the deamination reaction.

The high energy carbonium ion produced in the deamination reaction does not show any more tendency to rearrange than does the carbonium ion formed by simple ionization of an alkyl bromide or tosylate, at least in the α-phenylneopentyl system. Here the fate of the α-phenylneopentyl carbonium ion produced from a variety of leaving groups is similar.[11b,28]

Curtin, *et al.*, outlined two possible reasons why in the deamination of a series of diastereomeric amino alcohols X the migrating aryl group should be different for each diastereomer.[6a] In the first explanation, the relative stability of the various conformations of the starting molecule was considered as the controlling feature. However, it was pointed out[6g] that if the rate of conformational



equilibration is fast compared to rearrangement, the activation energy for one group migrating compared to a second in a given diastereomer is independent of the relative populations of the conformations of the initial molecule. The second and preferred[6g] explanation deals with the difference in energy of the transition states for rearrangement of two competing migrating groups in the same molecule, that transition state being the more stable in which the non-migrating groups are distributed *trans* to one another.[6a,6g] Implicit in both of these explanations is the assumption that the transition state for migration and for dissociation are one and the same; in other words, that the neighboring group participates in the dissociation. If on the other hand one assumes that a discrete intermediate, an open carbonium ion, intervenes between the dissociation and rearrangement processes, the analysis of this semipinacolic deamination reaction becomes similar to that applied to the deaminative Wagner–Meerwein rearrangement in this paper. Thus the first of Curtin's original hypotheses[6a] that the migrating group is controlled by the relative populations of conformations of the starting material might still apply to these pinacolic deamination reactions.

In the deamination of substituted cyclohexylamines, conformation control of the migrating

(26) (a) S. Winstein and D. Trifan, THIS JOURNAL, **74**, 1147, 1154 (1952); (b) D. J. Cram and F. A. Abd Elhafez, *ibid.*, **75**, 3189 (1953); (c) H. L. Goering, J. P. Blanchard and E. Silversmith, *ibid.*, **76**, 5409 (1954); (d) C. G. Swain, L. E. Kaiser and T. E. C. Knee, *ibid.*, **77**, 4684 (1955); (e) S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck and G. C. Robinson, *ibid.*, **78**, 328 (1956).

(27) P. D. Bartlett and L. H. Knox, *ibid.*, **61**, 3184 (1939).

(28) (a) P. S. Skell and C. R. Hauser, *ibid.*, **64**, 2633 (1942); (b) A. Brodhag and C. R. Hauser, *ibid.*, **77**, 3024 (1955); (c) I. Dros-[illegible] *Chimica Acta*, **37**, 658 (1954).

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group seems to be enforced.[29] In simple solvolysis, however, both equatorially and axially oriented cyclohexylamines give mainly equatorially oriented alcohols.[30] This fact is consistent with a high energy, relatively unsolvated carbonium ion intermediate whose stereochemical fate is controlled not by solvent participation in ionization, but by the relative proximity of solvent molecules to the equatorial or axial faces of the carbonium ion once the nitrogen molecule has left. Apparently the same carbonium ion is created from *cis* to *trans* diastereomers and solvent molecules can get closer to the equatorial than the axial face of the ion, thus giving equatorially oriented alcoholic product.

Experimental

Preparation of Optically Pure D(−)-*erythro*-3-Phenyl-2-butylamine.—The procedure employed is identical to that used previously[8] to make the benzamide of this amine,[8] except that a large enough amount of material was used to allow isolation of the amine itself. From 4.92 g. of D(−)-*threo*-3-phenyl-2-butyl tosylate[7a,b] (m.p. 64.8–65.1°, prepared from optically pure alcohol) was obtained 0.432 g. of D(−)-*erythro*-3-phenyl-2-butylamine as a colorless oil, $n^{25}D$ 1.5157, $\alpha^{26}D$ −9.21° (*l* 1 dm., neat).

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.46; H, 10.15. Found: C, 80.39; H, 10.37.

The enantiomer of this amine prepared by direct resolution gave $\alpha^{25}D$ +9.01° (*l* 1 dm., neat).[8]

Resolution of 2-Methyl-1-phenyl-1-propanol (II).—The racemic acid phthalate of this substance was resolved[15] in 24% yield (racemate = 100%) to give active acid phthalate, m.p. 93.6–94.1°, $[\alpha]^{23}D$ +45.1 (*c* 3.5, $CHCl_3$), lit.[15] $[\alpha]^{20}D$ +21.08° (*c* 9.2, solvent not reported). Further recrystallizations of the brucine salt (methanol–water) or of the acid phthalate (ether–pentane) did not change these values. Hydrolysis of this ester gave alcohol II in 94% yield, $n^{25}D$ 1.5113, $\alpha^{23}D$ +20.6° (*l* 1 dm., neat), $[\alpha]^{23}D$ +48.3° (*c* 6.7, ether), lit.[15] $[\alpha]^{20}D$ +47.7° (*c* 6.8, ether).

Preparation of L(−)-*threo*-2-Acetoxy-3-phenylbutane, D-(+)-*erythro*-2-Acetoxy-3-phenylbutane, (+)-1-Acetoxy-2-methyl-1-phenylpropane and 2-Acetoxy-2-phenylbutane.—L(−)-*threo*-2-Acetoxy-3-phenylbutane and D(+)-*erythro*-2-acetoxy-3-phenylbutane were prepared from L(+)-*threo*-3-phenyl-2-butanol ($n^{25}D$ 1.5160, $\alpha^{26}D$ +27.25°, *l* 1 dm., neat) and D(−)-*erythro*-3-phenyl-2-butanol ($n^{25}D$ 1.5168, $\alpha^{25}D$ −0.62°, *l* 1 dm., neat) by methods already reported[7b] in 93 and 96% yields, respectively, $n^{25}D$ 1.4877, $\alpha^{26}D$ −7.80° (*l* 1 dm., neat) and $n^{25}D$ 1.4877, $\alpha^{26}D$ +32.38° (*l* 1 dm., neat). The literature[7b] reports $n^{25}D$ 1.4877, $\alpha^{23}D$ −8.08° (*l* 1 dm., neat) and $n^{25}D$ 1.4877, $\alpha^{25}D$ +32.55 (*l* 1 dm., neat) for these compounds. (+)-1-Acetoxy-2-methyl-1-phenylpropane was prepared in an entirely analogous fashion from optically pure (+)-2-methyl-1-phenyl-1-propanol, $n^{25}D$ 1.5113, $\alpha^{26}D$ +21.57 (*l* 1 dm., neat), in a 96% yield, $n^{26}D$ 1.4853, $\alpha^{26}D$ +104.68° (*l* 1 dm., neat).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.38. Found: C, 75.06; H, 8.20.

Racemic 2-acetoxy-2-phenylbutane was prepared as before[7c] in 35% yield, $n^{25}D$ 1.4946 (lit.[7c] 1.4944).

Deamination Reactions of 3-Phenyl-2-butylamine.—Four reactions were carried out, one with optically pure L(+)-*erythro*-isomer, one with the optically pure D(−)-*threo*-isomer, one with partially optically pure D(−)-*erythro*-isomer and one with partially optically pure L(+)-*threo*-isomer. The reactions were all carried out in the same way, but in the two runs involving optically pure materials, different methods of isolation and analysis were employed from in the two runs involving partially optically pure amines. The procedure for the reaction itself is illustrated utilizing L(+)-*erythro*-3-phenyl-2-butylamine (run 1). To 4.63 g. of amine[8] ($\alpha^{23}D$ +8.91°, *l* 1 dm., neat; $n^{25}D$ 1.5159) dissolved in 300 ml. of dry glacial acetic acid was added over a period of 30 minutes, 31.4 g. of potassium nitrite. During this addition the temperature was held at 25–27° through external cooling. The resulting solution was stirred vigorously for one hour and shaken with 1.5 l. of water and 200 ml. of pure pentane. The aqueous layer was again washed with pentane, the pentane extracts were thoroughly washed with water, with dilute base, dried, and the solvent was evaporated through a short column. The residual oils were treated differently depending on which run was involved (see next section).

Isolation of Products from the Deamination Reaction; Method I.—This procedure is illustrated with the work up of the oil obtained from the deamination reaction in run 1 (see above). The residual oil was dissolved in 100 g. of anhydrous glacial acetic acid and maintained at 75° for 26 hours. This procedure has been demonstrated previously[7c] to completely convert 2-acetoxy-2-phenylbutane to olefin. Removal of this acetate in runs 1 and 2 simplified the analysis of the remaining components. The mixture was cooled, diluted with 1 l. of water and extracted twice with pure pentane. The pentane solution was washed with dilute sodium carbonate solution, water, dried, and the solvent was evaporated through a short column. The residual oil was a mixture of olefin, ketone and three acetates. The ketone was removed as follows: This oil was dissolved in 150 ml. of methanol containing 15 ml. of water, 15 g. of trimethylacethydrazine ammonium chloride (Girard reagent "T"), 4.1 g. of sodium acetate and 3.0 g. of glacial acetic acid. The resulting solution was heated at reflux for 90 minutes, cooled, diluted with 1 l. of water and extracted with pure pentane. The pentane extract was washed with dilute sodium bicarbonate solution, water, dried, and the solvent was evaporated through a short column. The residual oil was dissolved in dry ether and added to a slurry of 1.3 g. of lithium aluminum hydride in dry ether. In this fashion the acetates were converted to the parent alcohols. The excess hydride was decomposed with dilute hydrochloric acid, and the aqueous phase was extracted with pure pentane. The combined ether and pentane solutions were washed with dilute sodium bicarbonate solution, dried, and the solvent was evaporated through a short column. The residual oil was subjected to chromatography on 150 g. of activity I alumina[31] under pure pentane. The olefin fraction was washed from the column with pure pentane and was twice distilled at 18 mm. to give 0.43 g. (10% yield) of this product. The alcohol fraction was washed from the column with ethanol, the resulting solution being evaporated. The residual oil was distilled at 1 mm. through a short-path still to give 1.86 g. or 40% yield of a mixture of diastereomeric 3-phenyl-2-butanols and 2-methyl-1-phenyl-1-propanol, $\alpha^{23}D$ +3.18° (*l* 1 dm., neat), $n^{25}D$ 1.5167. This material was subjected to quantitative infrared analysis to determine the amount of each of the above three alcohols in the mixture (see later section). A sample (0.74 g.) of this alcohol fraction was converted by the pyridine–acetic anhydride method to acetate in 95% yield, $\alpha^{24}D$ −27.55° (*l* 1 dm., neat), $n^{25}D$ 1.4874. To 0.90 g. of the alcohol fraction was added 25 ml. of glacial acetic acid containing 2.5 g. of acetic anhydride and 0.25 g. of *p*-toluenesulfonic acid monohydrate, and the resulting solution was maintained at 75° for 18 hours. This treatment was demonstrated in control experiments (see later section) to completely racemize and partially convert to olefin the 2-methyl-1-phenyl-1-propanol component and to leave the diastereomeric 3-phenyl-2-butanols intact. The solution was cooled, diluted with 400 ml. of water, extracted with pure pentane, and the pentane extracts were washed with dilute base, dried and evaporated through a short column. The residual oil was dissolved in dry ether and added to a slurry of 0.3 g. of lithium aluminum hydride. This procedure converted any acetates formed back to alcohols. The olefin–alcohol mixture was isolated in the usual way and chromatographed on 50 g. of activity I alumina[31] as before. The fraction eluted with methanol was distilled at 15 mm. to give 0.72 g. of colorless oil, $\alpha^{23}D$ +3.21° (*l* 1 dm., neat). A sample (0.43 g.) of this alcohol was converted by the acetic anhydride–pyridine method to the acetate in 95% yield, $\alpha^{26}D$ −26.96° (*l* 1 dm., neat), $n^{25}D$ 1.4879. The rotational data on the alcohol and acetate before and after racemization of the 2-methyl-1-phenyl-1-propanol coupled

(29) (a) D. Nightingale and M. Maienthal, THIS JOURNAL, **72**, 4823 (1950); (b) D. Y. Curtin and S. Schmukler, *ibid.*, **77**, 1105 (1955).

(30) (a) J. A. Mills, *J. Chem. Soc.*, 260 (1953); (b) A. K. Bose, *Experientia*, **9**, 256 (1953); (c) W. G. Dauben, R. C. Tweit and C. Mannerskantz, THIS JOURNAL, **76**, 4420 (1954).

(31) H. Brockmann and H. Schodder, *Ber.*, **74**, 78 (1941).

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with the rotations of synthetic mixtures allowed the optical character of the three components to be determined (see later section).

In run 2, 4.70 g. of optically pure D(−)-*threo*-3-phenyl-2-butylamine[3] was employed, $\alpha^{23}D$ −42.33° (*l* 1 dm., neat), $n^{25}D$ 1.5143. From this was obtained 0.53 g. or 13% yield of olefin and 1.80 g. or 38% yield of the three isomeric alcohols, $\alpha^{23}D$ −5.78° (*l* 1 dm., neat), $n^{25}D$ 1.5143. This alcohol fraction was submitted directly to infrared analysis. A sample of this alcohol was converted to its acetate in 96% yield, $\alpha^{23}D$ +0.05° (*l* 1 dm., neat), $n^{25}D$ 1.4869. A portion of this alcohol (0.86 g.) was submitted to the action of *p*-toluenesulfonic acid in acetic acid as above to give a mixture of the two active diastereomers and racemic 2-methyl-1-phenyl-1-propanol, wt. 0.61 g., $\alpha^{23}D$ −4.21° (*l* 1 dm., neat). A sample of this alcohol was converted to its acetate by the acetic anhydride–pyridine method in 94% yield, $\alpha^{25}D$ +8.41° (*l* 1 dm. neat), $n^{25}D$ 1.4872.

Isolation of Products from the Deamination Reaction; Method II.—This procedure differs from method I in the following respects: (1) The original mixture obtained from the solvolysis (ketone, olefin and four acetates) was not heated to 75° to remove 2-phenyl-2-acetoxybutane but was treated directly with Girard reagent to remove ketone. (2) The olefin was examined by its reduction to 2-phenylbutane and measurement of this substance's optical purity. In this procedure olefin came only from deamination reaction itself. (3) The infrared analysis was performed on the final mixture of three alcohols, the two diastereomers of 3-phenyl-2-butanol and racemized 2-methyl-1-phenyl-1-propanol. The procedure is illustrated with run 4.

From the acetolysis of 9.83 g. of L(+)-*threo*-3-phenyl-2-butylamine[3] ($\alpha^{24}D$ +6.42°, *l* 1 dm., neat; $n^{25}D$ 1.5142) was obtained an oil which was 15.2% optically pure. This material was treated with Girard reagent "T" as in method I, and the product was reduced with lithium aluminum hydride as in method I. The product was chromatographed as in method I, the olefin fraction after distillation amounting to 1.03 g. (12% yield) and the alcohol fraction to 4.90 g. (50% yield).

This olefin fraction was reduced to 2-phenylbutane as follows. To a suspension of platinum black (from 50 mg. of PtO_2) in 25 ml. of methanol was added 0.51 g. of the olefinic fraction, and the mixture was shaken under 752 mm. of hydrogen. After hydrogen uptake had stopped (76 ml.), the mixture was filtered, and the filtrate was shaken with 350 ml. of water and pure pentane. The pentane extract was washed with water, dried and the solvent was evaporated through a short column. The residual oil was distilled through a short-path still to give 0.45 g. of crude 2-phenylbutane. Careful fractional distillation of this material (0.30 g.) gave 0.23 g. of L(+)-2-phenylbutane, $\alpha^{23}D$ +3.82° (*l* 1 dm., neat), $n^{25}D$ 1.4878. Optically pure 2-phenylbutane has a rotation $\alpha^{23}D$ +24.2° (*l* 1 dm., neat), $n^{25}D$ 1.4878.[32] This material is therefore 15.8% optically pure as compared to the 15.2% optical purity of the starting amine. Thus only optically pure 3-phenyl-1-butene survived the deaminative solvolysis.

The alcohol fraction (2.00 g.) was submitted to the action of an acetic acid, acetic anhydride and *p*-toluenesulfonic acid mixture to racemize 2-methyl-1-phenyl-1-propanol and destroy 2-phenyl-2-butanol, the procedure being the same as in method I. The product was reduced with lithium aluminum hydride as before and chromatographed on alumina. The olefin obtained (mixture of 2-phenylbutenes from dehydration of 2-phenyl-2-butanol) was distilled to give 0.38 g. (11% yield) of material, $n^{25}D$ 1.5190. Distillation of the alcohol fraction gave 1.09 g. (27% yield) of material, $\alpha^{23}D$ +0.63° (*l* 1 dm., neat), $n^{25}D$ 1.5147. This material was submitted to infrared analysis. A sample (0.76 g.) of this alcohol was converted by the acetic anhydride–pyridine method to acetate in 96% yield, $\alpha^{24}D$ −1.18° (*l* 1 dm., neat), $n^{25}D$ 1.4873.

In run 3, 10.0 g. of D(−)-*erythro*-amine[3] was employed, $\alpha^{25}D$ −4.91° (*l* 1 dm., neat), $n^{25}D$ 1.5160, 45% optically pure. From this material was obtained 0.463 g. of olefin (5% yield) and 5.05 g. of alcohol (50% yield). The total olefin fraction was reduced as before to give 0.396 g. of distilled 2-phenylbutane. Careful fractionation of 0.300 g. of this material gave 0.232 g. of 2-phenylbutane, $n^{25}D$ 1.4578, $\alpha^{24}D$ −8.70° (*l* 1 dm., neat), 36% optically pure.

(32) D. J. Cram, THIS JOURNAL, **74**, 2149 (1952).

A portion of the alcohol fraction (2.00 g.) was treated with *p*-toluenesulfonic acid as in the other runs to give, after lithium aluminum hydride reduction and chromatography, an olefin and alcohol fraction. The olefin fraction (distilled), wt. 0.215 g. (6% yield), came from the decomposition of 2-phenyl-2-butanol. The alcohol fraction (distilled) amounted to 1.22 g. (30% yield), $n^{25}D$ 1.5166, $\alpha^{24}D$ −1.42° (*l* 1 dm., neat) and was submitted to infrared analysis. This alcohol was converted to its acetate by the acetic anhydride–pyridine method in 94% yield, $\alpha^{24}D$ +12.53° (*l* 1 dm., neat).

Demonstration of the Presence of 2-Methyl-1-phenyl-1-propanol Among the Products of Deaminative Acetolysis of D(−)-*threo*-3-Phenyl-2-butylamine.—Because the product of methyl migration was unexpected in this deamination, qualitative proof of its presence was sought. A deamination reaction was run utilizing the conditions and isolation procedure of run 2 except that 35% optically pure (−)-*threo*-amine was employed. A portion (0.78 g.) of the alcoholic product (this material had not been treated with *p*-toluenesulfonic acid at 75°) was converted to its acid phthalate. The resulting oil was subjected to partition chromatography on 164 g. of a mixture of one part of silicic acid to two parts of Celite made up in 1% ethanol in chloroform. Elution of the material with 1% ethanol in chloroform resulted in a partial fractionation of the acid phthalates. Four fractions, each containing about 0.35 g. of solute, were collected. These materials were crystallized and recrystallized from chloroform–pentane to a constant melting point. The material from the first fraction (9 mg., m.p. 131.8–132.2°) gave a m.m.p. of 133–133.8° with authentic acid phthalate of racemic 2-methyl-1-phenyl-1-propanol[15] (m.p. 133.7–134°). The other fractions, although obtained in somewhat larger amounts, gave melting points and mixed melting points which indicated them to be mixtures of acid phthalates.

Preparation of the Acetates of Various Alcohols; Pyridine–Acetic Anhydride Method.—This preparation will be illustrated with the conversion of (+)-2-methyl-1-phenyl-1-propanol to (+)-1-acetoxy-2-methyl-1-phenylpropane. To 7.0 g. of (+)-2-methyl-1-phenyl-1-propanol[15] ($\alpha^{26}D$ +21.57°, *l* 1 dm., neat; $n^{25}D$ 1.5113) was added 30.0 g. of acetic anhydride and 75 g. of anhydrous pyridine. The resulting solution was heated on a steam-bath for 3 hours. At the end of this time, 250 ml. of water and 100 g. of ice were added, and the resulting mixture was extracted twice with pure pentane. The pentane extracts were combined, washed with water, dilute hydrochloric acid, dilute sodium bicarbonate and dried. The pentane was evaporated through a short column. The residual oil was subjected to chromatography on a 4 × 35 cm. column (140 g.) of alumina made up in pure pentane. The column was washed with pure pentane (the pentane washes were discarded) and was eluted with a solution of 10% ether in pentane. The ether–pentane was evaporated through a short column and the residual oil was distilled through a short-path still at 15 mm. to give 8.5 g. of (+)-1-acetoxy-2-methyl-1-phenylpropane,[15] $\alpha^{26}D$ 104.68° (*l* 1 dm., neat), $n^{25}D$ 1.4853.

Control Experiments.—The following experiment demonstrates: (1) that the solvolysis products once formed are stable, (2) that the ketone could be quantitatively removed, (3) that 2-acetoxy-2-phenylbutane is completely converted to olefin at 75° in glacial acetic acid and (4) the three secondary acetates are not fractionated during the isolation procedure. A mixture of 0.89 g. of L(−)-*threo*-3-acetoxy-2-phenylbutane ($\alpha^{24}D$ −7.80°, *l* 1 dm., neat; $n^{25}D$ 1.4877), 0.90 g. of (+)-acetoxy-2-methyl-1-phenylpropane ($\alpha^{26}D$ +104.68°, *l* 1 dm., neat; $n^{25}D$ 1.4853) gave $\alpha^{25}D$ +41.72° (*l* 1 dm., neat) and $n^{25}D$ 1.4870. To this mixture was added 0.60 g. of 2-acetoxy-2-phenylbutane ($n^{25}D$ 1.4946), 0.20 g. of acetophenone ($n^{25}D$ 1.5343) and 0.09 g. of 3-phenyl-2-butanone ($n^{25}D$ 1.5104). This mixture was subjected to the exact conditions of the deamination reaction, and the isolation procedure of method I (the final acid treatment of the alcohols was omitted). The product was 0.38 g. of olefin ($n^{25}D$ 1.5214) and 1.00 g. of alcohol, a sample (0.60 g.) of which was converted to its acetate, wt. 0.65 g., $n^{25}D$ 1.4871, $\alpha^{24}D$ +41.84° (*l* 1 dm., neat). The initial mixture of acetates had $\alpha^{25}D$ +41.72° (*l* 1 dm., neat) and $n^{25}D$ 1.4870.

That treatment of the 2-acetoxy-3-phenylbutanes and 2-acetoxy-2-phenylbutane with lithium aluminum hydride yields the corresponding alcohols in an essentially quantita-

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following experiment shows that 1-acetoxy-2-methyl-1-phenylpropane may be converted to 2-methyl-1-phenyl-1-propanol in a similar fashion and in a similarly high yield. A sample of 1.03 g. of (+)-1-acetoxy-2-methyl-1-phenylpropane, $\alpha^{26}D$ +104.7° (*l* 1 dm., neat), was prepared from the corresponding alcohol, $\alpha^{26}D$ +21.57° (*l* 1 dm., neat) $n^{25}D$ 1.5113. Reduction of this material with lithium hydride by the ordinary procedure gave 0.83 g. of (+)-2-methyl-1-phenyl-1-propanol, $n^{25}D$ 1.5112, $\alpha^{26}D$ +21.59° (*l* 1 dm., neat).

To demonstrate that (+)-acetoxy-2-methyl-1-phenylpropane was stable to the treatment at 75° in glacial acetic acid (no *p*-toluenesulfonic acid) used to decompose 2-acetoxy-2-phenylbutane, the following experiment was run. To 20 ml. of glacial acetic acid was added 0.8 ml. of acetic anhydride and 1.00 g. of (+)-1-acetoxy-2-methyl-1-phenylpropane, $\alpha^{26}D$ +104.7° (*l* 1 dm., neat), $n^{25}D$ 1.4853, and the resulting solution was heated at 75° for 26 hours. Isolation of the material in the usual way gave 0.96 g. of starting material, $\alpha^{26}D$ +104.3° (*l* 1 dm., neat), $n^{25}D$ 1.4853.

The following experiment demonstrates the facts: (1) conjugated olefin is destroyed under the conditions of the deaminative solvolysis, (2) unconjugated olefin survives without racemization and (3) active unconjugated olefin can be catalytically reduced to 2-phenylbutane essentially without racemization. To 0.28 g. of D(−)-3-phenyl-1-butene, $\alpha^{23}D$ −5.62° (*l* 1 dm., neat), $n^{25}D$ 1.5054,[33a] was added 0.13 g. of *cis*-2-phenyl-2-butene ($n^{26}D$ 1.5402)[33b] and 0.08 g. of *trans*-2-phenyl-2-butene ($n^{25}D$ 1.5193). This mixture was dissolved in 100 g. of glacial acetic acid, and 10.3 g. of solid potassium nitrite was added in eight portions with vigorous stirring over a period of 30 minutes. The resulting mixture was stirred for 45 minutes, and the product was subjected to the isolation procedure outlined in method II for the isolation and reduction of olefin except that the treatment with Girard reagent was omitted. For the catalytic reduction of olefin, 25 ml. of methanol and 25 mg. of platinum oxide were used, 37 ml. of hydrogen being absorbed (750 mm. and 22°). The D(−)-2-phenylbutane obtained amounted to 0.15 g., $n^{25}D$ 1.4878, $\alpha^{24}D$ −23.62° (*l* 1 dm., neat). The literature reports for optically pure L(+)-2-phenylbutane, $\alpha^{23}D$ +24.2° (*l* 1 dm., neat), $n^{25}D$ 1.4878.[32]

The following experiment demonstrates that: (1) (+)-2-methyl-1-phenyl-1-propanol racemized at 75° in glacial acetic acid in the presence of *p*-toluenesulfonic acid; (2) 2-acetoxy-2-phenylbutane is converted to olefin by this treatment. To 25 g. of glacial acetic acid containing 2.5 g. of acetic anhydride and 0.25 g. of *p*-toluenesulfonic acid monohydrate was added 1.00 g. of 2-phenyl-2-butanol ($n^{25}D$ 1.5167) and 0.90 g. of (+)-2-methyl-1-phenyl-1-propanol ($\alpha^{24}D$ +21.34°, *l* 1 dm., neat; $n^{25}D$ 1.5113), and the resulting solution was heated at 75° for 18 hours. The product was isolated, subjected to a lithium aluminum hydride treatment and chromatographed as in methods I and II. The olefin fraction amounted to 0.89 g., $n^{25}D$ 1.5192. The recovered (+)-2-methyl-1-phenyl-1-propanol (0.61 g.) gave $n^{25}D$ 1.5113, $\alpha^{24}D$ +0.13° (*l* 1 dm., neat) which corresponds to 99.4% racemization. The relatively poor recovery of this alcohol (68%) and the good recovery of olefin (101% based only on 2-acetoxy-2-phenylbutane) indicates that some of the secondary alcohol dehydrated to olefin.

The optical and structural stability of the diastereomeric 3-phenyl-2-butanols to the action of glacial acetic acid and *p*-toluenesulfonic acid at 75° was demonstrated as follows: A mixture of 0.90 g. of L(+)-*threo*-3-phenyl-2-butanol ($\alpha^{22}D$ +31.61°, *l* 1 dm.; $n^{25}D$ 1.5166), 25 g. of glacial acetic acid, 2.5 g. of acetic anhydride and 0.25 g. of *p*-toluenesulfonic acid monohydrate was maintained at 75° for 18 hours. The product was subjected to the lithium aluminum hydride and chromatographic procedures of methods I and II. No olefin could be isolated. Only L(+)-*threo*-3-phenyl-2-butanol was isolated (0.72 g., 80% recovery), $\alpha^{24}D$ +31.51° (*l* 1 dm., neat; $n^{25}D$ 1.5164). Since this *threo* isomer is the one that racemizes on ionization,[7a,b] the stability of this isomer demonstrates the stability of the *erythro* isomer as well.

The following experiments were run to measure the over-all accuracy of the isolation and analytical procedure used in the latter part of method I. Two synthetic mixtures of the three secondary alcohols were made up, mixture 1 simulating the composition of alcohols obtained in run 1 and mixture 2 simulating that of run 2. The composition of mixture 1 was as follows: 0.010 g. of (+)-2-methyl-1-phenyl-1-propanol ($\alpha^{23}D$ +21.21°, *l* 1 dm., neat; $n^{25}D$ 1.5113), 0.082 g. of racemic 2-methyl-1-phenyl-1-propanol ($n^{25}D$ 1.5113), 0.103 g. of L(+)-*threo*-3-phenyl-2-butanol ($\alpha^{25}D$ +31.61°, *l* 1 dm., neat; $n^{25}D$ 1.5167) and 0.917 g. of L(+)-*erythro*-3-phenyl-2-butanol ($\alpha^{26}D$ +0.76°, *l* 1 dm., neat; $n^{25}D$ 1.5163). This mixture had $\alpha^{24}D$ +4.59° (*l* 1 dm., neat), $n^{25}D$ 1.5167. A portion was converted to acetate by the usual method in 93% yield, $\alpha^{24}D$ −25.9° (*l* 1 dm., neat). The composition of alcohol was therefore: the benzyl alcohol, 8% (11% optically pure); *threo*-alcohol, 9% (100% optically pure); *erythro*-alcohol, 82% (100% optically pure). The composition of mixture 2 was as follows: 0.068 g. of (+)-2-methyl-1-pheuyl-1-propanol ($\alpha^{23}D$ +21.21°, *l* 1 dm., neat; $n^{25}D$ 1.5113), 0.356 g. of racemic 2-methyl-1-phenyl-1-propanol ($n^{25}D$ 1.5113), 0.108 g. of L(+)-*threo*-3-phenyl-2-butanol ($\alpha^{24}D$ +31.67°, *l* 1 dm., neat; $n^{25}D$ 1.5167), 0.215 g. of racemic *threo*-3-phenyl-2-butanol ($n^{25}D$ 1.5167), 0.199 g. of L(+)-*erythro*-3-phenyl-2-butanol ($\alpha^{26}D$ +0.76; *l* 1 dm., neat; $n^{25}D$ 1.5163), and 0.063 g. of racemic *erythro*-3-phenyl-2-butanol ($n^{25}D$ 1.5163). This mixture had $\alpha^{24}D$ +5.82° (*l* 1 dm., neat), $n^{25}D$ 1.5142. A portion of this alcohol was converted to its acetate in 92% yield, $\alpha^{24}D$ −0.50° (*l* 1 dm., neat). The composition of mixture 2 was therefore: the benzyl alcohol, 42% (16% optically pure); *threo*-alcohol, 32% (33% optically pure); *erythro*-alcohol, 26% (76% optically pure).

Mixtures 1 and 2 (0.50 g. each) were submitted to the action of acetic acid and *p*-toluenesulfonic acid at 75° for 18 hours, the product being put through the lithium aluminum hydride and chromatographic procedures employed in runs 1 and 2. The alcohol obtained from mixture 1 (0.36 g.) gave $\alpha^{24}D$ +4.59 (*l* 1 dm., neat), and its acetate (92% yield) gave $\alpha^{26}D$ −28.49° (*l* 1 dm., neat). The alcohol from mixture 2 (0.30 g.) gave $\alpha^{24}D$ +4.75° (*l* 1 dm., neat), and its acetate gave $\alpha^{26}D$ −8.72° (*l* 1 dm., neat). Infrared analysis (see later section) of the final alcohol obtained by acid treatment of mixture 1 was as follows: the benzyl alcohol, 6%; *threo*-alcohol, 9%; *erythro*-alcohol, 84%. Analysis of final alcohol from mixture 2 was: the benzyl alcohol, 37%; *threo*-alcohol, 35%; *erythro*-alcohol, 28%.

This experiment demonstrates that no selective loss of *threo*- or *erythro*-alcohol occurs during this acid treatment, but that a small selective loss of 2-methyl-1-phenyl-1-propanol occurs. Racemization and partial loss of this alcohol in mixture 1 made practically no difference in the rotations of alcohols or acetates as was the case in run 1. Racemization and partial loss of the benzyl alcohol in mixture 2 changed the rotation from +5.82 to +4.75° as compared to a change in rotation of run 2 from −5.78 to −4.20°. The changes in rotation of the acetates are far more significant: mixture 2, from −0.50 to −8.72°; run 2, from +0.05 to +8.41°.

To demonstrate that (+)-2-methyl-1-phenyl-1-propanol is stable under the conditions used for the saponification of its acid phthalate, the following experiment was run. To 250 ml. of 0.32 *N* sodium hydroxide was added 0.529 g. of (+)-2-methyl-1-phenyl-1-propanol ($\alpha^{22}D$ +20.41°, *l* 1 dm., neat). The resulting mixture was brought to reflux and allowed to steam distil. The alcohol was isolated in the usual way to give 0.465 g. of material, $\alpha^{23}D$ +20.00° (*l* 1 dm., neat).

Infrared Analysis of Alcohol Mixtures.—These analyses were made on a Perkin–Elmer infrared spectrophotometer, model 21, NaCl prism and cells, utilizing liquid films 0.030 mm. thick. The optical densities of 2-methyl-1-phenyl-1-propanol (II) and *threo*- and *erythro*-3-phenyl-2-butanol (III) were determined at those wave lengths most advantageous for analysis. The optical densities of these knowns were then determined. The amounts of these components were calculated by solving simultaneous equations assuming that Beer's law applied. Synthetic mixtures of the three components were then made which approximated the unknowns (to within 3% for each component based on the final values for each unknown), and these were then analyzed similarly. The unknown mixtures were now corrected to the known for deviations in Beer's law. Table III records samples of raw intensity data. Table IV records the percentage compositions of alcohol obtained in the

(33) Literature (ref. 11c) reports for these olefins: (a) $\alpha^{22}D$ −6.39°, 1 dm., neat; $n^{25}D$ 1.5055; (b) $n^{25}D$ 1.5402; (c) $n^{25}D$ 1.5193.

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four solvolytic runs corrected to the known synthetic mixtures. The facts that these percentages add up to almost 100% and that calculations based on different wave lengths give similar values indicate the absence of other components in the mixtures. The infrared analyses of the alcohols obtained in the control experiments were done the same way.

TABLE III

OPTICAL DENSITIES AT THE WAVE LENGTHS USED FOR INFRARED ANALYSES OF ALCOHOL MIXTURES

Composition, %			Optical density at λ in μ (slit width in mm.)				
threo III[a]	*erythro*-III[b]	II[c]	8.00 (0.142)	8.33 (0.148)	8.85 (0.163)	10.06 (0.222)	12.41 (0.322)
100	0	0	0.498	0.210	0.920	0.080	0.080
0	100	0	.324	.163	.626	.080	.081
0	0	100	.398	.418	.208	.275	.205
Unknown from run 1			.346	.180	.638	.091	.088
8	87	5	.348	.181	.639	.091	.095
Unknown from run 2			.426	.272	.590	.152	.129
36	33	31	.430	.262	.621	.142	.125

[a] *threo*-3-Phenyl-2-butanol, $n^{25}D$ 1.5167. [b] *erythro*-3-Phenyl-2-butanol, $n^{25}D$ 1.5163. [c] 2-Methyl-1-phenyl-1-propanol, $n^{25}D$ 1.5113.

The differences in results in Table IV between runs 1 and 3 and between 2 and 4 result from the fact that in runs 1 and 2 the analyses were made *before* the 2-methyl-1-phenyl-1-propanol was racemized and partially destroyed by treatment at 75° with an acetic acid–*p*-toluenesulfonic acid mixture. In runs 3 and 4 the analyses were made *after* this treatment. When runs 3 and 4 are corrected for loss of this component (as measured in the foregoing control experiments), the analyses for runs 1 and 3 and for 2 and 4 correspond to one another with a 1% maximum deviation.

The yields of 2-phenyl-2-butanol reported in Table I are based on the differences in total alcohol obtained in runs 1 and 3 and in 2 and 4. In runs 1 and 2 the acetate of 2-phenyl-2-butanol was destroyed before the alcohol was isolated. In runs 3 and 4 this acetate was preserved and carried into the alcohol initially isolated. Since almost twice as much amine was used as starting material in runs 3 and 4 as in 1 and 2, the mechanical losses in runs 1 and 2 were proportionately higher. Therefore the yields of 2-phenyl-2-butanol in Table I represent maximum values.

Calculations of the Optical Activities of Components in Alcohol Mixtures.—The infrared analyses give the percentages of the three secondary alcohol components both before and after the racemization of the 2-methyl-1-phenyl-1-propanol component. The optical activities of the *threo*- and *erythro*-alcohols were calculated as follows. After the benzyl alcohol was racemized, only the *threo*- and *erythro*-alcohols contributed to the rotation of the mixture. As noted earlier,[7b] the rotation of active *threo*-alcohol is about 30° and that of active *erythro*-alcohol is only about 1°, whereas the rotation of active *threo*-acetate is only 8° and that of *erythro*-acetate is about 32°. The optical purities of these two components were calculated first by solving two simultaneous equations in two unknowns, assuming the rotational contributions of the active alcohols and the active acetates were additive and that the racemized 2-methyl-1-phenyl-1-propanol component or its acetate had no effect on these rotations. Synthetic mixtures of these estimated compositions were then made, and the rotations of their alcohols and acetates used to calculate composition. The unknowns were then corrected to the knowns for the small deviations in additivity of the components. This gave the optical compositions of the *threo*- and *erythro*-alcohols both before and after the racemization of the 2-methyl-1-phenyl-1-propanol. The optical composition of this benzyl alcohol was then calculated making use of rotations of the alcohols and their acetates before the racemization reaction, the infrared data and the rotations of optically pure 2-methyl-1-propanol and its acetate. Fortunately the rotation of the acetate of 2-methyl-1-phenyl-1-propanol (105°) is an order of magnitude higher than those of the other acetates. Again additivity of the rotations of each component was assumed, synthetic mixtures of similar compositions were made and analyzed, and the unknowns were corrected to the knowns for small deviations in additivity of the components. Although these last calculations depend on a large number of separate experimentally determined values and are therefore not very accurate, there is no doubt about the following points. (1) The product of methyl migration from *threo*-amine is somewhere between 12 and 20% optically pure and of an identifiable configuration. (2) The product of methyl migration from *erythro*-amine is somewhere between 0 and 8% optically pure and of an identifiable configuration.

TABLE IV

RESULTS OF INFRARED ANALYSES OF ALCOHOLS FROM DEAMINATIVE ACETOLYSES

Run no.[a]	Configuration st. mat.	% *threo*-III[b] 1st.[c]	2nd.[d]	% *erythro*-III[b] 1st.[c]	2nd.[d]	% II[b] 1st.[c]	2nd.[d]	Total,[b] % 1st.[c]	2nd.[d]
1	L(+)-*erythro*	8	9	87	87	5	5	100	101
2	D(−)-*threo*	36	35	33	33	30	32	99	100
3	D(−)-*erythro*	8	9	84	84	9	8	101	101
4	L(+)-*threo*	33	34	25	25	42	42	100	101

[a] Run numbers throughout paper correspond. [b] Unknowns corrected to knowns of almost identical composition (3% maximum difference for any component). [c] Based on optical densities at λ 8.00, 10.06 and 12.41 μ. [d] Based on optical densities at λ 8.00, 8.33 and 8.85 μ.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

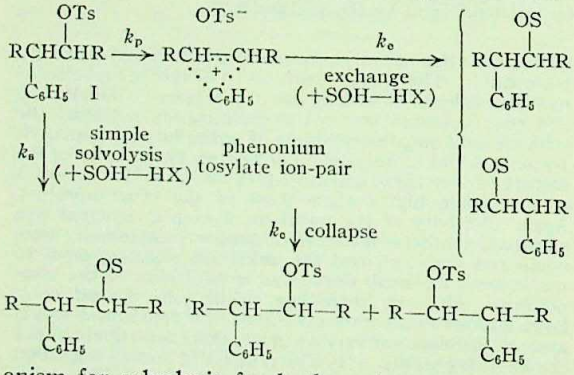
Studies in Stereochemistry. XXVIII. Reactivity Differences between Diastereomers in the Wagner–Meerwein Rearrangement[1]

BY DONALD J. CRAM, H. LEROY NYQUIST AND FATHY AHMED ABD ELHAFEZ

RECEIVED DECEMBER 7, 1956

The rates of formolysis and acetolysis of the diastereomers of 3-phenyl-2-butyl tosylate, 4-phenyl-3-hexyl tosylate and of 2,5-dimethyl-4-phenyl-3-hexyl brosylate have been measured. The $k_{erythro}/k_{threo}$(titrimetric) values for acetolysis are 1.2, 1.8 and 6.4, respectively, and 1.2, 2.6 and 8.2 for formolysis, respectively. That these ratios do not change much in the two solvents suggests that in each system, the division of phenonium tosylate (or brosylate) ion-pairs between collapse and exchange reactions with solvent is quantitatively similar for the *threo* and *erythro* diastereomers. The values of the ratios, k_α/k_t (polarimetric and titrimetric rate constants), decrease in value for the *threo* isomers in passing from the less to the more sterically hindered systems. As the bulk of the eclipsed groups increases, the ratio of exchange (with solvent) to collapse of these symmetrical *cis*-phenonium tosylate (or brosylate) ion-pairs increases. The products of solvolysis of 2,5-dimethyl-4-phenyl-3-hexyl brosylate have been examined in detail. Olefin or the products of hydrogen migration (mostly from the 2-position) dominate over those resulting from phenyl migration. Only traces of products of simple solvolysis were found. The yields of these various products indicate that the diastereomeric rate factor of 8.2 for the formolysis in this system is due not to differences in rate for the part of the reaction leading to phenonium ion, but to differences in rate for the part leading to olefin, and the products of hydrogen migration. These results suggest that in this system the differences in rate for solvolysis for the *threo* and *erythro* isomers reflect more the differences in energy of the diastereomeric starting states rather than differences in eclipsing effects for the diastereomeric transition states.

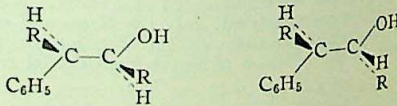
Previous studies of the Wagner–Meerwein rearrangement in systems represented by I have uncovered marked differences in behavior of I with R = CH_3[2] and R = C_2H_5.[3] Although the mechanism for solvolysis for both systems can be encompassed by the formulation, the ratios k_p/k_s and k_c/k_e vary enough to affect the balance of products. The rates of solvolysis (k_t is the titrimetric rate constant) and of change of optical activity (k_α is the polarimetric rate constant) have been reported for *threo*-I with R = CH_3 in both formic and acetic acids,[4] and k_t was reported for *erythro*-I with R = CH_3 in acetic acid.[4a] The rates k_t and k_α also were obtained in acetic acid for *threo*-I with R = C_2H_5, and k_α (but not k_t) was also determined in formic acid.



This paper is concerned with reactivity differences between diastereomers of I with R = CH_3, C_2H_5 and $CH(CH_3)_2$. The new kinetic data on particularly the *erythro* isomers of the first two systems coupled with product and kinetic data on the third system allow an evaluation of conformational and eclipsing effects in a series of homologous compounds of increasing steric constraints. All three of these systems possess symmetry properties which allow a maximum amount of information to be extracted concerning the role that phenonium ions play in the Wagner–Meerwein rearrangement.

Kinetics of Solvolyses

The kinetics of acetolysis and formolysis were followed utilizing methods previously described,[4b,3c] and in all cases were found to be cleanly first order. All four stereomers of 3-phenyl-2-butanol (II),[2] 4-phenyl-3-hexanol (III)[5] and 2,5-dimethyl-4-phenyl-3-hexanol (IV)[6] have been previously prepared in an optically pure state, and the absolute configurations of II and III have been completely assigned. As a result of the present work, all of the *relative* configurations of all four isomers of IV can be definitely assigned. None of the *absolute* configurations of the isomers of IV are known, and therefore a *completely arbitrary* assignment is made for convenience (see formulation).



L-*threo*	L-*erythro*
(+)-II, R = CH_3	(+)-II, R = CH_3
(+)-III, R = C_2H_5	(+)-III, R = C_2H_5
(+)-IV, R = $(CH_3)_2CH$	(+)-IV, R = $(CH_3)_2CH$

Table I reports the rate constants needed for comparison of the three systems and of the two diastereomers within each system. The rates were not all run under completely identical conditions. For instance, runs 1–6 were conducted in the absence of a salt for neutralization of the acid liberated, whereas runs 7–21 were made in the presence of such a salt. Enough data were obtained on system II[4a,4b] to indicate that the rate ratios reported in this paper were only slightly sensitive to the presence of salt. In the formolysis of systems III and IV, about 20% by volume of chloroform had

(1) This work was sponsored by the Office of Ordnance Research, U. S. Army.

(2) (a) D. J. Cram, THIS JOURNAL, **71**, 3863 (1949); (b) **74**, 2129 (1952); (c) **74**, 2137 (1952).

(3) D. J. Cram and F. A. Abd Elhafez, *ibid.*, **75**, 3189 (1953).

(4) (a) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse, *ibid.*, **74**, 1114 (1952); (b) S. Winstein and K. C. Schreiber, *ibid.*, **74**, 2164 (1952); (c) S. Winstein and H. Marshall, *ibid.*, **74**, 1120 (1952).

(5) D. J. Cram, F. A. Abd Elhafez and H. Weingartner, *ibid.*, **75**, 2293 (1953).

(6) D. J. Cram, F. A. Abd Elhafez and H. LeRoy Nyquist, *ibid.*, **76**, 22 (1954).

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TABLE I

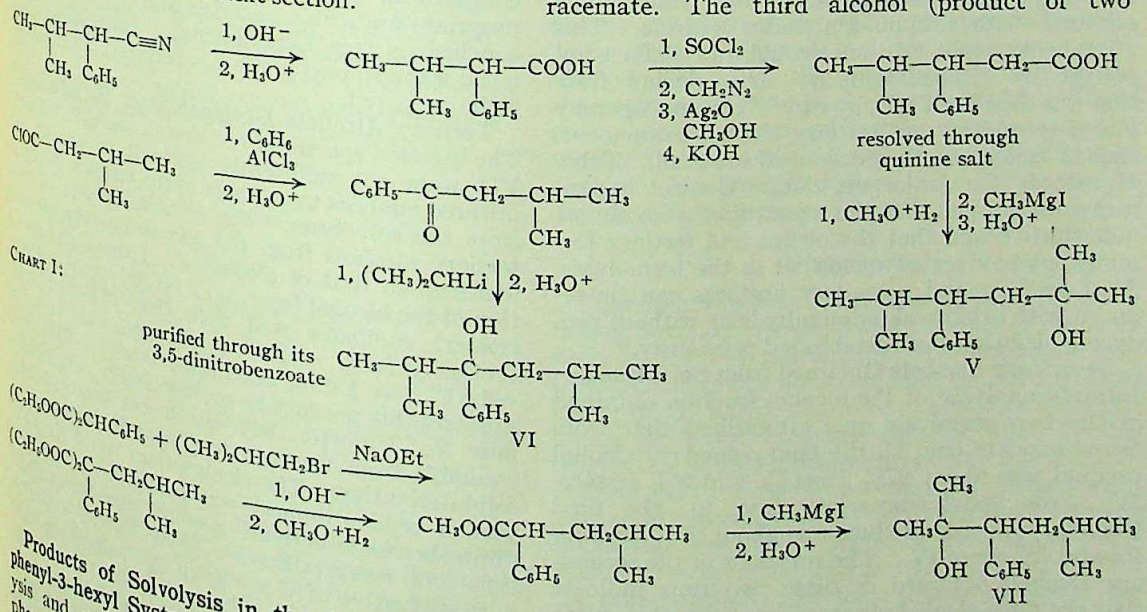
RATE CONSTANTS FOR SOLVOLYSES OF SULFONATE ESTERS OF DIASTEREOMERS OF ALCOHOLS II, III AND IV

Run	Compound	Solvent	Concn. ester, mole/l.	Salt added	Concn. salt, mole/l.	Proc.	T, °C.	Rotations α° Init.	Final	k, sec.$^{-1}$
		AcOH	0.030	....	....	Tit.	74.71	....	....	(4.95 ± 0.17) × 10^{-5}
1[a]	*threo*-II-Ts	AcOH	.116	NaOAc	0.0957	Tit.	74.91	....	....	(6.72 ± .16) × 10^{-5}
2[b]	*threo*-II-Ts	AcOH	.116	NaOAc	0.0957	Pol.[c]	74.91	0.53	−0.01	(3.33 ± .10) × 10^{-4}
3[b]	*threo*-II-Ts	AcOH	.032	....	....	Tit.	74.72	....	....	(5.77 ± .26) × 10^{-5}
4[a]	*erythro*-II-Ts	HCOOH	.070	....	....	Tit.	24.98	....	....	(2.28 ± .03) × 10^{-4}
5[b]	*threo*-II-Ts	HCOOH	.116	....	....	Pol.[c]	25.12	3.92	−0.04	(2.65 ± .12) × 10^{-4}
6[b]	*threo*-II-Ts	HCOOH	.096	NaOOCH	0.119	Tit.	25.00	....	....	(2.80 ± .02) × 10^{-4}
7	*erythro*-II-Ts	HCOOH	.098	NaOOCH	.119	Pol.[c]	25.00	−2.53	−1.60	(2.49 ± .18) × 10^{-4}
8	*erythro*-II-Ts	HCOOH	.0882	KOAc	.105	Tit.	74.64	....	....	(1.68 ± .03) × 10^{-4}
9[d]	*threo*-III-Ts	AcOH	.0882	KOAc	.105	Pol.[c]	74.64	−1.47	−0.06	(5.48 ± .19) × 10^{-4}
10[d]	*threo*-III-Ts	AcOH	.0900	KOAc	.120	Tit.[e]	50.08	....	....	(1.01 ± .02) × 10^{-5}
11[d]	*threo*-III-Ts	AcOH	.030	KOAc	.035	Tit.	50.00	....	....	(1.80 ± .01) × 10^{-5}
12	*erythro*-III-Ts	AcOH	.091	NaOOCH	.123	Tit.	25.00	....	....	(2.90 ± .03) × 10^{-4}
13	*threo*-III-Ts	HCOOH[f]	.103	NaOOCH	.130	Pol.[c]	25.2	−1.44	0.06	(3.90 ± .10) × 10^{-4}
14[d]	*threo*-III-Ts	HCOOH[f]	.030	NaOOCH	.034	Tit.	25.00	....	....	(7.65 ± .09) × 10^{-4}
15	*erythro*-III-Ts	HCOOH[f]	.079	KOAc	.105	Tit.	49.74	....	....	(4.97 ± .09) × 10^{-5}
16	*threo*-IV-Bs	AcOH	.079	KOAc	.109	Pol.[c]	49.74	−4.64	+0.84	(6.05 ± .05) × 10^{-5}
17	*threo*-IV-Bs	AcOH	.079	KOAc	.105	Tit.	49.74	....	....	(3.18 ± .03) × 10^{-4}
18	*erythro*-IV-Bs	AcOH	.079	KOAc	.109	Pol.[c]	49.74	−0.83	+1.65	(3.28 ± .07) × 10^{-4}
19	*erythro*-IV-Bs	AcOH	.035	NaOOCH	.041	Tit.	25.00	....	....	(3.10 ± .01) × 10^{-4}
20	*threo*-IV-Bs	HCOOH[g]	.034	NaOOCH	.041	Tit.	25.00	....	....	(2.53 ± .01) × 10^{-3}
21	*erythro*-IV-Bs	HCOOH[g]								

to be added to make the system homogeneous. The solvent was always the same for any two rates appearing as a ratio in this paper.

The polarimetric and titrimetric rates for *erythro*-II tosylate formolysis are almost the same (runs 7 and 8) and serve as a check on the method. Unfortunately the polarimetric rate of acetolysis could not be determined because some of the optically active products resulting initially underwent reaction at a rate comparable to that at which the solvolytic reaction occurred (see Discussion). An analysis of the meaning of these kinetic data depends upon a knowledge of the reaction products, a subject taken up in the next section.

CHART I:



Products of Solvolysis in the 2,5-Dimethyl-4-phenyl-3-hexyl System.—The products of formolysis and acetolysis of the tosylates of the 3-phenyl-2-butyl and 4-phenyl-3-hexyl systems have been previously reported.[2,3] The pattern of products obtained by the solvolyses of 2,5-dimethyl-4-phenyl-3-hexyl brosylate[7] (IV-Bs) is somewhat different from that found for the two simpler homologs. These products (alcohols V and VII) as well as the potential product VI were all prepared by conventional means since their detection in the alcohol mixtures from the hydrolysis of the solvolysis mixtures demanded a knowledge of their individual physical properties. Alcohol V was prepared in an essentially optically pure form since the analytical scheme necessitated a knowledge of its rotation. Alcohol VI was only prepared as its racemate. The third alcohol (product of two 1,2-H shifts) was also synthesized (see formulas) as a racemate.

(7) The tosylates of this system, although less reactive kinetically, are much harder to obtain in a pure state than the brosylates.

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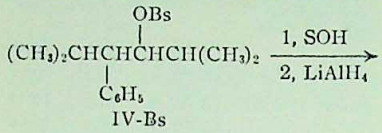
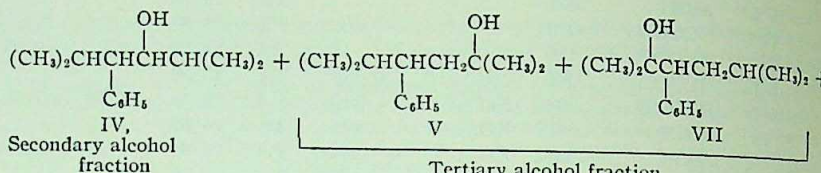
TABLE II

PRODUCTS OF ACETOLYSIS AND FORMOLYSIS OF BROSYLATE ESTERS OF IV



IV-Bs



IV, Secondary alcohol fraction

V

VII

Tertiary alcohol fraction

Products	Starting materials: (+)-*threo*-IV-Bs AcOH (run 1)	(+)-*erythro*-IV-Bs AcOH (run 2)	(−)-*threo*-IV-Bs HCOOH (run 3)	(−)-*erythro*-IV-Bs HCOOH (run 4)
Sec. alc. fraction				
Yield, %	28	3.8	15.3	6.9
$[\alpha]^{25}D$	+0.12°[b]	+16.4°[a] (+20.7°)[b]	−0.28°[c]	−16.6°[b]
Composition (fraction = 100%)	97% *threo*-IV, racemic; 3% *erythro*-IV	95% (+)-*erythro*-IV; 5% *threo*-IV	95–100% *threo*-IV, racemic; 0–5% *erythro*-IV	95–100% (−)-*erythro*-IV; 0–5% *threo*-IV
Tert. alc. fraction				
Yield, %	12	19	32	60
$\alpha^{25}D$ (l = 1 dm., neat)	−1.03°	−1.75°	+0.67°	+1 20°
$n^{25}D$	1.5022	1.5029	1.5022	1.5022
Composition	Partially racemic V + VII	Optically pure V + trace VII	Partially racemic V + VII	Optically pure V + VII
Olefin fraction				
Yield, %	53	70	43	14
$n^{25}D$	1.4992	1.4994	1.5011	1.5007
$\alpha^{25}D$ (l = 1 dm., neat)	−43.0°	−72.1°	+54.8°	+92.7°
ϵ (232 mμ)[d]	1594	474	1788	524

[a] (c, 2.4, $CHCl_3$). [b] After recrystallization (c 2, $CHCl_3$). [c] l = 1 dm., neat. [d] Cyclohexane as solvent.

The brosylates of all four of the optically pure isomers of IV[6] were prepared. The sulfonate esters of the (+)-*threo*- and (+)-*erythro*-alcohols (these isomers differ only in configuration at the carbon carrying the oxygen) were acetolyzed at 50° for 8 titrimetric half-lives. The brosylates of the (−)-*threo*- and (−)-*erythro*-alcohols were formolyzed at 25° for 5 titrimetric half-lives. The olefin–ester products were converted to olefin–alcohol mixtures with lithium aluminum hydride. This mixture was split into an alcohol and olefin component by chromatography. The alcohol fraction was then itself split by careful chromatography into a secondary and tertiary alcohol component, each of which was then examined in detail. Table II records the important data. Control experiments established that the separations were almost quantitative and that the olefins and tertiary formates interconverted somewhat in the formolyses. That tertiary and secondary acetates can be reduced with lithium aluminum hydride without producing olefin has been established previously.[2c]

Secondary Alcohols Obtained from Solvolyses.—Infrared analysis[6] of the alcohol fraction obtained in the two acetolysis runs established that from *threo*-brosylate (run 1), the final secondary alcohol product was about 97% *threo*-IV and 3% *erythro*-IV. From *erythro*-brosylate (run 2), the final secondary alcohol product was about 95% *erythro*-VI and 5% *threo*-IV. The rotations of the secondary alcohols obtained in these two runs indicate that the *threo*-alcohol obtained from *threo*-brosylate (run 1) is essentially racemic, whereas the *erythro*-alcohol obtained from *erythro*-brosylate (run 2) is essentially optically pure. Although the infrared analysis was not performed on the alcohol from run 1 (acetolysis of *threo* isomer) the formolysis, the similarity of the magnitudes of rotation in runs 1 and 3 and in runs 2 and 4 indicate the results to be similar. In runs 2 and 4 mixed melting point comparisons of the *erythro*-alcohol obtained with authentic material further established the above contentions. In runs 1, 3 and 4, *p*-nitrobenzoates of the secondary alcohols were prepared, and mixed melting point and rotational comparisons between these compounds and the appropriate authentic materials also supported these conclusions (see Experimental). Insufficient material was obtained in run 2 to permit this derivative to be prepared.

Tertiary Alcohols Obtained from Solvolyses.—The infrared spectra of tertiary alcohols, V, VI and VII were not sufficiently different to permit an infrared analysis to be made of the tertiary alcohols from the solvolyses. The infrared spectra of the tertiary alcohols from the solvolyses were almost identical to that of alcohol V. Indeed, the rotation of the alcohol from run 2 (acetolysis of *erythro*-isomer) compares well with that obtained synthetically ($\alpha^{25}D$ −1.75°, l = 1 dm., neat *vs.* $\alpha^{25}D$ +1.81°, l = 1 dm., neat, respectively). This fact suggests this product to consist largely of optically pure V. Unfortunately insufficient material was available from this run to permit formation of a solid derivative. The alcohol from run 4 (formolysis of *erythro*-isomer) was converted to its 3,5-dinitrobenzoate derivative, which upon crystallization and recrystallization gave almost optically pure derivative of V as shown by comparison with an authentic sample. From the filtrates was obtained ester which appeared to be a mixture of ester of V and some other ester, probably of VII.

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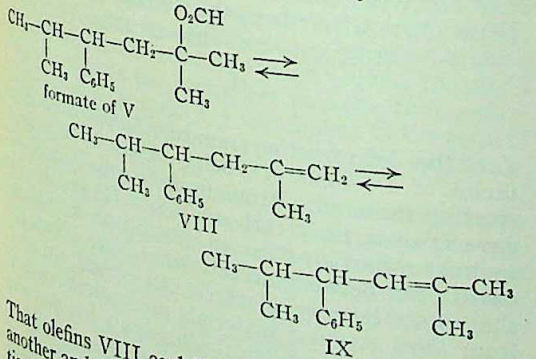
gave 3,5-dinitrobenzoate ester of partially racemized V and possibly some other ester. The alcohol from run 3 (formolysis of *threo* isomer) gave 3,5-dinitrobenzoate ester of partially racemized V. From the filtrates was isolated the 3,5-dinitrobenzoate ester of racemic VII, as shown by comparison with an authentic sample. The above evidence suggests that optically pure V is produced in both acetolysis and formolysis runs of the *erythro* derivative but that somewhat racemized V was produced from the *threo* derivative. Alcohol VII was demonstrated to arise in the formolysis of *threo* material, and its presence was likely in the formolysis of *erythro* and possible in the acetolysis of the *threo*-brosylate.

Attempts to form the 3,5-dinitrobenzoate of VI failed. The absence of liquid residues from the formation of this derivative of the tertiary alcohols from the solvolysis points to the absence of VI in these mixtures. Even had the formate of VI formed in the formolyses, it probably would have gone to olefin since even the acetate of V slowly went to olefin in formic acid.

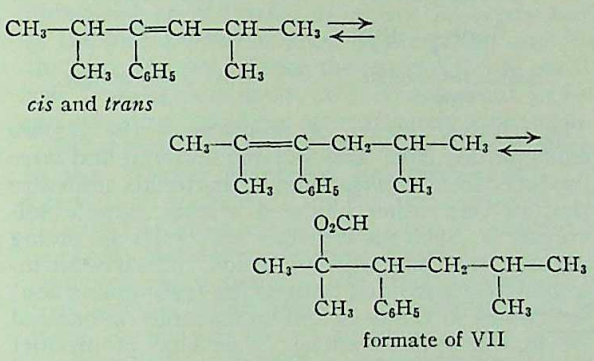
Olefins Obtained from Solvolyses.—During attempts to measure k_a for the formolysis of either *threo*-IV-Bs or *erythro*-IV-Bs, it became clear that two reactions were occurring in series with one another, each of which changed the rotation of the solution. The first and faster of these was the ionization of the brosylate, and the second was a reshuffling of certain of the initially formed (kinetically controlled) products. This result contrasts with that observed in the acetolyses where the products, once formed, persisted (see Experimental). To establish what secondary reactions were occurring in the formolyses, the following experiments were conducted.

Unfortunately the formate of V could not be prepared in a pure state. The acetate of active V was prepared and was found to give mixtures of olefins VIII and IX in formic acid under the conditions of the formolyses. Since formate is a better leaving group than acetate, it seems probable that the formate of V can interconvert with olefins VIII and IX under conditions of the formolysis.



That olefins VIII and IX can equilibrate with one another and with the formate of V under the conditions of the formolysis is suggested by the following experiment. The two olefin mixtures from acetolysis runs 1 and 2 were dissolved in the formolysis solutions and allowed to stand at 25° for the lifetime of a run. The rotations increased markedly and an ester band appeared in the infrared of the material isolated from this treatment.

Conjugated olefins were also produced during the solvolyses as shown by the ϵ's of the olefinic fraction at λ 232 mμ (see Table II). The total ultraviolet spectrum of these fractions showed no λ_{max} but only a general increase in absorption from 260 to 220 mμ. The same was true for the product obtained by treating IV-Bs with sodium ethoxide.[6] The absence of a maximum in this styrene region (230–250 mμ) undoubtedly is due to steric inhibition of resonance of the conjugated olefins. During the above equilibration of olefins in the formic acid solvolysis solutions, the ϵ's of the mixture at λ 232 mμ increased by about one-third. This result suggests that in formic acid the three conjugated olefins equilibrate with one another and that the increase of ϵ is associated with an accumulation of the more thermodynamically stable isomer, the isomer with the least degree of steric inhibition of resonance and the highest ϵ. When the equilibrating solutions were allowed to stand for a much longer time, both the rotations and the ϵ's stopped changing. This result demonstrates that the conjugated and unconjugated systems of olefins are not interconverting at any appreciable rate. Although not demonstrated, the formates of VII and possibly of VI also probably are involved in the equilibration of the conjugated olefins. These results are in harmony with those obtained with the simpler and more studied 2-phenylbutene system of olefins.[8] Attempts to reduce these olefins to 2,5-dimethyl-3-phenylhexane failed.



Discussion

Phenonium Ions as Intermediates in the Production of Secondary Acetate and Formate in Systems such as I.—The character of the secondary acetates and formates obtained from the solvolyses of the optically active diastereomers of 2,5-dimethyl-4-phenyl-3-hexyl brosylate indicate that in this reaction a bridged phenylcarbonium ion (a phenonium ion) intervenes as the chief intermediate leading to secondary ester. With one diastereomer, essentially completely racemized ester of the *same* diastereomeric configuration was obtained. With the other diastereomer the product possessed the same configuration as the reactant. Clearly the first diastereomer possesses the *threo* and the second the *erythro* configuration.

(8) D. J. Cram, C. A. Kingsbury and B. Rickborn, THIS JOURNAL, 83, 3688 (1961); D. J. Cram, C. A. Kingsbury, A. Langemann, H. Hecker and K. R. Kopecky, *ibid.*, 81, 5774 (1959); D. J. Cram and C. A. Kingsbury, *ibid.*, 83, 2037 (1961).

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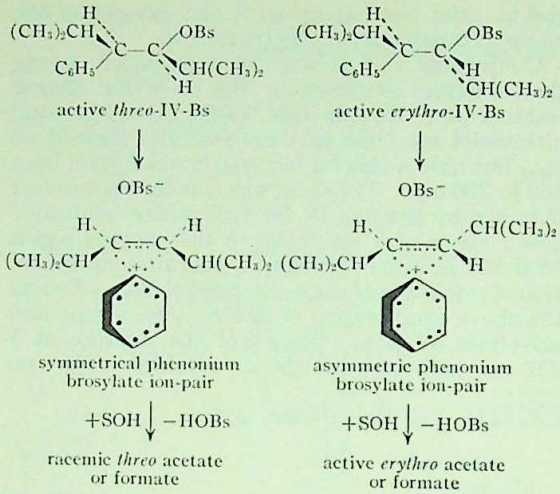
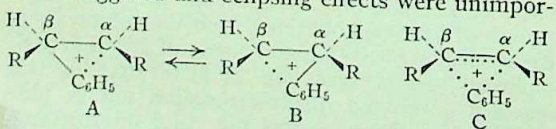


The relative absence of products of the *erythro* configuration from *threo* starting material and *threo* products from *erythro* starting materials indicates that in this rather hindered system, simple solvolysis is much slower than solvolysis involving phenyl participation in ionization. Clearly an internally compensated bridged ion (phenonium ion) intervened in the *threo* and an asymmetric bridged ion in the *erythro* system. This kind of product pattern resembles more that observed in the 3-phenyl-2-butyl than that of the 4-phenyl-3-hexyl system. In the former, *simple* acetolysis accounted for about 4–5% of the secondary acetates, and with the *threo* isomer inversion predominated over retention. In the 4-phenyl-3-hexyl system, *simple* acetolysis of the *threo* isomer accounted for about 15% of the secondary acetates, and retention predominated over inversion by a factor of about 5. In the 2,5-dimethyl-4-phenyl-3-hexyl system, *simple* acetolysis gave rise to about 3% of the secondary acetates, inversion being comparable to retention. Thus the most and least-hindered systems resemble each other more with regard to the amounts and direction of simple substitution than they resemble the intermediate system.

Two alternative hypotheses were offered for the marked predominance of retention over inversion in simple solvolysis in the *threo*-4-phenyl-3-hexyl system.[3] (1) A dynamic equilibrium between two unsymmetrical phenonium ions (A and B) might be substituted for the single symmetrical phenonium ion (C). In A and B the R groups were somewhat staggered and eclipsing effects were unimportant as compared to those in C, a species which might be either an intermediate or a transition state. As the bulk of R was increased, the activation energy for A → B would increase, and the competing simple solvolysis occurring with over-all retention at C_α would consume more of A. (2) Steric control of asymmetric induction by the substituents of the benzyl carbon atom might provide a larger amount of the *erythro* product in the simple solvolysis reaction involving an open carbonium ion.



The results of the solvolysis of the more hindered 2,5-dimethyl-4-phenyl-3-hexyl system make explanation (1) untenable, and are not inconsistent with (2). Since isopropyl is bulkier than ethyl, eclipsing effects in C should become more important. On the basis of (1), simple substitution with retention would become more prominent. The results are in the opposite direction. On the basis of (2), the ratio of *threo* to *erythro* product should vary with the steric situation at the benzyl carbon, and as phenyl and R approach each other in bulk, the degree of asymmetric induction might decrease.

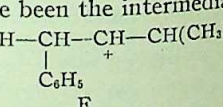
No evidence now exists which either suggests or demands the substitution of a dynamic equilibrium between unsymmetrical bridged carbonium ions for a single symmetrical bridged carbonium ion in systems where C_α and C_β carry the same substituents. Bridged ions such as C can provide a simpler and therefore better explanation of the facts until new evidence intrudes.

The Involvement of C_β–H in Production of Rearranged Tertiary Acetate and Formate in the 2,5-Dimethyl-4-phenyl-3-hexyl System.—A number of internal consistencies appear in the data of Table II which provide clues as to the mechanisms of olefin and tertiary ester formation. In runs 1 and 2 (acetolyses) where the products were kinetically controlled, the values of the ratios formulated are independent within experimental error of the configurations of the starting material. These data strongly imply that the tertiary ester and olefin had common intermediates, these intermediates being the same for each diastereomeric starting material.[9] The open secondary carbonium ion

CHART II

	$\frac{\alpha \text{ of olefin}}{\alpha \text{ of tert. alcohol}}$	$\frac{\text{Yield of olefin}}{\text{Yield of tert. alcohol}}$
threo acetolysis (run 1)	42	4.4
erythro acetolysis (run 2)	41	3.7
threo formolysis (run 3)	82	1.3
erythro formolysis (run 4)	77	0.23

(F) could not have been the intermediate since the



ϵ's of the olefin fraction from runs 1 and 2 differ by a factor of 4 (Table II), being higher for the *threo* starting material. More probably the brosylates gave open tertiary carbonium ions (G and H) by hydrogen participation in ionization, and these partitioned between acetate and olefin. The facts that both tertiary alcohols and olefins obtained from *threo* starting materials are optically active indicate that symmetrical phenonium ion was not

(9) A second condition for the equality of the ratios involving rotations is that the contributions of the active components to the rotation of the mixture are either proportional to their concentrations, or that deviations from proportionality are governed by the same factor in passing from mixtures obtained from run 1 to those of run 2. In the case of solutions of active 3-phenyl-1-butene in mixtures of *cis*- and *trans*-2-phenyl-2-butene and 2-phenyl-1-butene, the rotations were linear with concentration of the active component.[8] See Experimental for the rotation of a synthetic mixture of tertiary alcohols.

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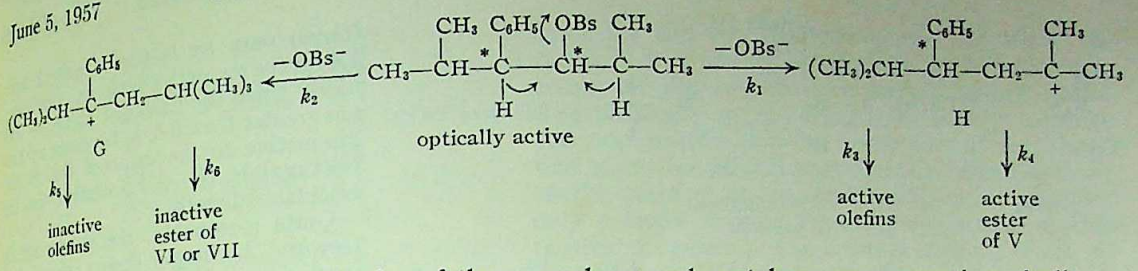

an important precursor in the production of these materials.

The rotation of the tertiary alcohol obtained in run 2 (*erythro*-acetolysis) was 97% that of optically pure V, so apparently $k_1 >> k_2$ with this diastereomer in this solvent. In run 1 (*threo*-acetolysis) the rotation was only about 60% that of optically pure V. With this isomer the starting brosylate ester racemizes at a rate which would make about 20% of alcohol V and of the active olefins racemic. Clearly in this run both the partially inactive tertiary alcohol and olefin fractions are diluted by about the same factor with optically inactive materials arising from the benzylcarbonium ion, G. The higher ϵ of the olefin (Table II) from run 1 also supports this thesis. Thus for the acetolysis of *threo*-brosylate, $k_1 \sim k_2$ and $k_5/(k_5 + k_6) \sim k_3/(k_3 + k_4)$ (this latter relationship is required by the constancy of the ratios of runs 1 and 2 in Chart II).

The results of the formolysis runs are complicated by the fact that the tertiary alcohol and olefin fractions once formed can interconvert to some extent. Runs 3 and 4 were allowed to go for 5 titrimetric half-lives, but since the *erythro* isomer solvolyzed 8 times as fast as the *threo*, the products once formed from the *threo*-brosylate (run 3) had a much longer period in which to approach equilibrium than did those from the *erythro*-brosylate (run 4). This fact accounts for the large differences in the yield ratios of Chart II for runs 3 and 4. That the rotation ratios are rather close for runs 3 and 4 suggests either that the two optically active olefins (VIII and IX) are produced in about the same ratio in a kinetically as a thermodynamically controlled process, or that both reaction times were long enough to allow these two olefins (not the tertiary formate) to equilibrate. The equilibration experiments conducted in formic acid on the olefin fractions from the acetolyses indicate that equilibration of VIII and IX is incomplete in the time of run 4. Thus the former interpretation appears to apply.

Perhaps the most striking internal consistency in the rotation data from the four runs is the constancy of the ratios of rotations of olefins obtained in runs 4 and 2 on the one hand and 3 and 1 on the other. The yields of these olefins varied by as much as a factor of 5, the rotations by as much as a factor of 2, and the starting materials in the formolyses and acetolyses were enantiomerically related. This similarity in ratios again emphasizes that the olefins are produced from the same intermediates (open carbonium ions) even though the starting materials are diastereomeric. Further, the fraction of olefinic product having arisen from racemized as compared to active brosylate ester in the *threo*-solvolysis must be about the same for the two solvents. Since the amount in the acetolysis (run 1) was about 20%, the amount in formolysis must have been approximately the same.

$$\frac{\text{(run 3) } \alpha \text{ olefin formolysis}}{\text{(run 1) } \alpha \text{ olefin acetolysis}}_{\textit{threo}\text{-solvolyses}} = 1.27$$

$$\frac{\text{(run 4) } \alpha \text{ olefin formolysis}}{\text{(run 2) } \alpha \text{ olefin acetolysis}}_{\textit{erythro}\text{-solvolyses}} = 1.29$$

Differences in Reactivity between Diastereomers in the Wagner–Meerwein Rearrangement.—The kinetic and yield data for the three systems (II, III and IV) when put together allow an analysis of reactivity differences between diastereomers to be examined as a function of the steric constraints of each system. Two general comparisons will be made. Partial rate factors for the various processes can be calculated in all three *threo* systems, and certain ratios compared with one another. The partial rate factors of the two diastereomers of each system will be compared with one another.

Chart III defines the partial rate factors and the configurational relationships involved, and Table III records the ratios of the partial rate factors of interest. Equations 2 and 3, coupled with the appropriate yield data,[3] were employed in converting the measured titrimetric (k_t) and polarimetric (k_α) rate constants into these ratios (ref. 3 provides sample calculations).

$$k_\alpha = k_0 + k_s + k_p \quad (2)$$

$$k_t = k_0 + k_s + k_p[k_c/(k_e + k_c)] \quad (3)$$

As the system becomes progressively more hindered, in acetic acid the value of $k_c/(k_c + k_e)$ passes from 0.12 for system II to 0.58 for system IV. In other words, ion-pair collapse becomes less favored. By contrast, in formic acid a slight trend in the opposite direction is evident, and in the most hindered system the values are rather close together. This pattern of results indicates that the exchange of an anion of an ion-pair with a solvent molecule is subject to a number of effects, some of which oppose one another.[10]

Of the other ratios of rates of Table III, the most interesting trend is that of $C_{\beta'}$–H (see part structure J) to become more involved in the solvolysis and for C_β–C_6H_5 to become less involved in passing from the least to the most ramified system (II to IV). This trend at least partially reflects the fact that $C_{\beta'}$–H can best participate in ionization at C_α

(10) Chloroform was present in the solvent in the formolysis of systems III and IV, so comparisons of these runs with those of II suffer somewhat. However, the dramatic changes in this ratio occur in passing from system III to IV, and about the same concentration of chloroform was present.

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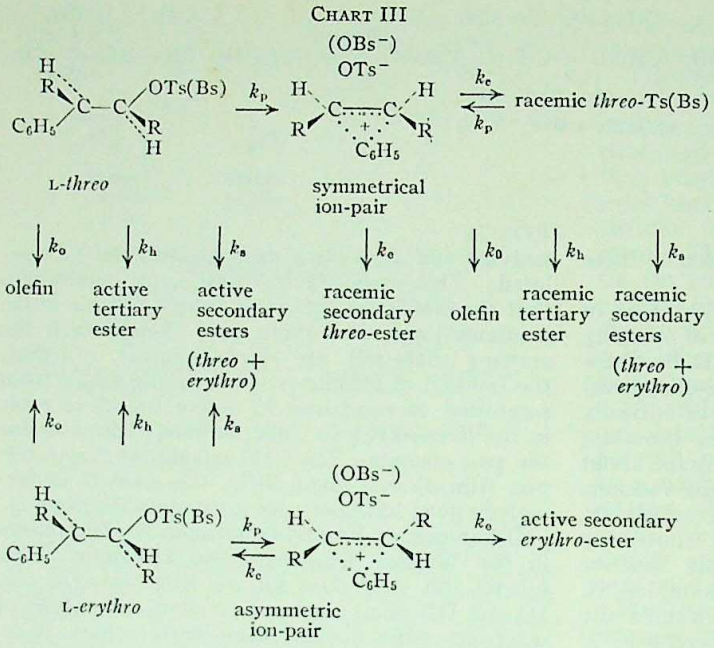
CHART III



when $C_{\beta'}$ is a tertiary carbon and least when $C_{\beta'}$ is methyl.

TABLE III

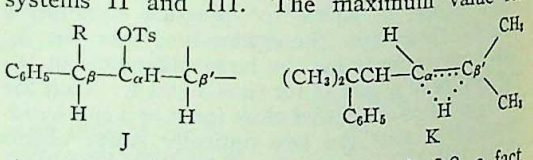
RATE RATIOS OF REACTIONS THAT OCCUR DURING SOLVOLYSIS OF THE *threo*-TOSYLATES OF 3-PHENYL-2-BUTANOL (II) AND 4-PHENYL-3-HEXANOL (III) AND OF THE *threo*-BROSYLATE OF 2,5-DIMETHYL-4-PHENYL-3-HEXANOL (IV)

Run	System	T, °C.	Solvent	$\frac{k_e}{k_e + k_s}$	$\frac{k_p}{k\alpha^a}$	$\frac{k_h + k_o}{k\alpha^a}$	$\frac{k_s}{k\alpha^a}$
2 + 3	II	75	AcOH	0.12	0.91	0.08	0.01
5 + 6[b]	II	25	HCOOH	.83	.82	.18	.0
9 + 10	III	75	AcOH	.16	.83	.13	.04
13 + 14[c]	III	25	HCOOH[d]	.71	.87	.09	.04
16 + 17	IV	50	AcOH	.58	.42	.57	.01
20	IV	25	HCOOH[e]	~ .5[f]	~ .3[g]	~ .7[g]	~ .0[g]

[a] $k\alpha = k_p + k_h + k_o + k_s$. [b] Temperature difference of 0.14° between runs 5 and 6, $k\alpha$ being the higher. [c] Temperature difference of 0.20° between runs 13 and 14, $k\alpha$ being the higher. [d] Actually a 3.33/1 mixture by volume of HCOOH–$CHCl_3$. [e] Actually a 2.86/1 mixture by volume of HCOOH–$CHCl_3$. [f] This ratio was calculated assuming that the same fractions of products were produced *via* racemized brosylate in formolysis and acetolysis, an assumption supported by the rotations of the olefins. [g] Calculations based on same assumptions as in (*f*).

Table IV compares the kinetics of the two diastereomers of each system in terms of the partial rate factors k_p (phenyl participation in ionization) and $k_h + k_o$ (a rough measure of hydrogen participation). The virtue of comparing reactivity differences between diastereomers lies in the fact that any differences must derive fundamentally from geometry. Unfortunately k_p cannot be calculated directly for the *erythro* runs, since the ratio $k_e/(k_e + k_e)$ cannot be determined. The best that can be done, therefore, is to calculate k_p (*erythro*) by assuming that the values of $k_e/(k_e + k_e)$ do not vary much between the diastereomers. This assumption is supported by the fact that although the values of k_α/k_t (Table IV) vary by factors of 4 and 2.5 in passing from acetic to formic acids (for systems II and III), the values of k_p (*erythro*)/k_p (*threo*) vary by factors of only 1 and 1.4 for the respective systems. Furthermore, when the values of $k_e/(k_e + k_e)$ are greater than 0.5, k_p becomes rather insensitive to the value of this ratio. Fortunately $(k_h + k_o)$ *erythro* can be calculated directly.

Quite reasonably, the values of k_t (*erythro*)/k_t (*threo*) depart more and more from unity as the system involved becomes more sterically constrained. The ratios of k_p (*erythro*)/k_p (*threo*) show about the same departure from unity in II and III as the ratios of k_t's, whereas the $(k_h + k_o)$ (*erythro*)/$(k_h + k_o)$ (*threo*) ratios are close to unity. In the much more hindered system, IV, the value of k_p (*erythro*)/k_p (*threo*) is about unity, and the $(k_h + k_o)$ (*erythro*)/$(k_h + k_o)$ (*threo*) ratio becomes about 9. On the basis of simple conformational *analysis*,[11] the *threo* isomers of systems II, III and IV are the more stable.[12] A comparison of the eclipsing effects[13] in each diastereomeric pair indicates that neighboring phenyl or hydrogen participation in ionization (from C_β) is more sterically feasible for the *erythro* than for the *threo* isomer (see Table IV). So both the starting states as well as the transition states for neighboring group participation would tend to favor k_p *erythro*/k_p *threo* > 1, and also to favor $(k_h + k_o)$ *erythro*/$(k_h + k_o)$ *threo* > 1 as long as $k_h + k_o$ measures mostly hydrogen involvement from the carbon carrying phenyl (C_β–H). This latter condition applies only to systems II and III. The maximum value for



these ratios in these two systems is 2.8, a fact which indicates both that eclipsing effects are small and that the differences in energy between the starting states are small. In IV, the ratio of k_p's remains near unity, but $(k_h + k_o)$ *erythro*/$(k_h + k_o)$ *threo* amounts to about 9. In this more hindered system, $k_h + k_o$ measures mostly involvement of $C_{\beta'}$–H. Since $C_{\beta'}$ carries two methyls, eclipsing effects in the transition state K should be about the

(11) (a) D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **75**, 339 (1953); (b) D. J. Cram and F. D. Greene, *ibid.*, **75**, 6005 (1956)] D. H. R. Barton and R. C. Cookson [*Quarterly Reviews*, **10**, 48 (1956)] have also recognized these principles and quote as an example the work of R. P. Linstead and M. Whalley [*J. Chem. Soc.*, 3722 (1954)] on the relative stability of *meso*- and DL-2,3-disubstituted succinic acids. In this and similar systems as well as those such as the stilbene dibromides [*e.g.*, R. E. Buckles, W. E. Steinmetz and N. G. Wheeler, THIS JOURNAL, **72**, 2496 (1950)], dipole–dipole interactions may play a much more important role than simple steric effects. In these types of systems, the electronic and steric effects happen to reinforce one another. The only tests of the purely steric principles (of which the authors are aware) are those quoted in ref. 11a and 11b.

(12) In the analysis of IV, phenyl is selected as being effectively more bulky than isopropyl, a choice supported by the direction of asymmetric induction in the preparation of the system (ref. 6).

(13) See D. Y. Curtin [*Record Chem. Progress*, **15**, 111 (1954)] for a general discussion.

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TABLE IV

RATE COMPARISONS FOR SOLVOLYSIS OF DIASTEREOMERIC ESTERS OF II, III AND IV

Run	System	Solvent	T, °C.	Groups eclipsed in bridges: *threo*	C$_6$H$_5$-bridge	H-bridge[b]	C$_3$H$_5$-bridge	*erythro*	H-bridge[b]	*threo* k_α[a]/k_t	$\frac{k_t\ (erythro)}{k_t\ (threo)}$	$\frac{k_p\ (erythro)}{k_p\ (threo)}$	$\frac{(k_h + k_s)\ (erythro)}{(k_h + k_s)\ (threo)}$
1 + 4	II	AcOH	75		$\left\{\begin{matrix}CH_3>\\C_6H_5>\end{matrix}\right.$—$<CH_3$		$\left\{\begin{matrix}CH_3>\\H>\end{matrix}\right.$—$<CH_3$		$\left\{\begin{matrix}C_6H_5>\\CH_3>\end{matrix}\right.$—$<H$	4.6	1.2	1.5	0.7
5 + 7	II	HCOOH	25		$\left\{\begin{matrix}C_2H_5>\\C_6H_5>\end{matrix}\right.$—$<H$				$\left\{\begin{matrix}CH_3>\\C_2H_5>\end{matrix}\right.$—$<CH_3$	1.2	1.2	1.2	1.2
11 + 12	III	AcOH	50		$\left\{\begin{matrix}C_2H_5>\\C_6H_5>\end{matrix}\right.$—$<C_2H_5$		$\left\{\begin{matrix}C_2H_5>\\H>\end{matrix}\right.$—$<H$		$\left\{\begin{matrix}C_6H_5>\\CH_3>\end{matrix}\right.$—$<H$	3.2	1.8	2.7[c]	1.3[c]
13 + 15	III	HCOOH	25		$\left\{\begin{matrix}C_6H_5>\\C_2H_5>\end{matrix}\right.$—$<H$				$\left\{\begin{matrix}C_2H_5>\\C_2H_5>\end{matrix}\right.$—$<C_2H_5$	1.3	2.6	2.8	1.1
16 + 18	IV	AcOH	50	$\left\{\begin{matrix}(CH_3)_2CH>\\C_6H_5>\end{matrix}\right.$—$<(CH_3)_2CH$		$\left\{\begin{matrix}C_6H_5>\\(CH_3)_2CH>\end{matrix}\right.$—$<H$		$\left\{\begin{matrix}(CH_3)_2CH>\\H>\end{matrix}\right.$—$<(CH_3)_2CH$		$\left\{\begin{matrix}C_6H_5>\\(CH_3)_2CH>\end{matrix}\right.$—$<H$	1.2	6.4	0.9	8.8
20 + 21	IV	HCOOH	25	$\left\{\begin{matrix}C_6H_5>\\(CH_3)_2CH>\end{matrix}\right.$—$<H$						[d]	8.2	.. [d]	9.0

[a] The run numbers obviously had to be different for this calculation—data are in Table I. [b] The bridges referred to here are those involving (either as transition states or intermediates) the hydrogen on the C_β carrying the phenyl. [c] The yield data were obtained at 75° and the rates at 50°. It was assumed that the yields in the two diastereomers varied the same way over the 25° range of temperature. [d] k_α could not be obtained in formic acid.

same for the two diastereomers. Therefore, the factor of 9 is mainly attributable to differences in energy of the two diastereomeric starting states. The proximity of k_p (*erythro*)/k_p (*threo*) to unity therefore implies that the geometries of the transition states for phenyl participation resemble those of the starting states, and that phenyl provides only a small driving force for ionization in this particular system. The relative absence of eclipsing effects in IV recalls the data obtained in a study of the E_2 reaction in the 1,2-diphenyl-1-propyl-X system. The ratio k_{E_2} (*threo*)/k_{E_2} (*erythro*) in this system could be varied from $\sim$ 1 to 57, depending on the strength of the base, the character of the solvent and of the leaving group.[14] In system IV and probably in II and III as well, the transition states for phenyl migration still leave the substituents on C_α and C_β well staggered, and the three-membered ring only slightly formed.

Experimental

Preparation of the Brosylates of the Stereoisomers of 2,5-Dimethyl-4-phenyl-3-hexanol (IV).—The ordinary methods of preparation of either tosylates or brosylates in this system failed. The following procedure was found applicable to the preparation of all four stereomers. The starting four alcohols were reported previously in an optically pure state, as well as in their two racemic forms.[6] To 25 ml. of benzene (distilled from potassium) were added 1.23 g. (1.42 ml.) of sodium–potassium alloy and 2.58 g. of (−)-*threo*-IV. The mixture was stirred under dry, pure nitrogen at 25° for one hour and at reflux for 4 hours. Control experiments indicated this to be the minimum time for formation of the alcoholate. The reaction mixture was cooled to 0°, the remaining alloy removed (under nitrogen), and a solution of 3.26 g. of pure *p*-bromobenzenesulfonyl chloride in 15 ml. of dry benzene was added rapidly. The resulting mixture was permitted to warm to 15° during the first hour and then stirred at 25° for an additional hour. A few drops of solution gave a neutral test with phenolphthalein solution. The reaction mixture was washed with water, dried (sodium carbonate), treated with a few drops of pyridine and evaporated at 25° under diminished pressure. The resulting oil was crystallized at −20° from an equal volume of pentane (containing a few drops of pyridine). The liquor was decanted quickly, and the crystals were dissolved at 25° in a minimum amount of ether containing a few drops of pyridine and recrystallized by cooling to −20°. After two recrystallizations, the sulfonate ester was obtained (by decantation), dried under vacuum, wt. 3.70 g. (70% yield), m.p. indeterminate because of decomposition.

Anal. Calcd. for $C_{20}H_{25}O_3SBr$: C, 56.46; H, 5.90. Found: C, 56.64; H, 6.12.

The other three stereomers were prepared in from 50–70% yields, and showed similar instability, which prevented the determination of any meaningful m.p.'s or rotations. The ester of (+)-*threo*-IV was not successfully analyzed because of its instability. The analyses of (+)-*erythro*-IV and (−)-*erythro*-IV, respectively, are as follows.

Anal. Calcd. for $C_{20}H_{25}O_3SBr$: C, 56.46; H, 5.90. Found: C, 56.54, 56.33; H, 5.88, 5.79.

Preparation of the Acetates of the Stereomers of 2,5-Dimethyl-4-phenyl-3-hexanol (IV).—In the hope that the acetates of the four stereomers of IV would have rotations that would aid in the analysis of unknown mixtures of stereomers, these esters were prepared by the usual pyridine method in yields of 85–93%. Isomer (+)-*threo*-IV gave $n^{25}D$ 1.4868, $\alpha^{25}D$ +104.3° (l = 1 dm., neat).

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.59; H, 9.72.

Isomer (−)-*threo*-IV gave $n^{25}D$ 1.4868, $\alpha^{25}D$ −104.4° (l = 1 dm., neat). *Anal.* Found: C, 77.31; H, 9.47.

(14) D. J. Cram, F. D. Greene and C. H. Depuy, THIS JOURNAL, **78**, 790 (1956).

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Isomer (+)-*erythro*-IV gave m.p. 45–46°, $\alpha^{25}D$ +85.7° (l = 1 dm., neat). *Anal.* Found: C, 77.15; H, 9.52.

Isomer (−)-*erythro*-IV gave m.p. 45–46°, $\alpha^{25}D$ −85.7° (l = 1 dm., neat). *Anal.* Found: C, 77.58; H, 9.64.

Kinetics of Solvolysis of the Brosylates of the Stereomers of IV.—The acetolysis solutions were prepared from C.P. acetic acid, anhydrous potassium carbonate and sufficient acetic anhydride to consume the water produced and leave a 1% excess. The ampoule technique was employed in both the titrimetric and polarimetric runs. The titration reagents and procedures have been reported previously.[4b] The polarimetric readings were taken in a thermostated 2-dm. tube at 25°. In all cases from 8 to 12 points were taken, and the reactions followed to 85–95% completion. A fixed infinity reading was obtained in the polarimetric runs.

The formic acid used in formolysis was purified as before[4c] (100.01% by titration with Karl Fischer reagent), and the requisite amounts of anhydrous sodium formate and of ethanol-free anhydrous chloroform were added. The amount of chloroform needed was determined by trial experiments, homogeneity throughout the run being the criterion. The titrimetric runs were followed by withdrawing 5-ml. aliquots of solution from the reaction and quenching this in 50 ml. of purified dioxane, and titrating this solution with standardized perchloric acid–dioxane solution (method of Winstein and Heck).[15] The indicator was bromcresol green and the light yellow end-point was always compared to a standardized end-point obtained by mixing equivalents of standard solutions together. Fifteen points were taken per run, and the reactions were followed to about 90% completion. The polarimetric formolyses were carried out in a 4-dm. thermostated polarimeter tube, fifteen points, a fixed infinity reading being taken.

4-Methyl-3-phenylpentanoic Acid.—Hydrolysis of 40 g. of 3-methyl-2-phenylbutyronitrile[6] with 56 g. of potassium hydroxide in 300 ml. of diethylene glycol (105° for 72 hours) gave 36 g. (81% yield) of 3-methyl-2-phenylbutanoic acid (recrystallized from pentane), m.p. 60.5–62.5° (reported[16] 62–63°). A solution of 20 g. of this acid in 16 g. of thionyl chloride was allowed to stand for 10 hours at 25°. The excess thionyl chloride was removed under reduced pressure, and the remaining liquid residue was distilled at 125° (13 mm.) to give 21.6 g. (98% yield) of acid chloride, $n^{25}D$ 1.5050. A solution of 20.4 g. of diazomethane in 500 ml. of dichloromethane was prepared from 50 g. of N-nitrosomethylurea.[17] To 400 ml. of this solution at 0° was added dropwise a solution of 20.6 g. of the above acid chloride in 50 ml. of dichloromethane (75 minutes). The resulting mixture was allowed to warm to 25°, the excess solvent was removed at 30 mm., and the bath temperature was raised to 35°. The remaining liquid residue was cooled, dissolved in 150 ml. of methanol, and 0.7 g. of powdered silver oxide was added. The resulting exothermic reaction was permitted to continue with occasional cooling until the reaction had subsided, when more oxide was added, and the mixture was refluxed for one hour. The mixture was cooled, filtered, evaporated (30 mm.), and the oil was distilled at 105–110° (pot temperature) at 2 mm. to give 19.3 g. (89% yield) of crude ester. Hydrolysis of the substance with 20 g. of potassium hydroxide in 150 ml. of diethylene glycol at 130° for 38 hours gave acid, which was recrystallized three times from pentane to give 12.8 g. (63% yield) of 4-methyl-3-phenylpentanoic acid, m.p. 48–49°. This acid has been reported previously as an oil.[18]

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39; neut. equiv., 192. Found: C, 75.26; H, 8.37; neut. equiv., 192.

The anilide was prepared in the usual way, m.p. 114.5–116° (ethyl acetate).

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 80.80; H, 7.92.

The above acid was also prepared by the following inferior sequence. The brosylate of 3-methyl-2-phenyl-1-butanol[6] was treated with potassium cyanide, and the resulting nitrile was hydrolyzed to acid, m.p. 48.5–49.5°, undepressed by admixture with an authentic sample.

This acid was resolved through its quinine salt as follows. A solution of 35.7 g. of acid and 52.7 g. of quinine was dissolved in a minimum amount of ethanol and held at 0°. The resulting solid was recrystallized 13 times (ethanol), the salt was converted to the acid to give m.p. 44–45°, $[\alpha]^{25}D$ +33.99° (c 3.3, $CHCl_3$). The acid was again converted to its quinine salt which was recrystallized three more times from methanol, and the resulting salt was again converted to the acid. This acid (recrystallized from pentane) gave wt. 0.0839 g., m.p. 44–45°, $[\alpha]^{33}D$ +34.4° (c 3.3, $CHCl_3$). Extensive recycling of the second crops gave more optically pure material of identical physical properties, enough to provide 0.88 g. of optically pure acid.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 75.21; H, 8.59.

2,5-Dimethyl-4-phenyl-2-hexanol (V).—A solution of 4.92 g. of 4-methyl-3-phenylpentanoic acid (racemic) in 26 ml. of absolute methanol containing 1.3 ml. of concd. sulfuric acid was refluxed for 10 hours. The ester was isolated in the usual way and distilled at a pot temperature of 118° (4.6 mm.) to give 4.91 g. (93% yield), $n^{25}D$ 1.4932.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.64; H, 8.85.

To a solution of methylmagnesium iodide prepared from 42.7 g. of methyl iodide and 8.0 g. of magnesium turnings, was added a solution of 3.0 g. of methyl 4-methyl-3-phenylpentanoate in 50 ml. of ether. The reaction mixture was stirred for 10 hours and then refluxed vigorously for one hour before decomposing the reaction mixture with 200 ml. of ice-cold saturated ammonium chloride solution. The phases were separated, and the aqueous phase was acidified with sulfuric acid and then extracted with ether. The ether extract was washed, dried, evaporated, and the remaining oil was absorbed on 200 g. of basic alumina of activity I.[19] After elution of the column with pentane had produced no residue, the product was eluted with 50% methanol in ether. The eluent was evaporated, and the liquid residue was dissolved in pentane, washed with water and dried. The pentane was evaporated, and the liquid residue was distilled at 100° pot temperature (1.4 mm.) to yield 2.76 g. (92% yield) of 2,5-dimethyl-4-phenyl-2-hexanol (V), $n^{25}D$ 1.5021.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.58; H, 10.60.

The 3,5-dinitrobenzoate of V was prepared from 0.10 g. of V, 0.3 ml. of reagent pyridine and 0.12 g. of freshly prepared 3,5-dinitrobenzoyl chloride at 90° (2 hours). The product was isolated in the usual way and recrystallized twice from ether–pentane to give 0.15 g. (77% yield) of light yellow needles, m.p. 89.5–90.5°.

Anal. Calcd. for $C_{21}H_{24}O_6N_2$: C, 62.99; H, 6.04. Found: C, 63.06; H, 6.13.

Hydrolysis of the above derivative in a mixture of 0.05 g. of potassium hydroxide in one ml. of water and 4 ml. of ethanol at 95° for 8 hours gave back the original alcohol V in almost quantitative yield.

The acetate of V proved difficult to prepare, the following method giving the best result. A mixture of 0.109 g. of V, 0.5 ml. of pure acetic anhydride and 0.4 ml. of pure pyridine was held at 50° for 12 days. The product was isolated in the usual way, absorbed on a column of 50 g. of neutral alumina of activity I[19] made up in pure pentane. The product was eluted with 350 ml. of 12% ether in pure pentane, the solvent first was evaporated at 30 mm., and then at 1 mm. The acetate was not distilled due to the possibility of slight decomposition but was analyzed directly, $n^{25}D$ 1.4864.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.28; H, 9.80.

Attempts to form the formate of V gave a mixture of olefin and formate.

Utilizing the above procedure, optically pure 4-methyl-3-phenylpentanoic acid (0.875 g.) was converted to its methyl ester (0.870 g.), $n^{25}D$ 1.4931, $\alpha^{25}D$ +33.47 (l = 1 dm., neat).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.64; H, 8.84.

The above ester (0.87 g.) was divided into two portions, the first being converted to alcohol V (see above) to give after distillation at 118° (pot temperature) and 2 mm. 0.34

(15) S. Winstein and R. Heck, THIS JOURNAL, **78**, 4801 (1956).

(16) S. V. Hintikka, *Ann. Acad. Sci. Fennicae*, **19A**, 4 (1924).

(17) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 461.

(18) E. Späth and P. Kainrath, *Ber.*, **71**, 1496 (1938).

(19) H. Brockmann and H. Schodder, *ibid.*, **74B**, 73 (1941).

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g. of alcohol, $n^{25}D$ 1.5019, $\alpha^{25}D$ +2.02 (l = 1 dm., neat). The other portion was subjected to the same procedure but the chromatographic step was omitted, 0.23 g. of V being obtained, $n^{25}D$ 1.5022, $\alpha^{25}D$ +2.68° (l = 1 dm., neat). The variation in rotation of these two preparations suggested contamination with small amounts of the highly rotating olefins derived from this tertiary alcohol. Therefore the combined alcohol portions were converted to the solid 3,5-dinitrobenzoate derivative (see above), which after a charcoal treatment and two recrystallizations from absolute ethanol gave 0.226 g. of ester, m.p. 89.5–90.5°, decomposition point 160–161° (dependent on heating rate), $[\alpha]^{25}D$ +15.01° (c 3.3, $CHCl_3$), m.m.p. with same derivative of racemic V, 80.5–82°.

Anal. Calcd. for $C_{21}H_{24}O_6N_2$: C, 62.99; H, 6.04. Found: C, 62.78; H, 6.07.

A second independent preparation of active alcohol V gave $\alpha^{25}D$ +2.79° (l = 1 dm., neat), and its 3,5-dinitrobenzoate gave $[\alpha]^{25}D$ +15.48° (c 3.3, $CHCl_3$). A total of 0.509 g. of this derivative of active V was hydrolyzed (see above) to give V as an oil which was submitted to chromatography on 50 g. of neutral alumina made up in pentane. A trace of olefin was eluted with pure pentane and alcohol was eluted with pure ether to give after distillation (90–95°, pot temperature, 0.9 mm.) 0.17 g. of optically pure V, $\alpha^{26}D$ +1.83° (l = 1 dm., neat). Another independent preparation gave $\alpha^{26}D$ +1.79° (l = 1 dm., neat).

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.22; H, 10.71.

2,5-Dimethyl-3-phenyl-3-hexanol (VI).—To a solution of 0.254 mole of isopropyllithium in 15.8 ml. of pentane[6] was added dropwise a solution of 25 g. of isovalerophenone in 75 ml. of pentane. The mixture was stirred for 10 hours, treated with ice-water, and the product isolated in the usual way. Distillation of the alcohol gave 20.6 g. (65% yield) of VI, b.p. 97–101° (3 mm.), $n^{25}D$ 1.5029–1.5016. This material (3.64 g.) was treated with a suspension of 0.9 g. of lithium aluminum hydride in ether, and worked up in the usual way. The resulting oil was treated with 4.0 g. of phthalic anhydride and 3 ml. of pure pyridine at 105° for 46 hours. The resulting solution was shaken with ether and dilute, cold hydrochloric acid, and the ether layer was washed with water, extracted with sodium bicarbonate solution and again with water. This operation removed the secondary alcohol present which had come from unreacted ketone. The ether layer was dried, evaporated, taken up in pure pentane and chromatographed on 200 g. of neutral alumina of activity I[19] in pure pentane. Elution of the column with pure pentane gave 0.43 g. of olefin (distilled at 90–95° pot temperature at 6 mm.), $n^{25}D$ 1.4981, λ_{232} (arbitrary), ϵ 4,805. Elution of the column with 9 liters of 32% ether in pure pentane gave alcohol VI which was distilled at pot temperature of 115–117° (4 mm.) to give 1.94 g. of V, $n^{25}D$ 1.5018.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.41; H, 10.57.

Repeated attempts to form a 3,5-dinitrobenzoate of this compound failed to yield any solid derivative.

4-Methyl-2-phenylpentanoic Acid.—To 100 ml. of absolute ethanol was added 5.1 g. of sodium, and the resulting solution was cooled to 50°. Diethyl phenylmalonate[20] (47.2 g.) was added (40 minutes), the mixture was maintained at 50°, and 30.4 g. of isobutyl bromide was added (90 minutes). The solution (pH 10) was brought to reflux, and within 10 minutes solid separated. After 19 hours of reflux the reaction mixture approached pH 7, and the excess ethanol was evaporated. The remaining material was diluted with water, extracted with ether, and the extract was washed, dried and evaporated. The resulting oil was distilled (10 mm.): 1st fraction, b.p. 101–105°, wt. 24.7 g., $n^{25}D$ 1.4921; 2nd fraction, b.p. 130–150°, wt. 6.28 g., $n^{25}D$ 1.4848 (diethyl phenylmalonate, b.p. 156–158° at 9.3 mm., $n^{25}D$ 1.4896); 3rd fraction, b.p. 165–167°, wt. 4.29 g., $n^{25}D$ 1.4861. Hydrolysis of the first fraction gave phenylacetic acid. The third fraction was hydrolyzed with 60 ml. of an aqueous 40% potassium hydroxide solution (20 hours), and the resulting acid was recrystallized once from ether–pentane to give 1.63 g. of 4-methyl-2-phenylpentanoic acid, m.p. 75.5–76.5° (reported[21] 78–79°).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 75.06; H, 8.47.

2,5-Dimethyl-3-phenyl-2-hexanol (VII).—A solution of 1.63 g. of 4-methyl-2-phenylpentanoic acid and 0.5 ml. of concd. sulfuric acid in 15 ml. of methanol was refluxed for 10 hours, and the resulting solution was worked up as usual. The resulting liquid was distilled at a pot temperature of 110–115° (2.5 mm.) to give 1.70 g. (97% yield) of 4-methyl-2-phenylpentanoate, $n^{25}D$ 1.4882.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.87; H, 8.74.

This ester (1.70 g.) was treated with methylmagnesium iodide (5 g. of magnesium and 29.6 g. of methyl iodide) in the usual way to give VII, wt. 1.53 g. (90% yield), distilling at a pot temperature of 118–122° (3 mm.), $n^{25}D$ 1.5009. A portion (0.8 g.) of this alcohol was chromatographed on 250 g. of neutral alumina of activity I[19] in pentane, and the column was eluted with 8 liters of 32% ether in pentane. The solution containing the alcohol fraction was washed with sodium sulfite solution to remove ether peroxides, and the alcohol was distilled at 122–126° (pot temperature), wt. 0.56 g., $n^{25}D$ 1.5009.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.27; H, 10.64.

A small portion of this alcohol was converted to the 3,5-dinitrobenzoate derivative, m.p. 133.5–134.5°, dec. 170.5–171.5° (depending on rate of heating somewhat), m.m.p. with the same derivative of 2,5-dimethyl-4-phenyl-2-hexanol 81–102°.

Anal. Calcd. for $C_{21}H_{24}O_6N_2$: C, 62.99; H, 6.04. Found: C, 63.10; H, 6.15.

The acetate of VII was prepared in 57% yield by the same method utilized in the preparation and purification of the acetate of V. The ester distilled at 110–115° (pot temperature) and 2 mm., $n^{25}D$ 1.4850.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.14; H, 9.52.

Preparation of Acetolysis Stock Solution.—Glacial acetic acid was distilled (b.p. 115–116°), titrated with standardized Karl Fischer reagent and found to contain 5.46 g. of water per 1400 ml. of acid. A solution of 1400 ml. of this acid, 11.090 g. of anhydrous potassium carbonate (dried for 48 hours at 125°) and 58 ml. of freshly distilled acetic anhydride was refluxed to yield an acetolysis medium, 0.110 molar in potassium acetate and containing 1% excess acetic anhydride (by volume).

Acetolysis of the Brosylate of (+)-*erythro*-2,5-Dimethyl-4-phenyl-3-hexanol (Run 2 of Table II).—This brosylate (5.60 g.) was dissolved in 137 ml. of acetolysis stock solution (0.096 molar in brosylate), and held at 49.97 ± 0.05° for 291 minutes (8 titrimetric half-lives). The solution was then shaken with 1 liter of ice-water and four successive 250-ml. portions of pure pentane. The aqueous layer was then extracted with 150 ml. of pure ether. The organic extracts were combined, washed with water, sodium bicarbonate solution and again with water. The solution was dried, evaporated through a 75-cm. Vigreux column. (All subsequent evaporations of solvent were through this column, and pure, peroxide-free ether and kerosene-free pentane were utilized throughout.) The residual oil was distilled at a pot temperature of 90–115° (2 mm.) to give 2.64 g. of oil and 0.10 g. of pot residue. A solution of the oil in 25 ml. ether was added dropwise to a suspension of 0.624 g. of lithium aluminum hydride in ether. After being stirred for 3.5 hours, the mixture was decomposed with 70 ml. of wet ether and then 50 ml. of ice-water. The product was isolated in the usual way, and the resulting oil was chromatographed on 175 g. of neutral alumina of activity I[19] in pentane. The residues from the pentane eluates were distilled at a pot temperature of 90° (3 mm.) to give 1.74 g. of olefin (see Table II). The residues from the ether eluates were combined with the aid of pentane, and the resulting solution was washed free of peroxides with sodium sulfite solution and water. The pentane layer was dried, evaporated, and the resulting alcohol fraction was distilled at a pot temperature of 102–105° (1.5 mm.) to give 0.57 g. of alcohol. At this point 91% of the starting brosylate ester

(20) P. A. Levene and G. M. Meyer, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 288.

(21) M. Bedroux and P. Tabourly, *Bull. soc. chim.*, [4] **7**, 669 (1910).

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TABLE V

INFRARED DATA CONCERNING ANALYSIS OF ALCOHOLS OBTAINED FROM ACETOLYSIS RUNS 1 AND 2

Sample	Slit, mm. → / wave no., cm.$^{-1}$ →	Absorbance in infrared[a] 1st set of equations 0.352 1149	0.461 1010	1.05 768	2nd set of equations 0.429 1049	0.690 858.4	1.20 746.3
threo-IV		0.254	0.232	0.620	1.16	0.012	0.109
erythro-IV		.530	.763	.061	.209	.271	.333
V		1.00	.061	.293	.014	.002	.985
Alcohol run 2		0.819	.219	.226	.052	.031	.800
87%-V, 12% *erythro*-IV, 1% *threo*-IV		.840	.174	.242	.041	.019	.839
Alcohol run 1		.404	.176	.490	.735	.012	.322
28%-V, 1% *erythro*-IV, 71% *threo*-IV		.385	.166	.479	.799	.006	.313

[a] Beckman IR2T infrared spectrophotometer. The readings were taken successively in a 0.03-mm. cell, homogeneous liquid films, NaCl prism.

was accounted for. This mixture was submitted to infrared analysis (see later section).

The alcohol fraction was chromatographed on 171 g. (3 cm. by 35 cm.) of neutral alumina of activity I[19] in pentane, the chromatograph column being wrapped in heavy paper to exclude light. The column was developed with 32% ether in pentane (ether was washed free of peroxides just prior to use and carefully distilled). The results are tabulated (the chromatograph was run continuously for 27 hours). The residues from cuts 1–19 were combined with pentane and dried to give 0.0426 g. of solid material, m.p. 65–68°, $[\alpha]^{25}D$ +17.3° (*c* 4.3, $CHCl_3$). Recrystallization of the material from pentane gave 0.0243 g., m.p. 68.4–69.2°, $[\alpha]^{25}D$ +20.7° (*c* 1.7, $CHCl_3$), undepressed by admixture with an authentic sample of optically pure (+)-*erythro*-IV.

Eluent	Vol. of eluent, ml.	Cut	Characteristics
32% ether in pentane	1550	1–10	Blank
	1350	11–19	Crystals
	450	20–22	Blank
	1000	23–28	Droplets
100% ether	500	29–30	Liquid
	800	31	Blank

The liquid residues from cuts 21–31 were dissolved in pentane, the solution was washed with sodium sulfite solution, water, dried and evaporated. Distillation of the oil at a pot temperature of 102–103° (2 mm.) gave 0.47 g. of tertiary alcohol fraction. See Table II for properties. The infrared spectrum of this material proved to be identical to that of 2,5-dimethyl-4-phenyl-2-hexanol and was demonstrated through comparisons of this spectrum with that of a synthetic mixture of V containing 2% of IV to contain less than 2% of this secondary alcohol. Unfortunately this material was lost before a derivative could be prepared.

Acetolysis of the Brosylate of (+)-*threo*-2,5-Dimethyl-4-phenyl-3-hexanol (Run 1 of Table II).—The brosylate ester (6.123 g.) of optically pure alcohol was acetolyzed as in run 2 in 150 ml. of stock solution for 31 hours (8 titrimetric half-lives). The products were isolated as in run 2 to give 3.03 g. of olefin–ester mixture, which gave 1.43 g. of olefin and 1.20 g. of a mixture of secondary and tertiary alcohol (see Table II for physical properties). This mixture was submitted to infrared analysis (see later section). The secondary and tertiary alcohol fractions were separated by chromatography, 1750 ml. of solvent developer coming through the column without any dissolved alcohol in between the secondary and tertiary alcohol fractions. The secondary alcohol fraction amounted to 0.69 g., its infrared spectrum being identical to that of racemic *threo*-IV. This material (0.161 g.) was converted to its *p*-nitrobenzoate derivative,[6] 0.197 g. (71% yield) being obtained after being crystallized once from ethanol, m.p. 115.5–118° (undepressed by admixture with an authentic sample),[6] $[\alpha]^{25}D$ +0.45° (*c* 3.3, $CHCl_3$). The same derivative of (+)-*threo*-IV has m.p. 145–146°, $[\alpha]^{25}D$ +105° (*c* 3.3, $CHCl_3$).[6]

Mixed melting points of the following *p*-nitrobenzoates were obtained: (1) 5% derivative of (−)-*threo*-IV +95% racemic derivative, 118.5–123°; (2) 0.5% derivative of (−)-*threo*-IV + 99.5% racemic derivative, 117.5–119.5°; 1% derivative of (+)-*erythro*-IV + 99% racemic derivative of *threo*-IV, m.m.p. 110.5–140°.

The tertiary alcohol fraction amounted to 0.24 g., and its infrared spectrum was almost identical to that of authentic alcohol V. This fraction (0.160 g.) was converted to its 3,5-dinitrobenzoate derivative (see previous section) to give upon crystallization from ethanol 0.1554 g. (50% yield) of orange derivative. This material was crystallized three times from ethanol (charcoal treatment) to give 0.048 g. of derivative, m.p. 82.5–84° (decomposition, 162.5–163.5°), $[\alpha]^{25}D$ −8.37 (*c* 3.3, $CHCl_3$). The same derivative of optically pure V (m.p. 89.5–90.5°) gave $[\alpha]^{25}D$ +15.01° (*c* 3.3 $CHCl_3$). The mixed melting point of this derivative of active and racemic V gave 80.5–82°. Fractional crystallization of the filtrates from the above purification gave no material that melted above the melting point of the derivative of optically pure V (89.5–90.5°).

Infrared Analysis of Secondary–Tertiary Alcohol Mixtures from Runs 1 and 2.—The infrared spectra of pure *threo*-IV, *erythro*-IV and V were determined, and the most advantageous wave lengths for analysis selected. The absorbance of the two unknown mixtures at these wave lengths was determined. Two independent sets of three simultaneous equations were solved to give estimates of the three components. Synthetic mixtures of approximately the same composition were prepared and similarly analyzed, and the unknown mixtures were corrected to the known for deviations from Beer's law. Table V records the pertinent data. For run 2, the first set of equations gave 1% *threo*-IV, 17% *erythro*-IV and 83% V, and the second set gave 1% *threo*-IV, 19% *erythro*-IV and 80% V. For run 1, the first set of equations gave 70% of *threo*-IV, 2% of *erythro*-IV and 28% of V, whereas the second set gave 66% of *threo*-IV, 3% of *erythro*-IV and 30% of V. These values compare well with those obtained for the balance of secondary and tertiary alcohol obtained from the chromatograms.

Preparation of Formolysis Stock Solution.—Formic acid was purified by the method of Winstein and Marshall,[16] and the chloroform was purified immediately before use. A mixture of 105 ml. (1.55 g.) of chloroform in 300 ml. of formic acid was prepared, and the solution made 0.040 *N* in sodium formate with anhydrous, analytical grade reagent.

Formolysis of the Brosylate of (−)-*erythro*-2,5-Dimethyl-4-phenyl-3-hexanol (Run 4 of Table II).—A mixture of 4.78 g. of brosylate in 320 ml. of stock formolysis solution was shaken vigorously until solution was complete, and the resulting solution was held at 25.00 ± 0.01° for 23 minutes (5 titrimetric half-lives). The products were isolated as in run 2 to give 0.295 g. of olefin and 1.552 g. of a mixture of the secondary and tertiary alcohols (81% yield of products at this point). The alcohol mixture was submitted to chromatographic separation to give a secondary and tertiary alcohol fraction with a large blank fraction intervening.

The secondary alcohol fraction came to 0.137 g. of material, m.p. 68.4–69°, m.m.p. with authentic (−)-*erythro*-IV, 69.5–70.5° (see Table II for other properties). A sample of this fraction (0.0795 g.) was converted to its *p*-nitrobenzoate derivative[6] to give 0.0913 g. (67% yield) of material, m.p. 168.5–169.5° (undepressed by admixture with authentic material), $[\alpha]^{25}D$ −46.1° (*c* 3.3, $CHCl_3$). Authentic material[6] gave m.p. 168.5–170.0°, $[\alpha]^{25}D$ −47.0° (*c* 3.3, $CHCl_3$).

The tertiary alcohol fraction came to 1.189 g. (see Table II for properties). Its infrared spectrum indicated the presence of less than 2% of *erythro*-IV. A sample (0.203 g.) of this material was converted to its 3,5-dinitrobenzoate (see previous section) to give 0.257 g. (65% yield) of crude orange

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product, m.p. 87–89°, $[\alpha]^{25}D$ +12.91° (*c* 3.3, $CHCl_3$). One recrystallization of this material from ethanol (charcoal) gave 0.145 g. of pure material, m.p. 89.3–90.2°, m.m.p. with an authentic sample, 89.5–90.5°, $[\alpha]^{25}D$ +14.2° (*c* 3.3, $CHCl_3$). Fractional crystallization of the filtrates gave crops melting above the melting point of the 3,5-dinitrobenzoate of V, *e.g.*, m.p. 87–104°. This material was probably contaminated ester of VII (m.p. 133.5–134.5°).

Formolysis of Brosylate of (−)-*threo*-2,5-Dimethyl-4-phenyl-3-hexanol (Run 3 of Table II).—A mixture of 5.0 g. of the above ester and 335 ml. of formolysis stock solution was shaken until homogeneous, and the resulting solution (0.035 molar in ester and 0.041 in sodium formate) was held at 25.00 ± 0.01° for 190 minutes (5 titrimetric half-lives). The products were isolated as in run 2 to give 0.960 g. of olefin (see Table II) and 1.141 g. of alcohol fraction (91% yield of products at this point). The alcohol mixture was chromatographically separated into secondary and tertiary alcohol components with a large blank fraction intervening.

The secondary alcohol fraction came to 0.226 g. (see Table II), and possessed an infrared spectrum identical to that of *threo*-IV. Its *p*-nitrobenzoate[6] was prepared from 0.129 g. of alcohol to give 0.158 g. (71% yield), m.p. 119–122° (undepressed by admixture with an authentic sample of derivative of racemic *threo*-IV), $[\alpha]^{25}D$ −2.13° (*c* 3.3, $CHCl_3$).

The tertiary alcohol fraction came to 0.536 g., and its infrared spectrum showed the presence of not more than 3% *threo*-IV. This fraction (0.201 g.) was converted to its 3,5-dinitrobenzoate derivative to give 0.270 g. (69% yield) of light orange crystals, m.p. 72–83°, $[\alpha]^{25}D$ +9.38° (*c* 3.3, $CHCl_3$). Three recrystallizations of this material from ethanol (charcoal treatment) gave 0.0348 g. of material, m.p. 83–87°, $[\alpha]^{25}D$ +13.1 (*c* 3.3, $CHCl_3$). This material was partially racemized derivative of V. Fractional recrystallization of the second crops gave 0.001 g. of the *p*-nitrobenzoate of 2,5-dimethyl-3-phenyl-2-hexanol (VII), m.p. 131.5–132.5°, m.m.p. with authentic material, 132–133.5°.

Controls on the Olefin Products of Acetolysis and Formolysis.—A solution of 0.208 g. of olefin from acetolysis run 1 in 20 ml. of acetolysis stock solution was held at 50° for 31 hours (8 titrimetric half-lives for acetolysis of the brosylate of *threo*-IV) and reisolated (a chromatographic step was included). This treatment changed the rotation of the olefin only slightly, from $\alpha^{25}D$ −42.91° (*l* = 1 dm., neat) to −43.94° (*l* = 1 dm., neat). A similar treatment of the olefin fraction from the formolysis run 3 only changed its rotation from $\alpha^{25}D$ +54.83° (*l* = 1 dm., neat) to $\alpha^{25}D$ +55.43° (*l* = 1 dm., neat).

A solution of 0.207 g. of olefin from acetolysis run 1 in 60 ml. of formolysis stock solution was held at 25° for 190 minutes (5 titrimetric half-lives for the formolysis of the brosylate of *threo*-IV). The olefin was reisolated, but showed a strong band in the infrared corresponding to formate ester at 1715 $cm.^{-1}$. This material was treated with lithium aluminum hydride, and the product chromatographed to give 0.0027 g. of an alcohol fraction. A similar experiment with the olefin from formolysis run 3 gave similar results.

A solution of 0.207 g. of olefin from acetolysis run 2 in 65 ml. of formolysis stock solution was held at 25° for 190 minutes (5 titrimetric half-lives for the formolysis of the brosylate of *threo*-IV). The product was isolated, treated with lithium aluminum hydride and the olefin fraction isolated by chromatography as before to give 0.16 g. of material. During this treatment the properties of the olefin changed as follows: at the start, $n^{25}D$ 1.4994, $\alpha^{25}D$ −72.09° (*l* = 1 dm., neat), λ_{232} gave ε 474 (cyclohexane); at the end, $n^{25}D$ 1.5016, $\alpha^{25}D$ −84.49° (*l* = 1 dm., neat), λ_{232} gave ε 595 (cyclohexane). A second experiment was carried out identical to that above except the reaction was permitted to proceed for 14 hours (20 titrimetric half-lives). The recovered olefin fraction gave $n^{25}D$ 1.5020, $\alpha^{25}D$ −88.12° (*l* = 1 dm., neat), λ_{232} gave ε 575 (cyclohexane).

A solution of 0.210 g. of olefin from acetolysis run 1 in 70 ml. of formolysis stock solution was held at 50° for 190 minutes. The product was isolated, treated with lithium aluminum hydride, chromatographed, and the olefin fraction was reisolated. During this treatment the properties of the olefin changed as follows: at the start, $n^{25}D$ 1.4992, $\alpha^{25}D$ −42.91° (*l* = 1 dm., neat), λ_{232} gave ε 1594 (cyclohexane); at the end, $n^{25}D$ 1.5007, $\alpha^{27}D$ −47.24° (*l* = 1 dm., neat), λ_{232} gave ε 2040 (cyclohexane).

Controls on the Stability of the Tertiary Esters Formed in the Solvolyses.—The formate of V could not be prepared, so the more stable acetate of V was used in the control experiment. A solution of 0.201 g. of material was dissolved in 40 ml. of formolysis stock solution and maintained at 25° for 190 minutes. The product was isolated in the usual way, treated with lithium aluminum hydride and chromatographed to give 0.0347 g. of olefin and 0.0749 g. of an alcohol fraction. Clearly the formate of V would have been unstable under the conditions of its formation in the formolyses.

A solution of 0.0346 g. of the acetate of 2,5-dimethyl-3-phenyl-2-hexanol (VII) in 5 ml. of acetolysis stock solution was held at 50° for 31 hours (8 titrimetric half-lives of the acetolysis of brosylate of *threo*-IV). The product was isolated, treated with lithium aluminum hydride, and the alcohol and olefin separated by chromatography. The olefin fraction amounted to 0.0013 g. and the alcohol fraction to 0.0225 g. (69% recovery). This acetate appeared to decompose only slightly under the conditions of its possible formation. The similarities in structure between V and VII indicate the acetate of V should be equally stable under the acetolysis conditions.

A solution of 0.0989 g. of the acetate of VII in 30 ml. of formolysis stock solution was held at 25° for 190 minutes. Work-up of the mixture gave 0.0066 g. of alcohol (37% recovery) and 0.0214 g. of olefin. This experiment indicates that the formate of VII would have been unstable under the conditions of the formolyses, probably equilibrating with the conjugated olefins.

Control on the Dilution Effect of Racemic 2,5-Dimethyl-3-phenyl-2-hexanol (VII) in Optically Pure 2,5-Dimethyl-4-phenyl-2-hexanol (V).—A solution of 0.0392 g. of pure racemic VII in 0.0832 g. of optically pure V ($\alpha^{25}D$ +1.81°, (*l* = 1 dm., neat) was prepared and gave $n^{25}D$ 1.5013, $\alpha^{25.6}D$ +0.82 ± 0.06° (*l* = 1 dm , neat). The infrared spectrum of this mixture was essentially identical with that of an authentic sample of V.

Control on the Extent of Resolution During the Fractional Crystallization of the 3,5-Dinitrobenzoate of Partially Active 2,5-Dimethyl-4-phenyl-2-hexanol (V).—Partially optically active 4-methyl-3-phenylpentanoic acid (1.06 g., m.p. 46–47.5°) was esterified to give 1.05 g. of methyl ester, $n^{25}D$ 1.4931, $\alpha^{25}D$ −17.77° (*l* = 1 dm., neat), 53% optically pure. This material gave 0.90 g. of V, $n^{25}D$ 1.5021, 0.305 g. of which was converted to its 3,5-dinitrobenzoate. This derivative was recrystallized from ethanol. The first crop of 0.33 g., m.p. 81.5–86°, $[\alpha]^{25}D$ −7.33° (*c* 3.3, $CHCl_3$), was recrystallized to yield 0.119 g., m.p. 81–87°, $[\alpha]^{26}D$ −7.25° (*c* 3.3, $CHCl_3$). A second crop of 0.090 g., m.p. 81–84, $[\alpha]^{24}D$ −8.58° (*c* 3.3, $CHCl_3$), was recrystallized to yield 0.0483 g., m.p. 81.5–83.5°, $[\alpha]^{25}D$ −9.37° (*c* 3.3, $CHCl_3$). The mother liquor after removal of the second crop gave material, 0.0251 g., $[\alpha]^{26}D$ −7.97° (*c* 2.5, $CHCl_3$). The percentage increase in resolution with each crystallization appears to be about +5 ± 12%.

Eluent	Volume of eluent, ml.	Cut	Characteristics
32% ether in pentane	1000	1– 52	Blank
	525	53– 75	Liquid
	1800	76–147	Solid
	75	148–150	Blank
	600	151–153	Blank
100% ether	800	154–155	Liquid
	400	156	Blank

Control on the Chromatographic Separation of 2,5-Dimethyl-4-phenyl-3-hexanol (IV) and 2,5-Dimethyl-4-phenyl-2-hexanol (V).—A mixture of 0.225 g. of (−)-*erythro*-IV, $[\alpha]^{25}D$ −19.02° (*c* 3.3, $CHCl_3$) and 0.232 g. of (−)-*threo*-IV, $[\alpha]^{25}D$ −7.25° (*c* 5, $CHCl_3$) was melted and well mixed, $[\alpha]^{25}D$ −12.69° (*c* 5, $CHCl_3$). A portion (0.3083 g.) of this mixture was diluted with 0.2465 g. of racemic V, and the resulting sample was chromatographed on 166 g. of neutral alumina (3 cm. by 25 cm. column) of activity I[19] made up in pentane. The secondary alcohol was eluted from the column with 32% ether, and the tertiary with 100% ether

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(the data are summarized below). Cuts 53 through 147 were combined to give 0.23 g. of secondary alcohol, $[\alpha]^{24}D$ −12.00° (*c* 5, $CHCl_3$). Cuts 154 and 155 were combined to give 0.25 g. of tertiary alcohol, $n^{25}D$ 1.5026, $[\alpha]^{24}D$ −0.21° (*c* 5, $CHCl_3$).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA, BERKELEY]

Stereochemistry of the Primary Carbon. VI. The Reaction of Optically Active 1-Aminobutane-1-*d* with Nitrous Acid. Mechanism of the Amine–Nitrous Acid Reaction[1]

BY ANDREW STREITWIESER, JR., AND WILLIAM D. SCHAEFFER[2,3]

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The reaction of *n*-butylamine with sodium nitrite in acetic acid gives a mixture of esters in which the ratio of *n*-butyl acetate to *sec*-butyl acetate is 2:1 and a small amount of alkyl nitrates. The 1-butyl-1-*d*-acetate obtained from optically active 1-aminobutane-1-*d* is 69 ± 7% inverted, 31 ± 7% racemized. A mass spectral investigation of the product from 1-aminobutane-1,1-d_2 shows that 0% ethyl rearrangement occurs. These results in conjunction with other data lead to a complete theory for the product-determining steps of the amine–nitrous acid reaction. The fundamental tenet of this hypothesis is that the alkyldiazonium ion, the last *common* intermediate in the reaction, can undergo a number of competing reactions because of its great instability.

Introduction

Since the first example of Piria[4] and the later extended investigations of Linnemann[5] the reaction of aliphatic primary amines with nitrous acid has been used extensively in preparative and theoretical organic chemistry. In aqueous solution, the reaction generally produces alcohols and olefins, frequently with rearrangement. Although the kinetics of the reaction has been investigated[6] it pertains only to the initial phase of the reaction of the amine with a nitrous acid moiety; the product-determining steps occur later in the reaction sequence and are not amenable to direct kinetic approaches. Analogy to the aromatic series strongly suggests that diazonium ions are intermediates in the reaction.[7] The nature of the reaction products and particularly the similarity of the many rearrangement products to products of typical carbonium ion reactions have led to the interpretation of the product-determining steps of the amine–nitrous acid reaction in terms of solvolytic displacement reactions. The commonly accepted mechanism of the reaction is a competing direct displacement (SN2) on the alkyldiazonium ion by solvent (reaction 1) and a unimolecular fission of the diazonium ion (SN1) to a carbonium ion which subsequently may react with solvent to form product, eliminate a proton to yield olefin or rearrange a hydrogen or a carbon function to a new carbonium ion which ultimately results in products of such rearrangement (reaction 2).[8–11]

$$H_2O \longrightarrow R\overset{\frown}{\text{—}}N_2^+ \longrightarrow ROH + H^+ + N_2 \quad (1)$$

$$R\text{—}N_2^+ \longrightarrow N_2 + R^+ \begin{cases} \xrightarrow{H_2O} ROH + H^+ + N_2 \\ \longrightarrow \text{Olefin} + H^+ + N_2 \\ \longrightarrow N_2 + R'^+, \text{ etc.} \end{cases} \quad (2)$$

In several cases the experimental observations are in accord with this hypothesis; *e.g.*, the reactions with aqueous nitrous acid of crotylamine, α-methylallylamine, α,α-dimethylallylamine and γ,γ-dimethylallylamine yield, respectively, the same mixtures of isomeric allylic alcohols as the silver ion-catalyzed aqueous solvolyses of the corresponding chlorides[12,13]; cyclopropylcarbinylamine and cyclobutylamine on treatment with aqueous nitrous acid give similar mixtures of cyclobutanol, cyclopropylcarbinol and allylcarbinol.[12] However, in some other examples, this interpretation is clearly not a happy one. *n*-Propyl-, *n*-butyl- and *n*-amylamines, etc., give rather large amounts of secondary carbinol, the product of a rearrangement.[5,b,c,f,14] In solvolytic displacement reactions, rearrangement of *n*-primary to second-

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ary compounds is observed only by the action of strong Lewis acids; *e.g.*, Friedel–Crafts reactions with aluminum halides and alkyl halides or with boron trifluoride and alcohol. These conditions are such that either the carbonium ion intermediate is formed repeatedly or the reactivity of the nucleophilic reagent is so low that reaction with the carbonium ion is slower than the rearrangement. These conditions are not likely to be met in aqueous nitrous acid. Moreover, in the reaction of optically active secondary carbinylamines, the product alcohol possesses some optical activity.[10,15] There is an apparent inconsistency in the interpretation of the net inversion of configuration observed as resulting from direct displacement by solvent (reaction 1) for the reaction of *sec*-butylamine with nitrous acid in water yields 2-butanol with 22% net inversion although in the far less nucleophilic solvent, acetic acid, 2-butyl acetate is formed with 28% net inversion.

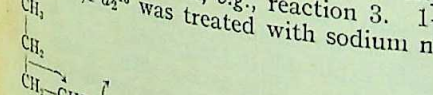
In order to specify in more detail these difficulties of the accepted mechanism, we chose to investigate the stereochemistry of a simple system in which partial rearrangement is known to occur.

Results

Treatment of a solution of *n*-butylamine in 1 *N* hydrochloric acid with sodium nitrite is reported to yield a mixture of 25% 1-butanol, 13% 2-butanol, 5% *n*-butyl chloride, 3% *sec*-butyl chloride, 30% butenes and a trace of butyl nitrites.[14f] The reaction of *n*-butylamine with sodium nitrite in acetic acid yields butenes and a mixture of *n*-butyl acetate and *sec*-butyl acetate which contains 4–8% of butyl nitrates. Reduction of this mixture with lithium aluminum hydride yields a mixture of 65% 1-butanol and 35% 2-butanol. The ratio of primary to secondary products in acetic acid is virtually identical to that found by Whitmore and Langlois[14f] in water.

Optically active 1-aminobutane-1-*d* has been described previously.[16] The 1-butyl-1-*d* acetate obtained by treatment with sodium nitrite in acetic acid corresponded to 69 ± 7% net inversion of configuration.[17] This result is remarkably similar to that obtained from *sec*-butylamine (*vide supra*).

Roberts and Halmann[14e] have reported that the *n*-propyl alcohol obtained by treatment of *n*-propylamine with nitrous acid has undergone 8.5% of methyl group rearrangement. It was necessary to establish whether an ethyl group rearrangement in the *n*-butyl case contributed importantly to the racemization observed, *e.g.*, reaction 3. 1-Aminobutane-1,1-d_2[16] was treated with sodium nitrite in



products (3)

acetic acid and the resulting mixture of esters was converted to alcohols. The primary alcohol obtained by fractionation was compared mass spectrographically with the 1-butanol-1,1-d_2 used to prepare the amine. Rearrangement of an ethyl group would produce 1-butanol-2,2-d_2 which could be detected easily in the mass spectrum, even in rather small amount. The analysis of the cracking patterns (see Appendix) indicated that none of the rearranged alcohol was present, hence 0% ethyl rearrangement had taken place in the amine–nitrous acid reaction.

It is unlikely that a significant amount of the observed racemization was due to the formation of a diazoalkane which had reacted with solvent to give racemic acetate. This reaction has been shown to be of minor importance with ethylamine[18] and is undetectable with allylic amines.[19] The mass spectral investigation of the product from 1-aminobutane-1,1-d_2 establishes that diazoalkane formation accounts for no more than about 1% of the reaction (see Appendix).

Discussion

The present stereochemical results may be compared with the results of some typical solvolyses. The acetolysis of 1-butyl-1-*d* *p*-nitrobenzenesulfonate at 114° yields 1-butyl-1-*d* acetate with 85 ± 2% net inversion. In 90% nitrobenzene–10% acetic acid at 91° the product shows 59 ± 2% net inversion and in 75% dioxane–25% acetic acid at 97°, 46 ± 2% inversion.[20] In all of these cases the amount of racemization observed is comparable to that observed in the corresponding amine–nitrous acid reaction and probably is due to the intervention of intermediates of the carbonium ion type[21]; yet, *in all of these solvolyses, no trace of rearrangement to sec-butyl compounds could be detected.* It follows that the product-determining intermediates in the amine–nitrous acid reaction must differ at least in part from the intermediates in the sulfonate acetolyses. The same conclusion may be derived from the observation that the composition of the butene mixture obtained from the reaction of *sec*-butylamine differs from that obtained by solvolysis of *sec*-butyl tosylate (*vide infra*).

If the racemized product in the acetolyses of 1-butyl-1-*d* *p*-nitrobenzenesulfonate arises from a carbonium ion intermediate which has lost asymmetry, it follows that the reaction of this intermediate with acetic acid must be considerably more rapid than a rearrangement to a secondary carbonium ion; *i.e.*, the free energy of activation for rearrangement is significantly higher than that for solvolysis. It also follows that a concerted rearrangement and expulsion of the leaving group, reaction 4, also requires considerably more energy than the direct formation of a primary carbonium ion.

(15) K. B. Wiberg, Dissertation, Columbia University, July, 1950.

(16) A. Streitwieser, Jr., and W. D. Schaeffer, This Journal, **78**, 5597 (1956).

(17) This number is obtained by a direct comparison of the rotation of the product acetate with that of acetate prepared from a sample of the same 1-butanol-1-*d* from which the amine was prepared. As discussed in the earlier paper[16] the latter preparation probably went with a single inversion of configuration and no racemization.

(18) J. D. Roberts and J. A. Yancey, This Journal, **74**, 5943 (1952).

(19) W. G. Young and D. Semenow, unpublished results; *cf.* ref. 11.

(20) A. Streitwieser, Jr., and W. D. Schaeffer, Absts. of the 129th Meeting of the American Chemical Society, Dallas, Texas, April 13, 1956, p. 52N, and unpublished results.

(21) A. Streitwieser, Jr., *Chem. Revs.*, **56**, 571 (1956).

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$$C_2H_5-\overset{H}{\underset{|}{CH}}-\overset{\curvearrowright}{CH_2}-X \longrightarrow C_2H_5\overset{+}{C}HCH_3 + X^- \quad (4)$$

In the reaction of *n*-butylamine with nitrous acid, if the *sec*-butyl products obtained are due to a process such as reaction 4 (X = N_2^+), it follows that the difference in free energies of activation between this process and the formation of a primary carbonium ion is much smaller than the corresponding difference in sulfonate solvolysis. To account for this change, we propose the following theory for the course of the product-determining steps in the amine–nitrous acid reaction.

Diazonium ions on the whole are rather unstable; because of the stability of the nitrogen molecule, the decomposition of an alkyldiazonium ion into nitrogen and a carbonium ion undoubtedly does not have high energy requirements and, indeed, may even be somewhat exothermic.[22] The activation energy is correspondingly rather small, perhaps of the order of 3–5 kcal./mole, compared to the corresponding dissociation of a primary alkyl sulfonate into carbonium ions for which the activation energy is about 30 kcal./mole.

The transition state for the decomposition of an alkyldiazonium ion more closely resembles the reactant than does the transition state for solvolysis of an alkyl sulfonate.[23] Correspondingly, the scale of energy differences for competing reactions would reasonably be expected to be compressed. Consider the following example (Fig. 1) of a system in which a

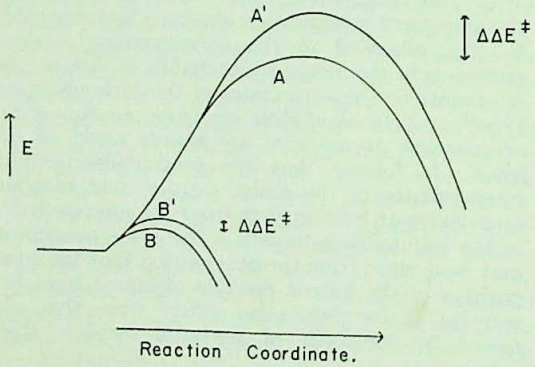
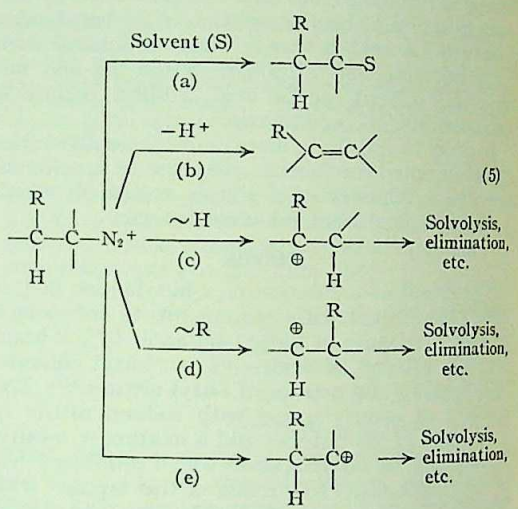


Fig. 1.—Illustrating the effect of total activation energy on the position of the transition state along a reaction coordinate and on the difference in activation energies between competing reactions.

competing concerted rearrangement (A′) requires 5 kcal./mole more energy than a "normal" solvolysis (A) having an activation energy of 25 kcal./mole; in the corresponding diazonium reaction for which the "normal" process (B) has an activation energy of, say, 5 kcal./mole, the rearrangement (B′) would require only 1 kcal./mole more energy to a first approximation. (In both cases the difference amounts to 20% of the activation energy of the "normal" reaction.) At room temperature, in the former case the rearrangement accounts for 0.02% of the product; in the latter case, 16%. Thus, a rearrangement which is not observed in solvolyses of halides and sulfonates can form a significant part of the product in the corresponding amine–nitrous acid reaction.

Because of this compressed scale of energy differences, *a number of different reactions can compete more or less successfully in various systems.* These reactions, *which derive from the diazonium ion as the common intermediate*, are summarized in reaction 5. The relative importance of each reaction is more or less predictable from modern organic chemical theory and by analogy with other reactions. In the following discussion, the theory is applied to the present results.



Reaction 5a: Direct Displacement.—One of the reactions which can compete with normal carbonium ion formation is direct displacement by solvent. The hypothesis that the structure of the transition state resembles the reactants carries the implication that the bond to the attacking solvent molecule at the transition state for displacement is long and weak. Steric hindrance effects are reduced and relatively small stereochemical differences are to be expected between primary and secondary systems. In acetic acid, *n*-butylamine reacts with 69% inversion, *sec*-butylamine with 28% inversion (*vide supra*). Since the bond to the solvent is relatively long and weak, the extent of the inversion process is expected to be relatively insensitive to the nucleophilicity of the solvent. The similarity of the stereochemical results observed for *sec*-butylamine in water and in acetic acid may be explicable in these terms.

Reaction 5b: Elimination.—The olefin obtained from *sec*-butylamine in aqueous nitrous acid consists of 25% 1-butene, 19% *cis*-2-butene and 56% *trans*-2-butene (Table I). This composition would not be expected to change significantly in acetic acid. The composition of this mixture differs greatly from the mixture of butenes obtained by the acetolysis of *sec*-butyl tosylate (Table I).[24] Of particular importance is the difference in the *cis/trans* ratio in the two cases. The olefin in the

(22) *Cf.* R. Huisgen and H. Reimlinger, *Ann.*, **599**, 183 (1956).

(23) Compare with ref. 21 and with G. S. Hammond, THIS JOURNAL, **77**, 334 (1955).

(24) H. C. Brown, M. Nakagawa, *ibid.*, **77**, 3614 (1955).

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Table I

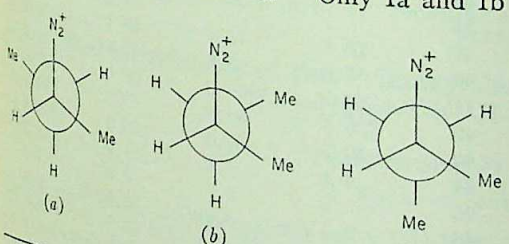
Composition of Butenes from Solvolysis and Amine–Nitrous Acid Reactions

Reaction	Butene composition, % 1-	*cis*-2	*trans*-2	Ratio *trans*/*cis*
s-BuOTs + AcOH[a]	10.3	43.2	46.5	1.1
s-BuNH$_2$ + HNO$_2$[b]	(25)[c]	19	56	2.9
n-BuNH$_2$ + HNO$_2$[b]	71	9	20	2.2
Equilibrium[d]	2	23	75	3.2

[a] At 70°; from ref. 24. [b] At room temperature. [c] By difference; direct analysis by infrared was prevented by the presence of a trace of butanol. Analysis of 2-butenes is not affected by the butanol. Less than 2% of isobutylene was present. [d] Gas at 25°; calculated from ref. 25.

sec-butyl tosylate and in similar solvolyses is considered to arise from a common carbonium ion intermediate because the olefin proportion and composition is the same when different leaving groups are used.[21,24,26] Consequently, the failure of this criterion with *sec*-butylamine demonstrates that at least part of the olefin formed in the amine–nitrous acid reaction does not arise from a carbonium ion intermediate.

An alternative is reaction 5b, a concerted elimination of a *trans*-hydrogen and nitrogen from the diazonium ion. Because the activation energy is presumed to be comparable to or less than the energy required for rotation about a carbon–carbon bond (3–4 kcal./mole for the central bond in *n*-butane[27]; undoubtedly more where groups bulkier than methyl are involved), the rates of such rotation will be of about the same magnitude or slower than the rate of decomposition. Hence, the relative populations of different conformations of the diazonium ion at the moment of formation will be important in determining the relative importance of possible subsequent reactions. In the case of 2-butylamine, three such conformations are important, Ia, b and c.[28] Ib is expected to be less populated than Ia and Ic.[29] Only Ia and Ib



I

can eliminate a *trans*-3-hydrogen; hence, consistent with the observed results, *cis*-2-butene which would arise from Ib is expected to be formed in smaller amount than *trans*-2-butene which arises from Ia. In elimination from a carbonium ion, the two types of hydrogen are conformationally equivalent and comparable amounts of the *cis*- and *trans*-olefins may be anticipated. Ic, which is relatively highly populated, cannot give a 2-butene by *trans* elimination. All three conformations (*i.e.*, the entire population of diazonium ions) can give rise to 1-butene; only a fraction of the entire population of diazonium ions (that part in Ia and Ib) can generate 2-butene; therefore, even if the specific rate constant for formation of 1-butene is somewhat lower than that for the more stable 2-butenes, a relatively large amount of 1-butene is produced in the reaction (Table I).

This hypothesis also serves to interpret the fact that in cyclohexyl systems, equatorial amines (in which there are no *trans*-hydrogens) give essentially no olefin although axial amines generally produce large amounts of olefin.[31]

Reactions 5c and 5d: Rearrangement.—Rearrangement of a hydrogen or carbon function is expected when the rearranging group is *trans* to the leaving nitrogen. However, rearrangement by reaction 5c and 5d apparently occurs only when a more stable carbonium ion results. In the case of *n*-butylamine a significant fraction of the total population of diazonium ion is expected to be in conformations having a *trans*-2-hydrogen. Such a hydrogen can eliminate (reaction 5b) or migrate (reaction 5c) perhaps by way of a common hydrogen-bridged intermediate. In cases in which the population of diazonium ions in conformations having *trans*-hydrogens is too small, no rearrangement is expected. The non-occurrence of hydrogen-rearranged products from 2,2-diphenylethylamine,[32] for example, is probably due to this cause.

It should be emphasized that because the total activation energy for reaction is presumed to be small, the rearrangements 5c and 5d should not be regarded as participations in the usual sense in which a neighboring group helps to *push* out the leaving group. Rather, these reactions are perhaps better regarded as resulting from the tendency of the leaving nitrogen to *pull* over the *trans*-group.

Reaction 5e: Carbonium Ion Formation.—The formation of a carbonium ion by loss of nitrogen, long thought to be the principal mode of decomposition of alkyl diazonium ions, is here regarded as being only one of several possible competing reactions. In the present case, the 31% racemization observed in the 1-butyl-1-*d* acetate obtained from 1-aminobutane-1-*d* is attributed to the formation in part of primary butyl-1-*d* cations which lose their asymmetry. We would expect that carbonium ions produced in the amine–nitrous acid reaction would be "normal" and would react in the

(25) F. D. Rossini, K. S. Pitzer, R. L. Arnett, R. M. Braun and G. C. Pimentel, "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," Carnegie Press, Pittsburgh, Pa., 1953, p. 475.

(26) E. D. Hughes, C. K. Ingold and U. G. Shapiro, *J. Chem. Soc.*, 1277 (1937).

(27) K. S. Pitzer, *Disc. Faraday Soc.*, **10**, 66 (1951).

(28) The notation is that of M. S. Newman, *J. Chem. Educ.*, **32**, 344 (1955).

(29) If the N_2^+ group (or its precursor) is regarded to a first approximation as equivalent to a methyl group, the 800 kcal./mole energy difference between *gauche* and *trans*-methyl groups (taken from *n*-butane) leads to relative populations in Ia, b and c of 1.0, 0.37 and 1.0, respectively.

(30) W. G. Dauben and K. S. Pitzer in M. S. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 9.

(31) (a) J. A. Mills, *J. Chem. Soc.*, 260 (1953); (b) A. K. Bose, *Experientia*, **9**, 256 (1953); (c) W. G. Dauben, R. C. Tweit and C. Mannerskantz, This Journal, **76**, 4420 (1954).

(32) L. Hellerman, M. L. Cohn and R. E. Hoen, *ibid.*, **50**, 1716 (1928).

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same manner as carbonium ions generated from other sources.[33]

Experimental

Reaction of *n*-Butylamine with Sodium Nitrite and Acetic Acid.—To a solution of 22 g. (0.30 mole) of *n*-butylamine in 200 ml. of acetic acid was added 40 g. of sodium nitrite over a period of 1 hr. at 0°. After stirring in the cold for an additional 2 hr. the mixture was allowed to warm to room temperature during 12 hr. The mixture was poured into an ice-cold solution of 200 g. of potassium hydroxide in 500 ml. of water. The resulting mixture was extracted four times with 100-ml. portions of pentane. After drying, the combined pentane extracts were distilled and yielded 13.6 ml. of material, b. 108–126°, which was a mixture of *n*-butyl acetate, *sec*-butyl acetate and *n*-butyl nitrate (identified by its intense absorption in the infrared at 6.13 μ; *sec*-butyl nitrate may have been present in small amount but was not identified), which presumably arose by a reaction with nitrate ion formed by the decomposition of nitrous acid. The nitrogen analysis (found: 0.96%)[36] corresponds to the presence of 8.2%[37] butyl nitrate. The mixture was hydrolyzed by refluxing with 25 g. of potassium hydroxide and 100 ml. of water for 24 hr. The product, 9.5 ml., b. 100–117°, still showed the presence of alkyl nitrate (infrared).

The nitrate present was cleaved with lithium aluminum hydride. After refluxing 9.2 ml. of the alcohol and nitrate mixture with 2.0 g. of lithium aluminum hydride in 35 ml. of ether, 7.9 ml. of butyl alcohols was obtained, b. 100–117°. The infrared spectrum of the mixture compared to those of the pure alcohols showed the presence of 65% of *n*-butyl alcohol and 35% of *sec*-butyl alcohol.

In a similar experiment, the butenes evolved were collected in a Dry Ice trap. Analysis of the mixture by infrared[38] gave the results in Table I. No isobutylene could be detected.

Reaction of Optically Active 1-Aminobutane-1-*d* with Sodium Nitrite in Acetic Acid.—Eleven grams (0.15 mole) of optically active 1-aminobutane-1-*d*[16] in 100 ml. of dry acetic acid was treated with 20 g. of sodium nitrite as described above. The product, 6.5 ml., b. 112–125°, had $\alpha^{25}D$ +0.206 ± 0.004° (*l* 4) and was a mixture of approximately 69% 1-butyl-1-*d* acetate, 23% 2-butyl-1-*d* acetate and 8% of alkyl nitrate. Distillation through a concentric tube column gave 2.2 ml., b. 123–126.5°, of a mixture having $\alpha^{25}D$ +0.120 ± 0.004° (*l* 2) and consisting of approximately 80% 1-butyl-1-*d* acetate, 13% 2-butyl-1-*d* acetate and 7% alkyl nitrate. The column did not function properly in this distillation. After thorough cleaning, a second fractionation gave 0.5 ml. of product having $\alpha^{25}D$ +0.052 ± 0.004° (*l* 1) and consisting of 75% 1-butyl-1-*d* acetate and 25% *n*-decane (used as a chaser in these distillations). The compositions were estimated by comparison of the infrared spectra with standard compounds. The final product, which contained no *sec*-acetate or alkyl nitrate, corresponds to a rotation for pure 1-butyl-1-*d* acetate of +0.069 ± 0.007° (*l* 1). The rotation of acetate prepared directly from the alcohol used to prepare the amine is $\alpha^{25}D$ +0.200 ± 0.004° (*l* 2).[39] Since the preparation of the amine from alcohol probably involved one inversion and no racemization,[16] it follows that the 1-butyl-1-*d* acetate formed in the amine–nitrous acid reaction is 69 ± 7% inverted, 31 ± 7% racemized.

Using this rotation for pure 1-butyl-1-*d* acetate product, the rotation of the initial product mixture corresponds to the presence of 75% of primary acetate since the 2-butyl-1-*d* acetate present is presumed to be racemic and if the rotation due to the small amount of nitrate present is neglected. Similarly, the rotation of the product from the first fractionation corresponds to the presence of 87% of 1-butyl-1-*d* acetate. These results are in reasonable agreement with the infrared spectra, especially if the nitrate present has about the same rotation as the *n*-acetate.

2-Butyl-1-*d* Acetate.—This material was prepared for infrared comparison purposes. 1,2-Epoxybutane (Dow) (6.85 g., 0.095 mole) was dropped into 1.0 g. (0.0238 mole) of lithium aluminum deuteride (Metal Hydrides, Inc., Beverly, Mass.) in 75 ml. of dry ether at a rate sufficient to maintain a gentle reflux. After refluxing for an additional two hours, the product was worked up in the usual manner. Distillation gave 5.5 g. (0.073 mole, 78%) of 2-butanol-1-*d*, b. 96–99°. The infrared spectrum of this alcohol shows important differences from 2-butanol. In addition to the C–D stretching band at 4.55 μ, other new bands appear at 7.84, 9.21 and 11.45 μ, although the peaks at 10.37 and 12.24 μ in 2-butanol are missing. In addition, other bands are changed in shape and intensity.

Part of the alcohol was converted to the acetate with acetyl chloride and pyridine.[40] In the ester, too, there are important differences in the infrared. New bands appear at 4.56 (C–D), 9.54, 10.17 and 11.76 μ; missing are the bands at 8.46, 10.04, 10.31, 11.56 and 11.95 μ present in 2-butyl acetate. There are many other differences in detail.

Reaction of 1-Aminobutane-1,1-d_2 with Sodium Nitrite in Acetic Acid.—Twenty-five grams (0.33 mole) of 1-aminobutane-1,1-d_2[16] in 226 ml. of dry acetic acid was treated with 45 g. of sodium nitrite as above and the products were isolated in the same manner. Distillation gave 16.0 g. (40% yield) of deuterated *n*- and *sec*-butyl acetates and nitrates. The mixture was reduced with 6.0 g. of lithium aluminum hydride in 100 ml. of ether and was refluxed for several hours. Distillation of the product through a glass

TABLE II

MASS SPECTRA OF DEUTERATED BUTYL ALCOHOLS

Mass no.	1-Butanol	1-Butanol-1-*d*	1-Butanol-1,1-d_2	1-Butanol-1,1-d_2 from amine
27	39.4	33.4	39.7	40.9
28	19.4	19.6	24.8	25.1
29	24.8	24.2	28.9	32.6
30	1.4	9.6	18.5	18.9
31	72.7	8.0	13.3	12.3
32	1.4	68.4	25.4	26.1
33	7.4	2.7	66.8	63.6
34	0.2	7.3	4.5	4.2
35	...	...	7.2	7.0
39	20.4	15.4	18.1	19.1
40	5.0	8.7	11.8	12.6
41	84.1	54.0	62.6	66.5
42	28.5	59.8	70.5	73.1
43	50.7	51.0	85.9	100.4
44	4.4	7.1	11.9	12.3
45	5.5	5.7	6.8	7.0
46	0.5	5.4	2.6	2.8
47	...	...	3.8	4.1
48	...	...	0.5	0.7
55	18.4	4.3	4.8	6.1
56	100.0	16.9	18.5	19.0
57	7.9	100.0	41.5	59.9
58	0.2	7.9	100.0	100.0
59	0.2	0.9	9.6	9.6
60	...	0.5	2.6	2.7
61	...	...	0.4	0.4
71	...	0.2	1.3	4.6
72	0.6	0.6	0.4	0.6
73	1.5	1.0	1.4	1.5
74	1.3	0.9	1.0	1.1
75	...	1.4	0.4	0.5
76	...	...	1.3	1.1

(33) This idea may be contrasted to the concept of "hot" or "high energy" carbonium ions having special characteristics which have been postulated in the decomposition of alkyldiazonium ions.[34,35]

(34) J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., THIS JOURNAL, **76**, 4501 (1954).

(35) D. J. Cram and J. E. McCarty, *ibid.*, **79**, 2866 (1957).

(36) Analysis by the Microanalytical Laboratory of the University of California.

(37) In another experiment, 4.3% of butyl nitrate was formed.

(38) Analysis was performed at the Shell Development Co., Emeryville, Calif., through the courtesy of Dr. D. P. Stevenson and Dr. J. W. Otvos.

(39) A. Streitwieser, Jr., and W. D. Schaeffer, THIS JOURNAL, **79**, 379 (1957).

(40) A. Streitwieser, Jr., THIS JOURNAL, **77**, 1117 (1955).

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June 5, 1957

spiral column using 2-octanol as a chaser gave the following fractions: 1, b. 96–113°, 3.9 ml.; 2, b. 113–117°, 3.1 ml.; 3, b. 117–117.4°, 3.3 ml.; 4, b. 117.4–117.5°, 1.6 ml. The infrared spectrum of fraction 4, 1-butanol-1,1-d_2, indicated the absence of deuterated secondary carbinol; however, the mass spectral cracking pattern showed the presence of an impurity which is probably 2-octanol. This cracking pattern is discussed in the appendix.

Reaction of *sec*-Butylamine with Nitrous Acid.—The object of this experiment was the analysis of the butene mixture obtained. To a solution of 20 g. (0.27 mole) of *sec*-butylamine in 300 ml. of water and 143 ml. of 3 *N* sulfuric acid (0.216 mole) was added in portions and with stirring 52.5 g. (0.229 mole) of barium nitrite. The barium nitrite was added from a flask attached with a rubber tube. The mixture was stirred at room temperature for 20 hours and the butenes produced were passed through 20% potassium hydroxide and a potassium hydroxide tower and were collected in a Dry Ice trap. The analysis of the mixture by infrared is given in Table I.[38]

Appendix

Cracking patterns for 1-butanol-1,1-d_2, and, for comparison, 1-butanol and 1-butanol-1-d, are given in Table II at an ionizing voltage of 75 v.[41] Column 4 contains the pattern for the 1-butanol-1,1-d_2 used to prepare the amine.[16] Column 5 contains the pattern for the 1-butanol-1,1-d_2 obtained from the reaction of the amine with nitrous acid (fraction 4). This material apparently contains an impurity (perhaps 2-octanol used as a chaser in the distillation) which contributes to some of the peaks. In the absence of this contribution and with no rearrangement of an ethyl group or loss of deuterium, the two patterns should be identical. The amount of $CH_3CH_2CD_2CH_2OH$ (II, product of an ethyl group rearrangement) present in the $CH_3CH_2CH_2CD_2OH$ (III) may be estimated in two independent ways: an important process in the electron impact of primary carbinols is the cleavage of the bond to the carbinol carbon with the formation of CH_2OH^+ (mass 31). To the extent that II is present in III, the 31 peak will be increased and the 33 peak lowered by a corresponding amount. Reference to Table II shows that the 33 peak is lowered (by ~5%) but the 31 peak *is not* increased by a corresponding amount; in fact, it is also lower (by 7.5%). Hence, these peaks indicate 0% rearrangement. The other fragment from the carbinol cleavage in *n*-butyl alcohol is a propyl (or isopropyl) cation, $C_3H_7^+$ (mass 43). The abnormally high 43 peak in column 5 is probably due to a contribution by the impurity. The presence of II will be manifested by an increase in the 45 peak ($C_3H_5D_2^+$). This peak is increased by only 0.2 unit which corresponds to 0.2% rearrangement but which is within the limits of the experimental uncertainties. Hence, ~0% ethyl rearrangement has occurred.

An indication may also be had of the proportion of the amine–nitrous acid reaction which proceeded through a diazobutane intermediate since an atom of deuterium would be lost in the process. The presence of an increased amount of 1-butanol-1-d would be shown by an increase in the 32 peak ($CHDOH^+$). The observed increase, 0.7 unit, corresponds to 1% of 1-butanol-1-d. This is a maximum figure because of the unknown contribution of the impurity.

Acknowledgment.—This research was supported in part by a grant from the Petroleum Research Fund of the American Chemical Society. We wish to thank Prof. Rolf Huisgen of the University of Munich and Prof. W. G. Dauben for stimulating discussions.

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(41) We are indebted to Dr. D. P. Stevenson, Shell Development Co., Emeryville, Calif., for these mass spectra.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA, BERKELEY]

Stereochemistry of the Primary Carbon. VII. The Decomposition of N-(1-Butyl-1-*d*)-N-nitrosoacetamide[1,2]

BY A. STREITWIESER, JR., AND W. D. SCHAEFFER[3]

RECEIVED SEPTEMBER 24, 1956

The thermal decomposition of optically active N-(1-butyl-1-*d*)-N-nitrosoacetamide gives an optically inactive mixture of 22% *n*-butyl acetate, 56% 1-butyl-1-*d* acetate and 22% 1-butyl-1,1-d_2 acetate. The decomposition of N-(1-butyl)-N-nitrosoacetamide in the presence of deuteroacetic acid gives butyl acetate containing some 1-butyl-1-*d* acetate. The results are interpreted by a mechanism which involves diazoalkane intermediates.

Methods for converting aliphatic amines to the corresponding alcohol or alcohol derivatives are rather limited. The most common method, the amine–nitrous acid reaction, generally furnishes low yields of alcohols frequently contaminated by rearrangement products. Consequently, considerable interest recently has been shown in the thermal decomposition of N-alkyl-N-nitrosoamides, the first examples of which are due to Pechmann[4] and Chancel.[5] Recent studies[6–9] have demonstrated the generality of this reaction which yields esters and olefins; from primary carbinylamines the corresponding esters are obtained in good yield with little or no rearrangement. White[9d] has inter-

(1) Part VI, A. Streitwieser, Jr., and W. D. Schaeffer, THIS JOURNAL, **79**, 2888 (1957).

(2) Taken in part from the dissertation of W.D.S. submitted in partial fulfillment of the degree of Doctor of Philosophy at the University of California, June, 1956.

(3) General Electric Fellow, 1955–1956.

(4) H. v. Pechmann, *Ber.*, **31**, 2640 (1898).

(5) M. F. Chancel, *Bull. soc. chim. France*, [3] **13**, 125 (1895).

(6) (a) R. Huisgen and J. Reinertshofer, *Ann.*, **575**, 174 (1952); (b) **575**, 197 (1952).

(7) G. Nischk and E. Muller, *ibid.*, **576**, 232 (1952).

(8) K. Heyns and W. v. Bedenberg, *Ber.*, **86**, 278 (1953).

(9) (a) E. H. White, THIS JOURNAL, **76**, 4497 (1954); (b) **77**, 6008 (1955); (c) **77**, 6011 (1955); (d) **77**, 6014 (1955).

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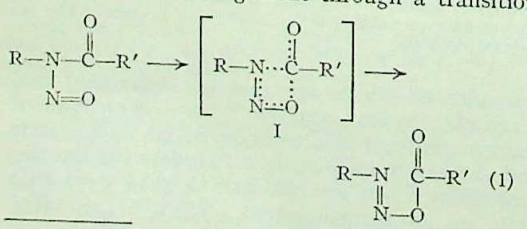
preted his stereochemical results in terms of a mechanism involving a set of cyclic transition states some of which are rather unusual and, to us, highly unlikely. It seemed clear that application of the reaction to the 1-aminobutane-1-*d* system could yield results which would be of significant interest from the standpoint of the reaction mechanism.

Results and Discussion

Optically active 1-aminobutane-1-*d*[10] was converted to N-(1-butyl-1-*d*)-N-nitrosoacetamide with acetic anhydride and nitrous acid. Since no bond to the asymmetric carbon is broken in these reactions, no loss in optical purity is expected in this sequence. The thermal decomposition of N-(*n*-butyl)-N-nitrosoacetamide in heptane solution at 85° is reported to yield 79% of *n*-butyl acetate and 16% of acetic acid.[9c] The decomposition of the deutero-nitrosoamide in cyclohexane solution at 80° gave 59% of deuterated butyl acetate having $\alpha^{25}D$ +0.005 ± 0.004° (*l* 2). 1-Butyl-1-*d* acetate of the same optical purity as the starting amine has $\alpha^{25}D$ +0.200 + 0.004° (*l* 2); hence 98 ± 2% of the optical activity has been lost. Analysis of the nitrosoamide decomposition product by comparison of its infrared spectrum with those of known mixtures showed it to consist of about 22% *n*-butyl acetate, 56% 1-butyl-1-*d* acetate and 22% 1-butyl-1,1-d_2 acetate. The analysis depended on the fact that *n*-butyl acetate is blank in the 4–5 μ region, 1-butyl-1-*d* acetate has a single intense C–D band at 4.54 μ, and 1-butyl-1,1-d_2 acetate has a C–D doublet at 4.46 and 4.63 μ, and on the differences between the three esters in the 8.5–9.0 μ region. The resulting analysis is probably better than ±5% in each component.

No mechanism involving only intramolecular transformations can account for the observed disproportionation of deuterium. A reasonable mechanism which accommodates both the complete loss of optical activity and the disproportionation of deuterium is one which involves a diazoalkane intermediate.

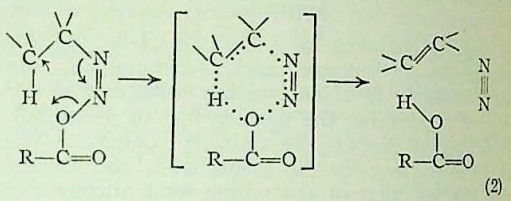
In the aromatic series the postulate that the first step in the decomposition of acylnitrosoarylamines involves an intramolecular rearrangement to the corresponding aryl diazoester[11] (equation 1) has been shown to be consistent with a variety of experimental observations.[12–15] Analogously the rearrangement through a transition



(1)

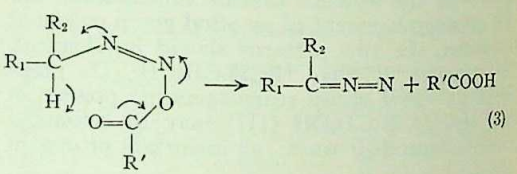
state such as I also has been postulated as the first and rate-determining step in the decomposition of aliphatic nitrosoamides.[4b,6b,9d,16,17] Huisgen and Reimlinger[17a] have recently shown that kinetic results may be accommodated readily on the basis of a rate-determining rearrangement to the diazoester; in particular, the rate pattern as a function of structure was shown to be in accord with reasonable hypotheses concerning the relative importance of steric and polar effects. Hence the reaction products may be regarded as resulting from subsequent reactions of the intermediate diazoester.

One of the subsequent reactions of the diazoester is an elimination to form olefins, nitrogen and the carboxylic acid for which the intramolecular mechanism proposed by White[9d] (reaction 2) is attractive, at least in non-polar solvents. A similar re-



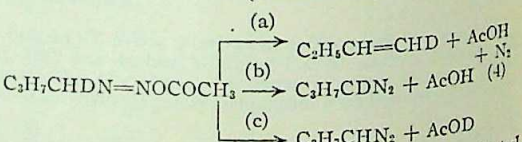
(2)

action with an α-hydrogen atom would result in the formation of a diazoalkane (reaction 3). Diazoalkanes are known to react rapidly with



(3)

carboxylic acids to form esters without rearrangement.[18,19,20] The postulate of a diazoalkane intermediate in the present case accounts for the loss of optical activity in an obvious manner. Furthermore, the deuterium migrations are readily accounted for. According to this mechanism 1-butyl-1-*d* diazoacetate can decompose by β-elimination to give acetic acid and olefin (reaction 4a), or by α-elimination to give either acetic acid and diazobutane-1-*d* (reaction 4b) or deuteroacetic acid and diazobutane (reaction 4c). The reaction



(4)

of diazobutane with acetic acid generates *n*-butyl acetate. Reaction of diazobutane-1-*d* with acetic acid or of diazobutane with deuteroacetic acid produces 1-butyl-1-*d* acetate. The reaction of diazobutane-1-*d* with deuteroacetic acid gives rise to 1-butyl-1,1-d_2 acetate.

(10) A. Streitwieser, Jr., and W. D. Schaeffer, THIS JOURNAL, 78, 5597 (1956).
(11) R. Huisgen, *Angew. Chem.*, 62, 369 (1950).
(12) R. Huisgen and L. Krause, *Ann.*, 574, 157 (1951).
(13) R. Huisgen, *ibid.*, 574, 171 (1951).
(14) D. H. Hey, J. Stuart-Webb and G. H. Williams, *J. Chem. Soc.*, 4657 (1952).
(15) D. F. DeTar, THIS JOURNAL, 73, 1446 (1951).
(16) K. Heyns and W. v. Bedenberg, *Ann.*, 595, 55 (1955).
(17) (a) R. Huisgen and H. Reimlinger, *ibid.*, 599, 161 (1956); (b) 599, 183 (1956).
(18) D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 286 (1935).
(19) A. F. McKay, W. L. Ott, G. W. Teller, M. N. Buchanan and J. F. Crooker, *Can. J. Research*, B28, 683 (1950).
(20) D. Curtin and S. M. Gerber, THIS JOURNAL, 74, 4052 (1952).

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June 5, 1957

The reaction of diazoalkanes with carboxylic acids is known to have a relatively large isotope effect; for example, the reaction of diphenyldiazomethane with acetic acid is about four times faster than the reaction with deuteroacetic acid.[21,22] Hence, if reactions 4b and 4c went at equal rates, excess deuteroacetic acid would remain at the end of the reaction (because of reaction 4a), and the product butyl acetate would manifest a net loss of some deuterium. The fact that such loss of deuterium is at most rather small suggests that the α-elimination reaction is also subject to an isotope effect; *i.e.*, reaction to 4b would seem to be faster than 4c. This point was not further investigated.

An obvious corollary of this mechanism is that the decomposition of undeuterated nitrosoamide in the presence of deuteroacetic acid should yield product ester containing some deuterium. The decomposition of N-(*n*-butyl)-N-nitrosoacetamide in cyclohexane containing 1.8 equivalents of deuteroacetic acid gave *n*-butyl acetate containing 26% of 1-butyl-1-*d* acetate; the decomposition in isopropyl ether containing 1.3 equivalents of deuteroacetic acid gave *n*-butyl acetate containing 21% of 1-butyl-1-*d* acetate.

The hypothesis also allows the interpretation of certain results in the decomposition of nitrosoamides in the presence of added salts. When N-(*n*-butyl)-N-nitrosoamide was allowed to decompose in cyclohexane in the presence of suspended sodium benzoate and calcium hydride, the ester produced was a mixture of butyl acetate and butyl benzoate. A rapid reaction of acetic acid with the sodium benzoate to form benzoic acid which reacts with the diazoester would account for the formation of butyl benzoate. The calcium hydride was used in this and in other experiments to react with the acid as produced. However, subsequent experiments demonstrated that the reaction of carboxylic acids with calcium hydride suspended in inert solvents is rather slow.

The postulate that diazoalkane intermediates are involved in the decomposition of aliphatic nitrosoamides was first offered by Heyns and Bedenberg.[8] These authors later discarded this mechanism on the basis of competition experiments[23]; for example, the thermal decomposition of a mixture of N-methyl-N-nitrosoacetamide and N-butyl-N-nitrosobutyramide without solvents gave a mixture of methyl acetate and butyl butyrate. The diazoalkane hypothesis predicts that a mixture of four esters should have resulted. Several aspects of the experimental procedure, however, seem to us to reduce the significance of these observations; *viz.*, the use of no solvent and of temperatures much higher than necessary to promote the reaction. Consequently, a competition experiment was run under conditions similar to those used generally in this investigation. When an equimolar mixture of N-ethyl-N-nitrosopropionamide and N-butyl-N-nitrosoacetamide was decomposed in hexyl ether solution at 80° for 24 hours, the product was a mixture containing comparable amounts of all four possible esters, ethyl acetate, ethyl propionate, butyl acetate and butyl propionate. A control experiment was also run in which a mixture of ethyl propionate and butyl acetate was heated in the presence of acetic acid and propionic acid in hexyl ether solution for 24 hours at 80°. The two starting esters were isolated in good yield with no evidence for the formation of ethyl acetate and butyl propionate. These results are completely consistent with the diazoalkane mechanism.

Comparison with Other Systems.—The mechanism of the nitrosoamide decomposition has been discussed by several authors, but no over-all picture has yet been presented consistent with all of the known facts. Although the present results indicate that essentially all of the decomposition of *primary* carbinyl nitrosoamides proceeds by reactions 2 and 3, the stereochemical results of White[9d] have conclusively demonstrated that these cannot be the exclusive modes of reaction in *secondary* carbinyl systems. Thus, in dioxane solution the decomposition of optically active N-(2-butyl)-N-nitrosobenzamide gave 2-butyl benzoate with about 40% retention of configuration. The intramolecular cyclic mechanism proposed by White[9d] to account for this stereochemistry would be expected, if correct, to apply at least as well to primary systems. Since our results show that the decomposition of primary alkyl nitrosoamides is actually intermolecular, the cyclic mechanism seems improbable for secondary systems.

On the other hand, the stereochemical results in secondary systems are readily accommodated by an "ion-pair" mechanism, reaction 5, analogous to that demonstrated in some decompositions of alkyl chlorosulfites.[24]

$$\mathrm{R{-}N{=}N{-}O{-}\overset{\overset{O}{\|}}{C}{-}R' \longrightarrow R^{\oplus} \cdots \ominus O_2CR' + N_2 \longrightarrow R{-}O{-}\overset{\overset{O}{\|}}{C}R' + N_2} \quad (5)$$

Reaction 5 involves a simple decomposition of the diazoester intermediate to nitrogen and a carbonium ion–carboxylate ion "ion-pair" in which the stereochemical configuration is largely preserved. Subsequent collapse of the ion-pair leads to product ester with predominant retention of configuration. Since this paper was first submitted for publication, the paper of Huisgen and Reimlinger[17b] appeared in which a similar mechanism was proposed.[25] These authors discussed the possible role of diazoalkanes without coming to definite conclusions.[26]

(21) J. D. Roberts, C. M. Regan and I. Allen, THIS JOURNAL, **74**, 3679 (1952).

(22) J. D. Roberts and C. M. Regan, *ibid.*, **74**, 3695 (1952).

(23) K. Heyns and W. v. Bedenberg, *Ann.*, **590**, 1 (1955).

(24) D. J. Cram, THIS JOURNAL, **75**, 332 (1953); C. E. Boozer and E. S. Lewis, *ibid.*, **75**, 3182 (1953).

(25) In personal discussions with Professor Huisgen, it developed that both groups had independently arrived at similar mechanisms.

(26) Huisgen and Reimlinger[17b] reported some interesting experiments which demonstrated that the reaction of diazomethane with a mixture of carboxylic acids yields the same product mixture as the decomposition of a methyl nitrosoamide in the same mixture of acids. They pointed out that these results require that either diazomethane is a common intermediate in both reactions or that diazomethane reacts with carboxylic acids to give the same intermediate (a diazonium ion–carboxylate ion ion-pair) produced in the nitrosoamide decomposition. Our present demonstration that diazoalkanes *are intermediates* in the decomposition of primary alkyl nitrosoamides indicates that the former of these alternatives is correct.

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TABLE I

INFRARED ANALYSES

Sample	Mole per cent. acetates: *n*-Butyl	1-Butyl-1-*d*	1-Butyl-1,1-d_2	log I_0/I: Found[a] 4.48μ	4.55μ	4.63μ	8.6μ[c]	Calcd.[b] 4.55μ	4.63μ
Mixt. 1	12.7	79.9	7.4	...[d]	0.652	0.180	0.07	0.625	0.180
Mixt. 2	11.1	69.8	19.1	0.160	.554	.253	.20	.569	.254
Mixt. 3	30.2	51.8	18.0	.147	.434	.219	.19	.429	.218
Reaction product	(20.4)[e]	(56.2)[e]	(23.4)[e]	.177	.473	.267	.22		

[a] For the pure liquid in a 0.095-mm. cell. The 8.6 μ band is for a 0.025-mm. cell. [b] Calculated from the equations: $\log (I_0/I)_{4.55\mu} = 0.765N_{d_1} + 0.183N_{d_2}$; $\log (I_0/I)_{4.63\mu} = 0.154N_{d_1} + 0.768N_{d_2}$. [c] For 1-butyl-1,1-$d_2$, $\log I_0/I = 1.1$. [d] Shoulder was not resolved. [e] Calculated from the found absorbancies and the equations in (*b*). The undeuterated acetate was found by difference.

However, all of the facts are explicable by the postulate that reactions 2, 3 and 5 are *competing* modes of decomposition of the diazoester. On this basis, the racemization found in secondary systems is due in large measure to the formation of a diazoalkane intermediate. In primary carbinyl systems, carbonium ion stability is so low that reaction 5 is slow compared to the formation of diazoalkane. In the chlorosulfite decomposition the formation of carbonium ion–chloride ion "ion-pairs" also has been demonstrated to be relatively slow for primary systems.[27] As the carbonium ion stability is increased the proportion of reaction *via* reaction 5 is also increased and product with increased *retention* of configuration is expected. Thus, N-(α-phenylethyl)-N-nitrosoamides give ester with greater retention of configuration (48–70% for different amides in various solvents[9d,17b,28]) than do the secondary alkyl systems.

A further corollary of the mechanism proposed here is that in reactions 3 and 5, a carboxylic acid or carboxylate ion is formed in which both oxygens become equivalent. By use of O^{18} tracer techniques, White and Aufdermarsh have recently reported that the two oxygens do, indeed, become completely equivalent.[29]

Experimental

Thermal Decomposition of Optically Active N-(1-Butyl-1-*d*)-N-nitrosoacetamide.[30]—To a 300-ml., three-necked flask equipped with stirrer, condenser and dropping funnel and containing 5.5 g. (0.075 mole) of optically active 1-aminobutane-1-*d*, $\alpha^{25}D$ −0.013 ± 0.004° (*l* 2),[10] was added 8.0 g. (0.133 mole) of acetic acid with cooling. The ice-bath was then removed and 75 ml. of acetic anhydride was added. The mixture was stirred at room temperature for 0.5 hour and was again chilled in an ice-bath. To the cold solution was added 10.0 g. (0.126 mole) of finely divided sodium nitrite in 5.0-g. portions. Additions were made 20 minutes apart. The mixture was cooled in the ice-bath for 3 hours following the addition of the sodium nitrite, and was then allowed to warm to room temperature with stirring during the next 12 hours. The reaction mixture was then poured into 300 ml. of ice and water. After stirring for several hours at room temperature until all of the acetic anhydride had hydrolyzed, the optically active nitrosoamide was extracted into two 50-ml. portions of cyclohexane. The combined cyclohexane extracts were washed with sodium hydroxide and water and were dried with sodium sulfate.

The cyclohexane solution containing the optically active nitrosoamide was transferred to a 250-ml. flask which was arranged for magnetic stirring and which contained 2.0 g. (0.048 mole) of calcium hydride. The reaction flask was fitted with a condenser carrying a drying tube and was immersed in a thermostat at 80 ± 1°. After heating for 24 hours the inorganic salts were filtered and the filtrate was distilled through a small glass spiral column. After removal of the cyclohexane, a 5.9-ml. fraction, b. 121–125°, was collected (59% yield). Redistillation of this fraction through the same column gave 3.5 ml. of deuterobutyl acetate, b. 124–125°, having $\alpha^{25}D$ +0.005 ± 0.004° (*l* 2) and d_4^{25} 0.8836.[31]

Infrared Analyses.—1-Butyl-1-*d* acetate has a single band in the C–D region at 4.55μ. 1-Butyl-1,1-d_2 acetate has a doublet at 4.48 and 4.63μ. The spectra were taken as the pure liquids in a 0.025-mm. cell against a salt plate as reference in a Baird double beam instrument. All of the spectra reported were taken under "routine" conditions; reproducibility was satisfactory. Under the same conditions the product of the nitrosoamide decomposition above had a rather broad band in the C–D region. The spectrum in this region using a 0.095-mm. cell showed a band centered at 4.54 μ with shoulders at 4.48 and 4.63μ. Three known mixtures were made up from *n*-butyl, 1-butyl-1-*d* and 1-butyl-1,1-d_2 acetates and the spectrum of each mixture was taken in both the 0.025-mm. and 0.095-mm. cells. The latter spectra in the C–D region resembled that of the reaction product and were used to analyze for the amounts of -d_1 and -d_2 acetates present. The amount of undeuterated acetate was then obtained by difference since it is blank in this region. The 8.4–9.0μ region of the former spectra provided an independent measure of the amount of -d_2 acetate present.

In Table I are given the compositions of the three mixtures and log I_0/I for the central peaks and the shoulders of the mixtures and the reaction product. For the range of compositions used the contributions of -d_1 and -d_2 to the 4.55 and 4.63μ bands were assumed to be linear. For each band, the absorbancies found and the known compositions were used in a least squares solution of three equations in the two unknowns: $\log I_0/I = aN_{d_1} + nN_{d_2}$, in which N_{d_1} is the mole fraction of 1-butyl-1-*d* acetate; N_{d_2} is the mole fraction of 1-butyl-1,1-d_2 acetate. The resulting equations (Table I) were used to calculate the absorbancies of each band for each mixture. The agreement to the observed values was generally excellent. From the equations and the absorbancies of the nitrosoamide product, the composition was calculated (Table I). The shoulder of the 4.48μ band was not resolved in mixture 1; the other mixtures were too close in -d_2 composition to allow a valid analysis based only on these points.

The spectra reproduced in Fig. 1 show that the three esters exhibit characteristic differences in the 8.4–9.0μ region. The nature of the data does not justify a complete analysis of the entire region, but the similarity of curves D and E demonstrates the essential similarity of the reaction product to a mixture such as mixture 3. The 8.6μ band in the -d_2 acetate does not appear significantly in the others and was used to estimate the amount present. Using the base line drawn from neighboring bands, log I_0/I was determined for each of the mixtures and for the reaction product. These absorbancies are roughly proportional to the mole per cent. of -d_2 ester present and gives an analysis of about 21% for the nitrosamide product.

The analyses are probably good to about ±5%; the average analysis is taken as 22% *n*-butyl acetate, 56%

(27) A. Streitwieser, Jr., and W. D. Schaeffer, THIS JOURNAL, **79**, 379 (1957).

(28) R. Huisgen, private communication.

(29) E. H. White and C. A. Aufdermarsh, Absts. of the 130th Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 18, 1956, p. 20-O.

(30) The procedure was adapted from that of [illegible]

(31) This deviation is about 5 units in the last place and corresponds to 0.90 ± 0.06 atom of deuterium per molecule.

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1-butyl-1-*d* acetate and 22% 1-butyl-1,1-d_2 acetate for the nitrosoamide reaction product.

1-Butyl-1,1-d_2 acetate.—The preparation from 1-butanol-1,1-d_2[32] and acetyl chloride was similar to that described earlier.[32]

Thermal Decomposition of N-Butyl-N-nitrosoacetamide in the Presence of Deuteroacetic Acid.—N-Butyl-N-nitrosoacetamide was prepared from 14.6 g. (0.20 mole) of *n*-butylamine as described above. However, before hydrolyzing the acetic anhydride, the reaction mixture was divided into equal parts and each part was treated separately with ice and water. When hydrolysis was complete one fraction was extracted into cyclohexane and the other fraction was extracted into isopropyl ether.

The cyclohexane solution was dried with sodium sulfate and was transferred to a 250-ml. flask which was arranged for magnetic stirring. To the mixture was added 11.0 g. (0.180 mole) of acetic acid-*d*. The flask was fitted with a condenser and drying tube and was immersed in a thermostat at 75 ± 1°. Not all of the deuteroacetic acid dissolved immediately, but after about 2 hours of heating and stirring a homogeneous solution resulted. After heating for a total of 24 hours the reaction mixture was cooled to room temperature and was washed with sodium hydroxide and water. After drying with anhydrous sodium sulfate the mixture was distilled, collecting 8.0 g. of butyl acetate, b. 124–125°. The infrared spectrum showed the presence of a C–D band at 4.54μ, the intensity of which corresponded to the presence of about 0.26 deuterium atom per molecule.

The isopropyl ether solution prepared above was dried with anhydrous sodium sulfate. Eight grams (0.131 mole) of acetic acid-*d* was added and the mixture was decomposed as above for 30 hours at 67 ± 1°. Isolation of the product as above yielded 4.5 g. of butyl acetate, b. 124–125°, which showed the presence of a C–D band in the infrared spectrum corresponding to the presence of about 0.21 deuterium atom per molecule.

Thermal Decomposition of N-Butyl-N-nitrosoacetamide in Cyclohexane in the Presence of Sodium Benzoate and Calcium Hydride.—A solution of N-butyl-N-nitrosoacetamide in 225 ml. of cyclohexane was prepared from 14.6 g. (0.20 mole) of butylamine as described above. The solution was placed in a 500-ml. flask arranged for magnetic stirring and 4.0 g. (0.029 mole) of sodium benzoate and 2.8 g. (0.067 mole) of calcium hydride was added. The reaction flask was fitted with a condenser and drying tube and was immersed in a thermostat at 80 ± 1° for 24 hours. After cooling to room temperature the solids were removed by filtration. The filtrate was distilled and yielded, after the removal of the cyclohexane, 9.2 g. of butyl acetate (40% yield based on butylamine), b. 124–125°, and 2.0 g. of butyl benzoate (40% yield based on sodium benzoate), b. 238–245°.

Thermal Decomposition of a Mixture of N-Ethyl-N-nitrosopropionamide and N-Butyl-N-nitrosoacetamide.—Five milliliters of 70% ethylamine in water (0.075 mole) was converted to the nitrosoamide as described above with 10 ml. of propionic acid and 75 ml. of propionic anhydride. After the final hydrolysis the mixture was extracted twice with 50-ml. portions of *n*-hexyl ether.

To a solution of 8.6 g. (0.075 mole) of *n*-butylacetamide in 15 ml. of acetic acid and 75 ml. of acetic anhydride in an ice-bath was added 10 g. of sodium nitrite in two portions one-half hour apart. After stirring in the ice-bath for about 10 hours the mixture was allowed to warm slowly to room temperature with stirring. The mixture was poured into 300 ml. of ice and water and was stirred for 4 hours to hydrolyze the anhydride. The mixture was then extracted with two 50-ml. portions of hexyl ether.

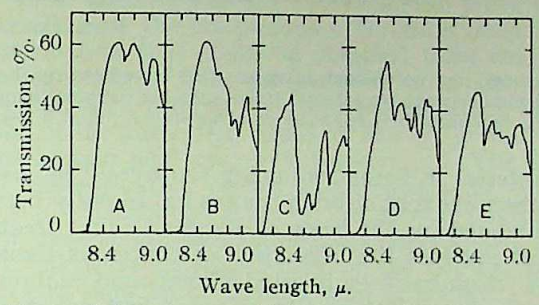

Fig. 1.—Infrared curves of butyl acetate (0.025-mm. cell): A, *n*-butyl acetate; B, 1-butyl-1-*d* acetate; C, 1-butyl-1,1-d_2 acetate; D, mixture 3; E, nitrosoamide reaction product.

The hexyl ether solutions of the two nitrosoamides were combined and were washed with water and with sodium bicarbonate. After drying with anhydrous sodium sulfate the mixture was placed in a constant temperature flask and was maintained at 80° (benzene was used as the refluxing heating bath) for 24 hours. After cooling, the mixture was washed with water and sodium bicarbonate and was dried with anhydrous sodium sulfate. The mixture was distilled until the boiling point rose to 200°. The distillate was redistilled through a spinning band column with intermittant take-off. The following fractions were taken in which the boiling points recorded are the temperatures of the thermometer at the time of take-off; 1, b. 76–81°, 2.3 ml. (ethyl acetate); 2, b. 97–102°, 2.2 ml. (ethyl acetate and ethyl propionate); 3, b. 114°, 0.3 ml.; 4, b. 121–127°, 2.2 ml. (butyl acetate and butyl propionate); 5, b. 132°, 0.3 ml.; 4, b. 142° 1.4 ml. (butyl propionate). The identifications were made by comparing the infrared spectra of the fractions with the infrared spectra of the authentic esters.

Control Stability of Esters in the Presence of Acid.—A mixture of 7.0 g. of butyl acetate (0.06 mole), 6.5 g. of ethyl propionate (0.064 mole), 0.9 g. of acetic acid (0.015 mole) and 1.1 g. of propionic acid (0.015 mole) in 200 ml. of hexyl ether was maintained for 24 hours at 80° using a constant temperature flask with benzene as the heating liquid. After cooling, the mixture was washed with water and with sodium bicarbonate and was dried with sodium sulfate. The mixture was distilled through a glass spiral column and the following fractions were collected, after redistillation of the intermediate cuts: 1, b. <96°, 0.3 ml.; 2, b. 98–103°, 7.2 ml.; 3, b. 106–120°, 1.7 ml.; 4, b. 122–128°, 5.6 ml.; 5, b. 141–170°, 1.4 ml. Fraction 1 contained no ethyl acetate and fraction 5 contained no butyl propionate (infrared). The yield of esters, b. 98–128°, is 95%.

Acknowledgment.—This research was supported in part by a grant from the Petroleum Research Fund of the American Chemical Society.

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(32) A. Streitwieser, Jr., THIS JOURNAL, **77**, 1117 (1955).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Azo Dyes Derived from *o*-Hydroxybenzeneboronic Acid Anhydride

BY HENRY GILMAN, LUDOVICO SANTUCCI, D. R. SWAYAMPATI AND R. O. RANCK

RECEIVED DECEMBER 26, 1956

Several new boron-containing azo dyes have been synthesized for testing in brain tumor therapy. Both ethylene chloride and nitrobenzene were found to be valuable recrystallizing solvents for this class of compounds. The infrared spectra of the compounds prepared show an absorption band at 9.1–9.2 μ which may be indicative of the carbon–boron bond.

Interest in boron-containing azo dyes[1,2] for use in the treatment of brain tumors has recently been stimulated by the work of Kruger.[3] This treatment involves the irradiation of cancerous tissue into which has been injected a compound containing the boron isotope 10.[4] Kruger[5] first proposed this type of therapy in 1940 and investigations along this same line have been carried out in the years following by a number of workers.[6–13] Borax was tested by Farr and co-workers,[12] and while this responded favorably to the irradiation treatment, it possessed several disadvantages, the most serious being the low differential uptake of the compound between normal and abnormal tissue,[13] the ratio being 1:2. This led to damage of a large amount of healthy tissue while the abnormal tissue was being destroyed.

Some non-boron containing dyes are absorbed preferentially by the cancerous tissue, and while many azo dyes are carcinogenic to the liver, their activity in this respect can be reduced, even to zero, by the introduction of certain groups such as the bromo, hydroxy, nitro and trifluoromethyl.[14] The azoboronic acids[1,2] which were tested by Kruger were also preferentially absorbed by the cancerous tissue, the differential uptake between the normal and abnormal tissue having a ratio of 1:100, thus indicating their superiority over borax in this respect. These encouraging results have demanded additional azoboron compounds as well as boron compounds in general for testing in the irradiation therapy of brain tumors.

In this most recent work, *o*-hydroxybenzeneboronic acid anhydride[15] was coupled with benzenediazonium chloride, *p*-bromobenzenediazonium chloride and the three nitrobenzenediazonium chloride isomers to give 2-hydroxy-5-(phenylazo)-benzeneboronic acid anhydride, 2-hydroxy-5-(*p*-bromophenylazo)-benzeneboronic acid anhydride and the three 2-hydroxy-5-(nitrophenylazo)-benzeneboronic acid anhydride isomers, respectively. Much lower yields of pure materials were obtained in these preparations than is usually experienced with dyes not containing the boronic acid or anhydride grouping. A 31% yield of pure 2-hydroxy-5-(phenylazo)-benzeneboronic acid anhydride was obtained while a 90% yield of its pure non-boron containing analog was prepared. In the case of the 2-hydroxy-5-(*p*-bromophenylazo)-benzeneboronic acid anhydride, a 20% yield of pure material was obtained while a 99% yield of the non-boron analog has been reported.[16] The three 2-hydroxy-5-(nitrophenylazo)-benzeneboronic acid anhydride isomers were all prepared in yields of less than 25%. Again the non-boron containing analogs can be prepared in much higher yields. For example, Elbs, *et al.*,[17] report a nearly quantitative yield of 4-(*o*-nitrophenylazo)-phenol. This much lower yield is partially explained by the deactivating effect of the boronic acid or anhydride group which certainly must be very pronounced in view of the electron deficiency of the boron atom. Decomposition during processing and purification perhaps also contribute to the lower yield.

Some improvement was noted in the yield and/or quality of the unpurified dye if the length of the coupling time was extended. Coupling times of 8 to 12 hr. were found to be noticeably superior to coupling times of 2 to 3 hr. For example, the melting point of the crude 2-hydroxy-5-(phenylazo)-benzeneboronic acid anhydride was increased 20 to 25° by use of this longer coupling time. There was no increase in the amount of crude material. The longer coupling time increased the amount of crude 2-hydroxy-5-(*p*-bromophenylazo)-benzeneboronic acid anhydride by 22% and raised the melting point by approximately 45°. Although this improvement probably carried through to the purified product, no such data were accumulated because of the difficulty involved in finding suitable purification procedures.

Recrystallization[18] of these dyes from an ethanol-water system, as was used by Snyder[1] for azoboronic acids derived from benzidine, failed to work satisfactorily. In most cases some purifica-

(1) H. R. Snyder and Clay Weaver, THIS JOURNAL, **70**, 232 (1948).
(2) H. R. Snyder and S. L. Meisel, *ibid.*, **70**, 774 (1948).
(3) P. G. Kruger, *Radiation Research*, **3**, 1 (1955).
(4) Naturally occurring boron contains 18.83% of this isotope. See NBS Circular No. 499, p. 7.
(5) P. G. Kruger, *Proc. Natl. Acad. Sci.*, **26**, 181 (1940).
(6) P. A. Zahl, F. S. Cooper and J. R. Dunning, *ibid.*, **26**, 589 (1940).
(7) P. A. Zahl and F. S. Cooper, *Science*, **93**, 64 (1941).
(8) P. A. Zahl and L. L. Waters, *Proc. Soc. Exper. Biol. Med.*, **48**, 304 (1941).
(9) P. A. Zahl and F. S. Cooper, *Radiology*, **37**, 673 (1941).
(10) W. H. Sweet and M. Javid, *J. Neurosurg.*, **9**, 200 (1952).
(11) M. Javid, G. L. Brownell and W. H. Sweet, *J. Clin. Invest.*, **31**, 604 (1952).
(12) L. E. Farr, W. H. Sweet, J. S. Robertson, C. G. Foster, H. B. Locksley, D. L. Sutherland, M. L. Mendelsohn and E. E. Stickley, *Am. J. Roentgenol. Radium Therapy Nuclear Med.*, **71**, 279 (1954).
(13) L. E. Farr, J. S. Robertson and E. E. Stickley, *Proc. Nat. Acad. Sci.*, **40**, 1087 (1954); E. E. Stickley, *Am. J. Roentgenol. Radium Therapy Nuclear Med.*, **75**, 609 (1956).
(14) J. P. Greenstein, "Biochemistry of Cancer," 2nd Ed., Academic Press, Inc., New York, N. Y., 1954.
(15) H. Gilman, L. Santucci, D. R. Swayampati and R. O. Ranck, THIS JOURNAL, **79**, (1957), in press.
(16) F. D. Chattaway and H. R. Hill, *J. Chem. Soc.*, **121**, 2756 (1922).
(17) K. Elbs, O. Hirschel, F. Wagner, K. Himmler, W. Turk, A. Henrich and E. E. Lehmann, *J. prakt. Chem.*, **108**, 209 (1924).
(18) In all cases where purification was accomplished by recrystallization, the crystal form, if any, was rather indefinite. The form ranged from an apparently amorphous powder to an indefinite fibrous

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tion resulted as noted by an increase in the melting point over that of the crude. However, the lack of purity was well established by either the neutralization equivalent or quantitative boron analysis, or both, on the dyes in this series.

Dry ethylene chloride[19] was found to be a good recrystallizing solvent for the 2-hydroxy-5-(phenylazo)-benzeneboronic acid anhydride, the 2-hydroxy-5-(*p*-bromophenylazo)-benzeneboronic acid anhydride and the 2-hydroxy-5-(*o*-nitrophenylazo)-benzeneboronic acid anhydride. Even though none of these compounds was exceptionally soluble in the refluxing solvent, 1 g. to 1.5 g./liter, the material recrystallized readily and was far superior with respect to melting point and neutralization equivalent to material which could be obtained from any other solvent or solvent system including benzene, benzene–petroleum ether (b.p. 77–115°), acetone–water and chloroform–carbon tetrachloride.

Both the *m*- and *p*-isomers of 2-hydroxy-5-(nitrophenylazo)-benzeneboronic acid anhydride were purified successfully using nitrobenzene as the recrystallizing solvent. The high boiling point of this solvent makes it difficult to remove from the crystals, this being best accomplished by a washing with petroleum ether (b.p. 28–38°). This particular work was carried out before that done with ethylene chloride, and these particular compounds were never subjected to recrystallization from this solvent, although it is quite possible that the ethylene chloride would be quite adequate.

In studying the purification of these azoboronic acids, the possibility of using chromatographic techniques was investigated, most of the work being carried out on 2-hydroxy-5-(phenylazo)-benzeneboronic acid anhydride and a smaller amount on the 2-hydroxy-5-(*p*-bromophenylazo)-benzeneboronic acid anhydride, the 2-hydroxy-5-(*m*-nitrophenylazo)-benzeneboronic acid anhydride and the 2-hydroxy-5-(*p*-nitrophenylazo)-benzeneboronic acid anhydride. This method looked very promising in the early stages, but it was not possible to get material of a quality equal to that which could be obtained by recrystallization from either ethylene chloride or nitrobenzene. The best results were obtained using chloroform or a chloroform–carbon tetrachloride system as the solvent and eluent and a 1:2 mixture of Celite and silicic acid as the adsorbent.

Melting points have long been regarded as a criterion of purity for most organic compounds. However, this does not seem to hold true for azoboronic acids and in general for organoboronic acids.[15,20] Materials having the same neutralization equivalent may vary considerably in melting point. The rate of heating appears to be very important, much more so for this class of compounds than for the usual organic compound. Also, a wide difference in melting point is experienced depending on whether the sample is immersed initially in an unheated bath or in a previously heated bath. For example, partially purified 2-hydroxy-5-(*p*-bromophenylazo)-benzeneboronic acid anhydride had a melting point of 183–184° when the sample was placed in a previously heated bath and a melting point of 250–251° when the sample was immersed initially in the unheated bath.

In no instance was any effort made to prove the structure of the compounds other than from the information that could be obtained from the infrared spectra. This was believed to be adequate even though little is known about the exact position of the absorption bands for the azo group and the boronic acid anhydride substituent. The first of these possibly occurs at approximately 6.35–6.4 μ,[21,22] although none of the spectra obtained for these compounds showed any sharp absorption at this wave length. Many of the boronic acid spectra show an absorption band at 9.1–9.2 μ[20] as do these azoboronic acids. This may be indicative of the carbon–boron bond, although this has not been established definitely. The greatest use of the infrared was to determine positions of substitution on the aromatic rings as well as to prove the existence of the hydroxy, nitro and bromo groups whose absorption bands are well known. Actually, the method of preparation should establish the structure reasonably well, and the color should give some evidence for the existence of the azo group while the neutralization equivalent should verify the presence of a boronic acid or anhydride group.

Additional attempts were made to produce other boron-azo compounds, but it has not yet been possible to purify these to an acceptable degree. These compounds include those formed by coupling *o*-hydroxybenzeneboronic acid anhydride with diazotized sulfanilic and *p*-aminobenzoic acids and tetrazotized benzidine.

Experimental[23]

2-Hydroxy-5-(phenylazo)-benzeneboronic Acid Anhydride.—The diazotization of 18.6 g. (0.2 mole) of aniline was carried out according to German Dyestuff information.[24] The benzenediazonium chloride solution was then added over a period of 30 minutes to a stirred solution composed of 22 g. (0.55 mole) of sodium hydroxide, 24 g. (0.2 mole) of 2-hydroxybenzeneboronic acid anhydride and 200 ml. of water, cooled to 5° by means of an ice–salt-bath; 200 g. of ice was added to the reaction flask immediately before the addition was started. Agitation was continued for 11 hr. at 0–5° following completion of the addition. The reaction mass was then filtered, the filter cake was suspended in 2000 ml. of water at 40° and was acidified by the addition of 10% hydrochloric acid. After cooling to room temperature, the precipitated solid was removed by filtration and was dried in a vacuum oven at 45°; 45 g. (100%) of crude reddish-brown material having a melting point range of 178–188° was obtained. Acidification of the filtrate from the reaction mass gave less than 1 g. of additional crude material which was combined with the bulk of the crude.

(19) Eastman Kodak white label 1,2-dichloroethane distilled over phosphorus pentoxide was used for this purpose.

(20) L. Santucci and H. Gilman, THIS JOURNAL, 79, [illegible].

(21) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 229.

(22) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 52.

(23) All melting points are uncorrected. In taking the melting points, the sample generally was immersed in a previously unheated bath. However, when it was noted that the rate of heating affected the melting point appreciably, a previously heated bath was used. The neutralization equivalents were obtained by complexing the compound with D-mannitol in an ethanol–water system and titrating with standard sodium hydroxide using a Beckman model G *p*H meter to detect the end-point.

(24) I. G. Farbenindustrie, British Intelligence Objectives Subcommittee, Report No. 1048, p. 58 (item 593).

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The crude material was washed with approximately 500 ml. of dry ethylene chloride. This removed a large portion of the impurities, the washed material now having a melting point range of 210–220°. This material was recrystallized three times from ethylene chloride to give 14 g. (31%) of bright yellow fibrous material melting at 236–238°. After each recrystallization the volume of the filtrate was reduced in order to recover the maximum amount of material. The infrared spectrum supported the expected structure.

Anal. Calcd. for $C_{12}H_9BN_2O_2$: B, 4.84; N, 12.51; neut. equiv., 224. Found: B, 5.08, 4.96; N, 12.63, 12.42; neut. equiv., 226, 227.

In an experiment where a 3-hr. coupling time was employed, the crude yield was 100% and the material had a melting point range of 150–185°. A 9-hr. coupling time gave a 94% yield of material isolated in two portions; the first had a melting point range of 170–180° and represents 21.3% of the yield while the second portion had a melting point range of 188–192° and represents 72.7% of the yield.

Chromatographic purification of this dye was studied to a reasonable extent without any outstanding success being attained. In one experiment, 2.25 g. of crude dye (m.p range 188–197°) was dissolved in 500 ml. of chloroform and was chromatographed on a column composed of 225 g. of a 1:2 mixture of Celite and silicic acid. The column was eluted with additional chloroform. Nine fractions were collected. Fractions 1 through 3 were semi-solids and represented 20% of the original weight. No melting point was obtained on this portion of the material. Fraction 4 which represented 11% of the original weight had a melting point range of 140–150°. Fractions 5 through 8 all had melting points higher than the crude, fraction 6 having the maximum range of 204–209°. This series represents 49% of the original weight. Fraction 9 was again a semi-solid, no melting point being obtained, and represents 4.5% of the original weight. Fraction 6 had a neutralization equivalent of 234 which indicates material of fair purity. The calculated value for the neutralization equivalent for the anhydride is 224.

The use of a 1:1 mixture of chloroform and carbon tetrachloride solution as the solvent and eluent was superior in one respect to chloroform alone in that sharper separations could be made but was inferior in another in that the solubility of the compound was less.

A 1:1 mixture of Celite and silicic acid showed no advantage while activated alumina was of no value whatsoever.

2-Hydroxy-5-(*p*-bromophenylazo)-benzeneboronic Acid Anhydride.—Eight and six-tenths grams (0.05 mole) of *p*-bromoaniline was diazotized according to the method of Gomberg and Bachmann.[25] This *p*-bromobenzenediazonium chloride solution was then added over a 10-minute period to a stirred solution composed of 5.5 g. (0.135 mole) of sodium hydroxide, 6.0 g. (0.05 mole) of 2-hydroxybenzeneboronic acid anhydride, 50 ml. of water and 50 g. of ice; and cooled in addition with an ice–salt-bath. Agitation was continued for 9 hr. following completion of the addition, the temperature being maintained at 0–5°. The reaction mixture was filtered, the filter cake was suspended in 500 ml. of water at 40° and was then acidified by the addition of 10% hydrochloric acid. The precipitated solid was removed by filtration after cooling to 20° and was dried at 45° in the vacuum oven. The dried material weighed 14.3 g., had a melting point range of 170–190° and represents a crude yield of 89%. Acidification of the filtrate from the reaction mass gave a small amount of additional, but worthless, material.

The brown crude material was washed with 200 ml. of dry ethylene chloride, a process which removed a large portion of the impurities, and the washed material was recrystallized three times from ethylene chloride to give 3 g. of bright yellow and rather fibrous material melting at 350–355°. This weight represents a 20% yield of pure material. After each recrystallization, the volume of the solvent was reduced in order to recover the maximum amount of material. The infrared spectrum supported the expected structure.

Anal. Calcd. for $C_{12}H_8BBrN_2O_2$: B, 3.57; Br, 26.38; neut. equiv., 302.9. Found: B, 3.95, 3.70; Br, 25.65, 25.44; neut. equiv., 308.

In an experiment where a 30-minute coupling time was employed, an 86% yield of crude material having a melting point range of 130–141° was obtained.

In the attempted chromatographic purification of this compound, 12 g. of crude (m.p. range 180–200°) was partially dissolved in 500 ml. of benzene and was poured on a column containing 450 g. of a 1:2 mixture of Celite and silicic acid. The purest material which could be obtained on elution with additional benzene had a melting point range of 210–220° which is far below that of the recrystallized material. Poorer separations were obtained when chloroform was substituted for benzene as the solvent and eluent. A mixture of chloroform and carbon tetrachloride (1:1) was superior to chloroform alone.

2-Hydroxy-5-(*o*-nitrophenylazo)-benzeneboronic Acid Anhydride.—Two and eight-tenths grams (0.02 mole) of *o*-nitroaniline was diazotized according to the method employed by Smith and Boyer.[26] The filtered *o*-nitrobenzenediazonium chloride solution was added to a stirred solution composed of 2.76 g. (0.023 mole) of 2-hydroxybenzeneboronic acid anhydride, 2.2 g. (0.055 mole) of sodium hydroxide and 25 ml. of water cooled to 0–5° by means of an ice–salt-bath. Agitation was continued for 2 hr. following completion of the addition, the temperature being maintained below 5°. The reaction mass was filtered after which the filter cake was suspended in 200 ml. of water and acidified by the addition of 10% hydrochloric acid. The product was filtered, washed and air-dried to give 4 g. of a brown product having a melting point range of 137–198°. This weight represents a 75% crude yield. Acidification of the filtrate from the reaction mixture gave a very small amount of even poorer quality material.

The crude material was recrystallized two times from benzene to give 1.3 g. of an orange colored solid melting at 213–214°. This weight represents a 24% yield of reasonably pure material. The infrared spectrum supported the structure.

Anal. Calcd. for $C_{12}H_8BN_3O_4$: N, 15.61; neut. equiv., 269. Found: N, 15.18, 15.24; neut. equiv., 290.[27]

After it was found that ethylene chloride was a good recrystallizing solvent for this type of compound, some of the benzene-recrystallized material, obtained in the experiment above, was also recrystallized from ethylene chloride. This gave orange colored material having a melting point of 236–238° and a neutralization equivalent closer to the anhydride than the material which was recrystallized from benzene.

Anal. Calcd. for $C_{12}H_8BN_3O_4$: B, 4.02; N, 15.61; neut. equiv., 269. Found: B, 4.46, 4.37; N, 15.15, 15.43; neut. equiv., 280.

In another experiment where an 8-hr. coupling time was used, a 78% yield of material having a melting point range of 150–180° was obtained. Recrystallization of this from ethylene chloride gave a 24% yield of material melting over the range of 230–235°. No chromatographic purification was attempted on this compound.

2-Hydroxy-5-(*m*-nitrophenylazo)-benzeneboronic Acid Anhydride.—To a stirred solution of 6.00 g. (0.05 mole) of *o*-hydroxybenzeneboronic acid anhydride and 10.0 g. (0.25 mole) of sodium hydroxide in 50 ml. of water, cooled to 0–5° in an ice–salt-bath, was added slowly a solution containing 6.9 g. (0.05 mole) of *m*-nitroaniline diazotized according to the method of Kaslow and Summers.[28] The alkaline reaction mixture (*p*H approximately 8) was stirred for 10 hr. at 0–5° and was then filtered. The orange filter cake was suspended in 500 ml. of water and was acidified by the addition of 10% hydrochloric acid. A 93% (12.37 g.) yield of material melting over the range of 168–180° was obtained. Acidification of the filtrate from the reaction mixture gave no appreciable amount of additional material.

The crude product was recrystallized twice from nitrobenzene, a Norit-A treatment being employed and care being taken not to heat the solution above 95°. Thorough washing of the recrystallized material with petroleum ether (b.p.

(25) M. Gomberg and W. E. Bachmann, *Org. Syntheses*, **8**, 42 (1928).

(26) P. A. S. Smith and J. H. Boyer, *ibid.*, **31**, 14 (1951).

(27) The calculated values shown in this analysis are for the anhydride. At the time this material was prepared it was believed that the acid was being formed, but later work on boron-azo compounds of this type indicated that it was more likely the anhydride. The calculated values for the acid are: N, 14.64; neut. equiv., 287.

(28) C. E. Kaslow and R. M. Summers, *Org. Syntheses*, **33**, 56 (1953).

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28–38°) was done in order to remove the nitrobenzene completely. A 20.5% (2.74 g.) yield of yellow material melting at 220–222° was obtained. The analytical sample was recrystallized a third time from nitrobenzene to give material melting at 221–222°. The infrared spectrum supported the expected structure.

Anal. Calcd. for $C_{12}H_8BN_3O_4$: C, 53.60; H, 3.00; N, 15.61; B, 4.02; neut. equiv., 269.06. Found: C, 53.73, 53.80; H, 3.27, 3.18; N, 15.39, 15.41; B, 4.00, 3.98; neut. equiv., 285.7.

In another experiment where the reaction mass was stirred at 0–5° for 8 hr., an 82.5% yield of crude material melting over the range of 144–170° was obtained. This gave a 17.5% yield of pure material.

For best results, the optimum *p*H was found to be about 8. Both sodium bicarbonate and sodium acetate were used as buffers in some experiments, but they did not seem to be particularly useful. Chromatographic purification was tried without any great success.

2-Hydroxy-5-(*p*-nitrophenylazo)-benzeneboronic Acid Anhydride.—To a stirred solution of 6.00 g. (0.05 mole) of *o*-hydroxybenzeneboronic acid anhydride and 10 g. (0.25 mole) of sodium hydroxide in 50 ml. of water, cooled in an ice–salt-bath to 0–5°, was added slowly a solution of 6.9 g. (0.05 mole) of *p*-nitroaniline diazotized according to the method of Ropp and Coyner.[29] The alkaline reaction mixture (*p*H approximately 8) was stirred at −10 to 0° for 6 hr. and was then filtered. The brick-red filter cake was suspended in 500 ml. of water, and this was acidified by the addition of 10% hydrochloric acid. A 70% (9.35 g.) yield of material melting over the range of 184–200° was obtained. Acidification of the filtrate from the reaction mixture gave an additional 0.51 g. (3.8%) of material having a melting point range of 205–225°. The combined crude materials could not be recrystallized directly from any solvent with much success. The crude was therefore extracted with a small amount of hot acetone and the residue was dissolved in 250 ml. of hot acetone. The insoluble portion was removed by filtration and the dye was reprecipitated from the filtrate by the addition of 900 ml. of warm water. The material, now having a melting point of 207–208°, was recrystallized from nitrobenzene using the procedure described above for the *m*-isomer; 1.4 g. (10.4%) of orange product melting sharply at 241.8–242° was obtained. The analytical sample was recrystallized one additional time from nitrobenzene to give material melting at 242–242.2°. The infrared spectrum supported the expected structure.

Anal. Calcd. for $C_{12}H_8BN_3O_4$: N, 15.61; B, 4.02; neut. equiv., 269.06. Found: N, 15.39, 15.16; B, 3.92, 4.22; neut. equiv., 290.1.

In another experiment an 84% yield of crude material was obtained when an 8-hr. coupling time at 0–5° was used. When the coupling time was increased to 10.5 hr., the amount of crude material did not change, but the product melted at 187° instead of over the range reported above. In this particular experiment 17% of the original *o*-hydroxybenzeneboronic acid anhydride was recovered. The pure yield was not determined exactly in these last two cases. The use of sodium bicarbonate as a buffer did not show any advantages. All of the couplings were run at a *p*H of 8. Chromatographic purification also was attempted on this compound, but it did not work very satisfactorily.

Acknowledgment.—We wish to thank Mr. Robert McCord and Mr. E. Miller Layton of the Ames Laboratory of the Atomic Energy Commission for the infrared spectra. We also wish to acknowledge the support of the Division of Biology and Medicine of the United States Atomic Energy Commission who have made this work possible. The results of the biological testing of these compounds will be reported by Dr. Otho D. Easterday of the Brookhaven National Laboratory.

AMES, IOWA

(29) G. A. Ropp and E. C. Coyner, *Org. Syntheses*, **31**, 80 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Terpenoids. XXVII.[1] The Structure of the Cactus Triterpene Myrtillogenic Acid[2]

BY CARL DJERASSI AND H. G. MONSIMER[3]

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Myrtillogenic acid has been shown to be 3β,16β,28-trihydroxy-Δ^{12}-oleanen-29-oic acid (Ia) by various degradation reactions and by conversion to longispinogenin triacetate (XIIb).

During an investigation[4] of the triterpene composition of the genus *Myrtillocactus*, there was isolated from several species in small amounts a new triterpene acid. Since this substance has not been encountered in any other genus of the cactus family, we have named it "myrtillogenic acid" and the present paper is concerned with its structure elucidation.

Myrtillogenic acid was separated from the other triterpenes as the methyl ester ($C_{31}H_{50}O_5$) and then saponified to the free acid ($C_{30}H_{48}O_5$). Mild acetylation with acetic anhydride–pyridine of either the ester or the acid led to the corresponding triacetate, thus accounting for all oxygen functions. The ease of acetylation suggested that the three hydroxyl groups were either equatorially oriented or that one or more were primary. Membership in the β-amyrin class of triterpenes was indicated[5] by the course of the selenium dioxide oxidation of triacetyl methyl myrtillogenate which furnished a $\Delta^{11,13(18)}$-diene (subsequently shown to be II) with the typical[6] triple ultraviolet absorption maxima at 240, 248 and 258 mμ.

All of the triterpene acids which have been encountered[1] so far among the *Cactaceae* contained the carboxyl group at C-17, but two different lines of evidence could be presented that this was not the case with myrtillogenic acid. Oleanolic acid (IIIa)

(1) Paper XXVI, "Cactus Triterpenes," by C. Djerassi in "Festschrift Arthur Stoll" Birkhäuser, Basel, 1957, pp. 330–352.

(2) This investigation was supported by a research grant (No. RG-3955) from the Division of Research Grants of the National Institutes of Health, U. S. Public Health Service.

(3) Taken from part of the Ph.D. dissertation of H. G. Monsimer.

(4) C. Djerassi, S. Burstein, H. Estrada, A. J. Lemin, A. E. Lippman, A. Manjarrez and H. G. Monsimer, THIS JOURNAL, in press.

(5) That this is not an unambiguous criterion, as had been believed earlier, was demonstrated recently in the case of the cactus triterpene dumortierigenin (C. Djerassi, C. H. Robinson and D. B. Thomas, *ibid.*, **78**, 5085 (1956)) which belongs to the β-amyrin series but does not react to any appreciable extent with selenium dioxide. However, a positive reaction, as was observed with myrtillogenic acid, appears to be conclusive.

(6) *Cf.* L. Ruzicka, G. Müller and H. Schellenberg, *Helv. Chim. Acta*, **22**, 767 (1939); D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.*, 257 (1951).

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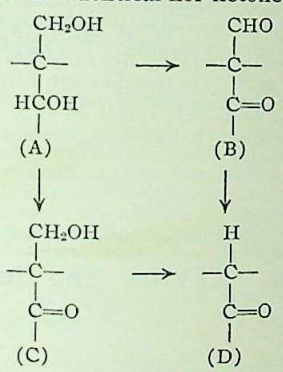
and related triterpenes are known to form bromolactones[7] and a 16β-acetoxy group does not interfere as shown by the facile formation of the bromolactone IV derived from cochalic acid (IIIc)[8] diacetate. Similar treatment of triacetyl myrtillogenic acid (subsequently shown to be Ic) led only to recovered starting material. Bromolactone formation requires the presence of a carboxyl group at C-17 as well as a double bond at 12–13, and since the presence of the latter was established by the course of the above-mentioned selenium dioxide oxidation as well as by allylic oxidation to an α,β-unsaturated 11-ketone (see Experimental), it was concluded that the carboxyl group of myrtillogenic acid was located elsewhere. Strong support for this supposition was provided by comparative saponification studies.

The methyl esters of oleanolic (IIIb), cochalic (IIId), desoxoglycyrrhetic (IIIf) and myrtillogenic (Ib) acids were refluxed for 8 hr. with 5, 7 and 10% methanolic potassium hydroxide and the extent of saponification determined quantitatively (see Table I, Experimental). The order of ease of saponification was found to be methyl myrtillogenate (Ib) > methyl desoxoglycyrrhetate (IIIf) > methyl cochalate (IIId) > methyl oleanolate (IIIb), the latter being recovered completely unchanged even after treatment with 10% alkali. The facility with which methyl myrtillogenate could be saponified—exceeding even the relatively unhindered methyl desoxoglycyrrhetate (IIIf)—definitely excluded any of the angular positions[9] as sites for the carboxyl group[10] thus leaving only C-4 and C-20 as possible points of attachment.[11]

Attention was next directed toward locating the three hydroxyl groups of myrtillogenic acid. Since the fifteen cactus triterpenes for which structures have been established[1] all possess a 3β-hydroxyl function, it was assumed that this also applied to myrtillogenic acid. The methyl ester did not react with lead tetraacetate nor did it form an acetonide, thus excluding a 1,2-glycol moiety as well as hydroxylation at C-23 or 24.[12] More precise information about the disposition of the hydroxyl groups could be adduced by oxidation experiments.

Oxidation of methyl myrtillogenate ($C_{31}H_{50}O_6$) with chromium trioxide in acetic acid–chloroform[13] led to a neutral substance ($C_{31}H_{44}O_5$), lacking hydroxyl absorption in the infrared, and mild treatment with base resulted in the loss of the elements of CO and the formation of a second neutral product ($C_{30}H_{44}O_4$). When the oxidation was carried out with chromium trioxide in pyridine solution,[14] there was isolated a new compound ($C_{31}H_{46}O_6$) which still exhibited infrared hydroxyl absorption. Treatment with base gave the above mentioned neutral product $C_{30}H_{44}O_4$, which did not show any high, selective ultraviolet absorption, did not give a color with ferric chloride but did possess a 3-keto group since its precursor exhibited a positive Zimmermann test comparable with that of β-amyrone.[15] These observations require the presence of a 1,3-glycol system of type A, chromium trioxide–acetic acid oxidation producing a keto-aldehyde B while chromium trioxide–pyridine apparently did not attack the primary hydroxyl function and led to a keto-alcohol C. Base treatment of B (reverse Claisen condensation)[16] or C (retro-aldol condensation)[17] then furnished the identical nor-ketone D.



With this information at hand it is possible by a process of elimination to reduce the structural alternatives for myrtillogenic acid to two (I or VI). The 1–3 glycol system A cannot involve C-3 since acetonide formation[12] should have been feasible. Furthermore, partial saponification of triacetyl methyl myrtillogenate (Id) under conditions where a 3β-acetoxy group is not attacked[18] gave a 3-monoacetate Ie which was oxidized with chromium trioxide–pyridine[14] to a ketone still showing a hydroxyl band in the infrared. This oxidation product is assigned structure VII since it gave a negative Zimmermann reaction[15] (absence of 3-keto function), exhibited a

(7) See E. J. Corey and J. J. Ursprung, THIS JOURNAL, **78**, 183 (1956), and earlier literature.

(8) C. Djerassi, G. H. Thomas and H. Monsimer, *ibid.*, **77**, 3579 (1955).

(9) Position 27 was eliminated at an early stage since myrtillogenic acid does not suffer decarboxylation upon melting as would be expected from a β,γ-unsaturated acid (*e.g.*, quinovic acid—H. Wieland and M. Erlenbach, *Ann.*, **453**, 83 (1927)).

(10) Suitably situated hydroxyl groups can have an activating effect (Table I—methyl oleanolate (IIIb) *vs.* methyl cochalate (IIId)) but only a carbonyl group (known to be absent in myrtillogenic acid) γ to the carboxyl group will produce a striking effect (*cf.* C. Djerassi and A. E. Lippman, THIS JOURNAL, **77**, 1825 (1955)).

(11) Since adjacent hydroxyl groups can have an effect upon the rate of saponification (ref. 10) and since the location of the hydroxyl substituents in myrtillogenic acid has not yet been discussed, both orientations (29 and 30) at C-20 should be considered. On the other hand, it is known that an axial (β) carboxyl group (24) at C-4 is extremely hindered (*e.g.*, β-boswellic acid—P. Bilham, G. A. R. Kon and W. C. J. Ross, *J. Chem. Soc.*, 35 (1942); J. L. Beton, T. G. Halsall and E. R. H. Jones, *ibid.*, 2904 (1956)), so that here only an equatorial substituent would be compatible with the experimental facts.

(12) A 3β,23-diol (W. Jacobs, *J. Biol. Chem.*, **63**, 631 (1925)) or a 3β,24-diol (J. L. Beton, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 2904 (1956)) is known to form an acetonide, but 1,3-glycols in other locations are not necessarily excluded. For instance, longispinogenin (XIIa) does not condense with acetone under standard conditions (L. E. Geller, M.S. Thesis, Wayne University, 1954; P. R. Leeming, unpublished observation).

(13) A. Zürcher, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **37**, 2145 (1954).

(14) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(15) We are greatly indebted to Drs. W. Klyne and P. M. Jones (Postgraduate Medical School, London) for carrying out the color reactions by the spectrophotometric procedure of I. E. Broadbent and W. Klyne, *Biochem. J.*, **56**, XXX (1954).

(16) Formyl ketones are very sensitive to base and lose formate under mild conditions (for pertinent examples see A. L. Wilds and C. Djerassi THIS JOURNAL, **68**, 1715 (1946)).

(17) A typical example is represented by icterogenin (D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 887 (1954)).

(18) C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins and F. Walls,

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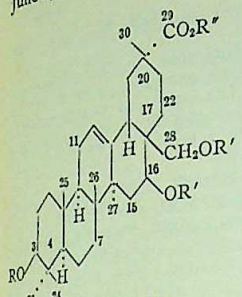
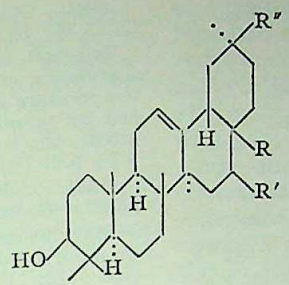
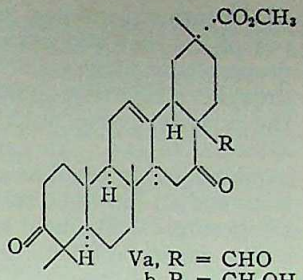


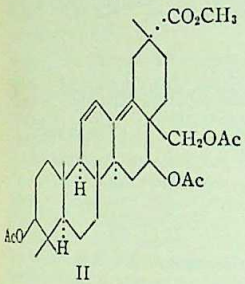
Ia, R = R′ = R″ = H
b, R = R′ = H; R″ = CH_3
c, R = R′ = Ac; R″ = H
d, R = R′ = Ac; R″ = CH_3
e, R = Ac; R′ = H; R″ = CH_3



IIIa, R = CO_2H; R′ = H; R″ = CH_3
b, R = CO_2CH_3; R′ = H; R″ = CH_3
c, R = CO_2H; R′ = OH; R″ = CH_3
d, R = CO_2CH_3; R′ = OH; R″ = CH_3
e, R = CH_3; R′ = H; R″ = CO_2H
f, R = CH_3; R′ = H; R″ = CO_2CH_3



Va, R = CHO
b, R = CH_2OH
c, R = H



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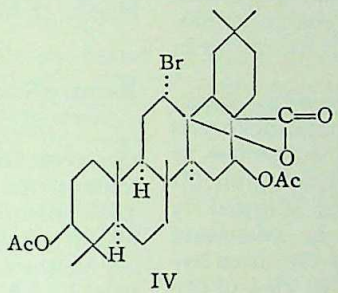
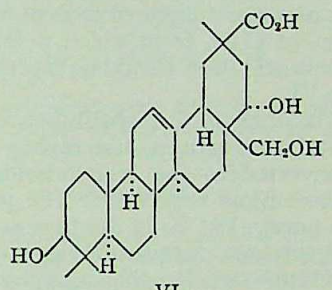
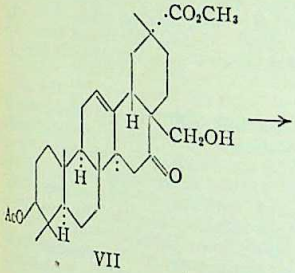


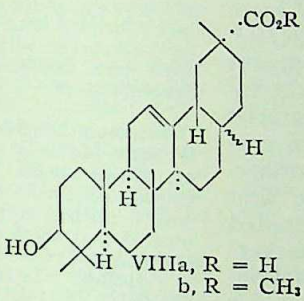
IV



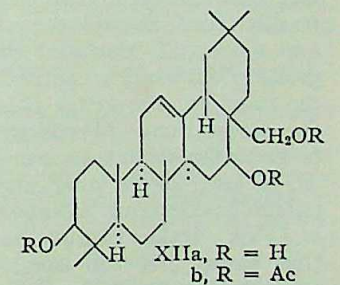
VI



VII



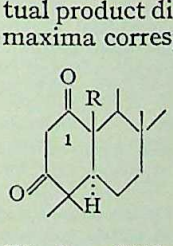
VIIIa, R = H
b, R = CH_3



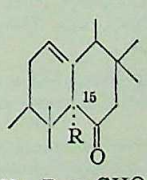
XIIa, R = H
b, R = Ac

rotatory dispersion curve suggestive of a 16-keto triterpene[19] and upon Wolff–Kishner reduction produced an acid VIIIa, further characterized as a methyl ester VIIIb, in which two of the oxygen functions had been lost. These missing oxygen atoms must have been derived almost certainly from a 1,3-glycol A *via* C followed by retro-aldolization and Wolff–Kishner reduction and cannot have involved C-3, which was protected (up to the Wolff–Kishner stage) by acetylation.

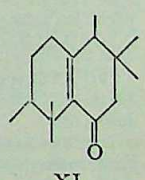
The 1,3-glycol system A cannot be located at C-1 and C-25 since the resulting keto-aldehyde B and keto-alcohol C would have to be represented by IXa and IXb. Base treatment would not only have resulted in expulsion of the angular substituent but the nor-ketone D, still possessing a 1,3-diketone moiety (IXc), would itself have been labile to base; furthermore its structure would not have been consistent with the spectroscopic properties of the product. Positions 7 and 26 were not considered seriously as sites for the glycol system A since no naturally occurring triterpenes are known which are oxygenated at those carbon atoms.[20] Finally C-15 and C-27 could be excluded since the oxidation products (B and C) would have to be represented by X (a and b) and base treatment would have led to an α,β-unsaturated nor-ketone XI, while the actual product did not show any infrared or ultraviolet maxima corresponding to such a chromophore.



IXa, R = CHO
b, R = CH_2OH
c, R = H



Xa, R = CHO
b, R = CH_2OH



XI

The above analysis indicated that the primary alcohol of the 1,3-glycol would have to be attached at C-17 or C-20. However, the latter (on the basis

(19) The use of rotatory dispersion curves for locating carbonyl groups in triterpenoids will be reported in a future paper.

(20) It was appreciated that rigorous elimination of this alternative would have to be based on an experimental connection with a known triterpene and this was eventually accomplished by conversion to longispinogenin (XIIa).

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of the earlier mentioned saponification studies) was one of the only two possible sites for the carboxyl group of myrtillogenic acid and if the primary hydroxyl function were in fact located in ring E, then the carboxyl group would have to be equatorially attached to C-4. An experimental test was now available in the pyridine–chromium trioxide oxidation product (now known to be Vb) of methyl myrtillogenate. As pointed out above, this substance had to possess a 3-keto function (positive Zimmermann test in contrast to VII), and if the carbomethoxyl group were attached to C-4, the substance would have to be a β-keto ester. Alkaline saponification followed by acidification yielded a crude acid which did not decarboxylate thus eliminating C-4 from further consideration and consequently requiring that the carboxyl group be situated at C-20. This in turn implied that the primary alcohol function of the 1,3-glycol moiety of myrtillogenic acid was at C-28, from which it follows that myrtillogenic acid itself should be expressed by structures Ia or VI.

In order to distinguish between these two structural alternatives, triacetylmyrtillogenic acid was converted to the acid chloride and subjected to Rosenmund reduction. The product was difficult to purify, but Wolff–Kishner reduction followed by acetylation furnished longispinogenin triacetate (XIIb)[21] thus locating unambiguously the three hydroxyl groups of myrtillogenic acid. In view of the fact that methyl myrtillogenate is saponified more readily than methyl desoxoglycyrrhetate (IIIf)[22] and since it is doubtful that the C-28 hydroxyl group could exert an activating effect upon the ester function, the latter is assigned the equatorial (α) orientation. Myrtillogenic acid (Ia) can now be given the systematic name 3β,16β,28-trihydroxy-Δ^{12}-oleanen-29-oic acid and represents the first naturally occurring triterpene which is oxygenated at C-29. It has already been pointed out earlier[1] that except for the usual 3β-hydroxyl function, oxygenation among cactus triterpenes has so far been found only in rings D and E. It is interesting to note that myrtillogenic acid falls into that same pattern which may eventually prove to be of some biogenetic significance.

Experimental[23]

Myrtillogenic Acid and Derivatives.—Crude methyl myrtillogenate (Ib), obtained by chromatography of the methylated acidic fraction of various *Myrtillocactus* species,[4] was recrystallized several times from methanol–acetone to yield an analytical sample, m.p. 249–250°,[24] $[\alpha]_D$ +85° (*c* 2.14), λ_{max}^{KBr} 3.0 and 5.79 μ.

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03. Found: C, 73.81; H, 10.21.

Triacetyl methyl myrtillogenate (Id) was obtained by acetylation of Ib with acetic anhydride–pyridine at room temperature overnight. The analytical sample was purified by chromatography followed by recrystallization from methanol; m.p. 146.5–148°, $[\alpha]_D$ +77° (*c* 0.75); $\lambda_{max}^{CHCl_3}$ 5.78, 5.81 (inflect.) and 8.0 μ.

Anal. Calcd. for $C_{37}H_{56}O_8$: C, 70.67; H, 8.98; acetyl, 20.27. Found: C, 70.88; H, 9.09; acetyl, 20.57.

Myrtillogenic acid (Ia) was obtained by saponification of its methyl ester with 10% methanolic potassium hydroxide (see Table I) and was recrystallized several times from acetone and then from methanol; m.p. 288–293°, $[\alpha]_D$ +84° (*c* 0.74 in methanol).

Anal. Calcd. for $C_{30}H_{48}O_5$: C, 73.73; H, 9.90. Found: C, 73.69; H, 9.91.

Acetylation of the acid Ia with acetic anhydride–pyridine and recrystallization from methanol furnished an analytical sample of **myrtillogenic acid triacetate** (Ic), m.p. 259–263°, $[\alpha]_D$ +65° (*c* 1.03).

Anal. Calcd. for $C_{36}H_{54}O_8$: C, 70.33; H, 8.85; O, 20.81. Found: C, 70.47; H, 9.20; O, 20.42.

TABLE I

RATES OF SAPONIFICATION OF TRITERPENE METHYL ESTERS[a]

Methyl ester \ Concn. of MeOH–KOH	5%	7%	10%
	Yield of acid %		
Oleanolate (IIIb)	0	0	0
Cochalate (IIId)	0	3	20
Desoxoglycyrrhetate (IIIf)	5	17(13)[b]	47(40)[b]
Myrtillogenate (Ib)	11	31	85(93)[b]

[a] A 100-mg. sample of the methyl ester was heated under reflux for 8 hr. in 5, 7 or 10% methanolic potassium hydroxide solution, much water was added and the unreacted ester was extracted with ether. The aqueous solution was acidified, extracted with ether, washed, dried and evaporated. Both ester and acid fractions were weighed. [b] Duplicate determination.

Selenium Dioxide Oxidation of Triacetyl Methyl Myrtillogenate (Id).—A solution of 125 mg. of triacetyl methyl myrtillogenate and 125 mg. of selenium dioxide in 10 cc. of glacial acetic acid was heated under reflux for 6 hr., diluted with water and extracted with ether. The residue from the washed and dried ether solution was chromatographed on alumina and recrystallized from methanol to furnish 76 mg. of methyl 3β,16β,28-triacetoxy-$\Delta^{11,13(18)}$-oleadien-29-oate (II), m.p. 178–180°; λ_{max}^{EtOH} 240, 248, and 258 mμ; log ϵ 4.38, 4.42 and 4.23.

Anal. Calcd. for $C_{37}H_{54}O_8$: C, 70.90; H, 8.68. Found: C, 71.07; H, 8.71.

Methyl 3β,16β,28-Triacetoxy-Δ^{12}-oleanen-11-one-29-oate.[25]—To a boiling solution of 200 mg. of triacetyl methyl myrtillogenate (Id) in 2 cc. of glacial acetic acid was added 208 mg. of chromium trioxide in 2 cc. of 90% acetic acid over a period of 30 minutes. After heating for an additional hour, the mixture was allowed to stand overnight and then diluted with water. The product was extracted with ether and recrystallized from methanol whereupon it showed a double m.p. at 159–163° and 190–192°. Chromatography and recrystallization gave material which partially melted near 150°, resolidified and melted at 192–195°, λ_{max}^{EtOH} 245 mμ, log ϵ 4.13.

Anal. Calcd. for $C_{37}H_{54}O_9$: C, 69.13; H, 8.47. Found: C, 68.58; H, 8.59.

Chromium Trioxide Oxidation of Methyl Myrtillogenate (Ib). (a) **With Chromium Trioxide–Acetic Acid–Chloroform.**[13]—To an ice-cooled solution of 250 mg. of methyl myrtillogenate (Ib) in 100 cc. of acetic acid and 10 cc. of chloroform was added over a period of 10 min. 565 mg. of chromium trioxide dissolved in 5 cc. of water and 15 cc. of acetic acid. After 75 min. at room temperature, the excess reagent was destroyed with methanol, water was added and the product was extracted with ether. The ether solution was washed with 5% potassium hydroxide, water, dried and evaporated to afford 240 mg. of semi-solid which crystal-

(21) C. Djerassi, R. N. McDonald and A. J. Lemin, THIS JOURNAL, **75**, 5940 (1953); C. Djerassi, L. E. Geller and A. J. Lemin, *ibid.*, **76**, 4089 (1954).

(22) The axial orientation of the carboxyl group in glycyrrhetic acid (and consequently also in desoxoglycyrrhetic acid (IIIe)) has been established by J. M. Beaton and F. S. Spring, *J. Chem. Soc.*, 3126 (1955).

(23) Melting points were determined on the Kofler block. Unless noted otherwise, all rotations were measured in chloroform solution in 1 dcm. tubes. We are indebted to Mrs. Dolores Phillips for all ultraviolet and infrared spectral measurements. The microanalyses were performed by Dr. A. Bernhardt (Mülheim, Germany) and by Mr. Joseph F. Alicino (Metuchen, N. J.).

(24) The melting point was depressed by over 50° when mixed with the isomeric methyl arjunolate (m.p. 248–250°, $[\alpha]_D$ +68°). We are indebted to Prof. F. E. King (Nottingham) for a sample (F. E. King, T. J. King and J. M. Ross, *J. Chem. Soc.*, 3995 (1954)).

(25) This experiment was carried out by Dr. A. E. Lippman.

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ized upon trituration with methanol (m.p. 150–200°). Chromatography on Merck acid-washed alumina and recrystallization from methanol afforded 69 mg. of methyl Δ^{12}-oleanen-3,16-dione-28-al-29-oate (Va), m.p. 202–204°, $\lambda_{max}^{CHCl_3}$ 5.79 and 5.86 μ but no free hydroxyl band.

Anal. Calcd. for $C_{31}H_{44}O_5$: C, 74.96; H, 8.93. Found: C, 74.86; H, 9.14.

(b) With Chromium Trioxide–Pyridine.[14]—A solution of 150 mg. of methyl myrtillogenate and 180 mg. of chromium trioxide in 18 cc. of pyridine was allowed to stand at room temperature overnight. After adding much water, the material was extracted with ether, washed well with dilute hydrochloric acid, dried, evaporated and triturated with hexane to give 140 mg. of crystals, m.p. 175–190°. Several recrystallizations from methanol led to the analytical sample of methyl Δ^{12}-oleanen-3,16-dione-28-ol-29-oate (Vb), m.p. 189–192°, $[\alpha]_D$ +47° (*c* 0.32); $\lambda_{max}^{CHCl_3}$ 2.95,[26] 5.80 and 5.87 μ. The rotatory dispersion curve[19] was very similar to that of methyl diketoechinocystate and the Zimmermann reaction over the range 300–700 mμ closely resembled that of β-amyrone.[15]

Anal. Calcd. for $C_{31}H_{46}O_5$: C, 74.66; H, 9.30. Found: C, 74.96; H, 8.90.

When 110 mg. of the oxidation product Vb was heated under reflux for 1 hr. with 25 cc. of 1% methanolic potassium hydroxide and extracted with ether, there was obtained 100 mg. of an oil. Chromatography and elution with benzene gave 90 mg. of solid, m.p. 175–190°, raised after several recrystallizations from methanol to m.p. 203–205°, $[\alpha]_D$ −25° (*c* 0.25), $\lambda_{max}^{CHCl_3}$ 5.78 and 5.83 μ, no strong ultraviolet absorption, negative ferric chloride reaction. The identical substance (mixture melting point and infrared comparison) was obtained when the oxidation product of procedure (a) was heated with 5% methanolic potassium hydroxide solution for 4 hr.

Anal. Calcd. for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46; O, 13.66. Found: C, 77.18; H, 9.70; O, 13.13.

When the oxidation product Vb was heated under reflux for 12 hr. with 10% methanolic potassium hydroxide solution, ether extraction did not remove any material. Acidification followed by ether extraction yielded in nearly quantitative yield an acidic oil which resisted all attempts at crystallization. As pointed out in the discussion, the isolation of an acid eliminates a β-keto ester formulation for Vb and *ipso facto* C-4 as the point of attachment of the carboxyl group of myrtillogenic acid.

Partial Saponification of Triacetyl Methyl Myrtillogenate (Id).—The triacetate (100 mg.) in 34 cc. of methanol was heated for 40 minutes with 2.6 cc. of a solution of 6.3 g. of potassium carbonate in 90 cc. of 1:1 dioxane–water,[18] about 15 cc. of methanol being distilled off during that time. The crude, ether-extracted product was chromatographed on 5 g. of Merck acid-washed alumina. Benzene removed 20 mg. of unreacted triacetate while 1:1 ether–chloroform yielded 56 mg. of the desired **methyl myrtillogenate 3-monoacetate (Ie)**, m.p. 274–280°. Further elution with chloroform–methanol (9:1) furnished 10 mg. of methyl myrtillogenate (Ib). The analytical sample of the monoacetate was obtained from methanol, m.p. 300–302°, $[\alpha]_D$ +77° (*c* 0.90); $\lambda_{max}^{CHCl_3}$ 2.90, 5.78 and 8.00 μ.

Anal. Calcd. for $C_{32}H_{52}O_6$: C, 72.75; H, 9.62; O, 17.63. Found: C, 72.76; H, 9.56; O, 18.01.

Chromium Trioxide–Pyridine Oxidation of Methyl Myrtillogenate 3-Monoacetate (Ie).—The oxidation was carried out exactly as described above for methyl myrtillogenate (Ib) and the crude product (m.p. 225–230°) upon recrystallization from chloroform–methanol yielded the analytical sample of **methyl Δ^{12}-oleanen-3β,28-diol-16-one-29-oate 3-acetate (VII)**, m.p. 237–239°, $[\alpha]_D$ +7° (*c* 0.53), negative Zimmermann reaction,[15] no high selective ultraviolet absorption; λ_{max}^{KBr} 2.90, 5.79, 5.84 and 8.00 μ. The rotatory dispersion curve[19] was very similar to that of methyl 16-keto-oleanolate.

Anal. Calcd. for $C_{33}H_{50}O_6$: C, 73.03; H, 9.29; O, 17.69. Found: C, 72.72; H, 9.54; O, 17.74.

Wolff–Kishner reduction of 114 mg. of VII by the Huang-Minlon modification[27] using hydrazine hydrate, ethylene glycol and potassium hydroxide gave 82 mg. of crude acid (m.p. 230–240°) which melted at 280–284° after two recrystallizations from methanol; it is most likely **3β-hydroxy-28-nor-Δ^{12}-oleanen-29-oic acid (VIIIa)**.

Anal. Calcd. for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.76; H, 10.78.

The mother liquors from the above recrystallizations were methylated with diazomethane and the resulting **methyl ester VIIIb** was recrystallized from methanol; m.p. 191–193°, $[\alpha]_D$ +60° (*c* 1.37), $\lambda_{max}^{CHCl_3}$ 2.8 and 5.77 μ. The analysis was not satisfactory, but insufficient material was available for a repetition.

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.07; H, 11.07.

Conversion of Triacetylmyrtillogenic Acid (Ic) to Longispinogenin Triacetate (XIIb).—Triacetylmyrtillogenic acid (750 mg.) was converted into the acid chloride by heating under reflux for 45 min. with 2 cc. of thionyl chloride. Benzene was added and all volatile material removed *in vacuo* on the steam-bath.

The crude acid chloride, dissolved in 30 cc. of xylene, was stirred at 120° with 0.8 g. of palladium–barium sulfate catalyst and 0.1 cc. of sulfur–quinoline poison, and hydrogen gas was bubbled for 3 hr. through the solution. The crude product, obtained by filtration, washing with dilute sodium hydroxide, water, drying and evaporation was chromatographed on 20 g. of alumina. Benzene elution afforded 500 mg. of solid (m.p. 188–194°), the melting point range of which could not be sharpened even after repeated crystallization from methanol.

A 350-mg. sample of the Rosenmund reduction product was subjected to Wolff–Kishner reduction[27] with 30 cc. of ethylene glycol, 1.5 cc. of hydrazine hydrate and 1.5 g. of potassium hydroxide. The total product was acetylated with acetic anhydride–pyridine and chromatographed on 10 g. of Merck acid-washed alumina. Elution with benzene and recrystallization from methanol yielded 110 mg. of **longispinogenin triacetate**, m.p. 220–222°, $[\alpha]_D$ +68° (*c* 0.64), which was shown to be identical with an authentic sample[21] by mixture melting point determination and infrared spectral comparison (Nujol mull).

Miscellaneous Experiments with Myrtillogenic Acid.—Methyl myrtillogenate was recovered in nearly quantitative yield when subjected to acetonide formation conditions[12] (acetone–hydrochloric acid or acetone–sulfuric acid). Triacetylmyrtillogenic acid was recovered unchanged under conditions where diacetylcochalic acid formed a bromolactone.

Diacetylcochalic Acid Bromolactone (IV).—A methylene chloride solution of 107 mg. of diacetylcochalic acid[8] was treated dropwise with 0.013 cc. of bromine in 1 cc. of methylene chloride, decolorization occurring immediately. Removal of the solvent and crystallization of the solid from methanol–methylene chloride gave 95 mg. of the desired bromolactone IV, m.p. 296–298°, $[\alpha]_D$ +60° (*c* 1.12); $\lambda_{max}^{CHCl_3}$ 5.61, 5.78 and 8.00 μ.

Anal. Calcd. for $C_{34}H_{51}BrO_6$: C, 64.24; H, 8.09; Br, 12.57; O, 15.10. Found: C, 63.70; H, 8.08; Br, 12.95; O, 15.41.

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(26) The presence of a hydroxyl group was confirmed further by acetylation with acetic anhydride–pyridine. The resulting oil could not be crystallized but its infrared spectrum now lacked absorption in the 3 μ region and showed an intense band at 8.0 μ, not present in the starting material.

(27) Huang-Minlon, THIS JOURNAL, **71**, 3301 (1949).

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

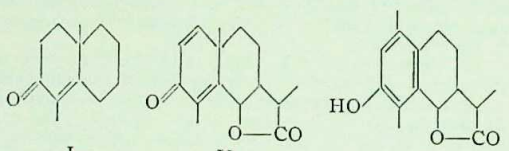
Synthesis of 4-Methylated Steroids[1]

BY FRANZ SONDHEIMER AND YEHUDA MAZUR

RECEIVED DECEMBER 18, 1956

Two methods of synthesis of 4-methyl-Δ^4-cholesten-3-one (Xa) are described. The first involves the reaction of the enol lactone VIa with ethylmagnesium bromide, followed by treatment with base. The second, which proceeds only in poor yield, involves the direct monomethylation of Δ^4-cholesten-3-one (IVa). The first method is applied to the synthesis of 4-methyltestosterone (Xb) and 4-methylprogesterone (Xd). 4-Methyltestosterone acetate (Xc) is dehydrogenated with selenium dioxide to 4-methyl-1-dehydrotestosterone acetate (XIc), which on dienone–phenol rearrangement and saponification produces 1,4-dimethylestradiol (XIIb). This rearrangement is an exact parallel in the steroid series to the santonin–desmotroposantonin rearrangement.

The possibility that a substance isolated in these laboratories from grapefruit oil was a 4-methylated steroid first aroused our interest in this class of compound. Such substituted steroids, in particular the 4-methyl-Δ^4-3-ketones (type X), were unknown, although in the bicyclic series the analogous 3-keto-4,9-dimethyl-Δ^4-octahydronaphthalene (I)[2] and substituted derivatives are well known. Thus, the sesquiterpenes α-cyperone[3a] and carissone[3b] contain the system I, and other derivatives have been



I II III

described in connection with studies related to the synthesis of santonin (II).[4] 4-Methylated steroidal Δ^4-3-ketones have furthermore become of considerable interest recently in view of the announcement that certain steroidal Δ^4-3-ketones methylated at the C-2 position possess higher biological activities than the unmethylated hormones.[5]

The preparation of a 4-methyl-Δ^4-3-ketone was first investigated in the cholesterol series. Two successful routes were found, both proceeding from Δ^4-cholesten-3-one (IVa) itself. The first utilized the enol lactone VIa, readily prepared from IVa through ozonolysis to the keto-acid Va, followed by heating with sodium acetate and acetic anhydride.[6] It is known that the enol lactone on reaction with methylmagnesium iodide, followed by base cyclization of the product, regenerates Δ^4-cholesten-3-one in high yield.[7] The analogous treatment of VIa with ethylmagnesium bromide when carried out with one equivalent at room temperature or below (conditions which have been used with the methyl Grignard reagent[6b,7a,8]) was unsatisfactory. However, when an excess of ethylmagnesium bromide was used in refluxing ether–benzene, the required 4-methyl-Δ^4-cholesten-3-one (Xa) was obtained in 65% yield after base cyclization.[9] The structure of Xa was confirmed by the infrared spectrum which indicated the presence of an α,β-unsaturated ketone and especially by the ultraviolet spectrum. The latter (λ_{max} 251 mμ, log ϵ 4.18) is in good agreement with the value (λ_{max} 252 mμ) to be expected of an α,β,β-trisubstituted α,β-unsaturated ketone with one exocyclic double bond.[10] Other substances containing the same chromophoric system as Xa have been shown to exhibit similar absorption (λ_{max} 248–251 mμ, log ϵ 4.13–4.21).[2,3,4,6b]

The substance produced by the reaction of Δ^4-cholesten-3-one with the ethyl Grignard reagent, which on base treatment furnishes the 4-methyl-Δ^4-3-ketone Xa, is presumably the unsaturated hemiketal VIIa or the corresponding diketone (*cf.* ref. 7b). No attempt at isolation of this intermediate was made in view of the known lability of the corresponding methyl compound.[7b] However, two further substances were produced by the Grignard reaction and could be isolated after the base treatment. The more polar of the two was a comparatively high melting substance, saturated to tetranitromethane, exhibiting an associated hydroxyl band at 3.08 μ, but no carbonyl bands in the infrared. The empirical formula appeared to be $C_{59}H_{54}O_2$, and we believe this compound to be the hemiketal VIIIa derived from VIa by reaction with two equivalents of the Grignard reagent. It has previously been reported[6b] that enol lactones of type VI on reaction with methylmagnesium iodide may yield a polar high-melting "over-reacted" product which very probably has a structure analogous to VIII. The other substance obtained from VIa and ethylmagnesium bromide was less polar than the 4-methyl-Δ^4-3-ketone Xa, was unsaturated to tetranitromethane and in the infrared showed no hydroxyl band but a medium intensity band at 5.98 μ. The empirical formula was $C_{30}H_{52}O$ and all these observations are consistent with the enol

(1) Presented in part at the 19th Meeting of the Chemical Society of Israel, June 11, 1956 (*cf. Bull. Research Council Israel*, **5A**, 283 (1956)).

(2) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1437 (1952); F. J. McQuillin, *ibid.*, 528 (1955); M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956).

(3) (a) *Inter al.* R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 2423 (1955), and previous papers; (b) K. Mohr, O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **37**, 462 (1954); D. H. R. Barton and E. J. Tarlton, *J. Chem. Soc.*, 3492 (1954).

(4) *Inter al.* Y. Abe, *et al.*, THIS JOURNAL, **75**, 2567 (1953); **78**, 1416, 1422 (1956).

(5) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *ibid.*, **77**, 6401 (1955).

(6) (a) R. B. Turner, *ibid.*, **72**, 579 (1950); (b) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

(7) (a) G. I. Fujimoto, *ibid.*, **73**, 1856 (1951); (b) R. D. H. Heard and P. Ziegler, *ibid.*, **73**, 4036 (1951).

(8) *Cf.* L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, *ibid.*, **76**, 5014 (1954).

(9) After completion of this part of our work, we were informed by Prof. E. R. H. Jones that this substance had also been prepared in his laboratory. An account of this preparation has now been published (G. D. Meakins and O. R. Rodig, *J. Chem. Soc.*, 4679 (1956)). The reported negative rotation ([α]D −108°) *versus* our positive value ([α]D +110°) is presumably a misprint.

(10) R. B. Woodward, THIS JOURNAL, **64**, 76 (1942).

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ether structure IX, the dehydration product of VIII.[11]

The other route to 4-methyl-Δ^4-cholesten-3-one involves the direct methylation of Δ^4-cholesten-3-one by means of methyl iodide and *t*-potassium butoxide in *t*-butyl alcohol. This reaction, when carried out with 3 molar equivalents of the potassium alkoxide, is known to produce 4,4-dimethyl-Δ^5-cholesten-3-one in over 60% yield.[12] The process presumably proceeds *via* the desired monomethylation product Xa, but the latter can only be formed in high yield by the monomethylation of IVa if this reaction takes place appreciably faster than the further methylation of Xa to the 4,4-dimethyl-Δ^5-compound. Unfortunately no indication of the first step occurring faster than the second could be found, as evidenced by the fact that the dimethylation of Δ^4-3-ketones can be brought about by means of methyl iodide and potassium *t*-butoxide in *t*-butyl alcohol even at room temperature[13] and that the further methylation of the 4-methyl-Δ^4-3-ketone Xa (obtained by the route described above) to the corresponding 4,4-dimethyl-Δ^5-3-ketone occurs very readily (see Experimental). Nevertheless the monomethylation of Δ^4-cholesten-3-one was studied under different conditions. It was found that when conditions were used so that unchanged ketone remained, already much of the dimethyl ketone was formed. However, the presence of the monomethyl ketone Xa could be detected by ultraviolet spectroscopy, and under suitable conditions this compound could be isolated in about 5% yield. Although this constitutes a one-step synthesis of Xa, the first-mentioned route is to be preferred in view of the much higher yield and ease of isolation of the product.

Methods for producing 4-methyl-Δ^4-3-ketones having been worked out in the cholesterol series, we applied the preferred one for making available the 4-methylated hormones in the testosterone, esterone and progesterone series. The enol lactone VIc readily obtained by ozonolysis of testosterone or of its acetate and treatment of the resulting keto acid with acetic anhydride and sodium acetate,[7a,14] was allowed to react with excesss ethylmagnesium bromide. Base treatment of the product then furnished 4-methyltestosterone (Xb) in *ca.* 25% yield,[15] and 40% of the keto-acid Vb could be recovered. 4-Methyltestosterone (Xb), as well as the corresponding 17-acetate (Xc), showed the expected maximum in the ultraviolet at 251 mμ.

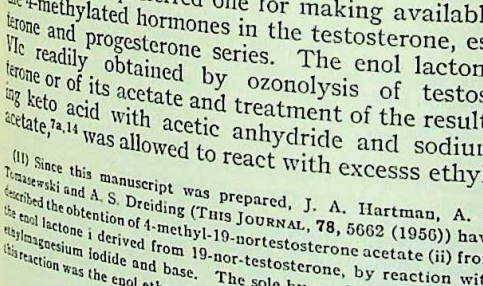
It has been shown that steroidal Δ^4-3-ketones may be dehydrogenated to the corresponding $\Delta^{1,4}$-dien-3-ones by means of selenium dioxide,[16] preferably in a tertiary alcohol containing some acetic acid.[17] We have found that 4-methyl-Δ^4-3-ketones may similarly be dehydrogenated, for 4-methyltestosterone (Xb) under these conditions produced 4-methyl-1-dehydrotestosterone (4-methyl-$\Delta^{1,4}$-androstadien-17β-ol-3-one) (XIb). Similarly, 4-methyltestosterone acetate (Xc) gave the acetate XIc.[18] Both XIb and XIc showed ultraviolet maxima at 244 mμ (log ϵ 4.16), in good agreement with the spectra of the various stereoisomers of santonin (II) (λ_{max} 242–246 mμ, log ϵ 4.01–4.27),[4] which contain the identical chromophoric system. The infrared spectra showed the doublets at 6.17 and 6.23 μ in the double bond region, typical of $\Delta^{1,4}$-dien-3-ones.[19]

In addition to the expected dienones, the selenium dioxide dehydrogenation of Xb and Xc produced selenium-containing substances (*cf.* ref. 17a), which are now being investigated.

The various stereoisomers of santonin (II) on treatment with acids[4,20] (most conveniently with acetic anhydride–sulfuric acid and subsequent saponification[21]) yield the desmotroposantonins (III), this reaction being the classical example of the so-called dienone–phenol rearrangement. The exact parallel in the steroid series was realized when 4-methyl-1-dehydrotestosterone acetate (XIc) was treated with *p*-toluenesulfonic acid in acetic anhydride and the product was saponified, thereby producing 1,4-dimethylestradiol (XIIb). The structure of this substance was confirmed by its ultraviolet spectrum (λ_{max} 288 mμ, log ϵ 3.23), very similar to that of the desmotroposantonins (λ_{max} 290 mμ, log ϵ 3.33–3.46)[4] and exhibiting the expected bathochromic shift compared to estradiol (λ_{max} 280 mμ, log ϵ 3.30)[22] and 1-methylestradiol (λ_{max} 284 mμ, log ϵ 3.28).[22]

In the progesterone series, the keto-acid Vd obtained by the ozonolysis of progesterone was converted to the enol lactone enol acetate VIe (stereo-

(11) Since this manuscript was prepared, J. A. Hartman, A. J. Tomaszewski and A. S. Dreiding (THIS JOURNAL, **78**, 5662 (1956)) have described the obtention of 4-methyl-19-nortestosterone acetate (ii) from the enol lactone i derived from 19-nor-testosterone, by reaction with ethylmagnesium iodide and base. The sole by-product isolated from this reaction was the enol ether iii, analogous to our by-product IX. It



i ii iii

was considered that the "over-reacted" material[6b] derived from enol lactones of type VI with methylmagnesium iodide therefore had a structure analogous to iii (and IX). However, this "over-reacted" material is polar and high-melting, like VIII, whereas the enol ethers iii and IX are non-polar (less polar than the corresponding 4-methyl-Δ^4-3-ketones) and comparatively low-melting.

(12) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *ibid.*, **76**, 2852 (1954).

(13) D. Elad and F. Sondheimer, *Bull. Research Council Israel*, **5A**, 295 (1956).

(14) C. C. Bolt, *Rec. trav. chim.*, **57**, 905 (1938); F. L. Weisenborn, D. C. Remy and T. L. Jacobs, THIS JOURNAL, **76**, 552 (1954).

(15) Drs. G. Rosenkranz and H. J. Ringold of Syntex S.A., Mexico City, have kindly informed us that they have independently prepared this substance by the same method (H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, in press).

(16) H. J. Ringold, G. Rosenkranz and F. Sondheimer, *ibid.*, **21**, 239 (1956).

(17) (a) C. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); (b) S. A. Spilfogel, T. A. P. Posthumus, M. S. de Winter and D. A. van Dorp, *Rec. trav. chim.*, **75**, 475 (1956).

(18) T. Miki (*J. pharm. Soc. Japan*, **75**, 403, 410 (1955)) and Y. Abe, *et al.* (latest reference of footnote 4), have now also described the dehydrogenation of 4-methyl-Δ^4-3-ketones in the decalin series (type I) to the corresponding dienones with selenium dioxide in acetic acid and pyrolysis of the product.

(19) R. N. Jones, P. Humphries, E. Packard and K. Dobriner, THIS JOURNAL, **72**, 86 (1950).

(20) *Cf.* G. R. Clemo, R. D. Haworth and E. Walton, *J. Chem. Soc.*, 1110 (1930).

(21) Huang-Minlon, Chien-Pen Lo and Ju-Yung Chu, THIS JOURNAL, **65**, 1780 (1943).

(22) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953), Table 31.

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isomeric mixture at C-20).[23] Reaction with ethylmagnesium bromide and base treatment, as previously, then produced 4-methylprogesterone (Xd) with the typical ultraviolet maximum at 251 mμ. In addition, a polar comparatively high-melting saturated by-product could again be isolated, to which the hemi-ketal structure VIIId is assigned.

In Table I, the molecular rotations ($[M]_D$) of the various 4-methyl-Δ^4-3-ketones are compared with those of the parent Δ^4-3-ketones. It can be seen that in all cases the introduction of the 4-methyl group results in an appreciable increase in the $[M]_D$, ranging from +91 in the cholestenone to +130 in the progesterone series. A similar increase is observed in passing from $\Delta^{1,4}$-dien-3-ones to the corresponding 4-methyl compounds. It is of interest to note that whereas testosterone and its acetate have almost the identical $[M]_D$, the increase in the $[M]_D$ which occurs in acetylating 1-dehydrotestosterone is also observed in the 4-methyl-1-dehydro series.

In preliminary assays carried out by the Endocrine Laboratories (Madison, Wis.), 4-methyltestosterone was found to possess *ca.* 40% of the androgenic and 120% of the myothrophic activity of testosterone, when tested by injection in castrated immature mice. 4-Methylprogesterone had *ca.* 50% of the progestational activity of progesterone, when tested by subcutaneous injection in estrogen-primed rabbits.

(23) G. I. Fujimoto and J. Pragan, THIS JOURNAL, 75, 5215 (1953).

TABLE I

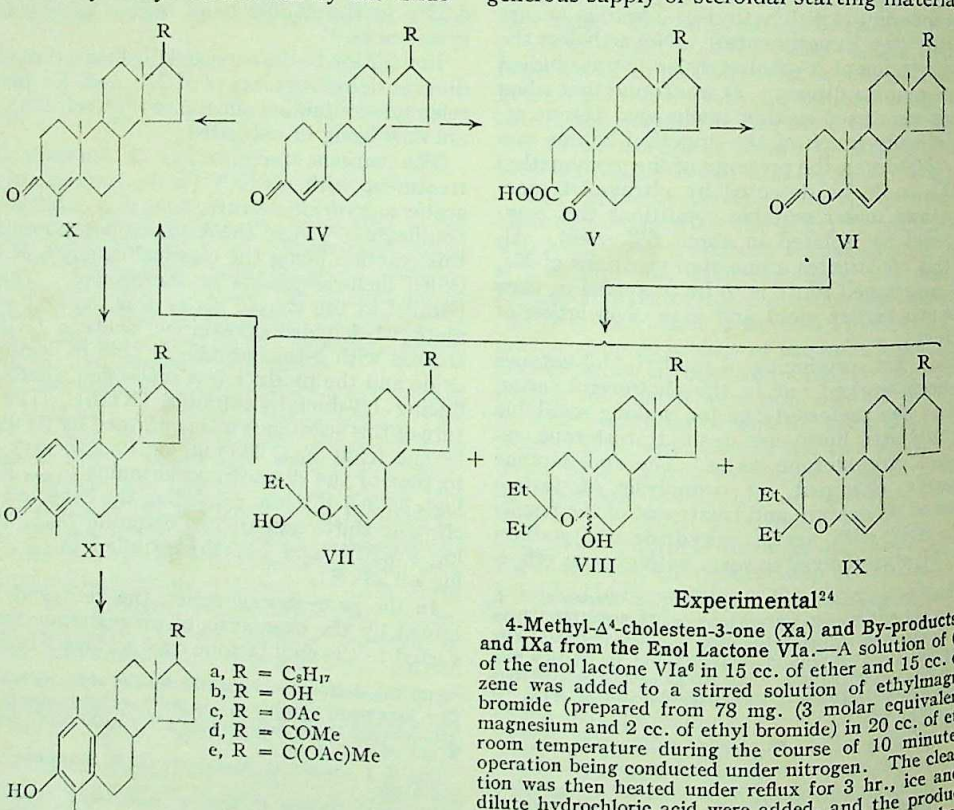
MOLECULAR ROTATION DATA OF 4-METHYL-Δ^4-3-KETONES

Series	$[M]_D$ of Δ^4-3-ketone	$[M]_D$ of 4-methyl-Δ^4-3-ketone	$\Delta[M]_D$
Δ^4-Cholesten-3-one	+342[a]	+438	+96
Testosterone	+314[b]	+405	+91
Testosterone acetate	+317[b]	+420	+103
Progesterone	+641[b]	+771	+130
1-Dehydrotestosterone	+57[c]	+138	+81
1-Dehydrotestosterone acetate	+92[c]	+205	+113

[a] L. F. Fieser, THIS JOURNAL, 75, 4377 (1953). [b] F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, *ibid.*, 75, 4712 (1953). [c] H. H. Inhoffen, G. Zühlsdorff and Huang-Minlon, *Ber.*, 73, 451 (1940).

Various reactions of the 4-methylated steroids described in this paper are now being investigated and will be reported in a subsequent publication.

Acknowledgment.—We are indebted to Dr. G. Rosenkranz of Syntex S.A., Mexico City, for the generous supply of steroidal starting materials.



Experimental[24]

4-Methyl-Δ^4-cholesten-3-one (Xa) and By-products VIIIa and IXa from the Enol Lactone VIa.—A solution of 0.42 g. of the enol lactone VIa[6] in 15 cc. of ether and 15 cc. of benzene was added to a stirred solution of ethylmagnesium bromide (prepared from 78 mg. (3 molar equivalents) of magnesium and 2 cc. of ethyl bromide) in 20 cc. of ether at room temperature during the course of 10 minutes, the operation being conducted under nitrogen. The clear solution was then heated under reflux for 3 hr., ice and then dilute hydrochloric acid were added, and the product was isolated with ether. The residue remaining after the evaporation of solvents was dissolved in 200 cc. of methanol and heated under reflux with 4 g. of sodium hydroxide in 40 cc. of water for 2 hr. Water and ether were then added, and the product, obtained by the evaporation of the dried ether extract, was chromatographed on 15 g. of alumina.

(24) Melting points are uncorrected. Rotations were determined (at 20°) in chloroform solution unless specified otherwise. Ultraviolet spectra were measured in 95% ethanol solution on a Uniecam Model S.P. 500 spectrophotometer and infrared spectra in chloroform solution on a Baird double beam recording spectrophotometer (for brevity only bands in the hydroxyl region (2.8–3.2 μ) and carbonyl region (5.5–6.0 μ) are mentioned). Analyses were carried out in our microanalytical department under the direction of Mr. Erich Meier.

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The solid fractions (56 mg., 12%) eluted with pentane yielded the enol ether IXa (see below). The next solid fractions, eluted with pentane–benzene (9:1) on crystallization from ether–methanol furnished 285 mg. (66%) of 4-methyl-Δ^4-cholesten-3-one, m.p. 102–103°, $[\alpha]_D$ +110°, λ_{max} 251 mμ (log ε 4.18), λ_{max} 6.02 and 6.18 μ.

Anal. Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.39; H, 11.65.

The fractions eluted with ether on crystallization from ether-pentane gave 66 mg. (14%) of the hemi-ketal VIIIa, m.p. 175–176°, $[\alpha]_D$ +31°, λ_{max} 2.91 and 3.08 μ.

Anal. Calcd. for $C_{30}H_{54}O_2$: C, 80.65; H, 12.18. Found: C, 80.29; H, 12.07.

The enol ether IXa, eluted first from the column, on crystallization from ether–methanol showed m.p. 103–104°, $[\alpha]_D$ +1°, λ_{max} 5.98 μ.

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 83.93; H, 12.28.

4-Methyl-Δ^4-cholesten-3-one (Xa) by Direct Methylation of Δ^4-Cholesten-3-one (IVa).—A solution of 300 mg. of potassium (3 molar equivalents) in 10 cc. of *t*-butyl alcohol was added to a boiling solution of 1 g. of Δ^4-cholesten-3-one in 30 cc. of benzene. Methyl iodide (3 cc.) in 30 cc. of benzene was then added and refluxing was continued for 5 minutes. The solution was cooled, 0.5 cc. of water was added and the solvents were evaporated to dryness under reduced pressure. Ether was added, the insoluble potassium iodide was collected and the filtrate was evaporated. Crystallization of the residue from methanol yielded 450 mg. of 4,4-dimethyl-Δ^4-cholesten-3-one,[12] m.p. 172–174°, no high-intensity absorption in the ultraviolet. The mother liquors (λ_{max} 243 mμ, log ε 4.01 and 250 mμ, log ε 3.95) were chromatographed on 20 g. of alumina. The fractions eluted with pentane furnished another 35 mg. of the 4,4-dimethyl-Δ^5-3-ketone (total yield 45%). The next solid fractions, eluted with pentane–benzene (9:1), on crystallization from ether–methanol produced 54 mg. (5%) of 4-methyl-Δ^4-cholesten-3-one, m.p. 101–103°, λ_{max} 251 mμ (log ε 4.16). The m.p. was undepressed on admixture with the sample prepared from VIa and the infrared spectra were identical. Further elution with pentane–benzene (8:2) gave an oil (102 mg.) which was not further investigated. Finally, pentane–benzene (6:4) eluted 150 mg. (15%) of unchanged Δ^4-cholesten-3-one, m.p. 79–81°.

When the methylation of cholestenone was carried out with 1 mol. of potassium *t*-butoxide and 1 mol. of methyl iodide (boiling for 15 minutes), 7.5% of the 4,4-dimethyl ketone, 3% of the 4-methylcholestenone (Xa) and 70% of unchanged starting material were obtained.

Methylation of 4-Methyl-Δ^4-cholesten-3-one (Xa) to 4,4-Dimethyl-Δ^5-cholesten-3-one.—Potassium (15 mg., 3 molar equivalents) dissolved in 0.5 cc. of *t*-butyl alcohol was added to a boiling solution of 50 mg. of 4-methyl-Δ^4-cholesten-3-one in 1.5 cc. of benzene. A solution of 0.5 cc. of methyl iodide in 5 cc. of benzene was added and boiling was continued for 5 minutes. The reaction mixture was worked up as described above for the methylation of Δ^4-cholesten-3-one. Crystallization of the residue (after removal of potassium iodide) from ether–methanol produced 32 mg. of 4,4-dimethyl-Δ^4-cholesten-3-one, m.p. 170–172°, undepressed on admixture with a sample prepared by the above-described method.

4-Methyltestosterone (Xb).—A solution of ethylmagnesium bromide (prepared from 0.41 g., 2 molar equivalents, of magnesium) in 40 cc. of ether was added dropwise to a stirred solution of 2.8 g. of the enol lactone acetate VIc[7a] in 50 cc. of ether and 50 cc. of benzene during 15 minutes, under nitrogen. The reaction mixture in which a heavy precipitate had formed was heated under reflux for 2 hr. and was then cooled and decomposed with dilute hydrochloric acid. Isolation with ether yielded a product which was triturated with 250 cc. of ether and the insoluble over-reacted material (0.76 g.), m.p. 273–276°, $[\alpha]_D$ +8° (pyridine) was collected. The filtrate was evaporated, and the residue was heated under reflux for 2 hr. with 1 g. of potassium hydroxide in 30 cc. of methanol. The neutral product was isolated with ether and chromatographed on 30 g. of alumina. The fractions eluted with benzene and benzene–ether (9:1) on crystallization from ether–pentane yielded 0.64 g. (25%) of 4-methyltestosterone, m.p. 172–173°, $[\alpha]_D$ +134°, λ_{max} 251 mμ (log ε 4.16); λ_{max} 2.82, 6.01 and 6.20 μ.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.52; H, 10.06.

The acetate Xc crystallized from methanol as needles, m.p. 158–160°, $[\alpha]_D$ +122°, λ_{max} 251 mμ (log ε 4.17); λ_{max} 5.78, 6.00 and 6.20 μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.89; H, 9.13.

The acidic material obtained after the base treatment on crystallization from acetone furnished 1.05 g. (40%) of recovered keto-acid Vb,[14] m.p. 202–203°.

4-Methyl-1-dehydrotestosterone (XIb).—4-Methyltestosterone (250 mg.) and selenium dioxide (125 mg.) were heated under reflux with 5 cc. of *t*-butyl alcohol and 0.05 cc. of glacial acetic acid under nitrogen for 8 hr., another 125 mg. of selenium dioxide was then added and refluxing was continued for another 16 hr. Ether and water were added, the organic layer was washed with sodium carbonate solution and water, dried and evaporated. The residue was chromatographed on 10 g. of alumina and the fractions eluted with benzene and benzene–ether (9:1) were crystallized from ether–hexane and sublimed in high vacuum. This procedure yielded 72 mg. (29%) of 4-methyl-1-dehydrotestosterone, m.p. 188–190°, $[\alpha]_D$ +46°, λ_{max} 244 mμ (log ε 4.16); λ_{max} 2.90, 6.01, 6.17 and 6.23 μ.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.76; H, 9.30.

Further elution of the chromatogram with ether yielded 75 mg. of a selenium-containing substance, m.p. *ca.* 290° (dec. with separation of red selenium).

4-Methyl-1-dehydrotestosterone Acetate (XIc).—4-Methyltestosterone acetate (400 mg.) in 8 cc. of *t*-butyl alcohol and 0.08 cc. of glacial acetic acid was dehydrogenated with two lots of selenium dioxide (2 × 200 mg.) as described above for the corresponding alcohol. Chromatography on 16 g. of alumina and crystallization of the fractions eluted with pentane–benzene (9:1 and 8:2) from pentane–ether yielded 84 mg. (21%) of 4-methyl-1-dehydrotestosterone acetate, m.p. 175–176°, $[\alpha]_D$ +60°, λ_{max} 245 mμ (log ε 4.17); λ_{max} 5.78, 6.02, 6.17 and 6.22 μ.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.02; H, 8.71.

The fractions eluted with pentane–benzene (2:1) on crystallization from acetone yielded 64 mg. of a selenium-containing substance, m.p. 240–245° dec.

4-Methyl-1-dehydrotestosterone acetate could alternatively be prepared by acetylating the free alcohol XIb (described above) with acetic anhydride and pyridine at room temperature.

1,4-Dimethylestradiol (XIIb).—A solution of 55 mg. of 4-methyl-1-dehydrotestosterone acetate and 15 mg. of *p*-toluenesulfonic acid in 5 cc. of acetic anhydride was heated on the steam-bath for 3 hr. The residue obtained by isolation with ether was heated under reflux with 0.5 g. of potassium hydroxide in 15 cc. of methanol for 1 hr., under nitrogen. Addition of water, isolation with ethyl acetate and crystallization from methylene chloride–methanol produced 35 mg. (73%) of 1,4-dimethylestradiol as long needles, m.p. 125–129°, $[\alpha]_D$ +155°, λ_{max} 288 mμ (log ε 3.23); λ_{max} 2.88 and 3.08 μ. This substance contained solvent of crystallization as evidenced by the bubbling observed at the m.p. and by the low carbon content. The solvent-free diol could only be obtained by sublimation at 140–160° in high vacuum.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.62; H, 9.65.

4-Methylprogesterone (Xd).—A solution of ethylmagnesium bromide (prepared from 0.67 g., 2.5 molar equivalents, of magnesium) in 50 cc. of ether was added to a stirred solution of 4 g. of the enol lactone enol acetate VIe[23] in 75 cc. of ether and 75 cc. of benzene during 15 minutes under nitrogen. The mixture was heated under reflux for 2.5 hr., cooled and decomposed with dilute hydrochloric acid. The residue remaining after evaporation of the dried organic extract was heated under reflux with 1.5 g. of potassium hydroxide in 50 cc. of methanol for 2 hr. under nitrogen. Ice was added and the non-acidic material was isolated with ether in the usual way. The resulting oil (2.8 g.) was chromatographed on 100 g. of alumina. The fractions eluted with pentane–benzene (9:1, 8:2 and 7:3) on crystallization from

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ether–methanol gave 4-methylprogesterone (0.36 g.) as needles, m.p. 155–157°, $[\alpha]D$ +235°, λ_{max} 251 mμ (log ε 4.18); λ_{max} 5.84, 6.00 and 6.20 μ.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.60; H, 9.69.

The fractions eluted with ether on crystallization from acetone–hexane yielded the hemi-ketal VIIId, m.p. 178–180°, $[\alpha]D$ +37°, λ_{max} 2.96 and 5.84 μ.

Anal. Calcd. for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.14; H, 10.60.

REHOVOTH, ISRAEL

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Acid-catalyzed Rearrangement of Cinenic Acid. III.[1] Structure and Synthesis of the Lactonic Product

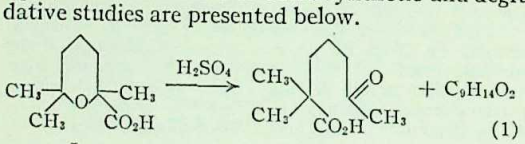
BY JERROLD MEINWALD AND HO CHIEN HWANG

RECEIVED DECEMBER 29, 1956

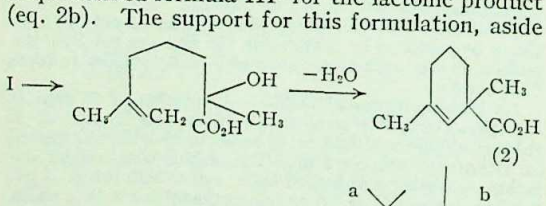
A crystalline lactone, isolated in 15% yield after treatment of α-cinenic acid (I) with concentrated sulfuric acid, has been shown to possess structure III. This lactone has been synthesized using a two-step procedure involving the Diels–Alder addition of isoprene to ethyl methacrylate and lactonization of the resultant adduct. The formation of III from I involves a reaction sequence which is unrelated to the carboxyl transfer process which produces geronic acid (II).

Introduction

As a continuation of our study of the acid-catalyzed rearrangements of α-cinenic acid (I), we have investigated the structure of the crystalline lactone, $C_9H_{14}O_2$, which is formed in about 15% yield when α-cinenic acid is isomerized to geronic acid (II) (see eq. 1).[2,3] The results of these synthetic and degradative studies are presented below.



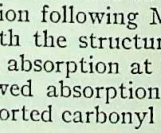
On the basis of a mechanism for the formation of II which is now known to be erroneous (eq. 2a), Rupe derived formula III[2] for the lactonic product (eq. 2b). The support for this formulation, aside

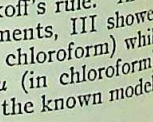


from these "theoretical" considerations, came only from the observations that the lactone was saturated (therefore bicyclic) and that it could be hydrolyzed to a hydroxy-acid which dehydrated to regenerate the original lactone. Since this rather incomplete evidence in favor of III is weakened by the discovery that the formation of II involves a carboxyl transfer process rather than the path shown in equation 2,[4] we have sought a rigorous proof of the lactone structure.

Structure Proof

The rearrangement of I was carried out as previously described, and a crystalline lactone, m.p. 50–51°, was obtained from the neutral portion of the product. A Kuhn–Roth determination indicated the presence of two C-methyl groups. The infrared spectrum of the crystalline lactone (in Nujol) showed a maximum at 5.60 μ. More significantly, in chloroform solution the lactone showed maximal absorption at 5.67 μ. Since these findings were in accord with the proposed structure, an independent synthesis of this structure was undertaken as the simplest method of unambiguous identification. The method chosen for the synthesis is outlined in Chart 1. Diels–Alder addition of isoprene to ethyl methacrylate gave a *mixture* of adducts, not easily separable into its individual components by fractional distillation. The formation of both of the theoretically possible products was anticipated, and ensured the success of the synthesis. Treatment of the mixture with sulfuric acid in acetic acid gave a mixture of lactones, from which III, m.p. 50–51°, and IV, m.p. 48–49°, were isolated by distillation and purified by crystallization. These were the lactones to be expected from acid-catalyzed cyclization following Markownikoff's rule. In accord with the structural assignments, III showed lactonic absorption at 5.67 μ (in chloroform) while IV showed absorption at 5.80 μ (in chloroform). The reported carbonyl bands for the known models





VI and VII are at 5.67 and 5.76 μ, respectively.[5] Finally, III was degraded in good yield to *m*-xylene (identified by conversion to its trinitro derivative, as well as by its infrared and ultraviolet spectra) by

(1) Presented at the 131st National Meeting, American Chemical Society, Miami, Florida, April, 1957. For the previous paper in this series see J. Meinwald and C. C. Cornwall, THIS JOURNAL, **77**, 5991 (1955).

(2) H. Rupe and C. Liechtenhan, *Ber.*, **41**, 1278 (1908).

(3) H. Rupe and H. Hirschmann, *Helv. Chim. Acta*, **16**, 555 (1933).

(4) J. Meinwald, THIS JOURNAL, **77**, 1617 (1955).

(5) R. Criegee, A. Kerckow and C. Sommer, *Chem. Ber.*, **89**, 1978 (1956).

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heating with a barium oxide–palladium-on-charcoal mixture. Similarly, degradation of IV gave rise to a good yield of *p*-xylene.

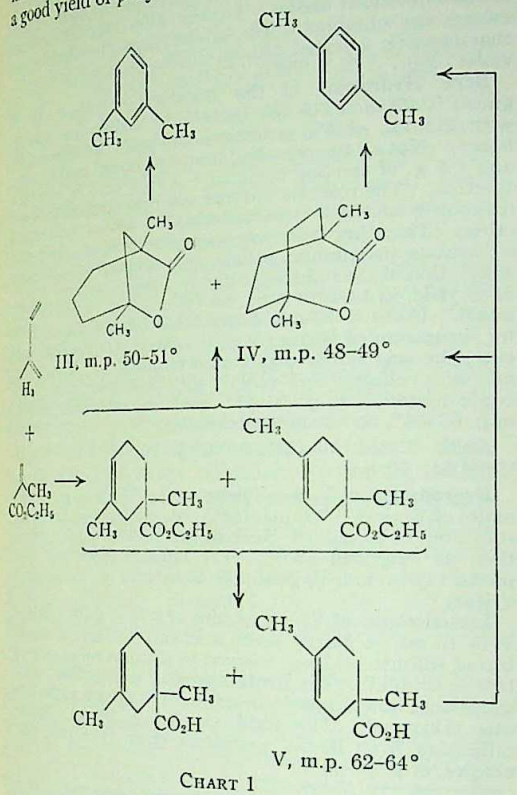


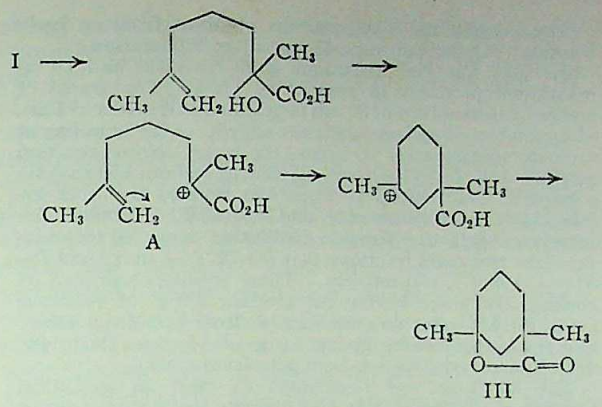
CHART I

In an effort to separate the hydrolysis and lactonization steps, and to characterize the acid intermediates, a base hydrolysis of the original adduct mixture was carried out. A liquid mixture of acids was obtained, which gave rise to a mixture of lactones on acid treatment. (Chromatography of this mixture produced III and IV, but this procedure for preparing the lactones was much more tedious than that described previously.) The acid V, m.p. 62–64°, was isolated from the crude adduct hydrolyzate by virtue of the fact that it slowly crystallized from the mixture of acids. Its structure was proven by degradation to *p*-xylene and cyclization to the δ-lactone, IV. Unfortunately, it was impossible to characterize the acid precursor to the γ-lactone, III.

An authentic sample of lactone III was now available from these synthetic experiments, and a direct comparison with the neutral α-cinenic acid product was possible. Indistinguishable infrared spectra and an undepressed mixture melting point proved these two samples to be identical. The melting point of the γ-lactone III was depressed strongly upon admixture with the δ-lactone IV.

Concluding Remarks

The transformation of I to III would seem to proceed by the series of steps outlined in equation 3, the essential features of which were present in Rupe's suggestion. It should be pointed out, however, that this sequence is not entirely satisfactory. It would be possible to circumvent the rather un-



attractive intermediate (A) by postulating a cyclization *concerted* with loss of the hydroxyl group. In any event, it is apparent that this reaction is quite unrelated to the carboxyl transfer reaction responsible for the production of geronic acid (II), and that II and III do not have a common carbocyclic precursor as previously postulated.[2] Nevertheless, insofar as the structure and genesis of III is concerned, these results pay tribute to Rupe's organic chemical intuition.

Acknowledgment.—The authors are indebted to the National Science Foundation, whose support in the form of a Research Grant has made this research possible.

Experimental

Rearrangement of α-Cinenic Acid.—The rearrangement of 30 g. of I was carried out as described previously.[2-4] A neutral fraction weighing 12.1 g. was obtained from the reaction product by the usual extraction procedures. This material yielded a crystalline solid on chilling. Recrystallization from 30–60° petroleum ether gave 4.6 g. (15%) of white plates, m.p. 50–51°. The infrared spectrum of this material showed maxima at 5.60 μ in Nujol and 5.67 μ in $CHCl_3$ solution.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15; $-CH_3$, 19.4. Found: C, 69.86; H, 9.03; $-CH_3$, 10.83.

Addition of Isoprene to Ethyl Methacrylate.—Two hundred grams (1.76 moles) of ethyl methacrylate, 120 g. (1.76 moles) of freshly distilled isoprene and 2 g. of hydroquinone were placed in a steel bomb, heated at 200° overnight, and cooled to room temperature. The crude reaction product (316 g.) was subjected to distillation at diminished pressure. A small amount of unreacted ethyl methacrylate (27 g.) was recovered. A mixture (24 g.) of ethyl methacrylate and adduct was collected below 65° (3 mm.) and the main portion of adduct (263 g.) was collected over the range 66–72° (2.3–2.5 mm.). The infrared spectrum of this adduct was free of the sharp maximum at 6.10 μ characteristic of ethyl methacrylate. The yield, based on unrecovered dienophile, corresponded to 95%. Slow redistillation of the main fraction failed to separate the two isomeric esters, but gave an analytical sample, b.p. 71–72° (2.5 mm.).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.53; H, 9.84. Found: C, 72.73; H, 9.94.

Lactonization of the Diels–Alder Adduct to III and IV. A.—Several techniques were used to prepare the desired lactones. In one experiment, the adduct (1 g.) was boiled with 50% sulfuric acid for about two days. The neutral product (85%) from this experiment was chromatographed on a Magnesol–Celite (1:1) column, using 30–60° petroleum ether as solvent. The early fractions showed carbonyl absorption at 5.80 μ, while later fractions showed a 5.65 μ maximum. Fractions showing chiefly γ-lactone absorption were combined and recrystallized to give about 7% of fine, colorless, platelike crystals, m.p. 50–51°, mixture m.p. with cinenic acid product 50–51°. The infrared spectra of the rearrangement product and the synthetic lactone were in-

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Some crystalline δ-lactone was obtained from an early fraction. It showed m.p. 48–49° after sublimation.

B.—The following technique gave both III and IV as crystalline products in reasonable yield. Ten grams of adduct was dissolved in 30 ml. of glacial acetic acid and 1 ml. of concentrated sulfuric acid was added. After standing at room temperature for 96 hours, the honey-colored reaction mixture was neutralized with saturated sodium bicarbonate solution. The neutral product was isolated by ether extraction in the usual manner, and 7 g. (83%) of lactone mixture was obtained. Vacuum distillation separated this mixture into two main fractions, b.p. 70–72° (1.5 mm.) and 79–81° (1.0 mm.), respectively. These products solidified on cooling, the lower boiling cut yielding 2.9 g. of γ-lactone (m.p. 50–51° after recrystallization from petroleum ether) and the higher boiling giving 4.0 g. of δ-lactone (m.p. 48–49° after recrystallization from petroleum ether).

The δ-lactone was resublimed to yield an analytical sample, m.p. 48–49°. It had a single sharp maximum in chloroform at 5.80 μ.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.91; H, 9.00.

Degradation of III to *m*-Xylene.—One gram (0.006 mole) of III (m.p. 50–51°) was ground to a fine powder and mixed thoroughly with 300 mg. of 10% palladium–charcoal and 3.0 g. of barium oxide. The mixture was placed in a 25-ml. distilling flask and heated gently over a micro-flame. The product, *m*-xylene, came over readily as a colorless liquid. The yield was 0.55 g. (80%). For complete identification of this product, infrared and ultraviolet spectra were taken and a nitro derivative was prepared. Maxima at 13.00, 13.75 and 14.50 μ in the infrared[6] and at 259, 265.4, 268.8 and 272.5 mμ in the ultraviolet,[7] all characteristic of *m*-xylene, were observed. Nitration of 500 mg. of the degradation product using 2 ml. of concentrated sulfuric acid and 2 ml. of fuming nitric acid, and keeping the mixture at 100° for 20 minutes, gave a white precipitate when the reaction mixture was poured onto ice. After recrystallization from 95% ethanol, fine, pale yellow, needles, m.p. 177–180° (lit.[8] 182°), were obtained. A melting point of 177–181° was observed on admixture with an authentic sample of 2,4,6-trinitro-*m*-xylene.

Degradation of IV to *p*-Xylene.—Five hundred mg. (0.003 mole) of IV (m.p. 48–49°) was degraded in a fashion parallel to that described above. A yield of 300 mg. (88%) of *p*-xylene was obtained. The product was identified by its characteristic infrared (12.58, 13.72, 14.41 μ)[9] and ultraviolet (260.7, 266.1, 269.0, 275.0 mμ)[10] spectra.

Base Hydrolysis of the Diels–Alder Adduct.—Forty grams (0.22 mole) of the Diels–Alder adduct was refluxed with 210 ml. of 5% potassium hydroxide solution for 70 hours. Not all the ester had been hydrolyzed at this point, and 8.5 g. of starting material was recovered by ether extraction. The reaction mixture was then acidified with hydrochloric acid and extracted with five 100-ml. portions of ether. The ether layer was washed with water, dried over anhydrous magnesium sulfate and evaporated. Vacuum distillation of the residual acid gave a main fraction (21.9 g., 82% yield on basis of ester converted), b.p. 104–105° (1.0 mm.). Using a 70-cm. Podbielniak column, no evidence for separation of isomers was obtained. On cooling, however, the acid slowly deposited crystals of V. These crystals were collected and washed with petroleum ether. The crude material, m.p. 60–64°, gave an analytical sample, m.p. 62–64°, on vacuum sublimation.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.84; H, 8.91.

Degradation of V to *p*-Xylene.—Five hundred mg. (0.003 mole) of V yielded 200 mg. (58%) of colorless distillate when subjected to palladium–charcoal and barium oxide degradation, as described above. The infrared spectrum of the product was indistinguishable from that of authentic *p*-xylene.

Lactonization of V.—A solution of 2.76 g. (0.018 mole) of V in 10 ml. of glacial acetic acid and 0.25 ml. of concentrated sulfuric acid was allowed to stand at room temperature overnight. The neutral product was isolated in the usual way, and appeared as long needles as soon as the ether was taken off. The yield was 1.9 g. (69%). Recrystallization from 30–60° petroleum ether gave pure white needles, m.p. 48–49°.

(6) F. D. Rossini, *et al.*, "Infrared Spectral Data," American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pennsylvania, 1955, Serial No. 311.

(7) "Ultraviolet Spectral Data," American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pennsylvania, 1946, Serial No. 56.

(8) I. M. Heilbron, "Dictionary of Organic Compounds," 2nd ed. Vol. IV, Oxford University Press, New York, N. Y., 1953, p. 627.

(9) See reference 6, spectrum Serial No. 312.

(10) See reference 7, spectrum Serial No. 57.

ITHACA, NEW YORK

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

The Synthesis of β-(3-Methoxy-2,6-dinitrophenyl)-D,L-alanine and β-(3-Methoxy-4,6-dinitrophenyl)-D,L-alanine. Proof of the Structures of Two Isomeric Dinitro-*m*-tyrosines

BY ERNEST L. JACKSON

RECEIVED DECEMBER 29, 1956

β-(3-Methoxy-2,6-dinitrophenyl)-D,L-alanine and β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine have been synthesized from 3-methoxy-2,6-dinitrobenzaldehyde and 3-methoxy-4,6-dinitrobenzaldehyde. These two amino acids have been correlated with two of the β-(3-methoxydinitrophenyl)-D,L-alanines that were obtained by way of the nitration of *m*-tyrosine, thus proving two of the nitration products to be β-(3-hydroxy-2,6-dinitrophenyl)-D,L-alanine and β-(3-hydroxy-4,6-dinitrophenyl)-D,L-alanine.

The nitration of *m*-tyrosine has been shown[1] to produce three crystalline isomers of β-(3-hydroxydinitrophenyl)-D,L-alanine which upon acetylation yielded three isomers of N-acetyl-β-(3-hydroxydinitrophenyl)-D,L-alanine; methylation of two of these compounds afforded two isomers of N-acetyl-β-(3-methoxydinitrophenyl)-D,L-alanine methyl ester. Hydrolysis and deacetylation of these two methyl esters gave the two isomeric β-(3-methoxydinitrophenyl)-D,L-alanines. The present paper describes the third isomer of β-(3-methoxydinitrophenyl)-D,L-alanine and its N-acetyl methyl ester; it also establishes the orientation of the nitro groups for two of the isomers by their comparison with the authentic compounds which have been synthesized from 3-methoxy-2,6-dinitrobenzaldehyde and 3-methoxy-4,6-dinitrobenzaldehyde, the structures of which were proved by Hodgson and Beard[2] and by Tröger and Eicker.[3]

(1) E. L. Jackson, THIS JOURNAL, 77, 4860 (1955).

(2) H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, 2375 (1927).

(3) J. Tröger and C. Eicker, *J. prakt. Chem.*, [2] 116, 17 (1927).

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3-Methoxy-2,6-dinitrobenzaldehyde in toluene solution yielded, by reduction of the aldehyde group with aluminum isopropoxide, 3-methoxy-2,6-dinitrobenzyl alcohol (m.p. 139.5–140.5°) which reacted with phosphorus pentachloride to produce 3-methoxy-2,6-dinitrobenzyl chloride (m.p. 103.5–104.5°). Ethyl α-acetamido-α-carbethoxy-β-(3-methoxy-2,6-dinitrophenyl)-propionate (m.p. 143°) resulted in 62% yield from the reaction of sodium ethyl acetamidomalonate with 3-methoxy-2,6-dinitrobenzyl chloride in ethanol solution at room temperature. This reaction was unsuccessful in boiling ethanol solution presumably due to the oxidizing[4] action of the nitro groups in the molecule of 3-methoxy-2,6-dinitrobenzyl chloride. β-(3-Methoxy-2,6-dinitrophenyl)-D,L-alanine (m.p. 209° dec.) was produced in 57% yield through reaction of a hot mixture of sulfuric and acetic acids with ethyl α-acetamido-α-carbethoxy-β-(3-methoxy-2,6-dinitrophenyl)-propionate. Acetylation of β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine in aqueous sodium hydroxide solution by acetic anhydride gave N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine (m.p. 252° dec.), methylation of which by either diazomethane or by the methanol–acetyl chloride method of Hanby, Waley and Watson[5] afforded N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine methyl ester (m.p. 158–159°).

The isomer of N-acetyl-β-(3-hydroxydinitrophenyl)-D,L-alanine[1] melting at 194–195°, the one previously designated N-acetyl-C, now has been found to react with diazomethane to produce N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine methyl ester (m.p. 157–158°). This product was shown by a mixed melting point determination and by comparison of the infrared spectra to be identical with the N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine methyl ester that was synthesized from 3-methoxy-2,6-dinitrobenzaldehyde. Hydrolysis and deacetylation of N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine methyl ester, derived from N-acetyl-C, by a hot mixture of sulfuric and acetic acids yielded β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine melting at 208° dec. alone or mixed with the compound which was synthesized from 3-methoxy-2,6-dinitrobenzaldehyde. Isomer C[1] of β-(3-hydroxy-dinitrophenyl)-D,L-alanine (m.p. 197°, explosively) consequently must be β-(3-hydroxy-2,6-dinitrophenyl)-D,L-alanine.

The synthesis of β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine from 3-methoxy-4,6-dinitrobenzaldehyde was accomplished by the preparation in successive steps of 3-methoxy-4,6-dinitrobenzyl alcohol (m.p. 135–136°), 3-methoxy-4,6-dinitrobenzyl chloride (m.p. 110–111°) and ethyl α-acetamido-α-carbethoxy-β-(3-methoxy-4,6-dinitrophenyl)-propionate (m.p. 167°) which was converted to β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine (m.p. 230° dec.) in 68% yield. The purification of the amino acid was facilitated greatly by the use of a Dowex-1 anion exchange resin. A mixed melting point determination and paper chromatography tests, employing both 60% ethanol and *t*-amyl alcohol as solvents, established the identity of this authentic β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine with the β-(3-methoxydinitrophenyl)-D,L-alanine (m.p. 231–232° dec.) which was prepared[1] from the isomer of N-acetyl-β-(3-methoxydinitrophenyl)-D,L-alanine methyl ester melting at 172–173°. Moreover, this methyl ester was prepared from the authentic β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine by acetylation to N-acetyl-β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine (m.p. 212–213°) which reacted with diazomethane to yield N-acetyl-β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine methyl ester melting at 172–173° alone or mixed with the compound derived from *m*-tyrosine. This proves isomer B[1] of β-(3-hydroxydinitrophenyl)-D,L-alanine (m.p. 235–236° dec.) to be β-(3-hydroxy-4,6-dinitrophenyl)-D,L-alanine.

Isomer A[1] of β-(3-hydroxydinitrophenyl)-D,L-alanine (m.p. 234° dec.) would be expected from orientation rules to be β-(3-hydroxy-2,4-dinitrophenyl)-D,L-alanine.

Experimental

Except where otherwise stated, melting points are corrected and, in the case of the amino acids, their N-acetyl derivatives and N-acetyl methyl esters the melting points were determined with the bath of the Hershberg apparatus preheated to 15–30° below the melting point.

3-Methoxy-2,6-dinitrobenzyl Alcohol and 3-Methoxy-4,6-dinitrobenzyl Alcohol.—To a solution of 2.5 g. of pure 3-methoxy-2,6-dinitrobenzaldehyde[2,3] in 40 ml. of anhydrous toluene was added 3.7 ml. of approximately 1.4 *M* solution of aluminum isopropoxide in anhydrous 2-propanol. After the solution had been refluxed for 3 hr., 10 ml. of anhydrous 2-propanol was added. The mixture was heated for 2 hr. on the steam-bath in an apparatus[6] that allowed slow distillation of the solvent and the acetone formed, 2-propanol being replenished as needed. The solvent was evaporated *in vacuo* and the solid residue was mixed thoroughly with 60 ml. of 5% hydrochloric acid. The crude 3-methoxy-2,6-dinitrobenzyl alcohol was collected, washed with water and recrystallized from ethanol as light-brown prismatic needles, yield 2 g. or 80%, m.p. 139.5–140.5°.

Anal. Calcd. for $C_8H_8N_2O_6$: C, 42.11; H, 3.53; N, 12.28. Found: C, 42.39; H, 3.46; N, 12.06.

Pure 3-methoxy-4,6-dinitrobenzaldehyde[2,3] (2.42 g.) in 38 ml. of anhydrous toluene was reduced by aluminum isopropoxide (3.6 ml. of 1.4 *M* solution in anhydrous 2-propanol) as described for the reduction of 3-methoxy-2,6-dinitrobenzaldehyde. Purified from ethanol and dried in an evacuated desiccator over calcium chloride, the light-brown crystals of 3-methoxy-4,6-dinitrobenzyl alcohol melted at 135–136°, yield 1.7 g. or 70%. Found: C, 42.27; H, 3.72; N, 12.20.

3-Methoxy-2,6-dinitrobenzyl Chloride and 3-Methoxy-4,6-dinitrobenzyl Chloride.—A mixture of 1.74 g. of 3-methoxy-2,6-dinitrobenzyl alcohol and 26 ml. of chloroform, which had been washed with water and dried over calcium chloride, was boiled for a few minutes, then cooled to 0–5° and treated with 1.91 g. of phosphorus pentachloride. The cold mixture was shaken until all solid dissolved. The solution was kept at room temperature for 2 hr., 16 ml. of *n*-hexane was added and a little amorphous solid was removed by filtration. The solution was washed once with water, four times with 5% sodium bicarbonate solution and finally with water. After the solution had been dried over calcium chloride and filtered, the solvent was evaporated *in vacuo* and the residue was recrystallized from a mixture of benzene and *n*-hexane; yield 1.6 g. or 84%, m.p. 103.5–104.5°.

(4) Cf. M. Harnik and E. Margoliash, *J. Org. Chem.*, **20**, 1650 (1955).

(5) W. E. Hanby, S. G. Waley and J. Watson, *J. Chem. Soc.*, 3239 (1950).

(6) A. L. Wilds in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 178.

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Anal. Calcd. for $C_8H_7ClN_2O_8$: C, 38.96; H, 2.86; Cl, 14.38; N, 11.36. Found: C, 39.31; H, 2.77; Cl, 14.89; N, 11.29.

3-Methoxy-4,6-dinitrobenzyl alcohol (1.25 g.) in 25 ml. of absolute chloroform was treated with phosphorus pentachloride (1.37 g.) as described for the similar reaction with 3-methoxy-2,6-dinitrobenzyl alcohol. The crude product was recrystallized as yellow prisms from absolute ethanol and dried in an evacuated desiccator over calcium chloride; yield 1.1 g. or 81%, m.p. 110–111°. Found: C, 39.30; H, 2.91; Cl, 14.17; N, 11.27.

Ethyl α-Acetamido-α-carbethoxy-β-(3-methoxy-2,6-dinitrophenyl)-propionate and Ethyl α-Acetamido-α-carbethoxy-β-(3-methoxy-4,6-dinitrophenyl)-propionate.—Ethyl acetamidomalonate (1.54 g.) was dissolved in a solution of 0.187 g. of sodium in 60 ml. of absolute ethanol. 3-Methoxy-2,6-dinitrobenzyl chloride (1.59 g.) was shaken with this solution at room temperature and nearly all of the crystals soon dissolved. It was kept at room temperature for 43 hr., some crystals of sodium chloride were removed and, after the solution had been made slightly acid with acetic acid, the solvent was evaporated at 25° *in vacuo*. The crystalline residue was taken up in hot absolute ethanol, some insoluble solid was filtered off and the filtrate was concentrated to deposit at 25° a dense mass of crystals of ethyl α-acetamido-α-carbethoxy-β-(3-methoxy-2,6-dinitrophenyl)-propionate, which was dried in an evacuated desiccator over calcium chloride; yield 1.7 g. or 62%, m.p. 143°.

Anal. Calcd. for $C_{17}N_{21}N_3O_{10}$: C, 47,77; H, 4.95; N, 9.83. Found: C, 47.63; H, 4.89; N, 9.86.

Ethyl acetamidomalonate (1.0 g.) was dissolved in a solution of 0.12 g. of sodium in 40 ml. of absolute ethanol. 3-Methoxy-4,6-dinitrobenzyl chloride (1.03 g.) was shaken mechanically with this solution at room temperature for 47 hr. The suspended crystals were collected, washed with absolute ethanol, dried and then stirred with 15 ml. of cold water. The undissolved crystals (1.0 g. melting at 159–163°) were purified by recrystallization first from absolute ethanol and then from ethyl acetate to give 0.75 g. of pure ethyl α-acetamido-α-carbethoxy-β-(3-methoxy-4,6-dinitrophenyl)-propionate melting at 167°. Found: C, 47.99; H, 4.81; N, 9.60.

β-(3-Methoxy-2,6-dinitrophenyl)-D,L-alanine and β-(3-Methoxy-4,6-dinitrophenyl)-D,L-alanine.—To a solution of 1.58 g. of ethyl α-acetamido-α-carbethoxy-β-(3-methoxy-2,6-dinitrophenyl)-propionate in 47 ml. of glacial acetic acid was added 63 ml. of 6.258 *N* sulfuric acid. After the solution had been refluxed for 8 hr., it was diluted with 60 ml. of water and concentrated *in vacuo* (bath 65°) to 20 ml., some sirup having separated. It was diluted with 50 ml. of water, the mixture was concentrated *in vacuo* to *ca.* 30 ml., then diluted with 70 ml. of water and heated on the steam-bath for a few minutes. After being cooled to room temperature, the mixture of solution and sirup was extracted six times with ethyl acetate. The hot aqueous solution was treated with sufficient barium hydroxide solution to remove sulfate ions exactly. The solution upon concentration *in vacuo* yielded in two crops 0.5 g. of crystalline β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine, most of which melted at 208°. The ethyl acetate extract was concentrated *in vacuo* to deposit a thick, brown sirup which was dissolved in 250 ml. of hot water. The filtered aqueous solution was extracted with benzene and then evaporated *in vacuo* to deposit solid material which, after further purification from water, increased the yield of β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine to 0.6 g. or 57%. The analytical sample was recrystallized from water as almost colorless needles and dried for 24 hr. in the air at room temperature. These crystals, which melted at 209° (uncor., dec.), lost 5.3% in weight at 100° *in vacuo*.

Anal. Calcd. for $C_{10}H_{11}N_3O_7$: C, 42.11; H, 3.89; N, 14.74; OCH_3, 10.88. Found (dried at 100° *in vacuo*): C, 41.91; H, 3.83; N, 14.51; OCH_3, 10.77.

β-(3-Methoxy-2,6-dinitrophenyl)-D,L-alanine was prepared also from N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine methyl ester, which was obtained as described below by the reaction of diazomethane with one of the isomers of N-acetyl-β-(3-hydroxydinitrophenyl)-D,L-alanine[1] (N-acetyl-C, m.p. 194–195°). A solution of 75 mg. of this N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine methyl ester (somewhat impure; m.p. 145–147°) in a mixture of 2 ml. of acetic acid and 2.3 ml. of 5.76 *N* sulfuric acid was kept at 100° under reflux for 5 hr. The product (47 mg.) was isolated as previously described[1] and purified by several recrystallizations from water as almost colorless needles. The air-dried crystals melted at 208° (uncor., dec.) and lost 5.8% in weight at 100° *in vacuo*. A mixed melting point determination with crystals of β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine prepared from ethyl α-acetamido-α-carbethoxy-β-(3-methoxy-2,6-dinitrophenyl)-propionate showed no depression. Found (dried at 100° *in vacuo*): C, 42.52; H, 4.09.

For the preparation of β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine, a solution of 0.542 g. of ethyl α-acetamido-α-carbethoxy-β-(3-methoxy-4,6-dinitrophenyl)-propionate in a mixture of 16 ml. of glacial acetic acid and 21.7 ml. of 6.258 *N* sulfuric acid was refluxed for 6 hr. The solution was diluted with 150 ml. of water and left overnight at 25° to deposit 26 mg. of crystalline ethyl α-acetamido-α-carbethoxy-β-(3-methoxy-4,6-dinitrophenyl)-propionate melting at 163–164°. The solution was concentrated *in vacuo* to a small volume, then diluted with water, and the concentration *in vacuo* was repeated. The solution was diluted with water and extracted twice with ethyl acetate. After treatment with barium hydroxide for exact removal of sulfate ions, the aqueous solution was evaporated *in vacuo* to dryness. The crystalline residue was taken up in water and the solution was evaporated again *in vacuo;* this operation was repeated until the distillate was free of acetic acid. The crystals were dissolved in 75 ml. of hot water, the yellow solution was filtered, cooled and passed through a column (13 × 1.7 cm.) of Dowex 1–X2, 200–400 mesh in the acetate form; the column was then washed with some water. The small residue left by evaporation of the solution, which had passed through the column, was found by paper chromatography to be free of β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine. The column was eluted with 200 ml. of *N* acetic acid, and the eluate was evaporated *in vacuo* to dryness. The crystalline residue was dissolved in hot water and the solution was evaporated *in vacuo;* this operation was repeated until the distillate was free of acetic acid. Recrystallization of the compound from water as slightly yellow needles gave in two crops 246 mg. (68%) of β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine, most of it melting at 228° dec. After another recrystallization from water and drying in the air at room temperature, the crystals melted at 230° (uncor., dec.) and lost 3.0% in weight at 100° *in vacuo*. Found (dried at 100° *in vacuo*): C, 42.45; H, 4.10; N, 14.96.

The melting point of a mixture of the above described crystals of authentic β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine with crystals of the previously reported[1] β-(3-methoxydinitrophenyl)-D,L-alanine (m.p. 231–232° dec.), which was prepared from the isomer of N-acetyl-β-(3-methoxydinitrophenyl)-D,L-alanine methyl ester melting at 172–173°, showed no depression. The melting point was depressed when crystals of the authentic compound were mixed with crystals of β-(3-methoxydinitrophenyl)-D,L-alanine[1] of m.p. 234–235° dec. which was prepared from the isomer of N-acetyl-β-(3-methoxydinitrophenyl)-D,L-alanine methyl ester melting at 128–129°. In paper chromatography tests, with the use of both water–ethanol (2:3) and *t*-amyl alcohol saturated with water, the authentic β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine showed R_f values in agreement with the values for the compound that was derived from N-acetyl-β-(3-methoxydinitrophenyl)-D,L-alanine methyl ester melting at 172–173°. The R_f value for the compound in water–ethanol (2:3) was 0.66, and in *t*-amyl alcohol the R_f was 0.32. For the isomer melting at 234–235° dec. the R_f value in water–ethanol (2:3) was 0.70, and *t*-amyl alcohol the R_f was 0.47.

N-Acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine and N-Acetyl-β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine.—A solution of 0.15 g. of β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine, derived from 3-methoxy-2,6-dinitrobenzaldehyde, in 0.4 ml. of water and 0.42 ml. of 1.92 *N* sodium hydroxide was kept in ice-water during the alternate addition of six 0.36-ml. portions of 1.92 *N* sodium hydroxide and six 0.06-ml. portions of acetic anhydride. After 4 hr. at room temperature the mixture of solution and solid was treated with 0.9 ml. of 6.258 *N* sulfuric acid. The somewhat impure crystals of N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine (0.15 g.) were collected, washed with water and purified by recrystallization from aqueous ethanol (1:1) or from ethyl acetate, being dried in an evacuated

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desiccator over calcium chloride, the pure light-yellow crystals melted at 252° dec.

Anal. Calcd. for $C_{12}H_{13}N_3O_8$: C, 44.04; H, 4.00; N, 12.84. Found (dried at 100° *in vacuo*): C, 44.25; H, 4.14; N, 12.65.

β-(3-Methoxy-4,6-dinitrophenyl)-D,L-alanine (50 mg.), derived from 3-methoxy-4,6-dinitrobenzaldehyde, was acetylated as described for β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine using one-third the quantities of sodium hydroxide, acetic anhydride and sulfuric acid. The crude product (50 mg., m.p. 205°) was purified from absolute ethanol; m.p. 212–213°. Found (dried at 79° *in vacuo*): C, 43.83; H, 3.98; N, 12.70.

N-Acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine Methyl Ester and N-Acetyl-β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine Methyl Ester.—A solution of 50 mg. of N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine in 2.5 ml. of pure dioxane was mixed with a dry ether solution of diazomethane, prepared[7] from 0.4 g. of N-nitrosomethylurea and 4 ml. of ether. After the solution had been kept at 26–27° for 16 hr., the solvent was evaporated to deposit a sirup which crystallized upon being stirred with ether. Purified by recrystallization as slightly yellow needles from aqueous methanol and dried in an evacuated desiccator over calcium chloride, the compound melted at 158–159°, yield 35 mg.

Anal. Calcd. for $C_{13}H_{15}N_3O_8$: C, 45.75; H, 4.43; N, 12.32. Found: C, 45.55; H, 4.54; N, 12.31.

The compound was prepared also by esterification of N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine with the use of methanol and acetyl chloride.[5] To a solution prepared by adding 0.5 ml. of acetyl chloride to 5 ml. of methanol was added at 0° 43 mg. of N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine. The solution was kept at 25° for 23 hr., and the solvent then was evaporated at 30° *in vacuo*; the sirup was taken up in methanol, the solvent was evaporated and the operation was repeated. The sirup was crystallized as needles from methanol and purification was completed by recrystallization from benzene; m.p. 157–158°, not depressed when the substance was mixed with crystals of the methyl ester prepared with the use of diazomethane.

The reaction of diazomethane with the isomer of N-acetyl-β-(3-hydroxydinitrophenyl)-D,L-alanine melting at 194–195° (N-acetyl-C)[1] gave N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine methyl ester identical with the authentic compound obtained by the esterification of N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine. A solution of 40 mg. of pure N-acetyl-β-(3-hydroxydinitrophenyl)-D,L-alanine (m.p. 194–195°) in 2 ml. of pure dioxane was treated with diazomethane as described for N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine; yield 28 mg., m.p. 157–158°. A mixed melting point with crystals of the methyl ester prepared from N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine showed no depression and the infrared spectra (solid potassium bromide disk method) of the compound from the two sources were identical. Found: C, 46.23; H, 4.43.

The reaction of diazomethane with N-acetyl-β-(3-methoxy-4,6-dinitrophenyl)-D,L-alanine (38 mg.) was carried out as described for the similar reaction with N-acetyl-β-(3-methoxy-2,6-dinitrophenyl)-D,L-alanine, using 0.3 g. of N-nitrosomethylurea, 3 ml. of ether and 2 ml. of dioxane. The product, after purification from methanol and drying in an evacuated desiccator over calcium chloride, melted at 172–173°, not depressed when mixed with crystals of the previously reported[1] isomer of N-acetyl-β-(3-methoxydinitrophenyl)-D,L-alanine methyl ester melting at 172–173°. Found: C, 45.78; H, 4.39.

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(7) W. E. Bachmann and W. S. Struve, in R. Adams, "Organic Reactions," Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1942, p. 50.

[CONTRIBUTION FROM THE GENERAL LABORATORIES, U. S. RUBBER CO.]

Chain Scission in the Oxidation of Hevea. IV. Low Molecular Weight Products from Dry Rubber

BY E. M. BEVILACQUA

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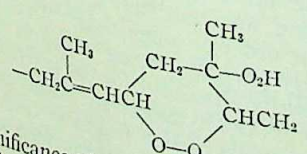
Estimates of yields of volatile products from the scission by oxygen of hevea rubber in latex[2] have been supplemented with measurements on dry rubber at 140°. The results make it possible to outline a mechanism for the scission reaction which accounts quantitatively for known products.

Some time ago Bolland and Hughes[1] deduced a structure (I) for the primary oxidation product of 1,5-dimethyl-1,5-dienes from the results of functional group analyses of partially oxidized squalene, oxidized under conditions of high chain length so that the primary product was obtained in high yield.



I

The significance of this result to the oxidation of hevea rubber was not known until quantitative estimates of the low molecular weight products of the oxidation of hevea in latex gave indirect evidence that a closely related structure must be formed in order to account for the observed products of the scission reaction.[2]

In latex the observed end-products, acetic acid, formic acid and carbon dioxide, are produced in stoichiometric ratios of 1:1:3. The yields relative to the production of new molecules by breaking the hydrocarbon chain show that six chain atoms appear as low molecular weight products at each scission.[3] A reasonable process involving six chain atoms in the scission reaction can be visualized readily by making use of a simple modification of the reaction mechanism postulated by Bolland and Hughes to account for I as a primary product. The important features of this mechanism are the ready addition of a peroxide radical to a double

(1) J. L. Bolland and H. Hughes, *J. Chem. Soc.*, 492 (1949).

(2) E. M. Bevilacqua, THIS JOURNAL, 77, 5394, 5396 (1955).

(3) E. M. Bevilacqua, *Rubber Chem. Technol.*, 30, 271 (1956).

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bond when a six-membered ring can be formed and the mobility of allylic radicals.[3]

The volatile compound of highest molecular weight previously identified with the oxidation of natural rubber is levulinaldehyde.[4] Although no clearcut evidence has been published for the direct formation of this material during oxidation with molecular oxygen, it generally has been assumed to be the product formed during aging of rubber which reacts with ammonia to give a compound which exhibits a positive "pyrrole" test. The present paper offers evidence supporting this belief and leading further to the conclusion that it is a direct intermediate in the scission reaction, which arises from the decomposition of a peroxide formed by the general process outlined by Bolland and Hughes.

Experimental

The molar ratio of volatile products from the oxidation of rubber to oxygen consumed is a function of temperature[2,3] approaching equivalence above 130°. In order to take advantage of this effect to obtain maximum yields of low molecular weight compounds, an apparatus was set up to permit experiments at elevated temperatures and to remove the volatile products from the reaction site as rapidly as possible.

In this apparatus the cell which contained the sample was mounted in a circulating air oven. The temperature was held constant to ±0.3°. In series with it were a trap immersed in a constant temperature bath and a gas circulating pump. The trap, outside the oven, was held at 0 or −80°, depending on what it was desired to collect. The pump, in the oven, was constructed according to the design of Cockett[5] modified only in that all moving parts in contact with the hot oxygen were of Teflon. A group of gas burets connected in parallel external to the cell were used to measure volume changes. They were surrounded by jackets in which water at 38° was circulated continuously during an experiment. All connections between parts not inside the oven or constant temperature baths were of capillary tubing to keep the volume subjected to uncontrolled temperature fluctuations as small as possible.

Pressure in the system was maintained constant during an experiment by periodic manual adjustment in which oil ("Hyvac" oil-93050) was added to the buret until a reference manometer containing a silicone oil (DC350) showed no head. The reference pressure was established in a sealed cell having nearly the same volume as the sample cell and mounted beside it in the oven. The volume of oil added was taken to be a direct measure of the volume of oxygen disappearing from the system by absorption in the sample. The oil, at 38°, absorbed oxygen at a negligible rate compared with the sample at 140°.

Low molecular weight products were recovered in the traps. The problem of quantitative recovery of very small amounts of products from large volumes of fast moving gas in one pass so that no product re-enters the oven, without raising the pressure drop in the apparatus, still has not been solved in a completely satisfactory way. However, the results indicate that nearly quantitative recovery of important products has been achieved. To trap acid gases two absorbers in series were used designed to give a high gas–liquid interface with a low resistance to flow. They were partially filled with standard alkali and held at 0° during a run. They were followed by a simple U-tube immersed in a Dry Ice–acetone-bath to remove water from the gas stream. In experiments in which it was attempted to estimate levulinaldehyde, this sequence of traps was replaced by a single small H-shaped trap cooled in a Dry Ice–acetone mixture.

Oxidized rubber samples were removed from the oven as soon as the desired amount of oxygen had been absorbed. They were cooled rapidly to room temperature in a stream of air or nitrogen, depending on how fast they absorbed oxygen. Intrinsic viscosities were determined in chloroform solution and molecular weights calculated on the basis of the relation determined by Carter, Scott and Magat,[6] as described previously.[2]

Results and Discussion

The first result using this apparatus was the observation that the condensate obtained in a trap held at −80° (from the gas stream passed over a sample in the oven at 140°) gave a strong positive test when heated with ammonium acetate, and the vapors were tested for pyrrole according to the procedure of Bruni.[4] The first few experiments were erratic and results depended on sample source and preparation. When a method for sample preparation was devised which gave consistently high yields of this product, as judged qualitatively, an effort was made to obtain quantitative determination.

It was assumed that the material is levulinaldehyde; no good quantitative test for this aldehyde is known. Although optical methods for carbonyl compounds based on the formation of the dinitrophenylhydrazone have been reported in the literature to give good results in the concentration range encountered here, they will not differentiate between aldehydes, and in our hands the results for other carbonyl compounds have not been nearly as satisfactory as could be desired at low concentrations. Since no other low molecular weight methyl ketone is suspected to be a probable product from the oxidation of rubber under our conditions, it was attempted to apply the iodoform reaction[7] for the quantitative estimation of levulinaldehyde in the volatile material collected in the trap. When this was done the results shown in Table I were obtained. In this and the other tables and figures in this report where units are not specified they are moles per 10^5 grams of rubber. Plotting the values of methyl ketone against "cuts" from this table we obtain Fig. 1. It is evident that a linear correlation exists between volatile methyl ketone, presumably levulinaldehyde, and cuts of the hydrocarbon chain, and that they are formed in amounts of the same order of magnitude. This observation immediately permits closing a gap in the mechanism originally advanced for the reaction by which oxygen severs the hydrocarbon chain,[2] in which the nature of the five carbon fragment from which low molecular weight products are formed was entirely

TABLE I

VOLATILE METHYL KETONE PRODUCED

(All units moles/10^5 grams rubber)

Oxygen absorbed	Cuts	Methyl ketone
6.0	1.2	0.19
12.0	1.6	.32
14.0	1.4	.37
17.5	1.8	.39
20.0	1.6	.64
23.8	2.2	.75
28.0	1.9	.65
36.6	2.9	.94

(4) This is reviewed by Dufraisse in "The Chemistry and Technology of Rubber," C. C. Davis and J. T. Blake, eds., Reinhold Publishing Corp., New York, N. Y., 1937, Ch. XIII.

(5) A. H. Cockett, *Nature*, **175**, 768 (1955).

(6) W. C. Carter, R. L. Scott and M. Magat, THIS JOURNAL, **68**, 1480 (1946).

(7) F. D. Snell and C. T. Snell, "Colorimetric Methods of Analysis," 3rd Ed., Vol. III, D. Van Nostrand Co., Inc., New York, N. Y., 1953, p. 263.

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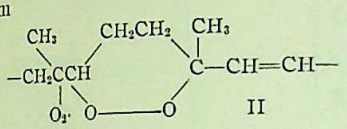
hypothetical. Levulinaldehyde clearly can be the source of both the acetic acid and the carbon dioxide found in the experiments in which rubber was oxidized in latex. The complete mechanism has been outlined elsewhere[3]; it gives a satisfactory explanation for all the known low molecular weight products of the oxidation of rubber, although details of certain steps still need to be worked out. It requires that each scission be accompanied by the loss of six carbon atoms from the hydrocarbon chain, the key intermediate having a structure of the form



II

Upon scission the entire material in the six-membered ring of the peroxide dissociates from the chain, giving as the first stable product levulinaldehyde. When the rubber is oxidized as latex, the aldehyde is trapped in the aqueous phase and rapidly oxidized to CO_2 and acetic acid.[2] Although this step has not been demonstrated experimentally, the readily available levulinic acid does undergo rapid oxidation in dilute aqueous ammonia solution under the same conditions as were used in the latex experiments, giving the theoretical yields of carbon dioxide and acetic acid.

Results of typical experiments are given in Table II. In these the acid[8] (98.1% levulinic acid

TABLE II

PRODUCTS OF LEVULINIC ACID OXIDATION

Oxygen consumed (mmoles)	Produced CO_2 (mmoles)	acid (meq.)	$\frac{CO_2}{acid}$
..	6.59	2.41	2.75
12.6	7.92	2.42	3.28

by titration) was oxidized at 90° as a 0.227 *N* solution in 2% ammonia containing a small amount of added copper. The apparatus and procedure have been described.[2] Acetic acid was identified by its volatility and characteristic odor and confirmed by partition chromatography on silica and by X-ray comparison of its silver salt with an authentic specimen.[9] These results correspond to substantially quantitative oxidation of the acid

$$CH_3CCH_2CH_2CO_2H \longrightarrow CH_3CO_2H + 3CO_2\ (+H_2O)$$

No other acids were identified among the products of these experiments, although the oxidation presumably must involve others as intermediates.

In the experiment described here the yield from the oxidation of dry rubber of approximately one-third mole of methyl ketone per mole of scissions is presumably a measure of the efficiency with which levulinaldehyde was removed from the reaction zone before it could undergo further oxidation. If this is so, the low molecular weight acids found as products of latex oxidation should also appear in this experiment, and if quantitative recovery can be obtained it should be possible to calculate roughly the amounts which will be found: One scission is

(8) Supplied by the Quaker Oats Co.
(9) F. W. Mathews, *et al.*, *Ind. Eng. Chem.*, **22**, 514 (1950).

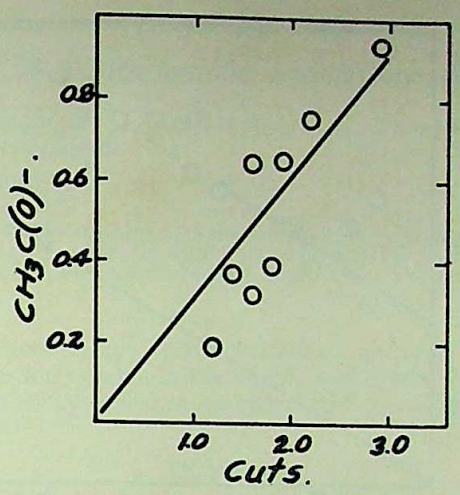


Fig. 1.—Volatile methyl ketone (levulinaldehyde) formed during oxidation of rubber at 140°.

equivalent to one levulinaldehyde plus one formaldehyde which yield as the completely oxidized end products three CO_2 plus one acetic acid from the first aldehyde and one formic acid from the second. Since one-third of the levulinaldehyde is removed as such, the final yields of CO_2 and volatile acids should be

$$CO_2 \approx 2/3 \times 3 = 2 \text{ moles/mole scissions}$$

$$\text{Volatile acid} \approx 2/3 \times 1 + 1 = 1.7 \text{ moles/mole scissions}$$

Experimental results of such determinations are assembled in Table III for the same type of rubber

TABLE III

ACIDS FORMED DURING OXIDATION

(Rubber leached with water)

Oxygen absorbed	Cuts	CO_2	Volatile acid
4.0	0.6	1.2	1.0
8.0	1.2	3.6	0.8
12.0	0.8	2.9	0.8
16.8	1.0	4.4	1.3
24.1	1.9	7.4	1.6
25.0	(2.0)	8.8	1.0
31.2	3.2	4.0	1.6
31.7	2.3	2.9	2.0
39.6	4.1	4.0	2.4
45.0	(3.3)	6.3	1.7

sample which was used to obtain the results of Table I. When the data of Table III are plotted for comparison with predicted values based on the calculations in the preceding paragraph, the yields of CO_2 and volatile acid are of the expected order of magnitude, although the scatter of the points for CO_2 is undesirably high and the acid yields are somewhat low. Although we can attribute part of the scatter to simple experimental error in separating and measuring the very small quantities of acids obtained from the necessarily small samples of rubber, the results shown in the next Fig. 2 and 3 indicate that fairly good precision can be obtained and some of the differences between prediction and experimental results are real and must be accounted for. The data presented in Fig. 1 and in Table III were obtained by the oxidation of rubber which was coagulated on a form from whole latex and then leached with boiling water for 2 hr. Data

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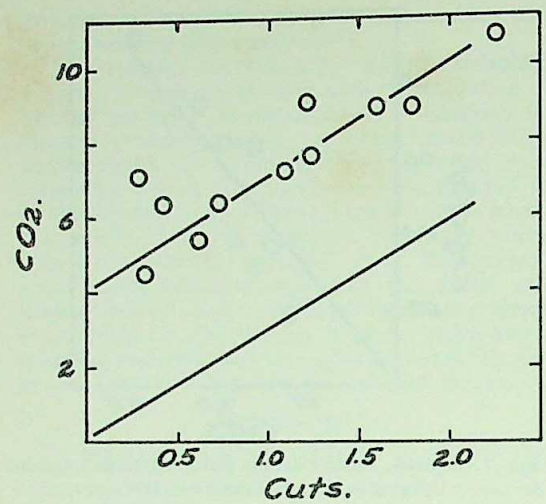

Fig. 2.—Yield of CO_2 from unleached rubber; solid line in Figs. 2 and 3 has slope calculated in text.

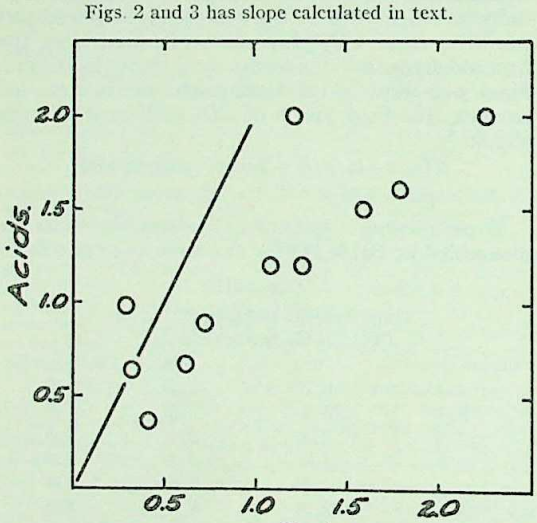

Fig. 3.—Yield of volatile acids same samples as Fig. 2.

in the following two figures were obtained using unleached samples (Table IV). In these figures the

TABLE IV
ACIDS FORMED DURING OXIDATION
(Rubber dried on form)

Oxygen	Cuts	CO_2	Volatile acid
3.15	0.29	7.1	0.98
5.77	.42	6.4	.36
6.30	.32	4.5	.64
8.65	.62	5.4	.67
9.45	.73	6.4	.89
12.60	1.09	7.2	1.2
15.7	1.26	7.6	1.2
15.7	1.21	9.1	2.0
18.9	1.80	8.9	1.6
22.1	2.26	10.8	2.0
23.6	1.60	8.9	1.5

solid lines have theoretical slopes. It is apparent that spuriously high yields of carbon dioxide are formed, probably resulting from [illegible]

bility of serum acids present in the unleached rubber. Presumably the scatter of the CO_2 results in Table III is attributable to incomplete removal of acids in the leaching process. On the other hand, the yields of volatile acids in this experiment are reasonably self consistent and about the same as in the previous one.

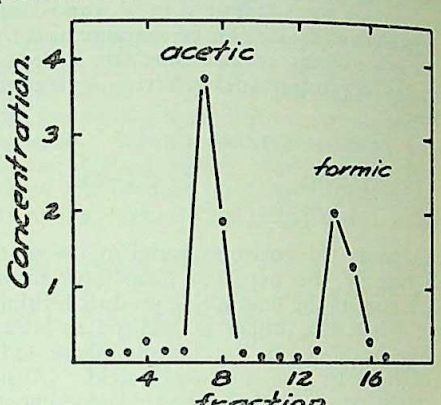

Fig. 4.—Separation of volatile acids on silica column; areas under peaks are proportional to concentrations.

Our calculations are based on the assumption that all the formic acid normally produced when latex is oxidized is formed in the present experiment also and that only the acetic acid yield is lowered by sweeping out the cell with gas. When the mixture of volatile acids actually obtained was analyzed by separation on a silica column, it was found that acetic acid is present in concentrations which are equal to or greater than that of formic acid (Fig. 4). The material which still remains to be accounted for, therefore, is formic acid or a precursor thereof.

Several explanations have been considered for the low apparent yield of formic acid, which has not been resolved experimentally. If formic acid were rapidly oxidized, CO_2 yields should be consistently high. This is not definitely excluded by our data but appears unlikely. If a non-acid intermediate (presumably formaldehyde) were distilled from the reaction cell, yields would be low. Formaldehyde has been found in the distillate, but it accounts for only about 10% of the missing formic acid. The results of end-group determinations[10] suggest that under the conditions used in these experiments about half the carbon from which formic acid is derived during oxidation of latex remains with the polymer, rather than appearing as a volatile product.

In summary, the results reported here, together with those reported previously, show that there is no significant change in the mechanism of degradation of rubber by oxygen over a wide temperature range. The over-all mechanism appears to be well established and able to account for the variations in product ratios caused by changing experimental conditions. Only the details of the final steps in the scission process remain to be clarified.[11]

PASSAIC, N. J.

(10) E. M. Bevilacqua, to be published.

(11) A report of this work was presented at a meeting of the Rubber Division of the American Chemical Society, September 20, 1956.

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[COMMUNICATION NO. 1826 FROM THE RESEARCH LABORATORIES, EASTMAN KODAK CO.]

Azomethine Dyes. II. Color and Constitution of Acylacetamide Azomethine Dyes

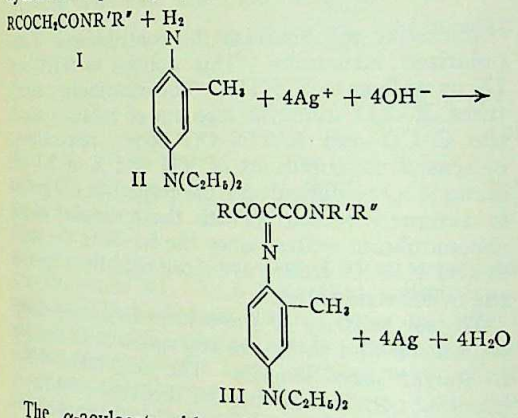
BY G. H. BROWN, J. FIGUERAS, R. J. GLEDHILL, C. J. KIBLER, F. C. MCCROSSEN, S. M. PARMERTER, P. W. VITTUM AND A. WEISSBERGER

RECEIVED JULY 2, 1956

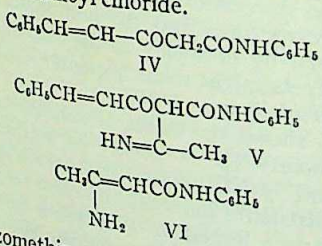
The synthesis and properties of a number of α-acylacetamides and the azomethine dyes derived from them are reported. The azomethine dyes are formed by oxidative condensation of the α-acylacetamides with 4-amino-3-methyl-N,N-diethylaniline. The effects of substituents and of changes in solvent on the absorption spectra of these dyes are interpreted on the basis of electronic and steric factors and hydrogen-bonding.

Introduction

A preceding investigation[1] dealt with the relation between color and structure of some magenta azomethine dyes derived from 5-pyrazolones. The present paper is concerned with a similar study of azomethine dyes (III) derived from acylacetamides, which are widely used as yellow-image dyes in color photography.[2]



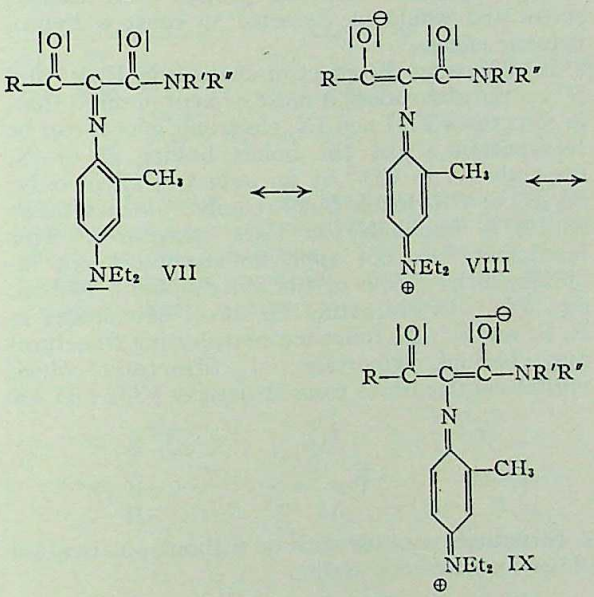
The α-acylacetamides (I) were prepared by condensing β-ketoesters with amines in boiling xylene.[3] Some vinylogs, *i.e.*, α-cinnamoylacetanilides (IV), not accessible in this manner, were prepared by solvolysis of iminoacyl compounds (V)[4] formed by acylation of β-aminocrotononanilides (VI) with cinnamoyl chloride.



The azomethine dyes (III) were prepared from the acylacetamides (I) and 4-amino-3-methyl-N,N-diethylaniline (II), using potassium ferricyanide (method A) or silver chloride (method B)[5] as the oxidant. The dyes were purified by chromatography and crystallization, and their absorption spectra in the visible region were determined in cyclohexane, *n*-butyl acetate and methanol.[6]

Discussion

Position of the Absorption Maximum.—The absorption in the visible region by the dyes under consideration can be attributed essentially to the resonance system VII, VIII, IX. Structure VII can be expected to make the preponderant con-



tribution to the resonance hybrid representing the ground state; it differs from the other major contributing structures VIII and IX by the aromaticity of the *p*-phenylenediamine moiety and by the absence of charge separation. When absorption of visible light or near-ultraviolet radiation raises the molecule to a higher-energy level, the polarized (ionic) structures VIII and IX make larger contributions to the excited state.[7] Structural changes which render the polarized structures more stable therefore decrease the energy difference between the ground and excited states and would be expected to cause a bathochromic shift. Structural changes which destabilize the polarized structures

(1) G. H. Brown, B. Graham, P. W. Vittum and A. Weissberger, THIS JOURNAL, **73**, 919 (1951).

(2) (a) R. M. Evans, W. T. Hanson, Jr., and W. L. Brewer, "Principles of Color Photography," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 259. (b) P. W. Vittum and A. Weissberger, *J. Phot. Sci.*, **2**, 81 (1954).

(3) C. J. Kibler and A. Weissberger, *Org. Syntheses*, **25**, 7 (1945).

(4) E. Benary and W. Kerckhoff, *Ber.*, **59**, 2549 (1926).

(5) P. W. Vittum and G. H. Brown, THIS JOURNAL, **68**, 2235 (1946).

(6) Data on similar yellow dyes which comprise moieties of polymeric systems [J. O. Corner and E. L. Martin, *ibid.*, **76**, 3593 (1954)] cannot be compared with our results, since Corner and Martin used a different developer (N,N-diethyl-*p*-phenylenediamine) and determined the absorption curves of photographic images and not of dyes in solution.

(7) A. Maccoll, *Quart. Revs.*, **1**, 39 (1947).

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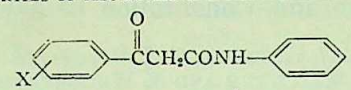
TABLE I

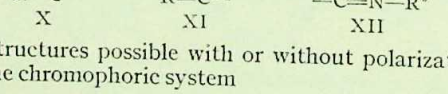
PROPERTIES OF AZOMETHINE DYES DERIVED FROM



X	M.p., °C.	λ_{max}, mμ (s) Cyclo	Bu-Ac	MeOH	$\epsilon_{max} \times 10^{-4}$ (s) Cyclo	Bu-Ac	MeOH	s Cyclo	Bu-Ac	MeOH	Calcd. C	H	N	Analyses, % Found C	H	N	Method
H	164–165	424	433	448	1.7	1.6	1.5	0.15	0.20	0.34	75.5	6.6	10.1	75.6	6.8	9.9	B
o-CH_3	146–147	424	434	450	1.7	1.6	1.6	.16	.21	.35	75.9	6.8	9.8	75.8	6.9	9.8	B
2,4,6-$(CH_3)_3$	149–150	439	446	466	1.3	1.8	2.4	.46	.24	.36	76.4	7.3	9.2	76.8	7.5	9.1	A
o-OCH_3	153–154	415	420	434	1.1	1.0	1.1	.27	.31	.38	73.1	6.6	9.5	73.3	6.2	9.4	B
m-OCH_3	144–145	425	434	448	1.7	1.6	1.5	.14	.20	.34	73.1	6.6	9.5	73.0	6.6	9.6	B
p-OCH_3	127–128	422	430	446	1.8	1.6	1.6	.13	.20	.31	73.1	6.6	9.5	73.2	6.4	9.5	B
p-Cl	148–149	427	436	455	1.7	1.6	1.5	.17	.25	.36	69.7	5.8	9.4	70.0	5.7	9.8	A
m-NO_2	169–170	434	443	472	1.5	1.4	1.5	.28	.38	.40	68.1	5.7	12.0	68.3	5.5	12.0	A
p-NO_2	167–168	420	430	460	1.7	1.5	1.4	.34	.42	.57	68.1	5.7	12.2	68.4	5.5	12.5	B
p-NH_2	192–193	422	426	444	..	1.4	1.5	.14	.18	.27	72.9	6.6	13.1	73.2	7.0	13.1	B
p-$NHCOCH_3$	274–275	..	432	447	..	..	..	..	.19	.36	71.5	6.4	12.0	71.3	6.4	12.3	B
p-$NHCOC_6H_5$	211–212	..	433	446	..	1.6	1.4	..	.24	.38	74.4	6.1	10.5	74.5	5.9	10.5	B
p-$NHSO_2C_6H_5$	204–205	..	434	447	..	1.6	1.5	..	.21	.32	67.6	5.7	9.9	68.1	5.7	10.3	B

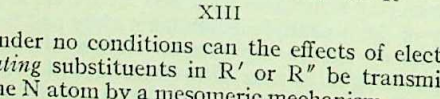
or stabilize the non-polarized structure increase the energy difference between ground and excited states and would be expected to cause a hypsochromic effect.

In discussing the effect of changes in R, R′ and R″ on the absorption, it must be kept in mind that, in structures VIII and IX, electronic effects can be transmitted across the bonds linking R or N, respectively, to $CO^{\ominus}$ by an inductive effect only; an RC or CN double bond required for mesomeric effects is impossible in these structures. This restriction does not apply to structures not involving polarization of the chromophoric system, *e.g.*, VII. In evaluating the effect of changes in R, R′ and R″, the following contributing structures may become important: 1. Structures which inhibit contributions from structures VIII and IX



X XI XII

2. Structures possible with or without polarization of the chromophoric system



XIII

Under no conditions can the effects of electron-*donating* substituents in R′ or R″ be transmitted to the N atom by a mesomeric mechanism.

Increased contributions by structures XII and X or XI will lower the energy of the ground state, interfere with contributions from structures VIII and IX and cause a hypsochromic effect. Increased contributions by structures X or XI will cause a shift in the same direction, although in one case electron-donating and in the other case electron-accepting substituents are involved.

Figure 1 shows the crowding of the dye molecule. For maximum interaction of the structures which contribute to a resonance hybrid, coplanarity of the groups connected by bonds with double-bond character is required; steric hindrance of coplanarity will diminish the contributions of the polarized structures. This applies to VIII and IX as well as to X–XIII. The contributing structures X–XII diminish freedom of rotation about the C–CO and R′R″N–CO bonds, respectively; increased contributions of XII and X or XI will make it more difficult for the respective CO groups to assume coplanarity with the remainder of the chromophoric system since the bonds to the bulky R and NR′R″ groups are more rigid than those in the other structures.

Higher polarity of the solvent facilitates charge separation and shifts the absorption of all the dyes to longer wave lengths. The magnitude of this effect is correlated with the dielectric constant of the solvent ($\epsilon_{25°}$ = 2.02 for cyclohexane, 4.94 for butyl acetate, 32.6 for methanol); its mechanism can be visualized as solvation in which neutralization of electric fields by oriented solvent dipoles and/or hydrogen-bonding play a role.

In the following interpretation of the spectra, restraint is exercised because the number of contributing structures and the additional complications caused by crowding of the molecule and by solvent effects might make a greater elaboration of details too arbitrary.

Table I shows the effect of substituents in the benzoyl moiety (R = aryl). In methanol, *p*-Cl, *m*-NO_2 and *p*-NO_2 have bathochromic effects; these substituents decrease the electron density at the ring carbon linked to –CO, which may increase the contribution of VIII and lower the energy of the excited state. The bathochromic effect of *p*-Cl is small; the mesomeric electron-donating nature of chlorine will increase the contribution of X, an effect which, by itself, would cause a hypsochromic shift. In cyclohexane and in butyl acetate *p*-NO_2 has a small hypsochromic effect, as have *o*- and *p*-methoxy and *p*-NH_2. This indicates increased contributions of X or XI under the influence of these groups. In methanol, the electron-attracting effect of NO_2 appears to be increased, probably by hydrogen-bonding of the NO_2 group [illegible] so that the greater stabilization

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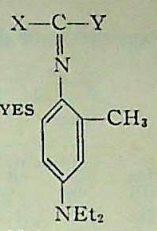
TABLE IIA

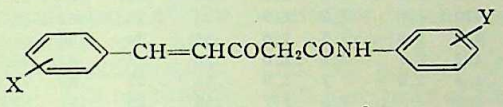
PROPERTIES OF AZOMETHINE DYES



X	Y	M.p., °C.	λ_{max}, mμ Cyclo	BuAc	MeOH	$\epsilon_{max} \times 10^{-4}$ Cyclo	Bu-Ac	MeOH	Calcd. C	H	N	Found C	H	N	Method
CH_3CO	$CONHC_6H_5$	104–105	423	433	448	1.5	1.6	1.9	69.5	7.9	10.6	69.5	8.0	10.5	B
C_6H_5CO	$CON(CH_3)C_6H_5$	138–139	448	457	474	0.9	1.2	1.7	75.9	6.8	9.8	76.2	6.5	9.8	B
			409	414	430		1.3	1.3							B
C_6H_5CO	$CONH_2$	153–154	405	413	433	1.1	1.0	1.1	71.8	7.2	12.0	72.2	7.6	11.7	B
C_6H_5CO	$CONHCH_3$		434	446	465	1.1	1.3	1.9	72.3	7.4	11.5	72.3	7.7	11.8	
C_6H_5CO	$CON(CH_3)_2$	122–123	446	461	478	1.2	1.5	1.7	78.4	6.6	7.0	78.0	6.8	7.0	
C_6H_5CO	C_6H_5CO														

TABLE IIB

PROPERTIES OF AZOMETHINE DYES DERIVED FROM



X	Y	M.p., °C.	λ_{max}, mμ Cyclo	Bu-Ac	MeOH	$\epsilon_{max} \times 10^{-4}$ Cyclo	Bu-Ac	MeOH	S Cyclo	Bu-Ac	MeOH	Calcd. C	H	N	Found C	H	N	Method
H	H	131–132	420	440	Unstable	0.7	1.1	Unstable	0.40	0.50	Unstable	76.4	6.6	9.6	76.6	6.5	9.6	B
H	o-OCH_3	141–142	414	427	454	1.3	1.6	1.6	.37	.34	0.45	74.1	6.7	8.9	74.1	6.6	8.9	B
p-OCH_3	o-OCH_3	166–167	414	427	450	1.3	1.1	1.1	.35	.30	.43	72.1	6.7	8.4	72.0	6.7	8.5	B

of VIII outweighs the effect caused by an increased contribution of XI. 2,4,6-Trimethyl substitution has a large bathochromic effect. Since the effect of mono-*o*-methyl substitution is small, we are inclined to ascribe the large bathochromic effect to steric causes. Steric interference with coplanarity of the chromophoric system would result in decreased stability of VIII and should therefore cause a hypsochromic shift. If, however, the steric interference reduces the contribution of X, the CO group will be freer to become coplanar with the rest of the chromophoric system (Fig. 1), and the bathochromic effect observed should result.

Replacement of benzoyl by acetyl (Table IIA) does not change λ_{max}, indicating a similar stabilization of structure X, by C_6H_5 and by CH_3, in which probably hyperconjugation of CH_3 plays a role. A very small hypsochromic shift by cinnamoyl (Table IIB) in cyclohexane solution may be attributed to a reduction in steric hindrance for structure X. Solvation of the vinyl system in butyl acetate may render it electron accepting and explain the bathochromic effect. *o*-Methoxy substitution in the cinnamoyl ring, as in the benzoyl derivative, results in a shift of λ_{max} to shorter wave lengths.

Substitution in the anilide ring (III, R′ = aryl) follows a similar pattern (Table III); electron-attracting groups, acting to stabilize structures XIII and to destabilize structure XII, will favor structure IX and produce bathochromic effects. Electron-donating groups (*o*- and *p*-methoxy and dimethylamino) cause very small hypsochromic shifts. At variance with substitution in the benzoyl ring, an electron-attracting substituent in the anilide ring will never interfere with polarization of the chromophoric system but will enhance it through lowering of the electron density of the amide nitrogen. One methyl group has little or no effect on the absorption. Two *o*-methyl or *o*-methoxy groups, however, cause strong hypsochromic effects, presumably because they destabilize for steric reasons structures XIII and, therefore, increase the relative contribution of structure XII.

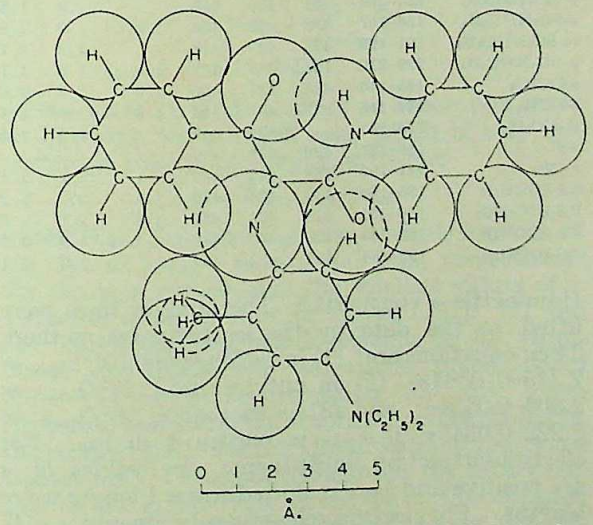


Fig. 1.—Scale drawing of α-benzoyl-α-(4-diethylamino-2-methylphenylimino)-acetanilide. The covalent bond radii and van der Waals' radii are those given by Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, N. Y.

In Fig. 2 are plotted reciprocals of λ_{max} for dyes substituted in the anilide ring (Table III) against

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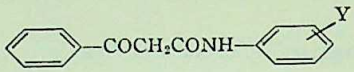
TABLE III

PROPERTIES OF AZOMETHINE DYES DERIVED FROM



Y	M.p., °C.	λ_{max}, mμ Cyclo	Bu-Ac	Me-OH	$\epsilon_{max} \times 10^{-4}$ Cyclo	Bu-Ac	Me-OH	s Cyclo	Bu-Ac	Me-OH	Analyses, % Calcd. C	H	N	Found C	H	N	Method
H	164–165	424	433	448	1.7	1.6	1.5	0.15	0.20	0.34	75.5	6.6	10.1	75.6	6.8	9.9	B
o-CH_3	142–143	425	434	447	1.7	1.8	1.7	.16	.19	.32	75.9	6.8	9.8	75.6	6.7	9.6	B
m-CH_3	156–157	426	434	450	1.6	1.6	1.5	.15	.21	.34	75.9	6.8	9.8	75.6	6.8	9.9	B
p-CH_3	152–153	425	434	448	1.7	1.6	1.6	.16	.21	.34	75.9	6.8	9.8	75.8	6.8	10.0	B
2,6-$(CH_3)_2$	148–149	411	417	438	1.3	1.2	1.1	.20	.28	.40	76.2	7.1	9.5	76.0	7.1	9.4	B
o-OCH_3	162–163	421	432	447	1.7	1.9	2.0	.16	.17	.25	73.1	6.6	9.5	72.7	6.8	9.1	B
m-OCH_3	151–152	427	436	451	1.8	1.7	1.6	.14	.20	.35	73.1	6.6	9.5	73.4	6.6	9.5	B
p-OCH_3	148–149	422	430	448	1.6	1.5	1.5	.18	.23	.35	73.1	6.6	9.5	72.8	6.3	9.5	B
o-Cl	163–164	432	442	453	2.0	2.2	2.1	.14	.18	.26	64.7	5.8	9.4	69.8	5.7	9.6	B
m-Cl	119–120	430	438	453	1.9	1.6	1.6	.15	.22	.35	69.7	5.8	9.4	69.6	6.0	9.1	B
p-Cl	165–166	430	438	452	1.8	1.7	1.5	.15	.22	.33	69.7	5.8	9.4	69.6	5.8	9.1	B
o-Br	165–166	431	440	452	1.9	2.0	2.0	.15	.19	.29	63.4	5.3	8.5	63.7	5.4	8.8	B
m-Br	132–133	430	438	452	1.9	1.6	1.6	.15	.22	.36	63.4	5.3	8.5	63.8	5.5	8.7	B
p-Br	170–171	431	437	452	1.9	1.7	1.6	.14	.22	.31	63.4	5.3	8.5	63.8	5.5	8.6	B
p-I	183–184	430	438	452	2.0	1.7	1.7	.14	.21	.33	57.9	4.9	7.8	58.1	4.6	7.6	B
o-NO_2	193–194	452	460	470	1.9	1.9	1.9	.16	.23	.32	68.1	5.7	12.2	68.1	5.6	12.0	B
m-NO_2	149–150	434	441	455	1.9	1.7	1.6	.16	.24	.36	68.1	5.7	12.2	68.2	5.7	12.1	B
p-NO_2	178–179	440	451	462	2.4	2.1	2.0	.15	.21	.32	68.1	5.7	12.2	68.2	5.4	12.2	B
m-CN	152–153	433	440	454	2.0	1.7	1.6	.15	.22	.35	73.9	6.0	12.8	73.8	6.3	12.8	A
p-CN	191–192	438	446	458	..	1.9	1.7	.15	.22	.32	73.9	6.0	12.8	74.0	5.9	13.1	B
o-NMe_2	126–127	423	433	448	1.7	1.9	2.0	.14	.17	.25	73.7	7.1	12.3	73.5	7.2	12.2	A
m-NME_2	164–165	420	430	447	1.6	1.8	1.4	.19	.24	.33	73.7	7.1	12.3	73.3	7.0	12.6	A
p-NME_2	160–161	421	431	450	1.6	1.7	1.6	.28	.31	.40	73.7	7.1	12.3	73.6	6.8	12.6	A
o-$NHCOC_6H_5$	218–219	436	438	451	S. sol.	1.7	1.6	.18	.23	.33	74.4	6.1	10.5	74.7	5.9	10.3	A
m-$NHCOC_6H_5$	.....	428	434	450	S. sol.	1.1	1.1	.16	.23	.33	74.4	6.1	10.5	74.5	6.3	10.1	A
p-$NHCOC_6H_5$	201–202	430	435	452	S. sol.	1.5	1.4	.18	.21	.33	74.4	6.1	10.5	74.9	6.5	10.2	A
m-$NHSO_2C_6H_5$	204–205	429	435	450	S. sol.	1.6	1.5	.20	.22	.34	67.1	5.7	9.8	67.6	6.0	9.9	A
p-$NHSO_2C_6H_5$	215–216	Ins.	436	452	Ins.	1.7	1.6	Ins.	.22	.34	67.6	5.7	9.8	67.9	5.8	9.8	A
m-$COCH_3$	154–155	430	436	453	1.8	1.6	1.5	0.16	.24	.33	73.8	6.4	9.2	74.1	6.4	9.2	A
p-$COCH_3$	184–185	434	442	456	2.1	1.9	1.8	.14	.21	.33	73.8	6.4	9.2	74.1	6.4	9.1	A
o-CO_2CH_3	181–182	432	441	454	1.6	1.8	1.7	.16	.22	.32	71.3	6.2	8.9	71.6	6.2	9.1	B
p-CO_2CH_3	171–172	432	441	455	2.1	1.9	1.8	.16	.21	.34	71.3	6.2	8.9	71.5	6.6	9.3	A
3,5-$(CO_2CH_3)_2$	173–174	432	439	454	..	1.6	..	.16	.24	.35	68.0	6.0	7.9	68.1	6.1	8.0	A
o-$CONHC_6H_5$	264–265	..	438	452	..	1.8	..	..	.19	.31	74.4	6.1	10.5	74.6	6.2	10.6	A
m-$CONHC_6H_5$	132–133	430	436	451	1.8	1.7	1.6	.15	.22	.34	74.4	6.1	10.5	74.4	5.8	10.6	A
p-$CONHC_6H_5$	221–222	434	440	455	..	1.9	1.8	.17	.22	.30	74.4	6.1	10.5	74.8	6.2	10.2	A
o-$SO_2NHC_6H_5$	166–167	438	442	456	1.8	1.9	1.8	.24	.23	.33	67.5	5.7	9.8	67.1	5.6	10.1	A
m-$SO_2NHC_6H_5$	191–192	433	439	454	..	1.7	1.7	.18	.23	.34	67.5	5.7	9.8	67.7	5.8	9.9	A
p-$SO_2NHC_6H_5$	229–230	Ins.	443	457	Ins.	1.8	1.7	Ins.	.21	.33	67.5	5.7	9.8	67.7	5.9	9.8	A
o-OC_6H_5	145–146	428	437	450	1.9	2.1	2.0	0.12	.16	.26	76.0	6.2	8.3	76.2	6.1	8.2	A
o-SCH_3	146–147	427	437	450	1.8	1.9	1.9	.15	.19	.31	70.6	6.4	9.1	70.6	6.4	9.5	B
m-CO_2H	238–239	..	434	447	..	1.5	1.5	..	.22	.34	70.9	5.9	9.2	70.5	6.0	9.3	A
o-F	186–187	428	439	449	..	..	..	.15	.18	.30	72.4	6.1	9.7	72.1	5.9	9.7	B
o-CF_3	151–152	433	442	453	2.1	2.2	2.1	.16	.20	.29	67.3	5.4	8.7	67.4	5.7	8.4	B
2,5-$(OCH_3)_2$	185–186	423	433	449	1.9	2.1	2.2	.15	.19	.27	71.0	6.6	8.9	71.0	6.4	8.9	A
2,5-$(OC_2H_5)_2$	150–151	422	434	450	1.8	2.0	2.0	.16	.19	.28	78.1	8.0	6.5	77.8	7.8	6.4	A
2,4-$(OCH_3)_2$	183–184	420	430	447	..	1.9	2.0	.17	.19	.28	71.0	6.6	8.9	71.4	6.8	9.2	A
2,6-$(OCH_3)_2$	193–194	411	420	439	..	1.3	1.4	.22	.25	.36	71.0	6.6	8.9	71.2	6.5	8.7	A

Hammett's σ-constants.[8] The straight lines were fitted to the data by the least-squares method. Their equations are: (1) in cyclohexane, $10^3/\lambda_{max} = 2.345–0.0564\sigma$; (2) in butyl acetate, $10^3/\lambda_{max} = 2.304–0.0554\sigma$; and (3) in methanol, $10^3/\lambda_{max} = 2.222–0.0345\sigma$, if λ_{max} is measured in mμ. For electron-attracting substituents, the values of σ are positive and λ_{max} is shifted toward longer wave lengths. For electron-releasing substituents, $\sigma < 0$, and λ_{max} shifts toward smaller values.

The marked hypsochromic effect on replacement of the phenyl ring in the anilide derivative by a methyl group or hydrogen (Table IIA) indicates that the phenyl ring acts as an electron acceptor; compared with methyl or hydrogen, phenyl stabilizes structures XIII and therefore increases the stability of structure IX. N-Methylation has a strong bathochromic effect. In view of the proximity of the amide hydrogen to the oxygen of the RCO group shown by Fig. 1, one might assume hydrogen bonding between amide hydrogen and carbonyl oxygen. Such hydrogen bonding should, however, stabilize VIII, and elimination of the chelation should cause a hypsochromic shift. The bathochromic shift observed can be explained by a decreased contribution of structure XII because of steric hindrance. It is noteworthy that the absorption of the methylanilide dye is very similar to that of the dibenzoylmethane dye, indicating a large reduction in the methylanilide dye of the contribution of structure XII.

The effects of substituents on both phenyl nuclei are roughly additive, as shown by Table IV.

It should be mentioned that geometrical isomerism about the C=N bond, if it should exist,

(8) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940; (b) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

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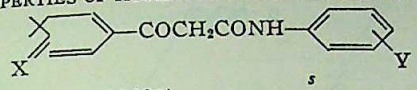
TABLE IV

PROPERTIES OF AZOMETHINE DYES DERIVED FROM



X	Y	M.p., °C.	λ_{max}, mμ Cyclo	Bu-Ac	Me-OH	$\epsilon_{max} \times 10^{-4}$ Cyclo	Bu-Ac	Me-OH	s Cyclo	Bu-Ac	Me-OH	Analyses, % Calcd. C	H	N	Found C	H	N	Method
H	H	164–165	424	433	448	1.7	1.6	1.5	0.15	0.20	0.34	75.5	6.6	10.1	75.6	6.8	9.9	B
o-OCH₃	p-NO₂	148–149	445	452	460	1.4	1.4	1.4	.15	.29	.35	64.4	5.8	11.5	66.6	5.9	11.2	B
p-OCH₃	p-OCH₃	165–166	420	430	446	1.8	2.0	2.1	.13	.15	.24	71.0	6.6	8.9	71.3	6.6	9.0	A
o-OCH₃	m-NO₂	187–188	428	432	443	..	1.2	1.1	.25	.26	.37	66.4	5.8	11.5	66.4	5.4	11.7	B
p-NO₂	o-OCH₃	213–214	416	429	444	1.8	1.9	1.8	.36	.32	.41	66.4	5.8	11.5	66.7	6.1	11.8	B
p-NH₂	o-OCH₃	201–202	..	425	442	..	2.0	1.9	..	.13	.25	70.7	6.6	12.2	70.5	6.8	12.5	B
p-NO₂	o-NMe₂	159–160	414	427	443	1.8	1.9	1.9	.34	.25	.41	67.0	6.2	14.0	67.2	6.2	13.7	B

would influence some of the steric effects just discussed. Our observations, however, do not demonstrate the presence of this geometrical isomerism.

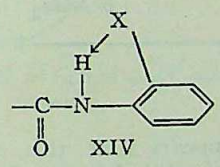
Extinction and Shape of the Absorption Curves.—Chemical constitution is better understood in its effect on the position of the absorption maximum than in its effect on extinction and shape of the absorption curve. These parameters are, however, of great importance in color photography, and some correlations can be made. The maximum extinction coefficient, ϵ_{max}, of a dye depends on the probability of the corresponding electronic transitions. Among the factors which determine this probability are the change in dipole moment accompanying the transition and the ability of the molecule to adopt the planar conformation required for excitation.[9] The change in dipole moment is not known from other data, but an effect of structural change on ϵ_{max} can be recognized, depending upon whether that change hinders or facilitates the adoption of a planar conformation of the molecule.

The anilide ring in the aroylacetanilide dyes has an intensifying (hyperchromic) effect on the absorption; ϵ_{max} of the benzoylacetanilide dye (Tables I and III) is about 20% larger than that of the benzoylacetamide dye (Table IIA). Introduction of two *o*-methyl groups in the anilide ring, however, more than obliterates this effect; the extinction coefficient of the dye from α-benzoyl-2,6-dimethylacetanilide (Table III) is lower than that of the benzoylacetamide dye and the absorption is broadened. Steric interference of the two *o*-substituents will diminish the contribution by XIII, and the electron-donating nature of methyl will stabilize XII. The latter structure is antagonistic to IX, and the observed hypochromic (and hypsochromic) effect of the *o*-methyl groups can be expected since the transition to the excited state is rendered more difficult.

N-Methylation of the anilide dye causes a hypochromic effect in cyclohexane and in butyl acetate solution, but increases the extinction coefficient in methanol (λ_{max} in all solvents is shifted to longer wave lengths). The methyl group can be expected to interfere sterically with structure XII. This will increase the relative importance of IX in agreement with the bathochromic effect observed in all three solvents and the hyperchromic effect in methanol. The hypochromic effect in the less polar solvents is not understood.

(9) E. A. Braude, F. Sondheimer and W. F. Forbes, *Nature*, **173**, 117 (1954).

Polar substituents in the anilide ring have a hyperchromic effect in cyclohexane, but the magnitude of the effect diminishes as the polarity of the solvent is increased, except in the case of *o*-substituents. Figure 2 shows that the relative effects of *m*- and *p*-substitution on λ_{max} are greater in butyl acetate or cyclohexane than in methanol, which may be connected with the proton-donating nature and the polarity of the alcohol. *o*-Substituents with lone pairs of electrons should stabilize a more nearly planar conformation[10] through hydrogen bond formation with the adjacent amide group, as shown in structure XIV. Similar chelation has been proposed by Ungnade[11] to explain certain features of the ultraviolet absorption spectra of substituted acetanilides. This chelation seems to make these substituents less susceptible to disturbances by the solvent as shown by the large hyperchromic effect in methanol (Table III).



XIV

As a measure of the slope of an absorption curve on the long wave length side, which is very important in color photography, we define

$$s = D_{(max + 60)}/D_{max}$$

where $D_{(max + 60)}$ and D_{max} are optical densities of the dye at $\lambda_{max} + 60$ mμ and λ_{max}, respectively; the sharpest curves have the smallest values of *s*. Values of *s* are reported in Tables I, IIB, III and IV. Since the band width depends on the vibrational and rotational transitions superimposed upon the electronic transition for any given electronic transition, the absorption curve should be the steeper, the fewer the vibrational and rotational transitions. Those substituents in the *ortho*-position of the anilide ring which form the chelated structures XIV should therefore narrow the absorption band and give smaller values of *s*. This is shown in Table III by the *s*-values for methanol solutions of the *o*-halo, *o*-alkoxy and *o*-alkylamino compounds. The effect is less pronounced for solutions in butyl acetate and absent in cyclohexane. The band widths and values of *s* are larger in the more polar solvents, presumably because solvation of the dye introduces new infrared fre-

(10) A. Weissberger, *J. Org. Chem.*, **2**, 245 (1937).
(11) H. E. Ungnade, THIS JOURNAL, **76**, 5133 (1954).

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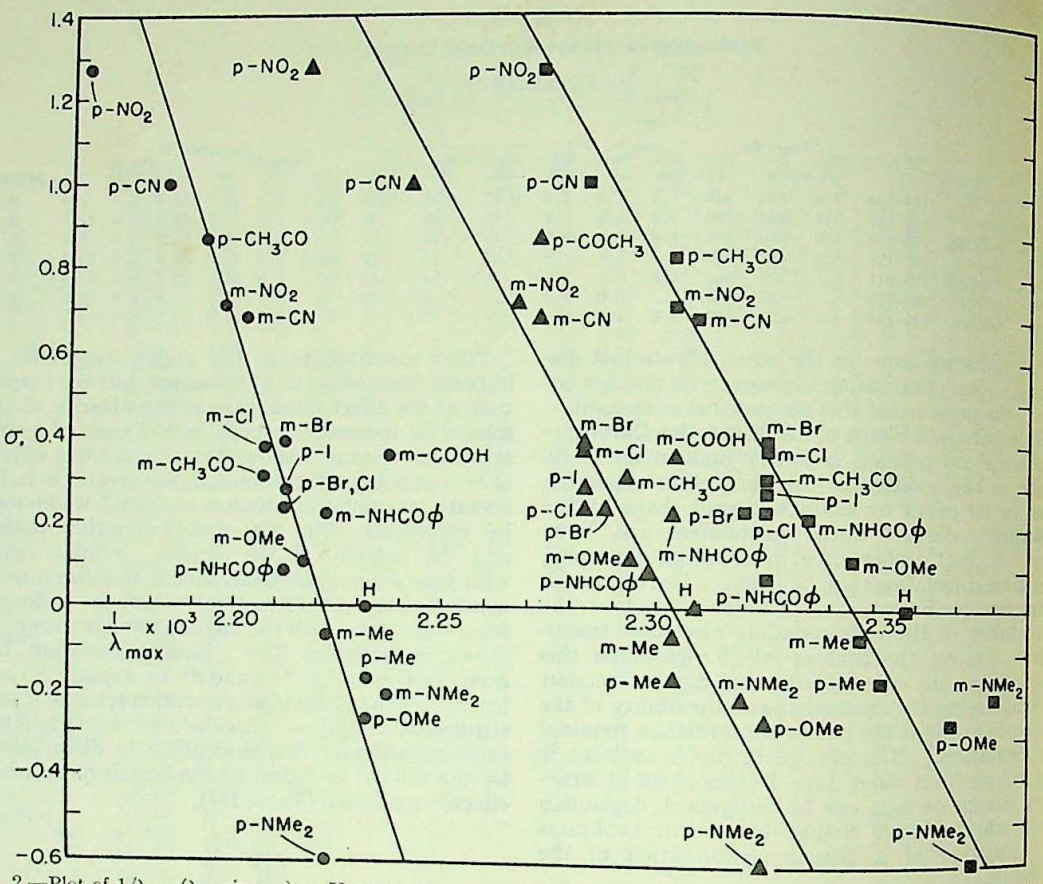

Fig. 2.—Plot of $1/\lambda_{max}$ (λ_{max} in mμ) *vs.* Hammett's σ-constants for azomethine (III) dyes substituted in the anilide ring; solvents: ■, cyclohexane; ▲, butyl acetate; ●, methanol.

quencies. It appears that this solvation does not interfere with the chelation XIV. It would be difficult to understand, however, why the chelating substituents do not cause an increase of sharpness of the dyes in cyclohexane, unless the chelation itself interferes with the solvation in methanol, *i.e.*, solvation takes place on the acetamido group.

Experimental

The requisite β-ketoesters were synthesized by previously described methods (see Table VA for references). **Anilines** needed for condensation with the β-ketoesters were generally prepared by low-pressure hydrogenation of nitro-compounds over Raney nickel rather than by the chemical methods of reduction given in the reference of Table VB. 2,4-Dimethoxyaniline[12] was obtained by hydrogenation of 2,4-dimethoxyazobenzene. *o*-Fluoroaniline was prepared by degradation of *o*-fluorobenzamide with sodium hypobromite. This reaction has been reported not to occur,[13] but gave good yields when carried out in the presence of a wetting agent (Nekal A).

***o*-Fluoroaniline from *o*-Fluorobenzamide.**—A mixture of 13 g. (0.09 mole) of *o*-fluorobenzamide and 0.5 g. of Nekal A wetting agent was added, with good stirring, to a solution containing 15 g. (0.37 mole) of sodium hydroxide and 15 g. (0.09 mole) of bromine in 325 ml. of water. The addition was carried out at room temperature, and stirring was continued at this temperature for 30 min. after addition. The mixture was heated at 70° (over a steam-bath) for 1 hr. The product was removed from the reaction mixture by steam distillation until 65 ml. of distillate was obtained, at which point 25 ml. of 40% sodium hydroxide solution was added, and steam distillation was resumed until a total volume of 200 ml. of distillate had been collected. The organic material in the distillate was extracted with benzene (100 ml. plus 2 times in 50 ml.). The combined extracts were washed with water and dried over magnesium sulfate. Fractional distillation gave 8 g. (77%) of product; colorless oil, b.p. 169–170°.

Aroylacetanilides (Tables VA, VB and VC) were prepared by condensation of equimolar amounts of β-ketoester and aniline in boiling xylene.[3,14]

Amino-substituted aroylacetanilides obtained by hydrogenation of the corresponding nitro compounds in ethanol over Raney nickel at two or three atmospheres hydrogen pressure were converted to amides with acid chlorides in sodium acetate–acetic acid solution.

Cinnamoylacetanilides (Table VI). A. Synthesis of Aminocrotonanilides.—**β-Aminocrotonanilide** and **β-amino-2-methoxycrotonanilide** were prepared by the method of Knorr[15] by reaction of acetoacetanilide and acet-*o*-anisidide, respectively, with concentrated aqueous ammonia in ethanol. The yield of β-aminocrotonanilide, m.p. 145–146° out of alcohol, was 93%. β-Amino-2-methoxycrotonanilide separated as an oil, which solidified after standing 15 months; m.p. 60–62°, yield 76%.

B. Acylation of the Crotonanilides. α-Cinnamoyl-α-(1-iminoethyl)-acetanilides (V).—The procedure of Benary and Kerckhoff[4] was employed. **α-Cinnamoyl-α-(1-iminoethyl)-acetanilide**, bright-yellow prisms, m.p. 200–201° out of

(12) J. Bechold, *Ber.*, **22**, 2374 (1889).
(13) G. Schiemann and H. G. Baumgarten, *ibid.*, **70B**, 1415 (1937).
(14) C. R. Hauser and G. A. Reynolds THIS JOURNAL, **70**, 4250 (1948).

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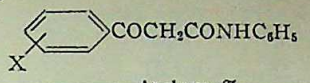
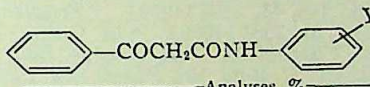
TABLE VA

PROPERTIES OF AROYLACETANILIDES 

X	Yield, %	Recrystd. from	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Source of β-ketoester
H	61	C_6H_6/petr. eth.	85	..	..	5.5	..	..	5.4	[a]
o-CH_3	..	Ligroin	97	76.9	6.8	5.0	77.0	7.1	4.9	[b]
2,4,6-$(CH_3)_3$	34	C_6H_6	116–117	..	..	5.2	..	..	4.8	[c]
o-OCH_3	49	C_6H_6/petr. eth.	95–96	..	..	5.2	..	..	5.2	[d]
m-OCH_3	80	C_6H_6	120–121	..	..	5.2	..	..	5.2	[e]
p-OCH_3	54	MeOH	136–137	..	..	5.1	..	..	5.0	[f]
p-Cl	48	EtOH	155–157	63.4	4.3	..	63.8	4.2	..	[g]
m-NO_2	84	EtOH	160–161	..	..	..	..	..	..	[a,i]
p-NO_2[h,i]	52	EtOH	165–166	..	..	..	..	..	..	
p-NH_2[h,i,k]	84	EtOH	206–208	68.9	5.4	..	68.7	5.2	..	
p-$NHCOCH_3$[l]	65	EtOH	222–224[n]	73.7	5.1	7.8	73.8	5.5	7.9	
p-$NHCOC_6H_5$[m]	35	EtOH	197–200	63.9	4.6	7.1	63.9	4.6	6.7	
p-$NHSO_2C_6H_5$[o]										

[a] A. Haller, *Compt. rend.*, 108, 1118 (1889). [b] C. F. H. Allen, J. VanAllan and C. V. Wilson, THIS JOURNAL, 66, 1805 (1944). [c] Eastman Kodak Co. [d] A. Wahl and C. Silberzweig, *Bull. soc. chim. France*, [4] 11, 25 (1912). [e] Fries Bros., New York, N. Y. [f] L. Thorp and E. R. Brunskill, THIS JOURNAL, 37, 1258 (1915). [g] C. Bülow and E. Hailer, *Ber.*, 35, 915 (1902). [h] B. Eistert, *Ann.*, 556, 91 (1944). [i] H. Krzikalla, B. Eistert, R. Schmitt and H. Kracker, German Patent 597,589 (1934). [j] W. H. Perkin, Jr., and G. Bellenot, *J. Chem. Soc.*, 49, 440 (1886). [k] From α-(4-nitrobenzoyl)-acetanilide by hydrogenation over Raney nickel. [l] From α-(4-aminobenzoyl)-acetanilide and acetic anhydride in acetic acid. [m] From α-(4-aminobenzoyl)-acetanilide and benzoyl chloride in sodium acetate–acetic acid. [n] Reported 198–199° (ref. *h*). [o] From α-(4-aminobenzoyl)-acetanilide and benzenesulfonyl chloride in sodium acetate–acetic acid solution.

TABLE VB

PROPERTIES OF AROYLACETANILIDES 

Y	Yield, %	Recrystd. from	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Source of amine
H	[a]									
o-CH_3	59	MeOH	138–139	75.9	6.0	..	76.3	6.0	..	[a]
m-CH_3	59	EtOH	101–102	..	..	5.5	..	..	5.5	[a]
p-CH_3	37	C_6H_6	131–132	75.9	6.0	..	75.7	6.0	..	[a]
2,6-$(CH_3)_2$	60	EtOH	151–152	76.4	6.4	..	76.7	6.5	..	[a]
o-OCH_3	53	MeOH	84–86	71.4	5.6	..	71.6	5.4	..	[a]
m-OCH_3	63	C_6H_6	84–85	71.4	5.6	..	71.2	5.7	..	[a]
p-OCH_3[b]	74	C_6H_6	127–128	71.4	5.6	..	71.1	5.5	..	[a]
o-Cl[c]	48	EtOH	135–137	..	..	5.1	..	..	4.9	[a]
m-Cl	35	...	115–117	..	..	5.1	..	..	5.2	[a]
p-Cl[b]	34	MeOH	154–156	..	..	5.1	..	..	5.1	[a]
o-Br	41	EtOH	123–125	56.7	3.8	4.4	56.9	3.9	4.3	[a]
m-Br	54	EtOH	118–120	56.7	3.8	4.4	57.0	3.9	4.5	[a]
p-Br	25	EtOH	170–172	56.7	3.8	4.4	56.8	3.8	4.5	[a]
p-I	17	EtOH	176–178	49.4	3.3	3.8	49.6	3.4	3.8	[a]
o-NO_2	40	MeOH	109–110	63.4	4.3	9.9	63.2	4.1	9.8	[a]
m-NO_2	53	EtOH	137–138	..	..	9.9	..	..	9.9	[a]
p-NO_2	36	C_6H_6	179–180	..	..	9.9	..	..	9.9	[a]
m-CN	65	MeOH	158–159	73.0	4.6	10.6	73.3	4.3	10.6	[a]
p-CN	68	EtOH	153–155	73.0	4.6	10.6	72.8	4.7	11.1	[a]
o-$N(CH_3)_2$	63	Ligroin	74–76	72.3	6.4	9.9	72.0	6.4	10.0	[d]
m-$N(CH_3)_2$	68	EtOH	138–140	72.3	6.4	9.9	72.4	6.4	9.9	[e]
p-$N(CH_3)_2$	43	$C_6H_5CH_3$	202–204	72.3	6.4	9.9	72.1	6.5	10.1	[a]
p-NH_2[f,g]	52	EtOH	158–159	..	..	11.0	..	..	11.2	..
o-$NHCOC_6H_5$	33	EtOH	168–170	73.7	5.1	7.8	73.0	5.0	8.1	[h]
m-$NHCOC_6H_5$[i]	67	EtOH	145–146	..	..	7.8	..	..	7.8	[j]
p-$NHCOC_6H_5$[k]	73	HAc	227–228	..	..	7.8	..	..	7.8	[l]
m-$NHSO_2C_6H_5$[m]	51	MeOH	157–159	..	..	7.1	..	..	7.0	..
p-$NHSO_2C_6H_5$[n]	62	EtOH	187–188	63.9	4.6	7.1	64.7	4.6	7.1	[o]
m-$COCH_3$	19	EtOH	121–123	72.6	5.4	5.0	72.5	5.2	5.0	[a]
p-$COCH_3$	71	EtOH	163–165	72.6	5.4	5.0	72.5	5.3	5.2	[a]
o-CO_2CH_3	44	MeOH	110–112	68.7	5.1	..	68.5	5.2	..	[a]
p-CO_2CH_3	30	MeOH	167–169	68.7	5.1	4.7	69.2	5.4	4.7	[a]
3,5-$(CO_2CH_3)_2$	68	C_6H_6	161–166	64.2	4.8	..	64.5	5.0	..	[p]
o-$CONHC_6H_5$	67	*n*-BuOH	185–186	73.7	5.1	7.8	73.8	5.2	8.0	[q]

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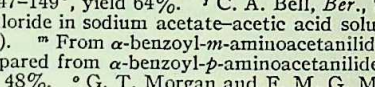
TABLE VB (*Continued*)

Y	Yield, %	Recrystd. from	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Source of amine
m-$CONHC_6H_5$	56	*n*-BuOH	180–181	73.7	5.1	7.8	74.0	5.2	8.2	[r]
p-$CONHC_6H_5$	57	Pyridine	231–233	73.7	5.1	7.8	73.9	5.0	8.1	[s]
o-$SO_2NHC_6H_5$	68	EtOH	162–164	63.9	4.6	7.1	64.0	4.7	7.4	[t]
m-$SO_2NHC_6H_5$	46	EtOH	188–190	63.9	4.6	7.1	64.2	4.5	7.2	[u]
p-$SO_2NHC_6H_5$	[a]	...	.....	..	..	..	..	..	..	[v]
o-OC_6H_5	55	C_6H_6	124–125	76.1	5.2	4.2	76.3	5.3	4.2	[w]
o-SCH_3	34	C_6H_{12}	89–90	67.5	5.3	4.9	67.8	5.8	4.9	[w]
m-CO_2H	53	HAc	210–212	..	..	5.0	..	..	4.9	[a]
o-F	30	C_6H_{12}–C_6H_6	103–105	70.0	4.7	5.5	70.3	4.7	5.7	[x]
o-CF_3	15	EtOH	103–105	62.5	3.9	4.6	..	..	..	[y]
2,5-$(OCH_3)_2$	68	MeOH	76–78	68.2	5.7	..	68.3	5.6	..	[a]
2,5-$(OC_2H_5)_2$	54	EtOH	118–120	69.7	6.5	..	70.4	6.3	..	[a]
2,4-$(OCH_3)_2$	42	EtOH	80–82	68.2	5.7	4.7	68.6	5.6	4.7	[z]
2,6-$(OCH_3)_2$	49	EtOH	151–153	68.2	5.1	4.7	68.2	5.7	5.0	[aa]

[a] Eastman Kodak Co. [b] R. Andrisano, *Bull. sci. Fascolta chim. ind. Bologna*, 8, 4 (1950); *C. A.*, 44, 9675 (1950). [c] I. G. Farbenindustrie A.-G., British Patent 355,709 (1930). [d] H. Rudy and K. Cramer, *Ber.*, 71, 1234 (1938). [e] A. Groll, *ibid.*, 19, 198 (1886). [f] A. Weissberger, C. J. Kibler and R. Young; Eastman Kodak Co., U. S. Patent 2,412,700 (1946). [g] Prepared by hydrogenation of α-benzoyl-4-nitroacetanilide in ethanol solution over Raney nickel catalyst at 50 p.s.i. [h] P. Ruggli and J. Rohner, *Helv. Chim. Acta*, 25, 1533 (1942). [i] Also obtained from α-benzoyl-*m*-aminoacetanilide and benzoyl chloride in sodium acetate–acetic acid solution: m.p. 147–149°, yield 64%. [j] C. A. Bell, *Ber.*, 7, 497 (1874). [k] Also obtained from α-benzoyl-*p*-aminoacetanilide and benzoyl chloride in sodium acetate–acetic acid solution: m.p. 208–210°, yield 67%. [l] C. E. Spencer, THIS JOURNAL, 65, 2470 (1943). [m] From α-benzoyl-*m*-aminoacetanilide and benzenesulfonyl chloride in sodium acetate–acetic acid solution. [n] Also prepared from α-benzoyl-*p*-aminoacetanilide and benzenesulfonyl chloride in pyridine–dioxane solution: m.p. 183–184°, yield 48%. [o] G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc.*, 87, 73 (1905). [p] B. Beyer, *J. prakt. Chem.*, 25, 465 (1882). [q] H. Kolbe, *ibid.*, 30, 467 (1884). [r] C. Engler and L. Volkhausen, *Ber.*, 8, 34 (1875); A. Piutti, *ibid.*, 16, 1319 (1883). [s] H. Rivier and S. Kunz, *Helv. Chim. Acta*, 15, 376 (1932). [t] F. Ullmann and C. Gross, *Ber.*, 43, 2694 (1910). [u] *Friedländer*, 10, 807 (1901). [v] F. Ullmann, *Ber.*, 29, 1878 (1896); C. M. Suter, THIS JOURNAL, 51, 2581 (1929). [w] M. Claasz, *Ber.*, 45, 2424 (1912); D. G. Foster and E. E. Reid, THIS JOURNAL, 46, 1936 (1924). [z] See ref. 13. [y] H. Rouche, *Bull. sci. acad. roy. Belg.*, 13, 346 (1927); *C. A.*, 22, 2149 (1928). [z] See ref. 12. [aa] T. Simada and K. Hata, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, 35, 365 (1939); *C. A.*, 33, 4594 (1939). These authors employed reduction with $SnCl_2$–HCl. The present authors obtained a 68% yield of 2,6-dimethoxyaniline by low pressure catalytic hydrogenation of the nitro compound.

TABLE VC

PROPERTIES OF AROYLACETANILIDES[a]

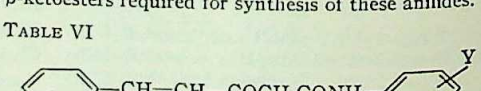


X	Y	Yield, %	Recrystd. from	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
o-OCH_3	*o*-NO_2	15	C_6H_6	115–117	61.1	4.5	..	61.6	4.2	..
p-OCH_3	*o*-OCH_3	63	EtOH	89–91	68.2	5.7	4.7	68.4	5.9	4.8
o-OCH_3	*m*-NO_2	50	EtOH	125–127	61.1	4.5	8.9	61.3	4.5	8.6
p-NO_2	*o*-OCH_3	68	EtOH	138–140	61.1	4.5	8.9	61.1	4.4	8.9
p-NH_2	*o*-OCH_3	47	CH_3CN	134–136	67.6	5.7	..	67.6	5.7	..
p-NO_2	*o*-$N(CH_3)_2$	65	CH_3CN	135–137	62.4	5.2	12.8	61.8	4.9	12.8

[a] See Tables VA and VB for references to amines and β-ketoesters required for synthesis of these anilides.

TABLE VI

PROPERTIES OF CINNAMOYLACETANILIDES



X	Y	Yield, %[a]	Recrystd. from	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	17–22	EtOH	107–108	77.0	5.7	5.3	76.6	6.0	5.3
H	*o*-OCH_3	20	EtOH	120–121	73.2	5.8	4.7	73.5	5.7	4.7
p-OCH_3	*o*-OCH_3	32	EtOH	136–137	70.2	5.9	4.3	70.3	5.7	4.5
p-OCH_3	H	22	EtOH	123–125	73.2	5.8	4.7	73.5	5.9	5.1

[a] For the yield from the imine, see Experimental section.

alcohol, yield 56%; α-cinnamoyl-α-(1-iminoethyl)-2-methoxyacetanilide, lemon-yellow powder, m.p. 157–158° out of alcohol, yield 79%; α-(4-methoxycinnamoyl)-α-(1-iminoethyl)-2-methoxyacetanilide,[16] m.p. 138–140° out of alcohol, yield 42%; α-(4-methoxycinnamoyl)-α-(1-iminoethyl)-acetanilide, yellow crystals out of alcohol, m.p. 146°, 57% yield.

C. Cleavage of the Imino Compounds: Cinnamoylacetanilides (IV). 1. α-Cinnamoylacetanilide.—A mixture of 8.0 g. (0.026 mole) of crude α-cinnamoyl-α-(1-iminoethyl)-acetanilide and 80 ml. of glacial acetic acid was heated at the boiling point until the imine dissolved. After addition of 40 ml. of water, the mixture was boiled 5 min. The cloudy mixture was allowed to cool slightly, decanted from dark gum and chilled. The light-yellow product was

(16) The 4-methoxycinnamic acid required for synthesis of this material was prepared according to the procedure given by J. R. Johnson in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 249. The acid chloride was prepared from 4-methoxycinnamic acid and excess thionyl chloride. The excess thionyl chloride was distilled and the residue used directly.

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collected on a filter, washed with dilute sodium bicarbonate solution and recrystallized from 50 ml. of 95% ethanol with the addition of Darco. After washing with cold alcohol, the material was recrystallized again from alcohol to give 2.5 g. (38% yield) of pale-yellow product, m.p. 107–108°. Subsequent runs gave 17–22% yields of the anilide.

The other anilides in Table VI were prepared from the corresponding imines in the same manner.

Preparation of the Azomethine Dyes (III) (Tables I–IV).

General Procedure.—Method A is carried out as follows: In a 1-l. beaker equipped with a stirrer was placed a solution of 0.01 mole of aroylacetanilide in 200 ml. of 95% ethanol. A solution of 5 g. of sodium carbonate in 50 ml. of water was added, followed by 0.011 mole (2.35 g.) of 4-amino-3-methyl-N,N-diethylaniline hydrochloride in 50 ml. of water. To the stirred mixture was added a solution of 0.04 mole of potassium ferricyanide in 100 ml. of water. Stirring continued for 15 min., and the dye was extracted with 250 ml. of ethyl acetate. The extract was washed several times with water and the solvent removed *in vacuo*. The residue was purified by chromatography over Doucil, with benzene or a mixture of ligroin (b.p. 60–90°) and acetone for development and elution; yield of dye 30–60%.

Method B, the use of silver chloride as the oxidant for preparation of the dyes, has been described previously.[5] The absorption spectra of the azomethine dye solutions, 8×10^{-5} molar concentration, for a 1-cm. thick sample against a water blank, were obtained with a General Electric recording spectrophotometer, using a constant spectral band width of 8 mμ.

Acknowledgment.—The authors thank Mr. E. E. Richardson, of these Laboratories, for the spectrophotometric curves.

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE MALLINCKRODT LABORATORIES OF HARVARD UNIVERSITY]

The Bromodesulfonation of Aromatic Sulfonate Salts. I. Sodium 3,5-Dibromo-4-hydroxybenzenesulfonate[1]

BY LAWRENCE G. CANNELL[2]

RECEIVED DECEMBER 20, 1956

The reaction of bromine with sodium 3,5-dibromo-4-hydroxybenzenesulfonate (I) to give tribromophenol has been studied in aqueous solution at 25.0°. Ultraviolet and visible spectra show that the reactants combine immediately to give a reaction intermediate which has a 2,6-dibromo-2,5-cyclohexandien-1-one structure. Kinetics (measured iodometrically) give additional support to a mechanism (eqs. 4 and 5) comprised of the formation of the intermediate and Br^- in a fast reversible step which is followed by the first-order decomposition of the intermediate in a rate-determining step. Specifically, the kinetics are zero order in whichever reactant, bromine or I, is in excess and first order in the other. The equilibrium of the first step greatly favors the formation of the intermediate, but the reverse reaction can be demonstrated both kinetically and spectrophotometrically when sodium bromide is added. The significance of these results in regard to the mechanism of electrophilic aromatic substitution is discussed.

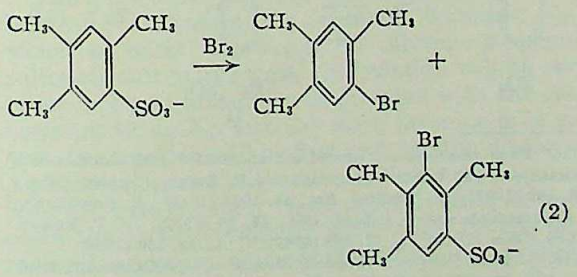
The bromodesulfonation reaction (eq. 1) has been investigated by measuring its reaction kinetics. Previous investigators have found that the reaction is greatly facilitated by amino, methoxy,

$$Br_2 + ArSO_3^- + H_2O \rightarrow ArBr + HSO_4^- + HBr \quad (1)$$

hydroxy or alkyl substituents *ortho* or *para* to the sulfonic acid group, but that these substituents in the *m*-position do not promote bromodesulfonation.[3-7] The reaction, then, appears to be an example of electrophilic aromatic substitution.

Comparable reactions have been reported with chlorine as a desulfonating agent,[8] but molecular iodine does not give the reaction.[9]

That the bromodesulfonation reaction does not proceed by a free-radical mechanism is indicated from the reaction with alkylbenzenesulfonate salts. Here bromination occurs on the aromatic ring and not on the side chain where it would be expected if the reaction takes place by a free-radical mechanism.[12]



(2)

In certain special cases the replacement of a sulfonic acid group by *chlorine* appears to be a free-radical reaction,[13] but these exceptions are charac-

(1) This paper was presented in part at a symposium on aromatic substitution held by the Division of Organic Chemistry at the 130th Meeting of the American Chemical Society, Atlantic City, N. J., September 20, 1956.

(2) Shell Development Co., Emeryville, Calif. National Science Foundation post-doctoral fellow 1955–1956.

(3) R. L. Datta and J. C. Bhoumik, THIS JOURNAL, **43**, 303 (1921).

(4) J. J. Sudborough and J. V. Lakhumalani, *J. Chem. Soc.*, **111**, 41 (1917).

(5) M. S. Van Dorssen, *Rec. trav. chim.*, **29**, 377 (1910); J. Obermiller, *Ber.*, **43**, 4361 (1909).

(6) A. N. Meldrum and M. S. Shah, *J. Chem. Soc.*, **123**, 1982 (1923).

(7) O. Heinichen, *Ann.*, **253**, 267 (1889).

(8) R. L. Datta and H. K. Mitter, THIS JOURNAL, **41**, 2028 (1919).

(9) Bromate,[3,4] iodate[4] or chlorate[3,8] salts in combination with the corresponding hydrohalic acid can also be employed as halogenodesulfonating agents.

(10) T. Callan and J. A. R. Henderson, *J. Soc. Chem. Ind.*, **41**, 161-T (1922).

(11) G. Heller, *Ber.*, **46**, 2703 (1913).

(12) W. Kelbe and K. Pathe, *ibid.*, **19**, 1546 (1886); W. Kelbe and H. Stein, *ibid.*, **19**, 2137 (1886).

(13) It was established by Kharasch and Eberly (1940) that, contrary to the claim of Eckert (*Ber.*, **58**, 313 (1925)), α- and β-anthraquinonesulfonic acids do not react with hydrochloric acid in the light to give the corresponding α- and β-chloroanthraquinones if oxygen is rigidly excluded from the system. However, if oxygen is present, the reaction studied by Eckert takes place readily. It was also established that, whereas water solutions of α- and β-anthraquinone sulfonic acids do not react with chlorine in the dark, a ready formation of the corresponding chloroanthraquinones takes place in the light. Results similar to the ones cited above have been obtained with anthraquinone-2,6-disulfonic acid. A free radical mechanism involving chlorine atoms has been postulated to explain these results. It was also established that bromine atoms do not replace sulfonic acid groups under the conditions cited above. A publication dealing with this topic in greater detail will appear shortly (private communication from M. S. Kharasch).

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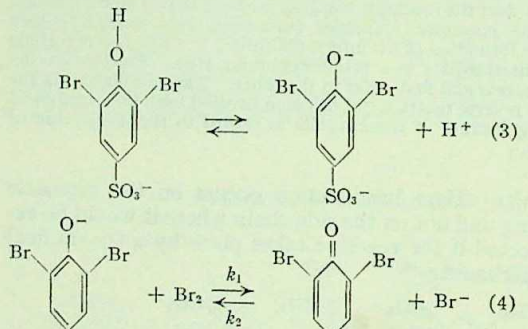
terized by the presence of electron-withdrawing substituents and usually require much more vigorous conditions.[14]

Many investigators, studying aromatic substitution reactions wherein hydrogen is replaced, have interpreted their results in terms of quinonoid intermediates or transition states.[15] In particular, Melander cited such intermediates to account for the isotope effects in the nitration and sulfonation of benzene,[16] and Zollinger[17] has found evidence for their existence by studying the effect of base on diazonium coupling reactions.[17,18] Grovenstein and Henderson recently have reported, in a kinetic investigation of the bromodecarboxylation of dibromo-*o*- and -*p*-hydroxybenzoic acids to give 2,4,6-tribromophenol, that the rate dependence on (Br^-) strongly suggests that there is a quasi-stable quinonoid intermediate which can react with bromide ion to give starting materials.[19]

In the present work, the bromodesulfonation of sodium 3,5-dibromo-4-hydroxybenzenesulfonate (I) was investigated, and in a subsequent paper the bromodesulfonation of various other aromatic sulfonate salts will be discussed.[20] The findings presented in this paper show that I reacts with bromine according to the scheme[21,22]



(3)

(4)

II

(14) These reactions are carried out at 90–250° with chlorine or a chlorate salt and hydrochloric acid; see K. Lauer, *J. prakt. Chem.*, **135**, 182 (1932); H. Schilling, *Ber.*, **46**, 1066 (1913); P. Friedländer, S. Karamessinis and O. Schenk, *ibid.*, **45**, 55 (1922); V. V. Koslov, *J. Gen. Chem.* (*U.S.S.R.*), **17**, 289 (1947); *C. A.*, **42**, 550 (1948).

(15) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp. 330–363; W. A. Waters, *J. Chem. Soc.*, 727 (1948).

(16) L. Melander, *Arkiv Kemi*, **2**, 211 (1951); U. Berglund-Larsson and L. Melander, *ibid.*, **6**, 219 (1953).

(17) Heh. Zollinger, *Helv. Chim. Acta*, **38**, 1597 (1955).

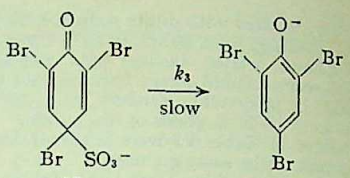
(18) See also W. M. Shubert and P. C. Myhre, Abs. of Am. Chem. Soc. Meeting, Atlantic City, N. J., September 16–21, 1956, p. 58-O.

(19) E. Grovenstein, Jr., and U. V. Henderson, Jr., THIS JOURNAL, **78**, 569 (1956). Their argument has been further strengthened by isotopic fractionation work; see E. Grovenstein, Jr., and G. A. Ropp, *ibid.*, **78**, 2500 (1956).

(20) L. G. Cannell, THIS JOURNAL, **79**, 2932 (1957).

(21) Datta and Bhoumik (ref. 3) have reported that I and an equal molar amount of bromine give a quantitative yield of 2,4,6-tribromophenol.

(22) The scheme shows bromination taking place with the phenoxide anion rather than with the phenol, although experiments have not yet shown this directly. Evidence has been found[19] that ionization of the phenol precedes the bromodesulfonation of sodium 4-hydroxy-3,5-dinitrobenzenesulfonate. Also, Grovenstein and Henderson[19] found that the rate of bromodecarboxylation of 3,5-dibromo-4-hydroxybenzoic acid is inversely proportional to $(H^+)^2$ and concluded that bromination occurs after the loss of two protons.



(5)

$$SO_3 + H_2O \longrightarrow H_2SO_4 \qquad (6)$$

The intermediate II is sufficiently stable that it can be detected spectroscopically. Kinetic and spectroscopic evidence confirm the presence of the equilibrium involving bromide ion which is shown in eq. 4, and the kinetic study indicates strongly that the rate-determining step is the unimolecular decomposition of the quinonoid, II.

Results

When dilute aqueous solutions of the dibromo-*p*-phenolsulfonate I and bromine were mixed, the bromine color disappeared immediately even at 0°; however, the immediate addition of iodide gave an iodine titer equal to that of the bromine originally used. Also, when compound I was mixed with an equal molar amount of bromine, the spectrum of I disappeared and an absorption peak appeared at 280 mμ (see Fig. 1). The peak height decreased slowly over a period of several hours, and the final spectrum closely resembled that of 2,4,6-tribromophenol. The iodine titer of the solution decreased with time. The kinetics were found to be first-order in bromine and zero-order in the dibromo-*p*-phenolsulfonate when the latter was in excess (see Table I). In a 0.15 *M* sodium bromide solution, the color of the tribromide ion appeared, and the rate of reaction was decreased by a factor of 1.6. When the dibromo-*p*-phenolsulfonate was in excess, the first-order rate constant, k_3, was equal to the slope of the line obtained by plotting ln (*B*) *vs.* *t* (where B is the iodine titer of the solution in moles/l. at time, *t*). The reproducibility of the rate constants were within 3%. The experiments were carried out at a constant ionic strength in order to avoid any interfering salt effect. The effect of ionic strength was not studied except to note that changes in the region 0.6 to 0.16 μ had little effect on the rate (see experiment 5).

With bromine in excess, the kinetics were found to follow the rate equation where A_0 is the initial concn. of I (see Table II). The data show the reaction to be zero order in bromine and first order in the dibromo-*p*-phenolsulfonate. Further work, which is discussed later in this paper, was undertaken in order to relate k_3 to k'.

$$(B_0 - B)/t = k'(A_0) \qquad (7)$$

Discussion

Spectral Measurements.—Spectral measurements provide not only evidence for a reaction intermediate but make it possible to assign the intermediate a 2,5-cyclohexadienone structure. Mixing an aqueous solution of sodium 3,5-dibromo-4-hydroxybenzenesulfonate (I) with an equal molar amount of bromine in water brought about the immediate disappearance of the bromine color. Also, the spectrum of I, which has only a

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TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE BROMODESULFONATION OF SODIUM 3,5-DIBROMO-4-HYDROXYBENZENESULFONATE

		Concn. given in moles/liter					
Expt.	Temp., °C.	$(ArSO_3Na)_0 \times 10^4$	$(Br_2)_0 \times 10^4$	$(HClO_4)_0$	$(NaBr)_0$	$(NaClO_4)_0$	10^3k_3, min.$^{-1}$
1	24.93	10.00	5.04	0.0100	0	0.1500	5.49
2	24.93	30.00	4.58	.0100	0	.1500	5.35
3	24.93	50.0	3.25	.0100	0	.1500	5.67
4	24.93	10.0	5.48	.0300	0	.1300	5.69
5	24.93	20.0	5.20	.0100	0.0200	.0300	5.34
6	24.93	10.0	5.41	.0100	.1500	0	3.32[a]
7	24.93	10.0	5.34	0	0	.1600	7.38
8	−0.10	5.12	2.61	.0023	.0025	.1475	0.197
9	−0.10	5.12	2.97	.0023	.1500	0	0.127[a]

[a] See footnote 28.

TABLE II

KINETIC DATA FOR THE REACTION OF SODIUM 3,5-DIBROMO-4-HYDROXYBENZENESULFONATE WITH EXCESS BROMINE AT 24.93 ± 0.02°

	Concn. given in moles/liter					
Expt.	$(ArSO_3Na)_0 \times 10^4$	$(Br_2)_0 \times 10^4$	$(HClO_4)_0$	$(NaBr)_0$	$(NaClO_4)_0$	$10^3k'$, min.$^{-1}$
10	2.40	5.03	0.0100	0	0.1500	8.37
11	2.40	10.1	.0100	0	.1500	8.46
12	2.40	4.92	.0100	0	.1500	6.76
13	1.20	5.23	.0100	0	.1500	8.62

k' is defined by equation 7.

small amount of absorption at longer wave lengths than 230 mμ, is replaced by a spectrum having one large peak with a λ_{max} at 278–279 mμ (see Fig. 1). On the basis that all of the dibromo-*p*-phenolsulfonate has been brominated, the new compound has an ϵ of 11,400. That the compound actually is an intermediate was shown by the observation that the absorption at 279 mμ decreased over a period of several hours and finally the spectrum closely resembled that of 2,4,6-tribromophenol, the reaction product under these conditions.

The identity of the intermediate as the 2,5-cyclohexadien-1-one (II), with the chief absorption being due to a conjugated carbonyl group, was indicated strongly by comparison with spectra previously reported by other investigators. Price has shown that 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one (III) has a λ_{max} at 280 mμ with an ϵ of 9,700 in chloroform.[23] Elston, Peters and Rowe[24] reported that 2,4,6-tribromo-4-chloro-2,5-cyclohexadien-1-one has a λ_{max} at 275–280 mμ with an ϵ of 10,000, and Denivelle and Fort have made similar observations with other structurally similar compounds.[25] The spectral evidence then shows that the formation of the 2,5-cyclohexadienone (eq. 4) is fast and indicates that the desulfonation step is rate-determining.

Kinetic Measurements with Bromine and Excess Sodium Dibromo-*p*-phenolsulfonate.—Kinetic measurements both confirm the presence of a reaction intermediate and show that the rate-determining step is its decomposition. The addition of aqueous potassium iodide to a solution of the inter-

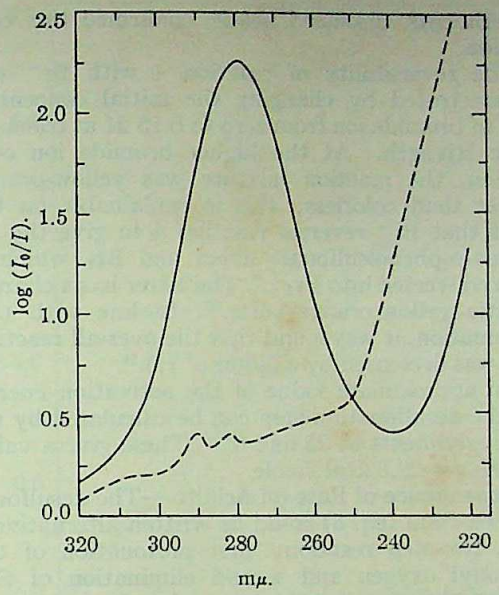

Fig. 1.—Ultraviolet spectra of quinonoid intermediate: ------, sodium 3,5-dibromo-4-hydroxybenzenesulfonate; ——, after mixing the sulfonate salt with an equal molar amount of Br_2 (taken in water at 25°).

mediate II, immediately after its preparation, liberated iodine quantitatively equal to the amount of bromine used. The amount of iodine liberated from aliquots of the reaction mixture decreased with time and so constitutes additional proof that there is a reaction intermediate. Thus it appears that iodide completely reverses eq. 4 to give iodine and I, and such an explanation is in accord with the accompanying change in the ultraviolet spectrum.[26]

The mechanism shown in eq. 4 and 5 predicts the following regarding the reaction kinetics: (a) when the initial amount of the dibromo-*p*-phenolsulfonate salt is in excess, the reaction will be zero order in I and first-order in bromine with the rate constant being k_3; and (b) when bromine is in excess, the reaction will be first order in the dibromo-*p*-phenolsulfonate salt and zero order in bromine with the rate constant being again k_3 since in both cases the rate-determining step would be the unimolecular decomposition of the intermediate quinonoid. The rates were followed iodometrically at 24.93 ± 0.02° Result (a) was kinetically verified; the initial ratio of the dibromo-*p*-phenolsulfonate salt I to bromine was varied from 2 to 15 and the first-order rate constant remained essentially constant as Table I shows. The value of k_3 is 5.51×10^{-3} min.$^{-1}$ and the intermediate has a half-life of 126 min.°. When the initial ratio of I to bromine was 15, the data followed a first-order rate law to 90% completion, but when it was 2 the first-order equation was followed only to 56% completion. This indicated that bromine was reacting further with the reaction product and subsequent

(23) J. A. Price, THIS JOURNAL, **77**, 5436 (1955).
(24) C. H. R. Elston, A. T. Peters and F. M. Rowe, *J. Chem. Soc.*, 3677 (1948).
(25) L. Denivelle and R. Fort, *Compt. rend.*, **238**, 1132 (1954); L. Denivelle, R. Fort and J. Favre, *ibid.*, **237**, 346 (1953).
(26) That the quinonoid intermediate II should oxidize iodide ion to iodine is in accord with its proposed structure. Structurally similar compounds, such as III, give the characteristic reactions of hypohalites. III with aqueous KI gives iodine and tribromophenol; J. H. Kastle and A. S. Loevenhart, *Am. Chem. J.*, **27**, 32 (1902); J. H. Kastle and J. W. Gilbert, *ibid.*, **27**, 43 (1902).

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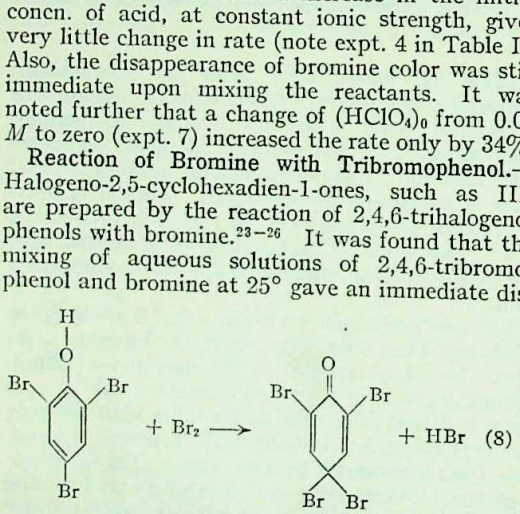
experiments, discussed below, confirmed this conclusion.

The reversibility of reaction 4 with Br^- was demonstrated by changing the initial concentration of bromide ion from zero to 0.15 M at constant ionic strength. At the higher bromide ion contration, the reaction mixture was yellow-orange rather than colorless; this is explainable on the basis that Br^- reverses reaction 4 to give the dibromo-*p*-phenolsulfonate anion and Br_2, which is then converted into Br_3^-. The latter has a characteristic yellow-orange color.[27] In line with this explanation, it was found that the over-all reaction rate was decreased by a factor of 1.6.[28]

An approximate value of the activation energy for the desulfonation step can be calculated by using experiments at 25 and 0°. These give a value of $\Delta H^{\ddagger} = 22.6$ kcal./mole.

Dependence of Rate on Acidity.—The desulfonation reaction (eq. 5) could be written alternatively as a two-step reaction: first protonation of the carbonyl oxygen and second elimination of SO_3 to give the phenol rather than the phenoxide ion. This mechanism is ruled out, however, by the observation that a threefold increase in the initial concn. of acid, at constant ionic strength, gives very little change in rate (note expt. 4 in Table I). Also, the disappearance of bromine color was still immediate upon mixing the reactants. It was noted further that a change of $(HClO_4)_0$ from 0.01 M to zero (expt. 7) increased the rate only by 34%.

Reaction of Bromine with Tribromophenol.—Halogeno-2,5-cyclohexadien-1-ones, such as III, are prepared by the reaction of 2,4,6-trihalogenophenols with bromine.[23-26] It was found that the mixing of aqueous solutions of 2,4,6-tribromophenol and bromine at 25° gave an immediate dis-



III

appearance of bromine color, appearance of a faint yellow color which could be attributed to III and appearance of an absorption max. at 279 mμ of $\epsilon = 8600$ (calculated by assuming complete reaction). The peak at 279 mμ, as discussed above, is due to the presence of the conjugated carbonyl of III. Therefore, reactions 4 and 8 are analogous in that both occur very rapidly at 25° and give a 2,5-cyclohexadien-1-one.

(27) In the ultraviolet region, Br_3^- has a large absorption peak at 267 mμ with an appreciable absorption at 279 mμ. When the reaction mixture was 0.15 M in NaBr, the spectrum showed a shift of the max. at 279 mμ to 276–278 mμ with an increase in absorption at 267 mμ. These observations are also in agreement with the above explanation.

(28) Since the analytical method gives the rate of the over-all reaction and the conversion of bromine to the intermediate 2,5-cyclohexadienone (II) was not complete at the outset of the reaction in 0.15 M NaBr, the smaller value of the rate constant serves only to show that the over-all reaction is slowed down and does not indicate a change in the value of k_1.

Kinetic Measurements with Excess Bromine and Sodium Dibromo-*p*-phenolsulfonate.—With bromine in excess the reaction kinetics are more complicated but give further support for the mechanism shown in eq. 4 and 5. All of the tribromophenol produced in reaction 5 would be converted into the tetrabromo-2,5-cyclohexadienone III in accord with equation 8. This alone, however, would not decrease the titer of the solution; nor would it decrease the concentration of the intermediate II; consequently, the rate of decomposition of the intermediate as determined by titration would be unchanged. Experimentally, however, it was found that more than twice the molar amount of bromine was consumed (per mole of the dibromo-*p*-phenolsulfonate salt initially present) and that the rate was much faster than that given by a first- or second-order expression. The data fit the empirical relationship given in eq. 7 and follow this straight line relationship beyond the point necessary for the consumption of two moles of bromine for one mole of dibromo-*p*-phenolsulfonate initially present (see Fig. 2). The data, given in Table II, show that doubling the concentration of I doubles the value of $(B_0 - B)/t$ but that doubling the amount of bromine has no effect on the rate.

The kinetics show that more reactions are occurring than those given in eq. 5 and 6, but as predicted by this reaction scheme, the rate is *zero order in bromine*. The initial rate of reaction follows eq. 7 wherein the concentration of I appears to the first power, and, therefore, the data support the further prediction of the mechanism scheme (eq. 5 and 6) that the rate should be first-order in sodium dibromo-*p*-phenolsulfonate. The one further prediction of the mechanism scheme is that k_3 will be the same whether I or bromine is in excess. In order to verify or disprove the latter, it was necessary to investigate the nature of the side reactions which become important when bromine is in excess and to find a way of comparing k' and k_3.

Decomposition of 2,4,4,6-Tetrabromo-2,5-cyclohexadienone (III) in Dilute Aqueous Solution.—Separate experiments showed that III decomposes in dilute aqueous solution to give at least two products.[29] The disappearance of III with time was followed by the decrease of iodine titer of the solution. For these experiments III was produced in aqueous solution by mixing aqueous solutions of bromine and tribromophenol at concentrations of 2×10^{-4} M or less. The ratio of the initial concentration of tribromophenol to bromine was varied from 4 to 0.5 (see Table III), and the initial concentration of III was varied by a factor of about 3.6. The reaction can be described approximately as being zero order with respect to whichever reactant (bromine or tribromophenol) is in excess and first-order with respect to the other reactant. Thus, over the range of concentrations studied, the reaction appeared to be first-order

(29) Grovenstein and Henderson[19] report that in a study of the bromodecarboxylation of 3,5-dibromo-4-hydroxybenzoic acid to give tribromophenol, the bromine consumption (as determined by the liberation of iodine with KI) after 256 hr. is just that calculated for the reaction of one mole of bromine. Therefore, under these conditions (in 80% acetic acid and 0.1 M HBr) there is no subsequent decrease in the iodine titer.

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with respect to III. The kinetic relationship was followed to 60–70% reaction after which the rate increased. The rate constant for the decomposition of III was found to be 2.24×10^{-2} min.$^{-1}$ which is four times as great as that for the decomposition of quinonoid intermediate II. The identity of the products of the decomposition was not established; however, the end-point of the iodine titration indicated that at least two products were being formed. One product gave no reaction with iodide whereas the other product (pink in color) gave a slow reaction with iodide to give iodine. Thus, the immediate titration of a sample, after mixing with potassium iodide solution, required about one-third less sodium thiosulfate than that required if the solution were allowed to stand for 45 min. before titration; but further standing produced no additional increase in titer. The same instability of the end-point from titration was observed with the reaction of sodium dibromo-*p*-phenolsulfonate (I) with excess bromine. Here, for example, aliquots of the pink reaction solution, after standing alone for 15 hr., gave no immediate production of iodine; however, after 45 minutes, with iodide solution, the molar amount of iodine was equal to about one-third that of the initial amount of I. The first iodometric end-point was used to calculate the rate constants in Table III and to give the data in Table II which fit eq. 7.

Kinetic Analysis of the Complex System.—The following method was devised in order to obtain a method of comparing k' and k_3. The entire reaction scheme can be summarized as a four-step reaction series: reaction 4 followed by reactions 5 and 8 with the fourth step being the decomposition of the tetrabromocyclohexadienone III to give products, designated only as P_2, which do not give an immediate reaction with aqueous potassium iodide. With P_1 to represent tribromophenol, the scheme is

$$\begin{aligned} I + Br_2 &\xrightarrow{\text{fast}} II + Br^- \\ II &\xrightarrow[k_3]{\text{slow}} P_1 \\ P_1 + Br_2 &\xrightarrow{\text{fast}} III \\ III &\xrightarrow[k_4]{\text{slow}} P_2 \end{aligned} \qquad (9)$$

The sequence can be treated kinetically as a two-step first-order series reaction

$$I \xrightarrow{k_3} P_1 \xrightarrow{k_4} P_2 \qquad (10)$$

The decrease in the iodine titer with time ($B_0 - B$), is equal to ($P_1 + 2P_2$). Equations[30] giving the values of P_1/A_0 and P_2/A_0 as a function of time were used to calculate values of $(P_1 + 2P_2)/A_0$ by taking the values of k_3 and k_4 to be 5.51×10^{-3} min.$^{-1}$ and 2.24×10^{-2} min.$^{-1}$ (see Table III), respectively. A plot of $(P_1 + 2P_2)/A_0$ against time shows that this function gives an almost straight line having a slope of 7.0×10^{-3} min.$^{-1}$ between $(P_1 + 2P_2)/A_0$ equals zero to 0.88.[31]

(30) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 153.

(31) Differentiation of the equations shows that the function goes through a maximum at $(P_1 - 2P_2)/A_0$ equal to 0.34 with a value of 7.3×10^{-3} min.$^{-1}$ but that in the region zero to 0.88 the average slope is about 7.0×10^{-3} min.$^{-1}$.

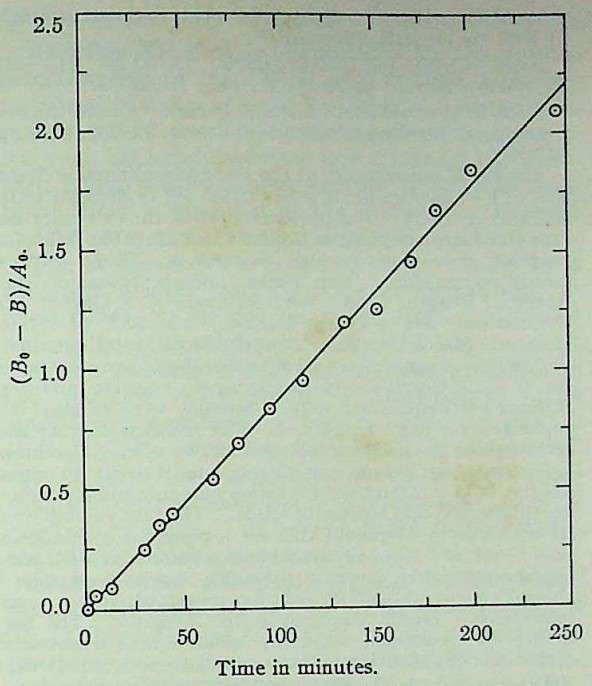

Fig. 2.—Reaction of sodium 3,5-dibromo-4-hydroxybenzenesulfonate with excess bromine; $A_0 = 1.20 \times 10^{-4}$ mole/l., $(Br_2)_0 = 5.23 \times 10^{-4}$ mole/l.

This calculated value is 16% lower than the experimental value for k' of 8.1×10^{-3} min.$^{-1}$ (the average of Table II). Because the experiments also show that there is an additional uptake of bromine which is not considered in eq. 9, the agreement is considered close enough to give support to the scheme shown in eq. 9. Therefore, the kinetics as a whole indicate that the mechanism of the bromodesulfonation of sodium 3,5-dibromo-4-hydroxybenzenesulfonate (I) is the same when bromine is in excess as it is with I in excess. The mechanism for the latter case has been shown above to be that given in eq. 4 and 5.

TABLE III

REACTION OF 2,4,6-TRIBROMOPHENOL WITH BROMINE. DECOMPOSITION OF 2,4,4,6-TETRABROMO-3,5-CYCLOHEXADIENONE IN WATER 24.93 ± 0.02°

	Concn. given in moles/liter					
Expt.	$(Br_3C_6H_1OH)_0 \times 10^4$	$(Br_2)_0 \times 10^4$	$(HClO_4)_0$	$(NaBr)_0$	$(NaClO_4)_0$	10^2k, min.$^{-1}$
14	1.95	0.487	0.0100	0	0.1500	2.55
15	1.95	0.765	.0100	0	.1500	2.24
16	1.93	1.01	.0100	0	.1500	2.24
17	1.89	1.52	.0100	0	.1500	2.12
18	1.79	4.43	.0100	0	.1500	1.86

Experimental

Sodium 3,5-Dibromo-4-hydroxybenzenesulfonate (I).—Sodium *p*-phenolsulfonate (one mole, Eastman White Label), sodium bromide (3.5 moles) and hydrochloric acid (4.3 moles) were dissolved in one l. of hot water. An aqueous solution of sodium bromate (0.7 mole) was added dropwise to the hot reaction mixture while it was stirred vigorously with a mechanical stirrer. The mixture was cooled and most of the excess acid was neutralized with aqueous sodium hydroxide. After standing, the mixture was filtered and, following treatment with Norite, the filtrate was reduced in volume. Compound I separated upon cooling and was recrystallized from water three times and once from 90%

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ethanol by cooling to −15°. When dried to constant weight at 100° the crystals pulverized.[32]

Anal. Calcd. for $C_6H_3Br_2O_4SNa$: C, 20.36; H, 0.85; Br, 45.16. Found: C, 20.17; H, 0.87; Br, 45.05.

2,4,6-Tribromophenol (Eastman Practical Grade) was recrystallized four times from ethanol, m.p. 94–95°, lit. m.p. 94°.[33]

Kinetic Measurements of the Bromodesulfonation Reaction of I.—Measurements were carried out in distilled water at 24.93 ± 0.02°. The concentrations of the reactants and rate constants are given in Tables I and II. The following reagents were used: sodium perchlorate, Fisher Purified Grade recrystallized from water; sodium bromide, Mallinckrodt Reagent Grade; perchloric acid, C.P. Grade; and the bromine was a center fraction, b.p. 58°, of refractionated Merck Reagent Grade. Stock solutions of I (0.0200 *M*), standardized perchloric acid and bromine water (*ca.* 5×10^{-3}) were used in preparing the reaction mixtures. Sodium perchlorate and sodium bromide were weighed out separately for each experiment. The reaction mixture was prepared, at the reaction temperature, by mixing a solution (a) containing sodium perchlorate and I with an equal volume (250 or 500 ml.) of a solution (b) containing bromine, perchloric acid and sodium bromide. The rate was followed by withdrawing aliquots (26.59 ml.), pipetting each aliquot into 10 ml. of 0.8% aqueous potassium iodide, and titrating the liberated iodine immediately with a standardized sodium thiosulfate (*ca.* 0.0027 *N*) solution measured from a semi-microburet. Starch was used as the indicator. The normality of the sodium thiosulfate solution was determined periodically by titrating against a standard potassium iodate solution. Sixteen to twenty points were taken in each experiment. When I was in excess, there was no problem with bromine volatility. However, when bromine was in excess, the loss of bromine became important (as determined by blank determinations) after one-third to one-half of the solution had been removed. Therefore, the volume of the solutions (a) and (b) was increased to 500 ml. and less than one-half of the mixture was used.

Reaction of 2,4,5-Tribromophenol with Bromine.—Solutions of 2.00×10^{-4} *M* tribromophenol were prepared by dissolving 0.0662 g. of the phenol in hot distilled water and then diluting to one l. upon cooling. The desired amounts of sodium perchlorate and sodium bromide were dissolved in a measured amount of tribromophenol solution. Standardized perchloric acid was added and, after bringing to 24.93 ± 0.02°, the solution was then mixed with bromine water such that the total volume was one liter. The initial concentration of tribromophenol was calculated from the volume of 2.00×10^{-4} *M* solution used to prepare the reaction mixture. The disappearance of bromine together with tetrabromocyclohexadienone III and other compounds which with iodide liberate iodine was followed. Aliquots (50 or 26.59 ml.) were withdrawn, added to 10 ml. of 0.8% potassium iodide solution, and the liberated iodine was titrated with standardized sodium thiosulfate solution. The reaction was homogeneous throughout the course of the reaction. The data are given in Table III. When tribromophenol was in excess, the values of the first-order rate constant, k_t, were taken as being equal to the slope of a plot of ln (B) *vs.* time, where B is the iodine titer in moles/l. With bromine in excess, k_4 was taken as being equal to the slope of a plot of ln ($A_0 - B_0 + B$) *vs.* time.

Ultraviolet spectra were taken in distilled water on a Cary recording spectrophotometer, model 11.

Acknowledgment.—The author wishes to express his gratitude to Dr. F. H. Westheimer for his encouragement and helpful discussions throughout the course of this work. The author is also indebted to the National Science Foundation for financial support.

CAMBRIDGE, MASSACHUSETTS

(32) Analysis was performed by Schwarzkopf Microanalytical Laboratories, Woodside 77, N. Y.

(33) I. Heilbron, *et al.*, "Dictionary of Organic Compounds," Vol. IV, Eyre and Spottiswoode Ltd., London, 1953, p. 551.

[CONTRIBUTION FROM THE MALLINCKRODT LABORATORIES OF HARVARD UNIVERSITY]

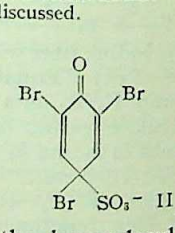
The Bromodesulfonation of Aromatic Sulfonate Salts. II. The Effect of Amino, Methoxy, Methyl and Nitro Substituents[1]

BY LAWRENCE G. CANNELL[2]

RECEIVED DECEMBER 20, 1956

The kinetics of the bromodesulfonation of a series of *p*-substituted aromatic sulfonate salts have been studied in aqueous solution at 0°. The results give additional experimental support to the theory that electrophilic aromatic substitution reactions proceed by way of quinonoid intermediates. The following *p*-substituents were studied: amino (III), methoxy (IV), methyl (V), and hydroxyl, with *m*-nitro groups (VI). All four compounds gave second-order kinetics, but they varied in regard to their dependence of rate on (Br^-). The kinetics for V showed little or no additional dependence on Br^- aside from that required by Br_3^- formation. However, with III, IV and VI it was found that decreases in rate occurred which cannot be accounted for by the Br_3^- effect alone (*cf.* Table II). The kinetics can be accounted for by a mechanism wherein bromine and the sulfonate anion undergo a *reversible* reaction to give Br^- and a "steady state" concentration of a quinonoid intermediate. To complete the reaction, the quinonoid intermediate decomposes in a unimolecular step (*cf.* eq. 1 and 2). Structural features affecting the stability of quinonoid reaction intermediates are discussed.

In a previous paper the bromodesulfonation of sodium 3,5-dibromo-4-hydroxy benzenesulfonate (I) was reported.[3] Spectral and kinetic data showed that the formation of a 3,5-cyclohexadien-1-one (II) as a reaction intermediate took place immediately upon mixing the reactants, and that the rate-determining step was the first-order decomposition of the quinonoid II to give tribromophenol.[4] Since the bromodesulfonation reaction is an example of electrophilic aromatic substitution,[3] this work constitutes a clear example of electrophilic aromatic substitution proceeding by way of a quinonoid intermediate.



II

(1) This paper was presented in part at a symposium on aromatic substitution held by the Division of Organic Chemistry at the 130th Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 20, 1956.

(2) Shell Development Co., Emeryville, Calif. National Science Foundation post-doctoral fellow, 1955–1956.

(3) L. G. Cannell, THIS JOURNAL, **79**, 2072 (1957).

(4) In aqueous solution at 25° the half-life of the intermediate was found to be [illegible]

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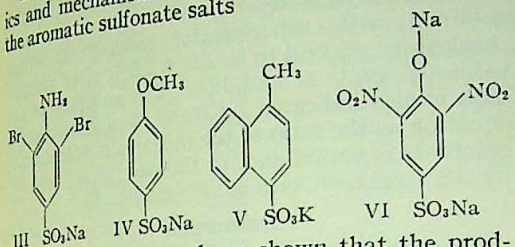
June 5, 1957

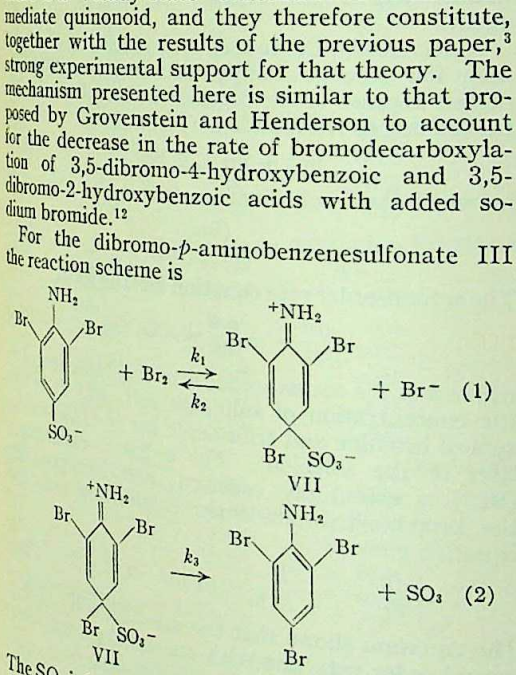
This paper reports the investigation of the kinetics and mechanism of the bromodesulfonation of the aromatic sulfonate salts



Previous investigators have shown that the products obtained in aqueous solution are, respectively: 2,4,6-tribromoaniline,[5,6] 4-bromoanisole,[7] 1-bromo-4-methylnaphthalene[8] and 4-bromo-2,6-dinitrophenol.[9-11]

A study of the rates of reaction as a function of (Br^-) shows that bromide ion retards the rate of product formation with III, IV and VI, but that the extent of this participation by bromide ion is dependent on the structure of the sulfonate salt. These results are explainable in terms of the usual mechanism for electrophilic substitution when there is a "steady state" concentration of an intermediate quinonoid, and they therefore constitute, together with the results of the previous paper,[3] strong experimental support for that theory. The mechanism presented here is similar to that proposed by Grovenstein and Henderson to account for the decrease in the rate of bromodecarboxylation of 3,5-dibromo-4-hydroxybenzoic and 3,5-dibromo-2-hydroxybenzoic acids with added sodium bromide.[12]

For the dibromo-*p*-aminobenzenesulfonate III the reaction scheme is



The SO_3 is hydrated to give sulfuric acid.

(5) J. J. Sudborough and J. V. Lakhumalani, *J. Chem. Soc.*, **111**, 41 (1917).
(6) O. Heinichen, *Ann.*, **253**, 268 (1889).
(7) A. N. Meldrum and M. S. Shah, *J. Chem. Soc.*, **123**, 1982 (1923); M. S. Shah, *et al.*, *J. Univ. Bombay*, **3**, 153 (1934), *C. A.*, **29**, 4747 (1935).
(8) L. F. Fieser and D. M. Bowen, THIS JOURNAL, **62**, 2103 (1940).
(9) E. Sakellarios, *Ber.*, **55**, 2846 (1922); *cf.* R. King, *J. Chem. Soc.*, **119**, 2105 (1921).
(10) M. M. Marqueyrol and P. Carré, *Bull. soc. chim. France*, [4] **27**, 127 (1920).
(11) Because 4-bromo-2,6-dinitrophenol reacts further with bromine under certain conditions, the products from this reaction are discussed separately in a later section.
(12) E. Grovenstein, Jr., and U. V. Henderson, Jr., THIS JOURNAL, **78**, 866 (1956); E. Grovenstein, Jr., and G. A. Ropp, *ibid.*, **78**, 2560 (1956).

Results

Reaction Kinetics.—The kinetics for the bromodesulfonation of III, IV, V and VI have been determined in water at $-0.10 \pm 0.02°$. The reaction rates were followed by removing aliquots, quenching with an iodide solution and titrating the liberated iodine with a known sodium thiosulfate solution. Starch was used as the indicator. Tables I and III summarize the findings.

The reactions were carried out essentially at a constant acidity and bromide concentration, in most cases, by having an initial concentration of sodium bromide and perchloric acid large enough that the amounts of acid and bromide produced in the reaction were small in comparison. The equilibrium constant for the formation of Br_3^- is 19.6 at 0.0° (equation 3)[13]; and, consequently, very little of the bromide produced during a reaction was converted to Br_3^-. For example, at 90% reaction in expt. 11 and 4 the ratios of Br_3^- to Br_2 are 0.01 and 0.005, respectively.

Second-order Kinetics.—By varying the initial ratio of the sulfonate salt to bromine by factors of 31, 13, 24 and 34 for III, IV, V and VI, respectively, the kinetics of these reactions were found to be second-order, that is, first order in each reactant.

Reactions with the anisole IV were homogeneous and followed the second-order equation to points beyond 93% completion when the anisole was in a fourfold excess but only to 60% completion when it was in a twofold excess. With the bromine in excess, the second-order expression was followed to only 35–40% completion. In all cases, the apparent rate constant for bromination increased with time, and, therefore, it appeared that *p*-bromoanisole, the reaction product, was undergoing further bromination. With V, 1-bromo-4-methylnaphthalene began to separate as an oil from the solution after about 25% reaction. The rate followed the second-order expression out to 40% reaction and then the rate constant drifted to a value 6 to 10% lower presumably because of bromine adsorbed on the product which thereby reduced the amount of bromine in solution. Reactions with the amine III gave a precipitation of 2,4,6-tribromoaniline after about 30% reaction, and the kinetics followed a second-order plot out to 60–70% reaction and then the rate decreased by about 10% apparently because of adsorption of bromine on the solid. Reactions with the dinitrophenol VI were homogeneous.

Bromide Dependence.—The kinetics of the reactions were studied as a function of bromide concentration over a change in $(Br^-)_0$ from zero to 0.15 *M*. The ionic strength was maintained constant by adjusting the amount of $(NaClO_4)_0$. Upon increasing $(Br^-)_0$ the rate constants decreased as shown in Tables I and III.

Ionic Strength.—Changes in the ionic strength had little effect on the rates.[14] For example, a change in ionic strength from 0.152 to 0.012 (expt. 6 and 10) changed the rate constant for the

(13) G. Jones and M. L. Hartmann, *Trans. Am. Electro. Soc.*, **30**, 295 (1916).
(14) The small salt effect is in line with the Brönsted equation which would predict no salt effect for the reaction of a neutral molecule, Br_2,

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bromodesulfonation of sodium dibromo-*p*-aminobenzenesulfonate from 6.02 to 5.91 liters/mole-sec. Similarly, only a small effect was noted with the *p*-methoxybenzenesulfonate IV (expt. 20 and 23). The essential point of interest is that small changes in media due to the substitution of one monovalent ion for another, at constant ionic strength, will not significantly alter the interpretation of the results which rely upon changes in rates by factors of 4 to over 1,000.

Effect of Acidity.—Increasing the amount of $(HClO_4)_0$ at constant ionic strength showed that the rates of bromodesulfonation of III, IV and V are quite insensitive to acid. The amount of acid was increased by factors of 43 (expt. 2 and 7), 2 (expt. 11 and 19)[15] and 4 (expt. 29 and 33) with the sulfonate salts: III, IV and V, respectively. With the dinitro-*p*-phenolsulfonate VI, however, an increase in acid by a factor of 5 decreased the rate by a factor of 4.4 (expt. 39 and 44).

Bromination of *o*-Methoxybenzoic Acid.—The decrease in rate of bromination of *o*-methoxybenzoic acid accompanying a change in bromide concentration from 0.0025–0.15 *M* was found to be slightly greater than 4 (see Table II).

Calculation of Rate Constants.—The second-order rate constants, k_{obs}, were calculated by plotting log $(A_0 - B_0 + B)/B$ *vs.* time (see eq. 8), where A_0 is the initial concentration of the aromatic sulfonate salt and B is the apparent bromine concentration (equal to the titer of iodine in mole/l.) at a specified time. The graphical method was preferred to the direct calculation of k_{obs} for each point because it gives less weight to the value of B_0. The rate constants obtained by using experimental method 1, where checked, were reproducible to 1 to 3% of the average value. The wider variation occurred with those experiments which had shorter half-lives (*cf.* expt. 34 and 31 where the half-life was 80 sec.). The reproducibility of rate constants obtained with experimental method 2, where checked, was found to be *ca.* ±1.5% of an average value (*cf.* expt. 11 and 12). The accuracy of the data is also indicated by its fit to a second-order equation as the ratio of the initial concentration of reactants is varied and, in the case of III and IV, by the agreement with eq. 13 (see Fig. 1).

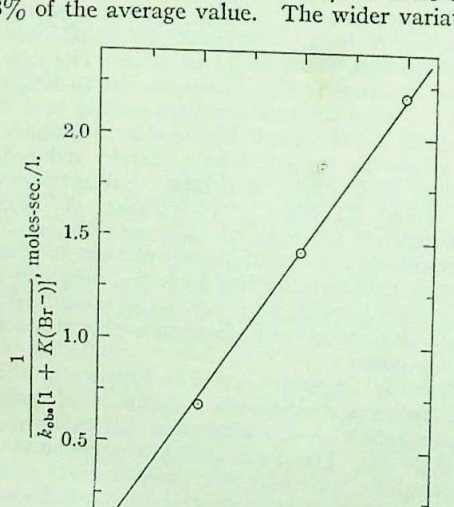

Fig. 1.—Plot of rate constants, corrected for Br_3^- effect, for the bromodesulfonation of sodium 3,5-dibromo-4-aminobenzenesulfonate *vs.* (Br^-).

(15) Also compare expt. 18 and 24 for an increase in acid by a factor of 5 but with a change of ionic strength.

Discussion

Kinetics of the Second-order Bromodesulfonation Reactions.—The second-order kinetics for the reaction of bromine with the dibromo-*p*-aminobenzenesulfonate (III), *p*-methoxybenzenesulfonate (IV) or 4-methylnaphthalenesulfonate (V), suggest a bimolecular mechanism between bromine and the aromatic sulfonate salt. Reactions with III, IV and V were insensitive to changes in acidity; this is in agreement with the expectations that the sulfonic acids would be completely ionized and that the anion would be the reactant. Further the observed independence of rate on acidity shows that neither HOBr nor H_2OBr^+ is the brominating agent.

A decrease in the rate of bromination as the bromide ion concentration is increased would be expected because of the decrease in bromine concentration due to tribromide ion formation

$$Br^- + Br_2 \rightleftharpoons Br_3^- \qquad (3)$$

for which the equilibrium constant is

$$K = \frac{(Br_3^-)}{(Br^-)\,(Br_2)} \qquad (4)$$

The second-order rate equation has the form

$$-\frac{dB}{dt} = -\frac{dA}{dt} = k(Br_2)(A) \qquad (5)$$

where k is the second-order rate constant, and A is the concentration of sulfonate salt, and B is the sum of bromine and tribromide ion (*i.e.*, the iodine titer of the solution). For a given experiment (Br^-) is essentially constant, and incorporating the bromine–tribromide ion equilibrium into the equation gives

$$-\frac{dB}{dt} = \frac{k}{1 + K(Br^-)}(B)[A_0 - (B_0 - B)] \qquad (6)$$

The equation shows that the reaction will follow a second-order rate law with an observed rate constant, k_{obs}, which obeys the relationship

$$k = k_{obs}\,[1 + K(Br^-)] \qquad (7)$$

Integration gives the rate equation used in finding k_{obs}

$$tk_{obs} = \frac{1}{A_0 - B_0} \ln\left[\frac{A_0 - B_0 + B}{B}\right]\left[\frac{B_0}{A_0}\right] \qquad (8)$$

The correction for reaction 3 has been applied to the data for the bromination of III, IV, V and *o*-methoxybenzoic acid and the corrected constants, $k_{obs}\,[1 + K(Br^-)]$, are given in Table I. It was found that $k_{obs}\,[1 + K(Br^-)]$ is nearly constant for the 4-methylnaphthalenesulfonate V and for *o*-methoxybenzoic acid. Table II summarizes the decrease in rate upon increasing $(Br^-)_0$ from 0.0025 to 0.1 *M*, with a value of $K = 19.6$,[13] eq. 7 pre-

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TABLE I

SECOND-ORDER RATE CONSTANTS FOR BROMODESULFONATION REACTIONS AT −0.10 ± 0.02°

Expt.	$(ArSO_3Na)_0 \times 10^4$	$(Br_2)_0 \times 10^4$	$(HClO_4)_0$	$(NaBr)_0$	$(NaClO_4)_0$	k_{obs}	$k_{obs}[1 + K(Br^-)]$
			Concn. given in moles/liter			Liters/mole-sec.	
			Sodium 3,5-dibromo-4-aminobenzenesulfonate				
	25.0	1.92	0.100	0.0500	0	0.734	
1	5.00	3.00	.100	.0500	0	.744	
2	2.50	5.97	.100	.0500	0	.692	
3	5.00	2.74	.0023	0	0.1500	153	153
4	5.00	2.95	.0023	.0025	.1475	26.4	27.7
5	5.00	2.65	.0023	.0100	.1400	6.02	7.20
6	5.00	2.93	.0023	.0500	.1000	0.707	1.40
7	5.00	2.92	.0023	.1000	.0500	.236	0.699
8	5.00	2.99	.0023	.1500	0	.116	0.457
9	5.00	2.87	.0023	.0100	0	5.91	
10			Sodium *p*-methoxybenzenesulfonate				
11	10.0	5.50	0.0100	0.0200	0.0300	0.184	
12	10.0	5.45	.0100	.0200	.0300	.189	0.264
13	15.0	5.58	.0100	.0200	.0300	.178	
14	20.1	5.53	.0100	.0200	.0300	.175	
15	2.51	5.13	.0100	.0200	.0300	.177	
16	2.20	7.93	.0100	.0200	.0300	.212	
17	10.0	5.08	.0100	.0050	.045	.322	.354
18	10.0	5.20	.0100	.0500	0	.0964	.191
19	10.0	4.72	.0200	.0200	.0200	.181	
20	5.00	2.83	.0015	.0100	0	.234	
21	5.00	2.62	.0023	0	.1500	.434	.434
22	5.00	2.94	.0023	.0025	.1475	.404	.424
23	5.00	2.95	.0023	.0100	.1400	.286	.342
24	5.00	2.84	.0023	.0500	.1000	.0986	.195
25	5.00	2.98	.0023	.1000	.0500	.0453	.134
26	5.00	3.08	.0023	.1500	0	.0254	.100
27			Potassium 4-methylnaphthalenesulfonate				
28	5.00	2.80	0.0023	0.0025	0.1475	0.134	0.141
29	5.00	2.46	.0023	.0200	.1300	.0857	.120
30	10.0	2.11	.0023	.0200	.1300	.0985	.138
31	12.5	1.04	.0023	.0200	.1300	.0878	
32	2.50	5.08	.0023	.0200	.1300	.0992	
33	5.00	3.30	.0023	.1500	0	.0274	.108
34	10.0	2.31	.1023	.0200	.0300	.105	
35			*o*-Methoxybenzoic acid				
36	5.00[a]	2.73	0.0103	0.0025	0.1475	19.1	20.0
37	5.00	2.50	.0103	.0025	.1475	18.0	18.9
38	5.00	2.95	.0103	.1500	0	3.70	14.6
	5.00	2.82	.0103	.1500	0	3.90	15.4
		2.55	.0206	.0025	.1475	13.0	

[a] $(CH_3OC_6H_4CO_2H)_0 \times 10^4$.

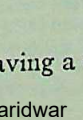
dicts a decrease by a factor of 3.76. For an increase from zero to 0.15 M $(Br^-)_0$ the factor is 3.94. The observed decrease of 4.5 and 4.8 for the 4-methylnaphthalenesulfonate V and *o*-methoxybenzoic acid, respectively, are in reasonable agreement with the calculated factor of 3.76.[16] However, for the *p*-methoxybenzenesulfonate IV and dibromo-*p*-aminobenzenesulfonate III the decrease in rate is too great to be accounted for by this correction for Br_3^- formation.

Therefore, the simple bimolecular mechanism scheme must be modified to account for this additional dependence on bromide ion. The proposed mechanism scheme is

$$ArSO_3^- + Br_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Ar\begin{matrix}Br\\SO_3^-\end{matrix} + Br^- \qquad (9)$$

$$Ar\begin{matrix}Br\\SO_3^-\end{matrix} \xrightarrow{k_3} ArBr + SO_3 \qquad (10)$$

Ar is an intermediate having a quinonoid structure



(16) It appears that K would not be affected greatly by changes in ionic strength since this is the case in the closely analogous system for the formation of I_3^- from I_2 and I^-. For the latter system, the work of W. C. Bray and C. M. J. McKay (THIS JOURNAL, **32**, 914 (1910)) and L. I. Katzin and E. Gebert (*ibid.*, **77**, 5814 (1955)) indicates that the maximum variation in K for changes in the concentrations of KI, $NaClO_4$ and NaI under 0.15 M would be less than 12%. For a 12% increase in the value of K for the formation of Br_3^- from Br^- and Br_2, eq. 7 predicts a decrease of 4.2 in rate of bromodesulfonation. Experiments with *p*-methoxybenzenesulfonate III wherein (Br^-) was varied from 0.05 to 0.005 at $\mu = 0.06$ showed that the large deviations from eq. 7 were not due to a salt effect on K (see expt. 12–17).

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which is assumed to be in a "steady state" with respect to the reactants. This mechanism is basically the same as that proposed earlier for the bromodesulfonation of sodium 3,5-dibromo-4-hydroxybenzenesulfonate (I); however, the magnitude of the rate constants are such that in the absence of bromide ion the bromination step, eq. 9, is now rate-determining. If a "steady state" concentration is assumed for the quinonoid, Q, the reaction scheme given by eq. 9 and 10 predicts that

$$-\frac{dB}{dt} = k_3(Q) = \frac{k_3k_1(Br_2)(A)}{k_2(Br^-) + k_3} \qquad (11)$$

Equation 11 has then the same form as eq. 5, and by making a similar correction for the formation of Br_3^- (*cf.* eq. 6) the following expression is obtained

$$\frac{1}{k_{obs}\,[1 + K(Br^-)]} = \frac{1}{k_1}\left[\frac{k_2}{k_3}(Br^-) + 1\right] \qquad (12)$$

Equation 12 predicts that a plot of $(k_{obs}\,[1 + K(Br^-)])^{-1}$ against (Br^-) will give a straight line. When the experimental data for the bromination of the dibromo-*p*-aminobenzenesulfonate III and *p*-methoxybenesulfonate IV are plotted in this manner, straight line correlations are obtained (see Fig. 1). The agreement further verifies the correctness of the mechanism scheme given by eq. 9 and 10. The intercept at $(Br^-) = 0$ becomes equal to $1/k_1$; this value can also be determined directly. The slope is equal to k_2/k_1k_3, and it is therefore possible to determine k_2/k_3. For the anisole IV k_2/k_3 is equal to 22 l./mole, and for the amine II it is 2,200 l./mole. Since the (rate forward/rate reverse) $= k_2(Br^-)/k_3$, it follows that when $(Br^-)_0$ is 0.10 *M* the intermediate quinonoid VII, formed from the amine, returns to the initial reactants 220 times for every time it goes on to products.

When k_2/k_3 is small, eq. 12 reduces to eq. 7 (*i.e.*, the bromination step is rate-determining regardless of the bromide ion concentration).

Dibromo-*p*-aminobenzenesulfonate III. Effect of Acidity.—As noted above, the rate of bromodesulfonation of the amine III is unaffected by increasing $(HClO_4)_0$ from 0.0023 to 0.100 *M*. This indicates that the concentration of the compound undergoing bromination is not significantly changed over this range of acidity. Also, the ultraviolet spectrum of III, which has maxima at 298 and 253 mμ, does not change even though the composition of the solution is changed from 0.1 *M* $HClO_4$ to 0.1 *M* NaOH. Sodium *p*-aminobenzenesulfonate[17] undergoes a 19-fold decrease in absorption at λ_{max} 247 mμ in acid solution due to protonation of the amine group. Therefore, the data indicate that the amine III is so weak a base that it remains unprotonated even in 0.1 *M* $HClO_4$. This behavior is in line with the expected base strength of III. Gillois and Rumpf[18] have shown that the 2,6-dibromoanilinium ion has a pK_H of 0.35 at 25°; and since the pK_H for the N-protonated *p*-aminobenzenesulfonate ion is 1.35 log units less than that for the anilinium ion,[19] the expected pK_H for the N-protonated 3,5-dibromo-4-aminobenzenesulfonate ion is about −1.0. Therefore, in 0.1 *M* acid only about 1% of the amino groups would be protonated.

TABLE II

DECREASE IN RATE OF BROMODESULFONATION ON INCREASING $(Br^-)_0$ FROM 0.0025 TO 0.1500 *M* AT 0.0°

Sodium 3,5-dibromo-4-aminobenzenesulfonate	230 (1300)[a]
Disodium salt of 3,5-dinitro-4-hydroxybenzenesulfonic acid	246
Sodium 4-methoxybenzenesulfonate	16
Potassium 4-methylnapthalenesulfonate	4.5
o-Methoxybenzoic acid	4.8
Predicted decrease due to Br_3^- effect only	3.76

[a] Experimentally determined for a change from $(Br^-)_0 = 0$ to $(Br^-)_0 = 0.15$ *M*. This value should be compared to a predicted decrease for the effect of Br_3^- formation of 3.94.

Destabilization of the Quinonoid State in Phenols by *o*-Nitro Groups.—The disodium salt of 4-hydroxy-3,5-dinitrobenzenesulfonic acid (VI), in contrast to the salt of dibromo-*p*-phenolsulfonic acid I, gave a very rapid reaction with bromine even at 0°, and the kinetics showed that the decomposition of the quinonoid intermediate was not rate-determining at low bromide concentrations.

The data (see Table III) can be summarized as follows: (1) the kinetics were second order. (2) An increase in (Br^-) from 0.0025 to 0.1500 *M* decreased the reaction rate by a factor of 246; the rate constant is still decreased by bromide by a factor of 65 after taking into account the Br_3^- effect (*cf.* Table II). The dependence of the rate on bromide ion was thus very similar to that found for the dibromo-*p*-aminobenzenesulfonate (III); the bromination step is rate-determining at low $(Br^-)_0$, but as $(Br^-)_0$ is increased, the desulfonation reaction begins to become rate-determining. (3) The rate was inversely dependent on acid (an increase in acid by a factor of 5 resulted in a 4.4-fold decrease in rate), and this stands as evidence that it is the phenoxide anion which undergoes bromination. The mechanism is comparable to that given in eq. 1 and 2.

The proposed explanation is given in the form of a potential energy curve, Fig. 2, which compares the bromodesulfonation of I and VI. It is well known that the introduction of a nitro group *ortho* to an OH group greatly increases the acidity of the phenol. This is attributed largely to the resonance stabilization of the anion.[20] A similar interaction would be expected in the ground state of the doubly charged anion of VI and, therefore, Fig. 2 shows a lower energy for the ground state of VI than for I. However, in the transition state, for the bromination step this interaction is partly lost because the phenoxide anion is being converted to a carbonyl group, and the C–C double bonds are becoming localized in positions unfavorable to resonance between the phenol oxygen and the nitro groups. Therefore, in the transition state, the energy difference between I and VI is considerably reduced.

It has been shown that quinones become better

(17) For previous work, see, for example, H. Böhme and J. Wagner, *Arch. Pharm.*, **280**, 255 (1942); *C. A.*, **37**, 2517 (1943).

(18) M. Gillois and P. Rumpf, *Bull. soc. chim. France*, **21**, 112 (1954).

(19) R. O. MacLaren and D. F. Swinehart, THIS JOURNAL, **73**, 1822 (1951).

(20) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 346.

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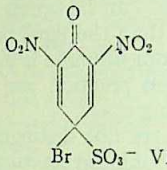
TABLE III

KINETIC DATA FOR THE BROMODESULFONATION OF DISODIUM SALT OF 3,5-DINITRO-4-HYDROXYBENZENESULFONIC ACID AT −0.10 ± 0.02°

	Concn. given in moles/liter					Liters/mole sec.	
Expt.	$(NaOArSO_3Na)_0$ × 10^4	$(Br_2)_0$ × 10^4	$(HClO_4)_0$	$(NaBr)_0$	$(NaClO_4)_0$	k_{obs}	$k_{obs}[1 + K(Br^-)]$
39	5.00	2.69	0.0200	0.0025	0.1475	13.1	13.7
40	5.00	2.56	.0200	.0100	.1400	2.26	2.70
41	1.60	5.56	.0200	.0100	.1400	2.40	
42	20.00	1.67	.0200	.0100	.1400	2.37	
43	5.00	2.67	.0200	.0100	.1500	0.0532	0.210
44	5.00	2.70	.100	.0025	.0675	3.00	

oxidizing agents when substituted with electronegative groups and that the nitro group is particularly effective in this regard.[21] Therefore, the potential energy of the tribromoquinonoid intermediate is represented in Fig. 2 as being less than that for the bromodinitroquinonoid intermediate VIII.



VIII

Finally, in the desulfonation step, as the C–S bond is broken the C–C double bonds again become delocalized and the resonance energy between the phenoxide anion and the nitro groups can again be important. Consequently, the activation energy for the desulfonation step for VI is much less than that for I. The over-all result is that in the absence of bromide ion the rate of desulfonation is increased to such a great extent that it is now no longer rate controlling. But the quinonoid has sufficient stability that with bromide ion the reverse reaction to give starting materials can take place and the desulfonation step then becomes important as the rate-determining step.

It should be noted that this change is brought about not by replacing one activating group by another but by modifying it through *ortho* substituents. The activation is clearly due to a combination of the phenoxide anion and the nitro groups and can be described as a resonance interaction. This is shown by the observation that potassium 4-methoxy-3-nitrobenzenesulfonate gives a much slower reaction with bromine than does sodium 4-methoxybenzenesulfonate (IV). The deactivating effect that introducing a nitro group has on the rate of bromination of sodium *p*-methoxybenzenesulfonate IV thus illustrates the effect which is usually observed: the nitro group retards electrophilic aromatic substitution by an inductive effect. In the bromination of the dinitrophenol VI the nitro groups must also deactivate the ring by an inductive effect, but this is completely hidden by the resonance interaction. The difference in the kinetics of bromination of the dibromophenol I and the dinitrophenol VI demonstrates that the rate-determining step in aromatic electrophilic substitution can be changed by the modification of substituents.

Dinitro-*p*-phenolsulfonate VI. Products.—

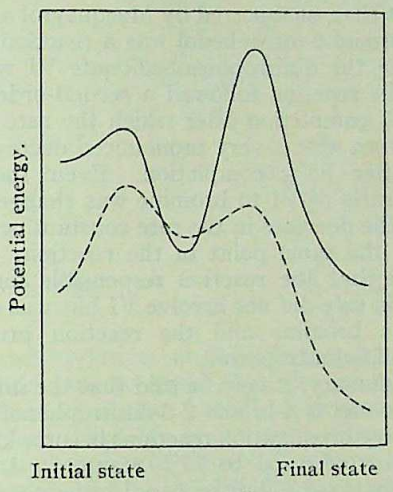
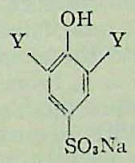


Fig. 2.—Bromodesulfonation of
—— Y is Br, (I)
----- Y is NO_2, (VI)



Sakellarios reports that the reaction of VI with an equal molar amount of bromine water at 24–30° gives a 93% yield of 4-bromo-2,6-dinitrophenol before recrystallization.[9] Marqueyrol and Carré report that VI with an equal molar amount of bromine in water gives a crude product which contains 31.7% bromine (a bromodinitrophenol has 30.4%) wherein the main product is 4-bromo-2,6-dinitrophenol.[10] With excess bromine at room temperature they reported that the crude product contained 45% bromine (54% required for a dibromonitrophenol) from which the chief product isolated was 2-bromo-4,6-dinitrophenol[22] and a smaller amount of 2,4-dibromo-6-nitrophenol. They further showed by titration data that VI reacted with more than a molar amount of bromine. The replacement of a nitro group on 4-bromo-2,6-dinitrophenol by bromine is not surprising in view of other work which shows that picric acid will brominate in aqueous solution at room temperature to give 2-bromo-4,6-dinitrophenol.[23]

Dinitro-*p*-phenolsulfonate VI. Side Reactions.—The reaction rate measurements, reported in this

(21) L. F. Fieser, THIS JOURNAL, **52**, 5204 (1930); **51**, 3101 (1929).

(22) Marqueyrol and Carré suggest that 4-bromo-2,6-dinitrophenol, the initial reaction product, isomerizes in the presence of excess bromine into 2-bromo-4,6-dinitrophenol (*cf.*, H. E. Armstrong, *J. Chem. Soc.*, **13**, 520 (1875); H. Gordon, *Chem. News*, **63**, 221 (1891)).

(23) J. Castets, *J. pharm. chim.*, **13**, 46 (1916); *C. A.*, **10**, 1486 (1916); H. Gordon, *Chem. News*, **63**, 249 (1873).

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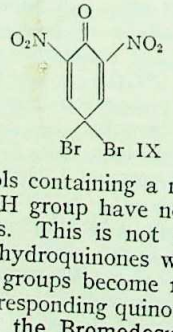
paper, also show that the dinitrophenolsulfonate VI will react with more than one mole of bromine. The reaction of VI with excess bromine followed a second-order rate law (having the same value of k as that obtained when bromine was not in excess, see Table III) until 0.5 mole of bromine had been taken up for each mole of VI initially present. The apparent rate constant then began to increase and bromination continued at a rapid rate until *ca.* 1.5 moles of bromine had disappeared and the reaction finally approached the stoichiometry of two moles of bromine consumed per mole of VI. These data suggest that, as reported by Marqueyrol and Carré, 2,4-dibromo-6-nitrophenol was a reaction product.

When the dinitrophenolsulfonate VI was in excess, the reaction followed a second-order rate to 70–75% completion after which the rate began to slow down with a very pronounced decrease occurring after 85% completion. Even though the initial ratio of VI to bromine was changed from 2 to 12, the decrease in the rate constant occurred at closely the same point in the reaction. This indicated that the reaction responsible for the decrease in rate did not involve VI but was evidently between bromine and the reaction product, 4-bromo-2,6-dinitrophenol.

In summary, it may be said that the initial reaction product is 4-bromo-2-6-dinitrophenol but that secondary bromination reactions become kinetically important after 50 to 75% reaction. It appears that 4-bromo-2,6-dinitrophenol brominates to give a reaction product, or intermediate, which slows down the rate of disappearance of bromine by tying up some of the bromine in a way such that it is less effective as a brominating agent but will, in the analytical method, still react with iodide to give iodine. With excess bromine, however, bromination occurs to give 2,4-dibromo-6-nitrophenol. In considering possible secondary bromination products it is interesting to note that 4-bromo-2,6-dinitrophenol might be expected to give the cyclohexadienone (IX) just as tribromophenol gives 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one.[24] However,



IX

apparently phenols containing a nitro group *ortho* or *para* to the OH group have not given isolable cyclohexadienones. This is not surprising since, as noted above, hydroquinones which are substituted with nitro groups become more difficult to oxidize to the corresponding quinones.

Comparison of the Bromodesulfonation Reactions.—The kinetics of the bromodesulfonation of I, III, IV and V, together with the spectral data, can be used to divide these compounds according to the stability of the intermediate quinonoid: (1) Bromination of sodium 3,5-dibromo-4-hydroxybenzenesulfonate (I) gives zero-order kinetics for the reactant (bromine or I) present in excess, and first-order kinetics for the other. The most evident explanation of the kinetics requires that the phenolsulfonic acid upon mixing with bromine is immediately transformed into a quinonoid intermediate II and demands that the *intermediate be present in large concentration.* This was verified by ultraviolet absorption spectra of the aqueous solution in this case. The rate-determining step is then the decomposition of the intermediate. Other phenols of closely similar structure would be expected to behave analogously.[25]

(2) By contrast, the kinetics for the bromination of potassium 4-methylnaphthalene-1-sulfonate (V) indicate a bimolecular mechanism between the sulfonate anion and Br_2; the reaction follows second-order kinetics which are first-order with respect to each reactant. The kinetics require *only a transition state,* and it is not necessary to propose that there is a reaction intermediate. The decrease in rate of bromodesulfonation as bromide ion concentration is increased can be satisfactorily accounted for by assuming that the equilibrium for the formation of Br_3^- from bromine is independent of the bromodesulfonation reaction and that Br_3^- is inert as a brominating agent.

These kinetics are not distinguishable from the usual bromodeprotonation reactions as is illustrated in the present work by the bromination of *o*-methoxybenzoic acid. Other workers have found similar results with bromodeprotonation reactions. Wilson and Soper[26] reported similar kinetics for the bromination of *o*-nitroanisole in water and so have Grovenstein and Henderson[12] for the bromination of 2,6-dibromophenol.

(3) The bromination of sodium *p*-methoxybenzenesulfonate (IV) and sodium 3,5-dibromo-4-aminobenzenesulfonate (III) also follows second-order kinetics, but here it was found necessary to postulate a *steady state concentration* of a reaction intermediate in order to account for the dependence of rate on (Br^-). When the observed rate constant was corrected for Br_3^- formation, the decrease in rate is only partly accounted for (see Table II). The magnitude of this additional decrease depends on the structure of the compound; the factor is 4 for sodium *p*-methoxybenzenesulfonate and 57 for sodium 3,5-dibromo-4-aminobenzenesulfonate upon changing the $(Br^-)_0$ from 0.0025 to 0.1500 *M*. This additional decrease in rate can be accounted for by a mechanism (eq. 9 and 10) which includes the reaction of bromide ion with a quinonoid intermediate to regenerate the starting sulfonate anion and Br_2. The rate-determining step is the attack of bromine on the sulfonate anion at low bromide concentrations but, as the concentration of bromide is increased, the step involving the elimination of SO_3 becomes rate-determining.

The substituent stabilizes the quinonoid structure by double bond formation with the benzene ring. The dibromo-*p*-phenolsulfonate I eliminates

(24) See ref. 3 for discussion of the displacement of [illegible]

(25) Sodium 3,5-dichloro-4-hydroxybenzenesulfonate in aqueous solution upon mixing with an equal molar amount of bromine water was found to give an immediate disappearance of the bromine color and a new absorption peak at 271–272 mμ of ϵ = 12,400. This behavior is closely similar to that for the dibromophenolsulfonate I and indicates that bromodesulfonation is by an identical mechanism.

(26) W. J. Wilson and F. G. Soper, *J. Chem. Soc.*, 3376 (1949), see also D. H. Derbyshire and W. A. Waters, *ibid.*, 564 (1950).

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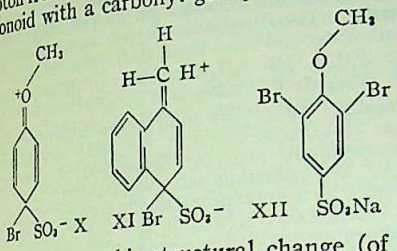
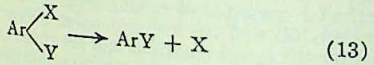
a proton from the OH group to give an intermediate quinonoid with a carbonyl group (II); the experiments show that this structural change (of those considered in this paper) is the most effective way of stabilizing a quinonoid.[27] With the dibromo-*p*-aminobenzenesulfonate III and the *p*-methoxybenzenesulfonate IV, double bond formation in the quinonoid can be brought about by forming an imine salt VII and oxonium cation X, respectively. For the methylnaphthalenesulfonate V a double bonded structure cannot be drawn but rather the transition state can be written as a resonance hybrid of various structures, one of which is the hyperconjugation structure XI.



Sodium 3,5-dibromo-4-methoxybenzenesulfonate (XII), in contrast to IV, was found to undergo no appreciable reaction with bromine at 25°, and even at 98° the reaction was slow. This fact can be explained by noting that, because of steric repulsion, the bromine atoms keep the methyl group from being planar with the ring, and therefore, the oxygen can form only a partial double bond with the ring. Much of the activating effect of the oxygen is then lost and XII is relatively unreactive.[28]

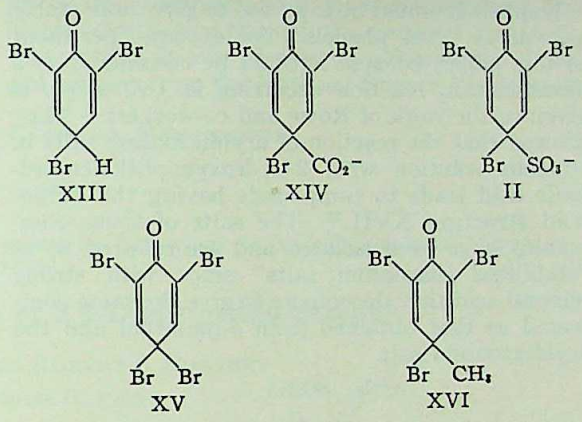
Structural Features which Favor the Formation of Stable Quinonoid Intermediates.—The decomposition of a quinonoid intermediate may be written as



(13)

where X is the group being replaced, Y is the group which became bonded to Ar in the initial step of the substitution reaction, and Ar<X Y is the reaction intermediate with a quinonoid structure. It is apparent that an additional means of increasing the stability of a quinonoid is to increase the activation energy for the decomposition step (*i.e.*, choose X such that the energy of activation for breaking the C-X bond is raised). The experimental work discussed above showed that, for bromodesulfonation at least, the OH group is more effective in stabilizing a quinonoid structure than any of a variety of other substituents. Therefore, for comparison purposes a series of phenols will be chosen wherein X is varied. Ar is chosen to be the 3,5-dibromo-4-hydroxyphenyl group; X is $-CO_2^-$, $-SO_3^-$, Br (or Cl) or $-CH_3$; and Y is Br (*i.e.*, the intermediates were derived by bromination of ArX). The various intermediates or stable compounds are XIV, II, XV and XVI, respectively, for the above-named substituents.

The relative stabilities of these quinonoids will now be compared. The work reported in this paper shows that in aqueous solution at 0° the



bromodecarboxylation of 3,5-dibromo-4-hydroxybenzoic acid was so rapid that the reaction was practically finished after 7 sec.[29] The intermediate II at 25° has a half-life of 126 min. Bromination of tribromophenol with aqueous bromine leads to the formation of the isolable 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one (XV).[24] Bromination of 2,6-dibromo-4-methylphenol leads to the cyclohexadien-1-one XVI which Fries and Oehmke have isolated and characterized.[30,31]

The increase of the stability of the intermediates where X is Br or CH_3 over those where X is $-CO_2^-$ or $-SO_3^-$ can be attributed to the higher energy of activation necessary for the breaking of the C–Br or C–CH_3 bond in the cyclohexadienones, XV and XVI, respectively, as indicated in reaction 13. The greater stability of the intermediate II where X is $-SO_3^-$ over that where X is $-CO_2^-$ can be explained in a similar manner. The case where X is hydrogen was studied by Grovenstein and Henderson[12] who found that the rate of bromination was *ca.* 200 times faster than that for X = $-CO_2^-$, and since in the latter case they demonstrated that the bromination reaction is reversible with bromide ion, whereas the former reaction showed little or no tendency for reversal, it would appear that the rupture of the C–CO_2^- bond of the intermediate XIV requires a higher activation energy than does the

(27) When the solvent is such that the phenol does not ionize appreciably, the stabilizing effect is not forthcoming. This is illustrated by the work of A. A. Yasnikov and E. A. Shilov (*Doklady Akad. Nauk S.S.S.R.*, **78**, 925 (1951); *C. A.*, **46**, 5009 (1952)) who report that 2,4,6-tribromophenol in anhydrous acetic acid will not brominate to give XV but that a small amount of water is necessary as a proton acceptor to bring about the reaction.

(28) *Cf.* ref. 20, pp. 157–160 and 238–243.

(29) XIV can be referred to here as a reaction intermediate because Grovenstein and Henderson have shown, as previously cited, that in 80% acetic acid–water 20% the kinetics of this bromodecarboxylation reaction require a "steady state" intermediate.[12]

(30) K. Fries and G. Oehmke, *Ann.*, **462**, 6 and 16 (1928); Fries and co-workers assigned this and many other closely related compounds a cyclohexadienone structure on the basis of chemical evidence (see K. Fries and E. Brandes, *Ann.*, **542**, 48 (1939); K. Fries and H. Engel, *ibid.*, **439**, 232 (1924)). In support of this view, G. M. Coppinger and T. W. Campbell (THIS JOURNAL, **75**, 734 (1953)) have assigned a compound formed by the bromination of 2,6-di-*t*-butyl-4-methylphenol as 4-bromo-2,6-di-*t*-butyl-4-methyl-2,5-cyclohexadien-1-one by means of its infrared spectrum.

(31) For examples showing the use of substituting agents other than bromine see: M. S. Newman and A. G. Pinkus, *J. Org. Chem.*, **19**, 978 (1954); J. F. Bunnett and W. C. Sears, THIS JOURNAL, **76**, 4977 (1954); H. E. Albert and W. C. Sears, *ibid.*, **76**, 4979 (1954).

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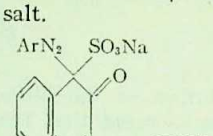
rupture of the C–H bond in XIII to give tribromophenol.

The unique feature of the intermediate II is that it is stable enough to be formed in large concentrations yet unstable enough that it will decompose at a conveniently measurable rate in a manner typical of substitution reactions (eq. 13). Thus, it is an ideal case for kinetic investigation.

Naphthols would be expected to give more stable quinonoids than phenols. An example pertinent to this paper, because it could be considered as a desulfonation reaction occurring in two steps, is given in the work of Rowe and co-workers. They showed that the reaction of aryldiazonium salts in aqueous solution with 2-hydroxynaphthalenesulfonic acid leads to compounds having the quinonoid structure XVII.[32] The salts of these compounds have been isolated and are referred to as "stabilized diazonium salts" since with strong mineral acid they decompose to give the same compound as that obtained from β-naphthol and the aryldiazonium salt.



XVII

Experimental

Sodium 3,5-Dibromo-4-aminobenzenesulfonate (III).—An aqueous solution of the salt was prepared by treating an aqueous solution of sulfanilic acid (Mallinckrodt Analytical Reagent) with sodium bromate and hydrobromic acid according to the directions of Heinichen.[6] The sodium salt was isolated by evaporation of the solution after neutralizing with sodium hydroxide and recrystallized twice from water and twice from 90% ethanol to give fine needles. The salt was dried at 200°.[33]

Anal. Calcd. for $C_6H_4Br_2NO_3SNa$: C, 20.42; H, 1.14; Br, 45.28. Found: C, 20.69; H, 1.28; Br, 45.21.

Sodium *p*-methoxybenzenesulfonate (IV) was prepared by the method of Moody[34] by sulfonating anisole (Eastman White Label). The salt was recrystallized twice from water, twice from 90% ethanol and dried at 100°.

Anal. Calcd. for $C_7H_7SO_4$: C, 40.00; H, 3.36; S, 15.25. Found: C, 40.23; H, 3.32; S, 15.01.

Potassium 4-methylnaphthalene-1-sulfonate (V) was prepared by the method of Fieser and Bowen.[8] The salt was recrystallized three times from water and twice from ethanol–water and dried at 100°, m.p. of *p*-toluidine salt 227–229° (lit.[8] m.p. 228–230°).

Sodium 3,5-dibromo-4-methoxybenzenesulfonate (XII) was prepared by treating I with a twofold excess of dimethyl sulfate in aqueous sodium hydroxide. Upon reducing the volume of the solution, XII separated out and was recrystallized twice from aqueous sodium hydroxide and once from water and dried at 200°. The product showed no violet coloration upon treating with aqueous ferric chloride.

Anal. Calcd. for $C_7H_5Br_2O_4SNa$: C, 22.84; H, 1.37; Br, 43.43. Found: C, 23.00, 23.13; H, 1.24, 1.47; Br, 43.31.

Disodium Salt of 3,5-Dinitro-4-hydroxybenzenesulfonate (VI).—By the substitution of sodium for potassium salts, the monosodium salt of the dinitrophenolsulfonic acid was prepared by the method given by Friedlaender.[35] The monosodium salt was recrystallized from water and converted into the disodium salt by the addition of sodium carbonate. No more carbonate was added than that required to neutralize the acid as was indicated by the effervescence of carbon dioxide. The disodium salt was recrystallized three times from water and dried to constant weight at 120°.[36]

Anal. Calcd. for $C_6H_2N_2O_8SNa_2$: C, 23.38; H, 0.65; N, 9.09. Found: C, 23.30; H, 0.68; N, 9.04.

Potassium 4-Methoxy-3-nitrobenzenesulfonate.—*o*-Nitroanisole (Matheson–Coleman and Bell) was sulfonated with chlorosulfonic acid by the method of Gnehm and Knecht.[37] The potassium salt was prepared from the acid and purified by recrystallization from water, m.p. of the sulfonyl chloride derivative 65.5–66.5° (lit.[37] m.p. 66°).

***o*-Methoxybenzoic acid** was prepared by treating sodium salicylate with dimethyl sulfate in aqueous base. The product was recrystallized several times from ethanol, m.p. 101–101.5° (lit.[38] m.p. 100–101°).

Sodium 3,5-dichloro-4-hydroxybenzenesulfonate was prepared from sodium *p*-phenolsulfonate (Eastman White Label) by chlorination with $NaClO_3$/HCl in a procedure similar to that used for the preparation of sodium dibromo-*p*-phenol sulfonate by bromination.[3]

3,5-Dibromo-4-hydroxybenzoic acid was prepared by the bromination of *p*-hydroxybenzoic acid (Eastman White Label) in aqueous solution by a hydrobromic acid–sodium bromate mixture. The acid was recrystallized three times from chloroform, m.p. 271.5–272.5° (cor.), lit.[39] m.p. 267–268°.

Measurement of the Bromodesulfonation Reaction.—The kinetics of the bromodesulfonation of the amine II, anisole III, methylnaphthalene IV and dinitrophenol VI were measured at −0.10 ± 0.02°. The data are summarized in Tables I and III. Distilled water was used as the solvent. The reagents were the same as previously described.[3] Solutions of the reactants were prepared by mixing at the reaction temperature equal volumes of solution (a) which contained the aromatic sulfonate salt and sodium perchlorate with solution (b) which contained bromine, sodium bromide and perchloric acid. In the case of VI, the perchloric acid was equally divided between (a) and (b). The acid was added to prevent hydrolysis of the bromine and also to determine the effect of acidity on rates. Solutions of the sulfonate salts (0.0200 *M*), standardized perchloric acid and bromine water (*ca.* 5×10^{-3} *M*) were used in preparing the reaction mixtures. Sodium perchlorate and sodium bromide were weighed out separately for each experiment.

Two methods of mixing the reactants were employed. Method 1 consisted of mixing separate 25.0-ml. portions of solutions (a) and (b) for each point taken. Method 1 was used for the faster reactions and for those in which the reaction product began to separate from solution before reaction was complete. The $(Br_2)_0$ was determined by using samples of solution (b) as blanks both at the time the experiment was started and also toward the conclusion of the experiment. It was thus shown that the loss of bromine by the volatilization was small over the time interval necessary to conduct an experiment. All reactions were carried out in glass stoppered flasks.

Method 2, which was used for the slower completely homogeneous reactions, consisted of mixing equal volumes of solutions (a) and (b), usually 250 ml. each, and then following the reaction by withdrawing a sample (26.59 ml.) by pipet. Between operations, the pipet was cooled at the bath temperature. The reaction time was taken as that from the mixing of the solutions until one-half of the pipet was emptied. The initial bromine concentration was determined by removing an aliquot immediately after mixing or by removing an aliquot from solution (b) in which case a compensating volume was taken from (a) also and discarded. Method 2 was used in expt. 11 to 29 inclusive; all other experiments in Tables I and III followed the procedure of method 1.

About 16 points were taken in each experiment. With a fast reaction, the first point was taken after 4 sec. The reaction was stopped by mixing each sample with 10 ml. of 0.8% aqueous potassium iodide in method 1 or by pipetting

(32) F. M. Rowe, E. Levin, A. C. Burns, J. S. H. Davis and W. Tepper, *J. Chem. Soc.*, 690 (1926); F. M. Rowe, E. Levin and A. T. Peters, *ibid.*, 1065 (1931).

(33) Analyses were performed by Schwarzkopf Microanalytical Lab., Woodside 77, N. Y., unless otherwise noted.

(34) G. T. Moody, *Chem. News*, **65**, 247 (1892).

(35) P. Friedlaender, "Fortschritte der Teerfarbenfabrikation," Vol. I, Julius Springer, Berlin, 1888, p. 824.

(36) Analysis was by Elek Micro Analytical Lab., Los Angeles 16, Calif.

(37) R. Gnehm and O. Knecht, *J. prakt. Chem.*, **74**, 92 (1906).

(38) I. Heilbron, *et al.*, "Dictionary of Organic Compounds," Vol. II, Eyre and Spottiswoode Ltd., London, 1953, p. 281.

(39) Reference 38, Vol. II, p. 91.

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an aliquot into aqueous potassium iodide in method 2. The sample was then analyzed immediately for the amount of iodine liberated by titrating against a standardized sodium thiosulfate solution measured from a semimicroburet. Starch was used as an indicator.

A reaction mixture which was 6.7×10^{-3} *M* in potassium 4-methoxy-3-nitrobenzenesulfonate and 4.3×10^{-3} *M* in bromine was kept at 50°; it was found that slightly less than half of the bromine disappeared after 17 hr. Sodium 3,5-dibromo-4-methoxybenzenesulfonate (XII) with bromine gave no appreciable reaction at 25°; but when a reaction mixture containing 6.7×10^{-3} *M* XII and 4.6×10^{-3} *M* bromine was heated in a sealed tube at 98°, the amount of bromine decreased to 2.4×10^{-3} *M* after 1.5 hr.

Bromodecarboxylation of 3,5-Dibromo-4-hydroxybenzoic Acid.—The procedure was similar to method 1 discussed above for the bromodesulfonation experiments. Solution (a) was prepared by dissolving 1.00×10^{-3} mole of the dibromohydroxybenzoic acid with 1.65×10^{-3} mole of NaOH in one l. of water. Solution (b) contained 4.84×10^{-4} mole/l. of Br_2; 25 ml. of each solution were mixed at 0°. The reaction was so rapid that with a time of 7 sec. it was over 90% complete.

Ultraviolet spectra were taken in aqueous solution on a Cary spectrophotometer, model 11.

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CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM JOHN HARRISON LABORATORY, UNIVERSITY OF PENNSYLVANIA, AND BROOKHAVEN NATIONAL LABORATORY]

The Free Radical Phenylation of 2,4-Dinitrotritiobenzene[1]

BY CHARLES C. PRICE AND ROBERT J. CONVERY

RECEIVED DECEMBER 15, 1956

The conversion of 2,4-dinitrotritiobenzene to 2,4-dinitrobiphenyl by treatment with benzoyl peroxide proceeds with the displacement of just one-half of the tritium. This proves that the product-determining step does not involve breaking the tritium- (or hydrogen-) carbon bond.

Two mechanisms have been advanced for free radical substitution in the benzene ring. One[2] involves initial hydrogen abstraction followed by coupling of two radicals.

$$C_6H_5\cdot + ArH \longrightarrow C_6H_6H + Ar\cdot \xrightarrow{C_6H_5\cdot} ArC_6H_5 \quad (1)$$

The other involves initial addition to the aromatic nucleus, followed by hydrogen abstraction.[2a,3]

$$C_6H_5\cdot + ArH \longrightarrow \left[\begin{array}{c} C_6H_5 \\ | \\ Ar \\ | \\ H \end{array}\right] \xrightarrow{R\cdot} RH + ArC_6H_5 \quad (2)$$

In order to obtain more unequivocal evidence, we have studied the phenylation of 2,4-dinitrotritiobenzene, since mechanism 1 should show a substantial isotope effect while mechanism 2 would have little or none.

Experimental

2,4-Dinitrotritiobenzene was prepared by dissolving 2,4-dinitrobenzoic acid (5 g.) in 5 ml. of tritiated water (20 mc./10 ml.) heated at 125°, followed by decarboxylation of 5 g. of the tritiated acid by heating to 240° in 25 ml. of quinoline with 0.02 g. of copper chromite catalyst. After thorough washing of an ether solution, evaporation and recrystallization from 95% ethanol, 1.5 g. (38%) of tritiated *m*-dinitrobenzene, m.p. 108–108.8°, was obtained. This sample was mixed with 40 g. of unlabeled material and recrystallized once more from ethanol. One sample prepared in this way assayed[4] for 51.7 ± 1.6 mμc./mg. of hydrogen, a second for 22.8 ± 0.7 mμc./mg. of hydrogen.

2,4-Dinitrobiphenyl.—A mixture of 4.3 g. of benzoyl peroxide (0.02 mole) and 29.6 g. of tritiated *m*-dinitrobenzene (0.2 mole) was heated, gradually increasing the temperature from 75 to 100° over a period of 5 hr. After dissolving in 400 ml. of ether, the product was washed with five 50-ml. portions of 10% sodium bicarbonate, with three 50-ml. portions of 15% hydrochloric acid and three 50-ml. portions of water. Drying and evaporation left a solid residue which was distilled at 0.4 mm. to remove most of the excess *m*-dinitrobenzene (b.p. 98° (0.4 mm.)). The still residue was extracted with 150 ml. of boiling methanol. After cooling to room temperature and evaporation to 10 ml., the precipitate was collected and recrystallized four times from methanol to yield 0.7 g. (16%) of 2,4-dinitrobiphenyl. Before assay, 0.1 g. of this material in 5 ml. of benzene was put through a column of magnesium oxide.[5] After development with additional benzene, elution of the purple band with benzene, followed by evaporation of the benzene and recrystallization from methanol gave material melting at 109.3–110°. The results of tritium assay are summarized in Table I.

TABLE I

TRITIUM CONTENT OF *m*-DINITROBENZENE AND 2,4-DINITROBIPHENYL (MμC./MG. OF HYDROGEN)

Sample	$C_6H_4(NO_2)_2$ (exptl.)	$C_6H_3C_6H_3(NO_2)_2$ (exptl.)	$C_6H_3C_6H_3(NO_2)_2$ (calcd.)[a]
1	51.7 ± 1.6	13.2 ± 0.4	12.9 ± 0.4
2	22.8 ± 0.7	5.54 ± 0.17	5.7 ± 0.2

[a] Calculated assuming starting material is exclusively 2,4-isomer and that replacement of hydrogen and tritium occur at identical rates.

An authentic sample of 2,4-dinitrobiphenyl was prepared by mixed Ullmann coupling of 2,4-dinitrochlorobenzene and iodobenzene in 3.5% yield,[6] m.p. 109.3–110°.[7] This showed no depression of melting point when admixed with the preceding sample.

Anal. Calcd. for $C_{12}H_8N_2O_4$: C, 59.01; H, 3.26; N, 11.47. Found: C, 58.96; H, 3.25; N, 11.39.

Discussion

The agreement of the tritium content of the

(1) Research carried out in part under the auspices of the U. S. Atomic Energy Commission.

(2) (a) W. A. Waters, *J. Chem. Soc.*, 727 (1948); (b) H. Lobel, G. Stein and J. Weiss, *ibid.*, 2704 (1950).

(3) C. C. Price, "Reactions at the Carbon–Carbon Double Bond," Interscience Publishers, Inc., New York, N. Y., 1946; D. H. Hey, A. Nechvatal and T. S. Robinson, *J. Chem. Soc.*, 2892 (1951).

(4) Tritium assay was performed at Brookhaven by Dr. D. R. Christman.

(5) K. Cruse and R. Mittag, *Z. anal. Chem.*, **131**, 273 (1950).

(6) By the procedure of N. Kornblum and D. L. Kendall, THIS JOURNAL, **74**, 5782 (1952).

(7) H. C. Gull and E. E. Turner, *J. Chem. Soc.*, 496 (1929).

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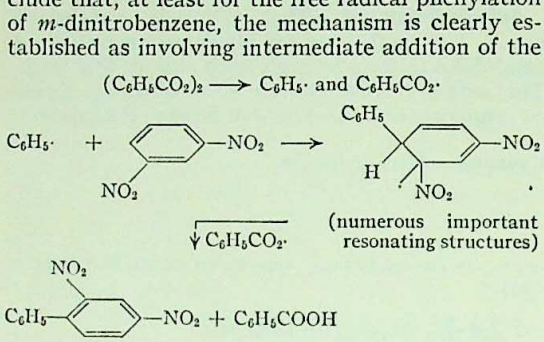
2,4-dinitrobiphenyl formed by benzoyl peroxide phenylation of 2,4-dinitrotritiobenzene with that calculated assuming no isotope effect is in accord with expectation if the phenylation occurred by mechanism 2. Mechanism 1 would have predicted a substantial isotope effect. We therefore conclude that, at least for the free radical phenylation of *m*-dinitrobenzene, the mechanism is clearly established as involving intermediate addition of the phenyl radical to the dinitrobenzene, followed by a non-rate controlling loss of hydrogen.



It should be pointed out that the mechanism demonstrated for the case of phenylation of *m*-dinitrobenzene may not necessarily hold for attack on less activated aromatic rings. For example, where resonance stabilization for the intermediate radical adduct with two groups as favorable for radical stability as the two nitro groups in *m*-dinitrobenzene is absent, radical abstraction could become more important. Such a mechanism would be particularly favored for a radical like the hydroxyl radical[2b] because of the contribution of the very strong hydrogen–oxygen bond that would be formed in the process.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

The Mechanism of the Sandmeyer and Meerwein Reactions

BY JAY K. KOCHI*

RECEIVED SEPTEMBER 4, 1956

The Sandmeyer and Meerwein reactions are postulated to proceed *via* a common aryl radical. Reaction of the aryl radical with metal halide or its addition to olefin followed by reaction with metal halide gives Sandmeyer or Meerwein products, respectively. Evidence is given for the existence of aryl and aralkyl radicals and for the radical chain termination properties of metal halides. By utilizing these reactions, Sandmeyer and Meerwein products are obtained from sources other than arenediazonium salts.

Previous kinetic studies of the Sandmeyer[1] and related Meerwein[2] reactions have shown that these reactions are first order in both diazonium ion and cuprous salt, but they have not given complete information on the mechanisms of these reactions. We wish to give evidence for a common mechanistic path involving free radical intermediates. The essential feature of this mechanism is the role of the metal ion (copper) in acting as an effective radical chain terminator.[3] In the case of the two metal ions we studied (copper and iron), the process can be formulated as

$$R\cdot + MCl_n^q \longrightarrow RCl + MCl_{n-1}^q \qquad (1)$$

$$R\cdot + MCl_m^p \longrightarrow R^+ + MCl_m^{p-1} \qquad (2)$$

These processes represent alternate routes by which radicals can react with metal and complex-metal ions; that is, (1) directly through a ligand bridge or (2) *via* an electron transfer process.[4,5] In the Sandmeyer reaction aryl radicals react predominantly by equation 1, whereas with alkyl radical sproduced in the Meerwein reaction, processes 1 and 2 sometimes appear to be competitive.

Sandmeyer Reaction.—The free radical nature of the Sandmeyer reaction has been most consistently advocated by Waters[6a] and more recently by Pfeil,[6b] who postulate a quasi-intramolecular reaction involving one-electron transfers as

$$ArN_2^+ + Cu^I Cl_n \rightleftharpoons ArN_2CuCl_n^{7}$$

$$ArN_2CuCl_n \longrightarrow N_2 + Ar\,..\,Cl\,..\,Cu^{II}Cl_{n-1} \longrightarrow Ar\text{–}Cl + N_2 + Cu^{I}Cl_n$$

The important characteristic of this mechanism is the unique role played by cuprous ion in an oxidation–reduction capacity. We believe that it is *not*

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(1) W. Cowdrey and D. Davies, *J. Chem. Soc.*, S48 (1949).

(2) J. K. Kochi, THIS JOURNAL, **78**, 1228 (1956).

(3) C. Bamford, A. Jenkins and R. Johnston, *Nature*, **177**, 992 (1956); F. Dainton and E. Collinson, *ibid.*, **177**, 1224 (1956); J. K. Kochi, THIS JOURNAL, **78**, 4815 (1956).

(4) The various aspects of these transfers have been elegantly presented by Taube and co-workers (H. Taube, *et al.*, THIS JOURNAL, **75**, 4119 (1953); **76**, 2103 (1954); **76**, 4053 (1954); **77**, 4481 (1955).

(5) The cupric ion alone is not wholly sufficient for its ability to act as a chain terminator. It appears that the most efficacious species is a higher chloro-complex, probably $CuCl_3^-$. Thus our experiments (*vide infra*) indicate that in the presence of limited chloride ions, an appreciable number of aryl radicals react by dimerization, while high chloride ion concentrations enhance the yields of Sandmeyer product (*cf.* references 1, 9b and 35).

(6) (a) W. Waters, "Chemistry of Free Radicals," 2nd Ed., Oxford Univ. Press, London, 1948, p. 163. (b) E. Pfeil and O. Velten, *Ann.*, **562**, 163 (1949); **565**, 183 (1949).

(7) Most mechanisms of the Sandmeyer reaction involve the intermediate formation of a diazonium–cuprous complex. This postulate is based partially on the observed formation of a colored complex when gross amounts of diazonium and cuprous salts are mixed. Whether these represent true intermediates has not been rigorously shown. For a discussion regarding the nature of these complexes see references 6b and 19a. It is not important for the purposes of what follows whether the reaction proceeds (a) through the rapid reversible formation of a complex intermediate followed by its slow decomposition or (b) by a slow bimolecular reaction of the diazonium ion (see Reaction 38). The contrary notwithstanding we shall treat the reaction as proceeding by the former path.

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essential that this process be cyclic; instead a discrete two-step process may be postulated

$$ArN_2CuCl_2 \longrightarrow Ar\cdot + Cu^{II}Cl_2 + N_2 \quad (3)^{8,9}$$

$$Ar\cdot + CuCl_2 \longrightarrow ArCl + Cu^{I}Cl \quad (4)^{10}$$

Our experiments indicate that free aryl radicals are present in the catalyzed decomposition of diazonium ions (equation 3). For example, when *p*-nitrobenzenediazonium chloride is decomposed in aqueous acetone solutions with cuprous chloride in the presence of iodine, iodine is consumed rapidly to give good yields of *p*-nitroiodobenzene

$$Ar\cdot + I_2 \longrightarrow ArI + I\cdot \quad (5)$$

The possibility that the iodo compound is formed by an ionic process involving iodide ion formed by reactions such as

$$I_2 + Cl^- \longrightarrow ICl + I^-$$

$$I^- + ArN_2^+ \longrightarrow ArI + N_2$$

is made unlikely by the greater than 100% yields of *p*-nitroiodobenzene based on one mole of product per mole of iodine taken. Furthermore, any iodide formed in such reactions would probably be oxidized rapidly by the cupric ion.

When *p*-nitrobenzenediazonium bisulfate is treated with cuprous chloride in the presence of limited amounts of chloride ions in aqueous acetone solutions at −25° in the presence of oxygen, in addition to a 42% yield of *p*-nitrochlorobenzene a 46% yield of *p*-nitrophenol is obtained.

$$Ar\cdot + O_2 \longrightarrow ArO_2\cdot \xrightarrow{Cu^+} ArOH \quad (6)$$

In the absence of oxygen, cupric sulfate also precipitates from solution and *p*-nitrochlorobenzene and 4,4′-dinitrobiphenyl[12] can be isolated in 76 and 9% yields, respectively. In the presence of excess cupric chloride the formation of the Sandmeyer product is increased at the expense of the coupling product.[13] Further substantiation of the

(8) Transient aryldiazo radicals may be formed. The significance of a particular chlorocuprous ion, $CuCl_2^-$, as the catalyst[1] in the Sandmeyer reaction, in this scheme, can be attributed to the favorable half-cell potential

$$CnCl_2^- \rightleftharpoons ClCl_2 + e^-$$

compared to the other chlorocuprous ions. (See, for example, N. Sidgwick, "The Chemical Elements and Their Compounds," Oxford Univ. Press, London, 1950, p. 103 ff.)

(9) (a) S. Dickerman, K. Weiss and A. Ingberman, *J. Org. Chem.*, **21**, 260 (1956); (b) W. Waters, private communication (see also D. Nonhebel and W. Waters, Abstracts, International Congress on Catalysis, Philadelphia, Pa., 1956.)

(10) Aryl radicals appear to react by process 1 which involves a direct halogen atom transfer to form the aryl halide. The alternative two-step process is an oxidation to an arylcarbonium ion followed by reaction with halide ion. This latter route appears untenable in view of the absence of phenols when the reaction is obtained in water as solvent. If carbonium ions were intermediates, phenols would be expected since arylcarbonium ions obtained in the ionic unimolecular solvolysis of aryldiazonium ions show little selectivity[11] for nucleophiles.

(11) E. Lewis and W. Hinds, THIS JOURNAL, **74**, 304 (1952); D. DeTar, *et al.*, *ibid.*, **76**, 1680 (1954); **72**, 865 (1950).

(12) W. Waters ("Chemistry of Free Radicals," 2nd Ed., Oxford Univ. Press, London, 1948, p. 165) postulates that biaryls arise by the coupling of aryl radicals (see, however, reference 19).

(13) That the *p*-nitrophenyl radical may not react instantaneously with oxygen is indicated by the small amount of 4,4′-dinitrobiphenyl which is obtained in the oxygen run. The yield of the biaryl appears to be proportional to the rate of addition of cuprous chloride. The precedent for this deduction appears in the works of Walling and Buckler and Muller and Topel who obtained considerable amounts of biphenyl in addition to phenol in the oxygenations of Grignard and lithium reagents, respectively.[14] Wieland, furthermore, reported that some biphenyl is obtained when phenylazotriphenylmethane is decomposed in the presence of oxygen[15] (*cf.* references 16). See further for indications of the selective reactions of radicals with oxygen.

(14) C. Walling and S. Buckler, THIS JOURNAL, **77**, 6032 (1955); E. Muller and T. Topel, *Ber.*, **72B**, 273 (1939).

(15) H. Wieland, *Ann.*, **514**, 145 (1934).

(16) J. Baxendale and J. Magee, *Disc. Faraday Soc.*, **14**, 160 (1953); D. DeTar and M. Turetzky, THIS JOURNAL, **78**, 3928 (1956).

(17) (a) Unpublished results with R. Keys; (b) J. Kumamoto, private communication.

(18) W. Leonhards, Doctoral Dissertation, Marburg, Germany, 1952.

(19) (a) E. Pfeil, *Angew. Chem.*, **65**, 155 (1953). (b) An alternative route for the diaryl formation in Sandmeyer type reactions may be *via* intermediate aryl copper compounds which may arise from the reaction of aryl radicals with cuprous chloride. Aryl copper compounds are known to undergo such decomposition to diaryls (H. Gilman, "Organic Chemistry," 2nd Ed., Vol. I, J. Wiley and Sons, Inc., New York, N. Y., 1943, p. 542). Similarly, it is possible for azo compounds to result from the reaction of these nucleophilic aryl copper compounds with diazonium salts. These alternatives must be held with a certain amount of reserve since aryldimethylcarbinols are not isolated when acetone is used as solvent.

(20) Rather the reverse process is obtained (J. Baxendale and J. Magee, *Trans. Faraday Soc.*, **51**, 204 (1955)).

production of aryl radicals under these conditions is the report of Dickerman, *et al.*,[9a] that aromatic solvents can be arylated. Waters and Nonhebel[9b] have been able to polymerize acrylonitrile in aqueous solutions under the conditions of the Sandmeyer reaction in the absence of oxygen. Aryl residues as end-groups were accounted for in good yields.

Systems other than arenediazonium and cuprous salts give indications of the chain-terminating properties of metal halides. For example, *p*-nitrochlorobenzene is formed in 84% yield from the decomposition of N-nitroso-*p*-nitroacetanilide in acetone solutions of ferric chloride. Chlorobenzene and trityl chloride are formed by a similar decomposition of phenylazotriphenylmethane in the presence of ferric chloride. Analogously, azobisisobutyronitrile produces significant amounts of cuprous chloride when it is decomposed in anhydrous *t*-butyl alcohol containing cupric chloride.[17a] Under similar conditions in acetonitrile, the rate of formation of cuprous chloride was found to be zero order in cupric chloride.[17b] The use of cupric salts as inhibitors of vinyl polymerization also points to their effectiveness as radical chain terminators.

That cupric chloride reacts with aryl radicals under the usual Sandmeyer conditions was shown by Pfeil and Velten[6b] who obtained quantitative yields of *p*-nitrochlorobenzene when aqueous solutions of *p*-nitrobenzenediazonium bisulfate were treated with sufficient quantities of cupric chloride at 100°. Furthermore, Leonhards[18] has shown that the addition of cupric chloride greatly reduced the amount of cuprous chloride required in the aqueous Sandmeyer reaction from as much as 0.2 to only 0.01 mole.

In aqueous solutions the destruction of the aryl radicals can occur by several competitive paths: (1) dimerization to yield biaryl,[19] (2) reaction with diazonium ion and cuprous salt to give azo compound[19] and (3) reaction with cupric chloride to give the Sandmeyer product. The solvent water does not appear to react significantly by the energetically less favorable process[20]

$$Ar\cdot + H_2O \longrightarrow ArH + HO\cdot \quad (7)$$

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In aqueous acetone solution, however, appreciable amounts of reduction (*i.e.*, chain transfer) by solvent[21] does take place to produce a more stable acetonyl radical

$$Ar\cdot + CH_3COCH_3 \longrightarrow ArH + CH_3\dot{C}OCH_2 \quad (8)^{22}$$

The resulting acetonyl radicals can either dimerize[23] or react with cupric chloride to form chloroacetone. The yields of the reduction product, ArH, are found to be approximately equal to the chloroacetone formed.[9]

$$CH_3COCH_2\cdot + CuCl_2 \longrightarrow CH_3COCH_2Cl + CuCl \quad (9)$$

In order to assess the efficiency with which cupric chloride reacts with aryl radicals, the relative amounts of reduction to substitution (equations 8 and 4) were measured by determining the amount of chloroacetone formed as a function of the cupric chloride concentration. Aqueous acetone solutions containing diazonium salt, cupric chloride and sealed breakable ampules of cuprous chloride were carefully degassed. The amounts of cuprous chloride remaining and chloroacetone formed were determined quantitatively after the diazonium decomposition was complete. As shown in Table I

TABLE I

EFFECTS OF CUPRIC CHLORIDE AND OLEFIN ON CHLOROACETONE FORMATION AND CUPROUS CHLORIDE CONSUMPTION[a]

Benzenediazonium chloride	Run	Cupric chloride, meq.	Chloroacetone,[b] meq.	Cuprous[c] chloride, meq.
2,4-Dichloro	1	0	0.68	0.0157
	2[d]	0	.12	.0690
	3[e]	0	.095	.0724
	4	0.88	.51	.0994
	5[e]	0.88	.10	.107
	6	7.04	.24	.116
Unsubstituted	7	0	.78	
	8[d]	0	.11	
	9[e]	0	.12	
	10	7.04	.19	
	11[e]	7.04	.17	
4-Chloro	12[f]	0	.73	
	13	0	1.02	
	14[g]	0	1.60	
	15[d]	0	0.11	

[a] In acetone (25 ml.) containing 2.84 meq. of diazonium salt, 18.60 meq. of chloride, 0.128 meq. of cuprous chloride and 8 ml. of water at 0°. [b] Total chloroacetone formed, including reaction between cupric chloride and acetone (in most cases negligible at these temperatures). [c] Cuprous chloride remaining after completion of reaction. [d] Contains 25 meq. of acrylonitrile. [e] Contains 25 meq. of styrene. [f,g] Contains 1.42 meq. and 5.42 meq. of diazonium salt, respectively.

the reduction of aryl radicals (as measured by the chloroacetone formed) can be effectively decreased by increasing the amount of added cupric chloride (*cf.* runs 1, 4 and 6; 7 and 11; 12, 13 and 14) It is apparent, moreover, that with increasing cupric chloride concentration less cuprous chloride is consumed, as would be expected from the preceding argument.

(21) It has been reported[6b] that the Sandmeyer reaction in methanol produces no formaldehyde.

(22) W. Waters, *J. Chem. Soc.*, 2007 (1937); 864, 1805 (1939).

(23) In none of our experiments could we find ethylene glycol diacetate.

Meerwein Reaction.—In the presence of olefin, aryl radicals produced from diazonium salts by cuprous chloride in a process such as (3), undergo a third important reaction, *viz.*, addition

$$Ar\cdot + >C{=}C< \longrightarrow Ar{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\cdot \quad (10)$$

In all cases known, the direction of addition to an unsymmetrical olefin corresponds to that producing the more stable radical.[24] In a subsequent reaction the aralkyl radical[25] can react with metal ion by either of the steps postulated previously (equations 1 and 2); *i.e.*, by a direct transfer of a halogen atom from copper to the radical or by an oxidation to a carbonium ion.[27] These two competitive processes are illustrated by the reaction of phenyl and *p*-nitrophenyl radicals with styrene. In the former case the exclusive product is α-chlorobibenzyl (equation 1); with the *p*-nitrophenyl radical, on the other hand, a mixture of α-chloro-*p'*-nitrobibenzyl and *p*-nitrostilbene is obtained. Under the conditions of the experiment the chloride does not eliminate to yield olefin. It is not quite certain at present whether the reactions of metal ions with radicals by these two processes involve the same complexed metal ion[4b] (*i.e.*, $m = n$). There is some evidence that the metal ion involved in the direct halogen transfer step is in a higher chloro-complex form than that involved in the electron transfer step. For example, when *p*-nitrobenzenediazonium bisulfate is decomposed in aqueous acetone solution containing styrene with cuprous chloride (*i.e.*, a limited amount of chloride ion present) a 21% yield of *p*-nitrostilbene is formed. The same reaction with an excess of chloride ion produces only 9% stilbene.

The presence of aralkyl radicals in the chain propagation step (equation 10) is shown by the trapping of this radical by iodine and oxygen. If iodine is added to a cuprous-catalyzed decomposition of *p*-nitrobenzenediazonium chloride in the presence of acrylonitrile, the intermediate hydro-

(24) (a) C. Koelsch and V. Boekelheide were the first to point out the free radical nature of this reaction (THIS JOURNAL, **66**, 412 (1944); **65**, 57 (1943)); (b) *Cf.* R. Huang, *J. Chem. Soc.*, 1749 (1956).

(25) O. Vogl and C. Rondestvedt[26] have shown in the case of the maleic–fumaric acid system that the addition to the double bond is not stereospecific, which indicates that the aralkyl radical is "free."

(26) O. Vogl and C. Rondestvedt, THIS JOURNAL, **78**, 3799 (1956).

(27) (a) Previous workers[28] have shown how it is possible for the carbonium ion to eliminate a β-proton or a β-carboxyl group to form olefins. (b) A case can be made, however, for the olefins to be formed from the aralkyl radicals by direct removal of the β-hydrogen atom by either cupric chloride or another radical. There is no precedent for cupric chloride acting in this capacity (see however reference 9 and 29). The removal of the β-hydrogen atom by radicals is analogous to the mechanism of homolytic aromatic substitution.[30] It is interesting to note that Vogl and Rondestvedt (reference 31) obtained phenylated coumarins, albeit in low yields, from aryl radical sources in the absence of metal ions. That the low yield is not due to the unreactivity of aryl radicals formed under these different conditions is borne out by the fact that the starting coumarin is isolated in poor yield. Instead it appears that the aralkyl radical resulting from the attack on coumarin disappears by reaction with solvent and/or reactants.

(28) H. Meerwein, E. Buchner and K. van Emster, *J. prakt. Chem.*, **152**, 237 (1939); R. Fusco and S. Rossi, *Gazz. chim. ital.*, **78**, 521 (1948).

(29) J. Kochi, THIS JOURNAL, **77**, 5274 (1955).

(30) D. Hey and G. Williams, *Disc. Faraday Soc.*, **14**, 216 (1953); W. Waters, M. Szwarc, J. Baxendale, A. Bickel, F. Mayo, etc., *ibid.*, pp. 246 ff.

(31) C. Rondestvedt and O. Vogl, THIS JOURNAL, **77**, 3067 (1955).

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cinnamonitrile radical is trapped as the iodide

$$Ar{-}CH_2{-}CH{=}CN + I_2 \longrightarrow Ar{-}CH_2{-}CHICN + I\cdot$$

In a like manner *p*-nitrobenzenediazonium bisulfate and styrene do not react with cuprous chloride and oxygen at −25° to form Meerwein product. Instead the aralkyl radical reacts with oxygen to form an intermediate peroxide which in the presence of cuprous ion is reduced[32] to the ketone, *p*-nitrodeoxybenzoin

$$Ar{-}CH_2{-}CH{-}C_6H_5 + O_2 \longrightarrow$$

$$Ar{-}CH_2{-}CH{-}C_6H_5 \xrightarrow{Cu^+} Ar{-}CH_2{-}CO{-}C_6H_5 \quad (12)$$
$$\quad\quad\quad

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centration (*cf.* 12 and 13) neither the rate of diazonium decomposition nor cuprous titer are affected. The yields of Sandmeyer and Meerwein products, however, are markedly different in each case as was shown previously.[2]

It is apparent that at low cupric and low olefin concentrations the bimolecular reaction of aryl radicals and olefin or metal halides is subverted by reactions involving consumption of cuprous catalyst (*e.g.*, dimerization of radicals or azo compound formation). Since the reaction in aqueous acetone is extremely sensitive to cuprous catalysts,[35] a small decrease in catalyst concentration due to these catalyst-destroying reactions would lead to significant changes in rate of diazonium decomposition. At low cupric, but high olefin concentrations, the olefin effectively competes with cuprous-consuming reactions as shown by the unchanged cuprous titer.

Thus, the observed qualitative variation in rates of diazonium decomposition with various olefins can be attributed to the efficiency with which each olefin competes with oxygen[36] and other side reactions which destroy catalyst. Although earlier mechanisms involving various forms of olefin complexation cannot be entirely discounted on the basis of these results, they appear to be unnecessarily involved.

The role of acetone in the decomposition of diazonium salts is threefold: (1) reaction with cupric chloride to produce cuprous chloride,[29] (2) solvent effects favoring higher chloro-complexes of cuprous and cupric ions[5,29] and (3) acceleration of the bimolecular reaction of diazonium and complex cuprous ions.[38] It is not necessary, moreover, that acetone acts in the first capacity since it is known that diazonium acetates and chlorides can be decomposed to give aryl radicals,[40] which can react with cupric chloride in a subsequent step (equation 4) to produce autocatalytic reactions. The essential requirement of the solvent, however, is that it does not effectively compete with olefin or metal halides for the aryl or aralkyl radicals in chain-terminating processes.

The unique feature of metal halides in acting as chain-terminating agents is the efficiency and selectivity with which they react with radicals. Thus, it is well known that olefins are not polymerized to any appreciable extent under the conditions of the Meerwein reaction despite the presence of radicals such as aryl and aralkyl which are known chain initiators. The selectivity with which metal halides react with aralkyl radicals (such as growing styryl and acrylonitrile radicals) may be interpreted in terms of the life-times (reactivities)[41] of these radicals in solution. This speculation must be subjected to further scrutiny.

Acknowledgments.—I would like to thank Dr. George S. Hammond for generous research facilities and the Institute for Atomic Research, Ames Laboratory, for numerous infrared spectra.

Experimental

Sandmeyer Reaction. Decomposition of *p*-Nitrobenzenediazonium Chloride.—A stock solution of *p*-nitrobenzenediazonium chloride was made by diazotizing 69 g. (0.5 mole) of *p*-nitroaniline with 108 ml. of concentrated hydrochloric acid, 200 g. of ice and 35 g. of sodium nitrite in 100 ml. of water. Excess nitrite was destroyed with urea and the clear filtered solution made up in 500 ml.

(a) **Oxygen-free.**—A 125-ml. portion of this stock solution was added to 500 ml. of acetone in a round-bottom flask at 0°. Oxygen-free argon was swept through the solution and a solution containing 2.0 g. of cuprous chloride and 1 g. of lithium chloride in 50 ml. of anhydrous acetone was added dropwise. Nitrogen was evolved immediately. Vacuum distillation of the acetone, followed by ether extraction, yielded 13.6 g. (68%) of *p*-nitrochlorobenzene (m.p. 82–84°). The mother liquors yielded 21% nitrobenzene.

When another 125-ml. portion of the diazonium solution was subjected to the same treatment except for the addition of 26 g. (0.2 mole) of cupric chloride, 82% *p*-nitrochlorobenzene and 9% nitrobenzene were isolated. Much less cuprous solution was needed for this reaction.

(b) **With Iodine.**—To a similar deoxygenated mixture was added a solution of 10 g. (0.039 mole) of iodine in 150 ml. of acetone, followed quickly by an acetone solution containing 5 g. of cuprous chloride and 3 g. of lithium chloride. The nitrogen evolution was instantaneous and a heavy precipitate of *p*-nitroiodobenzene formed. The solution was diluted with water and filtered. The extraction of the dried solid with ether leaves nearly pure *p*-nitroiodobenzene; the ether extracts lead to a 44% (8.7 g.) yield of *p*-nitrochlorobenzene. No nitrobenzene could be detected. The combined yields of *p*-nitroiodobenzene after crystallization (ligroin, m.p. 171–173°) and careful work-up of the mother liquors is 15.6 g. (162% based on I_2). The original acetone solution darkened on standing due to the oxidation of the hydrogen iodide. It is necessary that the cuprous solution follow soon after the addition of the iodine since there appears to be a slow reaction between diazonium salts and iodine in acetone solutions (*vide infra*).

With 5 g. of iodine a 178% yield (based on I_2) of *p*-nitroiodobenzene and a 65% yield of *p*-nitrochlorobenzene (based on diazonium salt) is obtained. Similarly, 23 g. of iodine gives a 93% yield of the iodo compound (based on the diazonium salt).

Decomposition of Diazonium Bisulfates (Minimum Chloride). (a) **Oxygen-free.**—Crystalline *p*-nitrobenzenediazonium bisulfate (NBDB)[42] (12 g., 0.0485 mole) was dissolved in 40 ml. of water and added to 400 ml. of redistilled acetone. Purified argon was bubbled through the chilled solution (−25°) and an anhydrous acetone solution of cuprous chloride (10 g.) and lithium chloride (7 g.) was added slowly to the anaerobic solution. The solution, after nitrogen evolution was complete, was decanted from the precipitated cupric sulfate and vacuum distilled at room temperature. Water was added to the residue and the mixture extracted with ether. Evaporation of the ether left 6.5 g. of solid residues which consisted of 5.7 g. (76%) of *p*-nitrochlorobenzene and 0.54 g. (9.1%) of 4,4′-dinitrobiphenyl (m.p. 233–235°). Nitrobenzene could be detected in the mother liquors.

This reaction was repeated with the addition of 10 g. of cupric chloride. Much less cuprous chloride was required for complete nitrogen evolution, and the yield of *p*-nitrochlorobenzene was 85%, and only 3% of the biphenyl compound was isolated.

(35) J. Kochi, THIS JOURNAL, 77, 5090 (1955).

(36) Previous workers have taken little pains to eliminate oxygen from their reactions. The retardation of the Meerwein and Sandmeyer reactions by oxygen[2,35] is now accounted for by reactions which destroy cuprous catalyst such as equations 5, 6 and 13 in addition to the direct oxidation of the cuprous ion.

$$CH_3COCH_2\cdot + O_2 \longrightarrow CH_3COCH_2O_2\cdot^{37} \quad (13)$$

(37) I. Kolthoff and A. Medalia, THIS JOURNAL, 71, 3784 (1949).

(38) Other solvents can serve the latter two purposes with varying degrees of efficacy. Thus, lower alcohols, dimethylformamide, acetonitrile, etc., increase the rate of reaction between these oppositely charged species. Similarly, the ionic reaction of iodide ion and diazonium ion is extremely rapid in acetone, alcohol and dioxane solutions.[29]

(39) Unpublished results.

(40) W. Waters, ref. 12, p. 148.

(41) M. Kharasch, E. Simon and W. Nudenberg, *J. Org. Chem.*, 18, 329 (1953).

(42) J. Kochi, THIS JOURNAL, 77, 3208 (1955).

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(b) With Oxygen.—Oxygen was bubbled through a chilled (−25°) solution containing 10.8 g. of NBDB, 50 ml. of water and 400 ml. of acetone. A solution of cuprous chloride (7 g.) was added slowly over a period of several hours while oxygen was bubbled vigorously through the solution under slight pressure (5 p.s.i.). Acetone was vacuum distilled from the decanted solution at room temperature and the residue extracted with chloroform. The dried chloroform solution (sodium sulfate) yielded 5.8 g. of solid residue. Extraction with petroleum ether gave 2.9 g. (42%) of *p*-nitrochlorobenzene. Sublimation of the residue resulted in 2.8 g. (46%) of *p*-nitrophenol (from water, m.p. 111–113°) and 0.1 g. of 4,4′-dinitrobiphenyl. If the cuprous solution is added too rapidly the amount of biphenyl increases.

Decomposition of N-Nitroso-*p*-nitroacetanilide (NNAA).—Solid NNAA[43] (5 g., moist) was dissolved in 45 ml. of anhydrous acetone and the solution added to a mixture of 6 g. of ferric chloride hexahydrate, and 3 g. of lithium chloride in 75 ml. of acetone. After argon was bubbled through the solution briefly, it was heated (with the exclusion of air) in a water-bath at 60° for 24 hr. Water was added to the reaction mixture; the precipitate was filtered, dried and crystallized from petroleum ether. The yield of *p*-nitrochlorobenzene is 2.1 g. (84% based on nitrogen evolution). Insoluble unidentified material weighed 0.3 g.; the mother liquors yielded small amounts of nitrobenzene.

Decomposition of Phenylazotriphenylmethane.—An acetone solution (100 ml.) containing 5 g. (0.0142 mole) of phenylazotriphenylmethane[44] and 10 g. of ferric chloride hexahydrate was heated at 60° in a water-bath for 12 hr. The nitrogen evolution was complete in approximately 2 hr. From the reaction mixture 1.1 g. of chlorobenzene and 3.3 g. of triphenylcarbinol were isolated. The trityl chloride which was presumably formed in the reaction mixture was hydrolyzed either during the heating or subsequent work-up.

Meerwein Reaction. Decomposition of *p*-Nitrobenzenediazonium Chloride. (a) Oxygen-free.—Forty ml. (0.04 mole) of the diazonium solution mentioned previously was added to a solution of 200 ml. of acetone and 10 g. of acrylonitrile. A solution of cuprous chloride (0.5 g.) and lithium chloride (0.3 g.) in anhydrous acetone (30 ml.) was added dropwise to the deoxygenated solution at 0° with stirring. Nitrogen was evolved immediately. The solution on dilution with water yielded 8.1 g. of α-chloro-*p*-nitrohydrocinnamonitrile which was recrystallized from ligroin as colorless needles (94%, m.p. 110–111°).

Anal. Calcd. for $C_9H_7N_2O_2Cl$: C, 51.3; H, 3.36; Cl, 16.9. Found[45]: C, 51.5; H, 3.48; Cl, 16.4.

(b) With Iodine.—An acetone solution of 16 g. of iodine was added to a deoxygenated solution containing 125 ml. of stock diazonium solution, 20 g. of acrylonitrile and 500 ml. of acetone at 0°. This was followed rapidly by an acetone solution of cuprous chloride (3 g.) and lithium chloride (2.5 g.). Nitrogen was evolved immediately and a heavy precipitate formed. The solution was diluted with water and filtered. The dried (30.3 g.) solid was triturated with small portions of ether. Evaporation of the ether left 6.6 g. of a solid from which no *p*-nitrochlorobenzene could be extracted with petroleum ether (b.p. 60–70°). It consisted wholly of a mixture of α-iodo and α-chloro-*p*-nitrohydrocinnamonitrile. These related compounds could not be separated. Neither careful fractional crystallization from ligroin or benzene nor partial vacuum sublimation were successful. In every case fine colorless needles (m.p. 103–104°, mix m.p. 107–109°) were obtained which on mild treatment with triethylamine in ligroin gave *p*-nitrocinnamonitrile (m.p. 198–201°). Iodide ion was present in the aqueous extracts of the ligroin solution. The infrared spectra (in CCl_4 and CS_2) were identical with those of the chlorononitrile. The elemental analysis, calculated on the assumption that the iodonitrocinnamonitrile was the sole contaminant, indicated that 13% of the mixture consisted of this unremovable impurity.

Anal. Calcd. for 13% iodo compound: C, 49.4; H, 3.22; total halide, 20.2. Found: C, 49.7, 5.00; H, 3.12, 2.99; total halide, 20.4, 20.3.

Decompositions of Diazonium Bisulfates (Minimum Chloride). (a) Oxygen-free.—To a deoxygenated solution of 12 g. of NBDB in 50 ml. of water, 9 g. of styrene and 300 ml. of acetone was added dropwise a solution of cuprous chloride (7 g.) and lithium chloride in acetone at −20°. The nitrogen evolution occurred immediately and only on the continued cuprous chloride addition. The solution was decanted from the cupric sulfate precipitate, vacuum distilled and extracted with ether. Basic extractions of the ethereal solution were colored dark red. Acidification of the aqueous extract followed by ether partition gave only a small amount (0.1 g.) of material which was not *p*-nitrophenol. The original ether solution after drying (sodium sulfate) yielded 8.4 g. of a semi-crystalline material, which on alumina chromatography with petroleum ether and benzene yielded 1.5 g. of *p*-nitrochlorobenzene, 2.1 g. (16.5%) of α-chloro-*p*′-nitrobibenzyl (m.p. 91–92°), 0.98 g. (9%) of *p*-nitrostilbene (m.p. 154–156°) and 0.1 g. of 4,4′-dinitrobiphenyl (m.p. 230–234°).

Anal. Calcd. for $C_{14}H_{12}NO_2Cl$: C, 64.2; H, 4.62; N, 5.35. Found: C, 64.8; H, 4.70; N, 5.38.

The addition of 14 g. of cupric chloride to a similar reaction yielded 3.4 g. (27%) of the chlorobibenzyl compound and 0.35 g. of *p*-nitrostilbene. On the other hand, the addition of 26 g. of cupric nitrate trihydrate increased the proportion of *p*-nitrostilbene (2.3 g., 21%) to α-chloro-*p*′-nitrobibenzyl (0.17 g.). The reaction was accompanied by larger amounts of colored material not eluted with chloroform.

(b) With Oxygen.—A solution of styrene (9 g.) and 400 ml. of acetone containing 12.7 g. of crystalline NBDB and 40 ml. of water was chilled to −25°. Oxygen was bubbled vigorously through the solution with a fritted glass tube and maintained at 4 p.s.i. A solution of 7 g. of cuprous chloride and 5 g. of lithium chloride in 150 ml. of anhydrous acetone was added dropwise with stirring. The solution was decanted after the reaction was complete and vacuum distilled without warming above room temperature. The residue was extracted with chloroform, the light yellow chloroform solution was dried and vacuum distilled leaving a semi-solid mass (9.4 g.). This mixture was repeatedly extracted with petroleum ether at room temperature to remove the *p*-nitrochlorobenzene (19 g.) and a small amount of unidentified aldehydic material (not benzaldehyde). The residue from the petroleum ether extraction was crystallized from ethanol (1.6 g., 13%). It was identified as *p*-nitrodesoxybenzoin (m.p. 142–144°,[46] 2,4-dinitrophenylhydrazone,[47] m.p. 234–235°, oxime,[48] m.p. 104–105°). In addition, less significant amounts of *p*-nitrochlorobenzene (0.2 g.), *p*-nitrostilbene (0.05 g.) and 4,4′-dinitrobiphenyl (0.02 g.) were obtained. No *p*-nitrophenol was found.

Decomposition of N-Nitroso-*p*-nitroacetanilide.—Styrene (2.2 g.) was added to an acetone (120 ml.) solution of ferric chloride (6 g.), lithium chloride (3 g.) and NNAA (5 g., moist) and heated at 60° for 12 hr. After the completion of the nitrogen evolution, water was added to the reaction mixture and the aqueous solution decanted from the brown oil. The styrene was allowed to evaporate and the semi-crystalline residue was chromatographed directly with ligroin and benzene mixtures. The yield of α-chloro-*p*′-nitrobibenzyl is 1.8 g. (43%); *p*-nitrochlorobenzene is 0.6 g. If present, *p*-nitrostilbene was not detected. Weight of tar is 0.6 g.

When 2.0 g. of acrylonitrile was added to the reaction as indicated above, 0.85 g. of *p*-nitrochlorobenzene, 0.51 g. (15%) of α-chloro-*p*-nitrohydrocinnamonitrile and 1.4 g. of tar was obtained. That acrylonitrile was incorporated in the tar is indicated by a nitrile absorption (2250 cm.$^{-1}$) in the infrared spectrum. These results are in qualitative accord with the observations of the relative efficiency of ferric ion in terminating growing styryl and acrylonitrile radicals.[3]

The decomposition of NNAA in the presence of metal ions is complicated by side reactions involving denitrosation.[43] Cuprous chloride denitrosates quantitatively in cold acetone solutions, whereas cupric chloride and chromic chloride do so only upon heating (probably due first to the reduction of the metal ion by acetone).[29] In the case of ferric chloride, *p*-nitroacetanilide formation is at its maximum when solu-

(43) R. Huisgen and G. Horeld, *Ann.*, **562**, 137 (1949).
(44) R. Huisgen and H. Nakaten, *ibid.*, **586**, 70 (1954).
(45) Microanalyses by Drs. G. Weiler and F. Strauss, Oxford, England.
(46) P. Petrenko-Kritschenko, *Ber.*, **25**, 2242 (1892).
(47) E. Womack, N. Campbell and G. Dodds, *J. Chem. Soc.*, 1402 (1938).
(48) O. Lange, *Ber.*, **33**, 1483 (1900).

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tions in acetone are saturated with lithium chloride (*i.e.*, in a highly complexed form). Ferrous chloride does not cause the formation of nitrous oxide; the products of this reaction consist of nitrobenzene and tar and are the same as those in the absence of metal ions. Decompositions of NNAA in anhydrous dimethylformamide containing metal salts are complicated by reaction with solvent.[49]

Decomposition of Phenylazotriphenylmethane.—Argon was flushed through an acetone solution (100 ml.) containing 5 g. (0.0143 mole) of PATM, 10 g. of ferric chloride and 15 g. of styrene. As the solution was heated at 60° in the absence of air, colorless needles of ferrous chloride were deposited on the sides of the flask. The solution was decanted, diluted with water and extracted with ether. The light yellow solution after washing with dilute sulfuric acid and water was dried and vacuum distilled. The semi-solid residue was extracted repeatedly with petroleum ether; the petroleum ether solution yielded on chromatography 1.7 g. of an oil. The oil easily solvolyzed in 50% aqueous acetone to give chloride and phenylbenzylcarbinol (m.p. 60–62°). Another portion of the oil was treated with alcoholic potassium hydroxide to yield stilbene (m.p. 123–125°). Authentic α-chlorobibenzyl made *via* the carbinol was the same as the oil. This compound eliminates hydrogen chloride spontaneously on standing.[35] The yield of chloride was based on the stilbene (46%) formed by basic treatment. The petroleum ether insoluble material was nearly pure triphenylcarbinol (3.4 g., 91%, m.p. 160–162°).

Benzoyl Peroxide Decomposition.—A mixture of 25 g. (0.206 equivalent) of benzoyl peroxide, 90 g. of ferric chloride hexahydrate, 20 g. of lithium chloride and 50 g. of styrene in 800 ml. of acetone was heated at 60° for 36 hr. in the absence of air. The carbon dioxide liberated was precipitated as barium carbonate (8.1 g., 0.041 mole). The acetone was vacuum distilled at room temperature and the residue was poured into dilute sulfuric acid and then extracted with ether. The ether extract was washed several times with 5% sodium bicarbonate (13.2 g. of benzoic acid, 0.108 mole). The ethereal solution after drying was distilled; it left an oily light residue (27 g.). The oil on fractionation *in vacuo* (0.35 mm.) gave: (a) 4.5 g., boiling 50–65°, mostly styrene; (b) 125–132°, 4.5 g.; (c) 160–165°, 13.5 g.; and (d) high boiling material, 2.1 g. Fraction b partially crystallized into a mixture of stilbene (2.7 g., 0.015 mole) and α-chlorobibenzyl (1.5 g., 0.007 mole) which were separated by solubility in petroleum ether (b.p. 30–40°). Fraction c on redistillation consisted almost wholly of a compound boiling at 164–165° at 0.7 mm. This chlorine-containing compound solvolyzed readily in aqueous acetone; basic hydrolysis of the resulting oil in dioxane–water solutions yielded benzoic acid and water-soluble styrenediol (m.p. 64–64°).[50] The compound probably has the structure $C_6H_5CO_2CH_2CHClC_6H_5$.

Anal. Calcd. for $C_{15}H_{13}O_2Cl$: C, 69.0; H, 5.02; Cl, 13.6. Found: C, 69.5, 69.7; H, 4.99, 5.10; Cl, 13.3.

The yields depend to a large extent on the ratio of ferric chloride to added lithium chloride. With no added lithium chloride the decomposition in the presence of styrene leads to more high boiling residue than those reactions with added chloride. Neither stilbene nor chlorobibenzyl could be isolated from the former solutions. It has not been determined yet whether the ester arises *via* a ferric-catalyzed homolytic or heterolytic[51] process. This reaction merits further investigation.

Decomposition of Diazonium Salts in the Presence of $CuCl_2$.—Standard stock solutions were made from crystalline diazonium chlorides, reagent cupric chloride and lithium chloride as described previously.[2] Freshly crystallized cuprous chloride was dissolved in anhydrous acetone (0.064 *M*) with the aid of lithium chloride and aliquots were sealed in 1-, 2- and 3-ml. thin walled ampules. The aqueous cupric chloride solution was placed in the center well of the reaction vessel; the diazonium salt, lithium chloride and vial of cuprous chloride solution together with acetone were placed in the outer well. The vessel was degassed by the standard procedure. The evacuated flask was then shaken at 0° to break the ampule containing cuprous chloride. After the reaction was complete (test with β-naphthol solution), acidic ferric ammonium sulfate solution was added and the solution vacuum distilled into a Dry Ice trap. Under these conditions acetone, chloroacetone and water were collected. To the thawed solution was added 4 g. of sodium iodide and the volume made up to 50 ml. with acetone. The iodoacetone was analyzed by acidifying an aliquot with aqueous perchloric acid and quickly titrating with standard sodium thiosulfate solution. Control runs proved to be accurate within 3%. The stoichiometry of the reactions are[52]

$$ClCH_2COCH_3 + I^- \longrightarrow ICH_2COCH_3 + Cl^-$$

$$ICH_2COCH_3 + HI \longrightarrow CH_3COCH_3 + I_2$$

The residual ferrous ion was titrated with standard ceric solution. The extent of oxidation of the ferrous salt during the distillation is negligible.

TABLE III

EFFECT OF IODINE ON CHLOROACETONE FORMATION[a]

Cuprous choride, meq.	Iodine, mg.	Chloroacetone,[b] meq.
0.128	..	1.02
.128	300	0.47
.128[c]	300	.17
.128[d]	300	.0
.256	..	1.75
.256	300	0.63
.256	600	.50
.256	900	.46

[a] Same as Table I for *p*-chlorobenzenediazonium chloride. [b] Includes iodoacetone formed from iodine. [c] No cuprous salt. [d] No diazonium salt.

AMES, IOWA

(49) P. Onyon, *Trans. Faraday Soc.*, **52**, 80 (1956).
(50) N. Milas and S. Sussman, THIS JOURNAL, **59**, 2345 (1937).
(51) J. Leffler, *ibid.*, **72**, 67 (1950); D. Bryce-Smith and P. Clarke, *J. Chem. Soc.*, 2264 (1956).
(52) J. Conant and W. Kirner, THIS JOURNAL, **46**, 233 (1925).

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CHICAGO]

The Optical Rotation and Configuration of a Pure Enantiomorph of Ethanol-1-*d*[1,2,3]

BY H. RICHARD LEVY,[4] FRANK A. LOEWUS AND BIRGIT VENNESLAND

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A method is described for the preparation of gram quantities of a pure enantiomorph of ethanol-1-*d*. CH_3CDO is reduced to ethanol-1-*d* by glucose in the presence of alcohol dehydrogenase, glucose dehydrogenase and a catalytic amount of DPN. The ethanol-1-*d* was shown by enzymatic analysis to contain no more than 0.1 % of its enantiomorph and the optical rotation was determined. A discussion is presented of the configuration of the ethanol and of the factors contributing to the steric specificity of the enzyme reaction.

Introduction

The reaction catalyzed by yeast alcohol dehydrogenase previously has been shown to involve a direct and reversible transfer of hydrogen between ethanol and diphosphopyridine nucleotide (DPN).[5,6] This transfer has been shown to be sterically specific, both for the DPN[6] and for the ethanol.[7] Loewus, *et al.*,[7] have used alcohol dehydrogenase to prepare both enantiomorphs of ethanol-1-*d*. In these experiments, one enantiomorph was prepared by reducing acetaldehyde-1-*d* (CH_3CDO) with unlabeled reduced DPN (DPNH), and the other enantiomorph was prepared by reducing unlabeled acetaldehyde with monodeuterio-reduced DPN (DPND). The enantiomorphs were identified by examining the products of their enzymatic reoxidation. Thus, the ethanol formed by reducing CH_3CDO with DPNH transferred only *hydrogen* back to DPN, forming CH_3CDO and DPNH; whereas the ethanol formed by reducing CH_3CHO with DPND transferred *deuterium* back to DPN, forming CH_3CHO and DPND. In both cases the cost of large quantities of reduced DPN set a practical limit to the quantities of ethanol-1-*d* which could be prepared conveniently, and insufficient quantities were obtained to determine optical rotation. Since the latter value is of some interest and since the ethanol-1-*d* may provide a useful tool for studying the mechanism of displacement reactions on primary alcohols,[7-9] a method was sought whereby gram quantities of this substance might be economically prepared. This report describes such a procedure.

Procedures, Results and Discussion

The synthesis of gram quantities of ethanol-1-*d* was carried out by reducing CH_3CDO with glucose in the presence of alcohol dehydrogenase (ADH), glucose dehydrogenase (GDH) and a catalytic amount of DPN (equation 1). By the use of such

$$CH_3CDO + \text{glucose} \xrightarrow[\text{GDH, ADH}]{\text{DPN}} CH_3CDHOH + \delta\text{-gluconolactone} \quad (1)$$

a coupled system, the requirement for stoichiometric quantities of DPN was avoided. In the coupled reaction, DPN is reduced by the glucose dehydrogenase reaction (equation 2) and reoxidized by CH_3CDO in the presence of ADH. The

$$\text{glucose} + DPN^+ \longrightarrow \delta\text{-gluconolactone} + DPNH + H^+ \quad (2)$$

GDH system was chosen to regenerate DPNH partly because the equilibrium of the reaction (equation 2) is favored in the direction of reduction of DPN. The non-enzymatic hydrolysis of the gluconolactone also helps to drive the reaction to completion.[10] The GDH has, of course, no effect on the steric specificity of the reaction for ethanol. This steric specificity is determined entirely by the ADH.

The ethanol-1-*d* formed by equation 1 was separated from the reaction mixture by distillation, as described in the Experimental section. The enantiomorphic purity of the ethanol was determined essentially as previously described,[7] *i.e.*, the material was oxidized to acetaldehyde by DPN in the presence of yeast ADH. Since the ethanol was prepared from CH_3CDO and DPNH, it should form CH_3CDO on reoxidation, and, if completely uncontaminated by its enantiomorph, it should transfer no excess deuterium to the DPNH. To determine the deuterium content of the DPNH with maximum accuracy, the DPNH was oxidized by pyruvate in the presence of lactic dehydrogenase (LDH), and the lactate was isolated as the phenacyl derivative and analyzed for deuterium. As demonstrated previously,[11] all the deuterium transferred to DPN from ethanol is in turn transferred to lactate when the DPND is reoxidized by pyruvate in the presence of LDH. This is because both enzyme reactions involve direct transfer of hydrogen and both have the same steric specificity for DPN.

The reactions involved in the synthesis and analysis of ethanol-1-*d* are summarized by equations 3–6.

(1) Supported by grants from the National Science Foundation, the National Institutes of Health, U. S. Public Health Service (G3222), and the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

(2) Part of this material is taken from a thesis submitted by H. Richard Levy in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Two preliminary reports of this work have been published previously: B. Vennesland, *J. Cell. Comp. Physiol.*, **47**, Suppl. 1, 201 (1956); *Disc. Faraday Soc.*, **20**, 240 (1955).

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(9) A. Streitwieser, THIS JOURNAL, **75**, 5014 (1953); **77**, 1117 (1955).

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(11) F. A. Loewus, P. Ofner, H. F. Fisher, F. H. Westheimer and B. Vennesland, *ibid.*, **203**, 699 (1953).

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$$\text{glucose} + \text{DPN}^+ \xrightarrow{\text{GDH}} \text{gluconic acid} + \text{DPNH} + \text{H}^+ \quad (3)$$

$$CH_3CDO + \text{DPNH} + \text{H}^+ \xrightarrow{\text{ADH}} CH_3CDHOH + \text{DPN}^+ \quad (4)$$

$$CH_3CDHOH + \text{DPN}^+ \xrightarrow{\text{ADH}} CH_3CDO + \text{DPNH} + \text{H}^+ \quad (5)$$

$$\text{DPNH} + CH_3COCO_2^- + \text{H}^+ \xrightarrow{\text{LDH}} CH_3CHOHCO_2^- + \text{DPN}^+ \quad (6)$$

The italicized compounds were converted to suitable derivatives and analyzed for deuterium.

Table I shows the results of the deuterium analyses obtained with two separate preparations, described as experiments 1 and 2 in the Experimental section. These preparations differed only in the scale on which they were carried out and in the source of the enzymes. The results given in Table I show that the original acetaldehyde, the ethanol-1-*d* formed from it and the acetaldehyde formed from the ethanol-1-*d* on enzymatic reoxidation, all contained about one atom of deuterium per molecule, as expected. The deviations from unity are all within the limit of experimental error. The results in Table I also show that the amount of excess deuterium in the lactate was negligible, as

Table I

Deuterium Content of Starting Materials and Products

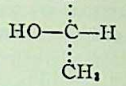
Expt.	Equation	Substance analyzed	Dilution factor	Atom % excess D Found	Atom % excess D Cor. for diln. factor	Atom D per molecule
1	4	Acetaldehyde[a]	12.1	0.316	3.82	1.00
	4	Ethanol[b,d]	44.1	.229	10.1	0.91
	5	Acetaldehyde[a]	13.4	.284	3.80	.99
	6	Lactate[c,d]	6.34	.0035	0.022	.003
2	4	Acetaldehyde[a]	23.4	.161	3.76	.98
	5	Acetaldehyde[a]	24.6	.141	3.46	.90
	6	Lactate[c]	2.13	.000	0.000	.000

[a] Analyzed as ethylidine dimethone; theory for 1 atom D per molecule, 3.84 atom % excess. [b] Analyzed as ethyl *p*-nitrobenzoate; theory for 1 atom D per molecule, 11.1 atom % excess. [c] Analyzed as phenacyl lactate; theory for 1 atom D per molecule, 8.33 atom % excess. [d] Derivatives not recrystallized.

expected from previous results.[7] The deuterium content of the lactate from experiment 1 appeared to be just above normal by an amount which was barely beyond the limit of detectability with the experimental method employed. The derivative had not been recrystallized, however. Since the amount of excess deuterium in the lactate is a measure of the maximum amount of "racemization" occurring in equations 4 and 5, special precautions were taken to obtain a more accurate analysis of the lactate of experiment 2. Larger quantities of ethanol were employed so that the dilution factor could be lower than in experiment 1. Under the conditions of analysis 0.005 atom % excess D in the sample, which could have been detected with certainty, would correspond to 0.001 atom D per molecule. The fact that no excess deuterium was found indicates that the sum of the racemizations occurring in equations 4 and 5 was less than one part in 1000.

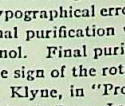
Prior to the final determination of optical activity, the ethanol-1-*d* was purified by vapor phase chromatography on a Carbowax column, a procedure which removed essentially all of the water and two other minor impurities. The ethanol-1-*d* (99+%) had $[\alpha]^{28}D$ $-0.28 \pm 0.03°$.[12] The enantiomorphic purity of the ethanol is more accurately established than the magnitude of the optical rotation.

From the sign of the rotation and some reasonable assumptions, one may conclude that the (−)-ethanol-1-*d* has the configuration



where the Fischer convention is used for the projection formula. (This may be designated ethan-1*L*-ol-1-*d* if italic capitals are used to designate configurations, as described by Mills and Klyne.[13] The choice of convention is of course arbitrary, and it should be noted that by the "sequence rule" of Cahn and Ingold, the configuration would be D[14] or R[14a]).

The above conclusion regarding configuration is based on the assumption that (−)-ethanol-1-*d* has the same configuration as (−)-butanol-1-*d*. This assumption seems reasonable in view of the correlations between sign of rotation and configuration which have been established for secondary alcohols.[13,15] Streitwieser[9] has prepared (−)-butanol-1-*d* by the reduction of butyraldehyde with (+)-2-octyl-2-*d* oxymagnesium halide. The reducing agent must be octan-2*D*-ol[13] since the configuration of (+)-octan-2-ol has been related to that of (+)-butan-2-ol which has in turn been shown to be butan-2*D*-ol.[13,15,16] (Note again that italic capital letters are used to represent configuration as described by Mills and Klyne.[13]) The rule deduced by Doering and Young[17] states that in a partially asymmetric Meerwein–Ponndorf–Verley reduction, the configuration of the reducing alcohol and the predominating enantiomer of the reduced alcohol are the same. If this rule is assumed to apply, then the configuration of the (−)-butanol-1-*d* prepared by Streitwieser should be



(12) In preliminary reports[1] the sign of the rotation was erroneously reported to be + due to a typographical error. This preliminary value was determined prior to final purification with a solution later found to contain about 70% ethanol. Final purification increased the magnitude but did not affect the sign of the rotation.

(13) J. A. Mills and W. Klyne, in "Progress in Stereochemistry," (ed. W. Klyne), Vol. I, Academic Press, Inc., New York, N. Y., 1954, pp. 177 ff.

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(17) W. E. Doering and R. W. Young, *ibid*, **72**, 631 (1950).

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since the H must be regarded as equivalent to the methyl groups of the secondary alcohols studied by Doering and Young. It seems preferable to write the projection formula with the deuterium on top, however, and thus to identify this configuration by use of the symbol *L* to indicate the position of the hydroxyl function, *viz.*, butan-1*L*-ol-1-*d*.

If the normal direction of enzymatic hydrogen transfer to CH_3CDO resulting in (−) CH_3CDHOH is represented by diagram (a), then diagram (b) represents the relative positions of the atoms leading to the enantiomorphic (+)-CH_3CHDOH. The high enantiomorphic purity of the ethanol-1-*d*

a b

formed by yeast alcohol dehydrogenase bears witness to the forces which must orient the substrate during the enzyme reaction. As pointed out previously,[7] the "normal" orientation of acetaldehyde probably is achieved by a combination of several factors. Thus, the acetaldehyde probably is bound by the polar oxygen atom, and, in addition, the methyl group may be held in a particular position by van der Waals attractive forces, "squeezed" out of the solution on to the protein by the cohesive force of the water molecules[18] and prevented by steric hindrance from occupying the position normally occupied by hydrogen (or deuterium). In this connection it is of interest that yeast ADH can catalyze the reduction of acetone to isopropyl alcohol.[19,20] In acetone, a methyl group occupies the position occupied by hydrogen (or deuterium) in acetaldehyde. The reduction of acetone thus resembles, in part, the reduction of acetaldehyde in the unnatural position shown in diagram (b),[21] where a methyl group also occupies a position "normally" occupied by hydrogen.

An examination of the kinetics of the oxidation of isopropyl alcohol (or the reduction of acetone) should indicate the extent to which steric hindrance to the methyl group may contribute to the normal orientation of acetaldehyde. The kinetics of the oxidation of methanol (or the reduction of formaldehyde) as catalyzed by alcohol dehydrogenase[19] are also of interest, since they might reflect the effect of the absence of the methyl group in the normal position.

No adequate kinetic studies of either the enzymatic oxidation of methanol and isopropyl alcohol or of the enzymatic reduction of formaldehyde and acetone could be found in the literature. Measurements were therefore made of the relative velocities of the reduction of DPN by ethanol, isopropyl alcohol and methanol at a series of different alcohol concentrations. Some measurements with ethanol-1,1-d_2 were included for comparison. The data obtained are assembled in Table II in the form of the calculated Michaelis constants (K_s)[22] and the relative maximum velocities.[23] The Michaelis constants were determined in the usual way from plots of the reciprocal of the velocity against the reciprocal of the substrate concentration.[22]

TABLE II

KINETIC MEASUREMENTS

Substrate	K_s, mole/liter	Maximum velocity relative to ethanol
Ethanol	2.1×10^{-3}	100
Isopropyl alcohol	1.4×10^{-1}	39
Methanol	1.3×10^{-1}	4
Ethanol-1,1-d_2	3.0×10^{-3}	69

For the purpose of this discussion, the K_s values may be regarded as a measure of the dissociation constants of the various enzyme–substrate complexes. Though this assumption is not strictly correct, it simplifies the discussion and introduces no apparent error in the nature of the conclusions drawn from the data of Table II. Comparison of the data for ethanol and isopropyl alcohol shows that the Michaelis constants differ by more than a hundred-fold, whereas the difference between the maximum velocities is only 2–3-fold. Thus the large difference noted in the relative velocity of the reactions at low alcohol concentrations is due mainly to the fact that isopropyl alcohol has a much lower affinity for the enzyme than does ethanol. The large dissociation constant for the enzyme–isopropyl alcohol complex can be most easily explained in terms of steric hindrance rather than in terms of the absence of any group which can be responsible for enzyme–substrate binding.

The data in Table II show that methanol also has a low affinity for the enzyme relative to ethanol, and this can most easily be explained in terms of the absence of the binding due to the methyl group. The maximum velocity of the oxidation of methanol is only one-twentieth of that of the ethanol, but the difference between the K_s-values is even larger. The data for methanol must be regarded with reservations, however, since the velocities measured tended to decline rapidly with time, and poor fits for the Lineweaver–Burke plots were the rule. Never-

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(20) K. Burton and T. H. Wilson, *Biochem. J.*, **54**, 86 (1953).

(21) The DPN has not been included in diagrams (a) and (b) because its orientation with respect to the acetaldehyde is not known. The DPN should, however, be understood to occupy the same relative position in (a) and in (b), and it is assumed that this position does not change when acetone is substituted for acetaldehyde. The unlikely possibility that the isopropyl alcohol reaction has a different steric specificity for DPN than does the ethanol reaction was ruled out by observing that deuterium, introduced into DPND by enzymatic reduction of DPN with ethanol-1,1-d_2 was removed when the DPND was oxidized enzymatically by acetone (unpublished experiment, H.R.L.).

(22) H. Lineweaver and D. Burk, THIS JOURNAL, **56**, 658 (1934).

(23) A. P. Nygaard and H. Theorell, *Acta Chem. Scand.*, **9**, 1300 (1955), have made a detailed kinetic study of the reaction catalyzed by yeast ADH, and have shown that the measured rates of ethanol oxidation in the presence of enzyme deviate from the theoretical Michaelis equation at very high ethanol concentrations. The maximum velocities calculated from the Michaelis equation are therefore open to some question. The values given in the second column of Table II were therefore obtained from the maximum velocities actually observed and not from the calculated maximum velocities. Use of the calculated maximum velocities gives similar values for the relative velocities, however, so the conclusions are not affected. The K_s values of Table II were calculated from the part of the curve which is the Michaelis relation.

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theless, the kinetic data are, on the whole, consistent with and reinforce the view that the "normal" orientation of acetaldehyde, shown in diagram (a), is due both to binding of the methyl group and to steric hindrance at the site occupied by hydrogen.

The effect of the substitution of deuterium in the ethanol is small relative to the effect of interchanging methyl groups and hydrogen, but the velocity of oxidation is definitely lower for dideuterioethanol than for ethanol at all alcohol concentrations. The transfer of hydrogen must therefore be at least partially rate-limiting in the enzyme reaction.[24] Nygaard and Theorell[23] have concluded that their kinetic data are consistent with a mechanism in which a ternary enzyme–coenzyme–substrate complex is converted into a second ternary complex in a rate-limiting reaction. This reaction may be the transfer of hydrogen between substrate and DPN. The effect of deuterium on the reaction kinetics has been investigated in more detail by Mahler.[25] An interesting and recent discussion of other facts which have a bearing on the question of the enzyme reaction mechanism can be found in a paper by Kosower.[26]

Experimental

Enzymes.—Yeast alcohol dehydrogenase prepared according to Racker[27] was used in experiment 1. A sample purchased from Nutritional Biochemicals Co. was used in experiment 2. Lactic dehydrogenase was prepared from heart muscle according to Straub.[28]

The glucose dehydrogenase used in experiment 1 was prepared according to Strecker and Korkes.[10] A fraction containing 220 units per mg. of protein[10] was stored as a solution at −15°. For experiment 2, the glucose dehydrogenase was prepared according to Brink.[29] The report that this procedure gives enzyme of higher specific activity than the procedure of Strecker and Korkes could not be verified. After the first two ammonium sulfate fractionations, the enzyme did not precipitate at the ammonium sulfate concentrations reported by Brink. Further fractionation was continued with recovery of the enzyme first between 25 and 30% saturation and then from a more dilute solution between 26 and 36% saturation. The specific activity in the units defined by Strecker and Korkes was 120 units per mg. of protein. The preparation was devoid of acetaldehyde dehydrogenase activity, but it contained both a DPNH oxidase activity and a DPN destroying enzyme which was not inhibited by nicotinamide. These latter enzyme activities were only partially removed by high speed centrifugation. Their presence complicates the use of the enzyme for the preparation of ethanol-1-*d*, and the procedure of Brink for the preparation of the glucose dehydrogenase is consequently not recommended.

Procedures.—Acetaldehyde-1-*d* was prepared as described by Loewus, *et al.*[7] The preparation of ethyl *p*-nitrobenzoate,[7] ethylidine dimethone,[7] and phenacyl lactate[11] were also carried out as previously described. Sigma Chemical Co. Cozymase "90" (*i.e.*, DPN) was employed. Enzymatic assays for acetaldehyde, ethanol and oxidized and reduced DPN were carried out spectrophotometrically, as previously described.[6]

The deuterium analyses were carried out by burning the samples to water, converting the water to H_2 plus HD[30] and analyzing the gas for deuterium with a mass spectrometer.[31]

Experiment 1.—The reaction mixture contained 40 ml. of 2 *M* phosphate of *p*H 7.1, 15 g. of glucose, 5 mg. of DPN, 44 ml. of a solution of GDH containing 9000 units per ml. and 0.1 ml. of a solution of ADH containing 6×10^5 units per ml. The acetaldehyde-1-*d* was freshly distilled before use and added to the reaction mixture as an aqueous solution containing 42 mg. of acetaldehyde-1-*d* per ml. The reaction was initiated by addition of 2 ml. of this acetaldehyde solution. When the acetaldehyde was almost entirely reduced, another 2-ml. portion was added, and this addition of small portions was continued until 43 ml. of the acetaldehyde solution had been added (corresponding to 1.8 g. of acetaldehyde reduced). This required a period of 405 minutes. The disappearance of the acetaldehyde after addition of each increment was most conveniently followed by making use of the fuchsin aldehyde reagent spot test. During the course of the reaction, the *p*H was checked periodically and readjusted to 7 with 5 *N* NH_4OH solution, whenever this was necessary. Toward the end of the reaction, further addition was made of 70 ml. of GDH solution, 0.15 ml. of ADH solution, 10 mg. of DPN and 5 g. of glucose.

At the conclusion of the reaction the flask containing the reaction mixture was connected to a receiving flask by a wide U-tube with a glass-stoppered outlet through which the system was evacuated. The reaction mixture was frozen before evacuation. Then the ethanol was distilled into the receiving flask by slowly raising the temperature of the reaction mixture. The receiving flask was cooled with Dry Ice–acetone. Three fractions were collected, and found by enzymatic analysis to contain the theoretical yield of ethanol. The first fraction from the vacuum distillation was distilled on a Vigreux column, and the fraction distilling between 72 and 95° was collected separately.

This fraction contained 78% of the total yield of ethanol with relatively little water. A small portion was withdrawn for enzymatic analysis of enantiomorphic purity and for preparation of a sample of ethyl *p*-nitrobenzoate for deuterium analysis. After a preliminary determination of optical rotation, the main portion of the ethanol-1-*d* was further purified by vapor phase chromatography as described below. The ethanol-1-*d* in the other fractions of the vacuum distillate was also fractionated on a Vigreux column and obtained in aqueous solutions of varying concentrations.

The *p*-nitrobenzoate of the ethanol-1-*d* was prepared by dissolving 0.05 ml. in 0.5 ml. of anhydrous pyridine, adding 40 mg. of *p*-nitrobenzoyl chloride and then 6 ml. of water. After gentle warming, the solution was cooled slowly. The crystals of ethyl *p*-nitrobenzoate were collected by centrifugation, washed with 5% sodium carbonate and dried under vacuum. For deuterium analysis, 1.26 mg. was diluted with 54.26 mg. of unlabeled ethyl *p*-nitrobenzoate.

For the enzymatic analysis of the enantiomorphic purity of the ethanol-1-*d*, the reaction mixture was made up as follows: 226 mg. of $Na_4P_2O_7 \cdot 10H_2O$ and 108 mg. of DPN were dissolved in 4.0 ml. of water, and 0.25 ml. of 1 *N* NaOH was added to adjust the *p*H to 9–9.5. The volume was adjusted to 5.0 ml. with water, and 20 μl. of ADH solution (1.2×10^5 units) was added. The reaction was initiated by addition of 0.1 ml. of the ethanol-1-*d*, and the course of the reduction of DPN was followed by measuring the optical density of dilutions of suitable aliquots at 340 mμ with a Beckman spectrophotometer. The *p*H was readjusted to 9.0–9.5 with 1 *N* NaOH when necessary. After 30 minutes, the reaction mixture was frozen and the acetaldehyde and most of the water were distilled *in vacuo* into saturated dimedon. The ethylidine dimethone obtained was recrystallized, and 4.07 mg. was diluted with 50.41 mg. of unlabeled ethylidine dimethone prior to analysis for deuterium. The remaining reaction mixture was restored to its original volume by addition of water and brought to 100° in a boiling water-bath to inactivate the enzyme. The *p*H was carefully adjusted to 7 by addition of dilute HCl. Enzymatic analysis showed that 83.0 μmoles of DPNH was present. Then 10 μl. of LDH solution (1×10^5 units) was added, followed by 83.0 μmoles of pyruvate. The oxidation of DPNH was complete in 10 minutes. The enzyme was heat-inactivated and 39.2 mg. of lithium L-lactate was added as a diluent. The lactic acid was extracted with ether and converted to the phenacyl derivative as previously described.[11]

Experiment 2.—This experiment was planned essentially as a repetition of experiment 1, except that the GDH and ADH were of different origin. Mainly because of the DPN-destroying activity of the GDH preparation, considerable

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(25) H. R. Mahler and J. Douglas, *Federation Proc.*, **15**, 307 (1956).
(26) E. M. Kosower, THIS JOURNAL, **78**, 3497 (1956).
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(28) F. B. Straub, *Biochem. J.*, **34**, 483 (1940).
(29) N. G. Brink, *Acta Chem. Scand.*, **7**, 1881 (1953).
(30) J. Graff and D. Rittenberg, *Anal. Chem.*, **24**, 878 (1952).
(31) R. B. Alfin-Slater, S. M. Rock and M. Swislocki, *ibid.*, **22**, 421 (1950).

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difficulties were experienced. A total of 163 mg. of DPN was eventually added in increments during the course of the reaction, and after 405 minutes only 450 mg. of acetaldehyde-1-*d* was reduced. The ethanol was distilled out of the reaction mixture *in vacuo* and redistilled on a Vigreux column. The fraction collected between 70 and 98° was used entirely for the enzymatic analysis of enantiomorphic purity as described in experiment 1. The ethylidene dimethone and phenacyl lactate were analyzed for deuterium after suitable dilution.

Purification and Optical Rotation of Ethanol-1-*d*.—The ethanol was separated on a vapor phase chromatography column[32] in 0.1-ml. batches. A 5-foot column packing of Carbowax 1540 on pulverized magnesia was used with t = 100° and a helium flow rate of 50 ml. per min. Two minor impurities (probably acetaldehyde and acetic acid) appeared before the ethanol peak. The ethanol was collected in a trap chilled in alcohol–Dry Ice. The ethanol appeared about 4 to 5 minutes after injection of the alcohol mixture, and the water peak appeared after 8–9 minutes. Collection of the ethanol was interrupted the moment the water peak began to appear, or earlier. Control experiments with 95% and absolute alcohol showed that complete separation of the azeotrope was achieved. A total of 0.9 ml. of purified ethanol-1-*d* was obtained.

The rotation was determined visually in a 1-dm. polarimeter tube of 0.25-ml. capacity, with a Rudolph precision polarimeter that could be read to 0.001° under ideal conditions. The readings were taken at maximum sensitivity, but due to the small bore of the polarimeter tube, a precision of about 10% was the best that could be achieved. The zero point reference was determined with unlabeled absolute ethanol under conditions comparable to those used for taking readings with the ethanol-1-*d*. The average of a large number of readings gave $\alpha^{28}D$ −0.22 ± 0.02° (l 1). If the density at 28° is assumed to be 0.80, the ethanol-1-*d* has $[\alpha]^{28}D$ −0.28 ± 0.03°.

The rotation was also determined with a Keston polarimeter attachment[33] on a Beckman DU spectrophotometer. The rotations measured at 26° in a 0.5-dm. tube were $\alpha_{460\ m\mu}$ − 0.123°, $\alpha_{546\ m\mu}$ − 0.095°, $\alpha_{584\ m\mu}$ −0.066°. These values are regarded as only approximate.

Kinetic Measurements.—The Michaelis constants for the various alcohols were determined by measuring the initial velocity of reduction of DPN in the presence of suitable amounts of a commercial sample of alcohol dehydrogenase with a specific activity of 86,200.[27] The K_s-values were calculated from Lineweaver, Burk plots.[22] The reactions were carried out in 3 ml. of 0.05 M pyrophosphate buffer of pH 9.3. The DPN was 1.35×10^{-3} M. In each series, four to six different concentrations of alcohol were used. The measurements were made at 340 mμ in a Beckman spectrophotometer with attached thermoregulator for the cell compartment to maintain the temperature at 25°. The reaction was initiated by addition of the enzyme, the contents of the cuvette were mixed rapidly, and readings were taken every 10 or 15 seconds for at least one minute. The amount of DPNH formed was calculated from the increase in optical density.

The isopropyl alcohol and the methanol were purified according to Gilson.[34]

Acknowledgments.—The authors acknowledge with gratitude the stimulating discussions of Professor F. H. Westheimer. The purification of the ethanol-1-*d* by vapor phase chromatography was carried out by F.A.L. under the guidance of Dr. K. Dimick, whose generous assistance is gratefully acknowledged. The authors are also indebted to Dr. Frank Young for the use of the Rudolph polarimeter and to Dr. Clinton Ballou for the use of the Keston polarimeter attachment to the Beckman spectrophotometer.

The lithium aluminum deuteride was purchased on allocation from the Atomic Energy Commission. The funds for the purchase of the mass spectrometer used in this research were supplied by the Atomic Energy Commission under contract No. At(11-1)-92.

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CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, AEROJET-GENERAL CORP.]

The Mannich Reaction of 2,2-Dinitro-1-alkanols with Ammonia, Glycine and Hydrazine[1]

BY MILTON B. FRANKEL AND KARL KLAGER

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The Mannich condensation of 2,2-dinitro-1-alkanols with ammonia, glycine and hydrazine has been studied and the importance of the pH in these reactions has been shown. 2,2-Dinitro-1-alkanols condense readily with ammonia in a buffered medium to give the corresponding bis-substituted amines. The condensation of these nitroalcohols with glycine gives a mono substituted product at a pH of 7 and a disubstituted product at a pH of 9. The reaction of methyl 5-hydroxy-4,4-dinitropentanoate with glycine results in the formation of 5,5-dinitro-2-piperidone-N-acetic acid. The condensation of 2,2-dinitropropanol with hydrazine gives bis-N,N′-(2,2-dinitropropyl)-hydrazine.

The Mannich reaction with *gem*-dinitroparaffins was first reported by Feuer and co-workers[2] who described the condensation of 2,2-dinitro-1,3-propanediol and sodium 2,2-dinitroethanol with glycine and ethanolamine. Feuer reported that the pH, the reaction temperature and the mole ratio of the reactants have a pronounced effect on the course of this reaction. Independent of this work, we studied the Mannich reaction of various 2,2-dinitro-1-alkanols with ammonia, glycine and hydrazine.

Inasmuch as the 2,2-dinitro-1-alkanols are converted in basic medium to the corresponding aci salts of 1,1-dinitroalkanes and formaldehyde,[3] this work was directed to a study of the influence of pH on the Mannich reaction in these systems. We observed that the reaction of 2,2-dinitro-1-alkanols with ammonium hydroxide gave little or no yield of the Mannich condensation product. However, it was found that if the solution was buf-

(1) Presented before the Division of Organic Chemistry at the 131st meeting of the American Chemical Society, Miami, Florida.

(2) H. Feuer, G. B. Bachman and W. May, THIS JOURNAL, **76**, 5124 (1954).

(3) A. Duden and C. Harding, *Ber.*, **38**, 2031 (1905).

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fered by using ammonium acetate instead of ammonium hydroxide, the condensation occurred readily. Thus, if an aqueous solution of ammonium acetate and the 2,2-dinitro-1-alkanols was warmed to 60°, quantitative yields of the bis-(2,2-dinitroalkyl)-amines separated on cooling. In this manner were prepared 2,2,6,6-tetranitro-4-azaheptane (Ia), 3,3,7,7-tetranitro-5-azanonane (Ib) and 4,4,8,8-tetranitro-6-azaundecane (Ic).

$$2RC(NO_2)_2CH_2OH + NH_3 \xrightarrow[\text{Buffer}]{\text{HOAc}} [RC(NO_2)_2CH_2]_2—NH$$

Ia, R = CH_3
Ib, R = CH_3CH_2
Ic, R = $CH_3CH_2CH_2$

Condensation of methyl 5-hydroxy-4,4-dinitropentanoate and ammonium acetate gave dimethyl 4,4,8,8-tetranitro-6-aza-1,11-undecanedioate (II). Compound II was prepared more conveniently by the direct condensation of the aci-sodium salt of methyl 4,4-dinitrobutyrate, formaldehyde and ammonium acetate.

$$2CNO_2CH_2CH_2CO_2CH_3 \\ \| \\ NO_2Na$$

$$+ 2CH_2O \longrightarrow 2HOCH_2C(NO_2)_2CH_2CH_2CO_2CH_3$$

$$\xrightarrow[\text{HOAc}]{\text{NH}_3} [CH_3O_2CCH_2CH_2C(NO_2)_2CH_2]_2—NH \quad (\text{II})$$

When amino acids or their esters were used in the condensation with 2,2-dinitro-1-alkanols, the importance of the *p*H in determining the course of the reaction was strikingly illustrated. The condensation of 2,2-dinitropropanol and methylglycine at a *p*H of 7 gave methyl 5,5-dinitro-2-azahexanoate (III), while the condensation of 2,2-dinitropropanol and glycine at a *p*H of 9 or higher, gave bis-(2,2-dinitropropyl)-glycine (IV). The structure of IV was confirmed by analysis and by the preparation of the corresponding methyl ester and acid chloride.

When methyl 5-hydroxy-4,4-dinitropentanoate was condensed with the sodium salt of glycine the expected methyl 4,4-dinitro-6-azaoctanedioic acid (V), cyclized to form 5,5-dinitro-2-piperidone-N-acetic acid (VI). The structure of VI was confirmed by analysis and by conversion into a monomethyl ester derivative VII.

2,2-Dinitropropanol and hydrazine react under buffered *p*H conditions to form bis-N,N′-(2,2-dinitropropyl)-hydrazine (VIII).

Oxidation of VIII with bromine in methanol solution yielded azo-(2,2-dinitropropane) (IX), a remarkably stable compound melting without decomposition at 101–101.5°. The results of the study of the decomposition of IX were rather surprising, since it is known that aliphatic azo compounds are thermally unstable and decompose into free radicals with the liberation of nitrogen.[4] However, azo-(2,2-dinitropropane) was almost quantitatively recovered after two hours refluxing in either toluene or chlorobenzene. Even after refluxing for 90 minutes in *o*-dichlorobenzene, 50% of the starting material was recovered. In the latter solvent the evolution of nitrogen dioxide was observed.

The physical properties and yields of the Mannich condensation products are listed in Table I.

(4) C. G. Overberger, *et al.*, THIS JOURNAL, **77**, 4651 (1955), and preceding papers in this series.

Experimental[5,6]

3,3,7,7-Tetranitro-5-azanonane (Ib).—This preparation is typical of the condensation of 2,2-dinitro-1-alkanols and ammonium acetate. A mixture of 30.0 g. (0.18 mole) of 2,2-dinitrobutanol,[7] 50 ml. of water and 30.0 g. (0.39 mole) of ammonium acetate was warmed to 60° for 20 minutes. The reaction mixture was cooled and the product was collected and dried, giving 28.0 g. (99%) of a cream-colored solid, m.p. 57–61°. Recrystallization from isopropyl alcohol gave white plates, m.p. 66–67°.

Dimethyl 4,4,8,8-Tetranitro-6-aza-1,11-undecanedioate (II). (a) From Methyl 5-Hydroxy-4,4-dinitropentanoate.—A mixture of 30.0 g. (0.13 mole) of methyl 4,4-dinitro-5-hydroxypentanoate,[8] 75 ml. of water and 30.0 g. (0.39 mole) of ammonium acetate was heated on the steam-bath for 10 minutes, on cooling a cream-colored solid separated. The product was collected, washed with water and dried to give 25.4 g. (88.6%) of a cream-colored solid, m.p. 65–69°. Recrystallization from methanol gave white needles, m.p. 79–80°.

(b) From Aci-sodium Salt of Methyl 4,4-Dinitrobutyrate.—Five hundred ml. of concentrated ammonium hydroxide, 800 ml. of water and 500 ml. of glacial acetic acid were mixed together. The temperature was allowed to rise to 60–70°, at which point a solution of 1000 g. (equivalent to 850 g. or 3.97 moles of dry salt containing 15% moisture) of the aci-sodium salt of methyl 4,4-dinitrobutyrate,[8] 2000 ml. of water and 324 g. (4.0 moles) of 37% formalin was added over a period of 15 minutes. The reaction mixture was stirred at 60° for one hour and then cooled to 10°. The solid product was collected, washed with water and dried *in vacuo* over potassium hydroxide to give 480 g. (56.8%) of cream-colored solid, m.p. 66–69°. Recrystallization from methanol gave white needles, m.p. 79–80°.

Methyl 5,5-Dinitro-3-azahexanoate (III).—A mixture of 12.6 g. (0.1 mole) of methylglycine hydrochloride,[9] 65 ml. of water, 15 g. (0.1 mole) of 2,2-dinitropropanol[7] and 8.2 g. (0.1 mole) of sodium acetate was heated at 70–85° for one hour. The reaction mixture was cooled and extracted with methylene chloride. The extracts were dried and concentrated *in vacuo* leaving 17.1 g. (77.3%) of a yellow oil.

The amine was identified by conversion to the corresponding nitraza derivative. Methyl 5,5-dinitro-3-azahexanoate, 2.2 g. (0.01 mole), was dissolved in 20 ml. of acetic anhydride and added to 20 ml. of 99% nitric acid at 0–5°. After stirring for 10 minutes the mixture was poured onto ice. The product was collected, washed with water and dried *in vacuo* over potassium hydroxide to give 1.64 g. (61.4%) of white solid, m.p. 76–79°. Recrystallization from isopropyl ether raised the melting point to 80–81°.

Bis-(2,2-dinitropropyl)-glycine (IV).—A solution of 7.5 g. (0.1 mole) of glycine, 4.0 g. (0.1 mole) of sodium hydroxide and 50 ml. of water was mixed with 15.0 g. (0.1 mole) of 2,2-dinitropropanol. The temperature rose to 42° and the yellow solution formed was allowed to stand overnight. Upon addition of dilute sulfuric acid a viscous, colorless oil separated and solidified on standing. The product 15.6 g. (92.0%) was collected and recrystallized from methanol-water to give white crystals, m.p. 123–124°.

Methyl Bis-(2,2-dinitropropyl)-glycine.—A mixture of 20 g. (0.059 mole) of bis-(2,2-dinitropropyl)-glycine, 100 ml. of methanol and 10.0 ml. of concentrated sulfuric acid was refluxed for 90 minutes. The solution was diluted with 250 ml. of methylene chloride and washed with water, 5% sodium carbonate solution and water. The solvent was evaporated to yield 14.0 g. (67.3%) of white solid. Recrystallization from methanol–ether gave crystals, m.p. 94–95°.

(5) All melting points are uncorrected.

(6) Microanalyses by Dr. A. Elek, Elek Microanalytical Laboratory, 4763 W. Adams Blvd., Los Angeles, Calif.

(7) O.S.R.D. Report No. 2016, Nov. 15, 1943.

(8) K. Klager, *J. Org. Chem.*, **16**, 161 (1951).

(9) C. Harries and M. Weiss, *Ann.*, **327**, 365 (1903).

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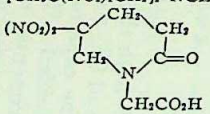
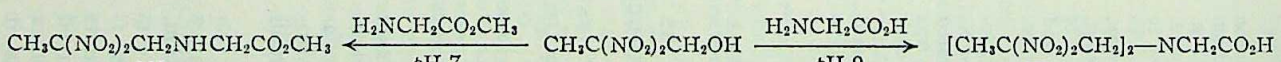
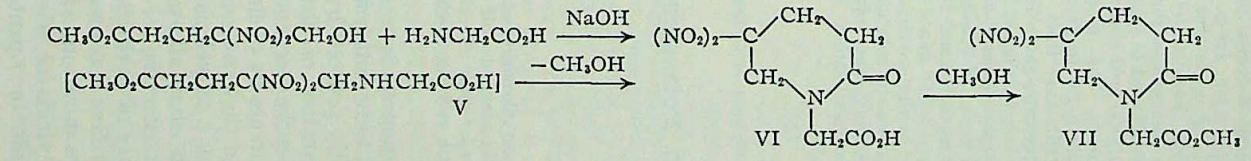
TABLE I

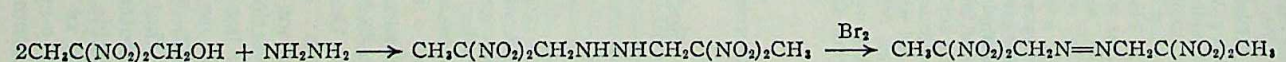
MANNICH CONDENSATION PRODUCTS

2,2-Dinitro-1-alkanol	Amine	Product	Yield, %	M.p., °C.	Recryst. solvent	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$CH_3C(NO_2)_2CH_2OH$	NH_3	$[CH_3C(NO_2)_2CH_2]_2$–NH	90.4	67–68	Isopropyl alcohol	$C_5H_{11}N_3O_5$	25.63	3.94	24.01	25.90	4.09	24.80
$CH_3CH_2C(NO_2)_2CH_2OH$	NH_3	$[CH_3CH_2C(NO_2)_2CH_2]_2$–NH	99.0	66–67	Isopropyl alcohol	$C_8H_{18}N_4O_8$	31.07	4.89	22.65	31.06	4.98	21.73
$CH_3CH_2CH_2C(NO_2)_2CH_2OH$	NH_3	$[CH_3CH_2CH_2C(NO_2)_2CH_2]_2$–NH	85.2	100–100.5	Ethanol	$C_{10}H_{19}N_4O_8$	35.61	5.68	20.77	35.78	5.58	19.75
$CH_3O_2CCH_2CH_2C(NO_2)_2CH_2OH$	NH_3	$[CH_3O_2CCH_2CH_2C(NO_2)_2CH_2]$–NH	88.6	79–80	Methanol	$C_{12}H_{19}N_5O_{12}$	33.89	4.50	16.47	33.91	4.52	16.86
$CH_3C(NO_2)_2CH_2OH$	$NH_2CH_2CO_2CH_3$	$CH_3C(NO_2)_2CH_2NHCH_2CO_2CH_3$[a]	77.3	80–81	Isopropyl alcohol	$C_6H_{12}N_4O_8$	27.07	3.79	21.05	27.20	4.09	21.43
$CH_3C(NO_2)_2CH_2OH$	$NH_2CH_2CO_2H$	$[CH_3C(NO_2)_2CH_2]_2$–NCH_2CO_2H	92.0	123–124	Methanol–water	$C_8H_{13}N_5O_{10}$	28.32	3.83	20.65	28.52	3.73	20.74
$CH_3O_2CCH_2CH_2C(NO_2)_2CH_2OH$	$NH_2CH_2CO_2H$		61.5	128–130	Ether	$C_7H_9N_3O_7$	34.01	3.67	17.00	34.37	3.92	17.62
$CH_3C(NO_2)_2CH_2OH$	NH_2NH_2	$CH_3C(NO_2)_2CH_2NHNHCH_2C(NO_2)_2CH_3$	73	85–86	Chloroform	$C_6H_{12}N_6O_8$	24.33	4.09	28.37	24.98	4.12	27.65

[a] Identified by conversion to the corresponding nitraza derivative whose melting point and analyses are given in the table.







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Anal. Calcd. for $C_9H_{16}N_3O_{10}$: C, 30.60; H, 4.24; N, 19.83; OCH_3, 8.78. Found: C, 31.17; H, 4.49; N, 20.11; OCH_3, 8.19.

Bis-(2,2-dinitropropyl)-glycyl Chloride.—A mixture of 78 g. (0.23 mole) of bis-(2,2-dinitropropyl)-glycine and 190 ml. of thionyl chloride was refluxed overnight. The solution was evaporated to dryness *in vacuo*, leaving a brown solid. Recrystallization from chloroform gave white crystals, 41.0 g. (50%), m.p. 64–65°.

Anal. Calcd. for $C_5H_{12}N_5O_9Cl$: C, 26.86; H, 3.38; N, 19.14; Cl, 9.91. Found: C, 27.48; H, 3.68; N, 19.27; Cl, 9.70.

5,5-Dinitro-2-piperidone-N-acetic Acid (VI).—A solution of 7.5 g. (0.1 mole) of glycine, 4.0 g. (0.1 mole) of sodium hydroxide and 50 ml. of water was mixed with 22.2 g. (0.1 mole) of methyl 5-hydroxy-4,4-dinitropentanoate. A yellow solution was formed and the temperature rose to 38°. The mixture was allowed to stand overnight. Acidification with dilute sulfuric acid caused an oil to separate, which soon crystallized. The product was collected, washed with water and dried to give 15.2 g. (61.5%) of white solid. Recrystallization from methanol–water and ether gave colorless crystals, m.p. 128–130°. This compound gave a negative test for the methoxyl group.

Methyl 5,5-Dinitro-2-piperidone-N-acetate (VII).—A mixture of 20.0 g. (0.081 mole) of 5,5-dinitro-2-piperidone-N-acetic acid, 150 ml. of methanol and 10 ml. of concentrated sulfuric acid was refluxed for 90 minutes. The solution was diluted with 250 ml. of methylene chloride and washed with water, 5% sodium carbonate solution and water. After drying over sodium sulfate, the solvent was evaporated leaving crystals. Recrystallization from methanol gave 16.0 g. (75.8%) of product, m.p. 126–130°. The mixed melting point with the free acid (m.p. 128–130°) was depressed to 105–111°.

Anal. Calcd. for $C_8H_{11}N_3O_7$: C, 36.79; H, 4.26; N, 16.09. Found: C, 37.51; H, 4.33; N, 16.32.

Bis-(2,2-dinitropropyl)-hydrazine (VIII).—A solution of 52.0 g. of 85% hydrazine hydrate, 300 ml. of water and 75 ml. of glacial acetic acid was heated to 60°. At this temperature a solution of 50.0 g. (0.33 mole) of 2,2-dinitropropanol in 150 ml. of methanol was added within 15 minutes. A viscous oil immediately separated. The mixture was stirred at 60° for one hour. After cooling the oily layer crystallized to give 36 g. (73.0%) of white solid, m.p. 83–85°. Recrystallization from ether or chloroform gave colorless prisms, m.p. 85–86°.

Azo-(2,2-dinitropropane) (IX).—A solution of 5.0 g. (0.017 mole) of bis-(2,2-dinitropropyl)-hydrazine in 50 ml. of methanol was cooled to 0° and bromine was added with vigorous stirring until the bromine was no longer bleached. The temperature was kept below 5° by means of external cooling. After a short time crystals precipitated, which were collected and washed with absolute ether. Recrystallization from methanol gave 2.3 g. (46.3%) of colorless crystals, m.p. 101–101.5°.

Anal. Calcd. for $C_6H_{10}N_6O_8$: C, 24.49; H, 3.43; N, 28.57. Found: C, 24.85; H, 3.49; N, 28.80.

Acknowledgment.—We are indebted to the Office of Naval Research for the financial support of this work.

AZUSA, CALIFORNIA

[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Sodium and Potassium Alkoxides as Catalysts for Carbanion Reactions of Hydrocarbons[1]

BY HERMAN PINES AND LUKE SCHAAP[2]

RECEIVED DECEMBER 3, 1956

Sodium and potassium alkoxides, when heated to decomposition temperatures, catalyze carbanion reactions such as the dehydrogenation of *d*-limonene, double bond isomerization of olefins, and the side chain alkylation of alkylarenes. Alkoxides of tertiary alcohols are far more effective than those of primary or secondary alcohols. A mechanism for the alkoxide decomposition is proposed, and some similar reactions are discussed.

Organosodium compounds and sodium hydride have been reported to be catalysts for certain reactions that apparently proceed by carbanion mechanism: (a) isomerization of olefins, (b) dehydrogenation of monocyclic terpenes, (c) side chain alkylation of alkylarenes by olefins.[3]

It has been found that potassium *t*-butoxide can promote reactions a, b as well as c at temperatures of 250–300°, which cause alkoxide decomposition, but that it is most effective for b. Reaction c is promoted by a trace of hydroxide ion with the *t*-alkoxide. An autoclave was used, the experiments being of 4–12 hours duration. Limonene changed into *p*-cymene in yields of 95–97% using either potassium *t*-butoxide or *t*-pentoxide, whereas it dropped to 3–4% with the isopropoxide, 1.5% with the methoxide, and 0% with the phenoxide or with no alkoxide. The experimental data obtained are summarized in Table I. The solid residue from the *t*-butoxide experiments, on acidification, yielded some 3,5-dimethylphenol and isovaleric acid.

Potassium *t*-butoxide caused 8% isomerization of 1-*p*-menthene on heating for 5.5 hours at 260–265°. The same catalyst, containing a trace of potassium hydroxide, was effective for the formation of *n*-propylbenzene from ethylene and toluene at 279–291°, or *t*-pentylbenzene (containing a trace of 1,1-dimethylindan) from cumene and ethylene. The experimental conditions and yields are summarized in Table II.

Methane was found in the reactions catalyzed by potassium *t*-butoxide while small amounts of ethane as well as methane were obtained from the experiments carried out with potassium *t*-pentoxide. The presence of methane is due to the decomposition of the alkoxide at 280° as shown in Experiment 8. No methane was produced however when powdered potassium hydroxide in *t*-butyl alcohol was heated to the same temperature (ex-

(1) Paper IX of the series of Base Catalyzed Reactions. For paper VIII see H. Pines and M. Kolobielski, THIS JOURNAL, **79**, 1698 (1957).

(2) Predoctoral Fellow: Universal Oil Products Company, 1954–1955, Standard Oil Company (Indiana) 1955–1956.

(3) (a) H. Pines, J. A. Vesely and V. N. Ipatieff, THIS JOURNAL, **77**, 347 (1955); (b) **77**, 554 (1955); (c) H. Pines and H. E. Eschinazi, *ibid.*, **77**, 6314 (1955); (d) **78**, 1178 (1956); (e) H. Pines and V. Mark, *ibid.*, **78**, 4316 (1956); (f) H. Hart, *ibid.*, **78**, 2619 (1956); (g) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **20**, 839 (1955); (h) **21**, 93 (1956).

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TABLE I

REACTIONS OF LIMONENE[a]

Expt.	Alkoxide	Conditions: Temp., °C.	Hr.	Pressure at max. temp. atm.	Recovered C_{10} Fraction: Wt. %	$\alpha^{25}D$	*p*-Cymene, %	Gases[b]: Kind	Mole %
1	*i*-PrOK	291	8.6	51	85	74	4.3	H_2	0.16
								CH_4	.062
2	*i*-PrONa	290 ± 3	6	28	77	86	3.0	H_2	.072
								CH_4	.054
3	*t*-PeOK	251	9	113	99[c]	0	97	H_2	.47
								CH_4	.06
								C_2H_6	.003
4	MeONa	300 ± 2	9	10	74	91	1.5	H_2	.03
								CH_4	.001
5	PhOK	285 ± 5	7	9	95	100	0	None	
6	None	281 ± 4	7.5	7	85[d]	97	0	None	
7	*t*-BuOK	257 ± 5	8.5	122	98	0	95[e]	H_2	.38
								CH_4	.24

[a] 68.1 g. (0.5 mole) of *d*-limonene, $\alpha^{25}D$ +100, was used in each experiment with an alkoxide prepared from 0.10 g. atom of sodium or potassium. [b] Small amounts of ethylene ranging from 0.001 to 0.002 mole were obtained from reactions with catalysts prepared from isopropyl, *t*-butyl and *t*-pentyl alcohols. [c] 0.50 g. of *t*-pentyl alcohol was recovered when the solid material from this reaction was treated with water. [d] About 15% of the liquid product consisted of limonene polymers boiling above 150° at 2 mm. [e] A similar experiment carried out at 290° for 4.3 hr. yielded 75% *p*-cymene.

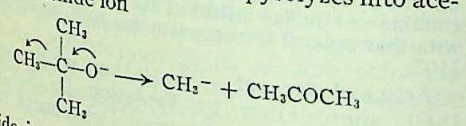
TABLE II

REACTION OF AROMATIC HYDROCARBONS WITH OLEFINS IN THE PRESENCE OF POTASSIUM *t*-BUTOXIDE

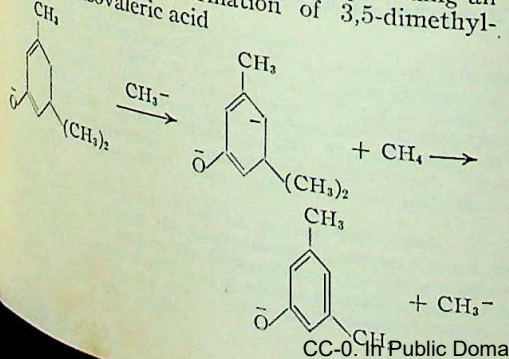
Expt.	Hydrocarbons charged: Aromatic[a]	Olefin (moles)		Catalyst[b]	Temp., °C.[c]	Product formed (moles)	Methane[d] (moles)
10	Toluene	C_3H_6	0.35	*t*-BuOK	279	0.0054[e]	...
11	Toluene	C_2H_4	.2	*t*-BuOK[f]	291	.026[g]	0.163
12	Benzene	C_2H_4	.2	*t*-BuOK	284 ± 4	.0031[h]	.160
						.0001[i]	
13	Isopropylbenzene	C_2H_4	.2	*t*-BuOK	285 ± 3	.132[j]	.162

[a] One mole of aromatic hydrocarbon was used in each experiment. [b] The catalyst, *t*-BuOK, was prepared using *t*-BuOH with 0.4 g (0.022 mole) of water added and 4 g. (0.1 g. atom) potassium. [c] The reaction was carried out for 4–5 hours at the given temperature. [d] Hydrogen was produced in amounts varying from 0.002 to 0.004 mole. [e] The product was isobutylbenzene. The low yield can in part be ascribed to stoppage of the stirrer during the reaction. [f] A similar reaction carried out with potassium *t*-butoxide prepared from anhydrous *t*-butyl alcohol produced insufficient *n*-propylbenzene to purify by distilling on a 12 in. column. [g] The product was *n*-propylbenzene. [h] Biphenyl: m.p. 68–70°, λ_{max} 246 mμ, ϵ_{mol} 16,500. [i] *p*-Terphenyl, m.p. 205–211°, λ_{max} 276 mμ, ϵ_{mol} 30,000. [j] The product was composed of *t*-pentylbenzene containing a very small amount of 1,1-dimethylindan. In check reactions carried out under apparently similar conditions the yields were smaller.

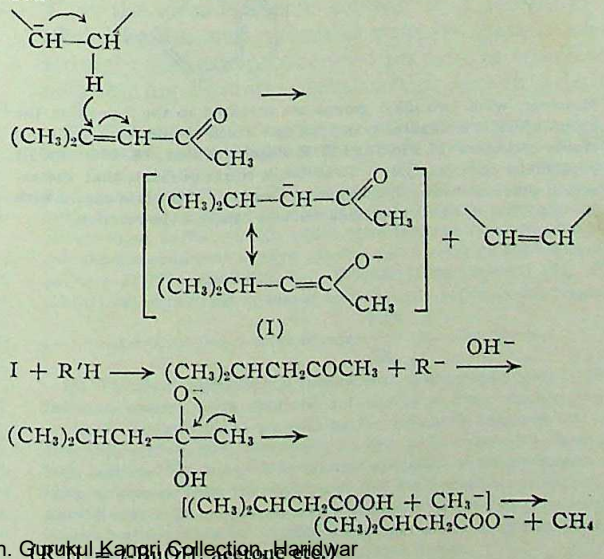
periment 9). To explain these observations it is assumed that the *t*-butoxide ion pyrolyzes into acetone and methide ion



Methide ion then promotes the dehydrogenation, side-chain alkylation, and isomerization effects which were noted. It (or *t*-butoxide) promotes aldolization in part of the acetone forming mesityl oxide, isophorone and water, thereby providing an explanation for the formation of 3,5-dimethylphenol and isovaleric acid



This explains the phenol. To explain the acid, it is assumed that mesityl oxide is changed to 4-methyl-2-pentanone by hydride transfer, after which this ketone is cleaved by the hot hydroxide ion



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It will be recalled that acetone is cleaved[4] into acetate ion by fused alkali at 250°. A similar type of decomposition takes place in the Guerbet reaction and when alcohols are heated with alkali.[5]

Alkoxide decomposition is not suitable for studying relative carbanion stabilities because subsequent condensation and elimination reactions make it impossible to study the primary elimination products, but it is evident from the gases recovered from potassium *t*-pentoxide reaction that the ethyl carbanion is eliminated much less readily than a methyl carbanion. Very little ethane was produced from potassium *t*-pentoxide at 250°.[6]

Experimental

Preparation of Alkoxides.—The *t*-pentyl, *t*-butyl, isopropyl and methyl alkoxides were prepared by refluxing 0.1 g. atom of sodium or potassium with 200 ml. of the corresponding anhydrous alcohol in a 500-ml. flask equipped with a reflux condenser and a drying tube. Water, 0.4 g. (0.022 mole) was added to the *t*-butyl alcohol used in making catalysts for the side-chain alkylation of alkylarenes. When a clear solution of the alkoxide was obtained, the excess of the alcohol was distilled off and the remaining alcohol was removed at 100° and at about 10 mm. of pressure. The white solid was then pulverized and introduced into the reaction vessel containing a weighed quantity of the liquid hydrocarbon. The alkoxides thus produced were not completely free of alcohol; no quantitative estimation of the alcohol content was made however.

The potassium phenoxide was prepared from phenol and potassium hydroxide.

Apparatus and Procedure.—A 250-ml. capacity Magne-Dash[7] autoclave was used for all the experiments. The liquid hydrocarbon and the alkoxide were placed in the autoclave. After sealing it the air was displaced from it by means of nitrogen. When required measured amounts of ethylene or propylene were introduced into the autoclave.

The reaction was judged to be finished when the pressure remained constant. The gases were then released, measured and analyzed by a mass spectrometer. The liquid product was filtered and distilled.

Experiments 1–7.—The *d*-limonene used was purified according to the method reported previously.[3c] It had the following physical constants: b.p. 71° at 20 mm.; $n^{25}D$ 1.4724, $\alpha^{25}D$ +100. The C_{10} fraction of the liquid product from each reaction was obtained by distillation at 20 mm. pressure using a 10 in. Vigreux column. Infrared spectra were used to show the presence of *p*-cymene and, in some cases, *p*-menthadienes. The percentage of *p*-cymene was determined using ultraviolet spectra in 95% ethanol according to the method reported previously.[3c]

Experiment 8.—*t*-Butyl alcohol, 37 g. (0.5 mole) with 1 g. (0.025 g. atm.) of potassium dissolved in it, when heated at 280° for 3.3 hr. yielded 0.087 mole of methane and 0.001 mole of hydrogen.

Experiment 9.—*t*-Butyl alcohol, 37 g. (0.5 mole) with 5.6 g. (0.1 mole) of powdered potassium hydroxide was heated at 292° for 1 hr. but yielded no gas.

Experiment 14.—1-*p*-Menthene had the following physical constants: $\alpha^{25}D$ +93.5, $n^{20}D$ 1.4560. This hydrocarbon, 34.5 g. (0.25 mole), was heated at 260–265° for 5.5 hr. with potassium *t*-butoxide prepared from 2 g. (0.05 g. atom) of potassium. The gaseous product consisted of 0.160 mole of methane and 0.003 mole of hydrogen. The C_{10} fraction obtained, $\alpha^{28}D$ +35, $n^{20}D$ 1.4560, was composed of 92% 1-*p*-menthene 1.5% 2-*p*-menthene, 2.0% 3-*p*-menthene and 4.5% 8-(9)-*p*-menthene. The analytical procedure was the same as reported previously.[3d]

Alkoxide Decomposition Products.—The white solid recovered from a potassium *t*-butoxide reaction with limonene was neutralized with 10% hydrochloric acid and acidic and phenolic fractions were extracted. A 3,5-dinitrobenzoate was prepared from the phenolic fraction according to the method of Keenan and Phillips.[8] Only 13.7 mg. of a cream-colored solid was obtained which when recrystallized twice from 95% ethanol melted at 192–194°. Mixed melting point with an authentic sample of the 3,5-dinitrobenzoate of 3,5-dimethylphenol was 192–194°; literature[8] 195.4°.

The acid fraction obtained gave an anilide which melted at 108°. A synthetic sample prepared from isovaleryl chloride and aniline melted at 107°. Mixed melting point with that isolated from reaction was 107°; literature[9] 109–110°.

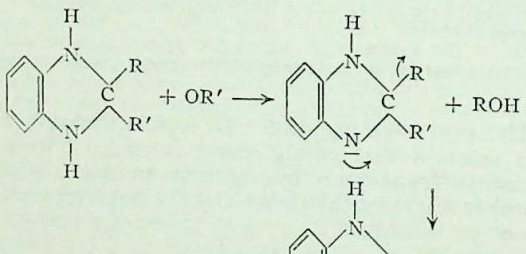
Acknowledgment.—The authors wish to express their appreciation to Professor D. F. Mason of the Chemical Engineering Department for the mass spectral analysis.

EVANSTON, ILLINOIS

(4) H. S. Fry and E. L. Schulze, THIS JOURNAL, **48**, 956 (1926).

(5) M. Guerbet, *Compt. rend.*, **128**, 511 (1899); **149**, 129 (1909); **151**, 222, 713 (1912); H. S. Fry and E. Ott, THIS JOURNAL, **50**, 1122 (1928); Ch. Weizmann, E. Bergmann and L. Haskelberg, *Chemistry & Industry*, **56**, 589 (1937).

(6) A mechanism similar to the elimination of carbanion by alkoxides has been proposed by Elderfield and co-workers for the elimination of alkyl groups from 2,3-dialkylbenzimidazolenes [R. C. Elderfield, *et al.*, THIS JOURNAL, (a) **70**, 44 (1948); (b) **73**, 975 (1951); (c) **76**, 1883 (1954)]. Alkoxides have been reported to catalyze the reaction for which the presumed mechanism is



However, when two alkyl groups are attached to the 2-position the group which is eliminated is not the one which should form the more stable carbanion (H. Pines and H. E. Eschinazi, *ibid.*, **78**, 5950 (1956)) even under base catalysis. Therefore it seems probable that the reaction proceeds by a radical type mechanism. This is in accord with the fact that di-*t*-butyl peroxide will also catalyze the reaction.[6c]

(7) Autoclave Engineers, Inc., Erie, Pa.

(8) G. L. Keenan and M. Phillips, THIS JOURNAL, **53**, 1924 (1931).

(9) E. K. Harvill, R. M. Herbst, E. C. Schreiner and C. W. Roberts, *J. Org. Chem.*, **15**, 662 (1950).

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June 5, 1957

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH & DEVELOPMENT, U. S. NAVAL POWDER FACTORY]

The Reaction of *dl*- and *meso*-2,3-Dibromobutane with Silver Nitrate in Acetonitrile. Failure of the Nitrate Ester Grouping to Exhibit the Neighboring Group Effect[1]

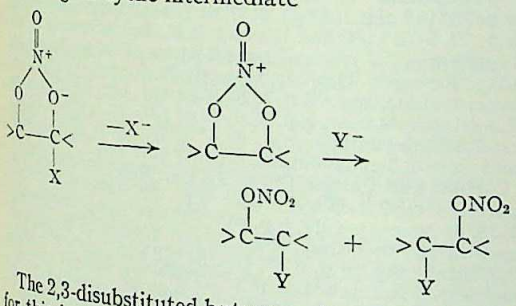
BY LEON FISHBEIN[2]

RECEIVED AUGUST 6, 1956

The reaction of *dl*-2,3-dibromobutane with silver nitrate in acetonitrile gives the mononitrate ester (of *threo*-2-bromo-3-butanol), and this in a somewhat slower reaction is then converted to the dinitrate of *meso*-2,3-butanediol. In other words, the first step occurs with retention of configuration, the second step with inversion. Precisely the same stereochemical results are obtained when *meso*-2,3-dibromobutane is treated with silver nitrate in acetonitrile; retention in the first step, inversion in the second. It is thus clear that while neighboring bromine participates, the neighboring nitrate ester group does not exhibit the neighboring group effect.

Winstein, Lucas and their co-workers have established the fact that an over-all retention of configuration results when an atom or a group of atoms participates in the displacement of a second functional group on an adjacent carbon atom.[3] The neighboring group reaction has been demonstrated for a large number of atoms or groups of atoms and include the following: $-I$, $-Br$, $-Cl$, $-CO_2^-$, $-OCOCH_3$, $-OCH_3$, $-OH$, O^-, $-NH_2$, $-NR_2$, $-SR$, benzamido and aryl.

This paper concerns itself with a study, by stereochemical means, of the effectiveness of a β-nitrate ester group as a neighboring group in the reaction of alkyl bromides with silver nitrate. The nitrate ester group, in a formal way, closely resembles an acetoxy group and this suggested the possibility of an analogous cyclic intermediate



The 2,3-disubstituted butane system was selected for this investigation because of the known configurational relationships of the *dl*- and *meso*-dibromides,[4] diols,[5] *cis*- and *trans*-epoxides[3a] and *erythro*- and *threo*-bromohydrins.[3c]

Discussion

The reaction of *meso*-2,3-dibromobutane with silver nitrate in acetonitrile for 24 hr. at room temperature yielded as the only product a bromonitroxybutane[6] which was identical with that obtained by the direct nitration of *erythro*-2-bromo-3-butanol (see Chart 1) as shown by their refractive indices and infrared spectra.

When either *meso*-2,3-dibromobutane or *erythro*-2-bromo-3-nitroxybutane was treated with silver nitrate in acetonitrile for *ca.* 45 days, there was formed a dinitrate ester of 2,3-butanediol which was identical with that obtained by the direct nitration of *dl*-2,3-butanediol (see Chart II)[7] as shown by their refractive indices and infrared spectra.

Complete duplication of results was obtained employing *dl*-2,3-dibromobutane. Thus, the reaction with silver nitrate for *ca.* 24 hr. yielded *threo*-2-bromo-3-nitroxybutane. Upon treating the *dl*-dibromide or the *threo*-bromonitrate with silver nitrate for *ca.* 45 days, there was obtained the dinitrate ester of *meso*-2,3-butanediol.

The demonstration that either *dl*- or *meso*-2,3-dibromobutane could be recovered unchanged from a mixture consisting of dibromide, silver bromide and acetonitrile dismisses the possibility that these dibromides undergo isomerization prior to the reaction which produces bromonitroxybutane. Similarly, no isomerization could be demonstrated to occur for the diastereomeric-2-bromo-3-nitroxybutanes.

These facts can be rationalized in the following manner: The first step in the reaction of *dl*-2,3-dibromobutane with silver nitrate consists in the formation of *threo*-2-bromo-3-nitroxybutane by a neighboring group participation of a bromine atom. That the *threo* isomer is formed with retention of configuration and unmixed with its diastereomer[8] strongly suggests a concerted process, in which the neighboring bromine atom participates in a back-

(1) Publication approved by the Bureau of Ordnance, Navy Department.

(2) Charles Bruning Co., Inc., Teterboro, N. J.

(3) (a) S. Winstein and H. J. Lucas, THIS JOURNAL, **61**, 1576, 2845 (1939); (b) H. J. Lucas and C. W. Gould, Jr., *ibid.*, **63**, 2541 (1941); (c) S. Winstein and R. E. Buckles, *ibid.*, **64**, 2780, 2787 (1942); (d) S. Winstein, H. V. Hess and R. E. Buckles, *ibid.*, **64**, 2796 (1942); (e) S. Winstein and R. B. Henderson, *ibid.*, **65**, 2196 (1943); (f) S. Winstein, C. Hanson and E. Grunwald, *ibid.*, **70**, 812 (1948).

(4) R. T. Dillon, W. G. Young and H. J. Lucas, *ibid.*, **52**, 1953 (1930).

(5) H. J. Lucas and C. E. Wilson, *ibid.*, **58**, 2396 (1936).

(6) The reaction of the diastereomeric 2,3-dibromobutanes with silver nitrate to prepare the bromonitroxybutanes is a rapid one (*ca.* 24 hr.) compared with that in which a dinitrate is obtained (*ca.* 45 days). This enables one to isolate the bromonitroxybutane uncontaminated with dinitrate.

(7) That nitration occurs with a retention of configuration and no loss in optical purity was demonstrated by A. F. McKay, R. H. Meen and G. F. Wright [THIS JOURNAL, **70**, 430 (1948)]. Levorotatory 2,3-butanediol, $[\alpha]^{20}D$ $-12.89°$ was nitrated with a mixture of fuming nitric acid and concentrated sulfuric acid to yield the levorotatory dinitrate ester, $[\alpha]^{20}D$ $-0.88°$, which upon hydrogenolysis employing a palladium-on-charcoal catalyst produced levorotatory 2,3-butanediol, $[\alpha]^{20}D$ $-12.90°$. Similarly, S. J. Cristol, [THIS JOURNAL, **77**, 2512 (1955)] has shown that no loss in optical purity occurs in the sequence

$$(-)\text{-2-octanol} \rightarrow (-)\text{-2-octyl nitrate} \xrightarrow[H_2]{PtO_2} (-)\text{-2-octanol.}$$

(8) The *threo* compound is formed with a stereospecificity > 95%. Infrared spectra were obtained for the pure *threo*- and *erythro*-2-bromo-3-nitroxybutanes as well as for synthetic mixtures of 95% *threo*–5% *erythro*, 90% *threo*–10% *erythro*, 95% *erythro*–5% *threo* and 90% *erythro*–10% *threo*. The infrared spectrum of the bromonitroxybutane, isolated from the reaction of *dl*-2,3-dibromobutane with silver nitrate over a 24-hr. period, was identical with that of pure *threo*-2-bromo-3-nitroxybutane. A similar high stereospecificity was observed for the reaction which produced the *erythro* isomer.

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CHART I.—PREPARATION OF THE DIASTEREOMERIC 2-BROMO-3-NITROXYBUTANES

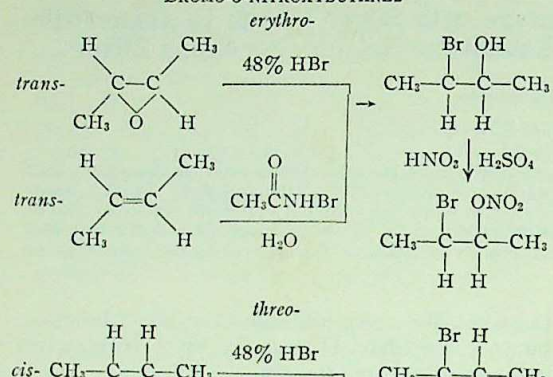
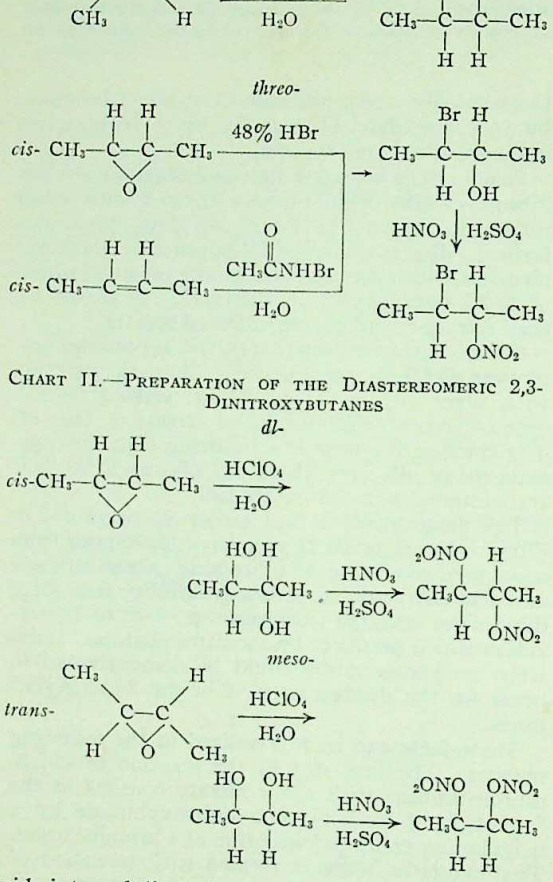
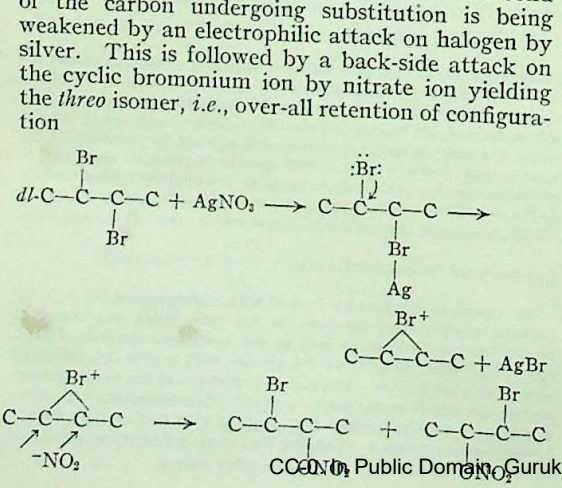


CHART II.—PREPARATION OF THE DIASTEREOMERIC 2,3-DINITROXYBUTANES



side internal displacing action while the C–Br bond of the carbon undergoing substitution is being weakened by an electrophilic attack on halogen by silver. This is followed by a back-side attack on the cyclic bromonium ion by nitrate ion yielding the *threo* isomer, *i.e.*, over-all retention of configuration



In the next step of the reaction sequence, the *threo*-2-bromo-3-nitroxybutane reacts with silver nitrate to yield the dinitrate ester of *meso*-2,3-butanediol, that is with inversion of configuration. Also noteworthy is the fact that the reaction occurs with complete stereospecificity: the *meso*-dinitrate contains less than 5% of the racemic stereoisomer.[9]

Kornblum, Smiley, Blackwood and Iffland[10] have as a result of a careful examination of the reaction of silver nitrite with 2-octyl halides provided a demonstration that this reaction proceeds *via* a transition state possessing both SN1 and SN2 character. The results of the present investigation are fully consonant with their pull–push mechanism.

Of special interest is the observation that the *threo*-bromonitrate reacts with silver nitrate with clean inversion for it serves to emphasize, once again, the importance of the push exerted by the anion in the reactions of silver salts with strictly aliphatic halides.[9]

The reaction of the 2-bromo-3-nitroxybutanes with silver nitrate is exceedingly slow being *ca.* 90% complete after 45 days.[11] It is to be expected that in this reaction, as well as those involving α-halocarbonyl compounds, α-haloesters and 1,2-dichloride,[12] the SN1 contribution to the transition state is minimized because of adjacent charge considerations.

Experimental

Preparation of Intermediates.—*dl*-2,3-Dibromobutane, b.p. 73° (47 mm.), n^{20}D 1.5147, and *meso*-2,3-dibromobutane, b.p. 71.5–72° (50 mm.), n^{20}D 1.5116, were prepared by the bromination of *cis*- and *trans*-2-butene (Phillips Petroleum Co., Research Grade), respectively [reported[4] *dl*-2,3-dibromobutane, b.p. 75.6–75.8° (50 mm.), n^{20}D 1.5147; *meso*-2,3-dibromobutane, b.p. 72.7–72.9° (50 mm.), n^{20}D 1.5116]. *cis*-2,3-Epoxybutane, b.p. 60.5° (747 mm.), n^{20}D 1.3826, and *trans*-2,3-epoxybutane, b.p. 55° (747 mm.), n^{20}D 1.3736 (Carbide and Carbon Chemicals Co., Research Grade) [reported[3a] *cis*-2,3-epoxybutane, b.p. 60° (742 mm.), n^{20}D 1.3828; *trans*-epoxide, b.p. 54° (742 mm.) n^{20}D 1.3736] were used in the procedure of Lucas and Wilson[5] to prepare *dl*-2,3-butanediol, m.p. 6.5°, b.p. 54° (2 mm.), $n^{19.4}$D 1.4320, and *meso*-2,3-butanediol, m.p. 33–34°, b.p. 60–61° (2 mm.) [reported[5] *dl*-2,3-butanediol, m.p. 7.6°, b.p. 86° (16 mm.); *meso*-diol, m.p. 34.4°, b.p. 89° (16 mm.)]. *threo*-2-Bromo-3-butanol, b.p. 49–50° (13 mm.), n^{25}D 1.4752, and *erythro*-2-bromo-3-butanol, b.p. 53–54° (13 mm.), n^{25}D 1.4763, prepared by the reaction of *cis*- and *trans*-2,3-epoxybutane, respectively, with 48% HBr[3a] were identical with the bromohydrins obtained from the reaction of the isomeric 2-butenes with N-bromoacetamide,[3c] as shown by their boiling

(9) N. Kornblum, L. Fishbein and R. A. Smiley [THIS JOURNAL, 77, 6261 (1955)] have shown that the reaction of optically active 2-octyl halides with silver nitrite (in diethyl ether) occurs with clean inversion. Also relevant is a recent report by N. Kornblum and D. Hardies [Abstracts of the 130th National Meeting of the American Chemical Society, Atlantic City, N. J., September 16–21, 1956, page 2-O] that in acetonitrile 2-octyl halides react with silver nitrite (and with silver nitrate) with inversion.

(10) N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, *ibid.*, **77**, 6269 (1955).

(11) It is interesting to note that 2-bromobutane reacts quantitatively with silver nitrate in acetonitrile within 5 minutes, 1-bromobutane in 20 hr. and 1,4-dibromobutane in 20 hr. (*cf.* Experimental).

(12) The extreme inertness of vicinal dichlorides is illustrated by experiments involving *dl*- and *meso*-2,3-dichlorobutane. When these dichlorides were treated with silver nitrate in acetonitrile under the identical conditions as described for the diastereomeric dibromides, the *meso*-dichloride was *ca.* 1% reacted in 5 months, the *dl*-isomer was completely unreacted in the same period. This is to be contrasted with the following reactivities: 1-chlorobutane, 55% reacted in 12 days; 2-chlorobutane, 86% in 10 days; 1,4-dichlorobutane, 80% in 33 days (*cf.* Experimental).

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points, refractive indices and infrared spectra [reported[3a] *threo*-2-bromo-3-butanol, b.p. 50.5° (13 mm.), n^{25}D 1.4756; *erythro* isomer, b.p. 53.1° (13 mm.), n^{25}D 1.4767].

threo-2-Bromo-3-nitroxybutane.—To a nitrating mixture consisting of 4 ml. (0.09 mole) of fuming nitric acid and 3.2 ml. (0.06 mole) of concentrated sulfuric acid at −20° was added dropwise over a 45-minute period, 9.18 g. (0.06 mole) of *threo*-2-bromo-3-butanol (prepared by the reaction of *cis*-2,3-epoxybutane with 48% HBr). After the addition was complete, the reaction mixture was kept at −15° for 10-minutes, then at 0° for 45 minutes, after which it was poured onto *ca.* 50 g. of crushed ice. The oily phase which separated was taken up in methylene chloride. The methylene chloride extract was successively washed with ice-water, aqueous 5% sodium bicarbonate solution, water, then dried over anhydrous magnesium sulfate. The methylene chloride extract was concentrated by removing the solvent *in vacuo* at room temperature. The residue was then distilled *in vacuo* yielding 10.2 g. (86% yield) of product having b.p. 58° (8 mm.), n^{20}D 1.4685.

Anal. Calcd. for $C_4H_8BrNO_3$: C, 24.24; H, 4.04; N, 7.07. Found: C, 24.45; H, 4.05; N, 7.32.

In a similar manner the nitration of the *threo*-bromohydrin (prepared from *cis*-2-butene and N-bromoacetamide) gave a 73% yield of product having b.p. 60.5–61.5° (8–9 mm.), n^{20}D 1.4686.

Anal. Calcd. for $C_4H_8BrNO_3$: C, 24.24; H, 4.04; N, 7.07. Found: C, 24.51; H, 4.21; N, 6.80.

The infrared spectrum of *threo*-2-bromo-3-nitroxybutane displayed absorption bands at 1065 and 1135 cm.$^{-1}$ which were absent in that of the *erythro* isomer.

erythro-2-Bromo-3-nitroxybutane.—When *erythro*-2-bromo-3-butanol (prepared by the reaction of *trans*-2,3-epoxybutane with 48% HBr) was nitrated in the same manner as that outlined for the *threo* isomer, there was obtained an 81% yield of product having b.p. 54° (6–7 mm.), n^{20}D 1.4695.

Anal. Calcd. for $C_4H_8BrNO_3$: C, 24.24; H, 4.04; N, 7.07. Found: C, 24.52; H, 4.26; N, 7.27.

The nitration of the *erythro*-bromohydrin (prepared from *trans*-2-butene and N-bromoacetamide) gave a 63% yield of product having b.p. 58° (8–9 mm.), n^{20}D 1.4694.

Anal. Calcd. for $C_4H_8BrNO_3$: C, 24.24; H, 4.04; N, 7.07. Found: C, 24.25; H, 4.17; N, 6.83.

The infrared spectrum of *erythro*-2-bromo-3-nitroxybutane exhibited bands at 1055, 1098 and 1155 cm.$^{-1}$ which were absent in that of the *threo* isomer.

dl-2,3-Dinitroxybutane.—To a nitrating mixture consisting of 17 ml. (0.4 mole) of fuming nitric acid and 16.3 ml. (0.3 mole) of concentrated sulfuric acid at −10° was added portionwise over a 30-minute period, 8.7 g. (0.097 mole) of *dl*-2,3-butanediol. After the addition was complete, the reaction mixture was kept at 0° for 2 hr., then poured onto *ca.* 100 g. of crushed ice. The oily phase which separated was taken up in methylene chloride and successively washed with ice-water, aqueous 5% sodium bicarbonate solution, water, then dried over anhydrous magnesium sulfate. The methylene chloride extract was concentrated by removing the solvent *in vacuo* at room temperature. The residue was then distilled *in vacuo* yielding 13 g. (75%) of colorless product having b.p. 71° (3 mm.), n^{20}D 1.4412.

Anal. Calcd. for $C_4H_8N_2O_6$: C, 26.67; H, 4.44; N, 15.56. Found: C, 26.68; H, 4.32; N, 15.55.

The infrared spectrum of this material exhibited bands at 1015, 1025 and 1145 cm.$^{-1}$ which were absent in the *meso* isomer.

meso-2,3-Dinitroxybutane.—The nitration of *meso*-2,3-butanediol by the procedure as outlined for the *dl*-isomer, yielded 75% of product having b.p. 65–66° (2 mm.), n^{20}D 1.4414.

Anal. Calcd. for $C_4H_8N_2O_6$: C, 26.67; H, 4.44; N, 15.56. Found: C, 26.94; H, 4.21; N, 15.56.

The infrared spectrum of this material displayed absorption bands at 1000, 1100 and 1175 cm.$^{-1}$ which were absent in the racemic isomer.

Reaction of *dl*-2,3-Dibromobutane with Silver Nitrate in Acetonitrile. Isolation of *threo*-2-Bromo-3-nitroxybutane.—To a solution of 10.8 g. (0.05 mole) of *dl*-2,3-dibromobutane in 25 ml. of acetonitrile at 25° was added in one portion a solution of 25.5 g. (0.15 mole) of silver nitrate in 40 ml. of acetonitrile. The reaction mixture was kept at room temperature in the absence of light for 24 hr., then filtered, producing a 96% yield of silver bromide as a by-product. This residue was washed with fresh portions of acetonitrile. The filtrate and washings were combined and poured into 100 ml. of distilled water. The oily phase which separated was taken up in methylene chloride. The aqueous solution was further extracted with two 20-ml. portions of methylene chloride. The methylene chloride extracts were combined, washed twice with 25-ml. portions of water, dried over anhydrous sodium sulfate and concentrated by removing the solvent *in vacuo* at room temperature. The residue was then distilled *in vacuo* yielding 7.3 g. (72%) of colorless product having b.p. 58° (8 mm.), n^{20}D 1.4680, and possessing an infrared spectrum identical with that of *threo*-2-bromo-3-nitroxybutane prepared by the nitration of *threo*-2-bromo-3-butanol.

Anal. Calcd. for $C_4H_8BrNO_3$: C, 24.24; H, 4.04; N, 7.07. Found: C, 24.52; H, 3.89; N, 6.92.

The Reaction of *meso*-2,3-Dibromobutane with Silver Nitrate in Acetonitrile. Isolation of *erythro*-2-Bromo-3-nitroxybutane.—This reaction was carried out in the same manner as that described for the *dl*-isomer. There was obtained a 73% yield of product having b.p. 58° (8–9 mm.), n^{20}D 1.4698, and possessing an infrared spectrum identical with that of *erythro*-2-bromo-3-nitroxybutane prepared by the nitration of *erythro*-2-bromo-3-butanol.

Anal. Calcd. for $C_4H_8BrNO_3$: C, 24.24; H, 4.04; N, 7.07. Found: C, 24.50; H, 4.08; N, 7.07.

The Reaction of *dl*-2,3-Dibromobutane with Silver Nitrate in Acetonitrile. Isolation of *meso*-2,3-Dinitroxybutane.—To a solution of 26 g. (0.120 mole) of *dl*-2,3-dibromobutane in 20 ml. of acetonitrile at 25° was added in one portion a solution of 60 g. (0.353 mole) of silver nitrate in 60 ml. of acetonitrile. The reaction mixture was kept at room temperature in the absence of light for 45 days then filtered, producing a 92% yield of silver bromide as a by-product. This residue was washed with small portions of acetonitrile. The filtrate and washings were combined and poured into 150 ml. of distilled water. The oily phase which separated was taken up in methylene chloride. The aqueous phase was washed with fresh portions of methylene chloride. The methylene chloride extracts were combined, washed twice with 25-ml. portions of water, dried over anhydrous sodium sulfate and concentrated by removing the solvent *in vacuo* at room temperature. The residue was then distilled *in vacuo* yielding 16.7 g. (80%) of colorless product having b.p. 55–56° (1 mm.), n^{20}D 1.4414, and identical with the dinitrate ester of *meso*-2,3-butanediol (prepared by the nitration of *meso*-2,3-butanediol) as shown by their infrared spectra.

Anal. Calcd. for $C_4H_8N_2O_6$: C, 26.67; H, 4.44; N, 15.56. Found: C, 26.67; H, 4.56; N, 15.62.

The Reaction of *meso*-2,3-Dibromobutane with Silver Nitrate in Acetonitrile. Isolation of *dl*-2,3-Dinitroxybutane. This reaction was carried out in the same manner as that outlined for the *dl*-isomer. There was obtained a 75% yield of product having b.p. 60° (2 mm.), n^{20}D 1.4412. The infrared spectrum of this material was identical with that of the dinitrate ester of *dl*-2,3-butanediol (prepared by the nitration of *dl*-2,3-butanediol).

Anal. Calcd. for $C_4H_8N_2O_6$: C, 26.67; H, 4.44; N, 15.56. Found: C, 26.77; H, 4.51; N, 15.56.

The Reaction of *threo*-2-Bromo-3-nitroxybutane with Silver Nitrate in Acetonitrile.—To a solution of 6.58 g. (0.0346 mole) of *threo*-2-bromo-3-nitroxybutane (prepared by the nitration of the *threo*-bromohydrin) in 5 ml. of dry acetonitrile, was added in one portion a solution of 7.36 g. (0.0433 mole) of silver nitrate in 10 ml. of acetonitrile. The reaction mixture was kept at room temperature in the absence of light for 40 days, then filtered, producing a 90% yield of silver bromide as a by-product. This residue was washed with fresh portions of acetonitrile. The filtrate and washings were combined and poured into 30 ml. of distilled water. The oily phase which separated was taken up in methylene chloride. The aqueous phase was washed with fresh portions of methylene chloride. The methylene chloride extracts were combined, washed with water, dried over anhydrous sodium sulfate and concentrated by removing the solvent *in vacuo* at room temperature. The residue was then distilled *in vacuo* yielding 7.9 g. (67%) of colorless prod-

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uct having b.p. 58° (1–2 mm.), $n^{20}D$ 1.4417, and possessing an infrared spectrum identical with that of pure dinitrate ester of *meso*-2,3-butanediol.

Anal. Calcd. for $C_4H_8N_2O_6$: C, 26.67; H, 4.44; N, 15.56. Found: C, 26.47; H, 4.23; N, 15.35.

The Reaction of *erythro*-2-Bromo-3-nitroxybutane with Silver Nitrate in Acetonitrile.—This reaction was carried out in the same manner as that described for the *threo*-isomer. There was obtained a 74% yield of product having b.p. 50° (1 mm.), $n^{20}D$ 1.4416, and possessing an infrared spectrum identical with that of pure dinitrate ester of *dl*-2,3-butanediol.

Anal. Calcd. for $C_4H_8N_2O_6$: C, 26.67; H, 4.44; N, 15.56. Found: C, 26.57; H, 4.67; N, 15.70.

The Attempted Isomerization of *meso*-2,3-Dibromobutane with Silver Bromide in Acetonitrile.—To a solution of 108.2 g. (0.5 mole) of *meso*-2,3-dibromobutane, b.p. 71° (50 mm.), $n^{20}D$ 1.5116, in 100 ml. of dry acetonitrile at 25° was added in one portion a solution of 42.4 g. (0.25 mole) of silver nitrate in 50 ml. of acetonitrile. The reaction mixture was stirred at room temperature in the absence of light for 24 hr. The reaction mixture was filtered and the silver bromide residue washed with fresh portions of acetonitrile. The filtrate and washings were combined and poured into 250 ml. of distilled water. The oily phase which separated was taken up in diethyl ether. The aqueous phase was washed with fresh portions of ether. The ether extracts were combined, washed with water, dried over sodium sulfate and concentrated by removing the solvent at atmospheric pressure. The residue was then distilled *in vacuo* through a 18" column packed with glass helices, a total of 10 fractions being collected.

Fractions 1–6 (48 g.) having b.p. 35–43° (8–9 mm.), $n^{20}D$ 1.5100–1.5040, were combined and rectified twice *in vacuo* yielding a 75% recovery of unreacted *meso*-dibromide, b.p. 61–62° (34 mm.), $n^{20}D$ 1.5112. The infrared spectrum of this material showed it to be 98% pure.

The infrared spectrum of pure *meso*-2,3-dibromobutane exhibits an absorption band at 1160 cm.$^{-1}$ which is absent in the racemic dibromide; the *dl*-2,3-dibromobutane displays an absorption band at 1100 cm.$^{-1}$ which is absent in the *meso*-dibromide. It was found that the isomeric dibromides could be detected to less than 2% in the presence of the other.

The Attempted Isomerization of *dl*-2,3-Dibromobutane with Silver Bromide in Acetonitrile.—Employing the procedure as described for the *meso* isomer led to an 80% recovery of the *dl*-dibromide. Infrared analysis showed this material to contain 3% of the isomeric impurity.

The Attempted Isomerization of *erythro*-2-Bromo-3-nitroxybutane with Silver Bromide in Acetonitrile.—A mixture of 15 g. (0.075 mole) of *erythro*-2-bromo-3-nitroxybutane, b.p. 54° (6–7 mm.), $n^{20}D$ 1.4695, and 18.8 g. (0.1 mole) of freshly precipitated silver bromide in 30 ml. of acetonitrile was allowed to stand at room temperature in the absence of light for 15 days. The reaction mixture was filtered and the residue washed with fresh portions of acetonitrile. The filtrate and washings were combined and poured into 75 ml. of water. The organic layer was separated and taken up in methylene chloride. The aqueous solution was further extracted with small portions of methylene chloride. The methylene chloride extracts were combined, washed with three 20-ml. portions of water, dried over anhydrous sodium sulfate and concentrated by removing the solvent at atmospheric pressure. The residue was then rectified *in vacuo* yielding 12.2 g. (82%) of *erythro*-2-bromo-3-nitroxybutane, b.p. 55° (7 mm.), $n^{20}D$ 1.4698. Infrared analysis of this material showed it to contain less than 5% of the *threo* isomer.

A complete duplication of results was obtained when *threo*-2-bromo-3-nitroxybutane was treated with silver bromide in the same manner as that described for the *erythro* isomer.

Reaction of 1-Bromobutane, 2-Bromobutane, 1,4-Dibromobutane, 1-Chlorobutane, 2-Chlorobutane, 1,4-Dichlorobutane, *dl*- and *meso*-2,3-Dichlorobutane with Silver Nitrate in Acetonitrile at Room Temperature.—A solution consisting of 0.025 mole of alkyl halide, 25 ml. of acetonitrile and a 25% molar excess of silver nitrate was maintained at room temperature (24–28°) in the absence of light. The extent of the reaction was determined by isolating the silver halide formed. The silver halide was separated by filtration, washed twice with acetonitrile and dried. Table I records the results.

TABLE I

REACTION OF SILVER NITRATE WITH BROMO- AND CHLOROBUTANES IN ACETONITRILE AT ROOM TEMPERATURE

Halide	Extent of reacn., %	Hours
2-Bromo	Quant.	0.1
1-Bromo	Quant.	20
1,4-Dibromo	Quant.	20
1-Chloro	55	288
2-Chloro	86	244
1,4-Dichloro	80	792
dl-2,3-Dichloro	No reacn.	3720
meso-2,3-Dichloro	1	3720

Infrared absorption spectra were obtained with a Perkin-Elmer model 21 double beam spectrophotometer using homogeneous samples, NaCl prism and cell thickness of 0.025 mm.

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INDIAN HEAD, MARYLAND

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Synthesis and Properties of an Allenic Nitrile

BY LEE IRVIN SMITH AND JACK S. SWENSON[1]

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Synthesis of the allenic nitrile, 2-cyano-2,3-pentadiene (I), has been achieved. The structure of the nitrile has been proved, and its behavior toward certain reagents has been studied. A combination of reduction and hydrolysis converted the allenic nitrile into 2-methylpentanamide, but reaction of the nitrile with Grignard reagents, phenyllithium or ethyl sodiomalonate all resulted in polymerization of the nitrile and no compounds formed by simple addition of these reagents could be isolated. The key to the synthesis of the allenic nitrile was the facile prototropic shift, occurring with 2-cyano-3-pentyne (IV) whereby the acetylenic nitrile rearranged into the allenic nitrile.

As a part of a program having as its object the synthesis of an allenic ketone, synthesis of the allenic nitrile I, 2-cyano-2,3-pentadiene, was undertaken. The route to the allenic nitrile involved the sequence of steps

$$CH_3C{\equiv}C\ Mg\ Br + CH_3CHO \longrightarrow CH_3C{\equiv}C\ CH(OH)\ CH_3$$

(1) Abstracted from a thesis by Jack S. Swenson, presented to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Ph.D. degree, August, 1956.

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$$\text{II} + PBr_3 \text{ in dry ether} \longrightarrow \underset{\text{III}}{CH_3C{\equiv}C\,CH\,Br\,CH_3}$$

$$\text{III} + Cu_2(CN)_2 \text{ in dry benzene} \longrightarrow \underset{\text{IV}}{CH_3C{\equiv}CCH(CN)CH_3}$$

$$\underset{\text{I}}{CH_3CH{=}C{=}C(CH_3)CN}$$

$$\text{Mixture of IV + I} \xrightarrow[\text{dry ether}]{NaOCH_3} \text{I}$$

Synthesis of 2-hydroxy-3-pentyne (II) was achieved *via* known reactions. The product, obtained in 64% yield, had the physical properties reported in the literature.[2] The infrared spectrum showed a strong absorption at 3360 cm.$^{-1}$ (hydroxyl) and a spilt absorption of medium intensity at 2250 and 2220 cm.$^{-1}$ (triple bond).

The acetylenic alcohol II was converted into 2-bromo-3-pentyne (III) by action of phosphorus tribromide. The bromide III, obtained in 68% yield, boiled at 42° (20 mm.), and the infrared spectrum showed a strong absorption at 2250 cm.$^{-1}$ (triple bond) and was very similar to spectra reported for analogous propargyl bromides.[3]

The reaction between the bromide III and cuprous cyanide required very careful control of conditions and led to a mixture boiling at 55–61° (30 mm.) in yields of 0 to 37%, depending upon the experimental conditions. Infrared spectra of these mixtures indicated that the principal constituents were the acetylenic nitrile IV and a product (I) resulting from a rearrangement. A brown polymer was also present, and often some of the starting bromide III was recovered. The infrared spectra of the mixtures distilling at 55–61° (20 mm.) showed several characteristic bands which could best be explained by the presence in the mixture of an acetylenic nitrile IV and its allenic isomer I. The intensities of the weak band at 2270 cm.$^{-1}$ and the medium band at 2250 cm.$^{-1}$ always appeared in direct proportion to each other; these bands arise from the acetylenic linkage in IV. The sharp and relatively strong band at 2220 cm.$^{-1}$ probably arises from the nitrile group of IV and I, but the intensity of the band at 2220 cm.$^{-1}$ generally was proportional to that of the band at 1970 cm.$^{-1}$ arising from the allenic linkage in I. This band at 1970 cm.$^{-1}$ varied in intensity according to the amount of I present in the mixture. There was a very strong band at 1445 cm.$^{-1}$ and a fairly strong band at 1380 cm.$^{-1}$; these bands are characteristic of methyl groups, and their intensities are proportional to the number of methyl groups present. The intensities and positions of these two bands were the same in the spectra of all the mixtures, and in the spectra of the samples of pure allenic nitrile—as would be expected of mixtures of IV and I, both compounds containing two methyl groups. There was a sharp band at 1305 cm.$^{-1}$, characteristic of the acetylenic nitrile IV, and varying in intensity with the amount of IV present in the mixture. This band varied inversely in intensity with the band at 1000 cm.$^{-1}$, characteristic of the allenic nitrile. There was also a band at 790 cm.$^{-1}$, very characteristic of the allenic nitrile. The intensities of the three bands at 790, 1000 and 1970 cm.$^{-1}$ varied in direct proportion with the amount of I present in the mixtures, and the ratio of these intensities to those of pure I was used in estimating the amount of I present in the mixtures. As determined in this way, the amount of the allenic nitrile in the mixtures varied from 20 to 55%; in the mixtures obtained under optimum conditions for maximum yields, the amount of I present was usually about 50%.

The mixture of I and IV could not be separated into pure constituents by careful distillation through a modified semi-micro wire column[4] or through a Piros–Glover spinning band column, although the distillations had to be performed under 20 mm. because of the sensitivity of the allenic nitrile to heat. Likewise, no separation resulted when the mixture was chromatographed using either anhydrous magnesium sulfate or potato starch in the columns.

The key to isolation of I in the pure state was the discovery that the acetylene IV could be rearranged by means of a base-catalyzed prototropic shift into the allene I as the only distillable product. The finely powdered base was suspended in a dry ethereal solution of the mixture, and the product was recovered after removal of the base and evaporation of the solvent. Of several bases tried—sodamide, potassium carbonate, potassium hydroxide and sodium methoxide—the last was found to be the most effective. The crude product from this reaction, distilled through a spiral wire column, was the pure allenic nitrile I which boiled at 55° (19 mm.), 39° (8 mm.), 31° (3.5 mm.) and had $n^{25}D$ 1.4647; d^{25}_4 0.860. The yield of pure I was 28–38%; the over-all yield of I based on methylacetylene was about 4%.

The nitrile I gave analytical values in good agreement with those required for C_6H_7N. Proof of the carbon skeleton in I was achieved by reduction of the allenic linkage and hydrolysis of the nitrile to the saturated amide, 2-methylpentanamide (V), which was identical with an authentic specimen independently synthesized. The reduction was carried out in steps, and conversion of I into V proceeded as

$$\text{I} + H_2 \xrightarrow[\text{30 lb., 12 hr.}]{\text{Raney Ni}}$$

$$[CH_3CH{=}CH{-}CH(CH_3)CN] \xrightarrow{KOH\text{–}H_2O_2}$$

$$[CH_3CH{=}CHCH(CH_3)CONH_2] \xrightarrow[\text{500 lb., 2 hr.}]{H_2,\ \text{Raney Ni}}$$

$$\underset{\text{V}}{CH_3CH_2CH_2CH(CH_3)CONH_2}$$

The stability of I toward catalytic reduction was remarkable; even at 30–50 lb., it appeared that only one of the double bonds was reduced. As the reduction proceeded, the intensity of the allenic band at 1970 cm.$^{-1}$ in the infrared spectrum de-

(2) G. I. Iotsitch, Cholokoff, Andereg and Levinson, *J. Russ. Phys. Chem. Soc.*, **41**, 529 (1909); *Bull. soc. chim.*, **8**, 889 (1910).

(3) J. H. Wotiz, F. A. Miller and R. J. Palchak, THIS JOURNAL, **72**, 5053 (1950).

(4) C. W. Gould, G. Holzman and J. C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

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creased, and a band of medium intensity appeared at 1640 cm.$^{-1}$, the region of absorption of unconjugated double bonds. Therefore, the structure of a β,γ-unsaturated nitrile was chosen for this first reduction product, although this structure was not proved. When this product was subjected to the action of hydrogen peroxide in 25% aqueous potassium hydroxide, a white crystalline material resulted. This was not a pure compound, for it had a wide melting point range of 62–76°. The infrared spectrum of this material still showed a band at 1640 cm.$^{-1}$, hence it is probably the β,γ-unsaturated amide. Finally, when this amide was subjected to action of hydrogen under 500 lb. at 100° in the presence of Raney nickel, a pure compound, melting at 77–80°, resulted. That this was 2-methylpentanamide was shown by its identity with a product synthesized from methyl-*n*-propylmalonic acid.

Having established the carbon skeleton of the nitrile I, the position of the allenic linkage follows from the fact that the same nitrile I was obtained as a result of two different types of propargylic rearrangement: formation of I from III by the carbonium type, or *via* an S$_N$2′ mechanism, and the carbanion type (IV → I).[5] The only structure consistent with this fact and with the other properties of the nitrile is I, 2-cyano-2,3-pentadiene. The bromide III underwent no rearrangement when subjected to action of base under the conditions used for rearrangement of IV into I.

The reactions of the nitrile I were disappointing; as mentioned before, it was hoped that I could be converted into an allenic ketone by action of organometallic compounds. In general, all attempts to add ethyl sodiomalonate, *p*-biphenylmagnesium bromide, ethylmagnesium bromide or phenyllithium to the nitrile resulted in production of high boiling polymeric materials.

Other experiments were carried out in the hope of obtaining an allenic ketone, as indicated below

$$C_6H_5C{\equiv}CCH_2OH\ (VI) \xrightarrow{PBr_3} \underset{VII}{C_6H_5C{\equiv}CCH_2Br}$$

$$VII + Zn + C_6H_5CHO \longrightarrow \underset{VIII}{C_6H_5C{\equiv}CCH_2CHOHC_6H_5}$$

$$VIII + CrO_3 \longrightarrow \underset{IX}{C_6H_5C{\equiv}CCH_2COC_6H_5}$$

$$IX + base \longrightarrow \underset{X}{C_6H_5CH{=}C{=}CHCOC_6H_5}$$

When γ-phenylpropargyl alcohol (VI) was subjected to action of phosphorus tribromide, the bromide VII was obtained in 85% yield; the physical properties of the bromide were in agreement with those reported by Lai[6] for this compound. The Reformatsky reaction between the bromide VII and benzaldehyde gave oils which boiled in the range 150–160° (0.3 mm.). The infrared spectra of these oils showed a band of medium intensity at 3430 cm.$^{-1}$ (hydroxyl) and a strong band at 1700 cm.$^{-1}$ (carbonyl) but no band arising from an acetylenic linkage. The carbonyl band arose from benzaldehyde, which was isolated as the 2,4-DNP from all the oils. No derivative which could be identified as the 2,4-DNP of an α,β-unsaturated ketone could be isolated; the transformation into an α,β-unsaturated ketone has been reported as a general reaction of β,γ-acetylenic alcohols.[7] Nevertheless, some of these oils were oxidized by action of chromic acid. The products were oils which contained a small amount of solid; the infrared spectra of these materials showed weak hydroxyl bands at 3430 cm.$^{-1}$, strong carbonyl bands at 1685 cm.$^{-1}$ but no significant bands arising from an acetylenic linkage. In one experiment, on a larger scale, the oxidation product, on standing, deposited several grams of a solid melting at 146–147° and identified as diphenacyl. This could arise from hydration of the triple bond in IX under the strongly acidic conditions used for the oxidation. Since isolation of diphenacyl indicated the presence of some IX in the mixture, the oil was subjected to action of bases in the hope that the prototropic shift would convert IX into the allenic isomer X. But action of the bases—potassium carbonate, potassium hydroxide, sodium methoxide and activated alumina[8]—again gave oils which were indistinguishable from the starting materials in any way and whose spectra in the infrared showed no bands arising from an allenic linkage.

An attempt was also made to condense the acetylenic bromide III with benzaldehyde in a Reformatsky type reaction and so to obtain the acetylenic alcohol XI which could be oxidized to the β,γ-acetylenic ketone XII.

$$C_6H_5CHO + III + Zn \rightarrow \underset{XI}{CH_3C{\equiv}CCH(CH_2)CHOHC_6H_5}$$

$$XI + CrO_3 \rightarrow \underset{XII}{CH_3C{\equiv}CCH(CH_3)COC_6H_5}$$

Again the Reformatsky reaction gave oils whose spectra in the infrared showed no acetylenic bands and from which only the 2,4-DNP of benzaldehyde could be isolated.

Experimental[9]

2-Hydroxy-3-pentyne (II) (268 g., 64%) was prepared from methylacetylene (210 g., 5.25 moles), ethylmagnesium bromide (from 554 g., 5.1 moles of ethyl bromide and 122 g., 5.0 gram atoms of magnesium) and acetaldehyde (230 g., 5.23 moles) essentially as reported in the literature.[5] The product boiled at 50–55° (16 mm.), had $n^{25}D$ 1.4467; d^{25}_4, 0.904.

Anal. Calcd. for C_5H_8O: C, 71.39; H, 9.59. Found: C, 71.01, 71.30; H, 10.04, 10.13.

2-Bromo-3-pentyne (III).—The alcohol II (100 g., 1.19 moles), dry pyridine (20 cc.) and dry ether (500 cc.) were placed in an apparatus equipped with a dropping funnel, reflux condenser with calcium chloride guard tube and a stirrer. Phosphorus tribromide (150 g., 0.56 mole) was added dropwise, with stirring and cooling (0°). After an initial period of five minutes, the cooling bath was removed and the ether was allowed to reflux while the rest of the phosphorus tribromide was added (30 minutes). The mixture, consisting at this point of a white precipitate and a clear yellow solution, was stirred and heated at 55° for 3 hr., after which it was cooled (0°) and ice was cautiously added to hydrolyze excess phosphorus tribromide. The ether

(5) J. H. Wotiz, THIS JOURNAL, **73**, 693 (1951).

(6) T. Y. Lai, *Bull. soc. chim.* [4] **53**, 543 (1933).

(7) H. B. Henbest, E. R. H. Jones and I. M. S. Walls, *J. Chem. Soc.*, 2696 (1949).

(8) T. L. Jacobs and S. Singer, *J. Org. Chem.*, **17**, 475 (1952).

(9) Melting points were determined on a Kofler micro hot-stage apparatus and are therefore corrected. Boiling points are uncorrected. Microanalyses by J. H. Cooley, C. B. Koons, R. F. Lange and Mrs. T. Y. Lee.

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layer was removed, the water layer was extracted three times with 100-cc. portions of ether. All the ether solutions were combined, washed successively with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride and water and then dried (magnesium sulfate). Ether was removed by distillation, and the residual yellow oil was distilled through a short (4″) column packed with glass helices. The bromide III (119 g., 68%) was collected at 41–44° (20 mm.). It had n^{25}D 1.4903; d^{20}_4 1.335.

Anal. Calcd. for C_5H_7Br: C, 40.84; H, 4.80. Found: C, 40.99, 40.60; H, 5.39, 5.37.

2-Cyano-3-pentyne (IV) and 2-Cyano-2,3-pentadiene (I).—The reaction between the bromide III and cuprous cyanide required very careful control of reaction conditions in order to obtain good yields of the mixture of IV and I. The reaction was carried out twenty-four times; the optimum conditions from the point of view of reproducibility, ease of control and yields were as follows: the apparatus (dried in a steam heated oven and assembled while still warm to ensure anhydrous conditions) consisted of a 500-cc. three-necked flask equipped with reflux condenser with calcium chloride guard tube, a mechanical stirrer with a sealed joint and a thermometer with the bulb suspended just above the level of the liquid in the flask. In the flask were placed dry cuprous cyanide (43 g., 0.48 mole, dried for one day under vacuum and 100° and stored under vacuum over phosphorus pentoxide), the bromide III (71 g., 0.48 mole) and dry benzene (71 cc., dried over sodium). The mixture was stirred just rapidly enough to bring the cuprous cyanide into good suspension and then an oil-bath, preheated to 120°, was placed in position so that the level of the liquid in the bath was even with that of the liquid in the flask. Stirring and heating at 120° were maintained for 3.5 to 4 hr. after the temperature of the vapors reached 90°, or until the solids began to coagulate and settle noticeably in spite of the stirring. The mixture was cooled to room temperature, and the solution was decanted from the solids through a filter. The solids were washed three times with ether, and the extracts were decanted through a filter into the benzene solution. At this point a brown polymeric material separated; it was removed by filtration. Solvents were removed from the filtrate by distillation under reduced pressure, and the residual yellow oil was distilled through the spiral wire column.[4] The product was collected at 55–61° (20 mm.). Normally some unchanged III was recovered at 40–45° (20 mm.). The product (IV + I) weighed 14.5 g. (32.5%) and contained about 50% of I as shown by the infrared spectrum. No separation of this mixture into pure components could be achieved by any of several distillation procedures or by chromatography.

Rearrangement of IV to I. 2-Cyano-2,3-pentadiene.—This reaction, carried out 37 times, also required very careful control of conditions. The best procedure was as follows: in a 500-cc. three-necked flask equipped with a mechanical stirrer and reflux condenser were placed fresh (commercial) sodium methoxide (1.5 g.) and dry ether (100 cc.). A solution of the mixture of IV and I (14.5 g.) in dry ether (50 cc.) was added all at once to the stirred suspension of the base. The reaction mixture soon acquired a yellow color, and the base became rust colored. After ten minutes a second portion of base (1.5 g.) was added; after another ten minutes a third portion (1.5 g.), and at this point the mixture was cooled (0°). After another ten minutes (total time 30 minutes), the ether solution was decanted through a filter, the solids were washed three times with ether, the extracts were decanted through the filter and the solvent was removed under reduced pressure from the combined ethereal solutions. The residual oil was distilled through the spiral wire column (with cold finger condenser, Dry Ice–acetone).[4] The product, I (4.1 g., 28%), collected at 31–35° (3.3 mm.), boiled at 55° (19 mm.), 39° (8 mm.), 31° (3.5 mm.) and had n^{25}D 1.4650, d^{25}_4 0.0860.

Anal. Calcd. for C_6H_7N: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.10; H, 7.60; N, 15.00.

Hydrogenation of I. 2-Methylpentanamide (V).—A solution of I (1 g.) in dry ether (20 cc.) was subjected to the action of hydrogen (30 lb.) for 11 hr. in the presence of an active Raney nickel catalyst. The product, a yellow oil, was distilled under 0.05 mm. and collected in a receiver cooled with Dry Ice. The infrared spectrum of the resulting colorless oil showed no band at 1970 cm.$^{-1}$ (allene) but did show a band at 1640 cm.$^{-1}$ (unconjugated double bond). This material, probably the β,γ-ethylenic nitrile, was stirred vigorously for 1 hr. with potassium hydroxide (1 cc., 25%) and hydrogen peroxide (1 cc., 30%) at 75°. The mixture was extracted three times with ether, and the solvent was removed under reduced pressure from the combined extracts. The residual oily material, crystallized several times from petroleum ether (b.p. 30–60°), gave a white solid which melted in the range 62–76°. The infrared spectrum of this material (in chloroform) showed the band at 1640 cm.$^{-1}$; it was probably the β,γ-ethylenic amide. This crystalline solid was dissolved in a few cc. of dry ether, and the solution was subjected to action of hydrogen (500 lb.) at 100° for 2 hr. in the presence of Raney nickel catalyst. After removal of the catalyst and solvent, the residual oily material gave a white crystalline product from petroleum ether (b.p. 30–60°). After three recrystallizations from the same solvent, the solid melted at 77–80°, alone or when mixed with a synthetic specimen of V. The infrared spectrum of this product was superimposable on that of synthetic V.

Ethyl *n*-propylmalonate (150 g., 74%) was synthesized from ethyl malonate and *n*-propyl bromide essentially according to directions in the literature.[10] The product boiled at 111–120° (19 mm.) and had n^{25}D 1.4180.[11]

Ethyl methyl-*n*-propylmalonate was prepared by methylation of the *n*-propylmalonate using methyl iodide and sodium ethoxide. The product (130 g., 80%) was collected at 114–120° (19 mm.). It had n^{25}D 1.4200.[12]

Methyl-*n*-propylmalonic acid was prepared by hydrolysis of the ester; the yield of acid was 35%, and, after crystallization from benzene, it melted at 106–108°.[13]

2-Methylpentanoic acid (18 g., 78%) was prepared by decarboxylation of the above malonic acid. The product was collected at 101–103° (20 mm.); it had n^{25}D 1.4117 and d^{20}_4 0.917.[12]

2-Methylpentanamide (V) was prepared from the above acid *via* the acid chloride. The product crystallized in colorless plates from petroleum ether (b.p. 30–60°) which melted at 80–81°[12] alone or when mixed with V obtained from I.

Action of Grignard Reagents upon I.—A Grignard reagent prepared from magnesium (1.9 g., 0.078 gram atom), *p*-bromobiphenyl (10.4 g., 0.043 mole) and ethyl bromide (0.5 g.) in ether was added through a glass wool filter to a stirred and cooled (Dry Ice) solution of I (1 g., 0.0107 mole) in ether. The reaction mixture immediately became yellow, and a yellow solid separated. The mixture was refluxed for ten minutes, then poured onto Dry Ice to carbonate the excess reagent, and the whole was poured into iced, saturated aqueous ammonium chloride. The solution was extracted twice with ether; the aqueous layer was acidified with hydrochloric acid and again extracted with ether. Both ether extracts were washed with aqueous sodium hydroxide (10%), then with water, dried (magnesium sulfate) and the ether was evaporated. From the ether extract after acidification, only a small scum of residue was obtained. From the extract before acidification, the residue was a thick yellow oil from which no crystalline material could be obtained and which, when heated under vacuum, gave a small sublimate of biphenyl. In a similar fashion, two experiments were made to determine the action of ethylmagnesium bromide and of phenyllithium upon I. The results were essentially the same.

Action of Ethyl Sodiomalonate upon I.—To a solution of ethyl sodiomalonate (from sodium, 0.3 g., 0.013 gram atom, ethyl malonate 2.1 g., 0.013 mole, and dry ethanol (30 cc.) there was added under nitrogen and at −80° a solution of I (1 g., 0.0107 mole) in ethanol (5 cc.). After addition was complete, the mixture was stirred at −80° for an hour and then was allowed to come to room temperature. At this point the mixture was a pale yellow solution with a white solid suspended in it. Ethanol was removed by distillation, under nitrogen, at 30–40° (20–25 mm.). The residual yellow material was dissolved in cold water (25 cc.) and the solution was extracted three times with ether. The combined ether extracts were dried (magnesium sulfate), and ether was removed under reduced pressure, leaving a yellow oil which gave only a few drops of distillate up to 380° (0.3 mm.). The infrared spectrum of the yellow oil (before

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attempted distillation) showed bands at 2240, 2210, 1730, 1670 and 1630 cm.$^{-1}$ but no band at 1970 cm.$^{-1}$. The few drops of distillate from the oil was saponified with hot aqueous potassium hydroxide (25%), but the only product was a brown oil containing a small amount of a white solid which melted between 140–340° with evolution of gas. In a second experiment similar to the above, the solution of ethyl sodiomalonate was added to a solution of I. The results, however, were essentially the same.

γ-Phenylpropargyl alcohol (VI) (128.7 g., 77.5%), prepared according to Bartlett and Rosen,[14] boiled at 121–123° (8 mm.), and had n^{25}D 1.5835.[15]

γ-Phenylpropargyl bromide (VII) (160 g., 85%) was prepared from VI (128.7 g.) by action of phosphorus tribromide (137 g.) and pyridine (15 cc.) in ether (250 cc.). The product boiled at 110–120° (8 mm.) and had n^{25}D 1.6172.[6]

The Reformatsky reaction between VII and benzaldehyde was first carried out according to an analogous procedure in the literature.[7] Dry, freshly etched zinc (70 g., 1.07 gram atoms) and enough dry benzene to cover the metal were placed in an apparatus equipped with a stirrer, reflux condenser with calcium chloride guard tube and a dropping funnel. A solution of VII (154.2 g., 0.79 mole) and benzaldehyde (100 g., 0.94 mole) in dry tetrahydrofuran (100 cc.) was added dropwise to the stirred mixture at such a rate as to maintain gentle refluxing. After the addition was completed (70 minutes), the mixture was refluxed for 30 minutes, cooled and poured into a mixture of acetic acid and ice. The orange oil was removed, the aqueous layer was extracted three times with ether, the extracts were combined with the orange oil and the whole was washed successively with saturated sodium bicarbonate, aqueous potassium iodide, three times with water and dried (magnesium sulfate). The solvent was removed and the residual dark oil was fractionated through a 10″ Vigreux column. The product (60.6 g., 34.4%) boiled at 157–161° (0.2 mm.) and had n^{25}D 1.5900.

Anal. Calcd. for $C_{16}H_{14}O$ (VIII): C, 86.45; H, 6.35. Found: C, 86.73; H, 6.54.

The infrared spectrum of this material showed a medium hydroxyl band at 3430 cm.$^{-1}$, a strong carbonyl band at 1700 cm.$^{-1}$ but no acetylenic band.

Some of the above material (59.2 g.) in acetone (300 cc.) was oxidized by action of a solution of chromic oxide (200 cc., 1 *M* in CrO_3 and 1.5 *M* in H_2SO_4) according to a procedure reported in the literature for similar oxidations.[16] The reaction mixture was poured into water (1 l.), the orange oil was removed and the green aqueous layer was extracted four times with ether, and the extracts were combined with the oil. This solution deposited a solid which was removed; then the solution was washed successively with aqueous sodium carbonate, aqueous potassium iodide, twice with water and dried (magnesium sulfate). The ether was removed by distillation and the residual oil was cooled in a Dry Ice-bath, when it deposited more solid. This was removed and the oil was then fractionated through a spiral wire column; the distillate (11.68 g., 20%) was collected in two fractions: A, b.p. 130–155° (0.05 mm.), n^{25}D 1.6212; B, b.p. 155–175° (0.05 mm.), n^{25}D 1.6153.

Anal. Calcd. for $C_{16}H_{12}O$ (IX): C, 87.24; H, 5.49. Found (fraction A): C, 87.52; H, 5.54; (fraction B), C, 87.05; H, 5.90.

The infrared spectra of these fractions showed a medium hydroxyl band at 3430 cm.$^{-1}$, a medium carbonyl band at 1710 cm.$^{-1}$, a strong carbonyl band at 1680 cm.$^{-1}$ but no significant band in the region typical of an acetylenic linkage. The material gave a 2,4-DNP melting at 126–127°, but this could not be identified and was certainly not a simple derivative of IX.

Anal. Calcd. for $C_{22}H_{16}O_4N_4$ (2,4-DNP of IX): C, 65.99; H, 4.03; N, 13.99. Found: C, 45.68; H, 4.68; N, 22.72.

The solids isolated above were the same substance. After several crystallizations from ethyl acetate, the material melted at 146–147° and gave an oxime which melted at 205–208°. These are the melting points of diphenacyl (144–145°)[17] and its dioxime (203–204°).[18] The substance gave a green solution in sulfuric acid, changing to a reddish brown with blue-green fluorescence when heated, as reported for diphenacyl.

Ten different experiments were conducted in an effort to rearrange the above oils (containing IX?) into the allenic ketone X. Attempts to bring about the rearrangement by action of bases (potassium carbonate, potassium hydroxide, sodium methoxide) patterned after similar work by Jones and his associates[19] with acetylenic acids, or by the chromatographic technique developed by Jacobs and Singer,[8] led in every case to products where infrared spectra were very similar to those of the starting materials and showed no bands in the allenic region.

The Reformatsky reaction between benzaldehyde (246 g.) and III (305 g.) was conducted essentially as described above for the reaction between VII and benzaldehyde. The product, a dark oil, was separated into two fractions by distillation through a 4″-column packed with glass helices. Fraction A (66.3 g., 18%) boiled at 88–106° (1 mm.) and had n^{25}D 1.5238. Fraction B (53 g., 15%) boiled at 106–116° (1 mm.) and had n^{25}D 1.5354.

Anal. Calcd. for $C_{12}H_{14}O$ (XI): C, 82.72; H, 8.10. Found: fraction A, C, 79.47; H, 7.71, fraction B, C, 79.45; H, 8.17.

The infrared spectrum of A had no absorption in the region characteristic of hydroxyl or acetylenic group but did show carbonyl bands, weak at 1710 cm.$^{-1}$, strong at 1675 cm.$^{-1}$. The spectrum of B showed no acetylenic band, but there was a weak hydroxyl band at 3425 cm.$^{-1}$ and a weak carbonyl band at 1710 cm.$^{-1}$. Both fractions gave the same 2,4-DNP melting, after several crystallizations from ethanol, at 141–143°; fraction B also yielded the 2,4-DNP of benzaldehyde, m.p. and mixed m.p. 236–237°.

Anal. Calcd. for $C_{18}H_{18}O_4N_4$ (2,4-DNP of XI): C, 61.01; H, 5.12; N, 15.81. Found: 2,4-DNP from A: C, 59.14; H, 5.64; N, 14.70. 2,4-DNP from B: C, 59.21; H, 5.69; N, 14.52.

Attempts were made to obtain pure XI from fraction B by chromatography using alumina in the column, but the results were indefinite and the infrared spectrum still showed a carbonyl band at 1700 cm.$^{-1}$. Quantitative catalytic hydrogenation of fraction B over Raney nickel at room temperature and atmospheric pressure resulted in uptake of 110% of the theoretical amount for addition of one mole of hydrogen; when platinum oxide was used as the catalyst under the same conditions, the uptake of hydrogen was 119% of the theoretical amount for addition of two moles of hydrogen. Fraction B liberated 0.975 mole of methane from methylmagnesium iodide, showing the presence of one active hydrogen atom per mole (assuming fraction B to consist largely of XI).

Oxidation of fraction B (3 g.) by action of chromic oxide in sulfuric acid, as described above for the oxidation of VIII, gave only 0.26 g. of a pale yellow oil boiling at 100–135° (30 mm.), with n^{25}D 1.5208.

Anal. Calcd. for $C_{12}H_{12}O$ (XII): C, 83.69; H, 7.02. Found: C, 73.57; H, 6.97.

From this oil, the 2,4-DNP of benzaldehyde could be obtained. The infrared spectrum showed weak hydroxyl bands at 3450 and 2240 cm.$^{-1}$, and a strong carbonyl band at 1700 cm.$^{-1}$.

Oxidation of fraction B (5 g.) by action of the pyridine–chromium oxide complex[20] gave a product (1.80 g., 36%) boiling at 70–85° (0.1–0.2 mm.), whose infrared spectrum showed no hydroxyl or acetylenic bands, although there were two strong carbonyl bands at 1700 and 1685 cm.$^{-1}$. This product obviously was not XII.

MINNEAPOLIS 14, MINNESOTA

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June 5, 1957

COMMUNICATIONS TO THE EDITOR

THE METHYL GROUP OF METHIONINE AS A SOURCE OF C_{28} IN ERGOSTEROL[1]

Sir:

It was reported recently that formate can serve as a source of C_{28} in the biosynthesis of ergosterol[2] or of eburicoic acid.[3] We have incubated cell-free yeast homogenates with labelled sodium bicarbonate, formaldehyde, propionate-(1 or 2)-C^{14} and methionine-methyl-C^{14} and have found that more C^{14} is incorporated into the non-saponifiable lipids and the digitonin-precipitable sterols from methionine than from any of the other compounds. Thus, in one experiment 20.2% of the methionine-methyl-C^{14} radioactivity was found in the non-saponifiable fraction, as compared to 1.2% for acetate-1-C^{14}, 1.0% for $NaHCO_3$, 0.4% for formaldehyde and 0.5% for propionate. In comparative experiments with the same yeast homogenate which we ran after the paper of Danielson and Bloch[2] came to our attention, methionine-methyl-C^{14} gave four times as much radioactivity in the digitonin-precipitable sterol fraction as sodium formate-C^{14}.

To determine whether the radioactivity is concentrated in C_{28}, samples of ergosterol from incubations with acetate-1-C^{14} and methionine-methyl-C^{14} were ozonized according to Hanahan and Wakil.[4] Comparison of the figures obtained with ergosterol made from acetate and from methionine by a yeast homogenate (Table I, Expt. 1) shows that in the

TABLE I

DEGRADATION OF ERGOSTEROL-C^{14}

Expt.	Substance	Source of C^{14}, counts/mmole carbon/min. Acetate-1-C^{14}	Methionine-methyl-C^{14}
1[a]	Ergosterol	5,540	3,843
	Steam volatile fraction[c]	6,220	11,480
	Residue from steam distillation		
2[c]	Ergosterol acetate	7,545	655
	α,β-Dimethylbutyraldehyde[b]	...	946
	Acetone[b] ($C_{25,26,27}$)	...	1,044
	C_{28}	...	165
	C_{28}[d]	...	110
		...	3,210

[a] The two samples of ergosterol in Expt. 1 are not directly comparable, since much more C^{14} was used in the case of acetate. [b] Isolated as dinitrophenylhydrazone. [c] All samples counted after combustion to $BaCO_3$, corrected to infinite thickness. [d] Combustion of CHI_3 reportedly gives $BaCO_3$ of low specific activity.[5]

first case the steam-volatile fraction, α, β-dimethyl-butyraldehyde, contains less radioactivity than the residue, representing the ring system. In the second case this relationship is reversed, as expected if the main incorporation of radioactivity were in C_{28}. In experiment 2, the ergosterol, obtained from incubation of whole yeast with methionine-methyl-C^{14}, although recrystallized to constant specific activity, was subsequently found to be impure. However, the dinitrophenylhydrazone of the α,β-dimethyl-butyraldehyde was carefully purified before counting. Further degradation of this aldehyde shows that a predominant portion of the total radioactivity is located in C_{28}. When the correction factor suggested by Ehrensvard, *et al.*,[5] for the combustion of $C^{14}HI_3$ to $BaC^{14}O_3$ is applied, the observed activity of C_{28} is in acceptable agreement with the figure calculated from the specific activity of the α,β-dimethyl-butyraldehyde. Carbon 28 contains 20–30 times the radioactivity of the other carbon atoms in the molecule. Such a randomization of radioactivity was also observed by Dauben, *et al.*, in the incorporation of C^{14} from formic acid into the analogous position in eburicoic acid.[3]

The major incorporation of C^{14} into C_{28} of ergosterol in our experiments may be accounted for by the well-known oxidation of the methyl group of methionine to formate in biological systems.[6] However, transmethylation from sulfur to carbon, which has not been observed up to now, cannot be excluded since we find that aminopterin decreases the incorporation of C^{14} into ergosterol from formate-C^{14} but not from methionine-methyl-C^{14}. Other experiments indicate that squalene, but not zymosterol, is converted to ergosterol in yeast homogenates.

(1) This investigation was supported by the U. S. Public Health Service Grant No. C321, an Institutional Grant from the American Cancer Society, The Schering Corporation, Bloomfield, New Jersey and the Jane Coffin Childs Memorial Fund.

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RECEIVED MARCH 16, 1957

DIFFUSION OF O^{18} AND OF PROTIUM IN D_2O–H_2O MIXTURES[1]

Sir:

We wish to report some interesting and unexpected results obtained in this Laboratory in the course of studies on diffusion in liquid systems.[2]

The data were obtained for 25 ± 0.02° by means of the diaphragm cell technique.[2] Deuterium analyses were made pycnometrically, and those for O^{18} by the gradient tube density method,[3] after first converting the samples of D_2O^{18}-H_2O^{18} to H_2O^{18}. This last was accomplished by vaporizing

(1) These investigations were supported in part by the Office of Ordnance Research.

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a few cc. of the mixture to be analyzed, and passing the vapor over hot copper wire; the resulting CuO^{18} was then converted to water and Cu by reaction with hydrogen gas.

Since the O^{18} data yielded essentially self-diffusion coefficients, these are plotted in the figure as points (reproducibility, ± 2%). The protium diffusion data were treated as giving *integral* diffusion coefficients, and the values are given as lines drawn between the average compositions of the upper and lower compartments of the diffusion cell (reproducibility, ± 4%).

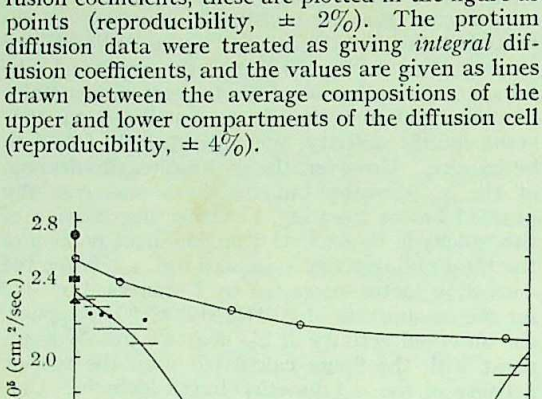

Fig. 1.—Variation of the diffusion coefficient with deuterium enrichment in water mixtures: present work, ○ O^{18} as tracer, — H_2O–D_2O; Longsworth, ●, H_2O–D_2O; Wang, *et al.*, ● O^{18} as tracer, ▲ H_2O–D_2O, ■ H^3 as tracer.

Considering first the region of low D_2O content, there has been a considerable fluctuation in literature values, but our results are in agreement with those of Wang, *et al.*,[4] and of Longsworth,[5] within experimental error. The point of interest, however, is that while the O^{18} diffusion coefficients varied with composition almost exactly as the inverse of the viscosity, the protium diffusion coefficients showed a marked minimum which, if corrected for the viscosity effect, fell at 50% D_2O content.

The explanation for these findings must be that somewhat different mechanisms are available for oxygen than for protium diffusion. For the former, there is the possibility of oxygen exchange between clusters, and for the latter, there is a variety of ways for a similar exchange to occur, since either long or short protium bonds and either a four or a five coördinated transition state may be involved. In any event, the results cannot be explained in terms of the usual assumption that diffusion in water occurs only by motion of individual molecules as units.

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Received March 25, 1957

Site of Vanadium Inhibition of Cholesterol Biosynthesis

Sir:

Vanadium compounds have been shown to inhibit the incorporation of radioacetate into cholesterol by rat and rabbit liver *in vitro* and *in vivo*.[1,2]

The following compounds have been generally accepted as intermediates in the biosynthesis of cholesterol from acetate: acetoacetate,[3] β-hydroxy-β-methyl glutarate (HMG),[4] β-methyl crotonate (BMC),[5] squalene,[6] lanosterol[7] and zymosterol.[8] Recently β,δ-dihydroxy-β-methyl valeric acid (mevalonic acid)[9] has been proposed as an intermediate because of its extremely efficient rate of conversion to cholesterol. This communication demonstrates that the inhibition by vanadium occurs between the six and five carbon intermediates.

Rat liver slices were incubated for two hours in phosphate buffer[1] containing 10 mg. of sodium acetate-1-C^{14} (1.0 mc./mM.) or 1 mg. of mevalonic acid-2-C^{14} (0.005 mc./mM.).[10] Aliquots of the same batch of slices were used for each experiment. Vanadium in a final concentration of 10^{-4} *M* was added to one flask as diammonium oxytartratovanadate.[10] An equimolar amount of tartrate was added to the control flask. Following incubation of the flasks containing acetate substrate, 30 mg. HMG, 40 mg. BMC, 35 mg. squalene, and 2 mg. of cholesterol were added to each flask as carrier. After saponification in 70% ethanol and 5% potassium hydroxide under nitrogen for one hour, the non-saponifiable fraction was extracted with petroleum ether and from it squalene and cholesterol were isolated by means of an alumina column.[6] The radioactivity of squalene was determined as the hexahydrochloride and cholesterol as the digitonide. The saponifiable fraction was acidified to *p*H 2 with concentrated hydrochloric acid and extracted continuously with ether for 24 hours. The ether was evaporated to dryness and HMG[4] and BMC[5] isolated and their radioactivity determined. Derivatives of each compound retained the calculated amount of radioactivity.

The radioactivity (Table I) of BMC, squalene and cholesterol from acetate as substrate was depressed by vanadium in comparison to the control. The increased radioactivity of HMG in the vanadium inhibited reaction might be expected since it is known that inhibition at any step in a sequence will produce an accumulation of the intermediate just below the inhibition with increased trapping of the radioactive molecules. The radioactivity of cholesterol obtained with mevalonic acid as substrate was also depressed by vanadium. When biosynthetic C^{14}-labeled squalene was employed as

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June 5, 1957

TABLE I

EFFECT OF VANADIUM ON THE INCORPORATION OF ACETATE-1-C^{14} AND MEVALONIC ACID-2-C^{14} INTO CHOLESTEROL

Each flask contained 20 ml. phosphate buffer,[1] C^{14}-labeled substrate, 1 g. liver slices, and tartrate (control) or diammonium oxytartratovanadate (vanadium) in a final concentration of $10^{-3}M$. Gas phase was 95% O_2–5% CO_2.

Substrate	Compound isolated	Experiment	Radioactivity recovered[a] Control	Vanadium
10 mg. sodium acetate-1-C^{14} (1.0 mc./mM.)	β-Hydroxy-β-methyl glutaric acid	1	2,908	4,820
		2	3,138	6,839
10 mg. sodium acetate-1-C^{14} (1.0 mc./mM.)	β-Methylcrotonic acid	1	3,510	482
		2	3,920	986
10 mg. sodium acetate-1-C^{14} (1.0 mc./mM.)	Squalene	1	280	92
		2	303	94
10 mg. sodium acetate-1-C^{14} (1.0 mc./mM.)	Cholesterol	1	41,248	9,446
		2	51,500	11,575
1 mg. mevalonic acid-2-C^{14} (0.005 mc./mM.)	Cholesterol	1	340	52
		2	388	26

[a] Recovered radioactivity is expressed as counts per minute per infinitely thick layer.

substrate,[11] no inhibition by vanadium was found between squalene and cholesterol.

These data are interpreted as demonstrating that vanadium inhibits cholesterol biosynthesis between HMG and BMC. Vanadium also inhibits the conversion of mevalonic acid to cholesterol.[12]

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(13) U.S.P.H.S. Research Fellow of the National Heart Institute.

(14) Established Investigator of the American Heart Association.

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GEORGE L. CURRAN[14]

RECEIVED MAY 6, 1957

TWO-DIMENSIONAL TRANSITIONS IN ADSORBED MONOLAYERS

Sir:

Because of the obvious interest[1,2] in theoretically-simple adsorption systems which exhibit transitions, we are moved to make this preliminary report on our measurements for krypton adsorbed on sodium bromide, Fig. 1.

Localized adsorption with nearest-neighbor interactions which, in addition to their usual effects, alter the *lateral* frequency $\omega_{||}$ of the adsorbed molecule with increasing coverage θ according to

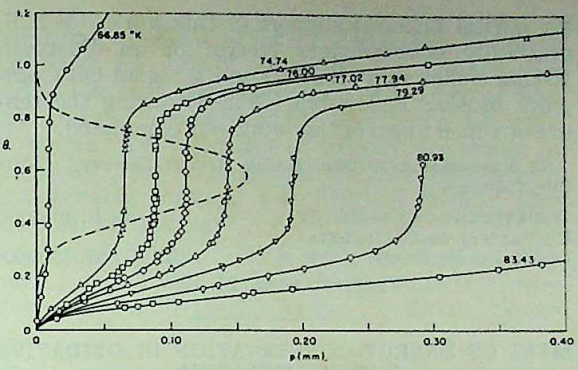

Fig. 1.—Adsorption isotherms of krypton on sodium bromide.

the prescription $\mathrm{d} \ln \omega_{||}^2 / \mathrm{d} \ln \theta = \gamma$ (= 1 for Kr) leads to the isotherm

$$\ln p(1-\theta)/\theta^{1+\gamma} = -\beta(\chi - 2w\theta) + \text{const.} \quad (1)$$

where $\beta = 1/kT$, and χ and w are the energies of adsorption and of lateral interaction as employed by Fowler and Guggenheim.[3] As a result of important but compensating differences, our equation with $\gamma = 1$ is similar to that of Rushbrooke.[4] With $\gamma = 0$ it reduces to the Fowler "crude" theory,[3] and with $w = 0$ in addition, to the Langmuir result.

In Fig. 2 we show how the data of Fig. 1 are rectilinearized according to the prescription of Eq. (1). Evidently the intercepts and slopes may be used

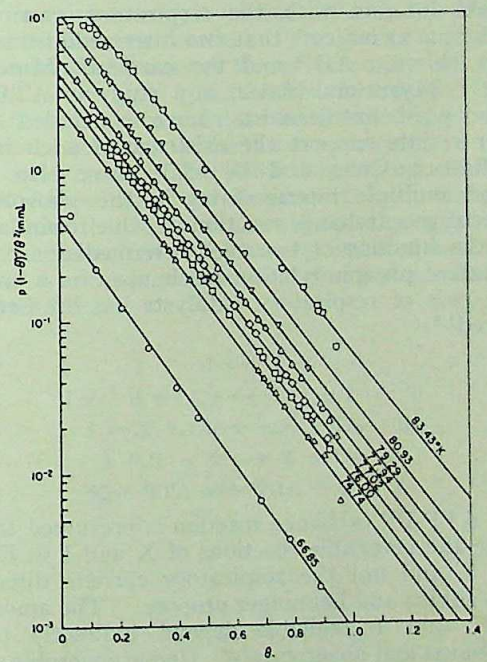

Fig. 2.—Adsorption isotherms of krypton on sodium bromide, plotted according to Eq. (1), $\gamma = 1$.

to evaluate χ and w, both of which are in reasonable agreement with independent theoretical calculations.

The authors wish to thank the Institute of Geophysics, University of California at Los Angeles,

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for partial financial support of this work. B.B.F. gratefully acknowledges receipt of an Eastman Kodak Fellowship (1951–2) and a Signal Oil Company Mosher Fellowship (1952–3) during the tenure of which much of this work was completed.

(5) Semiconductor Division, Hughes Aircraft Company, Culver City, California.

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SITES OF ENERGY CONSERVATION IN OXIDATIVE PHOSPHORYLATION

Sir:

Direct spectroscopic and kinetic studies of respiratory carriers in mitochondria have led to the conclusion that the *reduced* forms of the carriers, especially DPNH, are involved in the "high energy" complexes which are intermediates in the phosphorylation of ADP.[1] Wadkins and Lehninger reached the opposite conclusion on the basis of an experiment on the effect of aerobiosis and anaerobiosis on the ATP-P_i^{32} exchange reaction.[2] We show here that their interpretation of their experimental result is not unique and actually affords support for the conclusion they seek to refute.

The reaction mechanism for oxidative phosphorylation on which Wadkins and Lehninger based their conclusions ignores spectroscopic studies of the rate with which ADP and uncoupling agents interact with the respiratory carriers.[1,3] Such studies indicate that two intermediates intervene between ADP and the carriers. More recently, Myers and Slater, in a study of ATP-ase activity of mitochondria, have concluded that their results support the existence of such intermediates.[4] Cohn and Drysdale have also proposed multiple intermediates in the phosphorus and oxygen exchange reactions.[5] One formulation for the function of two such intermediates in the oxidative phosphorylation mechanism for a particular pair of respiratory catalysts has been represented[1,6]

$$b^{\cdot\cdot\cdot} + I \longleftrightarrow b^{\cdot\cdot\cdot} \cdot I \quad (1)$$

$$b^{\cdot\cdot\cdot} \cdot I + c^{\cdot\cdot} \longrightarrow c^{\cdot\cdot\cdot} + b^{\cdot} \sim I \quad (2)$$

$$b^{\cdot} \sim I + X \longrightarrow b^{\cdot} + X \sim I \quad (3)$$

$$X \sim I + P \longleftrightarrow X \sim P + I \quad (4)$$

$$X \sim P + ADP \longleftrightarrow ATP + X \quad (5)$$

The ATP-P^{32} exchange reaction is presumed to involve the reversible reactions of X and I in Eq. 4 and 5, and not the respiratory carriers directly, as Wadkins and Lehninger propose. The amounts of X and I available depend indirectly upon aerobiosis and anaerobiosis. Under anaerobic conditions X and I can be bound as $X \sim I$ and $b^{\cdot\cdot} \sim I$, and the exchange will be slow. Under aerobic conditions in the absence of substrate, less binding occurs and the concentrations of X and I are higher, and the exchange will proceed at high ATP concentrations, just as has been found in Wadkins and Lehninger's Table I.[2] If, on the other hand, we assume, as Wadkins and Lehninger assume, that the oxidized form of the respiratory enzyme is the high-energy carrier, we find that binding of X and I as $X \sim I$ and $b^{\cdot\cdot\cdot} \sim I$ is maximal under aerobic conditions and minimal under anaerobic conditions. This leads to the conclusion that the exchange reaction should have gone more rapidly under anaerobic conditions than under aerobic conditions which it did not do.

It now may be concluded that Wadkins and Lehninger's data on the 10-fold acceleration of the ATP-P_i^{32} exchange reaction under aerobic conditions support our earlier conclusions: (a) that the reduced forms of the respiratory pigments represent the carriers of the "high-energy" complex and (b) that intermediates exist between the respiratory carriers and ADP.

The ATP-P_i^{32} exchange reaction is at present poorly understood and may not yet provide a substantial basis for proof of any further hypothesis; the reaction is slow in the digitonin preparation, requires high ATP concentrations, and is affected by added ADP at concentrations outside the range of that needed for maximal rate of electron transfer.[7] However, Wadkins and Lehninger's data appear to provide additional evidence that the "high-energy" complex involves the reduced carrier. In their Table I, they find that the incorporation of P_i^{32} into ADP to form ATP^{32} gives over 67 times as much incorporation when the carriers are reduced than when they are oxidized. Since the mitochondria are stated to be anaerobic, this phosphorylation is attributed to the presence of the "high-energy" complexes of the reduced carriers.

Thus the data of Wadkins and Lehninger support in two ways our conclusion[1] that the reduced form of the respiratory carrier serves as the site of the "high-energy" complex. The transition from oxidized to reduced carriers gives first a one-tenth as rapid catalysis of the ATP-P_i^{32} exchange reaction caused by a binding of the reaction intermediates X and I by the reduced carriers and, second, a 67-fold greater anaerobic phosphorylation of ADP caused by "high energy" compounds of the reduced carriers.

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(5) M. Cohn and G. R. Drysdale, *J. Biol. Chem.*, **216**, 831 (1955).
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Received March 20, 1957

THE CONVERSION OF *myo*-INOSITOL TO GLUCURONIC ACID BY RAT KIDNEY EXTRACTS

Sir:

We wish to report the presence of a soluble enzyme system from rat kidney which catalyzes the conversion of inositol to glucuronic acid.

The enzyme was prepared by homogenizing rat kidneys in a Potter–Elvehjem homogenizer in a

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June 5, 1957

medium made of equal volumes of 0.2 *M* phosphate buffer *p*H 7.2 and 1.15% KCl. The homogenate was centrifuged in the Spinco ultracentrifuge at 60,000 × *g* for 30 minutes. The enzyme system contained in the supernatant fluid was salted out by the careful addition of solid ammonium sulfate at 0° (56 g. per 100 ml. initial volume) and was redissolved in 0.05 *M* phosphate buffer of *p*H 7.2. The assay for enzymatic activity was carried out in test tubes by incubating an aliquot of the enzyme solution with inositol. At the end of the incubation the tubes were heated for 2 minutes at 100° and the protein-free filtrate was assayed for glucuronic acid using the orcinol method of Mejbaum.[1] Table I summarizes a typical experiment. When inositol was omitted from the incubation mixture or when the enzyme solution was heat-

TABLE I

RATE OF FORMATION OF GLUCURONIC FROM INOSITOL

The reaction mixture contained 0.2 ml. of 1 *M* phosphate buffer *p*H 7.2, 0.2 ml. of 0.5 *M* inositol, 0.15 ml. of enzyme solution and distilled water to a final volume of 2 ml.; gas phase oxygen, incubation at 34°.

Time of incubation (minutes)	5	10	15	20	30	40
Glucuronic acid (γ)	50	75	101	118	147	160

inactivated prior to its use the amount of orcinol-reacting substances was 3–5% of that formed in the complete system.

In a large scale experiment in which 15 ml. of enzyme solution was used, 78.3 mg. of glucuronic acid was formed representing a 10% conversion of the added inositol. The glucuronic acid was isolated by column chromatography on Dowex-1 X10 (acetate form) using 0.4 *N* acetic acid as the eluting solvent and was identified by paper chromatography using the solvent systems: pyridine–ethyl acetate–acetic acid–water,[2] ethanol–water (88:12), acetone–water (80:20), *n*-butanol–acetic acid–water (100:21:50), and ethanol–acetic acid–water (80:10:10). The spots were revealed by spraying the paper with aniline oxalate and heating at 100° for 5 minutes. In all cases the isolated uronic acid migrated in a manner indistinguishable from authentic glucuronic acid and was resolved from guluronic, galacturonic, mannuronic, idur-onic, 2-ketogluconic, 5-ketogluconic, and ascorbic acid, as well as from the corresponding lactones of the above uronic acids.

The sodium salt of the isolated uronic acid was crystallized from ethanol (*Anal.* Calcd. for $C_6H_9O_7Na \cdot H_2O$: C, 30.77; H, 4.70. Found: C, 30.86; H, 4.74). The free acid has a m.p. of 162–163°, while the lactone had a m.p. of 176–178°. The brucine salt of the isolated uronic acid had a m.p. of 162–165°.

The isolated glucuronic acid as well as its lactone were optically inactive, indicating that it is a racemic mixture. *Escherichia coli* (Strain B) adapted on D-glucuronic acid utilized approximately half of a known amount of the isolated uronic acid. The remaining half was recovered from the culture medium and its specific rotation at equilibrium was found to be $[\alpha]^{24}D$ −33.3° (*c* 0.48 in H_2O, *1 l* dm.) compared to −36.0° expected for L-glucuronic acid. The enzymatic formation of glucuronic acid from inositol occurs with the simultaneous uptake of oxygen (1–1.2 μmoles of oxygen per μmole of glucuronic acid formed) and the disappearance of an equivalent amount (± 10%) of inositol (determined by bioassay[3]).

Acknowledgment.—This work was supported by grant No. C-2228(C2) from the National Institutes of Health, Public Health Service, Bethesda, Maryland.

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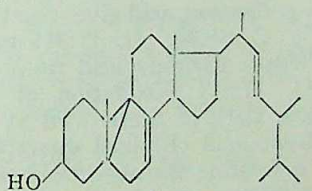
CHRYSSOULA LYRAS

RECEIVED MARCH 23, 1957

THE STRUCTURE OF PHOTOISOPYROCALCIFEROL[1]

Sir:

Recent studies by Velluz, Havinga and their associates[2] have established that the first step in the ultraviolet irradiation of ergosterol (9α-H, 10β-CH_3, 9,10-*anti*) is a bond cleavage reaction with the formation of a 9,10-*seco*-sterol type of intermediate. On the other hand, Dimroth and Windaus[3] have shown that a similar irradiation of the 9,10-*syn* epimer, isopyrocalciferol (9β-H, 10β-CH_3), is a bond forming reaction. The product, photoisopyrocalciferol, showed the presence of only two double bonds (on quantitative hydrogenation), showed no maximum in the ultraviolet spectrum and upon oxidation yielded a non-conjugated unsaturated ketone. The photo isomer, upon heating, was reconverted to the starting homoannular diene. On the basis of these data, the following two structures (I and II) were postulated and the present work has established the correctness of structure II.



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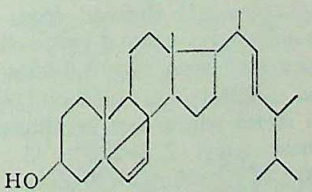

II

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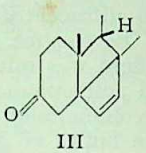
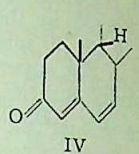
Photoisopyrocalciferol displays bands in the infrared at 970 and 748 cm.$^{-1}$, characteristic of *trans*- and *cis*-symmetrically disubstituted olefins, respectively, and the nuclear magnetic resonance spectrum shows vinyl proton bands at 0 and −1.0 (doublet) p.p.m.[4] The former band is characteristic of the 22-ene structure and thus the latter must be assigned to the remaining nuclear double bond. The large negative displacement is similar to that found for the vinyl proton in cyclobutene (−0.72 p.p.m.).[5] Upon oxidation, the photo compound is converted into a crystalline non-conjugated unsaturated ketone (m.p. 80–81°; C, 85.36; H, 10.62; $\lambda_{max.}$ 1705 cm.$^{-1}$; ϵ_{205} 2350, no. max. at higher wave length) which upon reduction by lithium aluminum hydride is converted to the starting alcohol. Upon ozonization of the acetate, there is obtained a tricarboxylic acid (m.p. 273–275°, C, 64.12; H, 7.51, neut. equiv. 157) which is readily transformed into a cyclic anhydride-carboxylic acid (m.p. 243–244°, C, 66.78; H, 7.62; $\lambda_{max.}$ 1770 and 1825 cm.$^{-1}$). The photo compound can be hydrogenated, stepwise, to yield a dihydro (m.p. 58–59°; C, 84.46; H, 11.58) and a tetrahydro alcohol (m.p. 51.0–52.5°; C, 84.02; H, 12.01); the nuclear double bond is attacked first. All of the foregoing compounds are stable to hydrogen chloride in chloroform solution.[6] These data clearly establish the presence of olefinic linkages at C_6,C_7 and C_{22},C_{23} and they also indicate the presence of a cyclobutene ring and the absence of a cyclopropane structure.

The tetrahydro alcohol upon oxidation with CrO_3 in acetic acid at 0° yields a ketone (m.p. 47.0–48.5°; C, 84.51; H, 11.47; $\lambda_{max.}$ 1705 cm.$^{-1}$; ϵ_{205} 680) whose infrared and ultraviolet spectra are normal for a saturated, isolated ketone. Either the tetrahydro alcohol or ketone upon oxidation with CrO_3 in acetic acid at 70°, followed by esterification with diazomethane, yields a diester (m.p. 65.0–66.5°; C, 77.68; H, 8.47; sapon. equiv., 229), showing the presence of at least one adjacent methylene group. The tetrahydro ketone upon reaction with perbenzoic acid gives rise to a lactone (m.p. 71–73°; C, 81.30; H, 11.31) which when saponified yields a hydroxy acid (m.p. 172–173°; C, 77.59; H, 11.01). Oxidation of the latter compound with CrO_3 in acetic acid at 60° forms the same dibasic acid obtained directly from the ketone, thus indicating the absence of substituents α to the carbonyl group.[7]

When the ketone III derived from the photo compound is allowed to stand with alcoholic alkali, it is converted into oily 4,6-dien-3-one, IV, ($\lambda_{max.}^{EtOH}$ 283 mμ, ϵ 21,00; $\lambda_{max.}$ 1650 cm.$^{-1}$) of the isopyrocalciferol series which can be characterized as a semicarbazone (m.p. 221–223°; C, 77.21; H, 10.12; N, 9.47; $\lambda_{max.}^{EtOH}$ 305 mμ, ϵ 38,500). The same compounds also can be prepared directly from isopyrocalciferol by oxidation followed by base and acid isomerization.



III



IV

Finally, the photo compound II upon heating to 160° in EtOD is reconverted into isopyrocalciferol which is devoid of deuterium. The above facts are only consistent with the valence tautomeric structure II for photoisopyrocalciferol.

Photopyrocalciferol also has been subjected to a similar sequence of reactions and shown to possess an analogous-type structure, different only in the stereochemistry at C_9-C_{10}. This formation of the valence tautomeric structures from 9,10-*syn* structures calls attention to the importance of stereochemistry in the irradiation of 5,7-dienes.

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RECEIVED APRIL 24, 1957

KINETIC ISOTOPE EFFECT IN THE IODINATION OF 2,4,6-TRIDEUTEROPHENOL

Sir:

The bromination of benzene and bromobenzene, and of their tritiated analogs as catalyzed by iodine proceeds without preferential displacement of hydrogen over tritium[1]; likewise bromination of benzene and hexadeuterobenzene by hypobromous acid with an acid catalyst proceeds at identical rates for these two compounds under similar reaction conditions.[2] Similarly no kinetic isotope effect has been found for nitration[1,3] of benzene, toluene, bromobenzene, naphthalene, or nitrobenzene containing tritium or deuterium nor for azo coupling with 1-naphthol-4-sulfonic acid.[4] The conclusion can be drawn that the breaking of the C–H bond has not made much progress in the transition state of the slow step of these electrophilic substitutions and, with less certainty,[5] that an intermediate[6] ArH·E, is formed during this slow step with electrophilic reagent E with loss of the proton occurring in a subsequent fast step.

While the above examples appear to be the only cases in which it has been proven that loss of the proton is kinetically insignificant during electrophilic aromatic substitution, it has been tempting to apply this generalization to other cases. In particular Painter and Soper[7] and Berliner[8] have implicitly or explicitly made this assumption in

(4) Parts per million displacement relative to ethanol.

(5) J. D. Roberts and A. T. Bottini, private communication.

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June 5, 1957

their interpretation of the kinetics of the iodination of phenol by solutions of iodine-triiodide ion in water. They concluded that the mechanism of the reaction probably involved attack of I^+ (or H_2OI^+) and acyl hypoiodite (or catalysis of HOI by a general acid HA) upon phenoxide ion. Grovenstein and Henderson[9] have pointed out that the kinetic results available do not exclude a rapid and reversible attack of iodine molecule upon phenoxide ion followed by a slow loss of proton to the solvent or to a general base A^- conjugate to the buffer acid HA.

In order to elucidate further the mechanism of the iodination of phenol, 2,4,6-trideuterophenol was prepared after the general procedure of Ingold[10] and co-workers. After two equilibrations of phenol with heavy water, a product which is estimated to be at least 99% 2,4,6-trideuterophenol was obtained. This phenol undergoes iodination at one fourth the rate of ordinary phenol. Thus in a typical experiment at 25° at initial concentrations of 0.0080 M in phenol and 0.00196 M in iodine, in aqueous solvent which was 0.500 M in acetic acid, 0.050 M in sodium acetate, 0.230 M in sodium perchlorate, and 0.020 M in sodium iodide, the initial apparent second order rate constants (calculated in terms of stoichiometric concentrations of phenol and iodine) were 1.21×10^{-3} l. mole^{-1} sec.$^{-1}$ for ordinary phenol and 3.05×10^{-4} l. mole^{-1} sec.$^{-1}$ for 2,4,6-trideuterophenol. These data give k_H/k_D 3.97. In related runs but in dilute perchloric acid in place of the acetate buffer, isotope effects of similar magnitude were obtained.

The present case, as far as we are aware, constitutes the first example of a hydrogen isotope effect during electrophilic aromatic halogenation. The only other known cases of hydrogen isotope effects during electrophilic aromatic substitution seem to be sulfonation[1,11] (k_H/k_T = 1.8), cyclodehydration[12] of 2-anilino-pent-2-ene-4-one (k_H/k_D = 1.5), and the reactions[4] of some diazonium ions upon hindered 2-naphthol-6,8-disulfonic acid (k_H/k_D = 3.6–6.6). Our present example shows that a phenol need not necessarily be hindered to give an isotope effect. We think it is significant that for the four types of electrophilic substitution reactions for which hydrogen isotope effects are known, three, including the present, involve reactions of phenols or aromatic amines. These are just the types of compounds which would be expected to give the most stable reactive intermediates, thus (I) for iodination of phenol. Substances analogous to (I)

(I)

have indeed been isolated from reactions of 2,4,6-trisubstituted phenols.[13] General evidence, therefore, favors (I) as an intermediate in the iodination of phenol. On this basis, in order to account for both the kinetic evidence and isotope effect, intermediate (I) must, under the kinetic conditions which have been studied,[7,8] be transformed back to reactants considerably faster than into the final products, *i.e.*, (I) must be essentially at equilibrium with the reactants. From such kinetic data, therefore, the nature of the iodinating agent for phenol *cannot be specified.* We hope to be able to find conditions in which intermediates such as (I) from phenols are formed in the rate-determining step; only under such conditions, at best, can the nature of the iodinating agent be ascertained by reaction kinetics. Meanwhile we are investigating the generality of isotope effects during electrophilic halogenation of phenols and related compounds.

(13) Thus see G. M. Coppinger and T. W. Campbell, THIS JOURNAL, **75**, 734 (1953); L. E. Forman and W. C. Sears, *ibid.*, **76**, 4977 (1954); J. A. Price, *ibid.*, **77**, 5436 (1955).

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RECEIVED APRIL 24, 1957

DETECTION OF FREE RADICAL INTERMEDIATES IN THE ACTION OF OXIDATION INHIBITORS

Sir:

Aromatic amines and phenolic compounds which inhibit oxidation have been presumed to act through the removal of hydrogen from the hydroxyl or amino group:

$$\mathrm{ArXH} + \mathrm{RO_2}\cdot \longrightarrow \mathrm{ArX}\cdot + \mathrm{RO_2H}$$
$$(\mathrm{ArX}\cdot \xrightarrow{k_1} \text{inactive products}) \qquad (1)$$

Recent investigations have brought alternative proposals for the terminating reaction involving these inhibitors. Kooyman and Bickel[1] now suggest two consecutive reactions, both of which terminate oxidation chains

$$\mathrm{ArXH} + \mathrm{RO_2}\cdot \longrightarrow \mathrm{ArX}\cdot + \mathrm{RO_2H}\ k_{1a} \qquad (1a)$$
$$\mathrm{ArX}\cdot + \mathrm{RO_2}\cdot \longrightarrow \text{Stable product}\ k'_{1a} \qquad (1'a)$$

In (1′a) the product is either an adduct or the result of a second hydrogen abstraction.

Boozer, Hammond, *et al.*,[2,3] suggest two consecutive reactions

$$\mathrm{RO_2}\cdot + \mathrm{ArXH} \rightleftharpoons (\mathrm{RO_2ArXH})\cdot K_{1b} \qquad (1b)$$
$$(\mathrm{RO_2ArXH})\cdot + \mathrm{RO_2}\cdot \longrightarrow \text{inactive products},\ k'_{1b} \qquad (1'b)$$

the first of which is reversible and leads to an equilibrium concentration of a radical complex.

Kinetic analysis of the course of an oxidation inhibition period, when the inhibitor acts by the Kooyman and Bickel processes, gives

$$[\mathrm{ArX}\cdot] = \frac{1}{k_c - 1}[\mathrm{ArXH}]\left\{1 - \left(\frac{[\mathrm{ArXH}]}{[\mathrm{ArXH}]_0}\right)^{k_c - 1}\right\} \qquad (2)$$

for the concentration of the intermediate radical, where $[\mathrm{ArXH}]_0$ is the concentration of inhibitor

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(2) C. E. Boozer, G. S. Hammond, C. E. Hamilton and J. N. Sen, THIS JOURNAL, **77**, 3233–3237 (1955).

(3) G. S. Hammond, C. E. Boozer, C. E. Hamilton and J. N. Sen, *ibid.*, **77**, 3238–3243 (1955).

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(10) C. K. Ingold, C. G. Raisin and C. L. Wilson, *J. Chem. Soc.*, 1637 (1936); A. P. Best and C. L. Wilson, *ibid.*, 28 (1938).

(11) U. Berglund-Larsson and L. Melander, *Arkiv Kemi*, **6**, 219 (1953).

(12) T. G. Bonner and J. M. Wilkins, *J. Chem. Soc.*, 2518 (1956).

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at the beginning of the inhibition period and $k_c = k'_{1a}/k_{1a}$.[4]

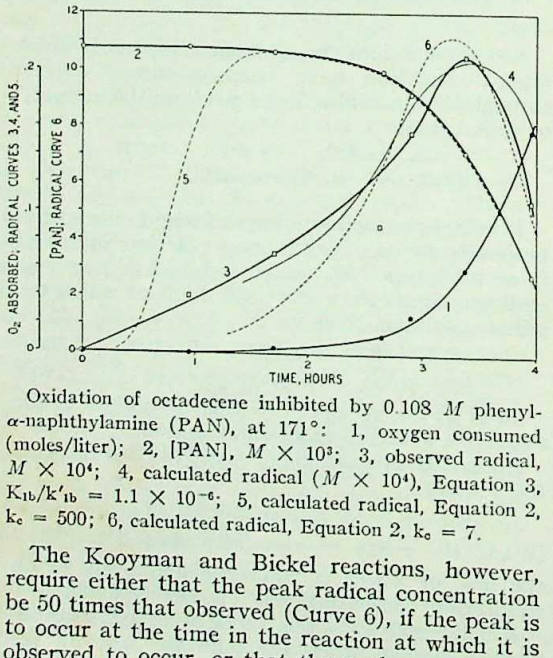
The Boozer and Hammond inhibition processes give

$$[(RO_2ArXH)\cdot] = \left(\frac{K_{1b}}{k'_{1b}}\right)^{1/2} [ArXH]^{1/2} (k_i + k_4[RO_2H])^{1/2} \quad (3)$$

during the inhibition period, where $(k_i + k_4[RO_2H]) = -d[ArXH]/dt$.

We have followed the concentration of a radical formed during the oxidation at 171° of octadecene, inhibited with phenyl-α-naphthylamine (PAN) at 0.0108 M initial concentration. The radical concentration was determined by electron paramagnetic resonance measurements[5] made upon samples withdrawn during the course of the oxidation reaction and immediately frozen in liquid nitrogen. The half-life of the radicals at 25° was estimated to be about 30 hours. No radicals were detected in the unoxidized sample, in the inhibitor by itself, or in octadecene oxidized in the absence of inhibitor.

The results of our measurements are shown in the accompanying figure. The radical concentrations observed during the course of the reaction agree approximately with those predicted by the Boozer and Hammond reactions (Equation 2) for $K_{1b}/k'_{1b} = 1.1 \times 10^{-6}$ hour.



Oxidation of octadecene inhibited by 0.108 M phenyl-α-naphthylamine (PAN), at 171°: 1, oxygen consumed (moles/liter); 2, [PAN], $M \times 10^3$; 3, observed radical, $M \times 10^4$; 4, calculated radical ($M \times 10^4$), Equation 3, $K_{1b}/k'_{1b} = 1.1 \times 10^{-6}$; 5, calculated radical, Equation 2, $k_c = 500$; 6, calculated radical, Equation 2, $k_c = 7$.

The Kooyman and Bickel reactions, however, require either that the peak radical concentration be 50 times that observed (Curve 6), if the peak is to occur at the time in the reaction at which it is observed to occur, or that the peak occurs much earlier in the reaction and that the shape of the curve (Curve 5) be quite different from that observed, if the observed peak radical concentration is to be matched.

The great stability of the radical at room temperature argues somewhat against the Boozer and Hammond mechanism, because if the radical is formed reversibly, radical decay by $RO_2\cdot + RO_2\cdot$ is possible.

The inhibitor decay curve measured by a fluorescence method and the oxygen absorption curve are acceptable by both mechanisms.

Reaction (1) can also provide the radical concentrations observed if it is assumed that the radical product is destroyed rapidly by some oxidation product, perhaps peroxide, which rises to high concentration near the end of the inhibition period.

Attempts were made to measure concentrations of radicals formed during inhibition periods in octadecene at 171° where the inhibitors were 4-amino-3-pentadecylphenol, di-*t*-butyl-*p*-cresol, and *t*-butylcatechol. No radicals were found. The experiments are being continued at lower temperatures in the hope that increased radical stability will permit detection.

We are indebted to Dr. R. H. Sands and to Varian Associates of Palo Alto, California, for the electron paramagnetic resonance measurements.

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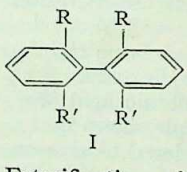
(4) Papers 22 (O. L. Harle and J. R. Thomas) and 23 (O. L. Harle) presented at the General Session of the Petroleum Division of the ACS, April 7–12, 1957; kinetic analyses available in Petroleum Division Preprints.

(5) J. E. Wertz, *Chem. Rev.*, 55, 829–955 (1955).

THE ABSOLUTE CONFIGURATION OF 6,6′-DINITRO-2,2′-DIPHENIC ACID AND 6,6′-DIMETHYL-2,2′-BIPHENYLDIAMINE

Sir:

Kuhn and Rometsch have assigned[1] the R-configuration to (−)-Ia as a result of calculations based on a theoretical model.[2] We have now obtained evidence directly at variance with the above conclusion.



I

Ia, R = CH_3, R′ = NH_2
b, R = COOH, R′ = NO_2
c, R = $COOCH_3$, R′ = NO_2
d, R = CH_2OH, R′ = NO_2
e, R = CH_2Br, R′ = NO_2
f, R = CH_3, R′ = NO_2

Esterification of (−)-Ib[3] (m.p. 230–233°, $[\alpha]^{23}D$ −125° (MeOH)) gave (−)-Ic (m.p. 141–142°, $[\alpha]^{28}D$ −113° (EtOAc)); found: C, 53.6; H, 3.2, N, 8.2), which was reduced to (−)-Id (m.p. 120–121°, $[\alpha]^{20}D$ −65° (EtOAc)); found: C, 55.5; H, 3.7; N, 9.1) with $LiAlH_4$–$AlCl_3$. Conversion to (−)-Ie (m.p. 172–173°, $[\alpha]^{32}D$ −8.9 (THF); found: C, 39.3; H, 2.1; N, 6.7) was followed by ring-closure to the iminonitrile (m.p. 295–300° dec., $[\alpha]^{28}D$ +837° (pyridine); found: C, 60.1; H, 3.7; N, 17.4). Hydrolysis gave DNDBCH-6-one[4] (m.p. 227–229°, $[\alpha]^{25}D$ +218° (EtOAc); found: C, 61.0; H, 3.8; N, 9.5). Since (+)-DNDBCH-6-one has the S-configuration,[4] the absolute configuration of (−)-Ib is thus established. Ib is of historical interest: it is the first compound[5] known to owe its optical activity to restricted rotation about a single bond.

(1) W. Kuhn and R. Rometsch, *Helv. Chim. Acta*, **27**, 1346 (1944).
(2) Reviewed by W. Kuhn, *Z. Elektrochem.*, **56**, 506 (1952).
(3) A. W. Ingersoll and J. R. Little, This Journal, **56**, 2123 (1934).
(4) C. Mistr and H. Pellmann, *ibid.*, **79**, 1769 (1957).
(5) G. H. Christie and J. Kenner, *J. Chem. Soc.*, 614 (1922).

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June 5, 1957

Reduction of (−)-Ie with $NaBH_4$-$AlCl_3$ to (−)-If (m.p. 95–97°, $[\alpha]^{27}D$ −25° (EtOH); found: C, 62.0; H, 4.2; N, 10.3), followed by hydrogenation over Pd/C, afforded (−)-Ia (m.p. 153–158°, $[\alpha]^{25}D$ −49° (EtOH)). The melting point, 232–233°, of the diacetamide, $[\alpha]^{30}D$ +134° (EtOH), was undepressed by admixture of authentic[6] diacetamide, m.p. 233–235°, $[\alpha]^{26}D$ +128° (EtOH), prepared from authentic[6] (−)-Ia, m.p. 156–158°, $[\alpha]^{24}D$ −47° (EtOH), +34° (*N* HCl).[7]

(−)-Ia and (+)-DNDBCH-6-one have thus been correlated *via* (−)-Ie; (−)-Ia therefore[4] has the S-configuration. It would appear that the assumptions underlying the theoretical treatment[1,2] deserve re-examination.

The absolute configurations of the many common hindered biphenyls related[8] to Ia and Ib will be listed in future publications.

(6) J. Meisenheimer and M. Höring, *Ber.*, **60**, 1425 (1927).
(7) The sign of rotation of Ia is *p*H dependent (F. A. McGinn, unpublished results).
(8) *Cf.* also K. Mislow, *Trans. N.Y. Acad. Sci.*, [2] **19**, 298 (1957).

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RECEIVED APRIL 18, 1957

LEWIS ACID CHARACTER OF TELLURIUM HEXAFLUORIDE

Sir:

In a previous communication,[1] the formation of fluorotellurate salts from tellurium hexafluoride and certain alkali metal fluorides was described. We have now found that tellurium hexafluoride will react exothermally with tertiary amines to form stable adducts of the composition $TeF_6 \cdot 2R_3N$. Analysis of the n-m-r data suggests that geometrical isomers are present in solutions of the trimethylamine complex.

Trimethyl- and triethylamines were added to tellurium hexafluoride in a vacuum system. The trimethylamine adduct was a white solid, but the ethyl analog had a dark color that apparently was due to minor secondary reactions. The pressure–volume relationships indicated a stoichiometry of two molecules of amine for one of the hexafluoride and analysis of the trimethylamine complex confirmed the indicated composition (*Anal.* Calcd. for $TeF_6 \cdot 2N(CH_3)_3$: C, 20.0; H, 5.04; F, 31.7. Found: C, 19.56; H, 5.10; F, 29.14). Pyridine formed a complex that was highly dissociated at 25°, but amides, ethers and nitriles did not absorb tellurium hexafluoride at this temperature. This low acceptor strength and the previously cited[1] low stability of fluorotellurate salts indicate that tellurium hexafluoride is a relatively weak Lewis acid.

The F^{19} magnetic resonance spectrum of the molten trimethylamine adduct showed only one sharp peak; amine exchange through simple dissociation of the complex was therefore indicated. A dimethylformamide solution of the trimethylamine adduct gave a single broad resonance at 25°, and at higher temperatures, the peak sharpened and shifted in the direction of the tellurium hexafluoride resonance. The amide solution was cooled to a glass that at ∼ −180° displayed three broad resonances of approximate intensities 1:1:0.4. On warming above −180°, these three peaks broadened rapidly (but at different rates) and finally merged into a single peak. It should be noted that the weak doublet due to spin–spin coupling of fluorine with the Te^{125} isotope persisted at 25° (masked at low temperatures by the broad resonances), and therefore no fluorine exchange was taking place in this system.

The n-m-r data are consistent with the behavior of an octacovalent complex which has geometrical isomers and which undergoes amine exchange through simple dissociation of the complex. At ∼ −180°, the three fluorine resonances may be ascribed to the three possible isomers. On steric grounds, the two peaks of relative intensity 1 probably arise from the 1,8- and 1,3-isomers, and the peak of relative intensity 0.4 from the 1,2-isomer. Above ∼−180°, slight dissociation of the complexes leads to amine exchange and this occurs at different rates for the three isomers. At higher temperatures the three isomers are indistinguishable in the n-m-r spectrum because of fast amine exchange. At temperatures above 25°, the complex is highly dissociated in solution and the position of resonance is a measure of the equilibrium constant for the dissociation. Without supporting data, these conclusions cannot be considered rigorously established. Unfortunately, the rapid amine exchange will not permit isolation of the postulated isomers by conventional techniques.

(1) E. L. Muetterties, THIS JOURNAL, **79**, 1004 (1957).

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RECEIVED APRIL 15, 1957

A CRYSTALLIZABLE ORGANOMETALLIC COMPLEX CONTAINING TITANIUM AND ALUMINUM

Sir:

Following our previous researches[1] concerning the nature of the catalytic agent promoting the α-olefins polymerization, we have isolated a crystallizable compound containing titanium, aluminum and organometallic bonds, which causes the polymerization of ethylene.

By treating 0.01 mole of bis-(cyclopentadienyl)-titanium dichloride[2] suspended in 50 ml. of *n*-heptane with 0.025 mole of triethylaluminum at 70°, in the absence of air and of moisture, a slow gas evolution takes place, the titanium compound is dissolved and the solution becomes dark blue. By cooling the solution at −50°, a blue crystalline solid has been obtained in good yield.

The macroscopic blue needles of the compound, recrystallized four times from *n*-heptane, melt at 126–130° without appreciable decomposition.

(1) G. Natta, P. Pino, E. Mantica, F. Danusso, G. Mazzanti and M. Peraldo, *La Chimica e l'Industria*, **38**, 124 (1956); G. Natta, P. Pino, G. Mazzanti, U. Giannini, E. Mantica and M. Peraldo, *ibid.*, **39**, 19 (1957).
(2) G. Wilkinson and G. M. Birmigam, THIS JOURNAL, **76**, 4281 (1954).

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The blue compound contains titanium, aluminum, chlorine and organic groups; from the elementary quantitative analysis a ratio Ti:Al:Cl = 1:1:2 has been found.

The values 331 and 339 have been calculated for the molecular weight of the blue compound from two different cryoscopic measurements in benzene.

By treating the blue product with 2-ethylhexanol, ethane is evolved; a quantitative gas volumetric determination shows that two moles of ethane are evolved per mole of compound.

By treating the product with anhydrous hydrochloric acid in ether solution bis-(cyclopentadienyl)-titanium dichloride is formed in almost quantitative yield (more than 90%).

The analytical data and the chemical behavior agree very well with a formula $(C_5H_5)_2TiCl_2Al(C_2H_5)_2$, as shown in the table for $(C_5H_5)_2TiCl_2Al(C_2H_5)_2$

	Calcd.	Found	
Cl, %	21.22	21.02[3]	20.78[4]
Al, %	8.073	7.92	7.90[3]
Ti, %	14.33	14.34	14.55[3]
$-C_2H_5$, %	17.40	16.07	17.67[5]
Mol. weight	334	331	339[6]

It seems probable that, in the complex, both C_5H_5- groups are bound to the titanium atom and that both C_2H_5- groups are bound to the aluminum atom.

By polymerizing ethylene in heptane solution in the presence of 0.6 g. of the Ti–Al complex at 40 atm. and 95° after a reaction time of 20 hours, 8.4 g. of white polymer has been obtained, which has been fractionated by boiling solvent extraction (acetone extractable fraction 10.1%; ether extractable fraction 1.8%, carbon tetrachloride extractable fraction 17.20%, residue 70.9% having intrinsic viscosity in tetralin at 135° = 1.55 × 100 ml./g.).

As it is reported in the next table, $(C_5H_5)_2TiCl_2$ alone is completely inactive for the ethylene polymerization; $Al(C_2H_5)_3$, accordingly with previously published data,[7] does not give solid polyethylene in the reaction conditions, but only low molecular weight oily polymers. Comparative experiments were carried out at 95° and 40 atm.

Soluble catalyst Type	Moles	Solvent Type	Cc.	Reaction time, hours	Crystalline polyethylene, g.	Oily polymers, g.
$(C_5H_5)_2TiCl_2$	0.005	Benzene	100	20	0	0
$Al(C_2H_5)_3$	.05	*n*-Heptane	300	8	0	11.07[a]
$(C_5H_5)_2TiCl_2$-$Al(C_2H_5)_2$	.003	*n*-Heptane	40	8	7	0.4

[a] 66% of the product consists of hydrocarbons lower than decane.

(3) Decomposition of the complex by H_2SO_4 5%; titanium has been determined as titanium cupferrate, aluminum as 8-oxyquinolinate, chlorine by gravimetric determination (I. Ubaldini and F. Capizzi, *Chimica e Industria*, **37**, 779 (1955)).

(4 Decomposition of the complex by Na_2O_2; chlorine has been determined by the Volhard titration.

(5) By gas volumetric determination.

(6) By cryoscopic determination in benzene solution.

(7) G. Natta, P. Pino, and M. Farina, *Supplemento Ric. Scient.*, **25**, 120 (1955).

Although the complex is a catalyst for the ethylene polymerization, less active than the catalyst prepared from $TiCl_4$ and $Al(C_2H_5)_3$, the composition of the complex strongly supports the hypothesis that the Ziegler type catalysts[8] for the polymerization of ethylene are, generally, bimetallic complexes containing organometallic bonds.

(8) K. Ziegler, Belgian Patent 533,362; K. Ziegler, E. Holzkamp, H. Breil and H. Martin, *Angew. Chem.*, **67**, 541 (1955).

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RECEIVED FEBRUARY 18, 1957

A NOVEL REARRANGEMENT IN THE 5-NITRONORBORNENE SERIES

Sir:

The failure of salts of 5-nitronorbornenes (Ia, R = H[1]; Ib, R = CH_3[2]; Ic, R = C_6H_5[3,4]; shown in the aci form) to undergo the Nef reaction[5] has been attributed[6] to homoallylic[7] resonance stabilization (I ⟷ II) of the aci forms. We find, however, that, although a ketone is not obtained, Ia does yield a nitrogen-containing transformation product under Nef reaction conditions.

Addition of an ice-cold aqueous methanolic slurry of the sodium salt of Ia to 8.5% (by wt.) hydrochloric acid at −20 to −10° gave in 30–37% yields a rearrangement product (VI), m.p. 104.5–106.5°, isomeric with 5-nitronorbornene. *Anal.* Calcd. for $C_7H_9NO_2$ (139.15): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.71; H, 6.63; N, 10.04; mol. wt. (Rast) 150. γ_{NH} 3380, 3150; $\gamma_{C=O}$ 1667; $\gamma_{C=C-H}$ 3040; $\gamma_{C=C}$ 1616 (shoulder) cm.$^{-1}$ in $CHCl_3$. As is true with hydroxamic esters,[8] VI and VII do not give a color test with ferric chloride and are weakly acidic; they can be extracted with ether from 10% sodium bicarbonate solution but not from 20% sodium hydroxide; they are regenerated upon acidification.

Hydrogenation of pure VI over platinic oxide at 2 atm. consumed 1.00 mole of hydrogen and gave in 96% yield a dihydro derivative (VII), m.p. 43–46°, $n^{25}D$ 1.5065 (on the supercooled liquid). *Anal.* Calcd. for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.93. Found: C, 59.41; H, 7.79; N, 9.68. γ_{NH} 3180; $\gamma_{C=O}$ 1668 cm.$^{-1}$. Dichromate oxidation of VII and VIII gave glutaric acid.

Hydrogenation of VI over Raney nickel catalyst at 2 atm. (92% yield) or reduction of VII with iron powder and aqueous ethanolic ammonium chloride solution[9] yielded a tetrahydro derivative

(1) W. C. Wildman and C. H. Hemminger, *J. Org. Chem.*, **17**, 1641 (1952).

(2) E. E. Van Tamelen and R. J. Thiede, THIS JOURNAL, **74**, 2615 (1952).

(3) W. E. Parham, W. T. Hunter and R. Hanson, *ibid.*, **73**, 5068 (1951).

(4) W. C. Wildman and R. B. Wildman, *J. Org. Chem.*, **17**, 581 (1952).

(5) W. E. Noland, *Chem. Revs.*, **55**, 137 (1955).

(6) W. C. Wildman and D. R. Saunders, *J. Org. Chem.*, **19**, 381 (1954).

(7) M. Simonetta and S. Winstein, THIS JOURNAL, **76**, 18 (1954).

(8) H. L. Yale, *Chem. Revs.*, **33**, 231 (1943).

(9) (a) V. O. Lukashevich and M. A. Voroshilova, *Compt. rend. acad. sci. U.R.S.S.*, **2**, 304 (1935); *Org. Chem. Ind. (U.S.S.R.)*, **4**, 253 (1937); C. A., **32**, 2091 (1938); Russian Patent 51,050, May 31, 1937;

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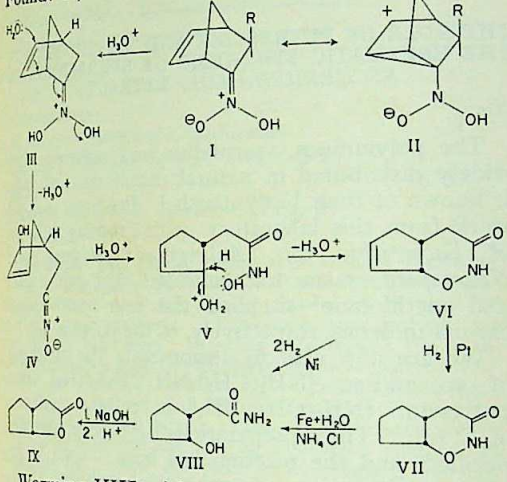
(VIII) of VI, m.p. 95.5–96°. *Anal.* Calcd. for $C_7H_{13}NO_2$ (143.18): C, 58.72; H, 9.15; N, 9.78. Found: C, 58.79; H, 8.98; N, 9.86; mol. wt. (Rast) 139; γ_{OH} 3500; γ_{NH} 3390, 1589; $\gamma_{C=O}$ 1668 in $CHCl_3$. VIII evolved a gas on treatment with nitrous acid. When warmed with 20% sodium hydroxide solution VIII evolved ammonia; under Schotten–Baumann conditions it yielded benzamide. Phenylurethan of VIII, m.p. 151.5–153.5°. *Anal.* Calcd. for $C_{14}H_{18}N_2O_3$: N, 10.68. Found: N, 10.67.



Warming VIII with 10–20% sodium hydroxide solution, followed by acidification, gave the known[10–13] lactone IX, b.p. 69° (0.5 mm.), $n^{25}D$ 1.4727, m.p. −13.5° to −12°. *Anal.* Calcd. for $C_7H_{10}O_2$ (126.15): C, 66.64; H, 7.99. Found: C, 66.54; H, 7.67; mol. wt. (Rast) 144; $\gamma_{C=O}$ 1759, 3520 (overtone; sample was shown to be pure by vapor phase chromatography). The infrared spectrum of our sample was identical with an authentic sample of IX,[11] and there was no depression in mixed m.p. Alkaline permanganate oxidation of our sample of IX gave glutaric acid; nitric acid oxidation of IX has been reported to give glutaric acid.[10]

The location of the double bond in VI has not been determined through chemical evidence; it is assigned tentatively on the basis of the mechanism (Ia → III → IV → V → VI) proposed to account for this novel fission of the norbornene ring system: Hydrolysis at C_2 of protonated Ia (III, or a more highly protonated version), with concerted shift of the double bond to C_3–C_4, fission of the C_1–C_5 bond, and elimination of hydroxyl to form the nitrile oxide IV. Hydrolysis of the nitrile oxide[14] to the hydroxamic acid followed by displacement, with inversion and ring closure, of the conjugate acid of the latter (possibly concerted as shown in V) would complete the *cis*-ring fusion of VI.

(15) Taken in part from the M. S. thesis of Patricia A. McVeigh, University of Minnesota, 1954.

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RECEIVED APRIL 2, 1957

SOLVENT EFFECTS IN THE REACTIONS OF FREE RADICALS AND ATOMS[1]

Sir:

Complexes between free radicals and aromatic hydrocarbons have been suggested,[2–5] but conclusive evidence supporting their existence is lacking. We have found that various aromatic solvents can drastically alter the position of attack of a chlorine atom on a branched-chain hydrocarbon and believe that this effect is connected with the ability of the aromatic hydrocarbon to form a complex with chlorine atoms. The data indicate that the complexed chlorine atom is much more selective than the free chlorine atom.

This effect was observed in the photochlorination of 2,3-dimethylbutane, analysis being performed by vapor phase chromatography. The 1- and 2-chloro-2,3-dimethylbutanes have retention times at 80° of 33 and 22 minutes, respectively, in a 2-m. B-column of a Perkin–Elmer model 154B Vapor Fractometer. Since we have previously demonstrated that the products of photochlorination are a true measure of the point of attack of the chlorine atom,[6] the relative reactivities of the tertiary and primary-hydrogen atoms were calculated by the equation

$$\text{Re. react. } (tert./prim.) = \frac{\text{moles } tert.\text{-chloride} \quad (12)}{\text{moles } prim.\text{-chloride} \quad (2)}$$

TABLE I

PHOTOCHLORINATION OF 2,3-DIMETHYLBUTANE AT 55°

Solvent (4.0 molar)	Rel. react. (*tert./prim.*)
2,3-Dimethylbutane	3.7
Carbon tetrachloride	3.5
Methyl acetate	4.3
Nitromethane	3.4
Trichloroethylene	3.4
Propionitrile	4.0
Nitrobenzene	4.7
Benzoyl chloride	6.4
Benzotrifluoride	6.9
Chlorobenzene	10
Benzene	14
Benzene (25°)	20
o-Xylene	15
Mesitylene	17
t-Butylbenzene	24
1-Chloronaphthalene	37

(1) Directive Effects in Aliphatic Substitutions. X.
(2) G. A. Russell and H. C. Brown, THIS JOURNAL, **77**, 4031 (1955).
(3) F. R. Mayo, *ibid.*, **75**, 6133 (1953).
(4) G. S. Hammond and C. E. Boozer, *ibid.*, **76**, 3861 (1954); G. S. Hammond, C. E. Boozer, C. E. Hamilton and J. N. Sen, *ibid.*, **77**, 3238 (1955).
(5) M. T. Jacquiss and M. Szwarc, *Nature*, **170**, 312 (1952).
(6) H. C. Brown and G. A. Russell, THIS JOURNAL, **74**, 3995 (1952).

(7) (a) W. Hückel, *Ann.*, **441**, 1 (1925); (b) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939).
(8) (a) W. Hückel, *Ann.*, **441**, 1 (1925); (b) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939).
(9) (a) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939); (b) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939).
(10) (a) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939); (b) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939).
(11) (a) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939); (b) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939).
(12) (a) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939); (b) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939).
(13) (a) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939); (b) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939).
(14) (a) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939); (b) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939).

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Table I shows that most aliphatic solvents have little effect upon the position of attack of a chlorine atom on 2,3-dimethylbutane. However, in the presence of aromatic solvents the chlorine atom is directed toward the tertiary hydrogen atoms, the effect increasing with the basicity of the aromatic hydrocarbon[7] and with a decrease in temperature.

Figure 1 demonstrates the effects of *t*-butylbenzene, benzene, and chlorobenzene on the relative reactivities of the tertiary and primary-hydrogen atoms of 2,3-dimethylbutane. Qualitatively, it is

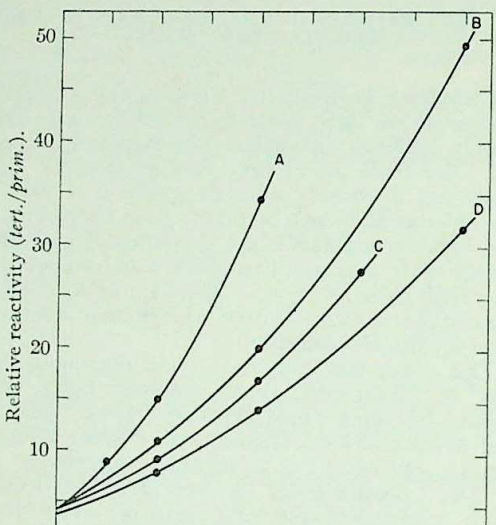
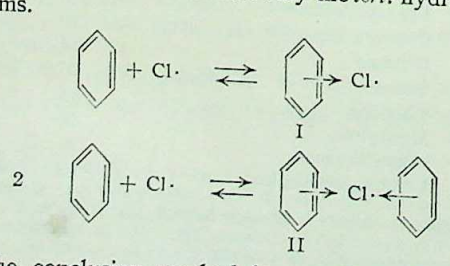


Fig. 1.—Relative reactivities of hydrogen atoms of 2,3-dimethylbutane in the presence of aromatic hydrocarbons: A, *t*-butylbenzene, 25°; B, benzene, 25°; C, chlorobenzene, 25°; D, benzene, 55°.

obvious that the attacking species is very selective at high concentrations of aromatic hydrocarbon. Quantitatively, the curves in Figure 1 fit the expression

$$\text{Rel. react. } (tert./prim.) = k + k'[\text{Ar}] + k''[\text{Ar}]^2$$

where Ar represents the aromatic hydrocarbon. An expression of this type can be derived if it is assumed that there are three types of chlorine atoms in an aromatic solvent, a free chlorine atom, I and II, and if I and II can attack only the *tert.*-hydrogen atoms.



The conclusion reached in regard to the complexing of free radicals by aromatic solvents calls for reappraisal of many homolytic substitutions, particularly those involving competition reactions. Complexing may also be important in other homolytic reactions, such as vinyl polymerization.[3,8] The study of solvent effects in free radical reactions is being extended to other solvents, substrates and free radicals.

(7) H. C. Brown and J. D. Brady, THIS JOURNAL, 74, 1113 (1952).

(8) W. H. Stockmeyer and L. H. Peebles, Jr., *ibid.*, **75**, 2278 (1953). G. M. Burnett and H. W. Melville, *Disc. Faraday Soc.*, **2**, 322 (1947).

GENERAL ELECTRIC RESEARCH LABORATORY
SCHENECTADY, NEW YORK GLEN A. RUSSELL

RECEIVED APRIL 3, 1957

THE ROLE OF PUTRESCINE AND METHIONINE IN THE ENZYMATIC SYNTHESIS OF SPERMIDINE IN *ESCHERICHIA COLI* EXTRACTS

Sir:

The polyamines, spermidine and spermine, are widely distributed in natural materials, but little is known of their biosynthesis.[1] Previous isotopic work from this laboratory, with growing cultures of *Escherichia coli*, *Aspergillus nidulans*, and *Neurospora crassa*, has indicated that putrescine[2] and methionine[3] supplied the four- and three-carbon moieties, respectively, of the polyamines.

We are now able to demonstrate the synthesis of spermidine $[NH_2(CH_2)_3NH(CH_2)_4NH_2]$ from putrescine $[NH_2(CH_2)_4NH_2]$ in cell-free extracts of *E. coli*. These preparations have been partially purified, and the reaction has been shown to require L-methionine, adenosine triphosphate (ATP), and Mg^{++} (Table I). The isotope of 1,4-C^{14}-putrescine and of 2-C^{14}-methionine, but not of $C^{14}H_3$-methionine or of $C^{14}OOH$-methionine, was incorporated into spermidine.

Preliminary data indicate that three steps are involved in this reaction

$$\text{ATP} + \text{L-methionine} \xrightarrow{Mg^{++}} \text{compound I} \xrightarrow[-CO_2]{Mg^{++}}$$

$$\text{compound II} \xrightarrow{\text{putrescine}} \text{spermidine}$$

(1) In the first step ATP and methionine form compound I. In the presence of 0.01 *M* NaCN this accumulates, and can be purified by chromatography. On the basis of preliminary data, compound I is believed to be adenosylmethionine.[4] It contains approximately one equivalent of methionine (as shown by the incorporation, in separate experiments, of the isotope from 2-C^{14}-methionine, $C^{14}H_3$-methionine, and $C^{14}OOH$-methionine), one equivalent of adenine (absorption maximum at 260 mμ) and no phosphorus. The R_f of compound I is very similar to that reported[4] for adenosylmethionine [0.12 in ethanol 80, HAc 5, H_2O 15; 0.07 in butanol–acetic acid–H_2O]. Compound I can serve as a methyl donor with nicotinamide methylpherase[4] [60% yield], in the absence of ATP, Mg^{++}, and methionine.

(1) For a literature review see: S. M. Rosenthal and C. W. Tabor, *J. Pharmacol. Exp. Therap.*, **116**, 131 (1956).

(2) H. Tabor, S. M. Rosenthal and C. W. Tabor, *Federation Proc.*, **15**, 367 (1956).

(3) R. C. Greene, *ibid.*, **16**, 189 (1957).

(4) G. Cantoni, *J. Biol. Chem.*, **204**, 403 (1953); G. Cantoni in "Methods in Enzymology," S. P. Colowick and N. O. Kaplan (eds.), Academic Press, Inc., New York, N.Y., Vol. II, 254, 257 (1955); Vol. III, 660 (1957).

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TABLE I

ENZYMATIC SYNTHESIS OF SPERMIDINE FROM 1,4-C^{14}-PUTRESCINE

The complete system contained C^{14}-putrescine dihydrochloride[a] (0.12 μmole, 8,000 c.p.m.), L-methionine (1 μmole), ATP (2.5 μmoles), $MgSO_4$ (30 μmoles), *E. coli* enzyme (10 mg. of an ammonium sulfate fraction), and triethanolamine buffer (*p*H 8.1) in a final volume of 0.3 ml. Incubation time was 3 hr. at 37°. Spermidine was isolated by Dowex 50 (H) and Amberlite XE-64 (H) chromatography by a modification of the methods previously reported (ref. 1).

	Spermidine,[b] c.p.m.
Complete system (C^{14}-putrescine, ATP, Mg^{++}, L-methionine, enzyme)	5070
No ATP	140
No Mg^{++}	220
No L-methionine	160
D-Methionine[c] instead of L-methionine	120
Compound I instead of ATP and L-methionine[d]	5700
Adenosyl-L-methionine instead of ATP and L-methionine[d]	6460

[a] Synthesized by catalytic reduction (in ethanol–H_2SO_4) of C^{14}-succinonitrile, formed from $NaC^{14}N$ and bromopropionitrile. We wish to thank Drs. H. Bauer and E. May for help with these syntheses. [b] For convenience isotopic assays usually were used. In other experiments the spermidine formed was assayed with dinitrofluorobenzene, demonstrating net synthesis. Further identification of the spermidine formed was attained by rechromatography and by recrystallization, with carrier, to constant specific activity. [c] 1 μmole of D-methionine. [d] The incubation mixtures in these two experiments contained buffer, $MgSO_4$, and enzyme (as indicated above), 0.12 μmole of C^{14}-putrescine (8,000 c.p.m.), and 0.17 μmole of compound I or adenosyl-L-methionine in a final volume of 0.3 ml. Control incubation mixtures without enzyme showed no synthesis of spermidine.

TABLE II

DECARBOXYLATION OF C^{14}OOH-DL-METHIONINE AND OF C^{14}OOH-COMPOUND I

The complete system in experiment A contained putrescine (0.12 μmole), $MgSO_4$ (30 μmoles), *E. coli* enzyme (5 mg. of an ammonium sulfate fraction), ATP (2.5 μmoles), triethanolamine buffer (*p*H 8.1), and C^{14}OOH-DL-methionine in a final volume of 0.3 ml. The complete system in experiment B contained the same additions of $MgSO_4$, enzyme and buffer plus C^{14}OOH-compound I in a final volume of 0.3 ml. Incubation time was 45 minutes at 37°.

	$C^{14}O_2$, c.p.m.
A. With C^{14}OOH-DL-methionine[a] (0.13 μmole, 40,000 c.p.m.)	
Complete system (putrescine, ATP, Mg^{++}, C^{14}OOH-methionine, enzyme)	1044
No putrescine	1146
No ATP	30
No Mg^{++}	24
Complete system + NaCN (3 μmoles)[b]	54
B. With C^{14}OOH-compound I (0.003 μmole, 800 c.p.m.)	
Complete system (Mg^{++}, C^{14}OOH-compound I, enzyme)	378
No Mg^{++}	98

[a] C^{14}OOH-DL-methionine was prepared by a modification of the non-isotopic synthesis of R. Gaudry and G. Nadeau, *Can. J. Research* 26B, 226 (1948). [b] In the presence of NaCN, compound I accumulated. Larger amounts of compound I were made with 2.6 μmoles of C^{14}OOH-DL-methionine (700,000 c.p.m.), 50 μmoles of ATP, 600 μmoles of $MgSO_4$, 60 moles of NaCN, *E. coli* enzyme (100 mg. of ammonium sulfate fraction) in a volume of 6 ml. Compound I was purified by Dowex 50 (H) or XE 64 (H) chromatography, or by paper chromatography.

(2) In the second step compound I undergoes enzymatic decarboxylation (Table II) in the presence of Mg^{++}. ATP is not necessary for this reaction, although, for the formation of $C^{14}O_2$ from C^{14}OOH-labeled methionine, both ATP and Mg^{++} are essential. 0.01 *M* NaCN markedly inhibits decarboxylation; putrescine is not required. Compound II has been partially purified by chromatography, but has not been separated from compound I.

(3) Either compound I or adenosylmethionine,[5] in the presence of putrescine and the enzyme, forms spermidine in the absence of ATP or methionine (Table I). The remainder of the molecule would be expected to form thiomethyladenosine[6]; some preliminary evidence for a product of this type has been obtained.

Experiments with intact *E. coli* demonstrate that the synthesis of spermidine represents an important pathway for the metabolism of methionine. A three-carbon transfer is involved, comparable to the methyl-transfer of Cantoni. Further work is in progress on the purification of the respective enzymes and products, and on the role of other substrates as three-carbon donors and acceptors.

(5) S-Adenosyl-L-methionine was prepared according to the method of Cantoni (ref. 4), using ATP, L-methionine, and a rabbit liver enzyme.

(6) F. Schlenk and R. L. Smith, *J. Biol. Chem.*, **204**, 27 (1953).

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
NATIONAL INSTITUTES OF HEALTH — HERBERT TABOR
PUBLIC HEALTH SERVICE — SANFORD M. ROSENTHAL
U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
BETHESDA, MARYLAND — CELIA W. TABOR

RECEIVED MAY 1, 1957

THE CRYSTAL STRUCTURE OF SODIUM PEROXIDE

Sir:

From single-crystal X-ray diffraction work on sodium peroxide, a unit cell has been deduced which indexes the powder pattern more satisfactorily than does the unit cell reported in the literature.[1] A single crystal of Na_2O_2 was found among the fragments from a cooled melt of high purity Na_2O_2 contained in a crystalline MgO crucible. From the Laue patterns taken it can be shown that sodium peroxide is hexagonal, belonging to Laue group 6/mmm. Single crystal rotation patterns and powder patterns taken with Cu Kα X-radiation yield the repeat distances $a = 6.22 \pm 0.01$ Å. and $c = 4.47 \pm 0.01$ Å. Interplanar spacings calculated from these dimensions agree well with those observed on a powder pattern taken with a camera of 114.6 mm. radius.

Since no systematic absences are found in the reflections, the space groups P622, P6mm, P$\bar{6}$2m, P$\bar{6}$m2 and P6/mmm remain as possibilities, from those having Laue symmetry 6/mmm. Density measurements on Na_2O_2(2.2 to 2.8 g./cc.) favor a unit cell containing three formula units (Na_2O_2), which gives a calculated density of 2.60 g./cc. Spatial considerations favor only the structure (of

(1) R. L. Prange, *Z. Krist.*, **A**, 197 (1938).

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symmetry P$\bar{6}$2m) with the following approximate positions: Oxygen: 0,0,p; 0,0, $-p$; $^1/_3$, $^2/_3$,q; $^2/_3$, $^1/_3$,q; $^2/_3$,$^1/_3$,$-q$; Sodium: r,0,$^1/_2$; 0,r,$^1/_2$; $-r$,$-r$, $^1/_2$; s,0,0; 0,s,0; $-s$,$-s$, 0; where p = 0.167, q = 0.333, r = 0.724, s = 0.366. Intensities calculated from these parameters are consistent with estimated powder and rotation intensities.

This structure has been deduced independently by Klemm and Foppl.[2]

In this structure, the peroxide ions lie parallel to the c-direction, one at the corner and two within the unit cell. Each peroxide ion is in contact with nine sodium ions, three about the middle and three about each end. A sodium ion of 0.98 Å. radius, and a peroxide ion regarded as a cylinder of radius 1.29 Å. and length 1.49 Å. with caps of radius 1.29 Å. are consistent with this structure and with other crystallographic data.[3,4]

There appears to be no direct correlation between this hexagonal unit cell and the tetragonal unit cell reported by Feher[1] with dimensions a = 6.65 Å., c = 9.91 Å., and Z = 8. The fact that the ASTM Index lists for Na_2O_2 at least 15 powder lines (of the 29 listed) either not observed or of significantly greater intensity than observed for pure Na_2O_2 is readily explained as due to the presence of impurities, principally NaOH, in the material which gave the ASTM pattern.

We wish to acknowledge the support of a du Pont Summer Fellowship (R.L.T.) and of funds from the Wisconsin Alumni Research Foundation in this work.

(2) W. Klemm, private communication, 1957.
(3) S. C. Abrahams and J. Kalnajs, *Acta Cryst.*, **7**, 838 (1954).
(4) T. Moeller, "Inorganic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1952, p. 140.

DEPARTMENT OF CHEMISTRY
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RECEIVED APRIL 22, 1957

ACETOLACTATE, AN EARLY INTERMEDIATE IN VALINE BIOSYNTHESIS[1]

Sir:

Strassman, *et al.*,[2,3] and Adelberg[4] have proposed schemes for the conversion of pyruvate to L-valine and of α-ketobutyrate to L-isoleucine. Each scheme involved a condensation of acetaldehyde and the appropriate keto acid followed by a pinacol rearrangement to account for the distribution of C^{14} in tracer studies. As pointed out by Adelberg,[4] the first step in L-valine biosynthesis might be a ketol (as first proposed by Strassman, *et al.*[2]) or an aldol condensation, since either reaction would be consistent with the data. Evidence that the initial step is acetolactate formation (ketol condensation) is presented here.

A valineless mutant of *Escherichia coli*, strain M4862,[5] accumulates α-acetolactic acid when grown in media supplemented with limiting amounts of L-valine. Extracts prepared by sonic oscillation of cells of this mutant, harvested when acetolactate accumulation was marked, were observed to produce at least ten times as much α-acetolactate from pyruvate as did an extract of the parent *E. coli* strain W (Table I, Expt. 1). The formation of acetolactate was inhibited by L-valine.

A similar valine sensitive system was also formed by a wild type *Aerobacter aerogenes*, strain 1033, when grown in minimal medium containing L-histidine as the sole carbon source (chosen so as to assure absence of the classical carboligase[6] system). The same strain grown in nutrient broth with 1% glucose exhibits virtually no carboligase activity at pH 8 but is extremely active when tested at pH 6 (Table I, Expt. 2). L-Valine does not inhibit this enzyme.

TABLE I

ACETOLACTATE FORMATION BY BACTERIAL EXTRACTS

Expt.	Extract	Moles/10 min. Without L-valine Acetoin	Without L-valine Acetolactate	With L-valine Acetoin	With L-valine Acetolactate
1	*E. coli* Strain W pH 8.0	0.04	0.14	..	..
	E. coli Strain M4862 pH 8.0	.05	1.74	0.01	0.28
2	*A. aerogenes* 1033 pH 8.0	<0.01	<0.01	<0.01	<0.01
	(Broth grown) pH 6.0	1.47	<0.01	1.52	<0.01
	A. aerogenes 1033 pH 8.0	<0.01	.06	<0.01	<0.01
	(Histidine grown) pH 6.0	<0.01	<0.01	<0.01	<0.01

Assay system contained 10^{-2} M pyruvate, 20 μg. cocarboxylase, 2×10^{-3} M Mg^{++} and cell-free extract equivalent to 25 mg. wet weight of cells in one ml. 0.1 M phosphate buffer. Ten minutes incubation at 37° in air. Reaction stopped with $Zn(OH)_2$. Acetoin and acetolactate determined by method of Westerfeld[7] before and after decarboxylation[6] of β-ketoacids with 1.8 N H_2SO_4. In a separate experiment the acetolactate was isolated and converted to the bis-phenylhydrazone of diacetyl. The melting point was 258–259° (uncorrected) and there was no depression upon mixing with the same derivative prepared from synthetic α-acetolactic acid.

If acetolactate is an intermediate in L-valine biosynthesis, the inhibition of its formation by L-valine could be the feedback loop by which L-valine controls its own biosynthesis.[8] That acetolactate is very likely on the pathway in question is indicated by the following observations: (1) acetolactate labeled in the β-methyl position was incorporated into L-valine and L-leucine of *E. coli* pro-

(1) Supported by Grant RG-4015 of the United States Public Health Service and by funds from the Eugene Higgins Trust.
(2) M. Strassman, A. J. Thomas and S. Weinhouse, THIS JOURNAL, **75**, 5135 (1953).
(3) M. Strassman, A. J. Thomas, L. A. Locke and S. Weinhouse, *ibid.*, **76**, 424 (1954).
(4) E. A. Adelberg, *ibid.*, **76**, 1251 (1954).
(5) H. E. Umbarger and E. A. Adelberg, *J. Biol. Chem.*, **192**, 85 (1951).
(6) E. Juni, *ibid.*, **195**, 715 (1952).
(7) W. W. Westerfeld, *J. Biol. Chem.*, **161**, 495 (1945).
(8) E. A. Adelberg and H. E. Umbarger, *ibid.*, **205**, 475 (1953).

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June 5, 1957

tein. (2) It was converted to an L-valine precursor, α,β-dihydroxyisovaleric acid, by an appropriately blocked mutant[5] in the presence of L-valine (which blocks the accumulation of this precursor if glucose or pyruvate only are supplied). (3) Like other 5-carbon precursors of L-valine, it inhibited the growth of *E. coli* strain K-12 but not of valine-resistant mutants and (4) the inhibition was non-competitively reversed by L-isoleucine. Further studies on the importance of this enzyme system in biosynthesis are in progress.

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RECEIVED APRIL 24, 1957

BOOK REVIEWS

Chemistry of Carbon Compounds. Volume III, Part B. Aromatic Compounds. Edited by E. H. RODD, D.Sc., F.C.G.I., F.R.I.C., D. Van Nostrand Company, Inc., 126 Alexander Street, Princeton, New Jersey. 1956. xx + pp. 687–1670. 16.5 × 23 cm. Price, $25.00.

This volume continues the excellent treatise on organic chemistry which began appearing in 1951, and which seems destined to be the standard reference on the subject for the next decade or two.

It completes the treatment of aromatic compounds begun in Volume IIIA and is largely devoted to polyfunctional benzene derivatives (some of which were treated in Volume IIIA) and polycyclic aromatic substances. A major share of the preparation of this volume has fallen to W. J. Hickinbottom who has prepared six of the twelve chapters. Other contributors are Z. E. Jolles, R. F. Garwood, M. F. Ansell, S. H. Harper, G. L. Buchanan, R. A. Raphael, E. H. Rodd, J. van Alphen, S. Coffey, G. M. Badger and J. W. Cook. It is highly recommended.

DEPARTMENT OF CHEMISTRY
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MARSHALL GATES

Perspectives in Organic Chemistry. A volume dedicated to Sir Robert Robinson, prepared by friends, colleagues and former pupils under the editorship of SIR ALEXANDER TODD. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1956. x + 527 pp. 16 x 23.5 cm. Price, $7.50.

Sir Robert Robinson has been one of the giants of the art and science of organic chemistry, and it is altogether fitting that a distinguished group of leaders in the practice of this art and science have been banded together under the leadership of Sir Alexander Todd to honor Sir Robert on his 70th birthday by the publication of this series of essays.

One of the most pleasant characteristics of the book is the frankly speculative nature of some of the chapters. Others are masterful syntheses of the state of knowledge in particular fields. These characteristics seem peculiarly appropriate in a book dedicated to Robinson, who has always been at his best and most forceful when advancing inspired speculation and when assembling and interpreting the widely divergent and often conflicting evidence applicable to problems falling within his interest. Likewise, the very breadth of the fields covered reflect Robinson's own catholic tastes.

Chapters have been contributed by Linus Pauling, Paul D. Bartlett, Wilson Baker, D. H. R. Barton, V. Prelog, A. J. Birch, R. B. Woodward, Karl Ziegler, E. L. Hirst, Sir Alexander Todd, L. Ruzicka, C. W. Shoppee, E. Schlittler, J. W. Cornforth, Karl Folkers, James Walker, Holger Erdtman and A. Butenandt.

The book is stimulating and entertaining.

DEPARTMENT OF CHEMISTRY
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MARSHALL GATES

Photoconductivity Conference. Held at Atlantic City November 4–6, 1954. Editorial Committee: R. G. BRECKENRIDGE, Chairman, B. R. RUSSELL and the late E. E. HAHN. Sponsored by University of Pennsylvania, Radio Corporation of America, Office of Naval Research. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 1956. xiii + 653 pp. 16 × 23 cm. Price, $13.50.

This large volume is a compilation of thirty papers which were presented at a conference in Atlantic City a little more than two years ago. As stated in the forward, "The purpose of this conference was to advance the science of photoconductivity through plenary discussion among the leading workers in the field. . . . Sensing keenly a gap in the literature, the sponsors considered it particularly desirable to publish the papers presented, together with pertinent discussions, as a comprehensive treatise on photoconductivity." There can be little doubt that the papers in this book span the science of photoconductivity no matter what definition of this field one chooses to use, and that there is at present no other source which can give one such a complete view of all of the avenues of research leading to an understanding of this complex phenomenon. However, it would be nearly miraculous if any collection of separately conceived papers in a new and controversial field could be arranged in such a manner as to give the reader a systematic exposition of all of the facts and principles involved, *i.e.*, a treatise. This is not the sort of book one starts at the front cover and finishes at the back cover. Any worker in this field will find some papers of immediate interest, other papers useful in gaining perspective for his own field, and still others of rather negligible interest. In many cases, the table of contents is not a sufficiently reliable guide to the selection of those papers in which one is most interested. Fortunately, almost all of the papers are concluded with brief summary paragraphs, and many of them have introductory paragraphs which are nearly abstracts.

The book has been divided into five sections: I. Phenomenological Theory of Photoconductivity (2 papers); II. Photon Absorption Process (6 papers); III. Electron Processes (6 papers); IV. Photoconducting Materials (7 papers); and V. Current Topics (9 papers). The first paper in Section I, by Rose, comes about as close as anything in the book to being a general introduction to photoconductive phenomena, and also gives sufficient warning that the subject is one of great complexity. The second paper in this section, by Petritz, is considerably more specialized, treating signal-to-noise problems in the use of photoconductors as signal detectors. The second section is the domain of the solid-state theoretical physicist, being an account of the quantum-mechanics of the interaction of photons with semiconductors and insulators and their imperfections (including phonons). The first article, by Herring, is fairly readable for the non-theoretician and gives one at least a feeling for theories of centers. Section III is largely concerned with the application of transistor physics to photoconduction and is of primary interest to the experimentalist. There does not appear to be much of a

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as both sections deal with the properties of particular photoconductive materials. Here one can perhaps better distinguish between groups of materials: the elemental semiconductors, germanium and silicon; the III-V compounds; lead sulfide, selenide and telluride; and ionic compounds such as zinc oxide. The degree to which the photoconductive phenomena can be discussed in terms of a detailed physical model is, not surprisingly, in direct proportion to the state of advancement of semiconductor technology for the material under discussion. At one end of the scale one finds the finely detailed study of minority carrier trapping in silicon by Haynes and Hornbeck and at the other the necessarily more speculative interpretation of experiments on zinc oxide by Mollwo and by Miller. In most of the papers, photoconductivity is treated as a bulk process, however for thin-film detectors of the lead sulfide group, and for sintered powders of zinc oxide it is pointed out that the important processes are localized at the inter-crystallite surfaces.

The art of actually making a useful photoconductor for a particular purpose is really never explicitly discussed, but this is probably a subject for another book.

BELL TELEPHONE LABORATORIES
MURRAY HILL, N. J. A. R. HUTSON

Technique of Organic Chemistry. Volume III. Second Completely Revised and Augmented Edition. Part I. Separation and Purification. Editor, ARNOLD WEISSBERGER, Research Laboratories, Eastman Kodak Co., Rochester, New York. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1956. ix + 873 pp. 16.5 x 23.5 cm. Price, $17.50.

The former Volume III of this series has been divided into two parts in order to permit addition of new chapters and more intensive treatment. Part I concerns Separation and Purification Methods, and Part II, which will appear later, deals with Laboratory Engineering techniques. Chapter I of the present book concerns Diffusion Methods. Four topics are included, three of them new. A. Letcher Jones describes the techniques of Thermal Diffusion of Organic Liquids; Karl Kammermeyer, Barrier Separations; R. Eliot Stauffer, Dialysis and Electrodialysis; and E. MacWilliam, Zone Electrophoresis. Chapter II is an expanded treatment of Laboratory Extraction and Countercurrent Distribution by Lyman C. Craig and David Craig. A new part (61 pp.) has been added to this topic by Edward G. Scheibel who discusses Liquid–Liquid Extraction for Increased Quantities. Chapter III, Crystallization and Recrystallization by R. Stuart Tipson has been expanded from 122 to 167 pp. Two new authors, C. M. Ambler and F. W. Keith, Jr., have revised and expanded Chapter IV on Centrifuging. The treatment of Filtration (Chapter V) also has been expanded by A. B. Cummins and F. B. Hutto, Jr. The last chapter (VI) concerning Solvent Removal, Evaporation and Drying by G. Broughton has been revised and increased from 30 pp. to 52 pp.

This second edition brings up-to-date the information, data and references on these useful techniques. The book is especially valuable for the excellent coverage of the literature by each of the authors. The revision has been well done and well edited. The discussions are good and the diagrams and illustrations are excellent. A good index to this volume is provided followed by Cumulative indices to Volumes I through IX, both Author and Subject. Although the material is primarily slanted to Organic Chemistry, the techniques of Separation and Purification and the discussions will be useful to inorganic and physical chemists also. This is a valuable reference volume for all research chemists.

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA RALPH L. SHRINER

BOOKS RECEIVED

April 10, 1957–May 10, 1957

C. J. GORTER, edited by. "Progress in Low Temperature Physics." Volume II. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1957. 480 pp. $10.75.

E. A. GUGGENHEIM. "Thermodynamics. An Advanced Treatment for Chemists and Physicists." Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1957. 476 pp. $9.75.

H. P. KAUFMANN. "Medicaments de Synthese." Masson et Cie, Editeurs, 120, Boulevard Saint-Germain, Paris VI^e, France. 1957. 853 pp. 11.500 Fr.

A. I. M. KEULEMANS. "Gas Chromatography." Reinhold Publishing Corporation, 430 Park Avenue, New York 22, N. Y. 1957. 217 pp. $7.50.

EDGAR LEDERER AND MICHAEL LEDERER. "Chromatography. A Review of Principles and Applications." Second, Completely Revised and Enlarged Edition. D. Van Nostrand Company, Inc., 120 Alexander Street, Princeton, New Jersey. 1957. 711 pp. $12.75.

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Mechanism Studies of the Fischer–Tropsch Synthesis. The Addition of Radioactive Methanol, Carbon Dioxide and Gaseous Formaldehyde

BY W. KEITH HALL, R. J. KOKES AND P. H. EMMETT

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When a gas mixture containing 1.4% radioactive carbon dioxide in a 50:50 H_2:CO synthesis gas is passed over an iron catalyst at 240°, very little carbon dioxide is converted to carbon monoxide or to hydrocarbons. Apparently the water gas conversion reaction under these conditions is very slow. Methanol can act as a chain initiator in hydrocarbon synthesis and to a slight extent can build into the chain to form higher hydrocarbons. It also forms considerable carbon dioxide by direct decomposition on the catalyst. Similar results were obtained with gaseous formaldehyde, except that it decomposes rapidly on the iron catalyst in the presence of synthesis gas to form carbon monoxide and carbon dioxide having activities almost as great as for complete equilibration between these two gases and the formaldehyde. Hence, in this instance, the slope of the activity *vs.* carbon number plot for the hydrocarbons formed can be accounted for by the radioactivity of the carbon monoxide. Apparently neither formaldehyde nor methanol forms on adsorption the type of C_1 complex identical to that occurring in actual synthesis.

Tracer studies reported in two previous communications[1,2] from this Laboratory have shown that when small amounts of radioactive primary alcohols are added to a 1:1 carbon monoxide–hydrogen synthesis gas mixture which is being passed over a reduced iron catalyst at about 235°, the hydrocarbon synthesis products of carbon number greater than that of the added alcohol have an approximately constant radioactivity per cc. This has been interpreted as indicating that the complex formed by the adsorption of the alcohol on the iron catalyst is capable of acting as an intermediate (a chain initiator) in the synthesis of higher hydrocarbons.

Of all the primary alcohols studied only radioactive methanol yielded hydrocarbon products, the radioactivity of which per cc. increased appreciably with increasing carbon number. Apparently the complex formed on addition of methanol not only initiates chains but also enters into chain building. With a view to investigating further the behavior of radioactive complexes containing a single carbon atom, the methanol experiments have now been extended into the higher pressure range of commercial synthesis. These are reported in the present paper together with experiments at one atmosphere pressure in which radioactive formaldehyde and radioactive carbon dioxide were used as tracers. Gaseous formaldehyde was used with a view to testing it as a possible source of a single carbon complex both for chain building and chain initiation.

Several other facts, pertinent to the discussion of the present paper, had also been established in the earlier work. Pyrolysis of the propane formed in experiments,[1] where methyl-labeled and methylene-labeled ethanol were added to the synthesis gas, showed that carbon atoms attach themselves preferentially to the methylene carbon atom of the alcohol complex. Further, all results obtained were in agreement with the pattern of build-up of hydrocarbon on the surface of the catalyst suggested by Weller and Friedel,[3] by Anderson, Friedel and Storch,[4] and by Weitkamp, *et al.*[5] In addition, it was possible to suggest[2] a modification of one of these reaction schemes[4] to allow for the enhanced reactivity of the carbon attached to the hydroxyl group; the result was a somewhat more descriptive picture of these surface processes than had previously been available.

(1) J. T. Kummer, H. H. Podgurski, W. B. Spencer and P. H. Emmett, THIS JOURNAL, **73**, 564 (1951).

(2) J. T. Kummer and P. H. Emmett, *ibid.*, **75**, 5177 (1953).

(3) S. Weller and R. A. Friedel, *J. Chem. Phys.*, **17**, 801 (1949); **18**, 157 (1950).

(4) R. B. Anderson, R. A. Friedel and H. H. Storch, *ibid.*, **19**, 313 (1951)

(5) A. W. Weitkamp, H. S. Seelig, N. J. Bowman and W. E. Cady, [illegible]

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The experiments with carbon dioxide were designed to ascertain whether or not the slope of the curves representing plots of radioactivity of the products as a function of carbon number obtained in the methanol and formaldehyde tracer runs could be explained as due to the incorporation of the moderately active carbon dioxide obtained as a reaction product.

Experimental

Most of the techniques involved in the radioactive analysis of the products had previously been standardized.[1,2] A description of these will not be repeated here. A few remarks are in order, however, relative to the analysis of the carbon monoxide and carbon dioxide in the tail gas for radioactivity. For measurements on the carbon monoxide, the tail gas was passed through a liquid nitrogen trap and over copper oxide heated to 360°. The exit gas containing water vapor, CH_4 and CO_2 was passed into a second trap where the CO_2 and water vapor were condensed and the methane was removed by pumping. The carbon dioxide was then evaporated from the trap at −78° and counted. Carbon dioxide in the tail gas was collected by passing a portion of the tail gas through barium hydroxide for about five minutes. Such pairs of samples were obtained from two to three times during a run.

In the methanol run, it was thought to be important to establish whether or not the activity of the olefin and paraffin fractions behaved similarly as a function of carbon number. Since the activity of the gaseous olefins and paraffins alone could not decide this point, an attempt was made to extend these measurements to the liquid product. This entailed a separation of the olefins and paraffins. To this end the liquids were passed through a chromatographic column packed with Davison code 923 silica gel (inactive toward the polymerization of olefins); ethanol was used as the eluting developer. The oil product was thus cut into 13 approximately equal cuts of about 2 cc. each. Refractive index measurements showed a sharp rise after the fourth cut and another after the twelfth cut. In the region between these points, there was a gradual decrease in refractive index with an increase in cut number indicating a small fractionation according to molecular weight. The thirteenth cut contained the entire colored band and was presumed to contain most of the oxygenated product obtained in synthesis. Beyond cut 13, the refractive index fell rapidly to that of the eluting ethanol. On the basis of these results, it could be inferred that the liquid had been at least partially fractionated into olefins and paraffins.

Since preliminary examination of the infrared spectrum of these fractions indicated that a major portion of the olefins present consisted of α-olefins, a group type analysis was set up for this species. The results of this analysis are contained in Table I, where the concentration of the $-HC{=}CH_2$ radical is expressed in moles per liter of liquid.

TABLE I

Fraction no.	Concn. α-olefin, moles/l. of liq.	Fraction no.	Concn. α-olefin, moles/l. of liq.
1	0.31	8	3.3
2	.23	9	3.4
3	.18	10	3.5
4	.16	11	3.7
5	1.9	12	3.5
6	2.8	13	1.1
7	3.1		

These data indicated that at least a semi-quantitative separation of olefins and paraffins occurred between cuts four and five. None of the fractions was found to be completely free of olefin, but since the concentration of α-olefin in fraction 10 was nearly 20 times that of fraction 3, an upper limit of about 5% α-olefin could be put on the latter fraction. The other question of interest is the purity of the olefin fractions with respect to paraffins; this may be defined as C/C_0, where C is the observed olefin concentration and C_0 is the concentration in moles per liter of the pure olefin of the same molecular weight. A minimum average molecular weight could be determined from the data, if it turned out to be greater than octane, the uncertainty existing because it was not possible to distil a small residual portion of the material in high vacuum at room temperature. On this basis, the purity of the predominant α-olefin turns out to be 55%. The spectra, however, showed also the presence of both *cis*- and *trans*-olefins of the type $R_1CH{=}CHR_2$. There is some uncertainty in treating the spectral data for these species, because the 965 cm.$^{-1}$ band of the *trans*-olefin overlaps the 990 cm.$^{-1}$ band of the α-olefin. In fraction 10, however, it was possible to establish that these species amounted to a total of 2.4 ± 0.3 mole/liter. Making this correction leads to a purity value for the olefin in this cut of 92%. Cuts 3 and 10 were used for the analysis of the radioactivity of the liquid paraffins and olefins, respectively. It is apparent from the above that these cuts were 90+% pure paraffin and olefin, respectively.

The runs with the gaseous formaldehyde and the carbon dioxide additions were made in our one atmosphere all-glass reactor previously described;[1,2] the run in which the radioactive methanol was added to the synthesis at 100 p.s.i.g. was made in the bench scale reactors[6] of the catalyst testing laboratories of the U. S. Bureau of Mines, Bruceton, Pennsylvania.

In the glass reactor several thermocouples were buried in the catalyst bed. The reduced catalyst was brought into synthesis at about 200° the gradual addition of carbon monoxide to the gas stream so as not to locally overheat the catalyst. Then, the temperature was slowly increased until a contraction of from 20 to 35% was reached. When these steady state conditions were attained, traps were put on and the run commenced. After a period comparable to that to be used in the radioactive run, the products were collected for analysis, and the synthesis was continued with the radioactive additive in the gas stream. Similarly, after the collection of the radioactive products, another non-radioactive test run was made. In the run in the pressure reactor, a similar procedure was followed, except that the catalyst was put on stream using the Bureau's standard test procedure,[7] and the radioactive run was started in the fourth week of operation. In all instances, the presence of the radioactive additive in the synthesis gas appeared to have no large effect on the catalytic activity or on the product distribution. Therefore, the data collected in Table II are representative not only of the tracer runs but also the control runs.

The catalysts used in the individual runs are noted in Table II. All were reduced fused iron oxides. Catalyst number 955 contained 7.95% Al_2O_3 and number 614, 2.0% ZrO_2 and 0.64% Al_2O_3 in addition to Fe_3O_4. Catalyst D-3001 is the standard doubly promoted catalyst of the Bureau of Mines; it contains 0.6% SiO_2, 0.6% Cr_2O_3, 4.6% MgO and 0.6% K_2O; its properties and behavior have been extensively described elsewhere.[8-11] It should be noted that catalyst 955 was used in the earlier[2] methanol run, so that the carbon dioxide addition experiment reported herein pertains more directly to the earlier than to the present methanol experiment. Since, however, the behavior of the methanol in both experiments is qualitatively similar, this makes little difference.

One millicurie lots each of carbon dioxide (as $BaCO_3$) and formaldehyde (as a dilute aqueous solution) were secured from the Atomic Energy Commission's laboratory at Oak Ridge, and two millicuries of methanol were obtained from Tracerlab, Inc., Boston.

The methanol was appropriately diluted with non-radioactive methanol to a volume of 35 cc. The carbon dioxide was liberated from the $BaCO_3$ with concentrated H_2SO_4 in a vacuum system and subsequently diluted to about 7.5 liters. This was transferred into a small (approximately 12 l.) steel cylinder where it was blended with

(6) R. B. Anderson, A. Krieg, B. Seligman and W. E. O'Neill, *Ind. Eng. Chem.*, **39**, 1548 (1947).

(7) R. B. Anderson, B. Seligman, J. F. Shultz, R. E. Kelly and M. A. Elliott, *ibid.*, **44**, 391 (1952).

(8) W. K. Hall, W. H. Tarn and R. B. Anderson, THIS JOURNAL, **72**, 5436 (1950).

(9) W. K. Hall, W. H. Tarn and R. B. Anderson, *J. Phys. Chem.*, **56**, 688 (1952).

(10) R. B. Anderson, L. J. E. Hofer, E. M. Cohn and B. Seligman, THIS JOURNAL, **73**, 944 (1951).

(11) W. K. Hall, W. H. Tarn, L. J. E. Hofer and R. B. Anderson, *ibid.*, **75**, 1442 (1953).

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TABLE II

SYNTHESIS VARIABLES AND PRODUCT DISTRIBUTION OF TRACER RUNS[a]

Radioactive additive	1.0% CH_3OH	1.4% HCHO	1.3% CO_2
Catalyst no.	D-3001	614	955
Space velocity[b]	100	244	228
Av. operating temp., °C.	237	227	230
Av. contraction, %	62	25	30
Duration of expt., hr.	73	25.4	22.5
Pressure, atm.	7.8	1	1
Total gas production, cc. gas, STP	51,000	4400	11,750[c]
Specific radioactivity of additive, c./min./cc.	6950	5010	9450
Liquid products, g.		14.8	
CO_2, g.		34.2	

PRODUCT DISTRIBUTION, % OF GAS

CH_4	49.9	25.3	17.6
C_2H_4	6.4	12.9	5.1
C_2H_6	15.8	19.9	27.8
C_3H_6	14.8	24.6	22.3
C_3H_8	4.2	5.0	12.5
C_4H_8	4.9	8.5	8.6
C_4H_{10}	1.8	1.5	3.0
C_5H_{10}	1.1	1.8	2.1
C_5H_{12}	0.5	0.4	1.0

[a] In all runs herein reported a 1:1 H_2:CO synthesis gas was used. [b] Space velocity is here defined as volume of entering gas per volume of catalyst space per hour; the catalyst volume was 100 cc. in the radioactive methanol addition experiment and 50 cc. in all others. [c] Contains an estimated 15% CO_2; exact figures are not available.

enough carbon monoxide to bring the final pressure up to about 285 p.s.i. Under these conditions, the tank was found to contain 2.6% radioactive CO_2. This gas, after passing through a Dry Ice trap, was blended with a separate stream of pure dry hydrogen to obtain a 1:1 H_2:CO synthesis gas.

The radioactive formaldehyde was mixed with an appropriate amount of a concentrated (40%) solution of formaldehyde. From this, paraformaldehyde was prepared by vacuum distillation of the water from the solution. This polymer was thoroughly dried over anhydrous magnesium perchlorate in a vacuum desiccator. Production of the formaldehyde gas was carried out in a vacuum system, which prior to the actual synthesis was baked out with a torch under vacuum to remove adsorbed water from the glass. The gas was generated when the paraformaldehyde was heated to 120° *in vacuo* and was passed through a line heated to the same temperature followed by a five-stage trap, the top stages of which were kept at 120° and the bottom stages at −78°; it was then collected in a receiver at liquid nitrogen temperature. This procedure is similar to that used by Spence and Wild.[12] Further purification was achieved by several distillations. The over-all yield of purified formaldehyde was better than 80%. A stream of hydrogen was passed through the liquid formaldehyde at −78° where it picked up approximately 2.8% gaseous formaldehyde. This was blended with an equal amount of CO to yield about 1.4% formaldehyde in the 1:1 synthesis gas. The concentration of formaldehyde in the synthesis stream was continuously monitored with a thermal conductivity gage. In spite of all the precautions taken in drying the hydrogen, after two to three hours the clear formaldehyde would become a stiff gel. It was discovered, however, that this gel would maintain the vapor pressure of pure formaldehyde for periods up to 20 hours; at the end of this period the vapor pressure would fall suddenly. It was found, furthermore, that a good percentage of the original liquid could be regenerated by a simple distillation. For these reasons, the addition to the synthesis was interrupted after about 18 hours for a few minutes to heat up the gel and regenerate the formaldehyde.

In the methanol experiment, the liquid was injected into the top of the reactor under pressure by a small single-stroke pump run by a synchronous motor. This pump, which operated much like a hypodermic syringe, was developed by the Bureau of Mines engineers and was found capable of delivering as little as 1/4 cc. per hour, accurately and reproducibly, under pressure up to 300 p.s.i. Under the conditions of the present experiment, this amounted to 1% of the synthesis gas.

Results

(a) **Methanol.**—The data collected from the hydrocarbon products of the methanol run are plotted in Fig. 1, where they are compared to those obtained earlier at lower pressure by Kummer and Emmett.[2] In the earlier run, the olefins and paraffins were determined separately only on the gaseous products (C_2 to C_4); the liquid products were fractionated by distillation and the activities of the individual cuts, which contained both olefins and paraffins, were determined. These data fall on a straight line indicating the "build-in" of at least enough of the complex formed on the adsorption of methanol to account for the difference between the observed slope of 70 counts/min./cc./carbon number and the activity increment due to the radioactivity of the carbon monoxide (32 counts/min./cc. in the exit gas). In the new runs, on catalyst D-300 under pressure, the data do not fall on a straight line, although the over-all trend indicates a similar "build-in" corresponding to about 38 counts/min./cc./carbon number, of which at most 23 counts/min./cc./carbon number may be attributed to the radioactivity contained in the carbon monoxide. These newer data were obtained with nearly pure fractions of olefins and paraffins; it should be noted that the olefin curve more or less parallels that of the paraffins, though it falls slightly

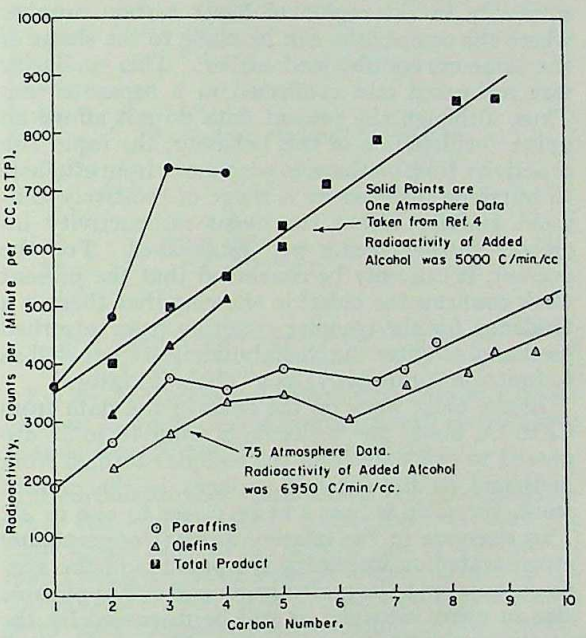

Fig. 1.—Radioactivity of hydrocarbons obtained in the experiment in which 1% radioactive methanol was added to the synthesis at 7.5 atmospheres. These data are compared to the earlier one atmosphere results of ref. 4.

(12) R. Spence and W. Wild, *J. Chem. Soc.*, 338 (1935).

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TABLE III

RADIOACTIVITY OF TAIL GAS AND OF THE METHANE OF SYNTHESIS RUNS (COUNTS/MIN./CC. (STP))

Radioactive additive	CO	CO_2	CH_4	CH_4/CO_2
Methanol, 1 atm.[a]	32	175	360	2.06
Methanol, 7.5 atm.[b]			186	
Sample no. 1	22	82		2.27
Sample no. 2	25	85		2.19
	Av. = 23.5 ± 1.5	Av. = 83.5 ± 1.5		
Formaldehyde, 1 atm.[c]				
Sample no. 1	150	128		1.73
Sample no. 2	129	126	221	1.75
Sample no. 3	135	142		1.55
	Av. = 138 ± 12	Av. = 132 ± 10		

[a] Taken from data of ref. 2; radioactivity of added alcohol was 5000 counts/min./cc. [b] Radioactivity of added alcohol was 6950 counts/min./cc [c] Radioactivity of added formaldehyde was 5010 counts/min./cc.

below it. Further, both curves show an amazing similarity in the region of lower carbon number where the comparison can be made to the shape of the same curves obtained earlier. This similarity was rechecked and confirmed in a separate run. Thus, although the present data do not afford an unique explanation of this behavior, the rapid rise in activity from methane to propane or from ethylene to butylene followed by a range of relatively constant activity before the molar radioactivity increases further seems well established. For the present, it can only be concluded that the present work confirms the older[2] in showing that there is a tendency for the complex resulting from adsorbed methanol to enter the chain building step as well as to function (principally) as a "chain initiator."

In the older work on the basis of the data from C_2 to C_3, about one molecule in from 10 to 15 appeared to originate from the complex formed from methanol on the catalyst surface; in the present work, the ratio is found to be closer to one in 35. This decrease in the relative amount of methanol incorporated on increasing the pressure of the synthesis appears to be perfectly general and applicable also to other alcohols; it will be discussed by the present authors in a paper to be published shortly.[13] It will suffice here to point out that it may be explained by the simple assumption that methanol must compete for adsorption sites with the complex formed from carbon monoxide and hydrogen, and that the fraction of the adsorbed layer consisting of radioactive methanol is smaller at 7.5 atmospheres than at one atmosphere pressure.

Further data of interest are collected in Table III. The activity of the carbon monoxide is low in both methanol runs, indicating that the amount of methanol which decomposes to carbon monoxide is a small but definite amount.

Had all the methanol entering the pressure reactor been decomposed at the entrance, the radioactivity of the emerging carbon monoxide would have been some six times higher (*i.e.*, 138 counts/min./cc). In the present instance in which 1% methanol was added, the activity is about $^2/_3$ that found in the earlier one atmosphere run in which 1.5% methanol was added.

The presence of the high activity carbon dioxide observed earlier[2] was confirmed by the present work; as before, the activity indicates that at least part of the radioactive CO_2 was not formed *via* CO. It is of interest to note that the radioactivity observed in the pressure run (83.5 c./min./cc.) has decreased with an increase in total pressure in almost exactly the same ratio as the fractional incorporation into hydrocarbons, suggesting that the reaction responsible is one involving a common intermediate on the catalyst surface.

(b) **Carbon Dioxide.**—The general trend of increasing radioactivity per cc. of hydrocarbon as a function of increase in carbon number observed in the methanol runs, might conceivably be attributed to the radioactive carbon dioxide formed in these runs. Thus, for example, the slope of 70 counts/minute/cc/carbon number observed by Kummer and Emmett[2] could easily be accounted for if a sufficient amount of the radioactive carbon dioxide (175 counts/min./cc.) were to enter into the chain building reaction. The present data appear to rule out this possibility.

In this experiment, a blend of 97.4% non-radioactive CO +2.6% radioactive CO_2 (9,450 counts/min./cc. of CO_2) was metered into the reactor along with an equal amount of hydrogen. The data collected are listed in Table IV. Since background on our tube ran from 40 to 46 counts/min., and since many observations (obtained by subtracting the background reading from the total reading) were only a fraction of this, the data obtained are admittedly crude; they are, however, adequate to show that the amount of carbon dioxide incorporated into the product (corresponding to about 2 atoms of carbon incorporated per 1000 carbon atoms) is much too small to account for the increasing activity as a function of carbon number found in the methanol runs. The activity of the carbon monoxide in the tail gas is found to be about 14 counts per minute per cc. This level of activity is high enough within our experimental error (probably ± 6 counts/min./cc.) to account for all of the activity found in the products. Thus the major portion of the entering carbon dioxide passes through the bed unchanged, but diluted with that formed in synthesis.

The low but detectable activity observed in the carbon monoxide could arise from either an exchange of an oxygen atom with the carbon monoxide, *viz.*

$$C^{14}O_2 + CO \rightleftharpoons CO_2 + C^{14}O \quad (1)$$

or by a reversal of the water gas shift reaction on the catalyst surface

$$C^{14}O_2 + H_2 \rightleftharpoons C^{14}O + H_2O \quad (2)$$

(13) R. J. Kokes, W. K. Hall and P. H. Emmett, THIS JOURNAL, 79, 2989 (1957).

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TABLE IV

RADIOACTIVITY OF TAIL GAS AND HYDROCARBONS FROM CARBON DIOXIDE EXPERIMENT[a] (COUNTS/MIN./CC. (STP))

Compound		Activity	Activity/C atom
Carbon monoxide, sample no. 1		13	13
Carbon monoxide, sample no. 2		14	14
Carbon dioxide, sample no. 1		532[b]	532[b]
Carbon dioxide, sample no. 2		1760[c]	1760[c]
Methane		22	22
Ethane		33	17
Ethylene		13	7
Propane		81	27
Propylene		21	7
Butanes		64	16
Butylenes		54	14
Liquid of av. carbon no.	5.00	65	13
	5.38	103	19
	5.73	120	21
	6.69	76	12
	7.16	118	16
	8.28	120	15
Av. of hydrocarbons = 16			

[a] Radioactivity of the 1.3% carbon dioxide in synthesis gas was 9450 counts/min./cc. STP of gas. [b] Sample taken at ~38% contraction. [c] Sample taken at about 32% contraction.

Had complete radioactive equilibrium been reached by either of these reactions, the observed level of activity in the exit carbon monoxide would have been raised to 246 counts/min./cc. It is particularly interesting to note that reaction 2 is shown by these data to be quite sluggish over a Fischer–Tropsch synthesis catalyst operating under the conditions used. It is equally true, however, that these results do not preclude the possibility that such a reversal may be less sluggish with the higher contractions and the somewhat higher temperatures usually employed in a commercial synthesis.

(c) **Formaldehyde.**—As noted in an earlier communication,[1] if it were possible to add to the synthesis a radioactive organic compound which on adsorption became identical with the C_1 complex formed from carbon monoxide and hydrogen on the surface and responsible for building into the hydrocarbon chains, the molar activity *vs.* carbon number curve would necessarily be a straight line passing through the origin (at zero carbon number). Since current theories[2,4,5] of the mechanism of the synthesis lead to the inference that this "chain-building" complex contains oxygen, the number of possibilities of radioactive additives is severely limited. It was for this reason that formaldehyde addition was studied.

The data obtained from the hydrocarbon product of the synthesis are plotted in Fig. 2. The solid line shows that a reasonably good linear relation exists between the molar radioactivity and the carbon number of the total product (our most accurate data). These data, like those for methanol, cannot conceivably be interpreted as being due to the formation of a single complex identical with that obtained from carbon monoxide and hydrogen. If such a complex were formed, the data would fall on a straight line passing through the origin. Since the left hand margin of Fig. 2 corresponds to

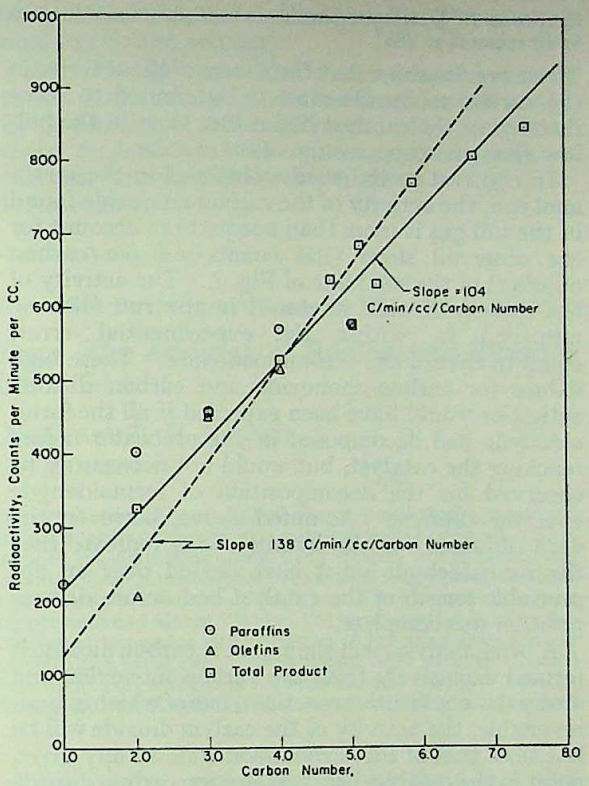

Fig. 2.—Radioactivity of hydrocarbons obtained in the experiment in which 1.4% radioactive gaseous formaldehyde was added to the synthesis at 1 atmosphere.

unit carbon number (rather than zero carbon number), the corresponding requirement is that the data would have to fall around one of a family of lines having the same slope as intercept, such as the dashed line shown. For the same reason, the data show that complete decomposition of the formaldehyde could not have taken place before an appreciable fraction of the bed length had been passed. Otherwise, all hydrocarbon activities would be the same per C atom as for CO, namely, 138 counts/min./cc. The data do not preclude but are actually consistent with the formation by the formaldehyde of a chain-initiating complex with or without a chain-building complex.

Data obtained for the pairs of carbon monoxide and carbon dioxide samples of the tail gases from the converter are shown in Table III. The average activity of 138 counts/min./cc. found for the carbon monoxide together with the observed activities for CO_2 and for the C_1—C_8 hydrocarbons show that the formaldehyde, in contrast to methanol, must have been nearly completely decomposed before the gases emerged from the reactor. (For complete decomposition outside the reactor, the activity of the carbon monoxide would have reached only 140 counts/min./cc.) In separate experiments, it was shown that

a. The expected amount of formaldehyde was delivered to the top of the reactor, undecomposed and unhydrogenated by the hydrogen carrying gas.

b. No appreciable decomposition of pure formaldehyde gas occurs in glass at temperatures up to 285° for periods of several hours up to 60 minutes.

c. Exchange between or decomposition of 27% formal-

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dehyde in 73% carbon monoxide is negligibly small in glass in 45 minutes at 285°.

These results show that the source of the activity in the carbon monoxide must be attributed to some reaction in the catalyst bed rather than in the hollow glass preheater section of the reactor.

In contrast to the results obtained in the methanol run, the activity of the carbon monoxide found in the tail gas is more than adequate to account for the observed slope (104 counts/min./cc./carbon number) of the solid line of Fig. 2. The activity of the carbon dioxide produced in the run (132 c./min./cc.) is, within the experimental error, equal to that of the carbon monoxide. These high values for carbon monoxide and carbon dioxide activities would have been expected if all the formaldehyde had decomposed in the preheater before reaching the catalyst, but would not necessarily be observed for the decomposition of formaldehyde over the catalyst. As noted above, however, the data obtained for the hydrocarbons indicate that the formaldehyde must have passed over an appreciable length of the catalyst bed before decomposition was complete.

A brief analysis will show that if carbon dioxide is formed exclusively from the carbon monoxide and always by consecutive reactions, one of which is nonreversible, the activity of the carbon dioxide will be less than that of the carbon monoxide at any given point in the catalyst bed. However, carbon dioxide *produced* in any increment of the catalyst bed will, of course, have the same molar activity as the carbon monoxide in the same increment.

If x is the distance along a catalyst bed, and l is the total bed length

$$A_{CO_2}(l) = \frac{\int_0^l A_{CO} \frac{d V_{CO_2}}{dx} dx}{V_{CO_2}(l)} \qquad (3a)$$

where A_{CO} is the activity of CO (counts/min./cc.) at point x in the bed, l is the length of the bed, $A_{CO_2}(l)$ is the activity of CO_2 in the tail gas and V_{CO_2} is the total amount of CO_2 present at x. Integration by parts yields

$$A_{CO_2}(l) = A_{CO}(l) - \frac{1}{V_{CO_2}(l)} \int_0^l V_{CO_2} \frac{d A_{CO}}{dx} dx \qquad (3b)$$

Thus, it is apparent that $A_{CO_2}(l)$ can approach $A_{CO}(l)$ only if the integral term in 3b is small compared with $A_{CO}(l)$. This could most reasonably be realized if the activity of the CO increases rapidly at first (and in this region $V_{CO_2}/V_{CO_2}(l)$ is very small) and rapidly attains its final value. This would mean that the integrand is essentially zero over most of the bed length. Thus, A_{CO} would have to reach its final value much faster than V_{CO_2} if the second term in eq. 3b is to be small.

The above analysis would require that the decomposition of formaldehyde to CO occurs before appreciable synthesis and concomitant production of CO_2 can take place. The data in Fig. 2 show that synthesis is occurring before the decomposition of formaldehyde is complete. Thus, it would be closer to the truth to assume that the production of radioactive CO from formaldehyde follows the same functional dependence on x as the formation of CO_2 from CO. In this case, according to eq. 3, the activity of the CO_2 would be only one-half as great at the exit as the activity of the carbon monoxide. Since the activity of the CO_2 in the exit gas is roughly the same as the activity of the CO, it appears that at least some of the CO_2 is formed *directly* from the adsorbed formaldehyde. Similar conclusions were reached regarding the CO_2 produced in methanol tracer experiments.

The calculations that are made on the basis of eq. 3a and 3b for the increase in the radioactivity of carbon dioxide with bed length are equally applicable to the consideration of the slope of the line in Fig. 2 for the activity of the hydrocarbon products as a function of carbon number. A nonreversible transformation of CO into hydrocarbons along the bed would, on the basis of the arguments given in connection with eq. 3a and 3b, result in the activity increment per added carbon in the hydrocarbon being always less than the activity of the CO. The exit values of 138 counts/min./cc. for the carbon monoxide and a slope of 104 counts/min./added carbon for the plot in Fig. 2 conform to expectation if the build-in step in forming the hydrocarbons is mostly from a complex formed from carbon monoxide but not directly from formaldehyde.

Discussion

A detailed evaluation of the present data in terms of an over-all synthesis picture will be deferred until data are presented relative to the incorporation of propionaldehyde and ethylene in experiments at one atmosphere[14] and ethanol in high pressure experiments.[13] It will suffice, therefore, to summarize here the firm conclusions that can be drawn from these data without reference to subsequent runs. The conclusions to which the present experiments lead may be summarized as follows.

(1) Carbon dioxide does not build into hydrocarbons appreciably during their synthesis from carbon monoxide and hydrogen over a singly promoted iron catalyst at one atmosphere pressure and 240°.

(2) The water–gas conversion reaction is extremely sluggish over a singly promoted iron catalyst at 240° at one atmosphere, as judged by the very small conversion of radioactive CO_2 to carbon monoxide.

(3) Methanol adsorbs on iron catalysts to form a complex capable of initiating hydrocarbon synthesis chains on the catalyst surface, though as a chain initiator it is only about $^1/_5$ as effective as ethanol; furthermore, its effectiveness decreases by a factor of two when the pressure is raised from one to 7.8 atm. This or a different complex formed by methanol builds into the hydrocarbon chain and also forms CO_2, as evidenced by the fact that the slope of the activity *vs.* carbon number curve and the absolute activity of the carbon dioxide are both too high to be accounted for by the radioactivity of the carbon monoxide.

(4) Formaldehyde appears to decompose almost completely into carbon monoxide and hydrogen, though a portion of the decomposition must be

(14) W. K. Hall, R. J. Kokes and P. H. Emmett, to be published.

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directly to CO_2. To a small but finite extent formaldehyde forms a complex capable of initiating hydrocarbon chains. The mechanism by which formaldehyde builds into the hydrocarbon chain involves either the carbon monoxide formed by decomposition or a second complex. The carbon monoxide at the exit has ample radioactivity (138 counts/min./cc.) to account for the observed slope of the activity *vs.* carbon number plot (104 counts/min./cc/carbon number).

Acknowledgment.—The authors are indebted to Dr. R. B. Anderson and his capable staff at the U. S. Bureau of Mines, Bruceton, Pa., for use of their facilities and for assistance rendered in carrying out the pressure experiments.

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Fischer–Tropsch Synthesis Mechanism Studies. The Addition of Radioactive Ethanol to the Synthesis Gas

BY R. J. KOKES, W. KEITH HALL AND P. H. EMMETT

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The incorporation of radioactive ethanol in the Fischer–Tropsch synthesis has been studied over reduced singly promoted iron catalysts, a reduced doubly promoted iron catalyst, a nitrided doubly promoted iron catalyst and a reduced cobalt catalyst. Most of the experiments were carried out with the synthesis gas containing about 1.5% ethanol, but in some runs the concentration was as low as 0.04%. At one atmosphere the incorporation is greatest for the reduced singly promoted iron catalyst, less for the reduced doubly promoted iron catalyst, and least by far for the cobalt catalyst. The incorporation over the reduced doubly promoted iron catalyst falls off with increasing pressure and also at 7.5 atm. the incorporation is lower for the nitrided catalyst than it is for the reduced catalyst. The average of the molar radioactivities of the alcohols produced over the nitrided catalyst is the same as for the hydrocarbons from the same run. Experiments with varying ethanol concentrations indicate that the ethanol adsorption is medium strong at concentrations between 1.5 and 0.04%. The results are discussed on the basis of Langmuir adsorption and stepwise growth of hydrocarbon chains involving an adsorbed alcohol as the principal intermediate.

It has been shown that when small amounts of C^{14}-labeled primary alcohols containing 2, 3 or 4 carbon atoms are added to a 1:1 H_2:CO synthesis gas at one atmosphere and passed over a singly promoted iron catalyst at about 235°, the resulting Fischer–Tropsch hydrocarbon products (at least up to C_{10}) have an approximately constant radioactivity per mole.[1,2,3] Thus it appears that these alcohols are acting as chain initiators. In the experiments involving ethanol, moreover, it has been shown[2] that the chain initiation occurred preferentially (90% of the time) at the methylene carbon atom. These results, together with the fact that $^1/_2$ to $^1/_2$ of the synthesis products originate from the added alcohols, which constitute only 1.5% by volume of the synthesis gas, clearly suggest that the complex formed from the adsorbed alcohol may well be an intermediate in the normal synthesis.

According to the picture put forward by Storch, Golumbic and Anderson,[3] the formation of hydrocarbons from CO and H_2 occurs in a stepwise fashion. Various schemes have been advanced on the basis of such a mechanism, several of which predict both the isomer and carbon number distributions in the products.[4–6] The best agreement with the experimental data is obtained using scheme A of ref. 5. This scheme is similar but not identical to the one which would be obtained if the single carbon chain building unit, as well as the chain initiation units, were adsorbed alcohols with a carbon–hydrogen bond of the carbinol carbon atom replaced by a carbon–metal bond.[1–3,7]

Tracer experiments[1,2] over singly promoted iron catalysts at one atmosphere are, by and large, consistent with this picture. Perhaps its most significant shortcoming is the suggestion that the single carbon chain building complex is an adsorbed alcohol. This, of course, suggests that the C_1 complex should be derivable from either adsorbed methanol or adsorbed formaldehyde (enol form). The present authors[8] have shown that neither of these acts as the primary build-in unit although they both function as chain initiators. In spite of the difficulty, the over-all success of the mechanism justifies additional tracer experiments to further test its applicability.

The alcohol tracer experiments reported previously[1,2,8] with the exception of one of the methanol experiments,[8] have all been carried out at atmospheric pressure on reduced, singly promoted, iron catalysts. Of these experiments, those in which primary alcohols having 2, 3 or 4 carbon atoms were used yielded results which lend themselves most easily to interpretation in terms of a simple chain building scheme. In order to test more completely this simple picture, some additional ethanol tracer experiments were made. These were carried out over a reduced, doubly promoted, iron catalyst at 1, 7.5 and 21 atmospheres; over a nitrided, doubly promoted, iron catalyst at 7.5 atmospheres; and over a cobalt catalyst at 1 atmosphere. The synthesis gas for these experi-

(1) J. T. Kummer, W. B. Spencer, H. H. Podgurski and P. H. Emmett, THIS JOURNAL, **73**, 564 (1951).
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TABLE I

SUMMARY OF SYNTHESIS VARIABLES FOR TRACER RUNS

Run no.	H7[d]	H19[e]	H15[e]	K20[e]	K10[d]	K16[e]	K13[a]
Catalyst[a]	Fe D3001[R]	Fe D3001[R]	Fe D3001[R]	Fe 614[R]	Fe D3001[N]	Co 108B[R]	Co 108B[R]
SVH	247	100	300	200	100	150	150
Temp., °C.	245–275[b]	241	242	239	215	190	187
% Contraction	15–7	62–63	68	29	70	52	53
Duration, hr.	37	27.5	8	26	~240	11	9
Pressure, atm.	1	7.5	21.5	1	7.5	1	1
% ethanol in syn. gas	1.5	1.0	1.3	.06	1.0	1.5	.04
Activity ethanol, c./min. cc.	6940	7000	5965	75000	7260	6030	75000
Total liq., g.	12.3	..	..	10.7	..	18.8	15.4
Total CO_2, g.	47.7	..	..	25.5	..	1.7	1.4
Gaseous products	Composition of gaseous products (vol. %)						
CH_4	5.1	54.7	39.1	16.7	48.6	64.6	72.9
C_2H_4	44.6	8.1	16.8	14.1	6.3	0.0	0.5
C_2H_6	5.8	10.7	12.6	22.1	15.4	9.4	8.1
C_3H_6	29.0	13.4	19.0	26.3	14.9	6.2	3.0
C_3H_8	2.0	3.9	4.7	6.0	4.9	11.0	8.8
C_4H_8	10.6	5.7	5.0	10.2	5.2	3.2	1.9
C_4H_{10}	1.0	1.5	1.7	1.8	2.3	3.8	3.2
C_5H_{10}	1.8	1.3	0.7	2.3	1.4	0.6	0.5
C_5H_{12}	0.1	0.6	0.2	0.5	1.0	1.1	1.0

[a] The symbols [R] and [N] mean reduced and nitrided. [b] The temperature was continuously raised during the run to maintain the same contraction. [c] In this run the methyl carbon atom was radioactive. [d] In this run the methylene carbon atom was radioactive.

ments contained about 1–1.5% radioactive ethanol. Also made were two experiments in which the synthesis gas contained about 0.05% strongly radioactive ethanol in the synthesis gas. These two runs, both at atmospheric pressure, were carried out over a singly promoted iron catalyst and over a cobalt catalyst.

Experimental

The experimental procedures are only outlined below, since detailed accounts of the equipment and the procedures used have been given in earlier publications.[1,2,8,9]

Syntheses at one atmosphere were performed in the fixed bed Fischer–Tropsch unit described in the first paper of this series. The runs at higher pressures were carried out in cooperation with the U. S. Bureau of Mines at Bruceton, Pennsylvania.

Gaseous synthesis products were separated into C_1, C_2, C_3, C_4 and C_5 cuts in a Podbielniak column. The individual cuts were analyzed for radioactivity, after which the olefins were removed in a scrubber and the residual gas was again analyzed for radioactivity. Subsequent mass spectrographic analysis made it possible to calculate the activity of olefins and paraffins as a function of carbon number.

Except for one instance, the liquid products were first washed with water, separated and then distilled from sodium hydride to remove the residual water, unreacted alcohol and other products containing oxygen. The liquids were then fractionated by low temperature distillation in high vacuum and burned to CO_2. From the volumes of the gaseous cut and the CO_2 produced, and the activity of the CO_2, the radioactivity of the cut could be calculated on a molar basis.

In run no. K10 over the nitrided catalyst, the procedure for handling the liquids was modified to permit separation of the alcohols from the hydrocarbons. The liquid products were first distilled to remove the waxes, and then refluxed with alkali to remove the acids and to saponify the esters. This step probably also removed aldehydes and/or ketones. The oil layer was then chromatographed using Davison silica gel No. 923 (inactive to olefins) as an adsorbent and methanol as a displacement agent. The alcoholic fraction obtained was then cut on a spinning band column into eight fractions, the last four of which were found to be substantially free of ethanol and methanol by mass spectrographic analysis. Except in the one case in which appreciable water was present, the carbon number was determined by a vaporometric method. From these data and the activity of the CO_2 formed on combustion, the radioactivity of the cuts could be calculated on a molar basis. Results of infrared analyses on these cuts showed that in spite of appreciable losses in the separation procedures, the cuts were substantially free of non-alcoholic organic contaminants and were 97 ± 2% pure on a molar basis. The hydrocarbon fraction from this run was analyzed in the standard fashion.

Three catalysts were used in this study. The singly promoted iron catalyst, no. 614, contained 0.64% Al_2O_3 and 2.00% ZrO_2 in addition to iron oxide. The doubly promoted iron catalyst, D3001, and the cobalt catalyst, 108B, are standard catalysts used by the U. S. Bureau of Mines at Bruceton, Pennsylvania.[3] Catalyst D3001 contains Fe_3O_4 + 4.6% MgO, 0.6% K_2O, 0.6% SiO_2 and 0.6% Cr_2O_3. The cobalt catalyst, 108B, has the composition Co:ThO_2: kieselguhr, 100:18:100. For the sake of completeness, the catalyst used by Kummer, *et al.*,[2] in run J4 was No. 333; in addition to iron oxide, it contained 2.82% Al_2O_3 and 1.39% ThO_2.

Results

The experimental conditions are summarized in Table I along with the product distributions for the various tracer runs. In Table II, the radioactivities per cc. are listed for the products of each of these runs. Previous[1,2] data have shown that a complete balance of inlet and exit radioactivity is not feasible owing to carbiding and wax retention on the catalyst; hence no attempts were made to effect a radioactive material balance.

In synthesis over the doubly promoted iron catalyst D3001, the gaseous product distribution is not strongly affected by increasing the pressure. The product distribution for a singly promoted catalyst was different from that for a doubly promoted catalyst. In the *control* runs at one atmosphere (not shown in Table I), it was found that the singly promoted iron catalyst was about 85% paraffinic, whereas for the doubly

(9) R. B. Anderson, "Catalysis," ed. by P. H. Emmett, Vol. IV, Reinhold Publ. Corp., New York, N. Y., 1956, p. 40.

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TABLE II

SUMMARY OF RADIOACTIVITY

Run no.	H7		H19		H15		K20		K10[a] Nitrided		K16[a,b,c]		K13[a,c]	
Catalyst	FeD3001		FeD3001		Fe614		Fe614		Fe D3001		Co108B		Co108B	
	C no.	Activity[d]	C no.	Activity[d]	C no.	Activity[d]	C no.	Activity[d]	C no.	Activity[d]	C no.	Activity[d]	C no.	Activity[d]
Pressure, atm.	1		7		21		1		7.5		1		1	
Ethanol activity		6940		7000		5965		75,000		7260		6000		75,000
Gaseous product														
CH_4	1	0	1	18	1	5	1	367	1	0	1	53	1	40
C_2H_4	2	918	2	332	2	56	2	2130	2	107	2	..	2	....
C_2H_6	2	1580	2	505	2	113	2	4330	2	107	2	120	2	72
C_2 as a whole	2	980	2	470	2	75	2	3475	2	107	2	120	2	72
C_3H_6	3	1285	3	700	3	138	3	3685	3	103	3	93	3	25
C_3H_8	3	1110	3	644	3	166	3	4760	3	107	3	69	3	69
C_3 as a whole	3	1260	3	680	3	144	3	3893	3	105	3	79	3	56
C_4H_8	4	992	4	603	4	145	4	3560	4	150	4	60	4	43
C_4H_{10}	4	1215	4	562	4	147	4	4500	4	110	4	75	4	57
C_4 as a whole	4	1010	4	585	4	145	4	3720	4	135	4	69	4	53
C_5H_{10}	5	..	5	467	5	104	5	3210	5	123	5	..	5	....
C_5H_{12}	5	..	5	417	5	152	5	3790	5	69	5	..	5	....
C_5 as a whole	5	940	5	460	5	124	5	3310	5	109	5	54	5	....
CO	~0		~0		~0		~0		~0		~0		~0	
CO_2	~0		~0		~0				~0		~0			
Liquid products	5.24	1225	5.10	530	5.42	131	5.04	3166	5.21	82	5.30	89	5.57	62
	6.24	1227	5.41	463	5.56	143	5.25	3274	7.06	97	6.31	110	5.83	49
	6.55	1265	6.40	489	5.78	124	5.57	3415	7.54	90	..	..	6.24	47
	6.69	1333	7.24	438	5.93	124	6.25	3570	6.60	86	6.78	105	6.80	53
	6.82	1329	8.23	415	6.74	131	5.90	3300	7.72	95	7.66	112	7.42	51
	7.76	1375			6.70	176	6.86	3600	8.00	99	7.53	108	7.73	50
	8.15	1328			6.65	159	6.42	3280	7.54	96				
					6.97	211	8.20	3670						

[a] The precision of these data is about ±7 c./m./cc. *hydrocarbon*. [b] In this run the activities of the olefins and paraffins of a given cut were calculated on the basis of the amount absorbed by an olefin scrubber rather than by a subsequent mass spectrographic analysis. [c] In these two runs the yield of C_5 products was so low only the activity of the total C_5 cut could be determined. The yield of ethylene was also quite low (~1% of the C_2 cut); hence, the activity of the ethylene could not be determined. [d] Activity in c./min./cc.

promoted catalyst it was 85% olefinic. This may be a consequence of the known lower hydrogenation activity of the doubly promoted iron catalyst compared to those containing no alkali.[10] Furthermore, although it had been previously noted[2] that ethanol addition definitely retarded the synthesis reaction over singly promoted catalysts at one atmosphere, this effect was not found in the present studies.

The gross results of these experiments are summarized in Table III, which gives the fraction of the products formed from the alcohol (per cent. incorporation) *vs.* synthesis variables for all the experiments herein reported. For the sake of comparison, a representative run reported by Kummer, *et al.*,[2] has been included. Runs H7, H19 and H15 yielded data for the same catalyst under different synthesis conditions. In these runs, the temperature, contraction and synthesis pressure vary. There does not appear to be a clear relation between the per cent. incorporation and either the temperature or the contraction; on the other hand, it does appear that the per cent. incorporation decreases with increasing pressure.

The variation of the molar radioactivities with carbon number for runs over the doubly promoted catalyst is illustrated by the curves in Fig. 1. Their qualitative features are quite similar, even though they were carried out at different pressures. The plots all show a maximum in the C_3–C_4 region and a trend toward a local minimum in the curves at about C_5.

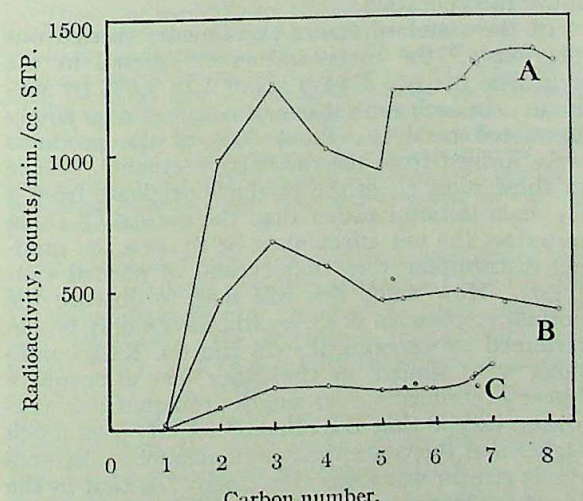

Fig. 1.—Influence of pressure in ethanol tracer runs over doubly promoted iron catalysts, D3001: A, H7, 1 atm., 245–275°; B, H19, 7.5 atm., 241°; C, H15, 21 atm., 242°.

(10) P. H. Emmett and J. B. Gray, THIS JOURNAL, 66, 1338 (1944).

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TABLE III

ETHANOL INCORPORATION

Run no.	Catalyst[a]	*t*, °C.	Pressure, atm.	% Contraction[b]	% Ethanol[c]	% Incorp.[d]
J4 R Fe	Singly promoted	225	1.0	23	1.5	35
K20 R Fe	Singly promoted	239	1.0	29	0.06	5
H7 R Fe	Doubly promoted[e]	245–275	1.0	7–15	1.5	18
H19 R Fe	Doubly promoted	241	7.5	63	1.0	7.2
H15 R Fe	Doubly promoted	242	21.0	68.70	1.33	2.7
K10 RN Fe	Doubly promoted	215	7.5	70	1.0	1.4
K13 R Co	On kieselguhr	187	1.0	53	0.04	0.07
K16 R Co	On kieselguhr	190°C.	1.0	52	1.5	1.6

[a] The symbols R and N refer to reduction and nitriding, respectively. [b] This is an average value for the whole run. [c] This is the volume % ethanol in the synthesis gas. [d] % incorporation = $\frac{\text{activity products } (C_2^+) \text{ c./m./cc.}}{\text{activity of added ethanol c./m./cc.}} \times 100$. [e] This doubly promoted catalyst was inferior to the singly promoted catalyst for synthesis at one atmosphere. In order to maintain even the low level of contraction the temperature was increased continuously throughout the run.

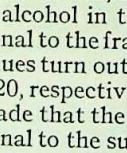
The effect of increased pressure on ethanol incorporation is clearly evident from Fig. 1. The average incorporation falls from 18 to 7 to 2.2% as the pressure is increased from 1 to 7.5 to 21 atm. In the case of one of these runs (H7), the catalyst was so unstable (see footnote *e* of Table III) that the *detailed* features of the plot of radioactivity *vs.* carbon number are questionable. For this reason, any general remarks made in the discussion pertaining to the shape of the activity *vs.* carbon number curves of all the tracer runs herein reported need not necessarily apply to run H7. In spite of this difficulty, it is clear that in this run as well as in runs H19 and H15 the ethanol is acting primarily as a chain initiator.

The effect of alkali on the incorporation of ethanol can be deduced from the data in Table III, where data obtained with the singly promoted iron catalyst at one atmosphere, run J4 previously reported by Kummer, *et al.*,[2] are compared with those obtained from run H7. In run H7, insofar as it was possible, the conditions were similar to those used in run J4, except that the doubly promoted catalyst was used. Incorporation in these two runs was found to differ by a factor of 2, with the run over the doubly promoted catalyst showing the lower incorporation.

In the standard tracer experiments carried out previously,[2] the concentration of ethanol in the synthesis gas was always about 1 to 1.5% by volume. In such runs at one atmosphere over singly promoted catalysts, about 35% of the products were formed from the radioactive ethanol. Since in these runs, $^1/_3$ of the products originate from a C_2 chain initiator rather than the normal C_1 chain initiator, the net effect must be to skew the product distribution from that typical of normal synthesis. How much this will tend to obscure the normal mechanism of the synthesis can only be determined by experiment. In run no. K20, conditions were similar to the other one atmosphere tracer experiments over singly promoted iron catalysts, except that the ethanol activity was much higher and the concentration of alcohol in the synthesis stream was lower, *i.e.*, about $^1/_{25}$ that in the standard tracer runs. The data obtained (Table III) show that the synthesis details for this experiment were quite similar to those for run no. J4. The incorporation (C₂ *vs.* C₁) was only about 5% or $^1/_7$th that of J4; consequently, the effect of alcohol addition on the product distribution was relatively small. In Fig. 2, activity *vs.* carbon number curves are given for runs K20 and J4. The qualitative differences in these two curves are striking; in fact, the curve for run K20 more closely resembles the runs over doubly promoted catalysts (Fig. 1) than it does J4. These results suggest that the qualitative differences between run J4 and all the runs herein reported for iron catalysts are principally a result of the higher incorporation in run J4 and the concomitant skewing of the product distribution rather than any fundamental difference brought about by changes in synthesis pressure or catalyst composition.

In runs J4 and K20, the over-all reaction rate is comparable. Thus, the incorporation divided by the per cent. alcohol in the synthesis stream is roughly proportional to the fraction of the alcohol that reacts. These values turn out to be about 23 and 83 for runs J4 and K20, respectively. If the reasonable assumption is made that the rate of build-in of the alcohol is proportional to the surface concentration of alcohol, θ, the fact that the fraction of alcohol reacting falls off with increasing alcohol partial pressure indicates that the adsorption of ethanol is medium strong.

In the chain building scheme put forward by Kummer, *et al.*,[2] adsorbed alcohol complexes of the type



R′ = CH_3 or H
R = alkyl group

are presumed to be the chain initiators and the complex where both R and R′ are H may also act as a build-in unit. Hydrocarbons may be produced by a variety of reactions.[3] Alcohol production could most simply be allowed for by hydrogenation of the carbon–metal bond, *i.e.*, reversal of the adsorption process. In any case, if this proposed mechanism is correct, the alcohol products (C_3 and higher) from tracer experiments wherein the synthesis gas contains labeled ethanol should give the same molar activity *vs.* carbon number plot as the hydrocarbons, as these alcohols stem from common intermediates. Unfortunately, such an experiment is ordinarily difficult in the usual synthesis over iron catalysts because the yield of oxygen-containing or-

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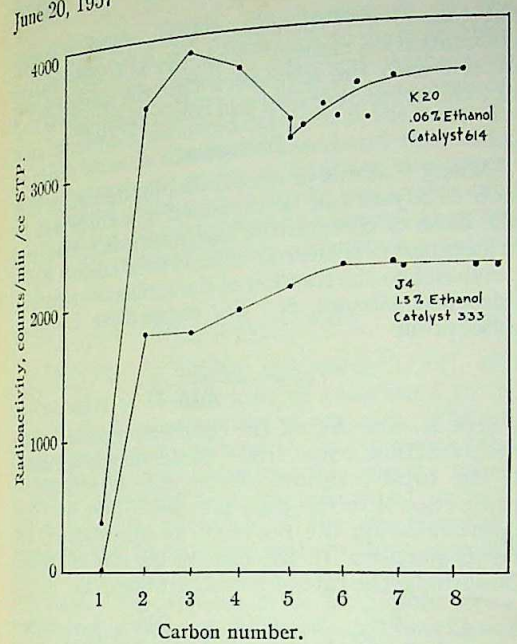

Fig. 2.—Concentration on incorporation over singly promoted catalysts. In run K20 the activity of the ethanol was 75,000 counts/min./cc. STP; in run J4, 6000 counts/min./cc. STP.

ganic products is so low. Recently,[11] however, it has been shown that nitrided iron catalysts yield a much higher percentage of alcohols than the reduced catalysts. This increased yield of alcohols does not require that the above discussed mechanism be discarded; it only requires that the relative rates of the various (particularly the chain termination) reactions involved be different on the nitrided catalyst. Tracer experiment No. K10 substantiates this view. In this experiment, the activities of the alcoholic products from C_3 through $C_{5,4}$ were determined. Synthesis details for this experiment are given in Table I, where it may be noted that it was considerably longer than any of the others. This was necessary in order to obtain a sufficient yield to permit an efficient separation of the alcohols. The activity data for the hydrocarbon products from this experiment are summarized in Table II, while results for the alcohol fractions are given in Table IV. These same data are also illustrated in Fig. 3. Qualitatively, the plots are similar to those obtained for the reduced doubly promoted catalyst at the same pressure. Quantitatively, there is a significant difference in the magnitude of the incorporation. That for the reduced catalyst is almost five times greater than that for the nitrided catalyst. This difference, together with the qualitative similarity of the curves, lends support to the contention that the mechanism of synthesis is similar over the two catalysts, but that the various rates involved are different. Although the activity data for the alcohols are subject to larger errors than those obtained from the hydrocarbons, it is quite evident that the *average* activities of the alcohols and hydrocarbons are the same within experimental

(11) J. F. Shultz, B. Seligman, L. Shaw and R. B. Anderson, *Ind. Eng. Chem.*, **44**, 397 (1952).

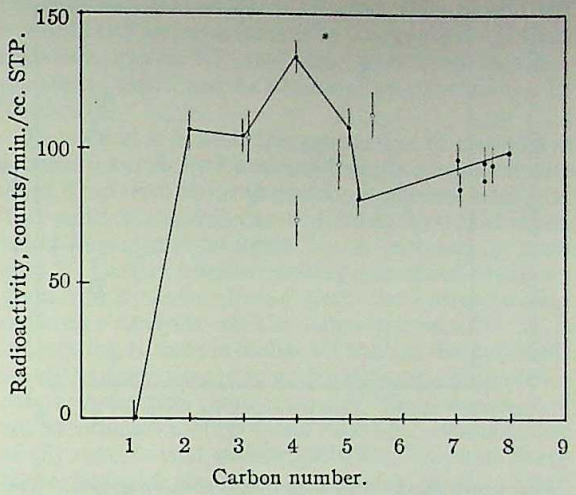

Fig. 3.—Ethanol tracer runs over a nitrided iron catalyst at 7.5 atm. and 215°. The assumed precision of the data is indicated by the length of the vertical lines: O, alcohols; ●, hydrocarbons.

error. This agreement would be expected on the basis of a mechanism which presumes that the alcoholic and hydrocarbon products both arise from the same complex. Qualitatively, the variation of alcohol activity with carbon number appears as if it might be different from that for the hydrocarbons insofar as it shows a minimum at C_4 rather than a maximum (Fig. 3).

TABLE IV

ACTIVITY OF ALCOHOL FRACTION OF LIQUID PRODUCTS FOR RUN NO. K10

Fraction[a]	Mol. wt.[b]	Carbon no.[b]	Activity, c./min./cc. CO_2	Activity, c./min./cc. Alcohol
5	62.4 (60.4)	3.1	33.5	104
6	59.4 (62.0)	4.0[c]	18.6[c]	74[c]
7	85	4.8	19.8	95
8	93.5	5.4	21.1	113
			Av.	96 ± 10
			Av. for hydrocarbons in this range	110

[a] These four samples were ethanol-free according to mass spectrographic analysis. [b] Molecular weights were determined vaporometrically. Check results are given in parentheses. Except for cut no. 6 carbon numbers were calculated using the data in column 2. [c] Mass spectrographic analysis showed this cut to be pure butanol plus some water. Distillation data also indicated this. Since small amounts of water would affect considerably the vaporometric molecular weight, the data in column 2 were ignored and those in columns 3, 4 and 5 were calculated assuming the cut was pure butanol.

In addition to the runs on iron catalysts, two runs were made on cobalt catalysts (K13 and K16). In these experiments, the H_2:CO ratio was 2:1 and, of course, the operating temperature was lower. In runs K16 and K13, the synthesis stream contained 1.5 and 0.04% ethanol, respectively. The plots of radioactivity *vs.* carbon number, constructed from the data obtained, are presented in Fig. 4. In contrast to the results with iron, the incorporation is quite low (~2%). The shape of the curves is such as to indicate that ethanol, on adsorption, forms a complex which acts primarily as a chain initiator. In striking contrast to *all* the re-

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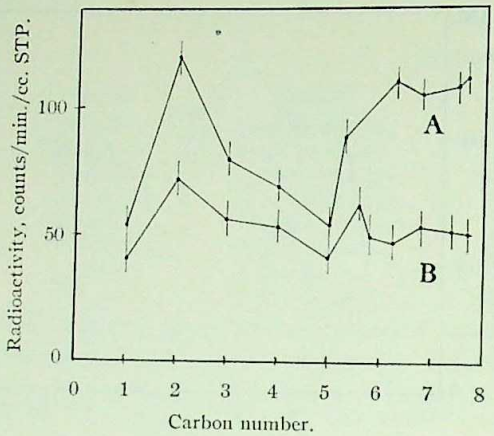

Fig. 4.—Ethanol tracer runs over a cobalt catalyst. The assumed precision of the data is as indicated by vertical lines. The activity of the ethanol in K13 was 75,000 counts/min./cc. STP; in run K16, it was 6030: A, K16, ethanol 1.5%; B, K13, ethanol 0.04%.

sults for ethanol tracer experiments with iron catalyst, however, the C_2 products had the highest activity. One possible explanation of this behavior is that the ethanol itself does not build-in, but that it does dehydrate to ethylene which will build-in over cobalt catalysts.[12] Since Co is an excellent hydrogenation catalyst, it would be expected that proportionately more ethylene would hydrogenate to ethane than would build-in, so that the C_2 products would have the highest radioactivity. An attempt was made to check this hypothesis by cracking the propane fraction. The results of this experiment were expected to show whether or not addition always took place preferentially on the carbinol carbon atom; unfortunately, the activities of the cracked products were so low that the experiment was inconclusive.

The activity of the methane fraction was quite high, indicating that appreciable cracking took place. If all of this came from the C_2 fraction, roughly one ethanol molecule cracked for every one that reacted to form higher molecular weight products. These results are definitely different from those obtained with iron catalysts. Even in the run in which cracking occurred to the greatest extent (K20), only about one ethanol molecule cracked to methane for every 10 or 15 that built in. It seems likely, therefore, that the same mechanism is not operative over iron and cobalt catalysts. This supposition finds some support in the available data on the product distributions and conditions required for synthesis over cobalt catalysts; these are quite different from similar data on iron catalysts.[3]

The effect of the ethanol concentration on its incorporation over cobalt catalysts is made evident by comparing runs K13 and K16 in Table III. Use of the same arguments here as for iron, shows that the fraction of the ethanol that undergoes build-in changes by less than a factor of 2 for an approximate 40-fold change in concentration, whereas in the case of iron the change was ~3.5 for a 25-fold concentration change. This, too, is in approximate accord with the suggestion that the mechanism is not the same over iron and cobalt catalysts.

(12) R. B. Anderson, "Catalysis," ed. P. H. Emmett, Vol. IV, 288, Reinhold Publ. Corp., New York, N. Y., 1956.

Discussion

Many features of the ethanol incorporation with iron catalysts can be explained in a crude way on the basis of competitive Langmuir adsorption, if it is assumed that the *rate* of build-in of ethanol is proportional to the fraction of the surface covered with adsorbed ethanol, θ_2. For competitive Langmuir adsorption

$$\theta_2 = \frac{K_2X_2P}{1 + P\Sigma K_iX_i} \qquad (1)$$

where K_i and X_i are the equilibrium constant and mole fraction, respectively, of the ith species, and P is the total pressure. If the rate of synthesis is proportional to the total pressure,[12] then, to a first approximation the per cent. incorporation, I, will be proportional to the ratio of the rate of ethanol build-in to the rate of normal synthesis, *i.e.*

$$I = k' \frac{K_2X_2}{1 + P\Sigma K_iX_i} = k' \frac{K_2X_2}{1 + PK_2X_2 + \Sigma' PK_iX_i} \qquad (2)$$

where k' is a ratio of rate constants and where the Σ' excludes the term for ethanol. Table III contains data for runs (K20 and J4) at $P = 1$, which differed only in the concentration of ethanol in the synthesis stream. The ratio of the incorporation (7/1 is the ratio of the incorporation for J4 to that for K20) can be used to obtain estimates of the θ_2 in these runs. Equation 2 (assuming $\Sigma' K_iX_i$ is about the same for both runs) yields

$$\frac{7}{1} = \frac{0.015\ K_2}{1 + 0.015K_2 + \Sigma' K_iX_i} \times \frac{1 + 0.0006\ K_2 + \Sigma' K_iX_i}{0.0006\ K_2} \qquad (3)$$

which reduces to $1 + \Sigma' K_iX_i = 5 \times 10^{-3}K_2$. Insertion of this admittedly crude estimate back into (1), reveals that in run J4 about 80% of the surface is covered with the ethanolic complex, while in run K20 the corresponding value is 12%.[12a]

The above estimates readily can be extended to the variation of incorporation with synthesis pressure for a fixed amount of alcohol in the synthesis gas. The data in Table III show that the incorporation at atmospheric pressure with a doubly promoted catalyst (run H7) is only about 1/2 that observed for the singly promoted catalyst. Provided that k' of (2) is independent of the alkali promoter, then θ_2 on the doubly promoted catalyst is about 1/2 that on a singly promoted catalyst, *viz.*, about 0.4, as with the singly promoted catalyst it was concluded above that in the neighborhood of 80% of the available surface was covered with ad-

(12a) The calculations based on equations (1), (2), (3) and (4) are admittedly speculative and involve numerous assumptions. They should probably be considered as more qualitative than quantitative. A typical difficulty that arises from a quantitative interpretation is illustrated by the figure "80%" for the percentage of the surface covered by "adsorbed ethanol complex" in run J4. If this adsorbed complex were identical to that formed from carbon monoxide and hydrogen during synthesis, then most of the hydrocarbon products would have been radioactive. Actually only one molecule in three of the hydrocarbon products in run J4 was radioactive. Presumably one must therefore conclude that only a fraction of the adsorbed ethanol complex is of the type that participates in the actual synthesis [illegible] bonds.

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sorbed ethanol. Within the framework of the present discussion, all precursors to hydrocarbon products may be viewed as adsorbed alcohols, so that in this instance there can be little bare surface. With the doubly promoted catalyst, if the same ratio exists between adsorbed ethanol and remaining alcoholic complexes, an upper limit for the coverage of the rest of the surface can be set, which cannot exceed 0.2. The total surface coverage then becomes ≈ 0.6 with the doubly promoted catalyst. Thus

$$1 - \theta = \frac{1}{1 + \Sigma K_i X_i} = 0.4 \qquad (4)$$

and $\Sigma K_i X_i = 1.5$. Using this value in (2), the incorporation at 21 atm. can be calculated to be about $^1/_{13}$th the incorporation at one atm. The actually observed value is about $^1/_8$, but in view of the crudeness of the approximations this may be taken as in fair agreement with the calculated value.[13] It is implicit in the solution of (4) that the relatively large uncovered fraction comes about through small values of the K_i, rather than mechanical blockage with alkali. This appears to be justifiable, since $\theta = \Sigma\theta_i$ may be taken as the fractional coverage of *available* surface, without altering the result.

This picture can be used to explain the fact that Kummer, *et al.*,[4] found that the addition of ethanol retards the synthesis, whereas in the present experiments, this was not found to be the case. Kummer found that when 1.5% ethanol was added to a synthesis gas stream, which was subsequently passed over a singly promoted iron catalyst, it was necessary to raise the temperature about 12° over that used for the control run with no ethanol added. Use of the experimentally determined activation energy (~20 kcal./mole)[14] indicates that the *normal* rate of synthesis should increase by a factor of 1.7 for such an increase in temperature. Moreover, since 35% of the products originate from the ethanol, the rate increase should be even greater (*i.e.*, ≈ 2.3). Thus, if the temperature were kept constant, the rate of synthesis from the normal C_1 complex would be reduced to about 40% of its value when the alcohol is introduced. Estimates presented above indicate that in the tracer runs of Kummer, *et al.*[2] (*e.g.*, J4, Table III), the adsorbed ethanol covered about 80% of the surface. Thus, at most, only about 20% of the surface was available for normal synthesis in those runs. Under the conditions where the ethanol build-in is small (run K20), only $\approx 12\%$ of the surface is covered with the ethanolic complex. In normal synthesis, therefore, as much as 85 to 90% of the surface is available for formation of the C_1 complex. Since it is likely that the rate of normal synthesis is proportional to the concentration of the C_1 complex,[7] a decided poisoning on ethanol addition would be expected for the former situation (*e.g.*, J4). This poisoning would be correspondingly less for runs in which the incorporation was small. In fact, in all the runs reported in Table III except for J4 and H7 it would not be experimentally observable. Unfortunately, in run H7 conditions were such that the poisoning could not be observed (see footnote *e* in Table III).

In normal synthesis the production of alcohols is generally smaller with reduced singly promoted catalyst than with reduced doubly promoted catalysts. The yield of alcohols can be further increased when using the latter catalysts by an increase in pressure.[3] Lastly, nitrided doubly promoted catalysts yield much more alcohol than the corresponding reduced catalysts at the same pressure.[11] It is interesting to note in Table III that as the synthesis conditions are altered in such a direction to make alcohol production more favorable, the percentage of tracer ethanol incorporated falls off. Examination of (2) reveals that such a fall off in I is most likely to be brought about by a decrease in K_2. Since presumably the adsorption of the alcohol-type complex is one point adsorption at the carbinol carbon atom,[2] this decrease in K_2 would indicate a similar decrease in the adsorption equilibrium constants for all the alcohols. This can be viewed as a relative increase in the desorption rate of the alcohols. This prediction, based on (2), would lead to the conclusion that in normal synthesis the alcoholic complex is more likely to evaporate from the surface and increase the yield of alcohols under the synthesis conditions which lead to a relatively low incorporation of ethanol in a tracer run.

It is interesting to note that whereas cobalt catalysts show a relatively low incorporation of ethanol it is also well-known that cobalt catalysts produce very low yields of alcohols. This discrepancy with the predictions of (2) in addition to the differences noted earlier between cobalt and iron catalysts, tend to support the suggestion that the predominant synthesis mechanism is not identical over the two metals.

In the discussion thus far, the qualitative differences in ethanol incorporation for different runs over iron catalysts under different synthesis conditions have been ignored. Figures 1, 2 and 3 illustrate the various types of behavior observed. In run J4 the incorporation was large (~35%). The activity per cc. was the same for the C_2 and C_3 products, but increased slightly between C_3 and C_6 ($\approx 20\%$); it again became constant for the C_6^+ hydrocarbons. In run K20, which like run J4 was carried out at one atmosphere over a singly promoted catalyst, the incorporation was low. This plot of radioactivity per cc. *vs.* carbon number shows a maximum in activity in the C_3–C_4 region and a local minimum at C_5 followed by a small increase in activity for C_5^+ products. The total variation in activity is about 20%. The curves for the reduced and nitrided doubly promoted catalysts all show the maximum in the C_3–C_4 region, although not all of them show the minimum at C_5. As already mentioned it appears that the maximum occurs whenever the incorporation is low, and is independent of the catalyst composition or the synthesis pressure.

In terms of the simple chain building picture mentioned earlier the molar activity should be independent of carbon number. The observed varia-

(13) In order to obtain a numerical estimate of the fall off in I with synthesis pressure, it is necessary to make some assumption regarding the surface coverage at one atmosphere, *i.e.*, that the surface was 60% covered. Even without this assumption, however, eq. 2 predicts, qualitatively, the fall off in incorporation as the pressure is increased.

(14) R. B. Anderson, "Catalysis," ed. by P. H. Emmett, Vol. IV, Reinhold Publ. Corp., New York, N. Y., 1956, p. 285.

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tion with carbon number appears to increase as the incorporation decreases. For example, the ratio of the peak activity to the C_2 activity (a measure of the variation) is 1.29 and 1.45, in runs H7 and H19, whereas the incorporation is 18 and 7.2%, respectively. This suggests that when the normal synthesis is least disturbed by the added alcohol the variation of radioactivity with carbon number is most pronounced. For the most part, however, the activity is fairly constant ($\sim \pm 20\%$) so that the simple hypothesis advanced by Kummer and Emmett[1] is probably close to the truth. These shortcomings of the theory do suggest, however, that even though the alcohol-type complexes are the principal chain initiators, some other species are also capable of acting in a similar capacity.

The nature of the chain initiator is indicated by the results obtained by Kummer, *et al.*[2] They found that 90% of the propane formed in ethanol tracer runs appeared to be obtained by addition to the α carbon atom of the methylene-labeled ethanol, and the remainder by the addition to the β-carbon atom. It was also established that the hydroxyl group of the unreacted ethanol had not migrated to the unlabeled carbon atom. Thus, it appears that a small fraction of the ethanol reacted to form some species *in which the two carbons were indistinguishable* and which could also build-in to form higher hydrocarbons. Clearly, this suggests that ethylene formed by the dehydration of ethanol is capable of build-in over iron catalysts to form higher hydrocarbons. This has been known to be the case with cobalt catalysts for some time[15] and the present authors have shown that when radioactive ethylene is introduced into the synthesis stream some build-in occurs.[7] Thus, the results with propane suggest that 80% of the propane comes from ethanol with all the addition taking place on the labeled (methylene) carbon atom and 20% of the propane comes from radioactive ethylene with the addition to the labeled carbon occurring only 50% of the time. It seems probable that this effect contributes heavily to the above-mentioned skewing of the radioactivity *vs.* carbon number curves.

In conclusion, it should be emphasized that the mechanism of synthesis appears to be complex, with two or more intermediates functioning as chain initiators. In spite of this, however, the mechanism suggested by Storch, *et al.*,[3] and Kummer, *et al.*,[1] is probably the predominant one operating in the synthesis over iron catalysts and is capable of explaining many of the observed facts.

Acknowledgment.—The authors gratefully acknowledge the technical assistance rendered by Dr. R. B. Anderson, Dr. R. A. Friedel and other members of the staff of the U. S. Bureau of Mines, Bruceton, Pa.

(15) R. B. Anderson, ref. 14, p. 317.

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, DAVIS]

The Free Radical Initiated Polymerization of Gaseous Unsaturated Hydrocarbons[1]

BY LESLIE C. LANDERS AND DAVID H. VOLMAN

RECEIVED JANUARY 26, 1957

Methyl radicals from thermally decomposing di-*t*-butyl peroxide were found to initiate the polymerization of gaseous acetylene, 1,3-butadiene, ethylene and propene in the temperature range 130–165°. The rate of polymerization of each unsaturated hydrocarbon was proportional to the first power of the concentration of monomer and to the square root of the concentration of di-*t*-butyl peroxide. This is consistent with a three-step polymerization mechanism consisting of initiation by a unimolecular split of the peroxide into free radicals, propagation by addition of radicals to a multiple bond and termination by radical combination. From a consideration of the relationship between the activation energies of chain initiation, propagation and termination, and of the known values of the activation energies for initiation and termination, the activation energies for propagation of polymerization of acetylene, butadiene, ethylene and propene were determined to be 5.1, 4.9, 8.2 and 5.6 kcal./mole, respectively.

Introduction

Few of the studies of the polymerization of the simpler unsaturated hydrocarbons in the gas phase have been concerned with obtaining values of the activation energies for the chain propagation reactions or, alternatively, for the addition of atoms or radicals to the multiple bond. Raal and Danby[2] reported 6.8 kcal./mole as the activation energy for propagation of ethylene polymerization initiated in the gas phase by methyl radicals. James and Steacie[3] give a preliminary value of 6–8 kcal./mole as the activation energy for the addition of ethyl radical to heptene-1. Volman[4] initiated the polymerization of butadiene by the thermal decomposition of di-*t*-butyl peroxide and reported 2.6 kcal./mole for the propagation activation energy. Volman and Graven[5] later initiated butadiene polymerization by the photolysis of di-*t*-butyl peroxide and acetone and reported 5.4 kcal./mole for the propagation activation energy, in good agreement with Gee's value of 5.5 kcal./mole for the propagation step in the gas phase mercury-photo-sensitized polymerization of butadiene,[6] and the estimate of White and Winkler[7] of 5 kcal./mole for the addition of a hydrogen atom to butadiene. More recently,

(1) Based on a portion of a thesis presented by L. C. Landers in partial satisfaction of the requirements for the degree of Doctor of Philosophy in the University of California.

(2) F. A. Raal and C. J. Danby, *J. Chem. Soc.*, 2219 (1949).

(3) D. G. L. James and E. W. R. Steacie, unpublished work cited in E. W. R. Steacie, "Atomic and Free Radical Reactions," 2nd ed., Reinhold Publ. Corp., New York, N. Y., 1954, p. 581.

(4) D. H. Volman, *J. Chem. Phys.*, **19**, 668 (1951).

(5) D. H. Volman and W. M. Graven, THIS JOURNAL, **75**, 3111 (1953).

(6) G. Gee, *Trans. Faraday Soc.*, **34**, 712 (1938).

(7) W. H. White and C. A. Winkler, *Can. J. Research*, **26B**, 3 (1948).

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Mandelcorn and Steacie[8] reported values of the activation energies for the addition of methyl radical to unsaturated hydrocarbons: acetylene 5.5 kcal./mole, ethylene 7.0 kcal./mole, propene 6.0 kcal./mole and butadiene *ca.* 2.5 kcal./mole.

Previous studies[4,5] in this laboratory of butadiene polymerization have involved initiation by the thermal and photochemical decompositions of di-*t*-butyl peroxide, which occur according to the well known mechanism[5,9,10]

$$(CH_3)_3COOC(CH_3)_3 \longrightarrow 2(CH_3)_3CO \quad (1)$$

$$(CH_3)_3CO\cdot \longrightarrow CH_3\cdot + CH_3COCH_3 \quad (2)$$

$$2CH_3\cdot \longrightarrow C_2H_6 \quad (3)$$

The thermal initiation technique is very convenient, since the peroxide decomposes at a readily measurable rate at 125°. It is assumed that the *t*-butoxy radical formed in (1) decomposes rapidly by (2) at temperatures at which the peroxide decomposes, thus di-*t*-butyl peroxide is a convenient source of methyl radicals at temperatures well below those at which the direct thermal polymerization of unsaturated hydrocarbons takes place.

In the present work this technique was extended to the initiation of polymerization of gaseous acetylene, butadiene, ethylene and propene.

Experimental

The di-*t*-butyl peroxide, kindly donated by the Shell Chemical Corporation, was of unspecified purity. It was deaerated and distilled bulb-to-bulb on the high vacuum line and the middle fraction was retained and stored over Dry Ice. Its refractive index ($n^{20}D$) was 1.3888, which compares well with published values of 1.3888,[5] 1.3889[9] and 1.3890.[10] The acetylene was Matheson Purified Grade, the 1,3-butadiene was Matheson Extra Pure Grade, and the ethylene and propene were Matheson C.P. Grade. Samples of these were condensed and distilled bulb-to-bulb on the high vacuum line, the middle fractions of each being retained. The ethylene was stored over liquid air, and the acetylene, butadiene and propene over Dry Ice.

The polymerizations were carried out in a one-liter Pyrex bulb immersed in an oil-bath thermostat. The temperature was maintained constant to within ±0.05°. Pressure changes during polymerization were measured by a mercury manometer.

Results and Discussion

Di-*t*-butyl peroxide was decomposed at various temperatures in the range 124–177°, and the first-order rate constant obtained was $k_i = 1.6 \times 10^{16} e^{-33.4/RT}$ sec.$^{-1}$, which is within the range of previously reported values.[10–12]

The kinetic data obtained from the polymerization experiments are shown in Tables I–IV. The rates of pressure change given are the initial rates. The values of k were calculated from

$$-\frac{dp}{dt} = k(M)(C)^{1/2} \quad (4)$$

where (M) is the pressure of monomer and (C) is the pressure of di-*t*-butyl peroxide.

It is seen that in each case the rate of pressure change in the system is given by eq. 4. This is of the expected form for a free radical initiated polymerization involving initiation *via* a unimolecular

Table I

Rate of Polymerization of Acetylene

C_2H_2, mm.	DTBP, mm.	$-dp/dt$, mm./min.	k, mm.$^{-1/2}$ sec.$^{-1}$ × 10^4
	131.8°		
53.2	6.8	0.023	1.7
74.4	7.0	.033	1.7
103.2	6.7	.043	1.6
129.4	7.1	.055	1.6
140.0	6.9	.060	1.6
	149.6°		
61.9	5.7	0.078	5.3
112.1	5.7	.16	6.0
160.2	5.7	.21	5.5
213.7	5.7	.28	5.5
275.7	5.7	.36	5.5
176.9	12.6	.37	5.9
181.9	2.1	.14	5.3
89.3	0.85	.043	5.3
	164.9°		
139.8	4.6	0.46	15.3
208.3	4.7	.69	15.3
274.3	4.9	.91	14.9
66.8	2.7	.19	17.2
303.9	0	0	

Table II

Rate of Polymerization of Butadiene

C_4H_6, mm.	DTBP, mm.	$-dp/dt$, mm./min.	k, mm.$^{-1/2}$ sec.$^{-1}$ × 10^4
	129.4°		
120.9	14.0	0.015	0.33
215.3	14.0	.025	.31
321.2	14.0	.039	.32
	140.5°		
110.6	15.3	0.030	0.69
167.2	15.3	.047	.71
353.2	15.3	.10	.72
	151.0°		
61.2	14.2	0.037	1.6
116.6	14.2	.064	1.5
154.6	14.2	.087	1.5
178.4	14.2	.083	1.2
296.2	14.2	.15	1.3
408.9	14.2	.24	1.6
413.8	14.2	.22	1.4
281.9	11.7	.14	1.5
288.4	9.1	.13	1.5
296.7	3.9	.085	1.4
296.5	1.1	.042	1.4
217.2	0	0	
	166.2°		
95.6	14.4	0.13	3.6
167.9	14.4	.24	3.8
220.3	14.4	.32	3.8
221.3	14.4	.33	3.9
277.1	0	0	

(8) L. Mandelcorn and E. W. R. Steacie, *Can. J. Chem.*, **32**, 474 (1954).
(9) L. M. Dorfman and Z. W. Salsburg, THIS JOURNAL, **73**, 255 (1951).
(10) J. Raley, F. F. Rust and W. E. Vaughan, *ibid.*, **70**, 88, 1336 (1948).
(11) J. Murawski, J. S. Roberts and M. Szwarc, *J. Chem. Phys.*, **19**, 698 (1951).
(12) R. K. Brinton and D. H. Volman, *ibid.*, **20**, 25 (1952).

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TABLE III

RATE OF POLYMERIZATION OF ETHYLENE

C_2H_4, mm.	DTBP, mm.	$-dp/dt$, mm./min.	k, mm.$^{-1/2}$ sec.$^{-1} \times 10^4$
	131.2°		
140.6	6.6	0.026	0.72
221.8	6.9	.0415	.71
285.1	7.0	.053	.70
290.2	7.0	.057	.74
356.2	7.0	.0655	.70
348.1	14.0	.089	.68
	146.0°		
224.6	7.1	0.14	2.3
289.5	7.0	.18	2.4
364.8	7.1	.22	2.3
422.7	14.1	.36	2.3
146.2	5.6	.094	2.7
195.0	2.8	.074	2.3
	160.1°		
122.8	5.7	0.16	5.5
199.8	5.7	.315	6.6
269.7	5.7	.44	6.8
364.2	5.7	.57	6.6
211.0	4.3	.27	6.2
137.3	2.9	.16	6.9
247.6	0	0	

TABLE IV

RATE OF POLYMERIZATION OF PROPENE

C_3H_6, mm.	DTBP, mm.	$-dp/dt$, mm./min.	k, mm.$^{-1/2}$ sec.$^{-1} \times 10^4$
	135.8°		
146.5	14.1	0.016	0.29
219.3	14.1	.022	.27
286.2	14.1	.030	.28
358.7	14.1	.365	.27
	147.9°		
215.3	14.2	0.049	0.60
286.2	14.2	.070	.65
359.0	14.2	.089	.66
432.3	14.1	.11	.68
286.8	10.4	.061	.66
250.9	7.1	.044	.66
290.0	3.5	.035	.65
290.1	1.0	.018	.62
	160.2°		
295.4	11.4	0.14	1.4
346.0	11.4	.17	1.5
384.9	11.4	.19	1.5
217.4	7.1	.087	1.5
194.4	0	0	

formation of free radicals, polymer growth by addition of radicals to monomer molecules and termination by bimolecular interaction of free radicals.[4] Since it has been shown that negligible amounts of ethane are formed when di-*t*-butyl peroxide is decomposed in the presence of butadiene,[4] it was assumed that each methyl radical formed adds to a monomer molecule, the polymerization proceeding as

$$(CH_3)_3COOC(CH_3) \xrightarrow{k_i} 2CH_3COCH_3 + 2CH_3\cdot \quad (5)$$

$$CH_3\cdot + M \xrightarrow{k_p} CH_3M\cdot \quad (6)$$

$$CH_3M\cdot + M \xrightarrow{k_p} CH_3M_2\cdot \quad (7)$$

$$CH_3M_x\cdot + CH_3M_y\cdot \xrightarrow{k_t} (CH_3)_2M_{(x+y)} \quad (8)$$

$$CH_3M_x\cdot + CH_3M_x\cdot \xrightarrow{1/2k_t} (CH_3)_2M_{(x+x)} \quad (9)$$

This formulation[13] yields, by the usual steady-state treatment

$$\frac{-d(M)}{dt} = k_p\left(\frac{2k_i}{k_t}\right)^{1/2}(M)(C)^{1/2} \quad (10)$$

For the determination of activation energies, the values of k in eq. 4 were calculated from the slopes of the straight lines obtained in plots of $-(dp/dt)/(C)^{1/2}$ *vs.* (M). These values are listed in Table V.

TABLE V

POLYMERIZATION RATE CONSTANTS

T, °C.	k, moles$^{-1/2}$/l. sec.$^{-1} \times 10^4$	T, °C.	k, (moles/l.)$^{-1/2}$ sec.$^{-1} \times 10^4$
Acetylene		Ethylene	
131.8	4.29	131.2	1.86
149.8	15.1	146.0	6.19
164.9	42.0	160.1	18.2
Butadiene		Propene	
129.4	0.85	135.8	0.73
140.5	1.93	147.9	1.77
151.0	3.91	160.2	4.07
166.2	10.5		

The activation energies E corresponding to the slopes in Fig. 1 were calculated to be as follows: acetylene 24.3, butadiene 24.1, ethylene 27.4 and propene 24.8 kcal./mole. Since

$$k = \left(\frac{2k_i}{k_t}\right)^{1/2}k_p \quad (11)$$

then

$$E = E_p + {}^1/_2E_i - {}^1/_2E_t \quad (12)$$

Although it is not possible to estimate E_t from the experimental data, there is abundant evidence that in general E_t is small, not far from zero. The kinetics of the liquid phase photopolymerization of vinyl acetate[14] and methyl methacrylate[15] have been studied by the rotating sector method and E_t was found to be zero in both cases. For the liquid phase benzoyl peroxide initiated polymerization of butyl acrylate, E_t has been found to be zero.[16] The combination of methyl radicals in the gas phase has been found to require no activation

(13) The justification for taking the termination rate constant for like radicals reacting equal to one-half the rate constant for unlike radicals reacting may be found in collision theory. *Cf.* P. J. Flory, "Principles of Polymer Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 200.

(14) G. M. Burnett and H. W. Melville, *Nature*, **156**, 661 (1945); *Proc. Roy. Soc. (London)*, **A189**, 456 (1947).

(15) M. H. Mackay and H. W. Melville, *Trans. Faraday Soc.*, **45**, 323 (1949).

(16) H. W. Melville and A. F. Bickel, *ibid.*, **45**, 1049 (1949).

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energy,[17] and an examination of the published data on the reactions of ethyl radicals in the gas phase discloses no good evidence that the activation energy for ethyl radical combination is other than zero.[15] E_t was therefore assigned the value zero for this study, so that

$$E_p = E - {}^1/_2E_i \qquad (13)$$

Using the value of E_i = 38.4 kcal./mole, the values of E_p obtained for the systems studied are: acetylene 5.1, butadiene 4.9, ethylene 8.2 and propene 5.6 kcal./mole. The value for butadiene agrees well with previous values of 5.4[5] and 5.5[6] kcal./mole. The value for ethylene is in fair agreement with the value of 6.8 kcal./mole given by Raal and Danby.[2] However, the results of Raal and Danby depended upon the value of 9.7 kcal./mole for the activation energy for hydrogen atom abstraction from acetaldehyde by methyl radical. If the more recent value of 7.5 kcal./mole given by Volman and Brinton[19] is taken, however, the work of Raal and Danby indicates a value of 4.6 kcal./mole for the propagation activation energy in ethylene polymerization, which does not agree with our results. If the values for E_p obtained in this study are compared with those of Mandelcorn and Steacie previously cited,[8] it is seen that the correspondence is quite good in the cases of acetylene and propene and is certainly within experimental error for ethylene. Since their value for butadiene is a rough approximation, the discrepancy with our value is not significant.

(17) R. Gomer and G. B. Kistiakowsky, *J. Chem. Phys.*, **19**, 85 (1951).
(18) K. J. Ivin, M. J. H. Wijnen and E. W. R. Steacie, *J. Phys. Chem.*, **55**, 967 (1952).
(19) D. H. Volman and R. K. Brinton, *J. Chem. Phys.*, **20**, 1764 (1952).

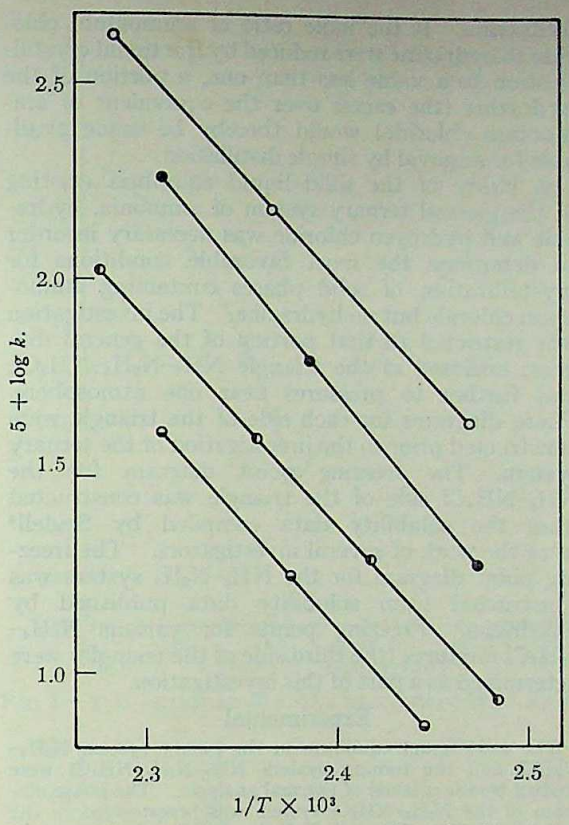

Fig. 1.—Effect of temperature on polymerization rate: O, acetylene; ●, ethylene; ◐, butadiene; ◒, propene.

Acknowledgment.—The authors wish to express their appreciation to the Research Corporation for financial aid.

DAVIS, CAL.

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORIES OF THE OHIO STATE UNIVERSITY]

The System Ammonia–Hydrazine–Ammonium Chloride

BY FORREST R. HURLEY AND HARRY H. SISLER[1]

RECEIVED JANUARY 5, 1957

A study of the solid–liquid equilibria in the general ternary system of ammonia, hydrogen chloride and hydrazine was restricted to that portion of the general diagram enclosed in the triangle NH_3–N_2H_4–NH_4Cl, and to pressures near one atmosphere. A ternary compound believed to be $NH_3 \cdot HCl \cdot N_2H_4$, but whose composition has not been established, melts incongruently at −2.5°. The conditions for removal of ammonium chloride from the system by crystallization were outlined.

Sisler and Mattair[2] have shown that hydrazine is formed when chloramine, produced from gaseous chlorine and ammonia, is dissolved in a large excess of liquid ammonia. Subsequent papers from this Laboratory[3] give additional details concerning this synthesis and the recovery of anhydrous hydrazine. In accordance with the equation

$$ClNH_2 + 2NH_3 = N_2H_4 + NH_4Cl$$

equivalent amounts of hydrazine and ammonium chloride are formed in the reaction. However, the over-all yield of hydrazine is reduced by its reaction with chloramine.

$$2ClNH_2 + N_2H_4 = N_2 + 2NH_4Cl$$

Therefore, the mole ratio of hydrazine to ammonium chloride in the product mixture is always less than unity. During the last stages of evaporation of excess ammonia, hydrazine, which has a lower volatility than ammonia, reacts with ammonium chloride in accordance with the equation

$$N_2H_4 + NH_4Cl = NH_3 + N_2H_5Cl$$

This reaction makes it difficult to distil the hydrazine from the reaction mixture since the ammonium chloride in the mixture is always in excess of the

(1) Department of Chemistry, University of Florida, Gainesville.
(2) R. Mattair and H. H. Sisler, THIS JOURNAL, **73**, 1619 (1951).
(3) H. H. Sisler, *et al.*, *ibid.*, **76**, 3909 (1954); **76**, 3912 (1954); **76**, 3914 (1954).

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hydrazine. If the mole ratio of ammonium chloride to hydrazine were reduced by fractional crystallization to a value less than one, a portion of the hydrazine (the excess over the equivalent of ammonium chloride) would thereby be made available for removal by simple distillation.

A study of the solid–liquid equilibria existing in the general ternary system of ammonia, hydrazine and hydrogen chloride was necessary in order to determine the most favorable conditions for crystallization of solid phases containing ammonium chloride but no hydrazine. The investigation was restricted to that portion of the general diagram enclosed in the triangle NH_3–N_2H_4–NH_4Cl, and further to pressures near one atmosphere. Phase diagrams for each side of the triangle were constructed prior to the investigation of the ternary system. The freezing point diagram for the NH_3–NH_4Cl side of the triangle was constructed from the solubility data compiled by Seidell[4] from the work of several investigators. The freezing point diagram for the NH_3–N_2H_4 system was constructed from solubility data published by Friedrichs.[5] Freezing points for various N_2H_4–NH_4Cl mixtures (the third side of the triangle) were determined as a part of this investigation.

Experimental

The solid–liquid equilibria in the binary system N_2H_4–NH_4Cl and the ternary system NH_3–N_2H_4–NH_4Cl were studied by the method of thermal analysis. The phase diagram of the N_2H_4–NH_4Cl system was investigated in the region from 60 to 100 mole % hydrazine. At lower concentrations of hydrazine the equilibrium pressure of the system is well in excess of one atmosphere. The ternary phase diagram was broken up into forty experimental sections for investigation. Each section was characterized by a fixed mole ratio of ammonia to ammonium chloride. Therefore, every ternary mixture investigated had a composition point falling on experimental sections which extended radially from the hydrazine corner to points on the NH_3–NH_4Cl side of the ternary phase diagram lying approximately between 10.5 and 98.7 mole % NH_3 (*e. g.*, see Figs. 3 and 4).

Apparatus.—All freezing point determinations were made in a glass freezing point cell shown in Fig. 1. The glass-spiral stirring rod was operated by intermittent magnetic interaction of a solenoid with the iron slug sealed into the top arm of the stirrer.

The time–temperature cooling curves were obtained by using a Leeds and Northrup Micromax Model S-40000 series self-recording potentiometer with a copper–constantan thermocouple immersed in the well of the freezing point cell. Petroleum ether (b.p. 30–60°) was used as a heat-transfer medium in the thermocouple well. The apparatus was calibrated at the freezing points of distilled water, carbon tetrachloride (−22.6°), chloroform (−63.5°), and the α- and β-forms of diethyl ether (−116.3° and −123.3°).

A cooling rate of 1 to 2 degrees per minute was regulated by the choice of coolant, and the type of jacket used to control the rate of heat transfer from the freezing point cell to the cooling bath.

Mixtures of N_2H_4 and NH_4Cl.—A weighed amount of ammonium chloride was transferred to the freezing point cell through a side arm which was then capped with a vaccine bottle stopper. It was necessary to cool the cell and ammonium chloride below −40° before hydrazine was added since a small amount of hydrazine coming in contact with solid ammonium chloride releases a considerable quantity of gaseous ammonia which could cause excessive pressures. Purified hydrazine was transferred to the freezing point cell from a glass syringe fitted with a No. 26 gage stainless steel hypodermic needle, 1.5 inches long. A glass syringe affords a convenient means of transferring and weighing hydrazine with a minimum of exposure to the atmosphere. At atmospheric pressure as many as 10–15 punctures of the Arthur H. Thomas No. 2330 vaccine bottle stoppers could be made without significant leakage. A freezing point of the mixture was obtained only after the contents of the cell was warmed sufficiently to completely melt the mixture. All freezing points were determined at least twice. The precision obtained was always within 0.5°. Successive additions of hydrazine were made so that freezing points of several compositions were obtained for one addition of ammonium chloride.

Mixtures of NH_3, N_2H_4 and NH_4Cl.—A weighed amount of ammonium chloride was transferred to the freezing point cell. Anhydrous ammonia was slowly distilled into the cell and condensed over the ammonium chloride by cooling the cell in a Dry Ice bath. The amount of ammonia condensed with the ammonium chloride was determined by one or both of the following methods: (1) by the difference in weight of the cell, and (2) by the freezing point of the binary mixture of ammonia and ammonium chloride. The first method was used in all cases where the mole per cent. of ammonia was less than 75. Both methods could be used for mixtures containing from 75 to 88 mole % ammonia, being restricted only by the ammonia pressure developed at the temperature of the measurement. For compositions greater than 88 mole % ammonia, the freezing point of the mixture was used as a measure of concentration, the percentage of ammonia being determined from the NH_3–NH_4Cl phase diagram (Fig. 5).

After the ammonia was added, the freezing point cell was sealed with a vaccine bottle stopper. Several additions of hydrazine were made in the manner described above. It was always necessary to cool the mixture with a Dry Ice bath before each addition of hydrazine.

Materials.—Synthetic anhydrous ammonia was obtained from the Verkamp Corporation. The ammonia was slowly distilled from a 50-pound cylinder through a glass wool plug, and condensed directly into the freezing point cell. Under these conditions the distilled ammonia froze at −77.5 to −78° which agrees well with the literature value.

Matheson Coleman and Bell anhydrous hydrazine was allowed to stand over flaked sodium hydroxide for 24 hours and then distilled. The distillate froze at 1.5 to 2.0° which agrees with the freezing point of hydrazine recorded in the literature.[6] The purified hydrazine was stored in the distillation receiver and under dry nitrogen at one atmosphere. A short side arm attached to the receiver was capped with a rubber vaccine bottle stopper so that the purified hydrazine could be pulled through the hypodermic needle into a glass syringe without exposure to the atmosphere.

Mallinckrodt Analytical Reagent grade ammonium chloride was dried overnight at 105°, and stored in a desiccator.

Results and Discussion

The System N_2H_4–NH_4Cl.—The freezing point diagram for mixtures of hydrazine and ammonium chloride is given in Fig. 2. Since it is known that the reaction $N_2H_4 + NH_4Cl \leftrightarrows NH_3 + N_2H_5Cl$ takes place, and since no satisfactory analyses of the equilibrium solid phase associated with the peritectic point could be obtained, there is uncertainty concerning the interpretation of these data. For the purpose of our study, we have assumed that the system N_2H_4–NH_4Cl is a quasi-binary section of the general ternary diagram NH_3–HCl–N_2H_4. For this assumption to be strictly valid, no ammonia or hydrazine must escape into the vapor phase, and the composition of the solid phases must be an additive compound of N_2H_4 and NH_4Cl. Under the conditions under which the system was studied, the amount of ammonia and hydrazine in the vapor phase was negligible. It is our belief that, in the presence of an appreciable concentration of ammonia, the more basic character

(4) A. Seidell, "Solubilities of Inorganic and Metal Organic Compounds," Vol. I, D. Van Nostrand Co., Inc., New York, N. Y., 1940, pp. 1091–1092.

(5) F. Friedrichs, *Z. anorg. allgem. Chem.*, **137**, 221 (1924).

(6) P. H. Mohr and L. F. Audrieth, *J. Phys. Colloid Chem.*, **53**, 901 (1949).

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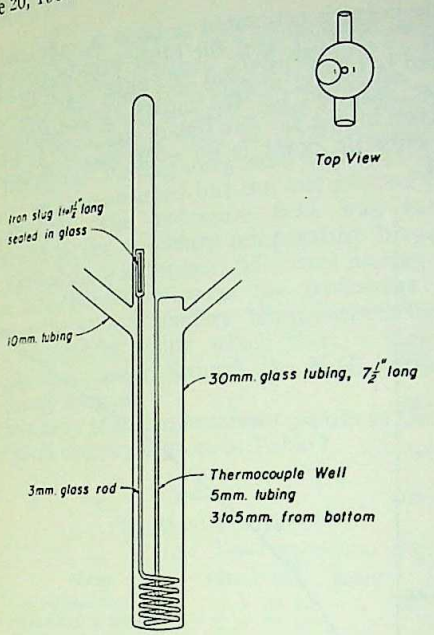

Fig. 1.—Freezing point cell.

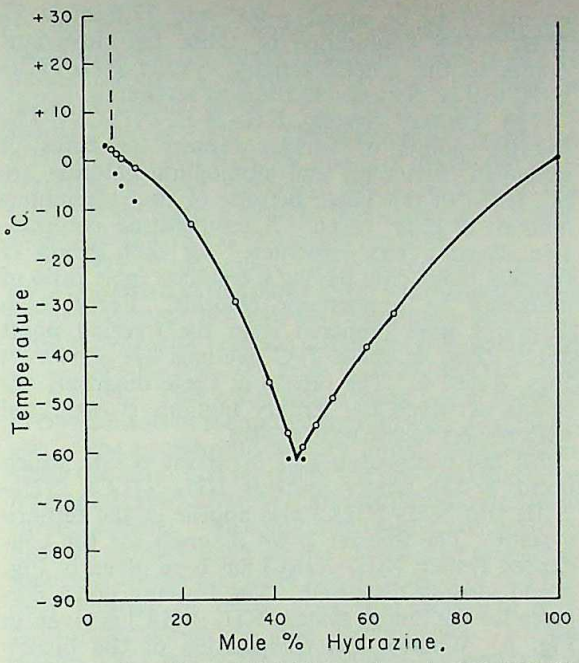

Fig. 3.—T–C section at 69.8/30.2 mole ratio NH_3/NH_4Cl

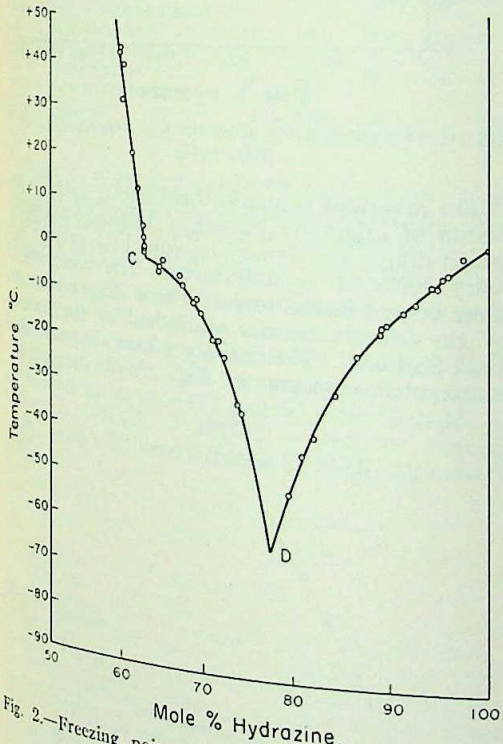

Fig. 2.—Freezing point diagram for the binary system N_2H_4–NH_4Cl.

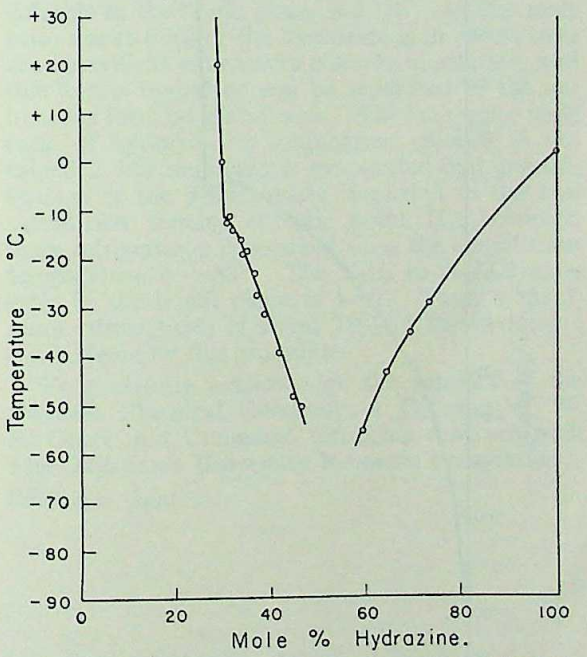

Fig. 4.—T–C section at 56.5/43.5 mole ratio NH_3/NH_4Cl.

of ammonia over hydrazine will inhibit the conversion of hydrazine and ammonium chloride mixtures to ammonia and hydrazine hydrochloride. In any case, these uncertainties concerning the interpretation of the N_2H_4–NH_4Cl section do not in any way invalidate the important synthetic implications involved, for the results obtained in this study help to form the experimental basis for an interesting and unique method for isolating anhydrous hydrazine.

The freezing point diagram shows two invariant points for the system. A peritectic point is located on the diagram at −2.5° and 63.0 mole % N_2H_4. The crystals which melt incongruently at this invariant point have been tentatively assigned the formula NH_4Cl–N_2H_4, but, for the reasons stated above, the composition of this phase is uncertain. The eutectic composition and temperature were not accurately established because of the viscous nature of the solutions in the vicinity of the eutectic point. However, the eutectic point has been

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estimated to be about −60° and 77.5 mole % N_2H_4. The significance of these two invariant points to the general ternary system NH_3–HCl–N_2H_4 will be discussed in the next section.

The Ternary System NH_3–N_2H_4–NH_4Cl.—The freezing points of various ternary mixtures of ammonia, hydrazine and ammonium chloride are not listed in this paper because of the voluminous amount of data[7] taken. A temperature–composition diagram was constructed for each group of freezing point data having a common mole ratio of ammonia to ammonium chloride. Forty such diagrams were prepared from the freezing point data. Two of these T–C Sections are shown in Figs. 3 and 4. The breaks in these diagrams are points at which the ternary liquidus is saturated with respect to two solid phases.

All the compounds and invariant points which occur in the binary systems NH_3–NH_4Cl, NH_3–N_2H_4 and N_2H_4–NH_4Cl also appear in the ternary system. The freezing point diagram for the condensed system N_2H_4–NH_4Cl has been given in Fig. 2 and already discussed. The freezing point diagram for the binary system NH_3–NH_4Cl is given in Fig. 5. Whereas the composition of the binary

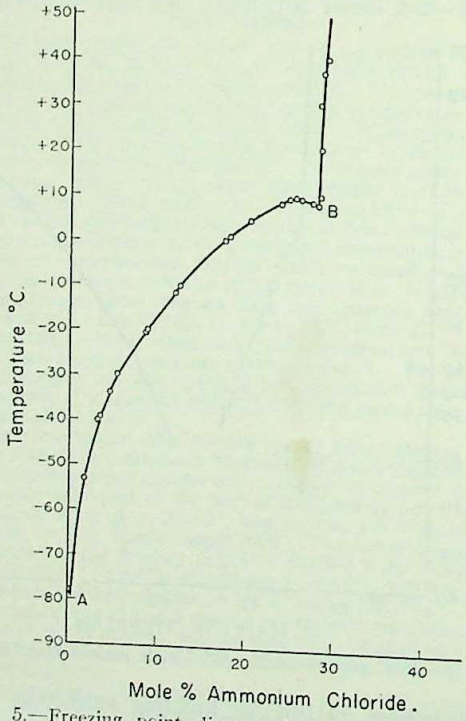

Fig. 5.—Freezing point diagram for the binary system NH_3–NH_4Cl.

compound $NH_4Cl{\cdot}3NH_3$ is well established, its melting point has been variously reported as 7, 7.6, 9.8 and 10.7°. The maximum in the curve in Fig. 5 occurs at 9.8°; however, Watt and McBride[8] in a recent paper seemed to prefer a lower value. Neither of the two eutectic points of the system are well defined by the data. The ammonia-rich eutectic point is estimated to be at *ca.* −81° and 0.5 mole % NH_4Cl, and the other eutectic point estimated to be at +8° and 27.5 mole % NH_4Cl. The phase diagram for the binary system NH_3–N_2H_4 is given in Fig. 6. No binary compound is formed; the eutectic point is at −80° and 7.36 mole % N_2H_4.

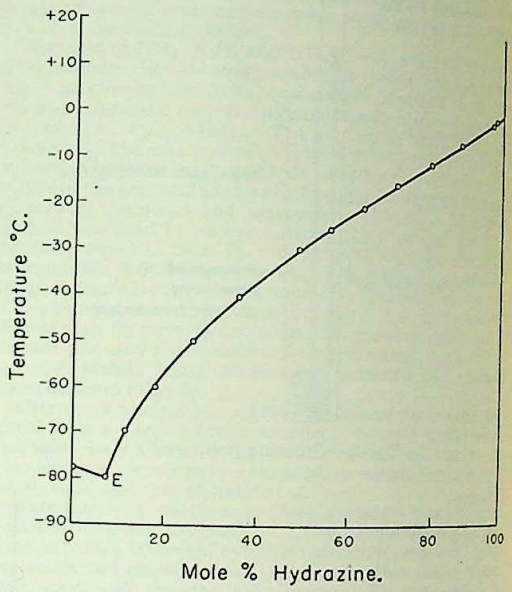

Fig. 6.—Freezing point diagram for the binary system NH_3–N_2H_4.

The invariant points in these binary systems are points of origin for curves of twofold saturation which divide the ternary liquidus into various primary fields of crystallization. The positions of these curves in the ternary phase diagram are set by the ternary breaks established by the ternary T–C Sections. The ternary phase diagram thus constructed appears in Fig. 7. Five primary

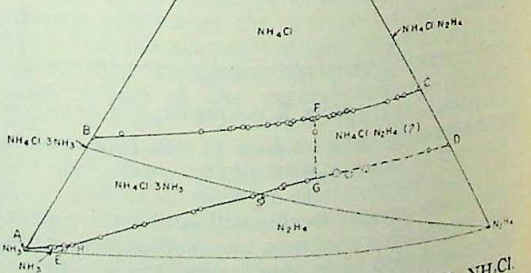

Fig. 7.—Phase diagram for the system NH_3–N_2H_4–NH_4Cl.

fields of crystallization appear in the ternary system NH_3–N_2H_4–NH_4Cl. The primary fields of crystallization for the congruent melting hydra-

(7) F. R. Hurley, Thesis, Ohio State University, 1954.
(8) G. W. Watt and W. R. McBride, THIS JOURNAL, 77, 1312 (1955).

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zine, ammonium chloride and ammonium chloride 3-ammoniate were assigned by inspection to those areas in which their composition points lie. The remaining area in the ternary phase diagram is assigned as the primary field of crystallization for the incongruent melting compound which, as stated above, we have assumed but not yet proved to be $NH_4Cl \cdot N_2H_4$. The hydrazine field was further confirmed by the secondary temperature breaks in the thermal analysis curve. Mixtures having constant NH_3/NH_4Cl ratios in the hydrazine field showing the same secondary temperatures breaks have composition points which form a series of straight lines passing through the N_2H_4 corner of the ternary diagram.

A summary of all the invariant points in the ternary phase diagram is given in Table I.

TABLE I

INVARIANT POINTS

Point	Solids	Liquid composition, % NH_4Cl	% NH_3	% N_2H_4	Temp., °C.
A	$NH_3 + NH_4Cl \cdot 3NH_3$	0.5	99.5	...	*ca.* −81
B	$NH_4Cl \cdot 3NH_3 + NH_4Cl$	27.5	72.5	...	+ 8
C	"$NH_4Cl \cdot N_2H_4$" + NH_4Cl	37.0	...	63.0	− 2.5
D	N_2H_4 + "$NH_4Cl \cdot N_2H_4$"	22.5	...	77.5	*ca.* −60
E	$NH_3 + N_2H_4$	..	92.64	7.36	−80
F	$NH_4Cl + NH_4Cl \cdot 3NH_3$ + "$NH_4Cl \cdot N_2H_4$"	32.3	25.0	42.7	−17
G	$N_2H_4 + NH_4Cl \cdot 3NH_3$ + "$NH_4Cl \cdot N_2H_4$"	18	32	50	*ca.* −67
H	$NH_3 + NH_4Cl \cdot 3NH_3 + N_2H_4$	2.0	89.0	9.0	−83
S	$NH_4Cl \cdot 3NH_3 + N_2H_4$	15.0	44.9	40.1	−60

Point F, a ternary peritectic point, is at −17° and 42.7 mole % N_2H_4, 32.3 mole % NH_4Cl. The invariant reaction occurring at this point is

Liquid + NH_4Cl = $NH_4Cl \cdot 3NH_3$ + "$NH_4Cl \cdot N_2H_4$" + heat

The curves FG and GD are dashed lines because the viscous nature of the solutions in this area of the phase diagram made it difficult to obtain freezing points. Point G, a ternary eutectic point, is estimated to be at −67° and 50 mole % N_2H_4, 18 mole % NH_4Cl. Point H, a ternary eutectic point, is at −83° and 9.0 mole % N_2H_4, 2.0 mole % NH_4Cl.

The temperature along the twofold saturation curve between the ternary eutectic points G and H passes through a maximum at point S which is called a saddle point. The temperature at the saddle point is −60°. The composition points for $NH_4Cl \cdot 3NH_3$ and N_2H_4 are points of maximum temperature in their respective areas, and with the saddle point form a straight line known as a quasi-binary section line of the ternary system.

In order to make clear the importance of the results presented in this paper to the synthesis of anhydrous hydrazine, the following example is given: A typical hydrazine reaction mixture may be composed of 99 mole % NH_3, 0.4 mole % N_2H_4 and 0.6 mole % NH_4Cl. This composition point lies in the field of crystallization for ammonium chloride 3-ammoniate. The equilibrium ternary liquid compositions along the curve GH represent the practical limits for fractional crystallization of ammonium chloride from these solutions. An equilibrium liquid composition near the saddle point S may be obtained by proper adjustment of the ammonia concentration of the ternary mixture by evaporation and cooling to crystallize ammonium chloride 3-ammoniate. At the saddle point where the equilibrium temperature is −60° the mole ratio of hydrazine to ammonium chloride in the liquid phase is 2.7:1. At this mole ratio about 63% of the hydrazine is in excess over the equivalent ammonium chloride in solution, and this excess hydrazine can be separated in the anhydrous form by distillation. The maximum mole ratio of hydrazine to ammonium chloride is obtained if less ammonia is evaporated and crystallization of the 3-ammoniate is carried to the ammonia-rich ternary eutectic point H; however, more refrigeration is required since the equilibrium temperature is −83°. The N_2H_4 to NH_4Cl mole ratio in the liquid phase is 4.5:1. Thus, a maximum (theoretical) of about 78% of the hydrazine can be freed by this procedure.

We gratefully acknowledge the support of the Davison Chemical Company, a Division of W. R. Grace and Company, through a contract with The Ohio State University Research Foundation.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KENTUCKY]

Solvents Having High Dielectric Constants. V. Limiting Ionic Equivalent Conductances in N-Methylacetamide at 40°[1,2]

BY LYLE R. DAWSON, EUGENE D. WILHOIT, RICHARD R. HOLMES AND PAUL G. SEARS

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Studies have been made concerning the conductance behavior at 40° of twenty uni-univalent electrolytes in N-methylacetamide at concentrations in the range 1–165 × 10^{-4} *N*. The limiting equivalent conductance for each electrolyte has been evaluated using a Shedlovsky plot of Λ'_0 *versus C*. Consistency within the results and with previous work is evidenced by numerous checks concerning independent conductances of ions. The results indicate that 2,4,6-trinitrophenol, hydrogen chloride and all of the salts are completely dissociated in dilute N-methylacetamide solutions. In contrast to the differentiating action of isomeric dimethylformamide, N-methylacetamide acts as a leveling solvent toward acids and partially substituted ammonium salts. Values of the limiting ionic equivalent conductances which are based upon the octadecyltrimethylammonium octadecylsulfate and the trimethylphenylammonium benzenesulfonate methods show good agreement.

Introduction

The second and the fourth papers in this series[3,4] have described the conductance behavior of thirty-one uni-univalent electrolytes in N-methylacetamide (NMA), an unusual organic solvent which is characterized by an extremely high dielectric constant (165.5 at 40°) and extensive dissolving and dissociating power. The results which have been reported heretofore indicate that most soluble salts are completely dissociated in dilute NMA solutions and that analyses of conductance data for solutions having concentrations greater than 1 × 10^{-2} *N* are complex owing to a very pronounced increase in viscosity with increasing concentration. NMA acts as a leveling solvent in its dissociating action toward partially substituted ammonium halides, and series of relative cationic and anionic limiting conductances provide considerable evidence that unusual relative solute–solvent interactions are operative in NMA solutions.

The objectives of the research which is reported herein were to determine the conductance behavior of some typical acidic electrolytes, to evaluate limiting ionic equivalent conductances by approximation methods and to extend generally the previous studies using NMA as an electrolytic solvent.

Experimental

Apparatus.—Resistances were measured with a Jones bridge assembly at frequencies of 500, 1000 and 2000 cycles per second. No significant dependence of resistance upon the frequency of the impressed signal was observed. Three flask cells, which have been described previously,[5] were used throughout this work. The cell constants were determined by the intercomparison method using Jones cells having constants which had been evaluated by the method of Jones and Bradshaw.[6] The cells and their contents were maintained at 40.00 ± 0.02° in a constant temperature bath filled with light mineral oil.

Salts.—Octadecyltrimethylammonium octadecylsulfate, octadecyltrimethylammonium nitrate, octadecyltrimethylammonium iodide and potassium octadecylsulfate were prepared by the methods described by Thompson and Kraus.[7] The observed melting points of the final products were 153–156°, 200–202°, 235–238° and 181–183°, respectively. These four salts and the two benzenesulfonates were considered suitable for use only when their equivalent conductances changed less than 0.15% after successive recrystallizations.

Reagent grade potassium and sodium bromates, ammonium perchlorate and ammonium nitrate were recrystallized twice from distilled water prior to drying under suitable conditions.

The preparation and/or purification of the remaining electrolytes have been described in previous papers.[5,8–10]

Solvent.—NMA was prepared and purified as described previously.[4] The solvent which was used in this work froze above 29.5° and had the following physical properties at 40°: conductivity, 1–3 × 10^{-7} ohm^{-1} cm.$^{-1}$; density, 0.9420 g./ml.; viscosity, 0.0302 poise; dielectric constant, 165.5 (at 10 megacycles).

Solutions.—All solutions were prepared on a weight basis and transfers were made in a dry box under a positive pressure of nitrogen. Friedman–La Mer weighing pipets were used for making successive additions of approximately 0.02 *N* stock solution to the solvent contained in a conductance cell. All weights were corrected to vacuum. The densities of the dilute solutions were assumed to be equal to that of the solvent. The conductivity of the electrolyte was obtained by subtracting the conductivity of the solvent from that of the solution. The maximum solvent correction usually did not exceed 3% of the total conductance.

Results

Owing to its extensive nature, a tabulation of corresponding values of the equivalent conductance and the concentration for each of the twenty electrolytes is not presented here.[11] The results are compactly summarized in Tables I, II and III. Similar trends in the data have been illustrated graphically in previous papers in this series.

Discussion

The plot of Λ *versus* $\sqrt{C}$ for each electrolyte is linear over the entire experimental concentration range which, as a result of limited solubilities in some cases, varied from 1–14 × 10^{-4} *N* for OctdMe$_3$NOctdSO$_4$ to 1–165 × 10^{-4} for KSCN. Ac-

(1) This work was supported in part by a contract with the Office of Ordnance Research.

(2) Taken from a thesis submitted by Richard R. Holmes and from a part of a dissertation submitted by Eugene D. Wilhoit in partial fulfillment of the requirements for advanced degrees.

(3) L. R. Dawson, E. D. Wilhoit and P. G. Sears, THIS JOURNAL, **78**, 1569 (1956).

(4) L. R. Dawson, P. G. Sears and R. H. Graves, *ibid.*, **77**, 1986 (1955).

(5) D. P. Ames and P. G. Sears, *J. Phys. Chem.*, **59**, 16 (1955).

(6) G. Jones and B. C. Bradshaw, THIS JOURNAL, **55**, 1780 (1933).

(7) W. E. Thompson and C. A. Kraus, *ibid.*, **69**, 1016 (1947).

(8) P. G. Sears, R. K. Wolford and L. R. Dawson, *J. Electrochem. Soc.*, **103**, 633 (1956).

(9) P. G. Sears, G. R. Lester and L. R. Dawson, *J. Phys. Chem.*, **60**, 1433 (1956).

(10) G. R. Lester, T. A. Gover and P. G. Sears, *ibid.*, **60**, 1076 (1956).

(11) Tables of corresponding equivalent conductance and concentration data have been deposited as Document number 5147 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting $1.25 for photoprints, or $1.25 for 35 mm. microfilm in advance by check or money order payable to: Chief, Photoduplication Service, Library of Congress.

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TABLE I

TEST OF ONSAGER'S EQUATION FOR SOLUTIONS OF SALTS IN N-METHYLACETAMIDE AT 40°

Electrolyte	Λ_0	Exptl. slope (S_E)	Theor. slope (S_T)	$(S_E - S_T)100/S_T$
HCl	20.65	13.4	13.4	0
HPi[a]	20.85	14.0	13.4	5
Na_2O_3SPh	18.41	15.0	13.3	13
Me_3PhNO_3SPh	20.47	14.4	13.4	8
$OctdMe_3Ni$[b]	21.76	16.2	13.5	20
$OctdMe_3NNO_3$	21.64	15.5	13.5	15
$KOctdSO_4$	15.47	14.0	13.1	7
$OctdMe_3NOctdSO_4$	14.27	14.5	13.0	11
NH_4ClO_4	26.45	14.2	13.8	3
NH_4NO_3	24.23	15.0	13.7	10
$KClO_4$	25.22	14.8	13.7	8
KSCN	24.48	14.7	13.7	7
KNO_3	22.94	15.8	13.6	16
$KBrO_3$	21.96	15.0	13.5	11
KPi	20.19	15.0	13.4	12
$NaClO_4$	24.96	14.2	13.7	4
NaSCN	24.24	14.7	13.7	8
$NaNO_3$	22.67	15.8	13.6	17
$NaBrO_3$	21.82	14.8	13.5	10
NaPi	20.17	13.8	13.4	3

[a] Pi represents picrate. [b] Octd represents octadecyl.

TABLE II

DATA DERIVED FROM PLOTS OF THE SHEDLOVSKY MODIFICATION OF THE ONSAGER EQUATION

Electrolyte	Λ_0	B	Electrolyte	Λ_0	B
HCl	20.68	0	$KClO_4$	25.22	−11
HPi	20.87	−11	KSCN	24.47	− 7
Na_2O_3SPh	18.37	−18	KNO_3	22.92	−28
Me_3PhNO_3SPh	20.46	−20	$KBrO_3$	21.95	−18
$OctdMe_3NI$	21.72	−32	KPi	20.18	−17
$OctdMe_3NNO_3$	21.60	−20	$NaClO_4$	24.95	− 2
$KOctdSO_4$	15.45	−10	NaSCN	24.14	− 6
$OctdMe_3NOctdSO_4$	14.26	−40	$NaNO_3$	22.65	−23
NH_4ClO_4	26.45	− 3	$NaBrO_3$	21.82	−15
NH_4NO_3	24.24	−13	NaPi	20.17	− 3

TABLE III

DATA PERTINENT TO LIMITING IONIC EQUIVALENT CONDUCTANCES IN NMA AT 40° BASED ON THE $OctdMe_3NOctdSO_4$ METHOD

Cation	λ_0^+	Anion	λ_0^-
$Me_2NH_2^+$	13.6	ClO_4^-	16.8
Me_3NH^+	12.9	SCN^-	16.1
Me_4N^+	12.0	I^-	14.6
$Et_2NH_2^+$	11.9	NO_3^-	14.5
$MeNH_3^+$	11.9	BrO_3^-	13.6
Et_4N^+	11.6	Br^-	12.8
$EtNH_3^+$	10.9	Pi^-	11.8
Me_3PhN^+	10.2	Cl^-	11.5
$BuNH_3^+$	9.8	$PhSO_3^-$	10.3
NH_4^+	9.7	$OctdSO_4^-$	7.1
$Bu_2NH_2^+$	9.4		
Pr_4N^+	9.1		
H^+	9.1		
K^+	8.4		
Na^+	8.2		
Bu_4N^+	7.8		
$OctdMe_3N^+$	7.1		
Li^+	6.6		

cording to the Onsager equation[12]

$$\Lambda = \Lambda_0 - \left[\frac{8.204 \times 10^5}{(DT)^{3/2}}\Lambda_0 + \frac{82.42}{(DT)^{1/2}\eta}\right]\sqrt{C}$$

the theoretical limiting slope of a plot of Λ *versus* $\sqrt{C}$ for a uni-univalent electrolyte in NMA at 40° should be $-[0.0695\ \Lambda_0 + 11.99]$. With the single exception for hydrogen chloride, the data presented in Table I show that the experimental slope in every case is numerically greater than the Onsager slope; the differences range from 0 to 20% with a mean of 9%. Although the numerically greater experimental slopes perhaps suggest some extent of ionic association, it is believed that the nature of the slopes of the plots of Λ *versus* $\sqrt{C}$ for electrolytes in NMA is greatly influenced by the viscosities of the solutions rapidly increasing with increasing concentration (for example, the approximate relative viscosities of 0.01, 0.5 and 1.0 *N* solutions of a typical uni-univalent electrolyte in NMA are 1.01, 1.55 and 2.25, respectively[13]).

Values of the limiting equivalent conductances were calculated directly from the experimental equivalent conductance data using the Shedlovsky rearrangement of the Onsager equation.[14] Values of the limiting equivalent conductance calculated in this manner are designated as Λ'_0 and generally are found to deviate from the true value for the limiting equivalent conductance by a linear function of the concentration as

$$\Lambda'_0 \equiv \frac{\Lambda + \beta\sqrt{C}}{1 - \alpha\sqrt{C}} = \Lambda_0 + BC$$

which for electrolytes in NMA at 40° becomes

$$\Lambda'_0 \equiv \frac{\Lambda + 11.99\sqrt{C}}{1 - 0.0695\sqrt{C}} = \Lambda_0 + BC$$

As in previous studies,[3,4] the plot of Λ'_0 *versus* C for each electrolyte is linear over the entire experimental concentration range and is characterized by a small negative slope probably resulting from viscosity effects. Data pertinent to plots of Λ'_0 *versus* C are summarized in Table II. Corresponding values of Λ_0 in Tables I and II in some cases differ by a few hundredths of a unit; however, it is believed that those in Table II are probably more accurate inasmuch as a preferable extrapolation procedure was used.

A survey of the values of Λ_0 in Table II together with those obtained in previous studies reveals numerous confirmations of the Kohlrausch law of independent ionic conductances therein indicating consistency within the results reported herein as well as with those published previously.

On the basis of experimental and theoretical structural considerations, Thompson and Kraus[7] have suggested that the limiting equivalent conductances of the $OctdMe_3N^+$ and the $OctdSO_4^-$ ions are approximately equal and can be evaluated by halving the limiting equivalent conductance of $OctdMe_3NOctdSO_4$. If the limiting equivalent conductances of these two large similarly-shaped ions are known, other limiting ionic equivalent

(12) L. Onsager, *Physik. Z.*, **28**, 277 (1927).
(13) P. G. Sears, Dissertation, University of Kentucky, 1953.
(14) I. Shedlovsky, *J. Franklin Inst.*, **54**, 1405 (1932).

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conductances can be evaluated from properly related data for electrolytes containing either the $OctdMe_3N^+$ or the $OctdSO_4^-$ ion and for other electrolytes having common anions or cations. Table III contains values of limiting ionic conductances in NMA at 40° which are based upon this approximation method. Data from previous papers[3,4] were utilized also in order to provide an up-to-date comprehensive tabulation for NMA solutions.

The trimethylphenylammonium and the benzenesulfonate ions, like the $OctdMe_3N^+$ and the $OctdSO_4^-$ ions, are relatively large similarly-shaped species having comparable dimensions and are characterized by almost equal limiting conductances in aqueous solutions.[15,16] Consequently, it is worthwhile to note that the results in Table II would be altered less than 0.5% if Me_3PhNO_3SPh were used as the reference electrolyte instead of $OctdMe_3NOctdSO_4$. On the basis of data for aqueous and NMA solutions, therefore, Me_3PhNO_3SPh is potentially applicable as a reference electrolyte for approximating limiting ionic equivalent conductances in other solvents. Inherent advantages may be utilized also inasmuch as Me_3PhNO_3SPh, NaO_3SPh and Me_3PhNI are commercially available, easily purified and readily soluble in several common solvents in which $OctdMe_3NOctdSO_4$ and $KOctdSO_4$ are practically insoluble.

Based on the data in Table III, the limiting equivalent conductance–viscosity products for the Bu_4N^+ and the Pi^- ions in NMA are 0.236 and 0.356 ohm^{-1} $cm.^2$ $equiv.^{-1}$ poise and are about 35% greater than the corresponding products for aqueous solutions. Nevertheless, the ratio of the limiting equivalent conductance of the picrate ion to that of Bu_4N^+ ion in NMA differs less than 3% from the same conductance ratio for aqueous solutions and consequently indicates considerable parallelism in the relative conductance behavior of these large ions in NMA and in water.

Although the ratio of the viscosity of NMA at 40° to that of water at 25° is 3.4, the ratio of the limiting equivalent conductance of an ion in water at 25° to that of the same ion in NMA at 40° varies from 2.5 for the Bu_4N^+ ion to 8.7 for the potassium ion, excluding the solvated proton and several ions for which proper comparison data are unavailable. The broad range of values for the conductance ratio together with the very high values for the conductance–viscosity products for the Bu_4N^+ and Pi^- ions suggests that unusual relative solute–solvent interactions and perhaps significant variations between the macroscopic viscosities of the solutions and the microscopic viscosities in the immediate vicinities of the ionic species may be operative in NMA solutions. Novel positions which are occupied by several ionic species in series of decreasing cationic and anionic limiting equivalent conductances are readily discernible from the data presented in Table III.

In comparing the behavior of hydrogen chloride and 2,4,6-trinitrophenol (picric acid) in the isomeric amides, N-methylacetamide and N,N-dimethylformamide, it is interesting to note that the former and the latter[8] act as leveling and differentiating solvents, respectively, toward the acidic solutes. The extent of substitution on the amide-N not only drastically affects the magnitudes of physical properties but also apparently is reflected in the proton-accepting properties of the medium.

Other conductance studies involving the behavior of multivalent electrolytes in NMA and also the behavior of uni-univalent electrolytes in iso-viscous mixtures of NMA and tertiary butyl alcohol and in mixtures of isomeric NMA and N,N-dimethylformamide are in progress in this Laboratory.

(15) W. J. McDowell and C. A. Kraus, THIS JOURNAL, **73**, 2173 (1951).

(16) G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 400 (1932).

LEXINGTON, KENTUCKY

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

Interaction of Polyelectrolytes with the Electrical Double Layer on Mercury–Water Interfaces. II. Influence of Added Ionized Polyacids on the Differential Capacity*

BY ISRAEL R. MILLER[1] AND DAVID C. GRAHAME

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The differential capacity of the electrical double layer at the interface between mercury and aqueous 0.1 *N* NaF solutions containing various amounts of the salts of dibasic and polybasic acids at different temperatures has been measured. A series of polyacids has been investigated, starting with simple dibasic acids, through the relatively low molecular weight polyaspartic and polyglutamic acids, and extending finally to very high molecular weight samples of polymethacrylic acid of various degrees of polymerization. It has been found that the results can be interpreted by assuming (a) that even short hydrocarbon chains produce a squeezing-out effect which appears as an adsorption of anions, and (b) that polybasic anions are completely expelled from the interface when the mercury carries even a small negative charge, and strongly attracted when the charge is slightly positive. Adsorption–desorption peaks are produced at the potential of the electrocapillary maximum through the operation of this effect. It seems clear that a monolayer of anions is formed.

Introduction

From the electrocapillary properties of soluble acetates and oxalates it is known,[2–4] that the car-

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(1) On leave of absence from the Weizmann Institute, Rehovot, Israel, during the execution of the experimental part of this work.

(2) G. Gouy, *Ann. chim. phys.*, [7] **29**, 145 (1903).

(3) D. C. Grahame, M. A. Poth and J. I. Cummings, THIS JOURNAL, **74**, 4422 (1952).

(4) D. C. Grahame and R. A. Soderberg, *J. Chem. Phys.*, **22**, 449 (1954).

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boxylate ion is little or not at all adsorbed on an uncharged mercury surface. The object of the present work has been to investigate the coöperative influence of a series of carboxylate groups located on a polymeric chain. The plan has been to start with the simplest dicarboxylate ion, oxalate, and to work up to ionized polymethacrylic acid in easy stages.

The adsorption of ions on mercury takes place in four somewhat different ways, and it is helpful to have these in mind even though it is not always possible to sort them out experimentally. There is, in the first place, simple electrostatic attraction (Type I adsorption). On an uncharged surface this type of attraction is deemed absent, and whatever adsorption is found is attributed to something else.

Electrostatic attraction gives rise to the diffuse double layer, whose mathematical exposition was given by Gouy and Chapman, but the effects of electrostatic attraction are not wholly predictable by means of that theory because the ions in question have a finite distance of closest approach to the interface, and the thickness and dielectric properties of this "inner region" of the double layer are of controlling importance in most cases, as was first pointed out by Stern. These properties are not even yet fully understood, although they have formed the subject of many publications.[5]

A second type of adsorption of ions (to be called Type II) is related to what is commonly called chemisorption. Many anions form chemical bonds with mercury, the strength of the bond depending upon the surface charge density. The concept of adsorption on mercury as chemical bond formation was clearly stated as long ago as 1908 by Gouy.[6] The ions which show this phenomenon most strongly ($S^=$, I^-, SCN^-, Br^-) are those which form highly insoluble salts with mercury, and the two phenomena are obviously related. One can say either that a covalent bond is formed between mercury and the anion, or one can attribute the attraction to the polarizability of the anion. Undoubtedly a large polarizability leads to strong covalent bond formation, so that the two statements are equivalent.

Type II adsorption is most clearly recognizable at the potential of the electrocapillary maximum (e.c.max.) because Type I adsorption is then absent. The adsorption of anions (from whatever cause) lowers the surface tension and shifts the potential of the e.c.max. toward more cathodic values. A more distinctive test for Type II adsorption lies in the rather rapid rise in the differential capacity which occurs as the surface is positively charged, but since this also happens with Type I adsorption of bivalent and polyvalent ions (especially when the charge is concentrated at the center of an ion, as in $SO_4^=$ rather than distributed along a chain, as in the adipate ion), both tests must be positive before one can safely conclude that Type II adsorption is operative.

A third type of adsorption (Type III) is that exhibited by such anions as NO_3^-, ClO_4^-, ClO_3^- and some others. These anions are known to be adsorbed on mercury[2-4] at the potential of the electrocapillary maximum (by the criteria mentioned under Type II adsorption), but it is almost inconceivable that they should form covalent bonds with mercury under these conditions. A more probable explanation was given many years ago by Frumkin, Reichstein and Kulvarskaja[7] in connection with their study of the adsorption of anions at an air–water interface. It was found that nitrate and perchlorate ions are adsorbed at an air–water interface (though not so strongly as at a mercury–solution interface) and it was pointed out that these ions, by virtue of their size, possess what we should nowadays call large structure-breaking tendencies. The latter effect can be seen, for example, by comparing the relative partial molal entropies of water in various solutions of 1:1 electrolytes.[8] Frank and Robinson say[8] "For the univalent electrolytes the maximum disturbing effect is shown by KNO_3. This might be attributed to the plane triangle structure of the nitrate ion and its inability to fit smoothly into the four coördinated structure of water." Although data for perchlorates are not available, we would predict an almost equally strong effect upon the relative partial molal entropy of water. It seems clear that nitrate and perchlorate ions at an interface are at a lower potential energy than ions in the interior of the solution because of the fewer hydrogen bonds broken by an ion in that location. The adsorption of nitrate ion on mercury is probably favored relative to its adsorption at an air–water interface by the effectively infinite dielectric constant of the metal, since this makes it possible for the ion to lose water of hydration on the side of the metal without a major loss of its energy of solvation.

It is convenient to say that these anions are squeezed out of solution, and the reality of the effect can hardly be doubted in the case of the adipate ion, for instance, where the hydrophobic part of the molecule unquestionably squeezes the ion to the interface.

A fourth type of adsorption is to be expected when one stops to consider the possibility of lateral interaction between ions which have been squeezed out of solution. It is well known that a monolayer of un-ionized molecules can form at an interface, and it is clear that in many cases lateral interaction (van der Waals forces) will help to stabilize the layer. The same type of interaction is to be expected with anions of long-chain organic acids and, when found, it will be called Type IV adsorption. Strictly speaking it is a sub-class of Type III adsorption, since anions which show strong lateral interaction would normally be expected to be of a type which would be squeezed out of solution also.

Experimental Details

The differential capacity measurements were carried out on an apparatus developed by one of us and described previously.[9] Some surface tension measurements also were made by the drop-time method, but better results could be obtained by integrating the differential capacity data twice

(5) The most recent is that of J. R. Macdonald, *J. Chem. Phys.*, **25**, 364 (1956), which will serve as a key to the earlier literature.

(6) G. Gouy, *Compt. rend. acad. sci.*, **146**, 290 (1908).

(7) A. Frumkin, S. Reichstein and R. Kulvarskaja, *Kolloid Z.*, **40**, 9 (1926).

(8) R. A. Robinson and A. L. Robinson, *J. Chem. Phys.*, **8**, 933 (1940).

(9) D. C. Grahame, THIS JOURNAL, **71**, 2975 (1949).

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with respect to potential in cases where this procedure is allowed. However, the most interpretable data turn out to be capacity values themselves, and the present paper will be concerned with these.

Although the adsorption process *per se* is usually very fast in measurements of this kind, considerable time is needed for large molecules to diffuse to the surface. The extent to which diffusion equilibrium is attained can be estimated by taking measurements at different times on a stationary droplet or by taking measurements on a moving droplet whose rate of growth is subject to control. In a series of control experiments the rate of flow of the mercury was altered, keeping constant the size of the droplet at the moment of measurement. No significant variations of capacity attributable to the slow rate of diffusion of the adsorbate could be noted except at or near the potential of the desorption peaks of polymeric anions. An example of the observed behavior in such a case is shown in Fig. 1 which shows the

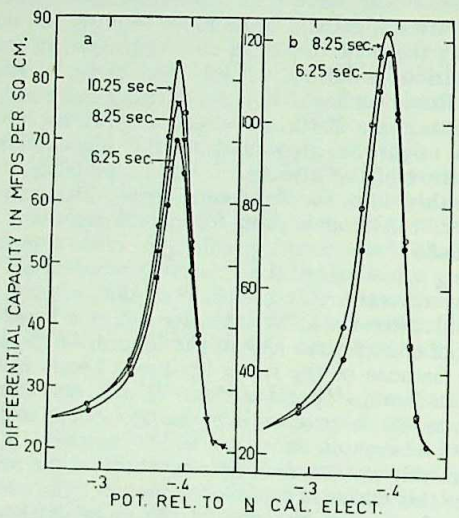

Fig. 1.—Differential capacity curves taken at same Hg drop size but different drop ages. Ionized PMA at 61°; $z = 4500$; supporting electrolyte, 0.1 N NaF + 0.001 N NaOH; concn. of PMA = 0.000125 N (a) or 0.00025 N (b).

diffusion lag to exert an appreciable effect on the measurements only in very dilute solutions of the adsorbate. To avoid this source of uncertainty, the measurements reported below deal only with solutions concentrated enough not to show this effect. The matter was very thoroughly checked over a wide range of conditions. For the purposes of the present paper, it does not matter greatly, however, since the capacity curves are to be used directly and not integrated. (It is the integrated curves which are most seriously in error if the diffusion is too slow.)

Results and Conclusions

Dibasic and Tribasic Acids.—The sodium salts of oxalic, adipic, glutaric and 1,2,3-propanetricarboxylic acids were dissolved in a supporting electrolyte composed of 0.1 N NaF + 0.002 N NaOH. The supporting electrolyte was added as a means of ensuring that the results would be comparable to those obtained later using polymeric acids in solution. The principal results are shown in Fig. 2.

It will be observed that the anions of these acids raised the capacity in a characteristic manner, different for each. The approximate values of the potential of the electrocapillary maximum (e.c. max.) are marked with short vertical lines on the figures. It is at these potentials that the influence of the anion is most simply seen.

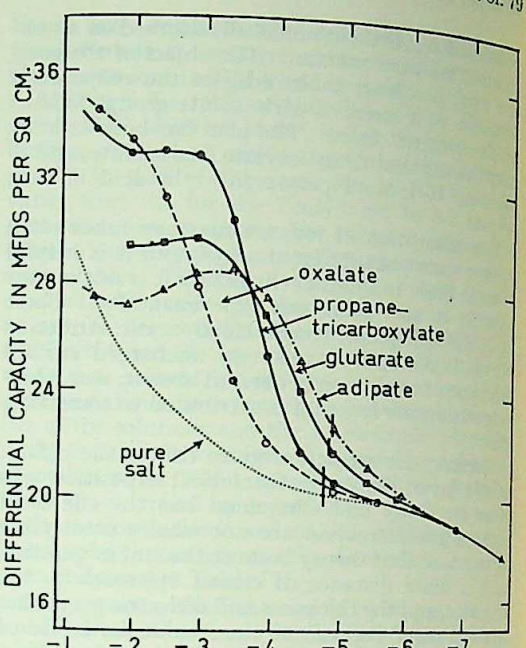

Fig. 2.—Differential capacity curves in presence of 0.06 N solutions of sodium salts as indicated. Supporting electrolyte, 0.1 N NaF + 0.002 N NaOH; $t = 25°$.

The oxalate ion raises the differential capacity of the double layer at the potential of the e.c.max. only very slightly, and its behavior is only a little different from that of the sulfate ion at all potentials (data not shown). From purely chemical considerations one would not expect either the sulfate or the oxalate ion to be chemisorbed even on positively charged mercury, and in spite of some conflicting evidence on this point with regard to the sulfate ion,[4] that is the assumption upon which we shall proceed to discuss further results.[10] Therefore the curve for the oxalate ion will be regarded as normal for a divalent anion with charges not much separated.

The glutarate ion, with three CH_2 links in the chain, would be expected to exhibit mild outsqueezing (Type III adsorption), and this is the presumed reason for the increased capacity (Fig. 2). It is usual for adsorption of an anion to increase the capacity of the double layer, no clear-cut exceptions to this rule being known, except as indicated below. The "hump" in the curve has been explained by one of us (D.C.G.)[11] as the result of the formation of a quasi-crystalline semirigid layer of solvent at the interface. A different interpretation relating to the orientation and re-orientation of the adsorbed molecules will be presented by the other author (I.R.M.) in a separate publication. In this paper we shall not defend either point of view.

The adipate ion, with four CH_2 groups, con-

(10) It does not really matter in the ensuing discussion whether this assumption is strictly correct or not, and it greatly simplifies the presentation.

(11) D. C. Grahame, *J. Chem. Phys.*, **23**, 1725 (1955); THIS JOURNAL, **79**, 2093 (1957).

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tinues the trend set by the glutarate ion and reinforces our explanation of it. It is interesting, then, to compare the behavior of the anion of 1,2,3-propanetricarboxylic acid. This can best be thought of as a glutarate ion with one H atom replaced by carboxylate. The marked change in the differential capacity curve shows two effects of increasing the charge on the ion. First, it suppresses the out-squeezing effect at the e.c.max. By increasing the energy of interaction of the ion with water, the ion is kept in solution, away from the interface. At more anodic potentials the capacity rises rapidly, and this is characteristic of an ion of multiple charge. In other words, Type I adsorption becomes dominant.

Although we do not have comparable data for the formate ion, it seems reasonable to suppose that its differential capacity curve on mercury under these conditions would resemble that of the pure salt shown as a dotted line in the figure. If so, the curves for formate, oxalate and propanetricarboxylate ions would illustrate well the effect of increasing the charge on an anion.[11a] (Cations show no such effect.)

Polyaspartic and Polyglutamic Acids.—The polymers used for this investigation were of relatively low molecular weight (degree of polymerization about 30). Their behavior is closer to that of the dibasic and tribasic acids than to that of the high molecular weight polymethacrylic acid (PMA). The repeating unit in polyaspartic acid is NHCH(CH₂COOH)CO which makes it roughly comparable to butyric or valeric acid. The relatively large number of hydrophobic groups per carboxylate ion accounts for the rather large capacity seen in Fig. 3 even at the potential of the e.c.max. This is strong Type III adsorption. Although each anion carries a total of about 30 negative charges, these are so uniformly distributed and so widely spaced along the chain that adsorption takes place even when the mercury surface is negatively charged, a somewhat noteworthy result.

The data for the curve at 0.000048 *N* are reproduced as a matter of interest, but at this low concentration it would be unwise to disregard the effect of the low rate of diffusion of the adsorbate, which may lead to considerable error in the results.

The absence of a "hump" (except at the lowest concentration) should be pointed out, although no explanation will be offered at this point.

The anion of polyglutamic acid, with one more CH_2 group in the side chain, shows (in Fig. 4) the beginning of what we have called Type IV adsorption. At the highest concentration studied a peak appears in the capacity curves, and the height of the peak is strongly frequency dependent. These peaks are characteristic of adsorption–desorption phenomena of the type studied extensively in the past using un-ionized adsorbates.[12–14] The appearance of such peaks has always been associated with the formation of a monolayer, and this appears to be a reasonable explanation here also, except that in this instance the monolayer is probably incomplete as indicated by facts which will be explained presently. The layer will be called a monolayer in what follows to avoid cir-

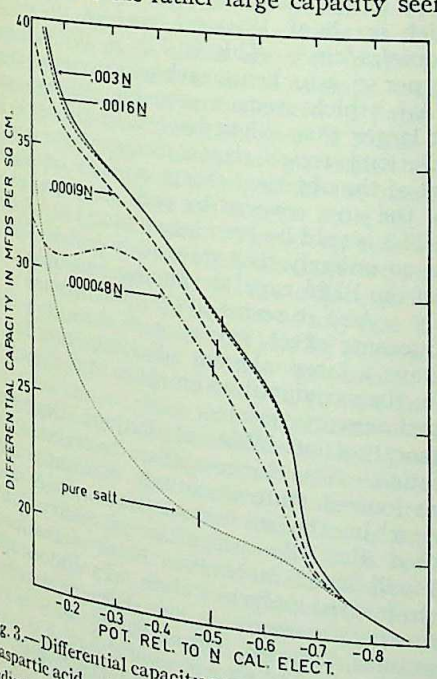

Fig. 3.—Differential capacity curves in presence of ionized polyaspartic acid. $t = 25°$; drop age = 30.25 sec.; concn. as indicated. Supporting electrolyte as in Fig. 2.

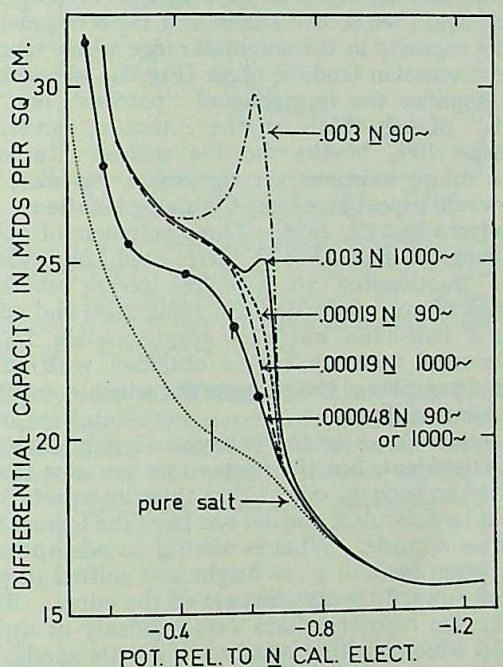

Fig. 4.—Differential capacity curves in presence of ionized polyglutamic acid. $t = 25°$; drop age = 30.25 sec.; freq. and concn. as indicated. Supporting electrolyte, 0.1 *N* NaF + 0.0015 *N* NaOH.

(11a) NOTE ADDED IN PROOF.—Strictly speaking one should compare the acetate, succinate, and tricarboxylate ions. The trend is the same as that shown in Fig. 2.

(12) M. A. Proskurnin and A. Frumkin, *Trans. Faraday Soc.*, **31**, 110 (1935).

(13) D. C. Grahame, *Chem. Revs.*, **41**, 441 (1947).

(14) V. I. Melik-Gaikazyan, *J. Phys. Chem. U.S.S.R.*, **26**, 1184 (1952).

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cumlocution. The significance of the peak in the capacity curve is that at the potential involved there is a sudden potential-dependent change in the composition of the double layer corresponding to the displacement of solvent by adsorbate. It is of interest that in Fig. 4 the peak occurs approximately at the potential of the e.c.max., which indicates, as one would expect, that a monolayer of anions does not form readily on a negatively charged surface even when the molecule has a considerable number of hydrophobic groups tending to put it there.

With non-electrolytes two desorption peaks are generally observed.[12] A second peak has not been observed in any of the work described in this paper, presumably because it is impossible to desorb a negatively charged ion from a positively charged surface by making the surface more positive.

In somewhat more dilute solutions of polyglutamic acid (~0.0002 *N*) there is a small dispersion of the capacity in the potential range where monolayer formation tends to occur (Fig. 4). Probably this signifies the formation of "patches" or "islands" of adsorbate at the interface, covering perhaps 10% of the metallic surface. In still more dilute solutions the dispersion vanishes, as one would expect according to this explanation.

Polymethacrylic Acid.—Three polymers of polymethacrylic acid (PMA) were used, and these were fractionated to samples having average degrees of polymerization z of 1950, 2600 and 4500 with a half-band width of approximately 7%.[15] Differential capacity curves obtained with fully ionized samples of the polymer for which $z = 1950$ are shown in Fig. 5.

A resemblance to the behavior of polyglutamic acid is evident, but the phenomena are now exaggerated to such an extent that their interpretation would be difficult if one did not have the former results as a guide. What is seen is an adsorption–desorption peak of great height and shifted in potential toward the anodic part of the curve. The rise in the capacity starts very suddenly at a potential which is either equal to or a little anodic to that of the e.c.max. To the left of the peak there is undoubtedly a surface layer of anions (analogous to the surface layer of polymethacrylic acid reported earlier[16]). The low value of the capacity in this state is attributed to the fact that once a monolayer of anions is formed, further increase in the concentration of anions occurs only slowly. Since the capacity was not abnormally low under similar conditions in Fig. 4, it was assumed that monolayer formation was incomplete, as stated above.

It is of interest that the results shown in Fig. 5 are frequency independent and occur at low temperatures (0°) as well as at higher temperatures, where the results (not shown) are not qualitatively different except that at higher temperatures (*i.e.*, 61°) the peak is about 20% higher than at 0°. The frequency independence indicates that whatever reorientation of molecules or bonds is needed for the formation of the adsorbed layer does not involve a significant activation energy. This fact is in agreement with the observation that the height of the peak is not strongly temperature dependent. A rather more complicated situation exists with un-ionized PMA, where the height of the peak is strongly temperature dependent and only in certain cases frequency dependent.[16] The difference is almost surely attributable to the well known dependence of configuration upon degree of ionization, the anion being relatively uncoiled. This uncoiling presumably involves the breaking of hydrogen bonds, which leaves the ion free to adsorb without further breaking of such bonds.

Samples of ionized PMA of higher molecular weight were indistinguishable in their behavior from the results here presented. The same result was also observed with un-ionized PMA and is attributed as before[16] to the fact that diffusion of whole molecules plays a negligible role. Those molecules which were able to reach the surface in the eight or ten seconds during which the mercury droplet was being formed in the solution gave rise to the observed results; the rest played no part.

The surface area per structural unit of the polymer can be computed as follows. At a potential somewhat to the left of the peak (say +0.180 v., relative to the e.c. max.) the total surface charge density is about 12 μcoul./cm.^{2} or 12×10^{-11} monomoles/cm.^{2}. This is 7.2×10^{13} structural units per sq. cm., hence each unit covers an area of 140 Å.^{2}, which seems reasonable, although somewhat larger than might have been guessed. This calculation is rough, since it disregards the fact that a part of the observed charge could be fluoride ion. If so, the area covered by each structural unit of the PMA would be even larger than 140 Å.^{2}, which seems so unlikely that we tend to believe that the ions of the PMA expel the fluoride ions almost completely. Also it seems likely that because of the outsqueezing effect, ions such as those from PMA will have a large inherent advantage over fluoride ions in their competition for space at the positively charged mercury surface.

Adsorption of PMA at Various Degrees of Ionization.—The electrocapillary behavior of PMA in the ionized state is entirely different from its behavior in the un-ionized state. It is to be expected that the properties of partly ionized PMA will stand in between those of the ionized and un-ionized polyelectrolyte. In Fig. 6 differential capacity curves at four different degrees of ionization are shown. From the figure it is clear that the height and sharpness of the peak diminish as the degree of ionization diminishes and the potential at which the rise starts to occur also becomes more cathodic. At $\alpha = 0.5$ traces of another peak are perceptible at a potential of about −0.7 volt. At $\alpha = 0.1$ this peak is much more pronounced and

(15) The approximate degree of polymerization of the PMA before fractionation was 4000. From this mixed polymer 14 fractions were obtained in a range of z-values from 500 to 5500. The degree of polymerization of the different fractions was obtained by light scattering measurements in a 90° turbidimeter coupled with a Pulfrich visual split-field photometer and also by viscosity measurements in an Ostwald–Fenske viscosimeter where the PMA was present first in 2 *N* NaOH and then in 0.002 *N* HCl. The results were interpreted by means of Figs. 6 and 7 of A. Katchalsky and H. Eisenberg, *J. Polymer Sci.*, **6**, 145 (1951). The mean half width of z was estimated from the differences in the z's as determined by the three methods.

(16) I. R. Miller and D. C. Grahame, THIS JOURNAL, **78**, 3577 (1956).

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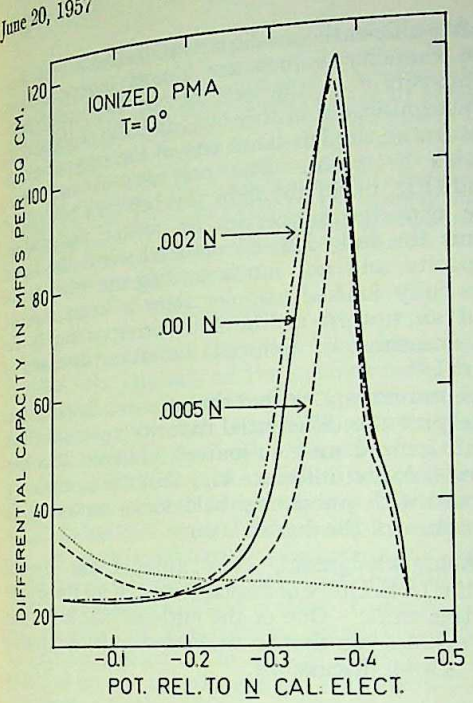

Fig. 5.—Differential capacity curves in presence of ionized polymethacrylic acid (PMA). $t = 0°$; $z = 1950$; freq. = 1000 cycles; concn. as indicated; supporting electrolyte as in Fig. 2.

has moved to a more negative potential. Nevertheless, the potential of this peak is more positive than the corresponding desorption potential of un-ionized PMA. The shift in the potential of the peak with the degree of ionization recalls the similar behavior of the peaks which are seen in the presence of monomeric substances at various concentrations (*cf.* behavior of butyric acid in paper I[15] or of aliphatic alcohols in the work of Melik-Gaikazyan[14]). In paper I attention was called to the fact that the desorption potential in the presence of un-ionized PMA does not depend upon the concentration of the polymer. The given reason for this behavior was the assumed constant concentration of polymer segments in the adjacent layers (called the surface phase) to the adsorption layer. This concentration was assumed to be close to the segment concentration in the polymeric coil. By ionizing part of the carboxylic groups and by diluting the surface phase as a consequence of electrostatic repulsion, which increases with the degree of ionization, the over-all concentration of the ionized groups in the surface phase decreases. Thus in this respect increased ionization of a polyelectrolyte is analogous to decreased bulk concentration of a monomeric surface-active substance.

The analogy just drawn is not complete, however, because each un-ionized segment of the chain is terminated by two ionized segments, and these inhibit and tend to prevent the adsorption of the un-ionized segments on the negatively charged surface. For this reason the change with concentration of the potential of the peak shifts in the opposite direction from that of un-ionized monomeric substances.

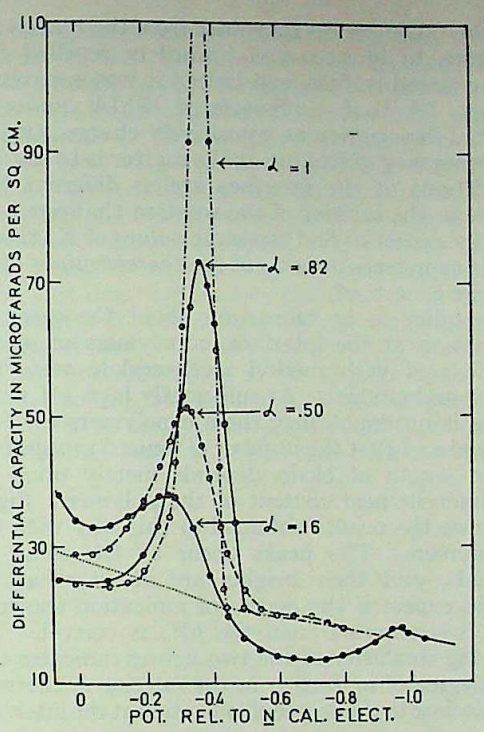

Fig. 6.—Differential capacity curves in presence of partially ionized PMA. When $\alpha = 1$, pH 11; $\alpha = 0.82$, pH 6.85; $\alpha = 0.50$, pH 5.7; $\alpha = 0.16$, pH 4.7. Supporting electrolyte = 0.1 N NaF + NaOH as needed to produce desired pH. $t = 25°$; $z = 1450$.

Copolymers of Methacrylic Acid with Methyl Methacrylate.—The degree of dissociation in the surface is not necessarily the same as the degree of dissociation of the same substance in the bulk

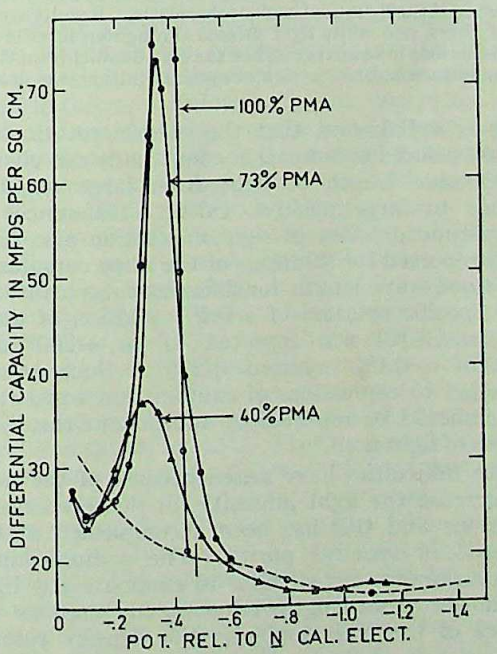

Fig. 7.—Differential capacity curves in presence of copolymers of methacrylic acid and methylmethacrylic acid in different ratios. $t = 25°$; composition of polymers as indicated; supporting electrolyte as in Fig. 2.

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phase. Differences may arise from the tendency of protons to be attracted toward or repelled from the charged surface, and indeed it was apparent in paper I[15] that undissociated PMA undergoes partial dissociation at a positively charged surface. Another way of looking at the matter is to say that conditions at the interface are so different from those in the interior of the solution that one could hardly expect to find the same values of K_a there if K_a is expressed in terms of the *concentrations* of the species concerned.

In order to be more sure about the extent of ionization at the interface, copolymers of methacrylic acid with methyl methacrylate were prepared and studied. At sufficiently high *p*H values there is no doubt that these copolymers are fully ionized and that the number of ionized groups for a given length of chain depends merely upon the methacrylic acid content of the polymer. Figure 7 shows the results obtained in this way with two copolymers. The peaks occur at the same potentials, and their heights are about what one would expect if the degree of ionization shown in Fig. 6 (computed from the *p*H) is correct. The striking similarity of the two figures indicates that the degree of ionization in the interior of the solution is close to the degree of ionization at the interface.

At sufficiently anodic potentials (below −0.23 v.) the capacity values are almost independent of composition in the case of the two copolymers. The significance of this fact, and also of the sudden upturn at the left-hand end of the two curves, remains in doubt. The polymers of methacrylic acid (Fig. 6) do not show this behavior but exhibit the expected properties on anodic polarization. Thus the fully ionized material shows the lowest capacity and not much turning up, whereas the less fully ionized samples show a larger capacity and an upturn at the end corresponding to the phenomenon of induced ionization discussed in part I.[15]

Summing up, we find that it is usually possible to interpret the differential capacity curves of PMA, both ionized and un-ionized, obtained at a mercury–solution interface and that the results are in accord with previously held views concerning the structure of the double layer.

Acknowledgment.—The authors are indebted to the U. S. Office of Naval Research for the support of this work. One of the authors (I.R.M.) wishes to express his thanks to Professor A. Katchalsky for helpful discussions.

AMHERST, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Anomalous Optical Rotations of Coördination Compounds[1]

BY BODIE E. DOUGLAS AND WILLIAM C. ERDMAN

RECEIVED FEBRUARY 9, 1957

The previously reported change in sign of optical rotation of *d-cis*-$[Co(en)_2Cl_2]Cl$ with a change in concentration is not observed if the light used is monochromatic. Results are compared using a sodium lamp, white light filtered through colored glass filters, and white light filtered through an interference filter plus colored glass filters. The effectiveness of the filter combinations in removing all but the NaD doublet from the spectrum produced by the sodium lamp are compared. A change in magnitude but not in sign of optical rotation was noted for K[Co(edta)] using different light sources.

It is well known that the specific rotations of highly colored coördination compounds can change with wave length of light from large negative values to large positive values. Differences in magnitude or even in sign of rotation also have been reported for solutions of the same complex at the same wave length for different concentrations. The specific rotation of a 0.4% solution of *d-cis*-$[Co(en)_2Cl_2]Cl$ was reported to be −200° and that of a 0.1% solution +215°.[2] Such results have led to expressions of caution that concentrations should be reported in addition to the wave length of light used.[3]

The difficulties have arisen because of the need to increase the light intensity for densely colored solutions and this has been accomplished at the expense of spectral purity. The sodium lamp, with an orange cut-off filter to eliminate any light of shorter wave length, is commonly used as the source of the NaD doublet. For densely colored coördination compounds a more intense source has been obtained by using various filter combinations which give very broad bands of transmitted light.

The purpose of this investigation was to study the change in sign of rotation with change in concentration and to determine the limits of usefulness of several light sources or filter combinations.

Experimental

The *d-cis*-$[Co(en)_2Cl_2]Cl$ was prepared and resolved by the method described by Bailar.[2] The directions refer to the compound as the *levo* form, but the rotation is actually positive at all concentrations for NaD light. The negative rotations are erroneous. The *d*-K[Co(edta)] (edta represents the ethylenediaminetetraacetate ion) was generously provided by Professor Francis P. Dwyer of the University of Sydney. The *d* prefix refers to the rotation of +1000° at 5461 Å.

Optical rotations were obtained with a Rudolph Model 70 Polarimeter. The readings for 0.3 and 0.4% solutions of *cis*-$[Co(en)_2Cl_2]Cl$ using the sodium lamp were obtained using a photoelectric attachment built by W. C. Erdman. All measurements were made at room temperature (25–30°) immediately after mixing the solutions.

The spectra of the sodium lamp with various filters were obtained with a Hilger constant deviation glass prism spectrograph. The transmission curves for the filters and solu-

(1) This work was supported by a grant from the Research Corporation. Presented at the 130th Meeting of the American Chemical Society in Atlantic City, New Jersey, September 19, 1956.

(2) J. C. Bailar, Jr., *Inorg. Syn.*, II, 224 (1946).

(3) W. C. Fernelius, *Advances in Chem.*, 8–9 (1950).

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tions of the complexes were obtained with a Beckman Model DU spectrophotometer. The transmission curves for solutions of *cis*-$[Co(en)_2Cl_2]Cl$ in methyl alcohol were found to be essentially identical with those obtained for freshly prepared aqueous solutions. However, the methyl alcohol solutions did not undergo color changes on standing for periods of an hour or two as was the case for aqueous solutions because of aquation reactions. For this reason methyl alcohol solutions of *cis*-$[Co(en)_2Cl_2]Cl$ were used for the spectral studies of the sodium lamp. The exposures required for the spectrum of the sodium lamp filtered through the solution of *cis*-$[Co(en)_2Cl_2]Cl$ were 30–60 minutes.

Discussion

For densely colored solutions such as *cis*-$[Co(en)_2Cl_2]Cl$ the intensity of the sodium lamp is inadequate for measurements over a wide range of concentrations. In such situations workers[4] have used filter combinations such as a solution of 9.4 g. of $K_2Cr_2O_7$ and 8.9 g. of $CuSO_4 \cdot 5H_2O$ in 300 cc. of water, or for a more intense source a 3% solution of $K_2Cr_2O_7$ has been used. Frequently the authors have not given information concerning the light source used. Werner[5] reported a rotation of −200° for a 0.25% solution of *d*-*cis*-$[Co(en)_2Cl_2]Cl$ in a 2 dm. tube, but does not give details concerning the light source used. The optical density of such a solution is only slightly greater than for a 0.4% solution in a 1 dm. tube for which the reported value[2,4] is also −200°. Presumably Werner used white light and a filter similar to the $CuSO_4$–$K_2Cr_2O_7$ solution.

Figure 1 shows the transmission curves for the $CuSO_4$–$K_2Cr_2O_7$ solution used by Bailar and Auten, for an interference filter (Baird Associates), and for

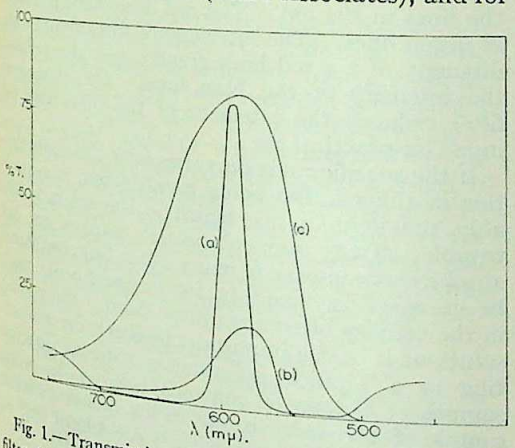

Fig. 1.—Transmission curves for a Baird interference filter, (a) a combination of Corning blue-green and orange cut-off filters, (b) and a $CuSO_4$–$K_2Cr_2O_7$ solution in a 1 cm. cell (c).

the combination of an orange cut-off filter (Corning 3-66) and a blue-green filter (Corning 4–70). The $CuSO_4$–$K_2Cr_2O_7$ solution gives a broad band which is not suitable for use with a solution which absorbs strongly in the vicinity of the NaD doublet. In fact the light transmitted through such a filter and a solution of *cis*-$[Co(en)_2Cl_2]Cl$ is red, not yellow. The 3% $K_2Cr_2O_7$ solution would be much worse as an effective filter. The combination of colored glass filters gives lower intensity in the vicinity of the NaD doublet than the $CuSO_4$–$K_2Cr_2O_7$ solution but the transmission in the red is also somewhat less which makes the glass filter slightly more effective. The interference filter gives a very narrow band with high transmission in the vicinity of the NaD doublet, but the transmission increases in the red and blue portions of the spectrum. The interference filter is provided with a yellow cut-off filter which is very effective in removing the blue light, but does not remove the red. It is the red light which is troublesome for the compounds investigated here.

The low transmission in the vicinity of the NaD doublet and high transmission in the red portion of the spectrum for $[Co(en)_2Cl_2]Cl$ and K[Co(edta)] are shown in Fig. 2. If one uses a filter combination which gives a broad band of yellow light the wave length of the maximum of the transmitted band is shifted appreciably toward the red after passing through a solution of either complex. Any shift in the wave length of the band of transmitted light will vary with the concentration of the solution of the complex through which the light passes and a shift in optical rotation is to be expected.

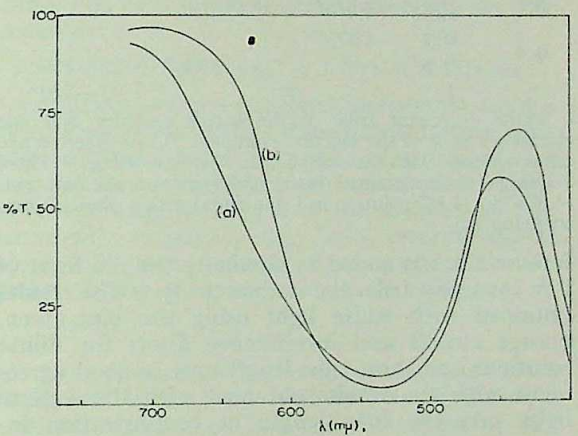

Fig. 2.—Transmission curves for a 0.4% solution of *cis*-$[Co(en)_2Cl_2]Cl$ (a) and a 0.2% solution of K[Co(edta)] (b) in 1 cm. cells.

The specific rotations for three different filter combinations and several concentrations of *d*-*cis*-$[Co(en)_2Cl_2]Cl$ are given in Table I. The values obtained with the sodium lamp using the orange cut-off filter for 0.05, 0.1 and 0.3% solutions can be considered to be identical within experimental error. An increase of 0.01° in the observed rotation of a 0.05% solution in a 0.5 dm. tube would increase the specific rotation by 40°. The dry sample used for the preparation of the 0.3 and 0.4% solutions used for readings with the sodium light had stood for over a year and a 0.1% solution in a 1 dm. cell gave a specific rotation of +575° indicating slight racemization. The readings for these solutions were obtained with a photoelectric attachment since the intensity of the transmitted light was too low for visual readings. The 0.3% solution in a 0.5 dm. tube represents the most dense solution (for concentration and tube length) for which reliable readings could be obtained. The specific rotation is slightly low for this solution unless an inter-

(4) J. C. Bailar and R. W. Auten, THIS JOURNAL, **56**, 774 (1934); R. W. Auten, B.S. Thesis, University of Illinois, 1933.
(5) A. Werner, *Ber.*, **44**, 3279 (1911).

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TABLE I

SPECIFIC ROTATIONS OF SOLUTIONS OF *d-cis*-$[Co(en)_2Cl_2]Cl$

Concn., %	Tube length, dm.	Na lamp Orange filter	White light blue-green, orange and interference filters	White light blue-green and orange filters
0.05	0.5	+600°	+600°	....
	1	+640°	+580°	....
	2	+640°	+550°	....
	2[a]	+600°	+540°	....
0.1	0.5	+620°	+640°	+520°
	1	+640°	+580°	+180°
	2	....	+410°	− 75°
	2[a]	....	+550°	+ 60°
0.25	0.5	+630°	+510°	+ 25°
	1	....	....	−160°
0.3	0.5	+515°[c]	....	....
	0.5	+575°[b,c]	....	....
0.4	0.1	+575°[c]	....	....
	0.5	....	+350°	−150°
	1	....	....	−220°

[a] One decimeter tube of the active complex and one decimeter tube of the inactive complex. [b] The interference filter was used with the orange filter for this reading. [c] These readings were obtained for a different sample (sp. rot. +575° for 0.1% solution in 1 dm. tube) with a photoelectric attachment.

ference filter is added to eliminate the red light of low intensity from the sodium lamp. The results obtained with white light using the blue-green, orange cut-off and interference filters for dilute solutions and short tube-lengths are in good agreement with the results obtained with the sodium light. As the tube length or concentration increases, a decrease in the specific rotation is observed.

The specific rotations for 0.1 and 0.4% solutions in 1 dm. tubes are nearly the same as the reported values[2,4] if one uses white light and the combination of blue-green and orange cut-off filters. The change from positive to negative values can be accomplished by increasing the tube length instead of changing the concentration. The fact that the effect is due to the filtering action of the complex is clearly demonstrated by the decrease in the rotation of a 0.1% solution in a 1 dm. tube which is brought about by introducing another 1 dm. tube containing the racemic complex. If the tube length of a 0.1% solution is decreased to 0.5 dm., the specific rotation is raised to a value almost as large as that obtained with the sodium lamp.

The absorption spectrum of K[Co(edta)] (Fig. 2) is similar to that of *cis*-$[Co(en)_2Cl_2]Cl$ and one might expect a similar change in specific rotation with change in concentration. The results in Table II indicate that a change in specific rotation with a change in concentration is observed using white light, but the negative rotation increases instead of changing sign.

TABLE II

SPECIFIC ROTATIONS OF SOLUTIONS OF *d*-K[Co(edta)]

Concn. and tube length	Na lamp orange filter	White light orange and interference filters	White light blue-green and orange filters
0.05% 0.5 dm.	−200°	−200°	−280°
0.2% 1 dm.	....	−440°	−525°

The change in rotation with concentration using filtered white light is understandable when one considers the filtering effect of the complex. Even the interference filter transmits enough red light to give erroneous readings except at low concentrations. The sodium lamp with an orange cut-off filter has been considered as an ideal light source for any concentration for which readings could be obtained. However, a slight deviation was observed at high concentration.

The spectrum of the sodium lamp was recorded with a spectrograph, but no lines in the red were observed unless the exposure was long enough to give a considerable amount of fogging in the vicinity of the NaD doublet. However, when the light was filtered through a solution of *cis*-$[Co(en)_2Cl_2]Cl$ or K[Co(edta)], the intensity of the NaD doublet was reduced to something comparable to some of the lines in the red. The red lines were identified as argon lines. The interference filter reduced the intensity of the red lines greatly, but also reduced the intensity of the NaD lines. The blue-green filter reduced the intensity of the NaD lines too much for practical use.

If the specific rotation varies with the concentration of the solution being investigated, it is probably the light source which is the origin of the trouble. Truly monochromatic sources are not absolutely necessary in many cases, but care should be exercised particularly for measurements made in the vicinity of an absorption band. For colored solutions it is also important to check the zero setting of a Lippich polarimeter with an inactive sample of the same concentration as the active sample if the light is not truly monochromatic. The zero setting shifts with wave length and an error can be introduced for colored solutions.

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June 20, 1957

[CONTRIBUTED FROM THE ROSS CHEMISTRY LABORATORY, ALABAMA POLYTECHNIC INSTITUTE]

The Activity Coefficients and Complex of Mercury(I) Sulfate in Sulfuric Acid Solutions at 25°[1]

BY SHIRLEY A. BROWN AND JAMES E. LAND

RECEIVED FEBRUARY 1, 1957

The solubility of mercury(I) sulfate in sulfuric acid solutions of various molalities was measured at 25°. By employing the values for the ratio of the concentration of hydrogen sulfate ions to the concentration of sulfate ions in these sulfuric acid solutions as given from Raman spectra, the ionic strengths of the mercury(I) sulfate, sulfuric acid solutions were calculated. From a plot of the reciprocal of the mean molality of the mercury(I) and sulfate ions *vs.* the cube root of the ionic strength, an extrapolation gave the theoretical solubility product constant for the mercury(I) sulfate in water. This constant then was used to compute the mean ionic activity coefficients of the mercury(I) sulfate in sulfuric acid solutions with concentrations between 0.002 and 2 *m*. A mechanism for the formation of the species $H[Hg_2(SO_4)(HSO_4)]$ was postulated and proof of its existence in solution advanced.

The use of mercury(I) sulfate in the preparation of standard e.m.f. cells has prompted many studies on its solubility in water and sulfuric acid solutions. A most complete and conclusive article on this topic is that of Craig, *et al.*,[2] who reported on the solubility of mercury(I) sulfate in sulfuric acid solutions from 0.002 to 3.5 *c* at 0 and 28°, and also they showed that a linear interpolation of their results to 25° agreed very closely with those reported by Hulett.[3]

Our interest in the mean ionic activity coefficients of mercury(I) sulfate grew out of an attempt to overcome certain difficulties in the calculation of the E^0 for the H_2, H_2SO_4, solvent, Hg_2SO_4, Hg e.m.f. cell used in determining the mean ionic activity coefficients of sulfuric acid at low molalities in mixed solvents.[4]

Not being able to compute the practical activity coefficients of mercury(I) sulfate in sulfuric acid solutions from the solubility results given in the literature, since they were recorded in molarities and density values were not reported, we performed enough solubility measurements over the range of acid molalities reported to give a relationship between concentration and density at 25°. With such results and those in the literature the mean ionic activity coefficients of mercury(I) sulfate in sulfuric acid were calculated and also it was possible to postulate the presence of a soluble mercury complex.

Experimental

Solid mercury(I) sulfate, prepared by the method of Hulett,[5] was added in excess to the sulfuric acid solutions contained in brown, ground glass stoppered bottles. The sealed bottles were agitated mechanically in a constant temperature bath maintained at 25 ± 0.02° for 3–4 days. After agitation the solutions were allowed to stand in the bath until clear, a sample removed by suction into a special pycnometer (previously described[6]) for the density determination, then analyzed for Hg and sulfuric acid using techniques described in reference 2.

Results and Discussion

Over the range of concentrations of sulfuric acid studied it was found that the density at 25° of the mercury(I) sulfate–sulfuric acid solutions could be represented as a function of acid molarity by the equation

$$d = 0.9975 + 0.0624c_{(H_2SO_4)} + 1.0918 \times 10^{-3}c_{(H_2SO_4)}$$

The molalities of the dissolved mercury(I) sulfate determined agreed within experimental error with those computed from the results of Craig, *et al.*,[2] using the above density, concentration relationship.

From a large scale plot of the molality of the mercury(I) sulfate (using both our measured values and those computed from reference 2) against the log of the molality of the sulfuric acid,

TABLE I

THE SOLUBILITIES, THE RECIPROCAL OF THE MEAN IONIC MOLALITIES, AND THE MEAN IONIC ACTIVITY COEFFICIENTS OF MERCURY(I) SULFATE AND THE MOLALITIES OF THE SULFATE ION AND THE FACTOR FOR ITS DETERMINATION IN SULFURIC ACID SOLUTIONS OF VARIOUS MOLALITIES

m of H_2SO_4	*m* × 10^4 of Hg_2SO_4	γ_R	*m* of $(SO_4)^-$	$1/m_\pm$	μ	$\gamma_\pm$
0.002	11.120	0.972	0.002	820.6	0.007	0.677
.003	10.158	.956	.002	679.8	.009	.561
.004	9.455	.942	.003	634.2	.011	.523
.005	8.923	.926	.003	601.2	.013	.496
.006	8.608	.912	.004	576.1	.015	.475
.007	8.386	.896	.004	553.0	.016	.456
.008	8.262	.882	.004	536.8	.018	.443
.009	8.141	.866	.005	516.7	.020	.426
.010	8.068	.852	.005	502.9	.021	.415
.020	7.574	.710	.008	416.8	.037	.344
.030	7.450	.582	.010	362.8	.052	.299
.040	7.557	.474	.013	320.3	.066	.264
.050	7.641	.380	.016	284.2	.082	.234
.060	7.746	.300	.020	254.1	.100	.210
.070	7.854	.250	.024	231.8	.117	.191
.080	7.968	.215	.027	214.4	.135	.177
.090	8.041	.189	.031	200.6	.152	.166
.100	8.119	.170	.034	189.2	.169	.156
.200	8.867	.108	.060	137.2	.320	.113
.300	9.373	.078	.086	111.6	.471	.092
.400	9.783	.054	.120	92.4	.640	.076
.500	10.062	.035	.170	76.6	.839	.063
.600	10.291	.032	.198	70.0	.997	.058
.700	10.463	.029	.216	66.6	1.132	.055
.800	10.555	.027	.240	62.9	1.279	.052
.900	10.573	.025	.265	59.8	1.430	.049
1.000	10.549	.019	.320	54.4	1.640	.045
1.500	9.966	.014	.467	46.4	2.434	.038
2.000	9.091	.010	.631	41.8	3.262	.034

(1) Presented at the Southwide Chemical Conference of The American Chemical Society, December 6–8, 1956.

(2) D. N. Craig, G. W. Vinal and F. E. Vinal, *J. Research Natl. Bur. Standards*, **17**, 709 (1936). This reference contains a bibliography and a critical evaluation of all articles published on this subject to 1936.

(3) G. A. Hulett, *Trans. Am. Electrochem. Soc.*, **6**, 109 (1904).

(4) J. E. Land and H. D. Crockford, THIS JOURNAL, **72**, 1895 (1950).

(5) G. A. Hulett, *Phys. Rev.*, **32**, 257 (1911).

(6) S. A. Brown and J. E. Land, *J. Chem. Eng. Data*, **2**, 72 (1956).

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the values recorded in the accompanying table were taken.

To calculate the mean ionic molality of the mercury(I) sulfate, the needed molality of the sulfate ion was computed from the mass law equation for the dissociation of the HSO_4^- ion

$$K_{HSO_4^-} = \frac{(m_{H^+})(m_{SO_4^=})}{(m_{HSO_4^-})} \times \gamma_R$$

Values for the factor γ_R listed in the accompanying table were taken from a large scale plot of the values reported by Smith.[7]

The concentration of the HSO_4^- ion can be taken as the difference between the molality of the sulfuric acid and the $SO_4^=$ ion since Smith's work demonstrated no undissociated sulfuric acid to be present in the range reported here. The value used for $K_{HSO_4^-}$ was 0.0120.[8]

The mean ionic activity coefficients listed in the accompanying table were determined from the equation $\gamma_\pm = (1/m_\pm)K^{1/2}$, where $m_\pm$ is the mean ionic molality and K is the hypothetical thermodynamic solubility product constant for the mercury(I) sulfate. $K^{1/2}$ was determined by plotting $1/m_\pm$ *vs.* the cube root of the ionic strength and extrapolating to zero ionic strength. The value found for K was 6.81×10^{-7}.

The behavior of $\gamma_\pm$ with changing ionic strength is illustrated in Fig. 1.

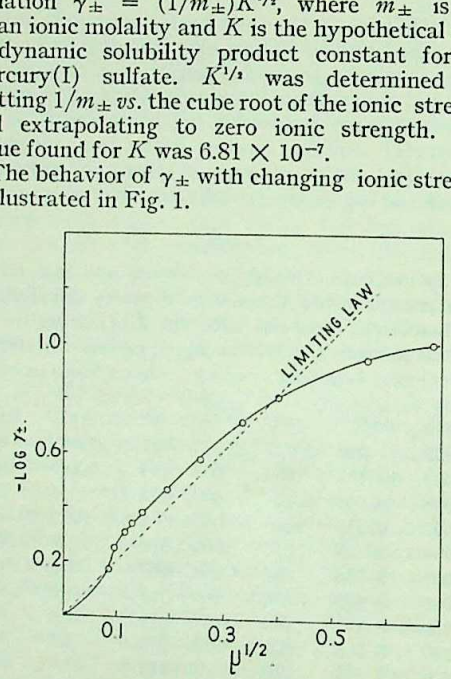

Fig. 1.

The shape of the solubility curve of mercury(I) sulfate in sulfuric acid solution indicated the formation of a soluble complex. Eppley[9] suggested that between 0 and 0.15 *c* sulfuric acid a basic, normal and acid species of Hg_2SO_4 existed. Craig, *et al.*,[2] postulated the formation of the compound $HgHSO_4$ to account for the increased solubility of the mercury(I) sulfate. Kendall and Davidson[10] reported the formation of the unstable acid salt $Hg_2SO_4 \cdot H_2SO_4$ from the analysis of the solid plase in contact with solutions of mercury(I) sulfate in 100% sulfuric acid.

Since the increase in solubility of the mercury(I) sulfate coincides with the increase in the HSO_4^- ion concentration, it was reasoned that such an equilibrium as this is possible

$$Hg_2SO_4 + n(HSO_4^-) \rightleftharpoons [Hg_2(SO_4)(HSO_4)_n]^{n-}$$

Taking the logarithm of both sides of the mass law equation for this equilibrium and rearranging gives

$$\log a_{[Hg_2(SO_4)(HSO_4)_n]^{n-}} = n \log a_{HSO_4^-} + \log K$$

thereby indicating that a plot of the log $a_{[Hg_2(SO_4)(HSO_4)_n]^{n-}}$ *vs.* log $a_{HSO_4^-}$ should produce a straight line of slope n and intercept equal to log K, if such an equilibrium is the case.

The concentration of the soluble mercury complex was taken as the difference between the molality of the mercury(I) sulfate at all values of $m_{H_2SO_4}$ between 0.06 and 0.4 and that at $m_{H_2SO_4} = 0.03$, since the mercury(I) sulfate concentration at this latter molality may be considered to be the maximum possible concentration of the Hg_2SO_4 species in sulfuric acid solutions more concentrated than 0.03 *m*. A plot of $-\log m_{[Hg_2(SO_4)(HSO_4)_n]^{n-}}$ *vs.* $-\log m_{HSO_4^-}$, shown in Fig. 2,[11] gave

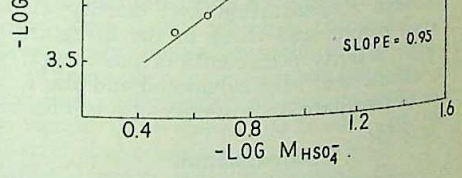

Fig. 2.

a series of points that fall close to a straight line with a slope of 0.95, thereby indicating the probable complex ion to be $[Hg_2(SO_4)(HSO_4)]^-$.

AUBURN, ALA.

(7) H. M. Smith, Ph.D. thesis, University of Chicago, 1949.

(8) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, N. Y., 1943, p. 430.

(9) M. Eppley, *Trans. Am. Electrochem. Soc.*, **53**, 172 (1928).

(10) J. Kendall and A. W. Davidson, THIS JOURNAL, **43**, 979 (1921).

(11) For an explanation of the use of concentration rather than activity terms, *cf.* A. B. Garrett, M. V. Noble and S. Miller, *J. Chem. Educ.*, **19**, 486 (1942).

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June 20, 1957

[CONTRIBUTION FROM THE INSTITUTE FOR ATOMIC RESEARCH AND DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

On the Crystal Structures of the Magnus Salts, $Pt(NH_3)_4PtCl_4$[1]

BY MASAO ATOJI, JAMES W. RICHARDSON AND R. E. RUNDLE

RECEIVED FEBRUARY 9, 1957

The crystal structure of the Magnus green salt, $Pt(NH_3)_4PtCl_4$, is tetragonal, $a = 9.03$ Å. and $c = 6.49$ Å., with space group D_{4h}^9–P4/mnc, and two formula units per unit cell, showing that the structure previously reported is incorrect. The planar $Pt(NH_3)_4^{++}$ and $PtCl_4^{--}$ ions are stacked over one another along the c-axis with Pt–Pt distance, $c/2 = 3.25$ Å. The bond distances of Pt–Cl = 2.34 Å. and Pt–N = 2.06 Å. are obtained with high accuracy by means of the generalized Fourier synthesis. The interatomic distances and the infrared spectrum indicate no significant NH...Cl hydrogen bonding in this compound. The comparison between the radial distribution functions of this salt and its isomeric pink salt reveals that there is no direct Pt–Pt contact in the Magnus pink salt, but other distances are comparable.

Introduction

The slightly soluble Magnus salts, Magnus green salt (MGS) and Magnus pink salt (MPS), result promptly from the mixing of solutions of K_2PtCl_4 and $Pt(NH_3)_4Cl_2$.[2] The reaction is capricious; which salt will result is as yet beyond control. The analysis of both salts is $Pt(NH_3)_4PtCl_4$, making the elucidation of their differences an interesting problem in chemical isomerism.

MGS has been studied previously by X-ray diffraction methods.[3] X-Ray rotation diagrams were indexed using a tetragonal unit cell with $a = 6.29$ Å. and $c = 6.42$ Å., and the suggested space group was C_4^1–P4. These results, as well as the structure, placing all $Pt(NH_3)_4^{++}$ groups in one layer and all $PtCl_4^{--}$ in the next, are found to be incorrect, though platinum positions are correct. Apparently, the former X-ray diagrams did not reveal the presence of very weak reflections.

The isomeric pink salt, MPS, was studied previously by the X-ray method,[3] but without any conclusive result regarding its color and its structural difference from MGS. The present study will show some details in this respect.

Methods and Results

The single crystal of MGS used in this study was a tetragonal needle, elongated along c. It approximated a cylinder 0.04 mm. in radius. Zero to sixth-level Weissenberg diagrams were taken by rotation about the needle axis, using Mo Kα and Cu Kα radiation. Precession diagrams, ($h0l$) and (hhl), were also obtained using Mo Kα radiation. The timed exposure and multiple film techniques were combined in both intensity determinations. The lattice constants are: $a = 9.03 \pm 0.02$ Å. and $c = 6.49 \pm 0.01$ Å. The calculated density of 3.77 g./cc. for two formula units in the unit cell agrees with the average value of the experimental density, 3.7 g./cc.[3] Systematic extinctions of ($0kl$) with $k + l$ odd, (hhl) with l odd, lead to the space group D_{4h}^9–P4/mnc or C_{4v}^6–P4nc.

The appropriate Lorenz and polarization factors were employed for reduction of the visual intensity estimates to structure factors. Phillips correction[4] was applied. The best available atomic scattering factors were used for Pt,[5] Cl[6] and N.[7] No calculations were made involving hydrogen atoms.

In both of the space groups above, there are two sets of Pt atoms. In P4nc both occupy 00z, $\frac{1}{2}\ \frac{1}{2}\ \frac{1}{2} + z$. In P4/mnc these positions with z-values of 0 and $\frac{1}{2}$ are required for the two sets. Since general reflections with $h + k = 2n$ and $l = 2n$ are very strong at low angles and show approximately normal decline of intensities, z-values of about 0 and $\frac{1}{2}$ are indicated. Point symmetries at Pt atoms are C_4 and C_{4h} for the two space groups, so that square planar ions in the planes $z = 0$ and $\frac{1}{2}$ are required for P4/mnc, and only slight deviations from this are reasonable for the lower space group.

Data from ($hk0$) are dominated by platinum scattering, and the Patterson projection onto (001) revealed only the Pt-Cl vectors. Data from (hkl) with l odd contain little or no platinum contributions (none if $z = 0$ and $\frac{1}{2}$) and are consequently of importance in determining positions of light atoms. The generalized Patterson projection[8] onto (001) using ($hk1$) data showed clearly both Pt–Cl and Pt–N vectors.

The light atom parameters were refined successively by means of the difference generalized Fourier-syntheses using ($hk1$) data. The final generalized electron density projection onto (001) is shown in Fig. 1. The peak positions were located by the twenty points graphical least square method. The final parameters obtained are listed in Table I. The observed and calculated structure factors for ($hk1$) and ($hk3$) reflections, which were found to contain no Pt atom contributions, are listed in Table III. The discrepancy factor, $\Sigma||F_0| - |F_c||/\Sigma|F_0|$ is 10.5% for these 89 reflections. The temperature factor

$$\exp\left\{-(B_1l^2 + B_2)\left(\frac{h^2 + k^2}{a^2} + \frac{l^2}{c^2}\right)\right\}$$

with $B_1 = 0.13_8$ Å.^{2} and $B_2 = 1.06$ Å.^{2}, has been applied.

TABLE I

	x	y	z
Cl	0.0563	0.2528	0.000
N	.5627	.7197	.000

(1) Contribution No. 510. Work was performed in the Ames Laboratory of the U. S. Atomic Energy Commission.

(2) Magnus, *Pogg. Ann.*, **14**, 242 (1828).

(3) E. G. Cox, F. W. Pinkard, W. Wardlaw and G. H. Preston, *J. Chem. Soc.*, 2527 (1932).

(4) D. C. Phillips, *Acta Cryst.*, **9**, 819 (1956).

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(6) H. Viervoll and O. Ögrim, *Acta Cryst.*, **2**, 227 (1949).

(7) J. Berghnis, I. M. Haanappel, M. Potters, B. O. Loopstra, H. McGillavry and A. L. Veenedaal, *ibid.*, **8**, 478 (1955).

(8) H. Lipson and W. Cochran, "The Determination of Crystal Structures," G. Bell and Sons, London, 1953, pp. 221–227.

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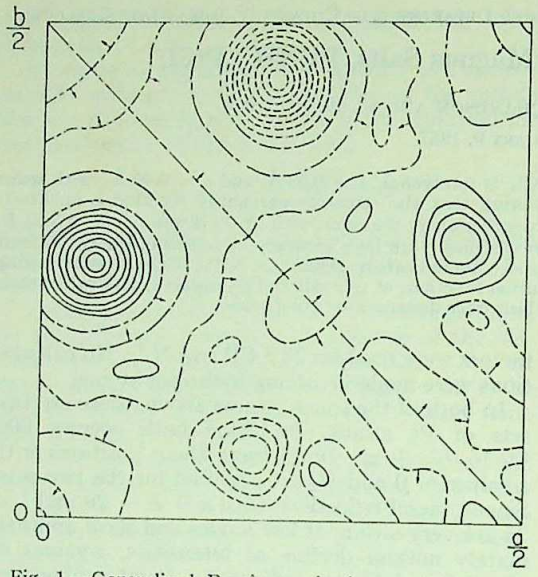

Fig. 1.—Generalized Fourier projection on (001) using (hkl) data. Contours are 0, 4, 8 . . . e.Å.$^{-2}$, but 0, 8, 16 . . . e.Å.$^{-2}$ for chlorine atoms. Positive, negative, zero contours are in solid, dotted and broken lines, respectively. Small arrows indicate the direction of the negative region.

Accuracy of the Structure.—Standard deviations of random errors were determined using Cruickshank's procedure,[9] which was modified appropriately for the generalized Fourier projection. For ($hk1$) data, $\sigma(A_h) = \sigma(A_k) = 1.624$ e.Å.$^{-3}$ and the peak constants are listed in Table II. The resultants, $\sigma(x) = \sigma(y) = 0.0037$ Å. for Cl and 0.018 Å. for N, give the standard deviations, 0.005 Å. for the Pt–Cl and 0.025 Å. for the Pt–N bond lengths.

TABLE II

OBSERVED AND CALCULATED PEAK CONSTANTS

	$\rho_L(0)$obsd. (e.Å.$^{-2}$)	$\rho_L(0)$calcd. (e.Å.$^{-2}$)		$\rho_L''(0)$obsd. (e.Å.$^{-4}$)	$\rho_L''(0)$calcd. (e.Å.$^{-4}$)	
N	10.2	11.4[a]	10.6[b]	− 92	−121[a]	− 92[b]
Cl	35.0	32.6	34.8	−440	−420	−440

[a] From equations 1 and 2. [b] From the generalized electron density map using the calculated structure factors.

The possibility that the structure was non-centrosymmetric was examined as follows. The peak height ρ_L (0) and the peak curvature ρ''_L (0) in the generalized Fourier projection along the z-axis, namely, using ($hk1$) data, are[10]

$$\rho_L(0) = \cos\left(2\pi\frac{LZ_0}{c}\right)\int_{L/c}^{s_{max}} 2\pi s f(s)\exp\left(-\frac{Bs^2}{4}\right)ds \quad (1)$$

and

$$\rho''_L(0) = \cos\left(2\pi\frac{LZ_0}{c}\right)\left[-\int_{L/c}^{s_{max}} 4\pi^2 s^2 f(s)\exp\left(-\frac{Bs^2}{4}\right)ds + \frac{2\pi^2L^2}{s^2}\rho_L(0)\right] \quad (2)$$

where z_0 is the atomic parameter in Å., c is the lattice constant along the z-axis, $f(s)$ is the atomic scattering factor and $s = 2(\sin\theta)/\lambda$. Although isotropic thermal vibrations are assumed in these equations, this should not cause the mean value of the observed peak constants to deviate greatly from the calculated value.[11] If $z = 0$ or $1/2$, $|\rho_L(0)|$ and $|\rho_L''(0)|$ give the maximum possible values. The graphically integrated results using equations 1 and 2 with $z = 0$, $B = 1.2$ Å.^{2}, $s_{max} = 1.275$ Å.$^{-1}$ and $L/c = 0.190$ Å.$^{-1}$ are listed in Table II. The chlorine peak constants are as high as expected for $z = 0$ or $1/2$, while those for the nitrogen atom may indicate some deviation. However, the latter peaks could be considerably affected by the Fourier ripple error. Moreover, the peak values in the observed and calculated Fourier maps are in good agreement, as can be seen in Table II. Ac-

TABLE III

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR ($hk1$) AND ($hk3$) ZONES

hkl	F_o	F_c	hkl	F_o	F_c
101	17.7	25.7	10,2,1	<4.0	2.2
301	30.3	27.1	11,2,1	14.6	15.0
501	16.7	−14.8	431	15.9	13.1
701	<4.8	− 2.3	531	65.7	69.0
901	26.0	−24.7	631	17.9	−16.0
11,0,1	3.6	− 3.5	731	6.0	− 5.4
211	32.0	−31.9	831	5.5	6.2
311	75.7	−75.6	931	16.6	13.8
411	27.5	25.4	10,3,1	13.7	−11.6
511	27.9	−29.1	541	<4.6	− 3.5
611	22.6	−22.1	641	7.2	6.5
711	26.0	−28.9	741	12.8	−13.5
811	21.3	22.4	841	<4.8	− 3.4
911	9.1	9.9	941	18.5	−16.0
10,1,1	20.5	−17.6	10,4,1	3.2	− 0.5
11,1,1	7.9	10.2	651	7.4	8.9
321	9.6	− 6.1	751	38.6	−37.6
421	10.1	− 8.9	851	<4.6	2.1
521	4.5	− 6.2	951	21.6	18.6
621	<5.0	2.4	10,5,1	6.0	7.3
721	20.0	21.3	761	8.3	8.8
821	<5.0	− 2.2	861	<4.2	− 0.5
921	6.2	9.5	961	18.6	19.3
871	21.5	−19.5	10,2,3	<1.8	1.3
971	7.6	8.1	433	10.8	10.0
103	18.5	17.2	533	46.0	50.0
303	22.4	18.4	633	11.8	−11.3
503	10.3	−10.4	733	3.1	− 3.8
703	<2.8	− 2.2	833	2.9	4.2
903	17.1	−16.0	933	9.7	8.7
213	21.7	−22.3	10,3,3	7.2	− 6.8
313	50.7	−50.4	543	4.5	− 2.7
413	19.7	19.3	643	5.0	4.3
513	16.8	−20.7	743	9.0	− 9.3
613	15.2	−16.5	843	4.7	− 2.1
713	16.5	−20.3	943	10.8	− 9.8
813	14.8	15.2	653	3.4	6.0
913	5.8	6.4	753	27.9	−24.8
10,1,3	14.1	−10.6	853	<2.6	1.3
323	8.6	− 5.6	953	11.9	11.1
423	6.2	− 5.3	763	6.6	5.7
523	4.0	− 3.7	863	<1.8	− 0.3
623	<2.8	1.5	873	10.0	−11.4
723	14.0	15.0			
823	<2.8	− 1.4			
923	4.3	6.2			

(9) D. W. J. Cruickshank, *Acta Cryst.*, **2**, 65 (1949).
(10) M. Atoji, *ibid.*, in press.
(11) P. W. Higgs, *ibid.*, **6**, 232 (1953).

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cordingly, no definite conclusion was deduced from these data.

In the series of generalized ($F_0 - F_c$) Fourier maps, the origin peak was always negative. In the final difference map, only the origin showed a density value larger than 1 e.Å.$^{-2}$, namely, 1.88 e.Å.$^{-2}$. $\rho_{Pt}(0)$ of equation 1 is 196 e.Å.$^{-2}$ for the Pt atom. Therefore, the separation of Pt atoms along c needs to be changed from $c/2$ by only ± 0.013 Å. to account for peak height at the origin in the generalized difference map made from ($hk1$) data and only 0.003 Å. in the map made from ($hk3$) data. Similar calculations were carried out for the peak curvatures with similar results. It is our conclusion that the experimental data do not disagree with the proposed centrosymmetric structure within the limits of ± 0.02 Å. in the z-parameters.

Radial Distribution Studies.—Since no success was met in obtaining a sufficiently large single crystal of MPS for single crystal diffraction work, the integrated intensities of the Debye–Scherrer lines of both MGS and MPS were measured on a Norelco X-ray diffractometer. Although the average particle size of the powdered crystals was less than 5 μ the preferred orientation effect was not avoidable by the usual mounting technique.[12] Moreover, the mica-like cleavage of the pink salt raises great difficulty in obtaining finer powders with spherical or random shapes. However, it was observed that by mixing and diluting MPS with a considerable amount of granular starch the preferred orientation effect was reduced appreciably. The absolute intensities were obtained approximately by scanning the diffraction lines of the powdered mixture of these salts and NaCl.

The radial distribution function derived by Schomaker[13]

$$A(r) = \sum_{s>0}^{s_{max}} \frac{\sin 2\theta}{1 + \cos^2 2\theta} I(s) \exp(-Bs^2) \sin 2\pi sr$$

where $I(s)$ is the observed intensity, was summed at intervals of 0.1 Å. in r. In our case, s_{max} was 0.8 Å.$^{-1}$, and summations made with and without an artificial temperature factor were similar in main details. In the resultant distribution functions, as shown in Fig. 3, with $B = 8$ Å.$^{-2}$, Pt–Cl peaks I and I′ appeared in both salts, while the shortest Pt–Pt interaction, II, in MGS was not observed in MPS. Since there existed many ambiguities in interpreting peak III′, attempts to solve the structure of MPS from the radial distribution function failed. Nevertheless, it may be concluded that in MPS there is no direct contact of Pt atoms as found in MGS, and that in MPS the smallest Pt–Pt vectors lie under peak III′ at about 5.6 Å.

(12) H. P. Klug and L. E. Alexander, "X-Ray Diffraction Procedures," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 290–305.

(13) J. Waser and V. Schomaker, THIS JOURNAL, **67**, 2014 (1945). The correct expression to define $A(r)$ is as follows: If we define

$$D(r) = \int_0^{2\pi}\int_0^{\pi} P(\vec{r}) \sin\theta \, d\theta \, d\phi$$

where $P(r)$ is the Patterson function, we have then

$$A(r) = \frac{2rV}{\lambda}\left[D(r) - \frac{4\pi}{V} F^2(000)\right]$$

where V is the volume of the unit cell.

Discussion of Structure

In MGS, Pt–Cl = 2.34 Å. and Pt–N = 2.06 Å. are in good agreement with the sum of the covalent radii, Pt–Cl = 2.31 Å. and Pt–N = 2.02 Å.[14,15] Other important interatomic distances are shown in Fig. 2. These indicate no strong hydrogen bonding in MGS. Moreover, the NH stretching frequencies recorded on the infrared spectrometer with a LiF prism are 3182 and 3277 cm.$^{-1}$ for symmetric and asymmetric vibrations, respectively. Although the corresponding frequencies of NH_3[16] are 3337 cm.$^{-1}$ and 3414 cm.$^{-1}$, these differences probably do not arise from strong hydrogen bonding for reasons previously reported.[17]

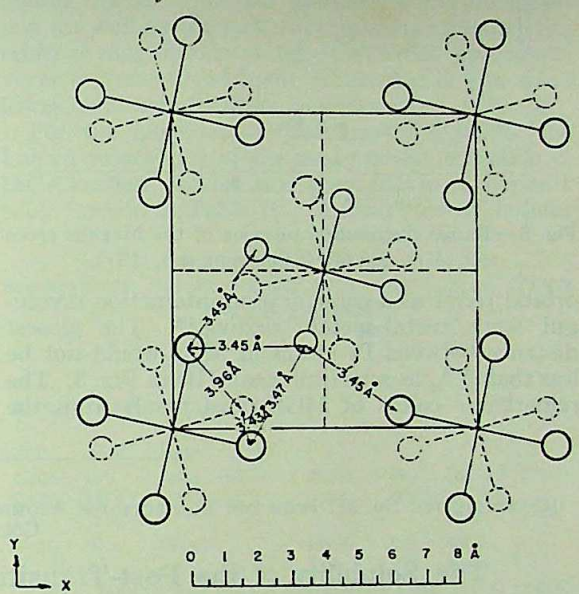

Fig. 2.—Atomic arrangement of the Magnus green salt projected on (001). Large circles represent chlorine atoms and small circles nitrogens. Solid and broken lines indicate $z = 0$ and $1/2$, respectively. Platinum atoms are at centers of square ions.

Remarkable dichroism of a single crystal of MGS was observed in the visible and ultraviolet region by Yamada.[18] His result and the chains of Pt atoms along the c-axis with a distance of 3.25 Å. suggested to him that there exists an interaction among Pt atoms. This seems to occur frequently in all square planar complexes except those of copper(II).[19] In valence bond terms the interaction can possibly be described as a slight mixing of octahedral with the square planar bonding with two of the octahedral bonds to adjoining metal atoms,[19a] or in molecular

(14) L. Pauling and M. L. Huggins, *Z. Krist.*, **87**, 205 (1934).

(15) Pt^{++}–Cl bond distances previously reported, but less exactly determined, are: in K_2PtCl_4, 2.32 Å. (R. G. Dickinson, THIS JOURNAL, **44**, 2404 (1922)), in $K(PtCl_3 \cdot C_2H_4)H_2O$, 2.32 Å. (J. A. Wunderlick and D. P. Mellor, *Acta Cryst.*, **7**, 130 (1954)). The Pt^{++}–N bond distance in $Pt(NH_3)_2Br_2$ is 2.16 Å. (C. Brosset, *Arkiv Kemi Min. Geol.*, **25A**, No. 19 (1948)).

(16) G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., New York, N. Y., 1945, p. 197.

(17) K. Nakamoto, M. Margoshes and R. E. Rundle, THIS JOURNAL, **77**, 6480 (1955).

(18) S. Yamada, *ibid.*, **73**, 1579 (1951).

(19) (a) L. E. Godycki and R. E. Rundle, *Acta Cryst.*, **6**, 487 (1953); R. Rundle, THIS JOURNAL, **76**, 3101 (1954); (b) R. Rundle, *J. Phys. Chem.*, **61**, 45 (1957).

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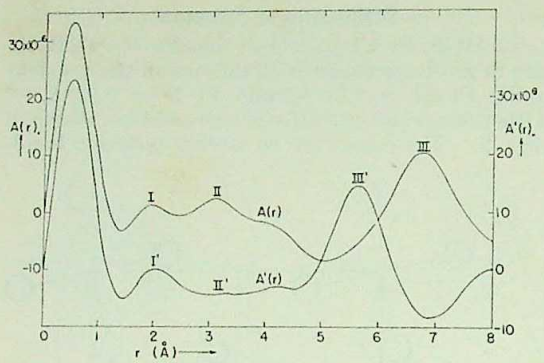

Fig. 3.—Radial distribution function of the Magnus green salt, $A(r)$, and of Magnus pink salt, $A'(r)$.

orbital terms as a configuration interaction involvgni some metal–metal bonding.[19b] The closest distance between Pt atoms in MPS would not be less than 5 Å. as seen from peak III′ in Fig. 3. The remarkable colors of MGS must result from the metal interaction, while MPS, which has no such interaction, does not differ materially in color from finely divided $Pt(NH_3)_4Cl_2$, and its pink color must be due to $Pt(NH_3)_4^{++}$ ions. Experimentally there is little doubt that MGS is the stable form of the Magnus salts, and this may be due to the extra metal interaction. Presumably accidents of nucleation produce the pink salt, but it may well be that packing considerations, by themselves, would favor the pink salt since the type of packing in the green salt is rare. It would also be interesting to learn whether there is an appreciable activation energy for forming the Pt–Pt bond in the green salt.

Acknowledgments.—The authors wish to express their thanks to Messrs. Russell A. Bonham and Peter Vossos for their assistance in some of the numerical computations and to Mr. E. Miller Layton for obtaining the infrared spectra. Dr. Don S. Martin and his students kindly supplied MGS and MPS, and contributed to our interest in this problem.

AMES, IOWA

[CONTRIBUTION NO. 511 FROM THE INSTITUTE FOR ATOMIC RESEARCH AND DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

The Solubility of the Post-Transition Metals in their Molten Halides[1]

BY JOHN D. CORBETT, SAMUEL VON WINBUSH AND FRANK C. ALBERS

RECEIVED FEBRUARY 20, 1957

The solubilities of the respective metals in molten PbI_2, $SbCl_3$, SbI_3, $ZnCl_2$, ZnI_2, CdI_2 and $GaBr_2$ are reported. An interpretation of the solution of the post-transition representative metals in their molten halides is presented in terms of the formation of slightly stable subhalides. The apparent stabilities of the lower halides increase both with increasing atomic weight of the metal within a group, and with increasing atomic weight of the halide with a given metal, except for cadmium. The halide effect is attributed to a corresponding decrease in the extent to which the higher oxidation state of the metal is stabilized by complex formation with halide. The relative stabilities of the metal–halide complexes observed parallel those reported in aqueous solution for the same ions, including the inversion in order found for cadmium. The formation of gaseous subhalides of antimony, bismuth and gallium is indicated by transport experiments. A direct correspondence is found between those systems in which gaseous subhalides of appreciable stability are formed and those in which metal dissolves in the molten salt to an appreciable extent. Diamagnetic solutes are formed in the zinc, cadmium, gallium, antimony and bismuth systems.

Introduction

The problem presented by the apparent solution of such metals as cadmium,[2] bismuth,[3] cerium,[4] the alkalies,[5,6] and the alkaline earths[7] in their respective molten halides has not received a completely satisfactory explanation. Although the possibility of the formation of colloidal metal or "pyrosoles" in the process has been eliminated, interpretations in terms of energy bands for the metal's electrons,[8] the formation of subhalides,[2,3,9] or a combination of these concepts[5] has been suggested. The phenomenon appears to be limited to the liquid state, in that only an intimate mixture of the original components is obtained on solidification of these solutions.

Although generally small metal solubilities had been found previously in this Laboratory for lead, tin, aluminum, thallium and silver systems,[10] subsequent investigations have revealed larger interactions in other post-transition metal–metal halide melts. In addition, evidence has been obtained supporting the interpretation of these solubilities in terms of the formation of slightly stable lower halides.

Results

The data obtained are given in Table I. The number of significant figures reported is indicative of the reproducibility of the measurement. In the liquid state only the Cd–CdI_2 system is different in color from the pure salt. The resulting solids are quite distinctive, however, for all but the Pb–PbI_2 and Zn–$ZnCl_2$ systems at the lowest temperatures

(1) Presented in part at the 129th meeting of the American Chemical Society, Dallas, Texas, April 12, 1956. Work was performed in the Ames Laboratory of the U. S. Atomic Energy Commission.

(2) G. von Hevesy and E. Löwenstein, *Z. anorg. allgem. Chem.*, **187**, 266 (1930).

(3) B. Eggink, *Z. physik. Chem.*, **64**, 449 (1908).

(4) D. Cubicciotti, THIS JOURNAL, **71**, 4119 (1949).

(5) M. A. Bredig, J. W. Johnson and W. T. Smith, *ibid.*, **77**, 307 (1955).

(6) M. A. Bredig, H. R. Bronstein and W. T. Smith, *ibid.*, **77**, 1454 (1955)

(7) D. D. Cubicciotti and C. D. Thurmond, *ibid.*, **71**, 2149 (1949).

(8) D. D. Cubicciotti, *ibid.*, **74**, 1198 (1952).

(9) K. Grjotheim, F. Grönvold and J. Krogh-Moe, *ibid.*, **77**, 5824 (1955).

(10) J. D. Corbett and S. von Winbush, *ibid.*, **77**, 3964 (1955).

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reported, and for the Ga–$GaBr_2$ system. These observations will be discussed subsequently.

TABLE I

System	Temp., °C.	Mole % dissolved metal	Method[a]	Color Liquid	Color Solid
Pb–PbI_2	438	0.024	B	Dark red	Yellow
	597	0.15	B	Dark red	Dirty-
	700	0.41	B	Dark red	yellow
Sb–$SbCl_3$	273	0.018	B	Clear	Gray
Sb–SbI_3	201	1.69	C	Black	Black
	300	3.5	C	Black	Black-
	400	5.8	C	Black	metallic
Zn–$ZnCl_2$	498	0.182	B	Clear	Clear
	298	1.64	B	Clear	Black
Zn–ZnI_2	498	0.28	B	Yellow	Black
	617	1.0	B	Yellow	Black
	667	1.65	B	Yellow	Black
Cd–CdI_2	410	0.63	B	Black	Dark-
	600	1.5	B	Black	gray
Ga–$GaBr_2$	170	9.30	B	Clear	Yellow

[a] Methods: B, loss in weight of metal phase; C, weight of dissolved metal.

Literature values are available for only the zinc chloride and the cadmium iodide systems. Von Hevesy and Löwenstein[2] reported that 10^{-4} mole % zinc dissolved in zinc chloride at 500°, as determined by a "titration" of a colored melt. Since no colored melts have been observed in the course of this work, it is uncertain as to what they were measuring. The same authors[2] reported a solubility of 7.8 mole % cadmium in cadmium iodide at 600°, about five times larger than that found here. As described in the Experimental section, values of this magnitude can be obtained readily by method B under non-isothermal conditions where metal may be transported to cooler portions of the salt or the container, for such distributed metal apparently does not readily reaggregate with the bulk phase.

Discussion

Any interpretation of the so-called "solution" of metals in their molten salts should account for a number of facts concerning these interactions. The formation of true solutions has been well substantiated for a large number of systems, where a marked depression of the freezing point of the salt is observed on solution of metal.[2–9] Moreover, these metals apparently are soluble only in salts of the same metal, indicating a specific interaction between the metal and the cation of the salt,[11] and yet only a mixture of the original components is usually obtained on solidification of the melt. In addition, any explanation should give reason to the marked variation in solubility of the various metals in their salts.

It will be seen that the formation of a class of slightly stable subhalides offers a satisfactory interpretation for the behavior of systems involving the post-transition representative metals and their halides. Although this concept has been suggested by previous workers, it has not received a general acceptance. This has been due to both the absence of a substantiated isolation of such a subhalide among the better known examples of this phenomenon, as well as the lack of correlation of either the relative magnitudes of the solubilities among diverse systems or with the occurrence of the same lower halides under other conditions.

For the purposes of qualitative discussion, the known solubilities of the post-transition metals in their molten halides are arranged in a periodic table fashion in Table II. Known "lower" halides

TABLE II

SOLUBILITIES OF POST-TRANSITION METALS IN THEIR MOLTEN HALIDES[a]

II		III		IV		V	
		$AlCl_3$	$\sim 10^{-4}$[d]				
		AlI_3	0.02[e]				
$ZnCl_2$	0.61[b]	$GaCl_2$	2[f]				
		$GaBr_2$	9[b]				
ZnI_2	0.87[b]	GaI_3	40[g]				
$CdCl_2$	15[c]	InX_3	50	$SnCl_2$	0.003[f]	$SbCl_3$	0.02[b]
$CdBr_2$	14[c]	(InX)		$SnBr_2$	.009[h]		
CdI_2	1.5[b]					SbI_3	3.1[b]
HgX_2	50	(TlX)		$PbCl_2$	.006[f]	$BiCl_3$	23[i]
(Hg_2X_2)				PbI_2	.05[b]	$BiBr_3$	40[i]

[a] Data for the four groups in mole per cent. metal at 600, 230, 500 and 270°, respectively (*cf.* footnote 12). [b] This work. [c] Ref. 2. [d] L. M. Foster, A. S. Russell and C. N. Cochran, THIS JOURNAL, 72, 2580 (1950); L. M. Foster, private communication. [e] Calculated from ref. 10 and ΔH^0 given by F. Irmann, *Helv. Chim. Acta*, 188, 1449 (1950). [f] Ref. 10. [g] Ref. 13. Similarly small temperature coefficients of solubility have been found in the other gallium systems. [h] Value reported in ref. 10 was in error. [i] Ref. 3.

are indicated in parentheses. For consistency the data are given at a fixed temperature in each group.[12]

Two systematic relationships are apparent in this arrangement. First, without exception, an increase in atomic weight of the metal within a group results in an increase in the solubility in a given halide. In the second and third groups this effect culminates in the formation of stable mercury(I) and indium(I) halides. A similar behavior is well known for the relative stabilities of the +2 and +3 states in the fourth and fifth groups. The implications of the trend observed in these two groups for still lower states will be discussed later.

These systems also show a rather marked regularity in the change in solubility of a given metal with variation in halide ion. In the third, fourth and fifth groups the solubility of metal, or the amount of the lower halide formed, increases in the order chloride, bromide, iodide. The trend is particu-

(11) The more trivial examples of direct reduction of the salt by added foreign metal are, of course, being disregarded. For example, the apparent solution of lead in cadmium chloride, as well as a large number of metals in bismuth trichloride, seemingly involves simple oxidation–reduction reactions. The initial metal addition produces the characteristic color of the metal–metal halide melt of the original salt; ultimately, the separation of a pure or alloyed phase containing the metal of the initial salt occurs.

(12) These temperatures, 600, 230, 500 and 270°, resp., were chosen so as to best fit the temperatures at which solubilities had been determined. For interpolation and extrapolation, plots of log solubility *vs.* $1/T$ were used; these have been found to be linear for all systems with solubilities of less than 2% that have been investigated at three temperatures. This behavior would be expected for equilibria of the type discussed herein. Exactly the same conclusions that follow could be obtained using a fixed temperature interval above the melting points of the salts in each group.

(13) J. D. Corbett and R. K. McMullan, THIS JOURNAL, 77, 4217 (1955).

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larly striking in the gallium systems; metal is precipitated when the metal-saturated chloride melt is solidified, while $GaBr$[14] and GaI,[13] stable in the solid state, are formed with the heavier halides.[15] Generally speaking, the stabilities of solid subhalides with respect to disproportionation show a corresponding relationship, being greatest with the iodide. At least in the molten state this halide effect can be attributed primarily to the decrease in basicity of the halide ion that accompanies an increase in atomic weight, in turn diminishing the extent to which the more acidic, higher oxidation state is stabilized by complex formation with halide ion. As a result greater reduction by metal, corresponding to greater stability toward disproportionation, is observed with the heavier halides.[16] Although the solubilities in the zinc systems show the same halide relationship, the inversion of the apparent stabilities of the cadmium(I) halides is quite evident (Table II). It is interesting to note that solid mercury(I) chloride, bromide and iodide behave similarly,[9] with standard free energies of disproportionation of 8.0, 6.6 and 2.5 kcal./mole, respectively.[17] Moreover, the reversal in the relative stabilities of the halide complexes of cadmium(II) and mercury(II) that is implied by these results is not without precedent. In aqueous solution the formation constants of the halide complexes of these two ions are in the order $I^- > Br^- > Cl^-$, whereas zinc(II) shows the more common relationship $Cl^- > Br^- > I^-$.[18] The anomalous behavior of cadmium and mercury has been attributed to multiple bond formation with the ligand.[19]

A strong point in favor of the interpretation of these metal–metal halide systems in terms of the formation of lower oxidation states is afforded by observations on the same systems in the gaseous state at comparable temperatures. In the cases under consideration there is a direct correspondence between the systems in which the metal dissolves in its fused halide to a significant extent and those in which gaseous subhalides of appreciable stability are known. As described in the Experimental section, rather definite evidence for a lower halide of antimony, bismuth and gallium has been obtained from observations on the transport of metal by vapors of the normal salt at temperatures where the vapor pressure of the metal alone is negligible. Similar or equivalent results have been reported for zinc, cadmium and bismuth, and for aluminum at higher temperatures.[20] On the other hand, visible transport of metal is not found in the lead and tin systems (Experimental section)[10,17] where the small solubilities are indicative of less stable, lower halides.

In this light the existence of these particular subhalides in the liquid but not the solid state is not unexpected. Although these compounds have insufficient stability to exist as pure solid phases, their presence at elevated temperatures when dissolved at less than unit activity in the parent salt is quite reasonable. Thus a stable solid subhalide can be obtained from such a solution only when reduction by metal produces a liquid that exceeds the composition of the normal halide–lower halide phase eutectic. Again, such a situation is observed in the Ga–$GaBr_2$ and Ga–GaI_2 systems, but not with Ga–$GaCl_2$. It may be that the inability to isolate cadmium(I) as well as possibly alkaline earth(I) and Ce(I?) halides from their respective binary systems, in spite of the rather large solubilities of metal observed,[2,4,7] is a consequence of the hypothetical eutectic being considerably removed in composition from the parent salt. Relatively low melting points for these lower halides might account for this. The possibility of the formation of lower oxidation states in the alkaline earth and cerium systems has been considered by Brewer.[21] However, extension of this concept to the rather unique alkali metal–alkali halide systems[5,6] would be quite speculative, particularly in view of the unusual M_2X product that would be involved.

In most cases it is possible to formulate the lower halides present in the systems under consideration on the basis of chemical knowledge and the observed magnetic properties. The formation of diamagnetic solutes has been specifically established for metal–metal halide melts involving $CdCl_2$,[22] $ZnCl_2$, GaX_2, SbI_3 and $BiCl_3$; the solubilities in the tin and lead halides are too small to allow detection of possible paramagnetic products (see Experimental section). Thus it seems fairly certain that Cd_2^{+2}, analogous to Hg_2^{+2}, occurs in the cadmium systems.[9,16] Similarly, Zn_2^{+2} is the most likely product from the solution of zinc in its halides. The simple monohalides are unquestionably formed in the aluminum and gallium systems.[10,15,16] The much smaller solubilities in the tin and lead systems only indicate a low stability for either the M_2^{+2} or M^+ products. In this connection it should be noted that Karpachev and co-workers[23] have concluded on the basis of e.m.f. measurements that Pb^+, Cd^0 (or Cd_2^{+2}) and Li^0 or Li_2^+ are formed in the respective metal–metal chloride solutions.

Bismuth(I) halides doubtless are formed in the bismuth systems,[16,24] although the observed dia-

(14) J. D. Corbett and A. Hershaft, unpublished research.

(15) Although the simplest formula has been used for the gallium "dihalides," these compounds have been shown to be $Ga(I)[Ga(III)X_4]$ (R. K. McMullan and J. D. Corbett, to be published; L. A. Woodward, G. Garton and H. L. Roberts, *J. Chem. Soc.*, 3723 (1956)).

(16) A reduction in the amount to which the higher oxidation state is complexed by halide ion and thereby stabilized can also be brought about by the introduction of a stronger Lewis acid. Use of $AlCl_3$ for this purpose has allowed the preparation of stable Cd(I), Bi(I) and Ga(I) tetrachloroaluminates from the respective metal–metal chloride systems (J. D. Corbett and R. K. McMullan, THIS JOURNAL, **78**, 2906 (1956)). The concepts developed in the present paper, together with the elucidation of the nature of $GaCl_2$ (footnote 15), led to these acid-stabilization results.

(17) L. Brewer, *et al.*, "The Chemistry and Metallurgy of Miscellaneous Materials—Thermodynamics," L. L. Quill, Ed., NNES IV-19B, McGraw-Hill Book Co., New York, N. Y., 1950, p. 113.

(18) S. Ahrland, *Acta Chem. Scand.*, **10**, 723 (1956).

(19) I. Leden and J. Chatt, *J. Chem. Soc.*, 2936 (1955).

(20) Summarized in ref. 17, pp. 121, 241–242, 252.

(21) Ref. 17, pp. 119, 124.

(22) J. Farquharson and E. Heymann, *Trans. Faraday Soc.*, **31**, 1004 (1935).

(23) S. Karpachev, A. Stromberg and E. Jordan, *Compt. rend. acad. sci. URSS*, **36**, 101 (1942); S. Karpachev and A. Stromberg, *Zhur. Fiz. Khim.*, **13**, 39 (1939); S. Karpachev and E. Jordan, *ibid.*, **14**, 1495 (1940).

(24) There is considerable disagreement in the literature as to the existence of Bi(I) and/or Bi(II) halides in the solid state. No isolation of a bismuth subhalide has been substantiated (Ref. 17, p. 251, see also T. Sokolova, *Izvest. Sektora Fiz-Khim Anal., Inst. Obshchei Neorg. Khim.*,

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magnetism is rather unexpected. Seemingly, either pairing of the $6p^2$ valence electrons or the formation of metal–metal bonds has occurred. The oxidation state present in the diamagnetic solutions of antimony in its triiodide is not as obvious. By analogy with bismuth a less stable Sb(I) might be expected. However, the +2 oxidation state, as known in P_2I_4 and As_2I_4,[25] cannot be ruled out solely by the magnitude of the solubility. Investigations of the equilibria in the gas phase are expected to allow a distinction to be made.

Experimental

Solubility Determination Methods.—In cases where the metal is liquid at the equilibration temperature, suspension of metal droplets in the salt is usually not observed.[10] In these cases, direct determination of the loss in weight of metal when equilibrated with a known amount of salt (method B) results in a considerable gain in accuracy and ease of measurement over that possible by direct analytical determination. The clear melt in the Sb–$SbCl_3$ system also allowed this method to be used with a solid metal. For the zinc halides, $SbCl_3$ and $GaBr_3$, the weight of salt sublimed *in vacuo* from the broken ampoule onto the weighed metal in the equilibration vessel was obtained by difference, as previously described for the tin systems.[10] The cadmium and lead iodides were weighed in air (see Materials).

The known amounts of salt and metal were equilibrated, except as later noted, in small evacuated tubes in tubular furnaces controlled with Celectray or Brown Proportioning controllers. The temperatures were measured with chromel-alumel couples calibrated by Leeds and Northrup. Equilibration times of 3–16, 1–2, 5–8, 5–10 and 24 hr. for PbI_2, $SbCl_3$, ZnX_2, CdI_2 and $GaBr_2$, resp., were used. The Pyrex or Vycor containers were then quenched with an air blast or cold water; there was no evidence of segregation during this process. The coherent metal button was recovered, washed with water and reweighed. With the Ga–Br_2 system, the metal was frozen prior to opening the tube. Acetone was used to separate the button from adhering salt in order to avoid the additional metal produced when $GaBr_2$ reacts with water. In cases where occlusion of salt within the button was suspected, the metal was remelted under vacuum, alone or with an alkali halide flux.[10] The buttons both before and after use could be so remelted with weight losses of 0.1 to 0.7 mg. No evidence for solution of salt in liquid metal was found in these systems.

With the Cd–CdI_2 system, the application of method B initially gave very erratic values of 2 to 5 mole % metal dissolved at 410°. More constant temperature control, as obtained with a shunted Marshall Tube Furnace and a proportioning controller, resulted in values of 0.8 to 1.5% at 410° and 6 to 10% at 600°. The scattered and, as were later found, high values were probably due to transport of the volatile metal, either directly (b.p. 765°) or as a subhalide, to the cooler upper walls of the container. This difficulty was substantially eliminated by equilibration of the salt and metal in containers in which the free volume was as small as possible. After the salt had been fused, the Vycor apparatus was sealed from the line and the salt quantitatively melted and sublimed down onto the metal in a 13 × 20 mm. bulb, which was then detached. In this fashion a sample was obtained which filled greater than 95% of the container (and only once exceeded that volume), thus reducing the possible temperature gradients within the system to a minimum. The bulbs were also jacketed by a closed tube within the furnace. The average deviations obtained at 410 and 600° were 0.014 and 0.17 mole %, respectively; the values reported are probably, at worst, 10% higher than the true solubilities.

With Sb–SbI_3, since the metal was solid at the temperature used, the saturated samples initially were gravity-filtered *in situ* through a medium or coarse sintered-glass disk sealed in the container. Sublimation of the salt from a weighed portion of the filtrate allowed a direct determination of the weight of metal therein (method C). This sublimation was initiated at 100° and the temperature slowly raised to 250° over a period of 12 hours; under these conditions loss of metal by entrainment or by subhalide formation (see Transport) was not encountered. However, particularly for equilibrations above 300°, erratic values were obtained due to transport of metal *via* a subhalide to other portions of the tube during the initial equilibration. Crystals of metal were often readily visible on the filtrate side of the sintered disk before the sample was inverted for filtration. The following technique was devised to overcome this difficulty: a 12 × 25 mm. tube, with a disk sealed near the middle, was almost completely filled with sublimed SbI_3. Metal had been previously placed on top of the filter, so that saturation of the lower portion of the salt was effected only by diffusion through the disk. In addition, the container was immersed in a molten $NaNO_3$ bath within the furnace. The values at 400° were thus reduced from a range of 3 to 8% to 5.8 ± 0.2% dissolved metal. Microscopic examination of metal remaining after sublimation of the salt showed the presence of only amorphous metal, and no crystals >1 μ in size.

During preliminary studies on this system, the formation of true solutions of metal in salt was established by the observation that metal lowered the vapor pressure of the triiodide. A small tube containing metal in a well in one end and salt in the other was placed in a furnace with a known temperature gradient; temperatures were also checked with couples in glass fingers projecting into salt and metal. It was observed that the salt distilled against a 4° temperature gradient onto the metal at 430°.

As indicated in Table I, the appearance of the quenched salts in most cases was typically that of an intimate mixture of salts and metal. However, with $ZnCl_2$ containing 0.18% metal, the water-quenched solid was a clear glass, quite similar to that obtained on rapid cooling of the pure molten salt. On heating, crystallization of the salt occurred at 120°, while the darkening characteristic of finely divided metal appeared rather sharply at 180°. The colorless glass was completely soluble in anhydrous ether, with the precipitation of metal after about 4 hr. Preliminary attempts to isolate the probable zinc (I) chloride therein were unsuccessful.

Materials.—The determination of solubilities by weight loss of the metal phase required the absence of non-metallic impurities soluble in the salt. For this reason zinc (Bunker Hill Electrolytic, 99.99%) was vacuum-fused and washed with acid to remove the oxide. Cadmium (Fisher Reagent) was repeatedly fused in a helium atmosphere alone, or with $CdCl_2$. Gallium (Aluminum Company of America, 99.9%) was treated with dil. HCl, frozen in small pellets and washed with distilled water. Lead (Fisher, Test Lead) was treated as previously described.[10] Antimony (Fisher Reagent) was used directly. The success of these procedures, as well as the absence of metallic reducing impurities, was shown by the consistency in results obtained on re-use of the same metal sample.

In order to avoid erroneous metal solubilities resulting from reactive impurities in the salts, particularly water and the resulting hydrolysis products, all the salts were prepared and handled by techniques dictated by their sensitivity to moisture, and, except for CdI_2, were vacuum sublimed onto metal just previous to equilibration.

Lead(II) iodide was precipitated from solutions of Reagent grade KI and $Pb(NO_3)_2$, vacuum dried and sublimed. The 20 to 30-g. portions used were weighed in air. For some of the measurements, metal-saturated salt was purified for re-use by heating the salt in a closed tube at 500° with excess I_2, separating the iodine in a side arm at −80° and then vacuum subliming the salt.

Antimony(III) chloride was prepared from the elements, using excess metal, and was vacuum-sublimed at about 100° into small fragile ampoules for storage.

Antimony(III) iodide (Fisher purified) was found to be sufficiently pure to be used directly after one sublimation. Measurements made with salt prepared from the elements

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Akad. Nauk. SSSR, **21**, 159 (1952)). ADDED IN PROOF.—The preparation of pure BiCl has been accomplished recently in this Laboratory, J. D. Corbett, unpublished research.

(25) F. Jaeger and H. Doornbosch, *Z. anorg. allgem. Chem.*, **75**, 261 (1912). The phase diagram presented by these authors for the Sb–SbI_3 system certainly seems in error. Although they indicate the formation of a solution of 13 mole % salt in metal at 169°, such a process has not been observed below 400°. They did not investigate the salt-rich phase.

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Zinc chloride also was prepared from the elements. Since $ZnCl_2$ cannot be separated from metal by sublimation, the salt was heated extensively with excess chlorine. It was then sublimed at 500°, and melted into fragile containers containing 3 to 5 g. each. The resulting salt evolved no hydrogen when contacted with metal; considerable amounts of this gas, presumably from dissolved water and HCl, were obtained when commercial $ZnCl_2$ was used after one vacuum sublimation.

Zinc iodide was prepared in a V-shaped Vycor tube from metal and excess, vacuum-sublimed iodine, heating the metal to 700° and the iodine to 200°. The product was transferred in air, triply sublimed after removal of the I_2, and similarly stored in 2 to 3-g. batches.

Owing to thermal decomposition, CdI_2 cannot be vacuum sublimed without appreciable contamination of the product with free metal. Hence it was prepared directly from the elements in a sealed tube and the excess I_2 and traces of HI condensed in a side arm at −190° and sealed off. The salt was then sublimed at 450° in the closed tube. For equilibration a 10 to 15-g. sample was weighed in air and then melted *in vacuo* (without decomposition) before the metal was introduced under helium.

For the Ga–$GaBr_3$ system, $GaBr_3$ was prepared from the metal and excess, P_2O_5-dried bromine, sublimed and sealed in ampoules. The $GaBr_2$ was then formed as the initial product during the equilibration with a weighed excess of metal.

Transport Studies.—Observations on the stabilities of gaseous subhalides were carried out in the manner already described for tin and lead.[10] Transport of antimony was obtained when SbI_3 was distilled at $<10^{-2}$ mm. over metal heated as low as 300°. Metal alone would not sublime at this temperature, as expected from a calculated vapor pressure of *ca.* 10^{-10} atm.[26] Similarly, $BiCl_3$ caused transport of Bi, and GaX_2 of Ga at 400°. Studies of this type with lead are, however, limited by the vapor pressure of the metal to temperatures below about 575°.[10] With PbI_2, where the natural color of the solid salt prevents visual detection of metal at less than about 0.1 mole %, transport of lesser amounts either directly or *via* a subhalide does occur below 500°, as detected by direct solubility measurements with salt sublimed from a metal-saturated sample.

Magnetic Susceptibility Observations.—A qualitative Gouy method was used to establish the diamagnetism of metal-containing melts of SbI_3, $ZnCl_2$, GaX_2 and $BiCl_3$. The salts, containing less metal than necessary for saturation at the temperature used, were sealed in small fused silica tubes equipped with evacuated jackets to lessen the rate of cooling. These were lowered from the furnace to between the pole pieces of a magnet with an inhomogeneous field of maximum intensity of about 12000 gauss. A deflection out of the field, indistinguishable from the pure molten salt, was always observed when the magnet was turned on. Experiments with dilute aqueous solutions of paramagnetic salts indicated that the method should be quite capable of detecting paramagnetism in the systems studied if such species had been formed in the expected amounts.

(26) Ref. 17, p. 31.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Praseodymium Oxides. IV. A Study of the Region $PrO_{1.83}$–$PrO_{2.00}$[1]

BY C. L. SIEGLAFF AND L. EYRING

RECEIVED JANUARY 19, 1957

This is a study of the phase relationships of the higher praseodymium oxides. X-Ray powder diagrams of quenched, analyzed samples were taken to determine the phases present. A two-phase system was found for the region $PrO_{1.83}$–$PrO_{2.00}$ at preparation temperatures below 350° and oxygen pressures less than ten atmospheres. Lattice constants are given for the various phases found.

Introduction

Several investigations of the praseodymium oxides beyond Pr_2O_3 have been reported recently.[2-8] The oxide system below Pr_6O_{11} has been extensively studied, but in the region Pr_6O_{11} to PrO_2 there is apparent disagreement as to the phases present. Through the use of X-ray diffraction techniques on samples prepared under equilibrium conditions a study of this region has been carried out.

Experimental Methods

Materials.—The Pr_6O_{11} used in these experiments was obtained from Professor F. H. Spedding, Iowa State College, Ames, Iowa, as 99.9+% pure Pr_6O_{11} with no other rare earth cations present in detectable amounts. The oxygen used in the preparation of quenched samples was commercial tank oxygen.

Apparatus for the Preparation of Quenched Samples.—The constant volume apparatus used in preparing the samples below ten atm. oxygen pressure was similar in principle to the one described previously.[8] Since the measurements were made at relatively high pressures, the system was constructed of metal instead of glass. The reaction vessel was an "Inconel X" cylinder bored and fitted with a flanged platinum liner. The brass valves used in the system were designed to have a very small internal free space and were constructed in a manner such that the volume was reproducible in either the open or closed positions.

The pressure was measured by a Wallace and Tierman, Model No. FA 145, 0-5080 mm. dial manometer. In order to maintain constant volume conditions the manometer had to be isolated from the sorption system, since the manometer worked on an expanding capsule principle. The isolation of the manometer was accomplished by means of a sensitive, specially designed small volume differential pressure gage operating as a null instrument.

The maximum uncertainty in the composition, as measured by the pressure change, is estimated at 0.4%. Weighing of the samples before and after the oxidation-quenching procedure gave a check of the method since there was no appreciable change in oxygen content when the samples were quenched.

Samples prepared at high temperatures and high oxygen pressures were treated in an "Inconel X" autoclave. The procedure and a similar apparatus have been previously described.[3]

X-Ray diagrams were taken in a 114.6 mm. diameter camera using exposure times of about 12 hours.

(1) Taken from a thesis by C. L. Sieglaff for the Ph.D. Degree, State University of Iowa, Iowa City, Iowa. Support for this work was given by the Atomic Energy Commission.

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TABLE I

PRASEODYMIUM OXIDES ($PrO_{1.833}$–$PrO_{2.000}$)

Composition (O/Pr)	Temp. (°C.)	Oxygen pressure (atm.)	Lattice constant Major phase	Minor phase	Quenching time (min.)
1.996	350	5.41	5.3932 ± 0.0009		30
1.909	350	4.25	5.3919 ± .0008	5.4694 ± 0.0007	30
1.847	350	3.29	5.465 ± .004		30
1.919	350	3.02	5.3918 ± .0001	5.471 ± 0.001	30
1.833	450	0.2	5.467 ± .002		Cooled slowly
1.895	470	27	$PrO_{2.00}$	$PrO_{1.83}$	10
1.855	550	34	$PrO_{1.83}$	$PrO_{2.00}$	10
1.933	600	109.00	5.399 ± 0.002		10
1.868	720	72	5.468 ± .005		10
2.01	720	92	5.392 ± .001	5.469 ± 0.002	Cooled slowly, pressure
1.833	760	112	$PrO_{1.83}$		10
1.839	760	224	5.467 ± 0.001		5
1.956	760	140	$PrO_{1.83}$	$PrO_{2.00}$	Quenched, pressure
1.997	450	231	5.3938 ± 0.0003		Cooled slowly, pressure

Results and Discussion

Table I shows the results of the X-ray analysis on quenched samples. All cell dimensions are reported in Å. units based on the wave lengths Cu K_1 1.5405 Å. and Cu K_2 1.5443 Å. The values for the cell dimensions reported in Table I are calculated by an analytical extrapolation of the back reflection data.[9]

Oxidation of a Pr_6O_{11} sample at 350° and an oxygen pressure of 4.25 atm. results in two crystalline oxide phases with lattice constants of 5.3919 ± 0.0008 Å. and 5.4694 ± 0.0007 Å. The phases are Pr_6O_{11} and PrO_2. A sample which was prepared by oxidation to PrO_2, and then reduced to a composition intermediate to Pr_6O_{11} and PrO_2, showed two phases, Pr_6O_{11} and PrO_2 with lattice constants of 5.3918 ± 0.0001 Å. and 5.471 ± 0.001 Å. One experiment, listed third in the table, gave only one phase, Pr_6O_{11}. This sample was only 12% oxidized which would give at best a very weak minor phase. Since the praseodymium oxides are highly absorbant it is not surprising that a minor phase did not appear.

Oxidation of Pr_6O_{11} with pressures up to 331 atm. and temperatures up to 760° yielded PrO_2 and/or $PrO_{1.83}$. No evidence of an intermediate phase was found. These high temperature-high pressure samples were prepared with questionable quenching techniques, since no check could be made of the sample composition before and after quenching. It is possible that an intermediate phase was present and changed into two phases during quenching.

A high temperature camera capable of keeping the sample under 300 atm. oxygen pressure near 1000° is needed to be certain that no phase changes occur when the sample is quenched. All that can be said is that at pressures less than ten atmospheres there was no appreciable composition change upon quenching.

From their studies, Gruen, *et al.*,[4] and Martin[5] concluded that a single phase inhabited the region $PrO_{1.83}$–$PrO_{2.00}$, whereas McCullough[2] observed a miscibility gap in this range. Also the extensive studies of mixed rare earth oxides by McCullough[10] and others,[11,12] indicated complete solid solution in this range.

It should be pointed out that in the study of the praseodymium system reported by Ferguson, *et al.*,[7] there were at least three regions of continuous non-stoichiometric composition which tended toward separation into two phases. Although these diphasic regions were not observed from X-ray studies, they were inferred from the nature of the $(P, X)_T$ isotherms. As the oxygen content increased, the apparent critical transition temperature decreased. Also, the dissociation pressure at the critical temperature increased. An extrapolation of this trend to the region above $PrO_{1.83}$ indicates a critical temperature of less than 585° and a dissociation pressure above one atmosphere should be expected.

Gruen, *et al.*,[4] using atomic oxygen to treat the praseodymium oxides, reported a reaction temperature of 450°. Similar experiments carried out in the present study showed that the surface of the oxide sample was heated to incandescence by the recombination of oxygen and reaction at the surface. Therefore, the temperature reported by Gruen, *et al.*, might have been that of the bulk of the material, not the surface temperature. It is then probable that the true reaction temperature was considerably higher than 450°.

The one mixed oxide study carried out at low temperatures was the Nd–Pr system studied by McCullough.[2] It was reported that at 300° one phase inhabited the region $RO_{1.83}$–$RO_{2.00}$. It is possible that the substitution of Nd^{+3} for Pr^{+3} lowers the critical temperature.

The existence of a solubility loop between similar phases is not unique. Grønvold and others[13–15] have shown that the uranium oxide system in the region UO_2–U_4O_9 is monophasic at low temperatures (equilibrium here is questioned) changing to a diphasic region as the temperature is raised to 250°. At approximately 350° the system again be-

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comes monophasic.[15] The phases present in this region are anion excess fluorite structures with lattice constants of 5.4704 and 5.4411 Å. for UO_2 and U_4O_9, respectively.[15]

It is apparent, then, that there is a solubility loop in the fluorite region between $PrO_{1.83}$ and $PrO_{2.00}$ below a temperature of at least 350° with a probable transition to a homogeneous system at elevated temperatures. This observation based on the present study apparently explains much of the work of others previously thought to be contradictory. It also appears to be a reasonable extension of the known facts of the PrO_x system, as determined by equilibrium dissociation pressure measurements, and is not at variance with observations on related oxide systems including many of the mixed oxides.

It is not possible from the present study to fix the transition temperature exactly, but it must be above 350°. From the extension of the lower oxide studies and the Nd–Pr system an upper limit of approximately 585° would be expected.

Reasonably complete studies of the oxide systems of cerium and praseodymium and preliminary studies on the oxides of terbium[7,8,16,17] have now been reported. It is of interest to compare the phase relationships of these lanthanide oxides. Each oxide system changes from a body-centered cubic to a rhombohedral to a face-centered cubic phase as the oxygen content is increased. Similar stable compositions exist in each system, with the major difference being the lack of an intermediate face-centered cubic phase in the cerium system. A given region of any of these systems can be either diphasic or monophasic depending upon the temperature and pressure of the preparation.

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IOWA CITY, IOWA

[CONTRIBUTION FROM THE CHEMISTRY LABORATORIES OF NORTHWESTERN UNIVERSITY]

Species of Molybdenum(VI) in Hydrochloric Acid[1]

BY H. M. NEUMANN[2] AND NANCY C. COOK

RECEIVED DECEMBER 21, 1956

Ultraviolet spectrophotometry has been applied in a study of the species of Mo(VI) present in hydrochloric acid solutions. Compounds of Mo(VI) containing molybdenum and chlorine in the ratios 1:2, 1:3 and 1:4 have been prepared and their spectra determined in ether solutions. Although all three types display a maximum at 226 mμ, each has a second maximum at longer wave lengths that is characteristic of the particular Mo:Cl ratio. These results have been applied to the analysis of the spectra of solutions of Mo(VI) in hydrochloric acid. The species containing two chlorines is the most important in these solutions, its maximum amount occurring in 6 *M* HCl. At greater acidities a species containing three chlorines becomes important. There is no evidence for species containing a larger number of chlorines. The species containing two chlorines is apparently the one extracted by ethers and bound by anion-exchange resins.

Although molybdenum is most commonly encountered as molybdenum(VI), the aqueous chemistry of this oxidation state is, to a large extent, unknown. The greatest difficulties in working out the details of molybdenum(VI) chemistry arise from the fact that in acidic solution polymerization occurs to form polymolybdates. By using an acid whose anion could become involved in complex formation, one is more likely to find the molybdenum(VI) present in monomeric form, and hence have some chance of identifying the species actually present. The work reported here is based upon the use of hydrochloric acid as the medium and ultraviolet absorption spectrophotometry as the means of studying the composition of the various solutions. This seemed a promising method since any chloro complexes would be expected to have absorption maxima in the ultraviolet region. In addition, several compounds of Mo(VI), containing various numbers of chlorine atoms, have been reported in the literature, and it seemed likely that a comparison of their spectra with those of solutions of Mo(VI) in hydrochloric acid would give information about the species of Mo(VI) present in the acid solutions.

The ultraviolet spectra of the compounds themselves are of interest, since at the present time there is little apparent correlation between the spectra and structure of halo complexes. In part, this is due to insufficient data, so that any additional data from known compounds, as is possible in the molybdenum(VI) case, may ultimately lead to some correlations.

Experimental

Analytical Methods.—Determinations for molybdenum in macro concentration were performed by the method described by Kolthoff and Sandell.[3] The chloride determinations employed the method suggested by Michael and Murphy[4] for chloride in the presence of molybdenum. The determination of the total molybdenum(VI) in ether solutions when the molybdenum concentration was of the order of 10^{-4} *M* was accomplished by completely transferring all the Mo(VI) into an aqueous 6 *M* HCl solution by evaporating a measured aliquot of the ether solution while in contact with the 6 *M* HCl solution, boiling to remove all the ether, and then diluting with additional 6 *M* HCl to a fixed volume. The absorption spectrum of the solution was then measured, and compared with the spectra of solutions of known concentrations in 6 *M* HCl.

Measurements of Absorption Spectra.—All absorption spectra were measured with a Beckman Model DU spectrophotometer using matched, fused silica cells having a light path of 1 cm. The cells were maintained at a constant temperature of 25° by means of a water jacket. The spectra of hydrochloric acid solutions were obtained from 212 to 350

(1) Taken in part from a thesis submitted by Nancy C. Cook in partial fulfillment of the requirements for the M.S. degree. Presented in part at the Dallas meeting of the American Chemical Society, April, 1956.

(2) School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia.

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mμ, and in ether solutions from 218 to 350 mμ. Readings were taken at 2 mμ intervals from 212 to 300 mμ, and at 5 mμ intervals thereafter. The slit width was varied from one wave length to another, but was maintained constant for a given wave length for all solutions in the same solvent.

A stock solution 0.114 *M* in Mo(VI) was prepared in concentrated hydrochloric acid. The solutions to be used for spectral determination were prepared by placing a measured aliquot of the stock solution in a 50-ml. volumetric flask and diluting to the mark with hydrochloric acid of the desired concentration.

The ether solutions used for spectral determination were prepared in the following way. A saturated solution was obtained by contacting the solid compound with anhydrous ether. The solution was then diluted until the optical density reached a reasonable value, and the spectrum then determined. The concentration of the Mo(VI) in the ether was then determined in the way previously outlined.

Preparation of Compounds: MoO_2.—The method of Guichard[5] was used. An approximately 1:1 volume ratio of molybdenum trioxide and ammonium molybdate was pulverized and heated to red heat in a platinum crucible. The molten mass was solidified by pouring it into cold water. The crystals were washed several times with ammonium hydroxide by decantation, then with 6 *M* hydrochloric acid until the hydrochloric acid ceased to be colored red. The crystals had a dark blue color.

MoO_2Cl_2.—The method of Wasmuht[6] was employed for the preparation of molybdenum dioxydichloride. A reaction chamber was constructed of two glass tubes 18 inches long, the smaller of which was 3/4 in. in diameter. The tubes were fitted together tightly with resistance wire wrapped between them, and the ends of the wire connected to a Variac. About 5 g. of MoO_2 was placed inside the tube at the center. One end of the tube was attached to a cylinder of anhydrous chlorine gas, and the other to the receiver, a large-mouthed bottle. The temperature was set at 360° and gradually increased until yellow powder crystals began to be formed rapidly in the receiver. These crystals were yellow in color, were not appreciably hygroscopic, and discolored only very slowly on exposure to air. *Anal.* Calcd. for MoO_2Cl_2: Mo, 46.4; Cl, 37.8. Found: Mo, 46.3; Cl, 37.7.

$MoO(OH)_2Cl_2$.—The general method given by Weinland and Knoll[7] was followed. Molybdic anhydride, which had been dried at 150° for two hours, was used as the starting material. The same reaction tube was used as for the preparation of MoO_2Cl_2. The chamber was heated to 150° at which time approximately 15 g. of the dry MoO_3 was spread inside the inner tube. A cylinder of anhydrous hydrogen chloride was connected to one end of the tube and the gas was allowed to stream slowly over the MoO_3. A large-mouthed bottle was used as the collection vessel. At 150° very little product was formed, so the temperature was increased slowly. At 250° yellow needle-like crystals formed abundantly in the collection vessel. The color of the crystals was like that of MoO_2Cl_2, but the compound was unlike MoO_2Cl_2 in that it was very hygroscopic, and rapidly turned from yellow to blue. Keeping the product in a dry atmosphere, in a vacuum, or in the dark did not prevent the rapid change in color. The blue material formed was similar in behavior to "molybdenum blue" that is formed as the first product in the reduction of molybdate in acid solution. The blue solid could be converted to a yellow form both by treatment with dilute sulfuric acid and with dilute sodium hydroxide. *Anal.* Calcd. for $MoO(OH)_2Cl_2$: Mo, 44.2; Cl, 31.6. Found: Mo, 44.2; Cl, 32.2.

$MoO(OH)Cl_3 \cdot 7H_2O$.—According to Weinland and Knoll,[7] when $MoO(OH)_2Cl_2$ is made into a mush with fuming hydrochloric acid and the mixture warmed with evolution of hydrogen chloride, the mass solidifies to form $MoO(OH)Cl_3 \cdot 7H_2O$. The compound is also formed by saturating with hydrogen chloride gas a solution of $MoO(OH)_2Cl_2$ in fuming hydrochloric acid and evaporating the liquid over sulfuric acid. The latter method was found more satisfactory. Freshly prepared $MoO(OH)_2Cl_2$ was dissolved in concentrated hydrochloric acid. Hydrogen chloride gas was bubbled into this viscous yellow solution for ten minutes and the solution was placed over sulfuric acid in a vacuum desiccator. As the solution decreased in volume over a period of days it also developed a greenish color. After several days light green crystals were formed which were very hygroscopic, and which turned slightly blue on exposure to air. *Anal.* Calcd. for $MoO(OH)Cl_3 \cdot 7H_2O$: Mo, 26.6; Cl, 29.4. Found: Mo, 26.5; Cl, 30.4.

Other Compounds.—Weinland and Knoll[7] have also reported the preparation of $KMoO_2Cl_3 \cdot H_2O$ and $K_2MoO_2Cl_4 \cdot 2H_2O$ by crystallization from solutions containing $MoO(OH)_2Cl_2$, HCl and KCl; the preparation of $(NH_4)_2MoO_2Cl_4 \cdot 2H_2O$ by crystallization from solutions containing $MoO(OH)_2Cl_2$, HCl and NH_4Cl. Compounds were prepared by these methods, and their properties agreed with those reported by Weinland and Knoll, and the molybdenum and chlorine analyses corresponded to the formulas as written above.

Results and Discussion

Spectra of Compounds in Ether.—The spectra of ether solutions of the prepared compounds were measured as previously described. Aqueous solutions could not be used as all the compounds react rapidly when added to water. Although reaction in ether is a possibility, the results indicate that if any reaction occurs it is limited to the loss of coordinated water molecules from the Mo(VI) complex.

The compounds MoO_2Cl_2 and $MoO(OH)_2Cl_2$ were expected to show good solubility in ether; the most concentrated solutions prepared indicate a solubility in the range 0.02–0.03 *M*. The solubility would be expected to be smaller for $MoO(OH)Cl_3 \cdot 7H_2O$, with a further decrease for $KMoO_2Cl_3 \cdot H_2O$, and with extremely small solubility for $K_2MoO_2Cl_4 \cdot 2H_2O$ and $(NH_4)_2MoO_2Cl_4 \cdot 2H_2O$. Because of the method of preparation of the last three compounds, $MoO(OH)Cl_3 \cdot 7H_2O$ is a possible contaminant. Even though its percentage abundance is small, its greater solubility might result in its being the predominant species present in the solution when the solid is contacted with ether. As a result, the spectra obtained from these three solutions must be interpreted with caution.

Spectra representative of these compounds are shown in Fig. 1. All show a maximum at approximately 226 mμ. The spectra of MoO_2Cl_2 and $MoO(OH)_2Cl_2$ are very similar, having in addition to the maximum at 226 mμ a shoulder in the region of 240–250 mμ. Some variations in the spectra were observed for different preparations and solutions of $MoO(OH)_2Cl_2$, and the same behavior was exhibited by solutions of MoO_2Cl_2. There was no change in the wave length of maximum absorption, but the value of the molar absorbancy index at the maximum varied from 5,500 to 6,200. Although the shoulder was more clearly defined in some samples than others the total variation in molar absorbancy index values did not exceed 5% in this region. The cause of these variations may be the varying amounts of water in the solutions, which can change the extent of oxygen coördination to the molybdenum.

The compounds $MoO(OH)Cl_3 \cdot 7H_2O$ and $KMoO_2Cl_3 \cdot H_2O$ do not have the shoulder, but have instead a second maximum at 290 mμ. The spectra of solutions of the compounds $K_2MoO_2Cl_4 \cdot 2H_2O$ and $(NH_4)_2MoO_2Cl_4 \cdot 2H_2O$ were similar to these, except that the second maximum occurred at 310 mμ rather than at 290 mμ.

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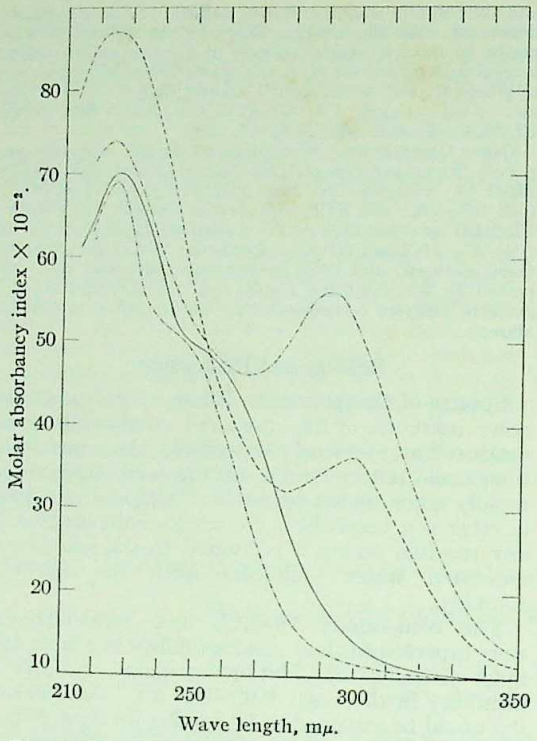

Fig. 1.—Representative spectra of compounds in ethyl ether: —·—·—, compounds containing two chlorines; – – ·– –, compounds containing three chlorines. Reconstructed spectra of species present in aqueous HCl solutions: ———, the species containing two chlorines; – – – –, the species containing three chlorines.

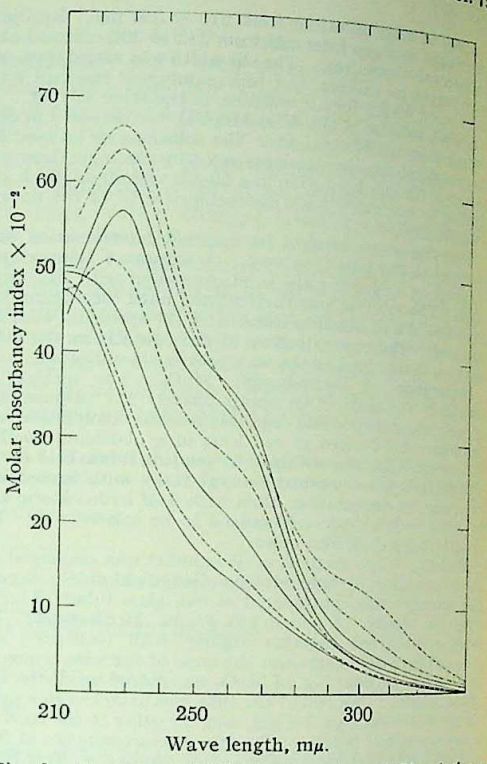

Fig. 2.—Spectra of Mo(VI) in various HCl solutions. Curves in ascending sequence are for the following HCl concentrations: 0.99, 1.98, 2.97, 4.00, 4.94, 6.94, 8.90 (curve only partially shown) and 10.82 *M*.

On the basis of these observations we conclude that all the chlorines appearing in the formula are coördinated to molybdenum, and that the position of the second (*i.e.*, longer wave length) maximum can be used as a measure of the number of coördinated chlorides.

Compounds with a Mo:Cl ratio of 1:2 are characterized by the shoulder at 240–250 mμ; 1:3 compounds by the maximum at 290 mμ. Because of the possibility of $MoO(OH)Cl_3 \cdot 7H_2O$ contributing to the spectra of the 1:4 compounds it cannot be stated that the second maximum for pure 1:4 compounds occurs at 310 mμ; but the maximum certainly must occur at a wave length greater than or equal to 310 mμ.

These spectra are also of interest in connection with the ether extraction of Mo(VI) from hydrochloric acid solutions. The spectra of ether phases obtained by extraction from 3, 6, 7, 8 and 9 *M* hydrochloric acid solutions were measured. All of these ether phases gave spectra characteristic of a compound containing Mo and Cl in the ratio of 1:2. This is in agreement with the ratio obtained by chemical analysis of the ether phase.[8]

Spectra of Hydrochloric Acid Solutions.—Solutions near integral molarities from 1 to 12 *M* were examined. The general characteristics of the spectra are apparent from the selected curves shown in Fig. 2. There is a general similarity to the curves of the pure compounds in ether, but with some shifts in the wave lengths of the maxima. The maximum at 226 mμ is present in the solutions 5 *M* or greater in acidity. The shoulder at 240–250 mμ in the ether solutions, characteristic of compounds containing two chlorines, has shifted to 260–270 mμ. At the highest acidities a second shoulder develops at approximately 300 mμ. This is the region in which we expect a peak due to a species containing three chlorine atoms.

The spectral changes in hydrochloric acid solutions have been interpreted on the assumption that the species containing two chlorines has an absorption maximum at 226 mμ in addition to the shoulder at 260–270 mμ, while the species containing three chlorines has absorption maxima at 226 and 290–300 mμ. The growth of the absorption maximum at 226 mμ with increasing acidity in the range 5–12 *M*, while that at 260–270 mμ decreases and that at 290–300 mμ increases, quite clearly indicates that the species containing two chlorines has a less intense absorption at 226 mμ than the species containing three chlorines.

It was found possible to resolve these spectra into their component parts by the following method, which is illustrated in Fig. 3. The logarithm of the absorbancy was first plotted *vs.* wave length. It was assumed that on this type of plot the tail from the peak at 226 mμ would be a straight line, and the most reasonable line was drawn. Subtraction of these values from those of the total spectrum gave a curve containing one or two maxima.

(8) I. Nelidow and R. M. Diamond, *J. Am. Chem. Soc.*, 57, 710 (1935).

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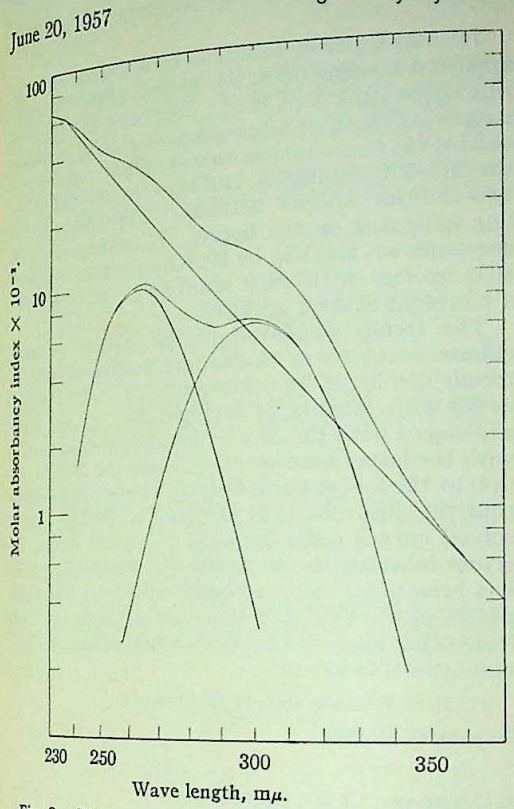

Fig. 3.—The spectrum of a solution 10.82 M in HCl, and the resolution of the spectrum into its component parts.

The absorption that causes the shoulder in the 260–270 mμ region resolved nicely by this method to give a maximum at 264 mμ (the species with two chlorines). In the solutions 10 M or greater in HCl a second maximum occurred at about 300 mμ. Since the resolved spectrum from the 6 M HCl solution was predominantly that of the two-chlorine species, it was used to further resolve the spectra in the higher acid concentrations. Figure 3 shows an example of how this leads to a resolved peak with a maximum at 302 mμ (the species with three chlorines). The height of each resolved peak then served as a measure of the amount of that component. The solutions 8–12 M in HCl display isosbestic points at 256 and 274 mμ, indicating the presence of only two species. This fact, in conjunction with the observed peak heights, allowed calculation of the peak heights for the pure components and the abundance of each component in the various solutions. Table I shows the abundances determined in this way.

It was possible to reconstruct the entire spectrum for each of these species in the following way. For a solution containing only two components, I and II, it is true that $A_{obsd} = A_I F_I + A_{II} F_{II}$, where A_{obsd} is the observed molar absorbancy index, A_I and A_{II} are the corresponding values for the pure components, and F_I and F_{II} are the fractional amounts of Mo(VI) present in the respective forms. Plotting A_{obsd} *vs.* F_I should then give a straight line which has A_I as an intercept when $F_I = 1$, and has A_{II} as an intercept when $F_I = 0$. The absorbancy data for the five solutions of greatest acidity were treated in this way, using values of F corresponding to the percentages of Table I. For the majority of wave lengths all five points fell on a line; at no wave length was more than one point badly off a line. This consistency lends additional support to the results listed in Table I. The values of the intercepts from these graphs gave the data necessary to reconstruct the spectra of the two components. These are shown in Fig. 1.

TABLE I

ABUNDANCES OF Mo(VI) SPECIES IN HYDROCHLORIC ACID

HCl, M	% present as 2-chlorine species	% present as 3-chlorine species
11.72	52	48
10.82	60	40
9.90	69	31
8.90	81	19
7.97	87	13
6.94	91	7
5.98	93	1
4.94	88	..
4.00	79	..
2.97	51	..
1.98	25	..
0.99	20	..

Conclusions

Figure 4 shows an interesting relationship between the abundance of the 2-chlorine species and the behavior of these solutions with respect to ether extraction and retention on an anion-exchange resin. The extraction work is that of Nelidow and Diamond[8] and the anion-exchange report that of

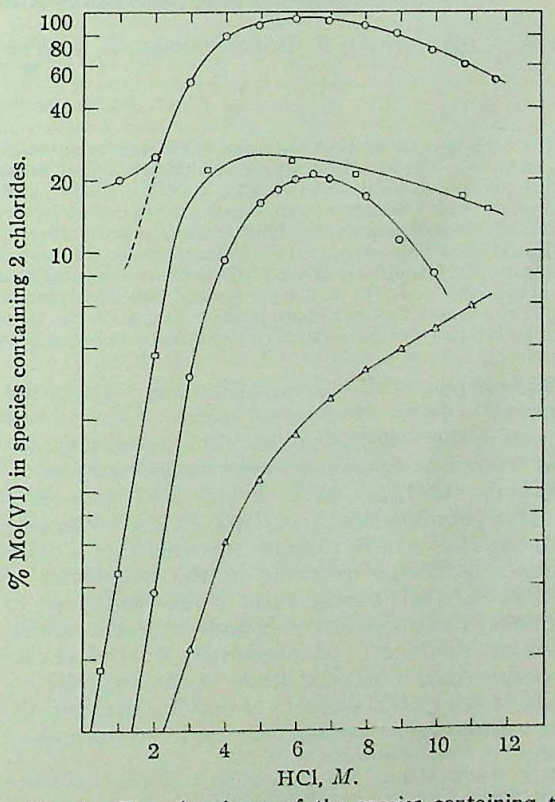

Fig. 4.—The abundance of the species containing two chlorines (upper curve, left hand ordinate), compared to distribution ratios for an anion-exchange resin[9] (□), isopropyl ether[8] (○), and diethyl ether[8] (△).

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Kraus, Nelson and Moore.[9] The values of the ordinates for the distribution data are purely relative for each of the functions plotted; the shapes of the curves are the feature of consequence. Although all the evidence relating to the extraction by ethers indicates that the extracted species contains two chlorines, the fact that the extraction curves do not correspond to the spectral data is not surprising; the distribution depends on many factors other than the equilibrium in the aqueous phase, and this equilibrium itself is shifted due to the presence of ether in the aqueous phase. For example, a decrease in the distribution ratio for isopropyl ether would be expected at the highest acidities even if there were no decrease in the amount of the extractable species in the aqueous phase.[10] The rapid rise of all curves for acidities up to 4 *M* indicates that the equilibrium in the aqueous phase is the most important factor in determining the distributions at these conditions.

The anion resin data corresponds sufficiently well with the spectral data to suggest that the species containing two chlorines is the form bound by the anion exchanger.

(9) K. A. Kraus, F. Nelson and G. E. Moore, THIS JOURNAL, **77**, 3972 (1955).

(10) D. E. Campbell, A. H. Laurene and H. M. Clark, *ibid.*, **74**, 6193 (1952).

The most glaring failure of correspondence is the apparent leveling off in the amount of the two-chlorine species in 1–2 *M* HCl. The most likely explanation is that these solutions contain another species of Mo(VI) that also has an absorption maximum in the 260–270 mμ region, and that the amount of the two-chlorine species actually follows the dashed line indicated on the figure. Examination of the spectrum of Mo(VI) in $HClO_4$ solutions indicates that species with such absorption characteristics are present at such acidities.

The trends displayed in the spectra of these chloro complexes of Mo(VI) are consistent with the trends displayed by other elements. The resolved peaks with maxima at 264 and 302 mμ are those associated with the Mo–Cl bond, and the complex with the larger number of chlorines has the absorption at the longer wave length. It is also of interest that the absorptions at the maxima of the two resolved curves differ by only 3% (well within the errors inherent in the method). This relationship has been observed previously with the chlorocomplexes of Sb(V),[11] but there are not sufficient data from other elements to decide whether this is a general type of behavior.

(11) H. M. Neumann, *ibid.*, **76**, 2611 (1954).

EVANSTON, ILLINOIS

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY]

Metal Chelate Compounds as Catalysts in the Hydrolysis of Isopropyl Methylphosphonofluoridate and Diisopropylphosphorofluoridate[1]

BY R. C. COURTNEY, R. L. GUSTAFSON, S. J. WESTERBACK, H. HYYTIAINEN, S. C. CHABEREK, JR., AND A. E. MARTELL

RECEIVED SEPTEMBER 7, 1956

The rates of hydrolysis of Sarin and DFP have been studied in the presence of a wide variety of metal chelate compounds as catalysts. The metal ion which yielded the largest number of catalytic metal chelates was found to be Cu(II), while a number of metal chelates of UO_2(VI), ZrO(IV), Th(IV) and MoO_2(VI) were also found to have considerable activity. Although the Cu(II) catalysts were apparently in a class by themselves, the following characteristics were found to be required in these hydrolytic catalysts: 1, incomplete coördination of the metal ion by the ligand; or 2, presence of oxy groups (or hydrated oxy groups) attached to the metal in certain cases where coördination was apparently complete. The wide variety of active metal complexes of Cu which were investigated made it possible to observe the following factors which favor maximum catalytic activity: 1, the presence of two aquo groups on the metal; 2, low stability of the metal chelate compound; and 3, the presence of maximum positive charge on the metal chelate. The importance of steric factors is indicated by the high activity of Cu(II) chelates of highly substituted diamines.

The purpose of this investigation was to study the catalytic effects of various metal chelate compounds in the hydrolysis of the cholinesterase inhibitors known as Sarin (isopropyl methylphosphonofluoridate $(C_3H_7O)(CH_3)POF$ and DFP (diisopropyl phosphorofluoridate, $(C_3H_7O)_2POF$). Wagner-Jauregg, *et al.*,[2] have recently reported that Cu(II) chelates active as catalysts in the hydrolysis of DFP contain a 1:1 molar ratio of the Cu(II) ion to a number of ligands, which include various α-amino acids and diamines. More recently Ryland, *et al.*,[3] have described a detailed study of the catalytic activity of the Cu(II) chelates of ethylenediamine, dipyridyl and *o*-phenanthroline, and have proposed a mechanism to explain the observed rates as a function of the metal chelate species present under their experimental conditions. The only other study of metal ion catalysis of hydrolysis of cholinesterase inhibitors is a report by Augustinsson and Heimbürger[4] which describes the effectiveness of Cu(II), Ni(II), Co(II), Ag(I), Au(III) and Pd(II) salts in accelerating the hydrolysis of Tabun (N,N-dimethyl - ethylphosphoroamidocyanidate). No previous reports on the catalysis of Sarin hydrolysis by metal chelate compounds have appeared in the literature.

(1) This paper reports work done under contract with the Chemical Corps, U. S. Army, Washington 25, D. C.

(2) T. Wagner-Jauregg, B. E. Hackley, Jr., T. A. Lies, O. O. Owens and R. Proper, THIS JOURNAL, **77**, 922 (1955).

(3) L. B. Ryland, F. M. Fowkes and G. S. Ronay, Paper No. 108, Division of Physical and Inorganic Chemistry, 128th National Meeting of the American Chemical Society, Minneapolis, Minn., September 11–16, 1955.

Experimental

The liberation of acid during hydrolysis of Sarin was measured as a function of time with a Beckman automatic titrator, which was operated so as to automatically maintain the experimental solution at constant *p*H by addition of

(4) K. B. Augustinsson and G. Heimbürger, *Acta Chem. Scand.*, 9

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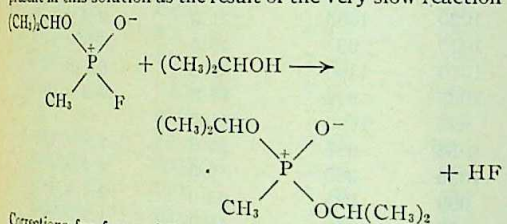
standard base from a micro-buret. The reaction was carried out in a multinecked glass flask fitted with a mercury-seal stirrer, nitrogen-inlet and outlet tubes, delivery tips for Sarin and potassium hydroxide solutions, and glass and calomel electrodes. The reaction vessel and the titrator head unit were mounted in a high-speed hood, the flask being immersed in a constant temperature bath which was maintained at 25.3 ± 0.05°.

In operation, an aliquot of metal chelate solution was introduced into the titration cell, presaturated nitrogen was bubbled through the solution to exclude CO_2, and the *p*H was adjusted as desired by means of the automatic titrator unit. An anticipation setting of 5 was used in most of the experiments. An aliquot of Sarin (approximately 150 μ moles) was now added by means of an automatic micro-buret. Time measurements were begun at the point at which half of the Sarin solution had been added. Readings of time *vs.* corresponding KOH consumption were recorded over the course of the titration. A plot of t *vs.* $\log a/(a-x)$ (where a is the amount of base required for complete hydrolysis and x is the amount of base consumed at the corresponding time t) gave a straight line in all cases studied. The half-time, that is the time required for the hydrolysis of one-half of the Sarin, is the time corresponding to a log $a/(a-x)$ value of 0.301. Two moles of acid per mole of Sarin are liberated upon hydrolysis.

The Sarin was used as a 0.05 *M* stock solution in anhydrous isopropyl alcohol. A small amount of free acid was present in this solution as the result of the very slow reaction



Corrections for free acidity were made by adding a corresponding amount of base to the reaction mixture before the introduction of the Sarin. The total volume of the solution at the start of a titration was 150 ml.

The electrode system was calibrated at *p*H 4, 7 and 9 by means of suitable buffers which were checked against an acetate buffer as the primary standard.

Reagent grade nitrates of all metals were used except for ZrO(IV) and Sn(IV) which were used in the form of chlorides, and VO(IV), which was obtained as the sulfate. Standardization of the metal solutions consisted for the most part of evaporation and subsequent ignition to the corresponding oxides. Copper was standardized by titration with standard Na_2EDTA reagent with murexide as an indicator in ammoniacal solution.[5] Thorium was standardized by means of Na_2H_2EDTA with alizarin red indicator,[6] while manganese was determined by titration with the salt of nitrilotriacetic acid, brom thymol blue being used as an indicator.[5] The vanadyl solution was standardized by titration with standard NaOH in the presence of excess Na_2H_2EDTA according to the method of Schwarzenbach.[7]

Samples of ethylenediaminetetraacetic acid, N-hydroxyethylethylenediaminetriacetic acid, N,N'-dihydroxyethylethylenediaminediacetic acid, N-hydroxyethyliminodiacetic acid, nitrilotriacetic acid, aspartic acid, N-hydroxyethylaspartic acid and N-aminoethylaspartic acid were obtained through the courtesy of Versenes, Inc., Framingham, Massachusetts. Samples of N-hydroxyethylethylenediamine, diethylenetriamine and triethylenetetramine were obtained from Carbide and Carbon Chemical Co., purified by fractional distillation, and converted to the corresponding hydrochlorides. Ethylenediamine, 5-sulfosalicylic acid and 1,8-dihydroxynaphthalene-3,6-disodium sulfonate were purchased from Eastman Kodak Co. The ethylenediamine was dried over solid potassium hydroxide, redistilled and isolated as the dihydrochloride. Pyrocatechol-3,5-disodium sulfonate was purchased from LaMotte Chemical Products Corp., Baltimore, Maryland. The 1,3-diaminopropane was obtained from the Sharples Chemical Company while the dipicolinic acid (pyridine-2,6-dicarboxylic acid) was donated by Dr. Stanley Chaberek, of the Dow Chemical Co., Framingham, Massachusetts. Samples of the dihydrochlorides of N,N'-dimethylethylenediamine and N,N,N',N'-tetramethylethylenediamine were prepared and recrystallized by conventional methods. Standardization of the aqueous solutions of the above chelating agents was effected by means of potentiometric titration with either standard carbonate-free potassium hydroxide or hydrochloric acid.

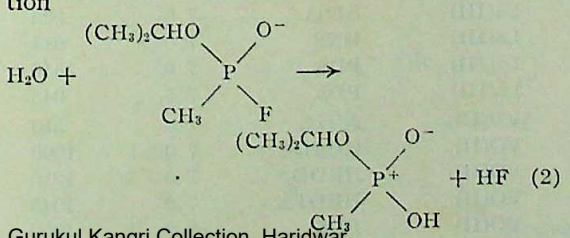
The Sarin was obtained through the courtesy of the Army Chemical Center. Standardization was effected using the automatic titrimeter in two ways: 1, neutralization of the hydrogen ions produced when an aliquot of Sarin was introduced into a 0.1 *M* nitrate solution at *p*H 10.0; and 2, neutralization of the acid produced upon catalytic hydrolysis by copper dipyridyl at *p*H 7.0. In the former case, hydrolysis was complete after approximately 40 minutes, while in the latter case, no further uptake of base was recorded after 60 minutes using approximately a five to one molar ratio of Sarin to copper dipyridyl.

In addition to the Sarin experiments, several metal chelate systems were studied to determine their effect as hydrolysis catalysts upon diisopropyl phosphorofluoridate (DFP). The DFP was obtained from the Colgate–Palmolive Company and had the following physical properties: b.p. 60–61° (8.2 mm.); density 1.055 at 25°; refractive index 1.3792 at 25°. A solution in anhydrous isopropyl alcohol was standardized by titration of acid liberated during catalytic hydrolysis by the copper chelate of N,N,N',N'-tetramethylethylenediamine at *p*H 9.0. Hydrolysis was complete in approximately 40 minutes when a molar ratio of ten to seven (copper chelate to DFP) was used. Attempts at standardization of DFP solutions by direct reaction with hydroxyl ion at a *p*H of 11.5 or greater required more than the theoretical two moles of base per mole of DFP. The exact nature of this phenomenon has not been determined but it is possible at such a high *p*H that alkyl groups also split off with consequent uptake of additional hydroxyl ions.

In order to check the accuracy of the instrument, several check runs were made using manual addition of base while recording the *p*H using a Beckman model G *p*H meter. Hydrolysis rates as determined by the manual method were approximately 10–16% greater than those observed using the automatic system. This increase in rate is probably due to the fact that in the former method the solution *p*H ranged from slightly below to slightly above the desired value, whereas due to a small lag in the instrument, the average *p*H in the automatic runs was probably lower than the desired value. For comparative purposes, the instrument seems to be quite suitable, since duplicate results agreeing within a few per cent. have been obtained in the great majority of cases.

Results

The metal chelate systems investigated for catalytic activity in the hydrolysis of Sarin are listed in Table I. The concentrations of metal chelate, Sarin and the solution *p*H are given in all cases. The metal chelates listed refer to the 1:1 chelates, unless otherwise noted. The stabilities of the metal chelate compounds investigated are sufficiently high (log $k \geq 10$) that they are not appreciably dissociated at *p*H 7. The total activities of the metal chelate species in solution are expressed as first-order hydrolysis rate constants for the reaction



Corresponding half-times of reaction also are listed.

(5) G. Schwarzenbach, "Die Komplexometrische Titrationen," Ferdinand Enke Verlag, Stuttgart, 1955, p. 68.
(6) J. J. Gritz and J. J. Ford, *Anal. Chem.*, **25**, 1640 (1953).
(7) G. Schwarzenbach and W. Biedermann, *Helv. Chim. Acta*, **31**, 331 (1948).

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TABLE I

Metal	Ligand	pH	Concn., μmoles/l. Metal	Ligand	Sarin	$t_{1/2}$ (min.)	k_1 (min.$^{-1}$)
Cu(II)	2-HxG	7.0	1020	1020	1005	25.0	2.8×10^{-2}
Cu(II)	HIMDa	7.0	995	995	955	57.0	1.2×10^{-2}
Cu(II)	HEDDA	7.0	1005	1005	960	32.0	2.2×10^{-2}
Cu(II)	HEDDA	7.0	9725	9725	960	19.0	3.6×10^{-2}
Cu(II)	HEDTA	7.0	1035	1035	945	29.0	2.4×10^{-2}
Cu(II)	HEDTA	7.0	10230	10230	975	25.0	2.8×10^{-2}
Cu(II)	HEN	7.0	10030	10030	970	4.6	1.5×10^{-1}
Cu(II)	2-HEN	7.0	10740	10740	955	4.1	1.7×10^{-1}
Cu(II)	HASPA	7.0	950	950	975	45.0	1.5×10^{-2}
Cu(II)	PDS	7.45	6286	6286	1593	10.0	6.9×10^{-2}
Cu(II)	PDS	7.45	653	653	1645	55.0	1.3×10^{-2}
Cu(II)	DNS	7.0	1313	1313	729	27.0	2.6×10^{-2}
Cu(II)	EN	7.20	980	980	1075	8.0	8.7×10^{-2}
Cu(II)	CU	7.20	995	995	1090	11.0	6.3×10^{-2}
Cu(II)	TU	7.20	995	995	980	8.5	8.2×10^{-2}
Cu(II)	CS	7.25	990	990	1070	8.5	8.2×10^{-2}
Cu(II)	TS	7.25	1000	1000	1015	10.5	6.6×10^{-2}
Cu(II)	2-HEN	6.10	1250	1250	1050	57.0	1.2×10^{-2}
Cu(II)	2-HEN	7.15	1135	1135	950	12.2	5.7×10^{-2}
Cu(II)	2-HEN	8.00	1050	1050	1050	11.0	6.3×10^{-2}
Cu(II)	2-HEN	8.00	1050	1050	1030	11.0	6.3×10^{-2}
Cu(II)	HEN	6.15	1020	1020	1080	71.0	9.8×10^{-3}
Cu(II)	HEN	7.00	1020	1020	990	15.5	4.5×10^{-2}
Cu(II)	HEN	8.00	1010	1010	1100	10.0	6.9×10^{-2}
Cu(II)	$Na_4P_2O_7$	7.00	1035	1035	995	75.0	9.2×10^{-3}
Cu(II)	$Na_5P_3O_{10}$	7.00	995	995	1000	$\gg$100	.....
Cu(II)	DIEN	7.10	1055	1055	995	25.0	2.8×10^{-2}
Cu(II)	DIEN	7.00	1555	1035	960	7.0	9.9×10^{-2}
Cu(II)	TRIEN	7.00	990	990	985	65.0	1.1×10^{-2}
Cu(II)	DPA	6.20	990	990	955	45.0	1.5×10^{-2}
Cu(II)	DAP	7.50	510	510	975	2.1	3.3×10^{-1}
Cu(II)	DAP	7.50	5340	5340	515	1.3	5.3×10^{-1}
Cu(II)	DIPY	7.40	436	436	850	7.1	9.8×10^{-2}
Cu(II)	DIPY	7.40	2236	2236	872	3.0	2.3×10^{-1}
Cu(II)	DMEN	7.00	1025	1025	1005	3.5	2.0×10^{-1}
Cu(II)	DMEN	7.00	5010	5010	1035	1.7	4.1×10^{-1}
Cu(II)	TMEN	7.00	970	970	925	1.0	6.9×10^{-1}
Cu(II)	TMEN	7.00	2425	2425	490	0.5	1.4
Cu(II)	PYR	7.00	785	1570	489	64.0	1.1×10^{-2}
Cu(II)	TEEN	7.00	398	1590	497	6.0	11.5×10^{-2}
Cu(II)	AE-ASPA	7.00	3270	3270	478	6.0	11.5×10^{-2}
Cu(II)	DAB	7.00	589	4710	504	9.0	7.7×10^{-2}
Cu(II)	GG	7.00	1400	1400	492	35.0	2.0×10^{-2}
Cu(II)	GGG	7.00	1190	1190	492	17.0	2.0×10^{-2}
UO_2(II)	2-HxG	7.2	515	1030	975	55.0	1.3×10^{-2}
UO_2(II)	HEDTA	7.0	1025	1025	955	33.0	2.1×10^{-2}
UO_2(II)	PDS	6.8	1027	1027	1471	>100	.....
UO_2(II)	DNS	7.0	411	822	1304	4.4	1.6×10^{-1}
UO_2(II)	DNS	7.0	819	1638	1317	3.2	2.2×10^{-1}
UO_2(II)	DNS	7.0	5521	11042	675	2.2	3.2×10^{-1}
La(III)	2-HxG	7.0	1000	1000	950	>100	.....
La(III)	HIMDA	7.0	1000	1000	955	>100	.....
La(III)	HEDDA	7.0	1005	1005	1000	>100	.....
La(III)	HEDTA	7.0	1040	1040	980	>100	.....
La(III)	5-SSA	7.0	525	1050	960	63.0	1.1×10^{-2}
La(III)	DNS	7.0	811	811	1285	52.0	1.3×10^{-2}
La(III)	PDS	7.0	5416	5416	1580	45.0	1.5×10^{-2}
La(III)	PDS	7.5	943	943	1498	56.0	1.2×10^{-2}
VO(II)	2-HxG	7.0	510	1020	975	63.0	1.1×10^{-2}
VO(II)	HIMDA	7.0	1000	1000	960	$\gg$100	.....
VO(II)	HEDDA	7.0	1010	1010	960	$\gg$100	.....
VO(II)	HEDTA	7.0	1045	1045	980	$\gg$100	.....
VO(II)	PDS	6.8	1000	1000	1345	>100	.....
VO(II)	DNS	7.0	1285	1285	1285	>100	.....

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TABLE I (*continued*)

Metal	Ligand	pH	Concn., μmoles/l. Metal	Ligand	Sarin	$t_{1/2}$ (min.)	k_1 (min.$^{-1}$)
Fe(III)	2-HxG	7.0	1035	1035	960	≫100	.....
Fe(III)	HIMDA	7.0	1005	1005	965	≫100	.....
Fe(III)	HEDDA	7.0	985	985	960	≫100	.....
Fe(III)	HEDTA	7.0	1020	1020	965	≫100	.....
Fe(III)	PDS	7.0	1010	1010	935	>100	.....
Fe(III)	DNS	7.0	950	950	855	>100	.....
MoO_2(VI)	...	7.00	1000	1000	1000	75	.....
MoO_2(VI)	HEN	7.00	1000	1000	1000	70	.....
MoO_2(VI)	EDTA	7.00	1000	1000	1000	105	.....
MoO_2(VI)	HEDTA	7.00	950	950	890	~95	.....
MoO_2(VI)	HEDDA	6.95	960	960	900	~75	.....
MoO_2(VI)	2-HxG	7.00	980	980	940	~75	.....
MoO_2(VI)	HIMDA	7.00	960	960	900	~100	.....
MoO_2(VI)	NTA	7.00	970	970	900	~60	.....
MoO_2(VI)	PDS	7.10	965	965	910	7.5	9.2×10^{-2}
MoO_2(VI)	PDS	7.00	4950	4950	975	1.5	4.6×10^{-1}
MoO_2(VI)	PDS	5.20	4950	4950	960	5.0	1.4×10^{-1}
MoO_2(VI)	5-SSA	6.90	990	990	890	~75	.....
MoO_2(VI)	DNS	7.10	890	890	940	~90	.....
MoO_2(VI)	CIT	7.00	890	890	890	~85	.....
MoO_2(VI)	ASPA	7.20	945	945	900	~75	.....
MoO_2(VI)	DPA	7.00	970	970	910	~70	.....
MoO_2(VI)	EN	7.15	950	950	900	~60	.....
MoO_2(VI)	TU	7.00	920	920	900	~85	.....
ZrO(II)	HEDDA	7.00	1000	1000	845	110	.....
ZrO(II)	PDS	7.00	995	995	850	78	.....
ZrO(II)	2-HxG	7.55	1013	1013	850	7.0	.....
ZrO(II)	HIMDA	7.45	988	988	838	7.0	.....
ZrO(II)	CIT	7.50	919	919	846	7.0	.....
ZrO(II)	EDTA	6.40	515	515	865	5.0	1.4×10^{-1}
ZrO(II)	EDTA	7.40	515	515	890	2.5	2.8×10^{-1}
ZrO(II)	EDTA	7.00	1005	1005	850	2.2	3.2×10^{-1}
ZrO(II)	EDTA	8.40	510	510	870	2.3	3.0×10^{-1}
ZrO(II)	HEDTA	6.00	990	990	840	21	3.3×10^{-2}
ZrO(II)	HEDTA	7.00	990	990	840	64	1.1×10^{-2}
Cr(III)	HEDTA	7.05	990	990	850	65	1.1×10^{-2}
Ti(IV)	2-HxG	7.0	900	900	915	Inactive	.....
Sn(IV)	PDS	7.0	2970	5940	503	100	.....
Sn(IV)	PDS	7.0	1510	3020	504	Very large	.....
Sn(IV)	DNS	7.0	Sat'd	3100	497	Very large	.....
Sn(IV)	5-SSA	7.0	Sat'd	3160	504	Very large	.....

The definitions of the abbreviations used to identify the various ligands employed are given in Table II. The corresponding catalytic activities of a number of Cu(II) chelates in the hydrolysis of DFP are listed in Table III.

Discussion

Effect of Ligand on Activity of Cu(II) Chelate Compounds.—The 29 catalytically active Cu(II) chelates listed in Table I may be classified into the following groups on the basis of the type of ligand involved: amino acids (7), phosphates (2), *o*-diphenols (2), peptides (2), diamines (12), hydroxyethylsubstituted diamines (2), and polyamines containing more than two basic nitrogen atoms (2). Of these, the diamines form the most active Cu(II) chelates, and have been explored to the greatest extent. The chelates of amino acids, peptides and phenolic ligands have somewhat less activity. The least active compounds listed in Table I are the Cu(II) chelates of the polyphosphates and of ligands with more than two donor groups per molecule. Not listed in Table I is a wide variety of chelate compounds which were not of sufficiently high activity to be interesting. These compounds

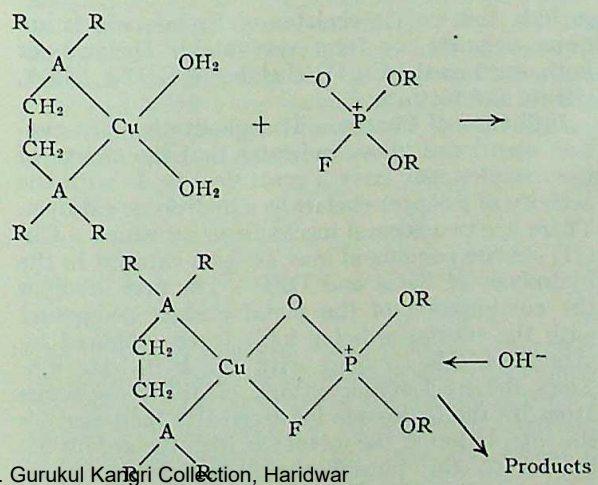

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TABLE II

KEY TO LIGAND ABBREVIATIONS

AE-ASPA	N-aminoethylaspartic acid
ASPA	aspartic acid
CIT	citric acid
CS	*cis*-1,2-diaminocyclohexane
CU	*cis*-Δ^4-1,2-diaminocyclohexene
DAB	1,4-diaminobutane
DAP	1,3-diaminopropane
DIEN	diethylenetriamine
DIPY	dipyridyl
DMEN	N,N′-dimethylethylenediamine
DNS	1,8-dihydroxynaphthalene-3,6-disodium sulfonate
DPA	pyridine-2,6-dicarboxylic acid
EDTA	ethylenediaminetetraacetic acid
EN	ethylenediamine
GG	glycylglycine
GGG	glycylglycylglycine
HASPA	N-hydroxyethylaspartic acid
HEDDA	N,N′-dihydroxyethylethylenediamine-diacetic acid
HEDTA	N-hydroxyethylethylenediaminetriacetic acid
HEN	N-hydroxyethylethylenediamine
2-HEN	N,N′-dihydroxyethylethylenediamine
HIMDA	N-hydroxyethyliminodiacetic acid
2-HxG	N,N-dihydroxyethylglycine
NTA	nitrilotriacetic acid
PDS	pyrocatechol-3,5-disodium sulfonate
PYR	pyridoxamine
5-SSA	5-sulfosalicylic acid
TEEN	N,N,N′,N′-tetraethylethylenediamine
TMEN	N,N,N′,N′-tetramethylethylenediamine
TRIEN	triethylenetetramine
TS	*trans*-1,2-diaminocyclohexane
TU	*trans*-Δ^4-1,2-diaminocyclohexene

TABLE III

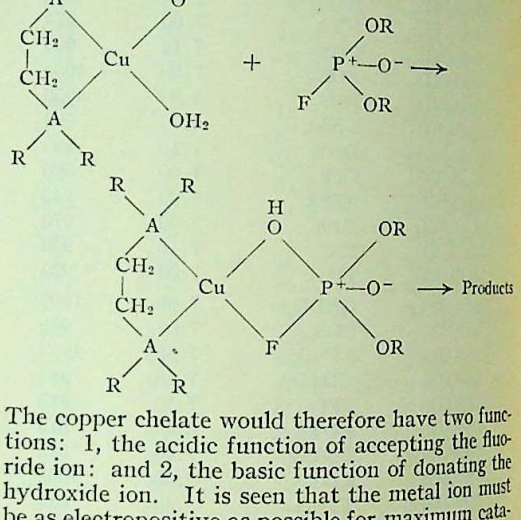
CATALYTIC EFFECTS OF Cu(II) CHELATES ON DFP HYDROLYSIS

DFP = 4.14×10^{-3} *M*; *p*H 7.00; μ = 0.1; T = 25.3°

Catalyst	Concn., μmoles/l.	$t_{1/2}$ (min.)
TMEN	2070	15
DIPY	2070	23
EN	2070	60
HEN	2070	96
2-HEN	2290	250
DIEN	2070	3000

include the Cu(II) chelates of ligands which are quite negative, or form very stable chelates, or both, such as the Cu(II) chelates of EDTA, NTA, citrate and tartrate.

Influence of Charge.—The qualitative observation mentioned above indicates that the charge of the complex may have a great deal to do with the activity of a copper chelate as a hydrolytic catalyst. There are two general mechanisms by which a Cu(II) chelate compound may act as a catalyst in the hydrolysis of Sarin and DFP. The first involves the combination of the metal chelate compound with the substance being hydrolyzed, followed by attack of this complex with the hydroxide ion. Thus the nucleophilic attack of the phosphorus atom by the hydroxide ion is greatly increased by the interaction of the metal ion with the groups attached to the phosphorus atom. It is evident that the more electropositive the Cu(II) atom is, the greater will be its effect on the acceptor activity of the phosphorus atom. Therefore, one would expect that an electron donor which carries considerable negative charge would tend to decrease the rate of the reaction outlined above. The alternate reaction mechanism may be considered analogous to the push–pull mechanism advanced by Swain[8] to explain the action of pyridone in the mutarotation of glucose. Thus the hydroxy form of the Cu(II) chelate may be considered to act as an amphoteric substance in the catalytic reaction, which may be formulated as



The copper chelate would therefore have two functions: 1, the acidic function of accepting the fluoride ion: and 2, the basic function of donating the hydroxide ion. It is seen that the metal ion must be as electropositive as possible for maximum catalytic activity. The more positive the metal ion in the normal 1:1 chelate, the greater will be its tendency to hydrolyze to give the monohydroxy chelate compound illustrated above. Also, the more positive the metal, the greater will be its residual affinity for attracting the fluoride ion from the phosphate group.

The results listed in Table I indicate that the reaction rate decreases with increasing negative charge of the Cu(II) chelate. The following ligands are arranged in the order of decreasing catalytic activities of their Cu(II) chelates in the hydrolysis of Sarin: HEN > HxG > HIMDA > ASPA > EDTA. A similar series may be taken from the data of Wagner-Jauregg, *et al.*,[2] for the catalysis of DFP hydrolysis by Cu(II) chelates: *o*-PHEN, EN > glycine, alanine >> EDTA. Further examples are the greater activity of the Cu(II) pyrophosphate chelate over that of the corresponding tripolyphosphate compound, and the higher activity of the Cu(II) HEDDA chelate over that of HEDTA.

Influence of Number of Donors in Ligand.—Inspection of the catalytic activities of Cu(II) chelates of various ligands listed in Table I indicates that the highest activity is obtained with bidentate donors, and that additional donor groups per mole of ligand reduce the effectiveness of the

(8) C. G. Swain and J. F. Brown, Jr., THIS JOURNAL, 74, 2534 (1952).

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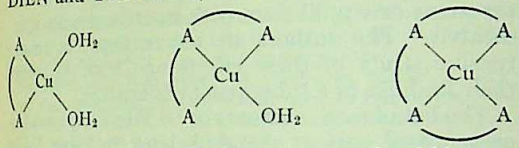
metal chelate as a catalyst. Thus the hydrolysis of Sarin in the presence of the 1:1 Cu(II)–ethylenediamine chelate is three times faster than it is in the presence of the corresponding chelate of diethylenetriamine. It is, of course, difficult to separate the simple structural or steric effect of the number of positions of the Cu(II) ion which are coördinated (see below), from allied effects such as the enhanced stability which results from the increased number of donor positions on the ligand. In the series of Cu(II) chelates of EN, HEN and 2-HEN, there is no additional stability resulting from the relatively weak coördination of the auxiliary hydroxyl groups, in contrast to analogous series EN, DIEN and TRIEN. (The steric factors resulting



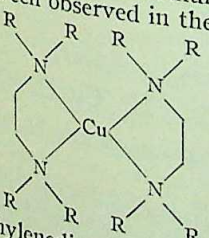
Bidentate Terdentate Quadridentate

Cu(II) chelates formed with bi-, ter-, and quadridentate ligands

from the substitution of alkyl groups on the basic nitrogen atoms are nearly compensated for by coördination of the hydroxyl groups so that the stabilities in the former series do not differ significantly.)

Since the catalytic activities of the HEN and 2-HEN chelates are about half of that of EN, it is seen that a bidentate chelate compound containing two water molecules bound directly to the metal ion is apparently the most favorable structure for producing catalytic activity in Cu(II) chelate compounds. There remains the possibility of catalysis on systems containing monodentate ligands. For the systems investigated, however, 1:1 Cu(II) complexes with monodentate reagents were not sufficiently stable to prevent precipitation at *p*H 7.

Steric Factors.—It has been shown previously[9] that the stability of a 1:1 Cu(II) chelate compound frequently is controlled by the tendency to disproportionate to the 2:1 chelate and copper hydroxide, as well as by its own intrinsic stability constant. Thus a 1:1 chelate with a high stability constant may be unstable in solution if the 2:1 chelate is also very stable. Since Cu(II) chelates are square planar, the substitution of alkyl groups in place of the amino hydrogen atoms would help to prevent this disproportionation reaction by steric repulsion between the substituents on two different moles of ligand, as is indicated by the formula shown below. This effect has been observed in the case of the N-



substituted ethylenediamines such as TMEN, DMEN, DIPY and *o*-PHEN. It is notable that all of these substances form soluble 1:1 Cu(II) chelates which do not disproportionate in aqueous solution at *p*H 7 and above, whereas the 1:1 Cu(II) chelate of ethylenediamine is not stable and is quickly converted to the 2:1 chelate with the precipitation of copper hydroxide. It is seen, therefore, that N-substitution of a 1,2-diamine is helpful in obtaining a stable aqueous catalytic chelate of Cu(II).

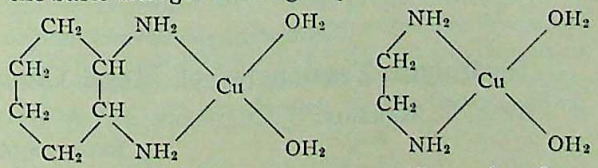
The influence of N-substitution on the specific catalytic activity of Cu(II)–ethylenediamine chelates cannot be determined unambiguously from the examples available since changes of structure also affect the stability of the metal chelate compound. The influence of stability on catalytic activity is discussed below.

Influence of Stability.—Although Wagner–Jauregg, *et al.*,[2] stated that stability of a Cu(II) chelate is not a significant factor in determining its catalytic activity, the evidence obtained in this research seems to indicate otherwise. While it is certain that many factors affect the catalytic activity of chelate compounds, the evidence in Table I seems to indicate that catalytic activity generally decreases with increasing stability of the metal chelate compound. This generalization is supported by a number of comparisons taken from the results of Table I.

1. In the series of 1:1 Cu(II) chelates formed by N-substituted ethylenediamines, the chelate stability constants decrease in the order: EN > DMEN > TMEN. The order of catalytic activity is seen to be exactly the reverse.

2. Although chelate stability constants are not available for monobipyridyl-Cu(II) and for mono-*o*-phenanthroline-Cu(II), the order of decreasing stability of these compounds and of the corresponding EN chelate may be deduced from the published stabilities of the chelates of other metal ions with these ligands to be: EN > *o*-PHEN > DIPY. It is seen that the order of increasing activity is the same: EN < *o*-PHEN[10] < DIPY.

3. Comparison of the Cu(II) chelates of the four diaminocyclohexenes and cyclohexanes with that of ethylenediamine shows no appreciable difference in catalytic activity, although it is known that the stability of the EN-Cu(II) chelate is 2 to 3 log *K* units lower than those formed from the cyclic diamines. A possible explanation of this anomaly is based on the fact that the two types of structures indicated below have equivalent electronic interaction (binding energy) between the Cu(II) ion and the basic nitrogen donor groups



The observed difference in stability, therefore, would be merely an entropy effect which depends on the initial and final states of the ligands in the formation of the metal chelate. Hence, the environment, or electronic condition of the Cu(II) ion, would be

(9) A. E. Martell, R. Gustafson and S. Chaberek, Jr., paper no. 34, International Congress on Catalysis, Philadelphia, Pa., Sept. 10–14, 1956 (to be printed in a special volume of "Advances in Catalysis," Academic Press, Inc., New York).

(10) *o*-Phenanthroline data observed from ref. 3.

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the same in both cases, and the similarity of catalytic activity is not surprising.

In view of these correlations with stability, one would look for the least stable metal chelate compound in order to obtain maximum catalytic activity. There is a definite limit beyond which this concept cannot be pushed, however, which is defined by the stability necessary to keep the metal ion in solution. Thus the most active catalyst would be the aquo ion itself. Since the aquo ion cannot be obtained in sufficient concentration at a *p*H where the hydroxide ion concentration is also sufficient to carry out the reaction at a reasonable rate, it seems that an important function of the metal chelate compound is to maintain the metal ion at a reasonably high concentration (and activity) in aqueous solution.

Influence of Metal Ion on Catalytic Activity.—Measurements of the catalytic activities of a number of stable aqueous metal chelates of the Fe(III), La(III), Cr(III), Ti(IV) and Sn(IV) ions are listed in Table I. Not listed are a number of additional measurements made on chelates of other common metal ions such as Zn(II), Cd(II), Co(II), Fe(II), Ni(II) and Pb(II). None of the metal chelates, listed and unlisted, showed interesting catalytic activity. The Zn(II) ion was unique in that it was the only third row metal for which no active chelates were found.

On the other hand, a number of metal chelate compounds of oxo- metal ions such as ZrO(IV), UO_2(VI) and MoO_2(VI) showed very high catalytic activity toward the hydrolysis of Sarin, the most active being the ethylenediaminetetraacetato-zirconyl ion ($t_{1/2}$ = 2.2 min.), the dioxomolybdenum(VI) chelate of 3,5-disulfopyrocatechol (~7.0 min.), and the dioxouranium(VI) chelate of 3,6-disulfo-1,8-dihydroxynaphthalene (~3.5 min.), the numbers corresponding to the approximate half times of hydrolysis in the presence of a 0.0010 molar solution of the catalyst. The lack of information on the stabilities of these chelate compounds and the small number of examples of very active chelates make correlation of activity with properties of the ligand impossible. It is noted, however, that all of the active catalysts contain one or more oxo groups bound to the metal ion. Although these chelates are in some instances formed with ligands containing many donor groups, it is possible to state in all cases that oxo- or hydroxy-groups are also present. It seems probable that these basic groups must be involved in the observed catalysis by a push–pull mechanism analogous to that already proposed for the Cu(II) chelates.

Although the uranyl 5-sulfosalicylate chelate has been reported by Ryland, *et al.*,[3] to be catalytically active, studies of systems containing this chelate indicate that it is unstable in aqueous solution at *p*H 7.

General Conclusions.—The catalytic activities of metal chelate compounds listed in Table I are seen to increase with increasing *p*H and increasing concentration of the chelate. The measured rate constants increase with an increase in hydroxide ion and metal chelate concentrations, in accordance with the mechanisms suggested above. The rate constants do not increase with the first power of the concentration of these substances, and possible side reactions or equilibrium with inactive species is indicated. The authors are now engaged in an extensive study of these effects and hope to report their findings in a subsequent publication.

The list of rate constants of DFP hydrolysis in the presence of various metal chelates in Table III is restricted to some of the more active catalysts with interesting structures. The results for these compounds, together with the results reported by Wagner-Jauregg, *et al.*, and by Ryland, *et al.*,[3] indicate that the generalizations made above for the hydrolysis of Sarin also apply to DFP, although the latter compound is more slowly hydrolyzed by all reagents investigated.

As a result of the correlation in this paper of the catalytic activity of metal chelates with structure and other properties of the ligand, the following generalizations may be made concerning the factors which tend to increase catalysis of hydrolysis by a metal chelate compound: 1, the presence of oxo, hydroxy or aquo groups bound directly to the metal; 2, bidentate ligands in the case of Cu(II) (does not hold for metals of higher valence); 3, minimum stability of the metal chelate compound which will still prevent dissociation to the metal ion; 4, high concentration (hence high solubility) of the metal chelate; 5, high *p*H.

The most active catalysts found in this investigation in the order of decreasing activity are

For Sarin: Cu(II)TMEN > Cu(II)DMEN > ZrO(II) EDTA > Cu(II) DAP > UO_2(II) $(DNS)_2$ > Cu(II) DIPY > MoO_2(VI) PDS > Cu(II) N > Cu(II) 2-HEN > Cu(II) HEN > Cu(II) DIEN

For DFP: Cu(II) TMEN > Cu(II) DIPY > Cu(II) EN > Cu(II) DAP > Cu(II) HEN > Cu(II) 2-HEN > Cu(II) 2-HEN >>> Cu(II) DIEN

The tetramethylethylenediamine-Cu(II) chelate is the most active catalyst found up to the present time.

WORCESTER, MASS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, CLARK UNIVERSITY]

Hydrolytic Tendencies of Metal Chelate Compounds. I. Cu(II) Chelates[1]

BY A. E. MARTELL, S. CHABEREK, JR., R. C. COURTNEY, S. WESTERBACK AND H. HYYTIAINEN

RECEIVED MARCH 4, 1957

The hydrolysis of 1:1 chelates of copper with thirty ligands has been studied potentiometrically with a view to determining relative tendencies to form hydroxy complexes. Most of the bidentate chelate compounds investigated were found to undergo hydrolysis in a limited *p*H range, with *pK* values of 7.5 ± 0.3. The number of donor groups in the ligand was found to be more important than stability in determining hydrolytic tendencies. In certain cases the existence of a highly stable 2:1 chelate resulted in disproportionation of the 1:1 chelate with simultaneous precipitation of half of the metal in the form of its hydroxide.

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(1) This paper reports work done under contract with the Chemical Corps, U. S. Army, Washington 25, D. C.

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June 20, 1957

Because of the interest in these laboratories in the study of incompletely coördinated metal chelate compounds as catalysts and as enzyme models, it was considered desirable to first investigate the behavior of copper chelates containing one or more uncoördinated positions on the metal ion. A search of the literature reveals very little information on this type of compound. Recently the monohydroxyl complex of dipyridyl-Cu(II) has been reported by Wagner-Jauregg, *et al.*,[2] while the equilibria involving this compound as well as the hydroxides of *o*-phenanthroline-Cu(II) and of ethylenediamine-Cu(II) have been measured quantitatively by Ryland, *et al.*[3]

Experimental

The experimental method consisted of potentiometric titration of the chelating agent in the absence of, and in the presence of, the metal ions being investigated.

Apparatus and Procedure.—A Beckman Model G *p*H meter with extension electrodes was used to record the hydrogen ion concentration. Titrations were carried out in a 200-ml. eight-neck flask designed to accommodate a mercury seal stirrer, microburet delivery tube, nitrogen inlet and outlet tubes, and glass and calomel electrodes. Measurements were made at a temperature of 25 ± 0.1° unless otherwise noted. The ionic strength was maintained relatively constant with a medium containing 0.10 *M* potassium nitrate and relatively low concentrations of ligand and metal ion. Carbonate-free potassium hydroxide prepared by the method of Schwarzenbach and Biedermann[4] was used as a titrant in all cases. In order to prevent absorption of atmospheric carbon dioxide, presaturated nitrogen was bubbled through the experimental solution during the course of the titrations. In all cases reported, titration data were obtained for solutions containing equimolar concentrations of ligand or metal ion.

When thermal equilibrium had been attained, *p*H readings were taken after the addition of small increments of 0.10 *M* potassium hydroxide until the *p*H reached values of 10.5–11.0. The *p*H meter-glass electrode-calomel electrode system was calibrated against standard acetate buffer to determine hydrogen ion concentrations.

Materials.—A solution of reagent grade copper(II) nitrate was standardized by titration with standard Na_2EDTA reagent with murexide as an indicator in ammoniacal solution.[5] Samples of ethylenediaminetetraacetic acid, N-hydroxyethylethylenediaminetriacetic acid, N,N′-dihydroxyethylethylenediaminediacetic acid, N-hydroxyethyliminodiacetic acid, nitrilotriacetic acid, aspartic acid, N-hydroxyethylaspartic acid and N-aminoethylaspartic acid were obtained through the courtesy of Versenes, Inc., Framingham, Massachusetts. Samples of N-hydroxyethylethylenediamine, N,N′-dihydroxyethylethylenediamine, diethylenetriamine and triethylenetetramine were obtained from Carbide and Carbon Chemical Co., purified by fractional distillation, and converted to the corresponding hydrochlorides. Ethylenediamine, 5-sulfosalicylic acid and 1,8-dihydroxynaphthalene-3,6-disodium sulfonate were purchased from Eastman Kodak Co. The ethylenediamine was dried over potassium hydroxide, redistilled and isolated as the dihydrochloride. Pyrocatechol-3,5-disodium sulfonate was purchased from LaMotte Chemical Products Corp., Baltimore, Maryland. The 1,3-diaminopropane was obtained from the Sharples Chemical Company while the dipicolinic acid (pyridine-2,6-dicarboxylic acid) was donated by Dr. Stanley Chaberek of the Dow Chemical Co., Framingham, Massachusetts. Samples of the dihydrochlorides of N,N′-dimethylethylenediamine and N,N,N′,N′-tetramethylethylenediamine were prepared and recrystallized by conventional methods. The hydrochlorides of *cis*- and *trans*-1,2-diaminocyclohexane and the corresponding cyclohexene derivative were prepared by the stereospecific method described by Craven.[6] N,N′-Dihydroxyethylethylenediaminediacetic acid (HEDDA) was prepared by cation exchange from a solution of the sodium salt in accordance with the method described by Chaberek and Martell[7] for the corresponding monohydroxyethyl compound (HEDTA). Standardization of the aqueous solutions of the above chelating agents was effected by means of potentiometric titration with either standard carbonate-free potassium hydroxide or hydrochloric acid.

Results

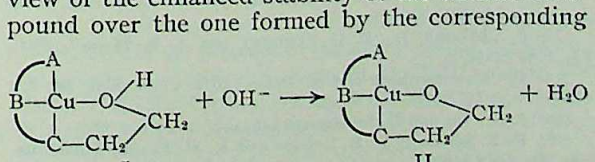
The potentiometric data obtained on the metal chelates outlined above are summarized in Table I. The symbols used to describe the formulas of the metal chelates in Table I involve the notation $H_mA(OH)_i$ for the ligand and the formula $(MAO_j(OH)_{i-j}[OH]_k)^{n-m-j-k}$ for the chelates formed by combination of one mole of ligand with one gram ion of the metal ion M^{+n}. The potentiometric titration curves of the various copper chelate systems investigated are reproduced in Figs. 1 and 2.

Discussion

Potentiometric Titration Curves.—Potentiometric measurements of stabilities of some of the Cu(II) chelates investigated as well as of their hydrolytic tendencies, are indicated in Figs. 1 and 2. Of the compounds listed in Table I, titration curves of metal chelates which have been investigated previously for hydrolytic tendencies have been omitted. Thus potentiometric measurements of the Cu(II) complex of EDTA, as well as those of HEDTA, HIMDA, ASPA, EN, DAP, DIEN, and TRIEN, have been described in sufficient detail by the investigators referred to in Table I.

For the ligands containing four or more strong coördinating groups, there is a single strong inflection in the 1:1 Cu(II) chelate titration curve corresponding to the neutralization of all the displaceable protons (four or less) of the ligand. This behavior is characteristic of EDTA, HEDTA, 2-HEDDA, TRIEN and DIEN. The titration curves of these compounds showed no evidence for the further coördination of the metal with hydroxyl groups derived from the solvent.

Ligands having hydroxyethyl groups in positions favorable for coördination constitute a special case in view of the weak coördinating tendencies of this group. In cases where the number of strong coordinating groups was too small to satisfy the requirements of the Cu(II) ion (*i.e.*, less than four), a step in the titration curve usually is observed. This is true of HASPA (Fig. 1), HEN and 2-HEN (Fig. 2) as well as HIMDA and HxG, titration curves of which have been given previously.[12,13] For these ligands, it is believed that the hydroxyethyl group is coördinated with the Cu(II) ion in view of the enhanced stability of the chelate compound over the one formed by the corresponding



I II

(2) T. Wagner-Jauregg, B. E. Hackley, Jr., T. A. Lies, O. O. Owens and R. Proper, THIS JOURNAL, **77**, 922 (1955).

(3) L. B. Ryland, F. M. Fowkes and G. S. Ronay, Paper No. 108, Division of Physical and Inorganic Chemistry, 128th National Meeting of the American Chemical Society, Minneapolis, Minn., September 11-16, 1955.

(4) G. Schwarzenbach and W. Biedermann, *Helv. Chim. Acta*, **31**, 339 (1948).

(5) G. Schwarzenbach, "Die Komplexometrische Titration," Ferdinand Enke, Stuttgart, 1955, p. 68.

(6) M. Craven, Thesis, Clark University, 1952.

(7) S. Chaberek and A. E. Martell, THIS JOURNAL, **77**, 1477 (1955).

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TABLE I

METAL–LIGAND INTERACTIONS AT 25°

Metal ion	Ligand	Formula of initial chelate formed	Log K^c	$pK_a{}^d$	Remarks
Cu(II)	ASPA (H_2A)	$(CuA[OH])^{-1}$	8.4[a]	7.3	.....
Cu(II)	EN (A)	$(CuA[OH])^{+}$	10.5[b]	7.1	Disproportionation above *p*H 7
Cu(II)	HEN (AOH)	$(CuAOH[OH])^{+}$	10.0	7.3	.....
Cu(II)	2-HEN ($A(OH)_2$)	$(CuA(OH)_2[OH])^{+}$	9.6	7.1	.....
Cu(II)	HEDTA (H_3AOH)	$(CuAOH)^{-1}$	17.4[10]	None	.....
Cu(II)	HEDDA ($H_2A(OH)_2$)	$(CuA(OH)_2)^0$	~16.5[11]	None	.....
Cu(II)	HIMDA (H_2AOH)	$(CuAOH)^0$	~10^{12} (30°)	9.1	.....
Cu(II)	2-HxG ($HA(OH)_2$)	$(CuAO(OH))^0$	8.15[13] (30°)	6.8	.....
Cu(II)	HASPA(H_2AOH)	$(CuAOH[OH])^{-1}$	....	7.5	.....
Cu(II)	5-SSA (H_2AOH)	$(CuAO)^{-1}$	....	..	Ppt. above *p*H 7
Cu(II)	PDS ($A(OH)_2{}^{-2}$)	$(CuAO_2[OH])^{-3}$	14.57	7.2	.....
Cu(II)	DNS ($A(OH)_2{}^{-2}$)	$(CuAO_2[OH])^{-3}$	13.80	7.8	.....
Cu(II)	CU (A)	$(CuA[OH])^{+}$	~11.0	7.2	Disproportionation above *p*H 7
Cu(II)	TU (A)	$(CuA[OH])^{+}$	11.5	7.1	Disproportionation above *p*H 7
Cu(II)	CS (A)	$(CuA[OH])^{+}$	10.87[14] (20°)	7.1	Disproportionation above *p*H 7
Cu(II)	TS (A)	$(CuA[OH])^{+}$	11.13[14] (20°)	7.2	Disproportionation above *p*H 7
Cu(II)	DIEN (A)	$(CuA[OH])$	16.0[15] (20°)	9.2 (25°)	.....
			16.1[16] (30°, μ = 1.0)		.....
Cu(II)	TRIEN (A)	$(CuA)^{+2}$	20.5[17] (20°)	None	.....
Cu(II)	DPA (A)	$(CuA)^0$	....	None	Ppt. of $Cu(OH)_2$ above *p*H 6
Cu(II)	DMEN	$(CuA[OH])^{+}$	9.69	7.4	.....
Cu(II)	TMEN (A)	$(CuA[OH])^{+}$	7.2	7.2	.....
Cu(II)	PYR (AOH)	$(CuAO)^{+}$	10.2	..	Ppt. above *p*H 7
Cu(II)	AE-ASPA	$(Cu_2A_2)^0$ Dimer	15.1[11]	None	.....
Cu(II)	GG (H_2A)	$(CuA[OH])^{-1}$	6.6[18]	9.0	.....
Cu(II)	GGG (H_3A)	$(CuA)^{-1}$	5.7[18]	None	.....
Cu(II)	DIPY	$(CuA[OH])^{+}$	....	6.6	.....
Cu(II)	PHEN	$(CuA[OH])^{+}$	....	6.9	.....

[a] Chaberek and Martell[8] report 8.5 at 30°. [b] Ackermann, *et al.*,[9] report log K_{CuEN} = 10.72 at 25°. [c] K is formation constant of normal chelate. [d] K_a is acid dissociation constant of normal chelate.

ligand in the absence of the hydroxyethyl group. The additional step in the titration curve would then be due to the dissociation of a proton from the hydroxyethyl group as shown by I → II. This reaction has no counterpart in the uncoördinated ligand, due to the very weak acidity of hydroxyethyl groups. Since it is not possible to give the stability constant of compound II in terms of the metal ion and ligand, the only other alternative, followed in Table I, is to give a stability constant for I and pK values for the subsequent dissociation steps.

The qualitative comparisons possible in the titration curves of ASPA and HASPA, given in Fig. 1, serve to illustrate the principles involved. The greater *p*H decrease of HASPA on coördination with Cu(II) ion (observed best between a = 1

TABLE IA

KEY TO LIGAND ABBREVIATIONS

ASPA	Aspartic acid
EN	Ethylenediamine
HEN	N-Hydroxyethylethylenediamine
2-HEN	N,N′-Dihydroxyethylethylenediamine
HEDTA	N-Hydroxyethyl-N,N′-ethylenediaminetriacetic acid
HEDDA	N,N′-Dihydroxyethyl-N,N′-ethylenediaminediacetic acid
HIMDA	N-Hydroxyethyliminodiacetic acid
2-HxG	N,N-Dihydroxyethylglycine
HASPA	N-Hydroxyethylaspartic acid
5-SSA	5-Sulfosalicylic acid
PDS	Disodium 3,5-pyrocatecholdisulfonate
DNS	Disodium 1,8-dihydroxynaphthalene-4,5 disulfonate
CU	*cis*-Δ^4-1,2-Diaminocyclohexene
TU	*trans*-Δ^4-1,2-Diaminocyclohexene
CS	*cis*-1,2-Diaminocyclohexane
TS	*trans*-1,2-Diaminocyclohexane
DIEN	Diethylenetriamine
TRIEN	Triethylenetetramine
DPA	2,6-Dipicolinic acid
DMEN	N,N′-Dimethylethylenediamine
TMEN	N,N,N′,N′-Tetramethylethylenediamine
PYR	Pyridoxamine
AE-ASPA	N-Hydroxyethylaspartic acid
GG	Glycylglycine
GGG	Glycylglycylglycine
DIPY	Dipyridyl
o-PHEN	*o*-Phenanthroline

(8) S. Chaberek, Jr., and A. E. Martell, THIS JOURNAL, **74**, 6021 (1952).

(9) H. Ackermann, J. E. Prue and G. Schwarzenbach, *Nature*, **163**, 723 (1949); *Helv. Chim. Acta*, **33**, 985 (1950).

(10) S. Chaberek and A. E. Martell, THIS JOURNAL, **77**, 1477 (1955).

(11) A. Frost, Dow Chemical Company, private communication.

(12) S. Chaberek, Jr., R. C. Courtney and A. E. Martell, THIS JOURNAL, **74**, 5957 (1952).

(13) S. Chaberek Jr., R. C. Courtney and A. E. Martell, *ibid.*, **75**, 2185 (1953).

(14) G. Schwarzenbach and R. Bauer, *Helv. Chim. Acta*, **39**, 722 (1956).

(15) J. E. Prue and G. Schwarzenbach, *ibid.*, **33**, 985 (1950).

(16) H. B. Jonassen, R. B. LeBlanc and R. M. Rogan, THIS JOURNAL, **72**, 4968 (1950).

(17) G. Schwarzenbach, *Helv. Chim. Acta*, **33**, 995 (1950).

(18) C. B. Murphy and A. E. Martell, *J. Biol. Chem.*, in press (1957).

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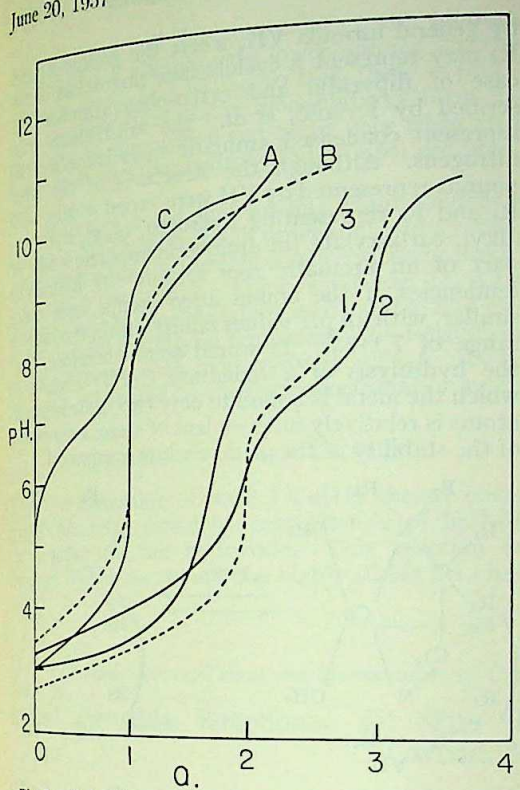
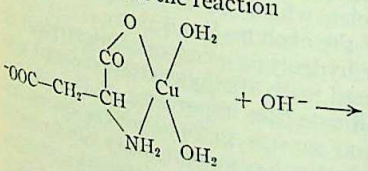
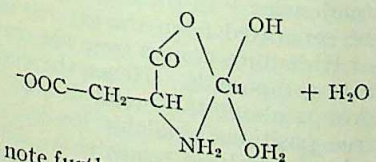


Fig 1.—Potentiometric titration of aspartic acid derivatives in the presence of (indicated by numbers) and in the absence of (indicated by letters) an equivalent molar amount of Cu(II) salt: HASPA, ASPA and AEASPA indicated by A, B, C, and 1, 2 and 3, respectively.

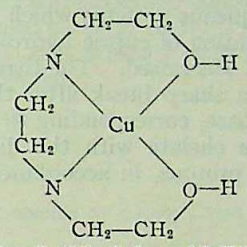
and $a = 2$) is an indication of the greater stability of the Cu-HASPA chelate, even though one would expect the reverse since HASPA is the more acidic ligand. This seems to indicate the participation of the hydroxyethyl group as a weak coördinating partner. For this reason the buffer region in the Cu(II)-HASPA curve is believed to correspond to a reaction similar to that illustrated above. Such a reaction is not possible with the Cu(II) aspartate, and the analogous buffer region must correspond to the dissociation of a coördinated water molecule in accordance with the reaction





It is interesting to note further that the more stable chelate (that of HASPA) shows the lower acidity of the proton attached to a coördinated oxygen. This may be due in part to the greater basicity of oxygen bound to alkyl groups over oxygen in water.

The question of participation of hydroxyalkyl groups in chelation of a metal ion has been considered by a number of investigators[10,13,19,20] with the weight of evidence in favor of direct coördination of the metal ion by the hydroxyalkyl groups. Thus for all of the Cu(II) chelates illustrated in Fig. 2, the coördination of the hydroxyalkyl group is believed to take place when such groups are present, in spite of the similarities of the buffer regions between $a = 2$ and $a = 3$. In the case of HASPA (Fig. 1) and HEN (Fig. 2), it should be pointed out that the hydroxy chelates and the alkoxy chelates would be tautomeric and that the product may actually be an equilibrium mixture of the two. It is noted that a similar interpretation cannot apply to the dihydroxyethyl derivative (III) without implying the displacement of a hydroxyalkyl group, which seems unlikely.



III. Cu(II) chelate of 2-HEN

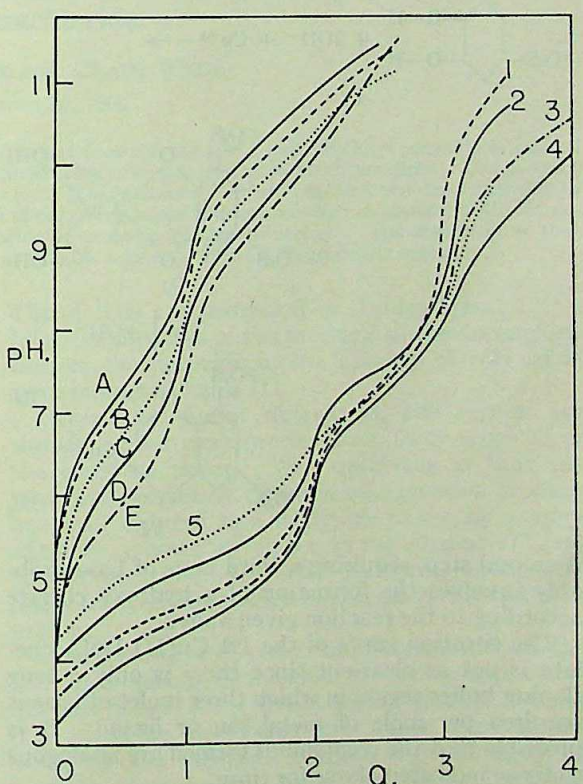


Fig. 2.—Potentiometric titration of ethylenediamine derivatives in the presence of (numbers) and in the absence of (letters) an equivalent amount of Cu(II) salt: EN, DMEN, HEN, 2-HEN and TMEN indicated by A, B, C, D, E, and 1, 2, 3, 4, 5, respectively.

(19) G. Anderegg and G. Schwarzenbach, *Helv. Chim. Acta*, **37**, 1940 (1955).

(20) S. Chaberek, Jr., and A. E. Martell, THIS JOURNAL, **76**, 215 (1954).

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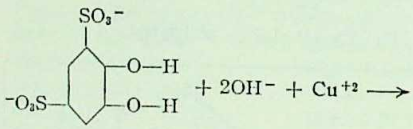
The titration curves of *cis*- and *trans*-1,2-diaminocyclohexane and *cis*- and *trans*-1,2-diaminocyclohexene indicate that the Cu(II) chelates are very similar to those of ethylenediamine, with somewhat enhanced stability of the normal chelate, but with little difference in the buffer regions resulting from hydroxy chelate formation. The synthesis and properties of these diamines and of their metal chelates will be given in a subsequent publication.[21]

The potentiometric titrations and related properties of the Cu(II) chelates of glycylglycine and of glycylglycylglycine are being reported elsewhere.[18]

A number of bidentate chelates of Cu(II) with only oxygen donors were also investigated. Thus far only tiron (PDS) and chromotropic salt (DNS) gave stable aqueous systems which did not result in the precipitation of cupric hydroxide as the *p*H of the solution was raised. The titration curve for PDS showed a sharp break after the addition of two moles of base, corresponding to the formation of a bidentate chelate with the displacement of both phenolic protons, in accordance with the reaction



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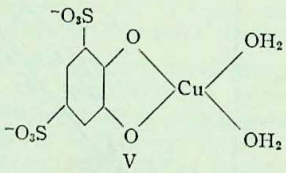
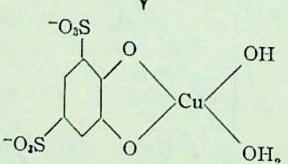


V

↓ +OH-



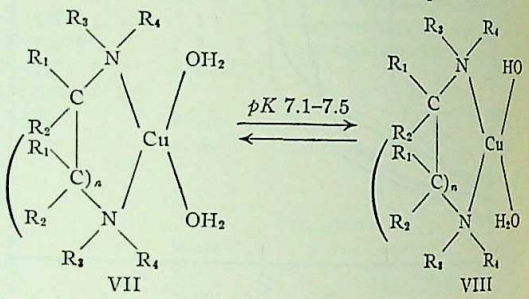
VI

A second step, requiring a third mole of base probably involves the formation of a hydroxy chelate according to the reaction given above.

The titration curve of the 1:1 Cu(II)-DNA chelate is not as clear-cut since there is only a long sloping buffer region in which three moles of base is required per mole of metal ion or ligand. It is probable that the compounds formed are analogous to those indicated above for tiron.

Among the bidentate ligands containing only oxygen donors, which failed to prevent precipitation of the metal at a 1:1 ratio of ligand to metal ion, may be mentioned 5-sulfosalicyclic acid and sodium pyrophosphate.

The majority of the Cu(II) complexes which were found to form soluble hydroxy chelate compounds are diamines with the structure indicated by general formula VII, where the groups R_1 and R_2 may represent a cyclohexane ring or, as in the case of dipyridyl and ortho-phenanthroline described by Ryland, *et al.*,[3] the substituents may represent condensed aromatic rings including the nitrogens. Although the structures of the compounds represented by VII were varied widely, with R_3 and R_4 representing hydrogen, alkyl, hydroxyalkyl, carboxylate (in aminoethylaspartic acid), or part of an aromatic ring system, the hydrolytic tendencies of the bound aquo groups were quite similar, with all *pK* values falling within the narrow range of 7.1–7.5. It would seem, therefore, that the hydrolysis of a bidentate Cu(II) chelate in which the metal is bound to only two basic nitrogen atoms is relatively independent of steric factors and of the stability of the metal chelate compound.



VII VIII

Thus the stabilities of ethylenediamine-Cu(II) and of tetramethylethylenediamine-Cu(II) differ widely, but their hydrolytic tendencies are almost identical. This is also true of the chelates formed from the mono- and dihydroxyethylethylenediamines.

The relative lack of influence of steric factors on the hydrolysis of substituted alkylenediamine-Cu(II) chelates is evidenced by the similarities between such widely different compounds as the Cu(II) chelates of dipyridyl, *o*-phenanthroline, ethylenediamine, and the *cis*- and *trans*-1,2-cyclohexanediamines. A number of Cu(II) chelates with oxygen donors or with oxygen and nitrogen donors show similar hydrolytic tendencies. Thus the Cu(II) chelates of tiron (PDS) and of chromotropic salt (DNS) and of aspartic acid have hydrolytic tendencies which do not differ appreciably from those of the chelates listed above.

The higher hydrolytic constants of the tridentate chelates formed with diethylenetriamine and glycylglycine indicate the importance of the number of bound aquo groups in determining hydrolytic tendencies. In these compounds this effect cannot be separated from the greater electronic influence of tridentate donors over the corresponding bidentate compounds. Hence the distribution of donor groups about the metal as well as the number of free positions available for hydrolysis may determine hydrolytic tendencies. Although one might be tempted to correlate the tendency of Cu(II) chelates toward hydrolysis with the asymmetry of the electronic field about the metal ion, the relative tendencies of stable tridentate and bidentate metal chelates can apparently be explained on much simpler grounds—the greater electron donor effect of the tridentate ligand on the remaining bound

(21) S. Westerback and A. E. Martell, unpublished work.

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water molecule and the consequent greater binding of protons (or alternatively lower affinity for the hydroxyl ion). In addition to this, there is probably a stabilization of the monohydroxy form by hydrogen bonding which can occur only when two water molecules (or hydroxylkyl groups) are present.

It is further noted that an important tendency in the Cu(II) chelates which prevents hydroxy chelate formation is the formation of a relatively stable 2:1 chelate compound. Thus, while the 1:1 Cu-(II)-ethylenediamine chelate is quite stable and exhibits normal hydrolytic tendencies, the formation of the corresponding monohydroxy chelate above *p*H 7.0 is prevented by the disproportionation reaction

$$2CuA(OH) \longrightarrow CuA_2 + Cu(OH)_2$$

Thus the formation of the 2:1 Cu(II) chelate compound is accompanied by precipitation of half of the copper as the hydroxide. This reaction is favored by the formation of a highly stable 2:1 chelate compound, with the result that the disproportionation reaction of the type given above results in a favorable free energy decrease. Such reactions are prevented in the hydroxyethylethylenediamines by higher stability of the 1:1 chelate as the result of participation of the weak ethanol donors in chelate formation. Disproportionation reactions are also prevented in the N-alkylated ethylenediamines through lowering of the stability of the 2:1 chelate compound as the result of steric repulsions between the alkyl groups.

On the basis of the behavior of the Cu(II) chelates listed in Table I, therefore, the factors favoring the formation of soluble hydroxy chelates are: 1, the formation of a sufficiently stable bidentate chelate to prevent precipitation of the Cu(II) as hydroxide; 2, high stability of the 1:1 chelate over the corresponding compound in which the ratio of ligand to metal ion is 2:1; 3, the absence of more than two strongly coördinating donor groups on the ligand.

WORCESTER, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF SOUTH CAROLINA]

Diacyl Peroxide Reactions. II. The Reaction of δ-Phenylvaleryl Peroxide with Carbon Tetrachloride

BY DELOS F. DETAR AND CLAUS WEIS[1]

RECEIVED AUGUST 30, 1956

A quantitative study has been made of the products of the thermal decomposition of δ-phenylvaleryl peroxide in carbon tetrachloride over a more than six hundred-fold variation in peroxide concentration and at two temperatures. The product yields are almost independent of concentration and of temperature. It is reasonably certain that induced decomposition of the peroxide is insignificant at concentrations below 0.02 *M* and of only very minor importance even at about 0.6 *M*. It appears that more than 55% of the radicals derived from the peroxide undergo geminate reaction. The results show that under certain conditions aliphatic diacyl peroxides can be used as reliable sources of free alkyl radicals in solution.

The present paper describes a detailed study of the products of the thermal decomposition of δ-phenylvaleryl peroxide in carbon tetrachloride. It is a continuation of work described in the first paper in the series,[2] and is part of a research program directed toward a study of elementary free radical processes in solution.

The decomposition of δ-phenylvaleryl peroxide in carbon tetrachloride was carried out over a range of concentrations from about 0.001 *M* to about 0.6 *M*, a more than 600-fold variation. Two temperatures were used, 55 and 77°. At the higher temperature the analyses of products accounted for 98 ± 1% of the phenylbutyl groups and for 97.5 ± 0.3% of the carboxyl groups. The solvent fragment balance was not quite so good in that the number of CCl_3 groups found in hexachloroethane did not usually agree very well with the number of Cl groups found in 4-phenyl-1-chlorobutane. It is possible that hexachloroethane was lost in the removal of the last traces of the solvent. Enough experiments were carried out to permit a valid estimate of the accuracy and reliability of the results. The details are presented in Tables I and II; a brief examination of the products of the decomposition of the peroxide in the absence of solvent is summarized in Table III.

Except for minor differences, the results are similar to, but more precise than, those reported in the previous paper.[2] One difference is that the phosgene previously reported as a reaction product has been reduced to a negligible factor by a more effective removal of oxygen in the runs at 77° (reported in Table I). The phosgene apparently arises from reaction of trichloromethyl radicals with oxygen.

Phosgene was evolved in small amounts from the 55° runs during distillation of the carbon tetrachloride through the fractionating column. Since free phosgene previously had been removed by sweeping the reaction mixture with nitrogen, it must be surmised that some unstable product was liberating the phosgene. The trichloromethyl ester of δ-phenylvaleric acid is possibly the phosgene precursor. Its decomposition would also yield δ-phenylvalerol chloride. The increased amount of δ-phenylvaleric acid found in these runs could be accounted for by this hypothesis. However, another potential phosgene source is hexachlorodimethyl peroxide from reaction of trichloromethyl radicals

(1) Postdoctoral Research Associate. This work was supported by National Science Foundation Grants NSF G 439 and NSF G 1863 and by a grant from the Research Committee of the University of South Carolina.

(2) D. F. DeTar and C. Weis, THIS JOURNAL, 78, 4296 (1956).

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TABLE I

PRODUCTS OF THE THERMAL DECOMPOSITION OF δ-PHENYLVALERYL PEROXIDE IN CARBON TETRACHLORIDE AT 77°[a]

Run no.	4	7	2	3	5	6	9	8	10	Std. dev.[b]	Av.[c]
Reactants											
Peroxide, mmoles	5.65	11.37	11.42	22.8	22.4	23.1	8.62	11.3	11.3		
CCl_4, liters	5.00	5.00	5.00	5.00	1.92	1.00	0.100	0.050	0.015		
Peroxide mole ratio (× 10^4)	1.09	2.20	2.22	4.42	11.3	22.4	83.5	219	730		
Products											
CO_2	1.69	1.680	1.684	1.678	1.686	1.644	1.616	1.614	1.564	0.017(5)[d]	1.677 ± 0.007[d]
C_2Cl_6	0.28	0.41	0.42	0.28	0.26	0.22	0.15	0.097	0.061		
$C_6H_5(CH_2)_4Cl$	.86	.83	.79	.90	.92	.86	.77	.76	.79	.05 (11)[e]	0.86 ± .02[d]
$C_6H_5(CH_2)_4COO(CH_2)_4C_6H_5$	.193	.198	.202	.195	.184	.195	.186	.197	.198	.006(8)[f]	.194 ± .002[f]
$C_6H_5(CH_2)_5C_6H_5$	.26	.32	.27	.24	.24	.21	.22	.22	.23	.03 (16)[g]	.246 ± .01[f]
$C_6H_5(CH_2)_2CHClCH_2CCl_3$	.12	.15	.16	.13	.13	.14	.17	.16	.17	.016(15)[h]	.148 ± .005[f]
$C_6H_5(CH_2)_4COOH$	.06	.06	.06	.06	.10	.10	.14	.17	.20	.03 (11)[e]	.073 ± .012[d]
Total CO_2 groups accounted for, %	97.1	97.1	97.5	96.5	98.3	96.9	97.0	99.0	98.2	0.8 (8)[f]	97.5 ± 0.3[f]
Total $C_6H_5(CH_2)_4$ groups accounted for, %	98	104	98	98	100	96	94	96	101	3 (16)[g]	98 ± 1[f]

[a] Entries are moles of product per mole of peroxide. The run numbers indicate the order of the runs. [b] Standard deviation of individual entries; the number in parentheses is the degrees of freedom. [c] Error estimate is standard deviation of the average. [d] Based on runs 2–7, incl. [e] Based on runs 2–7, 11, 13–18. [f] Based on runs 2–10. [g] Based on all runs, 2–19. [h] Based on runs 2–10, 11, 13–19.

TABLE II

PRODUCTS OF THE THERMAL DECOMPOSITION OF δ-PHENYLVALERYL PEROXIDE IN CARBON TETRACHLORIDE AT 55°[a]

Run no.	12[b]	19	11	17	16	18	14	15	13	Std. dev.[c]	Av.[d]
Reactants											
Peroxide, mmoles	5.45	5.76	11.46	11.46	22.6	22.4	22.4	22.6	22.4		
CCl_4, liters	5.00	5.00	5.00	5.00	5.00	5.00	2.00	2.00	1.00		
Peroxide mole ratio (× 10^4)	1.06	1.12	2.22	2.22	4.38	4.34	10.8	10.9	21.6		
Products											
CO_2	1.68	1.70	1.73	1.66	1.66	1.67	1.61	1.66	1.59	0.04 (8)[e]	1.66 ± 0.013[e]
C_2Cl_6	0.11	0.09	0.13	0.13	0.18	0.19	0.14	0.14	0.14		
$C_6H_5(CH_2)_4Cl$	.44	.40	.64	.66	.78	.79	.74	.74	.76	.05 (11)[f]	0.73 ± .02[g]
$C_6H_5(CH_2)_4COO(CH_2)_4C_6H_5$	.224	.187	.216	.208	.202	.182	.176	.177	.175	.019(8)[e]	.194 ± .006[e]
$C_6H_5(CH_2)_5C_6H_5$	.22	.24	.28	.22	.21	.22	.20	.20	.18	.03 (16)[h]	.22 ± .01[e]
$C_6H_5(CH_2)_2CHClCH_2CCl_3$	.05	.13	.12	.14	.14	.14	.11	.12	.14	.016(15)[i]	.131 ± .006[j]
$C_6H_5(CH_2)_4COOH$	.48	.46	.22	.22	.20	.14	.23	.24	.24	.03 (11)[f]	.21 ± .01[g]
Total CO_2 groups accounted for, %	120	117	109	105	103	100	101	104	99	3 (6)[g]	103 ± 1[g]
Total $C_6H_5(CH_2)_4$ groups accounted for, %	94	93	99	94	97	94	91	93	92	3 (16)[h]	94 ± 1[g]

[a] Entries are moles of product per mole of peroxide. [b] Order in which the runs were worked up. [c] Standard deviation of individual entries; the number in parentheses is the degrees of freedom. [d] Error estimate is standard deviation of the average. [e] Based on runs 11–19. [f] Based on runs 2–7, 11, 13–18. [g] Based on runs 11, 13–18. [h] Based on all runs, 2–19. [i] Based on runs 2–10, 11, 13–19. [j] Based on runs 11, 13–19.

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TABLE III

PRODUCTS OF THE THERMAL DECOMPOSITION OF PURE δ-PHENYLVALERYL PEROXIDE WITHOUT SOLVENT AT 65°[a]

Run	20	21
Peroxide, mmoles	19.67	18.92
Products		
CO_2	1.27	1.26
$C_6H_5(CH_2)_3CH_3$	0.30	0.28
$C_6H_5(CH_2)_3CH{=}CH_2$	.02	.32
$C_6H_5(CH_2)_3C_6H_5$	.23	.21
$C_6H_5(CH_2)_4COO(CH_2)_4C_6H_5$	.173	.175
$C_6H_5(CH_2)_4COOH$	.27	.53
Tetralin	.20	.27
Total CO_2 groups accounted for, %	85	98
Total $C_6H_5(CH_2)_4$ groups accounted for, %	88	108

[a] Entries are moles of product per mole of peroxide. The exothermic reaction goes out of control at higher temperatures.

with oxygen. In either event the amount involved was small.

The analysis of products formed in the absence of solvent was carried out as previously described for the benzene runs. It was not considered worthwhile to spend the time needed to perfect the analytical techniques for these runs; the error limits are somewhat larger than reported in Tables I and II, those for 1-phenylbutane, for 4-phenyl-1-butene and for tetralin may be fairly large.

The most striking feature of the results is the insensitivity of the product yields to the peroxide concentration and to the reaction temperature. The constancy is so pronounced that it is feasible to summarize many of the data in the form of averages as is done in the final columns of the tables. The deviations from the averages are generally only a few per cent. relative.

These results are strong evidence for the absence of induced decomposition, the usual types of which would lead to the ester, δ-phenylbutyl δ-phenylvalerate, or to the dimer, 1,8-diphenyloctane.[3] Since the yields of these particular products are invariant even for the reaction in absence of solvent, they cannot be produced by an induced chain mechanism. Products that might be expected from induced decomposition of the peroxide by trichloromethyl radicals are $RCCl_3$ or $RCOOCl_3$, in which R is a phenylbutyl group. However, no appreciable amount of these products was present, certainly not enough to account for more than a very few per cent. of induced decomposition. Furthermore kinetic studies[4] show that the reaction is quite accurately first order, and that the rate of disappearance of the peroxide is insensitive to oxygen.[5] The increase in initial rate with increase in peroxide concentrations can be accommodated by an estimated 5% of induced decomposition at an initial peroxide concentration of 0.1 *M*. These results all show that little induced decomposition takes place with δ-phenylvaleryl peroxide at low concentrations in carbon tetrachloride. It is thus possible in considering the reaction mechanism to eliminate the very large number of elementary steps that involve free radical attack on the peroxide.

The reaction products can be accounted for by means of the following series of elementary reactions, and there is some evidence to indicate that nearly all of these steps are occurring.

$$(RCOO)_2 \longrightarrow [2RCOO\cdot] \quad (1)$$

$$\longrightarrow [RCOO\cdot + R\cdot] + CO_2 \quad (2)$$

$$\longrightarrow [2R\cdot] + 2CO_2 \quad (3)$$

$$[2R\cdot] \longrightarrow 2R\cdot \quad (4)$$

$$\longrightarrow R{-}R \quad (5)$$

$$\longrightarrow C_6H_5(CH_2)_3CH_3 + C_6H_5(CH_2)_2CH{=}CH_2 \quad (6)$$

$$[RCOO\cdot + R\cdot] \longrightarrow R\cdot + RCOO\cdot \quad (7)$$

$$\longrightarrow RCOOR \quad (8)$$

$$\longrightarrow RCOOH + C_6H_5(CH_2)_2CH{=}CH_2 \quad (9)$$

$$[2RCOO\cdot] \longrightarrow 2RCOO\cdot \quad (10)$$

$$\longrightarrow (RCOO)_2 \quad (11)$$

$$RCOO\cdot \longrightarrow R\cdot + CO_2 \quad (12)$$

$$R\cdot + CCl_4 \longrightarrow RCl + \cdot CCl_3 \quad (13)$$

$$CCl_3\cdot + C_6H_5(CH_2)_2CH{=}CH_2 \longrightarrow C_6H_5(CH_2)_2\dot{C}HCH_2CCl_3 \quad (14)$$

$$\mathrm{I}$$

$$CCl_4 + \mathrm{I} \longrightarrow C_6H_5(CH_2)_2CHClCH_2CCl_3 + CCl_3\cdot \quad (15)$$

$$2CCl_3\cdot \longrightarrow C_2Cl_6 \quad (16)$$

Radicals capable of geminate reaction[6,7] in a solvent "cage" are shown in brackets as indicated in eq. 5, 6, 8, 9 and 11. Equations 4, 7 and 10 represent escape of the radical partners from the "cage," and eq. 12–16 represent reactions of the resulting "free" radicals. The principal evidence for the geminate reactions in this particular case is the absence of $C_6H_5(CH_2)_4CCl_3$, the cross termination product from phenylbutyl radicals and trichloromethyl radicals.[2,7] The geminate products are 1,8-diphenyloctane (eq. 5), δ-phenylbutyl δ-phenylvalerate (eq. 8) and δ-phenylvaleric acid (eq. 9). The 1,1,1,3-tetrachloro-5-phenylpentane is also a geminate product in the sense that all of the 4-phenyl-1-butene (eq. 9) is converted to the tetrachloro compound under the reaction conditions. The non-geminate products are 4-phenyl-1-chlorobutane and hexachloroethane. 1-Phenylbutane is absent.[2] In the 77° runs the yield of δ-phenylvaleric acid is nearly large enough to admit the formation of all of the 4-phenyl-1-butene by eq. 9. There is no excess of the acid, and therefore any δ-phenylvaleryloxy free radicals produced by eq. 7 and 10 must lead to 4-phenyl-1-chlorobutane and carbon dioxide either by eq. 12 and 13 or by formation of an unstable acyl hypochlorite which gives the same products: $RCOO\cdot + CCl_4 \rightarrow RCOOCl + \cdot CCl_3$; $RCOOCl \rightarrow RCl + CO_2$.

As an alternative to the geminate reaction hypothesis it has been suggested[8] that disproportionation products such as olefin and acid (*cf.*, eq. 9) are

(3) *Cf.* W. E. Cass, THIS JOURNAL, **69**, 500 (1947).
(4) D. F. DeTar and R. C. Lamb, unpublished results.
(5) *Cf.* K. Nozaki and P. D. Bartlett, THIS JOURNAL, **68**, 1686 (1946); **69**, 2299 (1947).
(6) R. M. Noyes, *ibid.*, **77**, 2042 (1955). *Cf.* J. C. Roy, R. R. Williams, Jr., and W. H. Hamill, *ibid.*, **76**, 3274 (1954), and J. Frank and E. Rabinowitsch, *Trans. Faraday Soc.*, **30**, 120 (1937).
(7) For other evidence *cf.*, D. F. DeTar and C. Weis, THIS JOURNAL, **79**, 3045 (1957).
(8) J. Smid, A. Rembaum and M. Szwarc, *ibid.*, **78**, 3315 (1956).

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formed by a rearrangement reaction. Ester may also presumably be formed by rearrangement. If there is only a single product to be explained by a rearrangement reaction, then it is difficult to find a good criterion for distinguishing between a rearrangement process and a geminate radical process. In the present example, however, there are three sets of products to be explained by rearrangement reactions, by geminate radical reactions, or by other as yet not postulated processes. If the ester, the dimer, and the 1,1,1,3-tetrachloro-5-phenylpentane are all ascribed to rearrangement reactions, then this is an example of the possible but remarkable circumstance of a compound undergoing three concurrent rearrangement reactions plus a free radical cleavage all at rather comparable rates. It is still more remarkable to have four such reactions with nearly identical temperature coefficients, yet the yields of the "rearrangement" reactions are indeed temperature independent over a more than 20° range. The geminate radical reaction hypothesis requires fewer coincidences: for reactions as fast as geminate combination, the temperature coefficients should be negligible. To attempt to select one product as arising by a rearrangement reaction and to ascribe the rest of the products to geminate radical reactions is wholly arbitrary. It is for these reasons that the rearrangement reactions have not been included in the mechanistic scheme.

The geminate products account for 59% of the peroxide at 77° and 55% at 55°; these yields are just significantly different at the 95% level in the statistical sense, but the difference is so small that they may be considered to be essentially the same from the chemical point of view. The only important direct free radical product is 4-phenyl-1-chlorobutane. Since induced decomposition reactions do not interfere under the present conditions, these results show that it is possible to find conditions under which aliphatic diacyl peroxides are a reliable source of free alkyl radicals in solution.

In eq. 1–3 it is postulated that the peroxide decomposition occurs by some combination of reactions involving cleavage of one, two or three bonds simultaneously in the initial step. With reasonable assumptions it is possible to account for the products on the hypothesis that reactions 2 and 3 are much faster than reaction 1, but the presence of ester and of acid exclude the occurrence of reaction 3 as the only cleavage. On the other hand if only reaction 1 can occur, then the decarboxylation reaction, eq. 12, must be able to compete with geminate radical reactions in order to give the products. This problem has been discussed previously,[9] but further work is clearly required before a decision is possible.

(9) P. D. Bartlett and F. D. Greene, THIS JOURNAL, **76**, 1088 (1954); D. F. DeTar and J. C. Howard, *ibid.*, **77**, 4393 (1955).

Experimental

The identification of the reaction products and the experimental procedure for carrying out the reaction has already been described.[2] The present runs were carried out with refinements of detail as in the better removal of oxygen.

In the quantitative determination of products, the solvent was removed using a 12 × 300 mm. column packed with glass helices. The residual 40–60 ml. of solution was then extracted with three 10-ml. portions of ice-cold 2 *N* potassium hydroxide solution, then with water, with dilute hydrochloric acid, and again with water. After drying over sodium sulfate, the carbon tetrachloride was removed through a small column, and the residue was quantitatively transferred to a small Claisen flask. At this point it contained about 5 ml. of CCl_4. In the subsequent distillation the receiver was cooled in Dry Ice, and the system was backed by traps. The oil-bath temperature was raised gradually to just under 130°, and two fractions were collected: distillate (b.p. up to 70° at 3 mm.) and residue. The distillate, containing hexachloroethane and 4-phenyl-1-chlorobutane, was analyzed by an infrared spectrophotometric procedure and the residue was analyzed by a combination utilizing chromatographic separation of the ester and infrared spectrophotometric analysis of the non-ester fraction. The carbon tetrachloride distilled into the traps.

Known mixtures of the reaction products were dissolved in 300 ml. of carbon tetrachloride and subjected to the complete separation and analytical procedure; the results are summarized in Table IV.

TABLE IV

TEST OF ISOLATION AND ANALYTICAL PROCEDURE ON KNOWN MIXTURES

	Taken,[a] mg.	Found, mg.	Taken,[b] mg.	Found, mg.
C_2Cl_6	179	180	930	880
$C_6H_5(CH_2)_3CH_3$	0	0	365	394
$C_6H_5(CH_2)_4Cl$	811	859	1520	1410
$C_6H_5(CH_2)_3C_6H_5$	471	460	792	809
$C_6H_5(CH_2)_2CHClCH_2CCl_3$	177	173	446	429
$C_6H_5(CH_2)_4COO(CH_2)_4C_6H_5$	437	456	900	917
$C_6H_5(CH_2)_4COOH$	208	211	210	210

[a] Receiver cooled in Dry Ice, preventing loss of 4-phenyl-1-chlorobutane. [b] Receiver cooled with ordinary ice.

The runs at 55° were carried out in sealed flasks of appropriate capacity. These flasks had a sealed-on head containing a gas inlet tube (sealed off during the runs), a filling tube of 12 mm. tubing, and a break-seal side tube attached to a ball joint. The carbon tetrachloride was refluxed while nitrogen was introduced through a tube extending into the filling tube. The flask was cooled to 40° and the peroxide introduced as a carbon tetrachloride solution. The filling tube was then sealed off so that the flask was completely sealed.

The flasks were placed in an oil-bath constructed from a 55-gal. drum and were maintained at 55.5–55.2° for the first 30 days, 55.2–54.8° for the next 30 days and 54.8–54.6° for the last 18 days. The flasks were then removed. At room temperature the pressure was less than atmospheric. The gas inlet was opened, the flask attached to the aniline bulb–cold trap–Ascarite tube train previously described, and the break-seal opened. A stream of nitrogen was passed through while the mixture was refluxed. Some phosgene was present in these runs. The isolation and analysis of the products was carried out as described.

COLUMBIA, S. C.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF SOUTH CAROLINA]

Diacyl Peroxide Reactions. III. The Behavior of the Optically Active 3-Phenyl-2-propyl Free Radical[1]

BY DELOS F. DETAR AND CLAUS WEIS[2]

RECEIVED AUGUST 30, 1956

The thermal decomposition of (+)- and (−)β-phenylisobutyryl peroxide in carbon tetrachloride gives products analogous to those formed in the corresponding δ-phenylvaleryl peroxide reaction. Similar mechanisms can therefore be assumed. The 2-chloro-1-phenylpropane (accounting for 30–40% of the 1-phenyl-2-propyl groups) was optically inactive, and the alcohol portion of the ester, 1-phenyl-2-propyl β-phenylisobutyrate, showed about 75% retention of configuration. The formation of inactive alkyl chloride demonstrates the reaction of an alkyl (rather than of an acyloxy) radical with carbon tetrachloride. Since the ester probably arises from the geminate combination of a 1-phenyl-2-propyl radical and a β-phenylisobutyryloxy radical, the partial racemization of the alcohol portion indicates a very low activation energy for racemization of a free radical of the structure $R_1R_2R_3C\cdot$.

The possible existence of optically active free radicals $R_1R_2R_3C\cdot$ has been discussed for many years.[3] The problem has been a difficult one to study effectively since free radical reactions are complex even at best and since in many cases highly speculative reaction mechanisms have been assumed. In addition the preparation of intermediates which will give free radicals is fraught with some difficulty.

One of the first mechanistically sound approaches was that of Brown, Kharasch and Chao[4] who carried out the chlorination of (+)1-chloro-2-methylbutane and found that the 1,2-dichloro-2-methylbutane fraction was optically inactive. The interpretation of this result is somewhat uncertain inasmuch as the dichloro compound has not been prepared in optically active form and the magnitude of its rotation is therefore not known. If the rotation should be appreciable, the chlorination experiment shows that the 2-(1-chloro-2-methylbutyl) radical racemizes faster than it reacts with chlorine. If the rotation should prove to be very small, then the experiment is inconclusive.

The isolation in 70% yields of similar mixtures of *meso* and *dl-sym*-dimethyldiisobutylsuccinonitrile from both *meso*- and *dl*-2,2′-azo-bis-2,4-dimethylvaleronitrile has been cited[5] as evidence for the existence of free and of planar aliphatic free radicals. This evidence is of uncertain value. If there is no geminate ("cage") reaction so that all radicals are free, then the *dl*-azonitrile and the *meso*-azonitrile will give rise to similar members of *d*- and *l*-radicals. Combination of these in statistical fashion will give identical mixtures of *dl*- and of *meso*- products even if the radicals are optically stable. On the other hand the argument would have some merit if all of the product were produced in geminate reaction, for then *dl*-azonitrile should give only *dl*-product and *meso*-azonitrile *meso*-product if the radicals were stable. Such products might predominate even from planar radicals since radicals may be unable to achieve random orientation before undergoing geminate combination. The authors isolated the crossed dimer product from the decomposition of a mixture of 2,2′-azobisisobutyronitrile and 1,1′-azobis-1-cyclopentanenitrile thus showing that some of the radicals are free in these reactions. Further interpretation of this type of experiment would require precise product analyses and an independent estimate of the amount of geminate reaction.[6]

The decarbonylation of (−)methylethylisobutylacetaldehyde with *t*-butyl peroxide is reported to give inactive 2,4-dimethylhexane due to racemization of the methylethylisobutylmethyl free radical prior to its abstraction of the aldehyde hydrogen atom.[7]

Recently two reports have appeared of the use of optically active diacyl peroxides to produce optically active free radicals.[8] Kharasch, Kuderna and Nudenberg carried out the decomposition of (+)α-methylbutyryl peroxide in benzotrichloride. The ester, *sec*-butyl α-methylbutyrate, was isolated in 30–40% yield. Both the acid portion and the *sec*-butyl alcohol portion were optically active; the rotation of the alcohol indicated some racemization, the configuration being retained. No other products were reported. The interpretation of this result requires information about the mechanism of ester formation. The occurrence of induced peroxide decomposition leading to ester would be a possible complication needing investigation.

Greene[8] attempted to prepare the peroxide of optically active α-phenylpropionic acid, but the peroxide decomposed so rapidly that preparation and decomposition had to be carried out simultaneously. This was done in the presence of ether or without solvent. The careful product analysis showed a 20–35% yield of the α-phenylethyl ester of α-phenylpropionic acid and 5–8% yield of 2,3-diphenylbutane. The alcohol portion of the ester was optically active with retention of configuration and with about 20–50% racemization. The diphenylbutane was a mixture of *dl*- and *meso*-products, perhaps altogether two-thirds racemized. These products were attributed either to the formation of free radi-

(1) Paper II. D. F. DeTar and C. Weiss, THIS JOURNAL, **79**, 3041 (1957).

(2) Postdoctoral Research Associate supported by the Research Committee of the University of South Carolina.

(3) *Cf.*, *e.g.*, R. L. Shriner, R. Adams and C. S. Marvel in "Organic Chemistry," ed. by H. Gilman, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 383.

(4) H. C. Brown, M. S. Kharasch and T. H. Chao, THIS JOURNAL, **62**, 3435 (1940).

(5) C. G. Overberger and M. B. Berenbaum, *ibid.*, **73**, 4883 (1951); *Ann. Repts.*, **49**, 116 (1952).

(6) *Cf.*, G. S. Hammond, J. H. Sen and C. E. Boozer, *ibid.*, NAL, **77**, 3244 (1955).

(7) W. von E. Doering, M. Farber, M. Sprecher and K. B. Wiberg, *ibid.*, **74**, 3000 (1952).

(8) M. S. Kharasch, J. Kuderna and W. Nudenberg, *J. Org. Chem.*, **19**, 1283 (1954); P. D. Greene, THIS JOURNAL, **77**, 4869 (1955).

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cals which rapidly underwent geminate combination or else to a rearrangement reaction. The former alternative was preferred by Greene on the grounds that a rearrangement reaction should be stereospecific. The relative insensitivity of product ratios to reaction procedure was cited as evidence that induced decomposition was not important.

α-Phenylpropionic acid is not entirely satisfactory as a tool for investigation of the optical stability of free radicals for the following reasons: (1) It has not been possible to isolate the peroxide because of its great lability. On this account the interpretation of the results must of necessity be speculative. (2) Since this is a substituted phenylacetic acid, the possibility of ionic decomposition paths for the peroxide requires a careful evaluation that was not feasible.[9] (3) If formation of ester and hydrocarbon dimer occur by geminate reactions as appears likely, then the optical stability of an isolated free radical has not been investigated.

It was therefore our objective to carry out a diacyl peroxide decomposition which would correlate with the detailed studies of the δ-phenylvaleryl peroxide reaction[1] and which would involve a nongeminate reaction of an optically active free radical of the type

$$R^{*}\cdot + CCl_4 \longrightarrow RCl + \cdot CCl_3$$

The choice of diacyl peroxide imposed certain restrictions if mechanistically conclusive results were to be obtained. The peroxides of the convenient and extensively studied α-substituted arylacetic acids suffer from the twin disadvantage of being especially unstable and of being subject to heterolytic as well as homolytic cleavage.[9] The possible occurrence of heterolytic cleavage renders the details of the over-all results somewhat less certain with these peroxides than with other types. α-Methylbutyryl peroxide is satisfactory except for the experimental inconvenience of the low boiling points of the products. Other dialkyl-substituted acetic acids also could be used.

β-Phenylisobutyryl peroxide appears to be one of the best possibilities for the study of optically active radicals. The relative configurations of the key compounds are known, and the rotations are about twice as great as in the α-methylbutyric acid series. Furthermore there is a possibility that the peroxide can be obtained in crystalline form, although this was not achieved in the present work. Since β-phenylisobutyryl peroxide is closely related to the previously studied δ-phenylvaleryl peroxide,[1] it should be possible to evaluate the details of the reaction mechanism with reasonable certainty.

β-Phenylisobutyric acid has been resolved by several workers.[10,11] The maximum reported rotation is $\alpha^{24}D$ +21.6 and $[\alpha]^{21}D$ +17.9 (in ethanol). 1-Phenyl-2-propanol has $\alpha^{14}D$ 27.3°(l = 1),[11] and 1-phenyl-2-chloropropane of unreported optical purity had $[\alpha]_{5461}$ 25°(no solvent).[11] Kenyon, Phillips and Pittman[11] have related the configurations in this series by an unambiguous method: those compounds with the same sign of rotation have the same configuration.

β-Phenylisobutyryl peroxide undergoes decomposition in carbon tetrachloride with a half-life of about an hour at 40°.[12] It is therefore much less stable than δ-phenylvaleryl peroxide, and was not obtained in pure form except in one run that decomposed prematurely on attempted storage at 0°. It was noted that explosive decomposition of this peroxide did not destroy the container; the brisance seems to be low. Very few secondary peroxides have been reported; hexahydrobenzoyl peroxide is one example, and it appears to be relatively unstable.[13] The secondary α-phenylpropionyl peroxide is much less stable than phenylacetyl peroxide.[8] Incidentally phenylacetyl peroxide itself has a half-life of only about seven hours at 0° in toluene.[9] The preliminary study of the kinetics of the decomposition of β-phenylisobutyryl peroxide in carbon tetrachloride shows that the amount of induced decomposition is small.

The samples of (+)β-phenylisobutyryl peroxide used in the present study were about 60–70% pure; the principal impurities seem to have been solvent and possibly ester, 1-phenyl-2-propyl β-phenylisobutyrate. The optical purity of the (+)peroxide present in the samples was estimated as 42% by reducing a portion back to β-phenylisobutyric acid.

The products of the decomposition of a dilute solution of the peroxide in carbon tetrachloride are summarized in Table I. While the yields of many of the products are only approximations, it is clear that there is a great deal of similarity between this reaction and that of δ-phenylvaleryl peroxide previously reported.[1] In particular it seems reasonably certain that none of the 1-phenyl-2-chloropropane nor of the 1-phenyl-2-propyl β-phenylisobutyrate is derived from induced decomposition of the peroxide.

The 2-chloro-1-phenylpropane was formed in nearly the same yield as was 1-chloro-4-phenylbutane from δ-phenylvaleryl peroxide.[1] This 2-chloro-1-phenylpropane was optically inactive ($\alpha^{25}D$ 0.02 ± 0.02°, pure liquid, l = 1). If the rotation of the pure isomer for the D-line is estimated as 20° ($[\alpha]_{5461}$ 25),[11] then the rotation expected if no racemization had occurred would have been 8°. The racemization reaction is therefore 200 or more times faster than the chlorine abstraction reaction.

The free acid isolated from the reaction mixture had a rotation experimentally the same as that of the acid resulting from reduction of the peroxide. Since this acid is fairly stable toward racemization, such a result is expected. The ester, 1-phenyl-2-propyl β-phenylisobutyrate, was also active. The acid fraction obtained on hydrolysis had the same rotation as observed for the other acid samples. The alcohol portion was also optically active, the OH group being in the position previously occupied by the carboxyl function. However, the alcohol had a somewhat lower optical purity than the acid fractions, indicating some 20–26% of racemization during its formation.

(9) P. D. Bartlett and J. E. Leffler, THIS JOURNAL, **72**, 3030 (1950).
(10) (a) F. S. Kipping and A. E. Hunter, *J. Chem. Soc.*, **83**, 1005 (1903); (b) R. H. Pickard and J. Yates, *ibid.*, **95**, 1019 (1909).
(11) J. Kenyon, H. Phillips and V. P. Pittman, *ibid.*, 1072 (1935).
(12) C. E. Boozer and W. S. Lamb, unpublished results.
(13) F. Fichter and W. Siegrist, *Helv. Chim. Acta*, **15** 1304 (1932).

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TABLE I

THE THERMAL DECOMPOSITION OF (+)- AND (−)β-PHENYLISOBUTYRYL PEROXIDE IN CARBON TETRACHLORIDE[a]

Products	Yield[b]	Rotation	% Opt. purity	Yield[b]	Rotation	% Opt. purity
	1.41			1.60		
CO_2	0.2[c]					
C_2Cl_6	.6[c]	0	0	0.8[c]	0	0
$C_6H_5CH_2CHClCH_3$	.04	+7.4[d]	41	.08	−7.3	41
$C_6H_5CH_2CH(CH_3)COOH$	.15[e]	0	0	.07[e]	....	..
$(C_6H_5C_3H_6CCl_3)$[e]	.6[c]	+9.6[f]	..	.8[e,g]	−9.5[f]	..
Ester	...	+7.8[d]	44	...	−8.5[f]	46
Acid from ester	...	+8.6[f]	31[h]	...	−9.6[d]	35[i]
Alcohol from ester						
Starting Material						
$[C_6H_5CH_2CH(CH_3)COO]_2$, mmoles	(83.6)[j]	+7.5[d,k]	42	(59.4)[l]	(−)	..

[a] Reaction in 5 l. of CCl_4 at 60–77°; the amount of peroxide used is given at the bottom of the table. [b] Moles per mole of peroxide. [c] Approximate figure. [d] $[\alpha]^{20}D$ in ethanol. [e] The identity of this compound has not been established. [f] $\alpha^{20}D$ (l = 1, no solvent). [g] This figure is much too large and indicates presence of ester as impurity in the (−)peroxide used. [h] 31/42 or 74% retention. [i] 35/44 or 80% retention. [j] Based on 37.95-g. sample of 71.8% pure peroxide. [k] This applies to the β-phenylisobutyric acid obtained from reduction of the peroxide. [l] Based on 30-g. sample of 64.5% pure peroxide.

Although ester may have been present as an impurity in the (−)peroxide before decomposition in carbon tetrachloride, there does not seem to be any reason to suppose that ester arose from a source other than peroxide decomposition, though some of the decomposition may have taken place in a solvent medium other than carbon tetrachloride. The infrared curve of the (+)peroxide showed that ester was not present as an impurity in this sample.

Discussion

The fact that *dl*-1-phenyl-2-chloropropane is formed in the reaction of active β-phenylisobutyryl peroxide with carbon tetrachloride makes it possible to eliminate decarboxylative substitution as the mechanism of formation of the alkyl chloride. Such a reaction

$$RCOO\cdot + CCl_4 \longrightarrow RCl + CO_2 + \cdot CCl_3 \quad (1)$$

should be stereospecific irrespective of whether it occurs by inversion or by retention of configuration. This leaves halogen abstraction by the alkyl radical as the only route (eq. 2). The reasoning is as follows

$$R\cdot + CCl_4 \longrightarrow RCl + \cdot CCl_3 \quad (2)$$

The only potential direct precursors of RCl are the alkyl radical, the acyloxy radical or the peroxide. The peroxide is ruled out on the basis that induced decomposition is at most a minor process, and since the acyloxy radical has been eliminated, only the alkyl radical remains. There is at present no evidence to require consideration of less direct mechanisms.

The decarboxylative substitution step was proposed by Edwards and Mayo to explain an apparent discrepancy in the reactivity of alkyl radicals.[14] Edwards and Mayo developed a method for evaluating the relative reactivities of various solvents toward hydrogen abstraction by methyl radicals. A careful determination was made of the methane–methyl chloride ratio obtained in the decomposition of acetyl peroxide in solvent mixtures that had carbon tetrachloride as one component. It was possible to compare

$$CH_3\cdot + S_1H \longrightarrow CH_4 + S_1\cdot \quad (3)$$

$$CH_3\cdot + CCl_4 \longrightarrow CH_3Cl + \cdot CCl_3 \quad (4)$$

the reactivity of each solvent in the hydrogen abstraction reaction (eq. 3) with the reactivity of carbon tetrachloride in the chlorine abstraction (eq. 4). This led to a series of relative reactivities of methyl radicals with S_1H, S_2H, etc. The order of reactivities found was so different from the order obtained for other alkyl radicals (in polymerization systems) that it seemed advisable to speculate that the acetyl peroxide reaction involved decarboxylative substitution by acetoxyl radicals (eq. 1) rather than the expected methyl radical reactions. Since publication of this work, accurate estimates have become available for the rates of methyl radical reactions in the gas phase.[15] It has been shown that the methyl radical reactivities obtained in solution by Edwards and Mayo correlate very well with the gas phase values.[16] The main reason for postulating decarboxylative substitution has thus evolved instead into a reason for preferring the methyl radical reaction hypothesis.

There is now direct experimental evidence against decarboxylative substitution for three types of radicals: $CH_3COO\cdot$, $R_2CHCOO\cdot$ and $ArCOO\cdot$. The aryl group studied was the optically active 2-(2′-methyl-6′-nitrophenyl)-phenyl group.[17] The optically active peroxide reacted with carbon tetrachloride to give low yields of 2-chloro-2′-methyl-6′-nitrobiphenyl with partial racemization.

Since direct alkyl radical and aryl radical halogen abstraction has been demonstrated for three very different types of radicals, the method of Edwards and Mayo can be expected to be of great significance for obtaining relative radical reactivities.

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In considering the optical properties of a free radical such as the 1-phenyl-2-propyl radical the extreme possibilities appear to be either a planar symmetrical structure or else a pyramidal structure with an optical stability of the same order as the structurally similar amine, methylbenzylamine. The activation energy for inversion of an amine is not known accurately, but estimates range around 5 kcal.[18] The activation energy for racemization should therefore be in the approximate range of 0 to 10 kcal. A reasonable estimate of the activation energy of the chlorine abstraction step (eq. 2) is 12 kcal., on the assumption that chlorine abstraction and hydrogen abstraction (*cf.* eq. 3 and 4) have similar activation energies.[15] Since an activation energy for halogen abstraction that is about 3 kcal. greater than that for racemization will lead to the observed complete racemization, the formation of racemic 1-phenyl-2-chloropropane is not unexpected.

Further information can be obtained from a consideration of the ester, 1-phenyl-2-propyl β-phenylisobutyrate. In the present investigations induced peroxide decomposition can be excluded as a source of ester. Two possibilities remain: (1) a rearrangement process involving loss of carbon dioxide and (2) a radical combination reaction (eq. 5). Since rearrangement reactions are usually

$$RCOO\cdot + R\cdot \longrightarrow RCOOR \qquad (5)$$

stereospecific and since there seems to be no reason for anticipating more than one rearrangement path for the peroxide, it appears that at least some of the ester must have been formed by a non-rearrangement process in order to account for the partial racemization of the alcohol portion.

Evidence has been presented that all of the ester is formed by a geminate radical combination reaction,[1,19] rather than by rearrangements. In this case the racemization of the 1-phenyl-2-propyl radical is competing with a radical combination reaction and the activation energy for racemization would be of the order of 2 kcal. It is even possible that a planar free radical could give an optically active ester providing that random rotational orientation of the radical is slow compared to the geminate combination. While "asymmetric induction" could be invoked, it is unlikely that the configuration of the acyloxy radical would have much effect in a radical combination reaction.

Experimental

***dl*-β-Phenylisobutyric Acid.**[20]—To a solution of 24 g. of sodium in 410 ml. of absolute ethanol was added 174 g. of commercial diethyl methylmalonate. This was followed by dropwise addition of benzyl chloride during a period of two hours at a reaction temperature of 40°. After removal of the ethanol by distillation, the diethyl benzylmethylmalonate was extracted with ether, and after washing and drying was finally distilled, b.p. 127–133° at 1.5 mm.; yield 62 and 66% in two runs.

The ester (174 g.) was hydrolyzed by refluxing it with a solution of 110 g. of potassium hydroxide in 300 ml. of water and 120 ml. of methanol. After removal of the methanol, the benzylmethylmalonic acid was precipitated with acid and, after drying, recrystallized from a benzene–hexane mixture to give 130 g. (95%) of colorless crystals, m.p. 136–138°. This was raised to 138–139.5° after recrystallization; the reported m.p. is 135°.[20c] In precipitating the benzylmethylmalonic acid it is necessary to add the solution of the salt to a solution of hydrochloric acid since the reverse procedure leads to precipitation of the insoluble monopotassium salt.

The acid was decarboxylated in 90-g. portions at a temperature of 190–210°, and the resulting β-phenylisobutyric acid purified by distillation; b.p. 118–122° at 1 mm.

Resolution of β-Phenylisobutyric Acid.[10]—To a solution of 500 g. of quinine in 650 ml. of hot ethanol was added 250 g. of *dl*-β-phenylisobutyric acid. The solution was cooled to 30° and seeded with the pure *d*-salt (obtained from a previous small scale run). The crystallization was allowed to proceed at room temperature for 24 hours and at 5° for another 24 hours. Filtration gave 265 g. of dry salt, $[\alpha]^{20}D$ +110° (*c* 0.0203 g./cc., in ethanol). Three additional crops totaling 167 g. and having the same or slightly higher rotation were obtained by partial evaporation of the solvent and re-seeding. It is worth notice that the rotation of the quinine salt remained essentially constant even though the acid was not completely resolved.[10]

To 450 ml. of 10 *N* sulfuric acid was added 398 g. of the recrystallized *d*-salt. The liquid (+)β-phenylisobutyric acid was extracted with ether, washed, dried and distilled; yield 96%; $\alpha^{20}D$ +13.73° (*l* = 1), $[\alpha]^{20}D$ +11.5° (*c* 0.0327, ethanol, *l* = 2); reported $\alpha^{24}D$ +21.6° (no solvent),[11] $[\alpha]^{21}D$ + 17.87° (in ethanol[11]).

The (−)acid was obtained from the residue resulting from evaporation of the mother liquors to dryness, b.p. 123–124° at 1.5 mm.; $[\alpha]^{20}D$ −11.2° (*c* 0.0245, ethanol, *l* = 2).[21]

The *p*-bromophenacyl ester of the (+)acid was obtained in 0.83-g. yield from 0.4 g. of acid and 0.71 g. of *p*-bromophenacyl bromide; m.p. 54.5–56°; $[\alpha]^{21}D$ +23.8° (*c* 0.0136, ethanol, *l* = 2).

Anal. Calcd. for $C_{18}H_{17}BrO_3$: C, 59.8; H, 4.7; Br, 22.1. Found: C, 59.7, H, 5.0; Br, 22.0.

(+)- and (−)β-Phenylisobutyryl Chloride.[10,11]—A mixture of 85 g. of (+)β-phenylisobutyric acid, $[\alpha]^{20}D$ +19.7° (*l* = 2) and 110 g. of purified thionyl chloride was warmed on the water-bath for 70 min. and then distilled; b.p. 72–73° at 1 mm.; yield 92.5 g.; $\alpha^{20}D$ + 22° (*l* = 2, no solvent); reported $[\alpha]D$ +26.3°. The (−)acid chloride was prepared similarly, b.p. 110° at 1.5 mm., $\alpha^{20}D$ −25.2° (*l* = 2, no solvent).

(+)- and (−)β-Phenylisobutyryl Peroxide.—This peroxide proved to be much less stable than δ-phenylvaleryl peroxide. A number of samples decomposed spontaneously even when kept in the refrigerator, although the peroxide can be preserved at Dry Ice temperatures. It is more stable in carbon tetrachloride than in ether.

To a stirred mixture of 70 g. of ice, 70 g. of water, 10.5 g. of sodium peroxide and 50 ml. of pentane was added slowly a solution of 12 g. of (+)β-phenylisobutyryl chloride in 80 ml. of pentane. The temperature was maintained at 2–2.5° during the addition (15 min.) and for an additional half hour. The pentane layer was separated, washed, dried over sodium sulfate, and the solvent removed under reduced pressure. The resulting viscous oil had a peroxide titer corresponding to 74.8%. Carbon tetrachloride was added and removed under reduced pressure at −10 to 0°, and the titer then corresponded to 71.8% of peroxide. It is possible that solvent is still present. The ester peak at 5.77 μ was negligible in the spectra of a carbon tetrachloride solution.

The rotation was obtained in carbon tetrachloride solution for a 40-g. peroxide sample obtained by combining two preparations; $[\alpha]^{20}D$ + 69° (*l* = 2); 0.425 g. of peroxide of 71.8% purity corresponds to a concn. of 0.305 g. of peroxide in 15 ml. of carbon tetrachloride.

The (−)peroxide was similarly prepared from 40 g. of the (−)acid chloride and 34 g. of sodium peroxide to give a

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sample containing 64.5% of (−)β-phenylisobutyryl peroxide.

A 0.7-g. sample of the above (+)β-phenylisobutyryl peroxide was reduced to the acid by treatment with 0.75 g. of potassium iodide and 3 ml. of water in 50 ml. of acetone. Sulfur dioxide was passed in to reduce the iodine, the acetone was evaporated, the oil treated with sodium carbonate and extracted with ether to remove neutral materials. The acid was recovered from the alkaline solution, the ether evaporated, and the residue kept *in vacuo* over phosphorus pentoxide for 24 hours; $[\alpha]^{20}D + 7.5°$ (*c* 0.0234, ethanol, *l* = 2), or 67% of that of the starting acid.

dl-1-Phenyl-2-propanol.[22]—Commercial phenylacetone was reduced in 96% yield with a suspension of lithium aluminum hydride in ether; b.p. 64–65° at 1 mm.; phenylurethan, m.p. 89.5–91° from hexane.

dl-1-Phenyl-2-chloropropane.—A solution of 50 g. of 1-phenyl-2-propanol in 100 ml. of benzene was added in dropwise fashion to a solution of 50 g. of purified thionyl chloride in 70 ml. of benzene maintained at gentle reflux. The solution was then warmed on a water-bath for another hour, poured into water, washed thoroughly, dried and distilled; b.p. 83–85° at 12 mm., yield 76%; reported b.p. 205–207°.[23]

dl-1-Phenyl-2-propyl β-Phenylisobutyrate.—This was prepared by direct esterification at 110° for 3 hours in the presence of sulfuric acid; b.p. 142–144° at 1 mm., $n^{25}D$ 1.5264, yield 87%.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.8; H, 7.86. Found: C, 80.7; H, 7.9.

Decomposition of (+)β-Phenylisobutyryl Peroxide in Carbon Tetrachloride.—In a 5-l. flask with sealed-on reflux condenser and gas inlet tube was placed 5 l. of repurified carbon tetrachloride. About 50 ml. of this was distilled through the drained condenser while a stream of high purity nitrogen was passed in. The nitrogen stream was continued while the temperature was reduced to 20–25°. A 37.95-g. portion of the combined sample of (+)β-phenylisobutyryl peroxide described above (purity 71.8%, equivalent to 27.3 g. (0.0836 mole) of pure peroxide) was added, the temperature raised to 65–70° over a period of one hour and maintained there for four hours and then refluxed overnight. The carbon dioxide yield was 5.191 g. (1.41 mole per mole of "pure" peroxide). No phosgene was produced.

The solvent was removed through a column until the volume was reduced to 50 ml. Extraction with alkali gave 0.670 g. of (+)β-phenylisobutyric acid, $[\alpha]^{20}D + 7.4°$ (*c* 0.0874, ethanol, *l* = 1) (0.037 mole per mole peroxide). The remainder of the solvent was removed with a small column and the residue fractionated through a small Vigreux column to give (1) 4.74 g. (mostly hexachloroethane), b.p. 60–66° at 12 mm.; (2) 3.25 g. of a hexachloroethane–2-chloro-1-phenylpropane mixture, b.p. 66–68° at 12 mm.; (3) 5.90 g. of 2-chloro-1-phenylpropane, b.p. 81–90° at 10 mm., and a residue of 17.70 g. of yellow oil. The hexachloroethane (3.25 g.) was frozen out of the first two fractions, and the remaining liquids redistilled to give 7.65 g. of 2-chloro-1-phenylpropane (0.59 mole per mole of peroxide). This had a $\alpha^{20}D$ +0.52°, but the infrared curve had some small peaks not present in 2-chloro-1-phenylpropane. After passage through a column of F-20 alumina, the extra peaks were no longer present and the rotation was nearly zero; $\alpha^{20}D$ +0.03 ± 0.01 (18 D.F.).

There was some evidence for the presence of allylbenzene in that the contents of the Dry Ice traps from the first vacuum distillation contained allylbenzene peaks in addition to those of CCl_4 and C_2Cl_6.

Since the residue showed incipient signs of decomposition on attempted distillation, it was instead purified by chromatography on a 17 × 550 mm. column of F-20 alumina (grade 1) using hexane as eluent. From 11.40 g. there was obtained 3.02 g. of pure 1-phenyl-2-propyl β-phenylisobutyrate and a larger less pure fraction. This impure remainder was rechromatographed. There was ultimately obtained 9.42 g. of ester and 1.58 g. of a chlorine-containing oil; the original 17.70 g. of residue therefore contained 15.2 g. of ester, (0.64 mole per mole "pure" peroxide) and 2.5 g. of chlorine-containing oil (0.15 mole per mole peroxide assuming it is $RCCl_3$), $[\alpha]^{20}D$ 0°.

Redistillation of the ester gave a fraction, b.p. 143–145° at 1 mm., $n^{25}D$ 1.5264, $\alpha^{20}D$ 9.65° (*l* = 1, no solvent), $[\alpha]^{20}D$ 15.1° (*c*, 0.046, ethanol, *l* = 1); the infrared curve matched that of the *dl*-ester. Hydrolysis of the ester at room temperature gave an acid (2.86 g.) with an infrared curve identical with that of β-phenylisobutyric acid; $[\alpha]^{20}D$ +7.8° (*c* 0.068, ethanol, *l* = 1) and an alcohol, b.p. 70–71° at 2 mm. (2.7 g.), $n^{25}D$ 1.5192, $\alpha^{20}D$ +8.55 (*l* = 1, no solvent); the infrared curve of the alcohol was identical with that of the *dl*-1-phenyl-2-propanol.

Decomposition of (−)β-Phenylisobutyryl Peroxide in Carbon Tetrachloride.—A 30-g. sample of the peroxide containing 64.5% or 19.35 g. (0.0594 mole) of pure peroxide was added to 5 l. of carbon tetrachloride prepared as described for the other run. The solution, initially at 25–30°, was heated at reflux overnight, and 4.168 g. of carbon dioxide was evolved (1.60 moles per mole of peroxide). From the solution there was obtained 1.62 g. of (−)β-phenylisobutyric acid, $[\alpha]^{20}D$ −7.3° in ethanol (0.084 mole per mole of peroxide); 7.85 g. of 2-chloro-1-phenylpropane, b.p. 90–91° at 15 mm., $n^{25}D$ 1.5152, and after passage through F-20 alumina the infrared curve was identical with that of an authentic sample, $\alpha^{20}D$ 0.00° (*l* = 1, no solvent) (0.85 mole per mole of peroxide); 13.30 g. of 1-phenyl-2-propyl β-phenylisobutyrate $\alpha^{20}D$ −9.50° (*l* = 1, no solvent), b.p. 150–151° at 1 mm., $n^{25}D$ 1.5266 (0.80 mole per mole of peroxide); and 0.87 g. of a chlorine-containing fraction. Saponification of the ester gave 4.7 g. of (−)β-phenylisobutyric acid, $[\alpha]^{20}D$ −8.5° in ethanol and 4.3 g. of 1-phenyl-2-propanol, b.p. 67–68° at 1 mm., $n^{25}D$ 1.5192, $\alpha^{20}D$ −9.55° (*l* = 1, no solvent). It is possible that ester was present as an impurity in the peroxide.

COLUMBIA, SOUTH CAROLINA

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[CONTRIBUTION FROM THE PHYSICAL CHEMISTRY DIVISION, NATIONAL CHEMICAL LABORATORY]

Metal Protein Interactions in Buffer Solutions.[1] I. An Electrophoretic Study of the Interaction of Copper, Zinc, Cadmium and Cobalt Ions with Native and Modified Bovine Serum Albumins

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General concepts governing the interpretation of metal–protein interactions in buffer solutions have been outlined. It has been shown that the binding data should be supplemented by mobility measurements if the interactions are to be treated as a competition between the metal and hydrogen ions for combining with a given set of sites on the protein molecule. The existing data for the binding of cupric and cobaltous ions by bovine serum albumin in an acetate buffer of *p*H 6.5 and ionic strength 0.20, together with the corresponding mobility data reported in the present communication, have been analyzed. The intrinsic constant for the association of cobaltous ion with the carboxyl groups of serum albumin remained constant over the entire binding range, and had a low value characteristic of metal–acetate complexes. The constant for the association of cupric ion with the imidazole groups of serum albumin, however, tended to decrease with the number of bound metal ions, due, possibly, to an increased interaction, in the higher binding region, with the free carboxyl groups of the protein.

The interaction of zinc ion with human serum albumin has been studied by Gurd and Goodman[3] in unbuffered solutions. These authors have shown that the binding data could be interpreted in terms of a competition between the metal and hydrogen ions for reaction with the same sites, *viz.*, the imidazole groups of the protein molecule. The difficulties associated with the measurement and interpretation of such a competition in buffered solutions have been pointed out by Scatchard.[4] Most measurements of the interaction of small ions with proteins have however been made in buffered solutions. It is therefore of interest to attempt an interpretation of binding data obtained in buffer solutions in terms of a competition phenomenon.

A competition between metal and hydrogen ions entails that the metal ions can combine only with the basic (unprotonated) functional groups. The uptake of metal ion will however shift the hydrogen ion equilibria in the direction of the basic (unprotonated) form of the functional groups. The hydrogen ion release, thus occasioned, results, in unbuffered systems, in a decrease in *p*H.[3] For metal–protein interactions in buffer solutions, however, the relevant quantities may be derived from the electrophoretic mobility data provided allowance is made, as in unbuffered systems, for the binding of anions by the protein.

The electrophoretic behavior of metal–protein systems has not, as far as we are aware, been reported so far.[5] Such a study of the interaction of cupric, zinc, cadmium and cobaltous ions with bovine serum albumin in an acetate buffer of *p*H 6.5, ionic strength 0.20 is presented in the present communication.

Experimental

Native Bovine Serum Albumin (NBSA).—Crystallized bovine serum albumin was an Armour product, Lot No. M 66909. A polarographic examination did not indicate any detectable amount of metallic impurities. It was electrophoretically homogeneous in an acetate buffer of *p*H 6.5 and ionic strength 0.20, and had a mobility of -3.12×10^{-5} cm.^{2}/volt/sec., corresponding to a net charge of approximately −16 (electron units) calculated on the basis of a 0.2×10^{-5} cm.^{2}/volt/sec. change in mobility per unit change in charge.[6]

Esterified Bovine Serum Albumin (EBSA).—Serum albumin was esterified according to the method of Fraenkel-Conrat and Olcott.[7] The ester was analyzed for its methoxy groups[8] and showed that all the free carboxyl groups of the albumin molecule had been esterified. The material was electrophoretically homogeneous and had a mobility of 6.02×10^{-5} cm.^{2}/volt/sec. (acetate buffer, *p*H 6.5, ionic strength 0.20) corresponding to a net charge of +30 units. It would appear from the mobility of EBSA as compared to that of NBSA that only 46 carboxyl groups of the albumin molecule had been esterified as against the value of 100 obtained from titration data.[9] This discrepancy has been attributed by Saroff, *et al.*,[10] to a splitting of the esterified derivative into two nearly equal halves. It is our opinion, however, that the discrepancy may possibly be due to an increased uptake of buffer anions by the highly positively charged esterified derivative (see Discussion).

Acetylated Bovine Serum Albumin (ABSA).—Serum albumin was acetylated by the method of Fraenkel-Conrat, *et al.*,[11] using acetic anhydride as the acetylating agent. Acetic anhydride is specific for the free α- and ε-amino groups.[12] It may be assumed, therefore, that other functional groups, such as the imidazolium and guanidinium, are not affected. The acetylated derivative was analyzed for its free amino groups by the Van Slyke nitrogen estimation as modified by Baddiley, *et al.*,[13] indicating 83% acetylation of the free amino groups of the albumin molecule.

The acetylated derivative was found to be electrophoretically inhomogeneous in an acetate buffer of *p*H 6.5 and ionic strength 0.20 (Fig. 2A). Two components were observed: a slow one, constituting about 60% of the total, had a mobility of -7.60×10^{-5} cm.^{2}/volt/sec., and a fast one, constituting the rest, had a mobility of -8.60×10^{-5} cm.^{2}/volt/sec. The mobility computed from the first moment of the gradient curve had a value of -7.87×10^{-5} cm.^{2}/volt/sec., corresponding to a net charge of about −39 units.

Solutions.—All studies, unless otherwise stated, were made in an acetate buffer of *p*H 6.5 and ionic strength 0.20. 1% protein solutions were used. Solutions of the protein

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were prepared by direct weighing, corrections being made for its moisture content.[14]

Electrophoresis.—Mobility measurements were made at 0.5° in a Tiselius electrophoresis apparatus (Perkin–Elmer Model 38[15]) using Longsworth's scanning system. A 2-ml. cell was used. The boundaries were formed between the protein and buffer solutions to which suitable additions of metal ion, corresponding to the metal distribution in equilibrium-dialyzed systems,[1,16–18] had previously been made. Standard procedure for the formation of boundaries was employed. After thermostating the cell assembly for three hours, the boundaries were brought into view and their positions photographed. The positions of the boundaries were also photographed at regular intervals during the electrophoresis run. The runs were usually made from 1–3 hours depending on the nature of the protein. Mobilities were calculated from the displacements in the descending boundary. Only those runs in which the boundary displacement was a linear function of time (at constant current) were used for the evaluation of mobilities.

The current passing through the cell was estimated to within ±0.1% from the potential difference developed across a standard resistance placed in series with the cell. The conductivity of protein solutions was measured at 0° with a Leeds and Northrup conductivity bridge using a conductivity cell of 0.5-ml. capacity (cell constant 12.6). The boundary displacements were measured from the schlieren patterns with a travelling microscope. In the systems involving non-homogeneous proteins, such as the acetylated serum albumin, the schlieren patterns were enlarged and the boundary displacements measured from the first moment of the entire gradient curve.

Analar cupric chloride and cupric acetate, and Merck zinc sulfate, zinc acetate, cadmium acetate and cobalt chloride were used as the source of metal ions.

Results

Metal–NBSA Systems.—The mobility increment $\Delta\mu$ ($= \mu_{PAi} - \mu_P$) is plotted in Fig. 1A as a function of $\bar{\nu}$, the number of metal ions bound per protein molecule. It may be noticed that the slope of the curves represented in Fig. 1A is positive for the system Co–NBSA and decreases in the order: Co–NBSA → Cd–NBSA → Zn–NBSA. The corresponding slope for the system Cu–NBSA, however, shows a negative slope—a result which is contrary to what should be expected from the uptake of a metal ion by the protein. As the metal uptake increases, however, the mobility of the protein is affected in a manner depending upon the nature of the metal ion bound. Thus the mobility of serum albumin tends toward a steady value as more and more cobalt ions are bound. This is in contrast to the behavior of Cd–NBSA and Zn–NBSA systems in which the mobility increases more and more as the value of $\bar{\nu}$ is increased, the effect being more pronounced in the former than in the latter. The mobility of the system Cu–NBSA passes through a minimum at $\bar{\nu} \simeq 2$.

Metal–ABSA Systems.—The $\Delta\mu$ *vs.* $\bar{\nu}$ curves for the metal–ABSA systems are shown in Fig. 1B.

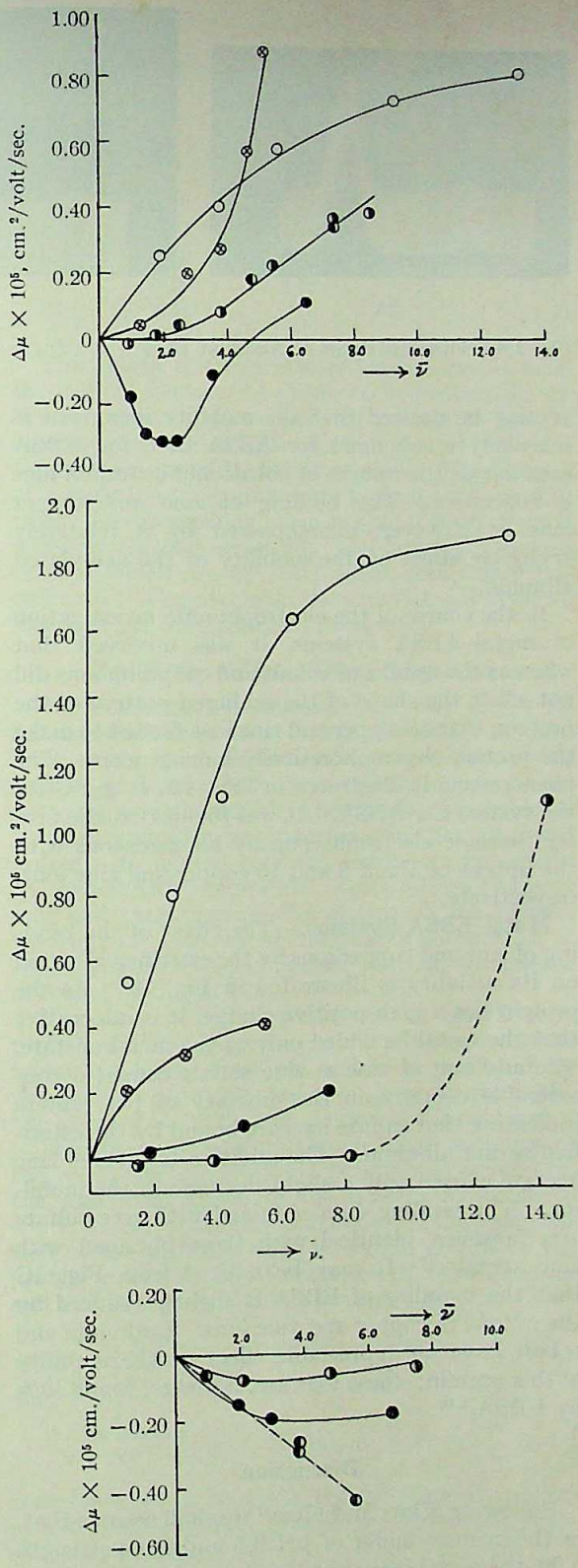

Fig. 1.—The effect of the binding of metal ions on the electrophoretic mobility of bovine serum albumins (0°, acetate buffer, *p*H 6.5, ionic strength 0.20): A, NBSA; B, ABSA; C, EBSA; —⊙—, Co^{++} as $CoCl_2$; —⊗—, Cd^{++} as $Cd(CH_3COO)_2$; —◑—, Zn^{++} as $Zn(CH_3COO)_2$; —◐—, Zn^{++} as $ZnSO_4$; —●— Cu^{++} as $Cu(CH_3COO)_2$.

(14) Stock solutions containing 2% protein in the acetate buffer medium were stored in a cold room maintained at 0°. The solutions containing EBSA, however, tended to hydrolyze on prolonged storage. This tendency toward hydrolysis was suppressed by storing the stock solution in a deep freeze.

(15) D. H. Moore and J. U. White, *Rev. Sci. Instruments*, **19**, 700 (1948).

(16) M. S. N. Rao, Ph.D. thesis, Poona University, 1956.

(17) I. M. Klotz and H. A. Fiess, *J. Phys. Colloid Chem.*, **55**, 102 (1951).

(18) In line with the molecular weight of NBSA assumed for the titration data of ref. 9, the binding data of ref. 1, 16 and 17 were recalculated on the basis of a molecular weight of 65000 for NBSA instead of 66000 for ABSA and EBSA.

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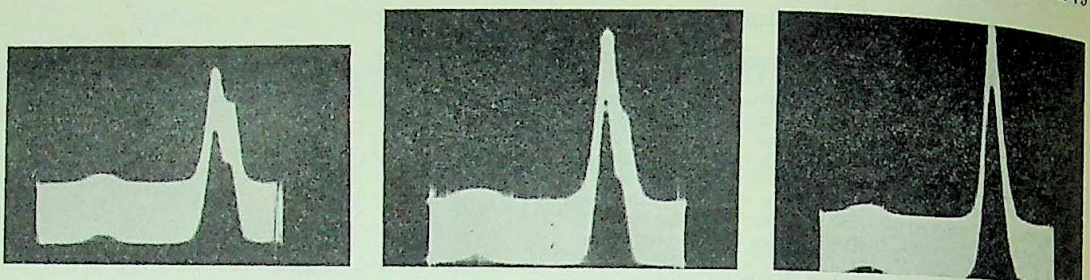

2A 2B 2C

Fig. 2.—Schlieren patterns of ABSA at (A) $\bar{\nu} = 0$, (B) $\bar{\nu} = 2$, (C) $\bar{\nu} = 8$ (0°, acetate buffer, *p*H 6.5, ionic strength 0.20)

It may be noticed that the mobility increment is relatively much more for ABSA than for NBSA in so far as the uptake of cobalt and cadmium ions is concerned. The binding of zinc and copper ions is, however, characterized by a relatively negligible effect on the mobility of the acetylated albumin.

In the course of the electrophoretic investigation of metal–ABSA systems, it was observed that whereas the uptake of cobalt and cadmium ions did not affect the shape of the schlieren pattern of the protein, that of copper and zinc ions tended to make the protein electrophoretically homogeneous. The phenomenon is illustrated in Figs. 2A, B and C for the system Cu–ABSA. It was found that the protein became electrophoretically homogeneous with the uptake of about 8 and 15 copper and zinc ions, respectively.

Metal–EBSA Systems.—The effect of the binding of zinc and copper ions by the esterified albumin on its mobility is illustrated in Fig. 1C. As the protein has a high positive charge, it is imperative that the metal be added only as the metal acetate. The addition of zinc as zinc sulfate caused a considerable decrease in the mobility of the protein indicating that sulfate ions are bound by the esterified serum albumin. The addition of zinc as zinc acetate caused only a slight decrease in the mobility. The binding data obtained with zinc sulfate are, however, identical with those obtained with zinc acetate.[16] It may be noticed from Fig. 1C that the mobility of EBSA is slightly reduced by the uptake of copper and zinc ions. Cadmium and cobalt have no appreciable effect on the mobility of this protein; these ions are, however, *bound little* by EBSA.[1,16]

Discussion

Following Klotz and Fiess[17] we shall assume that, in the acetate buffer of *p*H 6.5 and ionic strength 0.20, the metal ions exist largely as the MAc^+ complex ion and that this complex ion participates in the binding process. This assumption shall be tacitly adhered to in the following discussion. If the binding process were to involve the simple addition of MAc^+ ions, the charge on the protein would be a linear function of $\bar{\nu}$. Consequently, the slope of $\Delta\mu$ *vs.* $\bar{\nu}$ curves should be of the order of 0.2×10^{-5} cm.^{2}/volt/sec. An examination of Fig. 1, however, reveals that this simple state of affairs does not in fact exist and that the behavior of the metal–protein systems investigated depends in a rather complex manner on the nature of the metal ion and of the protein. It seems to us, therefore, that a proper evaluation of the electrophoretic mobility data must entail a definition of (i) the functional groups of the serum albumin molecule in terms of their equilibria in the acetate buffer of *p*H 6.5 and ionic strength 0.20, and (ii) the extent to which these equilibria are influenced by the uptake of MAc^+ ions.

Equilibria in Serum Albumin Solutions

Equilibria Involving Hydrogen Ions.—The dissociation of functional groups in a given set of sites may be represented by the equilibrium equation[9]

$$\frac{n_A}{n_B} = (H^+)k^0_H e^{-2\omega z^0_P} \qquad (1)$$

where n_A and n_B are the number of a given set of functional groups in the acid and basic forms, respectively, (H^+) the activity of hydrogen ions, k^0_H the proton affinity constant for the functional group, z^0_P the charge on the protein molecule and ω the familiar function of ionic strength. The hydrogen ion equilibria in bovine serum albumin solutions have been investigated by Tanford, Swanson and Shore.[9] It may be concluded from their data that the guanidinium, sulfhydryl, phenolic, α- and ϵ-amino groups, in view of their high proton affinities, are present in the acid form at *p*H 6.5, and are not available for binding metal ions. We are therefore interested only in the hydrogen ion equilibria involving imidazole and carboxyl groups of the protein molecule. It follows from eq. 1 that, of the 100 carboxyl groups of the protein molecule, 99.2 are dissociated in NBSA and 97.8 in ABSA. Similarly it may be shown that, of the 16 imidazole groups in the albumin molecule, 10 exist in the neutral (basic) form in EBSA, 2.5 in NBSA and only 0.9 in ABSA. The intrinsic proton affinity constant was assumed to be $\log k^0_H = 4.05$ for the carboxyl groups, and $\log k^0_H = 6.90$ for the imidazole groups, the function ω was given a value of 0.024,

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Table I

Charge Balance in Bovine Serum Albumin Solutions

(pH 6.5, ionic strength 0.20, 25°)

	Guanidinium (1)	α- + ϵ-amino (2)	n_{Hlm} (3)	(1) + (2) + (3) = n_c (4)	n_{COO^-} (5)	(4) − (5) (6)	z^0_p (7)	n_{Ac} (6) − (7) (8)	k^0_{Ac} (9)
NBSA	22	58	13.5	93.5	99.2	− 5.7	−16	10.3	1.33
ABSA	22	9.9	15.1	47.0	97.8	−50.8	−39	(−11.8)	..
EBSA	22	58	6.0	86.0	0	+86	+30	56	2.21
NBSA (pH 4.71)	22	58	16	96	82	+14	0	14	1.71

being 80% of the calculated value in a medium of ionic strength 0.20.[9]

Binding of Acetate Ions.—The interaction of proteins with anions may be assumed to occur at the charged cationic functional groups of the proteins. The equilibrium may be represented by the equation

$$\frac{n_{Ac}}{n_c - n_{Ac}} = (Ac^-)k^0_{Ac}e^{2\omega z^0_p} \qquad (2)$$

where n_c is the total number of charged cationic groups, n_{Ac} the number of acetate ions bound per protein molecule, (Ac^-) the activity of free acetate ions at equilibrium (assumed 0.20) and k^0_{Ac} the intrinsic association constant for the binding of the acetate ion by the protein.

No quantitative work on the binding of acetate ions by serum albumin has been reported so far. A reasonably accurate evaluation of this interaction may, however, be made from considerations of electroneutrality. The charge balance in serum albumin solutions in the acetate buffer indicates that if the albumin molecule were not to bind the acetate ion it should have a net charge of +86, −5.7 and −50.8 for EBSA, NBSA and ABSA, respectively (see Table I, column 6). These values differ markedly from those obtained from mobility measurements. It is therefore reasonable to assume that the acetate ion is bound to the extent of 56 and 10.3 acetate ions per mole of EBSA and NBSA, respectively (Table I, column 8). With the values of n_c, n_{Ac} and z^0_p given in the table, and with ω = 0.024, we may evaluate k^0_{Ac} from eq. 2. These values are also given in the table (column 9).

A fair estimate of the ability of bovine serum albumin to bind the acetate ion may also be obtained from the results of Longsworth and Jacobsen[6] who have reported the isoelectric pH of bovine serum albumin in 0.1 acetate solution to be 4.71. From the charge balance at pH 4.71, the number of acetate ions bound per mole of protein comes to 14 (Table I). The value of k^0_{Ac} as calculated from eq. 2 will then be 1.71, in good agreement with the values given in column 9 (Table I).

In what follows we have assumed that the intrinsic association constant governing the binding of acetate ion by bovine serum albumin has a value of 1.33 for NBSA and 2.21 for EBSA. As we are interested essentially in the change in acetate binding consequent on the uptake of metal ions by the protein, the dual value used for k^0_{Ac} may not be particularly objectional.

The ability of the acetylated derivative to bind the acetate ion may be shown to be practically nil. We are thus led to expect this protein to have a charge of −50.8 as against the value of −39 obtained from mobility measurements. The binding of acetate ions, even if it were to occur, will tend to make the discrepancy even larger. This protein is however electrophoretically non-homogeneous for reasons which are not at present completely understood. The charge on the acetylated derivative has therefore been assumed to be −39.

Equilibria in Metal–Protein Systems

The equilibrium conditions in bovine serum albumin solutions in an acetate buffer of pH 6.5 and ionic strength 0.20 have been discussed above. We shall now examine how these equilibria may be expected to be influenced by the uptake of metal ions. A tacit assumption has been made in that the metal uptake, as stated earlier, involves the singly charged MAc^+ complex ion. The binding of $\bar{\nu}$ metal ions will then increase the charge on the protein by $\bar{\nu}$ units. This will tend to favor the uptake of the negatively charged acetate ion and the release of bound hydrogen ion.

The effect of metal uptake on the acetate ion–protein equilibria may be evaluated from eq. 2, the factor z^0_p being now, by definition, replaced by ($z^0_p + \bar{\nu}$). With k^0_{Ac} and n_c as given in the table, the value of n_{Ac} may be evaluated as a function of $\bar{\nu}$.

The effect of metal uptake on the dissociation of the imidazole and carboxyl groups will depend on the functional group of the protein molecule to which the metal ion may be bound. If the combination occurs with the basic imidazole groups of the protein molecule, the dissociation of the imidazole and carboxyl groups will be governed by

$$\frac{n_{Hlm}}{16 - \bar{\nu} - n_{Hlm}} = (H^+)k^0_{Hlm}e^{-2\omega(z^0_p + \bar{\nu})} \qquad (3a)$$

and

$$\frac{n_{COOH}}{100 - n_{COOH}} = (H^+)k^0_{COOH}e^{-2\omega(z^0_p + \bar{\nu})} \qquad (4a)$$

respectively. If, however, the metal uptake occurs at the basic carboxyl groups, we have the corresponding equations

$$\frac{n_{Hlm}}{16 - n_{Hlm}} = (H^+)k^0_{Hlm}e^{-2\omega(z^0_p + \bar{\nu})} \qquad (3b)$$

and

$$\frac{n_{COOH}}{100 - \nu - n_{COOH}} = (H^+)k^0_{COOH}e^{-2\omega(z^0_p + \bar{\nu})} \qquad (4b)$$

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In the above equations, n_{HIm} represents the number of acid imidazole groups and n_{COOH} that of the acid carboxyl groups per protein molecule, k^0_{HIm} the intrinsic proton affinity constant for the imidazole group and k^0_{COOH} that for the carboxyl group.

The net increment, Δz_p, in the charge on the protein molecule consequent on the binding of metal ions may be represented as

$$\Delta z_p = \bar{\nu} - \Delta n_{Ac} + \Delta n_{HIm} + \Delta n_{COOH} \qquad (5)$$

The expected net increment in charge on the protein molecule, thus calculated, is plotted in Fig. 3 as a function of the number of metal ions, $\bar{\nu}$, bound

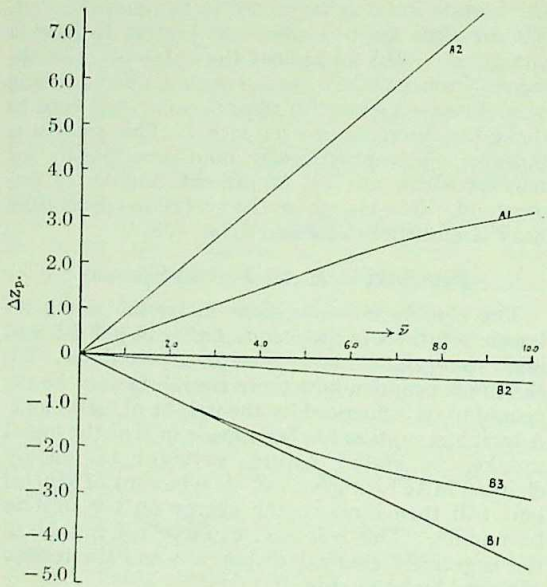

Fig. 3.—Calculated Δz_p *vs.* $\bar{\nu}$ curves, assuming interaction at: (A) carboxyl sites; (B) imidazole sites (25°, acetate buffer, *p*H 6.5, ionic strength 0.20); A1, B1, NBSA; A2, B2, ABSA; B3, EBSA.

per protein molecule. It may be immediately noticed from Fig. 3 that the electrophoretic mobility data may give useful information as to the nature of the functional group of the protein molecule with which a metal ion may react and the manner in which this interaction may be influenced by successive additions of metal ion.

A comparison of the experimental mobility data (Fig. 1A, B and C) with Fig. 3 reveals the following interesting features of the interaction process.

(i) The electrophoretic mobility data point distinctly to the conclusion that the cobaltous ion is bound essentially at the free carboxyl groups of the albumin molecule, thus supporting the conclusions derived earlier from equilibrium dialysis and optical absorption studies.[1]

(ii) The electrophoretic mobility data for the systems: copper–NBSA and copper–ABSA are characterized by the binding of the metal ions at the imidazole groups followed by an increasing participation of the carboxyl groups of the protein molecule in the interaction process after a few metal ions are bound by the protein. This participation of the carboxyl groups in the interaction process appears to increase in the direction: copper → zinc → cadmium, so much so that the mobility behavior of systems involving cadmium, especially of the system cadmium–ABSA, resembles that of the corresponding systems involving cobalt ions.

Calculation of Intrinsic Association Constants.—The calculations made in the preceding section have been shown to give useful qualitative information as to the nature of the interaction of bovine serum albumin with metal ions. These calculations, however, merely give the trend in which the equilibrium may be expected to move depending on whether the interaction involves the imidazole or the carboxyl groups of the albumin molecule. For a quantitative determination of intrinsic constants, however, we must analyze the equilibrium state as experimentally obtained. As there is little doubt that the interaction of cobaltous ion involves only the free carboxyl groups of the protein molecule, we shall in this section deal only with the equilibria involving bovine serum albumin and its derivatives on the one hand and copper, zinc and cadmium ions on the other. If the metal ion is bound at the basic imidazole groups, we have the equilibrium equation

$$\frac{\bar{\nu}}{16 - \bar{\nu} - n_{HIm}} = (A)k^0_{MIm}e^{-2\omega z_p} \qquad (6)$$

For the corresponding equilibrium between imidazole groups and hydrogen ion we have

$$\frac{n_{HIm}}{16 - \bar{\nu} - n_{HIm}} = (H^+)k^0_{HIm}e^{-2\omega z_p} \qquad (7)$$

In the above equations, (A) represents the activity of free metal ions in equilibrium with the metal–protein complex, z_p the charge on the metal–protein complex, and k^0_{MIm} an intrinsic constant representing the association of the metal ion with the imidazole group of the protein molecule. Combining eq. 6 and 7, we have

$$k^0_{MIm} = k^0_{HIm} \times \frac{\bar{\nu}}{n_{HIm}} \times \frac{(H^+)}{(A)} \qquad (8)$$

Assuming that interaction process involves the binding of MAc^+ ion at the imidazole sites of the albumin molecule and that all the imidazole sites are equivalent, k^0_{MIm} may be expected to be independent of $\bar{\nu}$, and have a value in reasonably good agreement with the first association constant of the metal ion with imidazole alone.

In eq. 8, $\bar{\nu}$ and (A) are known from separate equilibrium dialysis data[1,16,17] and k^0_{HIm} from the titration data of Tanford, Swanson and Shore referred to earlier.[9] The buffer medium of *p*H 6.5 fixes the value of (H^+). For an evaluation of k^0_{MIm}, we thus require to know the value of n_{HIm} at equilibrium at each stage of interaction process. The values of n_{HIm} at $\bar{\nu} = 0$ for the three protein solutions have already been listed (Table I). The increment, Δn_{HIm}, associated with the reaction of metal ion with the imidazole groups of the protein molecule can be calculated from eq. 5. In eq. 5, Δz_p is

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known from the electrophoretic mobility data; the values of n_{Ac}[19] and n_{COOH} (and hence Δn_{Ac} and Δn_{COOH}) at each stage of the interaction process may be evaluated from the following equations, respectively.

$$\frac{n_{Ac}}{n_c - n_{Ac}} = (Ac^-)k^0_{Ac}e^{2\omega z_p} \qquad (9)$$

$$\frac{n_{COOH}}{100 - n_{COOH}} = (H^+)k^0_{COOH}e^{-2\omega z_p} \qquad (10)$$

It would thus seem that the data for the binding of metal ions by bovine serum albumin together with the corresponding electrophoretic mobility data may be employed usefully to follow the course of the interaction process.

Data of Klotz and Fiess.—Klotz and Fiess[17] have studied the binding of cupric ion by bovine serum albumin at 25° in an acetate buffer of *p*H 6.5, ionic strength 0.20. We shall examine their data in detail in order to illustrate the concepts on which the binding data in buffer solutions may be analyzed. Taking electrostatic interaction into account, it can be shown that, for a set of n equivalent sites[20]

$$\frac{\bar{\nu}}{A}e^{-2\omega\Delta z_p} = kn - k\bar{\nu} \qquad (11)$$

where k is an intrinsic association constant uncorrected for the charge on the protein molecule. It is obvious from the electrophoretic mobility data presented in this paper that Δz_p (and hence the electrostatic interaction correction factor) is a complex function of $\bar{\nu}$. A plot of $(\bar{\nu}/A)e^{-2\omega\Delta z_p}$ *vs.* $\bar{\nu}$ should, however, give a straight line with the intercepts kn and n. Such a plot for the binding data obtained by Klotz and Fiess combined with the corresponding electrostatic interaction correction, as experimentally obtained from the mobility data presented in this paper, is given in Fig. 4.

It is immediately obvious from Fig. 4 that even when electrostatic interaction is taken into account the binding of copper ions by bovine serum albumin cannot be explained on a single value of n equivalent sites. The intercept kn ($=k_1$, the first association constant) can however be determined easily, and has a value of 3.8×10^5. For an evaluation of k, we require to know the value of n, the number of sites available for reaction with the first metal ion.

In view of the shape of the curve in Fig. 4, it is rather difficult to evaluate the intercept n by extrapolation. Fiess and Klotz[21] have indeed pointed out that this intercept may have a value of 20–100. The extrapolated value for n, even if extrapolation could be made precisely, should not however be used for the evaluation of the intrinsic association constant. Assuming that the interaction involves

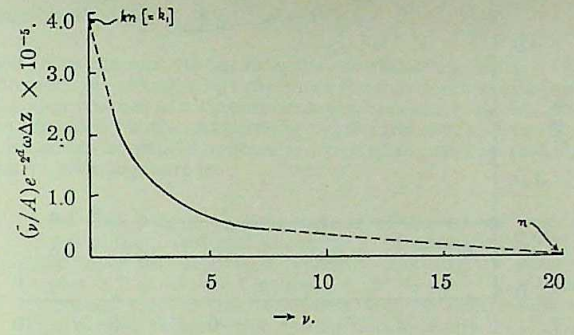

Fig. 4.—The interaction of cupric ion with NBSA (from the data of Klotz and Fiess): 25°, acetate buffer, *p*H 6.5, ionic strength 0.20.

the imidazole groups, it is reasonable to expect that it is only the unprotonated imidazole groups which are available for reaction with metal ions, and furthermore, that their value, as shown in the preceding sections, increases with $\bar{\nu}$. n is therefore dependent on the number of metal ions bound to the imidazole sites of the protein molecule. We may thus define

$$n = 16 - n_{Hlm} = n^3[1 + f\bar{\nu}] \qquad (12)$$

where n^0 is the number of basic imidazole groups present on the protein molecule at $\bar{\nu} = 0$, and f is a function governing the rate of change of n with $\bar{\nu}$. Substituting for n in eq. 11, we then have

$$\frac{\nu}{A}e^{-2\omega\Delta z_p} = kn^0 - [1 - n^0f]k\bar{\nu} \qquad (13)$$

It is obvious from eq. 13 that the intercept on the ordinate in Fig. 4 represents kn^0. With a value of 2.5 for n ($n^0_{Hlm} = 13.5$ at $\bar{\nu} = 0$, see Table I, column 3), and correcting for electrostatic effect due to the charge on the protein, the intrinsic association constant can be evaluated. A value of log $k^0 = 4.86$ was thus obtained.[22]

Assuming that the copper ion is bound at the imidazole sites of the albumin molecule, the in-

(19) As the metal uptake has been assumed to occur at the imidazole groups, the value for n_c, the number of charged cationic centers on the protein molecule, may be expected to depend on $\bar{\nu}$. Assuming that an imidazole group whether covered by metal ion or by hydrogen ion acts as a cationic center, the increase, Δn_c, in the number of cationic centers over the values given in Table I (column 4) may be expected to be $\bar{\nu} + \Delta n_{Hlm}$. For systems involving NBSA, Δn_c was assumed to be zero as the uptake of a metal ion may be expected to cause a nearly equivalent proton release from the imidazole sites of NBSA (assumptions concerning the value of n_c are not critical in their effect on the final value of n_{Hlm}). For systems involving EBSA, however, the values given for n_c are critical and must be accurately known; in these systems, Δn_c was assumed to be 0.6 $\bar{\nu}$ as, on an average, 0.4 proton may be expected to be released for every metal ion bound to EBSA. These estimates, necessarily approximate, were based on eq. 3a.

(20) G. Scatchard, *N. Y. Acad. Sci.*, **51**, 660 (1949).

(21) H. A. Fiess and I. M. Klotz, THIS JOURNAL, **74**, 887 (1952).

(22) The intrinsic constant (log $k^0_{Culm} = 4.86$) is much larger than the first association constant for the interaction of cupric ion with imidazole alone (log $k_1 = 4.3$[23] at 25°). In this connection it is of interest to note that the value of the intrinsic constant for the association of zinc ion with human serum albumin (ref. 3, log $k^0_{Znlm} = 2.82$ at 0°) needs to be revised in view of the recent titration data of Tanford, Swanson and Shore (ref. 9). Assuming that the intrinsic proton affinity constants of the imidazole groups in NBSA and HSA are identical (see Discussion in ref. 9), it is obvious in view of eq. 5 in ref. 3 that the intrinsic association constant for the interaction of zinc ion with HSA as reported by Gurd and Goodman should be upgraded by 0.8 logarithmic units to give log $k^0_{Znlm} = 3.62$. A comparison of this revised value with the first association constant for the interaction of zinc ion with imidazole alone (log $k_1 = 2.8$[23] at 0°) reveals a similar trend to the one observed in the corresponding systems involving cupric ion.

(23) J. T. Edsall, J. C. Rabinowitz, D. S. Goodman and F. R. N. Gurd, THIS JOURNAL, **76**, 3054 (1954).

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trinsic association constant was evaluated as a function of $\bar{\nu}$ (eq. 8). The relevant log k^0 *vs.* $\bar{\nu}$ plot is given in Fig. 5A. It may be noticed that k^0 decreases with $\bar{\nu}$—a fact which may be attributed, among others, to an increasing participation of the free carboxyl groups of the albumin in the interaction process as more and more metal ions are bound by the protein. The matter shall be discussed further in a later communication.

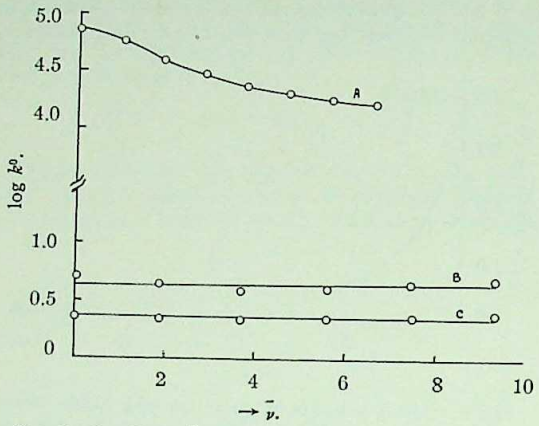

Fig. 5.—log k^0 *vs.* $\bar{\nu}$ curves: A, system copper–NBSA (from the binding data of Klotz and Fiess); B, system cobalt–NBSA (Rao and Lal); C, system cobalt–ABSA (Rao and Lal).

The Data of Rao and Lal.—The interaction of native and modified bovine serum albumins with the cobaltous ion in an acetate buffer of *p*H 6.5, ionic strength 0.20, has been studied by Rao and Lal.[1] There is conclusive evidence to show that the cobaltous ion is bound at the three carboxyl groups of the albumin molecule. Assuming that all the 100 carboxyl groups are in the basic form (see Table I, column 5), the value of the intrinsic association constant, k^0, evaluated from the first association constant, k_1, was found to be 5.1 for NBSA and 2.3 for ABSA. The intrinsic association constant remained independent of the number of cobaltous ions bound by the proteins (Figs. 5B and C). The low value of the intrinsic association constant together with the fact that it is independent of $\bar{\nu}$ point conclusively to the interaction of the cobaltous ion with the free carboxyl groups of the serum albumin molecule.

In the present work, we have outlined the general concepts governing the interpretation of metal-protein interactions in buffer solutions. A full treatment of our data for the binding of metal ions by bovine serum albumins and its modified derivatives shall be presented in a separate communication.

Acknowledgment.—The authors are grateful to Dr. A. B. Biswas for helpful discussions.

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ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BRITISH COLUMBIA]

The Mechanisms of Permanganate Oxidation. III. The Oxidation of Benzhydrol

BY ROSS STEWART

RECEIVED NOVEMBER 23, 1956

The permanganate oxidation of benzhydrol has been studied in an attempt to elucidate the reaction mechanism. The reaction kinetics, the existence of hydroxyl ion catalysis, the presence of a positive salt effect and the sign and magnitude of the entropy of activation all indicate that the rate-controlling step consists of a reaction between benzhydrylate ion and permanganate ion. The existence of an isotope effect (6.6:1) obtained for the oxidation of benzhydrol-α-*d*, and the fact that when potassium permanganate-O^{18} is used as the oxidant no excess oxygen-18 appears in the product, suggest that the reaction occurs by hydride ion transfer from benzhydrylate ion to permanganate ion.

Introduction

The previous papers in this series dealt with the permanganate oxidations of aromatic aldehydes[1] and formate ion[2] and demonstrated further the manifold character of permanganate ion as an oxidant.

The presently available evidence indicates that permanganate oxidizes each of the following groups or compounds by a distinctive reaction path: C=C,[3,4] ArCHO,[1] RCHO and R_2CO,[5] $-CH_3$,[6] $-HCO_2^-$[2] and $(CO_2H)_2$.[7]

Such versatility[8] is even more impressive when one considers that a change in reaction conditions can cause a change in mechanism as has been shown in the case of the permanganate oxidation of benzaldehyde.[1] The present study was undertaken to determine the mechanism of the reaction of this reagent with alcohols. It deals with the behavior of permanganate toward a typical secondary alcohol, benzhydrol, $(C_6H_5)_2CHOH$, which was chosen because of the stability of its oxidation product, benzophenone, to further attack.

Previous work on the reaction of alcohols with permanganate in acid media has been reported. Merz, Stafford and Waters showed that isopropyl alcohol in acid solution is oxidized by an induced process which probably involves Mn^{+4}.[9] Cullis and Ladbury have made a comprehensive study of reaction conditions for the acid permanganate oxidation of aromatic compounds including benzyl alcohol and 1-phenylethanol,[10] but the reaction mechanism remains obscure.

Experimental

Reagents.—Benzhydrol was crystallized from carbon tetrachloride to constant m.p. 64–65°. Benzhydrol-α-*d* was prepared as follows. Benzophenone (3.6 g., 0.02 mole) was dissolved in 30 ml. of dry ether and added dropwise to lithium aluminum deuteride (0.44 g., 0.01 mole) dissolved in 20 ml. of ether. The mixture was refluxed for ten minutes, cooled and poured on to a mixture of one ml. of concentrated sulfuric acid and about 20 g. of crushed ice. The ether layer was separated, washed, dried and evaporated to give 2.7 g. of white crystals, m.p. 63–64°. The benzhydrol-α-*d* used in the rate experiments was recrystallized from carbon tetrachloride to constant m.p. 64–65°. The infrared spectrum of the labeled alcohol showed a shift in the carbon–hydrogen stretching peak from 3.52 to 4.71 μ. The isotopic purity was shown to be high by the complete absence of a band at 3.52 μ in the benzhydrol-α-*d*.

Potassium permanganate-O^{18} and potassium manganate were obtained as previously described.[1]

Kinetic Method.—Two procedures, titration and measurement of light absorption, were used to follow the disappearance of permanganate and hence to determine the reaction rate.

In the first method an aqueous solution of benzhydrol, approximately 0.002 *M*, was obtained by dissolving a weighed amount of benzhydrol in hot distilled water which had been boiled to remove dissolved gases and making the solution up to the mark in a volumetric flask. In a typical experiment, 20 ml. of this solution, 10 ml. of 0.2 *M* carbonate-free potassium hydroxide and 18 ml. of boiled distilled water were brought to reaction temperature in a vessel immersed in a constant temperature bath controlled to ±0.04°. Two ml. of a standard solution of potassium permanganate was added to start the reaction, the progress of which was followed by titrating five-ml. aliquots iodometrically, essentially as described previously.[1] A slow flow of nitrogen through the system was maintained during the reaction.

Since most of the investigation dealt with the basic *p*H region where the permanganate oxidation of benzhydrol was fast and the manganate oxidation was shown to be slow, the reaction studied involved a valence change for manganese from +7 to +6. A very accurate titration is required if the points on the rate plot are to be precise since the titration measures the total oxidizing power of all manganese species above valence two. Reasonably good precision was obtained on most of the rate plots; nevertheless, there is a considerable scatter of points in Fig. 3, for example.

As a check on the titration method the disappearance of permanganate was also followed spectrophotometrically. The reaction mixture was made up essentially as in the previous method. After addition of the permanganate the solution was shaken and a portion of it transferred quickly to an absorption cell and placed in the cell compartment of a Beckmann spectrophotometer, model DU. Thermospacers kept the sample at a constant temperature and even when measurements were made at temperatures ten degrees above room temperature, no difficulty was experienced. In this case a drop in temperature of about one fifth of a degree in transferring the sample to the cell was observed. The temperature rose to that of the thermostat within a short time, however, and the rate constants were calculated from those points obtained after thermal equilibrium had been attained. Measurements of the light absorption were made at 522 and 426 mμ, the former wave length corresponding mainly to absorption by permanganate and the latter mainly to absorption by manganate. From the known values of the extinction coefficients of the two ions at these two wave lengths[11] the following equation was derived, where *D* stands for optical density.

(1) K. B. Wiberg and R. Stewart, THIS JOURNAL, **77**, 1786 (1955).
(2) K. B. Wiberg and R. Stewart, *ibid.*, **78**, 1214 (1956).
(3) W. A. Waters in H. Gilman, "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 1211, 1214.
(4) J. Boeseken, *Rec. trav. chim.*, **47**, 683 (1928).
(5) A. Y. Drummond and W. A. Waters, *J. Chem. Soc.*, 497 (1955).
(6) W. Griehl, *Ber.*, **80**, 410 (1947).
(7) J. M. Malcolm and R. M. Noyes, THIS JOURNAL, **74**, 2769 (1952).
(8) For a simpler view of organic oxidations see L. S. Levitt, *J. Org. Chem.*, **20**, 1297 (1955), and L. S. Levitt and E. R. Walinowski, THIS JOURNAL, **77**, 4517 (1955).
(9) J. H. Merz, G. Stafford and W. A. Waters, *J. Chem. Soc.*, 638 (1951).
(10) C. F. Cullis and J. W. Ladbury, *ibid.*, 4850 (1955).
(11) G. L. Zimmerman, Thesis, University of Chicago, 1949.

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$$[MnO_4^-] = D_{522} - 0.282D_{426}$$

In most of the rate experiments which were followed using this method, benzhydrol was present in considerable excess and the concentration of MnO_4^- need not be obtained in any specific units since only log $[MnO_4^-]$ is used in the calculations. The values of $[MnO_4^-]$ obtained by the use of the above equation are quite arbitrary.

The light absorption method for determining the rate is subject to the following disadvantages. For very slow permanganate oxidations some manganate is likely to be reduced to MnO_2 which can cause light scattering and may introduce errors in the estimate of the permanganate concentration. It is assumed, too, that no other light absorbing species are formed as the reaction proceeds (see Results and Discussion). The fact that the two methods gave rate constants in good agreement with each other indicates that the results obtained are reliable.

Oxidation with Potassium Permanganate-O^{18}.—A typical experiment was conducted as follows. Benzhydrol (0.45 g.) was dissolved in 860 ml. of hot, previously boiled, distilled water and, when the solution had cooled to 30°, 45 ml. of 0.2 *N* potassium hydroxide was added. Labeled potassium permanganate (1.55 g., onefold excess) was dissolved in 30 ml. of water and added to the reaction solution. After four minutes 30 ml. of 10% sodium bisulfite and one ml. of concentrated sulfuric acid were added to quench the reaction. The solution was immediately extracted with 30 ml. of petroleum ether which was washed, dried over anhydrous sodium sulfate and poured through a column of 3 g. of alumina. The column was eluted with three 15-ml. samples of petroleum ether and one sample of ether. The first two petroleum ether fractions yielded 0.25 g. of pure benzophenone, m.p. 49°. The third and fourth fractions contained small amounts of benzophenone, and the ether eluate contained about 0.06 g. of unreacted benzhydrol. The original reaction solution after the petroleum ether extraction was further extracted with 100 ml. of benzene and this, in turn, yielded about 0.11 g. of a mixture of benzophenone and benzhydrol, m.p. 46–54°.

Benzhydrol-O^{18}.—Benzhydryl chloride readily was prepared by shaking 14 g. of benzhydrol with 80 ml. of concentrated hydrochloric acid for 0.5 hr. Extraction with ligroin followed by distillation at reduced pressure yielded 12 g. of benzhydryl chloride, m.p. 18–19°, b.p. 100–102° at 0.3 mm. A solution of 5 g. of benzhydryl chloride, 6 ml. of dry pyridine and 1 ml. of H_2O^{18} (about 1.4 atom % O^{18}) was allowed to stand overnight and then heated for 2 hr. on the steam-bath. The liquid was distilled off under reduced pressure and the residual white solid was extracted with ether. Evaporation of the ether yielded 3.0 g. of white crystals which were recrystallized from carbon tetrachloride–ligroin. Repeated recrystallizations from this solvent did not raise the m.p. above 62–63°. One gram of ordinary benzhydrol was added to 2.5 g. of the labeled material and the whole dissolved in hot ether. Addition of petroleum ether produced 2.1 g. of crystals of benzhydrol which melted at 64–65° and gave no m.p. depression when mixed with an authentic sample.

Oxidation of Benzhydrol-O^{18}.—The same general procedure was used here as for the oxidation with potassium permanganate-O^{18} except that in one experiment the reaction was quenched with sodium bisulfite only. The unreacted benzhydrol which was recovered in this experiment was submitted to oxygen-18 analysis to determine whether or not any exchange of oxygen with solvent had occurred prior to reaction.

Results and Discussion

Kinetics.—The benzhydrol–permanganate reaction is strongly base catalyzed as can be seen from the results shown in Fig. 1.[12]

(12) Except for the few experiments required to establish the fact that the reaction is slow in neutral or acid solution, the only work done in these regions was an experiment to determine the effect of added manganous ion on the rate, a device which has been used to determine whether or not the oxidizing agent is some manganese species of intermediate valence. Addition of enough manganous sulfate to make the solution 0.00024 *M* in Mn^{++} compared to a permanganate concentration of 0.0013 *M*, caused a drop in the bimolecular rate constant k_2 from 0.48 to 0.32 in 0.18 *M* H_2SO_4, indicating that ions of intermediate valence produced by the manganous–permanganate reaction are not the active oxidizing species even in acid solution.

In all rate experiments in which equivalent quantities of benzhydrol and permanganate were used and in which hydroxyl ion was in excess the reaction was found to be second order in agreement with the rate law

$$\frac{-d\,[MnO_4^-]}{dt} = k_2[MnO_4^-][(C_6H_5)_2CHOH]$$

For those points in Fig. 1 below *p*H 12 the benzhydrol–permanganate ratio was kept at 3:2 since any manganate or hypomanganate formed in the process undergoes disproportionation to MnO_2 and MnO_4^-. This initial ratio of 3:2 ensures a constant ratio of the two reactants as the oxidation proceeds. The second-order rate constants were obtained using the expression

$$k_2 = \frac{1}{t[\text{benzhydrol}]_0} \times \frac{V_0 - V_t}{V_t - 2/5V_0} \qquad (1)$$

where V is the volume of thiosulfate required in the iodometric titration.[1] In sufficiently basic solution, however, the manganate formed does not disproportionate. Since it was shown that manganate reacts with benzhydrol at about one fortieth of the rate of permanganate in 0.1 *M* KOH solution, the manganate accumulates as the reaction proceeds and the reaction in basic solution, which was the one studied in detail, becomes

$$(C_6H_5)_2CHOH + 2MnO_4^- + 2OH^- \longrightarrow (C_6H_5)_2C{=}O + 2MnO_4^{=} + H_2O$$

To preserve a constant benzhydrol–permanganate ratio as the reaction proceeds a 1:2 initial ratio is required. It can be shown that in this case the rate constant is given by the expression

$$k_2 = \frac{1}{t[\text{benzhydrol}]_0} \times \frac{V_0 - V_t}{V_t - 4/5V_0} \qquad (2)$$

Linear relations were obtained when t was plotted against $V_0 - V_t/V_t - 4/5V_0$ showing the reaction to be second order but not proving it to be first order in each reactant. For this reason experiments were performed in which there was an initial benzhydrol–permanganate molar ratio of 1:1 and 1:4. It can be shown that when the initial molar concentrations of benzhydrol and permanganate are the same (two equivalents of benzhydrol to one of permanganate) relation (3) holds

$$k_2 = \frac{4.61}{y_0 t} \log \frac{V_t - 3/5V_0}{V_t - 4/5V_0} \qquad (3)$$

and that when the ratio of the initial concentration of benzhydrol to permanganate is 1:4 this expression holds

$$k_2 = \frac{-2.30}{y_0 t} \log \frac{V_t - 9/10V_0}{V_t - 4/5V_0} \qquad (4)$$

Equation 3 can be derived as (let $x = [MnO_4^-]$ and $y = [\text{benzhydrol}]$)

$$\frac{-dx}{dt} = k_2xy$$

if $x_0 = y_0$, $y = 1/2y_0 + 1/2x$

$$-1/2k_2t = \int \frac{dx}{(y_0x + x^2)}$$

$$= -\frac{1}{y_0} \ln \left(\frac{y_0 + x}{x}\right)$$

now $x = A[V_t - 4(V_0 - V_t)]$, where A is a con-

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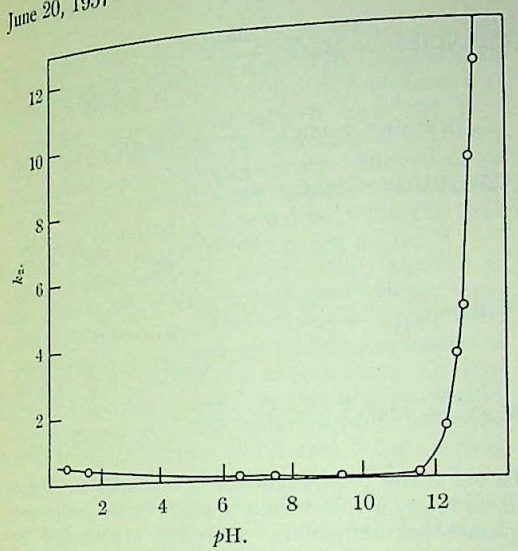

Fig. 1.—Effect of variation in pH on the bimolecular rate constant, k_2, for the permanganate–benzhydrol reaction; $T = 25°$.

stant, provided the only oxidizing species of manganese in solution are MnO_4^- and $MnO_4^{=}$.

$$\therefore 1/2k_2t = \frac{1}{y_0} \ln \frac{V_t - 3/5V_0}{V_t - 4/5V_0}$$

and

$$k_2 = \frac{4.61}{y_0 t} \log \frac{V_t - 3/5V_0}{V_t - 4/5V_0}$$

Equation 4 follows from a similar argument.

Good straight line relations were obtained for these two cases when t was plotted against the logarithmic function and the rate constants listed in Table I show that the reaction is indeed first order in MnO_4^- and first order in benzhydrol. Also listed in Table I are values for the rate constant obtained using benzhydrol in excess. These values were obtained from spectrophotometric experiments and the kinetics were, as expected, pseudo unimolecular.

TABLE I

RATE CONSTANTS FOR THE BENZHYDROL–PERMANGANATE REACTION FOR VARIOUS INITIAL CONCENTRATION OF REACTANTS

$(C_6H_5)_2CHOH$ × 10⁴, mole l.⁻¹	MnO_4^- × 10⁴, mole l.⁻¹	OH^-, mole l.⁻¹	Ionic strength	k_2, l. mole⁻¹ sec.⁻¹	Method
15.6	15.6	0.020	0.040	1.52[a]	Titration
7.80	15.6	.020	.040	1.54[b]	Titration
3.90	15.6	.020	.040	1.55[c]	Titration
7.80	15.6	.022	.040	1.79[b]	Titration
13.0	2.1	.022	.024	1.75[d]	Spectral
6.50	2.1	.022	.024	1.84[d]	Spectral

[a] Calculated using equation 3. [b] Calculated using equation 2. [c] Calculated using equation 4. [d] Calculated using the relation $k_2 = (2.30 \log x)/y_0't$ where $x = [MnO_4^-]$ and y_0' = mean concentration of benzhydrol over range studied.

Hydroxyl Ion Catalysis and Salt Effect.—The reaction rate was shown, too, to be directly proportional to the hydroxyl ion concentration (Fig. 2). A likely role for hydroxyl ion in the reaction would be to produce the anion of benzhydrol which, in turn, might undergo a rate-determining reaction with permanganate. This possibility can be further investigated by determining the effect of a change in ionic strength on the rate, since two anions would be reacting in the slow step. Unfortunately, a certain minimum hydroxyl ion concentration is required to ensure that the reaction one is studying is, indeed, the hydroxyl ion catalyzed one. This places the ionic strength in a region where the Brönsted–Debye–Hückel relation is not expected to hold. Harty and Rollefson[13] have recently had some success with a treatment for ionic reactions in more concentrated solution which involves plotting log k against a parameter which depends on both the ionic strength and the particular salt added. Using their value for the parameter when potassium sulfate is the added salt, as in the present case, one obtains the curve shown in Fig. 3. Although the precision of the results shown in this plot is not impressive (for reasons discussed in the Experimental section) the results do support the idea that the slow step is between two ions of like, single, charge. The over-all reaction may then be expressed as

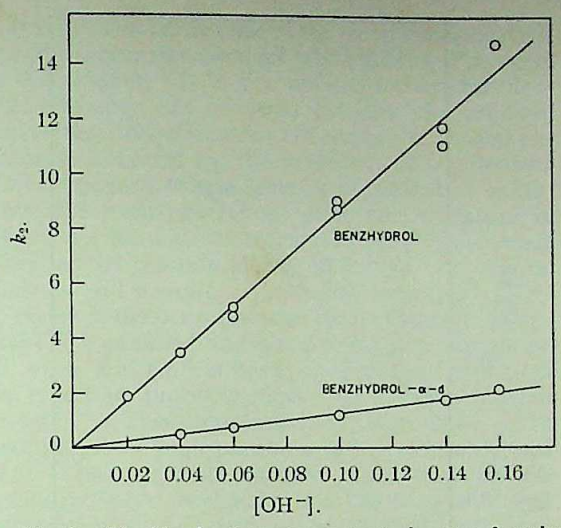

Fig. 2.—The bimolecular rate constant, k_2, as a function of the hydroxyl ion concentration for the permanganate oxidation of benzhydrol and benzhydrol-α-d; $T = 25.0°$.

$$(C_6H_5)_2CHOH + OH^- \overset{K}{\rightleftharpoons} (C_6H_5)_2CHO^- + H_2O$$

$$MnO_4^- + (C_6H_5)_2CHO^- \xrightarrow{k} \text{products}$$

The rate law which corresponds to this mechanism is

$$\frac{-d[MnO_4^-]}{dt} = k[MnO_4^-][(C_6H_5)_2CHO^-]$$

$$= kK[MnO_4^-][(C_6H_5)_2CHOH][OH^-]/[H_2O]$$

$$\therefore k_2 = kK[OH^-]/[H_2O]$$

These equations are in agreement with the observed kinetics.

Thermodynamic Functions.—A plot of log k/T against $1/T$ shows a satisfactory linear relation but leads to the rather low value for $\Delta H^{\ddagger}$ of 5.7 kcal. mole^{-1} and the rather high negative value for $\Delta S^{\ddagger}$

[13] W. W. Harty and G. K. Rollefson, THIS JOURNAL, 76, 4811 (1954).

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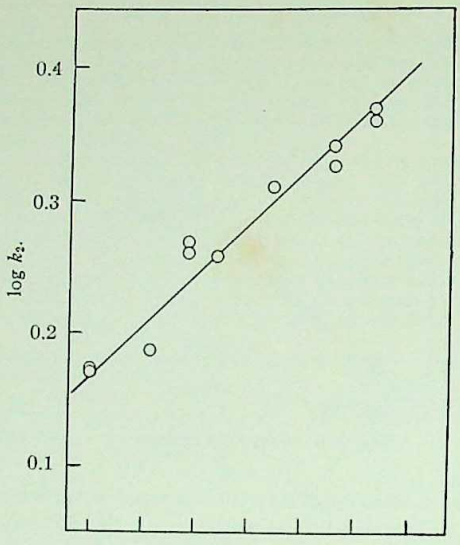


Fig. 3.—Log k_2 plotted against the parameter, $1/(3.26 + 1/\sqrt{u})$ for the permanganate–benzhydrol reaction; $T = 25.0°$.

of −38.4 e.u. It should be pointed out that these are composite values which include the thermodynamic parameters for the ionization step as well as for the rate-controlling step. The entropy of activation for the rate-controlling step must, in fact, be a much smaller negative quantity than the value of −38.4 e.u. calculated here since the equilibrium concentration of benzhydrylate ion is probably quite small in the solutions used in this work. In view of this the measured entropy of activation is not unreasonable since reactions between univalent anions in aqueous solution normally have activation entropies of the order of −20 e.u.[14]

Mechanism of the Rate-controlling Step.—If it is assumed that the first step in the reaction is the ionization of benzhydrol, then the following mechanisms for the rate-controlling step can be considered, each of which agrees with the observed kinetics.[15]

$$(C_6H_5)_2CHO^- + MnO_4^- \xrightarrow{\text{slow}} (C_6H_5)_2CHO\cdot + MnO_4^{=} \quad (5a)$$

$$(C_6H_5)_2CHO\cdot + MnO_4^- \xrightarrow{\text{fast}} (C_6H_5)_2C{=}O + MnO_4^{=} + H^+ \quad (5b)$$

$$(C_6H_5)_2CHO^- + MnO_4^- \xrightarrow{\text{slow}} (C_6H_5)_2C{=}O + HMnO_4^- \quad (6a)$$

$$HMnO_4^- + MnO_4^- \xrightarrow{\text{fast}} 2MnO_4^{=} + H^+ \quad (6b)$$

$$(C_6H_5)_2CHO^- + MnO_4^- \xrightarrow{\text{slow}} (C_6H_5C(OH)O^-) + MnO_3^- \quad (7a)$$

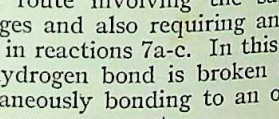
$$(C_6H_5)_2C(OH)O^- \underset{\text{fast}}{\rightleftharpoons} (C_6H_5)_2C(O^-)OH \xrightarrow{\text{fast}} (C_6H_5)_2C{=}O + OH^- \quad (7b)$$

$$MnO_4^- + MnO_3^- + 2OH^- \xrightarrow{\text{fast}} 2MnO_4^{=} + H_2O \quad (7c)$$

In eq. 5 the permanganate is acting as an electron abstractor, a role which it plays in the rapid manganate–permanganate exchange reaction.[16] Symons has suggested, with reference to permanganate oxidations, that direct electron exchange between negative oxy-ions may be facilitated by their size and ease of polarization.[17] This mechanism was shown to be incorrect by establishing the fact there is an isotope effect when the hydrogen on the α-carbon atom is replaced by deuterium. The ratio, k_H/k_D, the ratio of the slopes of the lines in Fig. 2, is 6.6:1 showing clearly that the rate controlling step involves the scission of the carbon-hydrogen bond.[18]

Reaction 6a is simply a transfer of hydride ion from benzhydrylate ion to permanganate producing Mn(V).[19] A species of this valence is believed to be the intermediate in the benzaldehyde–permanganate reaction,[1] and it has recently been shown that hypomanganate ion, Mn(V), is very rapidly oxidized by permanganate in basic solution.[20] Further, the kinetics of the homogeneous reaction between permanganate and molecular hydrogen have been interpreted in terms of a two electron or hydride transfer to permanganate to form Mn(V).[21]

A possible route involving the same over-all valence changes and also requiring an isotope effect is shown in reactions 7a-c. In this mechanism the carbon–hydrogen bond is broken by the two atoms simultaneously bonding to an oxygen atom donated by the permanganate.



This mechanism warrants consideration since the oxidation of formate ion which resembles the reac-

(14) The Arrhenius activation energy reported by L. M. Hill and F. C. Tompkins, *Trans. Roy. Soc. S. Africa*, **30**, 59 (1943), for the permanganate–formate reaction is 11.8 kcal. mole^{-1}. The value of $\Delta S^{\ddagger}$ which corresponds to this value is −22.7 e.u.

(15) A reaction such as the following involving hydroxyl radicals would require the rate to decrease with time because of the accumulation of manganate in the system.

$$MnO_4^- + OH^- \rightleftharpoons MnO_4^{=} + \cdot OH$$
$$(C_6H_5)_2CHOH + \cdot OH \longrightarrow (C_6H_5)_2COH + H_2O$$
$$(C_6H_5)_2COH + MnO_4^- \longrightarrow \text{products}$$

If the hydroxyl radicals were involved in a chain reaction or if the first step above was irreversible, one would not expect the kinetics to be first order in each of benzhydrol, permanganate and hydroxyl ion as was observed here.

(16) J. C. Sheppard and A. C. Wahl, THIS JOURNAL, **76**, 5133 (1953).

(17) M. C. R. Symons, *J. Chem. Soc.*, 3956 (1953).

(18) K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

(19) An equivalent reaction can be written in which the benzhydrylate ion gives up two electrons to MnO_4^- to produce $MnO_4^{=}$ and simultaneously gives up a proton to a water molecule present in the solvation sphere. Since $MnO_4^{=}$ is probably a fairly basic species, it does not seem unreasonable to picture the electron pair plus proton being transferred simultaneously to the same site, *i.e.*, a hydride ion transfer.

(20) J. S. F. Pode and W. A. Waters, *J. Chem. Soc.*, 717 (1956).

(21) A. T. Weibel and H. Taube, *Trans. Faraday Soc.*, in press (private communication).

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tion studied here in many respects[22] may occur partly by just such a process since it has been shown that a considerable fraction of the oxygen found in the product, carbonate, is derived from the permanganate. In addition, the reaction of carbene, CH_2, with carbon–hydrogen bonds is believed to go through a similar transition state since the methylene group is found to be inserted between the previously bonded carbon and hydrogen atoms.[23]

To determine whether the hydride transfer *to* permanganate or the oxygen transfer *from* permanganate is occurring, benzhydrol was oxidized with $KMnO_4^{18}$ under conditions resembling as closely as possible those for the kinetic experiments. It was anticipated that the product, benzophenone, would exchange oxygen with the water in basic solution since ketones are known to do this,[24] but it was hoped that complete equilibration would not take place in the short reaction times used. The results of the oxidation of both benzhydrol with $KMnO_4^{18}$ and benzhydrol-O^{18} with $KMnO_4$ are shown in Table II.

TABLE II

OXYGEN-18 ANALYSIS OF BENZOPHENONE AND BENZHYDROL[a]

Sample	Source	Atom % O^{18} in CO_2 from sample[b]	Atom % O^{18} in excess in sample[b]
Tank CO_2		0.204	...
$(C_6H_5)_2C{=}O$	$(C_6H_5)_2CHOH$ + $KMnO_4^{18}$	.200	...
		.206	...
		.205	...
$(C_6H_5)_2CHOH$	$(C_6H_5)_2CHCl$ + H_2O^{18}	.558	0.708
		.557	.706
$(C_6H_5)_2C{=}O$	$(C_6H_5)_2CHO^{18}H$ + $KMnO_4$	.557	.706
		.249	.090
$(C_6H_5)_2CHOH$[c]	$(C_6H_5)_2CHO^{18}H$ + $KMnO_4$	.254	.100
		.552	.696
		.552	.696

[a] See Acknowledgment. [b] CO from sample was oxidized to CO_2 and the O^{18} content determined mass-spectrometrically. If y = %O^{18} in CO_2, the atom %O^{18} in excess in the sample = $2(y - 0.204)$. [c] Recovered after the reaction.

(22) The permanganate oxidations of benzhydrol and formate ion resemble one another in the following respects: the size of the isotope effect, the sign and magnitude of the entropy of activation, the fact that the reaction in each case involves an anion, benzhydrylate ion and formate ion. In addition, the reaction of manganate with both formate ion and benzhydrol is slow.

(23) P. S. Skell and R. C. Woodworth, THIS JOURNAL, **78**, 4496 (1956).

(24) M. Cole, *Chem. Revs.*, **51**, 286 (1952).

It is apparent that none of the permanganate oxygen appears in the product when $KMnO_4^{18}$ is used as the oxidant. It is also apparent that considerable exchange has occurred between the product and water, since the excess O^{18} content of the benzophenone obtained by the oxidation of benzhydrol-O^{18} is reduced to one-seventh of its initial value. That the exchange occurs after the oxidation is shown by the fact that the benzhydrol recovered after partial reaction shows no loss of O^{18}. Since there is still a quite definite concentration of O^{18} in excess in the benzophenone formed when benzhydrol-O^{18} is oxidized and since there is no excess at all when $KMnO_4^{18}$ is used, one can conclude that the reaction probably does not involve oxygen transfer.[25] This conclusion is warranted only because of the high precision of the O^{18} analytical data. Thus, the route shown in reactions 6a and 6b is the probable mechanism for the base-catalyzed permanganate oxidation of benzhydrol and may, indeed, be the general course of permanganate–alcohol reactions in basic media.

Acknowledgments.—The author is grateful to Drs. K. B. Wiberg and J. Halpern for helpful discussions and to Mr. Klaus Saegebarth of the University of Washington for the O^{18} analytical data which appear in Table II. Certain of the experimental results reported herein were obtained by the author in the Chemistry Laboratories of the Canadian Services College, Royal Roads, B. C.

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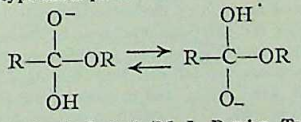
(25) Two other factors should be mentioned which might conceivably account for the absence of an excess of O^{18} in the benzophenone even though the mechanism shown in eq. 7a be correct. First, although permanganate by itself exchanges oxygen only slowly with water in neutral and basic solution, the exchange is more rapid in the presence of manganate (M. C. R. Symons, *J. Chem. Soc.*, 3676 (1954).) Since a onefold excess of permanganate was used in the tracer experiments and since the reaction time was short, this effect is not believed to be serious. Second, if the reaction shown on the left in eq. 7c is not a rapid equilibrium, the hydroxyl ion lost would be the one containing the excess of O^{18}. Since the equilibrium involves proton addition to an oxygen anion, it is believed that this would be a much faster reaction than the splitting of the oxygen–carbon bond to produce the products. An analogous situation exists for the case of ester hydrolysis where Bender has shown that rapid equilibration of the following type takes place



before the OR group is eliminated (M. L. Bender, THIS JOURNAL, **73**, 1626 (1951)).

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[CONTRIBUTION NO. 1251 FROM STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

π-Complexes of the Transition Metals. I. Hein's Polyaromatic Chromium Compounds[1,2]

BY HAROLD H. ZEISS[3] AND MINORU TSUTSUI[3]

RECEIVED NOVEMBER 29, 1956

The essential steps of Hein's methods for the preparation of polyphenylchromium compounds have been reproduced. The products of the chemical reduction of these compounds have led to a reformulation of their structures in terms of a bis-arene cation. This biconoidal structure is then discussed with respect to the formerly anomalous behavior reported for these complexes and the new chemistry which may now evolve.

Sidgwick's brief summary of the phenylchromium compounds[4a] provided the impetus for this introductory study of the transition metal complexes. The new experimental facts relating to the anomalous behavior and properties exhibited by these compounds and the concept of a new and fertile borderland of π-complexes between organic and inorganic molecules are now reported.

Repetition of the steps employed by Hein and his co-workers[4] in preparing the key compounds of the series, "pentaphenylchromium hydroxide" I, "tetraphenylchromium" iodide II and "triphenylchromium" iodide III, afforded these compounds, corresponding to their previous descriptions albeit in very small amounts. The basic reaction, formulated by Hein as (1), gave the amorphous, hygroscopic and impure "pentaphenylchromium bromide" which, with alcoholic potassium hydroxide (2), gave rise to "pentaphenylchromium hydroxide," which crystallized in the form of golden orange plates from water–chloroform mixture.

$$5C_6H_5MgBr + 4CrCl_3 \longrightarrow$$
$$\text{"}(C_6H_5)_5CrBr\text{"} + CrCl_2 + MgBr_2 + MgCl_2 \text{ (Hein)} \quad (1)$$

$$\text{"Raw bromide"} + KOH \longrightarrow$$
$$\text{"}(C_6H_5)_5CrOH\cdot 4H_2O\text{"} + KBr \quad (2)$$

$$\text{"}(C_6H_5)_5CrOH\text{"} + KI \longrightarrow$$
$$\text{"}(C_6H_5)_4CrI\text{"} + C_6H_5OH + KOH \quad (3)$$

The aqueous mother liquor, after concentration and cooling, deposited crystalline, orange "pentaphenylchromium carbonate," formulated as "$[(C_6H_5)_5Cr]_2CO_3\cdot 6H_2O$." The mother liquor resulting from this step consisted of a strongly alkaline, sirupy, water-soluble black mass which deposited orange-yellow plates of "triphenylchromium" iodide III when treated with aqueous potassium iodide; while a suspension of I in a mixture of aqueous potassium iodide and chloroform was transformed into an orange oil which slowly crystallized and was eventually obtained as golden orange plates of "tetraphenylchromium" iodide II (reaction 3).

The first series of anomalies is apparent from the reaction scheme just presented. Phenylmagnesium bromide is recognized to be a reducing agent but not one of oxidation. The separation of tetra-, penta- and hexavalent chromium compounds from the same solution (no free iodine formed) is unaccountable. The production of tetravalent II with the liberation of phenol by potassium iodide from pentavalent I is scarcely conceivable, and this difficulty is compounded by the fact that over 50 salts were prepared by Hein, *et al.*,[4] from I with organic and inorganic anions, of which upwards of 40 were formulated as *tetraphenyl*chromium derivatives. The remainder were written as pentaphenylchromium salts containing varying amounts of solvent of crystallization.

The second set of anomalies recognized at the time consisted of the uniform light absorption properties of these polyphenylchromium compounds. They were found to have similar color in the visible range (orange to yellow) and to exhibit similar chromium band absorption near 350 mμ in the ultraviolet region. In the only previous independent work on the Hein compounds Klemm and Neuber[5] measured the magnetic susceptibilities of representatives of each "valence class" and found them all to possess one free electron, *i.e.*, paramagnetic to the extent of 1.72 ± 5% Bohr magnetons. These authors suggested, therefore, that all of Hein's compounds were in the same valence state and that this state was probably Cr^V. We have confirmed this magnetic property also with our sample of II.[6] Unquestionably these observations cast serious doubt on the formulation of 5, 4 and 3 phenyl groups attached covalently to chromium.

The difficulties attending the synthesis of the polyphenylchromium compounds by the Hein procedure induced us to attack the structural problem imposed by degradation methods. At this stage

(1) The subject matter of this paper was presented in 1954, Abstr., 126th Meeting, Amer. Chem. Soc., p. 29-0, Sept., 1954, and also submitted to THIS JOURNAL as a preliminary Communication. The paper, however, was rejected by the referees chiefly on the grounds of insufficient evidence for our (with Professor L. Onsager) proposal of the π-complexed biconoidal structure. In 1955 a portion of our results was published in abbreviated form, *Yale Sci. Mag.*, **29**, 14 (1955); *Angew. Chem.*, **67**, 282 (1955); and in more complete form by F. A. Cotton, *Chem. Revs.*, **55**, 551 (1955). A series of lectures on this subject were also presented during June-July, 1955, at Heidelberg, Tübingen, Munich and Zürich, *Handbook, XIVth International Congress of Pure and Applied Chemistry*, p. 262. We have been informed (private discussion with Dr. E. O. Fischer) that the preparation of bis-benzenechromium from benzene, E. O. Fischer and W. Hafner, *Z. Naturforsch.*, **10b**, 665 (1955), was first realized after the above dates. This chronology is given here in an attempt to reduce the confusion which has arisen and is not to be construed as a detraction from the elegant method of preparation and structural proofs devised by Dr. Fischer and his colleagues.

(2) Taken from the doctoral dissertation of M. Tsutsui, Yale University, 1954, and supported by Contract No. DA-19-059-ORD-1494 between the Office of Ordnance Research, U. S. Army, and Yale University.

(3) Monsanto Chemical Co., Dayton 7, Ohio.

(4) (a) N. V. Sidgwick, "The Chemical Elements and Their Compounds," Oxford Univ. Press, New York, N. Y., 1950, p. 1001. For a modern review of Fr. Hein's original work see (b) F. A. Cotton, *Chem. Revs.*, **55**, 551 (1955); and also (c) H. J. Emeleus and J. S. Anderson, "Modern Aspects of Inorganic Chemistry," 1st Ed., D. Van Nostrand Co., Inc., New York, N. Y., p. 4[illegible]

(5) W. Klemm and A. Neuber, *Z. anorg. Chem.*, **227**, 261 (1936).

(6) We are indebted to Mr. R. Johnston of the Naval Research Laboratory, Wash., D. C., for this determination.

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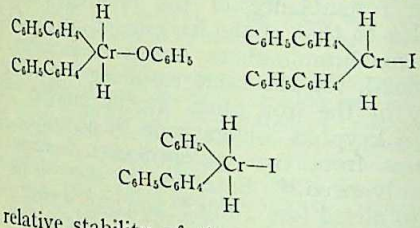
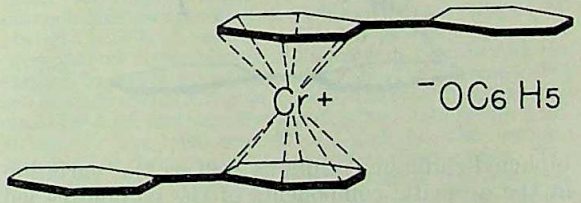
it was discovered that biphenylmercury was reduced smoothly in ether to benzene by lithium aluminum hydride without formation of biphenyl.[7] A similar reduction of "pentaphenylchromium bromide" demonstrated its grossly impure nature, for the organic product consisted of benzene, biphenyl, terphenyl and higher boiling polyphenyls. Reductions of I, II and III were next performed on a semi-quantitative basis owing to the small amounts of these substances available. "Tetraphenylchromium" iodide II on reduction gave biphenyl as the *sole* organic product and this in the amount of *two* mole equivalents. The degradation of "triphenylchromium" iodide III gave *both* benzene and biphenyl, each estimated to be present in a 1:1 mole ratio. Finally, "pentaphenylchromium hydroxide" I was reduced to a mixture of biphenyl and *phenol*, the molar ratio of which amounted to 2:1. Failure to detect benzene spectroscopically either from the hydride reduction of I or II clearly rendered the Hein formulation inadmissible. Also, the reappearance of phenol as a product from I, as it was in the reaction of I with potassium iodide, compelled the conclusion that I is a phenoxide rather than an hydroxide.

The pentavalent structures suggested by Klemm and Neuber[5] were next considered in the light of the new evidence. Rationalization of these structures with the experimental facts led to the following hydride structures for I, II and III. However,

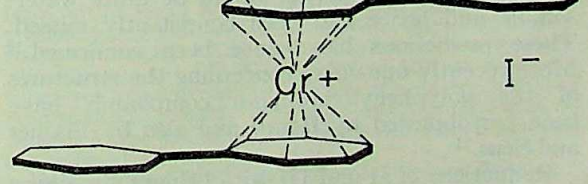


the relative stability of these compounds toward water, dilute acid and base, not being a typical property of metal–hydride bonds, invited considerable scepticism; and so an isotopic reduction method for testing the Klemm–Neuber structures was devised. A sample of II was reduced with lithium aluminum hydride and then hydrolyzed with deuterium oxide. As previously found, no benzene was formed; but the biphenyl was collected and burned to carbon dioxide and water. This water was reduced with zinc to hydrogen which was observed to be free of deuterium in the mass spectrometer.[8] This result of course eliminated a reduction mechanism which involved a displacement of biphenyl anion by aluminum hydride from chromium. But when II was reduced with lithium aluminum deuteride, the biphenyl produced contained 5.0 D% or one atom of deuterium per molecule of II or 2 molecules of biphenyl. It was supposed that the Klemm–Neuber structure for II would lead to biphenyl containing 10 D% or one atom of deuterium per molecule of biphenyl if reductive attack occurred on carbon as the previous experiment indicated. Deuteride reduction of III gave biphenyl containing 6.7 (6.55) D%,[9] or two-thirds of the amount predicted for the Klemm–Neuber structure. The benzene deuterium content was not determined. A sample of reagent biphenyl was subjected to the action of lithium aluminum deuteride in ether under the same conditions of time and temperature without becoming deuterated. While these isotopic results did not unequivocally dispose of the hydride structures, they did render them most unlikely.

In the course of a number of discussions which ensued after the results of the lithium aluminum hydride reductions became known, Professor L. Onsager proposed the bis-aromatic structure for II as shown below. It was reasoned that the chromium atom, atomic number 24, requiring 12 electrons to fill its 4s, 3d and 4p shells to reach the stable krypton level, could do so by the donation of 6 π-electrons each from two aromatic rings, thus becoming a bis-aromatic-chromium[0] complex of considerable stability. It was recalled too that Hein in his early work had reduced both I and II



I



II

electrolytically in liquid ammonia to, strangely enough, the *same* compound, formulated as "*tetraphenylchromium*." Also, III could be reduced, both electrolytically and by sodium metal in the same solvent, to "*triphenylchromium*." The corresponding cation, therefore, would arise by the loss of one electron, leaving the chromium atom with one unpaired electron and therefore paramagnetic. At the outset we were reluctant to believe that aromatic π-electrons could be donated in this manner and that the loss of resonance energy accompanying this process would be offset by the stability associated with the inert-gas configuration achieved. However, the weight of the

(7) In footnote 2, p. 569, of reference 4b there is a statement of misconception of the purpose of this experiment. It was meant to show that of the polyphenylchromium compounds possessed chromium–phenyl covalent bonds, such as exist in biphenylmercury and as suggested by Hein, then benzene would be produced by this ionic reduction and biphenyl could not arise by a free radical process. The importance of this observation, therefore, lay in testing the Hein formulation and not in determining others. The fact that the experiment showed the absence of biphenyl groups in biphenylmercury was gratuitous.

(8) We wish to express our appreciation for the assistance given us by Mr. J. Graff of the Department of Biochemistry, and by Dr. J. H. Wang, Department of Chemistry, Yale University, in the mass determinations and spectrometric determinations.

(9) The figure given here in parentheses was obtained several weeks after the first result with the remaining portion of biphenyl.

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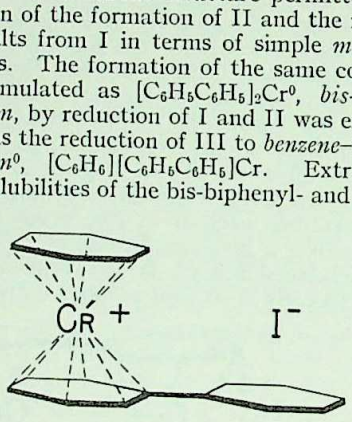
TABLE I

	Atomic no.	Group	1	2		3			4		
		Subgroup	*s*	*s*	*p*	*s*	*p*	*d*	*s*	*p*	
Cr	24		2	2	6	2	6	5	1		2
Mo								(5)	(1)	(6)	
W											
Fe	26		2	2	6	2	6	6	2		2
Ru								(4)		(6)	
Os											
Ni	28		2	2	6	2	6	8	2		2
Pd								(2)		(6)	
Pt											
Kr	36		2	2	6	2	6	10	2	6	

evidence became compelling. Reformulating I in terms of the bis-arene structure permitted an explanation of the formation of II and the numerous other salts from I in terms of simple *metathetical* reactions. The formation of the same compound, now formulated as $[C_6H_5C_6H_5]_2Cr^0$, *bis-biphenyl-chromium*, by reduction of I and II was explicable, as well as the reduction of III to *benzene–biphenyl–chromium*^{0}, $[C_6H_6][C_6H_5C_6H_5]Cr$. Extrapolation of the solubilities of the bis-biphenyl- and benzene-



III

biphenyl-chromium^I salts as well as the variation in the aromatic components of the complexes led to the prediction that the bis-benzene-chromium^I cation had also been formed in the course of the Grignard reaction, that it would be quite water-soluble and hence had been consistently missed. These predictions have since been confirmed.[10] More recently our views concerning the structures of the polyphenyl-chromium compounds have been corroborated by Hein[11] and also by Fischer and Seus.[11]

Reductions of II and III with lithium aluminum deuteride gave biphenyl in each case containing one-half and two-thirds of the deuterium, respectively, expected from a displacement by aluminum deuteride on carbon in the hydride structures. If, however, the assumption is made that the aromatic rings of the bis-arene structures for II and III are equivalent in reactivity and that the attack of one deuteride ion on any one aromatic ring is sufficient to cause the reductive collapse of the complex, then the fractional results are understandable on a statistical basis. Thus, a random collision with any of the four phenyl groups of II by a deuteride ion collapses the complex with expulsion of a non-deuterated biphenyl molecule and the formation of one monodeutero-biphenyl molecule per molecule of II with evolution of hydrogen. Since only biphenyl was measured for deuterium from the reduction of III, random distribution of deuterium by indiscriminate deuteride reduction at either benzene or biphenyl sites in the complex introduces deuterium two out of three effective reactions in biphenyl, or 6.7 D% in biphenyl. In terms of a nucleophilic displacement mechanism, this interpretation requires of course a 100% isotope effect as well as reliance on the deuterium analyses.[9] However, as long as the reactions of odd-electron, aromatic complexes are incompletely explored, an unforeseen reaction seems not as significant as an unexpected inhibition.

The resemblance of the bis-arene-chromium^I complex to that of the ferricinium ion, and of the bis-arene-chromium^0 to ferrocene, is more than superficial, for the same reasoning regarding the ability of the iron atom, atomic number 26, to reach a krypton configuration by accepting 10 π-electrons from two cyclopentadienyl anions has been advanced.[12] Extension of these considerations to nickel (see Table I) and its 8 π-electron requirement for a stable krypton configuration permits the prediction of the eventual capture of cyclobutadiene in a complex such as bis-cyclobutadiene-nickel^0 or its cation.[1] Longuet-Higgins and Orgel[13] have now applied the molecular orbital theory to the possible existence of such a complex with favorable results. More broadly, this new concept of transition metal complexes may be expected to lead to significant advances in the theory of catalysis.

Experimental[14]

"Pentaphenylchromium Bromide."[15]—Phenylmagnesium bromide solution prepared from 25 g. of magnesium, 150 g. of bromobenzene and 200 ml. of ether was treated with 40 g. of anhydrous chromium trichloride[16] according to Hein from which *ca.* 12 g. of orange-brown resinous solid was obtained from the chloroform layer. In only 3 out of over 50 runs did we obtain "raw bromide" from which "pentaphenylchromium hydroxide" could be prepared. We attribute these failures to our subsequent care in excluding oxygen from the Grignard flasks (no phenol formed). Many varia-

(10) H. H. Zeiss and W. Herwig, THIS JOURNAL, **78**, 5959 (1956).
(11) Fr. Hein, *Chem. Ber.*, **89**, 1816 (1956); E. O. Fischer and D. Seus, *ibid.*, **89**, 1809 (1956).
(12) E. Ruch and E. O. Fischer, *Z. Naturforsch.*, **7b**, 676 (1952).
(13) H. C. Longuet-Higgins and L. E. Orgel, *J. Chem. Soc.*, 1969 (1956).
(14) All m.p.'s are corrected. Combustion analyses were performed by the Schwarzkopf Microanalytical Laboratories, Woodside 77, N. Y.
(15) Fr. Hein, *Ber.*, **54**, 1905 (1921).
(16) Fr. Hein, *ibid.*, **54**, 2708 (1921).

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tions of time, temperature, reagent concentrations, added reactants and chromium trichloride purity were tried without success. In one run out of 3 using chromyl chloride in place of the trichloride, we obtained "raw bromide" of the "correct" composition.

"Pentaphenylchromium Hydroxide."[15]—The "raw bromide" (27 g.) was transformed into the "hydroxide" in ethanol with potassium hydroxide (7 g.), which was crystallized from water as large, deep orange plates, 2 g. These crystals were very hygroscopic and lost water of hydration when dried *in vacuo* over Drierite. Their color changed too to a deep olive-gray, m.p. 102–104°, as described by Hein. In water the orange color of the crystals returned and they absorbed at 248 and 345 mμ in the ultraviolet region in 95% ethanol.

"Tetraphenylchromium" Iodide.[16]—A solution of 0.05 g. of "pentaphenylchromium hydroxide" in chloroform was shaken with 1 ml. of a saturated solution of potassium iodide in water, and the chloroform solution was then washed with water. Petroleum ether was now added to the chloroform solution to incipient turbidity, and the mixture was then put aside in the cold. The orange-yellow flakes of "tetraphenylchromium" iodide (0.005 g.) which had crystallized were separated by centrifugation and washed thrice with ether, m.p. 160–165°. These were crystallized from chloroform as orange-red plates containing solvent of crystallization and this chloroform was removed by heating at 55° *in vacuo* for 7 hr. The pure iodide, m.p. 177–178°, was yellow-orange in color and absorbed at 250 and 342 mμ (log ε 4.01 and 3.39, resp., 0.0001 *M* in ethanol).

Anal. Calcd. for $C_{24}H_{20}ICr$: C, 59.13; H, 4.52; I, 26.07; Cr, 10.68. Found: C, 58.82; H, 4.46; I, 26.13; Cr, 10.58.

The *density* of the iodide was determined by suspending the solid in a mixed solution of iodobenzene and carbon tetrachloride: 1.6170 (16°). Its *molecular weight* was determined cryoscopically using *m*-dinitrobenzene as solvent and was found to be 482 (487) in dilute solution, *i.e.*, 0.00233 g. of iodide in 0.04898 g. of solvent. This value was reproducible so long as solutions of comparable concentration were employed. However more concentrated solution gave erratic results as would be expected for ionic compounds.

"Triphenylchromium" Iodide.[17]—One hundred ml. of the water layer remaining after the filtration of "pentaphenylchromium hydroxide" described above was concentrated to 50 ml. by freeze-drying (Hein performed this concentration at 40–45° also *in vacuo*). After standing in the refrigerator for one week, this solution had deposited red prisms which were separated by centrifugation and recrystallized from ethanol, m.p. 117–119°, and corresponding to the compound designated by Hein as "*pentaphenylchromium carbonate*." Four ml. of the deep-red filtrate was evaporated to dryness under freeze-dry conditions, leaving 0.82 g. of a yellow-brown, brittle resin whose chromium analysis corresponded to a trihydrate of "*triphenylchromium*" *hydroxide*. A solution of 0.75 g. of this hydroxide in 30 ml. of chloroform and 15 ml. of water was shaken with 2 ml. of a saturated aqueous solution of potassium iodide, and the aqueous layer was then extracted thoroughly with chloroform. The combined chloroform extracts, now red in color, were washed with water, poured over Drierite, filtered and then brought to turbidity with petroleum ether. After standing one week in the cold, the solution had deposited a red solid which after four recrystallizations from chloroform with tetrahydrofuran gave orange-yellow plates, m.p. 110–112°, when dried *in vacuo* at 60° for 9 hr. This "triphenylchromium" iodide is considerably more soluble in water than "tetraphenylchromium" iodide and absorbs weakly at 270 mμ and strongly at 343 mμ in 95% ethanol.

Anal. Calcd. for $C_{18}H_{16}ICr$: Cr, 12.64. Found: Cr, 11.88.

Its molecular weight was found to be 430 (theory 411) by cryoscopic measurement in *m*-dinitrobenzene. Fifteen similar recrystallizations of the iodide raised the m.p. to 146–148°, but the infrared spectrum of the iodide remained essentially unchanged. Analysis and molecular weight of the iodide, m.p. 112°, indicated that it was a monohydrate, but this was not confirmed.

Anal. Calcd. for $C_{18}H_{16}ICr \cdot H_2O$: C, 50.5; H, 4.24; I, 29.6; Cr, 12.1. Found: C, 50.6; H, 4.05; I, 27.3; Cr, 11.9.

(17) F. Hein, *Ber.*, **54**, 2727 (1921).

$LiAlH_4$ Reduction of "Tetraphenylchromium" Iodide.—To a solution of 0.50 g. of lithium aluminum hydride in 50 ml. of ether previously distilled from $LiAlH_4$ was added 0.0102 g. of "tetraphenylchromium" iodide. Vigorous reaction occurred at the surface of the ether-insoluble iodide with evolution of gas, presumably hydrogen, and complete disappearance of the iodide within a few minutes. The solution became brown and, after standing for 4 hr. in the cold, it turned clear with the deposition of a white, amorphous precipitate. The cold reaction mixture was then hydrolyzed with 0.5 ml. of water, the ether layer was decanted and the precipitate was dissolved in dilute hydrochloric acid. The acid solution was extracted with ether, and the ether extracts were distilled in a simple distilling flask. The residue consisted of pure biphenyl whose identity was confirmed by its ultraviolet absorption, determined in ether and a 10-cm. cell path, to be at 248 mμ. The distilled ether likewise showed absorption at 248 mμ and contained biphenyl in the amount of 0.0027 g. as determined from the optical density of the solution. A total of 0.0049 g. was thus determined, or 76% of the theoretical amount based on two molecules of biphenyl per mole of the iodide. Both the absence of benzene and amount of biphenyl produced in this reduction precluded a Klemm–Neuber formulation for the iodide such as bis-phenyl–biphenyl-chromium iodide.

$LiAlH_4$ Reduction of "Triphenylchromium" Iodide.—The iodide (0.2034 g.) was reduced in one l. of ether with 1.00 g. of $LiAlH_4$ by the general procedure just described. However, in this case the ethereal solution was distilled through a 12″ Vigreux column, for it was found that while ordinary distillation permitted co-distillation of biphenyl with the ether, the column perfectly inhibited this complication. The ether distillate was free, therefore, of biphenyl but was now found to contain benzene in the amount of 0.0010 g. by spectrophotometric determination. The residue from the distillation amounted to 0.0480 g. and was shown to be biphenyl both by sublimation and mixed m.p. and by ultraviolet absorption. Based on the benzene-biphenyl-chromium iodide structure these yields constitute 63% of biphenyl and 3% of benzene. The low recovery of benzene prompted us to determine the maximum efficiency of the method by treating a solution of 0.0135 g. of benzene in 585 ml. of ether with 0.150 g. of $LiAlH_4$, allowing the mixture to stand for 8 hr. and then hydrolyzing the solution with 1 ml. of water. The solids were filtered and the ether solution was distilled through the Vigreux column used above. The amount of benzene recovered as determined spectrophotometrically was 0.0041 g. or 31%. In a similar experiment freshly prepared biphenylmercury (0.0144 g.) was reduced with 0.080 g. of lithium aluminum hydride in 70 ml. of ether over a period of 4 hr. The solution was then hydrolyzed with a small amount of water and filtered, and the precipitate was dissolved in dilute hydrochloric acid and extracted with ether. The combined ether extracts were distilled through the 12″ Vigreux column, and the ether distillate was found to contain 0.0020 g. of benzene, or 32% of the theoretical amount. The small quantity of residue remaining in the distillation flask contained neither biphenyl nor biphenylmercury.

$LiAlH_4$ Reduction of "Pentaphenylchromium Bromide."—To a solution of 5.0000 g. of lithium aluminum hydride in 5 l. of ether was added 1.000 g. of "raw bromide" with evolution of gas. Shortly after the addition of the sample, it dissolved with a development of brown color in the ether solution. After 8 hr. in the refrigerator and occasional shaking, the solution became clear and yielded a white precipitate. This mixture was hydrolyzed with 20 ml. of water in the cold, the ether layer was decanted and the precipitate was dissolved in dilute hydrochloric acid and extracted with ether. The ether solutions were next distilled from an ordinary distilling flask, and the residue was separated into methanol-soluble (0.3108 g.) and insoluble (0.065 g.) fractions. A portion of the former fraction was first sublimed and then crystallized from methanol to give pure biphenyl, m.p. 68–69°, which melted undepressed with an authentic sample and which absorbed at 248 mμ in ether. The methanol-insoluble fraction was recrystallized from 95% ethanol as plates of *p*-biphenylbenzene, m.p. 210–212°, 0.007 g., melting undepressed with a reagent sample. The ether distillate now amounting to 4240 ml. was redistilled through the 12″ Vigreux column, leaving 0.3246 g. of biphenyl as residue. The ether distillate contained 0.0259 g. of benzene as determined spectroscopically.

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$LiAlH_4$ Reduction of "Pentaphenylchromium Hydroxide."—The "hydroxide" (0.0031 g.) was reduced with 0.020 g. of $LiAlH_4$ in 40 ml. of ether according to the general procedure previously described in detail. The reaction mixture was hydrolyzed with 0.5 ml. of water after the solution had come clear with the formation of the white precipitate. This precipitate, after separation by filtration, was dissolved in 1 ml. of dilute hydrochloric acid. This solution was saturated with sodium chloride and then extracted with 20 ml. of ether. The ether extract was combined with the ether filtrate, this solution washed with 3% sodium hydroxide twice, and the resultant ether solution was then distilled through the Vigreux column. No benzene was detected in the distillate, but biphenyl was left as residue, 0.0010 g., or 47% of the theoretical amount based on the bis-biphenyl-chromium phenoxide formulation. The alkaline solution was acidified and extracted exhaustively with ether. This ether solution absorbed at 273 mμ and was estimated to contain 0.0003 g. of phenol, or 47% of the theoretical amount.

$LiAlD_4$ Reduction of "Tetraphenylchromium" Iodide.—A solution of 0.0945 g. of the iodide was reduced with 0.200 g. of lithium aluminum *hydride* in 500 ml. of ether for 7 hr. and then hydrolyzed with 2 g. of *deuterium oxide*. After handling this mixture as already described, the ether solution was distilled, and no benzene was detected in the distillate. Biphenyl, 0.0122 g., was obtained by sublimation of the residue, 0.0310 g. (52%) and contained 0.31 D%.[8]

In a completely similar experiment 0.0520 g. of the iodide was reduced with 0.1500 g. of lithium aluminum *deuteride* in 260 ml. of ether. This mixture was hydrolyzed with 1.5 g. of deuterium oxide. Again, no benzene was found in the ether distillate, and biphenyl, containing 5.0 D%,[8] was obtained, 0.0083 g. , by the sublimation of the residue, 0.021 g. (64%), from the distillation.

Biphenyl (100 mg.) was treated with 500 mg. of lithium aluminum *deuteride* in 500 ml. of ether and hydrolyzed with 2.0 ml. of water. The sublimed biphenyl product contained 0.00 D%.[8]

$LiAlD_4$ Reduction of "Triphenylchromium" Iodide.—This iodide (0.300 g.) was reduced with 0.900 g. of lithium aluminum *deuteride* (97.8%) in 1500 ml. of ether and the solution hydrolyzed with 5 ml. of deuterium oxide. The ether solutions from the work-up procedure were distilled through the Vigreux column leaving 0.0890 g. of residue (79%) which gave 0.0470 g. of sublimed biphenyl. The ether distillate contained 0.0162 g. of benzene by spectrophotometric analysis, or 28% of the theoretical amount based on the benzene-biphenyl-chromium iodide structure. The biphenyl obtained above contained 6.7 D%. In a duplicate run made two weeks later the content was found to be 6.55 D%.[8]

DAYTON 7, OHIO

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, DOJINDO & CO., LTD., JAPAN]

Infrared Absorption Spectra of *o*-Hydroxyazobenzene and its Metal Chelate Compounds

BY KEIHEI UENO

RECEIVED DECEMBER 17, 1956

The infrared absorption spectra of *o*-hydroxyazobenzene and its Cu, Ni and Co chelates are reported. Disappearance of the OH band in 3300 cm.$^{-1}$ region and the bathochromic shift of the carbonyl band in 1600 cm.$^{-1}$ region indicate the presence of a resonating system involving the azo linkage and the *o*-hydroxy group. The carbonyl band and the azo band shift to lower frequencies in the metal chelates, and the extent of shift is in the order of Cu > Ni > Co.

Introduction

In connection with an infrared absorption study of polyazobenzenes,[1] an investigation of a series of *o*-hydroxy azo compounds has been undertaken. In spite of the need for fundamental information on infrared absorption spectra of aromatic azo compounds, very little work has been reported in this field. It is the purpose of this investigation to study the infrared absorption spectra of *o*-hydroxyazobenzene, the simplest of the *o*-hydroxy aromatic azo compounds, and its Cu, Ni and Co chelates. The result of such a study should be of importance in connection with infrared analysis of *o*-hydroxy azo dyes of more complicated structures.

Experimental

Preparation of Samples.—*o*-Hydroxyazobenzene was prepared by coupling diazotized aniline with phenol according to the method of Bamberger[2] and was purified *via* copper chelate and recrystallized from ethanol (m.p. 82.5°).

The metal chelates were prepared by refluxing an ethanol solution of ligand and metal acetate for 10 minutes. After cooling, the metal chelates separated as needles, which were then recrystallized from ethanol. Although an attempt was made to prepare the cadmium chelate, only the ligand was recovered. The copper chelate was most easily prepared, while the nickel and cobalt complexes were prepared with increasing difficulty. The metal content of these chelate compounds was determined by complexometric titration after decomposing the samples with fuming nitric acid in a sealed tube,[3] and all the chelate compounds were found to contain 2 moles of ligand per mole of metal. The properties and the result of analyses are shown in Table I.

TABLE I

METAL CHELATES OF *o*-HYDROXYAZOBENZENE

Metal chelated	Color	Metal, % Calcd.[a]	Found
Cu(II)	Brown	14.80	14.55
Ni(II)	Dark green	13.81	14.02
Co(II)	Dark blue	13.87	14.11

[a] Metal contents were calculated from the formula $(C_{12}H_9ON_2)_2M$, where M represented the metal chelated.

Infrared Spectra.—A Perkin–Elmer model 21 double beam spectrophotometer equipped with sodium chloride optics was used for the determination of infrared spectra, and samples were run both as Nujol mulls and as potassium bromide disks. For all the samples, these procedures gave almost identical spectra.

Results and Discussion

The significant absorption bands of these compounds below 1700 cm.$^{-1}$ are shown in Table II, along with assignments to group vibrations where possible.

The only absorption band observed in the 3300 cm.$^{-1}$ region is one due to the characteristic aromatic C–H stretching vibration at 3030 cm.$^{-1}$. This band is stable in position as well as in intensity when one goes from the ligand to the metal che-

(1) K. Ueno, THIS JOURNAL, **79**, in press (1957).

(2) E. Bamberger, *Ber.*, **33**, 3191 (1900).

(3) P. J. McCarthy, R. J. Hovey, K. Ueno and A. E. Martell, THIS JOURNAL, **77**, 5820 (1955).

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TABLE II

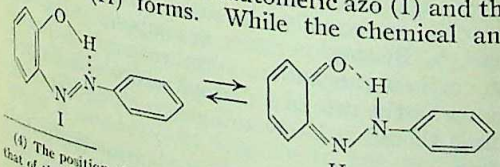
INFRARED ABSORPTION SPECTRA OF *o*-HYDROXYAZOBENZENE AND ITS METAL CHELATES

Azobenzene	*o*-Hydroxyazobenzene Ligand	Metal chelates Cu(II)	Ni(II)	Co(II)	Assignments
	1610s				C=O of H-bonded ring
		1602s	1600s	1603s	Phenyl
1575m	1596s	1540m	1535w	1531w	C=O of metal chelate ring
					Phenyl
1485s	1490s	1490w	1490w		Phenyl
	1471s	1474s	1473s	1475s	
1455s	1455s	1460s	1460s	1456s	
1385w	1418s	1400s	1396s	1390s	N=N
	1363m	1341w	1352w	1358w	
	1320w	1330m	1329s	1330s	
1298s	1305w	1296s	1300m	1301m	C–O–H bending of H-bonded ring
	1283s				
	1272s				
	1235w	1252s	1260m	1253w	
1220m	1214m	1212w	1220w	1215w	Phenyl
	1182m	1184m	1185w	1180m	
1156m	1157w	1158w	1157w	1150w	Phenyl
1150m	1143m	1145m	1142s	1138s	
	1111m	1120w	1119w	1119w	*o*-Disubst. phenyl
	1106m				
1069s	1067w	1070w	1070w	1075w	Phenyl
	1026w	1020w	1020w	1023w	*o*-Disubst. phenyl
1018m	1016w			1000w	
997m	997w				
981m		945w	952w	947m	
924s	935w	933w		917w	
	912w	907w		900w	
845w	855w	862w	871w	865w	
		838w		842w	
	807m		800w	794m	Phenyl
772s	770s	787w		760s	
	765s	758m	758s	757s	
	750s	755m		751s	
		750m			
	735m	744s	743s	741s	*o*-Disubst. phenyl
684s	675s	684s	688s	690s	Phenyl
		660w	664w	661m	

lates, indicating that it is due purely to the aromatic C–H stretching vibration.

It is striking that no other well-defined band can be found in and around the 3300 cm.$^{-1}$ region on the ligand, since an additional band due to O–H stretching vibration would be expected in this region, as is true of the corresponding *para* derivative, which has a strong band at 3150 cm.$^{-1}$.[4] The absorption due to O–H stretching vibration is known to shift to the lower frequency region and to decrease in intensity as the result of hydrogen bonding. Although a very weak band is found at around 2300 cm.$^{-1}$ on the ligand, it cannot be due to O–H bonding, because the corresponding band with increasing intensity is found on all metal chelates, in which no O–H bonding exists.

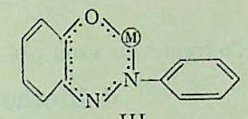
There have been many discussions on the structure of *o*-hydroxyazo compounds,[5] since the compounds can have the tautomeric azo (I) and the hydrazone (II) forms. While the chemical and



I II

absorption spectrophotometric evidence on the *o*-hydroxyazo compounds in solution favor the hydrazone structure,[6] it has been shown that *o*-hydroxyazobenzene appears in the azo form only, irrespective of the solvent.[7]

In accordance with these observations Hadzi[8] concluded, in his investigation on the *o*-hydroxyazo compounds, that the absorption band due to the O–H stretching vibration of *o*-hydroxyazobenzene was, owing to its intramolecular hydrogen bonding, too weak and too broad to be observed. A broad and rather strong band with a maximum at 1610 cm.$^{-1}$ is observed in the ligand, *i.e.*, *o*-hydroxyazobenzene, but is shifted to lower frequencies in its metal chelate compounds. This absorption probably is due to the C=O stretching vibration of the hydrogen bonded ring system as shown by the formula II. Although the free carbonyl band is expected at around 1700 cm.$^{-1}$, such a bathochromic shift is often observed in hydrogen-bonded ring systems.[9] In the metal chelates, this band is observed at around 1531–1540 cm.$^{-1}$, as the result of involvement of the C=O . . . linkage in the metal chelate ring as shown by formula III.



III

The shift of this band from the original position of the ligand probably is due to the increased mass of the metal attached to the oxygen atom relative to that of the proton and also due to the electronegativity of the metal ions.

Although no quantitative data are available on the stability of the metal chelates of *o*-hydroxyazobenzene, the ease of metal chelate formation and the stability order of metals[10] would indicate that the stability of the metal chelates of *o*-hydroxyazobenzene decreases in the order of Cu > Ni > Co. It may also be noted that the order of decreasing frequency of the band arising from the carbonyl linkage of the metal chelates is parallel to the order of decreasing stability.

Similar shifts of the carbonyl band by metal chelation also were reported for salicylaldehyde and its metal chelates.[9b] However, in these cases, the extent of shift was found to parallel the order of increasing stability of the salicylaldehyde metal chelates. It is not clear why the carbonyl band shifts with increasing stability in one case and with decreasing stability in other case. However, the results of this research indicate that the shift of carbonyl band by metal chelate formation does not result simply from a change of bond order but result from more complicated effects such as the mass of metal ions and the formation of π-orbitals in the

(4) The position of the band at 315 cm.$^{-1}$ is somewhat lower than that of the free O–H absorption band which appears at around 3500 cm.$^{-1}$. The details will be discussed elsewhere along with those of other polyazobenzenes.

(5) H. Gilman, "Organic Chemistry," Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1953, p. 265.

(6) Fierz-David, *et al.*, *Helv. Chim. Acta*, **29**, 1718 (1946).

(7) R. Kuhn and F. Bär, *Ann.*, **516**, 143 (1935).

(8) D. Hadzi, *J. Chem. Soc.*, 2143 (1956).

(9) (a) R. S. Rassmussen, D. D. Tunicliff and R. R. Brattain, THIS JOURNAL, **71**, 1068 (1949); (b) L. J. Bellamy and R. F. Branch, *J. Chem. Soc.*, 4491 (1954).

(10) The stability of complexes of bivalent metal ions generally follows the order of Cu > Ni > Co, irrespective of the nature of the ligands involved, D. P. Mellor and L. Maley, *Nature*, **159**, 370 (1947); 161, 436 (1948).

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chelate ring involving the d-orbitals of the metal ion.

Another considerable change of the spectra resulting from metal chelate formation is found in the bands at 1283 and 1272 cm.$^{-1}$. Although the 1283 cm.$^{-1}$ band appears as a shoulder on the main band at 1272 cm.$^{-1}$, both bands are rather strong and are missing in the metal chelates. Hadzi[8] assigned the band at 1272 cm.$^{-1}$ to the in-the-plane bending mode of the C–O–H group. The fact that the corresponding band is missing in the metal chelates supports this assignment, and either one of these two bands is possibly due to the C–O–H group of the ligand.

No conclusive assignment of absorptions due to the azo linkage has been reported in the literature. Le Fèvre[11] and his co-workers have investigated some 43 aromatic diazonium and azo compounds and found common absorption bands at around 1406 and 1577 cm.$^{-1}$. The main difficulty in the assignment of a frequency to the azo linkage is that the absorption frequency of N=N stretching vibration would overlap with other absorptions such as those of the aromatic ring which are usually of strong intensity.

Of the absorption bands due to the azo linkage, a band corresponding to 1405 cm.$^{-1}$ was found in the polyazobenzenes which we have investigated,[1] and it is believed that this band can be assigned to the azo linkage with certainty. For azobenzene and *o*-hydroxyazobenzene, this absorption band is found at 1395 and 1418 cm.$^{-1}$, respectively. For the metal chelate compounds of *o*-hydroxyazobenzene, this band shifts to lower frequencies as shown in the Table II. The extent of shift is again found to be parallel to the order of decreasing stability of metal chelate compounds.

Acknowledgment.—The author wishes to express his sincere appreciation to Prof. A. E. Martell of Clark University, Worcester, Mass., who so generously carried out the measurement of infrared spectra.

KUMAMOTO-SHI, JAPAN

(11) R. J. W. Le Fèvre, M. F. O'Dwyer and R. L. Werner, *Australian J. Chem.*, **6**, 341 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF FLORIDA STATE UNIVERSITY]

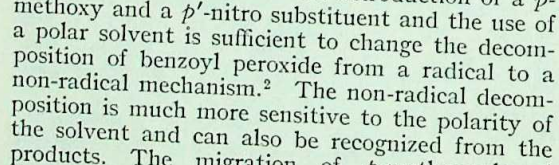
4-Methoxy-3′,5′-dinitrobenzoyl Peroxide[1]

BY JOHN E. LEFFLER AND CONSTANTINE C. PETROPOULOS

RECEIVED DECEMBER 20, 1956

The decomposition of 4-methoxy-3′,5′-dinitrobenzoyl peroxide is accelerated by a shift to a more polar solvent, by acids, and by 1,3,5-trinitrobenzene. Its behavior is compared with that of other diacyl peroxides.

The combined effect of the introduction of a *p*-methoxy and a *p*′-nitro substituent and the use of a polar solvent is sufficient to change the decomposition of benzoyl peroxide from a radical to a non-radical mechanism.[2] The non-radical decomposition is much more sensitive to the polarity of the solvent and can also be recognized from the products. The migration of *p*-methoxyphenyl from carbon to oxygen in the polar decomposition reduces the yield of anisic acid and its esters and in the case of thionyl chloride as a solvent produces the rearrangement or carboxy-inversion product (II).[2,3] The polar decomposition is accelerated by acids as well as by polar solvents.



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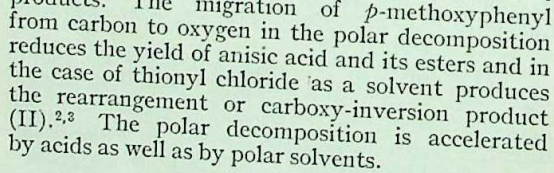

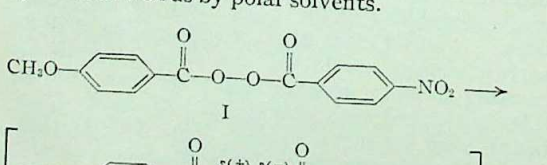

II

Similar experiments have now been done with 4-methoxy-3,′5′-dinitrobenzoyl peroxide. This peroxide is even more sensitive to solvent changes, but the reaction is less clean cut.

The Effects of Substituents and Solvents.—Table I summarizes the combined effects of the various substituents and solvents on the first-order rate constants for the peroxide decomposition; the results are remarkably different from those obtained with symmetrical peroxides. The effects of solvent changes or of symmetrical *meta* or *para* substitution on the rate of homolysis of benzoyl peroxide are usually less than one order of magnitude. For example in acetophenone at 80° the rate constants range from 1.46×10^{-3} min.$^{-1}$ for bis-(*p*-cyanobenzoyl) peroxide to 9.32×10^{-3} min.$^{-1}$ for bis-(*p*-methoxybenzoyl) peroxide.[4] In the solvents benzene, acetophenone, dioxane and styrene the first-order constants of a given benzoyl peroxide are usually the same within a factor of two.[4-6] Benzoyl peroxide decomposes at the same rate in benzene and in nitrobenzene.[7] A drastic change in the rate of a diaroyl peroxide decomposition is therefore likely to mean a change in mechanism.

In benzene the 4-methoxy-4′-nitro substitution

(1) This work was supported by a Frederick Gardner Cottrell grant from the Research Corporation.

(2) J. E. Leffler, THIS JOURNAL, **72**, 67 (1950).

(3) D. B. Denney, *ibid.*, **78**, 590 (1956).

(4) A. T. Blomquist and A. J. Buselli, *ibid.*, **73**, 3883 (1951).

(5) C. G. Swain, W. H. Stockmayer and J. T. Clarke, *ibid.*, **72**, 5426 (1950).

(6) W. Cooper, *J. Chem. Soc.*, 3106 (1951).

(7) E. G. Bolton, J. Hardwick and J. E. Leffler, THIS JOURNAL, **68**, 1686 (1946).

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Table I

Benzoyl Peroxide Decomposition Rate Constants

in sec.$^{-1}$ × 10^6

Substituents	Solvent: Benzene	Nitrobenzene
None	32.8 at 79.8°[a]	32.8 at 79.8°[a]
	7.8 at 70°[b]	
	0.44 at 51°[b]	
4-CH_3O-4′-NO_2	20.8 at 70°[c]	163 at 70°[c]
4-CH_3O-3′,5′-$(NO_2)_2$	10.2 at 51°	961 at 51°[d]

[a] K. Nozaki and P. D. Bartlett, This Journal, 68, 1686 (1946). [b] Estimated from E_{act} of reference (*a*). [c] Reference 2. [d] With 0.17 molar 1,3,5-trinitrobenzene added the rate constant is 1670 × 10^{-6} sec.$^{-1}$.

in the peroxide increases the rate by a factor of about 3 at 70°. The effect of substituents on the purely radical part of the rate can be estimated from data on symmetrically substituted benzoyl peroxides in dioxane[5] and in acetophenone,[4] except that there is undoubtedly some interaction of substituent and solvent effects even in the case of the radical reaction. Neglecting any perturbation by the difference in solvent, the 4-methoxy-4′-nitro substitution should decrease the purely radical decomposition rate somewhat. But the observed increase by a factor of three may not have any mechanistic significance since the reaction products in benzene are consistent with a purely radical decomposition. In nitrobenzene the same 4-methoxy-4′-nitro substituted peroxide decomposes about eight times as fast as in benzene. This might also be within the bounds of possible behavior for a radical reaction, but here the increase in rate is accompanied by a change in products suggesting an almost complete shift to the non-radical mechanism.[2]

The 4-methoxy-3′,5′-dinitro substitution has an even greater effect, producing a 23-fold acceleration in benzene at 51°. This is rather a large increase in rate for the radical reaction and suggests that this peroxide decomposes at least partly by a non-radical mechanism even in benzene. 4-Methoxy-3′,5′-dinitrobenzoyl peroxide decomposes in benzene without initiating the radical polymerization of styrene, although this might be due to the inhibitory effect of the dinitroaromatic compounds present. In nitrobenzene the 4-methoxy-3′,5′-dinitrobenzoyl peroxide decomposition at 51° is 94 times as fast as it is in benzene and about 2000 times as fast as the decomposition of benzoyl peroxide in benzene. Furthermore, 1,3,5-trinitrobenzene, a radical chain inhibitor, actually accelerates the reaction.

Acid Catalysis.—Figure 1 and Table II show the acceleration of the decomposition of 4-methoxy-3′,5′-dinitrobenzoyl peroxide by acids in benzene. The Brønsted plot of the catalysis in benzene (Fig. 1) is roughly linear with the expected exception of picric acid. Picrate ions (or ion pairs) are at a disadvantage relative to the un-ionized molecule because the latter should be more stabilized by π-complex formation with aromatic solvent molecules. Picric acid also has been observed to deviate from the Brønsted plot in the rearrangement of N-bromoacetanilide in benzene[8] and in the racemization of menthone in chlorobenzene.[9] In all three examples picric acid is less effective as a catalyst than would be predicted from its acid strength and by more than an order of magnitude. Our motive for including picric acid in the experiments is its well-known action as a radical inhibitor. However, we do not believe that the acid-

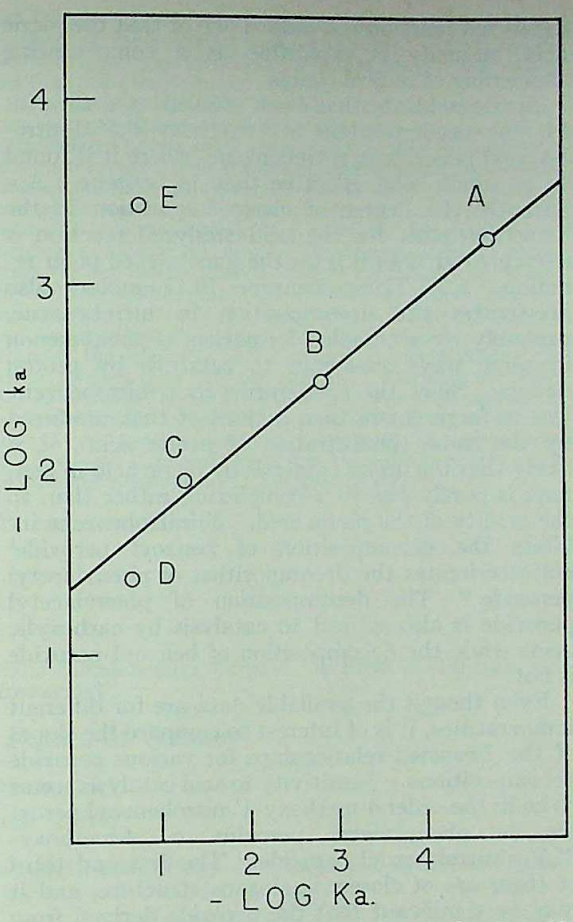

Fig. 1.—The Brønsted catalysis relationship for the acid-catalyzed decomposition of 4-methoxy-3′,5′-dinitrobenzoyl peroxide in benzene at 51°: A, acetic acid; B, chloroacetic acid; C, dichloroacetic acid; D, trichloroacetic acid; E, picric acid; k_a, the catalysis constant; K_a, the ionization constant of the catalyzing acid in water at 25°.

Table II

Acceleration of the Decomposition of 4-Methoxy-3′,5′-dinitrobenzoyl Peroxide by Acids and Complexing Agents

$k_{total} = k_1 + k_a$ [acid or complexing agent]

Acid or complexing agent	Catalysis constant,[c] k_a sec.$^{-1}$ l. moles^{-1} × 10^5
Acetic acid	56.8[a]
Chloroacetic acid	334[a]
Dichloroacetic acid	1160[a]
Trichloroacetic acid	3920[a]
Picric acid	36.8[a]
1,3,5-Trinitrobenzene	414[b]
Acetic acid	1130[b]

[a] In benzene as a solvent, 51°. [b] In nitrobenzene as a solvent, 51°. [c] The catalyst concentration was in the neighborhood of 0.17 *N*, the peroxide 0.01 *N*.

(5) R. P. Bell, *Proc. Roy. Soc.* (London), **A139**, 466 (1933).

(9) K. P. Bell and E. F. Caldin, *J. Chem. Soc.*, 382 (1938).

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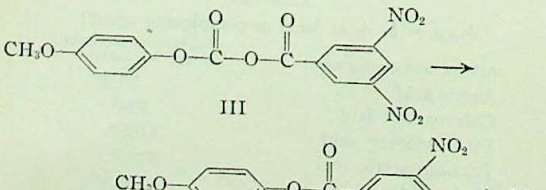
catalyzed reaction is a radical one or that the picric acid anomaly is explicable as a compensating shortening of radical chains.

Acetic acid also has been studied as a catalyst for the decomposition of 4-methoxy-3′,5′-dinitrobenzoyl peroxide in nitrobenzene, where it is found to be much more effective than in benzene. Apparently the degree of charge separation in the transition state for the acid-catalyzed reaction is even greater than it is for the uncatalyzed polar reaction. 1,3,5-Trinitrobenzene (0.17 molar) also accelerates the decomposition in nitrobenzene, probably by π-complex formation, a phenomenon in some ways analogous to catalysis by proton donors. Since the acceleration by trinitrobenzene was so large (more than a third of that produced by the same concentration of acetic acid), it is likely that the minor catalysis by picric acid in benzene is partly due to π-complexing rather than to the acidity of the picric acid. Trinitrobenzene inhibits the decomposition of benzoyl peroxide[7] and accelerates the decomposition of phenylacetyl peroxide.[10] The decomposition of phenylacetyl peroxide is also subject to catalysis by carboxylic acids while the decomposition of benzoyl peroxide is not.

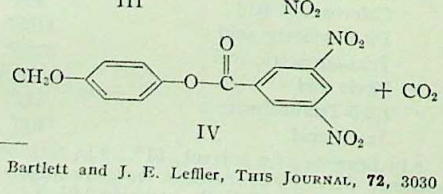
Even though the available data are for different temperatures, it is of interest to compare the slopes of the Brønsted relationships for various peroxide decompositions. Sensitivity to acid catalysis seems to be in the order 4-methoxy-4′-nitrobenzoyl peroxide > phenylacetyl peroxide > 4-methoxy-3′,5′-dinitrobenzoyl peroxide. The first and third of these are of closely analogous structure, and it may be significant that the peroxide derived from the stronger nitro-substituted acid is the less sensitive to acid catalysis.[11]

The Products of the Decomposition of 4-Methoxy-3′,5′-dinitrobenzoyl Peroxide.—The products of the decomposition of 4-methoxy-3′,5′-dinitrobenzoyl peroxide in various solvents are reported in Table III as per cent. of the acyloxy groups surviving in the form of free acid or ester. As in the case of 4-methoxy-4′-nitrobenzoyl peroxide, there is less conservation of anisoyloxy groups in nitrobenzene than in benzene, but the yields of both anisic and dinitrobenzoic acids and esters are lower. The low recovery of the dinitrobenzoyloxy part of the peroxide may be due to the instability of the carboxy-inversion product.

The carboxy inversion product III could not be purified but is undoubtedly present in the reaction



III



IV

(10) P. D. Bartlett and J. E. Leffler, THIS JOURNAL, **72**, 3030 (1950).

(11) See, for example, the acid catalysis mechanism and footnote 7 of reference 2.

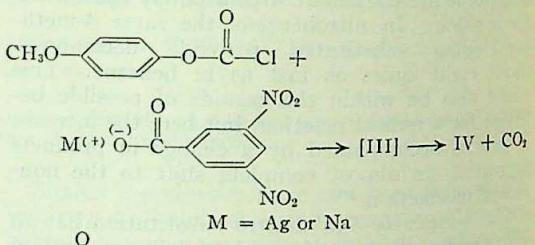
TABLE III

PRODUCTS OF THE DECOMPOSITION OF 4-METHOXY-3′,5′-DINITROBENZOYL PEROXIDE

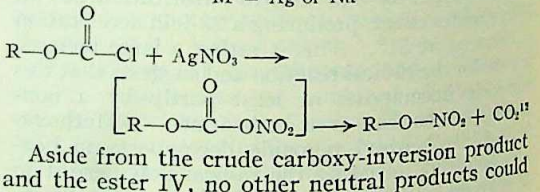
Conditions	% Yield of 4-methoxybenzoyloxy groups As free acid	% Yield of 4-methoxybenzoyloxy groups As esters	% Yield of 3,5-dinitrobenzoyloxy groups As free acid	% Yield of 3,5-dinitrobenzoyloxy groups As esters
In benzene at 51°	18	3	33	6
In nitrobenzene at 51°	2	0.4	10	7
In acetone at 25°	3		2	At least 19[a]
In benzene plus 0.17 *N* $ClCH_2COOH$ at 51°	Trace	9	46	0
In benzene plus 0.17 *N* picric acid at 51°	Trace		17	At least 31[a]

[a] Amount of 4-methoxyphenyl 3,5-dinitrobenzoate actually isolated. The other ester yields are yields of the acid after saponification of the neutral fraction.

mixtures from the polar solvents as is shown by the evolution of carbon dioxide and the formation of IV on recrystallization and by the formation of ethyl 3,5-dinitrobenzoate on treatment of the crude product with ethanol. The elimination of carbon dioxide also takes place in the attempted synthesis of III from anisyl chloroformate and salts of the dinitrobenzoic acid. An analogous reaction of chloroformate esters with silver nitrate gives similar results.[12]



M = Ag or Na



Aside from the crude carboxy-inversion product and the ester IV, no other neutral products could be isolated from the decomposition mixture.

Experimental

Preparation of 4-Methoxy-3′,5′-dinitrobenzoyl Peroxide.—To a freshly prepared solution of one gram of sodium in 40 ml. of absolute ethanol cooled to −20° is added dropwise, with stirring, a solution of 10 g. of anisoyl peroxide in 100 cc. of cold chloroform. After ten minutes of continued stirring and cooling in the Dry Ice–acetone bath, that bath is replaced with an ice-bath and the stirring continued for 20 minutes. The sodium peranisate is then extracted with two 60-ml. portions of cold water and the extract washed with 30 ml. of cold chloroform.

The aqueous peranisate solution is nearly neutralized with solid carbon dioxide pellets, and a concentrated solution of 7.6 g. of 3,5-dinitrobenzoyl chloride in dry acetone is added dropwise with stirring at 0°. Stirring is continued for 1 hr. The resulting precipitate is removed by filtration, washed with 10 ml. of 5% $NaHCO_3$ solution, dissolved in chloroform and filtered. After methanol is added to the chloroform solution, it is cooled in ice. The peroxide is obtained as white flaky crystals, wt. 4 g. after two recrystallizations, m.p. 97° with decomposition.

(12) R. Boschan, Abstracts of Papers Presented at the American Chemical Society Meeting, Atlantic City, N. J., September, 1956, page 9O.

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Anal. Peroxide assay, 96–97%. Calcd. for $C_{15}H_{10}O_9N_2$: C, 49.73; H, 2.78; N, 7.73. Found: C, 50.34; H, 2.94; N, 7.91.

Kinetics.—Solutions of the peroxide were degassed, sealed in ampules and placed in a constant temperature bath. The decomposition was stopped by cooling the ampules in Dry Ice–acetone, and aliquots were analyzed by the method of Nozaki[13] using a "dead-stop" end-point.[14] It was found necessary to use carbonated water in order to get good results (±0.2%) with thiosulfate from 0.001 to 0.005 *N*.

Product Analysis.—With the exception of anisyl 3,5-dinitrobenzoate and the crude carboxy inversion product, no neutral products were formed in sufficient quantity for isolation, although various chromatographic adsorbents were tried. The acid mixtures were removed by extraction with sodium bicarbonate and analyzed for anisic and 3,5-dinitrobenzoic acid by means of infrared bands at 1612 and 1350 cm.$^{-1}$. Control analyses indicate that the results are accurate to within 9% for the 3,5-dinitrobenzoic acid and 8% for the anisic acid. The mixture of acids is not readily separated by chromatography. Esters were estimated by saponification of the neutral fraction followed by infrared analysis of the resulting mixture of acids. Anisyl 3,5-dinitrobenzoate was identified by its melting point, mixed melting point and infrared spectrum.

The Carboxy-inversion Product III.—The neutral fraction of the decomposition products from the reaction in nitrobenzene gave a small amount of ethyl 3,5-dinitrobenzoate on treatment with ethanol, presumably because of the presence of III. The ester IV was isolated by crystallization of the decomposition products from the reaction in acetone and in benzene–picric acid, with the carboxy-inversion product as a likely precursor. The decomposition products from the reaction in thionyl chloride contained a substance of variable melting point (137–139 for one sample, 139–149 for another), evidently III in crude form. This crude product has an anhydride band at 1830 cm.$^{-1}$, absent in the spectrum of the ester IV. All attempts at recrystallizing the crude product gave only the ester IV. Warming the crude III in methanol evolved 70% of the theoretical amount of carbon dioxide; saponification gave 94% of the theoretical amount of *p*-methoxyphenol. Attempts at synthesizing III from anisyl chloroformate and the sodium or silver salt of 3,5-dinitrobenzoic acid also gave the ester IV.

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(13) K. Nozaki, *Ind. Eng. Chem., Anal. Ed.*, **18**, 583 (1946).

(14) E. W. Abrahamson and V. H. Linshitz, *Anal. Chem.*, **24**, 1355 (1952).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF WESTVACO CHLOR-ALKALI DIVISION OF FOOD MACHINERY AND CHEMICAL CORPORATION]

Phosphorus(V) Acid Esters of Oximes

BY J. FORREST ALLEN[1]

RECEIVED JANUARY 12, 1957

Alkyl esters of trivalent phosphorus acids react with α-halonitro compounds to form alkyl halide and oxime esters of the corresponding pentavalent phosphorus acids.

The similarity in the chemical behavior of the nitro and carbonyl groups in certain reactions suggested that α-halonitroparaffins should react with esters of trivalent phosphorus acids to form products which are analogous to the vinyl esters of pentavalent phosphorus acids which have recently been reported from this Laboratory[2] and by several other groups. The reaction of triethyl phosphite with several representative halonitroparaffins has been studied and the reaction shown to proceed according to the equation

$$RR'XCNO_2 + 2(R''O)_3P \longrightarrow RR'C{=}NOP(O)(OR'')_2 + (R''O)_3PO + R''X$$

I

Ia, R = R′ = Cl; R″ = Et
Ib, R = R′ = Me; R″ = Et

Trimethyl phosphite and diethyl phenylphosphonite react in an analogous fashion, but triphenyl phosphite appears to react by a different mechanism. The ease with which the reaction takes place increases with the number of halogen atoms on the α-carbon atom and bromine compounds are more active than chlorine compounds. 1-Chloro-1-nitroethane and triethyl phosphite did not react at 50°, but 1,1-dichloro-1-nitroethane and triethyl phosphite reacted rapidly at 25°, and trichloronitromethane reacted violently with the phosphite at −40° producing smoke and flame unless carefully controlled. 2-Bromo-2-nitropropane reacted rapidly with the phosphite at 50°.

Arbuzov and co-workers[3] reported the reaction of triethyl phosphite with α-bromonitro compounds but were able to identify only triethyl phosphate and ethyl bromide. These investigators observed a two-stage reaction, the first occurring at or below ordinary temperatures and the second at about 90–100°. They found that nitromethane did not react with triethyl phosphite, indicating that the halogen atom plays an important role in the oxidation of the phosphite to the phosphate. The work reported in this paper indicates that the second reaction observed by the Russian workers was probably the Beckmann rearrangement of the primary reaction product I as reported recently by Kenner, Todd and Webb.[4] Kamai[5] treated trichloronitromethane with triethyl phosphite and tributyl phosphite and reported the corresponding dialkyl phosphorochloridates as the only identifiable products. The author has found that the reaction of two moles of triethyl phosphite with one mole of trichloronitromethane converts about 3 to 11% of the phosphite to the phosphorochloridate, about 50% to the phosphate and the remainder to Ia and other products. Ia has been obtained in yields of 32 to 63%. When

(1) Food Machinery and Chemical Corporation, Chemical Divisions, Central Research Laboratory, Princeton, New Jersey.

(2) J. F. Allen and O. H. Johnson, THIS JOURNAL, **77**, 2871 (1955).

(3) A. E. Arbuzov, B. A. Arbuzov and B. P. Lugovkin, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 538 (1947).

(4) G. W. Kenner, A. R. Todd and R. F. Webb, *J. Chem. Soc.*, 1231 (1956).

(5) G. Kamai, *Doklady Akad. Nauk S.S.S.R.*, **79**, 795 (1951).

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other halonitro compounds were treated with triethyl phosphite, the triethyl phosphate fraction was contaminated with a small amount of halogen compound, but this could not be identified as the phosphorochloridate. Since Ford-Moore and co-workers[6] have reported the preparation of dialkyl phosphorochloridates from phosgene and trialkyl phosphites, it seemed possible that Ia, a phosgene derivative, might also convert phosphite to phosphorochloridate. However, when equimolar quantities of triethyl phosphite and Ia were heated at 75–150°, ethyl chloride (100%) was evolved slowly but the reaction mixture did not contain diethyl phosphorochloridate.

The assignment of structure I to the reaction products is based upon the following evidence: (a) elemental analysis and physical properties, including strong infrared absorption at 6.1–6.3 μ, characteristic of the carbon–nitrogen double bond; (b) the independent synthesis of Ib from acetone oxime, aqueous sodium hydroxide and diethyl phosphorochloridate; and (c) the hydrolysis of Ib to acetone.

It also should be noted that structure I is analogous to the vinyl phosphate structure, and it seems likely that both reactions proceed by the same mechanism. However, the reaction of the nitro compounds is complicated by the oxidation–reduction, and it is not apparent whether the nitro compound is first reduced to the nitroso compound which reacts with additional phosphite or whether the nitro compound forms an intermediate with the phosphite which is then reduced by additional phosphite. That the first route is possible was shown by the synthesis of Ib from 2-chloro-2-nitrosopropane and triethyl phosphite. But since the over-all reaction is usually very rapid, the initial stage must also be rapid, and it might be expected that the addition of phosphite to a large excess of nitro compound would result in the formation of nitroso compound which would be evident from its characteristic intense blue color. In no instance has more than a trace of color appeared, and in most reactions no color has been observed.

The presence of a hydrogen atom on the alpha carbon atom of the oxime moiety of I (R or R′) lends instability to the molecule and no product of this type has been distilled. When heated to about 100° these products undergo a vigorous exothermic reaction as reported by Arbuzov and co-workers.[3] The crude product of the reaction between trimethyl phosphite and 1-bromo-1-nitropropane at 30–40° showed strong infrared absorption at 6.3 μ which is assumed to indicate that the product had structure I (R = H, R′ = Et, R″ = Me). The product of the reaction between triethyl phosphite and 2-bromo-2-nitropropane, Ib, when heated rapidly did not give the second-stage reaction below 175°. Although it is assumed that the second-stage reaction is a Beckmann rearrangement of the oxime ester, it is obvious that the reaction is accompanied by decomposition and most of the product is converted to a tar from which no pure product has been isolated.

(6) A. H. Ford-Moore, L. J. Lermit and C. Stratford, *J. Chem. Soc.*, 1776 (1953).

Experimental

Preparation of Diethyl Isopropylideneamino Phosphate (Ib) (a) From 2-Bromo-2-nitropropane and Triethyl Phosphite.—One mole (166 g.) of triethyl phosphite was added dropwise with cooling and stirring to 0.5 mole (84.5 g.) of 2-bromo-2-nitropropane at 55–60°. The mixture was then heated to 75–85° for 30 minutes and the ethyl bromide (94%) removed at reduced pressure. Distillation of the reaction mixture through a 10-inch Vigreux column gave (a) 98 g., b.p. 57–85.5° (0.4 mm.), which is 108% of theory for triethyl phosphate, and (b) 66.5 g. (64%) of Ib, b.p. 101–110° (0.2 mm.). Redistillation gave an analytical sample, b.p. 95–98.5° (0.2 mm.), n^{25}D 1.4359, and d^{25}_4 1.0949.

Anal. Calcd. for $C_7H_{16}NO_4P$: P, 14.8. Found: P, 15.2.

(b) From 2-Chloro-2-nitrosopropane and Triethyl Phosphite.—A solution of 0.5 mole (53.8 g.) of crude 2-chloro-2-nitrosopropane in 200 ml. of carbon tetrachloride was cooled to 0°, and 0.5 mole (83 g.) of triethyl phosphite was added with stirring. When addition of the phosphite was complete, the temperature was raised to 75°, and 21 g. of ethyl chloride containing a small amount of carbon tetrachloride was collected in a cold trap. The remainder of the volatile matter was removed *in vacuo* and the product fractionated to yield 53 g. (51%) of oxime ester, b.p. 88–96° (0.1 mm.), n^{25}D 1.4360.

Anal. Calcd. for $C_7H_{16}NO_4P$: N, 6.7; P, 14.8. Found: N, 6.5; P, 14.9.

The nitroso compound used in this preparation was obtained by adding 1 mole of chlorine to 1 mole each of acetone oxime and sodium hydroxide dissolved in 400 ml. of water. The product was separated from the aqueous solution, dried with calcium sulfate and used without further purification.

(c) From Acetone Oxime and Diethyl Phosphorochloridate.—Two-tenths mole of diethyl phosphorochloridate was added gradually at 15–17° to 0.2 mole of acetone oxime and 0.3 mole of sodium hydroxide dissolved in 100 ml. of water. The mixture was shaken for 30 minutes, the 2 layers separated, and the aqueous layer extracted with ether. After drying the combined organic layers, the ether was evaporated and the product distilled to give 14 g. (33.5%) of oxime ester, b.p. 95–98° (0.2 mm.), n^{25}D 1.4358, and d^{25}_4 1.0940. Infrared spectrograms of this product and the product of method (a) were essentially identical, both absorbing intensely at 6.1 μ.

Anal. Calcd. for $C_7H_{16}NO_4P$: P, 14.8. Found: P, 15.0.

Preparation of Diethyl (1-Chloroethylidene)-amino Phosphate.—With stirring and mild cooling 0.5 mole (83 g.) of triethyl phosphite was added gradually to 0.25 mole (36 g.) of 1,1-dichloro-1-nitroethane at 25–40°. Stirring was continued without cooling, and the temperature rose to 90° where it was held by mild cooling until the reaction began to subside (about 5 minutes). The temperature was then raised to 100° for 15 minutes to complete the reaction. The yield of ethyl chloride was 12 g. (74%). Fractionation of the product gave 42 g. (73%) of oxime ester, b.p. 103° (0.3 mm.), n^{25}D 1.4408, and with intense infrared absorption at 6.1 μ.

Anal. Calcd. for $C_6H_{13}ClNO_4P$: Cl, 15.5; N, 6.1. Found: Cl, 15.2; N, 6.1.

Preparation of Diethyl (Dichloromethylene)-amino Phosphate.—One mole (166 g.) of triethyl phosphite was added gradually at 25° to 0.5 mole (82 g.) of chloropicrin dissolved in 300 ml. of carbon tetrachloride. The reaction was vigorous and appeared to be complete at the end of the mixing period. After removal of ethyl chloride and carbon tetrachloride by distillation, the resulting mixture was separated by fractionation (12 inch column Hastelloy B Heli-Pak) into 4 major fractions: (A) 14.3 g., b.p. 45–50° (0.7–0.3 mm.); (B) 46.4 g., b.p. 45–58° (0.3–0.2 mm.); (C) 26.0 g., b.p. 62.55° (1.4–1 mm.); and (D) 78.5 g. (63%) oxime ester, b.p. 80–85° (0.2 mm.), n^{25}D 1.4518.

Anal. Calcd. for $C_8H_{16}Cl_2NO_4P$: Cl, 28.4; N, 5.6; P, 12.4. Found: Cl, 28.1; N, 5.4; P, 12.4.

Fractions A and B contained 6.6 and 0.54% chlorine, respectively, and if it is assumed that all the chlorine was in the form of diethyl phosphorochloridate, the yield of the latter was 5.8 g. which is equivalent to 3.4% of the phos-

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phite used in the reaction. The chlorine-containing compound was identified as diethyl phosphorochloridate as follows. Thirteen grams of fraction A, containing 0.86 g. of chlorine, was treated with 4.5 g. of aniline (2 moles) and the mixture heated to 80° for 10 minutes. After adding 18 ml. of water, the solution was cooled to 5° and seeded with diethyl N-phenylphosphoroamidate. The resulting solid after recrystallization from ethanol–water had m.p. 95.5–96° which was not depressed by mixing with an authentic sample of diethyl N-phenylphosphoroamidate (lit.[7] m.p. 95–96°).

When this preparation was repeated without solvent at −40°, the reaction was very vigorous and smoke and flame were occasionally observed when a drop of phosphite entered the chloropicrin. The yield of oxime ester was 32% and about 11% of the phosphite was converted to phosphorochloridate.

Preparation of Ethyl Isopropylideneamino Phenylphosphonate.—Sixty-five grams (0.31 mole) of diethyl phenylphosphonite was added dropwise with stirring and cooling at 15–28° to 26 g. (0.155 mole) of 2-bromo-2-nitropropane. When addition was complete, stirring was continued at 30° for 1 hour. Distillation gave 14.5 g. (86%) of ethyl bromide and fractionation of the remainder gave 28.5 g. (82%) of diethyl phenylphosphonate, b.p. 100° (0.5 mm.), and $n^{35}D$ 1.4897 (lit.[8] b.p. 104–105° (0.5 mm.), $n^{25}D$ 1.4935), and 10 g. (27%) of oxime ester, b.p. 140° (0.5 mm.), and $n^{35}D$ 1.5082. There was a large tarry residue.

Anal. Calcd. for $C_{11}H_{16}NO_3P$: N, 5.8; P, 12.8. Found: N, 5.6; P, 12.5.

Preparation of Diethyl Benzylideneamino Phosphate.—To a mixture of 19.6 g. of benzaldehyde oxime (0.16 mole) and 12.6 g. of pyridine (0.16 mole) was gradually added at 0° 27.6 g. of diethyl phosphorochloridate (0.16 mole). The mixture was allowed to warm to room temperature where it was stirred for 1 hr. and then heated at 50–60° for 1 hr. After cooling, ether was added to the mixture and pyridine hydrochloride removed by filtration. Removal of volatile matter by heating *in vacuo* gave 36.5 g. (88%) of crude oxime ester which decomposed when distillation was attempted at 1 mm. pressure.

Anal. Calcd. for $C_{11}H_{16}NO_4P$: P, 12.1. Found: P, 11.9.

Pyrolysis of Diethyl Isopropylideneamino Phosphate.—Twenty grams of oxime ester was placed in a 50-ml. flask equipped with a thermometer dipping into the liquid and a water condenser. When heated to 175°, a vigorous exothermic reaction began which was controlled with difficulty by immersing the flask in a Dry Ice-bath. After the reaction subsided, heating was continued at 180–185° for 2 hr. Distillation at 0.6 mm. gave only 3 g., b.p. 53–55°, $n^{35}D$ 1.4060, the remainder being a viscous tar. Not only is the boiling point of the distillate considerably lower than would be expected for the Beckmann rearrangement product, but the phosphorus and nitrogen contents were low (12.4 and 4.45%, respectively).

Hydrolysis of Diethyl Isopropylideneamino Phosphate.—Ten grams of the oxime ester and 50 ml. of 5% hydrochloric acid were placed in a flask equipped with a distillation condenser. When heated to gentle boiling, a few drops of blue liquid distilled followed by 3.5 ml. of colorless distillate. This was identified as acetone by conversion to the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 126° (lit.[9] m.p. 126°).

(7) F. R. Atherton, H. T. Howard and A. R. Todd, *J. Chem. Soc.*, 1106 (1948).

(8) G. M. Kosolapoff, "Organic Phosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 162.

(9) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 262.

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM STANFORD RESEARCH INSTITUTE]

The Addition of Chloro- and Ethoxysilanes to Vinyl and Allyl Monomers[1,2]

BY LEON GOODMAN, ROBERT M. SILVERSTEIN AND ALLEN BENITEZ

RECEIVED NOVEMBER 6, 1956

The platinum-catalyzed addition of some chloro- and ethoxysilanes to a variety of vinyl and allyl monomers has been accomplished in good yield under mild conditions. Nuclear magnetic resonance spectra make it clear that the addition of methyldichlorosilane to vinyl acetate gives the linear compound $CH_3SiCl_2CH_2CH_2OCOCH_3$ while addition to methyl acrylate gives the branched compound $CH_3SiCl_2CH(CH_3)COOCH_3$. The latter compound represents the first reported example of a reversed addition orientation in additions of the elements of the Si–H bond to carbon–carbon double bonds.

The addition of the elements of the Si–H bond to a carbon–carbon double bond was first reported in 1947[3] and has been the object of much study since that time. Peroxides and ultraviolet light were used as catalysts in the original study,[3] and since that report the reaction has been carried out by employing high temperatures and pressures without catalyst[4] and by using platinum and palladium as catalysts.[5]

We have utilized this platinum-catalyzed reaction for the synthesis of silicon monomers which contain functional groups. The additions of trichlorosilane, methyldichlorosilane and methyldiethoxysilane to a variety of vinyl and allyl monomers were accomplished using mild conditions. These reactions are listed in Table I.

A 5% platinum-on-carbon catalyst was used in all these additions. It was demonstrated to be necessary in the trichlorosilane additions to vinyl acetate and to methyl acrylate, and we presume it to be necessary in all the reactions listed in Table I. The catalyst was used in the amount of about 0.25–0.50% by weight of the silane employed and, in most cases, that same weight of Ionol (2,6-di-*t*-butyl-4-methylphenol) was used as a polymerization inhibitor for the olefin.[6]

Two techniques were used in carrying out these reactions—use of a stainless steel sealed bomb

(1) This work was supported by the Wright Air Development Command under Contract AF 33(616)-2998.

(2) (a) A preliminary communication appeared in THIS JOURNAL, 78, 4493 (1956). (b) Presented in part at the 130th meeting of the American Chemical Society, Atlantic City, New Jersey, September, 1956.

(3) L. H. Sommer, E. W. Pietrusza and F. C. Whitmore, THIS JOURNAL, 69, 188 (1947).

(4) A. J. Barry, L. DePree, J. W. Gilkey and D. E. Hook, *ibid.*, 69, 2916 (1947).

(5) G. H. Wagner and C. O. Strother (to Union Carbide and Carbon), U. S. 2,632,013 (March 17, 1953).

(6) The effectiveness of polymerization inhibition is shown by an experiment in which methyl acrylate, Ionol and a large excess of trichlorosilane were heated in a steel bomb at 150° for 20 hr. No polymerization of the acrylate was detectable, and there was no evidence of a silane–acrylate addition product.

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TABLE I

SUMMARY OF SILANE ADDITIONS

$RSiX_2H + CH_2{=}CH(CH_2)_nY \longrightarrow$ Products[a]

RSiX₂H R	RSiX₂H X	CH₂=CH(CH₂)ₙY n	CH₂=CH(CH₂)ₙY Y	Method[b]	Conditions for method I °C. (hr.)	Conversion,[c] %	B.p.[d] °C.	B.p.[d] Mm.	Products Hydrolyzable chlorine (%)[g] Calcd.	Products Hydrolyzable chlorine (%)[g] Found	Silicon Calcd.	Silicon Found
Cl	Cl	0	$OCOCH_3$	II		76	44–46	1	48.0	47.7		
Cl	Cl	1	$OCOCH_3$	II		72	87.0	10	45.2	46.2	11.9	12.0
Cl	Cl	1	OC_2H_5	II		64	75.8	17	48.0	48.0		
Cl	Cl	0	CN	I	100(20)	42.5	70.0	8	56.4	59.0[e]	14.9	15.8
Cl	Cl	0	$COOCH_3$	I	100(20)	65[f]	88.5	20	48.0	47.9		
Cl	Cl	0	$COO(CH_2)_2OCH_3$	I	100(20)	70[f]	89–90	3	40.0	39.8		
CH_3	Cl	0	$OCOCH_3$	II		76	80.0	9.6	35.3	35.2		
CH_3	Cl	1	$OCOCH_3$	II		72	84.2	6.5	33.0	32.8		
CH_3	Cl	1	OC_2H_5	II		56	73.5	15	35.3	35.4		
CH_3	Cl	0	CN	I	75(26)	26	60–62.5	4	42.2	41.5[e]		
CH_3	Cl	0	$COOCH_3$	II		65[f]	71.0	12.8	35.3	35.0		
CH_3	Cl	0	$COO(CH_2)_2OCH_3$	II		59[f]	87–88	0.5	28.9	28.6		
CH_3	OC_2H_5	0	OC_2H_5	II		81	69–72	8			13.6	13.9
CH_3	OC_2H_5	0	OC_4H_9-*n*	II		75	88–90	5			11.9	12.3
CH_3	OC_2H_5	0	$CH(OCOCH_3)_2$	II		51	113.0	2			9.6	9.6

[a] Trichlorosilane and dimethyl itaconate gave a 40% conversion to 1:1 adduct, b.p. 106–107° (4 mm.), hydrolyzable chlorine, calcd. 36.2, found 35.5. [b] See Experimental. [c] Conversion based on total olefin used, some of which was recovered. Conversions based on wider boiling ranges than in next column. [d] Boiling ranges of analytical samples. [e] Unstable compounds which darkened rapidly and were difficult to handle. [f] Lower boiling materials were present in additions to acrylates. These appear to be isomeric with desired adducts and require further investigation. [g] Chlorine determined by Volhard method after hydrolysis in a water–isopropyl alcohol mixture.

which enabled higher temperatures to be attained, and simple refluxing of the silane while the olefin was slowly added. The sealed bomb technique was necessary in the additions of the low boiling (32°) trichlorosilane to acrylonitrile and to the α,β-unsaturated esters. In these additions a large excess of the silane was necessary in order to obtain good conversions to the 1:1 adduct. The technique of slowly adding the olefin to the refluxing mixture of silane and catalyst allowed good conversion to the 1:1 adduct to be realized when equimolar amounts of the silane and olefin were employed and was used in the additions of methyldichlorosilane[7] (b.p. 42°) and methyldiethoxysilane (b.p. 98°). In the chlorosilane additions to acrylonitrile and the acrylate esters, large residues remained after the distillation of the 1:1 adducts. These contained silicon–chlorine bonds, and it is felt that they are best explained as telomerization products wherein the ratio of olefin to silane is greater than 1. These residues were especially large in the acrylonitrile reactions and were much more prominent in the additions of methyldiethoxysilane than in those of the chlorosilanes.

Methyldiethoxysilane added in excellent yield to the two vinyl ethers, systems where telomerization is not a competing reaction. These olefins gave poor, or no, yields in the reactions with the chlorosilanes where traces of hydrogen chloride, which were present under our conditions, polymerized the ethers. It is interesting to note that Prober has obtained the same products by a base-catalyzed addition of alcohols to vinylmethyldiethoxysilane.[8] Addition of methyldiethoxysilane to acrolein diacetate gave a good conversion to 1:1 adduct. Under the same conditions, the attempted addition of methyldiethoxysilane or methyldichlorosilane to acrolein gave an intractable mixture as did the reaction between methyldichlorosilane and acrolein diacetate.

The additions of the elements of the Si–H bond to olefins, which were catalyzed by peroxides and ultraviolet light, have been regarded as typical free-radical reactions[3] and certainly obey the criteria of such a mechanism. There has been no speculation regarding the mechanism involved in the platinum-catalyzed addition. That addition has been shown to involve the addition of the silicon-containing moiety to the terminal carbon of the vinyl compound in several cases,[9,10] and no example of a reversed addition orientation has been noted. It is clear that the addition of a silane $RSiX_2H$ to an olefin $CH_2 = CHZ$ can lead to two possible products: $RSiX_2CH_2CH_2Z$ (A) or $RSiX_2CH(CH_3)Z$ (B).

Hydrolysis studies of the methyldichlorosilane and methyldiethoxysilane adducts indicated that two classes of compounds had been formed by these reactions. The adducts from vinyl acetate, the vinyl ethers and all of the allyl monomers yielded oils on hydrolysis that did not change after being heated at 200° *in vacuo*. The adducts from acrylonitrile and the acrylate esters gave oils on hydrolysis that became resinous solids after heating *in vacuo* at temperatures up to 200°. Methyl propionate and methoxyethyl propionate were isolated as decomposition products from the hydrolyzate of the methyldichlorosilane adducts with methyl acrylate and methoxyethyl acrylate, respectively. It is known that the ester $(CH_3)_3SiCH_2COOR$ yields CH_3COOR readily on neutral hydrolysis as a result of Si–C bond cleavage[11] while $(CH_3)_3SiCH_2CH_2$-

(7) The addition of methyldichlorosilane to acrylonitrile required the use of the bomb in order to achieve even low conversions to the 1:1 adduct.

(8) M. Prober, 130th Amer. Chem. Soc. Meeting, Sept., 1956, Abstracts of Papers, p. 53-O.

(9) G. H. Wagner, D. L. Bailey, A. N. Pines, M. L. Dunham and D. B. McIntire, *Ind. Eng. Chem.*, **45**, 367 (1953).

(10) J. W. Curry, THIS JOURNAL, **78**, 1686 (1956).

(11) C. R. Hance and C. R. Hauser, *ibid.*, **75**, 994 (1953).

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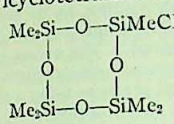
COOR gives $(CH_3)_3SiCH_2CH_2CCOH$ under severe conditions of acidic or basic hydrolysis.[12] The isolation of the above-noted decomposition products was the first hint that some of our adducts had the reversed addition orientation of structure B.

The cohydrolysis of dimethyldichlorosilane and the methyldichlorosilane–vinyl acetate adduct, using a 3:1 mole ratio of the silanes, respectively, gave a reasonable yield (*ca.* 30%) of the functionally substituted cyclic siloxane, β-acetoxyethylheptamethylcyclotetrasiloxane (III).



III

The isolation of III in a reasonable yield shows that this cohydrolysis method offers a convenient route to such unsymmetrical cyclic siloxanes.

Attempts were made to add trimethylsilane to ethyl acrylate using platinum catalysis in an effort to prepare a compound which could be compared with a known compound, $(CH_3)_3SiCH_2CH_2CO-OC_2H_5$, in physical constants and chemical behavior. Such a structure proof is based on the assumption that trimethylsilane and methyldichlorosilane would give the same addition orientation. The only product isolated from the reaction was a low yield of a high-boiling liquid which seems to contain about three acrylate ester units for each trimethylsilane unit. Attempts to add trimethylsilane to vinyl acetate gave no evidence of addition. It should be noted that the platinum-catalyzed addition of methyldichlorosilane to vinyl acetate gives high yields of 1:1 adduct under very mild conditions.

An unequivocal answer to the structure problem was available from a study of the proton nuclear magnetic resonance spectra of the silane adducts. The methyldichlorosilane adducts of vinyl acetate and methyl acrylate (these are isomeric compounds) were chosen as representative examples of compounds which give stable hydrolyzates and unstable hydrolyzates, respectively. Simply on the basis of the proton spin–spin interactions, it is clear that the structures of the two adducts are as shown in Fig. 1. The two triplet peaks (a) and (c) (of equal area) of the vinyl acetate adduct are assignable to the $-CH_2CH_2-$ structure and the doublet, quartet groupings (g) and (f) (with the areas in the ratio 3:1) of the methyl acrylate adduct clearly shows the presence of the $-\overset{CH_3}{\overset{|}{C}}H-$ structure. The fact that (h) lies at a higher field than (a) and that (b) lies at a higher field than (f) conforms to the general pattern of NMR spectra wherein the more highly protonated of two otherwise similar groups shows resonance at a higher field. The NMR spectrum of the methyldichlorosilane–allyl acetate adduct shows that it has the linear structure with three $-CH_2-$ groups. The NMR spectrum of the methyldiethoxysilane-allylidene diacetate adduct shows that it too has the linear structure. This indicates that a route is available to the stable isomers in the additions

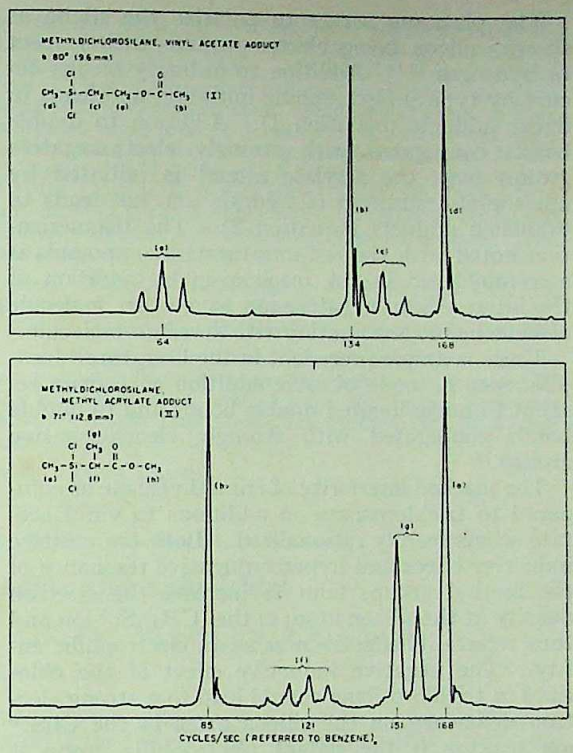
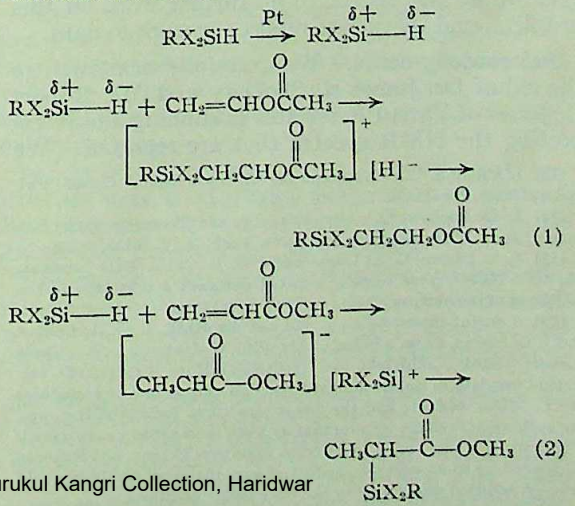


Fig. 1.—Proton nuclear magnetic resonance spectra of methyldichlorosilane adducts. Samples in 5 mm. tubes and Varian Associates High Resolution Spectrometer (V-4300B) at 30 mc. and 7050 gauss.

of Si–H-containing compounds to acrolein *via* acrolein diacetate or acrolein acetals. The methyldichlorosilane–methyl acrylate adduct (and presumably the acrylonitrile adduct and other adducts to α,β-unsaturated carbonyl compounds) then represents the first example of a reversed addition orientation in Si–H additions.

The fact that these platinum-catalyzed silane additions proceed well in the presence of a polymerization inhibitor is an indication, at least, that the reaction is not a typical free-radical reaction. We think that the difference of addition orientation in the two classes of olefins can be accommodated by the ionic mechanism



(12) L. H. Sommer and N. S. Marans, THIS JOURNAL, **72**, 1935 (1950).

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The platinum serves to polarize the silane as shown, silicon being electro-positive with respect to hydrogen.[13,14] Addition to ordinary olefins occurs by typical electrophilic initiation and leads to linear adducts (equation 1). Addition to double bonds conjugated with strongly electronegative groups (*e.g.*, the acrylate esters) is initiated by nucleophilic addition of hydride ion and leads to branched adducts (equation 2). The telomerization noted with the α,β-unsaturated compounds is accommodated in the mechanism by addition of the intermediate negative ion to another molecule of olefin before terminating with the silane molecule.

There is ample precedent in the literature[15] for a difference in mode of ionic addition of a given reagent to unconjugated double bonds and to double bonds conjugated with strongly electronegative groups.[16]

The marked inferiority of trimethylsilane as compared to trichlorosilane in additions to vinyl acetate seems readily rationalized. Both the positive inductive effect and hyperconjugative resonance of the methyl groups tend to increase the electron density at the silicon atom in the $(CH_3)_3Si^+$ ion and thus reduce its effectiveness as an electrophilic entity. The negative inductive effect of the chlorines in trichlorosilane should lead to a strong electron deficiency on the silicon atom in the Cl_3Si^+ ion making it the potent electrophilic group it seems to be. The NMR measurements show that the silane hydrogen peak in trimethylsilane occurs at 110 ± 5 cycles/sec. higher than in trichlorosilane while the peak in methyldichlorosilane occurs at about 26 cycles/sec. higher than in trichlorosilane. These measurements emphasize the inductive effect of chlorine and indicate that, at least in the ground state, the silane hydrogen in trimethylsilane has a higher electron density than that in trichlorosilane and would be expected to donate a hydride hydrogen better than trichlorosilane. In view of these data it is difficult to understand why trimethylsilane seems to be inferior to trichlorosilane in additions to the acrylate esters. We recognize that our postulated (and admittedly speculative) mechanism may be a gross oversimplification of the picture which neglects the adsorption, desorption interactions of the catalyst and reactants. However we do not expect to do further work on this problem, and we wish to report our work to date.

Acknowledgments.—We gratefully acknowledge the aid of Dr. James N. Shoolery and Mr. Robert C. Jones of Varian Associates in running and interpreting the NMR spectra that are reported. We also express our thanks to Mr. Oliver D. Smith and the members of the analytical staff of the Stanford Research Institute for the analytical data. The Divisional Research Committee of Stanford Research Institute furnished funds to complete certain phases of this work.

(13) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 64.

(14) E. G. Rochow, "An Introduction to the Chemistry of the Silicones," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 22.

(15) L. S. Luskin, G. E. Gantert and W. E. Craig, THIS JOURNAL, **78**, 4965 (1956), have recently pointed out such a difference in the additions of isothiocyanic acid.

(16) A recent report by G. J. M. van der Kerk, J. G. A. Luijten and J. G. Noltes, *Chem. and Ind.*, 352 (1956), is of interest here. These authors added $(C_6H_5)_2SnH$ and $(n\text{-}C_4H_9)_2SnH$ to acrylonitrile and methyl acrylate in an uncatalyzed reaction run at low temperatures (80°). Their adducts had the linear structures $R_3SnCH_2CH_2X$ and the authors were of the opinion that an ionic mechanism was involved. The systems studied seem to be quite analogous to ours, and it would be interesting to observe what effect, if any, platinum catalysis would have on addition orientation in the tin hydride additions.

Experimental[17]

Silane–Olefin Adducts. Method I.—A mixture of the olefin (*ca.* 0.10 mole), the chlorosilane (*ca.* 0.30 mole), Ionol (0.25 g.) and 5% Pt-on-carbon (Baker and Co., Newark, N. J.) (0.25 g.) was sealed in a 100-ml. stainless steel bomb and heated, with rocking, at the proper temperature for the desired time. The bomb was cooled and opened, and the contents were filtered. The excess silane was removed by distillation at atmospheric pressure, and the residue was distilled at reduced pressure using a simple Claisen flask. Analytical samples were obtained by redistillation using a 50 × 1 cm. column packed with glass helices.

When trimethylsilane was used, it was condensed into the bomb using a Dry Ice–acetone bath. Excess trimethylsilane was distilled from the bomb and collected at the end of the reaction. When vinyl acetate was used as the olefin with trimethylsilane, there was no distillation residue after heating at 60° and 35 mm., indicating that no addition had occurred. About 25% of the vinyl acetate was isolated from the distillation trap, and more was present in the trimethylsilane which was distilled from the bomb. When ethyl acrylate was used as the olefin, a brown liquid (4.2 g.) was the residue from 10 g. of ethyl acrylate and 23 g. of trimethylsilane heated at 75° for 30 hr. This residue could not be distilled at 130° and 1 mm.

Anal. Calcd. for $Me_3Si(CH_2CHCOOEt)_3H$: Si, 7.5. Found: Si, 7.1.

About 3.5 g. of ethyl acrylate was recovered from the distillation trap.

Method II.—A mixture of chloro- or ethoxysilane (0.10 mole) and 5% Pt-on-carbon (0.25 g.) was stirred magnetically under reflux, while a solution of Ionol (0.25 g.) in the olefin (0.10 mole) was added dropwise (3–6 hr. was required for the additions). After a further 18 hr. of heating (the temperature gradually rose from the reflux temperature of the silane to that of the adduct), the mixture was filtered, and the filtrate was distilled as in method I.

Hydrolysis Studies.—The adducts from methyldichlorosilane were added slowly to an aqueous solution of sodium sulfate according to the directions of Wright.[18] The siloxanes formed were extracted with ether and, after drying the extract over magnesium sulfate, the ether was evaporated and the residue heated under vacuum to remove volatile materials. The adducts from methyldiethoxysilane were hydrolyzed using 10% hydrochloric acid, and the hydrolyzates were recovered as above with the additional step of a sodium bicarbonate wash of the ether extract to remove acid.

The silane adducts with vinyl acetate, allyl acetate, allyl ethyl ether and the vinyl ethers yielded hydrolyzates that could be heated at 200° and 1 mm. for several hours without change.

The hydrolyzate of the methyldichlorosilane–acrylonitrile adduct was an oil which changed to a resinous solid when it was warmed on the steam-bath. No effort was made to collect volatile decomposition products. The hydrolyzate of the methyldichlorosilane–methyl acrylate adduct was an oil which slowly changed to a resinous solid when it was heated to 200° at 1 mm. The liquid condensed in the trap was redistilled using a Claisen flask and a fraction, presumed to be methyl propionate, b.p. 80–81° (lit.[19] 79.9°), was collected.

Anal. Calcd. for $C_4H_8O_2$: C, 54.46; H, 9.15. Found: C, 54.1; H, 9.01.

The hydrolyzate of the methyldichlorosilane–methoxyethyl acrylate adduct similarly yielded a resinous solid when it was heated *in vacuo* at 200°. The liquid condensed in the trap was redistilled using a 50 × 1 cm. packed column and a fraction, b.p. 92–93° (82.5 mm.), was collected. The in-

(17) Boiling points are uncorrected.

(18) J. G. E. Wright, U. S. Patent 2,426,912 (September 2, 1947).

(19) "Handbook of Chemistry and Physics," 13th Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1948, p. 1006.

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frared spectrum of this material showed the strong carbonyl band at 1750 cm.$^{-1}$, weak carboxyl carbonyl at 1725 cm.$^{-1}$, the C-O-C absorptions at 1205, 1136, 1090 and 1045 cm.$^{-1}$ and the absence of typical Si–O–Si bands. It appeared to be an impure sample of methoxyethyl propionate contaminated with propionic acid.

Anal. Calcd. for $C_8H_{12}O_3$: C, 54.5; H, 9.16. Found: C, 51.6; H, 8.75; Si < 0.5.

Cohydrolysis of Dimethyldichlorosilane and the Methyldichlorosilane–Vinyl Acetate Adduct.—A mixture of 53.7 g. of methyldichlorosilane (Dow–Corning, pure grade) and 28 g. of the methyldichlorosilane–vinyl acetate adduct (mole ratio 3:1) was added, over a 5-hr. period, to a well-stirred mixture of 250 ml. of water and 250 ml. of ether, maintained at 0–10°. The ether layer was separated and the aqueous phase was extracted with four 50-ml. portions of ether. The total ether solution was dried over magnesium sulfate and the ether was evaporated to leave a residue (49.5 g.). The residue was first distilled from a Claisen flask to give the following fractions: (1) 6.8 g., b.p. 48–57° (7 mm.), n^{20}D 1.3952–1.3970; (2) 2.1 g., b.p. 56–79° (2.5 mm.), n^{20}D 1.4112; (3) 11.3 g., b.p. 79–86° (2.5 mm.), n^{20}D 1.4137–1.4152; (4) 3.6 g., b.p. 86–91° (2.5 mm.), n^{20}D 1.4155–1.4157; (5) 8.2 g., b.p. 91–132° (2.0 mm.), n^{20}D 1.4198–1.4268. A residue of 14.4 g., n^{20}D 1.4291, remained. Fraction (1) was a mixture of hexamethylcyclotrisiloxane and tetramethylcyclotetrasiloxane. Fractions (3) and (4) were redistilled using a 50 × 1 cm. column packed with glass helices and gave the following fractions: (1) b.p. 75–80° (2 mm.), n^{20}D 1.4122; (2) b.p. 80–81.5° (2 mm.), n^{20}D 1.4141; (3) b.p. 81.5–82°, n^{20}D 1.4150; (4), (5) and (6) b.p. 82.0° (2.0 mm.), n^{20}D 1.4153. Fraction V, considered to be β-acetoxyethylheptamethylcyclotetrasiloxane (III), was analyzed.

Anal. Calcd. for $C_{11}H_{23}O_6Si_4$: C, 35.83; H, 7.65; Si, 30.48; mol. wt., 368.69. Found: C, 35.5, 36.1; H, 7.55, 7.86; Si, 30.85; mol. wt. (cryoscopic in benzene), 361, 353.

Nuclear Magnetic Resonance Spectra.—The samples were sealed in 5 mm. tubes and the spectra were measured by the audio side band method using the Varian Associates Model V-4300B High Resolution Spectrometer at 30 mc. and 7050 gauss.

Menlo Park, Calif.

[Contribution from the Department of Chemistry, Iowa State College]

Hydroxybenzeneboronic Acids and Anhydrides

By Henry Gilman, Ludovico Santucci, D. R. Swayampati and R. O. Ranck

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ortho-, *meta-* and *para*-hydroxybenzeneboronic acids and/or anhydrides were prepared by the reaction of tri-*n*-butyl borate with the corresponding organolithium compounds. The properties of the three "isomers" (boronic acid or anhydride), including anhydride formation ability, were found to vary considerably. The preparation of 2-(*m*-bromophenoxy)-tetrahydropyran and the optimum conditions for the halogen–metal interconversion of *m*-bromophenol also are reported.

In the approach to the synthesis of boron-containing azo dyestuffs,[1,2] which have been found to be of interest in the irradiation therapy of brain tumors,[3] it was thought that compounds such as *o*-hydroxybenzeneboronic acid and *m*-hydroxybenzeneboronic acid or their anhydrides would be active enough to couple with various diazonium salts. This coupling could occur either *ortho* or *para* to the hydroxy group, but primarily *para*. Perhaps the *p*-hydroxybenzeneboronic acid or its anhydride would also couple successfully with various diazonium salts. However, the possibility of losing the boronic acid group exists here more so than in the other two cases unless, of course, the coupling tends to go *ortho* to the hydroxy group. The *para* isomer was thus prepared primarily for comparison with the other members of this series.

In addition to the purposes already discussed, these compounds, as such, should also be of interest for testing in brain tumor therapy, since the work of several[3–12] has shown that any boron compound containing some of the boron isotope 10[13] might be useful in irradiation research of this type. In addition, other pharmacological studies indicate that the hydroxyl group should increase the efficacy of such compounds.

The *m*-hydroxybenzeneboronic acid has been prepared previously[1,14,15] and was used for the preparation of azo boronic acids.[1] In these instances, the compound was prepared from *m*-aminobenzeneboronic acid by diazotization followed by hydrolysis.

The preparation of *p*-hydroxybenzeneboronic acid has been attempted in the past[14] but it never has been isolated.

The *o*-hydroxybenzeneboronic acid anhydride has not been reported as yet.

Only one other arylhydroxyboronic acid is mentioned in the literature. This is 3-hydroxy-4-methylbenzeneboronic acid[14] which was prepared from the 3-nitro-4-methylbenzeneboronic acid using catalytic reduction followed by diazotization and hydrolysis.

In the work reported here, two different approaches were tried for the preparation of each of the three isomers and a third approach was attempted for the *ortho* and *para* isomers.

The best of the three approaches involved the halogen–metal interconversion of a bromophenol isomer with *n*-butyllithium using 2 moles of the lithium reagent to 1 mole of the halogen com-

(1) H. R. Snyder and Clay Weaver, This Journal, **70**, 232 (1948).
(2) H. R. Snyder and S. L. Meisel, *ibid.*, **70**, 774 (1948).
(3) P. C. Kruger, *Radiation Research*, **3**, 1 (1955).
(4) P. A. Zahl, F. S. Cooper and J. R. Dunning, *ibid.*, **26**, 181 (1940).
(5) P. A. Zahl and F. S. Cooper, *Science*, **93**, 64 (1941).
(6) P. A. Zahl and L. L. Waters, *Proc. Soc. Exper. Biol. Med.*, **48**, 304 (1941).
(7) P. A. Zahl and F. S. Cooper, *Radiology*, **37**, 673 (1941).
(8) W. H. Sweet and M. Javid, *J. Neurosurg.*, **9**, 200 (1952).
(9) M. Javid, G. L. Brownell and W. H. Sweet, *J. Clin. Invest.*, **31**, 604 (1952).
(10) L. E. Farr, W. H. Sweet, J. S. Robertson, C. G. Foster, H. B. Lockeley, D. L. Sutherland, M. L. Mendelsohn and E. E. Stickley, *Am. J. Roentgenol. Radium Therapy Nuclear Med.*, **71**, 279 (1954).
(11) L. E. Farr, J. S. Robertson and E. E. Stickley, *Proc. Nat. Acad. Sci.*, **40**, 1087 (1954). See, E. E. Stickley, *Am. J. Roentgenol. Radium Therapy Nuclear Med.*, **75**, 609 (1956).
(12) L. E. Farr, J. S. Robertson, H. B. Stickley and E. E. Stickley, *J. Neurosurg.*, **11**, 264 (1954).
(13) Naturally occurring boron compounds contain 18.83% of the boron isotope 10. See NBS Circular No. 499, p. 7.
(14) F. R. Bean and J. R. Johnson, This Journal, **54**, 4415 (1932).
(15) M. F. Lappert, *Chem. Revs.*, **56**, 959 (1956). This is a review article and contains most of the organoboronic acids that have been prepared up to the writing of this paper.

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pound followed by reaction with tri-*n*-butyl borate, usually,[16] and subsequent hydrolysis with dilute acid. Isolation of the *meta* and *para* isomers was somewhat difficult because of their water solubility. Each was isolated successfully from an ether solution by concentration which was preceded by a series of extractions to remove a large portion of the *n*-butyl alcohol and boric acid. The *ortho* isomer could have been isolated by a similar procedure, but this was not necessary due to its limited water solubility. Isolation was effected by acidification of an alkaline extract. The yields of the three compounds prepared by this halogen–metal interconversion procedure differed greatly. The *ortho* isomer was obtained in yields as high as 65%; the *meta* isomer in much lower yields of 32%; and the *para* isomer in intermediate yields of 40%.

Another approach which was used is somewhat the same as that which has just been described except that the hydroxy group of the bromophenol isomers was etherified by the use of dihydropyran.[17,18] Both the 2-(*o*-bromophenoxy)-tetrahydropyran[18] and the 2-(*p*-bromophenoxy)-tetrahydropyran[17] have been reported previously, but the 2-(*m*-bromophenoxy)-tetrahydropyran is new and is reported here. The procedure was the same as in the preparation of the *ortho* and *para* isomers.

In each of these cases, the 2-(bromophenoxy)-tetrahydropyranyl isomer was treated with an equimolar amount of *n*-butyllithium followed by reaction with tri-*n*-butyl borate at a low temperature and subsequent hydrolysis. A 55% yield of the *o*-hydroxybenzeneboronic acid anhydride, which was isolated by acidification of an alkaline extract, was obtained. This is quite comparable to that which was obtained when the unprotected *o*-bromophenol was used as the starting material. The main advantage of using the acetal is the smaller *n*-butyllithium requirement in this case, only half as much being necessary as when *o*-bromophenol is used as the starting material.

The attempt to prepare *m*-hydroxybenzeneboronic acid using 2-(*m*-bromophenoxy)-tetrahydropyran as the starting material was unsuccessful. A solid material which defied purification was isolated but never identified.

When the 2-(*p*-bromophenoxy)-tetrahydropyran was treated with *n*-butyllithium and tri-*n*-butyl borate, followed by acid hydrolysis, 2-hydroxy-5-bromobenzeneboronic acid was isolated instead of *p*-hydroxybenzeneboronic acid.[19]

The third approach to the synthesis of *ortho*- and *para*-hydroxybenzeneboronic acid or anhydride involved the reaction of *o*- and *p*-chloromercuriphenol with boron trichloride in chlorobenzene followed by hydrolysis. This work was unsuccessful. Both benzeneboronic acid[20] and *o*-methoxybenzeneboronic acid[21] have been prepared by similar methods. However, the conversion of *o*-chloromercuriphenol and acetoxymercuribenzene to the corresponding boronic acids with tri-*n*-butyl borate, made by Snyder and Weaver,[1] was not successful.

Purification of the *ortho* and *meta* isomers was best accomplished by recrystallization of the crude material from ethylene chloride.[22] Usually two or three recrystallizations were required to get material of the maximum melting point, both compounds crystallizing as the anhydride. The *para* isomer was purified by recrystallization from acetone containing a small amount of water; recrystallization of this purified acid from ethylene chloride seemed to produce a mixture of anhydride and acid.

In the course of the investigation numerous solvents for the recrystallization of the *ortho* and *meta* isomers were investigated. It was found that the *ortho* isomer could be purified successfully from many solvents including benzene, toluene, water, acetone–water and acetone–benzene. It is interesting to note that regardless of the solvent used, the material always separated as the anhydride. In contrast to this, no solvent other than ethylene chloride seemed to be suitable for recrystallization of the *meta* isomer. No extensive solvent study was made on the *para* isomer.

From these results, it is seen that the ease of anhydride formation of the three isomers varies considerably. The anhydride seems to be the stable form of the *ortho* isomer. Exposure of the *o*-hydroxybenzeneboronic acid anhydride to a moist atmosphere for 6 months failed to convert it to the acid.

Although Bean and Johnson[14] reported a possible acid–anhydride mixture for the *meta* isomer recrystallized from ethylene chloride containing a small amount of acetone (based on the carbon and hydrogen analyses), the material prepared in this current work seems to be definitely the anhydride (based on the neutralization equivalent and boron analysis) which may possibly be the more stable form, although this was not definitely established.

The stable form of the *para* isomer seems to be the acid. This is based on the difficulty of conversion to the anhydride either by heating in the vacuum oven for 70 hr. at 90° or recrystallization from ethylene chloride. In both cases, material having a neutralization equivalent intermediate between the acid and anhydride was obtained.

There was a wide variation in melting point of the *ortho* isomer depending on which solvent was used for recrystallization. For example, material recrystallized from toluene generally melted over the range of 170–175° while material recrystallized from ethylene chloride had a melting point as high as 193–194°, although this was not obtained consistently. What was believed to be an analytically pure sample, obtained by recrystallization from an acetone–water system, melted over the range of 180–183°. Despite these differences in melting points, all of these specimens had the

(16) In some experiments, trimethyl borate was used.

(17) W. E. Parham and E. L. Anderson, THIS JOURNAL, **70**, 4187 (1948).

(18) B. F. Hofferth, Doctoral Dissertation, Iowa State College, 1950.

(19) Ludovico Santucci, unpublished studies.

(20) L. O. Moore, unpublished studies. See A. Michaelis, *Ann.*, **315**, 19 (1901), for the preparation of benzeneboronic acid from diphenylmercury and boron trichloride.

(21) A. Michaelis and M. Behrens, *Ber.*, **27**, 244 (1894).

(22) Eastman Kodak white label 1,2-dichloroethane distilled over phosphorus pentoxide was used.

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same neutralization equivalent. We believe that the neutralization equivalent is more of a criterion of purity than the melting point. The large differences in melting point as well as the relatively large melting point range possibly can be explained by the ratio of monomer, dimer and perhaps even trimer in the purified material. The fact that these forms may exist is based on a molecular weight determination on material recrystallized from water and having a melting point of 194–195°. This was found to be approximately 200. The molecular weight for the monomer is 120.

Both the melting points and water solubilities of these boronic acids and/or anhydrides follow the general pattern established by their carboxylic acid analogs, although there is a much more pronounced difference between the solubilities of the *o*-hydroxybenzeneboronic acid anhydride and the *meta* and *para* isomers than exists in the carboxylic acid series. There does not seem to be any logical explanation for the good water solubilities of the *meta*-anhydride and the *para*-acid in the boron series. The poor water solubility of the *o*-hydroxybenzeneboronic acid anhydride with respect to the other two isomers might be explained partially by its polymer formation. However, it is not known whether the *meta* and *para* isomers prepared in this work tend to dimerize or not. Table I shows the melting point and solubility correlation of the two series.

TABLE I

CORRELATION OF MELTING POINT AND WATER SOLUBILITIES OF HYDROXYBORONIC ACID ISOMERS WITH THEIR CORRESPONDING CARBOXY ANALOGS

Isomer	Hydroxyboronic acid M.p., °C.	H_2O sol. (qual.)[c]	Hydroxycarboxylic acid M.p., °C.	H_2O sol. (g./100 cc.)
ortho	193–194[a,b]	Poor[c]	159	0.18[20]
meta	225[b]	Very good[c]	201.3	.92[18]
para	238	Very good[c]	213	.79[15]

[a] This is the highest melting point that was obtained for this isomer. Other material of this type with a suitable neutralization equivalent had a melting point range as low as 170–175° depending upon the solvent which was used for recrystallization. [b] The anhydride. [c] Only qualitative solubility information is available.

Since no halogen–metal interconversion study had ever been carried out on the *m*-bromophenol as has been done on the *ortho* and *para* isomers,[23,24] the optimal conditions for this were determined. The amount of halogen–metal interconversion, as determined by carbonation to form the carboxylic acid, increased up through a 4-hour reaction period at 20°. Longer reaction times at this temperature did not show any higher yields. There was some indication that the yield decreased slightly with the longer reaction times (up to 24 hr.), although this was not appreciable. For this reason no reaction temperature higher than 20° was studied. Lower temperatures were not investigated.

A 34% yield of pure *m*-hydroxybenzoic acid was obtained when the halogen–metal interconversion was carried out for 4 hr. at 20° followed by carbonation and hydrolysis. In previous studies,[23,24] a 67% yield of the *ortho* isomer and a 41% yield of the *para* isomer were obtained.

Experimental[25]

o-Hydroxybenzeneboronic Acid Anhydride. (a) From *o*-Bromophenol.—To 91 g. (0.525 mole) of *o*-bromophenol dissolved in 200 ml. of anhydrous ether, cooled in an ice-bath, was added 1.08 moles of *n*-butyllithium[26] in 800 ml. of anhydrous ether. This addition was made over a period of 75 minutes, and agitation was continued for 3 hr. at 20–25° following completion of the addition at which time Color Test II[27] was negative. This halogen–metal interconversion has been reported previously.[23,24] This ether solution of lithium *o*-lithiophenoxide was then added over a period of 1 hr. to a solution composed of 248 g. (1.08 moles) of tri-*n*-butyl borate and 200 ml. of anhydrous ether cooled to −70° by means of a Dry Ice–acetone bath. Color Test I[28] was negative immediately upon completion of the addition. The reaction was permitted to warm to 0° and was hydrolyzed by the addition of 360 ml. (1.045 moles) of 10% hydrochloric acid. The aqueous layer was separated from the ether layer and was washed twice with 200-ml. portions of ether which were combined with the main ether solution. This combined ether solution was then extracted with 800 ml. of 10% sodium hydroxide in three portions. The extract was washed once with 200 ml. of ether. This alkaline solution was heated on the steam plate to expel any residual ether, after which it was acidified by the addition of 10% hydrochloric acid. The solid which precipitated weighed 76 g. after drying and had a melting point range of 130–150°. This crude material was recrystallized twice from toluene to give 35 g. (55.5%) of material melting over the range of 170–175°. This yield includes the additional material obtained by concentration of the recrystallizing liquors.

Other experiments were conducted in which variations were made in the finishing procedure. Using the same procedure as described above for the preparation of the compound, isolation was accomplished after the acid hydrolysis by evaporating the ether layer to dryness. From 98.5 g. (0.57 mole) of *o*-bromophenol, 91 g. of crude product having a melting point range of 130–148° was obtained. This was washed thoroughly with 400 ml. of water leaving 47 g. of insoluble material having a melting point range of 165–170°. This represents a 69% yield of reasonably satisfactory material. Recrystallization of this material from approximately 1 liter of dry ethylene chloride gave 37 g. of material having a melting point range of 175–180°. This represents a 55% yield of nearly pure material.

When using this second finishing procedure, it was thought that trimethyl borate would be more adaptable than tri-*n*-butyl borate since it would then involve the evaporation of methyl alcohol along with the other volatile material instead of *n*-butyl alcohol. An experiment which employed 94 g. (0.545 mole) of *o*-bromophenol with 117 g. (1.12 moles) of trimethyl borate and using the technique just discussed gave 37 g. of washed semi-pure product having a melting point range of 170–175°. This represents a yield of 56.5%. Recrystallization of the product from ethylene chloride gave 30 g. (47%) of material melting over the range of 180–185°.

The analytical sample was recrystallized from an acetone–water system to give material melting over the range of 180–183°. The optimum amounts of material were found to be 5 g. of solute for 300 ml. of water and 60 ml. of acetone.

The infrared spectrum supported the structure.

(23) H. Gilman, C. E. Arntzen and F. J. Webb, *J. Org. Chem.*, **10**, 374 (1945).

(24) H. Gilman and C. E. Arntzen, THIS JOURNAL, **69**, 1537 (1947).

(25) All melting points are uncorrected and were measured using a previously unheated oil-bath. The neutralization equivalents were obtained by dissolving 50 to 100 mg. of the compound in 50 ml. of 50% ethanol or in 50 ml. of water if its solubility permitted, adding 20 times the sample weight of D-mannitol and then titrating with standard sodium hydroxide using phenolphthalein as the indicator. In the case of *p*-hydroxybenzeneboronic acid, darkening of the solution during the titration necessitated the use of a Beckman Model G *p*H meter to detect the end-point.

(26) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, THIS JOURNAL, **71**, 1499 (1949).

(27) H. Gilman and J. Swiss, *ibid.*, **62**, 1847 (1940).

(28) H. Gilman and F. Schulze, *ibid.*, **47**, 2002 (1925).

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Anal. Calcd. for $C_6H_5BO_2$: C, 60.09; H, 4.20; B, 9.02; neut. equiv., 119.94. Found: C, 60.24, 60.30; H, 4.12, 4.18; B, 9.12, 9.21; neut. equiv., 120.0.

(b) From 2-(*o*-Bromophenoxy)-tetrahydropyran.—To a stirred solution of 25.7 g. (0.1 mole) of 2-(*o*-bromophenoxy)-tetrahydropyran[18] and 100 ml. of anhydrous ether, cooled in an ice-bath, was added 0.1 mole of *n*-butyllithium[26] in 88 ml. of ether over a period of 15 minutes. Agitation was continued for 1 hr. at room temperature following completion of the addition. Color Test II[27] was negative at this time. The reaction mass consisted of a solid suspended in ether.

The 2-(*o*-lithiophenoxy)-tetrahydropyran suspension was then added over a period of 20 minutes to a stirred solution of 34.5 g. (0.15 mole) of tri-*n*-butyl borate in 100 ml. of anhydrous ether previously cooled to −70° by means of a Dry Ice–acetone bath. The temperature was maintained below −65° during the addition and for 2 hr. following completion of the addition at which time Color Test I[28] was negative. After warming to 0°, the reaction mass was hydrolyzed by the addition of 10% hydrochloric acid. The aqueous layer was separated from the ether and washed twice with fresh ether. The combined ether solutions were then extracted with two 50-ml. portions of 10% sodium hydroxide. The alkaline solution was washed with a 100-ml. portion of ether, warmed on the steam-bath to expel any residual ether, treated with Norit-A, filtered, cooled and acidified with 10% hydrochloric acid. The gray product which separated was filtered, washed with water and dried to give 10.0 g. (83%) of crude product melting over the range of 170–175°. Recrystallization of this material from a benzene–acetone system gave 6.6 g. (55%) of product melting at 180–181°. An admixture of this with authentic 2-hydroxybenzeneboronic acid anhydride melted undepressed.

***m*-Hydroxybenzeneboronic Acid Anhydride.**—Thirty-four and six-tenths grams (0.2 mole) of *m*-bromophenol was dissolved in 90 ml. of anhydrous ether in a nitrogen atmosphere. To this stirred solution was added 0.44 mole of *n*-butyllithium[26] in 332 ml. of anhydrous ether over a period of 50 minutes, the temperature being maintained at 20° by means of a water-bath. Agitation was continued for 4 hr. at 20° at which time Color Test II[27] was negative. This ether solution of lithium *m*-lithiophenoxide then was added over a 30-minute period to a stirred solution of 140 g. (0.6 mole) of tri-*n*-butyl borate in 220 ml. of anhydrous ether previously cooled to −70° by means of a Dry Ice–acetone bath. During this time the reaction mixture became extremely viscous. Upon completion of the addition, the mixture was permitted to warm to 0°. Color Test I[28] was negative. The reaction mixture was hydrolyzed with 250 ml. of a saturated ammonium chloride solution followed by 150 ml. of 10% hydrochloric acid to get the *p*H below 7 and 100 ml. of water to dissolve some still remaining solid. The aqueous layer was separated from the ether and was washed twice with 100-ml. portions of ether which were combined with the main portion. The ether solution was extracted ten times with 60-ml. portions of 10% sodium carbonate which were poured into a stirred mixture of 400 ml. of ether and 500 ml. of a saturated ammonium chloride solution. Four hundred milliliters of 10% hydrochloric acid also was added to get the *p*H to 6. The aqueous layer was separated from the ether and was extracted several times with additional ether which was combined with the main portion. Evaporation of the ether layer to dryness left a solid material which upon crystallization from ethylene chloride gave 6 g. (25%) of material having a melting point of 208–212°. The initial ether layer was evaporated to about one-fourth its original volume and the same process was repeated. This gave an additional 1.1 g. (4.5%) of material melting at 208–212°. The two final acid aqueous layers were combined and evaporated to one-fourth volume. This was extracted several times with ether to give 0.9 g. (3.8%) of material melting at 215–230°. All of the crude material was combined and recrystallized from ethylene chloride to give 7.3 g. (30.4%) of material melting at 215–225° dec. The analytical sample was recrystallized an additional time from ethylene chloride.

The infrared spectrum supported the structure.

Anal. Calcd. for $C_6H_5BO_2$: B, 9.02; neut. equiv., 119.94. Found: B, 9.11; neut. equiv., 117, 122.4.

***p*-Hydroxybenzeneboronic Acid.**—The halogen–metal interconversion carried out was essentially that which has been described previously,[23] although a larger excess of *n*-butyllithium was used.

To a stirred solution of 33.7 g. (0.2 mole) of *p*-bromophenol dissolved in 80 ml. of anhydrous ether, 415 ml. of 1.45 *N* *n*-butyllithium (0.6 mole) was added at room temperature over a 45-minute period. Following completion of the addition, the reaction mixture was refluxed for 2 hr. After cooling with an ice-bath, the lithium *p*-lithiophenoxide suspension was added over a period of 50 minutes to a stirred solution of 140 g. (0.6 mole) of tri-*n*-butyl borate in 200 ml. of anhydrous ether previously cooled to −70° by means of a Dry Ice–acetone bath. After agitating for 2 hr. at this temperature following completion of the addition, Color Test I[28] was negative. The mixture was permitted to warm to 0° and was hydrolyzed by the addition of a saturated solution of ammonium chloride. A small amount of 10% hydrochloric acid also was added to lower the *p*H to 6. The two layers which resulted were separated, the aqueous layer being washed with fresh ether which was combined with the main ether portion. This ether extract was concentrated and was shaken with 600 ml. of 10% sodium carbonate in nine portions. Each alkaline extract was poured into a flask containing a stirred excess of saturated ammonium chloride solution and ether. This ether layer was separated from the aqueous layer, the latter being extracted with fresh ether which was combined with this second main ether portion. The ether extract was concentrated under vacuum without applying heat. About 4 g. (14.5%) of product melting at 238° crystallized from the concentrated ether solution. Recrystallization of this material from acetone containing a few drops of water did not alter the melting point.

Evaporation of the ether solution to dryness left a semi-crystalline residue which, after drying on a porous plate, weighed 9.2 g. and melted at 187–191°. Recrystallization of this material from acetone containing a few drops of water and employing a Norit-A treatment gave 4.75 g. (17.4%) of crystals melting at 230.5–231°.

In other experiments, an extraction with 8% sodium bicarbonate preceding the one with sodium carbonate and an extraction with 5% sodium hydroxide following the sodium carbonate extraction, each yielded about 0.4 g. of crude material. A final extraction with 20% sodium hydroxide gave only 0.2 g. more of very impure product.

Other experiments carried out under a variety of conditions were inferior to the procedure described above.

The analytical sample was recrystallized two more times from acetone containing a small amount of water. This material melted at 238° and gave a violet-blue color with ferric chloride. The infrared analysis confirmed the expected structure.

Anal. Calcd. for $C_6H_7BO_3$: B, 7.85; neut. equiv., 137.93. Found: B, 7.82; neut. equiv., 138.4, 136.6, 137.0.

When recrystallizing the material from acetone–water a definite crystal structure first formed, but as the material dried it disintegrated into a powder. It was thought that the anhydride might be forming but the neutralization equivalent does not support this. The powdery product was recrystallized from ethylene chloride to give material having a neutralization equivalent of 130. Heating the acid in a vacuum oven for 70 hr. at 90° gave material having a neutralization equivalent of 125.

2-(*m*-Bromophenoxy)-tetrahydropyran.—To a stirred mixture of 33.6 g. (0.4 mole) of freshly distilled dihydropyran and 4 drops of concentrated hydrochloric acid previously heated to 60° was added 34.6 g. (0.2 mole) of *m*-bromophenol over a period of 30 minutes. The rate was such as to keep the temperature below 70°. Agitation was continued for 2 hr. following completion of the addition, the temperature being permitted to drop to that of the room. Eighty milliliters of ether was added to the reaction mass which was then extracted with three 20-ml. portions of 10% sodium hydroxide. These basic aqueous layers were combined and extracted with three 50-ml. portions of ether. An additional 100 ml. of water was put in to dissolve an orange-colored solid which separated during this operation. The ether extracts were combined and were dried with anhydrous sodium sulfate. The ether and excess dihydropyran were removed by distillation at atmospheric pressure after which the remaining material was subjected to vacuum distillation. The material boiled over the range of 98–105° at 2 mm. This material was distilled a second time, two

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fractions being collected. The first fraction weighed 5 g. and distilled at 119–120° (1 mm.), while the second fraction distilled at 115° (0.4 mm.), $n^{20}D$ 1.5504, d^{20}_{20} 1.3952, and weighed 38.5 g. This second fraction represents a 75% yield of 2-(*m*-bromophenoxy)-tetrahydropyran. The method used to prepare this compound follows closely that for the *o*-bromo[18] and *p*-bromo[17] isomers.

Anal. Calcd. for $C_{11}H_{13}BrO_2$: Br, 31.08; MR_D, 58.12. Found: Br, 30.60, 30.55; MR_D, 58.75.

***m*-Hydroxybenzoic Acid.**—Eight and sixty-five hundredths gram of *m*-bromophenol was treated with 0.11 mole of *n*-butyllithium for 4 hr. at 20°. The reaction was terminated by pouring it jet-wise into a stirred slurry of Dry Ice and ether. After the mixture had warmed to room temperature, it was hydrolyzed by the addition of 50 ml. of 10% hydrochloric acid. The aqueous layer was separated and was washed twice with 50-ml. portions of ether which were combined with the main portion. The ether solution was extracted with three 25-ml. portions of 10% sodium hydroxide which were combined and acidified with concentrated hydrochloric acid. The solid which precipitated was dried and sublimed under vacuum twice to give 2.3 g. (33.3%) of material melting at 196–198° (lit. value, 201°).

Acknowledgments.—We wish to thank Mr. Robert McCord and Mr. E. Miller Layton, Jr., of the Ames Laboratory of the Atomic Energy Commission for the infrared spectra.

We also wish to acknowledge the financial support of the Division of Biology and Medicine of the United States Atomic Energy Commission which has made this work possible. The results of the biological testing of these compounds will be reported by Dr. Otho D. Easterday of the Brookhaven National Laboratory.

AMES, IOWA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

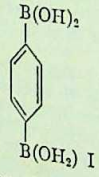
Benzenediboronic Acids

BY DONALD R. NIELSEN AND WILLIAM E. MCEWEN

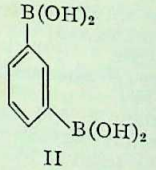
RECEIVED JANUARY 31, 1957

Benzene-1,4-diboronic acid (I) and benzene-1,3-diboronic acid (II) have been synthesized and characterized by conversion to the respective tetra-*n*-butyl esters and bis-(dichloroboryl)-benzenes.

Although more than 70 aliphatic and aromatic monoboronic acids have been described in the literature, there is no report of the synthesis of diboronic acids.[1] As part of a broad investigation of the physical and chemical properties of bifunctional organoboron compounds, syntheses of benzene-1,4-diboronic acid (I) and benzene-1,3-diboronic acid (II) have now been devised.

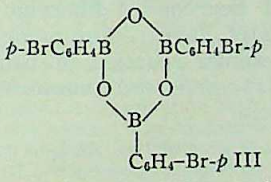


I

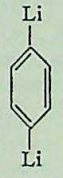


II

Benzene-1,4-diboronic acid (I) has been prepared in low yield by four different methods. When a mixture of *p*-bromophenylboronic anhydride (III), dispersed sodium and methyl borate in hexane was heated for two hours, then hydrolyzed, benzene-1,4-diboronic acid (I) was obtained in 4% yield. Reaction of di-*n*-butyl *p*-bromophenylboronate, magnesium and methyl borate in refluxing 1,2-dimethoxyethane for 30 hours gave, after hydrolysis of the reaction mixture, a 10% yield of I. The yield of benzene-1,4-diboronic acid (I) amounted to 26% in a reaction in which methyl borate, which had been frozen and pulverized, was added to a suspension of *p*-dilithiobenzene (IV) in petroleum ether at −30°, followed by hydrolysis of the reaction mixture. The dilithio compound IV was prepared by metal–halogen exchange between *n*-butyllithium and *p*-dibromobenzene according to the procedure of Gilman, Langham and Moore.[2] It is noteworthy that the yield of I is considerably below that of terephthalic acid, which may be obtained in 66–89% yield by an analogous carbonation reaction of the exchange mixture.



III



IV

The best yield of I was obtained by use of the Grignard reaction. A mixture of *p*-dibromobenzene and two equivalents of magnesium in tetrahydrofuran was refluxed for a period of seven hours, then methyl borate was added to the reaction mixture maintained at about −30°. After hydrolysis of the reaction products, the resulting acids were esterified with *n*-butyl alcohol and the esters fractionated. There was obtained tetra-*n*-butyl benzene-1,4-diboronate (V) in 35% yield, together with di-*n*-butyl *p*-bromophenylboronate (5%) and di-*n*-butyl phenylboronate (19%). Hydrolysis of the butyl esters gave quantitative yields of the respective arylboronic acids. The prolonged period of heating is evidently necessary for the formation of the dimagnesium Grignard compound in moderately satisfactory yield, since the yield of benzene-1,4-diboronic acid (I) dropped to 10% when the mixture of *p*-dibromobenzene and magnesium was heated for only 2.5 hours prior to the reaction with methyl borate. Extended refluxing of a solution of *p*-dibromobenzene in ethyl ether

(1) M. P. Lappert, *Chem. Revs.*, **56**, 959 (1956).

(2) H. Gilman, W. Langham and F. W. Moore, THIS JOURNAL, **62**, 2327 (1940).

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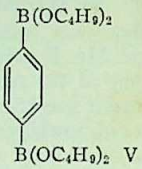
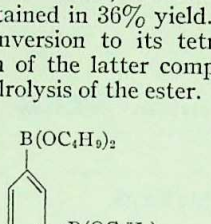
has been reported to give the dimagnesium Grignard reagent in yields of only 4–23%.[3–5]



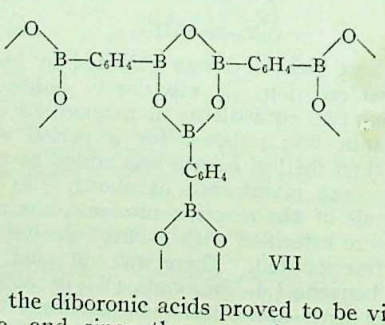
V

Benzene-1,3-diboronic acid (II) was obtained in 10% yield after hydrolysis of the product obtained by addition of methyl borate to the halogen–metal exchange mixture from *m*-dibromobenzene and *n*-butyllithium. By use of the dimagnesium Grignard compound of *m*-dibromobenzene instead of the dilithio derivative, however, the diboronic acid II was obtained in 36% yield. The acid was isolated by conversion to its tetra-*n*-butyl ester VI, purification of the latter compound by distillation, then hydrolysis of the ester.



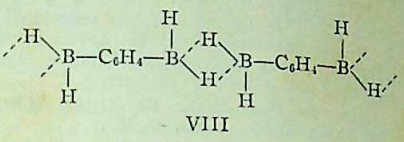
VI

Both of the diboronic acids I and II proved to have exceptionally high melting points. Neither compound melted at temperatures up to 420°. It is thought that the acids gradually lose water upon being heated and form polymers of the type shown in structure VII. The structures of the acids were established by application of Melnikov's procedure.[6] Treatment of benzene-1,4-diboronic acid (I) with bromine water gave *p*-dibromobenzene and boric acid. A similar reaction of benzene-1,3-diboronic acid (II) gave *m*-bromophenylboronic acid plus boric acid.



VII

Since the diboronic acids proved to be virtually infusible, and since the respective tetra-*n*-butyl esters were liquids, an attempt was made to prepare solid derivatives of the acids having convenient melting points. The tetrachlorides were chosen because our future plans include attempts to prepare polymers of the type shown in structure VIII (or polymers which would result upon disproportionation of VIII) by reduction of the tetrachlorides.

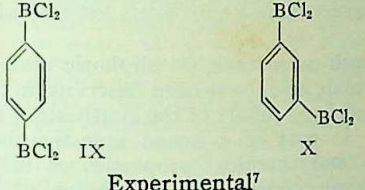


VIII

Inasmuch as the diboronic acids were isolated and purified most conveniently by way of their tetra-*n*-butyl esters, a method for the direct conversion of the esters to the halides was desired. In a model experiment it was found that di-*n*-butyl phenylboronate could be converted to the known phenyldichloroborane by reaction with phosphorus pentachloride. The stoichiometry was established as

$$C_6H_5B(OC_4H_9)_2 + 2PCl_5 \longrightarrow C_6H_5BCl_2 + 2POCl_3 + 2C_4H_9Cl$$

Treatment of tetra-*n*-butyl benzene-1,4-diboronate (V) with four equivalents of phosphorus pentachloride gave 1,4-bis-(dichloroboryl)-benzene (IX), m.p. 93–96°, in 84% yield. An analogous reaction with tetra-*n*-butyl benzene-1,3-diboronate (VI) gave 1,3-bis-(dichloroboryl)-benzene (X), m.p. 54–56°, in 58% yield. Both of the tetrachlorides underwent very rapid hydrolysis upon contact with moist air.



IX X

Experimental[7]

General Experimental Precautions.—All preparations of organoboron compounds were carried out in an atmosphere of dry, oxygen-free nitrogen. All transfer operations involving air-sensitive or moisture-sensitive organoboron compounds were carried out in a dry-box in an atmosphere of pure nitrogen.

Benzene-1,4-diboronic Acid (I). A. Use of 1,4-Dilithiobenzene (IV).—To a solution of 52.0 g. (0.22 mole) of *p*-dibromobenzene in 500 ml. of petroleum ether was added a solution containing 0.50 mole of *n*-butyllithium in petroleum ether. The mixture was heated with stirring for 20 hours. An insoluble solid began to form immediately after the addition of the *n*-butyllithium, and the solid increased in amount as the exchange reaction progressed.

The mixture was placed in an acetone–Dry Ice-bath, and 52 g. (0.50 mole) of methyl borate, which had been frozen and pulverized, was added. The reaction mixture was allowed to warm slowly to room temperature, then hydrolyzed and acidified by the addition of dilute hydrochloric acid. The layers were separated, and the aqueous layer was extracted with ether. The combined ether–petroleum ether solution was concentrated almost to dryness. A solid which had precipitated was collected by filtration, washed with petroleum ether and recrystallized from water. There was obtained 9.45 g. (26%) of benzene-1,4-diboronic acid (I), which did not melt up to a temperature of 420°.

Anal. Calcd. for $C_6H_8B_2O_4$: C, 43.47; H, 4.87; B, 13.06. Found: C, 43.41; H, 4.83; B, 13.28.

Further concentration of the combined ether–petroleum ether filtrate and wash solution left a residue consisting of a colorless solid and a yellow liquid. The solid was collected by filtration and dissolved in ether. Addition of ethanolamine caused a solid product to precipitate. This was recrystallized from benzene, giving a small amount of

(3) R. Quelet, *Bull. soc. chim.*, **41**, 933 (1927).

(4) Y. S. Zalkind and P. V. Raginova, *J. Russ. Phys. Chem. Soc.*, **59**, 1013 (1927).

(5) H. Gilman, H. J. Beaber and H. L. Jones, *Rec. trav. chim.*, **48**, 597 (1929).

(6) N. N. Melnikov, *J. Gen. Chem. (U.S.S.R.)*, **8**, 1766 (1938); *C. A.*, **33**, 4908 (1939).

(7) All melting points are uncorrected and all b.p.'s are uncorrected. Analyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

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aminoethyl di-*p*-bromophenylborinate, m.p. 235.6–237.2°, reported[8] m.p. 236–237°.

Anal. Calcd. for $C_{14}H_{14}BBr_2NO$: C, 43.91; H, 3.69; B, 2.83; Br, 41.74; N, 3.66. Found: C, 44.19; H, 3.50; B, 3.16; Br, 41.75; N, 3.62.

In a second run, liquid methyl borate was used in place of solid methyl borate. Benzene-1,4-diboronic acid was obtained in 23% yield.

When the exchange mixture, prepared as described above, was added to powdered Dry Ice, then acidified with dilute hydrochloric acid, there was obtained terephthalic acid in 66% yield and *p*-bromobenzoic acid in 13% yield. Gilman, Langham and Moore[2] obtained terephthalic acid in 89% yield in a similar experiment.

B. Use of the Dimagnesium Grignard Compound of *p*-Dibromobenzene.—A solution of 36.7 g. (0.155 mole) of *p*-dibromobenzene in 250 g. of anhydrous tetrahydrofuran was added over a period of 35 minutes to 7.45 g. (0.31 g. atom) of magnesium, reaction proceeding vigorously throughout this period. After all of the *p*-dibromobenzene had been added, the mixture was heated to 60–64° for seven hours. During the initial stages of the reaction a colorless solid precipitated, and the amount of this solid increased as the reaction progressed. The mixture was placed in an acetone–Dry Ice-bath, and 27 g. (0.26 mole) of methyl borate was added. The mixture was allowed to warm gradually to room temperature, then hydrolyzed and acidified with dilute hydrochloric acid. After ether extraction of the acid solution and distillation of solvent from the extract, an excess of 1-butanol was added to the residue. The mixture was distilled until the temperature of the distillate, which remained at 90–92° during distillation of the water-butanol azeotrope, rose to 115°. Distillation of the residue at reduced pressure gave 13.9 g. of *n*-butyl borate, b.p. 63–85° (0.1 mm.), and 6.93 g. (19%) of di-*n*-butyl phenylboronate, b.p. 85–90° (0.1 mm.). A dark solid distillation residue became colorless on addition of water. Recrystallization of this solid from water gave 12.31 g. of benzene-1,4-diboronic acid (I) contaminated with some *p*-bromophenylboronic acid. The mixture of acids was esterified with 1-butanol by distillation of the water–butanol azeotrope as described above; then the esters were purified by distillation. There was obtained 2.53 g. (5%) of crude di-*n*-butyl *p*-bromophenylboronate, b.p. 87–130° (0.4 mm.), and 17.9 g. (35%) of tetra-*n*-butyl benzene-1,4-diboronate (V), b.p. 160–176° (0.4 mm.).

Anal. Calcd. for $C_{22}H_{40}B_2O_4$: C, 67.72; H, 10.33; B, 5.55. Found: C, 67.85; H, 10.11; B, 5.83.

Each of the butyl esters cited above underwent rapid hydrolysis on contact with water to give the respective boronic acids and *n*-butyl alcohol in quantitative yield.

C. Use of Grignard Reagent Prepared from Di-*n*-butyl *p*-Bromophenylboronate.—A mixture of 64.0 g. (0.204 mole) of di-*n*-butyl *p*-bromophenylboronate, 21.0 g. (0.20 mole) of methyl borate, 200 ml. of 1,2-dimethoxyethane and 5.0 g. (0.208 g. atom) of magnesium turnings was refluxed for 50 hours. The mixture was hydrolyzed by addition of dilute hydrochloric acid and extracted with ether. The residue obtained upon distillation of the ether was crystallized from water, giving 3.38 g. (10%) of benzene-1,4-diboronic acid (I).

D. Use of *p*-Bromophenylboronic Anhydride (III), Sodium and Methyl Borate.—*p*-Bromophenylboronic anhydride (III) was prepared by dehydration of *p*-bromophenylboronic acid in an evacuated desiccator over concentrated sulfuric acid for one day. A mixture containing 8.0 g. (0.044 mole) of *p*-bromophenylboronic anhydride, 7.8 g. (0.295 g. atom) of dispersed sodium and 400 ml. of hexane was stirred for three hours at room temperature without any apparent reaction taking place. After addition of 15.4 g. (0.148 mole) of methyl borate, the mixture was heated to 75° for two hours. Hydrolysis of the reaction mixture with dilute hydrochloric acid and use of an isolation procedure similar to that described above gave 0.28 g. (4%) of benzene-1,4-diboronic acid (I).

Proof of Structure of Benzene-1,4-diboronic Acid (I).—A solution of 1.00 g. (0.00604 mole) of benzene-1,4-diboronic acid in dilute sodium hydroxide was neutralized to the phenolphthalein end-point with dilute hydrochloric acid. The mixture was cooled, and an excess of bromine in potassium bromide solution was added. The mixture was allowed to stand for several hours, then 1.06 g. (0.0045 mole, 75%) of *p*-dibromobenzene was collected by filtration. After two crystallizations from ethanol its m.p. was 90–92°, and its infrared absorption spectrum in chloroform solution was identical with that of a corresponding solution of authentic *p*-dibromobenzene.

p-Bromophenylboronic Acid.—This acid was prepared by a modification of the procedure of Konig and Scharrnbeck.[9] To *p*-bromophenylmagnesium bromide prepared from 11.3 g. (0.485 g. atom) of magnesium, 114.3 g. (0.485 mole) of *p*-dibromobenzene and 600 ml. of anhydrous ether, cooled in an acetone–Dry Ice-bath, was added 50.5 g. (0.485 mole) of methyl borate. The mixture was allowed to warm to room temperature, refluxed for 30 minutes, then hydrolyzed by addition of dilute hydrochloric acid and extracted with ether. Concentration of the ether solution and crystallization of the residue from water gave 51.9 g. (53%) of *p*-bromophenylboronic acid, m.p. 273–281°; reported[9] m.p. 266° for *p*-bromophenylboronic acid and m.p. 280° for *p*-bromophenylboronic anhydride.

In a second run, the crude acid from the ether extract was added to 110 ml. of *n*-butyl alcohol and distilled. After removal of the water–butanol azeotrope (b.p. 92°) and excess alcohol, the residue was distilled at reduced pressure. There was obtained a 57% yield of di-*n*-butyl *p*-bromophenylboronate, b.p. 122–126° (2 mm.).

1,4-Bis-(dichloroboryl)-benzene (IX).—To 88.9 g. (0.426 mole) of phosphorus pentachloride was added a solution of 41.7 g. (0.107 mole) of tetra-*n*-butyl benzene-1,4-diboronate (V) in 126 g. of carbon tetrachloride, and the mixture was refluxed for seven hours. Distillation of the carbon tetrachloride[10] (together with the by-products, *n*-butyl chloride and phosphorus oxychloride) and sublimation of the residue at 0.5 mm. pressure gave 21.5 g. (0.09 mole, 84%) of 1,4-bis-(dichloroboryl)-benzene (IX). After a second sublimation the material melted at 93–96° in a sealed tube.

Anal. Calcd. for $C_6H_4B_2Cl_4$: C, 30.08; H, 1.68; B, 9.03; Cl, 59.20. Found: C, 30.16; H, 1.86; B, 8.94; Cl, 58.85.

The compound is extremely sensitive to moisture and is hydrolyzed almost instantly on contact with moist air.

Benzene-1,3-diboronic Acid (II). A. Use of the Dimagnesium Grignard Compound of *m*-Dibromobenzene.—A solution of 38.8 g. (0.165 mole) of *m*-dibromobenzene in 410 g. of anhydrous tetrahydrofuran was added over a period of five hours to 8.15 g. (0.34 g. atom) of magnesium. After addition of the *m*-dibromobenzene, the mixture was maintained at a temperature of about 40° and stirred for another five hours. The mixture was then cooled in an acetone–Dry Ice-bath, and 40 g. (0.384 mole) of methyl borate was added. After being allowed to warm gradually to room temperature, the reaction mixture was hydrolyzed by addition of dilute hydrochloric acid and extracted with ether. The residue obtained on distillation of the ether was esterified with *n*-butyl alcohol by the azeotropic method cited for the preparation of tetra-*n*-butyl benzene-1,4-diboronate (V). Distillation at reduced pressure yielded only *n*-butyl borate and a small amount of di-*n*-butyl phenylboronate. The process of esterification of the residue and removal of esters by distillation at reduced pressure was repeated until no more ester distilled. The distillate was collected in four fractions: (1) *n*-butyl borate, b.p. 58–77° (0.1 mm.), 19.61 g.; (2) di-*n*-butyl phenylboronate, b.p. 77–100° (0.1 mm.), 9.97 g. (26%); (3) di-*n*-butyl *m*-bromophenylboronate, b.p. 100–123° (0.1 mm.), 3.56 g. (7%); (4) tetra-*n*-butyl benzene-1,3-diboronate, b.p. 170–181° (0.1 mm.), 22.9 g. (36%). The last fraction was analyzed.

Anal. Calcd. for $C_{22}H_{40}B_2O_4$: C, 67.72; H, 10.33; B, 5.55. Found: C, 67.89; H, 10.26; B, 5.68.

The identity of the major constituent of each of the distillation fractions was established by hydrolysis and isolation of the acid component of the ester. For example, hydrolysis of a portion of fraction 4 was effected by heating the ester in water until it dissolved, then collecting the acid which

(8) R. L. Letsinger and I. H. Skoog, THIS JOURNAL, **77**, 2491 (1955).

(9) W. Konig and W. Scharrnbeck, *J. prakt. Chem.*, **128**, 153 (1930).

(10) Much of the phosphorus pentachloride remained unchanged after the period of refluxing. It was only after the mixture had been concentrated to about 100 ml. that all of the phosphorus pentachloride was consumed.

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crystallized on cooling of the solution. After the product, benzene-1,3-diboronic acid (II), had been recrystallized from water and dried in an evacuated desiccator, it did not melt up to 420°.

Anal. Calcd. for $C_6H_8B_2O_4$: C, 43.47; H, 4.87; B, 13.06. Found: C, 43.71; H, 4.99; B, 12.77.

B. Use of 1,3-Dilithiobenzene.—To a solution of 15.9 g. (0.068 mole) of *m*-dibromobenzene in 300 ml. of petroleum ether was added 100 ml. of a petroleum ether solution containing 0.135 mole of *n*-butyllithium. The mixture was stirred for five hours, the temperature being maintained at about 34°. To the resulting mixture, cooled in an acetone–Dry Ice-bath, was added 14.0 g. (0.135 mole) of methyl borate. The mixture was allowed to warm gradually to room temperature, hydrolyzed with dilute hydrochloric acid and extracted with ether. After distillation of the ether and petroleum ether, the residue was digested with hot water and filtered. From the filtrate there was obtained 1.1 g. (10%) of benzene-1,3-diboronic acid (II).

When the exchange mixture was caused to react with carbon dioxide, rather than with methyl borate, isophthalic acid could be isolated in 30% yield.

Proof of Structure of Benzene-1,3-diboronic Acid (II).—The method used was the same as that described for the proof of structure of benzene-1,4-diboronic acid (I). However, in this experiment *m*-bromophenylboronic acid, m.p. 169–173° (reported[11] m.p. 170°), was isolated instead of *m*-dibromobenzene. The infrared spectrum of a chloroform solution of the product was identical with that of a chloroform solution of authentic *m*-bromophenylboronic acid.

In an independent experiment it was shown that *m*-bromophenylboronic acid is not cleaved by bromine water under the conditions used for the proof of structure of benzene-1,3-diboronic acid (II).

***m*-Dibromobenzene.**—This compound was prepared in 51% yield by a modification of the method of Mathieson and Newberry.[12] A cold solution of *m*-bromobenzenediazonium bisulfate was added to a suspension of cuprous bromide in water, through which a vigorous current of steam was being passed. Mathieson and Newberry[12] obtained *m*-dibromobenzene in 25% yield by adding cuprous bromide to *m*-bromobenzenediazonium bisulfate at 75°.

***m*-Bromophenylboronic Acid.**—The acid, m.p. 161–166°, was obtained in 46% yield from *m*-dibromobenzene, the procedure being the same as that employed for the preparation of *p*-bromophenylboronic acid.

1,3-Bis-(dichloroboryl)-benzene (X).—Tetra-*n*-butyl benzene-1,3-diboronate was caused to react with phosphorus pentachloride in the same manner as described for the preparation of bis-1,4-(dichloroboryl)-benzene (IX). After distillation of the carbon tetrachloride and the by-products *n*-butyl chloride and phosphorus oxychloride at atmospheric pressure, the residue was distilled *in vacuo*. There was obtained a 58% yield of 1,3-bis-(dichloroboryl)-benzene (X), b.p. 82–84° (1.2 mm.). After two sublimations at 50 mm. pressure, the colorless sublimate had a m.p. of 54–56° in a sealed tube.

Anal. Calcd. for $C_6H_4B_2Cl_4$: C, 30.08; H, 1.68; B, 9.03; Cl, 59.20. Found: C, 29.98; H, 1.78; B, 9.23; Cl, 58.95.

Phenyldichloroborane.—Di-*n*-butyl phenylboronate was prepared by the method of Torssell.[13] To a stirred suspension of 57.0 g. (0.274 mole) of phosphorus pentachloride in 130 g. of carbon tetrachloride was added 32.1 g. (0.137 mole) of di-*n*-butyl phenylboronate. A mildly exothermic reaction occurred, but only a small amount of the phosphorus pentachloride was consumed. Distillation of the solvent was commenced and as the distillation proceeded the remainder of the phosphorus pentachloride was consumed. After removal of solvent and the by-products *n*-butyl chloride and phosphorus oxychloride, the residue was distilled *in vacuo*. There was obtained 17.2 g. (79%) of phenyldichloroborane, b.p. 65–67° (14 mm.); reported b.p. 175°[14] and 178°[15] (760 mm.).

Anal. Calcd. for $C_6H_5BCl_2$: C, 45.37; H, 3.17; B, 6.81; Cl, 44.65. Found: C, 45.61; H, 3.44; B, 6.56; Cl, 44.84.

In order to determine the yields of by-products, the reaction was repeated without a solvent. To 130 g. (0.625 mole) of phosphorus pentachloride was added 68.5 g. (0.292 mole) of di-*n*-butyl phenylboronate. Much heat was evolved as the reagents were mixed, but not all of the phosphorus pentachloride was consumed until the mixture had been heated at about 70° for an additional two hours. Fractional distillation of the liquid product gave 53.1 g. (0.574 mole, 98%) of *n*-butyl chloride, b.p. 74–78°; 73.3 g. (0.479 mole, 82%) of phosphorus oxychloride, b.p. 90–105°; and 33.1 g. (0.208 mole, 71%) of phenyldichloroborane, b.p. 63–70° (14 mm.).

The crude *n*-butyl chloride was washed with dilute sodium carbonate solution, dried over anhydrous sodium sulfate, redistilled, converted to the Grignard reagent in ether solution and added to powdered carbon dioxide. *n*-Valeric acid was obtained by acidification of the mixture and extraction with ether. A portion of the acid was converted to the *p*-bromophenacyl ester, m.p. 73.6–75.2°, and another portion to the α-naphthalide, m.p. 112.4–113.8°, by conversion to the acid chloride and reaction of the latter with 1-aminonaphthalene.

(11) B. Bettman, G. E. K. Branch and D. L. Yabroff, THIS JOURNAL, **56**, 1865 (1934).

(12) D. W. Mathieson and G. Newberry, *J. Chem. Soc.*, 1133 (1949).

(13) K. Torssell, *Acta Chem. Scand.*, **8**, 1779 (1954).

(14) A. Michaelis and P. Becker, *Ber.*, **13**, 58 (1880).

(15) E. Pace, *Atti accad. Lincei*, **10**, 193 (1929); *C. A.*, **24**, 1360 (1930).

LAWRENCE, KANSAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Mechanism of Fluorination. III.[1] Fluorine Atom Reactions. The Olefin Dimerization Reaction[2,3]

BY WILLIAM T. MILLER, JR., AND STANLEY D. KOCH, JR.

RECEIVED AUGUST 10, 1956

A general mechanism is presented for the reactions of elemental fluorine with perhalo-olefins. This mechanism accounts for the formation of dimer addition products by the diffusion-controlled combination of free radicals which are produced in pairs with the intermediate formation of fluorine atoms. This process appears to be unique with fluorine. The important new steps in the mechanism are tested by reactions of fluorine with mixtures of perhalo-olefins of different reactivities and with an olefin and chloroform. The results obtained are shown to support the proposed mechanism and to demonstrate the very great and indiscriminate reactivity of fluorine atoms.

(1) Preceding paper in this series, W. T. Miller, Jr., S. D. Koch, Jr., and F. W. McLafferty, THIS JOURNAL, **78**, 4992 (1956).

(2) Presented at the 118th Meeting of the American Chemical Society, Chicago, Ill., Sept., 1950 (Abstracts of Papers, p. 23L).

(3) This work has been supported in part by the Office of Naval Research.

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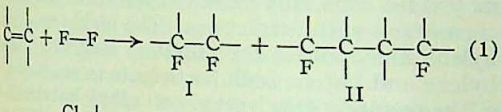
Introduction

A characteristic feature of the reactions of elemental fluorine with organic compounds is the formation of polymeric products.[4] With unsaturated compounds coupling can occur both by dehydrogenation and by reaction with olefinic bonds. As a result complicated mixtures of reaction products usually are formed. In contrast, reactions between fluorine and perhalo-olefins containing only chlorine and/or fluorine can be limited to attack at the double bond and useful yields of pure products obtained. A number of such reactions have been carried out by passing gaseous fluorine into rapidly stirred liquid olefins at 0° or below and described previously as synthetic procedures.[5,6] The principal products are the fluorine addition product I and the dimer addition product II. The yield of dimer addition product varies with olefin structure and parallels the rate of reaction with fluorine. An unreactive olefin yields little dimer while a highly reactive olefin always gives appreciable amounts.[7] Polymeric products higher than dimers are not obtained. With chlorine-containing olefins varying amounts of by-products corresponding to substitution of chlorine by fluorine III[9] and to the addition of chlorine fluoride IV are usually formed.



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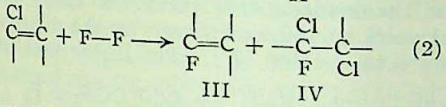

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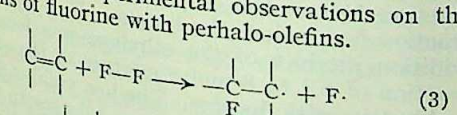
The present paper presents a general free radical mechanism that accounts for the formation of these typical reaction products, and the results of new experiments with mixtures of olefins designed especially to test the proposed mechanism for the formation of fluorine dimer addition products and to furnish information regarding the behavior of fluorine atoms.

Results and Discussion

General Reaction Mechanism.—The following series of reactions has been found to be consistent with available experimental observations on the reactions of fluorine with perhalo-olefins.



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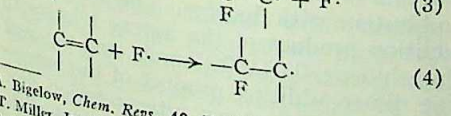

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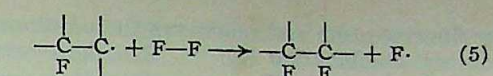

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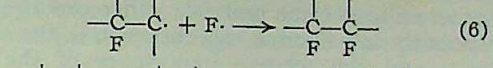

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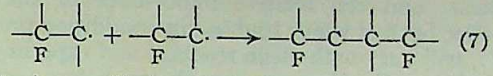

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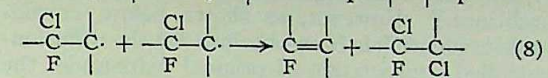

(8)

The key to the over-all mechanism is provided by the discovery that fluorine molecules react rapidly with olefinic bonds at low temperatures to produce a fluorinated free radical and a fluorine atom. This process is formulated as the rate-controlling initiation step 3. The fluorine atom can combine with an adjacent olefin molecule to yield a second free radical (4) or with the first-formed free radical (6). Combination of the radicals produced by reactions 3 and 4 yields fluorine dimer addition product (7).[10,12] Disporportionation and secondary reactions of the resulting olefin account for the principal by-products (8).[14] The occurrence of reactions 3 and 4 was shown by experiments with the addition of oxygen and of chlorine, in which fluorine served as a free-radical initiator. Products corresponding to the initial free radicals were isolated and the formation of the usual fluorination products was inhibited.[1,15] In the presence of an appreciable concentration of fluorine, reactions 5 and 4 similarly lead to the formation of fluorine addition product I. Such conditions are achieved when the rate of mixing of fluorine is fast in terms of reaction 3. However, with most of the olefins which have been investigated reaction 3 appears to occur so rapidly even at −75° (Dry Ice temperature) that it is difficult or impossible to attain an appreciable concentration of fluorine in the liquid phase. Under these conditions it is considered that the pairs of radicals formed in close proximity by reactions 3 and 4 have a relatively high probability of collision and of reaction before diffusing apart or encountering a fluorine molecule. The required very high efficiency of reaction 4 is consistent with the expected great reactivity and small steric requirement for reaction of

(4) L. A. Bigelow, *Chem. Revs.*, **40**, 51 (1947).

(5) W. T. Miller, Jr., R. L. Ehrenfeld, J. M. Phelan, M. Prober and S. K. Reed, *Ind. Eng. Chem.*, **39**, 401 (1947).

(6) W. T. Miller, Jr., Nat. Nuclear Energy Ser., Div. VII, I, "Prepn., Properties, and Technol. of Fluorine and Org. Fluorine Compds.," McGraw-Hill Book Co., Inc., New York, N. Y., 1951, Chap. 32, p. 567.

(7) The following olefins have yielded fluorine dimer addition products as indicated[5,6]: $CCl_2=CCl_2$, 43% at −15°[8]; CClF=CClF, 44% at −75°; $CF_3CCl=CCl_2$, 15% at 0°; $CF_3CCl=CF_2$, 63% at −75°.

(8) W. T. Miller, Jr., and E. Rutner, unpublished work.

(9) Often separated in the form of secondary reaction products.

(10) Bockemüller early proposed that the formation of fluorine addition and dimer addition products proceeded through an unstable intermediate addition compound formed between fluorine and the olefin.[11] Aside from the nebulous formulation of such a compound for which bonding orbitals are not available, it fails to explain the free radical nature of the fluorination process and the formation of the observed by-products.

(11) W. Bockemüller, *Ann.*, **506**, 20 (1933).

(12) Bigelow has suggested that the formation of fluorine dimer addition product may occur by combination of free radicals but without accounting for how such a process could become a probable one,[4] and, more recently, the possible formation of fluorine dimer addition product by free radical addition to olefin followed by reaction with fluorine.[13] The latter explanation is inconsistent with the failure of most perhalo-olefins to undergo free radical polymerization at low temperatures and with the complete lack of formation of polymers higher than dimers by reaction with fluorine.

(13) L. A. Bigelow, "Fluorine Chemistry," Vol. I, Chap. 11, Academic Press, Inc., New York, N. Y., 1950.

(14) Other by-products that have been isolated in low yields from chlorine-containing olefins[5,6] may be attributed to the presence of oxygen, which by reaction yields chlorine atoms.[15] Chlorine fluoride addition product (IV) may also result from the oxygen reaction.

(15) W. T. Miller, Jr., and A. L. Dittman, This Journal, **78**, 2793 (1956).

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the fluorine atom and minimizes the occurrence of primary combination (6).[16,19] Reactions between free radicals which diffuse away from their original partners also become probable under conditions of sufficiently low fluorine concentration in the liquid phase, and the relative importance of the two paths, both of which lead to dimer addition product (7), will vary with olefin reactant and experimental conditions.[20] However, as shown below, considerable evidence has been obtained for the diffusion-controlled combination of original pairs under the conditions of the present work.

Low temperatures to −75° have been shown, in general, to favor the formation of fluorine dimer addition product, to reduce the formation of by-products and to a lesser extent to reduce the amount of addition product.[5,6] These observations are consistent with the expected effect of increased viscosity of the reaction medium on the coupling of free radicals produced in pairs and with a lower activation energy for radical coupling (7) as compared with disproportionation (8), which requires transfer of halogen. 2-Chloropentafluoropropene, for which reaction 8 requires shift of fluorine, gave essentially no by-products at −75°.[5,6] On the other hand, it is to be expected that at sufficiently low temperatures the rate of reaction between fluorine and olefin (3) can be reduced to the point where the yield of dimer addition product will be lowered owing to increased concentration of fluorine in the liquid phase. This effect has been observed with hexachloropropene on going from 0 to −75°.[21] The temperature, through its effect on the vapor pressure of the olefin reactant, also controls the proportion of reaction occurring in the vapor phase above the liquid surface. Increased reaction in the vapor phase would be expected to increase the amount of fluorine addition product relative to dimer addition product because of the higher concentration of fluorine present and faster separation of radical pairs.

Fluorine Dimerization of Mixed Olefins.—Experiments designed to test the fluorine–olefin dimerization process outlined above, which requires the formation of pairs of free radicals with a high probability of combination, consisted of a series of reactions between elemental fluorine and mixtures of two olefins of different reactivities. Based on the assumptions that the fluorine atom reacts with all olefinic bonds indiscriminately and that free radical pairs combine with little selectivity, unambiguous predictions could be made regarding expected reaction products. For mixtures of two (or more) olefins participation in the initiation reaction 3 should vary with olefin reactivity and occur predominantly with the more reactive olefin. On the other hand, all olefins present, regardless of their reactivity toward molecular fluorine, should be attacked by fluorine atoms (4) to form free radicals which take part in reaction 7. Consequently, appreciable amounts of mixed-type dimer addition products should be produced as well as the products formed by reaction of each olefin separately with fluorine.[22]

Reactions of fluorine with the individual olefins *sym*-dichlorodifluoroethylene, 1,2-dichlorotetrafluoropropene, hexafluorocyclobutene and 2,3-dichlorohexafluoro-2-butene and with equimolar mixtures of *sym*-dichlorodifluoroethylene and each of the three other olefins were carried out at −75° under standardized reaction conditions. These olefins cover a wide range of reactivity toward fluorine, from fast to slow, and yield dimer addition products in the same order. *sym*-Dichlorodifluoroethylene is highly reactive and readily forms a dimer addition product; 2,3-dichlorohexafluoro-2-butene is unreactive by comparison and could not be shown to yield a dimer-addition product.

The reaction between fluorine and *sym*-dichlorodifluoroethylene and 2,3-dichlorohexafluoro-2-butene yielded especially clean-cut results which were in agreement with predictions. The highly reactive ethylene monopolizes the initiation step (3′); the ethylene and butene both participate in reaction 4′ and the resulting ethyl–ethyl and ethyl–butyl radical pairs combine as shown by the dimer addition products isolated (7′). The higher yield of mixed

$$CClF{=}CClF + F{-}F \longrightarrow CClF_2CClF\cdot + F\cdot \quad (3')$$

$$CClF{=}CClF + F\cdot \longrightarrow CClF_2CClF\cdot \quad (4')$$

$$CF_3CCl{=}CClCF_3 + F\cdot \longrightarrow CF_3CClFCCl(CF_3)\cdot$$

$$CClF_2CClF\cdot + CClF_2CClF\cdot \longrightarrow CClF_2CCClFCClFCClF_2 \quad (7')$$

V

$$CClF_2CClF\cdot + CF_3CClFCCl(CF_3)\cdot \longrightarrow CClF_2CClFCCl(CF_3)CClFCF_3$$

VI

dimer addition product (VI) compared with the dimer addition product of the ethylene (V), 0.13/0.061 mole, can be attributed to a concentration effect on reaction 4 since the ethylene disappears from the reaction faster than the butene. Very little dimer addition product of the ethylene was formed by reaction of a 1 to 8 molar mixture of the ethylene and butene with fluorine. The low yield of fluorine addition product of the butene relative to that of the ethylene, 0.011/0.12 mole, and the lack of fluorine dimer addition product of the butene provide support for the above interpretation and suggest that most of the butyl radicals react with the *corresponding* ethyl radicals of step 3. Other factors such as steric hindrance may conceivably prevent the formation of dimer addition product from the dichloro-2-butene and favor cross combination of the perhalo-radicals. However, no evidence for the importance of such effects has been obtained. Each

(16) Analogous to "primary recombination"[17] of pairs of radicals, produced by a dissociation, within the "cage" in which they are formed. Reaction 7 corresponds to diffusive[18] or "secondary recombination."[17]

(17) R. M. Noyes, THIS JOURNAL, **77**, 2042 (1955).

(18) J. C. Roy, R. R. Williams, Jr., and W. H. Hamill, *ibid.*, **76**, 3274 (1954).

(19) Experimental evidence for the occurrence of reaction 6 as a primary combination process is provided by the isolation of CCl_2FCCl_2F from the fluorine-sensitized oxidation[15] and chlorination[1] of $CCl_2{=}CCl_2$.

(20) Polymeric products have been obtained in relatively low yields by reaction of perfluoro-olefins with fluorine in the vapor phase due presumably to the production of high radical populations by very rapid reaction of the olefins with fluorine.[5]

(21) W. T. Miller, Jr., and G. Cavalli, unpublished work.

(22) At least one olefin must be sufficiently reactive with fluorine to form a dimer addition product when reacting alone and also to maintain a low concentration of fluorine in the liquid phase of the mixture.

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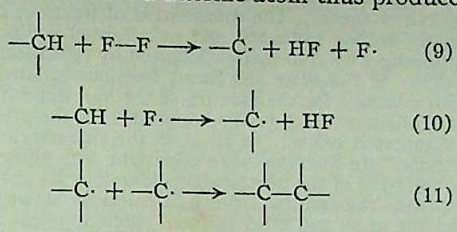
of the three possible dimer addition products was isolated from the reactions described below with hexafluorocyclobutene and 1,2-dichlorotetrafluoropropene. Further, 1,4-dichlorohexafluoro-2-butene, which is more reactive toward fluorine than the 2,3-dichloro isomer and is considered to be subject to a similar steric effect, has been shown to yield dimer addition product at 0°.[6]

Unlike 2,3-dichlorohexafluoro-2-butene, hexafluorocyclobutene and to a greater extent 1,2-dichlorotetrafluoropropene, are sufficiently reactive to take part in the initiation reaction 3 in competition with *sym*-dichlorodifluoroethylene. In all cases each of the three possible dimer addition products was isolated in an amount proportional to the relative reactivity of the olefins involved. These observations support the postulated non-selective combination of free radical pairs. The effect of fluorine concentration was also shown more clearly. Only a trace of fluorine dimer addition product, C_8F_{14}, was formed from hexafluorocyclobutene with incomplete absorption of fluorine under the standard reaction conditions. However, reaction of the butene mixed with *sym*-dichlorodifluoroethylene gave a higher yield of C_8F_{14}, 0.025 mole, with complete absorption of fluorine, as well as the dimer addition and mixed dimer addition products derived from the ethylene. The increased yield of butene dimer addition product is consistent with a reduced fluorine concentration in the liquid phase as a result of more rapid reaction with the ethylene.

Order of Olefin Reactivity with Fluorine.—The order of olefin reactivity toward molecular fluorine as shown both by amount of dimer addition product formed and by conversion under standard conditions is: $CClF{=}CClF > CF_2CF_2CF{=}CF > CF_3CCl{=}CClCF_3 > [(CF_3)_2C{=}C(CF_3)_2]$.[5] This order can be rationalized in terms of electron withdrawal and steric effects. The same reactivity sequence toward chlorine atoms is indicated by qualitative observations on the relative ease of photochemical chlorination.

Application of the Olefin Dimerization Reaction to Synthesis.—The mixed-type fluorine dimer addition products prepared in this work illustrate synthetic procedures of general application to symmetrically substituted perhalo-olefins.[23] Although yields of individual products are usually small, a wide range of compounds may be prepared by a one-step process for which alternative methods are not now available.

Reaction of Fluorine Atoms with Carbon–Hydrogen Bonds.—It has been shown previously that the formation of condensation products from saturated hydrogen-containing compounds by dehydrogenation with fluorine is most satisfactorily explained by combination of free radicals (9, 10, 11).[1] This mechanism, analogous to that for the formation of dimer addition products from olefins, was tested further by treating a mixture of chloroform and *sym*-dichlorodifluoroethylene with fluorine at −75°. At this temperature chloroform is unreactive with fluorine[24] but *sym*-dichlorodifluoroethylene reacts rapidly to produce a free radical and a fluorine atom (3′). It was of interest to determine whether or not a fluorine atom thus produced



would react with high enough efficiency with the carbon–hydrogen bond of chloroform to produce trichloromethyl radicals, in addition to fluoroethyl radicals formed from the olefin, and thus yield the mixed type condensation product $CClF_2CClFCCl_3$.

$$CHCl_3 + F\cdot \longrightarrow CCl_3\cdot + HF \qquad (12)$$

$$CClF_2CClF\cdot + CCl_3\cdot \longrightarrow \underset{\text{VII}}{CClF_2CClFCCl_3} \qquad (13)$$

Utilizing *sym*-dichlorodifluoroethylene and chloroform in the molar ratio of 1 to 2.6 for reaction, it was found possible to isolate the expected mixed condensation product VII, in addition to a larger quantity of the dimer addition product of the olefin.[25] These observations indicate a very low activation energy for reaction 12 and support the free-radical fluorine dehydrogenation mechanism presented previously. Although the fluorine atom reacted preferentially with the olefin, the selectivity is small and furnishes a striking demonstration of the high order of reactivity of the fluorine atom.

Acknowledgment.—The basic mechanism here presented for the reactions of elemental fluorine with perhalo-olefins has been developed gradually in this Laboratory over a period of years. We wish especially to acknowledge significant unpublished work by R. L. Ehrenfeld, H. F. Furber, G. Gavlin, J. M. Phelan, Maurice Prober and S. K. Reed.

Experimental Results

General Method.—Reactions were carried out with Dry Ice cooling under closely comparable conditions in a nickel U-shaped reaction vessel of the type previously described.[5] The reaction vessel was provided with a thermocouple well on the inlet side. For most of the reactions it was charged with either 0.8 mole of olefin and 1.2 moles of trichlorofluoromethane solvent or 0.8 mole of each of two olefins and 0.4 mole of trichlorofluoromethane. A 1.0-to-1.1 fluorine–nitrogen mixture was then passed in during approximately 7 hr. The fluorine–nitrogen mixture was prepared in a small brass storage tank of known volume and metered by pressure measurement.[1] Commercial tank fluorine was utilized as supplied by the Pennsylvania Salt Manufacturing Co. This was found to contain from 1.1 to 2.6% oxygen.[20] Nitrogen was utilized to exclude air during reaction and during separation of products. Reactions occurred smoothly in all cases but with an easily observable heat effect. For Dry Ice-cooled reactions internal temperatures

(23) From a symmetrical olefin and an unsymmetrical olefin two isomeric mixed-type dimer addition products are possible. However, one product may be formed preferentially. For example, $CF_3CCl{=}CF_2 + F_2$ or $F\cdot \rightarrow (CF_3)_2CCl\cdot$ as evidenced by the formation of $CF_3CCl(CF_3)_2$ in high yield.[5,6]

(24) W. T. Miller, This Journal, **62**, 341 (1940).

(25) Evidence for the presence of a small quantity of hexachloroethane (*ca.* 0.005 mole) pointed to the diffusive escape of some trichloromethyl radicals from the corresponding reaction 3 ethyl radicals.

(26) Analyses were carried out by the method previously described[17] but using apparatus equipped with glass stopcocks lubricated with Kel-F type chlorofluorocarbon grease in place of mercury cut-off valves.

(27) Kang Chang Collection, Harold Bigelow, This Journal, **58**, 1585 (1936).

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were maintained within the range −77 to −64° and largely below −70° (*ca.* −75°).

The reaction products were colorless and after transfer for distillation corresponded closely in weight to 95% of the combined weight of all reactants. They were separated by repeated distillations using glass and nickel wire helix packed columns. The composition of fractions containing closely boiling saturated and unsaturated compounds was determined by chlorination followed by redistillation. The weights of the more significant fractions isolated together with evidence for the identity of the new dimer-type products which are of primary importance to the present work are reported below. In all cases the characteristics of the intermediate fractions were consistent with those expected on the basis of the new products identified for the first time and with the results of previous reactions between fluorine and the same and other olefins. Boiling points are uncorrected but were determined within the range of 722 to 744 mm. pressure, unless otherwise noted. Molecular weights were determined cryoscopically in benzene. Chlorine was determined gravimetrically after sample decomposition in Parr bombs.

sym-Dichlorodifluoroethylene.—Reactants: 107 g. CClF=CClF, b.p. 20.8–21.1°, prepared from CCl_3CCl_3,[28] dissolved in 165 g. of CCl_3F, b.p. 23.6–24.6°, Freon 11, Kinetic Chemicals, Inc., and 18.6 g. of fluorine. The fluorine was added with nitrogen as described above and was completely absorbed. The following fractions were separated from the 277.4 g. of colorless liquid product.

$CClF_2CClF_2$: A saturated fraction, 14.2 g., 0.083 mole, b.p. 2.0–10.3°, was indicated as largely $CClF_2CClF_2$; previously reported[28] b.p. 3.8°.

CClF=CClF: Recovered as the dichloride, CCl_2FCCl_2F, 10.3 g., b.p. 90.7–91.2°, corresponding to 6.7 g., 0.051 mole, CClF=CClF; previously reported[28] for CCl_2FCCl_2F, b.p. 92.8°.

CCl_2FCClF_2: 5.3 g., 0.027 mole, b.p. 46–47°; previously reported[29] b.p. 46.5°.

$CClF_2CClFCClFCClF_2$: 22.4 g., b.p. 70.8–71.5° (100 mm.); 21.6 g., b.p. 71.0–71.6° (100 mm.), $n^{20}D$ 1.3849; total 44 g., 0.145 mole; previously reported[6] b.p. 134.1° $n^{20}D$ 1.3853.

2,3-Dichlorohexafluoro-2-butene (I).—Reactants: 188 g. of $CF_3CCl{=}CClCF_3$, b.p. 66.8–67.0°, Hooker Electrochemical Co., dissolved in 165 g. of CCl_3F and 19.4 g. of fluorine. Unreacted fluorine was present in the exit gases throughout the reaction. The following fractions were separated from 353.8 g. of colorless reaction product.

$CF_3CClFCClFCF_3$: 4.7 g., b.p. 50–57°; 22.6 g., b.p. 56.8–57.0°; 24.8 g., b.p. 57.5–60.5°; total 52.1 g., 0.19 mole; previously reported[30] b.p. 62.9°.

$CF_3CCl{=}CClCF_3$: Recovered as the dichloride CF_3CCl_2-CCl_2CF_3, 106.0 g., b.p. 130.5–132.5°, corresponding to 81.2 g., 0.35 mole, $CF_3CCl{=}CClCF_3$; previously reported[31] for $CF_3CCl_2CCl_2CF_3$, b.p. 131°.

$CF_3CCl_2CClFCF_3$: 1.2 g., b.p. 102–106° (micro-distillation), $n^{20}D$ 1.3529; previously reported[30] b.p. 97.5°, $n^{20}D$ 1.3530. Approximately 1 g. of higher boiling material was found.

2,3-Dichlorohexafluoro-2-butene (II).—A duplicate reaction was carried out with ice-bath cooling, internal temperature 0 to 2.3°. The fluorine was incompletely absorbed throughout.

$CF_3CClFCClFCF_3$: 62.5 g., 0.23 mole, b.p. 62.6–62.8°.

$CF_3CCl{=}CClCF_3$: Recovered as $CF_2CCl_2CCl_2CF_3$: 7.8 g., b.p. 128.0–131.1°; 78.6 g., b.p. 131.5–131.9°; corresponding to 66.2 g., 0.28 mole of $CF_3CCl{=}CClCF_3$.

$CF_3CCl_2CClFCF_3$: 10.2 g., 0.036 mole, b.p. 95.0–97.0°. Approximately 1 g. of higher boiling material was found.

sym-Dichlorodifluoroethylene and 2,3-Dichlorohexafluoro-2-butene (I).—Reactants: 107 g. of CClF=CClF and 187 g. of $CF_3CCl{=}CClCF_3$ dissolved in 107 g. of CCl_3F and 19 g. of fluorine. A trace of unabsorbed fluorine was detected in the exit gases.

$CClF_2CClF_2$: 20.7 g., 0.12 mole, b.p. 3–11°.

CClF=CClF: Recovered as the dichloride CCl_2FCCl_2F: 12.8 g., b.p. 85.0–89.5°; 23.6 g., b.p. 85.9–90.0°; corresponding to 25.4 g., 0.19 mole, CClF=CClF.

CCl_2FCClF_2: 5.0 g., 0.027 mole, b.p. 49–51°.

$CF_3CClFCClFCF_3$: 3.0 g., 0.011 mole, b.p. 56.0–56.5°.

$CF_3CCl{=}CClCF_3$: Recovered as $CF_3CCl_2CCl_2CF_3$, 154.9 g., b.p. 128.5–131.5°, corresponding to 119 g., 0.51 mole, $CF_3CCl{=}CClCF_3$.

$CF_3CCl_2CClFCF_3$: 1.6 g., 0.0056 mole, b.p. 96–100°.

$CClF_2CClFCClFCClF_2$: 18.4 g., 0.061 mole, b.p. 132–136°.

$CF_3CClFCCl(CF_3)CClFCClF_2$: 27.5 g., b.p. 171.2–*176.6*–176.8°; 19.8 g., b.p. 176.8–177.0°; 3.8 g., b.p. 175.0–175.5°; total 51.1 g., 0.13 mole. Redistillation yielded a center cut of 30.5 g., b.p. 107.7–*108.0–108.2*°–108.4° (100 mm.), formed glass between −75° and −100°, $n^{20}D$ 1.3861, d^{20}_4 1.9016. Calcd. for $C_6Cl_4F_{10}$: $MR^{20}D$, 50.1[32]; mol. wt., 404; Cl, 35.1. Found: $MR^{20}D$, 49.9; mol. wt., 415, 427, 421; Cl, 35.2, 35.2.

sym-Dichlorodifluoroethylene and 2,3-Dichlorohexafluoro-2-butene (II).—Reactants: 13.3 g., 0.10 mole, of CClF=CClF, and 186 g. of $CF_3CCl{=}CClCF_3$ dissolved in 151 g. of CCl_3F and 19.0 g. of fluorine. Small amounts of unabsorbed fluorine were detected throughout the reaction.

$CClF_2CClF_2$: 4.1 g., 0.024 mole, b.p. 5.0–6.5°.

$CF_3CClFCClFCF_3$: 44.7 g., 0.16 mole, b.p. 59.0–63.0°.

$CF_3CCl{=}CClCF_3$: Recovered as the dichloride CF_3CCl_2-CCl_2CF_3: 4.0 g., b.p. 125–132.0°; 127.1 g., b.p. 130.0–132.2°; corresponding to 100.2 g., 0.43 mole, of $CF_3CCl{=}CClCF_3$.

$CF_3CCl_2CClFCF_3$: 2.7 g., 0.0094 mole, b.p. 94.0–107.0°.

$CF_3CClFCCl(CF_3)CClFCClF_2$: 4.7 g., b.p. 102.0–107.8° (100 mm.); 4.3 g., b.p. 107.8–109° (100 mm.); 8.2 g., b.p. 108.8–110.0° (100 mm.), $n^{20}D$ 1.3861, mol. wt. 402, 408; 1.6 g., b.p. 110.0–110.5°; total 18.8 g., 0.047 mole.

Hexafluorocyclobutene.—Reactants: 125 g. of $\overline{CF_2CF_2}$-$\overline{CF{=}CF}$, b.p. 0.0–0.2°, prepared by dechlorinating $\overline{CF_2CF_2CClFCClF}$,[34] dissolved in 165 g. of CCl_3F and 18.6 g. of fluorine. About 10% of the fluorine was unabsorbed as determined iodometrically. A 61.3-g. loss was incurred in working up the fraction b.p. 2–19° obtained by initial distillation.

$\overline{CF_2CF_2CF_2CF_2}$: 26.6 g., 0.13 mole, b.p. −1.0 to 0.0°; previously reported[6] b.p. −4.0°.

$\overline{CF_2CF_2CF{=}CF_2}$: Recovered as the dichloride $\overline{CF_2CF_2}$-$\overline{CClFCClF}$, 54.0 g., b.p. 57.2–57.7°, corresponding to 37.5 g., 0.23 mole, $\overline{CF_2CF_2CF{=}CF}$; previously reported[35] for $\overline{CF_2CF_2CClFCClF}$, b.p. 59.87°.

$[\overline{CF_2CF_2CF_2CF}-]_2$: The presence of this compound was indicated by the isolation of 0.8 g., micro b.p. 85–93°, f.p. near 0° (see below for properties). Evidence for the formation of C_8F_{14}, b.p. within the range 85–102°, by reaction of fluorine with $\overline{CF_2CF_2CF{=}CF}$ had been obtained previously.[8]

sym-Dichlorodifluoroethylene and Hexafluorocyclobutene.—Reactants: 107 g. of CClF=CClF and 130 g. of $\overline{CF_2CF}$-$\overline{CF{=}CF}$ in 55 g. of CCl_3F, and 19.4 g. of fluorine. Complete absorption of fluorine was observed. An 81-g. loss was incurred from the initial fraction, b.p. 2.5–24.0°.

$\overline{CF_2CF_2CF_2CF_2}$ and $ClCF_2CClF_2$: 2.5 g., b.p. −6.9 to −5.9°; 3.6 g., b.p. −5.9° to −1.0°; 7.2 g., b.p. −1.0 to 5.3°, largely b.p. 1.3–3.2°.

$\overline{CF_2CF_2CF{=}CF}$: Recovered as dichloride $\overline{CF_2CF_2CClFC}$-

(28) E. G. Locke, W. R. Brode and A. L. Henne, THIS JOURNAL, **56**, 1726 (1934).

(29) H. S. Booth, W. L. Mong and P. E. Burchfield, *Ind. Eng. Chem.*, **24**, 328 (1932).

(30) A. L. Henne and T. H. Newby, THIS JOURNAL, **70**, 130 (1948).

(31) A. L. Henne, J. B. Hinkamp and W. J. Zimmerschied, *ibid.*, **67**, 1907 (1945).

(32) Molecular refractivities were calculated using the following values for $R^{20}D$; C, 2.584; Cl in CX_1, 5.69; Cl in CX_2, 5.85; F, 1.165; C_4 ring increment (+0.1).[33]

(33) A. H. Fainberg and W. T. Miller, Jr., unpublished work.

(34) Prepared by A. H. Fainberg.

(35) A. L. Henne and M. W. Ruh, THIS JOURNAL, **69**, 279 (1947).

(36) W. T. Miller, Jr., and S. K. Reed, unpublished work.

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ClF, 77.2 g., b.p. 51.7–75.0°, largely b.p. 58.0°; corresponding to 53.5 g., 0.33 mole, $CF_2CF_2CF{=}CF$.

ClF=ClF: Recovered as the dichloride, CCl_2FCCl_2F, 17.3 g., b.p. 89.5–90.0°; corresponding to 11.3 g., 0.085 mole, ClF=ClF.

$CClF_2CClFCClFCClF_2$: 21.2 g., 0.070 mole, b.p. 67.0–68.3° (100 mm.).

$[CF_2CF_2CF_2CF{-}]_2$: 6.1 g., b.p. 83.4–86.8°; 2.8 g., b.p. 87.4–92.7°, total 8.9 g., 0.025 mole. Redistillation yielded a center cut of 3.8 g., b.p. 85.2–86.3° (737 mm.), f.p. −6.8°, $n^{20}D$ 1.295[37]; d^{20}_4 1.7511. Calcd. for C_8F_{14}: $MR^{20}D$ 37.2; mol. wt., 362; Cl, 0.00. Found: $MR^{20}D$ 38.0; mol. wt., 368, 364; Cl, 0.7, 0.5.

$CF_2CF_2CF_2CFCClFCClF_2$: 6.9 g., b.p. 100.0–103.9°; 18.1 g., b.p. 103.7–104.1° (738 mm.), formed glass between −84 and −100°, $n^{20}D$ 1.3294, d^{20}_4 1.7410; total 25.0 g., 0.075 mole. Calcd. for $C_6Cl_2F_{10}$: $MR^{20}D$ 38.8; mol. wt., 333; Cl, 21.3. Found: $MR^{20}D$ 38.9; mol. wt. 343, Cl, 21.4, 21.0.

1,2-Dichlorotetrafluoropropene.—Reactants: 146.4 g. of $CF_3CCl{=}ClF$, b.p. 46.5° (742 mm.), dissolved in 164 g. of CCl_3F and 19.0 g. of fluorine. The $CF_3CCl{=}ClF$ was prepared by the following reaction sequence: $CF_3CCl{=}CCl_2 \rightarrow CF_3CCl_2CCl_3$[38] $\rightarrow CF_3CCl_2CCl_2F$[39] $\rightarrow CF_3CCl{=}ClF$.[40] Approximately 3% of the fluorine was not absorbed.

$CF_3ClFCClF_2$: 23.0 g., 0.10 mole, b.p. 32.7–35.2°; previously reported b.p. 34.7°.

$CF_3CCl{=}ClF$: 32.8 g., b.p. 43.4–46.5°; 4.9 g., b.p. 47–53°; total wt. 37.7 g., 0.21 mole.

$C_6Cl_4F_{10}$: 34.5 g., 0.09 mole, b.p. 107.5–110.0°, largely b.p. 108.0–109.1° (100 mm.), $n^{20}D$ 1.3883; previously found[41] b.p. 170.5–176.7° (732 mm.).

The fluorine dimer addition product $C_6Cl_4F_{10}$ may be composed of a mixture of three possible isomers. However, the symmetrical structure $ClF_2CCl(CF_3)CCl(CF_3)ClF_2$ is favored by analogy with the structure of the corresponding product obtained from $CF_3CCl{=}CF_2$.[23]

sym-Dichlorodifluoroethylene and 1,2-Dichlorotetrafluoropropene.—Reactants: 106.3 g. of ClF=ClF and 146 g. of $CF_3CCl{=}ClF$ dissolved in 54.9 g. of CCl_3F and 19.2 g. of fluorine. The fluorine was absorbed completely.

ClF_2CClF_2: 19.8 g., 0.12 mole, b.p. 1.5–3.7°.

ClF=ClF: Recovered as CCl_2FCCl_2F, 32.7 g., b.p. 90.0–92.0°, corresponding to 21.3 g., 0.16 mole, of ClF=ClF.

$CF_3CCl{=}ClF$: Recovered as $CF_3CCl_2CCl_2F$, 105.4 g., b.p. 110.2–111.2°, corresponding to 77.0 g., 0.42 mole, of $CF_3CCl{=}ClF$.

ClF_2CCl_2F: 2.5 g., 0.013 mole, b.p. 47.2–48.5°.

$ClF_2CClFCClFCClF_2$: 8.3 g., b.p. 130.1–135.9°; 6.1 g., b.p. 134.0–135.9°; 4.4 g., b.p. 135.9–146.1°; total 18.8 g., 0.062 mole.

$C_5Cl_4F_8$: 9.7 g., b.p. 146.1–153.0°; 5.5 g., b.p. 152.4–153.0° (738 mm.), forms glass between −111 and −126°, $n^{20}D$ 1.3885, d^{20}_4 1.8335; 10.1 g., b.p. 153.1–154.7°; total 25.3 g., 0.072 mole. Calcd. for $C_5Cl_4F_8$: $MR^{20}D$ 45.3; mol. wt., 354; Cl, 40.1. Found for fraction b.p. 152.4–153.0°: $MR^{20}D$ 45.5; mol. wt., 342, 353; Cl, 38.6, 39.4.

Two structures are possible for $C_5Cl_4F_8$ without rearrangement of groups initially present. Of these $ClF_2CCl(CF_3)$-$CClFClF_2$ is preferred by analogy with the reaction of CF_3-$CCl{=}CF_2$ with fluorine.[23]

$C_6Cl_4F_{10}$: 6.1 g., b.p. 96.0–102.5° (100 mm.); 1.2 g., b.p. 103.0° (100 mm.), $n^{20}D$ 1.3859; total wt. 7.3 g., 0.018 mole.

sym-Dichlorodifluoroethylene and Chloroform.—Reactants: 83 g., 0.62 mole, of ClF=ClF; 195 g., 1.63 moles, of chloroform; and 19.0 g. of fluorine. The fluorine was almost completely absorbed. Two duplicate reactions were carried out and the products combined for separation.

CF_3ClF_2: 3.2 g., 0.021 mole, b.p. −40.2 to −38.8°; previously reported[28] b.p. −38°.

ClF_2CClF_2: 5.6 g., b.p. −1.1 to 1.3°; 33.8 g., b.p. 1.3–2.7°; 7.7 g., b.p. 2.7–3.7°; total 47.1 g., 0.28 mole.

ClF=ClF: 20.7 g., 0.16 mole, b.p. 19.2–23.7°.

ClF_2CCl_2F: 19.6 g. of material, b.p. 37.9–50.1°, was collected.

$ClF_2CClFCClFCClF_2$: 7.5 g., b.p. 69.5–72.2° (100 mm.); 45.2 g., b.p. 72.0–72.2° (100 mm.); total 52.7 g., 0.17 mole.

$CCl_3CClFCClF_2$: 4.7 g., b.p. 87.2–87.3° (100 mm.); 3.7 g., b.p. 87.5–88.0° (100 mm.), estimated b.p. 153° (760 mm.), formed glass between −109° and −117°, $n^{20}D$ 1.4384, d^{20}_4 1.7603; 2.2 g., b.p. 88.3–88.8° (100 mm.); 5.1 g., b.p. 89.0–94.0° (100 mm.); total 15.7 g., 0.058 mole. Calcd. for $C_3Cl_3F_3$: $MR^{20}D$ 40.3; mol. wt., 270; Cl, 65.6. Found for fraction b.p. 87.5–88.0° (100 mm.): $MR^{20}D$ 40.3; mol. wt., 261, 261; Cl, 66.0, 66.1.

The following properties have been reported for CCl_3-$CClFCClF_2$: b.p. 153.3°, f.p. −14.8°, $n^{20}D$ 1.43919, d^{20}_4 1.7702, $MR^{20}D$ 40.18.[43] However, the evidence for the assigned structure is not entirely conclusive[44] and would now appear to require re-examination.

The residue from the above separation contained 1.2 g. of sublimable white solid which appeared to be hexachloroethane.

(37) Estimated using an Abbe refractometer equipped with a scale reading to ND 1.3000.

(38) A. L. Henne and A. M. Whaley, THIS JOURNAL, **63**, 3478 (1941).

(39) A. L. Henne and A. M. Whaley, *ibid.*, **64**, 1157 (1942).

(40) A. L. Henne and T. P. Waalkes, *ibid.*, **68**, 496 (1946).

(41) A reaction carried out on a larger scale with 1 part $CF_3CCl{=}ClF$ dissolved in 2 parts CCl_2FCClF_2 and fluorine at Dry Ice temperature yielded 41% $CF_3CClFCClF_2$, b.p. 33.0–34.1°, and 28% $C_6Cl_4F_{10}$, b.p. 170.5–176.7° (732 mm.).[42]

(42) W. T. Miller, Jr., and M. D. Hurwitz, unpublished work.

(43) A. L. Henne and M. W. Renoll, THIS JOURNAL, **61**, 2489 (1939).

(44) We are indebted to A. H. Fainberg for drawing our attention to this point.

ITHACA, NEW YORK

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Polyalkylene Disulfides

BY C. S. MARVEL AND L. ELMER OLSON[1]

RECEIVED FEBRUARY 20, 1957

The oxidation of alkylene dimercaptans by air in soap emulsion has been found to be a useful method of producing polyalkylene disulfides.

The oxidation of a dimercaptan by air to a polydisulfide has been patented as a polymer-forming reaction by Patrick,[2] but it has never been very widely used in scientific work.

In the distillation of some dimercaptans which were being purified for other uses, it was noted that a polymeric material built up in the flask apparently

(1) Some of the preliminary experiments which led to the work discussed in this manuscript were performed as a part of the research project sponsored by the Reconstruction Finance Corporation, Office of Synthetic Rubber, in connection with the government synthetic rubber program.

(2) J. G. Patrick, U. S. Patent 2,363,614 (November 28, 1944).

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TABLE I

AIR OXIDATION OF DIMERCAPTANS IN EMULSION WITHOUT CATALYST

Mercaptan	Time of oxidation, hr.	Yield of polymer, %	Inherent viscosity in chloroform
1-β-Mercapto-ethyl-3(or 4)-mercapto-cyclohexane[5]	24	13	0.09
	48	46	.27
	72	61	.50
	144	76	.59
1-(α-Methyl-β-mercaptoethyl)-3-mercapto-4-methyl-cyclohexane[6]	92[a]	47	.14
	236[a]	92	.46
	236[b]	77	.24
	236[c]	94	.33

[a] Three grams of potassium hydroxide was used in this run. [b] Two grams of potassium hydroxide was used in this run. [c] Four grams of potassium hydroxide was used in this run.

TABLE II

POLYDISULFIDES PREPARED BY AIR OXIDATION IN THE PRESENCE OF SELENIOUS ACID

Mercaptan	Oxidn. time, hr.	Yield, %[b]	Inherent viscosity[c]	Softening temp., °C.	Formula polymer unit	Analyses, % C Calcd.	C Found	H Calcd.	H Found	S Calcd.	S Found
1-β-Mercaptoethyl-3(or 4)-mercaptocyclohexane	144	80	0.23	110	$C_8H_{14}S_2$	55.12	55.19	8.10	8.09	36.79	36.68
1-(α-Methyl-β-mercaptoethyl)-3-mercapto-4-methylcyclohexane	83	76	.14	40[a]	$C_{10}H_{18}S_2$	59.35	58.95	8.97	9.16	31.69	31.58
Dithiol											
Hexamethylene-[d]	240	50	.226	57	$C_6H_{12}S_2$	48.7	48.55	8.1	8.28	...	...
Heptamethylene-	90	92	.59[e]	130	$C_7H_{14}S_2$	51.80	51.97	8.68	8.44	39.51	39.17
Nonamethylene-	90	92	.39	55	$C_9H_{18}S_2$	56.78	56.42	9.53	9.47	33.69	33.64
Decamethylene-	90	100	.30	45	$C_{10}H_{20}S_2$	58.76	59.08	9.86	9.92	31.38	31.14

[a] Polymer $[\alpha]^{25}D$ +19.5°, *c* 2 in chloroform. [b] Calculated after one reprecipitation from chloroform by methanol. [c] Measured in chloroform after one reprecipitation. [d] This polymer was prepared by Eugene D. Vessel. [e] Fractionation of the polymers by repeated reprecipitation from chloroform and methanol gave a rubber-like material with an inherent viscosity of 0.95.

due to oxidation. Some of these polymeric residues had inherent viscosities of 0.08. This observation suggested that the air oxidation of dimercaptans might be a useful polymer-forming reaction.

When a dimercaptan was dispersed in an aqueous soap solution and air was passed through the mixture, oxidation to a polydisulfide readily occurred and a stable polymer latex was produced. Foaming was troublesome but the addition of a little silicone antifoam agent[3] controlled it. It was also necessary to add water to the reaction mixture from time to time to maintain the volume. The reaction at room temperature was slow and required 4 to 10 days to yield a polymer with an inherent viscosity of 0.2 to 0.3. The addition of a little selenious acid[4] to the reaction mixture speeded up the oxidation so that high molecular weight polymers could be prepared in a shorter time. The limiting factors on the molecular size seem to be the purity of the dimercaptan and the time of oxidation. Tough, plastic, odorless polydisulfides with inherent viscosities as high as 1 have been obtained.

The polydisulfide derived from the dimercaptan prepared by adding two moles of thiolacetic acid to 4-vinyl-1-cyclohexene and hydrolyzing was heated with sulfur at 150° for three hours. This reaction yielded a more rubber-like polymer which was far less soluble in organic solvents than the untreated polymer. Analysis of the new polymer showed that approximately 0.7 atom of sulfur had been added for each disulfide link[5] in the original material.

Some experiments were conducted to determine whether such oxidizing agents as halogen, nitric acid or ferric chloride could be used in place of air, but none of these worked as satisfactorily as air in our emulsion systems. One experiment on the oxidation of hexamethylene dimercaptan with bromine is described in the Experimental part.

Experimental

Polymerizations.—A typical oxidation polymerization was carried out as follows. In a 4-ounce wide-mouth bottle were placed 50 ml. of distilled water, 1.5 g. of lauric acid, 4 g. of potassium hydroxide and 5 ml. of dimercaptan. When these ingredients were dissolved, 1 drop of Antifoam A was added. Filtered compressed air was bubbled through the mixture from a piece of 6 mm. glass tubing at a rate of about two bubbles a second for four to ten days. More Antifoam A was added as needed to control foaming and the volume of the mixture was maintained by adding distilled water as needed. At the end of the oxidation period the Antifoam A was removed by skimming it off the surface and the polymer latices were coagulated. Polymers coagulated with 20 ml. of alum coagulant, prepared by dissolving 100 g. of aluminum potassium sulfate in a mixture of 100 ml. of concentrated hydrochloric acid and one liter of distilled water, had up to 20% ash as residue after combustion. The ash could be diminished but not eliminated by repeated reprecipitations of the polymer from benzene or chloroform into methanol. Polymers coagulated by pouring the emulsion into methanol containing some hydrochloric acid and then reprecipitated gave satisfactory analyses. The polymers were dried in a vacuum desiccator, then dissolved in 50 ml. of chloroform and reprecipitated by pouring these solutions into 400 ml. of methanol.

In later runs approximately 5–20 mg. of selenious acid was introduced in the emulsion as a catalyst. When 20 mg. of this catalyst was used, the polymer obtained by breaking the emulsions varied in color from pink to red. This color could be removed by adding a small amount of sodium hydroxide (about 1 g. per 400 ml.) to the methanol used in the reprecipitation of the polymer from chloroform solution.

Some of the oxidation polymerization experiments are recorded in Tables I and II.

Addition of Sulfur to Polydisulfide from 1-β-Mercaptoethyl-3(or 4)-mercaptocyclohexane.—In a 125-ml. erlenmeyer flask containing 50 ml. of carbon disulfide were dissolved 0.60 g. of sulfur and 1.22 g. of disulfide polymer from β-mercaptoethyl-3(or 4)-mercaptocyclohexane, inherent viscosity 0.27. The carbon disulfide was allowed to evaporate in the hood and the flask and contents were heated in an oil-

(3) Dow Corning Antifoam A was used.

(4) G. H. Meguerian, U. S. Patent 2,710,788; C. A., 50, 9731 (1956).

(5) S. M. Martin, Jr., and J. C. Patrick, *Ind. Eng. Chem.*, **28**, 1144 (1936).

(6) C. S. Marvel and L. E. Olson, *J. Poly. Sci.*, **24**, in press (1957).

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bath at 150° for three hours. When the flask was removed from the bath for inspection, the molten contents solidified and would not remelt when heated to 165°. The polymer was suspended in 100 ml. of chloroform and slowly poured into 400 ml. of rapidly stirred methanol. The polymer was washed with methanol and dried for analysis; yield 1.35 g. The original polymer was tough and plastic while the final polymer was rubbery. The new polymer became tacky when heated to 245° and became molten at 320°. The new polymer was 34% soluble in chloroform and the soluble portion had an inherent viscosity of 0.39.

Anal. Calcd. for $C_8H_{14}S_2$: C, 55.12; H, 8.10; S, 36.79. Calcd. for $C_8H_{14}S_4$: C, 40.29; H, 5.92; S, 53.79. Found: C, 49.07; H, 7.29; S, 43.83. Calcd. for $C_8H_{14}S_{2.7}$: C, 48.84; H, 7.17; S, 44.00.

Oxidation of Hexamethylenedithiol with Bromine.—Five ml. of hexamethylenedithiol was added to 50 ml. of 2% MP-635-S[7] solution in a four-ounce polymerization bottle. Three grams of sodium hydroxide was added and the mixture shaken until solution was complete. Then 6 g. of bromine was added and the bottle was capped and shaken on a mechanical shaker for 3 hours. Some polymer formed almost immediately and separated as precoagulant. At the end of the shaking period alum coagulant[7] was added to break the emulsion and the polymer was collected on a filter. The precipitate contained a great deal of inorganic material. By extracting with chloroform and evaporating this solution, about 60% of the theoretical yield of polymer was obtained as a white powder with an inherent viscosity of 0.21.

Anal. Calcd. for $C_6H_{12}S_2$: C, 62.00; H, 10.41; S, 27.59. Found: C, 61.62; H, 9.98; S, 28.11.

(7) C. S. Marvel, V. C. Menikheim, H. K. Inskip, W. K. Taft and B. G. Labbe, *J. Poly. Sci.*, **10**, 39 (1953).

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEFENSE RESEARCH LABORATORY, THE UNIVERSITY OF TEXAS]

Allylic Chlorides. XXIV. 1,1,3-Trichloro-1-propene, 1,1-Dibromo-3-chloro-1-propene and Related Compounds[1,2]

BY LEWIS F. HATCH AND STANLEY D. ZIMMERMAN

RECEIVED DECEMBER 26, 1956

1,1,3-Trichloro-1-propene and 1,1-dibromo-3-chloro-1-propene have been prepared by conversion of the dihalopropenes to the corresponding allylic bromides using N-bromosuccinimide, basic hydrolysis of the bromides to the allylic alcohols and treatment of the alcohols with phosphorus trichloride. Relative reactivities of the allylic chlorides with sodium ethoxide in ethanol were determined. The reaction with potassium iodide in acetone gave kinetically anomalous data. The products from this reaction were 1,1-dihalo-3-iodo-1-propenes.

A number of closely related allylic chlorides have been prepared and their relative reactivities toward sodium ethoxide in ethanol and potassium iodide in acetone determined. The ones of interest in the present work are $CY_2{=}C(H){-}CH_2Cl$ (Y = H, CH_3) and $CCl_2{=}C(Y){-}CH_2Cl$ (Y = F, Cl, CH_3). The introduction of two methyl groups on the *gamma* carbon atom increases the reactivities of the allylic chlorine atom in both reactions. Since the methyl group is electron releasing, it was desirable to determine the effect of electron attracting groups in this position. For this purpose 1,1,3-trichloro-1-propene and 1,1-dibromo-3-chloro-1-propene have been prepared and studied.

Both of these allylic chlorides were prepared by the series of reactions shown in Fig. 1 for 1,1,3-trichloro-1-propene. The allylic chlorides and all of the intermediate compounds are lachrymators and vesicants. The preparation of 1,1,3-trichloro-1-propene by other methods has been reported.[3]

Attempts to prepare both 1,1,3-trichloro-1-propene and 1,1-dibromo-3-chloro-1-propene directly by the reaction between N-chlorosuccinimide and the corresponding dihalopropene ($CX_2{=}CHCH_3$) were unsuccessful. No definite product could be separated from either reaction. The oxidation of 1,1-dichloro-1-propene to 3,3-dichloro-2-propen-1-ol using selenium dioxide was attempted under various conditions of temperature and solvent. Apparently no oxidation took place.

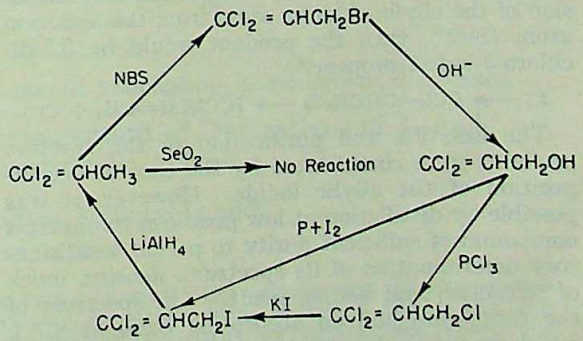

Fig. 1.—1,1-Dichloro-3-halo-1-propenes.

The relative reactivities of the two allylic chlorides with sodium ethoxide in ethanol are given in Table I. The greater reactivity of the dibromo compound is consistent with previous work with the 1,3-dichloropropenes[4] and the 1-bromo-3-chloro-1-propenes.[5] A comparison between the effect of halogen atoms and methyl groups in this position is complicated by the possibility of hydro-

(1) This research was supported by the Department of Navy at the Defense Research Laboratory, the University of Texas, under contract NOrd-9195.

(2) Presented in part at the 125th National Meeting of the American Chemical Society, Kansas City, Missouri, March, 1954.

(3) (a) A. Kirrman and G. Kremer, *Bull. soc. chim. France*, (5) **15**, 166 (1948); (b) G. W. Hearne, T. W. Evans, H. L. Yale and M. C. Hoff, THIS JOURNAL, **75**, 1392 (1953); (c) A. N. Nesmeyanov, R. Kh. Freidina and V. L. Firstov, *Izvest. Akad. Nauk. U.S.S.R. Otdel Khim. Nauk.*, 505 (1951); (d) United States Rubber Co., Brit. Pat. 660,475 (1951).

(4) L. F. Hatch and H. E. Alexander, THIS JOURNAL, **71**, 1037 (1949).

(5) L. F. Hatch and R. D. Maxwell, *ibid.*, **75**, 6002 (1953).

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gen atoms of the methyl groups participating in the transition state.[6]

TABLE I

RELATIVE REACTIVITIES OF 1,1,3-TRICHLORO-1-PROPENE AND 1,1-DIBROMO-3-CHLORO-1-PROPENE WITH SODIUM ETHOXIDE IN ETHANOL AT 50°

1,1,3-Trichloro-1-propene

Time, hr.	0.50	1.00	1.50	3.00	6.00
Reacted, %	26.3	42.4	51.3	68.2	81.2
k, hr.$^{-1}$ mole^{-1} l.	14.2	14.7	14.0	14.2	14.4
Av. k			14.3 ± 0.2		
Relative reactivity[a]			12.1		

1,1-Dibromo-3-chloro-1-propene

Time, hr.	0.10	0.25	0.50	0.75	1.00
Reacted, %	18.7	34.5	52.3	64.0	71.8
k, hr.$^{-1}$ mole^{-1} l.	22.7	23.1	20.1	23.9	22.1
Av. k			22.4 ± 1.0		
Relative reactivity[a]			19.0		

[a] Allyl chloride as 1.00 with k = 1.18.

The kinetic data for the reaction of 1,1,3-trichloro-1-propene and 1,1-dibromo-3-chloro-1-propene with potassium iodide in acetone were of such a nature that constant values of second-order rate constants were not obtained. This behavior of polyhalo allylic chlorides has been observed previously.[7] Since these kinetic studies with potassium iodide gave anomalous results, the products from each of the dihalo allylic chlorides were isolated and characterized.

If the reaction of 1,1,3-trichloro-1-propene with iodide ion is an SN2 reaction, there should be a simple exchange of the allylic chlorine atom by an iodine atom.

$$CCl_2{=}CHCH_2Cl + KI \longrightarrow CCl_2{=}CHCH_2I + KCl$$

If the reaction were to proceed by a nucleophilic attack on the γ-carbon atom followed by, or simultaneous with, an allylic rearrangement and expulsion of the allylic chlorine atom from the α-carbon atom (SN2′), then the product would be 3,3-dichloro-3-iodo-1-propene.[8,9]

$$I^- \longrightarrow CCl_2{=}CHCH_2Cl \longrightarrow ICCl_2CH{=}CH_2 + Cl^-$$

The isolation and purification of the reaction products were complicated by the ease of decomposition of the allylic iodide. However, it was possible by distillation at low pressures to obtain a compound of sufficient purity to permit a satisfactory determination of its spectrum, density, index of refraction and boiling point. The spectrum of the compound had an absorption band at 8.7 μ which was indicative of the allylic iodide structure ($CCl_2{=}CHCH_2I$).[10] It did not have an absorption band at 10.1 μ which is characteristic of a monosubstituted ethylene.

This compound also was treated with lithium aluminum hydride, and 1,1-dichloro-1-propene was obtained as the only product.[11] The structure was further established by comparison of the compound with an authentic sample prepared by the treatment of 3,3-dichloro-2-propen-1-ol with red phosphorus and iodine (Fig. 1). The spectrum of the allylic iodide was essentially identical with that obtained for the compound isolated from the reaction with potassium iodide. The physical properties of the two compounds were as close as expected for compounds as unstable as these.

As a further check on the identity of the unknown product from the potassium iodide reaction, its 3,5-dinitrobenzoate was prepared by the use of silver 3,5-dinitrobenzoate and compared with that obtained from an authentic sample of 1,1-dichloro-3-iodo-1-propene as well as with the 3,5-dinitrobenzoates of the corresponding chloride, bromide and alcohol. Mixtures of all possible pairs of these 3,5-dinitrobenzoates in no instance gave a lowering of the melting point.

The compound isolated from the reaction of 1,1-dibromo-3-chloro-1-propene and potassium iodide was shown to be 1,1-dibromo-3-iodo-1-propene in the same manner as that used for the identity of the product from 1,1,3-trichloro-1-propene.

Infrared spectra obtained for the various compounds prepared during this investigation were the same as would have been predicted for the particular compound. It is of especial significance that with the allylic chlorides there was always an absorption at 8.01 μ; with the allylic bromides the absorption was at 8.30 μ and with the iodides at 8.7 μ.[10]

Experimental

3-Bromo-1,1-dichloro-1-propene.—3-Bromo-1,1-dichloro-1-propene was prepared in a 75% yield by the bromination of 2.00 moles of 1,1-dichloro-1-propene (b.p. 76.5–77.0°; n^{25}D 1.4418; d^{25}_4 1.1675) using N-bromosuccinimide (1.00 mole) and conventional procedures. The 3-bromo-1,1-dichloro-1-propene had the following physical properties: b.p. 45.1° (10 mm.); n^{20}D 1.5363, n^{25}D 1.5337, n^{30}D 1.5310; d^{20}_4 1.7593, d^{25}_4 1.7506, d^{30}_4 1.7421. *Anal.* Calcd. for $C_3H_3BrCl_2$: total halogen, 79.4; Br, 42.1. Found: total halogen, 79.7, 79.5; Br, 41.8, 42.0.

3,3-Dichloro-2-propen-1-ol.—3-Bromo-1,1-dichloro-1-propene (1.00 mole) was hydrolyzed by use of a 7.5% sodium carbonate solution at 65 to 70° for 8 hr. An 85% yield of 3,3-dichloro-2-propen-1-ol was obtained. The dichloro-alcohol had the following physical properties: b.p. 75–77° (20 mm.); n^{20}D 1.4918, n^{25}D 1.4898, n^{30}D 1.4879; d^{20}_4 1.3830, d^{25}_4 1.3770, d^{30}_4 1.3718 (lit.[12] b.p. 72° (18 mm.); n^{16}D 1.4883; d^{16} 1.3617). *Anal.* Calcd. for $C_3H_4Cl_2O$: Cl, 55.9. Found: Cl, 56.1, 56.0.

1,1,3-Trichloro-1-propene.—1,1,3-Trichloro-1-propene was prepared by treating 3,3-dichloro-2-propen-1-ol (0.50 mole) with phosphorus trichloride (0.20 mole) in dry pyridine (0.11 mole) at 65° for 2 hr. A 90% yield was obtained. Physical properties of the 1,1,3-trichloro-1-propene were: b.p. 59.5° (50 mm.); n^{20}D 1.4958, n^{25}D 1.4930, n^{30}D 1.4904; d^{20}_4 1.4030, d^{25}_4 1.3953, d^{30}_4 1.3876 (lit.[3b] b.p. 132–133°; n^{20}D 1.4962; d^{20}_4 1.3983). *Anal.* Calcd. for $C_3H_3Cl_3$: Cl, 73.2. Found: Cl, 73.4, 73.6.

1,1-Dichloro-3-iodo-1-propene from the Alcohol, Red P and I_2.—A mixture of 3,3-dichloro-2-propen-1-ol (0.50 mole) and red phosphorus (0.10 mole) was stirred vigorously, and cooled while iodine (0.10 mole) was added portionwise and cautiously to the flask. After all of the iodine was added, the mixture was warmed to 70–80° until the iodine coloration of the condensate on the flask walls had disappeared. Then 0.05 mole of iodine was added and heating continued

(6) J. C. Charlton and E. D. Hughes, *J. Chem. Soc.*, 855 (1956); L. F. Hatch and P. R. Noyes, THIS JOURNAL, **79**, 345 (1957).

(7) L. F. Hatch and D. W. McDonald, *ibid.*, **74**, 3328 (1952).

(8) A. H. Fainberg and W. T. Miller, Jr., Abstracts of the 119th American Chemical Society Meeting, Boston, Massachusetts, April, 1951.

(9) G. Stork and W. N. White, THIS JOURNAL, **78**, 4609 (1956).

(10) R. E. Kitson, *Anal. Chem.*, **28**, 1437 (1956).

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(12) F. Kutscher and H. Steudel, *Z. physiol. Chem.*, **39**, 474 (1903).

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until once again the iodine coloration was gone. The mixture was cooled and filtered and the filtrate distilled. The 1,1-dichloro-3-iodo-1-propene had the following physical properties: b.p. 34° (1 mm.); $n^{20}D$ 1.6030, $n^{25}D$ 1.5998, $n^{25}D$ 1.5968; d^{20}_4 2.0480, d^{25}_4 2.0401, d^{30}_4 2.0300. *Anal.* Calcd. for $C_3H_3Cl_2I$: total halogen, 83.5; I, 53.6. Found: total halogen, 83.7, 83.7; I, 54.1, 54.0.

Lithium Aluminum Hydride Reduction of 1,1-Dichloro-3-iodo-1-propene from 3,3-Dichloro-2-propen-1-ol, Red P and I_2.—A mixture of 1,1-dichloro-3-iodo-1-propene (0.27 mole) and 10 ml. of ether was stirred rapidly while a suspension of lithium aluminum hydride (0.075 mole) in 20 ml. of ether was added at a rate to produce gentle refluxing. The excess lithium aluminum hydride was destroyed by 2% sulfuric acid and the organic layer was worked up in the usual manner. 1,1-Dichloro-1-propene (b.p. 75–76° (750 mm.); $n^{25}D$ 1.4441) was obtained as the only product.

1,1-Dichloro-3-iodo-1-propene from 1,1,3-Trichloro-1-propene and KI.—1,1,3-Trichloro-1-propene (0.25 mole) was added slowly to 0.25 mole of potassium iodide in 600 ml. of acetone at 10°. The reaction product was worked up in the usual manner and gave 1,1-dichloro-3-iodo-1-propene as the only product. Its physical properties were: b.p. 34.5–35° (1 mm.); $n^{20}D$ 1.6017, $n^{25}D$ 1.5990, $n^{30}D$ 1.5959; d^{20}_4 2.0529, d^{25}_4 2.0440, d^{30}_4 2.0346. *Anal.* Calcd. for $C_3H_3Cl_2I$: total halogen, 83.5; I, 53.6. Found: total halogen, 83.8, 83.9; I, 54.0, 53.7.

Lithium Aluminum Hydride Reduction of 1,1-Dichloro-3-iodo-1-propene from 1,1,3-Trichloro-1-propene and KI.—The same procedure was used as in the reduction of the product obtained from the reaction of 3,3-dichloro-2-propen-1-ol, red phosphorus and iodine. The physical properties of the 1,1-dichloro-1-propene were: b.p. 75–76° (750 mm.); $n^{25}D$ 1.4439.

1,1-Dibromo-3-chloro-1-propene.—A similar series of reactions were carried out for the preparation of 1,1-dibromo-3-chloro-1-propene from 1,1-dibromo-1-propene as used in the preparation of 1,1,3-trichloro-1-propene from 1,1-dichloro-1-propene. The yields and physical properties of the various compounds follow.

1,1-Dibromo-1-propene: b.p. 41.5° (30 mm.); $n^{25}D$ 1.5245.

1,1,3-Tribromo-1-propene: yield 73%; b.p. 62–64° (0.5 mm.); $n^{20}D$ 1.6030, $n^{25}D$ 1.6006, $n^{30}D$ 1.5980; d^{20}_4 2.4408, d^{25}_4 2.4304, d^{30}_4 2.4207. *Anal.* Calcd. for $C_3H_3Br_3$: Br, 86.0. Found: Br, 85.7, 85.7.

3,3-Dibromo-2-propen-1-ol: yield 80%; b.p. 62–64° (0.5 mm.); $n^{20}D$ 1.5652, $n^{25}D$ 1.5633, $n^{30}D$ 1.5611; d^{20}_4 2.1788, d^{25}_4 2.1707, d^{30}_4 2.1632. *Anal.* Calcd. for $C_3H_4Br_2O$: Br, 74.0. Found: Br, 73.5, 73.6.

1,1-Dibromo-3-chloro-1-propene: yield 81%; b.p. 35.5–36.0° (0.6 mm.); $n^{20}D$ 1.5663, $n^{25}D$ 1.5634, $n^{30}D$ 1.5610; d^{20}_4 2.1365, d^{25}_4 2.1260, d^{30}_4 2.1162. *Anal.* Calcd. for $C_3H_3Br_2Cl$: total halogen, 83.3; Cl, 15.1. Found: total halogen, 83.4, 83.6; Cl, 14.7, 14.8.

1,1-Dibromo-3-iodo-1-propene from 3,3-Dibromo-2-propen-1-ol, Red P and I_2: b.p. 50° (0.1 mm.); $n^{20}D$ 1.6737, $n^{25}D$ 1.6708, $n^{30}D$ 1.6681; d^{20}_4 2.7283, d^{25}_4 2.7171, d^{30}_4 2.7060. *Anal.* Calcd. for $C_3H_3Br_2I$: total halogen, 88.0; I, 39.0. Found: total halogen, 88.3, 88.3; I, 39.1, 39.2.

Lithium Aluminum Hydride Reduction of 1,1-Dibromo-3-iodo-1-propene from 3,3-Dibromo-2-propen-1-ol, Red P, and I_2.—1,1-Dibromo-1-propene was the only product; b.p. 40° (29 mm.); $n^{25}D$ 1.5245.

1,1-Dibromo-3-iodo-1-propene from 1,1-Dibromo-3-chloro-1-propene and KI: b.p. 51° (0.2 mm.); $n^{20}D$ 1.6731, $n^{25}D$ 1.6703, $n^{30}D$ 1.6675; d^{20}_4 2.7196, d^{25}_4 2.7082, d^{30}_4 2.6975. *Anal.* Calcd. for $C_3H_3Br_2I$: total halogen, 88.0; I, 39.0. Found: total halogen, 88.1, 88.2; I, 39.1, 39.3.

Lithium Aluminum Hydride Reduction of 1,1-Dibromo-3-iodo-1-propene from 1,1-Dibromo-3-chloro-1-propene and KI.—1,1-Dibromo-1-propene was the only product; b.p. 41° (30 mm.); $n^{25}D$ 1.5247.

3,5-Dinitrobenzoates.—3,5-Dinitrobenzoates of the alcohols and all of the allylic halides were prepared using 3,5-dinitrobenzoyl chloride for the alcohols and the silver salt of 3,5-dinitrobenzoic acid for the halides. All of the alcohol derivatives with each of the corresponding allylic halide derivative showed no melting point depression. The melting point range for the dichloro derivatives was 69.5–70.8° and 90.2–91.2° for the dibromo derivatives. *Anal.* Calcd. for $C_{10}H_6Cl_2N_2O_6$ (from the alcohol): Cl, 22.1; N, 8.73. Found: Cl, 21.8, 22.0; N, 8.94. Calcd. for $C_{10}H_6Br_2N_2O_6$ (from the alcohol): Br, 39.0; N, 6.83. Found: Br, 38.6, 38.8; N, 7.05.

Reaction with Potassium Iodide in Acetone at 20°.—No consistent rate data could be obtained with either 1,1,3-trichloro-1-propene or 1,1-dibromo-3-chloro-1-propene. The weight of potassium chloride formed during the reaction indicated a 66% reaction in 15 minutes and an 88% reaction in 30 minutes.

Reaction of Sodium Ethoxide in Ethanol at 50°.—The procedure was the same as that previously described[4] and the data were calculated using the rate expression for a second-order reaction. The sodium ethoxide solution was 0.09931 molar for the reaction with 1,1,3-trichloro-1-propene (0.1025 molar) and 0.09182 molar for 1,1-dibromo-3-chloro-1-propene (0.1025 molar). A plot of $\log b(a-x)/a(b-x)$ *vs.* time gave a straight line for 1,1,3-trichloro-1-propene between 26 and 81% reacted and for 1,1-dibromo-3-chloro-1-propene between 18 and 72% reaction. Selected data are given in Table I. Reaction of the vinyl halogens under these conditions was less than 1%.

AUSTIN, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA]

Studies of Configuration. III. The Rearrangement of Derivatives of 3- and 4-Methoxycyclohexanecarboxylic Acids[1]

BY DONALD S. NOYCE AND HAROLD I. WEINGARTEN[2]

RECEIVED NOVEMBER 10, 1956

The mechanism of the ether–acid halide rearrangement has been further clarified. The rearrangement of *cis*-3-methoxycyclohexanecarboxylic acid to methyl *trans*-3-chlorocyclohexanecarboxylate by the action of thionyl chloride has been studied. The *trans* isomer does not undergo rearrangement. These facts not only clarify the rearrangement process, but serve as independent evidence for the configuration of the isomers of 3-methoxycyclohexanecarboxylic acid. Similar results are obtained with 4-methoxycyclohexanecarboxylic acid. The cyclic oxonium ion intermediate opens by a process largely S_N2 in character, with an additional factor of accelerated reaction in the case of ring-breaking displacement on a five-membered ring. Olefin formation accompanies the rearrangement. The olefin formed, methyl 3-cyclohexene-1-carboxylate is free of isomers, and this suggests that the elimination process is a synchronous reaction not proceeding from the simple carbonium ion.

The cleavage of ethers by acid halides has been investigated sporadically for many years. Benzoyl iodide was shown to cleave ether by Kishner.[3] Acid halides and acid anhydrides cleave ethers in the presence of Lewis acids.[4] These reactions un-

(1) Presented at the 127th Meeting of the American Chemical Society, Cincinnati, Ohio, March, 1955; previous paper, THIS JOURNAL, **78**, 127 (1953).

(2) Du Pont summer research assistant, 1953; Eastman Kodak Co. Fellow, 1954–1955.

(3) N. Kishner, *J. Russ. Phys.-Chem. Soc.*, **41**, 651 (1909); *Chem. Zentr.*, **80**, II, 1132 (1909).

(4) E. Wedekind and J. Haeusserman, *Ber.*, **34**, 2081 (1901); H. Meerwein and H. Maier-Huser, *J. prakt. Chem.*, **134**, 51 (1932).

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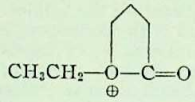
doubtedly involve the preliminary formation of an oxonium salt by reaction of the ether with the acid derivative, with concomitant weakening of the two carbon–oxygen ether bonds. The weakened carbon–oxygen bonds may then be subsequently cleaved bimolecularly or unimolecularly depending upon the structure of the molecule and the medium.

The intramolecular counterpart of these reactions also has received some attention. Blicke, Wright and Zienty[5] studied the rearrangement of γ-alkoxybutyryl chloride, but reached no conclusions concerning the mechanism. Prelog and Heinbach-Juhasz[6] investigated the kinetics of the rearrangement of ω-ethoxybutyryl chloride and ω-ethoxyvaleryl chloride to the ethyl ω-chloro esters, and found them to be first order in the acid chloride. The reaction was pictured as proceeding through the cyclic oxonium ion I which could react with chloride ion to form the ester. Wiberg[7] showed



I

that with an optically active homolog, the second step in this sequence was stereospecific with inversion.

In the present study, we have shown that the further consequence of this mechanism, namely, that a suitably chosen pair of *cis* and *trans* isomers should show distinctive differences in behavior, is correct.

Pure *cis*-3-methoxycyclohexanecarboxylic acid (*cis*-II) was obtained by fractional crystallization from pentane of the mixed *cis*- and *trans*-II obtained by reduction of *m*-methoxybenzoic acid. When *cis*-II was heated with phosphorus tribromide at 100° for two hours, there resulted 80% of methyl *trans*-3-bromocyclohexanecarboxylate (III) and a small quantity of an unsaturated ester. The structure of III was established by unambiguous synthesis. The lactone of *cis*-3-hydroxycyclohexanecarboxylic acid was converted to *trans*-3-bromocyclohexanecarboxylic acid of melting point 65°[8] with hydrogen bromide and esterified with diazomethane to give III. Though Perkin and Tattersall[9] originally assigned the *cis* configuration to the 65° isomer, Siegel and Morse have pointed out that it is undoubtedly *trans*. III could not be hydrolyzed successfully to the known acid of m.p. 65° due to its instability in hydroxylic solvents. This instability also has been observed by Siegel and Morse, and constitutes additional evidence for the *trans* configuration of the 65° isomer. Comparison of the infrared spectra of the synthetically prepared III and III resulting from the rearrangement revealed no differences.

When *cis*-II was heated in thionyl chloride for two hours, two products subsequently were isolated, the expected methyl *trans*-3-chlorocyclohexanecarboxylate (IV) and methyl 3-cyclohexene-1-carboxylate (V). IV and V, formed in the ratio of 3:5, were isolated in a combined yield approaching 90%. Acidic hydrolysis of IV gave *trans*-3-chlorocyclohexanecarboxylic acid, m.p. 52°. The structure was assigned on the basis of the analogous bromine compounds.

The olefinic ester V from the rearrangement, isolated in minor quantities in the treatment of *cis*-II with phosphorus tribromide, and in major quantities on treatment of *cis*-II with thionyl chloride, was shown to be methyl 3-cyclohexene-1-carboxylate by comparison of the infrared spectrum with that of an authentic sample prepared from methyl acrylate and butadiene. The infrared spectra of the two alternate isomers showed distinctive differences. There was no evidence for the presence of any of the isomers within the limits of accuracy of the analysis.

To determine the generality of the ether acid halide rearrangement in the cyclohexanecarboxylic acid derivatives, pure *cis*-4-methoxycyclohexanecarboxylic acid (*cis*-VI) was prepared and treated with both thionyl chloride and phosphorus tribromide. *cis*-VI was prepared by high pressure hydrogenation of methyl anisate, the derived methyl 4-methoxycyclohexanecarboxylate being then hydrolyzed and the 4-methoxycyclohexanecarboxylic acid separated into its component isomers by fractional crystallization.

On heating in thionyl chloride *cis*-VI gave rise to methyl *trans*-4-chlorocyclohexanecarboxylate (VII) and V in a ratio of 3:4 and in an over-all yield of 80%. Rearrangement of *cis*-VI in phosphorus tribromide led to the formation of 58% of methyl *trans*-4-bromocyclohexanecarboxylate (VIII) and 16% of *trans*-4-bromocyclohexanecarboxylic acid, which could have arisen either by cleavage of VIII or *cis*-VI.

VIII was hydrolyzed in low yield to the *trans*-4-bromocyclohexanecarboxylic acid, m.p. 170.8–171.4°, which compares favorably with the value, 167°, recorded by Perkin.[10] *trans*-4-Chlorocyclohexanecarboxylic acid, m.p. 159.0–159.8°, obtained by hydrolysis of VII in 88% yield, has to our knowledge not been reported previously in the literature. The structure is assigned by analogy with the acid obtained from VIII.

When the *trans*-3-methoxycyclohexanecarboxylic acid (*trans*-II) was subjected to treatment with thionyl chloride, the acid chloride was obtained. In fact, treatment of the mixed isomers of II obtained directly from the hydrogenation with thionyl chloride followed by treatment with water, led directly to the isolation of *trans*-II, with *cis*-II being converted to IV and V. In like fashion, *trans*-4-methoxycyclohexanecarboxylic acid (*trans*-VI) with thionyl chloride was converted to the acid chloride and did not undergo rearrangement. The treatment of *trans*-II and *trans*-VI led to reaction different from that observed with the *cis* isomers.

Discussion

The following sequence is in accord with the facts presented here and the discussion which fol-

(5) F. F. Blicke, W. B. Wright, Jr., and M. F. Zienty, THIS JOURNAL, **63**, 2488 (1941).
(6) V. Prelog and S. Heinbach-Juhasz, *Ber.*, **74**, 1702 (1941).
(7) K. B. Wiberg, THIS JOURNAL, **74**, 3957 (1952).
(8) S. Siegel and J. G. Morse, *ibid.*, **75**, 3857 (1953).
(9) W. H. Perkin and G. Tattersall, *J. Chem. Soc.*, **91**, 482 (1907).
(10) W. H. Perkin, *ibid.*, **85**, 431 (1904).

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lows. The first step is the formation of the acid halide (IX), which in the diaxial conformation IXa may undergo intramolecular displacement of the halide ion to give the bicyclic oxonium salt X. There are several pathways of reaction open to X, and each presents points of interest. X may undergo (a) elimination of a proton to give the unsaturated ester which has been shown to be V; (b) reaction with halide ion at carbon-3 to give III or IV; (c) reaction with halide ion at the methyl carbon to give the lactone or products resulting therefrom.

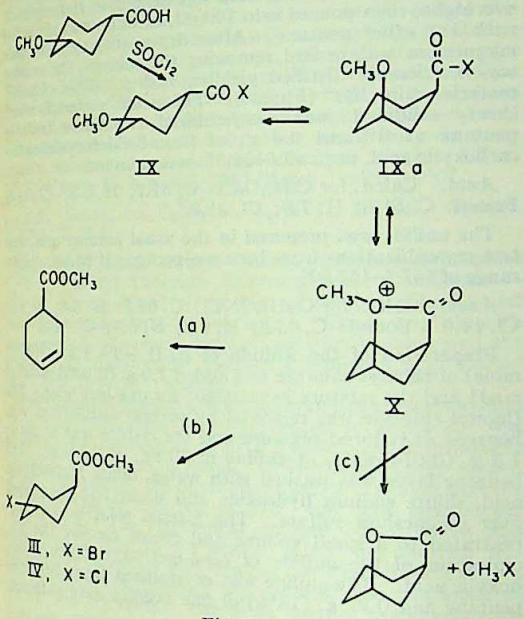
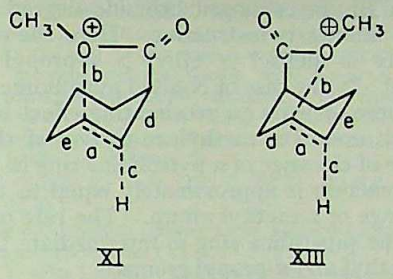


Fig. 1.

It is first instructive to consider the competitive formation of the unsaturated ester. In the present cases, there is a greater proportion of unsaturated ester formed than was reported by Winberg or Prelog. This is undoubtedly due to the fact that in the intermediate X, the planar four-center arrangement favorable to elimination is appropriately locked in place. This makes it possible for elimination to compete favorably on an energetic basis with further substitution.

The preference for elimination of the 4-hydrogen over the 2-hydrogen warrants further comment. Examination of the postulated transition state XI leading to methyl 2-cyclohexene-1-carboxylate (XII) reveals that as the double bond (a) is forming and bonds (b) and (c) are breaking, bonds (a), (d) and (e) must be rotated into coplanarity. These three events may be difficult to coördinate since (d) and (e) cannot be rotated a great deal until (b) is broken—*i.e.*, in order to rotate (d) into the (a)(e) plane the carbomethoxy group must be moved rather far from carbon-3.

In the postulated transition state (XIII) leading to methyl 3-cyclohexene-1-carboxylate (V), as the double bond (a) is forming and bonds (b) and (c) are breaking bonds (a), (d) and (e) must be rotated into coplanarity. The three events occurring in this transition state can be more easily coördinated since the carbomethoxy group formed is one carbon farther removed from the developing double bond. Furthermore, an investigation of a Fisher–Hirshfelder–Taylor model of V shows that the centers of the methoxyl oxygen and the center of the carbon-3, when in the conformation permitting their closest approach, are about 3.5 Å. apart. The corresponding distance in XII is about



4.0 Å. Therefore, at the instant bond (b) is broken, the conformation of the distorted XII will be at a higher energy than the distorted V by an amount related to the 0.5 Å. difference between the methoxyl oxygen and carbon-3 in the conformations pictured above. This energy difference will be reflected in their transition states.

It is further to be noted that the ionization of X to the ring carbonium ion is not consistent with the facts since it has been shown[11] that methyl *cis*-3-tosyloxycyclohexanecarboxylate (XV) undergoes normal solvolysis and elimination. The products of elimination resulting from XV are V and XII, with V predominating.

It is thus clear that the elimination process is synchronous, and that the geometry of the transition state exerts a profound control upon the product formed.

Turning now to the question of the two substitution processes available to the oxonium ion X, it is noteworthy that ring substitution occurs, with no evidence for substitution at the methyl carbon (pathway c above). The preference for reaction at a secondary carbon is not simply explicable upon the basis of SN1 behavior for the following reasons. The examples studied by Prelog and by Heinbach-Juhasz[6] would have been expected on this basis to give a mixture of products. This was not observed. The cleavage of methyl *sec*-butyl ether by acetyl iodide[12] affords 52% methyl iodide and 28% *sec*-butyl iodide. Were the cleavage SN1 in character, the secondary iodide should be the major product. Were the mechanism a normal SN2 displacement the methyl iodide should be more highly favored. It is suggestive at this point to conclude that the mechanism is of the displacement type, but with the effect of the positively charged leaving group being that differences in rate of reactions at primary, secondary and tertiary carbons are minimized or leveled.

Further comparison may be drawn with the displacement reaction accompanying the decomposition of sulfonium salts.[13] Methylethyl-*n*-propylsulfonium hydroxide affords both methanol and

(11) D. S. Noyce and H. I. Weingarten, forthcoming publication.
(12) P. G. Stevens, THIS JOURNAL, 62, 1801 (1940).
(13) E. D. Hughes, C. K. Ingold and G. A. Maw, *J. Chem. Soc.*, 2072 (1948).

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ethanol,[14,15] while dimethyl-2-phenylethylsulfonium iodide in sodium ethoxide affords more ethyl 2-phenylethyl ether than methyl ethyl ether. These results are consistent with the hypothesis that displacement of oxonium, sulfonium or ammonium groups shows less selectivity than simple SN2 displacement reactions.

In accord with this hypothesis, comparison with the von Braun cyanogen bromide degradation of tertiary amines is instructive. Here the order of reactivity is methyl > ethyl > *n*-propyl > isopropyl.[16] In the case of N-alkyl pyrrolidine derivatives, there appears an accelerating effect involved in attack upon the methylene carbon of the ring. The rate of cleavage of a pyrrolidine ring in the von Braun reaction is approximately equal to the rate of cleavage of a methyl group. The rate of cleavage of the piperidine ring is intermediate between that of ethyl and *n*-propyl groups.

It would thus appear that in reactions involving ring-breaking displacement,[17] increased rates of reaction are observed. This hypothesis then serves to correlate the reactions reported here with the previously observed examples.

Experimental[18]

Preparation of 3-Methoxycyclohexanecarboxylic Acid (II).—*m*-Methoxybenzoic acid, 65 g. (0.43 mole), dissolved in 300 ml. of 95% ethanol, to which 4 g. of platinum oxide was added, was reduced with hydrogen in 30 hours on a Parr low pressure hydrogenator at room temperature.

The catalyst was removed by filtration and most of the ethanol was removed under reduced pressure. The residue was poured into 500 ml. of water, extracted four times with 1:1 ether–pentane and the combined extracts dried over magnesium sulfate. After removal of the solvent the residue was fractionally distilled yielding 24.7 g. (43%) of cyclohexanecarboxylic acid, b.p. 103–104° (5 mm.), and 28.3 g. (40%) of 3-methoxycyclohexanecarboxylic acid, b.p. 140–142° (5 mm.).

Isolation of *cis*-3-Methoxycyclohexanecarboxylic Acid (*cis*-II).—The mixed acids, II, 28.3 g. (0.18 mole), obtained from the reduction of *m*-methoxybenzoic acid were dissolved in a minimum of refluxing *n*-pentane and seeded with *cis*-II. The precipitate obtained was recrystallized three times from *n*-pentane yielding 8.0 g. of *cis*-II, m.p. 51–52°. An additional 8.3 g. of *cis*-II, m.p. 51–52°, was obtained by continued fractional crystallization of the combined filtrates, a recovery of 60% from the mixed isomers.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.6; H, 8.9.

Rearrangement of *cis*-3-Methoxycyclohexanecarboxylic Acid (*cis*-II) in Thionyl Chloride.—To 10 g. (0.063 mole) of *cis*-II was added 15 g. (0.13 mole) of thionyl chloride. After the initial reaction subsided the resulting solution was heated under reflux on a steam-bath for two hours. The excess thionyl chloride was then removed by several distillations with benzene at reduced pressure. The residue was taken up in additional benzene and washed with sodium carbonate solution and then with water. After drying the benzene solution over magnesium sulfate and evaporating, the residue was fractionally distilled to give two main fractions. Fraction A afforded 2.4 g. (28%) of methyl 3-cyclohexene-1-carboxylate (V), b.p. 82–83° (26 mm.), $n^{25}D$ 1.4584. V was refractionated for analysis.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.5; H, 8.6. Found: C, 68.1; H, 8.8.

Fraction B, 5.7 g. (51%), b.p. 117° (22 mm.), $n^{25}D$ 1.4689, was methyl *trans*-3-chlorocyclohexanecarboxylate (IV). IV was refractionated for analysis.

Anal. Calcd. for $C_8H_{13}O_2Cl$: C, 54.4; H, 7.4; Cl, 20.0. Found: C, 54.4; H, 7.5; Cl, 19.9.

Hydrolysis of (IV).—A solution of 25 ml. of water and 20 ml. of dioxane containing 3.5 g. (0.02 mole) of IV and 2.5 ml. of concd. sulfuric acid was heated on a steam-bath overnight, then poured into 100 ml. of water and extracted with 1:1 ether–pentane. After drying the extracts over magnesium sulfate and removing the solvent, the residue was fractionally distilled yielding 1.35 g. (40%) of acidic material, b.p. 133° (5 mm.). This acidic material, which slowly solidified, was recrystallized two times from *n*-pentane at 0° and 0.4 g. of *trans*-3-chlorocyclohexanecarboxylic acid, m.p. 49.5–51.5°, was obtained.

Anal. Calcd. for $C_7H_{11}O_2Cl$: C, 51.7; H, 6.8; Cl, 21.8. Found: C, 51.8; H, 7.0; Cl, 21.6.

The anilide was prepared in the usual manner and after two crystallizations from benzene–pentane it had a melting range of 157.5–157.9°.

Anal. Calcd. for $C_{13}H_{16}ONCl$: C, 65.7; H, 6.8; N, 5.9; Cl, 14.9. Found: C, 65.8; H, 6.6; N, 6.1; Cl, 14.8.

Preparation of the Anilide of *cis*-II.—To 1.3 g. (0.012 mole) of thionyl chloride was added 1.0 g. (0.0063 mole) of *cis*-II and the mixture kept at 40° for one half hour. The thionyl chloride was removed by several distillations with benzene at reduced pressure and the residue was added to 1.3 g. (0.014 mole) of aniline in 20 ml. of benzene. The benzene layer was washed with water, dilute hydrochloric acid, dilute sodium hydroxide and water and then dried over magnesium sulfate. The filtered solution was concentrated to a small volume and cooled causing the precipitation of the anilide of *cis*-3-methoxycyclohexanecarboxylic acid. The anilide was crystallized from benzene–pentane and 0.27 g. (18%) of fine needles were obtained, m.p. 130.5–131.5°.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.2; H, 8.1; N, 5.9.

Preparation of the Anilide of *trans*-II.—A sample of 4 g. (0.025 mole) of the mixed *cis*-II and *trans*-II acids obtained by concentrating the combined filtrates from which *cis*-II had been removed was added to 6 g. (0.05 mole) of thionyl chloride. This solution was heated on a steam-bath for two hours and then treated as in the above experiment to afford 1.4 g. of the anilide of *trans*-II, m.p. 137.6–138.6°. A mixed melting point with the anilide of *cis*-II depressed to 109–115°.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.1; H, 8.3; N, 5.8.

Rearrangement of *cis*-3-Methoxycyclohexanecarboxylic Acid (*cis*-II) in Phosphorus Tribromide.—Ten grams (0.063 mole) of *cis*-I was added to 15 g. (0.055) mole of phosphorus tribromide and the mixture was heated on a steam-bath for two hours. At the end of this time the reaction mixture was poured into ice, neutralized with solid sodium carbonate and extracted three times with benzene. The benzene solution was dried and evaporated and methyl *trans*-3-bromocyclohexanecarboxylate (III), 9.75 g. (70%) was obtained upon fractional distillation of the residue, b.p. 129–131° (24 mm.).

A small forerun, 0.5 g., boiling at a temperature corresponding to V was also isolated but was not further characterized.

Preparation of III from the Lactone of *cis*-3-Hydroxycyclohexanecarboxylic Acid.—Gaseous hydrogen bromide was passed into a mixture of 6 g. (0.047 mole) of the lactone of *cis*-3-hydroxycyclohexanecarboxylic acid in 15 ml. of 40% hydrobromic acid until saturated at 0°, then permitted to stand overnight. The resulting solution was poured into water, extracted with 1:2 ether–pentane, dried, evaporated and the product fractionally distilled. The obtained *cis*-3-bromocyclohexanecarboxylic acid, 5.2 g. (35%),

(14) C. K. Ingold, J. A. Jessop, K. I. Kuriyan and A. M. M. Mandour, *J. Chem. Soc.*, 533 (1933).

(15) C. K. Ingold and K. I. Kuriyan, *ibid.*, 991 (1933).

(16) E. A. Hageman, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 198.

(17) This situation is to be contrasted to the normal displacement or solvolysis which takes place at a ring atom, but with the extra-annular atom leaving, *e.g.*, cyclohexyl chloride.

(18) All melting points are corrected; boiling points are uncorrected. An 18″ modified Podbielniak column was used for all fractionations. The infrared spectra were recorded by a Perkin–Elmer model 21 spectrophotometer using 0.1-mm. sodium chloride cells with solutions 0.2 *M* in chloroform. Microanalyses are by the Microanalytical Laboratory, University of California.

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b.p. 141–142° (5 mm.), was crystallized once from *n*-pentane, m.p. 64–65° (lit. m.p. 62–63°,[9] m.p. 67–68°[8]).

The bromo acid was dissolved in dry ether and an excess of diazomethane in ether was added. The ether was removed after drying and the residue fractionally distilled yielding 3.5 g. of authentic III, b.p. 120–121° (15 mm.), $n^{25}D$ 1.4923. Authentic III was characterized by infrared analysis.

Anal. Calcd. for $C_8H_{13}O_3Br$: C, 43.5; H, 5.9; Br, 36.2. Found: C, 43.1; H, 5.9; Br, 36.1.

Isolation of *trans*-3-Methoxycyclohexanecarboxylic Acid (*trans*-II).—Thirteen grams of the mixed acids (*cis*-II and *trans*-II), obtained from the combined filtrates which yielded *cis*-II, was dissolved in 20 g. of thionyl chloride and heated on a steam-bath for two hours. At the end of this time the excess thionyl chloride was removed by distillation with several portions of benzene. The reaction mixture was then poured into water, neutralized with solid sodium carbonate and extracted twice with pentane. The aqueous phase was acidified with hydrochloric acid to a *p*H of 2 and extracted with ether. This solution was dried over magnesium sulfate, evaporated and distilled to give 4.3 g. (33%) of *trans*-II, b.p. 123–125° (2 mm.), $n^{25}D$ 1.4661.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.8; H, 8.9.

Behavior of Methyl *trans*-3-Chlorocyclohexanecarboxylate (IV) in Thionyl Chloride Rearrangement Conditions.—IV, 4.3 g., was dissolved in 4 g. of thionyl chloride and placed on a steam-bath for two hours. The thionyl chloride was removed by several distillations with benzene and the residue was fractionally distilled yielding 3.8 g. (89%) of IV, b.p. 119–120° (25 mm.).

Preparation of Methyl 4-Methoxycyclohexanecarboxylate.—To a hydrogenation bomb preheated to about 30° was added a warm solution of 50 g. (0.3 mole) of methyl anisate in 50 ml. of absolute ethanol. Commercial Raney nickel, 3-6 g., was added, the bomb mounted on a shaker and the hydrogenation carried out at 170° and 3600 pounds per square inch. The theoretical amount of hydrogen was taken up in four to six hours. After the catalyst was removed by filtration and most of the ethanol removed by low pressure distillation, the residue was fractionated giving two fractions. The first, methyl cyclohexanecarboxylate, weighed 11.2 g. (26%) and had a boiling range of 85–110° (30 mm.). The second, methyl 4-methoxycyclohexanecarboxylate, weighed 29.0 g. (56%) and had a b.p. of 122–124° (30 mm.).

Hydrolysis of Methyl 4-Methoxycyclohexanecarboxylate.—Methyl 4-methoxycyclohexanecarboxylate, 29 g. (0.17 mole), was combined with a solution of 80 ml. of water, 30 ml. of methanol and 23 g. (0.41 mole) of potassium hydroxide. This mixture was heated on a steam-bath for 90 minutes then poured into 200 ml. of water. The aqueous solution was extracted once with *n*-pentane to remove any neutral material then acidified to a *p*H of 2 and extracted three times with 1:1 ether–pentane. The extracts were dried over magnesium sulfate and following the removal of the solvent the residue was fractionally distilled to yield 23.4 g. (90%) 4-methoxycyclohexanecarboxylic acid (VI), b.p. 142° (6 mm.).

Isolation of *cis*-4-Methoxycyclohexanecarboxylic Acid (*cis*-VI).—VI, 23.4 g., was dissolved in ether and then cooled in a Dry Ice-bath. The ether was decanted after precipitation without collecting the precipitate. This process was repeated and following the second crystallization the solid was collected, dried and recrystallized twice from *n*-pentane at room temperature. A sample of *cis*-VI, 7.2 g. (31%), m.p. 54.6–55.6°, was obtained.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.7; H, 8.8.

The anilide of *cis*-VI was prepared in the same way that the anilide of *cis*-II was prepared, m.p. 123.3–124.3°.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.1; H, 8.2. Found: C, 71.9; H, 7.9.

Isolation of *trans*-4-Methoxycyclohexanecarboxylic Acid (*trans*-VI).—An 8.6-g. sample of V was treated with thionyl chloride in the same process used to isolate *trans*-II. *trans*-VI, 1.65 g. (19%), was obtained and on several crystallizations from *n*-pentane gave a m.p. 0.5–60°.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.9; H, 8.8.

The anilide of *trans*-VI was prepared in the usual way and on recrystallization from benzene–pentane had a m.p. of 186.0–186.4°.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.2; H, 8.1; N, 6.1.

Rearrangement of *cis*-4-Methoxycyclohexanecarboxylic Acid (*cis*-VI) in Thionyl Chloride.—Seven grams (0.044 mole) of *cis*-VI was added to 14 g. (0.12 mole) of thionyl chloride and the solution heated on a steam-bath for 2.5 hours. At the end of this period the thionyl chloride was removed by repeated distillation with benzene and the product was then fractionally distilled. The first fraction proved to be 2.7 g. (44%) of V, b.p. 91° (39 mm.). V was refractionated and an infrared spectrum obtained, which was identical to that of authentic V.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.5; H, 8.6. Found: C, 68.4; H, 9.1.

The second fraction proved to be methyl *trans*-4-chlorocyclohexanecarboxylate (VII), 2.3 g. (30%), b.p. 119° (20 mm.), $n^{25}D$ 1.4670. This compound was also characterized by an infrared spectrum.

Anal. Calcd. for $C_8H_{13}O_2Cl$: C, 54.4; H, 7.4; Cl, 20.1. Found: C, 54.2; H, 7.3; Cl, 19.9.

Hydrolysis of VII.—To 40 ml. of 1:1 solution of water–dioxane was added 1.0 g. of VI and 2 ml. of concentrated sulfuric acid. This two-phase mixture was heated on a steam-bath for six hours. The resulting solution was then poured into 70 ml. of water and placed in a refrigerator overnight. The precipitate of *trans*-4-chlorocyclohexanecarboxylic acid was collected and on drying weighed 0.55 g. (61%), m.p. 157–159°. A second crop yielded 0.25 g. (27%). The first crop was crystallized from benzene–pentane giving 0.3 g. of acid having a m.p. of 159.0–159.8°.

Anal. Calcd. for $C_7H_{11}O_2Cl$: C, 51.7; H, 6.8. Found: C, 51.5; H, 6.7.

The anilide was prepared in the usual way, and recrystallized from benzene–pentane, m.p. 196.5–196.8°.

Anal. Calcd. for $C_{13}H_{16}ONCl$: C, 65.7; H, 6.8; N, 5.9; Cl, 14.9. Found: C, 65.4; H, 6.7; N, 6.1; Cl, 14.9.

Rearrangement of *cis*-4-Methoxycyclohexanecarboxylic Acid (*cis*-VI) with Phosphorus Tribromide.—*cis*-VI, 7 g. (0.044 mole), was added to 12 g. (0.044 mole) of phosphorus tribromide and the reaction mixture was heated on a steam-bath for 2.5 hours. The resulting mixture was then poured into water made basic with solid sodium carbonate and extracted with pentane. After drying the pentane extracts over magnesium sulfate and removing the solvent the product was fractionally distilled affording 5.7 g. (59%) of methyl *trans*-4-bromocyclohexanecarboxylate (VIII) b.p. 128–130° (18 mm.), $n^{25}D$ 1.4916. VII was characterized by an infrared spectrum.

Anal. Calcd. for $C_8H_{13}O_2Br$: C, 43.5; H, 5.9; Br, 36.1. Found: C, 43.8; H, 5.7; Br, 35.5.

The basic aqueous layer was acidified and yielded a precipitate of *trans*-4-bromocyclohexanecarboxylic acid, 1.5 g. (17%) with a melting point range of 160–170°. One crystallization from benzene–pentane raised the melting point to 169–171° (lit.[19] m.p. 167°).

No methyl cyclohexenecarboxylate was detected among the products.

Hydrolysis of VIII.—Four grams of VII was heated under reflux with a 1:1 solution of water–dioxane, 125 ml., containing 8 ml. of concentrated sulfuric acid for four hours. The resulting solution was poured into 150 ml. of water and placed in a refrigerator overnight. The precipitate of *trans*-4-bromocyclohexanecarboxylic acid weighed 0.8 g. (22%) and melted over a wide range to 170°. Three recrystallizations from benzene–pentane gave 0.5 g., m.p. 170.8–171.4° (lit.[19] m.p. 167°).

Anal. Calcd. for $C_7H_{11}O_2Br$: C, 40.6; H, 5.3; Br, 38.6. Found: C, 40.6; H, 5.2; Br, 38.6.

The anilide was prepared in the usual way and was crystallized from benzene–pentane, m.p. 191.0–191.7°.

Anal. Calcd. for $C_{13}H_{16}O_2NBr$: C, 55.3; H, 5.7; N, 5.0; Br, 28.4. Found: C, 55.6; H, 5.7; N, 5.3; Br, 28.4.

(19) W. H. Perkin, *J. Chem. Soc.*, **85**, 431 (1904).

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Methyl 3-Cyclohexene-1-carboxylate (V).—Methylacrylate and butadiene were heated at 140° in a steel bomb for five hours, and the mixture distilled to afford 85% of methyl 3-cyclohexene-1-carboxylate (V).[20]

Methyl 1-Cyclohexene-1-carboxylate and Methyl 2-Cyclohexene-2-carboxylate.—The mixture of cyclohexenecarboxylic acids obtained from cyclohexanone cyanohydrin through cyclohexenecarbonitrile was fractionally crystallized from pentane to afford 1-cyclohexene-1-carboxylic acid which was esterified with diazomethane to afford methyl 1-cyclohexene-1-carboxylate, b.p. 105° (40 mm.), n^{25}D 1.4808. The mother liquors from the fractional crystallization were fractionated, collecting the lower boiling fractions (enriched in 2-cyclohexene-1-carboxylic acid). Esterification with diazomethane was followed by fractionation to give the ester, methyl 2-cyclohexene-1-carboxylate, b.p. 94–95° (40 mm.), n^{25}D 1.4605.

(20) K. Alder and W. Vogt, *Ann.*, **564**, 120 (1949).

BERKELEY 4, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA]

Studies of Configuration. IV. The Rearrangement of Methoxycyclohexanecarboxylic Acids with Acetic Anhydride[1]

BY DONALD S. NOYCE AND HAROLD I. WEINGARTEN[2]

RECEIVED NOVEMBER 10, 1956

Treatment of *cis*-3-methoxycyclohexanecarboxylic acid with acetic anhydride and catalytic amounts of sulfuric acid leads to a mixture of three products, methyl cyclohex-3-ene-carboxylate, methyl *trans*-3-acetoxycyclohexanecarboxylate and methyl *trans*-4-acetoxycyclohexanecarboxylate. Under the same conditions *cis*-4-methoxycyclohexanecarboxylic acid leads to a mixture of the same products in different proportions. The mechanism of the rearrangement between the 3- and 4-positions is discussed. It is suggested that the rearrangement proceeds through a transition state which is doubly bridged.

In the previous paper of this series, it was shown[3] that the intramolecular rearrangement of γ- and δ-alkoxy carboxylic acid chlorides to the corresponding chloro esters could be extended to suitable derivatives of cyclohexanecarboxylic acid. Ethers may also be cleaved by acetic anhydride and acidic catalysts. Acetic anhydride has been reported to cleave ethers in the presence of catalytic amounts of Lewis acids such as boron trifluoride, zinc chloride, ferric chloride and aluminum chloride.[4] Nudenberg and Butz[5] reported the cleavage of 1,4-epoxycyclohexane with acetic anhydride and zinc chloride to *trans*-1,4-diacetoxycyclohexane. The cleavage of tetrahydrofurans has been investigated by Wilson[6] and Paul.[7]

In view of the apparent generality of the cleavage of ethers with acetic anhydride, it appeared feasible to demonstrate the intramolecular counterpart of this reaction. Such is the purpose of the present report.

The reaction between *cis*-3-methoxycyclohexanecarboxylic acid (*cis*-I), acetic anhydride and a small amount of sulfuric acid was investigated. Under these conditions, it would be expected that appreciable quantities of the mixed anhydride (II) of *cis*-I and acetic acid would be formed in equilibrium with acetic anhydride. The mixed anhydride (II) may then be expected to undergo intramolecular reaction to give methyl *trans*-3-acetoxycyclohexanecarboxylate (*trans*-III). The products were separated by fractional distillation. The lower boiling fraction was identified as methyl 3-cyclohexene-1-carboxylate (IV) as previously described,[3] and the higher boiling fraction (B) has the elemental composition and saponification equivalent appropriate for (*trans*-III).

It is to be noted that the isolation of esters III and IV clearly establishes the success of the *intramolecular* rearrangement. Were the methoxyl fragment ever to be released into solution, exclusive reaction with the solvent acetic anhydride would occur.

Further experiments designed to establish the structure of III showed that fraction B is in fact a mixture of isomers. Hydrolysis of fraction B afforded crystalline *trans*-4-hydroxycyclohexanecarboxylic acid (*trans*-V), identified by melting point and mixed melting point, and an oil. Crystallization of fraction B from pentane afforded the crystalline methyl *trans*-4-acetoxycyclohexanecarboxylate (*trans*-VI), identified by comparison with an authentic sample. Since it was apparent that fraction B was a mixture, several attempts were made to separate by crystallization some of the second component. These attempts failed. The composition of the mixture was determined by infrared analysis, by comparing the spectrum of fraction B with the infrared spectra of methyl *cis*-3-acetoxycyclohexanecarboxylate (*cis*-III), *trans*-III, methyl *cis*-4-acetoxycyclohexanecarboxylate (*cis*-VI) and *trans*-VI and with appropriate mixtures. The comparison of the infrared spectra indicated that only *trans*-III and *trans*-VI were present in the rearrangement product. Absorption bands at 12.22 and 10.15 μ characteristic of *trans*-III and at 7.60 μ, characteristic of *trans*-VI were observed. From the spectra of fraction B and of synthetic mixtures, it was determined that fraction B consisted of 57 ± 3% of *trans*-VI, and 43 ± 3% of *trans*-III.

cis-4-Methoxycyclohexanecarboxylic acid (*cis*-VII) was subjected to similar treatment with acetic anhydride and on fractional distillation two fractions were again obtained. The lower boiling fraction was IV, and the higher boiling fraction was

(1) Presented at the 127th Meeting of the American Chemical Society, Cincinnati, Ohio, March, 1955.

(2) Du Pont Summer Research Assistant, 1953; Eastman Kodak Fellow, 1954–1955.

(3) D. S. Noyce and H. I. Weingarten, THIS JOURNAL, **79**, 3093 (1957).

(4) H. Meerwein and H. Maier-Huser, *J. prakt. Chem.*, **134**, 51 (1932).

(5) W. Nudenberg and L. W. Butz, THIS JOURNAL, **66**, 307 (1944).

(6) C. Wilson, *J. Chem. Soc.*, 48 (1945).

(7) R. Paul, *Bull. soc. chim. France*, 13, 1 (1946).

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a mixture of ester acetates. The acetate fraction appeared at first to contain only *trans*-VI, but its infrared spectrum showed small inconsistencies in the regions where *trans*-III was known to absorb strongly. Therefore, the acetate fraction was crystallized from *n*-pentane yielding solid *trans*-VI and a filtrate. This filtrate was distilled and an infrared spectrum taken of the distillate. The analysis of this spectrum, made in the same way as before, revealed that the original acetate fraction contained approximately 5% of *trans*-III.

To show that the *cis* and *trans* isomers of the 3- and 4-methoxycyclohexanecarboxylic acids would behave differently, *trans*-I was subjected to the reaction conditions. Under these conditions *trans*-I yielded two products believed to be 3-cyclohexene-1-carboxylic acid and the anhydride of 3-cyclohexene-1-carboxylic acid.

Discussion

The first step in the intramolecular ether–acid anhydride rearrangement is clearly similar to that of the ether–acid chloride rearrangement,[2] the conversion of II (in the diaxial conformation) to the cyclic oxonium ion VIII. VIII may then proceed by any of three paths to products (Fig. 1). The first two, (a) elimination of a proton to yield methyl 3-cyclohexene-1-carboxylate (IV) and (b) solvolytic displacement by acetic acid to give methyl *trans*-3-acetoxycyclohexanecarboxylate (*trans*-III), completely parallel the analogous processes described previously.[3]

The third pathway (c), which produces methyl *trans*-4-acetoxycyclohexanecarboxylate (*trans*-VI) requires additional comment. The possibility that *trans*-VI arises by the addition of acetic acid to IV is ruled out by the fact that IV can be recovered in 80% yield from a reaction mixture of acetic anhydride, acetic acid and sulfuric acid after treatment under the conditions of the rearrangement. Further, the *cis*-3-methoxycyclohexanecarboxylic acid-*d* (prepared by equilibrating *cis*-I dissolved in toluene with D_2O) was treated with acetic anhydride with deuteriosulfuric acid as the catalyst. No deuterium could be detected in any of the products.

It is thus clear that an intramolecular hydrogen shift is responsible for the formation of *trans*-VI.

Intramolecular hydrogen shifts frequently have been suggested to proceed through a bridged cation transition state or intermediate.[8] Cram[9] has postulated ion-pair a as a possible intermediate in the rearrangement of 3-phenyl-2-butyl tosylates. Barnes[10] in proposing a mechanism for the formation of phenanthrene derivatives from β-arylethylcyclohexanols postulates ion b as an intermediate. To explain the formation of isobutyraldehyde in the solvolysis of 2-methoxy-2-methyl-1-propyl-*p*-bromobenzenesulfonate, Winstein, Lindegren and Ingraham[11] postulated ion c as a likely intermediate. Winstein and Holness[8a] also have postulated the bridged ions d and e to explain various products arising from the solvolysis of *cis*-4-*t*-butylcyclohexyl tosylate.

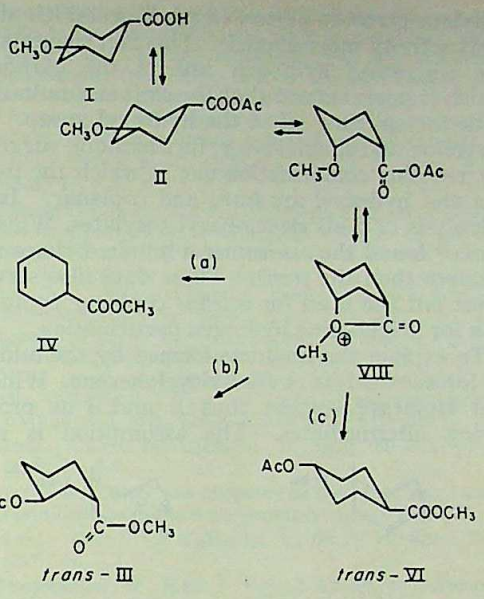
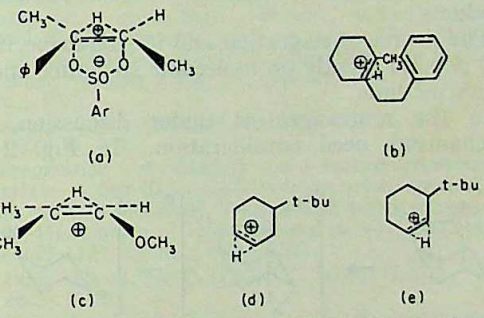
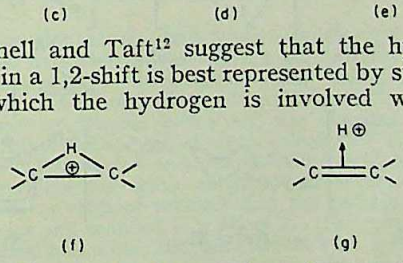


Fig. 1.



Cannell and Taft[12] suggest that the hydrogen bridge in a 1,2-shift is best represented by structure f in which the hydrogen is involved with the



sp^3-hybrid orbitals of the carbon atoms rather than the π-complex (g) suggested by Dewar.[8b] This conclusion was reached after a study of migrations occurring upon the diazotization of isobutylamine in a deuterated solvent. Since exchange with the deuterated solvent was observed, Taft eliminates the π-complex (g) from consideration, which would rapidly exchange with the solvent,[13] and demonstrates the intramolecular nature of the reaction.

Mislow and Siegel[14] observed that in the rearrangement of optically active α-phenyl β-(*o*-tolyl)-

(8) (a) S. Winstein and N. J. Holness, THIS JOURNAL, **77**, 5572 (1955); (b) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford Univ. Press, Oxford, 1949, p. 144, etc.

(9) D. J. Cram, THIS JOURNAL, **74**, 2137 (1952).

(10) R. A. Barnes, *ibid.*, **75**, 3004 (1953); R. A. Barnes and A. D. Olin, *ibid.*, **78**, 3830 (1956).

(11) S. Winstein, C. R. Lindegren and L. L. Ingraham, *ibid.*, **75**, 155 (1953).

(12) L. G. Cannell and R. W. Taft, Jr., *ibid.*, **78**, 5812 (1956).

(13) R. W. Taft, Jr., Abstract of Papers, Joint Symposium on Mechanisms of Homogeneous and Heterogeneous Hydrocarbon Reactions, March, 1954, Kansas City, Missouri, p. 33.

(14) K. Mislow and M. Siegel, THIS JOURNAL, **74**, 1060 (1952).

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ethylene glycol to phenyl-(*o*-tolyl)-acetaldehyde optical activity was retained. This fact suggests that the migrating hydrogen inverts the carbon to which it migrates and that the shift is simultaneous with the splitting off of the hydroxyl group. The inversion and simultaneity, furthermore, suggest as the reacting conformation one in which the hydrogen and hydroxyl are *trans* and coplanar. In the solvolysis of 2-alkylcyclohexyl tosylates, Winstein, *et al.*,[15] found the *cis* isomer a hundred times more reactive than the *trans*. These data also serve to point out the need for a *trans* coplanar conformation for neighboring hydrogen participation.

To explain the products formed by the addition of formic acid to 4-*t*-butylcyclohexene, Winstein and Holness[8a] suggest ions h and i as product giving intermediates. The assumption is made

(h) (i)

that the hydrogen-bridged ions tend to open stereospecifically to give axial products, by analogy with the direction of opening of steroidal epoxides[16] and with the addition of halogens to steroids.[17] The ion h yields *trans*-3 products while ion i yields *cis*-4 products.

The degree of migration and its stereospecificity will depend greatly on molecular structure and reaction medium.

In the rearrangement under discussion, two mechanisms need consideration. In Fig. 2 the

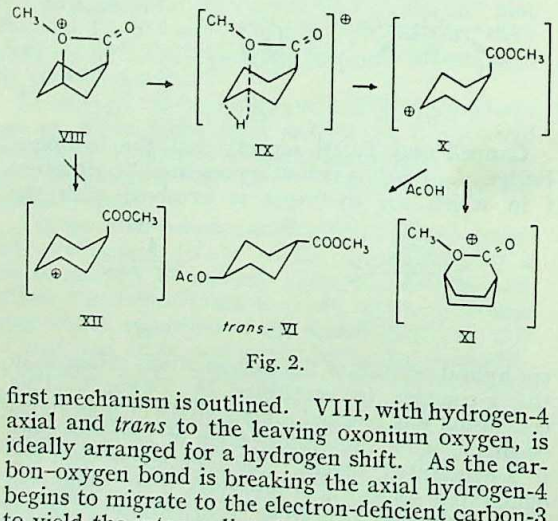

Fig. 2.

first mechanism is outlined. VIII, with hydrogen-4 axial and *trans* to the leaving oxonium oxygen, is ideally arranged for a hydrogen shift. As the carbon–oxygen bond is breaking the axial hydrogen-4 begins to migrate to the electron-deficient carbon-3 to yield the intermediate hydrogen bridged species IX. IX may open to give ion X which can react with acetic acid to form *trans*-VI, or it may internally coördinate to give oxonium ion XI, which can also react to give *trans*-VI. The possibility of ion VIII opening to the externally solvated ion XII prior to the migration of a hydrogen has been excluded for the following reason. If XII were formed, it would be expected to give largely *cis*-III; however, no *cis* products were ever observed. Likewise, *cis*-VI is the product expected to arise from the hydrogen bridged species, IX. Since no *cis* products are observed, the existence of IX is somewhat doubtful and it is preferable to exclude it as an intermediate. Further, were IX to open to the solvated "classical" carbonium ion X, the exclusive formation of *trans*-4 products would require internal participation by the ester grouping to give XI. The solvolytic studies of the 3-carbomethoxycyclohexyl tosylates reported[18] indicate that there is no transannular participation by the ester group. Such results make the transformation X → XI unlikely.

The mechanism for the rearrangement which is in accord with all the facts is presented in Fig. 3.

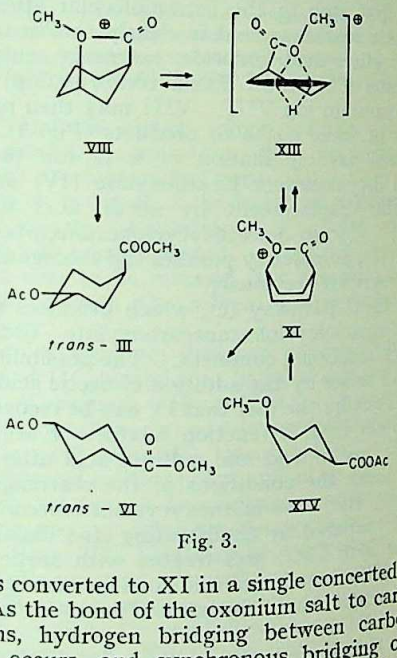

Fig. 3.

VIII is converted to XI in a single concerted process. As the bond of the oxonium salt to carbon-3 weakens, hydrogen bridging between carbons 3 and 4 occurs, and synchronous bridging of the oxygen to carbon-4 occurs. The doubly bridged ion XIII thus represents the transition state for that path leading to *trans*-VI from II. In like manner the small amount of *trans*-III resulting from the treatment of *cis*-VII with acetic anhydride and sulfuric acid may be considered to arise by the path VII → XIV, through XIII to VIII, to *trans*-III (Fig. 3). This pathway is then consistent with the formation of some *trans*-III to the exclusion of *cis*-III. Were the solvated carbonium ion XII formed by rearrangement from XI, the expected product would be largely *cis*-III.

An examination of the model of XIII reveals no unusual or prohibitive amounts of strain. An analogous doubly bridged species is suggested by Denney[19] as a transition state or short-lived intermediate for the rearrangement of the benzoate of

(15) S. Winstein, *et al.*, THIS JOURNAL, **74**, 1127 (1952).
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9-decalyl hydroperoxide to 1-benzoyloxy-1,6-epoxycyclodecane.

There are several other reactions in which facile rearrangements in cyclohexane systems are observed. Examples are the Friedel–Crafts reactions of cyclohexene with *t*-butyl chloride,[20,21] with acetyl chloride and benzene,[22] of 1,2-dibromocyclohexane with benzene,[23] the conversion of 3-methylcyclohexanol to 1-chloro-4-methylcyclohexane (as a minor product) with hydrochloric acid,[24] and the conversion of 4-chlorocyclohexanol to a mixture of 1,3- and 1,4-dichlorocyclohexanes.[25]

It is attractive to suggest that many of these transformations also proceed through hydrogen bridged species, rather than by addition–elimination as has been suggested.[21]

Experimental[26]

Rearrangement of *cis*-3-Methoxycyclohexanecarboxylic Acid (*cis*-I) in Acetic Anhydride.—To a solution of 10 g. (0.063 mole) of *cis*-I in 50 ml. of acetic anhydride was added 0.2 g. of concentrated sulfuric acid. The solution was heated on a steam-bath for six hours, diluted with water and the aqueous mixture was extracted three times with *n*-pentane. The pentane extracts were combined and washed with sodium carbonate solution and water. After drying the extract over magnesium sulfate, evaporating and fractionally distilling the residue, two fractions were obtained. The first fraction, methyl cyclohex-3-enecarboxylate (IV), b.p. 94° (40 mm.), n^{25}D 1.4570, weighed 3.25 g. (37%). The second fraction (fraction B) was a mixture of methyl *trans*-3-acetoxycyclohexanecarboxylate (*trans*-III) and methyl *trans*-4-acetoxycyclohexanecarboxylate (*trans*-VI). The mixture was obtained to the extent of 38% (4.8 g.), b.p. 116–119° (7 mm.), and was characterized by infrared spectrum.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 60.1; H, 7.8.

Hydrolysis of Fraction B.—Two grams (0.01 mole) of fraction B was added to a solution of 3 g. (0.053 mole) of potassium hydroxide in 6 ml. of water and 3 ml. of methanol and the mixture placed on a steam-bath for one hour. At the end of this time the solution was poured into 100 ml. of water, washed once with pentane and acidified to a *p*H of 3. The oily material obtained after 12 hours of continuous extraction with ether was recrystallized three times from acetonitrile at 0° yielding 0.2 g. of *trans*-4-hydroxycyclohexanecarboxylic acid, m.p. 147.4–148.0° (lit.[29] m.p. 148°). A mixed melting point with authentic *trans*-4-hydroxycyclohexanecarboxylic acid showed no depression (m.m.p. 147–148°). The filtrates from the above recrystallizations yielded an uncrystallizable oil believed to be a mixture of *trans*-4-hydroxycyclohexanecarboxylic acid and *trans*-3-hydroxycyclohexanecarboxylic acid.

Isolation of Methyl *trans*-4-Acetoxycyclohexanecarboxylate (*trans*-VI).—Fraction B, 2.8 g., was crystallized from *n*-pentane in a Dry Ice-bath and was crystallized three times by decantation. The third precipitate was collected and recrystallized from *n*-pentane at 0° giving 0.7 g. (25%) of *trans*-VI, m.p. 48.0–48.5°. A mixed melting point with authentic *trans*-VI showed no depression.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 59.8; H, 8.1.

Separation of *cis*- and *trans*-3-Hydroxycyclohexanecarboxylic Acids.—Crystallization of the mixed acids (obtained by reduction of methyl *m*-hydroxybenzoate, followed by saponification) from ethyl acetate afforded *cis*-3-hydroxycyclohexanecarboxylic acid, m.p. 131.6–132° (lit.[27] 131.5°).

The phenacyl ester was prepared in the usual way[28] and was crystallized from benzene–pentane, m.p. 89.6–90.3°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9. Found: C, 68.8; H, 6.3.

The combined ethyl acetate filtrates from the above separation were evaporated and the residue heated on an oil-bath between 170 and 190° until the water which was formed no longer distilled over. The products were then separated by distillation. The first fraction, the lactone of *cis*-3-hydroxycyclohexanecarboxylic acid, b.p. 130–140° (20 mm.), weighed 7.0 g. (23%). The second fraction, 4.2 g. (12%) of *trans*-3-hydroxycyclohexanecarboxylic acid, b.p. 140–160° (5 mm.), was recrystallized four times from acetonitrile, affording 2.0 g. of *trans*-3-hydroxycyclohexanecarboxylic acid, m.p. 118.8–119.6° (lit.[27] 119–120°).

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.3; H, 8.4. Found: C, 58.8; H, 8.8.

A phenacyl ester was prepared in the usual way, and was recrystallized from benzene–pentane, m.p. 97.7–98.5°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9. Found: C, 68.6; H, 7.1.

Preparation of Methyl *trans*-3-Acetoxycyclohexanecarboxylate (*trans*-III).—*trans*-3-Hydroxycyclohexanecarboxylic acid, m.p. 118.8–119.6°, 1.5 g. (0.01 mole), was dissolved in ether and an excess of diazomethane in ether was added. After drying and removal of the ether the methyl *trans*-3-hydroxycyclohexanecarboxylate was fractionally distilled, b.p. 115–115.5° (5 mm.), to give 1.4 g. of the ester.

The methyl ester was then dissolved in 10 ml. of pyridine and 3 ml. of acetic anhydride. The resulting solution was heated on a steam-bath overnight, poured into water, acidified and extracted with pentane. The extract was dried over magnesium sulfate, evaporated and fractionally distilled, yielding 1.6 g. of *trans*-III, b.p. 122° (9 mm.), n^{25}D 1.4510.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 60.0; H, 8.0.

Preparation of Methyl *cis*-3-Acetoxycyclohexanecarboxylate (*cis*-III).—*cis*-3-Hydroxycyclohexanecarboxylic acid, m.p. 131.6–132.0°, 2.4 g. (0.015 mole), was converted to *cis*-III as above. Three grams of *cis*-VIII was obtained, b.p. 112–113° (5 mm.), n^{25}D 1.4512.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 60.2; H, 8.3.

Separation of *cis*- and *trans*-4-Hydroxycyclohexanecarboxylic Acid Derivatives.—The crude mixture of *cis*- and *trans*-4-hydroxycyclohexanecarboxylic acid obtained by Raney nickel reduction of ethyl *m*-hydroxybenzoate, followed by alkaline hydrolysis, was dissolved in 100 ml. of pyridine and 100 ml. of acetic anhydride. The resulting solution was heated on a steam-bath overnight. Most of the pyridine and acetic anhydride were removed by distillation at reduced pressure and the residue was poured on to ice and acidified to a *p*H of 2. The resulting oil was extracted into ether, and the extracts were dried over magnesium sulfate, evaporated and the remaining oil distilled to yield two fractions. The first fraction, the lactone of *cis*-4-hydroxycyclohexanecarboxylic acid, 5.7 g. (21%), b.p. 120–140° (15 mm.), was recrystallized from benzene–pentane and 3.0 g. of lactone, m.p. 126–128° (lit.[29] m.p. 128°), was obtained. The second fraction, a mixture of *cis*- and *trans*-4-acetoxycyclohexanecarboxylic acids, b.p. 140–150° (3 mm.), weighed 18 g. (46%). Three recrystallizations from chloroform–pentane gave 6.2 g. of *trans*-4-acetoxycyclohexanecarboxylic acid, m.p. 137–139° (lit.[29] m.p. 139°). *cis*-4-Acetoxycyclohexanecarboxylic acid, 2.1 g., m.p. 81–83° (lit.[29] m.p. 80°), was obtained by repeated concentration and crystallization of the combined filtrates from which the *trans* isomer was largely removed.

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Preparation of Methyl *cis*-4-Acetoxycyclohexanecarboxylate (*cis*-VI).—Three grams (0.024 mole) of the lactone of *cis*-4-hydroxycyclohexanecarboxylic acid was heated with 10% potassium hydroxide for three hours. Following this period the solution was acidified to a *p*H of 2 and continuously extracted with ether. After drying the ether solution over magnesium sulfate, and evaporating to dryness, 2.4 g. (70%) of *cis*-4-hydroxycyclohexanecarboxylic acid was obtained. Crystallization from acetonitrile gave 2.0 g. of acid, m.p. 149.4–150.2° (lit.[29] m.p. 152°).

A phenacyl derivative was prepared in the usual way[28] and after one crystallization from benzene–pentane had m.p. 107.0–107.4°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9. Found: C, 68.6; H, 6.7.

The acid was dissolved in ether and an excess of diazomethane in ether was added. The solution was dried over magnesium sulfate, evaporated and the esterified product dissolved in 15 ml. of pyridine to which was added 7 ml. of acetic anhydride. The reaction mixture was heated on a steam-bath for six hours, poured into water, neutralized with dilute sulfuric acid and extracted twice with pentane. The pentane extracts were washed once with sodium carbonate solution, dried over magnesium sulfate, evaporated and the residual oil fractionally distilled. *cis*-VI, 2.3 g., b.p. 110° (5 mm.), $n^{25}D$ 1.4521, was obtained.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 60.2; H, 8.3.

Preparation of Methyl *trans*-4-Acetoxycyclohexanecarboxylate (*trans*-VI).—Two grams of 4-acetoxycyclohexanecarboxylic acid, m.p. 137–139°, was dissolved in ether and an excess of diazomethane in ether was added. The solution was dried over magnesium sulfate, the ether removed by distillation, and the residue was crystallized from *n*-pentane at −70°, yielding 1.4 g. of *trans*-VI. Two more crystallizations from *n*-pentane at 0° gave a product melting at 48.0–48.4°. The infrared spectrum was identical with that of the sample obtained from fraction B.

Behavior of Methyl 3-Cyclohexene-1-carboxylate (IV) under the Acetic Anhydride Rearrangement Conditions.—To 8.8 g. (0.063 mole) of IV was added 5.7 g. (0.095 mole) of acetic acid, 50 ml. of acetic anhydride and 0.2 g. of concentrated sulfuric acid. This solution was heated on a steam-bath for six hours and then poured into water and extracted into pentane. The pentane extracts were washed with water and sodium carbonate solution, dried, evaporated and the residue fractionally distilled. The recovered IV, 7.35 g. (83.5%), b.p. 94° (40 mm.), was the only product isolated.

Behavior of Methyl *trans*-3-Acetoxycyclohexanecarboxylate (*trans*-III) in the Acetic Anhydride Rearrangement Conditions.—To 4.25 g. (0.021 mole) of *trans*-III was added 30 ml. of acetic anhydride, 0.2 g. of concentrated sulfuric acid and 0.4 g. (0.022 mole) of water. This solution was treated in a manner identical with the foregoing experiment, and on fractional distillation of the crude product, 3.3 g. (77%) of *trans*-III was recovered. The infrared spectrum of the recovered ester was superimposable on that of authentic *trans*-III.

Behavior of *trans*-3-Methoxycyclohexanecarboxylic Acid (*trans*-I) in the Acetic Anhydride Rearrangement Conditions.—To 10 g. (0.063 mole) of *trans*-I was added 50 ml. of acetic anhydride and 0.2 g. of concentrated sulfuric acid and this solution was heated on a steam-bath for six hours. At the end of this time the solution was poured into water and extracted with pentane. The extracts were dried over magnesium sulfate, evaporated and the remaining oil fractionally distilled. The first fraction was 3-cyclohexene-1-carboxylic acid, b.p. 113–116° (5 mm.), m.p. 17–18.8° (lit.[30] m.p. 17°). The second fraction, believed to be the anhydride of the first, boiled at 128–132° (3 mm.) and had a saponification equivalent of 115 (calcd. 117).

Rearrangement of *cis*-4-Methoxycyclohexanecarboxylic Acid (*cis*-VII) in Acetic Anhydride.—*cis*-VII, 10 g. (0.063 mole), was treated in the same manner as *cis*-I and also yielded two fractions. The first, IV, weighed 3.2 g. (37%), b.p. 93° (40 mm.). The second was a mixture of *trans*-VI and *trans*-III, 4.7 g. (37%), b.p. 115° (5 mm.). This mixture was refractionated and an infrared spectrum obtained.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 60.3; H, 8.1.

Hydrolysis of the Mixed *trans*-VI and *trans*-III from the Rearrangement of *cis*-V.—Two grams (0.01 mole) of mixed *trans*-VI and *trans*-III was hydrolyzed under conditions identical to those employed for fraction B. Two crystallizations of the oily material obtained from the continuous extractions yielded 0.6 g. of *trans*-4-hydroxycyclohexanecarboxylic acid, m.p. 146.5–147.5° (lit.[29] m.p. 148°). A mixed melting point with authentic *trans*-4-hydroxycyclohexanecarboxylic acid showed no depression.

Isolation of Mixture of *trans*-III and *trans*-VI Enriched in *trans*-III from the Acetic Anhydride Rearrangement of *cis*-VII.—A sample of the mixed *trans*-III and *trans*-VI, 4.0 g., from the rearrangement of *cis*-VII, was recrystallized once from *n*-pentane at −70°. The supernatant solution was decanted and fractionally distilled to give a sample of the mixture enriched in *trans*-III, 0.8 g.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 59.9; H, 8.1.

Preparation of Sulfuric Acid-d_2.—From fuming sulfuric acid containing 30% sulfur trioxide was distilled 9.084 g. (0.1135 mole) of sulfur trioxide. This sulfur trioxide was then distilled into 2.26 g. (0.113 mole) of deuterium oxide through a simple distilling tube containing joints only for distilling flask, receiving flask and a vent leading to a calcium chloride drying tube. The distilling flask was heated in a water-bath while the very vigorous reaction of sulfur trioxide with heavy water was kept under control by keeping the receiving flask in cold water. A yield of 10.56 g. (93%) of product was obtained and shown by titration to be 97% deuteriosulfuric acid.

Preparation of *cis*-3-Methoxycyclohexanecarboxylic Acid-*d*.—To 20 g. (0.126 mole) of powdered *cis*-I in a dry separatory funnel was added 10.65 g. (0.53 mole) of deuterium oxide and the mixture was occasionally shaken over a 0.5-hour period. Dry toluene, 50 ml., was then added and the mixture shaken over another half-hour period. Then the two layers were separated and the toluene solution was placed in a distilling flask. The toluene and residual heavy water were distilled off at atmospheric pressure and the deuterated *cis*-I was distilled at 135–140° (3 mm.) yielding 18.9 g. (94%), m.p. 50.6–51.4°. Infrared analysis of deuterio *cis*-I showed the changes expected by deuteration.

Rearrangement of Deutero *cis*-I in Acetic Anhydride.—A solution of 9 g. (0.056 mole) of deuterio *cis*-I in 50 ml. of acetic anhydride, free of acetic acid, was prepared and 0.2 g. of 97% sulfuric acid-d_2 was added. The solution was kept on a steam-bath for 5.5 hours, then poured into 350 ml. of water and extracted with pentane. The extracts were washed with sodium carbonate solution, dried over magnesium sulfate, evaporated and the products fractionally distilled to give 3.2 g. (40%) of methyl 3-cyclohexene-1-carboxylate (IV), b.p. 92–93° (40 mm.). The infrared spectrum of IV was compared to the spectrum of an authentic sample and was shown to contain no deuterium. Also obtained was a mixture of *trans*-III and *trans*-VI, 4.5 g. (40%), b.p. 113–114° (5 mm.), from which pure *trans*-VI was isolated by crystallization from *n*-pentane, m.p. 48.0–48.5°. The infrared spectra of this *trans*-VI were compared with spectra of authentic samples at various concentrations and showed no deuterium content.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA]

The Solvolysis of the Methyl 3-Tosyloxycyclohexanecarboxylates

BY DONALD S. NOYCE AND H. I. WEINGARTEN[1]

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The acetolysis and formolysis of methyl *cis*-3-tosyloxycyclohexanecarboxylate (I) and methyl *trans*-3-tosyloxycyclohexanecarboxylate (II) have been shown to be normal. No rate acceleration is observed. The product formed is a mixture of olefins and the inverted acetate in each case.

Results

In connection with other studies concerning the rearrangement of disubstituted cyclohexane derivatives,[2,3] it became of importance to examine the solvolysis of the isomeric pair, methyl *cis*-3-tosyloxy cyclohexanecarboxylate (I) and methyl *trans*-3-tosyloxycyclohexanecarboxylate (II). Of importance was the question: would transannular participation manifest itself during these solvolyses, either structurally or kinetically? It is the purpose of the present report to answer this question.

The well known *cis*-3-hydroxycyclohexanecarboxylic acid was converted to its methyl ester and treated with *p*-toluenesulfonyl chloride to give I; and the *trans*-hydroxy acid similarly was converted to II. It also was found possible to separate by fractional crystallization the mixed isomers derived from methyl 3-hydroxycyclohexanecarboxylate.

The rate constants obtained for the solvolysis of I and II in acetic acid and formic acid are summarized in Table I, together with pertinent data for comparison from the work of Winstein and coworkers.[4,5]

TABLE I

RATES OF SOLVOLYSIS OF SUBSTITUTED CYCLOHEXYL TOSYLATES

Tosylate	$k_1 \times 10^5$ sec.$^{-1}$ Acetic acid, 75°	Formic acid, 40°	Rel. rate in acetic acid
Cyclohexyl	4.27[5]	28[a]	1.00
trans-4-*t*-Butylcyclohexyl (VII)	3.75[4]	23[a]	0.88
cis-4-*t*-Butylcyclohexyl (VIII)	10.2[4]	87[a]	2.39
cis-3-Carbomethoxycyclohexyl (I)	0.331 ± 0.008	0.62 ± 0.06	0.078
trans-3-Carbomethoxycyclohexyl(II)	1.59 ± 0.04	2.6 ± 0.2	0.37

[a] Interpolated from data at other temperatures, ref. 4.

Under the conditions of the solvolyses both elimination and substitution take place. From I there was isolated methyl *trans*-3-acetoxycyclohexanecarboxylate (III), 25%, and a mixture of methyl 3-cyclohexene-1-carboxylate (IV) and methyl 2-cyclohexene-1-carboxylate (V). III is the expected, normal, product of solvolytic substitution. The mixture of unsaturated esters, identified by infrared analysis, consisted largely of methyl 3-cyclohexene-1-carboxylate but contained 5–10% methyl 2-cyclohexene-1-carboxylate.

The products resulting from the acetolysis of II are similar. There was obtained methyl *trans*-3-acetoxycyclohexanecarboxylate (VI) in 20% yield and a mixture of IV and V, in similar ratio to that obtained above.

Discussion

The clean inversion accompanying the solvolysis of both I and II shows that the reactions are normal, and establishes the lack of transannular participation. Were such participation to occur, both I and II would be expected to give III.

The relative rate of solvolysis is also normal for each isomer in acetic acid. From the σ^*-value of Taft[6] for the carbomethoxyl group and from the recent correlation of Streitwieser[7] one may calculate the relative rate for I. In I both groups are equatorial, and hence the rate should be that of *trans*-4-*t*-butylcyclohexyl tosylate (VII), modified by the appropriate contribution for the polar influence of the carbomethoxy group. The calculated rate ratio of VII:I is 11:1. The observed ratio is 11:1. For II, the predominant conformation is probably that with the tosylate group in the axial position. This conclusion is reached by the following reasoning. The *A* value for the tosylate group is given by Winstein as 1.7.[4] The *A* value for the ester grouping may be estimated as being between that of ethyl and isopropyl, since there is branching adjacent to the ring. Using a value of 2.5, one concludes that the rate of reaction for II should show the same acceleration relative to I, that VIII shows relative to VII. The observed ratio, 4.5:1, is somewhat higher. However, there is an additional factor which requires consideration. The developing dipole associated with the solvolytic transition state is developing in a plane perpendicular to the dipole associated with the carbomethoxy group in II. In I, however, the developing charge separation will be developed largely in one plane at an angle of about 120°. This will make the polar retardation somewhat more effective for I than for II. Hence the rate ratio would be expected to be slightly larger for II to I, than the ratio of VIII to VII. The polar opposition to "ionization" is very similar to the polar assistance to ionization of *cis*- and *trans*-3-bromocyclohexanecarboxylic acids.[8] The acid dissociation constants of the acids show differences also due

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to the direction of the bond dipole associated with the carbon–bromine bond.

The polar effect of the carbomethoxy group is more effective in retarding the rate. The rate ratio VII:I in formic acid is 40:1. This effect would be anticipated on the basis of the greater ionizing power of formic acid as solvent. The rate ratio in formic acid, 4.3, is likewise similar. The evidence clearly establishes that the solvolysis of I and II is normal.

The olefins fraction formed during the solvolysis also gives no evidence of transannular interaction. Exclusive formation of methyl 3-cyclohexene-1-carboxylate was observed in the elimination reaction accompanying the rearrangement of 3-methoxycyclohexanecarboxylic acid chloride. Were transannular interaction important, similar results would be expected. The difference in the relative rates of formation of the two olefins IV and V reflects the inductive influence of the ester grouping in stabilizing the hydrogen in the two position.

Experimental[9]

Methyl *cis*-3-Tosyloxycyclohexanecarboxylate (I).—An authentic 1-g. sample of *cis*-3-hydroxycyclohexanecarboxylic acid,[2,3] m.p. 131.6–132.0°, was converted to its methyl ester with diazomethane in ether. The ether solution was dried over magnesium sulfate, evaporated, and 1.3 g. of *p*-toluenesulfonyl chloride and 10 ml. of pyridine were added. The mixture was allowed to stand overnight. It was then poured into water, acidified and extracted with ether; the ether extract was washed with dilute sulfuric acid, sodium carbonate solution and dried. Crystallization from pentane of the residue obtained on evaporating the ether afforded 1.0 g. of methyl *cis*-3-tosyloxycyclohexanecarboxylate (I), m.p. 86.2–86.5°.

Anal. Calcd. for $C_{15}H_{20}O_5S$: C, 57.7; H, 6.5; S, 10.3. Found: C, 57.8; H, 6.7; S, 10.1.

Methyl *trans*-3-Tosyloxycyclohexanecarboxylate (II).—*trans*-3-Hydroxycyclohexanecarboxylic acid,[2,3] m.p. 118.8–119.6°, 0.1 g., was converted to authentic II as in the above experiment. The m.p. of the II thus obtained is 90.0–90.5°.

Anal. Calcd. for $C_{15}H_{20}O_5S$: C, 57.7; H, 6.5; S, 10.3. Found: C, 57.7; H, 6.5; S, 10.0.

Preparation and Isolation of the Methyl *cis*- and *trans*-3-Tosyloxycyclohexanecarboxylates (I and II).—A 34-g. (0.22 mole) sample of methyl 3-hydroxycyclohexanecarboxylate (mixed isomers) was dissolved in 100 ml. of pyridine and 45 g. (0.24 mole) of *p*-toluenesulfonyl chloride was added and allowed to stand overnight. The solution was then poured into water and extracted with 3:1 ether–pentane. The extracts were washed with water, dilute sulfuric acid and sodium carbonate solution, then dried over magnesium sulfate. The dry extracts, about 400 ml., were concentrated to three-fourths their volume and 700 ml. of *n*-pentane was added, making the ether–pentane ratio approximately 1:4. By a process of fractional crystallization and mechanical separation of the differently appearing crystals, 12 g. (18%) of I (polyhedral prisms), m.p. 85.5–86.3°, and 31 g. (47%) of crude I, m.p. 85–86°, were obtained. A dimorph of I was isolated first (m.p. 63°, long needles from *n*-pentane) but no longer appeared after the isolation of the higher melting form.

Also obtained was 13 g. (19%) of II (soft light plates), m.p. 89–90.5°.

Kinetic Procedure.—Acetic anhydride, 0.1%, was added to purified acetic acid, which analyzed for water content 0.01% by Karl Fischer titration. It was used in this form as solvent.

Formic acid was treated with boric anhydride and fractionated. It titrated 99.95% formic acid.

The volumetric equipment was calibrated, and the progress of the reactions was followed by potentiometric titration, with sodium acetate in acetic acid using a procedure similar to that of Winstein and Marshall.[10] For the acetolyses of I and II, the course of the reaction was followed to 80% completion.

The formolysis experiments were carried out on a much more limited basis and the rate constants are likely to be precise to only 10%.

Product Analysis of I Acetolysis.—I, 10 g. (0.032 mole), was dissolved in 100 ml. of acetic acid and 3.2 g. (0.032 mole) of potassium acetate was added. The flask, equipped with a spiral condenser capped by a calcium chloride tube, was placed on a steam-bath for 48 hours (about three half-lives). The solution was then poured into water, neutralized with solid sodium carbonate and extracted two times with pentane. The extracts were dried, evaporated and the products separated by fractional distillation. Fraction 1, weighing 1.9 g. (40%), proved on infrared analysis to be a mixture of methyl 2-cyclohexene-1-carboxylate and methyl 3-cyclohexene-1-carboxylate, b.p. 92–93° (40 mm.), $n^{25}D$ 1.4598. Fraction 2, 1.6 g. (25%), proved on infrared analysis to be methyl *trans*-3-acetoxycyclohexanecarboxylate, b.p. 110–112° (5 mm.), $n^{25}D$ 1.4521.

Product Analysis of II Acetolysis.—II, 10 g. (0.032 mole), was solvolyzed as in the above experiment for 12 hours on a steam-bath (about three half-lives) and also yielded two fractions on fractional distillation. Fraction one, b.p. 93–94° (40 mm.), weighed 1.3 g. (29%) and on infrared analysis proved to be a mixture of methyl 2-cyclohexene-1-carboxylate and methyl 3-cyclohexene-1-carboxylate, $n^{25}D$ 1.4589. Fraction two, weighing 1.3 g. (20%), was shown to be methyl *cis*-3-acetoxycyclohexanecarboxylate, b.p. 115–117° (5 mm.), by infrared spectrum.

Fraction two was hydrolyzed in the usual way and yielded 0.3 g. of *cis*-3-hydroxycyclohexanecarboxylic acid, m.p. 131–131.9° (no depression on admixture with an authentic sample).

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(9) Melting points are corrected; boiling points are uncorrected. Distillations were carried out with an 18" modified Podbielniak column. Infrared spectra were recorded using a Baird infrared spectrometer in chloroform solutions at a concentration of 60 mg./ml. in a 0.1-mm. NaCl cell. Analyses are by the Microanalytical Laboratory of the University of California.

(10) S. Winstein and H. Marshall, THIS JOURNAL, 74, 1120 (1952).

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[Contribution from the Department of Chemistry, University of California, Los Angeles]

Neighboring Carbon and Hydrogen. XXVII. Ar_1-5 Aryl Participation and Tetralin Formation in Solvolysis[1,2]

By Richard Heck and S. Winstein

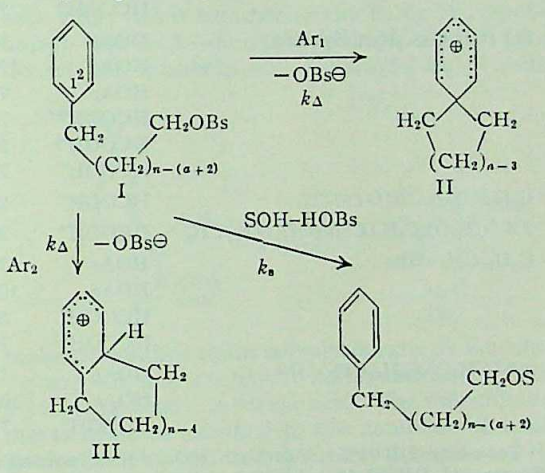
Received November 10, 1956

It is possible, by suitable choice of structure and solvent, to arrange for participation of δ-aryl groups in solvolysis of 4-aryl-1-butyl *p*-bromobenzenesulfonates. When the aryl group is activated by one *p*- or two *o,p*-methoxyl groups, the participation is Ar_1-5 in type; a spiro-carbonium ion is produced by anchimerically assisted ionization of the 4-aryl-1-butyl bromobenzenesulfonate. Rearrangement of the spiro-carbonium ion intermediate and proton loss give rise to a tetralin product. On the assumption that k_s, the rate constant of anchimerically unassisted solvolysis, is associated with formation of ester, and that k_Δ, the rate constant of anchimerically assisted ionization, is associated with formation of tetralin, it is possible to dissect the acetolysis and formolysis rate constants for 4-phenyl-1-butyl bromobenzenesulfonate into the appropriate k_s and k_Δ values. Assuming k_s is insensitive to methoxyl substitution, one can assign k_s and k_Δ values in solvolysis of the substituted 4-aryl-1-butyl bromobenzenesulfonates. These values of k_s and k_Δ predict product compositions within experimental error, assuming k_s and k_Δ are associated with formation of ester and tetralin, respectively. As regards variation of k_Δ in Ar_1-*n* participation with the size of the ring being formed in the intermediate spiro-carbonium ion, the observed rate sequence is $3 \gg 4 \ll 5 \gg 6$. Both the 3:5 and 5:6 ratios are of the order of 10^2. Of the *n* values, 4, 5 and 6, only in the case of 5 were substantial values of k_Δ and k_Δ/k_s observed.

Many cases of ionization of a β-arylethyl *p*-bromobenzenesulfonate, with the degree of methyl or phenyl substitution sufficiently large[3] on C_β and not too large[3] on C_α, are anchimerically[4] assisted,[3,5] leading to a bridged intermediate[6,7] or a rearranged carbonium ion. It is convenient to employ the symbol k_Δ for the rate constant of such anchimerically assisted ionization. Still other cases of ionization, rate constant k_s, are anchimerically unassisted. Such ionization may lead to an unrearranged carbonium ion intermediate which may rearrange subsequently. With a properly substituted structure, which is not too favorable[8] for one of the classical open forms of the carbonium ion, the bridged form of the carbonium ion is preferred.

It is convenient to adopt a notation[2] in which participation of a β-phenyl group is symbolized Ar_1-3. The general notation is Ar_a-*n*, where Ar denotes aryl and the subscript *a* refers to the position in the participating aryl group involved in the creation of the ring in the transition state for anchimerically assisted ionization. The size of the ring being made is indicated by the number *n*.

As has already been reported in preliminary communications,[2] it is possible, by suitable choice of structure and solvent, to arrange for participation of aryl groups more distant than β in solvolysis of arylalkyl benzenesulfonates I. Examples of such participation are Ar_1-5 and Ar_2-6, illustrated schematically by the conversion of I to II ($n = 5$) or III ($n = 6$), respectively.



In seeking information on Ar-4, 5 and 6 participation, a large number of arylsulfonates has been studied. Some of the results bearing principally on the Ar_1-variety are reported in the present paper, while Ar_2 is treated in the following one.

In searching for anchimeric effects of aryl groups, the procedure employed was first to explore the rates of solvolysis of various phenylalkyl bromobenzenesulfonates and the corresponding methoxyphenylalkyl esters. We expected[9] anchimerically unassisted solvolysis, with rate constant k_s, to be quite insensitive to methoxyl substitution, but anchimerically assisted solvolysis, with rate constant k_Δ, quite sensitive to suitably oriented methoxyl groups. On this basis, an anchimerically assisted process was not contributing seriously to the solvolysis of a methoxyphenylalkyl bromobenzenesulfonate unless the introduction of the methoxyl group was accompanied by an increase in solvolysis rate. Using kinetics as a guide, cases were selected for examination of the products of solvolysis for further elucidation of the nature of the solvolysis in question.

Arylalkyl Systems.—The various arylsulfonates employed in this work appear in Table I, which

(1) (a) Paper XXV, S. Winstein and E. T. Stafford, This Journal, **79**, 505 (1957); paper XXVI, S. Winstein and R. Baird, *ibid.*, **79**, 756 (1957); (b) Research supported by the Office of Naval Research.

(2) Most of the material of this paper has been reported in summary: (a) Paper by S. Winstein at the Symposium on Dynamic Stereochemistry of the Chemical Society, Manchester, England, March 31, 1954 (see *Chemistry & Industry*, 562 (1954); (b) S. Winstein, R. Heck, S. Lapporte and R. Baird, *Experientia*, **12**, 138 (1956).

(3) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse, This Journal, **74**, 1113 (1952).

(4) S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, *ibid.*, **75**, 147 (1953).

(5) E.g., S. Winstein and K. C. Schreiber, *ibid.*, **74**, 2171 (1952).

(6) D. J. Cram, *ibid.*, **71**, 3863 (1949); **74**, 2129 (1952).

(7) S. Winstein, M. Brown, K. C. Schreiber and A. H. Schlesinger, *ibid.*, **74**, 1140 (1952).

(8) (a) D. J. Cram and J. D. Knight, *ibid.*, **74**, 5839 (1952); (b) F. A. Abd Elhafez and D. J. Cram, *ibid.*, **75**, 339 (1953); (c) C. J. Collins and W. A. Bonner, *ibid.*, **77**, 92 (1955); (d) W. A. Bonner and C. J. Collins, *ibid.*, **77**, 99 (1955).

(9) S. Winstein and R. Heck, *ibid.*, **78**, 4801 (1956).

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TABLE I

SUMMARY OF SOLVOLYSIS RATE CONSTANTS

Compound	Solvent	Temp., °C.	Concn. × 10², *M*	*k* (sec.⁻¹)	Δ*H*‡, kcal./mole	Δ*S*‡, e.u.
$C_6H_5(CH_2)_3OBs$	HOAc	75.00	3.18	$(1.07 \pm 0.00) \times 10^{-6}$	24.0	−17.5
	HOAc	100.05	2.71	$(1.17 \pm .01) \times 10^{-5}$		
	HCOOH[a]	50.00	2.75	$(1.54 \pm .08) \times 10^{-6}$		
	HCOOH[a]	75.00	2.75	$(1.99 \pm .03) \times 10^{-5}$	22.2	−16.6
p-$CH_3OC_6H_4(CH_2)_3OBs$	HOAc	75.00	3.04	$(1.15 \pm .03) \times 10^{-6}$		
2,4-$(CH_3O)_2C_6H_3(CH_2)_3OBs$	HOAc	75.00	2.57	3.95×10^{-6}[b]		
$C_6H_5(CH_2)_4OBs$	HOAc	75.00	3.09	$(1.45 \pm 0.03) \times 10^{-6}$		
	HOAc	75.00	3.02	$(1.49 \pm .05) \times 10^{-6}$	23.9	−16.8
	HOAc	100.05	3.68	$(1.62 \pm .01) \times 10^{-5}$		
	HCOOH	75.00	2.70	$(3.35 \pm .01) \times 10^{-5}$		
	HCOOH[a]	25.00		1.41×10^{-7}[d]		
	HCOOH[a]	75.00	2.68	$(3.43 \pm 0.03) \times 10^{-5}$	22.0	−16.2
	HCOOH[a]	100.20	2.68	$(3.13 \pm .07) \times 10^{-4}$		
p-$CH_3OC_6H_4(CH_2)_4OBs$	HOAc	75.00	2.66	$(1.90 \pm .01) \times 10^{-6}$	24.4	−15.0
	HOAc	100.05	2.15	$(2.16 \pm .01) \times 10^{-5}$		
	HCOOH[a]	50.00	2.70	$(5.03 \pm .18) \times 10^{-6}$		
	HCOOH[a]	75.00	2.70	$(6.08 \pm .11) \times 10^{-5}$	21.6	−16.1
2,4-$(CH_3O)_2C_6H_3(CH_2)_4OBs$	HOAc	75.00	2.66	$(6.26 \pm .06) \times 10^{-6}$	25.0	−10.7
	HOAc	100.00	1.94	$(7.56 \pm .05) \times 10^{-5}$		
	HOAc[c]	75.00	2.89	$(7.2 \pm .1) \times 10^{-6}$		
	HCOOH[a]	25.00		1.27×10^{-6}[d]		
	HCOOH[a]	50.00	2.24	$(2.58 \pm 0.02) \times 10^{-5}$		
	HCOOH[a]	75.00	2.24	$(3.40 \pm .06) \times 10^{-4}$	22.4	−10.4
$C_6H_5(CH_2)_3CH(OTs)CH_3$	HCOOH[a]	25.00	3.13	$(5.43 \pm .10) \times 10^{-5}$		
2,4-$(CH_3O)_2C_6H_3(CH_2)_3CH(OTs)CH_3$	HCOOH[a]	25.00	3.63	$(1.36 \pm .13) \times 10^{-4}$		
$C_6H_5(CH_2)_5OBs$	HOAc	75.00	2.77	$(1.54 \pm .03) \times 10^{-6}$	23.8	−17.1
	HOAc	100.00	2.64	$(1.65 \pm .01) \times 10^{-5}$		
	HCOOH[a]	50.00	2.70	$(2.90 \pm .08) \times 10^{-6}$		
	HCOOH[a]	75.00	2.70	$(3.39 \pm .02) \times 10^{-5}$	21.3	−18.2
2,4-$(CH_3O)_2C_6H_3(CH_2)_5OBs$	HOAc	75.00	2.40	$(1.61 \pm .03) \times 10^{-6}$	23.9	−16.7
	HOAc	100.10	2.40	$(1.76 \pm .01) \times 10^{-5}$		
	HCOOH[a]	75.00	2.69	$(3.63 \pm .11) \times 10^{-5}$		

[a] Formic acid, 0.03151 *M* in NaOCHO. [b] Extrapolated initial constant from a plot of ln [(ROBs)₀/(ROBs)] *versus* time. [c] Acetic acid, 0.0300 *M* in $LiClO_4$. [d] Extrapolated from data at another temperature.

summarizes also the kinetic data obtained with them.

Of the required primary alcohols, 3-phenyl-1-propanol was available commercially. 3-*p*-Anisyl-1-propanol and 3-(2,4-dimethoxyphenyl)-1-propanol were prepared from the corresponding cinnamic acids by reduction with lithium aluminum hydride, the cinnamic acids being obtained from anisaldehyde[10] and 2,4-dimethoxybenzaldehyde[10] by the Knoevenagel reaction. The several butyl alcohols, 4-phenyl-, 4-*p*-anisyl-, and 4-(2,4-dimethoxyphenyl)-1-butanols were all prepared by Friedel–Crafts succinoylation of the proper benzene derivatives, followed by Clemmensen and lithium aluminum hydride reduction.

Of the two primary pentanols which were studied, the 5-phenyl-1-pentanol was prepared from γ-phenylpropylmagnesium chloride and ethylene oxide, while the 5-(2,4-dimethoxyphenyl)-1-pentanol was prepared from the corresponding acid by reduction with lithium aluminum hydride. The 5-(2,4-dimethoxyphenyl)-pentanoic acid was prepared by Clemmensen reduction of γ-(2,4-dimethoxybenzoyl)-butyric acid, prepared by a Friedel–Crafts reaction between *m*-dimethoxybenzene and glutaric anhydride.

One of the two secondary alcohols which were studied, 1-phenyl-4-pentanol, was prepared from γ-phenylpropylmagnesium chloride and acetaldehyde.[11] The 1-(2,4-dimethoxyphenyl)-4-pentanol was prepared from the corresponding ketone by reduction with lithium aluminum hydride. This ketone was obtained from the reaction of 4-(2,4-dimethoxyphenyl)-butyric acid with methyllithium.

Kinetic Search for Ar_1.—As summarized in Table I, all the arylsulfonates displayed good first-order kinetics of acetolysis and formolysis, except 3-(2,4-dimethoxyphenyl)-1-propyl *p*-bromobenzenesulfonate. This substance displayed a downward drifting first-order rate constant in acetolysis, an extrapolated initial value being given in Table I.

In the kinetic search for neighboring aryl participation, the ω-phenylalkyl arylsulfonates are reference compounds, and the relative rates of acetolysis and formolysis of these reference compounds are summarized in Table II. For this comparison, rate

(10) K. H. Slotta and H. Heller, *Ber.*, **63**, 3029 (1930).

(11) R. O. Roblin, Jr., D. Davidson and M. T. Bogert, THIS JOURNAL, **57**, 151 (1935).

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TABLE II

RELATIVE SOLVOLYSIS RATES OF PHENYLALKYL *p*-BROMOBENZENESULFONATES

Compound	AcOH, 75.00° Rel. rate	AcOH, 75.00° $\Delta S^{\ddagger}$, e.u.	HCOOH, 75.00° Rel. rate	HCOOH, 75.00° $\Delta S^{\ddagger}$, e.u.
$C_6H_5(CH_2)_2OBs$	0.79	−15.2	5.08	− 8.6
$C_6H_5(CH_2)_3OBs$	1.00	−17.5	1.00	−16.6
$C_6H_5(CH_2)_4OBs$	1.36	−16.8	1.72	−16.2
$C_6H_5(CH_2)_5OBs$	1.44	−17.1	1.70	−18.2
$CH_3(CH_2)_3OBs$	1.39[a]	−17.0	1.79[a]	−19.9
$CH_3(CH_2)_2OBs$	1.53[b]			

[a] Data of R. Glick. [b] Data of P. Magee.

ment is to be ascribed to participation of the *ortho* methoxyl group with formation of the intermediate IV. Such participation is common with ω-*o*-anisylalkyl arylsulfonates,[12,13] and the 3-*o*-anisyl-1-propyl *p*-bromobenzenesulfonate displays even a slightly higher rate constant[12] than the one observed with the 3-(2,4-dimethoxyphenyl)-1-propyl ester. Thus, the comparison in Table III shows that no appreciable incursion of Ar_1-4 (or Ar_2-5) aryl participation is indicated for the methoxyphenylpropyl esters examined.

With the 4-phenyl-1-butyl *p*-bromobenzenesul-

TABLE III

RELATIVE SOLVOLYSIS RATES OF SUBSTITUTED γ-PHENYLPROPYL *p*-BROMOBENZENESULFONATES AT 75.00°

	$C_6H_5(CH_2)_3OBs$	*p*-$CH_3OC_6H_4(CH_2)_3OBs$	2,4-$(CH_3O)_2C_6H_3(CH_2)_3OBs$	*m*-$CH_3OC_6H_4(CH_2)_3OBs$	3,5-$(CH_3O)_2C_6H_3(CH_2)_3OBs$
AcOH	1.00	1.07[a]	3.69	1.04[b]	1.03[b]
HCOOH	1.00				1.08[b]

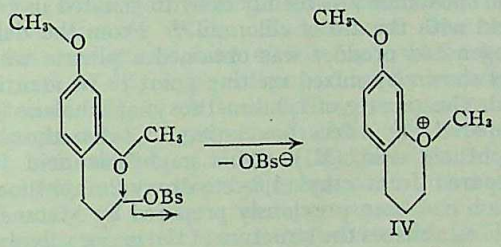
[a] k_Δ is below 8×10^{-8} sec.$^{-1}$. [b] From data reported in the following article.

constants for 3-phenyl-1-propyl *p*-bromobenzenesulfonate are taken as unity. Using the entropy of activation as a guide to mechanism,[9] the indications are that substantially the whole of the solvolysis is anchimerically unassisted in acetolysis of the 3-, 4- and 5-phenyl-1-alkyl esters. In formic acid, the ω-phenyl-1-alkyl esters except 2-phenylethyl again have the low $\Delta S^{\ddagger}$ characteristic of anchimerically unassisted solvolysis. The relatively high $\Delta S^{\ddagger}$ for the phenylethyl ester was ascribed previously[9] to the importance of anchimerically assisted ionization in formic acid.

The relative rates themselves support the conclusions derived on the basis of the $\Delta S^{\ddagger}$ values in Table II. The relatively smooth small increase in acetolysis rate, by less than a factor of two, in the series from phenylethyl to phenylpentyl is in line with the decreasing rate-retarding polar (and steric) effect of the phenyl group. The rate constants for the 4-phenyl-1-butyl and 5-phenyl-1-pentyl esters are essentially equal to the value for the *n*-butyl ester, giving no indication of substantial contribution from anchimerically assisted solvolysis. The situation is similar in formic acid, except that the rate-retarding effect of the phenyl group in phenylethyl *p*-bromobenzenesulfonate is more than compensated by the incursion of anchimerically assisted ionization.[4,9]

Methoxy substitution in the phenyl group of the ω-phenylalkyl esters will, of course, tend to favor aryl participation in solvolysis. In scrutinizing the effect of such substitution on solvolysis rate, it is convenient to consider first the series of 3-phenyl-1-propyl derivatives. In Table III are summarized the relative solvolysis rates of 3-phenyl-1-propyl *p*-bromobenzenesulfonate, together with those of the 4- and 2,4-methoxy derivatives, substituted so as to favor Ar_1-4 aryl participation. Included also in the comparison are the 3- and 3,5-methoxy derivatives, reported in detail in the next article. Examination of Table III reveals that all the 3-aryl-1-propyl *p*-bromobenzenesulfonates display nearly identical solvolysis rates, except the 2,4-dimethoxy derivative which displays a higher initial acetolysis rate constant than the others. However, there is no reason to ascribe the observed rate enhancement to Ar_1-4 participation. Instead, this

fonates, substantial rate enhancements are observed when methoxyl groups are substituted in the benzene ring. As is summarized in Table IV, the 4-*p*-anisyl- and 4-(2,4-dimethoxyphenyl)-1-butyl esters exceed the unsubstituted 4-phenyl-1-butyl *p*-bro-



IV

mobenzenesulfonate in solvolysis rate by factors of 1.3 and 4.3, respectively, in acetic acid and 1.77 and 9.91, respectively, in formic acid. The rate enhancements must be ascribed to the incursion of anchimerically assisted solvolysis in the case of the methoxyl-substituted 4-phenyl-1-butyl esters. Otherwise, methoxyl substitution would be expected to be without appreciable effect on solvolysis rate, just as in the case of the 3-phenyl-1-propyl esters.

Additional support for the idea that Ar_1-5 participation grows more important with methoxyl substitution in 4-phenyl-1-butyl bromobenzenesulfonate is provided by the $\Delta S^{\ddagger}$ values recorded in Table I. These change from the level of *ca.* −17 e.u. associated with anchimerically unassisted solvolysis (rate constant k_s) to a level of *ca.* −10 e.u. for 4-(2,4-dimethoxyphenyl)-1-butyl bromobenzenesulfonate. The latter substance, with the most enhanced formolysis rate, must undergo very largely anchimerically assisted solvolysis, so $\Delta S^{\ddagger}$ for Ar_1-5-assisted ionization in formic acid must be close to −10 e.u.

Products.—Further insight into the nature of the solvolytic reactions of the 4-aryl-1-butyl bromobenzenesulfonates is provided by the results of an examination of the derived products. In this examination, the crude product from formolysis or acetolysis was reduced with lithium aluminum hydride to reduce ester to alcohol. Then hydro-

(12) R. Heck, unpublished work.

(13) See, *e.g.*, S. Winstein, *Experientia Supplementum*, II, 137 (1955).

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TABLE IV

ANALYSIS OF SOLVOLYSIS RATES OF SEVERAL 4-ARYLBUTYL *p*-BROMOBENZENESULFONATES AT 75.00°

Compound	Relative rates AcOH	Relative rates HCOOH	Assignments of k_Δ and k_s AcOH 10^5k_s	AcOH 10^5k_Δ	HCOOH 10^5k_s	HCOOH 10^5k_Δ
$CH_3(CH_2)_3OBs$	1.03	1.04	1.49[a]		3.57[a]	
$C_6H_5(CH_2)_4OBs$	1.00	1.00	1.37[b]	(0.08)	2.78	(0.65)
p-$CH_3OC_6H_4(CH_2)_4OBs$	1.31	1.77	1.37	0.53	2.78	3.30
2,4-$(CH_3O)_2C_6H_3(CH_2)_4OBs$	4.32	9.91	1.37	4.89	2.78	31.22

[a] Data of R. Glick. [b] Assuming products are the same at 75° as at 100°. At 100°, k_s is 1.53×10^{-5} and k_Δ is 9×10^{-7} sec.$^{-1}$.

carbon and alcoholic products were separated by chromatography.

From formolysis of 4-(2,4-dimethoxyphenyl)-1-butyl bromobenzenesulfonate (V) was obtained an 8% yield of an alcohol which was converted into *p*-nitrobenzoate in *ca.* 70% yield. This was shown by mixed melting point to be the *p*-nitrobenzoate of 4-(2,4-dimethoxyphenyl)-1-butanol (VI). A second product, obtained in 76% yield, was a colorless liquid which later crystallized. It was inert to potassium permanganate in acetone, and it analyzed correctly for a tetralin. It yielded a monobromide on treatment with bromine in carbon tetrachloride. The substance was readily dehydrogenated in good yield with the aid of chloranil.[14] From the dehydrogenated product was obtained a picrate which was shown by mixed melting point to be identical with the picrate of 1,3-dimethoxynaphthalene (X) prepared by decarboxylating 1,3-dimethoxy-2-naphthoic acid (XI). This naphthoic acid was prepared from ethyl 1,3-dihydroxy-2-naphthoate, which had been previously prepared by Metzner.[15] This establishes the structure of the major solvolysis product as 5,7-dimethoxytetralin (IX).

Except for the proportions of tetralin and alcohol products, 4-*p*-anisyl-1-butyl bromobenzenesulfonate behaved analogously to the 4-(2,4-dimethoxyphenyl)-1-butyl derivative in formolysis. From the 4-*p*-anisyl-1-butyl ester was obtained a 43% yield of alcohol and a 51% yield of a material, inert to potassium permanganate in acetone, with physical properties in agreement with those reported for 7-methoxytetralin.[16,17]

The solvolysis of 4-phenyl-1-butyl *p*-bromobenzenesulfonate was also examined in both formic and acetic acids. In the former solvent, 4-phenyl-1-butyl bromobenzenesulfonate gave rise to a 16.7% yield of tetralin, identified by boiling point, refractive index, infrared spectrum and by its conversion in high yield to naphthalene by a dehydrogenation with tetrachloro-1,2-benzoquinone.[18] From the formolysis there was obtained also a 72% yield of 4-phenyl-1-butanol. In acetic acid, 4-phenyl-1-butyl bromobenzenesulfonate gave rise to an even smaller proportion of tetralin than in formic acid, the yield of tetralin being 4.9%.

For the solvolyses in which the products were examined, summarized in Table V, sufficient controls were run to establish that tetralin did not arise from the formate or acetate ester subsequent to its formation. Thus, 4-(2,4-dimethoxyphenyl)-1-butanol survived essentially quantitatively under the conditions for the formolysis. With 4-phenyl-1-butanol, no tetralin was observed after treatment in formic acid for the length of time involved in a solvolysis of the bromobenzenesulfonate, even when the formic acid solvent was acidified with toluenesulfonic acid. Similarly, no tetralin was observed to be formed from 4-phenyl-1-butyl acetate in acetic acid containing toluenesulfonic acid.

TABLE V

SUMMARY OF PRODUCTS OF FORMOLYSIS AT 75.00°

Compound	Total yield, %	% ROH	% Tetralin	$\frac{100\,k_\Delta}{(k_s + k_\Delta)}$
$C_6H_5(CH_2)_4OBs$	88.7[a]	81.0[a]	19.0[a]	..
	89.3[b]	94.5[b]	5.5[b]	..
p-$CH_3OC_6H_4(CH_2)_4OBs$[c]	93.8	45.8	54.2	54.3
2,4-$(CH_3O)_2C_6H_3(CH_2)_4$-OBs[d]	84.2	9.3	90.7	91.8

[a] 0.0500 *M* ROBs; 0.0500 *M* NaOCHO; 66 hours at 75°. [b] Acetolysis products at 100.0°, 0.0452 *M* ROBs; 127 hours at 100°. [c] 0.0286 *M* ROBs; 0.0302 *M* NaOCHO; 42 hours at 75°. [d] 0.0476 *M* ROBs; 0.0555 *M* NaOCHO; 6 hours at 75°.

Dissection of k into k_Δ and k_s and Mechanism of Tetralin Formation.—By dissecting the solvolysis rate constants for the 4-aryl-1-butyl *p*-bromobenzenesulfonates into k_Δ, the rate constant for anchimerically assisted solvolysis, and k_s, the rate constant for anchimerically unassisted solvolysis, composition of solvolysis products can be connected quantitatively with observed rates. The dissection of rate constants is based on the k_s assigned to 4-phenyl-1-butyl *p*-bromobenzenesulfonate on the assumption that anchimerically assisted solvolysis leads only to tetralin and anchimerically unassisted solvolysis gives no tetralin. This assumes that any intermediate[19,20] in the anchimerically unassisted solvolysis of a simple primary arylsulfonate, such as 4-phenyl-1-butyl, would be too unstable and short-lived to lead to serious amounts of electrophilic attack on the benzene ring instead of collapsing to acetate or formate. The values assigned to k_Δ and k_s on this basis are listed in Table IV.

For the methoxyphenylbutyl esters, k_s is assumed equal to k_s for the unsubstituted 4-phenyl-1-butyl derivative, by analogy with the 3-aryl-1-propyl esters, where k_s is insensitive to methoxyl substitution. Subtracting k_s from the observed solvolysis rate constants leads to the derived values of k_Δ

(14) R. T. Arnold and C. J. Collins, THIS JOURNAL, **61**, 1407 (1939).
(15) H. Metzner, *Ann.*, **298**, 388 (1898).
(16) R. B. Woodward and R. H. Eastman, THIS JOURNAL, **66**, 674 (1944).
(17) P. C. Mitter and S. De, *J. Indian Chem. Soc.*, **16**, 35 (1939).
(18) R. Linstead, *et al.*, *Chemistry & Industry*, 72 (1934).
(19) S. Winstein, E. Grunwald and H. W. Jones, THIS JOURNAL, **73**, 2700 (1951).
(20) See: (a) A. Streitwieser, Jr., *ibid.*, **77**, 1117 (1955); (b) A. Streitwieser, Jr., and W. D. Schaeffer, Page 52-N of Abstracts, American Chemical Society, Dallas, Texas, April 8–13, 1956.

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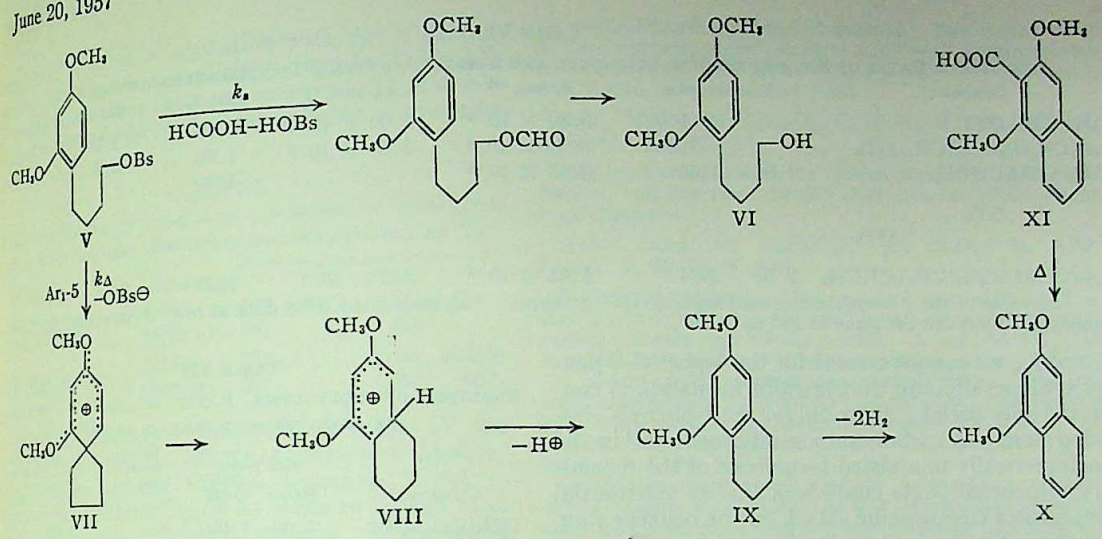


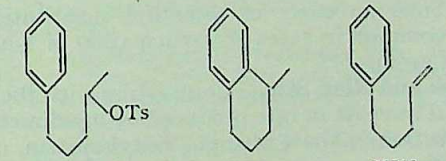
summarized in Table IV. These are, of course, much larger for the methoxyphenyl cases than for the unsubstituted phenyl derivative.

The assumption for the methoxy-substituted 4-phenyl-1-butyl esters, just as in the case of the 4-phenyl-1-butyl derivative, that k_Δ is connected with tetralin formation, allows one to calculate the expected product composition. The calculated values for per cent. tetralin in the product, namely, $100\,k_\Delta/(k_s + k_\Delta)$, are shown in Table V, along with the observed product compositions. It is apparent that the calculated and observed product compositions agree within experimental error, so that the underlying assumptions are at least semi-quantitatively valid.

The mode of formation of the observed tetralins from the methoxy-substituted 4-phenyl-1-butyl bromobenzenesulfonates is especially interesting, since the *ortho* and *para* methoxyl groups favor Ar_1-5 participation. It is reasonable to believe that k_Δ is predominantly connected with formation of a spiro-carbonium ion, VII in the case of solvolysis of the 4-(2,4-dimethoxy-phenyl)-1-butyl bromobenzenesulfonate. This must rearrange, as in the related dienone–phenol rearrangement,[21] probably to another intermediate VIII, finally leading to tetralin IX. In the present examples, no more direct evidence is available for the spiro-carbonium ion intermediate like VII, but such direct evidence is available in cases where, for example, C_δ of the original bromobenzenesulfonate is dimethylated.[2b]

Secondary Systems.—Two secondary arylsulfonates, 5-phenyl-2-pentyl (XII) and 5-(2,4-dimethoxyphenyl)-2-pentyl toluenesulfonates were examined for comparison with their primary analogs. As summarized in Table VI, the 2,4-methoxyl groups enhance formolysis rate in the 5-phenyl-2-pentyl system, but the factor is only 2.5 instead of *ca.* 10 observed in the primary case.

The products of formolysis of 5-phenyl-2-pentyl toluenesulfonate (XII), after lithium aluminum hydride reduction, were 46.6% 5-phenyl-2-pentanol and 47.8% hydrocarbon. The hydrocarbon contained 30% of olefin according to quantitative hydrogenation. Removal of olefin by reaction with osmium tetroxide left a hydrocarbon which was inert to potassium permanganate in acetone and analyzed correctly and possessed the correct physical properties for 1-methyltetralin (XIII). On this basis, the composition of solvolysis product may be restated as 35% tetralin, 50% alcohol and 15% olefin.



That the formation of the 1-methyltetralin (XIII) obtained in formolysis of 5-phenyl-2-pentyl toluenesulfonate is associated with the solvolysis reaction and it is not formed from reaction of formate ester or olefin subsequent to their formation is clear from control experiments. Under conditions of formolysis of the toluenesulfonate XII, 5-phenyl-2-pentanol yields no tetralin XIII. Similarly, the olefin produced in solvolysis of toluenesulfonate is quite inert to the solvolysis conditions. Even a sample of 5-phenyl-1-pentene (XIV), the straight chain olefin expected to be most reactive in tetralin formation, reacts only very slowly with formic acid. Even in the absence of added sodium formate, the 5-phenyl-1-pentene (XIV) in formic acid solution is only about one third converted to tetralin and formate ester in a ratio of 0.6:1 after a reaction time *ca.* 15 times that employed in solvolysis of the toluenesulfonate XII.

When it comes to dissecting the rate constant of solvolysis of the secondary toluenesulfonates into

(21) (a) See ref. 2b for other references; (b) a very closely related dienonephenol rearrangement is the following example studied in these Laboratories (R. Baird, unpublished work)

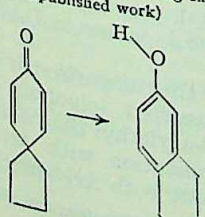


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TABLE VI

ANALYSIS OF RATES OF FORMOLYSIS OF 4-ARYLBUTYL AND 5-ARYL-2-PENTYL *p*-TOLUENESULFONATES AT 25.00°

Compound	Relative rates		k_s (sec.$^{-1}$)	k_Δ (sec.$^{-1}$)	Rel. k_s	Rel. k_Δ	k_Δ/k_s
$C_6H_5(CH_2)_4OTs$		1.00[a,b]	3.80×10^{-8}[c]	9.00×10^{-9}[c]	1.00	1.00	0.24
$2,4\text{-}(CH_3O)_2C_6H_3(CH_2)_4OTs$		9.00[a,b]	3.80×10^{-8}	3.85×10^{-7}	1.00	42.8	10.1
$C_6H_5(CH_2)_3CHCH_3$ (OTs)	1.00	1155	5.43×10^{-5}	.....	1429	...	...
$2,4\text{-}(CH_3O)_2C_6H_3(CH_2)_3CHCH_3$ (OTs)	2.50	2894	5.43×10^{-5}	8.2×10^{-5}	1429	9111	1.51

[a] The value of the *p*-bromobenzenesulfonate divided by three. [b] Extrapolated from data at other temperatures. [c] Assuming products are the same at 25° as at 75°.

k_s and k_Δ, we cannot assume for the 5-phenyl-2-pentyl toluenesulfonate that tetralin formation is connected only with k_Δ, as we did for the 4-phenyl-1-butyl system. A carbonium ion intermediate[19] in the anchimerically unassisted formolysis of the secondary toluenesulfonate could well lead to substantial amounts of electrophilic attack on the benzene ring, resulting finally in tetralin formation. Thus, at least part of the tetralin formation could be connected with k_s. What has been done in writing down the values of k_s and k_Δ in Table VI for 5-(2,4-dimethoxyphenyl)-2-pentyl toluenesulfonate is to assume the rate constant of 5-phenyl-1-pentyl toluenesulfonate is entirely k_s, k_Δ being zero. On this basis, the k_s values are maximal, and k_Δ for 5-(2,4-dimethoxyphenyl)-2-pentyl toluenesulfonate is a minimum figure.

The k_Δ and k_s values for the secondary toluenesulfonates listed in Table VI are sufficiently clear to bring out the point that the α-methyl group which converts the primary to secondary arylsulfonates increases k_s more than k_Δ. This results in a lower k_Δ/k_s ratio for secondary arylsulfonate than for primary, aryl participation being considerably less dominant with secondary than primary arylsulfonate. Such an effect of α-methyl substitution is quite common in cases of participation of β-neighboring groups.[3,22]

Ar$_1$-*n* and Ring Size.—Contrasting with the substantial increase in rate produced by *o,p*-dimethoxy substitution in the 4-phenyl-1-butyl system, is the small increase produced in the case of 5-phenyl-1-pentyl bromobenzenesulfonate. In Table VII are compared the 5-phenyl-1-pentyl and 5-(2,4-dimethoxyphenyl)-1-pentyl bromobenzenesulfonates. By using the rate constant for the 5-phenyl-1-pentyl ester as k_s, one obtains an estimate for k_Δ only *ca.* 0.07 times k_s in the case of 5-(2,4-dimethoxyphenyl)-1-pentyl bromobenzenesulfonate. Thus, it is clear that rates associated with Ar$_1$-6 participation are much lower than those associated with Ar$_1$-5. Consequently, it will be more difficult to arrange conditions of structure and solvent so as to have Ar$_1$-6 participation dominate the rate-determining step of solvolysis of an arylsulfonate.[23]

In Table VIII are summarized relative k_Δ values for acetolysis and formolysis of ω-aryl-1-alkyl bromobenzenesulfonates for alkyl systems from ethyl to pentyl. In this comparison, k_Δ for 4-*p*-anisyl-1-butyl was taken as unity. Also summarized in Table VIII are the corresponding values of k_Δ/k_s. These orient one on the extent to which Ar$_1$-*n* participation dominates the solvolysis, while the relative k_Δ values are useful for outlining the variation of k_Δ with ring size or degree of methoxyl substitution.

TABLE VII

ANALYSIS OF SOLVOLYSIS RATES OF 5-ARYL-1-PENTYL BROMOBENZENESULFONATES AT 75°

Compound	Rel. rates HOAc	Rel. rates HCOOH	10^5k in AcOH- (sec.$^{-1}$) k_s	10^5k in AcOH- (sec.$^{-1}$) k_Δ	10^5k in HCOOH (sec.$^{-1}$) k_s	10^5k in HCOOH (sec.$^{-1}$) k_Δ
$C_6H_5(CH_2)_5OBs$	1.00	1.00	1.54	..	3.39	..
$2,4\text{-}(CH_3O)_2C_6H_3\text{-}(CH_2)_5OBs$	1.05	1.07	1.54	0.07	3.39	0.24

TABLE VIII

RELATIVE VALUES OF k_Δ AND VALUES OF k_Δ/k_s FOR SOLVOLYSIS OF ω-ARYL-1-ALKYL BROMOBENZENESULFONATES AT 75°

Aryl group	Alkyl system	Rel. k_Δ AcOH	Rel. k_Δ HCOOH	k_Δ/k_s AcOH	k_Δ/k_s HCOOH
C_6H_5	Ethyl	....	3[a]	.....	6[a,b]
C_6H_5	Butyl	0.15	0.20	0.06	0.23
4-$CH_3OC_6H_4$	Ethyl	147[c]	161[d]	92[e]	310[b]
4-$CH_3OC_6H_4$	Propyl	<0.2	.....	<0.1	.....
4-$CH_3OC_6H_4$	Butyl	1.00	1.00	0.39	1.19
$2,4\text{-}(CH_3O)_2C_6H_3$	Ethyl	2420[f]	2060	1510[e]	4000[b]
$2,4\text{-}(CH_3O)_2C_6H_3$	Butyl	9.22	9.45	3.6	11.7
$2,4\text{-}(CH_3O)_2C_6H_3$	Pentyl	0.13	0.07	0.05	0.07

[a] Rough values based on a k_Δ equal to the solvolysis rate constant.[9] [b] Based on a k_s equal to twenty times the rate constant for acetolysis of β-phenylethyl *p*-bromobenzenesulfonate.[9] [c] Based on a k_Δ three times k^0_{ext} for the *p*-sulfonate.[9] [d] Based on rate constant three times toluenesulfonate.[24] [e] Based on a k_s equal the value for the toluenesulfonate.[4] [f] Based on salt-enhanced rate constant.[9] to rate constant for acetolysis of β-phenylethyl *p*-bromobenzenesulfonate.[9]

The values in Table VIII reveal that both Ar$_1$-4 and Ar$_1$-6 participations compete very poorly in solvolysis of ω-aryl-1-alkyl arylsulfonates in acetic or formic acid solvents. In fact, the measured solvolysis rate constants of the corresponding bromobenzenesulfonates were so little greater than the k_s values, that the k_Δ values in Table VIII are very rough.

It is clear from the comparison in Table VIII that anchimerically assisted solvolysis is much more dominant with β-arylethyl than 4-aryl-1-butyl systems, rate of ionization with Ar$_1$-3 being much higher than the one with Ar$_1$-5 participation. The

(22) S. Winstein and E. Grunwald, THIS JOURNAL, **70**, 828 (1948).

(23) See R. L. Letsinger and P. T. Lansbury [*ibid.*, **78**, 2648 (1956), Page 40-O of Abstracts, American Chemical Society, Atlantic City, N. J., Sept. 16–21, 1956] for a case of 1,5-phenyl migration during treatment of 8-benzhydryl-1-naphthoic acid under Friedel–Crafts acylation conditions. The relative timing of the steps which involve ionization of a group away from the acyl carbon atom and phenyl shift to the acyl carbon atom is not known.

(24) A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2767 (1956).

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sequence of rates of ionization with Ar$_1$-n participation as n varies is explicitly given in Table IX. From this it is clear that the sequence is $3 > 4 < 5 > 6$, both the 3:5 and the 5:6 ratios being of the order of 10^2.

TABLE IX

RELATIVE RATES OF Ar$_1$-n RING CLOSURES IN SOLVOLYSIS OF ω-ARYL-1-ALKYL BROMOBENZENESULFONATES AT 75°

Ar group	Solvent	Ring size, n: 3	4	5	6
4-$CH_3OC_6H_4$	AcOH	147	<0.2	1.00	
	HCOOH	161		1.00	
2,4-$(CH_3O)_2C_6H_3$	AcOH	262		1.00	0.014
	HCOOH	227		1.00	.007

Effect of Methoxy.—Reference to Tables IV and VIII reveals that the effects of methoxyl substitution in the benzene ring of 4-phenyl-1-butyl *p*-bromobenzenesulfonate on k_Δ tends to be less than with the 2-phenyl-1-ethyl system. The second methoxyl group (*ortho*) increases Ar$_1$-5 rate by a factor of 9 and Ar$_1$-3 by a factor of 13–16. The first methoxyl group (*para*) increases k_Δ in the 4-aryl-1-butyl system by a factor of only *ca.* 5–7, much smaller than in the case of Ar$_1$-3 rates. However, if the k_Δ for 4-phenyl-1-butyl *p*-bromobenzenesulfonate could be dissected into Ar$_1$-5 and Ar$_2$-6 components, the factor by which a *p*-methoxy group would be calculated to increase Ar$_1$-5 rate might be substantially larger than the value of *ca.* 5–7.

The factor by which a methoxyl group on the benzene ring facilitates electron-demanding reactions varies widely. In bromination,[25] for example, a *p*-methoxyl group increases rate by a factor of *ca.* 10^{10}. The relatively small effect of methoxyl in Ar$_1$-5 indicates a rather low degree of aryl involvement at the transition state configuration.

Experimental

3-*p*-Anisyl-1-propanol.—This alcohol was prepared in 44% yield by the reduction of *p*-methoxycinnamic acid[10] with lithium aluminum hydride, the acid being added to a stirred suspension of 1.5 moles of lithium aluminum hydride by means of a Soxhlet extractor.

3-(2,4-Dimethoxyphenyl)-1-propanol.—This material was prepared by addition of 46 g. of 2,4-dimethoxycinnamic acid[10] to an ether suspension of 12 g. of lithium aluminum hydride. The acid was added from a Soxhlet extractor, two days being required for the addition. The alcohol product, b.p. 144–145° (3.5 mm.), n^{25}D 1.5320, m.p. 36–38°, was obtained in 39% yield.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.16; H, 8.25.

4-Phenyl-1-butanol.—This material was prepared in high yield by lithium aluminum hydride reduction of γ-phenylbutyric acid.

Treatment of the alcohol with acetic anhydride and a few drops of pyridine for 1 hour on the steam-bath gave rise to 4-phenyl-1-butyl acetate, b.p. 120° (8.5 mm.), n^{25}D 1.4948.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.73; H, 8.10.

4-*p*-Anisyl-1-butanol.—The reduction of 4-*p*-anisylbutyric acid[26] with lithium aluminum hydride gave rise to 4-*p*-anisyl-1-butanol, b.p. 125–130° (1.5 mm.), n^{25}D 1.5201, in 91.5% yield. A small sample, redistilled for analysis, had n^{25}D 1.5200.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.43; H, 9.05.

(25) P. B. D. de la Mare and C. A. Vernon, *J. Chem. Soc.*, 1764 (1951).

(26) E. L. Martin, THIS JOURNAL, 58, 1438 (1936).

4-(2,4-Dimethoxyphenyl)-1-butanol.—The reduction of 4-(2,4-dimethoxyphenyl)-butyric acid[17] with lithium aluminum hydride afforded the alcohol, b.p. 157–161° (2.5 mm.), n^{25}D 1.5296, in quantitative yield.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.68; H, 8.40.

The *p*-nitrobenzoate of the alcohol prepared in the usual fashion, had the m.p. 52–53° after two recrystallizations from methanol.

Anal. Calcd. for $C_{19}H_{21}O_6N$: C, 63.50; H, 5.89. Found: C, 63.73; H, 6.01.

5-Phenyl-1-pentanol.—This material, b.p. 110–113° (3 mm.), n^{25}D 1.5149, was prepared from γ-phenylpropylmagnesium chloride and ethylene oxide. A b.p. of 151° (13 mm.) has been reported[11] for this alcohol.

ω-Aryl-1-alkyl *p*-Bromobenzenesulfonates.—The primary alcohols were converted to *p*-bromobenzenesulfonates by the low temperature method described previously,[9] the physical properties and analyses of the products being summarized in Table X.

γ-(2,4-Dimethoxybenzoyl)-butyric Acid.—To a mixture of 40 g. of glutaric anhydride and 50 g. of resorcinol dimethyl ether in 450 cc. of purified tetrachloroethane, cooled to 0°, was added 100 g. of anhydrous aluminum chloride in small portions with stirring. The mixture became purple and a viscous solid separated. After *ca.* 30 min. at 0°, ice and dilute hydrochloric acid were added. After working up the reaction mixture and recrystallizing the product from aqueous methanol, 18 g. of the desired acid was obtained. A small sample, recrystallized for analysis had a melting point of 106–107°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.61; H, 6.19.

5-(2,4-Dimethoxyphenyl)-valeric Acid.—The above keto acid (17 g.) was reduced by the Clemmensen method using 50 g. of zinc (amalgamated), 30 cc. of toluene, 30 cc. of water and 70 cc. of concd. hydrochloric acid. The mixture was refluxed for two days while 10 cc. of concd. hydrochloric acid was added every 6 hours. The product was extracted from the toluene phase with bicarbonate solution. Acidification of the bicarbonate extract gave the acid which was recrystallized from aqueous methanol to yield 5.5 g. of the acid, m.p. 95–98°. A small sample, recrystallized for analysis had m.p. 97–98.5°.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.72; H, 7.63.

5-(2,4-Dimethoxyphenyl)-1-pentanol.—This alcohol, b.p. 144–145° (2 mm.), n^{25}D 1.5247, was obtained in 96% yield by the lithium aluminum hydride reduction of 5-(2,4-dimethoxyphenyl)-valeric acid.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.55; H, 8.79.

The *p*-bromobenzenesulfonate of the alcohol was obtained as a liquid, 90% pure according to the equivalent weight in acetolysis and formolysis.

1-Phenyl-4-pentyl *p*-Toluenesulfonate.—To a solution of 15 g. of 5-phenyl-2-pentanol,[11] b.p. 80–84° (1 mm.), n^{25}D 1.5108, in 75 ml. of dry pyridine was added 25 g. of *p*-toluenesulfonyl chloride. The mixture was kept below room temperature until the exothermic reaction was over, and then it was left at room temperature for another 2 hours. Working up the reaction mixture and evaporation of an ether solution of the product gave rise to an oil which was chromatographed on alumina. From the fraction eluted by benzene–pentane was obtained 9.5 g. of product, n^{25}D 1.5382, 93% pure by equivalent weight in formolysis.

1-(2,4-Dimethoxyphenyl)-4-pentanol.—4-(2,4-Dimethoxyphenyl)-butyric acid (16 g.) in 50 ml. of ether was added dropwise with stirring to a solution of methyllithium prepared from 25 g. of methyl iodide and 2.5 g. of lithium ribbon in 200 ml. of ether. After 30 minutes stirring, cold dil. hydrochloric acid was added. The ether phase was separated and washed with water and a sodium bicarbonate solution. After being dried, the ether solution was distilled, the fraction, b.p. 120–150° (2 mm.), being then reduced with lithium aluminum hydride. A 3.5-g. quantity of the alcohol, b.p. 135–139° (2 mm.), n^{25}D 1.5219, was obtained.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.58; H, 9.20.

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TABLE X

PROPERTIES AND ANALYSES OF SOME *p*-BROMOBENZENESULFONATES

Compound	M.p., °C.	Formula	Analyses, % Calcd. Carbon	Found	Calcd. Hydrogen	Found
$C_6H_5(CH_2)_3OBs$	35.5–37.5	$C_{15}H_{15}O_3SBr$	50.71	50.72	4.26	3.98
p-$CH_3OC_6H_4(CH_2)_3OBs$	62–64	$C_{16}H_{17}O_4SBr$	49.88	50.03	4.44	4.36
2,4-$(CH_3O)_2C_6H_3(CH_2)_3OBs$	56–57	$C_{17}H_{19}O_5SBr$	49.16	49.08	4.61	4.76
$C_6H_5(CH_2)_4OBs$	21–23.5[a]	$C_{16}H_{17}O_3SBr$	52.04	52.09	4.64	4.56
p-$CH_3OC_6H_4(CH_2)_4OBs$	43–45	$C_{17}H_{19}O_4SBr$	51.13	51.33	4.80	4.63
2,4-$(CH_3O)_2C_6H_3(CH_2)_4OBs$	54.5–56.5	$C_{18}H_{21}O_5SBr$	50.35	50.63	4.93	4.99
$C_6H_5(CH_2)_5OBs$	34–35.5	$C_{17}H_{19}O_3SBr$	53.27	53.44	5.00	4.79

[a] $n^{25}D$ 1.5694.

The *p*-toluenesulfonate of the alcohol was obtained as an impure liquid, $n^{25}D$ 1.5250, 70% pure according to the equivalent weight in formolysis.

Kinetic Measurements.—The procedure for the kinetic measurements was identical to that employed previously.[9]

Only with 3-(2,4-dimethoxyphenyl)-1-propyl *p*-bromobenzenesulfonate did the acetolysis fail to obey first-order kinetics strictly. The rate constant drifted down in a run, as is illustrated in Table XI. The initial rate constant was obtained from a plot of log $[(ROBs)_0/(ROBs)]$ *vs.* time.

TABLE XI

ACETOLYSIS OF 0.0257 *M* 3-(2,4-DIMETHOXYPHENYL)-1-PROPYL *p*-BROMOBENZENESULFONATE AT 75.00°

Time, 10^{-2}, sec.	NaOAc, ml. per 5-ml. aliquot.	Integrated $10^5 k$, sec.$^{-1}$
0	0.015	..
289	.460	3.83
466	.685	3.68
892	1.180	3.60
1396	1.652	3.49
1812	1.970	3.41
3483	2.850	3.17
4722	3.260	3.06
∞	4.260	..
∞ (calcd.)	4.267	..

Products of Formolysis of 4-(2,4-Dimethoxyphenyl)-1-butyl *p*-Bromobenzenesulfonate.—A mixture of 18.4 g. of 4-(2,4-dimethoxyphenyl)-1-butyl *p*-bromobenzenesulfonate and 3.40 g. of sodium formate in 900 cc. of dry formic acid was heated at 75° for six hours. The resulting solution was diluted with water and extracted with four 500-ml. portions of ether. The combined extracts were washed with water and aqueous sodium bicarbonate. After the extract was dried, the solvent was removed and the residue was reduced with 2 g. of lithium aluminum hydride in ether. The reduction product was extracted with dilute sodium hydroxide. The basic extract became colored orange, but only a negligible amount of material appeared when this extract was acidified. The reduction product yielded three fractions when it was chromatographed on 500 g. of alumina.

The first fraction was eluted with 5 liters of pentane. The tetralin product, b.p. 102–105° (2 mm.), $n^{25}D$ 1.5454, weighed 5.5 g. This material was inert to potassium permanganate in acetone. A sample, b.p. 105° (2 mm.), was analyzed.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 75.14; H, 8.61.

This material crystallized after standing several months; m.p. 36.5–38°.

It formed a monobromide, m.p. 78–80°, when it was treated with bromine in carbon tetrachloride.

Anal. Calcd. for $C_{12}H_{15}O_2Br$: C, 53.15; H, 5.28. Found: C, 53.02; H, 5.51.

The dehydrogenation of 2 g. of the tetralin with 6 g. of chloranil in 20 ml. of xylene at reflux temperature for 15 hours as described by Arnold and Collins,[14] yielded 0.8 g. of the picrate of 1,3-dimethoxynaphthalene, m.p. 141–142°, undepressed by the synthetic material described below.

Anal. Calcd. for $C_{18}H_{15}O_9N_3$: C, 51.80; H, 3.62. Found: C, 51.84; H, 3.64.

A second fraction from the chromatography was eluted with four liters of ether. This material (0.8 g.) was also the tetralin mentioned above, b.p. 110° (3 mm.), $n^{25}D$ 1.5401, inert to potassium permanganate in acetone.

The third fraction was eluted with three liters of methanol. The product, 0.7 g., b.p. 130° (3 mm.), was converted into the *p*-nitrobenzoate. It was necessary to chromatograph the ester before it could be crystallized. Crystallization of the chromatographed product from methanol gave two fractions. The first fraction, m.p. 49–51°, mixed m.p. with authentic material 49–52°, weighed 0.8 g. The second fraction, m.p. 48–51°, mixed m.p. 48–51°, weighed 0.1 g.

In a control experiment, a solution of 2 g. of 4-(2,4-dimethoxyphenyl)-1-butanol in 150 ml. of 98–100% formic acid was heated at 75° for 15 hours. Working up in the manner described for the solvolysis reactions yielded 1.65 g. (82.5%) of recovered alcohol, b.p. 150–152° (2 mm.), $n^{25}D$ 1.5296.

In another control experiment, a solution of 0.5 g. of 4-(2,4-dimethoxyphenyl)-1-butanol in 30 cc. of 0.0315 *M* sodium formate in formic acid was heated at 75° for 10 hours. When the mixture was worked up as described for the solvolysis, 0.35 g. (70%) of the alcohol was recovered. This gave 0.40 g. (67%) of *p*-nitrobenzoate, m.p. 50–53°.

1,3-Dimethoxynaphthalene.—Ethyl 1,3-dihydroxy-2-naphthoate[15] (13 g.) was treated with a solution of diazomethane in 200 ml. of ether prepared from 15 g. of nitrosomethylurea. After the mixture was allowed to stand overnight, the ether was evaporated and the remaining oil was vacuum distilled. The fraction, b.p. 155–175° (2 mm.), weighing 11 g., was refluxed with 10 g. of sodium hydroxide in a mixture of 15 ml. of water and 15 ml. of ethanol overnight. The dark solution and solid was treated with water, and the product was extracted with ether. The product, b.p. 145–150° (3 mm.), was a dark colored oil weighing 2.8 g. The color was removed readily by chromatography on alumina, but the substance soon became colored again on standing. The purified product, $n^{25}D$ 1.6140, was analyzed.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.79; H, 6.45.

The picrate of this substance crystallized from ether in the form of long orange-red needles, m.p. 140–141°.

Products of Formolysis of 4-*p*-Anisyl-1-butyl *p*-Bromobenzenesulfonate.—A solution of 8 g. of 4-*p*-anisyl-1-butyl *p*-bromobenzenesulfonate in 700 ml. of 0.03022 *M* sodium formate in dry formic acid, was heated at 75° for 42 hours. After dilution with water, the products were extracted with three portions of pentane. The oil remaining after the pentane was evaporated was reduced with 1 g. of lithium aluminum hydride. The product mixture was then chromatographed on 100 g. of alumina. The 7-methoxytetralin was eluted with 700 ml. of pentane. This substance, b.p. 76° (1.5 mm.), $n^{25}D$ 1.5414, weighed 1.65 g. and was inert to potassium permanganate in acetone. The b.p. of this compound has been reported as 103–105° (5.5 mm.)[17] and 129–131° (11 mm.).[16] The 4-*p*-anisyl-1-butanol was eluted with 600 ml. of ether. This product, b.p. 118–119° (1.5 mm.), $n^{25}D$ 1.5239, weighed 1.55 g.

Products of Formolysis of 4-Phenyl-1-butyl *p*-Bromobenzenesulfonate.—To a solution of 3.4 g. of dry sodium formate in 1000 ml. of dry formic acid (containing 0.31% water by Karl Fischer titration) heated to 75.0° was added 18.5 g. of the purified bromobenzenesulfonate. The solution was mixed well and left at 75.0° for 66 hours. The resulting solution was cooled, poured into 3 liters of water, and ex-

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tracted with 4 portions of pure pentane. The extracts were washed with water and aqueous sodium bicarbonate. After they were dried, the solvent was distilled off carefully through a Vigreux column, and the products were reduced with 2 g. of lithium aluminum hydride in ether. The reduced products were chromatographed on 500 g. of alumina. The pentane eluates yielded 1.10 g. (16.7%) of hydrocarbon, b.p. 101–103° (22 mm.), $n^{25}D$ 1.5388 (reported[27] for tetralin, b.p. 89° (12 mm.), $n^{25}D$ 1.5392). The infrared spectrum of the hydrocarbon was identical with that of pure tetralin. Also, an 80% yield of naphthalene, m.p. 75–77°, mixed m.p. 77–80°, was obtained from the hydrocarbon by dehydrogenation with tetrachloro-1,2-benzoquinone in benzene.[18]

Elution with methanol, concentration and distillation gave 5.4 g. (72.0%) of alcohol, b.p. 87–90° (1.5 mm.), $n^{25}D$ 1.5191 ($n^{25}D$ 1.5202 for pure 4-phenyl-1-butanol). The infrared spectrum of the alcohol was identical with that of 4-phenyl-1-butanol.

Treatment of 4-Phenyl-1-butanol with Acidic Formic Acid.—A solution of 2.0 g. of 4-phenyl-1-butanol and 0.6 g. of *p*-toluenesulfonic acid in 100 cc. of dry formic acid (0.31% water) was heated at 75.0° for 67 hours. Cooling and pouring into water gave rise to an oil which was extracted with three portions of pure pentane. The extracts were washed, concentrated and reduced with lithium aluminum hydride. Distillation of the product gave 1.7 g. (85%) of alcohol, $n^{25}D$ 1.5189, b.p. 124–127° (10 mm.), with no sign of any lower boiling tetralin.

Products of Acetolysis of 4-Phenyl-1-butyl *p*-Bromobenzenesulfonate.—A 20.0-g. quantity of pure 4-phenyl-1-butyl *p*-bromobenzenesulfonate was added to 1200 cc. of dry acetic acid already heated to 100.0°, and the solution was kept at this temperature for 101 hours. The cooled solution was poured into 3 liters of water and extracted with 5 portions of pure pentane. The extracts were washed, concentrated and reduced with lithium aluminum hydride. The reduced products were chromatographed on alumina. There was obtained 0.35 g. (4.9%) of tetralin, b.p. 75° (10 mm.), $n^{25}D$ 1.5370, and 6.85 g. (84.4%) of alcohol, b.p. *ca.* 100° (2 mm.), $n^{25}D$ 1.5205. The infrared spectrum of the tetralin product was essentially the same as that of pure tetralin except for the presence of 2 small additional bands at 960 and 680 cm.$^{-1}$. The alcohol product had an infrared spectrum identical with that of pure 4-phenyl-1-butanol.

In a control experiment, a solution of 11.0 g. of 4-phenyl-1-butyl acetate, 11.4 g. of *p*-toluenesulfonic acid and 1 cc. of acetic anhydride in 1200 cc. of dry acetic acid was kept at 100.0° for 140 hours. The solution was cooled, poured into water, and the products were extracted as before. The crude acetates were reduced with lithium aluminum hydride and the product distilled. The product, b.p. 120–123° (8.5 mm.), $n^{25}D$ 1.5202, weighed 8.2 g. (95%). There was no sign of any lower boiling tetralin.

Formolysis of 5-Phenyl-2-pentyl *p*-Toluenesulfonate.—A solution of 9.2 g. of the toluenesulfonate (93% pure) and 2.45 g. of dry sodium formate in 600 cc. of dry formic acid (0.31% water) was kept at 25.0° for 43.5 hours. The products were isolated in the usual way. Chromatography on 200 g. of alumina yielded two fractions, a hydrocarbon fraction, 2.05 g., b.p. 112–115° (25 mm.), $n^{25}D$ 1.5229, and an alcohol fraction, 2.20 g., b.p. 95–100° (1.5 mm.), $n^{25}D$ 1.5107. The alcohol had an infrared spectrum identical with that of 5-phenyl-2-pentanol.

The hydrocarbon fraction contained 30% olefin according to quantitative hydrogenation. The 1-methyltetralin was isolated from the hydrocarbon mixture by oxidizing the olefin with osmium tetroxide. For this purpose, 0.75 g. of the mixture was added to 1.0 g. of osmium tetroxide in 20 cc. of ether containing 2 drops of pyridine. After standing for 30 minutes, 150 cc. of pure methylene chloride and a solution of 2.5 g. of potassium hydroxide and 2. 5 g. of mannitol in 50 cc. of water was added. The two phase mixture was shaken in a shaking machine for two hours. The aqueous phase was separated and extracted again with methylene chloride. The combined extracts were washed with water, dried and concentrated under a Vigreux column. Vacuum distillation yielded 0.4 g. (53%) of 1-methyltetralin, b.p. 55° (1.5 mm.), $n^{25}D$ 1.5323 (reported[28] for 1-methyltetralin, b.p. 87–88° (7 mm.), $n^{25}D$ 1.5332). The material was inert to potassium permanganate in acetone. The infrared spectrum indicated a trace (*ca.* 1–2%) of alcoholic impurity.

Anal. Calcd. for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.30; H, 9.46.

In a control experiment, a solution of 5.0 g. of the alcohol and 0.35 g. of sodium formate in 500 cc. of dry formic acid (0.14% water) was kept at 25.0° for 41 hours. The products were isolated as usual. Reduction with 1.5 g. of lithium aluminum hydride in ether gave 5.0 g. of alcohol, b.p. 117–120° (8 mm.), $n^{25}D$ 1.5108. There was no sign of any lower boiling material. An analogous treatment of 4.4 g. of alcohol in 500 ml. of formic acid without sodium formate for 27 days at 25° gave only 0.06 g. of a hydrocarbon fraction and 4.0 g. (91%) of alcohol, b.p. 145–148° (30 mm.), $n^{25}D$ 1.5106.

In another control experiment, a solution of 1.0 g. of the olefin–tetralin mixture obtained from solvolysis of 5-phenyl-2-pentyl *p*-toluenesulfonate was kept at 25.0° with 0.050 g. of pure sodium formate in 150 cc. of 98–100% formic acid for 42.5 hours. The products were isolated as usual and distilled. There was obtained 0.95 g. of product, $n^{25}D$ 1.5231, 26% olefin by quantitative hydrogenation. The infrared spectrum was nearly like that of the starting mixture except for weak bands at 1720, 1180 and 1110 cm.$^{-1}$, probably indicating a few per cent. of a formate ester.

Reaction of 5-Phenyl-1-pentene with Formic Acid.—A solution of 4.4 g. of 5-phenyl-1-pentene,[29] b.p. 77–78°, $n^{25}D$ 1.5019, in 500 ml. of 98–100% formic acid was kept at 25.0° for 27 days. The resulting solution was poured into water and extracted with 5 portions of pure pentane. The extracts were washed, dried, concentrated and reduced with lithium aluminum hydride. Chromatography yielded 3.2 g. (73%) of hydrocarbon, b.p. 106–108° (*ca.* 30 mm.), $n^{25}D$ 1.5054, and 1.0 g. (20%) of alcohol, b.p. 95° (2 mm.), $n^{25}D$ 1.5099. The hydrocarbon fraction was determined to be 16% tetralin by quantitative hydrogenation over palladium-on-charcoal.

Los Angeles, 24, California

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Neighboring Carbon and Hydrogen. XXVIII. Ar_2-6 Participation in Solvolysis of Some ω-Aryl-1-alkyl Bromobenzenesulfonates[1,2]

BY RICHARD HECK AND S. WINSTEIN

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In searching for Ar_2-participation in solvolysis, acetolysis and formolysis of suitably substituted ω-aryl-1-alkyl *p*-bromobenzenesulfonates have been studied. In the case of 4-aryl-1-butyl bromobenzenesulfonates, substantial rate enhancements result from introduction of one or two *m*-methoxyl groups into the benzene ring. These enhancements are ascribed to increased importance of Ar_2- assisted ionization in solvolysis. The product of formolysis of 4-(3,5-dimethoxyphenyl)-1-butyl *p*-bromobenzenesulfonate contains mainly 5,7-dimethoxytetralin, formate ester being a minor product. The product composition agrees within experimental error with that predicted from the k_Δ and k_s values obtained by dissection of the solvolysis rate constant by the method outlined in the previous paper. For Ar_2-*n* participation, the rate sequence is $5 \ll 6 \gg 7$, only Ar_2-6 being important in the present work. The observed sequence contrasts with that observed for Ar_1-*n*, for which $5 \gg 6$. This contrast may be understood by considering the respective transition states for the rate-determining steps. The comparison of rates of Ar_1- and Ar_2-assisted ionizations discloses that Ar_1-5 and Ar_2-6-assisted ionizations have nearly equal rates for equivalent degrees of activation of the benzene ring.

In this paper are presented more data bearing on anchimeric effects of aryl groups more distant than *beta*. In contrast with the ω-aryl-1-alkyl bromobenzenesulfonates stressed in the previous paper,[3] the compounds treated in the present manuscript were substituted so as to favor Ar_2- rather than Ar_1-participation in the rate-determining ionization step. The results obtained in the study of these compounds supply considerable orientation on the scope of Ar_2-participation and the comparison of such participation with the Ar_1-variety.

ω-Aryl-1-alkyl Systems.—The list of *p*-bromobenzenesulfonates examined in the present study is shown in Table I, which also summarizes their solvolysis rate constants.

The alcohols which were required for preparation of the bromobenzenesulfonates were obtained by a variety of methods. Of the propanols, 3-*m*-anisyl-1-propanol was prepared in fair yield by the reduction of *m*-methoxycinnamic acid with lithium aluminum hydride. 3-(3,5-Dimethoxyphenyl)-1-propanol was obtained by a lithium aluminum hydride reduction of 3-(3,5-dimethoxyphenyl)-propanoic acid, the latter being derived from the malonic ester synthesis on 3,5-dimethoxybenzyl chloride.

Of the butanols, 4-*m*-anisyl-1-butanol was prepared in poor yield from γ-*m*-anisylpropylmagnesium chloride and formaldehyde. 4-(3,4-Dimethoxyphenyl)-1-butanol was prepared by a lithium aluminum hydride reduction of 4-(3,4-dimethoxyphenyl)-butanoic acid, the latter being obtained by Clemmensen reduction of the Friedel–Crafts succinoylation product from veratrole.[4] The 4-(3,5-dimethoxyphenyl)-1-butanol was prepared by the reaction of β-3,5-dimethoxyphenylethylmagnesium bromide with ethylene oxide. The required bromide was obtained from a displacement reaction on the *p*-bromobenzenesulfonate of β-3,5-dimethoxyphenylethanol. The preparation of this material by way of 3,5-dimethoxyphenylacetic acid has been described previously.[5]

The pentanol, 5-(3,4-dimethoxyphenyl)-1-pentanol, was prepared by a Friedel–Crafts reaction between veratrole and glutaric anhydride,[6] followed by Clemmensen and lithium aluminum hydride reductions.

Kinetic Search for Ar_2-Participation.—All the substances investigated displayed good first-order behavior in acetolysis and formolysis. As regards enhancement of solvolysis rate by methoxyl substitution in the benzene ring, no substantial rate enchancement is observed with the ω-aryl-1-propyl esters, as was pointed out already in the previous paper.[3] This is true even for 3,5-dimethoxyl substitution.

In the 4-phenyl-1-butyl series, substantial rate enhancements are observed[2] on addition of *m*-methoxyl groups to the benzene ring. Thus, 4-*m*-anisyl-1-butyl *p*-bromobenzenesulfonate is 1.86 times as reactive, and the 4-(3,5-dimethoxyphenyl)-1-butyl ester I, 6.24 times as reactive, as the 4-phenyl-1-butyl derivative in formic acid at 75°. The rate comparisons are summarized in Table II. In line with the previous arguments,[3] the observed rate enhancements are ascribed to increased importance of Ar_2-participation in the case of solvolysis of the *m*-methoxyl-substituted derivatives.

The procedure for dissecting the solvolysis rate constant into k_Δ, the rate constant of anchimerically assisted ionization, and k_s, the rate constant of anchimerically unassisted solvolysis, which was applied previously,[3] may be employed on the present data. Using a k_s equal to that for 4-phenyl-1-butyl *p*-bromobenzenesulfonate,[3] one obtains the k_Δ and k_Δ/k_s values summarized in Table II. As in the case of Ar_1-participation,[2,3] two methoxyl groups suffice to make Ar_2-participation dominate formolysis of a 4-aryl-1-butyl ester. Just as for Ar_1-participation,[3] the importance of Ar_2-participation is greater in formic acid than in acetic acid solvent.

Since k_Δ is responsible for most of the formolysis rate constant of the 4-(3,5-dimethoxyphenyl)-1-butyl derivative I, the value for $\Delta S^\ddagger$ listed in Table I, namely, −15.8 e.u., is the value for Ar_2-6-assisted ionization. This is lower than the value[3] for Ar_1-5-assisted ionization, and not very different from the value for anchimerically unassisted formolysis.

(1) Research supported by the Office of Naval Research.

(2) Most of the material of this paper has been reported in summary: (a) Paper by S. Winstein at the Symposium on Dynamic Stereochemistry of the Chemical Society, Manchester, England, March 31, 1954 (see *Chemistry & Industry*, 562 (1954); (b) S. Winstein, R. Heck, S. Lapporte and R. Baird, *Experientia*, **12**, 138 (1956).

(3) R. Heck and S. Winstein, THIS JOURNAL, **79**, 3105 (1957).

(4) M. Haq, M. Kapur and J. N. Ray, *J. Chem. Soc.*, 1087 (1933).

(5) S. Winstein and R. Heck, THIS JOURNAL, **78**, 4801 (1956).

(6) R. D. Haworth and J. R. Atkinson, *J. Chem. Soc.*, 797 (1938).

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Table I

Summary of Solvolysis Rate Constants

Compound	Solvent	Temp., °C.	[ROBs] 10^2M	k (sec.$^{-1}$)	$\Delta H^{\pm}$, kcal./mole	$\Delta S^{\pm}$, e.u.
m-$CH_3OC_6H_4(CH_2)_3OBs$	HOAc	75.00	2.43	$(1.11 \pm 0.02) \times 10^{-6}$		
3,5-$(CH_3O)_2C_6H_3(CH_2)_3OBs$	HOAc	75.00	3.42	$(1.10 \pm .04) \times 10^{-6}$		
	HCOOH[a]	50.00	2.94	$(1.70 \pm .09) \times 10^{-6}$	22.0	−17.0
	HCOOH[a]	75.00	2.94	$(2.15 \pm .04) \times 10^{-5}$		
m-$CH_3OC_6H_4(CH_2)_4OBs$	HOAc	75.00	2.94	$(2.02 \pm .02) \times 10^{-6}$	24.5	−14.6
	HOAc	100.00	2.75	$(2.31 \pm .01) \times 10^{-5}$		
	HCOOH[a]	75.00	2.53	$(6.24 \pm .06) \times 10^{-5}$	22.4	−13.9
	HCOOH[a]	100.20	2.53	$(5.92 \pm .10) \times 10^{-4}$		
3,4-$(CH_3O)_2C_6H_3(CH_2)_4OBs$	HOAc	75.00	2.74	$(3.30 \pm .02) \times 10^{-6}$		
	HOAc	100.05	2.74	$(3.59 \pm .13) \times 10^{-5}$	23.9	−15.3
	HCOOH[b]	75.00	2.62	$(1.08 \pm .02) \times 10^{-4}$		
3,5-$(CH_3O)_2C_6H_3(CH_2)_4OBs$	HCOOH[a]	50.00	2.83	$(1.88 \pm .04) \times 10^{-5}$		
	HCOOH[a]	75.00	2.84	$(2.09 \pm .09) \times 10^{-4}$	20.9	−15.8
3,4-$(CH_3O)_2C_6H_3(CH_2)_3OBs$	HCOOH[a]	75.00	2.72	$(3.50 \pm .06) \times 10^{-5}$		

[a] 0.0315 M sodium formate. [b] 0.0302 M sodium formate. [c] 0.0291 M sodium formate.

Table II

Analysis of Solvolysis Rates of Some 4-Aryl-1-butyl p-Bromobenzenesulfonates at 75.00°

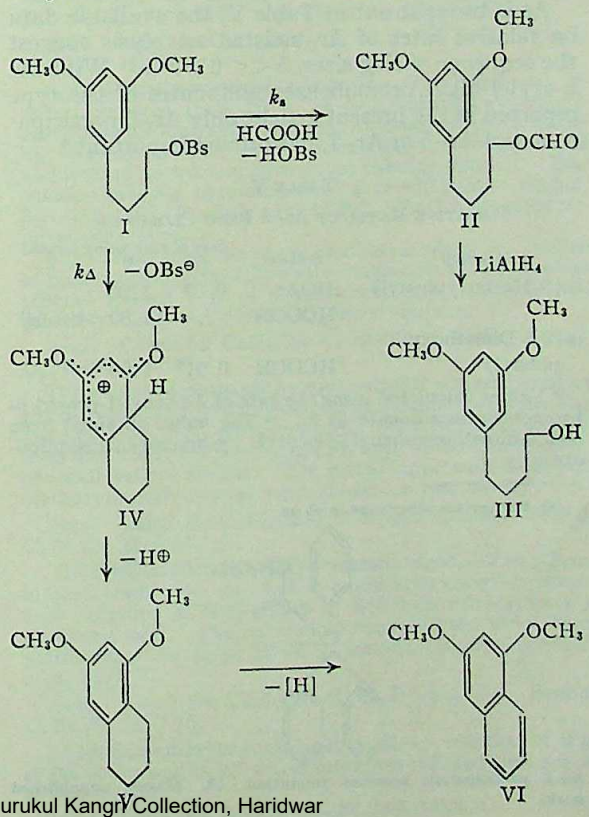
Compound	Rel. rates AcOH	Rel. rates HCOOH	AcOH 10^5k_s	AcOH 10^5k_Δ	AcOH k_Δ/k_s	HCOOH 10^5k_s	HCOOH 10^5k_Δ	HCOOH k_Δ/k_s	Rel. k_Δ HCOOH
$C_6H_5(CH_2)_4OBs$	1.00	1.00	1.37	0.08[a]	0.06	2.78	0.65[a]	0.23	1.00[a]
m-$CH_3OC_6H_4(CH_2)_4OBs$	1.39	1.86	1.37	0.65	0.47	2.78	3.46	1.24	5.32
3,4-$(CH_3O)_2C_6H_3(CH_2)_4OBs$	2.28	3.15	1.37	1.93	1.41	2.78	8.02	2.88	12.3
3,5-$(CH_3O)_2C_6H_3(CH_2)_4OBs$		6.24				2.78	18.1	6.51	27.9

[a] Not apportioned between Ar_1-5 and Ar_2-6.

Formation of Tetralin.—The products of formolysis of 4-(3,5-dimethoxyphenyl)-1-butyl p-bromobenzenesulfonate (I) were examined in the usual way.[3] Reduction of the crude formolysis products with lithium aluminum hydride and chromatography on alumina yielded a minor alcohol fraction and a major more easily eluted fraction. The alcohol yielded a p-nitrobenzoate which was shown by mixed melting point to be the p-nitrobenzoate of the parent alcohol, 4-(3,5-dimethoxyphenyl)-1-butanol (III).

The major fraction was a colorless liquid, inert to potassium permanganate in acetone. Dehydrogenation of this material with chloranil[7] produced 1,3-dimethoxynaphthalene (VI) which was characterized by mixed melting point of its picrate with the authentic material described previously.[3] Thus, the major solvolysis product was 5,7-dimethoxytetralin (V), the same substance obtained in formolysis of 4-(2,4-dimethoxyphenyl)-1-butyl p-bromobenzenesulfonate,[3] the isomer of I substituted so as to favor Ar_1-5 participation.

The products observed in formolysis of the 4-(3,5-dimethoxyphenyl)-1-butyl derivative I agree closely with those predicted on the basis of the k_s and k_Δ values in Table II, assuming k_s is associated with formation of formate II and k_Δ associated with formation of tetralin V. As is clear from Table III, the observed per cent. tetralin in the product agrees within experimental error with the value, 100 $k_\Delta/(k_\Delta + k_s)$, just as in the previous cases favoring Ar_1-participation.[3] The available facts, therefore, suggest that the formolysis of the 4-(3,5-dimethoxyphenyl)-1-butyl derivative I proceeds to the extent of 12% by the anchimerically unassisted process leading to formate II, and to the extent of 88% by anchimerically assisted ionization. Anchimerically assisted ionization must be very predominantly



(7) R. T. Arnold and C. J. Collins, This Journal, 61, 1407 (1939).

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Ar_2-6 in type, probably leading to an intermediate IV. Loss of a proton by IV leads to tetralin V.

TABLE III

PRODUCTS OF FORMOLYSIS OF 4-(3,5-DIMETHOXYPHENYL)-1-BUTYL *p*-BROMOBENZENESULFONATE AT 75°[a]

Total yield, %	% ROH	% Tetralin	$\frac{100\ k_\Delta}{k_\Delta + k_s}$
87.5	12.0	88.0	86.6

[a] 0.0454 *M* ROBs; 0.0515 *M* NaOCHO; 12 hours at 75.0°.

Ar_2-Participation and Ring Size. Comparison with Ar_1.—The tendency for Ar_2-7 participation in formolysis was assessed roughly by measuring relative rates of formolysis of 5-phenyl-1-pentyl and 5-(3,4-dimethoxyphenyl)-1-pentyl *p*-bromobenzenesulfonates. While the latter substance is substituted to favor both Ar_2-7 and Ar_1-6 participations, it was easily available, and its rate could be used to set an upper limit on the rate enhancement due to Ar_2-7-participation. As is brought out in Table IV, any increase in rate due to 3,4-dimethoxyl substitution in the 5-phenyl-1-pentyl system is small. Consequently, the k_Δ calculated on the assumption that k_s is equal to the rate constant of the 5-phenyl-1-pentyl ester is also small.

TABLE IV

ANALYSIS OF RATES OF FORMOLYSIS OF 5-ARYL-1-PENTYL *p*-BROMOBENZENESULFONATES AT 75°

Compound	Rel. rate	$10^5\ k_s$	$10^5\ k_\Delta$	k_Δ/k_s
$C_6H_5(CH_2)_5OBs$	1.00	3.39		
$3,4\text{-}(CH_3O)_2C_6H_3(CH_2)_5$-OBs	1.03	3.39	0.11	0.03

As is brought out in Table V, the available data on relative rates of Ar_2-assisted solvolysis suggest the sequence of ring sizes, $5 << 6 >> 7$. With the ω-aryl-1-alkyl bromobenzenesulfonates of the type reported in the present article, only Ar_2-6 participation, not Ar_2-5 or Ar_2-7, has proved important.[8]

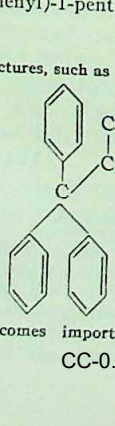
TABLE V

RELATIVE RATES OF Ar_2-*n* RING CLOSURES

Ar group	Solvent	Size of ring being formed 5	6	7
ω-(3-Methoxyphenyl)	HOAc	0.06[a]	1.00	
	HCOOH	..	1.00	<0.04[b]
ω-(3,5-Dimethoxyphenyl)	HCOOH	0.01[a]	1.00	

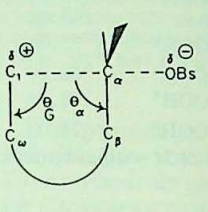
[a] Values calculated using the rate of 3-phenyl-1-propyl *p*-bromobenzenesulfonate as k_s. [b] The value obtained from 5-(3,4-dimethoxyphenyl)-1-pentyl *p*-bromobenzenesulfonate.

(8) For certain structures, such as

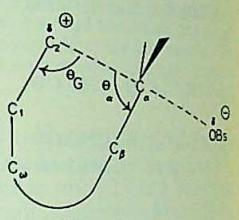


Ar_2-5 participation becomes important (P. Magee, unpublished work).

It is interesting that a maximum in rate is observed for $n = 6$ in the case of Ar_2-participation, whereas the rate sequence observed[3] for Ar_1 was $5 >> 6$. This contrast is relatively easy to understand by considering the transition states for the Ar_1- and Ar_2-assisted ionizations. These may be represented by VII and VIII, respectively, C_1 and C_2 denoting the respective carbon atoms of the neighboring phenyl group. The partial bonds between C_α and the leaving group, and between C_1 or C_2 and C_α in the transition state for the rate-determining step are symbolized by dotted lines. Also shown are the angles, θ_α and θ_G.



VII



VIII

In the transition states, the angle θ_α would have the value of 90° if the usual hybridization at C_α is assumed. In order to estimate θ_G, we should take into account the fact that the degree of involvement of the aryl group with C_α is quite small. For Ar_1, the low degree of involvement of aryl was clear from the relatively small effect of methoxyl substitution.[3] As is clear from Table II, methoxyl substitution has only a relatively small effect on rate in the case of Ar_2 also. This low degree of involvement of phenyl in the transition state suggests a value of θ_G close to 90°, the approach of C_α to C_1 or C_2 of the benzene ring being from a direction perpendicular to the plane of the benzene ring. Examination of models which employ a value of 90° for both θ_α and θ_G shows the transition state to be relatively strainless for Ar_1-5. However, it is quite strained in Ar_1-5, and becomes relatively comfortable when ring size is increased to Ar_2-6.

Comparing rates of Ar_1- and Ar_2-assisted solvolysis, the available data show that rates are comparable for Ar_1-5 and Ar_2-6 for equal degrees of activation of the benzene ring with methoxyl groups. This comparison is shown explicitly in Table VI.

TABLE VI

COMPARISON OF Ar_1-5 AND Ar_2-6 RING CLOSURES AT 75°

Compound	Main participation type	$10^5\ k_\Delta$ (sec.$^{-1}$) AcOH	HCOOH
$m\text{-}(CH_3O)C_6H_4(CH_2)_4OBs$	Ar_2-6	0.65	34.6
$p\text{-}CH_3OC_6H_4(CH_2)_4OBs$	Ar_1-5	0.53	33.0
$3,5\text{-}(CH_3O)_2C_6H_3(CH_2)_4$-OBs	Ar_2-6	..	181
$2,4\text{-}(CH_3O)_2C_6H_3(CH_2)_4$-OBs	Ar_1-5	4.89	312

From this table it is evident that Ar_1-5 is slightly slower than Ar_2-6 in the case of mono-methoxyl-substituted neighboring phenyl. On the other hand, Ar_1-5 is faster than Ar_2-6 for di-methoxyl-substituted neighboring phenyl. An amusing consequence of this is that the rate of formation of the tetralin V is smaller by the more direct Ar_2-6 route than it is by the less direct Ar_1-5 route from

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4-(2,4-dimethoxyphenyl)-1-butyl *p*-bromobenzenesulfonate.[3]

Since a maximum in rate occurs at the 5-ring for Ar$_1$- and the 6-ring for Ar$_2$-participation, and since Ar$_1$-5-assisted ionization results in final formation of a six-membered ring, the present results help one understand the pronounced tendency toward closure of 6- rather than 5-membered rings in cyclodehydrations and related reactions.[9] For neighboring vinyl rather than aryl, closure of 6-rings is similarly favored.[10]

An interesting compound, not yet commented on, whose solvolysis rate was investigated, is 4-(3,4-dimethoxyphenyl)-1-butyl *p*-bromobenzenesulfonate. This material is substituted so as to favor both Ar$_1$-5 and Ar$_2$-6 participation. If both Ar$_1$-5 and Ar$_2$-6 participations were completely independent of each other, and if a second methoxyl (*meta* to the substitution spot) had no significant effect on rate, one could expect k_Δ for the 3,4-dimethoxyl case to equal approximately the sum of the k_Δ values for the 4-methoxyl and 3-methoxyl cases. Actually, k_Δ for the 3,4-dimethoxyl case exceeds the calculated value. For example, in formic acid, k_Δ is 8.02×10^{-5} sec.$^{-1}$, as shown in Table II, while the calculated sum of the separate k_Δ values is 6.76×10^{-5} sec.$^{-1}$. The lack of agreement could conceivably be due to a rate-enhancing effect of a *meta* methoxyl group on either Ar$_1$-5 or Ar$_2$-6 or both. Such an effect is observed in bromination of the benzene ring.[11] However, it is doubtful that the Ar$_1$-5 and Ar$_2$-6 participation reactions in hand are sufficiently electron-demanding to bring forth a rate-enhancing response from a *meta* methoxyl group. For example, in Ar$_1$-3 participation, which is even more electron-demanding than the present examples of Ar$_1$-5 and Ar$_2$-6, a *meta* methoxyl is rate-retarding.[5]

It seems possible that Ar$_1$-5 and Ar$_2$-6 participations are not completely distinct in cases such as the 4-(3,4-dimethoxyphenyl)-1-butyl derivative. Whether C_α is lodging onto C_1 or C_2 of the benzene ring, it seems likely that, in the transition state, there is some bonding interaction between C_α and C_2 in the case of Ar$_1$-5 and between C_α and C_1 in the case of Ar$_2$-6.

Experimental Part

3-*m*-Anisyl-1-propanol.—The reduction of *m*-methoxycinnamic acid[12] with lithium aluminum hydride by the usual method gave 3-*m*-anisyl-1-propanol, b.p. 135–140° (3.5 mm.), n^{25}D 1.5339, in 57.5% yield.

3-(3,5-Dimethoxyphenyl)-propanoic Acid.—To a solution of 3.6 g. of sodium metal in 200 ml. of anhydrous ethanol was added 39 g. of ethyl malonate, followed by 20 g. of 3,5-dimethoxybenzyl chloride.[13] After the mixture was refluxed overnight, most of the alcohol was distilled off, and the residue was mixed with cold dil. hydrochloric acid. The product was extracted with ether. The extract was washed with water, and the solvent was evaporated. The residue was refluxed for 4 hours with 25 g. of sodium hydroxide in 100 ml. of water and 50 ml. of ethanol. About 100 cc. of the solvent was distilled, and water was added to the residue. A trace of oil was extracted with ether and the aqueous solution was acidified. The crude malonic acid was heated to 150° until carbon dioxide evolution ceased, and then the product was distilled *in vacuo*. The acid, b.p. 177–178° (3 mm.), crystallized on standing. Recrystallization from a mixture of ether and petroleum ether gave 15.5 g. of material, m.p. 59–61° (reported[14] 61–62°).

3-(3,5-Dimethoxyphenyl)-1-propanol.—The reduction of 3-(3,5-dimethoxyphenyl)-propanoic acid with lithium aluminum hydride gave the desired alcohol, b.p. 145–150° (3 mm.), n^{25}D 1.5332, in 63% yield; the remainder of the unreacted acid was recovered.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.83; H, 8.18.

The *p*-bromobenzenesulfonate of this alcohol was obtained as a viscous liquid, n^{25}D 1.5689, 93.3% pure as determined by equivalent weight measurements in acetic and formic acid, by the low temperature procedure previously described.[5]

4-*m*-Anisyl-1-butanol.—This alcohol, b.p. 112° (0.5 mm.), n^{25}D 1.5260, was prepared in poor yield by the action of the Grignard reagent from 3-*m*-anisylpropyl chloride, n^{25}D 1.5287, on formaldehyde.

4-(3,4-Dimethoxyphenyl)-butanoic Acid.—The Clemmensen reduction of 3-(3,4-dimethoxybenzoyl)-propanoic acid[4] gave 4-(3,4-dimethoxyphenyl)-butanoic acid, m.p. 56–58° after crystallization from a mixture of ether and pentane.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.15; H, 6.99.

4-(3,4-Dimethoxyphenyl)-1-butanol.—The reduction of the above acid with lithium aluminum hydride gave impure 4-(3,4-dimethoxyphenyl)-1-butanol, b.p. 155–157° (3 mm.), n^{25}D 1.5343, in 30% yield. The remainder of the material was unreacted acid.

2-(3,5-Dimethoxyphenyl)-ethyl Bromide.—A solution of 50 g. of lithium bromide and 35 g. of 2-(3,5-dimethoxyphenyl)-ethyl *p*-bromobenzenesulfonate[5] in 500 cc. of pure acetone was refluxed for one hour. The acetone was distilled off, the residue was dissolved in water, and the bromide was extracted with ether. The extracts were washed with water, dried and distilled. The bromide, b.p. 125–128° (1.5 mm.), n^{25}D 1.5573, m.p. 24–26°, weighed 20.5 g.

Anal. Calcd. for $C_{10}H_{13}O_2Br$: C, 49.00; H, 5.34. Found: C, 49.03; H, 5.39.

4-(3,5-Dimethoxyphenyl)-1-butanol.—To a Grignard reagent prepared from 20 g. of 2-(3,5-dimethoxyphenyl)-ethyl bromide under dry nitrogen, an excess of ethylene oxide was added. The solution was refluxed for three hours and worked up with an ammonium chloride solution. Distillation gave 8 g. of forerun and 7 g. of still impure alcohol, b.p. 162–168° (2 mm.), n^{25}D 1.5297, n^{25}D 1.5290 after another distillation.

The residue from the above distillation could be distilled at high temperatures. Two recrystallizations from absolute ethanol yielded 2 g. of a substance, m.p. 100.5–101.5°, probably 1,4-di-(3,5-dimethoxyphenyl)-butane.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.43; H, 7.63.

The *p*-nitrobenzoate of the above alcohol was prepared by the conventional pyridine method and chromatographed on alumina with 50% ether–pentane. Two recrystallizations from methanol gave the compound, m.p. 65–66°, in the form of small yellow needles. The mixed m.p. with 4-(2,4-dimethoxyphenyl)-1-butyl *p*-nitrobenzoate was 44–51°.

Anal. Calcd. for $C_{19}H_{21}O_6N$: C, 63.50; H, 5.89. Found: C, 63.65; H, 5.57.

5-(3,4-Dimethoxyphenyl)-pentanoic Acid.—The Clemmensen reduction of 4-(3,4-dimethoxybenzoyl)-butanoic acid[6] afforded a 50% yield of 5-(3,4-dimethoxyphenyl)-pentanoic acid. The substance, recrystallized twice from petroleum ether (b.p. 60–80°), formed colorless crystals, m.p. 75–76°.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.79; H, 7.75.

5-(3,4-Dimethoxyphenyl)-1-pentanol.—A solution of 8 g. of the above acid in 400 ml. of ether was refluxed with 3 g. of

(9) E.g., (a) R. O. Roblin, Jr., D. Davidson and M. T. Bogert, THIS JOURNAL, **57**, 151 (1935); (b) M. T. Bogert, Jr. and D. Davidson, *ibid.*, **56**, 185 (1934); (c) J. v. Braun and K. Weissbach, *Ber.*, **64**, 1755 (1931).

(10) E.g., (a) R. P. Linstead, A. B. Wang, J. H. Williams and K. P. Errington, *J. Chem. Soc.*, 1136 (1937); (b) R. P. Linstead, A. H. Millidge and A. L. Walpole, *ibid.*, 1140 (1937).

(11) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 1764 (1951).

(12) S. N. Chakravarti, R. D. Haworth and W. H. Perkin, *ibid.*, 2269 (1927).

(13) R. Adams, S. MacKenzie, Jr., and S. Loewe, THIS JOURNAL, **70**, 666 (1948).

(14) A. H. Salway, *J. Chem. Soc.*, **97**, 2412 (1910).

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TABLE VII

PROPERTIES AND ANALYSES OF SOME *p*-BROMOBENZENESULFONATES

Compound	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
m-$CH_3OC_6H_4(CH_2)_3OBs$	36–38	$C_{16}H_{17}O_4SBr$	49.88	49.72	4.44	4.27
m-$CH_3OC_6H_4(CH_2)_4OBs$	36–38	$C_{17}H_{19}O_4SBr$	51.13	51.08	4.80	4.75
3,4-$(CH_3O)_2C_6H_3(CH_2)_4OBs$	68–71	$C_{18}H_{21}O_5SBr$	50.35	50.65	4.93	4.80
3,5-$(CH_3O)_2C_6H_3(CH_2)_4OBs$	56–57	$C_{18}H_{21}O_5SBr$	50.35	50.20	4.93	4.83
3,4-$(CH_3O)_2C_6H_3(CH_2)_5OBs$	73–73.5	$C_{19}H_{23}O_5SBr$	51.47	51.19	5.23	4.99

lithium aluminum hydride for 12 hours. The alcohol, b.p. 160–163° (2 mm.), $n^{25}D$ 1.5278, was a viscous colorless liquid weighing 5 g. A small sample was redistilled for analysis; $n^{25}D$ 1.5272.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.87; H, 8.78.

2-(3,4-Dimethoxyphenyl)-ethanol.—The reduction of 3,4-dimethoxyphenylacetic acid with lithium aluminum hydride by the usual method afforded a 37% yield of alcohol, b.p. 140–143° (3 mm.), m.p. 43–45°.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.75. Found: C, 65.86; H, 7.75.

Preparation of Bromobenzenesulfonates and Kinetic Measurements.—The *p*-bromobenzenesulfonates of the various alcohols were prepared by the low temperature method described previously.[5] Physical properties and analyses of these derivatives are summarized in Table VII.

Kinetic measurements were carried out as described previously.[5]

Formolysis Products of 4-(3,5-Dimethoxyphenyl)-1-butyl *p*-Bromobenzenesulfonate.—A solution of 1.95 g. of the *p*-bromobenzenesulfonate was solvolyzed for ten hours at 75° in a solution of 0.35 g. of sodium formate in 100 ml. of anhydrous formic acid. The resulting solution was diluted with 700 ml. of water and extracted with 500 ml. of petroleum ether in three portions. The extracts were washed with water and a sodium bicarbonate solution. The solvent was carefully distilled off, and the residue was reduced with 2 g. of lithium aluminum hydride.

The reduced product was chromatographed on 50 g. of alumina. The first fraction was eluted with 500 ml. of pentane. This solution contained 0.67 g. of 5,7-dimethoxytetralin, b.p. 100° (1.55 mm.), $n^{25}D$ 1.5452. This material was dehydrogenated with 2 g. of chloranil in boiling xylene as described previously.[3,7] The 1,3-dimethoxynaphthalene formed gave 0.35 g. of pure picrate, m.p. 140–141°, mixed m.p. with the picrate obtained from the corresponding solvolysis product from 4-(2,4-dimethoxyphenyl)-1-butyl *p*-bromobenzenesulfonate,[3] 140–141°.

A second fraction from the chromatography was eluted with 700 ml. of ether. There was obtained from this fraction 0.10 g. of alcohol, $n^{25}D$ 1.5310, which formed 0.11 g. of a nitrobenzoate, m.p. 64.5–66°, mixed m.p. with 4-(3,5-dimethoxyphenyl)-1-butyl nitrobenzoate, 65–66°.

LOS ANGELES 24, CALIFORNIA

[CONTRIBUTION FROM THE INSTITUTE OF SCIENTIFIC AND INDUSTRIAL RESEARCH, OSAKA UNIVERSITY]

Reactivities of Several ω-Substituted Primary Alkyl Bromides with Tertiary Amines[1,2]

BY KATSUHIKO AKAGI, SHIGERU OAE[3,4] AND MASUO MURAKAMI

RECEIVED AUGUST 29, 1956

Rate constants, heats of activation and entropies of activation have been determined for a series of reactions between ω-substituted primary alkyl bromides and tertiary amines in two different solvents, *i.e.*, nitrobenzene and 50% ethanol. Alternation of reactivities was observed when nitrobenzene was used as a solvent, but no such phenomenon was observed when the solvent was 50% ethanol. The phenyl group showed little polar influence on the reactivities.

Our previous investigations[5] have been extended to the quaternization reactions of ω-substituted primary alkyl bromides with tertiary amines in two different solvents, *i.e.*, nitrobenzene and 50% ethanol, with the thought that these quaternization reactions might give a different trend from those of the reactions of the same bromides with thiosulfate ion, since it has been suggested[6] that the polar characteristic of the quaternization reaction is quite different.

Many studies of the quaternization reaction of alkyl halides with tertiary amines have been reported and our present experiments were carried out following the typical procedure used by Laidler and Hinshelwood[7] and later by Brown and Eldred.[8]

Experimental

The methods of preparations and purifications of all the organic halides have been described elsewhere.[5] The nitrobenzene was purified by partially freezing the fractionated material, which melted around 5.0–5.7°. The portions which melted from 5.5–5.7° were collected for use. Ethanol 50%, was made as reported in the previous paper.[5]

Investigation of Products.—It is known that primary alkyl halides gives quaternary ammonium salts in quantitative yield[9] and also that β-haloalkyl alcohols give quaternary ammonium chlorides in the reaction with trimethylamine.[10] No report has indicated any formation of olefin in the reaction of primary halide with tertiary amine.

In this study, the reaction products were investigated only in the case of β-bromoethyl ether in both 50% ethanol and in nitrobenzene, because among those studied kinetically this compound would be the most likely to give elimination products. The mixture of 1.53 g. of β-bromoethyl ethyl ether and 1.01 g. of triethylamine was placed in a 25-ml.

(1) Paper VI on "Relative Reactivities of Organic Halides in Displacement Reactions," Paper V, THIS JOURNAL, **78**, 4034 (1956).

(2) Presented at the 9th General Meeting of the Japanese Chemical Society, Kyoto, April, 1956.

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(4) To whom requests for reprint may be addressed.

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(7) K. J. Laidler and C. N. Hinshelwood, *J. Chem. Soc.*, 858 (1938).

(8) H. C. Brown and N. R. Eldred, THIS JOURNAL, **71**, 445 (1949).

(9) O. Westphal and H. Jeschel, *Ber.*, **73B**, 1002 (1940).

(10) J. W. LeHeus, *Arch. Pharm.*, **262**, 570 (1924).

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ampoule and was diluted either by 15 ml. of 50% ethanol or by 15 ml. of nitrobenzene and sealed. The sealed ampoules were heated at 80° for 144 hr. continuously to complete the reactions. Then the tubes were broken and the solvents were distilled very carefully in order to collect vinyl ethyl ether, but no trace of vinyl ethyl ether was obtained. Then the solvents were removed to complete dryness *in vacuo*, and from the 50% alcohol solution 2.45 g. of colorless crystalline solid (m.p. 87–90°) and from the nitrobenzene solution 2.48 g. of pale brown crystalline solid (m.p. 90–93°) were obtained in yields of 96.5 and 97.6%, respectively. After recrystallization from either ethanol–petroleum ether mixture or acetone–petroleum ether mixture the m.p. was 97–98°.

Anal. Calcd. for $C_{10}H_{24}ONBr$: Br, 31.5. Found: Br, 31.3.

Kinetic Studies.—Kinetic measurements and rate calculations were made by the procedure used by previous workers.[7,8] In this case, however, reaction was carried out in sealed tubes. Usually the concentration of the stock solutions was 0.20 *N*, so that on mixing equal volumes of the stock solutions the concentration would be 0.10 *N* with respect to both amine and alkyl bromide. After mixing, each 5-ml. of the well-cooled mixed sample was pipeted into a 10-ml. ampoule and sealed. The first tube was taken out for the initial concentration 15 minutes after all the sealed tubes were immersed in a well-controlled thermostat. At suitable time intervals, ampoules were taken out and placed in an ice–water mixture. Each ampoule was broken in standard 0.025 *N* hydrochloric acid and the excess acid was back-titrated with 0.025 *N* barium hydroxide using methyl red as the indicator. Calibration was made at each temperature in order to avoid large errors due to the expansion of the solutions at different temperatures. The rate constants were calculated using the second-order rate equation. Typical runs are given in Tables I, II and III.

Table I

Reaction Rate Data for Triethylamine and ω-Bromopropylbenzene in Nitrobenzene at 80.0°

Time, sec.	$(a - x) \times 10^{-2}$, mole/l.	$10^4 k$, l. mole^{-1} sec.$^{-1}$
0	9.3805	
5460	8.7755	1.30
5460	8.6814	1.36
8820	8.3985	1.30
11640	8.1149	1.35
14940	7.8533	1.34
18540	7.6026	1.35
22020	7.3655	1.35
24600	7.1327	1.36
	Mean	1.34 ± 0.02

Table II

Reaction Rate Data for Triethylamine and γ-Bromopropyl Ethyl Ether in Nitrobenzene at 104.8°

Time, sec.	$(a - x) \times 10^{-2}$, mole/l.	$10^4 k$, l. mole^{-1} sec.$^{-1}$
0	9.1033	
2370	7.8657	7.23
5040	6.8305	7.25
2440	6.1084	7.24
9840	5.5236	7.24
12180	5.0540	7.23
	Mean	7.24 ± 0.01

Table III

Reaction Rate Data for Trimethylamine and β-Bromoethyl Ethyl Ether in 50% Ethanol at 49.8°

Time, sec.	$(a - x) \times 10^{-2}$, mole/l.	$10^4 k_2$, l. mole^{-1} sec.$^{-1}$
0	9.0316	
2400	8.2058	
4200	7.6837	4.65
5880	7.2542	4.63
7560	6.8666	4.61
9960	6.3825	4.62
11400	6.1068	4.62
13200	5.8190	4.65
	Mean	4.63 ± 0.01

Results and Discussion

The rate-constants, calculated as described, together with the heats of activation, $\Delta H^{\ddagger}$, and entropies of activation, $\Delta S^{\ddagger}$, for the reactions studied are listed in Tables IV, V and VI. The individual points used to calculate the rate constants result in an average deviation of approximately 1% or less throughout the experiments.

Table IV

Rate Constants for the Reaction of ω-Substituted Primary Alkyl Bromides with Triethylamine in Nitrobenzene

Benzene	$10^3 k_2$, l. mole^{-1} sec.$^{-1}$ 60.0°	70.0°	80.0°	$\Delta H^{\ddagger}$ at 70°, kcal./mole	$\Delta S^{\ddagger}$ at 70°, e.u.
β-Bromoethyl-	0.0532	0.106	0.185	13.9	−36.6
γ-Bromopropyl-	.0400	.0748	.134	13.4	−38.6
δ-Bromobutyl-	.0438	.0836	.149	13.6	−37.8

Ethyl ether	$10^3 k_2$, l. mole^{-1} sec.$^{-1}$ 75.3°	90.3°	104.8°	$\Delta H^{\ddagger}$ at 90.3°, kcal./mole	$\Delta S^{\ddagger}$ at 90.3°, e.u.
β-Bromoethyl-	0.0628	0.145	0.322	13.6	−37.1
γ-Bromopropyl-	.156	.352	.724	13.0	−36.9
δ-Bromobutyl-	.134	.302	.633	13.0	−37.4

Table V

Rate Constants for the Reaction of ω-Bromoalkyl Ethyl Ether with Trimethylamine in Nitrobenzene

Ethyl ether	$10^3 k_2$, l. mole^{-1} sec.$^{-1}$ 24.9°	37.3°	49.8°	$\Delta H^{\ddagger}$ at 37.3°, kcal./mole	$\Delta S^{\ddagger}$ at 37.3°, e.u.
β-Bromoethyl-	0.110	0.255	0.570	12.0	−34.3
γ-Bromopropyl-	.422	.926	1.97	11.8	−34.4
δ-Bromobutyl-	.405	.856	1.73	10.5	−36.8

Table VI

Rate Constants for the Reaction of ω-Bromoalkyl Ethyl Ether with Trimethylamine in 50% Ethanol

Ethyl ether	$10^3 k_2$, l. mole^{-1} sec.$^{-1}$ 24.9°	37.3°	49.8°	$\Delta H^{\ddagger}$ at 37.8°, kcal./mole	$\Delta S^{\ddagger}$ at 37.3°, e.u.
β-Bromoethyl	0.0415	0.148	0.463	17.9	−16.6
γ-Bromopropyl	.116	.401	1.22	17.4	−16.1
δ-Bromobutyl	.316	1.01	3.19	16.9	−15.7

When nitrobenzene was used as the solvent, alternation of reactivities was observed with the increase of methylene linkage in the reaction of these ω-substituted primary alkyl bromides with both triethylamine and trimethylamine. With ω-phenyl-substituted primary alkyl bromides the phenyl group showed little polar influence on reactivities and the reactivities were affected only by the change in the entropy changes. It is particularly interesting that even in the reaction of ω-ethoxy-substituted alkyl bromides with triethylamine, the changes in the heat of activation were found to be rather small compared to that in the reaction with thiosulfate ion.[5] This seems to indicate that the transition stage is nearer to the ideal symmetrical transition step, where the bond-fission requirements are equal to bond-forming requirements,[11]

(11) Probably such a reaction as those between alkyl halides and the same halide ion would pass through such a symmetrical transition stage.

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when the concept of Hammond[12] on the transition state is applied in our case. Thus, the bond-fission requirements in this case are less than those in the case of the reaction with thiosulfate ion. But in the reactions of ω-ethoxy-substituted alkyl bromides, the heat of activation decreased with the increase of the connecting methylene group as in the previous reactions with thiosulfate ion, although alternation of rates was observed in this case. The relatively small values of the heat of activations in spite of rather lower rates of reaction would probably be due to large contribution of solvation in the transition states. Solvation seems also to be responsible for the relatively large values of activation entropies.

However, in 50% ethanol solution, the rate sequence and other kinetic values of ω-ethoxyalkyl bromides were quite different from those in nitrobenzene. No alternation of rates was observed; instead, reactivity increased while heat of activation decreased with the increase of connecting methylene group between ethoxy group and halogen, as in the previous reactions with thiosulfate ion. It is known that in quaternization reactions both the heat and entropy of activation varies a great deal depending upon the solvent used.[13]

(12) G. S. Hammond, THIS JOURNAL, **77**, 334 (1955).

(13) J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, 519, 1840 (1935).

For example, in the reaction of *p*-methylbenzyl bromide with pyridine the heat and entropy of activation in absolute acetone were 11.3 kcal. and −37.15 e.u., while those values in 90% ethanol were 15.4 kcal. and −22.5 e.u., respectively. Here also we found large differences of temperature coefficient values in two different solvents, *i.e.*, nitrobenzene and 50% ethanol. The differences in solvating power and in nature of solvation would be the responsible factor for these large changes from one solvent to another.[14]

Acknowledgment.—We wish to express our sincere thanks to the Ministry of Education for a Grant as well as the Grant-in-Aid for the Scientific Research and particularly to the Society of the Sigma Xi for the Grant-in-Aid which enabled us to purchase some chemicals from the United States. Our thanks are due both to Mr. Takuzo Fujino who kindly calibrated all our measuring apparatus and to Mr. Tsunehei Oki who carried out a part of the kinetic measurements.

(14) Both nitrobenzene and acetone have a rather highly negatively polarized oxygen atom in carbonyl and nitro group, which would easily solvate with positively charged quaternary nitrogen at the transition state, thus probably lowering the heat of activation; this strong solvation would also give relatively large negative values of entropy of activation. However, the oxygen atom in water or alcohol would not play such a large role.

OSAKA, JAPAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Ozonolyses of 1,2-Dibenzoylpropene and 1,2-Dibenzoylethylene. Markownikoff's Rule and the Initial Attack of Ozone on an Unsaturated System[1]

BY PHILIP S. BAILEY AND SHEAFFERS S. BATH

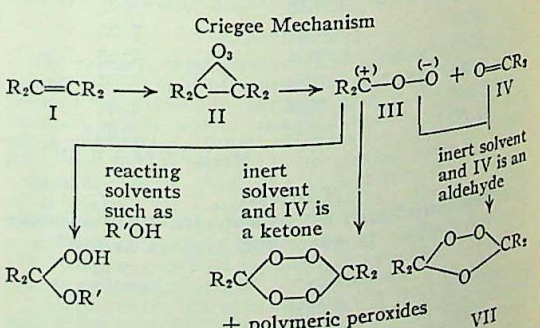
RECEIVED DECEMBER 8, 1956

The ozonolysis of 1,2-dibenzoylpropene in methanol furnishes direct evidence for the specificity previously noted in the attack of ozone on unsymmetrical olefins. The products were phenylglyoxal and α-hydroperoxy-α-methoxypropiophenone. The results are correlated with Markownikoff's rule and a mechanism is proposed which rationalizes the known facts concerning the initial attack of ozone on an unsaturated system. Decompositions of α-hydroperoxy-α-methoxypropiophenone and the corresponding hydroperoxide from the ozonolysis of 1,2-dibenzoylethylene in methanol are described.

The Criegee[2] mechanism for ozonolysis has been of tremendous importance in giving a better understanding of the course of the ozonolysis reaction, in particular, the character and fate of the most important intermediate in the reaction, the zwitterion III. It leaves in doubt, however, the nature of the initial attack of ozone on an unsaturated system and of the intermediates leading to the formation of the zwitterion III and the aldehyde or ketone IV.

Recent studies have shown that ozone, like hydrogen chloride and other unsymmetrical reagents, attacks unsymmetrical olefins in a specific manner.[3] This observation furnishes an important clue to the nature of the initial ozone attack.

Criegee Mechanism



The earlier examples of this specificity of ozone attack include isobutene (VIII), which produced an ozonide (XI) as the major product when ozonized in inert solvents, and camphene (XIV) which gave rearrangement products of zwitterion XV.[2c,3] This is, in the case of isobutene, that preferential

(1) A portion of this paper was presented at the International Ozone Conference, Chicago, Ill., November 28–30, 1956.

(2) (a) R. Criegee and G. Wenner, *Ann.*, **564**, 9 (1949); (b) R. Criegee and G. Lohaus, *ibid.*, **583**, 6 (1953); (c) R. Criegee, G. Blust and H. Zinke, *Chem. Ber.*, **87**, 766 (1954); (d) R. Criegee, A. Kerckow and H. Zinke, *ibid.*, **88**, 1878 (1955).

(3) P. S. Bailey, *ibid.*, **88**, 795 (1955).

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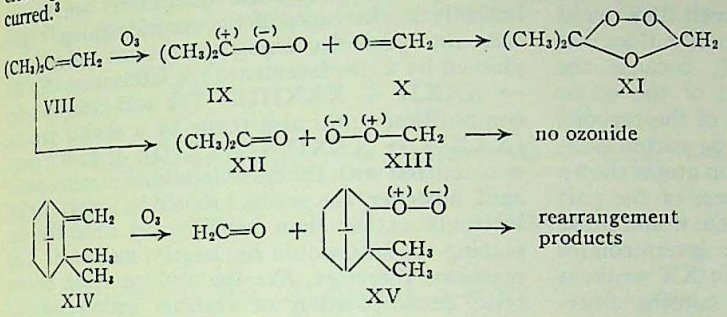
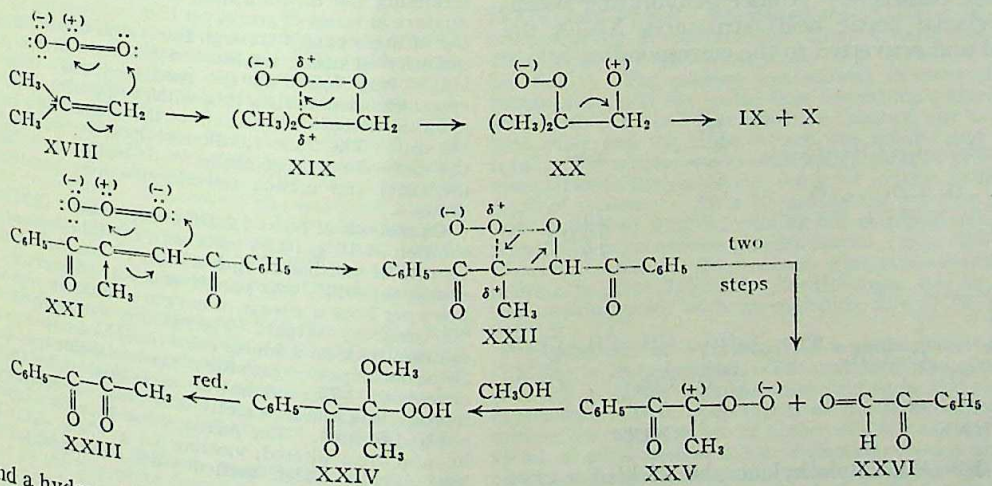
cleavage of the double bond occurred to give zwitterion IX and formaldehyde, rather than zwitterion XIII and acetone.[3] This reasoning is based on Criegee's[2] finding that ozonides cannot be produced by interaction of a zwitterion and a simple ketone. In the case of camphene, preferential cleavage to zwitterion XV and formaldehyde occurred.[3]



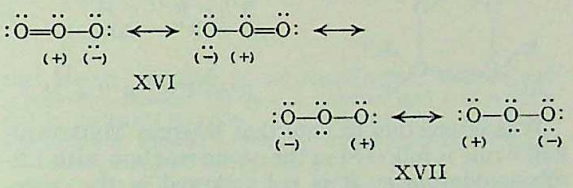
In the cases just discussed the evidence for the specificity of ozone attack was of an indirect nature. It would be much more conclusive if one could actually trap and identify the zwitterion preferentially formed. This has been done in the ozonolysis of *trans*-1,2-dibenzoylpropene (XXI) in methanol solution. The products were phenylglyoxal (XXVI) in 61% yield and α-hydroperoxy-α-methoxypropiophenone (XXIV) in 74% yield. The actual yields probably were much higher; both substances are difficult to isolate. The evidence for the structure assigned to XXIV, besides elemental analyses and the molecular weight determination, was the methoxyl group analysis, a positive lead tetraacetate test for a hydroperoxide,[4] the infrared spectrum which showed a strong carbonyl band at 5.9 μ and a hydroxyl band at 2.9 μ and reduction to 1-phenyl-1,2-propanedione (XXIII) in good yield. This reaction leaves no doubt concerning the specificity of ozone attack to produce preferentially phenyl glyoxal (XXVI) and zwitterion XXV, which was trapped through its reaction with methanol to give XXIV.



At first sight, as pointed out in the cases of isobutene and camphene,[3] these results seem to be in conflict with Markownikoff's rule, based on the usually assumed[5] electrophilic attack of the central carbon atom of the ozone molecule.

Meinwald[6] has pointed out, however, that the central oxygen atom of the ozone molecule cannot be electrophilic, since it has, in all of the structures (XVI and XVII) which make any appreciable contibution to the ozone molecule hybrid, its full quota of eight electrons. The electrophilic center in the ozone molecule, therefore, has to be a terminal atom as shown in contributing structures XVII.

On the basis of an initial terminal oxygen atom electrophilic attack and the assumption that the central oxygen atom completes the attack, the experimental results described can be correlated with Markownikoff's rule, as illustrated in the cases of isobutene (XVIII) and 1,2-dibenzoylpropene (XXI).



The experimental results also can be explained on the basis that the second step in the ozone attack involves the other terminal atom rather than the central atom, to give intermediates of type XXVII. Although these tructures could break down in two ways, it can be argued that they would break down preferentially to give zwitterions IX and XXV, because these zwitterions should be more stable than the other two possibilities through hyperconjugation with the methyl groups.

The intermediates with the four-membered ring

(5) (a) J. P. Wibaut, F. L. J. Sixma, L. W. F. Kampschmidt and H. Boer, *Rec. trav. chim.*, **69**, 1355 (1950); (b) F. L. J. Sixma, H. Boer and J. P. Wibaut, *ibid.*, **70**, 1005 (1951); (c) J. P. Wibaut and F. L. J. Sixma, *ibid.*, **71**, 761 (1952); (d) L. W. F. Kampschmidt and J. P. Wibaut, *ibid.*, **73**, 431 (1954).

(6) J. Meinwald, *Chem. & Ind. (London)*, 1889 (1955).

(4) R. Criegee, H. Pilz and H. Flygare, *Ber.*, **72**, 1799 (1939).

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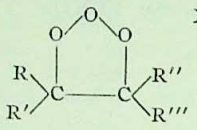
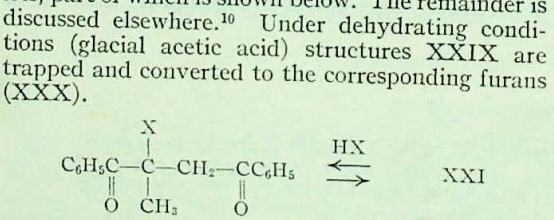
(XIX and XXII) are preferred by the present author for two reasons. First, they can break down in only one way, and this gives the required zwitterions (IX and XXV) and aldehydes (X and XXVI). Second, they explain better the easy cleavage of the double bond under the extremely mild conditions of the ozonolysis reaction. These structures (XIX and XXII) are formulated as activated complexes rather than real intermediates. As such they might be expected to be formed more readily than the more stable intermediates XXVII, because the length of the oxygen–oxygen bond of the ozone molecule is almost the same as that of the carbon–carbon double bond.[7] There would be partial positive charges on the oxygen and carbon atoms shown in structures XIX and XXII because of the partially formed and broken bonds. These would cause the election shift shown to produce intermediates such as XX. The positive charge in XX weakens the remaining carbon–carbon bond causing cleavage to IX and X and to XXV and XXVI.



XXVIIa, R = R′ = CH_3; R″ = R‴ = H

b, R = R″ = C_6H_5—C(=O)—; R′ = CH_3; R‴ = H

It is interesting to note that whereas Markownikoff's rule is followed in the ozone reaction with 1,2-dibenzoylpropene, it is not followed in the corresponding additions of hydrogen chloride and hydrogen bromide. Instead, in acetic acid solution the products are 3-chloro(or bromo)-4-methyl-2,5-diphenylfuran (XXX).[8–10] The reason for this appears to be that a complicated set of equilibria exists, part of which is shown below. The remainder is discussed elsewhere.[10] Under dehydrating conditions (glacial acetic acid) structures XXIX are trapped and converted to the corresponding furans (XXX).



XXVIII ⇌ XXI (HX)

XXVIII ⇅ HX ⟵ XXIX

X = Cl or Br

XXX

XXIX

trans-1,2-Dibenzoylethylene also yielded a crystalline methoxyhydroperoxide (XXXIa) upon ozonolysis in the presence of methanol. When this hydroperoxide and the one (XXXIb) from the ozonolysis of 1,2-dibenzoylpropene were heated in methanol or were treated with formic acid, sodium hydroxide or pyridine, decomposition occurred to give benzoic acid as the major product. In several instances spontaneous decompositions occurred when the ozonolysis reaction mixtures were evaporated to dryness before isolation of the hydroperoxides or when the impure hydroperoxides were allowed to stand. The pure crystalline hydroperoxides were stable at room temperature.

These decompositions to benzoic acid (and presumably methyl formate or acetate) are typical heterolytic cleavages of the peroxide group.[11] The base-catalyzed decomposition is most logically explained by a displacement type mechanism (XXXI → XXXII + XXXIII). The acid-catalyzed decomposition could also occur by a similar process (XXXIV → XXXII + XXXIII). If such a process occurred with the decompositions in warm methanol, however, the product should be largely methyl benzoate rather than benzoic acid since the displacing reagent would be, largely, methanol. This reaction, therefore, like the acid-catalyzed heterolytic decomposition of cumene hydroperoxide,[12] is best explained by a concerted rearrangement (XXXV → XXXVI → XXXII + XXXIII). This, of course, could also be the case with the acid-catalyzed decomposition. A similar rearrangement was found to occur during the ozonolysis of camphene in methanol.[3]

In two experiments small quantities of benzil were isolated. Products of this sort are typical of a competing homolytic cleavage of the peroxide group, involving changes such as shown in XXXV → XXXVII → XXXIX.

Experimental[13]

The ozonator used in this research was a Welsbach Corporation model T-23 laboratory apparatus. Oxygen dried to a dew-point of at least −60° was employed. The calculation of the quantity of ozone absorbed was done by determining the concentration of ozone in the oxygen–ozone mixture in terms of grams per liter, multiplying by the number of liters passed through the system and subtracting the quantity of ozone unabsorbed as shown in the potassium iodide trap following the reaction vessel. The reaction vessel was essentially a tube with the gas inlet at the bottom, a seal-in fritted disk just above the inlet and the outlet near the top. The *trans*-1,2-dibenzoylpropene was prepared by the method reported earlier.[14] It melted at 51–53°. The methanol and carbon tetrachloride were pure and anhydrous.

Ozonolysis of *trans*-1,2-Dibenzoylpropene (XXI).—Into a solution of 10 g. (0.04 mole) of *trans*-1,2-dibenzoylpropene, 15 ml. of methanol and 45 ml. of carbon tetrachloride, cooled to −40°, was passed at a rate of approximately 35 liters per hour a stream of oxygen containing approximately 6% ozone by weight. The reaction was stopped when the solution took on a bluish color (dissolved unreacted ozone). Some ozone passed into the potassium iodide trap during the ozonolysis. The amount of ozone used up by the reaction mixture was almost exactly 0.04 mole. A crystalline product had formed. The mixture was kept at −40° for 3–4 hr. and then filtered, yielding 5.8 g. (74% yield) of colorless crystals which melted with decomposition at 57°.

(7) R. Trambarulo, S. N. Ghosh, C. A. Burrus, Jr., and W. Gordy, *J. Chem. Phys.*, **21**, 851 (1953).

(8) R. E. Lutz and C. E. McGinn, THIS JOURNAL, **64**, 2585 (1942)

(9) R. E. Lutz and A. H. Stuart, *ibid.*, **59**, 2316 (1937).

(10) P. S. Bailey and S. H. Pomerantz, *ibid.*, **76**, 851 (1954).

(11) A. V. Tobolsky and R. B. Mesrobian, "Organic Peroxides," Interscience Publishers, Inc., New York, N. Y., 1954, p. 107.

(12) F. H. Seubold, Jr., and W. E. Vaughan, THIS JOURNAL, **75**, 3790 (1953).

(13) Melting points are corrected. Microanalyses were performed by the microanalytical laboratory of the University of Texas Biochemical Institute and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The molecular weight determination was done cryoscopically in benzene by Mr. S. B. Mainthia. The active oxygen determination was by the method of V. R. Kokatnur and M. Jelling, *ibid.*, **63**, 1432 (1941).

(14) P. S. Bailey, C. Nowlin, S. H. Pomerantz, J. V. Waggoner and [illegible], THIS JOURNAL, **73**, 3560 (1951).

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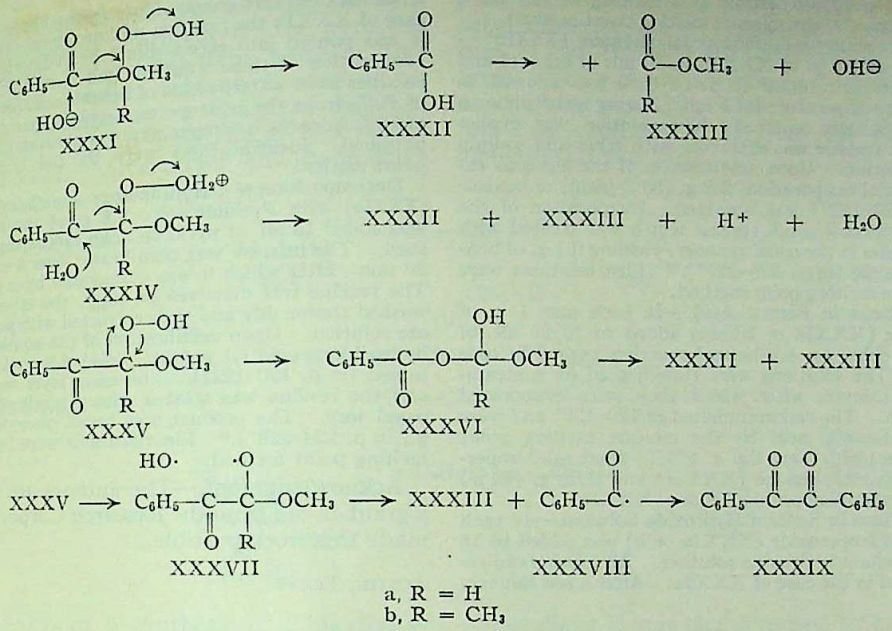

Several recrystallizations by the addition of petroleum ether (b.p. 60–68°) to an ethanol solution of the material gave a good recovery of material melting at 60–61°. The material is soluble in methanol, ethanol, acetic acid and benzene, and is insoluble in petroleum ether and carbon tetrachloride. It gave a negative hydroperoxide test with lead tetraacetate in acetic acid solution but a positive test in methanol solution.[4] The infrared spectrum, taken in chloroform, showed a broad hydroxyl band at 2.8–3.1 μ and a strong carbonyl band at 5.9 μ.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16; active O, 8.1; methoxyl, 15.82; mol. wt., 196.2. Found: C, 61.51; H, 5.65; active O, 7.7; methoxyl, 15.48, 15.66; mol. wt., 199.

The filtrate from which the hydroperoxide was originally filtered was evaporated under vacuum. The residue was warmed over a steam-bath for a few minutes to decompose any remaining peroxide material, after which it was extracted with ether and sodium bicarbonate solution. The aqueous layer was acidified and filtered, yielding 0.6 g. of benzoic acid (m.p. 120–122°, no depression in mixture melting point with an authentic sample). The ether layer was washed and evaporated. The residue was extracted several times with hot water. That which did not dissolve was treated with excess phenylhydrazine under the usual conditions; 0.2 g. of material melting at 227–228° was obtained and shown to be the phenylosazone of benzil by the mixture melting point method.[15]

The water extract was evaporated and the residue was dried, leaving 3.7 g. (61%) of colorless crystals melting at 78–85°. The material was identified as the hydrate of phenylglyoxal[15] by treating it with phenylhydrazine under the usual conditions; the osazone was obtained (m.p. 150–152°), identification was by the mixture melting point method.[15]

Ozonolysis of *trans*-1,2-dibenzoylethylene (10 g.) was carried out by the procedure described in the preceding experiment. The crude hydroperoxide XXXIa weighed 4.6 g. (60% yield) and melted with decomposition at 63–65°. Recrystallization was by addition of petroleum ether (b.p. 60–68°) to a concentrated ethyl acetate solution of the material, followed by cooling to about −15°; the pure material melted with decomposition at 68–69°. The substance was soluble in acetic acid, methanol, ethanol and ethyl acetate, insoluble in petroleum ether, benzene and carbon tetrachloride. It gave a positive lead tetraacetate test[4] in methanol solution. The infrared spectrum, taken in chloroform, showed a broad hydroxyl band at 2.9–3.0 μ and a strong carbonyl band at 5.9 μ.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53, active O, 8.78. Found: C, 59.68; H, 5.45; active O, 7.8.

The filtrate also was worked up as described in the preceding experiment, yielding 1.6 g. of benzoic acid (m.p. 120–122°), 0.5 g. of benzil phenylhydrazone (m.p. 226–228°)[15] and 4 g. (63% yield) of phenylglyoxal hydrate (m.p. 80–85°), identified through the osazone (m.p. 150–152°).[15] Identifications were by the mixture melting point method.

Reduction of α-Hydroperoxy-α-methoxypropiophenone (XXIV) to 1-Phenyl-1,2-propanedione (XXIII).—To a cold mixture of 8 g. of sodium iodide, 5 ml. of acetic acid and 10 ml. of methanol was added, slowly, 1 g. of the hydroperoxide XXIV. The mixture was allowed to come to room temperature, and the iodine thus formed was reduced with sodium thiosulfate. The resulting mixture was extracted with ether and the ether extract was washed and evaporated. The residue was treated with a solution of 0.6 g. of semicarbazide hydrochloride, 0.6 g. of sodium acetate and 5 ml. of methanol. After 30 minutes the reaction mixture was cooled and filtered, yielding 0.8 g. (75% yield) of 1-phenyl-1,2-propanedione semicarbazone (m.p. 203–205°). Recrystallization of the material from ethanol raised the melting point to 211–212°. Identification was by a mixture melting point with an authentic sample (m.p. 211–212°).[16]

Reduction of α-Hydroperoxy-α-methoxyacetophenone (XXXIa) to Phenylglyoxal.—The reduction was carried out with 1.5 g. of the hydroperoxide just as in the preceding experiment. After evaporation of the ether extract containing the reduction product, the residue was treated with 10 ml. of ethyl alcohol, 2.5 g. of phenylhydrazine and 1 ml. of acetic acid, and the mixture was refluxed for 1–2 hr. The resulting solution was diluted with water and cooled, yielding 1 g. of phenylglyoxal osazone melting at 146–149°; recrystallized from ethyl alcohol, 0.8 g., m.p. 151–153°. Identification was by the mixture melting point method.[15]

Decompositions in Alcohols. (a) **α-Hydroperoxy-α-methoxyacetophenone (XXXIa).**—A solution of 1 g. of XXXIa in 10 ml. of methanol was refluxed for 30 min., after which time it was evaporated under vacuum. The residue was extracted with sodium bicarbonate solution and ether. The aqueous fraction was acidified with hydrochloric acid and partially evaporated and cooled, yielding

(15) The reported melting point of benzil phenylosazone is 225°. The reported melting point for phenylglyoxal hydrate is 91° and that for the phenylosazone is 152°. See R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y.

(16) O. Diels and A. v. Dorp, *Ber.*, **36**, 3183 (1903), report a melting point of 211°.

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0.57 g. (85% yield) of benzoic acid melting at 121–122°; identification was by the mixture melting point method.

(b) α-Hydroperoxy-α-methoxypropiophenone (XXXIb).—A suspension of 5.6 g. of XXXIb in 20 ml. of ethanol and 10 ml. of petroleum ether (b.p. 60–68°) was allowed to stand at room temperature for 5 min., during which time an exothermal reaction occurred. The solution was evaporated and the residue was extracted with ether and sodium carbonate solution. Upon acidification of the aqueous extract and partial evaporation, 2.8 g. (80% yield) of benzoic acid (m.p. 120–122°) was obtained. Evaporation of the ether extract gave a small residue which was treated with phenylhydrazine in the usual manner, yielding 0.1 g. of benzil phenylosazone (m.p. 225–227°).[15] Identifications were by the mixture melting point method.

Decompositions in Formic Acid.—In each case 1 g. of hydroperoxide (XXXIa or b) was added to 10–20 ml. of cold formic acid. An exothermal reaction ensued in case of XXXIa. The solutions were then heated on a steam-bath for 30 minutes after which they were evaporated under vacuum. The residues melted at 120–122° and were identified as benzoic acid by the mixture melting point method. The yields were 0.6 g. (90%) from α-hydroperoxy-α-methoxyacetophenone (XXXIa) and 0.52 g. (84%) from the corresponding propiophenone (XXXIb).

Decompositions in Sodium Hydroxide Solution.—In each case 1 g. of hydroperoxide (XXXIa or b) was added to 15 ml. of 10% sodium hydroxide solution. An exothermal reaction occurred in the case of XXXIa. After a few minutes it was poured into excess dilute hydrochloric acid. In the case of XXXIb the reaction mixture stood overnight before it was poured into excess dilute hydrochloric acid. Upon evaporation of these solutions and recrystallization of the residues from water, yields of benzoic acid (m.p. 120–122°) of 79% from the hydroperoxyacetophenone (XXXIa) and of 72% from the hydroperoxypropiophenone (XXXIb) were obtained. Identifications were by the mixture melting point method.

Decomposition of α-Hydroperoxy-α-methoxyacetophenone (XXXIa) with Pyridine.—To 3.8 g. of the hydroperoxide was added 15 ml. of pyridine. An exothermal reaction ensued. The mixture was then heated over a steam-bath for 20 min., after which it was evaporated by a stream of air. The residue was dissolved in ether, the ether extract was washed thoroughly and then extracted with sodium carbonate solution. Upon acidification of the aqueous layer with hydrochloric acid 1.1 g. (43% yield) of benzoic acid was obtained (m.p. 120–122°). The ether layer was evaporated and the residue was treated with phenylhydrazine in the usual way. The product was benzil phenylosazone (0.14 g., m.p. 224–226°).[15] Identifications were by the mixture melting point method.

Acknowledgment.—The authors are grateful for a grant-in-aid from the Research Corporation which made this work possible.

AUSTIN, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Cyclic Dienes. XX. 4-*n*-Octyl-1,2-dimethylenecyclohexane[1]

BY WILLIAM J. BAILEY AND WILLIAM A. KLEIN[2]

RECEIVED OCTOBER 15, 1956

A convenient synthesis of a 2-alkyl-1,3-butadiene was developed from a commercially available alkenylsuccinic anhydride as the starting material. Thus 2-*n*-octyl-1,3-butadiene was prepared in four steps including a pyrolysis of a diacetate in an over-all yield of 53%. This 2-octylbutadiene was then converted in five steps to 4-*n*-octyl-1,2-dimethylenecyclohexane in an over-all yield of 40%. The final step in the synthesis involved the pyrolysis of a diacetate in a 55% yield. The structures of the dienes were proved by ultraviolet and infrared absorption spectra and conversion to solid Diels–Alder adducts.

A series of substituted 1,2-dimethylcyclohexanes[3–6] has been prepared in this Laboratory in an effort to determine the correlation between the molecular structure and the physical properties of the corresponding polymers. One of the objectives was the determination of the reason for the fact that the all-*cis* poly-1,2-dimethylenecyclohexane was a high melting crystalline polymer while the closely related all-*cis* natural rubber was an excellent rubber.[7] Since a methyl group located in the 4-position had very little effect on the softening point of an all-*cis* polymer, it was of interest to determine what effect a large group located in the 4-position would have on the physical properties of a poly-1,2-dimethylenecyclohexane. It had been shown previously that, as the size of the *n*-alkyl group in poly-*n*-alkyl methacrylates[8] and poly-*n*-alkylstyrenes[9] was increased, the softening point was decreased until a maximum depression occurred when the alkyl group contained eight to ten carbon atoms. Higher homologs reversed this trend and the softening points began to rise, presumably because the long alkyl side chains were capable of increasing the crystallinity of the polymers by the formation of crystallites involving only these side groups. For these reasons the synthesis of 4-*n*-octyl-1,2-dimethylenecyclohexane (I) was undertaken with the hope that a less crystalline and therefore a more rubbery all-*cis* polymer could be produced.

Since one of the key intermediates in the projected synthesis of I was 2-*n*-octyl-1,3-butadiene (II), an effort was made to find a convenient route to this diene. Previous work in this Laboratory has shown that the pyrolysis of esters is an excellent method for the preparation of unsaturated compounds and that, if charring is avoided, highly strained dienes, such as 1,2-dimethylene-4-cyclohexene, an isomer of *o*-xylene, can be prepared completely free of its aromatic isomer.[10] Marvel and

(1) Previous paper in this series, THIS JOURNAL, **79**, 1444 (1957).

(2) Office of Naval Research Fellow, 1951–1954; Union Carbide Fellow, 1954–1955.

(3) W. J. Bailey, J. Rosenberg and L. J. Young, THIS JOURNAL, **76**, 2251 (1954).

(4) W. J. Bailey and R. L. Hudson, *ibid.*, **78**, 670, 2806 (1956).

(5) W. J. Bailey, C.-W. Liao and G. H. Coleman, *ibid.*, **77**, 990 (1955).

(6) W. J. Bailey and W. B. Lawson, *ibid.*, **77**, 1606 (1955).

(7) W. J. Bailey and H. R. Golden, *ibid.*, **76**, 5418 (1954).

(8) C. E. Rehberg and C. H. Fisher, *Ind. Eng. Chem.*, **40**, 1431 (1948).

(9) C. G. Overberger, C. Frazier, J. Mandelman and H. F. Smith THIS JOURNAL, **75**, 3326 (1953).

(10) W. J. Bailey and J. Rosenberg, *ibid.*, **77**, 73 (1955); W. J. Bailey, J. Rosenberg and L. J. Young, *ibid.*, **77**, 1163 (1955).

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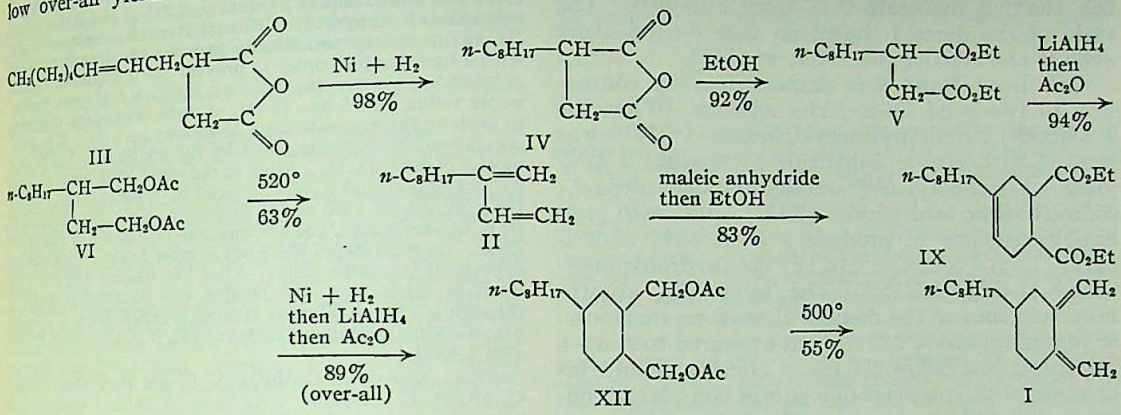
co-workers have developed a method for the synthesis of 2-alkylbutadienes involving the pyrolysis of a monoacetate as the final step; however, this procedure, which involves a Mannich reaction on an aldehyde, deamination, a Grignard reaction and esterification, is fairly long and gives a rather low over-all yield.[11] Overberger and co-workers also have developed a synthesis of 2-alkylbutadienes involving the pyrolysis of a diacetate as a final step; however, their starting material was prepared by a Stobbe condensation, esterification and catalytic reduction in only a fair over-all yield.[12] Since a series of alkenylsuccinic anhydrides, addition products of 1-olefins and maleic anhydride, are now commercially available,[13] it appeared that these adducts would make excellent starting materials for the preparation of 2-alkylbutadienes.

Thus the commercially available octenylsuccinic anhydride (III) was reduced catalytically to produce a 98% yield of *n*-octylsuccinic anhydride (IV) which was then esterified to give ethyl 3-carbethoxyundecylate (V) in a 92% yield. By a procedure which is essentially a one-step reductive acetylation with lithium aluminum hydride and acetic anhydride,[14] the ester V was reduced and the intermediate glycol in the reaction mixture was acetylated to yield the 3-acetoxymethylundecyl acetate (VI) in a 94% yield. An alternative procedure for the preparation of VI by the reductive acetylation of IV did not give as high a yield. Apparently the intermediate reduction products from IV were so insoluble that, even when the reduction was carried out for 96 hr., only a 78% yield of VI was obtained.

Pyrolysis of the diacetate VI at 520° was conducted by the dropwise addition of the liquid through a Vycor tube packed with Pyrex helices under such conditions that only 77% of two molar equivalents of acetic acid was liberated. Under these conditions little or no charring that could cause isomerization occurred. From the pyrolysis were obtained a 46% conversion to 2-*n*-octyl-1,3-butadiene (II) plus a 28% yield of a mixture of the two possible intermediate olefin acetates. The yield of II, based on unrecovered olefin acetate, was 63%. The over-all yield for the four-step synthesis of II from the commercially available III was 53%.



The diene II was characterized by conversion to two solid Diels–Alder adducts. Thus the 2-*n*-octyl-1,3-butadiene (II) plus maleic anhydride gave a 47% yield of 4-*n*-octyl-1,2,3,6-tetrahydrophthalic anhydride (VII), while treatment with 1,4-naphthoquinone produced a 67% yield of 2-*n*-octyl-1,4,4a,9a-tetrahydroanthraquinone (VIII). The ultraviolet absorption spectrum possessed a maximum ϵ of 20,400 at 226 mμ which indicated the presence of a pair of conjugated double bonds. Although the maximum is slightly higher than predicted from Woodward's rules,[15] it is in excellent agreement with that reported for 2-*n*-heptyl-1,3-butadiene.[12] The structure of II also was indicated by its infrared absorption spectrum which possessed strong bands at 722, 883–913, 986, 1367, 1443, 1619, 1789, 2245 and 2860 cm.$^{-1}$ and somewhat weaker bands at 757, 1015, 1066, 1111, 1155, 1195, 1232, 1298 and 1644 cm.$^{-1}$. The absence of a band in the 800 to 850 cm.$^{-1}$ region indicated that very little if any of the isomeric 3-methyl-1,3-undecadiene was present.

The 4-*n*-octyl-1,2-dimethylenecyclohexane was then prepared from II in five steps in an over-all yield of 40%, essentially by a procedure developed earlier for the ascending of a diene series by the addition of a cyclohexane ring.[3] The *n*-octylbutadiene II was treated with maleic anhydride and the solid adduct VII was not isolated, but the crude reaction mixture was esterified directly to produce an 83% yield of the diethyl ester IX. IX was catalytically reduced in a 96% yield to give the diethyl 4-*n*-octylhexahydrophthalate (X) which, in turn, was reduced nearly quantitatively to the glycol XI with lithium aluminum hydride. Acetylation with acetic anhydride produced a 95% yield of the 4-*n*-octylhexahydrophthalyl diacetate (XII).

The diacetate XII was pyrolyzed at 500° by dropwise addition to the apparatus described above under such conditions that only 54% of two molar equivalents of acetic acid was liberated. These rel-

(11) C. S. Marvel, R. L. Myers and J. H. Saunders, THIS JOURNAL, **70**, 1694 (1948); C. S. Marvel and J. L. R. Williams, *ibid.*, **70**, 3842 (1948).

(12) C. G. Overberger and C. W. Roberts, *ibid.*, **71**, 3618 (1949); C. G. Overberger, A. Fishman, C. W. Roberts, L. M. Arond and J. Lal, *ibid.*, **73**, 2540 (1951).

(13) Humphrey-Wilkinson, Inc., North Haven, Conn.

(14) W. J. Bailey and W. R. Sorenson, THIS JOURNAL, **78**, 2287 (1956); W. J. Bailey and J. Economy, *ibid.*, **77**, 1133 (1955).

(15) R. B. Woodward, *ibid.*, **63**, 1123 (1941); **64**, 76 (1942).

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atively mild conditions were chosen in order to prevent charring that could cause the formation of any polymerization inhibitors. Under these conditions a 26% conversion to the 4-*n*-octyl-1,2-dimethylenecyclohexane (I) was realized. In addition a 40% yield of a mixture of the two possible intermediate olefin acetates and a 13% recovery of the starting diacetate XII were obtained. The yield of the diene I, based on unrecovered olefin acetate and starting diacetate, was 55%.

The diene I also was characterized by conversion to two solid Diels–Alder adducts. Thus the 4-*n*-octyl-1,2-dimethylenecyclohexane (I) was treated with maleic anhydride to produce a 47% yield of 6-*n*-octyl-$\Delta^{9(10)}$-octahydronaphthalene-2,-3-dicarboxylic anhydride (XIII) and with 1,4-naphthoquinone to produce a 38% yield of 2-*n*-octyl-1,2,3,4,5,5a,6,11,11a,12-decahydronaphthacene-6,11-dione (XIV). The ultraviolet absorption spectrum of the diene I showed no maximum or minimum above 220 mμ but appeared to reach a maximum just below 220 mμ. This is a definite indication of the presence of a pair of non-planar conjugated double bonds exocyclic to a cyclohexane ring. Although this maximum is much lower than that predicted from Woodward's rules,[15] it is in excellent agreement with the maxima reported for similar cyclic dienes which have a pair of conjugated double bonds slightly askew.[3-5,10,16] For instance, 4-methyl-1,2-dimethylenecyclohexane also possesses no maximum or minimum above 220 mμ but appears to reach a maximum just below 220 mμ. Only when the two exocyclic double bonds are forced into the same plane, as in 2,3-dimethylenebicyclo[2.2.1]heptane, does the absorption maximum occur at longer wave lengths. The infrared absorption spectrum of the diene I also was very similar to that of closely related dienes. The strong absorption at 890 cm.$^{-1}$ indicated the presence of a terminal methylene group.

The polymers from these interesting dienes will be reported separately.

Experimental[17]

n-**Octylsuccinic Anhydride (IV).**—A solution of 368 g. (1.75 moles) of *n*-octenylsuccinic anhydride (III) (Humphrey–Wilkinson, Inc.) in 600 ml. of purified dioxane and 25 g. of W-5 Raney nickel catalyst were placed in a high pressure hydrogenation vessel. The hydrogenation was completed in 1 hr. at 100° and 160 atm. of hydrogen. After removal of the catalyst by filtration, the dioxane was removed by distillation under reduced pressure to yield 366 g. (98%) of *n*-octylsuccinic anhydride (IV), m.p. 62–64.5° (reported[8] m.p. 64–64.5°).

Ethyl 3-Carbethoxyundecylate (V).—A mixture of 3000 ml. of benzene, 1200 ml. of absolute ethanol, 775 g. (3.68 moles) of *n*-octylsuccinic anhydride (IV) and 10 ml. of concentrated sulfuric acid was heated under reflux until no further separation of an aqueous phase occurred (Dean–Stark trap). After the reaction mixture was washed with an aqueous sodium bicarbonate solution, the excess solvents were removed by distillation at atmospheric pressure through a 12-inch Vigreux column. The residue was fractionally distilled through the same column under reduced pressure to give 969 g. (92%) of ethyl 3-carbethoxyundecylate (V), b.p. 110° (0.07 mm.), n^{25}D 1.4350.

Anal. Calcd. for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 67.12; H, 10.26.

3-Acetoxymethylundecyl Acetate (VI). A. From *n*-Octylsuccinic Anhydride (IV).—To a slurry of 68.4 g. (1.8 moles) of lithium aluminum hydride in 2 liters of anhydrous ether was added slowly a solution of 315 g. (1.5 moles) of *n*-octylsuccinic anhydride (IV) in 2 liters of anhydrous ether. (It was necessary periodically to warm the dropping funnel with a heat lamp in order to prevent the precipitation of the anhydride.) After the reaction mixture had been heated under reflux for 96 hr., 75 ml. of water was added dropwise to destroy the excess lithium aluminum hydride. The complexes were then decomposed by the addition of 432 g. (7.2 moles) of acetic acid. Most of the ethyl ether was removed by distillation and it was replaced by *n*-butyl ether. After the addition of 1530 g. (15 moles) of acetic anhydride and 30 g. of acetic acid, the mixture was heated under reflux for 72 hr. It was filtered while hot in order to remove the heavy deposit of inorganic salts. After the solvent was removed by flash distillation, the residue was fractionally distilled through a 12-inch Vigreux column to yield 336 g. (78%) of 3-acetoxymethylundecyl acetate (VI), b.p. 118° (0.04 mm.), n^{25}D 1.4396.

Anal. Calcd. for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 67.39; H, 10.32.

B. From Ethyl 3-Carbethoxyundecylate (V).—To a cooled slurry of 160 g. (4.2 moles) of lithium aluminum hydride and 1.5 liters of dry ether was added slowly a solution of 962 g. (3.36 moles) of ethyl 3-carbethoxyundecylate (V) dissolved in 1.5 liters of dry ether. After addition had been completed, the reaction mixture was heated under reflux for an additional 72 hr. The excess lithium aluminum hydride was then destroyed by the dropwise addition of 100 ml. of water, and the complexes were decomposed with 1009 g. (16.8 moles) of acetic acid. The ethyl ether was replaced by *n*-butyl ether as described above, and the unisolated diol was heated under reflux for 120 hr. with 1500 ml. of acetic anhydride and 30 ml. of acetic acid. After the inorganic salts were removed by filtration of the hot mixture, the excess solvents were removed by flash distillation under reduced pressure. The residue was fractionally distilled through a 12-inch Vigreux column to yield 903 g. (94%) of 3-acetoxymethylundecyl acetate (VI), b.p. 127° (0.11 mm.), n^{25}D 1.4394.

2-*n*-Octyl-1,3-butadiene (II).—At the rate of 1.5 g. per minute, 100 g. (0.35 mole) of 3-acetoxymethylundecyl acetate (VI) was added dropwise to a vertical Vycor pyrolysis tube which was packed to a depth of 10 inches with 1/8-inch glass helices and heated externally at 520° by a FD 303 A Hoskins electric furnace as described previously.[18] The addition was conducted in an inert atmosphere by the introduction of a slow stream of oxygen-free nitrogen at the top of the tube. The pyrolysate was collected in a receiver cooled by a Dry Ice–cellosolve bath. (Titration of a 0.27-g. sample of the pyrolysate with standard sodium hydroxide solution indicated that 77% of two molar equivalents of acetic acid had been liberated.) Fractional distillation of the crude pyrolysate through a 6-inch, helix-packed column yielded 27 g. (46%) of 2-*n*-octyl-1,3-butadiene (II), b.p. 71° (4.3 mm.), n^{25}D 1.4514; and 22 g. (28%) of presumably a mixture of the two possible olefin acetates, 3-acetoxymethyl-1-undecene and 3-methylene-*n*-undecyl acetate. The yield of the diene II, based on the unrecovered olefin acetates, was 63%.

Anal. Calcd. for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found: C, 86.66; H, 13.52.

4-*n*-Octyl-1,2,3,6-tetrahydrophthalic Anhydride (VII).—To a filtered solution of 1.60 g. (0.016 mole) of maleic anhydride in 50 ml. of dry benzene was added 3.5 g. (0.021 mole) of 2-*n*-octyl-1,3-butadiene (II). After the solution had been heated under reflux for 24 hr., the benzene was removed by distillation under reduced pressure to yield 2.36 g. (47%) of the crude adduct VII, m.p. 45–58°. Recrystallization from petroleum ether gave an analytically pure sample of 4-*n*-octyl-1,2,3,6-tetrahydrophthalic anhydride (VII), m.p. 51.3–51.8°. (A mixed melting point with maleic anhydride exhibited a large depression.)

(16) W. J. Bailey and H. R. Golden, THIS JOURNAL, **75**, 4780 (1953).

(17) The authors are grateful to Dr. Mary Aldridge and Miss Kathryn Gerdeman for the microanalyses and to Miss Gerdeman and Dr. Ellis R. Lippincott for the infrared spectra. The infrared spectra were determined on the pure liquids with a sodium chloride prism in a Perkin–Elmer model 12-C infrared spectrometer modified for double-pass operation. The ultraviolet absorption spectra were determined in purified cyclohexane in a Beckman model DU spectrophotometer. All melting points are corrected.

(18) W. J. Bailey and J. J. Hewitt, *J. Org. Chem.*, **21**, 543 (1956).

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Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.41; H, 8.99.

2-*n*-Octyl-1,4,4a,9a-tetrahydroanthraquinone (VIII).—A solution of 1.58 g. (0.010 mole) of 1,4-naphthoquinone, 3.0 g. (0.018 mole) of 2-*n*-octyl-1,3-butadiene (II) and a few milligrams of N-phenyl-β-naphthylamine in 50 ml. of dry benzene was heated under reflux for 24 hr. The benzene was removed by distillation under reduced pressure to give 2.21 g. (67%) of the slightly impure adduct VIII, m.p. 84–86°. Recrystallization from ethanol produced analytically pure 2-*n*-octyl-1,4,4a,9a-tetrahydroanthraquinone (VIII), m.p. 85.8–86.4°.

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.65; H, 8.44.

Diethyl 4-*n*-Octyl-1,2,3,6-tetrahydrophthalate (IX).—After a filtered solution of 39.2 g. (0.40 mole) of maleic anhydride dissolved in 300 ml. of dry benzene and 50 g. (0.30 mole) of 2-*n*-octyl-1,3-butadiene (II) had been maintained at 55° for 20 hr., the unisolated adduct and excess maleic anhydride were esterified by the addition of 125 ml. of absolute ethanol and 1 ml. of concentrated sulfuric acid. The water formed in the esterification process was removed as the ternary azeotrope by means of a Dean–Stark receiver. After no more aqueous phase appeared in the distillate, the excess benzene and alcohol were removed by distillation through the Dean–Stark receiver. The residue, without further treatment, was fractionally distilled through a 12-inch Vigreux column to yield 84 g. (83%) of diethyl 4-*n*-octyl-1,2,3,6-tetrahydrophthalate (IX), b.p. 150° (0.15 mm.), $n^{25}D$ 1.4636.

Anal. Calcd. for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 71.01; H, 9.95.

Diethyl 4-*n*-Octylhexahydrophthalate (X).—A mixture of 114 g. (0.34 mole) of diethyl 4-*n*-octyl-1,2,3,6-tetrahydrophthalate (IX), 35 ml. of absolute ethanol and 6 g. of W-5 Raney nickel catalyst was added to a high pressure hydrogenation vessel. The hydrogenation was completed in 4 hr. at 100° and 170 atm. of hydrogen. After the catalyst was removed by filtration, the ethanol was removed by distillation under reduced pressure. The residue was fractionally distilled through a 6-inch, helix-packed column to yield 112 g. (96%) of diethyl 4-*n*-octylhexahydrophthalate (X), b.p. 149° (0.10 mm.), $n^{25}D$ 1.4562. (Similar results were obtained by the hydrogenation of IX in ethanol at 22° and atmospheric pressure by use of Adams catalyst, platinum oxide.)

Anal. Calcd. for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.70; H, 10.38.

4-*n*-Octylhexahydrophthalyl Alcohol (XI).—To a slurry of 14 g. (0.37 mole) of lithium aluminum hydride in 1 liter of anhydrous ether was added dropwise a solution of 96 g. (0.28 mole) of diethyl 4-*n*-octylhexahydrophthalate (X) in 100 ml. of ether. Near the end of the addition the reaction mixture became so viscous that it was necessary to add an additional 200 ml. of ether in order to facilitate stirring. After the reduction mixture had been heated under reflux overnight, the excess lithium aluminum hydride was destroyed by the dropwise addition of 50 ml. of water. A sufficient amount of 10% hydrochloric acid was added to the ice-bath cooled reaction mixture to cause the formation of two distinct layers. The clear ether layer was removed by decantation before the remainder of the salts was dissolved by additional dilute acid. The aqueous phase was extracted several times with ether, and these extracts were combined with the initial ether layer. After the ethereal solution had been dried with anhydrous potassium carbonate and sodium sulfate, the ether was removed by flash distillation under reduced pressure to give 70 g. (97%) of crude 4-*n*-octylhexahydrophthalyl alcohol (XI), m.p. 61–65°. Recrystallization of a small quantity from ether–petroleum ether gave an analytically pure sample, m.p. 64.0–64.6°.

Anal. Calcd. for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58. Found: C, 74.77; H, 12.31.

4-*n*-Octylhexahydrophthalyl Diacetate (XII).—After a mixture of 104 g. (0.41 mole) of the crude 4-*n*-octylhexahydrophthalyl alcohol (XI), 250 g. of acetic anhydride and 30 g. of acetic acid was heated under reflux in a 1-liter flask for 24 hr., the excess acetic acid and acetic anhydride were removed by distillation under reduced pressure through a 12-inch Vigreux column. The residue was distilled through the same column to yield 132 g. (95%) of 4-*n*-octylhexahydrophthalyl diacetate (XII), b.p. 140° (0.03 mm.), $n^{25}D$ 1.4605.

Anal. Calcd. for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.35; H, 10.49.

4-*n*-Octyl-1,2-dimethylenecyclohexane (I).—By the use of the pyrolysis apparatus described for the preparation of II, 36 g. (0.105 mole) of 4-*n*-octylhexahydrophthalyl diacetate (XII) was pyrolyzed at 500° at the addition rate of 1.5 g. per minute. A few milligrams of antioxidant, N-phenyl-β-naphthylamine, was added to an ether solution of the pyrolysate. Removal of the acetic acid by extraction with water and titration of an aliquot of these washings with standard sodium hydroxide solution indicated that 54% of two molar equivalents of acetic acid had been eliminated. After the ether solution was dried over anhydrous sodium sulfate, most of the ether was removed by distillation through a 6-inch, helix-packed column. The residue was then fractionally distilled through the same column to yield 6.2 g. (26%) of the light yellow 4-*n*-octyl-1,2-dimethylenecyclohexane (I), b.p. 79° (0.11 mm.), $n^{25}D$ 1.4707; 11.8 g. (40%) of presumably a mixture of the pair of intermediate olefin acetates, 1-methylene-2-acetoxymethyl-4-*n*-octylcyclohexane and 1-acetoxymethyl-2-methylene-4-*n*-octylcyclohexane, b.p. 106–118° (0.09 mm.), $n^{25}D$ 1.4645; and 4.5 g. (13%) of recovered diacetate XII. The yield of I, based on unrecovered olefin acetates and XII, was 55%.

Anal. Calcd. for $C_{16}H_{28}$: C, 87.19; H, 12.81. Found: C, 87.47; H, 12.80. Calcd. for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 76.80; H, 11.27.

6-*n*-Octyl-$\Delta^{9(10)}$-octahydronaphthalene-2,3-dicarboxylic Anhydride (XIII).—After a mixture of a filtered solution of 0.59 g. (0.006 mole) of maleic anhydride in 50 ml. of dry benzene and 1.59 g. (0.007 mole) of 4-*n*-octyl-1,2-dimethylenecyclohexane (I) had been allowed to stand at 25° for 2 hr., it was heated under reflux for 15 hr. The benzene was partially removed by distillation under reduced pressure and the precipitate which formed was removed by filtration and was washed with 30–60° petroleum ether. The crude adduct XIII weighed 0.90 g. (47%) and had a melting range of 89–95°. Two recrystallizations from 60–80° petroleum ether gave analytically pure 6-*n*-octyl-$\Delta^{9(10)}$-octahydronaphthalene-2,3-dicarboxylic anhydride (XIII), m.p. 103.8–105°.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.41; H, 9.64.

2-*n*-Octyl-1,2,3,4,5,5a,6,11,11a,12-decahydronaphthacene-6,11-dione (XIV).—A mixture of 1.72 g. (0.008 mole) of 4-*n*-octyl-1,2-dimethylenecyclohexane (I), 0.95 g. (0.006 mole) of 1,4-naphthoquinone and 50 ml. of dry benzene was heated under reflux for 15 hr. After the benzene was partially removed by evaporation of the solution on the steam-bath, the resulting precipitate was removed by filtration and was washed with hot ethanol. The yield of the crude light tan adduct XIV, m.p. 141–144°, was 0.87 g. (38%). Recrystallization from 60–80° petroleum ether gave analytically pure 2-*n*-octyl-1,2,3,4,5,5a,6,11,11a,12-decahydronaphthacene-6,11-dione (XIV), m.p. 145.8–146.6°.

Anal. Calcd. for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 82.65; H, 8.87.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Preparation and Polymerization of Unsaturated Quaternary Ammonium Compounds. VIII. A Proposed Alternating Intramolecular–Intermolecular Chain Propagation[1]

BY GEORGE B. BUTLER AND RUDOLPH J. ANGELO

RECEIVED NOVEMBER 23, 1956

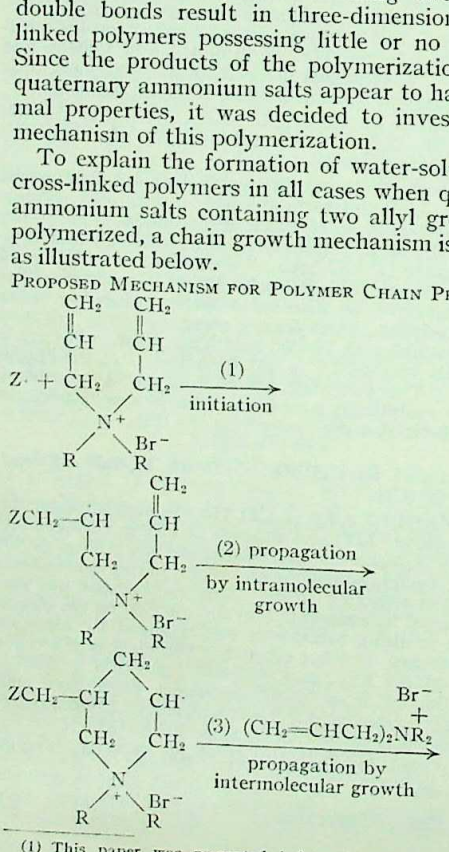
A mechanism is proposed for the polymerization of certain allyl unsaturated quaternary ammonium salts which involves an alternating intramolecular–intermolecular chain propagation leading to the formation of chains of piperidine rings. This mechanism is supported by results obtained using suitable monomers, by studies of solvent, initiator and oxygen effects and by hydrogenation evidence. An estimation of the molecular weight of the polymers has been made.

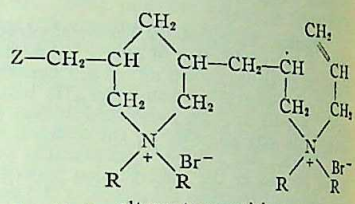
Previous work[2–6] carried out in this Laboratory on the free radical initiated polymerization of allyl or substituted allyl quaternary ammonium derivatives showed that infusible and water-insoluble polymers were obtained only from monomers containing three or more allyl groups. Polymers from monomers containing only two allyl groups were non-cross-linked, since they were completely soluble in water. Monomers containing only one allyl group did not undergo polymerization.

These results are contrary to the accepted views that monomers containing one double bond result in linear polymers possessing some degree of solubility, while monomers containing two or more double bonds result in three-dimensional, cross-linked polymers possessing little or no solubility. Since the products of the polymerization of allyl quaternary ammonium salts appear to have abnormal properties, it was decided to investigate the mechanism of this polymerization.

To explain the formation of water-soluble, non-cross-linked polymers in all cases when quaternary ammonium salts containing two allyl groups were polymerized, a chain growth mechanism is proposed as illustrated below.

PROPOSED MECHANISM FOR POLYMER CHAIN PROPAGATION





R = alkyl radical
Z· = free radical

alternate repetition of (2) and (3) → polymer

This would involve a free radical attack on one of the double bonds, followed by cyclization with the remaining favorably situated double bond within the same molecule; the resulting cyclic radical then attacks another molecule of monomer, and repetition of the process results in a growing chain.

In a somewhat related case, Simpson, *et al.*,[7] studied the structure of polydiallyl phthalate at the gel point and, by calculations from values of residual unsaturation and degree of polymerization, concluded that at the gel point about 40% of the reacted monomer units was used up in cyclization reactions and were, therefore, not available for further cross-link formation. In a later publication[8] these authors analyzed several other polydiallyl esters in a similar way, but only in the above case did cyclization appear to occur to any great extent. Such an intramolecular cyclization in the case of diallyl phthalate would lead to ten-, eleven-, twelve-membered, or even larger, rings. Such cyclizations are much less likely to occur than those we propose which lead to six-membered rings.

Through use of suitable monomers, studies of solvent, initiator and oxygen effects, hydrogenation studies and estimation of molecular weight, evidence has been obtained to support this proposed mechanism.

Experimental

Diallyldiethylammonium Bromide.—Allyl bromide, 60.5 g. (0.5 mole), was added to 50.0 g. (0.44 mole) of N,N-diethylallylamine dissolved in 100 ml. of acetone; the N,N-diethylallylamine had a boiling point of 110° and $n^{25}D$ 1.4198; Libermann and Paal[9] report the boiling point as 110–113°. Upon addition of the bromide, the mixture became cloudy and crystals began to form. The product was washed and decanted several times with cold acetone, filtered and dried in a vacuum desiccator. White, hygroscopic crystals, 87 g. (84% yield), m.p. 155° (closed capillary), were formed and were recrystallized from acetone–absolute ethanol.

Anal. Calcd. for $C_{10}H_{20}NBr$: Br, 34.15. Found: Br, 34.12.

Diallyldimethylammonium bromide and triallylbutylam-

(1) This paper was presented before the Division of Polymer Chemistry, American Chemical Society, Dallas, Texas, April, 1956.
(2) G. B. Butler and R. L. Bunch, THIS JOURNAL, **71**, 3120 (1949).
(3) G. B. Butler and F. L. Ingley, *ibid.*, **73**, 895 (1951).
(4) G. B. Butler, R. L. Bunch and F. L. Ingley, *ibid.*, **74**, 2543 (1952).
(5) G. B. Butler and R. L. Goette, *ibid.*, **74**, 1939 (1952); **76**, 2418 (1954).
(6) G. B. Butler and R. J. Angelo, *ibid.*, **78**, 4797 (1956).
(7) W. Simpson, T. Holt and R. Zeite, *J. Polymer Sci.*, **10**, 489 (1953).
(8) W. Simpson and T. Holt, *ibid.*, **18**, 335 (1955).
(9) C. Libermann and C. Paal, *Ber.*, **16**, 526 (1883).

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monium bromide were prepared as described in previous papers.[2,5]

Polydiallyldiethylammonium Bromide.—Twenty drops of 60% *t*-butyl hydroperoxide (approximately 0.012 g./drop) was added to a solution of 8.0 g. of diallyldiethylammonium bromide and 4.0 ml. of water. The mixture was allowed to remain open to the atmosphere in an oven at 60° for 48 hr. The resulting white hygroscopic product was ground to a fine powder and dried for several days in a vacuum desiccator. Eight grams of product, melting with considerable decomposition at 346–354°, was obtained. The product was quite soluble in water and ethanol and gave an immediate halogen test when treated with $AgNO_3$ solution.

Anal. Calcd. for $C_{10}H_{20}NBr$: C, 51.30; H, 8.20; N, 5.98; Br, 34.15. Found: C, 51.35; H, 8.32; N, 5.50; Br, 33.90.

Polydiallyldimethylammonium Bromide.—Twenty-five grams of the salt, 12.5 g. of water and 20 drops of *t*-butyl hydroperoxide were mixed and allowed to stand overnight at room temperature. The solution was then placed in an oven at 70° for 72 hr. when a white opaque, brittle mass resulted. This polymer was hygroscopic and soluble in water. After grinding and drying *in vacuo*, the m.p. was 348–352°.

Polydiallylamine Hydrochloride.—Ten grams of diallylamine hydrochloride (recrystallized from acetone–ethanol three times, m.p. 164–165°) was dissolved in 5 ml. of water and treated with 25 drops of 60% *t*-butyl hydroperoxide solution. The mixture remained in an open beaker at 60° for three days. Ten grams of polymeric product was obtained which was insoluble in water and ethanol. The wash ethanol on treatment with acetone showed only a faint cloudiness which indicated there was very little unreacted diallylamine hydrochloride present. After soaking in an acetone–ethanol mixture or absorbing moisture from the atmosphere, the product exhibited elastic properties. This was the only monomer in this study with two allyl groups to show characteristics of cross-linking upon polymerization.

Hydrogenation.—An infrared absorption band at 6.10 μ indicated some degree of unsaturation in the water-soluble polymers obtained from diallyldiethyl- and diallyldimethylammonium bromides. Quantitative hydrogenation of weighed samples of polydiallyldiethylammonium bromide over Adams catalyst at atmospheric pressure resulted in an average absorption of 0.193 mole of hydrogen per mole of monomer unit in the polymer.

Solvent interaction during the polymerization might affect the nature of the polymer. If a chain radical could react with a solvent radical in preference to a monomer molecule, the degree of polymerization would be reduced. Thus it might be possible to have a monomer molecule containing several unsaturated groups and yet obtain a polymer of a low degree of polymerization and slight cross-linking. The following experiments were carried out varying the solvent and solvent concentration. (a) A mixture of 3.0 g. of triallylbutylammonium bromide, 3.0 ml. of water and 6 drops of 60% *t*-butyl hydroperoxide solution was heated at 60° for 76 hr. A hard, water-soluble solid was obtained. The product was dissolved in 10 ml. of water, 10 drops of initiator was added and the mixture heated for an additional week at 60°. The product was still water soluble. (b) A mixture of triallylbutylammonium bromide (2 g.), 4 drops of initiator and 2.0 ml. of water was allowed to react at 100° for 38 hr. The product was again water soluble. (c) Two grams of triallylbutylammonium bromide, 2 drops of initiator and 0.08 ml. of water were allowed to react at 100° for 38 hr. The resulting hard, glassy product was soaked in hot water, filtered and dried; 1.7 g. (85% yield) of water-insoluble product was obtained. The procedure was that of Bunch,[10] who reported a 52.5% yield. (d) Three grams of diallyldiethylammonium bromide, 10 drops of initiator and 0.3 ml. of water were allowed to react at 100° for 38 hr. The product was water soluble. (e) Three grams of diallyldiethylammonium bromide, 10 drops of initiator and 50 drops of dimethylformamide were allowed to react at 100° for 38 hr. The product was water soluble.

Initiator Effect.—Various initiators were tried with monomers containing one and two double bonds to see whether *t*-butyl hydroperoxide is unique in its property of yielding non-cross-linked polymers with monomers containing two allyl groups.

One gram each of triethylallylammonium bromide and diallyldiethylammonium bromide were dissolved in 1.0 ml. of water and reacted for one week at 60° with 0.05 g. each of *t*-butyl hydroperoxide, di-*t*-butyl peroxide and benzoyl peroxide.

The lack of cross-linking was indicated by the water solubility of the products. Polymerization took place only in the reaction of diallyldiethylammonium bromide with *t*-butyl hydroperoxide. In the other cases, the starting monomers were recovered and identified.

In an attempt to evaluate the initiating property of 2,2′-azoisobutyronitrile, this initiator was treated with hexaallylethylenediammonium dibromide, since it was thought that an easily isolated, insoluble product would be obtained if polymerization occurred. The monomer (5 g.), dissolved in 10 ml. of dimethylformamide, was allowed to react with varying amounts of initiator for two weeks at 60° in an open vessel. These results are recorded in Table I (a to f).

TABLE I

Initiator, %	Weight of H_2O insoluble product	Remarks
(a) 0.1	Soluble	Light viscous liq. after 2 wk.
(b) 0.5	Soluble	Light viscous liq. after 2 wk.
(c) 1.0	Soluble	Viscous liq. after 2 wk.
(d) 2.0	0.75 g.	Heavy viscous liq. after 2 wk.
(e) 5.0	3.28 g.	Gelatinous after 12–15 hr., flexible solid 2 wk.
(f) 10.0	4.37 g.	Gelatinous after 6 hr.; brittle solid at 2 wk.
(g) 1.0	Soluble	Hot acetone–insol. portion, m.p. 295–300°
(h) 5.0	Soluble	M.p. 305–307°
(i) 10.0	Soluble	M.p. 306–307°

The effect of this initiator on the polymerization of diallyldiethylammonium bromide was determined in a similar manner. Two grams of diallyldiethylammonium bromide, dissolved in 10 ml. of dimethylformamide, was allowed to react with varying amounts of azo initiator at 75° for fifteen days. The product was water soluble in every case. Unreacted monomer was separated from the reaction product by extraction with hot acetone. Results are given in Table I (g to i).

Effect of Oxygen.—The following experiment, along with the molecular weight estimation, demonstrated the inhibiting effect of oxygen; a mixture of 8.0 g. of diallyldiethylammonium bromide, 4.0 ml. of water and 33 drops of 60% *t*-butyl hydroperoxide solution (approximately 0.012 g./drop) was allowed to react for 76 hr. at 60–65°. The reaction was carried out in an oxygen-free, dry nitrogen atmosphere. Eight grams of hygroscopic product was obtained after drying for several days in a vacuum desiccator. The product decomposed over a wide range and melted with decomposition at 355–360°, and was soluble in water but relatively insoluble in ethanol, forming some gel. The degree of solubility of this product in ethanol differed from that of the polydiallyldiethylammonium bromide, which was prepared open to the atmosphere.

Identical experiments, carried out quantitatively, open to the atmosphere, and under pure nitrogen, gave weight increments which showed that hydroxyl radical interaction from the solvent was not appreciable and could be neglected.

It was also considered that the formation of peroxide or hydroperoxide linkages might account for the utilization of some of the monomer double bonds during the polymerization. However, infrared spectra of the above products showed no absorption bands at 870 and 840 cm.$^{-1}$, which are characteristic of peroxide[11] and hydroperoxide,[12] respectively. Polarographic determinations[13] of polydiallyldiethylammonium bromide (prepared open to the atmosphere

(10) R. L. Bunch, Ph.D. Dissertation, University of Florida, 1949, p. 37.

(11) A. R. Philpotts and W. Thain, *Anal. Chem.*, **24**, 638 (1952).

(12) O. D. Shreve, M. R. Heether, H. B. Knight and D. Swern, *ibid.*, **23**, 282 (1951).

(13) A. H. Gropp and G. Lohr, private communication.

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and under nitrogen) gave no indication of a peroxide or hydroperoxide wave.

Estimation of Molecular Weight.—A crude approximation of the degree of polymerization was obtained as shown in Table II. This estimation involves the following assumptions: (1) Only the *t*-butoxide radical is to be considered as an initiating fragment. This assumption is probably valid, considering work carried out on the decomposition of *t*-butyl hydroperoxide in the gaseous and liquid phase.[14-17] In all cases cited, fission of the O–O linkage to produce *t*-butoxide and hydroxyl radicals was proposed to account for the formation of the reaction products. (2) The increase in weight during polymerization is due only to incorporation of initiator fragments. (3) The means of chain termination is either by combination or by disproportionation.

The polymerization reaction products were freed from any unreacted monomer by extraction with hot acetone. Samples of the reaction products were extracted in a fine filter funnel until a constant weight was obtained upon vacuum drying.

TABLE II

APPROXIMATION OF THE DEGREE OF POLYMERIZATION

	Open to atm.	Under N_2
Wt. increase (assuming only init. fragment incorporation), g.	0.1545	0.1038
Moles of radical (assuming only *t*-butoxide radical as init.), g.	0.00212	0.00142
Starting weight of monomer, g.	7.9061	8.5279
Fraction converted to polymer, g.	0.949	0.969
Polymer fract. expressed as mole of monomer	0.0321	0.0353
Moles monomer/mole of radical init.	15.1	24.8
Avg. degree of polymn. (assuming chain detmn. by dispropn.)	15.1	24.8
Avg. degree of polymn. (assuming chain termn. by combination)	30.2	49.6
Avg. mol. wt. (assuming chain termn. by combination	7066	11,606

Discussion of Results

Free radical catalyzed polymerization of quaternary ammonium salts containing only two allyl groups affords only water soluble, non-cross-linked polymers.

The polymers showed some unsaturation by their infrared absorption at 6.10 μ. Quantitative hydrogenation indicated that one free double bond was left for every five monomer units in the polymer chain. Linear intermolecular chain growth would have used five double bonds per five monomer units, leaving four double bonds unaccounted for in the polymerization. It appears probable that much of the unsaturation is used up in the formation of an intramolecular cyclic structure, since cross-linking does not occur to any significant extent. Under these circumstances, the suggested mechanism appears to be the obvious mode of chain propagation.

It appears that the solvent affects the polymerization to some extent, since the attempted polymerizations of triallylbutylammonium bromide at 60 and 100° indicated that the amount of water as solvent is rather critical in obtaining an insoluble product. Diallyldiethylammonium bromide did not yield a water-insoluble product under any circumstances, again showing that at least three allyl groups per molecule of quaternary ammonium salt are required to produce an insoluble product. Diallylamine hydrochloride was the only monomer with two double bonds that produced a water-insoluble product upon polymerization. This compound, however, is not a quaternary ammonium salt and steric considerations suggest that it would be less likely to favor cyclizations of the type proposed.

It was found that *t*-butyl hydroperoxide or 2,2'-azoisobutyronitrile would initiate the polymerization of allyl quaternary ammonium derivatives. Table I indicates that the effective amount of azo initiator is between 5 and 10%, which is higher than the effective initiator ratio of *t*-butyl hydroperoxide.

The polymerization appeared to be somewhat sensitive to oxygen, since the degree of polymerization of the product polymerized under nitrogen was higher than that prepared open to the atmosphere; this greater degree of polymerization also was evident from the different solubilities in ethanol. Chemical, infrared and polarographic analyses did not however, show the presence of peroxide linkages. It is likely that oxygen affects the rate of initiation rather than the formation of different polymers.

Since the soluble polymers are polyelectrolytes, a molecular weight determination of the products, as such, was very difficult. The usual molecular weight determinations, which are dependent on the colligative properties of polymer molecules in solution, were not useful since the degree of ionic dissociation of the polyelectrolytes was unknown. An attempt was made to convert polydiallyldiethylammonium bromide to the polyhydroxide form, degrade this product by the loss of ethylene and water and measure the molecular weight of the resulting polytertiary amine. Although the polyelectrolyte was degraded, a molecular weight determination of the product obtained could not be carried out because of the extreme insolubility of the product. A crude approximation of the molecular weight was obtained by polymerizing accurately weighed amounts of monomer and catalyst, determining weight increments, extracting unreacted monomer and by various assumptions arriving at a degree of polymerization. By assuming that the chain termination process is by disproportionation or combination, the data indicate the degree of polymerization to be from 15 to 30 for the product polymerized open to the atmosphere and 25 to 50 for the product polymerized under nitrogen.

This low degree of polymerization agrees with the results of Bartlett and Altschul[18] who found the degree of polymerization of allyl acetate to be

(14) M. S. Kharasch, A. Fono and W. Nudenberg, *J. Org. Chem.*, **15**, 763 (1950).

(15) M. S. Kharasch, A. Fono, W. Nudenberg and B. Bischof, *ibid.*, **17**, 207 (1952).

(16) M. S. Kharasch, F. S. Arimoto and W. Nudenberg, *ibid.*, **16**, 1556 (1951).

(17) E. R. Bell, J. H. Raley, F. F. Rust, F. H. Seubold and W. E. Vaughn, *Faraday Soc. Disch.*, **10**, 242 (1951).

(18) P. D. Bartlett and R. Altschul, THIS JOURNAL, **67**, 812 (1945); **67**, 816 (1945).

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from 13 to 14 and attributed this low degree of polymerization to resonance stabilization of the monomer by transfer of the α-hydrogen atom to a chain radical. Later work by these authors[19] showed that this was the case.

Consideration of the proposed cyclic intramolecular polymerization of diallyl phthalate by Simpson, Holt and Zeite[7] and the degradative chain transfer in the polymerization of allyl acetate by Bartlett and co-workers[18,19] leads to the belief that the polymerization of allyl quaternary derivatives is affected by both factors. Cyclic intramolecular polymerization, greatly influenced by chain termination caused by α-hydrogen transfer, could account for the soluble, non-cross-linked, low molecular weight and unsaturated polymers obtained in this work.

This study has provided evidence that a suggested alternating intramolecular–intermolecular chain propagation occurs when unsaturated quaternary ammonium salts are polymerized and shows that a polymer of average degree of polymerization of approximately 25 or 50 is obtained when diethyldiallylammonium bromide is polymerized under nitrogen with *t*-butyl hydroperoxide as catalyst. It also shows that this chain propagation mechanism is followed by an average of four-fifths of the monomer units entering the chain, leaving an average degree of unsaturation in the polymer equivalent to one-fifth double bond per monomer unit in the chain.

Acknowledgment.—We wish to express our appreciation to the Atomic Energy Commission who supported this work under terms of Contract No. AT-(40-1)-1353. Thanks are also due to Dr. C. S. Marvel of the University of Illinois for reading the original manuscript and to Dr. Alan Crawshaw of this Department for many helpful suggestions.

GAINESVILLE, FLORIDA

(19) P. D. Bartlett and F. A. Tate, THIS JOURNAL, **75**, 91 (1953).

[CONTRIBUTION FROM THE DEPARTMENTS OF BIOLOGICAL CHEMISTRY AND CHEMISTRY OF THE UNIVERSITY OF UTAH]

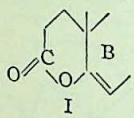
Rearrangement in the Addition of Grignard Reagents to Enol Lactones

BY KENNETH D. ZWAHLEN,[1] W. J. HORTON AND GEORGE I. FUJIMOTO

RECEIVED DECEMBER 6, 1956

Grignard reagents add to the acyl portion of enol lactones with rearrangement of this acyl carbon to the β-olefinic carbon atom. Further addition of Grignard reagent is subject to steric considerations. Such rearrangements were found in the case of a model steroid enol lactone and also in the addition of Grignard reagents to vinyl acetate and isopropenyl acetate.

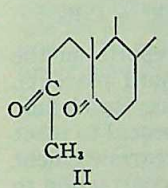
The addition of methylmagnesium halide to enol lactones derived from steroids (I) has been a useful method for the synthesis of Δ^4-3-keto steroids containing C^{14} at position 4[2] and for the closure of the A ring in the synthesis of steroids.[3]



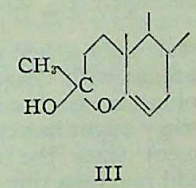
I

An intermediate in this process has been assigned various structures (II,[2a] III,[2c] with phenylmagnesium bromide IV).[4] Structure II for the intermediate from the enol lactone derived from cholestenone, however, is not identical with II from an independent source.[2c,5]

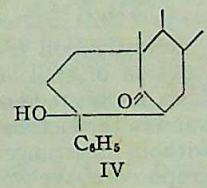
The present investigation was undertaken in order to test whether a structure of type IV would satisfy the requirements for the intermediate obtained when the enol lactone from cholestenone was combined with methylmagnesium halide.[6] For this purpose a model V of a steroid enol lactone was studied.



II



III



IV

Model V, when treated with methylmagnesium iodide or phenylmagnesium bromide, gave VI and VII, respectively. The structure of VII was confirmed by an independent synthesis (formulas V–X). Reduction of VII with lithium aluminum hydride gave VIII, thus adding support for VII. This diol formed a cyclic sulfite ester IX which enables the assignment of an $8\beta,11\alpha$-configuration. These reactions are not easily explainable on the basis of the hemiketal structure (type III).

The reaction of V to yield VI (or VII) involves the migration to an olefinic carbon atom. Such migrations occur when Grignard reagents are added to the simplest enol esters. Methylmagnesium iodide, added to isopropenyl acetate (XI), gave 2,4-dimethyl-2,4-pentanediol (XIII), identical with material prepared as reported.[7] Similarly, ethyl-

(1) From the Doctoral Dissertation of K. D. Zwahlen, Eastman Kodak Fellow, 1955–1956.

(2) (a) G. I. Fujimoto, THIS JOURNAL, **73**, 1856 (1951); (b) G. I. Fujimoto and J. Prager, *ibid.*, **75**, 3259 (1953); (c) R. D. H. Heard and P. Ziegler, *ibid.*, **73**, 4036 (1951).

(3) (a) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952); (b) P. Wieland, H. Ueberwasser, G. Anner and K. Miescher, *Helv. Chim. Acta*, **36**, 1231 (1953); (c) L. B. Barkley, *et al.*, THIS JOURNAL, **76**, 5014 (1954); **78**, 4111 (1956).

(4) S. A. Julia, A. Eschenmoser, H. Heusser and N. Tarköy, *Helv. Chim. Acta*, **36**, 1885 (1953).

(5) H. Schmid and K. Kagi, *ibid.*, **33**, 1583 (1950).

(6) The part of this work which was carried out on steroids is to be the material in a separate paper.

(7) (a) P. H. Hermans, *Z. anorg. Chem.*, **142**, 101 (1925); (b) J. English, Jr., and F. V. Brutcher, Jr., THIS JOURNAL, **74**, 4279 (1952); (c) J. Lemaire, *Ann. Pharm. Franc.*, **8**, 22 (1910).

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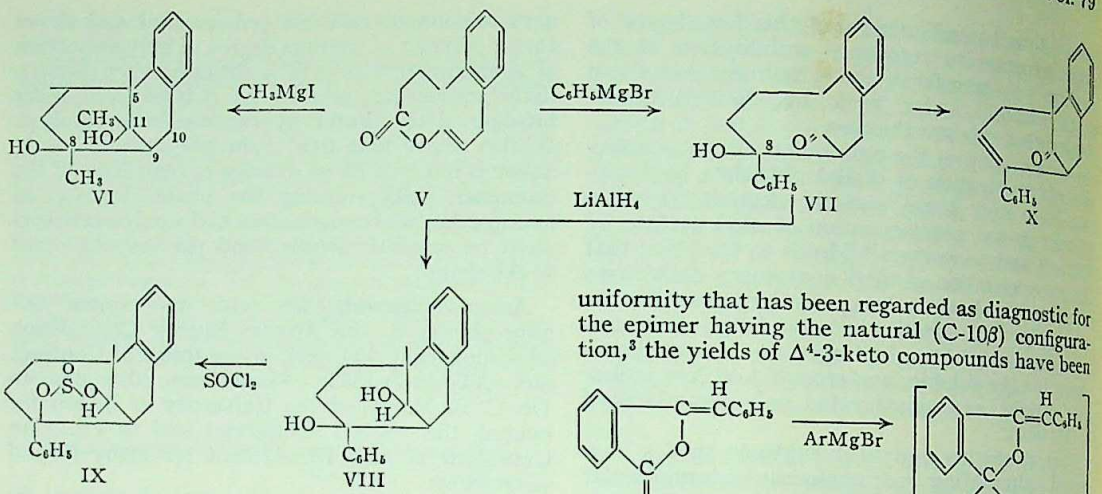
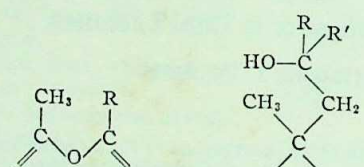


magnesium bromide, added to vinyl acetate (XII) gave 3-methyl-3,5-heptanediol (XIV).[8] In both cases the product obtained may be understood if the rearrangement proposed above is followed by further addition of Grignard reagent to the carbonyl group liberated from its enolic form.



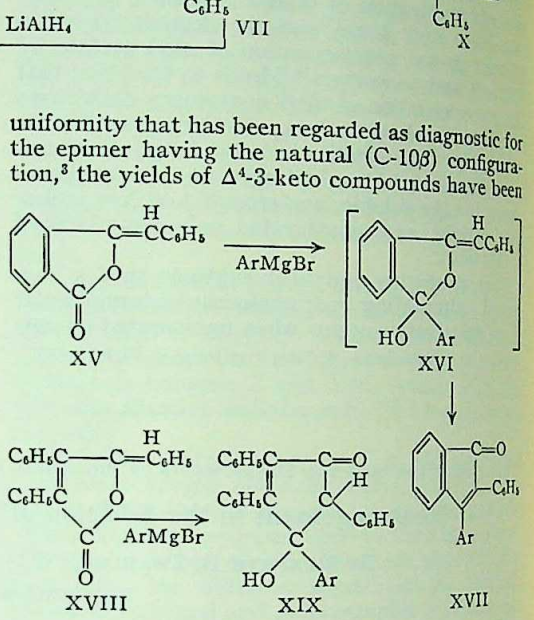
XI, R = CH_3
XII, R = H

XIII, R = R′ = CH_3
XIV, R = H; R′ = C_2H_5

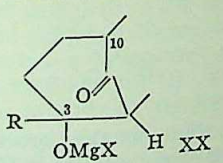
Investigation reveals only a few reports on the reaction of enol lactones with Grignard reagents. A six-membered enol lactone containing the olefinic bond in the lactone ring[9] might be expected to react without rearrangement since the rearrangement proposed above would require a ring contraction to a four-membered ring. Benzalphthalide (XV) gave XVII when treated with arylmagnesium bromides.[10a] The analogous reaction with benzaldiphenylmaleide[11] (XVIII) gave a colorless intermediate. The properties of the intermediate were satisfied by assigning to it a hemiketal structure (type III or XVI) and XVI was suggested[11] for the intermediate from XV which could not be isolated.

We propose that all of the properties found for the intermediate from XVIII would also be expected of the structure XIX which would arise if the Grignard–enol lactone rearrangement occurred. The single exception is the recovery of unchanged intermediate on treatment with phenylmagnesium bromide, a behavior which might be expected if XIX were highly enolic.

If the addition or non-addition of Grignard reagent to XX depended on steric factors, it would account for the experience of those employing this procedure for the synthesis of steroids. With a uniformity that has been regarded as diagnostic for the epimer having the natural (C-10β) configuration,[3] the yields of Δ^4-3-keto compounds have been



good, whereas the yields with the epimer having the C-10α-configuration have been poor. Variation in experimental conditions and in amounts of the methyl Grignard reagent did not improve this result.[3a] It, appears likely therefore, that akin to our reaction with V to yield VI, further addition of methyl Grignard reagent in the steroid synthesis work gave rise to a diol which could not dealdol with base and hence could not close again to the desired Δ^4-3-keto compound. In the natural series, steric factors prevented further Grignard addition to the carbonyl bridge, thus yielding a β-hydroxyketone which was converted by base to a Δ^4-3-keto compound. Our isolation of VII suggests that further addition of Grignard reagent in this case must be controlled by the configuration at C-8 (methanocycloöctabenzene numbering) since V is composed only of enantiomorphs.



The model compound V was obtained by lactonization of XXII which in turn was obtained from known[12] 1-methyl-2(1H)-3,4-dihydronaphthalenone (XXI) by alkylation with ethyl β-bromopropionate. Excess of methylmagnesium iodide at room temperature gave VI (42%). The analytical data clearly indicated that two moles of

(8) Pastureau and Zamenhof, *Bull. soc. chim.*, **39**, 1430 (1926).
(9) B. Belleau, THIS JOURNAL, **73**, 5441 (1951).
(10) (a) R. Weiss and R. Sauermann, *Ber.*, **58B**, 2736 (1925); (b) R. Weiss, K. Grobstein and R. Sauermann, *ibid.*, **59B**, 301 (1926).
(11) A. Lowenbein and G. Ulrich, *ibid.*, **58B**, 2603 (1925).
(12) (a) N. V. Organon, Dutch Patent 67,888, May 15, 1951 (*Chem. Abst.*, **46**, P2580 (1952)); (b) J. W. Cornforth, R. Cornforth and R. Robinson, *J. Chem. Soc.*, 689 (1942).

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the Grignard reagent had been acquired as opposed to three moles if a structure such as II had been available. An attempt to prepare the diketone similar to II by the addition of the methiodide of 1-diethylamino-3-butanone to XXI[13] failed because cyclization occurred to XXIV as shown by analytical data, ultraviolet absorption at 236 mμ and strong absorption at 5.97 μ (carbonyl group).

The addition of phenylmagnesium bromide to V gave VII (33%) identical with the product from XXI and β-dimethylaminopropiophenone. The identity of these materials was shown by their infrared and ultraviolet absorption curves. The carbonyl group was demonstrated by the preparation of an oxime and a 2,4-dinitrophenylhydrazone. The reduction of the carbonyl with lithium aluminum hydride to VIII, the formation of a cyclic sulfite ester IX and the dehydration of VII to an olefin X which contains a carbonyl group are reactions consistent with the proposed structure for VII. Catalytic hydrogenation of X gave a product whose analysis indicated that one mole of hydrogen had been added, but this material gave no 2,4-dinitrophenylhydrazone and was inert to Huang-Minlon reduction. By Clemmensen reduction, dihydro-X gave an oil, $C_{20}H_{20}$, according to the analytical data. The rearrangement which seems to take place was not investigated.

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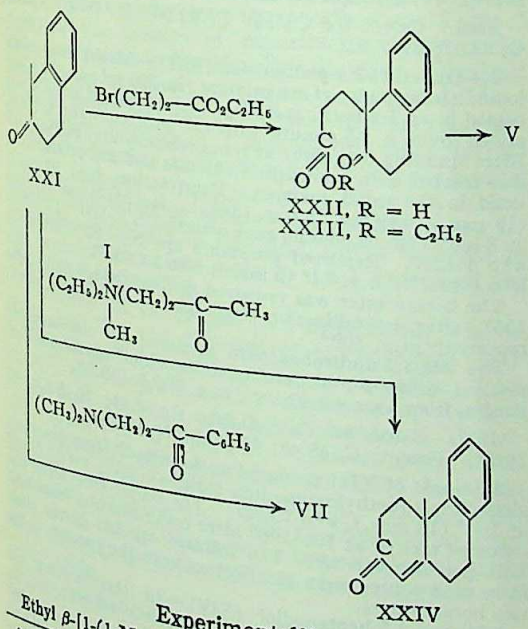

Experimental[14]

Ethyl β-[1-(1-Methyl-2-oxo-1,2,3,4-tetrahydronaphthyl)]-propionate (XXIII).—2(1H)-3,4-Dihydronaphthalenone was prepared according to a published procedure[15] in 68% yield, b.p. 132° (14 mm.), reported[12b] 139° (18 mm.). It was alkylated with methyl iodide[12a] to yield XXI in 50% yield, b.p. 134° (14 mm.), reported[12b] b.p. 137–138° (18 mm.). When the unreacted and the dimethylated compounds were not removed,[12b] lower yields were obtained in the subsequent reactions.

In an atmosphere of nitrogen 39.0 g. (0.238 mole) of XXI was added over a 30-minute period with stirring to 9.2 g. (0.236 mole) of powdered potassium in 500 ml. of benzene. The reaction was refluxed for 1 hr., cooled and 50.0 g. (0.275 mole) of ethyl β-bromopropionate was added dropwise. The reaction was refluxed for 1 hr. and allowed to stand overnight. After acidification with dilute sulfuric acid and addition of water, the benzene layer was separated, the aqueous layer was extracted with ether and the ether–benzene solution was washed with 5% sodium bicarbonate and with water. The solvents were removed at reduced pressure and the residue was rapidly distilled. The fraction b.p. 140–160° (0.5 mm.) (33.7 g.) was redistilled. The fraction b.p. 133–136° (0.2–0.3 mm.) (28.4 g., 48%) was a pale yellow viscous liquid. A portion redistilled for analysis boiled at 133–134° (0.2 mm.), $n^{26}D$ 1.5250.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.50; H, 7.70.

The semicarbazone crystallized from aqueous ethanol melted at 123.5–125°.

Anal. Calcd. for $C_{17}H_{23}O_3N_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.42; H, 7.22; N, 13.08.

The bicarbonate-soluble acid XXII obtained (88%) by saponification in aqueous alcoholic sodium hydroxide was a light yellow oil which was used without further purification.

The semicarbazone of the acid crystallized from absolute ethanol and melted at 189–190° (gas evol.) when inserted at 170° and heated 3° per minute.

Anal. Calcd. for $C_{15}H_{19}O_3N_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.02; H, 6.64; N, 14.00.

β-[1-(1-Methyl-2-hydroxy-1,4-dihydronaphthyl)]-propionic Acid Lactone (V).—A solution of 22.2 g. of XXII and 2 g. of *p*-toluenesulfonic acid in 75 ml. of acetic anhydride and 100 ml. of benzene was allowed to stand at room temperature overnight. After addition of 1 g. of sodium acetate the solvents were removed *in vacuo* at room temperature. The residue was combined with benzene, the salts were removed by filtration and the solution was distilled to yield 17.7 g. (87%), b.p. 155–162° (0.6 mm.). The distillate crystallized slowly to a pale yellow solid, m.p. 98–100°. The analytical sample sublimed at 95° (bath temperature) (0.2 mm.), m.p. 99–102°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.17; H, 6.70.

The compound was hygroscopic and hydrolyzed unless stored in a desiccator.

8,11-Dihydroxy-5,8,11-trimethyl-5,6,7,8,9,10-hexahydro-5,9-methanocycloöctabenzene (VI).—Methylmagnesium iodide (from 1.3 g. (54 mmoles) of magnesium) in 25 ml. of ether was treated with 2.00 g. (9.5 mmoles) of V in 50 ml. of ether. After 3 hr. at room temperature 100 ml. of saturated ammonium chloride was added, the layers were separated and the water layer extracted with ether. The combined ether layers, washed with water and dried over calcium sulfate, were distilled *in vacuo*. The residual pale yellow oil weighed 2.2 g. Chromatographed on 200 g. of acid-washed alumina, the acetone eluate weighed 0.97 g. (42%), m.p. 130–135°. Crystallized from benzene–petroleum ether and then several times from dilute methanol, the material melted at 143–145°, softening at 141°.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.00; H, 9.00. Found: C, 78.23; H, 8.82.

4a-Methyl-4,4a,9,10-tetrahydro-2(3H)-phenanthrone (XXIV).—The methiodide from 11 g. of 1-diethylamino-3-butanone was prepared by the addition of 11 g. of methyl iodide in small portions over a 30-minute period while cooling in an ice-bath. It was then allowed to stand in the ice-bath for 1 hr. and for 45 minutes at room temperature. A solution of 12.4 g. of XXI in 75 ml. of benzene was added, the air in the flask was replaced by nitrogen and a solution of 4.76 g. of potassium in 75 ml. of absolute ethanol was added

(13) A. L. Wilds and C. H. Shunk, THIS JOURNAL, 65, 469 (1943).

(14) Melting points of analytical material were taken on a Kofler hot-stage and are corrected. Petroleum ether refers to the fraction b.p. 30–60°.

(15) Kanojia Collection and H. R. Sexton, *J. Chem. Soc.*, 1038 (1952).

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over a 5-minute interval with cooling. After 1.5 hr. in the ice-bath with occasional swirling followed by 30 minutes of refluxing, the cooled mixture was acidified with dilute sulfuric acid and diluted with water. The benzene layer was separated, the aqueous layer was extracted with ether and the ether–benzene solution was washed with water, 5% sodium bicarbonate and finally with water. After drying over sodium sulfate the solvents were distilled *in vacuo* and the residue distilled, b.p. 130–160° (0.5 mm.), 5.60 g. (34%). The material crystallized from benzene–petroleum ether, m.p. 90–91°, $\lambda_{max}^{ethanol}$ 236 mμ (log ε 4.23), strong infrared absorption at 5.97 μ indicating an α,β-unsaturated carbonyl group.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.89; H, 7.56.

8-Hydroxy-5-methyl-11-oxo-8-phenyl-5,6,7,8,9,10-hexahydro-5,9-methanocycloöctabenzene (VII). (a).—Phenylmagnesium bromide (from 0.27 g. of magnesium) in 25 ml. of ether was added during 1 hr. with constant stirring to a suspension of 2.0 g. of V in 25 ml. of ether with cooling in an ice-bath. Stirring was continued for 30 minutes and then the mixture was refluxed for 1 hr. and allowed to stand overnight. The product was isolated according to the procedure with methylmagnesium iodide above and the pale yellow oil obtained crystallized when benzene and petroleum ether were added. The product weighed 0.87 g. (33%), m.p. 173–174°. Crystallized from benzene–petroleum ether, it melted at 178–179° and at 180–182° on admixture with the material obtained below. The infrared and ultraviolet spectra of the two products were identical.

(b).[16]—Thirty-nine grams (0.2 mole) of β-dimethylaminopropiophenone hydrochloride[17] in 400 ml. of ethyl alcohol at the boiling point was treated with 32 g. (0.2 mole) of XXI and then with 16 g. (0.4 mole) of sodium hydroxide in 80 ml. of water added in one portion. After 15 minutes refluxing, the solution was cooled in an ice-bath, acidified with hydrochloric acid and concentrated to one-third its volume by distillation from a steam-bath at reduced pressure. The waxy solid was filtered, washed with water and dried. Two crystallizations from benzene–petroleum ether gave 24.0 g. (41%) of crystals, m.p. 169–175°. Repeated crystallization from benzene–petroleum ether yielded material, m.p. 184.5–186°.

Anal. Calcd. for $C_{29}H_{29}O_2$: C, 82.16; H, 6.90. Found: C, 82.15; H, 6.90.

The oxime, crystallized from aqueous dioxane–ethanol, melted at 248–251° with slight darkening.

Anal. Calcd. for $C_{29}H_{21}O_2N$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.82; H, 6.72; N, 4.9.

The 2,4-dinitrophenylhydrazone from aqueous ethanol melted at 214–218°.

Anal. Calcd. for $C_{35}H_{24}O_5N_4$: C, 66.09; H, 5.12; N, 11.86. Found: C, 66.50; H, 5.21; N, 11.51.

8,11-Dihydroxy-5-methyl-8-phenyl-5,6,7,8,9,10-hexahydro-5,9-methanocycloöctabenzene (VIII).—A solution of 2.92 g. (10 mmoles) of VII in 200 ml. of anhydrous ether was added slowly to a slurry of 0.4 g. of lithium aluminum hydride in 50 ml. of ether. After 3 hr. a slight excess of water was added, the ether was decanted and the residual salts were washed with chloroform. On removal of the solvents 2.8 g. of colorless solid, m.p. 170–188°, remained. Crystallization from acetone gave 2.0 g. (68%), m.p. 178–184°, and further purification from acetone gave VIII, m.p. 197–198°.

Anal. Calcd. for $C_{29}H_{22}O_2$: C, 81.59; H, 7.53. Found: C, 81.66; H, 7.35.

The Cyclic Sulfite Ester IX from VIII.—The diol VIII (2.0 g.) suspended in 50 ml. of anhydrous ether and 1.6 g. of pyridine was cooled in an ice-bath and a solution of 1.2 g. of thionyl chloride in 25 ml. of ether was added over a 30-minute period with stirring. Stirring was continued for 2 hr. while the reaction mixture came to room temperature. The pyridine hydrochloride was filtered and washed well with ethyl acetate. Evaporation of the ether–ethyl acetate solution gave 1.8 g. of colorless crystals which decomposed below 150° with gas evolution. Crystallization from benzene–petroleum ether and then repeatedly from acetone gave IX, m.p. 142–143° dec., if inserted at 120° and heated 3° per minute.

Anal. Calcd. for $C_{29}H_{20}O_3S$: C, 70.56; H, 5.92; S, 9.42. Found: C, 70.28; H, 5.88; S, 9.55.

5-Methyl-11-oxo-8-phenyl-5,6,9,10-tetrahydro-5,9-methanocycloöctabenzene (X).—After 40 hr. refluxing of a solution containing 24 g. of VII in 750 ml. of acetic acid and 125 ml. of hydrochloric acid, the solution was distilled under reduced pressure on the steam-bath. A benzene solution of the residue was washed with water, 5% sodium bicarbonate and finally with water. The dried benzene was then distilled at reduced pressure and the residue was distilled. The fraction b.p. 160–175° (0.5 mm.) was a pale yellow extremely viscous oil (16.9 g., 75%). The analytical sample boiled at 168° (0.4 mm.).

Anal. Calcd. for $C_{29}H_{18}O$: C, 87.55; H, 6.61. Found: C, 87.21; H, 6.59.

The 2,4-dinitrophenylhydrazone was obtained from ethyl acetate–ethanol as orange crystals, m.p. 206–206.6°. From chloroform–ethanol yellow crystals were obtained, m.p. 150° (gas evol.), with solidification and remelting at 205–206°.

Anal. Calcd. for $C_{35}H_{22}O_4N_4$: C, 68.71; H, 4.88; N, 12.33. Found: C, 68.50; H, 4.96; N, 12.32.

When a solution of 7.0 g. of X in 75 ml. of absolute ethanol with 500 mg. of platinum oxide was shaken under hydrogen at slightly above atmospheric pressure, one mole of hydrogen was consumed in 20 minutes and hydrogenation stopped. The product, isolated after removal of the catalyst, solidified when benzene and petroleum ether were added. It was crystallized once from aqueous ethanol (5.2 g., m.p. 135–139°) and repeated crystallization brought the melting point to 147.8–149°.

Anal. Calcd. for $C_{29}H_{20}O$: C, 86.91; H, 7.29. Found: C, 86.86; H, 7.17.

This dihydro-derivative of X failed to react with 2,4-dinitrophenylhydrazine and was recovered unchanged from hydrazine–sodium hydroxide treatment according to Huang-Minlon.[18]

On Clemmensen reduction of 4.0 g. of the dihydro-derivative of X, an oil (2.1 g.), b.p. 160–175° (0.6 mm.), was obtained. The sample for analysis boiled at 168° (0.5 mm.).

Anal. Calcd. for $C_{29}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.37; H, 7.22.

2,4-Dimethyl-2,4-pentanediol (XIII).—Methylmagnesium iodide (from 23 g. of magnesium) in 500 ml. of ether was cooled in an ice-bath, and 40 g. of isopropenyl acetate was added over a 45-minute interval with constant stirring. After standing overnight at room temperature, the mixture was treated with ammonium chloride and the product isolated in the usual manner. The fraction, b.p. 102–104° (19 mm.), weighed 28.6 g. (54%). Redistillation through an 8-inch Vigreux column gave material, b.p. 100° (17 mm.), $n^{20}D$ 1.4327. Reported constants are b.p. 89° (5 mm.), $n^{20}D$ 1.4327[7a]; b.p. 64° (2 mm.), $n^{20}D$ 1.4378.[7b]

The borate ester was prepared as described,[7a] m.p. 103–105°, after crystallization from benzene–petroleum ether; reported[7a] m.p. 102°.

The bis-3,5-dinitrobenzoate prepared by the excellent method using *p*-toluenesulfonyl chloride[19] gave colorless needles from aqueous ethanol, m.p. 166.5–168.2°.

Anal. Calcd. for $C_{21}H_{20}O_{12}N_4$: C, 48.46; H, 3.87; N, 10.77. Found: C, 48.43; H, 3.83; N, 10.88.

A sample of XIII prepared as described[7c] from diacetone alcohol and methylmagnesium iodide (in 34% yield) boiled at 100° (18 mm.), $n^{20}D$ 1.4327. The borate ester from this material melted at 104–106° after crystallization from benzene–petroleum ether. The infrared spectra of the diols from each source were identical as were the spectra of the two borate esters.

3-Methyl-3,5-heptanediol (XIV).—In the manner described above, vinyl acetate (0.4 mole) was added to 1 mole of ethylmagnesium bromide. The product boiled at 120–122° (19 mm.) (34%). The sample obtained on fractionation through an 8-inch Vigreux column boiled at 117° (16

(16) A. C. Cope and E. C. Herman, THIS JOURNAL, **72**, 3405 (1950).

(17) C. E. Maxwell, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 305.

(18) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(19) J. H. Brewster and C. J. Ciotti, Jr., *ibid.*, **77**, 6214 (1955).

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mm.), $n^{21}D$ 1.4416, $n^{18}D$ 1.4430; reported b.p. 112–114° (12 mm.), $n^{21}D$ 1.441[20]; b.p. 121° (23 mm.), $n^{18}D$ 1.4467.[8] The bis-3,5-dinitrobenzoate prepared as in the above case crystallized from acetone–methanol; m.p. 156.3–157°.

Anal. Calcd. for $C_{22}H_{22}O_{12}N_4$: C, 49.44; H, 4.15; N, 10.48. Found: C, 49.77; H, 4.32; N, 10.30.

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(20) J. E. Dubois, *Ann. chim.* (*Paris*), **6**, 406 (1951).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH INSTITUTE OF NON-AQUEOUS SOLUTIONS, TOHOKU UNIVERSITY]

The Beckmann Rearrangement in Liquid Sulfur Dioxide. II.[1] Rearrangement by Halogen

BY NIICHIRO TOKURA, RYUZO ASAMI AND RITSURO TADA

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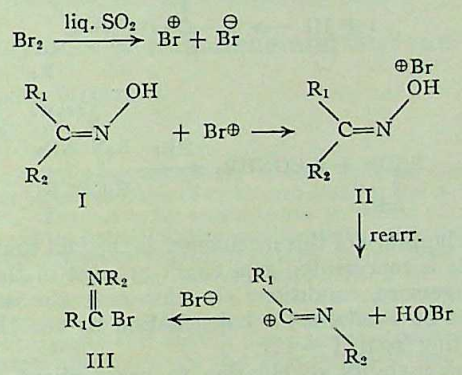
The Beckmann rearrangement of ketoximes may be effected by bromine and iodine in liquid sulfur dioxide at room temperature. Chlorine and sulfuryl chloride are without effect, but the addition of a small quantity of bromine (0.02:1 mole ratio) to these reagents leads to rearrangement. The oximes studied were those from cyclohexanone, cyclopentanone, acetophenone and benzophenone; in the case of aromatic oximes the reaction products were brominated or chlorinated amides. A possible mechanism is discussed.

Previous work has shown that the Beckmann rearrangement may be carried out in liquid sulfur dioxide at room temperature with sulfur trioxide,[1,2] with thionyl chloride and with a variety of phosphorus compounds.[1] It now has been found that the rearrangement may also be effected in sulfur dioxide solution by bromine, by iodine and by chlorine or sulfuryl chloride in the presence of small amounts of bromine (1:1:0.02 mole ratio for oxime:chlorine:bromine). Chlorine and sulfuryl chloride did not induce rearrangement when they were used without added bromine.

Rearrangements of the oximes of cyclohexanone, cyclopentanone, acetophenone and benzophenone were studied under varying conditions. Table I contains the results of experiments with cyclohexanone oxime in liquid sulfur dioxide. The best results were obtained with a 1:1 mole ratio of bromine to oxime (58 and 64% yield of ε-caprolactam for reaction periods of 1 and 24 hr., respectively) and with chlorine and sulfuryl chloride containing a small amount of bromine (67–72% yield of lactam). The yield of amide was not increased by increasing amounts of bromine, but a decrease in the bromine to oxime ratio to 0.5:1 decreased the yield of amide to 39%.

The bromine procedure (1:1 mole ratio, 1 hr. at 20°) and the chlorine–bromine procedure (1:1:0.02 mole ratio for oxime:chlorine:bromine, 1 hr. at 20°) were applied to the oximes of cyclopentanone, acetophenone and benzophenone. The results are given in Table II. Amides from acetophenone oxime and benzophenone oxime were halogenated under these conditions. Halogenation evidently occurred after the rearrangement reaction, since the products from benzophenone oxime were those to be expected from the halogenation of benzanilide.

The mechanism of the rearrangement is thought to be



This mechanism requires a 1:1 mole ratio of bromine to oxime for complete reaction. The formation of an amide from the intermediate III may occur during the reaction or at the time of addition of water to the reaction mixture. An alternate

TABLE I

ACTION OF HALOGEN ON CYCLOHEXANONE OXIME IN LIQUID SO_2[a]

Reagent	Molar ratio of oxime to halogen	Lactam formed, yield, %
Br_2,H_2O[b]	1:1	0
Br_2,H_2O[c]	1:1	0
Br_2	1:0.5	39.2[e]
Br_2	1:1	58.0
Br_2	1:1.4	59.2
Br_2[d]	1:1	64.0
I_2	1:1	34.0
Cl_2	1:1	0
SO_2Cl_2	1:1	0
Cl_2,Br_2	1:1:0.1	72.4
Cl_2,Br_2	1:1:0.02	67.2
Cl_2,Br_2	1:1:0.02	66.8
Cl_2,I_2	1:1:0.1	12.4
SO_2Cl_2,Br_2	1:1:0.02	70.4

[a] Reaction carried out at 20° for 1 hr., with 25 g. (0.22 mole) of the oxime and 200 ml. of liq. SO_2. [b] Molar ratio of bromine to water was 1:2. [c] Molar ratio of bromine to water was 1:1. [d] Reaction carried out at 20° for 24 hr. [e] 78.4% on the basis of bromine used.

(1) For the first paper of this series, see N. Tokura, R. Asami and R. Tada, *Sci. Reports Research Inst., Tohoku Univ.*, **8**, 149 (1956).

(2) German Patent 858,397 (1952); *C. A.*, **48**, 12810 (1954); British Patent 732,890 (1955); *C. A.*, **50**, 5738 (1956).

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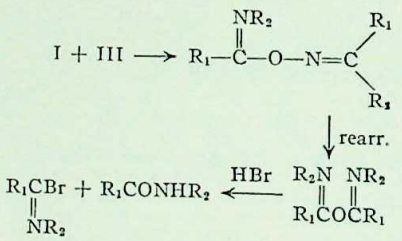
TABLE II

ACTION OF HALOGEN ON KETOXIMES IN LIQUID SO_2[a]

Oxime of	Reagent	Molar ratio of oxime to halogen	Rearrangement product	Yield, %
Cyclopentanone	Br_2	1:1	δ-Valerolactam	37.2
Acetophenone	Br_2	1:1	*p*-Bromoacetanilide	32.0
Benzophenone	Br_2	1:1	N-Benzoyl-*p*-bromoaniline	51.6
Cyclopentanone	Cl_2,Br_2	1:1:0.02	δ-Valerolactam	52.2
Acetophenone	Cl_2,Br_2	1:1:0.02	Acetanilide	32.5
			p-Chloroacetanilide	22.3
			N-Benzoyl-*o*-chloroaniline	28.4
Benzophenone	Cl_2,Br_2	1:1:0.02	N-Benzoyl-*p*-chloroaniline	51.7

[a] Reaction carried out at 20° for 1 hr. in liquid SO_2.

possibility also must be considered. From the work of Stephen and Staskun,[3] it is likely that III and the oxime might also react to form an intermediate in the Stephen–Staskun proposal for the Beckmann rearrangement. Thus



An advantage of this mechanism is the fact that the amide is represented as a direct product of the rearrangement condition. In this case the amide would be available for halogenation by the HOBr resulting from II → III.

The inability of chlorine to bring about rearrangement of an oxime under these circumstances may be due to a failure to form $Cl^{\oplus}$. The catalytic effect of bromine, when used with chlorine, can be ascribed to the regeneration of $Br^{\oplus}$ in the following way

$$Cl_2 + HOBr \longrightarrow ClBr + HOCl$$

$$ClBr \xrightarrow{\text{Liq. } SO_2} Cl^{\ominus} + Br^{\oplus}$$

The effect of bromine and water on the rearrangement reaction was also investigated. It is known that the reaction of bromine and water in liquid sulfur dioxide is[4]

$$Br_2 + 2H_2O + SO_2 \longrightarrow 2HBr + H_2SO_4$$

The hydrogen bromide remains in solution, but the sulfuric acid forms an insoluble lower layer. A mixture prepared in this way was not effective in bringing about the rearrangement of cyclohexanone oxime.

From the fact that the hydroxyl of the oxime undergoes reaction with a halogen in liquid sulfur dioxide, the hydroxyl of a substituted alcohol –C–OH should also undergo substitution with a halogen by the same procedure. Data on such a reaction will be published at later date.

(3) H. Stephen and B. Staskun, *J. Chem. Soc.*, 980 (1956).

(4) J. Ross, J. H. Percy, R. L. Brandt, A. I. Gebhart, J. E. Mitchell and S. Tolles, *Ind. Eng. Chem.*, **34**, 924 (1942).

Acknowledgment.—The authors wish to thank a reviewer for his help and Emeritus Prof. Dr. R. Hara for his interest and encouragement in this investigation. The authors are indebted to Miss Y. Endo for the microanalyses, to the Befu Chemical Industries Co. for donation of the liquid sulfur dioxide used in this research and to the Ministry of Education of Japan for a grant.

Experimental

Reagents.—Oximes were made by reaction of the appropriate ketone and hydroxylamine according to the references indicated; the oximes were cyclohexanone oxime[5] (m.p. 89–90.5°), cyclopentanone oxime[6] (m.p. 56.5–57°), acetophenone oxime[7] (m.p. 59.5–60.5°) and benzophenone oxime[8] (m.p. 141.5–142°).

Liquid sulfur dioxide was used as a solvent. Commercial material was used after filtration. It was found unnecessary to redistil the liquid or to dry it with sulfuric acid or phosphorus pentoxide.

The chlorine was distilled before use. Bromine was dried with sulfuric acid in the usual way. The iodine was washed with water and dried before use. The sulfuryl chloride was distilled (b.p. 66.5–67.5° (760 mm.)).

Apparatus and General Procedure.—Glass pressure vessels (300-ml. capacity) equipped with metal joints were used. Liquid sulfur dioxide was added to the oxime, with ice-cooling of the vessel, and a solution of the halogen or other reagents in sulfur dioxide was then added. Reverse addition was used for iodine reactions, since this material is sparingly soluble in sulfur dioxide. Chlorine solutions were best prepared by the addition of chlorine to sulfur dioxide.

Rearrangement of Cyclohexanone Oxime (Table I).—To a solution of 25 g. (0.22 mole) of cyclohexanone oxime in 100 ml. of sulfur dioxide there was added 100 ml. of sulfur dioxide containing the reagents indicated in Table I in various molar ratios. After the indicated time at 20° (usually 1 hr.), water was added with chilling and the solvent was allowed to evaporate. The residue was neutralized with 25% sodium hydroxide solution, and the products were extracted with chloroform. The chloroform was removed (reduced pressure) and the mixture was distilled under reduced pressure to yield cyclohexanone (b.p. 55–65° (35–36 mm.)), unchanged oxime (b.p. 95–115° (10–11 mm.)) and ε-caprolactam (b.p. 120–130° (7–8 mm.)). The ε-caprolactam was recrystallized from ether to yield a product with m.p. 67–68°. This was hydrolyzed with 15% sodium hydroxide solution and benzoylated to ε-benzoylaminocaproic acid,[9] m.p. 80–80.5°, for identification purposes (a mixed m.p. with an authentic sample was not depressed).

Yields obtained with a variety of reagents and conditions are in Table I.

Rearrangement of Ketoximes (Table II).—A solution of 35.5 g. (0.22 mole) of bromine in 100 ml. of sulfur dioxide was added to a solution of 22 g. (0.22 mole) of cyclopentanone oxime in 100 ml. of sulfur dioxide. After 1 hr. at 20°, the reaction mixture was treated as in the previous set of experiments. From the chloroform extract there was obtained by distillation 8.2 g. (37.2%) of δ-valerolactam, collected at 130–140° (15–16 mm.). This material, m.p. about 30°, was converted for identification into 1,3-dioxo-2-isoindolinevaleric acid[10] by treatment with phthalic anhydride; the m.p. and mixed m.p. with an authentic sample was 117–118°.

When this reaction was repeated with a chlorine–bromine mixture (1:0.02 mole ratio), the yield was 52.2% of δ-valerolactam, collected at 130–140° (15–16 mm.) and identified as before.

For acetophenone oxime, the reaction was carried out in the following way. A solution of 16 g. (0.1 mole) of bromine in 50 ml. of sulfur dioxide was added to a solution of 13.5 g.

(5) E. W. Bousquet, *Org. Syntheses*, **11**, 56 (1931).

(6) S. W. Fox, M. S. Dunn and M. P. Stoddard, *J. Org. Chem.*, **6**, 411 (1941).

(7) A. Janny, *Ber.*, **15**, 2781 (1882).

(8) A. Lachman, *Org. Syntheses*, **10**, 10 (1930).

(9) A. Galat, THIS JOURNAL, **69**, 86 (1947).

(10) M. Taniyama, T. Takata and K. Sayama, *J. Chem. Soc. Japan, Ind. Sect.*, **53**, 645 (1950).

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(0.1 mole) of acetophenone oxime in 50 ml. of sulfur dioxide. After the reaction period, the sulfur dioxide was removed as usual and the residue was treated with 25% sodium hydroxide solution. The products were extracted with ether; the ether solution was dried and evaporated to yield 14.8 g. of material. Trituration with ether gave 7.9 g. of soluble material and 6.9 g. of colorless residue, m.p. *ca.* 155°, which was recrystallized from benzene to give a crystalline product with m.p. 164–165.5°, not depressed on mixture with authentic *p*-bromoacetanilide.

When the reaction was repeated on the same scale with a chlorine–bromine mixture, a yield of 14.5 g. of crude mixed products was obtained. This was triturated with benzene–ligroin (6.3 g. was soluble) to give 7.9 g. of colorless residue. Fractional crystallization from water gave 4.4 g. of material melting at about 100° and 3.8 g. of material melting at about 165°. Each fraction was crystallized from benzene; the products were identified as acetanilide (m.p. and mixed m.p. 113–114°) and *p*-chloroacetanilide (m.p. and mixed m.p. 171–172.5°).

The reaction with benzophenone oxime (19.7 g., 0.1 mole) was carried out in the usual way in 100-ml. total volume of sulfur dioxide. The yield of 18.7 g. of crude product was triturated in ether (4.4 g. of soluble material) to give 14.3 g. of orange powder, m.p. 201–202°. The m.p. was not depressed on mixture with authentic N-benzoyl-*p*-bromoaniline.

When a chlorine–bromine mixture was used with 0.1 mole of benzophenone oxime, crude product amounted to 20.3 g. This was triturated with benzene, and the benzene solution yielded 6.6 g. of N-benzoyl-*o*-chloroaniline, m.p. and mixed m.p. 99–101° after recrystallization from ethanol. The benzene-insoluble residue was fractionally crystallized to give 12 g. of N-benzoyl-*p*-chloroaniline, m.p. and mixed m.p. 187–188.5°, and an unidentified material (1.7 g.) with m.p. 150–152°.

Satisfactory nitrogen analyses were obtained for all reaction products.

Reactions with Bromine–Water Mixture.—When a bromine–water mixture was used in sulfur dioxide with cyclohexanone oxime, a rearrangement did not occur (Table I). Cyclohexanone and cyclohexanone oxime were recovered. For the reactions in Table I, the recovery of oxime was 74.0 and 87.6%.

SENDAI, JAPAN

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, POLYMER CORPORATION LTD.]

The Synthesis and Identification of Block Polymers of Butadiene and Styrene

BY R. J. ORR AND H. LEVERNE WILLIAMS

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A method of synthesizing polymeric dihydroperoxides in which the hydroperoxy groups are terminal has been evolved. The monomers are polymerized in emulsion at 12.8° using sufficiently large quantities of complexed iron(II) and *p*-diisopropylbenzene dihydroperoxide that mutual termination is dominant. The molecular weight of the polymeric dihydroperoxide is controlled by adjusting the emulsifier, the dihydroperoxide and the iron(II) sulfate concentrations. The residual hydroperoxide group on the polymer is protected from reaction by the short residence time in the aqueous phase. Such polymers after purification will initiate polymerization of a second monomer. The iodine monochloride adduct of butadiene–styrene copolymers is insoluble in carbon tetrachloride for high-butadiene polymers and soluble for low-butadiene polymers. This permitted verification that the polymers produced by initiating styrene polymerization with polybutadiene dihydroperoxide were not mixtures of polystyrene and polybutadiene but were composed of chemically linked blocks of polymers of the two compositions. This was supported by fractionation experiments which indicated that some bound styrene could not be extracted after cross-linking such a polymer. Evidence is presented that such results do not arise from chain transfer.

Introduction

Active interest in the field of block and graft polymers is comparatively recent, stimulated by the potential economic value of some novel product. While methods of grafting are numerous, since they depend only on placing side chains randomly along the main chain, the methods of forming block polymers are few due to the restriction on the location of the points of union of the blocks in the molecule. Several reviews[1–3] summarize methods. The methods have the defect that if they are simple and commercially feasible they offer little control over the structure of the final polymer. The problem of exerting control over the process and product seems to be the major difficulty.

It is important to establish by analytical methods the structure of the polymer postulated from kinetic reasoning. Fractionation of the product of the reaction may be tedious, and success in separating differing polymers depends on the difference in solubilities of the polymers. There is little difference between the solution properties of polybutadiene and polystyrene, so that this approach offers little promise, although some workers report successful fractionations of similar polymer mixtures.[4]

During the course of the study of the decomposition of hydroperoxides by iron(II), *p*-diisopropylbenzene dihydroperoxide was used.[5] This gave a free radical which underwent little side reaction relative to reaction with monomer. Considering the theories of emulsion polymerization as outlined by Harkins[6] and Smith and Ewart[7] suggested that sufficiently rapid decomposition of hydroperoxide might result in appreciable amounts of mutual termination according to the mechanism

$$\text{HOOROOH(aq)} + \text{Fe(II)} \longrightarrow \text{HOORO}\cdot\text{(aq)} + \text{Fe(III)}$$

$$\text{HOORO}\cdot\text{(aq)} + \text{M(aq)} \longrightarrow \text{HOOROM}\cdot\text{(aq)} \xrightarrow{(n-1)\text{M}} \text{HOOROM}_n\cdot\text{(oil)}$$

$$\text{HOOROM}_n\text{(oil)} + p\text{M(oil)} \longrightarrow (\text{HOOROM}_{n+p})\text{(oil)}$$

$$\text{HOOROM}_n\text{(oil)} + \text{HOOROM}_{n+p}\text{(oil)} \longrightarrow \text{HOOROM}_{2n+p}\text{OOROOH}$$

(1) H. W. Melville, *Plastics Inst., Trans. and Jour.*, **23**, 146 (1955).
(2) L. Valentine, *Fibres*, **16**, 12, 60 (1955).
(3) H. Mark, *Angew. Chem.*, **61**, 53 (1955).
(4) J. A. Blanchette and L. E. Melsen, *J. Polymer Sci.*, **20**, 317 (1956).
(5) R. J. Orr and H. Leverne Williams, THIS JOURNAL, **78**, 3273 (1956).
(6) W. D. Harkins, *J. Chem. Phys.*, **13**, 581 (1945); THIS JOURNAL, **69**, 1425 (1947); *J. Polymer Sci.*, **5**, 217 (1950).
(7) W. V. Smith and R. H. Ewart, *J. Chem. Phys.*, **16**, 592 (1948); THIS JOURNAL, **70**, 3695 (1948).

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This would be much more likely with diisopropyl benzene dihydroperoxide than other hydroperoxides since at the high steady state concentrations of hydroperoxy free radicals in the aqueous phase necessary to bring about rapid initiation of polymerization there would be less chance that the free radical would undergo side reactions with iron(II) or with the parent dihydroperoxide. If the residence time of the initiating radical in the aqueous phase be sufficiently short, then little opportunity of reaction of the remaining hydroperoxide group with the water-soluble iron(II) would occur, and a polymeric dihydroperoxide would be formed. Once this is formed, the polymeric hydroperoxide groups would be protected from decomposition by isolation from the water-soluble iron(II). Such a polymer when mixed with another monomer and heated should be capable of forming diradicals which would give rise to block polymer.

Experimental Methods.—The diisopropylbenzene dihydroperoxide (DHP) was obtained in solution in acetone. It was reported as being mostly *para*, although some of the *meta* form may have been present. The product was contaminated with an oil-soluble hydroperoxide, probably diisopropylbenzene monohydroperoxide. No attempt was made to remove it. The compound (DHP) was insoluble in hydrocarbons, probably due to the lipophobic nature of the hydroperoxide groups. The solubility in carbon tetrachloride was less than 0.085%. The solid dihydroperoxide was added to the 7-ounce reaction bottle initially followed by the emulsifier solution and high boiling monomers. The activator (an aqueous solution of iron(II) pyrophosphate) was added. Premature reaction was minimized by the separation of the activator from the dihydroperoxide. Excess volatile monomer was added last and allowed to evaporate to the correct weight to expel residual air. The beginning of agitation of the reaction was taken as zero time. The recipe was composed of 5 parts of potassium fatty acid soap and 320 parts of water per 100 parts of monomer. The large amount of water was necessary to accommodate the catalyst and activator. Reaction temperature was 12.8°.

Experimental

(a) **Molecular Weight of Polymeric Dihydroperoxides.**—The obvious method of controlling molecular weight of the polymeric dihydroperoxide is by changing the rate of free radical production by varying the activator and catalyst concentration in the recipe. The results are in Table I for a 72/28 butadiene/styrene ratio. The branching constants (k') were measured from the slope of the plot of ln η_{rel} *versus* c according to the Mead–Fuoss equation. These compare favorably at the lower molecular weights with those observed for polystyrene.[8]

The polymeric dihydroperoxides were soluble in benzene except when prepared with 0.2 and 0.5 part DHP. The intrinsic viscosity was determined on the soluble fraction of these, which accounts for the decrease in the value of k' from that obtained for the polymer prepared with 1.0 part of dihydroperoxide. The experiments were done using 5.3 parts of emulsifier and conducting the reaction to 100% conversion which was reached by 17 hr. Assuming mutual termination to be responsible for molecular weight control, then the molecular weight at any given rate of free radical production should be dependent on the ratio of the number of particles containing growing chains to the total number of particles. If this ratio be dependent on emulsifier concentration, molecular weight should be dependent on emulsifier concentration. This was investigated. The results are in Table II.

TABLE I

MOLECULAR WEIGHT CONTROL BY ACTIVATOR–CATALYST SYSTEM

Parts DHP	$[\eta]$	k'
0.2	1.64	0.50
0.5	1.01	.53
1.0	0.84	.58
3.0	.83	.46
5.0	.78	..
6.0	.52	.41
7.0	.74	..
10.0	.61	.31

TABLE II

MOLECULAR WEIGHT CONTROL BY VARIATION OF EMULSIFIER CONCENTRATION

100% Conversion in 17 hours; DPH, 10 parts; FESO·7H$_2$O/DHP/K$_4$P$_2$O$_7$,1/1/1

Parts emulsifier	$[\eta]$
7	0.4
10	0.7
15	1.0
20	1.0

(b) **Effect of Monomer Structure on Polymeric Dihydroperoxide Formation.**—Several monomers were polymerized in the preceding recipe containing 10 parts of DHP and DHP/FeSO$_4$·7H$_2$O/K$_4$P$_2$O$_7$ = 1. Those for which intrinsic viscosity data were obtained are in Table III.

TABLE III

FORMATION OF POLYMER DIHYDROPEROXIDES FROM VARIOUS MONOMERS

Initial monomer composition	$[\eta]$
Styrene	0.7
72% butadiene/28% α-methylstyrene	.8
Butadiene	.6
72% isoprene/28% styrene	.7
72% butadiene/28% *p*-chlorostyrene	.7
72% butadiene/28% vinylpyridine	.3

Other butadiene-containing polymers were prepared with a 72/28 charge ratio of butadiene to acrylonitrile, acrylamide or methyl methacrylate using gel as a criterion for molecular weight changes. The latter two pairs gave gel-free, low molecular weight polymers at 100% conversion. With the first-mentioned pair, it was necessary to reduce the proportion of acrylonitrile in the charge to 5% before the resulting polymer was soluble in benzene or methyl ethyl ketone. On replacing the anionic emulsifier with dodecylamine hydrochloride and reducing the *p*H to 4.5 with acetic acid, a polymer soluble in methyl ethyl ketone with an intrinsic viscosity of 0.3 in this solvent was obtained. This is believed to be related to a tendency[9] of hydroperoxides to react with acrylonitrile at high *p*H.

(c) **Stability of Polymeric Dihydroperoxides.**—When purifying butadiene-containing polymeric dihydroperoxides, the dry polymer cross-linked easily even after precipitation 3 or 4 times from benzene solution, due to the reactive nature of the polymeric dihydroperoxides. The polymers could be stored as 10% solutions in benzene or toluene at 50° without change of the intrinsic viscosity for at least 72 hr.

A characteristic behavior of the polymeric dihydroperoxides containing butadiene was the tendency for reaction of the double bounds when stored in carbon tetrachloride solution as shown by Fig. 1. After about 50% reaction of the double bonds (as measured by an iodine monochloride titra-

(8) J. A. Manson and L. H. Cragg, *J. Polymer Sci.*, **29**, 481 (1958).

(9) R. J. Orr and H. Leverne Williams, *Faraday Soc. Disc.*, **14**, 170 (1953).

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tion), the polymer began to precipitate. This cannot be due to cross-linking since reaction of less than 5% of the double bonds by such a process should yield 100% gel. It appears reasonable that addition of carbon tetrachloride imparting solvent resistance to the polymer is occurring. To confirm if this were the case, reaction of double bonds of mercaptan-modified polymers in the presence of free hydroperoxide was studied by iodine monochloride titration. It was necessary to treat the remaining hydroperoxide by shaking with aqueous iron(II) sulfate or to carry out a blank titration without polymer since the hydroperoxide reacted with iodine monochloride. With a saturated solution of dihydroperoxide, no reaction of double bonds occurred in 8 days at 50°. With diisopropylbenzene monohydroperoxide higher concentrations of hydroperoxide were attainable. There was an initial reaction of about 4% of the double bonds at 50° in 30 hr. after which time the double bond analysis became constant.

(d) **Initiation by Polymeric Dihydroperoxides.**—Polymeric dihydroperoxides will be formed if the residence time of the hydroperoxy terminated radical in the aqueous phase is sufficiently short that reaction with iron(II) sulfate cannot occur. If this is the case, the polymeric dihydroperoxide should initiate polymerization. To test this the polymer was dissolved in a benzene solution of monomer to give a solution 5.5% polymer and 55% monomer which was heated to 50° for 17 hr. According to Smets and Woodward,[10] the presence of benzene suppresses the formation of branched chains. Since care had to be exercised that the polymerization of the second monomer did not result from peroxidic impurities in the polymer, all polymers were purified by reprecipitation from benzene solution with methanol. In all instances, one precipitation was sufficient to reduce the hydroperoxide concentration in the polymer so that subsequent extraction with methanol did not remove sufficient hydroperoxide to detect by iodimetric methods. Removal of hydroperoxide reflects the insolubility of the free dihydroperoxide in benzene compared with methanol. At least one more purification step was applied to the polymer. Some data on the effect of the number of purifications on the activity of the polymer are in Table IV.

TABLE IV

EFFECT OF PURIFICATION ON POLYMERIZATION ACTIVITY AT 50°

Polymer type	No. of purifications	Increase in total polymer present, %
72/28 Bd/Sty	2	38
	4	10
Polystyrene	2	228
	3	166

The polymer retains initiating activity after concentrations of free hydroperoxide sufficiently large to be detected have disappeared. The difference in activity between the polymeric dihydroperoxides suggests that different structures for the dihydroperoxides must be assigned. This would not be so if free hydroperoxides were catalyzing the reaction. Under comparable condition it was found that a 0.7% solution of dihydroperoxide would polymerize styrene equivalent to only 44% of the total polymer. This amount of hydroperoxide is detectable by iodimetric analysis.

To investigate the factors affecting the activity of the polymeric dihydroperoxide, a series of polymeric dihydroperoxides of varying composition was prepared and chain-extended with a series of monomers with the results shown in Table V. The polymers were purified twice. The value at 1100% polymer increment indicates that polymerization had proceeded till the monomer supply was exhausted. Those reactions which proceeded only at 100° were preaged 17 hr. at 50°. While the data in this table may be affected by the tendency of the polymeric dihydroperoxide to lose activity during purification, there seems to be an inverse correlation between the polarity of the monomer–polymer pair and the reactivity. Experiments containing monomeric dienes proved to be exceptions since they were less reactive than monovinyl compounds.

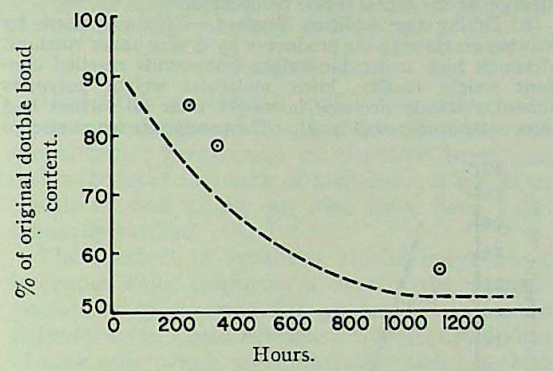

Fig. 1.—Double bond disappearance of polybutadiene dihydroperoxide in CCl_4 at 25°.

(e) **Effect of Iodine Monochloride on Copolymers and Their Mixtures.**—Consideration was given to methods other than fractional precipitation to prove that the polybutadiene chains were chemically linked to polystyrene units. Kemp and Peters[11] utilized iodine monochloride analyses for butadiene in a copolymer. This added quantitatively to the double bond in the polymerized butadiene in dichlorobenzene solution. It was noted that when carbon tetrachloride was used as a solvent, iodine monochloride consumption gave reproducible values for the bound butadiene and that a voluminous white precipitate formed with polymers richer in butadiene. Since no reaction between polymers of monovinyl compounds and iodine monochloride occurred, it was felt that this would be a method for analyzing polymeric mixtures in which one substituent was a polymer or copolymer of a diene.

(f) **Determination of Iodine Monochloride Consumption.**—Since the addition product may weigh nearly four times as much as the polymer from which it is formed, the importance of a precise determination of the iodine monochloride consumption is obvious; 0.05 molar solution iodine monochloride was added to 0.12 g. of polybutadiene or its equivalent so as to give an amount of iodine monochloride 100% in excess of the theoretical requirement. After the reaction proceeds to completion, the residual iodine monochloride was titrated with 0.1 *N* sodium thiosulfate to a starch endpoint. With 100% excess, no changes in iodine monochloride reacted occurred between 15 minutes and 1 hr. so that the titration could be made after 15 minutes. A polymer was prepared in a conventional recipe with a charge ratio of 72/28 butadiene/styrene. It was possible to determine the butadiene content (and hence the iodine monochloride

TABLE V

EFFECT OF COMPOSITION ON REACTIVITY OF MONOMER–POLYMER PAIR

Monomer	Increment in polymer during reaction, %									
	Chlorostyrene		Styrene		Methyl methacrylate		Vinylpyridine		72/28 Bd/Sty	
Polymer	50°	100°	50°	100°	50°	100°	50°	100°	50°	100°
Butadiene	600	..	122	..	0	500	0	..	0	300
72/28 Bd/Sty	..	1100	38	332	0	1100	0	200	..	332
Styrene	..	1100	228	..	0	1100	0	119	0	134
72/28 Bd/MMA	0	1100	0	1100	0	1100	0	270	..	..
Methyl MA	0	1100	0	615	..	..	0	43	0	173

(10) G. Smets and A. E. Woodward, *J. Polymer Sci.*, **14**, 1 (1954).

(11) A. R. Kemp and H. Peters, *Ind. Eng. Chem., Anal. Ed.*, **15**, 453 (1943).

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content of the precipitate) as 75.28 ± 0.15% based on 12 determinations.

(g) **Filtration of the Addition Product.**—Filtration of the addition products for high molecular weight polymers proved much easier than for low molecular weight compounds. The latter plugged the pores of sintered glass filters and necessitated the use of ground glass as a filtration aid. The precipitate particles were trapped in a thick pad of ground glass over the fritted disk. The precipitate adhered to the walls of the flask if there was water in the reaction flask. Each experiment was done using two identical samples, since filtration could not be done with the sample intended for back titration of the excess iodine monochloride.

(h) **Drying the Addition Product.**—This was done by drawing air through the product or by drying under vacuum. Although high molecular weight compounds reached constant weight readily, lower molecular weight polymers showed a steady decrease in weight after all solvent had apparently vanished (Fig. 2). The precipitate may undergo

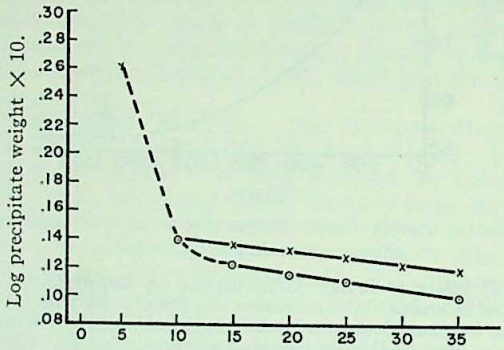

Fig. 2.—Dependence of weight of ICl addition product on drying time for low molecular weight polybutadiene.

some thermal change. By choosing the point of inflection in the weight *vs.* time curve as the correct weight, it was possible to account for all polymer present within ±2%. The precision could be improved to that characteristic of analysis of high molecular weight polymers on a relative scale. To determine the amount of styrene which had been blocked onto the ends of a polybutadiene chain, the weight–time curve of the block polymer precipitate was compared with that curve derived from a precipitate of an equal amount of the original polybutadiene. The difference was nearly independent of time. For higher molecular weight products it was possible to recover 99.5% ± 0.6% of the total for four polymer samples.

(i) **Effect of Styrene Content on Precipitation.**—Polymers were prepared from varying charge ratios, and the effect of styrene content on the tendency to precipitate was investigated. The results are in Table VI. It is interesting that the total change in solubility occurs over a region of less than 10% bound styrene.

Table VI

Influence of Styrene Content on Recovery of Precipitate

Styrene, %	[η]	Theor. ppt., %
0	0.6	100
25	1.5	99.7
40	1.5	100.2
50	1.5	Cloudy
70	1.5	Clear

(j) **Analysis of Mixtures of Polymers and Copolymers of Butadiene and Polystyrene.**—A 75/25 butadiene/styrene copolymer was mixed with twice its weight of polystyrene. The butadiene-containing portion was precipitated with iodine monochloride. Complete recovery of this portion could be made in this fashion when the volume of CCl_4 present was 600 cc. When only 300 cc. was used, it was difficult to wash the precipitate free of polystyrene. The precision of determinations in a volume of 600 cc. is that predicted from the reproducibility of each step in the process, indicating no significant absorption of polystyrene on the precipitate. Polystyrene, when mixed with polybutadiene, showed no effect on recovery up to 4/1 ratio.

(k) **Effect of Various Solvents.**—Carbon tetrachloride was the only suitable solvent found for this precipitation. No precipitation occurred in benzene, chlorobenzene, ether, pentane, ethylene dichloride, chloroform or ethanol–carbon tetrachloride mixes. Addition of the ICl to the double bond occurred in all instances.

(l) **Study of Chain Extension Step by Iodine Monochloride Technique.**—Two aspects were considered: (i) The tendency of the iodine monochloride adduct to become soluble in CCl_4 when chain extension was great. (ii) The degree to which it was possible to recover in this adduct all of the polymer formed when chain extension was little.

In each series polybutadiene dihydroperoxide was dissolved in benzene, styrene added to the solution and the temperature raised to 50°. In one series, designed for low amounts of chain extensions, the polymer concentration was 2.34% and the polymer/styrene ratio either 85/15 or 50/50. At the required degree of chain extension, the sample containing styrene and its styrene-free control were cooled and the benzene and residual styrene removed by evaporation from aliquots and replaced with CCl_4. Precipitation, when combined with the ICl reaction by an aliquot from which the residual styrene had not been removed, permitted calculation of percentage polymer relative to total polymerization. For higher chain extensions the styrene/polymer ratio was 10, in about 5.5% solution of polymer in benzene–styrene. The polymer was coagulated, purified by reprecipitation and analyzed. After precipitation, all samples of the addition product showed continuous decrease of weight on drying, a characteristic noted previously for polybutadiene. The weight difference between the precipitate of the chain-extended sample and the polybutadiene control was found to be independent of drying time. This weight difference must be equivalent to the weight of styrene bound to the ends of the polybutadiene chain. The precision involved in the determination will be double that of the weighing and filtering processes which was determined as ±0.1%.

Figure 3 shows the percentage recovery of the polymer in the addition product against the total amount of polymerized styrene in the polymer. This is compared with the curve to be expected if subsequent polymerization were formation of polystyrene.

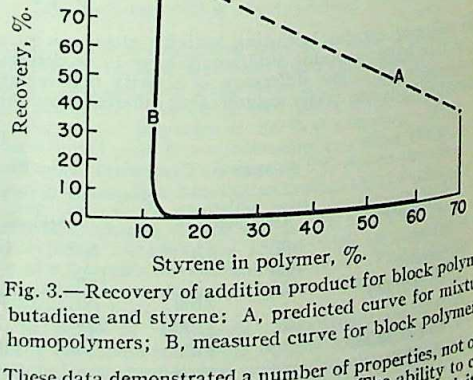

Fig. 3.—Recovery of addition product for block polymers of butadiene and styrene: A, predicted curve for mixtures of homopolymers; B, measured curve for block polymer.

These data demonstrated a number of properties, not only of the process but also of the product. The ability to convert polybutadiene to a polymer which did not precipitate upon addition of iodine monochloride permitted no interpretation other than the elimination of polybutadiene as a separate chemical entity. Previous experiments indicated that up to a 4-to-1 ratio of polystyrene to polybutadiene did not interfere with the recovery of the addition product. The maximum ratio of polystyrene to polybutadiene in the above was 1/1. Such interference could not result from polystyrene. During the initial portion of the reaction the polymerized styrene in the addition product was recovered to be quantitative after the bound

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styrene reached about 6%. After this, the amount of addition product and the recovery of the polymer decreased and reached zero at about 10% bound styrene. This indicates that some of the polymer chains contained sufficient styrene to make the iodine monochloride addition product soluble. This effect was also noted with random copolymers in increasing the styrene content, but not until about 50% bound styrene had been reached. The average bound styrene content necessary to make the addition product soluble showed that styrene had a much greater effect when blocked onto the ends of a polymer than when copolymerized randomly. The tendency of the incoming styrene to make the addition product soluble made any estimate of the amount of styrene polymerizing to the homopolymer unrealistic. The possibility of forming graft polymers by chain transfer between a polystyrene radical and polybutadiene was checked by polymerizing a similar amount of styrene with diisopropylbenzene dihydroperoxide in 2.75% polybutadiene solution to give an apparent 95% chain extension. By removal of the gelled fraction and purification of the sol fraction, it was established by the iodine monochloride technique that all the polymerized butadiene present was in the form of polybutadiene. This corresponds with the conclusions drawn by Smets and Woodward.[10]

(m) **Chain Extension of Polybutadiene Dihydroperoxide with Methyl Methacrylate and Analysis of Products.**—In an attempt to obtain more precise results on the rate of homopolymer formation, polybutadiene was chain extended with methyl methacrylate. It was possible to show a minimum of 200% weight increase in the polymer precipitated with iodine monochloride. However, interpretation of these results was complicated by the ability of iodine monochloride to precipitate polymethyl methacrylate from carbon tetrachloride solution, even though there was no chemical reaction between the polymer and iodine monochloride. This method of investigating chain extension may have limitations for polar–non-polar monomer–polymer pairs.

(n) **Fractionation of Butadiene–Styrene Block Copolymers.**—Polybutadiene, twice purified, was chain extended with styrene as in the preceding experiments. A film was cast from solution and allowed to stand in air at 45° for 72 hr. This polymer was found to be partly gelled. The gel portion was loose and swelled in benzene. Benzene was added until the gel had imbibed its maximum and allowed to come to equilibrium before the soluble fraction was removed. Several extractions were carried out until the extract showed no evidence of dissolved polymer. The sol fraction contained large quantities of bound butadiene as evidenced by reaction with iodine monochloride. The swollen gel fraction was pressed into a film and dried. Refractive index of the film indicated 14% bound styrene which was unextractable. This styrene must have been bound directly to the butadiene in a block and cannot be considered to indicate the total amount of block polymer present, since this will consist of the higher end of the molecular weight distribution which may or may not contain the same proportion of active polymers as does the lower end of the distribution. The film of block polymer was not subjected to quantitative measurements, but it differed from a normal copolymer with 14% bound styrene. It was hard and stiff and not rubbery, which may be a result of a higher second-order transition point.

(o) **Intrinsic Viscosity Changes During Chain Extension.**—The change in intrinsic viscosities during chain extension was investigated. A polymeric dihydroperoxide composed of 72% butadiene and 28% styrene increased in intrinsic viscosity from 0.61 to 1.20 when styrene was blocked on the ends to give a polymer containing 35% styrene. Any polystyrene formation will tend to increase the intrinsic viscosity of the resultant mixture since the intrinsic viscosity of bulk polymerized polystyrene was found to be about 3.0. However, if this be neglected, as the analytical data indicate to be reasonable, then it is possible to calculate the Staudinger K and α values for a block polymer.

The Staudinger equation for the molecular weight of GR-S types at 50° is: $\eta = 5.25 \times 10^4 M^{0.667}$.[12]

Considering the above polymer and postulating that the total number of molecules in the system did not change, then if the system were always monodisperse, the molecular weight would increase from 7.6×10^4 to 1.1×10^5. Each styrene block has a molecular weight of 1.7×10^4 or approximately 1700 styrene units. α does not differ markedly for GR-S and styrene in solution being 0.69 for polystyrene.[13] If α for the block polymer be taken as that of polystyrene, then the Staudinger formula is $4.9 \times 10^4 M^{0.69}$.

Conclusions

This work provides a qualitative confirmation of the mechanisms assigned to emulsion polymerization. Predictions which have been made on the basis of the work of Harkins and Ewart and Smith as well as on our own have been experimentally verified.

The method of synthesis of the polymeric dihydroperoxides conforms to one of the more important requirements for preparing any active polymer to be chain extended, that is, the isolation of such polymers from conditions which may result in destruction of some of the active centers. This is accomplished since the polymeric dihydroperoxide becomes oil-soluble so quickly that there is no significant reaction with the iron(II) sulfate. If this is not done, subsequent deactivation of such active centers will give rise to an inactive polymer and result in contamination of the product. The fact that little of this exists is confirmed by the disappearance of insoluble ICl adduct characteristic of high styrene polymers. The use of the iodine monochloride technique allows rapid analysis of the polymers resulting from non-polar monomer polyperoxide pairs. The method does not appear to be applicable to non-polar–polar pairs, but other methods such as turbidimetric titration[14] exist which are useful.

Acknowledgments.—Helpful discussions were held with Dr. L. A. McLeod of Polymer Corporation Limited and Dr. M. H. Jones of Ontario Research Foundation. R. Wunder was technical assistant. The sample of dihydroperoxide of diisopropylbenzene was supplied by Hercules Powder Co. The authors thank Polymer Corporation Limited for permission to publish this data. Presented at the 130th Meeting, American Chemical Society, Atlantic City, N. J., Sept., 1956.

SARNIA, ONTARIO, CANADA

(12) R. L. Scott, W. C. Carter and M. Magat, THIS JOURNAL, **71**, 220 (1949).

(13) T. Alfrey, A. Bartovics and H Mark, *ibid.*, **65**, 2319 (1943).

(14) H. W. Melville and B. D. Stead, *J. Polymer Sci.*, **16**, 505 (1955).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Alkylation of Diphenylmethane with Alkyl Halides by Sodium Amide. Substitution *versus* β-Elimination. Relative Acidities of Diphenylmethane and Ammonia

BY CHARLES R. HAUSER AND PHILLIP J. HAMRICK, JR.[1]

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Diphenylmethane was metalated by sodium amide in liquid ammonia and ether, and the resulting sodium diphenylmethide was alkylated with alkyl halides to produce excellent yields of hydrocarbons having the benzhydryl group. The method is superior to other methods of synthesis of such hydrocarbons. Sodium diphenylmethide shows a strong affinity for the carbon nucleus producing largely the alkylation product even with β-phenylethyl chloride which has been shown to undergo predominantly β-elimination with other strong bases. Potassium diphenylmethide yields some styrene with this halide. Sodium diphenylmethide was unaffected by *t*-butyl chloride. Evidence is presented that diphenylmethane is a stronger acid than ammonia in liquid ammonia.

Reactions of diphenylmethane involving one of its active methylene hydrogens have generally been effected through the intermediate formation of an ether suspension of potassium diphenylmethide. This red intermediate has been prepared by adding the hydrocarbon to potassium amide in liquid ammonia, and then replacing the ammonia with ether.[2] For example, the resulting suspension has been carbonated to form diphenylacetic acid in 91% yield (equation 1).[3,4]

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. } NH_3]{KNH_2} (C_6H_5)_2CHK \xrightarrow[2,\ CO_2\\ 3,\ \text{acid}]{1,\ \text{ether}} (C_6H_5)_2CHCOOH \quad (1)$$

Although ether is a suitable medium for many reactions of carbanions, liquid ammonia is sometimes an even better medium. Thus certain alkylations of sodio- or potassiophenylacetonitrile have been realized in better yields in a mixture of liquid ammonia and ether than in ether alone.[5]

In the present investigation alkylations and aralkylations of sodium diphenylmethide with alkyl and aralkyl halides were effected in a mixture of liquid ammonia[6] and ether to form hydrocarbons having the benzhydryl group. The reaction may be illustrated with benzyl chloride which formed hydrocarbon I in 99% yield (equation 1).

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. } NH_3]{NaNH_2} (C_6H_5)_2CHNa \xrightarrow[\text{ether}]{C_6H_5CH_2Cl} (C_6H_5)_2CHCH_2C_6H_5 \quad (2)$$
$$\text{I}$$

Similarly, benzhydryl and α- and β-phenylethyl chlorides gave hydrocarbons II, III and IV in yields of 96, 97 and 88%, respectively. The last two yields were based on slightly impure products which are low melting solids.

$$(C_6H_5)_2CHCH(C_6H_5)_2 \qquad (C_6H_5)_2CHCHC_6H_5 \qquad (C_6H_5)_2CHCH_2CH_2C_6H_5$$
$$\text{II} \qquad\qquad \text{III} \qquad\qquad \text{IV}$$

The purely aliphatic halides, isopropyl chloride, and 2-ethylbutyl and *n*-octyl bromides, produced hydrocarbons V, VI and VII in yields of 86, 94 and 99%, respectively.

$$(C_6H_5)_2CHCH(CH_3)_2 \qquad (C_6H_5)_2CHCH_2CH(C_2H_5)_2 \qquad (C_6H_5)_2CH(CH_2)_7CH_3$$
$$\text{V} \qquad\qquad \text{VI} \qquad\qquad \text{VII}$$

These results are summarized in Table I. This method is convenient to carry out. The diphenylmethane is added to an equivalent of sodium amide in liquid ammonia, followed by an equivalent of the halide in ether. The metalation of the hydrocarbon occurs immediately, and the alkylation of the resulting sodium diphenylmethide takes place rapidly (see Experimental).

TABLE I

ALKYLATIONS OF SODIUM DIPHENYLMETHIDE WITH HALIDES TO FORM HYDROCARBONS

Halide	Hydrocarbon	Yield, %
Benzyl chloride	I	99
Benzhydryl chloride	II	96
α-Phenylethyl chloride	III	97
β-Phenylethyl chloride	IV	88
Isopropyl chloride	V	86
2-Ethylbutyl bromide	VI	94
n-Octyl bromide	VII	99

This procedure is more convenient than the related earlier method involving the preparation of sodium diphenylmethide from benzhydryl methyl ether and sodium in ethyl ether (equation 3).[7,8]

$$(C_6H_5)_2CHOCH_3 \xrightarrow[\text{ether}]{Na} (C_6H_5)_2CHNa \xrightarrow{RX} (C_6H_5)_2CHR \quad (3)$$

Not only is diphenylmethane more readily available than benzhydryl methyl ether, but the con-

(1) Carbide and Carbon Chemicals Co. Fellow, 1955–1956.

(2) In contrast to potassium diphenylmethide, sodium diphenylmethide, prepared from diphenylmethane and sodium amide in liquid ammonia, reverts to the hydrocarbon and sodium amide on replacing the ammonia with ether; see ref. 3, and C. R. Hauser, D. S. Hoffenberg, W. H. Puterbaugh and F. C. Frostick, Jr., *J. Org. Chem.*, **20**, 1531 (1955).

(3) R. S. Yost and C. R. Hauser, THIS JOURNAL, **69**, 2325 (1947).

(4) Other reactions of potassium diphenylmethide in ether include acylations with acid chlorides (S. W. Kantor and C. R. Hauser, *ibid.*, **72**, 3290 (1950)), silicoalkylation with trimethylchlorosilane (C. R. Hauser and C. R. Hance, *ibid.*, **23**, 5846 (1951)), and nitrosation with butyl nitrite (ref. in note 2).

(5) C. R. Hauser and W. R. Brasen, *ibid.*, **78**, 494 (1956).

(6) The carbethoxylations of sodium and potassium diphenylmethides with ethyl carbonate to form ethyl diphenylacetate have been effected in this medium in yields of 38 and 45%, respectively; ref. 3. Also the additions of sodium diphenylmethide to benzophenone and certain aldehydes have been realized in this medium; these results will be published soon. However, such reactions as acylations with acid chlorides or carbonation with Dry Ice appear not to be feasible in liquid ammonia.

(7) W. Schlenk and E. Bergmann, *Ann.*, **479**, 72 (1930).

(8) C. R. Hauser and J. Chem. Soc., 412 (1936).

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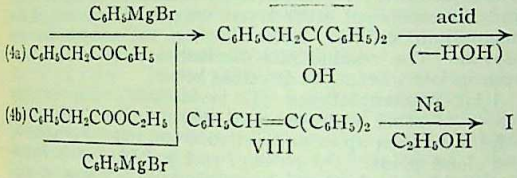
version of the hydrocarbon to the sodio derivative can be accomplished in much less time than that of the ether. In fact the ether was shaken with finely divided sodium for two days.[8] Moreover, the yields of hydrocarbons III and IV were 97 and 88%, respectively, by our method, and only 42 and 65%, respectively, by the earlier method.[8] However, the earlier method has been reported to produce hydrocarbon V in quantitative yield.[7]

The present method also appears preferable to known indirect methods, the most widely employed of which involves the synthesis of the corresponding olefin, and its reduction or hydrogenation. The olefins have generally been obtained by the dehydration of carbinols which usually have been synthesized by appropriate Grignard reactions. For example, olefin VIII, which was reduced to form hydrocarbon I, was synthesized by the action of phenylmagnesium bromide on the appropriate ketone[9] or ester[10] (equations 4a and 4b). No yields were reported.



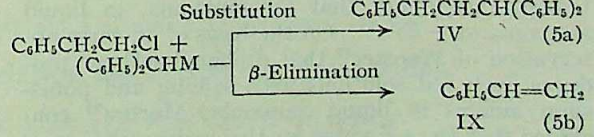
Similarly hydrocarbons III[10] and V[11] have been synthesized through the corresponding olefins and carbinols which were obtained from Grignard reactions. The yield for the former hydrocarbon was not given but that for the latter was reported to be good.

Hydrocarbon II has been prepared in this Laboratory by the reduction of tetraphenylethylene which was synthesized through the selfalkylation of benzhydryl chloride by means of sodium amide in liquid ammonia.[12] The over-all yield was good, but the present alkylation method is more convenient.[13]

Substitution *versus* β-Elimination.—It is rather remarkable that even β-phenylethyl and isopropyl chlorides and 2-ethylbutyl bromide underwent predominantly the substitution type of reaction with sodium diphenylmethide to form alkylation products (Table I), since such halides generally exhibit largely β-elimination with strong bases to yield the corresponding olefins.[14] For example, β-phenylethyl bromide is converted by ethanolic sodium ethoxide at 25° to styrene in almost quantitative yields (93–96%).[15] Although the low temperature (−33°) at which the reactions with sodium diphenylmethide were carried out should favor substitution,[16] the more strongly basic nature of this reagent compared to sodium ethoxide might be expected to more than compensate for the influence of temperature and to produce appreciable β-elimination. Apparently sodium diphenylmethide shows less tendency to attack the β-hydrogen of an alkyl halide than would be anticipated from its basic strength.[17]

The lack of appreciable tendency for sodium diphenylmethide to effect β-elimination was further demonstrated by its failure to react with *t*-butyl chloride which generally undergoes this type of reaction with bases.[18] Thus, in contrast to the halides listed in Table I, this halide failed to react with sodium diphenylmethide in liquid ammonia and ether, the red color of this reagent remaining even after four hours in the presence of two equivalents of the halide. That no appreciable amount of the sodium diphenylmethide had reacted was shown by the addition of benzhydryl chloride which produced the corresponding hydrocarbon II in 94% yield. Not only did the *t*-butyl chloride fail to react with the sodium diphenylmethide but apparently no appreciable amount of it underwent ammonolysis with the ammonia since much of the tertiary halide was recovered.

Since the potassium amide in liquid ammonia is known to effect relatively more β-elimination than sodium amide with certain halides,[19] it seemed likely that potassium diphenylmethide would effect relatively more β-elimination than sodium diphenylmethide under similar conditions. In agreement with expectation, potassium diphenylmethide converted β-phenylethyl chloride to styrene in 18% yield, although even the potassium reagent underwent mainly (70%) alkylation to form hydrocarbon IV. The influence of the metallic cation of the two courses of reaction may be illustrated by equations 5a and 5b.



M = Na; yields 88% of IV, trace of IX
M = K; yields 70% of IV, 18% of IX

Relative Acidities of Diphenylmethane and Ammonia.—The fact that the yield of the alkylation product of sodium diphenylmethide with benzyl chloride or certain other halides was essen-

(9) A. Klages and S. Heilmann, *Ber.*, **37**, 1455 (1904).
(10) W. Schlenk and E. Bergmann, *Ann.*, **463**, 44 (1928).
(11) P. Sabatier and M. Murat, *Ann. chim. phys.*, [9] **4**, 294 (1915).
(12) See C. R. Hauser, W. R. Brasen, P. S. Skell and A. E. Brodhag, THIS JOURNAL, **78**, 1653 (1956). The analogous reaction with benzyl chloride is represented by equation 7.
(13) Hydrocarbon II is generally formed as by-product in the conversion of benzhydryl halides to Grignard reagents, but this coupling reaction appears not to have been employed as a preparative method. Hydrocarbon II has also been obtained in connection with a study of active hydrogen compounds, such as ethanol, on the di-sodium derivative of tetraphenylethylene which was synthesized from diphenylchloromethane and copper bronze; W. Schlenk and E. Bergmann, *Ann.*, **463**, 44 (1928).
(14) See especially, C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, p. 457.
(15) E. D. Hughes, C. K. Ingold, S. Masterman and B. J. MacNulty, *J. Chem. Soc.*, 899 (1940).
(16) See Ingold, ref. 14, p. 460.
(17) This tendency for sodium diphenylmethide to react at the α-carbon atom rather than at the β-hydrogen of the halides, together with the high rate at which these substitutions occur (see Experimental), suggests the mutual activation of both components through coordination of the sodium with the halogen leading to a low energy transition state.
(18) J. U. Nef, *Ann.*, **309**, 136 (1899).
(19) For example, 2-ethylbutyl bromide has been reported to undergo β-elimination to the extents of 75 and 45% with potassium amide and sodium amide, respectively; see R. N. Shreve and L. W. Rothenburger, *Ind. Eng. Chem.*, **29**, 1361 (1937).

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tially quantitative indicates that the equilibrium of the acid–base reaction between equivalents of diphenylmethane and amide ion in a mixture of liquid ammonia and ether is far on the side of the diphenylmethide ion (equation 6). Otherwise

$$(C_6H_5)_2CH_2 + \bar{N}H_2 \underset{\longleftarrow}{\xrightarrow{\text{liq. } NH_3}} \underset{\text{(red)}}{(C_6H_5)_2\bar{C}H} + NH_3 \quad (6)$$

the amide ion present in the equilibrium mixture might be expected to react with the halide. For example, benzyl chloride is rapidly converted by the amide ion in liquid ammonia to stilbene (equation 7).[12] This reaction is accompanied by the production of violet color.[12]

$$2C_6H_5CH_2Cl \xrightarrow[\text{liq. } NH_3]{NaNH_2}$$

$$C_6H_5CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HC_6H_5 \xrightarrow[\text{liq. } NH_3]{NaNH_2} C_6H_5CH{=}CHC_6H_5 \quad (7)$$

The possibility that an appreciable concentration of amide ion is present at equilibrium but that the diphenylmethide ion reacts more rapidly with the halide than the amide ion was eliminated by a competitive experiment. Thus, the addition of an equivalent of benzyl chloride to a mixture of one equivalent each of sodium diphenylmethide and sodium amide gave only a 35% yield of the alkylation product, hydrocarbon I. The main product was stilbene (62%), the violet color associated with its formation being observed (equation 7).

These results lead to the conclusion that diphenylmethane is a considerably stronger acid than ammonia.[20] This conclusion might appear to be at variance with reported pK values for diphenylmethane and ammonia which are 35[21] and 33,[22] respectively. On the basis of these values the hydrocarbon would be expected to be ionized by an equivalent of the amide ion to the extent of only about 10%. However, these values should probably not be compared since the value for diphenylmethane was determined in ether at room temperature,[21] and that for ammonia, in liquid ammonia at −55°.[22] On the basis of an early observation of Wooster[23] that diphenylmethane produces deep red solutions with sodium and potassium amides in liquid ammonia, Morton[24] concluded that the pK value for this hydrocarbon may be considerably lower than the reported value of 35.

Finally it should be mentioned that, in contrast to diphenylmethane, di-*p*-methoxyphenylmethane (X) is evidently a weaker acid than ammonia (equation 8). Thus, although the addition of

$$\underset{\text{X}}{(p\text{-}CH_3OC_6H_4)_2CH_2} + NaNH_2 \underset{\longleftarrow}{\xrightarrow{\text{liq. } NH_3}} (p\text{-}CH_3OC_6H_4)_2CHNa + NH_3 \quad (8)$$

compound X to an equivalent of sodium amide in liquid ammonia produced a red color, only about one-twentieth of an equivalent of benzyl chloride was required to change this color to the purple color associated with stilbene formation. On adding an equivalent of the halide, an 89% yield of stilbene was obtained, and 94% of X was recovered.

Experimental[25]

Alkylations and Aralkylations of Diphenylmethane (Table I).—To a stirred suspension of 0.1 mole of sodium amide in 200 ml. of anhydrous liquid ammonia[3] was added 16.8 g. (0.1 mole) of diphenylmethane in 100 ml. of dry ether. The red color of sodium diphenylmethide appeared immediately. After 10 minutes, 0.1 mole of the halide in 100 ml. of dry ether was added rapidly. Benzyl chloride, benzhydryl and α-phenylethyl chlorides decolorized the red solution as soon as all the halide solution was added. The other halides listed in Table I required a few minutes to discharge the red color. When no color remained the liquid ammonia was removed on the steam-bath to produce a suspension of salt in ether. An additional 100 ml. of ether was added and the mixture cooled. Water (100 ml.) was added to dissolve insoluble salts and the ether layer was separated. The aqueous layer was extracted twice with 50 ml. of ether and the combined ether layers were dried over anhydrous magnesium sulfate. After filtering, the solvent was removed. The residue was distilled or recrystallized from appropriate solvents as described below.

1,1,2-Triphenylethane (I) crystallized when the last traces of ether were removed under suction. The crude solid was taken up in warm ethanol and water was added to the cloud point. On cooling, 15.4 g. (99%) of the hydrocarbon was obtained which melted at 55–56°, reported m.p. 54°[9] and 56°.[7]

1,1,2,2-Tetraphenylethane (II) precipitated from the ether in the reaction mixture. The solid was filtered from the ether and water layers. The ether layer was then separated and the ether removed to obtain more solid. The combined crude solids were dissolved in excess hot benzene and the benzene solution was filtered. The clear filtrate was heated to remove excess solvent and ethanol was added from time to time. When white solid began to separate, the hot solution was allowed to cool. The yield of pure hydrocarbon was 32 g. (96%), melting at 214–215°. A mixed melting point with an authentic sample[26] (m.p. 214–215°) showed no depression.

1,1,2-Triphenylpropane (III) was taken up in hot ethanol (75 ml.) and filtered. Water was added until the solution was cloudy, and a few drops of ethanol were then added to clarify the solution. On standing, white cubic crystals separated. A total of 26 g. (97%) of the compound was obtained from the original crystallization and from the mother liquor. The crude solid melted at 68–71°. Two crystallizations from aqueous ethanol gave pure material, m.p. 73–75°, reported[10] m.p. 73–75°.

1,1,3-Triphenylethane (IV) was obtained from the residue remaining after attempted isolation of styrene by distillation in the presence of a few crystals of hydroquinone. Only a few drops of distillate were obtained at 50 mm. which decolorized bromine in carbon tetrachloride, but no styrene dibromide was obtained. The viscous residue was taken up in 50 ml. of ethanol and filtered. Cooling gave 24 g. (88%) of IV melting at 41–45°. Two recrystallizations from ethanol gave pure IV, m.p. 47°, reported[8] m.p. 47°.

1,1-Diphenyl-2-methylpropane (V) distilled at 126–127° at 5 mm. to produce 18 g. (86%) of V (reported b.p. 158–159° at 19 mm.[7] and 285–286° at 760 mm.[11]), $n^{25}D$ 1.5551, reported[11] $n^{16}D$ 1.560.

Anal. Calcd. for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.35; H, 8.43.

1,1-Diphenyl-2-ethylpentane (VI) was distilled to give 23.7 g. (94%) of the product, b.p. 157–158° at 5 mm., $n^{25}D$ 1.5415.

(20) These results evidently are not due merely to physical factors. Indeed, essentially complete metalation of diphenylmethane occurs in spite of the fact that sodium amide is partly in suspension while sodium diphenylmethide dissolves in the medium, and also in spite of the mass action effect of the solvent, ammonia.

(21) W. K. McEwen, THIS JOURNAL, **58**, 1124 (1936).

(22) W. C. Fernelius and G. B. Bowman, *Chem. Revs.*, **26**, 5 (1940).

(23) C. B. Wooster and N. W. Mitchell, THIS JOURNAL, **52**, 688 (1930).

(24) A. A. Morton, *Chem. Revs.*, **26**, 5 (1940).

(25) Melting points were taken on a Fisher–Johns melting point apparatus. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(26) This sample was prepared by the catalytic hydrogenation of triphenylethylene.

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Anal. Calcd. for $C_{19}H_{24}$: C, 90.41; H, 9.58. Found: C, 90.38; H, 9.85.

1,1-Diphenylnonane (VII) distilled at 173–174° at 0.75 mm. to produce 37 g. (99%) of VII, $n^{25}D$ 1.5310.

Anal. Calcd. for $C_{21}H_{28}$: C, 89.93; H, 10.07. Found: C, 90.08; H, 10.15.

Attempted Alkylation with *t*-Butyl Chloride.—To a stirred solution of 0.1 mole of sodium diphenylmethide in 250 ml. of liquid ammonia and 100 ml. of ether was added 9.3 g. (0.1 mole) of freshly distilled *t*-butyl chloride in 100 ml. of ether. A Dry Ice–acetone reflux condenser was fitted to the flask. After two hours the red color of sodium diphenylmethide remained. An additional 0.1 mole of *t*-butyl chloride in 100 ml. of ether was added and ammonia was refluxed an additional two hours. Finally 0.1 mole of benzhydryl chloride in 100 ml. of ether was added, the red color being discharged. The reaction mixture was worked up as described above for hydrocarbon II. The ether solution was distilled after solid 1,1,2,2-tetraphenylethane was filtered off. Ether and *t*-butyl chloride were difficult to separate, but 12.5 g. of *t*-butyl chloride was recovered. The residue after distillation was solid 1,1,2,2-tetraphenylethane. The combined solids were recrystallized from benzene and ethanol to give 31.5 g. (94%) of the hydrocarbon, m.p. and mixed m.p. 214–215°.

Reaction of Potassium Diphenylmethide with β-Phenylethyl Chloride.—To a stirred solution of 0.1 mole of potassium amide[3] in 200 ml. of anhydrous liquid ammonia was added 16.8 g. (0.1 mole) of diphenylmethane in 100 ml. of anhydrous ether. To the resulting deep red solution was added after 10 minutes 14.05 g. (0.1 mole) of β-phenylethyl chloride in 100 ml. of anhydrous ether. The red solution turned gray after 7 minutes. The ammonia was removed on the steam-bath, and water and ether were added. The ethereal layer was dried and, after adding a few crystals of hydroquinone, the solvent was removed. The residue was distilled at 50 mm. to give 1.9 g. (18%) of styrene, b.p. 70–71°; styrene dibromide, m.p. and mixed m.p. 72–73°, reported[27] m.p. 72–73°. The residue remaining after removing styrene yielded 3.85 g. of recovered diphenylmethane, b.p. 105° at 5 mm. The residue was taken up in 30–60° petroleum ether, filtered and methanol was added. There was obtained 18 g. (70%) of 1,1,3-triphenylpropane, m.p. 47°, on cooling in a Dry Ice–acetone-bath.

Competitive Experiment of Sodium Diphenylmethide and Sodium Amide with Benzyl Chloride.—To 0.11 mole of sodium amide in 200 ml. of anhydrous liquid ammonia was added with stirring 9.24 g. (0.055 mole) of diphenylmethane in 100 ml. of dry ether. After 10 min. 6.96 g. (0.055 mole) of benzyl chloride in 50 ml. of dry ether was added rapidly. The red color of sodium diphenylmethide remained until ammonia was removed on the steam-bath. The red color faded to become purple when only ether remained. After cooling the reaction mixture, 100 ml. of water was added. The purple color was discharged and the ether layer was separated. The aqueous layer was extracted with two 50-ml. portions of ether and the combined ether layers were dried and filtered. Ether was removed from the filtrate and the residue was dissolved in 75 ml. of ethanol. A few drops of water clouded the solution which was clarified by adding a small amount of ethanol. On standing overnight in a refrigerator white crystals of stilbene separated. The solid was recrystallized from ethanol to give 2.5 g. (62%) of stilbene, m.p. 123–125°, reported[28] 125°. A mixed m.p. with an authentic sample (m.p. 124–125°) showed no depression. The mother liquor was treated with more water and cooled in a Dry Ice–acetone-bath. Crude 1,1,2-triphenylethane (I) crystallized to give 5 g. (35%) of the product, m.p. 51–56°. It was recrystallized from ethanol, m.p. 55–56°, reported m.p. 56°[7] and 54°.[9]

Attempted Benzylation of Sodium Di-*p*-methoxyphenylmethide.—To a stirred suspension of 0.05 mole of sodium amide in 250 ml. of anhydrous liquid ammonia was added with stirring 11.4 g. (0.05 mole) of di-*p*-methoxyphenylmethane in 100 ml. of ether. A red color developed and after 15 minutes 6.33 g. (0.05 mole) of benzyl chloride in 50 ml. of ether was added. The red color was discharged when only a small fraction of the halide solution was added. A purple color was produced when the remaining halide was added. After 15 minutes solid ammonium chloride (4 g.) was added and ammonia was removed on the steam-bath. More ether (100 ml.) was added and then 100 ml. of water. The ether layer was separated and the aqueous layer was extracted with two 50-ml. portions of ether. The ether solvent was removed to give an oil which was taken up in ethanol. Stilbene (4.0 g., 89%) was obtained by alternately adding water and cooling in a Dry Ice–acetone-bath. The pure product melted at 124° after crystallization from methanol and chloroform. A mixed melting point with an authentic sample (m.p. 124–125°) showed no depression. Water was added to the remaining solution to precipitate unchanged di-*p*-methoxyphenylmethane (10.7 g., 94%).

(27) I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953, Vol. IV, p. 380.

(28) I. Heilbron, ref. 27, p. 374.

DURHAM, NORTH CAROLINA

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Reactions of Amines. II. Degradation via Tertiary Amine Oxides[1]

BY HENRY E. BAUMGARTEN, FRANK A. BOWER[2] AND TED T. OKAMOTO[3]

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Degradative sequences (see chart) for amines derived from acids related to the naphthenic acids are described that include as an important step the pyrolysis of a *t*-amine N-oxide. Evidence is offered indicating that in the pyrolysis of *t*-amine N-oxides the direction of elimination may follow the Hofmann rule.

One of the most attractive procedures for the degradation of naphthenic acids in structural studies is the conversion of the acids into the amines of one less carbon atom by the Schmidt reaction.[4,5] The utility of this procedure is lessened somewhat, however, by the apparent unavailability of entirely satisfactory, unambiguous processes for the further degradation of the resultant amines. Of the reactions previously used, the Hofmann degradation[4] to the olefin is reasonably unambiguous but, as carried out by von Braun,[6] requires an undue amount of manipulation with a resultant relatively low yield of olefin (20–35%). The reaction of naphthenylamines with nitrous acid[7] to give olefins and alcohols has been shown to lead to extensive rearrangements of the Demjanov type, and the amine phosphate degradation to the olefin has been found also to proceed with considerable

(1) Paper I, THIS JOURNAL, **76**, 4561 (1954).
(2) Standard Oil Co. (of Indiana) Fellow, 1951–1953.
(3) Standard Oil Co. (of Indiana) Fellow, 1953–1955.
(4) J. von Braun, *Ann.*, **490**, 100 (1931).
(5) H. L. Lochte and E. R. Littmann, "Petroleum Acids and Bases," Chemical Publishing Co., Inc., New York, N. Y., 1955, p. 100.

(6) Reference 5, pp. 103, 149.
(7) B. Shive, J. Horeczy, G. Wash and H. L. Lochte, THIS JOURNAL, **64**, 385 (1942).

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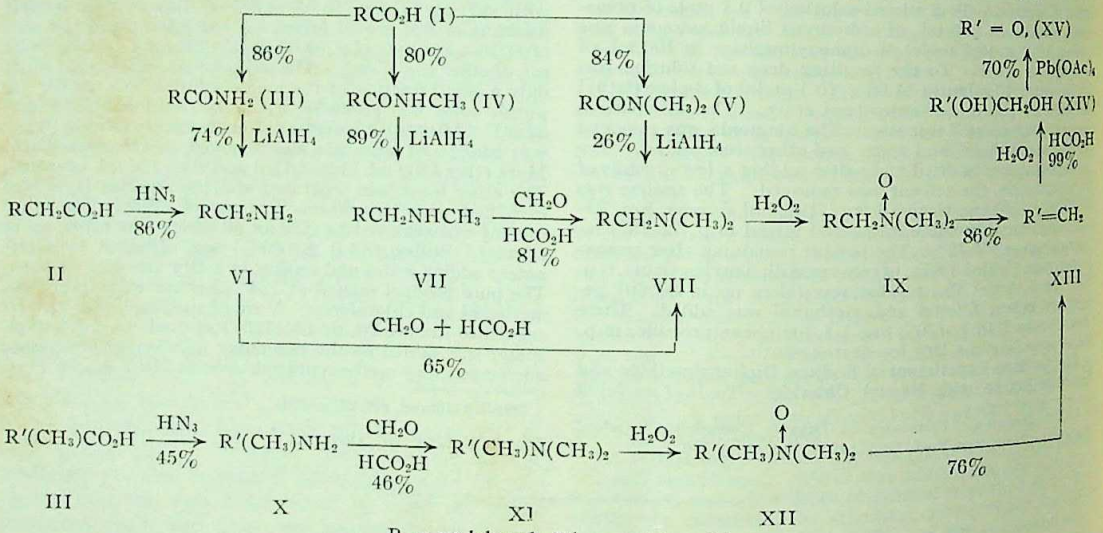
rearrangement.[8] This communication is the first of a series to be devoted to the study of the degradation of naphthenylamines (and other types) to olefins of the same number of carbon atoms by various procedures, both old and new. Of the procedures studied to date that described here based upon the pyrolysis of tertiary amine oxides, recently rediscovered and elegantly applied by Cope and co-workers,[9] has been most satisfactory and will be used in future papers as a standard for comparison.

For use as model compounds in these studies three acids were selected, cyclohexanecarboxylic acid (I), cyclohexaneacetic acid (II) and 1-methylcyclohexanecarboxylic acid (III). At the time this work was started both I and II were commercially available and III was synthesized readily in 81% over-all yield by condensation of butadiene with methacrylic acid,[10] followed by catalytic hydrogenation of the intermediate, 1-methyl-3-cyclohexenylcarboxylic acid.



R = cyclohexyl; R′ = cyclohexylidene

The individual steps required for the degradation of I to cyclohexene in about 52% over-all yield, *via* the successive application of the Schmidt reaction,[11] the Eschweiler–Clarke reaction[12] and the Cope amine oxide pyrolysis,[9] have already been described. In the chart several alternative degradations of I as well as degradations of II and III are outlined.

The key sequence in the chart is the degradation of II. Application of the Schmidt reaction to II gave cyclohexylmethylamine (VI) in 86% yield. Methylation of VI *via* the Eschweiler–Clarke procedure (formaldehyde and formic acid) gave dimethylcyclohexylmethylamine (VIII) in 65% yield. From oxidation of the latter with hydrogen peroxide an 89% yield of crude dimethylcyclohexylmethylamine oxide (IX) was obtained. Pyrolysis of the oxide at 115–160° under reduced pressure gave an 86% yield (based on VIII) of methylenecyclohexane (XIII), free from any detectable amounts of isomerization products (based on infrared spectra).

An attractive degradation of I based on that of II was developed as outlined in the flow sheet. Conversion of I, *via* treatment of the acid chloride with ammonia or the appropriate amine, into cyclohexanecarboxamide (III), N-methylcyclohexanecarboxamide (IV) and N,N-dimethylcyclohexanecarboxamide proceeded in 86, 80 and 84% yields. Reduction of III, IV and V with lithium aluminum hydride, using the excellent technique of Micovic and Mihailovic[13] as a model, gave VI, N-methylcyclohexylamine (VII) and VIII in 74, 89 and 26% yields, respectively. From the reaction mixture from the reduction of V, crude cyclohexanemethanol was isolated in 32% yield as a by-product. Other workers have reported alcohol by-products in the lithium aluminum hydride reduction of disubstituted amides.[13–16] The crude cyclohexanemethanol was converted into its acetate, and the latter was pyrolyzed in the usual manner to give XIII in 71% over-all yield.

The further methylation of VII by the Eschweiler–Clarke technique gave VIII in 81% yield. From these results it appears that the maximum yield of VIII (57% over-all) was obtained by the sequence I → IV → VII → VIII. Indeed, this sequence gave essentially the same yields as the shorter sequence II → VI → VIII (56% over-all yield). It is interesting to note that the yield of

(8) Reference 5, pp. 104, 177.

(9) A. C. Cope, T. T. Foster and P. H. Towle, THIS JOURNAL, **71**, 3929 (1949); A. C. Cope, R. A. Pike and C. F. Spencer, *ibid.*, **75**, 3212 (1953); A. C. Cope, D. C. McLean and N. A. Nelson, *ibid.*, **77**, 1628 (1955); A. C. Cope and C. L. Bumgardner, *ibid.*, **78**, 2812 (1956).

(10) A. A. Petrov and N. P. Sopov, *J. Gen. Chem. U.S.S.R.*, **18**, 1781 (1948); *C. A.*, **43**, 3373 (1949).

(11) M. Oesterlin, *Z. angew. Chem.*, **45**, 536 (1932).

(12) A. Skita and H. Rolfes, *Ber.*, **53**, 1239 (1920).

(13) V. M. Micovic and M. L. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

(14) R. F. Nystrom and W. B. Brown, THIS JOURNAL, **70**, 3738 (1948).

(15) A. L. Morrison, R. F. Long and M. Konigstein, *J. Chem. Soc.*, 952 (1951).

(16) From the reduction of V using inverse addition of reagents M. Mousseron, R. Jacquier, M. Mousseron-Canet and R. Zagdoun (*Bull. soc. chim. France*, 1042 (1952)) obtained 25% of VIII, 60% recovered V and 5% of cyclohexanecarboxaldehyde.

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VIII by the monomethylation of VII was appreciably higher than that by dimethylation of VI, due in large part to a smaller incidence of by-product formation in the former example.

The degradation of III to 1-methylcyclohexylamine (X) by the Schmidt reaction has been reported to proceed in only 42% yield,[17] and a rationale explaining in part this behavior has been offered. In our hands a similar yield (45%) of X was obtained. Treatment of X by the Eschweiler–Clarke procedure gave N,N-dimethyl-1-methylcyclohexylamine (XI) in 46% yield. Oxidation of the amine to the N-oxide XII and pyrolysis of XII gave a 76% yield of methylenecyclohexane (XIII). The identity of the latter was established by distillation through a precision distillation column and examination of the infrared spectra of the distillate and the column holdup and pot residue for evidence of the other most probable olefinic product, 1-methylcyclohexene. As far as we were able to determine by physical constants and infrared spectra, the pyrolysis product consisted solely of XIII.

Since general conclusions drawn from a single example are not especially compelling, the above result can only suggest that the direction of elimination in the Cope pyrolysis of tertiary amine oxides may follow the Hofmann rule much as in the controlled pyrolysis of acetates.[18] The validity of this generalization is under study. Very probably considerations[19] similar to those already suggested for acetate pyrolysis play a large part in determining the selectivity, even though the present elimination apparently takes place in the liquid phase and acetate pyrolysis in the vapor phase. Furthermore, in the pyrolysis of XII no special precautions as to technique (such as are required in acetate pyrolysis[18,19]) other than those normally observed appeared to be necessary to ensure this high degree of selectivity.

Studies of the further degradation of olefins such as XIII have not progressed to the point where an entirely satisfactory procedure can be offered; however, a procedure based on the conversion of methylenecyclobutane to cyclobutanone[20] has been very successful with XIII itself.[21] Oxidation of XIII with performic acid (formic acid and hydrogen peroxide) followed by alkaline hydrolysis of the resultant hydroxyformate gave up to 99% yields of crude 1-hydroxymethylcyclohexanol (XIV). Yields of this magnitude were made possible by the following deviation from the usual isolation procedure.[22] The alkaline reaction mixture from the hydrolysis was saturated with potassium carbonate and the glycol was extracted with ethanol.[23] Oxidation of XIV with lead tetraacetate in benzene solution gave cyclohexanone in 67% yield.[24] The oxidation of XIV with periodic acid under a variety of conditions gave only traces at best of ketone. This observation is consistent with that of Roberts and Sauer[20] relative to the oxidation of 1-hydroxymethylcyclobutanol.

Evaluations of the original degradation procedure of von Braun[4] by application of the process to the model acid II have been carried out by Lochte and co-workers[25] and in this Laboratory. Employing as nearly as possible the original techniques of von Braun (reagents over the arrows) in the sequence

$$\text{II} \longrightarrow \text{VI} \xrightarrow[\text{or MeI}]{Me_2SO_4} \underset{\text{XVI}}{RCH_2N(CH_3)_3X} \xrightarrow[\text{IRA-400-OH}]{\text{KOH or}} RCH_2N(CH_3)_3OH \xrightarrow[\text{heat}]{} \underset{\text{XIII}}{R'{=}CH_2} \xrightarrow{O_3} \underset{\text{XV}}{R'{=}O}$$

$$\text{XVII}$$

Lochte and co-workers obtained an 89% yield of VI, an undetermined yield of trimethylcyclohexylmethylammonium sulfate (XVI) and of the corresponding hydroxide XVII and a 19–25% yield (over-all from VI) of XIII. Ozonolysis of XIII gave a 39% yield of XV (as the semicarbazone). In our study (reagents under the arrow) the reaction of VI with methyl iodide gave trimethylcyclohexylmethylammonium iodide in 94–98% yield. The latter was converted into the quaternary ammonium hydroxide XVII and decomposed by the excellent modification of the Hofmann procedure described recently by Weinstock and Boekelheide,[26] giving XIII in 31–38% yield together with 34–21% of recovered VIII. The maximum over-all yield of XIII from the von Braun degradation as run by Lochte was about 7% (this would be about 11% if the modified Hofmann degradation were employed), compared with a maximum over-all yield of about 32% using the tertiary amine oxide pyrolysis and subsequent oxidation as described herein. Even in comparing only the over-all change VI → XIII by the Hofmann degradation and by the Cope amine oxide pyrolysis, the results favor the latter (56 to 37%).[27]

Details of the application of the degradation described here to the naphthenic acids will be reported elsewhere. However, the results may be summarized by noting that, in applying this procedure to some twenty fractions of acids in the C_8–C_{12}

(17) C. Schuerch, Jr., and E. H. Huntress, THIS JOURNAL, **71**, 2233 (1949).

(18) (a) W. J. Bailey and C. King, *ibid.*, **77**, 75 (1955); (b) W. J. Bailey, J. J. Hewitt and C. King, *ibid.*, **77**, 357 (1955); (c) W. J. Bailey and L. Nicholas, *J. Org. Chem.*, **21**, 854 (1956).

(19) S. Siegel and M. Dunkel, Abstracts of Papers, Meeting of the American Chemical Society, Dallas, Texas, April 8–13, 1956, p. 28N.

(20) J. D. Roberts and C. W. Sauer, THIS JOURNAL, **71**, 3925 (1949).

(21) Extension of this procedure, unmodified, to the olefins derived from naturally occurring naphthenic acids has not given as satisfactory results as of this writing.

(22) A. C. Cope, H. E. Johnson and J. S. Stephenson, THIS JOURNAL, **78**, 5599 (1956).

(23) This procedure was suggested to us several years ago by Dr. G. H. Richter. A similar procedure (without the ethanol extraction) was reported recently by C. C. Price and G. Berti, *ibid.*, **76**, 1211 (1954).

(24) Although the cyclohexanone obtained appeared to be substantially free of by-products arising from attack of lead tetraacetate on the ketone, the possibility of such attack should be recognized in using this procedure and may account for some of the results observed with ketones derived from the naphthenic acids (*cf.* O. Dimroth and R. Schweizer, *Ber.*, **56**, 1375 (1923); G. W. K. Cavill and D. H. Solomon, *J. Chem. Soc.*, 4426 (1955)).

(25) Reference 5, p. 174.

(26) J. Weinstock and V. Boekelheide, THIS JOURNAL, **75**, 2546 (1953).

(27) Recyclization of the recovered VIII would be expected to raise the over-all yield of XIII in the modified Hofmann reaction, but in small runs this recyclization is often impractical.

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range, in the majority of the experiments yields of olefin equal to or greater than that reported here for the degradation of II were obtained.

In the Experimental section the results of some orienting experiments are described in which β-phenylethylamine was converted *via* the tertiary amine N-oxide into styrene in 56% over-all yield.

Experimental[28]

1-Methylcyclohexanecarboxylic Acid (III).—1-Methyl-3-cyclohexenecarboxylic acid, m.p. 77–78°, was prepared in 85% yield as described by Petrov and Sopov,[10] substituting an equivalent quantity of hydroquinone for pyrogallol and effecting a first isolation of the crude acid by steam distillation. In one run at the boiling point of toluene[29] none of the desired product was obtained. Hydrogenation of 61 g. of the unsaturated acid was carried out in usual manner in 150 ml. of ethanol at 45 p.s.i. over platinum oxide and required 2 hr. for completion. Distillation of the product gave 59 g. (96%) of 1-methylcyclohexanecarboxylic acid, b.p. 133–135° (17 mm.) (lit.[30] b.p. 137–138° (24 mm.)).

Amides of Cyclohexanecarboxylic Acid (III, IV and V).—Cyclohexanecarboxylic acid (90 g., 0.7 mole) was refluxed with 166 g. (1.4 moles) of thionyl chloride for 2 hr. Distillation of the reaction mixture gave 102 g. (99%) of cyclohexanecarbonyl chloride, b.p. 77° (21 mm.) (lit.[31] b.p. 76° (17 mm.)).

Dropwise addition of 130 g. (0.8 mole) of cyclohexanecarbonyl chloride to 400 ml. of chilled, concentrated ammonium hydroxide, filtration, washing with water and drying gave 98 g. (86%) of crude cyclohexanecarboxamide, m.p. 184–186° (lit.[32] m.p. 184°), which was used without further purification.

From the similar treatment of 80 g. (0.55 mole) of cyclohexanecarbonyl chloride and 200 g. of ice-cold 33% aqueous methylamine, 63.5 g. (80%) of crude N-methylcyclohexanecarboxamide, m.p. 109–111° (lit.[14] m.p. 110–111°), was obtained and was used without further purification.

Cyclohexanecarbonyl chloride (120 g., 0.83 mole) was added dropwise with stirring to 143 ml. of cooled 33% aqueous dimethylamine. After stirring the solution for 1 hr., the organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer and ether extracts were dried over magnesium sulfate, filtered and distilled, giving 107.5 g. (84%) of N,N-dimethylcyclohexanecarboxamide, b.p. 158° (44 mm.) (lit.[14] b.p. 135–140° (20 mm.)).

Cyclohexylmethylamine (VI). (a) **From Cyclohexaneacetic Acid.**—Concentrated sulfuric acid (175 g., 1.80 moles) was added to a solution of 28.4 g. (0.20 mole) of cyclohexaneacetic acid in 200 ml. of chloroform. While maintaining the temperature between 52–55°, 14.3 g. (0.22 mole) of sodium azide was added in small portions over a 3-hr. period to the stirred solution (hood). Heating was continued overnight to complete the evolution of nitrogen. The reaction mixture was chilled to freeze the sulfuric acid–amine sulfate layer, and the chloroform was removed by decantation. The sulfuric acid solution, diluted with 400 ml. of ice-water, was added cautiously to 1 l. of 5 *N* sodium hydroxide solution in a flask arranged for steam distillation. The mixture was steam distilled and the distillate layers separated. The aqueous layer was extracted with ether. The combined organic layers were dried over potassium carbonate, filtered and distilled, giving 19.6 g. (86%) of cyclohexylmethylamine, b.p. 98–100° (98 mm.) (lit.[33] b.p. 56–58° (12 mm.)). In three runs, two of which were on twice the scale described, the yields were 83–86%.

(b) **From Cyclohexanecarboxamide.**—Cyclohexanecarboxamide (205 g., 1.63 moles) was powdered and suspended in 2 l. of dry ether. Lithium aluminum hydride (215 g., 5.67 moles) was added at such a rate as to maintain gentle reflux. The reaction mixture was allowed to stand overnight and then treated with water as described by Micovic and Mihailovic[13] to decompose the excess reducing agent. The inorganic solids were removed by filtration and the ethereal solution was dried and distilled giving 136 g. (74%) of cyclohexylmethylamine, b.p. 74° (35 mm.). An unidentified by-product (15 g., b.p. 180–190° (35 mm.)) was also obtained.

N-Methylcyclohexylmethylamine (VII).—N-Methylcyclohexanecarboxamide (63.5 g., 0.45 mole) was reduced with 34 g. (0.8 mole) of lithium aluminum hydride in the manner described above, giving 51 g. (89%) of N-methylcyclohexylmethylamine, b.p. 160–162° (lit.[34] b.p. 161–162° (748 mm.)).

N,N-Dimethylcyclohexylmethylamine (VIII). (a) **From Cyclohexylmethylamine.**—Technical grade 90% formic acid (89.5 g., 1.9 moles) was added with cooling to 39 g. (0.34 mole) of cyclohexylmethylamine. Formalin (10 g. of 40% solution) was added, and the mixture was warmed under reflux on the steam-bath until the evolution of carbon dioxide subsided. Additional small portions of formaldehyde were added until the total was 29.5 g. (0.7 mole). The mixture was heated for 10–15 hr. after which time the evolution of carbon dioxide had ceased. Concentrated hydrochloric acid (42.5 ml., 0.5 mole) was added and the excess formic acid and water were removed under reduced pressure. The viscous residue was made alkaline with 120 ml. of 10% sodium hydroxide solution, and the mixture was steam distilled. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried over potassium carbonate and distilled, giving 31.2 g. (65%) of N,N-dimethylcyclohexylmethylamine, b.p. 102–103° (100 mm.), micro b.p. 173° (lit.[14] b.p. 75–76° (15 mm.)). Yields in other experiments ranged from 62–64%.

(b) **From N-Methylcyclohexylmethylamine.**—Following the procedure described in (a) above, from 51 g. (0.40 mole) of N-methylcyclohexylmethylamine 46 g. (81%) of N,N-dimethylcyclohexylmethylamine was obtained.

(c) **From N,N-Dimethylcyclohexanecarboxamide.**—N,N-Dimethylcyclohexanecarboxamide (41 g., 0.27 mole) was reduced with 15.2 g. of lithium aluminum hydride in the manner described for the reduction of cyclohexanecarboxamide. Distillation of the product gave 10 g. (26%) of N,N-dimethylcyclohexylmethylamine, b.p. 102–105° (100 mm.), micro b.p. 172–173°, and a second fraction, 11.8 g., which boiled at 117° (83–89 mm.), micro b.p. 184°. The latter fraction was apparently a crude mixture consisting largely of cyclohexanemethanol (b.p. 182°). This fraction was converted into the acetate, b.p. 101–103° (30 mm.), and pyrolyzed in the usual manner, giving a 71% over-all yield of methylenecyclohexane, b.p. 101–103°.

N,N-Dimethylcyclohexylmethylamine Oxide (IX).—To 31 g. (0.22 mole) of N,N-dimethylcyclohexylmethylamine 125 g. (1.09 moles) of 30% hydrogen peroxide was added with shaking while maintaining the temperature between 35–40°. The completion of the reaction was gaged by the complete solution of the amine, requiring 48–72 hr. of shaking depending on the amount of tertiary amine being oxidized. The excess hydrogen peroxide was decomposed with a small amount of platinum oxide shaken in the solution overnight. The solution was filtered and the water was evaporated at 35–40° under reduced pressure, giving 28.3 g. (83%) of semi-solid N,N-dimethylcyclohexylmethylamine oxide. The yields in several other experiments ranged from 73–89%. The amine oxide was pyrolyzed without further purification.

Pyrolysis of N,N-Dimethylcyclohexylmethylamine Oxide.—The pyrolysis was conducted in a 100-ml., round-bottomed flask equipped with a side arm for introduction of nitrogen. The flask was connected in turn to a 6-in. Vigreux column, a Claisen head, two receivers connected in series and a vacuum pump. The receivers were immersed in a Dry Ice–acetone-bath.

The flask was charged with 5–20 g. of N,N-dimethylcyclohexylmethylamine oxide, evacuated to 10 mm. pressure and immersed in an oil-bath. The Vigreux column was heated to 120–130° and the oil-bath temperature was raised from 30–130° during 30 minutes. The amine oxide liquefied before pyrolysis, which took place at about 115–125°. The temperature was elevated to 160° for a few minutes to complete the pyrolysis. The contents of the receiver were separated and the hydrocarbon layer was washed with 2 *N* hydrochloric acid and water, dried over magnesium sulfate

(28) Melting points are uncorrected. Analyses by Micro-Tech Laboratories, Skokie, Ill.

(29) A. C. Cope and E. C. Herrick, *Org. Syntheses*, **30**, 93 (1950).

(30) J. Gutt, *Ber.*, **40**, 2069 (1970).

(31) G. Darzens and H. Rost, *Compt. rend.*, **153**, 773 (1911).

(32) J. S. Lumsden, *J. Chem. Soc.*, **87**, 90 (1905).

(33) L. Ruzicka and W. Brugger, *Helv. Chim. Acta*, **9**, 402 (1926).

(34) F. F. Blicke and F. B. Zienty, THIS JOURNAL, **61**, 93 (1939).

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and distilled, giving yields ranging from 71–86% of methylenecyclohexane, b.p. 102–103° (lit.[35] b.p. 102–103.5°).

1-Methylcyclohexylamine (X).—1-Methylcyclohexanecarboxylic acid (52 g., 0.37 mole) was converted to the amine by the Schmidt reaction as described above for the preparation of cyclohexylmethylamine. Distillation of the product gave 18.6 g. (45%) of 1-methylcyclohexylamine, b.p. 143–145° (lit.[17] b.p. 142–142.5° (750 mm.)).

N,N-Dimethyl-1-methylcyclohexylamine (XI).—1-Methylcyclohexylamine (14 g., 0.12 mole) was methylated using the procedure described for the preparation of N,N-dimethylcyclohexylmethylamine. Distillation of the product gave 8.1 g. (46%) of N,N-dimethyl-1-methylcyclohexylamine, b.p. 88.5–90° (31 mm.).

Anal. Calcd. for $C_9H_{19}N$: C, 76.52; H, 13.56; N, 9.92. Found: C, 76.81; H, 13.76; N, 9.70.

N,N-Dimethyl-1-methylcyclohexylamine Oxide (XII).—N,N-Dimethyl-1-methylcyclohexylamine (8.0 g., 0.06 mole) was oxidized as described above for the preparation of N,N-dimethylcyclohexylmethylamine oxide. The crude oxide was pyrolyzed without further purification; however, a small sample of the oxide was converted into the picrate, m.p. 163–164°, for analysis.

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 46.7; H, 5.75; N, 14.3. Found: C, 46.94; H, 5.63; N, 14.05.

Pyrolysis of N,N-Dimethyl-1-methylcyclohexylamine Oxide.—Utilizing the technique employed for the pyrolysis of N,N-dimethylcyclohexylmethylamine oxide, the oxide of N,N-dimethyl-1-methylcyclohexylamine was pyrolyzed and the olefinic product was distilled through a concentric-tube column rated at 45 theoretical plates or better, giving 4.1 g. (76%, based on tertiary amine) of methylenecyclohexane, b.p. 100.0–101.5° (730 mm.), $n^{25}D$ 1.4481 (lit.[18b] b.p. 100–101° (730 mm.), $n^{25}D$ 1.4484). The infrared spectrum of the product was identical with that of methylenecyclohexane prepared by the pyrolysis of cyclohexylmethyl acetate and of N,N-dimethylcyclohexylmethylamine oxide. In the event that the other isomer, 1-methylcyclohexene (lit.[36] b.p. 110° (760 mm.), $n^{20}D$ 1.4503; our values for authentic material distilled through an 85-plate concentric-tube column, b.p. 106–107° (730 mm.), $n^{20}D$ 1.4498, $n^{25}D$ 1.4475), might be present in small amount, the column hold-up and pot residue was collected, flash distilled from a small distilling flask and submitted to infrared analysis. The spectrum and refractive index of this material were identical with those from the main body of the distillate.

1-Hydroxymethylcyclohexanol (XIV).—Methylenecyclohexane (4.8 g., 0.05 mole) was added slowly with continuous shaking to a solution consisting of 60 g. (1.1 moles) of 90% formic acid and 10 g. (0.08 mole) of 30% hydrogen peroxide. The rate of addition was such as to maintain the temperature at 40–45°. After addition of the olefin was complete, the mixture was shaken overnight. The excess reactants were removed under reduced pressure. The residual ester was hydrolyzed with 50 ml. of 10% sodium hydroxide solution warmed to 50°. The solution was saturated with potassium carbonate and the organic layer separated. The aqueous layer was extracted with absolute ethanol. The combined organic layers were dried over potassium carbonate, and the ethanol was removed carefully under reduced pressure. The yield of the crude glycol was essentially quantitative (about 97–99% in most runs). Recrystallization of the crude product from benzene gave 4.8 g. (72%) of 1-hydroxymethylcyclohexanol, m.p. 73–75° (lit.[37] m.p. 74–75°).

Oxidation of 1-Hydroxymethylcyclohexanol.—A solution of 1-hydroxymethylcyclohexanol (4.8 g., 0.04 mole) in 100 ml. of dry benzene was refluxed in a Soxhlet extractor in which the siphon tube had been replaced by a direct return tube to the distillation pot. The thimble of the extractor contained 14 g. of 90% lead tetraacetate. The benzene was refluxed for 1 hr. after the lead tetraacetate dissolved. After standing overnight the solution was filtered from the lead diacetate and the filtrate was washed with 0.5 *N* potassium carbonate and water. After drying over magnesium sulfate, the benzene solution was fractionally distilled giving 2.5 g. (70%) of cyclohexanone, b.p. 50–51° (20 mm.). In other experiments, oxidation of the crude glycol gave yields of 53–67%.

Trimethylcyclohexylmethylammonium Iodide (XVI).—To an ice-cooled solution of N,N-dimethylcyclohexylmethylamine (28 g., 0.20 mole) in 100 ml. of ether was added in four portions 18.6 ml. (0.3 mole) of methyl iodide, and the mixture was allowed to stand overnight. Evaporation of the ether left 55.4 g. (98%) of trimethylcyclohexylmethylammonium iodide, m.p. 220° (lit.[38] m.p. 225°), which was used without further purification. In other experiments the yields varied from 94–98%.

Anal. Calcd. for $C_{10}H_{22}NI$: I, 44.82. Found: I, 45.05.

Decomposition of Trimethylcyclohexylmethylammonium Iodide.—A solution of 12.3 g. (0.044 mole) of trimethylcyclohexylmethylammonium iodide in 50 ml. of water was passed through a 2 × 22-cm. column packed with ion-exchange resin, Amberlite IRA-400(OH). The methiodide was washed down the column with water until the final volume of solution was 300 ml. The solution was concentrated under reduced pressure to 50 ml. The solution was refluxed for 1 hr. in an apparatus similar to that described by Fieser,[39] and the distillate collected from the side arm was washed with 5% hydrochloric acid and with water. The hydrocarbon layer was separated, dried over magnesium sulfate and distilled, giving 1.60 g. (38%) of methylenecyclohexane. From the acid wash, 1.3 g. (21%) of dimethylcyclohexylmethylamine was recovered. In other experiments the yields of methylenecyclohexane varied from 31–34% and the yields of recovered tertiary amine from 21–34%.

Degradation of β-Phenylethylamine.—β-Phenylethylamine was methylated as described above for the methylation of cyclohexylmethylamine, giving dimethyl-β-phenylethylamine, b.p. 200–208° (lit.[40] b.p. 198–202°), in 70% yield. Oxidation of the tertiary amine and pyrolysis of the resultant N-oxide were carried out as described above for the degradation of N,N-dimethylcyclohexylmethylamine except that a few crystals of hydroquinone were added to the receiver to inhibit polymerization of the styrene. Distillation of the crude product gave an 82% yield of styrene, b.p. 46° (17 mm.), identified by oxidation in 94% yield, by the procedure described above for the oxidation of methylenecyclohexane, to phenylethylene glycol, m.p. 66–68° (lit.[41] m.p. 67–68°).

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, YALE SCHOOL OF MEDICINE]

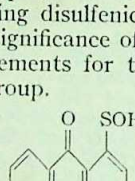
The Synthesis of a Disulfenic Acid. Anthraquinone-1,4-disulfenic Acid

BY THOMAS C. BRUICE AND R. T. MARKIW

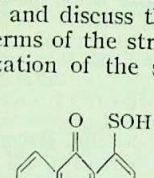
RECEIVED DECEMBER 13, 1956

The synthesis of anthraquinone-1,4-disulfenic acid (II) is described. This compound represents the first disulfenic acid and the second sulfenic acid to be isolated.

Sulfenic acids, generally designated as RSOH, may be considered as the parent compounds of the sulfenyl thiocyanates (RSSCN), sulfenyl halides (RSCl), sulfenic acid esters (RSOR′) and the sulfenamides ($RSNR_2'$). They have been suggested to be hydrolytic scission products of disulfides[1-5] and S-arylthiosulfuric acids,[6] while certain sulfenic acids have been proposed as intermediates in the chemical or metabolic oxidation of thiols,[7] participants in the photosynthetic processes of plants[1,8] and as possible intermediates in the oxidation of proteins.[9] However, with the single exception of the isolation of 1-anthraquinonesulfenic acid (I) in 1912,[10] all attempts to isolate other sulfenic acids in the anthraquinone, benzene or aliphatic series have been unsuccessful.[1,11-19] In this paper, we describe the synthesis of the corresponding disulfenic acid (II) and discuss the possible significance of this in terms of the structural requirements for the stabilization of the sulfenic acid group.



I



II

The synthetic sequence leading to II, as well as the conversions effected in the present study, are summarized in Fig. 1. The potassium salt of 1-anthraquinonesulfonic acid (III) was converted to 1-chloroanthraquinone by the procedures of Scott and Allen.[20] Nitration of 1-chloroanthraquinone according to the method of Eckert and Steiner[21] yielded IV. Treatment of IV at reflux with sodium disulfide, in aqueous dioxane, yielded a brick-red, high melting, nitrogen-free substance whose structure has been established as that of V. In the preparation of V, if solvent conditions other than those specified were used, various mixtures were obtained whose color and composition depended upon the time of reflux, solvent, stoichiometry, etc. The polymeric disulfide V is insoluble in all solvents investigated and, therefore, could not be freed of the usual impurities accompanying reactions of this nature. The structure of V was established by conversion to anthraquinone-1,4-disulfonic acid (IX), a previously reported compound.[22] The disulfonic acid was then converted to the also known 1,4-dichloroanthraquinone (X) which, in turn, was reconverted to V by the same procedures employed for the sequence IV → V. The polymeric disulfide, prepared in this manner, was of lighter color but otherwise identical in its reactions and high decomposition point (> 360°) to that prepared from IV. Conversion of IV to V involves replacement of a nitro group (situated *ortho* to a strong electron attracting substituent) by a nucleophilic agent. Reactions of this type are well known and the use of S^- as the nucleophile has been reported previously.[23]

Chlorinolysis of V, under anhydrous conditions, employing aluminum chloride (formed *in situ*) catalysis,[24] gave 1,4-anthraquinonedisulfenyl chloride (VI) as balls of red needles from benzene. Treatment of VI with anhydrous methanol in benzene (trace of pyridine)[25] yielded dimethylanthraquinone-1,4-disulfenate (VII), which crystallized as red, glistening needles from benzene and methanol. When either VII or VI were treated with boiling morpholine, the same dimorpholide (VIII) was obtained. Compounds VI and VIII are stable when pure. The dimethyl ester VII is particularly stable and no precautions are required for its storage. Compounds VI, VII, VIII and, as previously noted V, were all converted in high yield to IX by oxidation with moist chlorine.

Fries[10] accomplished the synthesis of 1-anthraquinonesulfenic acid (I) by hydrolyzing the corresponding methyl sulfenate with strong potassium hydroxide solution, followed by the liberation of the free sulfenic acid with acetic acid. The hydrolysis of VII to 1,4-anthraquinonedisulfenic acid (II) was carried out similarly and, for comparative purposes, the hydrolysis of methyl 1-anthra-

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quinonesulfenate to I was repeated.[26] A comparison of the observations on the hydrolysis and products formed from methyl 1-anthraquinonesulfenate and VII are recorded in Table I.

TABLE I

COMPARATIVE OBSERVATIONS ON 1-ANTHRAQUINONESULFENIC ACID AND 1,4-ANTHRAQUINONEDISULFENIC ACID

	I	II
Methyl esters in ethanol	Yellow	Red
Dil. ethanolic soln. of free acids	Orange	Magenta
Aqueous soln. of potassium salts	Blue	Blue
Acetone soln. of potassium salts	Green	Green
Lead salts	Blk. ppt.	Blk. ppt.
Barium salts	Green	Green
Dil. aq. acetone soln. of barium salts	Blue	Blue
Crystalline form of acid from acetone–water	Red microscopic needles	Purple microscopic needles
Color change on heating above 100°	Red → Yellow	Purple → Brick-red

Though II was found to be stable to desiccation (see following discussion) attempts at recrystallization were always accompanied by the formation of small quantities of bright red alkali-insoluble material, which prevented the preparation of a suitable analytical sample. As expected, also, the product presumed to be the disulfenic acid (II) was readily oxidizable. Thus, in dilute methanolic solution, the characteristic purple color persisted for about a week, slowly changing to a pale yellow; and, in dilute base, the blue color of the potassium salt persisted for many weeks before fading, if the solution was kept in the dark and free of air. However, either the potassium salt or the free acid were immediately destroyed if their alcohol solutions were shaken with activated carbon (Norite). When treated with moist chlorine, II was converted to IX.

The strongest evidence for the proposed structure for II was obtained by converting the purple acid to the dimethyl sulfenate (VII). When II was treated with anhydrous hydrogen chloride in an inert solvent, followed by solution in absolute methanol, the methyl ester VII could be regenerated in 47–55% over-all yield from II. This conversion of the purple acid to the methyl sulfenate, *via* the sulfenyl chloride (VI), corresponds to the like reactions of I,[10] and we interpret this as unequivocal evidence that the oxidation state of the purple acid is at the sulfenic acid level. The stability of II, in the dry state and in the absence of air, was confirmed by the finding that weeks after its isolation it could be converted to the methyl sulfenate in yields corresponding to those obtained when freshly prepared acid was employed. Simply treating II with methanol did not yield VII.

The barium salt of II was obtained by treatment of either the free disulfenic acid or its dimethyl ester with barium hydroxide. When carbon dioxide was passed through a dilute aqueous ethanol solution of either the barium or potassium salt of II, the blue color faded to the red of the sulfenic acid. The sodium salt, but not the barium salt, could then be regenerated by removing excess carbon dioxide *in vacuo*. This would tend to place the first ionization constant of II at between 10^{-6} and 10^{-12}. The black amorphous lead salt of II was prepared easily by adding an acetone solution of II to an aqueous solution containing excess lead acetate. The lead salt was insoluble in water and all neutral organic solvents but dissolved readily if a suspension of the salt in aqueous ethanol was acidified with acetic acid, to yield the color of the free sulfenic acid, or when the solution is made alkaline with potassium hydroxide, to yield the blue color of the potassium salt.

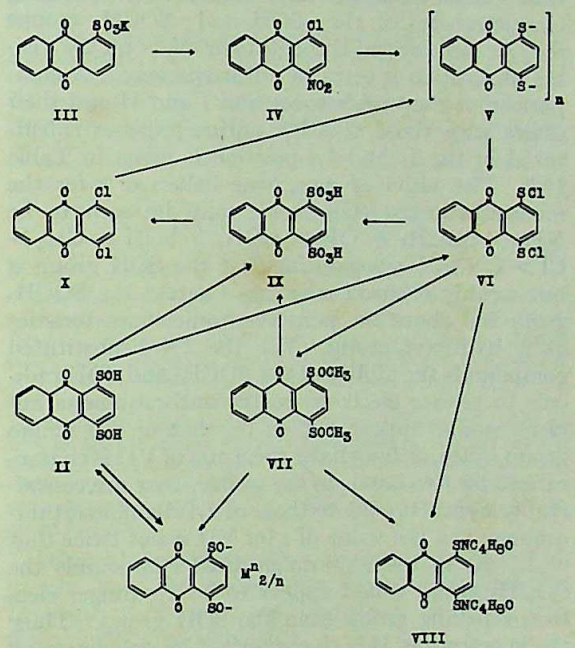

Fig. 1.

The reason for the stabilities of I and II, at least so far as to permit their isolation, as contrasted to the complete instability of 2-anthraquinonesulfenic acid[11] (XI) and 4-amino-1-anthraquinonesulfenic acid (XII)[12] as well as the apparent non-existence of 1-fluorenonesulfenic acid (XIII),[13] is not evident. Stabilization through hydrogen bonding of the acid hydrogen to the carbonyl group of anthraquinone,[27] or interaction of the sulfur with the carbonyl oxygen,[6] do not appear to offer a complete explanation, since XII and XIII are not so stabilized. It appears reasonable to suppose that, in addition to the interaction of the sulfenic acid group with the carbonyl oxygen of anthraquinone, there is required for the stabilization of the sulfenic acid grouping its attachment to a highly electronegative carbon atom.[28] Employing such a dual prerequisite for the stabilization of the SOH group, the instability of XI would be explained on the basis of the inability of SOH to interact with the carbonyl group, while for XII and

(26) The original work of Fries has been confirmed previously by A. T. Fowler (see footnote 12 of ref. 18) and C. W. Jefferys, *Helv. Chim. Acta*, **35**, 845 (1952).

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(28) Similar reasoning can be used in the case of the selenenic acids, where *o*-nitro or *o*-keto groups apparently are required for stability (see ref. 27). Sulfenic acids are not stabilized by *o*-nitro groups, in part due to the intermolecular oxidation of the sulfenic acid moiety and reduction of the nitro group to yield aminosulfonic acids (see ref. 19).

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XIII instability could be ascribed to the decreased positive nature of the 1-position as compared to anthraquinone. This may be a logical argument, since it is certain that a *p*-amino group would lower the positive character or the 1-position of anthraquinone and the fluorenone nucleus is known to be not as electron deficient as that of anthraquinone.[29]

Since II is less stable than I but of greater stability than XII, the above reasoning suggests that the *p*-SOH group is electron releasing but not to such a degree as the *p*-amino group. From the known properties of the *p*-sulfhydryl and *p*-hydroxyl groups, this would appear to be a logical supposition. Semi-quantitatively, the electron releasing characteristics of the –SOH and $-SOCH_3$ groups may be determined through their effect on the visible absorption spectra of anthraquinone. A comparison of the visible spectra of I and II and their esters with those of other anthraquinones substituted in the 1- and 1,4-position is given in Table II.[30] The order of increasing values of *e* for the monosubstituted compounds may be seen to be $NH_2 > SOCH_3 = OH > OCH_3 > SOH > CH_3 > Cl > CN > NO_2$ suggesting that the SOH group is but weakly electron releasing whereas the $SOCH_3$ group has about the same electronic characteristics as a hydroxyl group. For the 1,4-disubstituted compounds the ability of the $SOCH_3$ and SOH radicals to release electrons to the anthraquinone nucleus would appear not to be that of the amino group, since, although the spectrum of VII is characterized by two bands in the visible, they are considerably hypsochromic to those of 1,4-diaminoanthraquinone and the value of *e* for VII is not twice that of I. As in the monosubstituted compounds the $SOCH_3$ group would appear to be a stronger electron repelling group than the SOH group. Thus, the spectrum of II is characterized by only one peak in the visible, and the value of *e* for II is smaller than that for VII.

On the basis of spectral evidence alone, it would appear that in accordance with the hypothesis presented above, the 1- and 4-positions of II are more positive than the 1-position of XII but less positive than the 1-position of I. As an extension of the present work, a study of the stabilities of a series of anthraquinone-1-sulfenic acids substituted with various groups in the 4-position is desirable as a further test of the hypothesis.

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TABLE II

A COMPARISON OF THE VISIBLE SPECTRA OF SULFENIC ACIDS AND THEIR ESTERS TO THOSE OF OTHER ANTHRAQUINONES

Substituents	λ_{max}	*e*
Hydrogen[a]	410	60
1-NO_2[a]	..	...
1-CN[a]	417	70
1-Cl[a]	415	100
1-CH_3[a]	415	150
1-OCH_3[a]	378	5,200
1-OH[a]	402	5,500
1-SOH[b]	460	4,700
1-$SOCH_3$[b]	455	5,500
1-NH_2[a]	475	6,300
1,4-$(SOH)_2$[c]	524	5,100
1,4-$(SOCH_3)_2$[b]	520	6,400
	545	7,000
1,4-$(NH_2)_2$[a]	596	13,800
	554	13,400

[a] Data of Peters and Summers, see footnote 30; solvent methanol. [b] Solvent chloroform. [c] Solvent acetone.

Experimental

Poly-1,4-dithioanthraquinone (V).—1-Chloro-4-nitroanthraquinone (IV) was recrystallized several times from chlorobenzene and then from equal volumes of hot dioxane and ethyl acetate, m.p. 262° (lit.[20] 259°). The so purified IV (4.40 g., 0.0153 mole) was suspended in 400 ml. of a good grade of dioxane (Fisher Certified) to which was added 0.512 g. (0.0157 mole) of sulfur. The solution was brought to a boil when 3.84 g. (0.0238 mole) of sodium sulfide nonahydrate dissolved in 80 ml. of dioxane and 160 ml. of water was added. The reaction mixture was heated under reflux for 5 hr. when the amorphous, brick-red precipitate of V was immediately collected and washed with large quantities of hot dioxane, water and acetone and dried at 80° (3.2 g., 77%), m.p. > 350°.

Because V was completely insoluble in all solvents, it could not be freed from silicate and other contaminants, and analyses were not performed. The compound was identified, however, in the manner given under preparation of IX and X.

1,4-Anthraquinone Disulfenyl Chloride (VI).—V (2 g., 0.0074 mole) was suspended in 100 ml. of chloroform in a flask fitted with side arm, gas inlet tube and condenser for downward distillation. One-half of the solvent was removed by distillation and a small piece of clean aluminum foil added. Into the cooled solution there was passed a stream of dry chlorine. After 3 hr., the flask was tightly stoppered and set aside at room temperature for at least 12 hr. After refrigeration for an additional several hours, the product was collected, washed with dry ether and the small pieces of unreacted aluminum picked out. The product (2.2 g., 87.5%) was used without further purification in the preparation of VII, VIII and IX.

For analysis the sulfenyl halide was recrystallized to constant melting point from anhydrous benzene and dried at 130° over P_2O_5 at 1 mm., m.p. 270°.

Anal. Calcd. for $C_{14}H_6S_2Cl_2O_2$: C, 49.4; H, 1.77; S, 18.8. Found: C, 49.57; H, 2.01; S, 18.15.

Dimethyl 1,4-Anthraquinonedisulfenate (VII).—Two grams (0.0059 mole) of VI was suspended in 250 ml. of absolute methanol, and there was then added 150 ml. of anhydrous benzene and 1 ml. of dry pyridine. The mixture was then brought to a boil when all but a trace of the solid material dissolved. The flask containing the reaction mixture was tightly stoppered and set aside for two days.

The reaction mixture was brought to a boil for a few minutes, a small amount of activated carbon (Norite) added, boiling continued for 5 min. when the red solution was filtered and concentrated to one-half volume. After several hours, long red needles begin to form. At this time the reaction mixture was chilled for 12 hr. and the product collected. In this manner there was obtained 1.0 g. (51%) of VII, m.p. 170–170°. For analysis the product was recrystallized several times from a mixture of benzene and

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methanol and dried at 100° for 2 hr. over P_2O_5 at 1.0 mm., m.p. 189–190°.

Anal. Calcd. for $C_{16}H_{12}O_4S_2$: C, 57.81; H, 3.64; S, 19.30. Found: C, 58.1; H, 3.81; S, 19.45.

1,4-Anthraquinonedisulfenyl Morpholide (VIII).—Either VI or VII when boiled for a short time in a small volume of morpholine dissolves, and on cooling, red-brown needles of the dimorpholide are deposited. After collecting and washing with hot ethanol and benzene the product was found to sinter at 271° and not to melt below 300°, though decomposition was complete. For analysis the compound was recrystallized from pyridine (charcoal) several times (melting characteristic unchanged) and dried at 100° for 12 hr. over P_2O_5 at 1.0 mm.

Anal. Calcd. for $C_{22}H_{22}O_4S_2N_2$: C, 59.9; H, 5.01; N, 6.34; S, 14.49. Found: C, 59.91; H, 5.21; N, 6.33; S, 14.14.

1,4-Anthraquinonedisulfenic Acid (II).—The disulfenate ester VII (0.5 g., 0.0015 mole) was suspended in 20 ml. of absolute ethanol which was brought to a boil and 1.0 ml. of 33% aqueous potassium hydroxide (0.006 mole) added. Boiling was continued for 4 min. when 100 ml. of hot distilled water was added. The resultant clear blue solution was then quickly chilled, filtered and the filtrate made weakly acid with acetic acid. The purple coagulant was collected and washed with a large quantity of cold water. The moist precipitate was then taken up in cold acetone, the deep magenta solution filtered, and to the filtrate there was added water until the solution became just slightly cloudy. The solution was then refrigerated and water added very gradually until precipitation was completed. In this manner the acid II was obtained as purple microscopic needles (0.1 to 0.12 g., 22–26%). When heated above 100° II turned from purple to yellow.

Additional recrystallizations from acetone always resulted in the formation of small amounts of alkali-insoluble material. No other solvent was found that was better for recrystallization than acetone and an analytical sample could not be prepared.

The Stability of II and the Conversion of II to VII.—Anhydrous chloroform (100 ml.) previously saturated with dry hydrogen chloride at 0° was added to 118 mg. (0.00039 mole) of dry II and the reaction mixture allowed to set at 0° for 12 hr. All the solvent was then aspirated off, and to the dry residue there was added 100 ml. of anhydrous methanol and 1 ml. of dry pyridine. The flask was then warmed to a boil and set aside for 12 hr. The methanolic supernatant solution was decanted and the residue taken up in 50 ml. of hot, anhydrous benzene. The benzene and methanolic solutions were then combined and allowed to cool. After a few hr. the precipitation of a high melting amorphous material (*ca.* 40 mg.) was complete. This substance was removed and the filtrate concentrated to 100 ml. and set aside. The characteristic crystals of the diester soon appeared. These were collected and the filtrate concentrated in turn to 50 and 25 ml., respectively, the crystalline ester being removed each time. In this fashion there was obtained a total of 60–70 mg. of VII, m.p. 176–179° (47–55% yield from II). The melting point was identical to that of VII as obtained from the reaction of VI and methanol, and on recrystallization several times from benzene and methanol the melting points were found to be between 185–188° which is very close to that of the analytical sample of VII (no mixed melting point depression with an authentic sample of VII).

This procedure was carried out on samples of the sulfenic acid prepared a month in advance with no appreciable difference in yield of VII if II were kept in a desiccator under refrigeration.

1,4-Anthraquinonedisulfonic Acid (IX) and 1,4-Dichloroanthraquinone (X).—The disulfonic acid IX was obtained in good yield when either V, VI, VII or II was suspended in 200 volumes of 90% aqueous acetic acid which was then saturated, in the cold, with chlorine gas. The reaction mixture was filtered and allowed to set for 10 hr. when the white to yellow needles were collected. The crude acid is best recrystallized from 90% acetic acid, m.p. 269–269.5° (lit.[21] 264–265°). The crude yield from 0.4 g. (0.0015 mole) of V was 0.41 g. or 75% of theory (m.p. 263–264°).

Anal. Calcd. for $C_{14}H_8O_8S_2 \cdot H_2O$: C, 43.52; H, 2.61; S, 16.60. Found: C, 43.61; H, 2.85; S, 17.47.

The disulfonic acid could be converted to 1,4-dichloroanthraquinone by the usual procedure,[20] m.p. 190° (lit.[21] 186.5°). When the dihalide, so obtained (0.531 g., 0.0019 mole), was treated in the same manner as in the preparation of V from IV, the polymeric disulfide was obtained (0.52 g., 100% yield), m.p. > 360°.

Absorption Spectra.—These were determined with a Model DU Beckman spectrophotometer. Extinction coefficients were calculated from spectral measurements made with $\sim 10^{-4}$ molar solutions; the maximum absorbances were all between 0.5 and 0.8. The solvents employed are as noted in Table II .

Acknowledgments.—This work was supported by grants from the Rockefeller Foundation and the Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ALBERTA, AND THE RESEARCH COUNCIL OF ALBERTA]

Observations on Some Alkyl Substituted Anthracenes and Anthraquinones

BY ROBERT J. CRAWFORD, SIDNEY LEVINE, RICHARD M. ELOFSON AND REUBEN B. SANDIN

RECEIVED JANUARY 9, 1957

1,2-Dimethylanthraquinone and some related alkyl substituted anthraquinones have been examined from the standpoint of polarographic and chemical reduction and controlled potential electrolysis. The effectiveness of alkyl substitution in lowering the negative potential is: $\alpha > \beta$, dimethyl > monomethyl, six-membered ring > five-membered ring and 1,2-dimethyl > six-membered ring. The α-substituted anthraquinones show evidence of oxanthrol isomerization. It is suggested that 1,2,9,10-tetramethylanthracene behaves as a crowded molecule from the standpoint of preparation and properties.

It is known that 9,10-dihydro derivatives of 1,2-dimethylanthracene are very resistant to aromatization. For example, compound II resists demethoxylation and does not yield 1,2,9,10-tetramethylanthracene (I) even after shaking for six days with sodium powder in ether.[1] On the other hand, 9,10-dimethylanthracene is obtained in good yield from the corresponding dimethoxy compound. Again, compound III does not undergo dehydrogenation to yield I, whereas 9,10-dihydroanthracene is smoothly transformed into 9,10-dimethylanthracene with sulfur at 230°.[2]

In contrast to this behavior it is known that compound I tends to lose aromaticity and to revert to the 9,10-dihydro state. For example, I has been

(1) G. M. Badger, J. W. Cook and F. Goulden, *J. Chem. Soc.*, 16 (1940).

(2) G. M. Badger, F. Goulden and F. L. Warren, *ibid.*, 18 (1941).

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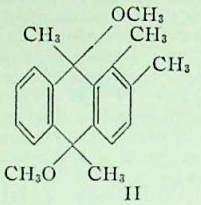
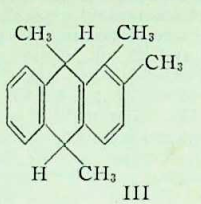
found to undergo peroxidation after brief periods of storage in the solid state.[3]



II



III

The marked stability of the 9,10-dihydro derivatives of 1,2-dimethylanthracene appeared to us to justify a polarographic study of 1,2-dimethylanthraquinone and some related compounds. Therefore in this paper are reported some observations which have been made on the polarographic reduction and also the chemical reduction and the controlled potential electrolysis of 1,2-dimethylanthraquinone and some related quinones. A difference has also been noted in the stability of some 1,2-disubstituted hydrocarbons.

Experimental

Anthraquinones.—The quinones were for the most part well known and all of them have been described previously. Anthraquinone (Eastman Kodak Co.) melted at 286–288°. 2-Methylanthraquinone (Eastman Kodak Co.) was crystallized from alcohol and melted at 175°. 1,2-Dimethylanthraquinone,[3] m.p. 156–157°, 1,4-dimethylanthraquinone,[4] m.p. 140.5–141.5°, 1-methylanthraquinone,[5] m.p. 172–173°, and 1′,2′,3′,4′-tetrahydro-1,2-benzanthraquinone,[6] m.p. 153–154°, were made by the ring closures of the substituted *o*-benzoylbenzoic acids. 1,2-Cyclopenteno-9,10-anthraquinone[7] melted at 126.5–127.5°.

9,10-Dimethyl-1′,2′,3′,4′-tetrahydrobenzanthracene (IV).—To a solution of the Grignard reagent from 0.5 g. of magnesium and methyl iodide (2.0 ml.) in anhydrous ether (15 ml.) was added 0.5 g. of 1′,2′,3′,4′-tetrahydro-1,2-benzanthraquinone. The flask was stoppered and after standing at 0° for four days, the fluorescent solution was poured dropwise and with constant stirring into a cold solution of 50% hydriodic acid (5.7 ml.), hydrobromic acid (d. 1.4, 4 ml.) and methanol (15 ml.). Glacial acetic acid (15 ml.) was added and the iodo compound (0.6 g.) separated as an orange solid. A solution of the iodo compound (1.2 g.) in dioxane (45 ml.) was added to a solution of stannous chloride (7.5 g.) in dioxane (40 ml.) and concentrated hydrochloric acid (12 ml.). The solution was brought to its boiling point, diluted with water (250 ml.) and extracted with benzene. The highly fluorescent benzene extract was washed with water and dried by filtering through ordinary filter paper. The benzene was evaporated under diminished pressure, which afforded a brown sirupy material which was extracted with alcohol. The alcohol extract was saturated with picric acid and yielded a black crystalline picrate. It was crystallized from alcohol; weight 0.6 g., m.p. 153–154°.

Anal. Calcd. for $C_{26}H_{23}N_3O_7$: C, 63.81; H, 4.74. Found: C, 64.09; H, 4.93.

The picrate was dissolved in benzene (30 ml.), and the solution was passed through a column consisting of an equal part mixture of activated alumina and Super-cel. The benzene was evaporated under reduced pressure and afforded 9,10-dimethyl-1′,2′,3′,4′-tetrahydrobenzanthracene as a yellow solid, m.p. 89–90°.

Anal. Calcd. for $C_{20}H_{20}$: C, 92.23; H, 7.73. Found: C, 91.98; H, 7.65.

Reduction at the Dropping Mercury Electrode.—A Leeds and Northrup Electro-chemograph, type E, was used to record the polarograms. A minimum of damping (position 1) was used to prevent distortion of the waves. Half-wave potentials were measured with both increasing and decreasing cathodic voltage and the average was computed. The capillary used was made from marine barometer tubing obtained from the Corning Glass Works. The value of the capillary constant $M^{2/3}\,t^{1/6}$ was 2.27 at h equal to 35.6 cm. The drop time was measured with the current flowing in the region of the half-wave potential. The electrolysis cells were of the usual type. A saturated calomel electrode was used as the anode and was connected by means of a flexible saturated potassium chloride agar bridge to the electrolysis cell. The quinones were dissolved in a 50:50 mixture of reagent grade isopropyl alcohol and 0.1 *M* acetate buffer, *p*H 5.6, or in 0.1 *M* hydrochloric acid in 50% isopropyl alcohol, *p*H 1.5, to give a final concentration of 5×10^{-4} *M*. The *p*H measurements were recorded with a Beckman model G *p*H meter. All of the solutions were kept out of direct sunlight and preferably in the dark to prevent any possible reaction between the alcohol and the quinone. Also determinations were carried out as soon as possible after the solutions had been made, and all determinations were carried out under the same conditions. The nitrogen used was purified grade supplied by Canadian Liquid Air. The temperature during the experiments was thermostated at 25°. A summary of observed half-wave potentials is given in Table I. In the acetate buffer the waves did not show semiquinone formation. Instead, perfectly smooth waves were obtained, corresponding to a reversible two-electron reduction. In strongly acid solutions the waves were not quite so well formed, but the potentials correspond quite closely with those measured in the acetate buffer and indicate quite clearly the reliability of the measurements to the nearest 0.01 V.

TABLE I

$E_{1/2}$ *vs.* THE SATURATED CALOMEL ELECTRODE FOR ANTHRAQUINONES IN VARIOUS BUFFERS AND 50% ISOPROPYL ALCOHOL. ALL $E_{1/2}$ VALUES ARE NEGATIVE

Quinone	0.1 *M* Acetate buffer, *p*H 5.6	0.1 *M* HCl, *p*H 1.5
Anthraquinone	0.43[a]	0.18
2-Methylanthraquinone	.44[a]	.19
1-Methylanthraquinone	.48	.23
1,2-Dimethylanthraquinone	.51	.25
1,3-Dimethylanthraquinone	.50	..
1,2-Cyclopenteno-9,10-anthraquinone	.47	..
1′,2′,3′,4′-Tetrahydro-1,2-benzanthraquinone	.49	..
1,4-Dimethylanthraquinone	.53	0 29

[a] These values correspond to E_0 values of +0.15 and +0.14 v. for anthraquinone and 2-methylanthraquinone, respectively. This is in good agreement with the values of +0.155 and +0.150 v. obtained by J. B. Conant and L. F. Fieser, *ibid.*, 46, 1858 (1924). See also (a) H. Adkins and F. W. Cox, *ibid.*, 60, 1151 (1938); (b) S. Wawzonek, H. A. Laitinen and S. J. Kwiatkowski, *ibid.*, 66, 827 (1944); (c) N. H. Furman and K. G. Stone, ref. 8.

Polarograms which were run in 0.1 *M* tetramethylammonium hydroxide, *p*H 13.7, and which are not reported in this paper, indicated semiquinone formation by the fact that two-step waves, each involving one electron, were noticed. The separation of the two waves varied considerably from one compound to another but was greatest with anthraquinone and a minimum with 1,4-dimethylanthraquinone. Furman and Stone[8] in their careful work have attributed this phenomenon to complex formation with the buffer. However, in the present work the waves were too indistinct to permit quantitative measurements of the differences.

In order to establish whether the systems studied were strictly reversible or not, the quinones were reduced to the hydroquinones and then the oxidation waves of the hydroquinones were determined. Reduction was carried out by chemical means and also by controlled potential electrolysis as described by Lingane.[9]

(3) R. B. Sandin, R. Kitchen and L. F. Fieser, THIS JOURNAL, **65**, 2018 (1943).

(4) G. Heller, *Ber.*, **43**, 2890 (1910).

(5) L. F. Fieser and H. Heymann, THIS JOURNAL, **64**, 376 (1942).

(6) L. F. Fieser and E. B. Hershberg, *ibid.*, **59**, 2331 (1937).

(7) H. J. Backer and J. R. van der Bij, *Rec. trav. chim.*, **62**, 561 (1943).

(8) N. H. Furman and K. G. Stone, THIS JOURNAL, **70**, 3055 (1948).

(9) J. J. Lingane, "Electroanalytical Chemistry," Interscience Publishers, Inc., New York, N. Y., 1953. Chapter XII.

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Chemical Reduction.—Titanous chloride in the acetate buffer reduced all compounds smoothly and produced anodic waves, the potentials of which were in exact agreement with the cathodic waves of the hydroquinones. In hydrochloric acid solution the expected anodic waves were likewise obtained for all compounds except 1,4-dimethylanthraquinone, which was not reduced under these conditions. When sodium hydrosulfite reduction of the quinone in 0.1 *M* tetramethylammonium hydroxide was carried out, anodic waves were obtained and the potential agreed within experimental error with the cathodic waves of the quinone. In the case of anthraquinone and 2-methylanthraquinone, the anodic waves were of the same height as the original cathodic waves. However, with the 1-substituted anthraquinones, the hydroquinone waves were greatly reduced in height. Apparently the hydroquinone primarily formed was changing rapidly to some other form such as the oxanthrol. No reduction wave could be found for the postulated oxanthrol.

Electrochemical Reduction.—In order to check the results of chemical reduction, 1,2-dimethylanthraquinone was reduced by controlled potential electrolysis. In these experiments 0.5×10^{-4} *M* solutions in 50% isopropyl alcohol were electrolyzed under purified nitrogen using a large mercury pool stirred magnetically as cathode and a saturated calomel electrode as anode. The cathode potential was controlled manually.

In 0.1 *M* tetramethylammonium hydroxide the reduction of 1,2-dimethylanthraquinone proceeded smoothly, but the height of the anodic wave decreased rapidly to a small fraction of the original height of the cathodic wave. The half-wave potential of this wave was the same as that of the quinone. Bubbling oxygen through the solution followed by nitrogen produced the original cathodic wave corresponding to the original concentration. This indicated that the isomerization that was taking place was completely reversible. Anthraquinone under these conditions showed no decrease in height of the anodic wave over a 12-hr. period.

Electrolysis of 1,2-dimethylanthraquinone in the acetate buffer produced an anodic wave, with unchanged half-wave potential. The height of this wave decreased to about 60% of its original value after 4 hr. and 30% of its former value after 8 hr. In addition, a reduction wave developed at −1.1 v. which probably corresponds to the oxanthrol. The over-all height of the two waves equalled that of the original quinone. When the solution was oxidized with oxygen, the cathodic wave of the quinone was produced, but its height was only slightly higher than that of the hydroquinone. This indicated that the isomerization between the hydroquinone and oxanthrol was much slower at the lower *p*H.

In 0.1 *M* HCl, 1,2-dimethylanthraquinone was reduced smoothly to the hydroquinone which did not indicate any appreciable isomerization to the oxanthrol. In 0.1 *M* HCl, 1,4-dimethylanthraquinone, which was not reduced by titanous chloride, was reduced smoothly to the hydroquinone with no evidence of isomerization. In both cases the potentials of the hydroquinone were the same as that of the original quinones.

Air Oxidation of 1,2,9,10-Tetramethylanthracene (I) and 9,10-Dimethyl-1′,2′,3′,4′-tetrahydrobenzanthracene (IV) in the Solid State.—Freshly prepared hydrocarbon I, m.p. 52–54°,[3] and hydrocarbon IV, m.p. 89–90°, were exposed to air in the solid state. Compound I, after 7 days exposure, had a m.p. 50–73° and gave off bubbles of gas at 109°. Freshly prepared I gave no reaction with starch–potassium iodide solution, whereas the exposed material gave a definite test. In contrast to this behavior, IV after 7 days exposure had a m.p. 89.5–91° and gave no evidence of having undergone oxidation. Moreover, IV after one month of exposure showed no appreciable change in chemical composition as indicated by analysis.

Anal. Calcd. for $C_{20}H_{20}$: C, 92.23; H, 7.73. Found: C, 91.56; H, 7.86.

Discussion

The influence of alkyl substitution upon the ease of polarographic reduction is indicated in Table I. α-Substitution yields a more negative potential than β-substitution. Potentials become more negative with disubstitution and a six-membered ring is more effective in lowering the potential than the five-membered ring.[10] Our observed value for 2-methylanthraquinone probably gives a rough estimate of the conjugative and inductive effects of the methyl group.[11] However, our recorded potential difference between anthraquinone and the 2-methylanthraquinone may not be too significant.

The lower negative value for α-methylanthraquinone brings in an added steric effect.[12,13]

Leonard, Laitinen and Mottus[14] have given a very clear picture of the type of polarization which is believed to occur at the electrode in the case of the polarography of certain 1,2-diketones. They have also suggested that the lowering of the potential is due in part to a steric hindrance to coplanarity of the dicarbonyl system. In the present work it is quite possible that the steric requirements of the carbonyl group and the α-substituent are involved. Gill and Stonehill[12a] suggest a steric hindrance which pushes both the =O and large α-substituent out of the ring plane. This would inhibit any resonance of the carbonyl group and also of the α-substituent with the ring. The enhanced effect of 1,2-dimethyl substitution over an additive effect may be due to a buttressing action where the α-methyl group is buttressed by the adjacent methyl group.[15] That the six-membered ring is more effective in lowering the potential than the five-membered ring may be due to the greater amount of crowding associated with the conformation of the six-membered ring. However, a six-membered ring is not as important from the standpoint of crowding as 1,2-dimethyl substitution. This is particularly noticeable when the stabilities of the two hydrocarbons I and IV are compared. The chemical and electrochemical reduction of α-substituted anthraquinones indicates isomerization to an oxanthrol. Gill and Stonehill[16] have shown that certain anthrahydroquinones give polarographic oxidation waves which decrease in height with time. This decrease is attributed to a reversible change to oxanthrols. The latter are polarographically reducible only at highly negative potentials. There are two possible structures for

(10) This is consistent with the interesting work of Arnold and co-workers who have shown that the relative steric influence of methylene groups decreases in the order CH_2 (in CH_3) > CH_2 (in a six-membered ring) > CH_2 (in a five-membered ring). For leading references see S. W. Fenton, A. E. DeWald and R. T. Arnold, THIS JOURNAL, **77**, 979 (1955); R. T. Arnold, V. J. Webers and R. M. Dodson, *ibid.*, **74**, 368 (1952).

(11) The classic work of Fieser and collaborators has shown that electron-donating substituents lower the potential. For a bibliography and reviews of the work of Fieser, *et al.*, see (a) M. G. Evans and J. De Heer, *Quart. Revs.*, **4**, 94 (1950); (b) G. K. Branch and M. Calvin in "The Theory of Organic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1946, p. 315; (c) L. F. Fieser and M. Fieser in "Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1956, p. 710.

(12) (a) R. Gill and H. I. Stonehill, *J. Chem. Soc.*, 1845 (1952); (b) R. H. Peters and H. H. Sumner, *ibid.*, 2101 (1953).

(13) Prelog, *et al.* (V. Prelog, O. Häfliger and K. Wiesner, *Helv. Chim. Acta*, **31**, 878 (1948); V. Prelog, K. Wiesner, W. Ingold and O. Häfliger, *ibid.*, **31**, 1325 (1948); V. Prelog, *J. Chem. Soc.*, 420 (1950)) have concluded that hydrogen-bridge formation between methylene groups and the oxygen atoms of certain *p*-benzoquinone derivatives is also responsible for the lowered potential.

(14) N. J. Leonard, H. A. Laitinen and E. H. Mottus, THIS JOURNAL, **75**, 3300 (1953).

(15) See F. H. Westheimer in the excellent treatise "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 552. See also L. L. Ingraham in the same treatise, p. 486.

(16) R. Gill and H. I. Stonehill, *J. Chem. Soc.*, 1857 (1952).

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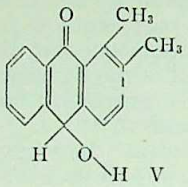
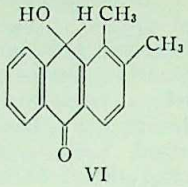
the oxanthrol from 1,2-dimethylanthraquinone, *viz.*, V and VI.

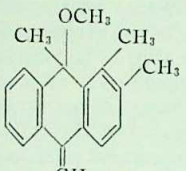


V

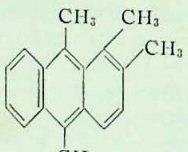


VI

The preferred structure is believed to be VI, *i.e.*, the carbon atom which is the more crowded is believed to be the one which becomes tetrahedral. Moreover there is a precedent for this type of structure in the 1,2-benzanthracene series.[17] It is also interesting that a mixture of the compounds VII and VIII has been isolated.[3] It is quite possible that the isomerization may be due to the resistance



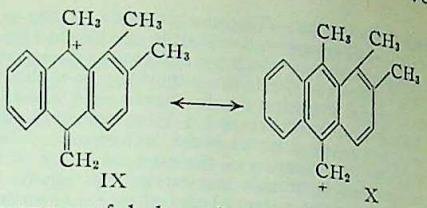
VII



VIII

offered to the formation of a planar crowded molecule, which in this case is the hydroquinone.

From our study we conclude that compounds such as 1,2,9,10-tetramethylanthracene and the corresponding hydroquinones behave as crowded molecules. Superficially, from the standpoint of structure, I resembles the crowded molecule of octamethylnaphthalene.[18] The successful preparation of hydrocarbon I evidently requires, besides the driving force of aromatization, the added effect of a carbonium ion stabilized by the resonance forms IX and X.[3]



IX X

The unsuccessful demethoxylation[1] and dehydrogenation[2] attempts to prepare I, compared with the successful reactions where there is no 1,2-disubstitution, may involve an unfavorable reaction mechanism. Again it is possible that a hindered or unfavorable conformation of the starting material is involved, where a preferrred conformation for 9,10-elimination is necessary. Some recent interesting work has been carried out[19] which indicates that 9,10-dihydroanthracenes may be considered as cyclo-1,4-hexadienes and therefore may have bond orientations at the 9- and 10-positions which are not equivalent. For example, *cis*-9,10-dihydro-9,10-dimethylanthracene[19c] is stable to aluminum chloride in benzene, whereas the *trans* isomer[19c] is dehydrogenated under the same conditions.[20] Evidently in the former compound both hydrogen atoms are in equatorial positions, and in the latter compound one hydrogen is in an axial position. It should be mentioned, however, that the first compound, in spite of its stability to aluminum chloride in benzene, is dehydrogenated with sulfur without any difficulty.

Acknowledgment.—We take pleasure in expressing our appreciation to Dr. Richard T. Arnold of the Sloan Foundation for very stimulating discussions and suggestions, to Dr. Walter Harris for his help in connection with polarographic technique, and to Dr. Robert Christiansen for his help in the preparation and analysis of some of the compounds.

(17) R. B. Sandin and L. F. Fieser, THIS JOURNAL, **62**, 3098 (1940).

(18) (a) D. M. Donaldson and J. M. Robertson, *J. Chem. Soc.*, 17 (1953); (b) M. S. Newman and R. M. Wise, THIS JOURNAL, **78**, 450 (1956).

(19) (a) S. J. Cristol, W. Barasch and C. H. Tieman, *ibid.*, **77**, 583 (1955); (b) A. H. Beckett and B. A. Mulley, *Chemistry & Industry*, 146 (1955); (c) A. H. Beckett and B. A. Mulley, *J. Chem. Soc.*, 4159 (1955); (d) W. G. Ferrier and J. Iball, *Chemistry & Industry*, 1296 (1954).

(20) G. M. Badger, M. L. Jones and R. S. Pearce, *J. Chem. Soc.*, 1700 (1950).

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[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The *para* Claisen Rearrangement: Rearrangement of 6-Allyl-2,6-dimethyl-2,4-cyclohexadienone[1]

BY DAVID Y. CURTIN AND ROBERT J. CRAWFORD

RECEIVED JANUARY 10, 1957

The synthesis of 6-allyl-2,6-dimethyl-2,4-cyclohexadienone from sodium 2,6-dimethylphenoxide and allyl bromide is here reported. The dienone rearranges to a mixture of 4-allyl-2,6-dimethylphenol and allyl 2,6-dimethylphenyl ether in a ratio of 2.7/1 when heated to 70°. On standing at room temperature it yields a dimer. The rates of the rearrangements have been measured at three temperatures. The results are compared with data of previous workers. The steady state concentration of dienone in the *para* Claisen rearrangement is shown by examination of the reaction mixture to be of the order of 0.1%.

Studies[2] of the mechanism of the *para* Claisen rearrangement have indicated that allyl-cyclohexadienones are intermediates in this reaction. It was the purpose of the present investigation to prepare such a compound and examine its behavior under the conditions of the Claisen rearrangement. The

(1) Taken from a Ph.D. thesis submitted by Robert J. Crawford to the University of Illinois, August, 1956.

(2) See D. Y. Curtin and H. W. Johnson, Jr., THIS JOURNAL, **76**, 2611 (1956), for references.

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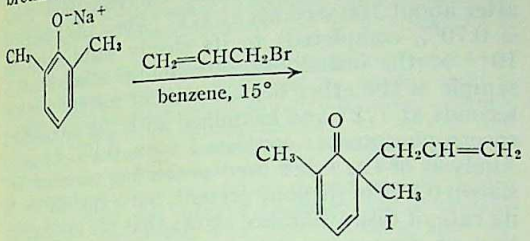
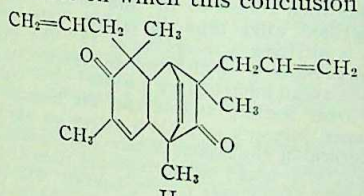
methyl-2,4-cyclohexadienone (I) which was prepared in 60% yield based on unreacted starting material by treatment of a suspension of the sodium salt of 2,6-dimethylphenol in benzene with allyl bromide.[3,4]



I

The allyldienone I rearranges readily when heated, but could be purified by distillation at reduced pressure. It was characterized by comparison of its infrared and ultraviolet spectra with those of other 2,4-cyclohexadienones. It reacted with maleic anhydride in benzene at 100° to form an adduct which is apparently identical with that which had been obtained by Conroy and Firestone[5] when they carried out the Claisen rearrangement of allyl 2,6-dimethylphenyl ether (IV) in the presence of maleic anhydride. When the dienone I was allowed to stand for several weeks, it was found to have undergone extensive reaction and eventually a crystalline compound, m.p. 92°, having twice the molecular weight of the dienone was formed. This substance is undoubtedly one of the diastereoisomers of the two Diels–Alder products II or III formed by condensation of the dienone I with itself. Evidence on which this conclusion is based



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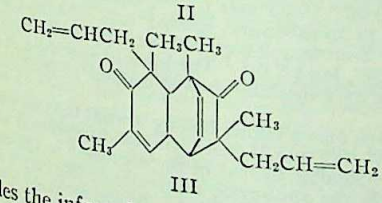
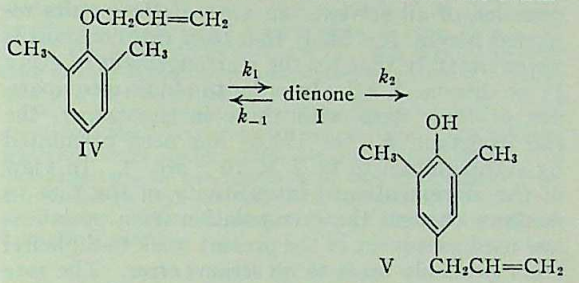


III

includes the infrared and ultraviolet spectra, a molecular weight determination in camphor and the observation that hydrogenation over platinum resulted in the rapid uptake of three moles of hydrogen followed by a slower uptake of a fourth. The three unconjugated carbon–carbon double bonds in the structures II or III account for the rapid hydrogenation. The dimer when heated at 120° underwent what is apparently the reversal of its formation followed by a Claisen rearrangement of the dienone I to yield 4-allyl-2,6-dimethylphenol in 64% yield. A similar dimerization reaction was observed by Conroy and Firestone when they prepared 2,6-dimethyl-6-*n*-propyl-2,4-cyclohexadienone.[5b] The allyldienone I rearranges at temperatures above 70° to give a mixture of allyl 2,6-dimethylphenyl ether (IV) and 4-allyl-2,6-dimethylphenol (V). The reaction was conveniently carried out in cyclohexane solution. Under the conditions employed, the ratio of *p*-allylphenol V to allyl ether IV was 2.7.



Kinetics.—The rearrangement of the dienone I in cyclohexane at temperatures of 75–100° was conveniently followed with an ultraviolet spectrophotometer. At these temperatures the rearrangement of the allyl ether IV is negligible. Concentrations employed were low enough so that the Diels–Alder dimerization of I (which is presumably second order) was negligible. The disappearance of the dienone I followed a first-order rate law. If the reasonable assumption is made that dienone I is disappearing by two simultaneous first-order paths with constants k_{-1} and k_2 (each irreversible under the reaction conditions), then the measured rate constant is $k_{-1} + k_2$. Values of the experimental constants calculated from the data by the method of least squares are shown in Table I. The ratios k_2/k_{-1} in the table were obtained by an analysis of the products of the completed rearrangement with the ultraviolet spectrophotometer. It will be seen that this ratio is independent of temperature over the range studied.

TABLE I

RATE CONSTANTS FOR THE REARRANGEMENT OF THE DIENONE I

Run	Temp., °C.	Init. concn., *M*	$10^5(k_{-1} + k_2)$, sec.$^{-1}$	k_2/k_{-1}	$10^6 k_{-1}$	$10^5 k_2$
1	75.00 ± 0.01	0.617	2.20			
2	75.00 ± .01	0.0305	1.44 ± 0.01	2.8	3.89	1.05
3	83.96 ± .01	.0249	3.56 ± .17	2.7	9.62	2.60
4	101.68 ± .01	.0305	20.7 ± .2	2.7	56.0	15.1

This conclusion was confirmed by the fact that infrared spectra of the products of rearrangement of 10% solutions at each of the temperatures studied were identical. The separate rate constants, calculated by partitioning the total rate constant, are shown in Table I. Quantities of activation calculated from these data are given in Table II.

The rate of rearrangement of the allyl ether IV to the 4-allylphenol V in diphenyl ether solution at 171.6° was measured by Tarbell and Kincaid.[6]

(3) D. Y. Curtin and R. J. Crawford, *Chemistry and Industry*, 313 (1956). This reaction was suggested by the report of L. Claisen, F. Kremers, F. Roth and E. Tietze [*Ann.*, **442**, 210 (1925)] that the sodium salt of phenol underwent alkylation in an *o*-position when suspended in benzene and treated with allyl halides.

(4) The factors which determine whether the phenoxide ion undergoes alkylation on carbon to give dienone or on oxygen to give ether have been made the object of a more extended investigation and will be reported in a separate communication.

(5) H. Conroy and R. A. Firestone, (a) THIS JOURNAL, **75**, 2530 (1953); (b) **78**, 2290 (1956).

(6) D. S. Tarbell and J. F. Kincaid, *ibid.*, **62**, 1728 (1940).

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TABLE II

QUANTITIES OF ACTIVATION FOR THE REARRANGEMENT AT 83.96° OF THE DIENONE I

Rate constant	E_a, kcal./mole	$\Delta H\ddagger$, kcal./mole	$\Delta S\ddagger$, cal./mole deg.	$\Delta F\ddagger$, kcal./mole
k_{-1}	26.8	26.1	−8.8	29.3
k_2	26.8	26.1	−7.1	

They found the reaction to be first order and quite insensitive to such changes in the reaction medium as added acetic acid or dimethylaniline or even omission of all solvent. In view of the results reported herein, it is likely that their rate constant is approximately that for the rearrangement of ether IV to dienone I, k_1.[7] In order to obtain a comparison of their data with those in this paper, the rate constant, k_{-1}, at 171.6° has been calculated by extrapolation to be 2×10^{-2} sec.$^{-1}$. In view of the aforementioned insensitivity of the rate to medium changes the extrapolation from cyclohexane used as solvent in the present work to diphenyl ether probably leads to no serious error. The rate constants together with the quantities of activation obtained by extrapolation of the present data may be compared with those of Tarbell and Kincaid. Their value for the entropy of activation was −10.1 e.u. at 171.6°. It was calculated from the Eyring equation with the assumption that $\Delta H^{\ddagger} = E_a$. A recalculation using the relationship[8] $\Delta H^{\ddagger} = E_a - RT$ gives a value of −12.1 e.u. A further correction must be applied before their value may be compared with that reported here for the reverse reaction. Their rate was the rate of rearrangement to two *o*-positions and must be corrected with a statistical factor of 2. Such a correction gives $\Delta S^{\ddagger}$ for rearrangment of the allyl ether IV to one *o*-position equal to −13.5 e.u. This is to be compared with the value of −8.5 e.u. for the reverse reaction obtained from the extrapolated values of $\Delta H^{\ddagger}$ and $\Delta F^{\ddagger}$ in the present work. If interpreted literally, this difference requires that the entropy of the dienone I be lower than that of the ether IV by some 4 e.u.[9] However, in view of the possible errors in these values, it is not clear how valid such a comparison may be. It is of interest that ΔH for the process IV $\rightleftarrows$ I when calculated as $\Delta H_1^{\ddagger} - \Delta H_{-1}^{\ddagger}$ amounts to +3.5 kcal./mole as compared with the value of +7 calculated by Conroy and Firestone[5] from bond energies.

A further point of interest is the steady-state concentration of the dienone I in the rearrangement of the ether IV. From the integrated rate expression of Lowry and John[10] for two successive reversible reactions and the data discussed above, it has been calculated that the dienone concentration rises after about 100 seconds at 171° (when the reaction is 0.70% completed) to its steady state value of $10^{-3} \times$ the initial concentration of ether IV. A sample of the ether heated without solvent for 100 seconds at 172° and examined with the ultraviolet spectrophotometer contained some 0.1% dienone. Analysis of the ether used as starting material had shown 0.2% of dienone present, but a calculation of its rate of disappearance shows that the concentration of dienone remaining from that present initially would be less than 10^{-5}% at that time. It was reported by Conroy and Firestone[5a] that when the allyl ether IV was heated to 200° and treated with maleic anhydride at 100° (at which temperature it no longer rearranged), that the maleic anhydride adduct of the dienone I was obtained in small yield. Calculation of the yield from data given in the Experimental section of their paper[5b] indicates that it was 0.6% of incompletely purified product. This is in fair agreement with our value of 0.1% estimated from ultraviolet spectral data.

Experimental[11]

6-Allyl-2,6-dimethyl-2,4-cyclohexadienone (I).—A solution of 2,6-dimethylphenol (12.2 g., 0.10 mole) was treated with 5.6 g. (0.10 mole) of sodium methoxide in 300 ml. of dry benzene under a nitrogen atmosphere and the mixture distilled until the refractive index of the distillate corresponded to that of benzene (*ca.* 100 ml. of distillate). The mixture was then cooled to 15° and 30 ml. (0.38 mole) of freshly distilled allyl bromide added. After 44 hr. of stirring in a nitrogen atmosphere at 15°, the solid sodium bromide was removed by filtration and the filtrate extracted with Claisen alkali and then with water. The organic layer was dried over sodium sulfate and the benzene removed under reduced pressure to yield a yellow oil which, on distillation through a Holzmann column at 0.05 mm. pressure, gave 3.8 g. (60% based on unrecovered phenol) of dienone I, b.p. 36–37° (0.05 mm.), n^{25}D 1.5050. The ultraviolet spectrum in cyclohexane showed λ_{max} 303 mμ, ε 4,400. [Compare 2-acetoxy-2-methyl-3,5-cyclohexadienone[12] which has λ_{max} 292, log ε 3.6.] The infrared spectrum of a 10% solution in cyclohexane[13] showed maxima at 1663 and 1645 cm.$^{-1}$.

There was also a higher boiling neutral fraction (*ca.* 1 g., b.p. 72–73° (0.2 mm.)) which showed absorption at 1640 and 1670 cm.$^{-1}$ similar to that of the dienone I in the carbonyl region while the absorption maximum at 920 cm.$^{-1}$ was approximately double that of I. It seems likely that this material is a dienone–ether mixture formed from the reac-

(7) ADDED IN PROOF.—It will be noted that application of the steady state approximation shows that the observed rate constant of Tarbell and Kincaid is equal to the constant $k_1 \times f$ where f is the fraction of dienone molecules which go on to 4-allylphenol rather than back to ether I. Their constant should therefore be multiplied by $1/f$ to give k_1 for their rearrangement. Unfortunately $1/f$ is unknown for their rearrangement conditions. In the present work it is 3.7/2.7 or 1.4 but previous results have suggested that it may be sensitive to changes in medium.[2] Since the correction is probably not large in any case no attempt has been made to apply one in the following comparisons of our data with those of Tarbell and Kincaid. While this paper was in press a report on the kinetics of the rearrangement of carbon-four-teen-labeled allyl 4-allyl-2,6-dimethylphenyl ether has appeared [F. Kalberer and H. Schmid, *Helv. Chim. Acta*, **40**, 13 (1957)].

(8) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., p. 97.

(9) For the calculation of the entropy change for the reaction IV $\rightleftarrows$ I the rate constant for the total rate of conversion of IV to I (*i.e.*, without the statistical correction for the two *o*-positions) has been used.

(10) T. M. Lowry and W. T. John, *J. Chem. Soc.*, **97**, 2673 (1910).

(11) Microanalyses were carried out by Mr. J. Nemeth, Mrs. K. Pih, Mrs. L. Chang, Mrs. E. Pett, Mr. R. N. Benassi and Miss C. Higham. Certain of the ultraviolet spectra were determined by Miss Gerardine Meerman. Infrared spectra were recorded by Mr. James Brader and Mrs. Louise Griffing. All melting points are corrected. The ultraviolet and infrared spectra and also detailed kinetic data are available in the Ph.D. Thesis, of Robert J. Crawford and reproduced by University Microfilms, Ann Arbor, Mich.

(12) F. Wessely and F. Sinwel, *Monatsh.*, **71**, 1055 (1950).

(13) Because of the small difference between the b.p. of the allyl ether IV, b.p. 50° (0.5 mm.), and the dienone I and because of the ease of rearrangement of I to IV, it was not possible to prepare dienone I demonstrably free from the ether IV. However, the ether IV has absorption at 837, 1097 and 1267 cm.$^{-1}$ in the infrared which is apparently absent in the dienone spectrum. Using these bands, it was possible to set an upper limit of approximately 5% on the amount of ether present in the best sample of dienone. This means that the [illegible] is lower by that amount.

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tion with allyl bromide with 4-allyl-2,6-dimethylphenol which was produced by a small amount of rearrangement of the dienone I under the reaction conditions.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.3; H, 9.0. Found: C, 83.1; H, 9.0.

Acidification of the alkaline extracts gave 7.0 g. of a phenol fraction which was estimated by infrared analysis to contain about 55% of 2,6-dimethylphenol and 44% of 4-allyl-2,6-dimethylphenol.

The maleic anhydride adduct (m.p. 139–140° uncor.) of dienone I was formed in 40% yield by heating 0.50 g. (0.0030 mole) of dienone with 0.35 g. (0.0035 mole) of maleic anhydride in a nitrogen atmosphere for 3 hr. at 100° and washing the product with ether after it solidified.

Dimerization of Dienone I.—A sample of the dienone I after 3 weeks at room temperature showed an entirely different ultraviolet and infrared spectrum and eventually crystallized. The product after recrystallization from petroleum ether melted at 92–93°. The infrared spectrum of a 10% solution in carbon tetrachloride shows weak absorption at 1638 cm.$^{-1}$ and strong bands at 1680 and 1715 cm.$^{-1}$. The ultraviolet spectrum (in cyclohexane) had a shoulder at 237 mμ, ε 5700.

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.5; H, 8.7; mol. wt., 324. Found: C, 81.9; H, 8.8; mol. wt., 320.

Hydrogenation of the dimer in ethyl acetate at room temperature with hydrogen at one atmosphere pressure and Adams platinum catalyst led to the rapid absorption of 2.95 moles of hydrogen and an additional mole over a period of 4 hr., after which no further hydrogen reacted. No attempt was made to isolate the reduced product.

When the dimer of I (0.5 g.) was heated at 150° for 3 hr. and the product distilled (only a portion was distillable), 4-allyl-2,6-dimethylphenol was formed as shown by its solubility in alkali and the identity of its infrared spectrum with that of a known sample. The dimer when heated at 120° for 8 hr. gave 64% of the phenol.

Rearrangement of Dienone I.—After 12 hr. at 135°, the product from 2 g. of dienone was added to 15 ml. of cyclohexane, extracted with Claisen alkali washed with water, dried over sodium sulfate and the solvent evaporated at room temperature. Distillation of the remaining oil gave 0.55 g. of the allyl ether IV, b.p. 63° (1.2 mm.), $n^{25}D$ 1.5045. The ultraviolet spectrum showed no absorption at 303 mμ (where the dienone has strong absorption) but instead λ_{max} 270, ε 500, in agreement with that characteristic of the allyl ether IV.

Acidification of the Claisen alkali-soluble fraction above followed by extraction with 15 ml. of cyclohexane, drying over magnesium sulfate, evaporation of the solvent and distillation of the residual oil under vacuum gave 1.0 g. of 4-allyl-2,6-dimethylphenol (V), b.p. 87° (1.8 mm.), $n^{25}D$ 1.5365 (lit.[6] b.p. 90.5° (2 mm.), $n^{25}D$ 1.5370).

Determination of the Rates of Rearrangement of the Dienone I.—Since the dienone rearranges slowly at room temperature, only freshly prepared samples could be employed. Its infrared spectrum was determined as a check on its purity. There was always a trace of the ether IV present which could be determined by its absorption at 1698 cm.$^{-1}$. The sample was diluted to the appropriate concentration and stored at −10° until used. The cyclohexane was purified by washing with cold concentrated sulfuric acid and fractionation from calcium oxide through a 30-cm. Widmer column. The first and last 10% fractions were discarded.

Pyrex tubing (6 mm. o.d.) was cut into 10-cm. lengths and soaked in a solution of chromium trioxide in sulfuric acid. The tubes were thoroughly rinsed in deionized water and dried. They were then sealed at one end, constricted at a distance of 3 cm. from the unsealed end, flushed with dry nitrogen and filled with the dienone in cyclohexane (concentrations indicated in Table I). The contents were frozen in a brine–ice mixture and the tubes sealed. The tubes were then inserted into an oil-bath thermostatically regulated to within ±0.05°. The temperature of the bath was measured with a totally immersed thermometer graduated in tenths of a degree and calibrated by the Bureau of Standards.

At the proper time intervals the samples were removed from the bath and immersed in an isopropyl alcohol–Dry Ice mixture. After completion of the reaction the tubes were brought to 20°, opened and the solutions diluted to the appropriate concentrations (*ca.* 3×10^{-4} *M*) with cyclohexane. The absorbancies at 303 mμ were determined by the use of a Cary model 11 ultraviolet recording spectrophotometer using 1.00-cm. matched cells. At this wave length ε for the dienone I is 4,400 while the ether IV has ε < 5 and the *p*-allylphenol V has ε 30. The infinity absorbance is thus negligible compared to the measured absorbance over the range studied.

The complete spectrum was recorded for a control tube and for the infinity tube at each temperature. The infrared spectrum of the product (10% solution in cyclohexane) of a rearrangement for ten half-lives at each temperature confirmed the product analysis with the ultraviolet spectrophotometer. The rate constants ($k_{-1} + k_2$) were evaluated from the equation

$$\ln A_0 - \ln (A) = kt$$

where A_0 = initial absorbancy and A = absorbancy at time t, using the method of least squares.[14] At each temperature the reaction was followed to greater than 60% completion, and the least squares calculation is based on measurements of twelve points.[10]

Use of the ultraviolet spectrum to calculate the composition of the product mixture is illustrated by the data for the run at 75 ± 0.01°. The absorbancy at 303 mμ was used to calculate the concentration (1.0×10^{-5} *M*) of dienone I remaining in the sample assuming that the absorbancies of ether IV and *p*-allylphenol V are negligible. The concentration of total starting material was 3.57×10^{-4} *M*. These data together with the absorbancy at 280 mμ where the dienone has ε 2200, the phenol has ε 1630 and the ether has ε 38 were used to calculate the concentrations of *p*-allylphenol (2.31×10^{-4}) and ether (1.16×10^{-4}). However, the starting material was shown to contain 0.33×10^{-4} *M* ether (from comparison of its infrared spectrum with those of authentic samples) and the ether concentration of 1.16×10^{-4} was corrected by the subtraction of this amount to yield the amount of ether formed in the reaction (0.83×10^{-4}). The ratio ether/*p*-allyl ether formed in the reaction is therefore 2.78. Values of 2.7 were obtained for reactions at each of the other temperatures employed. The individual rate constants were calculated using the assumption that the measured $k = k_{-1} + k_2$ and that $k_2/k_{-1} = 2.7$.

Detection of Dienone I in the Rearrangement of the Ether IV.—A sample of allyl 2,6-dimethyl ether sealed in a Pyrex tube was heated in refluxing phenetole (b.p. 172°) for 100 seconds. Samples of the product and the unheated starting solution were diluted to concentrations of 1.00×10^{-2} *M* in cyclohexane and their ultraviolet spectra determined. The absorbancy at 303 mμ showed that the unheated sample contained 0.20% of dienone I, whereas the heated sample contained 0.13%. Calculation from the rate constants ($k_{-1} + k_2$) for the rearrangement of the dienone I shows that only 1×10^{-5} % of the dienone present in the heated sample can be left from the dienone originally present.

URBANA, ILLINOIS

(14) L. P. Hammett, "Introduction on the Study of Physical Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1952, pp. 410–411.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

1,3-Shifts. V. The Intermolecular Nature of Some 1,3-Shifts

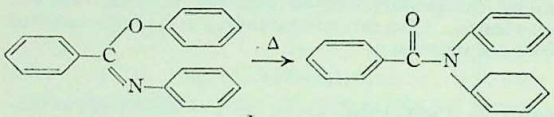
BY KENNETH B. WIBERG, THOMAS M. SHRYNE AND R. ROY KINTNER

RECEIVED JANUARY 16, 1957

It has been found that the rearrangements of α-methoxystyrene to propiophenone, of methyl benzoate with oxygen-to-oxygen migration of the methyl group, of methyl N-phenylformimidate to N-methylformanilide and of 2-methoxypyridine to N-methylpyridone are all intermolecular. The reactions were studied using a C^{13}-labeled methyl group as the tracer, and analyzing for the mixed reaction product with a mass spectrometer. The mechanisms of the reactions are discussed.

Introduction

We have shown previously that the thermal rearrangement of phenyl N-phenylbenzimidate (I) to N-phenylbenzanilide is intramolecular,[1] whereas the corresponding rearrangement of an alkyl N-phenylbenzimidate or an alkyl styryl ether is probably a free radical chain reaction.[2] In order to



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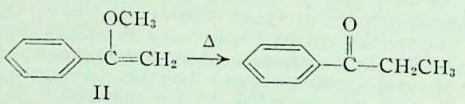
obtain further evidence on this matter, we have examined four reactions in order to determine whether they are inter- or intramolecular. The examples chosen were the rearrangements of α-methoxystyrene (II), methyl benzoate (III), methyl N-phenylformimidate (IV) and α-methoxypyridine (V). The reactions were studied in a manner which permitted the use of a mass spectrometer's unique ability to sort molecular species on a mass basis.



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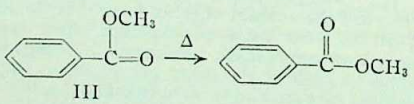

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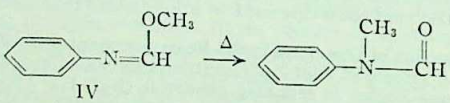

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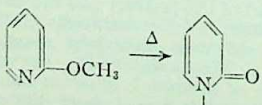

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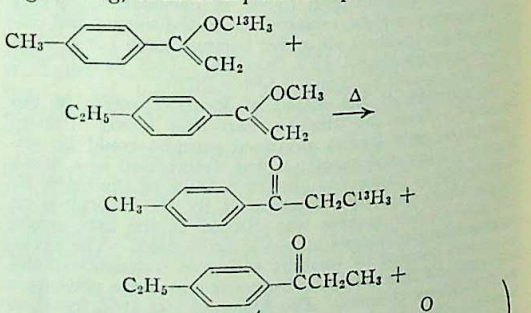
Results

The most common method of determining whether a reaction is inter- or intramolecular involves carrying out the reaction using a mixture of two similar compounds which undergo the reaction, and analyzing the product for a mixed compound which would arise from an intermolecular reaction. For a satisfactory determination of this type, three factors must be considered. First, the two compounds must react at very similar rates. Second, the migrating groups must have essentially equal reactivity toward either of the two reactants. Third, it should be possible to quantitatively isolate any mixed products which might be formed.

In the rearrangement of α-alkoxystyrenes, the rates of reaction will be essentially the same if the two compounds are substituted in the *p*-position with methyl and ethyl groups, respectively, since the σ-values for these groups are very close.[3] Ordinarily, it would be difficult to separate the mixed product if two such similar groups were used, since all of the products would have very similar properties. However, the use of a mass spectrometer obviates this difficulty if the reactants can be separated from the products, or if the reaction is carried to completion, since it can quantitatively separate the products on a mass basis. One may use essentially the same migrating group in both compounds if one contains an ordinary methyl group and the other contains a C^{13}-labeled methyl group. The only difference would be due to the C^{13} isotope effect which would be negligible in this case. If the lower molecular weight reactant is labeled, one may analyze for a mixed compound in the product by examining the mass spectrum of the product and determining if a new peak appears at a mass number one higher than that of the higher molecular weight reactant. In this way, one can quantitatively determine the amount of mixed product without resorting to long, tedious separation procedures.



The alkyl styryl ethers were prepared by treating the appropriately substituted styrene with methanol or methanol-C^{13}, mercuric oxide and iodine, followed by dehydrohalogenation of the intermediate iodoether. The rate of rearrangement of each of the two alkoxystyrenes was determined using the infrared spectrum, and in each case somewhat more than half-reaction was noted after heating for four hours at 220°. The C^{13} content of the α-methoxy-*p*-methylstyrene was determined by com-

(1) K. B. Wiberg and B. I. Rowland, THIS JOURNAL, **77**, 2205 (1955).

(2) K. B. Wiberg and B. I. Rowland, *ibid.*, **77**, 1159 (1955).

(3) H. H. Jaffé, *Chem. Revs.*, **53**, 222 (1953).

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paring its mass spectrum with that of an unlabeled sample,[4] both spectra being obtained at a low ionizing potential in order to minimize cracking (Table I).

TABLE I

MASS SPECTRA FOR VINYL ETHER REARRANGEMENT

	Reactant α-Methoxy-p-methylstyrene, ionizing potential 7.0 v.		Product p-Ethylpropiophenone, ionizing potential 14 v.		
Mass	Labeled	Unlabeled[a]	Mass	Labeled	Unlabeled[a]
147	0.0	0.0	161	18.4	12.3
148	100.0	100.0	162	100.0	100.0
149	40.4	12.5	163	23.9	13.8
% C^{13}	28.8	11.1		20.0	12.3
Excess C^{13}	17.7	0.0		7.9	0.0

[a] Containing the natural abundance of C^{13}.

A mixture of equal amounts of labeled α-methoxy-p-methylstyrene and ordinary α-methoxy-p-ethylstyrene was heated to 250° for a time corresponding to several half-lives. The mass spectrum of the product, and of unlabeled p-ethylpropiophenone was determined, allowing a calculation of the amount of C^{13} in the p-ethylpropiophenone from the reaction. Starting with α-methoxy-C^{13}-p-methylstyrene containing 17.7% excess C^{13} over normal abundance, the p-ethylpropiophenone was found to contain 7.9% excess C^{13}. For an intermolecular reaction, if the rates were equal, this product should contain 8.9% excess C^{13} since it can be equally distributed between the two mixed products. The good agreement between the observed and calculated values indicates the reaction to be intermolecular.

In the rearrangement of methyl benzoate, the requirement for equal rates of rearrangement for the two reactants is of little consequence so long as the rates are comparable, since the products and reactants are identical, and the rearrangement can be observed only by using O^{18} labeling.[5] Methyl-C^{13} benzoate was mixed with methyl p-toluate and the mixture was heated to 410° for a time corresponding to about three half-lives for the methyl benzoate rearrangement.

The mass spectra of the methyl-C^{13} benzoate and the product were compared with that of methyl benzoate and methyl toluate giving the data in Table II. Starting with methyl-C^{13} benzoate having 17.9% excess C^{13}, the product methyl toluate had 8.7% excess C^{13} indicating the rearrangement to be intermolecular.

(4) In this and subsequent compounds, the unlabeled material was found to have a C^{13} content very close (±0.2%) to the expected amount (1.1% times the number of carbons). The precision of the results determined from duplicate spectra was also about ±0.2% in the observed values.

The C^{13} content was determined by dividing the $(p + 1)$ peak by the sum of the parent and $(p + 1)$ peaks. In the cases in which cracking was found, this was corrected for by subtracting the product of the intensities of the $(p + 1)$ and $(p - 1)$ peaks divided by 100 from the parent peak before calculating the C^{13} content. Since the observed C^{13} content of the unlabeled compounds was very close to the expected amount, the excess C^{13} in the labeled compounds was taken as the observed C^{13} content less that expected in the unlabeled compound.

In the case of methyl benzoate and methyl toluate, it was shown that the C^{13} found in the product did not arise from an exchange process occurring in the mass spectrometer since the observed C^{13} content of methyl toluate mixed with an equal amount of methyl benzoate having 17.9% excess C^{13} was identical with that of pure methyl toluate.

(5) K. B. Wiberg, THIS JOURNAL, 75, 2662 (1953).

TABLE II

MASS SPECTRA FOR METHYL BENZOATE REARRANGEMENT

	Reactant Methyl benzoate, ionizing potential 10 v.		Product Methyl p-toluate, ionizing potential 10 v.		
Mass	Labeled	Unlabeled[a]	Mass	Labeled	Unlabeled[a]
135	1.5	1.5	149	0.0	0.5
136	100.0	100.0	150	100.0	100.0
137	36.3	9.4	151	22.8	10.7
% C^{13}	26.7	8.6		18.6	9.7
Excess C^{13}	17.9	0.0		8.7	0.0

[a] Containing the natural abundance of C^{13}.

The product of the rearrangement of methyl N-phenylbenzimidate is of too high molecular weight for a mass spectrometric analysis. Its hydrolysis product is also not desirable since it contains a readily exchangeable hydrogen, and the mass spectrometer had previously been used for the analysis of methanol-d and contained some exchangeable deuteriums adsorbed on its walls. Consequently, the corresponding methyl N-phenylformimidates[6] were used.

Methyl-C^{13} N-(p-tolyl)-formimidate was prepared by treating the silver salt of p-methylformanilide[7] with methyl-C^{13} iodide. Methyl N-(p-ethylphenyl)-formimidate was prepared by the same method, and a mixture of the two esters was rearranged at 300° for four hours. It had been found that either of the esters was about three-quarters decomposed (as indicated by the infrared spectrum) under these conditions. The products were separated from the reactants, and then reduced with lithium aluminum hydride to the N,N-dimethylanilines. This was necessary since the formanilides had too low a vapor pressure to be analyzed directly with the mass spectrometer. The data are given in Table III.

TABLE III

MASS SPECTRA FOR N-PHENYLFORMIMIDATE ESTER REARRANGEMENT

Ionizing potential = 10 v.

Mass	Labeled	Unlabeled[a]
148	1.7	0.8
149	100.0	100.0
150	22.8	12.4
% C^{13}	18.6	11.0
Excess C^{13}	7.5	0.0

[a] Containing the normal abundance of C^{13}.

The methyl-C^{13} N-(p-tolyl)-formimidate was assumed to have the C^{13} content of the alcohol from which it was prepared, 17.8% excess C^{13}. The product N,N-dimethyl-p-ethylaniline was found to contain 7.5% excess C^{13} indicating the rearrangement to be intermolecular.

The rearrangement of α-methoxypyridine to N-methylpyridone was found to proceed in essentially quantitative yield in contrast to previous reports.[8] α-Methoxy-C^{13}-4-methylpyridine was prepared by the reaction of 2-bromo-4-methylpyridine with methoxide-C^{13} ion. The α-methoxy-4-ethylpyridine was prepared in a corresponding manner, and a mixture of the methoxypyridines was heated

(6) W. Wislicenus and M. Goldschmidt, *Ber.*, **33**, 1471 (1900).

(7) M. P. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2543 (1924).

(8) H. Meyer, *Monatsh.*, **28**, 47 (1907).

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to 200° for 14 hours. It had been found that the two methoxypyridines rearranged at essentially the same rate (as indicated by the infrared spectra) and that this length of time gave almost complete reaction. The N-methylpyridones obtained as the product were reduced to the N-methylpiperidones before being analyzed since the latter gave more satisfactory mass spectra. The spectra of the products and the reduced reactants are given in Table IV.

TABLE IV

MASS SPECTRA FOR METHOXYPYRIDINE REARRANGEMENT

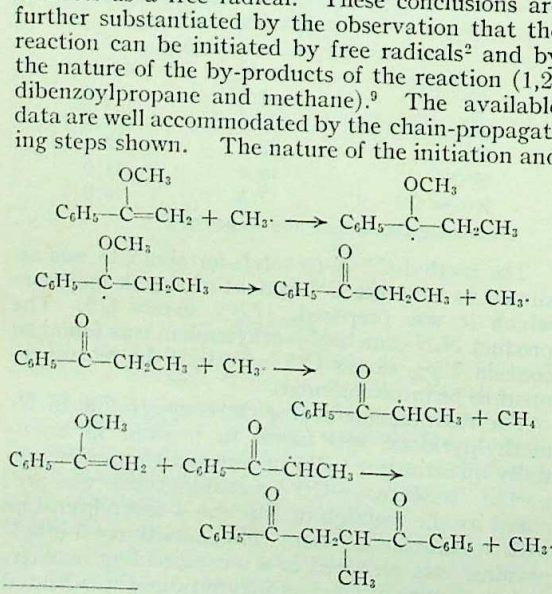
	Reactant α-Methoxy-4-methylpyridine, ionizing potential 7.5 v.		Product N-Methyl-4-ethyl-2-piperidone, ionizing potential 35 v.		
Mass	Labeled	Unlabeled[a]	Mass	Labeled	Unlabeled[a]
126	25.2	26.4	144	20.5	22.8
127	100.0	100.0	145	100.0	100.0
128	30.9	8.4	146	20.4	9.6
% C^{13}	24.8	7.8		17.6	8.9
Excess C^{13}	17.1	0.0		8.8	0.0

[a] Containing the normal abundance of C^{13}.

Starting with α-methoxy-4-methylpyridine containing 17.1% excess C^{13}, the product N-methyl-4-ethyl-2-piperidone was found to contain 8.8% excess C^{13} indicating the reaction to be intermolecular.

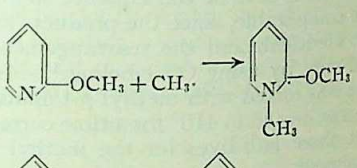
Discussion

The relationship of the above results to the mechanisms of the reactions may now be considered. In the vinyl ether rearrangement, it is known that the migrating group, if optically active, is racemized during the reaction.[2] The rearrangement of α-neopentoxystyrene led to the formation of a ketone without skeletal rearrangement of the migrating group.[2] These data, coupled with the observation of an intermolecular path for the reaction, demonstrate that the migrating group is free at some time during the rearrangement and strongly suggest that it exists as a free radical. These conclusions are further substantiated by the observation that the reaction can be initiated by free radicals[2] and by the nature of the by-products of the reaction (1,2-dibenzoylpropane and methane).[9] The available data are well accommodated by the chain-propagating steps shown. The nature of the initiation and termination steps are not known, although the former possibly involves the decomposition of a hydroperoxide formed by the autoöxidation of the vinyl ether. The kinetics of the rearrangement of α-benzyloxystyrene, a case which gives essentially no by-products, is now being studied.



In contrast to the rearrangement of phenyl N-phenylbenzimidate,[1] the rearrangement of methyl N-phenylformimidate was found to be intermolecular. The yield of rearranged product is quite low (about 40% from the unsubstituted compound and about 20% from the *p*-ethyl or *p*-methyl substituted compounds) and a principal by-product is N,N′-diphenylformamidine.[10] There are no available data on which to base a mechanistic hypothesis for this reaction, although it is possible that it may be similar in nature to the vinyl ether rearrangement. The reason for the difference between the phenyl migration and the alkyl migration has been discussed already.[1]

The rearrangement of 2-methoxypyridine to 2-pyridone also has been found to be intermolecular. This fact, coupled with the observations that the reaction may be catalyzed by benzoyl peroxide and that old samples of 2-methoxypyridine rearrange at a much faster rate than fresh samples (probably due to hydroperoxide formation), suggest that this is also a free radical chain reaction. In contrast to the previously mentioned reactions, this one leads to a nearly quantitative yield of rearranged product with a negligible amount of side reaction. If the radical chain mechanism is correct, it would appear that the attack of a methyl radical on a hydrogen is much less favorable than the attack on nitrogen, in contrast to the vinyl ether rearrangement.



The rearrangement of methyl benzoate, although found to be intermolecular, may be different from the previously discussed rearrangements. A rather high temperature (400°) is required for this reaction, whereas the others proceed at 250° or below. This may indicate a change in mechanism, or may be a consequence of the fact that only the ester cannot form hydroperoxides which may be chain initiators. In the case of methyl toluate, no gas formation was noted, whereas if methyl radicals were formed as an intermediate one might expect that a certain proportion of them would react with the methyl group attached to the ring to give methane and *p*-carbomethoxybenzyl radicals. It is somewhat unlikely that a methylcarbanion or carbonium ion was formed in the reaction.

(9) E. H. MacDougall, W. M. Lauer and M. A. Spielman, THIS JOURNAL, **55**, 4089 (1933); W. M. Lauer and M. A. Spielman, *ibid.*, **55**, 4923 (1933); M. A. Spielman and C. W. Mortenson, *ibid.*, **61**, 666 (1939); **62**, 1609 (1940).

(10) W. Wislicenus and M. Goldschmidt, *Ber.*, **33**, 1471 (1900), reported that the rearrangement of methyl N-phenylformimidate gave (CH3)2C6H3NCHO, methylformanilide and considerable diphenylformamidine.

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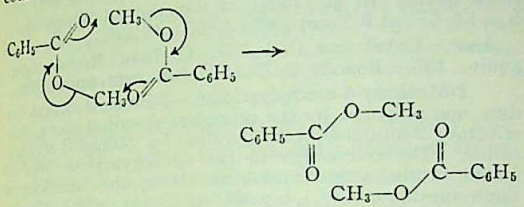
This suggests that the mechanism could involve the formation of an eight-membered cyclic activating complex. This is of course speculation, and a knowledge of the rate law for the reaction would be required before any mechanism for the reaction could be accepted.



Acknowledgment.—We wish to acknowledge the invaluable assistance of Mr. B. J. Nist in obtaining the mass spectra. The work was supported by the Office of Ordnance Research, U. S. Army, and assistance in purchasing certain equipment for the mass spectrometer was given by the Atomic Energy Commission.

Experimental[11]

Methanol-C^{13}.—Methanol-C^{13} was prepared by the lithium aluminum hydride reduction of carbon-C^{13} dioxide using essentially the same procedure as described by Nystrom, Hanko and Brown for the reduction of carbon-C^{14} dioxide.[12] On a tenth-mole scale, 85% of the theoretical amount of methanol was obtained.

Methyl-C^{13} Iodide.—Methanol-C^{13} was converted to the iodide by the procedure previously described for the conversion of methanol-C^{14} to the iodide.[12] On a 0.03-mole scale, 90% of the theoretical amount of methyl-C^{13} iodide was obtained.

α-Methoxy-*p*-ethylstyrene.—To a mixture of 16.3 g. (0.075 mole) of mercuric oxide, 25.0 g. of methanol and 36.5 g. (0.15 mole) of iodine in a glass stoppered bottle cooled in an ice-bath was added, with shaking, 20.0 g. (0.15 mole) of *p*-ethylstyrene (b.p. 74–76° at 15 mm., n^{25}D 1.5364)[13] in 50 ml. of pentane. The bottle was sealed, placed in an ice-bath and shaken for four hours. The reaction mixture was filtered and the precipitated mercuric iodide was washed twice with 10-ml. portions of pentane. The combined pentane solutions were washed with sodium bisulfite solution to remove excess iodine, and then washed with water and dried over anhydrous potassium carbonate.

The pentane was removed under reduced pressure and the residue was treated with a solution of 16.8 g. (0.30 mole) of potassium hydroxide in 78 ml. of 95% ethanol. The reaction mixture was heated to reflux for three hours, and then cooled and filtered; 30 ml. of water was added and the solution was extracted three times with 30-ml. portions of pentane. The combined pentane extracts were dried over potassium carbonate. Distillation gave 13.3 g. (51%) of α-methoxy-*p*-ethylstyrene, b.p. 110° at 12 mm., n^{25}D 1.5334, d^{25} 0.965.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.4; H, 8.7. Found: C, 81.2; H, 8.6.

α-Methoxy-C^{13}-*p*-methylstyrene.—The unlabeled material was prepared by the above procedure substituting *p*-methylstyrene (b.p. 65° at 20 mm., n^{25}D 1.5364) for *p*-ethylstyrene. The methoxy-*p*-methylstyrene had b.p. 94° at 10 mm., n^{25}D 1.5397, d^{25} 0.977, and was obtained in 60% of the theoretical amount.

Anal. Caled. for $C_{10}H_{12}O$: C, 81.0; H, 8.2. Found: C, 80.8; H, 8.4.

To a mixture of 3.5 g. (0.016 mole) of mercuric oxide, 1.0 g. (0.031 mole) of methanol-C^{13} and 7.9 g. (0.062 g. atom) of iodine in a glass stoppered bottle cooled in an ice-bath was added with shaking, 3.7 g. (0.031 mole) of *p*-methylstyrene in 6 ml. of freshly distilled ether. The bottle was sealed with paraffin, and placed in an ice-bath and shaken for four hours. The solution was filtered and the precipitated mercuric iodide was washed with a few ml. of ether. The ether solution was washed with sodium bisulfite solution, water and then dried over anhydrous potassium carbonate.

The ether was removed under reduced pressure and the residue was treated with a solution of 3.5 g. (0.063 mole) of potassium hydroxide dissolved in 16 ml. of 95% ethanol. The mixture was warmed briefly on a steam-bath, and then allowed to stand overnight. The solution was filtered and diluted with 20 ml. of water followed by extraction with three 10-ml. portions of pentane. The pentane extracts were dried over potassium carbonate and distilled giving 2.13 g. (46%) of α-methoxy-C^{13}-*p*-methylstyrene, b.p. 93–94° at 10 mm., n^{25}D 1.5370.

Rearrangement of α-Methoxystyrene.—α-Methoxy-*p*-methylstyrene was found to be slightly less than one-half decomposed (as indicated by the infrared spectrum) after heating for four hours at 220°.

α-Methoxy-*p*-ethylstyrene was found to be slightly less than one-half decomposed after heating for four hours at 220°. In one case the product, *p*-ethylpropiophenone, was isolated (60%), b.p. 112–114° at 10 mm. The oxime had m.p. 57–58° and the 2,4-dinitrophenylhydrazone had m.p. 167° and showed no depression on admixture with an authentic sample.[14]

A mixture of 1.0 g. of α-methoxy-C^{13}-*p*-ethylstyrene and 1.0 g. of α-methoxy-*p*-ethylstyrene was heated in a sealed tube for 2 hours and 45 minutes at 250°. The reaction mixture was distilled, collecting the fraction having b.p. 112–114° at 10 mm. (largely *p*-ethylpropiophenone). This material was analyzed for its C^{13} content giving the data shown in Table I.

***p*-Ethylformanilide.**—To 50 ml. of 90% formic acid was added 25 g. (0.21 mole) of *p*-ethylaniline (b.p. 94–95° at 11 mm., n^{25}D 1.5524)[15] which had been purified *via* the *p*-toluenesulfonamide. The mixture was heated for one hour on a steam-bath. The liquid was poured onto cracked ice and separated and distilled giving 28 g. (96%) of *p*-ethylformanilide, b.p. 132–134° at 0.8 mm., m.p. 42.5–44.2°.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.4; H, 7.4; N, 9.4. Found: C, 72.1; H, 7.4; N, 9.1.

Silver Salt of *p*-Ethylformanilide.—To a filtered solution of 28 g. of *p*-ethylformanilide and 29 g. of silver nitrate in 250 ml. of 50% ethanol was added slowly with stirring at 0°, a solution of 4.9 g. of sodium dissolved in 25 ml. of ethanol. The precipitate was washed by decantation, filtered and dried in a vacuum oven at 85–90°. The dark brown material was ground to a powder and dried over phosphorus pentoxide in an evacuated desiccator. The yield was quantitative.

Methyl N-(*p*-Ethylphenyl)-formimidate.—To 30 g. (0.12 mole) of the silver salt of *p*-ethylformanilide was added 10 ml. (0.16 mole) of methyl iodide and sufficient anhydrous ether to make a paste. The reaction mixture was allowed to stand for one week. The silver iodide was filtered and washed twice with 20-ml. portions of pentane. The combined extracts were concentrated and the residue was distilled giving 10.9 g. (56%) of methyl N-(*p*-ethylphenyl)-formimidate, b.p. 106° at 13 mm., n^{25}D 1.5288.

Anal. Calcd. for $C_{10}H_{13}ON$: C, 73.5; H, 8.0. Found: C, 73.6; H, 8.2.

Methyl-C^{13} N-(*p*-Tolyl)-formimidate.—This compound was prepared by the procedure previously described for the unlabeled compound[16] except that methyl-C^{13} iodide was used instead of methyl iodide. The compound had b.p. 92–93° at 10 mm., n^{25}D 1.5335, and was obtained in 56% of the theoretical amount.

Rearrangement of Methyl N-Phenylformimidates.—Both methyl N-(*p*-tolyl)-formimidate and methyl N-(*p*-ethylphenyl)-formimidate were found to be about three-quarters decomposed (as indicated by the infrared spectrum)

(11) All melting points are corrected; boiling points are not corrected. The mass spectra were obtained using a Consolidated Engineering Corp. model 21-103 mass spectrometer. The analyses were obtained by B. J. Nist.

(12) R. F. Nystrom, W. H. Hanko and W. G. Brown, THIS JOURNAL, **70**, 411 (1948).

(13) D. Mowry, M. Renoll and W. F. Huber, *ibid.*, **68**, 1105 (1946).

(14) O. Klages, *Ber.*, **32**, 1558 (1899), reported m.p. 58–59° for the oxime.

(15) W. C. Davies and E. L. Hulbert, *J. Soc. Chem. Ind.*, **57**, 394T (1938).

(16) M. D. Farmer and C. K. Ingold, *J. Chem. Soc.*, **125**, 2543 (1924).

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after heating to 300° for four hours. In each case, the amide was obtained in about 20% yield, whereas the unsubstituted compound gave the amide in approximately 40% yield.

A mixture of 1.25 g. of methyl-C^{13} N-(*p*-tolyl)-formimidate and 1.25 g. of methyl N-(*p*-ethylphenyl)-formimidate was heated in a sealed evacuated tube for four hours at 300°. The reaction mixture was distilled and the fraction having b.p. 132–140° at 10 mm. (largely N-methyl-*p*-ethylformanilide) was collected (0.24 g.). This material was not sufficiently volatile for mass spectrometric analysis, and thus it was treated with 50 mg. of lithium aluminum hydride dissolved in 8 ml. of anhydrous ether and the solution was heated to reflux for three hours. Water was added, and the ether solution was separated and concentrated to a small volume. The solution was distilled in a micro still at 10 mm. with a bath temperature of 135–140° giving 0.05 ml. of N,N-dimethyl-*p*-ethylaniline. The infrared spectrum of this material was identical with that of an authentic sample of N,N-dimethyl-*p*-ethylaniline.[15] The C^{13} content was determined giving the data in Table II.

Methyl-C^{13} Benzoate.—To 0.75 ml. (0.0185 mole) of methanol-C^{13} dissolved in 3.1 g. (0.039 mole) of pyridine was added 2.5 ml. (0.02 mole) of benzoyl chloride, and the resulting mixture was shaken for one-half hour. The reaction mixture was poured into 10 ml. of water and extracted three times with 5-ml. portions of ether. The ether extracts were washed with dilute hydrochloric acid and with water. After drying over potassium carbonate, distillation gave 1.32 g. (53%) of methyl-C^{13} benzoate, b.p. 198–199°, $n^{25}D$ 1.5131.

Rearrangement of Methyl Benzoate.—A mixture of 1.0 g. of methyl-C^{13} benzoate and 1.0 g. of methyl *p*-toluate was heated in an evacuated sealed tube at 410–412° for six hours. The reaction mixture was distilled, and the fraction having b.p. 215–217° (mainly methyl toluate) was collected and analyzed for its C^{13} content. The data are given in Table II.

2-Methoxy-4-ethylpyridine.—A mixture of 99 g. (0.93 mole) of 4-ethylpyridine, 42.5 g. (1.09 moles) of sodium amide and 210 ml. of xylene was heated to reflux for 11 hours. The solution was cooled in an ice-bath and cautiously treated with water, followed by concentrated hydrochloric acid. The aqueous layer was separated and made basic by the addition of potassium hydroxide. The amine was extracted with ether, and isolated by distillation giving 42 g. (37%) 2-amino-4-ethylpyridine, b.p. 140–148° at 20 mm., m.p. 64–66°.[17]

To 210 ml. (1.86 moles) of 48% hydrobromic acid was added 40 g. (0.33 mole) of 2-amino-4-ethylpyridine. The solution was cooled to 0° and 64 ml. (1.25 moles) of bromine was added with stirring. A solution of 73 g. (1.16 moles) of sodium nitrite in 100 ml. of water was then added over a period of 90 minutes, maintaining the temperature between 5–10°. After an additional 30 minutes, a solution of 160 g. (4.0 moles) of sodium hydroxide in 150 ml. of water was added with cooling. The amine was extracted with ether, and the ether solution was dried over potassium hydroxide and distilled giving 41.7 g. (62%) of 2-bromo-4-ethylpyridine, b.p. 124–125° at 28 mm., $n^{25}D$ 1.5511, d^{25} 1.425.

(17) German Patent 398,204 (*Chem. Zent.*, **95**, **II**, 1409 (1924)) reported b.p. 134–139° at 14 mm., m.p. 68–69°.

Anal. Calcd. for C_7H_8NBr: C, 45.2; H, 4.3. Found: C, 45.1; H, 4.5.

A solution of 20 g. (0.097 mole) of 2-bromo-4-ethylpyridine and 8.1 g. (0.150 mole) of sodium methoxide in 120 ml. of *t*-butyl alcohol was heated to reflux for 6 hours. Most of the *t*-butyl alcohol was then removed by distillation. The solution was filtered and the precipitate of sodium bromide was washed with ether. The combined filtrates were distilled giving 10 g. (75%) of 2-methoxy-4-ethylpyridine, b.p. 66–67° at 9.5 mm., $n^{25}D$ 1.4970, d^{25} 1.001.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.0; H, 8.1; neut. equiv., 137. Found: C, 70.1; H, 8.3; neut. equiv., 139.

2-Methoxy-4-methylpyridine.—2-Bromo-4-methylpyridine was prepared by the procedure described above, substituting 2-amino-4-methylpyridine for 2-amino-4-ethylpyridine. The conversion to the methoxypyridine was effected in the same manner as above, and 2-methoxy-4-methylpyridine (65%), b.p. 67° at 21 mm., $n^{25}D$ 1.5021 was obtained. The 2-methoxy-C^{13}-4-methylpyridine was obtained in the same manner.

Anal. Calcd. for C_7H_9NO: C, 68.3; H, 7.4. Found: C, 68.1; H, 7.5.

Rearrangement of Methoxypyridines.—Both 2-methoxy-4-methylpyridine and 2-methoxy-4-ethylpyridine were found to be one-third rearranged (as indicated by the infrared spectrum) after heating at 210° for 4.5 hours in a sealed tube. The rearrangement of 1.0 g. 2-methoxy-4-methylpyridine at 210° for 20 hours gave 0.9 g. of N-methyl-4-methylpyridone, m.p. 56–59°; hydrochloride, m.p. 169–171°; picrate, m.p. 167–168°.[18]

The rearrangement of 1.2 g. of 2-methoxy-4-ethylpyridine at 210° for 20 hours gave 0.98 g. of N-methyl-4-ethyl-2-pyridone, b.p. 152° at 14 mm., $n^{25}D$ 1.5462; hydrochloride, m.p. 129–130°; neut. equiv. calcd. 174; found 175; picrate, m.p. 132.5–133.0°.

Anal. Calcd. for $C_{14}H_{14}N_4O_8$: C, 45.9; H, 3.9. Found: C, 46.2; H, 4.2.

The rearrangement of a mixture of 0.6 g. of 2-methoxy-C^{13}-4-methylpyridine and 0.6 g. of 2-methoxy-4-ethylpyridine was effected at 200° for 14 hours. Since the pyridones did not give good mass spectra, the crude product was reduced with platinum and hydrogen in dilute aqueous hydrochloric acid solution giving the corresponding piperidones.[19] The fraction (0.3 g.) having b.p. 115–118° at 13 mm. (largely N-methyl-4-ethyl-2-piperidone, b.p. 117–121° at 12 mm., $n^{25}D$ 1.4755) was collected and analyzed for its C^{13} content, giving the data in Table IV.

Peroxide Catalysis of 2-Methoxy-4-methylpyridine Rearrangement.—A mixture of 0.5 g. (4.06 mmoles) of 2-methoxy-4-methylpyridine and 22.6 mg. (0.1 mmole) of benzoyl peroxide was heated to 165° for 22.5 hours giving an essentially quantitative yield of N-methyl-4-methylpyridone, m.p. 54.5–57.5°, and which did not depress the m.p. of an authentic sample on admixture. In the absence of benzoyl peroxide, less than one-quarter of complete rearrangement was observed.

SEATTLE 5, WASH.

(18) R. Adams and A. W. Schrecker, THIS JOURNAL, **71**, 1186 (1949), reported m.p. 59°; hydrochloride, m.p. 173–174°; picrate, m.p. 168–169°.

(19) The procedure was essentially that described by T. B. Grave, *ibid.*, **46**, 1470 (1924).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

The Ozonolysis of Indene in Ethanol

BY JOSEPH L. WARNELL[1] AND R. L. SHRINER

RECEIVED AUGUST 9, 1956

The use of ethanol as a solvent for selective ozonolysis has been explored using indene. No true ozonide was isolated: the product has been shown to be 3-hydroxy-4,5-benzo-7-ethoxy-1,2-dioxacycloheptane. Its structure was established by conversion to 3,7-diethoxy-4,5-benzo-1,2-dioxacycloheptane, homophthalic acid, homophthaldehyde, homophthalyl alcohol, *o*-carboxyphenylacetaldehyde and 1-isochromanone.

The cleavage of olefins by ozone is usually carried out in two steps: reaction with ozone in an inert solvent to form ozonides and subsequent oxidation or reduction in the presence of water or acetic acid. Since ozonides are somewhat unstable,[2] have variable composition,[3] form polymeric ozonides,[4,6] disproportionate,[5] and because occasionally other oxidations occur during the reaction of olefins with ozone–oxygen mixtures,[2–4] ozonolyses have been carried out in glacial acetic acid which presumably reacts with the ozonide as soon as it is formed; however, the primary reaction product has not been characterized.

Until recently, alcohols have seldom been employed as solvents for ozonizations because of their ease of oxidation.[6,7] However, methanol has been used by a number of investigators[8–10] and also a *t*-butyl alcohol–sulfuric acid medium has been employed in studies on the mechanism of ozonolysis.[11]

In the present work, the use of absolute ethanol as a solvent for ozonolysis was found to be possible because passage of a stream of 3% ozone in oxygen through 500 ml. of absolute ethanol for one hour at 0–5° produced less than 0.1 mole of acetic acid, 0.03 mole of peroxide and 0.01 mole of acetaldehyde. This slight attack made it possible to explore the use of ethanol as a solvent, using an olefin, indene, which reacted rapidly and selectively with 3% ozone.

Ozonolysis of 0.1 mole of indene in absolute ethanol at 0–5° was complete in one hour; removal of the alcohol left a 99% yield of a white, non-explosive compound melting at 105–108°. Analytical data gave the formula $C_{11}H_{14}O_4$ and showed one ethoxyl group and one peroxide grouping. Infrared analysis indicated the presence of a hydroxyl group and an acetal linkage but the complete absence of any carbonyl. No oxygen was liberated when this product was treated with lead tetraacetate which indicates that the peroxide grouping is not –OOH but must be of the ROOR type.[12] The most probable structure is shown by formula I which is analogous to the structure assigned by Bailey[9] to the product obtained by ozonolysis of phenanthrene in methanol. This structure also provides a reasonable explanation of the degradation products shown in Chart I.

The acid-catalyzed reaction of I with ethanol yielded the diethoxy compound II. Alkali converted both compounds I and II to *o*-carboxyphenylacetaldehyde (VIII). The structure of the latter was shown by: (a) solubility in dilute alkali, (b) positive Benedict test, (c) formation of a monosemicarbazone, and (d) reduction of the aldehyde group to the alcohol by means of either sodium borohydride or aluminum isopropoxide and loss of water to yield the lactone, 1-isochromanone (IX). The properties of the latter agreed with those given by Wegler and Frank[13] but differed from the properties of 3-isochromanone prepared by Murahashi.[14] The formation of IX shows that the carboxyl group of VIII is attached to the ring and not to the side chain.

The oxidation of both peroxy compounds I and II with hydrogen peroxide produced homophthalic acid (III) in good yield. The homophthalic acid was identified by converting it into 1,3(2,4)-isoquinolinedione[15] by heating its ammonium salt.

Reduction of the peroxide I with zinc dust and a trace of acetic acid at room temperature produced homophthalaldehyde[16] (IV), an oil, which was characterized by the formation of its bis-*p*-nitrophenylhydrazone. This dialdehyde IV when treated with zinc dust and acetic acid at 80° was further reduced to *o*-hydroxymethylphenylacetaldehyde (V). Reduction of the hydroperoxide I with lithium aluminum hydride in ether produced a nearly quantitative yield of homophthalyl alcohol[17] (VI). This compound on refluxing with a trace of sulfuric acid was converted completely into isochroman[17] VII.

This use of ethanol as a solvent for ozonolysis not only avoids the handling of explosive ozonides but also furnishes a stable intermediate I valuable for the synthesis of compounds IV through IX which are otherwise difficult to obtain.

Experimental

3-Hydroxy-4,5-benzo-7-ethoxy-1,2-dioxacycloheptane (I).—The indene was purified by fractionally distilling it twice

(1) United States Public Health Post-Doctoral Fellow 1955–1956.
(2) L. Long, *Chem. Revs.*, **27**, 437 (1940).
(3) J. E. Leffler, *ibid.*, **45**, 385 (1949).
(4) C. S. Marvel and V. Nichols, *J. Org. Chem.*, **6**, 296 (1941).
(5) R. Criegee, *Ann.*, **583**, 1 (1953).
(6) F. L. Greenwood, *J. Org. Chem.*, **10**, 414 (1945).
(7) C. Harries, *Ann.*, **343**, 311 (1906); **374**, 288 (1910).
(8) E. Briner and D. Frank, *Helv. Chim. Acta*, **21**, 1297 (1938); R. Criegee and G. Lohaus, *Ann.*, **583**, 6 (1953); E. I. duPont de Nemours and Co., British Patent 709,450 [*C. A.*, **50**, 401 (1956)].
(9) P. S. Bailey, THIS JOURNAL, **78**, 3811 (1956).
(10) At the International Conference on Ozone, Chicago, Ill., Nov. 28–30, 1956, a considerable number of ozonolyses in methanol and methanol–methylene chloride mixtures were reported.
(11) N. A. Milas, P. Davis and J. T. Nolan, Jr., THIS JOURNAL, **77**, 2536 (1955).
(12) R. Criegee, H. Pilz and H. Flygare, *Chem. Ber.*, **72**, 1799 (1939); R. Criegee, *Fortschr. Chem. Forsch.*, **1**, 536 (1950).
(13) R. Wegler and W. Frank, *Ber.*, **70B**, 1279 (1937).
(14) S. Murahashi, *Sci. Papers, Inst. Phys. Chem. Res.* (*Tokyo*), **30**, 180 (1936).
(15) Buu-Hoi, *Bull. soc. chim.*, **12**, 313 (1945).
(16) K. Ziegler and B. Krollpfeiffer, *Ann.*, **408**, 314 (1915).
(17) S. Siegel and S. Coburn, THIS JOURNAL, **73**, 5494 (1951).

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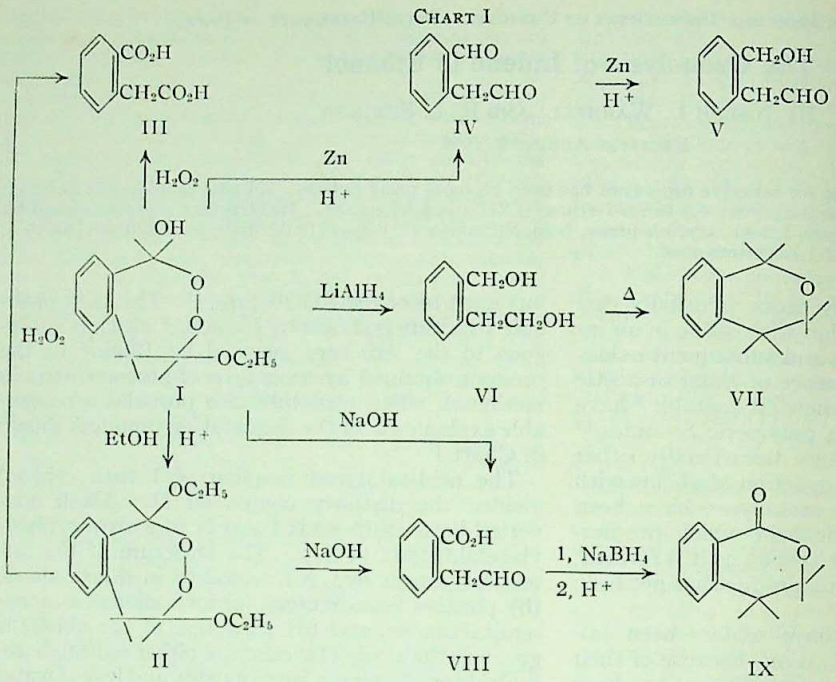
CHART I



at 10 mm. pressure, and storing it at −3° until used. A solution of 11.6 g. (0.1 mole) of indene in 500 ml. of anhydrous ethanol was cooled in an ice-bath and a 3% stream of ozone in oxygen was passed through the solution for 55 minutes. When the ozonization was carried out under the above conditions, only a trace of unreacted ozone passed through the ethanol into the potassium iodide trap during the reaction. The potassium iodide trap was changed once or twice during the experiment and thus the end-point of the reaction was easily detectable by the sudden liberation of iodine in the trap. The flow rate of ozonized oxygen was 80 l./hr.

The peroxide I was isolated by concentrating the ethanol solution to dryness under vacuum at room temperature. The weight of white, solid, amorphous product was 21 g. (99%), m.p. 105–108° (softens 95–105°). The product was not crystalline but was similar to paraffin wax in appearance. It did not decompose explosively when subjected to a variety of thermal and physical shocks.

Analysis of the peroxide I for active oxygen was carried out by the following method. The peroxide, approximately 0.001 mole, was dissolved in 25 ml. of glacial acetic acid, and 2 g. of potassium iodide and 1 ml. of concentrated hydrochloric acid were added. The solution was warmed to 50–70° for 10 minutes, poured into 400 ml. of water and the liberated iodine titrated with standard sodium thiosulfate solution. Infrared absorption curves obtained in Nujol paste showed a peak at 3.05 μ and broad peaks at 9.30 and 9.65 μ.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71; active oxygen, 7.61; ethoxyl, 21.4; mol. wt. 210.2. Found: C, 63.17; H, 6.56; active oxygen, 7.53; ethoxyl, 21.0; mol. wt. (cryoscopic), 214.

The Criegee[12] lead tetraacetate test for the hydroperoxy grouping was carried out by treating 1 g. of the compound I in 25 ml. of glacial acetic acid with 3 g. of lead tetraacetate in 50 ml. of glacial acetic acid. No evolution of oxygen occurred. Control tests with peracetic acid and ethyl hydroperoxide were positive.

CAUTION: Absolute ethanol has been used satisfactorily as a solvent in over 25 ozonolyses without the formation of explosive products. However, only a dilute (3%) stream of ozone in oxygen, and temperatures of 0–5° have been employed for selective ozonolyses of olefins. Use of 9–10% ozone leads to attack of aromatic nuclei and more concentrated ozone–oxygen mixtures should be investigated with great caution.[18]

(18) M. L. Kilpatrick, C. C. Herrick and M. Kilpatrick, THIS JOURNAL, 78, 1784 (1956).

During the ozonolysis the exit gases from the reaction flask appeared as a dense white smoke. The amount of smoke produced can serve as a method for following the progress of the reaction; as the concentration of unreacted olefin in the solvent decreases so does the volume of smoke produced. When vapors of indene at 182° were mixed with a stream of 3% ozone in oxygen, again copious amounts of dense white colloidal particles were produced. These may possibly arise from the polymerization of intermediates in the vapor phase. These colloidal particles could not be removed from the gas stream by either a Dry Ice trap or by passing the vapors through various solvents. The colloidal particles were removed from the gas stream by a small copper grid charged to approximately 25,000 volts with a Tesla coil. The actual weight of material in the smog was too small to permit purification and identification.

3,7-Diethoxy-4,5-benzo-1,2-dioxacycloheptane (II).—To a solution of 21 g. (0.1 mole) of the peroxide I in 500 ml. of anhydrous ethanol was added 3 drops of concentrated sulfuric acid. The anhydrous solution was kept at room temperature for 24 hours and the solution was evaporated to dryness under vacuum. The precipitate was filtered, washed with water and after recrystallization from either acetone or glacial acetic acid, there resulted 15.5 g. (65%) of white needles, m.p. 80–81°.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61; active oxygen, 6.72; ethoxyl, 37.8. Found: C, 65.42; H, 7.41; active oxygen, 6.72; ethoxyl, 37.3.

Homophthalic Acid (III).—To a solution of 3.0 g. of the peroxide I in 20 ml. of acetic acid was added 30 ml. of 15% hydrogen peroxide. After warming to 60° for 10 hours the mixture was concentrated to 20 ml. by boiling and upon cooling, crystals of homophthalic acid separated. Recrystallization from acetic acid gave 1.6 g. of material, m.p. 180°. Homophthalic acid also was obtained from the diethoxy compound II under similar conditions.

For the large-scale preparation of homophthalic acid it was preferable to carry out the ozonization reaction in glacial acetic acid. The acetic acid was removed under vacuum leaving a non-explosive viscous colorless sirup.

This sirup could not be obtained analytically pure. However, the gain in weight corresponded to the combination of one mole of indene with one mole of ozone plus one mole of acetic acid. It contained approximately one peroxy group and one acetoxy group indicating that this product of ozonolysis in acetic acid may be an acetoxy derivative analogous to compound I. Treatment of the sirup with hot aqueous sodium carbonate and hydrogen peroxide followed by acidification gave an 82% yield of homophthalic acid, m.p. 180°. The latter was identified by conversion to 1,3-(2,4)-isoquinolinedione, m.p. 233°, by heating the ammonium salt as described by Buu-Hoi.[15] Both compounds I and II were also converted to homophthalic acid by refluxing with dilute nitric acid for one hour.

Homophthalaldehyde (IV).—A solution of 21 g. (0.1 mole) of compound I in 500 ml. of ethanol, 50 ml. of water and 15 ml. of acetic acid was vigorously stirred while 10 g. of zinc dust was added in 1-g. amounts approximately every six minutes. After one hour the reaction mixture was filtered to remove the zinc dust and evaporated to dryness under vacuum. The residue, a yellow gum, was mixed with 50 ml. of water and ether extracted. The ether layer was washed with dilute sodium carbonate solution and dried over sodium carbonate. Evaporation of the ether gave homophthalaldehyde, 14.5 g. (98%), as a yellow oil. This aldehyde is very unstable since it undergoes self-condensation.

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It was identified as homophthalaldehyde by treating 1 g. of the oil with excess *p*-nitrophenylhydrazine and isolating the bis-*p*-nitrophenylhydrazone derivative in quantitative yield. Recrystallization from 80% ethanol gave orange crystals, m.p. 220–221°. The literature[16] listed the m.p. as 185–190°; hence an elemental analysis was obtained.

Anal. Calcd. for $C_{21}H_{18}N_6O_4$: C, 60.28; H, 4.34; N, 20.09. Found: C, 60.29; H, 4.39; N, 19.83.

o-**Hydroxymethylphenylacetaldehyde** (V).—A solution of 14.8 g. (0.1 mole) of homophthaldehyde in 100 ml. of ethanol was stirred vigorously with 200 ml. of 50% acetic acid and an excess of zinc dust for 2 hours at 80°. The zinc dust was added in 1-g. quantities to maintain a constant suspension in the solution. The mixture was filtered and evaporated to dryness under vacuum leaving a yellow gum. This was mixed with 100 ml. of water and ether extracted. The ether solution was washed with dilute sodium carbonate solution and dried over sodium carbonate. Upon evaporation of the ether, *o*-hydroxymethylphenylacetaldehyde was obtained as a yellow oil, b.p. 116–120° (5 mm.), $n^{25}D$ 1.5240.

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.03; H, 7.22.

Homophthalyl Alcohol (VI).—To a solution of 20 g. of lithium aluminum hydride in 200 ml. of ether was slowly added 21 g. (0.1 mole) of the peroxide I over a 30-min. period. The solution was vigorously stirred under reflux for an additional 20 minutes and water was added slowly to decompose the excess lithium aluminum hydride. The solution was acidified with 25% sulfuric acid, and the water and ether layers were separated. The water solution was ether extracted with an additional 200 ml. of ether and the ether extracts were combined, washed with dil. sodium carbonate solution, and dried over sodium carbonate. Removal of the ether under vacuum gave 14.5 g. (95%) of colorless oil of homophthalyl alcohol.[17] Identification of the oil was carried out by treating 1 g. of the oil with excess *p*-nitrobenzoyl chloride in pyridine to form the di-*p*-nitrobenzoate derivative, m.p. 134–135°.

Anal. Calcd. for $C_{23}H_{18}O_8N_2$: C, 61.33; H, 4.03; N, 6.22. Found: C, 61.36; H, 4.32; N, 6.24.

Isochroman VII.—The distillation of homophthalyl alcohol at 70° (3 mm.) with a drop of sulfuric acid gave a nearly quantitative yield of isochroman and water. Redistillation yielded a fraction boiling 69–70° at 3 mm. The isochroman[17] was a colorless liquid; m.p. 3–4°, $n^{20}D$ 1.5422, d^{25}_4 1.0707.

Anal. Calcd. for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.42; H, 7.26.

o-**Carboxyphenylacetaldehyde** (VIII).—A solution of 21 g. (0.1 mole) of the peroxide (I) in 200 ml. of ethanol was warmed with 200 ml. of 5% sodium hydroxide solution. The mixture turned a dark red as an exothermic reaction occurred and the temperature rose to 50°. The alkaline solution was kept at this temperature for 20 minutes, acidified with acetic acid, and concentrated to a viscous oil under vacuum. The oil was dissolved in ether and extracted with cold 1 *N* sodium hydroxide. Careful neutralization of the alkaline solution with dilute acetic acid precipitated yellow crystals of *o*-carboxyphenylacetaldehyde, 14.7 g. (90%), m.p. 130–140°. This substituted phenylacetaldehyde is unstable and the melting point decreased with standing and the compound finally became an oil. This probably accounts for the range of melting and for the fact that the m.p. observed in this work is higher than that previously reported by Schopf and Kuhne.[19] The semicarbazone derivative melted sharply at 209–210° and analyzed correctly.

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.28; H, 5.06; N, 19.34.

The compound VIII differed from the known isomeric *o*-formylphenylacetic acid[20] whose semicarbazone melts at 220°.

1-Isochromanone (IX).—A solution of 16.4 g. (0.1 mole) of *o*-carboxyphenylacetaldehyde in 200 ml. of isopropyl alcohol was refluxed with 400 ml. of isopropyl alcohol and 82 g. (0.4 mole) of aluminum isopropoxide for 9 hours. The apparatus was arranged with a fractionating column which permitted the slow distillation of acetone and isopropyl alcohol (200 ml.) during the reaction. The solution was evaporated to dryness under vacuum, mixed with 200 ml. of 6 *M* sulfuric acid, and ether extracted. The ether extract was washed with water, dried over sodium sulfate, and evaporated under vacuum. The residue, a yellow oil, was vacuum distilled to yield 12 g. (79%) of 1-isochromanone, b.p. 148–150° (5 mm.), $n^{25}D$ 1.5622, d^{25}_4 1.1996; Wegler and Frank[13] report a b.p. of 165° (16 mm.).

Reduction of *o*-carboxyphenylacetaldehyde with excess sodium borohydride in water at 30–40° also gave 1-isochromanone in 40% yield.

Anal. Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.44; H, 5.21.

Acknowledgment.—The authors wish to thank Dr. Philip S. Bailey for valuable suggestions in interpreting these results.

(19) C. Schopf and R. Kuhne, *Ber.*, **83**, 390 (1950).

(20) J. O. Halford and B. Weissmann, *J. Org. Chem.*, **18**, 30 (1953).

IOWA CITY, IOWA

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Tetrachloroisoindolines and Related Systems. Alkylation Reactions and Inductive Effects[1]

BY WILLIAM E. ROSEN, VIRGINIA P. TOOHEY AND ANTHONY C. SHABICA

RECEIVED DECEMBER 13, 1956

The basicity of an isoindoline nitrogen atom is profoundly affected by inductive factors. Four chlorine atoms on the four available positions of the benzene ring or a positively charged nitrogen atom β to the isoindoline nitrogen decrease the reactivity of the isoindoline nitrogen toward alkylation. These effects cannot be results of resonance interaction and are, therefore, either steric (unlikely) or inductive (most probable). These conclusions, based on observations of alkylation behavior under certain conditions, are supported by pK_a determinations which are consistent with relative basicities of model amines. Stabilities of quaternized nitrogens, especially those with bromoethyl substituents, are also discussed.

The interesting physiological action of the ganglionic blocking agent 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline dimethochloride (VIIb)[2] has focused attention on the tetrachloroisoindoline system itself. Although isoindolines have been considered[3] typical amines, the alkylabe extended to related isoindolines, is 4,5,6,7-tetrachloro-2-methyl-2-(2-trimethylammonioethyl)-isoindolinium dichloride. The term "ammonio" was originally proposed by J. F. Bunnett and co-workers [*Chem. Revs.*, **49**, 291 (1951); THIS JOURNAL, **75**, 642 (1953)]. It has also been mentioned in A. M. Patterson's column on Nomenclature in *Chem. Eng. News*, **32**, 2320 (1954); **33**, 5262 (1955). It is used in this paper for the tetrasubstituted terminal nitrogen.

(1) Presented before the 130th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956.

(2) Ecolid (CIBA Trade Mark). See A. J. Plummer, J. H. Trapold, J. A. Schneider, R. A. Maxwell and A. E. Earl, *J. Pharmacol. Exptl. Therap.*, **115**, 172 (1955). An alternative name for VIIb, which can

(3) D. R. Boyd and D. L. Ladhams, *J. Chem. Soc.*, 2089 (1928).

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tion behavior of the 2-substituted isoindolines proved to be of considerable interest. Rice and coworkers have prepared[4,5] 2-dialkylaminoalkylisoindolines and 2-methylisoindolines, characterizing these compounds as hydrochlorides, picrates and methiodides. The work described in this paper contrasts the alkylation behavior of 2-substituted isoindolines and 2-substituted *tetrachloro*isoindolines.

Methyl iodide is, of course, a better alkylating agent than methyl chloride. 2-Methylisoindoline[5,6] (Ia) and 4,5,6,7-tetrachloro-2-methylisoindoline (Ib) were both alkylated readily by methyl iodide under mild conditions. With methyl chloride, however, a difference in the reactivity of the isoindoline and the tetrachloroisoindoline was evident. Gaseous methyl chloride quaternized 2-methylisoindoline (Ia) completely in chloroform or in hot dimethylformamide solution giving the methochloride salt IIa. Tetrachloro-2-methylisoindoline (Ib), on the other hand, was little affected by methyl chloride in chloroform, although in hot dimethylformamide it was converted to the methochloride IIb in 79% yield.

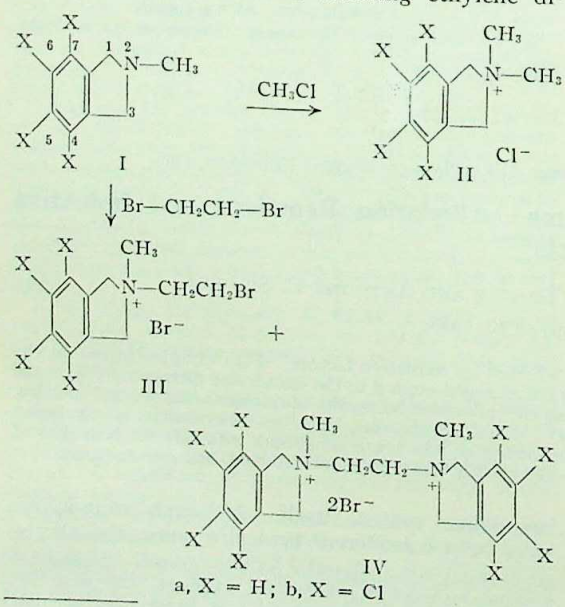
2-Methylisoindoline (Ia) and ethylene dibromide, in refluxing acetone, gave a bromoethyl salt IIIa in which only one end of the molecule had reacted; it has been reported[5] that no bis-salt IVa forms even when a large excess of base is used. The tetrachloro compound Ib, on the other hand, was completely unaffected under these conditions. It was possible to get 50–60% yields of the tetrachloroisoindolinium bromide IIIb but only at considerably higher temperatures. Under such conditions, a small amount (8%) of the symmetrical dibromide IVb was also isolated.

Although the tetrachloroisoindoline Ib was completely unreactive toward refluxing ethylene dichloride, 2-methylisoindoline (Ia) did form a small amount of 2-(2-chloroethyl)-2-methylisoindolinium chloride; this is consistent with the greater activity of the unchlorinated isoindoline nitrogen toward ethylene dibromide.

When the 2-substituent was dimethylaminoethyl, the contrast between isoindoline and tetrachloroisoindoline was even more striking. With the unchlorinated 2-dimethylaminoethylisoindoline (Va) practically no dimethochloride VIIa formed under the mild conditions of chloroform reflux. This was in contrast to the ready quaternization of 2-methylisoindoline (Ia). In hot dimethylformamide, the unchlorinated dimethylaminoethylisoindoline (Va) formed an approximately 1:1 mixture of monomethochloride VIa and dimethochloride VIIa. Under the same conditions, the tetrachloroisoindoline nitrogen was little affected; the monomethochloride VIb[7] was isolated in over 90% yield. In order to get a satisfactory conversion to the dimethochloride VIIb with the tetrachloroisoindoline compound Vb, it was necessary to go to higher pressures.

These alkylation experiments indicate that four chlorine atoms on the benzene ring decrease the basicity of the isoindoline nitrogen. The effect cannot be one of resonance interaction and is not likely to be steric. It therefore appears to be an *inductive* effect. A positively charged nitrogen atom β to the isoindoline nitrogen likewise decreases the reactivity of the isoindoline nitrogen. This decrease is also attributable to inductive factors. These conclusions are supported by pK_a determinations.

As may be seen from Table I, the inductive effect of the aromatic chlorines decreases the basicity of the isoindoline nitrogen almost a thousand-fold (pK_a from 7.7 to 4.8). Replacing the methyl substituent with a group having a β-ammonio cation decreases the basicity about four thousand-fold (pK_a from 7.7 to 4.1). When both influences are present, the basicity is decreased by a factor of about 50,000 to 65,000 (pK_a from 7.7 to 2.9–3.0). A β-ammonio cation decreases basicity one thousand-fold compared with a β-amino group (terminal nitrogen pK_a from 8.2–8.4 to 5.3). Similar inductive effects[8] are known for simple amines. The base strength of the amine nitrogen of ethylenediamine is one thousand times greater than that of ethylenediamine monoacid salt,[11] but it is only about one-fourth as strong as alkylamines[10-12]; benzylamine is a weaker base than either ethylamine (35-fold) or isobutylamine (13-fold).[12] It is interesting that the effect of the β-ammonio cation



(4) L. M. Rice, E. E. Reid and C. H. Grogan, *J. Org. Chem.*, **19**, 884 (1954).

(5) L. M. Rice, C. H. Grogan and E. E. Reid, THIS JOURNAL, **77**, 616 (1955).

(6) J. v. Braun and Z. Kohler, *C. A.*, **11**, 1690 (1917).

(7) First observed by C. F. Huebner and co-workers of these laboratories.

(8) The term "inductive effect" in this paper is meant to include any contribution made by the so-called "direct field effect."[9,10] Although the "direct field effect" has been shown to be considerable with cyclic amines, accounting for one-half[9] or more[10] of the total effect, proportions cannot be assigned in the examples discussed here. The inductive effect of the aromatic system on the isoindoline nitrogen probably has a large "direct field" component, whereas the "direct field effect" of the linear β-ammonio cation is probably small.

(9) J. D. Roberts and W. T. Moreland, Jr., THIS JOURNAL, **75**, 2167 (1953).

(10) H. K. Hall, *ibid.*, **78**, 2570 (1956); C. A. Grob, E. Renk and A. Kaiser, *Chemistry & Industry*, 1222 (1955).

(11) D. H. Everett and B. R. W. Pinsent, *Proc. Roy. Soc.* (London), **215A**, 416 (1952).

(12) "Handbook of Chemistry," 8th Ed., Ed. by N. A. Lange, Handbook Publishers, Inc., Sandusky, Ohio, 1952, p. 1233.

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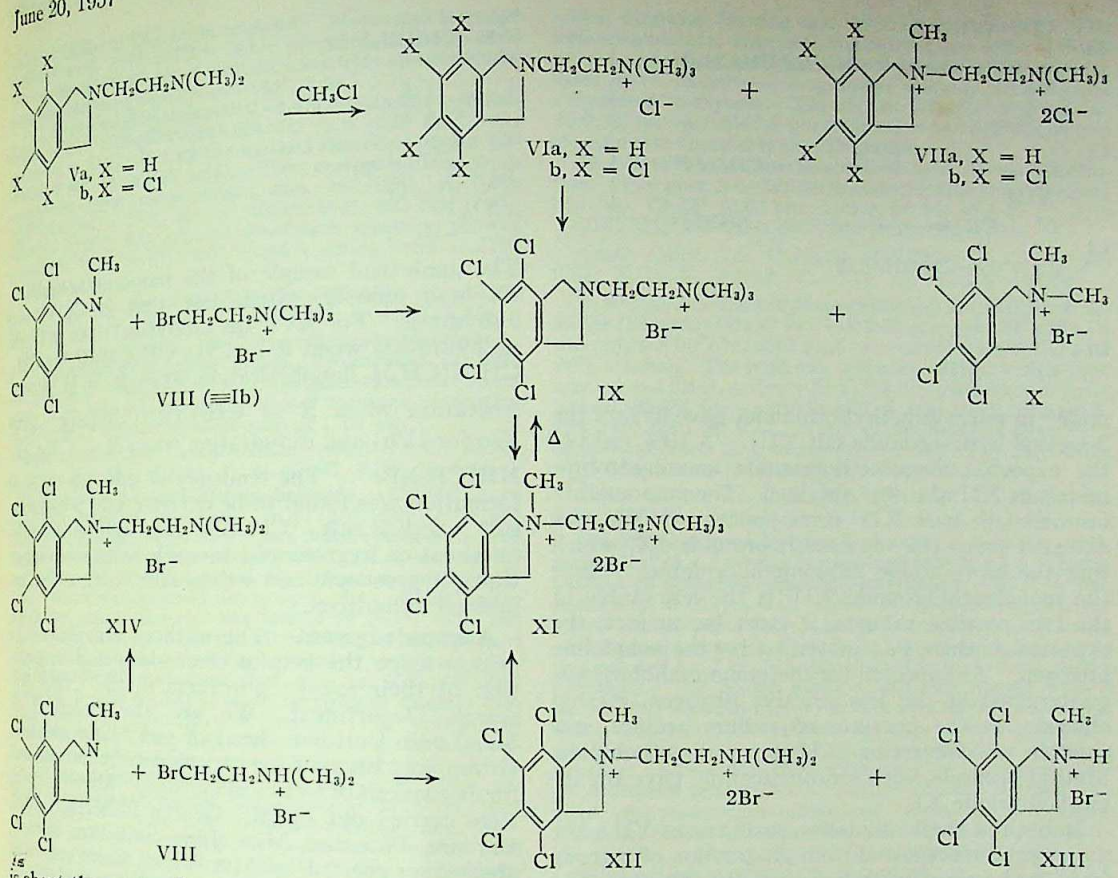


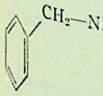
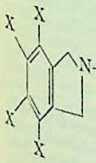
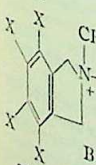
is about the same whether the cation be a quaternary salt or an acid salt.

A series of reactions starting with 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) showed some additional aspects of the chemistry of the isoindoline nitrogen. Bromoethyltrimethylammonium bromide, prepared from ethylene dibromide and trimethylamine, reacted with 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) in refluxing dimethylformamide to give two products. The major product, isolated in 57% yield, was the transquaternized methobromide salt X. The other product, isolated in 7% yield, was 4,5,6,7-tetrachloro-2-(2-trimethylammonioethyl)-isoindoline bromide (IX). This monomethobromide IX was identical with that prepared from monomethochloride VIb by halide exchange. The monomethochloride VIb was formed, as mentioned above, from 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (Vb) and methyl chloride gas. The monomethobromide IX was further quaternized by methyl chloride to only a small extent but gave in good yield the diquaternary salt XI with methyl bromide.[13] Evidently the first-formed dimethobromide from VIII and bromoethyltrimethylammonium bromide dequaternized under the reaction conditions. When dimethobromide XI was subjected to these conditions, about 80% monomethobromide IX was isolated.[14] Attempts to isolate the first-formed dimethobromide under these or milder conditions were unsuccessful.

An alkylation which went through the other monomethobromide XIV led to the same dibromide. 4,5,6,7 - Tetrachloro - 2 - methylisoindoline (VIII) and bromoethyldimethylammonium bro-

TABLE I

pK_a VALUES OF ISOINDOLINE BASES (IN 80% METHYL CELLOSOLVE)

Isoindoline base			
X		R	pKa
			9.0
	H	CH_3	7.7
	Cl	CH_3	4.8
	H	$CH_2CH_2\overset{+}{N}H(CH_3)_2Cl^-$	4.1 (8.4)[a]
	Cl	$CH_2CH_2\overset{+}{N}H(CH_3)_2Cl^-$	2.9 (8.2)[a]
	Cl	$CH_2CH_2\overset{+}{N}(CH_3)_3Cl^-$	3.0
	Cl	$CH_2CH_2—N(CH_3)_2$	(5.3)[a]

[a] Figure in parentheses is pK_a of the second nitrogen.

(13) The dimethobromide XI can be prepared directly by the diquaternization of tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (Vb) with methyl bromide in hot dimethylformamide (G. A. Nussberger, unpublished work).

(14) The same treatment of dimethochloride VIIb and dimethiodide gave 95% and 75% monomethobromide, respectively.

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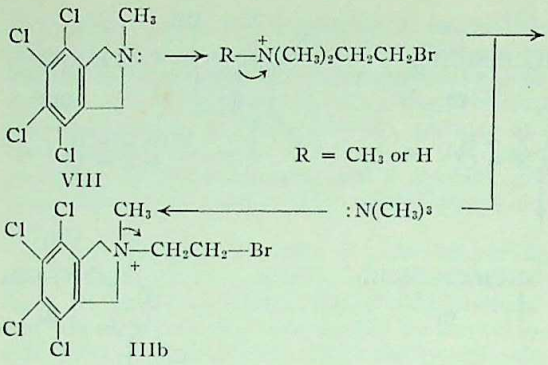

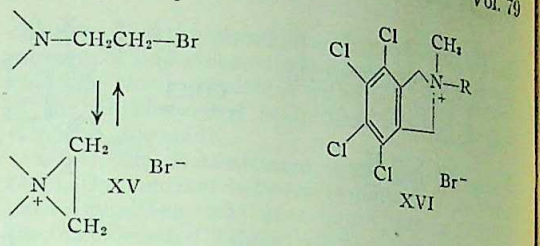

mide[15] in warm dimethylformamide gave 65% of the 2-methyl hydrobromide salt XIII. A 10% yield of the expected monomethobromide monohydrobromide salt XII also was obtained. The monomethobromide-free base XIV corresponding to XII was different from the monomethobromide IX, which was the more stable monomethobromide. Since the monomethobromide XIV is the less stable of the two possible isomers, it must be, in fact, the expected product, *i.e.*, quaternized at the isoindoline nitrogen. As expected for the monomethobromide quaternized at the less reactive nitrogen, methyl chloride, in the presence of sodium acetate, *was* capable of converting XII to a dimethohalide. Methyl bromide, with sodium acetate, gave the dimethobromide XI.

In both of these alkylation reactions of VIII, the major product resulted from abstraction of a group from the bromoethylammonium salt. This was surprising at first, because the isoindoline nitrogen is a much weaker base than a tertiary amine. On the other hand, 4,5,6,7-tetrachloro-2-(2-bromoethyl)-2-methyl isoindolinium bromide (IIIb) was dequaternized in 83% yield by trimethylamine. Evidently the basicity of the nitrogens is not the important factor. In all three cases the nitrogen which was readily dequaternized had a bromoethyl substituent. Bromoethylamine formation may be favored because of its ability to react further as a nitrogen mustard, to give an ethyleneimmonium salt (XV)[17] (or possibly to give a piperazinium salt[15]).

Hydration.—The quaternized terminal nitrogen of XI, rather than the quaternized isoindoline nitrogen, seems to be responsible for hydration. The analytical sample of the monomethobromide IX was monohydrated, but that of XIV was anhydrous. For XVI, the analytical data indicate no hydration when R = CH_3, CH_2CH_2Br, or $CH_2CH_2N(CH_3)_2$, hemihydration when R = H, monohydration when R = $CH_2CH_2\overset{+}{N}(CH_3)_2Br^-$ (and also for IVb) and dihydration when R = $CH_2CH_2\overset{+}{N}H(CH_3)_2Br^-$. The tendency of salts for hydrate formation was found to be chloride salt > bromide salt > iodide salt. Chloride salts were either deliquescent or hygroscopic, bromide salts were sometimes hygroscopic and iodide salts, once dried, remained anhydrous.

Acknowledgment.—The authors are pleased to acknowledge the helpful discussions and coöperation of their many co-workers in the CIBA Research Department. We are also indebted to Mr. Louis Dorfman, head of our Microanalytical Group, and his staff for various determinations and for discussions of technical matters. Microanalyses were carried out by Mr. George Robertson, Mrs. Barbara Pita and Miss June Swantko, infrared absorption spectra by Mrs. Violet Loire and Miss Margaret Jones; and ultraviolet absorption spectra by Miss Natalie Cahoon. We thank Dr. M. J. Allen and Miss Verda Powell for the electrometric titrations.

Experimental[18]

N-(2-Dimethylaminoethyl)-phthalimide.—To a stirred suspension of 35.0 g. (0.236 mole) of phthalic anhydride in 350 ml. of acetic acid was added 27.0 g. (0.242 mole) of 77% dimethylaminoethylamine[19] dropwise over 30 minutes. The colorless solution was refluxed for 4 hr. (yellow color developed), the bulk of the solvent was removed *in vacuo* and the concentrated solution was made basic by slow addition of 15% ammonium hydroxide solution with stirring and cooling. The white solid which separated was collected, washed once with water and dried *in vacuo* at 70°, giving 31.0 g. (60%) of N-(2-dimethylaminoethyl)-phthalimide, m.p. 103–105°. Recrystallization from hexane (charcoal) gave 27.2 g. (53%) of white crystals, m.p. 104–106.5°, R_f 0.52.[20] The imide carbonyl groups absorbed at 1770 cm.$^{-1}$

(15) An attempt was made to alkylate 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) with the tosylate of dimethylaminoethanol. When tosyl chloride and 2-dimethylaminoethanol were combined in pyridine in an attempt to form the tosylate, and VIII was added, the isoindoline was recovered and some 1,1,4,4-tetramethylpiperazinium dichloride was isolated. When tosyl chloride was added to a dioxane solution of VIII and 2-dimethylaminoethanol, the acid generated resulted in formation of salts (hydrochloric or *p*-toluenesulfonic acid salts) of VIII. In a run using excess VIII in the presence of excess sodium bicarbonate, 1,1,4,4-tetramethylpiperazinium ditosylate was isolated. Evidently dimerization of 2-dimethylaminoethyl tosylate (or chloride) occurred more rapidly than did alkylation of VIII, thereby permitting isolation of starting VIII (or its chloride or tosylate salt) and piperazinium dichloride or ditosylate, depending on the reaction conditions. Dimethylaminoethyl chloride itself is known to dimerize rapidly to 1,1,4,4-tetramethylpiperazinium dichloride.[16]

(16) L. Knorr, *Ber.*, **37**, 3507 (1904); W. Hanhart and C. K. Ingold, *J. Chem. Soc.*, 1014 (1927); L. Ruzicka, Pl. A. Plattner and B. A. Engel, *Helv. Chim. Acta*, **27**, 1553 (1944).

(17) G. Girault and P. Rumpf, *Compt. rend.*, **243**, 663 (1956); H. Freundlich and H. Kroepelin, *Z. physik. Chem.*, **122**, 39 (1926).

(18) Melting points were taken on an electrically heated aluminum block in open capillaries and are uncorrected. Infrared absorption spectra were determined on a double-beam Perkin-Elmer model 21 infrared spectrophotometer using a sodium chloride prism. Ultraviolet absorption spectra were determined on a Beckman DK-1 spectrophotometer. Analytical samples were dried at water-pump vacuum over Drierite at 75° for 3–5 hr. and then permitted to equilibrate in air of 40–45% relative humidity at 23°, unless otherwise specified. All *pKa* values were determined in 80% methyl Cellosolve solutions. Melting points of methohalide salts were not reliable indices of purity or identity. Samples varied in decomposition range depending on the method of preparation, the age of the sample, solvation, etc. Mixtures of different salts frequently did not show a depression of melting point.

(19) R. A. Turner, THIS JOURNAL, **68**, 1607 (1946).

(20) Paper chromatography of tertiary amines and quaternary ammonium salts was carried out on Whatman No. 1 filter paper, using 1-butanol saturated with 0.1 *N* aqueous ammonia as developing solvent and Dragendorff[21] spray reagent. Details of the paper chromato-

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(m) and 1709 cm.$^{-1}$ (s) in the infrared. Moore and Rapala[22] reported m.p. 104–105° for imide prepared in 2.5% yield from equimolar amounts of phthalic anhydride and dimethylaminoethylamine (oil-bath 160–180°, 1 hr.).

N-(2-Dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide.—The tetrachlorophthalimide, m.p. 183–185°, was prepared in 85% yield by the method described above (refluxed 4 hr. in acetic acid). Two crystallizations from chloroform gave yellow prisms, m.p. 183–186°, R_f 0.70; λ_{max}^{EtOH} 288 mμ (ε 570), 298 (shoulder, 540), 322–328 (190), 333–335 (200). The infrared absorption spectrum showed a medium band at 1774 cm.$^{-1}$ and a strong band at 1707 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{10}O_2N_2Cl_4$ (356.06): C, 40.48; H, 2.83; N, 7.87. Found: C, 40.73; H, 3.05; N, 7.55.

The monomethiodide, **N-(2-trimethylammonioethyl)-3,4,5,6-tetrachlorophthalimide iodide**, decomposed at 303–304°, R_f 0.42 (weak), after one crystallization from methanol. The infrared spectrum showed medium absorption at 1776 cm.$^{-1}$ and strong absorption at 1704 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{13}O_2N_2Cl_4I$ (498.00): C, 31.35; H, 2.63; N, 5.63. Found: C, 31.35; H, 2.88; N, 5.63.

N-Methyl-3,4,5,6-tetrachlorophthalimide.—To 500 g. of tetrachlorophthalic anhydride, m.p. 256–259° (Niagara Alkali Co., Niagara Falls, N. Y.), in a 2-liter round-bottomed flask, was added with intermittent shaking and cooling 275 g. (25% excess) of 25% aqueous methylamine over 20 minutes. Water was removed slowly by heating at 100°, after which the yellow material was heated to 250°. The hot liquid was poured into a mortar, allowed to cool and the hard cake was then crushed to a fine, granular, yellow powder. The 516 g. (98%) of crude product, m.p. (s. 159) 203–205° (particles of solid to 230°), could be reduced directly (see below), but one crystallization from 10 to 20 volumes of chloroform (or ethylene dichloride or ethyl acetate, in decreasing order of solubility) gave a 75% yield of N-methyl-3,4,5,6-tetrachlorophthalimide, m.p. 210–212°. The infrared absorption spectrum had bands at 1775 (m) and 1714 (s) cm.$^{-1}$. Allen and Nicholls[23] reported m.p. 210–211° for their pure material, prepared by a sealed tube alkylation of the potassium salt of 3,4,5,6-tetrachlorophthalimide (no yield was given).

3,4,5,6-Tetrachlorophthalimide.—A mixture of 193.0 g. (0.676 mole) of tetrachlorophthalic anhydride and 80.0 g. (1.3 moles) of 29% ammonium hydroxide was heated to 340° and then allowed to cool. An additional 80.0 g. of 29% ammonium hydroxide was added and the mixture was heated again until completely liquid (over 350°). The brown liquid was poured into a mortar and pulverized when cool, m.p. (335) 342–347°. Crystallization from 6–7 volumes of dimethylformamide afforded yellow needles in 85% yield, m.p. (340) 345–347°, soluble in aqueous sodium carbonate; λ_{max}^{EtOH} 234 mμ (ε 8,230), 253 (sh., 8,120), 318 (sh., 2,080), 330 (2,350). The infrared spectrum showed typical imide absorption at 1775 (m) and 1708 (s) cm.$^{-1}$; phthalimide itself absorbs at 1777 (m) and 1752 (s) cm.$^{-1}$.

This procedure is essentially that described in "Organic Syntheses" (Coll. Vol. I, p. 457) for phthalimide. Previous workers have reported: (a) 91% yield, m.p. 336–337°, by fusion of tetrachlorophthalic anhydride and ammonium carbonate[23] and (b) 90% yield, m.p. 338–339°, by heating tetrachlorophthalic anhydride with formamide.[24]

Lithium Aluminum Hydride Reduction of N-(2-Dimethylaminoethyl)-phthalimide to 2-(2-Dimethylaminoethyl)-isoindoline (Va).—After 17.3 g. (0.456 mole) of lithium aluminum hydride had been refluxed in one liter of anhydrous ether for 30 minutes, 24.8 g. (0.114 mole) of N-(2-dimethylaminoethyl)-phthalimide was added portionwise over 10 minutes. The suspension was refluxed for 6 hr. with stirring, and then further stirred at room temperature overnight (16 hr.). The solution was cooled in an ice-bath, decomposed with 70 ml. of 10% aqueous sodium sulfate added dropwise (stirring and cooling) and filtered. The lithium aluminate cake was washed 3 times with 200-ml. portions of ether, and the combined ether solutions were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The 21.1 g. (97.5%) of green oil, R_f 0.89, was suitable for quaternization (see below); it was stored under nitrogen in the refrigerator.

An analytical sample was obtained by fractional distillation. The pure 2-(2-dimethylaminoethyl)-isoindoline (Va) had b.p. 72–75° (0.06 mm.), m.p. (s. 18) 19.5–21.7°, $n^{23}D$ 1.5276; λ_{max}^{EtOH} 258 mμ (ε 660), 265 (860), 272 (850).

Anal. Calcd. for $C_{12}H_{18}N_2$ (190.29): C, 75.74; H, 9.53; N, 14.72. Found: C, 75.74; H, 9.32; N, 14.58.

2-Methyl-2-(2-trimethylammonioethyl)-isoindolinium Diiodide (Dimethiodide of Va).—A 2.00-g. sample of crude Va was refluxed for 1 hr. with 5 ml. of methyl iodide in 10 ml. of 95% ethanol. The solid was collected, washed with a little ethanol and dried, giving 4.21 g. (84.4% yield from isoindoline oil, 82.3% from phthalimide) of light green solid, m.p. 238–240° dec., R_f 0.13. Three crystallizations from 95% ethanol afforded long white prisms, m.p. 243–245° dec.; λ_{max}^{EtOH} 216–219 mμ (ε 29,440), 266 (490), 272 (490).

Anal. Calcd. for $C_{14}H_{24}N_2I_2$ (474.18): C, 35.46; H, 5.10; N, 5.91. Found: C, 35.41; H, 5.34; N, 5.72.

Lithium Aluminum Hydride Reduction of N-(2-Dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide to 4,5,6,7-Tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (Vb).[7]—A suspension of 3.56 g. (0.01 mole) of N-(2-dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide and 1.5 g. (0.04 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether was refluxed for 3 hr. and then stirred at room temperature overnight. The cooled solution was decomposed with 8 ml. of 10% aqueous sodium sulfate and further stirred for 1 hr. The pale yellow ether solution was filtered and the granular white cake was washed 5 times with 25-ml. portions of ether; further extraction with ether or chloroform gave no additional product. The combined ether solution was dried over magnesium sulfate and evaporated to dryness. When the residual oil was triturated with dimethylformamide, white crystals of 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (Vb) separated, m.p. 67.5–69.5°. Chromatography on alumina and crystallization from acetone gave pure Vb, m.p. 71.5–73°, R_f 0.98; λ_{max}^{EtOH} 236 mμ (sh., ε 18,550), 282 (530), 289–292 (450).

Anal. Calcd. for $C_{12}H_{14}N_2Cl_4$ (328.09): C, 43.93; H, 4.30; N, 8.54. Found: C, 43.98; H, 4.58; N, 8.75.

4,5,6,7-Tetrachloro-2-methyl-2-(2-trimethylammonioethyl)-isoindolinium Diiodide.[7]—The crude Vb oil from lithium aluminum hydride reduction of 3.56 g. (0.01 mole) of imide was stirred and refluxed for 4 hr. with 7 ml. of dimethylformamide and 3 ml. of methyl iodide. After the suspension had been diluted with 20 ml. of acetone and further stirred for 2 hr., the gray crystals were collected, washed with acetone and dried, giving 3.34 g. of crude product, m.p. 232–235° dec. Recrystallization from 500 ml. of methanol plus 25 ml. of water gave 2.34 g. (38% yield from starting phthalimide) of fine off-white needles, m.p. 239–241° dec.; a second crop of 0.45 g. (7.3%) was obtained after concentration of the mother liquors.

An analytical sample was obtained after three recrystallizations, m.p. 241–243° dec., R_f 0.25; λ_{max}^{EtOH} 237 mμ (sh., ε 17,740), 275 (340), 284–286 (350), 295 (260).

Anal. Calcd. for $C_{14}H_{20}N_2Cl_4I_2$ (611.98): C, 27.48; H, 3.29; N, 4.58. Found: C, 27.61; H, 3.41; N, 4.69.

Methyl iodide quaternization of pure Vb under the same conditions gave 93% pure dimethiodide (see below).

4,5,6,7-Tetrachloro-2-methylisoindoline (VII, Ib).—To a cooled and stirred suspension of 20.4 g. (0.54 mole) of lithium aluminum hydride in 400 ml. of ether was added 40.0 g. (0.13 mole) of N-methyl-3,4,5,6-tetrachlorophthalimide portionwise over 20 minutes (exothermic reaction). After the green suspension had been refluxed for 5 hr. and stirred at room temperature overnight, it was decomposed with 80 ml. of 10% aqueous sodium sulfate (stirred 1 hr. at room temperature) and filtered. Five ether and five chloroform washings (each of 100 ml.) of the lithium aluminate cake were combined with the original ether solution, solvent was removed *in vacuo* and the residue was crystallized from 500 ml. of acetone. The 4,5,6,7-tetrachloro-2-methylisoindoline separated as long, white prisms, 15.6 g. (43%), m.p. 156–158°. A reduction using only 2 moles of lithium aluminum hydride per

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ammonium salts and tertiary amines, will be published in a separate communication.

(21) H. M. Bregoff, E. Roberts and C. C. Delwiche, *J. Biol. Chem.*, **205**, 565 (1953).

(22) M. B. Moore and R. T. Rapala, THIS JOURNAL, **68**, 1657 (1946).

(23) C. F. H. Allen and R. V. V. Nicholls, *ibid.*, **56**, 1409 (1934).

(24) D. S. Pratt and G. A. Perkins, *ibid.*, **40**, 198 (1918).

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mole of imide yielded only 10% pure plus 24% crude isoindoline.

Using the crude N-methyl-3,4,5,6-tetrachlorophthalimide described above (obtained in 98% yield from anhydride and methylamine) with 3 moles of lithium aluminum hydride afforded 24% pure product, m.p. 159–162° plus 17% crude product. Recrystallization of the pure product from acetone gave white prisms of the same melting point, R_f 0.96.

Anal. Calcd. for $C_9H_7NCl_4$ (270.99): C, 39.89; H, 2.60; N, 5.17. Found: C, 40.24; H, 2.80; N, 5.40.

2,2-Dimethylisoindolinium Halides.—A chloroform solution of 2-methylisoindoline (Ia)[5,6,25] (purified by sublimation and containing 0.5 mole of water, m.p. 45–47°, pK_a 7.7, volatile and unstable. *Anal.* Found: C, 76.02; H, 8.51) was refluxed on the steam-bath for 15 minutes with excess methyl iodide. The methiodide derivative was collected and dried in air, m.p. 253–255° dec., R_f 0.34. Rice and co-workers[5] reported m.p. 253–255°.

The methochloride derivative IIa, m.p. 206–209°, R 0.25, was a deliquescent white solid, prepared by bubbling methyl chloride gas for 0.5 hr. into a chloroform solution of 2-methylisoindoline either at reflux temperature or at 25–30° (or into a hot dimethylformamide solution). Paper chromatographic analysis showed that practically no starting isoindoline remained.

4,5,6,7-Tetrachloro-2,2-dimethylisoindolinium Halides. Chloride Salt IIb.—Gaseous methyl chloride was bubbled for 30 minutes through a heated (steam-bath) solution of 2.71 g. (0.01 mole) of 4,5,6,7-tetrachloro-2-methylisoindoline (Ib), m.p. 159–162°, in 10 ml. of dimethylformamide. The 2.80 g. of solid which separated after the solution had cooled to room temperature was collected, washed once with cold acetone and extracted once with boiling acetone. The hot acetone extracted 0.28 g. (11.4%) of starting Ib, m.p. 157–159°, and dilution of the dimethylformamide mother liquor (plus cold acetone wash) with water gave 0.08 g. (3%) more Ib. The 2.52 g. (78.5%) of acetone-insoluble 4,5,6,7-tetrachloro-2,2-dimethylisoindolinium chloride (IIb) melted 304–306°, R_f 0.34. Two crystallizations from methanol–ethyl acetate gave hexagonal white prisms, m.p. (s. 313) 315–317°.

Anal. Calcd. for $C_{10}H_{10}NCl_5$ (321.48): C, 37.36; H, 3.14. Found: C, 37.74; H, 3.27.

A 90.4% yield of IIb, m.p. 307–309°, was obtained when the reaction was run in refluxing dimethylformamide. In refluxing chloroform, on the other hand, 75% of the starting material Ib, m.p. 159–160°, was recovered and paper chromatographic examination of the mother liquors showed only traces of IIb.

Bromide Salt X.—Addition of gaseous methyl bromide to a refluxing chloroform solution of Ib gave the methobromide salt X, m.p. 309–310° sl. dec. (melting point decreased on standing or on grinding to a powder), R_f 0.55, molecular weight determination by isothermal distillation 378 (calcd. 366). The infrared spectrum was very similar to that of the chloride salt IIb.

Anal. Calcd. for $C_{10}H_{10}NCl_4Br$ (365.94): C, 32.82; H, 2.75; N, 3.83. Found: C, 32.91; H, 2.82; N, 3.94.

Iodide Salt.—The corresponding iodide salt, prepared in refluxing chloroform, melted 242–250° dec., R_f 0.61.

2-(2-Bromoethyl)-2-methylisoindolinium Bromide (IIIa)—One gram of 2-methylisoindoline was warmed on the steam-bath with 10 ml. of ethylene dibromide. After 15 minutes, the gray solid was collected and washed with ethylene dibromide and ether, giving 1.54 g. (64%) of light gray solid, m.p. 210.5–211° dec., R_f 0.43. Further heating of the mother liquors for a total of 1 hr. afforded 0.12 g. (5%) of more gray solid, m.p. 219–220° dec. Rice and co-workers[5] reported 223–224°. For yields under other conditions, see following table.

2-(2-Bromoethyl)-4,5,6,7-tetrachloro-2-methylisoindolinium Bromide (IIIb). (1).—Ten grams (0.037 mole) of 4,5,6,7-tetrachloro-2-methylisoindoline (Ib) and 30.0 ml. (65.4 g., 0.35 mole) of redistilled ethylene dibromide, b.p. 129–134° (atm.), were refluxed (temperature of the wet cake 135°) for 30 minutes using a heating mantle. After the slurry had cooled, 40 ml. of ether was added with swirling, and the suspension was filtered. The red ether solution on evaporating to dryness left 1.7 g. of red-brown tar. The ether-insoluble tan solid was extracted three times with hot water, (a) 40 ml., (b) 80 ml., (c) 80 ml. First crops from portions a and b and all of portion c darkened over 220° but did not melt to 300°; this combined white solid (6.32 g., 37.3%) was recrystallized from methanol to give 4.34 g. (25.5%) of white platelets of IIIb, shrinking 225°, black > 280°, not melted to 300°; R_f 0.61.

Anal. Calcd. for $C_{11}H_{11}NCl_4Br_2 \cdot CH_3OH$ (490.92): C, 29.35; H, 3.08; N, 2.85. Found: C, 29.27; H, 2.92; N, 3.07.

The aqueous mother liquors from portion a above were stripped to dryness, leaving 1.30 g. (7.7%) of off-white solid, m.p. 278–284° dec. One crystallization from 95% ethanol afforded white crystals of IVb, m.p. 274–289° dec., R_f 0.53.

Anal. Calcd. for $C_{20}H_{18}N_2Cl_8Br_2 \cdot H_2O$ (747.88): C, 32.12; H, 2.70; N, 3.75. Found: C, 32.33; H, 2.86; N, 4.03.

Neither the analysis nor the infrared spectrum nor the R_f value distinguished this compound from the hemihydrate of 4,5,6,7-tetrachloro-2,2-dimethylisoindolinium bromide (X). A molecular weight determination by isothermal distillation, however, gave 837, whereas X gave 378. The data is consistent with assignment of a 1,2-bis-(4,5,6,7-tetrachloro-2-methylisoindolinium)-ethane dibromide structure (IVb) formed by displacement reaction at *both* ends of the ethylene dibromide.

(2).—A suspension of 20.0 g. of 4,5,6,7-tetrachloro-2-methylisoindoline (Ib) in 20 ml. of ethylene dibromide was stirred and heated in an oil-bath to 170° over a period of 1 hr. and was then maintained at 165–175° for 15 minutes (moderate to vigorous boiling). After cooling to room temperature, it was diluted with 40 ml. of ether and filtered. The pink cake was washed twice with 40-ml. portions of ether, and crystallized from methanol. A first crop of 17.4 g. (51.5%) darkened but did not melt to 300°, R_f 0.65, was obtained, followed by 3.5 g. (10%) of a second crop which contained some isoindoline starting material.

(3).—When Ib and excess ethylene dibromide were refluxed in toluene for 6 hr., a 15% yield of white solid separated on cooling; this material darkened but did not melt to 320°, R_f 0.64; λ_{max}^{EtOH} 237 (ϵ 13,055), 284 (402), plateau 294 (347). Increasing the reflux time to 22 hr. raised the yield to 22%.

Anal. Calcd. for $C_{11}H_{11}NCl_4Br_2$ (458.88): C, 28.79; H, 2.42; N, 3.05. Found: C, 28.83; H, 2.51; N, 3.03.

(4).—Survey of reaction conditions for preparation of IIIb and IIIa:

Conditions for reaction of I and ethylene dibromide		Yield, %	
Solvent, reflux	Time, hr.	Of IIIb	Of IIIa
Acetone	0.25[b]	0	17
Acetone	5	0	
Methyl ethyl ketone	1	0	69
No solvent[a]	1	*ca.* 4	
Toluene	6	15	60
Toluene	22	22	
Xylene	0.5	3	
Ethylene dibromide	[b]	Up to 60	

[a] Steam-bath. [b] Various times.

(5) Dequaternization.—Gaseous trimethylamine was bubbled for 1 hr. into a refluxing solution of 2.00 g. of IIIb in 20 ml. of dimethylformamide. From the cooled solution, 0.56 g. (83%) of tetramethylammonium bromide was collected, not melting to 320°, R_f 0.11.

Anal. Calcd. for $C_4H_{12}NBr \cdot H_2O$ (172.08): N, 8.15. Found: N, 7.99.

2-Methyl-2-(2-trimethylammonioethyl)-isoindolinium Dichloride (VIIa).—Gaseous methyl chloride was bubbled for 45 minutes into a heated (steam-bath) solution of 5.00 g. of 2-(2-dimethylaminoethyl)-isoindoline in 25 ml. of dimethylformamide. The cooled solution was diluted with 25 ml. of acetone, and the dark solid was collected, washed with acetone and dried *in vacuo* at 60° for 16 hr. The 4.04 g. (53% yield) of deliquescent green-brown dimethochloride VIIa melted 209–215° dec., R_f 0.05; it was soluble in water, methanol and isopropyl alcohol and insoluble in acetone, ethyl acetate and chloroform. A paper chromatogram of the mother liquors showed the presence of both mono- (VIa)

(25) E. W. Cook and W. G. France, *J. Phys. Chem.*, **36**, 2383 (1932).

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and dimethochloride (VIIa). Two crystallizations of the solid from 1-butanol–acetone gave deliquescent green prisms of VIIa. A sample was dried *in vacuo* at 75° over Drierite for 24 hr., and precautions were taken to obtain data on the anhydrous material: m.p. 223–225° dec.; λ_{max}^{EtOH} 254 mμ (ε 300), 256–258 (310), 263 (390), 269 (370).

Anal. Calcd. for $C_{14}H_{24}N_2Cl_2$ (291.28): C, 57.73; H, 8.31; N, 9.62. Found: C, 57.32; H, 8.51; N, 9.38.

4,5,6,7-Tetrachloro-2-methyl-2-(2-trimethylammonioethyl)-isoindolinium Dihalide.—A solution of 1.00 g. of 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (Vb) m.p. 71.5–72.5°, in 4.2 ml. of dimethylformamide and 1.3 ml. of methyl iodide was refluxed for 2 hr. with stirring. The dimethiodide product was collected by filtration from the cooled solution and washed twice with acetone. The dried product, m.p. 241–243° dec., R_f 0.25, weighed 1.73 g. (93.5%) and was identical with that described above.

Methyl bromide in dimethylformamide converted Vb into the dimethobromide, m.p. 246–247° dec., R_f 0.23.

A mixture of 32.8 g. (0.10 mole) of 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline Vb, 32.8 ml. of formamide and 35.3 g. (0.70 mole, 250% excess) of methyl chloride in a pressure bomb was heated to 90–100° with shaking for 5 hr.; the pressure rose to 172 p.s.i.g. After the bomb had been cooled and vented, the tan-colored formamide cake was diluted with 328 ml. of acetone and chilled. The white crystalline product melted 246–254° dec., and one recrystallization from absolute ethanol afforded 41.2 g. (86.7%) of dichloride VIIb, m.p. 264–266° dec., R_f 0.16. It was identical with material prepared from the dimethiodide by halide exchange.

Anal. Calcd. for $C_{14}H_{20}N_2Cl_6 \cdot {}^1/_2H_2O$ (438.08): C, 38.38; H, 4.83; N, 6.40. Found: C, 38.32; H, 4.96; N, 6.22.

4,5,6,7-Tetrachloro-2-(2-trimethylammonioethyl)-isoindoline Chloride (VIb).—Methyl chloride gas was bubbled into a hot (steam-bath) solution of 5.00 g. of Vb in 50 ml. of dimethylformamide for 0.5 hr. The white crystalline product was collected, washed with acetone and dried *in vacuo*, giving 5.36 g. (93.3%) of monomethochloride VIb, m.p. 256–260° dec. The mother liquors, which contained traces of dimethochloride (R_f 0.16), afforded an additional 0.27 g. (4.7%) of monomethochloride on dilution with acetone. Recrystallization from isopropyl alcohol gave 4.95 g. of product, m.p. 265–267° dec., R_f 0.55, which was dried *in vacuo* over Drierite at 100° for 5 hr.

Anal. Calcd. for $C_{13}H_{17}N_2Cl_5 \cdot {}^1/_2H_2O$ (387.59): C, 40.29; H, 4.68; N, 7.23. Found: C, 40.12; H, 4.70; N, 7.12.

Crystallization from water gave a monohydrate, m.p. 280–281° dec.

Bromoethyltrimethylammonium Bromide.[26]—A clear, colorless solution of 10 ml. (21.8 g., 0.115 mole) of ethylene dibromide and 15 ml. (11.3 g., 0.47 mole) of 25% methanolic trimethylamine was refluxed for 1 hr. When the yellow solution cooled to room temperature, white crystals separated. After being chilled overnight, the solution was filtered and the collected crystals washed once with methanol and dried, giving 3.6 g. (13%) of white prisms, m.p. (s. 238) 251–253° dec. (red, foaming), R_f 0.22. Its water solution gave an immediate precipitate of silver bromide on addition of silver nitrate solution.

Anal. Calcd. for $C_5H_{13}NBr_2$ (247.00): N, 5.67. Found: N, 5.68.

Concentration of the methanol mother liquors gave 1.60 g. (6%) of a second crop, m.p. 239–243° dec. (orange foam); one crystallization raised the melting point to 248–250° dec. When the reflux period was increased to 2 hr., a 22% yield of salt, m.p. 237–240° dec., was obtained.

A mixture of 25 ml. (0.29 mole) of ethylene dibromide, 10 ml. (0.32 mole) of 25% methanolic trimethylamine and 25 ml. of benzene, after standing at room temperature for three days and then being chilled to 5°, gave 7.7 g. (11%) of product, m.p. 245–247° dec. (orange foam).

4,5,6,7-Tetrachloro-2-(2-trimethylammonioethyl)-isoindoline Bromide (IX) from VIII and Bromoethyltrimethylammonium Bromide.—A mixture of 2.00 g. (7.4 millimoles) of 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) and 2.00 g. (8.1 millimoles) of bromoethyltrimethylammonium bromide was refluxed (153°) for 3 hr. in 10 ml. of dry dimethylformamide. The liquid darkened on heating, the bromide salt gradually dissolved and the solution became cloudy. After the cloudy solution had been cooled to room temperature and diluted with 10 ml. of acetone, it was filtered, removing 0.20 g. of light yellow solid, which decomposed but did not melt to 320°. The filtrate gave 2.40 g. of pale tan solid, m.p. (s. 226) 238–243° dec., after standing in the refrigerator (*ca.* 5°) for two weeks. Crystallization of this material from methanol afforded a first crop of 0.75 g. of off-white solid, m.p. (s. 255) 262–271° dec., R_f 0.56; the infrared spectrum was identical with authentic 4,5,6,7-tetrachloro-2,2-dimethylisoindolinium bromide (X). A second crop of 0.80 g. from methanol was similar to the first crop, but when slurried with 40 ml. of water at room temperature, it left 0.23 g. of insoluble off-white solid, m.p. (s. 245) 247–250° dec. Recrystallization of this water-insoluble material from methanol afforded 0.05 g. of IX, m.p. (s. 250) 252–255° dec. (reddish melt); R_f 0.55; the melting point was depressed 5° when mixed with X.

Anal. Calcd. for $C_{13}H_{17}N_2Cl_4Br \cdot H_2O$ (441.06): C, 35.40; H, 4.34; N, 6.35. Found: C, 35.74; H, 4.46; N, 6.64.

The infrared spectrum was identical with and the melting point was not depressed by authentic 4,5,6,7-tetrachloro-2-(2-trimethylammonioethyl)-isoindoline bromide (IX) (see below).

Treatment of the monomethobromide IX with methyl chloride (DMF, steam-bath, 1 hr.) gave recovered IX containing trace quantities of the dimethohalide (detectable by paper chromatography R_f 0.16). Treatment of IX with excess methyl bromide (DMF, steam-bath, 1 hr.) afforded 4,5,6,7-tetrachloro-2-methyl-2-(2-trimethylammonioethyl)-isoindolinium bromide (XI), m.p. 246–247.5° dec., R_f 0.23.

Anal. Calcd. for $C_{14}H_{20}N_2Cl_4Br_2 \cdot H_2O$ (536.01): C, 31.37; H, 4.14; N, 5.23. Found: C, 31.31; H, 4.41; N, 5.39.

A mixture melting point with authentic dibromide XI, m.p. 246–247° dec., prepared by methyl bromide quaternization of the diamine Vb, showed no depression. Furthermore, the infrared spectra of the two were identical.

Formation of IX by Demethobromination of XI.—When 2.08 g. of dimethobromide XI, m.p. 246–248° dec., was refluxed in 10 ml. of dimethylformamide for 3 hr., it gradually dissolved. The 1.11 g. (65%) of white needles of monomethobromide IX which separated on cooling melted 252–253° dec., R_f 0.54. An additional 0.40 g. of material was obtained by dilution of the dimethylformamide mother liquors with acetone. This material was separated into 0.23 g. (14%) more IX, plus 0.16 g. (8%) of recovered XI by extraction of IX with 5 ml. of hot dimethylformamide.

Dimethiodide analogous to the dimethobromide XI did not dissolve completely in refluxing dimethylformamide even after 10 hr. The filtered hot solution was evaporated *in vacuo* and the residue was diluted with acetone. The brown solid was washed well with ether, leaving 75% crude monomethiodide. Crystallization from methanol (charcoal) gave yellow crystals, m.p. 230–231° dec., R_f 0.62. The infrared spectrum was very similar to that of the monomethobromide IX.

Anal. Calcd. for $C_{13}H_{17}N_2Cl_4I$ (470.03): C, 32.22; H, 3.65; N, 5.96. Found: C, 32.77; H, 3.93; N, 6.20.

Three hours refluxing of VIIb in dimethylformamide gave a 95% yield of VIb.

4,5,6,7-Tetrachloro-2-(2-trimethylammonioethyl)-isoindoline Bromide (IX) from the Chloride VIb.—A 1.00-g. sample of VIb, m.p. 261–263° dec., was dissolved in 25 ml. of water and 25 ml. of 48% hydrobromic acid and boiled gently on a hot-plate for 20 minutes. The cloudy, yellow-brown solution was filtered and allowed to cool. The sticky, off-white semi-solid which separated was taken up in methanol, charcoaled, filtered and diluted with two volumes of ether. An off-white solid (0.39 g.), m.p. 237–264° dec., R_f 0.55, was collected, which was the hydrobromide salt of the desired product. Recrystallization of this material from

(26) Bromoethyltrimethylammonium bromide was first prepared by A. W. Hofmann, *Jahresb. Chem.*, **11**, 338 (1858). M. Kruger and P. Bergell, *Ber.*, **36**, 2901 (1903), obtained a 71% yield of the salt, m.p. 239–231°, from the reaction of ethylene dibromide and trimethylamine (no solvent), whereas R. R. Renshaw, THIS JOURNAL, **34**, 1615 (1912), got a 90% yield, m.p. 235.5° (corr.), in a bomb tube reaction. A. P. Gray, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, *ibid.*, **77**, 3948 (1955), in a study of the reactions of tertiary amines and dibromoalkanes in benzene solution (giving ω-bromoalkyl quaternary ammonium salts), reported m.p. 229° for bromoethyltrimethylammonium bromide but did not give the yield.

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methanol containing some sodium acetate (solution color changed from yellow to colorless as the *p*H was raised to about six) gave 0.24 g. (21.4%) of white crystals of 4,5,6,7-tetrachloro-2-(2-trimethylammonioethyl)-isoindoline bromide (IX), m.p. 254–256° dec., R_f 0.55.

Anal. Calcd. for $C_{13}H_{17}N_2Cl_4Br \cdot H_2O$ (441.06): C, 35.40; H, 4.34; N, 6.35. Found: C, 35.58; H, 4.42; N, 6.39.

4,5,6,7-Tetrachloro-2-(2-dimethylaminoethyl)-2-methylisoindolinium Bromide (XIV).—A suspension of 2.71 g. (0.01 mole) of 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) and 4.66 g. (0.02 mole) of bromoethyldimethylammonium bromide in 25 ml. of dimethylformamide was heated until completely dissolved, 0.90 g. (0.011 mole) of sodium acetate was added and the solution was swirled and allowed to cool to room temperature. After removal by filtration of 2.60 g. (96%) of starting VIII, m.p. 159–161°, R_f 0.94, the mother liquors were chilled to −15° for several days. The 0.15 g. of off-white solid which precipitated, m.p. (s. 215) 257–275° dec., was recrystallized from methanol. A tiny amount of VIII, m.p. 158–160°, was removed first, and spontaneous evaporation slowly deposited white prisms of 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-2-methylisoindolinium bromide (XIV), m.p. (s. 215) 255–265° dec., R_f 0.73.

Anal. Calcd. for $C_{13}H_{17}N_2Cl_4Br$ (423.04): C, 36.91; H, 4.05; N, 6.62. Found: C, 37.05; H, 4.19; N, 6.56.

4,5,6,7-Tetrachloro-2-(2-dimethylaminoethyl)-2-methylisoindolinium Bromide Hydrobromide (XII).—A solution of 2.71 g. (0.01 mole) of 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) and 4.66 g. (0.02 mole) of bromoethyldimethylammonium bromide[27] in 25 ml. of dimethylformamide was heated on the steam-bath for 3 hr. After the solution had cooled to room temperature, 1.88 g. (53.5%) of 4,5,6,7-tetrachloro-2-methylisoindoline hydrobromide (XIII) was collected and washed with 25 ml. of acetone; m.p. (s. 267) 277–280° dec., R_f 0.94. Chilling the combined mother liquors and acetone washings at −15° for 18 hr. gave 0.40 g. (11.4%) more XIII, m.p. (s. 259) 262–275° dec., R_f 0.94. The first crop of XIII was washed twice with hot acetone and crystallized from methanol, giving white solid decomposing 305–309°.

Anal. Calcd. for $C_9H_8NCl_4Br \cdot {}^1/_2H_2O$ (360.92): C, 29.95; H, 2.51; N, 3.88. Found: C, 30.03; H, 2.46; N, 4.09.

Crystallization from 95% ethanol containing excess sodium acetate gave 4,5,6,7-tetrachloro-2-methylisoindoline (VIII), m.p. 158–160°.

The dimethylformamide–acetone mother liquors deposited 0.50 g. (10%) of white crystals, m.p. 250–265° dec. after standing for several days at room temperature. One crystallization from methanol gave white needles of XII, m.p. (s. 250) 256–264° dec., R_f 0.73, pK_a 5.3.

Anal. Calcd. for $C_{13}H_{18}N_2Cl_4Br_2 \cdot 2H_2O$ (540.09): C, 28.92; H, 4.11; N, 5.19. Found: C, 29.46; H, 4.43; N, 5.32.

Infrared Spectra.—The two products XII and XIII showed absorption in the infrared between 2300–2700 cm.$^{-1}$ typical of hydrohalide salts.[28] 4,5,6,7-Tetrachloro-2-methylisoindoline hydrobromide (XIII) absorbed strongly at 2625, 2548, 2490 and 2384 cm.$^{-1}$, whereas the free base VIII and its methobromide X did not. The hydrobromide XII absorbed at 2636 (ms), 2510 (w) and 2464 (m) cm.$^{-1}$; this region of the infrared spectrum was clear with the corresponding base XIV and the dimethobromide XI.

A solution of 0.10 g. (0.2 millimole) of the hydrobromide XII, 0.05 g. (0.6 millimole) of sodium acetate and excess methyl bromide in 5 ml. of dimethylformamide was warmed on the steam-bath for 1 hr. Solvent was removed *in vacuo* and the residue was taken up in methanol. When the solution was chilled to −15° 0.06 g. (58%) of white crystals separated, m.p. 239–243° dec., R_f 0.23. A mixture melting point with authentic dimethobromide XI, m.p. 246–247° dec., showed no depression. The infrared spectrum was identical with that of the dimethobromide, confirming the paper chromatographic and melting point data.

Treatment of XII with methyl chloride in hot dimethylformamide in the presence of sodium acetate gave the dimethohalide (R_f 0.17).

1,1,4,4-Tetramethylpiperazinium Salts. Dichloride.—A mixture of 1.8 g. (0.02 mole) of 2-dimethylaminoethanol, 1.9 g. (0.01 mole) of *p*-toluenesulfonyl chloride and 10 ml. of dry pyridine (exothermic reaction) was allowed to stand 18 hr. at room temperature. After addition of 2.71 g. (0.01 mole) of 4,5,6,7-tetrachloro-2-methylisoindoline (VIII), the solution was refluxed for 3 hr. The cooled solution deposited 2.9 g. of solid, of which 2.60 g. (96%) was recovered VIII, m.p. 158–160°, isolated by ether extraction. The 0.30 g. of ether-insoluble material was crystallized from methanol, giving material darkening 218–320° without melting, R_f 0.00, positive Beilstein test.

Anal. Calcd. for $C_8H_{20}N_2Cl_2$ (215.18): C, 44.66; H, 9.37. Found: C, 44.26; H, 9.18.

1,1,4,4-Tetramethylpiperazinium dichloride readily is formed from dimethylaminoethyl chloride and is reported to decompose over 300°.[16]

Di-*p*-toluenesulfonate.—To a solution of 2.71 g. (10 millimoles) of VIII in 150 ml. of dioxane was added 1.85 g. (22 millimoles) of sodium bicarbonate, 3.80 g. (20 millimoles) of *p*-toluenesulfonyl chloride and 1.80 g. (20 millimoles) of 2-dimethylaminoethanol. After the suspension had been stirred for 16 hr., the white solid was collected and dried giving 3.18 g. of mixed salts, darkening over 250° but not melting to 310°, positive Beilstein and silver nitrate tests (presence of chloride), no bubbling of an aqueous solution on addition of acid (no bicarbonate). This solid was extracted with hot 95% ethanol, and the filtered ethanol solution deposited 1,1,4,4-tetramethylpiperazinium di-*p*-toluenesulfonate on cooling, not melted to 310°, R_f 0.00, negative silver nitrate test. The infrared spectrum showed strong bands at 1012, 1035, 1124 and 1182 cm.$^{-1}$ typical of *p*-toluenesulfonate anion.

Anal. Calcd. for $C_{22}H_{34}O_6N_2S_2 \cdot {}^1/_2H_2O$ (495.67): C, 53.31; H, 7.12. Found: C, 53.33; H, 7.51.

SUMMIT, N. J.

(27) F. Cortese, *Org. Syn.*, Coll. Vol. II, Ed. by A. H. Blatt, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 91.

(28) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, Chapter 13; B. Witkop, THIS JOURNAL, **76**, 5597 (1954).

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, KANSAS STATE COLLEGE]

Oxidative Cleavage of the Pyrazole Ring and the Structure of Azipyrazole

BY SCOTT SEARLES, JR., AND WILLIAM ROBERT HINE, JR.

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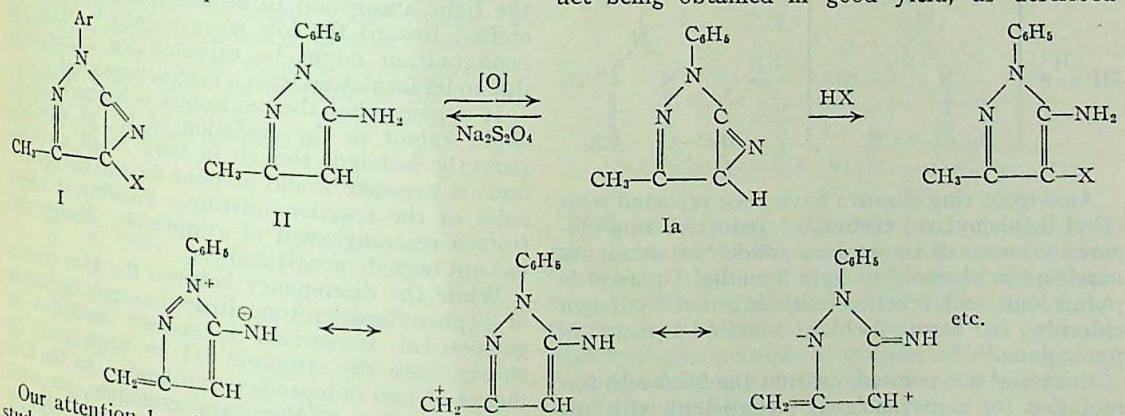
Azipyrazole, a compound formed by the action of hydrogen peroxide on 5-amino-3-methyl-1-phenylpyrazole (II), was previously assigned a structure possessing the 2,3,6-triazabicyclo[3,1,0]-3,6-hexadiene ring system, in common with several other closely related compounds. Reinterpretation of the old chemical evidence for this structure, as well as new data, leads to reformulation of the structure of azipyrazole as 3-(phenylazo)-crotononitrile. Confirmation of this structure was obtained by two independent syntheses. Evidence was obtained for two geometrical isomers. A mechanism is proposed for the oxidative cleavage of the pyrazole ring, which is apparently a new reaction. Other products of the oxidation of II are 3-(phenyl-NON-azoxy)-crotonamide and di-(3-methyl-1-phenyl-5-pyrazolyl)-amine 2,2′(?)-dioxide.

An unusual new class of compounds, called "azipyrazoles," was reported by Michaelis and associates during the period 1905–1915.[1] These compounds seem of particular interest because of the 2,3,6-triazobicyclo[3,1,0]-3,6-hexadiene ring system[2] assigned to them. The assigned structures of the compounds known in this series can be generalized as I, with X and A_2 varying but all alike with regard to the methyl group.

Such a fusion of 3- and 5-membered unsaturated rings not only is unique but would be expected to lead to extremely high internal strain. The reported properties of the compounds, however, indicate ordinary stability. Nevertheless, the assigned structures cannot be immediately dismissed, for they are supported by several lines of experimental evidence. The paradox has been recognized recently by Erickson, who has reviewed the chemistry of these compounds.[3]



Our attention has been directed in the present study to the first and simplest azipyrazole reported, which has the specific name, "azipyrazole," and which seems typical of the general class. It had been assigned the structure Ia on the following bases: (1) its synthesis from 5-amino-3-methyl-1-phenylpyrazole (II) by mild oxidation with nitrous acid or with hydrogen peroxide in aqueous acetic acid, reportedly a general method of synthesis of azipyrazoles; (2) the elemental analyses and molecular weight determinations, which were in excellent agreement with the assigned structure and showed that the synthesis had caused loss of two hydrogens; (3) the general stability of the pyrazole ring toward oxidizing agents[4]; (4) easy formation of known pyrazoles as derivatives—compound II by sodium hydrosulfite reduction and the 4-halogeno derivatives of II by treatment with aqueous hydrochloric, hydrobromic and hydriodic acids.

Erickson[3] made the interesting suggestion that the structure of azipyrazole could be more plausibly interpreted by the mesoionic formulation

A third isomeric structure for azipyrazole is also possible, as will be shown below. It was the purpose of this work to determine which formulation might be correct.

The procedure described by the previous workers[1c] for the preparation of azipyrazole gave different results in our hands, a quite different product being obtained in good yield, as described later. By carrying out the oxidation with 90% hydrogen peroxide in glacial acetic acid and using high vacuum sublimation for purification, however, a compound was isolated, which fitted the description of azipyrazole exactly, except for its having an ivory rather than light brown color. This is understandable since the previous isolation was by crystallization of the dark brown crude product. The melting point (109°) checked with the literature, as well as the facile formation of 5-amino-3-methyl-1-phenylpyrazole (II) on reduction and the corresponding 4-bromo- and 4-iodo compounds on treating with hydrobromic and hydriodic acids.

The infrared spectrum of this compound differed from that of its precursor, II, in having new bands

(1) (a) A. Michaelis and E. Brust, *Ann.*, **339**, 138 (1905); (b) A. Michaelis and L. Klappert, *ibid.*, **397**, 149 (1913); (c) A. Michaelis and A. Schafer, *ibid.*, **397**, 119 (1913); (d) **407**, 234 (1915).

(2) R. I. no. 449, A. M. Patterson and L. T. Capell, "The Ring Index," Reinhold Publ. Corp., New York, N. Y., 1940, p. 86.

(3) J. G. Erickson in "1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines," A. Weissberger, ed., Interscience Publishers, Inc., New York, N. Y., 1957.

(4) See, for example, R. H. Wiley, "Organic Chemistry," H. Gilman, ed., Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1953, p.

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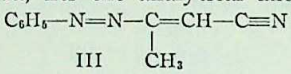
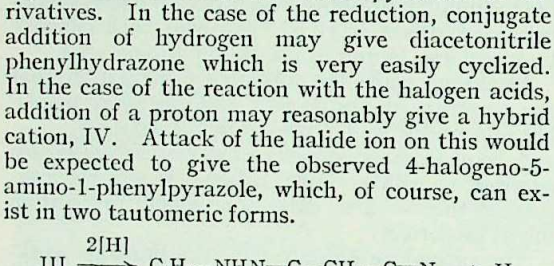
at 4.45 μ, indicative of a nitrile structure,[5] and at 6.20 and 6.25 μ, which might be assigned to a conjugated double bond and to an azo linkage. Furthermore, it lacked a band for N–H (found at 2.9 μ in II) and the bands characteristic of the pyrazole ring[6] (6.8 and 10.9 μ in II).[7] The spectrum contained bands at 7.18 and 6.76 μ which may be assigned to symmetrical and asymmetrical CH_3 deformation[5]; these would not be expected for the mesoionic formation.

It will be observed that the structure of 3-(phenylazo)-crotononitrile (III) closely fits the spectral features observed. This structure, being isomeric with Ia, fits the analytical and molecular



III

weight data, and it also provides a rational basis to explain the formation of 5-aminopyrazoles as derivatives. In the case of the reduction, conjugate addition of hydrogen may give diacetonitrile phenylhydrazone which is very easily cyclized. In the case of the reaction with the halogen acids, addition of a proton may reasonably give a hybrid cation, IV. Attack of the halide ion on this would be expected to give the observed 4-halogeno-5-amino-1-phenylpyrazole, which, of course, can exist in two tautomeric forms.



IV

Analogous ring closures have been reported with ethyl 3-(phenylazo)-crotonate: reductive ring closure by means of ammonium sulfide[8,9] or aluminum amalgam in alcohol[10] to form 3-methyl-1-phenyl-5-pyrazolone and reaction with ethereal hydrogen chloride to form 4-chloro-3-methyl-1-phenyl-5-pyrazolone.[11,12]

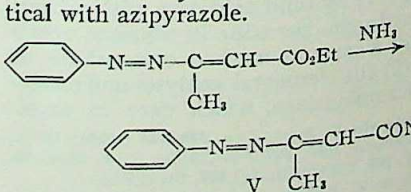
Erickson[3] has pointed out that the Michaelis formulation for azipyrazoles is inconsistent with the fact that in the presence of free halogen the phenyl group does not become halogenated, as might be expected by analogy with aniline. The new structure III is consistent with this observation, of course, because of the electron-withdrawal properties of the unsaturated nitrile side chain, due to resonance effects.

At this point it was discovered that 3-(phenylazo)-crotononitrile (III) previously had been reported in the literature as having properties distinctly different from those found for azipyrazole (orange-red color, m.p. 81°). This substance had been obtained by degradation of eulite[13] and had been synthesized also by treating the chlorination product of 5-methylisoxazole with sodium ethoxide and then with phenylhydrazine.[14] The structure III for the product of this sequence seems probable, but it was not confirmed by any supplementary work. Its *p*-nitro analog, however, was stated to react with boiling hydrochloric acid to form a compound considered to be 3-(2-chloro-4-nitrophenylhydrazino)-crotonitrile. The latter could well have been the isomeric 5-amino-4-chloro-3-methyl-1-(4-nitrophenyl)-pyrazole, which would be consistent with an azo-nitrile structure for its precursor.

It is, of course, feasible that both azipyrazole and this red compound are geometrical isomers of 3-(phenylazo)-crotononitrile, there being four such isomers theoretically possible. The lighter color of azipyrazole could reasonably be due to its configuration being more *cis* than that of the other compound, as it has been shown for polyenes that the *cis* arrangement of conjugated double bonds causes the light absorption to be less intense and to be shifted toward the low wave lengths.[15] The *cis*-configuration might be expected for azipyrazole due to its formation from a cyclic compound.

It appears that the red isomer is formed also to slight extent in the oxidation of II; it was apparently isolated, though in very small amount, and its presence would account for the orange-red color of the reaction mixture. Possibly it arises from a rearrangement of azipyrazole, though this has not been demonstrated yet.

While the discrepancy between the two reports of 3-(phenylazo)-crotononitrile thus may be due to geometrical isomerism, it seemed desirable to substantiate the structure III for azipyrazole by means of two independent syntheses. In the first of these, ethyl 3-(phenylazo)-crotonate, prepared by the mercuric oxide oxidation of the phenylhydrazone of acetoacetic ester,[9] was treated with ammonia to form 3-(phenylazo)-crotonamide (V). The reaction of this with phosphoric anhydride gave a brown solid, from which a white crystalline solid was obtained by sublimation. This proved identical with azipyrazole.



V

(5) L. J. Bellamy, "The Infrared Spectra of Complex Organic Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

(6) C. S Rondestvedt and P. K. Chang, THIS JOURNAL, **77**, 6532 (1955).

(7) Also absent from the spectrum was any band in the 5.5 μ region, which is reported (D. J. Cram and M. J. Hatch, *ibid.*, **75**, 33 (1953)) to be characteristic of the azirine ring. The azirine ring is present, fused to the pyrrolidine ring, in the Michaelis structure.

(8) G. Bender, *Ber.*, **20**, 2747 (1887).

(9) J. U. Nef, *Ann.*, **266**, 71 (1891).

(10) J. Van Alphen, *Rec. trav. chim.*, **64**, 109 (1945), considered that aluminum amalgam reduction proceeded by conjugate addition of hydrogen to form the phenylhydrazone of acetoacetic ester, which then cyclized.

(11) P. W. Neber, G. Knoller, K. Herbst and A. Trissler, *Ann.*, **471**, 135 (1929), observed the reaction but formulated the structure of the product incorrectly.

(12) J. Van Alphen, ref. 10, writes this reaction as proceeding by conjugate addition of hydrogen chloride to form an α-chlorophenylhydrazone which then cyclizes, but the cyclic transition state above seems more likely.

(13) A. Quilico, R. Fusco and V. Rosanti, *Gazz. chim. ital.*, **76**, 30 (1946).

(14) A. Quilico and R. Justoni, *Rend. inst. lombardo sci.*, **69**, 587 (1936).

(15) L. Zechmeister, *Chem. Revs.*, **34**, 267 (1944).

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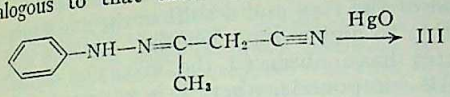
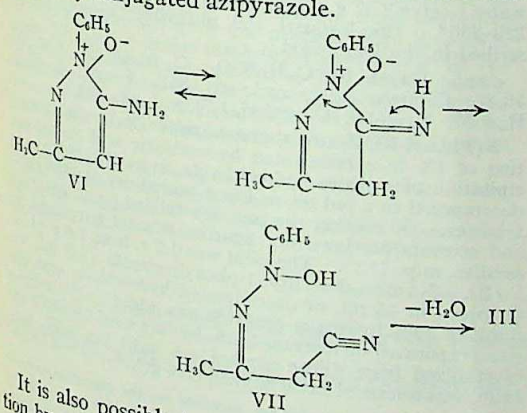
The second confirmatory synthesis of azipyrazole consisted of oxidizing diacetonitrile phenylhydrazone with mercuric oxide in alcohol. This reaction, analogous to that used for the preparation of



ethyl 3-(phenylazo)-crotonate, gave two crystalline products: one tan colored, m.p. 105–107°, and the other red, m.p. 82–83°. The former was identical to the azipyrazole previously obtained, and the latter appears to be the isomer described by Quilico and Justoni.[14] In view of so much evidence, there can hardly be any doubt that azipyrazole is one geometrical isomer of 3-(phenylazo)-crotononitrile.

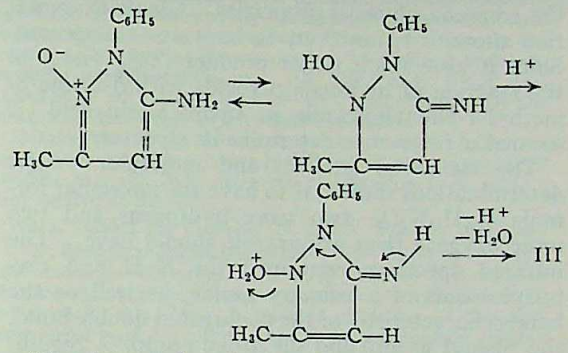
Since oxidative cleavage of the pyrazole ring to form an unsaturated azo compound appears to be novel, one is tempted to speculate on the course of the reaction. 1-Phenylpyrazoles being actually cyclic phenylhydrazones, a formal similarity to the recently studied per-acid oxidation of acyclic phenylhydrazones is evident. The elegant study of this reaction by Lythgoe and co-workers[16] indicates that the first step in the oxidation of aldehyde phenylhydrazones is coördination of oxygen at the phenyl-substituted nitrogen, forming an N-oxide. This is followed by a tautomeric shift of hydrogen, giving the final product, an azoxy compound.

In the present case formation of the analogous pyrazole-1-oxide (VI) could be followed by an easy shift of a proton from the amino or imino group to the electro-negative oxygen and the shift of an electron pair as shown. The resulting hydroxyhydrazononitrile (VII) would be unstable in the acidic medium, losing the elements of water to form the completely conjugated azipyrazole.

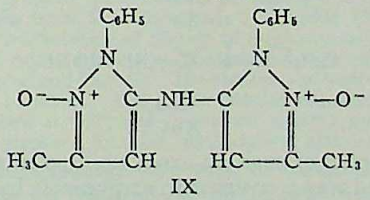


It is also possible to explain azipyrazole formation by a smooth mechanism starting with formation of the pyrazole-2-oxide (VIII).[17]

Other Products from Oxidation of II.—In the reaction of 5-amino-3-methyl-1-phenylpyrazole with hydrogen peroxide in acetic acid under all conditions used, a white crystalline compound melting at 229–230° separated quickly and could be isolated in 70% yield (pure). It seems peculiar that it was not mentioned by Michaelis and co-workers.[1] Because of its possible role as an intermediate in azipyrazole formation, its structure was investigated.



The elemental analysis and molecular weight determinations for this compound indicated an empirical formula of $C_{20}H_{19}N_5O_2$. Its infrared spectrum contained strong bands at 6.82 and 10.70 μ characteristic of the pyrazole ring,[6] at 2.85 μ characteristic of a secondary amine[5] and at 6.85 μ characteristic of an N-oxide or azoxy structure.[18,19] These data suggested that the compound was di-(3-methyl-1-phenyl-5-pyrazolyl)-amine 2,2′-dioxide (IX) or the corresponding 1,1′-dioxide.



IX

This product may be formed by condensation of two molecules of the aminopyrazole and N-oxide formation. Although the sequence of these two steps is unknown, the presence of the N-oxide function suggests that the first reaction of the pyrazole with hydrogen peroxide is transfer of an oxygen to the ring nitrogen, just as in the case of pyridine and other nitrogen heterocycles.

The 2,2′-dioxide structure is favored over the 1,1′-analog, because the ultraviolet spectrum of the compound has its maximum at 247 mμ. This is practically the same as for 5-amino-3-methyl-1-phenylpyrazole (II) (246 mμ). If the oxygen were at N-1, there would be no unshared pairs of electrons on the nitrogen to conjugate with the benzene ring, and the bond maximum should be observed at a shorter wave length; also the N–H bond in the infrared spectrum should be shifted to a higher wave length, because of the possibility of strong hydrogen bonding to a 1-oxide function.

The 2-oxide structure for IX favors the second mechanism postulated for azipyrazole formation,

(16) J. N. Brough, B. Lythgoe and P. Waterhouse, *J. Chem. Soc.*, 4969 (1954).

(17) It is, of course, possible to postulate other mechanisms for azipyrazole formation. A Referee has pointed out that it is conceivable that azipyrazole is formed by oxidation of the phenylhydrazone of diacetonitrile, which may be present in very small concentrations in tautomeric equilibrium with the pyrazole (II). We are planning to do further experimental work on the mechanism of oxidative cleavage of pyrazoles.

(18) B. Curnutte, Jr., S. Searles, Jr., and W. R. Hine, Jr., to be published.

(19) Another strong band at 7.76 μ was in the region for symmetric stretching of the $N{=}\overset{+}{N}{-}O^-$ group, as assigned by B. W. Langley, B. Lythgoe and L. S. Reyner, *J. Chem. Soc.*, 419 (1952).

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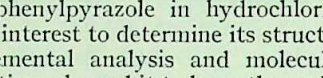
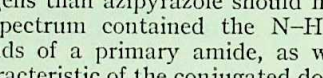
because the intermediate VIII for the latter could give rise to IX by means of self-condensation. It is uncertain whether IX is an intermediate in azipyrazole formation, but several experiments were attempted to see if it could be converted to azipyrazole. The most interesting one was that in which the hydrochloride of IX was heated at 160°, giving a material closely resembling azipyrazole in the common physical properties. Closer examination showed it, however, to be a new compound. Since it also was a major product (38% yield) of the reaction of hydrogen peroxide with 5-amino-3-methyl-1-phenylpyrazole in hydrochloric acid, it seemed of interest to determine its structure.

The elemental analysis and molecular weight determinations showed it to have the molecular formula $C_{10}H_{11}N_3O_2$—two more hydrogens and two more oxygens than azipyrazole should have. The infrared spectrum contained the N–H and carbonyl bands of a primary amide, as well as the bands characteristic of the conjugated double bond, the phenyl group[5] and the azoxy group.[18] Significantly, the pyrazole bands were completely absent. The two oxygens are thus accounted for by the amide and the azoxy functions. It will be recognized that all the structural features, as well as the analytical data, fit 3-(phenyl-NON-azoxy)-crotonamide (Xa) as well as 3-(phenyl-NNO-azoxy)-crotonamide (Xb).[20]



Xa



Xb

In support of such an azoxyamide structure, the compound was converted to azipyrazole by heating with phosphorus trichloride in chloroform.[21] Furthermore, the reaction of 3-(phenylazo)-crotonamide (V) with perphthalic acid gave the same azoxyamide, thus providing an independent synthesis.

Comparison of the ultraviolet spectra of V and the azoxyamide then permitted assignment of the position of the N-oxide oxygen atom in the latter. The maximum for the azoamide was at 250 mμ while that for the azoxyamide was 244. This shift to shorter wave length indicates less conjugation of the benzene ring in the azoxyamide. Such would be the case with the oxygen on the phenyl-substituted nitrogen, since the oxygen would compete with the benzene ring to supply electrons to the carbonyl group. If the oxygen were on the other nitrogen, however, its unshared electrons would be able to conjugate with the benzene ring and would not compete with the latter in resonance with the conjugated chain; the result would be more conjugation of the ring and a shift of the maximum absorption to higher wave lengths. Lythgoe and associates have observed the maximum in ArN=N(O)R compounds, where R is saturated, to be at 292–300 mμ.[16] Similarity of the ultraviolet spectrum to that of nitrobenzene (λ_{max} 260 mμ) also may be used as an indication of the ArN(O)=NR structure.[25] Thus structure Xa is indicated for the azoxyamide, rather than Xb.[22]

The formation of this compound from II probably proceeded *via* azipyrazole. It is well known that hydrogen peroxide is able both to oxidize the azo group to azoxy and (due to its superior nucleophilic property)[23] to hydrolyze the nitrile group to the amide group. The formation of the azoxyamide from the (probably hydrated) hydrochloride of IX suggests that it may have first hydrolyzed to VIII and the corresponding pyrazolone-2-oxide, with VIII cleaving to azipyrazole which was subsequently oxidized by hydrogen peroxide from the pyrazolone-2-oxide and water.

Experimental[24]

5-Amino-3-methyl-1-phenylpyrazole was prepared in 75% yield by cyclizing diacetonitrile phenylhydrazone[26] with dry hydrogen chloride in absolute ethanol and treating the intermediate hydrochloride with ammonia in aqueous solution. The product was obtained as white needles from toluene, m.p. 112–114° (lit.[26] m.p. 115–116°).

Di-(3-methyl-1-phenyl-5-pyrazyl)-amine 2,2′(?)-Dioxide (IX).—A solution of 3.0 ml. of 30% hydrogen peroxide and 5.0 g. of 5-amino-3-methyl-1-phenylpyrazole in 50 ml. of 50% aqueous acetic acid was heated on a steam-bath for 5 hr. A red color developed in a few minutes and after about 30 minutes a yellow precipitate began to separate. It was removed by filtration and recrystallized from pyridine-water to give 3.57 g. (70%) of a white crystalline solid, m.p. 229–230°. The infrared and ultraviolet spectra are described in the Discussion.

Anal. Calcd. for $C_{20}H_{19}N_5O_2$: C, 66.48; H, 5.26; N, 19.39; C-methyl, 2.0; mol. wt., 361. Found: C, 66.47; H, 5.30; N, 19.38; C-methyl, 1.7; mol. wt., 339.

3-(Phenyl-NON-azoxy)-crotonamide (Xa). (A).—Addition of IX to concentrated hydrochloric acid caused precipitation of a white hydrochloride, m.p. 178–180°, which decomposed to a red oil on being heated dry at 160° for 15 minutes. On cooling the red oil solidified (m.p. 109–113°) and recrystallization from aqueous ethanol gave light tan needles, m.p. 113°. The yield was 0.2 g. from 1.0 g. of IX.

(B).—5-Amino-3-methyl-1-phenylpyrazole (5.0 g.) was dissolved in 35 ml. of concentrated hydrochloric acid, and 3 ml. of 30% hydrogen peroxide was added. The solution was evaporated on a steam-bath, leaving a red oil which was crystallized from dilute alcohol. A light tan solid, m.p. 113°, was obtained in 38% yield (2.4 g.).

(20) According to a new method of naming azoxy compounds suggested by J. N. Brough, B. Lythgoe and P. Waterhouse (ref. 16), Xb would be termed 3-(phenylazoxy)-crotonamide and Xa would have to be named 1-carbamoylpropen-2-ylazobenzene. Because the latter name seems cumbersome and screens the α,β-unsaturated amide structure, we feel the NON and NNO designation of the oxide function, used by C. S. Stevens, B. T. Gillis, J. C. French and T. H. Haskell (THIS JOURNAL, **78**, 3229 (1956)), is preferable.

(21) Use of phosphorous trichloride here was suggested by its demonstrated ability to convert pyridine N-oxides to the corresponding pyridines (E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953)). The phosphorous oxychloride formed in removing the oxygen from the azoxy group may then dehydrate the [illegible]

(22) The attack of hydrogen peroxide on the phenyl-substituted nitrogen seems contrary to expectation, since the reagent should be electrophilic in this reaction and the other nitrogen of the azo group should have the higher electron density. A similar result, however, has been observed on oxidation of aryl alkyl azo compounds (ref. 16).

(23) K. B. Wiberg, THIS JOURNAL, **75**, 3961 (1953). In the coiled form of the azipyrazole molecule these two groups are in close proximity, perhaps permitting both processes to go on almost simultaneously and explaining why neither azoamide nor azoxynitrile was found.

(24) Carbon–hydrogen microanalyses were performed by Weiler and Straus, Oxford, England. Melting points are uncorrected. Nitrogen analyses were by the Dumas method; molecular weight determinations by the Rast method; and C-methyl numbers by the Kuhn-Roth method (E. J. Eisenbraun, S. M. McElvain and B. F. Aycock, THIS JOURNAL, **76**, 607 (1954)).

(25) P. S. Burns, *J. prakt. Chem.*, [2] **47**, 131 (1893).

(26) R. Walther, *ibid.*, **59**, 143 (1897).

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(C).—Five drops of concentrated sulfuric acid was added to a solution of 5 g. of 5-amino-3-methyl-1-phenylpyrazole and 1 ml. of 90% hydrogen peroxide[27] in 30 ml. of glacial acetic acid, cooled in ice so that the temperature remained below 40° (otherwise the reaction is very exothermic). The deep-red solution was evaporated *in vacuo*. Extraction of the red oil with 95% alcohol left a residue of 1.8–2.0 g. of compound IX. The sticky red-brown semi-solid left on evaporation of the alcohol was extracted with ether to give 0.1 g. of tan needles, m.p. 113°; mixed m.p. with products from (B) and (C) undepressed. (In one experiment 0.2 g. of orange-red needles, m.p. 70–80°, was obtained from this ether solution (lit. m.p. for Quilico and Justoni's isomer,[14] 81°). On recrystallization from dilute ethanol it was converted to light tan needles, m.p. 103–106°.) The infrared spectrum was characterized by prominent bands at 2.96, 3.15, 3.28, 3.42, 3.53, 5.9, 6.1, 6.18, 6.25, 6.54, 6.66, 6.76, 6.87, 7.18, 7.63, 10.1, 10.9, 11.9 and 13.1 μ.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.5; C-methyl, 1.0; mol. wt., 205. Found: C, 58.22; H, 5.42; N, 19.8; C-methyl, 0.96; mol. wt., 188.

In the early stages of this work, when this compound was thought possibly to be "azipyrazole," its dipole moment was determined to check the possibility of a mesoionic structure. The dielectric constant of benzene solutions was determined by the standing microwave technique.[28] The calculated dipole moment was 0.86 *D*.

3-(Phenylazo)-crotononitrile (Azipyrazole). (A).—To 0.05 g. of 3-(phenyl-NON-azoxy)-crotonamide dissolved in 15 ml. of chloroform at 0°, 0.05 ml. of phosphorus trichloride was added, and the solution was refluxed 1 hr. After cooling, 25 ml. of water was added and the mixture was made alkaline with sodium hydroxide. The chloroform layer was dried with sodium sulfate and the solvent then was removed *in vacuo*. The light brown residual solid was sublimed at 90° (0.05 mm.) to give 10 mg. (30%) of ivory-white needles, m.p. 109°. The m.p. was unchanged after recrystallization from dilute alcohol.

(B).—Vacuum sublimation of the red oil described in (C) for the azoxy compound gave 20 mg. of the same product.

(C).—To a solution of 1.0 g. of diacetonitrile phenylhydrazone in 35 ml. of absolute alcohol was added 2 g. of yellow mercuric oxide, and the mixture was refluxed for 2 hr. The free mercury was filtered off and most of the alcohol distilled off, leaving a red oil. This was partially soluble in light petroleum ether; the insoluble part was then dissolved in ethyl ether. Evaporation of the solvent from the ethyl ether solution gave 0.3 g. of tan needles, m.p. 105–107°. Vacuum sublimation as described above gave 0.20 g. (26%) of ivory-colored needles, m.p. 109°. The mixed melting points of the 109° products from these three methods were undepressed and all had the same infrared spectrum. The latter was characterized by prominent bands at 4.45, 6.20 and 6.25 μ, as well as at 3.53, 3.44, 5.80, 5.87, 5.93, 6.07, 6.31, 6.65, 6.73, 7.31, 7.95 and 8.25 μ.

Anal. Calcd. for $C_{10}H_9N_3$: N, 24.55. Found: N, 24.22.

Derivatives were prepared as follows: **5-amino-3-methyl-1-phenylpyrazole**, m.p. 113–115° (lit.[26] m.p. 115–116°), when azipyrazole was boiled a few minutes in 10% sodium hydrosulfite solution and filtered. **5-Amino-4-iodo-3-methyl-1-phenylpyrazole**, m.p. 75° (lit.[1a] m.p. 75°), when azipyrazole was warmed a few minutes with concentrated hydriodic acid, followed by saturating the solution with sodium hydroxide, extracting with ether and removing the ether from the extract by evaporation. **5-Amino-4-bromo-3-methyl-1-phenylpyrazole**, m.p. 105° (lit.[1a] m.p. 106.5° and mixed m.p. with azipyrazole 83–99°), was obtained by the same procedure using 48% hydrobromic acid.

Evaporation of the solvent from the petroleum ether extract of the reaction mixture in (C) left 50 mg. of stout red needles, m.p. 73–76°; after recrystallization from alcohol they melted at 82–83°.

Anal. Calcd. for $C_{10}H_9N_3$: N, 24.55. Found: N, 24.83.

3-(Phenylazo)-crotononamide (V).—Ethyl 3-(phenylazo)-crotonate was prepared in 10% yield by the reaction of mercuric oxide on ethyl acetoacetate phenylhydrazone[9]; red crystals, m.p. 50°. A solution of 80 mg. of this azoester and 2 g. of dry ammonia in 10 ml. of absolute ethanol was heated in a sealed tube 10 hr. at 110°. On subsequent evaporation of the solvent 60 mg. (90%) of a black crystalline solid, m.p. 74°, remained. (In another run the yield on this reaction was 60%.)

Anal. Calcd. for $C_{10}H_{11}N_3O$: N, 22.22. Found: N, 21.92.

The above amide (40 mg.) was added to 5 ml. of an ether solution of monoperphthalic acid,[29] containing 1×10^{-3} mole of the latter. After standing two days, sodium bicarbonate was added to neutralize the acid present. The ether solution was separated, dried and evaporated *in vacuo*, leaving tan needles, melting at 113°, identical with the 3-(phenyl-NON-azoxy)-crotonamide previously described.

Azipyrazole from V.—Phosphoric anhydride (100 mg.) was added to a solution of 50 mg. of 3-(phenylazo)-crotonamide in 15 ml. of benzene. The mixture was refluxed 30 minutes, cooled and filtered. The solvent was removed from the filtrate *in vacuo*. The white needles obtained (about 15 mg.) melted at 109° and the mixed melting point with azipyrazole prepared by other methods was also 109°.

Acknowledgments.—We wish to thank Dr. John G. Erickson for his kind encouragement and valuable comments, Dr. Louis D. Ellsworth for his aid with the dipole moment measurement and Dr. Basil Curnutte for his assistance in selecting the N–O bands in the infrared spectra of the azoxy compounds.

(27) The generous gift of Becco Chemical Division, Food Machinery and Chemical Corporation, Buffalo, New York.

(28) M. G. Haugen and W. B. Westphal, N.D.R.C. Report 541, Insulation Res. Lab., Mass. Inst. Tech., Oct., 1945.

(29) H. Bohme, *Org. Syntheses*, **20**, 70 (1940).

MANHATTAN, KANSAS

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORIES OF HARVARD UNIVERSITY]

Preparation and Thermal Rearrangement of Several Dicyclopentadiene Derivatives

BY MYRON ROSENBLUM[1]

RECEIVED DECEMBER 20, 1956

Oxidation of dicyclopentadiene with selenium dioxide in aqueous dioxane solutions has been shown to yield 1-dicyclopentadienol. The oxidation of this alcohol under Oppenauer conditions affords 1-dicyclopentadienone, and its pyrolysis leads to the formation of cyclopentadiene and 2-cyclopentenone. Treatment of 1-dicyclopentadienone with both methyl and phenyl Grignards leads to the formation of the corresponding tertiary alcohols, 1-methyldicyclopentadiene-1-ol and 1-phenyldicyclopentadiene-1-ol. Pyrolysis of 1-acetoxydicyclopentadiene, prepared by acetylation of 1-dicyclopentadienol, affords azulene in low yield.

The synthesis of oxygenated derivatives of dicyclopentadiene has hitherto been confined to the di- and tetrahydro members of the parent diene,[2] although a considerable number of polyalkyl,

(1) Department of Chemistry, The Illinois Institute of Technology, Chicago 16, Ill.

(2) *Cf.* "Elsevier's Encyclopedia of Organic Chemistry," Vol. XIII, Elsevier Publishing Co., N. Y., 1948, pp. 1018–1032.

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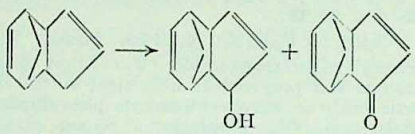
polyaryl and polyhalo dicyclopentadienes possessing oxygen functions at either or both positions 1 and 8 of the tricyclic system are known.[3,4]

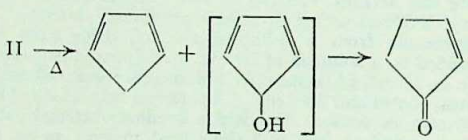
The present paper describes the preparation of several new oxygenated derivatives of dicyclopentadiene and includes a preliminary account of the behavior of some of these on pyrolysis.

Oxidation of dicyclopentadiene (I) with selenium dioxide in dioxane–water solutions afforded 1-dicyclopentadienol (II) in 57% yield, together with a small amount of 1-dicyclopentadienone (III). This alcohol had previously been prepared by Vanelli[5] by hydrolysis of 1-acetoxydicyclopentadiene (IV), obtained by treatment of dicyclopentadiene with selenium dioxide in acetic acid medium.



I II III

Slow distillation of II at atmospheric pressure gave cyclopentadiene and 2-cyclopentenone (V) in 42% yield, while vapor phase pyrolysis at reduced pressures resulted in an essentially quantitative conversion of II to V and cyclopentadiene. The formation of V may be viewed as proceeding *via* an initial reverse Diels–Alder reaction followed by isomerization of the transient 2,4-cyclopentadienol (VI).



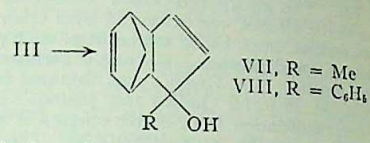
VI V

The reaction sequence I → II → V constitutes a useful procedure for the preparation of 2-cyclopentenone which has heretofore been obtained either by allylic oxidation of cyclopentene[6] or by dehydrohalogenation of 1-halocyclopentanone.[7] Of these methods only that of Treibs[6b] and of Corey[7c] are of preparative value.

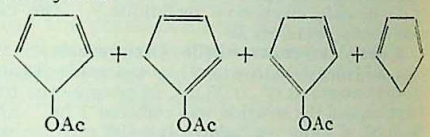
Oppenauer oxidation of II, employing *p*-quinone as oxidant, gave 1-dicyclopentadienone (III) in 79% yield.[8] Attempts to effect the thermal reversal of III to cyclopentadiene and the unknown cyclopentadienone were unsuccessful. Unlike II, the ketone III resisted pyrolysis at temperatures well above those sufficient to effect reversal of II to its diene and dienophile components.

(3) *Cf.* C. F. H. Allen, *Chem. Revs.*, **37**, 209 (1945).
(4) E. T. McBee and R. K. Meyers, THIS JOURNAL, **77**, 88 (1955).
(5) R. Vanelli, Ph.D. Thesis, Harvard University, 1950.
(6) (a) E. Dane and K. Eder, *Ann.*, **539**, 207 (1939). (b) W. Treibs, B. Franke, G. Leichsenring and H. Roder, *Ber.*, **86**, 616 (1953).
(7) (a) M. Godchot and F. Taboury, *Bull. soc. chim. France*, **13**, 545 (1913); (b) M. Mousseron, R. Jacquier and A. Fontaine, *ibid.*, 767 (1952); (c) E. J. Corey and Kunizo Osugi, *Pharm. Bull. Japan*, **1**, 99 (1953).
(8) H. Hock and F. Depke, *Ber.*, **84**, 356 (1951), have reported the isolation of a ketone $C_{10}H_{10}O$ from the air oxidation of dicyclopentadiene to which they ascribe the structure of 1-dicyclopentadienone (III). However, their observation that the substance was an oil which resisted crystallization must cast doubt upon its identity, since the ketone prepared as described in this report is a readily crystallizable solid melting at 59°.

Treatment of II with both methyl and phenyl Grignards afforded the corresponding tertiary alcohols, 1-methyldicyclopentadiene-1-ol (VII) and 1-phenyldicyclopentadiene-1-ol (VIII). The pyrolysis of these compounds has not as yet been explored.



Pyrolysis of 1-acetoxydicyclopentadiene, prepared by acetylation of II, led to the formation of cyclopentadiene and a mixture of acetoxycyclopentadienes (IX, X, XI).[5] When this mixture was heated at 150° for 3 hr. and then repyrolyzed at atmospheric pressure, acetic acid was evolved and azulene, identified by its melting point and its ultraviolet absorption spectrum,[9] was isolated in low yield.



IX X XI

The identity of the isomer, present in the complex mixture of diacetoxydicyclopentadienes formed by dimerization of IX, X and XI, which on rearrangement gives rise to azulene, is being investigated.

Acknowledgment.—We are indebted to Professor R. B. Woodward, who suggested this problem, for many valuable discussions during the course of the investigation.

Experimental

1-Dicyclopentadienol (II).—Freshly distilled dicyclopentadiene, 185 g. (1.4 moles), was dissolved in a mixture of 500 ml. of dioxane and 50 ml. of water. Selenium dioxide, 66.5 g. (0.6 mole), was added, and the solution was stirred and heated under reflux for 3 hr. The resulting dark brown mixture was then filtered from selenium and poured into two liters of water. The heavy dark oil was drawn off and the aqueous solution was extracted with 600 ml. of ether in three portions. The organic solutions were combined, washed with water and dried over magnesium sulfate. Removal of solvent, followed by fractionation of the crude product, gave 1-dicyclopentadienol as a pale yellow, viscous oil; yield 100.2 g. (57%), b.p.'s 84° (3 mm.), 90° (5 mm.) and 106° (7 mm.). Redistillation resulted in a colorless product whose infrared spectrum was identical with that of II prepared earlier by Vanelli[5] by hydrolysis of 1-acetoxydicyclopentadiene.

1-Dicyclopentadienone (III).—A mixture of 52.5 g. of 1-dicyclopentadienol (0.36 mole), 48.0 g. of *p*-quinone (0.45 mole) and 87.0 g. of aluminum *t*-butoxide (0.36 mole) in 650 ml. of dry benzene was stirred at 50° for 6 hr. At the end of this period, the dark purple solution was allowed to cool and was decomposed with water. Aluminum hydroxide was filtered off and washed thoroughly with ether. The combined benzene–ether solution was extracted five times with 100-ml. portions of 5% sodium hydroxide solution, washed with water to neutrality and finally dried over magnesium sulfate. After evaporation of solvent, the product was distilled at 82–87° (4 mm.) as a pale yellow oil, which crystallized on being cooled to room temperature; yield 41.0 g. (79%). A portion was recrystallized several times from low boiling petroleum ether to give the pure ketone as colorless plates, m.p. 59.0–59.5°.

(9) H. A. Plattner and E. Heilbronner, *Helv. Chim. Acta*, **31**, 504 (1948).

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Anal. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 82.67; H, 7.18.

A 2,4-dinitrophenylhydrazone derivative, crystallized from ethyl alcohol, melted at 203.5–204.0°.

Anal. Calcd. for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.71; H, 4.54; N, 17.13.

1-Acetoxydicyclopentadiene (IV).—1-Dicyclopentadienol, 50 g., was dissolved in 130 ml. of pyridine containing 100 ml. of acetic anhydride. After standing at room temperature for 12 hr., the solution was poured onto ice and the heavy dark oil was separated. The aqueous solution was extracted twice with 100-ml. portions of ether, and these extracts were combined with the oil. The organic solution was washed several times with dilute hydrochloric acid and then with water to neutrality. After drying the solution over Drierite, solvent was evaporated and the residue was fractionated. The ester distilled at 118.5–120.5° (14.5 mm.), yield 55.6 g. (87%). Its infrared spectrum was identical with that of 1-acetoxydicyclopentadiene prepared earlier by Vanelli.[6]

2-Cyclopentenone (V). By Pyrolysis of 1-Dicyclopentadienol at Atmospheric Pressures.—1-Dicyclopentadienol, 48.85 g., was placed in a 250-ml. claisen flask having a six-inch side arm. The flask was heated over a free flame as a slow stream of dry nitrogen was passed through the alcohol. The distillate temperature was maintained at 140–150°. A slower rate of distillation resulted generally in greater polymerization of the material in the distilling flask. The distillate, containing unchanged alcohol, cyclopentadiene and 2-cyclopentenone, was fractionated to give 8.29 g. of ketone V, b.p. 50° (15 mm.), $n^{25}D$ 1.4753 (lit.[7c] b.p. 53° (16 mm.), $n^{18.2}D$ 1.4780), and 13.13 g. of unchanged 1-dicyclopentadienol. The yield of 2-cyclopentenone, corrected for recovered alcohol, was 42%. Its dinitrophenylhydrazone derivative, m.p. 169–171°, was identical by mixed m.p. determination with that prepared from an authentic sample of 2-cyclopentenone.

2-Cyclopentenone (V). By Vapor Phase Pyrolysis of 1-Dicyclopentadienol at Reduced Pressures.—The apparatus used in these and later experiments consisted of a 25-ml. round-bottom flask, surmounted by a small addition funnel. One of two side-arm tubes joined to the flask served as an inlet for nitrogen while the other led directly to the pyrolysis chamber. The latter consisted of a horizontally mounted Pyrex tube, 30 cm. in length and 1.8 cm. in diameter, heated by means of a multiple unit electric furnace. The pyrolysis tube was connected to a receiver flask, vacuum gage and pump. Temperatures within the pyrolysis chamber were measured by means of an iron–constantan thermocouple.

With the apparatus evacuated to a pressure of 5–7 mm. (nitrogen atmosphere) and the pyrolysis tube heated to a temperature of 450°, the alcohol was allowed to drop slowly from the addition funnel into the distilling flask, heated by means of a oil-bath to 200°. The alcohol was thus immediately volatilized and swept into the pyrolysis chamber by the nitrogen stream and thence into the receiver flask cooled in a Dry Ice–acetone-bath. Infrared spectra taken of the products of several runs, after allowing the cyclopentadiene to evaporate, failed to reveal the presence of any unchanged alcohol and were essentially identical with that of 2-cyclopentenone obtained by pyrolysis of II at atmospheric pressures. Polymeric residues in the distillation flask and the pyrolysis chamber were negligible.

Attempted Pyrolysis of 1-Dicyclopentadienone (III).—When small amounts of the ketone III were heated in a distilling flask at 200–250° in an attempt to effect a reverse Diels–Alder reaction, a part of the ketone distilled unchanged while the remainder polymerized in the distilling flask.

1-Methyldicyclopentadiene-1-ol (VII).—1-Dicyclopentadienone, 10.0 g. (0.069 mole), dissolved in 20 ml. of anhydrous ether, was added dropwise to a stirred solution of methylmagnesium iodide prepared from 1.75 g. (0.069 mole) of magnesium turnings and 12.0 g. (0.085 mole) of methyl iodide in 40 ml. of anhydrous ether. The solution was refluxed on the steam-bath for 30 minutes following addition of the ketone and was then cooled and decomposed with saturated ammonium chloride solution. The aqueous phase was separated, extracted several times with ether, and the ethereal extracts were combined, washed to neutrality with water and dried over calcium sulfate. Evaporation of solvent left 7.85 g. (70%) of pale yellow oil which solidified on cooling. A portion of this material, after several recrystallizations from low boiling petroleum ether, followed by sublimation, yielded pure 1-methyldicyclopentadiene-1-ol as fine colorless needles, m.p. 49.0–49.5°.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.50; H, 8.70. Found: C, 81.50, 80.71; H, 9.08, 8.77.

1-Phenyldicyclopentadiene-1-ol (VIII).—1-Dicyclopentadienone, 2.0 g. (0.014 mole), dissolved in 10 ml. of anhydrous ether, was added dropwise to a stirred solution of phenylmagnesium bromide prepared from 2.15 g. (0.14 mole) of bromobenzene and 0.38 g. (0.016 mole) of magnesium turnings in 45 ml. of anhydrous ether. The solution was refluxed on the steam-bath for 30 minutes following addition of the ketone and was then cooled and decomposed with saturated ammonium chloride solution. The aqueous phase was separated and extracted several times with ether. The ether solutions were combined, washed to neutrality and dried over calcium sulfate. The crude solid, isolated on evaporation of solvent, was recrystallized twice from low boiling petroleum ether to give 0.75 g. (33%) of 1-phenyldicyclopentadiene-1-ol, m.p. 65.5–66.5°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 86.28, 85.76, 85.79; H, 7.33, 7.39, 7.22.

Azulene. By Pyrolysis of 1-Acetoxydicyclopentadiene.—The apparatus described above in the pyrolysis of 1-dicyclopentadienol was employed in this experiment. The acetate, 10.4 g., was allowed to drop slowly into the distilling flask which was heated to a temperature of 190–200°. A pressure of 5–7 mm. (nitrogen atmosphere) was maintained during the course of the pyrolysis, and the pyrolysis chamber was heated to 440–475°. At the end of 1 hr. addition of the acetate was complete, and 10.4 g. of orange oil had been collected in the receiver flask. The product was heated in an atmosphere of nitrogen at a temperature of 150° for 3 hr. A portion of this material, 7.8 g., was placed in a short path distillation flask containing 1.95 g. of calcium oxide powder, and the flask was immersed in a Woods metal-bath preheated to 240°. A slow stream of nitrogen was bubbled through the mixture during the course of the pyrolysis. After the contents of the flask had been heated for 15 minutes and the bath had reached a temperature of 255°, vacuum was applied, and 1.70 g. of pale blue distillate was collected. Following another brief period of heating, when the bath temperature had risen to 265°, vacuum was again applied, and an additional 1.12 g. of dark blue liquid was collected. The two distillate fractions were combined and placed on a chromatographic column prepared from 16 g. of alumina. On elution with low boiling petroleum ether, the blue component moved rapidly down the column as a well defined zone. This material was rechromatographed three times on 8-g. alumina columns, and in this manner 2.5 mg. of dark blue crystalline material, m.p. 92–95° (with sublimation), was isolated after removal of solvent. The ultraviolet spectrum of the product, taken in 95% ethanol solution, was identical with that of azulene reported by Plattner and Heilbronner.[9]

CHICAGO 16, ILL.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Kolbe Electrolyses[1] of Perhydrodiphenic Acids

BY C. G. OVERBERGER AND PETER KABASAKALIAN[2]

RECEIVED JANUARY 7, 1957

The Kolbe electrolysis of *cis–syn–cis*-, *trans–anti–trans*- and *trans–syn–trans*-perhydrodiphenic acids in anhydrous methanol is described. In all cases, the principal product was a γ-lactone. The structure of the γ-lactone was established by chemical synthesis. The formation of the γ-lactone may involve a hydrogen radical transfer reaction.

The electrolysis of dibasic acids (from malonic to sebacic) in aqueous media have been reported[3] to yield olefins and alcohols, containing two carbons less than the starting material. The structures of the olefins and the alcohols obtained were both the expected ones as well as their isomers. The latter may have been formed by migration of hydrogen atoms in the originally formed radicals.

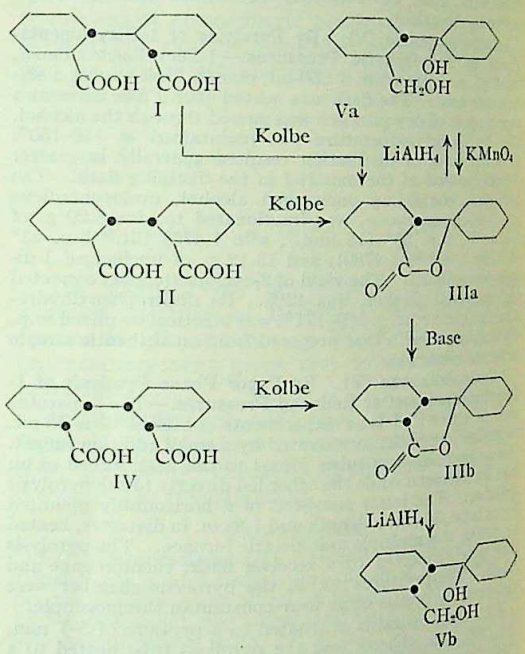
Although all attempts to isolate the coupled product, cycloalkanes, have not been successful, Vanzetti[3d] has reported the formation of a small amount of lactone during the electrolysis of suberic acid. This paper describes an initial phase of the study of Kolbe electrolyses of dibasic acids in anhydrous methanol.

The Kolbe electrolysis products from the perhydrodiphenic acids were separated into a steam-distillable fraction (monomeric) and a non-steam-distillable fraction (polymeric). The non-steam-distillable fractions account for about 20–25% of the product and were presumed to be made up of polymeric material. The steam-distillable fractions, which account for about 60% of the product, contain about 20% of non-lactonic material which was not identified.

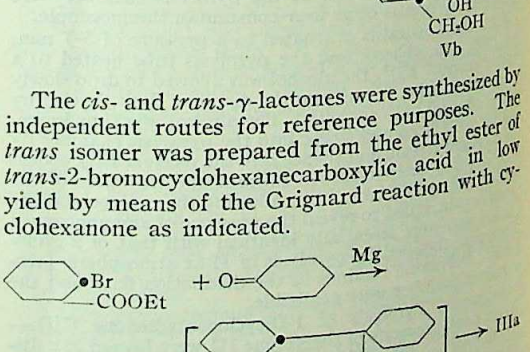
The Kolbe electrolysis of the three perhydrodiphenic acids studied here gave as a minor product (about 5%) δ-lactones. These probably were formed by the intramolecular coupling of the primary and the secondary radicals formed at the anode and were identified only by their infrared spectrum. Their infrared absorption band at 5.76 μ is indicative of a saturated six-membered lactone, but an open chain ester[4] cannot be excluded.

The electrolysis of *trans–anti–trans* (I) and *trans–syn–trans* (II) perhydrodiphenic acids gave as the major product (about 45%) the *trans*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (IIIa), while the electrolysis of *cis–syn–cis* (IV) perhydrodiphenic acid gave the *cis*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (IIIb). These isomeric γ-lactones from the Kolbe electrolyses could not be obtained stereochemically pure since isomerization conditions prevailed during their preparation.

The structure of the *trans*-γ-lactone was verified in the following way. Reduction with lithium aluminum hydride gave the *trans*-glycol (90%). This product was found to have only one hydroxyl group which could be acetylated easily. The *trans*-γ-lactone (37%) was regenerated when the *trans*-glycol was oxidized with alkaline potassium permanganate.



The *cis*- and *trans*-γ-lactones were synthesized by independent routes for reference purposes. The *trans* isomer was prepared from the ethyl ester of *trans*-2-bromocyclohexanecarboxylic acid in low yield by means of the Grignard reaction with cyclohexanone as indicated.



The cylization of the initial Grignard product of this type also has been reported by Cason, Adams, Bennett and Register[5] who prepared γ-substituted γ-lactones by the action of Grignard reagents on levulinic esters.

The *cis* isomer was prepared by two methods. The first method[6] involved a Diels–Alder reaction

(1) For the previous paper, see C. G. Overberger and P. Kabasakalian, *J. Org. Chem.*, **21**, 1124 (1956).

(2) This paper comprises a portion of a thesis presented by Peter Kabasakalian in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

(3) (a) B. L. Vanzetti, *Gazz. chim. ital.*, **34**, II, 511 (1904); (b) B. L. Vanzetti, *ibid.*, **37**, II, 340 (1907); (c) B. L. Vanzetti, *ibid.*, **38**, I, 47 (1908); (d) B. L. Vanzetti, *ibid.*, 390 (1907).

(4) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).

(5) J. Cason, C. E. Adams, L. L. Bennett, Jr., and U. D. Register, *ibid.*, **66**, 1764 (1944).

(6) We are indebted to Mr. John Whelan for the initial suggestion.

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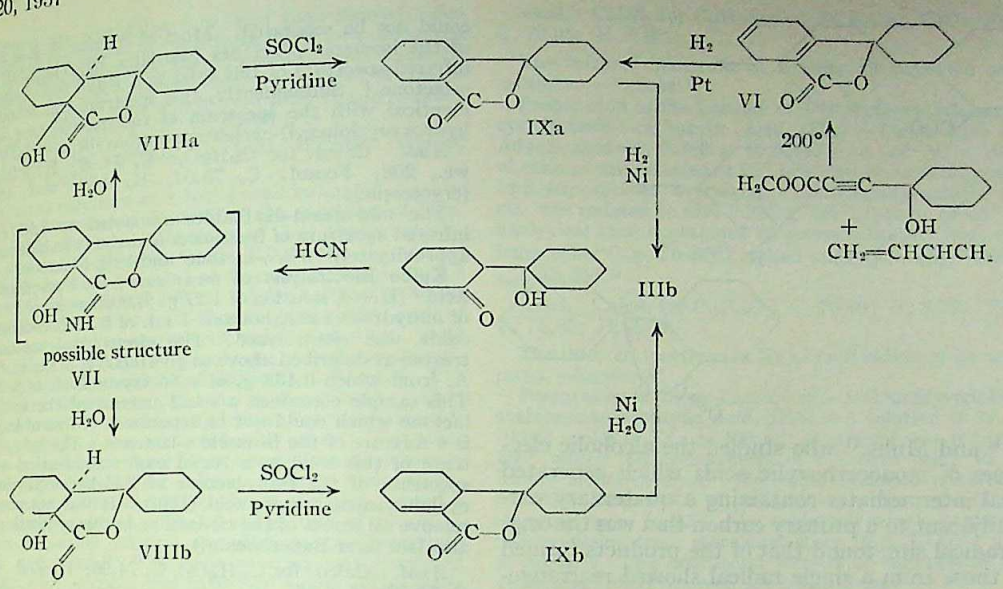

between butadiene and the methyl ester of β-(1-hydroxycyclohexyl)-propiolic acid to give the lactone of 2-(1-hydroxycyclohexyl)-1,4-cyclohexadiene-1-carboxylic acid (68%). Catalytic reduction with the aid of Adams catalyst eliminated the isolated double bond to form the lactone of 2-(1-hydroxycyclohexyl)-1-cyclohexene-1-carboxylic acid (89%). Further reduction with the aid of Raney nickel and high pressure yielded the *cis*-γ-lactone (82%).

The second method for the preparation of the *cis* isomer used 2-(1-hydroxycyclohexyl)-cyclohexanone as starting material. Two methods are reported for the preparation of this compound and different melting points are recorded. Colonge's[7] method involved treating cyclohexanone with the reaction product from methyl Grignard reagent and N-methylaniline (m.p. 56°). Stanek's[8] method involved the self-condensation of cyclohexanone with ethanolic potassium hydroxide as the basic catalyst (m.p. 160°). The first step in this route involved the formation of cyanohydrins, which immediately cyclized to form probably five-membered cyclic imidic acid esters. These were not purified and on hydrolysis gave hydroxy-γ-lactones. Although Stanek's β-ketol gave a hydroxy-γ-lactone, the carbon and hydrogen analyses of the β-ketol and the hydroxy-γ-lactone were not in agreement with the proposed structure.

Colonge's β-ketol gave two isomeric hydroxy-γ-lactones (89%). One was a solid which is presumed to be the *trans* form from the stereochemistry of the subsequent dehydration step. It accounted for 20% of the total hydroxy lactone. The major fraction was a liquid and is presumed to be the *cis* form from the stereochemistry of the following dehydration step.

Parham, Moulton and Zuckerbraun[9] have reported that the dehydration of 2-phenylcyclohexanone cyanohydrin with thionyl chloride in pyridine is kinetically controlled, resulting in the *trans* elimination of the hydroxyl group. Using the same reaction conditions, thionyl chloride in pyridine, each of the isomeric hydroxy-γ-lactones was dehydrated and found to yield a different unsaturated lactone. The *trans* isomer gave the $\Delta^{1,2}$-product (90%) while the *cis* isomer gave the $\Delta^{1,6}$-product (72%). High pressure reduction, using Raney nickel catalyst, of the $\Delta^{1,6}$-unsaturated lactone also gave the *cis*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (75%). The *cis*-γ-lactone was reduced with lithium aluminum hydride to give the *cis*-glycol (98%).

Both the *cis*- and *trans*-γ-lactones were isomerized separately with sodium methoxide in anhydrous methanol. Identical equilibrium mixtures were obtained from both; the equilibrium mixture from the *cis* isomer was found to contain 90% *cis*- and 10% *trans*-γ-lactone while the equilibrium mixture from the *trans* isomer was found to contain 91% *cis*- and 9% *trans*-γ-lactone. Thus, the *cis* isomer seemed to be the most stable one at equilibrium.

The melting points of various pairs of isomers obtained in this study are listed in Table I.

TABLE I

ISOMERIC PAIRS

Compound	Isomer	M.p., °C.
Lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid	*cis*	55–56
	trans	99–99.5
2-(1-Hydroxycyclohexyl)-cyclohexanemethanol	*cis*	117–118
	trans	92.5–93
Lactone of 2-(1-hydroxycyclohexyl)-1-hydroxycyclohexanecarboxylic acid	*cis*	?
	trans	159–161
Lactone of 2-(1-hydroxycyclohexyl)-cyclohexene-1-carboxylic acid	$\Delta^{1,2}$	79–80
	$\Delta^{1,2}$	71–72

A possible mechanism for the formation of the γ-lactones may involve a hydrogen radical transfer at the location of the secondary radical, followed by an intramolecular coupling of the rearranged radical and the primary radical formed at the anode.

(7) J. Colonge, *Bull. soc. chim. France*, [5] **1**, 1101 (1934).
(8) J. Stanek, *Chem. Listy*, **46**, 110 (1952).
(9) W. E. Parham, W. N. Moulton and A. Zuckerbraun, *J. Org. Chem.*, **21**, 72 (1956).

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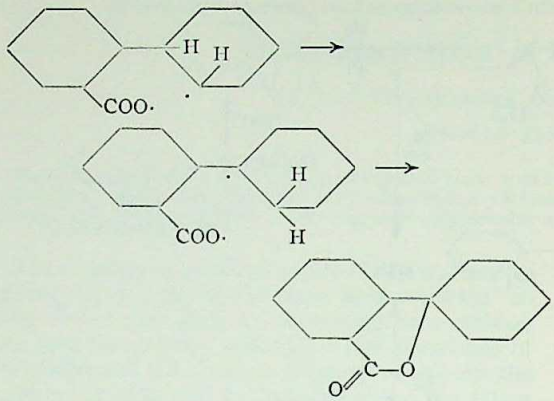

Urry[10] and Muhs,[11] who studied the alcoholic electrolyses of monocarboxylic acids which generated radical intermediates containing a quaternary carbon adjacent to a primary carbon that was the original radical site, found that of the products formed only those from a single radical showed rearrangement. The products formed from two radicals (coupled and ester products) were unrearranged.

The possibility of other mechanisms to explain the five-membered lactone cannot be excluded. Thus, lactonization could have occurred by ionic processes involving addition of a radical or an ion derived from one carboxyl group to an olefin linkage in the adjacent ring formed from radical disproportionation. The possibility that hydrogen migration occurred by an ionic transfer to a carbonium ion formed by oxidation of the radical at the anode also cannot be discounted completely until further evidence is obtained.

Acknowledgment.—We wish to thank the Schering Corporation for the generous use of their laboratory facilities in this work.

Experimental[12]

Absorption Spectra.—The ultraviolet absorption spectra were measured in 1-cm. quartz cells in methanol solutions using a Cary model 11 recording spectrophotometer. Infrared absorption spectra were obtained with a Perkin–Elmer model 21 double beam recording spectrophotometer with a sodium chloride prism.

Electrolyses.—The electrolysis equipment, conditions and electrode preparation were identical to those reported by Overberger and Kabasakalian.[1]

Kolbe Electrolysis of *trans–syn–trans*-Perhydrodiphenic Acid[13] (II).—A solution of 1.7 g. (0.050 mole) of II in 60 ml. of anhydrous methanol and 10 ml. of 0.20 *N* sodium methoxide was electrolyzed. The electrolysis required about 6 hr. (the current continually decreased and the anode became coated with insoluble material). The electrolyzed solution which was almost neutral was distilled under atmospheric pressure until the distillation temperature started to rise above 70° and most of the methanol was removed. The reaction mixture was then subjected to steam distillation; 6.0 l. of distillate was collected and extracted with ether. The extracts were dried over calcium chloride and concentrated to give 6.46 g. of liquid, fraction A, from which 0.63 g. of solids crystallized, m.p. 87–90°. This sample contained a small amount of the isomeric γ-lactone which could not be separated. Most of fraction A is a mixture of the isomeric γ-lactones (see later Experimental). The infrared spectrum of this solid in a Nujol mull indicated a γ-lactone.[4] Subsequently, this spectrum was found to be identical with the spectrum of the *trans*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (IIIa).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; mol. wt., 208. Found: C, 75.04; H, 9.62; mol. wt., 213 (cryoscopic).

The non-steam-distillables amounted to 1.95 g. The infrared spectrum of fraction A in carbon disulfide indicated approximately 70% γ-lactone[4] and 10% δ-lactone.[4]

Kolbe Electrolysis of *trans–anti–trans*-Perhydrodiphenic Acid[13] (I).—A solution of 1.27 g. (0.0050 mole) of I in 70 ml. of anhydrous methanol and 1 ml. of 0.20 *N* sodium methoxide was electrolyzed. The electrolyzed solution was treated as described above to give 0.605 g. of liquid, fraction A, from which 0.138 g. of solid crystallized, m.p. 84–86°. This sample contained a small amount of the isomeric γ-lactone which could not be separated. Most of fraction A is a mixture of the isomeric γ-lactones. The infrared spectrum of this solid in a Nujol mull was identical with the spectrum of the *trans*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (IIIa). It was not possible to remove all traces of the *cis*-lactone in this synthetic product also (see later Experimental).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.78; H, 9.64.

Fraction B, the non-steam-distillables, amounted to 0.197 g. The infrared spectrum of fraction A in carbon disulfide indicated approximately 70% γ-lactone and 10% δ-lactone.

Kolbe Electrolysis of *cis–syn–cis*-Perhydrodiphenic Acid[13] (IV).—A solution of 1.27 g. (0.0050 mole) of IV in 70 ml. of anhydrous methanol and 5 ml. of 0.20 *N* sodium methoxide was electrolyzed. The electrolyzed solution was treated as described above to give 0.479 g. of liquid, fraction A, from which 0.1 g. of solid crystallized, m.p. 48–52°. This sample contained a small amount of the isomeric γ-lactone which could not be separated. Most of fraction A is a mixture of the isomeric γ-lactones. The infrared spectrum in Nujol mull was identical with the spectrum of the *cis*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (IIIb).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.14; H, 9.68.

Fraction B, the non-steam-distillables, amounted to 0.139 g. The infrared spectrum of fraction A in carbon disulfide indicated approximately 70% γ-lactone and 10% δ-lactone.

Preparation of *trans*-2-(1-Hydroxycyclohexyl)-cyclohexanemethanol (Va).—To 0.40 g. (0.10 mole) of lithium aluminum hydride suspended in 50 ml. of anhydrous ether, a solution of 1.00 g. (0.0048 mole) of IIIa, from the Kolbe electrolysis, in 50 ml. of ether, was added dropwise according to the general procedure of Nystrom and Brown.[14] The mixture was refluxed for 1 hr., cooled and 10% sodium hydroxide was added. The ether was decanted and the precipitate which had formed was triturated with more ether. The combined ether extracts were dried over calcium chloride and concentrated to give 0.918 g. (90%) of the glycol. Recrystallization from pentane yielded a solid, m.p. 92.5–93°.

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39; primary OH equiv., 212. Found: C, 73.40; H, 11.32; primary OH equiv., 233.[15]

The infrared spectrum of a Nujol mull indicated the OH frequency.[16] The quantitative determination of total primary and secondary hydroxyls was made according to the method of Ogg, Porter and Willits.[15]

Oxidation of *trans*-2-(1-Hydroxycyclohexyl)-cyclohexanemethanol (Va).—To a mixture of 0.100 g. (0.00047 mole) of Va, 0.150 g. of potassium hydroxide and 7.5 ml. of water, was added 5 ml. of aqueous potassium permanganate (1:15) according to the general procedure of Billman and Parker.[17]

(10) W. H. Urry, Abstracts of the Twelfth National Organic Chemistry Symposium of the American Chemical Society, Denver, Colo., 1951, p. 36.

(11) M. A. Muhs, Ph.D. Thesis, University of Washington, Seattle, Washington, 1954.

(12) All melting points are corrected.

(13) R. P. Linstead and W. E. Doering, THIS JOURNAL, 64, 1985 (1942).

(14) R. F. Nystrom and W. G. Brown, *ibid.*, 69, 1197 (1947); 69, 2548 (1947).

(15) C. L. Ogg, W. L. Porter and C. O. Willits, *Ind. Eng. Chem., Anal. Ed.*, 17, 394 (1945).

(16) W. Weniger, *J. Opt. Soc. Amer.*, 7, 517 (1923); *Phys. Rev.*, 21, 68 (1923).

(17) J. H. Billman and E. E. Parker, THIS JOURNAL, 65, 2455 (1943).

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The mixture was stirred for 1 hr. and then filtered. Sodium bisulfite was added to the filtrate to remove unreacted potassium permanganate and then the solution was acidified. A cloudy solution was obtained which was placed in the refrigerator. Crystals grew which were filtered and washed with water to give 0.036 g. (37%), 99–99.5°.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.97; H, 9.45.

The infrared spectrum in a Nujol mull indicated a γ-lactone. The spectrum was identical to the spectrum of IIIa.

Preparation of the *trans*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIa).—To a mixture containing 16 g. (0.67 g. atom) of magnesium turnings, 0.5 g. of mercuric chloride and 100 ml. of dry tetrahydrofuran, was added a solution of 94 g. (0.40 mole) of the ethyl ester of *trans*-2-bromocyclohexanecarboxylic acid[18] and 40 g. (0.41 mole) of cyclohexanone in 100 ml. of tetrahydrofuran according to the general procedure of Miller and Nord.[19] The mixture was refluxed overnight on a steam-bath. After stopping the reaction by addition of dilute hydrochloric acid, the reaction solution was extracted with ether. The ether layer was washed with water, aqueous sodium bicarbonate and water again, dried over calcium chloride and concentrated to an oil. The infrared spectrum of a film showed a small amount of γ-lactone. The oil was saponified with 25% potassium hydroxide solution according to the procedure of Miller and Nord.[19] The basic solution was extracted with ether, then acidified and extracted again. The ether extract of the acid solution was dried over calcium chloride and concentrated to a residue. The infrared spectrum of this acid fraction indicated a small amount of γ-lactone. With the aid of a *p*H meter, this acid, dissolved in methanol, was titrated to an equivalence point with aqueous sodium hydroxide. After the addition of water, the solution was extracted with ether and the extract concentrated to an oil. Steam distillation of this oil gave 3.809 g. (4.6%) of the γ-lactone from which 0.740 g. of solid crystallized, m.p. 86–91°. This sample contained a small amount of the isomeric γ-lactone which could not be separated.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.86; H, 9.69.

The infrared spectrum in a Nujol mull indicated a γ-lactone which was identical to the spectrum of the γ-lactone obtained from the electrolyses of I and II.

Isomerization of the *trans*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIa).—A solution containing 0.500 g. (0.0024 mole) of IIIa and 10 ml. of 0.20 *N* sodium methoxide in 200 ml. of anhydrous methanol was refluxed for 12 hr. according to the general procedure of Asselineau, Bory and Lederer.[20] The solution was neutralized with acetic acid, the methanol distilled, and the remainder of the reaction mixture was submitted to steam distillation. Ether extraction of the distillate gave 0.319 g. (64%) of liquid. The infrared spectrum in carbon disulfide indicated it to be a mixture consisting of 9% of the *trans*- and 91% of the *cis*-lactones of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid.

Preparation of the Lactone of 2-(1-Hydroxycyclohexyl)-1,4-cyclohexadiene-1-carboxylic Acid (VI).—A solution of 15 g. (0.082 mole) of the methyl ester of β-(1-hydroxycyclohexyl)-propiolic acid[21] and 70 ml. of freshly distilled butadiene in 150 ml. of benzene was heated for 15 hr. at 190–200° in a glass lined bomb according to the general procedure of Joshel and Butz.[22] The benzene was then removed by distillation under reduced pressure to give 46 g. of gummy residue. This material was leached with hot methanol to give 15.47 g. of an oily solid. Recrystallization from petroleum ether (b.p. 30–60°) gave 11.41 g. (68%) of product, m.p. 90–95°. An analytical sample obtained by further recrystallization melted at 96–97°; λ_{max}^{MeOH} 230 mμ, ϵ_{max} 3,800, ε 210 mμ 6,900.[23]

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.45; H, 7.80.

The infrared spectrum in Nujol mull indicated an unsaturated γ-lactone.[24]

Preparation of the Lactone of 2-(1-Hydroxycyclohexyl)-1-cyclohexene-1-carboxylic Acid (IXa).—Using 0.50 g. of Adams catalyst, 0.300 g. (0.00147 mole) of VI in 100 ml. of ethanol was reduced at 25° in a Parr reduction apparatus at 3 atmospheres, overnight. The partially reduced material was isolated to give 0.268 g. (89%), m.p. 70–73°. An analytical sample obtained by recrystallization from petroleum ether (b.p. 30–60°) melted at 79–80°, λ_{max}^{MeOH} 220 mμ, ϵ_{max} 11,200.[25]

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.53; H, 8.58.

The infrared spectrum in Nujol mull indicated an unsaturated γ-lactone.[24]

Preparation of the *cis*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIb).—A solution of 10.74 g. (0.053 mole) of IXa in 500 ml. of ethanol was reduced at 150° under 100 atmospheres of hydrogen using 10 g. of Raney nickel catalyst. The totally reduced material was recovered to give 9.0 g. (82%) of oil which crystallized on standing, m.p. 50–52°. An analytical sample prepared by recrystallizing from petroleum ether (b.p. 30–60°) melted at 55–56°. This compound showed no appreciable ultraviolet absorption between 400 and 215 mμ.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.75; H, 9.70.

The infrared spectrum in Nujol mull indicated a γ-lactone. The spectrum was distinctly different from the spectrum of the *trans* isomer IIIa.

Preparation of the *cis*- *and trans*-Lactone of 2-(1-Hydroxycyclohexyl)-1-hydroxycyclohexanecarboxylic Acid (VIIIa, VIIIb). Using Colonge's β-Ketol.—To a solution of 50 g. (0.252 mole) of 2-(1-hydroxycyclohexyl)-cyclohexanone[7] and 100 g. of potassium cyanide in 500 ml. of ethanol, 100 ml. of glacial acetic acid was added cautiously in a hood according to the general procedure of Boekelheide and Schilling.[26] The mixture was refluxed overnight, the ethanol removed by atmospheric distillation and the remainder of the reaction mixture poured into water. The infrared spectrum of the water-insolubles indicated an imidic acid ester[27] (VII). The aqueous suspension was digested for 3 hr. on a steam-bath and ether extraction of the cooled mixture gave 50 g. (89%) of product. On standing for a week in a refrigerator, 10 g. of a solid, fraction A, m.p. 150–155°, crystallized out. For convenience, the residual liquid will be called fraction B. Fraction A VIIIa was the *trans* isomer; an analytical sample obtained by several recrystallizations from ethyl ether melted at 159–161°. The infrared spectrum in Nujol mull indicated a hydroxyl group as well as a γ-lactone.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.86; H, 8.99.

Fraction B (VIIIb) was the *cis* isomer; this liquid could not be induced to crystallize. The infrared spectrum of a film indicated a hydroxyl group as well as a γ-lactone.

Using Stanek's β-Ketol.—The above procedure was repeated using 50 g. (0.252 mole) of Stanek's β-ketol,[8] m.p. 166.5–167°, which had given an incorrect analysis (*Anal.* Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 75.65, 75.75; H, 9.76, 9.82), to give 51 g. (89%), m.p. 173–175°. An analytical sample obtained by several recrystallizations from benzene melted at 183–184.5°, but again gave an incorrect analysis. The structure of this compound was not

(18) E. L. Foreman and S. M. McElvain, THIS JOURNAL, **62**, 1438 (1940).

(19) R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 728 (1951).

(20) C. Asselineau, S. Bory and E. Lederer, *Bull. soc. chim. France*, 1524 (1955).

(21) E. R. Jones and M. C. Whiting, *J. Chem. Soc.*, 1423 (1949).

(22) L. M. Joshel and L. W. Butz, THIS JOURNAL, **63**, 3350 (1941).

(23) S. L. Emerman and J. Meinwald, *J. Org. Chem.*, **21**, 375 (1956). The isolated double bond in 1,4-cyclohexadienyl methyl ketone and 1,4-cyclohexadiene-1-carboxylic acid have been reported to show about a shift in both wave length and intensity of maximal absorption; 1,4-cyclohexadienyl methyl ketone exhibits a λ_{max}^{EtOH} at 245 mμ, ϵ_{max} 4000, while 1-cyclohexenyl methyl ketone has a λ_{max}^{EtOH} at 232 mμ, ϵ_{max} 12,500. Similarly, 1,4-cyclohexadiene-1-carboxylic acid exhibits a λ_{max}^{EtOH} at 235 mμ, ϵ_{max} 2500, while 1-cyclohexene-1-carboxylic acid has a λ_{max}^{EtOH} at 212 mμ, ϵ_{max} 11,000.

(24) J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

(25) L. J. Haynes and E. R. H. Jones, *ibid.*, 954 (1946), have reported for the lactone of 2-(1-hydroxycyclohexyl)-acrylic acid λ^{EtOH} 214 mμ, ε 10,000.

(26) V. Boekelheide and W. M. Schilling, THIS JOURNAL, **72**, 712 (1950).

(27) The five-membered cyclic imidic acid ester absorption at 5.9 μ

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determined, but it was obvious that the desired lactone was not obtained.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 69.61; H, 8.99. Found: C, 71.99, 72.16; H, 9.07, 9.16.

The infrared spectrum of a Nujol mull indicated a hydroxyl group as well as a γ-lactone.

Preparation of the Lactone of 2-(1-Hydroxycyclohexyl)-6-cyclohexene-1-carboxylic Acid (IXb) from the Dehydration of the *cis*-Lactone of 2-(1-Hydroxycyclohexyl)-1-hydroxycyclohexanecarboxylic Acid (VIIIb).—To a solution of 50 g. (0.223 mole) of VIIIb in 150 ml. of dry pyridine was added, cautiously, 50 ml. of thionyl chloride according to the general procedure of Boekelheide and Schilling.[26] The mixture was heated overnight on a steam-bath, cooled and poured into ice-water. Ether extraction gave 33 g. (72%) of product, m.p. 67–69°. An analytical sample obtained by several recrystallizations from petroleum ether (b.p. 30–60°) melted at 71–72°, λ_{max}^{MeOH} 220 mμ, ϵ_{max} 11,100. The melting point was depressed, m.p. 63–64°, on admixture with IXa. The infrared spectrum in Nujol mull indicated an unsaturated γ-lactone. The spectrum was distinctly different from IXa.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.90; H, 8.54.

Preparation of the Lactone of 2-(1-Hydroxycyclohexyl)-1-cyclohexene-1-carboxylic Acid (IXa) from the Dehydration of the *trans*-Lactone of 2-(1-Hydroxycyclohexyl)-1-hydroxycyclohexanecarboxylic Acid (VIIIA).—To a solution of 2.0 g. (0.0089 mole) of VIIIa in 10 ml. of dry pyridine was added 4 ml. of thionyl chloride. The reaction was carried out as described above to give 1.65 g. (90%) of product, m.p. 68–75°. An analytical sample obtained by several recrystallizations from petroleum ether (b.p. 30–60°) melted at 79–80°. It was found to be identical (mixed melting point 79–80°, ultraviolet and infrared spectra) with IXa obtained from the reduction of the lactone of 2-(1-hydroxycyclohexyl)-1,4-cyclohexadiene-1-carboxylic acid (VI).

Preparation of the *cis*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIb) from the Reduction of the Lactone of 2-(1-Hydroxycyclohexyl)-6-cyclohexene-1-carboxylic Acid (IXB).—A solution of 33 g. (0.160 mole) of IXb in 500 ml. of ethanol was reduced, using 10 g. of Raney nickel catalyst at 150° and 100 atmospheres of hydrogen. The totally reduced material was recovered to give 25 g. (75%) of an oil which solidified on standing, m.p. 50–53°. An analytical sample obtained by several recrystallizations from petroleum ether (b.p. 30–60°) melted at 55–56° with no appreciable ultraviolet absorption between 400 and 215 mμ. It was found to be identical (mixed melting point, 55–56° and infrared spectra) with IIIb obtained from the reduction of IXa.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; mol. wt., 208. Found: C, 74.76; H, 9.52; mol. wt., 213 (cryoscopic).

Preparation of *cis*-2-(1-Hydroxycyclohexyl)-cyclohexanemethanol (Vb).—A solution of 1.00 g. (0.0048 mole) of IIIb was reduced with lithium aluminum hydride as described above to give 1.00 g. (98%) of glycol. Recrystallization from hexane gave a solid, m.p. 117–118°.

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.42; H, 11.12.

The infrared spectrum in a Nujol mull indicated a hydroxyl group and was distinctly different from the spectrum of the *trans* isomer Va.

Isomerization of the *cis*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIb).—A solution containing 0.104 g. (0.0005 mole) of the *cis*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid was isomerized as described for the *trans* isomer to give 0.047 g. (45%) of liquid. The infrared spectrum in carbon disulfide indicated it to be a mixture consisting of 10% of the *trans*- and 90% of the *cis*-lactones of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid, identical to that obtained from the isomerization of the *trans*-lactone IIIa.

BROOKLYN 1, NEW YORK

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. IX. 1-Azaspiro[4.5]decane and Derivatives[1]

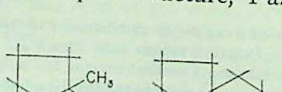
BY ROBERT BRUCE MOFFETT

RECEIVED FEBRUARY 13, 1957

Previous studies in these laboratories have demonstrated that certain compounds containing 2,2-dimethylpyrrolidine (I) are particularly potent anticholinergics. The structurally similar compound, 1-azaspiro[4.5]decane (II), has now been prepared, in which the two methyl groups are joined in a ring. This was incorporated into a variety of compounds of types known to be in general powerful anticholinergics (VIII, IX and XII); however, they had surprisingly little of this type of activity.

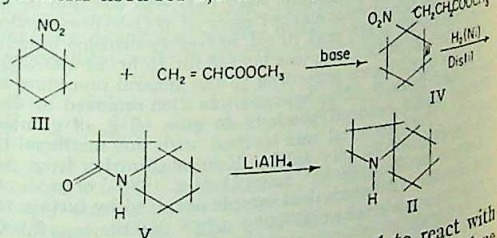
A considerable number of compounds containing the pyrrolidine group have been studied in these laboratories.[2] Of these the 2,2-dimethylpyrrolidine group (I) has been found to be particularly potent when combined, for example, in esters of the type generally used in antispasmodics.[2c]

In extending this work we have investigated the effect of joining the two methyl groups in a ring thus creating the spiro structure, 1-azaspiro[4.5]-decane (II).

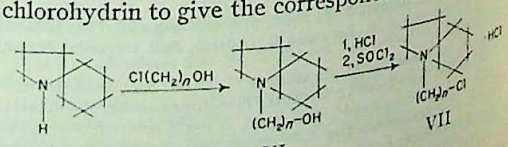


I II

This was accomplished by a modification of the synthesis used for 2,2-dimethylpyrrolidine.[2b]



This spiropyrrolidine was allowed to react with ethylene chlorohydrin and with trimethylene chlorohydrin to give the corresponding 1-(hydroxy-



(1) Presented before the Division of Medicinal Chemistry, A.C.S., at Atlantic City, New Jersey, September, 1956, Abstracts, page 4-N.

(2) (a) R. B. Moffett, *et al.*, *J. Org. Chem.*, **14**, 862 (1949); (b) **17**, 407 (1952); (c) THIS JOURNAL, **77**, 1565 (1955), and preceding papers in this series.

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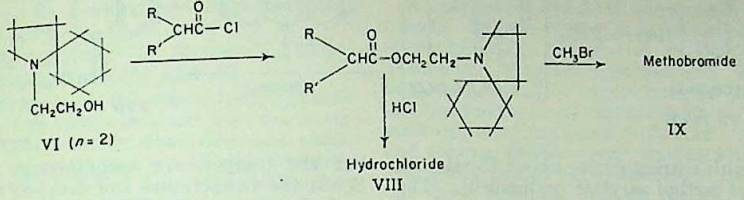
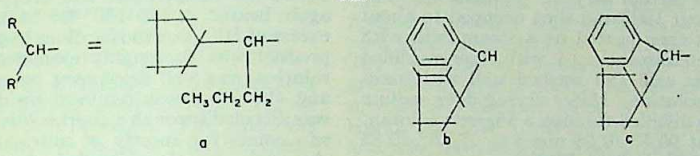
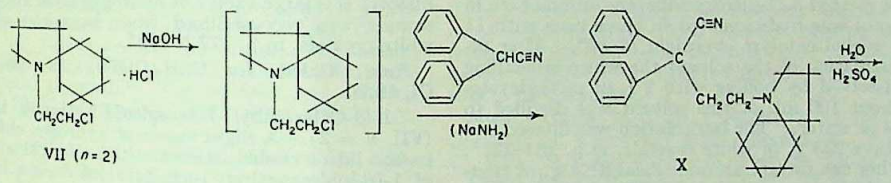
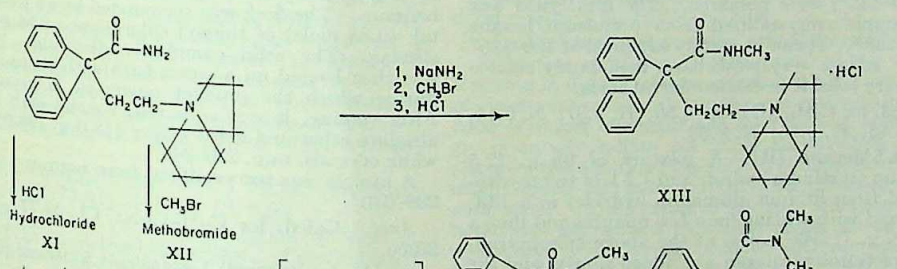
alkyl)-azaspiro[4.5]decane (VI). These in turn were converted to the corresponding chloride hydrochlorides VII with thionyl chloride. The ethanol derivative (VI, $n=2$) was allowed to react with the acid chlorides of several acids which had previously given good anticholinergics.[2c]

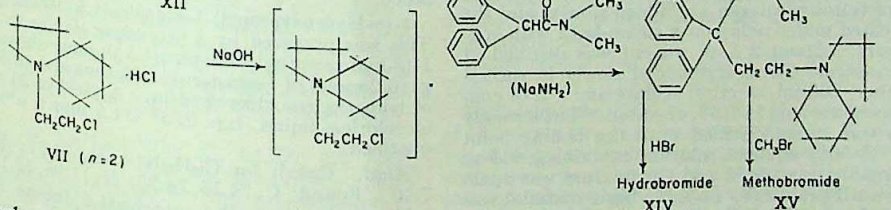




The chlorethyl intermediate was used to alkylate diphenylacetonitrile and the product hydrolyzed to give amides of the type known to include powerful anticholinergics.[3] The mono- and dimethylamides also were prepared.







A few analogs of the phenothiazine antihistamines,[4] antispasmodics[5] and tranquilizing drugs[6] were also prepared.

Pharmacology.—These spiro compounds were tested as anticholinergics both in Thiry-Vella dogs and for their ability to block the depressor response of methacholine in anesthetized dogs. In comparison with structurally related potent anticholinergics such as 2-(2,2-dimethyl-1-pyrrolidyl)-ethyl cyclopentylvalerate hydrochloride (atropine index 1.2)[2c] and α,α-diphenyl-γ-(2,2-dimethyl-1-pyrrolidyl)-butyramide methobromide[7] (atropine index 4), their activities proved to be somewhat lower than anticipated. Compound XII had an atropine index of about 0.5 in Thiry-Vella dogs while the rest had indexes of less than 0.15.

These compounds have been screened in a variety of other pharmacological tests. Preliminary data appear interesting and detailed results will be published elsewhere.

Acknowledgments.—The author is indebted to Dr. Patrick H. Seay, Dr. Walter A. Freyburger and associates of the Department of Pharmacology for the pharmacological results, and to Dr. Richard V. Heinzelman of the Department of Chemistry for guidance.

Experimental[8]

Methyl β-(1-Nitrocyclohexane)-propionate (IV).—To a mixture of 333 g. (2.55 moles) of nitrocyclohexane (du Pont technical grade redistilled), 300 ml. of dioxane (treated with lithium aluminum hydride and redistilled) and 30 ml. of a 35% methanolic solution of benzyltrimethylammonium

(3) M. Bockemühl and G. Ehrhart, *Ann.*, **561**, 52 (1948).
(4) W. B. Reid, J. B. Wright, H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **70**, 3, 100 (1948).
(5) R. A. Robinson and J. W. Cusic, U. S. Patent 2,590,125 (1952).
(6) P. Viaud, *J. Pharm. Pharmacol.*, **6**, 361 (1954).
(7) R. B. Moffett and B. D. Aspergren, U. S. Patent 2,782,206 (1957).
(8) Elemental analyses are by Mr. William A. Struck and staff of the Analytical Chemistry Laboratory.

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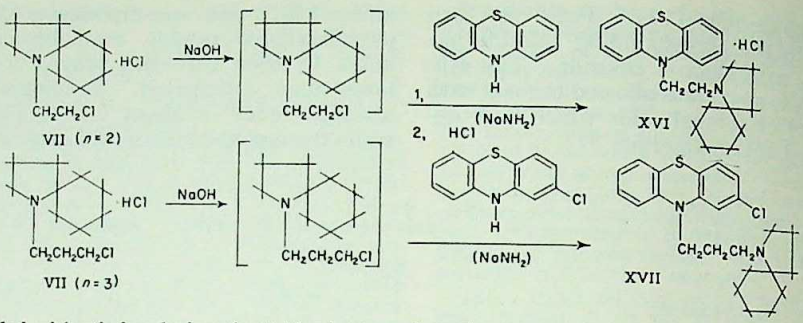

hydroxide was added with stirring during about 15 minutes 227.5 g. (2.55 moles) of methyl acrylate (redistilled). The temperature rose to about 100° and then dropped to about 55°. The mixture was then heated on a steam-bath with stirring for 3 hours, diluted to about 1 l. with ether, acidified with dilute hydrochloric acid and washed well with saturated sodium chloride solution. After drying over sodium sulfate the solution was distilled through a Vigreux column. The product distilled at 96.5° (0.05 mm.) to 124.5° (0.35 mm.); yield 532 g. (96.8%); $n^{25}D$ 1.4710.

A sample redistilled through a short packed column gave a middle fraction of colorless liquid; b.p. 96° (0.025 mm.) $n^{25}D$ 1.4711.

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 56.05; H, 8.02; N, 6.48.

1-Azaspiro[4.5]decan-2-one (V).[9]—A solution of 453.3 g. (2.11 moles) of methyl β-(1-nitrocyclohexane)-propionate in 1.26 l. of ethanol was hydrogenated in three runs with 11 tsp. of Raney nickel catalyst overnight at 50°. After filtration and distillation of the solvent the white crystalline residue was dissolved by boiling with 2 l. of methylcyclohexane and about 100 ml. of this solvent was distilled to remove alcohol or water. The hot solution was filtered and on cooling it gave 253 g. of white crystals, m.p. 131–133°. By concentrating the filtrate an additional 31.4 g. of crystals, m.p. 129–132°, were obtained. The total yield was 88.2%. A sample recrystallized from petroleum hexane had m.p. 132–133°. It can be readily sublimed at 100–135° (0.012 mm.). It is a very weak base, moderately soluble in water and very soluble in dilute mineral acids.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.45; H, 9.85; N, 9.03.

1-Azaspiro[4.5]decane (II).—A mixture of 95 g. (2.5 moles) of lithium aluminum hydride and 1.5 l. of tetrahydrofuran (distilled from lithium aluminum hydride) in a 12-l. flask was refluxed with stirring for a few minutes and then a solution of 206 g. (1.343 moles) of the above spiropyrrolidone in 1.1 l. of tetrahydrofuran was added slowly, and the mixture was heated under reflux on a steam-bath with stirring for 18 hours. About 2 l. of solvent was distilled at atmospheric pressure. Then were added slowly in succession: 1 l. of ether, 200 ml. of ethyl acetate and 1 l. of concentrated hydrochloric acid in 1.5 l. of water. The strongly acidic solution was steam distilled until the boiling point reached 100°. A 50% aqueous solution containing 680 g. of sodium hydroxide was added and the mixture was again steam distilled until practically no more basic material was coming over. About 4 l. of distillate was collected which separated into two layers. This was extracted twice with ether and then continuously extracted with ether for 6 hours. The ether solutions were well dried by shaking with potassium carbonate. After filtration the solution was distilled through an efficient column. After removing the solvent the fraction boiling at 99–104° (42 mm.) was collected; yield, 84%; $n^{25}D$ 1.4817. A sample was redistilled giving a middle fraction of colorless liquid, b.p. 96° (33 mm.), $n^{25}D$ 1.4814.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06; equiv. wt., 139.24. Found: C, 77.95; H, 11.88; N, 9.24; equiv. wt., 140.16.

1-(β-Hydroxyethyl)-1-azaspiro[4.5]decane (VI, $n = 2$).—A mixture of 146.6 g. (1.05 moles) of 1-azaspiro[4.5]decane and 64.6 g. (0.8 mole) of ethylene chlorohydrin was stirred and heated under reflux to 120°. The heating was stopped but the temperature spontaneously rose to about 167°. When the temperature had dropped to 120° the flask was again heated at 130–150° for 15 minutes. After cooling an excess of 50% aqueous sodium hydroxide was added and the product was thoroughly extracted with ether. The ether solution was well dried over potassium carbonate, filtered, and the ether was removed by distillation. The product was distilled through a short column. After removing a forerun consisting mostly of unreacted 1-azaspiro[4.5]decane, the main fraction distilled, b.p. 138° (12 mm.). The yield was 126.2 g. (86.2%) of colorless liquid; $n^{25}D$ 1.5010.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.41; H, 11.87; N, 7.66.

Hydrochloride.—Hydrogen chloride gas was passed into a cooled benzene solution of the above free base. The hydrochloride separated in crystalline form but tended to redissolve if a large excess of hydrogen chloride was used. A sample was recrystallized from isopropyl alcohol giving white crystals, m.p. 177.5–179°.

Anal. Calcd. for $C_{11}H_{22}ClNO$: Cl, 16.13. Found: Cl, 16.30.

1-(β-Chloroethyl)-1-azaspiro[4.5]decane Hydrochloride (VII, $n = 2$).—A slight excess of hydrogen chloride gas was passed into a cooled, stirred solution of 121 g. (0.676 mole) of 1-(β-hydroxyethyl)-1-azaspiro[4.5]decane in 250 ml. of benzene. The flask was surrounded by an ice-bath, and 60 ml. (0.88 mole) of thionyl chloride was added slowly with stirring. The solid completely dissolved. The solution was then heated on a steam-bath with stirring for 2 hours during which the product separated in crystalline form. After cooling, it was collected, washed with benzene and absolute ether and dried giving 158.0 g. (98.0%) of nearly white crystals, m.p. 239–240°.

A sample was recrystallized from isopropyl alcohol, m.p. 239–240°.

Anal. Calcd. for $C_{11}H_{21}Cl_2N$: Cl, 29.77. Found: Cl, 29.50.

1-(γ-Hydroxypropyl)-1-azaspiro[4.5]decane (VI, $n = 3$).—This was prepared by a procedure similar to that used for 1-(β-hydroxyethyl)-azaspiro[4.5]decane above using 27.84 g. (0.2 mole) of 1-azaspiro[4.5]decane and 18.9 g. (0.2 mole) of trimethylene chlorohydrin. A yield of 23.43 g. (59.5%) of colorless liquid, b.p. 155° (11.5 mm.), $n^{25}D$ 1.4979, was obtained.

Anal. Calcd. for $C_{12}H_{23}NO$: C, 73.21; H, 11.75; N, 7.10. Found: C, 74.13, 74.35; H, 11.98, 12.13; N, 7.12.

1-(γ-Chloropropyl)-1-azaspiro[4.5]decane Hydrochloride (VII, $n = 3$).—This was prepared by a procedure similar to that used for 1-(β-chloroethyl)-1-azaspiro[4.5]decane hydrochloride above using 22.4 g. (0.1135 mole) of 1-(γ-hydroxypropyl)-1-azaspiro[4.5]decane, 50 ml. of benzene and 15 ml. (0.2 mole) of thionyl chloride. The product consisted of 26.8 g. (93.6%) of white crystals, m.p. 224–226.5°.

A sample was recrystallized from isopropyl alcohol, m.p. 225–227°.

Anal. Calcd. for $C_{12}H_{23}Cl_2N$: Cl, 28.11. Found: Cl, 28.07

Cyclopentyl-*n*-propylacetate Ester of 1-(β-Hydroxyethyl)-1-azaspiro[4.5]decane Hydrochloride (VIIIa).—To a solution of 9.33 g. (0.05 mole) of 1-(β-hydroxyethyl)-1-azaspiro[4.5]decane in 50 ml. of dry benzene was added 11.3 g. (0.06 mole) of cyclopentyl-*n*-propylacetyl chloride.[10] A white

(9) Swiss Patent 227,125 (1943).

(10) R. B. Moffett, C. A. Hart and J. Neil, *J. Org. Chem.*, **15**, 343

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precipitate separated almost immediately but redissolved on heating under reflux for 3 hours. The red solution was treated with 30 ml. of 10% aqueous sodium hydroxide and extracted well with ether. After washing with water the ether was removed and the product was distilled. A middle fraction of 8.34 g., b.p. 146–147° (0.04 mm.), was dissolved in absolute ether, made acidic with ethanolic hydrogen chloride and further diluted with absolute ether. The hydrochloride was obtained as a white crystalline material, m.p. 151–152°; weight 8.2 g.

Anal. Calcd. for $C_{21}H_{38}ClNO_2$: C, 67.80; H, 10.30; Cl, 9.53. Found: C, 68.21; H, 10.16; Cl, 9.53.

Free Base.—The filtrate from the above hydrochloride was reconverted to the free base, combined with the lower and higher boiling fractions from the distillation and redistilled. A yield of 7.0 g. of nearly colorless oil was obtained, b.p. 146° (0.05 mm.); $n^{25}D$ 1.4879. The total yield of hydrochloride and free base amounted to 85.8%.

Anal. Calcd. for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12; N, 4.17. Found: C, 76.15, 76.53; H, 10.93, 11.16; N, 4.00.

Methobromide (IXa).—To a cold solution of 6.5 g. (0.0194 mole) of the above free base in 25 ml. of methyl ethyl ketone was added 6.2 g. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 2 days. Crystals separated and were collected, washed with methyl ethyl ketone and dried giving 5.06 g. (60.6%) of product, m.p. 152–153°. A small additional yield was obtained from the filtrate.

Anal. Calcd. for $C_{22}H_{40}BrNO_2$: C, 61.38; H, 9.37; Br, 18.57. Found: C, 61.64; H, 9.34; Br, 18.58.

Phenyl-Δ^2-cyclopentenylacetate Ester of 1-(β-Hydroxyethyl)-1-azaspiro[4.5]decane.—This was prepared by a procedure similar to that used for the above ester using 11.6 g. (0.0634 mole) of 1-(β-hydroxyethyl)-azaspiro[4.5]decane, 50 ml. of dry benzene and 15.5 g. (0.07 mole) of phenyl-Δ^2-cyclopentenylacetyl chloride.[11] The product was distilled giving 22.17 g. (95%) of viscous light yellow liquid, b.p. 163° (0.01 mm.).

Anal. Calcd. for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05; N, 3.81. Found: C, 78.80; H, 8.88; N, 3.84.

Hydrochloride (VIIb).—To a solution of 16.3 g. (0.0444 mole) of the above free base in absolute ether was added a slight excess of ethanolic hydrogen chloride. Dilution with more ether caused the hydrochloride to separate as an oil. The solvent was removed by distillation under reduced pressure below 90° and the glassy residue was crystallized from ethyl acetate giving 12.7 g. (71%) of white crystals, m.p. 140–142°.

Anal. Calcd. for $C_{24}H_{34}ClNO_2$: C, 71.33; H, 8.48; Cl, 8.78. Found: C, 71.31; H, 8.37; Cl, 8.96.

Methobromide (IXb).—To a cold solution of 4.55 g. (0.0124 mole) of the above free base in 25 ml. of methyl ethyl ketone was added 5 g. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 5 days. White crystals separated and were collected, washed with methyl ethyl ketone and then with absolute ether and dried; yield 5.0 g. (87.2%); m.p. 167.5–169°.

Anal. Calcd. for $C_{25}H_{36}BrNO_2$: C, 64.92; H, 7.85; Br, 17.28. Found: C, 65.01; H, 7.98; Br, 17.49.

Phenylcyclopentylacetate Ester of 1-(β-Hydroxyethyl)-1-azaspiro[4.5]decane Hydrochloride (VIIIc).—A solution of 9.47 g. (0.0234 mole) of the above hydrochloride in 150 ml. of 95% ethanol was hydrogenated at room temperature and 40 lb. pressure with 0.1 g. of platinum oxide catalyst. The theoretical amount of hydrogen was taken up in 10 minutes. The solution was filtered from the catalyst and distilled nearly to dryness below 40° under reduced pressure. The residue crystallized from ethyl acetate on the addition of ether, giving 7.88 g. (83%) of white crystals, m.p. 152–153.5°.

Anal. Calcd. for $C_{24}H_{36}ClNO_2$: C, 70.99; H, 8.94; Cl, 8.73. Found: C, 71.21; H, 8.99; Cl, 8.77.

α,α-Diphenyl-γ-[1-(1-azaspiro[4.5]decane)]-butyronitrile (X).—A mixture of 38.6 g. (0.2 mole) of diphenylacetonitrile, 300 ml. of dry toluene and 5.06 g. (0.22 mole) of lithium amide was heated under reflux under nitrogen with vigorous stirring for 4 hours.

A solution of 1-(β-chloroethyl)-1-azaspiro[4.5]decane was prepared by shaking 85.9 g. (0.36 mole) of the hydrochloride with ice and 35 ml. of 50% aqueous sodium hydroxide. The mixture was extracted five times with toluene, the toluene solution was well dried over potassium carbonate, and made up to 400 ml.

An aliquot of 244.5 ml. (equivalent to 0.22 mole) of the toluene solution of the chloride was added dropwise with stirring during 30 minutes to the above suspension of lithium salt of diphenylacetonitrile. The mixture was then heated under reflux with stirring for 19 hours. After cooling the mixture was washed with water and the aqueous washings were extracted with ether. The combined ether and toluene solutions were shaken with dilute hydrochloric acid which caused the separation of the hydrochloride as an oily layer insoluble in both the water and toluene. The hydrochloride and aqueous layers were separated, washed with ether and made basic with dilute sodium hydroxide. The free base was extracted with ether and benzene and after washing with water the solvent was removed. The product was distilled giving 46.3 g. of light brown viscous liquid, b.p. 160° (0.02 mm.). On standing, it crystallized and was recrystallized from isopropyl alcohol giving 33.85 g. (47.2%) of white crystals, m.p. 85–90°. A sample was recrystallized again, m.p. 90–92°.

Anal. Calcd. for $C_{25}H_{30}N_2$: C, 83.75; H, 8.44; N, 7.82. Found: C, 83.95; H, 8.45; N, 7.80.

Hydrochloride.—The above moist toluene and ether solutions, from which the oily hydrochloride had separated, on standing deposited white crystals; weight 5.56 g. (7%). This was recrystallized from isopropyl alcohol giving 5.35 g. of white crystals which on slow heating in m.p. tube melted at 123–128° with foaming, then crystallized and remelted at 195–197°. Infrared spectrum and analysis shows this to be a hydrate.

Anal. Calcd. for $C_{25}H_{31}ClN_2 \cdot 2H_2O$: C, 69.67; H, 8.19; Cl, 8.42; N, 6.50; H_2O, 8.36. Found: C, 71.19; H, 8.42; Cl, 8.22; N, 6.80; H_2O (loss of wt. on drying), 8.56.

Calcd. for $C_{25}H_{31}ClN_2$: C, 76.01; H, 7.91. Found (on dried sample): C, 75.74; H, 8.04.

α,α-Diphenyl-γ-[1-(1-azaspiro[4.5]decane)]-butyramide.—A solution of 32.8 g. (0.0915 mole) of the above nitrile free base in 5.5 ml. of concentrated sulfuric acid and 55 ml. of water was heated with stirring on a steam-bath for 4 hours. After standing overnight the solution was poured onto ice giving an oily sulfate salt which dissolved in the aqueous phase on the addition of ether. The aqueous layer was extracted again with ether and the ether solutions were washed with water. The combined aqueous fractions were made basic with ammonium hydroxide giving an oil which soon crystallized. The crude product was recrystallized from 500 ml. of 80% ethanol giving 22.95 g. (66.8%) of crystals, m.p. 169.5–172°.

Anal. Calcd. for $C_{25}H_{32}N_2O$. C, 79.74; H, 8.57; N, 7.44. Found. C, 79.84; H, 8.32; N, 7.40.

Hydrochloride (XI).—A solution of 6.5 g. (0.0173 mole) of the above free base in methanol and 1.6 ml. of concentrated aqueous hydrochloric acid was concentrated on a steam-bath by a stream of nitrogen. Benzene was added and the solution was further concentrated. On cooling it crystallized giving 7.3 g. of white crystalline powder, m.p. 212.5–214.5° (heated slowly in m.p. tube). A sample in a tube placed in the bath at 175° immediately melted, placed in the bath at 160° it partly melted, and placed in the bath at 155° it did not melt.

Anal. Calcd. for $C_{26}H_{33}ClN_2O$: C, 72.70; H, 8.05; Cl, 8.59. Found: C, 72.77; H, 8.12; Cl, 8.63.

Methobromide (XII).—To a cold suspension of 7.53 g. (0.02 mole) of the above free base in 50 ml. of methanol was added 16 g. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 4 days, during which the starting material completely dissolved. The solution was concentrated and diluted with ether giving a gum. This was dissolved in methanol, filtered, concentrated and diluted with methyl ethyl ketone. On boiling on a steam-bath it crystallized giving 8.84 g. (93.7%) of white crystals, m.p. 200–202°.

Anal. Calcd. for $C_{26}H_{35}BrN_2O$: C, 66.23; H, 7.48; Br, 16.95. Found: C, 66.11; H, 7.52; Br, 16.56.

(11) R. Horclois, *Chimie et Industrie*, Special No. p. 357 (April, 1954).

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α,α-Diphenyl-γ-[1-(1-azaspiro[4.5]decane)]-N-methylbutyramide Hydrochloride (XIII).—A suspension of 8.28 g. (0.022 mole) of the above amide free base and 0.97 g. (0.025 mole) of sodium amide in 75 ml. of dry toluene was heated under reflux with stirring for 2 hours. After cooling in an ice-bath, a solution of 2.3 g. (0.024 mole) of methyl bromide in 35 ml. of cold toluene was added dropwise with stirring during 30 minutes. The mixture was stirred at room temperature for 3 hours, cooled and extracted with dilute hydrochloric acid. The solution was made basic with sodium hydroxide giving an oily free base which was extracted out with ether and washed with water, and dried. A slight excess of ethanolic hydrogen chloride was added giving a gummy hydrochloride which crystallized on standing. This was recrystallized from methyl ethyl ketone giving 5.95 g. (63.4%) of white crystals, m.p. 186–188°.

Anal. Calcd. for $C_{26}H_{35}ClN_2O$: C, 73.13; H, 8.26; Cl, 8.30. Found: C, 73.29; H, 7.96; Cl, 8.33.

α,α-Diphenyl-γ-[1-(azaspiro[4.5]decane)]-N,N-dimethylbutyramide.—A mixture of 14.4 g. (0.06 mole) of diphenyl-N,N-dimethylacetamide,[12] 100 ml. of dry toluene and 2.65 g. (0.068 mole) of sodium amide was heated for 2 hours under reflux, under nitrogen with vigorous stirring. After cooling, 72.2 ml. (equivalent to 0.065 mole) of a toluene solution of 1-(β-chloroethyl)-1-azaspiro[4.5]decane (see above under preparation of the nitrile) was added dropwise with stirring during 20 minutes. The mixture was then heated under reflux for 1 hour and allowed to stand overnight. It was washed with water, the washings were extracted with ether, and the ether and toluene solutions were extracted with dilute hydrochloric acid. The extracts were washed with ether and made basic with dilute sodium hydroxide giving a gummy free base which soon crystallized to 23.7 g. of light yellow solid, m.p. 133–145°. This was recrystallized from isopropyl alcohol giving 17.8 g. of nearly white crystals, m.p. 147–152°. Recrystallization from benzene gave 11.32 g. (46.6%) of white crystals, m.p. 149–152°.

Anal. Calcd. for $C_{27}H_{36}N_2O$: C, 80.15; H, 8.97; N, 6.93. Found: C, 80.44; H, 8.93; N, 6.87.

Hydrobromide (XIV).—The filtrates from the recrystallization of the free base were acidified with 48% hydrobromic acid and concentrated. Ether was added giving a gum which solidified on standing. This was dissolved in methyl ethyl ketone and concentrated. Acetone was added and crystals immediately separated. This was recrystallized from methyl ethyl ketone giving 5.7 g. (17.5%) of white crystals, m.p. about 103–110° dec. The total yield of free base and hydrobromide was 64.1%.

This appeared to be a solvate so a 0.1-g. sample in a little ethanol was treated with 2,4-dinitrophenylhydrazine solution giving a 2,4-dinitrophenylhydrazone. This was recrystallized from ethanol, m.p. 116–121°. A mixed melting point with authentic acetone 2,4-dinitrophenylhydrazone (m.p. 125–127°) gave no depression (mixed m.p. 118–124°). A mixed melting point with authentic methyl ethyl ketone 2,4-dinitrophenylhydrazone (m.p. 111–112°) gave a good depression (mixed m.p. 100–102°).

Anal. Calcd. for $C_{27}H_{37}BrN_2O \cdot CH_3COCH_3$: C, 66.28; H, 7.97; Br, 14.70. Found: C, 66.48; H, 7.77; Br, 14.59.

Methobromide (XV).—To a cold suspension of 8.09 g. (0.02 mole) of the free base in 25 ml. of acetone and 40 ml. of methanol was added 10 g. of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 3 days. The starting material completely dissolved. The solution was concentrated on a steam-bath by a stream of nitrogen giving an oil which crystallized. This was triturated with absolute ether, collected and dried giving 9.9 g. of white crystalline product. Recrystallization from methanol gave 9.85 g. (98.8%), m.p. 191–193°.

Anal. Calcd. for $C_{28}H_{39}BrN_2O$: C, 67.32; H, 7.87; Br, 16.00. Found: C, 67.12; H, 8.09; Br, 16.06.

10-[β-(1-(1-Azaspiro[4.5]decane))-ethyl]-phenothiazine Hydrochloride (XVI).—A mixture of 14.0 g. (0.07 mole) of phenothiazine, 100 ml. of dry toluene and 2.93 g. (0.075 mole) of sodium amide was heated under reflux under nitrogen with vigorous stirring for 2 hours. After cooling, 83.3 ml. (0.075 mole) of a toluene solution of 1-(β-chloroethyl)-1-azaspiro[4.5]decane (see above under preparation of the nitrile) was added dropwise with vigorous stirring during 15 minutes. It was then heated under reflux for 19 hours. The mixture was washed with water and then the toluene solution was shaken with 400 ml. of water containing 15 ml. of concentrated hydrochloric acid. An oil separated which soon crystallized. The solid was collected, washed with water and ether and dried, giving 26.8 g. (91.3%) of tan crystals, m.p. 107–130°. This was recrystallized from water giving 25.7 g. of nearly white crystals, m.p. 120–130° dec. Infrared spectrum indicates it is a hydrate.

Anal. Calcd. for $C_{23}H_{29}ClN_2S \cdot H_2O$: C, 65.93; H, 7.46; N, 6.69; Cl, 8.46; S, 7.65. Found: C, 66.10; H, 7.50; N, 6.47; Cl, 8.54; S, 7.96.

10-[γ-(1-(1-Azaspiro[4.5]decane))-propyl]-2-chlorophenothiazine (XVII).—A mixture of 11.7 g. (0.05 mole) of 2-chlorophenothiazine,[13] 2.06 g. (0.053 mole) of sodium amide and 75 ml. of dry toluene was heated under reflux under nitrogen with vigorous stirring for 2 hours.

A mixture of 13.4 g. (0.053 mole) of 1-(γ-chloropropyl)-1-azaspiro[4.5]decane hydrochloride and dilute sodium hydroxide was extracted with 100 ml. of toluene in four portions. The toluene extracts were washed with a little water and well dried over potassium carbonate.

This toluene solution was added slowly during 10 minutes to the suspension of the sodium salt of chlorophenothiazine with vigorous stirring. The mixture was heated under reflux for 8 hours, cooled, washed twice with water and the washings were extracted with ether. The toluene and ether solutions of the free base were shaken with dilute hydrochloric acid. An oily hydrochloride separated insoluble in both layers. The hydrochloride and aqueous layers were separated, washed with ether and made basic with sodium hydroxide. The free base separated as an oil which soon crystallized. The solid was collected, washed with water and dried giving 19 g. of tan solid, m.p. 108–112°. This was crystallized from 100 ml. of ethyl acetate (with treatment with decolorizing charcoal) giving 15.3 g. (74%) of cream-colored crystals, m.p. 114–116°. A small sample recrystallized from acetone gave crystals with the same color and melting point.

Anal. Calcd. for $C_{24}H_{29}ClN_2S$: C, 69.79; H, 7.08; Cl, 8.58. Found: C, 69.83; H, 7.08; Cl, 8.78.

KALAMAZOO, MICHIGAN

(12) B. G. Gokhale, N. L. Pholikar and B. V. Bhide, *J. Univ. Bombay*, **16**, No. 5, 32 (1948); *C. A.*, **43**, 1144 (1949).

(13) P. Charpentier, U. S. Patent 2,645,640 (1953).

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Studies on the Chemical and Enzymatic Oxidation of Lysergic Acid Diethylamide[1]

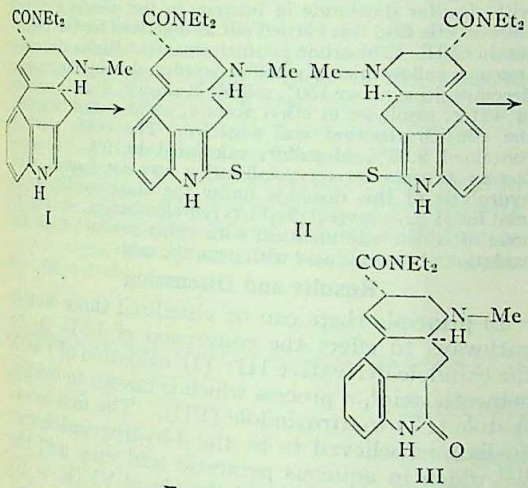
BY K. FRETER, J. AXELROD AND B. WITKOP

RECEIVED OCTOBER 27, 1956

The reaction of the trichloroacetate of lysergic acid diethylamide (I) with disulfur dichloride in benzene yielded the symmetric disulfide II which on reductive acid hydrolysis and purification by multiple countercurrent distribution gave a non-crystalline compound, which was identical in all respects with a product obtained by enzymatic oxidation of I. On the basis of color reactions, alkaline opening to a diazotizable amine and ultraviolet absorption spectrum the oxindole structure III is suggested for this oxidation product.

Introduction

Whereas studies on the metabolic fate of the hallucinogenic (psychotomimetic) lysergic acid diethylamide LSD in intact animals[2-4] have been handicapped by the great potency of I, the formation of a physiologically inactive metabolite (presumably III) was observed in the oxidation by an enzyme present in liver microsomes.[5] This paper describes the formation of III from I by reductive hydrolysis of the disulfide II.



Experimental

Purification of the LSD-Metabolite Obtained by Enzymatic Oxidation.—The solution of the crude metabolite from 5 mg. of LSD[5] in 0.1 *N* hydrochloric acid was evaporated to dryness at 20° in a vacuum desiccator. The residue was taken up in as little methanol as possible and filtered. The concentrated solution was evenly distributed (micropipet) along the starting line of several sheets of Whatman No. 1 filter paper. After completion of the chromatographic process (ascending technique, mixture of 2,4-lutidine–*t*-amyl alcohol, 1:1, saturated with water) the sheets were dried. Stripes of the area corresponding to an R_F-value of 0.85 were cut out under an ultraviolet light and eluted by a descending solvent front of methanol. After evaporation of the solvent there remained about 3 mg. of colorless residue which defied crystallization. No crystalline salts could be obtained. The ultraviolet absorption spectrum showed a sharp peak at 259 mμ.

Conversion of Lysergic Acid Diethylamide (I) to the Disulfide II.—To a suspension of 300 mg. of LSD (I) in 100 ml. of anhydrous benzene was added 500 mg. of anhydrous trichloroacetic acid. A clear solution was obtained by gentle warming. To this solution which was cooled to the point of near-solidification was added within 15 minutes a solution of 69 mg. of disulfur dichloride (S_2Cl_2) in 10 ml. of benzene. After ten more minutes the strongly yellow reaction mixture was poured into 700 ml. of petroleum ether (30–40°). The trichloroacetate of the disulfide II which separated in yellow flakes was collected and washed thoroughly with petroleum ether and ether. The salt was then transferred into a separatory funnel, decomposed with *N* alkali and the free disulfide II exhaustively extracted into ethyl acetate. The orange-colored solution was washed, dried and concentrated. The disulfide was recrystallized for analysis from dioxane–water, m.p. 184°, yield 200 mg. (60% theor.), R_F 0.95 descending technique, 2,4-lutidine–amyl alcohol, 1:1, saturated with water, Fig. 1. The Ehr-

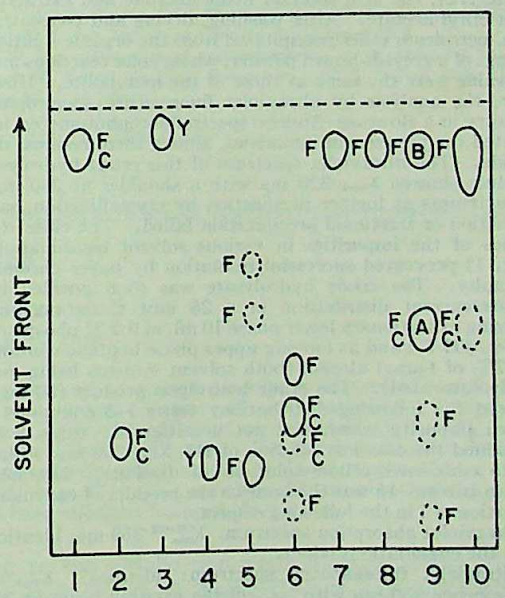


Fig. 1.—R_F-values and analytical determination of the various compounds; solvent system 2,4-lutidine-*t*-amyl alcohol (1:1, saturated with water): 1 = LSD (I); 2 = lysergic acid; 3 = disulfide (II) of LSD; 4 = disulfide of lysergic acid; 5 = hydrolysate of disulfide of lysergic acid; 6 = oxidation of lysergic acid; 7 = hydrolysate of II; 8 = enzymatic oxidation product of I; 9 = oxidation of LSD (I) by peracetic acid to a labile Ehrlich-positive compound A and a stable Ehrlich-negative compound B; 10 = stable Ehrlich-negative oxidation product B of I from Ehrlich-positive oxidation product A by the action of acid. Methods for characterization: F = fluorescence under ultraviolet light; C = color developing after spraying with cinnamaldehyde solution; Y = yellow original color.

(1) Oxidation Mechanisms. XVIII. Previous paper in this series, THIS JOURNAL, **78**, 2873 (1956).

(2) E. S. Boyd, E. Rothlin, J. F. Bonner, I. H. Slater and H. C. Hodge, *J. Pharmacol. and Exper. Therap.*, **113**, 6 (1955).

(3) A. Stoll, E. Rothlin, J. Rutschmann and W. R. Schalch, *Experientia*, **11**, 396 (1955).

(4) V. Lanz, A. Cerletti and E. Rothlin, *Helv. Physiol. Pharmacol. Acta*, **13**, 207 (1955).

(5) J. Axelrod, R. O. Brady, B. Witkop and E. V. Evarts, *Nature*, **178**, 143 (1956); Symposium on Psychotomimetic and Psychotherapeutic Agents, Annals of the New York Academy of Sciences, in press.

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lich reaction was negative, the Keller reaction (concentrated sulfuric acid containing a trace of ferric ion) gave a green color, as a result of the combination of the blue color, characteristic of β-substituted indoles, and of the yellow color of the disulfide II. Reduction with zinc dust in pyridine–glacial acetic acid according to Kuhn and Winterstein[6] gave a colorless solution which formed an insoluble red-brown mercaptide with lead acetate and on standing reoxidized to the yellow solution of the disulfide. The ultraviolet spectrum of II showed the expected displacement to longer wave length: $\lambda_{max}^{CH_3OH}$ 324 (log ε 3.54); lysergic acid tartrate, $\lambda_{max}^{CH_3OH}$ 312 (log ε 3.93).

Anal. Calcd. for $C_{40}H_{48}N_6O_2S_2 \cdot 2H_2O$: C, 64.53; H, 6.98; N, 11.31; S, 8.60. Found: C, 64.72; H, 6.79; N, 11.46; S, 8.83.

No weight loss was observed when the material was dried at 100° *in vacuo*.

Dr. A. Hofmann, Sandoz A. G., Basle, Switzerland, had the kindness to inform us that the same disulfide, m.p. 182°, $[\alpha]^{20}D$ −1020° (pyridine), analyzing for $C_{40}H_{48}N_6O_2S_2$ (recrystallized from dioxane–water, dried at 90° *in vacuo*) has been obtained in his laboratory. A direct comparison of our, with his, sample established the identity.

Hydrolysis of the Disulfide II.—Refluxing of II with 20% acetic acid after a short time led to the evolution of hydrogen sulfide which was trapped as lead sulfide. Although the rate of liberation of H_2S decreased markedly it was still noticeable after 6 hr. On a preparative scale, 200 mg. of disulfide II was dissolved in 30% acetic acid and equidistributed into 5 small glass tubes each of which contained 100 mg. of C.P. zinc dust. The tubes were sealed *in vacuo* and heated to 110° for 16 hr. The contents of the tubes was cooled, lyophilized and the residue taken up in a small volume of methanol, filtered, mixed with a fivefold volume of ether, and filtered again. The filtrate was extracted with dilute HCl, the acid solution made alkaline and extracted with ethyl acetate. After washing, drying and concentration, petroleum ether precipitated from the organic solution 30 mg. of a greyish-brown powder, whose color reactions and R_F-value were the same as those of the metabolite. However, the analysis by ultraviolet fluorescence spectrophotometry in a Bowman–Aminco spectrofluorophotometer[7] indicated the presence of impurities, among them residual disulfide. The ultraviolet spectrum of this crude hydrolysis product showed λ_{max} 320 mμ with a shoulder at 260 mμ. All attempts at further purification by crystallization, salt formation or fractional precipitation failed. The close R_F-values of the impurities in various solvent combinations (Fig. 1) prevented successful resolution by paper chromatography. The crude hydrolysate was then purified by countercurrent distribution in a 25 unit Craig machine utilizing as stationary lower phase 10 ml. of 0.2 *M* phosphate buffer, *p*H 7.4 and as moving upper phase heptane containing 7% of *t*-amyl alcohol (both solvent systems being mutually saturated). The crude hydrolysis product (30 mg.) showed the following distribution: tubes 1–5 contained a brown impurity which was not investigated; tubes 8–15 contained the colorless solution of III, λ_{max} 259 mμ; tubes 20–25 contained yellow solutions of disulfide. The solution in tubes 8–15 was the same as the product of enzymatic oxidation of I in the following respects:

Ultraviolet absorption spectrum: $\lambda_{max}^{CH_3OH}$ 259 mμ, identical with the enzymatic product.

Ultraviolet fluorescence spectrum: identical; λ_{max} of fluorescence 430 mμ with λ_{max} of the exciting beam at 335 mμ.

Distribution Coefficients.—The relative concentrations in aqueous solutions of varying *p*H before and after extraction with various organic solvents were determined by measurement of the per cent. transmission of the maximum of fluorescence at 430 mμ in a Bowman–Aminco spectrofluorophotometer,[7] adjusting the transmission to 100 at the beginning of extraction.

Biphasic systems		Relative concn. of metabolite III	
Inorganic	Organic	By hydrolysis of II	By enzymatic oxidation of I
Phosphate buffer *p*H 7.8	Heptane–5% isoamyl alcohol	70	69
Phosphate buffer *p*H 7.8	Ethylene dichloride	14	15
0.1 *N* hydrochloric acid	Ethyl acetate	42	39

R_F-Values: identical, 0.85, *cf.* Fig. 1.

Ehrlich Reaction: both negative.

Azotest.—Both compounds, after treatment with hot aqueous alcoholic alkali, but not before, showed a diazotizable amino group which coupled after diazotization with an alkaline solution of β-naphthol.

Reaction of Folin and Ciocalteu[8]: both positive.

Oxidation of LSD (I) with Peracetic Acid.—Five milligram samples of LSD (I) were oxidized with 1 ml. of a mixture of glacial acetic acid and 30% hydrogen peroxide ("Superoxol," C.P.) in a ratio of 5:1 at room temperature for ten minutes up to one hour. The reaction mixtures were freeze-dried and chromatographed using the usual solvent mixture. Two discrete spots were observed (Fig. 1). The compound A with R_F 0.5 was obtained on brief oxidation. It gave a positive Ehrlich reaction and had $\lambda\lambda_{max}$ 249 and 310 mμ. On standing in solution or, more rapidly on treatment with acid, rearrangement to an Ehrlich-negative compound B, R_F 0.85 occurred.

Similarly, the action of peracetic acid on lysergic acid produced two different compounds with R_F-values of 0.3 (Ehrlich-positive) and 0.4 (Ehrlich-negative, Fig. 1).

Lysergic Acid Disulfide.—The reaction of lysergic acid with disulfur dichloride in benzene in the presence of trichloroacetic acid was carried out as described for the preparation of II. The crude product separated during the reaction as a yellow microcrystalline powder, showing increasing decomposition above 150°, soluble in alcohol, slightly soluble in water, insoluble in ethyl acetate, acetone and benzene; the Ehrlich reaction was negative. The crude product contained 9.66% of sulfur, calculated 10.70%. A satisfactory process for recrystallization was not found. The hydrolysis of this disulfide under the same conditions as used for II gave several products (chromatogram, see Fig. 1) none of which was identical with either product from the oxidation of lysergic acid with peracetic acid.

Results and Discussion

In principle there can be visualized three simple pathways to effect the conversion of LSD (I) to the oxindole derivative III: (1) oxidation of I with peracetic acid[9], a process which is known to oxidize skatole (IV) to atroxindole (VII). The first intermediate is believed to be the β-hydroxyindolenine V[10] which in aqueous peracetic acid may add the elements of water to yield the glycol VI (R = H) which undergoes acid-catalyzed loss of water (*via* a benzylcarbonium ion) to the oxindole VII. With perbenzoic acid in chloroform the common intermediate V may add peracid to form VI (R = $OCOC_6H_5$) undergoing ring-fission with loss of benzoate anion to give VIII.[11] Two products are formed from I and peracetic acid; an Ehrlich-positive compound A rearranging on standing or by the action of acid to an Ehrlich-negative compound B. If the glycol analog of VI in the lysergic acid series were stable one would have to assume that any possible reaction with *p*-dimethylaminobenzaldehyde would be faster than rearrangement catalyzed by the acid present. No stable α-unsubstituted β-hydroxyindolenines are known and so one does not know whether such compounds may give a color with Ehrlich reagent. However, the scheme glycol (VI) → oxindole (VII) seemed unlikely since it was found that the acid-catalyzed rearrangement of the Ehrlich-positive

(6) R. Kuhn and A. Winterstein, *Ber.*, **65**, 1737 (1932).

(7) R. L. Bowman, P. A. Caulfield and S. Udenfriend, *Science*, **122**, 32 (1955).

(8) O. Folin and V. Ciocalteu, *J. Biol. Chem.*, **73**, 627 (1927).

(9) B. Witkop, *Ann.*, **558**, 98 (1947).

(10) B. Witkop and J. B. Patrick, THIS JOURNAL, **73**, 2196 (1951).

(11) B. Witkop and H. Weitzler, *Ann.*, **558**, 91 (1947).

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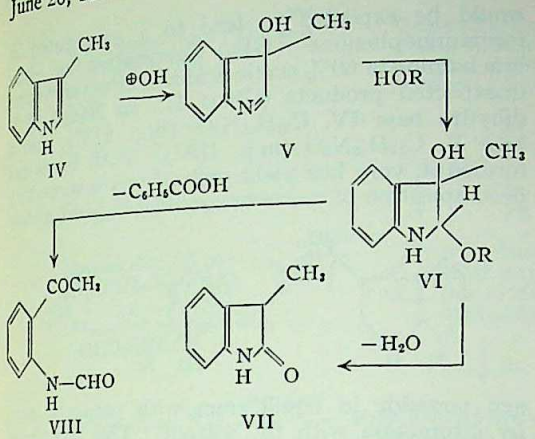

oxidation product of lysergic acid gave a product whose R_F-value was definitely different from the R_F of the presumable oxindole prepared by a more direct method. Such a distinction by paper chromatography was not possible for the analogous products from LSD.

(2) The attempted solvolysis of the commercially available bromination product of LSD, believed to be 2-bromo-LSD because of the negative Hopkins–Cole and Ehrlich reactions, was without success. Even heating with silver oxide for several hours failed to produce silver bromide.

(3) Finally, the reaction of LSD with disulfur dichloride (S_2Cl_2) was investigated. Pyrroles with free α and β-positions[12] and indoles with free α-position[13] are converted by this reagent to symmetrical disulfides. This procedure was applied to the trichloroacetate of LSD in order to prevent the basic tertiary nitrogen from reacting with the disulfur dichloride. The product obtained in this way had all the properties expected from a compound of the disulfide structure II. II is no longer physiologically active.[14] Whereas hydrolysis of the disulfide from tryptophan proceeds smoothly even with water alone, II had to be heated under fairly vigorous conditions with dilute acetic acid and zinc dust. Mineral acid led to resinification, and base could not be used without the danger of losing the amide group. The purification of the hydrolysis mixture by fractionation and countercurrent distribution finally yielded a pure compound which, though not obtained crystalline, was identical with regard to ultraviolet and fluorescence spectra, color reactions, distribution coefficients and R_F-values with the metabolite obtained by enzymatic oxidation of LSD. In addition to the negative Ehrlich and the positive Folin reactions the formation of a diazotizable amino group on treatment with base and the sharp absorption maximum at 259 mμ[15] support the oxindole structure III for this metabolite.

(12) H. Fischer and M. Herrmann, *Hoppe Seyler's Z. Physiol. Chem.*, **122**, 4 (1922).

(13) Th. Wieland, O. Weiberg, E. Fischer and G. Hörlein, *Ann.*, **587**, 146 (1954).

(14) E. V. Evarts, Proc. Symposium on Neurochemistry, Vol. 3, Paul B. Hoeber, Inc., New York, N. Y., in press, 1956.

(15) For a discussion of oxindole spectra, *cf.* R. Goutarel, M. M. Janot, V. Prelog, R. P. A. Sneeden and W. I. Taylor, *Helv. Chim. Acta*, **34**, 1145 (1951).

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

Quebrachamine. I

BY BERNHARD WITKOP

RECEIVED NOVEMBER 19, 1956

Dehydrogenation of quebrachamine, $C_{19}H_{26}N_2$ (II), furnished a mixture of homologous indoles, a mixture of 3-methyl-5-ethyl- and 3,5-diethylpyridine, a mixture of homologous carbazoles and a propyl derivative of α- or β-carboline. Two major oxidation products, the hydroxy base $C_{19}H_{26}N_2O$, m.p. 188° (V), and an N(a)-acetyldihydroindole base, $C_{21}H_{28}N_2O_2$, m.p. 213° (IV), were obtained on oxidation of II with ozone or hydrogen peroxide in acetic acid. The hydroperoxide VI, formed by catalytic oxygenation of II, on sublimation or warming in polar solvents disproportionated to V and oxygen. V, on catalytic hydrogenation, yielded the hexahydrohydroxy base $C_{19}H_{32}N_2O$, m.p. 177° (IX), which on dehydrogenation with palladium gave a base, $C_{11}H_{17}N$, isolated as the picrate, which also has been obtained from aspidospermine.

Quebrachamine has been isolated from the bark of *Aspidosperma quebracho blanco*,[1] together with aspidospermine and yohimbine or quebrachine, from *Aspidosperma chakensis*, together with spegazzinine,[2] and from the bark of *Gonioma kamassi*.[3,4] It belongs to the small group of crystalline oxygen-free plant bases. It contains an indole system, possibly unsubstituted at the α-position (positive Hopkins–Cole and Ehrlich reactions, red picrate),[5,6] and, judging from its resistance to mild catalytic hydrogenation, no other unsaturation. In addition to the indolic non-basic nitrogen N(a), there is a basic (pK 6.76, Table II) nitrogen N(b) which must be tertiary. The structure of a N-(3-indolylethyl)-1,2,3,4-tetrahydroisoquinoline (I, ring junction *cis* or *trans*)[7] is ruled out for, at least, two reasons: (i) the Hofmann degradation of compounds of type I, *e.g.*, of *chano*desoxyyohimbol[8] gives a volatile base, optically active N-methyl-*trans*-decahydroisoquinoline, in good yield. (ii) Catalytic dehydrogenation of I would lead to isoquinoline. Quebrachamine methiodide gives no easily volatile base on attempted Hofmann degradation, and the dehydrogenation of the free alkaloid does not lead to an isoquinoline.

(1) O. Hesse, *Ann.*, **211**, 249 (1882).
(2) O. O. Orazi, R. A. Corral, J. S. E. Holker and Carl Djerassi, *J. Org. Chem.*, **21**, 978 (1956).
(3) E. Schlittler and E. Gellért, *Helv. Chim. Acta*, **34**, 920 (1951).
(4) E. Gellért and B. Witkop, *ibid.*, **35**, 114 (1952).
(5) A. J. Ewins, *J. Chem. Soc.*, **105**, 2738 (1914).
(6) E. Field, *ibid.*, **125**, 1444 (1924).
(7) C. Scholz, Dissertation, "Eidgenössische Technische Hochschule," Zürich, 1934, p. 32.
(8) B. Witkop, *this Journal*, **71**, 2559 (1949).

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Dehydrogenation with zinc dust under the conditions applied to yohimbine,[9] C-dihydrotoxiferine-I,[10] gelsemine[11] and aspidospermine[12] yielded four products: (i) The picrate of a base $C_9H_{13}N$. Its melting point (180–181°) was undepressed on admixture with 3,5-diethylpyridine picrate from aspidospermine (m.p. 180–182°).[12] The pyrolytic product apparently contains some 3-methyl-5-ethylpyridine whose picrate (m.p. 191–192°)[13] must be isomorphous with that of the homolog. It is present in an amount small enough not to alter significantly the analysis. The pyrolytic cracking of an ethyl to a methyl side chain is a frequent phenomenon observed also with the indolic degradation products. (ii) The steam-volatile indole fraction yielded a mixture of picrates which were exceedingly difficult to purify. One probably is dealing here with a similar mixture of β-alkylindole picrates as observed in the pyrolysis of yohimbine,[9] C-dihydrotoxiferine[10] and aspidospermine.[12] The non-volatile non-basic fraction formed needles, m.p. 218°, probably a mixture of carbazole and its 2-(or 3-)methyl homolog.[14] Dehydration of quebrachamine with palladium black gave ammonia and, in a yield of 1%, the picrate (m.p. 257°) of a base $C_{14}H_{16}N_2$ (m.p. 202°). Its ultraviolet spectrum (Table I) is suggestive of an α- or β-carboline system of which the dehydrogenation product may be a propyl derivative.

If quebrachamine contains an α-unsubstituted indole system, its formula can be resolved into II. Oxidation by ozone,[15] peracids[16] and oxygen[17] would be expected to lead to a substituted *o*-formaminophenone (III). Ozonization of quebrachamine in 60% acetic acid led, however, to two unexpected products (Chart I): an N(a)-acetyldihydro base IV, $C_{21}H_{28}N_2O_2$ (m.p. 213°), and a base V, $C_{19}H_{26}N_2O$ (m.p. 188°). Both bases are formed in very low yield probably by a secondary decomposition of ozone or ozonides to yield hydrogen peroxide in equilibrium with peracetic acid by interaction with the solvent. The ultraviolet spectra of both compounds ruled out a γ-quinolone system as is sometimes formed from 2,3-disubstituted indoles by intramolecular condensation of the ozonolysis product.[18] The products resulting from prolonged ozonolysis of quebrachamine could not be precipitated by base and were not obtained crystalline. The nature of base IV is disclosed by its spectral resemblance to N-acetylhexahydrocarbazole and by the loss of acetyl on acid hydrolysis to yield a dihydroindole base $C_{19}H_{26}N_2O$ (VII, m.p. 103°) isomeric with the hydroxy base V. The oxygen function in IV is lost on reduction with $LiAlH_4$ and an N(a)-substituted indole base (VIII) is obtained. The unusual N(a)-acetylation in the formation of IV is reminiscent of the acylating power of peracetic acid–sodium bisulfite mixtures[19] and may reflect on the role of quebrachamine as a biogenetic precursor of aspidospermine.

As expected, much higher yields of bases IV and V were observed in the oxidation of quebrachamine with peracetic acid, *i.e.*, mixtures of acetic acid and hydrogen peroxide. By careful control of time and temperature of the reaction (*cf.* Experimental) 90% of base V and 10% of base IV were obtained. With perbenzoic acid only base V was produced.

The infrared and ultraviolet spectra of the base $C_{19}H_{26}N_2O$ (V) suggest a dihydroindole derivative rather than a β-hydroxyindolenine (XII). The second tertiary nitrogen atom N(b) could possibly add to the β-hydroxyindolenine (XII) to form in aqueous or alcoholic solutions a quaternary eseroline type compound XIII. Base V in alcoholic solution does not obey Beer's law and in the determination of the *pK* value (inflection points at 11.9 and 5.65, Table II) which is higher than that of quebrachamine (6.76 in methyl Cellosolve) a marked hysteresis was observed on back-titration indicative of tautomerism (*e.g.*, XII ⇄ XIII). Lithium aluminum hydride reduces base V smoothly to quebrachamine, a type of reduction typical of β-hydroxyindolenines[20] or derivatives such as quinamine,[21] and catalytic reduction of V leads to a hexahydro base IX in which apparently full saturation has been achieved by hydrogenation of

TABLE I

ULTRAVIOLET SPECTRUM OF THE PRODUCT OF PALLADIUM DEHYDROGENATION OF QUEBRACHAMINE IN COMPARISON WITH α- AND β-CARBOLINE

Carboline, m.p. 202°, from quebrachamine	α-Carboline	β-Carboline
349 (3.70)	348 (3.72)[a]	342 (3.71)[a]
335 (3.70)	338 (3.70)	328 (3.70)
288 (4.24)	288 (4.23)	285 (4.2)
235 (4.57)	237 (4.61)	220–230 (4.6)

[a] L. Horner, *Ann.*, **540**, 77 (1939).

(9) B. Witkop, *Ann.*, **554**, 122 (1943); **556**, 111 (1944).
(10) H. Wieland, B. Witkop and K. Bähr, *ibid.*, **558**, 153 (1947).
(11) B. Witkop, THIS JOURNAL, **70**, 1424 (1948).
(12) B. Witkop, *ibid.*, **70**, 3712 (1948).
(13) R. Goutarel, M.-M. Janot, F. Mathys and V. Prelog, *Compt. rend.*, **237**, 1718 (1953).
(14) *Cf.* 1-methylcarbazole, m.p. 120°, has been obtained from C-curarine by H. Schmid, A. Ebnöther and P. Karrer, *Helv. Chim. Acta*, **33**, 1486 (1950); 2-methylcarbazole melts at 259°; 3-methylcarbazole (m.p. 207°) has been identified in the mixture of products from the soda-lime distillation of strychnine acetic acid by K. H. Pausacker and R. Robinson, *J. Chem. Soc.*, 1557 (1947).
(15) B. Witkop, *Ann.*, **556**, 103 (1944).
(16) B. Witkop and H. Fiedler, *ibid.*, **558**, 91 (1947).
(17) B. Witkop and J. B. Patrick, *ibid.*, **567**, 213 (1950).
(18) B. Witkop and S. Goodwin, *ibid.*, **75**, 3371 (1953).
(19) A. H. Soloway and S. L. Friess, *ibid.*, **73**, 5000 (1951).
(20) B. Witkop, *ibid.*, **72**, 2311 (1950).
(21) R. Goutarel, M.-M. Janot, V. Prelog and W. I. Taylor, *Helv. Chim. Acta*, **33**, 150 (1950).

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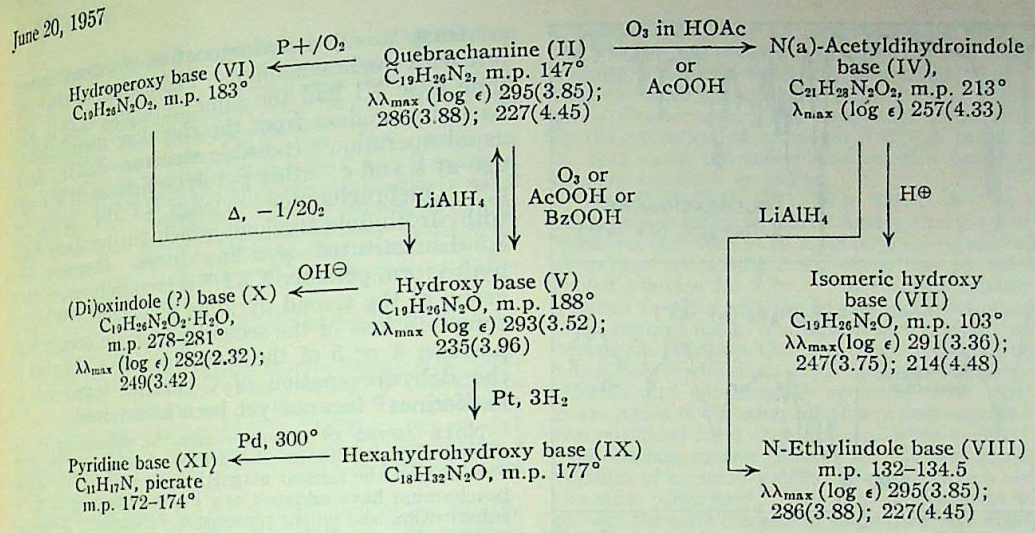
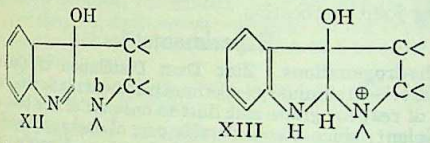


Chart I.—Products obtained in the oxidation of quebrachamine with ozone oxygen and peracids.

the benzene ring (*cf.* infrared spectra, Fig. 1) but with no loss of the hydroxyl group located initially



probably at a benzyl position. This retention of a hydroxyl group would indicate that the reduction of the aromatic ring is faster than the hydrogenolysis of a substituted benzyl alcohol. Base V is also formed from the hydroperoxide VI, obtained by catalytic oxygenation of quebrachamine, by thermal disproportionation: 2R–OOH → 2R–OH + O_2.[22] The most likely position for the initial attack of oxygen is again the β-indole carbon rather than a methylene group adjacent to the indole system or to N(b). Further evidence for the β-hydroxyindoline nature of V comes from the action of alkali which leads to two fractions, one having oxindole or dioxindole properties, the other displaying the spectral characteristics of indoxyl compounds. The formation of indoxyls under much less vigorous conditions has been observed in the autoxidation and rearrangement of the indole alkaloids

TABLE II

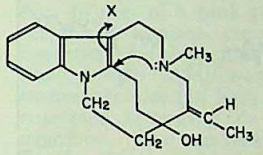
RELATIVE *p*H AND *pK* VALUES OF QUEBRACHAMINE AND SOME OXIDATION PRODUCTS

Compound	Relative basicity 0.01 *M* soln. *p*H, 20°	*pK'* and apparent *pK'* (inflections)	Solvent system
Quebrachamine (II)	8.53	6.76	80% methyl Cellosolve
Hydroxy base V $C_{19}N_{26}N_2O$, m.p. 188°	11.36	(7.43) (10.57)	Water
	12.62	(5.65) (11.9)	80% methyl Cellosolve
Hydroperoxy base VI $C_{19}H_{28}N_2O_2$, m.p. 183°	12.30	(9.65) (12.13)	50% water–ethanol
	12.28	(5.5) (11.0)	80% methyl Cellosolve
N(a)-Acetyl base IV $C_{21}H_{28}N_2O_2$, m.p. 213°	9.1	7.85	40% water–ethanol

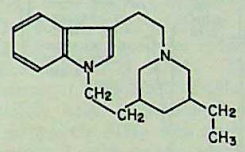
(22) The acid-catalyzed rearrangement of the hydroperoxide VI in chloroform (ref. 17) led to traces only of ketonic material.

(nor)mavacurine to (nor)fluorocurine[23] and of ibogaine to iboluteine.[24]

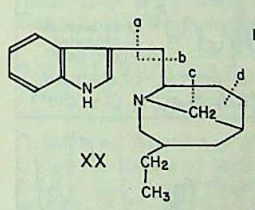
The interaction of N(b) with the double bond of the indole system as the result of a transannular or proximity effect is observed in ϵ_2-dihydromavacurine XVIII which adds a proton (X = H^+) or



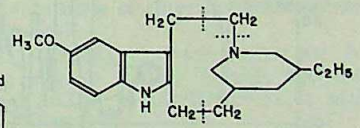
XVIII



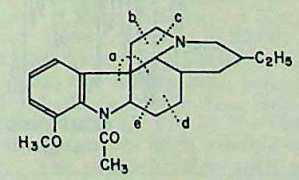
XIX



XX



XXI



XXII

methyl iodide (X = CH_3^+) as indicated by the arrows.[23] A related system XIX would be capable of similar effects. However, the isomeric quebrachamine has a strong narrow NH band in the infrared spectrum (Fig. 1), characteristic of an indole imino group, and its methiodide has an N-methyl and no additional C-methyl group.[25] The expression XX for quebrachamine offers no explanation

(23) H. Bickel, H. Schmid and P. Karrer, *Helv., Chim. Acta*, **38**, 649 (1955); P. Karrer and H. Schmid, *Angew. Chem.*, **67**, 361 (1955).

(24) M. Goutarel, M.-M. Janot, F. Mathys and V. Prelog, *ibid.*, **39**, 742 (1956).

(25) Unambiguous evidence for the presence of an indole imino group in quebrachamine has been obtained by Dr. A. Brossi in these laboratories by ultraviolet observation.

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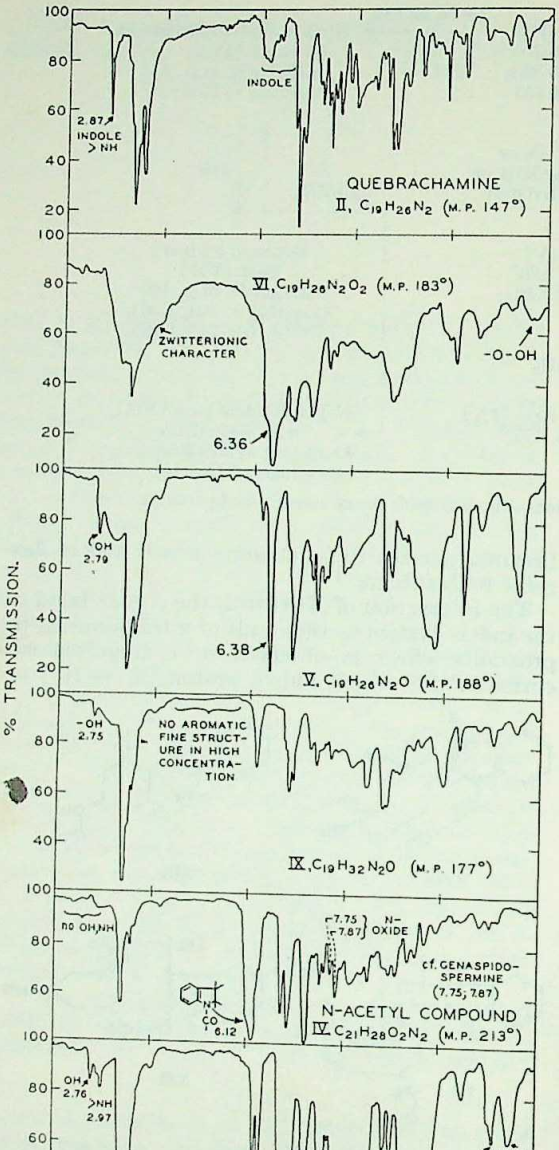

Fig. 1.—Infrared spectra of quebrachamine (II), bases VI, V, IX, IV and VII in chloroform.

for the reactions in chart I but serves as a model to illustrate formally the types of fission observed on dehydrogenation: b → skatol, c → 3-ethylindole + 3,5-diethylpyridine, d → 3-methyl-5-ethylpyridine. Rupture at a would yield indole and 3-ethyl-5 *n*-butylpyridine. The picrate (m.p. 172–174°) of a base of this composition was obtained when the hexahydrohydroxy base, m.p. 177° (IX), was dehydrogenated with palladium. No evolution of ammonia was observed in this dehydrogenation in contrast to all dehydrogenation reactions carried out with quebrachamine. The picrate of the pyridine base XI had the same m.p. and m.m.p. as a basic by-product from the zinc dust distillation of aspidospermine[12] (possible structure XXII, cleavage at a and c; other pyrolytic fissions at b, d and e.[26] Quebrachamine belongs to the family of (dihydro)indole alkaloids which on pyrolysis yield 3,5-disubstituted pyridine bases. Ibogaine (dihydro form possibly XXI)[27] retains only one methyl group of the second pyridine side chain. Whether complete loss of the second side chain occurs from position 4 or 5 of the 3-ethylpyridine obtained in the dehydrogenation of C-curarine[14] and the C-toxiferines[10] has not yet been ascertained.

NOTE ADDED IN PROOF.—Since the submission of this manuscript studies on the deuterium exchange (with K. Freter) and the nuclear magnetic resonance spectra of quebrachamine have adduced new evidence bearing on the α-substitution and on the presence of a N-methyl group. In coöperation with D. H. Conroy, to whom I am most indebted for discussions, NMR spectra and the communication of his results with aspidospermine [H. Conroy, P. N. Brook, K. Rout and N. Silverman, THIS JOURNAL, 79, in press (1957)], formulas for quebrachamine and its transformation products have been postulated which will be discussed in a forthcoming joint publication.

Experimental[28]

Dehydrogenations. Zinc Dust Distillation of Quebrachamine.—Preliminary experiments showed that a ratio of 25 parts of reagent grade zinc dust to one part of free base was insufficient, since a considerable part of unchanged quebrachamine was found in the volatile fraction. For every distillation 50 mg. of quebrachamine was intimately mixed with 7 g. of zinc dust. Fifty such distillations were carried out using the same conditions and equipment as used previously for the dehydrogenations of yohimbine,[9] C-dihydrotoxiferine-I,[10] gelsemine[11] and aspidospermine.[12]

Basic Fraction.—The combined ethereal solutions of the volatile degradation products were concentrated to 50 cc. and extracted with dilute hydrochloric acid. The free bases were liberated from the solution of their hydrochlorides with base and taken up into ether. The more volatile bases were separated from the dark colored residue by steam distillation. The volatile bases were obtained from the steam distillate by salting out with ammonium chloride and extraction with ether. After evaporation of the ether there remained a few drops of a colorless oil with a strong collidine-like odor. The base was dissolved in 2 cc. of dilute hydrochloric acid, and excess aqueous picric acid solution was added. After 1 hr. the supernatant was clear and the flocculent picrate was collected and washed with water. The dry picrate crystallized on trituration with 0.5 cc. of cold acetone. The acetone washing was separated from the residue which on recrystallization from 1 cc. of acetone appeared in fine glistening needles, m.p. 179°. One more recrystallization raised the m.p. to 180–181°, undepressed on admixture with the 3,5-diethylpyridine picrate from aspidospermine.[12]

Anal. Calcd. for $C_9H_{13}N \cdot C_6H_3N_3O_7$: C, 49.45; H, 4.39; N, 15.38. Found: C, 49.23; H, 4.15; N, 15.21.

The basic residue from the steam distillation was taken up into ether. On slow evaporation, or on rubbing the residue with methanol, unchanged quebrachamine (m.p. 144°) was obtained.

Non-basic Fraction.—The ethereal solution from which the bases had been extracted with hydrochloric acid was evaporated and separated into a steam-volatile and non-volatile part. The volatile part had a strong indolic odor and was purified further by distillation *in vacuo*. This purified fraction was dissolved in petroleum ether and con-

(26) J. B. Patrick and B. Witkop, THIS JOURNAL, 76, 5604 (1954).

(27) R. Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955, p. 119.

(28) All melting points are corrected, all boiling points are uncorrected. The analyses were performed by Dr. W. C. Alford and his associates of the Institutes' Analytical Service Laboratory.

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verted into the picrate free of excess picric acid by cautious addition of a warm solution of anhydrous picric acid in petroleum ether (b.p. 60°). Not until after three recrystallizations from benzene–petroleum ether had the picrate lost its stickiness. Four more recrystallizations from benzene raised the m.p. as follows: 104°, 128°, 132°. From the last fraction which was just sufficient for C and H analysis, there was obtained after one more recrystallization a small sample, m.p. 143°, mixed m.p. with the isomorphous mixture of β-methyl- and β-ethylindole picrates (m.p. 154°) from yohimbine, 135–140°. The analysis was done on the picrate, m.p. 132°, and points to the presence of higher homologs of ethylindole.[29]

Anal. Calcd. for $C_{11}H_{13}N \cdot C_6H_3N_3O_7$: C, 52.58; H, 4.15. Found: C, 52.48; H, 4.15.

The analysis of a picrate from mother liquor, m.p. 128°, gave: C, 53.63; H, 4.31. From 3.64 mg. of this picrate there was obtained 0.713 mg. of AgI under the conditions of the Zeisel determination (2.57% "OCH_3") but no AgI under the conditions of the Herzig–Meyer determination.[8] This excludes methylation of the indole imino group in the course of dehydrogenation.[30]

The dark residue of the steam distillation of the volatile indoles was distilled at 140° (0.01 mm.). The colorless crystalline distillate on recrystallization from benzene appeared as sheaves of fine needles, m.p. 218°. The compound has all the properties of the product from the zinc distillation of C-dihydrotoxiferine-I[10] and is probably a mixture of carbazole and some homolog.[14] The Hopkins–Cole reaction is negative, the Ehrlich reaction gives a light-red color in the cold, dark-red on warming, fading on cooling, changing to dark blue-violet on addition of a trace of potassium nitrite.

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.16; H, 6.07; N, 7.73. Found: C, 85.86; H, 5.86; N, 7.51.

Dehydrogenation of Quebrachamine with Palladium Black.—A mixture of 0.5 g. of quebrachamine and 0.5 g. of freshly prepared palladium black was heated in a metal-bath to 320° for 4 hr. At 220° the odor and alkaline reaction (litmus paper) of ammonia was distinctly noticeable and persisted for about 3 hr. The crude dehydrogenation product was taken up in ether and separated from the palladium. The bases were extracted with dilute hydrochloric acid, liberated with alkali and again extracted into ether. After evaporation of the ether the brown semi-solid residue was freed of pyridines at 100° (1 mm.). Subsequent distillation at 180° (0.01 mm.) gave a droplet of a light-yellow oil, solidifying in the cold, which was dissolved in 1.0 *N* HCl and converted into the picrate. The dry picrate was triturated with 0.2 cc. of glacial acetic acid which dissolved dark-colored impurities. The yellow residue was freed of acetic acid with ether. The purified picrate was recrystallized from acetone, in which it is moderately soluble, yielding clusters of needles, m.p. 257° dec. On slow crystallization from more dilute solutions in acetone the picrate appeared in short prisms with the same m.p.

Anal. Calcd. for $C_{14}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 54.67; H, 3.87. Found: C, 54.83; H, 3.73.

By comparison the picrate of β-carboline (norharman) showed a similar dimorphism: from acetone it crystallized in light-yellow fine needles or yellow-red prisms, m.p. 265°, crystalline transformation at 220°, mixed m.p. with picrate from quebrachamine 240°.

Hydrochloride.—The solution of the picrate in acetone was acidified with 4 *N* hydrochloric acid and the picric acid extracted into ether. The solution of the base in hydrochloric acid shows in great dilution the same blue fluorescence as harman or norharman. The dry hydrochloride was recrystallized from ethanol–ether in sheaves of colorless needles, m.p. 210°.

Free Base.—The free base was liberated from the aqueous solution of its hydrochloride by the addition of alkali and extracted into ether. It crystallized from ether in colorless needles, m.p. 202°, mixed m.p. with norharman (m.p. 200°) 186°. For the ultraviolet spectrum *cf.* Table I.

Dehydrogenations of quebrachamine with selenium at 300° led to the evolution of ammonia and yielded, besides volatile products, a neutral compound whose solution in benzene after filtration through alumina showed a strong green fluorescence. The dehydrogenation with sulfur led to the evolution of ammonia and H_2S beginning at 150°. In both cases the amorphous reaction products seemed to contain selenium or sulfur.

Base $C_{21}H_{28}N_2O_2$ (IV), M.p. 213°. A. By Ozonization of Quebrachamine in Acetic Acid.—One gram of quebrachamine was dissolved in 10 cc. of 60% acetic acid and a stream of oxygen containing 2.5% ozone was passed through the cooled solution for 2 hr. The reaction mixture was made alkaline to *p*H 8 and the base which precipitated collected. One obtained 0.4 g. of a light-brown powder, which showed a negative Hopkins–Cole reaction and did not react with dinitrophenylhydrazine. This material was placed in a filter thimble and continuously extracted with ether. On slow evaporation of the ether solution prisms appeared which were recrystallized from acetone in colorless needles, m.p. 213°. The viscous mother liquors on micro-sublimation in the vacuum of a mercury diffusion pump gave a second crop of the same compound. Whereas, on treatment with hot acid or base the pure compound showed no diazotizable aromatic amino group, the same test was positive with the crude ozonization product.

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.2; H, 8.29; N, 8.23. Found: C, 74.74; H, 8.37; N, 7.68.

B. By Oxidation with Peracetic Acid.—A solution of 0.5 g. of quebrachamine in a mixture of 3 cc. of glacial acetic acid and 3 cc. of 30% hydrogen peroxide (Superoxol) was left for 40 hr. at 20°. The slightly pink solution was cooled and brought to a *p*H of 7.5–8.0 with alkali.

The precipitated base, after collecting, washing and drying, 45 mg. of a pink powder, was easily soluble in ether, methanol, acetone, etc. The solution in acetone on slow concentration deposited long glistening needles which were washed with little ice-cold acetone; m.p. 213°. The substance sublimed in high vacuum at 180–200° (bath). The reactions according to Ehrlich and Hopkins–Cole were negative. The azo test for aromatic NH_2 was ambiguous: By the short action of 2 *N* mineral acid on the steam-bath, a diazotizable amine seemed to be formed whereas longer action of 4 *N* hydrochloric acid led to the new base $C_{19}H_{26}N_2O$, m.p. 103° (see below). When analytically pure, negative diazo tests were given regardless of short or prolonged action of acid or alcoholic alkali.

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.2; H, 8.29; N, 8.23; N–$COCH_3$, 12.64; mol. wt., 340.4. Found: C, 74.98, 74.84; H, 8.40, 8.26; N, 8.08; N–CO–CH_3,[31] 11.4; mol. wt., 351, 357 (Rast), 358 (Signer[32]).

Infrared Spectrum ($CHCl_3$).—No band in the OH, NH region; strong and broad band at 6.12 μ (*cf.* aspidospermine 6.13 μ, but N-acetyltetrahydrocarbazole, 5.91 μ); shoulders at 6.20, 6.26; 6.72s; 6.85s; 6.93sh; 7.22s; 7.51w; 7.60w; 7.75w; 7.87m; 8.15w; 8.37vw; 8.50w; 8.95w; 9.08w; 9.33w; 9.49w; 9.68w; 9.92w; 10.29vw; 10.83vw; 11.0w.

Ultraviolet Spectrum (95% EtOH).—λ_{max} (log ε) 257 mμ (4.33); 220 (4.52) end absorption; $\lambda_{min.}$ (log ε) 235 (3.94); *cf.* N-acetylhexahydrocarbazole, λ_{max} (log. ε) 254 (4.21).[33]

Microtitration (Table II, Fig. 2).[34]—The basicity of a $^1/_{250}$ *M* solution of the base in 60% ethanol–water was 9.1 *p*H units at 20°. The microtitration with glass electrode according to Ingold[35] carried out under nitrogen gave *pK* 7.85.[36]

Base VIII, M.p. 132–134.5°, by Reduction of IV with $LiAlH_4$.—When a solution of 80 mg. of base IV in ether was treated with excess $LiAlH_4$ there was a distinct reaction. After the usual work-up an oily reduction product was obtained which crystallized on rubbing with methanol. A still somewhat sticky sample of these crystals showed m.p.

(29) Isomorphous melting point curves (ref. 9) so far have not been recorded for 3-propylindole picrate (m. p. 113–114°).

(30) Cf. Cornanthine → N(a)-methylyobyrine (J. Le Men, *Compt. rend.*, **234**, 1559 (1952); ibogaine → 1,2-dimethyl-3-ethyl-5-hydroxyindole (E. Schlittler, C. A. Burckhardt and E. Gellért, *Helv. Chim. Acta*, **36**, 1237 (1953)).

(31) There was no O–$COCH_3$ according to the micro method of J. F. Alicino, *Anal. Chem.*, **20**, 590 (1948).

(32) R. Signer, *Ann.*, **478**, 246 (1930); *cf.* E. P. Clark, "Semimicro Quantitative Analysis," Academic Press, Inc., New York, N. Y., 1943, p. 78.

(33) H. T. Openshaw and G. F. Smith, *Experientia*, **4**, 428 (1948).

(34) Carried out by A. Peisker-Ritter, Brugg, Switzerland.

(35) W. Ingold, *Helv. Chim. Acta*, **29**, 1929 (1946).

(36) I am greatly indebted to Dr. Henry M. Kissman for carrying out the titrations in methyl Cellosolve.

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132–134.5°. The infrared spectrum of the crude material has no bands in the OH–NH region, 6.22m; 6.72vs; 6.83–6.86s; 7.24–7.26m. The ultraviolet spectrum ($\lambda\lambda_{max}$ (log ϵ) 294 (3.83); 288 (3.85); 231 (4.55)] was almost identical with that of quebrachamine [$\lambda\lambda_{max}$ (log ϵ) 295 mμ (3.85); 286 (3.88); 227 (4.45)]. An analysis of the best crystalline fraction obtained (Found: C, 80.03; H, 12.34) gave a surprisingly high value for hydrogen (Calcd. for $C_{21}H_{26}N_2$: C, 79.68; H, 11.46). The hydrochloride was precipitated from ethereal solution with gaseous HCl as a hygroscopic powder, unsharp m.p. 155–165°; Hopkins–Cole and Ehrlich reactions essentially negative. By carrying out the Ehrlich directions according to Dutcher[37] with material from mother liquors, no color was observed until nitrite was added which produced a dark purple color.

Base VII, $C_{19}H_{26}N_2O$, M.p. 103°, by Acid Hydrolysis of IV.—A solution of 50 mg. of base IV in 4 cc. of 4 *N* HCl was left on the steam-bath for 3 hr. and then taken to dryness in a desiccator at room temperature. The colorless residue was easily soluble in water. From this solution alkali precipitated the flocculent base. The dry base, after two recrystallizations from ether, formed fine colorless needles, m.p. 103°.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.58; H, 8.61; N, 9.14.

Infrared Spectrum ($CHCl_3$).—2.76, 2.96 (NH and OH); 6.18s; 6.27s; 6.73vs; 6.85vs; 6.93sh; 7.21m; 7.27sh; 7.53m; 9.67s; 10.48m; 11.12m; 11.45m.

Ultraviolet Spectrum (95% ethanol).—$\lambda\lambda_{max}$ (log ϵ) 291 (3.36); 247 (3.75); 214 (4.48); $\lambda\lambda_{min}$ (log ϵ) 271 (3.12); 234 (3.65); 222 (4.09). A comparable dihydroindole, *e.g.*, deacetylaspidospermine, shows $\lambda\lambda_{max}$ (log ϵ) 291 3.48); 245 (3.77); 215 (4.42).

Base $C_{19}H_{26}N_2O$ (V), M.p. 188°. A. By Ozonization of Quebrachamine.—The solution from the ozonization of 1 g. of quebrachamine from which the base m.p. 213° had been precipitated at *p*H 8 was made very strongly alkaline with excess 50% NaOH and extracted with ether. On slow evaporation of the ether extract colorless clear prisms were obtained, m.p. 188°.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.82; H, 9.01; N, 9.49.

The ozonization of quebrachamine, even with less than the calculated amount of ozone, invariably led to water-soluble or acidic compounds which were no longer precipitated with base of any strength. When 1 g. of quebrachamine in 15 cc. of methanol was treated with excess 3% ozone under ice cooling, on evaporation 1.3 g. of a light-brown powder was obtained, insoluble in ether, easily soluble in alkali, which did not blue potassium iodide–starch paper. The reaction product with dinitrophenylhydrazone could not be crystallized.

B. By the Action of Perbenzoic Acid on Quebrachamine.—The solution of 184 mg. of quebrachamine in chloroform was left for 24 hr. with 140 mg. of perbenzoic acid in chloroform. The red solution was extracted with dilute alkali to remove the benzoic acid. After evaporation of the solvent the residue was taken up in 2 *N* HCl, brought to *p*H 8, and a small amount of basic material (starting material) removed by extraction with ether. On addition of strong alkali and extraction with ether, 110 mg. of the base $C_{19}H_{26}N_2O$, m.p. 186–188°, was obtained on recrystallization from ether.

C. By the Action of Peracetic Acid on Quebrachamine.—From the filtrate, *p*H 8, of the preparation of the base m.p. 213°, strong alkali precipitated more of a colorless base which on dilution with water went into solution again but which could be extracted with ether. The residue of the dried ether extract weighed 450 mg. Table III lists the yields of the two bases from quebrachamine as function of the time the peracetic acid is allowed to react.

Two recrystallizations from ether furnished large glass-clear prisms, m.p. 188°. After reaction with excess acetic anhydride at room temperature for 24 hr. unchanged starting material was recovered.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.75; H, 8.86; N, 9.68.

On slow recrystallization from acetone clusters of needles were obtained, m.p. 115°. The material gave an insoluble dinitrophenylhydrazone which indicates an acetone adduct. The compound was dried for two days at 100° *in vacuo* and then melted at 178–180°. The analysis was performed on material dried at 20°.

TABLE III

YIELDS OF THE TWO BASES V (M.P. 188°) AND IV (213°) IN THE REACTION OF 500 MG. OF QUEBRACHAMINE WITH A MIXTURE OF 3 CC. OF GLACIAL ACETIC ACID AND 3 CC. OF 30% HYDROGEN PEROXIDE FOR VARIOUS LENGTHS OF TIME AT 20°

Time of reacn., 20° hours	Recovd. quebrachamine, mg.	Base (V) $C_{19}H_{26}N_2O$ m.p. 188°, mg.	Base (IV) $C_{21}H_{28}N_2O_2$ m.p. 213°, mg.	Acidic products not pptd. by base, %
14	200	290	..	...
24	..	470	35	...
40	..	450	45	Little
100	..	..	..	>90

Anal. Calcd. for $C_{19}H_{26}N_2O \cdot CH_3COCH_3$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.52; H, 8.53; N, 8.26.

Rapid recrystallization from acetone led to pure base, m.p. 186–188°, which was used for rotation: $[\alpha]^{20}D$ −504° (*c* 1.0 in 50% aqueous EtOH).

Color Reactions.—Quebrachamine gives a lasting strong purple color in the Hopkins–Cole test; the base m.p. 188° gives a red color (fading to blue-green after 20 hr.) similar to that shown by quebrachamine in high dilution. The Ehrlich reaction gives a pink color in the cold, which becomes red on warming. Samples recrystallized from acetone showed weak or no color in these tests.

Infrared Spectrum ($CHCl_3$).—Distinct sharp band at 2.78, broad and flat band at 3.15, characteristic C–H doublet at 3.42 and 3.57; slight but distinct dip at 4.04 (zwitterionic ammonium structure), very weak aromatic band at 6.20; 6.38vs; 6.86vs; 7.26m; 7.40s; 7.54w; 7.80m; 8.76s; 8.90m; 9.80vs; 10.39s; 10.71m; 11.17vw; 11.54s.

Ultraviolet Spectrum (95% EtOH).—$\lambda\lambda_{max}$ (log ϵ): 293 mμ (3.52); 235 (3.96) at a molar concentration of 1.57×10^{-5}; 294 (3.48) at *c* 1.57×10^{-4}; at *c* 1.57×10^{-3} only linear absorption is observed which at 340 mμ has log ϵ 2.90 and at 360 mμ, 2.0; Beer's law is *not* obeyed.

Microtitration.—The basicity of a 0.01 *M* solution in water was 11.36 *p*H units at 20°. On titration with 0.01 *N* HCl two points of inflection were found: pK 10.57 and 7.43. On back-titration with 0.01 *N* NaOH a marked hysteresis was observed indicating rearrangement during titration.[37] In 80% methyl Cellosolve the *p*H of comparable solutions at the starting point was: quebrachamine 8.53; base V, 12.62. While quebrachamine gave a distinct pK of 6.76, only inflection points at 11.9 and 5.65 were observed for base V. The observed neutralization equivalent was within 3% of the calculated value. The maximum change in *p*H was observed after the addition of the amount of 0.01 *N* HCl in 80% methyl Cellosolve corresponding to 60% of the neutralization equivalent.

Hydrochloride.—The hydrochloride was prepared from ethereal solution with gaseous HCl. It formed a crystalline powder which appeared from chloroform solution on slow concentration in colorless clear prisms, m.p. 285–287° (sublimation 200–240°). Found: C, 65.44; H, 8.54; N, 8.12; Cl, 10.85. Calcd. for $C_{19}H_{26}N_2O \cdot HCl \cdot {}^3/_4H_2O$: C, 65.52; H, 8.25; N, 8.04; Cl, 10.3.

Infrared Spectrum ($CHCl_3$).—2.73vw; 3.14 (broad and strong band); 4.07 (saturated ammonium); 4.27vw, 4.93vw; 6.19m (phenyl or protonated azomethine?), 6.37sh; 6.80vs; 7.25m.

Picrate.—From the solution of the hydrochloride, aqueous picric acid precipitated the amorphous picrate which after collecting, washing and drying crystallized from aqueous acetone in glistening yellow scales, m.p. 173° (clear yellow melt).

Anal. Calcd. for $C_{19}H_{26}N_2O \cdot C_6H_3N_3O_7$: C, 56.02; H, 5.54; N, 13.28. Found: C, 56.49; H, 5.86; N, 13.04.

Hydriodide.—The addition of excess methyl iodide to an ethereal solution of base V led after a few minutes to the precipitation of a crystalline powder which was recrystallized from methanol–ether as needles, m.p. 280° (dec., darkening The reduction of the hydriodide

(37) J. D. Dutcher and A. Kjaer, This Journal, 73, 4140 (1951); [illegible]

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with lithium aluminum hydride or sodium borohydride yielded quebrachamine in good yield.[38]

Anal. Calcd. for $C_{19}H_{26}N_2O\cdot HI$: C, 53.52; H, 6.38; N, 6.58. Found: C, 53.62; H, 6.91; N, 6.88.

The picrate from this hydriodide melted at 172°, the free base, after recrystallization from hexane, melted at 186°, undepressed on admixture with the starting material.

Ultraviolet Spectrum (95% EtOH).—$\lambda\lambda_{max}$ (log ϵ): 291 (3.50); 285 (3.51); 220 (4.38). The solutions obeyed Beer's law.

Reduction of Base V to Quebrachamine with $LiAlH_4$.—To a solution of 200 mg. of base V in ether was added excess $LiAlH_4$. After the reaction had subsided the mixture was left for 1 hr. at room temperature. After the usual work-up the ether-soluble fraction was dissolved in 0.1 *N* HCl and brought to *p*H 7.5. The precipitated base was recrystallized from methanol as colorless prisms, m.p. 145–147°, undepressed on admixture with quebrachamine. The comparison was confirmed by infrared analysis and by conversion to the picrate, red prisms from methanol, m.p. 194°, undepressed on admixture with authentic quebrachamine picrate. A by-product of this reduction was isolated when the aqueous solution was brought from *p*H 8 to 11. In addition to about 60 mg. of an oily ether-soluble base (picrate yellow prisms from MeOH, m.p. 170–172°) 10 mg. of a flocculent ether-insoluble product separated at the interface between water and ether; it formed short prisms from chloroform, m.p. 183–186° (yellow melt). The analysis (C, 66.79; H, 8.57) is reminiscent of the hydrochloride of base V. There was insufficient material for investigation. The infrared spectrum was that of an indole and very similar to, though not identical with, that of quebrachamine. Quebrachamine itself was recovered unchanged after refluxing for 1 hr. with excess $LiAlH_4$ in tetrahydrofuran.

Catalytic Hydrogenation of Base V.—A solution of 0.3 g. of base V in 4 cc. of glacial acetic acid was allowed to take up to 2 equivalents of hydrogen in the presence of 100 mg. of PtO_2. The uptake of hydrogen was slow (10, decreasing to 4 cc./hour). The reduction mixture after separation from the catalyst was brought to *p*H 8. A flocculent base (about 40 mg.) separated which formed beautiful prisms from acetone, m.p. 165°, after two recrystallizations 177°. The mixed m.p. with the starting base was 135–155°. The compound gave negative Hopkins-Cole and Ehrlich tests. Its solution in 95% ethanol had only end absorption in the ultraviolet. A highly concentrated saturated solution in chloroform showed no aromatic fine structure, a narrow band at 2.80 μ, 2.86sh; 3.05sh; 3.12sh; 3.17 (broad band), 6.16m; 6.84s; 6.92sh; 7.27w; 7.41m; 7.70w; 8.85m; 10.05m; 10.37w; 11.05.

Anal. Calcd. for $C_{19}H_{32}N_2O$: C, 74.95; H, 10.59; N, 9.20. Found: C, 74.78; H, 10.47; N, 8.91.

Further addition of 50% alkali to the aqueous reaction mixture precipitated two additional basic fractions at *p*H 12 and 14, which were taken up in ether separately. Slow crystallization of the latter fraction from acetone overnight at 0° yielded cushions of colorless needles, m.p. 136–138°. The Ehrlich reaction gave a wine-red color.

Anal. Calcd. for $C_{19}H_{28}N_2O$: C, 75.95; H, 9.39; N, 9.33. Found: C, 76.38; H, 9.48; N, 9.15.

The ultraviolet and infrared spectra of this "dihydro base" were practically identical with those of the starting material.

Further hydrogenation of the "dihydro base" m.p. 138° gave in the usual work-up at *p*H 8 some hexahydro base (m.p. 175°; C, 74.29, H, 10.45) and at *p*H 14 crystals from acetone, m.p. 141–145° (loss of acetone), resolidification at 165°, second m.p. 175°, mixed m.p. with starting base (m.p. 188°) 135–170°. Found: C, 74.11; H, 9.48; N, 8.65. Calcd. for $C_{19}H_{28}N_2O\cdot CH_3COCH_3$: C, 73.70; H, 9.56; N, 7.81.

Palladium Dehydrogenation of Hexahydrohydroxy Base IX.—In a preliminary experiment *no odor of ammonia* was noticeable when equal parts of base V and palladium black were heated to 300°. The same absence of ammonia was noticed when 500 mg. of the hexahydro base IX and 300 mg. of palladium black were heated in a Späth tube to 300–320° (metal-bath). During the course of 2 hr. 120 cc. of hydrogen was evolved. The dehydrogenation mixture was extracted with ether and the oily bases (104 mg.), after distillation at 150° (14 mm.), extracted into 0.1 *N* HCl. The picrate was made in aqueous solution and recrystallized from methanol; yellow needles were obtained, m.p. 168–170°, recrystallized from acetone, m.p. 172–174°, undepressed on admixture with "picrate A," m.p. 168–172° from aspidospermine.

Anal. Calcd. for $C_{11}H_{17}N\cdot C_6H_3N_3O_7$: C, 52.04; H, 5.14; N, 14.28. Found: C, 51.64; H, 5.43; N, 13.88.

Action of Potassium Hydroxide in Refluxing Amyl Alcohol on V.—A solution of 0.3 g. of the base V and of 1 g. of KOH in 5 cc. of amyl alcohol was refluxed for 1 hr. and then taken to dryness *in vacuo*. In the usual manner the mixture was separated into acidic, neutral and basic fractions. The acid fraction amounted to a few mg. of an ether-soluble oily product with a strong odor reminiscent of butyric or hexahydrobenzoic acid and showed a strong infrared band at 5.85 μ. The ether-soluble neutral fraction was negligible. The ether-soluble basic fraction (120 mg.) was slightly yellow with a powerful green fluorescence. It was purified on a small column of alumina. By careful elution with 10-cc. portions of chloroform–benzene (1:1), the *indoxyl fraction* was obtained pure enough for spectral characterization.

A crystalline fraction from ether, m.p. 142°, was analyzed: C, 67.19; H, 8.33 (Calcd. for $C_{19}H_{26}N_2O_2\cdot 1^1/_2H_2O$: C, 66.83; H, 8.56).

Infrared Spectrum of Indoxyl Fraction ($CHCl_3$).—2.88 μ (NH); 3.05; 4.07 (ammonium); 5.89s (CO of indoxyl); 6.15s (phenyl); 6.72–6.78 (sharp doublet); 7.23w; 7.45m; 7.55m; 8.57m; 9.07s; 10.35m; 11.25w; 11.57w.

Ultraviolet Spectrum of Indoxyl Fraction (95% EtOH).—$\lambda\lambda_{max}$ 392, 290, 234 mμ (log ϵ was not determined because there was not enough material to make a solution of known concentration); *cf.* isoquinamine: $\lambda\lambda_{max}$ (log ϵ): 397 (3.51); 255 (4.0); 232 (4.46).

Oxindole Fraction.—Elution with pure chloroform gave a colorless fraction whose spectral characteristics agree with an oxindole or dioxindole structure. Analysis of a sample, obtained crystalline on trituration with ether (m.p. 295–315° dec.) showed C, 68.65; H, 8.69 (Calcd. for $C_{19}H_{26}N_2O_2\cdot H_2O$: C, 68.64; H, 8.49. Calcd. for $C_{19}H_{26}N_2O\cdot HCl$: C, 68.26; H, 8.14). There was insufficient material for a chlorine determination. The high m.p. and part of infrared data support the salt, the method of preparation and the ultraviolet spectrum and oxindole band do not.

Infrared Spectrum ($CHCl_3$).—2.89 (sharp and narrow NH); 3.13 (broad on band); 3.98 (zwitterion or salt?), 5.84vs (CO of oxindole); 6.15s; 6.80s; 7.25m; 7.37m; 7.53s; 8.52w; 8.72w; 8.88w; 9.08s; 9.34w; 9.55w; 9.82m; 10.05m; 10.19m; 11.20w; 11.58m. By comparison dioxindole showed the following bands (Nujol): 2.92; 3.15; 5.85s; 6.13s; 6.80s; 7.14m; 7.39m; 7.65w; 7.82m; 7.89m; 8.12w; 8.35s; 8.48s; 8.68w; 9.01s; 9.35m; 9.86w; 10.70w; 10.96vw; 11.52w.

Ultraviolet Spectrum (95% EtOH).—$\lambda\lambda_{max}$ (log ϵ): 282 (2.32); 249 (3.42); *cf.* gelsemine: 282 (2.69); 252 (3.33).

A similar compound had been obtained before from a preparation of 2 g. of base V, when the latter was not extracted immediately with ether but left in contact with strong alkali overnight. Most of the collected product was easily soluble in ether. However, there remained a small part which was almost insoluble in ether but soluble in chloroform. On slow evaporation from acetone it formed buttons of birefringent needles, showing a crystalline transformation into slim rods at 212–240°, 273° subliming, 278–281° melting with decomposition. Found: C, 68.57; H, 8.65; N, 8.14. For calcd. values see above.

The infrared spectra of this oxindole (or dioxindole) fraction showed the following bands ($CHCl_3$): 2.70w; 2.78sh; 3.15 (broad); 4.05w; 5.83vs; 6.18s; 6.37vs; 6.84vs; 7.25vw; 7.37s; 7.55m; 7.67w; 7.88w; 8.76w; 8.84–8.88m; 9.24w; 9.81m; 10.15w; 10.38m; 10.70m; 11.55m.

Catalytic Peroxidation of Quebrachamine to the Hydroperoxy Base VI.—A solution of 300 mg. of quebrachamine in 5 cc. of glacial acetic acid was added to a suspension of platinum, obtained by reduction of 100 mg. of PtO_2 in 3 cc. of glacial acetic acid, and shaken under oxygen. One molar equivalent of oxygen (25.5 cc.) was taken up in 90 minutes.

(38) Originally the hydriodide was considered to be the methiodide and the $LiAlH_4$ reduction erroneously interpreted to involve loss of a methyl group; *cf.* B. Witkop and J. B. Patrick, THIS JOURNAL, **75**, 4474 (1953).

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No oxygen uptake was observed when ethyl acetate served as the solvent. The solution was filtered from the catalyst and brought to *p*H 9 by adding 4 *N* KOH at 0°. A negligible amount of basic material separated and was discarded. Concentrated alkali was added at 0°. The resulting base was extracted into ether, in which it was not very soluble. Some of the base crystallized at the interface and was collected by filtration. The residue from the ether extract as well as the crystals from the interface were recrystallized from acetone. Short colorless needles were obtained, m.p. 183° (yellow melt, evolution of gas). The compound turned starch–iodide paper blue.

Anal. Calcd. for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 73.08; H, 8.04; N, 9.24.

Infrared Spectrum ($CHCl_3$).—2.84 μ (weak, broad band); 3.16 (shallow, broad band); 3.98 (shoulder); 4.35vw; 6.20vw; 6.36s; 6.85vs; 7.26w; 7.9w; 7.52w; 8.76m; 8.90m; 9.88w; 10.40m; 11.55m. When VI was left in chloroform solution for two days, a strong new band at 3.17 and a weak band at 5.74 μ developed.

Microtitration.—A 0.01 *M* solution in 50% water–alcohol showed 12.3 *p*H units at 20°. The microtitration gave values of *pK* 12.13 and 9.65. In 80% methyl Cellosolve (starting *p*H 12.28) *pK* inflection points at 11.0 and 5.5 were observed on titration with 0.01 *N* HCl. The neutralization equivalent was within 2% of theory.

Hydrochloride.—The addition of HCl gas to a chloroform solution of the hydroperoxide yielded tufts of needles, sintering and partial melting 180–185°, subliming in needles at 210°, melting again at 275–278°. Found: C, 61.76; H, 7.49; N, 7.33. (Calcd. for $C_{19}H_{26}N_2O_2 \cdot HCl \cdot H_2O$: C, 61.95; H, 7.93; N, 7.60.)

Conversion of the Hydroperoxide VI into the Base V.

A. By Sublimation *in Vacuo*.—A small sample of the hydroperoxide was warmed in a molecular still to 180° (0.001 mm.). The crystalline material, washed down from the "cold finger," crystallized from ether in prisms, m.p. 188°, undepressed on admixture with base V, m.p. 188. The picrate was prepared (m.p. 172°) and identified with the picrate of base V by mixed m.p. and analysis.

B. By Rearrangement of the Hydroperoxide in Chloroform.—A solution of 0.5 g. of hydroperoxide VI in 40 cc. of chloroform, containing a few drops of a 4 *N* solution of HCl in ether, was refluxed until the test with potassium iodide-starch paper was negative. This took 50 minutes. From the chloroform solution there crystallized on cooling clear colorless prisms of a hydrochloride, m.p. 285–287° (sublimation 200–240°). Found: C, 65.68; H, 8.71; N, 8.12; Cl, 11.51. Calcd. for $C_{19}H_{26}N_2O \cdot HCl \cdot {}^3/_4H_2O$: C, 65.52; H, 8.25; N, 8.04; Cl, 10.6.

The infrared spectrum of this hydrochloride was practically identical with that of base V (2.73; 3.14; 4.06w; 6.18vs).

The mother liquors were fractionated on a column of 20 g. of alumina using 10-cc. portions of chloroform for elution. Fractions 4 and 5 (24 mg.) were ether-soluble, gave an ether-insoluble hydrochloride and showed the following bands in the infrared; 3.05 (broad); 5.98vs; 6.21s; 5.97vs; 6.01vs; 6.21s; 6.37m; 6.73vs. The ultraviolet spectrum showed only very weak absorption at 310 mμ where *o*-acylaminophenones absorb. A later fraction 13 (5 mg.) showed the following infrared bands: 3.10 (broad); 5.73s; 6.18s; 6.34s.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

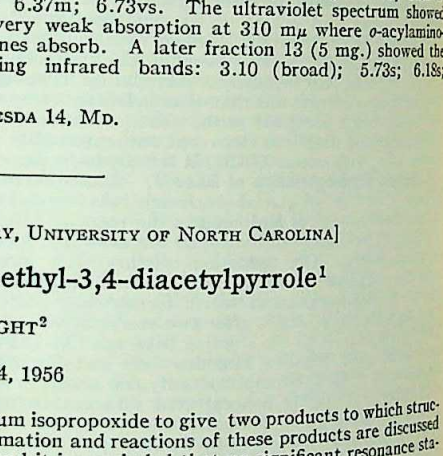
The Self-condensation of 1,2,5-Trimethyl-3,4-diacetylpyrrole[1]

BY D. BRUCE BRIGHT[2]

RECEIVED NOVEMBER 24, 1956

1,2,5-Trimethyl-3,4-diacetylpyrrole condenses in the presence of sodium isopropoxide to give two products to which structures VIII and IX have been assigned as the most probable. The formation and reactions of these products are discussed in connection with the possible aromaticity of the pentalene system, and it is concluded that no significant resonance stability of the pentalene type is present in an apparently favorable case.

With the exception of a few dibenzo-derivatives,[3] previous attempted syntheses of the pentalene system[4] (I) have been unsuccessful. The present work is concerned with the attempted synthesis of an azapentalene. This plan was chosen because the nitrogen analog would be expected to have about the same resonance energy as the carbocycle and the fact that suitable starting materials were readily available. The scheme adopted was to start with a suitably substituted pyrrole nucleus and to form the second five-membered ring by a cyclization reaction. The attempted cyclization of 2,5-dimethyl-3,4-diacetylpyrrole (II) with several basic catalysts was unsuccessful, presumably because of the initial formation of the salt from the acidic N–H group rather than an active methyl group.



Such a cyclization would have resulted in the formation of the bicyclic product IV or its enol VI, a hydroxytrimethylazapentalene. To test the feasibility of this type of cyclization, 1,2,5-trimethyl-3,4-diacetylpyrrole (III), in which the N–H group is substituted, was subjected to treatment with sodium isopropoxide in isopropyl alcohol. The expected product (V) was not obtained but instead two isomeric compounds (A and B) whose analyses

(1) Presented at the 129th Meeting of the American Chemical Society, Dallas, Texas, April, 1956.

(2) Department of Chemistry, Purdue University, Lafayette, Indiana.

(3) C. T. Blood and R. P. Linstead, *J. Chem. Soc.*, 2263 (1952).

(4) For a review see J. W. Cook, "Progress in Organic Chemistry," Vol. III, Butterworths Publications, Ltd., London, 1955, p. 66.

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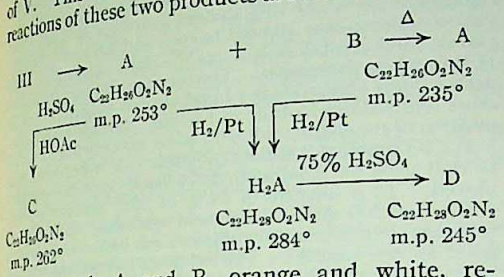
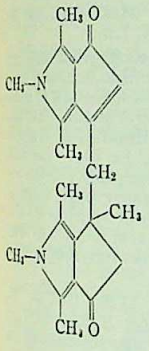
and molecular weights indicated them to be dimers of V. This reaction and some of the subsequent reactions of these two products are shown

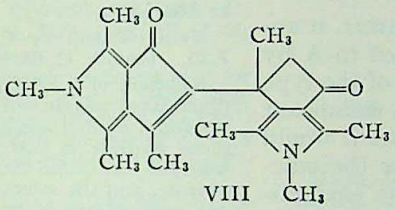


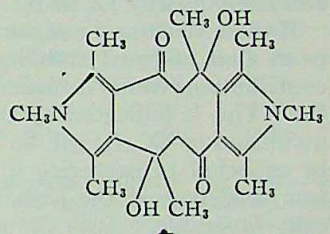
Compounds A and B, orange and white, respectively, could be separated by fractional recrystallization. From a rough separation of A and B from the reaction mixture, it is estimated that A is formed in about 45% yield and B in about 15%. Compound B when heated at its melting point underwent considerable decomposition but was in part converted to its isomer, A. It was observed that A is very sensitive to acids, a fact which hindered the formation of carbonyl derivatives. From the treatment of A with acidic solutions, a light yellow compound (C), isomeric with A and B, was formed in low yield in addition to considerable tar. The hydrogenation of both A and B proceeded readily with platinum oxide catalyst to give the same dihydro-derivative (H_2A). In view of this fact and the marked difference in the ultraviolet spectra of the compounds (see Experimental), it can be concluded that A and B differ only in the position of a double bond. Since compound C is difficult to obtain in a pure state, it proved unfeasible to obtain its hydrogenation product. However, the striking similarity in the ultraviolet spectra of B and C suggests that they have closely related or identical electronic systems. The infrared spectra of both A and B and their derivatives indicated in the above chart all exhibit carbonyl absorption at 5.96–6.01 μ and no absorption in the N–H or O–H regions (see Experimental).

The evidence is fairly conclusive that compound A does not have an acetyl group. The compound is recovered unchanged when treated with sodium hypoiodite while an acetylpyrrole would be expected to undergo the iodoform reaction or suffer replacement of the acetyl group.[5] Furthermore, treatment of H_2A with 75% sulfuric acid, a method for removing acyl and ester groups from a pyrrole nucleus,[6] results only in the isomerization of H_2A to D. The ultraviolet spectra of H_2A and D are essentially identical, suggesting that the conversion may involve only a stereochemical change. The product obtained from the lithium aluminum hydride reduction of A proved to be too unstable to be isolated in a pure state. The attempted oxidation of A with potassium permanganate also was unsuccessful.

Of the possible structures for A consistent with these data and which might logically be formed from III, the most likely appear to be VII and VIII. Their formation can be visualized as an initial cyclization to form V, followed by a Michael reaction with another molecule of V or the intermediate


VII


VIII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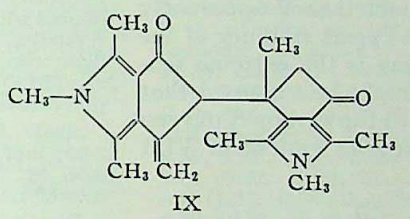
IX

hydroxyketone. An initial intermolecular condensation to form a compound such as X, which might conceivably react further undergoing cyclization and dehydration to form a product with only one double bond outside of the pyrrole rings, appears unlikely since a preparation of A using the dilution technique gave essentially the same results as the normal procedure. Furthermore, the presence of methyl groups in the 1-, 2- and 5-positions of the starting pyrrole (III) would be expected to favor an initial intramolecular condensation.

The experimental facts can be accounted for more readily on the basis of structure VIII rather than VII. Thus if compound A is VIII, B must be IX, since no other position of the double bond is possible. Catalytic hydrogenation of both these structures would be expected to give the same dihydro-derivative with the adjacent substituents on the five-membered ring in a *cis* configuration. The observed isomerization with strong acid may involve conversion to the more stable *trans* isomer. It would be predicted that the dimerization of V *via* a Michael reaction would give VIII (through the intermediate IX) rather than VII, by analogy to the fact that the alkylation of γ-extended enolate ions takes place preferentially in the α-position.[7]

A definite decision between the possible structures VII and VIII for A can be made on the basis of whether or not a methylene group is present in

(5) See H. Fischer and H. Orth, "Die Chemie Des Pyrrols," Vol. I, Akademische Verlagsgesellschaft G.m.b.H., Leipzig, 1934, p. 183.

(6) H. Fischer and E. Bartholomäus, *Z. physiol. Chem.*, **80**, 6 (1912).

(7) E. J. Corey, H. J. Burke and W. A. Remers, THIS JOURNAL, **78**, 189 (1956).

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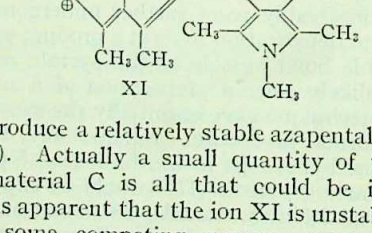
its double bond isomer B. This group would be present in B (IX) if A is correctly formulated as VIII but absent if A is VII. A clear-cut distinction between these two possibilities could not be made by an examination of the infrared spectrum of B. Although the spectrum shows a strong band characteristic of a methylene group[8] (11.47 μ), it is also consistent with a structure containing a trisubstituted ethylene group (the group which would be present in B if A were VII) having an absorption band at 12.06 μ.[8a] However, the presence of a methylene group in B was confirmed readily by ozonolysis of the material, from which formaldehyde was obtained, isolated as its demethone derivative. Thus VII is eliminated as a possibility leaving VIII as the most probable structure for A and consequently IX as B.[9]

If these structural assignments are correct, it appears that no great stability is conferred to A by contributions from resonance structures of the type Va. This is indicated by the fact that significant quantities of IX (B) can be isolated, since it would be expected to isomerize to VIII under the reaction conditions if the isomerization were energetically favorable. Also, the fact that V apparently dimerizes readily indicates no great stability of the system. Especially surprising is the extreme sensitivity of A to acids, as it might be supposed that the attachment of a proton to the carbonyl oxygen of the more unsaturated bicyclic system in VIII



XI

would produce a relatively stable azapentalene cation (XI). Actually a small quantity of the isomeric material C is all that could be isolated. Thus it is apparent that the ion XI is unstable relative to some competing process—presumably a carbonium ion rearrangement. In contrast to this behavior the stability of the more saturated compound D to strong acids should be noted. Thus it appears that these results offer no evidence for the formation of a resonance-stabilized system of the pentalene type in a case which otherwise appears favorable.

(8) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954, pp. 31–46. (b) D. E. Applequist and J. D. Roberts, THIS JOURNAL, **78**, 4012 (1956).

(9) The referee has pointed out an apparent inconsistency in the ultraviolet spectra of the products with the proposed structures; namely, that the spectrum of A should exhibit absorption bands at approximately 255 and 310 mμ as found in the spectra of B, C, H_2A and D, since the proposed formulation contains one β-acylpyrrole portion. Two such isolated portions would be present in H_2A and D as formulated. Taking into account the factor of 1/2, the contribution of one acylpyrrole system to the log ϵ values for A is calculated to be 4.11 and 3.64 at 258 and 305 mμ, respectively (using the spectrum of H_2A as a basis). The actual spectrum of A is characterized by lack of fine structure, and the log ϵ values found at these wave lengths are 4.26 and 3.78, respectively. Thus, the spectrum of A is consistent with structure VIII.

Experimental[10]

Attempted Cyclization of 2,5-Dimethyl-3,4-diacetylpyrrole.—One gram of 2,5-dimethyl-3,4-diacetylpyrrole[11] was refluxed in 20 ml. of 10% sodium hydroxide for 1 hr. The yellow solution was allowed to cool, and 0.8 g. of a slightly yellow solid crystallized, m.p. 177–180°; mixed m.p. with II showed no depression. The reaction also was attempted with sodium *t*-butoxide in *t*-butyl alcohol, sodium hydride in ether and sodium hydride in toluene. In each case decomposition of the sodium salt with water gave starting material.

1,2,5-Trimethyl-3,4-diacetylpyrrole.—A procedure similar to that used for 2,5-dimethyl-3,4-diacetylpyrrole[11] was employed. To a mixture of 64 g. of 25% aqueous methylamine and 200 ml. of acetic acid was added 50 g. of *sym*-tetraacetylethane, and the mixture was heated at its boiling point for ten minutes. The red-black solution was allowed to cool and was then basified with an excess of saturated sodium carbonate solution. The solid was removed by filtration and recrystallized from a water–ethanol mixture; yield 29.5 g. (60%)' m.p. 138–140°. A sample purified for analysis by four recrystallizations from dilute ethanol melted at 143–144°.

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.36; H, 7.83; N, 7.25. Found: C, 68.68; H, 7.78; N, 7.18.

Reaction of 1,2,5-Trimethyl-3,4-diacetylpyrrole with Sodium Isopropoxide.—A solution of sodium isopropoxide in isopropyl alcohol was prepared by dissolution of 8 g. of sodium hydride in 800 ml. of isopropyl alcohol. To this solution was added 29.5 g. of 1,2,5-trimethyl-3,4-diacetylpyrrole, and the solution was refluxed for 4 hr. The dark red solution was concentrated at water-pump pressure and diluted with water to precipitate an orange solid. After recrystallization from 95% ethanol, about 11 g. (41%) of a light orange product (A) was obtained, m.p. 247–252° with considerable darkening. A sample was recrystallized four times from 95% ethanol; m.p. 251–253°.

Anal. Calcd. for $C_{22}H_{26}O_2N_2$: C, 75.39; H, 7.48; N, 8.00; mol. wt., 350. Found: C, 75.60; H, 7.49; N, 7.91, mol. wt. (cryoscopic in camphor), 306, (ebullioscopic in chloroform), 362.

From a collection of residues from the recrystallization of different fractions of A, recrystallization from 95% ethanol resulted in the separation of two types of crystals: the small orange crystals (A) described above and also some large light yellow crystals with hexagonal faces. Mechanical separation and repeated recrystallization of the yellow crystals from 95% ethanol with treatment with decolorizing charcoal finally gave a white crystalline product (B), m.p. 231–235°.

Anal. Found: C, 74.98, 74.87; H, 7.68, 7.57; N, 7.73, 7.80.

In another experiment a solution of 10 g. of III in 50 ml. of benzene and 250 ml. of isopropyl alcohol was added dropwise to a refluxing stirred solution of the catalyst over a period of 24 hr. The reaction mixture was neutralized with concentrated hydrochloric acid, the sodium chloride removed and the black solution evaporated to dryness *in vacuo*. A rough separation of the products was effected by extraction of B with small portions of 95% ethanol, crystallization of the extract, concentration and further recrystallization. By this procedure a portion of 6.5 g. of the residue gave 3 g. (46%) of crude A, 1.2 g. (18%) of crude B and a tar-like black material (36%) from which no crystalline substance could be isolated. Compound A did not give a positive 2,4-dinitrophenylhydrazine test but apparently underwent the change caused by the acidic solution (see below). Compound A was recovered unchanged when subjected to the iodoform test.

Conversion of B to A.—Two hundred milligrams of B was heated in a test-tube at approximately 230° for five minutes. During this time the material melted and turned black. After cooling, the contents of the tube was dissolved in hot 95% ethanol and allowed to cool. The small quantity of dark orange solid which separated was recrystallized and shown to be A by the identity of its infrared spectrum with that of another sample of A.

(10) Melting points are corrected. Microanalyses were carried out by Weiler and Strauss Microanalytical Laboratory, Oxford, England, and Micro-Tech Laboratories, Skokie, Ill.

(11) See Bellamy and Zimmerman, *Ber.*, **20**, 1760 (1887).

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Conversion of A to C.—One gram of A was dissolved in 10 ml. of acetic acid, and 1 ml. of concentrated sulfuric acid was added at room temperature. The solution immediately turned dark green. The temperature was prevented from rising by cooling in an ice-bath. After five minutes of swirling, the mixture was poured into ice-water from which an oil separated which solidified after a few minutes. Four recrystallizations from absolute ethanol and two from 95% ethanol gave a small amount of light yellow crystals, m.p. 258–262° with darkening.

Anal. Calcd. for $C_{22}H_{26}O_2N_2$: C, 75.39; H, 7.48; N, 8.00; mol. wt., 350. Found: C, 75.17; H, 7.50; N, 8.18; mol. wt. (cryoscopic in camphor), 306.

Hydrogenation of A.—A solution of 2 g. of A in 100 ml. of 95% ethanol with 0.2 g. of Adams catalyst was hydrogenated at about three atmospheres pressure at 55° for 4 hr. After removal of the catalyst, the yellow solution was concentrated and cooled to give 0.8 g. of white solid, m.p. 274–278°, and a second crop of 0.3 g., m.p. 265–270°. Combination and recrystallization raised the melting point to 276–284°. An analytical sample melted at 281–284°.

Anal. Calcd. for $C_{22}H_{28}O_2N_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.94, 75.09; H, 7.78, 7.92; N, 7.65, 7.79.

Hydrogenation of B.—Employing the conditions used for A, 430 mg. of B gave 320 mg. of white crystals which after one recrystallization from 95% ethanol melted at 280–284°. The infrared spectrum of this product was identical with that of the hydrogenation product of A; mixed m.p. 280–283°.

Conversion of H_2A to D.—A mixture of 400 mg. of H_2A and 2.7 ml. of 75% sulfuric acid was heated at approximately 100° for 30 minutes. The solution turned dark red during this period. A solid separated when the mixture was poured into ice-water. Two recrystallizations from 95% ethanol gave 140 mg. of white solid, m.p. 240–243°. An analytical sample melted at 241–243°.

Anal. Calcd. for $C_{22}H_{24}O_2N_2$: C, 74.97; H, 8.01; N, 7.95; mol. wt., 352. Found: C, 74.79, 75.03; H, 7.79, 7.89; N, 7.9, 8.25; mol. wt. (cryoscopic in camphor), 310, 303.

Ozonolysis of B.—A solution of 290 mg. of B in about 100 ml. of ethyl acetate was treated with ozone for 30 minutes after which time the absorption of ozone ceased. The solution was evaporated to dryness under reduced pressure to give a yellow oil. The oil was treated with 75 ml. of 10% sulfuric acid, and about 50 ml. of the mixture was collected by distillation. To the distillate was added a solution of 125 mg. of methone in a few cc. of 95% ethanol followed by a few drops of piperidine. After the solution had been allowed to stand, about 140 mg. of solid separated which after one recrystallization from dilute ethanol melted at 187–188°; mixed m.p. with an authentic sample of the dimethone derivative of formaldehyde showed no depression.

Ultraviolet Spectra.—All the spectra were determined in 95% ethanol.

	λmax, mμ	log ε	λmin, mμ	log ε
A	236	4.42	285	3.68
	338	3.84	405	2.95
	420	2.97		
B	255	4.41	225	4.20
	310	3.80	300	3.78
C	255	4.43	223	4.04
	315	3.80	300	3.75
D	258	4.40	230	3.88
	307	3.94	280	3.78
H_2A	258	4.40	230	3.88
	305	3.94	285	3.82

Major Infrared Absorption Bands.—The potassium bromide pellet technique was employed with a Baird double beam instrument, unless otherwise noted. Bands in the 5–13 μ region are given (in microns). A: 5.96, 6.01 (shoulder at 6.10), 6.23, 6.39, 6.96, 7.13, 7.77, 9.49, 9.82, 11.34, 12.61; B: 5.97 (shoulder at 5.92), 6.10, 6.23, 6.42, 6.92, 7.18, 7.92, 8.10, 8.67, 9.61, 9.88, 11.31, 11.47, 12.06; C (in Nujol): 5.97, 6.08, 6.24, 6.42, 8.07, 8.58, 10.25; D: 6.01 (shoulder at 5.98), 6.27, 6.43, 6.92, 7.18, 7.77, 8.10, 8.59, 8.92; H_2A: 6.00, 6.22, 6.41, 6.97, 7.17, 7.82, 8.60, 9.22, 9.82, 10.66, 11.17; 1,2,5-trimethyl-3,4-diacetylpyrrole (III): 6.08 (shoulder at 6.03), 6.52, 7.07, 7.23, 7.78, 8.59, 10.27, 10.48.

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE DIVISION OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF WISCONSIN]

Analogs of Tetracycline. I. Preparation of 1-(2-Hydroxyphenyl)-3-(2-ketocyclohexyl) Propane-1,3-dione and 1-(2-Hydroxyphenyl)-3-(2-ketocyclohexyl)-3-keto-1-propene

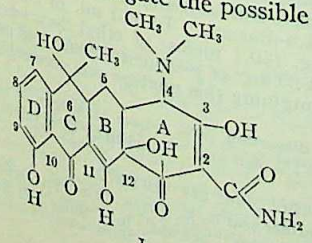
BY EDWARD E. SMISSMAN AND R. BRUCE GABBARD

RECEIVED DECEMBER 3, 1956

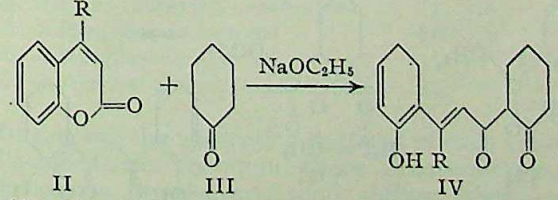
A method for the preparation of A and D ring analogs of tetracycline is discussed. This method, the reaction of coumarins with cyclohexanone, gave rise to 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-3-keto-1-propene and 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-propane-1,3-dione. A preparation for ethyl-2,2-ethylenedioxycyclohexane-carboxylate is given.

We have initiated a study of A-D ring analogs of the tetracycline molecule, I. Our interest was directed toward the preparation of a molecule having the same four oxygen functions as are present in position 1, 10, 11 and 12 of the parent compound.

We decided to investigate the possible formation of our desired system by the reaction of the sodio derivative of cyclohexanone, III, and the properly substituted coumarin, II. The reaction between coumarin and sodio-organic compounds other than sodium alkoxides[1] has not been reported.



I



II III IV

(A) R = H–
(B) R = $-OC_2H_5$
(C) R = –OH

(1) K. Fries and W. Klostermann, *Ann.*, **362**, 1 (1908).

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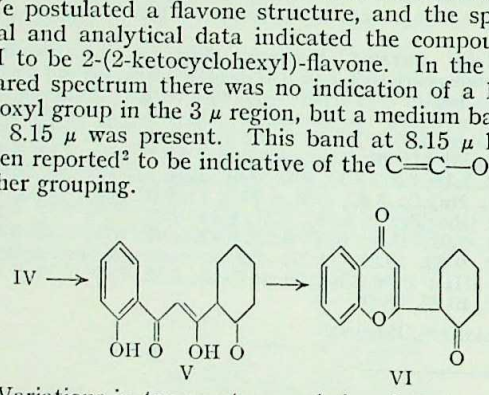
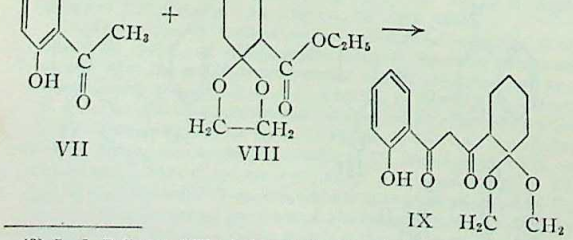
The initial reaction in the series was between coumarin (IIA) and cyclohexanone (III). This reaction was carried out in the presence of sodium ethoxide and gave a 19% yield of 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-3-keto-1-propene (IVA). The reaction was then extended to the use of 4-hydroxycoumarin (IIC), but insolubility of the sodium salt in the reaction solvent prevented it from condensing with the cyclohexanone anion. Logically, we protected the enolic hydroxyl group as the enol ether, and using 4-ethoxycoumarin (IIB), in the reaction with cyclohexanone we obtained 1-(2-hydroxyphenyl)-1-ethoxy-3-keto-3-(2-ketocyclohexyl)-1-propene (IVB). We acidified this product during the workup and the enol ether, IVB, produced 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-propane-1,3-dione (V) in 6% yield. After standing in a 10% aqueous hydrochloric acid solution, V formed a compound VI, which was soluble in 10% sodium hydroxide but not in saturated sodium bicarbonate solution. This compound gave a deep-red color with sulfuric acid. We postulated a flavone structure, and the spectral and analytical data indicated the compound VI to be 2-(2-ketocyclohexyl)-flavone. In the infrared spectrum there was no indication of a hydroxyl group in the 3 μ region, but a medium band at 8.15 μ was present. This band at 8.15 μ has been reported[2] to be indicative of the C=C—O-R ether grouping.



V VI

Variations in temperature and time failed to increase the poor yield of V. We attempted to use sodamide, triphenylmethylsodium and sodium dispersion as catalysts but to no avail.

A second method of preparing the desired compound V was tried. The condensation of 2-hydroxyacetophenone (VII) with ethyl 2,2-ethylenedioxycyclohexanone carboxylate (VIII) would give a product IX, which on acidification should lead to V. The synthesis of ethyl 2,2-ethylenedioxycyclohexanecarboxylate had not been reported, and we were successful in preparing this compound. However, the condensation, using sodium ethoxide as a catalyst, did not take place in amounts great enough to allow us to isolate the desired compound. We did not attempt the condensation using other catalysts.



VII VIII

(2) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

Experimental

1-(2-Hydroxyphenyl)-3-(2-ketocyclohexyl)-3-keto-1-propene (IVA).—A solution of 6 ml. of absolute ethanol in 100 ml. of dry toluene was placed in a 500-ml. three-necked flask. In the presence of a nitrogen blanket, dispersed sodium[3] was added (CARE!) until the toluene solution turned gray (excess sodium). One to two ml. of absolute ethanol was added to discharge the gray color of the suspension. A solution of 9.8 g. (0.1 mole) of cyclohexanone and 14.6 g. (0.1 mole) of coumarin in 100 ml. of dry toluene was added to the contents of the flask. The stirred suspension, initially yellowish-white in color, immediately changed to dark brown and considerable heat was evolved. The solution was stirred for 4 hr. The mixture was shaken with 200 ml. of water and the non-aqueous layer discarded. The aqueous layer was acidified to *p*H 2 with concd. HCl. The milky suspension was extracted twice with ether and on evaporation the ether extracts gave a dark brown viscous oil. This oil was dissolved in 50 ml. of ethanol and a saturated solution of cupric acetate was added until precipitation was complete. The greenish precipitate of the cupric complex was collected and placed in a separatory funnel containing 100 ml. of H_2O and 50 ml. of ether; 25 ml. of concd. HCl was added. The funnel was shaken occasionally to facilitate the decomposition of the copper complex. The ether layer on evaporation gave a brown viscous oil. The oil was dissolved in saturated sodium bicarbonate solution. On acidification, a solid product, 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-3-keto-1-propene monohydrate, separated. It required three to four repetitions of the procedure of dissolving the original material in sodium bicarbonate and acidifying to convert all of the material to the tan monohydrate; yield 5 g. (19%), m.p. 127° dec.

Anal. Calcd. for $C_{15}H_{16}O_3 \cdot H_2O$: C, 68.75; H, 6.88; neut. equiv., 262. Found: C, 68.80, 69.04; H, 6.49, 6.94; neut. equiv., 259.

4-Ethoxycoumarin (IIB).—The method of Anschütz[4] was followed; 4-hydroxycoumarin was treated with equal molar quantity of sodium ethoxide and then allowed to react with ethyl iodide. From 48.6 g. (0.3 mole) of 4-hydroxycoumarin, 25 g. (44%) of colorless prisms of 4-ethoxycoumarin was obtained, m.p. 136–138° (lit. 136°).

1-(2-Hydroxyphenyl)-3-(2-ketocyclohexyl)-propane-1,3-dione (V).—A solution of 3 ml. of absolute ethanol in 100 ml. of dry xylene was placed in a 500-ml. three-necked flask. The procedure was identical to that described for the preparation of IVA using a solution of 9.5 (0.05 mole) of 4-ethoxycoumarin and 5.3 g. (0.5 mole) of cyclohexanone in 100 ml. of dry xylene. The ether extract of the copper complex decomposition gave 0.80 g. of a brownish yellow oil. One hundred mg. of the compound was treated with a solution of 2,4-dinitrophenylhydrazine as described by Shriner and Fuson.[5] Orange needles were obtained from chloroform–alcohol recrystallization, m.p. 206–208°.

Anal. Calcd. for $C_{27}H_{24}N_8O_{10}$: C, 52.26; H, 3.87. Found: C, 52.20; H, 3.89.

2-(2-Ketocyclohexyl)-flavone (VI).—Two hundred milligrams of 1-(2-hydroxyphenyl)-3-(2-ketocyclohexyl)-propane-1,3-dione was allowed to stand in 50 ml. of 10% HCl. The oil solidified to a yellow amorphous mass within two days. After recrystallization from acetic acid–water, 150 mg. (80%) of a yellowish amorphous powder, m.p. 102–104°, was obtained.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.06; H, 6.26. Found: C, 73.72; H, 6.40.

Ethyl 2,2-Ethylenedioxycyclohexanecarboxylate (VIII).—A homogenous, clear solution was prepared by mixing 50 ml. of thiophene-free benzene, 50 ml. of ethylene glycol and 100 ml. of 1,4-dioxane. To 125 ml. of this solution was added 17.6 g. (10.1 moles) of ethyl 2-cyclohexanone carboxylate and 20 mg. of *p*-toluenesulfonic acid monohydrate. The flask containing this mixture was connected to a mois-

(3) Sodium dispersion, 50% sodium by weight, in xylene with 1% Armeen 12 and 1% oleic acid. Supplied by U. S. Industrial Chemicals Company.

(4) R. Anschütz, *Ann.*, **367**, 169 (1909).

(5) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

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June 20, 1957

ture trap and the mixture refluxed until water no longer separated in the trap. The time required was 18 hr. The benzene and dioxane were distilled and the residue was treated with 100 ml. of 1% aqueous sodium hydroxide and the solution extracted twice with 50-ml. portions of ether. The ether was evaporated leaving a liquid which was distilled to give 13 g. (60%) of a colorless material, b.p. 259–261° (atmosphere); 170–174° (14 mm.); $n^{25}D$ 1.4640.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.12; H, 8.24.

MADISON 6, WISCONSIN

[CONTRIBUTION FROM THE RESEARCH LABORATORY, DOJINDO & CO., LTD.]

Polyazobenzenes. III. Infrared Absorption Spectra of Some Polyazobenzenes

BY KEIHEI UENO

RECEIVED DECEMBER 26, 1956

Infrared absorption frequencies from 4000 to 650 cm.$^{-1}$ are reported for seventeen polyazobenzenes including their nitro, amino and hydroxy derivatives. Frequencies are assigned in most cases to bond or group vibrations, and the results are discussed in relation to their structure. Tentative assignment was made for the N=N bond at 1400 and 1455 cm.$^{-1}$.

Introduction

Le Fèvre and his co-workers[1] have investigated some 43 aromatic diazonium and azo compounds and found common absorption bands at around 1406 and 1577 cm.$^{-1}$. However, their result was not conclusive, and more fundamental information on the infrared absorption spectra of aromatic azo compounds is badly needed from both theoretical and practical standpoints. It is the purpose of this investigation to analyze the infrared absorption spectra of polyazobenzenes and their nitro, amino and hydroxy derivatives, as well as polyazostilbenes, which can be considered as model structures of commonly used azo dye molecules. The result of such a study should be of importance in connection with the infrared analysis of azo dyes of more complicated structures.

Experimental

Compounds chosen for this investigation are identical with those which were previously synthesized for our ultraviolet absorption study, and details of their syntheses have been described.[2] Since it was almost impossible to prepare solid samples of stereochemically pure isomers for most of the compounds, the infrared absorption measurements were carried out on samples neglecting their stereochemical purity, although they are believed to consist mainly of *trans* isomers.

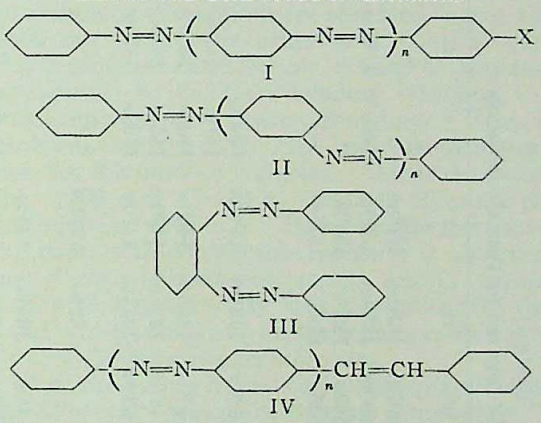
A Perkin-Elmer model 21 double beam spectrophotometer equipped with sodium chloride optics was used for the measurements, and samples were run both as Nujol mulls and as potassium bromide disks. For most of the samples, the Nujol run and the potassium bromide disk run gave almost the same absorption spectra; however, better resolution was observed in the latter technique, and additional bands were found in the region where the Nujol bands overlap.[3]

Result and Discussion

The significant absorption bands observed below 1650 cm.$^{-1}$ are presented in Table II, along with the assignments to the group vibrations wherever possible.

TABLE I

LIST OF THE COMPOUNDS INVESTIGATED



Compound no.	Name of compound	Structural description: Type	n	X
1	Azobenzene	I	0	H
2	4-Phenylazo-azobenzene	I	1	H
3	4,4′-Bis-(phenylazo)-azobenzene	I	2	H
4	4-Hydroxy-azobenzene	I	0	OH
5	4-Hydroxy-4′-phenylazo-azobenzene	I	1	OH
6	4-Phenylazo-4′-(*p*-hydroxyphenylazo)-azobenzene	I	2	OH
7	4-Aminoazobenzene	I	0	NH_2
8	4-Phenylazo-4′-aminoazobenzene	I	1	NH_2
9	4-Phenylazo-4′-(*p*-aminophenylazo)-azobenzene	I	2	NH_2
10	4-Nitroazobenzene	I	0	NO_2
11	4-Phenylazo-4′-nitroazobenzene	I	1	NO_2
12	4-Phenylazo-4′-(*p*-nitrophenylazo)-azobenzene	I	2	NO_2
13	3-Phenylazo-azobenzene	II	1	
14	3,3′-Bis-(phenylazo)-azobenzene	II	2	
15	2-Phenylazo-azobenzene	III		
16	4-Styryl-azobenzene	IV	1	
17	4-Styryl-4′-phenylazo-azobenzene	IV	2	

In general, the absorption patterns of each set of polyazobenzenes are found to be almost identical but become broader and more diffuse when the number of azo linkages increases. The same tendency was reported for the amino acids and the corresponding polypeptides.[4]

(1) R. J. W. Le Fèvre, M. F. O'Dwyer and R. L. Werner, *Australian J. Chem.*, **6**, 341 (1953).

(2) K. Ueno, THIS JOURNAL, **74**, 4508 (1952); K. Ueno and S. Akiyoshi, *ibid.*, **76**, 3667 (1954).

(3) Infrared absorption spectra of some of these compounds have been published in the Sadtler Infrared Catalog; however, their spectra were taken by the Baird double beam spectrophotometer of linear wave length on Nujol mull samples. Since our spectra were recorded in linear wave number with potassium bromide technique, more precise investigation was possible, especially in the 3000 and 1600 cm.$^{-1}$ regions.

(4) H. Neurath and G. R. Schoenborn, THIS JOURNAL, **78**, 366 (1956).

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TABLE II

INFRARED ABSORPTION SPECTRA OF POLYAZOBENZENES

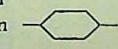
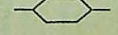
Compound[a]																	
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Assignment
						1621s	1617s	1613s									N–H deform. of $-NH_2$
									1607m	1610m	1609m				1612m		
1575m	1585m	1589s	1600s	1594s	1590s	1601s	1598s	1598s	1590m	1589m	1590m	1585s	1585m	1584s	1595s	1585m	Phenyl ring vibration
			1587s	1565w	1570m	1582m	1586m	1587m	1562w	1565w	1562w				1573m	1565m	
									1525s	1522s	1525s						NO_2 stretch.
	1525w			1520m													
		1502m	1506m	1504s	1502s	1508m	1505s	1505s							1501m	1501w	
1485s	1485m	1484m	1468m	1477m	1485m				1480w	1484m	1482m	1490m		1487s	1485w	1483m	Phenyl ring vibration
												1471s	1470s	1469s			
1455s	1461m	1463m	1456m	1469m	1462w	1465m	1451w	1457w	1467w	1455w	1460w	1460w	1460w	1452s	1462w	1462w	–N═N– stretch.?
	1441m	1440s		1440m	1439w	1450w	1440w	1436w	1455m	1436m	1430w	1457s	1446s	1440s	1450s	1441m	
1395w	1398w	1400m	1417m	1425w		1420m	1417w	1417w	1408w	1411w	1410w	1420w	1420w		1414m	1405w	–N═N– stretch.?
								1402w									
	1382w	1363s	1378m	1379m	1380w					1370w	1371w			1380w	1363w		
					1345w												
									1345s	1341s	1340s						NO_2 stretch.
	1312m		1315w				1316w	1315m	1327m	1322s	1315m	1318w	1318w		1331m		
1298s	1303s	1304s		1305m	1303m	1309s	1300w	1300s	1302m	1306m	1305m	1302m	1303m	1305m	1300m	1302s	–C–N═
						1300m	1276s	1273m									C–N stretch. of $C-NH_2$
								1240w					1268w	1258m	1265w		
			1278s		1288m												} O–H deform.
			1240s	1240s													
1220m	1208m	1212s	1230m	1215m	1212s		1214m	1215s	1212w	1213m	1210m	1227m	1232m	1216m	1220m	1210s	
												1202m	1190w		1190w		
1166m	1166w	1170m	1165m	1162m	1177w		1171m	1175w	1158w	1160w	1170w				1178w		
			1155m								1159w			1157m	1153m		
1150m	1136m	1139m	1143s	1145s	1140m	1141s	1145s	1146s	1138m	1147w	1145w	1149s	1142s	1146s	1140w	1140w	–C—N═
							1136s	1133m		1128w	1118w						
						1125m	1120w	1120m									
		1110s	1114w		1112s		1110w										
	1099s	1100s		1100m	1100s		1100w	1100m	1102m	1104m	1101m	1101m	1103s	1095s	1103m	1098m	
1069s	1065m	1069m	1075w	1070w		1068w	1066w	1068w	1068w	1070w	1068w	1075s	1070s	1070s	1068m	1068m	
															1023w		
1018m	1015m	1016m		1017w	1015w	1020w	1017w	1015w				1016m	1015m	1016m	1015w	1015w	
997m	995m	998m	1000w	997w	997w		998w	1000w	997w	997w	997w	997w	995m	996w	998w	996w	
981m												985w		982w	980w		
												967w		957m	966s	962w	*C–H deform. of –CH═CH–*
			965w	940w											952s		

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TABLE II (*continued*)

Compound[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Assignment
	924s	917m	914m	916w	912w	915w	920w	920w	920w	925w	929w	925w	923s	915s	918s	923w		
													907s	900s				
																914w	914w	
	856s		861s		851s	860m		860s	865m	856s	856s	856s				867m	855s	
845w			852s		845m	852s			858s									
			825m	837s	831m	835m	834s	835m	835m									
				790w		797w		806w		800w	729m	784w				825s	825m	
													803s	800s				
	772s	763s		765m	757m	760m	770m	769m	767m	771s	772s	770s	758s	760s	764s	745s		
		760s	758s					765m		747w	751s	752m						
			730m	718w	728w	731w	722w	715w			735w	732w					732m	
					708w													
	834s	680s	677s	680m	677s	678s	689s	680m	684m	684s	683s	681s	680s	680s	679s	684s	681s	

[a] Compound number refers to Table I.

As would be expected, there are several strong absorptions arising from the phenyl rings, which are indicated in the table. For the *p*-hydroxy, *p*-amino and *p*-nitro compounds, there are additional bands due to these substituents. Of these absorption bands, the hydroxy and the amino groups should give rise to absorptions in the 3300 cm.$^{-1}$ region.

For *p*-hydroxyazobenzene, an O–H stretching absorption band is found at 3140 cm.$^{-1}$ [5]; however, for the corresponding polyazo compounds no well defined absorption band can be observed. The bathochromic shift of this band from the normal position of the 3590–3650 cm.$^{-1}$ region is due to the intermolecular hydrogen bonding as was indicated by Hadzi.[6]

The hydroxy group is also expected to give absorptions at the lower frequency regions which are caused by the O–H bending and C–O–H deformation vibrations. For the compounds investigated, two common absorptions are observed, one at 1378–1380 cm.$^{-1}$ and the other at 1240–1288 cm.$^{-1}$. Hadzi assigned the 1280 cm.$^{-1}$ band of *p*-hydroxyazobenzene to the O–H bending vibration which was confirmed by a deuteration study.[6] Thus it is probable that the 1240–1288 cm.$^{-1}$ band is responsible for this mode of vibration. Hadzi also assigned the 1230 cm.$^{-1}$ band to the C–O–H in-the-plane deformation vibration. However, the corresponding band with comparable intensity is observed in many other polyazo compounds, and it cannot be said with any certainty that the 1230-1212 cm.$^{-1}$ band of *p*-hydroxypolyazobenzene is caused purely by C–O–H deformation vibration.

It is interesting to find three absorption bands in the 3300 cm.$^{-1}$ region for *p*-amino compounds. The frequencies of these bands are listed in Table III.

TABLE III

ABSORPTION BANDS OF *p*-AMINOPOLYAZOBENZENE IN 3300 CM.$^{-1}$ REGION

	Frequencies in cm.$^{-1}$		
	Overtone	$-NH_2$ stretch.	
Monoazo	3220	3400	3510
Disazo	3220	3350	3440
Trisazo	3210	3380	3480
Aniline		3395	3481

The bands are clear in the monoazo compound, but they become broader and more diffuse in polyazo compounds. The primary amine usually gives rise to two absorption bands in this region; for instance, aniline gives absorptions at 3481 and 3395 cm.$^{-1}$ [7a] which are assigned to the N–H stretching modes of vibration. Thus, of the three absorption bands of aminoazo compounds, two corresponding bands at the higher frequency side can be assigned to the N–H stretching vibration. With regard to the remaining band at 3220 cm.$^{-1}$, which is the weakest in intensity of these three bands, one can reasonably explain it as an overtone of the 1620

(5) No corresponding band can be observed for *o*-hydroxyazobenzene, where strong intramolecular hydrogen bonding exists; *cf.* K. Ueno, THIS JOURNAL, **79**, 3066 (1957).

(6) D. Hadzi, *J. Chem. Soc.*, 2143 (1956).

(7) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 214; (b) p. 249; (c) p. 31.

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cm.$^{-1}$ band. Since this strong band at 1620 cm.$^{-1}$ is characteristic of the aminoazo compound and since the frequency is in a region where the N–H deformation band of primary amines appears, this band can be assigned to N–H deformation mode of vibration. In this connection, it is noteworthy that the trisazo compound (compound 9) which has the lowest N–H deformation band (1613 cm.$^{-1}$) also has the lowest overtone band at 3210 cm.$^{-1}$. An additional band at the lower frequency region of 1300–1273 cm.$^{-1}$ can likewise be assigned to the C–N stretching vibration of the *p*-amino group.

For the nitro derivatives, two strong bands at 1525 and 1345 cm.$^{-1}$ are observed in addition to the absorption bands of the non-substituted polyazobenzenes, and these two bands are, without doubt, due to the NO_2 group.[7b]

With regard to the absorption bands due to the azo linkage, no conclusive result has been reported, although Le Fèvre and his co-workers assigned two bands near 1406 and 1577 cm.$^{-1}$ to the —N=N— linkage.[1] The main difficulty is that the azo absorptions are expected to appear in the double bond region, so that they may well be merged with the stronger aromatic ring absorptions. For the compounds under investigation, two common absorption bands at around 1455 and 1400 cm.$^{-1}$ are observed. The former band probably was overlooked by Le Fèvre, because the region is overlapped by a Nujol band. Although it is not clear which band is responsible for which mode of vibration of —N=N— bonding, these two bands can tentatively be assigned to the azo linkage.

Azo compounds are also expected to give rise to other bands at lower frequency regions, which originate in the C—N= linkage. The assignments for these bands in the literature are rather confusing, spreading over the range of 900–1325 cm.$^{-1}$.[8]

(8) H. W. Thompson, *J. Chem. Soc.*, 328 (1948); N. V. Colthup, *J. Opt. Soc. Amer.*, **40**, 397 (1950); W. West and R. B. Killingsworth, *J. Chem. Phys.*, **6**, 1 (1938); S. Imanishi and Y. Kanda, *J. Sci. Res. Inst. Tokyo*, **43**, 17 (1949); H. Stammreich, *Experientia*, **6**, 225 (1950); W. J. C. Thomas, *Chemistry & Industry*, **23**, 567 (1953).

However, according to Le Fèvre, three bands of aromatic azo compounds in the regions of 900, 1150 and 1300 cm.$^{-1}$ were assigned to the C–N linkage. For the polyazobenzenes under investigation, three bands at 920, 1140 and 1300 cm.$^{-1}$ regions correspond to those assigned by Le Fèvre, and these three bands are tentatively assigned to the —C—N= linkage.

As was reported in the previous papers,[2] the frequencies of absorption maxima in the ultraviolet region were related to the number of azo linkages and with the relative position of azo linkages against the phenyl ring. However, there is no simple relationship between the infrared absorption frequencies of the —N=N— or —C—N= linkage and the number of azo groups. Although some differences in the double bond region of the infrared spectra of *p*-, *m*- and *o*-polyazobenzenes were observed, no clear-cut rule was found for these absorption spectra.

For the polyazostilbenes, the steric configuration of the C=C bond is understood to be *trans*,[2,9] so that the C=C stretching absorption would be too weak to be observed, and moreover it may well overlap with the aromatic ring vibrations. Thus, the only characteristic absorptions of these compounds are to be observed in the —CH=CH— deformation region, and the C–H out-of-plane deformation vibration is expected to appear in a region of 970–960 cm.$^{-1}$.[7c] The observed band of the polyazostilbenes at 960–962 cm.$^{-1}$ can accordingly be assigned to this mode of vibration.

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KUMAMOTO-SHI, JAPAN

(9) R. Stoermer and H. Oehlert, *Ber.*, **55**, 1239 (1922).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, KANSAS STATE COLLEGE]

Interactions of Homologs of Carcinogenic Azo Dyes and Proteins[1-3]

BY R. K. BURKHARD, ROGER BAUER AND R. M. GROSSMAN

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The interactions of 4-aminoazobenzene, 3′-methyl-4-aminoazobenzene, 4′-methyl-4-aminoazobenzene with bovine serum albumin and the proteins contained in rat liver extracts have been studied by the equilibrium dialysis technique at 0° and *p*H 6.8. The interaction between methyl orange and bovine serum albumin was repeated as a reference interaction. The data suggest the following order among the quantities of these dyes bound to bovine serum albumin: 3′-methyl-4-aminoazobenzene (greatest), 4′-methyl-4-aminoazobenzene, 4-aminoazobenzene, methyl orange (least). However, only in certain cases were the differences between these quantities found to be statistically significant at the 5% level. The data also suggest that the interaction of 4′-methyl-4-aminoazobenzene with bovine serum albumin is less temperature dependent than the interactions involving the other two uncharged dyes and this protein. The methylated aminoazobenzenes bind to the proteins in the rat liver extracts in larger quantities than aminoazobenzene and these quantities are about one third to one half as large as those observed with bovine serum albumin when both sets of data are expressed in terms of moles of dye bound per milligram of nitrogen.

It has been suggested that in the interaction of an uncharged azo dye such as 4-aminoazobenzene with bovine serum albumin cationic sites from the lysine residues and phenolic hydroxyl groups from the tyrosine residues in the protein engage in hydrogen bonding to the amino group of the dye.[4] Subsequent to this report it was found that the differences observed in the interactions of 4-aminoazobenzene, 3′-methyl-4-aminoazobenzene and 4′-methyl-4-aminoazobenzene with bovine serum albumin at 25° could not be accounted for solely by differences in basicities of the three dyes and it was suggested that factors other than basicity could be of major importance in interactions of this type.[5] In order to gain further insight into the nature of these protein–dye interactions it was thought desirable to study their temperature dependences for which the temperature of 0° was selected for additional studies. Along with these studies it was also thought desirable to repeat earlier studies involving the interactions between the proteins in rat liver extracts and azo dyes at 0°[6] and thus establish a firmer foundation for further studies involving the interactions of rat liver proteins and dyes. This paper reports the results obtained from these two lines of investigation.

Experimental

Sources of Dyes and Proteins.—The dyes used in these studies were prepared as previously outlined.[5] The serum protein was Crystallized Bovine Plasma Albumin (referred to as bovine serum albumin in this paper) as obtained from the Armour Laboratories. The albumin was dried over P_2O_5 *in vacuo* prior to its use. The rat liver extracts were prepared by the extraction of a dried blood-free rat liver homogenate with phosphate buffer near 0°. The livers used in this preparation were obtained by the *in situ* perfusion of these organs with cold 0.89% saline during anesthesia followed by extirpation and quick freezing. These livers were then pooled, homogenized near 0° in a Waring Blendor, dialyzed near 0° against distilled water until the resistance of the dialyzate matched that of the distilled water and the resultant material lyophilized. This dried homogenate was then examined for the presence of carbohydrates, blood and lipids. The di-*o*-anisidine test was used to test for carbohydrates[7]; the benzidine test (after a short period of boiling) was used to test for blood[8]; exhaustive extraction with chloroform by use of a Soxhlet extractor followed by gravimetric determination of the chloroform soluble material was used to test for lipids. These tests indicated that carbohydrates, blood and lipids were not present in detectable quantities in this rat liver homogenate. The quantity of nitrogen in each extract prepared from this homogenate was determined by the micro-Kjeldahl method of Stover and Sandin[9] using the mixed indicator of Sobel, *et al.*[10] Crushed ice-water baths were used to maintain the desired temperature during the preparation of the homogenate and extracts.

Interactions.—The equilibrium dialysis technique as developed by Klotz and his co-workers was used for these studies.[11] The fact that the optical densities of solutions containing dyes and rat liver extracts did not change over a 24-hour period was considered as evidence that the dyes were not undergoing metabolic changes during this period and that differences in optical densities observed during equilibrium dialysis studies were due to protein–dye interactions. All spectral data were obtained by use of a Beckman model DU spectrophotometer. A crushed ice-water bath was used to maintain the temperature for the equilibrium dialysis experiments. The dye solutions used varied in concentration from approximately 3×10^{-6} to 10×10^{-6} moles per liter. The protein solutions involving serum albumin were 0.2% by weight. The rat liver extracts contained approximately 0.1 mg. of nitrogen per ml. The exact nitrogen content of each extract was determined and was taken into consideration when computations were made. All interactions and extractions made use of a phosphate buffer (*p*H 6.8) which contained 0.055 mole of Na_2HPO_4 and 0.044 mole of KH_2PO_4 per liter of solution.

Treatment of Data.[12]—The data obtained from studies involving bovine serum albumin were converted into values for $1/r$ (the reciprocal of the moles of dye bound per mole of protein) and $1/A$ (the reciprocal of the free dye concentration). The method of least squares was then used to calculate the intercepts and slopes for the equations having the form[13]

$$\frac{1}{r} = \frac{1}{n} + \frac{1}{nkA}$$

The correlation coefficients for these lines were then calcu-

(1) Contribution No. 552, Department of Chemistry, Kansas Agricultural Experiment Station, Manhattan, Kansas.

(2) Supported by a grant-in-aid from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

(3) A portion of the data reported in this paper has been abstracted from a thesis to be presented by Roger Bauer, in partial fulfillment of the requirements for the degree of Master of Science at Kansas State College.

(4) I. M. Klotz and J. Ayers, THIS JOURNAL, **74**, 6178 (1952).

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(9) N. M. Stover and R. B. Sandin, *Ind. Eng. Chem., Anal. Ed.*, **3**, 240 (1931).

(10) A. E. Sobel, H. Yuska and J. Cohen, *J. Biol. Chem.*, **118**, 443 (1937).

(11) I. M. Klotz, F. M. Walker and R. B. Pivan, THIS JOURNAL, **68**, 1486 (1946).

(12) The terminology and methods used in the statistical analysis of the data can be found in G. W. Snedecor, "Statistical Methods," Iowa State College Press, Ames, Iowa, 1956, 5th edition.

(13) I. M. Klotz, *Arch. Biochem.*, **9**, 109 (1946).

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lated to establish the validity of such treatment. The data were also converted into values of r/A and the method of least squares again used to calculate the intercepts and slopes for the equations having the form[14]

$$r/A = nk - kr$$

Correlation coefficients were then calculated for the lines obtained from these plots but it was found in all cases that much higher correlation coefficients were obtained by the first method of analysis. The reason for this was probably due to the fact that when the Klotz type of plot was used each set of experimental points was almost equally spaced along the abscissa but when the Scatchard type of plot was used each set of experimental points formed a cluster. Since statistical analysis of the data ultimately was used it was felt that the precision of any calculated value could still be represented adequately even though the Klotz type of plot was used. Thus all values reported in this paper regarding bovine serum albumin were obtained by the method introduced by Klotz.[13] Estimated values for $1/r$ and the corresponding 95% confidence intervals were then calculated at selected values for $1/A$. The t-test was then used to determine the significance of the differences between these values and between the slopes of the least squares lines. The 5% probability level was used as the criterion for significance in all such comparisons. Thermodynamic quantities were then calculated from the slopes of the least squares lines obtained at 0° and 25°.[5] In the case of the free energy data calculations also were made from the 95% confidence limits to indicate the precision of each calculation but this treatment was not extended to the enthalpy and entropy calculations.

Results and Discussion

The values for $1/n$, $1/nk$ and the correlation coefficients associated with each least squares line involving bovine serum albumin interactions are listed in Table I. Estimated values for $1/r$ and the corresponding 95% confidence intervals are listed in Table II. From these data it was concluded that in the majority of the cases an excellent linear relationship existed between $1/r$ and $1/A$. Even though the correlation coefficient associated with 4′-methyl-4-aminoazobenzene was small it still indicated a linear relationship did exist between $1/r$ and $1/A$. Statistical analysis of the data revealed that over the common free dye concentration range 3′-methyl-4-aminoazobenzene was bound in significantly larger quantities than 4-aminoazobenzene, however, in the case of 3′-methyl-4-aminoazobenzene and its 4′-isomer only at concentrations less than 6×10^{-6} mole per liter were significantly larger quantities of the 3′-substituted dye bound. It was also found that over the common range examined no significant differences were found in the amounts of binding of 4′-methyl-4-aminoazobenzene and 4-aminoazobenzene. These results again suggest[5] that factors other than basicity are of major importance in determining the abilities of these uncharged dyes to complex to bovine serum albumin.

It has been reported that 4-aminoazobenzene binds to bovine serum albumin in somewhat smaller quantities than methyl orange at *p*H 6.9 and 25°.[4]

TABLE I

VALUES FOR $1/n$, $1/nk$ AND CORRELATION COEFFICIENTS ASSOCIATED WITH LEAST SQUARES LINES (0°) AND THE THERMODYNAMIC FUNCTIONS FOR THE BINDING OF THE FIRST DYE MOLECULE OR ION TO BOVINE SERUM ALBUMIN

Dye[a]	No. of detn.	$1/n$	$1/nk \times 10^5$	Cor. coeff.	$-\Delta F_1°$ (0°) (kcal./mole) From slope	$-\Delta F_1°$ (0°) (kcal./mole) From 95% limits	$-\Delta F_1°$ (25°)[b] (kcal./mole) From slope	$-\Delta F_1°$ (25°)[b] (kcal./mole) From 95% limits	$-\Delta H_1°$ (kcal./mole)	$\Delta S_1°$ (cal./mole/deg.)
AB	10	0.050	14.9	0.99	6.03	5.97–6.10	6.30[c]	6.19–6.44	3.3[c]	11[c]
3′-Me-AB	11	.432	8.87	.99	6.31	6.30–6.32	6.47	6.38–6.57	4.6	6
4′-Me-AB	9	− .0856	13.8	.85	6.07	5.87–6.55	6.44	6.34–6.56	2.0	15
MO	10	− .183	17.3	.94	5.95[d]	5.80–6.16	..	.....	..	..

[a] Abbreviations: AB, (4-aminoazobenzene); 3′-Me-AB, (3′-methyl-4-aminoazobenzene); 4′-Me-AB, (4′-methyl-4-aminoazobenzene; MO, (methyl orange). [b] The 25° values were obtained from data of Burkhard and Moore.[5] [c] Literature values for these thermodynamic functions are −6150 cal./mole for the free energy change at *p*H 6.9, −3700 cal./mole and 11 cal./mole/deg. for the enthalpy and entropy changes, respectively, at *p*H 9.2.[4] [d] Literature value for this free energy change is −6049 cal./mole.[17]

The data obtained from studies involving the rat liver extracts were converted into units of the percentage of total dye bound per milligram of nitrogen in the extract. These rather unusual units were used in reporting these data since it was felt that a preparation such as this type of rat liver extract was too heterogeneous to allow a rigorous analysis of the data. Correlation coefficients relating these percentages to the total dye concentrations were calculated and it was found that over the concentration range studied these percentages were independent of the total dye concentration. Thus these percentages were merely averaged and the arithmetic means and standard deviations reported. The F-test was used to determine whether significant differences existed among these means. The t-test was then used to locate wherein these differences lay. The 5% probability level was again used as the criterion for significance in these comparisons. For the purpose of comparing these data to the data associated with bovine serum albumin certain of both sets of data were selected and converted into units of moles of dye bound per milligram of nitrogen. To achieve this conversion the value of 16.07[15] was used for the percentage of nitrogen in bovine serum albumin.

Burgert also has studied these interactions at 25° but at *p*H 7.3.[16] He obtained the same results that Klotz and Ayers did in that at a free dye concentration of 1×10^{-5} mole per liter, for example, the amount of methyl orange bound to the protein was 0.40 mole per mole of protein and with 4-aminoazobenzene the amount was 0.35. Thus while there appears to be greater binding of methyl orange at 25° it does not appear to be true at 0° and *p*H 6.8. The data in Table II even suggest that methyl orange is bound in smaller quantities than 4-aminoazobenzene but statistical analysis of these data revealed that the differences between these amounts were not significant. Comparison of methyl orange to 3′-methyl-4-aminoazobenzene, however, revealed that over the entire common range the unchanged dye was bound in larger quantities, but in the case of 4′-methyl-4-aminoazobenzene *versus* methyl orange the uncharged dye was bound in significantly larger quantities only at concentrations lower than 6×10^{-6} mole per liter.

Comparison of these results with those obtained

(14) G. Scatchard, *Ann. N. Y. Acad. Sci.*, **51**, 660 (1949).
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TABLE II

ESTIMATED VALUES AND 95% CONFIDENCE INTERVALS FOR $1/r$ AT GIVEN VALUES OF $1/A$ FOR BINDING OF DYES TO BOVINE SERUM ALBUMIN

$1/A$ (L/mole $\times 10^{-5}$)	Dye[a]	$1/r$	95% Confidence interval
1.67	AB	2.54	2.30–2.78
	3′-Me-AB	1.91	1.88–1.94
	4′-Me-AB	2.26	1.58–2.94
	MO	2.71	2.41–3.01
2.00	AB	3.03	2.80–3.26
	3′-Me-AB	2.20	2.17–2.23
	4′-Me-AB	2.70	2.20–3.20
	MO	3.28	3.00–3.56
2.50	AB	3.77	3.35–4.19
	3′-Me-AB	2.65	2.60–2.70
	4′-Me-AB	3.33	2.94–3.72
	MO	4.14	3.69–4.59
2.86[b]	3′-Me-AB	2.97	2.94–3.00
	4′-Me-AB	3.80	3.31–4.29

[a] Abbreviations: same as in Table I. [b] Values for AB and MO systems are not listed at 2.86×10^5 due to the fact that observations involving these dyes did not extend to this concentration.

at 25°[5] reveals an inverse relationship between temperature and extent of interaction for the uncharged dyes. However, this temperature dependence must not be identical in all cases since at 25° it was found that at most of the concentrations examined 3′-methyl and 4′-methyl-4-aminoazobenzene were not bound in significantly different quantities but both were bound in significantly larger amounts than 4-aminoazobenzene while at 0° 3′-methyl-4-aminoazobenzene was bound in significantly greater quantities at most concentrations examined than both 4′-methyl-4-aminoazobenzene and 4-aminoazobenzene and that these latter two dyes were not bound in significantly different quantities. If the natures of the interactions of 4-aminoazobenzene and 3′-methyl-4-aminoazobenzene with bovine serum albumin are such that the equilibrium constants associated with these two are more temperature dependent than that involving 4′-methyl-4-aminoazobenzene then one can qualitatively account for these observations. That this might be the case is suggested by the thermodynamic functions listed below.

In order to evaluate the thermodynamic functions for these interactions it was first thought desirable to calculate the correlation coefficients for the 25° data previously reported.[5] These coefficients were found to be 0.94, 0.96 and 0.94 for 4-aminoazobenzene, 3′-methyl-4-aminoazobenzene and 4′-methyl-4-aminoazobenzene, respectively. Thus from the previously and currently reported $1/nk$ values the thermodynamic functions associated with these interactions were calculated.

TABLE III

AMOUNTS OF DYE BOUND TO PROTEINS IN RAT LIVER EXTRACT AND THEIR COMPARISONS TO AMOUNTS BOUND TO BOVINE SERUM ALBUMIN (0°, *p*H 6.8)

Dye[a]	No. of detn.	Mean % of total dye bound per mg. N in RLE[a]	Stand. dev.	Binding expressed as moles of dye bound per mg. N $\times 10^5$ at total dye concn. of 5×10^{-6}, mole/l. RLE	BSA[a,b]
AB	19	18	6	1.1	2.98
3′-Me-AB	15	28	4	1.9	4.09
4′-Me-AB	18	26	8	1.8	3.35

[a] Abbreviations: same as Table I for the dyes; RLE (rat liver extract); BSA (bovine serum albumin). [b] These values were obtained from the data used to prepare Tables I and II.

It was stated previously that there was not a significant difference between the slopes of the lines derived from data involving the methylated uncharged dyes at 25°.[5] Further calculations involving 4-aminoazobenzene revealed, however, that the slope of this line was significantly different from that involving 3′-methyl-4-aminoazobenzene (t = 2.27, D.F. = 27) but not different from the slope of the line involving 4′-methyl-4-aminoazobenzene (t = 1.64, D.F. = 33).[12] Calculations involving the slopes obtained at 0° revealed that these relationships held also at the lower temperature. The slope of the line involving methyl orange was found to differ significantly only from that observed with 3′-methyl-4-aminoazobenzene (t = 4.24, D.F. = 17).

The thermodynamic functions associated with the binding of each first dye molecule or ion are shown in Table I. It should be noted that the free energy changes include values calculated from the 95% confidence limits of the various slopes while the enthalpy and entropy changes do not. Comparison of these values with previously reported ones shows favorable agreement.[4,17] They, however, do not allow one to evaluate with certainty the importance of the various factors which might be involved in the binding of such dyes to bovine serum albumin. Further experimentation is now in progress in this Laboratory in an attempt to correlate the structure of uncharged dyes with their ability to form complexes with proteins.

The correlation coefficients for the dependence of the percentage of total dye bound per milligram of nitrogen on total dye concentration in the case of the rat liver extracts were found to be 0.09 (D.F. = 17) for 4-aminoazobenzene, −0.22 (D.F. = 15) for 3′-methyl-4-aminoazobenzene, and 0.30 (D.F. = 18) for 4′-methyl-4-aminoazobenzene.[12] From these it was concluded that the percentage of total dye bound was independent of the total dye present and thus these percentages could be averaged for each system and the mean percentages reported. These values and the standard deviations are listed in Table III.

Analysis of variance revealed that these means were not all the same (F = 10, D.F.$_1$ = 2, D.F.$_2$ = 49). Further analysis revealed that there was not a significant difference between the means for the methylated compounds but that there were significant differences between the means for the methylated compounds and aminoazobenzene (for example, t = 3.31, D.F. = 35 for 4′-methyl-4-aminoazobenzene *vs.* 4-aminoazobenzene).[12] These results agree with those obtained earlier by Grossman[6] and also suggest that factors other than basicity are of major importance in determining the extents of interaction of these three uncharged dyes with the proteins in these rat liver extracts.

The amounts of these uncharged dyes bound to both bovine serum albumin and the proteins in the

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rat liver extracts at a free dye concentration of 5×10^{-6} mole per liter are also listed in Table III. It will be noted that at this particular free dye concentration and in terms of the units used the amount of any one dye bound to the proteins in the rat liver extracts is approximately one third to one half of the amount bound to bovine serum albumin. This observation may be of some significance since it has been found by other investigators that neutral dye molecules do not bind to bovine γ-globulin or pepsin.[4] The composition of these rat liver extracts is currently unknown, but an attempt is being made in this laboratory to isolate and characterize the protein or proteins involved in the formation of these complexes with uncharged dyes.

Acknowledgment.—The authors are indebted to Dr. Holly C. Fryer, Statistical Laboratory, Kansas State College, for advice regarding the statistical analysis of the observed data.

MANHATTAN, KANSAS

[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, ST. LOUIS RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

Studies in Steroid Total Synthesis. V. Abnormal Cleavage of Some Tricyclic Ketone Epoxides

BY WILLIAM S. KNOWLES AND QUENTIN E. THOMPSON

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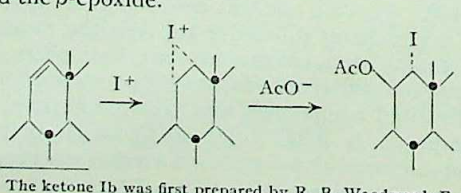
Reductive cleavage of the 5β,6β-epoxide function of the tricyclic ketone IIIa does not give the axial 5β-ol (IIc) predicted by conformational theory but gives the equatorial 6β-ol (IId). Both IIIa and the isomeric 5α,6α-epoxide IIIb are opened abnormally by methoxide and thiophenoxide anions giving products to which we have assigned structure VIIIa,b,c and IXa,b.

In the course of work designed to prepare ring B,C,D-tricyclic intermediates containing a potential C-11 oxygen, the chemistry of the isomeric 5,6-oxides derived from *dl-anti-trans*-1,6a,7,7a,10a,-11,11a,11b - octahydro - 4,6a,9,9 - tetramethylphenanthro[2,3][1,3]dioxol-3(2H)-one (Ic) was investigated. The course of the reactions in most cases was found to be extremely unpredictable. Abnormal cleavage by methoxide and thiophenoxide anions and the abnormal reductive cleavage of the β-oxide form the subject of the present paper.

The readily available tricyclic ketone Ic[1] served as the starting point for the preparation of both oxides. Reaction of Ic with approximately one mole of silver acetate and iodine in glacial acetic acid gave the 5β-acetoxy-6α-iodoketone IIa which upon treatment with aqueous base gave the 5β,-6β-epoxide IIIa, m.p. 200–201°.[2] The isomeric 5α,6α-epoxide IIIb, m.p. 214–217°, readily was obtained by treatment of Ic with perbenzoic or monoperphthalic acids. Configurational assignments were made assuming backside attack by peracids would give the α-epoxide, whereas silver acetate–iodine treatment would result in an initial α-oriented attack by I^+ followed by opening with acetate ion to form the 5β-acetoxy-6α-iodo configuration assigned. Base treatment would then yield the β-epoxide.



(1) The ketone Ib was first prepared by R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore (THIS JOURNAL, **74**, 4223 (1952)) as the minor β-*cis*-glycol resulting from osmium tetroxide oxidation of the unsaturated ketone Ia. Subsequently, Woodward and Brutcher (private communication) prepared the same glycol (m.p. 181–182°) by silver acetate–iodine oxidation of Ia.

(2) Compounds IIa and IIIa were first prepared at Harvard by F. V. Brutcher and R. B. Woodward and were disclosed to us by private communication.

Catalytic reduction of the α-epoxide IIIb yielded the 6α-alcohol IIb. As expected for an axial hydroxyl located vinylogously beta to a carbonyl group, mild treatment with base caused elimination of water and formation of the dienone Ic. Several attempts to reduce the isomeric epoxide IIIa catalytically did not give clear results. Reduction with zinc and acetic acid proceeded smoothly to yield a new alcohol, m.p. 187–188°, λ_{max}^{alc} 250, ϵ 15,380. If the reduction had occurred in a normal manner, IIc would be the expected structure for the product. However, ready acetylation at room temperature with pyridine and acetic anhydride indicated the presence of an equatorial hydroxyl function.[3] Attempts to oxidize the alcohol with manganese dioxide[4a,b] or chromic anhydride in pyridine[5] yielded chiefly starting material, again indicative of a non-allylic equatorial hydroxy group.

The rearrangement of Δ^4-cholestenone-6-ol systems to the corresponding 3,6-diones under alkaline conditions has been well established.[6a,b,c] Moreover, it has been shown both in the Δ^4-3-one-6-ol[6b] system and the Δ^8-11-α-ol-7-one[7] system that it is significantly easier to effect rearrangement when the hydroxyl group is axial than when it is equatorial. The axial alcohol represented by

(3) The isomeric alcohol IIb acetylated incompletely under the same conditions. This somewhat slower acetylation would be expected for an axial hydroxyl at C-6. The analogous C-12 α- and β-alcohols in the bile acid series show similar behavior [B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **25**, 918 (1942)].

(4) (a) *Cf.* S. Ball, T. W. Goodwin and R. A. Morton, *Biochem. J.*, **42**, 516 (1948); F. Sondheimer, C. Amendola and G. Rosenkranz, THIS JOURNAL, **75**, 5930, 5932 (1953). (b) Sondheimer, *et al.* [*J. Chem. Soc.*, 1226 (1954)], has used manganese dioxide for the oxidation of 6β-hydroxyprogesterone to the corresponding 6-ketoprogesterone. thus effecting successful oxidation of a system structurally similar to our formula IIc.

(5) *Cf.* G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(6) (a) B. Ellis and V. A. Petrow, *J. Chem. Soc.*, 1078 (1939); (b) P. T. Herzig and M. Ehrenstein, *J. Org. Chem.*, **16**, 1050 (1951); (c) see reference cited in footnote.[4b]

(7) J. Romo, G. Stork, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 2918 (1952).

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structure IIc thus would be expected to undergo facile conversion to the corresponding saturated diketone IV. All attempts to effect rearrangement failed. When the product was subjected to hot potassium *t*-butoxide treatment,[7] only dehydration occurred giving the dienone Ic. These facts indicated that in all probability the alcohol was not IIc but rather IId, the isomer obtained by abnormal epoxide opening. This result represents an exception to the general rule that in a polycyclic cyclohexane system an epoxide always opens to give the axial alcohol.[8]

Reduction of IIIa with lithium aluminum hydride to the epimeric diols V followed by oxidation with manganese dioxide likewise yielded IId indicating that abnormal epoxide cleavage was not peculiar to the method of reduction.[8a]

Sulfide anions have been shown to be excellent reagents[9] for opening epoxides, and thus it was of interest to see whether they would behave in a normal manner on IIIa. A base-catalyzed reaction of the β-epoxide IIIa with excess thiophenol in *t*-butyl alcohol at room temperature gave a high yield of crystalline adduct, m.p. 140–142°. Infrared and ultraviolet spectra (λ_{max}^{alc} 254, ϵ 15,000) and analyses showed clearly that the material was an α,β-unsaturated ketone containing one hydroxyl group and one phenylthioether group. Normal addition of thiophenol to IIIa would be expected to give a 5β-ol-6α-thiophenyl ether, *i.e.*, IIe. However, desulfurization of the adduct with Raney nickel gave the 6β-alcohol IId, m.p. 187–188°, thus indicating again an abnormal epoxide cleavage. Furthermore, treatment of the adduct for ten minutes with hot alcoholic alkali gave a new compound, $C_{25}H_{30}O_3S$, m.p. 128–129°, which arose from the loss of a mole of water and not a mole of thiophenol as would be expected for a structure IIe. These facts would seem to suggest the adduct had the 5-thiophenol-6β-ol structure IIf and the $C_{25}H_{30}O_2S$ dehydration product was VIa. However, examination of the ultraviolet spectrum of the latter product clearly indicated that it could not be VIa. The observed spectrum showed a single peak at 280 mμ, ϵ 17,500, a figure quite inconsistent with structure VIa since the unsubstituted dienone chromophore of Ic has a peak at 289 mμ, ϵ 25,400. An appreciable bathochromic shift would be expected for dienones substituted as in VIa with an electron-rich thiophenyl group. No specific example of a thioenol ether cross-conjugated with a dienone was found in the literature. However, $\Delta^{4,6}$-cholestadien-3-one absorbs at 284 mμ, ϵ 26,300,[10] while the corresponding 6-ethoxy-$\Delta^{4,6}$-cholestadien-3-one absorbs at 295 mμ, ϵ 16,800.[11] In this case, the ethoxyl group causes an 11 mμ bathochromic shift. The greater bathochromic effect of RS-groups as compared to RO-groups has been shown clearly.[12] Therefore, the hypsochromic shift observed in our dienone thioether, m.p. 128–129°, rules out structure VIa. These conclusions are supported by chemical evidence also. Enol thioethers like their oxygen analogs are acid labile.[13]

Solution of our unknown dienone in a small amount of trifluoroacetic acid followed by trituration with water resulted in the quantitative removal of the acetonide groups without affecting the phenyl thioether linkage.

Desulfurization of the dienone acetonide with Raney nickel in ethyl acetate gave the known ketone IIg thus indicating no rearrangement of the carbon skeleton. The dihydroketone IIg had been previously prepared by catalytic hydrogenation of Ic using palladium-on-strontium carbonate.[14] The reduction of the 5,6-double bond during desulfurization was not unexpected since other work in this Laboratory has shown it to be very easily reduced. Attempts to effect desulfurization while preserving the dienone were not completely successful. Use of deactivated nickel at low temperature in ethyl acetate gave what appeared to be a mixture of Ic and IIg since the ultraviolet spectra showed maxima at 289 and 250 mμ the correct positions for the dienone and its dihydro-derivative, respectively.

It can be concluded from the evidence cited that the dienonethioether has the intact carbon skeleton of Ic, and the point of substitution of the thioether linkage cannot be at positions 3, 4, 4a, 5 or 6.[12] However, other points of substitution which would be expected to satisfy the spectral requirements are positions 2 (VIIa), on the methyl group attached to the 4-position (VIIb) and position 11b (IXa). Reasonable mechanisms can be written for the formation of the sulfide linkage at each of these points. However, in work to be cited below, all but the last have been eliminated. Thus, structure VIIIa has been assigned to the adduct of IIIa with thiophenol and IXa for the dehydrated product.

Reaction of the isomeric epoxide IIIb with thiophenol gave an adduct VIIIb apparently differing from VIIIa only in the configuration of the hydroxyl group since dehydration with base yielded IXa.

Because of the unexpected course of base-catalyzed mercaptan opening, the nucleophilic cleavage with methoxide ion was investigated. Treatment of IIIa at reflux with excess sodium methoxide in methanol gave a complex mixture of methoxy tricyclic ketones. The major product, a methoxydienone, m.p. 108–110°, λ_{max}^{alc} 289 mμ, ϵ 25,200, was obtained in 60–70% yield. Treatment with acid removed the acetonide group without affecting the methoxyl or the ultraviolet spectrum, since the glycol could be converted back to the parent ketone with acetone and copper sulfate. On the basis of these data and the arguments presented below, the ketone and glycol resulting from acid treatment were assigned the structures IXb and Xb, respectively.

(5) *Cf.* D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953), D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

(8a) *Cf.* W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954), and P. L. Julian, W. Cole, E. W. Meyer and B. M. Regan, THIS JOURNAL, **77**, 4601 (1955).

(6) F. N. Woodward, *J. Chem. Soc.*, 1892 (1948); C. D. Nenitzescu and N. Scarlatescu, *Ber.*, **68**, 587 (1935); H. Gilman and L. Fullhart, THIS JOURNAL, **71**, 1478 (1949).

(10) A. L. Wilds and C. Djerassi, *ibid.*, **68**, 1712 (1946).

(11) L. Dorfman, *Chem. Revs.*, **53**, 78 (1953).

(12) Bowden Braude and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(13) S. Bernstein and L. Dorfman, THIS JOURNAL, **68**, 1152 (1946), and G. Rosenkranz, St. Kaufmann and J. Romo, *ibid.*, **71**, 3689 (1949).

(14) L. B. Barkley, W. S. Knowles, H. Raffelson and Q. E. Thompson, *ibid.*, **73**, 4111 (1950).

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In addition to the major product Xb, three other pure compounds were isolated from the reaction mixture. The first minor product was merely the undehydrated precursor to IXb. Thus its structure was VIIIc, and further treatment with methoxide converted it to IXb. The other compounds, m.p. 142–143° and m.p. 152–153°, were isomeric with IXa. The ultraviolet spectrum of the higher melting compound had a single maximum at 304 mμ, ε 15,300, indicating that it was probably VIb, since the observed bathochromic shift of 15 mμ would be expected for this type of substitution on the dienone chromophore.[10] The lower melting isomer had an ultraviolet maximum at 294 mμ, ε 24,000. Because of the limited quantity, the structure of this compound remained unknown.

Cleavage of the α-epoxide IIIb with sodium methoxide gave an even more complex mixture of products from which could be isolated the methoxydienone IXb previously obtained from the β-epoxide. Thus, both the mercaptide and methoxide anions cleaved the α- and β-epoxides IIIa and IIIb in a closely analogous and abnormal manner.

The possibility still remained that the methoxyl and the thiophenyl groups could reside on the C-4 methyl group as far as could be deduced from spectral data. This position was ruled out by running Kuhn–Roth C-methyl determinations which conclusively showed the presence of two C-methyl groups in Xa and Xb. Obviously, only one could be present if the thioether or the methoxyl function were located as in VIIc or VIIb.

In addition, it can be argued that the alkoxyl or the thiophenyl group might occupy the 2-position. This alternative has been excluded by synthesis of VIIa. Treatment of the potassium salt of Ic with phenylsulfenyl chloride gave a low yield of an epimeric mixture of the two phenylthioethers VIIa. Extensive crystallization yielded an apparently pure isomer, m.p. 195–197°, λ_{max}^{alc} 293 mμ, ε 19,800. Alkali caused a shift of the maximum to 287 mμ, ε 22,400. The infrared spectra of the crude epimers VIIa or of the purified isomer in no way resembled IXa. Moreover, the ultraviolet spectrum of IXa was unaffected by base.

Though deduced from evidence of a negative nature, the structural assignments made appear to be the only ones consistent with the known facts. The mechanism of the reaction can be readily rationalized. Under the influence of base, the α,β-unsaturation in the epoxides III is isomerized to some extent to the β,γ-position. Attack by sulfide or methoxide anion then in essence becomes a 1,4-addition to an unsaturated system. Analogous addition to α,β-unsaturated ketones are of course well known. Subsequent abstraction of a proton from the solvent gives the primary adduct shown. Isomerization of the double bond to the α,β-position followed by loss of water would give IXa.

Acknowledgments.—We thank Dr. Bernart Katlafsky and Mr. O. E. Kinast for their help with the numerous spectra required in this work. We also are indebted to Dr. R. B. Woodward for valuable advice and discussion and to Drs. F. C. Meyer and O. J. Weinkauff whose interest and cooperation made this work possible.

Experimental[15]

dl-anti-trans-1,6a,7,7a,10a,11,11a,11b-Octahydro-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxol-3(2H)-one (Ic).—To a slurry of 30.9 g. of silver acetate in 350 ml. of glacial acetic acid at 25° was added 18.3 g. of *dl-anti-trans*-4,4a,4b,5,8,8a-hexahydro-1,8a-dimethyl-2(3H)phenanthrone (Ia).[16] The mixture was stirred rapidly and 21.5 g. of iodine was added over a period of 15 minutes. When addition of iodine was complete, 3.0 ml. of water was added. The temperature was raised to 90–95° and held for 3 hr. The reaction mixture was then cooled, filtered and the filter cake washed thoroughly with 100 ml. of chloroform and discarded. The filtrate was dried *in vacuo* with the temperature kept below 85°. The thick residue remaining was dissolved in 500 ml. of methanol and filtered to remove a small amount of solid. Strong aqueous base was added dropwise to the methanol solution until just basic to litmus. A solution of 4.8 g. of potassium hydroxide in 100 ml. of methanol was added, and the dark solution was allowed to stand under nitrogen for 16 hr. at room temperature. Following this, the solution was acidified to test paper with a few ml. of acetic acid. Most of the solvents were then removed under reduced pressure at water-bath temperature. The residue was dissolved in 200 ml. of chloroform and washed with 200 ml. of water in two portions. The chloroform layer was then dried with calcium sulfate and the solvent removed under reduced pressure. When about 90% of the chloroform had been removed, the residue was triturated with 75 ml. of hot ethyl acetate. A copious precipitate of glycol Ib separated. The first crop amounted to 14.9 g., m.p. 180–182°. A second crop, 0.60 g., m.p. 170–180° (74%), was obtained from the mother liquors. The infrared spectrum of this glycol was identical with the minor osmium glycol obtained by Woodward.[1]

The glycol was converted to the acetonide (Ic) by dissolving (both crops) in 1 liter of dry acetone and stirred for 48 hr. with 90 g. of anhydrous copper sulfate. The latter was then removed by filtration and the solvent distilled out. The crude acetonide crystallized from the residue and amounted to 13.7 g., m.p. 152–154°. Second and third crops, 1.9 g., m.p. 147–151°, and 0.35 g., m.p. 138–148°, respectively, were obtained by further concentration of the mother liquors. Recrystallization of first crop acetonide once from acetone gave pure material, m.p. 153–154°, λ_{max}^{alc} 289 mμ, ε 25,400.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.18; H, 8.71.

dl-anti-trans-1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one (IIg).—One gram of dienone Ic, dissolved in 30 ml. of isopropyl alcohol and treated with 3 drops of 10% aqueous sodium hydroxide solution, was hydrogenated exactly as described for optically active Ia in a previous paper.[17] The yield of crystalline dihydro-ketone was 1.0 g., m.p. 155–158°. One recrystallization from ether gave pure material, m.p. 157–159°, λ_{max}^{alc} 250 mμ, ε 15,400.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.97; H, 9.31. Found: C, 74.51; H, 9.30.

dl-anti-trans-1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-5β-hydroxy-6α-iodo-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one Acetate (IIa).[2]—To a suspension of 15 g. of silver acetate in 270 ml. of glacial acetic acid and 90 ml. of chloroform was added 25 g. of crystalline acetonide Ic. The mixture was then stirred rapidly at 25–30° and 22.1 g. of iodine was added over a period of 15 minutes. Stirring was continued for 1.5 hr. after addition of the iodine. The suspension was filtered and the solid washed thoroughly with 300 ml. of chloroform. The filtrate was then quenched with about 400 ml. of ice-water and the chloroform layer was separated and washed twice with 200 ml. of water, once each with 200 ml. of 5% bicarbonate solution and finally once with water. The organic layer was dried with Drierite and the chloroform was removed under slightly reduced

(15) Melting points are uncorrected. Infrared spectra were run in chloroform on a Perkin–Elmer recording spectrophotometer, model 21. Ultraviolet spectra were run on a Cary recording spectrophotometer, model 11. Analyses were done by Mr. A. Bybell of this Laboratory and by Du Good Chemical Laboratory of St. Louis.

(16) See footnote 1 and reference cited therein.

(17) L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and

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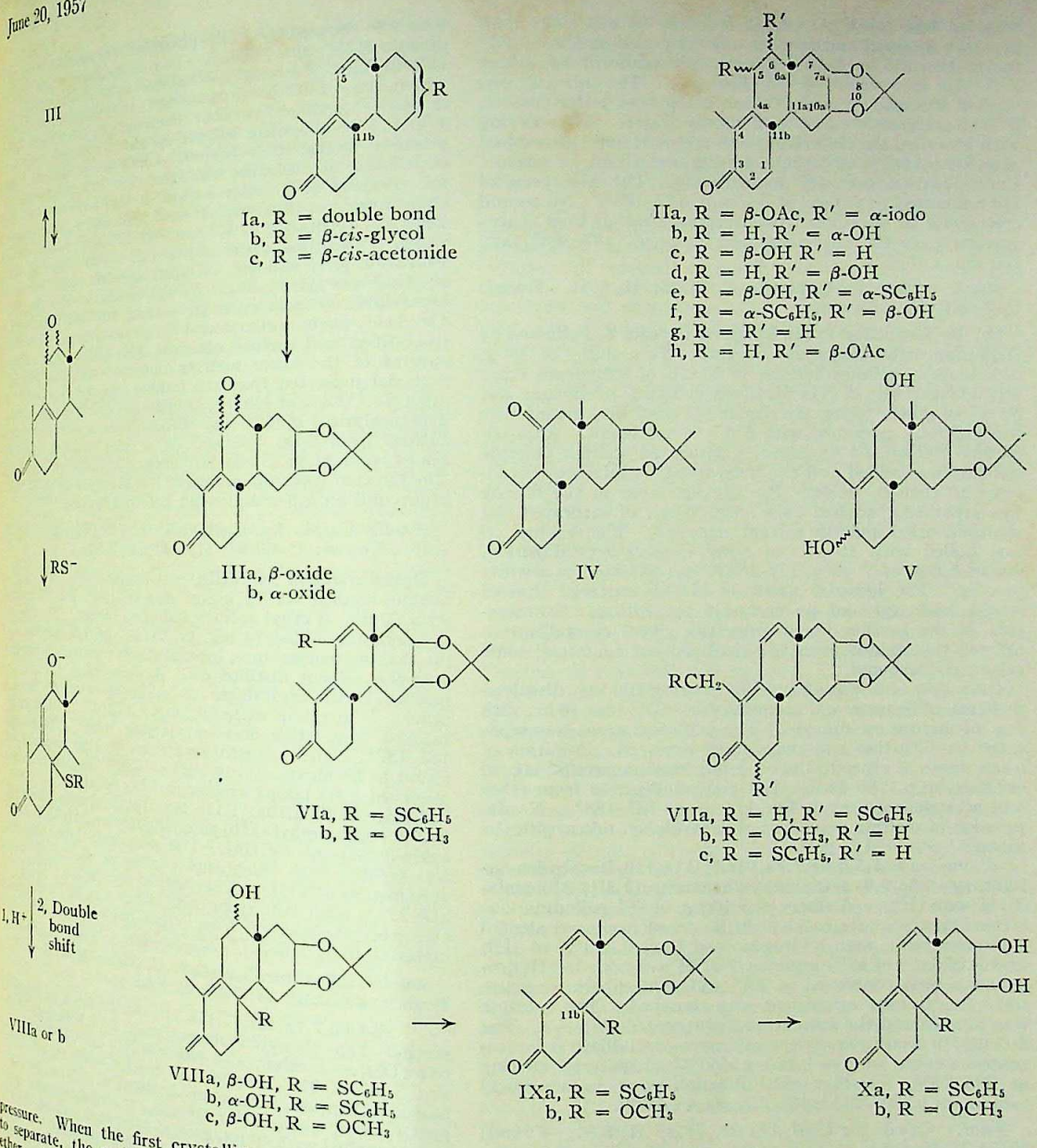

pressure. When the first crystalline material had begun to separate, the residue was quenched with 300 ml. of ether. A copious white precipitate of IIa amounting to 34.2 g. (88.5%), m.p. 194–196° dec., was obtained.

Anal. Calcd. for $C_{21}H_{29}O_5I$: C, 51.64; H, 5.98; I, 26.06. Found: C, 51.54; H, 6.08; I, 25.99.

dl-anti-trans-5β,6β-Epoxy-1,5,6a,7,7a,10a,11,11a,11b-decahydro-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one (IIIa).[2]—A suspension of 34 g. of IIa in 300 ml. of benzene was treated with 12.6 g. of potassium hydroxide in 30 ml. of water and 250 ml. of methanol. The three-phase system was stirred vigorously under nitrogen at room temperature until all of the solid had dissolved (3 hr.). Water (200 ml.) was added and the benzene phase was separated. After washing once with water, the benzene was dried and distilled off under slightly reduced pressure. When the volume of solution reached one-third, crystalline epoxide began separating. Evaporation to dryness gave 19.5 g. (87% from Ic) of white crystals, m.p. 198–200°. Recrystallization of a small portion once from benzene gave pure material, m.p. 200–201°, λ_{max}^{alc} 251.5 mμ, ε 16,270.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.61; H, 8.27.

dl-anti-trans-5α,6α-Epoxy-1,5,6,6a,7,7a,10a,11,11a,11b-decahydro-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one (IIIb).—A solution of 3.02 g. of Ic in about 50 ml. of anhydrous ether was treated with 45.7 ml. of 0.328 *M* ethereal monoperphthalic acid solution[18] and allowed to stand at room temperature for 5 days. During this time, large rice-like crystals of epoxide separated. This crop of essentially pure IIIb amounted to 1.5 g. The filtrate was washed with aqueous base, dried and concentrated to give a second crop of 750 mg., m.p. 212–214°, of good quality epoxide. The total yield was 2.32 g. (73%). One recrystallization of first crop material from acetone gave pure IIIb, m.p. 215–217°, λ_{max}^{alc} 251 mμ, ε 14,200.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.71; H, 8.36.

dl-anti-trans-1,5,6,6a,7,7a,10a.11,11a,11b-Decahydro-6β-hydroxy-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one (IId). (a). By Zinc–Acetic Acid Reduction of IIIa.—Four grams of zinc dust was added at room temperature to a solution of 2.85 g. of IIIa in 25 ml. of glacial acetic acid. Vigorous stirring was begun and the temperature kept at 38–40° by cooling until the initial surge of the

(18) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1948, p. 708.

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reaction had subsided. After the first 15 min., the temperature dropped and stirring was continued at around 30° for another 3.5 hr. before 120 ml. of chloroform was added and the zinc removed by filtration. The filtrate was washed successively with 100-ml. portions of water (twice), 5% bicarbonate solution and finally water. After drying with Drierite, the chloroform was removed and the residual glass triturated with 10 ml. of ether and 10 ml. of hexane. Crystallization occurred immediately. The first crop of IId amounted to 2.0 g. (70%), m.p. 187–188°. No second crop could be obtained. One recrystallization from ether–acetone gave the analytical sample, m.p. 187–188°, λ_{max}^{alc} 250 mμ, ε 15,400.

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 70.93; H, 8.58.

(b) By Reduction to the Epimeric Glycols V, Followed by Oxidation with Manganese Dioxide.—To a slurry of 2.0 g. of lithium aluminum hydride in 50 ml. of anhydrous ether was added 2.4 g. of IIIa dissolved in 15 ml. of dioxane and 50 ml. of ether. After stirring at 25° for 2 hr., the mixture was carefully quenched with 5 ml. of methanol. Approximately 100 ml. of an aqueous saturated sodium chloride solution was added and the heterogeneous mixture was filtered to remove solids. The organic layer in the filtrate was separated, washed once with 50 ml. of saturated salt solution, dried and the solvent removed. The residual oil was boiled with 10 ml. of ether causing crystallization. About 1.5 g. of V, m.p. 177–184°, was obtained as a white powder. The infrared spectrum of this material showed strong hydroxyl and no carbonyl absorption. Examination of the mother liquor from the glycol crystallization showed that it was primarily alcoholic but contained some saturated carbonyl.

Oxidation of V was effected by stirring 100 mg. dissolved in 40 ml. of benzene and acetone (about 25%) for 16 hr. with 1 g. of manganese dioxide. The oxidizing agent was separated by filtration and the solvent removed. Addition of a few drops of ether to the clear oily residue gave 85 mg. of crystals, m.p. 185–186°. One recrystallization from ether and acetone gave crystalline IId, m.p. 187–188°. No depression of melting point was observed when taken with the material obtained in part a.

dl-anti-trans-**1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-6α-hydroxy-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one (IIb).**—A slurry of 0.100 g. of 2% palladium-on-strontium carbonate catalyst in 50 cc. of isopropyl alcohol was prereduced with hydrogen, and then 0.300 g. of IIIb and 0.05 cc., of 10% aqueous NaOH was added. Hydrogenation was continued at 25° and atmospheric pressure until exactly one equivalent was absorbed. The catalyst was filtered and the solvent was evaporated *in vacuo*. The 300 mg. of crude gummy crystals were crystallized from isopropyl alcohol to give 0.152 g. (50%) of material melting at 205–210°. Further crystallization gave an analytical sample, m.p. 208–211°, λ_{max}^{alc} 250 mμ, ε 15,000.

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.2; H, 8.81. Found: C, 71.7; H, 9.14.

Dehydration of IIb.—A solution of 0.050 g. of IIb in 1 cc. of *t*-butyl alcohol and 1 ml. of 0.95 *N* potassium *t*-butoxide was allowed to stand at 25° 1 hr. After neutralizing the base with acetic acid, the mixture was poured into water and was extracted with chloroform. The extract was washed with bicarbonate and water and dried. Removal of the solvent *in vacuo* followed by trituration with ether gave crystals, m.p. 153–154°, which showed no depression with authentic Ib.

Dehydration of IId.—An identical procedure with the β-alcohol IId at 25° gave back only starting material. However, at boiling temperatures, Ib was obtained in low yield.

dl-anti-trans-**1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-6β-hydroxy-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one Acetate (IIh).**—A mixture of 160 mg. of IId, 300 mg. of acetic anhydride and 3 ml. of pyridine was allowed to stand at room temperature for 16 hr. Water (5 ml.) was added and crystals began to separate. These were collected and when dry amounted to 100 mg., m.p. 173–175°. Recrystallization from ether–petroleum ether gave pure IIh, m.p. 174–175°, λ_{max}^{alc} 247 mμ, ε 15,350.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.55; H, 8.31.

dl-**1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-6β-hydroxy-4,6a,9,9-tetramethyl-11b-phenylthiophenanthro[2,3][1,3]dioxole-3(2H)-one (VIIIa).**—To a suspension of 396 mg. of IIIa in 5 ml. of *t*-butyl alcohol and 3 ml. of thiophenol was added 1 ml. of 0.9 molar potassium *t*-butoxide solution. The mixture was stirred at room temperature under nitrogen for 4 hr. The difficultly soluble epoxide gradually went into solution during this period. Chloroform (50 ml.) was added and this solution was extracted three times with 50-ml. portions of 1 molar sodium hydroxide solution. The chloroform was then washed once with water and dried with Drierite. Removal of solvent left 535 mg. of oily residue which crystallized upon addition of a few drops of ether. Filtration gave 485 mg. of white crystals, m.p. 109–114°. Melting was accompanied by the evolution of a gas. Recrystallization from ether gave sharp melting prisms, m.p. 110–111°, again accompanied by gas evolution. The melts resolidified and melted again at 140–142°. The infrared spectra of the lower melting material and the 140–142° material indicated that the former was very probably an etherate. Loss of ether accompanied the melting process. The analytical sample was obtained by several recrystallizations from ether followed by a final melting under reduced pressure, m.p. 140–142° (pure), λ_{max}^{alc} 254 mμ, ε 15,000. The infrared spectrum indicated the presence of an hydroxyl group and an α,β-unsaturated ketone function.

Anal. Calcd. for $C_{25}H_{32}O_4S$: C, 70.06; H, 7.53; S, 7.48. Found: C, 69.94; H, 7.51; S, 7.53.

Desulfurization of VIIIa.—Approximately 500 mg. of alcohol-washed Raney nickel was refluxed for 10 minutes with 20 ml. of ethyl acetate and then cooled. To this suspension was added 74 mg. of VIIIa. After stirring for 6 hr. at room temperature, the nickel was removed by filtration and the solvent distilled off. A clear glass (51 mg.) remained which crystallized on addition of a few drops of ether. The crude material, m.p. 172–177°, was recrystallized from ether–acetone yielding white needles, m.p. 185–187°. The infrared spectrum of this material was found to be identical with that of IId. No depression was observed upon taking a mixed melting point.

dl-**1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-6α-hydroxy-4,6a,9,9-tetramethyl-11b-phenylthiophenanthro[2,3][1,3]dioxole-3(2H)-one (VIIIb).**—The α-epoxide IIIb (309 mg.) was treated with thiophenol exactly as described for the preparation of VIIIa. The yield of crystalline VIIIb, m.p. 215–217°, after trituration with ether was 400 mg. (96%). One recrystallization from ether–chloroform gave pure material, m.p. 216–217°, λ_{max}^{alc} 254 mμ, ε 14,200.

Anal. Calcd. for $C_{25}H_{32}O_4S$: C, 70.06; H, 7.53; S, 7.48. Found: C, 70.12; H, 7.48; S, 7.50.

dl-**1,6a,7,7a,10a,11,11a,11b-Octahydro-4,6a,9,9-tetramethyl-11b-phenylthiophenanthro[2,3][1,3]dioxole-3(2H)-one (IXa).**—A mixture of either VIIIa or VIIIb (1.41 g.) and 5 ml. of 95% ethanol was treated with 10 ml. of 1.2 molar ethanolic potassium hydroxide. After refluxing gently under nitrogen for 10 min., the reaction was cooled and quenched with 40 ml. each of saturated sodium chloride solution and chloroform. The chloroform layer was separated, washed again with salt solution, dried and the solvent removed. The residual oil was dissolved in a few ml. of ether and allowed to crystallize in an ice-bath. The yield of first crop crystalline IXa was 875 mg., m.p. 126–128°, second crop 200 mg., m.p. 118–124°. The analytical sample was prepared by recrystallizing first crop material from a small amount of ether, m.p. 128–129°, λ_{max}^{alc} 280 mμ, ε 17,500. Careful comparison of material obtained starting with either VIIIa or VIIIb failed to show any difference. Both yielded IXa as evidenced by comparison of ultraviolet and infrared spectra and mixed melting points.

Anal. Calcd. for $C_{25}H_{30}O_3S$: C, 73.14; H, 7.37; S, 7.81. Found: C, 72.87; H, 7.46; S, 7.94.

Desulfurization of IXa.—Approximately 1.0 g. of alcohol-washed Raney nickel was added to a solution of 98 mg. of IXa in 20 ml. of acetone. After the mixture had been stirred overnight at room temperature, the nickel was removed by filtration. After evaporation of solvent, the crystalline residue, m.p. 140–150°, amounting to 50 mg. was dissolved in 20 ml. of ether and filtered through a few grams of alumina to remove hydroxylic materials. The clear oil obtained upon removal of ether yielded 35 mg. of material, m.p. 156–158°. Infrared and mixed

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m.p. showed this material to be identical with IIg, obtained by hydrogenation of Ic.

dl-4,4a,4b,5,6,7,8,8a-Octahydro-6β,7β-dihydroxy-1,8a-dimethyl-4a-phenylthio-2(3H)-phenanthrone (Xa).—Approximately 350 mg. of IXa was dissolved at room temperature in 2 ml. of glacial trifluoroacetic acid. As soon as the solid had dissolved (5 min.), the mixture was quenched with 15 ml. of saturated sodium chloride solution and 30 ml. of chloroform. The aqueous phase was extracted with another small portion of chloroform and discarded. The chloroform solutions were combined, washed once with salt solution, dried and the solvent removed. The good quality glycol remaining amounted to 271 mg. (86%), m.p. 178–180°. A single recrystallization from ethyl acetate gave pure Xa, m.p. 179–180°, λ_{max}^{alc} 282 mμ, ϵ 15,000, as colorless needles.

Anal. Calcd. for $C_{22}H_{26}O_3S$: C, 71.31; H, 7.07; S, 8.65. Found: C, 71.19; H, 7.05; S, 8.70.

dl-*anti*-*trans*-1,6a,7,7a,10a,11,11a,11b-Octahydro-4,6a,-9,9-tetramethyl-2-phenylthiophenanthro[2,3][1,3]dioxole-3(2H)-one (VIIa).—A suspension of 3.6 meq. of potassium *t*-butoxide in toluene was prepared by adding 3.8 ml. of 0.95 molar potassium *t*-butoxide in *t*-butyl alcohol to 80 ml. of boiling anhydrous toluene. All of the alcohol was fractionated out. The fine suspension of potassium *t*-butoxide at reflux temperature under nitrogen was treated with 1.0 g. of Ic dissolved in 15 ml. of anhydrous toluene. The suspension was then heated and the additional *t*-butyl alcohol formed was distilled out. The potassium salt of the ketone separated as a yellow-white powder. After the alcohol had been removed, the suspension was cooled to −5° and 570 mg. of benzenesulfenyl chloride[19] in 10 ml. of anhydrous toluene was added. A rapid reaction occurred and the heavy suspension was replaced by a fine precipitate of potassium chloride. Water (50 ml.) and ether (50 ml.) were added and the organic layer separated. After washing and drying, the organic solvents were removed under reduced pressure. The residual orange oil which partially crystallized on trituration with ether yielded 600 mg. of impure crystals, m.p. 150–165°. About 200 mg. of diphenyl disulfide was isolated from the mother liquors. Recrystallization of the crude crystalline product 5 times from ethyl acetate and acetone and finally from ethanol gave what appeared to be a pure compound, m.p. 192–194°. Infrared spectra on intermediate fractions had shown the presence of small amounts of saturated carbonyl-containing impurities. The spectrum of the 192–194° material showed only dienone absorption and bands characteristic of an aromatic ring. The ultraviolet spectrum in 95% ethanol showed λ_{max}^{alc} 293 mμ, ϵ 19,800. When this solution was treated with two drops of sodium hydroxide solution, a shift to λ_{max}^{alc} 287 mμ, ϵ 22,400, occurred.

Anal. Calcd. for $C_{25}H_{30}O_3S$: C, 73.14; H, 7.37; S, 7.81. Found: C, 73.18; H, 7.15; S, 7.65.

Reaction of IIIa with Sodium Methoxide.—Four grams of IIIa was refluxed under nitrogen for 4 hr. with 40 ml. of 1.2 molar sodium methoxide in methanol. The greenish-yellow solution was cooled and quenched with 150 ml. of aqueous saturated sodium chloride solution. The oil which separated was extracted with 200 ml. of ether in three portions. The ether extracts were washed with salt solution, dried with Drierite and the solvent removed. The yellow glass remaining amounted to 3.75 g. and partially crystallized on standing. The crude mass was boiled with 100 ml. of petroleum ether (b.p. 60–70°). The hot liquor was decanted from some insoluble residue, treated with a little carbon and concentrated. A yellow oil separated on cooling and slowly crystallized on standing. This crop of material amounted to 1.35 g., m.p. 105–108°. Three recrystallizations from petroleum ether gave a pure sample of the methoxy dienone IXb, m.p. 108–110°, λ_{max}^{alc} 289 mμ, ϵ 25,200. A comparison of the infrared spectrum of this pure ketone with that of the initial reaction product indicated that IXb was present in the crude material roughly to the extent of 70%.

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; CH_3O–, 9.34. Found: C, 72.63; H, 8.75; CH_3O–, 9.35.

Mother liquors from preceding crystallizations were combined and concentrated to about 50 ml. This solution was then placed on a column of 100 g. of alumina and eluted with a mixture of hexane (80%) and ether; 23 fractions of 50 ml. each were collected. Fraction 1 contained 150 mg. of a new methoxy ketone, m.p. 149–151° (crude) and m.p. 152–154°, λ_{max}^{alc} 304 mμ, ϵ 15,300, shoulder at 256 mμ, after several recrystallizations from ether. On the basis of its spectra, this material was tentatively identified as VIb, since it was undoubtedly isomeric with IXb.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 72.26; H, 8.49; CH_3O–, 9.34. Found: C, 72.18; H, 8.46; CH_3O–, 9.49.

Fractions 2, 3 and 4 and the mother liquors from 1 appeared to contain, in addition to IXb and VIb, another unidentified methoxydienone which was indicated by the presence of several extremely distinct diamond-shaped crystals. These fractions, amounting to about 80 mg., were combined and chromatographed separately on 5 g. of alumina using the same ether–hexane eluent as in the previous chromatogram. Eight fractions were collected. The third fraction, 22 mg., appeared to be relatively pure, m.p. 141.5–143°. These crystals were recrystallized twice from ether and hexane giving 8 mg. of a new C_{20}-methoxy dienone, m.p. still 141.5–143°, λ_{max}^{alc} 294 mμ, ϵ 24,000. The infrared spectrum closely resembled that of IXb and VIb in the carbonyl region but showed distinct differences in the fingerprint region. The structure of this material is still unknown. Again, however, it is almost certainly isomeric with IXb and VIb. It was an extremely minor product in the methoxide cleavage reaction, however.

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; CH_3O–, 9.34. Found: C, 72.33; H, 8.32; CH_3O–, 9.48.

Still a fourth compound was isolated from the original chromatogram. Fractions 5 to 23 consisted mostly of IXb. The eluent was changed to acetone for fractions 24 to 27. Fraction 24 contained 100 mg. of hard ether-insoluble crystals, m.p. 195–200°, recrystallized from acetone, m.p. 198–202°, λ_{max}^{alc} 250 mμ, ϵ 12,700. The infrared spectrum showed the presence of one hydroxyl group and an α,β-unsaturated ketone. This material was shown to be VIIIc, the undehydrated precursor to IXb, by its conversion to the latter. Seventy-seven milligrams of VIIIc, refluxed for 3 hr. under nitrogen with 5 ml. of 1.1 molar sodium methoxide solution, yielded upon workup (as previously described) 50 mg. of crude IXb. This was cleaned up by filtration through about 700 mg. of alumina and gave 22 mg. of pure IXb, m.p. 108–110°. Comparison of infrared spectra and a mixed m.p. established their identity.

Reaction of α-Epoxide IIIb with Sodium Methoxide.—To 5 ml. of 1.1 molar sodium methoxide–methanol solution was added 260 mg. of IIIb. The mixture was refluxed under nitrogen for 7 hr. and worked up as described for the reaction of IIIa. The oily product, amounting to 248 mg., was dissolved in 2 ml. of ether, cooled to 0° and seeded with a microcrystal of IXb. After standing at 0° for 60 hr., 77 mg. of crystals, m.p. 113–121°, had formed. These were collected, dissolved in benzene and chromatographed on 15 g. of alumina. In all, 45 fractions were collected. Fractions 22 to 31 contained 20 mg. of crystals, m.p. 105–108°. These were combined and recrystallized twice from petroleum ether giving 10 mg. of pure IXb, m.p. 108–110°. The infrared spectrum of this material was identical with IXb obtained by methoxide cleavage of the β-epoxide IIIa. A mixed m.p. showed no depression. Comparison of the infrared spectrum of the crude product obtained and pure IXb indicated that the latter was present in the crude to the extent of about 30–40%. No other pure material was isolated from the very complex reaction product, although infrared spectra on various fractions suggested that VIb also might be present.

dl-4,4a,4b,5,6,7,8,8a-Octahydro-6β,7β-dihydroxy-4a-methoxy-1,4a-dimethyl-2(3H)phenanthrone (Xb).—Treatment of 480 mg. of purified IXb, m.p. 108–110°, with 3 ml. of trifluoroacetic acid exactly as described previously for the preparation of Xa, gave 350 mg. of crude glycol Xb, m.p. 162–165°. Two melting points, m.p. 165–166° (metastable) and 177–178° (stable), were found for the pure glycol upon several recrystallizations from ethyl acetate. When the melt from the 165–166° material was allowed to resolidify, it remelted at the higher temperature. Furthermore, a solution of the lower melting material seeded with the higher melting form crystallized completely as the latter, λ_{max}^{alc} 289 mμ, ϵ 25,800.

The acetonide group was also removed with the same results using aqueous mineral acids and dioxane. A number

(19) H. Lecher and F. Holschneider, *Ber.*, **57**, 755 (1924).

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of attempts to remove the methoxyl group by heating with strong aqueous mineral acids either caused general decomposition or failed to change the dienone absorption in the ultraviolet.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27; CH_3O–, 10.61. Found: C, 69.65; H, 8.18; CH_3O–, 10.51.

Treatment of Xb with anhydrous copper sulfate in acetone by standard procedures[1] reconverted the glycol back to its acetonide IXb in essentially quantitative yield.

C-Methyl Determinations.—Compounds of Xa and Xb along with model compounds of established structure (Ia), and the norketone corresponding to Ia but without the methyl group in the 4-position[20], were submitted without structural identification to an independent analyst[21] for Kuhn–Roth C-methyl determination. The observed number of C-methyl groups for Xa, Xb, Ia and the norketone were 1.19, 1.18, 1.31 and 0.58 indicating that both Xa and Xb correspond to Ia in the number of C-methyl groups present.

(20) Prepared as outlined in footnote 25 of the Woodward paper cited in reference 1.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

C-22 Isomeric Dihydrosapogenins from Kryptogenin

BY IRVING SCHEER, MALCOLM J. THOMPSON AND ERICH MOSETTIG

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In the reduction of kryptogenin in acidic media three compounds have been obtained: dihydrotigogenin and two new sapogenin derivatives. It is shown that the new compounds are isomeric at C-22 and are 22,26-epoxycholestane-3β,16ξ-diol and 22,26-epoxy-22-isocholestane-3β,16ξ-diol. The preparation of cholestane-3β,22,26-triol and cholestane-3β,26-diol-22-one is described. The latter was converted to 22,26-epoxycholestan-3β-ol and 22,26-epoxy-22-isocholestan-3β-ol.

The reduction of kryptogenin (I) yields a variety of products, depending on the experimental conditions employed. Thus, Marker, *et al.*,[1] obtained diosgenin when reducing I with sodium in ethanol, tigogenin (II) and dihydrotigogenin (III) when using platinum oxide in acid media, and dihydrokryptogenin with the same catalyst in a neutral medium. On the other hand, Kaufmann and Rosenkranz[2] obtained "16-dihydrokryptogenin" (XVII) by hydrogenating I in neutral solution with Raney nickel catalyst. In our hands the hydrogenation of kryptogenin (I) with platinum oxide in glacial acetic acid at 25° gave a mixture of at least three compounds which were separated by chromatography on alumina. The main product was dihydrotigogenin (III) and was obtained in a yield of about 80%. The two other products each being formed in an approximate yield of 10% were unknown derivatives.[3] We could show that these new compounds differ only in their configuration at C-22 and have the structures of a 22,26-epoxycholestane-3β,16ξ-diol (IV) and a 22,26-epoxy-22-isocholestane-3β,16ξ-diol (V).[4] The reduction of kryptogenin diacetate under similar conditions yielded only dihydrotigogenin diacetate as previously reported.[1] The infrared spectra of IV and V exhibited strong hydroxyl absorption at 3571 cm.$^{-1}$ (unassociated) and at 3401 cm.$^{-1}$ (associated), no carbonyl absorption, and differed decidedly in the fingerprint region. The bands characteristic for sapogenins were absent, and there was no resemblance to the infrared spectra of dihydrosapogenins. Elemental analysis established for IV and V the empirical formula $C_{27}H_{46}O_3$, *i.e.*, they are isomeric with dihydrotigogenin. Esterification readily gave diesters, indicating that each, IV and V, contained two hydroxyl groups and a third oxygen in an inert ether-like linkage. Oxidation of IV and V with chromic acid led to the diketo-compounds VI and VII, respectively. The strong bands at 1712 and at 1736 cm.$^{-1}$ suggested a 3-ketone and a 16-ketone. Reduction of VI and VII, either catalytic (with PtO_2 in acetic acid) or with sodium borohydride in methanol, gave nearly quantitatively the dialcohols IV and V, respectively, *i.e.*, in either instance only one isomer.

The deoxylation of 22,26-epoxycholestane-3β,16ξ-diol (IV) and 22,26-epoxy-22-isocholestane-3β,16ξ-diol (V) yielded 22,26-epoxycholestane (VIII) and 22,26-epoxy-22-isocholestane (IX), respectively. Compounds VIII and IX contain only two asymmetric centers (C_5 and C_{22}) not found in the original kryptogenin. The remote possibility that these isomers differ at C_5 was eliminated by showing that 5,6-dihydrokryptogenin (XII) was also reduced to III, IV and V.

In order to confirm the structures of VIII and IX, these compounds were also prepared by a different route. Treatment of 5,6-dihydrokryptogenin diacetate (XIII) with ethane dithiol gave a monoethylenethioketal derivative. Infrared analysis showed that it was not the C-22 carbonyl group that had reacted and that XIV was a C_{16}-ethylenethioketal. Desulfurization with freshly prepared Raney nickel in dioxane yielded a mixture from which after hydrolysis and chromatography on alumina cholestane-3β,22,26-triol (XV) and cholestane-3β,26-diol-22-one (XVI) were obtained in an approximate ratio of 6:1. For the routine preparation of XVI the crude mixture from the desulfurization of XIV was oxidized gently with chromic acid to give XVI as the sole product after saponification. Catalytic reduction (PtO_2, acetic acid) of XVI led to a mixture of the triol XV, 22,26-epoxycholestan-3β-ol (X) and 22,26-epoxy-22-isocholestan-3β-ol (XI). By chromatography and fractional crystallization compounds

(1) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. J. P. Goldsmith and C. H. Ruof, THIS JOURNAL, **69**, 2167 (1947).

(2) S. Kaufmann and G. Rosenkranz, *ibid.*, **70**, 3502 (1948).

(3) In one instance when for some reason the reduction did not go to completion a small amount of tigogenin (II) could be isolated.

(4) The configuration at C-22 as shown in the structural formulas V and V is arbitrary. The naming of V as an iso compound is provisional.

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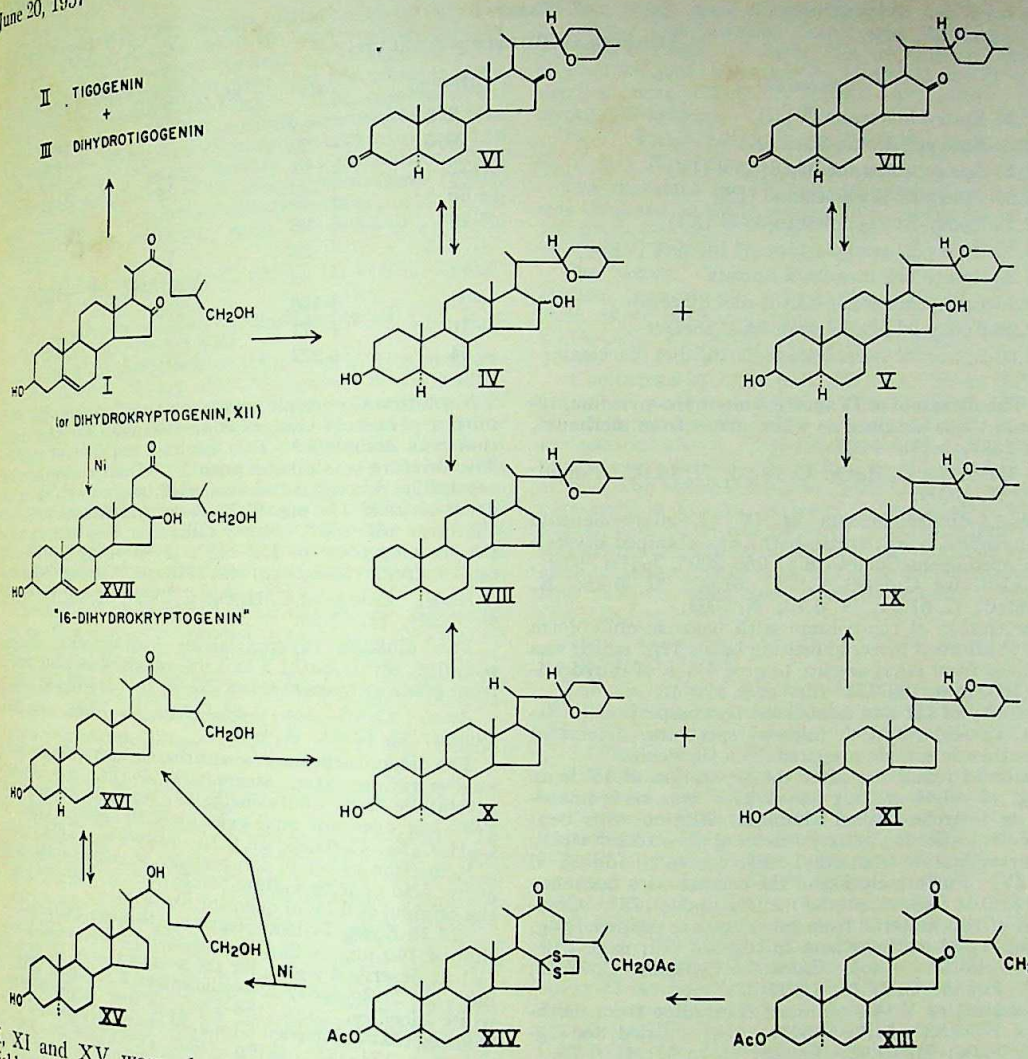

X, XI and XV were obtained in the respective yields of 23, 43 and 15%. Deoxylation of X and XI gave VIII and IX showing that X and XI were the 16-deoxy analogs of IV and V. Reduction of XVI with sodium borohydride in methanol gave the triol XV in excellent yield. Deoxylation of XV gave cholestane.

It should be noted that no definite assignment of configuration at C-16 of IV and V can be made at this time. Hirschmann, *et al.*,[5] had postulated that reduction of a 16-ketosteroid leads to a 16β-hydroxy compound. Hence we were inclined to assign to IV and V the 16β-hydroxy configuration. The $\Delta M_{D^{16\text{-OH}-H}}$ values for IV and V, however, are -72 and $-70°$, respectively (Table I), agreeing fairly well with the average value $\Delta M_{D^{16\alpha\text{-OH}-H}} -60°$ in ethanol which Fukushima, *et al.*,[6] attributed to a 16α-hydroxyl group. Furthermore, these authors have shown that the contribution of a 16α-acetoxy group is about $-300°$ and of a 16β-acetoxy approximately $+100°$. The contribution of the 16-acetoxy group in our 22,26-epoxycholestane derivatives (see acetates of X and IV and of XI and V, respectively) is approximately $+200°$. Even though no configuration can be assigned to the 16-oxygen functions of IV and V on the basis of the anomalous rotational data, the indications are very strong that the configuration is the same in both series.

Experimental[7]

Reduction of Kryptogenin.—A mixture of 10.0 g. of rigorously purified kryptogenin (I, m.p. 192–193°, $[\alpha]^{20}D$ -198 to $-200°$), 1.0 g. of Adams catalyst and 350 ml. of glacial acetic acid was shaken with hydrogen at room temperature and atmospheric pressure for 24 hr. Three molecular equivalents of hydrogen was absorbed. The crystalline residue obtained from the mixture was chromatographed on benzene-washed alumina. The first few fractions eluted with benzene–chloroform 9:1 yielded 5.0 g. of a mixture melting above 175°. This material was fractionally crystallized from ethyl acetate to give 1.0 g. of **22,26-epoxycholestane-3β,16ξ-diol** (IV) as thin, white needles, melting at 265–268°, $[\alpha]^{20}D$ $-22°$.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.59; H, 11.22.

IV was obtained in several polymorphic forms melting at 240–240.5°, 265–268°, 276–277°. Their identity was established by infrared analysis, optical rotation and interconversion of one form to another by seeding and crystalli-

(5) R. Hirschmann, F. B. Hirschmann and M. A. Daub, THIS JOURNAL, **74**, 539 (1952); see also leading references in this paper.

(6) D. K. Fukushima and T. F. Gallagher, *ibid.*, **73**, 196 (1951).

(7) All melting points were determined on the Kofler block. Unless otherwise noted, rotations were determined in approximately 1% solutions in chloroform. Infrared spectra were obtained with a Perkin-Elmer double beam spectrophotometer with sodium chloride prism and cells.

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TABLE I

MOLECULAR ROTATION ANALYSIS

Compound	$[\alpha]^{CHCl_3}D$	M_D	ΔM_D M_D 16-OH−H	M_D 22-"normal" − 22-"iso"
22,26-Epoxycholestane (VIII)	− 1.5°	− 6°		
22,26-Epoxycholestan-3β-ol (X)	− 5.5	− 22		−141°
22,26-Epoxycholestane-3β,16ξ-diol (IV)	−22	− 94	− 72°	−115
22,26-Epoxy-22-isocholestane (IX)	+35	+135		−117
22,26-Epoxy-22-isocholestan-3β-ol (XI)	+23	+ 93		
22,26-Epoxy-22-isocholestane-3β,16ξ-diol (V)	+ 5.5	+ 23	− 70	
22,26-Epoxycholestan-3β-ol acetate	−14	− 62	$M_{D16\text{-}OAc-H}$	−133
22,26-Epoxycholestane-3β,16ξ-diol diacetate	+31	+156	+218	
22,26-Epoxy-22-isocholestan-3β-ol acetate	+16	+ 71		−116
22,26-Epoxy-22-isocholestane-3β,16ξ-diol diacetate	+54	+272	+201	

zation. **The diacetate of IV** (acetic anhydride–pyridine, reflux, 30 min.) was obtained as white plates from methanol, m.p. 152–153°, $[\alpha]^{20}D$ +31°.

Anal. Calcd. for $C_{31}H_{50}O_6$: C, 74.06; H, 10.02. Found: C, 74.32; H, 10.09.

The di-3,5-dinitrobenzoate of IV (3,5-dinitrobenzoyl chloride–pyridine, 4 hr., steam-bath) was obtained crystalline from acetone–methanol, m.p. 268–269°, $[\alpha]^{20}D$ +19°. *Anal.* Calcd. for $C_{41}H_{50}O_{13}N_4$: C, 61.02; H, 6.25; N, 6.94. Found: C, 61.24; H, 6.13; N, 7.03.

Further elution of the column with benzene–chloroform 9:1 and 1:1 afforded material melting below 175° which was recrystallized from ethyl acetate to give 4.4 g. of **dihydrotigogenin (III)**, m.p. 169–171° (lit.[1] m.p. 170°).

The identity of III was established by comparison (melting point, optical rotation, infrared spectrum, diacetate) with an authentic sample prepared from tigogenin.

The material remaining after the separation of IV from the 5.0 g. of solids melting above 175° was rechromatographed on benzene-washed alumina. Elution with benzene–ether 3:1 afforded material melting above 230° which upon recrystallization from ethyl acetate gave an additional 0.2 g. of **IV**. Further elution of the column with benzene–ether 3:1 and 1:1 gave material melting above 175°. Crystallization of this material from ethyl acetate yielded 1.0 g. of **22,26-epoxy-22-isocholestane-3β,16ξ-diol (V)**, m.p. 212–215°, $[\alpha]^{20}D$ +5.5°. *Anal.* Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.18; H, 11.37.

The diacetate of V was obtained crystalline from methanol, m.p. 179–182°, $[\alpha]^{20}D$ +54°. *Anal.* Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.02. Found: C, 74.07; H, 9.75.

The di-3,5-dinitrobenzoate of V was crystallized from acetone–methanol, m.p. 235–237, $[\alpha]^{20}D$ +36°. *Anal.* Calcd. for $C_{41}H_{50}O_{13}N_4$: C, 61.02; H, 6.25; N, 6.94. Found: C, 60.87; H, 6.37; N, 6.93.

Elution of the column with chloroform yielded an additional 2.2 g. of **III**.

Thus from 10.0 g. of kryptogenin (I) was obtained 1.2 g. (12.4%) of 22,26-epoxycholestane-3β,16ξ-diol (IV), 1.0 g. (10.3%) of 22,26-epoxy-22-isocholestane-3β,16ξ-diol (V) and 6.6 g. (68%) of dihydrotigogenin III.

The infrared spectra of IV and V in chloroform solution (3%) were distinctly different. IV showed a weak band at 1129 cm.$^{-1}$ and twin bands at 907 and 871 cm.$^{-1}$, while V showed a strong absorption maximum at 1129 cm.$^{-1}$ and twin bands at 905 and 895 cm.$^{-1}$, other differences useful for distinguishing the two isomers were medium bands at 978, 967 and 957 cm.$^{-1}$ in IV which appeared at 983, 969 and 954 cm.$^{-1}$ in V.

In another reduction experiment under these same conditions, 0.4 g. of **tigogenin (II)** was isolated from 12.0 g. of kryptogenin in addition to III, IV and V which were obtained in their usual proportions. The tigogenin was identified by direct comparison with an authentic sample.

Reduction of 5,6-Dihydrokryptogenin.—A mixture of 1.0 g. of 5,6-dihydrokryptogenin (XII), 0.1 g. of Adams catalyst and 50 ml. of glacial acetic acid was shaken with hydrogen at room temperature and atm. pressure for 24 hr. Two molecular equivalents of hydrogen were absorbed. Separation of the reduction mixture as described above yielded 0.1 g. of IV, 0.09 g. of V and 0.6 g. of III.

22,26-Epoxycholestane-3,16-dione (VI).—To a stirred solution of 160 mg. of 22,26-epoxycholestane-3β,16ξ-diol (IV) in 200 ml. of acetone at 20° was added, dropwise, 0.8 ml. of 8 *N* solution of chromic acid in dilute sulfuric acid (*ca.* 40%) until a persistent orange-brown coloration indicated oxidation was complete.[8] This addition required 45 minutes. The mixture was diluted with 2 l. of water and the white crystalline precipitate was collected, washed with water and dried to yield 140 mg. of **22,26-epoxycholestane-3,16-dione VI**, m.p. 167–169°. Recrystallization from ethanol raised the melting point to 172–173°, $[\alpha]^{20}D$ − 107°, ν^{CHCl_3} 1736 cm.$^{-1}$ strong (16-ketone) and 1716 cm.$^{-1}$ strong (3-ketone).

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.28; H, 10.26.

The dioxime (hydroxylamine hydrochloride, ethanol-pyridine, steam-bath, 2 hr.) was obtained as white needles from ether–petroleum ether (30–60°), m.p. 246–248° dec.

Anal. Calcd. for $C_{27}H_{44}O_3N_2$: C, 72.93; H, 9.97. Found: C, 72.60; H, 9.75.

The disemicarbazone (semicarbazide hydrochloride, methanol–pyridine–water, steam-bath, 16 hr.) was obtained crystalline from dilute methanol, begins to decompose at 278° but does not melt even at 320°. *Anal.* Calcd. for $C_{29}H_{48}O_3N_6$: C, 65.87; H, 9.15. Found: C, 65.65; H, 9.01.

Reduction of VI in the presence of Adams catalyst and acetic acid or with sodium borohydride in methanol yielded the original diol IV in quantitative yield.

22,26-Epoxy-22-isocholestane-3,16-dione (VII).—Oxidation of 140 mg. of 22,26-epoxy-22-isocholestane-3β,16ξ-diol (V) as described above for the preparation of VI gave 130 mg. of **22,26-epoxy-22-isocholestane-3,16-dione (VII)** as white needles, m.p. 138–175°. Three recrystallizations from methanol afforded 65 mg. of constantly melting material, m.p. 171–175°, $[\alpha]^{20}D$ −104°. ν^{CHCl_3} 1736 cm.$^{-1}$ strong (16-ketone) and 1716 cm.$^{-1}$ strong (3-ketone). A polymorphic form was also obtained which melts at 133–135°.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 77.97; H, 10.19.

Treatment of VII under the conditions which yielded a disemicarbazone from VI afforded a monosemicarbazone, **22,26-epoxy-22-isocholestane-3,16-dione 3-semicarbazone**, m.p. 236–243° dec. The infrared spectrum of this derivative exhibits the typical bands of a semicarbazone[9] and in addition retains the strong absorption band at 1736 cm.$^{-1}$ attributed to the 16-ketone.

Anal. Calcd. for $C_{28}H_{45}O_3N_3$: C, 71.30; H, 9.61. Found: C, 71.60; H, 9.80.

Reduction of VII in the presence of Adams catalyst and acetic acid yielded the original diol V.

22,26-Epoxycholestane (VIII).—To a solution of 0.3 g. of 22,26-epoxycholestane-3β,16ξ-diol (IV) in 12 ml. of dry pyridine at 0° was added an ice-cold solution of 0.6 ml. of methanesulfonyl chloride in 3 ml. of pyridine, and the mixture was kept at 3° overnight. The orange solution was poured into ice and water, and the oily precipitate was extracted with ether. The ethereal solution was washed with cold 5% hydrochloric acid, water, 2% sodium bicarbonate solution, water and dried over sodium sulfate. The solution was evaporated *in vacuo* to an oil which was dissolved in 30 ml. of benzene, distilled to a volume of 18 ml., and 18 ml. of dry ether and 4 ml. of a 1.6 *M* solution of lithium aluminum hydride in ether were added and the mixture was

(8) A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(9) L. Ruzicka, P. A. Plattner and P. E. Christie, *ibid.*, 3389 (1955).

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refluxed overnight. The reaction mixture was cooled and after the addition of a few drops of ethyl acetate, treated with 10 ml. of 6 *N* hydrochloric acid. The aqueous layer was separated, extracted with ether and the extracts combined with the benzene–ether layer. The combined extracts were washed with 10% sodium bicarbonate solution and with water, dried over sodium sulfate and evaporated to dryness *in vacuo*. The oily residue was crystallized from methanol to yield 0.2 g. of **22,26-epoxycholestane (VIII)**, m.p. 149–152°. One recrystallization gave 0.18 g. of analytically pure material, m.p. 151.5–152.5°, $[\alpha]^{20}D$ −1.5°.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.71; H, 11.97.

The reduction of 22,26-epoxycholestan-3β-ol (X) in a similar manner also yielded VIII.

22,26-Epoxy-22-isocholestane (IX).—As in the preparation of VIII above, 150 mg. of 22,26-epoxy-22-isocholestane-3β,16ξ-diol (V) in 5 ml. of dry pyridine was treated with 0.3 ml. of methanesulfonyl chloride in 1.5 ml. of dry pyridine at 3°. The oil thus obtained was dissolved in 15 ml. of benzene and distilled to a volume of 9 ml. To the solution was added 9 ml. of dry ether and 2 ml. of a 1.6 *M* solution of lithium aluminum hydride in ether, and the mixture was refluxed overnight. The oil obtained from the reduction mixture gave a slight positive test with tetranitromethane and was dissolved in 10 ml. of dioxane and shaken under hydrogen in a stainless steel bomb for 24 hr. at 150° and 1500 p.s.i. in the presence of 2 ml. of Raney nickel in ethanol. The mixture was filtered and concentrated *in vacuo* to a colorless oil which gave a negative test with tetranitromethane. Crystallization from methanol yielded 70 mg. of **22,26-epoxy-22-isocholestane (IX)**, m.p. 159–163°, $[\alpha]^{20}D$ + 35°. Recrystallization did not alter the melting point.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.70; H, 11.87.

The reduction of 22,26-epoxy-22-isocholestan-3β-ol (XI) in a similar manner, also yielded IX.

Cholestane-3β,26-diol-16,22-dione 3,26-Diacetate 16-Ethylenethioketal (XIV).—To a solution of 3.0 g. of 5,6-dihydrokryptogenin diacetate (XIII) in 2 ml. of ethanedithiol was added 1.5 ml. of a solution of boron fluoride in ether (Eastman Kodak Co. practical 45% BF_3 in ether). The mixture was hand stirred and set to a stiff paste in about one minute. The paste was thinned with methanol and the white solid collected and washed with methanol. Recrystallization from ethanol gave 3.1 g. of **cholestane-3β,26-diol-16,22-dione 3,26-diacetate 16-ethylenethioketal (XIV)** as white needles, m.p. 193–194°, $[\alpha]^{20}D$ −37°, ν^{CS_2} 1739 cm.$^{-1}$ strong (acetate) and 1706 cm.$^{-1}$ strong (22-ketone).

Anal. Calcd. for $C_{33}H_{52}O_6S_2$: C, 66.85; H, 8.84; S, 10.82. Found: C, 67.00; H, 8.91; S, 11.10.

Saponification of XIV with 2% potassium hydroxide in methanol for 2 hr. at reflux temperature afforded **cholestane-3β,26-diol-16,22-dione-16-ethylenethioketal (kryptogenin 16-ethylenethioketal)** in quantitative yield as white needles from methanol, m.p. 194–195°, $[\alpha]^{20}D$ −28°. For analysis a sample was recrystallized from ethyl acetate, m.p. 195–197°.

Anal. Calcd. for $C_{29}H_{48}O_3S_2$: C, 68.45; H, 9.51; S, 12.60. Found: C, 68.30; H, 9.39; S, 12.30.

Cholestane-3β,26-diol-22-one (XVI).—A mixture of 1.0 g. of cholestane-3β,26-diol-16,22-dione 3,26-diacetate 16-ethylenethioketal (XIV), 4 teaspoons of Raney nickel and 150 ml. of dioxane was refluxed for 16 hr. The Raney nickel was filtered and washed several times with hot dioxane. The combined filtrate and washings were concentrated to dryness *in vacuo* to yield a solid residue. The residue was dissolved in 300 ml. of acetone at 20° and oxidized by dropwise addition of an 8 *N* solution of chromic acid in sulfuric acid and water until a persistent orange color remained. The solution was poured into 3 l. of water and extracted with ether. The ethereal solution was washed with water, 2% aqueous sodium bicarbonate, water, dried over sodium sulfate and concentrated to dryness *in vacuo*. The resultant residue was dissolved in 120 ml. of ethanol and saponified by refluxing for 5 hr. with 6.0 g. of potassium bicarbonate in 100 ml. of water. The solution was concentrated *in vacuo* to one-half its volume and extracted with ether. The ethereal solution was washed with water, dried over sodium sulfate and concentrated to dryness *in vacuo* to yield a crystalline residue which was chromatographed on benzene-washed alumina. The fractions eluted with benzene–chloroform 9:1 and 6:1 were combined and crystallized from benzene to yield 0.6 g. of **cholestane-3β,26-diol-22-one (XVI)** as white needles, m.p. 173–175°, $[\alpha]^{20}D$ +6°, ν^{CHCl_3} 1706 cm.$^{-1}$ strong (22-ketone).

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.54; H, 11.05.

The diacetate (acetic anhydride–pyridine, 18 hr., 25°) was obtained as white needles from methanol, m.p. 102.5–103.5°, $[\alpha]^{20}D$ −8.5°. *Anal.* Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.02. Found: C, 74.35; H, 10.08.

The oxime (hydroxylamine hydrochloride, pyridine–ethanol, steam-bath, 4 hr.) was obtained as thin plates from dilute methanol, m.p. 192–194°. *Anal.* Calcd. for $C_{27}H_{47}O_3N$: C, 74.78; H, 10.92. Found: C, 74.62; H, 10.89.

Cholestane-3β,22,26-triol (XV). a. From XIV.—Three grams of cholestane-3β,26-diol-16,22-dione 3,26-diacetate 16-ethylenethioketal (XIV) was reduced with Raney nickel as described above. The dioxane solution was concentrated to dryness *in vacuo*. The residue was dissolved in 200 ml. of ethanol and refluxed for 5 hr. with 12.0 g. of potassium bicarbonate in 140 ml. of water. The solution was cooled, diluted with water and filtered. The crystalline precipitate was triturated with benzene and recrystallized from methanol–benzene to yield 1.2 g. (47.5%) of **cholestane-3β,22,26-triol (XV)** as white needles, m.p. 229–232°, $[\alpha]^{20}D$ +15° (EtOH).

Anal. Calcd. for $C_{27}H_{48}O_3$: C, 77.09; H, 11.50. Found: C, 76.91; H, 11.53.

The triacetate of XV (acetic anhydride–pyridine, 18 hr., 25°) was obtained as needles from methanol, m.p. 98–100°. *Anal.* Calcd. for $C_{33}H_{54}O_6$: C, 72.49; H, 9.96. Found: C, 72.68; H, 9.72.

The benzene solution which was recovered after the trituration of the crystalline precipitate from the Raney nickel was chromatographed on benzene-washed alumina. Elution with benzene yielded 0.20 g. (8%) of **XVI**, m.p. 172–175°. One hundred milligrams of another crystalline material was obtained from a fraction eluted with benzene–chloroform 9:1. This compound melted at 163–171°, exhibited strong absorption in chloroform at 1678 cm.$^{-1}$ (—C═C—?) and gave a positive tetranitromethane test. Reduction of this material (PtO_2, acetic acid) yielded **22,26-epoxy-22-isocholestan-3β-ol (XI)** from methanol, m.p. 150–153°. Concentration of the mother liquor gave an unsharply melting compound which is very likely the impure C-22-isomer of XI. The unsaturated parent compound is probably a 22,26-epoxide with a double bond at C-20,22 or at C-22,23, but no further work has been done with this compound.

b. From XVI.—A mixture of 0.050 g. of XVI, 0.150 g. of sodium borohydride, 5 ml. of methanol and 0.5 ml. of water was allowed to stand overnight at room temperature. Three drops of acetic acid were added, and the mixture was diluted with water and filtered to yield 0.045 g. (90%) of **cholestane-3β,22,26-triol (XV)**, m.p. 210–220°. Crystallization from methanol–benzene afforded 0.040 g. of **XV** as white needles, m.p. 227–230°, identical with the material obtained from procedure a above.

Cholestane from Cholestane-3β,22,26-triol.—Reduction of 0.150 g. of cholestane-3β,22,26-triol as previously described[10] for the reduction of tetrahydrotigogenin afforded 0.080 g. (60%) of cholestane, identical with an authentic sample.

22,26-Epoxy-22-isocholestan-3β-ol (XI).—A mixture of 1.0 g. of cholestane-3β,26-diol-22-one (XVI), 0.2 g. of Adams catalyst and 100 ml. of glacial acetic acid was shaken with hydrogen at room temperature and atm. pressure for 3 hr. until hydrogenation was complete. The crystalline residue obtained from the reaction was triturated with 50 ml. of benzene. The benzene-insoluble material yielded 0.10 g. of **cholestane-3β,22,26-triol (XV)**. The benzene-soluble material was chromatographed on benzene-washed alumina and a mixture was obtained from the fraction eluted with benzene–chloroform 98:2. From the fraction eluted with ethanol an additional 0.05 g. of XV was obtained. Repeated recrystallization of the mixture from the benzene–chloroform eluate yielded 0.42 g. of **22,26-epoxy-22-isocho-**

(10) I. Scheer and D. Mosettig, This Journal, **77**, 1820 (1955).

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lestan-3β-ol (XI), m.p. 152–158°. Another recrystallization from methanol yielded constant melting material, 0.33 g., m.p. 155–158°, but still not pure. From the combined recrystallization mother liquors was obtained 0.10 g. of pure XI, m.p. 161–163°, $[\alpha]^{20}D$ +23°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.42; H, 11.64.

The acetate was obtained as white crystals from dilute methanol, m.p. 131–133.5°, $[\alpha]^{20}D$ +16°. *Anal.* Calcd. for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.02; H, 10.92.

22,26-Epoxycholestan-3β-ol (X).—The mother liquors from the above reduction and subsequent purification procedures were combined and concentrated to dryness *in vacuo*. The residue was crystallized from ethyl acetate to yield thick plates of X, m.p. 215–219°. Recrystallization from methanol yielded 0.23 g. of 22,26-epoxycholestan-3β-ol (X) as needles, m.p. 211–214°, $[\alpha]^{20}D$ −5.5°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.51; H, 11.78.

The acetate was obtained as needles from methanol, m.p. 188.5–190°, $[\alpha]^{20}D$ −14°. *Anal.* Calcd. for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.46; H, 10.73.

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BETHESDA 14, MD.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. XXXVI. Side Chain Bromination Isomers of Diosgenin and Tigogenin[2]

BY MONROE E. WALL AND HOWARD W. JONES

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Bromination of diosgenin acetate with 3 moles of bromine in acetic acid solution for 2 to 3 hr. gave a mixture of 5α,6β,23a-tribromodiosgenin acetate (I) and the corresponding 23b isomer II which could be separated by fractional crystallization. Treatment of I with sodium iodide in ethanol gave 23a-bromodiosgenin acetate (III). Similar treatment of II yielded 23b-bromodiosgenin acetate (IV). Catalytic hydrogenation of III and IV gave, respectively, 23a-bromotigogenin acetate (V) and 23b-bromotigogenin acetate (VI). V and VI were also obtained by monobromination of tigogenin acetate. Prolonged treatment of diosgenin with $3^1/_3$ to $3^1/_2$ moles of bromine gave two isomeric tetrabromide isomers, arbitrarily designated tetrabromodiosgenin acetates A (VII) and B (VIII). Treatment of VII and VIII with sodium iodide gave the same dibromodiosgenin acetate (IX) which on catalytic hydrogenation gave dibromotigogenin acetate (X). Bromination of tigogenin acetate gave two dibromotigogenin acetate isomers, A (X) and B (XI). Dibromotigogenin acetate A was identical with the product obtained by hydrogenation of dibromodiosgenin acetate IX. Treatment of X and XI with sodium iodide in ethanol resulted in conversion of XI to X.

Bromination of the steroidal sapogenin side chain has received sporadic attention in the past 15 years. Marker and Rohrmann,[3] who first investigated the problem, stated that only one bromine atom could be introduced in the side chain of 25D ("iso") or 25L ("normal") sapogenins. Later Djerassi[4] and co-workers found that two atoms of bromine could be introduced in the side chain of sarsasapogenin (25L series). More recently Ziegler, Rosen and Shabica[5] have found that smilagenin (25D) series) can also be dibrominated in the side chain. In addition there have been several reports of the existence of bromine side chain isomers.[6] Recently Barton, Page and Shoppee[7] have on the basis of infrared spectra in the 700–500 $cm.^{-1}$ region assigned the equatorial position to the 23a compounds of the type described by Mueller and Norton[6a] and Dickson and Page.[6b] The 23b isomers were accordingly designated axial. The location of the bromine in the various side-chain brominated sapogenins has been placed at C_{23}[8] and accepted by subsequent workers. Although this assignment is logical, since the bromine atoms are located on a carbon atom adjacent to a potential carbonyl, it must be emphasized that the C_{23} assignment is not based on a rigid structure proof.

The experiments to be reported in this paper were the outgrowth of our interest in the stereochemistry of the spiroketal side chain.[9] On bromination of diosgenin acetate with 3 moles of bromine in acetic acid at 15–20°, a precipitate was noted. After filtration, the products in both the precipitate and filtrate fractions were isolated. It was apparent from the properties of the two fractions that they were isomeric. Since the infrared spectra of the soluble and insoluble fractions resembled, respectively, those of the 23a and 23b series described by Dickson and Page,[6b] we designated the acetic acid soluble fraction as 5α,6β,23a-tribromodiosgenin acetate (I) and the insoluble, precipitate fraction as 5α,6β,23b-tribromodiosgenin acetate (II). The structural assignments of I and II were on the following evidence. Bromine analysis showed that three bromine atoms were present. The infrared absorption bands between 800–840 $cm.^{-1}$ characteristic of the Δ^5-ethylenic moiety in diosgenin[10] and

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(2) Presented in part at the Delaware Valley Regional Meeting, American Chemical Society, February 16, 1956. Paper XXXV in this series, to *J. Org. Chem.*, in press.

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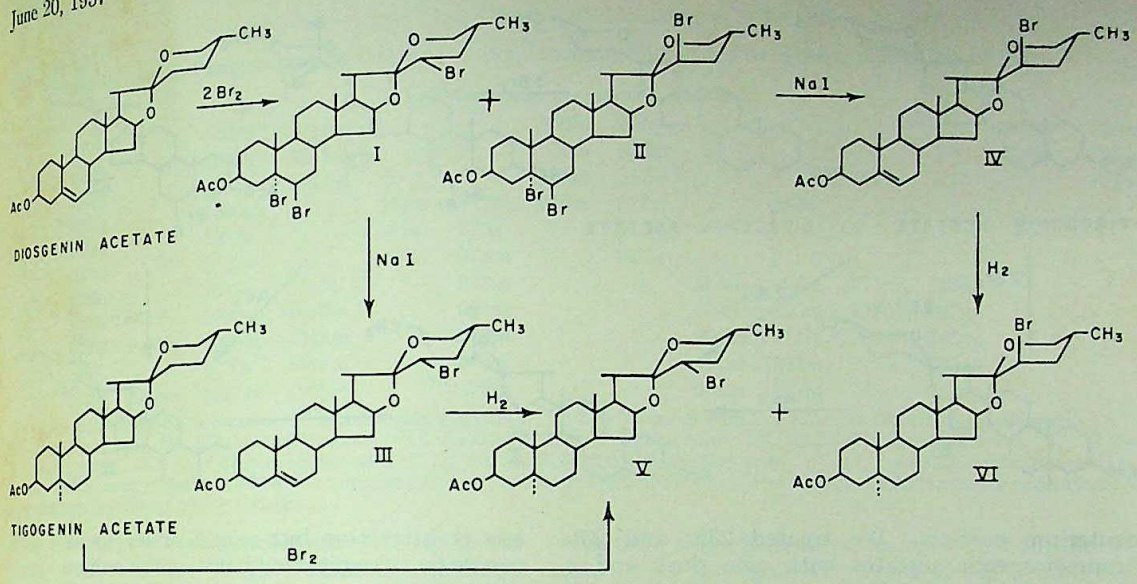


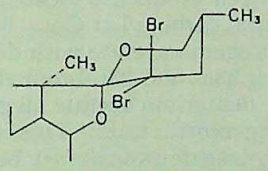
other steroids[11] were absent. It is reasonable to conclude therefore that two bromine atoms were located at carbons 5 and 6. By analogy with the bromination of cholesterol, the structure should be 5α,6β.[12] The assignment of two bromine atoms in the 5α,6β location was further strengthened by the finding that I and II on refluxing with sodium iodide in ethanol were smoothly converted to 23a-bromodiosgenin acetate (III) and 23b-bromodiosgenin acetate (IV). Compounds III and IV on analysis showed only one bromine atom. The infrared spectra showed that the Δ^5-moiety had been regenerated. Since only the bromine atoms in the diaxial 5α,6β grouping are smoothly eliminated by sodium iodide,[12a] the structural assignments of I and II at carbons 5 and 6 seem justified. Treatment of I, II, III and IV with zinc–acetic acid removed the bromine and in all cases gave the original diosgenin acetate. Bromination of tigogenin acetate with 1.5 moles of bromine under the previously described conditions gave a mixture of 23a-bromotigogenin acetate (V) and 23b-bromotigogenin acetate (VI). The mixture could be separated partially by chromatography, and final purification was achieved by fractional crystallization. Compounds V and VI analyzed for one bromine atom. The infrared spectra showed the typical 23a and 23b-bromosapogenin bands. Catalytic hydrogenation of III and IV with platinum oxide (Adams catalyst) in ether containing 5% acetic gave the corresponding 23a- (V) and 23b-bromotigogenin acetate (VI). Treatment of V and VI with zinc–acetic acid gave tigogenin acetate.

Introduction of one bromine atom into the sapogenin side chain proceeded smoothly with both diosgenin and tigogenin acetates, yields averaging about 65–75%. The 23a bromo isomers were always the predominant by a large factor, although the ratio of 23a to 23b could not be determined exactly because of losses incurred during the separation of the isomers.

(11) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

(12) (a) D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950); (b) J. B. Ziegler and A. C. Shabica, *ibid.*, **74**, 4891 (1952).

The problem of the stereochemistry of the 23a- and 23b-bromosapogenins is of interest. The partial formulation shown below represents a conception of the 25D type of bromosteroids. The configuration of ring F has been accepted by a number of groups.[9] It is assumed that the bromine atoms are located at C-23. Inspection of Fisher–Hirschfelder models constructed as formulated above would indicate little stereochemical preference for either the 23a- or 23b-isomers. If the mechanism of bromination of the sapogenin side chain bears any relationship or analogy to that of α-brominated ketones, then the axial epimer should be the product of kinetic control and formed first. The most stable epimer (which in this case could be either axial or equatorial) would be the product of thermodynamic control.[13] We attempted to determine which isomer was the most stable by equilibrating 23a-bromodiosgenin and -tigogenin acetates and the corresponding 23b-epimers with hydrogen bromide in ether or glacial acetic acid. In all cases the starting materials were recovered *unchanged*. In another experiment the two isomeric 23-bromodiosgenin acetates III and IV were treated with 2 moles of bromine for 5 hr. Only the corresponding 23a- and 23b-tribromides I and II could be isolated. Thus the methodology applicable to the prediction of the stereochemistry of α-bromoketones is not applicable to the bromosapogenin side chain. Another attempt to determine the stereochemistry of the 23a- and 23b-epimers involved the use of deuterium. Corey, *et al.*,[14] had shown that there was a difference in the C–D stretching absorption between equatorial and axial



(13) E. J. Corey, *Experientia*, **9**, 329 (1953).

(14) R. N. Jones, G. Ramsay, R. A. Shaw, W. G. Danaker, R. L. Young and R. L. Rutledge, *Chem. and Ind.*, 1294 (1954).

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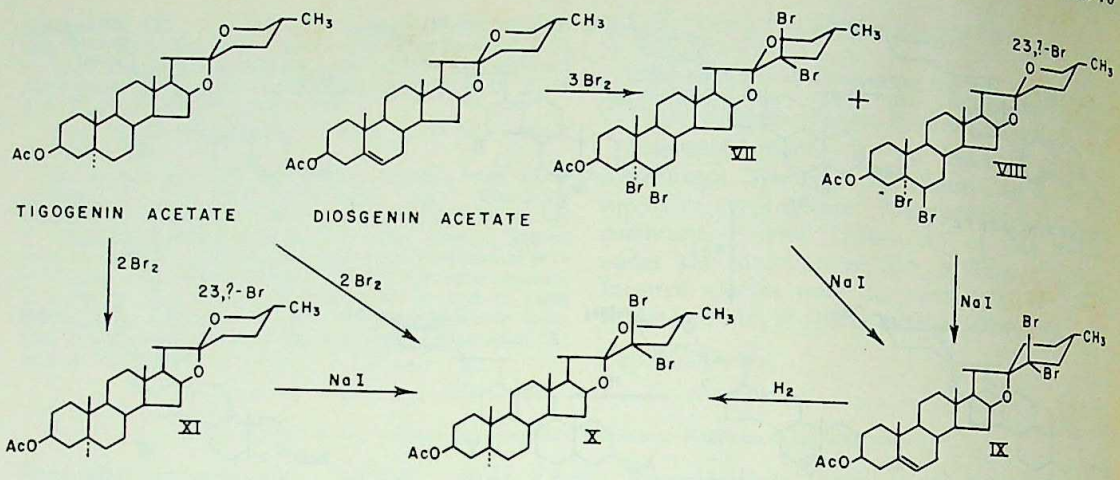

deuterium epimers. We treated 23a- and 23b-bromodiosgenin acetates with zinc dust and *o*-deuteroacetic acid. However, we obtained the same deuterated compound in both instances. Callow, James and Massy–Beresford[15] have shown that the same reaction takes place with tigogenin bromide isomers and that deuterium will also replace two hydrogen atoms in tigogenin acetate (presumably at C_{23}) when the latter is refluxed with deuterium actate.[16] It seems likely that the replaceable hydrogen atoms are located at C_{23} adjacent to a potential carbonyl at C_{22}. We found that treatment of diosgenin acetate with deuterium acetate or refluxing 23a- and 23b-bromodiosgenin acetates with zinc–deuterium acetate all gave the same deuterated diosgenin acetate. This indicates that the replaced hydrogen atoms must be labile. The corresponding deuterium atoms are also labile. Bromination of the deuterated diosgenin acetate gave a tribromo compound in which deuterium was absent. Similarly treatment of the former with acetic anhydride–pyridine hydrochloride gave a pseudodiosgenin acetate with no deuterium. It is apparent therefore that the deuteration procedure of Corey[14] cannot be applied to determination of the conformation of the bromine atoms at C_{23} in the sapogenin side chain.

Recently Barton, Page and Shoppee studied the infrared spectra of epimeric pairs of halogenated steroids of known conformation. They found that steroids with an equatorial carbon–halogen linkage invariably had C–halogen bands absorbing at a higher frequency than the corresponding axial epimer. Similar differences were noted between epimeric 23a- and 23b-bromosapogenins in the 25D series. We have confirmed these findings with 23a-bromodiosgenin acetate and its 23b-epimer. Barton, *et al.*,[7] concluded that if the bromine atoms were in fact attached to C_{23}, the 23a- type was equatorial and the 23b- axial. We feel that this hypothesis is attractive but would prefer to have more conclusive chemical evidence on this subject.

Turning next to the subject of dibromination of the spiroketal side chain, it will be recalled that conducting the bromination in acetic acid with a large excess of bromine for time periods up to 2 hr. did not lead to the introduction of a second atom of bromine.[17] Changing the solvent to chloroform, benzene, carbon tetrachloride or methylene chloride had no effect, nor did use of anhydrous glacial acetic acid. However, when diosgenin acetate was treated with $3^1/_3$–$3^1/_2$ moles of bromine in acetic acid at room temperature and allowed to stand for 72 hr., a poor yield of tetrabromodiosgenin acetate was obtained. Most of the material was resinous. Chromatography of the tetrabromodiosgenin acetate gave a major fraction (VII) which was eluted in hexane and a minor product (VIII), eluted with benzene. Bromine analysis showed that both VII and VIII had four bromine atoms. The infrared spectra of the two isomers were markedly different. On refluxing VII and VIII with sodium iodide–ethanol, the same dibromodiosgenin acetate (IX) was obtained. Catalytic hydrogenation of IX gave dibromotigogenin acetate (X).

Bromination of tigogenin acetate under similar conditions gave a low yield of crystalline dibromotigogenin acetate. Chromatography gave a major fraction identical to X above and a minor isomer XI. The infrared spectra of X and XI differed characteristically and were similar to the spectra of VII and VIII, respectively. Compound X was not affected by sodium iodide–ethanol whereas XI was converted to X. Neither X nor XI was affected by treatment with hydrogen bromide in glacial acetic acid. From the data it is apparent that VII, IX and X have bromine atoms in the same location in the side chain. We have tentatively assigned the 23,23-dibromo- configuration to these compounds. The unstable compounds VIII and XI obviously must have one bromine atom located in some position other than C_{23}. Attempts to

(15) R. K. Callow, V. H. T. James and P. N. Massy–Beresford, *Chem. and Ind.*, R26 (1956).

(16) We conducted the deuteration experiments on the isomeric diosgenin bromides prior to the publication of reference 15. Shortly after we carried out this experiment we had the pleasure of an interesting discussion with Dr. Callow at which time he was kind enough to give us information in advance of the publication of reference 15.

(17) The replacement of the first hydrogen atom by bromine proceeds rapidly, the rate being comparable to the addition of bromine to the Δ^5-ethylenic bond. This is indicated by the fact that addition of one mole of bromine to diosgenin acetate invariably gave mixtures of unbrominated, monobrominated, dibrominated, tribrominated and tetrabrominated.

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TABLE I

CHARACTERISTIC FREQUENCIES OF DIOSGENIN AND TIGOGENIN ACETATES WITH BROMINATED SIDE CHAINS

Compound[a]	Wave number in reciprocal centimers[b]												
V	1058s		1030s	1015m			950m	915m				732w	725w
III	1055s		1035s	1013m			950m	915m				732w	725w
I	1057s		1031s	1012m			950m	917w			765w		727w
VI	1050s		1030s		983m	973m	912m	912w		886w			
IV	1050s		1035s		985s	975s		910m					
II	1050s		1027s		985s	973m		912w					
IX	1056s		1033s	1015s		973m			901m	875m	777m	748m	
X	1056s		1030s	1015m		971m			901m	875w	777m	747m	
XI	1056s	1040m	1029m	1014m		973m			901m	875w	776w	745m	
VII	1056s		1030s	1010m		974m			900m	875m	777m	750m	
VIII	1055s	1040m	1027m	1012m		972m			900m	873m	776w	750m	

[a] All compounds were 3-acetates: V, 23a-bromotigogenin; III, 23a-bromodiosgenin; I, 5α,6β,23a-tribromodiosgenin; VI, 23b-bromotigogenin; IV, 23b-bromodiosgenin; II, 5α,6β,23b-tribromodiosgenin; IX, 23,23-dibromodiosgenin; X, 23,?-dibromotigogenin; XI, 23,?-dibromotigogenin; VII, 5α,6β,23,23-tetrabromodiosgenin; VIII, 5α,6β,23,?-tetrabromodiosgenin. [b] The relative intensities of the various bands at a concentration of 10 g./liter, 1 mm. cell length are indicated by s (strong), m (medium) and w (weak).

further brominate the monobrominated tigogenin acetate isomers V and VI gave resinous products. Treatment of the various sapogenins dibrominated in the side chain with zinc–acetic acid regenerated the original tigogenin acetate indicating that no major structural changes took place during dibromination.

The infrared spectra of the various brominated sapogenins were invaluable in detecting mixtures and determining the effectiveness of the various procedures used to resolve these mixtures. Table I gives the characteristic frequencies of the diosgenin and tigogenin isomers; Figures 1, 2 give the infrared curves for the various tigogenin isomers. Some general observations on the subject are pertinent. Bromination of the side chain completely changes the typical spiroketal band system.[18] Addition of bromine in the nucleus such as at carbons 5 and 6 had little effect on the infrared spectra as shown by the fact that the spectra of compounds with nuclear and side-chain bromination were similar to those with only side-chain substitution. In addition we noted that the infrared spectra of 5α,6β-dibromodiosgenin acetate closely resembled that of diosgenin acetate. As shown in Table I, the monobrominated 23a- and 23b-isomers readily could be distinguished, the former being characterized by bands absent in the latter (near 1015 and 950 cm.$^{-1}$) and the latter having bands absent in the former (near 985 and 975 cm.$^{-1}$).

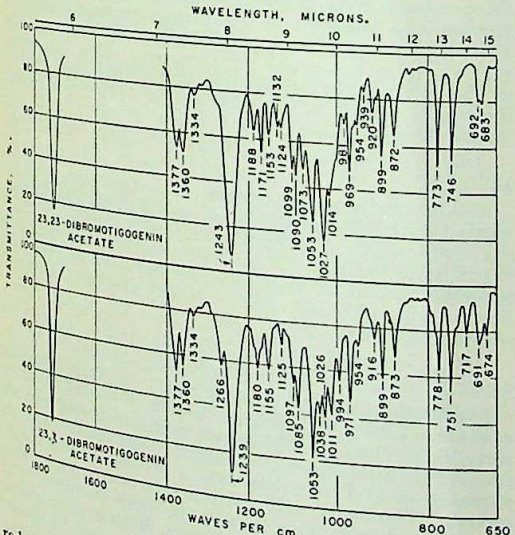

Fig. 1.

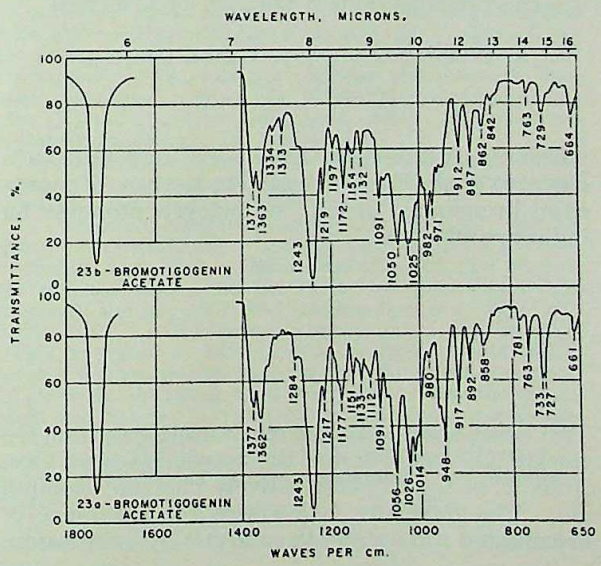

Fig. 2.

The sapogenin isomers containing two bromine atoms in the side chain could be easily differentiated from each other and from the monobrominated compounds. As shown in Table I, this group was characterized by a doublet (probably C–Br) in the region of 745 and 775 cm.$^{-1}$. In the case of the 23,23,-dibromo- group the band near 775 cm.$^{-1}$ was invariably slightly stronger than that at 750 cm.$^{-1}$, whereas the reverse was true in the group designated as 23,?-dibromo. In addition, this latter group had a band absent in the 23,23-dibromo- series near 1040 cm.$^{-1}$.

During the course of these investigations, it was noted that the presence of bromine in the side

(15) (a) M. E. Wall, C. R. Eddy, M. L. McClennan and M. E. Klumpp, *Anal. Chem.*, **24**, 1337 (1952); (b) R. N. Jones, E. Katzenellenbogen and K. Dobriner, THIS JOURNAL, **74**, 80 (1952).

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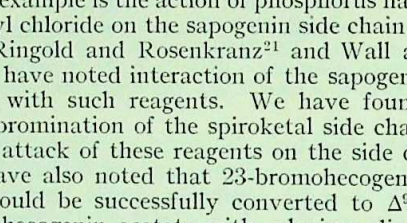
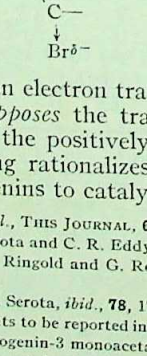
chain markedly stabilized the spiroketal moiety against attack by acidic reagents. For example, it is well known that catalytic hydrogenation of sapogenins in acidic media opens ring F with the formation of dihydrosapogenins.[19] A rationalization of this attack on the spiroketal side chain has been given in previous papers of this series[9,20] Under our experimental conditions using acetic acid as a solvent, diosgenin and tigogenin were rapidly hydrogenated in 1–2 hr. Under the same conditions, the side chains of the corresponding 23a- and 23b-bromo analogs were not appreciably affected up to 8 hr., after which time disappearance of bromine and formation of dihydrosapogenins occurred. Another example is the action of phosphorus halides or thionyl chloride on the sapogenin side chain. Djerassi, Ringold and Rosenkranz[21] and Wall and Serota[22] have noted interaction of the sapogenin side chain with such reagents. We have found that monobromination of the spiroketal side chain prevents attack of these reagents on the side chain.[23] We have also noted that 23-bromohecogenin acetate could be successfully converted to $\Delta^{9(11)}$-23-bromohecogenin acetate with selenium dioxide in acetic acid whereas this reagent attacks the side chain of hecogenin acetate.[24] The stabilizing effect of the bromine atom on the spiroketal side chain may be explained as follows. When unbrominated sapogenins are subjected to a proton attack, it seems probable that an oxonium ion is formed



which under favorable conditions may lead to a cleavage of the C_{22}–O– bond. In the case of sapogenins brominated at C_{23}, the halogen produces an inductive effect as



This bring about an electron transmission from C_{22} toward C_{23} and *opposes* the transmission of electrons from C_{22} to the positively charged oxonium ion. The foregoing rationalizes the resistance of brominated sapogenins to catalytic hydrogenation, no reaction occurring until the bromine atom is removed, and the increased stability of brominated sapogenins in general toward attack by Lewis acids.

Experimental[25]

5α,6β,23a-Tribromodiosgenin Acetate (I).—18.24 g. of diosgenin acetate (0.04 mole) was dissolved in 2.0 liters of glacial acetic acid. To the solution were added 8 drops of acetic acid saturated with hydrogen bromide. The solution was cooled to 15–20°. A solution of 0.12 mole of bromine in 160 ml. of acetic acid was added dropwise over a period of 30 minutes to the above solution with constant stirring. About 2 hr. after the addition of the bromine, a precipitate was noted in the orange solution. The precipitate was filtered. The filtrate, containing I, was mixed with two volumes of water and the solids filtered. Crystallization from acetone gave 13.5 g. of crude I. Purification was carried out by triturating the product in warm acetic acid and discarding insoluble material. The analytical sample after several crystallizations from acetone was obtained as rods, m.p. 158–162°, $[\alpha]^{25}D$ −108°, infrared spectrum shown in Table I.

Anal. Calcd. for $C_{29}H_{43}O_4Br_3$: Br, 34.53. Found: Br, 34.30.

5α,6β,23b-Tribromodiosgenin Acetate (II).—The precipitate obtained during the bromination described in the preceding section was crystallized from acetone to give 4.9 g. of II. Purification was carried out by trituration with warm acetic acid and discarding *soluble* material. The insoluble fraction was crystallized from acetone to give plates, m.p. 174–176°, $[\alpha]^{25}D$ −112°, principal infrared bands shown in Table I.

Anal. Calcd. for $C_{29}H_{43}O_4Br_3$: Br, 34.53. Found: Br, 34.29.

23a-Bromodiosgenin Acetate (III).—One gram of I was refluxed for 2 hr. with 200 ml. of ethanol containing 0.2 g. of sodium iodide. The solvent was removed *in vacuo* and the residue taken up in ether. The ethereal solution was washed with a dilute sodium thiosulfate solution, then with water, dried over sodium sulfate and the solvent removed. The residue was dissolved in hexane and chromatographed on Florisil. A small fraction was eluted with hexane. The major portion was eluted with benzene. After evaporation of the solvent, the residue was crystallized from acetone–methanol, rods, m.p. 171–175°, $[\alpha]^{25}D$ −111°, chief infrared bands shown in Table I.

Anal. Calcd. for $C_{29}H_{43}O_4Br$: Br, 14.95. Found: Br, 14.72.

23b-Bromodiosgenin Acetate (IV).—One gram of II was treated with sodium iodide as described above and the product chromatographed on Florisil. The main fraction was eluted with hexane. The hexane was evaporated and the residue crystallized from acetone–methanol to give thick plates, m.p. 195–198°, $[\alpha]^{25}D$ −138°, chief infrared bands shown in Table I.

Anal. Calcd. for $C_{29}H_{43}O_4Br$: Br, 14.95. Found: Br, 14.62.

23a-Bromotigogenin Acetate (V). (a) From Tigogenin Acetate.—9.16 g. of tigogenin acetate (0.02 mole) was dissolved in 1.0 liter of glacial acetic acid and treated with 0.03 mole of bromine exactly as described previously under the preparation of I. In this case a precipitate was not observed. The acetic acid solution was poured with stirring into two volumes of water and the solids recovered by filtration. Repeated fractional crystallization from acetone separated two isomers. The separation could be followed by infrared (see Table I, Compounds V and VI) microscopic observation and melting point differences. In this manner pure V, 1.5 g., was obtained in the fractions relatively less soluble in acetone as thick hexagonal plates, m.p. 205–210°, $[\alpha]^{25}D$ −60°.

(19) R. E. Marker, *et al.*, THIS JOURNAL, **69**, 2167 (1947).

(20) M. E. Wall, S. Serota and C. R. Eddy, *ibid.*, **77**, 1230 (1955).

(21) C. Djerassi, H. J. Ringold and G. Rosenkranz, *ibid.*, **73**, 5513 (1951).

(22) M. E. Wall and S. Serota, *ibid.*, **78**, 1747 (1956).

(23) Thus in experiments to be reported in a separate paper we have noted that 23 bromo-rockogenin-3 monoacetate and 23 bromo-11 keto rockogenin-3 monoacetate retained the sapogenin side chain on reaction with reagents such as phosphorus tribromide or thionyl chloride. Unfortunately, the desired replacement of the equatorial 12β-hydroxyl group by halogen (*cf.* E. Borgstrom and T. F. Gallagher, *J. Biol. Chem.*, **177**, 951 (1949)) did not occur. Instead under mild conditions no reaction took place, under more drastic conditions ester formation or ring C/D contraction–expansion took place (*cf.* R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, THIS JOURNAL, **76**, 4013 (1954)).

(24) Selenium dioxide was first used on bromosapogenins by Marker and co-workers[19] and later by Hirschmann, *et al.*, *ibid.*, **75**, 3252 (1953). The former group noted the increased stability of bromosapogenins toward attack by selenium dioxide.

(25) All melting points were obtained with a Köfler micro melting point apparatus. Optical rotations were determined in chloroform solution, concentration *ca.* 8.0 mg./ml. The infrared spectra were obtained on a Perkin–Elmer Model 21 spectrophotometer using a sodium chloride prism, in carbon bisulfide solution, concentration 10.0 grams per liter. We wish to thank S. Serota for the optical rotation determinations, C. R. Eddy and C. S. Fenske for infrared and Ruth B. [illegible] for the analyses.

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Anal. Calcd. for $C_{29}H_{45}O_4Br$: Br, 14.87. Found: Br, 14.50.

(b) **From Bromodiosgenin Acetate (III).**—0.1 g. of III was dissolved in glacial acetic acid and hydrogenated for five hours at room temperature and three atmospheres in the presence of 0.1 g. of platinum oxide (Adams catalyst). After filtering the catalyst and evaporating the solvent, the residue on crystallization from acetone gave V, m.p. 204–208°. Similar results were obtained by hydrogenating III in the same manner in ether containing 5% acetic acid or ethanol acidified with a few drops of hydrochloric acid. Similar hydrogenation in acetic acid for 15 hr. gave a product free from bromine identified as dihydrotigogenin-3 monoacetate. Tigogenin acetate was converted to the same product in 2 hr. under the above conditions.

23b-Bromotigogenin Acetate (VI). (a) From Tigogenin Acetate.—The *more soluble* acetone fractions, described under V above, contained VI, 1.2 g., rods, m.p. 220–230°, $[\alpha]^{25}D$ −81°.

Anal. Calcd. for $C_{29}H_{45}O_4Br$: Br, 14.87. Found: Br, 14.80.

(b) **From 23b-Bromodiosgenin Acetate (IV).**—Catalytic hydrogenation of IV in the manner described under V, part (b), gave VI, m.p. 222–229°.

5α,6β,23,23-Tetrabromodiosgenin Acetate (VII).—Diosgenin acetate (9.12 g., 0.02 mole) was dissolved in one liter of glacial acetic acid. To this solution 0.08 mole of bromine in 100 ml. of acetic acid was added in the usual manner. No precipitation occurred. After standing 3 hr. at 15–20°, the solution was allowed to come to room temperature and then to stand for 72 hr. The acetic acid solution was poured into excess water precipitating the brominated sapogenin and the solids collected by filtration. They were taken up in hexane, acetic acid neutralized with sodium bicarbonate solution and the hexane dried over anhydrous sodium sulfate. Chromatography on Florisil gave 0.75 g. of crystalline product on hexane elution and 1.0 g. of product on benzene elution. Elution with chloroform and alcohol accounted for the bulk of the weight. These products were dark resins. Acetone crystallization of the solids from the hexane elution gave VII, 0.3 g. prisms, m.p. 177–180°, $[\alpha]^{25}D$ −105°, chief infrared bands shown in Table I.

Anal. Calcd. for $C_{29}H_{42}O_4Br_4$: Br, 41.34. Found: Br, 41.92.

5α,6β,23,?-Tetrabromodiosgenin Acetate (VIII).—Acetone crystallization of the *benzene* eluate described above gave VIII, 0.2 g., rods, m.p. 188–191°, $[\alpha]^{25}D$ −43°, chief infrared bands shown in Table I.

Anal. Calcd. for $C_{29}H_{42}O_4Br_4$: Br, 41.34. Found: Br, 40.92.

23,23-Dibromodiosgenin Acetate (IX).—One-tenth gram of VII or VIII was refluxed with sodium iodide in ethanol as described previously. After acetone crystallization only IX was obtained in each case, m.p. 193–198°, $[\alpha]^{25}D$ −94°, chief infrared bands shown in Table I.

Anal. Calcd. for $C_{29}H_{42}O_4Br_2$: Br, 25.97. Found: Br, 25.77.

23,23-Dibromotigogenin Acetate (X).—Tigogenin acetate (9.16 g., 0.02 mole) in one liter of glacial acetic acid was brominated with 0.06 mole of bromine as described under the preparation of VII with the exception that the product was held at room temperature for 24 hr. The brominated sapogenin was transferred to hexane as under VII and then chromatographed on silica gel. Elution with hexane–benzene, 1:1, gave 6.0 g. of semicrystalline product; elution with benzene gave 1.0 g. of crystals mixed with resin, further elution with more polar solvents yielded only dark resins. Methanol crystallization of the residue from the hexane–benzene eluates gave X, 0.5 g., m.p. 199–200°, $[\alpha]^{25}D$ −68°, chief infrared bands shown in Table I.

Anal. Calcd. for $C_{29}H_{44}O_4Br_2$: Br, 25.89. Found: Br, 25.60.

X was also obtained by catalytic hydrogenation of IX using platinum oxide catalyst and ether containing 5% acetic acid as the solvent.

23,?-Dibromotigogenin Acetate (XI).—The *benzene* eluate obtained in preparation of X above was evaporated and the residue crystallized from methanol repeatedly to yield XI, 0.06 g., m.p. 178–182°, $[\alpha]^{25}D$ −40°, chief infrared bands shown in Table I.

Anal. Calcd. for $C_{29}H_{44}O_4Br_2$: Br, 25.89. Found: Br, 25.42.

23,23-Dibromotigogenin acetate (X), 0.025 g., and 23,?-dibromotigogenin acetate (XI), 0.015 g., were refluxed with sodium iodide as described under III. The infrared spectra of the crystalline residues showed that X was unchanged and that XI was completely converted to X.

Compounds X and XI were dissolved in acetic acid and heated in the presence of zinc dust. Infrared examination of the crystalline reaction products indicated that each compound had been converted to tigogenin acetate.

Equilibration Experiments.—(a) 23a-Bromodiosgenin acetate (III) (0.2 g.), in 100 ml. of ethanol containing 1 ml. of 48% hydrobromic acid was refluxed 12 hr. The product obtained by ethereal extraction in the usual manner was acetylated and found to be unchanged III. Similar treatment of 23b-bromodiosgenin acetate (IV), yielded unchanged starting material.

(b) 23a-Bromotigogenin acetate (V) (0.1 g.), in 30 ml. of anhydrous ether containing 3 ml. of acetic acid saturated with hydrogen bromide (approximately 38% solution) was allowed to stand overnight. After the usual work-up, only unchanged V was isolated. Similar treatment of 23b-bromotigogenin acetate (VI), 23,23-dibromotigogenin acetate (X) and 23,?-dibromotigogenin acetate (XI) gave, respectively, unchanged VI, X and XI.

Deuteration of Sapogenins.—Deuterium acetate was prepared by mixing acetic anhydride with the appropriate quantity of deuterium oxide (98%).

(a) 23a-Bromodiosgenin acetate (III) (0.5 g.), was refluxed 5 hr. with 75 ml. of deuterium acetate in the presence of 10.0 g. of zinc dust. The residue obtained after filtering the zinc and evaporating the solvent was crystallized from methanol and gave 0.3 g. of long needles, m.p. 196–199°, $[\alpha]^{25}D$ −117°. The infrared spectrum of the product, which we regard as 23,23-deutero-diosgenin acetate (XII), showed marked deviations from that of diosgenin acetate. In particular the strong band near 900 cm.$^{-1}$ and the weaker band near 865 cm.$^{-1}$, typical of the 25D series, were absent.

Similar treatment of 23b-bromodiosgenin acetate (IV) gave a compound identical to XII, the identity being verified by comparison of infrared spectra and X-ray diffraction patterns.

(b) Diosgenin acetate (0.1 g.), was refluxed 2 hr. with deuterium acetate.[15,16] The product isolated in the usual manner was XII.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. XLII. Partial Synthesis of 11-Ketodiosgenin[2]

BY EDWARD S. ROTHMAN AND MONROE E. WALL

RECEIVED DECEMBER 13, 1956

The steroidal sapogenin gentrogenin (3β-hydroxy-22a,25D-spirost-5-en-12-one, I), considered as a suitable cortisone precursor substance, was transformed to 11-ketodiosgenin (3β-hydroxy-22a,25D-spirost-5-en-11-one, VIa) and to 11α-hydroxydiosgenin (22a,25D-spirost-5-en-3β,11α-diol, Va). The route employed involved the tetrabromination of I to 3β-acetoxy-5α,6β,11α,23-tetrabromo-22a,25D-spirostan-12-one (II). This tetrabromide was selectively debrominated to restore the olefinic bond by means of iodide ion to form 3β-acetoxy-11α,23-dibromo-22a,25D-spirost-5-en-12-one (III). Hydrolysis of III formed, after acetylation, 23-bromo-3β,12β-diacetoxy-22a,25D-spirost-5-en-11-one (IVb) which was debrominated with zinc dust in acetic acid to form 3β,12β-diacetoxy-22a,25D-spirost-5-en-11-one (IVc). Selective deacetoxylation of IVc with calcium, sodium or lithium in liquid ammonia gave rise to 11-ketodiosgenin (VIa) or to 11α-hydroxydiosgenin, depending on reaction conditions utilized. Small amounts of 3-desoxy sapogenins also were detected as by-products.

In the course of examination of natural steroidal materials of botanic origin as possible source materials for steroid hormones, we have been studying the 12-ketosteroids hecogenin, gentrogenin[3] and correllogenin.[3] When we read of the discovery by Chapman, Elks and Wyman[4] of the conversion of hecogenin to 11-ketotigogenin by the route of selective deacetoxylation of 3β,12β-diacetoxy-5α,22a,25D-spirostan-11-one by means of calcium in liquid ammonia, it seemed that such a method might be advantageously applied to gentrogenin to prepare the unknown C-11 oxygenated derivatives of diosgenin. Since 11-ketotigogenin is a commercially utilized intermediate for cortisone production, it was reasonable to expect that its 5,6-dehydro derivative, 11-ketodiosgenin, might be similarly used. The present communication describes the preparation of 11-ketodiosgenin and 11α-hydroxydiosgenin.

For this work we had available a ketonic sapogenin fraction obtained from *Dioscorea spiculiflora*[5] containing a mixture of the 25D- and 25L-diastereoisomeric sapogenins gentrogenin and correllogenin, the 25D-isomer greatly predominating in the mixture. Fortunately, separation of isomers is unnecessary for practical work since conversion to derivatives in the C-21 series expels the single differing asymmetric center and leads to a single series of compounds. The constants reported in this paper are for sterically pure 25D-gentrogenin derivatives, although we have carried out the same transformations on the natural mixtures as well.

Bromination of I[6] gave a 90–94% yield of crystalline 3β-acetoxy-5α,6β,11α,23-tetrabromo-22a,25D-spirostan-12-one (II). This crystalline tetrabromide on treatment with zinc in refluxing acetic acid for 1.5 hr. regenerated starting material I essentially completely (95%). However, selective regeneration of the 5,6-olefinic bond with iodide gave only a 48–63% yield of the desired dibromide 3β-acetoxy-11a,23-dibromo-22a,25D-spirost-5-en-12-one (III).[7] The mother liquors were not useful for reconversion to starting material. The speed of the debromination was surprisingly rapid. The reaction in acetone solution was complete in less than six minutes at room temperature.

The hydrolysis of 11α,23-dibromohecogenin acetate had been studied by Mueller, *et al.*,[6] and by Rosenfeld and Gallagher.[8] We applied the conditions of the latter authors to 11α,23-dibromogentrogenin acetate (III) and obtained, after reacetylation and debromination, the desired product 3β,12β-diacetoxy-22a,25D-spirost-5-en-11-one (IV c).[9] The 12β-hydroxyl group adjacent to the 11-ketone group does not reliably acetylate with pyridine and acetic anhydride on the steam-bath so that we used perchloric acid catalysis.[10] When we attempted to carry out the hydrolysis reactions in smaller volumes by using refluxing ethanol in 2-hr. reactions or when we used water-miscible co-solvents (*e.g.*, tetrahydrofuran), the yields were sharply reduced.

A carboxylic acid by-product was obtained in low yields from the hydrolysis reactions. Wendler, Hirschmann, Slates and Walker,[11] working with 11,12-dimesylates, obtained by alkaline treatment a C-ring carboxylic norsteroid.[12] We suspect a

(1) A laboratory of the Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture. Article not copyrighted.

(2) Paper XLI, H. E. Kenney and M. E. Wall, *J. Org. Chem.*, **22**, 468 (1957).

(3) For a preliminary description of these new sapogenins see H. A. Walens, S. Serota and M. E. Wall, THIS JOURNAL, **77**, 5196 (1955). A more complete description has been submitted to *J. Org. Chem.*

(4) J. H. Chapman, J. Elks and L. J. Wyman, *Chemistry & Industry*, 603 (1955).

(5) This material was collected in Chiapas, Mexico, by Drs. H. S. Gentry and D. S. Correll, Horticultural Crops Research Branch, Agricultural Research Service, Beltsville, Md.

(6) The conditions of the bromination were essentially those used by J. W. Cornforth, J. M. Osbond and G. H. Phillips, *J. Chem. Soc.*, 907 (1954), but several differences from results with hecogenin acetate are worth mentioning. We obtained a 37% yield of crystalline 11α,23-dibromohecogenin acetate, melting point 188–190°, rather than the 54% yield reported by Cornforth, *et al.* (See also G. P. Mueller, L. L. Norton, R. E. Stobaugh, L. Tsai and R. S. Winniford, THIS JOURNAL, **75**, 4892 (1953), for yield and melting point data.) The mother liquors from the crystallization were deep green, viscid residues which could be freed of bromine by treatment with zinc and refluxing acetic acid but which yielded only half the calculated content of crystallizable hecogenin acetate.

(7) Attempts to improve the yield of III by treating II with zinc dust in benzene or tetrahydrofuran were not successful since the 11α-bromine atom was more susceptible to reductive attack than the 5,6-bromine atom pair. The direction of attack could be indirectly observed by infrared spectral means since the 11α-bromo ketone absorbs at 1735 cm.$^{-1}$, while the free 11-ketone absorbs in the usual region near 1709 cm.$^{-1}$.

(8) R. S. Rosenfeld and T. F. Gallagher, THIS JOURNAL, **77**, 4367 (1955).

(9) We confirm the 92% yield for 20-hour, room temperature hydrolysis of 11α,23-dibromo hecogenin acetate reported by Rosenfeld and Gallagher; however, identical reaction conditions applied to the closely related III gave IVc in somewhat lower yields averaging 50 to 65%.

(10) See in this connection the observations of Mueller, *et al.*, ref. 6.

(11) N. L. Wendler, R. F. Hirschmann, H. L. Slates and R. W. Walker, *Chemistry & Industry*, 901 (1954).

(12) The carboxylate was obtained by air-oxidation of an intermedi-

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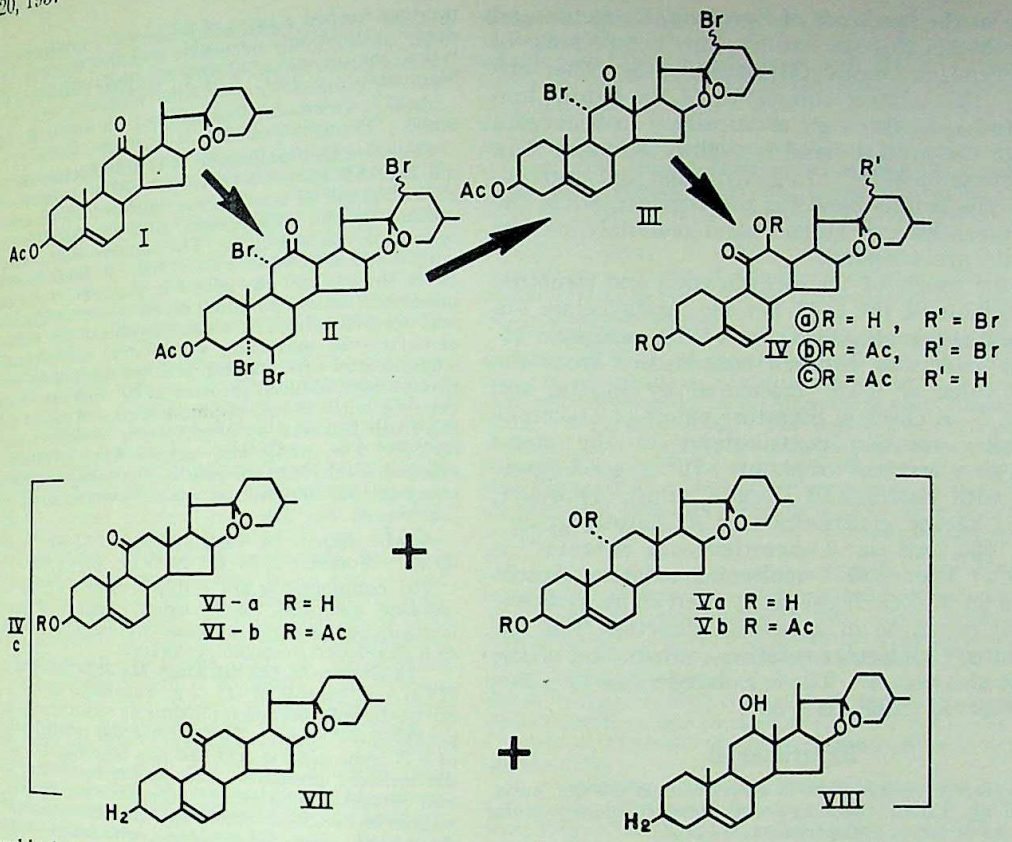

relationship between these two products but have as yet no experimental verification.

We carried out our preliminary C-12 deacetoxylation experiments of conversion of IVc to 11-ketodiosgenin and to 11α-hydroxydiosgenin on the basis of the communication of Chapman, Elks and Wyman.[4] These authors described the parallel experiments in the hecogenin series but in their preliminary disclosure gave no experimental details. In view of the fact that even closely related sapogenins often have inherent peculiarities that affect direction of reaction and yield it may not be amiss to note here some observations on the metal–ammonia reduction systems as applied to the compound IVc.

The selective deacetoxylations were carried out in liquid ammonia using calcium or *sodium* or *lithium* as the reducing element. The primary product of the reduction was 11-ketodiosgenin, 3β-hydroxy-22a,25D-spirost-5-en-11-one (VIa), which may further react with protonic materials (*e.g.*, water, alcohol) to form 11α-hydroxydiosgenin, 22a,25D-spirost-5-en-3β,11α-diol (Va), in a secondary reaction.[13] When water is used to quench the reaction and decompose excess metal reagent, a greater or lesser amount of 11α-ol is formed. Henry A. Walens of this Laboratory devised an experiment avoiding this quenching operation. The immiscible toluene layer could be separated from the liquid ammonia metal solution phase in a separatory funnel provided with a fritted glass disk. We have also used bromobenzene to quench the reaction as suggested by Chapman, Elks and Wyman.[14] Reduction of IVc gave a 90% yield of products consisting chiefly of 11-ketone VIa but containing about 10–20% of 11α-diol Va. The conversion of gentrogenin to 11-ketodiosgenin is effected in about 35% over-all yield. A further observation in the calcium deacetoxylation experiments is the formation by the reduction system of small amounts of 3-desoxysapogenins by apparently non-specific deacetoxylation. Isolated and identified were 3-desoxy-11-ketodiosgenin (22a,25D-spirost-5-en-11-one, VII) and 3-desoxy-12β-hydroxydiosgenin (22a,25D-spirost-5-en-12β-ol, VIII). The latter compound was characterized by oxidation to the 12-ketone, 3-desoxygentrogenin (22a,25D-spirost-5-en-12-one). The 12β-configuration is tentatively suggested since the 12β-configuration is the equatorial one usually favored by metal reduction systems. The C-11 ketones can be distinguished from the C-12 ketones not only by reduced chemical reactivity of the former but also by infrared differences. Thus, the 11-ketones show a band at 1704–1710 cm.$^{-1}$ (VIb at 1706 cm.$^{-1}$)[15] while the 12-ketones show the band at 1706–1712 cm.$^{-1}$ (I at 1713 cm.$^{-1}$).[15] In addition the 11-ketones show a band[16] at 970 cm.$^{-1}$ not given by the 12-ketones. Such a band occurs also for ex-

(13) F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **75**, 1282 (1953), using calcium, sodium or lithium in liquid ammonia to reduce 3β-propionoxy-5α,22a,25D-spirost-8(9)-en-11-one reported formation of the saturated ketone in the absence of ethanol and the 11α-ol in the presence of ethanol. S. Bernstein, R. Littell and J. H. Williams, *ibid.*, p. 1481, used lithium–ammonia–ethanol to reduce a saturated 11-ketone to an 11α-ol in a similar manner.

(14) Private communication.

(15) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1256 (1954).

(16) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **36**, 1245 (1953); cf. Fig. 1 of article for spectra.

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ample in the spectrum of tigogenin, diosgenin and 3,5-cyclo-22a,25D-spirostane, but compounds of these types are easily distinguished by other criteria. The relative intensities of the ketone and acetate bands also vary erratically. In hecogenin acetate the acetate band is slightly stronger than the ketone band.[16,17] In gentrogenin and correllogenin, the ketone band[18] is the stronger, while the 11-ketones have a ketone band definitely weaker than the acetate band.

In the course of the identification and structure assignments of the C-11 ketonic products, we observed a substantial deviation of the sapogenin 11-ketone molecular rotation contribution from the mean value of +79° calculated by Barton and Klyne.[19] A check of literature values of 11-ketone molecular rotation contributions in the sterol series gave a value[20] of about +72° in good agreement with Barton and Klyne's value. However, the 11-ketone contribution in 11-ketotigogenin[21] is +150° and in 11-ketotigogenin acetate[16] is +169°. The +207° molecular rotation contribution in 11-ketodiosgenin is even more positive. Similar deviation in a positive direction from the calculated[19] molecular rotation contribution of the 11α-ol also occurs. The calculated value is −29°; the observed value[13] is +35°.

Experimental

Rotations were measured in chloroform in a 2 dm. tube, c = 25 mg./1.5 ml. Melting points were determined on the Kofler block but are otherwise uncorrected.

3β-Acetoxy-5α,6β,11α,23-tetrabromo-22a,25D-spirostan-12-one (II).—Gentrogenin acetate (I), 7.0 g. (0.01486 mole), in 76 ml. of ordinary C.P. chloroform was treated at room temperature with a solution of 0.01486 mole of bromine in 59 ml. of carbon tetrachloride in the course of 5 minutes time. The initial uptake was slow, but the rate of uptake accelerated with time. The bromine was added in batches rather than dropwise. The colorless solution was further treated with 1.9 ml. of liquid bromine dissolved in 15 ml. of chloroform. Various colorations, sometimes yellow-orange, pink or green developed during this second bromination, again carried out in only 5 minutes time despite difficulties in visual observation of the bromine uptake. The solution was stirred, still at room temperature, for an additional 10 minutes, and then all solvents were removed at 30° using water aspiration. The residue was a pale green, glassy froth which on dissolution in 25 ml. of methylene chloride[22] gave a dark green solution. Addition of ethanol incrementally caused color change to a pale pink. Absolute ethanol was then added as rapidly as possible without causing flocculation until a volume of 250 ml. of clear, nearly colorless solution was obtained. Stirring with scratching caused sudden crystallization of 11.1 g. of snow-white product (decomposing at 193° with effervescence and reddening).

Recrystallization was effected by dissolution in a minimal volume of hot methylene chloride, dilution with ether and boiling off the methylene chloride azeotropically. The product formed a mass of felted micro-needles melting suddenly at 199° with browning and effervescence. The analytical sample was recrystallized from methanol to give silky filaments, m.p. 199°, $[\alpha]^{25}D$ −84.5°.

Anal. Calcd. for $C_{29}H_{38}O_5Br_4$: C, 44.30; H, 4.87; Br, 40.66. Found: C, 44.16; H, 5.04; Br, 40.65.

Selective Debromination of II to 3β-Acetoxy-11α,23-dibromo-22a,25D-spirost-5-en-12-one (III).—A sample of II, 11 g., in 250 ml. of ethanol was refluxed for 2 hr. with 14 g. of sodium iodide. The solids went into solution during the course of the reaction. The mixture was cooled, diluted with water and ether was added. A dilute solution of sodium thiosulfate was added in portions to just decolorize molecular iodine, avoiding excess reagent. The ether layer was washed with 1% sodium hydroxide (to remove traces of carboxylic material), with water, with saturated saline solution and after drying with sodium sulfate, was evaporated under reduced pressure at 30° to a pale-orange froth. Stirring with 35 ml. of absolute ethanol caused solution of the froth followed by precipitation of white crystalline III, 63%.[23] The analytical sample was recrystallized from ethanol–methylene chloride to fine hexagonal blades blackening at 152° and melting with effervescence from 160–170°, $[\alpha]^{25}D$ −81.9°.

Anal. Calcd. for $C_{29}H_{38}O_5Br_2$: C, 55.60; H, 6.11; Br, 25.51. Found: C, 54.14; H, 6.18; Br, 24.99.

The compound is not stable in chloroform or methylene chloride solutions for prolonged periods of time. Analytically pure samples let stand overnight in chloroform solution developed deep pink coloration.

23-Bromo-3β,12β-diacetoxy-22a,25D-spirost-5-en-11-one (IVb).—A sample of III, 5 g., suspended in 4.5 l. of 0.3 *N* 80% ethanolic potassium hydroxide was stirred at room temperature for 20 hr. The mixture was treated with 250 ml. of 6 *N* hydrochloric acid and was evaporated to 400 ml. under reduced pressure. The residue was diluted with water and extracted with ether. The ether was washed with 2% sodium hydroxide to remove a solid carboxylic acid[11] and was dried with saturated brine and with sodium sulfate. The solid froth obtained by reduced pressure evaporation of the dried ether extract was acetylated in 50 ml. of acetic acid and 15 ml. of acetic anhydride in the presence of 1 ml. of 2.5 *N* perchloric acid in acetic acid during 1.5 hr. at room temperature. The product was obtained by pouring the acetylation mixture into an excess of cold water and filtering off the flocculent precipitate. Crystallization of the air-dried product from ether gave 3.5 g. of IVb, m.p. 212–215°. The analytical sample, $[\alpha]^{25}D$ −88.7°, crystallized from ether, melted from 214–216° without decomposition, although the colorless melt turned slightly brown soon after melting was completed.

Anal. Calcd. for $C_{31}H_{43}O_7Br$: C, 61.28; H, 7.13; Br, 13.15. Found: C, 61.30; H, 7.02; Br, 13.25.

3β,12β-Diacetoxy-22a,25D-spirost-5-en-11-one (IVc).—The product from the preceding preparation, diminished by the removal of 121 mg. for analytical and reference purposes, was refluxed 6 hr. with zinc dust in acetic acid and the product isolated by dilution with water and extraction with ether and washing in the usual manner. A sample (after removal of zinc halide) gave a positive Beilstein flame test even after multiple crystallizations. The materials were recombined and retreated for an additional 4 hr. without change. Apparently the residual halogen content was vanishingly small since the infrared spectrum of the product was typical of 25D-sapogenins and showed no band at 739 cm.$^{-1}$. The product, 2.13 g., obtained by crystallizing the evaporated ether extract from ethanol, formed feathery, branched masses, m.p. 195–218°. The analytical sample, $[\alpha]^{25}D$ −106°, recrystallized from ethanol, began to undergo transition over 202° to elongated needles, but melting occurred at 221–225° before the transition was completed.

Anal. Calcd. for $C_{31}H_{44}O_7$: C, 70.43; H, 8.39. Found: C, 70.71; H, 8.53.

A. Reduction of 3β,12β-Diacetoxy-22a,25D-spirost-5-en-11-one (IVc) with Calcium and Ammonia to Give a Mixture of Products.—A sample of IVc, 0.85 g., in 9 ml. of tetrahydrofuran was added to a solution of 0.67 g. of calcium in 200 ml. of liquid ammonia. The reactants were stirred 2 hr.

(17) C. R. Eddy, M. E. Wall and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953).

(18) M. E. Wall, J. J. Willaman, T. Perlstein, D. S. Correll and H. S. Gentry, *J. Am. Pharm. Assoc.*, in press (1957).

(19) D. H. R. Barton and W. Klyne, *Chemistry & Industry*, 755 (1948).

(20) From K. Tsuda and R. Hayatsu, THIS JOURNAL, **77**, 6582 (1955).

(21) From C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *ibid.*, **74**, 1712 (1952).

(22) If isolation of the tetrabromide is not required, the methylene chloride should not be added, but the product should be triturated with ethanol to loosen any crystalline residues from the walls of the flask to pervent scorching during subsequent heating. Debrominative regeneration of the Δ^5-bond with sodium iodide does not require that the tetrabromide be in solution initially.

(23) The yield was about 50–55% when the reaction was carried out with the natural mixture of C-25 diastereoisomers.

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during which time the solvent boiled away. The residue was sifted into water to form a flocculent precipitate. The mixture was acidified, extracted with ether and evaporated. The residue was saponified with 5% methanolic sodium hydroxide. The resulting product was dissolved in 50 ml. of ethanol and 5 ml. of acetic acid. Girard reagent T, 2 g., was added and the mixture was refluxed for 1 hr., poured into dilute aqueous sodium carbonate and extracted with ether. The aqueous layer and aqueous washings of the ether on acidification and isolation with ether yielded a negligible quantity of steroid, *i.e.*, the metal–ammonia reduction product was non-reactive with the Girard reagent.[24] The infrared spectrum of the reduction product was similar to that of 11α-hydroxydiosgenin but showed, in addition, the presence of some 11-ketonic material by a weak to medium strength band at 1707 cm.$^{-1}$.

The reduction mixture was resolved in the following manner by chromatography. Seven hundred milligrams of the reduction product was chromatographed on a column of Florisil 20 by ¾ inches. Benzene, 900 ml., eluted no material. Chloroform–benzene (1:20) eluted 30 mg. of **3-desoxy-11-ketodiosgenin (VII) (22a,25D-spirost-5-en-11-one)**, m.p. 178–184°, $\nu_{max}^{CS_2}$ 1705 and 970 cm.$^{-1}$. Chloroform–benzene (1:10), 600 ml., eluted traces of material not examined. Chloroform–benzene (1:5), 500 ml. eluted 30 mg. of **22a,25D-spirost-5-en-12β-ol (VIII)**.—The infrared spectrum showed the absence of ketone and ester bands and showed absorption bands in the hydroxyl region and olefinic absorption band between 800 and 850 cm.$^{-1}$. Oxidation of VIII with pyridine–chromium trioxide produced **3-desoxygentrogenin (22a,25D-spirost-5-en-12-one IX)**, a monoketone forming a water-soluble Girard T complex. The ketone, m.p. 209–213°, $[\alpha]^{25}D$ −65°, formed prisms from ethanol and underwent sequential transition on the Kofler block to rectangular scales and then to elongated blades. The infrared spectrum of IX, $\nu_{max}^{CS_2}$ 1713 cm.$^{-1}$, was different from that of VII and showed Δ^5-unsaturation. Chloroform, 100%, eluted 110 mg. of **11-ketodiosgenin (3β-hydroxy-22a,25D-spirost-5-en-11-one, VIa)** which was unreactive to Girard T complex formation (11-ketone). The infrared spectrum showed bands at 1707 cm.$^{-1}$ (11-ketone) and at 970 and 984 cm.$^{-1}$. The analytical sample recrystallized from hexane melted from 180 to 183°, $[\alpha]^{25}D$ −76.4°. *Anal.* Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.92; H, 9.60. The acetylated substance **11-ketodiosgenin acetate (3β-acetoxy-22a,25D-spirost-5-en-11-one, VIb)**, prepared using pyridine–acetic anhydride at room temperature, formed transparent pearly scales from aqueous methanol, $[\alpha]^{25}D$ −85°, m.p. 221–222° after incomplete transition to rhombic scales. *Anal.* Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 73.69; H, 9.28. Further elution[25] with chloroform yielded 184 mg. of **11α-hydroxydiosgenin (22a,25D-spirost-5-en-3β,11α-diol, Va)**. Crystallization from hexane and from ether of the unusually soluble material gave thick, hexagonal, bladed or prism-like forms, $[\alpha]^{25}D$ −116°, m.p. 233–235° after incomplete transition over 228° to whips. *Anal.* Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.37; H, 10.00. Acetylation of Va in pyridine–acetic anhydride on the steam-bath for 0.75 hr. gave **11α-acetoxydiosgenin acetate (3β,11α-diacetoxy-22a,25D-spirost-5-ene, Vb)**. Crystallization from methanol gave the analytical sample, m.p. 195–198°,[26] $[\alpha]^{25}D$ −116°. *Anal.* Calcd. for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 72.41; H, 9.33. Elution with 5% ethanol in benzene gave 160 mg. of amorphous, colorless material that did not crystallize even after acetylation and chromatography of the acetylated product.

B. Reduction of IVc with Calcium–Ammonia to Give Essentially VI.—Liquid ammonia, 1000 ml., was dried by treating with portions of calcium metal until a persisting blue color developed (1.7 g.) after which point reagent calcium, 4.2 g., was added. The steroid IVc, 14.3 g., was dissolved in 250 ml. of toluene, the volume was reduced somewhat by distillation to remove traces of water and addition was carried out during 8 minutes time. After stirring an additional 5 minutes a solution of 12 ml. of bromobenzene in 50 ml. of toluene was added to decolorize the solution after which 50 ml. of water was added cautiously. The ammonia was allowed to evaporate, the residue was taken up in ether and the ether was evaporated *in vacuo* to dryness. The residue was saponified with 10% sodium hydroxide at reflux for 0.5 hr. and isolated with ether to give a crystalline residue, 10.7 g. (92%), consisting essentially of VIa but containing a small proportion of diol Va. The ketone was eluted from a Florisil column with benzene–hexane 1:1, while chloroform was required to elute the diol. The overall yield of 11-ketodiosgenin from gentrogenin is approximately 35%.

C. Reduction of IVc with Sodium in Ammonia and with Lithium in Ammonia.—Treatment of IVc with sodium or with lithium in ammonia under reaction conditions as in procedure B gave the same products. If instead of decomposing the excess calcium metal the reaction flask is opened to the air with access to atmospheric moisture, an essentially quantitative yield of diol Va is obtained after the usual saponification.

Acknowledgment.—The authors wish to express their thanks to H. A. Walens who carried out certain experiments in ketol–acetate reductions with metal–ammonia systems, to R. B. Kelly, D. McClelland and C. L. Ogg for microanalyses, to C. Fenske for infrared spectra and to S. Serota for optical rotation measurements.

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(24) W. P. Long and T. F. Gallagher, *J. Biol. Chem.*, **162**, 511, 521 (1946), have noted that 11-hydroxy-12-ketones react normally with ketone reagents.

(25) The diol, Va, gives a sensitive and intense red-black color reaction with sulfuric acid, while the ketone, VIa, gives only a pale yellow color. This difference is useful in locating the point of division in the chromatogram.

(26) It has just come to our attention that J. Romo, *Bol. inst. quim. nacl. auton. Mex.*, **7**, 53 (1955), *C. A.*, **50**, 12088 (1956), has recently prepared this compound from 3β,11α-diacetoxy-5α,22a,25D-spirostan-7-one, but reported m.p. 95–98°, $[\alpha]^{25}D$ −106°. We are unable to account for the melting point difference.

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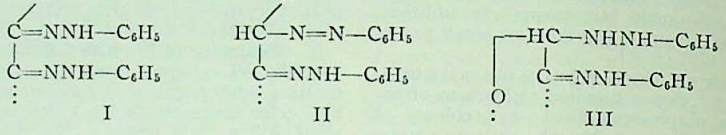
[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY, TECHNICAL UNIVERSITY, BUDAPEST]

A New Interpretation of the Mutarotation of Sugar Osazones

BY LÁSZLÓ MESTER AND ADAM MAJOR

RECEIVED AUGUST 6, 1956

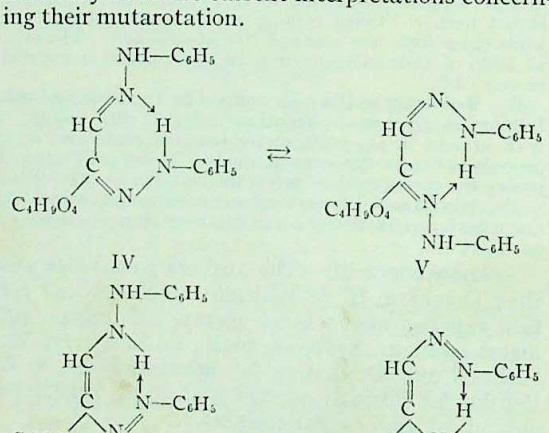
Mutarotation of a sugar osazone was first observed by Levene and Jacobs,[1] but they did not attempt to explain the phenomenon. Zerner and Waltuch[2] suggested that it should be ascribed to the tautomeric change of the bishydrazone form I into the azohydrazone form II. Haworth[3] favored the production of an equilibrium with the cyclic form III.



I II III

Discarding all earlier views, Engel,[4] in studying glucosazone, endeavored to show that mutarotation is due to hydrolysis, with phenylhydrazine splitting off.

Since evidence has lately been provided for the acyclic structure of sugar osazones[5,6,7] and since the previously postulated presence of a chelate ring (Fig. 1) has been confirmed,[5,6] it now appears necessary to revise current interpretations concerning their mutarotation.



IV V IV′ V′

Fig. 1.

Experimental

Mutarotation of D-glucose phenylosazone[9] and D-glucose-1-methylphenyl-2-phenylosazone[10] was measured (c = 0.5) in a 1:1 mixture of pyridine and ethanol at 20 ± 2°; for D-glucose phenylosazone: $[\alpha]^{20}D$ −67.3° (10 min.), −45.5° (1 hr., 10 min.), −27.7° (5 hr., 10 min.), −23.8° (8 hr.), −23.8° (11 hr., 15 min.), −23.8° (24 hr.); for D-glucose-1-methylphenyl-2-phenylosazone: $[\alpha]^{20}D$ −52.2° (10 min.), −42.1° (1 hr., 15 min.), −36.1° (2 hr.), −26.1° (5 hr., 40 min.), −24.1° (7 hr., 10 min.), −20.1° (24 hr., 5 min.). The solutions were evaporated to dryness, and mutarotation was repeated with the substances recovered without purifying them; the same mutarotations were observed.

Ultraviolet spectra were determined with a Beckman DU-type spectrophotometer in samples taken from time to time from the above solutions and diluted with ethanol to 0.0001 mole (Fig. 2 for D-glucose phenylosazone).

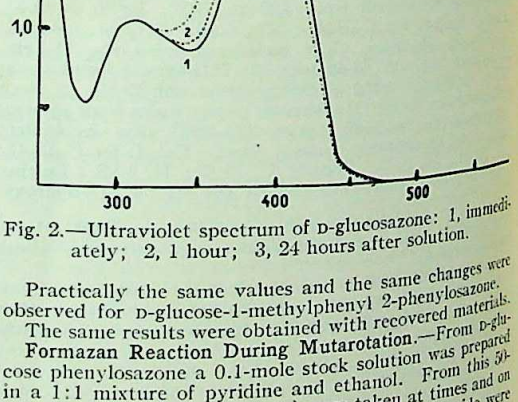


Fig. 2.—Ultraviolet spectrum of D-glucosazone: 1, immediately; 2, 1 hour; 3, 24 hours after solution.

Practically the same values and the same changes were observed for D-glucose-1-methylphenyl 2-phenylosazone.

The same results were obtained with recovered materials.

Formazan Reaction During Mutarotation.—From D-glucose phenylosazone a 0.1-mole stock solution was prepared in a 1:1 mixture of pyridine and ethanol. From this 50-ml. samples (1.8 g. of osazone) were taken at times and on adding 50 ml. of 2 N alcoholic potassium hydroxide were coupled to formazan with diazo solution prepared from 0.75 g. of aniline.[5] The crude formazans obtained were twice recrystallized from a mixture of four times the volume of pyridine and ten times the volume of ethanol; m.p. 198°.

Simultaneously, samples taken from the stock solution were diluted with a 1:1 mixture of pyridine and ethanol (c = 0.5), and the rotational changes observed. On completion of the mutarotation the stock solution was evaporated to dryness *in vacuo* and the above experiment repeated with the substances obtained without purifying them (Fig. 3).

Mutarotation of tetra-O-acetyl-D-galactose phenylosazone[11] was measured in dioxane (c = 0.5): $[\alpha]^{20}D$ +56° (10 min.), +80° (1 hr., 35 min.), +80° (38 hr., 40 min.). The solution on concentration to dryness, yielded the osazone unchanged; dissolving the recovered material in dioxane gave the same rotational values.

(1) P. A. Levene and W. A. Jacobs, *Ber.*, **42**, 3249 (1909).

(2) E. Zerner and R. Waltuch, *Monatsh.*, **35**, 1025 (1914).

(3) W. N. Haworth, "The Constitution of Sugars," Edward Arnold & Co., London, 1929, p. 7.

(4) L. L. Engel, THIS JOURNAL, **57**, 2419 (1935).

(5) L. Mester, *ibid.*, **77**, 4301 (1955).

(6) L. Mester and A. Major, *ibid.*, **77**, 4305 (1955).

(7) In the meantime V. C. Barry and co-workers[8] have proved that in dilute solution the osazones are present in the acyclic form only.

(8) V. C. Barry, J. E. McCormick and P. W. D. Mitchell, *J. Chem. Soc.*, 222 (1955).

(9) E. Fischer, *Ber.*, **17**, 579 (1884); **20**, 821 (1887).

(10) S. Akija and S. Tejima, *J. Pharm. Soc. Japan*, **72**, 1574 (1952); *C. A.*, **47**, 9275 (1953).

(11) M. L. Wolfrom, M. Königsberg and S. Soltzberg, THIS JOURNAL, **71**, 3468 (1949).

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The ultraviolet spectra were determined in samples taken from time to time from the mutarotational solution and diluted with dioxane to 0.0001 mole. They showed the same changes for both the original and the recovered material, and these changes were identical with those for D-glucose phenylosazone.

4-Desoxy-L-glycerotetrose phenylosazone dissolved in pyridine was subjected to mutarotation and evaporated to dryness; the osazone recovered was again dissolved in pyridine, and once more the mutarotation as described by Fried, *et al.*,[12] was observed.

Result and Discussion

Since mutarotation, spectral displacement and formazan formation after distillation of the solvent in the redissolved substance are reiterating processes, Engel's[4] view that mutarotation depends on the hydrolysis of osazones seems to be excluded.

The reaction of the glucosazone with the diazo solution in samples taken from the mutarotating solution yields less and less osazone formazan (Fig. 2). This is due obviously to the same structural change which is optically perceivable during mutarotation. Since Haworth's cyclic formula III is unable to yield formazan, the transformation of the two anomers into each other cannot possibly be regarded as the cause of mutarotation. It now remains to be ascertained whether the open-chain compound I changes into Haworth's cyclic form III during mutarotation. Were it so, owing to the disappearance of one chromophoric group, the maximum of the ultraviolet spectrum would have to show a substantial alteration of the characteristics.[5]

The observations of Weygand, *et al.*,[13] on the mutarotation of 5,6-di-O-methyl-D-glucose *p*-bromophenylosazone, and those of Gorin, *et al.*,[14] on the mutarotation of L-*glycero*tetrulose phenylosazone and its derivatives, leave no room for a concept which holds that mutarotation might be caused by cyclization departing from the second carbon.

Finally, the mutarotation in tetra-O-acetyl-D-glucose phenylosazone,[11] in tetra-O-acetyl-D-galactose phenylosazone and in 4-desoxy-L-glycero-D-tetrose phenylosazone,[12] can in no way be explained by cyclization, since in these cases there is definitely no possibility for ring formation to take place.[15]

It also seems impossible that a stable conjugated system I of double bonds should change into an unstable compound II of isolated double bonds, as has been suggested by Zerner and Waltuch.[2] Nevertheless, on the evidence of our findings above it would appear that the real cause of the mutarotation is to be sought in the electron displacement which takes place in the chelate structure of the osazones upon the action of the solvent,[17-19] and which amongst others reveals itself in a displacement of the ultraviolet spectra and in a decrease of the coupling capacity.

The two latter observations suggest the conclusion that in the course of mutarotation there is a structural shift from somewhere near the IV state toward the IV′ state, since while the former is suitable, the latter is definitely unsuited for coupling and for the change in the ultraviolet spectra, the above structural shift seem to be responsible.[24,26]

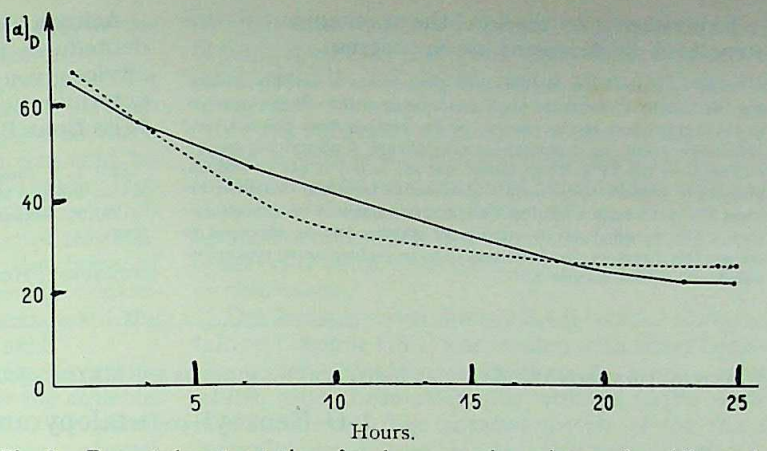

Fig. 3.—Repeated mutarotation of D-glucosazone in a mixture of pyridine and alcohol.

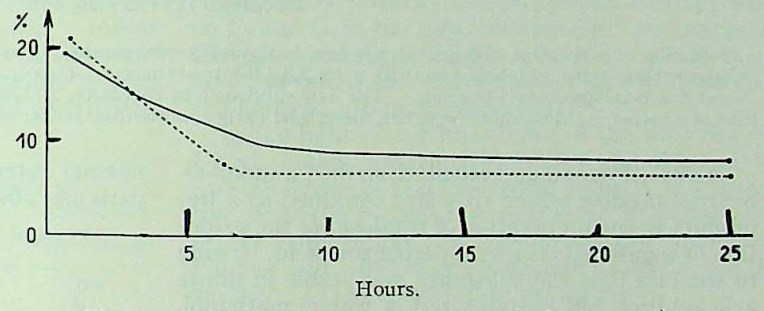

Fig. 4.—Yields of D-glucosazone formazan (twice recrystd).

(12) J. Fried, S. E. Walz and O. Wintersteiner, THIS JOURNAL, **68**, 2746 (1946).

(13) F. Weygand, H. Grisebach, K. Kirchner and M. Haselhorst, *Ber.*, **88**, 487 (1955).

(14) P. A. J. Gorin, L. Hough and J. K. N. Jones, *J. Chem. Soc.*, 3096 (1955).

(15) Some objections expressed by E. E. Percival and E. G. V. Percival[4] to the acyclic structure of the osazone acetates proposed by M. L. Wolfrom, *et al.*,[11] are contradictory to our findings concerning the structure of tetra-O-acetyl-D-glucose phenylosazone formazan.[5]

(16) E. E. Percival and E. G. V. Percival, *J. Chem. Soc.*, 1320 (1957).

(17) Reference is made to Burawoy, *et al.*,[18] concerning 1-phenylazo-2-naphthol and 1,2-naphthoquinon-2-phenylhydrazone, the chelate structure of which can be influenced by the solvent.

(18) A. Burawoy, A. G. Salem and A. R. Thompson, *J. Chem. Soc.*, 4793 (1952).

(19) There are several references in the literature pointing out that an α,β-unsaturated azo-structure forms in the *p*-nitrophenylhydrazones of unsaturated ketones[20-22] and that the rearrangement of hydrazone of the compound of azo-structure takes place upon the action of a solvent, finally that this is a somewhat slow process causing changes in the optical rotation.[23]

(20) F. Ramirez and A. F. Kirby, THIS JOURNAL, **75**, 6026 (1953).

(21) J. van Alphen, *Rec. trav. chim.*, **64**, 305 (1945).

(22) R. J. W. Le Fèvre, M. F. O'Dwyer and R. L. Werner, *Chemistry & Industry*, 378 (1953).

(23) W. F. McGuckin and E. C. Kendall, THIS JOURNAL, **74**, 5812 (1952).

(24) As regards D-glucose 1-methylphenyl-2-phenylosazone, of the chelate structures proposed by Fieser and Fieser[25] the V and V′ structures must be discarded because of the presence of the methyl group, and only the IV and IV′ structures can be taken into consideration. In our view, the extraordinary resemblance of the mutarotation, the ultraviolet spectrum and the polarographic behavior of glucosazon

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Experiments to disclose the mechanism of this structural displacement are in progress.

to those of glucose-1-methylphenyl-2-phenylosazone justifies discarding the V and V′ formulas of glucosazone as well. All the more so, as the methylation of glucosazone, as has already been pointed out,[5] invariably leads to D-glucose-1-methylphenyl 2-phenylosazone derivable from the IV and IV′ forms, and so, so far, it has proved impossible to prepare methylated D-glucosazone from the chelate structures V and V′ neither by direct methylation nor in some roundabout way. The so-called mixed osazone B, which could be supposed to possess this structure, has been proved to be D-glucosazone contaminated with mixed osazone A.[5]

Acknowledgment.—We wish to express our indebtedness to Professor G. Zemplén for valuable advice given and to thank Dr. W. Cieleszky for the determination of the ultraviolet spectra, finally, Miss Ilona Batta for the microanalyses.

(25) L. F. Fieser and M. Fieser, "Organic Chemistry," D. C. Heath & Co., Boston, Mass., 1944, p. 351.
(26) F. Ramirez and R. J. Bellet, THIS JOURNAL, **76**, 491 (1954).

BUDAPEST, HUNGARY

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

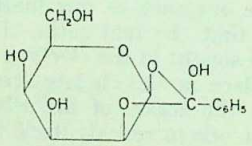
1-*O*-Benzoyl-α-D-talopyranose

BY HARRY B. WOOD, JR., AND HEWITT G. FLETCHER, JR.

RECEIVED JANUARY 26, 1957

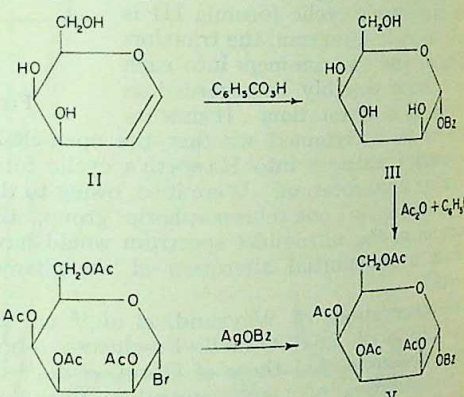
Oxidation of D-galactal with perbenzoic acid has given a new D-talose monobenzoate. Acetylation of this ester afforded an amorphous ester which is identical with 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-α-D-talose synthesized from 2,3,4,6-tetra-*O*-acetyl-α-D-talopyranosyl bromide. The new substance is, therefore, 1-*O*-benzoyl-α-D-talopyranose. The possible structure of another D-talose monobenzoate, described earlier in the literature, is discussed.

In 1937, Pigman and Isbell[1] described a mono-*O*-benzoyl-D-talose which they had obtained as a by-product in the preparation of D-talose *via* the oxidation of D-galactal (II) with perbenzoic acid. Owing to the fact that the substance was stable in dilute acid solution but mutarotated in water, methanol, dilute alkali and pyridine, a cyclic orthoacid structure (I) was assigned to it.



I

The lability of this substance compared with the stability of the well-characterized 1-*O*-benzoyl-β-D-glucopyranose prepared somewhat earlier by Zervas[2] and the widespread currency of the cyclic orthoacid concept which had first been suggested by Emil Fischer,[3] combined to make such a tentative assignment of structure a reasonable one at that period.[4] However, subsequent advances in the chemistry of the sugar esters have shown (a) that acyl groups are very prone to migrate from C_1 to C_2 of an aldose when the hydroxyl at C_2 is free and spatially accessible to C_1[5,6] and (b) that cyclic orthoacid structures such as I are not likely to be sufficiently stable for isolation.[6] Furthermore, Isbell and his co-workers[7] have shown recently that the sample of D-talose monobenzoate prepared in 1937 had undergone no change in physical properties during the intervening years and was indeed a normal ester as shown by its characteristic ester carbonyl absorption in the infrared.



II III IV V

In all known additions to the double bond of glycals[8] the anionic portion of the adding molecule has been found attached to C_1 of the sugar and it seems reasonably certain, therefore, that the substance reported by Pigman and Isbell is a 1-*O*-benzoyl-D-talopyranose. Its failure to mutarotate in acid solution[1] and to give a phenylhydrazone[7] appear to support this assumption. The mutarotations in water, methanol, dilute alkali and pyridine reported by Pigman and Isbell[1,7] may then represent acyl migration from C_1 to C_2 or some other position. Indeed these mutarotations, which start in a *levo* direction and then turn in the *dextro* direction, suggest that an initial acyl migration frees a β-hydroxyl at C_1 and that normal equilibration of the anomeric forms then ensues. If the instability of the ester is due to a $C_1 \rightarrow C_2$ migration we must expect it to be the β- rather than the α-1-*O*-benzoyl-D-talopyranose, for such a *cis* isomer would resemble the easily rearranged 1-*O*-mesitoyl-α-D-glucose[5] and 1,3,5-tri-*O*-benzoyl-α-D-ribose[6] while the

(1) W. W. Pigman and H. S. Isbell, *J. Research Natl. Bur. Standards*, **19**, 189 (1937).
(2) L. Zervas, *Ber.*, **64**, 2289 (1931).
(3) E. Fischer, *ibid.*, **53**, 1624 (1920).
(4) *Cf.* E. Pacsu, *Advances in Carbohydrate Chem.*, **1**, 78 (1945).
(5) H. B. Wood, Jr., and H. G. Fletcher, Jr., THIS JOURNAL, **78**, 2849 (1956).
(6) R. K. Ness and H. G. Fletcher, Jr., *ibid.*, **78**, 4710 (1956).
(7) H. S. Isbell, J. E. Stewart, H. L. Frush, J. D. Moyer and F. A. Smith, *J. Research Natl. Bur. Standards*, **57**, 179 (1956).
(8) See, for instance, B. Helferich, *Advances in Carbohydrate Chem.*,

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α-(*trans*) isomer should be similar in stability to the well-known 1-*O*-benzoyl-β-D-glucopyranose.

On the other hand, the mechanism postulated for the oxidation of double bonds by per-acids[9,7] is such as to lead to *trans* products and this generalization has been made specifically for perbenzoic acid by Posternak and Friedli.[10] Levene and Tipson,[11] for instance, obtained 3,4,6-tri-*O*-acetyl-1-*O*-benzoyl-β-D-galactopyranose through the action of this reagent on D-galactal triacetate.[12] In the hope of throwing some light on these apparently contradictory indications[13] we have now re-examined the reaction of D-galactal with perbenzoic acid.

Preliminary experiments, following the directions which Pigman and Isbell[1] described for the aqueous oxidation of D-galactal, failed to yield us a crystalline, water-soluble product having ester carbonyl absorption. However, the second, non-aqueous oxidation procedure of these authors readily afforded a crystalline monobenzoylhexose; minor changes in the work-up procedure raised the yield to 13%. However, the physical constants of this monobenzoylhexose as shown in Table I clearly distinguish our substance from that described by the earlier authors. Not only does the new substance have an infrared absorption spectrum which distinguishes it from that reported earlier[1] but its stability is markedly greater, no mutarotation being detected in water, methanol or pyridine. All our attempts to obtain a product similar to Pigman and Isbell's have thus far failed although the oxidation produced, in addition to the new crystalline product, a large quantity of amorphous material which, upon acid hydrolysis, afforded D-talose and benzoic acid.

TABLE I

PROPERTIES OF D-TALOSE MONOBENZOATES

	Compound of Pigman and Isbell[1,7]	1-*O*-Benzoyl-α-D-talopyranose
$[\alpha]^{25}D$ in water	+21.2 (0.08 hr.) → + 5.1° (54 hr.) → 24.2° (648 hr.)	+72.4°
$[\alpha]^{25}D$ in 0.01 *N* HCl	+22.6°	+72.5°
$[\alpha]^{25}D$ in methanol	+15.4° (2.96 min.) → −33.3° (60.1 min.) → +11° (2550 min.)	+74°
$[\alpha]^{25}D$ in pyridine	+16.5° (0.1 hr.) → −12.5° (191.3 hr.) → + 4.8° (430.5 hr.)	+53°

The nature of the new monobenzoyl hexose was investigated in the following fashion. Infrared absorption measurements showed the presence of a normal ester carbonyl group. Hydrolysis with barium methoxide afforded crystalline D-talose in good yield.[14] In glacial acetic acid solution the compound consumed two moles of lead tetraacetate. Since the substance showed no mutarotation in pyridine, a sample was acetylated in this solvent. Unfortunately the product could be obtained only as a sirup, but chromatography readily gave a homogeneous fraction which had the composition of a tetra-*O*-acetyl-*O*-benzoylhexose and showed $[\alpha]^{20}D$ +84° in chloroform.

The known, crystalline 2,3,4,6-tetra-*O*-acetyl-D-talosyl bromide (IV)[1] was treated with silver benzoate under anhydrous conditions to give a sirup which, after chromatography, rotated $[\alpha]^{20}D$ +83° in chloroform. The infrared spectra of the sirups from the two sources (III and IV) were identical in all respects. Since such reactions of acylated glycosyl halides normally lead to products with groups on C_1 and C_2 in the *trans* relationship[15] we conclude that the product is 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-α-D-talose (V) and that our monobenzoate is 1-*O*-benzoyl-α-D-talopyranose (III).

In the light of our knowledge of the behavior of 1-acyl aldoses, the relative stability of 1-*O*-benzoyl-α-D-talopyranose (III) is wholly normal; in a negative sense the evidence here adduced lends support to the supposition that the compound made by Pigman and Isbell may be, despite its origin, the β-anomer, 1-*O*-benzoyl-β-D-talopyranose.[16]

Experimental[17]

1-*O*-Benzoyl-α-D-talopyranose (III).—The procedure followed for the oxidation was modeled after that of Isbell and Pigman[1]; repeated trials led, however, to a modified method of isolation, giving higher yields of crystalline product. D-Galactal[18] (10 g.) and benzoic acid (10 g.) were dissolved in a mixture of 300 ml. of dioxane and 200 ml. of acetone. The solution was cooled to +5° and a methylene chloride solution (167 ml.) containing perbenzoic acid (18 g.)[19] added. After stirring, the solution was held at 0° for 24 hr. and then at 5° for 24 hr. Solvent was then removed *in vacuo* at less than 30° and the resulting semi-crystalline

(9) Cf. W. A. Waters in "Organic Chemistry," ed. by H. Gilman, John Wiley & Sons, Inc, New York, N. Y., 1953, p. 1165.

(10) T. Posternak and R. S. Tipson, *J. Biol. Chem.*, **93**, 631 (1931). These authors found that further acetylation of their tri-*O*-acetyl-α-D-galactosyl bromide with silver benzoate. As will be mentioned later, such a condensation produces *trans* products.

(11) P. A. Levene and R. S. Tipson, *Helv. Chim. Acta*, **36**, 251 (1953). acetyl-1-*O*-benzoyl-D-galactopyranose afforded a product identical with that which they obtained through condensation of 2,3,4,6-tetra-*O*-

(12) Naturally, the identification of the parent sugar as D-talose, rather than D-galactose, is vital here. While Pigman and Isbell's evidence in this regard seemed unequivocal we have hydrolyzed a minute sample of their material and, by paper partition chromatography in a suitable solvent system, confirmed the fact that talose and only talose is present.

(14) To ensure the absence of alkali-induced rearrangements here, the reaction mixture was chromatographed on paper using a system known to separate talose and galactose. Only one spot was observed; chromatography of an acid hydrolyzed mixture gave identical results.

(15) As far as the present authors are aware, this generalization was first made by R. S. Tipson [*J. Biol. Chem.*, **130**, 55 (1939)] and first received theoretical interpretation by H. S. Isbell, *Ann. Revs. Biochem.*, **9**, 65 (1940); *J. Research Natl. Bur. Standards*, **26**, 35 (1941). It should be noted that while the high dextrorotation of tetra-*O*-acetyl-D-talopyranosyl bromide ($[\alpha]^{20}D$ +165.6° in $CHCl_3$; see ref. 1) indicates that the substance is almost certainly the α-anomer, the validity of the evidence presented here is independent of the anomeric configuration of this halide.

(16) It may be noted here that lead tetraacetate oxidation of 1-*O*-benzoyl-β-D-talopyranose and of 1-*O*-benzoyl-β-D-glucopyranose should produce the same dialdehyde and thus possibly provide a simple proof of the anomeric configuration of the D-talose monobenzoate reported by the earlier authors. Unfortunately the quantity of material available to us precluded such a test.

(17) Melting points are corrected for stem exposure.

(18) 3,4,6-Tri-*O*-acetyl-D-galactal was prepared by the method of C. Tamm and T. Reichstein [*Helv. Chim. Acta*, **31**, 1630 (1948)]; deacetylation with anhydrous, methanolic ammonia [R. Kuhn and H. H. Baer, *Chem. Ber.*, **88**, 1537 (1955)] gave D-galactal which showed $[\alpha]^{20}D$ −21.3° (MeOH, *c* 1.2) and gave satisfactory analyses for carbon and hydrogen.

(19) Perbenzoic acid was prepared by the method of G. Braun ["Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431], the final extraction being made with methylene chloride and the extract, dried over sodium sulfate, used directly after titration of an aliquot to determine the perbenzoic acid content.

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mass extracted with benzene–pentane (3 × 100 ml. of 1:2 v./v.). The mixture was dissolved in 100 ml. of water and the resulting solution extracted thrice with 1:2 benzene–pentane to remove remaining traces of acid. The aqueous solution was then extracted continuously with warm ether until no further material was removed. On concentration, the ethereal extract afforded crude crystalline product (2.6 g., 13%). Recrystallization from either ethyl acetate, acetone or 1,2-dimethoxyethane gave, with little loss, pure material melting at 165–166° and rotating $[\alpha]^{20}D$ +72.4° (H_2O, *c* 0.5), no mutarotation being observed within 1 hr. Rotations in other solvents were observed as follows: 0.01 *N* HCl, $[\alpha]^{20}D$ +72.5° (*c* 0.5); methanol, $[\alpha]^{20}D$ +74° (*c* 0.49); pyridine, $[\alpha]^{20}D$ +53° (*c* 1.1).

Anal. Calcd. for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67. Found: C, 54.84; H, 5.78.

A sample (36.5 mg.) of the substance was treated with lead tetraacetate in glacial acetic acid as described by Hockett and McClenahan.[20] After 355, 1340 and 1867 minutes, analyses indicated the consumption of 1.98, 2.09 and 2.07 molar equivalents of oxidant.

D-Talose from 1-*O*-Benzoyl-α-D-talopyranose (III).—A sample (0.1616 g.) of the ester was dissolved in absolute methanol to make a total volume of 10 ml. and the rotations observed in a 1.5-dm. tube. Over a period of 8 min. at 20° no change was observed, the rotation corresponding to $[\alpha]^{20}D$ +72.8°. Four drops of 1.3 *N* barium methoxide was then added. After 43 min. the rotation had become constant at a value of +0.34°, corresponding to $[\alpha]^{20}D$ +22.7°, based on the theoretical yield of hexose. Barium ions were removed with Amberlite IR-120 and the solution concentrated *in vacuo* to a sirup. From ethanol the handsome prisms characteristic of D-talose were deposited: 0.065 g. (64%), m.p. 130–131°, $[\alpha]^{20}D$ +20.1° (H_2O, *c* 1.2). Isbell and Pigman[21] recorded m.p. 133–134° and $[\alpha]^{20}D$ +20.8° (H_2O, *c* 4) for pure D-Talose.

2,3,4,6-Tetra-*O*-acetyl-1-*O*-benzoyl-α-D-talose (V). (a) From 1-*O*-Benzoyl-α-D-talopyranose (III).—To a mixture of 2 ml. of pyridine and 10 ml. of acetic anhydride cooled to 0° was added 1.0 g. of 1-*O*-benzoyl-α-D-talopyranose. After 3 days at 0° the reaction mixture was poured into cold water and worked up in the usual fashion. The sirup (1.41 g., 89%) which resisted all attempts at crystallization was dissolved in 4:1 hexane–benzene and adsorbed on a column of 56 g. of alumina.[22] Successive elution with 4:1 hexane–benzene, benzene and 1:1 benzene–ether eluted no material from the adsorbent. With ether a well-defined "peak" was eluted; several of the amorphous fractions before and at the top of the peak showed $[\alpha]^{20}D$ +84° in chloroform (*c* 0.3).

Anal. Calcd. for $C_{21}H_{24}O_{11}$: C, 55.75; H, 5.35. Found: C, 56.18; H, 5.51.

(b) From 2,3,4,6-Tetra-*O*-acetyl-α-D-talosyl Bromide (IV).—A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-talosyl bromide (6.5 g., m.p. 83–84°[23]), silver benzoate (10 g.) and benzene (50 ml.) was stirred at room temperature for 1 hr. and then filtered. Removal of solvent from the filtrate gave a sirup (6.5 g.) which could not be induced to crystallize. The sirupy product was, therefore, chromatographed on alumina as described in part (a) above. Elution with ether afforded a number of fractions showing $[\alpha]^{20}D$ +83° in chloroform; these were combined and rechromatographed to give a clear, colorless sirup showing $[\alpha]^{20}D$ +83° in chloroform (*c* 0.66).

Anal. Calcd. for $C_{21}H_{24}O_{11}$: C, 55.75; H, 5.35. Found: C, 55.96; H, 5.54.

Infrared absorption spectra of solutions of the products from (a) and (b) above appeared to be identical in all respects.

Acknowledgments.—We wish to express our indebtedness to Dr. H. S. Isbell for his helpful cooperation and interest in this research. We also wish to thank Mr. H. W. Diehl for the preparation of a quantity of D-galactal. Analytical determinations and absorption spectra measurements were carried out in the Institutes' microanalytical laboratory under the direction of Dr. W. C. Alford.

(20) R. C. Hockett and W. S. McClenahan, THIS JOURNAL, **61**, 1667 (1939).

(21) H. S. Isbell and W. W. Pigman, *J. Research Natl. Bur. Standards*, **18**, 141 (1937).

(22) "Alcoa" alumina, Grade F-20, mesh 80–200 manufactured by the Aluminum Company of America, Pittsburgh, Pa., was washed thoroughly with 5% hydrochloric acid and then with water until neutral. After activation at 200° the material was deliberately exposed to atmospheric humidity before use. The adsorptive capacity of alumina thus treated is inferior to that which has been kept under rigorously anhydrous conditions but its reproducibility is superior and the use of such partially hydrated alumina has the marked advantage of obviating the use of specially dried eluents.

(23) Pigman and Isbell (ref. 1) reported m.p. 84–84.5° for this substance.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC.]

Synthesis of Cycloserine and a Methyl Analog

BY CHARLES H. STAMMER, ANDREW N. WILSON, CLAUDE F. SPENCER, FRANK W. BACHELOR, FREDERICK W. HOLLY AND KARL FOLKERS

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DL-4-Carbomethoxy-2-phenyl-2-oxazoline (V) was converted into the corresponding hydroxamic acid VI. Dry hydrogen chloride in dioxane opened the oxazoline ring to a β-chloropropionohydroxamic acid which in aqueous alkali formed DL-4-benzamido-3-isoxazolidone (VIII). Treatment of VIII with ethanolic hydrogen chloride gave the aminoxy ester IX which cyclized in potassium hydroxide solution to DL-4-amino-3-isoxazolidone (X) (DL-cycloserine). The L-form of VIII was synthesized by the same series of reactions from L-serine. Both the benzamido (VIII) compound and DL-cycloserine were resolved. DL-4-Amino-5-methyl-3-isoxazolidone (XII) was synthesized from DL-threonine by the same series of reactions.

Cycloserine,[1] a broad-spectrum antibiotic, has been shown to be D-4-amino-3-isoxazolidone.[2,3] Preliminary reports of syntheses[3,4] of the racemate DL-4-amino-3-isoxazolidone (X) and a resolution[4] of the racemate have been published. The details of our synthesis and resolution together with the synthesis of an analog, DL-4-amino-5-methyl-3-isoxazolidone (XII), are described in this paper.

Since 3-isoxazolidone (I) had been synthesized[5]

(1) Cycloserine has been accepted as the generic name for this antibiotic. Oxamycin is now the trademark of Merck & Co., Inc., for cycloserine.

(2) F. A. Kuehl, F. J. Wolf, N. R. Trenner, R. L. Peck, E. Howe, B. D. Hunnewell, G. Downing, E. Newstead, R. P. Buhs, I. Putter, R. Ormond, J. E. Lyons, L. Chaiet and K. Folkers, THIS JOURNAL, **77**, 2344 (1955).

(3) P. H. Hidy, E. B. Hodge, V. V. Young, R. L. Harned, G. A. Brewer, W. F. Phillips, W. F. Runge, H. E. Stavely, A. Pohland, H. Boaz and H. R. Sullivan, *ibid.*, **77**, 2345 (1955).

(4) C. H. Stammer, A. N. Wilson, F. W. Holly and K. Folkers, *ibid.*, **77**, 2346 (1955).

(5) C. H. Shunk, F. W. Bachelor and K. Folkers, *J. Org. Chem.*, **22**,

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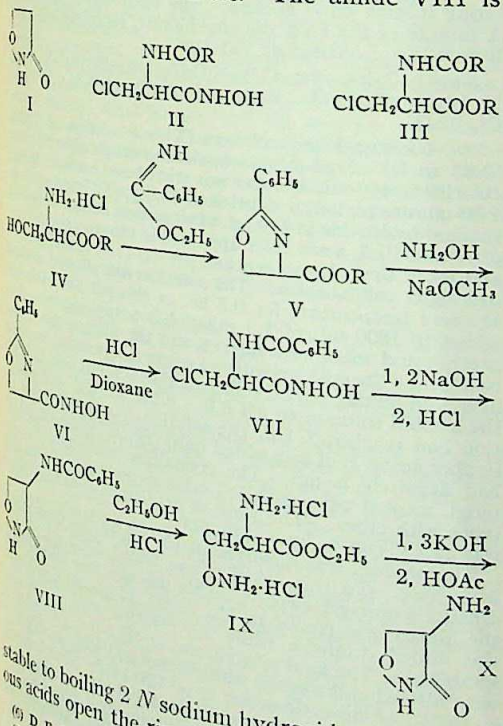
by cyclization of β-chloropropionohydroxamic acid, a key intermediate for synthesis of cycloserine appeared to be a β-chloro-α-acylaminopropionohydroxamic acid (II). The preparation of such a hydroxamic acid from the corresponding ester III was complicated by side reactions occurring in the necessarily alkaline reaction medium. Consequently, a structure was needed which was stable to alkali and convertible to the β-chloro-α-acylaminopropionohydroxamic acid. An oxazoline fulfils both of these requirements and was used in this synthesis.

DL-Serine methyl ester hydrochloride (IV, R = CH_3) was converted into DL-4-carbomethoxy-2-phenyl-2-oxazoline (V, R = CH_3) by the procedure of Elliott.[6] This ester yielded 4-carbohydroxamido-2-phenyl-2-oxazoline (VI) when treated with one equivalent each of hydroxylamine and sodium methoxide in methanol at room temperature. When the hydroxamic acid VI was heated on a steam-bath for 15 minutes in dioxane containing one equivalent of hydrogen chloride, α-benzamido-β-chloropropionohydroxamic acid (VII) was formed.[7] The β-chloropropionohydroxamic acid (VII) was cyclized to 4-benzamido-3-isoxazolidone (VIII) by aqueous alkali.[8]

Removal of the benzoyl group from the benzamidoisoxazolidone VIII by either acid or alkaline hydrolysis was not feasible. The amide VIII is

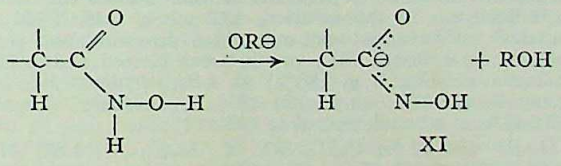


stable to boiling 2 *N* sodium hydroxide, while aqueous acids open the ring in addition to cleaving the amide. However, boiling ethanol saturated with hydrogen chloride removed the benzoyl group and also opened the isoxazolidone ring giving the hydrochloride of DL-β-aminoxyalanine ethyl ester (IX).[2] When this ester was treated with potassium hydroxide in aqueous solution, it cyclized rapidly to DL-cycloserine (X).

The resolution of DL-4-amino-3-isoxazolidone was accomplished with tartaric acid. Treatment of DL-cycloserine with D-tartaric acid gave D-4-amino-3-isoxazolidone-D-tartrate. This salt was converted by Amberlite IR-120 resin into D-4-amino-3-isoxazolidone, which was identical in all respects to cycloserine. Thus, the structure of cycloserine, deduced from degradation studies,[2,3] has been confirmed by synthesis. Using L-tartaric acid as resolving agent, we were able to prepare the unnatural L-cycloserine by the same procedure.

DL-4-Benzamido-3-isoxazolidone (VIII) was also resolved. This compound formed a crystalline cinchonidine metho-salt which on treatment with acid gave D-4-benzamido-3-isoxazolidone.

L-Serine ethyl ester hydrochloride (IV, R = C_2H_5) was prepared and converted into the optically active oxazoline ester (V, R = C_2H_5). When this ester was converted into the oxazoline hydroxamic acid VI by the procedure used on the racemic ester, about 50% racemization occurred. Variation of the reaction time, temperature or order of addition of the reactants to each other did not decrease the amount of racemization. It was interesting to note that the optically active hydroxamic acid VI did not racemize on standing in 0.1 *N* methanolic sodium methoxide overnight, but that the optically active ester V racemized so rapidly that its rotation in 0.1 *N* methanolic sodium methoxide when taken immediately was zero.[9] It is well known[10]



that optically active carboxylic acids racemize only with difficulty in alkali, whereas the corresponding esters racemize readily. Thus, the optical stability of the oxazoline hydroxamic acid in alkali may indicate that in the salt the negative charge resides next to the α-carbon (XI) just as the charge on a carboxylic acid salt does. This interpretation conflicts with the view[11] that hydroxamic acid salts have the charge on the hydroxyl oxygen.

The L-oxazoline hydroxamic acid VI was separated from its racemate by fractional crystallization. The 4-benzamido-3-isoxazolidone (VIII) formed from the L-hydroxamic acid VI by the reactions shown in the flow sheet was the optically pure L-4-benzamido-3-isoxazolidone. The conversion of this compound to L-cycloserine was not carried out,

(6) D. P. Elliott, *J. Chem. Soc.*, 589 (1949).

(7) Rearrangements of oxazoline hydrochlorides to β-haloalkylamides have been discussed by E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949); **15**, 438, 802 (1950).

(8) There is a surprisingly large effect of temperature on the direction of the reaction between the β-chloropropionohydroxamic acid (VII) and aqueous alkali. At room temperature these reactants gave the oxazoline hydroxamic acid VI in 79% yield, but at 60–65° the isoxazolidone VIII was isolated in 82% yield. The oxazoline VI was not converted into VIII by aqueous alkali at 60–65°.

(9) In the light of our work, a report by Fry, *J. Org. Chem.*, **15**, 438 (1950), that the oxazoline ester (V, R = CH_3) is hydrolyzed in aqueous alkali to the corresponding acid *without racemization* was surprising. We confirmed this result. Apparently, in this case the rate of saponification is much greater than that of racemization.

(10) C. L. Bickel, THIS JOURNAL, **60**, 927 (1938).

(11) J. Kenyon, *Chem. Ind.*, 79 (1953).

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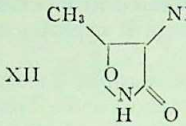
because the resolution of DL-cycloserine had been accomplished previously.

DL-4-Amino-5-methyl-3-isoxazolidone (XII), an analog of cycloserine, was synthesized from DL-



XII

threonine by the reaction series already described. This compound has two asymmetric centers and thus may exist as two DL-pairs. Our synthesis gave only one DL-pair since DL-threonine was used as starting material.[12]

Acknowledgment.—We are indebted to Dr. N. R. Trenner and Mr. R. W. Walker for infrared analyses and to Mr. R. N. Boos and associates for microanalyses.

Experimental

All melting points were taken on a Kofler micro hot-stage.

DL-4-Carbomethoxy-2-phenyl-2-oxazoline (V).—This compound was prepared by allowing ethyl benzimidate[13] and serine methyl ester hydrochloride[6] to react according to the procedure of Elliott.[6] A 45% yield of the oxazoline ester, b.p. 118–122° (0.15 mm.), $n^{24}D$ 1.5480, was obtained.

DL-4-Carbohydroxamido-2-phenyl-2-oxazoline (VI).—To a cooled solution of 4 g. (0.06 mole) of hydroxylamine hydrochloride in 100 ml. of absolute ethanol was added 35 ml. of 1.82 *N* (0.06 mole) sodium methoxide in methanol. The mixture was cooled to 0°, the sodium chloride was filtered and a solution of 10 g. (0.05 mole) of 4-carbomethoxy-2-phenyl-2-oxazoline in 20 ml. of ethanol was added to the filtrate. This solution was cooled to 0°, and 25 ml. of 1.82 *N* (0.05 mole) sodium methoxide was added slowly. The reaction mixture was allowed to stand overnight. The solution was concentrated *in vacuo* at room temperature to about 75 ml. When about 100 ml. of water was added to the solution, rapid and exothermic crystallization of what was probably the sodium salt of the oxazoline hydroxamic acid occurred. Further addition of water caused the solid to redissolve. To this solution, 43.3 ml. of 1.16 *N* (51.5 mmoles) hydrochloric acid was added dropwise, and the product crystallized. The product was filtered and dried *in vacuo* yielding 8 g. (80%) of 4-carbohydroxamido-2-phenyl-2-oxazoline, m.p. 174–176°. A sample, recrystallized from ethanol, melted at 176–179° dec.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.20; H, 4.88; N, 13.60. Found: C, 58.38; H, 5.05; N, 13.41.

Our subsequent work indicated that the reaction of the oxazoline ester V with hydroxylamine and sodium methoxide is complete after 15 minutes at 0°.

DL-α-Benzamido-β-chloropropionohydroxamic Acid (VII).—To a mixture of 4 g. (0.02 mole) of 4-carbohydroxamido-2-phenyl-2-oxazoline and 50 ml. of dry dioxane, was added 44 ml. of 0.46 *N* hydrogen chloride (0.02 mole) in dry dioxane, and the resulting mixture was heated on a steam-bath for 15 minutes. During the heating period, the solution became pink and then colorless, and the solid dissolved. The hot solution was filtered and evaporated *in vacuo* to a thick mass of crystals. These crystals were dissolved in approximately 25 ml. of hot isopropyl alcohol, and 175 ml. of low-boiling petroleum ether was added slowly to the solution. Crystallization occurred and, after two days at 5°, the DL-α-benzamido-β-chloropropionohydroxamic acid, 4.4 g., m.p. 148–152°, was filtered. A second crop, weighing 0.2 g., brought the total yield to 94%. A small sample, recrystallized from isopropyl alcohol–petroleum ether, melted at 153–155°.

Anal. Calcd. for $C_{10}H_{11}N_2O_3Cl$: C, 49.40; H, 4.56; N, 11.54; Cl, 14.60. Found: C, 48.94; H, 4.49; N, 11.77; Cl, 14.31.

DL-4-Benzamido-3-isoxazolidone (VIII).—To a solution of 4.0 g. (0.017 mole) of α-benzamido-β-chloropropionohydroxamic acid in about 30 ml. of hot methanol was added dropwise 31.5 ml. of 1.0 *N* sodium hydroxide (0.032 mole, 1.9 equivalents). When 16 ml. of the sodium hydroxide solution had been added, a phenolphthalein end-point was reached; the solution was heated to 60°, the remaining alkali was added and the end-point became permanent. To the cold basic solution, 4.2 ml. of 1.16 *N* hydrochloric acid (0.017 mole) was added, and the solution was immediately extracted with one 100-ml. portion and five 50-ml. portions of chloroform. The combined chloroform extracts were concentrated to about a 225-ml. volume, filtered and further concentrated to a 200-ml. volume. Crystallization began and, after the mixture was cooled, 2.1 g. of DL-4-benzamido-3-isoxazolidone, m.p. 167–170°, was filtered. A second crop weighed 0.5 g., m.p. 158–168° (total yield 75%). An analytical sample melting at 165–168° was obtained by recrystallization of the crude product from ethyl acetate.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.24; H, 4.89; N, 13.59. Found: C, 58.45; H, 4.70; N, 13.37.

DL-β-Aminoxyalanine Ethyl Ester Dihydrochloride (IX).—A rapid stream of hydrogen chloride was passed for 3 hr. into 2500 ml. of absolute ethanol cooled in an ice-bath. To this solution was added 100 g. (0.48 mole) of DL-4-benzamido-3-isoxazolidone, and this solution was refluxed for 3 hr. After standing at 3–5° overnight, the solution was concentrated at reduced pressure giving 83 g. of DL-β-aminoxyalanine ethyl ester dihydrochloride, m.p. 128–135°. An additional 3.6 g. of product was obtained by concentrating the mother liquor to about a 300-ml. volume and diluting it with ethyl acetate. The yield was 87 g. (81%). A sample of the ester dihydrochloride, recrystallized twice from ethanol, melted at 123–130°.

Anal. Calcd. for $C_5H_{14}N_2O_3Cl_2$: C, 27.16; H, 6.38; N, 12.67; Cl, 32.07. Found: C, 28.09; H, 6.35; N, 12.63; Cl, 32.00.

DL-4-Amino-3-isoxazolidone (X).—A solution of 73.3 g. (0.33 mole) of DL-β-aminoxyalanine ethyl ester dihydrochloride in 100 ml. of water was stirred and cooled. During a 30-minute period, a solution of 65.6 g. (1.17 moles) of potassium hydroxide in 100 ml. of water was added. Between *p*H 7 and 10.5, a red color appeared in the reaction mixture; and when the solution reached *p*H 11–11.5, it had changed to a light yellow color. The solution was allowed to stand at room temperature for 0.5 hr. at this *p*H and then was added to 1800 ml. of 1:1 ethanol–isopropyl alcohol. The precipitated salts were filtered and the filtrate was cooled to 5°. To the cold well-stirred solution was added dropwise over a 35-minute period sufficient glacial acetic acid to bring the alcohol solution to *p*H 6.0. When the *p*H of the solution had reached 7–7.5, the solution was seeded; and no further acetic acid was added until crystallization of the oil had definitely begun. The crystalline precipitate was filtered, washed twice with 1:1 ethanol–isopropyl alcohol and twice with ether. The yield of DL-4-amino-3-isoxazolidone was 22.7 g. (65%), m.p. 140–143°.

The product was dissolved in 152 ml. of 7% ammonium hydroxide. To this solution was added 1215 ml. of 1:1 ethanol–isopropyl alcohol. This mixture was filtered and the filtrate was cooled to 5°; 21 ml. of glacial acetic acid was added dropwise while the solution was seeded and scratched. The final solution was at *p*H 6.0. The crystals were filtered and washed with ethanol and ether giving 17.7 g. (52%) of DL-cycloserine, m.p. 137–140°. The infrared spectrum showed absorption in the 6.1–6.6 μ region characteristic of the zwitterion form of cycloserine. The spectra of the racemic and natural compounds differed in the 10–12 μ region.

Anal. Calcd. for $C_3H_6N_2O_2$: C, 35.29; H, 5.90; N, 27.45. Found: C, 35.11; H, 5.70; N, 27.14.

Resolution of DL-4-Amino-3-isoxazolidone.—A solution of 7.5 g. of D-tartaric acid in 25 ml. of water was cooled to 3°. To this solution was added rapidly 5.0 g. (0.05 mole) of DL-cycloserine and the mixture was stirred vigorously. Crystallization began almost immediately. After ten minutes, the crystals were filtered and washed with 5 ml. of cold water and three 20-ml. portions of acetone yielding

(12) The oxazoline ring opening and isoxazolidone ring closure are most probably S_N2 reactions, each of which inverts the β-carbon atom. Since the starting amino acid had the *threo* configuration, the aminoisoxazolidone XII should also have the *threo* configuration. The methyl and amino groups of XII will thus be *cis*.

(13) H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941, p. 336.

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cycloserine-D-tartrate, 5.2 g. (84%), m.p. 166–168° dec., $[\alpha]^{25}D$ +35.7° (*c* 0.7 in H_2O).

The D-cycloserine-D-tartrate was passed through a column of 200 g. of Amberlite IR-120 (Na^+ cycle). The column was washed free of sodium tartrate (eluate tested with lead acetate) with water, and D-cycloserine was eluted from the column with 2% ammonium hydroxide. The eluate was collected and lyophilized. The residue, 2.1 g., was dissolved in 14 ml. of 7% ammonium hydroxide, and 112 ml. of 1:1 ethanol–isopropyl alcohol was added. Super-Cel and Darco were added to the cloudy solution and the mixture was filtered. The clear filtrate was cooled to 5° and acetic acid was added dropwise to *p*H 6.0. The crystalline precipitate (1.1 g.) was filtered, washed with ethanol and ether and dried, m.p. 151–153° dec., $[\alpha]^{29}D$ +112° (*c* 1.0 in H_2O).

Recrystallization from 7 ml. of 7% ammonium hydroxide and 28 ml. of 1:1 ethanol–isopropyl alcohol in the manner described above gave 0.9 g. (39%) of D-cycloserine, m.p. 153–154° dec., $[\alpha]^{29}D$ +109° (*c* 1.0 in H_2O).

Anal. Calcd. for $C_3H_6N_2O_2$: C, 35.29; H, 5.92; N, 27.45. Found: C, 35.65; H, 5.78; N, 27.30.

The infrared spectrum of the synthetic D-cycloserine was identical with that of the natural compound.

L-Cycloserine-L-tartrate, $[\alpha]^{30}D$ −36.6° (*c* 0.79 in H_2O), was prepared as described above for the D-isomer. This tartrate was converted into L-cycloserine, $[\alpha]^{33}D$ −110° (*c* 0.83 in H_2O), as described above for the D-isomer.

Resolution of DL-4-Benzamido-3-isoxazolidone.—A solution of cinchonidine methohydroxide was prepared by dissolving 8.0 g. (18.4 mmoles) of cinchonidine methiodide in a few milliliters of water and shaking the solution for 4 hr. with 2.3 g. (10 mmoles) of silver oxide. Titration of an aliquot with 0.01 *N* hydrochloric acid showed that the solution contained 12.3 mmoles of the methohydroxide. To this solution was added 5.0 g. (24.3 mmoles) of DL-4-benzamido-3-isoxazolidone. The solution was kept overnight at room temperature. A small amount of undissolved isoxazolidone was filtered and the filtrate was evaporated *in vacuo* to a syrupy residue. The residue was dissolved in 500 ml. of hot methyl ethyl ketone, and the solution was cooled slowly to room temperature. The cinchonidine metho-salt of D-4-benzamido-3-isoxazolidone separated as small white needles. After two days at room temperature, the crystals were filtered, washed with ice-cold methyl ethyl ketone and dried *in vacuo* over phosphorus pentoxide yielding 2.0 g. of product, m.p. 192–195° dec., $[\alpha]^{25}D$ −80° (*c* 1.0 in H_2O).

A sample of this salt was recrystallized from water and dried at 100° (0.5 mm.).

Anal. Calcd. for $C_{20}H_{24}N_4O_4$: C, 70.01; H, 6.66; N, 16.89. Found: C, 69.82; H, 7.25; N, 10.81.

A sample of the cinchonidine metho-salt of D-4-benzamido-3-isoxazolidone, prepared from natural D-cycloserine, melted at 192–195° dec., $[\alpha]^{25}D$ −78° (*c* 0.9 in H_2O).

D-4-Benzamido-3-isoxazolidone.—A solution of 1.90 g. of the cinchonidine metho-salt of D-4-benzamido-3-isoxazolidone in 25 ml. of ice-water was acidified to *p*H 2 with concentrated hydrochloric acid. The solution was extracted with four 20-ml. portions of ether. The combined ether extracts were dried and evaporated *in vacuo*, giving a residue weighing 0.62 g. (86%). Crystallization from chloroform–petroleum ether gave 0.37 g. of D-4-benzamido-3-isoxazolidone, m.p. 172–175° dec., $[\alpha]^{25}D$ +16° (*c* 2.5 in pyridine). A sample, after recrystallization from water, melted at 173–175° dec.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.24; H, 4.89; N, 13.59. Found: C, 58.42; H, 5.11; N, 13.09.

D-4-Benzamido-3-isoxazolidone, prepared from natural D-cycloserine, melted at 174–176° dec., $[\alpha]^{25}D$ +17° (*c* 2.6 in pyridine). The infrared absorption spectrum of this compound was identical with that of the resolved product.

L-Serine Ethyl Ester Hydrochloride.—Dry hydrogen chloride was passed into a suspension of 95 g. of L-serine in 950 ml. of ethanol until the amino acid dissolved. About 200 ml. of ethanol was distilled from the solution and the residue was concentrated *in vacuo* to a thick sirup. When triturated with ether the product crystallized. It was filtered, washed with ether and dried, yielding 148 g. (97%) of L-serine ethyl ester hydrochloride, m.p. 126–127°, $[\alpha]^{25}D$ −5.5° (*c* 9.9 in 95% ethanol). After three recrystallizations from ethanol–ether, the product showed m.p. 130–131°, and $[\alpha]^{25}D$ −5.7° (*c* 10.2 in 95% ethanol).

Anal. Calcd. for $C_5H_{12}NO_3Cl$: C, 35.40; H, 7.13; N, 8.26. Found: C, 35.00; H, 6.96; N, 7.82.

L-4-Carbethoxy-2-phenyl-2-oxazoline.—This compound was prepared from L-serine ethyl ester hydrochloride and ethyl benzimidate in 68% yield by the procedure described for synthesis of the racemate. After distillation at 100–130° (1 mm.), the product crystallized, m.p. 42–47°. A small sample, recrystallized from ether–petroleum ether, melted at 47–48°, $[\alpha]^{25}D$ +134.5° (*c* 10.0 in 95% ethanol).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.34; H, 5.14; N, 6.05.

A 2.5% solution of this ester in 0.2 *N* sodium methoxide showed no optical rotation when examined immediately.

L-4-Carboxy-2-phenyl-2-oxazoline.—To 5 ml. of 2 *N* sodium hydroxide was added 2.2 g. (0.01 mole) of L-4-carbethoxy-2-phenyl-2-oxazoline. The mixture became warm and was stirred intermittently for 3 hr. After dilution with about 20 ml. of water, 200 ml. of acetone was added slowly and the mixture was cooled in an ice-bath. The product was filtered and dried, giving 2.0 g. of L-4-carboxy-2-phenyl-2-oxazoline sodium salt, $[\alpha]^{27}D$ +82.4° (*c* 5.0 in H_2O).

A suspension of 1 g. of the sodium salt in 5 ml. of water was cooled and 4.4 ml. of 1 *N* hydrochloric acid was added. The precipitated acid was filtered and washed with cold water, giving 0.5 g. of L-4-carboxy-2-phenyl-2-oxazoline, m.p. 131–135°, $[\alpha]^{27}D$ +219° (*c* 1.0 in pyridine). Insoluble products were formed and the melting point was lowered when the acid was recrystallized from benzene. Recrystallization from a 1:2 mixture of ether–petroleum ether gave the acid, m.p. 135–138°, $[\alpha]^{27}D$ +200° (*c* 1.0 in pyridine).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.81; H, 4.75; N, 7.33. Found: C, 62.68; H, 4.75; N, 7.29.

L-4-Carbohydroxamido-2-phenyl-2-oxazoline.—This compound was prepared in 81% yield from L-4-carbethoxy-2-phenyl-2-oxazoline essentially by the procedure used for the preparation of the racemic compound. However, the reaction mixture was allowed to stand at 0° overnight in order to lessen the amount of racemization. The product, m.p. 167–168°, had $[\alpha]^{25}D$ +65° (*c* 2.0 in 0.2 *N* sodium hydroxide).

One gram of this partially racemized hydroxamic acid was crystallized from 350 ml. of boiling 6:1 methyl isobutyl ketone–ethanol giving 0.3 g. of material, m.p. 180–181°, $[\alpha]^{27}D$ +2.4° (*c* 2.0 in 0.2 *N* sodium hydroxide). When the filtrate was cooled, 0.4 g. of a second crop was obtained, m.p. 179–180°, $[\alpha]^{29}D$ +97° (*c* 2.0 in 0.2 *N* sodium hydroxide). The filtrate from the second crop, when concentrated to 50 ml., yielded 0.15 g. of a third crop, m.p. 170–171°, $[\alpha]^{28}D$ +94.3° (*c* 2.0 in 0.2 *N* sodium hydroxide). The combined second and third crops were again recrystallized from 117 ml. of 6:1 methyl isobutyl ketone–ethanol giving 0.2 g. of product, m.p. 179–180°, $[\alpha]^{27}D$ +119.5° (*c* 2.0 in 0.2 *N* sodium hydroxide). Further recrystallization gave no increase in rotation.

L-4-Benzamido-3-isoxazolidone.—To a solution of 0.57 (2.8 mmoles) of L-4-carbohydroxamido-2-phenyl-2-oxazoline, $[\alpha]^{26}D$ +113° (*c* 2.0 in 0.2 *N* sodium hydroxide), in 20 ml. of dry dioxane was added 1.4 ml. of 2.2 *N* hydrogen chloride in dioxane. The solution was heated for 15 minutes on a steam-bath and was evaporated *in vacuo*. The residue was dissolved in 20 ml. of water, and the solution was heated at 55–65°, while 51.5 ml. of 0.1 *N* sodium hydroxide was added dropwise to a permanent phenolphthalein end-point. The solution was cooled to 10° and, after addition of 2.8 ml. of 1 *N* hydrochloric acid, was extracted with four 50-ml. portions of ethyl acetate. The extracts were dried and evaporated to 10 ml. This solution was cooled giving 0.24 g. of L-benzamido-3-isoxazolidone, m.p. 163–171°, $[\alpha]^{27}D$ −17.6° (*c* 2.5 in pyridine). The filtrate gave an additional 0.12 g., $[\alpha]^{27}D$ −17.5° (*c* 2.5 in pyridine), which brought the yield to 0.36 g. (63%).

DL-4-Carbohydroxamido-5-methyl-2-phenyl-2-oxazoline.—The procedure for the preparation of 4-carbohydroxamido-5-methyl-2-phenyl-2-oxazoline is similar to that described for the 4-carbohydroxamido-2-phenyl-2-oxazoline. From 187 g. of the oxazoline ester,[14] 149 g. (79%) of the oxazoline

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hydroxamic acid, m.p. 152–154°, was obtained. A sample, recrystallized from isopropyl alcohol, melted at 148–150°.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.73. Found: C, 59.98; H, 5.31; N, 12.91.

DL-α-Benzamido-β-chlorobutyrohydroxamic Acid.—To a stirred refluxing solution of 9.6 g. (0.044 mole) of 4-carbohydroxamido-5-methyl-2-phenyl-2-oxazoline in approximately 500 ml. of dry dioxane (distilled from sodium three times) was added dropwise over a period of 1 hr. 120 ml. of dioxane containing 1.8 g. (0.05 mole) of hydrogen chloride. During the addition of the hydrogen chloride solution, the reaction mixture became pink and a small quantity of a flocculent precipitate appeared. The solution was cooled, treated with Darco G-60 and filtered. The residue obtained from lyophilization of the filtrate was extracted with one 400-ml. and three 50-ml. portions of boiling ethyl acetate, and the combined extracts were diluted with an equal volume of chloroform. This solution was cooled and 6.6 g. (59%) of α-benzamido-β-chlorobutyrohydroxamic acid, m.p. 139–143°, was obtained. A sample, recrystallized from chloroform, melted at 141–142.5°. The ethyl acetate-insoluble portion of the residue was apparently unrearranged oxazoline hydrochloride and was not further investigated.

Anal. Calcd. for $C_{11}H_{13}N_2O_3Cl$: C, 51.47; H, 5.10; N, 10.89; Cl, 13.81. Found: C, 51.72; H, 5.40; N, 10.94; Cl, 13.72.

DL-4-Benzamido-5-methyl-3-isoxazolidone.—To a stirred slurry of 6.4 g. (0.025 mole) of α-benzamido-β-chlorobutyrohydroxamic acid in 100 ml. of water at 65–75°, 46 ml. (1.83 equivalents) of 1 *N* sodium hydroxide was added over a period of 1 hr. A permanent phenolphthalein end-point was obtained. The solution was cooled in an ice-bath and 21.4 ml. of 1.16 *N* (0.025 mole) hydrochloric acid was added. The acidic solution was extracted with three 250-ml. portions of chloroform, and the combined dried extracts were concentrated to approximately 225 ml. The DL-4-benzamido-5-methyl-3-isoxazolidone, 3.3 g., m.p. 188–194°, was filtered. The filtrate was concentrated and yielded another 1.0 g., m.p. 187–192°, bringing the total yield to 4.3 g. (79%). A small sample, recrystallized from chloroform, melted at 187–190°.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.62; H, 5.14; N, 12.56.

Methyl DL-α-Amino-β-aminoxybutyrate Dihydrochloride.—A rapid stream of hydrogen chloride was passed into 250 ml. of dry methanol for approximately 40 minutes. To this solution was added 5 g. (0.02 mole) of 4-benzamido-5-methyl-3-isoxazolidone, and the solution was refluxed for 2 hr. The solvent was removed *in vacuo*. The crystalline residue was extracted with 150 ml. of boiling isopropyl alcohol leaving 2.1 g. (42%) of crystalline methyl α-amino-β-aminoxybutyrate dihydrochloride, m.p. 139–145°. A small sample, triturated with boiling isopropyl alcohol, melted at 136–138°.

Anal. Calcd. for $C_5H_{14}N_2O_3Cl_2$: C, 27.16; H, 6.38; N, 12.67; Cl, 32.07. Found: C, 27.44; H, 6.46; N, 12.46; Cl, 31.27.

In some runs only amorphous ester dihydrochloride was obtained. The amorphous product was used successfully in the next step.

DL-4-Amino-5-methyl-3-isoxazolidone (XII).—To a cold solution of 2.0 g. (9.1 mmoles) of methyl α-amino-β-aminoxybutyrate dihydrochloride in 2 ml. of water was added dropwise a cold solution of 1.8 g. (>3 equivalents) of potassium hydroxide in 2 ml. of water. During the addition of the alkali, the reaction mixture became pink and then colorless as the solution reached *p*H 11. The precipitate, after removal of the supernatant solution, was washed twice with 0.5 ml. of water. The washings and supernatant solution were combined and then diluted with 40 ml. of 1:1 ethanol-isopropyl alcohol. The resulting precipitate was filtered and was washed with a small volume of the 1:1 alcohol solution. The filtrate was cooled to 0–5° and was acidified to *p*H 6 by the dropwise addition of glacial acetic acid. The crystalline precipitate, 923 mg. (88%), was recrystallized in the same manner as DL-4-amino-3-isoxazolidone giving 761 mg. of DL-4-amino-5-methyl-3-isoxazolidone, m.p. 170–173°.

Anal. Calcd. for $C_4H_8N_2O_2$: C, 41.36; H, 6.94; N, 24.13. Found: C, 41.31; H, 6.68; N, 23.88.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES DIVISION OF MERCK & CO., INC.]

Some Reactions of *erythro*- and *threo*-β-*p*-Nitrophenylserine

BY ARTHUR F. WAGNER

RECEIVED DECEMBER 29, 1956

Ethyl *erythro*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate (I) was converted to the corresponding 2-oxazoline, 4-carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (II), by an SNi displacement using *p*-toluenesulfonyl chloride in pyridine solution. The 4-carbethoxy-2-oxazoline II was converted to the 4-carbohydroxamido-2-oxazoline IV which was opened to the *erythro*-β-chlorohydroxamic acid V. Among the products resulting from the alkaline cyclization of the *erythro*-β-chlorohydroxamic acid V was the 4-carbohydroxamido-2-oxazoline IV. Ethyl *erythro*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate (I) reacted with thionyl chloride to yield the corresponding β-chloro compound III with retention of configuration. The corresponding *threo* isomer VI in the same reaction underwent nitrogen-to-oxygen acyl migration and inversion at the β-carbon to yield ethyl *erythro*-α-amino-β-benzoyloxy-β-*p*-nitrophenylpropionate hydrochloride (VII).

The characterization and synthesis of chloramphenicol[1] did much to stimulate interest in the stereochemistry and reactivity of the β-*p*-nitrophenylserines. More recently publications from these laboratories[2] described the synthesis of the antibiotic cycloserine[3] using serine as the precursor for the 3-isoxazolidone nucleus. This synthesis used a 4-carbethoxy-2-oxazoline intermediate to protect the α- and β-positions of the original serine molecule while the carbethoxy group was converted to a carbohydroxamido group. In contrast to the alternative of converting a β-chloroester to a β-chlorohydroxamic acid directly, the alkaline stability of the 2-oxazoline ring effectively protected the α- and β-positions of serine from undergoing any reaction during the conversion of the ester to a hydroxamic acid. The carbohydroxamido-2-oxazoline was opened to a β-chlorohydroxamic acid which was then cyclized to a 3-isoxazolidone.

This paper describes the behavior of *erythro*- and *threo*-β-*p*-nitrophenylserine in a similar sequence of reactions designed to synthesize 2-oxazolines and

(1) M. C. Rebstock, H. M. Crooks, Jr., J. Controulis and Q. R. Bartz, THIS JOURNAL, **71**, 2458 (1949).

(2) C. H. Stammer, A. N. Wilson, F. W. Holly and K. Folkers, *ibid.*, **77**, 2346 (1955); C. H. Stammer, A. N. Wilson, C. F. Spencer, F. W. Holly and K. Folkers, *ibid.*, **79**, 3236 (1957).

(3) D-4-Amino-3-isoxazolidone. Our generic name for this antibiotic has been changed from oxamycin to cycloserine. Oxamycin is now the registered trade-mark of Merck & Co., Inc., for this antibiotic.

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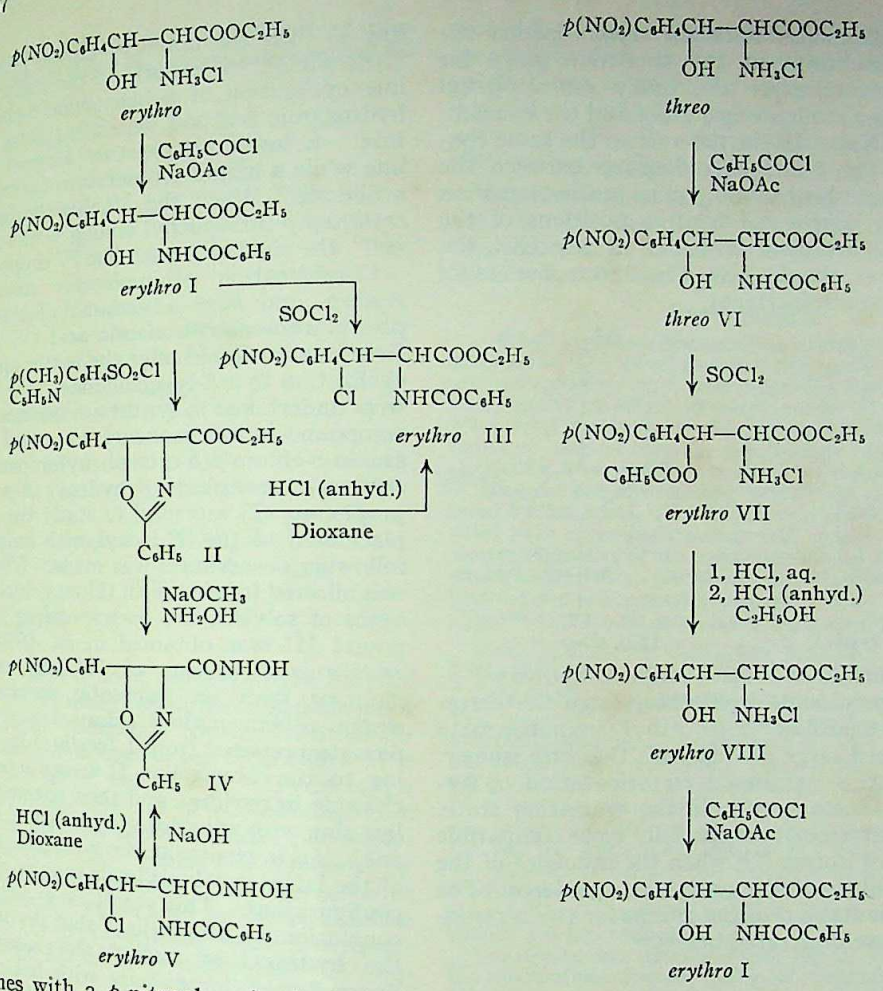

2-isoxazolidones with a *p*-nitrophenyl substituent. Striking differences were observed in the behavior of *erythro*- and *threo*-β-*p*-nitrophenylserine derivatives at two steps of the reaction sequence. For the preparation of 2-oxazolines it was noted that "*cis* effects" of the substituents dictate the choice of reaction for the cyclization of either isomer. In reactions with thionyl chloride, ethyl *erythro*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate (I) gave a different type of product from that isolated from the corresponding *threo* isomer II in the same reaction. A difference in reaction mechanism is clearly indicated here. All of these observations are presented below and some of the reactions are discussed in the light of recently confirmed configurations of the two diastereomers.[4]

As noted earlier, the key intermediate of the 3-isoxazolidone synthesis is a 2-oxazoline. Two courses were open for the synthesis of 4-carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (II). The first involves reaction of ethyl α-amino-β-hydroxy-β-*p*-nitrophenylpropionate hydrochloride with ethyl iminobenzoate[5,6] and the second consists of an SNi displacement[7] at the β-carbon in ethyl α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate. In the former case the participating groups should be *cis* oriented, while in the latter case they should be in a *trans* orientation. In the reaction of ethyl *erythro*-α-amino-β-hydroxy-β-*p*-nitrophenylpropionate hydrochloride with ethyl iminobenzoate at room temperature, no 2-oxazoline could be isolated.[8] When ethyl *erythro*-α-amino-β-hydroxy-β-*p*-nitrophenylpropionate hydrochloride was first benzoylated on nitrogen and the resulting amide I then allowed to react with *p*-toluenesulfonyl chloride in pyridine,[7] the 2-oxazoline II was isolated in yields up to 70%.

Considering the *cis* orientation requirements for cyclization with ethyl iminobenzoate and the *trans* orientation necessary for SNi cyclization, it can be seen that a "*cis* effect"[9] will play an important role in the transition state of each of these diastereomers

(4) For a comprehensive review of the data describing the synthesis and stereochemistry of the two diastereoisomers see D. O. Holland, P. A. Jenkins and J. H. C. Naylor, *J. Chem. Soc.*, 273 (1953).

(5) D. F. Elliott, *ibid.*, 589 (1949).

(6) W. S. Johnson and E. N. Schubert, THIS JOURNAL, **72**, 2187 (1950).

(7) R. N. Boyd and R. H. Hansen, *ibid.*, **75**, 5896 (1953).

(8) A similar observation has been reported by E. D. Bergmann, H. Bendas and W. Taub, *J. Chem. Soc.*, 2673 (1951). These workers report no 2-oxazoline isolated from the reaction between *erythro*-β-*p*-nitrophenylserine ethyl ester and ethyl iminobenzoate in refluxing dichloroethane, tetrachloroethane or dibromoethane. With the corresponding *threo* isomer, however, I. Elphimoff-Felkin, H. Felkin and Z. Welvart, *Compt. rend.*, **234**, 1789 (1952), report a facile conversion to the 2-oxazoline with ethyl iminobenzoate. With the β-phenylserine ethyl esters, however, both the *erythro* and *threo* isomers yield 2-oxazolines on treatment with ethyl iminobenzoate either in the presence or absence of solvent. See M. Viscontini and E. Fuchs, *Helv. Chim. Acta*, **36**, 1 (1953), and I. Elphimoff-Felkin, H. Felkin, B. Tchoubar and Z. Welvart, *Bull. soc. chim. France*, 252 (1952).

(9) D. Y. Curtin, *Record Chem. Progr.* (Kresge–Hooker Sci. Lib.), 16, 111 (1954).

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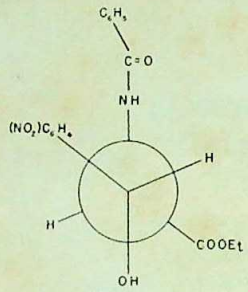
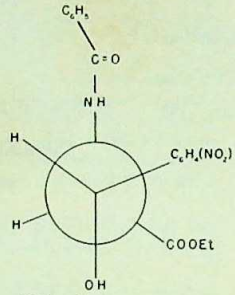
prior to cyclization. With the *erythro* isomer the necessary conditions at the transition stage for SNi displacement place the bulky *p*-nitrophenyl group between the hydrogen atom and the benzamido group (IXa). In the *threo* series the same conditions put the *p*-nitrophenyl group between the carbethoxy and benzamido groups in the transition state (IXb). Since the relative positions of the bulky groups are more favorable in case IXa, the *erythro* isomer should give the 2-oxazoline more readily by SNi displacement.

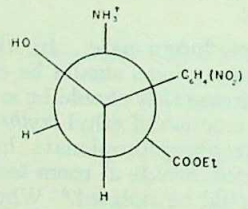


IXa, *erythro*

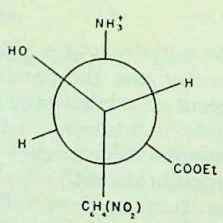


IXb, *threo*

The conversion of ethyl α-amino-β-hydroxy-β-*p*-nitrophenylpropionate hydrochloride to the corresponding 2-oxazoline with ethyl iminobenzoate should proceed more readily with the *threo* isomer. This cyclization requires a *cis* orientation of hydroxyl and amino groups in the transition state. Such a *cis* arrangement is spatially more compatible with the *threo* isomer Xb when the influence of the "*cis* effect" of the bulky groups is considered. The preferred orientations of the groups for this *cis* transition state are illustrated below.[10]



Xa, *erythro*



Xb, *threo*

The 2-oxazoline II was converted in 60% yield to 4-carbohydroxamido-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (IV) with sodium methoxide and hydroxylamine.[11] The 2-oxazoline hydroxamic acid IV on treatment with anhydrous hydrogen chloride in dioxane solution yielded the β-chloro acid, *erythro*-α-benzamido-β-chloro-β-*p*-nitrophenylpropionohydroxamic acid (V).[12] When the hydroxamic acid V was cyclized with alkali at about 70°, the 2-oxazoline IV was the only crystalline product isolated (30% yield). As reported,[2] the course of the alkaline cyclization of α-benzamido-β-chloropropionohydroxamic acid was dependent upon the temperature. A lower temperature favored the 2-oxazoline while a higher temperature favored the 3-isoxazolidone. When the alkaline cyclization of the *erythro*-β-*p*-nitrophenyl analog V was carried out at 100°, the yield of 2-oxazoline IV dropped to 20%.

Consideration of molecular models of both *erythro*- and *threo*-α-benzamido-β-chloro-β-*p*-nitrophenylpropionohydroxamic acid (V) shows that a *threo* isomer should offer the better opportunity for cyclization to a 3-isoxazolidone. Accordingly steps were undertaken to synthesize this isomer. The key compound in this sequence was ethyl *threo*-α-benzamido-β-chloro-β-*p*-nitrophenylpropionate. Ethyl *erythro*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate (I) was used to study the course of displacement of the hydroxyl with halogen, and the following observation was made. When I (*erythro*) was allowed to react with thionyl chloride in the absence of solvent, the corresponding β-chloro compound III was obtained in *ca.* 60% yield. The *erythro* configuration of III was established by identity with an authentic specimen of ethyl *erythro*-α-benzamido-β-chloro-β-*p*-nitrophenylpropionate prepared from I (*erythro*) by first converting to the 2-oxazoline II using *p*-toluenesulfonyl chloride in pyridine and then opening the 2-oxazoline ring with anhydrous hydrogen chloride in dioxane. An inversion at the β-carbon in each step[7,13] of the latter synthesis leads to over-all retention of configuration. This result is in accord with the conclusion reached earlier[13] that the displacement of the hydroxyl of methyl *threo*-α-acetamido-β-hydroxy-β-phenylpropionate with halogen using thionyl chloride proceeds with retention of configuration.

When ethyl *threo*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate (VI) was allowed to react with thionyl chloride in the absence of solvent, the only product which could be isolated was ethyl *erythro*-α-amino-β-benzoyloxy-β-*p*-nitrophenylpropionate hydrochloride (VII) (*ca.* 50% yield). The identity of the rearranged and inverted product was confirmed by the conversion of VII to ethyl *erythro*-α-amino-β-hydroxy-β-*p*-nitrophenylpropionate hydrochloride (VIII) by acid hydrolysis followed by esterification. The configuration was further confirmed by the conversion of VIII to ethyl *erythro*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate (I) by benzoylation in the presence of sodium acetate.

The displacement of hydroxyl with halogen by thionyl chloride in the *erythro*-isomer with retention of configuration can occur in either of two ways. In one instance an SNi displacement by the halogen of the intermediate ester halide[14] would yield the corresponding halide with retention of configuration. On the other hand, the same intermediate ester halide can cyclize to the corresponding oxazoline which in turn can be converted to the chlorobenz-

(10) The stereochemical notations follow the suggestion of M. S. Newman, *Record Chem. Progr.*, **13**, 111 (1952).

(11) The racemization of optically active esters by bases is well known (see C. L. Bickel, THIS JOURNAL, **60**, 927 (1938)). Under these conditions, therefore, one would expect racemization at the α-carbon to give a mixture of *cis*- and *trans*-oxazolines. It has been found, however (D. F. Elliott, *J. Chem. Soc.*, 62 (1950)), that *cis*-oxazolines mutarotate at the α-carbon in alkali to give *trans*-oxazolines. The rate of mutarotation is even faster in alcoholic sodium ethoxide solution. Thus the *trans*-oxazoline ester II on treatment with sodium methoxide and hydroxylamine will yield the *trans*-oxazoline hydroxamic acid IV.

(12) For a discussion of the rearrangements of oxazoline hydrochlorides see E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949); **15**, 438, 802 (1950).

(13) D. O. Holland, P. A. Jenkins and J. H. C. Nayler, *J. Chem. Soc.*, 273 (1953).

(14) E. R. Alexander, "Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 94.

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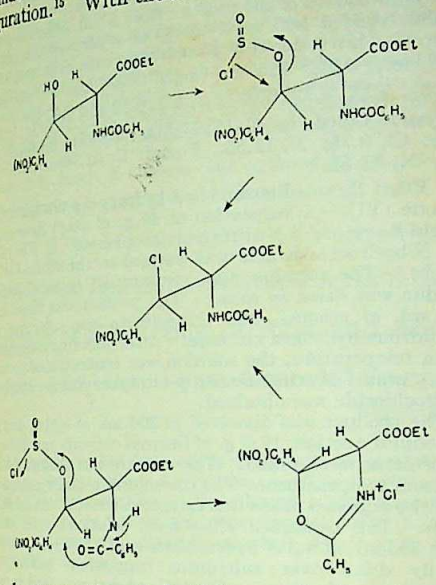
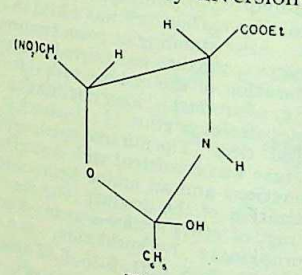
amido compound with over-all retention of configuration.[15] With the *threo* isomer in thionyl chlo-



ride, however, there is both benzoyl migration and inversion at the β-carbon rather than displacement of hydroxyl with halogen.[16] Since 1,2-*trans*-cyclization of the *threo* isomer to the 2-oxazoline II is unfavorable because of the role of "*cis*-effects," a mechanism involving cleavage of a 2-oxazoline to a rearranged and inverted product would not apply. Nitrogen-to-oxygen acyl migrations proceed by way of a cyclic transition state.[17] In this instance a 1,2-*cis*-cyclization[18] would lead to the oxazolidine XI; therefore, the acyl migration would not necessarily in itself be attended by inversion.[17] A suggested mechanism then in the case of the *threo* isomer might first involve migration of the benzoyl group from nitrogen to oxygen through 1,2-*cis*-cyclization and subsequent epimerization at the β-carbon to give the thermodynamically more stable[19] *erythro* configuration.



XI

Acknowledgment.—The author is indebted to Mr. R. N. Boos and associates for elemental analyses and to Dr. N. R. Trenner and Mr. R. W. Walker for infrared spectral data.

Experimental

Ethyl *erythro*-α-Benzamido-β-hydroxy-β-*p*-nitrophenylpropionate (I).—Five grams (0.017 mole) of *erythro*-β-*p*-nitrophenylserine ethyl ester hydrochloride[20] was suspended in a mixture of 50 ml. of water and 50 ml. of chloroform. Then 3.4 g. (0.043 mole) of sodium acetate and 2.4 g. (0.018 mole) of benzoyl chloride were added. The mixture was shaken for 2 hr. and then acidified by the addition of 1 ml. of concentrated hydrochloric acid. The product was isolated by filtration. The chloroform phase was separated, dried over magnesium sulfate and concentrated *in vacuo*. Recrystallization of the combined solid products from ethanol yielded 3.6 g. (60%) of ethyl *erythro*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate, m.p. 158.5–160.5°; $\lambda_{max}^{Nujol\ mull}$ 2.99, 5.75, 6.07, 6.2–6.28, 6.6 and 7.4 μ.

Anal. Calcd. for $C_{18}H_{18}N_2O_6$ (358.34): C, 60.33; H, 5.06; N, 7.82. Found: C, 60.31; H, 5.17; N, 7.65.

4-Carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (II).—Ten grams (0.028 mole) of ethyl *erythro*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate (I) was dissolved in 40 ml. of anhydrous pyridine. The solution was cooled and 5.3 g. (0.028 mole) of *p*-toluenesulfonyl chloride was added. After standing overnight at room temperature, the solution was poured into 100 ml. of 10% aqueous sodium bicarbonate, and the product was isolated by chloroform extraction. The chloroform extract was washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Removal of the pyridine by distillation *in vacuo* at 75–80° yielded a 9.1-g. residue.

The residue was triturated with 100 ml. of dry ether and the mixture was filtered; 2.5 g. of starting material, m.p. 158–160°, was isolated. Concentration of the ether solution *in vacuo* yielded 6 g. of the 2-oxazoline. Recrystallization of the product from 20 ml. of ethanol gave 4.2 g. (45%) of 4-carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline, m.p. 88–91°, λ_{max}^{EtOH} 255 mμ (log ε 4.240); $\lambda_{max}^{CCl_4}$ 5.77, 6.04, 6.2, 6.28, 6.5, 6.6 and 7.4 μ.

Anal. Calcd. for $C_{18}H_{16}N_2O_5$ (340.33): C, 63.51; H, 4.74; N, 8.23. Found: C, 63.29; H, 4.39; N, 8.21.

Ethyl *erythro*-α-Benzamido-β-chloro-β-*p*-nitrophenylpropionate (III). (a) From 4-Carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline.—One and nine-tenths milliliters of an anhydrous dioxane solution of hydrogen chloride (0.776 *N*) was added to 500 mg. (1.47×10^{-3} mole) of 4-carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (II) dissolved in 10 ml. of anhydrous dioxane. The solution was heated on the steam-bath and concentrated *in vacuo*. Final traces of dioxane were removed by dissolving the residue in ether and concentrating *in vacuo* several times. Crystallization of the product from ethanol–ether–petroleum ether yielded 280 mg. of material melting at 120–122°. The product was taken up in chloroform and the solution was washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Recrystallization of the product from ethanol–ether–petroleum ether gave 140 mg. of ethyl *erythro*-α-benzamido-β-chloro-β-*p*-nitrophenylpropionate, m.p. 121–124°.

(15) The experimental conditions do not allow a choice between these two mechanisms.

(16) The difference in the course of reaction of the two diastereomers is not unusual. Thus, J. Weijlard, K. Pfister, E. F. Swanezy, C. A. Robinson and M. Tishler, THIS JOURNAL, **73**, 1216 (1951), report that *N*-formyl-*erythro*-2-amino-1,2-diphenylethanol is 1,2-*trans*-cyclized with inversion to the oxazoline salt by thionyl chloride under conditions which do not affect the *N*-formyl derivative of the *threo* isomer. On the other hand, G. Fodor, V. Bruckner, J. Kiss and G. Ohegyi, *J. Org. Chem.*, **14**, 337 (1949), showed that *N*-acetyl-*threo*-2-amino-1,2-diphenylethanol undergoes nitrogen-to-oxygen acyl migration through 1,2-*cis*-cyclization to the oxazolidine with alcoholic hydrogen chloride, while similar conditions leave the *erythro*-isomer unchanged.

(17) L. H. Welsh, THIS JOURNAL, **71**, 3500 (1949).

(18) The rate of 1,2-*cis*-cyclization will be greater for the *threo*-isomer since the smaller rather than the large groups are eclipsed in the intermediate or planar transition state (see D. H. R. Barton and R. C. Cookson, *Quart. Revs.* (*London*), **10**, 51 (1956)). Examples of this effect are found in the slower rates of acyl migration observed in *erythro*-1,2-amino-alcohols as compared to the rates with corresponding *threo* isomers (see L. H. Welsh, ref. 17, and G. Fodor, *et al.*, ref. 16).

(19) According to D. H. R. Barton and R. C. Cookson, *Quart. Revs.* (*London*), **10**, 49 (1956), the *erythro* isomer is the more stable isomer of diastereoisomeric pairs of non-polar compounds in which differences of free energy are mainly due to differences in compression energy. This order of stability has been established experimentally by direct equilibration or by the introduction of a second asymmetric center in reactions known to result (by mechanism) in mixtures approximating to the equilibrium mixture.

(20) E. D. Bergmann, H. Bendas and W. Taub, *J. Chem. Soc.*, 2676 (1951).

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Anal. Calcd. for $C_{15}H_{17}ClN_2O_5$ (376.80): C, 57.36; H, 4.55; Cl, 9.41; N, 7.44. Found: C, 57.14; H, 4.37; Cl, 9.96; N, 7.58.

(b) From Ethyl *erythro*-α-Benzamido-β-hydroxy-β-*p*-nitrophenylpropionate.—One gram (2.8×10^{-3} mole) of ethyl *erythro*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate (I) was dissolved in 3 ml. of thionyl chloride. The mixture was cooled until solution was complete. After standing at room temperature for 3 hr., the solution was concentrated *in vacuo*. Ether was added to the residue and final traces of thionyl chloride were removed by concentration *in vacuo*. The residue was triturated with ether and the product was isolated by filtration; 650 mg. of product, m.p. 122–124°, was obtained.

Recrystallization of a portion of the product (250 mg.) from ethanol–ether–petroleum ether yielded 150 mg. of ethyl *erythro*-α-benzamido-β-chloro-β-*p*-nitrophenylpropionate, m.p. 122–124°. Admixture with an authentic specimen of this compound (IIIa) caused no depression in the melting point of the specimen.

The infrared spectrum of the compound in chloroform solution showed functionality consistent with the proposed structure; $\lambda_{max}^{CHCl_3}$ 2.93, 5.76, 6.01, 6.2 and 6.28, 6.5–6.6 and 7.4 μ.

4-Carbohydroxamido-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (IV). (a) From 4-Carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline.—One gram of hydroxylamine hydrochloride was dissolved in 25 ml. of warm ethanol. When the solution had cooled to room temperature, 13.8 ml. of methanolic 1.16 *N* sodium methoxide was added. The mixture was cooled and filtered. The filtrate was added to a solution of 4.06 g. (0.012 mole) of 4-carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (II) in 50 ml. of ethanol. The reaction mixture was cooled to *ca.* 0°, and 10 ml. of methanolic 1.16 *N* sodium methoxide was added slowly. The solution turned red; in the course of ten minutes the color of the solution faded to pale yellow.

After standing at room temperature for 1 hr., the solution was concentrated *in vacuo* to a volume of *ca.* 20 ml. The mixture was diluted with 50 ml. of water and acidified with 14.2 ml. of 0.99 *N* hydrochloric acid. The product was isolated by filtration and dried *in vacuo* over phosphoric anhydride. Recrystallization of the product from dioxane–ether yielded 2.25 g. (60%) of 4-carbohydroxamido-5-*p*-nitrophenyl-2-phenyl-2-oxazoline, m.p. 201–203° dec., λ_{max}^{EtOH} 255 mμ (log ε 4.255); $\lambda_{max}^{Nujol\ mull}$ 3.1, 5.95, 6.05, 6.2, 6.28 and 6.54 μ.

Anal. Calcd. for $C_{16}H_{13}N_3O_5$ (327.28): C, 58.73; H, 3.88; N, 12.84. Found: C, 58.74; H, 3.88; N, 12.80.

(b) From *erythro*-α-Benzamido-β-chloro-β-*p*-nitrophenylpropionohydroxamic Acid.—A suspension of 500 mg. (1.4×10^{-3} mole) of *erythro*-α-benzamido-β-chloro-β-*p*-nitrophenylpropionohydroxamic acid (V) in 5 ml. of ethanol was gently refluxed and titrated with 0.99 *N* sodium hydroxide until the phenophthalein end-point was permanent for several minutes (2×10^{-3} equivalent of alkali was consumed). The solution was cooled in an ice-bath and 10 ml. of water was added. The mixture was acidified with 1 ml. of 0.99 *N* hydrochloric acid and stirred. The product was isolated by filtration and dried *in vacuo;* 320 mg. of material melting at 175–178° dec. was obtained.

The product was boiled with 25 ml. of ethanol and the mixture was filtered. The residue (90 mg.) melted at 194° dec. The ethanolic filtrate was cooled and filtered; an additional 30 mg. of product, m.p. 194° dec., was obtained. The two crops of crystalline product (120 mg.) were combined and characterized as 4-carbohydroxamido-5-*p*-nitrophenyl-2-phenyl-2-oxazoline, m.p. 194° dec.; λ_{max}^{EtOH} 250 mμ (log ε 4.297).

The infrared spectrum of the product was identical to that of an authentic specimen of 4-carbohydroxamido-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (IVa). Admixture of the product with the same authentic specimen (IVa) gave no depression in the melting point.

***erythro*-α-Benzamido-β-chloro-β-*p*-nitrophenylpropionohydroxamic Acid (V).**—Two milliliters of an anhydrous dioxane solution of hydrogen chloride (1.09 *N*) was added to a suspension of 640 mg. (0.002 mole) of 4-carbohydroxamido-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (IVa) in 6 ml. of anhydrous dioxane. The mixture was warmed on the steam-bath for five minutes. The solution was cooled, and the product which precipitated was collected by filtration; 660 mg. of hydroxamic acid, m.p. 179–182° dec., was obtained. Recrystallization of the product from 40 ml. of hot isopropyl alcohol yielded 200 mg. (28%) of *erythro*-α-benzamido-β-chloro-β-*p*-nitrophenylpropionohydroxamic acid, m.p. 182–183° dec.; λ_{max}^{EtOH} 235 mμ (log ε 4.129) and 260 mμ (log ε 4.099); λ_{max}^{solid} 3.12, 6.09, 6.2, 6.9, 6.52 and 6.67 μ.

Anal. Calcd. for $C_{16}H_{14}ClN_3O_5$ (363.75): C, 52.84; H, 3.88; Cl, 9.75; N, 11.55. Found: C, 52.84; H, 3.47; Cl, 9.5; N, 11.55.

Ethyl *threo*-α-Benzamido-β-hydroxy-β-*p*-nitrophenylpropionate (VI).—A suspension of 49 g. of ethyl *threo*-α-acetamido-β-acetoxy-β-*p*-nitrophenylpropionate[21] in 500 ml. of 2.5 *N* hydrochloric acid was warmed on the steam-bath for 2.5 hr. The solution was concentrated *in vacuo* and the residue was dried *in vacuo*. The product was dissolved in 250 ml. of ethanol, and the solution was saturated with anhydrous hydrogen chloride. After standing overnight at room temperature, the solution was concentrated *in vacuo*. Forty grams of crude *threo*-β-*p*-nitrophenylserine ethyl ester hydrochloride was obtained.

The product was dissolved in 300 ml. of water, and 28 g. of sodium acetate, 19.2 g. of benzoyl chloride and 300 ml. of chloroform were added. The mixture was shaken for 2 hr. at room temperature. The chloroform phase was separated and the aqueous phase was extracted with 200 ml. of chloroform. The combined chloroform solutions were washed with 350 ml. of 0.3 *N* hydrochloric acid, then with water and finally dried over anhydrous magnesium sulfate. The chloroform solution was filtered and concentrated *in vacuo*. Crystallization of the residue (44 g.) from 100 ml. of ethanol yielded 16 g. of product melting at 126–134°. Recrystallization of this fraction from ethanol yielded 11 g. of ethyl *threo*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate, m.p. 136–138°. The infrared spectrum in chloroform solution confirms the presence of an N-benzoyl function; $\lambda_{max}^{CHCl_3}$ 2.98, 5.78, 6.0, 6.2, 6.3, 6.55 and 7.4 μ.

Anal. Calcd. for $C_{18}H_{18}N_2O_6$ (358.34): C, 60.33; H, 5.06; N, 7.82. Found: C, 60.59; H, 5.13; N, 7.77.

Reaction of Ethyl *threo*-α-Benzamido-β-hydroxy-β-*p*-nitrophenylpropionate with Thionyl Chloride. (a) Ethyl *erythro*-α-Amino-β-benzoyloxy-β-*p*-nitrophenylpropionate Hydrochloride (VII).—A mixture of 4 g. of ethyl *threo*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate and 4 g. of anhydrous calcium carbonate[22] was added to 25 ml. of thionyl chloride. After standing at room temperature for three days, the reaction mixture was filtered and concentrated *in vacuo*. Trituration of the residue with ether and filtration yielded 3.45 g. of product. Recrystallization of the product from ethanol–petroleum ether (1:1) gave 1.9 g. of product melting at 180° dec. The infrared spectrum of the product in the solid state was consistent with a structure containing two ester functions and an amine hydrochloride function.

Recrystallization of the product (660 mg.) from ethanol yielded 250 mg. of ethyl *erythro*-α-amino-β-benzoyloxy-β-*p*-nitrophenylpropionate hydrochloride, m.p. 197° dec.; λ_{max}^{solid} 3.5–4.4, 5.70, 5.85, 6.21, 6.35, 6.57 and 7.38 μ.

Anal. Calcd. for $C_{18}H_{19}ClN_2O_6$ (394.81): C, 54.75; H, 4.85; Cl, 8.98; N, 7.10. Found: C, 54.81; H, 4.75; Cl, 9.03; N, 7.09.

(b) Confirmation of Configuration of VII. (i) Ethyl *erythro*-α-Amino-β-hydroxy-β-*p*-nitrophenylpropionate Hydrochloride (VIII).—A mixture of 900 mg. of VII and 15 ml. of 2.5 *N* hydrochloric acid was warmed on the steam-bath. Ethanol was added to make the mixture homogeneous, and the solution was warmed on the steam-bath for 2 hr.

The reaction mixture was concentrated *in vacuo*, and the residue was leached with hot benzene to remove benzoic acid. The residue was taken up in ethanol, and the solution was saturated with anhydrous hydrogen chloride.

After standing at room temperature overnight, the solution was concentrated *in vacuo* and the residue was crystallized from ethanol; 350 mg. of ethyl *erythro*-α-amino-β-hydroxy-β-*p*-nitrophenylpropionate hydrochloride, m.p.

(21) B. N. Feitelson, J. T. Gunner, R. J. Moualim, V. Petrow, O. Stephenson and S. W. F. Underhill, *J. Pharm. Pharmacol.*, **3**, 154 (1951).

(22) The same product is obtained when anhydrous calcium carbonate is omitted.

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177° dec., was obtained. A second crystallization yielded 170 mg. of the compound melting at 188° dec. (lit.[23] *erythro*-, m.p. 182–184° dec.; *threo*-, m.p. 153–155° dec.

(ii) Ethyl *erythro*-α-Benzamido-β-hydroxy-β-*p*-nitrophenylpropionate (I).—A mixture of 40 mg. of VIII, 28 mg. of sodium acetate and 19 mg. of benzoyl chloride in 4 ml. of water and 4 ml. of chloroform was shaken for 2 hr. About 20 ml. of chloroform was added to the reaction mixture, and the aqueous phase was acidified with a few drops of 2.5 *N* hydrochloric acid. The chloroform phase was separated and dried over anhydrous magnesium sulfate. The chloroform solution was filtered and concentrated *in vacuo*. Crystallization of the residue from ethanol gave 30 mg. of ethyl *erythro*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate, m.p. 154–156°. A second crystallization from ethanol yielded 18 mg. of product melting at 158–160°. There was no depression in melting point on admixture of the product with an authentic specimen of ethyl *erythro*-α-benzamido-β-hydroxy-β-*p*-nitrophenylpropionate.

RAHWAY, NEW JERSEY

(23) C. G. Alberti, B. Camerino and A. Vercellone, *Experientia*, **8**, 261 (1952).

[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING DIVISION OF CORNELL UNIVERSITY MEDICAL COLLEGE]

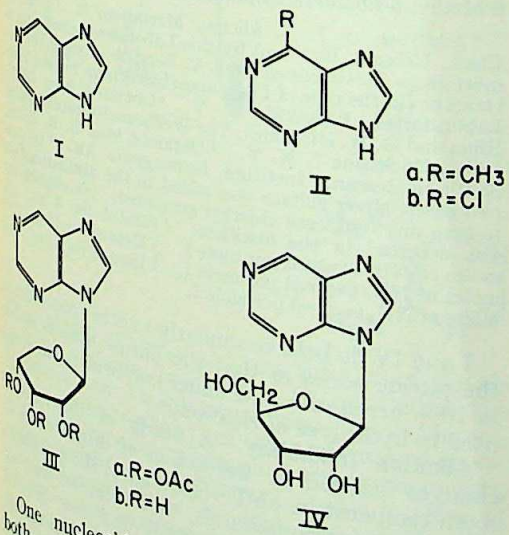
A Study of the Action of Acid and Alkali on Certain Purines and Purine Nucleosides[1]

BY MILTON PAUL GORDON,[2] VIRGINIA S. WELIKY AND GEORGE BOSWORTH BROWN

RECEIVED NOVEMBER 16, 1956

A series of glycosyl derivatives of various purines was found to be extremely labile toward dilute alkali at room temperature. In studies with 9-β-D-ribofuranosylpurine two products resulting from cleavage of the imidazole ring, with loss of carbon-8 but without loss of the ribosyl group, were partially characterized. Purine, its ribofuranosyl and ribopyranosyl derivatives evolve formic acid when heated with *p*-toluenesulfonic acid. Studies of the reaction indicate a complex decomposition pattern, including some loss of carbon-8. Syntheses of 9-D-ribopyranosylpurine and 6-methyl-D-ribofuranosylpurine are described.

In the course of studies of the properties of several derivatives of purine (I to IV), it was observed that the spectrum of 9-β-D-ribofuranosylpurine (IV, nebularine)[3] and of related glycosyl derivatives, underwent drastic and irreversible changes in dilute aqueous alkali at room temperature. It was also observed that 9-(2′,3′,4′-tri-*O*-acetyl-D-ribopyranosyl)-purine (IIIa) and other derivatives of purine yielded anomalous "acetyl" analyses. Such chemical behaviors have not previously been observed with any nucleosides of purines.



One nucleoside, namely, IV, which possesses both of these unusual properties occurs in the mushroom *Agaricus* (*Clitocybe*) *nebularis* Batsch.[4a,b,5] It is inhibitory toward *Mycobacteria*,[4a,b] is highly toxic to mammals[3,6,a,b] and exhibits selective toxicity toward cells of mouse sarcoma 180 in culture.[7] Purine I, IV and other purine derivatives, 6-methylpurine (IIa) and 6-chloropurine (IIb), have some selective inhibitory effects on the growth of experimental tumors.[8]

Investigations of these unusual chemical behaviors, including attempts to elucidate the structural factors responsible and of possible correlations with the pharmacodynamic properties of certain of these compounds are in progress.[9] Consideration of these newly recognized chemical behaviors was necessary in studies of the metabolic fates of IV[10a] and I[10b] as well as in the work described in the following three papers; these properties must be considered when investigating new purine derivatives from natural sources.

Results and Discussion

Acid Instability.—The analysis for the formation of volatile acids involved heating the compound in question with a 25% aqueous solution of *p*-toluenesulfonic acid at 100° for 4 hr., steam distillation

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, Public Health Service, Grant No. C-471, and from the Atomic Energy Commission, Contract No. AT(30-1)-910.

(2) Post-doctoral Research Fellow of the National Cancer Institute, 1953–1955.

(3) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

(4) (a) N. Löfgren and B. Lüning, *Acta Chem. Scand.*, **7**, 225 (1953); (b) N. Löfgren, B. Lüning and H. Hedström, *ibid.*, **8**, 670 (1954).

(5) E. Fischer, "Untersuchungen in der Purin Gruppe," Springer, Berlin, 1907, p. 68, suggested that purine (I) would probably be found in nature.

(6) (a) F. S. Philips and D. A. Clarke, personal communication; (b) A. P. Truant and H. E. D'Amato, *Federation Proc.*, **14**, 391 (1955).

(7) J. J. Biesele, M. C. Slautterback and M. Margolis, *Cancer*, **8**, 87 (1955).

(8) (a) D. A. Clarke, F. S. Philips, S. S. Sternberg and C. C. Stock, *Ann. N. Y. Acad. Sci.*, **60**, 235 (1954); (b) F. S. Philips, S. S. Sternberg, L. Hamilton and D. A. Clarke, *ibid.*, **60**, 283 (1954); (c) K. Sugiura, Special Lectures of the 14th Japan Medical Congress, Kyoto, Japan, 697–714 (1955).

(9) G. B. Brown, M. P. Gordon, A. Hampton and D. I. Magrath, "The Chemistry and Biology of Purines," CIBA Symposia, Churchill, London, 1957, p. 192.

(10) (a) M. P. Gordon and G. B. Brown, *J. Biol. Chem.*, **220**, 927 (1956); (b) M. P. Gordon, unpublished observation.

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and titration of the volatile acid produced.[11] The volatile acid obtained from I (*ca.* 0.9 mole/mole I) was identified as formic acid through conversion to the S-benzylisothiouronium salt,[12] by its conversion to benzimidazole and benzimidazole picrate[13] and by its reconversion to I.

When purine-8-C^{14} was similarly treated, the formate carbon of the S-benzylisothiouronium derivative had approximately one-third of the specific activity of the 8-carbon of the parent I. The residue after the completion of the steam distillation was quite dark, evolved ammonia with alkali and gave a test for reducing agents with alkaline phosphomolybdate.[14] When purine-8-C^{14} was treated for 12 hr., 1.8 moles of formic acid was evolved per mole of I, and this formic acid was reconverted to I before determination of the radioactivity. It was again found to have about one-third of the specific activity of the 8-carbon of the starting material.

The residue from the 12 hr. treatment contained 1.9 moles of ammonia per mole of I used. The ninhydrin positive[15] component found in the residue had the same paper chromatographic behavior as glycine in three different chromatographic systems. The presence of a small amount of unchanged I was also detected.

The evolution of formic acid, ammonia and the formation of glycine indicate extensive degradation. The threefold dilution of the radioactivity of carbon atom 8 may well be due to the more rapid liberation of formic acid from other parts of the molecule (*i.e.*, to the initial formation of imidazole derivatives, see below), since a maximum of two moles of acid was evolved on prolonged heating. The positive reactions with the Bratton–Marshall reagent,[16] diazotized sulfanilic acid[17] and alkaline phosphomolybdate,[14] the variable ratio of ammonia produced to formic acid evolved and the marked darkening of the reaction mixture all indicate a complex decomposition pattern. The three color tests were all positive with 4,5-diaminopyrimidine; however, 4-amino-5-imidazolealdehyde, which might result if carbon 2 was lost, would also be expected to react with these color reagents.

It is known that the purine ring system can be cleaved by acids under sufficiently rigorous conditions to yield carbon dioxide, ammonia, carbon monoxide and/or formic acid and glycine. (For a review of the older literature see ref. 18 and 19.) Less drastic hydrolyses of adenine and guanine result in the formation of 4-amino-5-imidazolecarboxamidine[18] and 4-guanidoimidazole,[20] respectively. Although 9-methylpurine and 2-hydroxypurine are decomposed by hot sulfuric acid,[21] I has been reported to be stable toward the action of hot dilute acids[22] or to undergo slight decomposition in more concentrated acid.[21,23] In our hands I appears to be one of the least stable purines toward the action of hot *p*-toluenesulfonic acid or sulfuric acid. In the pteridine series the parent compound was also found to be exceptionally unstable toward acid.[24]

A series of various purines and purine nucleosides were also analyzed for the formation of volatile acid. 9-Methylpurine and nucleosides of I were the only additional compounds that evolved appreciable amounts of volatile acid (Table I).

TABLE I

MOLES VOLATILE ACID EVOLVED PER MOLE OF COMPOUND[a]

Purine[b]	0.87,[f] 1.8,[g] 2.0[h]
9-Methylpurine[b]	0.63
6-Methylpurine[c]	Trace
6-Dimethylaminopurine[d]	0.0
6-Chloropurine[e]	.0
Adenine	.0
Guanine	.0
Xanthine	Trace
9-β-D-Ribofuranosylpurine	0.92
9-D-Ribopyranosylpurine	.84
9-D-(2′,3′,4′-Tri-*O*-acetylribopyranosyl)-purine	4.8
Adenosine	0.0
Guanosine	.0
6-Dimethylamino-9-β-D-ribofuranosyl-purine[d]	.0
6-Chloro-9-β-D-ribofuranosylpurine[e]	.0
6-Dimethylamino-9-β-D-(3′-amino-3′-deoxyribofuranosyl)-purine[d]	.0
6-Methyl-D-ribofuranosylpurine	Trace

[a] Analyses by J. F. Alicino, Metuchen, N. J.; H. B. Clark, Urbana, Ill.; and by this Laboratory, duplicates in most cases. [b] Obtained from A. Bendich of these Laboratories or (in the case of I) also purchased from Francis Earle Laboratories, Peekskill, N. Y. [c] Obtained from G. B. Elion and G. H. Hitchings, The Wellcome Research Laboratories, Tuckahoe 7, N. Y. [d] Obtained from B. R. Baker, Southern Research Institute, Birmingham, Ala. [e] In these two cases, silver sulfate was added to the distillation flask to trap any hydrogen chloride generated. No chloride ion was detected in the distillate. [f] Heated for 4 hr. 1.35 moles of NH_3 evolved per mole I. [g] Heated for 12 hr. 1.93 moles of NH_3 evolved per mole I. [h] Heated for 24 hr. 2.25 moles of NH_3 evolved per mole I.

I and IV do behave similarly to other members of the purine series in that the purine base is stable in 70% perchloric acid under conditions which are used to hydrolyze nucleic acids.[25]

Alkaline Instability.—A study of the spectral changes induced by the action of dilute alkali at room temperature on IV (see Fig. 1) showed that a compound (or compounds) were formed that exhibited two maxima in alkali and one in acid. Eventually the solution showed only non-specific end absorption. The similarity of the intermediate

(11) F. Pregl, "Quantitative Organic Microanalysis," revised by J. Grant, The Blakiston Co., Philadelphia, Pa., 1945, p. 161.
(12) J. J. Donleavy, THIS JOURNAL, **58**, 1004 (1936).
(13) E. L. Brown and N. Campbell, *J. Chem. Soc.*, 1699 (1937).
(14) A. Bendich and G. C. Clements, *Biochem. et Biophys. Acta*, **12**, 462 (1953).
(15) R. Consden, A. H. Gordon and A. J. P. Martin, *Biochem. J.*, **38**, 224 (1944).
(16) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).
(17) B. N. Ames and H. J. Mitchell, THIS JOURNAL, **74**, 252 (1952).
(18) L. F. Cavalieri, J. F. Tinker and G. B. Brown, *ibid.*, **71**, 3973 (1949).
(19) Reference 5, p. 69.
(20) G. Hunter, *Biochem. J.*, **30**, 183 (1936).
(21) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).
(22) A. Bendich, P. J. Russell, Jr., and J. J. Fox, THIS JOURNAL, **76**, 6073 (1954).
(23) E. Fischer, *Ber.*, **31**, 2564 (1898).
(24) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 4219 (1952).
(25) E. Chargaff, C. Levine and H. J. Vogel, *J. Biol. Chem.*, **189**, 597 (1951).

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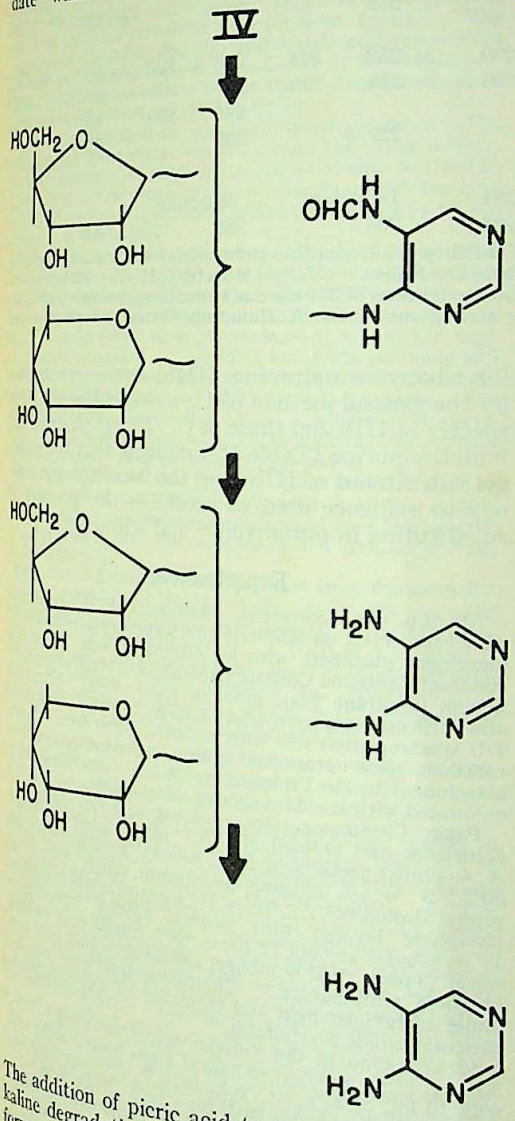
spectra with those of 4,5-diaminopyrimidine and 4-methylamino-5-aminopyrimidine strongly suggested that cleavage of the imidazole ring had occurred with the resulting formation of a derivative of 4,5-diaminopyrimidine. The solution was strongly reducing toward alkaline phosphomolybdate[14] which is also true for 4,5-diaminopyrimidine.



The addition of picric acid to a solution of the alkaline degradation products of IV resulted in the formation of 4,5-diaminopyrimidine picrate. Paper chromatography of the original reaction mixture indicated the presence of three components, each of which had spectra very similar to those of 4,5-diaminopyrimidine in acid and alkali. The fastest moving component, which was present in trace amounts, migrated with the R_f of 4,5-diaminopyrimidine. The two slower components gave positive tests for *cis*-glycol groups,[26] and these materials, when eluted from paper, gave strongly positive orcinol reactions.[27] The relatively large yield of the picrate of 4,5-diaminopyrimidine and the small amount of the free base in the reaction mixture indicate that some of the ribose-containing diamino compounds were cleaved by the aqueous picric acid.

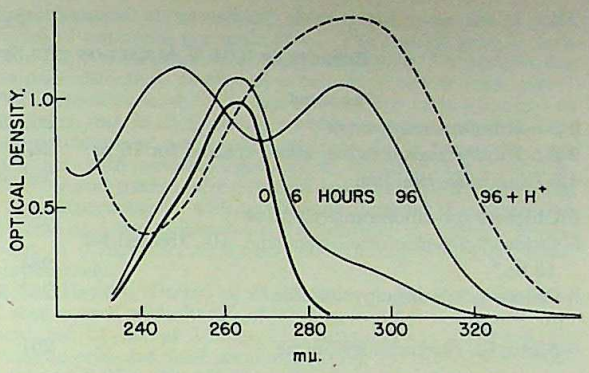


Fig. 1.—Spectral changes, with time, of 9-β-D-ribofuranosylpurine in 0.04 *N* sodium hydroxide.

The reaction which the nucleoside undergoes in alkaline solution may be related to the Bamberger reaction,[28] or it may be viewed as a reversal of the Traube purine synthesis.[29]

The reaction is depicted as in Scheme I.

Little evidence was obtained for intermediate formyl compounds, but they are logically expected.[30] The two ribosyl-4,5-diaminopyrimidines are depicted as furanose and pyranose forms, but the possibility of α- and β-isomers cannot be excluded.[32] Further decomposition of such products could lead to the formation of 4,5-diaminopyrimidine and its eventual decomposition products. The possibility that the two postulated ribosyl compounds could actually be Amadori-type rearrangement products was excluded by the following considerations: (a) the ready liberation of 4,5-diaminopyrimidine by picric acid, (b) the Amadori rearrangement is acid catalyzed,[33] whereas the reaction in question takes place in alkaline solution, (c) the intensities of the orcinol reactions of the glycosyl decomposition products of IV indicated the presence of *ca.* one mole of pentose per mole of 4,5-diaminopyrimidine. Products resulting from an Amadori rearrangement would be expected[34] to give very low values in a color test of this type, which depends upon a dehydration to a furfural derivative.

The ribofuranosyl derivatives of the IIa and IIb, as well as pyranosyl I (IIIb), were unstable in dilute aqueous alkali at room temperature. The

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TABLE II

EFFECTS OF 0.04 *N* ALKALI ON THE SPECTRA OF CERTAIN PURINE NUCLEOSIDES

Compound	Alkali[a] Max., mμ		Alkali[a] Min., mμ		Acid[b] Max., mμ		Acid[b] Min., mμ	
9-β-D-Ribofuranosylpurine[c,d]	262.5		230		262.5		230	
9-β-D-Ribofuranosylpurine, alkali treated for 76 hr.	244	290	225	269	289		242	
4,5-Diaminopyrimidine	245.5	288	226.5	266.5	285		237.5	
6-Chloro-9-β-D-ribofuranosylpurine	264		232		264		*ca.* 227	
6-Chloro-9-β-D-ribofuranosylpurine, alk. treated for 16 hr.[d]	254	290	*ca.* 232	274	250.5	292	*ca.* 230	*ca.* 275
6-Chloro-4,5-diaminopyrimidine	253.5	290.5	230	270	270	306	237.5	282
					255	292	226	270[e]
6-Methyl-D-ribofuranosylpurine	261		227.5		265		235	
6-Methyl-D-ribofuranosylpurine, alkali treated for 150 hr.[d,f]	245	284	Indefinite		Indefinite			
4,5-Diamino-6-methylpyrimidine	248	286	264		288		238	

[a] 0.04 *N* sodium hydroxide. [b] 0.1 *N* hydrochloric acid. [c] 9-D-Ribopyranosylpurine gave similar spectral changes upon treatment with alkali. [d] The parent purine was stable under these conditions. [e] Values in water (*p*H 5) which agree more closely with those of the ribose derivative in acid. [f] There is also a maximum of 261 mμ due to unchanged starting material. A further study of the alkali lability of this compound is being carried out by Dr. A. Hampton. Some formyl compound has been detected among the reaction products.

absorption spectra of the decomposition products again indicated that the imidazole ring had been cleaved (Table II). A possible mechanism of this cleavage is considered in an accompanying paper.[31]

Examples of the instability of the 9-methylpurine[21] and of methylated oxypurines[35] in hot alkali have been reported. The formation of the compound $C_6H_7N_4Cl$ (which could be 4-amino-2-chloro-5-methylaminopyrimidine), by the action of hot potassium hydroxide on 2-chloro-7-methylpurine, could be explained by this same type of reaction.[36] Other known instances of the rupture of the purine ring system such as the cleavage of the imidazole ring of 2-methylmercaptopurine by mono- or dimethylamine[21] and the decomposition of 6-amino-2-methylmercaptopurine by alkylamines[37] are possibly due to similar mechanisms. The alkaline disruption of the pyrimidine ring of 3,5′-cyclo-6-dimethylamino-9-(3′-amino-3′-deoxy-β-D-ribofuranosyl)-purine-2′-3′-carbonate methanesulfonate[38] is not related. The stability[39] of most common naturally occurring purine nucleosides in dilute alkali at room temperature has been confirmed.[40]

TABLE III

ABSORPTION MAXIMA OF DERIVATIVES OF PURINE

	Max. in acid	Max. in water	Max. in base
Purine[a]	260	262.5	270
9-Methylpurine[a]	262.5	264	264
7-Methylpurine[a]	257.5	266.5	266.5
9-β-D-Ribofuranosylpurine[b]	262.5	262.5	262.5
9-D-Ribopyranosylpurine[c]	262.5	262.5	262.5

[a] Ref. 22. [b] Ref. 3. [c] See Experimental.

Syntheses.—Purine-8-C^{14} prepared from hypoxanthine-8-C^{14},[10] was diluted with non-radioactive I. The 6-methyl-D-ribofuranosylpurine and the 9-D-ribopyranosylpurine (IIIb) were synthesized by the general method of Davoll and Lowy.[41] The spectra of IIIb and those of IV, 7-methylpurine and 9-methylpurine (Table III) indicate that the glycosyl substituent of IIIb is on the 9-nitrogen, in analogy to evidence used to establish the position of substitution in puromycin[42] and adenosine.[43]

Experimental

All m.p.'s are corrected. Radioactivity determinations were carried out on infinitely thin samples plated on 10 cm.² aluminum planchets with an internal Geiger–Müller flow counter (Radiation Counter Laboratories, Mark 12, model 1, helium isobutane gas), probable error ±5%. Ultraviolet absorption spectra were determined with the Beckman model DU spectrophotometer with matched 1-cm. cells. Optical rotations were determined with a polarimeter, model D, attachment to the Beckman model DU spectrophotometer, calibrated with standard sucrose solutions.[44]

Paper Chromatography.—Solvent systems (descending, Schleicher and Schuell No. 597 paper) were (vol./vol.): A = glacial acetic acid 20%, *n*-butyl alcohol 50%, water 30%, B = 1% aqueous ammonium sulfate 33⅓%, isopropyl alcohol 66⅔%,[45] C = 5% aqueous monobasic sodium phosphate layered with isoamyl alcohol (ascending)[46]; D = *n*-butyl alcohol 77 parts, 88% formic acid 10 parts, water 13 parts,[47]; E = *n*-butyl alcohol saturated with water at room temperature.[48] Chromatograms were inspected under ultraviolet light and examined for the formation of mercuric sulfide precipitates.[49]

Identification of the Volatile Acid from Purine (I).—A 200-mg. (1.66 mmoles) sample of I was heated under reflux with 10 ml. of 25% (w./vol., *ca.* 1.3 *M*) *p*-toluenesulfonic acid in a boiling water-bath for 4 hr.[11] Then 6 ml. of *ca.* 0.8 *N* sodium hydroxide was added to partially neutralize the *p*-toluenesulfonic acid. The volatile acid was steam distilled, and 50-ml. fractions were titrated to the phenolphthalein end-point with sodium hydroxide until a constant titer was obtained. This large-scale procedure yielded 1.44 mmoles of volatile acid. The solutions of the sodium salt of

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the volatile acid were combined and concentrated *in vacuo* to 2.0 ml. One-half of the sodium formate was converted to S-benzylisothiouronium formate.[12] The m.p. was 149–149.5°, mixed with the known formate derivative 149–149.5°, mixed with reagent 122–142° (capillary). The remaining sodium formate was converted to benzimidazole,[13] m.p. 172–173°, picrate 230–232°, no depression on admixture with known samples.

Action of Concentrated Perchloric Acid on I and the Purine Moiety of IV.—A 9.0-mg. sample of I was heated with 1 ml. of 70% perchloric acid for 1 hr. at 100°. The solution was diluted to 500 ml. with water, and the spectra in acidic and basic solutions were found to be unchanged. The values at the maximum and at the isosbestic point, 275 mμ,[11] indicated recoveries of 97 to 98%.

A 7.0-mg. sample of IV was hydrolyzed as above. The carbonaceous precipitate, resulting from the sugar moiety, was finely ground and thoroughly extracted with hot water. Spectrophotometric assay at the maximum and at the isosbestic point indicated recoveries of the purine moiety of 100 to 103%, respectively.

Action of Sulfuric Acid.—Two hundred mg. (1.66 mmoles) of I was heated 4 hr. at 100° with 15.0 ml. of 1.3 *N* sulfuric acid. The solution became bright yellow in 10 minutes and later brownish. Steam distillation, as above, yielded a total of 1.04 mmoles (0.62 mole per mole of I) of volatile acid. The residue contained 1.3 moles of ammonia per mole of I and gave positive tests with alkaline phosphomolybdate, the Bratton–Marshall, and the Ehrlich reagents. The spectrum of the diluted residue, at *p*H 4, indicated the presence of *ca.* 50% of unchanged I. A shoulder at 280 mμ indicated the presence of decomposition products.

Recovery of Formic Acid from *p*-Toluenesulfonic Acid.—A mixture of 3.41 mmoles of formic acid in 15 ml. of 25% aqueous *p*-toluenesulfonic acid was treated as in the analysis for acetyl groups, with the recovery of 3.47 mmoles of volatile acid (101%).

Formation of Radioactive Formic Acid from Purine-8-C^{14}.

A. Heating Period of 4 Hours.—Purine-8-C^{14}, 321 mg. (2.68 mmoles, 28.0 c.p.m./μmole) was treated with *p*-toluenesulfonic acid as described above. A total of 0.87 mole of formic acid and 1.35 moles of ammonia was found per mole of I. The sodium formate obtained was converted to S-benzylisothiouronium formate, which was recrystallized from aqueous ethyl alcohol, m.p. 149–149.5°.

Anal. Calcd. for $C_9H_{12}N_2O_2S$ (212.3): C, 50.9; H, 5.70; N, 13.2; S, 15.1. Found: C, 51.2; H, 5.66; N, 13.6; S, 15.3; specific activity, 8.2 c.p.m./μmole.

B. Heating Period of 12 Hours.—A 250-mg. sample of purine-8-C^{14} (2.08 mmoles, 86 c.p.m./μmole) yielded 3.72 mmoles of volatile acid. The neutralized steam distillate was concentrated and brought to exactly 5.00 ml. A 1.25-ml. (0.93 mmole) aliquot was placed in a 25-ml. flask with 102 mg. (0.93 mmole) of 4,5-diaminopyrimidine and 0.20 ml. of 5 *N* hydrochloric acid. The solution was refluxed 1 hr. at 100° and evaporated to dryness under nitrogen. The yellowish residue was heated at 210° for 5 minutes in a nitrogen atmosphere. The residue was dissolved in 15 ml. of water and 0.2 ml. of 70% perchloric acid, and excess 10% silver nitrate was added. The mixed silver chloride and silver salt of I were collected by centrifugation and washed twice with 10 ml. of water. The salts were decomposed by two hot 10-ml. portions of 1 *N* hydrochloric acid. The acidic solution of I was evaporated to dryness *in vacuo*, redissolved in water, adjusted to *p*H 7 and evaporated in a sublimation apparatus. Compound I was sublimed at 0.01 mm. pressure at a bath temperature of 120°, giving 39 mg. (0.33 mmole, 35% yield) of material melting at 213–215°. The admixed with an authentic sample of I, 214–215°. The spectrum was identical with that of I except for slight end absorption. Samples of the material were purified by chromatography on Whatman No. 3 MM paper in solvent systems D and E, with good separation from trace amounts of both a slower moving yellow and a fluorescent blue impurity. The spectra of aqueous solutions of samples thus purified were identical with that published. Radioactivity measurements gave values of 29.2 and 29.6 c.p.m./μmole for materials purified in solvents D and E, respectively (an average of 34% of the specific activity of the starting material).

The dark brown residue from the steam distillation of the formic acid was neutralized with 10 *N* sodium hydroxide and determination of ammonia[50] showed the presence of 1.93 moles of ammonia per mole of I. The residue gave a dark blue color with alkaline phosphomolybdate,[14] a pink in the Bratton–Marshall test[16] and a brownish-yellow with diazotized sulfanilic acid.[17] In the above color tests solutions of *ca.* 1 mg./ml. in 25% aqueous *p*-toluenesulfonic acid of I reacted uniformly negatively, whereas all of the tests were positive with similar solutions of 4,5-diaminopyrimidine. Glycine and purine were detected in the residue by ascending chromatograms, in which reference samples of purine and glycine and the unknowns gave identical R_f values: in solvent A, 0.73, 0.37; in B, 0.71, 0.29; and in C, 0.67, 0.84, respectively.

C. Heating Period of 24 Hours.—A 151-mg. sample of I was heated with 60 ml. of 25% aqueous *p*-toluenesulfonic acid for 24 hr. at 100°. The mixture was analyzed for volatile acid and base as above giving 2.0 moles of volatile acid and 2.25 moles of ammonia per mole of I, respectively. It was noticed that with the large excess of *p*-toluenesulfonic acid the solution did not darken appreciably.

Spectral Studies of Alkaline Instability.—A solution of IV with an optical density of about 1 at 260 mμ was prepared in 0.04 *N* sodium hydroxide. The solution was kept tightly stoppered in the dark, and at appropriate intervals the spectrum was determined on aliquots against the appropriate blank (Fig. 1). After 96 hr. the spectrum of an aliquot was determined both in acid and alkaline solution. A similar procedure was used to determine the alkali instability of the compounds listed in Table II.

Isolation of 4,5-Diaminopyrimidine from the Degradation of IV.—A 500-mg. sample of IV was treated with 40 ml. of saturated barium hydroxide for 4 days. At this time the spectrum in alkali exhibited the two peaks characteristic of 4,5-diaminopyrimidine. The solution was neutralized with carbon dioxide, filtered, the precipitate washed and the filtrate and washings combined to give 60 ml. of a clear yellow solution. This solution gave a deep blue color when tested with alkaline phosphomolybdate. A 10-ml. portion (estimated to contain 0.33 mmole of free and combined 4,5-diaminopyrimidine) was treated with 10 ml. of saturated aqueous picric acid, and a yellow crystalline precipitate formed immediately. This was collected, recrystallized from 15 ml. of 1:1 ethyl alcohol:water to yield 51 mg. (0.15 mmole, 47%) of material, m.p. 264–266° dec.; admixture with an authentic sample[51] of 4,5-diaminopyrimidine picrate did not lower the melting point.

Anal. Calcd. for $C_{10}H_9O_7N_7$ (339.2): N, 28.9. Found: N, 28.8.

Paper Chromatographic Studies.—A 10.7-mg. sample of IV was dissolved in 1.0 ml. of saturated barium hydroxide. Aliquots withdrawn at 0, 24, 72, 96 and 120 hr. were chromatographed (ascending, solvent E) in parallel with control spots of starting material, R_f 0.32, and 4,5-diaminopyrimidine, R_f 0.40. Upon visual inspection under ultraviolet light, the riboside spot was dark while that of the diaminopyrimidine was a fluorescent blue. After 24 hr. some starting material remained; however, two additional fluorescent blue spots of R_f's 0.084 and 0.17, respectively, had appeared. After 72 hr., these latter two spots had increased in intensity, and a small amount of material at the position of 4,5-diaminopyrimidine was evident. All three of these components showed ultraviolet absorption spectra identical to that of 4,5-diaminopyrimidine. The parent nucleoside was no longer detectable. Chromatograms at 96 and 120 hr. were similar to that after 72 hr.

Chromatograms prepared from the 96-hr. reaction mixture were examined more closely with the results shown in Table IV. If it is assumed that the molar extinction coefficients of these three components are equal, it may be concluded that about 90% of the 4,5-diaminopyrimidine was combined with a pentose moiety.

No evidence was seen for any formylated derivatives on the above chromatograms. When 0.04 *N* sodium hydroxide was used and the solution tested after 4 hr., the trailing edges of the two pentose-containing spots had a dark appearance characteristic of 5-formamido-4-aminopyrimidine; however, the separation from other components was very poor.

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TABLE IV

PROPERTIES OF THE DEGRADATION PRODUCTS

Rf	*cis*-Glycol test[26]	Orcinol test[27]	Optical density at 288 mμ, *p*H 5.2[a]
0.084	+	+	0.78
.17	+	+	.75
.40	−	−	.16

[a] Determined on the material eluted from one lane with 4 ml. of water. Assuming an ϵ_{max} of 7250 for the products (ϵ_{max} at 289 = 7250 for the uncharged molecule of 4,5-diaminopyrimidine[52]), the two slow moving compounds each contained *ca.* one mole of ribose per mole of 4,5-diaminopyrimidine.

6-Methyl-D-ribofuranosylpurine.—A 402-mg. (3 mmoles) sample of IIa was converted to its chloromercuri derivative[41] giving 0.900 g. (2.44 mmoles, 81.5%) of product. The chloromercuri-6-methylpurine was condensed with 2,3,5-tri-*O*-acetyl-D-ribosyl chloride[53] prepared from 0.945 g. (3.0 mmoles) of tetraacetylribofuranose,[54] and the product was worked up as described below, except that the intermediate triacetyl compound was not obtained in crystalline form. Two recrystallizations of the crude 6-methyl-D-ribofuranosylpurine from ethyl alcohol gave 100 mg. (0.38 mmole, 12.5%) of product in the form of fine needles, m.p. 209–210°. In another preparation, from 2.6 g. of IIa, a yield of 21% was obtained.

Anal. Calcd. for $C_{11}H_{14}O_4N_4$ (266.3): C, 49.6; H, 5.29; N, 21.0. Found: C, 49.7; H, 5.50; N, 21.2.

The absorption maxima were: ϵ_{265} = 6340 at *p*H 1, ϵ_{261} = 7640 at *p*H 5.5 and 11 (when determined immediately).

9-D-Ribopyranosylpurine (IIIb).—A 1.00-g. (8.3 mmoles) sample of I was converted to its chloromercuri derivative (2.74 g., 7.8 mmoles),[3] and the dried, powdered chloromercuri salt was condensed with 2.8 g. (9.5 mmoles) of crystalline 2,3,4-tri-*O*-acetyl-D-ribosyl chloride[55] by refluxing in xylene for 4 hr. By previously described procedures,[41] 3.19 g. of crude crystalline 9-D-triacetylribopyranosylpurine (IIIa) was obtained, which, when recrystallized from ethyl alcohol, gave 1.1 g. of product (2.9 mmoles, 35%) melting at 169–171°.

Treatment of 570 mg. of IIIa (1.45 mmoles) for 16 hr. at 5° with methanolic ammonia gave 410 mg. of IIIb. After two recrystallizations from *n*-butyl alcohol, the product, 280 mg. (1.1 mmoles), melted at 250–252° (76% yield from the acetyl derivative, 13% over-all yield from I). A sample recrystallized from ethyl alcohol was analyzed.

Anal. Calcd. for $C_{10}H_{12}O_4N_4$ (252.2): C, 47.5; H, 4.80; N, 22.2. Found: C, 47.6; H, 4.73; N, 21.7; $[\alpha]^{20}_{546m\mu}$ −33.8°; $[\alpha]^{20}_{589m\mu}$ −28.7° (0.5% in water).

The absorption spectrum possessed a maximum at 262.5 mμ, the position of which did not change in acid or alkali (when determined immediately). The ϵ_{max} at *p*H 0.3 was 5.65 × 10³, at *p*H 7.7 was 6.91 × 10³ and at 12.3 was 7.06 × 10³. There were two isosbestic points: one at 231.5 mμ with ε 2.64 × 10³ and one at *ca.* 268 mμ with ε 4.67 × 10³. The apparent pK_a was found to be 1.80 ± 0.05 by the procedure outlined by Fox and Shugar.[56]

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[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING DIVISION OF CORNELL UNIVERSITY MEDICAL COLLEGE]

Synthesis of an Isopropylidene Derivative of an Alkali-labile Nucleoside: 2′,3′-O-Isopropylidene-9-β-D-ribofuranosylpurine[1]

BY ALEXANDER HAMPTON AND DAVID I. MAGRATH

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2′,3′-*O*-Isopropylidene-9-β-D-ribofuranosylpurine can be prepared in good yield by condensation of 9-β-D-ribofuranosylpurine with acetone in the presence of zinc chloride or in the presence of *p*-toluenesulfonic acid. The techniques should be useful for the preparation of isopropylidene derivatives of other alkali-labile purine nucleosides. With *p*-toluenesulfonic acid the conversion is rapid and quantitative at room temperature and the method may be applicable to nucleosides in general.

2′,3′-*O*-Isopropylidene-9-β-D-ribofuranosylpurine was desired for the synthesis of 9-β-D-ribofuranosylpurine-5′-phosphate,[2] and a number of procedures for its preparation have been examined.

The 2′,3′-*O*-isopropylidene derivatives of many nucleosides[3–6] have been prepared by condensations with acetone in the presence of zinc chloride. The resulting complex of the product with zinc chloride was in each case decomposed with warm barium hydroxide. 9-β-D-Ribofuranosylpurine[7] and its 2′,3′-*O*-isopropylidene derivative were found to be alkali-labile, and application of the usual work-up led to considerable losses. Milder conditions for breakdown of the zinc chloride complex were investigated. Ion-exchange chromatography of an aqueous solution of the reaction products using Dowex-50 resin (NH_4^+) effected the removal of the zinc ions without decomposition of the isopropylidene derivative, but a large excess of resin was required and 60% of the product was retained on the column. A more satisfactory procedure was treatment of the reaction mixture at 0° with aqueous sodium carbonate, whereupon the 2′,3′-*O*-isopro-

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pylidene compound could be isolated in 80% yield.

Weakly basic ribonucleosides, *e.g.*, uridine,[8] or ones that form acetone-soluble sulfates[9] have given 2′,3′-*O*-isopropylidene derivatives when treated with acetone in the presence of sulfuric acid and anhydrous copper sulfate, but 9-β-D-ribofuranosylpurine did not react under these conditions. It has been shown in the case of 2-methylmercapto-6-dimethylamino-9-β-D-xylofuranosylpurine that the yield of the 3′,5′-*O*-isopropylidene derivative can be improved by replacing the sulfuric acid with ethanesulfonic acid, thereby forming a more acetone-soluble salt.[10] In the present work, when *p*-toluenesulfonic acid was substituted for sulfuric acid, 50% of the 9-β-D-ribofuranosylpurine was converted to the isopropylidene derivative, with dissolution of some copper (presumably as copper *p*-toluenesulfonate) and concomitant production of sulfuric acid, and prolonging the reaction yielded no more isopropylidene compound. The effect of omitting copper sulfate from the mixture was accordingly examined. In the presence of a sufficient quantity (10 equivalents) of *p*-toluenesulfonic acid monohydrate, 9-β-D-ribofuranosylpurine formed a salt which was readily soluble in acetone, and in 30 minutes quantitative conversion to the isopropylidene derivative occurred.

Conversions to isopropylidene derivatives by the acetone–sulfuric acid–copper sulfate method are either slow[8] or incomplete[9,10] and the use of acetone and *p*-toluenesulfonic acid monohydrate (or anhydrous) may prove generally useful.

Experimental

Paper chromatograms were run by the ascending method using Schleicher and Schuell No. 597 paper and were inspected in ultraviolet light.

Zinc Chloride Method.—A solution of zinc chloride (43 g.) in acetone (450 cc., distilled from a slight excess of potassium permanganate, then dried over sodium sulfate) was filtered into a dry flask containing 9-β-D-ribofuranosylpurine (13.7 g., dried over phosphorus pentoxide for 3 hr., 110°, 0.4 mm.). The cloudy solution was refluxed for 30 hr.[11] with exclusion of moisture. About half the acetone was removed under vacuum and the pale yellow solution poured into a solution of anhydrous sodium carbonate (43 g., 30% excess) in water (450 cc.) containing ice (50 g.). The mixture was stirred for 10 minutes and the zinc carbonate collected, washed with water and then with acetone. A solution of barium chloride dihydrate (33 g., 50% excess) in water (100 cc.) was added to the combined filtrate and washings and the barium carbonate collected. The filtrate was evaporated to dryness *in vacuo* and the residue dried azeotropically with benzene, then triturated with hot benzene (2 × 100 cc.). The benzene extract was concentrated *in vacuo* to *ca.* 80 cc., treated with charcoal (0.5 g.) and evaporated to dryness *in vacuo*. A solution of the yellow gum (14.6 g.) in methanol (25 cc., concentrated to *ca.* 15 cc.) furnished white hygroscopic needles (dried over phosphorus pentoxide at 0.1 mm.; 12.8 g., 80% yield), m.p. 44–45° (uncor.); light absorption in water, maximum 262.5 mμ; R_f 0.80 and 0.87 for paper chromatography in 1-butanol–water and in 1-butanol–water–acetic acid (5:3:2), respectively.

Anal.[12] Calcd. for $C_{13}H_{16}N_4O_4$: C, 53.40; H, 5.52; N, 19.17. Found: C, 53.03; H, 5.75; N, 19.03.

***p*-Toluenesulfonic Acid Method.**—*p*-Toluenesulfonic acid monohydrate[13] (7.5 g., 10 equivalents; dried over NaOH) was added to a magnetically-stirred suspension of dry 9-β-D-ribofuranosylpurine (1.0 g.) in acetone (150 cc., dried with Drierite and distilled). The pale yellow solution was kept at 25° and protected from moisture. At intervals, portions were withdrawn, treated with a small excess of 0.5 *N* sodium bicarbonate and examined by paper chromatography, using ethanol (85%)–water(15%) as the solvent system. After 30 minutes, conversion of the ribosylpurine (R_f 0.53) to the isopropylidene derivative (R_f 0.79) was complete. The solution was then added to 0.5 *N* aqueous sodium bicarbonate (170 cc.) and the mixture evaporated to dryness *in vacuo*. The residue was extracted with benzene and the product purified as described above, giving white needles, m.p. 44–45°, of the isopropylidene derivative (1.05 g., 90%).

When a solution of the product in 0.2 *N* NaOH was allowed to stand at room temperature for 24 hr., the initial single-peak ultraviolet spectrum (262.5 mμ) was replaced by a spectrum showing two well-defined maxima at 249 and 288 mμ, respectively (ratio of ϵ_{249} to ϵ_{288} = 0.92). This is similar to the spectrum[2,14] of 4,5-diaminopyrimidine in alkaline solution and to the ratio of ϵ_{246} to ϵ_{289} of 0.93[14] for that pyrimidine.

Acknowledgment.—The authors wish to thank Dr. George Bosworth Brown for continued interest and encouragement and for helpful discussions.

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(8) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **106**, 113 (1934).

(9) F. W. Holly, C. H. Shunk, E. W. Peel, J. J. Cahill, J. B. Lavigne and K. Folkers, THIS JOURNAL, **74**, 4521 (1952), prepared 2′,3′-*O*-isopropylidene-1-β-D-ribofuranosyl-5,6-dimethylbenzimidazole by this method.

(10) B. R. Baker and R. E. Schaub, *ibid.*, **77**, 5900 (1955).

(11) With shorter periods of reaction conversion was incomplete.

(12) Analysis by J. F. Alicino, Metuchen, N. J.

(13) Substitution of anhydrous *p*-toluenesulfonic acid, obtained by drying the monohydrate at 64° (0.1 mm.) over P_2O_5 for 4 hr., gave a similar yield.

(14) S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

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[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING DIVISION OF CORNELL UNIVERSITY MEDICAL COLLEGE]

The Synthesis of 9-β-D-Ribofuranosylpurine-5′-phosphate and its Behavior Toward Aqueous Alkali[1]

BY DAVID I. MAGRATH[2] AND GEORGE BOSWORTH BROWN

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The synthesis of 9-β-D-ribofuranosylpurine-5′-phosphate is reported. Two substances formed by the action of dilute aqueous alkali on the nucleotide, and also isolated as by-products during its synthesis, have been tentatively identified as 5-amino and 5-formamido derivatives of 4-(5′-phosphoribofuranosylamino)-pyrimidine.

In studies of potential tumor-inhibiting agents, 9-β-D-ribofuranosylpurine (I) was synthesized in this Laboratory and shown[3,4] to be identical with nebularine, a toxic, naturally occurring material.[4-6] The metabolism[7] of this compound led to three derivatives of purine-C^{14} in the soluble nucleotide fraction from the liver. From their behavior on the ion-exchange resin, these were postulated to be the 5′-mono-, di- and triphosphates of the administered ribosylpurine. Since it was desirable to have an authentic specimen for comparison and for investigation of potential pharmacodynamic properties, the synthesis of 9-β-D-ribofuranosylpurine-5′-phosphate (II) was undertaken.

2′,3′-*O*-Isopropylidene-9-β-D-ribofuranosylpurine[8] was treated with dibenzylphosphorochloridate in pyridine solution to give 2′,3′-*O*-isopropylidene-9-β-D-ribofuranosylpurine-5′-dibenzylphosphate. Hydrogenation effected smooth removal of both benzyl groups, and the isopropylidene group could then be removed from the product by allowing the free acid to stand in aqueous solution.[9]

Examination of this solution by paper chromatography revealed the main product and two other phosphorus-containing, ultraviolet light-absorbing materials, as well as a small amount of free ribosylpurine. The contaminants were separated from the main product by chromatography over a column of powdered cellulose. The main product contained organically-bound phosphorus and a *cis*-glycol[10] system and, in several paper chromatographic systems, gave only one ultraviolet light-absorbing spot with R_f values of the order to be expected of a mononucleotide. Further purification over Dowex-50 resin furnished the free acid as a pale cream-colored solid. Its ultraviolet spectrum in acid, alkali and water was almost identical with that of 9-β-D-ribofuranosylpurine,[3] and analysis indicated it to be a monohydrate of the 5′-monophosphate. It was eluted as a single, sharp peak from a Dowex-2 (formate) ion-exchange column at a position on the elution diagram consistent with its being a mononucleotide.

9-β-D-Ribofuranosylpurine-5′-phosphate was not unstable in 0.1 *N* acid at room temperature but in alkali was decomposed readily to give a mixture of two substances similar to the by-products formed during its synthesis.[12] A mixture of the latter, recovered as a cream-colored powder from the cellulose column, yielded, upon acid hydrolysis, a number of products. The main ultraviolet light-absorbing component had R_f values and spectral characteristics the same as 4,5-diaminopyrimidine. Examination of chromatograms showed a pattern of phosphorus and aniline phthalate-positive (*i.e.*, reducing carbohydrate[13]) spots identical with that obtained with a similar hydrolysate of adenosine-5′-phosphate: namely, two aniline phthalate-positive spots, one faint and having R_f values similar to D-ribose, the other, present in considerable amount, containing phosphorus and having R_f values similar to D-ribose-5-phosphate. Inorganic phosphate was distinguished from the sugar phosphate on chromatograms run in acetone–water–acetic acid.[14]

The two by-products were separated on a small scale by chromatography on paper. Both contained organically bound phosphate and a *cis*-glycol system and migrated on paper chromatography and electrophoresis as typical mononucleotides. The chromatographically faster-moving by-product could be converted into the slower-moving component by further alkaline hydrolysis.

The slower-moving component appeared as a fluorescent blue spot under ultraviolet light, gave positive reactions in the alkaline phosphomolybdate test[15] and the Bratton–Marshall test[16] and had a spectrum in acid, alkali and water generally similar to that of 4,5-diaminopyrimidine (Fig. 1). Its pK_a, determined spectrophotometrically, was 5.7 (4,5-diaminopyrimidine, 6.03).[17] The chromatographically faster-moving by-product gave a negative reaction in both the above color tests. The

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(3) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

(4) N. Löfgren, B. Lüning and H. Hedström, *Acta Chem. Scand.*, **8**, 670 (1954).

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(8) A. Hampton and D. I. Magrath, THIS JOURNAL, **79**, 3250 (1957).

(9) Attempts to remove simultaneously the isopropylidene and one benzyl group by acid hydrolysis led to considerable hydrolysis of the glycosyl linkage.

(10) See footnote 26 of ref. 11.

(11) M. P. Gordon, V. S. Weliky and G. B. Brown, THIS JOURNAL, **79**, 3245 (1957).

(12) It was also found that extensive degradation occurred during an attempt to prepare the dimethyl ester by reaction with diazomethane.

(13) S. M. Partridge, *Nature*, **164**, 443 (1949).

(14) S. Burrows, F. S. M. Grylls and J. S. Harrison, *ibid.*, **170**, 800 (1952).

(15) A. Bendich and G. C. Clements, *Biochim. et Biophys. Acta*, **12**, 462 (1953).

(16) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).

(17) S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

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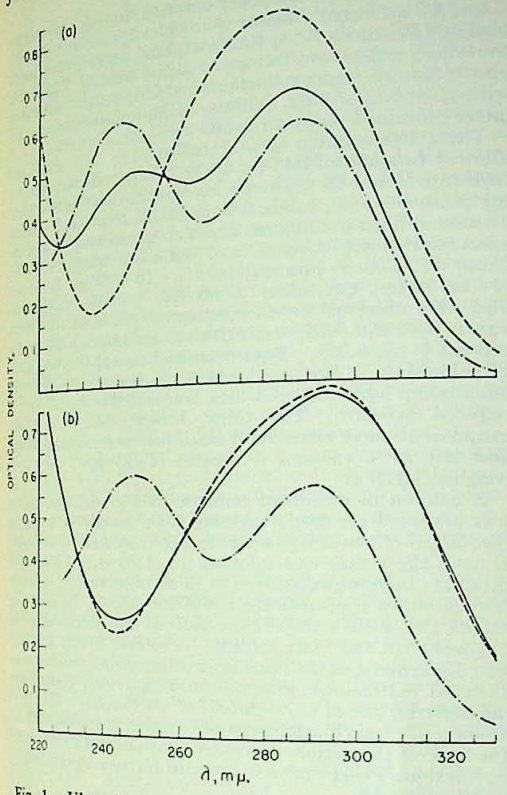
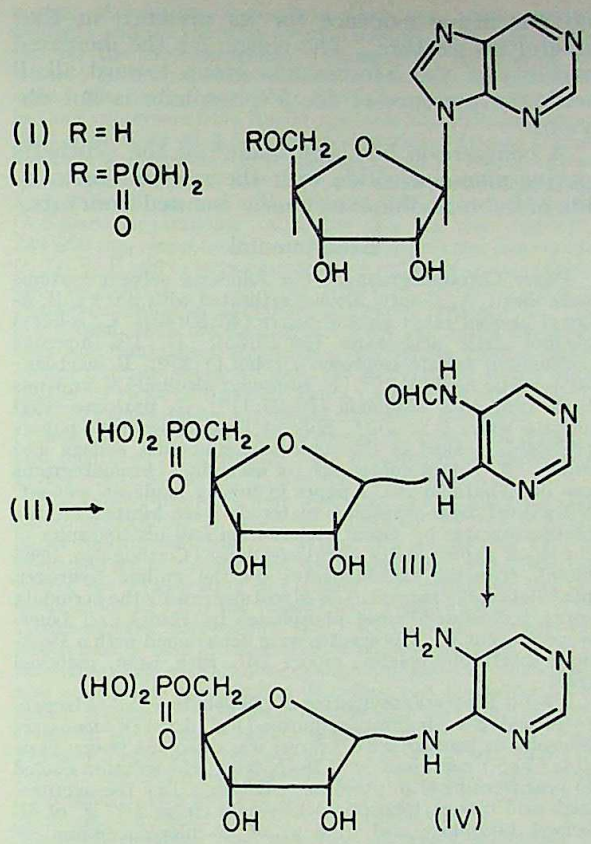


Fig. 1.—Ultraviolet spectra of: (a) 4,5-diaminopyrimidine; (b) chromatographically slower-moving by-product. In 0.1 *N* HCl (.....), 0.1 *N* NaOH (—·—·) and H_2O (——, *p*H 6.48 and 4.51, respectively).

similarity of its ultraviolet spectrum with that of 4-amino-5-formamidopyrimidine[18] is apparent (Fig. 2). The latter was found to possess a pK_a value of 11.40, which may be attributed to the 5-formamido group, and a value of 11.43 was found for the by-product.

It appears that the two substances produced by the alkaline hydrolysis of 9-β-D-ribofuranosylpurine-5′-phosphate, and also found as by-products during its synthesis, are 5′-phosphoribofuranosyl derivatives of 4,5-diaminopyrimidine (III and IV), one (III) still carrying the 8-carbon atom of the original molecule as a formyl group attached to the primary[19] amino group of IV. The presence of the 5′-phosphate group precludes furanose–pyranose isomerization, although mutarotation at the glycosyl linkage is still possible for either compound.

The initial step in the alkaline degradation of the purine nucleoside[11] and of this nucleotide probably involves a nucleophilic attack on the 8-carbon atom by hydroxyl ion; the subsequent ring opening is perhaps facilitated by conjugation of the resulting ionized formamido group with the pyrimidine ring.



The alkali degradation products of 9-β-D-ribofuranosylpurine are thought[11] to be ribofuranosyl and -pyranosyl derivatives of 4,5-diaminopyrimidine, which had resulted from the loss of the 8-carbon atom. The degradation was postulated as proceeding by way of the intermediate formation of the 5-formamido compound, although there was

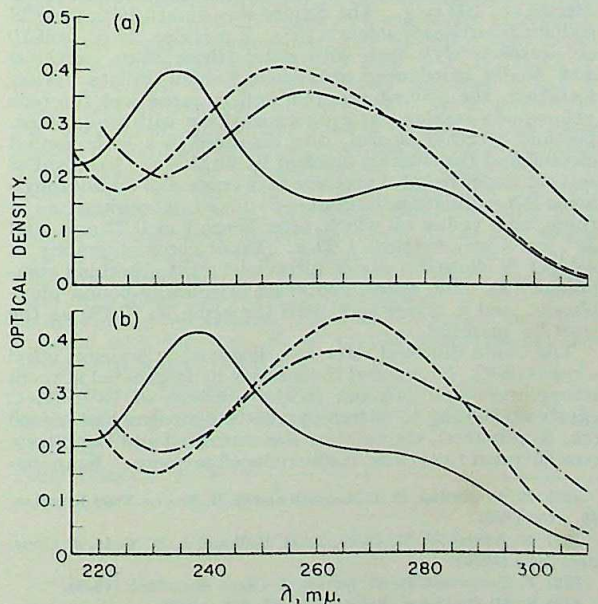


Fig. 2.—Ultraviolet spectra of: (a) 4-amino-5-formamidopyrimidine; (b) chromatographically faster-moving by-product, in 0.1 *N* HCl (.....), 0.1 *N* NaOH (—·—·) and H$_2$O (——, *p*H 5.88 and 5.23, respectively).

(18) Authentic samples of this and related compounds were kindly sent us by Professor Adrien Albert and Dr. D. J. Brown, Department of Medical Chemistry, the Australian National University. For proof of the position of the formyl group see D. J. Brown, *J. Applied Chem.*, **5**, 358 (1955).

(19) A formyl group attached to the ribosylamino group of IV should not give rise to the pK_a value of 11.4 observed for the faster-moving by-product.

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no conclusive evidence for its presence in that hydrolysis mixture. The reason for the increased stability of the 5-formamido group toward alkali with the presence of the 5′-phosphate is not obvious.

A comparison has been made[20] of the synthetic purine mononucleotide with the relevant metabolite of 9-β-D-ribofuranosylpurine isolated from rats.

Experimental

Paper Chromatography.—The following solvent systems were used: A, *n*-butyl alcohol saturated with water; B, *n*-butyl alcohol–ethyl alcohol–water (45:30:40); C, *n*-butyl alcohol–acetic acid–water (50:20:35); D, 1% aqueous ammonium sulfate–isopropyl alcohol (1:2)[21]; E, acetone–30% acetic acid (1:1)[14]; F, isopropyl alcohol–1% aqueous boric acid–10% ammonia (50:25:1)[22]; G, pyridine–ethyl acetate–water (1:2:2).[23] Solvent D was used with papers previously soaked in 1% aqueous ammonium sulfate and dried. R_f values quoted are for ascending chromatograms run on Whatman No. 1 paper in freshly made up solvent. Ultraviolet light-absorbing materials were located on the chromatograms by visual examination and photography of the dried papers under ultraviolet light (Corning No. 9863 filter), reducing carbohydrates by the aniline hydrogen phthalate spray reagent,[13] *cis*-glycol systems by the periodate spray technique[10,24] and phosphates by Hanes and Isherwood reagent.[25] The spectra were determined with a Beckman spectrophotometer, model DU, with 1-cm. matched cells.

9-β-D-Ribofuranosylpurine-5′-phosphate.—2,3-*O*-Isopropylidene-9-β-D-ribofuranosylpurine (1 g., dried *in vacuo* over phosphorus pentoxide for 3 days) was dissolved in dry pyridine (5 cc.) contained in a 25-cc. flask, the solution cooled to near freezing (f.p. pyridine −42°) in a Dry Ice–acetone-bath and dibenzylphosphorochloridate (from 2.17 g. of dibenzyl phosphite and 1.44 g. of N-chlorosuccinimide)[26] added and the residual reagent washed from the container with *ca.* 3 cc. of cold pyridine. The flask was stoppered and the reaction mixture kept in a semi-frozen condition for 5 hr., then left in the cooling bath overnight. After removal from the cooling bath, a solution of sodium acetate (4 g. anhydrous) in water (10 cc.) was added and the mixture shaken vigorously for 1.5 hr., then evaporated to dryness under reduced pressure (bath temperature <30°). The crystalline residue was thoroughly triturated with chloroform and the solid collected and washed with more solvent (total filtrate *ca.* 100 cc.). The filtrate was shaken with ice-cold sodium bicarbonate solution (5%; 2 portions, 25 cc. and 10 cc., respectively), then with water (three 25-cc. portions) and finally dried over anhydrous sodium sulfate. After filtration, the solvent was removed *in vacuo* and the pale yellow, oily residue was evaporated down with three 10-cc. portions of ethyl alcohol, then dissolved in a little methyl alcohol and the solution clarified by filtration. Removal of solvent under reduced pressure gave crude 2′,3′-*O*-isopropylidene-9-β-D-ribofuranosylpurine-5′-dibenzylphosphate as a thick, pale yellow oil which, after keeping at 0.22 mm. and 30° for 2 hr., weighed 1.69 g. Paper chromatography in solvent A showed a major ultraviolet light-absorbing component (R_f 0.89) which contained organically-bound phosphorus, and a minor spot with the same R_f (0.79) as the starting material.

The crude dibenzyl ester was dissolved in aqueous ethyl alcohol (60%, 50 cc.) and the solution hydrogenated at room temperature and pressure in the presence of 10% Pd-C catalyst (160 mg.). After uptake of hydrogen had ceased (*ca.* 50 minutes), the catalyst was separated and the filtrate concentrated to *ca.* 5 cc. under reduced pressure. Examination of this solution by paper chromatography (solvents A, B and C) indicated a major ultraviolet light-absorbing component (R_f values 0.14, 0.60 and 0.61, respectively) which contained phosphorus but no *cis*-glycol system. There were also traces of isopropylideneribosylpurine and a substance with R_f values of 0.02, 0.40 and 0.36, respectively, and the latter contained phosphorus and a *cis*-glycol system.

The above solution was diluted to 30 cc. with water and allowed to stand at 24° for 48 hr. Paper chromatography (solvents B and C) showed a major ultraviolet light-absorbing component (R_f values 0.40 and 0.36, respectively) which contained both phosphorus and a *cis*-glycol system, and the spectra of which in water, acid and alkali closely resembled those of 9-β-D-ribofuranosylpurine. In addition to a trace of the latter, two other ultraviolet light-absorbing spots also were observed on chromatograms run in solvent B (R_f values 0.34 and 0.26, respectively); they ran as one spot in solvent C (R_f 0.26). Both contained phosphorus and a *cis*-glycol system. The solution was adjusted to *ca.* *p*H 7 with ammonium hydroxide and then evaporated to dryness under reduced pressure. The thick, brown, oily residue was evaporated three times with small portions of ethyl alcohol and left in a vacuum desiccator (P_2O_5) for 2 days. It weighed 1.126 g.

A column of powdered cellulose (350 g., 6.5 cm. diam.) was prepared by firmly pressing down successive additions (*ca.* 50 g.) of the dry powder, and then washed with solvent C until the eluate was colorless (*ca.* 1300 cc.). The crude product above was dissolved in 10 cc. of solvent C, the solution carefully applied to the top of the column, the container rinsed out with a little more solvent and the column developed with the same solvent. The first 230 cc. of eluate was discarded and the remainder collected in fractions of *ca.* 18 cc. at 7–10 minute intervals until ultraviolet light-absorbing material ceased to be eluted (*ca.* fraction 60). The small amount of ribosylpurine present appeared in fractions 19–31, the bulk of the major ultraviolet light-absorbing component in fractions 34–41 and a mixture of the two by-products in fractions 49–58.

Fractions 34–41 were combined and evaporated to dryness *in vacuo;* small white crystals separated during the latter stages of the evaporation. The pale brown residual sirup was evaporated down once with methyl alcohol and then left in a vacuum desiccator (P_2O_5) overnight, when it became converted to a hygroscopic frothy solid, weight 0.61 g. Paper chromatograms of this material, run in solvent C, showed only one ultraviolet light-absorbing spot (R_f 0.36), giving tests for both phosphorus and a *cis*-glycol system. The molybdate spray reagent, however, revealed the presence of a small amount of inorganic phosphate[27] traveling just ahead of the ultraviolet light-absorbing compound. A further 61 mg. of almost chromatographically pure material was recovered from fractions 42–44.

The solid (0.60 g.) was dissolved in water (10 cc.), the *p*H adjusted to *ca.* 7 with dilute ammonium hydroxide and the solution applied to a column (1 cm. diam.) of Dowex-50 ion-exchange resin (H^+; 5 cc. wet resin).[28] The column was then washed with water until ultraviolet light-absorbing material ceased to be eluted and early fractions of eluate, containing inorganic phosphate[29] but no ultraviolet light-absorbing material, were discarded. Vacuum evaporation of the eluate (bath temperature <25°) gave a semi-solid residue which was redissolved in water (10 cc.) and the ice-cooled solution brought to *p*H 8–9 by the dropwise addition of 7% aqueous barium hydroxide (*ca.* 5 cc.), with any excess being removed quickly by passing in carbon dioxide. Only a very slight precipitate of barium phosphate formed. The solution was concentrated somewhat under reduced pressure, then clarified by filtration and the filtrate concentrated to 5–10 cc. This solution was applied to a second column of Dowex-50 resin (H^+; 5.5 cc. of wet resin), which was then washed with water and the eluate collected and evaporated as before. The gummy residue was evaporated

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(21) N. Anand, V. M. Clark, R. H. Hall and A. R. Todd, *J. Chem. Soc.*, 3665 (1952).

(22) F. Baron and D. M. Brown, *J. Chem. Soc.*, 2855 (1955).

(23) S. M. Partridge, *Biochem. J.*, **42**, 238 (1948).

(24) J. G. Buchanan, C. A. Dekker and A. G. Long, *J. Chem. Soc.*, 3162 (1950).

(25) C. S. Hanes and F. A. Isherwood, *Nature*, **164**, 1107 (1949).

(26) G. W. Kenner, A. R. Todd and F. J. Weymouth, *J. Chem. Soc.*, 3675 (1952).

(27) In an early experiment most of the inorganic phosphate was removed at this stage by precipitation as barium phosphate.

(28) The use of a larger quantity of resin should permit the complete removal of inorganic phosphate at this stage and thus make unnecessary the further steps of purification described.

(29) Reducing phosphorylated carbohydrate was also present, indicating that some hydrolysis of the glycosyl linkage had occurred on the resin. This could be minimized by jacketing the column with circulating ice-water.

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down once with a little methyl alcohol and twice with ethyl alcohol, giving 9-β-D-ribofuranosylpurine-5′-phosphate as a pale cream-colored solid, melting with decomposition at 149–150°. After drying in a vacuum desiccator (P_2O_5) for 3 days, it weighed 0.32 g. (26.5%, based on the isopropylidenepurineriboside used). *Anal.*[30] Calcd. for $C_{10}H_{13}O_7N_4P \cdot H_2O$: C, 34.30; H, 4.32; N, 16.00; P, 8.85. Found: C, 34.16; H, 4.57; N, 15.92; P, 8.75. Light absorption in water at *p*H 3.9, 0.1 *N* hydrochloric acid and 0.1 *N* sodium hydroxide: λ_{max} 263 mμ (ε 7350, 5900 and 7500, respectively); λ_{min} 223.5, 235.5 and 227.5 mμ, respectively. The substance was freely soluble in water and gave a single ultraviolet light-absorbing spot on paper chromatograms run in solvents A, B, C and D (R_f values, 0.02, 0.40, 0.36 and 0.47, respectively), which gave a positive reaction in the molybdate spray test for phosphorus and in the periodate spray test for *cis*-glycols. It was free of inorganic phosphate and was eluted from a column (11 × 1 cm.) of Dowex-2 (formate), using 0.1 *M* formic acid which was 0.02 *M* with respect to sodium formate as eluent, as a single, symmetrical peak.[31] Fractions of 11 cc. were collected every 18–20 minutes, the highest O.D. at 260 mμ occurring at fraction 71. When subjected to electrophoresis in sodium phosphate–citric acid buffer (*p*H 8.25), on an 18.8-cm. wide strip of Whatman No. 3 mm. paper, at 860 volts and 90 milliamp. for 45 minutes, it migrated 10 cm. toward the anode (adenosine-5′-phosphate, 9.3 cm.; ribosylpurine moved 1.4 cm. toward the cathode).

Action of Acid and Alkali.—Hydrochloric acid (0.1 *N*) for 48 hr. at 24° had no appreciable effect. Sodium hydroxide (0.1–0.2 *N*) for 24 hr. at 24° caused extensive decomposition to a mixture of two substances having the same chromatographic, electrophoretic and ultraviolet spectral characteristics and giving the same color reactions as the two by-products formed in the synthesis. To provide material for the spectral measurements and color tests, 2-mg. lots of the 5′-phosphate were dissolved in *ca.* 0.2 *N* sodium hydroxide (0.23 cc.), and the solution was allowed to stand at 24° for 30 hr. After neutralization with dilute hydrochloric acid, the solution was applied as a band to a 19 cm. wide strip of Whatman No. 1 paper (previously treated with 1% aqueous ammonium sulfate[21]), the chromatogram developed with solvent D and the various bands eluted with water. Determination of the O.D. at 263 mμ (OH^-) of the eluate containing the residual purine nucleotide indicated that *ca.* 69% had been decomposed.

Isolation and Nature of the By-products Formed in the Synthesis.—Fractions 49–58 from the cellulose column experiment were bulked and worked up as described for the ribosylpurine-5′-phosphate. A cream-colored powder (0.079 g.) was obtained, which on chromatography in solvents B and D gave two ultraviolet light-absorbing spots, one (R_f values, 0.34 and 0.29, respectively) dark and the other (R_f values, 0.26 and 0.15, respectively) fluorescent blue; like 4,5-diaminopyrimidine, the latter tended to become brown on the dried chromatogram. Both compounds contained phosphorus and a *cis*-glycol system, and both were eluted from a column of Dowex-50 resin (H^+) with water. On electrophoresis they migrated 9.6 cm. toward the anode, as one spot.

A solution of this material (1–2 mg.) in 0.5 *N* sulfuric acid (0.2 cc.) was heated in a stoppered tube at 100° for 2.5 hr. The dark solution was cooled, neutralized with ammonium hydroxide and examined for ultraviolet light-absorbing and reducing-carbohydrate components by paper chromatography. Adenosine-5′-phosphate (1–2 mg.) was treated similarly and the resulting solution used as a reference material on the chromatograms. Commercial samples of D-ribose-5-phosphate and D-ribose were also included as standards. The major ultraviolet light-absorbing spot present in the hydrolysate from the by-products had R_f values identical with those of 4,5-diaminopyrimidine. It was eluted from chromatograms run in solvents C and D, and its ultraviolet spectra in 0.1 *N* acid and 0.1 *N* alkali were determined: λ_{max} 283–284 mμ and 245–246, 288–289 mμ, respectively (4,5-diaminopyrimidine, λ_{max} 284–285 mμ and 246–247, 289–290 mμ, respectively). Chromatograms run in solvents C, D, E, F and G were examined for reducing carbohydrate and phosphorus by spraying with the aniline hydrogen phthalate and acid molybdate reagents, respectively. In every case, both the hydrolysate from the mixed by-products and that from adenosine-5′-phosphate gave a faint aniline phthalate-positive spot, the R_f values of which were similar to those of D-ribose, and a much more intense spot with R_f values similar to those of D-ribose-5-phosphate. Inorganic phosphate was also detected in both hydrolysates and separated from carbohydrate phosphates on chromatograms run in solvent E or, less efficiently, in solvent F.

The two by-products were separated in mg. quantities by chromatographing as bands on Whatman No. 1 or 3 MM. paper as described above. Where the presence of ammonium sulfate in the product was undesirable, most was removed by evaporating the eluate and extracting the organic material from the residue with methyl alcohol. The slower-moving component (*i.e.*, R_f 0.15 in solvent D) which had a blue fluorescence in ultraviolet light, gave a blue coloration with alkaline phosphomolybdate[15] and a positive reaction in the Bratton–Marshall test for diazotizable amino groups[16]; 4,5-diaminopyrimidine also reacted positively in both tests; light absorption in 0.1 *N* HCl, λ_{max} 294–294.5 mμ; in water (*p*H 4.51), 294–294.5 mμ; in 0.1 *N* NaOH, 249–249.5 and 294–294.5 mμ (Fig. 1b); pK_a value (determined spectrophotometrically), 5.70 ± 0.05 (4,5-diaminopyrimidine, 6.03[17]). The values for λ_{max} of 4,5-diaminopyrimidine, the spectrum of which is shown in Fig. 1a, are given by Mason.[17]

The faster-moving component (*i.e.*, R_f 0.29 in solvent D), which appeared as a dark spot on chromatograms viewed in ultraviolet light, gave a negative reaction in both the above tests; light absorption in 0.1 *N* HCl, λ_{max} 267.5 mμ; in water (*p*H 5.23), 238 mμ with a pronounced shoulder at about 275 mμ, in 0.1 *N* NaOH 264 mμ with a shoulder at about 290 mμ (Fig. 2b). The spectrum of 4-amino-5-formamidopyrimidine is shown in Fig. 2a: in 0.1 *N* HCl, λ_{max} 253 mμ; in water at *p*H 5.88, at both 234 mμ and 278.5 mμ; in 0.1 *N* NaOH, 258.5 mμ with a shoulder at 285 mμ; pK_a values, spectrophotometric, 3.82 ± 0.05, 11.40 ± 0.1 (4-amino-5-formamidopyrimidine, 4.42 ± 0.05, 11.43 ± 0.1). A sample of the material was dissolved in 0.2 *N* NaOH and the solution set aside at 24°. At 24 and 48 hr. the solution was chromatographed in solvent D; the spots applied to the origin were dried in a stream of carbon dioxide. Examination of the chromatograms in ultraviolet light showed that the material was being converted gradually (*ca.* one-third after 24 hr.) to a phosphorus-containing, blue-fluorescent substance having the same R_f as the slower-moving by-product. The substance was eluted, and its ultraviolet spectra in 0.1 *N* acid, 0.1 *N* alkali and water were determined and found to be identical to those of the slower-moving by-product. After 48 hr., a small amount of material with the same R_f as 4,5-diaminopyrimidine was also present in the hydrolysate.

Acknowledgment.—The authors wish to acknowledge the capable assistance of Mrs. Elizabeth Carroll.

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(30) C, H and N analyses by J. F. Alicino, Metuchen, N. J. Phosphorus was determined according to R. J. L. Allen, *Biochem. J.*, **34**, 858 (1940).

(31) Slow decomposition tended to occur on this resin also. Quantitative recovery was not achieved, and end-absorbing material trailed the major peak.

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[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING DIVISION OF CORNELL UNIVERSITY MEDICAL COLLEGE]

The Identification of Phosphorylated Metabolites of 9-β-D-Ribofuranosylpurine[1]

BY MILTON PAUL GORDON,[2] DAVID I. MAGRATH[3] AND GEORGE BOSWORTH BROWN

RECEIVED NOVEMBER 16, 1956

9-β-D-Ribofuranosylpurine-5′-phosphate and 5′-diphosphate have been obtained from the livers of rats previously injected with the corresponding nucleoside. The possible implications of this finding are discussed.

Previous studies of the metabolism of 9-β-D-ribofuranosylpurine-8-C^{14} (I-8-C^{14}) in the rat have shown that the purine moiety of this nucleoside is converted to polynucleotide adenine and guanine and is catabolized to urinary allantoin. The presence of three derivatives of purine in the perchloric acid extracts of rat liver was demonstrated.[4] The pattern of their elution from a column of Dowex-1 (formate)[5] suggested the possibility that these materials are, respectively, the 5′-mono-, di- and triphosphoric acid derivatives of 9-β-D-ribofuranosylpurine. A comparison has now been made of synthetic 9-β-D-ribofuranosylpurine-5′-phosphate (II)[6] and the major component of the first peak (the postulated monophosphate). The purine-containing material in the second peak (the postulated diphosphate) also has been partially characterized.

Results and Discussion

In these experiments it was desirable to obtain the largest possible amount of the metabolites without death of the animals from the toxicity of the 9-β-D-ribofuranosylpurine. Single intraperitoneal injections at the level of 100 mg./kg. were found to be suitable for these studies.[7] Material with an 8-C^{14} label was used to facilitate isolation procedures.

The cold perchloric acid soluble fraction from the livers of the injected animals was chromatographed by the use of a column of Dowex-1 (formate). Only 6% of the radioactivity placed on the column was removed by the water wash (in which purine and Compound I would appear). This compares favorably with the amount of radioactivity not retained by the resin (5%) when the animals were given much smaller injections of 9-β-D-ribofuranosylpurine-8-C^{14}.[4] Since previous experience had indicated that the purine-containing compounds undergo decomposition on anion exchange resins,[8] the present fractionations were done at 4°. Three main peaks of radioactivity were again found in the positions[4] where nucleoside-5′-mono-, di- and triphosphoric acids are normally eluted. The radioactive material in the first peak was shown to be identical with synthetic II by means of the following criteria: (a) migration in four paper chromatographic systems with concomitant positive tests for the *cis*-glycol[9] and the phosphate moieties,[10] (b) ultraviolet absorption spectra in acid, neutral and alkaline solutions, (c) electrophoretic mobility and (d) in two solvent systems the radioactivity, determined by radioautography, migrated with II. The relative specific activity of the II obtained was, within experimental error, identical with that of the administered nucleoside, and the probable absence of an endogenous pool of purine nucleoside or nucleotides is indicated.

The purine-containing compound in the second peak was admixed with other ultraviolet absorbing materials. Electrophoresis permitted the separation of a material which migrated at the rate characteristic of a diphosphate. This material gave a positive test for *cis*-glycol groups, gave spectra in acid, neutral and alkaline solutions similar to those of I, and its relative specific activity was approximately identical with that of the administered compound. These properties indicate that 9-β-D-ribofuranosylpurine-5′-diphosphate was the major radioactive component of the second peak.

High salt concentration made work with the third peak difficult; however, the above results strengthen the possibility that it was 9-β-D-ribofuranosylpurine-5′-triphosphate.

It has been postulated that the extreme toxicity of 9-β-D-ribofuranosylpurine is due to formation of analogs of normal nucleoside phosphates.[4] Thus, the 9-β-D-ribofuranosylpurine-5′-phosphate and the corresponding di- and triphosphates may interfere with some of the myriad metabolic reactions of the corresponding normal metabolites, adenosine-5′-phosphate (AMP), diphosphate (ADP) and triphosphate (ATP).[11]

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, Public Health Service, Grant No. C-471, from the Atomic Energy Commission, Contract No. AT(30-1)-910, and from the American Cancer Society upon recommendation of the Commitee on Growth, National Research Council, MET-27.

(2) Post-doctoral Research Fellow of the National Cancer Institute 1953–1955.

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(4) M. P. Gordon and G. B. Brown, *J. Biol. Chem.*, **220**, 927 (1956).

(5) R. B. Hurlbert, H. Schmitz, A. F. Brumm and V. R. Potter, *ibid.*, **209**, 23 (1954).

(6) D. I. Magrath and G. B. Brown, THIS JOURNAL, **79**, 3252 (1957).

(7) A. P. Truant and H. E. D'Amato, *Fed. Proc.*, **14**, 391 (1955), report a subcutaneous LD_{50} of 220 mg./kg. for this compound in rats. Death occurred 6 to 48 hr. after injection.

(8) In previous work with these materials, poor recovery of the total radioactivity was obtained,[4] and attempts to purify purine-containing components by rechromatography on the same resin resulted in complete loss of the material. In view of the decomposition of the synthetic II on Dowex-2 (formate),[6] we believe the previous poor recoveries of radioactivity were due to a decomposition of the topically labeled carbon atom 8.

(9) J. G. Buchanan, C. A. Dekker and A. G. Long, *J. Chem. Soc.*, 3162 (1950).

(10) C. S. Hanes and F. A. Isherwood, *Nature*, **164**, 1107 (1949).

(11) It is significant that the toxicity of I toward tissues in culture is most effectively reversed by AMP and ATP; J. J. Biesele, M. C. Slautterback and M. Margolis, *Cancer*, **8**, 87 (1955); II is as inhibitory as I, and the alkali degradation products of either are inhibitory only at 100-fold greater concentrations; I and II show equal toxicity in Swiss mice, and the alkali degradation products of I show no toxicity at 30-fold greater doses; Dr. D. C. Clarke, private communication. The fact that 5′-deoxy-9-β-D-ribofuranosylpurine also did not lead to toxicity (H. M. Kissman, B. R. Baker and M. J. Weiss, N. Y. Section, Meeting in Min., March, 1957) can be correlated with the impossibility of the formation of a 5′-phosphate from it.

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Experimental

Radioactivity determinations were carried out on infinitely thin samples plated on 10 cm.[2] aluminum planchets with an internal Geiger–Müller flow counter (Radiation Counter Laboratories, Mark 12, model 1, helium–isobutane gas), probable error ±5%, except when otherwise specified. Ultraviolet absorption spectra were determined with the Beckman model DU spectrophotometer with matched 1-cm. quartz cells.

Toxicity Studies.—Male Sherman strain rats (obtained from Rockland Farms, New City, N. Y.) weighing 200 to 300 g. were used in these studies. Animals given intraperitoneal injections of 9-β-D-ribofuranosylpurine (I) at levels of 200, 150 and 100 mg./kg. died after 3, 5 and 20 hours, respectively.

Formation of Phosphorylated Derivatives of 9-β-D-Ribofuranosylpurine.—Eleven male Sherman strain rats, each weighing *ca.* 140 g., were given single intraperitoneal injections of 9-β-D-ribofuranosylpurine-8-C^{14} (I-8-C^{14}) (prepared by diluting I-8-C^{14} [4] with non-radioactive I to give material with a specific activity of 2280 c.p.m./μmole) at the level of 100 mg./kg. After 4 hr. the livers were excised under ether anesthesia and immediately frozen on Dry Ice to give 70 g. of material. All of the subsequent manipulations were done at 4°. The livers were extracted with 3% and then with 2% perchloric acid. The combined extracts were neutralized with 5 *N* potassium hydroxide and clarified by filtration through a Celite pad. The clear filtrate (520 ml.) contained 8840 optical density units[12] and radioactivity totaling 156,000 c.p.m. The material was fractionated by gradient elution chromatography which made use of a 1-liter mixing chamber and a 21.5 × 2 cm. column of Dowex-1 ion exchange resin (formate). After the entire sample of liver perchloric acid-soluble material had been absorbed on the resin, the column was washed with water until the optical density at 260 mμ of the effluent had fallen to 0.06. The water wash contained 1300 optical density units and a total of 9000 c.p.m. The column was then successively eluted with 2.5 *N* formic acid (fractions 1–100, 2 ml. each; fractions 101–520, 4 ml. each), 4.0 *N* formic acid (fractions 521–640, 5 ml. each), 8.0 *N* formic acid (fractions 641–820, 10 ml. each), 8.0 *N* formic acid + 0.4 *M* ammonium formate (fractions 821–900, 10 ml. each) and finally 8.0 *N* formic acid + 1 *M* ammonium formate (fractions 901–960, 10 ml. each). Major peaks of radioactive material were located in tubes 471–500, 760–800 and 881–900. Radioactive fractions were combined and lyophilized in groups consisting of tubes 471–480, 481–489, 490–499, 761–800 and 881–900. Spectral studies indicated that the pooled fractions 471–480 contained the largest amount of a derivative of I uncontaminated by other materials.

The Identification of 9-β-D-Ribofuranosylpurine-5′-phosphate (II).—The R_f values (ascending) of synthetic II, of the major component of fractions 471–480, of 9-β-D-ribofuranosylpurine and of adenosine-5′-phosphate, are, respectively, as follows: (A) 0.50, 0.50, 0.74, 0.35 (1% aqueous ammonium sulfate 33⅓%, isopropyl alcohol 66⅔%)[13]; (B) 0.83, 0.84, 0.72, 0.67 (5% aqueous monobasic sodium phosphate layered with isoamyl alcohol[14]; (C) 0.44, 0.45, 0.58, 0.48 (isopropyl alcohol 75 ml., water 25 ml., trichloroacetic acid 5 g., 28% ammonia 0.3 ml.)[15]; (D) 0.39, 0.39, 0.65, 0.29 (glacial acetic acid 20%, *n*-butyl alcohol 50%, water 30%). The unknown material corresponding to II in each of the above solvent systems gave positive tests for *cis*-glycol groups[9] and for organically bound phosphate[10] (except in solvent B). The spectrum of the material eluted from papers developed using solvent A was identical with that of II, in 0.1 *N* hydrochloric acid, water at *p*H *ca.* 5 and 0.1 *N* sodium hydroxide. The specific activity, calculated with the ε for synthetic II, of the material eluted from papers developed using solvent D was 2100 c.p.m./μmole. Radioautographs prepared from papers developed in solvents B and D showed that the only detectable radioactivity was associated with the material with R_f values corresponding to II, although faint AMP spots were detectable by inspection with ultraviolet light.

Electrophoresis was carried out at *p*H 8.25 as described.[6] The principal component of fractions 471–480, 9-β-D-ribofuranosylpurine-5′-phosphate, and adenosine-5′-phosphate migrated 9 to 10 cm. toward the anode, while 9-β-D-ribofuranosylpurine migrated 1.4 cm. toward the cathode.

The only other component detected in fractions 471–480 during these studies was a small amount of adenosine-5′-phosphate.

The Partial Identification of 9-β-D-Ribofuranosylpurine-5′-diphosphate.—The *p*H of the material in pooled fractions 761–800 was adjusted to 5 with ammonium hydroxide and submitted to electrophoresis. The conditions were the same as those above except that the *p*H of the buffer was 5.25 and the duration of the run was 75 minutes. Seven compounds clearly separated. Guanosine-5′-diphosphate was used as a marker because previous experience[4] indicated that it would be the major contaminant of the metabolite. The guanosine-5′-diphosphate and the major rapidly moving component of the mixture migrated 15 to 16 cm. toward the anode. The latter material gave a positive test for *cis*-glycol groups; its spectrum in 0.1 *N* hydrochloric acid, water and 0.1 *N* sodium hydroxide was very similar to that of 9-β-D-ribofuranosylpurine. The specific activity of the material (assuming an ε at 263 mμ equal to that of the monophosphate) was 1900 ± 200 c.p.m.[16]

Acknowledgments.—The authors wish to thank Mrs. Orsalia Intrieri for competent assistance, and Miss Eva Simmel for the radioautographs.

(12) Optical density units equal the optical density at 260 mμ times the volume in ml.

(13) N. Anand, V. M. Clark, R. H. Hall and A. R. Todd, *J. Chem. Soc.*, 3665 (1952).

(14) C. E. Carter, THIS JOURNAL, **72**, 1466 (1950).

(15) J. P. Ebel, *Bull. soc. chim. France*, 1089 (1953).

(16) A correction factor for the salt present was determined by plating small amounts of 9-β-D-ribofuranosylpyrine-8-C^{14} in the presence of buffer. In view of this correction factor and the use of an uncertain ϵ_{max}, there is no significant difference between this specific activity and those of the II and the administered I.

NEW YORK 21, N. Y.

[CONTRIBUTION FROM THE CHEMICAL PHYSICS SECTION, DIVISION OF INDUSTRIAL CHEMISTRY, COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANIZATION]

Tosyl-α-amino Acids. I. Degradation of the Acid Chlorides and Azides by Aqueous Alkali

BY A. F. BEECHAM

RECEIVED OCTOBER 15, 1956

The decompositions resulting from the treatment of certain tosyl (*p*-toluenesulfonyl)-α-amino acid chlorides and azides with aqueous alkali are described and the mechanisms discussed.

In 1952, Wiley, *et al.*,[1a] observed that α-(benzenesulfonamido)-phenylacetyl chloride undergoes decomposition when treated with aqueous sodium hydroxide forming benzenesulfonamide, benzaldehyde and carbon monoxide. Wiley and Davis[1b] later

(1) (a) R. H. Wiley, H. L. Davis, D. E. Gensheimer, N. R. Smith, THIS JOURNAL, **74**, 936 (1952); (b) R. H. Wiley and R. P. Davis, *ibid.*, **76**, 3496 (1954).

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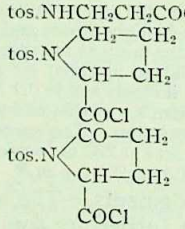
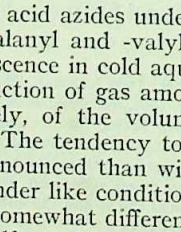
found that several α-(arylsulfonamido)-propionyl and -phenylacetyl chlorides were similarly degraded. The present author, unaware until recently of this work, already has reported briefly[2] that certain tosyl-α-amino acid chlorides undergo this reaction in the presence of cold aqueous alkali with the formation of *p*-toluenesulfonamide, a carbonyl compound arising from the α-carbon atom with its side chain or chains, carbon monoxide and the chloride ion.

$$CH_3C_6H_4SO_2NHCRR'COCl + OH^- \longrightarrow CH_3C_6H_4SO_2NH_2 + RR'CO + CO + Cl^-$$

Tosylglycyl chloride is only slightly decomposed, being largely hydrolyzed to the parent acid, but with the tosylated chlorides of those α-amino acids in which the α-carbon atom is alkyl substituted, degradation is the main reaction. The amount of carbon monoxide evolved from each of the compounds tested is shown in Table I.

TABLE I

Tosylated acid chloride	R	R′	CO, %
Glycyl	H	H	<2
Alanyl	CH_3	H	86
α-Amino-*n*-butyryl	CH_3CH_2	H	94
α-Amino-isobutyryl	CH_3	CH_3	94
Norleucyl	$CH_3[CH_2]_3$	H	97
Leucyl	$(CH_3)_2CHCH_2$	H	99
Valyl	$(CH_3)_2CH$	H	99
β-Alanyl	tos.NHCH$_2$CH$_2$COCl		0
Propyl			0
Pyroglutamyl			0

The tosyl-α-amino acid azides undergo a similar reaction. Tosyl-DL-alanyl and -valyl azides both dissolve with effervescence in cold aqueous sodium hydroxide, the production of gas amounting to 11 and 50%, respectively, of the volumes expected from the equation. The tendency to degradation is, therefore, less pronounced than with the corresponding chlorides under like conditions. Also the degradation takes a somewhat different path since, although *p*-toluenesulfonamide and the aldehyde are again produced, the evolved gas is nitrogen containing no trace of carbon monoxide. The residual solution contains the cyanate ion

$$CH_3C_6H_4SO_2NHCHRCON_2 + OH^- \longrightarrow CH_3C_6H_4SO_2NH_2 + RCHO + N_2 + NCO^-$$

Since both the chlorides and the azides appear to be unaffected by suspension in cold water alone and since the chlorides are hydrolyzed normally when such a suspension is heated, it may be assumed that the first step in the alkaline degradation of either class of derivative is formation of the sulfonamide anion. All the susceptible chlorides can ionize in this way, whereas tosyl-L-prolyl chloride, a tosylated secondary amine, cannot and is not degraded.

$$tos.NHCRR'COCl(N_3) + NaOH \longrightarrow tos.\bar{N}CRR'COCl(N_2) + Na^+ + H_2O$$

In the anion formed the tendency to undergo hydrolysis would be reduced by the increased electron density at the carbon atom of the modified carboxyl group resulting from the negative charge on the nitrogen. It would also seem that acquirement of the negative charge imparts a degree of instability to the structure. Apparently with tosylglycyl chloride this is not sufficient for breakdown to predominate over hydrolysis, but in those chlorides in which the α-carbon atom carries an alkyl substituent the disruption becomes the main reaction. Presumably this is due to an added increase in electron density at the carbonyl carbon atom arising from the alkyl group. As may be seen from Table I, in the chlorides tested the extent of degradation increases with increasing electron-releasing power of the alkyl side chain. The same holds for the two azides examined. Of course, steric hindrance to hydrolytic attack would also favor the disruptive reaction.

It was suggested earlier[1a] that, in the chloride degradation, breakdown of the sulfonamide anion might proceed by severance of the ion fragment, $COCl^-$, from which carbon monoxide and the chloride ion might be expected to arise immediately. Similarly, in the azide degradation, ejection of CON_3^- giving rise to nitrogen and the cyanate ion might be postulated. However, if this were so, there seems to be no reason why similar fragments should not be evolved from tosyl α-amino acid derivatives other than the chlorides and azides: esters, for instance, giving $COOR^-$ and amides $CONH_2^-$. But the amides and ethyl esters of tosyl-DL-alanine and -DL-valine were found to be hydrolyzed quantitatively, if sluggishly, by aqueous alkali with regeneration of the tosyl α-amino acids.

Alternatively then, it may be proposed that, in the chloride degradation, the sulfonamido anion breaks down by fission of the carbon–chlorine bond with the chlorine retaining the bonding electrons. The combined electron-releasing effects of the charged nitrogen and the alkyl side chain acting on the already highly polar carbon–chlorine link would be expected to favor this ionization. Such a process would be less likely in the less polar esters and amides. After severance of the chloride ion, internal neutralization of charge in the residual dipolar structure, with elimination of carbon monoxide, would be expected to follow.

$$tos.\bar{N}CRR'COCl \longrightarrow tos.\bar{N}CRR'—\overset{+}{C}O + Cl^-$$

$$\downarrow$$

$$tos.NH_2 + RR'CO \xleftarrow{H_2O} tos.N{=}CRR' + CO$$

Wiley[1b] suggests that the chloride degradation may involve displacement at the α-carbon atom of the un-ionized sulfonamido acid chloride in the following way

$$ArSO_2NHCHRCOCl + OH^- \longrightarrow ArSO_2NHCHR + COCl^-$$

$$|$$

$$OH$$

$$ArSO_2NH_2 + RCHO \longleftarrow$$

However, this proposal appears to be invalidated by the fact that tosyl-L-prolyl chloride is not de-

(2) A. F. Beecham, *Chemistry & Industry*, 1954.

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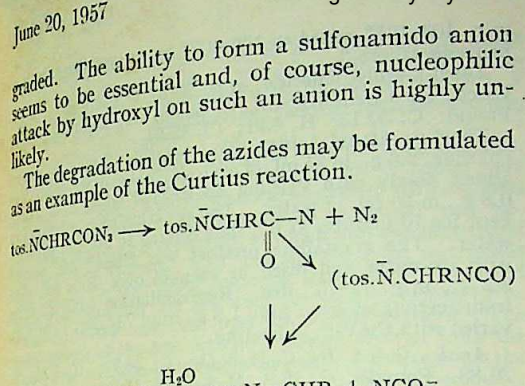
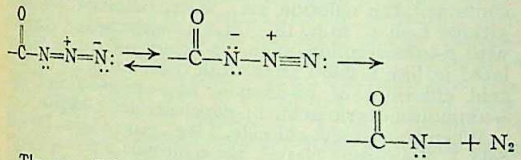
graded. The ability to form a sulfonamido anion seems to be essential and, of course, nucleophilic attack by hydroxyl on such an anion is highly unlikely.

The degradation of the azides may be formulated as an example of the Curtius reaction.

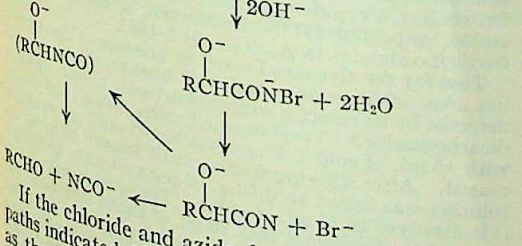


Here the same electron-releasing factors would be operating within the sulfonamido anion as in the chloride reaction and would be expected to promote the evolution of a molecule of nitrogen. Analogously in the Hofmann and Lossen rearrangements the rate-determining release of X^- from the intermediate $RCONX^-$ is favored by electron-releasing substituents at R.[3,4] The nitrogen evolution is akin to an ionization since it leaves an electron-deficient nitrogen atom attached to the organic residue.[3]



The remaining entity may then be visualized either as losing the cyanate ion directly or as rearranging to the organic isocyanate with subsequent loss of the cyanate ion. In view of the negative charge present, perhaps the former alternative is the more likely.

It is interesting to recall that α-hydroxy acid amides when subjected to degradation by alkaline hypohalite yield the next lower aldehyde and the cyanate ion.[5] It may be suggested that this mode of breakdown is favored by electronic factors similar to those operating in the alkaline degradation of the tosyl α-amino acid azides.



If the chloride and azide degradations follow the paths indicated, both give rise to a tosylated imine as the precursor of the carbonyl compound and sulfonamide finally obtained. It is assumed that this imine adds water and disrupts to give the observed products. An attempt was made to isolate the intermediate by dropwise addition of the calculated quantity of aqueous sodium hydroxide to a dioxane solution of tosyl-DL-valyl chloride, followed at once by extraction with ether. Under these conditions, with the chloride dissolved before the base is added, degradation is so rapid that the solution is never more than faintly and transiently alkaline. However, the solid isolated from the ether was *p*-toluenesulfonamide, indicating that the imine, if formed, suffered rapid hydrolysis even in the absence of alkali. The moisture sensitivity of similar structures is mentioned by Lichtenberger, Fleury and Barette.[6]

As shown in Table I, three of the chlorides tested gave no carbon monoxide. If the factors affecting the degradation are those suggested, tosyl-β-alanyl chloride would be expected to be inert, both because the α-carbon atom carries no side chain and because the acid chloride function is insulated from the seat of charge in the sulfonamido anion by the extra methylene group. In tosyl-L-prolyl chloride the nitrogen atom is tertiary so that salt formation is not possible. This also applies to tosyl-L-pyroglutamyl chloride which, however, unlike the prolyl compound, contains an alkali-labile lactam bond. For alkaline degradation to occur, through a sulfonamido anion intermediate, hydrolysis of the lactam system would need to be more rapid than hydrolysis of the acid chloride group. That Swan and du Vigneaud[7] were able to hydrolyze the compound to tosyl-L-pyroglutamic acid using aqueous magnesia indicates that the reverse is true and this is indirectly confirmed by the absence of degradation in the present work.

There are obvious ways in which the range of the degradations described here could be further explored. The tosylated acid chlorides and azides of the more complex α-amino acids might be tested. The reactions are probably general for those compounds capable of forming a sulfonamido anion and bearing an electron-releasing side chain at the α-carbon atom.[1a,b] The arylsulfonyl group might be varied with the expectation that degradation would still occur with derivatives of those amino acids whose tosyl compounds were disrupted.[1a,b] As well as the acid chlorides and azides, other anhydride-type structures might evince instability. Some reference to the effect of bases other than aqueous alkali is made in a subsequent article[8] which deals with the use of tosyl α-amino acid chlorides in the synthesis of peptides.

Experimental[8a]

Tosylamino Acids.—These compounds were prepared by the method used by Harington and Moggridge[9] for tosyl-L-glutamic acid. *p*-Toluenesulfonyl chloride, 0.1 mole, was

(3) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Clarendon Press, Oxford, 1949, p. 222.
(4) E. S. Wallis and J. F. Lane, "The Hofmann Reaction" in "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 270.
(5) R. A. Weerman, *Rec. trav. chim.*, **37**, 16 (1917).
(6) J. Lichtenberger, J.-P. Fleury and B. Barette, *Bull. soc. chim. France*, 669 (1955).
(7) J. M. Swan and V. du Vigneaud, THIS JOURNAL, **76**, 3110 (1954).
(8) A. F. Beecham, *ibid.*, **79**, 3262 1957.
(8a) Melting points (capillary) are not corrected. Microanalyses are by the C.S.I.R.O. Microanalytical Service at the University of Melbourne. Mass spectra were determined by Drs. J. D. Morrison and F. H. Dorman of this Section.
(9) C. R. Harington and R. C. G. Moggridge, *J. Chem. Soc.*, 706 (1940).

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added to a solution of the amino acid, 0.1 mole, in 100 ml. of water containing NaOH, 0.2 mole (0.3 mole for L-glutamic acid), and the suspension heated at 70–80° with shaking until a clear solution resulted (5–10 minutes). After cooling, acidification caused the product to precipitate except in the case of tosyl-L-glutamic acid which was isolated as described[9] and recrystallized from methyl ethyl ketone–carbon tetrachloride. The products from glycine[10] and DL-alanine[10] were immediately crystalline; those from DL-norleucine,[10] L-leucine,[10] β-alanine[11] and L-proline[12] were oils which crystallized on standing, tosyl-L-proline being hydrated. This last compound was obtained as the hemibenzenate[12] after azeotropic drying.

Tosyl-α-aminoisobutyric Acid.—Acidification gave a clear solution from which the product crystallized during 2 hr. at 0°, yielding 23%, softening 145°, m.p. 148.5–149.5° raised to 149–150° by recrystallization from water (lit.[13] m.p. 147°).

Anal. Calcd. for $C_{11}H_{15}NO_4S$: C, 51.34; H, 5.88; N, 5.44; O, 24.87; S, 12.46. Found: C, 51.71; H, 5.97; N, 5.13; O, 24.4; S, 12.88.

Further crystalline material obtained by concentration of the mother liquor from this preparation consisted largely of a second acidic substance, melting 205–218°, equivalent weight ≃400. This was not further characterized, but may have been the crude ditosyl compound.

Tosyl-DL-α-amino-*n*-butyric Acid.—The compound crystallized rapidly in 62% yield, m.p. 151–152°, after softening at 145°. A sample recrystallized twice from water had m.p. 152–153°.

Anal. Calcd. for $C_{11}H_{15}NO_4S$: C, 51.34; H, 5.88; N, 5.44; O, 24.87; S, 12.46. Found: C, 51.81; H, 5.88; N, 5.16; O, 24.59; S, 12.49.

Tosyl-DL-valine.—The product crystallized rapidly in 71% yield, m.p. 165–166° raised to 166–167° by recrystallization from acetone–water.

Anal. Calcd. for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16; O, 23.59; S, 11.82. Found: C, 53.31; H, 6.18; N, 5.09; O, 23.9; S, 12.26.

Tosylamino Acid Chlorides.—The tosylamino acid, 0.01 mole, and PCl_5, 0.015 mole (0.025 mole for tosyl-L-glutamic acid), were suspended in 20–30 ml. of anhydrous ether (200 ml. for the isobutyryl derivative) and shaken until all the organic material had dissolved, then for a further 30 minutes. Excess PCl_5 was removed by filtration, 100 ml. of anhydrous petroleum ether, b.p. 80–100°, added and the solution set aside at 0° for several hours. The crystalline acid chlorides were then filtered off, washed with petroleum ether and dried in vacuum over solid caustic soda and paraffin wax. The following compounds were prepared in this way.

Tosylglycyl chloride, m.p. 82–84° (lit.[14] m.p. 82–83°).

Tosyl-DL-alanyl chloride, m.p. 93–94°. *Anal.* Calcd. for $C_{10}H_{12}NO_3SCl$: C, 45.89; H, 4.62; Cl, 13.55. Found: C, 46.16; H, 4.69; Cl, 13.37.

Tosyl-DL-α-amino-*n*-butyryl chloride, m.p. 56–57°. *Anal.* Calcd. for $C_{11}H_{14}NO_3SCl$: C, 47.91; H, 5.12; Cl, 12.86. Found: C, 48.21; H, 5.06; Cl, 12.86.

Tosyl-α-amino-isobutyryl chloride, m.p. 115–116°. *Anal.* Calcd. for $C_{11}H_{14}NO_3SCl$: C, 47.91; H, 5.12; Cl, 12.86. Found: C, 47.58; H, 5.09; Cl, 12.76.

Tosyl-DL-valyl chloride, m.p. 76–78°. *Anal.* Calcd. for $C_{12}H_{16}NO_3SCl$: C, 49.74; H, 5.57; Cl, 12.24. Found: C, 49.66; H, 5.59; Cl, 12.13.

Tosyl-DL-norleucyl chloride, m.p. 70–72°. *Anal.* Calcd. for $C_{13}H_{18}NO_3SCl$: C, 51.39; H, 5.97; Cl, 11.67. Found: C, 51.29; H, 6.03; Cl, 11.45.

Tosyl-L-leucyl chloride, m.p. 83–85°. *Anal.* Calcd. for $C_{13}H_{18}NO_3SCl$: C, 51.39; H, 5.97; Cl, 11.67. Found: C, 51.47; H, 6.03; Cl, 11.66.

Tosyl-β-alanyl chloride, m.p. 82–84°. *Anal.* Calcd. for $C_{10}H_{12}NO_3SCl$: C, 45.89; H, 4.62; Cl, 13.55. Found: C, 46.17; H, 4.72; Cl, 13.58.

Tosyl-L-pyroglutamyl chloride, m.p. 103–105° (lit.[12] m.p. 103–105° raised to 106–107° by recrystallization from benzene–ether).

Tosyl-L-prolyl chloride, m.p. 56–57.5° (lit.[12] oil). *Anal.* Calcd. for $C_{12}H_{14}NO_3SCl$: C, 50.08; H, 4.91; Cl, 12.32. Found: C, 50.13; H, 4.91; Cl, 12.24.

Tosyl-DL-Alanyl Azide.—To a solution of tosyl-DL-alanyl chloride, 2.6 g., in 35 ml. of acetone, cooled in ice-water, was added slowly with swirling an ice-cold solution of NaN_3, 0.8 g., in 20 ml. of water. The resulting clear solution was kept for 10 minutes at 0°, then diluted to 200 ml. with ice-water. The crystalline product was filtered off, washed with ice-water and dried in vacuum over silica gel, yield 2.2 g., m.p. 72–73° dec. Reprecipitation with ice-water from acetone solution gave 1.9 g., m.p. 74° dec. The m.p. varied with the rate of heating.

Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 44.77; H, 4.51; N, 20.88. Found[15]: C, 45.8; H, 4.7; N, 18.0.

Tosyl-DL-valyl Azide.—Tosyl-DL-valyl chloride, 2.9 g., was converted to the azide by the procedure used for the alanyl derivative, yield 2.8 g., m.p. 65–66° dec. Reprecipitation gave 2.8 g., m.p. 66° dec. The m.p. varied with the rate of heating.

Anal. Calcd. for $C_{12}H_{16}N_4O_3S$: C, 48.63; H, 5.44; N, 18.91. Found[15]: C, 49.7; H, 5.6; N, 15.9.

The Action of Aqueous NaOH on the Tosylamino Acid Chlorides.—When tosyl-DL-valyl chloride, 2.9 g., was added to 20 ml. of cold 1 *N* aqueous NaOH, the crystals dissolved with effervescence leaving a solution smelling strongly of isobutyraldehyde. Acidification with concentrated HNO_3 gave a crystalline precipitate, 1.64 g., m.p. 135–137°, after drying in a vacuum at 70°. The filtrate contained the chloride ion. Recrystallization from water yielded 1.45 g., m.p. 137–137.5°, undepressed on admixture with *p*-toluenesulfonamide. *p*-Toluenesulfonamide was isolated in like fashion after alkali treatment of the tosylated acid chlorides of DL-alanine, DL-α-amino-*n*-butyric acid, α-aminoisobutyric acid, DL-norleucine and L-leucine.

When tosylglycyl chloride, 1.0 g., was added to 10 ml. of cold 1 *N* aqueous NaOH, the compound dissolved with no apparent effervescence. After 10 minutes, concentrated HCl was added causing separation of tosylglycine, 0.8 g., m.p. and mixed m.p. 147–148° after recrystallization from water. Similarly tosyl-β-alanyl chloride or tosyl-L-prolyl chloride dissolved without effervescence in 1 *N* aqueous NaOH, and addition of HCl caused separation of the regenerated tosylamino acid. Tosyl-L-pyroglutamyl chloride dissolved without effervescence in cold 1 *N* aqueous NaOH. Acidification with concentrated HNO_3 caused no separation of sulfonamide or other material. Addition of $AgNO_3$ solution produced a copious precipitate of AgCl.

The Action of Aqueous NaOH on Tosyl-DL-valyl Azide.—The azide, 1.0 g., on treatment with 10 ml. of cold 1 *N* aqueous NaOH dissolved, with effervescence, leaving a solution smelling of isobutyraldehyde. This was filtered to remove a small amount of gummy material and the filtrate acidified with 1 ml. of 10 *N* HCl to give a crystalline precipitate, 0.60 g., m.p. 103–107°, which was added to 10 ml. of 1 *N* aqueous $NaHCO_3$. Part of the solid dissolved in the cold with effervescence, the remainder dissolved on heating. On cooling, crystals separated, 0.22 g. of *p*-toluenesulfonamide, m.p. 136–137°. Acidification of the filtrate gave tosyl-DL-valine, 0.18 g., m.p. 164.5–166°.

Test for the Cyanate Ion.—The presence of the cyanate ion after alkaline degradation of tosyl-DL-valyl azide was detected by its reaction with semicarbazide to form hydrazodicarboxamide.[5] Tosyl-DL-valyl azide, 1.46 g., was shaken with 15 ml. of cold 1 *N* aqueous NaOH until gas evolution ceased. After filtering from a small amount of gum, the solution was added to 0.56 g. of semicarbazide hydrochloride dissolved in 10 ml. of water. The solution was allowed to stand for 5 minutes, then 20 ml. of glacial acetic acid was added. After 10 minutes the resulting solution deposited crystals, 0.12 g., m.p. 251–252° dec. This material did not depress the m.p. of hydrazodicarboxamide prepared from semicarbazide hydrochloride, sodium acetate and potassium cyanate.

The Action of Aqueous NaOH on Tosyl-DL-alanyl Azide.—The azide, 0.51 g., dissolved with effervescence in 10 ml. of cold 1 *N* aqueous NaOH, producing the odor of acetalde-

(10) E. W. McChesney and W. K. Swann, THIS JOURNAL, **59**, 1116 (1937).

(11) R. W. Holley and A. D. Holley, *ibid.*, **71**, 2131 (1949).

(12) Z. Pravda and J. Rudinger, *Collection Czechoslov. Chem. Communs.*, **20**, 1 (1955).

(13) Fr. Fichter and M. Schmid, *Helv. Chim. Acta*, **3**, 711 (1920).

(14) J. M. Swan, *Australian J. Sci. Research, Ser. A*, **5**, 728 (1952).

(15) Accurate analysis figures for the azides could not be obtained since they proved unstable at room temperatures.

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hyde. Addition of 1 ml. of 10 *N* HCl gave an oil which quickly crystallized; 0.33 g., m.p. 136–138°. This material dissolved with effervescence in 10 ml. of cold 0.5 *N* aqueous $KHCO_3$. Acidification yielded tosyl-DL-alanine, 0.26 g., m.p. 137–138°.

Identification of Volatile Products from the Degradations.—Crystals of the tosylamino acid chloride or azide were allowed to react in a closed evacuated system with aqueous sodium hydroxide. Volatile material produced was isolated in a liquid-air cooled trap, in which part condensed and part remained gaseous. The mass spectra of the permanent gas and of the condensed material were then determined separately, showing the gas from the acid chlorides to be carbon monoxide and that from the azides, nitrogen. The mass spectra of the less volatile products evolved from the alanyl and α-amino-isobutyryl derivatives showed, as the main components, acetaldehyde and acetone, respectively. Also present were trace amounts of material of higher mass, presumably resulting from self-condensation of the carbonyl compounds. With the remaining tosyl derivatives which underwent degradation, the appropriate aldehyde was the sole volatile product apart from the permanent gas. In each case the mass spectrum of the carbonyl compound evolved was identical with that obtained from an authentic specimen.

Measurement of Gas Evolved in the Degradations.—The tosylated acid chloride or azide was allowed to react with 1 *N* aqueous NaOH in a closed system and the evolved gas collected over water. The results were reproducible to within 1%.

Attempted Isolation of the Tosylated Imine.—Ten ml. of cold 1 *N* aqueous NaOH was run into a solution of tosyl-DL-valyl chloride, 2.9 g., in 10 ml. of dioxane, producing effervescence. Seventy ml. of ether was added at once, the mixture shaken and the aqueous layer separated. This gave a neutral reaction. The ether solution was dried over Na_2SO_4, filtered, diluted with 80 ml. of dry petroleum ether, b.p. 60–80°, and partly evaporated. Crystals formed, 1.4 g. Two recrystallizations from dry ether–petroleum ether gave 0.7 g., m.p. 124.5–125.5°.

Anal. Calcd. for $C_{11}H_{15}NO_2S$ (tosylated imine): C, 58.64; H, 6.71; N, 6.22; S, 14.23. Calcd. for $C_7H_9NO_2S$ (*p*-toluenesulfonamide): C, 49.10; H, 5.30; N, 8.18; S, 18.73. Found: C, 49.43; H, 5.36; N, 8.12; S, 18.80.

Recrystallization from water gave material of m.p. 137–137.5° not depressed on admixture with *p*-toluenesulfonamide. The substance, m.p. 124.5–125.5°, is apparently a dimorph of *p*-toluenesulfonamide.

Hydrolysis of Tosyl-DL-valyl Chloride.—The chloride, 1.0 g., was suspended in cold water. Over 30 minutes there was no effervescence, no odor of aldehyde and little of the solid dissolved. On heating under reflux the solid reverted to oily drops, which did not dissolve at 100°. After 5 minutes at this temperature, crystallization commenced. Dilution to 300 ml. with boiling water gave a clear solution from which, on cooling, tosyl-DL-valine separated; 0.7 g., m.p. 165.5–166.5°.

Samples of tosylglycyl chloride and tosyl-DL-valyl chloride were each suspended in 2% aqueous $AgNO_3$. The suspension of the glycine derivative became cloudy within one minute, that of the valyl compound remained clear for several minutes.

Tosyl-DL-alanine Ethyl Ester.—Tosyl-DL-alanyl chloride, 5.2 g., was dissolved in hot ethanol to form the ester and the product crystallized from benzene–petroleum ether; yield 5.1 g., m.p. 66–67° (lit. m.p. 66–67°,[16] m.p. 68°[17]).

Tosyl-DL-valine Ethyl Ester.—Tosyl-DL-valyl chloride, 2.9 g., was dissolved in hot ethanol. On removal of the solvent under reduced pressure, the ester crystallized; yield 2.7 g., m.p. 86–88° unchanged after recrystallization from petroleum ether, b.p. 60–80°.

Anal. Calcd. for $C_{14}H_{21}NO_4S$: C, 56.16; H, 7.07; N, 4.68; O, 21.38. Found: C, 56.27; H, 6.98; N, 4.54; O, 21.2.

The Action of Aqueous NaOH on the Esters.—Tosyl-DL-valine ethyl ester, 0.29 g., was added to 2 ml. of 1 *N* aqueous NaOH. The solid dissolved slowly to give an odorless solution which was heated at 70° for 8 hr., cooled and treated with 2 ml. of 1 *N* aqueous HCl. A crystalline precipitate formed; 0.25 g., m.p. 165–166°, not depressed when mixed with tosyl-DL-valine. Tosyl-DL-alanine ethyl ester, similarly treated, yielded tosyl-DL-alanine. When either ester was dissolved in 2 equivalents of *N* aqueous NaOH and the solution allowed to stand at room temperature for 8 hr., hydrolysis was not complete. Acidification in each case caused precipitation of material only part of which was soluble in cold aqueous bicarbonate.

Tosyl-DL-alanyl Amide.—Tosyl-DL-alanyl chloride treated with concentrated aqueous ammonia gave the amide, m.p. 195–196°, in 95% yield.

Anal. Calcd. for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56; O, 19.81; S, 13.23. Found: C, 49.64; H, 5.83; N, 11.32; O, 20.05; S, 13.58.

Tosyl-DL-valyl Amide.—Tosyl-DL-valyl chloride on suspension in concentrated aqueous ammonia was converted quantitatively to the amide, m.p. 245–246°.

Anal. Calcd. for $C_{12}H_{18}N_2O_3S$: C, 53.31; H, 6.71; N, 10.36; O, 17.76; S, 11.86. Found: C, 53.67; H, 6.68; N, 9.71; O, 17.9; S, 11.96.

The Action of Aqueous NaOH on the Amides.—Tosyl-DL-alanyl amide, 0.65 g., dissolved in 6 ml. of 1 *N* aqueous NaOH without the production of any aldehyde odor. The solution was heated under reflux for 3 hr., cooled and acidified with 6 ml. of 1 *N* aqueous HCl. An oil separated which crystallized on standing; 0.55 g., m.p. 133–135°, raised to 137–138° by recrystallization, undepressed by admixture with tosyl-DL-alanine. Tosyl-DL-valyl amide, 1.3 g., was dissolved in 10 ml. of 1 *N* aqueous NaOH and heated under reflux for 7.5 hr., during which time the solution became cloudy. Dilution with water to 100 ml. gave a clear solution. After addition of 10 ml. of 1 *N* HCl and cooling, there separated 0.62 g. of unchanged amide, m.p. 245–246°. The filtrate, on evaporation to 10 ml., yielded crystalline material which dissolved in aqueous bicarbonate. Acidification gave tosyl-DL-valine, 0.57 g., m.p. 164–165°.

Solutions of each amide in 2 equivalents of 1 *N* aqueous NaOH, after standing at room temperature for 24 hr., gave, on acidification, unchanged amide, with over 90% recovery.

(16) W. Cocker, *J. Chem. Soc.*, 373 (1943).
(17) R. Schönheimer, *Z. physiol. Chem.*, **154**, 203 (1926).

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[CONTRIBUTION FROM THE CHEMICAL PHYSICS SECTION, DIVISION OF INDUSTRIAL CHEMISTRY, COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANIZATION]

Tosyl-α-amino Acids. II. The Use of the Acid Chlorides for Peptide Synthesis in the Presence of Aqueous Alkali

BY A. F. BEECHAM

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Degradation of those tosyl-α-amino acid chlorides in which the side chain is strongly electron-releasing proceeds more rapidly than peptide formation (with glycine) in strong aqueous alkali. To inhibit degradation, the alkalinity must be reduced to a level at which coupling is slow. Hydrolysis of the acid chloride then interferes.

It has been shown recently that tosyl-α-amino acid chlorides,[1a] like other arylsulfonyl-α-amino acid chlorides,[1b] are liable to rapid degradation by cold aqueous alkali in accordance with the scheme

$$\text{tos.NHCRR'COCl} + \text{OH}^- \longrightarrow \text{tos.NH}_2 + \text{RR'CO} + \text{CO} + \text{Cl}^-$$

Evidence was presented[1a] consistent with the postulates that, for such decomposition to occur, the tosylated acid chlorides must be capable of forming a sulfonamido anion, $\text{tos.}\overline{\text{N}}\text{CRR'COCl}$, and must carry an electron-releasing side chain at the α-carbon atom. It was apparent that this reaction would need to be taken into account if the susceptible compounds were to be used for peptide syntheses in basic aqueous media. Some experiments designed to test the extent of interference with the peptide forming reaction were, therefore, carried out.

It was shown readily that where the tosylamino acid chloride is not degraded, coupling with a second amino acid dissolved in aqueous alkali proceeds smoothly. When tosyl-L-prolyl chloride was caused to react with L-hydroxyproline under these conditions, the tosylated dipeptide was obtained in excellent yield. In tosyl-L-prolyl chloride the nitrogen is tertiary so that sulfonamide salt formation is not possible.[2] Under similar conditions tosylglycyl-L-proline was prepared, with tosylglycyl chloride as the acylating agent. Although this chloride is capable of conversion to the sulfonamido anion, no side chain is present and degradation is slight.[1a]

Tosyl-DL-alanyl chloride is degraded by cold aqueous sodium hydroxide to the extent of 86% as measured by the amount of carbon monoxide evolved.[1a] This compound in the L-form was used by Schönheimer[3] for peptide synthesis, his technique being to shake a benzene solution of the chloride with a solution of the second amino acid in aqueous sodium hydroxide. In the present work, tosyl-DL-alanyl chloride and glycine were coupled by this method. With the reagents in the proportions required by the equation, the peptide was obtained in 80% yield. When solid tosyl-DL-alanyl chloride was added to a solution of glycine in aqueous sodium hydroxide, efferverscence was apparent as the chloride dissolved and the odor of acetaldehyde became evident, but the coupling product was again isolated in 80% yield.

$$\text{tos.NHCHRCOCl} + \text{NH}_2\text{CH}_2\text{COOH} + 2\text{NaOH} \longrightarrow \text{tos.NHCHRCONHCH}_2\text{COONa} + \text{NaCl}$$

Tosyl-L-leucyl chloride is 99% degraded by cold aqueous sodium hydroxide.[1a] When this compound was substituted for tosyl-DL-alanyl chloride under either of the foregoing conditions, a different result was obtained. Effervescence was more pronounced and no coupling product could be isolated. Tosyl-DL-valyl chloride, which is also 99% degraded by cold aqueous sodium hydroxide,[1a] reacted similarly to the leucyl compound. Addition of tosyl-DL-valyl chloride to the solution of glycine in aqueous sodium hydroxide resulted in evolution of 60% of the theoretical quantity of carbon monoxide and *p*-toluenesulfonamide was isolated from the solution.

These results may be interpreted as follows. As already has been shown,[1] when tosyl-α-amino acid chlorides capable of sulfonamido anion formation are treated with aqueous alkali, both hydrolysis and degradation occur. Degradation predominates where the α-carbon atom bears an electron-releasing side chain and predominates increasingly as the inductive power of the side chain increases. When the aqueous alkali contains a second amino acid, a third reaction competes, namely, attack on the acid chloride function by the amino group to form a peptide bond. Under strongly alkaline conditions, the second amino acid is almost wholly in the anionic form and coupling proceeds more rapidly than hydrolysis. With tosyl-DL-alanyl chloride, whose methyl side chain is only weakly electron releasing, coupling is also faster than degradation; but with tosyl-L-leucyl and tosyl-DL-valyl chlorides, which carry the more strongly inductive isobutyl and isopropyl side chains, respectively, degradation is again the main reaction.

A comparison of the proportions of reagents required by the coupling reaction with those recorded by Schönheimer[3] is interesting. To prepare tosyl-L-alanyl-L-leucine he used tosyl-L-alanyl chloride (1 part), L-leucine (1.7 parts) and sodium hydroxide (2.2 parts), but for tosyl-DL-leucylglycine he employed tosyl-DL-leucyl chloride (1 part), glycine (2.5 parts) and sodium hydroxide (0.85 part). Evidently in the second case he found a reduction in alkalinity necessary, although he makes no comment on this.

Reducing the alkalinity seemed the obvious way of modifying the reaction conditions for peptide syntheses involving the more easily degraded chlo-

(1) (a) A. F. Beecham, *Chemistry & Industry*, 1120 (1955); THIS JOURNAL, **79**, 3257 (1957); (b) R. H. Wiley, H. L. Davis, D. E. Gensheimer and N. R. Smith, *ibid.*, **74**, 936 (1952); R. H. Wiley and R. P. Davis, *ibid.*, **76**, 3496 (1954).

(2) This consideration also applies to tosyl-L-pyroglutamyl chloride which has been used successfully for peptide syntheses in the presence of aqueous base; *vide* J. M. Swan and V. du Vigneaud, *ibid.*, **76**, 3110 (1954), and J. Rudinger, *Collection Czechoslov. Chem. Commun.*, **19**, 365 (1954).

(3) R. Schönheimer, *Z. physiol. Chem.*, **154**, 203 (1926).

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rides. Tosyl-DL-valyl chloride was chosen for study, since in this compound susceptibility to degradation is high and steric obstruction to coupling is considerable. Reaction with glycine in aqueous media of various alkalinities was attempted, but no conditions were found under which interference was suppressed. At *p*H <8 hydrolysis was the main reaction and at *p*H >8 degradation occurred. For glycine, $pK'_2 = 9.60$,[4] so that at *p*H 8, although degradation proceeds at a much reduced rate, coupling is also slow, since the concentration of the glycine anion is low. The best yields of tosyl-DL-valylglycine (36–38%) were obtained when a dioxane solution of the chloride was added portionwise to ice-cold aqueous glycine, kept at *p*H 8–9 with sodium hydroxide or containing excess solid magnesium oxide. In the latter case the initial *p*H of the aqueous solution was 10.5, but this quickly dropped to lower values as dissolved base was consumed.

Tosyl-L-isoleucyl chloride would be expected to be as readily degraded by aqueous alkali as tosyl-DL-valyl chloride, but Katsoyannis and du Vigneaud[5] have used the compound, in the presence of aqueous magnesia, to prepare tosyl-L-isoleucyl-L-glutamine and tosyl-L-isoleucyl-L-glutaminyl-L-asparagine. The yield of the dipeptide obtained was low but that for the tripeptide was 55–60%. These results are probably accounted for by the different concentrations of the anions of the second component in the two cases; pK'_2 for glutamine is 9.13.[4] The value for glutaminylasparagine is not recorded, but it would be expected to be below 8 (since, *e.g.*, glutaminylglycine has $pK'_2 = 7.52$[4]).

Experimental[6]

Tosyl-L-prolyl-L-hydroxyproline.—To a solution of L-hydroxyproline, 1.31 g. (0.01 mole) in 1 *N* NaOH, 20 ml., was added tosyl-L-prolyl chloride, 2.875 g. (0.01 mole), and the whole shaken with ice cooling for 20 minutes. Addition of 1 *N* HCl, 10 ml., to the resulting solution caused precipitation of an oil which quickly crystallized to give 3.4 g. of material, m.p. 219–221°. After several recrystallizations, from water or by precipitation with acid from bicarbonate solution, the product had m.p. 224–224.5°, $[\alpha]^{36}D$ −198° (*c* 1 in 0.5 *N* $KHCO_3$).

Anal. Calcd. for $C_{17}H_{22}N_2O_6S$: C, 53.39; H, 5.80; N, 7.33; O, 25.10; S, 8.28. Found: C, 53.19; H, 5.98; N, 6.89; O, 24.9; S, 8.51.

Tosylglycyl-L-proline.—To a solution of L-proline, 5.75 g. (0.05 mole), in a mixture of 1 *N* NaOH, 100 ml., and dioxane, 100 ml., was added tosylglycyl chloride,[7] 12.4 g. (0.05 mole), in portions, with swirling to dissolve after each addition. After standing for 18 hr., the solution was brought to *p*H 6 by addition of hydrochloric acid, concentrated to 30 ml. and acidified. The oily precipitate crystallized after 3 days at 0°; 13.6 g., m.p. 176–180° after softening at 170°. Three recrystallizations from bicarbonate solution by addition of acid gave 8.2 g. of product, m.p. 183–184°, $[\alpha]^{27}D$ −71° (*c* 1 in 0.5 *N* $KHCO_3$).

Anal. Calcd. for $C_{14}H_{18}N_2O_5S$: C, 51.52; H, 5.57; N, 8.58; O, 24.51; S, 9.82. Found: C, 51.48; H, 5.46; N, 8.57; O, 24.6; S, 9.99.

Tosyl-DL-alanylglycine.—A solution of tosyl-DL-alanyl chloride, 2.61 g. (0.01 mole), in 80 ml. of benzene was shaken with 20 ml. of 1 *N* NaOH containing glycine, 0.75 g. (0.01 mole), for 16 hr. The benzene layer was separated, the aqueous solution warmed to 90°, 10 ml. of 1 *N* HCl added and the solution allowed to cool slowly. Crystals of the tosyl dipeptide separated, 2.35 g., m.p. 149–150° (lit. m.p. 147° cor.,[3] m.p. 150–151° cor.[8]).

When tosyl-DL-alanyl chloride, 2.61 g., was added to a solution of glycine, 0.75 g., in 20 ml. of 1 *N* NaOH, the solid dissolved slowly with effervescence and the production of the odor of acetaldehyde. From the solution, after acidification, was obtained 2.4 g. of the crude tosyl dipeptide, m.p. 147–149°. Recrystallization from 50 ml. of water yielded 1.9 g., m.p. 149–150°.

Tosyl-DL-valylglycine. A.—Tosyl-DL-valyl chloride, 2.895 g. (0.01 mole), was added to a solution of glycine, 0.75 g. (0.01 mole), in 20 ml. of 1 *N* NaOH and the evolved gas collected. The volume of gas produced indicated that 60% of the chloride had suffered degradation. The aqueous liquor contained suspended solid, from which was obtained by recrystallization from aqueous bicarbonate *p*-toluenesulfonamide, 0.7 g., m.p. 136–137.5°.

B.—Addition of the chloride (0.01 mole) to aqueous glycine (0.01 mole) containing triethylamine (0.02 mole) at *p*H 12 resulted in strong effervescence. The products were not examined.

C.—The chloride, 2.895 g., glycine, 0.75 g., and MgO, 1.0 g., were shaken for 6 hr. in a mixture of 20 ml. of water and 20 ml. of dioxane. After standing overnight the mixture was acidified, the oily precipitate taken into ether, the ether solution dried over Na_2SO_4, evaporated to dryness and the residue dissolved in 400 ml. of hot anhydrous benzene. On cooling crystals separated, 1.3 g., m.p. 165–168° after softening at 160°. This material after three recrystallizations from water yielded tosyl-DL-valylglycine, 0.7 g., m.p. 174–175°.

Anal. Calcd. for $C_{14}H_{20}N_2O_5S$: C, 51.20; H, 6.14; N, 8.53; O, 24.36; S, 9.76. Found: C, 51.25; H, 6.14; N, 8.06; O, 24.2; S, 9.83.

From the benzene filtrate was obtained tosyl-DL-valine, 0.4 g., m.p. 165–166° unchanged when mixed with an authentic sample.[1a]

D.—To a solution of glycine, 0.75 g., in 20 ml. of water containing magnesium oxide, 1.0 g., at *p*H 10.5 was added, over 20 minutes with shaking and ice cooling, a solution of tosyl-DL-valyl chloride in 20 ml. of dioxane. Shaking with cooling, was continued for 10 minutes, the suspension set aside for 20 minutes and then filtered. The filtrate (*p*H 8) was acidified and the resulting oily suspension shaken with ether when crystallization commenced. The crystalline material, 1.4 g., m.p. 160–165°, dissolved in aqueous bicarbonate to yield, on acidification, tosyl-DL-valylglycine, 1.06 g., m.p. 173.5–174.5°.

Evaporation of the ether gave further crystalline material from which no pure compound could be obtained.

E.—A solution of glycine, 0.375 g., in 20 ml. of water was maintained at *p*H 9.6–9.7 by addition of aqueous sodium hydroxide while tosyl-DL-valyl chloride, 1.45 g., was added in portions. Effervescence was noticeable as the chloride dissolved and only *p*-toluenesulfonamide, 0.56 g., was obtained on working up.

F.—From an ice-cooled solution of glycine, 0.375 g., in 10 ml. of water and 10 ml. of dioxane kept at *p*H 9–10 with sodium hydroxide while tosyl-DL-valyl chloride, 1.45 g., was added, there was obtained *p*-toluenesulfonamide, 0.43 g., and tosyl-DL-valylglycine, 0.52 g.

G.—To a solution of glycine, 0.75 g., in 10 ml. of water were added a solution of tosyl-DL-valyl chloride, 2.895 g., in 20 ml. of dioxane, and 1 *N* sodium hydroxide at such a rate that the *p*H was kept at 8.5–9. Tosyl-DL-valylglycine, 1.2 g., and *p*-toluenesulfonamide, 0.22 g., were obtained as well as further material which could not be purified.

H.—A solution of glycine, 0.75 g., in water containing sodium bicarbonate had *p*H 8.2. After addition of tosyl-DL-valyl chloride there was obtained *p*-toluenesulfonamide, 0.77 g., and tosyl-DL-valine, 0.30 g.

I.—Addition of tosyl-DL-valyl chloride, 2.895 g., to a solution of glycine in aqueous pyridine at *p*H 7.6 resulted in the production of tosyl-DL-valine, 2.0 g.

MELBOURNE, AUSTRALIA

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[CONTRIBUTION FROM THE DEPARTMENT OF PEDIATRICS, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA AND THE CHILDREN'S HOSPITAL OF PHILADELPHIA]

Structural Effects of the Interaction of Human Serum Albumin with Sodium Decyl Sulfate[1]

BY GABOR MARKUS AND FRED KARUSH

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The optical rotatory and viscosity behavior of human serum albumin was investigated as a function of sodium decyl sulfate concentration. At concentrations up to 5×10^{-3} *M*, *i.e.*, in the region where 10–14 molecules of detergent are bound per albumin molecule, the levorotation drops from 64 to 58°. A similar change is observed when the *p*H is raised from 8 to 9.4 in the absence of detergent. In both cases the reduced viscosity remains constant. Acetylated albumin fails to show a decrease in levorotation upon the addition of small amounts of detergent. It is concluded that the observed drop is associated with the loss of charge from ϵ-ammonium groups and arises from a small change in the secondary structure of the protein. Upon further increase in the detergent concentration the levorotation rises and reaches its maximum of 70° at 3.4×10^{-2} *M* decyl sulfate. A similar rise in levorotation (from 61 to 70°) can be brought about by raising the *p*H from 2 to 8 at a constant detergent concentration (0.1 *M*). In both cases these changes are interpreted as a result of the increase in the net charge of the protein. In the first case, the binding of the detergent anions neutralizes the cationic charges of the protein, in the second case, the ionization of the carboxyl groups increases the net charge. The rise in reduced viscosity which accompanies the rotatory change in both instances and the reversal of these changes in high salt concentrations support the interpretation that high detergent concentrations effect an increase in the hydrodynamic volume of the protein molecules due to the intramolecular electrostatic repulsion within the protein–detergent complex. The observed changes in the physical properties are discussed in reference to the secondary and tertiary structures of serum albumin.

Among the substances used in the study of protein denaturation detergents have lately received particular attention due to the relatively mild physical changes caused by them. Unlike urea and similar substances, the detergents are unable to compete for the peptide hydrogen bonds that stabilize the secondary structure of proteins. Their interaction must, therefore, be largely restricted to the side chains of the protein including both the charged groups and the non-polar groups. It should be noted, however, that the binding of ionic detergents may disrupt peptide hydrogen bonds indirectly. This effect would result from intramolecular electrostatic repulsion or from the competitive breaking by the detergent of non-polar side chain interactions whose integrity is required for the stabilization of the helical structure. The physical changes proteins undergo in the course of their interaction with detergents can, therefore, to a large degree, be evaluated in terms of changes in their tertiary structure. That some effects are also exerted on the helical organization of the peptide chain is indicated by changes in optical rotation, which regularly accompany the binding of detergent molecules. Since the measurement of viscosity yields information on changes in molecular volume and asymmetry, the combined measurement of these two physical properties greatly facilitates the characterization of a given structural state.

The interaction between the alkyl sulfate homologs and serum albumin has been the subject of several studies. Putnam and Neurath,[2] studying the interaction of dodecyl sulfate and horse serum albumin found that the uptake of detergent occurred in several successive steps involving distinct electrophoretic species with fixed numbers of detergent molecules attached. The number of detergent anions bound by the second new component (AD_{2n}) was found equivalent to the sum of the cationic groups of the protein. Karush and Sonenberg[3] working at low detergent concentrations measured the association constants for three alkyl sulfate homologs (C_8, C_{10}, C_{12}) with bovine serum albumin and found that the affinity increased with increasing chain length. Pallansch and Briggs[4] confirmed and extended the findings of these two groups of workers. As the result of these studies it has become apparent that combination with detergents involves interaction between the charged and the non-polar portions of both detergent and protein, and as a result of this interaction the protein undergoes structural changes. The character and the extent of these changes depends on the number of detergent molecules bound for each homolog.

The purpose of the present study was to evaluate the structural changes that accompany detergent binding by human serum albumin largely by the measurement of optical rotation and viscosity as a function of decyl sulfate concentration.

Experimental

Human serum albumin (HSA) was contributed by Cutter Laboratories and was 99% pure by electrophoretic analysis. A 9% stock solution was prepared in distilled water, adjusted to *p*H 7.4 with NaOH and stored in the frozen state. Its concentration was determined by micro-Kjeldahl analysis. Acetylated serum albumin was prepared according to the method described by Fraenkel-Conrat[5] with some modifications. It was found that unless the *p*H is kept near 8 by the dropwise addition of NaOH while the acetic anhydride is added, only 80% acetylation can be achieved, as against 97% when this modification is introduced. The acetylated protein was dialyzed at 5° against running distilled water for 5 days. The degree of acetylation was determined by the ninhydrin method of Harding and MacLean.[6] Sodium decyl sulfate (SDeS) was kindly prepared by Mr. Robert Marks according to the method of Dreger, *et al.*[7] It was twice recrystallized from *n*-butanol. Optical rotations were measured at room temperature with a Bellingham and Stanley polarimeter, which could be read to 0.01 of a degree, using a sodium vapor lamp and a 100 mm. cell. The specific rotations are accurate to ±1°. Viscosity measurements were made in Ostwald–Fenske viscosimeters in a 25° water-

(1) These studies were aided by a grant from the National Science Foundation and by a research grant (H-869) from the National Heart Institute of the National Institutes of Health, Public Health Service.

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(3) F. Karush and M. Sonenberg, THIS JOURNAL, **71**, 1369 (1949).

(4) M. J. Pallansch and D. R. Briggs, *ibid.*, **76**, 1396 (1954).

(5) H. Fraenkel-Conrat in D. M. Greenberg, ed., "Amino Acids and Proteins," Charles C Thomas, Springfield, Ill., 1951, p. 547.

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bath. The blanks used for the determination of reduced viscosities differed from the samples only by the absence of protein. The uncertainty in the reduced viscosities is ±0.005. The titration of HSA was carried out in 20 ml. of a 0.89% solution of HSA in 0.1 *M* SDeS by addition of standard 1 *N* HCl and NaOH from a micro-buret.

The binding of sodium decyl sulfate to HSA was determined by equilibrium dialysis. The dialysis was carried out at 25° for a period of 14 days. This interval was necessary since the effective rate of diffusion at high concentrations is considerably reduced by the micellar structure of the detergent. Ten ml. of 0.89% HSA containing the detergent was dialyzed against 10 ml. of distilled water. Since no salt was added, it was possible to calculate the amount of bound SDeS from the Donnan distribution. For this purpose the determination of the equilibrium concentrations of detergent on both sides of the cellophane membrane were required. These were obtained by the determination of the Na^+ concentration on both sides by flame-photometric analysis. The outside concentration of Na^+ was assumed to be equal to the detergent anion concentration outside, and the concentration of free detergent inside the bag was then calculated from the Donnan equation

$$[DeS^-]_i = \frac{[Na^+]_o^2}{[Na^+]_i}$$

Correction was made for the small amount of $NaHCO_3$ contained in the SDeS stock solution. The quantities of detergent in each compartment were calculated by multiplication of the concentrations by the respective volumes. These were determined by the dilution the known original concentration of the protein had undergone, as measured by the biuret method we have previously employed.[8] The molecular weight of HSA was taken to be 65,000.

Results and Discussion

When a 1% solution of human serum albumin (HSA) containing 0.15 *M* NaCl and 0.02 *M* phosphate (*p*H 7.4), is treated with sodium decyl sulfate in concentrations ranging from 1×10^{-3} *M* to 2×10^{-1} *M* the optical rotation of the protein undergoes a characteristic series of changes (Fig. 1).

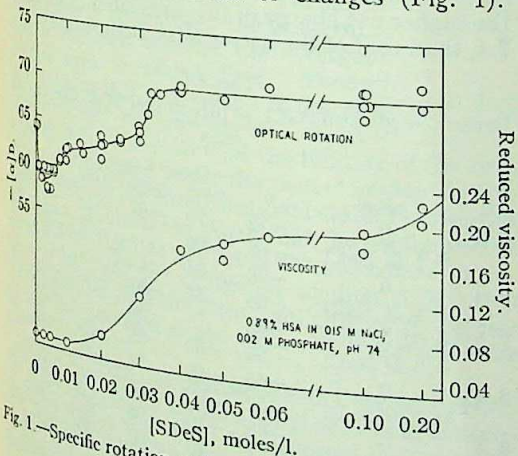

Fig. 1.—Specific rotation and reduced viscosity of HSA as a function of SdES concentration.

From 0 to 4×10^{-3} *M* sodium decyl sulfate the levorotation drops from the native value of 64° to about 58°. It then gradually increases to reach the value for the native protein at 3×10^{-2} *M* sodium decyl sulfate. Above this concentration the levorotation rises steeply and at 3.3×10^{-2} *M* reaches the value of 70°. Beyond this concentration the rotation stays at 70° up to 2×10^{-1} *M*, the highest concentration used.

Effect of Low Detergent Concentrations on the Optical Rotation.

—It will be convenient to consider first the initial phase of the rotation *versus* concentration curve, the one characterized by the decrease in levorotation. Figure 2 shows that this

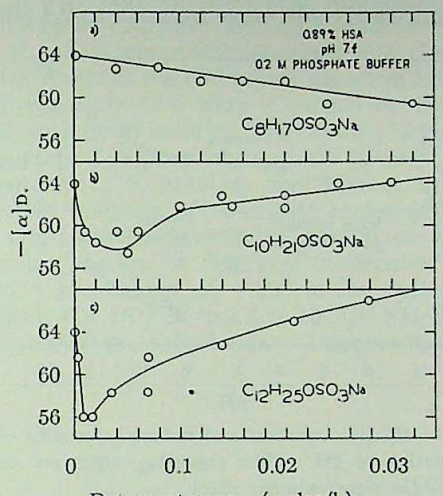

Fig. 2.—Specific rotation of HSA at low concentrations of three alkyl sulfate homologs.

drop is not restricted to sodium decyl sulfate, since both sodium octyl sulfate and sodium dodecyl sulfate cause a similar depression in the levorotation. The difference in their effectiveness is indicated by the variation of the detergent concentration at which the minimum occurs. The lowest homolog, octyl sulfate, reduces the rotation to 59° at a concentration between 2×10^{-2} to 3×10^{-2} *M*, whereas the highest homolog, dodecyl sulfate, causes the minimum of 56° to occur at 1×10^{-3} *M*. The order of effectiveness in evoking this decrease in levorotation corresponds to the order of the affinities of these detergents for bovine serum albumin as determined by Karush and Sonenberg.[3] From the data of these authors it can be calculated that for decyl sulfate at 4×10^{-3} *M* total concentration, there would be 11 moles of detergent bound per mole of protein. For dodecyl sulfate the binding of 10 molecules occurs at 1.9×10^{-3} *M*. In the above-mentioned study the cited values represent the highest ones measured and are close to the extrapolated maximum binding, *n*, which is taken to be 14. This *n* refers to the group of sites that are first to combine with detergent. Pallansch and Briggs[4] arrive at an *n* value of 10 for dodecyl sulfate under somewhat different conditions. Their work indicates that beyond this value the protein changes its binding properties. A new set of binding sites opens up accompanied by the appearance of a faster migrating electrophoretic component. This indicates that at this point some configurational change has occurred. Our results show that this change is associated with a transition from decreasing to increasing levorotation.

Since anionic detergents appear to interact with the cationic sites of the protein, the question may be asked whether the decrease in levorotation might not be associated with the charge neutralization of some of these cationic sites. It has been ob-

(8) G. Markus and F. Karush, THIS JOURNAL, **79**, 134 (1957).

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served by Jirgensons[9] that the optical rotation of native serum albumin decreases between *p*H 7 and 9.5 just before the steep rise at still higher *p*H values. We have confirmed this finding and found a drop of 6° in the optical rotation in that *p*H range (Fig. 3). In the *p*H range from 7.2 to 9.4 albumin

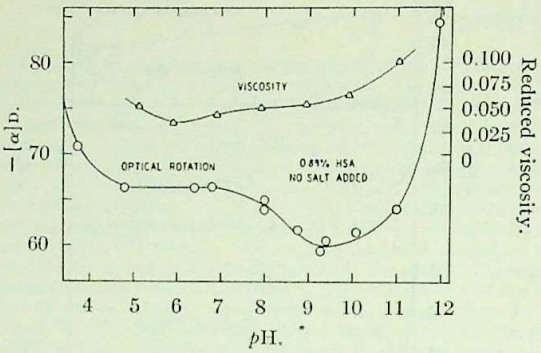

Fig. 3.—Specific rotation and reduced viscosity of HSA as a function of *p*H. (The viscosity values are not corrected for the electroviscous effect.)

dissociates about 15 H^+ ions,[10] some of which must come from the imidazolium groups (intrinsic pK 6.9), others from the ε-ammonium groups (pK 9.8). Since the dissociation of the former groups starts well below *p*H 6.9, where there is no change observed in the optical rotation, it is likely that the configurational change indicated by the decreased levorotation is associated with the loss of charge of the ε-ammonium groups.

Further evidence of the role of the ε-ammonium groups is provided by experiments with acetylated HSA in which these groups are masked. Figure 4a

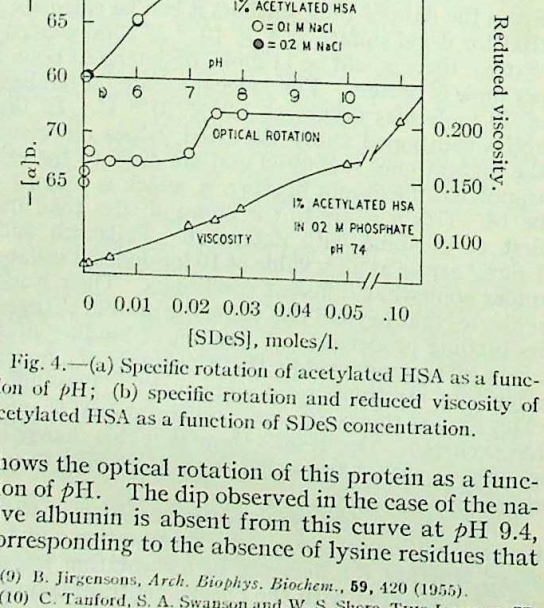

Fig. 4.—(a) Specific rotation of acetylated HSA as a function of *p*H; (b) specific rotation and reduced viscosity of acetylated HSA as a function of SDeS concentration.

shows the optical rotation of this protein as a function of *p*H. The dip observed in the case of the native albumin is absent from this curve at *p*H 9.4, corresponding to the absence of lysine residues that could be titrated in this *p*H region. The effect of the absence of these cationic groups, however, is implicit in this curve, since extrapolation to the region of insolubility, *i.e.*, to *p*H values below 5, would give a specific rotation of about −57°. Similarly, addition of SDeS to acetylated HSA at *p*H 7.4 (Fig. 4b) fails to cause the drop in levorotation observed in the native albumin at this *p*H. Since it can be shown (see below) that for the native HSA this effect is independent of the net charge within wide limits, as demonstrated by the same rotatory

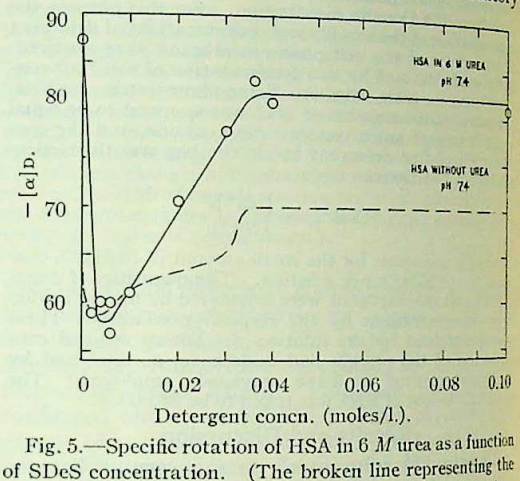

Fig. 5.—Specific rotation of HSA in 6 M urea as a function of SDeS concentration. (The broken line representing the same relation in the absence of urea is taken from Fig. 1.)

decrease upon the addition of detergent at *p*H 3 and *p*H 5 when 0.1 M NaCl is present (Table I), the elimination of the effect is not likely to be due to the higher net charge of the acetylated HSA at *p*H 7.4, than that of the native HSA at the same *p*H.

TABLE I

EFFECT OF *p*H AND NaCl ON $[\alpha]_D$ IN LOW SDeS CONCENTRATION

*p*H	Salt added	SDeS, moles/l. 0	0.001	0.002	0.003	0.004	Max. $\Delta[\alpha]_D$
3.0	0	−72	−70	−67	−64	−62	10
	0.1 M NaCl	−66	−65	..	−62	−60	6
5.0	0	−66	64	−61	61	..	5
	0.1 M NaCl	−65	65	−58	−58	−58	7
7.4	0.04 M NaCl	−65	..	−58	..	−57	9
	0.3 M NaCl	−64	−60	−58	−60	−60	6
8.0	0	−65	−60	58	−60	..	7
	0.1 M NaCl	−62	−62	58	−60	−58	4
9.4	0	−62	−60	−59	−59	−59	3
	0.1 M NaCl	−61	−62	−60	−60	−59	2

The intimate connection between the drop caused by titration with OH^- ions and with detergent anions is further revealed when HSA is treated with increasing concentrations of decyl sulfate at *p*H values between 3 and 9.4. Table I shows that the maximum levorotatory decrease in 0.1 M NaCl between *p*H 3 and 8 is 7°; at *p*H 9.4, however, it is only 2°. (The small value observed on the addition of the detergent at this *p*H indicates that the effective charge neutralization of only a fraction of the lysine residues is sufficient to suppress the effect. At high concentrations of detergent there is

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(10) C. Tanford, S. A. Swanson and W. S. Shore, THIS JOURNAL, **77**, 6414 (1955).

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levorotation (−70°) in 0.1 *M* SDeS at *p*H 9.4 (Fig. 6).) The influence which the partial neutralization of lysine residues exerts on the structure of the protein is a subtle one, since it is not accompanied by measurable changes in viscosity (Fig. 1, 3, 4). The effect probably is not due to the increase in net negative charge that occurs between *p*H 7 and 9.4, since increase in net charge tends to increase the levorotation rather than decrease it and usually causes a corresponding rise in the viscosity (see below). The observed phenomenon may be due to a *local* charge effect, whereby loss of the positive charge from neighboring residues permits a portion of the protein molecule to acquire additional secondary structure.

Protective Action of SDeS against Urea.—In 1948 the significant observation was made by Duggan and Luck[11] that certain organic anions at appropriate concentrations prevented the rise in viscosity of bovine serum albumin in 6 *M* urea. Among the anions studied, dodecyl sulfate was found most effective. Figure 5 shows the effect of sodium decyl sulfate concentration on the optical rotation of HSA in 6 *M* urea at *p*H 7.4. The most striking feature of this curve is that about 0.005 *M* SDeS completely prevents the rise in optical rotation caused by 6 *M* urea. The maximal protective effect thus occurs in the region of the minimal rotation caused by the decyl sulfate alone (Fig. 5, dotted line), *i.e.*, where 10–14 molecules of detergent are bound per molecule of HSA. The effect is completely reversible: the same rotation is obtained whether the detergent or the urea is added first. Though at this point it is not possible to describe unequivocally the mechanism of protection, it is quite clear that the binding of the first group of detergent molecules causes a very significant change in the configurational stability of serum albumin. It should be noted that the configuration assumed by HSA at *p*H 9.4 in the absence of detergent is in itself not protective against 6 *M* urea. This indicates that the structural change giving rise to the low rotation is not sufficient to provide the protective effect.

Effect of High Concentrations at Constant *p*H.—As indicated above, sodium decyl sulfate in concentrations above 4×10^{-3} *M* increases the levorotation of HSA to yield the native value of −64° at 3×10^{-2} *M*. Binding data are difficult to obtain in this region due to micelle formation by the detergent, but the best data available (Table II) indicate that it is between 2.7×10^{-2} and 3.4×10^{-2} *M* SDeS that the binding of 96 moles of detergent per mole of HSA occurs. This range includes the steep rise in optical rotation between 3×10^{-2} and 3.4×10^{-2} *M* SDeS (Fig. 1). The maximum observed rotation of −70° is reached at 3.4×10^{-2} *M* SDeS, i.e., in the concentration range where all the 96 cationic sites are probably combined with detergent.

(11) E. L. Duggan and J. M. Luck, *J. Biol. Chem.*, **172**, 205 (1948).

Subtracting the 10–14 molecules involved in the first phase of the interaction, we note that there are about 80 additional molecules bound when the levorotation of 70° is reached. We know from both binding and viscosity data that combination with the detergent continues beyond 3.4×10^{-2} *M* detergent. This concentration then is a significant one, for it marks the end of one aspect of the structural transformation that is caused by the interaction with decyl sulfate. The binding beyond this concentration is probably entirely hydrophobic in character, *i.e.*, it involves the interaction of the non-polar moieties of detergent molecules, either with non-polar residues of the protein, or with the non-polar portion of detergent molecules already bound. The change of −12° in the optical rotation from 4×10^{-3} *M* to 3.4×10^{-2} *M* SDeS is then the result of the attachment of approximately 80 additional molecules of detergent to one molecule of HSA.

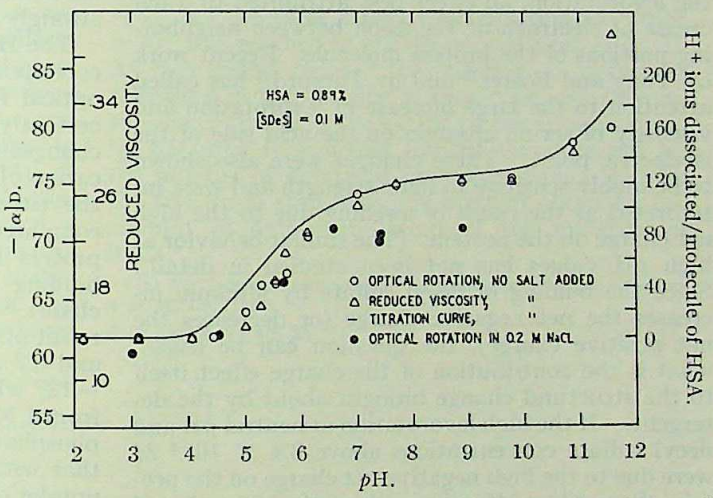

Fig. 6.—Specific rotation, reduced viscosity and H^+ ion dissociation of HSA in 0.1 *M* SDeS as a function of *p*H.

TABLE II

BINDING OF SODIUM DECYL SULFATE BY HSA AT *p*H 7.4, 25° BY EQUILIBRIUM DIALYSIS

HSA = 1.34×10^{-6} mole; no salts added

SDeS total, moles × 10^4	SDeS in outside soln., moles × 10^4	SDeS in inside soln., moles × 10^4	SDeS bound, moles × 10^4	Total concn. of SDeS inside, moles/l.	Moles SDeS bound/ mole HSA
4.32	2.03	1.68	0.61	0.023	46
5.19	2.54	1.82	.83	.027	62
6.93	3.21	2.05	1.67	.034	125
8.65	3.81	2.91	1.93	.049	144
17.30	7.66	7.52	2.12	.099	158

The value of the maximum attainable levorotation depends on the alkyl sulfate homolog used. This value for octyl sulfate is 64° and for dodecyl sulfate 68°. These variations must be due to the effect of the non-polar portions of these detergents. A rotation of −80° obtained in a saturated solution of octadecyl sulfate indicates that the effect on the levorotation increases with increasing chain length.

Effect of High Detergent Concentrations as a Function of *p*H.—High values of levorotation and

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viscosity caused by interaction with detergents make a partial unfolding or swelling of the protein molecule very probable, but the cause of this transformation has not been clearly defined. Table III shows the effect of salt concentration on the optical rotation of HSA in 0.1 *M* SDeS at

TABLE III

EFFECT OF NaCl ON $-[\alpha]_D$ OF HSA IN 0.1 *M* SDeS AT *p*H 7.4, HSA = 0.89%

NaCl, moles/l.	$-[\alpha]_D$
0	73-75
0.1	70
.2	70
.5	67
1.0	66

*p*H 7.4 and room temperature. These results demonstrate that increasing ionic strength depresses the levorotation, an effect best attributed to a decrease of electrostatic repulsion between neighboring portions of the protein molecule. Recent work by Yang and Foster[12] and by Tanford[13] has called attention to the large increase in levorotation and viscosity of serum albumin on the acid side of the isoelectric point. These changes were also shown to be highly sensitive to ionic strength and were interpreted as the result of swelling due to the high net charge on the protein. (The similar behavior at high *p*H values has not been studied in detail.) Since the binding of decyl sulfate by albumin increases the net negative charge (or decreases the net positive charge), the question can be asked, what is the contribution of the charge effect itself to the structural change brought about by the detergent. If the high levorotation at neutral *p*H and decyl sulfate concentrations above 3.4×10^{-2} *M* were due to the high negative net charge on the protein, then at low *p*H values, where the 100 carboxyl groups carry no charge, the net charge on the protein would be much less, and the levorotation should be markedly reduced, whereas in the *p*H range where the carboxyl groups dissociate the levorotation should increase. Figure 6 shows that this analysis is essentially correct. In this experiment 0.89% HSA in 0.1 *M* SDeS was adjusted to *p*H values ranging from 2.2 to 12.0 without added salt and in 0.2 *M* NaCl. When the ionic strength is high the flat portion of the curve on the acid side is at $-60°$ and the plateau in the neutral region at $-70°$. In the absence of detergent the optical rotation at *p*H 3 at high ionic strength is $-66°$. The difference of 6° between this value and the $-60°$ in 0.1 *M* dodecyl sulfate at the same *p*H corresponds to the specific effect of the ϵ-amino groups described in the first part of this paper. This difference is established at a concentration as low as 4×10^{-3} *M* SDeS, beyond which no further change in the optical rotation is observed.[14] Thus, beside this specific one, SDeS has no other effect on the optical rotation in this *p*H range.

However, the acquisition of negative charges by the dissociation of the carboxyl groups in the presence of 0.1 *M* SDeS increases the levorotation from 62 to 75° in the absence of added salt, and from 60 to 70° in 0.2 *M* added salt. This effect is associated with an increase in apparent hydrodynamic volume as indicated by the proportionally rising reduced viscosity. It is improbable that this effect would be due to further binding of SDeS molecules, since with higher *p*H values the negative net charge on the protein would reduce the binding rather than increase it.

In order to establish the correlation between the measured physical changes and the change in charge of the albumin molecule, the protein was titrated from *p*H 2 to 12 in the presence of 0.1 *M* SDeS and no added salt. In calculating the number of H^+ ions dissociated from HSA, correction was made for the titration curve of 0.1 *M* SDeS alone, since it was found that the detergent micelles strongly buffer in the region from *p*H 3 to 6.

The H^+ ion dissociation curve (Fig. 6) is seen to correspond fairly well to the *p*H-dependence of both optical rotation and viscosity. The agreement is certainly close enough to suggest that the physical changes are brought about by the ionization of the carboxyl groups. The shift of the buffering zone in the titration curve toward higher *p*H values, as compared to the corresponding zone in the native protein is due to the well-known effect of anion binding on the H^+ ion equilibria of protein side chains.[15] The rise of $-10°$ in optical rotation as a result of raising the *p*H from 2 to 7.4 in 0.1 *M* SDeS and 0.2 *M* NaCl can be compared with the rise of $-12°$ when the concentration of SDeS is increased from 4×10^{-3} to 3.4×10^{-2} *M* at *p*H 7.4 and 0.2 *M* phosphate buffer. In the latter case we concluded that within this concentration range there was an uptake of about 80 moles of detergent or the neutralization of about 80 positive charges.

Effects of High Concentrations on Acetylated HSA.—The findings on the acetylated serum albumin are in qualitative agreement with the above considerations. Here the maximum rotatory increase brought about by the addition of SDeS at *p*H 7.4 (Fig. 4b) is less than half of the corresponding change in the unmodified protein, in agreement with the 60% reduction in the number of available cationic sites. The data on the *p*H dependence of acetylated HSA in the absence of SDeS (Fig. 4a) indicates again that the increase in charge increases the levorotation. The protein when de-ionized with a mixed ion-exchange resin is insoluble and the supernatant has a *p*H of 4.5; at *p*H 5.0 the protein will stay in solution. Extrapolation of the curve to *p*H 4.5 yields $-57°$ for the isoelectric rotation. The difference of $-7°$ between this value and the $-64°$ characteristic for the unmodified protein at the isoelectric point shows, as mentioned above, the effect of the blocking of the ϵ-amino groups.

Unmasking of Disulfide Bonds.—A striking property of detergents, shared by other "denaturing agents," is their ability to make available groups for chemical reactions. In 0.2 *M* SDeS, *e.g.*,

(12) J. T. Yang and J. F. Foster, THIS JOURNAL, **76**, 1588 (1954).

(13) C. Tanford, J. G. Buzzell, D. G. Rands and S. A. Swanson, *ibid.*, **77**, 6421 (1955).

(14) In bovine γ-globulin, where the specific effect on the lysine residues is absent, the addition of 0.1 *M* SDeS at *p*H 2 gives a $-[\alpha]_D$ of 45°, in agreement with the rotation of the native protein.

(15) I. M. Klotz and J. M. Urquhart, THIS JOURNAL, **73**, 315[illegible]

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all of the 17 disulfide bonds of HSA are reduced by 0.1 M β-mercaptoethylamine–HCl, whereas only 1 disulfide bond is split in the absence of the detergent.[8] Furthermore, the facilitation of the reduction of disulfide bonds in HSA in 0.1 M reducing agent increases as the maximum initial rotation of $-70°$ has been attained at 0.03M. The relative viscosity increases further and binding data indicate that the number of detergent molecules combined has not reached its maximum even at 0.1 M concentration.

Structural Considerations.—What structural change of the protein is reflected in the constant optical rotation of $-70°$? Since optical rotation in polypeptides is regarded as a function of the degree of secondary organization of the chain, it is reasonable to assume that this value expresses the maximal transformation of the secondary structure caused by the combination with decyl sulfate. The continuing increase in viscosity and in the availability of disulfide bonds for reduction reflects further loosening of the molecule on the level of its tertiary structure. Electrostatic repulsion between neighboring polypeptide segments would be expected to separate these segments and thus to contribute to both viscosity and accessibility of bonds situated in the interior of the molecule. The latter function is more indicative of such a process than is viscosity because of the difficulty of ascertaining how much of the viscosity rise is due just to the increase in molecular volume and asymmetry caused by the attachment of a large number of detergent molecules. Since detergents do not compete for the H-bonds of the secondary structure, the rotation of $-70°$ probably represents the extent to which the secondary structure of HSA can be distorted by charge effects. In this connection it is significant that in preliminary studies on the rotatory dispersion of HSA we found that λ_0, the extrapolated intercept of the curve with the wave length axis in linear Drude plots, was 2660 Å. for both native HSA and the same protein in 8% sodium "lorol" sulfate ($-[\alpha]_D$ 72.0), whereas 10 M urea shifted λ_0 to 2340 Å. If the value of λ_0 is indicative of the degree of secondary structure,[16] this finding would indicate that, unlike urea, the detergent did not interfere extensively with the helical organization.

In this connection it is significant that the optical rotation of HSA in 6 M urea and increasing concentrations of SDeS reaches the plateau of $-81°$ at the same SDeS concentration at which $-70°$ was reached in the absence of urea (Fig. 5). As mentioned before, the binding of detergent measured in the absence of urea continues beyond this concentration; the extent of disruption caused by 6M urea is probably limited therefore not by the number of detergent molecules bound, but by the structural state which is brought about by the amount of detergent bound at the molarity of 0.034.

(16) K. Linderstrøm-Lang and J. A. Schellman, *Biochim. Biophys. Acta*, **15**, 156 (1954).

PHILADELPHIA 46, PA.

[CONTRIBUTION FROM THE U. S. NAVAL MEDICAL RESEARCH INSTITUTE]

The Acetylcholinesterase Surface. VIII. Further Observations on Bifunctional Inhibition of the Enzyme[1]

BY S. L. FRIESS

RECEIVED FEBRUARY 8, 1957

It has been observed that the bifunctional aminoalcohol *cis*-2-dimethylaminocyclohexanol (I) at *p*H 7.4 acts as a mild inhibitor of the acetylcholinesterase system, with an unexpected strength about one order of magnitude greater than that of its methiodide derivative or the natural inhibitor choline. This inhibition appears to be of the reversible, non-competitive type at substrate concentration levels below 4×10^{-3} M, leading to the possibility that the Michaelis–Menten constant at these levels is a true equilibrium constant. This possibility is strengthened by the observation of Jenden, *et al.*, that a bis-quaternary salt III also displays non-competitive inhibition of AChE at the same substrate levels. The order of strength of I has been interpreted in terms of a zwitterion as the effective inhibitory species. Esterase inhibition by I is also found with the frog *rectus abdominis* preparation, with a discrepancy factor between *rectus* and *in vitro* estimations of strength approximating that found for the more potent inhibitor eserine. Further study of the inhibition produced by the bifunctional diamine N-(β-dimethylamino)-ethylpiperidine (II) in the 10^{-4}–10^{-7} M concentration range has revealed a decrease in effectiveness on incubation in glass which appears to depend largely on reaction volume and incubation time. This has been interpreted in terms of sorption on protein and on glass at these low levels, and is in accord with previous observations that appreciable amounts of II readily can be absorbed from solution by such proteins as gelatin and serum components. A further test of the steric requirements of the enzymatic surface between those loci capable of adsorbing the polar functions of inhibitors or substrates has been made with the compound 1,4-diazabicyclo[2,2,2]octane. Kinetic tests indicate that the size of the cage structure of this molecule exceeds the sterically acceptable limits of the surface.

Introduction

In continuation of previous studies designed to probe into chemical and stereochemical aspects of the catalytic regions on the surface of acetylcholinesterase (AChE), with aminoalcohols[2] and diamines[3] being used as bifunctional inhibitors to reveal ele-

(1) The opinions in this paper are those of the author and do not necessarily reflect the views of the Navy Department.

(2) (a) H. D. Baldridge, W. J. McCarville and S. L. Friess, THIS JOURNAL, **77**, 739 (1955); (b) S. L. Friess and H. D. Baldridge, *ibid.*, **78**, 2482 (1956).

(3) (a) S. L. Friess and W. J. McCarville, *ibid.*, **76**, 1363 (1954); (b) S. L. Friess and H. D. Baldridge, *ibid.*, **78**, 199 (1956).

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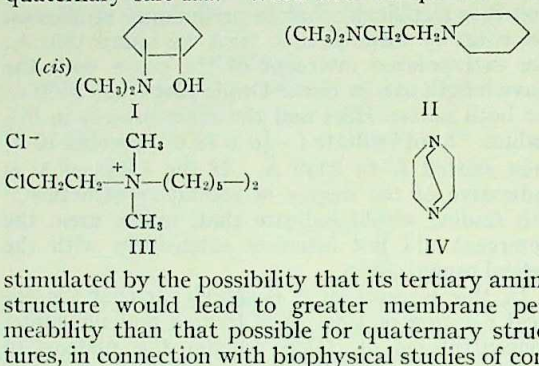
ments of surface detail, the present work deals with certain interesting features of the inhibition produced by the tertiary aminoalcohol I, the substituted ethylenediamines II and IV, and the bis-quaternary salt III. Work with compound I was



stimulated by the possibility that its tertiary amino structure would lead to greater membrane permeability than that possible for quaternary structures, in connection with biophysical studies of conduction in nerve,[4] while that with II was prompted by enzymatic indications[5] that its inhibitory effect at very low concentration levels depended on the time sequence of operations involved in the activity measurements. Experiments with compound III were undertaken to expand the picture of non-competitive inhibition developed with I, while tests of compound IV were made to continue the process of probing the nature of the steric requirements of the intersite surface of AChE.

Results

Inhibition with the Aminoalcohol I.—In the previous studies[2] of the AChE surface using stereospecific inhibitors as test agents it was observed that *cis*-derivatives in the 2-aminocyclohexanol series are in general more potent than the *trans*-isomers. A key intermediate in the preparation of these *cis*-compounds was the aminoalcohol I, and it was of considerable interest to determine whether at *p*H 7.4 compound I possessed any residual inhibitory activity so characteristic of its methiodide.[2] The results of these tests were surprising in several respects.

First, the compound was more active as an inhibitor than might have been expected from its tertiary aminoalcohol structure, with effective inhibition in the concentration range 10^{-4} to 10^{-5} M indicating a strength better by at least one order of magnitude than that displayed[2a] by its methiodide. But of greater interest was the observation that although its inhibition obeys the linear, competitive plot[6] (eq. 1) of v/v_I *vs.* [Inhibitor] at a fixed initial substrate concentration, the slope of this plot appears to be independent of substrate in its concentration range below 4×10^{-3} M. This kind of behavior has been taken[6] as one of the means of distinguishing between competitive and non-competitive inhibition of the reversible type, with the latter obeying an inhibition equation in a form independent of substrate concentration

$$v/v_I = 1 + [I] \frac{K_m}{K_I(K_m + [S]_0)} \qquad (1)$$

v_I = inhibited velocity
K_m = Michaelis–Menten constant
K_I = enzyme·inhibitor dissociation constant

$$v/v_I = 1 + \frac{[I]}{K_I} \qquad (2)$$

The results of v/v_I *vs.* [I] plots using eq. 1 and 2 for inhibition of the AChE–acetylcholine system at two levels of substrate concentration are summarized in Table I below. It is seen that over a twofold substrate range, the competitive K_I values vary by more than a factor of two, but the non-competitive K_I value of $6.0 \pm 0.4 \times 10^{-5}$ is roughly constant as predicted by eq. 2.

TABLE I

COMPETITIVE *vs.* NON-COMPETITIVE INHIBITION PLOTS
*p*H 7.4, 25.14°

Inhibitor	[Substrate]$_0$, $M \times 10^3$	Slope $\times 10^{-4}$ of v/v_I *vs.* [I] Plot	$K_I \times 10^4$ by eq. 1	$K_I \times 10^4$ by eq. 2
I	1.68	1.588 ± 0.027	8.4 ± 0.2	6.3
I	3.41	1.787 ± 0.027	4.0 ± 0.1	5.6
III	1.70	36.34	0.37	0.28
III	3.41	41.88	0.17	0.24

This result is of more than cursory interest in the field of AChE kinetics, in view of the generalization developed by Morales[7] that non-competitive inhibition for an enzyme system requires that the Michaelis–Menten constant K_m be a true equilibrium constant under the given conditions, and hence be a direct reflection of the strength of binding between enzyme and substrate.

Further support is added to this indication of the existence of non-competitive inhibitors by the observations of Jenden and Baldridge[8] on the anti-cholinesterase activity found in a series of bis-quaternary salts. In particular, the decamethylene derivative III was shown to be non-competitive in its inhibitory action, with the degree of inhibition over a given inhibitor range independent of substrate concentration, on the low side of the substrate concentration *vs.* activity profile. These results have been confirmed in the present study, with the data for compound III inhibition summarized in Table I. It is seen that the non-competitive K_I values again are essentially constant on changing initial substrate concentration, in accordance with eq. 2, whereas the competitive K_I values change with substrate level. This finding of non-competitive AChE-inhibitory characteristics in compounds as widely different in structure as I and III would appear to make the general theorem that K_m directly measures AChE–substrate binding, under these conditions, most attractive.

A further interesting comparison was afforded by the experimental evaluation[9] of the AChE-inhibitor dissociation constant for I on a frog *rectus*

(4) J. W. Moore, S. L. Friess and R. H. McCoy, *Federation Proc.*, **13**, Part I, 101 (1954).

(5) Private communications from Dr. D. J. Jenden of these laboratories, and Dr. I. B. Wilson.

(6) P. W. Wilson, "Respiratory Enzymes," H. A. Lardy, ed., Burgess Publishing Co., Minneapolis, Minn., 1949, p. 48.

(7) M. F. Morales, THIS JOURNAL, **77**, 4169 (1955).

(8) D. J. Jenden and H. D. Baldridge, "Dose-Response Relationships in a Series of Bis-quaternary Anticholinesterases," paper presented before the British Pharmacological Society, Edinburgh, July, 1956.

(9) Kindly performed by Dr. D. J. Jenden of these laboratories using the technique described in the paper: D. J. Jenden, *J. Comp. Cell.*

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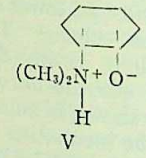
abdominis preparation, in which the effect of the inhibitor on potentiation of the action of acetylcholine through its blockade of tissue-localized enzyme is employed. This determination is somewhat clouded by neuromuscular block which sets in at the higher inhibitor concentrations, but readings of contracture at the lower levels led to a K_I value of about 2.1×10^{-3} at 37°. The ratio of K_I (frog rectus) to K_I (non-competitive) is therefore about 35, which approximates both in magnitude and in direction the discrepancy factor of about 20 found[9] for the competitive inhibitor eserine on comparing the kinetic and frog rectus values. It would appear then that the order of magnitude difference in K_I values afforded by these two techniques does not rest primarily on whether the AChE is inhibited competitively or non-competitively (eserine *vs.* I) or even on whether the inhibitor is comparatively strong (eserine) or moderate (I) in its action. A portion of this difference undoubtedly depends on the temperature difference between the two determinations.

On the point of the absolute inhibitory strength of I, its unexpected power against both isolated enzyme and tissue-localized enzyme has led to scrutiny of its tertiary structure for a clue as to its source of activity. One fruitful suggestion[10] draws upon the special geometry of I in respect to the relatively small (2.5 to 2.9 Å.) separation distance[11] between N and O atoms of the polar functions of I, leading to the possibility of prototropy and a stabilized zwitterion V as the effective inhibitory



V

species. Such a species would fulfill the previous postulated[3a] requirements (a polymethylated, charged N atom and a properly situated locus of high electron density) for strong binding at the bifunctional[12] catalytic unit of the enzymatic surface and account for the observed order of activity of the inhibitor.

Inhibition with the Diamine II.—In continued study of the enzymatic and physical properties of the diamine II, a mild detergency action in dilute solution was noted, leading to some speculation as to the concentration stability with time of the very dilute (10^{-6} to 10^{-7} *M*) solutions used in the inhibition work. Now, inhibition measurements have pointed out some peculiar features of the retention of power of dilute aqueous solutions of II, including an effectiveness varying with the volume of solution in contact with the Pyrex glass of the titration apparatus and with the contact time.

Initial enzymatic indications pointed[5] to a disappearance of effective inhibitory amounts of II in the 5×10^{-7} *M* range and upward on incubation with AChE in dilute buffer for periods of 5 minutes and more, when the reaction volume was of the order of 5 ml. or greater. Since these same concentrations of inhibitor were highly effective[3] in a smaller reaction volume of 3.20 ml., with constancy of action over a relatively long (10–15 minute) time interval, it was of considerable interest to investigate the influence of solution volume and incubation time, with or without enzyme, on the subsequent degree of inhibition of an initially fixed concentration of II.

The water-jacketed, cylindrical titration cell (27 mm. in diameter, 25 mm. deep) fitted with a pair of two-inch Beckman *p*H electrodes, capillary stirrer and microburet could accommodate reaction volumes up to 10 ml., so that for the present comparative study three sets of inhibition determinations at 3.20, 6.40 and 9.60 ml. (1×, 2×, and 3×) volumes were employed to furnish the volume variants. For certain comparisons at fixed enzyme concentration but varying volume it was also necessary to use one-, two- and threefold aliquots (1×, 2× and 3×) of enzyme solution. The initial inhibitor concentration was fixed at 1.1×10^{-6} *M* for the bulk of the determinations, all of which were carried out at *p*H 7.4 and 25.14°. Experiments to determine effects on inhibition were controlled with respect to the aging period in the cell of II dissolved in buffer, before the addition of enzyme (preincubation) and after enzyme addition (postincubation). The results of the total sequence of kinetic determinations are summarized in Table II. Figure 1 presents a representative

TABLE II

AChE-DIAMINE INCUBATION *vs.* INHIBITORY ACTIVITY

Phosphate buffer, *p*H 7.4, 25.14°, $[II]_0 = 1.1 \times 10^{-6}$ *M*, $[\text{Substrate}]_0 = 3.36 \times 10^{-3}$ *M*

Run	Units of enzyme	Total units of reaction vol.	Incubation period (min.) Pre-enzyme	Post enzyme	Inhibition results after substrate addn. Initial inh., %	Duration, min.	Subsequent inh., %
1	1X	1X	0	5	54	3	38
2	1X	1X	5	5	46	5	52
3	1X	1X	5	1	58	>10	
4	1X	1X	30	1	6	>10	
5	1X	2X	0	1	47	4;	
					then 32	10	0
6	1X	2X	0	5	51	2	4
7	1X	2X	5	1	Slight	1	0
8	2X	2X	0	1	58	2	37
9	2X	2X	0	6	57	3	31
10	2X	2X	5	1	16	5	..
11	2X	2X	5	5	2	>10	..
12	1X	3X	0	1	52	5	5
13	1X	3X	5	1	49	4–5	~40
14	1X	3X	15	1	4	>10	..
15	1X	3X	30	1	0	..	..
16	1X	3X	5	5	44	6	0
17	3X	3X	0	1	65	~10	8
18	3X	3X	0	5	<1	..	..
19[a]	1X	2X	0	2	48	~4	0
20[b]	1X	2X	24 hrs.[b]	2	2	..	..

[a] Initial concentration of II, 1.29×10^{-6} *M*. [b] Buffer containing an initial 8.23×10^{-6} *M* concentration of II aged in Pyrex at 4° for 24 hours; an aliquot then placed in the titration cell followed by enzyme and substrate as indicated. Final [II] if no less to glass, 6.68×10^{-6} *M*.

(10) By Dr. S. A. Bernhard of these laboratories.

(11) C. E. McCasland and D. A. Smith, THIS JOURNAL, **72**, 2190 (1950).

(12) D. Nachmansohn and I. B. Wilson, *Advances in Enzymol.*, **12**, 259 (1951).

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comparison of inhibition results at the three volume levels with initial enzyme (1X), substrate and inhibitor fixed, and total incubation times of the order of 5–10 minutes as in runs 3, 6 and 16.

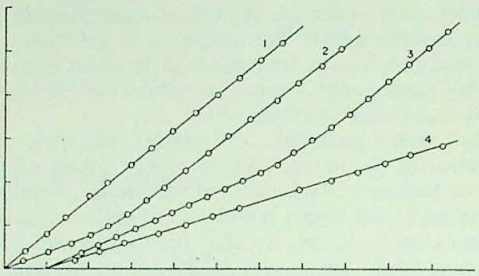

Fig. 1.—Rates of acetylcholine cleavage for: (1) uninhibited hydrolysis at 1× enzyme and 2× volume; (2) inhibited run 6 at 2× volume; (3) inhibited run 16 at 3× volume; (4) inhibited run 4 at 1× volume.

The results of Table II as illustrated in Fig. 1 seem to fit a pattern in which the time sequence of disappearance of inhibitory activity on incubation of a fixed inhibitor concentration depends on the volume of solution involved during the aging process, and also to some extent on the presence of enzyme in solution during this period. For example, keeping all variables constant except volume and time during incubation of inhibitor with buffer, runs 2 and 3 at the 1× volume level show relatively little difference created in the 50% inhibition mark by an additional period of 5 minutes of incubation after enzyme is added; at the 2× volume level (runs 6 and 7) essentially equal 5–6 minute periods of incubation *before or after* enzyme addition lead to the loss of virtually all inhibitory activity; and for the 3× volume (runs 13 and 16) further incubation of 5 minutes after enzyme addition causes a rapid drop to zero inhibition as contrasted with the smaller drop in inhibition when substrate is added 1 minute after enzyme. At both high and low volumes (runs 4, 14 and 15) periods of incubation in buffer ranging from 15 to 30 minutes prior to addition of enzyme are sufficient to lower the percentage inhibition to essentially zero.

The kinetic results at higher (2×, 3×) total amounts of enzyme for the most part show similar decreases in inhibition resulting from short-time incubation periods before or after addition of enzyme. Runs 8, 9, 11, 17 and 18 all show the effects of disappearing inhibition that seems to run to completion within about 15 minutes of total contact time. No order of magnitude differences in speed of disappearance as a function of total amount of enzyme can be detected, although runs 17 and 18 at 3× enzyme appear to show loss of inhibition somewhat more rapidly than runs 8 or 9 at 2× enzyme.

That this loss of inhibition can be completely independent of the presence of the enzyme during the aging process and also free of dependence on the geometry of the cell plus electrode system as incubating space is indicated by the results of run 20, in which aging in buffer for the extended period of 24 hours at 4° of an eightfold higher concentration of II than that in the rest of the runs was permitted to occur in a Pyrex volumetric flask. On pipetting of a sample into the titration cell, followed by the rapid addition of enzyme and substrate, only minimal inhibition was observed.

These results indicate that constancy of inhibition at the 10^{-6} to 10^{-7} M concentration levels generally employed in the *in vitro* enzymatic work with compound II is only to be found at the low volumes previously employed.[3] Further, severe limitations are also necessarily imposed on the preparation and storage of very dilute solutions of II in glass, considering the loss of inhibitory activity resulting from such storage in buffered medium as shown in run 20.

This disappearance of inhibitory activity by II has also been followed at inhibitor concentrations several orders of magnitude higher, with conclusive results following the pattern of those at the lower concentration levels. For example, in a representative set of experiments, a 2× concentration of enzyme in a final reaction volume of 6.40 ml. was subjected to the action of high concentrations of II in a controlled sequence. First, the incubation of enzyme at 25.14° in *p*H 7.4 buffer was allowed to occur in the presence of a 1.20×10^{-4} M concentration of II, for a 30-minute period. Following the addition of acetylcholine substrate (3.36×10^{-3} M) and kinetic assay for activity, it was found that only 42.7% inhibition of the standard activity remained. This value corresponds to the loss of 99.4% of the inhibitory power of II that might have been expected, based on the effectiveness[3a] of the thousand-fold lower concentrations of II in smaller reaction volume. That this effect is essentially independent of any direct denaturing action of II on the enzyme during this extended incubation time was shown in an accompanying experiment in which the incubation of a 1.31×10^{-4} M concentration of II in *p*H 7.4 buffer for 30 minutes prior to the addition of 2× enzyme, followed by addition of enzyme and only 5 minutes of further incubation before assay with substrate, produced virtually the same result; *i.e.*, a 39.4% inhibition of AChE activity which corresponds to a loss of 99.5% of the inhibitory power which the given aliquot of II would possess under high dilution–low volume conditions.

The striking inability of II to cause irreversible damage to the enzyme protein or in turn be irreversibly absorbed by the enzyme with subsequent loss of activity was illustrated by the following, high concentration level experiment. A buffered solution containing 15.6 mg. of enzyme protein (dry weight) and a 1.07×10^{-3} M concentration of II was incubated at 4° for a period of 2.78 hours. It was then placed in a cellophane dialysis sack and dialyzed against the standard *p*H 7.4 buffer in the cold for a period of 15 hours, with frequent changes of buffer to remove II. The residual solution in the sack was then diluted and assayed for total enzymatic activity, with a resulting small deviation (+ 2.7%) from the original standard activity well within the estimated uncertainty of the determination. Accordingly, incubation of the enzyme with even this relatively high concentration of the II results in no significant ir-

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reversible loss of catalytic activity of the recovered protein.

It would appear from these data that the phenomenon of disappearance of inhibition recorded in the low concentration experiments of Table II is not unique to these low levels. It seems likely that it is related to a sorption process of II on both protein and glass, although the latter's ability in this respect is clouded by the observation that the smallest loss of activity occurs at 1× volume, where the surface/volume ratio is greatest.

The inference with respect to possible sorption of II on protein (both catalytic and non-catalytic portions) is supported by previous observations[13] that such polyelectrolyte solutions as diluted cat serum (containing its own serum esterase) or 0.10% gelatin in buffer can cause the disappearance of esterase inhibition to be expected from relatively large concentrations of II, on incubation with the inhibitor prior to kinetic analysis, and the related observation[13] that inhibition of AChE by the monomethiodide of I can be lowered by a factor of 50% after preincubation in the presence of 0.5% bovine serum albumin.

Inhibition with the Diamine IV.—An interesting type of interference with AChE surface binding of diamines of the type II was previously shown[14] in the inhibitory action of the α- and β-methyl substituted derivatives of II. It was observed that substitution of a methyl group on either of the methylene carbons of II seriously lowers the inhibitory activity, with a slight differentiation in effect of α *vs.* β-substitution reflecting a corresponding difference in steric requirements of the enzyme surface lying under these portions of a given adsorbed molecule. In an attempt to probe further into this region of protein surface between the dual sites[12] responsible for binding of the two polar functions of inhibitor or substrate, the compound IV has been prepared[15] as its dihydrochloride and tested for its inhibitory activity on the AChE–acetylcholine system at *p*H 7.4.

With the two nitrogen functions of IV serving for adsorption at the anionic and esteratic sites of AChE (one of the N atoms in all probability being monoprotonated at *p*H 7.4 in view of the nearly fixed pairs of pK_a' values observed[16] for these ethylenediamines) it was thought that the cage or barrel configuration lent to IV by the three N-linking $-CH_2CH_2-$ bridges would lead to a serious bulk problem on attempted adsorption at the protein surface. Models indicated that interference with a surface by the barrel structure of IV might be more serious than with either methylated derivative of II.

In terms of the resulting inhibition produced by adsorption at the catalytic region, this expectation has been fully borne out. It was observed that at *p*H 7.4 and 25.14°, compound IV is completely inactive as an inhibitor of AChE at concentrations ranging up to the high value of 1.1×10^{-2} *M*. Part of this lack of inhibitory activity may perhaps be due to a lack of methyl groups *per se* on the positively charged N atom, to lend additional binding strength *via* van der Waals interaction with the anionic site,[12] but the completeness of the phenomenon indicates that bifunctional adsorption to the surface over a region where chain-linked methyl groups interfere is entirely obviated by the steric requirements of the cage in IV.

Experimental

Kinetic determinations of enzymatic activity at 25.14 ± 0.03° and *p*H 7.4 were carried out by the constant-*p*H titration technique previously described.[3a] The enzyme preparations from electric eel tissue[17] assayed at 1.02×10^4 and 6.97×10^3 μmoles acetylcholine hydrolyzed/hr./mg. of dry weight protein at the substrate optimum of 3.3×10^{-3} *M*. Doubly recrystallized acetylcholine chloride, triply distilled water and a freshly distilled sample of II were used throughout. The aminoalcohol I was a freshly distilled sample prepared as in the previous work,[2] with m.p. 34–35°. The poorly poised buffer employed was 0.015 *M* in phosphate, 0.10 *M* in NaCl and 0.01 *M* in $MgCl_2$, and adjusted to *p*H 7.4. Compounds III and IV dihydrochloride were freshly recrystallized before use.

Incubations at any given volume level were carried out in the thermostated cell with constant stirring. Following completion of the final incubation after addition of the desired aliquot of enzyme, an aliquot of freshly prepared substrate solution was added and kinetic measurements started within one minute's time. Non-inhibited reference runs at the higher total amounts of enzyme (especially 3×) showed a pronounced tendency to decelerate slightly after some 5–10 minutes of reaction time, whereas hydrolysis rates at the 1× and 2× levels by and large remained quite constant with time over the 10–20% extent of reaction studied. The unit of enzyme designated as IX amounted to 6.2×10^{-4} mg. of protein on the dry weight basis in runs with II.

Rate runs with and without inhibitor were in general reproducible to within ±5%. K_I values were obtained from least-squares evaluation of the slopes of v/v_I *vs.* [I] plots, with a K_m value of 2.6×10^{-4} for these experimental conditions being employed in the slope calculations from eq. 1. The values tabulated were for a fixed temperature of 25.14 ± 0.03°.

Acknowledgment.—We are indebted to Dr. H. S. Polin for his generous aid in procurement of electric eel tissue and its initial extracts, to Dr. D. J. Jenden for the frog rectus assay, and to Mr. P. A. French for technical assistance.

BETHESDA, MD.

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[CONTRIBUTION FROM THE SECTION ON METABOLISM, LABORATORY OF CELLULAR PHYSIOLOGY AND METABOLISM, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Studies on the Mechanism of Enzymatic Decarboxylation[1a]

BY SIMON ROTHBERG[1b] AND DANIEL STEINBERG

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A number of bacterial decarboxylases (aspartic acid, glutamic acid, tyrosine, malonic acid) were investigated in an attempt to determine the role of the carboxyl group in decarboxylation. Decarboxylations were carried out in the presence of H_2O^{18} and the evolved carbon dioxide was examined for oxygen-18 enrichment. There was very little enrichment and this was attributable to exchange reactions occurring even in the absence of decarboxylation. The level of enrichment was in any case too low to support any mechanism in which the water oxygen is stoichiometrically involved. The carbon dioxide evolved appears to be derived exclusively from the substrate with no labilization of the oxygen atoms. Similar results were found in the non-enzymatic metal catalyzed decarboxylation of oxalacetic acid. The results are compatible with the mechanism of Metzler, Ikawa and Snell[40] which proposed a non-hydrolytic cleavage of carbon–carbon bond with the release of the carboxyl group intact. The linkage of the carboxyl group to the enzyme surface may be electrostatic or possibly in the form of an ester, but an acyl intermediate is ruled out.

The mechanism of enzymatic amino acid decarboxylation has been the subject of a number of studies.[2–5] It appears to be well established that pyridoxal phosphate is an obligatory coenzyme for most, if not all, amino acid decarboxylases and that this coenzyme is tightly bound to the enzyme surface.[6–9] The decarboxylases are stereospecific[10] and one of the enzyme–substrate points of attachment is accounted for by the formation of a Schiff base between the α-amino group of the substrate and the aldehyde group of the bound coenzyme, as proposed originally by Werle and coworkers.[2a] More recent studies by Mandeles, Koppleman and Hanke,[3,5] showing that only one atom of deuterium from D_2O becomes incorporated into the product amine, led to a revision (proposed with F. Westheimer) of the Werle scheme with respect to the nature of the intermediate forms but the involvement of a Schiff base intermediate was confirmed.

In none of the studies to date has the possible involvement of the carboxyl group in enzyme–substrate complex formation been specifically investigated. Substrate specificity studies indicate that the carboxyl group must be free for scission of the C_1–C_2 bond and there is thus, presumably at least, an electrostatic binding of the carboxyl group to the enzyme. The present studies were undertaken in an attempt to further define the mechanism of decarboxylation by determining to what extent the oxygen atoms of the carboxyl group are labilized during the reaction and to what extent oxygen atoms of water in the medium participate in the CO_2 formation. Four bacterial amino acid decarboxylases and the malonic acid decarboxylase of *Pseudomonas fluorescens* were investigated. In addition, the metal catalyzed decarboxylation of oxalacetic acid was examined as a model of non-enzymatic decarboxylation.

Materials and Methods

Enzyme Preparation and Enzyme Assays.—*Clostridium welchii S.R. 12.* ATCC #8009 was grown and lyophilized as described by Meister and co-workers.[11] Reference is always to the dried cells of *Clostridium welchii* unless otherwise specified.[12] *Escherichia coli* ATCC #11246 was grown, harvested and an acetone powder prepared as described by Najjar and Fisher.[13]

Streptococcus faecalis R. cultured by the method of Gale[14] was used as an acetone dried powder.[12]

Pseudomonas fluorescens 23 was prepared as described by Hayaishi and Stanier[15] and purified as described by Hayaishi and Fraser.[16]

Enzyme activities were determined manometrically in the Warburg apparatus at 37° according to standard procedures.[17]

Partial Purification of Glutamic Acid Decarboxylase from *Clostridium welchii*.—Dried cells were ground with three aliquots of Alumina (Alcoa A-301) in a mortar. The material was centrifuged 20 minutes at 18,000 × g in a Servall angle-head centrifuge. The supernatant was brought to 80% saturation by the addition of solid ammonium sulfate. The sediment was separated and redissolved in water. This was divided into three crude fractions by ammonium sulfate precipitation—a fraction precipitated at 40% saturation (f_1), a fraction precipitated between 40 and 55% saturation (f_2), and the fraction soluble at 55% saturation (S_3). All fractions were dialyzed 18 hours against distilled water. The fractionations and dialyses were carried out at about 4°.

CO_2 Collection Technique.—A major technical problem was the elimination or minimizing of non-enzymatic exchange between CO_2 and H_2O^{18} during and subsequent to decarboxylation. A number of experimental arrangements were tried and discarded because of the considerable and variable non-enzymatic exchange observed. The extent of such exchange in closed vessels of various sizes and shapes

(1) (a) Based on a thesis submitted to the Graduate faculty of Georgetown University by Simon Rothberg in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Presented in part before the Division of Biological Chemistry, A.C.S., Atlantic City, Sept. 1956. (b) Dermatology Service, General Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, Md.

(2) (a) E. Werle and K. Heitzer, *Biochem. Z.*, **299**, 420 (1938); (b) E. Werle and W. Koch, *ibid.*, **319**, 305 (1949).

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is indicated in Table I.[18] It will be noted that the extent of exchange was a direct function of the surface area of the liquid phase and an inverse function of the over-all volume of the vessel. From these studies it was clear that it would be necessary to remove the CO_2 from the H_2O^{18}-containing reaction vessel as rapidly as formed to reduce non-enzymatic enrichment. A system in which N_2 was constantly bubbled through the reaction vessel and into a CO_2 trap was tried but proved unsuitable. The experimental conditions finally settled on and used in all the experiments reported here virtually eliminated non-enzymatic enrichment by (1) removing the gas rapidly from the reaction vessel into a large collection bulb, (2) shortening the reaction time to a minimum necessary to obtain enough CO_2 for mass spectrometry and (3) running the decarboxylations at 25° instead of 37°.

TABLE I

NON-ENZYMATIC H_2O^{18}–CO_2 EXCHANGE AT 37°

Expt.	Vessel[a]	Vol. of vessel cc.	Vol. H_2O, cc.	Mole ratio H_2O/CO_2	% Enrichment at 15 min.	30 min.	45 min.	60 min.
18	A	7.685	1.0	844	10.2	16.9	28.0	38.6
29	B	9.848	1.0	944	26.5	50.2	66.3	..
30	B	9.848	1.0	1125	28.6	53.8	69.7	..
41	C	24.04	1.0	4320	7.4	13.2	18.4	..
42	C[1]	24.04	1.0	3550	12.1	25.2	36.8	..
44	D	236	2.0	8460	3.7	8.1	11.8	15.8

[a] The shapes and dimensions of the vessels used were as follows: A, simple equilibration tube—10 mm. × 135 mm.; B, simple equilibration tube—10 mm. × 135 mm. with bottom blown to diameter of 15 mm.; C, modified double-arm Sprinson-Rittenberg tube—1.0 cc. of H_2O^{18} all in one arm; C[1], same tube as in C, but 0.5 ml. H_2O^{18} in each arm; D, modified Sprinson–Rittenberg tube with 200-cc. bulb separating vacuum stopcock and arms.

Apparatus.—The *reaction vessel* used was a spherical 25-ml. flask containing the enzyme, H_2O^{18} and a magnetic stirrer. An *addition tube*, fitted to the reaction vessel with a standard taper joint, contained substrate, buffer and H_2O^{18}. The reaction vessel was connected through an over-flow trap and a manifold system to a series of 500-ml. *collection bulbs* fitted with vacuum stopcocks. The entire system, including the collection bulbs, was degassed and at time zero the contents of the *addition tube* were dumped into the *reaction vessel*. The CO_2 liberated during successive time intervals was collected in separate 500-ml. bulbs. When the collection bulb stopcock was closed at the end of a collection period Dry Ice was brought up beneath the bulb to condense water in an effort to minimize any continuing non-enzymatic exchange. Storing the gas in the collection bulb for as much as four hours under these conditions did not increase the enrichment. The special glassware used was fabricated at the glass shop, Instrument Section, National Institutes of Health.

Isolation and Purification of Products.—The decarboxylation was halted by immersion of the reactor tube in Dry Ice-alcohol. The reaction mixture was then thawed, centrifuged at 2° for 15 minutes at 3000 r.p.m. and the supernatant was immediately removed, frozen and lyophilized. Aliquots were streaked on specially washed[19] Whatman #3 paper and chromatographed ascending in 70% propanol: water in a tank 12" high by 9" in diameter. The partition was allowed to go for about seven hours and the paper was dried in a circulating oven at 65° for 15 minutes. The amino acid fractions eluted by water were lyophilized and the dried material was stored in a desiccator over $CaSO_4$.

Preparation of O^{18}-Organic Compounds for Mass Spectrometry.—The O^{18}-content of substrates and products was in every case determined by analysis of CO_2 derived from them. Two different pyrolysis techniques were employed for converting the oxygen of organic compounds quantitatively to carbon dioxide. The first, that of Doering and Dorfman,[20] was used only in the early part of the work. The second, that of Rittenberg and Pontocorvo,[21] was used for most of the studies reported here. The purified, dry compounds were pyrolyzed at 350° for 30 minutes with dried $HgCl_2$ as a catalyst.

The O^{18}-content of water[22] was determined by equilibration with carbon dioxide as described by Cohn and Urey.[23]

Mass Spectrometry.[24]—The O^{18}-content of the carbon dioxide liberated in decarboxylation experiments and that obtained in equilibration experiments was measured by obtaining the ratio of mass 46 to mass 44.[25,26]

Tank carbon dioxide[27] was obtained by passing the gas through a Dry Ice–alcohol trap and collecting in a bulb previously evacuated to better than 10^{-4} mm. Although ten micromoles of gas was necessary for optimal operational conditions, an accurate ratio could be determined with as little as one micromole of gas. The reproducibility of a ratio on the same sample was ±0.5%. Thus for a sample with 0.2 atom % excess O^{18} the maximum error was of the order of 1%.

In the manifold collection system, the gas in the 500-cc. bulb was passed through two traps, the first immersed in Dry Ice–alcohol and the second in liquid nitrogen. The carbon dioxide admitted to the inlet system passed back again through the first trap.

A special breakoff leading to the inlet system of the mass spectrometer[28] accommodated the tube used in the Rittenberg–Pontocorvo pyrolysis procedure.[21] The Dry Ice–alcohol non-condensable gases were passed into a quinoline trap and allowed to react so as to effect complete removal of HCl. The CO_2 was passed through a Dry Ice–alcohol trap and admitted to the inlet system of the spectrometer.

Results and Discussion

Control Experiments.—The degree of O^{18}-enrichment in CO_2 expected on the basis of factors other than the decarboxylation process itself was determined in control studies like those shown in Table II. Tank CO_2 was incubated with an approximately equimolar amount of product (γ-aminobutyric acid) under conditions otherwise paralleling those used in subsequent decarboxylation experiments. A sample of CO_2 taken at six minutes showed 4.8% enrichment. Omitting enzyme from the incubation did not decrease the rate of enrichment, showing that it was not attributable to a catalytic activity of *Cl. welchii*, but rather to non-enzymatic H_2O^{18}–CO_2 exchange. The somewhat greater enrichment observed in the second experiment probably is due to the use of a smaller quantity of CO_2.

In these experiments CO_2 was present in the gas phase *above* the medium throughout the incubation whereas in the decarboxylation experiments the gas is continuously formed *within* the H_2O^{18} medium during the incubation. As a control more nearly approximating the actual experimental conditions

(18) Throughout this paper the degree if O^{18} enrichment of substrates and products is expressed as a percentage of that expected if equilibration with the H_2O^{18} of the medium employed were complete:

$$\% \text{ enrichment} = \frac{\text{atoms \% excess } O^{18} \text{ in compd.}}{\text{atoms \% excess } O^{18} \text{ in } H_2O^{18} \text{ of medium}} \times 100.$$

(19) The Whatman #3 paper was prepared by percolation in water for four days and then in alcohol for four additional days. This was found to be necessary because of water-soluble oxygen-containing impurities in the paper as supplied.

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TABLE II

% ENRICHMENT OF CARBON DIOXIDE IN CONTROL EXPERIMENTS

System: reaction vessel—106 mg. *Clostridium welchii*, 12.8 mg. γ-aminobutyric acid, 130 μmoles tank carbon dioxide. Addition tube—1.8 cc. H_2O^{18} (1.276 atoms % excess—final), 0.2 cc. 3 *M* acetate buffer (*p*H 4.9)

Time (min.)	6[a]	9[a]
% enrichment	4.8	7.8
% enrichment/min.	0.80	0.86
μmoles gas in sample	116	14

System: reaction vessel—13 mg. γ-aminobutyric acid, 65μ moles tank carbon dioxide. Addition tube—1.8 cc. H_2O^{18} (1.276 atoms % excess—final), 0.2 cc. 3 *M* acetate buffer (*p*H 4.9)

Time (min.)	6[a]	9[a]
% enrichment	5.7	11.4
% enrichment/min.	0.94	1.27
μmoles gas in sample	58	7

[a] CO_2 samples were withdrawn from the reaction flask at the end of the sixth and ninth minute of reaction.

the enrichment of CO_2 formed by addition of H_2O^{18}-containing acetate buffer (*p*H 4.9) to sodium bicarbonate was studied. The CO_2 derived in this manner had less than 0.5% enrichment.

The non-enzymatic, metal-catalyzed decarboxylation of oxalacetic acid was studied, again under conditions similar to those used in the subsequent enzymatic experiments and with a rate of decarboxylation approximately the same as that in the enzymatic experiments. The enrichment observed in the CO_2 was less than 5% and probably can be attributed to CO_2–H_2O^{18} exchange occurring *subsequent* to the decarboxylation process.

Glutamic Acid Decarboxylation.—The glutamic acid decarboxylase of *E. coli* gave CO_2 in which the % enrichment was less than 5% (Table III),

TABLE III

% ENRICHMENT OF CARBON DIOXIDE OBTAINED FROM L-GLUTAMIC ACID IN ENZYMATIC DECARBOXYLATION WITH *E. coli*.

Expt.	Temp., °C.	Time, min.	% Enrichment
120	25	1	2.7
121	25	0.5	4.2

as in the control experiments just described. The % enrichment in CO_2 formed by the action of the glutamic acid decarboxylase of *Cl. welchii* was somewhat higher and varied considerably from experiment to experiment, ranging from 5.9 to 12.8 (Table IV).

TABLE IV

% ENRICHMENT OF CARBON DIOXIDE OBTAINED FROM L-GLUTAMIC ACID IN ENZYMATIC DECARBOXYLATION WITH *Cl. welchii*.

Expt.	Temp., °C.	Time, min.	% Enrichment
60	25	1	7.7
64	25	1	5.9
76	25	5	12.8
83	25	3	11.5
92	25	1	7.4

While the enrichment observed in these experiments was well below that anticipated for any stoichiometric involvement of water in the decarboxylation process, as discussed later, it was nevertheless well above that anticipated from the control experiments on non-enzymatic CO_2–H_2O^{18} exchange.

The possibility of accelerated CO_2–H_2O^{18} exchange due to the presence of carbonic anhydrase in the preparation was considered. However, repetition of the experiments in the presence of 0.05 *M* Diamox, an effective inhibitor of carbonic anhydrase,[29] did not decrease the observed enrichment.

Non-enzymatic enrichment of unreacted substrate was ruled out by control incubations of glutamic acid and H_2O^{18}-containing medium under several different conditions. After 30 minutes incubation at 25° glutamic acid was reisolated from the medium by paper chromatography and O^{18} enrichment determined after pyrolysis. At *p*H 3.75 there was no measurable enrichment but at *p*H 1.5 there was 3.9% enrichment. Under the conditions used in the decarboxylation studies (*p*H 4.9), omitting only the enzyme, the glutamic acid substrate showed only 0.8% enrichment.

In the next experiments unreacted substrate and reaction product were isolated after 6 minutes incubation with *Cl. welchii* or with partially purified enzyme under the usual conditions. Both glutamic acid and γ-aminobutyric acid were found to be enriched in O^{18}. The relative enrichment in glutamic acid was 24.2 and 33.8% in two incubations. Because of the presence of endogenous γ-aminobutyric acid in the enzyme preparation, enrichment in the product could not be readily quantitated. However, the very high % enrichment in the unreacted glutamic acid under conditions in which the CO_2 liberated by the decarboxylase showed only up to 12.8% enrichment indicates that the γ-carboxyl group must be most heavily enriched. The O^{18} in the CO_2 most probably is due to enrichment in the α-carboxyl group catalyzed by one or more enzymes in the crude *Cl. welchii* preparation.

Incubations of the complete system were carried out in the presence of 0.01 *M* hydroxylamine, a concentration sufficient to inhibit completely the glutamic acid decarboxylase, probably by complexing with the coenzyme.[30] Despite the complete inhibition of the decarboxylation reaction, examination of the unreacted glutamic acid showed that enrichment had proceeded at about the same rate as in the fully active system (enrichment, 26.9%). This strongly suggests that the observed substrate enrichment is not catalyzed by the glutamic acid decarboxylase itself but rather by other enzymes in the *Cl. welchii* preparation. The possibility that the decarboxylase, while incapable of splitting off CO_2 in the presence of hydroxylamine, is still capable of catalyzing an exchange reaction cannot be ruled out, however. The observed substrate enrichment could be due to reversible reactions such as amide formation and splitting; it could also be due to a "virtual reaction" of the type catalyzed by chymotrypsin in the studies of Doherty and Vas-

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low[31] and observed in several other enzymatic systems.[32–35]

Aspartic Acid Decarboxylation.—The CO_2 derived from decarboxylation of aspartic acid by *Cl. welchii* showed considerably higher % enrichment than that derived from the action of glutamic acid decarboxylase (Table V).

TABLE V

% ENRICHMENT OF CARBON DIOXIDE OBTAINED FROM L-ASPARTIC ACID DECARBOXYLATION IN ENZYMATIC DECARBOXYLATION WITH *Cl. welchii*

Expt.	Temp., °C.	Time, min.	% Enrichment
94	25	5	22.7
95	25	1	19.0
96	25	3	17.4

Again, however, the enrichment observed was less than that anticipated for a reaction involving a stoichiometric contribution from water oxygen. Examination of unreacted aspartic acid again revealed considerable substrate enrichment but the product, α-alanine,[11] was free of O^{18}, indicating that the exchange was limited to the β-carboxyl group.

As in the case of the glutamic acid decarboxylase, enrichment of substrate proceeded even in the presence of inhibitory concentrations of hydroxylamine, suggesting that the exchange was catalyzed by an enzyme or enzymes other than the decarboxylase itself. Further evidence for this was obtained by partial purification of the enzyme system. The fraction between 40 and 55% ammonium sulfate saturation (f_2), which was rich in glutamic acid decarboxylase activity, contained little or no aspartic acid decarboxylase activity. This fraction nevertheless was active in catalyzing enrichment of aspartic acid.

Tyrosine Decarboxylation.—CO_2 derived from decarboxylation of tyrosine by *Strep. faecalis* under conditions similar to those used above showed 8 to 12.2% enrichment. Substrate was not examined for possible enrichment.

Malonic Acid Decarboxylation.—This reaction has been studied by Gray[36] and Hayaishi[37] and has been shown to be a coenzyme-A dependent reaction. Wolfe and Rittenberg proposed that a malonyl-di-coenzyme-A complex plays a catalytic role and by a transfer reaction yields a monosubstituted derivative which is the form decarboxylated. Studies by Hayaishi suggest that only one of the carboxyl groups becomes conjugated with coenzyme A.

In the present studies decarboxylation in the presence of H_2O^{18} led to the formation of CO_2 with only 10.1 and 14.2% enrichment. The results are compatible with the different mechanisms proposed by Hayaishi[38] and Wolfe and Rittenberg[39] and indicate that the CO_2 originates from the carboxyl group beta to the coenzyme-A activated group.

Discussion

There are several mechanisms by which the carboxyl group might be involved in enzyme–substrate complex formation prior to decarboxylation. A number of these, listed below, should be readily distinguishable on the basis of enrichment in the CO_2 when decarboxylation proceeds in the presence of H_2O^{18} (Fig. 1).

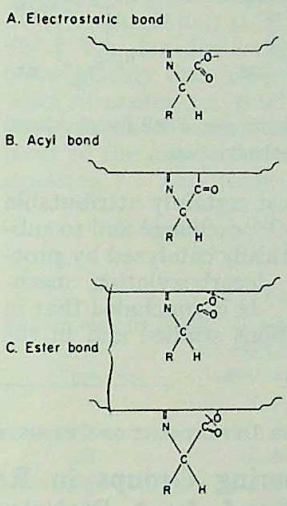

Fig. 1.—Possible modes of bonding between carboxyl group and enzyme surface.

1. Formation of an acyl–enzyme bond. Cleavage should yield CO_2 with one-half the atoms % excess O^{18} of that in the H_2O^{18} of the medium, *i.e.*, relative *per cent. enrichment*, 50.

2. Formation of an ester–enzyme bond. Cleavage on one side of the ester oxygen could yield CO_2 free of O^{18}; cleavage on the other side would yield CO_2 with 50% enrichment.

3. Exclusively electrostatic bonding to the enzyme surface. Elimination of CO_2 by simple carbon–carbon bond scission would result in no enrichment.

4. In each of the above schemes additional enrichment might occur due to hydration either before or after splitting off of CO_2. For example, in case 1 above, hydration of the CO_2 released from enzyme–substrate combination with 50% enrichment would enrich it further so that the CO_2 as collected would show 66⅔% enrichment. The expected enrichment would be the same if hydration of the enzyme–substrate complex occurred prior to CO_2 release.

In none of the five decarboxylation reactions studied did the enrichment of the released CO_2 approach the levels predicted for stoichiometric involvement of water oxygens in the mechanism. The minimal enrichment observed in the case of

(31) D. G. Doherty and F. J. Vaslow, THIS JOURNAL, **74**, 931 (1952).
(32) F. Vaslow, *Biochem. Biophys. Acta*, **16**, 601 (1955).
(33) D. B. Sprinson and D. Rittenberg, *Nature*, **167**, 484 (1951).
(34) R. Bentley and D. Rittenberg, THIS JOURNAL, **76**, 4883 (1954).
(35) S. S. Stein and D. E. Koshland, Jr., *Arch. Biochem. Biophys.*, **39**, 220 (1952).
(36) C. T. Gray, *J. Bact.*, **63**, 813 (1952).
(37) O. Hayaishi, THIS JOURNAL, **75**, 4367 (1953).
(38) O. Hayaishi, *J. Biol. Chem.*, **215**, 125 (1955).
(39) D. E. Wolfe and D. Rittenberg, *ibid.*, **209**, 885 (1954).

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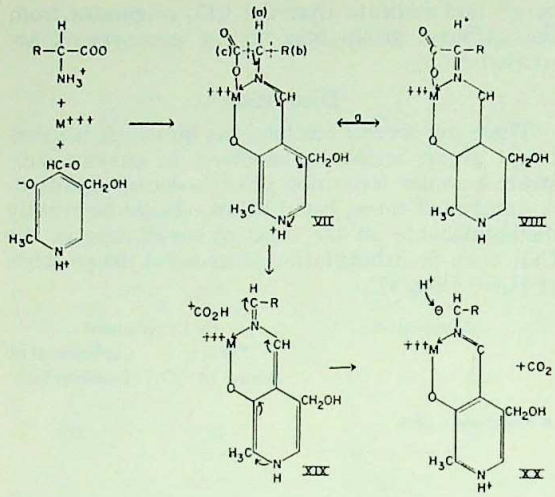

Fig. 2.—Scheme of Metzler, Ikawa and Snell for pyridoxal catalyzed decarboxylation.

some of the studies is almost certainly attributable to non-enzymatic CO_2–H_2O^{18} exchange and to substrate enrichment enzymatically catalyzed by processes independent of the decarboxylation mechanism, as discussed above. It is concluded that in all of the enzymatic reactions studied and in the metal-catalyzed decarboxylation of oxalacetic acid as well, the carboxyl group is released intact by simple cleavage of a carbon–carbon bond. Water does not appear to play a role in the CO_2-release mechanism nor does the CO_2 equilibrate with water in the course of the reaction except at the rate anticipated for non-enzymatic CO_2–H_2O^{18} exchange.

On the basis of these studies it is possible to rule out any of the mechanisms described above which would result in enrichment of the CO_2. The results are compatible with the mechanism recently proposed by Metzler, Ikawa and Snell on the basis of their studies of pyridoxal phosphate catalyzed reactions.[40] These workers propose that the formation of an amino acid–pyridoxal complex as shown in Fig. 2, with the carboxyl group involved only electrostatically can weaken the carboxyl carbon–α-carbon bond by electromeric displacement of electrons to the heterocyclic nitrogen. The enzyme or an enzyme–metal complex[41] is presumed to be equivalent to the simple metal ion used in the non-enzymatic model experiments. The present results show that splitting of this carbon–carbon bond does not involve water and that the carboxyl group is released intact.

(40) D. E. Metzler, M. Ikawa and E. E. Snell, THIS JOURNAL, **76**, 648 (1954).

(41) B. M. Guirard and E. E. Snell, *ibid.*, **76**, 4745 (1954).

BETHESDA, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Role of Neighboring Groups in Replacement Reactions. XXII. Competition between *o*-MeO-5 and Ar_1-3 Participation in Solvolysis of *o*-Methoxyneophyl Toluenesulfonate[1,2]

BY R. HECK, J. CORSE, E. GRUNWALD AND S. WINSTEIN

RECEIVED JANUARY 7, 1957

Solvolysis of *o*-methoxyneophyl *p*-toluenesulfonate involves two competing anchimerically assisted ionization processes. One of the ionization modes is the Ar_1-3-assisted one; the other involves *o*-MeO-5 participation. From Ar_1-3-assisted ionization, rearranged substitution and elimination products are obtained. From *o*-MeO-5-assisted ionization is obtained mainly 3,3-dimethyl-4,5-benzodihydrofuran. From the composition of the isolated products it is possible to dissect the first-order rate constants of acetolysis and formolysis into component k_Δ^{Ar} and k_Δ^{OMe} values corresponding to each of the anchimerically-assisted ionizations. The ratio, $k_\Delta^{OMe}/k_\Delta^{Ar}$, is quite sensitive to the nature of the solvent, being much smaller in formic than in acetic acid. Ar_1-3-assisted ionization of *o*-methoxyneophyl toluenesulfonate is unusually slow in comparison with the *p*-isomer, while *o*-MeO-5-assisted ionization is approximately as fast as that of δ-methoxybutyl toluenesulfonate.

In solvolysis of 2-*o*-anisylethyl *p*-toluenesulfonate (I), there is no indication[3] of substantial competition of *o*-methoxyl participation, in the sense of I → II, with Ar_1-3[4] participation to yield III. On the other hand, with *o*-methoxyneophyl toluenesulfonate (VII), *o*-MeO-assisted ionization competes very successfully with the Ar_1-3-assisted process. The results obtained in a study of this solvolysis are now reported and discussed.

(1) Research supported by the Office of Naval Research.

(2) Some of the material of this paper has been reported in summary by S. Winstein at the Symposium on Dynamic Stereochemistry of the Chemical Society, Manchester, England, March 31, 1954 [*Chemistry & Industry*, 562 (1954)].

(3) S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, THIS JOURNAL, **75**, 147 (1953).

(4) (a) S. Winstein, R. Heck, S. Lapporte and R. Baird, *Experientia*, **12**, 138 (1956); (b) R. Heck and S. Winstein, THIS JOURNAL, **79**, 3105 (1957).

Results

***o*-Methoxyneophyl *p*-Toluenesulfonate.**—The *o*-methoxyneophyl alcohol was obtained from the sequence of reactions previously employed for neophyl alcohol[5,6] itself. This sequence involves formation of the neophyl chloride from methallyl chloride and anisole, followed by oxidation of the Grignard reagent of the chloride. Originally, the sequence of reactions was employed with the intention of preparing *p*-methoxyneophyl alcohol.[7] However, alkylation of anisole with methallyl

(5) F. C. Whitmore, C. A. Weisgerber and A. C. Shabica, Jr., *ibid.*, **65**, 1469 (1943).

(6) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse, *ibid.*, **74**, 1113 (1952).

(7) S. Winstein and R. Heck, *ibid.*, **78**, 4801 (1956).

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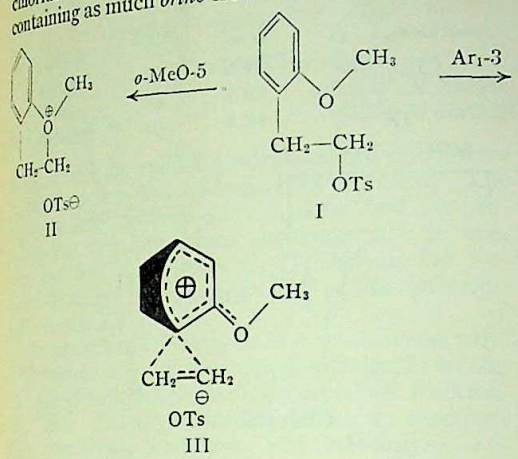
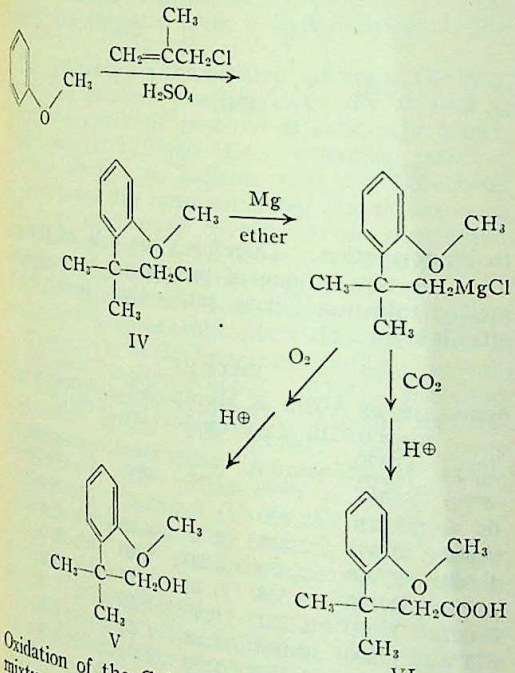
chloride and sulfuric acid yields a chloride mixture containing as much *ortho* isomer IV as *para*.



Carbonation of the Grignard reagent of the chloride mixture gave an acid mixture from which approximately equal quantities of β-*p*-anisylisovaleric and β-*o*-anisylisovaleric (VI) acids were isolated.



Oxidation of the Grignard reagent gave rise to a mixture of methoxyneophyl alcohols which led to an inseparable mixture of *p*-nitrobenzoates. Fortunately, the *p*-toluenesulfonate of *o*-methoxyneophyl alcohol (V) is considerably higher melting and less soluble than the *p*-isomer,[7] so that it was possible to obtain a *ca.* 50% yield of pure *o*-methoxyneophyl *p*-toluenesulfonate (VII) from the methoxyneophyl alcohol mixture.

Kinetics of Solvolysis.—The *o*-methoxyneophyl *p*-toluenesulfonate exhibited good first-order behavior in ethanolysis and formolysis, the pertinent rate constants being summarized in Table I. As indicated in Table I, nearly theoretical infinity titers were observed in ethanol and formic acid solvents.

TABLE I

SOLVOLYSIS RATES OF *o*-METHOXYNEOPHYL *p*-TOLUENESULFONATE

Solvent	Added salt	Temp., °C.	[ROTs], 10²*M*	% ∞	*k*, sec.⁻¹
EtOH		75.00	3.60	98.2	(1.43 ± 0.03) × 10⁻⁴
HOAc		48.90	0.83	56.0	(2.63 ± .08) × 10⁻⁵[a]
HOAc		74.81	1.44	63.2	(4.26 ± .05) × 10⁻⁴[a]
HOAc		75.00	2.87	63.4	(4.21 ± .10) × 10⁻⁴
HOAc	0.0310*M* NaOAc	75.00	2.74	96.4	(4.88 ± .04) × 10⁻⁴
HCOOH		25.00	2.94	99.3	(1.33 ± .01) × 10⁻⁴
HCOOH	0.0317*M* NaOCHO	25.00	2.63	98.4	(1.37 ± .01) × 10⁻⁴

[a] $\Delta H^{\ddagger} = 23.2$ kcal./mole; $\Delta S^{\ddagger} = -7.5$ e.u.

In acetic acid solvent, the solvolysis of *o*-methoxyneophyl toluenesulfonate (VII) appeared to stop at 63% completion at 75° and at a smaller figure at 49°. The data for a typical acetolysis which gave a low infinity titer are given in Table II. In these cases of acetolysis, good first-order rate constants were obtained when these were calculated on the basis of the experimental infinity titers employing equation 1. This point is illustrated in Table II.

$$2.303 \log \left[\frac{(\mathrm{HOTs})_\infty - (\mathrm{HOTs})_0}{(\mathrm{HOTs})_\infty - (\mathrm{HOTs})}\right] = kt \qquad (1)$$

TABLE II

ACETOLYSIS OF 0.0287 *M* *o*-METHOXYNEOPHYL *p*-TOLUENESULFONATE AT 75.00°

Time, sec.	NaOAc soln., ml.[a]	10⁴*k*, sec.⁻¹
0	0.510	
180	.694	4.22
480	.972	4.19
840	1.290	4.38
1440	1.675	4.27
3060	2.300	3.99
5160	2.680	(3.73)
∞	3.050	
∞ calcd.	4.808	
	Mean	4.21 ± 0.10

[a] Per 5-ml. aliquot.

The inclusion of 0.03 *M* sodium acetate in the glacial acetic acid solvent brought the infinity titer nearly to the theoretical value, the first-order rate constant being slightly increased (Table I).

The low infinity titers observed in acetolysis appear to be connected with the formation of methyl toluenesulfonate. This substance solvolyzes[8] at a rate one-five-hundreth of that of the *o*-methoxyneophyl ester, explaining why the low infinity titer in acetolysis was relatively constant over many solvolytic half-lives of the *o*-methoxyneophyl toluenesulfonate. A rough determination of the rate constant of acetolysis of the slow material remaining after the first infinity titer was reached gave a value approximately equal to the previously[8] reported value for methyl toluenesulfonate.

It is clear that no significant amount of methyl *p*-toluenesulfonate is being formed in ethanolysis because the rate constant for *o*-methoxyneophyl *p*-toluenesulfonate is twice that for methyl *p*-toluenesulfonate.[8] A drifting rate constant would have been observed if methyl *p*-toluenesulfonate were formed. Also, there can be no formation of

[8] S. Winstein, C. Hanson and E. Grunwald, THIS JOURNAL, **74**, 1120 (1952).

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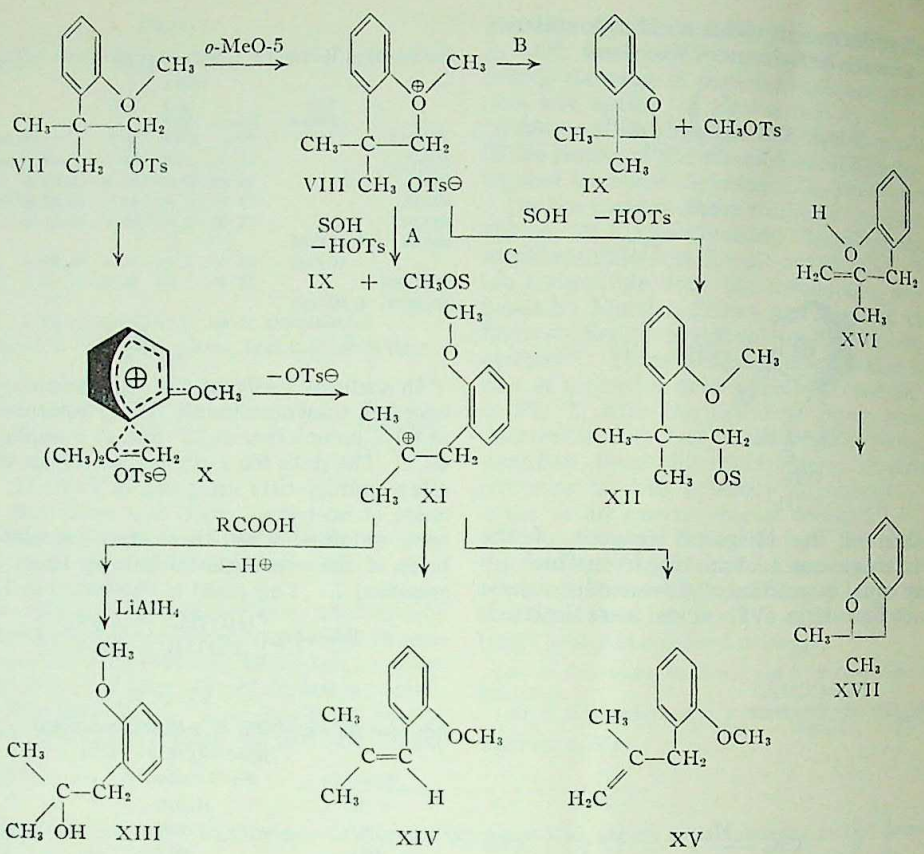

methyl *p*-toluenesulfonate in formolysis, because *o*-methoxyneophyl *p*-toluenesulfonate solvolyzes 10^3 times as rapidly as the methyl ester,[8] yet high infinity titers are observed after only 10 half-lives of the neophyl ester.

In order to acertain the reason for the high infinity value observed in acetolysis of *o*-methoxyneophyl toluenesulfonate in the presence of added sodium acetate, the second-order rate constant for reaction of methyl *p*-toluenesulfonate with sodium acetate was measured. An acetolysis run on 0.0313 *M* methyl *p*-toluenesulfonate in acetic acid, 0.0310 *M* in sodium acetate, at 75° is summarized in Table III. Because of the importance of second-order substitution of methyl toluenesulfonate by sodium acetate, a downward trend is observed both in the integrated first-order constants or the instantaneous first-order constants, k_i, obtained from the slopes of a plot of ln $[(ROTs)_0/(ROTs)]$ *vs.* time. Second-order rate constants, k_2, were evaluated with the aid of equation 2, using for k_1 the previously[8] reported first-order constant for acetolysis of methyl toluenesulfonate at 75°. The relatively constant value for k_2 is listed in the last column of Table III, the mean value being 6.8×10^{-5} l. mole^{-1} sec.$^{-1}$.

$$k_i = k_1 + k_2(\mathrm{NaOAc}) \qquad (2)$$

The reaction of methyl toluenesulfonate with sodium acetate turns out to be too slow to account for the high infinity titers observed in acetolysis of *o*-methoxyneophyl toluenesulfonate on the basis of reaction of methyl toluenesulfonate, subsequent to its formation. Therefore, the role of the sodium acetate is one of preventing formation of methyl toluenesulfonate, rather than destroying it after it is formed.

TABLE III

ACETOLYSIS OF 0.0313 *M* METHYL *p*-TOLUENESULFONATE WITH 0.0310 *M* SODIUM ACETATE AT 75.00°

Time, 10^{-5} sec.	$HClO_4$ soln., ml.[a]	[NaOAc], $10^2 M$	Integ. $10^5 k$	$10^5 k_1$	$10^5 \frac{(k_i - k_1)}{[\mathrm{NaOAc}]}$
0	4.310	3.029		3.17	7.8
0.907	3.340	2.347	2.84	2.40	6.6
1.669	2.950	2.073	2.30	2.10	6.0
3.293	2.160	1.518	2.13	1.74	5.9
5.021	1.570	1.131	1.99	1.58	6.5
6.375	1.290	0.935	1.88	1.47	6.6
10.283	0.790	0.555	1.69	1.31	8.3
∞	0.040				
				Mean	6.8 ± 0.6

[a] Per 5.14-ml. aliquot.

Products of Solvolysis.—The products from acetolysis and formolysis of *o*-methoxyneophyl *p*-toluenesulfonate in solvent containing excess sodium acetate or formate, respectively, were treated with lithium aluminum hydride to reduce any esters to alcohols. By chromatography, each product was separated into an easily-eluted fraction and a more difficultly-eluted alcohol fraction.

The easily-eluted material in each case gave rise to two fractions on vacuum distillation. The lower-boiling material was inert to potassium permanganate in acetone, and its C, H and methoxyl

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TABLE IV

PRODUCTS OF SOLVOLYSIS OF o-METHOXYNEOPHYL p-TOLUENESULFONATE

Solvent	Temp., °C.	[ROTs], 10^2 M	Added base	Reacn. time, hours	Total yield, %	% of product Olefin	Alcohol Tert.	Alcohol Prim.	Furan
EtOH	78	3.97	$CaCO_3$	5					46
AcOH	75	2.89	0.0310 M NaOAc	4	96	8	15	4	73
HCOOH	50	4.84	0.0515 M NaOCHO	2	92	32	42	..	26

analyses and ultraviolet absorption spectrum were proper for a dimethyl-4,5-benzodihydrofuran. The higher-boiling material gave a slow test for unsaturation with potassium permanganate in acetone and had the correct C, H analysis for 1-*o*-anisyl-2-methyl-1-propene (XIV) or its unconjugated isomer XV.

The product of ethanolysis of *o*-methoxyneophyl *p*-toluenesulfonate was examined sufficiently to isolate the dimethyl-4,5-benzodihydrofuran fraction. All three dimethylbenzodihydrofuran fractions from formolysis, acetolysis and ethanolysis appeared to be the same. The infrared spectra of the materials from formolysis and ethanolysis were compared and found to be identical. It is clear that the dimethylbenzodihydrofuran product is not 2,2-dimethyl-4,5-benzodihydrofuran (XVII) which was prepared from *o*-methallylphenol (X-VI).[9]

The differences in the infrared spectra of the synthetic and isolated materials, especially at 10.2 μ, where the synthetic material is relatively transparent, and at 11.3 and 14.4 μ, where the product has low absorption, indicate that the solvolysis product is not the synthetic one. For this reason, and from mechanistic considerations mentioned later, the structure of 3,3-dimethyl-4,5-benzodihydrofuran (IX) is assigned to the product.

The alcohol product from acetolysis of *o*-methoxyneophyl *p*-toluenesulfonate (VII) contained a large proportion of the rearranged tertiary alcohol, 1,1-dimethyl-2-*o*-anisylethanol (XIII), prepared from methyl *o*-methoxyphenylacetate and methylmagnesium iodide. The tertiary alcohol was conveniently characterized by means of its *p*-nitrobenzoate. The presence of *ca.* 20% of *o*-methoxyneophyl alcohol (V) in the solvolysis alcohol was demonstrated by treatment of a sample of the alcohol with *p*-toluenesulfonyl chloride in pyridine and acetolysis of the crude toluenesulfonate. The observed rate constant was that for *o*-methoxyneophyl toluenesulfonate (VII) and the observed infinity titer provided an estimate of the proportion of *o*-methoxyneophyl component in the solvolysis alcohol.

The alcohol product from formolysis of *o*-methoxyneophyl *p*-toluenesulfonate also gave rise to pure *p*-nitrobenzoate of 1,1-dimethyl 2-*o*-anisylethanol (XIII), the proportion of this material in the product apparently being very high.

In Table IV are summarized the results of the examination of the solvolysis products.

Discussion

Mechanism.—The absence of 2,2-dimethyl-4,5-benzodihydrofuran (XVII) in the solvolysis product indicates that cyclic ether does not arise from cyclization of olefin XIV or XV or rearranged tertiary solvolysis product such as the acetate of alcohol XIII. The formation of cyclic ether IX and the other solvolysis products requires a mechanism involving two competing anchimerically-assisted ionization processes in the solvolysis of *o*-methoxyneophyl *p*-toluenesulfonate (VII). One of the ionization modes is the Ar_1-3-assisted one; the other involves *o*-MeO participation, leading to the intermediate oxonium toluenesulfonate ion pair VIII. A convenient designation for the *o*-MeO participation in this specific case is *o*-MeO-5, the number 5 designating the size of the ring created by the anchimerically-assisted ionization.

From Ar_1-3-assisted ionization, tertiary solvolysis product, *e.g.*, acetate of alcohol XIII, and olefins XIV and XV are expected, just as in solvolysis of neophyl bromobenzenesulfonate.[10] From *o*-MeO-5-assisted ionization, the benzodihydrofuran IX and unrearranged *o*-methoxyneophyl substitution product XII are presumed to arise, the former by nucleophilic attack on methyl, the latter by such attack on C_α. The formation of methyl toluenesulfonate in the absence of sodium acetate, but not in its presence, is due to ion pair chemistry which has been studied[11] and discussed[12] further elsewhere. For present purposes, the *o*-MeO-5 reaction pathway will be subdivided into: A, leading to furan IX, but not methyl toluenesulfonate; B, leading to furan IX and methyl toluenesulfonate; and C, leading to *o*-methoxyneophyl substitution product XII.

Dissection of Solvolysis and Related Rate Constants.—The division of the solvolysis reactions into the Ar_1-3 and *o*-MeO-5 paths and the subdivision of *o*-MeO-5 into the A, B and C pathways may be carried out by reference to the composition of the reaction products summarized in Table IV. In Table V are summarized the resulting rough figures for percentage reaction along each reaction route.

TABLE V

ASSIGNMENT OF REACTION PATHS IN SOLVOLYSIS OF *o*-METHOXYNEOPHYL *p*-TOLUENESULFONATE

Solvent	Temp., °C.	Percentage reaction along path: Ar_1-3	*o*-MeO-5: Total	A	B	C
EtOH	78	<55	>45	45		
AcOH	75	25[a]	75[a]	31	40	4[a]
AcOH (0.031 M NaOAc)	75	25	75	68	3	4
HCOOH	50	73	27	*ca.* 27[b]	0	Small

[a] Assumed the same as in presence of sodium acetate. [b] Neglecting any possible *o*-methoxyneophyl alcohol in the product; the latter must be relatively small, judging by the much greater importance of Ar_1-3-assisted ionization than in acetic acid.

(9) Q. R. Bartz, R. F. Miller and R. Adams, THIS JOURNAL, **57**, 371 (1935).

(10) R. Heck and S. Winstein, *ibid.*, **79**, July (1957).

(11) R. Heck, unpublished work.

(12) (a) S. Winstein, *Experientia Supplementum II*, 153 (1955); (b) S. Winstein, VIth Reaction Mechanisms Conference, Swarthmore, Pa., September 12, 1956.

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Having divided ionization of *o*-methoxyneophyl *p*-toluenesulfonate into Ar_1-3- and *o*-MeO-5-assisted portions, one may dissect the observed solvolysis rate constants into k_Δ^{Ar} and k_Δ^{OMe}, the rate constants corresponding to each one of the anchimerically-assisted ionizations. The estimated rate constants are summarized in Table VI, along with the ratios, $k_\Delta^{OMe}/k_\Delta^{Ar}$.

The ratios, $k_\Delta^{OMe}/k_\Delta^{Ar}$, in Table VI point out most clearly the large solvent dependence of the competition between the Ar_1-3 and *o*-MeO-5 reaction paths.

TABLE VI

ASSIGNMENT OF RATE CONSTANTS IN ACETOLYSIS AND FORMOLYSIS OF *o*-METHOXYNEOPHYL TOLUENESULFONATE

Solvent	Temp., °C.	k_Δ^{OMe}, sec.$^{-1}$	k_Δ^{Ar}, sec.$^{-1}$	$k_\Delta^{OMe}/k_\Delta^{Ar}$
HCOOH[a]	25	2.6×10^{-5}	7.5×10^{-5}	0.35
AcOH	75	3.7×10^{-4}	1.1×10^{-4}	3.4

[a] Assuming products the same at 25° as those observed at 50°.

The ratio of *o*-MeO-5 to Ar_1-3 drops from 3.4 in acetic acid to 0.35 in formic acid. While we have not explored how much of this change can be due to change in temperature, most of the change is due to much smaller sensitivity to solvent ionizing power[13] in the case of *o*-MeO-5-assisted ionization than for the Ar_1-3 variety.

It is worthwhile to consider the competition between Ar_1-3 and *o*-MeO-5-assisted ionizations of *o*-methoxyneophyl *p*-toluenesulfonate (VII) in terms of the individual k_Δ^{Ar} and k_Δ^{OMe} values and their relation to similar rate constants for other systems. Taking the k_Δ^{Ar} values for *o*-methoxyneophyl *p*-toluenesulfonate and contrasting them with the values for the neophyl,[6] *p*-methoxyneophyl[7] and *o*- and *p*-anisylethyl[3] systems, one obtains the comparison summarized in Table VII.

From Table VII, it is clear that k_Δ^{Ar} for *o*-methoxyneophyl is slower than for *p*-methoxyneophyl by factors of 15 in acetic acid and 11 in formic acid. The *gem*-dimethyl grouping increases k_Δ^{Ar} from the level observed with the anisylethyl systems by factors of only 9.7 in formic acid and 5.7 in acetic acid, when the anisyl group is *ortho*, but by factors of 107 and 77 when the anisyl group is *para*. It would seem that there is steric retardation of k_Δ^{Ar} in *o*-methoxyneophyl relative to *p*-methoxyneophyl, due to the accumulation of both the *o*-methoxyl and the *gem*-dimethyl groupings. Steric interferences not present in the *p*-methoxyneophyl case make it more difficult to reach the Ar_1-3 transition state. The steric retardation of Ar_1-3- assisted ionization serves to increase the $k_\Delta^{OMe}/k_\Delta^{Ar}$ ratio observed with the *o*-methoxyneophyl system.

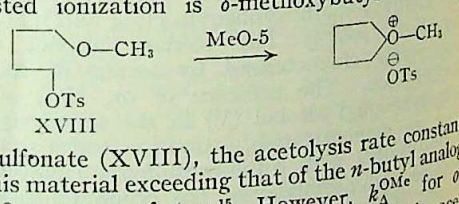
While the structure of *o*-methoxyneophyl *p*-toluenesulfonate (VII) is relatively unfavorable for Ar_1-3 participation, it is very suitable for *o*-MeO-5-assisted ionization. The k_Δ^{OMe} in this case is *ca.* 20 times as large as the whole solvolysis rate constant (at least mainly k_Δ^{Ar}) observed for the *o*-anisylethyl ester in acetic acid. A typical substance which is well-disposed toward MeO-5-assisted ionization is δ-methoxybutyl[2,12b,15] toluenesulfonate (XVIII), the acetolysis rate constant of this material exceeding that of the *n*-butyl analog by 3 powers of ten.[15] However, k_Δ^{OMe} for *o*-methoxyneophyl *p*-toluenesulfonate (VII) in acetic acid is approximately equal to that for the δ-methoxybutyl derivative XVIII, even though the *o*-methoxyl group is rendered less nucleophilic by resonance interaction with a benzene ring.

TABLE VII

SOME RELATIVE RATES INVOLVING ANISYL PARTICIPATION

Compound	Rel. k_Δ values HCOOH 25.00°	AcOH 75.00°
$(CH_3)_2C(OTs)CH_2$–	1.00[a]	1.00[a]
VII	72[b]	88[b]
I	6.47	5.5
	0.66[c]	0.99[e]
	0.67[d]	1.3[f]

[a] Based on data of A. H. Fainberg; $k = 1.16 \times 10^{-5}$ sec.$^{-1}$ in HCOOH at 25.00°, 2.00×10^{-5} sec.$^{-1}$ in AcOH at 75.00°. [b] Based on data[7] of R. Heck; $k = 8.31 \times 10^{-4}$ sec.$^{-1}$ in HCOOH at 25.00°, 1.77×10^{-3} sec.$^{-1}$ in AcOH at 75.00°. [c] $k = 7.7 \times 10^{-6}$ sec.$^{-1}$ in HCOOH at 25.00° by extrapolation of the value reported at 75.01°, assuming the same $\Delta H^\ddagger$ as for *p*-anisylethyl *p*-toluenesulfonate.[3] [d] $k = 7.8 \times 10^{-6}$ sec.$^{-1}$ in HCOOH at 25.00° by extrapolation of data reported at higher temperatures.[3] [e] $k^\circ_{ext.} = 1.98 \times 10^{-5}$ sec.$^{-1}$ in AcOH at 75.00°, reported by A. Fainberg.[14] [f] $k^\circ_{ext.} = 2.6 \times 10^{-5}$ sec.$^{-1}$ in AcOH at 75.00°, reported by A. Fainberg.[14]



XVIII

In a following paper, more cases of *o*-MeO-5 and related participations will be presented, and the connection between structure and rate of *o*-MeO-assisted ionization will be discussed further.

Experimental Part

o- and p-Methoxyneophyl Chloride Mixture.—To a cooled solution of 1226 ml. of concd. sulfuric acid and 774 ml. of water, heated to 70°, 162 g. of anisole and 166 g. of methallyl chloride were added with stirring. The reaction mixture was kept at 70–80° for 2 hr. After the mixture was cooled, the products were extracted with two portions of low-boiling

(13) (a) E. Grunwald and S. Winstein, THIS JOURNAL, **70**, 846 (1948); (b) S. Winstein, E. Grunwald and H. W. Jones, *ibid.*, **73**, 2700 (1951); (c) A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 1956).

(14) A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2767 (1956).

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petroleum ether. The extracts were washed with water and sodium bicarbonate solution. After the extract was dried, the solvent was removed and the residue was vacuum distilled. After a small forerun of anisole, the chloride mixture, b.p. 91–100° (2 mm.), n^{25}D 1.5268, was collected. The nearly colorless product weighed 78 g. (26%). A redistilled sample, b.p. 111–112° (3 mm.), was analyzed.

Anal. Calcd. for $C_{11}H_{15}OCl$: C, 66.75; H, 7.61. Found: C, 67.21; H, 7.74.

***o*- and *p*-Methoxyneophyl Alcohol Mixture.**—To 8.3 g. of magnesium covered by 700 cc. of ether, 76 g. of the above *o*- and *p*-methoxyneophyl chloride mixture was added. Several grams of methyl iodide was added and the mixture was refluxed and stirred for 6 hr. Then, while the mixture was stirred at room temperature, a slow stream of dry oxygen was passed in until no further heat of reaction was observed. The reaction mixture was worked up in the usual way to yield 29.5 g. (43%) of methoxyneophyl alcohols, b.p. 93–98° (2 mm.), n^{25}D 1.5291. The residue remaining after the distillation crystallized on standing. Two recrystallizations from pentane gave 5–10 g. of what is probably a methoxyneophyl dimer, m.p. 83.5–84.5°.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 80.93; H, 9.26. Found: C, 80.65; H, 8.97.

The preparation of the *p*-nitrobenzoate from the alcohol mixture led to a mixture which could not be separated even after several crystallizations from methanol or ligroin.

***o*-Methoxyneophyl *p*-Toluenesulfonate.**—Tosylation of 28 g. of the *o*-methoxyneophyl alcohol mixture by the usual method afforded 27 g. (49%) of pure *o*-methoxyneophyl *p*-toluenesulfonate, m.p. 67–69°. The substance formed large prisms when crystallized from a mixture of carbon tetrachloride and petroleum ether (b.p. 60–80°). It decomposes in a few days at room temperature but is stable for months at 0°.

Anal. Calcd. for $C_{18}H_{22}O_4S$: C, 64.64; H, 6.63. Found: C, 64.84; H, 6.76.

β-*o*-Anisylisovaleric Acid.—A Grignard reagent was prepared from 230 g. of the *o*- and *p*-methoxyneophyl chloride mixture and 24 g. of magnesium. Dry carbon dioxide was passed into the Grignard solution until the ether became cold. Cold dil. hydrochloric acid was added and the ether phase was separated. After the ether solution was washed with water, the acid product was extracted with aqueous sodium bicarbonate. Acidification of the extract produced an oil. This was isolated and crystallized, first from a small volume of pentane and then four times from petroleum ether (b.p. 60–80°). The product, m.p. 83–85°, mainly the *p*-isomer, weighed 12 g. Concentration of the mother liquors yielded a crop of crude *o*-acid in the form of large prisms. Another crystallization from petroleum ether (b.p. 60–80°) produced 14 g. of pure β-*o*-anisylisovaleric acid, m.p. 70.5–71°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.35; H, 7.94.

A mixed m.p. of the β-*o*-anisylisovaleric acid with the *p*-isomer described below was 55–67°.

β-*p*-Anisylisovaleric Acid.—Methyl β-(*p*-hydroxyphenyl)-isovalerate, b.p. 153–155° (1.5 mm.), was prepared by esterification of the acid[16] with methanol and hydrogen chloride.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.3; H, 7.86.

A solution of 0.695 g. of methyl β-(*p*-hydroxyphenyl)-isovalerate in 3.3 ml. of 1.03 *N* sodium methoxide in methanol was heated in a sealed tube for 5 hr. at 100–105° with 0.3 ml. of methyl iodide. The methanol was distilled, and the residue was treated with ether and water. The ether layer was separated, washed with two 4-ml. portions of 1 *N* sodium hydroxide solution, with water and then dried over magnesium sulfate. Saponification of the crude methyl β-*p*-anisylisovalerate was carried out by refluxing 0.424 g. with a solution of 0.25 g. of potassium hydroxide in 2 ml. of ethanol and 1 ml. of water for 4 hr. The acid was separated in the usual manner and recrystallized several times from ether–petroleum ether, m.p. 90–91°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.30; H, 7.87.

(16) J. Corse and E. Rohrmann, THIS JOURNAL, **70**, 370 (1948).

Methyl *o*-Methoxyphenylacetate.—To a mixture of 20 g. of *o*-methoxyphenylacetic acid[17] and 100 cc. of ether was added an excess of diazomethane in ether. After 10 minutes the ether was evaporated and the residue was vacuum distilled. The ester, b.p. 94–98° (2 mm.), n^{25}D 1.5160, weighed 16 g.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 67.11; H, 6.64.

1,1-Dimethyl-2-*o*-anisylethanol.—To a Grignard reagent prepared from 16 g. of methyl iodide and 3 g. of magnesium in 100 ml. of ether, 10 g. of methyl *o*-methoxyphenylacetate was added slowly. After a further 30 minutes of stirring, a cold saturated solution of ammonium chloride was added. The ether phase was separated and washed with water and aqueous sodium bicarbonate. After the ether phase was dried, the ether was evaporated and the alcohol was distilled in vacuum. The tertiary alcohol, 9.7 g., b.p. 87–89° (2 mm.), n^{25}D 1.5174, was a colorless, odorless liquid.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.04; H, 8.67.

The alcohol formed a *p*-nitrobenzoate readily when it was treated with *p*-nitrobenzoyl chloride in pyridine for 24 hr. After two recrystallizations from a mixture of ether and pentane, the ester formed long pale yellow needles, m.p. 77.5–78.5°.

Anal. Calcd. for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.81. Found: C, 65.61; H, 5.92.

2,2-Dimethylbenzofuran.—This material was prepared by the method of Bartz, Miller and Adams[9] and fractionated. The pure material had b.p. 97–98° (25 mm.) and n^{25}D 1.5161 [reported[9] b.p. 62° (7 mm.), n^{20}D 1.5190]. The ultraviolet spectrum in methanol showed $\lambda_{max.}$ 287 mμ, ε 840; 278 mμ, ε 1730; 271 mμ, ε 1670; and 227 mμ, ε 10,200.

Ethanolysis of *o*-Methoxyneophyl *p*-Toluenesulfonate.—A solution of 13.3 g. of *o*-methoxyneophyl *p*-toluenesulfonate in 1 l. of anhydrous ethanol was refluxed with 10 g. of calcium carbonate for 5 hr. The cooled solution was filtered, and most of the alcohol was distilled off through a fractionating column. The residue was again filtered and distilled rapidly. The distillate, 7.2 g., b.p. 90–130° (20 mm.), was fractionated through a 60-plate center-rod column using 10 ml. of purified diethyl phthalate as a pusher. Five fractions were collected. The first 3 fractions, combined weight 2.60 g., b.p. 89.5–100.5° (20 mm.), n^{25}D 1.5161–1.5168, were mainly 3,3-dimethylbenzofuran. The infrared spectrum of a fraction of b.p. 91.2–92.5° (20 mm.) and n^{25}D 1.5161 was essentially the same as the furan fraction obtained from the formolysis described below. Two higher boiling fractions were obtained from this fractionation, but they were not homogeneous and were not examined further.

Acetolysis of *o*-Methoxyneophyl *p*-Toluenesulfonate.—A solution of 12.0 g. of *o*-methoxyneophyl *p*-toluenesulfonate in 1200 cc. of 0.0310 *M* sodium acetate in dry acetic acid was heated at 75° for 4 hr. The cooled solution was then diluted with four liters of water and the products were extracted with several portions of pentane. The extracts were washed and concentrated, and then the residue was reduced with 1.5 g. of lithium aluminum hydride. The reduced product was chromatographed on 500 g. of activated alumina. The first fraction, eluted with 1.5 liters of pentane, gave two distinct fractions when it was distilled. The lower boiling fraction, b.p. 40–45° (2 mm.), n^{25}D 1.5175, weighed 3.35 g. This material was inert to potassium permanganate in acetone.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16; MeO, 0.00. Found: C, 81.01; H, 8.25; MeO, 0.90.

The higher boiling fraction, b.p. 58–60° (2 mm.), n^{25}D 1.5298, weighed 0.8 g., and it reacted slowly with potassium permanganate in acetone.

A second fraction was eluted from the alumina with one liter of ether. This material, b.p. 78–80° (2 mm.), n^{25}D 1.5166, weighed 1.2 g.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.06; H, 9.00.

A *p*-nitrobenzoate was prepared from 0.5 g. of the above alcohol fraction. The once crystallized product, 0.45 g., had m.p. 67–72.5°. A second crystallization from ether–

(17) F. Bergel, J. W. Haworth, A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, 261 (1944).

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pentane gave 0.2 g. of material, m.p. 74–76°, mixed m.p. with the *p*-nitrobenzoate of 1,1-dimethyl-2-*o*-anisylethanol, 74.5–76.5°.

In order to determine the amount of *o*-methoxyneophyl alcohol in the alcohol fraction, 0.40 g. of this material was treated with 1 g. of *p*-toluenesulfonyl chloride in dry pyridine at room temperature for 30 minutes. The sulfonate was isolated in the usual way and dissolved in 50 ml. of 0.0310 *M* sodium acetate in dry acetic acid. The acetolysis rate constant was $3.5 \pm 0.3 \times 10^{-4}$ sec.$^{-1}$ at 75°, the infinity titer being taken after 20 hr.

Formolysis of *o*-Methoxyneophyl *p*-Toluenesulfonate.—To a solution of 3.5 g. of sodium formate in 720 cc. of dry formic acid, heated to 50°, was added 12 g. of *o*-methoxyneophyl *p*-toluenesulfonate. After 2 hr. at 50°, the reaction mixture was cooled and worked up exactly as described for the acetolysis. The chromatography yielded 1.8 g. of benzofuran, b.p. 41–42° (2 mm.), n^{25}D 1.5251, 1.2 g. of olefin, b.p. 60° (2 mm.), n^{25}D 1.5458, and 2.5 g. of alcohol, b.p. 78–82° (2 mm.), n^{25}D 1.5183.

The benzofuran fraction was redistilled to give material with n^{25}D 1.5178. The infrared spectrum of this material was essentially the same as that of the ethanolysis product mentioned above. In ultraviolet absorption in methanol, λ_{max} 285 mμ, ε 2170; 279 mμ, ε 2700; and 224 mμ, ε 4720.

The olefin fraction reacted slowly with potassium permanganate in acetone.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.35; H, 8.71.

The alcohol fraction, 0.5 g., gave 0.2 g. of a *p*-nitrobenzoate of m.p. 76.5–77.5° after two crystallizations from ether-pentane. A mixed melting point with authentic material was 76.5–78°.

Kinetic Measurements.—Solvolysis rates were measured by the usual methods.[6,7] An attempt was made to follow the acetolysis of *o*-methoxyneophyl toluenesulfonate after the first infinity value. The solvolysis solution became yellow and difficult to titrate, a rough rate constant of *ca.* 6×10^{-7} sec.$^{-1}$ being obtained at 75°. A value of 8.5×10^{-7} sec.$^{-1}$ has been reported[8] for methyl *p*-toluenesulfonate at 75°.

LOS ANGELES 24, CALIF.

COMMUNICATIONS TO THE EDITOR

EVIDENCE ON MECHANISMS OF HALOGEN AND TRITIUM RECOIL LABELLING REACTIONS

Sir:

Displacement reactions very different from ordinary atom and radical reactions have been observed between gaseous alkanes and iodine,[1a,1b] bromine,[1c] and chlorine[1d,1e] activated by the (n,γ) process. Tritium activated by the $Li^6(n,\alpha)H^3$ process in the presence of liquid or solid organic compounds gives superficially similar reactions.[2] Tritium is of particular interest in this connection because of its chemical differences from the halogens and because a much larger fraction of its recoil kinetic energy is available for internal energy of the activated complex.

We have used the $He^3(n,p)H^3$ reaction to produce tritons in gaseous alkanes[3] under conditions[4] similar to those for which the halogen reactions have been studied. With a given target compound a multiplicity of tritium containing compounds is formed which cannot be explained by "conventional" reaction steps. In the absence of scavengers about 45% of the tritium appears as HT, 30% in the alkane target species and the remainder in four to ten other products. Halogen scavengers decrease or eliminate the yield of tritiated products with more carbons than the target but have relatively little effect on the HT, or the tritiated target compound or fragments thereof.

The only reaction steps which seem capable of explaining the extensive chain-lengthening are ion-molecule reactions[8] (such as, for example, $T^+ + CH_4 \rightarrow CH_3T^+ + H_2$ and $CH_3T^+ + CH_4 \rightarrow C_2H_4T^+ + H_2$, followed by similar steps leading to further chain lengthening). Ion-molecule steps

(1) (a) J. F. Hornig, G. Levey and J. E. Willard, *J. Chem. Phys.*, **20**, 1556 (1952); (b) G. Levey and J. E. Willard, *J. Chem. Phys.*, **25**, 904 (1956); (c) A. Gordus and J. E. Willard, THIS JOURNAL, in press; (d) J. C. W. Chien and J. E. Willard, *ibid.*, **75**, 6160 (1953); (e) J. E. Quinlan and J. E. Willard, unpublished.

(2) (a) R. Wolfgang, F. S. Rowland and C. N. Turton, *Science*, **121**, 715 (1955); (b) R. Wolfgang, J. Eigner and F. S. Rowland, *J. Phys. Chem.*, **60**, 1137 (1956); (c) F. S. Rowland, C. N. Turton and R. Wolfgang, THIS JOURNAL, **78**, 2354 (1956); (d) F. S. Rowland and R. Wolfgang, *Nucleonics*, **14**, 58 (1956).

(3) While this work was in progress, we received word from R. Wolfgang that he had observed the production of CH_3T and higher hydrocarbons from the $He^3(n,p)H^3$ reaction in CH_4.

(4) A typical run consisted of irradiating a 5-ml., thin-walled, quartz bulb containing 6 mm. He^3, 6 mm. H_2, and 1 atm. of alkane in the isotope tube of the CP 5 reactor of the Argonne National Laboratory for one hour. The neutron flux[5] was 3×10^{12} n.cm.$^{-2}$ sec.$^{-1}$ The bulb was broken in a stream of methane at the inlet of a 12 ft. long, 4 mm. i.d. spiral Pyrex column containing 30–80 mesh silica gel. The general technique was the same as reported earlier,[6] the main difference being that a flow proportional counter[7] was used to detect the radioactive components. The fraction of [illegible] in each component was estimated from the peak area; the identification of the minor components is tentative.

(5) The accompanying gamma flux was about 5×10^5 r./hr. That the gamma radiation was not the cause of the chain lengthening or the large fraction of tritium in the target compound seems evident from the three CH_4-He^3-H_2 samples which received about 7×10^5 r. from a Co^{60} source after the usual pile irradiation. This did not change the percentage of CH_3T much, but raised the percentage of HT slightly and lowered the percentages of the higher hydrocarbons somewhat.

(6) J. B. Evans and J. E. Willard, THIS JOURNAL, **78**, 2903 (1956).

(7) A. Gordus, Ph.D. thesis, University of Wisconsin, 1956, available from University Microfilms, Inc., Ann Arbor, Michigan.

(8) (a) V. L. Tal'roze and A. K. Lyubimova, *Doklady Akad. Nauk S.S.S.R.*, **86**, 909 (1952) (*Chem. Abs.*, **47**, 2590 (1953)); (b) D. O. Schissler and D. P. Stevenson, *J. Chem. Phys.*, **24**, 926 (1956); (c) D. P. Stevenson and D. O. Schissler, *ibid.*, **23**, 1353 (1955); (d) G. G. Meisels, W. H. Hamill and R. R. Williams, Jr., *ibid.*, **25**, 790 (1957); (e) F. H. Field, J. L. Franklin and F. W. Lampe, THIS JOUR-

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also seem to be required[1c,9] to explain gas phase halogen atom recoil reactions. Reactions such as $CH_4T^+ + CH_4 \rightarrow C_2H_6T^+ + H_2$ which may not be observable at mass spectrometer pressures may be among those which contribute to chain lengthening. The absence of a scavenger effect on the yield of tritiated parent indicates that the neutral stable molecule is formed by a single step such as $T^+ + CH_4 \rightarrow CH_3T + H^+$, or $T + CH_4 \rightarrow CH_3T + H$, or that its formation from a species such as CH_4T^+ is not altered by halogen.

Although it usually is not possible to differentiate hot radical reactions from ion-molecule reactions in condensed phases, it seems plausible that ion-molecule steps such as seem to be required above may also be involved in tritium labelling in condensed phases[2] and in a number of other unique processes recently reported. These include the reactions of tritons[10] and C^{14} ions[11] accelerated by electric fields, and the tritium labelling method of Wilzbach.[12,13] It is probable that such steps also account[9] for part, but not all, of the products of halogen recoil reactions in solution.

TABLE I

PRODUCTS OF THE $He^3(n,p)H^3$ REACTION IN GASEOUS CH_4, C_2H_6, AND C_3H_8[a]

	Alkane reactant					
Tritiated[b] product	CH_4	CH_4 (I_2 or Br_2)	C_2H_6	C_2H_6 (Br_2)	C_3H_8	C_3H_8 (I_2)	C_3H_8 (Br_2)
	Per cent. of total T in each product						
HT	46	40	43	42	43	42	50
CH_3T	31	50	5	2	4	4	3
C_2H_5T	6.8	Trace	28	37	2.5	1.5	1.5
C_3H_7T	5	Trace	9	0	36	47	39
C_4H_9T	1.5	0	7	0	3	1	0
$C_5H_{11}T$	1.7	0	0	0	2	1	0
$C_6H_{13}T$	1.2	0	4	0	5	1.5	0
$C_7H_{15}T$	1.9	0	0	0	0	0	0
$C_8H_{17}T$	1.9	0	3	0	4	1	0
Iodides or bromides	1	0	0	0	0	1	0
	0	10	0	18	0	?	6

[a] The reaction mixtures contained about 1 atm. of alkane, 6 mm. of He^3 and either 6 mm. of H_2, 0.2 mm. of I_2 or 200 mm. of Br_2. [b] Duplicate formulas indicate isomers.

(9) S. Aditya and J. E. Willard, THIS JOURNAL, **79**, 2680 (1957).
(10) R. Wolfgang, T. Pratt and F. S. Rowland, *ibid.*, **78**, 5132 (1956).
(11) R. M. Lemmon, F. Mazzetti, F. L. Reynolds and M. Calvin, *ibid.*, **78**, 6414 (1956).
(12) K. E. Wilzbach, *ibid.*, **79**, 1013 (1957).
(13) R. W. Ahrens, M. C. Sauer, Jr., and J. E. Willard, *ibid.*, **79**, 3285 (1957).

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RECEIVED APRIL 8, 1957

HYDROGEN LABELLING OF HYDROCARBONS USING IONIZING RADIATION

Sir:

Wilzbach has demonstrated that exposure to tritium gas is an effective method of labelling complex organic compounds.[1] It seems possible that such reactions are similar in mechanism to tritium recoil labelling by the $He^3(n,p)H^3$ [2] and $Li^6(n,\alpha)H^3$ [2] processes and to recoil labelling by the halogens,[2] which appear to involve ion-molecule steps.[2]

Typical distributions of tritiated products which we have obtained by gas chromatographic analysis[2] of mixtures of hydrocarbons with T_2 or HT, activated by self irradiation with about 2×10^7 roentgens of tritium beta radiation or by doses of about 5×10^6 roentgens of Co^{60} gamma rays are shown in Table I. Both chain lengthening and

TABLE I

RELATIVE AMOUNTS OF TRITIATED PRODUCTS FROM THE IRRADIATION OF VARIOUS MIXTURES CONTAINING CH_4, C_2H_6, HT, H_2 AND I_2[a]

Sample	CH_4	C_2H_6	C_3H_8	C_4H_{10}	C_5H_{12}	C_6H_{14}
CH_4-HT-H_2[b]	[h]	2.5	1	2.8	2.7	4.1
CH_4-HT-H_2[c]	[h]	6.7	1	2.8	11.5	15.8
CH_4-HT-H_2-I_2[d]	5.4	1.4	1	2.7	1.3	0.4
CH_4-HT-H_2-I_2[e]	1.6	1.9	1	2.2	*ca.* 0.0	*ca.* 0.0
CH_4-T_2[f]	[h]	3.5	1	(12.8)	3.9	1.9
C_3H_8-T_2[g]	1.2	0.4	1	[h]	[h]	[h]

[a] CH_4, C_2H_6, C_3H_8, C_4H_{10} characterized with known samples: C_5H_{12} and C_6H_{14} identity assumed from position on gas chromatogram. [b] *ca.* 5×10^5 r. Co^{60} gamma radiation, 2.5 μc. tritium, 7 mm. H_2, 60.7 cm. CH_4. [c] *ca.* 6×10^6 r. Co^{60} gamma radiation, 2.5 μc. tritium, 57 mm. H_2, 52.4 cm. CH_4. [d] *ca.* 3.5×10^6 r. Co^{60} gamma radiation, 2.5 μc. tritium, 5 mm. H_2, 64.5 cm. CH_4, solid I_2. [e] *ca.* 3.0×10^6 r. Co^{60} gamma radiation, 2.5 μc. tritium, 6 mm. H_2, 61.0 cm. CH_4, solid I_2. [f] *ca.* 5 mc. T_2, 50 cm. CH_4, 72 days standing. [g] *ca.* 5 mc. T_2, 48 cm. C_3H_8, 49 days standing. [h] Relative abundance of this species not determined in this experiment.

chain degradation occur, as with activation by the $He^3(n,p)H^3$ process. Methane–HT mixtures irradiated with gamma radiation appear to show higher yields of tritiated pentanes and hexanes than of propane. The ratio of yields is changed by a change in the methane–H_2 ratio. Iodine scavenger causes a drop in the tritiated C_5H_{12} and C_6H_{14} components relative to the other components. In view of the chain lengthening observed, the conclusion seems nearly inescapable that these reactions are ion-molecule processes.[2] Quantitative studies on such systems should be rewarding by revealing the most probable stage of the chain lengthening process for reaction of the chain carrying species with hydrogen and with halogens.

Three possibilities must be considered for the primary step in these tritiation reactions: (1) the step $T\text{-}T \rightarrow T^+ + He^3$ (or, say, He^3T^+); (2) ionization of T_2 or HT by beta or gamma radiation; (3) ionization of the organic compound by beta or gamma radiation. The fact that reaction occurs in HT–CH_4 mixtures indicates that the molecule T_2 is not essential.

If reaction were initiated solely by ionization of H_2 and HT a G value of about 100 would be required to account for the yields of tritiated products obtained in Table I, assuming no isotope effect. Consequently it seems probable that much, if not all, of the reaction is due to ionization of the methane.

The ratios of tritiated C_4H_{10}, C_5H_{12} and C_6H_{14} to tritiated C_3H_8 produced from CH_4 are significantly higher when tritiation is induced by radiation

(1) K. E. Wilzbach, THIS JOURNAL, **79**, 1013 (1957).
(2) A. A. Gordus, M. C. Sauer, Jr., and J. E. Willard, *ibid.*, **79**, 3781 (1957).

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(Table I) than when it is induced by the $He^3(n,p)H^3$ process. This seems to indicate that the mechanisms are different. In the $He^3(n,p)H^3$ case the formation of each carbon chain presumably is initiated by attack of a tritium ion on a CH_4 molecule.

The many products formed in these reactions offer a valuable source of high specific activity labelled compounds when these non-parent "by-products" can be separated in carrier-free form by gas chromatography or otherwise.

This work was supported in part by the Atomic Energy Commission and in part by the Wisconsin Alumni Research Foundation.

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RECEIVED APRIL 8, 1957

CHEMICAL REACTION OF RECOIL TRITIUM WITH GASEOUS ALKANES[1]

Sir:

We have studied the reaction of high energy tritium, as produced by nuclear reaction, with gaseous methane and ethane. The reactions $He^3(n,p)H^3$ (0.78 Mev.) and Li^6 $(n,\alpha)H^3$ (4.7 Mev.) were used to supply the "hot" tritium. In the He^3 runs about 0.1 cm. He^3 was sealed with 10–60 cm. CH_4 in a $\sim$ 7 ml. quartz ampoule. In the Li^6 runs a film of normal lithium nitrate formed the inside coating of similar vessels. After irradiation in the Brookhaven reactor, carriers were added and the various tritium labeled species separated and counted, largely as described elsewhere.[2]

A summary of some of our results on the chemical state of the tritium following interaction with methane is shown in Table I. This distribution of

TABLE I

CHEMICAL STATE OF RECOIL TRITIUM STOPPED IN METHANE
Expressed as % of total gaseous activity in absence of I_2

Chemical state	Irradiation conditions: $10^{12.6}$ neutrons cm.$^{-2}$ sec.$^{-1}$, no I_2 present	$10^{9.3}$ neutrons cm.$^{-2}$ sec.$^{-1}$, no I_2 present	$10^{9.3}$ neutrons cm.$^{-2}$ sec.$^{-1}$, I_2 present
HT	50.6	61.9	29.8
CH_3T	30.9	29.1	26.0
$C_2H_5T + C_2H_3T$	8.2	2.9	0.1
C_2(T) hydrocarbons	5.0	2.4	0.2
Higher tritiated hydrocarbons and iodides	5.3	3.7	43.9

activity is independent of the source of the tritium, the pressure and the temperature (range 30–200°). However, a drastic reduction of neutron flux, with accompanying decrease in radiation density, although having little effect on the production of CH_3T, seems to reduce significantly the yields of labeled higher hydrocarbons while increasing the amount of HT. The addition of 0.2 mm. of iodine as a radical scavenger has little effect on the yield of CH_3T but virtually eliminates the yield of higher labeled hydrocarbons and reduces the yield of HT.

Studies on the slowing of charged particles passing through matter[3] indicate that the tritium is uncharged on reaching its final reaction site. Taking this into account, our observations suggest two distinct modes of reaction of the tritium atom: (A) Most tritium combines by direct hot replacement reaction. For methane

$$T^* + CH_4 \longrightarrow CH_3T + H$$

$$T^* + CH_4 \longrightarrow HT + CH_3$$

Radical intermediates are definitely ruled out and Walden inversion probably is involved. (B) Some tritium escapes incorporation in stable molecules by hot reaction and becomes thermalized. Its reactions then become sensitive to radical scavengers, such as I_2. In their absence the tritium can react competitively to (1) abstract H to form part of the HT observed, or (2) combine with radiation produced radicals or ions to form the higher labeled hydrocarbons. (Production of the latter probably involves hydrocarbon chains lengthened by ion molecule reactions.[4])

The results observed with ethane are consistent with this picture. Most of the activity appears in HT and C_2H_5T with smaller amounts in CH_3T and higher hydrocarbons. Only C_3 and higher hydrocarbons are eliminated by I_2. This means that degradation products such as CH_3T from ethane are largely formed by direct hot replacement reactions (type A).

It has been demonstrated that neither radical intermediates nor a solvent cage, the central concepts of earlier theories of hot-atom reactions,[5] are necessary for hot reaction of hydrogen. Whether the reaction model postulated here holds also for recoil tritium reactions in the condensed phase remains to be seen. The similar product distributions in gaseous and liquid[2] alkanes are suggestive. But the retention of configuration observed in the solid phase[6] would require further explanation.

(1) Research supported by the Atomic Energy Commission. See also accompanying communication by Gordus, Sauer and Willard, p. 3284.

(2) Wolfgang, Eigner and Rowland, *J. Phys. Chem.*, **59**, 1137 (1955).

(3) S. K. Allison and S. D. Warshaw, *Rev. Mod. Phys.*, **25**, 779 (1953).

(4) Meisels, Hamill and Williams, *J. Chem. Phys.*, **25**, 790 (1957).

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(6) Rowland, Turton and Wolfgang, THIS JOURNAL, **78**, 2554 (1956); F. S. Rowland, private communication.

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RECEIVED APRIL 22, 1957

DEGRADATION OF BRAIN GANGLIOSIDE TO GLUCOCEREBROSIDE

Sir:

Since Klenk first described the brain gangliosides,[1] evidence has been presented that they are

(1) E. Klenk, *Z. physiol. Chem.*, **273**, 76 (1942).

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macromolecular glycolipids[2-4] which contain neuraminic acid, sphingosine,[5] fatty acid (stearic),[6] hexoses, and a hexosamine. Earlier studies have demonstrated the hexoses to be exclusively glucose and galactose and the hexosamine to be exclusively galactosamine.[4,8] However, little is known of the manner in which these constituents are linked. A cerebroside frequently has been postulated to be the basic unit in the structure of the gangliosides. The present communication reports the successful hydrolytic degradation of a purified preparation of brain ganglioside to a glucocerebroside.

Bovine brain ganglioside was prepared as an ash-free fraction (I) homogeneous by electrophoretic and ultracentrifuge studies (minimal molecular weight 250,000), completely water-soluble, free of phosphatides (P 0.07%) and of dialyzable contaminants.[4,7,8] (I) contains nitrogen 2.9%, hexose 24.0% (expressed as galactose), and galactosamine 10.0%.

Optimal conditions for the isolation of the constituent glucocerebroside have been defined as follows: a 2% aqueous solution of I is autohydrolyzed at 100° for a critical time interval of 25 minutes, then exhaustively dialyzed. The dialyzate contains 66% of the neuraminic acid and 5.2% of the galactosamine of I. The non-dialyzable residue (II) accounts for 80% by weight of I. II is hydrolyzed with 0.09 *N* HCl (sealed tube, 100°, 16 hours) then exhaustively dialyzed. The resulting non-dialyzable residue (III), still water-soluble, is further hydrolyzed (0.09 *N* HCl, sealed tube, 100°, 5 hours). The hydrolyzate, which now contains a brown insoluble material (IV), is exhaustively dialyzed. IV is separated by centrifugation, dried *in vacuo*, and taken up in clear solution with warm methanol:chloroform (9:1). 12% of IV remains as an insoluble black residue which is discarded. When this solution (40 mg./cc.) is allowed to cool to room temperature, birefringent spherocrystals (MCS) are formed. To date, yields of MCS represent between 26 and 30% by weight of I. MCS crystals contain no neuraminic acid and no galactosamine. The analysis, compared with that expected for a glucostearocerebroside crystallized with one mole of water,[9] is

	N, %	C, %	H, %	Hexose (as glucose), %
Found	1.86	67.13	10.95	21.8
Calcd. for $C_{48}H_{91}O_8N(H_2O)$	1.88	67.65	11.14	22.0

MCS is insoluble in water, slightly soluble in pure chloroform, very soluble in mixtures of chloroform:methanol. MCS shows slight liquefication at 165°, then melts sharply between 172–174°. The iodine number is 23.2. In chloroform:methanol (2:1) (1 mg./cc.), it is levorotatory ($[\alpha]^{20}D$ −2.08°). The infrared spectrum is consistent with that of a cerebroside.[10] A sample of crystalline MCS gave these spacings by X-ray diffraction[11]: 2.41, 4.10, 9.1, 10.4, 15.6, 21.1, 30.6, 49.2, 55.5, and 63.5 Å.

Hydrolysis of MCS in *N* HCl (sealed tube, 100°, 16 hours) liberated the hexose quantitatively. This was shown to be exclusively glucose by paper chromatography. The remaining water-insoluble residue contained 2.3% nitrogen, as expected for a ceramide. It is yet to be established whether the base is sphingosine or dihydrosphingosine.[12]

The melting point, specific rotation, iodine number and the elementary analysis, distinguish MCS from the previously described cerebrosides phrenosine, cerasine and nervone.[13] A glucostearocerebroside has not been described previously. Its presence as the basic constituent of brain ganglioside would be consistent with the demonstration by Klenk that the constituent fatty acid of brain ganglioside is stearic acid.[6] The isolation of this glucocerebroside is of interest with regard to the over-all structure and biosynthesis of the gangliosides.

(2) J. B. Finnean, *Arch. Biochem. Biophys.*, **52**, 38 (1954).
(3) C. Chatagnon and P. Chatagnon, *Bull. Soc. Chim. Biol.*, **35**, 1519 (1953).
(4) Samuel Bogoch, Harvard University Ph D. Thesis, April, 1956.
(5) A. Rosenberg and E. Chargaff, *Biochim. Biophys. Acta*, **21**, 588 (1956).
(6) E. Klenk, *Z. physiol. Chem.*, **273**, 76 (1942).
(7) J. Folch, J. A. Meath and S. Bogoch, *Federation Proc.*, **15**, 254 (1956).
(8) Samuel Bogoch, Studies on the Structure of Brain Ganglioside, in preparation.
(9) O. Rosenheim, *Biochem. J.*, **8**, 121 (1914).
(10) Kindly performed by Dr. E. R. Blout, Children's Medical Center, Boston.
(11) Kindly performed by Dr. C. Cohen, Massachusetts Institute of Technology, Boston.
(12) H. E. Carter and W. P. Norris, *J. Biol. Chem.*, **145**, 709 (1942).
(13) H. J. Deuel, Jr., "The Lipids," Vol. I, Interscience Publishers, New York, N. Y., 1951, p. 484 ff.

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RECEIVED JANUARY 12, 1957

SYNTHESIS OF ±-CRYPTOPLEURINE[1]

Sir:

The vesicant alkaloid cryptopleurine[2] has interesting physiological properties[3] and has been stated to possess a skeletal structure of a novel type. Although the alkaloid could not be degraded to compounds of known structure,[3] chemical,[3,4] spectroscopic,[4] and, in particular, crystallographic (X-ray)[5] evidence was adequate to allow the base to be designated as 2′,3′,6′-trimethoxyphenanthro-[9′,10′,2,3]quinolizidine (I).

By the use of the general methods described earlier[6] we have accomplished the first synthesis of ±-cryptopleurine. Condensation of 6-nitroveratraldehyde with homoanisic acid yielded 6-nitro-3,4,4′-trimethoxy-α-phenylcinnamic acid (m.p. 185–186°; *Anal.* Calcd. for $C_{18}H_{17}NO_7 \cdot H_2O$: C,

(1) This investigation was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health, Public Health Service.
(2) R. Price, *Record Chem. Progress*, **16**, 153 (1955).
(3) I. S. de la Lande, *Australian J. Exptl. Biol. Med. Sci.*, **26**, 181 (1948).
(4) E. Gellert and N. V. Riggs, *Australian J. Chem.*, **7**, 113 (1954).
(5) J. Fridrichsons and A. M. Mathieson, *Acta Cryst.*, **8**, 761 (1955).
(6) C. K. Bradsher and L. E. Beavers, THIS JOURNAL, **77**, 4812 (1955); **78**, 2459 (1956).

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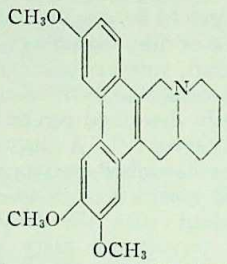
57.29; H, 5.08; N, 3.71. Found: C, 57.11; H, 4.77; N, 3.90). Reduction yielded the corresponding amino derivative (m.p. 206–207°) which when diazotized underwent the Pschorr cyclization to yield 2,3,6-trimethoxyphenanthrene-9-carboxylic acid (m.p. 222°; Calcd. for $C_{18}H_{16}O_5,H_2O$: C, 65.44; H, 5.49. Found: C, 65.54; 5.36). The phenanthroic acid was converted to the ethyl ester (m.p. 136.5–137°), which was reduced to the corresponding carbinol (m.p. 184–187°; *Anal.* Calcd. for $C_{18}H_{18}O_4$: C, 72.56; H, 6.17. Found: C, 72.46; H, 6.08) by the action of lithium aluminum hydride.



I, Base II, Methiodide

The bromide obtained from 2,3,6-trimethoxyphenanthryl-9-carbinol was not purified, but allowed to react immediately with pyridine-2-aldehyde. The salt thus obtained was cyclized by heating it in polyphosphoric acid at 80° for five hours. The cyclization product, presumably a 2,3,6-trimethoxydibenzo[h,j]acridizinium salt, could not be recrystallized satisfactorily and therefore was converted to the chloride by means of ion exchange and hydrogenated directly using platinum oxide catalyst. The product, purified by chromatography, melted at 199–200° (lit.[4] m.p. 197–198°; *Anal.* Calcd. for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71. Found: C, 75.85; H, 7.17; N, 4.00) did not depress the melting point of an authentic sample,[7] and had ultraviolet and infrared spectra like those reported for cryptopleurine. The methiodide (II, m.p. 272–274°, lit.[4,8] 270–272° did not depress the melting point of an authentic sample of ±-cryptopleurine methiodide, and the infrared spectra (potassium bromide plate method) of the two substances were identical.

(7) We are indebted to Dr. E. Gellert for making this comparison for us and for furnishing us with a sample of ±-cryptopleurine methiodide.

(8) E. Gellert, *Australian J. Chem.*, **9**, 489 (1956). Since Dr. Gellert's method for obtaining the ± base from natural (optically active) cryptopleurine is somewhat involved, he has taken pains to demonstrate rigorously that the optically inactive methiodide is actually ±-cryptopleurine methiodide.

DEPARTMENT OF CHEMISTRY
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RECEIVED MAY 11, 1957

PHASE EQUILIBRIUM IN THE HYDROTHERMAL SHRINKAGE OF COLLAGEN

Sir:

The shrinkage of collagen has been shown to denote a first order transition between crystalline and amorphous phases.[1,2] This being the case, the stress τ_{eq} required to maintain a state of equilibrium between the phases should be related to the temperature T according to an analog of the Clausius–Clapeyron equation[3,4]

$$d(\tau_{eq}/T)/d(1/T) = (\Delta\bar{H}/V_c)/(\Delta\bar{L}/L_c) \quad (1)$$

where $\Delta\bar{H}$ and $\Delta\bar{L}$ are the latent enthalpy and length changes accompanying melting and subsequent swelling in the excess of surrounding solvent, V_c and L_c are the volume and length of the (dry) crystalline fiber, and τ_{eq} is the stress referred to the cross section of the fiber in the same state. Tobolsky, Haselkorn and Catsiff[5] have attempted recently to apply this relationship to the spontaneous shrinkage temperature T_s for bovine tendon at various stresses τ_s, the sample being immersed in water. Their results, like those similarly obtained a number of years ago by Wöhlisch,[6] yield a value of about 1.7 cal. $g.^{-1}$ for the latent enthalpy.[7]

We wish to point out that the temperature for the onset of shrinkage is substantially higher than that required for equilibrium between crystalline and amorphous phases. The values of τ_s and T_s which pertain to the shrinkage phenomenon as ordinarily determined should not therefore be employed in the foregoing equation, which is applicable only at thermodynamic equilibrium. We have found, however, that the equilibrium stress τ_{eq} at a given temperature T_m may be determined readily by the procedure outlined below.

Fresh rat-tail tendons were cross-linked (*i.e.*, tanned) with formaldehyde in order to suppress flow in the amorphous phase. A single tanned fiber about 10 cm. in length was suspended vertically between a fixed lower clamp and an upper clamp attached to a strain gage. The fiber and clamps were immersed in thermostated 3 *M* KCNS solution and the fiber was allowed to undergo partial contraction, such that one or more totally amorphous (shrunken) regions formed adjacent to (native) crystalline regions. The length was then adjusted to yield a force which remained constant for at least 30 minutes. Close approach to equilibrium is indicated by the fact that a small change in force, induced by slight alteration of the length, was succeeded by a change in the force toward the equilibrium value. The observed force is independent of the degree of shrinkage of the fiber, provided that a crystalline section remains. By measuring the thus established τ_{eq} as a function of temperature, we have obtained the results summarized below for two samples differing in degree of cross-linking.

The first two rows of the table emphasize the disparity between T_s and T_m^i, the equilibrium melting temperature established by extrapolation to zero force. The latent enthalpies $\Delta\bar{H}/V_c$ per unit volume of collagen given in the fifth row have been calculated from eq. (1) using the results in the

(1) R. R. Garrett and P. J. Flory, *Nature*, **177**, 176 (1956).

(2) P. J. Flory, *Science*, **124**, 53 (1957).

(3) G. Gee, *Quart. Rev.*, **1**, 265 (1947).

(4) P. J. Flory, THIS JOURNAL, **78**, 5222 (1956).

(5) A. Tobolsky, R. Haselkorn and E. Catsiff, *ibid.*, **78**, 5957 (1956).

(6) E. Wöhlisch, *Naturw.*, **28**, 305, 326 (1940).

(7) Professor Tobolsky has informed us that the results in their paper (ref. 5) are referred to 1 g. of *swollen* collagen, and hence that a factor of approximately 4 must be applied to convert their results to a "per unit of dry collagen" basis. Such correction has been introduced in the values of $\Delta\bar{H}/V_c$ quoted above.

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	28	35
T_s ($f_s = 0$), °C.	20	28
T_m^0 ($f_{eq} = 0$), °C.		
$-d(r_{eq}/T)/d(1/T)$ dynes cm.$^{-2}$	9.1×10^8 (40°)	11×10^8 (50°)
	0.48 (40°)	0.57 (50°)
$-\Delta\bar{L}/L_0$	10.5	15.0
$(\Delta\bar{H}/V_0)$ cal. cc.$^{-1}$	17.5	22
$(\Delta H/V_0)$ cal. cc.$^{-1}$	1200	1500
ΔH_u, cal./peptide unit		

third and fourth rows. The negative contribution to $\Delta\bar{H}$ from the heat of dilution of collagen, estimated from the temperature coefficient of the degree of swelling in the amorphous state, has been deducted to obtain the latent heats of fusion expressed in cal. cc.$^{-1}$ and in cal. per mole of peptide units, respectively, in the last two rows of the table.

The values of ΔH_u are in satisfactory agreement with previous results derived from calorimetric measurements (1180 cal.[8]) and from depression of the melting point of collagen by glycol (2200 cal.[1]). The heat and entropy of fusion compare favorably with those for other crystalline polymers, contrary to the conclusions reached by Tobolsky and co-workers.[5]

Tanning with quinone yields more stable cross linkages, thus permitting investigation of the phase equilibrium in pure water at temperatures up to 70° under stress. Experiments on this system are in progress.

Similar experiments have been carried out on the shrinkage of racked rubber cross-linked by gamma radiation.[9] The heat of fusion obtained through the use of eq. (1) stands in good agreement with independent values.

(8) A. Künzel and K. Doehner, *Angew. Chem.*, **52**, 175 (1939).
(9) J. F. M. Oth and P. J. Flory, to be published.

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RECEIVED MAY 7, 1957

THE NUCLEAR MAGNETIC RESONANCE SPECTRUM OF RIBONUCLEASE[1]

Sir:

We wish to report the observation of a nuclear magnetic resonance spectrum of the protein ribonuclease. In previous investigations[2] of macromolecules in solution, it had been reported that deoxyribonucleic acid markedly altered the proton magnetic resonance spectrum of water. The two proteins studied concurrently, hemocyanin and ovalbumin, neither modified the water spectrum nor exhibited independent peaks attributable to protein protons, at the concentrations used. We have found that concentrated aqueous solutions of bovine serum albumin (20%) gave no protein peaks, when the solutions were treated as below. An observable spectrum for ribonuclease might be attributed to internal flexibility of the molecule, absent in the other proteins, although there are other possible explanations.

Bovine pancreatic ribonuclease (Armour Lot No. 381–059) was dialyzed for 12 hours against several changes of glass-redistilled water and then equilibrated for 20 hours with a similar dialysis bag containing only water. Both solutions were deionized by passage through a column of ion-exchange resins.[3] The final ribonuclease concentration was about 15%, as determined spectrophotometrically. Investigation of the ribonuclease solution in a Varian High Resolution NMR Spectrometer operating at 40 Mc. showed a small protein peak in addition to the large water peak. Exchange of the protein solution with deuterium oxide removed the interfering protons of water, as well as the exchangeable protons of ribonuclease. Using a sample tube 4.9 mm. in inner diameter, we obtained the detailed spectrum shown in Fig. 1. The sharp peak indicated by the arrow decreased in relative intensity with successive exchanges and hence is due to residual water protons. The control solution described above showed only an unmodified water peak before exchange with D_2O and no spectrum at all afterward, making it unlikely that the peaks are due to low molecular weight contaminants in the ribonuclease preparation, the dialysis casing, or the resin column.

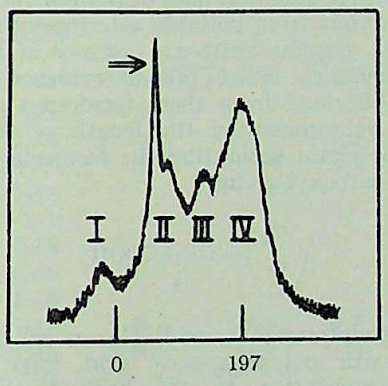

Fig. 1.—Nuclear magnetic resonance spectrum of ribonuclease.

The scale shown was established using the aromatic peak of toluene in an introduced capillary as zero. Since the spectrum range is the range of usual proton chemical shifts and since it does not change noticeably with concentration, it seems that we have an essentially unbroadened spectrum of the non-exchangeable protons of ribonuclease.

Because of their location, peaks I and IV can be assigned tentatively to aromatic hydrogens and to hydrogens on aliphatic carbon atoms attached only to other aliphatic carbons. The relative areas of each peak, after subtracting the estimated contribution of water protons, obtained from several spectra of two independently prepared samples were: I, 9 ± 1%, II, 26 ± 2%, III, 18 ± 3%, IV, 47 ± 3%. From the known composition

(1) This work was carried out partly with the help of funds provided by the Office of Naval Research, Contract No. Nonr-609(24).
(2) H. Jacobson, W. A. Anderson and J. T. Arnold, *Nature*, **173**, 772 (1954).
(3) H. M. Pinteris, Ph.D. Thesis, Harvard University, 1952.

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of ribonuclease, of the 664 non-exchangeable hydrogens 7.1% are aromatic and 45.0% are on aliphatic carbon atoms attached only to other aliphatic carbons. Of the remaining protons, 19.0% are on α carbons, 8.1% are on carbons attached to carboxyls and amides, 6.0% are on carbons with hydroxyl substituents, 5.4% are on carbons attached to sulfur, 4.2% are on carbons bonded to positively charged nitrogen, 3.9% are on carbons attached to aromatic nuclei, and 1.2% are on carbons bound to amide nitrogen. All of these categories could reasonably be expected to give rise to peaks between the extremes, but their positions in peaks II and III cannot be assigned with certainty at this time.

CONTRIBUTION NO. 1448 FROM THE
STERLING CHEMISTRY LABORATORY
YALE UNIVERSITY
NEW HAVEN, CONNECTICUT

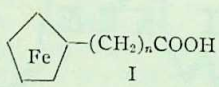
MARTIN SAUNDERS
ARNOLD WISHNIA
JOHN G. KIRKWOOD

RECEIVED MAY 20, 1957

FERROCENE BRIDGING AND HOMOANNULAR CYCLIZATIONS[1]

Sir:

The question of homoannular *vs.* heteroannular intramolecular acylation in substituted ferrocenes has been raised recently by Nesmeyanov.[2] We wish to report here examples of both of these types of cyclizations from suitable ω-ferrocenylaliphatic acids[3] (I), together with an instance of intermolecular acylation, and to present evidence that the product obtained from these ferrocenyl aliphatic acids is determined by the length of the polymethylene chain separating the ferrocene nucleus from the carboxyl group.



I

β-Ferrocenylpropionic acid[3] (Ia, $n = 2$), when treated with polyphosphoric acid, gave heteroannular cyclization to the bridged compound 1,1′-(α-ketotrimethylene)-ferrocene,[4] m.p. 144–144.5°.[5] *Anal.* Calcd. for $C_{13}H_{12}FeO$: C, 65.03; H, 5.04; Fe, 23.26; mol. wt., 240. Found: C, 64.50; H, 5.04; Fe, 23.98; mol. wt. 281 (ebull., benzene), 324 (ebull., butanone). The infrared spectrum contains ketone bands at 1682 and 1266 cm.$^{-1}$, but no bands near 1110 or 1004 cm.$^{-1}$. Presence of 1110 and 1004 cm.$^{-1}$ bands would indicate an unsubstituted cyclopentadienyl ring.[3,6] The ultraviolet spectrum of this ketone is highly characteristic in that it shows no maximum near 225 or 270 mμ, regions where maxima have been shown to occur for ketones conjugated with the ferrocene nucleus.[7] Such spectral behavior is reasonable for a compound of this structure since the stereochemistry of the 3-carbon bridge prevents coplanarity, and thus conjugation, of the carbonyl with the adjacent ring.

γ-Ferrocenylbutyric acid[3] (Ib, $n = 3$), when treated with either polyphosphoric acid or trifluoroacetic anhydride, gave as the major product the homoannular cyclized ketone, 1,2-(α-ketotetramethylene)-ferrocene,[8] m.p. 85.4–85.7°, λ_{max} 226, 270 mμ, ϵ_{226} 17,600, ϵ_{270} 7,500, infrared bands: 1679, 1281, 1109, 1003 cm.$^{-1}$. *Anal.* Calcd. for $C_{14}H_{14}FeO$: C, 66.19; H, 5.55; mol. wt., 254. Found: C, 66.59; H, 5.69; mol. wt., 286 (ebull., butanone).

δ-Ferrocenylvaleric acid[3] (Ic, $n = 4$), with either polyphosphoric acid or trifluoroacetic anhydride, gave the homoannular product, 1,2-(α-ketopentamethylene)-ferrocene, m.p. 65.5–66.5°, λ_{max} 227, 269 mμ, ϵ_{227} 15,500, ϵ_{269} 7,400, infrared bands: 1655, 1290, 1110, 1004 cm.$^{-1}$. *Anal.* Calcd. for $C_{15}H_{16}FeO$: C, 67.19; H, 6.02; mol. wt., 268. Found: C, 66.99; H, 6.18; mol. wt., 314 (ebull., butanone). The shift in the infrared carbonyl band to lower frequency[9] and the reduction in the extinction coefficient in the ultraviolet spectrum,[10] when compared to similar spectral features of the lower, homologous, ketone from IIb, containing a 6-membered ring, are in agreement with like shifts found between the corresponding 7- and 6-membered benzocyclanones.[9,10]

The principal product from the treatment of ϵ-ferrocenylcaproic acid[3] (Id, $n = 5$) with polyphosphoric acid was a red-brown solid, apparently polymeric,[11] insoluble in usual organic solvents, decomposing slowly above 200°. The material exhibits strong infrared ketonic absorption (1660 cm.$^{-1}$), weaker carboxyl absorption (1725, 2700, 2620 cm.$^{-1}$) and gives analytical data consistent with those for a condensation trimer, as $H[C_{16}H_{24}Fe(CH_2)_5CO]_3OH$, though it is more likely a mixture of compounds of varying molecular weight. *Anal.* Calcd. for $C_{48}H_{56}Fe_3O_4$: C, 66.68; H, 6.53; Fe, 19.38. Found: C, 66.76; H, 6.58; Fe, 18.95.

(1) Presented in part at the 131st Meeting of the American Chemical Society, Miami, Florida, April 7–12, 1957; *cf.* Abstracts, p. 46-O.

(2) A. N. Nesmeyanov, N. A. Volkenau and V. D. Vilchevskaya, *Doklady Akad. Nauk S.S.S.R.*, **111**, 362 (1956).

(3) K. L. Rinehart, Jr., R. J. Curby, Jr., and P. E. Sokol, THIS JOURNAL, **79**, in press (1957).

(4) Ferrocene substituents on the same cyclopentadienyl ring are numbered "1, 2, 3," etc., as in the benzenoid compounds, while substituents on the second cyclopentadienyl ring are indicated by an accent, as "1′, 2′, 3′," etc. [*cf.*, *e.g.*, P. L. Pauson, THIS JOURNAL, **76**, 2187 (1954)].

(5) Woodward and Csendes obtained what is apparently the same compound (m.p. 141–142°) from treatment of β-ferrocenylpropionic acid with trifluoroacetic anhydride, though the ketone was incompletely characterized (R. B. Woodward and E. Csendes, personal communication; *cf.* ref. 6, Appendix).

(6) M. Rosenblum, Ph.D. Thesis, Harvard University, August, 1953.

(7) K. L. Rinehart, Jr., K. L. Motz and S. Moon, THIS JOURNAL, **79**, 2749 (1957).

(8) Nesmeyanov[2] has recently assigned a di-homoannular structure similar to this to the polyphosphoric acid cyclization product from 1,1′-ferrocenedibutyric acid.

(9) W. M. Schubert and W. A. Sweeney, THIS JOURNAL, **77**, 4172 (1955).

(10) G. D. Hedden and W. G. Brown, *ibid.*, **75**, 3744 (1953).

(11) Homoannular cyclization of Id would require the formation of an 8-membered ring expected to form with difficulty. A similarly difficult cyclization would be anticipated from ferrocenylacetic acid (I, $n = 1$), which must give either a highly strained 4-membered benzocyclobutanone ring or a 2-carbon bridge, for which the interannular distance probably is too great.[12] In preliminary experiments in polyphosphoric acid, no ketonic product has been obtained.

(12) P. F. Eiland and R. Pepinsky, THIS JOURNAL, **74**, 4971 (1952); J. D. Dunitz and L. E. Orgel, *Nature*, **171**, 121 (1953).

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June 20, 1957

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KENNETH L. RINEHART, JR.
RONALD J. CURBY, JR.

RECEIVED APRIL 29, 1957

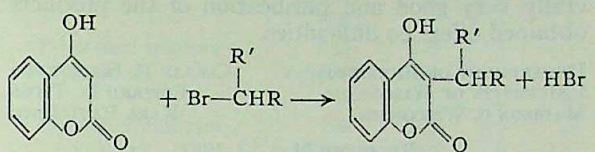
A NEW SYNTHETIC APPROACH TO SOME 3-ARALKYL-4-HYDROXYCOUMARINS[1]

Sir:

Since the introduction of the anticoagulant Dicumarol[2], 3,3′-methylenbis-(4-hydroxycoumarin) for clinical purposes,[2] interest in the synthesis of new 3-substituted-4-hydroxycoumarins and in new methods of synthesizing them has been maintained. While the reactivity of the 3-position of 4-hydroxycoumarin (I) is well known,[3,4,5] the direct alkylation of the 3-position of 4-hydroxycoumarin with reactive halides under acidic conditions has not been reported. Grüssner[6] had reported the alkylation of 4-hydroxycoumarins with reactive allyl and substituted allyl bromides under alkaline conditions. This method leaves much to be desired with respect to the yields obtained (usually 10–15%) and the scope of the procedure.

saturated compounds and which upon catalytic hydrogenation give the desired 3-aralkyl-4-hydroxycoumarins.

In a recent paper Ziegler and Roszmann[8] reported the synthesis of 3-substituted benzyl-4-hydroxycoumarins by condensing 4-hydroxycoumarin and substituted benzyl alcohols directly using phosphorus oxychloride as the catalyst and solvent.



I II III–XII

We have found that 4-hydroxycoumarin (I) can be alkylated readily in the 3-position by heating it in the molten state with certain reactive aralkyl halides (II) at temperatures of 130–180°. The 3-aralkyl-4-hydroxycoumarins (III–XII) are readily isolated in the pure state and usually in very good yields.

Alkylation of 4-hydroxycoumarin with certain aralkyl bromides (II) (or chlorides) in the molten state (length of heating period and temperature vary depending on the bromide used) gave 3-aralkyl-4-hydroxycoumarins (III–XII) in good yields. The physical and analytical data for the compounds reported herein are in the table.

TABLE I

3-SUBSTITUTED-4-HYDROXYCOUMARINS

	R	R′	M.p.,[a] °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
III	Phenyl[b]	H	197–200	53	$C_{16}H_{12}O_3$				
IV	*o*-Methylphenyl	H	202–206	95	$C_{17}H_{14}O_3$	76.7	76.8	5.3	5.4
V	*o*-Chlorophenyl	H	229–232	28	$C_{16}H_{11}ClO_3$	67.0	66.6	3.8	4.1
VI	Benzyl[c]	H	195–198	82	$C_{17}H_{14}O_3$				
VII	Phenyl[d]	CH_3	201–202	97[d]	$C_{17}H_{14}O_3$				
VIII	Phenyl[d,e,f]	C_2H_5	175–177	98	$C_{18}H_{16}O_3$				
IX	Phenyl[f]	*n*-C_3H_7	191–194	95	$C_{19}H_{18}O_3$				
X	Phenyl[f]	*n*-C_4H_9	179–180	97	$C_{20}H_{20}O_3$				
XI	Phenyl	*n*-C_5H_{11}	148–149	96	$C_{21}H_{22}O_3$	78.4	78.1	6.8	6.8
XII	Phenyl	Phenyl	177–178	99	$C_{22}H_{17}O_3$	80.5	80.3	4.9	5.0

[a] Melting points are uncorrected. [b] I. M. Heilbron and D. W. Hill, *J. Chem. Soc.*, 1705 (1927), report a m.p. of 205°. [c] H. Pauli and K. Lockemann, *Ber.*, **48**, 28 (1915), report a m.p. 205–206°. [d] H. Junek and E. Ziegler, *Monatsh.*, **87**, 218 (1955), report a m.p. 202° and a yield of *ca.* 10% for VII and a m.p. 175–176° for VIII. [e] F. Litvan and W. Stoll, U. S. Patent 2,647,681, Aug. 11, 1953, report a m.p. 179°. [f] A. Grüssner and B. Hegedüs (see ref. 7) report a m.p. 179–180° for VIII, a m.p. of 201–202° for IX, a m.p. 178–180° for X, no yields were reported.

Recently Grüssner and Hegedüs[7] reported a novel, mutiple-step procedure for the preparation of 3-aralkyl-4-hydroxycoumarins, in which organometal compounds are condensed with 3-acyl-4-hydroxycoumarins to form tertiary carbinols which are in turn dehydrated to the corresponding unsaturated compounds.

Benzylation of the 3-position of 4-hydroxycoumarin by heating with benzyl *p*-toluenesulfonate[9] in the molten state at 100–120° gave 3-benzyl-4-hydroxycoumarin (III) in 15% yield.

The synthesis of some of the 3-aralkyl-4-hydroxycoumarins listed here by the older procedures would be very tedious if indeed it could be realized.[10,11] The recent method of Grüssner and

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.
(2) K. P. Link, *The Harvey Lecture Series*, **39**, 162 (1943–1944).
(3) M. Ikawa, M. A. Stahmann and K. P. Link, THIS JOURNAL, **66**, 902 (1944).
(4) C. F. Huebner and K. P. Link, *ibid.*, **67**, 99 (1945).
(5) H. R. Eisenhauer and K. P. Link, *ibid.*, **75**, 2044 (1953).
(6) A. Grüssner, "Jubilee Volume," F. Hoffman-La Roche and Co., Ltd., Basle, 1946, p. 238.
(7) A. Grüssner and B. Hegedüs, U. S. Patent 2,723,276, Nov. 8, 1955.
(8) E. Ziegler and U. Roszmann, *Monatsh.*, **88**, 25 (1957).
(9) J. K. Kochi and G. S. Hammond, THIS JOURNAL, **75**, 3443 (1953), report the preparation of benzyl *p*-toluenesulfonate.
(10) R. C. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 174–194.
(11) H. Simonis, "Die Cumarine," Ferdinand Enke, Stuttgart, 1916, pp. 200–205.

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Hegedüs[7] has made it possible to synthesize various 3-aralkyl-4-hydroxycoumarins not realizable heretofore by the conventional methods.[10,11] The primary advantage of the method reported herein resides in the fact that the aralkyl halides are either commercially available or can be made readily in the laboratory by conventional methods. The alkylation of 4-hydroxycoumarin is direct without passing through intermediates, the yields are generally very good and purification of the products obtained offers no difficulties.

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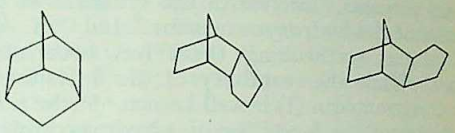
RECEIVED MAY 13, 1957

A SIMPLE PREPARATION OF ADAMANTANE

Sir:

Because of the analogy with the structure of the diamond, the highly symmetrical molecule, adamantane (tricyclo[3.3.1.1^{3,7}]decane) (I), has occasioned interest for many years.[1] The total synthesis of this hydrocarbon, first isolated from petroleum naphtha[2] in minute yields,[3] has been accomplished several times, utilizing a number of modifications of the same general approach.[1,4] The over-all yields of even the best of these methods, involving a moderately large number of steps, did not exceed a few per cent.; therefore, investigations of the chemistry of this compound have been hindered to a large extent by its unavailability. We wish to report a facile two-step preparation of adamantane from the very readily available compound, dicyclopentadiene (II).

endo-Trimethylenenorbornane[5] (tetrahydrodicyclopentadiene, III), which can be prepared from II in essentially quantitative yield by hydrogenation,[6] was refluxed with 10 per cent. of its weight of $AlBr_3$ or $AlCl_3$ overnight.[7] At the end of this time the products were distilled directly from the reaction pot, with no attempt at fractionation. The precipitation of adamantane was completed by cooling the distillate to Dry-Ice temperature; a yield of about 10 per cent. of crude I could be obtained by filtration through a coarse filter. Additional I could be obtained by subjecting the filtrate to fractional distillation through an efficient column. The forecuts, b.p. to 185°, contained a large number of components. The main fraction, b.p. 185.0°, $n^{20}D$ 1.4871, consisted of *exo*-trimethylenenorbornane (IV),[8] the expected product of the reaction.[9] The yield of this material, about 50 per cent., could be improved considerably by conducting the isomerization at lower temperatures. From the higher boiling cuts, b.p. to 195°, approximately 5 per cent. additional crude I was recovered. After washing with ethanol, fractional sublimation of the combined samples of I gave a 12–13 per cent. yield of pure adamantane, m.p. 269.6–270.8° (sealed tube). Reported m.p. 268.5–270°.[1] *Anal.* Calcd. for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.31; H, 11.99. The infrared spectrum[10] and mass spectral pattern[11] of the rearrangement product further established its identity as adamantane.



Since, as would be anticipated, IV, under the same conditions, gave a similar yield of I, it may be possible to improve the yield of I considerably The driving force for the rearrangement is undoubtedly the result of the fact that I, in contrast to III and IV, possesses an arrangement of atoms uniquely free from angular and conformational strain. Conceptually, it is possible to visualize several routes for the conversion of III or IV into I. The simplest of these necessitates only three steps involving carbon-to-carbon rearrangements. The possible mechanisms of these unusual transformations will be commented on in greater detail later.

(1) *Cf.* an excellent review, H. Stetter, *Angew. Chem.*, **66**, 217 (1954). More recent references will be found below.[3,4,10]

(2) S. Landa and V. Macháček, *Coll. Czech. Chem. Comm.*, **5**, 1 (1933).

(3) S. Landa, Š. Kriebel and E. Knobloch, *Chem. Listy*, **48**, 61 (1954) (*C. A.*, **49**, 1598 (1955)).

(4) V. Prelog and R. Seiwerth, *Ber.*, **74**, 1644, 1769 (1941); H. Stetter, O.-E. Bänder and W. Neumann, *ibid.*, **89**, 1922 (1956).

(5) The nomenclature used here will be that suggested previously (P. R. Schleyer and M. M. Donaldson, THIS JOURNAL, **78**, 5702 (1956)).

(6) For references, *cf.* E. Josephy and F. Radt, Eds., "Elsevier's Encyclopaedia of Organic Chemistry," Vol. 13, Elsevier Publishing Co., Inc., New York, N. Y., 1946, p. 1022.

(7) For a recent review of the action of Lewis acids upon alkanes, *cf.* H. Pines and J. Mavity in B. T. Brooks, *et al.*, Eds., "The Chemistry of Petroleum Hydrocarbons," Vol. III, Reinhold Publishing Corp., New York, N. Y., 1955, Chap. 36, p. 73.

(8) H. Bruson and T. W. Riener, THIS JOURNAL, **67**, 723 (1945); *cf.* P. D. Bartlett and A. Schneider, *ibid.*, **68**, 6 (1946).

(9) M. M. Donaldson, unpublished results from this laboratory. *Cf.* J. F. Eykman, *Chem. Weekblad*, **1**, 7 (1903); **3**, 687 (1906).

(10) R. Mecke and H. Spiesecke, *Ber.*, **88**, 1997 (1955). The author is indebted to Dr. R. A. Dean, The British Petroleum Co., Ltd., for a copy of the spectrum of synthetic adamantane.

(11) Catalog of Mass Spectral Data, A.P.I. Research Project 44 Carnegie Institute of Technology, Pittsburgh, Pennsylvania, No. 939

FRICK CHEMICAL LABORATORY
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RECEIVED MAY 17, 1957

SELENIUM AS AN INTEGRAL PART OF FACTOR 3 AGAINST DIETARY NECROTIC LIVER DEGENERATION

Sir:

Factor 3 is a dietary agent which prevents liver necrosis in the rat.[1] Concentrates of Factor 3 also protect against multiple necrotic degeneration (heart, liver, kidney and muscle necrosis) in the mouse,[2] as well as against exudative diathesis in the chick.[3] These fatal diseases result from a multiple deficiency. They are produced by diets which are low in cystine and simultaneously defi-

(1) K. Schwarz, *Proc. Soc. Exp. Biol. and Med.*, **78**, 852 (1951).

(2) W. B. DeWitt and K. Schwarz, *Experientia*, in press.

(3) M. L. Scott, J. G. Bieri, G. M. Briggs and K. Schwarz, to be published.

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cient in vitamin E and Factor 3. Each of these substances protects by itself. Details of the rat assay for Factor 3, using a ration based on Torula yeast as the sole source of protein, have been described.[4]

During the fractionation of Factor 3 from acid hydrolysates of natural source materials we detected that at least two chemically closely related substances with Factor 3 activity were present. These have been designated α- and β-Factor 3.[5] α-Factor 3 was found to be water soluble, strongly anionic, stable against oxidation, but sensitive to reducing agents. Dry ashing eliminated Factor 3 activity entirely.

The fractionation of α-Factor 3 has led to highly concentrated, semi-crystalline preparations. Some of these were found to develop a characteristic, garlic-like odor upon addition of alkali. This observation led to the discovery that selenium is an integral part of Factor 3. The element is present in bound form. Qualitative tests for selenium were observed only upon decomposition of active preparations. Various α-Factor 3 fractions were analyzed for selenium; for this purpose the reaction with codeine[6] was adapted to the Beckman spectrophotometer.[7] It is seen that Factor 3 activity is correlated with the selenium content (Table I).

TABLE I

SELENIUM DETERMINATIONS IN FACTOR 3 PREPARATIONS

Prepn. no.[a]	Units of F3[a,b] in aliquot analyzed	μg. Se[c] found
4737	Inactive	<1
4759	Inactive	<1
4760	72	7
4197B	330	3.5
4757	410	9
4741	430	12

[a] Fractions of greatly varying degrees of purity, prepared from dried, defatted kidney powder hydrolysate. [b] Dietary rat assay against liver necrosis; ref. 4. [c] Standardized against the selenium analog of cystathionine (M. J. Horn and D. B. Jones, *J. Biol. Chem.*, **139**, 649 (1941)). The authors wish to thank Dr. M. J. Horn for a generous sample of this material.

The conclusion that selenium is an essential part of the active organic material is borne out by the finding that inorganic selenium salts are remarkably effective in protecting against necrotic liver degeneration (Table II). As little as 13.33 μg. of sodium selenite, *i.e.*, 4 μg. of the element, in 100 g. of diet suffice to afford complete protection. This amounts to a daily intake of about 0.250 μg. of selenium per rat. Protection was also obtained by the daily subcutaneous injection of 0.167 μg. of selenium as sodium selenite. Preliminary indications are that potassium selenate is less potent. Potassium tellurite and sodium arsenate were without effect. The latter substance is known to antagonize selenium poisoning successfully in various species.[8]

TABLE II

EFFECT AGAINST DIETARY NECROTIC LIVER DEGENERATION

Supplement[a]	Salt mg. per 100 g. of diet	Element μg. per 100 g. of diet	No. of animals Total	No. of animals Dead on 30th day
None (Controls)	...	...	18	17[b]
Sodium selenite	0.0199	6	10	0
($Na_2SeO_3 \cdot 5H_2O$)	.0133	4	10	0
	.0067	2	10	3
	.0033	1	5	4
Potassium selenate	.280	100	5	0
(K_2SeO_4)	.028	10	5	4
	.003	1	5	4
Potassium tellurite	.199	100	5	5
(K_2TeO_3)	.020	10	5	5
Sodium arsenate	.470	100	5	5
($Na_2HAsO_4 \cdot 7H_2O$)	.047	10	5	5

[a] Composition of the basal diet: *Torula* feed yeast 30, sucrose 59, vitamin-E free lard 5, salts 5, vitamins (in lactose) 1; K. Schwarz, *Proc. Soc. Exp. Biol. Med.*, **77**, 818 (1951). [b] Inbred animals of the Fisher strain were used. The average survival time on the basal diet is 21 days. The incidence of necrotic liver degeneration is 100%. The tests were terminated after 30 days.

Our results show that, at least for the rat, Factor 3 is not an essential *organic* dietary constituent, since it can be replaced by selenite. The specific potencies of various inorganic and organic selenium compounds remain to be established. Most of the selenium in normal diets appears to be organically bound. The dose needed for the prevention of dietary necrotic liver degeneration amounts to less than 1% of the chronic toxic dose, which has been placed at 300–400 μg./100 g. of ration.[9]

In comparison with previously reported values for vitamin E and cystine,[10] selenium is exceedingly effective in the prevention of necrotic liver degeneration. When applied in form of sodium selenite it is approximately 500 times as active as vitamin E and 250,00 times as active as L-cystine. The element has been shown to be constantly present in tissues of higher animals.[11] It can be inferred from our results that *selenium is an essential trace element.* A characteristic defect, respiratory decline, is present in oxidative metabolism of liver slices from animals on necrogenic diets several weeks before necrosis occurs[12]; this suggests that selenium may act in intermediary metabolism by participating in oxidation reduction reactions.[13,14]

(1) K. Schwarz, *Proc. Soc. Exp. Biol. and Med.*, **80**, 319 (1952).
(5) K. Schwarz, L. H. Mason and C. M. Foltz, to be published.
(6) M. J. Horn, *Ind. Eng. Chem.*, **6**, 34 (1934).
(7) M. A. Malm and K. Schwarz, to be published. The authors are indebted to Dr. M. A. Malm for the selenium analyses.
(8) A. L. Mozon and M. Rhian, *Physiol. Revs.*, **23**, 305 (1953).
(9) H. E. Munsell, G. M. Devaney and M. H. Kennedy, U. S. Dept. Agr. Tech. Bull. No. 534 (1936).
(10) K. Schwarz, *Ann. N. Y. Acad. Sci.*, **57**, 878 (1954).
(11) E. J. Underwood, "Trace Elements," Academic Press, Inc., New York, N. Y., 1956, p. 2.
(12) S. S. Chernick, J. G. Moe, G. P. Rodnan and K. Schwarz, *J. Biol. Chem.*, **217**, 829 (1955).

(13) The authors are indebted to Dr. DeWitt Stetten, Jr., for helpful suggestions, stimulating discussions and for his sustained interest.
(14) The efficient technical assistance of Edward E. Roginski, Clifford E. Lee and H. Haskell Parker is gratefully acknowledged.

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CYCLIZATION OF ACETYLENE-d_2 TO BENZENE-d_6

Sir:

Benzene-d_6 may be prepared directly from acetylene-d_2 at room temperature by use of a modified silica–alumina catalyst. Previously described methods of preparation of benzene-d_6 required either high-temperature (650°) pyrolysis[1] of acetylene-d_2 or the exchange[2] of benzene with D_2SO_4. Both of these methods are inherently wasteful of deuterium in that the pyrolysis reaction results in a number of undesirable deuterium-containing products while the exchange reaction requires a number of exchanges. Also, the subsequent separation and purification procedures are laborious and time-consuming. On the other hand, the preparation described here is relatively easy and efficient. No products other than benzene-d_6 are formed in the reaction.

The deuterium content of the benzene-d_6 depends only on the purity of the deuterium oxide[3] used to form acetylene-d_2 from calcium carbide. Prior to reaction with deuterium oxide, the calcium carbide is heated to 600° to remove all traces of hydrogen or acetylene from the solid. By this means acetylene-d_2, analyzed mass spectrometrically to contain 99.5% D, is prepared.

The modified catalyst is prepared by repeatedly exposing Houdry Type M-46 silica–alumina cracking catalyst (previously dried at 275°) to diborane.[4] The drying temperature is not critical but does determine the amount of bound water[5] retained by the catalyst and, consequently, the amount of diborane that will react with the hydroxyl groups on the surface.[6]

In a typical preparation approximately 300 cc. of acetylene-d_2 was circulated through a 3-cm.-thick bed of the modified catalyst (10 g.) in a closed system whose total capacity was 600 cc. As it was formed, the product was collected in a trap cooled by Dry Ice. After circulation for forty-five minutes the Dry Ice was replaced by liquid nitrogen to condense the unused acetylene-d_2. The catalyst was then heated to 150° *in vacuo* to recover any adsorbed benzene-d_6. The benzene-d_6 was separated from the acetylene-d_2 by high-vacuum fractionation. Under these conditions approximately 50% of the acetylene-d_2 had been converted to benzene-d_6. By mass spectral analysis the benzene-d_6 was found to contain 2.7% of the C_6D_5H species (equivalent to 0.45%H). The mass spectrum of the product compared favorably with that of the API[7]; however, the product prepared here had a slightly higher deuterium content.

When the acetylene-d_2 was first exposed to the catalyst bed, an appreciable amount of heat was evolved; consequently, for larger scale preparations it may be advisable to cool the catalyst.

Significantly, there was no exchange of deuterium or hydrogen between the modified catalyst and the acetylene or benzene. It was possible to prepare, alternately, benzene and benzene-d_6 on the same catalyst bed without forming partially-deuterated products. However, when a mixture of acetylene and acetylene-d_2 was passed through the modified catalyst, the product consisted of both even and odd numbered deuteriated benzenes with deuterium and hydrogen statistically distributed among these species. A detailed study of the cyclization reaction, directed toward shedding light both on the mechanism of cyclization of acetylene and the catalytic nature of silica–alumina gels, is being carried out and will be reported later.

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RECEIVED MAY 13, 1957

(1) G. R. Clemo and A. McQuillen, *J. Chem. Soc.*, 851 (1935).
(2) C. K. Ingold, C. G. Raisin and C. L. Wilson, *ibid.*, 915 (1936).
(3) Obtained from Stuart Oxygen Co., 99.5% D_2O.
(4) I. Shapiro, H. G. Weiss, M. Schmich, S. Skolnik and G. B. L. Smith, THIS JOURNAL, **74**, 901 (1952).
(5) I. Shapiro and I. M. Kolthoff, *ibid.*, **72**, 776 (1950).
(6) I. Shapiro and H. G. Weiss, *J. Phys. Chem.*, **57**, 219 (1953).
(7) American Petroleum Institute Research Project No. 44, Carnegie Inst. of Tech., Serial No. 609.

RESOLUTION OF DL-MEVALONIC ACID AND THE SYNTHESIS AND BIOLOGICAL ACTIVITIES OF DL-3-HYDROXY-3-METHYLGLUTARALDEHYDIC ACID

Sir:

The discovery of mevalonic acid, a new acetate-replacing and growth factor for lactobacilli, was reported recently,[1,2] and its structure was proven to be 3,5-dihydroxy-3-methylpentanoic acid (I).[3,4] The synthesis of DL-mevalonic acid has been reported,[3,4,5] and it was found to have one-half the microbiological activity of the natural compound.[3,4]

Fractional crystallization of the amides obtained by reaction of DL-mevalonic acid lactone with (+)-α-phenyl-1-naphthalenemethylamine yielded an amide melting at 151–152° (*Anal.* Calcd. for $C_{25}H_{25}NO_3$: C, 76.00; H, 6.93; N, 3.85. Found: C, 76.28; H, 6.90; N, 3.81) $[\alpha]^{25}D + 29°$ (*c*, 1.1 in chloroform). Alkaline hydrolysis of this amide yielded mevalonic acid (isolated as the crystalline N,N′-dibenzylethylenediammonium salt, m.p. 125–126°; *Anal.* Calcd. for $C_{28}H_{44}N_2O_3$: C, 62.66; H, 8.26. Found: C, 62.60; H, 8.28) which had microbiological activity for *Lactobacillus acidophilus*, ATCC 4963,[1] equal to that of the natural isomer.

When it became known[6] that mevalonic acid is a precursor in the formation of cholesterol, consideration of alternative biosynthetic reactions led to an evident interest in the closely related aldehyde, 3-hydroxy-3-methylglutaraldehydic acid (mevaldic acid, II). This new aldehyde has now been synthesized for study in "isoprenoid" biosynthetic systems.

A Reformatsky reaction involving the dimethyl-acetal of acetoacetaldehyde and ethyl bromoacetate

(1) H. R. Skeggs, L. D. Wright, E. L. Cresson, G. D. E. Macrae, C. H. Hoffman, D. E. Wolf and K. Folkers, *J. Bact.*, **72**, 519 (1956).
(2) L. D. Wright, E. L. Cresson, H. R. Skeggs, G. D. E. Macrae, C. H. Hoffman, D. E. Wolf and K. Folkers, THIS JOURNAL, **78**, 5273 (1956).
(3) D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright and K. Folkers, *ibid.*, **78**, 4499 (1956).
(4) D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright and K. Folkers, *ibid.*, **79**, 1486 (1957).
(5) C. H. Hoffman, A. F. Wagner, A. N. Wilson, E. Walton, C. H. Shunk, D. E. Wolf, F. W. Holly and K. Folkers, *ibid.*, **79**, 2316 (1957).
(6) P. A. Tavormina, M. H. Gibbs and J. W. Huff, *ibid.*, **78**, 4498 (1956).

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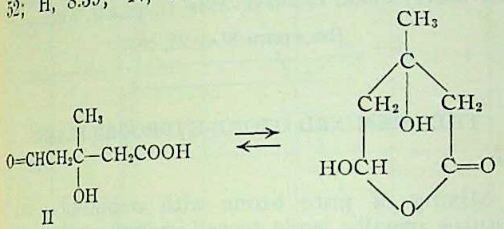
yielded ethyl DL-3-hydroxy-3-methyl-5,5-dimethoxypentanoate (III), b.p. 61–63° (0.1 mm.), $n^{25}D$ 1.4353. (*Anal.* Calcd. for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 54.79; H, 8.95.) Hydrolysis of III with sodium hydroxide yielded DL-3-hydroxy-3-methyl-5,5-dimethoxypentanoic acid (IV) which was isolated as the crystalline N,N′-dibenzylethylenediammonium salt, m.p. 107–107.5°. (*Anal.* Calcd. for $C_{32}H_{52}N_2O_{10}$: C, 61.52; H, 8.39; N, 4.48. Found: C, 61.32; H, 8.73; N, 4.60.) Hydrolysis of IV at 25° with 0.1*N* hydrochloric acid yielded DL-3-hydroxy-3-methylglutaraldehydic acid (II) in solution. The presence of the unstable and reactive aldehyde II was proven by reduction of it with either hydrogen over a platinum catalyst or with sodium borohydride in alkaline solution to give DL-mevalonic acid (I) in apparently quantitative yield as based on microbiological assay. Varying the time of acid hydrolysis of IV from 15 minutes to 5 hours did not appreciably reduce the high yield of DL-mevalonic acid, although dehydration and decarboxylation of II to 3-methylcrotonaldehyde was observed when more vigorous hydrolysis conditions were employed. After either reduction step, the DL-mevalonic acid was isolated as its crystalline N,N′-dibenzylethylenediammonium salt in *ca.* 30% yield. This product was shown to be identical with an authentic sample of N,N′-dibenzylethylenediammonium bis-(DL-mevalonate) by comparison of the infrared spectra, by a mixed melting point determination and by microbiological assay with *Lactobacillus acidophilus*, ATCC 4963.



II

Solutions of the aldehyde were prepared from the acetal immediately before biological testing. The microbiological activity of DL-3-hydroxy-3-methylglutaraldehydic acid for *Lactobacillus acidophilus* was found to be about 1/200 that of DL-mevalonic acid. The corresponding dimethylacetal (IV) was essentially inactive in this test. The effect of the aldehyde II on the incorporation of acetate into cholesterol was studied. Experiments (Table I) show that DL-3-hydroxy-3-methylglutaraldehydic acid suppresses the incorporation of 1-C^{14}-labelled acetate into cholesterol by rat liver homogenate to about the same degree as mevalonic acid. The corresponding acetal was inactive in this system. Work is in progress to prepare the labelled aldehyde so that it can be studied in this and other biosynthetic systems.

TABLE I

INHIBITION OF THE INCORPORATION OF 1-C^{14}-LABELLED ACETATE INTO CHOLESTEROL

Each flask contained 5 ml. of rat liver homogenate, 1 mg. each of ATP and DPN, and 0.2 mg. 1-C^{14}-acetate (2.44 μcurie). Compounds were added as indicated. Final volume was 10 ml. Gas phase was 95% O_2–5% CO_2. Incubation with agitation was carried out at 37° for 4.5 hr. Cholesterol was isolated and counted as the digitonide.

Compound added	Level, mg.	Experiment 1 Recovered cholesterol c.p.m./mg. C	Experiment 1 % Inhibition	Experiment 2 Recovered cholesterol c.p.m./mg. C	Experiment 2 % Inhibition
None	...	5,294	..	16,519	..
DL-Mevalonic acid	1.0	...	..	9,288	44
	3.0	1,808	66	6,340	62
DL-Mevaldic acid	1.0	212	96	305	96
	3.0	4,294	19	11,919	28
DL-3-Hydroxy-3-methyl-5,5-dimethoxypentanoic acid	1.5	1,349	75	11,007	33
	3.0	184	97	2,221	87
	1.5	5,574	0	17,030	0
	3.0	...	..	16,828	0

CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES DIVISION OF MERCK & CO., INC. RAHWAY, NEW JERSEY

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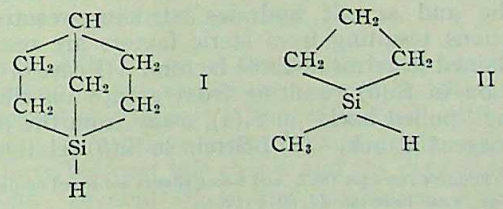
RECEIVED MAY 13, 1957

STEREOCHEMISTRY OF HYDRIDE ION DISPLACEMENT FROM SILICON. ENHANCED RATES AT BRIDGEHEAD AND 4-RING SILICON ATOMS[1]

Sir:

The reactions of triorganosilanes, R_3SiH, with hydroxide ion in 95% ethanol have received much study and proceed $R_3SiH + OH^- + SH \rightarrow R_3SiOH + H_2 + S^-$, where SH represents solvent. Hydroxide is not consumed and hydrogen formation (which is quantitative) follows a pseudo first order rate law. These reactions are first order with respect to both silane and hydroxide, $-d[\text{silane}]/dt = k_2[\text{silane}][OH^-]$,[2] and are thus formally similar to SN2 displacements on carbon from the standpoint of kinetics.

In this communication we wish to record data on the reactivities of bridgehead (I) and 4-ring (II)



silicon hydrides relative to the reactivities of acyclic and other previously known cyclic silicon hydrides.[3,4]

(1) Paper 53 in a series on organosilicon chemistry; for 52 see L. H. Sommer, O. W. Steward and P. G. Campbell, THIS JOURNAL, **79**, in press (1957).

(2) For a recent paper on hydrogen isotope effects and pertinent references to earlier work on these reactions see L. Kaplan and K. E. Wilzbach, *ibid.*, **77**, 1297 (1955).

(3) The bridgehead silane, I, has been reported, L. H. Sommer and O. F. Bennett, *ibid.*, **79**, 1008 (1957).

(4) The 4-ring silane, II, 1-methyl-1-silacyclobutane, b.p. 63° (733 mm.), $n^{20}D$ 1.4313 was prepared by a conventional 3-step procedure from allyl chloride and methyldichlorosilane as starting materials. *Anal.* Calcd. for $C_4H_{10}Si$: Si, 32.6; H (attached to Si), 1.16. Found: Si, 32.2; H (attached to Si), 1.11. The infrared spectrum of II had the sharp maximum at 8.9 μ characteristic of four other silacyclobutane compounds prepared in This Laboratory.

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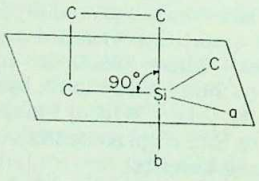
For reactions of R_3SiH with OH^- in 95% ethanol at 35° relative rates (k_2) are, for $(C_2H_5)_3SiH$ = 1; I, 10^3; II, 10^4–10^5; $(CH_2)_4Si(CH_3)H$, 10; $(CH_2)_5Si(CH_3)H$, 10^{-1}. For $(C_2H_5)_3SiH$ at 35°, k_2 = 0.1 min.$^{-1}$, mole^{-1} l.[5,6]

The corresponding disiloxane, bis-(1-silabicyclo-[2.2.1]heptyl) oxide,[3] m.p. 76°, was isolated in 40% yield (62 mg.) from the kinetics runs with I and perfectly linear pseudo first order plots were obtained. The 4-ring silane, II, gives 60% of the theoretical hydrogen at an extremely fast rate and 40% at a different rate which is smaller than the first by a factor of about three powers of ten. The latter rate has been shown to comprise hydrogen evolution from *sym*-di-*n*-propyldimethyldisiloxane which is formed by ring-opening of II (C-Si cleavage by OH^-) in competition with the evolution of hydrogen from the 4-ring silane.[7]

Thus, it is clear that displacement of hydride ion by hydroxide ion proceeds *far more rapidly* at bridgehead[8] and 4-ring silicon atoms than at silicon in ordinary a-cyclic and 5- as well as 6-ring silicon hydrides. These results comprise a complete reversal of the structure-reactivity relationships observed for displacements at carbon when the same comparisons are made.[9]

The above facts are in accord with the hypothesis outlined in our earlier communication.[3] Thus, in the reaction of II with hydroxide the geometry of the Si(5) addition compound would approximate one of two (idealized) structures: (1) a = H, b = OH; (2) a = OH, b = H.



On the above model of Si(5) complex for II with hydroxide ion[10] and similar models for I and other cyclic and acyclic hydrides, structure-reactivity relations resulting from steric factors are readily explained in terms of three factors: (1) ease of formation of Si(5) resulting from groups on silicon being "pulled back" in Si(4), away from the path of reagent attack. (2) I-Strain in Si(5) relative to Si(4).[11] (3) Steric strain in Si(5) relative to Si(4) due to increased "crowding" of groups in the former.[12]

(5) Relative rates for the 5- and 6-ring silanes are based on data in R. West, THIS JOURNAL, **76**, 6015 (1954).

(6) Salt effects on k_2 resulting from change in KOH concentration should not appreciably affect the above relative rates tabulation which covers the range 0.003 *N* to 0.2 *N* KOH; see J. E. Baines and C. Eaborn, *J. Chem. Soc.*, 813 (1955).

(7) In 95% ethanol at 35° the 4-ring silane gives 60% of the theoretical hydrogen with an ammonia–ammonium iodide buffer (0.5 *N* NH_3, 0.05 *N* NH_4I) at a rate which corresponds to a half-life of 7.5 minutes. The same reagent gives *no hydrogen* in a reasonable time with the highly reactive triphenylsilane.

(8) Energies of activation, E_a, for $(C_2H_5)_3SiH$ and I are 16 kcal./mole and 7 kcal./mole, respectively. The latter value was calculated from rate data at 0 and −24° using 0.0579 *N* KOH. Relative rate for I at 35° is a calculated value based on the E_a.

(9) For a recent excellent summary of data on effects of ring size on reactivity, see A. Streitwieser, Jr., *Chem. Rev.*, **56**, 666–670 (1956).

(10) There are, of course, four possible structures of Si(5) for II which would have the H-Si-OH angle near 90°, but two of these would be energetically unfavorable since the C-Si-C angle would be constrained from an ideal angle of 120° to *W*90° by the silacyclobutane system.

(11) H. C. Brown and M. Borkowski, THIS JOURNAL, **74**, 1894 (1952), and other earlier papers on the elegant I-Strain hypothesis.

(12) Relative rate (k_2) for t-$C_4H_9Si(CH_3)_2H$ is 10^{-2}. Unpublished work of L. H. Sommer and W. P. Barie, Jr.

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RECEIVED MAY 23, 1957

THE PREMIXED OZONE-HYDROGEN FLAME[1]

Sir:

Mixing of pure ozone with combustible substances usually leads to self-ignition, explosion or detonation and *premixed* pure ozone–fuel flames have not been reported. They are interesting not only because of the higher enthalpy content of the O_3–fuel *vs.* the O_2–fuel system, but primarily because the combustion kinetics in the flame front of the O_3-systems can be expected to be substantially faster than for the corresponding O_2–systems.

We have described recently the combustion flame of ozone to oxygen.[2] We also found that pure ozone can be mixed with pure hydrogen at −78° and even at 20° and 1 atm. without explosion and with no, or practically no, reaction for several hours.

Pure ozone–hydrogen mixtures of any desired composition were prepared by mixing known volumes of the two gases. The mixtures were burned at −78° initial temperature using the same technique as before.[2] (The Reynolds numbers of all flames were below 2000.) The burning velocities were determined by the standard schlieren method. The same apparatus was used to measure the burning velocity of the H_2–O_2 system. The results are presented in Fig. 1. The experimental burning velocities at 195°K. initial temperature and 1.0 atm., were for 6.0, 12.0, 18.2, 18.5, 25.0 and 100.0 mole % O_3, respectively, 207 ± 5, 664 ± 57, 1290 ± 20, 1330 ± 30, 1680 ± 80 and 270 ± 7 cm./sec.

Mixtures of 94.0 to 75.0% H_2 (rest pure ozone) could be burned readily. These O_3–H_2 flames are brighter than the corresponding O_2 flames but like the latter their luminosity is low. The stoichiometric mixture, *i.e.*, 3.0 vol. H_2 + 1.0 vol. O_3, which could be appropriately called "super-knall gas," burns very rapidly at a velocity of 1680 ± 80 cm./sec., whereas "knall gas," classically considered the fastest burning gas mixture, burns at 610 cm./sec. or 1/2.75 as rapidly. In mixtures on the ozone-rich side of the stoichiometric point the flame front degenerates very rapidly to a detona-

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under Contract No. AF18(600) 1475. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) A. G. Streng and A. V. Grosse, THIS JOURNAL, **79**, 1517 (1957); see also *Proc. VIth International Symposium on Combustion*, Aug. 19–24, 1956; *Proc. International Ozone Conference*, Chicago, Ill., Nov. 28–30, 1956.

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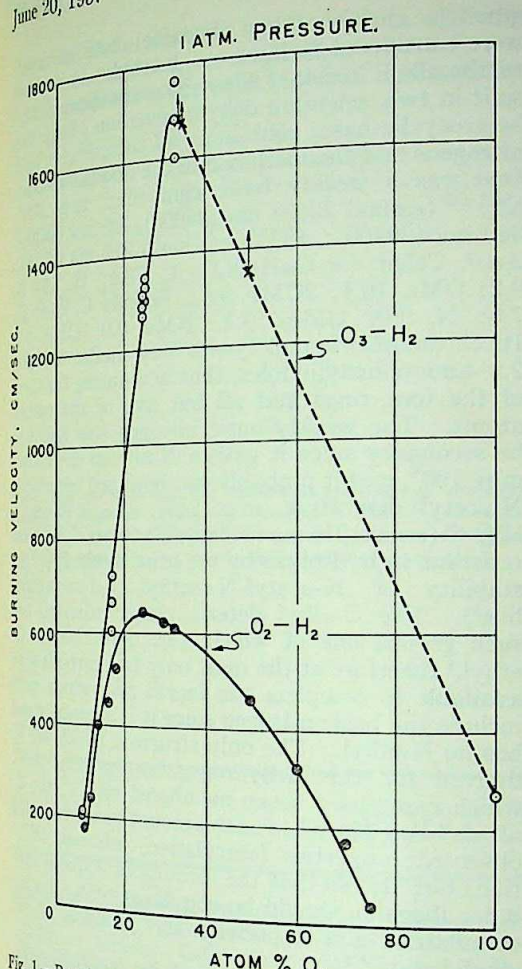

Fig. 1.—Burning velocities of $O_3 + H_2$ and $O_2 + H_2$ mixtures at 195°K. initial temperature and 1 atm. pressure.

tion front; it has not been possible as yet to burn such mixtures successfully.

The expected substantially faster burning velocity of the H_2–O_3 *vs.* the H_2–O_2 system has thus been proven experimentally. An intensive study of other O_3 flames is warranted.

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RECEIVED MAY 2, 1957

THE CONFIGURATION OF BASE-DENATURED β-LACTOGLOBULIN[1]

Sir:

It has been shown by Cannan, Palmer and Kibrick[2] that titration curves of β-lactoglobulin, in acid and neutral solutions at 25°, obey the Linderstrøm-Lang equation,[3] with a value for the electrostatic interaction factor w which is reasonable for a molecule of molecular weight 40,000. Above *p*H 10, however, the titration curves were found to be steeper, indicative of a considerably smaller value of w. A change in the properties of this protein near *p*H 10 is in accord with the finding of Groves, Hipp and McMeekin[4] that β-lactoglobulin becomes denatured near this *p*H. The titration curve above *p*H 10 thus represents the behavior of the denatured protein.

To investigate this behavior further, we have studied the dissociation of the phenolic groups of β-lactoglobulin, using the spectrophotometric method of Crammer and Neuberger.[5,6] The results are reported in the form of the logarithmic plot of Fig. 1.[7] The ordinate of such a plot represents the effective *pK* of the groups being titrated. According to any simple theory, such as the Linderstrøm-Lang theory, it should *increase* with increasing net negative charge because of the attractive force between this charge and the dissociating protons. In contrast to this prediction, Fig. 1 shows *p*H–log $\alpha/(1-\alpha)$ to be essentially independent of charge. This same phenomenon is served in serum albumin,[8] for the phenolic and amino groups above *p*H 11, and for the carboxyl

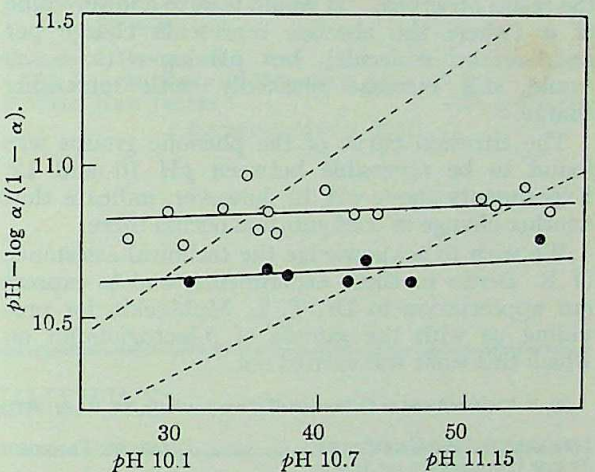

Fig. 1.—Titration of the phenolic groups of β-lactoglobulin at 25° and ionic strengths 0.08 (○) and 0.27 (●): the dotted lines show the predicted slopes for a compact sphere of molecular weight 35,000 to 40,000 at ionic strength 0.08 (upper line) and 0.27 (lower line). For a molecular weight of 17,500 the slopes of these curves would be reduced to about 0.6 of these values. The *p*H values are those at ionic strength 0.08; at ionic strength 0.27 the corresponding *p*H values are roughly 0.2 *p*H unit lower.

(1) This work was supported by research grant G-1805 from the National Science Foundation and by research grant RG-2350 from the National Institutes of Health, Public Health Service.

(2) R. K. Cannan, A. H. Palmer and A. C. Kibrick, *J. Biol. Chem.*, **142**, 803 (1942).

(3) K. Linderstrøm-Lang, *Compt. rend. trav. Lab. Carlsberg*, **15**, No. 7 (1924).

(4) M. L. Groves, N. J. Hipp and T. L. McMeekin, THIS JOURNAL, **73**, 2790 (1951).

(5) J. L. Crammer and A. Neuberger, *Biochem. J.*, **37**, 302 (1943).

(6) C. Tanford and G. L. Roberts, Jr., THIS JOURNAL, **74**, 2509 (1952); C. Tanford, J. D. Hauenstein and D. G. Rands, *ibid.*, **77**, 6409 (1955).

(7) The charge at a given *p*H is based on a molecular weight of 40,000 and was taken from the titration curves of Cannan, *et al.*[2] Above *p*H 10.8 the charges represent an extrapolation of their results. Neither the assumed molecular weight nor the accuracy of the extrapolation affects our conclusions, for *p*H–log $\alpha/(1-\alpha)$ is an experimental parameter independent of these variables, and we wish only to show that this parameter is virtually independent of charge.

(8) C. Tanford, J. G. Buzzell, D. G. Rands and S. A. Swanson, THIS JOURNAL, **77**, 6421 (1955).

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groups below *p*H 4. It was interpreted as indicating that serum albumin exists below *p*H 4 and above *p*H 11 in an expandable configuration, resembling the configuration to be expected of a simple flexible polyelectrolyte with relatively few cross-links. In such a configuration an increase in charge is accompanied by an increase in charge separation, so that the force acting on the dissociating protons remains virtually unchanged.

Figure 1 thus indicates that above *p*H 10 β-lactoglobulin also exists in an expandable configuration. The work of Townend and Timasheff[9] suggests that, in addition, the molecular weight above *p*H 10 could well be much lower than 40,000. Dissociation by itself, however, will not account for the result observed. It would lead to a lower value of w (where the abscissa represents charge per *undissociated* molecule), but *p*H–log $\alpha/(1-\alpha)$ would still increase markedly with increasing charge.

The titration curve of the phenolic groups was found to be reversible between *p*H 10 and 12. Experiments above *p*H 12, however, indicate that another change in configuration occurs there.

We wish to acknowledge the technical assistance of R. Berdo in these experiments, and to express our appreciation to Dr. T. L. McMeekin for providing us with the sample of β-lactoglobulin on which this work was carried out.

(9) R. Townend and S. N. Timasheff, THIS JOURNAL, **79**, July (1957).

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IOWA CITY, IOWA

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SIGURD A. SWANSON

RECEIVED MAY 15, 1957

IBOGA ALKALOIDS. II.[1] THE STRUCTURES OF IBOGAINE, IBOGAMINE AND TABERNANTHINE

Sir:

The principal base of *Tabernanthe iboga Baillon*, the pentacyclic alkaloid ibogaine $C_{20}H_{26}N_2O$, has been shown to contain a 5-methoxyindole moiety,[1,2] but apart from the isolation of 3-methyl-5-ethylpyridine[3] no clue as to the nature of the hydroaromatic portion of the molecule is available. We have now found contrary to current belief that the C-alkyl[4] of ibogaine is a C-ethyl since propionic acid can be shown to be an important component of the volatile acids formed in the Kuhn-Roth determination.[5] This result eliminates from discussion the structure proposals for ibogaine[6] and voacangine[7] (a carbomethoxy ibogaine) both of which were considered to have a C-methyl. In contrast to the alkali fusion,[1,3] where ibogaine appears to be split in two, selenium dehydrogenation affords two heterocyclic bases containing all the carbons, both nitrogens and the methoxyl of the original alkaloid. One was a weakly basic compound, m.p. 208°; $\lambda_{max}^{95\%\ alc}$ (ε max) 226–8 mμ (34600), 308 mμ (16100), 340 mμ (20400); $\lambda_{max}^{0.1NHCl}$ (ε max) 317 mμ (25250). *Anal.* Calcd. for $C_{20}H_{22}N_2O$: C, 78.4; H, 7.2; N, 9.2; OMe, 10.1; 2CMe, 9.8. Found: C, 78.4; H, 7.5; N, 9.0; OMe, 10.1; NMe, 0.0; CMe, 6.7. Its chromophoric moiety was very similar to model 2,2[1]-aminophenylindoles, thus accounting for three of the four rings and all but five of the carbon atoms. The weakly basic nitrogen was found to be secondary since it gave a N-nitroso derivative, m.p. 196°, and it probably was hindered because its N-acetyl derivative, m.p. 246°, $\nu_{C=O}$ 1640 cm.$^{-1}$, $\lambda_{max}^{95\%\ alc}$ (ε max) 216 mμ (34580), 321-2 mμ (27,200) was resistant to hydrolysis by the usual methods (*cf.* the stability of N-acetyl-N-methyl-2,6-dimethylaniline[8]). The C-alkyl determination indicated two such groups one of which must have been a C-ethyl,[5] therefore at the most only two carbons were available to complete the fourth ring which must include the basic nitrogen since it is secondary and has no N-alkyl. The only structure which can be derived for this dehydrogenation product is II which contains a seven-membered ring C, the C-alkyls being placed so as to account not only for the observed properties (acetylation, infrared, oxidation) but also so that the formula Ia deduced from it for ibogaine should be consistent with other accumulated facts especially the products of the alkali fusion.[1,3]

The structure of the second selenium degradation product, the indoloquinoline III, m.p. 176°, follows from its analytical data, infrared and ultraviolet spectra, $\lambda_{max}^{95\%\ alc}$ (ε max) 237 mμ (39030), 276 mμ (43930), 298 mμ (22750), 333 mμ (5766), 349 mμ (2857); $\lambda_{max}^{0.1NHCl}$ (ε max) 219 mμ (27700), 230 mμ(28130), 269–71 mμ (43130), 296–7 mμ (27800), 310 mμ (19910), 327–35 mμ plateau (9450). *Anal.* Calcd., for $C_{20}H_{26}N_2O$: C, 78.9; H, 6.6; 3CMe, 13.8. Found: C, 78.5; H, 6.8; CMe, 8.8.

In view of the parallelism which has been demonstrated between the chemistry of ibogaine and its companion alkaloids,[4] tabernanthine can now be represented as Ib and ibogamine as Ic. In agreement with this deduction ibogamine on dehydrogenation with selenium affords products analogous to those obtained from ibogaine, *i.e.*, a weakly basic substance, II (MeO = H), m.p. 214° (*Anal.* Calcd. for $C_{19}H_{20}N_2$: C, 82.6; H, 7.3. Found: C, 82.4; H, 7.4), and a base III (MeO = H), m.p. 196–7°. *Anal.* Calcd. for $C_{19}H_{18}N_2$: C, 83.3; H, 6.6. Found: C, 83.2; H, 6.6. A confirmation of the proposed structures of the selenium degradation products has been provided by MacPhillamy, Lucas and Dziemian of these laboratories, who synthesized the indoloquinoline III (MeO = H) which

(1) E. Schlittler, C. A. Burkhardt and E. Gellért, *Helv. Chim. Acta*, **36**, 1337 (1953), this paper is regarded as part I of the series.

(2) M.-M. Janot, R. Goutarel and R. P.-A. Sneedon, *ibid*, **34**, 1205 (1951).

(3) R. Goutarel, M.-M. Janot, F. Mathys and V. Prelog, *Compt. rend.*, **237**, 1718 (1953).

(4) The C-allyls recorded in the analytical data are presented as C-Me for convenience.

(5) The technique developed in these laboratories by Mr. L. Dorfman is a modification of that already used by H. Bickel, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **38**, 649 (1955). By the same method we have shown a C-ethyl to be present in dihydrogelsemine, aspidospermine, ajmaline, tabernanthine and ibogamine.

(6) R. Goutarel, These Doct. ès Sciences, Paris, 1954.

(7) M.-M. Janot and R. Goutarel, *Compt. rend.*, **241**, 986 (1955). If the decarboxylation of voacangine to ibogaine does not involve a rearrangement then the most likely position for the carbomethoxy group is on the asterisked carbon in Ia.

(8) P. Friedländer and Brand, *Monatsh.*, **19**, 642 (1898).

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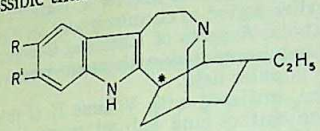
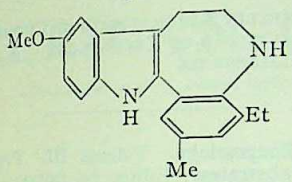
was found to be identical in all respects with the compound obtained from ibogamine.

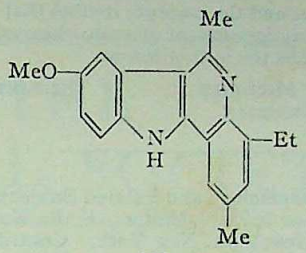
It is possible that the work reported here and the structure Ia[9] derived for ibogaine may prove applicable to the group of indole alkaloids which are known to furnish 3,5-dialkylpyridines by drastic methods of degradation.



I



II



III

a: R = OMe, R^1 = H
b: R = H, R^1 = OMe
c: R = R^1 = H

(9) It is of interest to note that Robinson's hypothetical "dihydroibogaine" ("Structural Relations of Natural Products," Clarendon Press, 1955) is closely related to this structure. A seven-membered ring C for ibogaine was also a feature of the earlier proposal, ref. 6.

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RECEIVED MAY 9, 1957

BOOK REVIEWS

Introduction to Solid State Physics. Second Edition. By CHARLES KITTEL, Professor of Physics, University of California, Berkeley, California. John Wiley & Sons, Inc., Publishers, 440 Fourth Avenue, New York 16, New York. 1956. xvii + 617 pp. 16 × 23 cm. Price, $12.00.

This book is the first volume in a new series on the science and technology of materials. It is intended as an introductory textbook in solid state physics for students of physics, chemistry, and engineering. The second edition is about two hundred pages longer than the first and is superior, both in the clarity of the explanations and in the extent of the material. A good general knowledge of physics and mathematics is required for complete understanding of the argument, but the non-mathematical reader will find a large amount of interesting and helpful information. Although the chemical topics of heterogeneous catalysis, thermal and photochemical decomposition, and adsorption are neglected, the neglect is compensated by a thorough discussion of the topics that are included and by excellent references at the end of each chapter.

The sections on the classification of solids and on crystal structure have been greatly expanded and clarified by the use of two-dimensional crystal models. The discussions of lattice energy, lattice vibrations, elastic constants, heat capacity, thermal and dielectric properties, ferroelectrics and diamagnetism and paramagnetism are essentially unchanged. However, they have been modernized and recent data are included.

The free electron theory of metals and the band theory of solids are introduced relatively early in the book and they are used to explain the properties of metals, alloys, insulators and semiconductors. Again, the theoretical discussion is supplemented by two-dimensional models. New information about cyclotron resonance and transistor manufacture is included.

The discussion of ferromagnetism, antiferromagnetism and superconductivity has been modernized and placed after the theoretical sections.

The description of imperfections in solids has been rewritten. The discussion of lattice vacancies, diffusion, color centers and excitons is improved. The problem of describing three-dimensional dislocation structures with two-dimensional pages has been reasonably well solved, and several striking pictures of dislocation phenomena have been included.

Occasionally, some humor enlivens the grim procession of solid state phenomena. The author describes the difference of e^{-3000} between the experiments of Volmer and Schultze and the theory of growth of ideal crystals, and then states, "This has been referred to as an all-time record for disagreement between observation and theory." At another point, he reports, "The highest surface recombination velocities are found for sand-blasted surfaces; the lowest velocities are found for surfaces polished smooth and then etched with empirical solutions. A certain amount of magic is thought to be involved in a good etch." This is a real challenge to the chemist to help the alphysicist.

The new series on materials begins well. If succeeding books maintain the high standards set by this one, they will be a valuable addition to the library of every chemist who is interested in solids.

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EASTMAN KODAK COMPANY GEORGE W. LUCKEY
ROCHESTER 4, NEW YORK

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pH Measurements. Their Theory and Practice. By VICTOR GOLD, B.Sc., Ph.D., Reader in Physical Organic Chemistry, King's College, University of London. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y., 1956. 125 pp. 11 × 17 cm. Price $2.25.

This little monograph covers quite thoroughly the subject of *p*H measurements, particularly from the theoretical side. It discusses the theory of proton transfer equilibria, of galvanic cells, the definition and interpretation of the *p*H scale. The determination of *p*H by potential measurements and by optical methods is described. There is a discussion of *p*H relations in the ionization of acids and bases, including titrations of strong and weak acids and bases. Buffers are also discussed. The relation between *p*H and reaction ve-

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locities is considered. One chapter is devoted to measurements in non-aqueous solvents.

The author states in the preface that the book is intended primarily for non-specialists. A large amount of information has been condensed into a small book. The treatment of *p*H is rigorous and the reviewer doubts that a person with only a small background of physico-chemical theory will find it as useful as the author hopes.

UNIVERSITY OF MICHIGAN HOBART H. WILLARD
ANN ARBOR, MICHIGAN

Advances in Enzymology and Related Subjects of Biochemistry. Volume XVII. Editor: F. F. NORD, Fordham University, New York, New York. Contributors: R. H. ALBERTY, University of Wisconsin, Madison, Wisconsin; B. AXELROD, Purdue University, Lafayette, Indiana; B. CHANCE, University of Pennsylvania, Philadelphia, Pennsylvania; S. J. COOPERSTEIN, Western Reserve University, Cleveland, Ohio; A. G. DE BUSK, University of Texas, Austin, Texas; E. C. DE RENZO, Lederle Laboratories, American Cyanamid Company, Pearl River, New York; J. EDELMAN, Imperial College of Science and Technology, London, England; R. JEENER, University of Brussells, Brussells, Belgium; H. R. MAHLER, Indiana University, Bloomington, Indiana; I. MANDL, Columbia University, New York, New York; C. NEUBERG, New York Medical College, New York, New York; W. W. WAINIO, Rutgers University, New Brunswick, New Jersey; G. R. WILLIAMS, University of Toronto, Toronto, Canada. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, New York. 1956. vii + 556 pp. 16 × 23.5 cm. Price $11.00.

The most recent volume of this well known series contains a number of notable reviews.

A lucid account of the situations most frequently encountered in the interpretation of the kinetics of enzyme-catalyzed reactions is given by Alberty. The general discussion, which is characterized by its restraint and avoidance of complicated reaction representations whose consideration at the present time can be no more than a demonstration of facility in algebraic manipulation, will be welcomed by many investigators who are seeking a summary of the more common representations with their corresponding rate equations expressed in terms of a consistent set of symbols. This article also contains a brief description of the kinetic behavior of six enzyme systems, *i.e.*, alcohol dehydrogenase, cholinesterase, α-chymotrypsin, fumarase, peroxidase and urease, that have been studied more or less extensively in recent years.

Chance and Williams have provided a welcome summary of their views on the functions of the respiratory chain in terms of spectroscopically detectable electron transport components of intact mitochondria, on how the process of respiratory control can be used to localize sites of energy conservation, on possible mechanisms for the conservation and phosphorylation processes and how such mechanisms can operate in isolated mitochondria, in intact cell suspensions or in solid tissue. The fluid and controversial nature of interpretations in this area of enzymology is emphasized by the timely and well documented article of Wainio and Cooperstein entitled "Some Controversial Aspects of the Mammalian Cytochromes" appearing later in the same volume.

Surveys of the present status of two important types of enzyme-catalyzed processes, *i.e.*, phosphate transfer and the formation of oligosaccharides *via* transglycosylation are provided by Axelrod and Edelman, respectively. Each of these articles is presented in a critical vein and they are valuable additions to the literature of enzyme chemistry.

Mahler has considered the nature and functions of the metalloflavoproteins and De Renzo the chemistry and biochemistry of xanthine oxidase. Both provide an authoritative account of two areas of enzymology that are in an early stage of development.

Of the remaining three chapters only that of Jeener on "Ribonucleic Acids and Virus Multiplication" appears to be of stature comparable to those noted above. The article by Mandl and Neuberg entitled "Solubilization, Migration and Utilization of Insoluble Matter in Nature" clearly belongs to an earlier period of chemistry and De Busk's review of the "Metabolic Aspects of Chemical Genetics" appears inadequate when compared with many recent reviews of this currently popular field.

The practice, initiated with Volume II of this series, of providing both author and subject cumulative indices is continued in the present volume.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
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Methods in Enzymology. Volume III. Preparation and Assay of Substrates. Edited by SIDNEY P. COLOWICK and NATHAN O. KAPLAN, McCollum-Pratt Institute, The Johns Hopkins University, Baltimore, Maryland. Academic Press Inc., 111 Fifth Avenue, New York 3, N. Y. 1957. xxiv + 1154 pp. 16 × 24 cm. Price, $26.00.

This volume is divided in the following sections: I, Carbohydrates; II, Lipides and steroids; III, Citric acid components; IV, Proteins and derivatives; V, Nucleic acids and derivatives; VI, Coenzymes and related phosphate compounds; VII, Determination of inorganic compounds. The seven sections contain one hundred and fifty procedures which were used by the authors in their investigations. This type of presentation no doubt offers the most desirable results. Occasionally, however, there is evidence of incompleteness, perhaps because of an author's limited interest. For example, on p. 334 the preparation of lecithin from beef hearts is described. It is stated that the $BaCl_2$-precipitate can be processed for cardiolipin but no directions are given for the procedure. Cardiolipin is also an important product since both compounds are employed in certain serological tests for syphilis. While much useful detail is presented on lecithin, nothing is said about cardiolipin.

On p. 414 a method for the determination of α-keto acids is described. This method has been in use for many years. It may be of interest, however, to note that Neish (*Rec. trav. chim.*, 72, 105 (1953)) has shown recently that the 2,4-dinitrophenylhydrazones of α-ketoglutaric acid and pyruvic acid may be separated by paper electrophoresis. In this method the separated nitro compounds, after extraction from filter paper, are reduced in acid solution and estimated by polarography. The electrophoretically separated hydrazones may also be determined colorimetrically (Tauber, *Anal. Chem.*, 27, 287 (1955)).

The reviewer notes with regret that the modern scientist at times is oversimplifying his method of writing. For example, on p. 334 "The cadmium-free chloroform solution is evaporated to dryness and taken up in 180 ml. of anhydrous ether," when what is meant is that the residue is taken up in ether. On the same page the term "amount" is used several times when volume and quantities were intended. On p. 416 and p. 417 one is directed to "incubate" samples for coupling of α-keto acids with hydrazine at 25 ± 2°. What is really meant is to place the samples in a water-bath at ± 2° for a certain number of minutes. Many enzymes, coenzymes and substrates which are difficult to prepare are now commercially available at reasonable prices. Mention should have been made of this fact more extensively in the individual contributions.

There is no serious defect in this extremely important volume. Editors, authors and publisher rendered a great service to biochemistry for making the appearance of these volumes possible.

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VOLUME 79 JULY 10, 1957 NUMBER 13

PHYSICAL AND INORGANIC CHEMISTRY

[CONTRIBUTION NO. 1430 FROM STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Ionic Association. I. Derivation of Constants from Conductance Data

BY RAYMOND M. FUOSS

RECEIVED MARCH 1, 1957

By combining the Fuoss–Onsager conductance equation with the law of mass action, a generalized conductance equation is obtained which includes the case of association of free ions to ion pairs. This equation can then be transformed into a linear equation in appropriate variables. It is shown that limiting conductance, ion size and association constant may be obtained by graphical treatment of conductance data at low concentrations ($\kappa a < 0.2$). A viscosity correction is also required if one ionic species is bulky compared to the solvent molecules.

When the classical mass action constant describing the dissociation of ion pairs is less than about 0.01, it can be easily determined to a good approximation from conductance data by application of a suitably modified form of the Ostwald dilution law.[1] But when the fraction of solute present as ion pairs is small, as is the case for ionophores[2] in solvents of high dielectric constant, the constant calculated by this method is necessarily incorrect, because it is forced by the method of calculation to absorb other (now calculable) effects which also lead to terms of the same order in concentration as the one due to association. When the phoreogram lies above the Onsager tangent, the older method cannot give even a poor approximation; from the classical point of view, the only conclusion which can be drawn is that "dissociation is complete," although there may be good reason to suspect that some association nevertheless is occurring.

The origin of the ambiguity lies in the form of the conductance function. If higher terms from long range interactions are ignored, the conductance equation would simply be

$$\Lambda = \Lambda_0 - Sc^{1/2} - cA_0/K \qquad (1)$$

where S is the Onsager coefficient

$$S = \alpha\Lambda_0 + \beta \qquad (2)$$

and K is the mass action constant. But the square root term is only the leading term of the relaxation and electrophoresis functions, and coefficients of terms of order c and c log c clearly would be included in the value of K derived from (1). When $K << 1$, the error is small, but when K approaches unity, the other terms can completely mask association. A recent calculation[3] of the next higher long range terms now provides a means of modifying (1) so that realistic values of K can be obtained, regardless of the magnitude of K.

Before starting the derivation, it seems advisable to introduce a change in nomenclature, which will place proper emphasis on the molecular mechanism under consideration. Traditionally, we speak of "dissociation" constants of electrolytes, following the proposal of Arrhenius that neutral molecules of solute electrolyte partially dissociate into free ions in solution. We now know that in the case of ionophores the ions exist *ab initio;* in a suitable environment, they may cluster to pairs or to higher aggregates under the influence of mutual attraction. Since the primary act therefore is the association of free ions rather than the dissociation of neutral molecules, it appears preferable to introduce the symbol A for the association constant which describes the associative equilibrium

$$A^+ + B' \rightleftharpoons A^+ \cdot B' \qquad (3)$$

We therefore write

$$[A^+ \cdot B']/[A^+][B'] = A \qquad (4)$$

where the bracketed quantities refer to activities. As usual, we shall assume that f_{AB} is unity and use the Debye–Hückel equation to calculate the activity coefficient f of the free ions. If γ denotes

(1) R. M. Fuoss, *Chem. Revs.*, **17**, 27 (1935); R. M. Fuoss and T. Shedlovsky, THIS JOURNAL, **71**, 1496 (1949).

(2) R. M. Fuoss, *J. Chem. Education*, **32**, 527 (1955).

(3) R. M. Fuoss and L. Onsager, *Proc. Nat. Acad. Sci.*, **41**, 274, 1010 (1955).

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the fraction of solute present as free ions, (4) then becomes

$$(1 - \gamma)/c\gamma^2 f^2 = A \quad (5)$$

whence

$$\gamma = 1 - Ac\gamma^2 f^2 \quad (6)$$

where

$$-\ln f = \beta' c^{1/2}\gamma^{1/2}/(1 + \kappa a\gamma^{1/2}) \quad (7)$$

and the other symbols have their usual meanings.

At low concentrations ($\kappa a \gg 0.2$), the conductance equation for unassociated electrolytes can be approximated closely[4] by

$$\Lambda = \Lambda_0 - Sc^{1/2} + Ec\log c + J_1 c(1 - \alpha c^{1/2})(1 - J_2 c^{1/2}/J_1) + O(c^2) \quad (8)$$

where

$$0.4343E = (\kappa^2 a^2 b^2/24c)\Lambda_0 - \kappa ab\beta/16c^{1/2} \quad (9)$$

$$b = e^2/aDkT \quad (10)$$

$$J_1 = \theta_1\Lambda_0 + \theta_4 \quad (11)$$

$$\theta_1 = (\kappa^2 a^2 b^2/12c)[g(b) + \ln(\kappa a/c^{1/2}) + 0.9074] \quad (12)$$

$$g(b) = (1 + 2b)/b^2 \quad (13)$$

$$\theta_4 = \alpha\beta + 8\beta\kappa a/9c^{1/2} - \theta_2 \quad (14)$$

$$\theta_2 = (\beta\kappa ab/8c^{1/2})[\ln(\kappa a/c^{1/2}) + 0.8504] \quad (15)$$

$$J_2 = \theta_3\Lambda_0 + 8\beta\kappa^2 a^2/9c \quad (16)$$

and

$$\theta_3 = [(ab\kappa/c^{1/2})^3 2^{1/2}/24b][g(b) - 1.0774] \quad (17)$$

(It will be noted that E, the coefficient of the c log c term, is independent of ion size and concentration, although the symbols a and c appear in (9); the θ's, on the other hand, are functions of a, both explicitly and also implicitly through b, but naturally are independent of c, which only appears in the ratio $\kappa^2/c = \pi e^2 N/125DkT$.)

Now let us assume that the conductance Λ_i due to the free ions is given by (8), if c is replaced consistently by $c\gamma$ which gives the actual concentration of free ions (in equivalents per liter). Then

$$\Lambda = \gamma\Lambda_i \quad (18)$$

where Λ is the observed equivalent conductance Combining (18) and (6) immediately gives

$$\Lambda = \Lambda_i - Ac\Lambda\gamma f^2 \quad (19)$$

and substitution of (8) (with $c\gamma$ in place of c) then gives

$$y = J_1 - Ax - J_2 c^{1/2}\gamma^{1/2} \quad (20)$$

where

$$y = \Delta\Lambda/c\gamma(1 - \alpha c^{1/2}\gamma^{1/2}) \quad (21)$$

$$\Delta\Lambda = \Lambda + Sc^{1/2}\gamma^{1/2} - Ec\gamma\log c\gamma - \Lambda_0 \quad (22)$$

and

$$x = \Lambda f^2/(1 - \alpha c^{1/2}\gamma^{1/2}) \quad (23)$$

At low concentrations, the J_2 term is small and may be neglected in first approximation, so that

$$y \approx J_1 - Ax \quad (24)$$

Therefore a plot of y against x should be linear; the slope evaluates the association constant A, and

$$J_1 = y(0) + A\Lambda_0 \quad (25)$$

where $y(0)$ is the ordinate at $c = 0$. From the value of J_1, a can then be found by interpolation on a J_1–a plot.

In order to begin the above computation of $\Delta\Lambda$ and f it is, however, necessary to have values for Λ_0 and γ. Extrapolation by Shedlovsky's method[5] gives a suitable starting value for Λ_0; the value found by this method is usually a little too small. At low concentrations, y is approaching 0/0; if the incorrect value of Λ_0 is inserted in (22), y will obviously approach $\pm\infty$ as concentration approaches zero. Hence, if the initial y *vs.* x plot shows a minimum, a larger value of Λ_0 should be used; if it becomes sharply concave downward at low concentrations, a smaller value is needed. For γ, the approximation

$$\gamma_0 = \Lambda/(\Lambda_0 - Sc^{1/2}\Lambda^{1/2}/\Lambda_0^{1/2}) \quad (26)$$

is used; the E and J_1 terms have opposite signs and to a considerable extent the errors so made compensate if both are neglected in (26). Then having determined J_1 by (25) (and hence a) to first approximation, the calculation may be repeated with γ to second approximation, given by

$$\gamma = \Lambda/(\Lambda_0 - Sc^{1/2}\gamma_0^{1/2} + Ec\gamma_0\log c\gamma_0 + J_1 c\gamma_0 - J_2 c^{3/2}\gamma_0^{3/2}) \quad (27)$$

Finally

$$y' = y + J_2 c^{1/2}\gamma^{1/2} \quad (28)$$

is plotted against x', also computed to second approximation, using (27) in (7) and (23). For $A \leqslant 15$, the values of a and A obtained from the original y–x plot do not differ by more than a few per cent. from those obtained from the y'–x' plot.

When A becomes small, *i.e.*, when the phoreogram lies near (or above) the Onsager tangent, γ may be safely approximated by unity in calculating the various interionic terms which appear in y and x. When A drops to values near unity, the y–x plot becomes practically horizontal within experimental error; in this case, it is necessary to have data for the salt in solvents of lower dielectric constant. These serve to determine a and hence J_1 and J_2 if we may assume that a is independent of composition in mixed solvents. Then one plots Λ''' against $c\Lambda f^2/(1 - \alpha c^{1/2})$; the slope is equal to A. Here Λ''' is defined as

$$\Lambda''' = \Lambda'' - J_1 c + J_2 c^{3/2} \quad (29)$$

where

$$\Lambda'' = (\Lambda + \beta c^{1/2} - Ec\log c)/(1 - \alpha c^{1/2})$$

and

$$\Lambda''' = \Lambda_0 - A[c\Lambda f^2/(1 - \alpha c^{1/2})] = \Lambda_0 - As \quad (30)$$

The intercept at $c = 0$ is the final value of Λ_0.

When large ions, such as quaternary ammonium ions (or picrates) are involved, a modification of (8) becomes necessary. These bulky ions interfere with the motion of the balancing counter ions, which in effect are moving in a medium of higher viscosity than that of the pure solvent. We recall that the equivalent conductance is proportional to the mobility which in turn is inversely proportional to the viscosity of the solvent medium to first approximation. In order to estimate this correction, we shall assume that the viscosity η at non-zero concentrations is given by the Einstein equation

$$\eta = \eta_0(1 + 5\phi/2)$$

(4) R. M. Fuoss and L. Onsager, *J. Phys. Chem.*, **61**, 668 (1957).

(5) T. Shedlovsky, *J. Franklin Inst.*, **225**, 739 (1938); R. M. Fuoss, THIS JOURNAL, **57**, 488 (1935); R. M. Fuoss and C. A. Kraus, THIS JOURNAL, **54**, 1405 (1932).

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July 5, 1957

where ϕ is the volume fraction of solute. If we assume that the cations have a hydrodynamic radius R, then

$$\phi = (4\pi R^3/3)(Nc/1000) = \delta c \qquad (31)$$

where N is Avogadro's number. Then the conductance equation becomes

$$\Lambda = [\Lambda_0 - \beta c^{1/2}/(1 + \kappa a)](1 + \Delta X/X)(1 + 5\delta c/2)^{-1} \qquad (32)$$

because viscosity appears in the denominator of both limiting mobility and the electrophoresis term. If $(1 + 5\delta c/2)^{-1}$ is approximated by $(1 - 5\delta c/2)$ in (31) and the same expansion is made as before, the final result, which replaces (24), is

$$y = J_1 - 5\Lambda_0\delta/2 - Ax \qquad (33)$$

This means that a plot of y against x should still be linear, with slope equal to A, but the ordinate at $c = 0$ ($x = \Lambda_0$) is now

$$y(0) = J_1 - 5\Lambda_0\delta/2 - A\Lambda_0 \qquad (34)$$

Hence if J_1 is known (*i.e.*, if a can be evaluated), δ and hence R are known. Examples of the various cases discussed will be given in the following paper. As will be emphasized there, it would be futile to attempt to apply the equations developed in this paper to data of low precision ($\pm$ 0.1% or worse).

There are several other corrections due to the actual volume of the ions which should be considered in the next higher approximation. The first is the modification of K which accounts for the fact that an ion and a solvent molecule cannot simultaneously occupy the same site.[6] The second is the change of dielectric constant produced by the ions: a decrease with respect to that of the solvent could be expected as a consequence of dielectric saturation in the close vicinity of ions, or merely due to a dilution effect if one species of ions were essentially paraffin, as is the case with quaternary ammonium ions. Both of these effects would lead to terms of order $c^{1/2}$ in the conductance equation. There may well be, of course, other still unknown terms. Over the range of concentration where we propose to apply the present analysis ($\kappa a < 0.2$), these terms are small. At higher concentrations, where the formally computed values of these terms would become numerically significant compared to the $c^{1/2}$, c and $c \log c$ terms, their inclusion appears to be irrelevant, because the continuum model for the ion atmosphere no longer is a valid physical approximation.[4] Consequently there is no need to contemplate the difficult and tedious task of integrating the equation of continuity to the next higher order of approximation in order to obtain the $c^{3/2}$ and $c^{3/2} \ln \kappa a$ terms.

(6) H. Falkenhagen, M. Leist and G. Kelbg, *Ann. Phys.*, (6) **11**, 51 (1952); M. Eigen and E. Wicke, *Naturwiss.*, **38**, 453 (1951); M. Dutta and S. N. Bagchi, *Ind. J. Phys.*, **24**, 2 (1950); S. N. Bagchi, *J. Ind. Chem. Soc.*, **27**, 4 (1950).

Finally we consider the association constant A. If association is solely due to electrostatic forces, then a correlation between A and the dielectric constant of the solvent should appear. The relation proposed by Bjerrum[7] has been found to describe ion association satisfactorily in solvents of low dielectric constant,[8] but $Q(b)$ contains a completely arbitrary cut-off limit at $r = e^2/2DkT = ab/2$. This limit is an artifact; convergence of the integral can be attained[9] by a more careful definition of ion pairs than that proposed by Bjerrum. But even so, the statistical approach to the problem still suffers from the esthetic handicap that ions which are not in actual contact still are counted as pairs. The Bjerrum cut-off also leads to another unrealistic situation: beyond a precisely and sharply definable critical limit of dielectric constant, ion association should cease abruptly. Actually, just as soon as the point charge model for the ions is replaced by one in which the ions are assigned a non-zero electrostatic radius a, we are admitting the existence of non-conducting ion pairs at any value (however high) of dielectric constant, because a non-zero size can only manifest itself when ions come into actual contact, and for the duration of the contact the pair can only react as a dipole to the external field. The dilemma can be neatly circumvented by a thermodynamic approach, as proposed by Ramsey,[10] who used a Born cycle to show that

$$K^{-1} \approx e^b \qquad (36)$$

in solvents of low dielectric constant. If the entropy terms[11] are included, (36) becomes

$$A = \exp(b + \Delta S/R) = A_0 e^b \qquad (37)$$

Here b is the Bjerrum parameter $e^2/aDkT$ defined by (10). If other interactions in addition to charge-charge forces are involved

$$A = A_0 \exp(b + u/kT) \qquad (38)$$

where u is the potential of the mean force concerned. For example, if one ion carries a dipole

$$u = \mu e/a^2 D \qquad (39)$$

provided a continuum model may be used. Arguments presented by Gurney appear to justify the use of the macroscopic dielectric constant in the cases of ion–ion and ion–dipole contacts.[12]

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(7) N. Bjerrum, *Kgl. Danske Vidensk. Selskab.*, **7**, No. 9 (1926).

(8) R. M. Fuoss and C. A. Kraus, THIS JOURNAL, **55**, 1019 (1933).

(9) R. M. Fuoss, *Trans. Faraday Soc.*, **30**, 967 (1934).

(10) J. T. Denison and J. B. Ramsey, THIS JOURNAL, **77**, 2615 (1955).

(11) W. R. Gilkerson, *J. Chem. Phys.*, **25**, 1199 (1956); J. G. Kirkwood, *ibid.*, **18**, 380 (1950).

(12) R. W. Gurney, "Ionic Processes in Solution," McGraw-Hill Book Co., New York, N. Y., 1953, Chap. 2.

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[Contribution No. 1431 from the Sterling Chemistry Laboratory of Yale University and the Metcalf Research Laboratory of Brown University]

Ionic Association. II. Several Salts in Dioxane–Water Mixtures

By Raymond M. Fuoss and Charles A. Kraus

Received March 1, 1957

A new method of mathematical analysis is applied to conductance data for several salts in dioxane–water mixtures. It is shown that the association constant A is a simple function $A_0 \exp(e^2/aDkT)$ of the dielectric constant of the solvent mixture, unless a dipole is present in one of the ions (*e.g.*, the bromate ion), when an additional ion–dipole free energy appears in the exponent. Data for quaternary ammonium salts show the presence of a previously unsuspected linear term in conductance, which is due to the viscosity increase produced by bulky ions. Consequently solution viscosity rather than solvent viscosity should be used in treating conductance. Finally, it is concluded that the Bjerrum theory of ion association and the Fuoss–Shedlovsky extrapolations should both be replaced by the methods used in the present analysis.

In the preceding paper,[1] it was shown that association constants may be derived from conductance data, even when the fraction of ions associated to pairs is small. A fundamental prerequisite is that the data be of high precision (± 0.02% at least); at a concentration of 0.005 N, for example, an association constant $A = 5$ corresponds to only about 2.5% association. A further prerequisite is that data be available over a range of values of dielectric constant; the range must be wide enough to include solvent mixtures in which the association constant has a value of at least 10. The reason for the latter requirement is simply that association gives a leading term of order concentration in the conductance equation, and there are also present linear terms from long range ionic interaction. When A is small, the difference of the interaction term $J_1(a)$ and $A\Lambda_0$ can be determined but the quantity cannot be resolved into its components. When one (or both) of the ions is bulky compared to the solvent molecules, an additional linear term $(5\Lambda_0\delta c/2)$ also appears, which can only be separated from the coefficient of the linear term if A and $\mathring{a}$ are independently known. From the data in solvents of low dielectric constant, the ion size a can be determined; given the ion size, A can be calculated for the solvents of higher dielectric constant, within the validity of the assumption that the parameter a is independent of composition. Recent work by Kraus[2] and co-workers satisfy the criteria described above. (There are many data of high precision in the literature for aqueous solutions, but they cannot be examined for ionic association because, if association occurs for say the alkali halides in water, it is so slight that it is undetectable by our present analysis; a small A would be absorbed in $J_1(a)$, and merely appear as a slightly different value of ion size from the one which should have been found.) In this paper, we shall present an analysis of several cases where the method is applicable. They will serve to show that conductance can become a considerably more powerful research tool than has previously been realized, in that it can serve to evaluate parameters characteristic of ions in addition to the limiting conductance.

Sodium Bromate.[2]—The conductance of this salt has been measured in water–dioxane mixtures covering the range $78.48 \geqslant D \geqslant 31.53$. When treated by the method appropriate for unassociated electrolytes,[3] the data give linear Λ''' *vs.* c plots and extrapolate to an unambiguous value of Λ_0, but the value of a required to make the Λ''' *vs.* c plot horizontal is only 3.00 Å., which seems unrealistically small. Hence, despite the fact that the conductance curve lies above the Onsager tangent, we are led to suspect ion association. In 55% dioxane, the phoreogram is catabatic, clearly indicating association. On the basis of the Bjerrum theory, it would be possible to have ion association at low dielectric constants, with an abrupt cessation of pairing above a critical value of the dielectric constant.[4] But this critical value is merely the consequence of a device used by Bjerrum to avoid divergence of an integral and corresponds to no physical reality; it seems more reasonable to assume that, as the dielectric constant is raised, the fraction of solute present as ion pairs gradually decreases at a given stoichiometric concentration, but never completely vanishes. Indeed, as already has been pointed out,[1] just as soon as a non-zero ion size is introduced into the model, the existence of ion pairs is tacitly admitted, because a non-zero size can only make itself visible experimentally by the effects of actual contacts of ions, and for the duration of the contact, neither ion can be considered to be "free" in any of the senses implied by that adjective. Availability of data for a salt over a range of dielectric constant in which the phoreogram starts below the Onsager tangent and crosses it as dielectric constant increases provides an ideal means of testing the above hypotheses.

For the four mixtures of lower dielectric constant, the functions y and x defined by equations 21 and 22 of the preceding paper were computed; the corresponding plots are shown in Fig. 1. For the 55 and 50% mixtures, the calculation was made to second approximation, as described in the previous paper. It should be emphasized that y is extremely sensitive to experimental error at low concentrations, because it contains in the numerator a *difference* which approaches zero as c approaches zero, while the denominator is proportional to c itself. For example, at 5×10^{-4} N in the 55% mixture, an error of only 0.020 A-unit in Λ makes an error of 10% in y. Hence relatively more weight is given to the points at higher concentrations; the latter must, of course, satisfy the condition $\kappa a < 0.20$, in order to permit application of the model

(1) R. M. Fuoss, This Journal, **79**, 3301 (1957).

(2) R. W. Martel and C. A. Kraus, *Proc. Nat. Acad. Sci.*, **41**, 9 (1955).

(3) R. M. Fuoss and L. Onsager, *J. Phys. Chem.*, **61**, 668 (1957).

(4) R. M. Fuoss and C. A. Kraus, This Journal, **55**, 1019 (1933).

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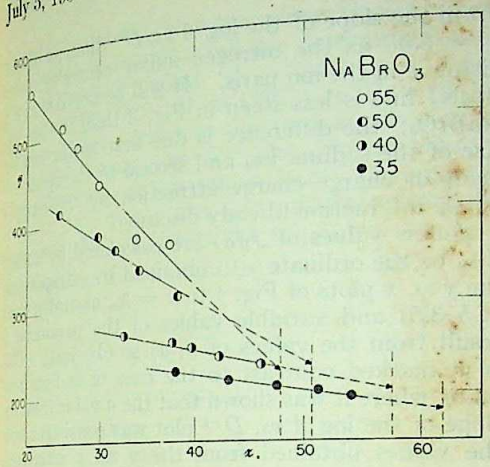

Fig. 1.—Extrapolation plots for sodium bromate in low range of dielectric constants.

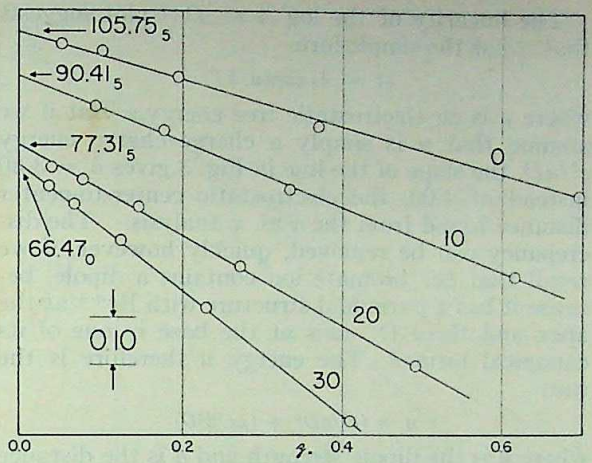

Fig. 2.—Extrapolation plots for sodium bromate in high range of dielectric constants.

and method.) Within experimental error, the plots are linear; the slopes determine the association constants A immediately. Extrapolation to $x = \Lambda_0$ gives the ordinate

$$y(0) = J_1(a) - A\Lambda_0$$

from which $J_1(a)$ is evaluated, because the product $A\Lambda_0$ is now known. Then from a plot of $J_1(a)$ against a, the value of a is determined. The results of these calculations are shown in the last four lines of Table I; it will be noted that the parameter a remains substantially constant.

TABLE I

SODIUM BROMATE IN DIOXANE–WATER MIXTURES AT 25°

% Dioxane	D	A	$J_1(a)$	a	λ_0
0	78.48	0.50	191	(4.00)	105.755
10	70.33	0.68	202	(4.00)	90.415
20	61.86	0.90	225	(4.00)	77.315
30	53.28	1.33	272	(4.00)	66.47
40	48.91	2.10	307	3.96	61.785
50	44.54	2.73	360	3.94	57.66
55	35.85	6.87	570	4.03	50.74
	31.53	11.8	790	4.17	47.92

At dioxane contents of less than 35% ($D > 50$), the y *vs.* x plots are so nearly horizontal that no reliable value of the slope (and hence of A) could be obtained; that is, the (nearly) constant ordinate evaluates the quantity $(J_1 - A\Lambda_0)$ but separation of the terms is no longer possible. We therefore assumed that a remained constant at 4.00, and computed Λ''', using $a = 4.00$ to evaluate J_1 and J_2, and plotted Λ''' against $z = c\Lambda f^2/(1 - \alpha c^{1/2})$; according to equation 30, the plot should be linear with slope A and intercept Λ_0. The graphs are shown in Fig. 2, where for compactness in presentation, the ordinate scales are shifted vertically by arbitrary amounts. The values of Λ_0 are indicated by the arrows. The unit of the vertical scale is shown by indicating 0.10 Λ-unit between the vertical lines at the lower left; this distance corresponds to about 0.10% for the aqueous system and 0.15% for the 30% mixture. The points lie on the lines within 0.0C%. The numerical results are summarized in the upper half of Table I.

$$\Lambda''' = \Lambda_0 - Az$$

The A column of Table I thus contains two sets of values: four values directly determined as slopes of the y–x plots where a was simultaneously evaluated with A and Λ_0, and four values from the slopes of the Λ''' *vs.* z plots, whose construction required an *a priori* value of a. For the latter, we used the average of the first four values; the self-consistency of the ensemble of values of the constants is tested in Fig. 3, where log A is plotted against the reciprocal of the dielectric constant. Both sets of points line on the same graph, which moreover is linear. If a were not a constant, the lowest points in Fig. 3 obviously could not lie on a prolongation of the line through the top four, except by an amazing compensation.

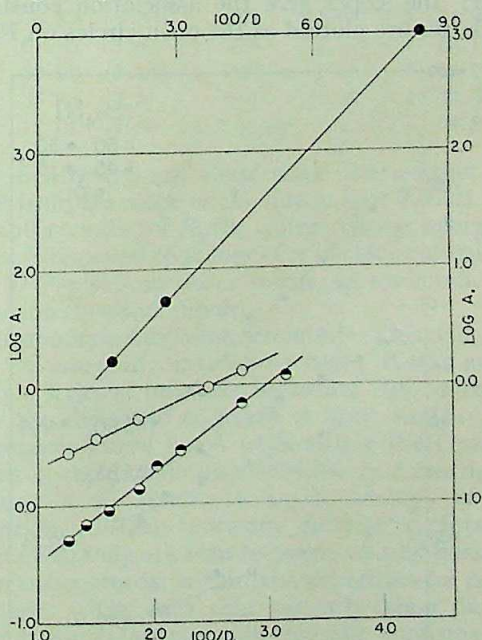

Fig. 3.—Dependence of association on dielectric constant: ○, tetrabutylammonium iodide, from y *vs.* x plots; ◓, sodium bromate, from y *vs.* x plots; ◒, sodium bromate, from Λ''' *vs.* z plots; coördinates left and below. ●, tetraisoamylammonium nitrate, from y *vs.* x plots; coördinates, right and above.

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The linearity of the log A *vs.* D^{-1} plot suggests that A has the simple form

$$A = A_0 \exp(u/kT)$$

where μ is an electrostatic free energy. But if we assume that u is simply a charge–charge energy e^2/aD, the slope of the line in Fig. 3 gives $\mathring{a} = 3.30$ instead of 4.00, the electrostatic center-to-center distance found from the y *vs.* x analysis. The discrepancy can be removed, quickly however, if we recall that the bromate ion contains a dipole, because it has a pyrimidal structure with Br^{+++} at the apex and three O^- ions at the base in one of its canonical forms.[5] The energy u therefore is the sum

$$u = (e^2/aD) + (\mu e/d^2D)$$

where μ is the dipole strength and d is the distance from the center of the cation to the electrostatic center of the dipole. For $10^8 d = 2.00$, $10^{18}\mu = 1.03$ and for $10^8 d = 4.00$, $10^{18}\mu = 4.10$, if we set $\mathring{a} = 4.00$ above. These values lie in an entirely reasonable range.

This result naturally suggests a conductimetric study of a variety of other ions; nitrates, for example, should give the same value of a from the y *vs.* x plot and the log A *vs.* D^{-1} plot, because the nitrate ion is electrically symmetrical.[5] Chlorates, on the other hand, should have a steeper log A *vs.* D^{-1} plot than corresponds to the a determined from the y *vs.* x plot. Conversely, conductance data should be helpful in determining previously unknown structures.

Tetrabutylammonium Iodide.[2]—The conductance was measured in water and in four dioxane–water mixtures, covering the range $35.85 \leqslant D \leqslant 78.48$. As is shown in Fig. 4, the y *vs.* x plots are linear; the slopes give the association constants. The latter are plotted as the open circles on Fig. 3.

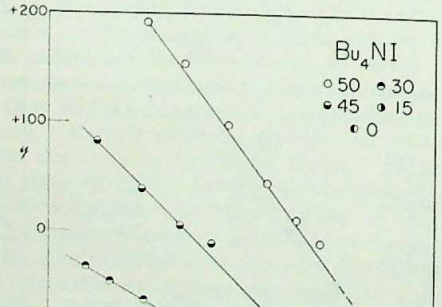

Fig. 4.—Extrapolation plots for tetrabutylammonium iodide. Abscissa scales: 50%, as shown; 45%, $(x - 10)$; 30%, $(x - 20)$; 15%, $(x - 30)$; 0%, $(x - 60)$.

From the slope of the log A *vs.* D^{-1} line, we obtain $\mathring{a} = 5.55$ as the nitrogen–iodine center-to-center distance in the ion paris. It will be noted that the Bu_4NI line is less steep in Fig. 3 than the one for $NaBrO_3$; the difference is due first to the smaller size of the sodium ion and second to the reinforcement of charge–charge attraction by the charge–dipole interaction already discussed.

If now values of $J_1(a)$ are calculated by adding $A\Lambda_0$ to the ordinate $y(0)$ obtained by extrapolating the y *vs.* x plots of Fig. 4 to $x = \Lambda_0$, absurdly small (1.5–3.5) and variable values of the parameter $\mathring{a}$ result from the values of $J_1(a)$ so obtained. This is in marked contrast to the case of sodium bromate, where it was shown that the $\mathring{a}$ value from the slope of the log A *vs.* D^{-1} plot was consistent with the values obtained from the y *vs.* x intercepts, *i.e.*, remained constant over the entire range of solvents investigated. Clearly, an effect is appearing in Bu_4NBr which is absent (or at least negligible) in the case of $NaBrO_3$. The outstanding physical difference between the two salts is the disparity in size of the cations; the tetrabutylammonium ion, according to molecular models, should exclude a spherical volume $7–8 \times 10^{-8}$ cm. in radius, while the sodium ion is about the same size as a water molecule. Using equation 34 of the preceding paper in the form

$$5\Lambda_0\delta/2 = J_1(a) - y(0) - A\Lambda_0$$

and using $\mathring{a} = 5.55$ to evaluate $J_1(a)$, the values of δ obtained are shown in the fifth column of Table II. The next column gives the corresponding values of the hydrodynamic radius R, calculated as

$$R = 7.32\delta^{1/3} \times 10^{-8}$$

The resulting quantity is reasonably constant and agrees remarkably well with the value expected on the basis of the model, assuming the Einstein formula to give the viscosity contribution due to the large cations. It should be mentioned that earlier work on the viscosity of bolaform electrolytes[6] shows that the Einstein limit of 5/2 for the ratio of specific viscosity to volume fraction is approached as these ions approach spherical shape. Introduction of the $(5\delta c/2)$ term into the conductance equation is thus not completely an *ad hoc* hypothesis. The fact that the viscosity term leads to reasonable R values argues for its reality; granting this, the long debated question of solution viscosity *versus* solvent viscosity as the pertinent variable in conductance theory appears to have found its answer.

TABLE II

TETRABUTYLAMMONIUM IODIDE IN DIOXANE–WATER MIXTURES AT 25°

% Dioxane	D	A	$J_1(5.5)$	δ	$\mathring{R}$	Λ_0
0	78.48	2.73	245	0.98	7.3	96.30
15	66.10	3.65	253	1.03	7.3	70.74
30	53.28	5.1	303	1.30	8.0	53.835
45	40.20	9.5	476	1.46	8.3	43.805
50	35.85	13.0	604	1.56	8.5	41.69

Tetraisoamylammonium Nitrate.[2]—This salt was measured in 0, 10, 20, 30 and 50% dioxane, but

(5) J. C. Slater, *Phys. Rev.*, **38**, 325 (1931).

(6) P. Goldberg and R. M. Fuoss, *Proc. Nat. Acad. Sci.*, **38**, 758 (1952).

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only at 20 and 50% was the concentration range wide enough to permit a reliable determination of slope (A) and intercept ($J_1 - 5\Lambda_0\delta/2 - A\Lambda_0$). The span from D = 61.86 (20%) to D = 35.85 (50%) is rather narrow to use to evaluate $\mathring{a}$ from the slope of the log A *vs.* D^{-1} plot, but fortunately some older data on this salt in 79.8% dioxane are available[7]; the y *vs.* x plot (second approximation) is shown in Fig. 5. From the slope, we obtain A

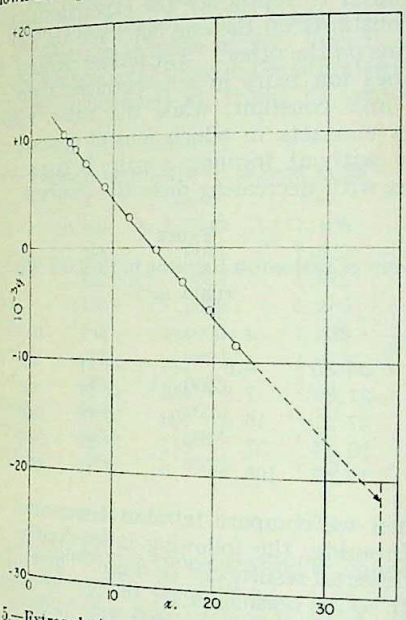

Fig. 5.—Extrapolation plot for tetraisoamylammonium nitrate in 79.8% dioxane.

= 1050. This point, together with the points for the 20 and 50% mixtures, establish a satisfactory straight line (solid points, Fig. 3): A = 0.354 exp(96.1/D). Equating the exponent to $e^2/aDkT$, we find $\mathring{a}$ = 5.83. This equation was then used to evaluate A for the 0, 10 and 30% mixtures, and the corresponding values of J_1 and J_2 were computed, using $\mathring{a}$ = 5.83. Using these constants, the quantity was then computed; if the conductance obeys the equations derived in the previous paper, Λ^{IV} includes the effect of both ion association and ion atmosphere, leaving only the viscosity term to be evaluated. From equation 33, we have

$$\Lambda^{IV} = \Lambda''' + Az$$

$$\Lambda^{IV} = \Lambda_0 - 5\Lambda_0\delta c/2$$

The corresponding plots are shown in Fig. 6; they are linear, well within the limit of experimental error, and δ is determined from the slopes. For the 20 and 50% mixtures, δ was determined from $y(0)$ as for tetrabutylammonium iodide, using $\mathring{a}$ = 5.83 to evaluate $J_1(a)$; for the 79.8% mixture, the $(J_1 - A\Lambda_0)$ term is so large that it completely masks the $5\Lambda_0\delta/2$ term. From Fig. 5, $J_1(a)$ = 1.47 × 10⁴; calculated for $\mathring{a}$ = 5.83, J_1 = 1.20 × 10⁴. Considering the sensitivity of $J(a)$ to a when b is large (low dielectric constant) and the uncertainty in determining J_1 from the graph when A is so large, we consider the agreement

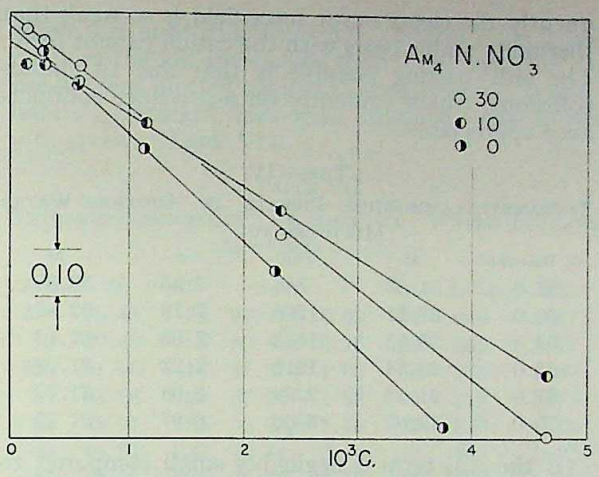

Fig. 6.—Extrapolation plots for tetraisoamylammonium nitrate in 0, 10 and 30% dioxane.

satisfactory. Other details of the calculation are summarized in Table III. Again, an entirely reasonable value of the hydrodynamic radius is found; since this constant in effect collects *all* of the residual uncertainties of the calculation in this particular example, we are inclined to place considerable confidence in both the data and the theoretical treatment, because such agreement among six sets of data has practically zero probability of being fortuitous.

TABLE III

TETRAISOAMYLAMMONIUM NITRATE IN DIOXANE–WATER MIXTURES AT 25°

% Dioxane	D	A	$J_1(5.83)$	δ	$\mathring{R}$	Λ_0
0	78.48	(1.20)	248	1.02	7.3	89.275
10	70.33	(1.38)	252	1.04	7.4	74.845
20	61.86	1.67	274	1.17	7.7	63.13
30	53.28	(2.14)	320	1.13	7.6	54.04
50	35.85	5.2	. 643	1.53	8.4	42.575
80	12.01	1050	1.2×10^4	..	..	34.8

We finally remark that, since the a-value obtained from the slope of the line in Fig. 3 leads to a satisfactory value of R, the charge–charge energy is all that is required to account for the slope of the log A *vs.* D^{-1} plot; in other words, as expected, the nitrate ion shows no dipole.

Tetramethylammonium Picrate.[8]—This salt presents an unusually interesting case: it was measured in a series of mixtures including 70% dioxane, where the dielectric constant is only 19.07. The conductance curve lies a little below the Onsager tangent in the dioxane-rich systems, and one might be tempted to assume a small amount of ion association. When, however, the y *vs.* x plots are constructed, they are seen to be practically horizontal; in other words, within the experimental error, A is zero. The fact that no association due to Coulomb forces appears for this salt confirms the generally accepted picture of the picrate ion: the single negative charge is not localized at the phenolic oxygen but is distributed over the peripheral π-electron system of the whole molecule. Conse-

(7) R. M. Fuoss, Thesis, Brown University, 1932; C. A. Kraus and R. M. Fuoss, THIS JOURNAL, **55**, 21 (1933).

(8) P. L. Mercier and C. A. Kraus, *Proc. Nat. Acad. Sci.*, **41**, 1033 (1955).

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quently the electrostatic force field is so weak that thermally stable pairs with the cation cannot form. The only pairing possible is that due to chance collisions, which evidently do not reduce conductance appreciably.

TABLE IV

TETRAMETHYLAMMONIUM PICRATE IN DIOXANE–WATER MIXTURES AT 25°

% Dioxane	D	$J_1(a)$	$\mathring{a}$	Λ_0
55.0	31.53	848	7.35	33.335
60.0	27.21	1269	7.78	32.425
62.5	25.15	1533	7.85	32.12
65.0	23.14	1812	7.22	31.935
67.5	21.12	2290	7.08	31.77
70.0	19.07	3030	6.97	31.75

If the $A\Lambda_0$ term is negligibly small compared to the other terms, then

$$y(0) = J_1 - 5\Lambda_0\delta/2$$

and the problem is to separate the components. In the mixtures of higher dielectric constant, J_1 and the hydrodynamic terms are of comparable magnitude; as the dielectric constant decreases, J_1 increases rapidly while δ remains constant, according to our hypotheses. The data were therefore treated as follows. A series of a-values were chosen, and Λ''' was computed and plotted against concentration. If the association term is negligible

$$\Lambda''' = \Lambda_0 - 5\Lambda_0\delta c/2$$

Each value of a will obviously give a straight line with a different slope; from the slopes in the water-rich mixtures, $\delta(a)$ was thus determined. Plots of $\delta(a)$ against the selected a-values were then made for the systems with 0, 20, 35 and 45% dioxane. Ideally, these curves should have intersected at a single point, corresponding to the unique values of a and δ theoretically required to describe the system. Actually, the curves gave a cluster of intersections: the range of $\mathring{a}$-values was from 7.48 to 8.00 (average, 7.73) while the δ-values ran from 0.39 to 0.55, averaging to 0.48. Both values seem quite reasonable. If we assume that $\delta \sim (R_1^3 + R_2^3)$ and further assume equal radii for the two ions as a rough approximation, $\delta = 0.48$ leads to $R = 4.54$ for the equivalent hydrodynamic radius. Then, using $\delta = 0.48$ to calculate $5\Lambda_0\delta/2$ for the dioxane-rich systems, values of $J_1(a)$ were obtained from the (practically constant) values of $y(c) \approx y(0)$. The corresponding values of $\mathring{a}$ were then obtained by interpolation on J_1–a plots. The results are shown in Table IV; there is a slight systematic trend to lower values as D decreases, but the average of 7.38 is in excellent agreement with the values obtained as described above in the water-rich mixtures. The decrease in $\mathring{a}$ may foreshadow the onset of association, which must eventually occur in solvents of sufficiently low dielectric constant. But when J_1 is so large, a small Ax term is practically invisible.

Tetrabutylammonium Bromide.[8]—This salt was also measured over the range 0–70% dioxane. Even a rough estimate shows that its association at a given value of dielectric constant is *less* than that for the iodide; it was only possible to obtain reliable values of A from the slopes of the $y(c)$ vs. $J(a)$ plots in the mixtures containing 50% or more dioxane. These values gave a straight line on a log A *vs.* $1/D$ plot, which can be represented by the equation $A = 0.11 \exp(133/D)$; the corresponding $\mathring{a}$-value is 4.21. On the other hand, if we calculate $\mathring{a}$ from $J_1(\mathring{a})$ obtained from the intercepts $y(0)$, using $\delta = 0.535$ (see later), the values shown in Table V result. Unlike tetrabutylammonium iodide and tetraisoamylammonium nitrate, a different ion size is required to reproduce the experimental association constants on the one hand and the long range J_1-terms on the other. The former constant, which describes ion pairs in semi-permanent contact, is small and constant, while the latter, which describes contacts in which ions of opposite charge collide without forming a pair, is larger and increases with decreasing dielectric constant.

TABLE V

TETRABUTYLAMMONIUM BROMIDE IN DIOXANE–WATER MIXTURES AT 25°

% Dioxane	D	A	$y(0)$	Λ_0	$J_1(a)$	$\mathring{a}$
50	35.85	4.6	345	43.71	605	5.22
55	31.53	7.8	456	41.54	835	5.42
60	27.21	16.4	600	39.76	1305	6.24
65	23.14	37	615	38.32	2090	6.90
70	19.07	103	0	37.11	3870	8.12

When we compare tetrabutylammonium iodide and bromide, the following rationalization of the experimental results can be made. The small value of 4.21 seems reasonable for the N^+–Br distance in an ion pair. We note that the iodide is more highly associated than the bromide: for the former, $A = 0.78 \exp(101/D)$ while for the latter, $A = 0.11 \exp(133/D)$. The smaller exponent for the iodide corresponds of course to the greater size of the iodide ion compared to the bromide, but the large difference in coefficients A_0 requires comment. Part of A_0 is an entropy term $\exp(-\Delta S/R)$, but this should be practically the same for Bu_4NBr and Bu_4NI. Therefore the only explanation remaining is that the association constant of Bu_4NI contains an additional energy term $\exp(u/kT)$ which is independent of dielectric constant. The ratio 0.78/0.11 equals $e^{1.95}$, so an energy of about $2kT$ is required to stabilize iodide–N^+ pairs with respect to bromide–N^+ pairs. We suggest that this energy is the potential between the N^+ center and the dipole which it induces in the highly polarizable iodide ion, after coulomb forces have brought the pair to near contact (and withdrawn from the medium of dielectric constant D). The larger values of $\mathring{a}$ from J_1 then represent averages between contact diameters in stable pairs and diameters from collisions which do not lead to pair formation, *i.e.*, collisions with the periphery of the quaternary ion from which the bromide ion diffuses away again. In the case of the iodide ion, the additional induction force comes into play at contact and makes most collisions lead to pairs which later disassociate when they acquire sufficient thermal energy.

Another difference between bromide and iodide must be mentioned: the Walden product for the former drops sharply, starting at about 50% dioxane, which we mean some specific interaction

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between the bromide ion and dioxane which does not occur with the iodide (and picrate), and which increases the effective size of the free bromide ion. Until bromide–iodide comparisons are made in other solvent mixtures, however, further speculations seem pointless.

Before discussing the results in the mixtures of higher dielectric constant, we shall present some data on the viscosity of aqueous solutions of tetrabutylammonium bromide. We acknowledge with thanks measurements made by Dr. Joan B. Berkowitz, which supplement those in the literature.[6] The results are summarized in Table VI, where the

TABLE VI

VISCOSITY OF Bu_4NBr IN WATER AT 25°

c	η_{sp}	$S_\eta c^{1/2}$	η'_{sp}/c	R
0.290	0.430	0.0049	1.466	6.16
.204	.284	.0041	1.372	6.03
.144	.192	.0034	1.312	5.94
.0692	.130	.0029	1.280	5.89
.1064	.145	.0030	1.333	5.96
.1007	.131	.0029	1.272	5.88
.0635	.086	.0023	1.31	5.94
.0610	.081	.0022	1.30	5.91
.0321	.045	.0016	1.34	5.97
.0175	.026	.0012	1.43	6.10
			1.34	5.98

first two columns give concentration in equivalents per liter and specific viscosity $\eta_{sp} = (\eta - \eta_0)/\eta_0$, respectively. As is well known, there is a square root term in the viscosity of electrolytic solutions in addition to the Einstein term $5\phi/2$ (and also higher terms than $c^{1/2}$ from long range forces, which we shall neglect here). For 1 – 1 salts

$$\eta/\eta_0 = 1 + S_\eta c^{1/2} + 5\phi/2$$

where

$$S_\eta = \frac{\beta^*\Lambda_0}{320\lambda_0^+\lambda_0^-}\left\{1 - 0.6863\left(\frac{\lambda_0^+ - \lambda_0^-}{\Lambda_0}\right)^2\right\}$$

For Bu_4NBr in water, $S_\eta = 9.07 \times 10^{-3}$. The quantity η'_{sp} in the table is defined as

$$\eta'_{sp} = \eta_{sp} - S_\eta c^{1/2}$$

It serves to isolate the volume effect in which we are interested. It will be seen that $\eta'_{sp}/c = 5\phi/2c$ is quite constant; further, if we equate $\phi/c = \delta$ with $4\pi NR^3/3000$, we obtain the average value 5.98 Å. for the hydrodynamic radius of the tetrabutylammonium ion. Thus direct viscosity measurements confirm the hydrodynamic term whose presence was suggested first by the conductance data for tetrabutylammonium iodide. It should perhaps be mentioned that the Dole–Falkenhagen term $S_\eta c^{1/2}$ in the viscosity is to be omitted in the conductance equation, because it describes transfer of momenta over distances large compared to $(1/\kappa)$, *i. e.*, refers to bulk flow of the solution.

Finally, we consider tetrabutylammonium bromide in the range of higher dielectric constants. Here, association is so slight that the y *vs.* x method becomes far too sensitive to experimental error. The conductance equation was therefore rearranged to the form

$$\Lambda'' + J_2c^{1/2} = \Lambda_0 - y(0)c$$

where the approximations $\Lambda = \Lambda_0$ and $f^2 = 1$ are made in the ion association term. The quantity on the left was plotted against c, using $\mathring{a} = 5.5$ to evaluate J_2; straight lines were obtained, with slopes $y(0)$ given in Table VII.

TABLE VII

TETRABUTYLAMMONIUM BROMIDE IN WATER–DIOXANE MIXTURES AT 25°

% Dioxane	D	$y(0)$	Λ_0	A	$A\Lambda_0$	$J_1(5.5)$	$5\delta/2$
0	78.48	−28	97.475	0.62	61	248	(2.2)
10	70.33	8	80.805	0.76	62	255	(2.3)
20	61.86	110	67.575	1.00	68	273	1.40
30	53.28	163	57.26	1.38	79	319	1.34
35	48.91	185	53.085	1.78	95	357	1.45
40	44.54	235	49.44	2.24	110	415	1.42
45	40.20	272	46.30	3.16	146	498	1.73

The problem then is: given the sum $y(0) = J_1(a) - A\Lambda_0 - 5\Lambda_0\delta/2$; to evaluate the components. The plot of log A *vs.* $1/D$ from the dioxane-rich range was extrapolated linearly into the water-rich range to give the values of A shown in the table. Then the round value $\mathring{a} = 5.50$ was used to evaluate J_1; this value was chosen to be consistent with the value which $\mathring{a}$ from Table V appeared to be approaching in the mixtures of higher dielectric constant. We then were able to evaluate

$$5\Lambda_0\delta/2 = J_1(5.50) - A\Lambda_0 - y(0)$$

The results are given in the last column; if we disregard the first two values (where the uncertainty in the slopes of the Λ''–c plots is naturally very great and for which the longest log A *vs.* D^{-1} extrapolation was made), we obtain $5\delta/2 = 1.47 \pm 0.13$. to compare with the direct viscometric value of 1.34 ± 0.06 of Table VI.

Discussion.—If ion association depends on the parameter $b = e^2/aDkT$, then there are two ways of varying the extent of association of a given electrolyte: by varying the DT product by change of temperature, or by using solvent mixtures to change D. The latter is by far the more convenient method, and the constancy of the a-values reported here argues that it is an experimentally valid method. One might have some misapprehensions on the score of selective solvation, but when it is recalled that both solvents are usually present in tremendous molar excess over the electrolyte present in the range ($\kappa a < 0.2$) where the data are susceptible to the present analysis, constancy of solvation appears to be a safe assumption. Exceptions might be expected to appear only when one component of the mixed solvent is present at minute concentrations.

While we report here only four cases which show that the logarithm of the association constant is a simple linear function of reciprocal dielectric constant, we believe that the result is general. Seen in retrospect, it does seem logical that a thermodynamic approach[9] to the problem of ion pair formation should be preferable to a statistical one, because the former concerns itself only with reagents and products and the associated free energy difference and ignores mechanism. The Denison–Ramsey treatment has further advantages over the

(9) J. T. Denison and J. B. Ramsey, THIS JOURNAL, **77**, 2615 (1955).

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Bjerrum model which we have used for so long: (1), only ions in contact are counted as pairs; (2), no quibbles about an arbitrary limit of integration arise; and (3), association is not automatically excluded beyond a critical value of the parameter b.

Another former tool must, in our opinion, also be discarded as obsolete in the analysis of conductance data. Our earlier calculations[10] of limiting conductance and "dissociation" constants by various modifications of the Ostwald dilution law were subject to the recognized (but then unknown) hazard of error due to the inclusion in K of terms of higher order arising from long range interionic forces. In solvents of low dielectric constant, the association term is the controlling one, so the error there was not very large: for example, our early analysis[4] of the data for Am_4NNO_3 in 80% dioxane gave $K = 9.0 \times 10^{-4}$ which is in almost exact agreement with the value of A^{-1} given in Table III. These earlier methods may therefore still be used as a convenient approximation for $A \gtrsim 100$. But in solvents where association is less marked, and especially when it is only moderate, then the earlier methods can only lead to erroneous results.

Our present point of view is that association can in principle and does in fact occur in any solvent. The extent to which the alkali halides, for example, associate in water is presumably small, but if the limit of A as D increases is not zero, then a non-zero concentration of ion pairs must be present at any non-zero concentration. We hasten to admit that the actual amount may be quite small. The device of mixed solvents offers an experimental approach to a quantitative answer to the question, of course.

It should be mentioned that the presence of a non-vanishing A will not change the value of Λ_0 found by the Λ'''–c extrapolation method,[3] but a small change in $\mathring{a}$ will result. Likewise, inclusion of the $5\Lambda_0\delta/2$ term for most simple inorganic salts will only change $\mathring{a}$ by a small amount; since $\delta \sim R^3$ and since the alkali ions certainly have radii not greater than half that of the tetrabutylammonium ion, the δ-term will be roughly an order of magnitude smaller for the alkalies than that for the quaternaries, *i.e.*, $5\Lambda_0\delta/2 \approx 0.25\Lambda_0$. Since $J_1(a)$ is several times Λ_0 in aqueous solutions, no drastic change in $\mathring{a}$ is to be expected from inclusion of the viscosity term. Self-consistency, however, requires that if one linear term is retained, all should be.

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PROVIDENCE, RHODE ISLAND

(10) R. M. Fuoss and T. Shedlovsky, THIS JOURNAL, **71**, 1496 (1949).

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Microwave Absorption and Molecular Structure in Liquids. XIX. The Effect of Internal Field upon Molecular Relaxation Times in Liquids[1]

BY ROBERT C. MILLER[2] AND CHARLES P. SMYTH

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The effect of the internal field in a liquid upon the dielectric relaxation time of its molecules is examined by comparing the macroscopic relaxation time of a highly polar liquid with that of a liquid consisting of molecules of the same size and shape as those of the polar liquid, but with very small dipole moment. Alternatively, the comparison is made between the pure polar liquid and its dilute solutions in a non-polar solvent. After correction for viscosity differences in most cases, the assumption is made that the macroscopic relaxation time of the pure liquid of low polarity or of the dilute solutions of the polar liquid is equal to the molecular relaxation time of the highly polar liquid. The molecular relaxation times thus obtained are compared graphically with those calculated by means of the various available equations. It becomes evident that the relation of the molecular relaxation time to the macroscopic relaxation time is dependent not only upon the dielectric constant of the liquid, but also, to some extent, upon the molecular shape. Consequently, no equation thus far proposed for calculating the molecular relaxation time from the directly measured macroscopic relaxation time of a polar liquid is wholly adequate, but that proposed by Powles and obtained by O'Dwyer and Sack as a first approximation is the most nearly adequate.

It has been common practice in discussing the relations between dielectric relaxation and molecular size and shape and liquid viscosity to use as the basis of discussion the macroscopic relaxation time τ_M or the critical wave length, $\lambda_m = 6\pi \times 10^{10}\tau_M$, at which the measured dielectric loss is a maximum. This is certainly justified in the case of dilute solutions and, in the case of pure polar liquids, has been commonly considered preferable to the use of a molecular relaxation time calculated by means of the Debye theory based upon the Lorentz expression for the internal field of the liquid.

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Calculation of Molecular Relaxation Times.—The macroscopic relaxation time may be written

$$\tau_M = \beta\tau_\mu \tag{1}$$

where τ_M is the molecular relaxation time and β a factor correcting for the effect of internal field. From the original equations of Debye[3] based on the Lorentz internal field

$$\beta = \frac{\epsilon_0 + 2}{\epsilon_\infty + 2} = 1 + \frac{\epsilon_0 - \epsilon_\infty}{\epsilon_\infty + 2} \tag{2}$$

where ϵ_0 is the static dielectric constant and ϵ_∞ is the optical or infinite frequency dielectric constant. Powles[4] has proposed an approximate expression for the internal field which gives

$$\beta = \frac{3\epsilon_0}{2\epsilon_0 + \epsilon_\infty} = 1 + x \tag{3}$$

(3) P. Debye, "Polar Molecules," Chemical Catalog Co., New York, N. Y., 1929, Chap. V.

(4) J. G. Powles, *J. Chem. Phys.*, **21**, 633 (1953).

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where

$$x = \frac{\epsilon_0 - \epsilon_\infty}{2\epsilon_0 + \epsilon_\infty} \quad (4)$$

O'Dwyer and Sack,[5] in a more exhaustive treatment, have obtained an expression which leads to

$$\beta = 1 + x + \frac{3x^2}{(1-2x)(1+x)} = \frac{1-2x^3}{(1-2x)(1+x)} \quad (5)$$

where x is given by eq. 4.

When ϵ_0 approaches infinity, both equations 2 and 5 require that β also approach infinity, while equation 3 requires that it approach 1.5 as a limit. As a first approximation, neglect of the third term, equation 5 becomes identical with (3). Neglect of the difference between the macroscopic and the molecular relaxation time is equivalent to taking β as equal to 1.

Consideration[6] of the relaxation times and viscosities of the closely related liquids, pyridine, γ-picoline and toluene, led to the conclusion that equation 3 was the best approximation for these liquids. It is the purpose of this paper to apply a similar approach to the considerable body of results now available for testing these equations. For toluene, the dipole moment of the molecule is so small that the internal field is too small to produce any considerable difference between the macroscopic relaxation time and the molecular, that is, $\epsilon_0 - \epsilon_\infty = 0.11$ at 20° gives $\beta = 1.025$ from equation 2, $\beta = 1.016$ from equation 3, and $\beta = 1.005$ from equation 5. When the experimental results are examined presently, it will be evident that these small departures of the values of β from 1 are negligible in comparison with other factors. It is, therefore, justifiably assumed that the macroscopic relaxation time and the molecular are indistinguishable for toluene and for other molecules of similarly small polarity. It is reasonable to assume that γ-picoline or 4-methylpyridine, which has a molecule almost identical in size and shape with that of toluene, has a molecular relaxation time practically identical with that of toluene except for the effects of viscosity. For a spherical or nearly spherical molecule, it has been found[7,8] that the effect of viscosity is small. For such molecules, it has, therefore, been neglected, as a rough approximation, in the following discussion. In previous papers of this series, it has been found that many liquids with unsymmetrical molecules show a rough proportionality between relaxation time and viscosity as indicated by the Debye theory.[3] Consequently, for the comparison of two liquids other than those with nearly spherical molecules, the relaxation time of one is multiplied by the inverse ratio of the two viscosities. If τ_1 is the observed macroscopic relaxation time for a liquid with unsymmetrical molecules of low polarity or for dilute solutions of molecules of high polarity in a non-polar solvent ($\tau_1 = \tau_{M_1} = \tau_{\mu_1}$) and τ_{M_2} is the observed macroscopic relaxation time for a liquid 2 with molecules of high polarity ($\tau_2 = \tau_{M_2}$) and size and shape similar to those of liquid 1, it is assumed that

$$\tau_{\mu_2} = \tau_{\mu_1}(\eta_2/\eta_1) \quad (6)$$

or

$$\beta = \tau_{M_2}/\tau_{\mu_2} = \tau_2\eta_1/\tau_1\eta_2 \quad (7)$$

Equation 7 provides a means of obtaining approximate values of β for comparison with those calculated by means of equations 2, 3 and 5.

Experimental Results

Table I gives for the pair of liquids, 1 and 2, in the first column the difference between the static dielectric constant and the optical dielectric constant of the polar liquid, the ratio of the two observed relaxation times, and the ratio corrected by means of equation 7 for the assumed effect of viscosity. For the nearly spherical molecules, τ_{M_2}/τ_1 is taken as β. When liquid 1 is indicated as a solution, liquid 2 is the solute. In Fig. 1 these values of β are plotted against the corresponding values of $\epsilon_0 - \epsilon_\infty$, while the three curves represent the values of β calculated by each of the three equations.

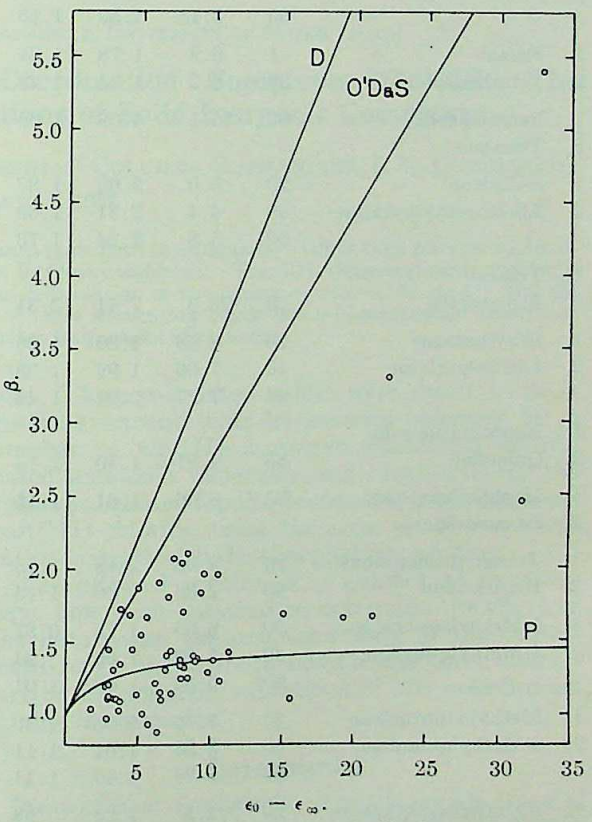

Fig. 1.—Plot of β against $\epsilon_0 - \epsilon_\infty$. Circles represent experimental values. Curve D represents values calculated by means of Debye equation 2; curve O'D & S, values calculated by means of O'Dwyer and Sack equation 5; curve P, values calculated by means of Powles equation 3.

Discussion of Results

The equations under examination by means of the data in Table I were derived for the case of a spherical molecule in a continuous medium and do not take into account the effects of differences in molecular shape and dipole location in the molecule. They may, therefore, be expected to apply with different degrees of approximation to different liq-

(5) J. J. O'Dwyer and R. A. Sack, *Australian J. Sci., Research*, **A5**, 647 (1952).
(6) R. S. Holland and C. P. Smyth, *J. Phys. Chem.*, **59**, 1088 (1955).
(7) A. J. Curtis, P. L. McGeer, G. B. Rathmann and C. P. Smyth, THIS JOURNAL, **74**, 644 (1952).
(8) C. P. Smyth, *J. Phys. Chem.*, **58**, 580 (1954).

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TABLE I

INTERNAL FIELD CORRECTIONS FOR POLAR LIQUIDS

	Liquid	t, °C.	$\epsilon_0 - \epsilon_\infty$	τ_2/τ_1	β
1.	Benzene soln.	20	11.3	2.09	1.43
2.	Pyridine	40	10.2	2.06	1.37
		60	9.1	2.07	1.39
1.	Toluene	1	10.7	2.02	1.23
2.	γ-Picoline	20	9.9	2.06	1.29
		40	9.0	2.04	1.37
		60	8.2	1.96	1.33
1.	Toluene	1	3.76	1.82	1.35
2.	Chlorobenzene	20	3.35	1.78	1.31
		40	2.99	1.62	1.21
		60	2.79	1.62	1.20
1.	Toluene	20	2.99	2.86	1.45
2.	Bromobenzene				
1.	Toluene	20	31.7	8.33	2.45
2.	Nitrobenzene				
1.	*p*-Xylene soln.	20	3.69	1.43	1.03
2.	*p*-Chlorotoluene	40	3.47	1.52	1.11
		60	3.18	1.50	1.13
1.	Furan	1	6.9	1.78	1.31
2.	Tetrahydrofuran	20	6.2	1.64	1.22
1.	Benzene soln.	60	15.1	4.08	1.69
2.	Trioxane				
1.	*m*-Xylene	20	5.0	2.63	1.87
2.	2,6-Dimethylpyridine	40	4.4	2.31	1.69
		60	3.8	2.24	1.73
1.	Toluene				
2.	Benzonitrile	20	22.3	7.41	3.31
1.	Ethylbenzene	20	8.43	1.89	1.25
2.	4-Ethylpyridine	40	7.96	1.99	1.38
		60	7.27	2.04	1.44
1.	Naphthalene soln.				
2.	Quinoline	85	4.91	1.40	1.14
1.	Naphthalene soln.	85	6.06	1.61	1.16
2.	Isoquinoline				
1.	Tetrahydronaphthalene	20	8.08	2.18	1.25
2.	Isoquinoline	40	7.36	2.00	1.15
1.	1-Methylnaphthalene	20	6.36	1.75	0.87
2.	4-Methylquinoline	40	5.86	1.66	.94
		60	5.36	1.60	1.01
1.	Methylnaphthalene	20	3.76	1.58	1.10
2.	8-Methylquinoline	40	3.33	1.51	1.11
		60	2.94	1.43	1.11
1.	1-Methylnaphthalene	20	2.8	1.05	0.98
2.	1-Chloronaphthalene	60	2.2		
1.	1-Methylnaphthalene	20	1.9	1.68	1.04
2.	1-Bromonaphthalene	60	1.5		
1.	1-Methylnaphthalene	60	15.7	2.84	1.11
2.	1-Nitronaphthalene				

		t, °C.	$\epsilon_0 - \epsilon_\infty$	τ_2/τ_1	$\tau_2\eta_1/\tau_1\eta_2$
1.	CCl_4 soln.	4	5.6	1.67	1.83
2.	CH_3CCl_3	20	5.2	1.55	1.79
		40	4.6	1.45	1.71
1.	CCl_4 soln.	2	10.5	1.96	
2.	$(CH_3)_2CCl_2$	20	9.3	1.84	2.51
		40	8.2	1.74	
1.	CCl_4 soln.	4	8.9	1.41	
2.	$(CH_3)_3CCl$	20	8.0	1.34	2.59
		40	7.0	1.41	
1.	$CBrCl_3$	1	9.5	1.97	
2.	$(CH_3)_3CBr$	20	8.4	2.11	4.19
		40	7.4	2.08	
		60	6.4	1.91	
1.	CBr_2F_2	1	8.0	2.04	
2.	CH_3CH_2Br	20	7.1	1.81	2.44
1.	CBr_2Cl_2	60	33.0	5.4	4.3
2.	$(CH_3)_2C(NO_2)_2$				
1.	$CFCl_3$	1	21.4	1.67	2.31
2.	$(CH_3)_2CO$	20	19.3	1.66	

uids. The application of a viscosity correction in the case of non-spherical molecules and its neglect in the case of approximately spherical molecules is arbitrary, but, in view of the observed behavior of a large number of liquids, seems to be the best available approximation. An unavoidable approximation is the use of the viscosity of the solvent in place of that hindering the rotational orientation of a solute molecule completely surrounded by solvent molecules. However, when the highly polar molecule is of the same size and shape as the solvent molecule or the molecule of low polarity with which it is compared, the error resulting from this approximation is probably not serious. In the calculation of the curves in Fig. 1 a single value, 2.0, is used for the optical dielectric constant in calculating the Debye and the O'Dwyer and Sack curves, although higher values would lower the curves and give somewhat better agreement with the values of β in Table I. However, the effect of using permissibly higher values for ϵ_∞ would not be sufficient to alter the conclusions as to the applicability of the equations.

In Fig. 1, where the values of β in Table I are plotted against those of $\epsilon_0 - \epsilon_\infty$, the points scatter widely, as might be expected in view of the approximations which have been pointed out. The points lie well below the curve based on the Debye application of the Lorentz internal field and, except for four points just outside this area, between the abscissa axis corresponding to $\beta = 1$ and the O'Dwyer and Sack curve, these two lines forming approximate lower and upper limits for the values of the internal field correction. For values of $\epsilon_0 - \epsilon_\infty$ below about 16, the Powles curve seems to give a very rough average of the observed values of β. For the few points above $\epsilon_0 - \epsilon_\infty = 16$, that is, for high internal field, the Powles equation undercorrects, while that of O'Dwyer and Sack overcorrects. If the values of β in Table I are plotted against $(\epsilon_0 - \epsilon_\infty)/(\epsilon_\infty + 2)$ from equation 2 instead of against $\epsilon_0 - \epsilon_\infty$, the points do not fall as far below the curve given by equation 2 as they do in Fig. 1, but they still show clearly the inapplicability of equation 2. If they are plotted against $x = (\epsilon_0 - \epsilon_\infty)/(2\epsilon_0 + \epsilon_\infty)$ from equation 4, the points lie between the abscissa axis and the curve given by equation 5 as approximate lower and upper limits, respectively. As in Fig. 1, many of the points lie below and many above the curve given by equation 3, which may still be regarded as giving the most adequate approximation for the largest number of liquids.

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The influence of molecular shape upon the internal field is evident in the values of β in Table I and the points in Fig. 1. For the roughly spherical molecules of the substituted methanes, the effect of the internal field is greater than that calculated by means of the Powles equation, a discrepancy which would be still greater if the correction for the effect of viscosity were not omitted. The flattening of the sphere to the roughly oblate spheroidal form of the substituted benzene and pyridine molecules reduces the effects of the field to amounts close to those calculated by means of the Powles equation, an apparent exception being 2,6-dimethylpyridine, the points for which lie close to the O'Dwyer and Sack curve. Elongation of the flattened structure as in the quinoline, isoquinoline and substituted naphthalene molecules reduces the effects of the field below those calculated by the Powles equation. That the decrease in field effect is not merely the result of increase in molecular volume is shown by the fact that pyridine and the monomethyl and monohalogenated pyridines and benzenes have about the same molar volumes as the tetrasubstituted methanes under consideration. The strong local fields of the highly polar cyanide and nitro groups raise the effects of field well above those calculated by the Powles equation for nitrobenzene and benzonitrile, but the effect is much smaller in the case of the larger 1-nitronaphthalene.

It is evident that the macroscopic dielectric relaxation time of a polar liquid is usually greater than the molecular relaxation time but not nearly as much greater as is indicated by calculation based on the Lorentz internal field. The Powles equation and the identical first approximation obtained by O'Dwyer and Sack seems to be the best approximation for the calculation of the molecular relaxation time from the macroscopic, but it is a very rough approximation.

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Infrared Absorption Spectra of Inorganic Coördination Complexes.[1a,b] XII. The Characteristic NH_3 Deformation Vibrations of Solid Inorganic Complexes

BY G. F. SVATOS, D. M. SWEENY, SAN-ICHIRO MIZUSHIMA,[2] COLUMBA CURRAN AND J. V. QUAGLIANO

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The infrared spectra of a number of solid metal ammine complexes have been investigated. It has been possible to determine the three deformation vibrations of the ligated molecules in these complexes. The NH_3 degenerate deformation is observed in the region of 1650–1560 cm.$^{-1}$; the NH_3 symmetric deformation in the region of 1350–1150 cm.$^{-1}$; and the NH_3 rocking frequency in the region of 950–650 cm.$^{-1}$. Each of these absorption bands has a characteristic absorption profile. A theoretical explanation for the range of these deformation frequencies is presented.

Introduction

Infrared spectra of solid ammine coördination compounds of the transition metals have been subject to several investigations.[3-7] The comparative ease of preparation and the wide diversity of substituents possible in this series have emphasized the importance of a definite characterization of the absorption bands, which may be attributed to the NH_3 grouping upon complex formation.

Mizushima, Nakagawa and Quagliano have recently characterized the deformation vibrations of coördinated ammonia molecules in Co(III) ammines.[8] Using a Urey–Bradley type potential function, the frequencies of the degenerate and symmetric deformations and the rocking vibrations have been calculated for the $Co(NH_3)_6^{+++}$ ion. These calculated values were shown to be in good agreement with frequencies observed for a number of Co(III) ammines containing coördinated ammonia molecules and, furthermore, the values calculated for the deuterated hexammine cobalt(III) chloride, using the same set of force constants, agreed with the observed frequencies.

The infrared spectra of a number of ammines have now been obtained to determine the effect of the nature and the oxidation state of the central metal atom on the frequencies of the three characteristic deformation vibrations of the coördinated ammonia molecules.

Experimental

Preparation of Compounds.—The compounds listed in Table I were prepared by methods similar to those given in the references in the last column. Most of the compounds were dried by heating under reduced pressure in an Abderhalden apparatus for several hours at 110°. All other compounds listed in Table II were supplied by Dr. D. N. Sen.[9]

Absorption Measurements.—Spectra were obtained by means of a Perkin–Elmer Infrared Spectrophotometer Model 21 with a sodium chloride prism. Preparation of the potassium bromide disks was carried out according to the procedure of Stimson and O'Donnell[10] as described in a previous article.[4]

The frequency values for the NH_3 deformation vibrations are listed in Table II.

(1) (a) Paper XI in series, *Spectrochim. Acta*, in press. (b) Abstracted from the Ph.D. theses of G. F. Svatos, 1954, and D. M. Sweeny, 1955. Supported in part under AEC Contract AT(11-1)-38, Radiation Project of the University of Notre Dame. Presented before the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Pittsburgh, Pa., Feb., 1955.

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TABLE I

ANALYSIS OF COMPOUNDS

Compound	Component analyzed	% Calcd.	% Found	Ref.
$[Co(NH_3)_6]Cl_3$	NH_3	38.20	37.94	10
$[Co(NH_3)_6]Cl_2$	NH_3	44.04	43.71	11
$[Ag(NH_3)_2]_2SO_4$	NH_3	17.93	17.58	11
$[Cu(NH_3)_4]SO_4 \cdot H_2O$	NH_3	27.72	27.34	11
$[Ni(NH_3)_6]Cl_2$	NH_3	44.08	43.83	11
$[Cr(NH_3)_6]Cl_3$	NH_3	39.22	38.77	11
$[Cr(NH_3)_5Cl]Cl_2$	NH_3	34.96	34.58	11
$[Co(NH_3)_5Br]Br_2$	NH_3	22.18	22.06	12
$[Co(NH_3)_5NO_2]Cl_2$	NH_3	32.62	32.38	13
$[Co(NH_3)_5NO_3]Cl_2$	NH_3	30.74	30.64	14
$[Co(NH_3)_5H_2O]Cl_3$	NH_3	31.71	31.58	11
$[Co(NH_3)_4(H_2O)_2]Cl_3$	NH_3	25.28	24.99	15
trans-$[Co(NH_3)_4(NO_2)_2]Cl$	NH_3	26.76	26.71	11
$[Co(NH_3)_3(NO_2)_3]$	NH_3	20.60	20.57	11
$[Co(NH_3)_5Cl]Br_2$	NH_3	25.09	25.20	16
$[Co(NH_3)_5ONO]Cl_2$	NH_3	32.62	32.75	13
$[Co(NH_3)_5SO_4]Cl$	NH_3	30.98	30.98	17
$[Co(NH_3)_5CO_3]NO_3 \cdot {}^1/_2H_2O$	NH_3	26.40	26.11	18
$[Co(NH_3)_5OH]Br_2 \cdot H_2O$	NH_3	25.12	25.10	19
$[Co(NH_3)_5C_2O_4]Br \cdot HBr$	NH_3	21.67	21.76	20
$[Co(NH_3)_4CO_3]Cl$	NH_3	30.62	30.35	21
$K[Co(NH_3)_2(NO_2)_4]$[22]	NH_3	10.77	11.19	11

Discussion

The previous calculation[8] of normal frequencies for the NH_3 ligand was based on the following potential function

$$V = \Sigma \frac{1}{2}K_i(\Delta r_i)^2 + \Sigma \frac{1}{2}H_{ij}r_i^0 r_j^0 (\Delta\alpha_{ij})^2 + \Sigma \frac{1}{2}F_{ij}(\Delta q_{ij})^2 + \text{linear terms}$$

where r_i and r_j are bond lengths with equilibrium values r_i^0 and r_j^0; α_{ij} bond angles and q_{ij} distances between non-bonded atoms. In addition K, H and F represent stretching, bending and repulsive force constants, respectively.

The deformation frequencies depend on the bending force constants H(HNH) and H(HNM), and the repulsive force constants, F(H· · ·H) and F(H· · ·M), where M denotes the central metal. Of these constants H(HNH) and F(· · ·H) are the same as those used for the calculation of the vibrations of ammonia (NH_3), ammonium ion (NH_4^+), and the deuterated products (ND_3 and ND_4^+).[23] Therefore, these two constants have the same value throughout the series, whereas the remaining two, H(HNM) and F(H· · ·M), depend considerably on the nature of the central metal, M.

The calculation showed that the degenerate deformation frequency depends on H(HNH) and F(H· · ·H), the rocking frequency on H(HNM) and F(H· · ·M), and the symmetric deformation frequency on all four constants. It follows from these relationships that the difference in the nature of the central metal atom should be reflected very strongly in the value of the rocking frequency, considerably in the symmetric deformation frequency and little in the degenerate deformation frequency.

The frequencies of the deformation vibrations fall in characteristic regions of the spectra for all metal–ammine complexes reported. The degenerate deformation appears between 1650 and 1560 cm.$^{-1}$, the symmetric deformation between 1350 and 1150 cm.$^{-1}$ and the rocking vibration between 950 and 650 cm.$^{-1}$. The absorption profiles of the deformation are also quite characteristic. The degenerate deformation is broad and of moderate intensity, the symmetric deformation is quite sharp and very intense, and the rocking vibration band is very broad and intense.[24]

The effects of the nature and oxidation state of the central metal atom on the deformation frequencies are revealed by the data in Table II. It is evident that the rocking frequency decreases

TABLE II

DEFORMATION FREQUENCIES IN CM.$^{-1}$ FOR METAL AMMINE COMPLEXES

	Compound	Degenerate	Symmetric	Rocking
1	$[Ag(NH_3)_2]_2SO_4$	1650	1215	738
2	$[Co(NH_3)_6]Cl_2$	1610	1158	650
3	$[Ni(NH_3)_6]Cl_2$	1610	1175	678
4	$[Cu(NH_3)_4]SO_4 \cdot H_2O$	1615	1285	732
5	$[Cr(NH_3)_6]Cl_3$	1620	1314	757
6	$[Pd(NH_3)_4]Cl_2$	1610	1304	827
7	$[Co(NH_3)_6]Cl_3$	1620	1325	827
8	$[Pt(NH_3)_4]Cl_2$	1570	1350	850
9	$[Pt(NH_3)_5Cl]Cl_3$	1560	1355	935
10	$[Cr(NH_3)_5Cl]Cl_2$	1600	1290	724
11	$[Cr(NH_3)_5NO_2]Cl_2$	1620	1305	768
12	*trans*-$[Pt(NH_3)_2Cl_2]$	1605	1295	815
13	*trans*-$[Pd(NH_3)_2Cl_2]$	1614	1250	756
14	$[Co(NH_3)_5NO_2]Cl_2$	1595	1315	850
15	*trans*-$[Co(NH_3)_4(NO_2)_2]Cl$	1620	1300	840
16	$[Co(NH_3)_3(NO_2)_3]$	1630	1290	815
17	$K[Co(NH_3)_2(NO_2)_4]$	1630	1265	790
18	$[Co(NH_3)_5Cl]Br_2$	1600	1310	840
19	$[Co(NH_3)_5Br]Br_2$	1590	1312	832
20	$[Co(NH_3)_5OH]Br_2$	1620	1303	806
21	$[Co(NH_3)_5ONO]Cl_2$	1620	1320	845
22	$[Co(NH_3)_5H_2O]Cl_3$	1620	1325	835
23	*cis*-$[Co(NH_3)_4(H_2O)_2]Cl_3$	1620	1320	850
24	$[Co(NH_3)_5CO_3]NO_3$	1603	1305	830
25	$[Co(NH_3)_4CO_3]Cl$	1600	1280	850
26	$[Co(NH_3)_5NO_3]Cl_2$	1600	1315	855
27	$[Co(NH_3)_5SO_4]Cl$	1615	1315	830
28	$[Co(NH_3)_6(C_2O_4)]Br \cdot HBr$	1625	1310	835

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in the following order: Pt(IV) > Pt(II) > Co(III) > Pd(II) > Cr(III) > Cu(II) > Ni(II) > Co(II). Univalent silver is somewhat out of line, the ammonia ligands in $[Ag(NH_3)_2]^+$ having a rocking frequency slightly greater than that in $[Cu(NH_3)_4]^{++}$. The presence of rocking frequencies in the spectra of the hexammine Ni(II) and Co(II) complex ions indicates that the nitrogen-to-metal bonds have covalent character; the relatively low frequencies along with the paramagnetism of these complexes indicate sp^3d^2 outer orbital type bonds.

The rocking frequencies show a large variation and are thus very sensitive to the nature and oxidation state of the central metal ion. This is understandable from the above discussion of the nature of the rocking vibration.

The symmetrical bending frequencies of coördinated ammonia molecules show a similar variation with the nature of the N–M bond but the percentage difference in frequency in going from the Co(II) to Pt(IV) ammines is not so great as for the rocking frequencies. Moreover, the degenerate frequencies show little variation with the nature of the N–M bond. These observations are also in accord with the foregoing discussions of the natures of the symmetric and degenerate deformation vibrations.

The neutral $Pt(NH_3)_2Cl_2$ molecule (12) has a lower rocking and a lower symmetric deformation frequency than the $[Pt(NH_3)_4]^{++}$ ion (8) and a similar effect is observed in the Pd(II) compounds (13 and 6). The effect of the charge of the complex itself on the ammonia deformation frequencies is seen also in the series of cobalt(III) ammines (compounds 17, 16, 15 and 14). (The position of the rocking band at 790 cm.$^{-1}$ in compound 17 is not accurately known as the NO_2 group also absorbs strongly in this region). Both the rocking and symmetrical deformation frequencies increase, in general, with increasing positive charge on the complex. This increasing positive charge coincides with increasing number of ammonia molecules in these Co(III) complexes.

The replacement of the carbonate group in the $[Co(NH_3)_5CO_3]^+$ ion (compound 24) by a sulfate group (compound 27) has no effect on the rocking frequency, and replacement by an oxalate group (compound 28) has very little effect on either the rocking or the symmetric deformation frequencies. In the $[Co(NH_3)_5X]^{+2}$ ions (compounds 18 to 21 and 26), an appreciable lowering of the rocking and symmetric deformation frequencies occurs only where X is a hydroxyl group. The replacement of an inner chlorine atom by a nitro group in the $[Cr(NH_3)_5Cl]^{++}$ ion (compounds 10 and 11) results in an appreciable increase in the these deformation frequencies.

The spectra of these metal ammine complexes are being determined in the cesium bromide region in these laboratories to study the nature of the lower frequencies, as reported in a previous paper.[25]

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NOTRE DAME, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

The Synthesis of Certain Ethylenediamineplatinum(II) and (IV) Bromides and Iodides[1]

BY GEORGE W. WATT AND ROBERT E. MCCARLEY

RECEIVED MARCH 16, 1957

Methods for the synthesis of ethylenediamine coördination compounds of certain halides of platinum(II) and (IV) in high yield and high purity are described. It is shown that $[Pt(en)Br_2]$ and its isomer $[Pt(en)_2]PtBr_4$ may be separated quantitatively owing to the solubility of the former in liquid ammonia at −33.5°.

In the course of studies on the lower oxidation states of platinum,[2] we have had occasion to prepare numerous ethylenediamine coördination compounds of platinum halides. Although many of the corresponding chlorides have been synthesized and are well characterized, they are not desirable as starting materials for reactions in liquid ammonia owing to their generally low solubility. Accordingly, the necessary bromides and iodides were prepared. The syntheses described below either correspond to compounds not previously reported or represent new and/or improved procedures.

Experimental

Methods.—Platinum, when present as the only nonvolatile component, was determined by ignition to the metal; otherwise, platinum was reduced to the metal with hydrazine, dissolved in aqua regia, and determined spectrophotometrically.[3] Halogens were determined as silver halide; where halogen was covalently bonded in complexes, it was displaced with ethylenediamine prior to precipitation.

All X-ray diffraction patterns were obtained using a Hayes unit, Cu Kα radiation, an Ni filter, a tube voltage of 35 kv., a filament current of 15 ma. and exposure times that varied with the nature of the sample. All of the X-ray diffraction data reported here are assembled in Table I and include only the six most intense lines for each compound for which such data are not already available; more nearly complete data are tabulated elsewhere.[4]

For potentiometric titrations, the potential was measured with a Leeds and Northrup type K potentiometer, a platinum indicator electrode, and a saturated calomel reference electrode.

Materials.—Unless otherwise indicated, all chemicals employed in this work were reagent grade materials that were used without further purification.

Hexabromoplatinic acid was obtained by dissolving finely divided platinum in bromine and concentrated hydrobromic acid followed by boiling to remove excess bromine and acid. Massive platinum was dissolved in aqua regia and the re-

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TABLE I

X-RAY DIFFRACTION DATA

d, Å.	I/I_0	d, Å.	I/I_0	d, Å.	I/I_0
K_2PtBr_6		$(enH_2)PtBr_6$		$[Pt(en)Br_2]$	
5.98	1.0	6.50	0.9	6.99	1.0
5.19	0.8	5.97	1.0	6.46	0.5
3.13	.6	5.49	0.4	4.94	.7
2.99	.6	3.81	.6	3.83	.6
2.59	.9	2.98	.7	3.49	.8
1.93	.7	2.40	.7	3.12	.7
$[Pt(en)_2]PtBr_4$		$[Pt(en)_2]Br_2$		$[Pt(en)Br_4]$	
7.81	0.9	7.88	1.0	6.32	1.0
5.91	1.0	6.56	0.4	5.83	0.5
5.21	0.5	4.92	.6	5.28	.4
4.94	.5	4.03	.9	4.77	.8
3.85	.4	3.76	.7	3.87	.4
3.48	.7	3.53	.9	3.07	.6

$[Pt(en)Cl_2]$		$[Pt(en)I_4]$	
d, Å.	I/I_0	d, Å.	I/I_0
7.43	0.5	6.63	Strong
6.73	1.0	5.82	Strong
6.14	0.5	5.11	Very strong
5.63	.5	4.42	Medium
3.37	.9	3.84	Strong
3.02	.7	3.31	Weak

sulting solution was evaporated to dryness several times with concentrated hydrobromic acid to expel hydrogen chloride and oxides of nitrogen.

Potassium hexabromoplatinate(IV) was prepared from solutions of hexabromoplatinic acid by the method of Weber.[5]

Ethylenediammonium hexabromoplatinate(IV) was formed by slow addition of ethylenediamine to a cold solution of hexabromoplatinic acid. This brilliant red salt is only sparingly soluble in water. *Anal.* Calcd. for $(C_2H_{10}N_2)_2PtBr_6$: Pt, 26.5; Br, 65.1. Found: Pt, 26.5; Br, 64.7.

Tetrabromoplatinate(II) ion was, in some instances, prepared by the reduction of potassium hexabromoplatinate(IV) with potassium oxalate by the method of Bülman and Anderson.[6] This reaction however is quite slow, and complete reduction is achieved only by evaporating the reaction mixture to a small volume.

Since, in other cases, it was desirable to form the free acid in the absence of extraneous by-product ions, conditions were devised for the production of this ion by electrolytic reduction. A platinum wire cathode was immersed in 220 ml. of solution containing 3 g. of platinum as hexabromoplatinic acid. A platinum wire anode was immersed in a solution of potassium chloride that was connected to the cathode compartment by a potassium chloride–agar bridge. The catholyte was stirred vigorously, the current was maintained at *ca.* 0.1 amp., and the cathode potential was followed by means of a Leeds and Northrup No. 7664 *p*H meter using a saturated calomel reference electrode. During the course of the electrolysis, the color of the solution changed progressively from maroon-red to the deep red-brown color characteristic of the tetrabromoplatinate(II) ion. Concurrently, the potential gradually became more positive but there was no definite break in the time *vs.* potential curve. Accordingly, the appearance of a deposit of platinum on the cathode that appeared after about 60 hr. was taken as the end-point for the reduction process. As evidenced by the nature of the products obtained upon treatment of the product solutions with ethylenediamine, reduction is incomplete unless time is allowed for deposition of a considerable quantity of platinum on the cathode. The current efficiency is *ca.* 10%.

Synthesis of Platinum(II) and (IV) Halides.—In several of the cases that follow, numerous procedural variables were studied, but only the final procedures that gave optimum results are described.

Ethylenediaminedibromoplatinum(II), $[Pt(en)Br_2]$.—This compound was prepared by a method similar to that used by Basolo, *et al.*,[7] for the synthesis of the corresponding chloride.

A suspension of 10.5 g. (0.0140 mole) of potassium hexabromoplatinate(IV) in 50 ml. of water was reduced to potassium tetrabromoplatinate(II) with 2.57 g. (0.0140 mole) of potassium oxalate 1-hydrate,[6] and treated with 1:10 aqueous ethylenediamine *in 0.1-ml. portions* at room temperature. After each addition, the reaction was allowed to proceed to completion (*i.e.*, until the *p*H of the reaction mixture $\cong$ 6) before the next portion was added. During the reaction of the first portion of ethylenediamine solution, iridescent green crystals [see ref. 2] separated and continued to form until 0.5 ml. of the base had been added. This product (0.85 g.) was removed by filtration and the reaction was continued in the same manner. Upon addition of the next portion of the diamine, bright yellow crystals formed and after addition of 5 ml. of the diamine, 2.60 g. of this product was separated. Another crop (1.87 g.) of this same product was separated after adding an additional 3 ml. of ethylenediamine solution. A final incremental addition of 2 ml. of ethylenediamine solution provided a mixture of yellow crystals contaminated with a pale green solid. (Subsequent work—see below—has shown that this yellow product $[Pt(en)Br_2]$ is contaminated with a polymerization isomer. Conditions leading to the formation of $[Pt(en)Br_2]$ while minimizing the formation of the isomer are embodied in the procedure given.) The total yield was 4.47 g. or 77% based on potassium hexabromoplatinate(IV). *Anal.* Calcd. for $[Pt(en)Br_2]$: Pt, 47.0; Br, 38.5. Found: Pt, 46.9; Br, 38.7.

Ethylenediaminedibromoplatinum(II) is soluble in liquid ammonia at −33.5° apparently without reaction. Evaporation of the solvent from the yellow solution provided yellow crystals that gave an X-ray diffraction pattern identical with that of the solid originally dissolved. When a mixture of the yellow solid and its green polymerization isomer is treated with liquid ammonia at −33.5°, the former dissolves while the latter remains as a brown insoluble ammoniate. Pure $[Pt(en)Br_2]$ was recovered from the ammonia solution; the ammonia-insoluble brown ammoniate was deammoniated at 10^{-2} mm. at room temperature to provide the original green component of the mixture. Yellow $[Pt(en)Br_2]$ is also readily soluble in *N*,*N*-dimethylformamide, from which the bromide may be recrystallized by addition of water. If, however, these solutions are heated to *ca.* 50°, decomposition resulting in deposition of elemental platinum occurs.

Bisethylenediamineplatinum(II) Tetrabromoplatinate(II), $[Pt(en)_2]PtBr_4$.—A solution of tetrabromoplatinic acid was divided into two equal portions, ethylenediamine was added to one portion at 80–90° until all of the solid dissolved whereupon this was added to the other portion of the original solution. The pale green crystals that separated in quantitative yield were washed with water and dried at 110° for 2 hr. *Anal.* Calcd. for $[Pt(en)_2]PtBr_4$: Pt, 47.0; Br, 38.5. Found: Pt, 47.1; Br, 38.5.

As a means of providing evidence (other than that arising from the mode of synthesis) for the identity of the ionic components of this salt, precipitation of $PtBr_4^{2-}$ as the silver salt proved unsuccessful at or below room temperature owing to incomplete reaction; precipitation at elevated temperatures is impractical because of formation of silver bromide. Accordingly, the presence of two distinctly different ionic species containing platinum(II) was demonstrated by the potentiometric titration method of Grinberg and Ryabchikov.[8] Thus, 0.2801 g. of the salt was suspended with efficient stirring in 110 ml. of 1.0 *N* hydrochloric acid solution at 25° and titrated with 0.1384 *N* sodium bromate solution; the results are given in Fig. 1. About 4 hr. was required for the titration to the first end-point, at which stage all of the solid had dissolved and the color of the solution was pale yellow. Titration to the second end-point required only 30 min.; the final solution had an intense yellow color, and should be expected to contain $[Pt(en)_2Br_2]PtCl_4$ and/or its isomers. Evaporation of the solution to a small volume yielded 0.1 g. of orange colored crystals. *Anal.* Calcd. for

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$[Pt(en)_2Br_2]PtCl_6$: Pt, 45.0. Found: Pt, 44.3. The calculated end-points for oxidation of half and all of the platinum to the 4^+ oxidation state are 4.87 and 9.75 ml. of titrant, respectively. The end-points established by means of a differential plot are 4.68 and 9.75 ml.

Bisethylenediamineplatinum(II) Bromide, $[Pt(en)_2]Br_2$.—Although this compound should be formed readily by the action of ethylenediamine upon either $[Pt(en)Br_2]$ or $[Pt(en)_2]PtBr_4$, the reaction with the latter was found to be impractically slow. Accordingly, 1.87 g. of $[Pt(en)Br_2]$ was suspended in 30 ml. of water, treated with 1 ml. of ethylenediamine and heated at 80–90° for 4 hr. A small quantity of residual solid was removed by filtration, the filtrate was diluted with 500 ml. of ethanol, and cooled to 0°. The fine white crystals that separated were filtered, washed with ethanol, and dried at 110°. The yield was 1.96 g. or 92% based on $[Pt(en)Br_2]$. *Anal.* Calcd. for $[Pt(en)_2]Br_2$: Pt, 41.1; Br, 33.6. Found: Pt, 41.1; Br, 33.4.

***trans*-Bisethylenediaminedibromoplatinum(IV) Bromide, $[Pt(en)_2Br_2]Br_2$.**—This synthesis was effected by a procedure similar to that used by Schleicher, Henkel and Spies[9] for the preparation of $[Pt(en)_2Br_2]Cl_2$. Thus, 0.424 g. of $[Pt(en)_2]Br_2$ was dissolved in 25 ml. of water and treated with 0.2 ml. of bromine at 50°. After 15 min., the temperature was raised to 100° and air was blown over the surface of the solution to remove excess bromine. When the volume of the solution was reduced to 10 ml., it was cooled to room temperature, treated with 1 ml. of concentrated hydrobromic acid solution, and finally diluted with 100 ml. of 2:1 ethanol–acetone mixture. The fine yellow crystals that separated were filtered, washed with ethanol and acetone, and dried in air.[10] *Anal.* Calcd. for $[Pt(en)_2Br_2]Br_2$: Pt, 30.7. Found: Pt, 29.7.

Ethylenediaminetetrabromoplatinum(IV), $[Pt(en)Br_4]$.—Although this compound was formed successfully by the oxidation of $[Pt(en)Br_2]$ with bromine, this procedure[7,9] was found to be much less satisfactory than that which follows. An excess of 50% aqueous ethylenediamine was added to 2.99 g. of K_2PtBr_6 in 100 ml. of water at room temperature. After 3 hr., the solution was acidified with hydrobromic acid, heated to 90°, then cooled to 10°. The orange-colored powder that separated was filtered, washed with water followed by ethanol and ether, and dried in air. The yield was 1.78 g. or 78% based on K_2PtBr_6. *Anal.* Calcd. for $[Pt(en)Br_4]$: Pt, 34.0; Br, 55.6. Found: Pt, 34.0; Br, 55.3. This substance is soluble in both N,N'-dimethylformamide and γ-butyrolactone, and dissolves in liquid ammonia owing to the occurrence of reactions described elsewhere.[2]

Ethylenediaminedichloroplatinum(II), $[Pt(en)Cl_2]$.—Although another method of synthesis has been reported,[7] the following procedure is both simple and efficient. To 1.30 g. (0.0013 mole) of $[Pt(en)Br_2]$ suspended in 75 ml. of water was added to 1.064 g. (0.00626 mole) of silver nitrate and the mixture was acidified with 1 ml. of 6 *N* nitric acid. After heating the reaction mixture at 90° for 2 hr., the precipitated silver bromide was filtered off, and the filtrate was treated with excess potassium chloride solution. Golden yellow needles of the desired chloride separated after about 5 min., whereupon the solution was cooled to 0° and filtered. The product was washed with water, ethanol, and dried for 12 hr. at 110°. The yield was 0.93 g. or 91% based on $[Pt(en)Br_2]$. *Anal.* Calcd. for $[Pt(en)Cl_2]$: Pt, 59.8; Cl, 21.7. Found: Pt, 59.6; Cl, 21.7.

Ethylenediaminediiodoplatinum(II), $[Pt(en)I_2]$.—This substance was prepared by a method analogous to that used by Schleicher, *et al.*[9] Thus, 1.4445 g. (0.0035 mole) of $[Pt(en)Br_2]$ slurried in 150 ml. of water was treated with 1.1913 g. (0.0070 mole) of silver nitrate for 1 hr. at 90°. The precipitated silver bromide was removed by filtration and excess potassium iodide was added to the filtrate. The fluffy yellow solid that separated immediately was filtered, washed with water and with ethanol and dried in air. The yield was 1.73 g. or 96.7% based on $[Pt(en)Br_2]$. *Anal.* Calcd. for $[Pt(en)I_2]$: Pt, 38.3; I, 49.8. Found: Pt, 38.4; I, 49.5.

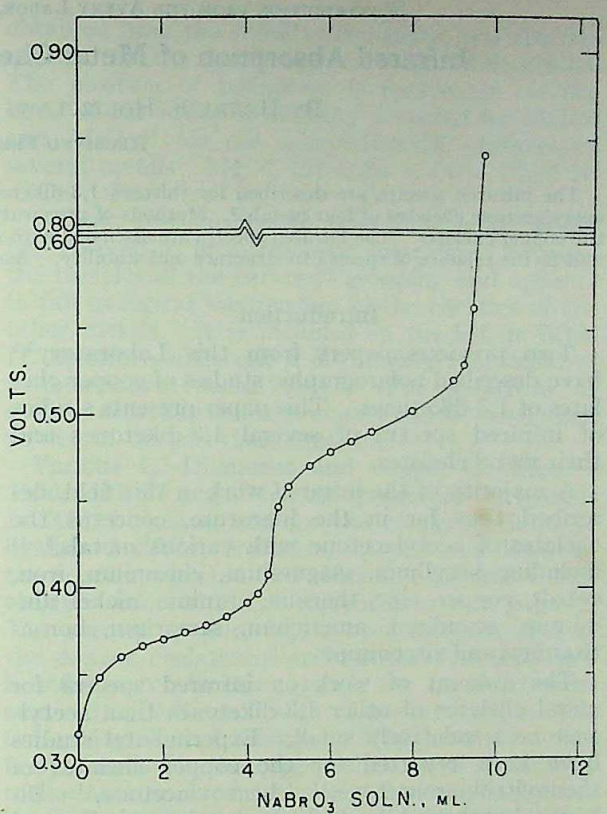

Fig. 1.—Potentiometric titration of $[Pt(en)_2]PtBr_4$ with sodium bromate.

Platinum(IV) Iodide, PtI_4.—In accordance with the procedure described by Pigeon,[11] PtI_4 was prepared in quantitative yield by heating 5.54 g. of platinum as H_2PtCl_6 with 19 g. of KI at 80°. *Anal.* Calcd. for PtI_4: Pt, 27.8. Found: Pt, 27.8.

Ethylenediaminetetraiodoplatinum(IV), $[Pt(en)I_4]$.—Approximately 1 g. of PtI_4 was dissolved in a slight excess of aqueous potassium iodide solution to provide a solution of K_2PtI_6 which was treated dropwise with 50% aqueous ethylenediamine. A very fine maroon-red precipitate separated at once and continued to form until the solution was colorless. Since analysis showed that this product was impure, it was treated with 100 ml. of γ-butyrolactone at room temperature; this resulted in a deep red solution and a bronze colored solid that was removed and discarded. The filtrate was diluted fivefold with water and fine glistening black crystals separated. This product was filtered, washed with water and with ethanol and dried in air; the yield was *ca.* 1 g. *Anal.* Calcd. for $[Pt(en)I_4]$: Pt, 25.6; I, 66.5. Found: Pt, 25.5; I, 66.5.

AUSTIN, TEXAS

(9) A. Schleicher, H. Henkel and L. Spies, *J. prakt. Chem.*, **105**, 91 (1922).

(10) It is assumed that this product is the *trans* isomer since it seems well established that complexes of the type $[Pt(en)_2]Br_2$ retain their configuration upon oxidation [see F. Basolo, *Chem. Revs.*, **52**, 459 (1953)].

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[CONTRIBUTION FROM THE AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

Infrared Absorption of Metal Chelate Compounds of 1,3-Diketones[1]

BY HENRY F. HOLTZCLAW, JR., AND JAMES P. COLLMAN

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The infrared spectra are described for thirteen 1,3-diketones, the copper chelates of seventeen 1,3-diketones, and the acetylacetone chelates of four metals.[2] Methods of preparation are described, including an improved method of preparing the copper chelates. The infrared spectra are discussed with respect to a comparison with spectra reported in the literature and to the relation of spectra to structure and stability. Assignments are made for several absorption frequencies.

Introduction

Two previous papers from this Laboratory[3,4] have described polarographic studies of copper chelates of 1,3-diketones. This paper presents studies of infrared spectra of several 1,3-diketones and their metal chelates.

A majority of the infrared work in this field, described thus far in the literature, concerns the chelates of acetylacetone with various metals,[5-11] including beryllium, magnesium, chromium, iron, cobalt, copper, zinc, thorium, uranium, nickel, aluminum, scandium, americium, samarium, borontitanium and zirconium.

The amount of work on infrared spectra for metal chelates of other 1,3-diketones than acetylacetone is relatively small. Experimental studies have been reported for the copper chelates of thenoyltrifluoroacetone,[11] benzoylacetone,[11] dibenzoylmethane,[9,11] trifluoroacetylacetone[12] and hexafluoroacetylacetone.[12]

A few studies have been made of the infrared spectra of unchelated 1,3-diketones, including acetylacetone,[13] dibenzoylmethane,[13] and several fluorinated 1,3-diketones.[14]

The present paper describes preparation and infrared studies of thirteen 1,3-diketones, the copper chelates of seventeen 1,3-diketones, and the acetylacetone chelates of several metals.

(1) Abstracted from the M.S. Thesis of James P. Collman, June, 1956, University of Nebraska.

(2) Tables I, III, IV and V, containing the spectra referred to in the body of this paper, have been deposited as Document number 5129 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting $1.25 for photoprints, or $1.25 for 35 mm. microfilm, in advance by check or money order payable to: Chief, Photoduplication Service, Library of Congress.

(3) H. F. Holtzclaw, Jr., K. W. R. Johnson and F. W. Hengeveld, THIS JOURNAL, **74**, 3776 (1952).

(4) H. F. Holtzclaw, Jr., A. H. Carlson and J. P. Collman, *ibid.*, **78**, 1838 (1956).

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(9) D. N. Shigorin, *Izvest. Akad. Nauk. S.S.S.R., Ser. Fiz.*, **17**, 596 (1953) [*C. A.*, **48**, 5651h (1954)]; *Zhur. Fiz. Khim.*, **27**, 554 (1953); [*C. A.*, **48**, 7478i (1954)].

(10) L. J. Bellamy, G. S. Spicer and J. D. H. Strickland, *J. Chem. Soc.*, 4653 (1952).

(11) L. J. Bellamy and R. F. Branch, *ibid.*, 4491 (1954).

(12) R. L. Belford, A. E. Martell and M. Calvin, *J. Inorg. Nucl. Chem.*, **2**, 11 (1956).

(13) R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, THIS JOURNAL, **71**, 1068 (1949).

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Results and Discussion

The wave numbers of bands in the infrared spectra for the ligands and chelates studied are given in Tables I, III, IV and V.[2] Infrared intensity abbreviations used in the tables are: s, strong; m, medium; w, weak; b, broad; sh, shoulder. Bands in the Nujol region are not listed. Exact information on the origin of bands for metal coördination compounds is still relatively meager. Several of the assignments made in the tables and in the discussion, therefore, should be considered as tentative.

The following key to the Roman numeral designations used in Tables III, IV and V lists the ligand molecules

I. 3-Ethyl-2,4-pentanedione
II. 3-*n*-Propyl-2,4-pentanedione
III. 3-Chloro-2,4-pentanedione
IV. 3-Phenyl-2,4-pentanedione
V. 3-Benzyl-2,4-pentanedione
VI. Isovalerylacetone (6-methyl-2,4-heptanedione)
VII. Benzoylacetone (1-phenyl-1,3-butanedione)
VIII. Dibenzoylmethane (1,3-diphenyl-1,3-propanedione)
IX. 2-Furoyltrifluoroacetone [1-(2-furyl)-4,4,4-trifluoro-1,3-butanedione]
X. 2-Furoylperfluorobutyrylmethane [1-(2-furyl)-4,4,5,5,6,6,6-heptafluoro-1,3-hexanedione]
XI. 2-Thenoyltrifluoroacetone [1-(2-thienyl)-4,4,4-trifluoro-1,3-butanedione]
XII. 2-Thenoylperfluorobutyrylmethane [1-(2-thienyl)-4,4,5,5,6,6,6-heptafluoro-1,3-hexanedione]
XIII. 3-Bromo-2,4-pentanedione
XIV. 3-Iodo-2,4-pentanedione
XV. 3-Methyl-2,4-pentanedione
XVI. Trifluoroacetylacetone (1,1,1-trifluoro-2,4-pentanedione)
XVII. Hexafluoroacetylacetone (1,1,1,5,5,5-hexafluoro-2,4-pentanedione)

Metal Chelates of Acetylacetone.—The infrared spectra of the acetylacetone (2,4-pentanedione) chelates of copper(II), palladium(II), nickel(II), cobalt(II), manganese(II), magnesium(II), cadmium(II), aluminum(III), chromium(III), iron(III) and sodium(I) were determined. Of the 11, only the four not previously reported in the literature (palladium, manganese, cadmium and sodium) are listed in Table I.[2]

Although the spectrum of acetylacetone contains no intense bands in the 1500 cm.$^{-1}$ region, metal chelates of acetylacetone do absorb strongly in this region. Following the assigment of Lecompte,[5] the uppermost band is assigned to a perturbed (or chelated) carbonyl and the lower band to a perturbed carbon–carbon double bond. In the conjugated chelate ring, the carbonyl and carbon–carbon double bonds have less double bond character and more single bond character, accounting for

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the large frequency shifts of the carbon–carbon double bond adsorption band and the carbonyl absorption band upon chelation.

The position of the perturbed carbonyl band, usually the strongest band found in the spectrum of a given chelate, is perhaps largely dependent upon three factors: (1) the masses of the groups attached, at the ends of the ligand molecule, to the carbonyl groups, (2) interaction of the carbonyl with neighboring π or d-orbitals, and (3) the relative electron density of the σ bonds. The latter factor is, for the most part, controlled by the electronegativity of the groups attached to the carbon atom of the carbonyl group. For chelates of different metals but the same ligand, the mass effect probably has very little relation to the strength of the metal–oxygen bond. If more conjugation between the metal ion and the carbonyl exists in one metal acetylacetonate than another, this might be expected to result in a stronger metal–oxygen bond, less double bond character in the carbonyl group, and a lowering of the frequency of the perturbed carbonyl band.

Previous attempts to find a band or bands related to the stability of the chelates have met with only partial success. Bellamy and Branch[11] found that for bivalent metal complexes of salicylaldehyde, the shift of the carbonyl band followed the usual order of stabilities. A rough measure of stability was obtained from the positions of this band with bivalent metal chelates of 2-thenoyltrifluoroacetone. They reported, however, that there was no apparent relation between chelate stability and position of the carbonyl band for the bivalent metal chelates of acetylacetone.

The bands selected by Bellamy and Branch appear to have been, in each case, the most intense band found in the 1500 cm.$^{-1}$ region rather than the first or uppermost band in each case. Selection of the uppermost of the two bands seems to yield a significant relationship. The uppermost band in this region, from the spectra measured in the present work, is listed for several metals in Table II in order of decreasing frequency.

Van Uitert, Fernelius and Douglas,[15] from stability constants calculated from *p*H measurements, have reported the order of increasing stability of several metal chelates of acetylacetone to be: Mg(II) < Cd(II) < Mn(II) < Co(II) < Zn(II) < Ni(II) < Cu(II).

TABLE II

FREQUENCIES OF PERTURBED CARBONYL BANDS IN ACETYLACETONE CHELATES OF SEVERAL METALS

Metal	Frequency, cm.$^{-1}$	Metal	Frequency, cm.$^{-1}$
Na(I)	1630	Mn(II)	1607
Ni(II)	1618	Co(II)	1595
Mg(II)	1615	Cu(II)	1580
Cd(II)	1613	Pd(II)	1577

A comparison of these two series indicates, with nickel an exception, a qualitative relationship between the strength of the metal–oxygen bond, as obtained from the stability constants, and the frequency of the perturbed carbonyl absorptions. The position of palladium is reasonable on the basis of the order of stability reported by Mellor and Maley[16] for the salicylaldehyde chelates of several metals: Mg < Cd < Zn < Co < Pb < Ni < Cu < Pd.

Sodium acetylacetonate, essentially ionic, would be expected to have the least interaction between the metal and the carbonyl grouping and appears to fall in logical relationship to the chelates of the other metals. It is included in the list in Table II, therefore, although it is the only compound of a monovalent metal listed. The spectrum of sodium acetylacetonate probably can be considered as that of the acetylacetonate ion.

Various 1,3-Diketones and Copper Chelates.—Tables III, IV and V[2] list the spectra for the ligands I—XII, inclusive, and for the copper chelates of ligands I–XVII, inclusive. Agreement between the spectra reported in Tables III, IV and V and the few reported in the current literature is good. The spectra of pure liquid acetylacetone and of the copper chelates of trifluoroacetylacetone and hexafluoroacetylacetone agree, for most frequencies, within 0–3 cm.$^{-1}$ with values reported by Belford, Martell and Calvin.[12] The perturbed carbonyl bands for the copper chelates of 2-thenoyltrifluoroacetone and 1-phenyl-1,3-butanedione correspond closely with the values reported by Bellamy and Branch,[11] but that for the copper chelate of dibenzoylmethane (1552 cm.$^{-1}$) does not agree with the value of Bellamy (1524 cm.$^{-1}$). The discrepancy may be explained by the choice of the most intense band by Bellamy rather than the first strong band in the 1500 cm.$^{-1}$ region. Some other values reported by Bellamy vary a few wave numbers from those reported in this work. These differences are thought to be accounted for by the use of dilute chloroform solution by Bellamy, whereas Nujol suspensions were used in the present work. Bellamy reports a free carbonyl band for benzoylacetone which was not found in this work. His spectrum of dibenzoylmethane agrees with that reported in Table IV.

4000-1650 Cm.$^{-1}$ Region.—Very few copper chelates of 1,3-diketones absorb in this region. The origin of the weak absorption bands for the copper chelates of 2-thenoyltrifluoroacetone and 2-furoylperfluorobutyrylmethane at 3110 and 3140 cm.$^{-1}$, respectively, and the moderate band for the copper chelate of hexafluoroacetylacetone at 3550 cm.$^{-1}$ is uncertain.

Seven out of the thirteen 1,3-diketones examined show one or more hydroxyl bands in the 3600 to 3000 cm.$^{-1}$ region. The diketones in which such bands are not found may perhaps have absorptions in this region which are weak or poorly resolved. The molecules containing electronegative groups such as trifluoromethyl or perfluoropropyl are found to have hydroxyl bands at a lower frequency than the other 1,3-diketones in agreement with Belford, who in a recent study of fluorinated copper chelates[12] attributed the lowering of the hydroxyl frequency to the presence of a more acidic hydrogen.

(15) L. C. Van Uitert, W. C. Fernelius and B. E. Douglas, This Journal, **75**, 2736 (1953).

(16) D. P. Mellor and L. Maley, *Nature*, **159**, 370 (1947).

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These bands are not sharp enough to provide more quantitative information about the acidity.

The next important absorption bands are the sharp, usually strong bands thought to be caused by free carbonyl absorptions of the keto form of the 1,3-diketone. These bands, present in the spectra of six of the thirteen diketones studied, disappear upon chelation. Except for 3-chloro-2,4-pentanedione, which has only one band centered at about 1725 cm.$^{-1}$, the diketones exhibit two such bands, one centered around 1700 cm.$^{-1}$ and the other around 1725 cm.$^{-1}$.

1650 to 1500 Cm.$^{-1}$ Region.—A strong, usually broad, band around 1610 cm.$^{-1}$, which disappears upon chelation, was observed in all of the diketones studied. The position of this band, which is characteristic of 1,3-diketones and which has been referred to as the "enol-chelate" band by Bellamy and Beecher,[17] does not seem to be related to the inductive or resonance effects of the group attached to the hydrogen-bonded, six-membered ring of the enol form.

The most important chelate band is the perturbed carbonyl band, usually the first strong band found in the spectrum of a copper chelate of a 1,3-diketone and ordinarily located around 1580 cm.$^{-1}$. In 11 of the 12 copper chelates for which the free diketone is also reported, the perturbed carbonyl bands of the chelate are at a lower frequency than the hydrogen-bonded carbonyl (enol chelate) band of the unchelated ligand. An exception is the copper chelate of 2-furoylperfluorobutyrylmethane, in which there are three bands which might conceivably be assigned to the perturbed carbonyl absorption, 1615 cm.$^{-1}$, 1598 cm.$^{-1}$ and 1580 cm.$^{-1}$. The 1598 band is probably caused by absorption of the furan ring. The 1615 band has been arbitrarily designated as the perturbed carbonyl band, because it is the first strong absorption and is higher than the expected furan absorption. The two bands at 1615 and 1598 cm.$^{-1}$ may, alternatively, both arise from furan absorptions, with the strong band at 1580 cm.$^{-1}$ originating from the chelated carbonyl group.

In contrast to the acetylacetonates of the various metals reported above, a comparison of the perturbed carbonyl bands of the copper chelates of the seventeen 1,3-diketones shows no apparent relationship to the stability of the chelates. Neither does the difference between the enol–chelate band of the ligand and the perturbed carbonyl band of the chelate, nor the difference between the perturbed carbonyl band and the perturbed carbon–carbon double bond, seem to have a direct relation to stability of the metal chelate. The absence of a relationship is not entirely unexpected. In comparing the acetylacetonates of various metals, the action of the ligand is essentially the same in each case and, except for the differences in the masses of the metals, any effect which strengthens the metal–oxygen bond weakens the carbon–oxygen carbonyl bond. For the copper chelates of various 1,3-diketones, on the other hand, the differences in resonance, inductive, and mass effects between the various chelates must be attributed essentially all to the ligand, the metal remaining the same, and may differ in their relative effects upon the metal–oxygen bond and the carbonyl bond. For example, a phenyl group attached to a carbonyl group in the ligand might set up an interfering conjugation through a quinoid-like structure, thereby decreasing the double bond character of the adjacent carbonyl group, lowering the frequency of the perturbed carbonyl band, and decreasing the strength of the copper–oxygen bond. This is illustrated by the spectrum of bis-(1-phenyl-1,3-butanediono)-copper(II), which has a perturbed carbonyl band at 1561 cm.$^{-1}$, compared to 1580 cm.$^{-1}$ for bis-(2,4-pentanediono)-copper(II) which is known to have a stronger copper–oxygen bond.[4] On the other hand, strong electronegative groups attached to the chelate ring cause a decrease in the stability of the chelate[4] but an increase in the strength of the carbon–oxygen carbonyl bond and therefore an increase in the frequency of the perturbed carbonyl absorption band. This is exemplified by bis-(hexafluoroacetylacetone)-copper(II) in which there are two strong bands at 1645 and 1615 cm.$^{-1}$ (either or both of which could be perturbed carbonyl absorptions). The increase in the first strong absorption band of the spectra of fluorinated copper chelates may be caused by the electron-attracting group increasing the force constant of the carbonyl bond.

Further, if a group capable of acting as an electron sink through resonance were attached to one of the carbonyls of a 1,3-diketone, and a strongly electronegative group were attached to the other carbonyl, the spectrum of the resulting chelate might contain two different perturbed carbonyl absorptions. The 1608 and 1568 cm.$^{-1}$ bands of bis-(2-furoyltrifluoroacetono)-copper(II) and the 1615 and 1580 cm.$^{-1}$ bands of bis-(2-furoylperfluorobutyrylmethane)-copper(II) may be explained in this manner. The analogous 2-thenoyl compounds are complicated by the presence of thiophene bands which may be at the same frequency as the second perturbed carbonyl band. In the furan-containing compounds, three bands were found, one of which logically is assigned to the furan ring.

The perturbed carbonyl band seems to be at a lower frequency for each of the copper chelates in which the carbon between the two carbonyl groups is substituted. This may be in part a mass effect. Although the information concerning mass effects upon absorption bands is meager at present, it is interesting to note that for chelates of 3-substituted 2,4-pentanedione a comparison of perturbed carbonyl frequencies with the masses of the substituted groups produces a reasonably good inverse relationship

Substituted group	Relative mass of group	Frequency of perturbed carbonyl
(Hydrogen)	1	1580
Methyl	15	1577
Ethyl	30	1571
Chloro	35.5	1577
n-Propyl	43	1575
Phenyl	77	1558
Bromo	80	1570
Benzyl	91	1547
Iodo	127	

(17) L. J. Bellamy and L. Beecher, *J. Chem. Soc.*, 1487 (1954).

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The additional factor of positive inductive effect of groups such as benzyl further complicates the factors controlling the position of the perturbed carbonyl absorption band.

Other bands in the 1650 to 1500 cm.$^{-1}$ region in either the free ligand or the chelate can be attributed to vibrations of functional groups, such as phenyl, furan and thiophene rings.

1500-800 Cm.$^{-1}$ Region.—A band centered around 1425 cm.$^{-1}$ in many of the 1,3-diketones and their chelates is probably caused by a methyl deformation. Similar assignments have been given by other workers, including Belford, Martell and Calvin[12] who have assigned the 1425 cm.$^{-1}$ band in acetylacetone to a methyl deformation. The compounds which have no methyl group substituted in the chelate ring fail to absorb in the 1425 cm.$^{-1}$ region.

Strong carbon–fluorine bands appear from 1300 to 1000 cm.$^{-1}$.

A range of additional perturbed carbonyl absorption has been reported by Lecompte[5] and by Bellamy and Branch[11] in the 1400 to 1300 cm.$^{-1}$ region. A comparison of several of the ligand and chelate spectra studied in the present work reveals a band which could, perhaps, be an additional perturbed carbonyl.

800-650 Cm.$^{-1}$ Region.—Strong bands occur in the upper 700 cm.$^{-1}$ region in the 1,3-diketones and their metal chelates. Ueno and Martell[18] ascribe similar bands in the range 779 to 740 cm.$^{-1}$ for metal chelates of bisacetylacetone–ethylenediimine and related compounds to C–H out-of-plane deformation vibrations. In compounds of the type $R'R''C{=}CHCH_3$, such vibrations are usually in the range 840-800 cm.$^{-1}$. Ueno and Martell reasoned that the aromatic nature of the six-membered hydrogen-bonded ring of the enol form of the ligand or of the conjugated chelate ring explains the lowering of these absorptions.

The 1,3-diketones which are substituted at the methylene carbon between the two carbonyl groups could have no hydrogen on the carbon–carbon double bond of the ligand enol form nor on the carbon–carbon double bond of the chelated ligand. The spectra of the chelates and free ligands are listed in Table III for compounds in which ethyl, *n*-propyl, chloro, phenyl and benzyl groups have been substituted at the number three carbon of 2,4-pentanedione. In Table V, the spectra of chelates are listed in which bromo, iodo and methyl groups have been substituted. The spectra of several of these ligands and chelates show bands in the 700 cm.$^{-1}$ region which cannot be attributed to a hydrogen out-of-plane deformation. The origin of this absorption is the more puzzling, inasmuch as the absorption band, in agreement with the observations of Ueno and Martell for the ethylenediimine compounds, seems to be almost unaffected by chelation of the ligand or by drastic alteration of the metal used in chelating the ligand.

Below 700 cm.$^{-1}$, absorption bands are expected which are caused by metal–oxygen vibrations.[5] Such bands, however, are conspicuously absent down to 650 cm.$^{-1}$ in most of the spectra of copper chelates of 1,3-diketones studied in the present work. In only a few instances (the copper chelates of 2,4-pentanedione, isovalerylacetone, 3-benzyl-2,4-pentanedione and 3-*n*-propyl-2,4-pentanedione) were bands found in this region which could be so assigned after comparing the spectra of the chelate and of the corresponding free 1,3-diketone. The possibility exists that an examination of the frequency region below 650 cm.$^{-1}$ might reveal additional bands which could be assigned to metal–oxygen vibrations.

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Experimental

Spectra.—All spectra were determined in the frequency range 4000-650 cm.$^{-1}$ with a Perkin–Elmer Model 21 recording spectrophotometer, using sodium chloride optics.[19] Compounds usually were examined as solids in Nujol mulls. A few samples, as indicated in the tables, were studied as pure liquid films.

Preparation and Purification of Compounds. Metal Chelates.—1. The acetylacetonates of palladium(II), manganese(II) and cadmium(II) were prepared and analyzed by Wenz.[20] The copper chelates of hexafluoroacetylacetone and trifluoroacetylacetone were obtained from Professor A. L. Henne of The Ohio State University. Preparation and analysis of the copper chelates of acetylacetone, 1-phenyl-1,3-butanedione, 1,3-diphenyl-1,3-propanedione, 3-methyl-2,4-pentanedione, 3-ethyl-2,4-pentanedione, 3-*n*-propyl-2,4-pentanedione and 3-phenyl-2,4-pentanedione and the respective ligands are described in previous articles.[3,4]

2. **Sodium Acetylacetonate.**—The method of Morgan and Rawson[21] was used. The white precipitate was filtered, washed successively with cold, absolute ethanol and cold ether, dried and weighed; yield 23.0 g. (78%).

3. **Bis-(isovalerylacetono)-copper(II).**—A dioxane solution of the diketone was added slowly, with stirring, to an ammoniacal water solution of copper nitrate. The precipitate was filtered, washed with water, dioxane and ether, and dried. The sample was recrystallized from chloroform and sublimed at 110° at 0.005 mm. *Anal.* Calcd.: Cu, 19.87. Found: Cu, 19.25, 19.30.

4. **Bis-(2-thenoyltrifluoroacetono)-copper(II).**—An improved procedure was developed and was used in the preparation of several of the chelates.

A slurry of 11.1 g. of thenoyltrifluoroacetone (0.05 mole), 5.0 g. of copper acetate monohydrate (0.025 mole) and 100 ml. of 80% acetone–water solution was stirred for 24 hours, after which the acetone was removed on a steam-bath. The precipitate, after successive washing with ice-cold 50% water–ethanol solution, cold 5% aqueous ammonia (to remove excess copper acetate) and ice-water, was dried under vacuum and extracted in a Soxhlet extractor with 150 ml. of chloroform until the liquid extract became colorless. The chloroform solution was allowed to stand for 12 hours at room temperature and then was cooled to 0° and filtered. The dark-green crystals, superior to those produced without the extraction technique, were dried in a vacuum desiccator; yield 11.1 g. (88.7%). The compound would not sublime without decomposition. *Anal.* Calcd.: Cu, 12.56; C, 37.98; H, 1.58. Found: Cu, 12.72, 12.67; C, 38.34; H, 1.76.

5. **Bis-(2-furoyltrifluoroacetono)-copper(II).**—This compound was prepared and purified in the same manner as bis-(2-thenoyltrifluoroacetono)-copper(II). The green, crystalline compound decomposes upon sublimation; yield 99%. *Anal.* Calcd.: Cu, 13.41; C, 40.55; H, 1.69. Found: Cu, 13.87, 13.92; C, 40.07; H, 2.10.

(18) K. Ueno and A. E. Martell, *J. Phys. Chem.*, **59**, 998 (1955).

(19) We are indebted to the Infrared Laboratory, University of Illinois, for determining in 1953 the spectra of our samples of the copper chelates of I, II, IV, V, VII, VIII, XV, XVI and XVII and of the copper chelate of acetylacetone. The other spectra were measured at the University of Nebraska Spectroscopy Laboratory.

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6. **Bis-(2-thenoylperfluorobutyrylmethane)-copper(II).**—The method described for bis-(2-thenoyltrifluoroacetono)-copper(II) was used. The green, crystalline compound decomposes with sublimation; yield 99%. *Anal.* Calcd.: C, 33.92; H, 1.41. Found: C, 34.20; H, 1.43.

7. **Bis-(2-furoylperfluorobutyrylmethane)-copper(II).**—The compound was prepared and purified by the method described for bis-(2-thenoyltrifluoroacetono)-copper(II). The green, crystalline compound decomposes with sublimation; yield 98%. *Anal.*: Calcd. C, 35.53; H, 1.48. Found: C, 35.63; H, 1.32.

8. **Bis-(3-chloro-2,4-pentanediono)-copper(II).**—The method was similar to that described for bis-(2-thenoyltrifluoroacetono)-copper(II). A mixture of 44.6 g. of crude 3-chloro-2,4-pentanedione[22] (0.318 mole), 33.3 g. of copper acetate monohydrate (0.166 mole) and 200 ml. of acetone was allowed to stand in a stoppered flask for 24 hours. The crude precipitate, which was filtered from the slurry after cooling to 0°, was three times stirred with 200 ml. of water, filtered and dried on a fritted disc; yield 60 g. (80%). A small sample was recrystallized successively from benzene and chloroform and dried 48 hours in a vacuum desiccator. The green crystals decompose with sublimation and are unstable in alcohol and dilute, aqueous ammonia. *Anal.* Calcd.: Cu, 19.21; C, 36.31; H, 3.63. Found: Cu, 19.42; C, 35.93; H, 3.69.

9. **Bis-(3-bromo-2,4-pentanediono)-copper(II).**—A mixture of 25 g. of acetylacetone (0.25 mole) and 25 ml. of chloroform was placed in a 500-ml. three-neck, round-bottom flask fitted with a dropping funnel, stirrer and a tube leading to an aspirator (to remove hydrogen bromide). The aspirator was adjusted so that pressure inside the flask was approximately 50 mm. less than atmospheric pressure. The flask was immersed in an ice-bath and stirring commenced. A solution of 44 g. of bromine (0.275 mole) in 115 ml. of chloroform was added through the dropping funnel during a period of one-half hour, after which stirring was continued for an additional one-half hour. The solution was washed in a separatory funnel (good hood required) with eight 100-ml. portions of cold tap water. The last portion of wash water had a *p*H over 5. After removal of the chloroform under reduced pressure at room temperature, the remaining liquid was combined with 25 g. of copper(II) acetate monohydrate (0.125 mole) and 200 ml. of a 90% acetone–water mixture. After the slurry had stood for 24 hours, it was cooled to 0° and filtered. The green powder was washed by stirring three times with 200 ml. of water and dried; yield 60 g. (75%, calculated from acetylacetone). A sample was recrystallized twice from benzene and dried 48 hours in a vacuum desiccator. The compound decomposes upon sublimation and is unstable in alcohol and in dilute, aqueous ammonia. *Anal.* Calcd.: Cu, 15.14; C, 28.64; H, 2.86. Found: Cu, 15.37; C, 28.61; H, 3.04.

10. **Bis-(3-iodo-2,4-pentanediono)-copper(II).**—The chelate was precipitated by adding a water solution of copper(II) acetate monohydrate to an acetone solution of 3-iodo-2,4-pentanedione prepared by the method of Kumler.[23] Inasmuch as every attempt to recrystallize the chelate resulted in decomposition, the product never was obtained in really pure form. *Anal.* Calcd.: C, 23.37; H, 2.34. Found: C, 20.58; H, 2.17.

11. **Bis-(3-benzyl-2,4-pentanediono)-copper(II).**—A method used in previous work in this Laboratory[4] involved refluxing the sodium salt of acetylacetone with benzyl chloride, followed by fractional distillation under reduced pressure. The following new procedure represents some improvement over the former procedure. A mixture of 10 g. of sodium acetylacetonate (0.082 mole) and 14 g. of benzyl bromide (0.082 mole) was placed in a 250-ml. flask fitted with a reflux condenser. Approximately 150 ml. of nitrobenzene was added to raise the boiling temperature of the solution and for convenience in later separation of the product (soluble in nitrobenzene) from excess sodium acetylacetonate (relatively insoluble). The mixture was refluxed for eight hours and filtered. The filtrate was distilled at 90° and 10 mm. pressure until no more distillate came over. The solution obtained by dissolving the residue in 80 ml. of acetone was mixed with 10 g. of copper(II) acetate monohydrate (0.05 mole) and 20 ml. of water. After the mixture had stood for 24 hours, the precipitate was filtered off and washed four times by stirring in water and filtering. The dark grey compound, after drying, weighed 8 g. (25%). A small sample was recrystallized four times from 95% ethanol. The infrared spectrum of this sample was the same as the spectrum of a sample previously prepared by the other method and characterized by analysis.

1,3-Diketones.—Samples of 3-chloro-2,4-pentanedione, 3-ethyl-2,4-pentanedione, 3-*n*-propyl-2,4-pentanedione, 3-phenyl-2,4-pentanedione and 3-benzyl-2,4-pentanedione were prepared in our laboratories subsequent to preparing the copper chelates.[3,4] Purified samples of these diketones were recovered from the pure copper chelates by the following procedure. Approximately 1.5 g. of the copper chelate was decomposed by stirring for two hours in 100 ml. of 20% sulfuric acid, followed by washing the acid solution with three 10-ml. portions of ether. The ether washings were dried over 10 g. of anhydrous sodium sulfate for 24 hours and filtered. The sodium sulfate was washed with 10 additional ml. of dry ether and the washing added to the original ether filtrate. After removal of the ether under reduced pressure, the remaining oil was transferred to a vacuum, microdistillation apparatus and distilled. For 3-phenyl-2,4-pentanedione, which is a solid at room temperature, recrystallization from petroleum ether was used in place of the distillation step.

Samples of 1,3-diphenyl-1,3-propanedione and 1-phenyl-1,3-butanedione, purchased from Eastman Kodak Company, were recrystallized three times from 95% ethanol. Samples of 2-furoyltrifluoroacetone, 2-thenoyltrifluoroacetone, 2-furoylperfluorobutyrylmethane and 2-thenoylperfluorobutyrylmethane, purchased from the Midcontinent Chemical Company, were purified by vacuum distillation. Acetylacetone, purchased from Eastman Kodak Company, was purified by distillation.

Efforts to prepare sufficiently pure samples of 3-bromo-2,4-pentanedione and 3-iodo-2,4-pentanedione failed because of their instability. An attempt to alkylate acetylacetone by refluxing a solution of sodium acetylacetonate and methyl iodide in ethylene glycol likewise was unsuccessful.

Methods of Analysis.—Analysis for copper was made by means of a standard potassium iodide–sodium thiosulfate titration, using a starch indicator. Prior to titration, the chelates were decomposed (1) with 20% sulfuric acid, or (2) by heating followed by treatment with concentrated nitric and sulfuric acids, or (3) by precipitation with hydrogen sulfide followed by treatment of the precipitated sulfide with concentrated nitric and sulfuric acids.

Carbon–hydrogen analyses were performed by the Micro-Tech Laboratories, Skokie, Illinois.

LINCOLN, NEBRASKA

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Hydrogen Bonding and Electronic Transitions: The Role of the Franck–Condon Principle

BY GEORGE C. PIMENTEL

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The influence of hydrogen bond formation on electronic transitions (including the $n \rightarrow \pi^*$ blue shift phenomenon) is discussed in terms of the Franck–Condon principle. The resultant frequency shift in absorption is equal to $W_0 - W_1 + w_1$ where W_0 and W_1 are the energies of hydrogen bond formation in the ground and excited states, respectively, and w_1 is the excitation implied by the Franck–Condon principle. The necessity of combining absorption and emission data to determine $W_0 - W_1$ is noted. The available absorption data indicate that the spectral shifts caused by water are usually about twice as big as those caused by methanol, suggesting that the hydrogen bond energy of water exceeds that of methanol to a given base.

Several studies have been made of the effect of hydrogen bonding (hereafter called H-bonding) on electronic transitions. For example, the absorption of phenol near 36,000 cm.$^{-1}$ has been observed for solutions containing phenol and one of several bases.[1-4] Another large body of applicable data relates to electronic transitions of bases dissolved in either alcohol or water. These data established an empirical correlation among solution spectra (apparently first suggested by Kasha[5] and substantiated by a compilation of data by McConnell[6]) called the "$n \rightarrow \pi^*$ blue shift phenomenon." In this correlation the absorption maximum of an $n \rightarrow \pi^*$ electronic transition is found to shift toward higher frequency if the solvent is changed from an alkane to an alcohol (this direction of shift being defined as a blue-shift). Recently Brealey and Kasha[7] recognized and established the importance of H-bonding in this solvent effect. Yet their discussion does not recognize the role of the Franck–Condon principle. Consequently their detailed interpretations are indeed oversimplified. We shall examine this role to determine the relationship between H-bond formation and the resultant spectral changes. The present discussion applies to all electronic transitions, including but not restricted to the $n \rightarrow \pi^*$ type.

The Franck–Condon Principle and Hydrogen Bonding.—Both McConnell[6] and Bayliss and McRae[8] have discussed in terms of the Franck–Condon principle the effect of solvation on an electronic transition. The equilibrium distances and orientations of solvent molecules around a solute molecule are dictated by the energetics of solvation. If this solute molecule makes an electronic transition, the solvation arrangement of the initial state is not necessarily the most stable for the new electronic distribution and, indeed, could be energetically repulsive. Since the solvent molecules cannot reorient during the transition (Franck–Condon principle) such a change in solvation energetics would result in a change in the energy separation of the two states (*i.e.*, there would be a solvent shift).

Bayliss and McRae[8] have attempted to enumerate the contributing factors to the solvation effects. Their treatment does not give adequate attention to the H-bonding interaction which, when present, dominates such forces as are usually described in terms of dispersion, dipole-polarizability and dipole–dipole forces. The dispersion effects are of the order of the van der Waals energy and the change of this term during an electronic transition is likely to be even smaller (as is assumed by Bayliss and McRae[8]). The comparison of dipolar and H-bonding effects is more subtle. We are here concerned with that part of the solute–solvent interaction which is attributed to the presence of permanent dipole moments in some or all of the molecular species present but which is *not* part of the specific interaction designated the H-bond. Most often, the functional groups possessing high bond dipoles will be involved in H-bond formation and any residual capacity for dipolar interactions of a non-H-bonding type will be small indeed. Experimental confirmation of these views is evident in the spectra of pyridazine in hexane–ethanol mixtures, as presented by Brealey and Kasha (their Fig. 3). This figure shows frequency invariance of band features of the pyridazine (not H-bonded) during a solvent change from pure hexane to a mixture of about 2 *M* ethanol in hexane. This indicates that this transition is little influenced by the dispersive and non-H-bonding dipolar effects that accompanied the drastic solvent change.[9] A further indication that the orientation effects associated with H-bonding far exceed those of dipolar interactions is given by the Trouton's rule constants. These constants, which contrast entropies of vaporization, are relatively close to a "normal" value (near 20–21) for polar compounds (*e.g.*, diethyl ether, 20.2; acetone, 21.9; 1,1,2,2-tetrachloroethane, 22.1) compared to the high values for H-bonding compounds (*e.g.*, methanol, 24.9; water, 26.0; ethanol, 26.9). Consequently the following discussion will ignore the dispersive and dipolar interactions. In any particular system where these neglected terms are unusually large and the H-bonding terms are small, the present treatment will then account for only that portion of the spectral perturbation due to the H-bonding.

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In an H-bonding system, the interaction is localized at functional groups with either proton donor or acceptor properties. A solvent shift then indicates that the H-bonding properties of these functional groups in the initial state differ from the H-bonding properties of these same groups in the final state. The magnitude of the shift must be evaluated, however, in terms of the Franck–Condon principle.

Figure 1 portrays potential functions for formation of an H-bond A-H· · ·B where R is the A· · ·B distance. Figure 1a portrays the situation

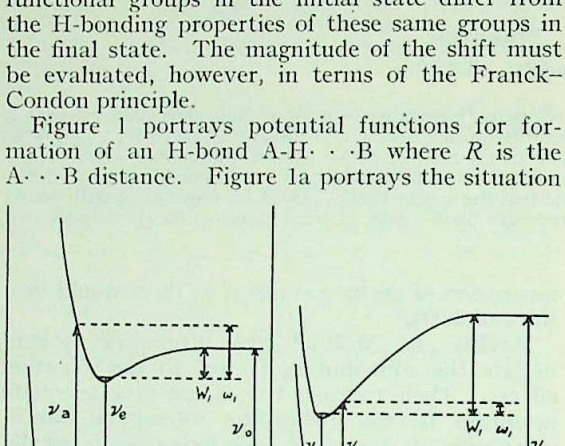

Fig. 1.—Hypothetical potential curves: energy *vs.* H-bond length: A–H. . .B; R = (A. . .B) distance; a, left, $W_0 > W_1$; b, right, $W_0 < W_1$.

when the excited state forms a weaker H-bond and in Fig. 1b the excited state forms the stronger H-bond. In each case the energy separation of the non-H-bonded species ($R = \infty$) is assumed to be identical to ν_0, the energy separation in a non-H-bonding solvent of the same refractive index. The H-bond energy is designated W ($W = -\Delta H$) and the excitation energy implied by the Franck–Condon principle is labeled w. (By these definitions, W and w are always positive numbers. Of course either W_0 or W_1 could be zero.)

There are three quantities of interest which might be experimentally accessible, ν_a, ν_e and ν_{0-0}, the frequencies appropriate to maximum of absorption, maximum of emission (*e.g.*, in a fluorescence spectrum), and the O–O transition, respectively.[10] These frequencies are related to the quantity ν_0 by the relations

$$\nu_a - \nu_0 = \Delta\nu_a = W_0 - W_1 + w_1 \quad (1)$$

$$\nu_e - \nu_0 = \Delta\nu_e = W_0 - W_1 - w_0 \quad (2)$$

$$\nu_{0-0} - \nu_0 = \Delta\nu_{0-0} = W_0 - W_1 \quad (3)$$

Clearly the most interesting quantity is $\Delta\nu_{O-O}$, which gives directly the difference in H-bond energies of ground and excited states. Since the quantity W_0 (for the ground state) usually can be determined by conventional methods and is known for many systems, eq. 3 offers a measure of W_1. The determination of $\Delta\nu_{O-O}$ requires both absorption and fluorescence studies. Although such studies do not involve any new techniques, they are subject to the usual difficulties (particularly the interference of overlapping bands).[11] None of the data recorded so far give $\Delta\nu_{O-O}$ but there are a number of measurements of values of $\Delta\nu_a$'s. It is notable that w_1 and w_0 are determined if all three data, $\Delta\nu_a$, $\Delta\nu_e$ and $\Delta\nu_{O-O}$, are measured (with the reservation expressed in footnote 10).

In Fig. 1a ($W_0 > W_1$) we see that the usual expectations of potential form predict that $W_0 > w_0$ and $w_1 > w_0$. No upper limit can be set on w_1 since the steep side of the potential function could rise sufficiently fast to make $w_1 > W_1$ (as is pictured in Fig. 1a). In any event, it will only be a coincidence if $w_1 = W_1$ and we see that $\Delta\nu_a$ cannot be expected, *a priori*, to measure W_0. Since w_1 is positive, eq. 1 predicts that if $W_0 > W_1$ then $\Delta\nu_a > 0$, *i.e.*, a blue-shift which exceeds the difference $W_0 - W_1$ by w_1 will be observed in absorption. Similarly, in emission, a shift will be observed which is less than $W_0 - W_1$ by w_0 (*i.e.*, either a red shift or blue shift may be observed; in either case, the shift will be small compared to W_0). If $W_1 = 0$, no shift will be observed in emission since then $W_0 = w_0$.

In Fig. 1b ($W_0 < W_1$) the anharmonicity expectations predict that $W_1 > w_1$ and $w_0 > w_1$. Now the absorption spectrum will show a shift which is less by w_1 than the red shift implied by the negative value of $W_0 - W_1$. The emission spectrum will show a red shift exceeding $|W_0 - W_1|$ by w_0.

Turning now to the interpretation of observations, a blue shift in absorption which is comparable in magnitude to W_0 implies Fig. 1a is applicable ($W_0 > W_1$) and the blue shift *exceeds* the difference $W_0 - W_1$. If a red shift is observed in absorption then Fig. 1b is applicable ($W_0 < W_1$) and the red shift is *less than* the difference $W_1 - W_0$. If only a small blue shift is observed in absorption, either of Figs. 1a or 1b could be applicable. Similarly, in emission, a blue shift implies Fig. 1a, a large red shift implies Fig. 1b, and a small red shift is ambiguous. Under any circumstances, $\Delta\nu_a$ and $\Delta\nu_e$ bracket the quantity $\Delta\nu_{O-O} = W_0 - W_1$.

The Expected Magnitude of Spectral Shifts.—The well characterized H-bonds have energies in the range 1–7 kcal. per bond (350–2500 cm.$^{-1}$). As mentioned above, a blue shift in absorption may exceed the ground state H-bond energy, hence blue shifts are expected in the range 350–2500 cm.$^{-1}$ and occasionally larger than 2500 cm.$^{-1}$. A red shift (in absorption) should never be as large as W_0, hence should not exceed 2500 cm.$^{-1}$. Even if a much stronger H-bond is formed in the excited state, the red shift reflects only the *difference* in energies of the ground and excited state H-bonds *at an H-bond distance optimum for the ground state but not for the excited state.*

The number of H-bonds influenced by the transition is, of course, an important factor. A monobasic proton donor can form only a single H-bond,

(10) The following discussion assumes "vertical" transitions for ν_0, ν_a and ν_e, without any consideration of transition probability as a function of configuration. It is difficult to assess this assumption, particularly for forbidden transitions which specifically depend upon vibration–electronic interaction. It is probably not drastically unsound for absorption in most cases.

(11) Kasha has pointed out that "fluorescence for $n \rightarrow \pi^*$ transitions) is characteristically non-existent; or, in rare cases, is extremely ..." [illegible] Communication from Dr. M. Kasha, Florida State University.

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but a base molecule can form H-bonded complexes with two or more acid molecules. Thus Barrow and Yerger[12] identified the species A_2B in the system A = acetic acid, B = triethylamine. Similarly, complexes including several HX molecules have been proposed in HX–ether systems.[13] The solvent shift would be larger in a multiple H-bond complex in accordance with the number of H-bonds affected. Similarly, more than one H-bonding functional group may be present. If these groups are equivalent because of molecular symmetry, the electron distribution must necessarily change similarly at these sites. Again the observed shift would reflect the energies of all of the H-bonds affected. For strongly bonding systems (such as a dilute solution of pyridazine in ethanol) most of the pyridazine is expected to be in the 1:2 complex form and the blue shift will be determined by the sum of the changes of the first and second H-bond energies.

Experimental Data.—For electronic transitions of bases, the expectations concerning the magnitudes of H-bonding shifts are corroborated, as is revealed in the compilation of McConnell.[6] Except for glyoxal, all shifts induced by water or alcohol are in the range -1700 to $+4000$ cm.$^{-1}$ (20 examples). Furthermore, the red (negative) shifts are generally smaller than the blue (positive) shifts, again as expected. Tables I and II list a portion of these data, those systems for which both methanol and water solvents have been studied. Table III lists the available data for transitions in proton donors. All shifts are given as $\Delta\nu_a = \nu - \nu_0$ where ν is the frequency of maximum absorption in the H-bonding solvent and ν_0 is the corresponding frequency in a suitable reference solvent. Unless noted otherwise, the data in Tables I and II are from ref. 6 and the reference solvent is in every case a paraffin hydrocarbon.

It is interesting that the shifts caused by water are invariably higher than those in methanol and in six of eight examples, roughly double. Two possible explanations are suggested: more H-bonds may be formed between solvent and solute in water than in methanol; and/or the H-bonds with water may be stronger than those with methanol. The infrared spectral data provide support for the second proposal. The shifts in the stretching frequencies of water and alcohol in basic solvents are generally considered to be related to the corresponding H-bond energies. The shifts observed for water are usually about one and a half times those for methanol, as is evident in the compilation of data presented by Gordy.[15] Thus the infrared shifts also suggest that water forms stronger H-bonds to a given base than does methanol.

TABLE I

H-BOND SOLVENT SHIFTS FOR TRANSITIONS IN CARBONYL BASES

Base	ν_0 (cm.$^{-1}$)	Methanol $\Delta\nu_a$ (cm.$^{-1}$)	Water $\Delta\nu_a$ (cm.$^{-1}$)	Transition
Diazoacetic ester	25,500	+ 800	+1500	n-π
Acetone	35,960	+ 900	+1900	n–π
Mesityl oxide	30,760	+1200[a,7]		
		+1000	+3200	n–π
Diazoacetic ester	41,000	+1180[a,7]		
Mesityl oxide	43,000	− 550	− 600	π–π
		−1000	−1700	π–π

[a] Ethanol solvent.

TABLE II

H-BOND SOLVENT SHIFTS IN MISCELLANEOUS BASES

Base	ν_0 (cm.$^{-1}$)	Methanol $\Delta\nu_a$ (cm.$^{-1}$)	Water $\Delta\nu_a$ (cm.$^{-1}$)	Transition
Nitrosobenzene	13,000	+ 50	+ 450	n–π
Pyrazine	31,500	+ 700	+1800	n–π
Pyridazine	29,450	+2440[7]	+4000[14]	n–π

TABLE III

H-BOND SOLVENT SHIFTS FOR TRANSITIONS IN PROTON DONORS

Acid	Base	ν_0 (cm.$^{-1}$)	$\Delta\nu_a$ (cm.$^{-1}$)	Ref.
Phenol	Methyl acetate	36,010	−240	2,3
Phenol	Ethyl acetate	36,010	−350	2,3
Phenol	Ether	36,010	−360	1
	Diethyl ether	36,010	−423	4
Phenol	Acetone	36,010	−397	4
Phenol	N,N-Dimethyl-acetamide	36,400	−500	4
Acetanilide	Diethyl ether	35,600	−189	10
Aniline	Ether		−540	11

Discussion

The Franck–Condon argument presented here implies a more complicated interpretation of the magnitude of the n $\rightarrow \pi^*$ "blue-shift" than the interpretation of Brealey and Kasha. Their comparison of the blue shift to the quantity W_0 is presumably based on the expectation that $W_1 = 0$ and no consideration is given to the large value of w_1 implied by the short interatomic distances of the H-bonded ground state. This suggests that the agreement between blue shift and H-bond energy found for each of the two systems pyridazine–ethanol and benzophenone–ethanol is fortuitous. This possibility is strengthened by noting that the blue shift used for pyridazine applies to a mixture containing about 25% uncomplexed pyridazine (using the K given by Brealey and Kasha), that the blue shift for benzophenone was corrected by about 20% because of overlap of an adjacent transition, and that the infrared shifts give only a coarse indication of the H-bond energy, possibly in error by as much as one kcal. On the other hand, their qualitative discussion seems to be correct. If a non-bonding electron localized on the basic functional group is transferred to an anti-bonding orbital, the change of electron density undoubtedly reduces base strength. Hence it is expected that $W_1 < W_0$ (though W_1 is not necessarily zero).

The red shifts of the π–π transitions indicate that the base strengths have been increased. This is no doubt to be attributed to a transition involving electron redistribution in the same space but

(12) G. M. Barrow and E. A. Yerger, THIS JOURNAL, **76**, 5211 (1954).

(13) G. L. Vidale and R. C. Taylor, *ibid.*, **78**, 294 (1956).

(14) F. Halverson and R. C. Hirt, *J. Chem. Phys.*, **19**, 711 (1951).

(15) W. Gordy, *ibid.*, **9**, 215 (1941). The approximate factor 1.5 is obtained by Gordy as an empirical correction for the fact that his shifts are referred to the gas state for D_2O and benzene solution for CH_3OD.

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with enhanced electron density in the more peripheral portions. This is a characteristic difference of bonding and anti-bonding orbitals. Although this may be the expected behavior, again it is not necessary that every $\pi-\pi$ redistribution give a red shift since the basic functional groups may not be affected or the nodal properties may actually deplete the electron density at the basic sites.

The red shifts observed for the proton donors may be rationalized. All of these data refer to the transitions corresponding to the $A_{1g} \rightarrow B_{2u}$ transition of benzene, a transition to an excited state containing nodal planes perpendicular to the plane of the ring. The red shift suggests that this orbital places a nodal plane through the H-bonding functional group, so as to reduce the electron density at this site. This would cause an acidic group to become a better proton donor. Aromatic acids (phenol, aniline) should display red shifts whereas aromatic bases (anisole, dimethylaniline) should display no shift in basic solvents (as is observed, see ref. 1) and a blue shift in acidic solvents (no data available).

Conclusions

It seems clear that the solvent shifts caused by H-bonding solvents contain interesting information. In addition to empirical correlations which may aid in establishing the type of transition, these solvent shifts provide clues to the locale and nature of electron redistribution in the electronic transition. Perhaps the unique aspect is the promise for understanding the electronic distribution and H-bonding properties of excited states. For this purpose absorption and emission studies should be combined, if possible, to give the shift corresponding to the O–O transition.

Acknowledgment.—The author wishes to thank Dr. M. Kasha and Dr. Sydney Leach for helpful and critical comments on the subject matter of this paper.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Equations for the Limiting Current at the Rotated Dropping Mercury Electrode[1]

BY YUTAKA OKINAKA AND I. M. KOLTHOFF

RECEIVED JANUARY 26, 1957

This paper describes results of a theoretical and experimental study of the relationship between the limiting current at the rotated dropping mercury electrode on the one hand and the diffusion coefficient of the electroactive species, the kinematic viscosity of the solution, and the characteristics of the electrode on the other. Two theoretical equations are derived on the basis of hydrodynamics, one for the case when no surface-active substance is present and the other for the case when such substances are present. In view of the fact that the presence of a suitable surface-active substance is necessary for most practical purposes, the relations in the presence of a capillary-active substance were studied more extensively than those in its absence. The proposed equation in the presence of surface-active compounds involves an experimentally determined numerical constant and yields satisfactory agreement between observed and calculated limiting currents in the range of 75 to 210 r.p.m., provided that an electrode of the proper dimensions is employed. At a suitable speed of rotation in the presence of a surface-active substance, the limiting current at the rotated dropping mercury electrode, as a first approximation, is proportional to $D^{2/3}(mt)^{1/2}$, while at the unrotated conventional dropping mercury electrode it is proportional to $D^{1/2}m^{2/3}t^{1/6}$. Limitations of the derived equations are discussed both from theoretical and practical viewpoints.

The rotated dropping mercury electrode (R.D.M.E.) recently developed in this Laboratory[2] is of practical importance because it allows polarographic determinations at concentrations of an order of magnitude of one smaller than with the conventional dropping mercury electrode (D.M.E.). The quantitative dependence of the limiting current upon various factors is quite different at these two electrodes. In the present paper the results of a theoretical and a systematic practical study of the factors which affect the limiting current at the R.D.M.E. are described. In order to determine the effect of the height of mercury on the limiting current, it was necessary to revise the construction of the electrode previously described.[2] The expressions derived at 25° for the average limiting current in the absence (eq. 1) and presence of a surface-active compound which completely suppresses stirring at the mercury surface (eq. 2) are

$$i_l = 230nCD^{1/2}\{m^{2/3}t^{1/6} + 103D^{1/2}(mt)^{1/3} + 7.45U_0^{1/2}(mt)^{1/2}\} \quad (1)$$

$$i_l = 230nCD^{1/2}\{m^{2/3}t^{1/6} + 103D^{1/2}(mt)^{1/3} + 5.76U^{1/2}\nu^{-1/6}D^{1/6}(mt)^{1/2}\} \quad (2)$$

where i_l is the average limiting current in $\mu a.$, n the number of electrons involved in the electrochemical reaction, C the concentration of the electroactive species in mM, D the diffusion coefficient in cm.^{2}/sec., m the rate of flow of mercury in mg./sec., t the drop time in sec., U_0 the uniform velocity of the solution at the surface of the mercury drop in cm./sec., U the speed of rotation of the electrode in cm./sec. and ν the kinematic viscosity of the solution in cm.^{2}/sec. In the presence of surface-active substances satisfactory agreement between calculated (eq. 2) and observed limiting currents was found only when the electrode has a relatively small orifice (<0.75 mm. in diameter) and a small distance between the orifice and center of rotation (<8.5 mm.).

As shown in this paper, the first and second

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. AF18(600)-1516. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) W. Stricks and I. M. Kolthoff, THIS JOURNAL, 78, 2085 (1956).

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terms are much smaller than the third term in the brackets of both equations 1 and 2 when U_0 or U is not very small. Therefore, as a rough approximation, we can write

$$i_l \sim nCD^{1/2}U_0^{1/2}(mt)^{1/2} \quad (1a)$$

$$i_l \sim nCD^{2/3}U^{1/2}\nu^{-1/6}(mt)^{1/2} \quad (2a)$$

If we compare these relationships with the Ilkovic equation at the D.M.E.

$$i_d = 607nCD^{1/2}m^{2/3}t^{1/6}$$

the following noticeable differences between the two types of electrodes are evident: (1) the effect of the height of mercury is much smaller at the R.D.M.E. than at the D.M.E., because at the former the product mt is practically constant with varying height of mercury, (2) the effect of applied potential and hence drop time t is much larger at the R.D.M.E. ($\sim t^{1/2}$) than at the D.M.E. ($t^{1/6}$), (3) in the presence of a surface-active substance i_l is not proportional to $D^{1/2}$ at the R.D.M.E., but closely to $D^{2/3}$.

Theoretical

When the current is controlled by diffusion and the effect of electrical migration is eliminated, the current at an instant, t, in the reduction (or oxidation) of an electroreducible (or oxidizable) substance is generally expressible by

$$i_t = nFD\iint_S \left(\frac{\partial c}{\partial x}\right)_{x=0,\,t} dS \quad (3)$$

where F is the faraday, S the area of the electrode, c the concentration at distance x from the electrode surface. As far as mass transfer is the only process controlling the current, the above fundamental equation is applicable to the R.D.M.E. if the concentration gradient at the surface of the electrode is explicitly expressible. According to the so-called "Nernst diffusion layer" concept,[3] when an electrode is placed in a stirred solution, there exists at the surface of the electrode a thin diffusion layer in which there is no motion of the solution. In view of the known fact that this simple assumption is not generally justified in stirred solutions,[3] it is necessary to apply hydrodynamic principles in order to take into account the effect of convection on mass transfer. Assuming that a mercury drop is a perfect sphere at any instant, the general equation of mass transfer[3] is given by

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial r^2} + \frac{2}{r}\frac{\partial c}{\partial r} + \frac{1}{r^2}\Delta c\right) - \left(v\frac{\partial c}{\partial r} + \frac{u}{r}\frac{\partial c}{\partial \theta} + \frac{w}{r\sin\theta}\frac{\partial c}{\partial \phi}\right) \quad (4)$$

where

$$\Delta = \frac{1}{\sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta\,\frac{\partial}{\partial\theta}\right) + \frac{1}{\sin^2\theta}\frac{\partial^2}{\partial\phi^2}$$

v, u and w are the velocity components in r, θ and ϕ directions, respectively. The spherical coördinates were chosen as shown in Fig. 1. Making suitable assumptions to obtain the concentration gradient at the mercury surface, equation 4 was

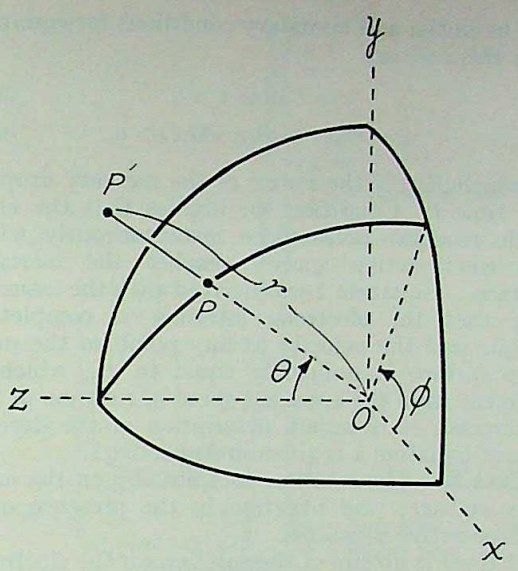

Fig. 1.—Spherical coördinates for equation 4.

solved, which allowed the calculation of the current using equation 3.

When a mercury drop is moved in an aqueous solution, two extreme situations can be considered at the mercury surface. One is the case in which flow velocities do not vanish; in other words, the solution slips on the mercury surface. This phenomenon occurs when the solution does not contain surface-active substances.[4] The other is the case in which flow velocities vanish on the mercury surface. Frumkin and Levich[5] showed that when a mercury drop falls into a solution containing a surface-active substance, the slip of the solution on the mercury surface is partly or completely inhibited by the formation of an elastic film of the surface-active substance on the mercury drop. These two different situations on the mercury surface are relevant to the experimental results at the rotated dropping amalgam electrode introduced by Stricks and Kolthoff.[2] They found that the limiting anodic current at a rotated dropping thallium amalgam electrode increases with rate of rotation in the absence of gelatin but remains unaffected by the speed of rotation in its presence. The larger current at higher speeds of rotation in the absence of gelatin is considered to be caused by the fact that the tangential flow on the amalgam surface enhances a motion within the amalgam drop, whereas in the presence of gelatin this motion does not occur since there are no flow velocities on the amalgam surface. We shall deal with these two cases separately, for they are entirely different from the hydrodynamic viewpoint. The following theoretical statements are made by considering for the sake of convenience that the electrode is placed in a solution flowing at a speed of U, instead of considering that the electrode is moved at this speed in the solution.

Case A.—The solution slips on the mercury surface, the situation in the absence of a surface-active substance.

(2) P. Delahay, "New Instrumental Methods in Electrochemistry," Interscience Publishers, Inc., New York, N. Y., 1954, Chapter 9.

(4) B. Levich, *Disc. Faraday Soc.*, **1**, 37 (1947).

(5) A. Frumkin and V. Levich, *Zhur. Fiz. Khim.*, *U.S.S.R.*, **21**, 1183 (1947).

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The initial and boundary conditions for equation 4 in this case are

$$c = C \text{ when } t = 0 \quad (5)$$

$$c = 0 \text{ at } r = R(t) \text{ when } t > 0 \quad (6)$$

in which $R(t)$ is the radius of the mercury drop at the time t. Condition (6) implies that the electrode reaction takes place instantaneously when the electroactive species reaches the mercury surface. Equation 1 was derived with the assumption that the electrode interface is completely mobile and the velocity at any point on the mercury surface is uniformly equal to U_0, which is different from the apparent speed of rotation of the electrode. A complete description of the derivation of equation 1 is given in Appendix 1.

Case B.—The solution does not slip on the mercury surface; the situation in the presence of a surface-active substance.

If there is no slip of the solution on the electrode surface as in the case of a solid placed in a moving fluid, there must be a velocity gradient between the surface of the electrode and the bulk of the solution. The type of flow around the mercury drop can be estimated by evaluating the Reynolds number, $Re = Ul/\nu$, where l is the length representing the dimension of the electrode, which may be taken to be equal to the diameter of the mercury drop. For example, for one of our suitable electrodes the distance between the orifice and the center of rotation, d, was 0.74 cm. and the weight of a drop of mercury 0.037 g. at 210 r.p.m. The linear speed of rotation, U, of this electrode is calculated to be about 16 cm./sec., and the diameter of a mercury drop 0.13 cm. just before it is ejected from the orifice. Putting these values and 0.9×10^{-2} cm.^{2}/sec. as ν of water at 25° in the Reynolds number expression, Re is calculated to be equal to 230. Provided that there is no significant disturbance in the character of flow caused by the part of the glass end tube of the electrode dipped in the solution, it is considered from this Reynolds number that there will be a laminar boundary layer around the mercury drop, at least after it has grown to some extent.[6] However, at the very beginning of the growth of a mercury drop, when its size is small, the Reynolds number is certainly very small and the type of flow is considered to be rather close to Stokes' motion. This stage is of short duration and the type of flow will soon become laminar with a boundary layer. For example, the Reynolds number of the above electrode becomes 100 at 0.9 sec. with a drop life of 3.1 sec. Thus it is reasonable to assume that the type of flow is that with a laminar boundary layer during most of the drop life.

In order to solve equation 4 with this assumption, it is necessary to have expressions for the velocity distribution in the boundary layer and for its thickness, δ. Assuming a curvilinear system of coordinates (Fig. 2), whose x-axis is in the direction of the wall, the y-axis being perpendicular to it, the Prandtl boundary layer equations for steady flow[7] generally are given by

$$u\frac{\partial u}{\partial x} + v\frac{\partial u}{\partial y} = -\frac{1}{\rho}\frac{dp}{dx} + \nu\frac{\partial^2 u}{\partial y^2} \quad (7)$$

$$\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} = 0 \quad (8)$$

where u and v are the velocity components in x- and y-directions, respectively, ρ the density of the solution and p the pressure. Assuming that the velocity of flow outside the boundary layer around the small mercury drop is uniformly equal to the speed of rotation of the electrode, U, equations 7 and 8 can be solved by analogy to the case of a flat plate.[8] In view of the known fact that the tangential velocity distribution can be successfully approximated by a parabolic or polynomial function with respect to δ and y,[8] we shall make the further assumption that it is given by a polynomial of nth degree, which can be written as

$$u = U - U(\delta - y)^n/\delta^n \quad (9)$$

Prescribing the boundary conditions

$$u = 0, v = 0 \text{ where } y = 0 \quad (10)$$

$$u = U \text{ where } y = \delta \quad (11)$$

$$\delta = 0 \text{ where } x = 0 \quad (12)$$

we obtain the following expression for δ from (7), (8) and (9) (the mathematical process follows the case of a flat plat[8])

$$\delta = \sqrt{2(2n+1)(n+1)\nu x/U} \quad (13)$$

Thus if a parabolic distribution is assumed, *i.e.*, $n = 2$, we obtain

$$\delta = \sqrt{30\nu x/U} \quad (14)$$

The numerical constant of 30 in equation 14 must be determined experimentally because there is no theoretical support for the above velocity distribution. Somewhat arbitrarily we adopt the value of 30 in the mathematical treatment, a complete description of which is given in Appendix 2.

For case B the initial and boundary conditions for equation 4 are

$$c = C \text{ when } t = 0 \quad (15)$$

$$c = 0 \text{ at } r = R(t) \text{ when } t > 0 \quad (16)$$

$$c = C \text{ at } r = R(t) + \delta \text{ when } t > 0 \quad (17)$$

in which conditions 15 and 16 are the same as in case A and condition 17 implies that the concentration outside the boundary layer is always kept equal to the bulk concentration. Under these conditions we obtain the following equation for the limiting current at 25° in the presence of a surface active substance

$$i_l = 230nCD^{1/2}\{m^{2/3}t^{1/6} + 103D^{1/2}(mt)^{1/3} + KU^{1/2}\nu^{-1/6}D^{1/6}(mt)^{1/2}\} \quad (18)$$

where K becomes equal to 5.38, 5.82, 6.00 or 6.10 depending on whether the tangential velocity distribution is assumed to be a linear, a parabolic, a third or a fourth degree polynomial.

Experimental

Materials.—Conductivity water and 99.99% pure Linde nitrogen and C.P. chemicals were used without further puri-

(6) The transition from laminar to turbulent flow takes place at $Re = 3 \times 10^5$ in the case of a sphere. See, for example, H. Schlichting, "Boundary Layer Theory," translated by J. Kestin, McGraw-Hill Book Co., Inc., New York, N. Y., 1955, p. 31.

(7) Ref. 6, pp. 89–90.

(8) Ref. 6, pp. 201–206.

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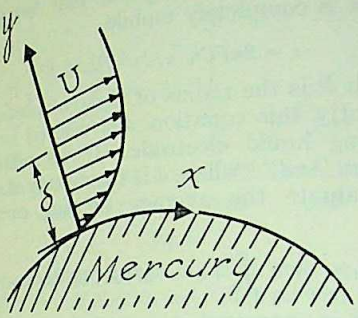

Fig. 2.—Curvilinear coördinates for equations 7 and 8.

feration except thallous chloride, which was purified by recrystallization. Solutions of known concentration of thallium and lead were prepared by dissolving weighed amounts of thallous chloride or lead nitrate in the appropriate amount of water. A zinc solution of known concentration was prepared by dissolving a weighed amount of pure zinc in dilute sulfuric acid and adjusting the volume. A solution of known cadmium concentration was obtained by dissolving an approximately weighed amount of cadmium sulfate in water and weighing as anhydrous salt after evaporation of an appropriate volume of the solution and drying. Nickel(II) perchlorate was prepared by adding an excess perchloric acid to the nitrate and evaporating to dryness. The nickel content of a solution of the perchlorate was determined gravimetrically by weighing as nickel dimethyl glyoxime.

Current Measurements.—Limiting currents were measured with a Leeds and Northrup Electrochemograph Type E with damping switch in a suitable position,[2] and with a manual apparatus as described by Lingane and Kolthoff.[9] All experiments were carried out at 25.0 ± 0.1°. All reported values of limiting currents have been corrected for residual currents.

Measurements of Kinematic Viscosity.—In the experiments in the presence of glycerol and sucrose the kinematic viscosity was measured with Ubbelohde suspended level viscometers, which had been calibrated with standard glycerol-water mixtures.

Electrode.—The R.D.M.E. described by Stricks and Kolthoff[2] was modified so that the height of the mercury column could be varied. The construction and manipulation of the modified R.D.M.E. are similar to those of the original one. The top and bottom of the plunger of a 2-ml. syringe are cut off (see Fig. 3) and the resulting tube is connected by Tygon tubing to a top tube as used with a D.M.E.; this constitutes the upper part of the electrode. The lower part consists of two units. One of these is made by connecting an end tube to a capillary. The other unit consists of the outer tube of the syringe, the bottom of which has been cut off, joined to the wide end of the glass tube A (Fig. 3). The lower part of the electrode is assembled by placing the mercury filled end tube and capillary in the holder of the rotating apparatus, and by connecting the small end of the glass tube A to the capillary. After this part is positioned properly, it is filled with mercury up to the top and the upper part of the electrode is connected through the two syringe pieces. The syringe is so well ground that the rotation is completely smooth; the height of mercury can be raised to about 100 cm. from the tip of the end tube without leakage of mercury. A detailed description concerning the treatment of the end tube with Silicone Dri Film and the rotating device is in the previous paper.[2] Eccentric rotation must be avoided.

The lower part of the end tube was 50 mm. in length and had an outside diameter of 3.5 to 4 mm. (see Fig. 3). The distance between the orifice and the bottom of the end tube was about 10 to 12 mm. for all electrodes used in the present experiments. The diameter of the orifice varied from 0.4 to 1.1 mm.; the distance between the orifice and center of rotation, d, was from 5 to 16 mm.

The electrolysis vessel used was a beaker of 250 ml. capacity. The volume of the solution was 100 ml. in all experiments.

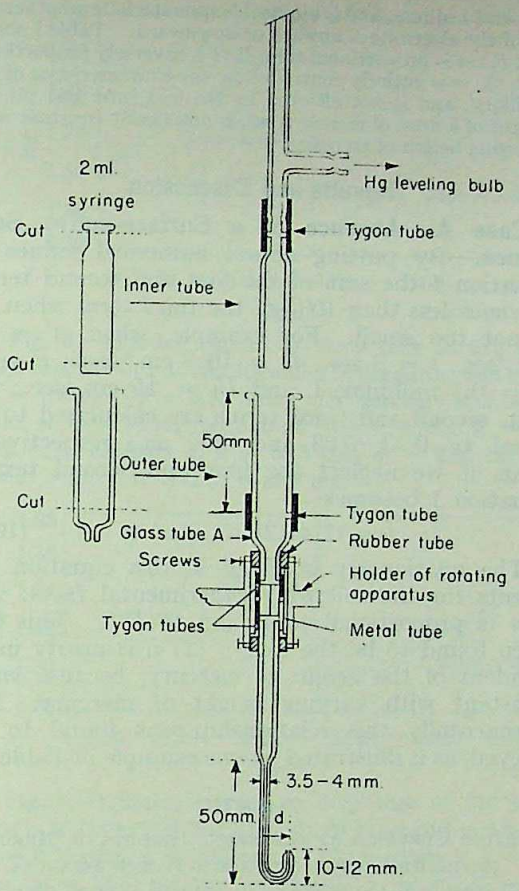

Fig. 3.—Assembly of the modified R.D.M.E.

General Characteristics of the Modified R.D.M.E. Relationship between the Height of Mercury, h, and m and t.—The general characteristics of the electrode were determined by using the same capillary with three different end tubes. The capillary used was 3.5 cm. in length of Sargent's capillary for D.M.E., the drop time of which was specified as 2 to 5 sec. The diameter of the orifice ϕ was measured with a microscope provided with an eye-piece micrometer. The distance between the orifice and center of rotation, d, was measured with a micrometer caliper. The results are listed in Table I, in which h is the height of mercury corrected for back pressure,[10] $h_{back} = 3.1/(mt)^{1/3}$ cm. This expression was derived from the fundamental formula $P_{back} = 2\sigma/r$ which gives the difference in pressure between outside and inside of a spherical surface of a liquid whose surface tension

TABLE I

GENERAL CHARACTERISTICS OF THE MODIFIED R.D.M.E. DETERMINED IN 1 M $NaClO_4$ WITH AN OPEN CIRCUIT AT 210 R.P.M.

End tube	d, mm.	ϕ, mm.	h, cm.	m,[a] mg./sec.	t, sec.	mt, mg.	m/h	ht
1	8.74	1.0	91.4	20.26	2.56	51.9	0.222	234
			61.4	13.86	3.72	51.0	.226	228
			51.4	11.52	4.56	52.5	.224	234
2	6.93	1.1	91.4	20.29	3.34	67.7	.222	306
			61.4	13.81	4.84	66.9	.225	298
			51.4	11.55	5.78	66.9	.225	298
3	7.31	0.75	91.3	20.21	1.91	38.6	.221	174
			61.3	13.81	2.77	38.3	.225	170
			51.3	11.53	3.31	38.1	.225	170

[a] The m values were determined without rotation.

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[9] J. J. Lingane and I. M. Kolthoff, THIS JOURNAL, **61**, 825 (1939).

[10] See, for example, I. M. Kolthoff and J. J. Lingane, "Polarography," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1952, pp. 79–81.

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is σ and radius r, and is applicable immaterially whether the tip of the electrode is upward or downward. Table I shows that (1) m is proportional to h, (2) t is inversely proportional to h, (3) m is entirely controlled by the characteristics of the capillary, and is not affected by the end tube and (4) the weight of a drop of mercury, mt, is practically constant with changing height of mercury.

Results and Discussion

Case A. Absence of a Surface-active Substance.—By putting actual numerical values in equation 1 the sum of the first and second terms becomes less than 10% of the third term when U_0 is not too small. For example, when $m = 15$ mg./sec., $t = 3$ sec., $D = 10^{-5}$ cm.^{2}/sec., $n = 1$, $C = 0.1$ millimole/l. and $U_0 = 15$ cm./sec., the first, second and third terms are calculated to be equal to 0.53, 0.03 and 9.59 μa., respectively. Thus if we neglect the first and second terms, equation 1 becomes

$$i_l = 1714nCD^{1/2}U_0^{1/2}(mt)^{1/2} \qquad (19)$$

The relationship involved in this equation accounts for the following experimental facts: (1) i_l/n is proportional to C and to $D^{1/2}$. This has been found to be the case[2]; (2) i_l is nearly independent of the height of mercury, because mt is constant with varying height of mercury. Experimentally this relationship was found to be obeyed, as is illustrated by one example in Table II.

TABLE II

LIMITING CURRENTS AT DIFFERENT HEIGHTS OF MERCURY IN THE ABSENCE OF SURFACE-ACTIVE SUBSTANCES

(End tube 3, 0.400 millimole/l., Tl^+ in 1 M $NaClO_4$, 210 r.p.m.)

V (*vs.* S.C.E.)	i_l (μa.) h = 93.5 cm.	h = 63.5 cm.
−0.7	44.0	43.2
−0.9	43.3	43.1
−1.1	42.8	42.8
−1.3	41.0	41.4
−1.5	38.0	38.5
−1.7	34.5	34.5

In the derivation of equation 1, we made an assumption that the velocity of flow on the mercury surface is uniformly equal to U_0. This surface velocity is not simply equal to the speed of rotation of the electrode, U, as there are complications caused by the viscosity of a real fluid, which exerts frictional forces on the mercury–solution interface, and by the mutual interaction between the motion inside the mercury drop and the tangential motion of the solution on the mercury surface. The presence of even trace amounts of surface active substances in the solution lowers the limiting current. At potentials other than the electrocapillary zero, the existence of an electrical double layer exerts a viscous drag resulting from the forces acting on the two sheets of the double layer and decreases the mobility of the interface.[11] Since the actual surface velocity is unknown, a direct comparison between calculated and observed limiting currents cannot be made.

Levich[4] derived the following equation for currents involving maxima of the second kind at the D.M.E. with the assumption that the electrode interface is completely mobile

$$i = 8nFC\sqrt{\pi/2}\sqrt{DU_0/R}\,R^2$$

in which R is the radius of a given spherical drop. Apparently this equation was derived for an unexpanding liquid electrode. If we substitute R with $(3mt/4\pi d)^{1/3}$ where d is the density of mercury, and evaluate the average limiting current, we obtain

$$i_l = (1/t)\int_0^t i\,dt = 2710nCD^{1/2}U_0^{1/2}(mt)^{1/2}$$

where i_l is expressed in terms of μa. This equation is identical with equation 19 except for the numerical constant.

Case B. Presence of a Surface-active Substance. Relation between i_l and t.—A number of experiments were carried out with several different end tubes and capillaries at various heights of mercury at 210 r.p.m. in solutions of 0.400 mM in thallous ion and 1 M sodium perchlorate in the presence of 0.01% gelatin. Some typical examples of plots of log i_l *vs.* log t using different end tubes and different capillaries are given in Figs. 4 to 6. The limiting currents were measured at various applied potentials, and hence at various drop times, the other conditions being kept constant. The points obtained with end tube 2 (Fig. 4) were scattered in a somewhat irregular way, but with the other end tubes reasonably good straight lines were obtained at voltages between −0.7 and −1.6 v. *vs.* S.C.E. It is seen that the slope increases with the diameter ϕ of the orifice, and hence with the drop weight mt. Equation 2 or 18 predicts that the slope should be close to 0.5, because under our experimental conditions the sum of the first and second terms is of the order of only 15% or less of the third term (for some numerical examples, see Table IV). The theoretical relationship is obeyed approximately with end tube 3 which has a relatively small orifice. The deviation in the slope from 0.5 for the other end tubes with larger orifice must be attributed to the deformation of the shape of a mercury drop from a sphere.

Experimental Determination of K in Equation 18.—As mentioned in the theoretical part, we made the assumption that the tangential velocity distribution is parabolic or polynomial in the boundary layer. Since this assumption affects only the numerical constant K, we must find the proper value of K experimentally. This was performed by comparing experimental values of limiting currents with theoretical values calculated from equation 18 where K tentatively was put equal to 5.82 (corresponding to a parabolic distribution).

In the calculation of limiting currents, it is important to use correct D values which were determined under the actual experimental conditions. The D values at infinite dilution calculated from equivalent conductance data are often quite different from those under the working conditions in polarography, although they are frequently used with the original Ilkovic equation for the D.M.E. In connection with the development of revisions of the original Ilkovic equation, several

(11) A. Frumkin and B. Levich, *Acta physicochim. U.R.S.S.*, **20**, 769 (1945).

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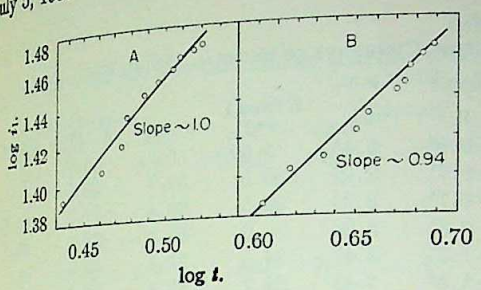

Fig. 4.—Limiting current *vs.* drop time at 210 r.p.m. (0.4 m*M* Tl^+ in 1 *M* $NaClO_4$ and 0.01% gelatin; end tube 2, ϕ = 1.1 mm., d = 6.93 mm.). (A) capillary 3, h = 60.6 cm., m = 20.77 mg./sec., mt at −0.7 v. *vs.* S.C.E. = 69.0 mg. (B) capillary 1, h = 62.2 cm., m = 13.81 mg./sec., mt at −0.7 v. *vs.* S.C.E. = 67.5 mg.

attempts have been made recently to determine diffusion coefficients independently by the radiotracer technique,[12,13] the Cottrell technique in connection with a proposal of a new modified Ilkovic equation[14] and the diaphragm-cell technique.[15] However, the reported values, as summarized in Table III, do not agree with each other. Since

TABLE III

DIFFUSION COEFFICIENTS OF METAL IONS AT 25°

Ion	Supporting electrolyte	$D \times 10^5$, cm.²/sec. Wang, *et al.*[a]	Stackelberg, *et al.*[b]	Rulfs[16]	Infinite[c] dilution
Tl^+	0.1 *M* KCl	1.827	1.744	1.67	2.00
	0.005 *M* KCl	1.92	1.91[d]	..	
Pb^{++}	1 *M* KCl	1.001	0.920	..	0.98
	0.1 *M* KCl	0.970	.867	0.75	
Cd^{++}	0.1 *M* KNO_3	...	.690	0.76	0.72
Zn^{++}	1 *M* KNO_3	0.73	.619	..	0.72
	0.05 *M* KNO_3	.69	.653	..	
	2 *M* KCl	.940	.743	..	
	1 *M* KCl	.818	.723	..	
	0.1 *M* KCl	.729	.673	..	
Ni^{++}	.01 *M* KCl	.712[d]	.676	..	
	.1 *M* $NaClO_4$ + .001 *M* $HClO_4$	.60 (by Sanborn and Orlemann[13])			0.69

[a] Determined in the presence of 0.0005 *M* $[H^+]$ except for Tl^+. Ref. 12a and 12b. [b] Determined in the presence of 0.1% acetic acid except for Tl^+ and 0.01% gelatin. Ref. 14. [c] Ref. 10, p. 52. [d] Estimated by an interpolation of the curve $D - \sqrt{c}$ (c is concentration of the supporting electrolyte).

there are three different D values reported for thallous ion in 0.1 *M* potassium chloride, we carried out a series of experiments with 0.404 mmole/l. thallous ion in 0.1 *M* potassium chloride in the presence of 0.01% gelatin at 210 r.p.m. and calculated K by comparing observed and theoretical limiting currents using each of the three D values. The experiments were conducted with end tube 3 which has a small orifice. This end tube is suitable for theoretical studies because the deformation from a sphere of the growing drop is small. An

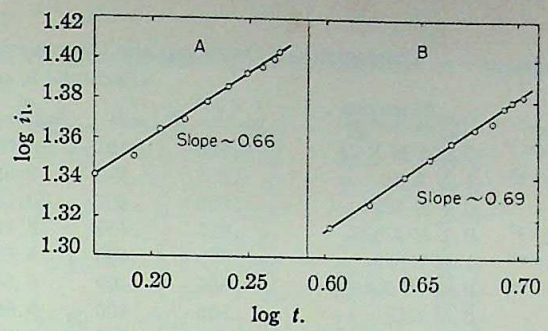

Fig. 5.—Limiting current *vs.* drop time at 210 r.p.m. (0.4 m*M* Tl^+ in 1 *M* $NaClO_4$ and 0.01% gelatin; end tube 4, ϕ = 0.9 mm., d = 6.55 mm.). (A) capillary 3, h = 75.6 cm., m = 26.90 mg./sec., mt at −0.7 v. *vs.* S.C.E. = 49.5 mg. (B) capillary 4, h = 63.5 cm., m = 9.60 mg./sec., mt at −0.7 v. *vs.* S.C.E. = 48.7 mg.

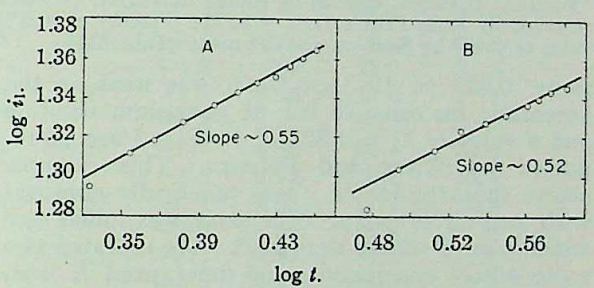

Fig. 6.—Limiting current *vs.* drop time at 210 r.p.m. (0.4 m*M* Tl^+ in 1 *M* $NaClO_4$ and 0.01% gelatin; end tube 3, ϕ = 0.75 mm., d = 7.31 mm.). (A) capillary 1, h = 62.2 cm., m = 13.81 mg./sec., mt at −0.7 v. *vs.* S.C.E. = 38.2 mg. (B) capillary 4, h = 63.5 cm., m = 9.70 mg./sec., mt at −0.7 v., *vs.* S.C.E. = 36.8 mg.

example of sets of calculated and observed values is shown in Table IV. The last column of Table IV is the experimental factor which should be multiplied by the tentative value of K, 5.82, in equation 18. In the calculation of limiting cur-

TABLE IV

DETERMINATION OF K

(0.404 m*M* Tl^+ in 0.1 *M* KCl, 0.01% gelatin. End tube 3, 210 r.p.m.)

Capillary no.	h, cm.	m, mg./sec.	V *vs.* S.C.E.	t, sec.	i_l obsd., μa.	Calcd. values (μa.) 1st term	2nd term	3rd term	x[a]
1	72.2	15.87	−0.7	2.36	23.5	2.89	0.58	20.21	0.991
			−1.0	2.28	22.8	2.88	.58	19.86	.974
			−1.3	2.13	21.9	2.84	.56	19.20	.964
			−1.5	2.00	21.1	2.81	.55	18.61	.953
1	52.2	11.47	−0.7	3.24	23.0	2.46	0.58	20.13	0.992
			−1.0	3.13	22.5	2.44	.58	19.79	.984
			−1.3	2.90	21.2	2.41	.56	19.04	.957
			−1.5	2.76	21.1	2.39	.55	18.58	.977
4	78.5	12.10	−0.7	3.12	23.3	2.53	0.59	20.29	0.995
			−1.0	2.95	22.9	2.51	.58	19.72	1.005
			−1.3	2.74	21.9	2.48	.56	19.01	0.992
			−1.5	2.57	20.9	2.45	.55	18.42	.972
4	63.5	9.77	−0.7	3.79	22.7	2.27	0.58	20.09	0.988
			−1.0	3.62	22.1	2.25	.57	19.64	.982
			−1.3	3.36	21.3	2.22	.56	18.92	.979
			−1.5	3.14	20.6	2.20	.55	18.29	.976
4	53.5	8.21	−0.7	4.49	22.3	2.07	0.58	20.04	0.981
			−1.0	4.28	21.6	2.06	.57	19.57	.969
			−1.3	4.00	20.8	2.03	.56	18.92	.962
			−1.5	3.71	20.2	2.01	.55	18.23	.968

[a] x = {i_l(obsd.) − (1st + 2nd terms)}/(3rd term), K = 5.82x.

(15) (a) J. H. Wang, THIS JOURNAL, **76**, 1528 (1954); (b) J. H. Wang and F. M. Polestra, *ibid.*, **76**, 1584 (1954).
(13) R. H. Sanborn and E. F. Orlemann, *ibid.*, **77**, 3726 (1955).
(14) M. v. Stackelberg, M. Pilgram and V. Toome, *Z. Elektrochem.*, **57**, 343 (1953).
(15) C. L. Rulfs, THIS JOURNAL, **76**, 2071 (1954).

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TABLE V

COMPARISON OF OBSERVED AND CALCULATED LIMITING CURRENTS OF SEVERAL METAL IONS

(End tube 3, capillary 4, 210 r.p.m.)

Ion	Supporting electrolyte	$\nu \times 10^2$, cm.²/sec.	C, mM	m, mg./sec.	V	t, sec.	i_l (obsd.), μa.	i_l (calcd.), μa. K:5.76[a]	K:5.97[b]	K:6.16[c]
Tl^{+a}	0.005 M KCl	0.898	0.101	6.68	−0.9[d]	5.45	5.59	5.71	5.82	..
Pb^{++h}	1 M KCl	.853	.502	9.86	−0.7[e]	3.99	39.0	39.4	38.5	..
	0.1 M KCl	.892	.507	12.19	−0.7[e]	3.24	38.6	39.3	37.7	35.3
Cd^{++h}	0.1 M KNO_3	.887	.460	12.19	−0.8[e]	3.24	31.0	30.4[f]	29.5	32.2
Zn^{++h}	1 M KNO_3	.825	.400	9.83	−1.3[e]	3.47	24.6	24.1	22.3	..
	0.05 M KNO_3	.894	.400	6.66	−1.5[d]	5.43	22.7	23.4	22.9	..
	2 M KCl	.825	.400	9.86	−1.45[e]	3.29	28.2	28.0	24.6	..
	1 M KCl	.853	.400	9.86	−1.35[e]	3.40	25.4	25.6	24.4	..
	0.1 M KCl	.892	.400	12.19	−1.2[e]	3.02	25.6	25.0	24.5	..
	.01 M KCl	.898	.200	9.84	−1.3[d]	3.72	11.8	12.1	12.0	..
Ni^{++h}	.1 M $NaClO_4$ + 0.001 M $HClO_4$	.897	.378	9.86	−1.3[e]	3.52	20.3	19.9[i]	20.5[i]	21.1[i]

[a] With the D values reported by Wang, *et al.* (Table III). [b] With the D values reported by Stackelberg, *et al.* (Table III). [c] With the D values reported by Rulfs (Table III). [d] *Versus* mercury pool anode. [e] *Versus* S.C.E. [f] Using the D value reported by Rulfs (Table III). [g] In the presence of 0.01% gelatin. [h] In the presence of 0.01% starch. [i] Using the D value reported by Sanborn and Orlemann (Table III).

rents, 0.892×10^{-2} cm.²/sec. was used as the kinematic viscosity of 0.1 M potassium chloride and a value of $D = 1.827 \times 10^{-5}$ cm.²/sec. as reported by Wang and Polestra. This example shows that the factor x was practically constant with varying m and t. The same was found also when other D values were used. We repeated two more sets of experiments and determined K from a total of 56 measurements of limiting currents, all of which were obtained with the same end tube at 210 r.p.m., but with various capillaries at various heights of mercury. The average values of x were calculated to be 0.990 ± 0.021, 1.025 ± 0.021 and 1.059 ± 0.022 with D values of 1.827×10^{-5}, 1.744×10^{-5} and 1.67×10^{-5} cm.²/sec., respectively. By multiplying 5.82 by these x values, the average values of K became 5.76, 5.97 and 6.16, respectively. These K values are used in Table V for the calculations of the limiting currents of ions different from thallium.

Typical experimental data in Table IV also show that the effect of the height of mercury on the limiting current is much smaller than at the D.M.E. as predicted from the theoretical equation because $(mt)^{1/6}$ in the third (principal) term of the equation is constant with varying height of mercury.

Comparison of Observed and Calculated Limiting Currents of Several Metal Ions with Different Diffusion Coefficients.—In order to examine the validity of the proposed equation with respect to the relationship between i_l and D, several experiments were carried out with solutions of thallium, lead, cadmium, zinc and nickel at various concentrations of supporting electrolytes. The experiments were conducted with end tube 3 and capillary 4 at 210 r.p.m. In the experiments with heavy metal ions starch was used as a surface-active substance instead of gelatin because a small fraction of the heavy metals is bound by gelatin.[2] Starch is not bound by the heavy metal ions and 0.01% was found sufficient to suppress completely maxima of the second kind. The kinematic viscosities were calculated from densities and specific viscosities, which were taken from the International Critical Tables, or measured with an Ubbelohde viscometer.

The observed and calculated limiting currents are tabulated in Table V. Using the above three values of K the calculated values of limiting currents were obtained by employing the various values of D listed in Table III. The best agreement between calculated and observed values was obtained with diffusion coefficients determined by the radiotracer technique. This result lends support to the reliability of the D values determined by this technique and to the conclusion that reliable values of D can be derived from measurements with the R.D.M.E. The good agreement between the theoretical value of K of 5.82 and the experimental value of 5.76 indicates that the average tangential velocity distribution in the boundary layer is closely approximated by a parabolic function. v. Stackelberg, Pilgram and Toome[14] determined their values of D in the presence of gelatin for all of the ions used in the present experiments, while we did not use gelatin except for thallous ion. This accounts, in part at least, for the lower values of the limiting currents calculated with their D values.

Results Obtained with Various End Tubes at Various Speeds of Rotation.—The validity of the proposed equation 18 was further tested with respect to the correlation between i_l on the one hand and m, t and U on the other. Experiments were carried out with solutions of thallous ion in 1 M sodium perchlorate, 0.05 M potassium nitrate and 0.1 M potassium chloride in the presence of 0.01% gelatin.

The tracer diffusion coefficients of thallous ion in sodium perchlorate and potassium nitrate are not available in the literature. However Wang[12a] and Wang and Polestra[12b] concluded from experimental results that observed diffusion currents at a D.M.E. agree better with values calculated from the Strehlow–Stackelberg equation[16,17]

$$i_d = 607nCD^{1/2}\{m^{2/3}t^{1/6} + AD^{1/2}(mt)^{1/6}\}$$

where A is equal to 17, or more accurately 16.7, than with values calculated from the original

(16) H. Strehlow and M. v. Stackelberg, *Z. Elektrochem.*, **54**, 51 (1950).

(17) O. H. Müller, Natl. Bur. Stand. Circular 524, Aug. 14 (1953).

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TABLE VI

COMPARISON OF OBSERVED AND CALCULATED LIMITING CURRENTS OF Tl^+ IN THE PRESENCE OF 0.01% GELATIN AT VARIOUS ELECTRODES

End tube	d, mm.	ϕ, mm.	C, mM	r.p.m.	Capillary	h, cm.	m, mg./sec.	V vs S.C.E.	t, sec.	i_l (obsd.), μa.	i_l (calcd.), μa.
2	6.93	1.1	0.400	210[a]	3	75.6	25.63	−0.7	2.66	29.7	29.9
								−1.3	2.40	27.6	28.5
					1	52.2	11.55	−0.7	5.86	29.2	28.5
								−1.3	5.37	26.6	27.3
4	6.55	0.9	.402	300[b]	4	64.0	9.80	−0.7	3.66	25.0	25.1
								−1.3	3.26	23.2	23.8
			.400	210[a]	3	75.6	26.90	−0.7	1.84	25.3	25.4
								−1.3	1.65	23.4	24.2
					4	78.5	11.84	−0.7	4.11	24.2	23.9
								−1.3	3.69	22.3	22.8
3	7.31	.75	.402	600[b]	4	35.8	5.46	−0.7	2.17	16.8	20.9
								−1.3	1.96	14.8	19.9
			.400	210[a]	1	92.2	20.29	−0.7	1.92	23.1	23.4
								−1.3	1.66	21.6	21.9
					4	53.5	8.14	−0.7	4.51	22.1	21.6
								−1.3	4.00	21.0	20.5
			.400	150[a]	4	93.5	13.87	−0.7	3.25	20.6	21.1
								−1.3	2.87	19.5	20.0
						53.5	8.15	−0.7	5.56	20.4	20.6
								−1.3	4.92	19.1	19.4
			.400	75[a]	4	93.5	13.87	−0.7	4.03	17.2	17.5
								−1.3	3.59	16.4	16.6
							8.15	−0.7	6.87	16.7	16.8
								−1.3	6.11	16.0	16.0
6	6.58	.42	1.00	210[a]	5	87.3	8.92	−0.7	2.92	43.8	44.6
								−1.3	2.60	40.9	41.9
5	6.32	.35	1.00	210[a]	5	60.2	6.15	−0.7	3.33	38.0	38.2
								−1.3	2.98	36.4	36.2
7	5.16	.5	0.392	210[a]	6	90.2	7.79	−0.7	4.48	17.7	17.7
								−1.3	4.00	16.9	16.8
10	8.46	.5	.404	210[c]	5	75.0	7.47	−0.7	3.42	20.5	20.1
				150[c]	5	75.0	7.47	− .7	4.19	19.4	19.1
				75[c]	5	75.0	7.47	− .7	5.31	15.7	15.8
9	10.54	.7	.404	150[c]	4	78.0	12.00	− .7	3.87	24.4	25.8
				75[c]	4	78.0	12.00	− .7	4.90	20.3	21.4
8	15.98	.7	.404	150[c]	5	90.0	9.02	− .7	4.02	24.9	27.4
				75[c]	5	90.0	9.02	− .7	5.60	20.6	23.5

[a] In 1 M $NaClO_4$ ($\nu = 0.870 \times 10^{-2}$ cm.²/sec.). [b] In 0.05 M KNO_3 ($\nu = 0.894 \times 10^{-2}$ cm.²/sec.). [c] In 0.1 M KCl ($\nu = 0.892 \times 10^{-2}$ cm.²/sec.).

Ilkovic equation ($A = 0$)[18] and the Lingane–Loveridge equation ($A = 39$),[18] when tracer diffusion coefficients are used for D. In accordance with the above conclusion, we calculated the diffusion coefficient of thallous ion in the given media from the diffusion current data obtained with a D.M.E. and the Strehlow–Stackelberg equation. The D values of thallous ion in 1 M sodium perchlorate and in 0.05 M potassium nitrate thus calculated are 1.74×10^{-5} and 1.85×10^{-5} cm.²/sec., respectively.

Experimental and calculated limiting currents are listed in Table VI. With end tubes 2 and 4, which have a large orifice, the differences between the observed and calculated values at −1.3 v. were consistently more negative than those at −0.7 v. probably as a result of deviation from a sphere of a drop. The observed values with end tubes 3, 6, 5, 7 and 10 at 210, 150 and 75 r.p.m. are in agreement within a few per cent. with the calculated values at both of the applied potentials.

The diameter of the orifice of these end tubes varied between 0.35 and 0.75 mm., and the distance between the orifice and center of rotation varied between 5.2 and 8.5 mm. At 600 r.p.m. with end tube 3, the observed results failed to fit the equation. A possible reason for this discrepancy is that the fraction of the surface area of the mercury drop inside the orifice and therefore not in contact with the solution at a higher speed of rotation is greater than at a lower speed of rotation, because the ejected mercury drops are smaller at a higher speed of rotation than those at a lower speed of rotation because of centrifugal force effects. The main reason for the discrepancy found at high speeds of rotation is attributed to the effect of the motion of the solution caused by the vigorous rotation of the electrode. We assumed in the derivation of the proposed equation that the velocity of outer flow is equal to the apparent speed of rotation; in other words, the electrode rotates at a medium at rest. Actually, however, especially at a high speed of rotation, the

[18] Ref. 10, pp. 34–46.

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TABLE VII

EFFECT OF THE KINEMATIC VISCOSITY ON THE LIMITING CURRENT OF THALLOUS ION IN THE PRESENCE OF 0.01% GELATIN

(End tube 3, capillary 4, 210 r.p.m., m = 12.05 mg./sec.[a])

Wt. % glycerol	Supporting electrolyte	$\nu \times 10^2$, cm.²/sec.	$D \times 10^5$, cm.²/sec.	C, mM	V vs. S.C.E.	t, sec.	i_l (obsd.), μa.	i_l (calcd.), μa.
26.7	0.1 M KCl	1.827	0.968	0.804	−0.7	3.11	26.0	27.4
					−1.3	2.78	24.3	26.1
26.7	.05 M KNO_3	1.829	0.999	.804	−0.7	3.13	27.0	28.1
					−1.3	2.81	25.3	26.8
10.2	.05 M KNO_3	1.138	1.57	.804	−0.7	3.12	40.3	40.3
					−1.3	2.83	37.8	38.6
Sucrose								
30.9	0.05 M KNO_3	2.673	0.781	0.804	−0.7	3.10	21.8	22.6
					−1.3	2.80	20.6	21.6
14.2	.05 M KNO_3	1.309	1.34	.804	−0.7	3.11	35.4	35.6
					−1.3	2.80	33.0	33.9
0	.05 M KNO_3	0.894	1.85	.402	−0.7	3.13	23.7	23.3
					−1.3	2.79	22.3	22.1

[a] The m value was constant within the viscosity range investigated.

end tube serves as a stirrer giving rise to a swirling of the solution, and the solution moves in the same direction as the rotation of the electrode. Thus the velocity of rotation *relative* to the solution becomes smaller than the apparent speed of rotation and accounts for the fact that the calculated value of the limiting current is considerably greater than the experimental one. A similar effect is observed at the lower speeds of rotation when the distance between the orifice and center of rotation of the electrode is increased; this results in an effective swirling motion of the liquid caused by the rotation of the end tube. The effect is particularly pronounced with end tube 8 (d = 16 mm.) even at 75 r.p.m. and is still observed with end tube 9 (d = 10.5 mm). It is clear that for theoretical studies it is essential to choose an end tube of proper dimensions so that more or less well-defined and reproducible hydrodynamic conditions can be obtained.

Influence of the Kinematic Viscosity on the Limiting Current.—It is known that the diffusion current at the D.M.E. is greatly affected by the change of viscosity of the solution to be electrolyzed because of the variation of diffusion coefficients of electroactive species. In the case of the R.D.M.E., the viscosity of the solution is expected to exert an effect on the hydrodynamic boundary layer thickness in addition to the variation of the diffusion coefficient. This effect is related to the term $\nu^{-1/6}$ in equation 2. In order to examine the validity of the expected relation, experiments were carried out with thallous ion in 0.1 M potassium chloride and in 0.05 M potassium nitrate in the presence of 0.01% gelatin, the viscosity being varied by adding glycerol or sucrose.

Experimental and calculated limiting currents are tabulated in Table VII in which the values of D were calculated with the aid of the Strehlow–Stackelberg equation from the data obtained with a D.M.E. The equation was found valid when ν was varied from 0.89 to 1.3 × 10^{-2} cm.²/sec., but at higher viscosities the apparent effect of viscosity tended to become greater than expected from the equation. This is a natural result of the fundamental assumptions underlying the boundary layer theory itself. Prandtl's boundary layer, equations 7 and 8, on which our theoretical treatment is based, are derived from the general Navier-Stokes equations with the aid of the simplifications which can be introduced as a consequence of the small values of viscosity. This corresponds to the condition that the boundary layer thickness should be very small as is clear from the relation that the thickness of the boundary layer, δ, is proportional to $\nu^{1/2}$. From equation 14 the boundary layer thickness in 30.9% sucrose solution under the present experimental conditions, for example, is computed to be 0.83 mm. at 90° from the forward stagnation point just before the mercury drop comes off. This amounts to about a half of the maximum diameter of the mercury drop, 1.7 mm., which is contrary to our original assumption that δ is very small compared with the size of a mercury drop. The boundary layer theory is a limiting theory at zero viscosity, and the assumptions made in the derivation of the boundary layer equations are satisfied with an increasing degree of accuracy as the Reynolds number increases, *i.e.*, the viscosity decreases.[19] Thus it is to be expected that the proposed equation will also give more satisfactory results as the viscosity decreases.

A theoretical treatment may be possible also for the other limiting case of a very large viscosity. However, as is known from hydrodynamics, the experimental results at intermediate viscosities cannot be interpreted by an interpolation between the two limiting cases. In addition, the quantitative effect of the viscosity on the diffusion current at the D.M.E. is still incompletely known. Because of such difficulties, a quantitative interpretation of experimental results at moderately high viscosities is at present impossible.

Current–Time Relation during Individual Drop Life.—From equation 2 it follows that the equation of the instantaneous limiting current in the presence of a surface-active substance is given by

$$i_t = 230nCD^{1/2}\{(7/6)m^{2/3}t^{1/6} + (4/3)103D^{1/3}(mt)^{1/6} + (3/2)5.76U^{1/2}\nu^{-1/6}D^{1/6}(mt)^{1/2}\} \quad (24)$$

A few experiments were conducted to examine the validity of this equation. The current was measured in terms of the iR drop across a 10,000 ohm

(19) Ref. 6, p. 115.

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standard resistor in series with the R.D.M.E. cell by using a fast response Sanborn Industrial Recorder, Model 127, combined with a preamplifier, Model 126. The maximum sensitivity of this instrument is 50 mv. per cm., and the paper was driven at a speed of 25 mm./sec. A manual polarograph was used to apply the constant voltage to the cell circuit.

Although the total applied voltage can be kept constant, the actual potential of the R.D.M.E. decreases as the drop grows because of the iR loss across the standard resistor. In the example given here, the maximum current was 18.1 μa., so that the decrease of the actual potential of the R.D.M.E. amounted to 0.181 v. However, as shown by Lingane[20] with a D.M.E., this magnitude of the variation in potential causes no perturbation of the current–time curves provided the total applied voltage is large enough to keep the potential of the R.D.M.E. in the limiting current region during the lifetime of a drop.

The present experiments were carried out with a 0.201 mM thallium solution in 0.05 M potassium nitrate in the presence of 0.01% gelatin with end tube 3 at 210 r.p.m. The m value was equal to 12.05 mg./sec. The total applied potential was −0.9 v. *vs.* S.C.E., and hence the potential of the R.D.M.E. decreased to −0.719 v. at the end of the drop life. An example of the current–time curve is shown in Fig. 7.

The disagreement between the observed and calculated current–time curves was significant in the region of early drop life. This trend is also observed with the D.M.E. Lingane[20] attributed it mainly to the variability of m during the drop life caused by the larger back pressure exerted on the young drop and also to the non-sphericity in the early life of the drop. In the case of the R.D.M.E. the variation of m is much smaller because the lumen of the orifice is larger than that of the capillary used with a D.M.E. For example, for the end tube used in the present experiment whose diameter of orifice is 0.75 mm., the back pressure calculated from the formula $P_{back} = 2\sigma/r$[10] amounts to *ca.* 1.7 cm. at the beginning and *ca.* 0.8 cm. at the end of the drop life. Therefore, from the expression $m = k(h - h_{back})$, the variation of m is calculated to be only *ca.* 2.5% when the height of mercury is kept at 40 cm.; this variation is too small to account for the difference between the experimental and theoretical curves in Fig. 7. With reference to the non-sphericity of the mercury drop, the deviation of the shape from a sphere at the early life of the drop is considered to be greater at the R.D.M.E. than at the D.M.E. because of the larger lumen of the orifice at the R.D.M.E. As the most important reason for the discrepancy, however, one cannot overlook the variation of the hydrodynamic conditions during the drop life. As mentioned in the theoretical part, at the beginning of the growth of the mercury drop, the Reynolds number is so small that the boundary layer theory fails to account for the hydrodynamic situation at the very early drop life. There is no doubt that a few mathematical simplifications are also responsible which

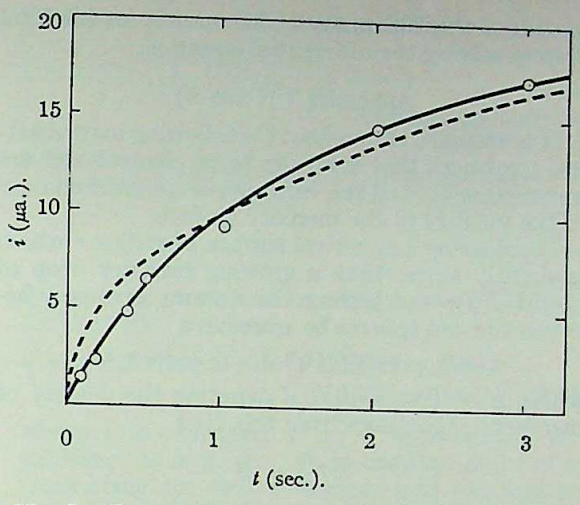

Fig. 7.—Current–time curve; end tube 3, capillary 4, 210 r.p.m., h = 78.5 cm., 0.201 mM, Tl^+ in 0.05 M KNO_3 and 0.01% gelatin; ———, experimental; – – –, theoretical.

were made for the purpose of obtaining a practical expression of the *average* limiting current.

We have discussed so far several aspects on the applicability of the proposed equation of the limiting current. Limitations of the equation are, of course, ascribed to the fact that some ideal situations were assumed which are somewhat different from the actual conditions. For example, the following assumptions are not fully justified even with an end tube whose dimension is in the recommended range; (1) the mercury drop is at any instant a perfect sphere which expands from its center outwards symmetrically, (2) the rotation of the electrode does not swirl the solution at all, (3) a laminar boundary layer is developed at any instant in the drop life, (4) the thickness of the boundary layer is expressed by the simple function (13). The fourth assumption is considered to be only a rough approximation from the purely hydrodynamic viewpoint, because it does not account for the separation of the boundary layer, which occurs on a body of revolution such as a sphere as a result of the acceleration in the front half and the deceleration in the rear half of the sphere. Since the expression for the boundary layer thickness was obtained by analogy with a flat plate, this assumption corresponds to a neglect of the curvature of the mercury drop as far as the boundary layer thickness is concerned. An attempt was made to make use of the expressions for the boundary layer thickness and the velocity distributions derived by taking the effect of curvature into consideration.[21] The final equation thus obtained is so involved and impractical that it is not given in this paper. At any rate, it is gratifying that only one numerical constant had to be determined empirically to obtain a satisfactory equation of the limiting current. It is considered that this empirical factor probably compensates on the average for the error resulting from the simplifications mentioned above.

Acknowledgment.—We wish to express our thanks to Dr. S. Ito of the Department of Mathe-

(20) I. J. Lingane, THIS JOURNAL, 75, 788 (1953).

(21) Ref. 6, p. 165, p. 218.

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matics of the University of Minnesota for his kind help in solving the differential equation.

Appendix 1 (Case A)

It is assumed throughout the following mathematical treatment that solutions to be electrolyzed are incompressible and the variation of c is marked only in the vicinity of the mercury surface.

Considering a spherical surface of radius r which is slightly larger than a growing mercury drop of radius $R(t)$, and letting the volume enclosed between the two spheres be ϵ, we have

$$4\pi r^3/3 = 4\pi\{R(t)\}^3/3 + \epsilon = 4\pi a^3 t/3 + \epsilon$$

where $a = (3m/4\pi d)^{1/3}$, d denoting the density of mercury. It follows from this that

$$3r^2 \frac{\mathrm{d}r}{\mathrm{d}t} = a^3$$

and hence

$$\frac{\mathrm{d}r}{\mathrm{d}t} = \frac{a^3}{3r^2} = \frac{1}{3r^2}\left(\frac{r^3 - 3\epsilon/4\pi}{t}\right)$$

When we consider the velocity of motion of a point on the spherical surface of radius r resulting from the growth of the mercury drop, it is clear that $r - R(t) << R(t)$ and $4\pi r^3/3 >> \epsilon$, and hence $\mathrm{d}r/\mathrm{d}t \cong r/3t$. Assuming that the r component of the flow velocity is negligible in comparison with the θ-component we get

$$v \cong r/3t \qquad \text{(A1)}$$

By putting $u = U_0$ and (A1) into equation 4 and neglecting w, we obtain

$$\frac{\partial c}{\partial t} = \mathrm{D}\left(\frac{\partial^2 c}{\partial r^2} + \frac{2}{r}\frac{\partial c}{\partial r} + \frac{1}{r^2}\Delta c\right) - \frac{r}{3t}\frac{\partial c}{\partial r} - \frac{U_0}{r}\frac{\partial c}{\partial \theta} \qquad \text{(A2)}$$

Substituting the variables r and t by

$$\sigma = 3t^{1/3} \text{ and } \eta = r/at^{1/3}$$

equation (A2) becomes

$$\frac{\partial c}{\partial \sigma} = \frac{D}{a^2}\left(\frac{\partial^2 c}{\partial \eta^2} + \frac{2}{\eta}\frac{\partial c}{\partial \eta} + \frac{1}{\eta^2}\Delta c\right) - \frac{U_0\sigma}{3a\eta}\frac{\partial c}{\partial \theta}$$

Putting $\tau = D\sigma/a^2$, $\xi = \eta - 1$ and $f = \eta c/C$, we get from the above equation

$$\frac{\partial f}{\partial \tau} = \frac{\partial^2 f}{\partial \xi^2} + \frac{\Delta f}{(1+\xi)^2} - \frac{a^3 U_0 \tau}{3D^2(1+\xi)}\frac{\partial f}{\partial \theta} \qquad \text{(A3)}$$

Since the condition $r - R(t) << R(t)$ is equivalent to $\xi << 1$, we can put $1 + \xi \cong 1$. For the sake of simplicity, we put $A = a^3 U_0/3D^2 = \text{const.}$ Then (A3) becomes

$$\frac{\partial f}{\partial \tau} = \frac{\partial^2 f}{\partial \xi^2} + \Delta f - A\tau\frac{\partial f}{\partial \theta} \qquad \text{(A4)}$$

By changing the variables as above, the initial and boundary conditions 5 and 6 become

$$f = 1 + \xi \text{ when } \tau = 0 \qquad \text{(A5)}$$

$$f = 0 \text{ when } \xi = 0;\ \tau > 0 \qquad \text{(A6)}$$

In order to solve (A4), we define the functions G and W as

$$G(\omega,\xi,\xi') = \frac{1}{2\sqrt{\pi\omega}}\left[\exp\left\{-\frac{(\xi-\xi')^2}{4\omega}\right\} - \exp\left\{-\frac{(\xi+\xi')^2}{4\omega}\right\}\right] \qquad \text{(A7)}$$

$$W(\tau,\theta,\theta',\varphi,\varphi') = \sum_{l,k}\exp\{-\tau l(l+1)\}\, Y_l^{(k)}(\theta,\varphi)\, Y_l^{(k)}(\theta'\varphi')$$

in which $Y_l^{(k)}$'s are spherical surface harmonics. Function (A7) has the properties

$$G(\omega,0,\xi') = G(\omega,\xi,0) = 0, \quad \frac{\partial G}{\partial \omega} = \frac{\partial^2 G}{\partial \xi^2} = \frac{\partial^2 G}{\partial \xi'^2} \text{ and}$$

$$\lim_{\omega\to 0}\int_0^\infty G(\omega,\xi,\xi')g(\omega,\xi')\mathrm{d}\xi' = g(0,\xi) \qquad \text{(A9)}$$

for any bounded continuous function $g(\omega, \xi)$ such as $g(\omega, 0) = 0$. Function (A8) is the fundamental solution of the following differential equation on the unit sphere

$$\frac{\partial H}{\partial \tau} = \Delta H$$

and W has the properties

$$\frac{\partial W}{\partial \tau} = \Delta W = \Delta' W \text{ where } \Delta' W = \frac{1}{\sin\theta'}\frac{\partial}{\partial \theta'}\left(\sin\theta'\frac{\partial W}{\partial \theta'}\right) + \frac{1}{\sin^2\theta'}\frac{\partial^2 W}{\partial \varphi'^2}$$

$$\lim_{\tau\to 0}\iint_S W(\tau,\theta,\theta',\varphi,\varphi')H(\tau,\theta',\varphi')\mathrm{d}S' = H(0,\theta,\varphi)$$

for any continuous function $H(\tau,\theta,\varphi)$, and

$$\iint_S W(\tau,\theta,\theta',\varphi,\varphi')\mathrm{d}S = \iint_S W(\tau,\theta,\theta',\varphi,\varphi')\mathrm{d}S' = 1 \qquad \text{(A10)}$$

where S is the unit sphere, $\mathrm{d}S = \sin\theta\mathrm{d}\theta\mathrm{d}\varphi$, and $\mathrm{d}S' = \sin\theta'\mathrm{d}\theta'\mathrm{d}\varphi'$ which is an area element on the unit sphere.

Now we consider the differential equation

$$\frac{\partial^2 h}{\partial \xi^2} - A\tau\frac{\partial h}{\partial \theta} = 0 \qquad \text{(A11)}$$

The solution of this equation, which satisfies the conditions $h = 1 + \xi$ when $\theta = 0$, and $h = 0$ when $\xi = 0$, $\theta \neq 0$, is given by

$$h = \int_0^\infty G\left(\sqrt{\frac{\theta}{A\tau}},\xi,\xi')(1+\xi')\mathrm{d}\xi' = \frac{2}{\sqrt{\pi}}\int_0^{\xi\sqrt{A\tau/\theta}/2}\exp(-\lambda^2)\mathrm{d}\lambda + \xi \qquad \text{(A12)}$$

If we put $g = f - h$, we obtain the following equation for g from (A4) and (A11)

$$\frac{\partial g}{\partial \tau} = \frac{\partial^2 g}{\partial \xi^2} + \Delta g - A\tau\frac{\partial g}{\partial \theta} + \Delta h - \frac{\partial h}{\partial \tau} \qquad \text{(A13)}$$

The initial and boundary conditions for this equation are

$$g = 1 \text{ when } \tau = 0 \qquad \text{(A14)}$$

$$g = 0 \text{ when } \xi = 0, \tau \neq 0 \text{ (except where } \theta = 0) \qquad \text{(A15)}$$

Now we consider the function

$$\frac{\partial}{\partial \tau'}\iint_S \mathrm{d}S'\int_0^\infty G(\tau-\tau',\xi,\xi')W(\tau-\tau',\theta,\theta',\varphi,\varphi')g(\tau',\xi',\theta',\varphi')\mathrm{d}\xi' =$$

$$\iint_S \mathrm{d}S'\int_0^\infty GW\left\{-A\tau'\frac{\partial g}{\partial \theta'} + \Delta' h(\tau',\xi',\varphi') - \frac{\partial h(\tau',\xi',\varphi')}{\partial \tau'}\right\}\mathrm{d}\xi'$$

By integrating both sides of the above expression from 0 to τ and using (A14), (A15) and the properties of G and W explained above, we obtain

$$g(\tau,\xi,\theta,\varphi) - \int_0^\infty G\mathrm{d}\xi' = \int_0^\tau \mathrm{d}\tau\iint_S \mathrm{d}S'\int_0^\infty\left(-GWA\tau'\frac{\partial g}{\partial \theta} + GW\Delta' h - GW\frac{\partial h}{\partial \tau'}\right)\mathrm{d}\xi' \qquad \text{(A16)}$$

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and hence

$$\iint_S \frac{\partial g}{\partial \xi} dS = 4\pi \int_0^\infty \frac{\partial G}{\partial \xi} d\xi' + \iint_S dS \int_0^\tau d\tau \iint_S \int_0^\infty \left(-\frac{\partial G}{\partial \xi} WA\tau' \frac{\partial g}{\partial \theta'} + \frac{\partial G}{\partial \xi} W\Delta' h - \frac{\partial G}{\partial \xi} W \frac{\partial h}{\partial \tau'} \right) d\xi' dS' \quad (A17)$$

From (A10) the second term of the right-hand side of the above equation becomes

$$\int_0^\tau d\tau' \iint_S dS' \int_0^\infty \left(-\frac{\partial G}{\partial \xi} A\tau' \frac{\partial g}{\partial \theta'} + \frac{\partial G}{\partial \xi} \Delta' h - \frac{\partial G}{\partial \xi} \frac{\partial h}{\partial \tau'} \right) d\xi'$$

If we define $h(0, \xi) = 1 + \xi$ in (A12), then h is infinitely differentiable on the surface S. Thus $\iint_S \Delta' h \, dS' = 0$. From (A12) we obtain

$$\frac{\partial h}{\partial \tau'} = \frac{\xi}{2} \sqrt{\frac{A}{\pi \theta' \tau'}} \exp\left(-\frac{A\tau'\xi'}{4\theta'} \right) \quad (A18)$$

Except the region of very small τ', (A18) is small. Because we integrate the concentration gradient with respect to time to obtain the average limiting current expression, the effect of the contribution of (A18) at small values of τ' on the final expression can be neglected. Thus we neglect the third term in the brackets of (A17). It can be seen, furthermore, by applying the successive substitution method to equation (A16) that the first term in the brackets of equation (A17) is also small. Thus (A17) can be simplified as

$$\iint_S \frac{\partial g}{\partial \xi} dS = 4\pi \int_0^\infty \frac{\partial G(\tau, \xi, \xi')}{\partial \xi} d\xi' = 4\pi \left\{ \frac{2}{\sqrt{\pi}} \frac{1}{2\sqrt{\tau}} \exp\left(-\frac{\xi^2}{4\pi} \right) \right\}$$

and therefore

$$\iint_S \left(\frac{\partial g}{\partial \xi} \right)_{\xi=0} dS = 4 \sqrt{\frac{\pi}{\tau}} \quad (A19)$$

From equation (A12), we obtain

$$\iint_S \left(\frac{\partial h}{\partial \xi} \right)_{\xi=0} dS = \sqrt{\frac{A\tau}{\pi}} 2\pi \int_0^\pi \frac{\sin\theta}{\sqrt{\theta}} d\theta + 4\pi = 2(1.790)\sqrt{\pi A\tau} + 4\pi \quad (A20)$$

From (A19), (A20) and the relation $f = g + h$ it follows that

$$\iint_S \left(\frac{\partial f}{\partial \xi} \right)_{\xi=0} dS = \frac{4\pi^{1/2}}{\tau^{1/2}} + 4\pi + 3.580\, \pi^{1/2} A^{1/2} \tau^{1/2} = \frac{4\pi^{1/2} a}{D^{1/2} t^{1/2}} + 4\pi + \frac{3.580 \pi^{1/2} U_0^{1/2} a^{1/2} t^{1/4}}{3^{1/2} D^{1/2}} \quad (A21)$$

On the other hand, we have

$$\left(\frac{\partial c}{\partial r} \right)_{r=R(t)} = \left(\frac{\partial \xi}{\partial r} \right)_{r=at^{1/2}} \left[\frac{\partial \{ C(1+\xi)^{-1} f \}}{\partial \xi} \right]_{\xi=0} = \frac{C}{at^{1/2}} \left(\frac{\partial f}{\partial \xi} \right)_{\xi=0} \quad (A22)$$

Thus, from (A21) and (A22) we obtain the following expression for the concentration gradient in the radial direction on the surface of the electrode integrated over the total surface area

$$\iint_S \left(\frac{\partial c}{\partial r} \right)_{r=R(t)} \{R(t)\}^2 dS = \frac{C}{at^{1/2}} \iint_S \left(\frac{\partial f}{\partial \xi} \right)_{\xi=0} (at^{1/2})^2 dS = C \left(\frac{4\pi^{1/2} a^2 t^{1/4}}{3^{1/2} D^{1/2}} \right) + 4\pi a t^{1/2} + \frac{3.580 \pi^{1/2} U_0^{1/2} a^{3/2} t^{1/2}}{D^{1/2}} \Bigg)$$

Therefore the average limiting current is given by

$$i_l = nFCD \frac{1}{t} \int_0^t \left(\frac{4\pi^{1/2} a^2 t^{1/4}}{3^{1/2} D^{1/2}} + 4\pi a t^{1/2} + \frac{(3.580)\pi^{1/2} U_0^{1/2} a^{3/2} t^{1/2}}{D^{1/2}} \right) dt$$

$$= nFCD^{1/2} \left\{ \frac{(6) 4^{1/2} 3^{1/4} m^{2/3} t^{1/6}}{7\pi^{1/6} d^{2/3}} + \frac{3^{4/3} \pi^{2/3} D^{1/3} (mt)^{1/2}}{4^{1/3} d^{1/3}} + \frac{(3.580) U_0^{1/2} (mt)^{1/2}}{3^{1/2} d^{1/2}} \right\}$$

By putting numerical constants $\pi = 3.1416$, $d = 13.54$ at 25°, we obtain

$$i_l = nFCD^{1/2} \{ 0.238 m^{2/3} t^{1/6} + 2.452 D^{1/2} (mt)^{1/2} + 0.562 U_0^{1/2} (mt)^{1/2} \} \quad (A23)$$

where i_l is expressed in a., C in mole/ml., D in cm.^{2}/sec., m in g./sec., U_0 in cm./sec. and t in sec. Converting the unit of current into μa., and putting $F = 96500$ coulombs, equation 1 is obtained.

Appendix 2 (Case B)

The tangential velocity component in the boundary layer can be written as

$$u = U[2\{r - R(t)\}/\delta - \{r - R(t)\}^2/\delta^2] \quad (A24)$$

where $\delta = \sqrt{30\nu R(t)\theta/U}$. The velocity component, v, is given by (A1), and $w = 0$ as in Case A (Appendix 1).

Changing the variables r and t by $\eta = rt^{-1/3}$ and $s = 3t^{1/3}$, equation 4 can be written as

$$\frac{\partial c}{\partial s} = D \left(\frac{\partial^2 c}{\partial \eta^2} + \frac{2}{\eta} \frac{\partial c}{\partial \eta} + \frac{1}{\eta^2} \Delta c \right) - \left(\frac{sv}{3} - \frac{\eta}{s} \right) \frac{\partial c}{\partial \eta} - \frac{su}{3\eta} \frac{\partial c}{\partial \theta} \quad (A25)$$

From (A1), $v \cong 3\eta/s^2$ in the region $r - R(t) << R(t)$ and hence $\eta - a << a$, in which $a = (3m/4\pi d)^{1/3} = R(t)/t^{1/3}$. In addition, $\partial c/\partial t, \partial c/\partial r$, $\partial^2 c/\partial r^2$, Δc, $\partial c/\partial \theta \cong 0$ outside the range $r - R(t) << R(t)$, and therefore $\partial c/\partial \eta \cong 0$ outside the range $\eta - a << a$. Hence $\left(\frac{sv}{3} - \frac{\eta}{s} \right) \frac{\partial c}{\partial \eta} \cong 0$ in equation (A25). Putting $\eta c(s, \eta, \theta, \varphi) = f(s, \eta, \theta, \varphi)$, equation (A25) becomes

$$\frac{\partial f}{\partial s} = D \left(\frac{\partial^2 f}{\partial \eta^2} + \frac{1}{\eta^2} \Delta f \right) - \frac{su}{3\eta} \frac{\partial f}{\partial \theta}$$

In the vicinity of $r \cong R(t)$, $\eta \cong a$. If we put $\xi = \eta - a$, this equation becomes

$$\frac{\partial f}{\partial s} = D \left(\frac{\partial^2 f}{\partial \xi^2} + \frac{1}{a^2} \Delta f \right) - \frac{su}{3a} \frac{\partial f}{\partial \theta} \quad (A26)$$

By transforming the variables as above, the initial and boundary conditions 15, 16 and 17 can be written as

$$f(0, \xi, \theta, \varphi) = (a + \xi) C \quad (A27)$$

$$f(s, 0, \theta, \varphi) = 0 \text{ when } s > 0 \quad (A28)$$

$$f\{s, \delta(s,\theta), \theta, \varphi\} = \{a + \delta(s,\theta)\} C \quad (A29)$$

where

$$\delta(s, \theta) = \sqrt{90\nu a\theta/Us}$$

In order to obtain a solution of equation (A26), first we consider the differential equation

$$D \frac{\partial^2 h}{\partial \xi^2} - \frac{su}{3a} \frac{\partial h}{\partial \theta} = 0 \quad (A30)$$

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A solution of this equation must satisfy the conditions

$$h(s,0,\theta) = 0 \tag{A31}$$

$$h\{s,\delta(s,\theta),0\} = \{a + \delta(s,\theta)\}C \tag{A32}$$

$$\frac{\partial h}{\partial \theta} \cong 0 \text{ except when } \xi << a \tag{A33}$$

When $\xi << a$, we obtain from (A24)

$$\frac{su}{3a} \cong \frac{s}{3a}\, U \frac{2U^{1/2}s^{1/2}\xi}{\sqrt{90\nu a\theta}} = \frac{2U^{3/2}s^{1/2}\xi}{\sqrt{810\nu a^3\theta}} = bs^{1/2}\theta^{-1/2}\xi$$

where

$$b = 2U^{3/2}/\sqrt{810\nu a^3} = \text{constant}$$

Therefore, (A30) becomes

$$D\frac{\partial^2 h}{\partial \xi^2} - bs^{1/2}\theta^{-1/2}\xi\frac{\partial h}{\partial \theta} = 0 \tag{A34}$$

Changing the variables by putting

$$z = (b/D)^{1/3}s^{1/2}\theta^{-1/2}\xi \text{ and } \omega = \theta \tag{A35}$$

(A34) becomes

$$D^{1/3}b^{2/3}s\omega^{-1}\left(\frac{\partial^2 h}{\partial z^2} + \frac{z^2}{2}\frac{\partial h}{\partial z}\right) - b^{2/3}D^{1/3}sz\frac{\partial h}{\partial \omega} = 0 \tag{A36}$$

A particular solution of (A36) can be obtained by substituting h, which satisfies the equation

$$\frac{\partial^2 h}{\partial z^2} + \frac{z^2}{2}\frac{\partial h}{\partial z} = 0$$

by z given by (A35). It is

$$h(s,\xi,\theta) = A\int_0^z \exp\left(-\frac{\zeta^3}{6}\right)d\zeta + B = A_1\gamma\,(1/3,\, bs^{2/3}\xi^3/6D\theta^{2/3}) + B \tag{A37}$$

where A, A_1 and B are constants, and

$$\gamma(X,Z) = \int_0^Z e^{-t}t^{X-1}\,dt$$

which is an incomplete gamma function. Since (A37) is a particular solution

$$h(s,\xi,\theta) = A_1\gamma(1/3,bs^{2/3}\xi^3/6D\theta^{2/3}) + A_2\xi + B \ (A_2\text{:const.}) \tag{A38}$$

is also the same. From (A31), (A32), (A33) and (A38), we obtain

$$B = 0$$

and $A_1\gamma(1/3,\, 30\nu/6D) + A_2\delta(s,\theta) = Ca + C\delta(s,\theta)$. Therefore

$$A_1 = Ca/\gamma(1/3,\, 30\nu/6D),\quad A_2 = C$$

Thus we obtain from (A38)

$$h(s,\xi,\theta) = \frac{Ca\gamma(1/3,bs^{2/3}\xi^3/6D\theta^{2/3})}{\gamma(1/3,\, 30\nu/6D)} + C\xi \tag{A39}$$

This is the unique solution of (A30) which satisfies the given conditions.

Next putting $f - h = g$, we can write the following equation from (A26), (A27), (A28) and (A29)

$$\frac{\partial g}{\partial s} = D\left(\frac{\partial^2 g}{\partial \xi^2} + \frac{1}{a^2}\Delta g\right) - \frac{su}{3a}\frac{\partial g}{\partial \theta} + \frac{D}{a^2}\Delta h - \frac{\partial h}{\partial s} \tag{A40}$$

with the boundary conditions

$$\left.\begin{aligned} &g(0,\xi,\theta,\varphi) = aC,\ (h(0,\xi,\theta) = C\xi \text{ from (A39)}) \\ &g(s,0,\theta,\varphi) = 0 \text{ when } s > 0 \\ &g\{s,\delta(s,\theta),\theta,\varphi\} = 0 \end{aligned}\right\} \tag{A41}$$

In order to solve equation (A40), we define the functions G and W as

$$G(s,\xi,\xi') = \frac{1}{2\sqrt{\pi Ds}}\left[\exp\left\{-\frac{(\xi-\xi')^2}{4Ds}\right\} - \exp\left\{-\frac{(\xi+\xi')^2}{4Ds}\right\}\right] \tag{A42}$$

$$W(s,\theta,\theta',\varphi,\varphi') = \sum_{l,k}\exp\left\{-\frac{Ds}{a^2}l(l+1)\right\} - Y_l^{(k)}(\theta,\varphi)\,Y_l^{(k)}(\theta',\varphi') \tag{A43}$$

in which $Y_l^{(k)}$'s are spherical surface harmonics. Functions (A42) and (A43) have the properties similar to (A7) and (A8) in Appendix 1.

With reference to f we can ignore the slight discontinuity at $\xi = \delta(s,\theta)$ when it is integrated to obtain (A44); and h is a smooth function over the whole region. Therefore, from $f - h = g$, g can be regarded as a function which can satisfy (A41). Thus

$$\frac{\partial}{\partial s'}\iint_S dS'\int_0^\infty G(s-s',\xi,\xi')W(s-s',\theta,\theta',\varphi,\varphi')g(s',\xi',\theta',\varphi')d\xi'$$
$$= \iint_S dS'\int_0^\infty GW\left\{-\frac{su(s',\xi'\theta')}{3a}\frac{\partial g}{\partial \theta'} + \frac{D}{a^2}\Delta' h(s',\xi',\theta') - \frac{\partial h(s'\xi',\theta')}{\partial s'}\right\}d\xi'$$

By integrating both sides of the above equation from 0 to s and using (A41) and the characteristic properties of G and W, we obtain

$$\iint_S g(s,\xi,\theta,\varphi)dS = 4\pi C\int_0^\infty G(s,\xi,\xi')a\,d\xi' + \int_0^s ds'\int_0^\infty G(s-s',\xi,\xi')d\xi'\iint_S\left\{-\frac{su}{3a}\frac{\partial g}{\partial \theta'} + \frac{D}{a^2}\Delta' h - \frac{\partial h}{\partial s'}\right\}dS' \tag{A44}$$

In (A44) the term

$$\iint_S\left(-\frac{su}{3a}\right)\frac{\partial g}{\partial \theta'}\,dS'$$

is negligibly small compared with the first term of the right-hand side, as can be seen by applying the successive substitution method. From the property of the Laplacian on a sphere it follows that

$$\iint_S \Delta' h\,dS' = 0$$

It can be seen that the value of

$$\int_0^s ds'\int_0^\infty G(s-s',\xi,\xi')d\xi'\iint_S\frac{\partial h}{\partial s'}\,dS'$$

is also negligible as is clear from the fact that the following expression is evaluated to be very small

$$\frac{\partial h}{\partial s} = \frac{C}{\gamma(1/3,\, 30\nu/6D)}\left\{\exp\left(-\frac{bs^{2/3}\xi^3}{6D\theta^{2/3}}\right)\right\}\frac{3^{2/3}b^{1/3}\xi}{2^{4/3}D^{1/3}s^{1/3}\theta^{1/3}}$$

Thus, (A44) can be simplified as

$$\iint_S g(s,\xi,\theta,\varphi)\,dS \cong 4\pi C\int_0^\infty G(s,\xi,\xi')a\,d\xi' = \frac{4\pi C}{2\sqrt{\pi Ds}}\int_0^\infty\left[\exp\left\{-\frac{(\xi-\xi')^2}{4Ds}\right\} - \exp\left\{-\frac{(\xi+\xi')^2}{4Ds}\right\}\right]a\,d\xi'$$

It follows from this that

$$\iint_S\frac{\partial g(s,0,\theta,\varphi)}{\partial \xi}\,dS = \frac{4\pi C}{2\sqrt{\pi D^2 s^3}}\int_0^\infty\left\{\exp\left(-\frac{\xi^2}{4Ds}\right)\right\}\xi a\,d\xi = 4\pi aC/\sqrt{\pi Ds} \tag{A45}$$

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On the other hand, we obtain from (A39)

$$\frac{\partial h(s,0,\theta,\varphi)}{\partial \xi} = \frac{Ca}{\gamma(1/3,\ 30\nu/6D)} \frac{3^{1/3}b^{1/3}s^{1/3}}{2^{1/3}D^{1/3}\theta^{1/3}} + C \quad \text{(A46)}$$

Generally, when Z is very large

$$\gamma(X,Z) \sim \Gamma(X) - Z^{X-1}e^{-Z}\{1 + O(1/Z)\}$$

where $\Gamma(X)$ is a gamma function. In our case, $Z = 30\nu/6D = 5 \times 10^{-2}/10^{-5} > 10^3$. Therefore

$$[\Gamma(1/3) - \gamma(1/3,Z)] \sim e^{-1000}$$

Accordingly we can put $\gamma(1/3,\ 30\nu/6D) = \Gamma(1/3)$. Thus from (A46) we obtain

$$\iint_S \frac{\partial h(s,0,\theta,\varphi)}{\partial \xi} dS = \frac{3^{1/3}b^{1/3}s^{1/3}aC}{2^{1/3}\Gamma(1/3)D^{1/3}} 2\pi \int_0^{\pi} \frac{\sin\theta}{\sqrt{\theta}} d\theta + 4\pi C$$

$$= \frac{2^{1/3}3^{1/3}(1.79)\pi b^{1/3}s^{1/3}Ca}{\Gamma(1/3)D^{1/3}} + 4\pi C \quad \text{(A47)}$$

From $c(t,r,\theta,\varphi) = \eta^{-1}f(s,\xi,\theta,\varphi) = (a + \xi)^{-1}f(s, \xi,\theta,\varphi)$ and $f(s,0,\theta,\varphi) = 0$ we can write the relation

$$\left(\frac{\partial c}{\partial r}\right)_{r=R(t)} = \frac{\partial f(s,0,\theta,\varphi)}{\partial \xi} \frac{1}{a} \left(\frac{\partial \xi}{\partial \eta}\right)_{\eta=a} \left(\frac{\partial \eta}{\partial r}\right)_{r=R(t)} =$$

$$a^{-1}t^{-1/3} \frac{\partial f(s,0,\theta,\varphi)}{\partial \xi} = a^{-1}t^{-1/3} \left\{\frac{\partial g(s,0,\theta,\varphi)}{\partial \xi} + \frac{\partial h(s,0,\theta,\varphi)}{\partial \xi}\right\} \quad \text{(A48)}$$

From (A45), (A47) and (A48) we obtain the following expression for the concentration gradient in the radial direction at the surface of the mercury drop integrated over the total surface area

$$\iint_S \left(\frac{\partial c}{\partial r}\right)_{r=R(t)} \{R(t)\}^2 dS = C\left\{\frac{4^{1/3}3^{1/3}m^{2/3}t^{1/3}}{\pi^{1/3}d^{2/3}D^{1/3}} + \frac{2^{1/3}3^{1/3}\pi^{2/3}(mt)^{1/3}}{d^{1/3}} + \frac{3^{1/3}(1.79)\pi^{1/3}U^{1/3}(mt)^{1/3}}{\Gamma(1/3)\ 30^{1/3}\nu^{1/3}d^{1/3}D^{1/3}}\right\} \quad \text{(A49)}$$

where $\Gamma(1/3)$ is equal to 2.680. Using the same numerical constants as for (A23) we obtain the following equation for the average limiting current expressed in terms of amp.

$$i_l = \frac{1}{t}\int_0^t \left[nFD \iint_S \left(\frac{\partial c}{\partial r}\right)_{r=R(t)} \{R(t)\}^2\, dS\right] dt$$

$$= nFCD^{1/3}\{0.238m^{2/3}t^{1/6} + 2.452D^{1/3}(mt)^{1/3} + 0.438U^{1/3}\nu^{-1/6}D^{1/6}(mt)^{1/3}\}$$

The numerical constant of the third term in the brackets corresponds to a parabolic velocity distribution. Converting the unit of current into μa. we obtain equation 18.

MINNEAPOLIS, MINNESOTA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK STATE COLLEGE OF FORESTRY AT SYRACUSE UNIVERSITY]

Addition of Methyl Radicals to Acetylenic Compounds

BY M. GAZITH AND M. SZWARC

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The addition of methyl radicals to several acetylenic compounds was investigated. The activation energies of these addition reactions were found to be higher than those observed in the addition reactions involving the corresponding ethylenic compounds. At the same time it was observed that the entropies of activation are also higher in the additions to the acetylenic compounds. The following pair of compounds were compared: acetylene–ethylene, methylacetylene–propylene, dimethylacetylene–the butenes–2, phenylacetylene–styrene, and diphenylacetylene–the stilbenes. It is suggested that the difference in the reactivity of a C≡C triple bond as compared with a C=C double bond arises from two factors. The π electrons in the shorter C≡C bond interact more strongly and consequently higher activation energy is necessary for the addition process which utilizes one of these electrons. On the other hand, the cylindrical symmetry of the C≡C bond leads to higher entropy of activation than the planar symmetry of the C=C double bond.

During the last few years a considerable amount of work has been carried out in these laboratories on the addition of radicals to aromatic and olefinic compounds.[1-6] The reactions investigated are represented by the general equation

$$R + A \longrightarrow R.A$$

where R denotes a radical, A represents a molecule of an aromatic or an olefinic compound, and R.A represents the primary addition product which, of course, is also a radical. Most of these investigations dealt with the addition of methyl radicals, and the relative rate constants of such additions, denoted as methyl affinities, were measured by the ratios k_2/k_1, where the subscripts refer to the two reactions[7]

$$CH_3 + \text{solvent} \longrightarrow CH_4 + \text{solvent radical} \quad (1)$$

$$CH_3 + A \longrightarrow A.CH_3 \quad (2)$$

The investigation reported in the present communication deals with the addition of methyl radicals to acetylenic compounds. The main purpose of this study was to find how the reactivity of a C≡C triple bond differs from that of a C=C double bond, and to interpret this difference in terms of electronic structures of the respective compounds.

Experimental

The following acetylenic compounds were investigated: acetylene, methylacetylene, dimethylacetylene, phenylacetylene, diphenylacetylene, and dimethyl ester of acetylene dicarboxylic acid. Acetylene was purchased from Matheson Co. and was 99.5% pure. The gas was deaerated and then distilled from trap to trap, the middle portion being collected. In some experiments the gas used was twice distilled. This additional purification did not affect the results indicating that our rate constants for acetylene are genuine.

High purity grade methylacetylene and dimethylacetylene were obtained from Farchan Research Laboratories. These compounds were used without further purification. Phenylacetylene and diphenylacetylene were prepared and purified by Dr. Bader from Aldrich Chemicals.[8] Finally, the dimethyl ester of acetylene dicarboxylic acid was prepared in our laboratories from the respective dicarboxylic acid. The ester was purified by fractionation *in vacuo*.

(1) M. Levy and M. Szwarc, THIS JOURNAL, **77**, 1949 (1955).
(2) M. Szwarc, *J. Polymer Sci.*, **16**, 89 (1955).
(3) A. Rembaum and M. Szwarc, THIS JOURNAL, **77**, 4468 (1955).
(4) F. Leavitt, M. Levy, M. Szwarc and V. Stannett, *ibid.*, **77**, 5493 (1955).
(5) R. P. Buckley and M. Szwarc, *ibid.*, **78**, 5696 (1956).
(6) J. Smid and M. Szwarc, *ibid.*, **78**, 3322 (1956).
(7) The same solvent was used in each series of investigated compounds A's. Hence, k_1 remains constant throughout the series.

(8) We take this opportunity to thank Dr. Bader for his assistance.

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Acetyl peroxide was prepared by the method described previously[9]; the compound was twice crystallized in an apparatus described by Mundy[10] and then dissolved in spectroscopically pure isoöctane. We used in our work 5×10^{-2} M and 5×10^{-3} M solutions of acetyl peroxide.

Experiments were carried out at four temperatures, namely, 55, 65, 75 and 85°. The experimental procedure and the method of analysis were described previously[1,11] and need not be repeated again. However, some modifications were introduced in the work involving gaseous compounds. For these compounds we used a reaction vessel shown in Fig. 1. The solution of acetyl peroxide in isoöctane was introduced into the spherical container, deaerated by the repeated freezing and thawing technique. Thereafter, the desirable amount of the gaseous compound was condensed in it by cooling the flask with liquid nitrogen. The stopcock leading to the vacuum line was then closed, and by turning the reaction flask round the ground joint No. 2, all the contents were transferred into ampoule A cooled now by liquid nitrogen.[12] Finally the ampoule was sealed off at constriction C, heated for a desired time at the required temperature, and then quickly cooled by immersion in a solid carbon dioxide–acetone bath. Eventually the ampoule was placed in a special device in which the tip of the ampoule could be broken *in vacuo*. Then the contents of the ampoule were analyzed in the usual way.

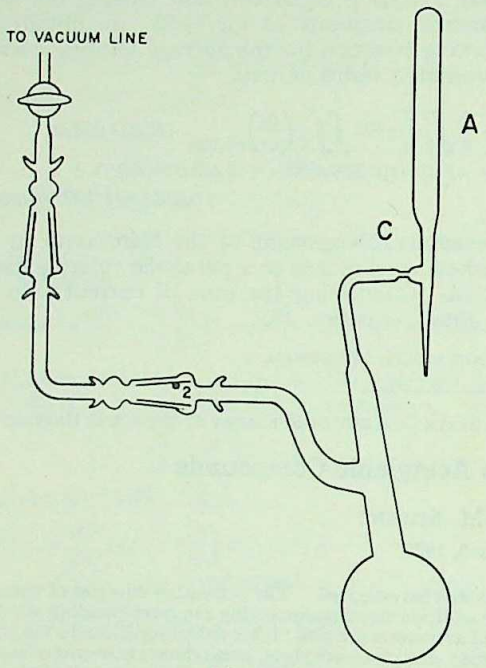

Fig. 1.

Results and their Evaluation

It was shown previously[1,2] that the ratio of the rate constants k_2/k_1 can be evaluated from the equation

$$k_2/k_1 = \{[A^0(CH_4) - A(CH_4)]/A(CH_4)\}(X_{HS}/X_A)$$

In this equation $A^0(CH_4)$ and $A(CH_4)$ denote the amounts of methane formed in two experiments carried out under identical conditions except that in one the olefinic or aromatic compound was present, while in the other was absent. The symbols X_{HS} and X_A denote the mole fractions of the solvent and the investigated olefinic or aromatic compound.

It was considered[4] that the substitution of $A^0(CH_4)$ and $A(CH_4)$ by $A^0(CH_4)/(CO_2)$ and $A(CH_4)/(CO_2)$ might be advantageous. While the former entities are dependent on the time of experiment, on the amount of the peroxide used, and are very sensitive to small changes in the temperature, the latter are independent of the amount of the peroxide used and the time of experiment, and only slightly affected by the temperature. The experimental advantage is therefore obvious.

On the other hand, the determination of $A^0(CH_4)$ and $A(CH_4)$ requires one measurement for each, while the ratios $A^0(CH_4)/(CO_2)$ and $A(CH_4)/(CO_2)$ are derived from two measurements for each ratio. Hence, the experimental errors are squared in the latter method and this drawback might outweight the advantages mentioned previously. In this investigation both methods were used in determining the k_2/k_1 ratios for phenylacetylene and diphenylacetylene in order to find which of these is more reliable. The results are given in Table I and they show that both methods lead to values which essentially are identical within their respective experimental errors. The only considerable deviation was observed in experiments involving diphenylacetylene and carried out at 85°. We believe that the value based on the $A(CH_4)/(CO_2)$ ratio obtained in this particular series of experiments is less reliable and it appears to be too high. It is also worth noticing that the scatter of the results appears to be nearly the same in both methods, indicating that both are equally reliable.

The reliability of these two methods was tested further by plotting the $\log(k_2/k_1)$ against the reciprocal of absolute temperature, as shown in Fig. 2.

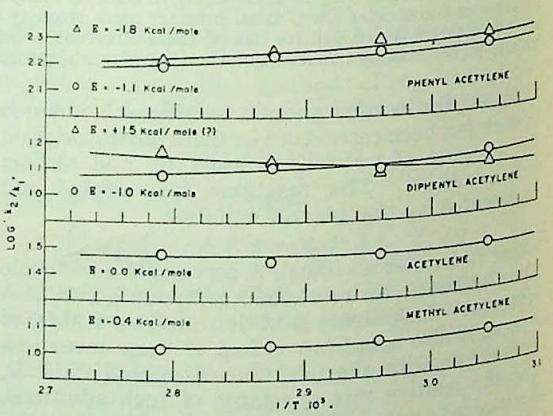

Fig. 2.

The differences in activation energies and A_2/A_1 factors calculated for the reaction involving phenylacetylene were well within the experimental errors (see Table III). However, the agreement does not seem as good for diphenylacetylene, apparently because of the high value of k_2/k_1 determined at 85° by the $A(CH_4)/(CO_2)$ method. We mentioned earlier that this determination seems to be inaccurate and if this result is discarded the respective E and A_2/A_1 values agree reasonably with those obtained by the alternative method.

(9) M. Levy and M. Szwarc, This Journal, **76**, 5978 (1954).
(10) Mundy, Ph.D. Thesis, 1951, Cornell University.
(11) M. Levy and M. Szwarc, This Journal, **76**, 5981 (1954).
(12) The amount of solution used was chosen in such a way that the ampoule A was nearly full, thus the error caused by the volatility of the gaseous olefins was minimized.

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TABLE I

Temp., °C.	Mole %	CH_4,[a] mm. Hg	CH_4/CO_2[b]	k_2/k_1, based on CH_4	k_2/k_1, based on CH_4/CO_2
			Phenylacetylene		
54.7	...	0.266	0.805	...	...
	0.260	.183	.515	174	216
	0.519	.135	.373	187	222
	1.04	.090	.281	188	174
	2.07	.056	.159	179	192
			Av.	182 ± 7	201 ± 22
64.9	...	0.199	0.805	...	...
	0.260	.139	.514	166	217
	.579	.105	.417	195	178
	.778	.086	.330	166	184
	1.04	.071	.267	173	193
	1.04	.067	.252	187	210
	2.07	.044	.161	167	189
			Av.	177 ± 12	195 ± 15
74.8	...	0.242	0.805	...	...
	0.260	.169	.550	166	178
	.519	.128	.424	170	172
	1.04	.085	.282	177	177
	2.07	.049	.167	185	180
			Av.	174 ± 8	177 ± 4
85.2	...	0.187	0.805	...	...
	0.260	.130	.561	168	167
	.519	.104	.435	154	163
	1.04	.071	.289	156	170
	1.04	.071	.297	156	164
	2.07	.045	.186	149	158
			Av.	157 ± 7	164 ± 5
			Diphenylacetylene		
54.7	..	0.266	0.805	...	...
	1.02	.222	.682	(19.3)	(17.6)
	2.01	.202	.633	15.5	13.2
	4.01	.163	.518	15.1	13.3
	8.70	.123	.379	12.3	11.8
			Av.	13.7 ± 1.6	12.4 ± 0.9
64.9	..	0.199	0.805	...	...
	1.02	.174	.686	(14.0)	(16.9)
	2.01	.159	.644	12.3	12.2
	4.01	.125	.539	14.3	11.8
	8.70	.095	.375	11.5	12.1
			Av.	12.7 ± 1.2	12.0 ± 0.2
74.8	..	0.242	0.805	...	...
	1.02	.215	.713	12.2	12.6
	2.01	.185	...	(15.1)	...
	4.01	.152	.493	14.2	15.2
	8.70	.113	.381	12.0	11.7
			Av.	12.8 ± 1.5	13.2 ± 1.5
85.2	..	0.187	0.805	...	...
	1.02	.170	.684	(9.75)	(17.3)
	2.01	.152	.612	11.1	15.4
	4.01	.121	.471	13.1	16.4
	8.70	.089	.363	11.6	12.8
			Av.	11.9 ± 0.9	14.9 ± 1.5

[a] The amount of CH_4 formed in absence of acetylenes is the average of a few experiments carried out simultaneously with various runs. Such experiments were carried out at each of the temperatures used in this investigation. [b] The ratio CH_4/CO_2 is the average of *all* the experiments carried out at temperatures 55–85°. It appears that this ratio is temperature independent within the investigated range of temperature.

Discussion

Inspection of Tables I and II shows that the values of k_2/k_1 calculated for acetylene, methylacetylene, phenylacetylene and diphenylacetylene are constants independent of the concentration of the acetylenic compound. This means that the abstraction of hydrogen atoms by methyl radicals from these compounds is negligible as compared to the methyl radical addition reaction, a conclusion particularly significant for methylacetylene.

TABLE II

Compound	T, °C.	Range of concn., %	No. expt.	k_2/k_1
Acetylene	54.7	2.8–6.6	6	30.1 ± 1.63
	64.9	2.8–7.6	5	29.4 ± 3.26
	74.8	3.0–7.8	4	28.4 ± 0.70
	85.2	3.0–6.5	4	30.1 ± 1.66
Methylacetylene	54.7	4.8–11.6	4	11.05 ± 1.69
	64.9	4.2–12.0	4	10.85 ± 0.95
	74.8	4.9–11.7	3	10.86 ± 0.69
	85.2	5.2–11.5	3	10.39 ± 0.70
				$(k_2/k_1)_{exp}$
Dimethylacetylene	54.7	5.6–19.1	3	1.26–0.44
	Extrapolated to 0%; k_2/k_1 = 4.7			
	64.9	7.8–22.0	3	0.8–0.4
	Extrapolated to 0%; k_2/k_1 = 1.4			
	74.8	9.2–20.9	3	1.16–0.21
	Extrapolated to 0%; k_2/k_1 = 2.0			

On the other hand, the same calculations applied to the results obtained for dimethylacetylene lead to a variable entity, denoted in Table II as $(k_2/k_1)_{exp}$ which decreases with the increasing mole fraction of the compound. It was shown elsewhere[13] that such a result is due to the abstraction of hydrogen atoms from the investigated compound by methyl radicals, and that the ratio k_2/k_1 is then obtained by plotting the reciprocal of $(k_2/k_1)_{exp}$ *versus* the mole fraction of the investigated compound. Such a plot results in a straight line, intercept of which gives the reciprocal of the k_2/k_1. Using this method we computed the respective k_2/k_1 listed in Table II. However the experimental data lead to considerable uncertainties and therefore the quoted values represent only the magnitude of the respective rate constants.

It is interesting to compare the addition of radicals to C≡C triple bonds and to the corresponding C=C double bonds. The addition of a radical leads eventually to the formation of a new C–C σ bond, and this process utilizes one of the π electrons of the multiple bond. Hence, whenever the interaction of the π electrons is stronger, *i.e.*, whenever the exchange integral β is more negative, the activation energy of the addition reaction should be larger. Since C≡C triple bonds are shorter than the C=C double bonds, the interaction between their π electrons is more powerful. Therefore, the activation energy of the addition reaction involving a C≡C bond should be larger than the activation energy of the reaction involving a corresponding C=C double bond, if our argument is correct. This conclusion seems to be confirmed by the data listed in Table III. All the activation energies quoted in this

(13) R. P. Buckley, F. Leavitt and M. Szwarc, THIS JOURNAL, 78, 5557 (1956).

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TABLE III

Acetylenic compd.	k_2/k_1 at 65°	$E_2 - E_1$, kcal./mole	A_2/A_1	Olefinic compd.	k_2/k_1 at 65°	$E_2 - E_1$, kcal./mole	A_2/A_1
Acetylene	29.4	0.0	30	Ethylene[a]	34.0	−0.6	13.0
Methylacetylene	10.8	−0.4	5.0	Propylene[a]	22	−1.1	4.3
Dimethylacetylene	~2	...	..	Butene-2[a]			
				trans	6.9	−1.9	0.4
				cis	3.4	−1.9	0.2
Phenylacetylene				Styrene[b]			
(CH_4)	177	−1.1	32		792	−3.0	9.0
(CH_4/CO_2)	195	−1.8	95				
Diphenylacetylene				Stilbene[b]			
(CH_4)	12.7	−1.0	3.4	*trans*	104	−2.4	3.1
(CH_4/CO_2)	12.0	+1.5 (?) or +0.7[c]	80 (?) or 37[c]	*cis*	29	−1.0	5

[a] R. P. Buckley, A. Rembaum and M. Szwarc, *J. Polymer Sci.*, 24, 135 (1957). [b] F. Leavitt, M. Levy, M. Szwarc and V. Stannett, THIS JOURNAL, 77, 5493 (1955). [c] These values were obtained by discarding the results obtained at 85°.

table were calculated by the least square method. Although the differences which interest us are small, and in some cases their magnitude is comparable to the experimental errors, the consistency of the observed trends supports our suggestion that in the addition reaction a C≡C triple bond acts as a "compressed" C=C double bond.[14]

The cylindrical symmetry of a C≡C bond as compared to the planar symmetry of a C=C double bond implies that the A factors (*i.e.*, entropy of activation) should be greater for the addition of radicals to the acetylenic compounds. This conclusion seems also to be substantiated by the data listed in Table III.

Since the nature of the C≡C bond affects in the same direction the activation energy and the *A* factor, one cannot predict how the rate of addition to the C≡C bond would compare with the rate of addition to the C=C double bond. For example, the rate of addition of methyl radicals to acetylene is comparable with the rate of addition to ethylene; on the other hand, the rates of addition to the other investigated acetylenic compounds are lower than those observed for the respective olefinic compounds.

Finally, let us compare the rate of addition of methyl radicals to acetylenic compounds with those of addition of other radicals. The only quantitative data available came from the studies of copolymerization processes. Thus, Doak[15] investigated the copolymerization of methyl acrylate and acrylonitrile with phenylacetylene, diphenylacetylene and hexyne. From his data one derives the values listed in Table IV for the relative rate constants of the addition of methyl acrylate radicals and acrylonitrile radicals to the acetylenic compounds. The results show some similarities for all the three radicals investigated. The steric hindrance is probably responsible for lower reactivity of diphenylacetylene as compared with phenylacetylene, and the smallest effect is observed in the attack by the smallest radical, *i.e.*, methyl radical. On the other hand, the lower reactivity of hexyne (or propyne) as compared with phenylacetylene reflects the higher resonance stabilization of the radical formed from the latter molecule and therefore the effect is shown for each of the three radicals listed in Table IV.

TABLE IV

	Methyl acrylate radical		Acrylonitrile radical		Methyl radical at 65°
Acetylenic compd.	$1/r_1$ at 60°	Relative value of the addition constant	$1/r_1$ at 60°	Relative value of the addition constant	relative value of the addition constant
Phenylacetylene	1.6	(1.0)	3.85	(1.0)	(1.0)
Diphenylacetylene	0.018	0.011	0.074	0.019	0.071
Hexyne (or propyne)	0.09	0.056	0.018	0.0047	0.06

The data listed in Table IV can be compared in a different way, namely, by computing the ratio of the rates of addition of radicals to phenylacetylene and to styrene. The following results are obtained

	Methyl acrylate radical	Acrylonitrile radical	Methyl radical
$\frac{k \text{ for addition to styrene}}{k \text{ for addition to phenylacetylene}}$	~6	3.5	4.5

The higher reactivity of styrene as compared with phenylacetylene was discussed by Doak in terms of higher resonance energy of the radical Ph.CH.CH_2.X as compared with Ph.Ċ = CH.X. We believe, however, that our explanation is more correct, namely, the uncoupling of a π electron is more difficult in a short C≡C bond than in the longer C=C bond.

The fact that the ratios of the rate constants of addition to styrene and to phenylacetylene is approximately the same for three radicals of different polarities seems to indicate that the polarities of both styrene and phenylacetylene are close to zero.

After completion of this work, Mr. Buckley, working in our laboratories, investigated the addition of methyl radicals to pentyne-1 and hexyne-1. These results are summarized in Tables V and VI and Fig. 3. They lead to the following conclusions. Methyl radicals react with pentyne-1 and hexyne-1 in a dual fashion: add to the triple C≡C bond or abstract α hydrogen atom from the CH_2 group adjacent to the C≡C bond. The relevant rate constants are calculated from the plots of $(k_2/k_1)^{-1}_{exp}$ *versus* x_a/x_s (for the details of the method see ref. 10) by the least square method. These calculations show that k_2/k_1 for pentyne-1 and hexyne-1 at 65° are 13.7 and 17.5, respectively. Both these values

(14) See in this connection a paper by F. Leavitt and M. Szwarc, THIS JOURNAL, 78, 3590 (1956), in which the reactivity of a stretched C=C double bond is discussed.

(15) K. W. Doak, *ibid.*, 72, 4681 (1950).

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TABLE V

T = 65°C., SOLVENT ISOÖCTANE

Hydrocarbon	Mole, %	$(k_2/k_1)_{exp.}$
Pentyne-1	10.51	4.61
Pentyne-1	7.88	5.94
Pentyne-1	5.26	7.30
Pentyne-1	2.63	9.26
Pentyne-1; k_2/k_1 extrapolated to 0 mole % = 13.7		
Hexyne-1	10.45	6.00
Hexyne-1	7.84	7.00
Hexyne-1	5.24	8.86
Hexyne-1	2.62	12.50
Hexyne-1; k_2/k_1 extrapolated to 0 mole % = 17.5		

TABLE VI

T = 65°C., SOLVENT ISOÖCTANE

Hydrocarbon	k_2/k_1	k_1/k_2	k_5/k_1	k_5'/k_1
Pentyne-1	13.7	1.2	16.3	8.1
Hexyne-1	17.5	0.97	17.0	8.5

compare reasonably with the k_2/k_1 value determined for methylacetylene, namely, 10.85, and thus it appears that the rate of addition of methyl radicals to an acetylene of the type CH≡C—R is, at least approximately, independent of the length of the group R.

It is interesting to compare the rate of abstraction of hydrogen atoms from the CH_2 group α to C≡C triple bond with the rate of abstraction from the same group α to C=C double bond. The results arrived at from the study of reactions of pentyne and hexyne lead to values 8.1 and 8.5, respectively, for the ratio k_5'/k_1 (k_5' represents the rate constant of hydrogen abstraction reaction per active hydrogen, *i.e.*, $k_5/2$ for the discussed hydrocarbons). On the other hand, the work of Buckley and Szwarc[12] demonstrated that the corresponding values of k_5'/k_1 for butene-1, pentene-1, heptene-1, decene-1 and hexadecene-1 are 3.3, 4.1, 6.3, 6.4 and 6.4, respectively. It appears, therefore, that the rate of abstraction of a hydrogen atom from a CH_2 group adjacent to a C≡C triple bond is slightly higher than the corresponding rate for a reaction involving a CH_2 group adjacent to a C=C double bond. This point will be discussed further in a forthcoming publication.

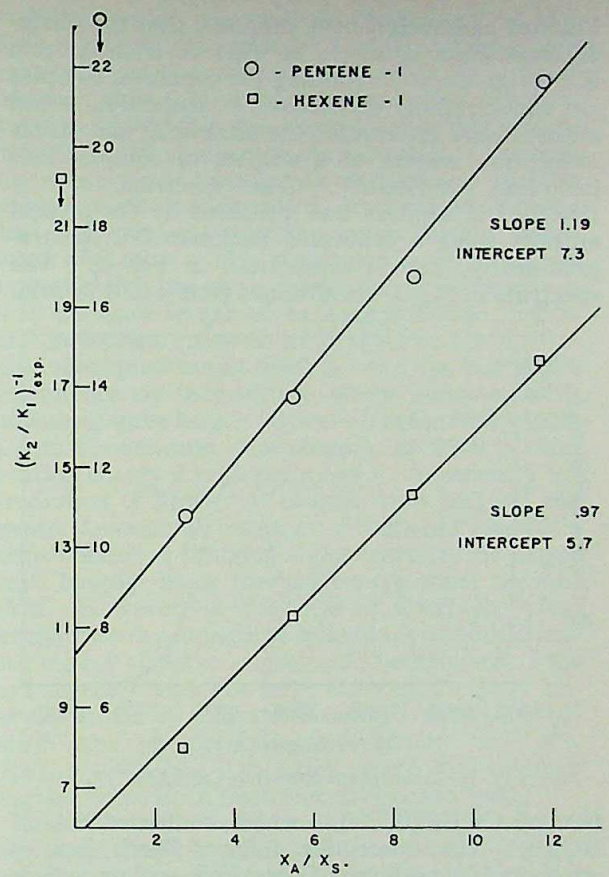

Fig. 3.

In conclusion we wish to thank the National Science Foundation for their support of this investigation.

SYRACUSE, N. Y.

[CONTRIBUTION FROM BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

Photochemical Exchange of Water between $Cr(H_2O)_6^{+3}$ and Solvent[1]

BY ROBERT A. PLANE AND JOHN P. HUNT

RECEIVED DECEMBER 3, 1956

Studies have been made on the rate of the reaction $Cr(H_2O)_6^{+3} + 6H_2O^{18} \rightarrow Cr(H_2O^{18})_6^{+3} + 6H_2O$ in the presence of light of various wave lengths. Quantum yields have been obtained for the three $Cr(H_2O)_6^{+3}$ absorption bands (2610, 4080, 5740 Å.) at three temperatures (0, 10, 27°). At 27°, the quantum yields for all bands are of the order of magnitude 10^{-2}, and decrease with decreasing temperature. Solutions of $Cr(H_2O)_6(ClO_4)_3$ were carefully checked for fluorescence which was found to be absent even at −196° in glasses prepared by dissolving $Cr(H_2O)_6(ClO_4)_3$ in isopropyl alcohol. In order to account for the low quantum yields and absence of fluorescence, it seems most likely that the electronically excited chromic species converts to the ground state by radiationless transitions to high vibrational states of the ground electronic level. Because of the large temperature dependence of the photochemical reaction, it appears more probable that reaction occurs from an excited electronic state rather than from an excited vibrational state. However, such an interpretation seems to demand that during deactivation, some of the chromic species must pass through a spin forbidden (doublet) state.

For many years it has been known that some substitution reactions of complex ions are hastened by light. Most such reactions seem to be particularly sensitive to ultraviolet radiation, and the mechanisms which have been proposed usually involve an electron transfer followed by rapid substitution. For example, for a series of complex ions of the type $[Co(NH_3)_5X]^{++}$ (in which X is F^-, Cl^-, Br^- or I^-)

(1) Presented at 128th National Meeting of the American Chemical Society, Minneapolis, Minnesota, 1955.

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Linhard and Weigel have proposed that the photodecomposition is due to an electron transfer from X^- to the Co atom forming the cobaltous complex ion which rapidly decomposes.[2] Recently, several authors have interpreted the ultraviolet and visible absorption spectra of a number of complex ions including $Cr(H_2O)_6^{+3}$.[3] The spectrum of $Cr(H_2O)_6^{+3}$ in solution was measured by the present authors using a calibrated Beckman DU spectrophotometer, and is reproduced in Fig. 1. The spectrum in Fig. 1 was obtained from a 0.04 *M* solution of $Cr(H_2O)_6(ClO_4)_3$ which contained 0.1 *M* $HClO_4$. The absorption follows Beer's law, is unaffected by addition of perchloric acid or sodium perchlorate, and is essentially temperature independent. At very short wave lengths (below 2400 Å.) there is a strong absorption which has been attributed to an electron transfer. However, the three weak absorption bands at longer wave lengths are assigned to forbidden electronic transitions within the 3d subshell of the chromium atom.[3] The present work was undertaken to determine whether irradiation of the three weak absorption bands of $Cr(H_2O)_6^{+3}$ might hasten its substitution reactions which normally are quite slow.[4]

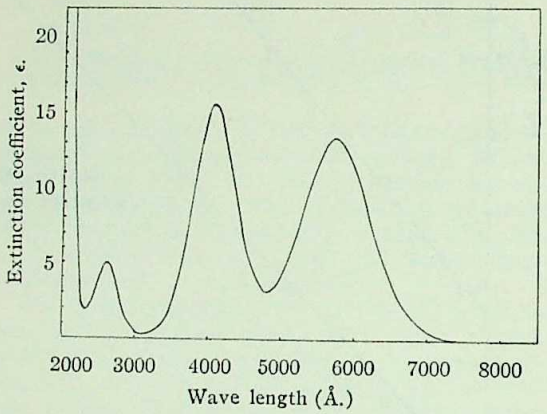

Fig. 1.—Absorption spectrum $Cr(H_2O)_6^{+++}$.

The particular substitution reaction chosen for study was the isotope exchange reaction

$$Cr(H_2O)_6^{+3} + 6H_2O^{18} \longrightarrow Cr(H_2O^{18})_6^{+3} + 6H_2O$$

It was chosen because considerable data already exist for the "dark" reaction,[4] there is no change in spectrum during the course of the reaction, and this reaction should be relatively simple in nature.

Experimental

The general procedure followed involved preparation of a solution of $Cr(ClO_4)_3$ and $HClO_4$ in which the solvent water (but not $Cr(H_2O)_6^{+3}$) was initially enriched in O^{18} by about a factor of 3. A portion of the solution was taken for analysis of the initial O^{18} content of the $Cr(H_2O)_6^{+3}$ and the remainder was then irradiated for a number of hours. After irradiation, the solution was again sampled and the remainder allowed to stand until isotopic equilibrium had been attained and then sampled again. The rate of the "dark" reaction was obtained either from the previous data,[4] or in some cases from new experiments run parallel with the photoreactions. In all cases, ClO_4^- was the only anion present.

The materials used were prepared by methods described previously,[4] and the sampling procedure was essentially the $Cr(H_2O)_6PO_4$ precipitation and ignition used earlier.[4] The only difference in sampling procedure was that the precipitate was ignited at 160° without the subsequent heating to 750° as done in earlier work. Despite the fact that this lower temperature ignition served to remove but *ca.* $4H_2O$/Cr, the elimination of oxygen exchange between water and phosphate seemed to allow slightly greater reproducibility of results.

For irradiations, a cylindrical cell was used with light filters serving as a cover. The light came from above the cell in a slightly divergent beam which did not strike the walls of the cell. In most experiments, nearly all of the light was absorbed in the solution. In cases where this condition did not obtain, appropriate corrections were applied to the results. During irradiation, solutions were thermostated and were stirred using a magnetic stirrer. Light sources were the General Electric Co. AH-4, AH-5 and 4-watt germicidal lamp. Appropriate Corning filters were used to select wave lengths such that each absorption band could be irradiated separately. The light was monitored during the experiments using a Weston Photronic cell and was found to be constant in intensity during an experiment to ±3%. Quantum fluxes were measured in the reaction cell, before and after a run, using the uranyl oxalate actinometer.[5] For wave lengths longer than 4500 Å., the photochemical experiment was run with one set of filters and the actinometer with another set. Results were then calculated from data supplied by the lamp manufacturer on the relative intensities of various spectral bands and by measuring the transmission of the various filters. This method was checked by direct measurement with a calibrated photronic cell giving good agreement.

Results

The data obtained and results calculated are summarized in Table I.

TABLE I

PHOTOCHEMICAL RESULTS

Range (Å.) irradiated	*t*, °C.	Moles quanta l.-hr.	Total rate (*M*/hr.) × 10^4	Dark rate (*M*/hr.) × 10^4	Quantum yield
2537	−0.35	0.015	0.66	0.14	0.0035 ± 0.0007
2537	10.20	.032	9.4*	4.2*	.016 ± .006
2537	27.53	.016	17.7	13.3	.028 ± .008
2537	27.90	.038	74.4*	65.9*	.022 ± .014
2537	27.53	.012	15.5	13.3	.019 ± .010
2537	27.53	.013	15.7	13.3	.018 ± .009
3500–4800	−0.40	.041	1.32	0.14	.0029 ± .0006
4300–4900	10.50	.0078	1.42	0.91	.007 ± .004
4300–4900	27.62	.0089	16.3	13.5	.031 ± .014
4300–4900	27.93	.0070	15.8	14.2	.023 ± .017
4300–4400	27.65	.0039	14.8	13.5	.033 ± .028
3500–4800	27.65	.043	17.4	13.3	.010 ± .004
3300–3800	27.95	.0090	15.3	14.0	.013 ± .012
3300–7300	28.00	.12	31.5	14.0	.015 ± .003
5400–7300	−0.30	.073	2.18	0.14	.0029 ± .0006
5400–7300	10.50	.013	4.46	0.91	.027 ± .006
5400–7300	27.65	.029	18.8	13.8	.017 ± .004
5400–7300	27.93	.013	18.1	14.0	.032 ± .011

* Concn. of $Cr(ClO_4)_3$ 0.43 *M* and of $HClO_4$ 0.45 *M* instead of concentrations of both 0.10 *M* as in all other experiments.

The data in the table are arranged in three groups corresponding to the three absorption bands of $Cr(H_2O)_6^{+3}$. In all experiments, except the two marked with asterisks, the concentrations of both $Cr(H_2O)_6(ClO_4)_3$ and $HClO_4$ are 0.10 *M*. In the other two $Cr(H_2O)_6(ClO_4)_3$ is 0.43 *M* and $HClO_4$ is 0.45 *M*. In all experiments the rate of the isotope

(2) M. Linhard and M. Weigel, *Z. anorg. allgem. Chem.*, **266**, 49 (1951).

(3) J. Owen, *Proc. Roy. Soc.* (*London*), **A227**, 183 (1955); L. E. Orgel, *J. Chem. Phys.*, **23**, 1004 (1955); C. K. Jorgensen, *Acta Chem. Scand.*, **9**, 116 (1955).

(4) J. P. Hunt and R. A. Plane, THIS JOURNAL, **76**, 5960 (1954).

(5) W. G. Leighton and G. S. Forbes, *ibid.*, **52**, 3139 (1930); G. S. Forbes and L. J. Heidt, *ibid.*, **56**, 2363 (1934).

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exchange reaction is increased slightly on irradiation. The increase corresponds to a quite small quantum yield (molecules reacted per quantum absorbed) which is therefore subject to large experimental error. The probable limits of uncertainty placed on the resultant values of the quantum yield reflect, in most cases, only the ±5% uncertainty in measuring the reaction rates in the presence and absence of radiation. Within the rather large limits of error, there seems to be no dependence of quantum yield on wave length even though different absorption bands are irradiated.

It is seen from Table I that the quantum yield increases with increasing temperature. Although the results are too uncertain to permit accurate evaluation of the activation energy of the photochemical process, they are consistent with a value of 13 kcal. per mole for all three absorption bands. This value is about half of that found for the activation energy of the same reaction in the absence of light (26.7 kcal. per mole).[4]

In order to interpret the photochemical results, solutions of chromic perchlorate were checked for fluorescence.[6] Solutions of chromic concentrations 10^{-4} to 10^{-1} *M* were irradiated with a mercury arc lamp and observed (using either the eye or a photocell with photomultiplier) at right angles to the incident beam. Each of the three absorption bands was irradiated by using filters between the sample and the light source. When observed through a filter which passed only light of wave length longer than the incident beam, no light was detected even when the light source was very intense such as that obtained from the AH-5. Low temperature studies were made on solutions of $Cr(H_2O)_6(ClO_4)_3$ dissolved in isopropyl alcohol and frozen to a clear glass at liquid nitrogen temperature. Again no fluorescence was detected. It should be noted that the solutions in isopropyl alcohol must have a somewhat different absorption spectrum than the aqueous solutions since they appear green rather than violet.

Discussion

Although the rate of the exchange reaction of $Cr(H_2O)_6^{+3}$ is clearly increased by light absorption, the over-all quantum yield for reaction is quite small. The small yield might result from an extremely large "cage effect," but such an explanation does not seem probable for this particular reaction in which the solvent "cage" is itself a reactant. A more plausible explanation for the small quantum yield might involve a series of events somewhat similar to those described by Zimmerman to account for very small quantum yields (1.4×10^{-5} to 5.4×10^{-2}) for the photodecomposition of permanganate.[7] After excitation of $Cr(H_2O)_6^{+3}$ to any one of the three electronic states corresponding to the three absorption bands, it is expected that rapid radiationless transition should occur to the lowest lying of these, since all three are of the same spin multiplicity (quartet).[8] Since no fluorescence is observed for $Cr(H_2O)_6^{+3}$, it like MnO_4^- might well undergo further radiationless transition to a high vibrational level of the ground electronic state (also a quartet state). The question arises as to whether the exchange reaction occurs during the period of electronic excitation, or during the subsequent vibrational excitation. In the permanganate decomposition, it seems most probable that chemical reaction occurs during vibrational excitation. This conclusion is convincingly supported by the strong dependence of quantum yield on wave length of exciting radiation (5.4×10^{-2} molecules/quantum at 2537 Å. to 1.4×10^{-5} molecules/quantum at 5640 Å.) and the but slight dependence on temperature which increases with increasing wave length (at wave lengths below 4360 Å., no temperature dependence; at 5640 Å., activation energy 4 kcal. per mole).[7] Apparently for irradiation of MnO_4^- at shorter wave lengths, the greater amount of resultant vibrational energy is more efficient in bringing about reaction; at longer wave lengths, some thermal energy must be supplied. However, in the case of $Cr(H_2O)_6^{+3}$, essentially no dependence of quantum yield or activation energy on wave length could be detected. This fact together with the large activation energy observed seems to indicate a marked difference between the photoreactions of MnO_4^- and $Cr(H_2O)_6^{+3}$. In fact, the latter might well undergo reaction while in an electronically excited state.

That electronic excitation should affect reaction rate seems likely in terms of Taube's striking correlation of reaction rate and electronic configuration.[9] Whereas the normal $Cr(H_2O)_6^{+3}$ falls in Taube's class of "inert" complex ions, excitation of the 3d electrons, might be expected to produce a "labile" complex ion.[10] Furthermore, if the exchange reaction occurs while $Cr(H_2O)_6^{+3}$ is in an excited electronic state, the relatively large activation energy can be understood. This energy would correspond to the activation energy for the exchange of the excited species. In the case of other labile complex ion substitution reactions which have been studied by Bjerrum and Poulsen at very low temperatures,[11] activation energies are of the same magnitude. For example, an activation energy of 12.7 kcal./mole was determined for the reaction

$$Fe^{+3} + SCN^- \longrightarrow FeSCN^{+2}$$

However, if the temperature dependence of the present photochemical reaction is due to the excited species requiring activation energy for reaction, it is necessary that the excited species be relatively long lived. An activation energy of 13 kcal./mole would correspond, if the pre-exponential rate factor were the same as for the normal ion (5×10^{14} sec.$^{-1}$),[4] to a mean life for reaction of 6×10^{-6} sec. at 25°. This value should be compared with an estimate of the mean life of the excited state.

From the integrated intensity of absorption bands it is possible to obtain an estimate of the maximum mean lifetime of an excited state.[12]

(6) The aid of Dr. M. L. Hunt and Dr. A. C. Albrecht is gratefully acknowledged.

(7) C. Zimmerman, *J. Chem. Phys.*, **23**, 825 (1955).

(8) In molecules where fluorescence is observed, it is found to originate only from the lowest state of given multiplicity. G. M. Kasha, *Discs. Faraday Soc.*, **9**, 14 (1950).

(9) H. Taube, *Chem. Revs.*, **50**, 69 (1952).

(10) L. E. Orgel, *J. Chem. Soc.*, 4756 (1952).

(11) J. Bjerrum and K. G. Poulsen, *Nature*, **169**, 463 (1952).

(12) G. N. Lewis and M. Kasha, THIS JOURNAL, **67**, 994 (1945).

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Of the three absorption bands of $Cr(H_2O)_6^{+3}$ only the lowest energy state is considered, since it is assumed that there is quite rapid internal conversion from the higher states. This assumption is consistent both with previous fluorescence studies,[8] and with the observation that in the present case, the quantum yield does not depend upon which absorption band is irradiated. Such an estimate for the lowest energy band is 1.4×10^{-5} sec., which should correspond to the mean life of that state if the only mode for return to the ground state is direct fluorescence. The lack of fluorescence indicates that the actual lifetime of this state is many orders of magnitude less; in fact, too short for any detectable reaction to occur. However, the life time of electronic excitation may actually be much longer than the lifetime of the lowest excited quartet state. According to the spectral assignment of Finkelstein and Van Vleck for solid chrome alum,[13] there is a doublet state which lies fairly close to the lowest excited quartet state. If before conversion to the ground state, some of the excited $Cr(H_2O)_6^{+3}$ passed into such a spin forbidden state of long life time, it could well have sufficient time to undergo the chemical exchange reaction while still electronically excited.

Acknowledgment.—The authors would like to thank their colleagues for many helpful discussions concerning the interpretation of the results. We are especially indebted to Prof. R. Bersohn and Dr. A. C. Albrecht.

(13) R. Finkelstein and J. H. Van Vleck, *J. Chem. Phys.*, 8, 790 (1940).

ITHACA, N. Y.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Mechanism of Chemisorption: Ethylene and Ethane on Nickel

BY P. W. SELWOOD

RECEIVED AUGUST 23, 1956

Magnetization–volume isotherms have been obtained for ethylene and for ethane on a commercial nickel–kieselguhr catalyst, and for ethylene on a coprecipitated nickel–silica catalyst. Isotherms have also been obtained for hydrogen on a nickel surface already covered in part with chemisorbed ethylene, and for ethane on a surface already covered with hydrogen. It has been shown that if the d-band of the nickel in these catalysts gains one electron per chemisorbed hydrogen atom, the d-band gains on the average a little over two electrons for each ethylene molecule chemisorbed at room temperature. Admission of ethylene to nickel at higher temperatures is followed by dissociative adsorption or fragmentation. On a coprecipitated catalyst at 100° this fragmentation yields approximately a six-electron transfer per molecule of chemisorbed ethylene. Ethane at room temperature is chemisorbed on a bare nickel surface with somewhat more than a six-electron gain by the nickel per molecule of ethane. Ethane is not chemisorbed on a nickel surface already covered with hydrogen. In these catalyst systems there are three or four times as many nickel sites available to hydrogen as to ethylene, and over six times as many to hydrogen as to ethane. Admission of hydrogen to a nickel surface already covered with ethylene leads both to the formation of ethane and to the chemisorption of hydrogen.

The purpose of this work was to extend the method of magnetization–volume isotherms to ethylene, to ethane, and to certain aspects of the ethylene hydrogenation reaction.[1]

Experimental

All the results reported below were obtained by the induction method previously described.[1] Adsorptions were made and magnetizations were measured at 27° except as otherwise stated.

Two catalyst samples were used. One was Universal Oil Products Company nickel–kieselguhr hydrogenation catalyst, containing 52.8% nickel. This catalyst has an approximate surface area (B.E.T., N_2) of 175 sq. m. per g. The other catalyst was a coprecipitated nickel–silica prepared as described by Van Eyk Van Voorthuisjen and Franzen,[2] and designated by them CLA 5421. This sample contained 37.5% nickel, and had a surface area of about 200 sq. m. per g. Specific magnetization *vs.* temperature for samples similar to these already have been published.[1]

Each sample was reduced in flowing hydrogen before each series of measurements. Reduction was at 360° for 12 hr., followed by evacuation at 10^{-6} mm. for 1 hr. at 360°, and cooling *in vacuo* to 27°.

Hydrogen used for reduction and for adsorption measurements was purified as previously described,[1] as was the helium used for dead-space determination. The ethylene was Phillips Research Grade guaranteed to be 99.9+% pure. The ethane was Mathieson Technical Grade.

The results reported below were obtained on samples weighing 6 to 8 g.

Results

Figure 1 shows automatically recorded changes of magnetization observed when ethylene was flushed over evacuated U. O. P. catalyst, up to atmospheric pressure. The change is negative, that is, in the same direction as that caused by chemisorbed hydrogen on nickel at room temperature. The effect is, however, considerably smaller than that for hydrogen. This accounts for our failure to observe the effect for ethylene at room temperature in our first experiments in which the less sensitive Faraday method was used.[3] We did observe and report the effect of ethylene at higher temperatures, as described below.

It will be seen that there is a fairly large thermal transient caused by the heat of chemisorption. After temperature equilibrium had been reached the sample was evacuated with the result shown, namely, a small positive transient appeared. No permanent change of magnetization was produced by evacuation even though, as will be shown below, over half the ethylene was thus removed. This result merely shows, as is well known, that a large fraction of the ethylene adsorbed on nickel–silica at room temperature is held by van der Waals forces.

Figure 2 shows both magnetization–volume isotherms and, the more familiar, pressure–volume iso-

(1) P. W. Selwood, THIS JOURNAL, 78, 3893 (1956).

(2) J. J. B. Van Eyk Van Voorthuisjen and P. Franzen, *Rec. trav. chim.*, 70, 793 (1951).

(3) P. W. Selwood, S. Adler and T. R. Phillips, THIS JOURNAL, 77, 1462 (1955).

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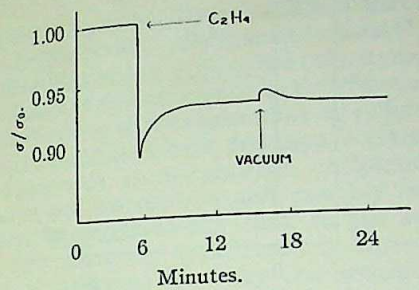

Fig. 1.—Automatic recording of magnetization changes during admission and evacuation of ethylene on nickel–kieselguhr.

therms for hydrogen on a U. O. P. catalyst sample. The result is similar to that already described for hydrogen on nickel,[1] but is needed here in connection with interpretation of the new results on ethylene hydrogenation.

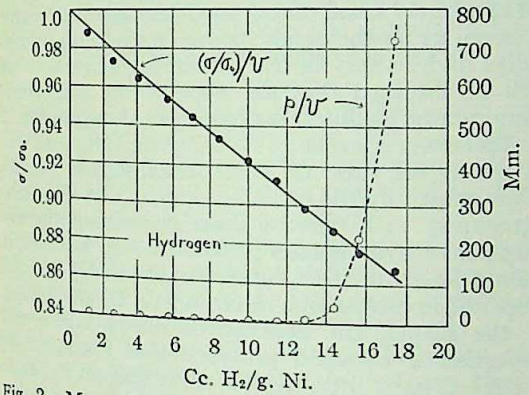

Fig. 2.—Magnetization–volume and pressure–volume adsorption isotherms for hydrogen on nickel–kieselguhr at 27°.

In Fig. 3 there are shown the results for ethylene adsorption on U. O. P. catalyst. After atmospheric pressure had been reached the sample was evacuated for 15 minutes. This resulted in the removal of considerable gas but with no change of magnetization. After a few minutes pumping no further gas could be removed, at room temperature. The volume of residual ethylene was then found by adding ethylene again up to atmospheric pressure. The total volume of ethylene first adsorbed was 10.8 cc. (S. C.) per g. of nickel. The volume taken up in the second addition was 6.0 cc. This was taken to mean that 4.8 cc. of ethylene remained chemisorbed on the sample. The second addition of ethylene caused no change of magnetization and was thereby proved to be all physical adsorption.

This procedure for finding the volume of residual chemisorbed ethylene ignores the fact that certain reactions may take place in this system at room temperature. One possibility is that of polymerization. But under the conditions and short time (15 min.) of the experiment it is hard to believe that polymerization could have introduced any serious error. Another possibility is that of self-hydrogenation. This, if occurring to any appreciable degree, could seriously impair the interpretations given below. The desorbed gas was therefore analyzed by absorption in bromine water. It was found

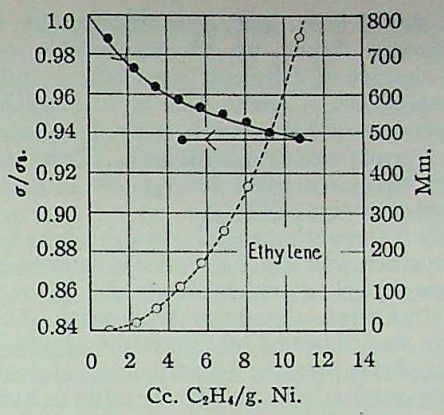

Fig. 3.—Magnetization–volume and pressure–volume adsorption isotherms for ethylene on nickel–kieselguhr at 27°.

found that no saturated hydrocarbon was present in sufficient amount to warrant consideration for the purposes of this work.

Two further points may be mentioned. All the adsorption results reported here are given for convenience in cc. of gas adsorbed (S. C.) per g. of nickel. It will be understood that the silica support must contribute to the van der Waals part of the total adsorption. The other point is that one may wonder why more ethylene cannot be pumped off if the pressure at 4.8 cc. residual ethylene is actually over 100 mm. as seems to be indicated in Fig. 3. But this was doubtless due to hysteresis in the desorption isotherm. The actual pressure at 4.8 cc. ethylene after desorption was very small.

Figure 4 shows the results for a hydrogen isotherm *over* the 4.8 cc. of chemisorbed ethylene, on the same sample as for Fig. 3.

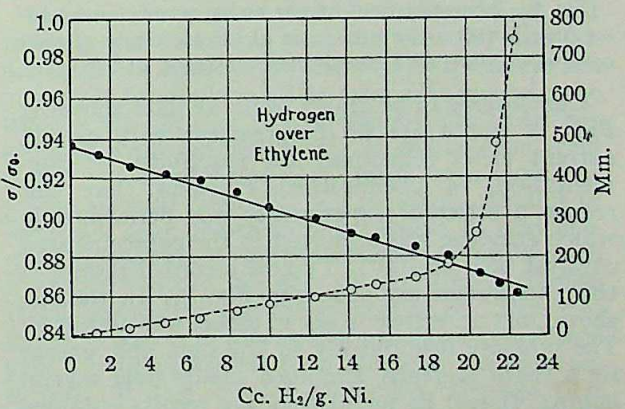

Fig. 4.—Magnetization–volume and pressure–volume isotherms for hydrogen on nickel–kieselguhr already partially covered with chemisorbed ethylene at 27°. The p–v isotherm shown has not been corrected for the modest amount of ethane present in the gas phase at the higher pressures.

In view of the rather unexpected result shown in Fig. 4, namely, that hydrogen may in fact be chemisorbed on a nickel surface already covered (so far as possible) with chemisorbed ethylene, this experiment was repeated on the coprecipitated catalyst. The results were qualitatively the same as shown in Fig. 4. The volume of chemisorbed ethylene, being in this case determined by removal of the excess by exhaustion through a Toepler

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pump, was 5.0 cc. per g. of nickel, the volume of hydrogen taken up to atmospheric pressure in the absence of ethylene was 22.0 cc., and in the presence of the ethylene 27.0 cc. Coprecipitated catalysts are subject to a very large magnetic change on exposure to hydrogen. For this catalyst the effect for hydrogen was the largest so far observed, namely, 48%.

Figure 5 gives ethane isotherms on a bare U. O. P. nickel surface, and Fig. 6 shows ethane isotherms on the same nickel on which about 12.5 cc. of chemisorbed hydrogen already was present. This last isotherm was obtained by first adding hydrogen up to atmospheric pressure over the bare catalyst, then pumping out for 15 min., that is, until the hydrogen pressure was a fraction of a mm. The ethane was then added in successive increments in the usual way.

Fig. 5. Fig. 6.

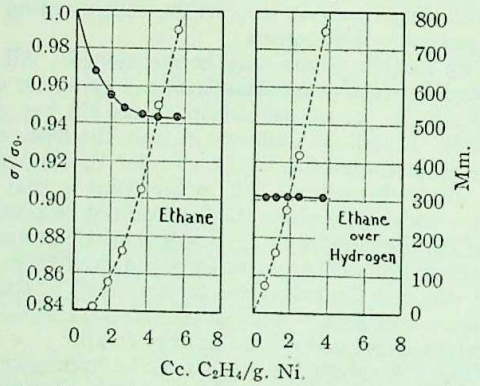

Fig. 5.—Magnetization–volume and pressure–volume adsorption isotherms for ethane on nickel–kieselguhr at 27°.

Fig. 6.—Magnetization–volume and pressure–volume adsorption isotherms for ethane on nickel–kieselguhr already covered (in part) with chemisorbed hydrogen, at 27°.

Conclusions to be drawn from the data shown in Figs. 3 and 4 are in disagreement with certain current views concerning the reactivity, or fragmentation, of chemisorbed ethylene. For this reason a series of experiments was performed in which ethylene was admitted to the coprecipitated catalyst held at 100°. Typical recorded results of this experiment are shown in Fig. 7. In the run shown, 6.2 cc. ethylene per g. nickel was admitted. The pressure rose quickly to 159 mm. and, except for a slight increase, remained steady over several hours. It will be noted that the results obtained in this experiment are in sharp contrast to those in which the ethylene is admitted to the nickel at room temperature, even though the quantity of ethylene chemisorbed in these cases is very nearly the same.

At the conclusion of the run shown in Fig. 7 the sample was cooled to 27°, evacuated to remove excess ethylene, and treated with hydrogen. The hydrogen uptake to atmospheric pressure was only 20.6 cc. and the magnetization fell to $\sigma/\sigma_0 = 0.58$.

Discussion

In a previous paper[4] we showed that the magnetization results are, in general, consistent with

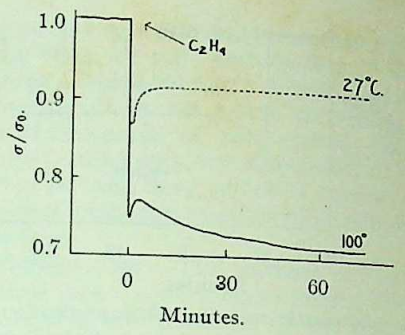

Fig. 7.—Automatic recording of magnetization changes during admission of ethylene on nickel–silica at 100°, as compared with admission at 27°.

the idea, often expressed, that each chemisorbed hydrogen atom contributes one electron to the nickel particle to which it becomes attached. The possible complication that hydride ions are formed on extremely small nickel particles does not greatly concern us on the catalysts and in the temperature range under study in the present investigation. It will be assumed that the slope of the magnetization-volume isotherm for hydrogen shown in Fig. 2 is, therefore, a measure of the adsorption condition in which the ratio of atoms chemisorbed to electrons gained by the nickel is unity. This view is in agreement with current ideas concerning the adsorption of hydrogen on palladium. If, however, it should be shown that formation of the Ni–H bond does not involve a one-electron gain by the d-band of the nickel, the conclusions drawn below will nevertheless be valid provided that formation of the Ni–C bond produces the same magnetic change as does the Ni–H bond. That this is a reasonable assumption is supported by consideration of the magnetic properties of coördination complexes involving metal–carbon bonds.

It will be noted that the initial slope of the magnetization isotherm shown for ethylene in Fig. 3 is a little larger than that for hydrogen. This is to say that the nickel gains on the average a little more than two electrons for every ethylene molecule chemisorbed. This is clear confirmation for the view that ethylene is, in the system studied, held principally by two-site attachment,[5] and that a moderate fraction of the ethylene dissociates hydrogen to occupy four or more sites—two for the dissociated hydrogen and two or more for the acetylenic residue.

One sees, however, that additional increments of ethylene have a smaller effect on the magnetization. It might be surmised that this is due to one-site attachment, but the easy removal of over half of the ethylene with no attendant change of magnetization shows clearly that a substantial fraction of the ethylene is held by van der Waals forces. The actual fraction of physically adsorbed ethylene at one atmosphere pressure is 55.5%.

It will be noted that the volume of chemisorbed ethylene is much smaller than the volume of hydrogen which may be adsorbed on the same catalyst. This observation has been made several

(4) L. E. Moore and P. W. Selwood, This Journal, 58, 695 (1954).

(5) J. Horiuti and M. Polanyi, *Trans. Faraday Soc.*, **30**, 1164 (1934); G. C. Bond and P. B. Wells, *Australian J. Sci. Res.*, **A4**, 385 (1951).

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times in the past, as has the implication that there are at least two kinds of nickel surface sites.[6,7] One class of sites is accessible to ethylene or to hydrogen, another class of sites is accessible to hydrogen alone. The actual fraction of sites accessible to ethylene is not readily determined with precision because hydrogen apparently is chemisorbed completely at pressures of one atmosphere and possibly higher. We believe it correct to say that, in the system studied here, there are approximately three sites accessible to hydrogen for every one accessible to ethylene. All the conclusions drawn for the U. O. P. catalyst are equally valid for the coprecipitated catalyst except that for the latter there are three and a half to four sites accessible to hydrogen for every site accessible to ethylene.

Turning now to the hydrogen isotherms obtained on a nickel surface already saturated with chemisorbed ethylene, as shown in Fig. 4, it will be seen that a very large volume of hydrogen is taken up. But, the total hydrogen taken up at one atmosphere pressure is 4.9 cc. greater than the volume of hydrogen adsorbed on a bare nickel surface at one atmosphere. This excess volume of hydrogen is the same as the volume of chemisorbed ethylene present. There can be little doubt that the excess hydrogen is used in the expected fashion to hydrogenate the ethylene, and this is confirmed by the appearance of ethane in the gas phase.

It is, of course, far from surprising to find that hydrogen reacts with ethylene to form ethane over a nickel catalyst. But if the fraction of hydrogen used in hydrogenation is actually 4.9/22.2 as indicated in Figs. 2 and 4, then after the addition of, say, 12 cc. of hydrogen the volume of ethane liberated should be 12 cc. $\times$ 4.9/22.2 = 2.6 cc. In a dead-space of 8.6 cc. this should exert a pressure of 230 mm., whereas the actual pressure was only 100 mm.

In the above calculation it has been assumed that the product ethane is not adsorbed. Turning to Figs. 5 and 6, one sees that while ethane is chemisorbed on a bare nickel surface it is not chemisorbed at room temperature in the presence of an adsorbed layer of hydrogen. Ethane is, however, physically adsorbed on such a catalyst surface at room temperature to the extent of almost 4 cc. per g. of nickel at one atmosphere. We have then a complete explanation for the pressure–volume isotherm shown in Fig. 4. After the addition of 12 cc. of hydrogen there has been formed 2.6 cc. of ethane. At a partial pressure of 100 mm. almost 1 cc. of this would be physically adsorbed. The remaining 1.6 cc. of ethane in 8.6 cc. dead space would exert a pressure of 140 mm., which is fairly close to that actually observed.

The above reasoning involves two assumptions: first, that the hydrogen is chemisorbed in more or less normal fashion in spite of the presence of ethylene and ethane and, second, that the hydrogen neither hydrogenates the ethylene preferentially nor is it adsorbed preferentially but rather that it reacts purely according to chance impact on the surface. Justification for these two assumptions follows.

The magnetization isotherm in Fig. 4 is a straight line with a negative slope. Yet replacement of a chemisorbed ethylene molecule by two atoms of hydrogen would produce either no change or a slight positive change of magnetization. There can, therefore, be no question that hydrogen is chemisorbed in the presence of ethylene. On the other hand, the regular increase of pressure with added hydrogen in Fig. 4 shows that the generation of ethane is linear with each increment of hydrogen. There seems little doubt that for approximately every four molecules of hydrogen taken up under the conditions of Fig. 4, one molecule is used to hydrogenate the ethylene.

Another observation in connection with Fig. 4 is that the slope of the magnetization isotherm is much less than that for the corresponding hydrogen isotherm shown in Fig. 2. It requires 2.4 atoms of hydrogen on a nickel–ethylene surface to lower the magnetization the same fraction as may be achieved by one hydrogen atom on a bare nickel surface. To express this in another way: if one electron is gained by the bare nickel for each hydrogen atom adsorbed, then one electron is gained by the nickel–ethylene surface for each 2.4 hydrogen atoms taken up.

The problem of interpretation now resolves itself into finding a structural relationship that will account for the following two observations: (1) the number of sites accessible to ethylene is only one-third of the number accessible to hydrogen, and (2) a net gain of one electron by the nickel during hydrogenation of ethylene requires 2.4 atoms of hydrogen.

Table I shows some possible configurations and mechanisms. Class (A) sites and class (B) sites are accessible to hydrogen; Class (A) sites alone are accessible to ethylene. The ratio e/H given in the table is the net gain of electrons by the nickel per atom of hydrogen taken up. It will be clear from Table I that situation (III) must be a close approximation to the truth. Of the sites accessible to hydrogen only one-third is accessible to ethylene, and the addition of eight atoms of hydrogen to such a surface yields a net gain of only four electrons. It will be recalled that the adsorption of ethylene as in Fig. 3 results in a little more than a two-electron gain by the nickel for each ethylene molecule adsorbed. If this modest correction is made then the ratio e/H for situation (III) in Table I is found to be almost exactly 1/2.4, as observed experimentally.

For the coprecipitated catalyst the corresponding figures for e/H are (before correction for some dissociation of the ethylene): calcd. 1.7 to 1.8; found, 2.2.

The conclusions drawn above are in sharp disagreement with the fact that the hydrogen–deuterium exchange reaction is strongly inhibited by the presence of chemisorbed ethylene on nickel, and the inference that hydrogen is not chemisorbed as atoms under these conditions.[6,8] None of the situa-

(6) G. H. Twigg and E. K. Rideal, *Proc. Roy. Soc.* (*London*), **A171**, 55 (1939).

(7) O. Beeck, A. E. Smith and A. Wheeler, *ibid.*, **A177**, 62 (1940).

(8) This poisoning effect of ethylene has been confirmed amply by several workers.

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TABLE I

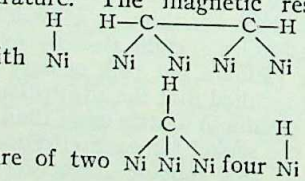
NET ELECTRON GAIN PER HYDROGEN ATOM TAKEN UP, FOR THREE DIFFERENT NICKEL–ETHYLENE SURFACE CONFIGURATIONS

		e/H
(I)	$H_2C{-}CH_2$ (A) + $2H_2$ → H H (B) + C_2H_6	0
(II)	$H_2C{-}CH_2$ (A) + H H (B) + $3H_2$ → H H (B) + H H (B) + C_2H_6	1/3
(III)	$H_2C{-}CH_2$ (A) + H H (B) + H H (B) + $4H_2$ → H H (B) + H H (B) + H H (B) + C_2H_6	1/2

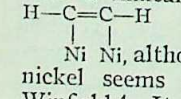
tions represented in Table I could be expected to poison the nickel surface for the hydrogen–deuterium exchange.

Our results for the mode of attachment of ethylene on a bare nickel surface are also in apparent disagreement with those reported by Pliskin and Eischens,[9] who on the basis of infrared absorption studies found extensive fragmentation of the ethylene. These workers did, however, find results in agreement with those reported here for ethylene adsorbed on a nickel surface containing some chemisorbed hydrogen.

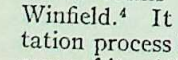
A clue to these discrepancies is found in the paper of Turkevich, *et al.*,[10] who found no poisoning by ethylene on nickel–kieselguhr at −78°, but marked poisoning on a nickel wire at 90°. This result suggests that some secondary reaction of the ethylene is responsible for the poisoning and this view is supported strongly by the results shown in Fig. 7. When ethylene is admitted to the catalyst at 100° the loss of magnetization is much greater than when admission is at room temperature. Furthermore, progressive fragmentation of the ethylene is readily followed for an hour or more until a steady state is reached corresponding to over six bonds to the nickel for every ethylene molecule adsorbed, instead of the two bonds found at room temperature. We have insufficient information to determine the nature of the adsorption complex formed at the higher temperature. The magnetic results are consistent with



with a mixture of two



four Ni and one



Ni, although carbon bonding to more than one nickel seems not to have been considered by Winfield.[4] It will be noted that after the fragmentation process had taken place the catalyst had lost some of its ability to adsorb hydrogen.

These results which demonstrate progressive fragmentation of the adsorbed ethylene clear up most of the difficulty mentioned above. When ethylene is admitted to bare nickel at low temperature it is adsorbed primarily by the familiar two-site attachment and in this way can exert little or no poisoning effect on the hydrogen–deuterium exchange reaction. As the temperature is raised fragmentation of the ethylene occurs; this results in increased occupation of nickel sites, and poisoning becomes marked. Whether or not poisoning becomes complete doubtless will depend on the initial ratio of sites accessible to hydrogen and to ethylene. The lower this ratio the more effective, it may be predicted, will poisoning become. Actually the coprecipitated catalyst on which fragmentation was demonstrated above was not the best choice to show this effect because the H_2/C_2H_4 ratio of accessible sites is fairly high.

In the work described here slight fragmentation of the ethylene was observed at room temperature, while extensive fragmentation is implied by the work of Eischens and by others. There is no real conflict here because the fragmentation process which is rapid at 100° must certainly occur also at room temperature. How much fragmentation occurs will depend on the intrinsic activity of the surface, on the time elapsed between admission of the ethylene and further testing of the surface (all room temperature experiments reported here were completed in less than one hour), and also on the rate of admission of the ethylene, the adsorption of which heats the nickel appreciably.

Pliskin and Eischens report evidence for the presence of adsorbed ethyl radicals on a sample to which first ethylene and then hydrogen was admitted. The results reported here do not deny this possibility. They do, however, require the added hydrogen to be used at random for hydrogenation and for chemisorption, and not for hydrogenation before chemisorption or *vice versa*. The results reported here are also not inconsistent with the view that ethylene is hydrogenated from the gas phase.

A few further conclusions may be drawn. From Fig. 5 it will be seen that the initial magnetization slope for ethane on bare nickel is twice that observed for ethylene and over four times that for hydrogen. The chemisorption of a molecule of ethane clearly involves a minimum four-site attachment, thus confirming the well-established dissociative mechanism for paraffin–deuterium exchange.[11] Actually the dissociation probably preceeds even further with some ethane molecules requiring six or more sites.

(9) W. A. Pliskin and R. P. Eischens, *J. Chem. Phys.*, **24**, 482 (1956).

(10) D. O. Schissler, S. O. Thompson and J. Turkevich, International Congress on Catalysis, Philadelphia, Sept. 10–14, 1956. Preprint Lecture 6.

(11) K. Morikawa, W. S. Benedict and H. S. Taylor, THIS JOURNAL, **58**, 1445, 1795 (1936).

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The total volume of ethane which may be chemisorbed appears (by comparison of Figs. 3 and 5) to be a little under half the volume of ethylene which may be chemisorbed. This result suggests that hydrogen dissociated during the chemisorption of ethane cannot (at room temperature) migrate to class (B) sites.

Figure 6 confirms the view that the relatively slow exchange reaction of paraffins with deuterium is due to the strong chemisorption of hydrogen on all sites which might otherwise be accessible to the paraffin molecules.[12]

Acknowledgment.—This work was performed under contract with the Office of Naval Research. It is a pleasure also to acknowledge the assistance of Dr. Jean A. Sabatka.

(12) J. Turkevich and H. S. Taylor, THIS JOURNAL, **56**, 2254 (1934).

EVANSTON, ILLINOIS.

[CONTRIBUTION FROM CLIMAX MOLYBDENUM COMPANY OF MICHIGAN]

Preparation and Characterization of a New Crystalline Form of Molybdenum Disulfide

BY RONALD E. BELL AND ROBERT E. HERFERT

RECEIVED FEBRUARY 26, 1957

During an investigation involving preparation of a quantity of synthetic molybdenum disulfide, X-ray techniques were applied to evaluate purity where ordinary wet chemical methods could not be used. The X-ray examinations indicated diffraction patterns differing from the pattern of natural molybdenite. An intensive study by single crystal X-ray techniques revealed that instead of the customary hexagonal molybdenum disulfide structure a hitherto unreported rhombohedral form of the compound had been prepared.

Introduction

The synthesis of molybdenum disulfide by chemical means has been described by a number of early researchers.[1-9] Such various methods of preparation as that proposed by Berzelius,[1] wherein molybdenum trisulfide is decomposed by vacuum heating; or the method of Svanberg and Struve,[2] involving reaction of molybdenum trioxide with hydrogen sulfide gas at red heat; the procedure of heating molybdenum and sulfur in an iron tube as proposed by van Arkel[3]; the procedure of de Schulten,[4] in which molybdenum trioxide, sulfur and potassium carbonate are fused together; the method used by Milbauer,[5] wherein molybdenum dioxide reacted with molten potassium thiocyanate; finally, Lander and Germer deposited molybdenum disulfide coatings from molybdenum carbonyl in atmospheres containing rather critical ratios of hydrogen sulfide and carbon monoxide; are among those listed in the literature.

In these earlier experiments evidence that molybdenum disulfide had been prepared synthetically was based on chemical analysis and, in some cases, also on microscopic examination. Van Arkel[3] reported Debye–Scherrer patterns identical to those obtained with natural molybdenum disulfide for his synthetic product. Other than this, there are no references in which the crystal structure of synthetic molybdenum disulfide has been established by modern crystallographic techniques.

A quantity of molybdenum disulfide of a purity that was not readily obtained by purification of the natural product was required at the authors' laboratory for standardization as to physical, chemical and mechanical properties; therefore, it was proposed to prepare the material by chemical synthesis.

As will be shown, it developed that the material eventually prepared differed from natural molybdenum disulfide in that the crystal structure was not the same.

Experimental

Preparation.—After experimenting with several of the procedures described in the literature and finding them to yield products unsatisfactory for this investigation, the procedure described by de Schulten[4] was applied to the preparation of the subject material. Briefly, this procedure is as follows: four parts by weight of potassium carbonate (reagent grade) are fused with six parts by weight of flowers of sulfur in a 250-ml. covered porcelain crucible at 675°, the reaction being conducted in a gas-fired furnace until evolution of sulfur dioxide is complete. The crucible and contents are removed from the furnace (taking precaution to avoid thermal shock) and allowed to cool. One part of sublimed molybdenum trioxide is added and the crucible is reheated at 900° for 30 minutes. Additional molybdenum trioxide is added in the same manner and the contents of the crucible are reheated at 900° after each addition, until a total of six parts by weight of molybdenum trioxide has been added. The entire mass is solidified, and the excess reagents and impurities are removed from the molybdenum disulfide by prolonged boiling with dilute ammonia, followed by washing with distilled water, boiling for a short time (20 to 30 min.) in dilute hydrochloric acid, and finally, by thorough washing with water, alcohol and ether. The material is then vacuum dried at 75°. The above treatment will not remove the MoO_2 impurity.

Purification.—The chemical reaction involved in de Schulten's method for synthesizing molybdenum disulfide is believed to proceed in two steps

$$2MoO_3 + S \longrightarrow 2MoO_2 + SO_2 \quad (1)$$

$$MoO_2 + 3S \longrightarrow MoS_2 + SO_2 \quad (2)$$

(It is assumed that potassium carbonate merely acts as a flux without actually entering into the reaction.)

The procedure just described includes measures which were intended to remove all ammonia and acid-soluble impurities. Upon X-ray diffraction examination of the product, the only detectable impurity not removed by this treatment was molybdenum dioxide.

The presence of molybdenum dioxide as an impurity in the product may be attributed to inhomogeneities in the fusion mass which result in local deficiencies of available

(1) J. J. Berzelius, *Pogg. Ann.*, **7**, 261 (1826).
(2) L. Svanberg and H. Struve, *J. prakt. Chem.*, **44**, 257 (1848).
(3) A. E. van Arkel, *Rec. trav. chim.*, **45**, 442 (1926).
(4) A. de Schulten, *Bull. soc. mineral. France*, **12**, 545 (1889).
(5) J. Milbauer, *Z. anorg. Chem.*, **42**, 441 (1904).
(6) M. Guichard, *Compt. rend.*, **129**, 1239 (1899).
(7) H. Arctowski, *Z. anorg. Chem.*, **8**, 213 (1895).
(8) M. Guichard, *Anal. Chem. Phys.*, [7] **23**, 498 (1901).
(9) J. J. Lander and L. H. Germer, *AIME Tech. Pub.* 1505 (1941).

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sulfur with subsequent failure of the reaction to go to completion.

A satisfactory method was not developed, despite many attempts, which would result in complete reaction of the MoO_2 with sulfur (eq. 2) to form MoS_2. The products of all the experiments contained various amounts of molybdenum dioxide with the molybdenum disulfide product.

No suitable method was found for detecting and estimating the molybdenum dioxide content by chemical means. However, by means of X-ray diffraction examination, the presence of molybdenum dioxide was determined readily (Fig. 2A).

In order to utilize X-ray methods for quantitative determinations of molybdenum dioxide in molybdenum disulfide, mixtures of known molybdenum dioxide and molybdenum disulfide contents were prepared. A direct reading X-ray spectrometer with copper radiation at 50 kvp.-16 ma. and a nickel filter was used to obtain X-ray diffraction patterns for samples containing 2.135, 5.31 and 9.36% molybdenum dioxide by weight. The X-ray intensity for the molybdenum dioxide phase was based on the absolute intensity of the (110) reflection from the molybdenum dioxide phase.

To reduce the lower limit of detection of the molybdenum dioxide phase in a mixture with molybdenum disulfide, specimens containing known amounts of the dioxide and the disulfide were compressed into pellets at a stress of 12,000 p.s.i. The application of stress to the powder mixture resulted in preferred orientation of the phases present. Preferred orientation of the dioxide phase resulted in greater intensity of the (110) planes compared to that of the randomly distributed powder. The development of preferred orientation in the powder mixture is, of course, highly dependent upon such factors as powder particle size, purity, method of compression and the total stress exerted on the mixture.

X-Ray diffraction data on pellets containing preferredly oriented molybdenum dioxide yielded a sensitivity of 325 counts per second per per cent. molybdenum dioxide contained in the mixture. Thus, the lower limit of detection was placed at about 3.25 counts per second, or 0.01% molybdenum dioxide. Figure 1 represents a plot of the absolute intensity of the (110) reflection from molybdenum dioxide as a function of concentration of molybdenum dioxide in a mixture with molybdenum disulfide.

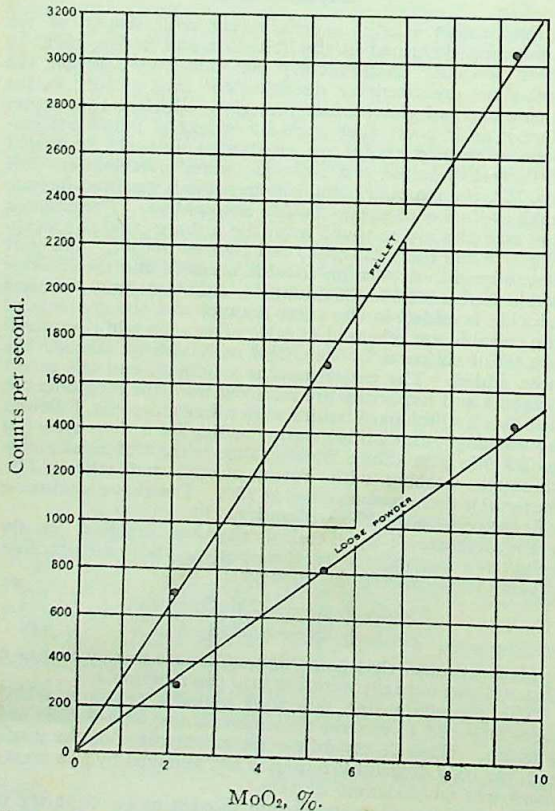

Fig. 1.—X-Ray calibration curve for determination of MoO_2 in MoS_2.

In order to remove the molybdenum dioxide present as impurity in the synthetic product, a procedure similar to that developed by Milbauer[5] was employed. Briefly, this consists of digesting the synthetic molybdenum disulfide in molten potassium thiocyanate, followed by digestion with dilute aqueous ammonia and dilute hydrochloric acid as previously described. This method was successful in decreasing the molybdenum dioxide content to a level below 0.01%, the limit of X-ray diffraction analysis. This treatment did not affect the crystallinity of the product.

Chemical Analysis of the Product.—A total of about 1500 g. of synthetic molybdenum disulfide was prepared and purified as described above. On the basis of the amount of molybdenum trioxide used, this represents a recovery of about 45%.

The product was analyzed by quantitative chemical methods for total molybdenum, total sulfur, carbon, titanium, insolubles and silica. The titanium was believed to result from the decomposition of the glaze on the porcelain crucibles. The results of these analyses are summarized in Table I.

TABLE I

CHEMICAL ANALYSIS OF SYNTHETIC MOLYBDENUM DISULFIDE

	Assay, %
Total molybdenum	60.17
Total sulfur	39.87
Carbon	0.04
Titanium	.005
Insolubles (including Ti as TiO_2 and most of the SiO_2)	.16
Silica	.10

X-Ray fluorescence analysis of the synthetic molybdenum disulfide showed the material to contain 59.9% molybdenum, which is in close agreement with the value obtained by chemical analysis as shown above.

Silicon and titanium in small amounts were the only impurities revealed by a semi-quantitative optical spectrographic analysis.

Crystallographic Examination.—During the processes of verifying the purity of product and determining of crystallinity by X-ray diffraction techniques, a marked difference was noted between the diffraction patterns obtained from the natural molybdenum disulfide and the synthetic molybdenum disulfide. The synthetic molybdenum disulfide exhibited differences in the reflections occurring in the vicinity of the $(10\,l + 2)$ reflections of the natural material (Figs. 2B and 2C). Instead of the (103), (105) and (107) reflections characteristic of the natural MoS_2, the synthetic material had doublets centered about the normal reflection position for the (103), (105) and (107) planes.

Crystallographic data describe natural molybdenum disulfide as a hexagonal layered structure. It has a dihexagonal dipyramidal unit cell with two molecules per unit cell. It is further characterized as a "P" Bravis lattice with a $P6_3/mmc$. symmetry. Under these limitations no reflections could occur at the positions found in the diffraction pattern from the synthetic molybdenum disulfide. Either an abnormality exists in the atomic positions of the unit cell or there is an entirely different crystal structure present. Due to the complexity of the diffraction pattern, structure determination from the powder patterns was not attempted.

Since crystal structure is determined most readily by single crystal X-ray techniques, an attempt was made to obtain crystals large enough for analysis. A single crystal platelet with a trigonal outline was obtained from one of the melts. A transmission Laue pattern was obtained from this crystal. This showed a threefold symmetry, instead of the sixfold symmetry characteristic of the naturally occurring molybdenum disulfide. This same crystal was used for obtaining both 0-level and 1-level Weissenberg photographs with rotation about an axis parallel to one of the edges of the three-sided crystal and also a rotation and 0-level Weissenberg photograph about an axis normal to one of the edges.

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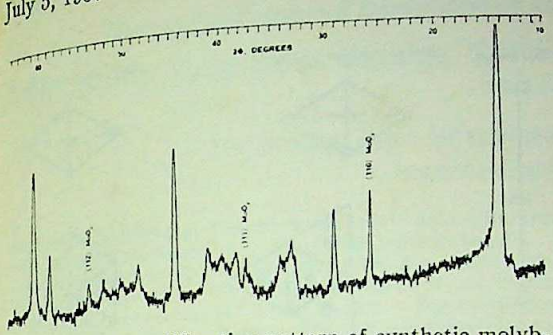

Fig. 2A.—X-Ray diffraction pattern of synthetic molybdenum disulfide containing molybdenum dioxide (copper radiation, 50 kvp-16 ma. nickel filter).

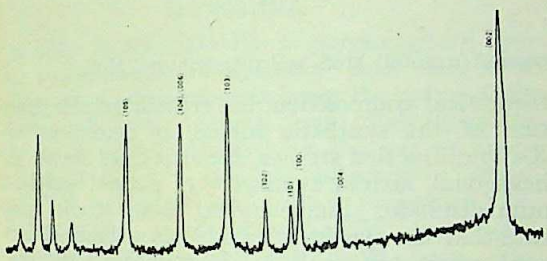

Fig. 2B.—X-Ray diffraction pattern of purified naturally occurring molybdenum disulfide.

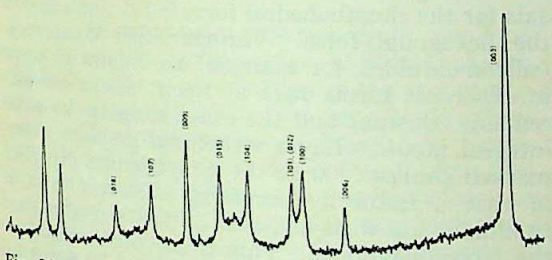

Fig. 2C.—X-Ray diffraction pattern of synthetic molybdenum disulfide with (*hkl*) as designated.

Indexing of these photographs showed that only reflections with $h + k + l = 3n$ were present. This indicated the presence of a rhombohedral lattice which is also in harmony with the threefold axis symmetry of the Laue photograph. Therefore, the crystal was assigned an "R" Bravis lattice with a "3m" symmetry. Referred to the hexagonal lattice, the *a*-axis was found to be identical with that of natural molybdenum disulfide. However, the *c*-axis of the rhombohedral was found to be 1.5 times greater. This means that the (002), (004) and (006) reflections of the hexagonal type would now correspond to (003), (006) and (009) for the rhombohedral lattice. The transformation from hexagonal to rhombohedral axis is H = *h*, K = *k* and L = 3/2 *l*.

The appearance of the doublets in the Debye–Scherrer pattern for the (103), (105) and (107) reflections of the natural molybdenum disulfide are now fully explained by the rhombohedral symmetry. The (101) plane of the hexagonal symmetry now becomes the (101) and (012) reflections of the rhombohedral planes. Similarly, the (103) is replaced by (104) and (015), and the (105) by (107) and (018). The (001) reflections of the rhombohedral type show a very slight displacement away from the zero beam. Positional measurements of the powder photograph peaks of hexagonal (008) and rhombohedral (0012) reflections are, respectively, 1.540 and 1.533 Å.

The unit cell of the molybdenum disulfide has two molybdenum atoms at $^2/_3$, $^1/_3$, 0; and $^1/_3$, $^2/_3$, $^1/_2$, which places them on the two vertical axes. Pairs of sulfur atoms are on these same vertical axes, one above and one below each molybdenum atom at a distance of $^1/_8$ (equivalent to 4.61 Å.), as shown in Fig. 3. The three molybdenum atoms in the rhombohedral unit would have to lie on three vertical threefold axes and could be placed at 000; $^2/_3$, $^1/_3$, $^1/_3$; and $^1/_3$, $^2/_3$, $^2/_3$, with a sulfur atom above and below each molybdenum atom at a distance of $^1/_4$ (equivalent to 4.61 Å.). Both types would have the same interatomic distances, but in the hexagonal form the molybdenum atom would lie at the center of a trigonal prism, with the three upper sulfur atoms directly above the three lower sulfur atoms. In the rhombohedral form, the three sulfur atoms above would be in alternate positions with respect to the three below, that is, rotated 60°.

There is also an alternative description possible for the hexagonal molybdenum disulfide atoms. The molybdenum atoms could be located on the threefold symmetry axes alternating with pairs of sulfur atoms 3.08 Å. apart. However, this description does not apply to the rhombohedral form—there are no sulfur pairs.

In order to compare the relative intensities obtained from the powder patterns, theoretical determinations were made for the atomic contributors to the (00 *l*) reflections. Using the parameter ($^1/_4$) for the sulfur atoms the contributors to the (00 *l*) reflections of the synthetic molybdenum disulfide would be

(003)	Mo
(006)	Mo − 2S
(009)	Mo
(0012)	Mo + 2S
(0015)	Mo
(0018)	Mo − 2S
(0021)	Mo

There is reasonably good correlation between the theoretical values obtained from the structure factor determinations for intensities and those observed on the powder patterns. A comparison of the "*d*-values" and relative intensities for the natural and synthetic molybdenum disulfides is presented in Table II.

TABLE II

COMPARISON OF THE "*d*-VALUES" AND RELATIVE INTENSITIES FOR HEXAGONAL MOLYBDENUM DISULFIDE AND RHOMBOHEDRAL MOLYBDENUM DISULFIDE

Molybdenum disulfide (hexagonal)			Synthetic molybdenum disulfide (rhombohedral)		
hkl	*d*, Å.	I/I_1	*hkl*	*d*, Å.	I/I_1
002	6.16	100	003	6.18	100
004	3.00	50	006	3.05	3
100	2.71	70	100	2.72	19
101	2.63	50	101, 012	2.64	14
102	2.52	70			
103	2.26	100	104	2.359	18
			015	2.205	20
006, 104	2.04	50	009	2.051	11
			107	1.897	9
105	1.83	70			
			018	1.766	5
106	1.75	20			
			109	1.703	1
110	1.58	50	110	1.586	15
112, 008	1.54	70	0012, 1010	1.534	18
107	1.48	20			
			0111	1.429	1
200	1.36	20	200	1.369	2
			203	1.314	2
202	1.29	70			
			204	1.286	2
203	1.25	50		1.253	5
116	1.22	50		1.228	3
0010	1.19	50		1.217	2

Density of Rhombohedral and Hexagonal Molybdenum Disulfide.—Since it has been established definitely that synthetic molybdenum disulfide prepared by the procedures described has a crystal structure related to, but decidedly different from, that of natural molybdenum disulfide, the

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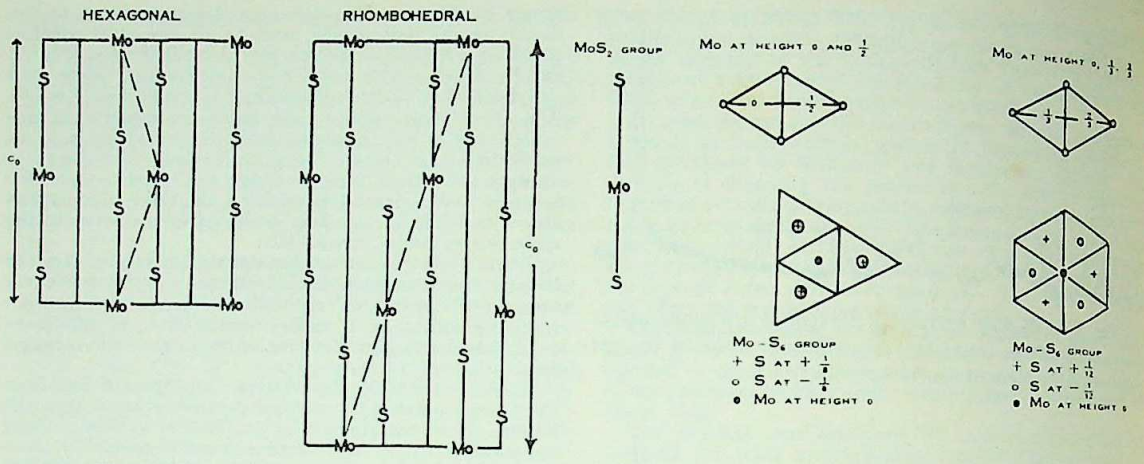

Fig. 3.—Comparison of single crystal structures of hexagonal (natural) MoS_2 and rhombohedral MoS_2.

theoretical density of the newly discovered crystallographic form was computed from X-ray measurement of the interplanar spacings. Computation of the theoretical density is based on the relation

$$\rho = \frac{1.6602 \times M \times \text{at. wt.}}{\text{volume}}$$

where $M = 3$, the number of atoms per unit cell. Lattice parameter measurements permit determination of the volume of the unit cell. The lattice parameters and theoretical density of rhombohedral molybdenum disulfide are presented in Table III.

TABLE III

DENSITY OF RHOMBOHEDRAL MOLYBDENUM DISULFIDE

X-Ray reflections for lattice parameter meas. (*hkl*)	Angle of diffraction 2θ, deg.	Lattice parameters, Å. *c*-axis	*a*-axis	Density, g./cm.³	
0021	123.35	18.375			
118 and 0021	88.82	18.375	3.16	5.025	
0018	97.90	18.390		Av. =	5.024
118 and 0018		18.345	3.171	5.022	±0.002
Hexagonal					
Natural MoS_2[a]				5.05	
Natural MoS_2[a]				4.9951	±0.008
Repurified MoS_2 obtd. from molybdenite, computed from X-ray diffraction measurements				4.96	±0.03

[a] Gmelin's "Handbuch, System No. 53, Molybdän," p. 183.

Conclusion

In the course of preparing molybdenum disulfide by synthetic methods, a product has been made which resembles natural molybdenum disulfide, but is of higher chemical purity. However, the synthetic sulfide has a crystal form different from that of the natural sulfide. Although the chemical composition of the synthetic sulfide coincides with the theoretical composition, the crystallographic structure of the synthetic sulfide, as determined by X-ray diffraction studies, does not have the normal hexagonal, sixfold symmetry of natural molybdenum disulfide. Single-crystal X-ray studies indicate that the synthetic sulfide has a threefold trigonal symmetry with a rhombohedral unit cell. The lattice parameter of the *a*-axis is identical for the two crystal forms, but the parameter of the *c*-axis for the rhombohedral form is 1.5 times that of the hexagonal form. Various other compounds (silicon carbides, for example) are known to occur in allotropic forms such as these, where one axis remains constant and the other increases by some integral factor. Layer structured graphite shows marked similarity with the molybdenum disulfide, in that a naturally occurring allotropic form is rhombohedral with its *c*-axis 1.5 times greater than the hexagonal form. This is the first indication, however, of the existence of allotropic forms of molybdenum disulfide.

In view of the crystal structure, it is suggested that other crystallographic forms of the sulfide could exist, depending upon the mode of preparation.

The various lubrication studies performed in an attempt to compare naturally occurring molybdenum disulfide and synthetic molybdenum disulfide showed the two had essentially the same lubricating qualities.

For all practical purposes, the theoretical densities of the synthetic disulfide and the natural hexagonal disulfide are equal.

Acknowledgments.—Our appreciation is due Dr. L. S. Ramsdell, Department of Mineralogy, University of Michigan, for the single crystal Weissenberg photographs and interpretations.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

Studies of the Tungsten-containing Species Present in Acidified Sodium Tungstate Solutions[1]

BY DONALD JOHN BETTINGER[2] AND S. YOUNG TYREE, JR.

RECEIVED DECEMBER 19, 1956

Rayleigh turbidities and differential indices of refraction were measured and weight average ionic weights were calculated for sodium tungstate solutions acidified with perchloric acid. Aggregation or polymerization of the tungstate species as the solution is acidified is verified by this technique. Although the degree of polymerization does not change suddenly at certain H^+/WO_4^{2-} ratios, the change in degree of polymerization is not so uniform as to exclude the possibility of predominant species at certain H^+/WO_4^{2-} ratios. Some evidence for an intermediate predominant species between the monomer and hexamer is cited. Definite evidence is obtained for continued polymerization beyond the hexamer toward a possible dodecamer. The extent of polymerization beyond the hexamer is dependent both on H^+/WO_4^{2-} ratio and total tungsten concentration. It appears to be possible to use the light scattering technique to study the rate of polymerization of freshly prepared tungstic acid up to the point where precipitation commences.

Introduction

In order to elucidate the isopolytungstate system measurements of diffusion[3] and dialysis[4,5,6] coefficients of solutions containing the polyanionic species have been carried out. Polytungstate solutions have been studied by the use of spectrophotometric,[3,7-9] conductometric,[7,9,10] cryoscopic,[11,12] isopiestic[13] and pH[9,14] measurements. Thermometric,[7] conductometric,[7-9,15] and potentiometric[6,8,9,11,15,16] titrations have been employed in studies of these solutions. Self-diffusion[17] studies have been made over a limited range of concentrations.

It may be regarded as certain from the forementioned studies that as acid is added to a solution of $Na_2WO_4 \cdot 2H_2O$ polymerization of the monotungstate ion commences. The first very predominant species is the hexatungstate although, as Jander predicted and Anderson's, Biehler's and Pan and Hseu's data indicate there is reason to believe an intermediate predominant species may exist between the monotungstate and the hexatungstate. According to Jander depending on the concentration of the tungstate solution and the hydrogen ion concentration an equilibrium either between $HW_6O_{21}^{5-}$ and $H_3W_6O_{21}^{3-}$ or between $HW_6O_{21}^{5-}$ and a dodecatungstate apparently exists.

The question arises as to whether there are rather sharp lines of demarcation between the point where a given species is predominant and another species is predominant or whether there are no predominant species at any time. Also if predominant species exist the question arises as to what factors cause a change in the species predominant at a given time. Jander[4] has set ranges of pH and concentration in which he believes a given species to be very predominant.

This paper deals with the application of the light scattering and related techniques to a study of sodium tungstate solutions of several concentrations to which various amounts of perchloric acid are added. If polymerization of monotungstate does take place with increase in hydrogen ion concentration it should prove possible to follow the change in weight average ionic weight of the isopolytungstate species with change in H^+/WO_4^{2-} ratio. Likewise some indication as to the effect of tungstate concentration on the degree of polymerization at a given H^+/WO_4^{2-} ratio may be available from these studies.

Experimental

Instruments.—A standard Phoenix Precision Instrument Company differential refractometer designed according to Brice[18] was used to obtain differences between the refractive indices of the solution and solvent as the concentration of the solution was varied. This instrument was standardized using standard sucrose solutions and light of wave length 589 mμ from a sodium lamp source.

Turbidity measurements were made using a light scattering photometer fabricated in this Laboratory, similar in design to that described by Brice,[19] and calibrated using purified thiophene-free benzene, the absolute turbidity of which is given by the National Bureau of Standards[20] as 46×10^{-6} cm.$^{-1}$. Carbon tetrachloride, as would be expected if the instrument were functioning correctly, showed no dissymmetry.

Since the light scattering photometer was standardized using benzene and employed for aqueous solutions the usual correction was applied to account for the difference between the refractive index of benzene and that of water.[21,22]

A Leeds and Northrup line operated pH meter was used for potentiometric titrations, while a Beckman Model G pH meter was used to determine the pH of the polytungstate solutions. The meters were standardized against known buffer solutions.

Chemicals.—The chemicals were C.P. or reagent grade except for the sodium tungstate which in addition to being reagent grade met the specifications according to Dr. Folin.[23]

(1) Abstracted from the Ph.D. dissertation of Donald John Bettinger. Presented at the Fall Meeting of the American Chemical Society, Atlantic City, New Jersey, September, 1956.

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Results and Calculations

Debye[24,25] has derived the expression for the turbidity of dilute solutions. It can be expressed as

$$\tau = \frac{32\pi^3 Mcn_0^2}{3\lambda^4 N}\left(\frac{n - n_0}{c}\right)^2 \quad (1)$$

where M equals the weight average ionic or molecular weight of the solute. Let

$$H = \frac{32\pi^3 n_0^2}{3\lambda^4 N}\left(\frac{\Delta n}{\Delta c}\right)^2 \quad (2)$$

Then

$$\tau = HMc \text{ or } Hc/\tau = 1/M \quad (3)$$

Equation 3 is for ideal solutions. The addition of the term $2Bc/RT$, where B is an empirical constant which expresses the interaction between the solvent and the individual segments of dissolved polymer molecules, gives an equation for non-ideal solutions.

$$Hc/\tau = 1/M + 2Bc/RT \text{ or } c/\tau = 1/MH + 2Bc/RTH \quad (4)$$

If c/τ is plotted against c and a straight line is drawn through the points and extrapolated to zero concentration then the intercept represents the value of c/τ at infinite dilution and is equal to $1/MH$ or in other words

$$(c/\tau)_{c=0} = 1/MH \text{ or } M = 1/H\,(c/\tau)_{c=0} \quad (5)$$

Thus by plotting two graphs (1) Δn *versus* c in order to obtain the slope and thus $\Delta n/\Delta c$ so that H can be calculated and (2) c/τ *versus* c and extrapolate to $c = 0$ to obtain $(c/\tau)_{c=0}$ it is possible to calculate M, the weight average molecular or ionic weight of the solute.

Δn for a given sodium tungstate solution to which a certain amount of perchloric acid has been added is corrected by subtracting a Δn for the sodium perchlorate formed assuming complete consumption of the acid to form sodium perchlorate. The corrected Δn is divided by the appropriate Δc expressed in g./cc. and the value is squared to obtain $(\Delta n/\Delta c)^2$ which is used in the equation for M.

The τ value used in the equation for M is obtained from the τ value for the solution, determined experimentally for a given sodium tungstate solution to which a certain amount of perchloric acid is added, by subtracting a τ value for the sodium perchlorate formed assuming complete conversion of acid to salt. The tungstate concentration expressed in g./cc. is divided by the corresponding corrected τ value to obtain c/τ for a given concentration and H^+/WO_4^{2-} ratio. c/τ values are obtained for concentrations ranging from 0.5 to 0.025 molar in sodium tungstate and 1/2 to 3/2 H^+/WO_4^{2-} ratio. For a given H^+/WO_4^{2-} ratio these values are plotted against c in g./cc. A straight line is drawn through the points and extrapolated to zero concentration to obtain $(c/\tau)_{c=0}$ needed in the equation for M.

The assumption as to what constitutes the solute is important. The two extreme cases would be (1) to calculate c/τ as if the solute were WO_4^{2-} neglecting the excess Na^+ over and above that accounted for in the $NaClO_4$ or (2) to calculate c/τ as if the solute were Na_2WO_4 neglecting the Na^+ accounted for in the $NaClO_4$. The true value of the solute is somewhere between these extremes. In all cases the H^+ is neglected. This is justified since in many cases the solutions are approximately neutral. In those cases where the H^+/WO_4^{2-} ratio is 7/6 or more and the pH of the solution is in the acid region the hydrogen ion concentration is still negligibly small as compared to the tungstate ion and sodium ion concentrations. Any hydration of the tungstate ion is neglected as being too uncertain to incorporate in these calculations.

Determinations of the weight average ionic weight of Na_2WO_4 in solution and the weight average molecular weight of raffinose in solution were made to check the sensitivity and resolution of the photometer. These proved quite satisfactory as indicated in Table II.

TABLE I

SAMPLE DATA FOR SOLUTIONS WITH H^+/WO_4^{2-} RATIO 3/2

Concn. of Na_2WO_4, g./cc.	Concn. of WO_4^{2-}, g./cc.	Na_2WO_4 $c/\tau \times 10^{-2}$	WO_4^{2-} $c/\tau \times 10^{-1}$
0.1470	0.1240	0.6691	0.5644
.1176	.0992	.8134	.6872
.0882	.0744	.9476	.8009
.0735	.0620	1.0135	.8570
.0588	.0496	1.0877	.9146
.0294	.0248	1.2030	1.0135
.0074	.0062	1.3102	1.0877
		H	$(c/\tau)_{c=0}$
For Na_2WO_4 as solute		2.61×10^{-6}	1.360×10^2
For WO_4^{2-} as solute		3.69×10^{-6}	1.137×10^2

Sample calculation

$M = 1/H(c/\tau)_{c=0}$ according to eq. 5

$M = 1/(2.61 \times 10^{-6})(1.36 \times 10^2)$

$M = 2820$

TABLE II

WEIGHT AVERAGE IONIC WEIGHT OF TUNGSTEN-CONTAINING SPECIES[a]

H^+/WO_4^{2-} ratio	Na_2WO_4 for solute	WO_4^{2-} for solute	Theoretical
1/2	613	519	
2/3	839	709	$W_3O_{11}^{4-} = 728$
5/6	1026	860	
1/1	1254	1062	
7/6	1684	1405	$HW_6O_{21}^{5-} = 1441$
4/3	2073	1723	
3/2	2820	2380	$W_{12}O_{40}^{8-} = 2848$
	Na_2WO_4	271	$WO_4^{2-} = 248$

[a] The weight average molecular weight for raffinose was found to be 584. The theoretical value for hydrated raffinose is 594 and for anhydrous raffinose is 504.

Table I contains sample data and sample calculations for solutions with H^+/WO_4^{2-} ratio 3/2. Table II shows the weight average ionic weight for the solute at the various H^+/WO_4^{2-} ratios studied.

Discussion

The data given in Table II verify the fact that aggregation or polymerization of the tungstate species takes place as the solutions are acidified. Note the agreement between the observed values at the 2/3 and 7/6 ratios and the theoretical values for octatungstate and heptamer, respectively.

(24) P. Debye, *J. Appl. Phys.*, **15**, 388 (1944).

(25) P. Debye, *J. Phys. Chem.*, **51**, 18 (1947).

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Figure 1 is a plot of τ, turbidity, *versus* H^+/WO_4^{2-} ratio. The rate of increase of τ increases above the 7/6 ratio in all cases. This increase is more striking the greater the total tungsten concentration. It would seem from these observations that an equilibrium exists between the tungsten-containing species (hexamer) found at a H^+/WO_4^{2-} ratio of 7/6 and a larger species, possibly the dodecamer, such that this larger species becomes increasingly more predominant not only as the 3/2 ratio is approached but also as the total tungsten concentration is increased. In other words, for a given ratio above 7/6 the more concentrated the solution the more predominant the larger species.

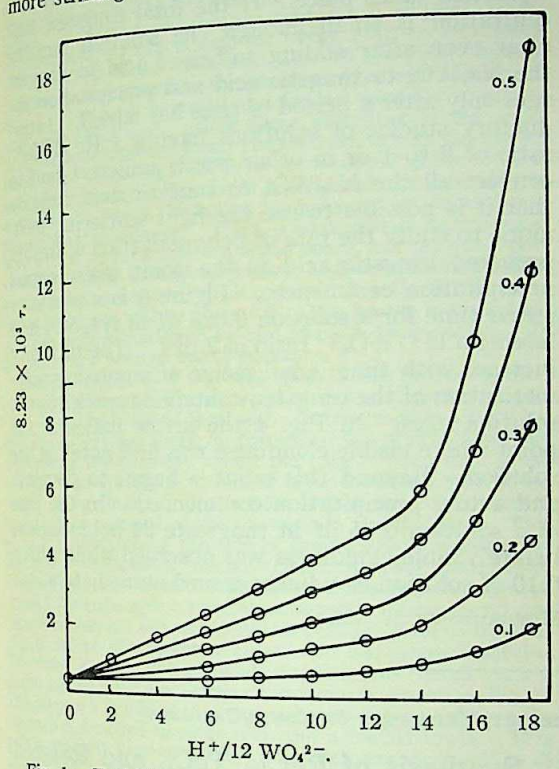

Fig. 1.—Turbidity, τ, as a function of H^+/WO_4^{2-} ratio for solutions 0.1, 0.2, 0.3, 0.4 and 0.5 M in sodium tungstate.

Figure 2 is a plot of Δn, the difference between the index of refraction of the solution and solvent, *versus* H^+/WO_4^{2-} ratio for a solution 0.5 M in tungstate. A theoretical Δn value was obtained for a given solution by adding together the Δn value for a tungstate solution of that concentration plus a Δn value for the perchloric acid used in that case, assuming no reaction between the tungstate and the perchloric acid. (It should be noted that indices of refraction of dissolved salts are additive if no reaction takes place.[1,26]) The observed Δn values for these solutions always fall below the theoretical values indicative of reaction at all H^+/WO_4^{2-} ratios. An inflection in the observed curve at the 7/6 ratio is indicative of a predominant species (hexamer) present at this ratio. The gradual inflection between H^+/WO_4^{2-} ratios 0 and 7/6 indicates the possibility of an intermediate pre-

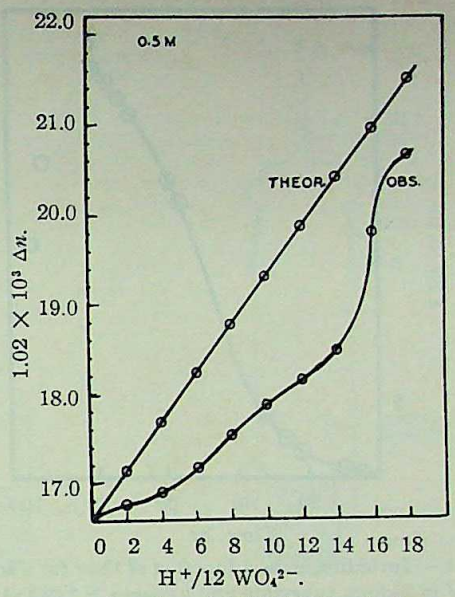

Fig. 2.—Δn as a function of H^+/WO_4^{2-} ratio for a solution 0.5 M in sodium tungstate.

dominant species between the monomer and the hexamer.

Figure 3 is a differential curve of the data plotted in Fig. 2. Here $\Delta(\Delta n)$, the difference between the observed Δn and theoretical Δn is plotted *versus* H^+/WO_4^{2-} ratio for a solution 0.5 M in tungstate. The sharp break at H^+/WO_4^{2-} ratio

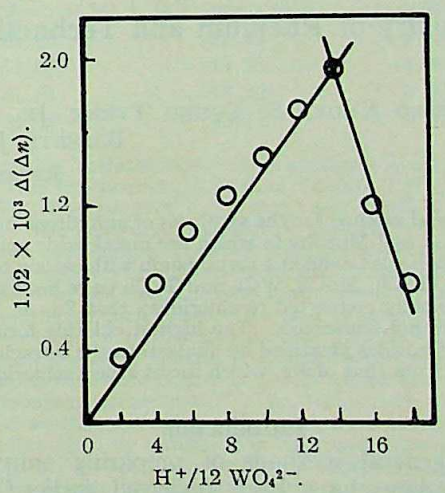

Fig. 3.—A differential curve of the data plotted in Fig. 2.

of 7/6 is indicative of the predominance of the hexamer at this ratio. If no intermediate species existed between the monomer and hexamer one would expect the points on the $\Delta(\Delta n)$ *versus* ratio curve between the 0 and 7/6 ratio to fall on the straight line drawn between these points. As is shown in Fig. 3 the observed points do not fall on the expected line but rather veer away from the expected line and then about half way between the 0 and 7/6 ratio turn back toward the expected line. This could be interpreted to be indicative of an intermediate about half way between the 0 and 7/6 ratio. In support of this idea note again the fact that the observed weight average ionic weight at the

(26) T. G. Berg, *Z. anorg. allgem. Chem.*, **273**, 291 (1953).

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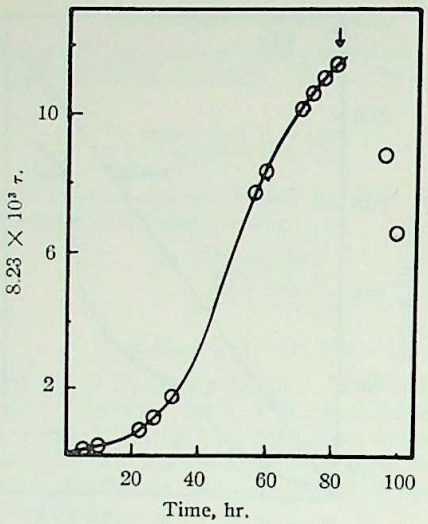

Fig. 4.—Turbidity, τ, as a function of time for a solution 0.025 M in sodium tungstate and having a H^+/WO_4^{2-} ratio of 2 to 1. The arrow indicates the point when cloudiness was first noted in the solution.

2/3 ratio agreed remarkably well with the theoretical value for a trimer. This indication of an intermediate between the monomer and the hexamer is most evident in the solutions of high total tungsten concentration.

On treating a tungstate solution with sufficient acid to convert the Na_2WO_4 to tungstic acid precipitation takes place. If the total tungsten concentration is small enough the solution remains clear even after adding sufficient acid to convert the Na_2WO_4 to tungstic acid and precipitation ensues only after a period of time has lapsed. Introductory studies of solutions having a H^+/WO_4^{2-} ratio of 2 to 1 or in other words sufficient acid to convert all the Na_2WO_4 to tungstic acid indicate that it is possible to use the light scattering technique to study the rate of polymerization of freshly prepared tungstic acid to the point where actual precipitation commences. Figure 4 is a plot of τ *versus* time for a solution 0.025 M in Na_2WO_4 and having a H^+/WO_4^{2-} ratio of 2 to 1. The turbidity increase with time is indicative of increasing polymerization of the tungsten containing species as the solution ages. In Fig. 4 the arrow indicates the point where visible cloudiness was first noted in the solution. Beyond this point τ began to decrease and actual precipitation commenced. In the case of a solution 0.05 M in tungstate 24 hours passed before visible cloudiness was observed while with a 0.10 M solution cloudiness ensued immediately.

MORGANTOWN, W. VA.

[CONTRIBUTION FROM VENABLE HALL OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

Chemistry of Rhenium and Technetium. I. Synthesis of $ReCl_5$, $TcCl_4$ and Related Compounds

BY KERRO KNOX,[1] S. YOUNG TYREE, JR., RAM DULARAY SRIVASTAVA, VELLO NORMAN, JOSEPH Y. BASSETT, JR., AND J. H. HOLLOWAY

RECEIVED FEBRUARY 7, 1957

A general method for the synthesis of anhydrous metal chlorides has been developed. It is a modification of the method of Michael and Murphy in which the metal oxide and carbon tetrachloride are heated to 400° in a sealed glass tube. The glass tube is contained in a metal bomb with carbon tetrachloride or water in it to equalize the pressure. Pure preparations of $ReCl_5$, $TcCl_4$, $MoCl_5$, WCl_6 and $TaCl_5$ have been made. Preliminary results also indicate that Fe, Zr, Be and V oxides are completely converted to chlorides; that Zn, Al, La, Th and Nb oxides are partially converted; and that Co and Ni oxides are not converted. The highest chloride formed by the metal is found in all known cases. Technetium yields a blood-red powder identified by analysis as the tetrachloride. Thus, under ordinary conditions, the highest chloride of Tc is different from that of Re, which forms a pentachloride.

Introduction

The general methods of preparing anhydrous metal halides have been reviewed earlier.[2] The method of Michael and Murphy,[3] in which the metal oxide and carbon tetrachloride react in a sealed tube, has been modified to overcome the difficulty of frequent breaking of the glass tubes at higher temperatures. At the temperature required to bring about the complete conversion of some oxychlorides to the chlorides, high pressures are generated which must be balanced by an external pressure. The balancing pressure is supplied by placing the sealed tube inside a high-pressure steel reaction vessel with heater[4] containing the proper amount of a liquid. Then the whole assembly is heated. If water is used as the external liquid, heavy wall tubes must be used, because although the pressure at the reaction temperature can be made equal inside and outside the glass tube, the pressure difference at intermediate temperatures is great enough to break standard wall tubing. If carbon tetrachloride is used outside, standard wall glass tubing can be used. In the latter case, however, corrosion of the containing steel vessel is more rapid, but not alarmingly so.

Experimental

Method.—The standard conditions used in this Laboratory are 8 cc. of liquid carbon tetrachloride at room temperature for every 26 cc. of volume in the glass reaction vessel. The amount of metal oxide is that calculated to have a five-fold excess of carbon tetrachloride present, according to the equation for the reaction; *e.g.*, $Re_2O_7 + 7CCl_4 \rightarrow 2ReCl_5 + 7COCl_2 + 2Cl_2$. The excess CCl_4 is needed to dissolve and

(1) Bell Telephone Labs., Inc., Murray Hill, N. J.
(2) S. Y. Tyree, Jr., *Inorg. Syntheses*, **4**, 104 (1953).
(3) A. Michael and A. Murphy, *Am. Chem. J.*, **44**, 365 (1910).
(4) Obtainable from the American Instrument Company, Silver Spring, Md.

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thereby reduce the final pressure of the product gases, $COCl_2$ and sometimes Cl_2, and to dissolve the solid chlorocarbon by-products which would otherwise contaminate the product. If standard wall glass tubes are used, the same proportion of CCl_4 to free volume is maintained in the steel bomb. If heavy wall tubes are used, 66 cc. of liquid water at room temperature is used for every 1410 cc. of outside volume. The metal oxide and C.P. CCl_4 without further purification are placed in the glass reaction vessel shown in Fig. 1. The neck is sealed and heated carefully to give a uniformly thick seal. After flame annealing of the neck, the glass tube is placed inside the steel bomb with the proper amount of balancing fluid in it (commercial grade CCl_4 is satisfactory here). Closure is made, and the assembly is heated to 400° for a few hours, the pressure developed being about 100 atmospheres. There is no danger of an explosion here with a properly selected metal bomb, but the usual precautions taken in high-pressure, high-temperature work should be observed. If a leak should develop in the seal, obnoxious gases will be given off. The heater is turned off and the assembly allowed to cool to room temperature. It is opened in a hood or out of doors.

The glass tube now contains gases under pressure, estimated to be about 1–2 atm. excess at room temperature, and so it should be handled carefully. It is opened in a hood by playing an oxy-gas flame on the sealed tip, which blows out because of the pressure inside the tube. (Caution: Heat the tip on a side which will make it blow out in a safe direction.) The whole top of the tube is then taken off in order to facilitate removal of the contents in the dry box. This is done by scratching the side of the tube with a sharp file just below the shoulder (the scratch is most easily made before opening the tip with the flame) and leading the scratch around the tube with a red-hot glass rod. These operations should be carried out as rapidly as possible so as to be completed before effervescence ceases and air enters the tube. The tube is then placed inside another tube fitted with a ground-glass joint and stopcock at the top, shown in Fig. 2. The stopcock is joined to a vacuum system by a rubber tube through a Dry Ice–acetone trap and a NaOH tower. It is partly opened very carefully, adjusting the stopcock so as to give a steady but not violent ebullition. The rapid boiling causes cooling which tends to slow down the rate of boiling to the point where bumping can be very bad. The external application of sufficient heat by means of an infrared lamp has been found very effective in overcoming the trouble and in maintaining a steady ebullition. About one-half of the volume of the liquid is slowly pumped away in order to remove dissolved $COCl_2$ and Cl_2. It is not all pumped away, otherwise the solid chlorocarbons deposit. The tube is removed to an efficient dry-box, opened, the product filtered and washed with CCl_4.

Rhenium Pentachloride.—Rhenium metal is burned in oxygen to the heptoxide[5] which is sublimed into the glass reaction vessel previously sealed onto the oxidation apparatus. The oxygen pressure is brought to just above atmospheric pressure, the connecting tube cut, and the CCl_4 quickly poured in through a funnel. The tube is sealed and heated as above. The product is large green-black crystals of $ReCl_5$ beneath a green liquid. The over-all yield is about 90%; in one preparation, 1.2 g. of Re gave 2.0 g. of $ReCl_5$, 87%; in another starting with the heptoxide, 9.0 g. of Re_2O_7 gave 13.4 g. of $ReCl_5$, 99%. Rhenium pentachloride can be kept indefinitely in the sealed tube, but once this is opened, the product must be used promptly because it slowly decomposes, probably losing chlorine.

For analysis, samples of about 200 mg. are weighed out in a dry box, removed and dissolved in a sodium hydroxide–hydrogen peroxide mixture. The solution is evaporated to dryness in a platinum casserole to decompose any hexachlororhenate(IV) formed. If the residue is not colorless, more sodium hydroxide-hydrogen peroxide solution is added and evaporation repeated. This treatment is sometimes required as many as three times to break up this robust complex. The residue is taken up with water, neutralized and made slightly acidic with nitric acid, and titrated potentiometrically with standard silver nitrate, care being taken not to go too far over the end-point. Hydrochloric acid is then added to remove excess silver. The precipitate is digested and filtered off. Since nitrate interferes with tetraphenylarsonium perrhenate precipitation, it is removed by adding concentrated hydrochloric acid and evaporating a few times. Then tetraphenylarsonium perrhenate is precipitated and weighed according to the method previously described for perchlorate analysis.[6] The results on several preparations are

% Re (theory 51.24)	% Cl (theory 48.76)	Cl/Re
51.69	47.90	4.87
50.85	48.25	4.99
51.61	48.12	4.90
51.59	48.17	4.91

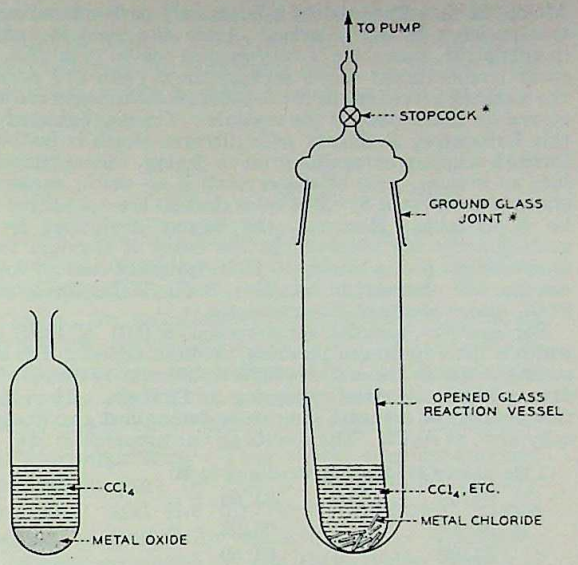

Fig. 1 (Left).—Glass reaction vessel.

Fig. 2 (Right).—Container for removal of opened reaction vessel to dry-box. *The best grease to use here is holocarbon chemically inert stopcock grease, obtainable from Holocarbon Products Corp., 2012–88th St., North Bergen, N. J.

Technetium Tetrachloride.—This synthesis is exactly the same as that for rhenium; 0.14 g. of Tc gave 0.27 g. of $TcCl_4$, 79%. The product is, in this case, small blood-red crystals. The analytical procedure is essentially the same, except that considerable Tc is lost for some unknown reason upon evaporation with concentrated HCl, and so this step is omitted. In addition, the halo-complexes of Tc are more easily hydrolyzed than those of Re, and so ammonia can be used as the base for the dissolution of the chloride. Thereby, only a small amount of nitric acid is needed after evaporation, and so no interference occurs in the precipitation of tetraphenylarsonium pertechnate.[7] The technetium is easily recovered as the metal from the analytical precipitate in quantitative yield by reduction in hydrogen according to a method described for the reduction of ammonium perrhenate.[8] The results of triplicate analyses on two different preparations are

% Tc (theory 41.09)[9]	% Cl (theory 58.91)	Cl/Tc
41.00	58.00	3.95
41.28	58.91	3.98

Molybdenum Pentachloride.—In this case a weighed amount of reagent grade MoO_3 is placed directly into the reaction vessel, CCl_4 is added, and the synthesis is carried out as above; in one synthesis, 5.1 g. of MoO_3 gave 8.1 g. of

(5) A. D. Melavan, J. N. Fowle, W. Brickell and C. F. Hiskey, *Inorg. Syntheses*, **3**, 188 (1950).

(6) C. S. Patterson, S. Y. Tyree, Jr., and K. Knox, THIS JOURNAL, **77**, 2195 (1955).

(7) Elision of the -et- in naming technetium anions is recommended for consistency with the names of the parent acids, such as pertechnic acid. As with molybdenum, the names of the anions and particularly of the acids are then much easier to pronounce.

(8) L. C. Hurd and E. Brimm, *Inorg. Syntheses*, **1**, 177 (1939).

(9) The mass spectroscopic chemical atomic weight of 98.913 is used for Tc; M. G. Ingram, D. C. Hess, Jr., and R. J. Hayden, *Phys. Rev.*, **72**, 1269 (1947).

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$MoCl_5$, 85%. The product is large, very dark-colored crystals under a brown solution. Again the yield is nearly quantitative, indicative of very modest solubility in CCl_4 at room temperature. Upon sucking the crystals dry during the washing procedure in the dry box, color changes are observed on the surface of the crystals. The dry box used in this Laboratory is flushed with nitrogen which is bubbled through alkaline pyrogallol prior to drying. Since the surface to volume ratio of the crystals is so small, chemical changes manifested by these color changes are not judged to be appreciable. However, the largest deviations from stoichiometry are observed in the cases of rhenium and molybdenum pentachlorides. It is significant that no color changes are observed in handling $TcCl_4$, WCl_6, $TaCl_5$ and $FeCl_3$ under identical circumstances.

For analysis, samples are dissolved in 0.01 *M* KOH to which a little hydrogen peroxide has been added. The resulting solutions are analyzed for molybdenum by the molybdate method, ultimately weighing as $PbMoO_4$. The chloride content of separate samples is determined gravimetrically also, as AgCl. The results on one preparation are

% Mo (theory 35.12)	% Cl (theory 64.88)	
35.46	64.63	
35.47	64.63	
35.38	64.59	
Av. 35.44	Av. 64.62	Cl/Mo = 4.93

Tungsten Hexachloride.—Reagent grade tungsten(VI) oxide is used as starting material; in one synthesis, 6.8 g. of WO_3 gave about 10 g. of WCl_6, 86%. Large crystals of WCl_6 are obtained which are so dark as to appear black beneath a dark reddish liquid. Samples prepared by this method are not easily soluble in water, as reported of the direct synthesis product[10]; nor are they very soluble in CCl_4 at room temperature. It is observed that digestion with hot, aqueous ammonia for one hour is necessary to dissolve completely samples of WCl_6 prepared by this procedure.

For analysis, samples of about 275 mg. are weighed in the dry box and dissolved, after removal, by digestion in aqueous ammonia. The solutions are neutralized to a *p*H between 2 and 4 with nitric acid and titrated potentiometrically for chloride content, using a silver electrode with a calomel reference electrode. Samples of about 1 gram are weighed directly into platinum crucibles for the W determinations. After removal from the dry box the samples are metathesized by digestion with concentrated aqueous ammonia, carefully evaporated to dryness, ignited at 800°, and weighed as WO_3. The results on one preparation are

% W (theory 46.37)	% Cl (theory 53.63)	
46.17	53.43	
46.22	53.54	
46.35	53.52	
Av. 46.25	Av. 53.50	Cl/W = 6.000

Tantalum Pentachloride.—Reagent Ta_2O_5 is converted to $TaCl_5$ as above. The product is white crystals, in agreement with the color of the pure preparations of Alexander and Fairbrother[11] and contrary to the yellow color previously reported.[12] The supernatant liquid is yellow, due to dissolved chlorine and phosgene (CCl_4 alone turns yellow under these conditions), but the solid is white when filtered, washed and dried.

For analysis, samples of a few hundred milligrams are weighed out in a dry-box and treated with a large excess of water. The tantalum precipitation is completed by ammonia, the precipitate ignited and weighed as Ta_2O_5. Chloride is determined gravimetrically or potentiometrically as AgCl. Analysis of two samples of one preparation gave

% Ta (theory 50.51)	% Cl (theory 49.49)	Cl/Ta
50.88	49.17	4.93
50.79	49.46	4.97

(10) M. H. Lietzke and M. L. Holt, *Inorg. Syntheses*, **3**, 163 (1950).

(11) K. M. Alexander and F. Fairbrother, *J. Chem. Soc.*, S223 (1949).

(12) See *e.g.*, N. V. Sidgwick, "The Chemical Elements and Their Compounds," Oxford Univ. Press, London, 1950, p. 847.

Other Metal Halides.—The method is of wider applicability than the few syntheses reported here indicate. The extensive studies of Camboulives,[13] of Michael and Murphy,[3] and of many others, indicate that many metal oxides are converted to chlorides by CCl_4 under a variety of conditions. In fact, we have reacted a number of other oxides with CCl_4 under these conditions, but we have not analyzed all the products yet nor, in some cases, obtained good looking products, and so only qualitative observations on other metals will be reported now.

Iron(III) oxide reacts easily and completely to give large flat dark green plates that are very probably pure $FeCl_3$; some of the smaller crystals exhibit dichroism, being reddish brown by transmitted light.

Zirconium oxide gives white needles without any finely powdered oxide residue visible. The crystals are expected to be $ZrCl_4$.

Beryllium oxide appears to be completely converted also, since the finely powdered oxide is replaced entirely by white crystals.

Vanadium(V) oxide yields liquid products only; a red liquid phase under a yellow vapor appeared in the tube. From the color and the phase, it is expected that the product is VCl_4. Its separation from the excess CCl_4 would involve a fractional distillation under anhydrous conditions.

For refractory oxides the extent of reaction is quite sensitive to the history of the oxide. It appears that the activated oxides, that is, those precipitated as hydrous oxides and ignited at low temperature, will react, whereas they become inert when ignited to high temperature. Activated Al_2O_3 reacted completely to give large crystals with no residual oxide powder. Highly ignited Al_2O_3, on the other hand, gave a few small crystals but the bulk of the product was identical in appearance with the original oxide. With Nb_2O_5, two solids were present; one consisted of nice yellow needles which, when picked out, analyzed close to $NbCl_5$, while the other was a button of white powder which was largely, but not completely, converted to hydrous Nb_2O_5 by water. It is peculiar that we have found Ta_2O_5 more reactive to CCl_4 than Nb_2O_5, contrary to previous experience.[14] The Nb case is complicated by dimorphism,[11] and it may be that both the low and high temperature phases of $NbCl_5$ were present.

For the oxides of metals with relatively non-volatile chlorides (we have made preliminary investigations on ZnO, La_2O_3, and ThO_2), a few crystals usually are produced, but the oxide appears not to have reacted completely. The material is always partially water-soluble after reaction but never completely so.

Cobalt and nickel oxides did not appear to react at all.

Preliminary experiments have also been carried out on the preparation of bromides by a similar technique. Carbon tetrabromide and bromoform have been used primarily as the brominating agents. A considerable amount of free bromine is produced in the reaction. After washing with CCl_4, however, products were obtained which analyzed close to $ReBr_3$ and $FeBr_3$.

Work is continuing in this Laboratory on the wider applicability of the method.

Discussion

The Method.—There are several advantages of this method of preparing anhydrous chlorides, when applicable, over other procedures. Oxides of the metals are generally available or easily made in pure form. The reagents need not be excessively dry because small amounts of water are converted to $COCl_2$ and HCl, which are easily removed from the product. Manipulation of the starting materials, except the hygroscopic Tc_2O_7 and Re_2O_7, is easy, and the subsequent operations are not difficult when a dry-box is available. The conversion is complete and the only losses are manipulative ones. In most cases rather large crystals are formed which then tend to be quite pure and are relatively insensitive to hydrolysis by virtue of their small surface to volume ratio.

(13) P. Camboulives, *Compt. rend.*, **150**, 175 (1910).

(14) Ref. 12, pp. 838, 847.

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The method is especially valuable for those metals which have volatile oxychlorides, such as Nb, Ta, Mo, W, Tc and Re, thereby requiring repeated sublimation of the chloride to free it from oxychloride even when the preparation is begun with "pure" metal.

It appears to be the method of choice for Tc since direct synthesis and other methods do not work.[15] In fact, interest in the method was greatly stimulated by the search for a means of synthesizing technetium chloride in pure form.

Technetium Tetrachloride.—Since previous work and these experiments prove that this reaction gives the highest known chloride of the metal in question (*cf.* $MoCl_5$, WCl_6, $ReCl_6$, etc.), it is of interest that technetium forms a tetrachloride rather than a penta- or trichloride as rhenium does. In this respect it resembles manganese more than rhenium. The fact that technetium tetrachloride can be isolated in a pure state bears out its expected greater stability over manganese tetrachloride. Thus, technetium, whose oxides differ from those of rhenium only in degree,[16] has a highest chloride which differs in kind from rhenium chlorides.[17] When compared to the behavior of the elements near Tc and Re in the periodic table, this reduced affinity of technetium for chlorine is not surprising on an empirical basis, as can be seen by considering the highest known anhydrous chlorides in this region

$NbCl_5$	$MoCl_5$	$TcCl_4$	$RuCl_3$
$TaCl_5$	WCl_6	$ReCl_5$	$OsCl_4$

The affinity for chlorine definitely falls off in going up as well as across the periodic table. The fluorides of these metals follow a similar pattern. To our knowledge, no satisfactory explanation has been given for the general phenomenon; stereochemical grounds alone are not sufficient.[18] We have none to offer, and regard the question as one of the interesting unsolved problems in inorganic chemistry.

Acknowledgments.—This work was financially supported in part by the U. S. Atomic Energy Commission and the du Pont Company, whose assistance is gratefully acknowledged. Appreciation is also expressed to the Oak Ridge National Laboratory for the loan of the technetium.

(15) C. M. Nelson, G. E. Boyd and W. T. Smith, Jr., THIS JOURNAL, **76**, 348 (1954).

(16) W. T. Smith, Jr., J. W. Cobble and G. E. Boyd, *ibid.*, **75**, 5773, 5777, 5783 (1953).

(17) As pointed out by one referee, a higher chloride of Tc may later be found under conditions other than those of this experiment, maybe "as a constituent of the vapor phase or perhaps even as a solid at lower temperatures and higher chlorine pressures." Except for $MnCl_4$, the discussion refers to the highest chlorides stable at room temperature with no excess chlorine gas present. They are, in all the cases cited, the highest known chlorides under any condition thus far studied.

(18) Ref. 12, pp. 1301–1302.

CHAPEL HILL, N. C.
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WEST VIRGINIA UNIVERSITY]

Complexes Formed between Copper(II) Ion and N,N,N′,N′-Tetrakis-(2-hydroxypropyl)-ethylenediamine[1,2]

BY JAMES L. HALL, F. ROBERT JONES,[3] C. EUGENE DELCHAMPS AND CHARLES W. MCWILLIAMS[3]

RECEIVED JANUARY 7, 1957

The compound N,N,N′,N′-tetrakis-(2-hydroxypropyl)-ethylenediamine, "Quadrol" (abbreviated "Q"), reacts with copper(II) ion in aqueous solution to form the complex ion CuQ^{+2}. This ion reacts further with Quadrol to form $Cu(Q-H^+)^{+1}$, and reacts with strong base to form successively, $Cu(Q-H^+)^{+1}$ and $Cu(Q-2H^+)^0$. The ions CuQ^{+2} and $Cu(Q-H^+)^{+1}$ have distinctly different absorption maxima in the vicinity of 700 mμ in the visible region but the two have nearly identical absorption maxima at about 280 mμ in the ultraviolet region. The ion CuQ^{+2} may be considered as a dibasic acid in solution and as such gives successive dissociation constants of 1.41×10^{-7} and 8.92×10^{-9}. The formation constant for formation of CuQ^{+2} from Cu^{+2} and Q is of the order of 10^9.

Introduction

This paper reports a study of the complexes of copper(II) ion with the compound N,N,N′,N′-tetrakis - (2 - hydroxypropyl) - ethylenediamine, "Quadrol" (abbreviated "Q"), with and without additional strong base added to the solutions. In the Quadrol molecule the nitrogen atoms and the hydroxyl radicals are in favorable position for the formation of stable five-membered chelate rings. The hydroxyl radicals of the Quadrol have nearly negligible acidic properties in solution in water but become appreciably acidic whenever the hydroxyl radical becomes a part of the chelate ring. These complexes have been investigated in aqueous solution by spectrophotometric methods and by potentiometric and conductometric titrations.

Experimental

The Quadrol was a gift of the Wyandotte Chemicals Corporation, and was designated as being at least 99.5% pure, the principal impurity being water. It was used without further purification. The concentration of the solutions as determined by titration with acid corresponded very closely to the concentration calculated from the weight of Quadrol used. The pure Quadrol and its dilute solutions are quite stable toward change on contact with the atmosphere. An 0.5 *M* solution, stored in contact with air, developed a slight yellow color after a few months.

Carbonate-free sodium hydroxide solutions and solutions of hydrochloric, nitric and perchloric acids were prepared from reagent-grade stock and were standardized by the usual methods. Sodium perchlorate was prepared by neutraliza-

(1) The work upon which this paper is based was sponsored, in part, by the Office of Ordnance Research, U. S. Army.

(2) Presented before the Division of Physical and Inorganic Chemistry at the 130th Meeting of the American Chemical Society, Atlantic City, Sept. 17 to 21, 1956.

(3) Abstracted, in part, from M.S. theses presented at West Virginia University by Charles W. McWilliams, 1955, and F. Robert Jones, 1956.

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tion of perchloric acid. Copper(II) perchlorate solutions were prepared from G. F. Smith Co. reagent or from basic copper carbonate as described previously.[4] The copper(II) perchlorate solutions were standardized by titration with disodium Versenate.[5]

The spectral data were obtained with a Beckman Model DU spectrophotometer, using 1 cm. matched silica cells. The solutions for spectrophotometric studies were made up to a constant ionic strength of 0.5 by addition of $NaClO_4$. Conductometric titrations were performed using a highly precise conductance bridge built around the Leeds and Northrup Co. No. 1553 ratio box.[5] A dip-type cell with a cell constant of approximately 0.1 was used. The potentiometric titrations were performed with a Beckman Model H-2 *p*H meter with appropriate calomel and glass electrodes. For all potentiometric and conductometric titrations the temperature was maintained constant at 25 ± 0.02°. The solutions for potentiometric titrations were made 0.5 *M* in KNO_3.

Results

Complexes Identified.—The complexes identified are believed to have the formulas CuQ^{+2}, $Cu(Q-H^+)^{+1}$ and $Cu(Q-2H^+)^0$. The first of these is believed to have the four coördination positions of the copper(II) ion occupied by the two nitrogen atoms and two oxygen atoms of the Quadrol, forming three five-membered chelate rings. The other two complexes have had removed one and two protons, respectively, from the two coördinated oxygen atoms of the first-formed complex.

Spectrophotometric Work.—Figure 1 shows the spectra in the visible region of solutions 0.005 *M* in copper(II) ion and containing varying amounts of Quadrol. The intermediate position of the 1:05 (Cu^{+2}:Q) curve midway between the 1:0 and 1:1 curves indicates that there is no complex of ratio less than 1:1. The intersection of the 1:1 and 1:2 curves near 850 mμ and the near coincidence of the 1:2, 1:3 and 1:4 curves strongly suggests that 1:1 and 1:2 complexes exist in these solutions. A series of solutions of various ratios of copper(II) ion to Quadrol was prepared at a constant total concentration of 0.005 *M*. Their spectra were determined and analyzed by the method of Vosburgh and Cooper.[6] The Y and Y′ curves at 850 and 675 mμ are shown in Fig. 2. Reaction of copper(II) ion with one and two moles of Quadrol is thus indicated.

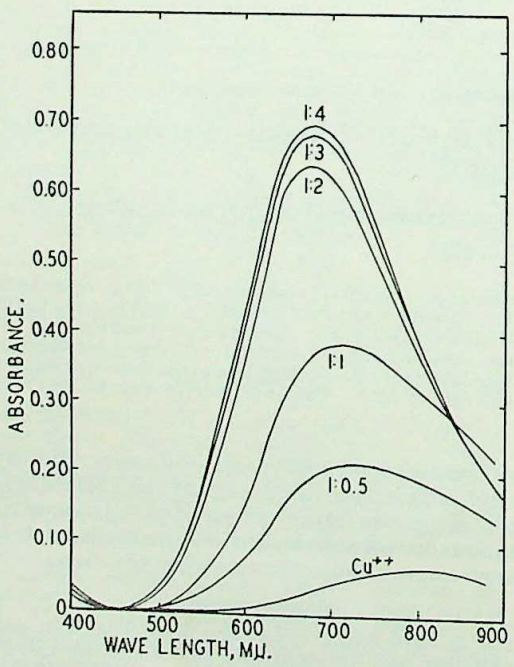

Fig. 1.—Absorption spectra of solutions 0.005 *M* in $Cu(ClO_4)_2$ with varying amounts of quadrol.

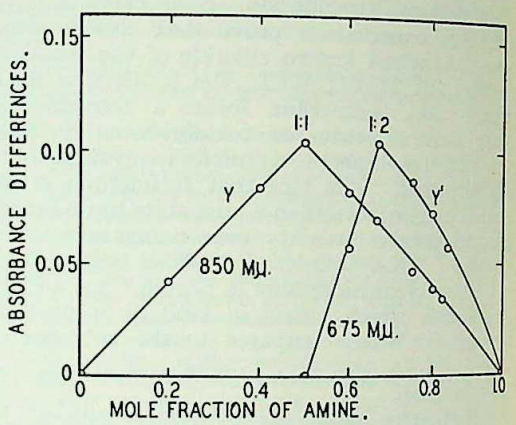

Fig. 2.—Derived absorbance curves for the copper(II) ion-quadrol system at 850 and 675 mμ.

In addition to the absorption maximum near 675 mμ, these copper(II) ion–Quadrol solutions show a second and much more intense absorption at about 280 mμ. Absorption curves for solutions 0.00025 *M* in copper(II) ion with varying amounts of Quadrol are shown in Fig. 3. In contrast to the results in the visible part of the spectrum, these curves show definite indication of only one complex with a Cu^{+2}:Q ratio of 1:1. Spectra were obtained for a series of solutions of constant total composition, copper(II) ion plus Quadrol, of 0.0005 *M*, and these data were analyzed by the method of continuous variations. At any wave

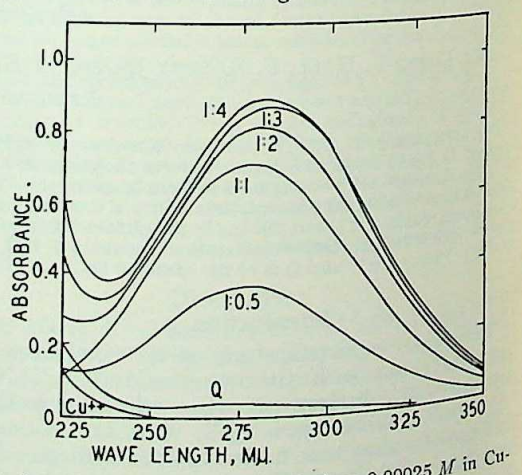

Fig. 3.—Absorption spectra of solutions 0.00025 *M* in $Cu(ClO_4)_2$ with varying amounts of Quadrol.

(4) J. M. Bolling and J. L. Hall, THIS JOURNAL, **75**, 3953 (1953).

(5) J. L. Hall, J. A. Gibson, Jr., P. R. Wilkinson and H. O. Phillips, *Anal. Chem.*, **26**, 1484 (1954).

(6) W. C. Vosburgh and G. R. Cooper, THIS JOURNAL, **63**, 437 (1941).

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length in the vicinity of the maximum of absorption a Y curve was obtained with a simple sharp maximum showing the 1:1 complex and giving no indication of any other complex.

The small increase in absorbance at the maximum, beyond the 1:2 ratio in the visible region and beyond the 1:1 ratio in the ultraviolet region was attributed to reaction of the complex with base formed by the additional Quadrol in solution. To further study this question, spectra were determined for solutions having a copper(II) ion concentration of 0.005 *M* and to which Quadrol and sodium hydroxide had been added to obtain final solutions with Cu^{+2}:A:OH^- ratios of 1:1:0, 1:2:0, 1:1:1, 1:2:1, 1:1:2 and 1:2:2. These are shown in Fig. 4. The near identity of the spectra of the 1:2:0 and 1:1:1 solutions indicates that these both contain the complex $Cu(Q-H^+)^{+1}$. The near identity of the spectra of the 1:1:2 and 1:2:2 solutions suggests that these both contain the complex $Cu(Q-2H^+)^0$.

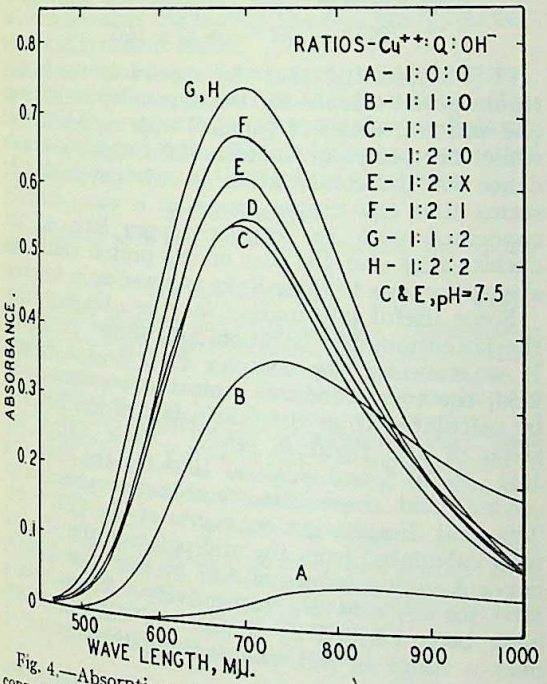

Fig. 4.—Absorption spectra of solutions made by mixing copper(II) perchlorate, Quadrol and sodium hydroxide in various ratios.

Potentiometric Titrations.—Figure 5 shows the results of addition of 1.0097 *M* sodium hydroxide solution to solutions initially 0.5 *M* in KNO_3, 0.01 *M* in Quadrol, 0.03 *M* in HNO_3, and with solution A containing no copper(II) ion, solution B being 0.005 *M* in $Cu(ClO_4)_2$, and solution C being 0.01 *M* in $Cu(ClO_4)_2$. At corresponding values of *p*H, curve B is nearly midway between curves A and C, indicating that the complex formed in these solutions contains only one mole of Quadrol per mole of copper(II) ion. After neutralization of the excess acid in addition to that required to form the amine salt, curve C, for the solution containing Cu^{+2} and Q in the ratio 1:1, shows definite end points corresponding to 2, 3 and 4 moles of hydroxyl ion.

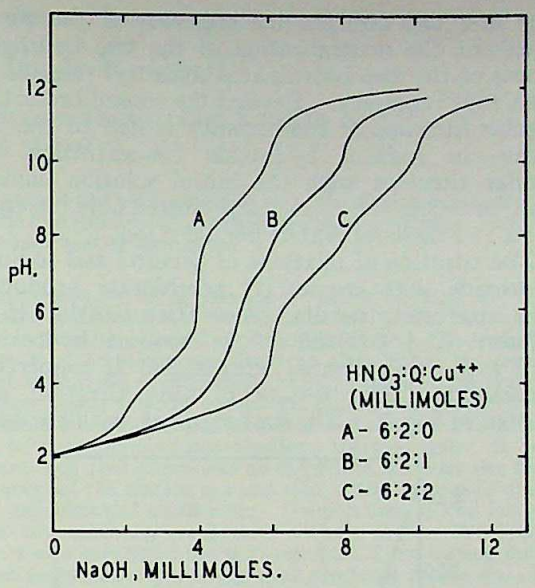

Fig. 5.—Titration of acid-Quadrol and acid-Quadrol-copper-(II) ion mixtures with sodium hydroxide.

Conductometric Titrations.—The addition of Quadrol to copper(II) perchlorate solution was studied conductometrically. Quadrol solution, 0.1005 *M*, was added to a solution 0.00493 *M* in copper(II) perchlorate. The conductance decreased throughout. The plot of conductance as a function of the mole ratio of Quadrol added showed three straight-line segments, with decreasing slope, and with distinct breaks corresponding to 1 and 2 moles of Quadrol per mole of copper(II) ion. The decrease of conductance to the first break is due to the decreased mobility of the copper(II) ion as its size is increased by addition of the ligand. The further decrease to the second break is due to a reduction in the charge of the complex ion from +2 to +1.

A conductometric titration was performed by adding 0.4653 *M* sodium hydroxide to a solution made 0.00493 *M* in both copper(II) perchlorate and Quadrol. The results are shown in Fig. 6.

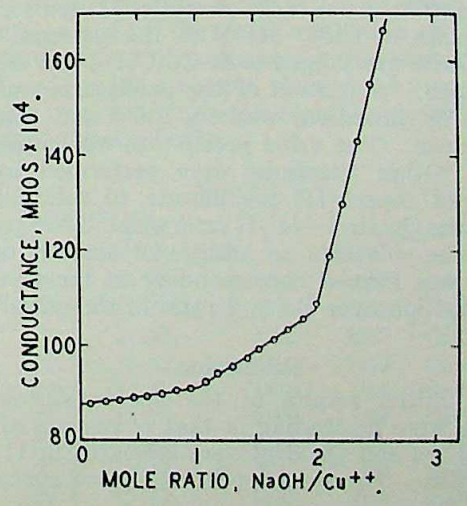

Fig. 6.—Conductometric titration of a solution 0.00493 *M* in CuQ^{+2} with 0.4653 *M* NaOH.

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The first two straight-line segments of the curve represent the neutralization of the two hydrogen atoms of the two coördinated hydroxyl radicals of the CuQ^{+2} complex. Beyond the second break the regular increase in conductance is due to the increase in sodium hydroxide concentration. A similar titration with the initial solution having Cu^{+2} and Q in the ratio 1:2 produced only one end-point at 2 moles of NaOH per Cu^{+2} ion.

The titration of mixtures of Quadrol and sodium hydroxide with copper(II) perchlorate produced very interesting results. A solution 0.00493 *M* in Quadrol and 0.00985 *M* in sodium hydroxide (1:2 ratio) was titrated with 0.0985 *M* copper(II) perchlorate. The results of this titration are plotted in Fig. 7. The first segment, with the end-

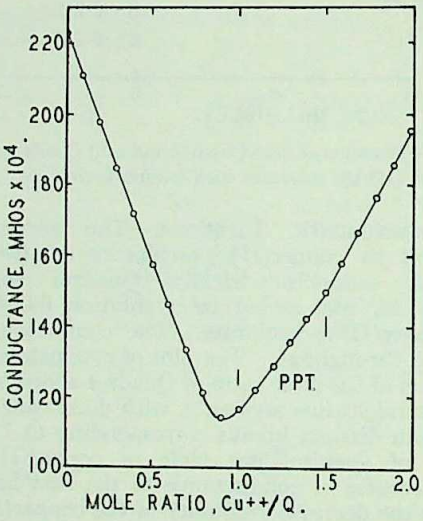

Fig. 7.—Conductometric titration of a solution 0.00493 *M* in Quadrol and 0.00985 *M* in NaOH with 0.0985 *M* $Cu(ClO_4)_2$.

point at the end of the rounded section, corresponds to the formation of the compound $Cu(Q–2H^+)^0$. The second segment, of increasing conductance, is accompanied by the formation of a precipitate and the length of the segment indicates the reaction of one mole of copper(II) ion for each two moles of $Cu(Q–2H^+)^0$ in the solution. The precipitate was judged to be $Cu(OH)_2$, and this was confirmed. A portion of the precipitate was separated by filtration, washed, dried and analyzed for copper. The dried precipitate was copper(II) oxide. Other titrations were performed by addition of copper(II) perchlorate to solutions for which the Quadrol–NaOH ratio was 1:3 and greater. For these solutions an additional amount of $Cu(OH)_2$ was formed corresponding to the excess of hydroxyl ion over the 1:2 ratio in the initial solution.

Discussion

The initial results of the spectrophotometric studies were misleading in that complexes of copper(II) ion and Quadrol were indicated in 1:1 and 1:2 ratios. The spectra of the solutions containing added sodium hydroxide and the titration curves show that the second molecule of Quadrol serves as a base to neutralize a hydrogen atom from one of the two coördinated hydroxyl radicals of the first Quadrol molecule. The successive acid ionization constants of the two acidic hydrogen atoms of the complex and the dissociation constants of the QH_2^{+2} ion are such that the second hydrogen atom of the complex is only partially neutralized in solutions containing a considerable excess of Quadrol. If sodium hydroxide is added to any solution containing copper(II) ion and an equivalent or greater amount of Quadrol, an end-point is always obtained at the ratio of two equivalents of hydroxyl ion per mole of copper(II) ion. The reactions which take place in the various solutions may be written as follows where OH^- represents hydroxyl ion from sodium hydroxide.

$$CuQ^{+2} + Q \longrightarrow Cu(Q–H^+)^{+1} + QH^+$$
$$Cu(Q–H^+)^{+1} + OH^- \longrightarrow Cu(Q–2H^+)^0 + H_2O$$
$$CuQ^{+2} + 2OH^- \longrightarrow Cu(Q–2H^+)^0 + 2H_2O$$
$$QH^+ + OH^- \longrightarrow Q + H_2O$$

It is interesting that the spectra in the visible region give evidence for the successive reaction of one and two moles of Quadrol with copper(II) ion while the spectra in the ultraviolet region give evidence for the combination of only one mole. It seems that the visible spectrum is more directly concerned with the copper–oxygen links in the chelate ring and the loss of the proton shifts the absorption due to these links to lower wave lengths.

Some useful information may be obtained from the potentiometric titration data shown in Fig. 5. If we consider the complex CuQ^{+2} as a dibasic acid, the two successive ionization constants may be calculated from the mid-points of the last two steps of the titration curve. These values are 1.41×10^{-7} and 8.92×10^{-9} for the first and second acid dissociation constants, respectively. The acid dissociation constants of the QH_2^{+2} ion were calculated from the mid-points of the steps of curve A giving values of 4.67×10^{-5} and 1.45×10^{-9} for K_1 and K_2, respectively. These values have been verified by a series of determinations over a range of *p*H values using the method of Bjerrum.[7]

The very distinct rise of *p*H after addition of two equivalents of hydroxyl ion to the Cu^{+2} and QH_2^{+2} mixture indicates that the formation of CuQ^{+2} ion is essentially complete before neutralization of the hydrogen atoms of the bound hydroxyl radicals is begun. One should then be able to calculate a stability constant for the formation of CuQ^{+2} from Cu^{+2} and Q by the method of Bjerrum.[7] Values of [Q] and $\bar{n}$ were calculated for the interval *p*H 2.3 to 5 and the corresponding values of *K* were determined. The value of *K* is approximately 2.9×10^9 if $\bar{n}$ is between 0.2 and 0.5. The values of *K* decrease outside this range.

MORGANTOWN, W. VA.

(7) J. Bjerrum, "Metal-Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, 1941.

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[CONTRIBUTION FROM HOKKAIDO UNIVERSITY, SAPPORO, JAPAN]

Equilibrium in the System GeO_2–H_2–Ge–H_2O[1]

BY TOSHIO YOKOKAWA, MASUMICHI KOIZUMI, MITSUO SHIMOJI AND KICHIZO NIWA[2]

RECEIVED JANUARY 3, 1957

A measurement has been carried out as to equilibrium in the system GeO_2–H_2–Ge–H_2O by a circulation method over the temperature range of 500–650°. An equation is obtained for the free energy of formation of germanic oxide: $\Delta F^0 = -131{,}700 + 41.4T$, and −132.3 kcal./mole is derived for the standard heat of formation.

The free energy of formation of germanic oxide has not yet been measured experimentally in spite of its great practical importance. Becker and Roth[3] and Hahn and Juza,[4] respectively, found the heat of oxidation of germanium to be −128.1 and 128.6 kcal./mole at 298°K. Jolly and Latimer[5] measured the heats of solution of germanium and of its oxide in an alkaline solution of hypochlorite. From those values they determined the heat of formation of the oxide to be −129.2 kcal./mole. By using these data and other thermodynamic quantities, Coughlin[6] calculated the free energy of formation of germanic oxide.

In the present paper a measurement of the reduction and oxidation equilibrium in the system GeO_2–H_2–Ge–H_2O is reported and some thermodynamic values computed from those results are compared with the data shown in the table of Coughlin.

Experimental

Experiments were performed for measuring the equilibrium

$$Ge(s) + 2H_2O(g) = GeO_2(s) + 2H_2(g) \qquad (1a)$$

from both the reduction and oxidation sides. A circulation method was selected in preference to a simple static method, because in the latter, (1) a much longer time (50–60 hr. in this case) is necessary to reach equilibrium; (2) the effect of thermal diffusion must be taken into consideration; and (3) side reactions involving gaseous germanous oxide make the measurement erroneous by the following reason. In this germanium–germanic oxide coexisting system, germanous oxide vaporizes by the reaction

$$Ge(s) + GeO_2(s) = 2GeO(g)$$

Thus the vapor pressure of germanous oxide is of the order of 10^{-6} atm. at 800°K.[5] This vapor diffuses from the part surrounding the sample toward the colder part of the reaction tube, being accompanied by the reactions

$$GeO(g) + H_2(g) = Ge(s) + H_2O(g)$$

or

$$GeO(g) + H_2O(g) = GeO_2(s) + H_2(g)$$

Then, the partial pressure ratio of hydrogen to water vapor tend to vary with the temperature along the tube as far as the both ends of the furnace, where the vapor of germanous oxide condenses on the wall.

The effects (2) and (3) overlapping each other, it is quite difficult to estimate the final deviation. These difficulties seem to be diminished considerably when the circulation method is employed, since the gas mixture, after having reacted with the sample, flows away through a narrow tube (B in Fig. 1) at a sufficient speed not to be influenced by the reaction with the germanous oxide produced as above mentioned. For the sake of comparison an ordinary static method also was used at two temperatures.

Apparatus.—The apparatus is shown in Fig. 1. The furnace was made of a porcelain tube, 25 cm. long and 3 cm. in diameter, wound with nichrome wire. The reaction tube A of porcelain was fitted to glass tubes by ground joint with picein at both ends; through one of these tubes a narrow quartz tube B, 4 mm. int. diam., was fixed. Temperature was measured at the outer wall of the reaction tube by a platinum–platinum–rhodium thermocouple; it was ascertained that there was no difference between the temperature of the flowing gas and that of the outer wall under the experimental conditions. Temperature of the furnace was automatically regulated within ±2°. The water vapor was supplied from a Pyrex flask C containing redistilled water, kept in a thermostat regulated within ±0.01°. Total pressures were read to 0.01 mm. by a cathetometer.

Material.—Germanic oxide (Eagle Picher product) was powdery and of hexagonal modification, having a purity of 99.999%.

Procedure.—A high alumina boat filled with about 1 g. of sample was set in the reaction tube, which was then evacuated to the pressure of 10^{-5} mm.; hydrogen, generated by electrolysis of a potassium hydroxide solution, was introduced up to the desired pressure. The rate of gas flow was 100–200 cc./min. The measurements were thus carried out over the temperature range of 500–650°.

Results

The results are shown in Table I. The 2nd column gives the equilibrium total pressures and the next denotes the water vapor pressures at the temperature of thermostat. The values in the 2nd and 3rd lines of Table I are obtained by using the static method; in these cases each P_{H_2O} value is corrected as to the effect of thermal diffusion. The equilibrium constants K shown in the 4th column have been calculated by the equation

$$\Delta F^\circ_{(1)} = -RT \ln K;\ K = \left(\frac{P_{H_2}}{P_{H_2O}}\right)^2 \qquad (1b)$$

The values of K, thus obtained, are plotted against reciprocal temperature in Fig. 2. The deviation of the data gained by the static method is attributed both to the effect of germanous oxide slightly produced and to the frequent changes of room temperature, which disturb the reaction steadily proceeding to the equilibrium.

TABLE I

Temp., °C.	Pressure, mm. Total	Water vapor	log K	ΔF^0, cal.	Reaction side
500	36.4	13.42	0.4670	−1651	Oxidn.
500[a]	32.0	13.60	.2626	− 929	Oxidn.
530[a]	30.5	11.53	.4322	−1587	Oxidn.
550	31.7	13.42	.2682	−1010	Oxidn.
575	29.2	13.42	.1410	− 549	Reductn.
600	27.1	13.42	.0160	− 64	Oxidn.
600	27.3	13.42	.0290	− 114	Reductn.
625	25.7	13.42	− .0772	316	Reductn.
650	24.8	13.42	− .1432	604	Reductn.

[a] Data from static method; each p_{H_2O} is corrected as to thermal diffusion.

(1) Presented before the annual meeting of Chemical Society of Japan held on April 3, 1956.

(2) K. Niwa, Faculty of Science, Hokkaido University, Sapporo, Japan.

(3) G. Becker and W. A. Roth, *Z. physik. Chem.*, **A161**, 69 (1932).

(4) H. Hahn and R. Juza, *Z. anorg. allgem. Chem.*, **224**, 120 (1940).

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(6) J. P. Coughlin, Bureau of Mines Bull., No. 542, 22 (1954).

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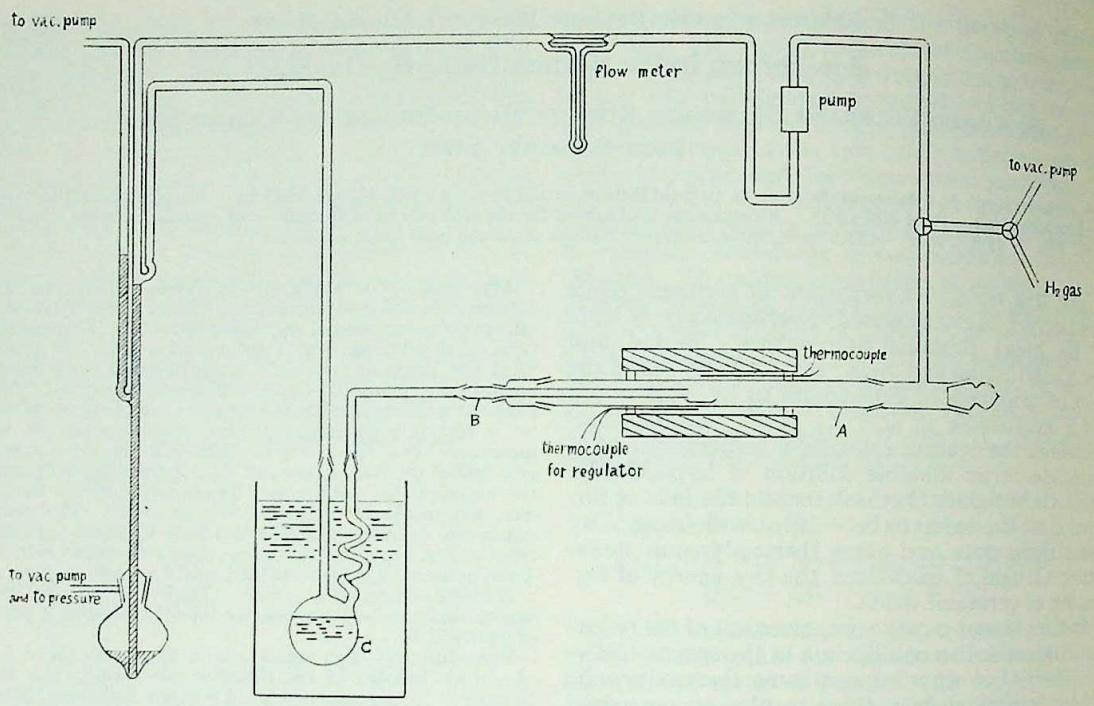

Fig. 1.—Apparatus for circulation method.

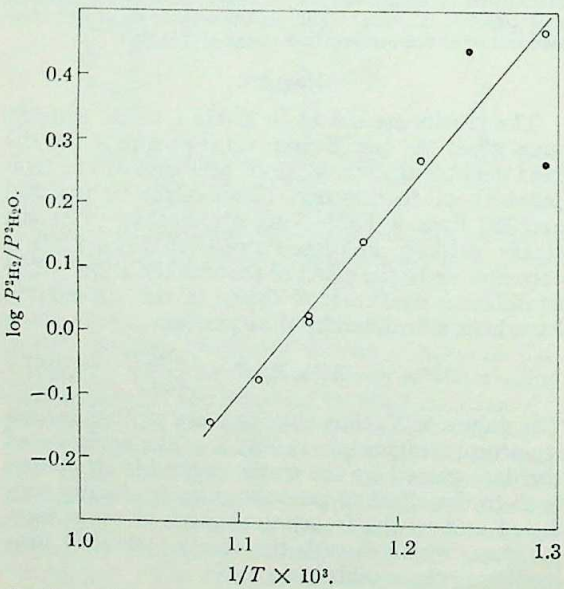

Fig. 2.—Relation between log K and $1/T$: ●, static method; ○, circulation method.

Thermodynamic Calculation and Discussion

By the method of least squares, the temperature dependence of ΔF^0 is obtained

$$\Delta F^0_{(1)} = -13{,}750 + 15.60T \ (\pm 100 \text{ cal./mole})$$

giving the heat of reaction −13,750 cal./mole with an estimated standard deviation of 560 cal./mole. Here the data obtained by the static method are excluded in the calculation.

The heat and free energy of formation of water vapor are $\Delta H^0_{850} = -58{,}070$ cal./mole and ΔF^0_{850} = −47995 cal./mole, according to Rossini, *et al.*[7] Then with regard to the formation of germanic oxide the following results are obtained

$$Ge + O_2 = GeO_2 \quad (2a)$$

$$\Delta F^0_{850} = -96{,}480 \pm 200 \text{ cal./mole}$$

$$\Delta H_{850} = -131{,}700 \pm 1000 \text{ cal./mole}$$

$$\Delta F^0_{(2)} = -131{,}700 + 41.4T \ (\pm 200 \text{ cal./mole}) \quad (2b)$$

A corresponding formula is derived from the values calculated by Coughlin, that is

$$\Delta F^0_{(2)} = -127{,}600 + 40.6T$$
$$(\pm 1500 \text{ cal./mole at } 700\text{–}1000°\text{K.})$$

Using the heat capacities of germanium and its oxide,[8] the standard heat and free energy of formation of germanic oxide can be calculated.

The results are

$$\Delta H_{298} = -132{,}300 \pm 1000 \text{ cal./mole}$$

$$\Delta F^0_{298} = -119{,}700 \pm 1500 \text{ cal./mole}$$

On the other hand, the values in Coughlin's table are

$$\Delta H_{298} = -128{,}300 \pm 1000 \text{ cal./mole}$$

$$\Delta F^0_{298} = -115{,}900 \pm 1500 \text{ cal./mole}$$

ΔH in the present work is more negative than that of Coughlin by 4 kcal/mole at 850°K. ΔS shows a similar deviation, though within uncertainty. These discrepancies seem to be due mainly to the difference of the structure of germanic oxide employed which is hexagonal in the present work but was amorphous in the case of Coughlin. The above result, however, cannot be discussed only from the viewpoint of the modifications of the oxide sample, since ΔH in the present work has uncertainty of 1

(7) F. D. Rossini, D. D. Wagman, W. H. Evans, S. Levine and I. Jaffe, "Selected Values of Chemical Thermodynamic Properties," Series III, Nat. Bur. of Standard.

(8) K. K. Kelley, Bureau of Mines, Bull., No. 476, 208 (1949).

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kcal. and Coughlin's free energy values show a probable error due to using an estimated entropy of germanic oxide. Table II shows the heat and entropy of formation of germanic oxide, both amorphous and hexagonal, together with the corresponding values of silica.[9] For germanium the comparison was made at 850°K. in order that the error due to the use of the estimated heat capacity may be avoided in the data for the hexagonal modification.

TABLE II

	State	H, kcal.	S, e.u.
GeO_2 (at 850°K.)	Amorphous	−127.6	−40.6 (calcd.)
	Hexagonal	−131.7	−41.4
SiO_2 (at 298°K.)	Amorphous	−202.5	−42.27
	Tridymite	−204.8	−43.11

Solubility of Oxygen.—In the above discussion it was assumed that germanium metal does not dissolve oxygen. However, if there is any solubility in this case, it would decrease the activity of germanium. Contrary to this apprehension, Candidus and Tuomi[10] have reported that the solubility is negligible, and Trumbore and his coworkers[11,12] have shown error in the work of Hoch and Johnston[13] who observed a large solubility of oxygen. It may be concluded, therefore, that germanium does not dissolve oxygen appreciably.

Supplement.—After the present experiment had finished, the authors found that Ono and coworkers[14] had investigated the same equilibrium by a flow method. They obtained −141.8 kcal./mole as the standard heat of formation of germanic oxide. They measured only from the reduction side, while the present measurement were carried out from both the reduction and oxidation sides with sufficient agreement. Besides, the present results seem to show that a circulation method is more suitable than a flow method, since hydrogen pressure is comparable to water vapor pressure in equilibrium. Then, the present results may be more accurate.

Acknowledgment.—The authors wish to express their thanks to Prof. Leo Brewer for his friendly criticism and to Prof. Isao Kayama, Hokkaido Teachers College, who persuaded them to participate in the research group studying germanium. The sample of germanic oxide was supplied by Mr. Hideo Baba, Electrical Communications Laboratory. The preliminary testing of this experiment was carried out by Mr. Satoshi Kado, to whom the authors are also indebted.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Halogen Atom Reactions Initiated by Nuclear Processes in Hydrocarbon Solutions

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The organic yields of I^{128} and Br^{80} activated as a result of the $I^{127}(n,\gamma)I^{128}$, $Br^{79}(n,\gamma)Br^{80}$ and $Br^{80m} \xrightarrow{I.T.} Br^{80}$ processes are higher in dilute hydrocarbon solutions than in pure organic halides. They increase with increasing chain length of the hydrocarbon. For the (n,γ) activations in hydrocarbon solutions they decrease by about one-fifth in going from 0 to 100°. These variations in yield are all rather insensitive to the addition of free halogen as scavenger and therefore involve "hot" processes. The results, correlated with those of other investigations, suggest that a number of previously unexplained facts about reactions of hydrogenous material with I^{128}, Br^{80} and Cl^{38} activated by the (n,γ) process may be explained by ionic reactions. The organic yields from the Br^{80m} isomeric transition in liquid hydrocarbons depend on the source molecule containing the Br^{80m} to an extent which is consistent with earlier observations of failure of the transition to rupture C–Br bonds in liquid bromine as the solvent.

Introduction

There are several reasons for studying the chemical consequences of activation of halogen atoms by nuclear processes[2] in each of a series of hydrocarbons: (1) the sizes and weights of the molecules with which the energetic halogen atom is surrounded while losing its energy can be varied without varying the types of bonds to be broken (*i.e.*, only C–C and C–H); (2) conservation of momentum requirements make it impossible for a halogen atom to enter organic combination in such a medium by a "billiard ball collision" mechanism; (3) preliminary observations[3] on such systems have shown changes in organic yields[4] dependent on the size of the hydrocarbon molecules; (4) such studies should contribute to a better understanding of the mechanisms of the various hydrogen replacement reactions cited in the next paragraph; (5) the mechanism of replacement of H^1 by H^3 in tritium recoil reactions[5a] (and possibly also in systems activated by the decay of tritium[5b] may be similar to

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(2) For a discussion of the physical processes involved and a review of earlier work on their chemical consequences see: J. E. Willard, *Ann. Rev. Nucl. Sci.*, **3**, 193 (1953); *Ann. Rev. Phys. Chem.*, **6**, 141 (1955).

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(4) The organic yield is the percentage of the atoms produced by nuclear transformation which become stabilized in organic rather than inorganic combination.

(5) (a) See, for example, and references: R. Wolfgang, J. Eigner and F. S. Rowland, *J. Chem. Phys.*, **60**, 1137 (1956); (b) K. E. Wilzbach,

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that of replacement of hydrogen by halogens activated by nuclear processes.

It has been shown that both iodine[6] and bromine[7] atoms activated by the (n,γ) process can replace hydrogen in pentane, forming the amyl halide, that Cl^{38} atoms from the $Cl^{37}(n,\gamma)Cl^{38}$ process undergo similar reactions in heptane,[8] cyclohexane and benzene,[9] and that the $I^{127}(n,\gamma)I^{128}$ reaction in liquid CH_4 produces both CH_3I^{128} and $C_2H_5I^{128}$.[10a] Further evidence indicates that substitution for hydrogen can occur by a unique "hot" non-radical reaction; *i.e.*, I^{128} atoms or ions freshly formed by the $I^{127}(n,\gamma)I^{128}$ process react[10] with *gaseous* CH_4 in a process of the type $I^{128} + CH_4 \rightarrow CH_3I^{128} + H$, and freshly formed Cl^{38} atoms give a similar reaction with gaseous butane or butyl chloride.[8]

Experimental

Reagents.—Eastman white label C_2H_5Br was purified by mechanical stirring with successive portions of concentrated H_2SO_4 for 12 hours each until further portions showed no coloration. It was then washed with water, dried with $MgSO_4$ and fractionally distilled. Phillips "pure" grade pentane, hexane, heptane and nonane were used. The first three of these were treated with H_2SO_4 in the same way as the C_2H_5Br following which they were stirred with 0.5 *N* $KMnO_4$ solution 6 *N* in H_2SO_4 for 12 hours before drying and distillation. The nonane and decane (Matheson) were fractionally distilled and then subjected to the H_2SO_4 treatment, washing and drying. Following purification all of the hydrocarbons were tested by adding 10^{-3} cc. of elemental bromine labeled with Br^{82} (36 hr.) to 25 cc. of the liquid. The solution was allowed to stand in the dark for about two hours, following which the Br_2 was extracted with aqueous sulfite and the radioactivity in the aqueous and organic layers was determined by counting. The fraction of the bromine which entered organic combination was always less than 0.2%. Hydrocarbons purified only by passing through a column of silica gel showed a high bromine pick-up in similar tests. Michigan Chemical Co. CCl_3Br was freed from stabilizer by distillation, illuminated while containing dissolved Br_2, extracted with aqueous sulfite, washed with water and dried.

Preparation of Organic Compounds Containing Br^{80m}.—$C_2H_5Br^{80m}$ and $CHBr_2Br^{80m}$ were prepared by allowing vapors of the non-radioactive compounds to stand for a few minutes in a flask coated with freshly sublimed $AlBr_3$, which had been prepared by adding radioactive Br_2[11] to dry aluminum, using vacuum system techniques. CCl_3Br^{80m} was prepared by illuminating a mixture of CCl_3Br and radiobromine.

Neutron Irradiations.—All neutron irradiations for studies of the (n,γ) process were made with an Sb–Be photoneutron source[12] which contained about 10 curies of Sb^{127} and emitted about 10^7 neutrons/sec. when received. The liquids to be irradiated were contained either in soft glass test-tubes set in a paraffin block, or in the annular space between the walls of a vessel shaped like a wide mouthed dewar, which was surrounded with water. During irradiations the source was positioned in the center of the paraffin block or of the dewar-like vessel. The γ-ray dosage received by the samples was in the range of about 10^3 to 10^4 r./hr. Irradiations for the production of Br^{80m} (4.4 hr.) were of 8–12 hours duration and those for the production of I^{128} (25 min.) lasted 1–2 hr. The samples irradiated at temperatures above 25° were contained in sealed tubes in a bath of thermostated paraffin oil.

Extraction and Counting.—Following neutron exposure of solutions of the alkyl iodides, a small amount of elemental halogen was added to the irradiation vessel to prevent sticking of tracer amounts of inorganic halogen on the walls. The liquid was then extracted with aqueous sulfite–halide solution. Counting was done by placing the liquid in an annular jacket designed to slide over a type 90NB Amperex Geiger tube. All counts were corrected for the composition of the medium,[13] the relative counting efficiency of the jacket, the volumes of the solutions, and for radioactive decay. In the studies of the $Br^{79}(n,\gamma)Br^{80m}$ reaction, the aqueous and organic layers were allowed to stand 2 to 3 hours following separation, before counting, to allow the Br^{80m} (4.4 hr.) to re-establish equilibrium with the Br^{80} (18 min.) daughter which emits the radiation which is counted. When Br^{80m} was to be determined following irradiation of CCl_3Br, or of alkyl bromides scavenged with I_2, adequate time was allowed for the Cl^{38} (37 min.) or I^{128} (25 min.) activity to decay. Two or more experiments were run for each condition tested and the results given in the tables are the averages of the values obtained. The organic yields[3] of individual determinations regularly agreed within ±0.5% of the average for the (n,γ) studies and ±1% for the isomeric transition studies.

Isomeric Transition Experiments.—For the isomeric transition experiments, the Br_2 or organic compound containing the Br^{80m} was added to 25 ml. of the hydrocarbon to be tested in a glass-stoppered flask and allowed to stand for 2–3 hours. Extraction was carried out as described above. The time of separation was taken as the time when the Br_2 color had just disappeared from the organic layer. When the source of Br^{80m} was Br_2, the activity in the organic layer decayed with an 18 min. half-life. The aqueous layer was allowed to stand until parent–daughter equilibrium was reached, before counting to determine the total 4.4 hr. activity. When the Br^{80m} was in an organic compound the 18 min. activity was counted in the aqueous phase and the 4.4 hr. in the organic. In the latter case the organic yield was given by one minus the ratio of the aqueous 18 min. activity to the organic 4.4 hr. activity, both activities being corrected to the time of extraction.

I_2 as Scavenger for (n,γ) Reactions on Bromides.—Br_2 has been demonstrated[3b,14] to be a powerful tool as a scavenger for thermal atoms and radicals produced by the (n,γ) process in alkyl bromides and I_2 has been shown[15] to serve similarly for alkyl iodides. In the present work I_2 was used as a scavenger for the (n,γ) reaction on solutions of C_2H_5Br in various hydrocarbons in order to minimize the problems of the reactivity of Br_2 with hydrocarbons in the presence of light and γ-radiation. The data of Table I show that its scavenger effect on bromides is equivalent to that reported earlier[3b,14] for Br_2.

TABLE I

ORGANIC YIELDS OF THE (n,γ) PROCESS IN C_2H_5Br AND IN CCl_3Br AS A FUNCTION OF CONCENTRATION OF IODINE

C_2H_5Br		CCl_3Br	
I_2, mole fraction	Av. org. yield, %	I_2, mole fraction	Av. org. yield, %
0.000	32.0	0.000	39.0
.001	31.3	.001	37.5
.002	28.4	.002	33.5
.005	27.1	.004	31.5
.010	26.7	.0066	29.5
.015	24.5		
.020	23.0		

Results and Discussion

Effect of Dilution of Alkyl Halide with Hydrocarbon.—The data of Table II show that, consistent with results reported earlier for C_2H_5Br and C_2H_5I in hexane,[3b] the organic yield for the $Br^{79}(n,\gamma)Br^{80m}$ process on bromine in the form of C_2H_5Br is increased by dilution with either pentane or heptane, a limiting value characteristic of the pure hydrocarbon.

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(11) Made by irradiation of ampoules of liquid bromine in the CP5 nuclear reactor of the Argonne National Laboratory.

(12) The source was obtained from the Oak Ridge National Laboratory (Radioisotopes Catalogue page 141 (1952)) and irradiated at the Brookhaven National Laboratory.

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drocarbon apparently being reached at concentrations between 0.1 and 0.01 mole fraction. The increase over the value in pure C_2H_5Br toward this limiting value is qualitatively proportional to the mole fraction of hydrocarbon. The increase is predominantly, and possibly wholly, the result of a type of chemical event which occurs to the tagged halogen atoms before they have had an opportunity to diffuse as thermal atoms in the system; that is it is the result of a "hot"[2,3b] process. This is illustrated by the fact that the difference in organic yields between pure C_2H_5I and hydrocarbon solutions containing 0.05 mole fraction C_2H_5I is, within the experimental error, independent of the concentration of I_2 scavenger present (Fig. 1).

TABLE II

ORGANIC YIELDS OF THE $Br^{79}(n,\gamma)Br^{80m}$ PROCESS IN SOLUTIONS OF C_2H_5Br IN *n*-PENTANE AND *n*-HEPTANE AT DIFFERENT CONCENTRATIONS

C_2H_5Br, mole fraction	Av. organic yield, % In pentane	In heptane
1.00	32.0	32.0
0.80	..	37.3
.75	..	37.7
.66	37.0	40.0
.50	37.5	42.0
.20	38.0	44.8
.10	40.4	46.0
.02	41.0	47.1
.01	42.2	47.4

Effects of Chain Length of Hydrocarbon and of Temperature.—From Table III and Fig. 1 it may be seen that the organic yields of I^{128} from the $I^{127}(n,\gamma)I^{128}$ process in solutions of 0.05 mole fraction

TABLE III

ORGANIC YIELDS OF THE (n,γ) PROCESS ON ETHYL HALIDES IN HYDROCARBONS IN THE PRESENCE OF IODINE SCAVENGER

I_2, mole fraction	Organic yield in Pentane	Heptane	Decane
	Yields from C_2H_5I,[a] %		
0.000	45.0	47.0	52.5
.001	..	44.2	48.2
.0013	39.0	..	..
.0019	37.0	..	..
.002	37.8	41.6	45.6
.004	35.0	..	..
.005	..	38.0	..
	Yields from C_2H_5Br[b]		
0.000	40.4	46.0	49.0
.007	..	34.1	39.0
.0015	..	33.3	37.8

[a] The mole fraction of C_2H_5I was 0.05. [b] The mole fraction of C_2H_5Br was 0.10.

of C_2H_5I in *n*-pentane, *n*-heptane and *n*-decane, and of Br^{80} from the $Br^{79}(n,\gamma)Br^{80}$ process on C_2H_5Br at 0.1 mole fraction in *n*-heptane and *n*-decane, increase with increasing chain length of the hydrocarbon. Because the difference persists even in the presence of sufficient scavenger to nearly eliminate encounters of the thermalized tagged atom with radicals by diffusion, it must be concluded that the chain length of the hydrocarbon molecules affects the probability that the tagged atom will enter organic combination before diffusion as a thermalized atom. The most probable cause of such an effect seems to be a difference in the effectiveness of the solvent cages for retaining the tagged atom in contact with an organic radical it has just formed long enough for a stable compound to be formed.

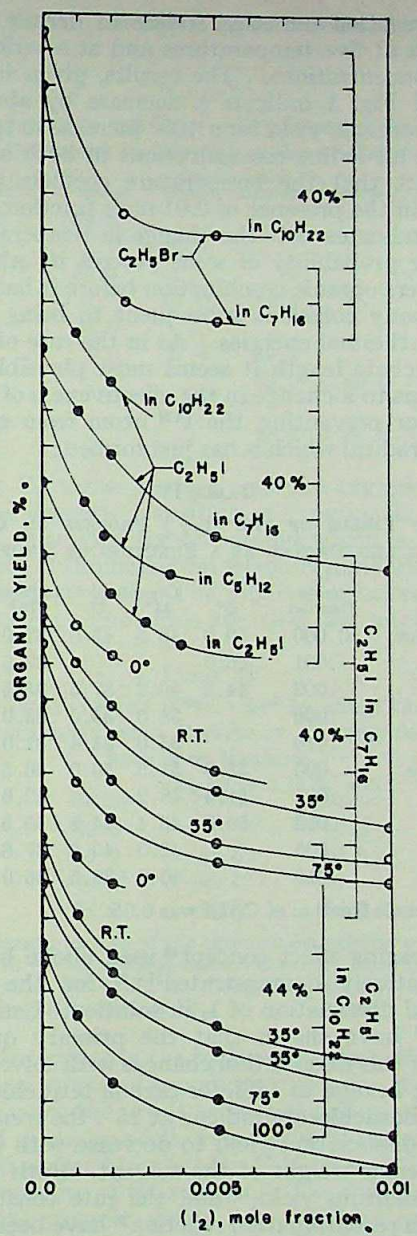

Fig. 1.—Effect of iodine scavenger on the organic yields of the $Br^{79}(n,\gamma)Br^{80}$ and $I^{127}(n,\gamma)I^{128}$ processes in hydrocarbon solutions as a function of solvent and temperature. Concentration of C_2H_5Br for upper two curves 0.10 mole fraction; concentration of C_2H_5I for lower three groups of curves 0.05 mole fraction. Each division on the scales at the right represents 2% in organic yield. The scale for each group of curves is labeled with a single percentage value opposite the center of the curves to which it applies.

Because the effectiveness of the solvent cages might be expected to decrease with increasing temperature, and also because the higher solubility of iodine at higher temperatures makes it possible to use higher concentrations of iodine scavenger, determinations were made of the organic yields of the

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(n,γ) reaction on ethyl iodide in decane and in heptane at five temperatures and at a series of iodine concentrations. The results, given in Table IV and Fig. 1 indicate a decrease by about one fifth in organic yield for a 100° increase in temperature at all iodine concentrations in both solvents. The fact that the temperature coefficient is observed in the presence of 0.01 mole fraction I_2 scavenger indicates that the change in temperature alters the probability of some process by which the I^{128} enters organic combination before it has undergone many collisions subsequent to being moderated to thermal energies. As in the case of the effect of chain length it seems most plausible to ascribe this to a change in the effectiveness of solvent cages for preventing the I^{128} atom from escaping from a radical which it has just formed.

TABLE IV

ORGANIC YIELDS OF THE (n,γ) PROCESS ON C_6H_5I[a] IN HEPTANE AND DECANE AS A FUNCTION OF TEMPERATURE

	I_2, mole fraction	Organic yield in % at 0°	35°	55°	75°	100°
Heptane	0.000	50.0	46.5	45.0	41.0	
	.001	46.0	..	..	37.5	
	.002	44.2	40.2	37.5	35.5	
	.005	..	38.0	34.0	33.0	
	.010	..	35.0	33.4	31.0	
Decane	.000	55.0	51.5	50.0	46.5	45.5
	.001	51.4	48.2	..	42.6	..
	.002	50.0	45.4	44.8	40.5	39.0
	.005	..	42.0	40.5	37.8	36.5
	.010	..	40.0	38.5	36.0	34.4

[a] The mole fraction of C_2H_5I was 0.05.

The caging effect concept[16] used above has been quantitatively demonstrated[17-19] for the photochemical dissociation of I_2 in solution. Lampe and Noyes[18] have shown that the primary quantum yield for this dissociation changes with solvent from 66% for hexane to 14% for carbon tetrachloride to 4% for hexachlorobutadiene at 25°, the trend being for the dissociation yield to decrease with increase in molecular weight of the solvent. Both the primary quantum yield,[18] and the rate constant for the atom recombination reaction[20] have been shown to increase with increase in temperature.

The only report in the literature on the effect of temperature on the organic yields of the (n,γ) process in pure liquid ethyl halides,[21] of which we are aware gives values of 37.0 and 38.6% for C_2H_5I at −78 and 20° and of 34.5 and 31.8% for C_2H_5Br at −78 and 0° indicating less temperature sensitivity than that shown in the present work for hydrocarbon solutions at higher temperatures. Limited data[3a] indicate a small negative temperature coefficient for the organic yield of Br^{80} from the (n,γ) and isomeric transition processes in CCl_3Br and little or no temperature effect for Cl^{38} in CCl_4.

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(17) R. Marshal and N. Davidson, *J. Chem. Phys.*, **21**, 2086 (1953).

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Consideration of Mechanisms.—The "hot" reactions observed as described above must involve one of the following mechanisms: (a) combination of a neutral recoil atom with an organic radical it had just formed, and with which it combines either before escaping from their common solvent cage or after only a few diffusive encounters with solvent molecules; (b) attack of an energetic neutral recoil atom on a solvent molecule in a displacement reaction in which it replaces a radical or atom; (c) formation of a molecule–ion by reaction of a recoil halogen ion with a solvent molecule, followed by neutralization or reaction of the molecule–ion to yield a stable organic halide molecule. It is impossible, at present, to distinguish between these mechanisms for liquid systems. Gas phase studies have shown, however, that I^{128}, Br^{80} and Cl^{38} when activated as a result of formation by the (n,γ) process can all enter organic combination by displacement reactions between the halogen atom or ion and hydrocarbon molecules, under conditions where the possibility of reaction of the tagged species with free radicals is eliminated.[8,10,22] There is evidence that the atom must have a charge for this type of reaction to occur.[10b] It is probable, therefore, that reactions of ions contribute to the "hot" portions of the reactions discussed in this paper and to many other "hot" reactions initiated by nuclear transformations in both the gas and condensed phases. It is reasonable to assume that these ionic reactions are related in type to the highly efficient ion–molecule reactions[23] currently under intensive study by mass spectrometric techniques. It seems probable that the formation of carbon chains by recoil tritium atoms in methane,[5a] and the other highly efficient reactions of tritium atoms activated by recoil and by tritium decay[5b] are due to ionic reactions of the type revealed by the mass spectrometric studies.

The organic yield of 50% observed for the gas phase reactions of methane with iodine activated by the $I^{127}(n,\gamma)I^{128}$ process is drastically lowered by a few mole per cent. of C_2H_5I and the yield in pure C_2H_5I gas is only about 1%.[10] Because the ionization potential of the C_2H_5I (9.5 e.v.) is lower than that of the I atom (10.4 e.v.) the effect of C_2H_5I in lowering the yield with CH_4 has been ascribed to neutralization of the $I^{128}+$ ions by C_2H_5I before their kinetic energy has been sufficiently reduced to allow them to form a stable combination. It is possible that similar factors may play some role in the reactions of mixtures of liquid alkyl halides and hydrocarbons with halogens activated by the (n,γ) processes. Major differences from the gas phase results might be expected, however, due to caging effects, differences in charge transfer potentials, and differences in the nature and stability of the molecule ions formed. Among the experimentally observed differences are the low organic yields of I^{128} in gaseous C_2H_5I(1%)[10] as compared to liquid C_2-

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H_2I(42%),[24] and in gaseous C_2H_6(3%), C_3H_8(4%) and C_4H_{10}(5%)[22] as compared to the liquid hydrocarbons tested in the work of this paper (Table III). Likewise the organic yield of I^{128} reacting with CH_4 in the gas phase is much more sensitive to added C_2H_5I (*i.e.*, 5 mole % C_2H_5I reduces the yield in gaseous CH_4 by more than 50%)[10b] than are the yields from the hydrocarbons of this paper in the liquid phase. In all probability these differences are due in part to the fact that non-ionic reactions in which the recoil atom can combine with a radical it has formed are made possible by the caging effect and greater probability of diffusive recombination in the liquid.

Correlation with Reactions of Cl^{38}.—Unlike the reactions of I^{128} and Br^{80}, the reactions of Cl^{38} activated by the (n,γ) process in liquid hydrogenous media give a constant organic yield (21%) which is independent of whether the solvent is an alkyl chloride or a hydrocarbon or a mixture of the two, and is independent of the chain length.[8] This unexpected independence of the yield on environment has had no satisfactory explanation. Consistent with the discussion in the preceding paragraphs it may now be explained tentatively by the hypothesis that only ionic reactions lead to organically bound Cl^{38} in liquid hydrogenous media, that 21% of the $Cl^{37}(n,\gamma)Cl^{38}$ events occur with internal conversion which produces ions,[25] and that all such ions result in organically bound chlorine. Chlorine atoms, unlike bromine and iodine atoms abstract H from C–H bonds with very low activation energy. In media where such bonds are available, every neutral chlorine atom would be expected to be fixed in inorganic combination as HCl. Br^{80} and I^{128} atoms, which do not abstract hydrogen as readily, have a greater opportunity to react with radicals which they form in losing the energy from the (n,γ) process. Consequently they may be expected to show organic yields which vary with the varying fragmentation and caging characteristics of different media. Similar variations are to be expected for Cl^{38} in non-hydrogenous solvents where the activation energy for reaction of chlorine atoms with the solvent is high. This is illustrated by the relatively high organic yield (44% total, *ca.* 32% "hot") and scavenger effect observed[8] with carbon tetrachloride in contrast to the 21% total organic yield with no scavenger effect for hydrogenous solvents.

Reaction of Hydrocarbons with Bromine Activated by the Br^{80} Isomeric Transition.—The data of Table V show that the organic yields of bromine activated by the isomeric transition process in hydrocarbons increase with increasing chain length of hydrocarbon regardless of scavenger concentration, as in the case of (n,γ) activation. Although the two nuclear processes are very different both can contribute both charge and recoil energy to the atoms involved. These data add further to the growing evidence[14,26,27] that the chemical events induced by the two types of activation are largely identical.

TABLE V

ORGANIC YIELDS OF THE $Br^{80m} \rightarrow Br^{80}$ ISOMERIC TRANSITION IN SOLUTIONS OF BROMINE IN HYDROCARBONS

Br_2, mole fraction	Organic yield, %, in Pentane	Hexane	Heptane	Nonane	Decane
9×10^{-6}	39.5	..	..	..	..
1×10^{-5}	..	42.5	..	..	..
9×10^{-5}	39.0	..	..	..	..
0.0001	..	41.0	42.3	45.5	49.1
.0009	33.0	..	..	..	..
.001	..	37.4	39.2	..	..
.005	..	..	35.0	40.5	42.0
.01	..	..	..	..	40.5
.02	..	..	27.4	30.8	..

Table VI shows further that the organic yields from the isomeric transition of bromine in hydrocarbons vary with the compound which is used as the source of bromine even when its mole fraction is as low as 1×10^{-5}. The differences between different source compounds are, to a first approximation, independent of the hydrocarbon solvent and of the concentration of bromine scavenger. It appears that they are the result of partial failure of the C–Br bond to rupture following isomeric transition, as observed earlier[28] for CCl_3Br, C_6H_5Br and CH_3Br in liquid bromine as the solvent. The differences between the organic yields from CCl_3Br and from Br_2 observed for the solvents of Table VI are 12.5, 11.0 and 11.0%, in striking agreement with the bond rupture failure of 10–13%[22,28] observed for CCl_3Br in the previous work; the differences between C_2H_5Br and Br_2 of 5, 9.5 and 6% are similar to the failure value of 6.5% for CH_3Br[28]; and the differences between CH_2Br_2 and Br_2 of 3.4, 8.5, 5.5 and 5.0% correspond to the failure value of 4.3%.[22] If the interpretation here is correct, it is of particular interest that the retention, in the parent molecule, of bromine atoms which have undergone isomeric transition, is so similar in hydrocarbon solvents and in liquid bromine.

TABLE VI

ORGANIC YIELDS OF THE $Br^{80m} \rightarrow Br^{80}$ ISOMERIC TRANSITION IN HYDROCARBONS WITH DIFFERENT COMPOUNDS AS THE SOURCE OF BROMINE

	Organic yield, in %, with $CHBr_3$[a]	CCl_3Br[a]	C_2H_5Br[a]	Br_2[a]
Pentane	43.0	..	44.5	39.5
Heptane	51.0	55.0	52.0	42.5
	40.5[b]	46.0[b]	..	35.0[b]
Decane	54.0	60.0	55.0	49.0

[a] The concentration of the bromine containing compound was 1×10^{-5} mole fraction in each case except for the second row of values for heptane. [b] Reaction solution contained 5×10^{-3} mole fraction of Br_2.

Acknowledgment.—This work was supported in part by the United States Atomic Energy Commission and in part by the University Research Committee with funds made available by the Wisconsin Alumni Research Foundation.

MADISON, WISCONSIN

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND INSTITUTE FOR ATOMIC RESEARCH, IOWA STATE COLLEGE]

Antiferromagnetic Ordering and Electronic Structure of $CuCl_2 \cdot 2H_2O$ as Determined from Nuclear Magnetic Resonance[1]

BY R. E. RUNDLE

RECEIVED JANUARY 18, 1957

The nuclear magnetic resonance study of $CuCl_2 \cdot 2H_2O$ by Poulis and Hardeman is coupled with neutron diffraction data on proton positions to obtain the type of antiferromagnetic ordering in $CuCl_2 \cdot 2H_2O$, and the distribution of the odd-electron in the $CuCl_2 \cdot 2H_2O$ "molecule." It is found that the odd-electron must be about 25% on each chlorine, 50% on copper. This distribution is consistent with a molecular orbital treatment of the complex, but not with crystal field theory or with Pauling's theory of directed valence in square copper complexes. The use of nuclear magnetic resonance in crystals as a probe for determining the distribution of magnetic electrons appears to be sensitive and deserving of further use.

Introduction

Recently Poulis and Hardeman (P and H) have examined proton magnetic resonance in $CuCl_2 \cdot 2H_2O$ down to very low temperatures, finding that below 4.3°K. $CuCl_2 \cdot 2H_2O$ is antiferromagnetic.[2] By studying the proton resonance in single crystals both above and below the Néel point they have attempted to determine both the magnetic structure and the proton positions in this compound.[2] These problems are related since, in a paramagnetic or antiferromagnetic crystal, the magnetic field at the proton is a function of the crystal field as well as the external field.

The conclusions of P and H on the magnetic structure are shown in Fig. 1. The positions of copper, oxygen and chlorine were determined by Harker, using X-ray diffraction,[3] which, of course, did not yield proton positions. In Fig. 1 the arrows give the spin arrangement inferred by P and H.

The proton positions of P and H are quite unsatisfactory, leading to O–H distances of 1.7 Å. within the water molecules, whereas positions determined by neutron diffraction yield O–H distances and HOH angles which are nearly the same as in free water molecules[4] (0.97 Å. and 104.5°, respectively).[5] Since, as noted above, the proton positions and antiferromagnetic ordering are related, it seems likely that the erroneous proton positions resulted from an erroneous magnetic structure.

In the subsequent sections of this paper using proton positions as obtained by Peterson and Levy,[4] it is shown that the magnetic ordering suggested by P and H is unable to account for the field at the proton. A different magnetic ordering is next shown to be more consistent with the structure of $CuCl_2 \cdot 2H_2O$, and, finally, taking the proton position and the magnetic ordering to be known, it is shown that the odd-electron in $CuCl_2 \cdot 2H_2O$ is not localized on copper but is distributed over copper and chlorine sites. In an independent paper it is shown that this electron distribution arises naturally from a molecular orbital treatment of square, planar copper complexes.[6]

Proton Magnetic Resonance and the Proton Position.—In a proton magnetic resonance experiment the energy difference between parallel and antiparallel arrangements of the proton magnetic moment in the field at the proton is measured. Under these circumstances the energy difference is proportional to the magnitude of the field at the proton, or

$$\Delta E = K|\mathbf{H}| \tag{1}$$

In a magnetic substance, such as $CuCl_2 \cdot 2H_2O$, the local field at the proton is the vector sum of the external field, $\mathbf{H}_0$, and the crystal field, $\mathbf{H}_c$, and since $\mathbf{H}_c$ depends upon the location of the electrons giving rise to the magnetic properties of the compound, proton resonance may yield information concerning electronic structure by serving as a measure of $\mathbf{H}_c$.

In the antiferromagnetic region at low fields, $H_0 < 2000$ oersteds P and H have shown that the moments in $CuCl_2 \cdot 2H_2O$ point parallel and antiparallel to a, and this result seems certain although their exact arrangement of spins may be in error. Let the moment on the jth atom be μ_j. Then

$$\mathbf{H}_c = \sum_j - \text{grad}\, \frac{\mu_j \cdot \mathbf{r}_j}{r_j^3} \tag{2}$$

where $\mathbf{r}_j$ is the vector from the jth atom to the proton in question. It follows that

$$H_{c_x} = \sum_j \pm \mu_j \frac{[2(X - x_j)^2 - (Y - y_j)^2 - (Z - z_j)^2]}{r_j^5} \tag{3}$$

$$H_{c_y} = 3\sum_j \pm \mu_j \frac{(X - x_j)(Y - y_j)}{r_j^5} \tag{4}$$

$$H_{c_z} = 3\sum_j \Sigma \pm \mu_j \frac{(X - x_j)(Z - z_j)}{r_j^5} \tag{5}$$

where H_{c_x}, H_{c_y}, H_{c_z} are the components of $\mathbf{H}_c$, and the sign of μ_j is positive or negative depending upon whether the moment on the jth atom is parallel or antiparallel to a. X, Y, Z are coördinates of the proton under consideration, and x_j, y_j, z_j are the coördinate of the jth atom. In the crystal there are many hydrogen positions, all related by symmetry, so that only one is unique.

For $\mathbf{H}_0$ in the ab plane, $H_{0_x} = H_0 \sin\alpha$ and $H_{0_y} = H_0 \cos\alpha$ where α is the angle between b of the crys-

(1) Paper presented at Spring A.C.S. Convention, Dallas, April, 1956. Contribution No. 426. Work was supported in part by the Ames Laboratory of the U.S.A.E.C.

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(6) R. E. Rundle and J. W. Richardson, presented at the Dallas Meeting of the A.C.S., April, 1955.

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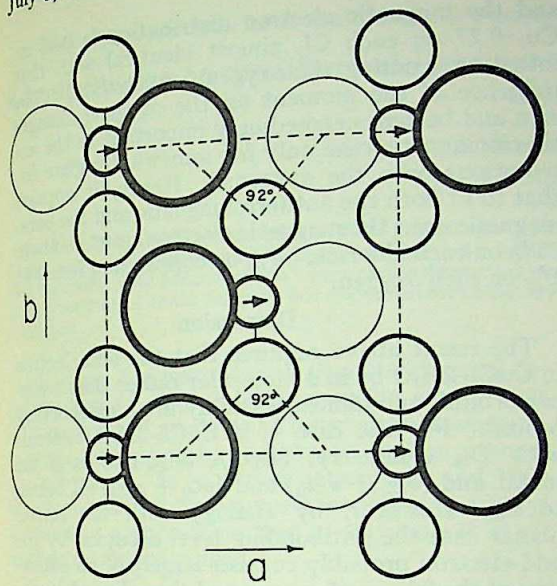

Fig. 1.—Structure of $CuCl_2 \cdot 2H_2O$. Large circles are chlorine atoms, medium are oxygen atoms, small are copper atoms. Arrows show magnetic ordering on (001) as proposed by Poulis and Hardeman. Copper atoms in alternate planes have antiparallel moments.

tal and the external magnetic field vector $\mathbf{H}_0$. Then

$$|H| = [(H_0 \sin \alpha + H_{c_x})^2 + (H_0 \cos \alpha + H_{c_y})^2 + H_{c_z}^2]^{1/2} \quad (6)$$

The maximum energy difference between the parallel and antiparallel proton alignments will then occur at H_{max}, and setting $\partial |H|/\partial\alpha = 0$

$$\tan \alpha_{ab_{max}} = H_{c_x}/H_{c_y} \quad (7)^7$$

where $\alpha_{ab_{max}}$ is the direction of $\mathbf{H}_0$ which maximizes the proton resonance energy for $\mathbf{H}_0$ in the *ab*-plane. P and H have examined resonance in the *ab* plane, and find $\alpha_{ab_{max}} = 56°$.

To find H_{c_y} and H_{c_x} at the proton it is necessary to sum over the copper atoms. P and H summed over the nearest nine coppers which form a trigonal prism with the proton in question off-center within the prism. Convergence is not excellent, and we have summed over the nearest thirty copper atoms. This results in a correction of several per cent. It was found that for the known proton position the calculated $\alpha_{ab_{max}}$ was ~12°, far from that observed by P and H. In this stage of the calculation the magnetic ordering suggested by P and H, Fig. 1, was used, and it was assumed that the magnetic moment was localized on copper.

In another paper we show that localizing the odd-electron, responsible for the moment, upon copper cannot be justified[6]; consequently, the calculations were repeated with part of the moment on chlorine. Taking the moment on chlorine to be $\lambda\mu_{Cu}$, the magnetic ordering suggested by P and H produced negative values for λ. This is physically unacceptable since the moment of an electron shared between copper and chlorine should surely have the same orientation on both. A similar negative value arose when the moment was delocalized onto oxygen *and* chlorine.

(7) These equations are equivalent to those of P and H except for some typographical errors.[1]

The Antiferromagnetic Ordering.—Having been satisfied that the suggested magnetic ordering is incorrect we have considered what to expect for magnetic ordering from the structure. Here it is to be noted that $CuCl_2 \cdot 2H_2O$ is unusual among known antiferromagnetic materials, in that the metal ions are not bridged together into a three-dimensional network. Along the **C**-axis of the crystal run chains, Fig. 2, with short (3.73 Å.) copper–copper distances. Two oxygen and/or chlorine atoms separate each chain from its neighbors, and the Cu–Cu distance between chains is 5.5 Å. Hence, it seems unreasonable to expect super-exchange to cause the ordering except within the chains, where the spin arrangement along the chains should be alternate.

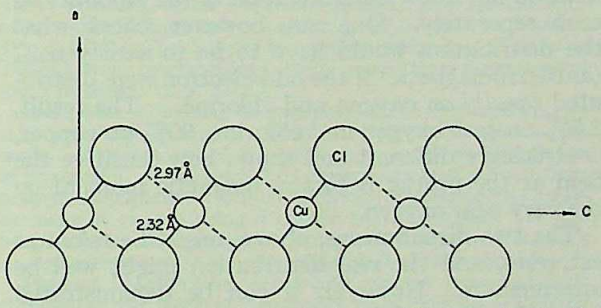

Fig. 2.—$CuCl_2$ chain in the hydrate. Water molecules lie above and below each chain, so that copper atoms in neighboring chains are well shielded from each other.

If it is correct that super-exchange is important only along the chains, it then seems likely that direct magnetic interaction among the chains is responsible for the rest of the ordering. Looking at the (001) face, the copper arrangement within the face is face-centered (Fig. 3). It is, then, easily seen that spin arrangement (A) (Fig. 3) is favored

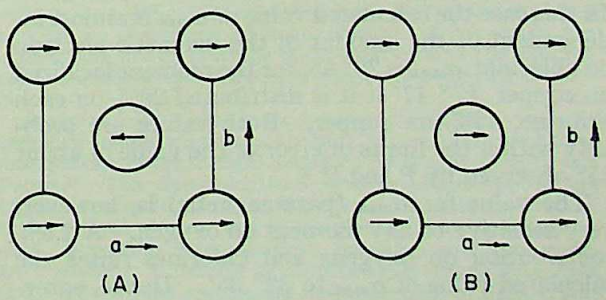

Fig. 3.—(A) is magnetic ordering proposed in this paper; (B) is the magnetic ordering of P and H. In both cases, alternate planes are antiparallel.

by magnetic interactions if an appreciable part of the moment is on chlorine, as seems likely, while B is the arrangement suggested by P and H. It is to be noted that the chains with alternating spins run normal to (001), and in proposing arrangement (A) we are proposing not that direct magnetic interactions of spins cause antiferromagnetic ordering, but that whole chains of already ordered spin-moments interact magnetically to cause the three-dimensional magnetic ordering.

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Electron Distribution in $CuCl_2 \cdot 2H_2O$.—The proton position and magnetic arrangement (A), Fig. 3, still will not explain the proton resonance data of P and H if all the magnetic moment is centered on copper. (A calculation of α_{max} for this case yielded $\sim 80°$ *vs.* 56° observed.) It is necessary, therefore, to again consider whether the odd-electron is also distributed over chlorine positions. To do this we have considered that the moment on copper is μ, while that on chlorine is $\lambda\mu$, and have carried out the sums in equations 3 and 4 over the nearest thirty coppers and the nearest forty-four chlorine atoms, assuming the magnetic ordering (A) above. For this model, equation 7, above, yields $\lambda = 0.55$, whence the odd-electron distribution is approximately 26% on each chlorine, 48% on copper.

The magnetic electron might well be distributed over oxygens *and* chlorines, but unfortunately the data do not allow determination of the amounts on each separately. One can, however, check what the distribution would have to be to satisfy α_{max} (antiferromagnetic) if the odd-electron were distributed *equally* on oxygen and chlorine. The result, 2.5% on *each* oxygen and chlorine, 90% on copper, is strikingly different and shows how sensitive the field at the proton is to any magnetic moment on the very near oxygen.

The two distributions, above, might be taken as extremes, and the real distribution might well be intermediate. However, it can be demonstrated from the data of P and H in the paramagnetic range[2] that the former is more nearly correct than the latter.

Neutron Resonance in the Paramagnetic Region.—In the paramagnetic case, proceeding as before, but assuming that on the average field and proton moment are parallel, it is found that

$$\tan 2\alpha_{max} = \frac{-2\sum_j (X - x_j)(Y - y_j)/r^5}{\sum_j (X - x_j)^2 - (Y - y_j)^2/r^5} \qquad (8)$$

In this case the calculated value of α_{max} is almost independent of the amount of the magnetic electron on chlorine; α_{max} is 26° 45′ for the moment localized on copper, 27° 17′ if it is distributed 26% on each chlorine, 48% on copper. Both values are probably within the limits of error of the value of about 25° observed by P and H.[2]

The value for α_{max} (paramagnetic) is, however, very sensitive to any moment on oxygen. A 2.5% contribution on oxygens and chlorines raises the calculated value of α_{max} to 32° 35′. Hence, agreement with the observed value of α_{max} (paramagnetic) is lowered by putting any amount of the odd-electron onto oxygen.

It seems reasonable to assume that the observed value of α_{max} may be in error by several degrees. (P and H gave no estimate of their error in mounting the crystals, etc.). Setting an upper limit upon α_{max} (paramagnetic) of 29°, the maximum allowable part of the magnetic electron on each oxygen is 0.008. Using this value, and solving for λ_{Cl} in the antiferromagnetic case, it is found that $\lambda = 0.63$ and the magnetic electron distribution is 0.44 on Cu, 0.27 on each Cl, almost identical with that found by ignoring the oxygen contribution. (The influence of the moment on the oxygens changes sign and becomes exceedingly important in the antiferromagnetic case only for somewhat higher distributions onto the oxygens.) Hence, it appears that to fit both the antiferromagnetic and the paramagnetic data the magnetic electron must be about 25% on each chlorine, 50% on copper, and less than 1% on each oxygen.

Discussion

The result above requires that the odd-electron in $CuCl_2 \cdot 2H_2O$ be in a molecular rather than a copper orbital, and almost certainly in an antibonding orbital. For the case of a $CuCl_2 \cdot 2H_2O$ molecule with D_{2h} symmetry, $3d_{x^2-y^2}$, $3d_{z^2}$, and 4s of the metal, and $(\sigma_{Cl_I} + \sigma_{Cl_{II}})$ and $(\sigma_{O_I} + \sigma_{O_{II}})$ all belong to a_{1g}. However, by analogy with the square planar case the antibonding level occupied by the odd-electron probably consists largely of an admixture of the $3d_{x^2-y^2}$ of copper and the σ-ligand levels. The strong mixing in the antibonding level suggests a similar strong mixing in the corresponding bonding level.

These results are clearly incompatible with crystal field theory, where the odd-electron is assumed to be localized in a 3d-orbital of copper, or with Pauling's theory of directed valence, where the odd-electron is localized in a 4p-orbital of copper. They are, however, in keeping with other recent work where quite generally magnetic electrons of transition metal complexes are found to occupy antibonding molecular orbitals rather than localized metal orbitals.[8]

It is to be noted that the conclusions reached here relative to magnetic ordering and odd-electron distribution are, in principle, and probably in fact, subject to check by neutron diffraction. It is hoped that studies along these lines will be possible in spite of the very low temperature required for the neutron diffraction work.

Finally, the method employed, of using a nucleus with spin as a probe for the magnetic field within a magnetic crystal, appears to give a sensitive method for discovering the magnetic electron distribution within the crystal. The interpretation of the experimental results appears to be straightforward when the crystal structure is known, and the method appears to deserve wide use.

Acknowledgment.—Thanks are due to Drs. S. W. Peterson and H. A. Levy of the Oak Ridge National Laboratory for making their proton positions available to me prior to publication, and for their interest in the problem. Both have made some refinements of this paper possible.

AMES, IOWA

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[CONTRIBUTION FROM THE CHEMISTRY BRANCH OF THE AERONAUTICAL RESEARCH LABORATORY]

Kinetic Studies on the Thermal Decomposition of *t*-Butyl Hydroperoxide in Dodecane Solution

BY B. KATHLEEN MORSE[1]

RECEIVED NOVEMBER 5, 1956

The kinetics of the decomposition of *t*-butyl hydroperoxide in dodecane solution, 0.05–0.6 molal, were studied in a closed system and in a helium-swept apparatus at 98.5°. An initial first-order rate constant prevails for the helium-swept reaction over the twelve-fold concentration range and is dependent upon the removal of evolved oxygen. This initial decomposition is apparently not a chain reaction nor does it involve *t*-butoxy radicals. A mechanism is suggested, and an approximate E_a is calculated.

Milas and Surgenor[2] found that the thermal decomposition of *t*-butyl hydroperoxide above 150° led to an array of products: *t*-butyl alcohol, acetone, methane, methanol, formaldehyde, carbon monoxide and water. In contrast between 95 and 100° they found that it decomposed smoothly to *t*-butyl alcohol and oxygen according to equation 1[3] in almost quantitative yields.

$$\mathrm{ROOH} \longrightarrow \mathrm{ROH} + {}^1/_2\mathrm{O}_2 \qquad (1)$$

This decomposition has been one of the curiosities of the literature in view of the mechanistic studies conducted at higher temperatures. The qualitative work in the vapor phase[4,5] and kinetic studies in octane solution[4] between 150 and 195° led to the conclusion that the decomposition occurred by a combination of unimolecular and chain processes dependent upon the fission of the O–O bond (equation 2), the ability of *t*-butoxy radical to liberate a methyl group[6] (equation 3), the hydrogen-abstraction reactions of these radicals with either the solvent or the hydroperoxide (equation 4), and the conversion of the alkyl peroxy radicals to alkoxy radicals either bimolecularly or *via* peroxide formation by reaction with an alkyl radical.

$$\mathrm{ROOH} \longrightarrow \mathrm{RO}\cdot + \cdot\mathrm{OH} \qquad (2)$$

$$\mathrm{RO}\cdot \longrightarrow \mathrm{MeCOMe} + \mathrm{Me}\cdot \qquad (3)$$

$$\mathrm{X}\cdot + \mathrm{ROOH} \longrightarrow \mathrm{XH} + \mathrm{ROO}\cdot \qquad (4)$$

The decomposition below 100° (equation 1) is difficult to understand in terms of the mechanism found at higher temperatures. The relative stability of the *t*-butoxy radical seems an insufficient basis for the difference in the course of the two reactions. In this paper kinetic evidence for a non-chain reaction independent of equation 2 and dependent upon the evolution of oxygen is presented. It is believed that the evidence reported is important not only in itself but with respect to the mechanism of oxidation where the hydroperoxide has a nebulous role as a source of chain-branching.

Experimental

Reagents.—*t*-Butyl hydroperoxide (Lucidol) carefully fractionated at reduced pressure in a 1 m. vacuum-jacketed column packed with 1/4" helices could be stored in the refrigerator six months without change in the infrared spectrum, peroxidic titer, or refractive index. A typical sample had the following properties: b.p. 36.5° at 15 mm.; n^{17}D 1.4012; 98.56% ROOH by iodometric titration. Dodecane (Eastman practical grade) was distilled from sodium at reduced pressure, stored over sodium wire, and flushed with oxygen-free helium before use; b.p. 97.5–99.5° at 5 mm.; n^{19}D 1.4215. The 2,6-di-*t*-butyl-4-methylphenol (Eastman Tenox) was recrystallized from methylcyclohexane and dried *in vacuo;* m.p. 71.5°.

Inert Gas.—Flushing or sweeping of the system to maintain anaerobic conditions was necessary throughout the work. The removal of oxygen from nitrogen by absorption in pyrogallol, metal ketyl,[7] or chromous chloride[8] solutions proved inadequate for some concurrent studies on the measurement of oxygen using a carrier gas so purified. It was necessary therefore to use helium which was passed through an Ascarite tower to remove water and carbon dioxide.

Product Identification.—Infrared spectra were obtained throughout the work in matched 1 mm. cells on a Perkin–Elmer Double Beam Spectrophotometer with sodium chloride optics. Spectral changes throughout a run indicated *t*-butyl alcohol and acetone were the major products; comparisons were made with the spectra of the pure substances at comparable concentration in dodecane solution. The characteristic absorption bands used for identification in dodecane solution were 5.78–5.80 μ for acetone, 10.98–11.00 μ for *t*-butyl alcohol and 11.98–12.00 μ for *t*-butyl hydroperoxide.[9] There was no spectral evidence for the formation of di-*t*-butyl peroxide which has a characteristic absorption band at 11.4 μ.[9] The absorption at 2.7–3.0 μ was sufficiently ambiguous to preclude any interpretation for the absorption band for water. Chromous chloride solutions[8a] were investigated for quantitative work on the measurement of oxygen, but difficulties in maintaining a standard solution and in the absorption of small amounts of oxygen in the effluent gas stream preclude the presentation of the data except as qualitative evidence for the early evolution of oxygen.[10]

Analyses.—The change in hydroperoxide titer was determined iodometrically in absolute isopropyl alcohol by a modification of the method described by Wagner, Smith and Peters.[11] The determinations were reproducible within 1%. At room temperature (or 0°) no difficulty was experienced with an oxygen error so samples could be handled with ease. Peroxidic determinations by iodometric procedures are equivocal; a number of iodometric methods have been used to determine specifically hydroperoxide or dialkyl peroxide which depend only upon differences in reaction time, solvent and temperature.[12] In the present work a depend-

(1) For reprints address: Commander, Hq., Wright Air Development Center, Attn.: B. K. Morse, WCRRC, Wright-Patterson Air Force Base, Ohio.

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able method for *t*-butyl hydroperoxide in conjunction with spectral checks for its presence and the absence of other peroxide bands was considered more reliable than an empirical method. In experiments where additional hydroperoxide could be formed the titer was treated as total peroxidic titer and is so noted. Acetone was the only product of the decomposition which lent itself to spectrophotometric determination in dodecane solution. Above 0.01 molal, the concentration could be determined within 7%. The detectable limit was about 0.005 molal.

Kinetics.—The apparatus for the swept experiments, shown in Fig. 1, consisted of a conical flask with a condenser

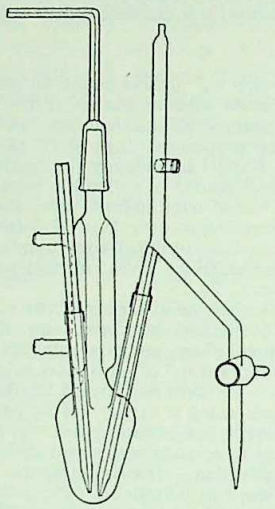

Fig. 1.—Apparatus for the helium-swept experiments.

and two side arms. One side arm held a capillary as an inert gas inlet, the other a λ-pipet[13] designed to allow the removal of liquid samples under a stream of inert gas. A hypodermic syringe was used to pull the sample into the arm of the pipet while the inert gas flow at the "T" was closed off. The condenser was packed with Pyrex wool to act as a vapor barrier; the temperature of the column was maintained at about 20°. Solutions were prepared by weight, transferred to the apparatus which had been flushed with oxygen-free helium for at least an hour. Sweeping of the system at 14–22 ml./hr. was continued another five minutes before the solution was thermostated in an oil-bath at 98.5 ± 0.1°. The apparatus was cleaned between experiments by various methods, ranging from a few rinses with isopropyl alcohol to treatment with hot nitric acid followed by a final rinse with ammonia before drying at 110°; the method of cleaning did not have any effect upon the experimental reproducibility.

The initial titer was determined 15 or 20 minutes after thermostating. Since there was danger of entrainment of the hydroperoxide at this temperature, each run was checked finally by pouring the remaining solution through the condenser to determine the increase, if any, in the hydroperoxide titer. All experiments in which the number of milliequivalents of entrained hydroperoxide exceeded the initial drop in titer upon thermostating were rejected. In illustration at 86° over a period of 11 days the total entrainment represented only 3% of the hydroperoxide initially in the solution.

The experiments in a closed system were conducted by the usual sealed ampoule technique. The ampoules were flushed with inert gas, filled, flushed again, and sealed with about a 1 cc. "air-space."

Calculations.—The order of the initial reaction in the swept system was found to be one by the ordinary procedures or the more precise method of Bateman.[14] Linear relationships between the logarithm of the concentration and time were obtained from the data throughout the period of observation. Representative data are so plotted in Fig. 2. The specific first-order rate constants for the respective slopes in each experiment (11–15 points per run) were determined however by an unweighted least-squares method which was independent of the initial titer. These data are presented in Table I. The probable error in the initial rate constants so calculated lay between 1 and 5%. Since the calculation reflects the fit of the line to the data, and there seemed to be no real trend in the variation of the rate constants with concentration, the rate constants for the helium-swept reactions were averaged. The average deviation of 10% is a realistic error for this experimental razor's edge between maximum rate of decomposition and excessive entrainment.

TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE DECOMPOSITION OF *t*-BUTYL HYDROPEROXIDE IN DODECANE AT 98.5°

Run no.	Hydroperoxide Initial molal concn. Expt.	Calcd.	$k \times 10^4$, sec.$^{-1}$ k_1[a]	k_2[a]
	A. Helium-swept			
I-23	0.05435	0.05430	5.79	17.0
I-12	.1848	.1970	6.38	24.7
I-21	.3206	.3204	5.17	(1.2)[b]
I-15	.6345	.6265	4.88	11.4
		Av.	5.55	
II-3	0.05545[c]	0.05415	5.15[c]	16.7[c]
	B. Sealed ampoule[d]			
I-4	0.06210	0.06375	0.112[e]	
I-9	.4738	....	.159[e]	
		Av.	.136	
II-2	.05630[f]	0.05705	.125[f]	
	C. Partially swept			
I-9	0.3412[e,g,h]	0.3423	6.43[e,g,h]	
I-10	.2159[e,h]	....	2.91[e,h]	16.1
I-18	.5125[i]	0.5377	3.44	2.60

[a] The first-order rate constants, k_1 and k_2 (pseudo first-order), are those of the initial and final decompositions, respectively. [b] An air leak developed overnight. [c] 0.04037 molal in 2,6-di-*t*-butyl-4-methylphenol. The solution showed a transition rate between k_1 and k_2 of 10.0×10^{-6}. [d] Pseudo first-order rate constants. [e] At 98.1° flushed or swept with "ketyl" treated nitrogen. [f] 0.05008 molal in 2,6-di-*t*-butyl-4-methylphenol. [g] Swept with "ketyl" treated nitrogen after heating 404 hours in a sealed tube. [h] System opened through a second condenser to remove samples. [i] Surface of the solution swept with helium.

Also shown in Fig. 2 are two representative growth curves of acetone.

Results and Discussion

Oxygen Evolution.—From a survey of Table I and Fig. 2 the slowness of the decomposition reaction at 98.5° is evident as well as the inhibitory effect of oxygen which was first noted by Stannett and Mesrobian.[15] The rate of the reactions is dependent not only upon the exclusion of air but also upon the removal of evolved oxygen. Maximum rates of decomposition were observed only if the solution were swept with a fine stream of bubbles of oxygen-free helium to remove the evolved oxygen. Under these conditions a constant first-order rate of decomposition was obtained over a twelve-fold concentration change (Table IA). The initial rate of decomposition, k_1, then increased somewhat erratically about threefold after a period of 20 to 22 hours when the hydroperoxide concentration had decreased by one third. In ampoules, though (Table IB), the hydroperoxide persisted

(13) Patent being applied for.

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over a 404-hour period, decomposing only 28% at a rate 1/40.8 (to 1/130) as rapidly as in the helium-swept reaction.

Between these two extremes intermediate rates were observed depending upon the nicety of the system. If the helium stream were passed over the surface of the solution, the observed maximum rate of reaction (anaerobic conditions) decreased almost twofold initially and as much as sevenfold during the last two-thirds of the reaction. If an air-leak developed, as in run I-21, the initial rate decreased over fourfold instead of increasing three-fold. If nitrogen containing a trace of oxygen were used to sweep the system (I-10) again the initial rate decreased.

The Reaction Intermediates.—The contrast in the rates of the swept and partially swept reactions observed throughout the experiments suggests that oxygen is retained by compound formation since the titer of the solution could not be altered by refluxing the samples in isopropyl alcohol solution before analysis. In peroxide decompositions or hydrocarbon oxidations three types of free radicals have been shown to be participants: alkyl, alkoxy and alkyl peroxy.[4,16-18] Of the three the alkyl radical is the one which may react rapidly, if not instantaneously with dissolved oxygen. This could be derived either from the solvent by the hydrogen-abstraction reaction of an oxygenated precursor or from the *t*-butoxy radical if it is formed, which liberates methyl radicals in reaction 3. Thus along with the evolution of oxygen concurrent alkyl radical formation to some extent must take place. Again comparison of the difference in the rates in the two systems, swept and partially swept, after 20 to 30 hours indicates the importance of the alkyl radical for the subsequent swept reaction, and one concludes that the retention of oxygen (Table IC) removes alkyl radicals which are necessary to realize the enhanced reaction identified by the specific rate constant k_2 in Table IA. The threefold increase in the rates of the swept reactions can best be attributed to the occurrence of reaction 4 between the hydroperoxide and an alkyl radical derived from the solvent. The occurrence of the abstraction reaction has been demonstrated in the vapor phase at 195° by the identification of methane-*d* in the reaction of methyl radicals with *t*-butyl deuteroperoxide.[5]

The reaction of the alkyl radicals with oxygen has been well established in oxidation reactions[16-18]

$$S\cdot + O_2 \longrightarrow SOO\cdot \qquad (5)$$

$$SOO\cdot + HS \longrightarrow SOOH + S\cdot \qquad (6)$$

where S· is an alkyl radical derived from the hydrocarbon, HS. In view of the important role of alkyl radicals in supporting the rapid reaction one concludes that in the unswept reactions the decreased rate may be attributed not only to the formation of a hydroperoxide (SOOH) but also to the exclusion of reaction 4. Experimental confirmation for the existence of *t*-butyl hydroperoxide was obtained by a prolonged period of observation of its characteristic absorption band when oxygen was left in the system to participate in reactions 5 and 6.

(16) C. E. Frank, *Chem. Revs.*, **46**, 155 (1950).
(17) J. L. Bolland and G. Gee, *Trans. Faraday Soc.*, **42**, 236 (1946).
(18) L. Bateman, *Quart. Rev.*, **8**, 147 (1954).

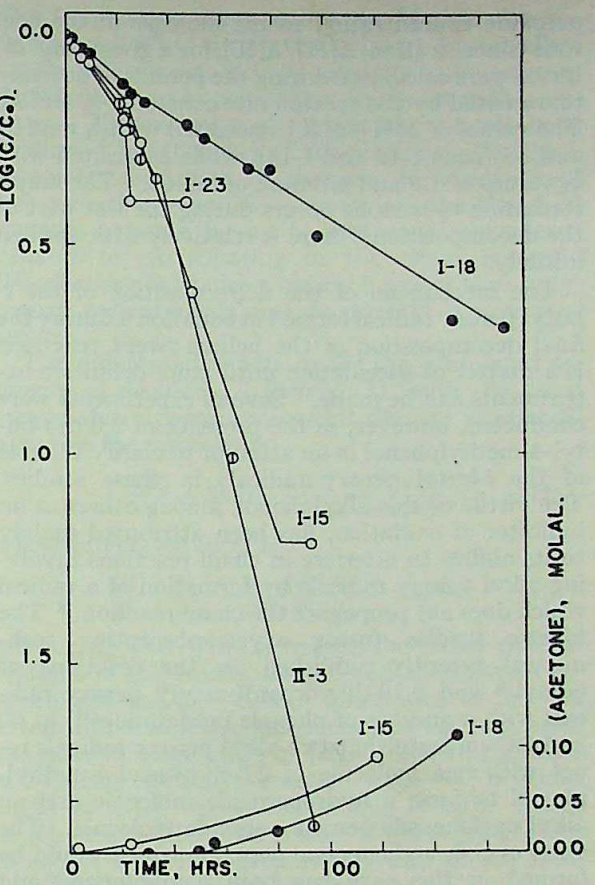

Fig. 2.—Representative data illustrating the effect of oxygen (●) and 2,6-di-*t*-butyl-4-methylphenol (Φ) on the first-order decomposition of ROOH (O) and on the formation of acetone.

Associated with the decrease in the rate when oxygen was allowed to remain or was added to the solution was an inhibition period in the formation of acetone. Representative curves of acetone formation for the anaerobic and aerobic reactions are shown in Fig. 2. When oxygen was allowed to remain in the solution acetone formation was delayed 30 or as many as 72 hours. The rate of formation of acetone after the period of inhibition was approximately the same for both the swept and the partially swept reactions, and could not be identified specifically with either the slow or rapid reaction. The absence of acetone during a period of net hydroperoxide decrease denotes the absence of *t*-butoxy radical (or the acetone precursor) and implies that *t-butoxy radical is not formed by an independent unimolecular cleavage* such as reaction 2. The absence of acetone during this period of oxygen absorption when reaction 4 is believed to be prohibited implies a dependence of acetone formation upon alkyl peroxy radical formation. Thus one is led to the interpretation that *t*-butyl peroxy radical is the precursor of *t*-butoxy radical or that acetone is formed directly from the alkyl peroxy radicals.

In the swept reactions where the observed hydroperoxide concentration is real, *i.e.*, no hydroperoxide is formed by the solvent radicals, there was little acetone formation during the initial decomposition. The ratios of the decrease in the hydro-

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peroxide concentration to the increase in the acetone concentration, $\Delta[H]/\Delta[K]$, for a given time interval were calculated during the periods of decrease represented by the specific rate constants k_1 and k_2. The values of $\Delta[H]/\Delta[K]$ associated with k_1 were 51 and 88 (runs I-12 and I-15), while associated with k_2 values of 1.9 and 4.8 were obtained. The major formation of acetone occurs during the last part of the decomposition; there is relatively little formed initially.

The mechanism of the decomposition of the *t*-butyl peroxy radical formed in equation 4 during the final decomposition of the helium-swept reactions is a matter of speculation until more definitive experiments can be made. Several experiments were conducted, however, in the presence of 2,6-di-*t*-butyl-4-methylphenol in an attempt to clarify the role of the *t*-butyl peroxy radicals in these studies. The virtue of this alkylphenol, among others as an inhibitor of oxidation, has been attributed mainly to its ability to interfere in chain reactions involving alkyl peroxy radicals by formation of a radical which does not propagate the chain reaction.[16] The kinetic studies (using oxygen-absorption techniques) recently published on the reactions of cumyl[19] and 9,10-dihydroanthracyl[20] peroxy radicals with a number of phenols (and amines[19]) at 60 and 62° indicate that two alkyl peroxy radicals react with one molecule of 2,6-di-*t*-butyl-4-methylphenol to form a hydroperoxide molecule and an alkyl cyclohexadienenone peroxide molecule. The alkyl cyclohexadienenone peroxide which would be formed in this case has been characterized and studied under a number of conditions.[21]

In contrast between 80–100° the 4,4′-dihydroxybiphenyl derivative as well as the stilbene quinone has been isolated from this alkylphenol under a variety of oxidative conditions: with benzoyl peroxide in chloroform,[22] with air in cumene containing ferric stearate,[23] and air in aqueous alkali.[24]

In the helium-swept experiments neither the rate nor the duration of the initial decomposition was affected by the alkylphenol (runs I-23 and II-3) as would be expected where one has evidence for a non-radical oxygen evolution with some concurrent alkyl radical formation. (The amount of alkyl peroxy radical formation was negligible.) The final stage of the decomposition is considered to be dependent upon the reaction of the remaining hydroperoxide with alkyl radicals and is probably responsible for the major destruction of the hydroperoxide at the enhanced rate k_2. But here also the rate, k_2, is unaffected. The only marked difference made by the alkylphenol is that it aids in effecting the completeness of the decomposition.

The experiment with the alkylphenol in the swept system (as well as the ampoule experiment) verifies the interpretation that the observed rates are measures of the (slowest) initiation and not the (fastest) termination reaction. Since the initial decomposition was totally unaffected by the alkylphenol one may assume that it is not a chain reaction and is indeed not dependent upon alkyl peroxy radical as the amounts of acetone obtained indicate. The concurrent alkyl radical formation is evidently unimpaired since the rate increases as before. The fact that there is an effect only on the final decomposition leads one to believe that the interpretation of the final decomposition based on equation 4 is correct. The present kinetic results though are incompatible with the formation of peroxides in the termination step as found in the oxygen-rich systems at 60°. Peroxide formation in the termination step by the postulated mechanisms[19,20] would mean in these experiments that every two alkyl peroxy radicals formed in equation 4 form a hydroperoxide and an alkyl cyclohexadienenone peroxide molecule, so that the net rate of decrease in the titer would be at most equal to that of the initial reaction, and no increase from k_1 to k_2 would be observed with the change in mechanism.[25] That only the completeness of the final decomposition is affected and not the rate suggests that the alkylphenol is more efficient than the solvent in irreversibly terminating the reaction (in a non-rate-determining step). It seems more reasonable to assume that alkyl peroxy radical–solvent interaction leading to equivalent amounts of hydroperoxide accounts for the final *impasse* observed in all the experiments without the alkylphenol (two are shown in Fig. 2) where the hydroperoxide concentration finally ceases to decrease at the rate k_2 than to attribute the effect to the alkylphenol–peroxy radical interaction. A termination step for the fast reaction (k_2) comprising the formation of two peroxidic molecules (one of which is determinable analytically) from every two alkyl peroxy radicals is hardly compatible with the observations in this oxygen-depleted system. The formation of non-peroxidic products such as the dihydroxybiphenyls and stilbene quinones in these experiments with the alkylphenol would appear to give a more consistent over-all kinetic picture at these temperatures.

Conclusions

From the data obtained under the various experimental conditions several facts emerge: (1) oxygen is evolved quite rapidly at the beginning of the decomposition in a reaction which is first order with respect to the hydroperoxide concentration; (2) the termination step during this part of the reaction does not depend upon alkyl peroxy radical; (3) alkyl radicals appear to be a critical intermediate for the subsequent reaction; (4) acetone and hence *t*-butoxy radicals, if formed, are apparently derived solely from *t*-butyl peroxy radical; and (5) the peroxy radicals are involved in the chain terminating reaction which is not rate determining.

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(22) S. L. Cosgrove and W. A. Waters, *ibid.*, 388 (1951).

(23) (a) R. F. Moore and W. A. Waters, *ibid.*, 243 (1954); (b) M. E. Hey and W. A. Waters, *ibid.*, 2753 (1955).

(24) G. R. Yohe, D. R. Hill, J. E. Dunbar and F. M. Sabic, THIS JOURNAL, **75**, 2688 (1953).

(25) The *t*-butyl 3,5-di-*t*-butyl-1-methylcyclohexa-2,5-diene-4-one peroxide which could be formed in these experiments from the alkylphenol would yield only 5% of its peroxidic oxygen by the analytical method used, therefore only the hydroperoxide was considered in the approximation. If every alkyl peroxy radical reformed a hydroperoxide (no alkylphenol present), then the rate would decrease to one-half of the initial rate.

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The decomposition in an anaerobic system evidently may occur by at least two related mechanisms, one, which rapidly evolves oxygen, occurs at relatively high hydroperoxide concentration, is first order with respect to the hydroperoxide concentration, and to which alkyl peroxy radical termination with acetone formation is incidental, the other reaction which follows after about 31% of the hydroperoxide has decomposed proceeds by a chain reaction dependent upon the existence of alkyl radicals. During the first reaction there is little ketone formation, the major product is *t*-butyl alcohol. During the more rapid decomposition which follows, ketone formation is fairly consistent with about one mole of acetone being formed for every 2 to 5 moles of hydroperoxide decomposing. The facts and their interpretation at this stage of experimentation are not sufficient to permit the derivation of a wholly satisfying mechanism or a precise mathematical expression for the decomposition.

Tentatively the following mechanism is proposed for the initial reaction.

$$\mathrm{ROOH} \xrightarrow{a} \underset{\mathrm{I}}{\mathrm{ROOH^*}} \qquad (7)$$

$$\mathrm{ROOH^* + ROOH} \xrightarrow{b} \mathrm{2ROH + O_2} \qquad (8)$$

The conditions imposed by the observed first-order kinetics and the specificity of the initial reaction are met by reaction steps 7 and 8. The nature of intermediate I and the transition state for step 8 can only be surmised. The experimental observations indicate that the hydroperoxide yields an intermediate which initially is able to liberate oxygen from the hydroperoxide or alkyl radicals by reaction with the solvent and which is not a precursor to acetone formation, *i.e.*, it is neither *t*-butoxy nor *t*-butyl peroxy radical. It is suggested that the driving force of step 8 is the formation of molecular oxygen and hence that I may be an excited form of the hydroperoxide akin to the oxo-oxide structure suggested by Milas[26] to account for the observed exaltations in the molecular refraction of a number of peroxidic compounds. The atomic refractivity of the peroxidic oxygen was found to be equal to that of a carbonyl oxygen. The transition state for step 8 probably depends upon hydrogen bonding. Both the decomposition of cyclohexenyl hydroperoxide[14] and the oxidation of a sulfide to a sulfoxide with a hydroperoxide[27] were reported to proceed *via* a hydrogen-bonded dimer. Reaction of intermediate I with the solvent liberates alkyl radicals

$$\mathrm{ROOH^* + 2HS} \xrightarrow{c} \mathrm{ROH + H_2O + 2S\cdot} \qquad (9)$$

which in turn destroy the hydroperoxide.

$$\mathrm{S\cdot + ROOH} \xrightarrow{d} \mathrm{HS + ROO\cdot} \qquad (4)$$

The chain termination which may be composed of several steps for convenience is envisioned as

$$\mathrm{ROO\cdot + HS'} \xrightarrow{e} \mathrm{(ROO{\cdot}HS')} \qquad (10)$$

$$\mathrm{(ROO{\cdot}HS') + ROO\cdot + HS} \xrightarrow{f} \mathrm{ROH + MeCOMe + CH_4 + S\cdot + S'\cdot + O_2} \qquad (11)$$

The termination steps utilize the bimolecular destruction of alkyl peroxy radical, but do not allow for the reformation of hydroperoxide in an oxygen-depleted system as pointed out in the preceding sections. The evolution of oxygen has not yet been confirmed for this part of the reaction. The stoichiometry (equation 11) requires the liberation of two radicals, S· and S′·; to explain the threefold increase between k_1 and k_2 only one is considered capable of participating in the chain reaction. Whether or not *t*-butoxy radical forms or the *t*-butyl peroxy radical yields acetone directly is pure conjecture.

The differential equations for the postulated sequence of reactions, 7 through 11, with the usual steady-state approximations for the four intermediates give the relationship

$$-\frac{\mathrm{d[H]}}{dt} = 2k_a[\mathrm{H}]\left\{\frac{[\mathrm{H}] + 2.5\alpha[\mathrm{HS}]^2}{[\mathrm{H}] + \alpha[\mathrm{HS}]^2}\right\} \qquad (12)$$

whose integrated form is

$$\frac{[\mathrm{H}]}{[\mathrm{H_0}]}\left\{\frac{[\mathrm{H}] + 2.5\alpha[\mathrm{HS}]^2}{[\mathrm{H_0}] + 2.5\alpha[\mathrm{HS}]^2}\right\}^{2/5} = e^{-5k_a t} \qquad (13)$$

where [H] and [HS] represent the molal concentrations of the hydroperoxide and the solvent, respectively, and $\alpha = k_c/k_b$. Expression 13 to some extent illustrates the dependency of the rate upon the relative magnitudes of [H], [HS] and the ratio α. During the initial reaction when [H] is about equal to [H_0], regardless of the relative values of [H_0] and α[HS]^2, the value of the second factor in equation 13 is approximately that of the ratio [H]/[H_0] and equation 13 becomes

$$[\mathrm{H}]/[\mathrm{H_0}] = e^{-2k_a t} \qquad (14)$$

The observed initial rate, k_1, may be identified with the value $2k_a$.

The value of α may be approximated by two methods: from the rate of ketone formation and by extrapolation of the enhanced rate of decomposition $(k)_2$ to its intercept at zero time. The rate of formation of acetone, d[K]/dt, based upon equations 7 to 11 with the same steady-state approximations used above is expressed by the equation

$$\frac{d[\mathrm{K}]}{\mathrm{d}t} = \frac{2k_a\alpha[\mathrm{HS}]^2[\mathrm{H}]}{[\mathrm{H}] + \alpha[\mathrm{HS}]^2} \qquad (15)$$

The solution of the simultaneous differential equations 12 and 15 is

$$\ln\left\{\frac{[\mathrm{H}] + 2.5\alpha[\mathrm{HS}]^2}{[\mathrm{H_0}] + 2.5\alpha[\mathrm{HS}]^2}\right\} = -\frac{[\mathrm{K}]}{\alpha[\mathrm{HS}]^2} \qquad (16)$$

Substitution of the logarithmic form of equation 13 into equation 16 gives the expression

$$\frac{[\mathrm{K}]}{\ln\{[\mathrm{H}]/[\mathrm{H_0}]\} + 5k_a t} = \frac{2\alpha[\mathrm{HS}]^2}{3} \qquad (17)$$

from which a value of $(2 \pm 1.5) \times 10^{-3}$ for α is obtained upon substitution of the appropriate values of [K], [H], [H_0], [HS] (5.6 molal), t and either k_2 or $5k_a$ from the data of run I-15. In dilute solution the value of the hydroperoxide concentration rapidly drops below that of $2.5\alpha[\mathrm{HS}]^2$ so that equation 13 may be expressed as

$$\ln[\mathrm{H}] = -5k_a t + \ln[\mathrm{H_0}] + \frac{3}{2}\ln\left\{\frac{[\mathrm{H_0}]}{2.5\alpha[\mathrm{HS}]^2} + 1\right\} \qquad (18)$$

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The experimental intercept obtained by extrapolation of the k_2 slope may be equated to the last two terms at the right in equation 18. Evaluation of the intercepts for runs I-23 and I-12 gives values of 0.9 and 1.3×10^{-3} for α.

In the partially swept reactions, where initially reaction 8 prevails but the oxygen is not removed and may react with any alkyl radicals formed in reaction 9 by reactions 5 and 6 to form a hydroperoxide, SOOH, $-\mathrm{d}\ \ln\{[\mathrm{H}] + [\mathrm{SOOH}]\}/\mathrm{d}t = k_a$. (It was assumed that SOOH may be treated as ROOH and that $\mathrm{d}[\mathrm{O}_2]/\mathrm{d}t = 0$.) Thus the proposed mechanism and the assumptions above can account for the fact that the observed rates in the partially swept system were about half of those in the swept system.

The extremely slow decomposition in sealed ampoules can be explained in terms of the postulated mechanism with the additional assumptions that the evolution of oxygen is prohibited in a closed system and instead reaction 8 leads to a dimer, D, which effectively lowers the hydroperoxide concentration available for reaction with any alkyl radicals. The dimer would still have peroxidic properties toward iodide ion and would be so determined throughout the observation period. The rate under these circumstances would be a function of the total peroxide concentration, [P], where $[\mathrm{P}] = [\mathrm{H}] + 2[\mathrm{D}]$, and $-\mathrm{d}\ \ln[\mathrm{H}]/\mathrm{d}t = 2k_a$ and $\mathrm{d}[\mathrm{D}]/\mathrm{d}t = k_a k_b[\mathrm{H}]^2/\{[\mathrm{H}] + \alpha[\mathrm{HS}]^2\}$. These equations may be solved to give the relationship

$$[\mathrm{P}] = \alpha[\mathrm{HS}]^2 \ln \left\{ \frac{[\mathrm{H}_0]e^{-2k_a t} + \alpha[\mathrm{HS}]^2}{[\mathrm{H}_0] + \alpha[\mathrm{HS}]^2} \right\} + [\mathrm{H}_0] \quad (19)$$

which cannot be conveniently used. The pseudo first-order rates in Tables IB are of value only for orientation. That the formation of a dimer is not unreasonable was demonstrated by one of the experiments, run I-9, which was initially heated in a sealed tube for 404 hours before being transferred to a swept system in which there was a trace of oxygen being added systematically. The remaining hydroperoxide still had an absorption band appearing at 12 μ, and decomposed at a rate equal to that of the anaerobic system. This observation (similar results were noted qualitatively on dilute solutions) would only be possible if conversion to the dimer occurred in the sealed tube and it could decompose unaffected by the trace of added oxygen. (Run I-10 affords a comparison for the aerobic system.)

An approximate E_a may be calculated for the reaction from data obtained at 86.1° in the helium-swept apparatus: $k_1 = 1.32 \times 10^{-6}$, $k_2 = 3.88 \times 10^{-6}$ sec.$^{-1}$. From the respective values of k_1 at the two temperatures one obtains a value of 30.7 kcal./mole for the E_a of reaction 7. Using the absolute rate equation

$$k = (kT/h)e^{-\Delta H^*/RT}e^{\Delta S^*/R}$$

and assuming that Δv^* is equal to zero for reaction 7 in the expression, $\Delta H^* = E_a - RT + p\Delta v^*$, one obtains the following values: $\Delta H^* = 30.0$, $\Delta F^* = 30.9$ kcal./mole, and $\Delta S^{\ddagger} = -2.3$ cal./deg./mole.

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[CONTRIBUTION FROM THE DEPARTMENT OF PEDIATRICS, UNIVERSITY OF PENNSYLVANIA AND THE CHILDREN'S HOSPITAL OF PHILADELPHIA]

The Interaction of Purified Anti-β-lactoside Antibody with Haptens[1]

BY FRED KARUSH

RECEIVED FEBRUARY 16, 1957

A study has been made of the combination of purified anti-β-lactoside antibody with the uncharged azo dye p-(p-dimethylaminobenzeneazo)-phenyl β-lactoside by the method of equilibrium dialysis. The extrapolation of the binding curves yields a value of 2.0 for the valence of the antibody. The values of ΔF^0 fall within the same range previously observed for another system involving an anionic haptenic group. The temperature dependence of the binding curves reveals, however, a substantial difference in the values of ΔS^0 and ΔH^0 for the two systems. These differences are related to the absence of a charge in the β-lactoside haptenic group. The heterogeneity of the antibody as shown by the non-linearity of the binding curves can, except in one case, be described by a Gauss error function with a value of 1.5 for the heterogeneity index. The large value of ΔH^0, about -10 kcal./mole of hapten, is interpreted to mean that the R groups of the antibody can form strong hydrogen bonds with the disaccharide portion of the hapten, sufficient to withstand the disruptive effects of competing water molecules. The association constants of a number of sugar derivatives have been evaluated by their inhibition of the dye binding. These results demonstrate in quantitative energetic terms the selective character of the combining region of the antibody with respect to the configuration of the terminal hexoside and the geometry of the glycosidic linkage (α or β), as well as the participation of the non-terminal hexoside in the specific interaction.

In a previous communication[2] we have presented the results of a study of the structural and energetic aspects of the combination of haptens with a purified antibody specific for the haptenic group phenyl-(p-azobenzoylamino)-acetate (I_p). In order to extend our understanding of these aspects of antibody–hapten interaction, it appeared desirable to obtain similar results with an antibody homologous to a different type of haptenic group. The particular differences that were of greatest interest were the absence of a charged group in the new haptenic group and a strong affinity for water in contrast to the uncharged form of the earlier haptenic group.

The choice of p-azophenyl β-lactoside as the haptenic group to be studied was based largely on the investigations of Goebel, Avery and

(1) This investigation was supported by a research grant (H-869) from the National Heart Institute of the National Institutes of Health, Public Health Service.

(2) F. Karush, THIS JOURNAL, 78, 5519 (1956).

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Babers.[3] Following the demonstration by Avery and Goebel[4] that antibodies were formed against the azophenyl β-glycosides of glucose and galactose which could distinguish between these sugars, these authors investigated the properties of antisera specific for the azophenyl β-glycosides of several disaccharides, maltose, cellobiose, gentiobiose and lactose. This work showed that the homologous antibody was complementary to both hexose units of the disaccharide and sufficiently closely fitted to the contour of the latter to be able to distinguish between a galactose unit and a glucose unit as the terminal hexoside and between the 1,4-α- and 1,4-β-linkages. The use of a disaccharide as the main portion of the haptenic group was also of interest because of its close relationship to the large number of naturally occurring polysaccharide antigens.

To secure the information desired we have studied the combination of purified antibody specific for the *p*-azophenyl β-lactoside group (Lac group) with the uncharged azo dye *p*-(*p*-dimethylaminobenzeneazo)-phenyl β-lactoside (Lac dye) and quantitatively evaluated the competitive effect on this combination of structurally related haptens.

Experimental

Materials.—The compound which was required for the preparation of the immunizing and precipitating antigens and for the synthesis of Lac dye was *p*-aminophenyl β-lactoside. The first step in its synthesis was the preparation of acetobromolactose by the adaptation of a method described for acetobromoglucose.[5] The main difference in the procedures is that the reaction product in our case was suspended in isopropyl ether rather than recrystallized from the solvent because of its relative insolubility. This crude preparation of acetobromolactose was then employed for the synthesis of *p*-aminophenyl β-lactoside in accordance with the procedure of Babers and Goebel.[6] The acetobromolactose was converted to heptaacetyl *p*-nitrophenyl β-lactoside according to the method of Glaser and Wulwek[7] as described by Babers and Goebel. It was found that an improvement in yield was obtained if the reaction was carried out at *p*H 9 for three hours and the *p*H maintained constant by addition of 50% NaOH solution. After one recrystallization from methanol the product melted at 131–133°. It was then deacetylated with barium methylate to yield *p*-nitrophenyl β-lactoside which melted at 259° with decomposition as reported by Babers and Goebel. The reduction of this material was effected by hydrogenation in aqueous solution at a pressure of 45 p.s.i. with 5% Pd on alumina as the catalyst. The product was crystallized from 70% ethyl alcohol and melted at 240°. Recrystallization of the material left the melting point unchanged. The value of $[\alpha]_D$ at room temperature was −35° (*c* 2.5) as compared with $[\alpha]^{27}_D$ −36° reported by Babers and Goebel.[6]

The antigens used in this study were prepared by diazotizing *p*-aminophenyl β-lactoside and coupling to bovine γ-globulin and human fibrinogen to yield Lac-BγG and Lac-HF. The former was employed as the immunizing antigen and was obtained by the method previously described.[2] The human fibrinogen used to prepare the precipitating antigen, Lac-HF, was contributed by the American Red Cross and was further purified by the method of Laki.[8] Some modification of the previously reported procedure[9] for the preparation of azofibrinogen was necessary. The coupling was done at *p*H 10 to keep the product in solution and the reaction mixture was dialyzed *vs.* twenty volumes of 0.01 *M* borate buffer, *p*H 10 for several days in the cold room with daily changes of the outside solution. Prior to its use as a precipitating agent the Lac-HF was diluted in 0.15 *M* NaCl to a concentration of 400 μg. N/ml. and the solution adjusted to *p*H 7.4. This was done at least 24 hours preceding its addition to antiserum. The original solution at *p*H 10 was stored in the frozen state.

The binding experiments were carried out with the Lac dye prepared by coupling diazotized *p*-aminophenyl β-lactoside with dimethylaniline at *p*H 4.1 to give *p*-(*p*-dimethylaminobenzeneazo)-phenyl β-lactoside. The product was separated from the reaction solution by virtue of its low solubility at *p*H 7 and recrystallized twice from 95% ethanol; m.p. 238°. On drying to constant weight *in vacuo* over P_2O_5 at 80° the melting point remained unchanged. However, when the product was subjected to prolonged heating (44 hr.) at 170° there was a weight loss of 2.8%, before evidence of decomposition was observed, compared to a calculated value of 3.1% for a monohydrate. On the basis of this information and its elementary composition, the compound obtained after drying at 80° was considered to be a monohydrate.

Anal. Calcd. for $C_{26}H_{35}O_{11}N_3.H_2O$: C, 53.51; H, 6.40. Found: C, 53.44; H, 6.32.

The absorption spectrum of Lac dye in 0.15 *M* NaCl, 0.02 *M* phosphate, *p*H 7.4 is shown in Fig. 3. The molar extinction coefficient, ε, at the wave length of maximum absorption λ 455 mμ is 2.48×10^4. A minimum occurs at λ 340 mμ with a value of ε of 0.52×10^4.

Of the nine compounds used in the inhibition experiments lactose, galactose, cellobiose and maltose were commercial products of which all but cellobiose were reagent grade. Methyl α-D-galactoside, methyl β-D-galactoside and methyl β-lactoside were generously provided by Dr. N. K. Richtmyer and methyl β-D-glucoside by Dr. H. B. Wood, Jr. The remaining compound, *p*-nitrophenyl β-lactoside, was the intermediate used in the preparation of the corresponding amino compound.

Preparation of Antisera.—The same procedures for injection, bleeding and pooling of sera were employed in the preparation of anti-Lac antisera as were described for the anti-I_p system.[2]

Purification of Anti-Lac Antibody.—The purification of anti-Lac antibody follows the same general procedure which has been presented for anti-I_p antibody.[9] After removal of complement by the BγG–anti-BγG precipitate the anti-Lac antibody was precipitated by the addition of Lac-HF in the amount of 10 μg. N/ml. of serum. The washed specific precipitate was extracted with 25 ml. of a solution containing 0.1 *M* lactose in 0.05 *M* phosphate, *p*H 7.4. The extraction was carried out for one hour at 37° and provided a solution which contained almost all of the originally precipitated antibody. The amount of antigen which was solubilized could be judged from the color of the solution and was quite variable. When the quantity was more than negligible it was removed from the extract by precipitation with 0.8 *M* phosphate, *p*H 7.4, with some loss of antibody. The antibody was then precipitated in an ice-bath by the addition of the quantity of 4 *M* phosphate solution required to give a final concentration of 1.6 *M*. The 4 *M* phosphate solution was a mixture of K_2HPO_4 and KH_2PO_4 whose *p*H was adjusted so that on dilution to 1.6 *M* a *p*H of 7.4 was obtained. The precipitated antibody was dissolved with 24 ml. of 0.05 *M* phosphate and reprecipitated in an ice-bath by the addition of 16 ml. of the 4 *M* phosphate solution. This step was repeated two times and the antibody was then dissolved in 25 ml. of 0.15 *M* NaCl. The solution was dialyzed against 2 liters of 0.15 *M* NaCl in the cold for several days with daily changes of the outside solution. The small amount of precipitate which was formed during the dialysis was removed by centrifugation. The N content of the supernatant was determined by micro-Kjeldahl analysis. Finally, 1% of its volume of 2 *M* phosphate was added to give 0.02 *M* phosphate, *p*H 7.4. The yield of antibody appears to be about 50% of that initially precipitated. A quantitative precipitin analysis with one preparation of purified antibody showed that 144 μg. N/ml. of antibody could be precipitated with Lac-HF from a solution containing 150 μg. N/ml.

Binding Experiments.—The binding of Lac dye by the purified antibody was measured in the specially designed cells and under the same conditions as described for our previous investigation.[2] One ml. of 2.5×10^{-5} *M* antibody,

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(4) O. T. Avery and W. F. Goebel, *ibid.*, **50**, 533 (1929).
(5) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., p. 81.
(6) F. H. Babers and W. F. Goebel, *J. Biol. Chem.*, **105**, 473 (1934).
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(9) F. Karush and R. Marks, *J. Immunology*, in press.

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based on a molecular weight of 156,000, in 0.15 M NaCl, 0.02 M phosphate, pH 7.4, was used in one compartment of the cell and one ml. of dye in the same solvent in the other. In the experiments involving inhibitors these were included in the dye solutions. The dye concentrations measured after equilibration ranged from 0.2×10^{-5} M to 5×10^{-5} M. In calculating the amount of dye bound to antibody correction was made for the dye adsorbed to the cellulose casing. The amount of adsorbed dye relative to the amount bound to antibody ranged from 11 to 22% at 25° and from 6 to 19% at 7°.

Absorption Spectrum.—The absorption spectrum of the Lac dye bound to antibody was determined as previously described.[2] The total concentration of the dye in the solution measured was 1.72×10^{-5} M of which 93% was bound to the antibody present at a concentration of 2.64×10^{-5} M.

Results and Discussion

The Binding of Lac Dye by Antibody.—The binding curves for the combination of Lac dye with its homologous antibody are shown in Figs. 1 and 2 for two different pools of purified antibody. Data

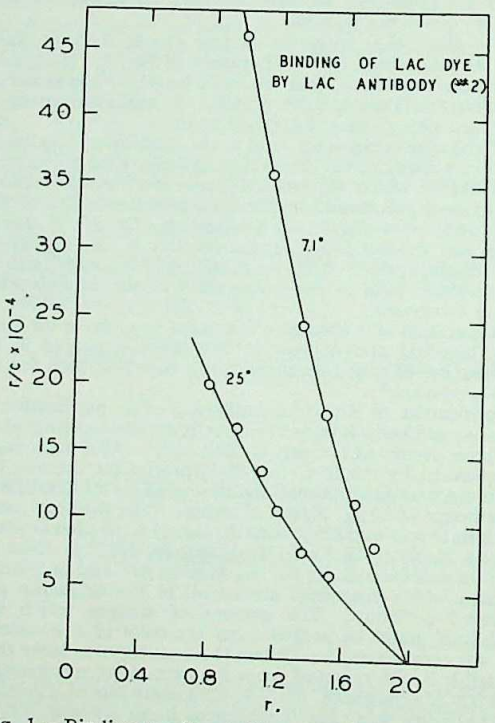

Fig. 1.—Binding results at 25 and 7.1° for the reaction between Lac dye and purified anti-Lac antibody (#2). The points are experimental and the curves are theoretical.

were obtained at two temperatures and the results were plotted in the form of r/c *vs.* r, for reasons previously given,[2] where r is the average number of dye molecules bound per antibody molecule at the equilibrium concentration of free dye c. In agreement with the results of the earlier study the present data allow the unambiguous extrapolation of the binding curves to yield a value of 2.0 for the binding capacity (n) or valence of the antibody. The same result was found with binding curves obtained at 25° with two other pools of purified antibody.

The deviation of the binding curves from linearity reflects the heterogeneity of the purified antibody with respect to its affinity for the Lac dye. It was found previously that such heterogeneity could

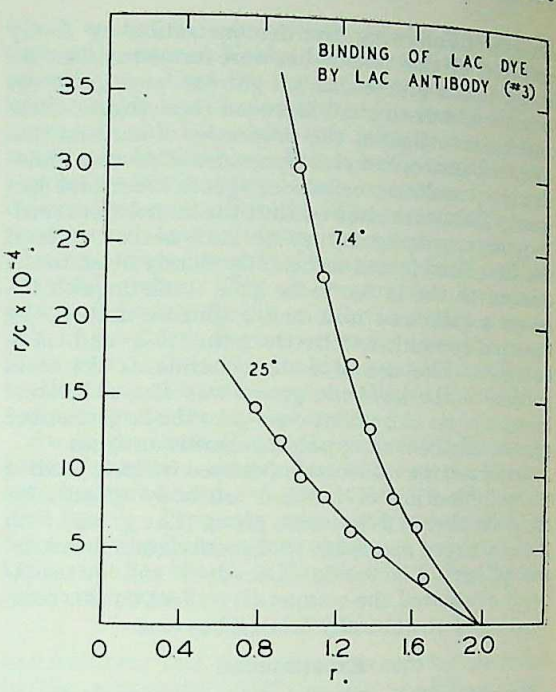

Fig. 2.—Binding results at 25 and 7.4° for the reaction between Lac dye and purified anti-Lac antibody (#3). The points are experimental and the curve for 25° is theoretical.

be adequately described by a Gauss error function in terms of the free energy of binding. Except for the measurements at 7.4° the present data can be satisfactorily fitted by such a function with a value of 1.5 for the heterogeneity index σ. The curves shown for the three sets of points involved are theoretical curves calculated assuming values of σ and n of 1.5 and 2.0, respectively. The average value of the association constant, K_0, which must also be known for the calculation, was taken as equal to the experimental value of r/c for r equal to 1. The reason for the failure to describe adequately the data at 7.4° with σ equal to 1.5 is not clear. It is of interest to note that the heterogeneity of the purified antibody specific for the Lac group is considerably less than that observed previously with the anionic hapten. In the latter case a value of 2.3 for σ was required to fit the experimental results.

The values of the thermodynamic quantities shown in Table I were calculated in the usual way using the indicated association constants. Comparison with our earlier results shows that the present values of ΔF^0 fall within the range observed before in spite of the considerable difference in the chemical nature of the hapten groups under comparison. This difference does, however, manifest itself in the comparative values of ΔS^0 and ΔH^0. Whereas the anionic hapten gave a value of ΔS^0 of about zero for the association reaction, the combination of the Lac dye with its homologous antibody yields a substantially lower value, −9 e.u. per mole of dye. Such a negative value is not unexpected in view of the fact that it refers to an association reaction, although the loss of translational and rotational degrees of freedom is probably not the only contribution to entropy change for the process of combina-

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tion. Since complex formation between the anionic dye and its antibody most probably involves charge neutralization, the difference in the entropy results may be reasonably attributed to the positive entropy contribution which arises from the release of ion-bound water on ion-pair formation.

TABLE I

THERMODYNAMIC RESULTS FOR THE BINDING OF LAC DYE BY PURIFIED ANTI-LAC ANTIBODY[a]

Plac no.	n	σ	25° $K_0 \times 10^{-4}$, l./mole	25° $-\Delta F^0$, kcal./mole	7° $K_0 \times 10^{-4}$, l./mole	7° $-\Delta F^0$, kcal./mole	$-\Delta H^0$, kcal./mole	ΔS^0, e.u./mole
2	2.0	1.5	15.7	7.09	44.8	7.25	9.7	−8.8
3	2.0	1.5	10.4	6.85	29.0	7.01	9.7	−9.5

[a] The lower temperatures for Plac #2 and Plac #3 were 7.1 and 7.4°, respectively. The value of 1.5 for σ applies, in the case of Plac #3, only to the results obtained at 25°. The values of the thermodynamic functions are expressed as per mole of Lac Dye.

The large negative value of ΔH^0, about −10 kcal./mole of hapten, is of considerable interest, particularly since by far the greatest portion of it, as will be seen from the inhibition results, is due to the interaction between the disaccharide portion of the hapten and the antibody. This result emphasizes the capacity of the antibody to provide attractive interactions, for this type of molecule, which in their total energetic effect greatly exceed the competitive interactions between solvent molecules and the disaccharide. The latter interactions, which are primarily hydrogen bonding, are of considerable magnitude as is evident from the high solubility of sugars, including lactose, in aqueous solution. We surmise from these considerations that the R groups of antibody, and of proteins in general, can form hydrogen bonds with hapten, and with each other, of such stability as to withstand the disruptive competitive influence of water molecules.

The similarity in the ΔF^0 values for the two kinds of haptens in spite of the large difference in ΔH^0 is noteworthy. The reason for this may be, as was originally suggested by Pauling,[10] that the process of antibody formation and release into the circulation provides an effective selection of only those antibody molecules whose affinity does not exceed some maximum value. A lower limit for the affinity could, of course, result from the procedure employed to isolate the antibody, namely, specific precipitation.

Absorption Spectrum of Bound Dye.—It is evident from the spectra of bound Lac dye and free dye shown in Fig. 3 that complex formation in this system leads to a spectral shift similar to that observed in our earlier study. This consists of an increase in the molar extinction coefficient, ϵ, at the wave length of maximum absorption, accompanied by a broadening of the absorption band. Although the effect is less pronounced in the case of the Lac dye than in the case of the anionic dye, we interpret the spectral shift of the bound Lac dye to be due, as before, to the formation of a hydrogen bond between the azo group of the dye and a proton-donating group of the antibody.

(10) L. Pauling, THIS JOURNAL, 62, 2643 (1940).

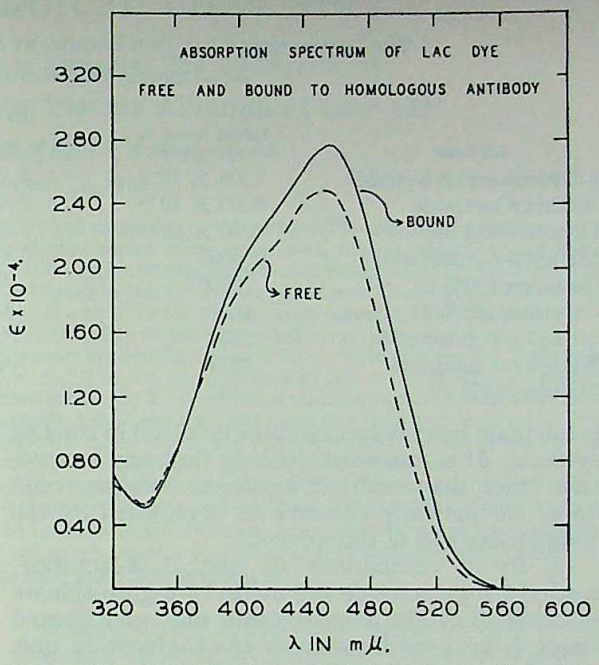

Fig. 3.—The absorption spectra of Lac dye free and bound to anti-Lac antibody.

Inhibition by Structurally Related Haptens.—Further information about the scope and selectivity of the combining region of the antibody has emerged from inhibition experiments. These experiments were designed to give the association constants for combination with antibody of the compounds listed in Table II. The values were obtained in an indirect manner, namely, by measuring the capacity of these colorless compounds to inhibit the binding of Lac dye by the antibody. The calculation of the constants utilized equations 4 and 5 of our previous paper. Several preliminary experiments were done to establish the concentrations of the inhibitors which would yield the most accurate results. The concentrations which were finally selected are shown in Table II. Except for methyl β-D-glucoside and maltose, they gave a degree of inhibition which minimized the uncertainty in the calculation of the average association constants due to experimental error and the heterogeneity of the antibody.

A close examination of Table II allows a number of interesting conclusions to be drawn regarding the combining region of the antibody:

(1) The fact that the ΔF^0 value for *p*-nitrophenyl β-lactoside is only slightly greater (0.4 kcal.) than that for the Lac dye indicates that the size, or volume, of the energetically effective region is probably not much larger than that required to accommodate this hapten. This inference agrees well with our earlier estimate of the size of the combining region specific for the anionic hapten group.

(2) The large negative values of ΔF^0 for methyl β-lactoside and lactose demonstrate that the interaction between the disaccharide portion of the haptenic group and the antibody provides the dominant contribution to the stability of the complex. From this conclusion we further deduce, as has already been mentioned, that hydrogen bonding

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TABLE II

THE INHIBITION OF LAC DYE BINDING BY STRUCTURALLY RELATED MOLECULES AT 25°

p-(*p*-Dimethylaminobenzeneazo)-phenyl β-Lactoside

Inhibitor	Initial concn. in dye soln., moles/l.	Plac #12 (K_0 = 13.4 × 10^4, $-\Delta F^0$ = 7.00 kcal./mole) $K_I \times 10^{-4}$, l./mole	Plac #12 $-\Delta F^0$, kcal./mole	Plac #13 (K_0 = 11.9 × 10^4, $-\Delta F^0$ = 6.92 kcal./mole) $K_I \times 10^{-4}$, l./mole	Plac #13 $-\Delta F^0$, kcal./mole
p-Nitrophenyl β-lactoside	1.00 × 10^{-4}	6.75	6.60	7.26	6.63
Methyl β-lactoside	2.00 × 10^{-4}	2.02	5.88	2.38	5.98
Lactose (64% β)	4.00 × 10^{-4}	1.10	5.52	....	..
Methyl β-D-galactoside	0.0600	0.00747	2.56	0.0114	2.81
Galactose (69% β)	.0600	.00457	2.27	....	..
Cellobiose (66% β)	.100	.00275	1.96	....	..
Methyl α-D-galactoside	.200	.00134	1.54	0.00130	1.52
Methyl β-D-glucoside	.200	.00051	0.97	.00059	1.05
Maltose (64% β)	.200	.00033	0.70	....	..

is the main intermolecular force involved in the Lac system. It seems most unlikely that any interaction other than multiple hydrogen bonding could be as energetically effective as is required by the competitive role of the solvent.

(3) By a comparison of methyl β-lactoside, methyl β-D-galactoside and methyl β-D-glucoside we estimate that the β-galactoside unit contributed about 5 kcal./mole whereas the β-glucoside unit contributes only 3 kcal./mole. Thus the terminal hexoside is the dominant one of the two hexosides of the haptenic group although both play a major energetic role. These conclusions are entirely consistent with those drawn by Goebel, Avery and Babers[3] from their observations on cross-reactivity and the inhibition of specific precipitation in their disaccharide systems.

(4) The sharp specificity of the antibody with respect to the configuration of the terminal hexoside is clearly demonstrated by the difference of 3.6 kcal. between lactose and cellobiose. These sugars differ only in the reversal of the positions of the hydrogen atom and the hydroxyl group on carbon atom 4 in the terminal hexoside, and yet their association constants differ by a factor of 400. The difference in free energy is probably compounded of two factors. One would be the loss of a hydrogen bond and the other steric repulsion arising from the presence of an hydroxyl group in a position for which, in the original antigenic group, the antibody needed to provide accommodation only for the much smaller hydrogen atom.

(5) Finally, the specificity of the antibody with respect to the configuration of the linkage between the hexosides, α or β, may be noted. This is shown by the lower affinity of methyl α-D-galactoside compared to methyl β-D-galactoside and by the comparison between maltose and cellobiose. In both instances the homologous β-configuration is more stable than the α-configuration by about one kcal.

Acknowledgment.—I am indebted to Mr. Robert Marks for carrying out the organic syntheses and antibody purification and to Mrs. F. Karush for the binding and spectrophotometric measurements.

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ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Electrophoretic Behavior of Bovine Plasma Albumin at Low pH[1]

BY KOICHIRO AOKI AND JOSEPH F. FOSTER

RECEIVED DECEMBER 15, 1956

Electrophoresis of bovine plasma albumin was carried out in the pH range 2.0 to 4.7 using 0.2% solutions mainly at 0.02 ionic strength chloride and at 0°. Some experiments were conducted under other conditions, that is, changing the ionic strength (0.10) or temperature (25°), or changing the medium (0.02 ionic strength acetate and thiocyanate). In 0.02 ionic strength chloride and at 0°, there were two boundaries (F and N forms) in the pH region between 3.5 and 4.5, and the percentage composition changed continuously with pH. At pH 4.0 N and F forms existed approximately in equal amounts. The results are explained by an equilibrium, $N + 3H^+ \rightleftarrows F$. Reversibility of the isomerization process was demonstrated. Thermodynamic parameters of the reaction were calculated by comparing results at 0 and 25°. Values when the N form is changed to the F form are: $\Delta F^0 = -15.0$ kcal./mole, $\Delta H^0 = +3.0 \pm 1.5$ kcal./mole and $\Delta S^0 = +66 \pm 4$ e.u./mole. The magnitude and the sign of ΔH^0 is similar to that found calorimetrically by Gutfreund and Sturtevant. The half-time of the N–F equilibrium could not be determined in the present study, but it was deduced to be less than two hours. Under other experimental conditions similar results were obtained except for minor shifts in the equilibrium constant and possibly in the number of hydrogen ions involved. Charge–mobility curves were drawn at the two ionic strengths. It was found that the slopes of these curves changed at pH 3.5, indicating that the electrophoretic behavior was different above and below this pH. Radius of bovine plasma albumin was calculated from electrophoretic mobility and Z value using Henry's equation. It was 33 ± 2 Å. above pH 3.5 at the two ionic strengths for both N and F forms, agreeing with previous estimates. With decrease of the pH from 3.5 the molecule expanded. At pH 2.0 the radius was 50 Å. at 0.02 ionic strength and 43 Å. at 0.10 ionic strength. The isoelectric point varied with the medium and its ionic strength.

Introduction

It has been known that serum albumin is not electrophoretically homogeneous in the pH region near 4; that is, two or more boundaries exist in the electrophoretic pattern. Luetscher[2] observed that crystallized human and horse serum albumins showed two electrophoretic boundaries in acetate buffer of pH 4.0 and ionic strength 0.02. Neurath and co-workers[3] stated that, while horse serum albumin migrated with a single boundary in pH regions remote from the isoelectric point, such as 7.6 and 3.6, the boundary became complex as the pH of the solution approached that of the isoelectric point. More recently, Longsworth, *et al.*,[4] made an electrophoretic study of bovine plasma albumin (BPA) associated with anion binding to that protein. They obtained heterogeneous boundaries in pH regions near the isoelectric point. Alberty[5] observed that BPA was resolved into three components in 0.15 *M* sodium chloride between pH's 4.0 and 4.5. Alberty and co-workers[6,7] made extensive studies of the heterogeneity of proteins by the "reversible boundary spreading" method at their isoelectric points. Furthermore, the heterogeneity of human serum albumin in the acidic region was observed by Miller, *et al.*,[8] and by Saifer, *et al.*[9]

Independently it has been suggested that serum albumin expands at low pH. Both Scatchard[10] and Tanford[11] suggested such expansion to account for the character of the titration curve of this protein. Measuring viscosity and optical rotation of BPA, Yang and Foster[12] interpreted the behavior at low pH in terms of molecular expansion. More recently Tanford and co-workers[13] suggested the existence of an additional intermediate form, the "expandable" form.

The object of the present investigation was to gain more insight into the heterogeneity of BPA as related to the molecular expansion of this protein. The electrophoretic behavior of BPA was investigated over a wider pH region, 2.0 to 4.7. Experiments were carried out mainly in chloride media of 0.02 ionic strength and 0°. Other experiments were carried out in chloride media changing the temperature (25°) or the ionic strength (0.10). Electrophoresis was also conducted in other media, such as acetate and thiocyanate of 0.02 ionic strength.

Experimental

Materials.—Pentex bovine plasma albumin, Lot No. A 1201, was used without further purification. All the reagents used, except thiocyanic acid, were of C.P. grade. Thiocyanic acid was obtained by passing potassium thiocyanate solution through cationic ion exchanger (IR-120) in the hydrogen form.[14]

Procedure.—Electrophoresis was carried out at 0° in a Tiselius type electrophoresis apparatus, Model 35 of the Perkin–Elmer Corporation, equipped with the schlieren scanning system. The pH of the sample was measured with a Beckman Model G pH meter. Concentration of BPA was determined spectrophotometrically using a Beckman Model DU spectrophotometer. Extinction of BPA in distilled water was assumed to be $E^{1\%}_{1\,cm.}$ 6.67 at 279 mμ.[15] Electri-

(1) Supported in part by the National Cancer Institute, National Institutes of Health, Grant C-2248. Presented in part before the Division of Biological Chemistry, American Chemical Society, September, 1956.

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TABLE I

ELECTROPHORETIC DATA AND RADIUS OF BPA AT 0.02 CHLORIDE IONIC STRENGTH AND 0°

pH	Mobility, U_0, cm.²/v. sec. × 10⁵ Slow	Fast	Area, % Slow	Fast	Z Total (N, F)	$Z/u_0 \times 10^{-5}$ Slow	Fast	Radius, Å. Slow	Fast
2.11		+13.7			+73		5.3		50
2.55		+13.1			+63		4.8		47
2.99		+11.9			+46		3.9		41
3.08		+11.7			+43		3.7		40
3.42		+ 9.7	0	100	+28		2.9		34
3.62	+7.8	+ 8.6	19	81	+21 (+19, +22)	2.4	2.6	31	33
3.75	+6.6	+ 7.4	23	77	+18 +(16, +19)	2.4	2.6	31	33
3.82	+5.2	+ 6.6 (+7.0, +6.2)	23	77	+16 (+14, +17)	2.7	2.6	33	33
3.90	+4.5	+ 5.7 (+6.0, +5.3)	27	73	+13.5 (+12, +15)	2.7	2.6	33	33
4.00	+3.5	+ 5.3	60	40	+11.0 (+9.5, +12.5)	2.7	2.4	33	31
4.11	+2.5	+ 4.1	64	36	+ 8.5 (+7, +10)	2.8	2.4	34	31
4.16	+2.3	+ 3.7	67	33	+ 7.5 (+6.5, +9.5)	2.8	2.6	34	33
4.30	+1.2	+ 2.6	86	14	+ 4.5 (+3.5, +6.5)	2.9	2.5	34	32
4.55	−1.0	+ 0.8	94	6				33 ± 2 Å.	

cal conductivity was measured by a conductivity bridge, Model RC 16 of the Industrial Instruments, Inc. The *p*H values described in this paper were obtained by measuring at room temperature the *p*H of the protein solution after dialysis. The conductivity of the protein solution was measured at 0°.

Three different supporting media were used in the present investigation. They were (1) mixtures of hydrochloric acid and sodium chloride, (2) acetic acid and sodium acetate, and (3) thiocyanic acid and potassium thiocyanate. The total ionic strength of the media was kept constant, 0.02 or 0.10. Dialysis was carried out in a cold room at 1–2° for at least 15 hours with continuous mechanical agitation. A protein concentration of 0.2% was employed when the ionic strength was 0.02 for the reason described in the next section. For analysis, patterns were enlarged approximately eight diameters and traced carefully on graph paper. Resolution of components was carried out in the customary manner by sketching Gaussian peaks in such a manner that they summed to yield the observed gradient curve. Areas were measured using a planimeter and the percentage composition obtained from relative areas on the assumption that each component had the same refractive increment.

Results

Effect of Protein Concentration and Determination of Limiting Mobilities.—Since most of the studies were conducted at relatively low ionic strength (0.02) and in poorly buffered media (chloride) one must be concerned with the possibility of salt and *p*H gradients which would vitiate interpretation of the patterns. The only practical criterion of such effects appears to be the degree of enantiography of the patterns obtained on the rising and descending sides. At 0.5% protein and above, in the low ionic strength media, patterns were far from enantiographic, the rising boundary being very sharp, the descending boundary broad and diffuse. At 0.2% boundaries were reasonably enantiographic, in general showing the same number of boundaries and very nearly the same relative areas under such boundaries. At 0.05% results were qualitatively very similar to those at 0.2% but areas could not be estimated with sufficient precision. Mobilities could, however, be determined with no difficulty.

The relationship between electrophoretic mobilities and protein concentration was studied in a mixture of hydrochloric acid and sodium chloride at ionic strength 0.02, *p*H 2.1 and temperature 0°. As is seen in Fig. 1, the difference in mobility calculated from the ascending side and that from the descending one became greater with increasing protein concentration. When the protein concentration was 0.5% or greater, a diffuse and asymmetric boundary was obtained on the descending side. In this case the centroidal ordinate[16] was used to calculate the mobility. It was found that the mobility value U_0, mobility corresponding to zero protein concentration, could be given by the following empirical equation at any protein concentration in 0.02 chloride ionic strength at 0°

$$U_0 = U_D + \frac{2}{3}(U_A - U_D) \qquad (1)$$

where U_D and U_A represent the electrophoretic mobility found on the descending side and that found on the ascending side, respectively. This relation was found to hold at *p*H 2.6 and 3.0 as well as at *p*H 2.1. At *p*H 3.5 and above the concentration dependence was less pronounced and U_0 could be calculated equally well by eq. 1 or by simple averaging of U_A and U_D.

***p*H–Mobility Curves.**—Figure 2 shows typical electrophoretic patterns obtained in chloride at 0.02 ionic strength. Below *p*H 3.5 and above 4.6 there was a single boundary; between 3.5 and 4.6 there were, in general, two. Strictly speaking, in the narrow *p*H range between 3.80 and 3.95 there were three boundaries. At *p*H lower than 3, where the mobility calculated from the migration velocity in the ascending limb was appreciably different from that calculated from the descending limb, the empirical eq. 1 was used to give the mobility value U_0 at zero protein concentration. Mobility values are shown in Table I. The *p*H–mobility curve is shown in Fig. 3. In the *p*H region above 3.5 there are two curves. When three components existed, mobilities of the two faster components are shown in parentheses in Table I, and mobility of the slowest component and the mean of the two faster components were plotted.

Electrophoretic data obtained in chloride media of 0.10 ionic strength are shown in Table II. In this case the pattern was single below *p*H 3.5 and was not single between *p*H 3.5 and 4.6. In the latter *p*H region the pattern usually consisted of three components, similar to those obtained by Alberty.[5]

Electrophoretic data at 25° and at 0.02 chloride ionic strength are shown in Table III. Below *p*H

(16) L. G. Longsworth, THIS JOURNAL, 65, 1755 (1943).

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TABLE II

ELECTROPHORETIC DATA AND RADIUS OF BPA AT 0.10 CHLORIDE IONIC STRENGTH AND AT 0°

*p*H	Mobility, U_0, cm.²/v. sec. × 10⁵ Slow	Fast	Area, % Slow	Fast	*Z* Total (N, F)	$Z/u_0 \times 10^{-5}$ Slow	Fast	Radius, Å. Slow	Fast
2.12		+8.1			+59		7.3		43
2.66		+7.8			+49		6.2		40
3.20		+6.4			+35		5.5		37
3.50		+5.4			+26		4.8		34
3.79	+3.4	+4.1	21	79	+17 (+15, +18)	4.4	4.4	32	32
3.95	+2.1	+2.8 (+2.9, +2.5)	30	70	+11 (+9.5, +12.5)	4.5	4.5	33	33
4.01	+1.6	+2.4 (+2.5, +2.2)	52	48	+ 9 (+8.5, +10.5)	4.7	4.4	34	32
4.10	+0.7	+1.5 (+1.6, +1.4)	56	44	+ 4 (+3, +6)	4.3	4.0	32	31
4.13	+0.4	+1.4 (+1.6, +1.2)	70	30				33 ± 2 Å.	
4.30	−0.5	+0.4	82	18					
4.50	−2.1	−0.4	93	7					
4.69	−2.7								

3.5 there was a single boundary, and between *p*H 3.5 and 4.7 there were two or three boundaries in agreement with the results at 0°.

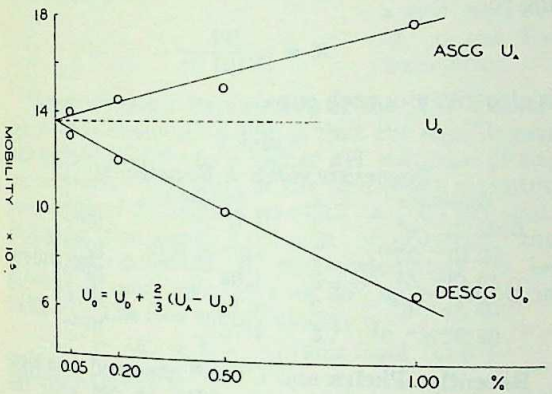

Fig. 1.—Relation between the mobility and the concentration of BPA: *p*H 2.1, 0.02 ionic strength chloride.

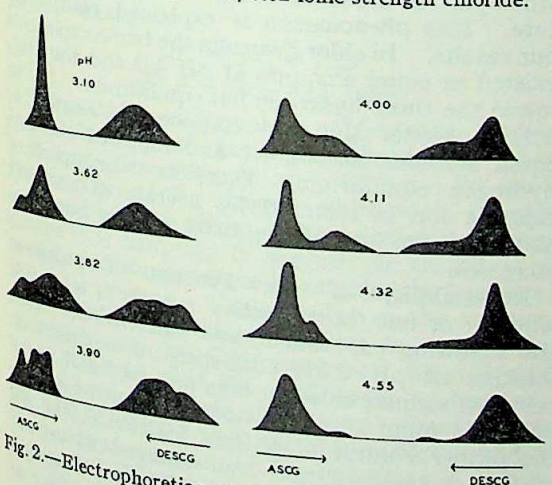

Fig. 2.—Electrophoretic patterns, 0.02 ionic strength chloride, 4800 sec., 7.7 volt cm.⁻¹.

Electrophoresis was carried out in acetate media and in thiocyanate media at 0.02 ionic strength. Mobilities obtained in acetate media are shown in Table IV.[17] The degree of resolution of the boundaries in acetate media was almost the same as in

(17) Detailed discussion of the results in thiocyanate media will be given in a later publication.

TABLE III

ELECTROPHORETIC DATA OF BPA AT 0.02 CHLORIDE IONIC STRENGTH AT 25°

*p*H	Mobility, cm.²/v. sec. × 10⁵ Slow	Fast	Area, % Slow	Fast
2.10		+26.6		
2.42		+26.3		
2.97		+23.7		
3.48		+18.6		
3.65		+16.2		
3.71	+13.5	+15.3	30	70
3.91	+10.1	+11.8	32	68
4.01	+ 8.1	+10.3	42	58
4.05	+ 7.0	+ 9.1	53	47
4.12	+ 6.1	+ 8.0	62	38
4.25	+ 4.5	+ 6.0	70	30
4.39	+ 4.2	+ 1.9	86	14

the mixture of hydrochloric acid and sodium chloride. Below *p*H 4.6 there were two boundaries. In a narrow *p*H range between 3.80 and 3.95 (the same region as in the chloride media), there were three boundaries. When the *p*H was around 4.5

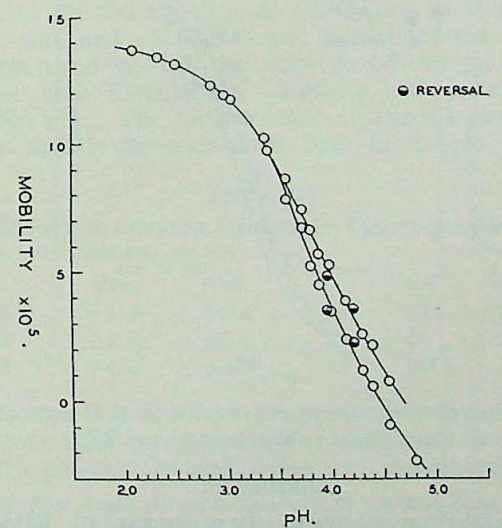

Fig. 3.—*p*H-mobility curve at 0.02 ionic strength chloride and at 0°.

the pattern was better in the acetate media than in chloride, possibly due to the improved buffering

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TABLE IV

ELECTROPHORETIC DATA OF BPA AT 0.02 ACETATE IONIC STRENGTH AT 0°

pH	Mobility, U_0, cm.²/v. sec. × 10^{-5} Slow	Fast	Area, % Slow	Fast
3.79	+6.5	+7.3		
3.84	+6.2	+6.9	23	77
3.92	+5.8	+6.6	35	65
4.07	+4.5	+5.7	61	39
4.17	+3.7	+5.3	73	27
4.26	+3.0	+4.4	77	23
4.46	+1.6	+3.0	85	15
4.60	+0.7	+2.1	92	8
4.79	−0.3		100	0
5.00	−1.7			

in the acetate media.[18] In thiocyanate the resolution was poor, but two boundaries were separated after prolonged migration. In thiocyanate the migration was slow, therefore the difference in the electrophoretic mobilities of two components was smaller. This is doubtless the reason that a longer time was necessary to attain resolution. Below *p*H 3.2 and above *p*H 4.3 there was a single boundary. In the region between these two *p*H's there were two boundaries.

Percentage of the Two Components.—As was described above, the relative area of each component changed continuously with *p*H within a particular *p*H range. Percentages of the areas of each component were calculated on the ascending pattern. When three boundaries were observed, the ratio of the sum of areas of the faster two boundaries to that of the slowest one was taken. The results are shown in Tables I to IV. The results in chloride at 0.02 ionic strength and at 0°, and those at the same ionic strength at 25°, are plotted in Fig. 4.

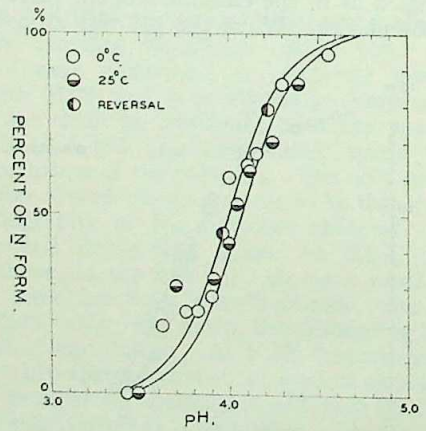

Fig. 4.—Relation between *p*H and the % of the area, 0.02 ionic strength chloride at 0° and 25°.

Discussion

Equilibrium between Two Forms of BPA.—In all of the experiments conducted the percentage composition was found to change continuously with *p*H over the *p*H range in which two or more components existed. This range depended primarily on the medium employed, slightly on temperature and ionic strength. If we term the slow or normal electrophoretic form N and the faster form F, the percentage composition is found to conform closely in all cases to an equilibrium of the form

$$N + nH^+ \rightleftharpoons F$$

Further, the value of n is in all cases between 2 and 3, usually closer to 3. It is inferred that there is an equilibrium of this nature between two discrete forms of the protein which differ in hydrogen-ion binding by approximately three ions. The results in various media are summarized according to this interpretation in Table V which gives the value of n as well as the *p*H of the mid-point of the transition curve (*p*H at which two forms exist in equal amounts). The equilibrium constant corresponding to

$$K = \frac{[F]}{[N][H^+]^n}$$

is also given in each case.

TABLE V

CONSTANTS FOR N–F EQUILIBRIUM

Conditions	n	Mid-point	K
0.02 Cl⁻, 0°	3	4.0	$10^{12.0}$
.02 Cl⁻, 25°	3	4.07 ± 0.03	$10^{12.2 \pm 0.1}$
.10 Cl⁻, 0°	3	4.05	$10^{12.15}$
.02 Ac⁻, 0°	2	4.1	$10^{8.2}$
.02 SCN⁻, 0°	3	3.75	$10^{11.1}$

Recently, Phelps and Cann[20] observed two electrophoretic components in BPA at *p*H near the isoelectric point and noted further that the relative proportion of faster form increased, at constant *p*H, when part of the chloride ion was replaced by acetate. This phenomenon is explained readily by our results. In chloride media the two components existed in equal amounts at *p*H 4.0 and they followed the three hydrogen ion equilibrium. In the acetate media the two components existed in equal amounts at *p*H 4.1 and followed the two hydrogen equilibrium. Therefore when part of chloride ion is replaced by acetate at any *p*H above 3.8 the area of the faster moving boundary increases.

Reversibility of the Process.—To observe whether or not the transition process is reversible the following experiment was carried out. BPA solution of *p*H 2.11, consisting of hydrochloric acid and sodium chloride, was prepared and stored in a cold room about 24 hours. Then by adding the proper volume of sodium hydroxide, the *p*H of the protein solution was changed to around 4.0. The final solution had 0.02 ionic strength and 0.2% protein concentration. After dialysis

(18) The slower moving boundary in chloride media around *p*H 4.5 separated into two after a longer migration as was described before.[19] This phenomenon was not observed in acetate media at the same *p*H.

(19) K. Aoki and J. F. Foster, THIS JOURNAL, 78, 3006 (1956).

(20) R. A. Phelps and J. R. Cann, *ibid.*, **78**, 3539 (1956). While there is qualitative agreement between their results and ours, there does appear to be a serious quantitative discrepancy. Thus their patterns at *p*H 4.7 in 0.025 ionic strength chloride are complex whereas we find only one boundary under such conditions. In a private communication Dr. Cann has informed us that the protein concentration employed in their published experiments was 1%. He further states that they have obtained less complex patterns in subsequent experiments at lower concentration.

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in a cold room overnight, the protein solution was analyzed electrophoretically. Electrophoretic mobility and relative area of the two components, with the experimental condition, are shown in Table VI. These data are plotted in Figs. 3 and 4. It is observed that the data obtained in this experiment are the same as those obtained on the fresh BPA solution. This means that the transition process is reversible, at least insofar as electrophoretic behavior is concerned.

TABLE VI

DATA OF THE REVERSAL EXPERIMENT

pH		Mobility, cm.²/v. sec. × 10⁵		Area, %		Exptl. condition
Initial	Final	Slow	Fast	Slow	Fast	
2.11	→ 3.96	+3.5	+4.8	45	55	Kept at pH 2.11 in a cold room for 23 hr. and dialyzed 20 hr.
2.11	→ 4.22	+2.3	+3.6	79	21	Kept at pH 2.11 in a cold room for 23 hr. and dialyzed 24 hr.

Thermodynamic Parameters of the N–F Transition.—It is observed in Fig. 4 that the equilibrium was shifted slightly to a higher pH with rise of the temperature. The shift of the mid-point resulting from a rise of 25 degrees was 0.07 ± 0.03 pH unit. Assuming the three hydrogen equilibrium, the equilibrium constant K was calculated to be $10^{12.0}$ at 0° and $10^{12.2 \pm 0.1}$ at 25° as is shown in Table V. The free energy change is

$$\Delta F^\circ = -RT \ln K = -15 \text{ kcal./mole. (at } 0^\circ)$$

Enthalpy change is

$$\log \frac{K_0}{K_{25}} = -\frac{\Delta H^\circ}{2.303R}\left(\frac{1}{T_0} - \frac{1}{T_{25}}\right)$$

$$\Delta H^\circ = +3.0 \pm 1.5 \text{ kcal./mole}$$

Entropy change is

$$\Delta H^\circ = \Delta F^\circ + T\Delta S^\circ$$

$$\Delta S^\circ = +66 \pm 4 \text{ e.u./mole}$$

The enthalpy of formation of side-chain hydrogen bonds in protein has been estimated as −5 to −10 kcal., the entropy as −20 to −30 e.u.[21] On the basis of the observed third-order dependence on hydrogen ion and the calculated entropy change it is tempting to suggest the transition as involving rupture of three intramolecular hydrogen bonds by protons. The enthalpy of the reaction, while small, is strikingly similar to that found calorimetrically by Gutfreund and Sturtevant.[22] They observed that 3.1 kcal./mole of heat was absorbed when the pH of BPA was changed from 4.5 to 3.4. These two pH values correspond to the practical extremes of the transition in our experiments. They also stated that the process is reversible, had a half-time of 2.5 to 3 minutes, and is first order with respect to protein concentration.

Half-time of the Transition Reaction.—It was observed that the electrophoretic pattern was not affected by the time of dialysis; that is, when the time of dialysis was changed between 19 and 75 hours in 0.02 ionic strength and at 0°, the pattern was not changed. When the medium of HCl–NaCl was used, prolonged dialysis was necessary because of the poor buffering.

In an attempt to estimate the rate of attainment of the N–F equilibrium electrophoresis of BPA was carried out without dialysis in the acetate buffer. The electrophoresis was conducted directly after the protein was dissolved in the buffer solution at pH 4.11 and 0.02 ionic strength. A picture taken two hours after dissolving the protein, however, showed the same resolution as obtained on a sample at the same pH and ionic strength and dialyzed 18 hours. It seems that the N–F equilibrium is completed in a shorter time than two hours, hence is too rapid to study by the electrophoretic technique.

It has been realized that no resolution of boundaries will occur in moving boundary transport experiments, electrophoresis or sedimentation, where two or more components are in an equilibrium which is established rapidly compared with the differential rate of migration. A single boundary will be observed which moves with the weight-mean velocity of its components, and which spreads more rapidly than is accounted for by diffusion. Some discussions have been given[23–25] on this problem. Accordingly, the fact that the two forms were resolved electrophoretically tends to indicate the transition reaction to be slower than that of Gutfreund and Sturtevant.[22] As there is no sufficient theory applicable to the present system, the following experiment was conducted[26] to see whether or not the pattern was affected by the re-equilibration of the system. Protein solution of the same pH and ionic strength was electrophoretically analyzed changing the current density. BPA solution at pH 4.08 and 0.02 ionic strength was analyzed with different currents of 2.2, 1.1 and 0.4 ma. Pictures were taken when the same number of coulombs had passed, that is, at 6,000 sec. in the 2.2-ma. run, at 12,000 sec. in the 1.1-ma. run, and at 33,000 sec. in the 0.4-ma. run. These runs yielded the same mobilities and the same area distribution. Results are shown in Table VII. The picture taken in the 0.4 ma.-run was slightly broader than that in 2.2-ma. run.

TABLE VII

EFFECT OF CURRENT DENSITY ON ELECTROPHORESIS

pH	Mobility, cm.²/v. sec. × 10⁵		Area, %		Voltage gradient, v./cm.
	Slow	Fast	Slow	Fast	
4.08	+4.6	+3.1	75	25	5.80
4.08	+4.6	+3.1	73	27	2.90
4.08	+4.5	+3.0	72	28	1.05

Although it is not known whether this broadening is more than expected only by diffusion, the value of the per cent. of area agrees with the other results

(21) M. Laskowski and H. A. Scheraga, THIS JOURNAL, **76**, 6305 (1954).

(22) H. Gutfreund and J. M. Sturtevant, *ibid.*, **78**, 3547 (1953).

(23) R. F. Smith and D. R. Briggs, *J. Phys. Colloid Chem.*, **54**, 33 (1950); R. A. Alberty and H. H. Marvin, *ibid.*, **54**, 47 (1950).

(24) E. O. Field and A. G. Ogston, *Biochem. J.*, **60**, 661 (1955).

(25) G. A. Gilbert and R. C. L. Jenkins, *Nature*, **177**, 853 (1956).

(26) This experiment was suggested by Dr. S. J. Singer, Department of Chemistry, Yale University, and is the same kind of experiment done by him and his co-workers.[27]

(27) S. J. Singer and D. H. Campbell, THIS JOURNAL, **77**, 3499, 4851 (1955).

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within experimental error. This indicates the area distribution was not disturbed seriously by the re-equilibration in the present system.[28]

The Third Component.—As was described above, there were three boundaries in the *p*H region between 3.80 and 3.95 at 0.02 chloride or acetate ionic strength and at 0°. There were three boundaries over a wider *p*H region at higher ionic strength or at room temperature. Even when the BPA was dissolved and dialyzed in a cold room, there were three components in this particular *p*H region. This boundary probably was not caused by thermal convection.[30]

It has been observed by the ultracentrifuge[32] and by light scattering[33] that BPA aggregates under some conditions. BPA has more tendency to aggregate at higher ionic strength and at lower *p*H. Aggregation of BPA was demonstrated by the above techniques in media, the ionic strength of which was more than 0.1. Kronman, *et al.*,[33] observed the effect of ionic strength on the aggregation of BPA at *p*H around 3. There is hence some possibility that the third component may be aggregated form. Ultracentrifuge runs were made at 0.02 ionic strength and at *p*H 3.85 both at room temperature and around 6°. There was a single boundary with a minor faster boundary amounting to only a few per cent. This minor boundary in the ultracentrifuge pattern is interpreted as the "dimer impurity" which exists in a wider *p*H region. Therefore the third component is not the aggregated form.

Another possibility is that the third component may be the denatured form. Levy and Warner[34] studied the effect of *p*H on the denaturation of BPA, and found that the denaturation velocity was maximum in the *p*H region between 3.5 and 4.0 at 46.2°. It seems probable that this is not the explanation since the component was present even when care was taken not to expose the protein solution to temperatures above 2°.

It seems probable that the third component is real and may in fact represent an intermediate in the transition.[28]

Calculation of the Net Charge of BPA.—The charge Z at a particular *p*H is governed by the total ion binding, *i.e.*, both cations and anions. The number of hydrogen ions bound may be determined from the titration curves of Tanford, *et al.*,[35] or of Foster and Sterman.[15] Chloride binding data are available from the work of Coleman,[36] Carr[37] and Alberty and Marvin.[38] Since it is known that sodium ion does not combine,[39,40] or at most combines only very slightly,[41] to BPA the net charge below the isoelectric point is given by the difference between hydrogen ion binding and chloride binding. The two sets of data on hydrogen ion binding agree reasonably well; the chloride ion binding data are not so complete and not in such good agreement and hence constitute the main uncertainty in calculation of net charge.

Coleman's studies were conducted with bovine mercaptalbumin and chiefly at the isoionic point. According to his results the chloride binding may be calculated under a given set of experimental conditions through the equation

$$\nu_{x^-} = \sum \frac{k_i n_i C_{x^-} \exp(2Zw)}{1 + k_i C_{x^-} \exp(2Zw)} \qquad (2)$$

where ν_{x^-} represents the number of anion x^- bound to one BPA. C_{x^-} is the molar concentration of the anion. Z is the net charge and n_i is the number of groups with intrinsic constant of k_i. w is a function expressed as

$$w = \frac{e^2}{2DkT}\left(\frac{1}{b} - \frac{\kappa}{1 + a\kappa}\right) \qquad (3)$$

where e, D, k and T, represent the electronic charge, dielectric constant, Boltzmann's constant and the absolute temperature, respectively. b and a are the radius of the protein and the exclusion radius of the protein. κ is the Debye–Hückel function expressed as

$$\kappa = \sqrt{\frac{8\pi e^2 N}{1000DkT}}\sqrt{\mu} \qquad (4)$$

where N and μ represent Avogadro's number and the ionic strength, respectively. At 25° κ is

(28) While this result would seem to justify the quantitative deductions we make with respect to the equilibrium between, and properties of, the N and F forms, the important question of why re-equilibration is not serious remains unanswered. This is especially true in light of the earlier mentioned experiment which indicates the half-time for the transition to be much shorter than two hours (possibly approximately 30 minutes). The theory of Gilbert and Jenkins[25] would offer a possible explanation if the equilibrium were of the nature A + B ⇄ C, but this seems most improbable. Another explanation which we have considered is that the boundaries are stabilized by a *p*H gradient arising in electrophoretic separation. This seems doubtful on two grounds: (1) in such case the observed enantiography would not be expected; (2) resolution is very similar in the very poorly buffered chloride systems and in the somewhat better buffered acetate systems. Dr. Charles Tanford has suggested to us that resolution might conceivably be explained along the lines of the Gilbert–Jenkins theory if the transition were actually stepwise, involving one or more intermediates. This suggestion is of great interest to us because we had already reached the conclusion that the transition must indeed be stepwise, probably involving three intermediate forms.[29] If this is true, it must be considered that the thermodynamic parameters given herein refer to some composite of the separate steps rather than to any one step.

(29) J. F. Foster and K. Aoki, *J. Phys. Chem.*, in press.

(30) The heat H developed in the cell by the current is expressed by

$$H = i^2/q^2k \text{ watt/cm.}^3$$

where i is the current, q is the cross-sectional area of the cell, and k is the specific conductivity. According to Alberty[31] experience has shown that when the thermostat temperature is about 1°, the maximum power which might be dissipated in the electrophoresis cell without causing convection at the usual protein concentration is about 0.15 watt/cm.³. In the present study the H value was 0.08 at these *p*H's. Therefore it seems probable that there was no convective disturbance.

(31) R. A. Alberty, *J. Chem. Education*, **25**, 426, 619 (1948).

(32) H. A. Saroff, G. J. Loeb and H. A. Scheraga, THIS JOURNAL, **77**, 2908 (1955); P. Bro, S. J. Singer and J. M. Sturtevant, *ibid.*, **77**, 4924 (1955); M. E. Reichman and P. A. Charlwood, *Can. J. Res.*, **32**, 1092 (1954).

(33) M. J. Kronman, M. D. Stern and S. Timasheff, *J. Phys. Chem.*, **60**, 829 (1956).

(34) M. Levy and R. Warner, *ibid.*, **58**, 106 (1954).

(35) C. Tanford, S. A. Swanson and W. S. Shore, THIS JOURNAL, **77**, 6414 (1955).

(36) J. S. Coleman, Ph.D. thesis, Massachusetts Institute of Technology, 1953.

(37) C. W. Carr, *Arch. Biochem. Biophys.*, **40**, 286 (1952); **46**, 417 (1953).

(38) R. A. Alberty and H. H. Marvin, THIS JOURNAL, **73**, 3220 (1951).

(39) G. Scatchard, I. H. Scheinberg and S. H. Armstrong, *ibid.*, **72**, 535, 540 (1950).

(40) I. M. Klotz, "Modern Trends in Physiology and Biochemistry," E. S. G. Barron, Ed., Academic Press, New York, N. Y., 1952, p. 430.

(41) C. Coleman, *Arch. Biochem. Biophys.*, **62**, 476 (1956).

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0.47×10^7 at 0.02 ionic strength, and 1.03×10^7 at 0.10 ionic strength. Using these values of κ and taking a as 30 Å.[42] and b as 32.5 Å., w is calculated at 25° to be 0.053 at 0.02 ionic strength and 0.035 at 0.10 ionic strength. Again in Coleman's equation, constants are

$n_1 = 1, n_2 = 8, n_3 = 18, k_1 = 2400, k_2 = 100$ and $k_3 = 3.3$

Using eq. 2, a relation between Z and ν_{Cl^-} is obtained. Since $Z = \nu_{H^+} - \nu_{Cl^-}$, and since ν_{H^+} at a particular pH is given by the titration curve, a curve relating ν_{Cl^-} and pH is obtained. If this chloride binding curve is perfectly correct, the pH at which Z is zero should agree with the isoelectric point found in the present study. Actually there was some discrepancy between the experimental isoelectric points and those calculated, amounting to approximately three charge units and nine units at 0.02 and 0.10 ionic strength, respectively. Accordingly, the entire chloride binding curves were increased by 3 and 9 chloride ions in the two cases. The resulting Z values are given in Tables I and II and are employed in further calculations below.[44]

Charge–Mobility Curve.—Using the pH–mobility curve and the pH–charge curve, the charge–mobility curves were drawn for cases of 0.02 and 0.10 ionic strengths. The charge–mobility curves in the pH region above 3.5, where two components exist, were determined in the following way. In this pH region at 0.02 ionic strength and room temperature, only a single boundary was obtained in the ultracentrifuge pattern.[45] This means that the F and N forms have similar size and different charge. The Z values shown in Tables I and II are the average ones. From these values the net charge of each form, F and N, was found, assuming that the difference in net charge of the two forms is three and that the chloride ion binds in the same way to the two forms, and considering that average Z is calculated using the charge of each form and its percentage in the electrophoretic pattern. The Z values of each form thus calculated are shown in parentheses in Tables I and II. The mobility values of each form were plotted against the Z values of each form. As is seen in Fig. 5 these plots lie on a common straight line, showing that the assumption that the charge difference in the two forms is three is probably right. This is additional evidence that the equilibrium is $N + 3H^+ \rightleftarrows F$. Charge–mobility curves over the whole pH region are shown in Fig. 6. It is seen that the relation between charge and mobility is linear above pH 3.5 but not below that pH. This indicates that the radius of BPA is constant above pH 3.5 but increases at lower pH, in accord with previous conclusions.

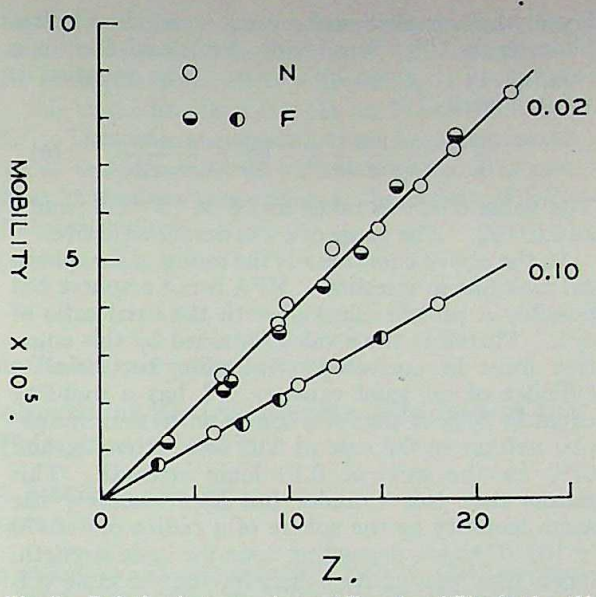

Fig. 5.—Relation between charge (Z) and mobility in the pH region above 3.5.

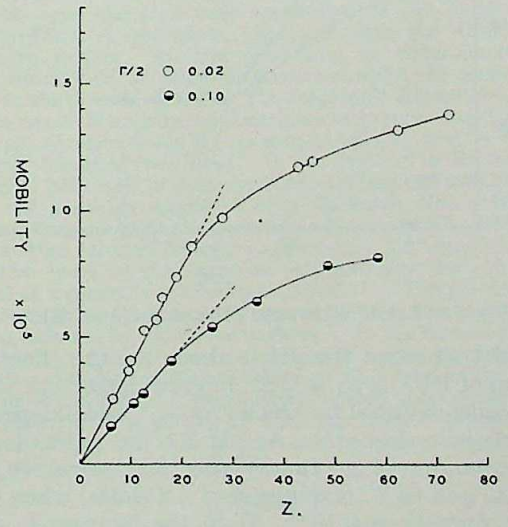

Fig. 6.—Relation between charge (Z) and mobility in the whole pH region.

Calculation of the Radius of BPA.—By use of Henry's equation[46] the radius of BPA was calculated from electrophoretic mobility data and Z values. Henry's equation is

$$Q = \frac{6\pi\eta r(1 + \kappa r + \kappa r_i)}{f(\kappa r)(1 + \kappa r_i)} u \qquad (5)$$

where, Q is the charge (coulomb per molecule), r, the radius of molecule (cm.), r_i, the average radius of electrolyte ion, η, the viscosity coefficient of the solvent, κ, the reciprocal thickness of double

(42) Serum albumin approximates a prolate ellipsoid of 150 Å. major axis and 38 Å. minor axis.[43] Molecular volume of this prolate ellipsoid corresponds to a sphere of 30 Å. radius.

(43) J. L. Oncley, G. Scatchard and A. Brown, *J. Phys. Colloid Chem.*, **51**, 184 (1947).

(44) This mode of correction of the Z values is of course rather arbitrary. It leads to better agreement with the binding data of Carr at low pH but poorer agreement in the pH range 4 to 5. Carr's data would predict an isoelectric point of approximately 5.0 at ionic strength 0.02, a result which is far outside the experimental error. It appears that either both the binding data of Carr and of Coleman are too low near the isoelectric point, or the titration data are in error. The later possibility appears much less likely. Another conceivable explanation lies in the fact that we have restricted our consideration to the titration of carboxyl groups exclusively. This amounts to the assumption that all of the (16) imidazole groups are in the acid (cationic) form at the isoelectric point. It is conceivable that the discrepancy of 3 charge units observed in 0.02 ionic strength could result from this assumption, but not the discrepancy at 0.1 ionic strength.

(45) M. J. Kronman and J. F. Foster, *Arch. Biochem. Biophys.*, in press.

(46) D. C. Henry, *Proc. Roy. Soc.* (*London*), **A133**, 106 (1931).

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layer which is expressed by eq. 4, μ, the electrophoretic mobility (cm.^{2}/volt. sec.), and $f(\kappa r)$ is a function of κr given by Henry. The equation is written using Z as

$$\frac{Z}{u} = \frac{300}{4.80 \times 10^{-10}} \frac{6\pi\eta r(1 + \kappa r + \kappa r_i)}{f(\kappa r)(1 + \kappa r_i)} \qquad (6)$$

The value of r_i was taken as 2.5×10^{-8} cm., and η as 0.01792. The value of κ was described above.

In the above equation r is the radius of the spherical molecule in question. BPA is not a sphere but possibly a prolate ellipsoid with the axial ratio of 4/1. Therefore the r value obtained by this equation must be corrected. According to Gorin[47] a cylinder of an axial ratio of 4/1 has a mobility equal to 70% of that of a sphere of the same molecular volume in the case of 0.02 ionic strength, and 67% in the case of 0.10 ionic strength. This means that this cylinder has approximately the same mobility as the sphere of a radius of 100/70 or 100/67 times, depending upon the ionic strength, larger than that of the sphere having the same volume as the cylinder. The effective radius of the BPA molecule is thus taken to be 70/100 or 67/100 that of r obtained from Henry's equation. Results obtained after correction in this manner are shown in Tables I and II, and also shown in Fig. 7. It is

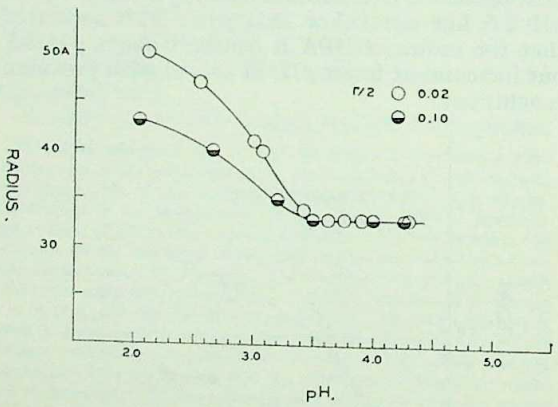

Fig. 7.—Relation between pH and radius of BPA.

found that when the pH is above 3.5 the effective radius of BPA is 33 ± 2 Å., in good agreement with the value deduced by Oncley, *et al.*,[43] and independent of ionic strength. At pH 2.1 the radius is 50 Å. (expansion of 3.4 times) when the ionic strength is 0.02, and 43 Å. (expansion of 2.2 times) when the ionic strength is 0.10.[48] With the increase in the ionic strength, the expansion is suppressed, which is the same conclusion obtained from the measurement of viscosity and optical rotation.[12]

Isoelectric Point.—As is shown in Table VIII, the isoelectric point differs with the media in which the protein is dissolved. Both the isoelectric point and the mid-point were changed with the composition of the media, in the order of higher pH, $SCN^- < Cl^- < Ac^-$. This series is in accord with the result by Longsworth, *et al.*[4] They showed that the isoelectric point of BPA was changed in the order shown above, when a part of the acetate buffer was replaced by other media. So far as the present study, at 0.02 ionic strength, is concerned, the pH at which the F form appears is close to the isoelectric point.

TABLE VIII

MEAN ISOELECTRIC POINT OF BPA IN VARIOUS MEDIA AT 0°

0.02 Cl^-	4.52
.10 Cl^-	4.22
.02 SCN^-	4.25
.02 Ac^-	4.72

A relation between the isoelectric point and ion binding is derived readily. At the isoelectric point $Z = 0$ and $r = \nu_{H^+} = \nu_{x^-}$ so that the titration equation becomes (assuming binding only to carboxyl groups of pK_0)

$$(pH)_I = pK_0 + \log \frac{n - (\nu_{x^-})_I}{(\nu_{x^-})_I} \qquad (7)$$

where x^- is the anion in the medium, $(pH)_I$ represents the isoelectric point, and $(\nu_{x^-})_I$ means the number of anions x^- which bind to the protein at the isoelectric point. It is recognized that the pH at which $r = 1$ is approximately equal to the isoionic point. At this pH, $Z = \nu_{x^-}$ and $\log(n - r)/r$ becomes very nearly $\log n$. Thus eq. 2 is written as

$$(pH)_0 = pK_0 - 0.868(\nu_{x^-})_0 w + \log n \qquad (8)$$

where, $(pH)_0$ represents the isoionic point and $(\nu_{x^-})_0$ the number of the anions bound to the protein at the isoionic point. Combining eq. 7 and 8 equation (9) is obtained

$$(pH)_I = (pH)_0 + \log\left(\frac{1}{(\nu_{x^-})_I} - \frac{1}{n}\right) - 0.868\,(\nu_{x^-})_0 w \qquad (9)$$

It is seen that the difference between the isoionic point and the isoelectric point is a function of the medium and its ionic strength, because w is a function of the ionic strength and ν_{x^-} changes with the media and its ionic strength. In the case of BPA at 0.02 chloride ionic strength the calculated $(pH)_I$ is 4.5 ± 0.1, the experimental value 4.52.

Effect of Temperature.—Comparing the mobility values at 25° and those at 0° at 0.02 ionic strength, it is found that the former are almost exactly double the latter within experimental error. The ratio of viscosity coefficient at 0° to that at 25° is 2.005. Therefore the product of ηu is seen to be constant[49] in this pH region. In Henry's eq. r_i is thought to be constant regardless of temperature. It is found also that κ is nearly independent of temperature.[51] Thus when the ratio of Henry's

(47) H. A. Abramson, L. S. Moyer and M. H. Gorin, "Electrophoresis of Proteins," Reinhold Publ. Corp., New York, N. Y., 1942, p. 131.

(48) Values of the radius found in the present study are smaller than those found at room temperature by Tanford, *et al.*,[12] and by Kronman and Foster.[46] The main reason is that the authors assumed BPA as a prolate ellipsoid, not only as a sphere.

(49) Watanabe, *et al.*,[50] studied the change of the mobility of horse serum albumin with temperature. It was found that the product ηu increased with temperature at pH 7.7. This may be attributed to the increase of the dissociation of the basic groups with temperature. This is reasonable when we consider that the heat of dissociation of the amino groups is much larger than that of the carboxyl group.

(50) I. Watanabe, N. Ui and M. Nakamura, *J. Phys. Colloid Chem.*, **54**, 1366 (1950).

(51) In eq. 4 variables are T and D. The ratio of κ at 25° (κ_{25}) to that at 0° (κ_0) is almost unity as

$$\frac{\kappa_{25}}{\kappa_0} = \sqrt{\frac{273D_0}{298D_{25}}} = 1.013$$

since D_0 (dielectric constant at 0°) is 87.8 and D_{25} (that at 25°) is 78.3.[52]

(52) "International Critical Tables," McGraw-Hill Book Co., New York, N. Y., Vol. VI, p. 78.

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eq. at 25° to that at 0° is taken (suffix means the temperature), it becomes

$$\frac{Z_{25}}{Z_0} = \frac{r_{25}g(r_{25})}{r_0 g(r_0)}$$

where $g(r)$ is a new function of r. The hydrogen ion binding of proteins in the carboxyl titration region is known to be nearly temperature independent.[53,54] Evidence also exists that chloride ion binding to human serum albumin has a low temperature coefficient (enthalpy).[39] The change of the isoelectric point with temperature is not great, in this study less than 0.1 pH unit between 0 and 25°. These results suggest Z to be nearly independent of temperature. If we assume that Z is constant at the two temperatures, the radius of BPA is also constant.

(53) C. Tanford, THIS JOURNAL, **72**, 441 (1950).
(54) J. Wyman, *J. Biol. Chem.*, **127**, 1 (1939).

LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Electrophoretic and Hydrogen Ion Binding Behavior of Bovine Plasma Albumin in the Presence of 0.02 *M* Thiocyanate Ion[1,2]

BY KOICHIRO AOKI[2] AND JOSEPH F. FOSTER

RECEIVED FEBRUARY 2, 1957

Electrophoretic studies have been conducted on bovine plasma albumin over the pH range 2.0–4.5 in 0.02 *M* thiocyanate. Below pH 3.0 and above 4.3 single boundaries were obtained. Between 3.2 and 4.3 two boundaries were found, the composition varying continuously with pH in accord with the same N–F equilibrium previously reported in presence of chloride. The mid-point of the equilibrium occurs at pH 3.75 in comparison to 4.0 in chloride. Hydrogen ion titration studies were conducted in the region acid to the isoionic point in presence of 0.02 *M* thiocyanate. Molecular radii estimated from electrophoretic mobilities through Henry's equation are in agreement with values in chloride and indicate no appreciable molecular expansion to take place over the pH range of the molecular transition. Assuming a constant value for the electrostatic interaction parameter w, and constant number of binding sites, the apparent intrinsic pK of the carboxyl groups is shown to parallel very closely the electrophoretic composition in both chloride and thiocyanate. These results strongly suggest that the anomaly in the titration behavior of this protein is due essentially to the N–F transition, the carboxyls in the N form having a pK of approximately 3.7 due to stabilization by the native protein structure, while in the F form these stabilizing interactions are largely removed (pK = 4.4).

Introduction

It has been shown in chloride media that bovine plasma albumin (BPA) undergoes an isomerization reaction (N–F equilibrium)[3] in the pH range 4.5 to 3.5, and that the molecule expands below pH 3.5.[3,4] It has been suggested that the anomalous character of the titration curve of this protein above pH 3.5 can be explained on the basis of this equilibrium if it is assumed that the carboxylate groups are stabilized in the N form.[5] To test this idea further, electrophoretic studies have been conducted in the presence of 0.02 *M* thiocyanate ion, which is known to be much more strongly bound to this protein than is chloride. In addition hydrogen ion titration curves were determined in the same medium.

Experimental

Materials.—Pentex bovine plasma albumin, Lot No. A1201, was used. In the electrophoretic study this was used without further purification. In the titration study the protein solution was deionized by passing through the mixed ion-exchange column of Dintzis.[6] Potassium thiocyanate was of C.P. grade. Thiocyanic acid was obtained by passing potassium thiocyanate solution through cationic ion exchanger in the hydrogen form. In the titration study only ion-exchanged water was used.

Procedure.—Electrophoresis was carried out at 0° in a Tiselius type electrophoresis apparatus, Model 35 of the Perkin–Elmer Corporation, equipped with the schlieren scanning system. All the procedures in electrophoresis and the method of calculation were exactly the same as used in the previous work.[3] The total ionic strength of the media was 0.02 and the concentration of protein was 0.2%.

In the titration study the same apparatus as used by Foster and Sterman[7] was used. It consisted of a Beckman Model G pH meter and an external electrode cell assembly. The cell assembly consisted of a Beckman No. 1190-80 General Purpose glass electrode and a Beckman No. 1070-71 sleeve type calomel reference electrode. All temperature sensitive parts of the electrode cell assembly were maintained at a constant temperature, 25 or 0°. The procedure for determining the titration curve at 25° was also the same as was followed by the above workers.[7] In the studies at 0° the electrode system was standardized at each measurement against a standard phthalate buffer of pH 4.00, and the pH reading of the solution, which was prepared in a cold room, was taken after attaining thermal equilibrium (about 15 minutes).[8] In the calculations the molecular weight of BPA was assumed to be 70,000.

Results

Electrophoresis of BPA in the thiocyanate media of 0.02 ionic strength and at 0° was carried out in the pH range of 2.0 to 4.5. Below pH 3.0 there was a single boundary, and between this pH and 4.3 there were two boundaries. The percentage of the area of each form changed continuously with pH in the same way as in chloride media.[9] Here

(1) Supported in part by the National Cancer Institute, National Institutes of Health, Grant C-2248.
(2) Presented in part at the 41st Meeting of the Federation of American Societies for Experimental Biology, Chicago, 1957.
(3) K. Aoki and J. F. Foster, THIS JOURNAL, **78**, 3538 (1956); **79**, 3385 (1957).
(4) J. T. Yang and J. F. Foster, *ibid.*, **76**, 1588 (1954); C. Tanford, *et al.*, *ibid.*, **77**, 6421 (1955); W. F. Harrington, P. Johnson and R. H. Ottewill, *Biochem. J.*, **62**, 569 (1956).
(5) J. F. Foster and K. Aoki, Abstracts 130th ACS Meeting, September 1956.
(6) H. M. Dintzis, Ph.D. thesis, Harvard University, 1952.
(7) J. F. Foster and M. D. Sterman, THIS JOURNAL, **78**, 3656 (1956).
(8) In measurements at 0°, the temperature dial of the pH meter was adjusted to 25° and the pH reading multiplied by 1.09 (=298/273).
(9) The areas were measured on the ascending pattern. Patterns were reasonably enantiographic in all cases. Resolution of the two components was not quite as good as in either chloride or acetate probably because of the decreased mobility in presence of thiocyanate. Mobilities at zero concentration were estimated using equation 1 in the earlier paper.[3]

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again we call the faster moving component F form and the slower one N form. The *p*H–mobility curve[9] is shown in Fig. 1. The percentages of the areas are plotted against *p*H in Fig. 2.

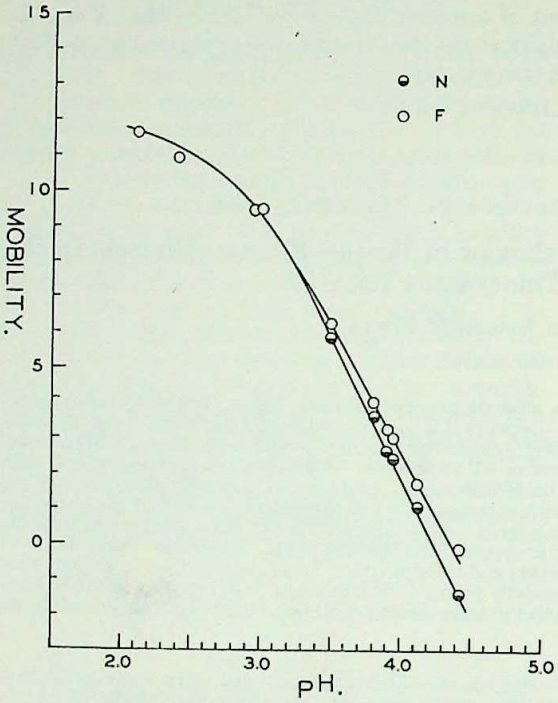

Fig. 1.—*p*H–mobility curve of BPA in 0.02 ionic strength SCN^- and at 0°. The mobility is given in the units cm.²/volt sec. × 10^5.

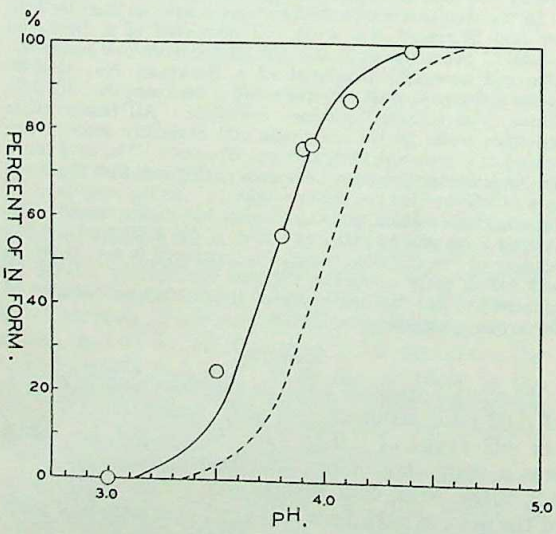

Fig. 2.—Dependence of electrophoretic composition on *p*H at 0°: ——, 0.02 SCN^-; - - - -, 0.02 Cl^- (ref. 2).

Titration curves of BPA in 0.02 thiocyanate media were determined at two temperatures, 25 and 0°. These are shown in Fig. 3, to which the titration curve in 0.02 chloride media at 25° by Foster and Sterman[7] is added.

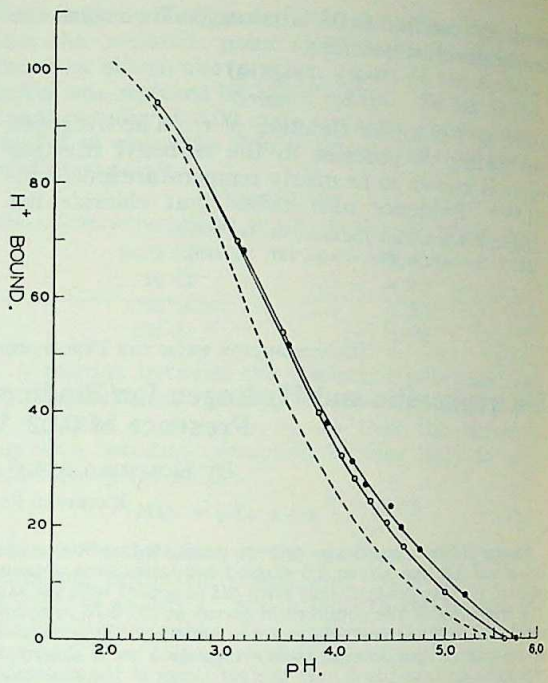

Fig. 3.—Titration curves of BPA in 0.02 ionic strength SCN^- at 25° (o) and at 0° (●). Equivalents H^+ bound per mole of BPA are shown against *p*H; - - - -, 0.02 Cl^- (ref. 6).

Discussion

In all experiments between *p*H 3.2 and 4.3, two boundaries were observed in the electrophoretic patterns. Further, the percentage composition changed continuously with *p*H in close accord with the equilibrium

$$N + 3H^+ \rightleftharpoons F$$

The result is in qualitative agreement with the finding of Longsworth and Jacobsen[10] that BPA gives a single boundary, in presence of thiocyanate, at *p*H 4.31 and 4.61 but two boundaries at *p*H 4.06. The results supplement and extend our earlier finding[2] that such an equilibrium exists in both chloride and acetate. (In the case of acetate the equilibrium corresponded more closely to a two-hydrogen-ion equilibrium.) The "mid-point" *p*H values in the three systems are, respectively, 3.75, 4.0 and 4.1 in 0.02 *M* thiocyanate, chloride and acetate. It should be emphasized that a third component such as was observed over a narrow *p*H range in chloride (3.80–3.95) was not observed in the present studies.

The net charge *Z* was calculated at various *p*H values using the hydrogen-ion titration curve at 25° and the thiocyanate binding equation of Coleman.[11] The latter may be expressed as

$$\nu_{x^-} = \sum \frac{k_i n_i C_{x^-} \exp(2Zw)}{1 + k_i C_{x^-} \exp(2Zw)}$$

where ν_{x^-} represents the number of anions (x^-) bound to one BPA molecule. C_{x^-} is the molar concentration of the anion and n_i the number of

(10) L. G. Longsworth and C. F. Jacobsen, *J. Phys. Colloid Chem.*, 53, 126 (1949).

(11) J. S. Coleman, Ph.D. thesis, Massachusets Institute of Technology, 1953.

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binding sites with intrinsic constant k_1. In the case of thiocyanate, $n_1 = 1$, $n_2 = 8$, $n_3 = 18$, $k_1 = 45{,}000$, $k_2 = 1925$, and $k_3 = 63$. The parameter w is a function which mainly depends upon the molecular size and the ionic strength. The method of calculation of Z is exactly the same as previously used on the data in chloride media. The Z–pH curve thus calculated predicted the isoelectric point to be pH 4.50. The value found experimentally was 4.25. Therefore the thiocyanate binding curve was corrected so that the Z–pH curve yielded the isoelectric point experimentally found. This was carried out by raising the thiocyanate binding curve by four units over the entire range. Using the Z–pH curve thus corrected a plot of mobility (μ) *versus* net charge (Z) was drawn (Fig. 4).[12] Employing Henry's equation, the effective

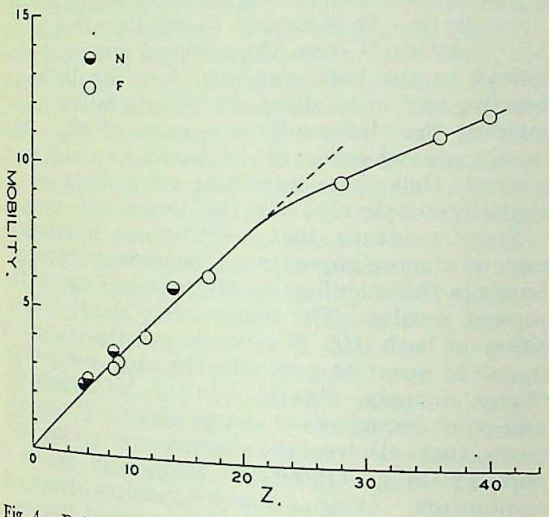

Fig. 4.—Relation between electrophoretic mobility (u) and net charge (Z).

radius of the BPA molecule was calculated from Z/u, in the same manner as previously, at the various pH values. Results are shown in Fig. 5. The radius is constant, 32 ± 2 Å., for both F and N forms above pH 3.2, and is the same as found in chloride media.[3] Slight expansion of BPA takes place below pH 3.2, considerably less than was observed in chloride media. This is in agreement with the finding of Kronman and Foster[14] that the sedimentation constant of BPA at pH 2 and 0.02 ionic strength is larger in thiocyanate media than in chloride. They have estimated effective radii at pH 2.0 of 57.0 and 40.5 Å. in chloride and thiocyanate media, respectively.

It is seen in Fig. 3 that hydrogen ion binding is enhanced in thiocyanate over that in chloride media at similar pH. This is in agreement with

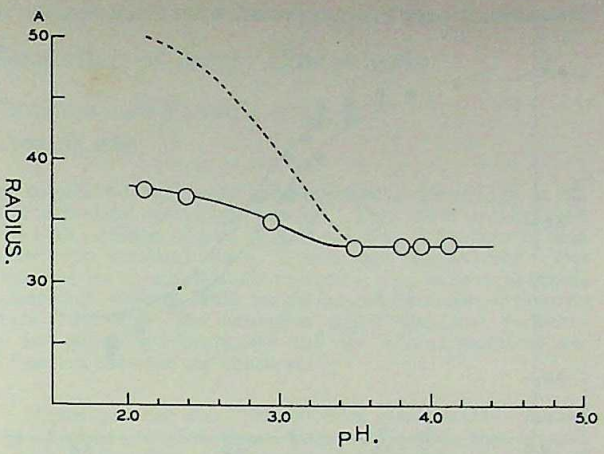

Fig. 5.—Radius of BPA *versus* pH as calculated by Henry's equation: ——, 0.02 SCN^-; - - - -, 0.02 Cl^- (ref. 2).

results described by Scatchard and Black[15] and is also to be expected on the basis of the enhanced binding of thiocyanate ion. This is seen easily from the following form of the titration equation

$$pH = pK_0 + \log \frac{n - r}{r} - 0.868Zw \qquad (I)$$

where n is the total number of basic sites of a particular species in the protein molecule, r the number of hydrogen ions bound to such sites, pK_0 the negative logarithm of the intrinsic dissociation constant for the particular species considered, Z the net charge on the protein and w the Debye–Hückel parameter.[16] Clearly, enhanced anion binding will diminish Z, which is in every case positive on the acid side of the isoelectric point, hence increasing the number of bound hydrogen ions (r).

Tanford has pointed out the inadequacy of eq. I in accounting for the titration behavior of plasma albumin acid to the isoelectric point.[17] In particular, he has shown the titration curve to be too steep in the carboxyl titration region and has suggested that this results from expansion of the protein molecule with a resultant decrease in the interaction parameter w. While the now well-known low pH expansion of this protein appears at first glance to be in good accord with this idea, it has been pointed out that gross molecular expansion takes place only at pH values below that range in which most of the apparent decrease in w occurs.[5,7,18] It has been suggested alternatively that the titration anomaly in the pH region above 3.5 is to be associated with the N–F transition.[5] The present data provide a further test for this idea.

(12) The calculation of the net charge on N and F involved the assumption that $Z_F = Z_N + 3$. The procedure and assumptions were identical with those used earlier.[3] The Z–pH curve was also drawn by use of the thiocyanate binding data of Carr.[13] This Z–pH curve predicts the isoelectric point to be around 4.8. However, there is agreement at pH 3.0 between the Z value calculated by this method and that calculated by our curve.

(13) C. W. Carr, *Arch. Biochem. Biophys.*, **40**, 291 (1953).

(14) M. J. Kronman and J. F. Foster, *ibid.*, in press.

(15) G. Scatchard and E. S. Black, *J. Phys. Colloid Chem.*, **53**, 88 (1949).

(16) See, for example, C. Tanford, in T. Shedlovsky, ed., "Electrochemistry in Biology and Medicine," John Wiley and Sons, Inc., New York, N. Y., 1955.

(17) C. Tanford, THIS JOURNAL, **72**, 441 (1950); *Proc. Iowa Acad. Sci.*, **59**, 206 (1952).

(18) The alternative assumption, n variable (unmasking of binding sites) is considered less likely for reasons that will not be discussed here. This problem, together with a more detailed consideration of the mechanism implied in the present discussion, will be presented in a future paper.[19]

(19) J. F. Foster and K. Aoki, *J. Phys. Chem.*, in press.

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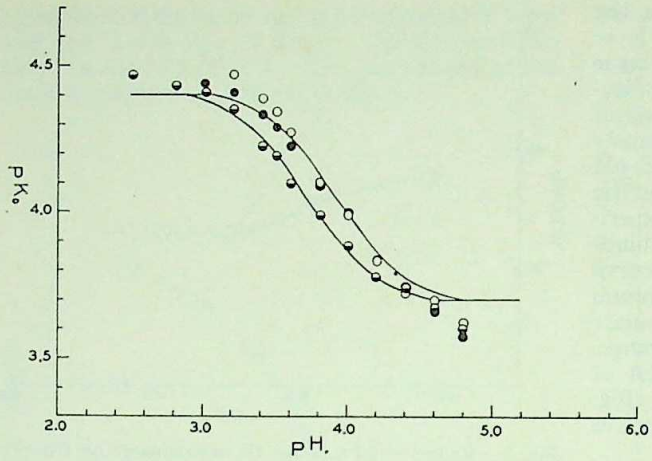

Fig. 6.—Relation between pK_0 and pH: ◒, 0.02 SCN^-; ○, 0.02 Cl^-; and ●, 0.10 Cl^-.

Tanford's calculations of w clearly pre-suppose the constancy of pK_0 and of n, the number of binding sites. We adopt instead the approximation that w is constant over the pH range in which no significant increase in molecular radius occurs. In case of chloride, the radius is substantially constant down to pH 3.5; in thiocyanate down to pH 3.2. We further adopt tentatively the position that n is constant and that all of the deviation from ideal behavior is to be attributed to changes in the intrinsic constant, pK_0.[18] Figure 6 shows results of calculations utilizing data in chloride at two ionic strengths, 0.02 and 0.10, and in thiocyanate at 0.02 ionic strength. The radius of the protein was assumed to be 33 Å. in all cases, corresponding to a w value of 0.046 at 0.02 ionic strength, and 0.029 at 0.10 ionic strength. It is seen that in all cases sigmoid curves are obtained which coincide remarkably well with the electrophoretic composition curves. In particular, the curves in chloride are seen to be independent of ionic strength, as was essentially true also of the electrophoretic composition. The mid-point of the pK_0–pH curve is shifted toward the acid side, when chloride is replaced by thiocyanate, by 0.2 pH unit in comparison with a shift of 0.25 unit in the electrophoretic composition curve. A minor discrepancy is the fact that the pK_0–pH curves in both thiocyanate and chloride appear to fit a two hydrogen ion equilibrium somewhat better than three.[20] The fact that calculated pK_0 values deviate from the drawn curves near pH 5 as well as at the lower end of the curves is not at all surprising. Near pH 5, imidazolium groups must almost certainly begin to titrate, a fact which is not taken into account in the present calculations. At the lower end of the transition, all evidence indicates that molecular expansion is beginning to take place, which will result in a decrease in w and an increase in the apparent pK_0.

To a reasonably close approximation it appears that the anomalous character of the titration curve can be accounted for through the N–F transition. It further appears that the mean pK_0 value for the carboxyl groups is about 3.7 for N form and 4.4 for F form, and that in each case these intrinsic pK_0's are substantially independent of such environmental factors as ionic strength and salt type. It is natural to conclude that in the native N form the carboxyl groups are stabilized in the basic (anionic) form by hydrogen bonding and/or localized electrostatic interactions[21] yielding the abnormally low value of pK_0. The nearly normal value of 4.4 found for the F form suggests that these stabilizing interactions are essentially completely lost in the "isomerized" protein.

Some evidence that electrostatic interactions may be of more importance than carboxyl hydrogen bonds in this stabilization may also be found in the present results. The mid-point of the N–F transition in both 0.02 M chloride and thiocyanate is found to occur at precisely the same net protein charge, namely, plus 11. In 0.1 M chloride the mid-point occurs at net charge plus 8. It thus appears that electrostatic factors are of key importance in governing the position of the N–F equilibrium. *Were carboxyl hydrogen bonds of primary importance it would be expected that thiocyanate binding would actually shift the equilibrium to higher pH rather than lower.* This inference is based on the patent fact that competition of hydrogen ions for hydrogen-bonded carboxylate anions would be greater, at given pH, in the presence of thiocyanate, due to the enhanced hydrogen ion binding. Tanford, *et al.*,[23] have similarly concluded that the forces stabilizing this protein against molecular expansion may be predominantly electrostatic.

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(20) A possible explanation for this fact can be given on the basis of a mechanism to be presented in a future paper.[19]

(21) The importance of such localized electrostatic effects has been emphasized recently by Hill.[22]

(22) T. L. Hill, THIS JOURNAL, **78**, 5527 (1956).

(23) C. Tanford, J. G. Buzzell, D. G. Rands and S. A. Swanson, *ibid.*, **77**, 6421 (1955).

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[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, THE FACULTY OF ENGINEERING, KYOTO UNIVERSITY]

Kinetics and Mechanism of the Formation of Azoxy Compounds

BY YOSHIRO OGATA, MASARU TSUCHIDA AND YASUO TAKAGI

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The condensation of phenylhydroxylamine and nitrosobenzene to yield azoxybenzene has been studied kinetically at 50, 40, 30 and 20° in pure and aqueous methanolic solutions using the ultraviolet spectrophotometer. The rate is proportional to the concentration of both reactants. The rate constant varies with addition of acid (0.0001–0.1 *N*). The plots of acid concentration *versus* rate constant show downward and upward curves in pure and 30 vol. % methanol, respectively. The rate data and the acidity–rate relationship show that two mechanisms are simultaneously operating, *i.e.*, in neutral media the reaction of the free amine and the free nitrosobenzene is predominant, while in acidic media the condensation of phenylhydroxylamine and protonated nitrosobenzene becomes important. Moreover, the formation of *p,p'*-dichloro-, *p*-chloro- and unsubstituted azoxybenzenes from *p*-chloronitrosobenzene and phenylhydroxylamine and the related reactions are confirmed; the fact implies a preliminary rapid and reversible reaction between the reactants.

It has been supposed that the formation of azoxy compound by the reduction of nitrobenzene results from condensation between phenylhydroxylamine and nitrosobenzene. However, strange to say, the condensation of *p*-substituted phenylhydroxylamine with nitrosobenzene has been reported to give a mixture containing unsubstituted and *p,p'*-disubstituted azoxybenzene.[1] Since then, little theoretical attention has been paid to this phenomenon, and therefore it appeared valuable to examine the reaction mechanism in detail.

Our experiments indicate the truth of these observations not only with *p*-methyl or *p*-chlorophenylhydroxylamine and nitrosobenzene but also with *p*-chloronitrosobenzene and phenylhydroxylamine. These facts seem to indicate that azoxybenzene formation is truly a reaction between phenylhydroxylamine and nitrosobenzene, but that the reaction between substituted phenylhydroxylamines and nitrosobenzene or substituted nitrosobenzenes and phenylhydroxylamine is complicated by a preliminary rapid equilibrium between phenylhydroxylamine and nitrosobenzene.

$$p\text{-X—C}_6\text{H}_4\text{NO} + \text{C}_6\text{H}_5\text{NHOH} \rightleftharpoons p\text{-X—C}_6\text{H}_4\text{NHOH} + \text{C}_6\text{H}_5\text{NO}$$

Thence we investigated spectrophotometrically the kinetics of the condensation of phenylhydroxylamine with nitrosobenzene in methanol. The reaction was found to be first-order with each reactant, and its second-order rate constant was influenced by the addition of acid or water. The present report summarizes these data which suggest a plausible mechanism.

Experimental

Materials.—Phenylhydroxylamine was prepared from nitrobenzene by reduction with zinc dust in aqueous ammonium chloride solution.[2] The crude material was purified by dissolving it in benzene and then precipitating it by the addition of petroleum ether. Repeated purification gave fine needles of m.p. 82° (lit.[3] m.p. 82°). For each kinetic run freshly purified material was used. *p*-Methyl- and *p*-chlorophenylhydroxylamine were prepared and purified in the same way, m.p. 94° (lit.[4] m.p. 94°) and 88° (lit.[5] m.p. 87.5°), respectively.

Nitrosobenzene was obtained from phenylhydroxylamine by chromic acid oxidation. Recrystallization from a small amount of methanol gave colorless crystals, m.p. 67.5° (lit.[6] m.p. 68°). The product was stored in a dark place. *p*-Chloronitrosobenzene was prepared and purified similarly, m.p. 93° (lit.[7] m.p. 92–93°). The methanol used was of best grade and purified by rectification, b.p. 65°.

Products from *p*-Substituted Phenylhydroxylamine or Nitrosobenzene.—As an example, the condensation of phenylhydroxylamine and *p*-chloronitrosobenzene is described below. A methanolic solution (15 ml.) of phenylhydroxylamine (2 g.) was mixed with a methanolic solution (15 ml.) of *p*-chloronitrosobenzene (2 g.) at room temperature. The greenish color of *p*-chloronitrosobenzene gradually darkened on standing, and after five minutes the color became yellow by warming to 50°. A small amount of water was added, and the solution was warmed until the precipitate dissolved and then chilled. The crystalline material deposited was collected. The mother liquor was worked up similarly until no more precipitation was observed, and the last filtrate was evaporated to dryness in vacuum. Each crop was then carefully submitted to fractional recrystallization. There were obtained pure crystals of *p,p'*-dichloroazoxybenzene, 1.4 g., m.p. 158° (lit.[8] m.p. 158°); azoxybenzene, 0.9 g., m.p. 35° (lit.[9] m.p. 35.5°); and *p*-chloroazoxybenzene, 0.5 g., m.p. 62° (lit.[10b] m.p. 62°).

p-Chloroazoxybenzene was converted to *p*-chloroazobenzene by heating in concentrated sulfuric acid. Recrystallization from aqueous methanol gave orange-red crystals, 0.26 g., m.p. 92°, which showed no depression of m.p. on admixture with authentic specimen, m.p. 92°.[10]

In an analogous manner, the condensation of *p*-chlorophenylhydroxylamine (2 g.) and nitrosobenzene (2 g.) gave *p,p'*-dichloroazoxybenzene, 0.9 g.; azoxybenzene, 0.6 g.; and *p*-chloroazoxybenzene, 0.2 g. From *p*-methylphenylhydroxylamine (2 g.) and nitrosobenzene (2 g.) there was obtained *p,p'*-dimethylazoxybenzene, 1.7 g., m.p. 71° (lit.[11] m.p. 71°); and azoxybenzene, 1.0 g., m.p. 35°.

Determination of Basicity Constants.—The basicity constant[12] of phenylhydroxylamine, $K_1 = [\text{PhNH}_2\text{OH}^+]/[\text{PhNHOH}][\text{H}^+]$, and that of nitrosobenzene, $K_4 = [\text{PhNOH}^+]/[\text{PhNO}][\text{H}^+]$, were determined by measuring at appropriate wave lengths the optical densities of these materials at 0.0002 *M* concentration in acidic methanolic solutions as a function of acid concentrations.[13] From the estimated values of optical densities in neutral, weakly acidic and strongly acidic solutions of these materials con-

(1) (a) E. Bamberger and E. Renauld, *Ber.*, **30**, 2278 (1897); E. Bamberger and A. Rising, *Ann.*, **316**, 257 (1901); (b) V. O. Lukashevich, *Compt. rend. acad. sci. U.R.S.S.*, **21**, 376 (1938); *C. A.*, **33**, 3769 (1939).

(2) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 445.

(3) R. Willstätter and H. Kubli, *Ber.*, **41**, 1936 (1908).

(4) E. Bamberger, *ibid.*, **28**, 245 (1895).

(5) M. D. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2550 (1924).

(6) E. Bamberger and L. Storch, *Ber.*, **26**, 472 (1893).

(7) C. K. Ingold, *J. Chem. Soc.*, **127**, 517 (1925).

(8) L. Zechmeister and P. Rom, *Ann.*, **468**, 130 (1929).

(9) S. Sugden, J. B. Reed and H. Willkins, *J. Chem. Soc.*, **127**, 1537 (1925).

(10) J. Burns, H. McCombie and H. A. Scarborough, *ibid.*, 2933 (1928).

(11) E. Bamberger, *Ber.*, **59**, 429 (1926).

(12) In general, the basicity constant is expressed as $[\text{BH}^+][\text{OH}^-]/[\text{B}]$, where B is a base; hence these K_1 and K_4 values should be multiplied by the solubility product of water according to this definition for coincidence with the idiomatic expression.

(13) For convenience, the acid (hydrogen chloride) concentration, measured by the acidimetry, was assumed equal to $[\text{H}]^+$, since no appreciable *p*H change was observed on addition of these substrates.

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taining no, partly and wholly protonated substrates, respectively, the basicity constants were calculated by means of the above equations. With phenylhydroxylamine, the difference between optical density at 236 mμ and that at 280 mμ was used, while with nitrosobenzene the optical density at 260 mμ was utilized. With phenylhydroxylamine, an increase of the protonated amine concentration with increasing acid concentration became negligible at *ca.* 0.04, 0.2 and *N* acid concentrations in pure, 96 and 70% methanol, respectively; *e.g.*, a plot of $E_{236} - E_{280}$, the difference between optical density of 0.0002 *M* methanolic solution of this material at 236 mμ and that at 280 mμ, against acid concentration *c* approaches the extreme value (zero) corresponding to complete ionization when *c* is 0.04 *N*. Using this value, zero and that for neutral solution ($E_{236} - E_{280})_0 = 0.720$, the basicity constant of phenylhydroxylamine, K_1, can be calculated by means of the relation

$$K_1 = [PnNH_2OH^+]/[PhNHOH]c = \frac{0.720 - (E_{236} - E_{280})_c}{\{(E_{236} - E_{280})_c - 0\}\, c}$$

Similarly, K_1 values in 96 and 70% methanolic solutions were obtained, the complete protonation here being reached when *c* is about 0.2 and *N*, respectively; the fact seems to indicate that water is a weaker acid than methanol.

The basicity of nitrosobenzene is so small that it is decomposed by acid before complete protonation of the substrate is attained, even in pure methanol. Therefore, the basicity constant K_4 was calculated by means of two simultaneous equations by inserting two different $(E_{260})_c$ values.

$$K_4 = \frac{(E_{260})_0 - (E_{260})_c}{\{(E_{260})_c - (E_{260})_\infty\}\, c} = \frac{0.320 - (E_{260})_c}{\{(E_{260})_c - (E_{260})_\infty\}\, c}$$

Here (E_{260})'s are optical densities at 260 mμ and the indicated acid concentrations, and *c* means any acid concentration. These data are summarized in Table I.

TABLE I

BASICITY CONSTANTS OF PHENYLHYDROXYLAMINE AND NITROSOBENZENE

Temp., °C.	Phenylhydroxylamine K_1, l. mole^{-1} 100% MeOH	96% MeOH	70% MeOH	Nitrosobenzene K_4, l. mole^{-1} 100% MeOH
5	4.75×10^3	4.77×10^2	15.0×10	1.8
25	2.90×10^3	3.02×10^2	7.95×10	1.3
40[a]	2.14×10^3	2.24×10^2	5.37×10	1.0

[a] The data were obtained by the extrapolation from the values at 5 and 25° by means of the Arrhenius equation.

Analysis of the Components of the Reaction Mixture.—Phenylhydroxylamine, nitrosobenzene and azoxybenzene absorb strongly in the range between 240–300 mμ (Fig. 1).

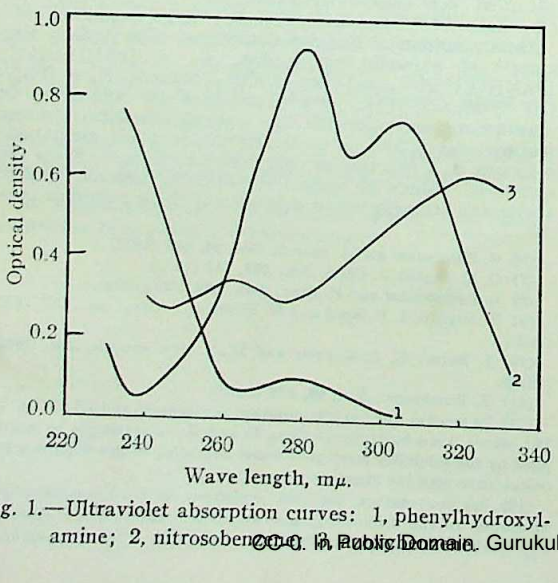

Fig. 1.—Ultraviolet absorption curves: 1, phenylhydroxylamine; 2, nitrosobenzene; 3, azoxybenzene.

An inspection of Fig. 1 will show that Vaughn's method[14] can be used to follow this condensation.

The following relationship will be deduced from Beer's law and the stoichiometry of the reaction.

$$E_1 - E_2 = (\epsilon_a^1 - \epsilon_a^2)(a - x) + (\epsilon_b^1 - \epsilon_b^2)(b - x) + (\epsilon_x^1 - \epsilon_x^2)x$$

$$E_3 - E_4 = (\epsilon_a^3 - \epsilon_a^4)(a - x) + (\epsilon_b^3 - \epsilon_b^4)(b - x) + (\epsilon_x^3 - \epsilon_x^4)x$$

Here, E_i is the optical density of a solution at wave length *i*; *a* and *b* are initial concentrations of phenylhydroxylamine and nitrosobenzene, respectively; *x* is the concentration of azoxybenzene produced; ϵ_a^i, ϵ_b^i and ϵ_x^i are the extinction coefficients of the subscripted materials at wave length *i*. This is a linear or first-order function of *x*; hence a plot of $E_1 - E_2$ (or $E_3 - E_4$) against *x* will show a set of parallel straight lines corresponding to each set of *a* and *b*. Accordingly, plots of $E_1 - E_2$ *vs.* $E_3 - E_4$ with varying *x* will again be represented by a set of parallel straight lines (not curves) each of which corresponds to a run with a set of *a* and *b*.

If the sum of *a* and *b* is constant, *e.g.*, 0.0002 *M*, the variation of the composition of the reaction mixture during the reaction may be represented, just as Vaughn's chart, by a triangular composition diagram of Fig. 2, where P, N and A

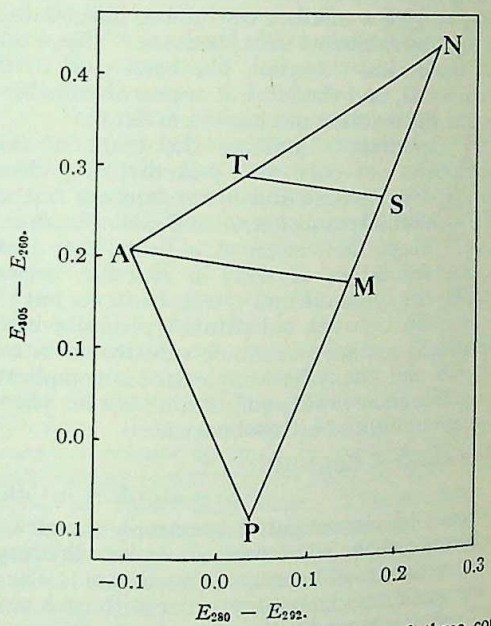

Fig. 2.—Vaughn's chart for the estimation of three components.

represent pure solutions of phenylhydroxylamine (0.0002 *M*), P′, nitrosobenzene (0.0002 *M*), N′, and azoxybenzene (0.0002 $M \times 1/2$), respectively. For example, a reaction course of the equivolume mixture of P′ and N′, represented by the mid-point M of line PN, may be expressed as line MA, since the sum of [PhNO], [PhNHOH] and 2[PhN$_2$O] is constant during the reaction.[14] Analogously, it is apparent that with reactants containing N′ and P′ in a ratio of SP:NS, the reaction course is represented by line ST, where line ST is parallel to line AM and T is an intersection of NA and ST, as is apparent from the above reasoning. This is a modification of Vaughn's chart and seems very useful for the detection of side reactions, since the method determines the concentrations of all reactants and product.

Therefore, methanolic solutions of phenylhydroxylamine (0.0002 *M*), nitrosobenzene (0.0002 *M*) and azoxybenzene (0.0001 *M*) were prepared, their optical densities being determined at 260, 280, 292 and 305 mμ and compared with that of pure methanol by means of a Beckman DU spectrophotometer. Differences of the optical densities, $E_{280} -$

(14) R. T. Vaughn and A. E. Stearn, *Anal. Chem.*, **21**, 1361 (1949).

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E_{292} and $E_{305} - E_{260}$, were calculated with each compound, the data being plotted in Fig. 2.

Typical Procedure for Rate Measurements.—An appropriate amount of a methanolic solution (0.002 *M*) of nitrosobenzene was introduced into a 200-ml. three-necked flask equipped with an ice-cooled reflux condenser, nitrogen-introducing tube and a tube suitable for withdrawing samples and immersed in a thermostat. Since phenylhydroxylamine is very sensitive to air oxidation, all kinetic experiments were carried out in nitrogen atmosphere. The nitrogen was purified by passing through three washing bottles each containing an aqueous alkaline solution of pyrogallol, then dried over potassium hydroxide and bubbled during the measurement. After bubbling for *ca.* 10 minutes to remove a trace of oxygen, the reaction was initiated by the addition of a methanolic solution (0.0002 *M*) of phenylhydroxylamine. At appropriate time intervals, aliquots (5 ml.) were taken out, poured into a 50-ml. volumetric flask containing an appropriate amount of methanol, diluted accurately to 50 ml. and then cooled to 0°. It was confirmed in preliminary tests that such a procedure would stop the reaction. At the end of the reaction, usually 30–100 minutes, the optical density of the resulting solution was measured at 260, 280, 292 and 305 mμ, and the second-order rate constant was calculated using the method mentioned previously.

The hydrogen-ion concentration was determined by acidimetry, since it was confirmed that the reactants and the product have no appreciable effect on the hydrogen-ion concentration.

Results

Second-order Rate Constants and Temperature Coefficients.—The rates were measured in three media, *i.e.*, 100, 96 and 70% methanol (vol. %), the apparent second-order rate constants being given in Table II with varying molar ratio of both reactants (the molar ratio of phenylhydroxylamine to nitrosobenzene varies from 5 to 1/4). As is shown in the table, the constancy is satisfactory, implying that the condensation involves a rate-determining combination of both reactants. The variation of the rate with temperature is shown in Fig. 3, from which the energy and entropy of activation is calculated to be 10.8 kcal. mole^{-1} and −32.5 cal. deg.$^{-1}$mole^{-1}, respectively.

TABLE II

SECOND-ORDER CONSTANTS FOR THE FORMATION OF AZOXYBENZENE IN PURE METHANOL AT 40°

Initial concentration, *M* $[C_6H_5NHOH]$	$[C_6H_5NO]$	k, l. mole^{-1} min.$^{-1}$
0.00034	0.00166	18.3
.00051	.00149	19.9
.00079	.00121	21.4
.00118	.00082	20.4
.00146	.00054	17.9
.00158	.00042	20.5
	Av.	19.7

Acidity Dependence.—In alkaline solutions oxidation of phenylhydroxylamine to nitrosobenzene was so rapid that accurate determination of the rate was impossible, since the oxidation proceeds during the optical density estimation. On the other hand, in strong acidity nitrosobenzene was converted to an unknown substance. Hence the kinetic experiments were confined to the acidity range from 0.0001 to 0.1 *N*. As the acid source, hydrogen chloride and in a few cases sulfuric acid were used. The variation of the apparent second-order rate constants with acid concentration is given with solvent composition is given in Table III. The data with hydrogen chloride as an acid source agree with those of sulfuric acid of the same normality. No salt effect was observed with added lithium chloride.

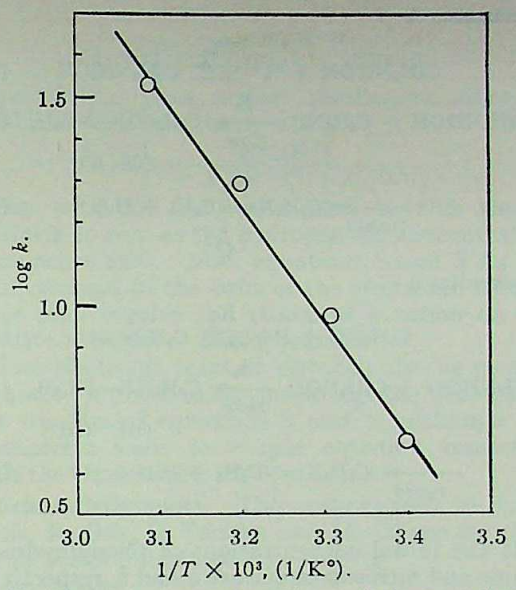

Fig. 3.—The temperature dependence of the second-order constant.

TABLE III

VARIATION OF SECOND-ORDER CONSTANTS WITH ACID CONCENTRATION AND WITH SOLVENT COMPOSITION AT 40°

$[H^+]$, *N*	k, l. mole^{-1} min.$^{-1}$ 100% MeOH	96% MeOH	70% MeOH
0	19.7	22.1	39.5
.0001	18.9		
.0004	14.0		
.001	16.0[a]		
.002	11.5		
.004	11.8		42.0
.004	13.0[a]		
.005		22.3	
.005		21.0[a]	
.0086	10.8		
.01	13.6[a]	22.0	49.5
.015			56.5
.018	11.2		
.0184	12.5		
.0184	10.5[b]		
.02		23.1	57.3
.028		22.3	
.03	11.7	22.9	
.0324	12.4[b]		
.04		21.8	
.046	11.7		
.062	10.0		

[a] Sulfuric acid-catalyzed. [b] LiCl was added.

Discussion

The results obtained, *i.e.*, the second-order constant and its acidity dependence, may best be explained by assuming two simultaneous mechanisms,

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Mechanism A

$$C_6H_5NHOH + H^+ \underset{}{\overset{K_1}{\rightleftharpoons}} C_6H_5\overset{+}{N}H_2OH \quad (1)$$

$$C_6H_5NHOH + C_6H_5NO \xrightarrow[\text{slow}]{k_2} C_6H_5\overset{+}{N}H(OH)-NC_6H_5(O^-) \quad (2)$$

$$\xrightarrow[\text{rapid}]{} C_6H_5N=\overset{+}{N}C_6H_5(O^-) + H_2O \quad (3)$$

Mechanism B

$$C_6H_5NO + H^+ \underset{}{\overset{K_4}{\rightleftharpoons}} C_6H_5\overset{+}{N}OH \quad (4)$$

$$C_6H_5NHOH + C_6H_5\overset{+}{N}OH \xrightarrow[\text{slow}]{k_5} C_6H_5\overset{+}{N}H(OH)-NC_6H_5(OH) \quad (5)$$

$$\xrightarrow[\text{rapid}]{} C_6H_5N=\overset{+}{N}C_6H_5(O^-) + H_2O + H^+ \quad (6)$$

If the initial concentrations of phenylhydroxylamine and nitrosobenzene are a and b, respectively, and that of the azoxybenzene produced at time t is

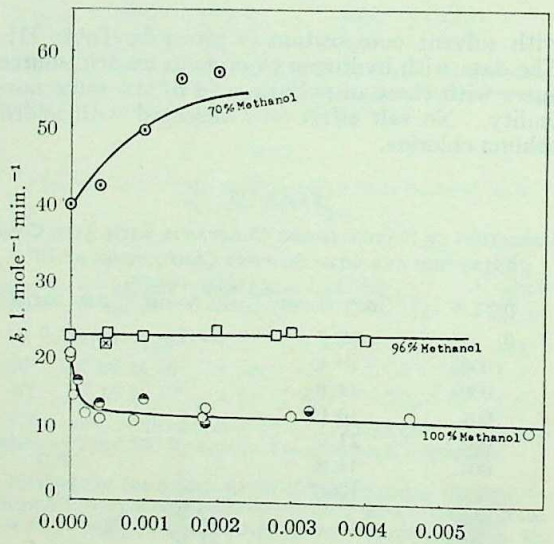

Fig. 4.—k *vs.* acid concentration: ◓ ⊠, sulfuric acid-catalyzed; ◒, LiCl was added; ○ ⊙ □, hydrogen chloride-catalyzed with various solvents.

x, the following relation is required by these mechanisms, where v, k and K are rate, rate constant and equilibrium constant of the subscripted step, respectively.

$$a - x = [C_6H_5NHOH] + [C_6H_5\overset{+}{N}H_2OH]$$

$$b - x = [C_6H_5NO] + [C_6H_5\overset{+}{N}OH]$$

$$[C_6H_5NHOH] = (a - x)\left(\frac{1}{1 + K_1[H^+]}\right)$$

$$[C_6H_5\overset{+}{N}H_2OH] = (a - x)\left(\frac{K_1[H^+]}{1 + K_1[H^+]}\right)$$

$$[C_6H_5NO] = (b - x)\left(\frac{1}{1 + K_4[H^+]}\right)$$

$$[C_6H_5\overset{+}{N}OH] = (b - x)\left(\frac{K_4[H^+]}{1 + K_4[H^+]}\right)$$

$$v_2 = k_2[C_6H_5NHOH][C_6H_5NO] = \frac{k_2(a - x)(b - x)}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

$$v_5 = k_5[C_6H_5NHOH][C_6H_5\overset{+}{N}OH] = \frac{k_5K_4[H^+](a - x)(b - x)}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

Since the over-all rate v is the sum of v_2 and v_5, the apparent second-order rate constant k with varying hydrogen ion concentration should be expressed as

$$k = \frac{k_2 + k_5K_4[H^+]}{(1 + K_1[H^+])(1 + K_4[H^+])} \quad (7)$$

Equation 7 reveals that k approaches k_2 in very weak acidity. The value of k_2 is equal to that of k in a neutral medium, hence k_5 may be calculated from the values of k_2 and k at known acidities using values of K_1 and K_4 in Table I. The values of k_5 thus calculated are shown in Table IV and hold constant over a thousand fold variation in the acid concentration, in agreement with these mechanisms. Using average values of k_5K_4 (Table IV) with the three solvents, the k values were calculated again and are shown in Fig. 4 in comparison with the observed values.

TABLE IV

CALCULATED VALUES OF k_5K_4 AND k_5 AT 40°

[H⁺], N	$k_5K_4 \times 10^{-3}$, l.² mole⁻² min.⁻¹ 100% MeOH	96% MeOH	70% MeOH
0.0001	33[a]		
.0004	17.3		
.002	20.6		
.004	26.5		2.88
.005		5.04	
.0086	23.3		
.01	28.8	4.92	3.65
.015			4.13
.018	23.9		
.02		5.31	3.97
.03	25.2	5.15	
.046	26.0		
.062	22.6		
	Av. 24.7	5.10	3.66

k_5 (av.) 2.61×10^4 l. mole^{-1} min.$^{-1}$

[a] At lower acid concentration, the values show a remarkable departure from constancy. This seems unavoidable, since at 0.0001 N, for instance, a 5% decrease of k (from 18.9 to 18.0) results in a 33% decrease of k_5K_4. The k_5K_4 values calculated from the other mechanisms show over a hundred fold variation.

These mechanisms indicate that in neutral solutions a reaction between free phenylhydroxylamine and free nitrosobenzene (eq. 2) predominates, while in acidic solutions a reaction of free phenylhydroxylamine with protonated nitrosobenzene (eq. 5) becomes important, just like the amine–carbonyl condensation.[15] Neither equation 2 nor 5 alone explains the rate–acidity relationship, *i.e.*, the rate constant would decrease with an increase of acidity if equation 2 alone were operating, while the rate would become equal to zero in a neutral solution if equation 5 alone were operating.

(15) J. B. Conant and P. D. Bartlett, THIS JOURNAL, **54**, 2881 (1932); M. Okuno and Y. Ogata, *ibid.*, **74**, 5727 (1952).

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Furthermore, the possibilities of the other mechanisms will be discussed below. A rate-determining reaction of protonated phenylhydroxylamine with nitrosobenzene

$$C_6H_5\overset{+}{N}H_2OH + C_6H_5NO \xrightarrow{k_8} C_6H_5N{=}\overset{+}{N}C_6H_5 \\ | \\ O^- + H_2O + H^+ \quad (8)$$

or a rate-determining condensation of both protonated reactants should lead to the rate constant expression

$$k = \frac{k_8K_1[H^+]}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

or

$$C_6H_5\overset{+}{N}H_2OH + C_6H_5\overset{+}{N}OH \xrightarrow{k_9} C_6H_5N{=}\overset{+}{N}C_6H_5 \\ | \\ O^- + H_2O + 2H^+ \quad (9)$$

$$k = \frac{k_9K_1K_4[H^+]^2}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

respectively; hence neither mechanism alone or combined with equation 5, where

$$k = \frac{k_5K_4[H^+]}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

agrees with the fact, since each k value should diminish to zero as the hydrogen ion concentration approaches zero. Also, equations 8 and 9 do not seem rational in the light of the electronic theory, since they involve the attack of a cation on the positive nitrogen of nitrosobenzene.

This electronic point of view can also be used to eliminate a mechanism involving the simultaneous reaction of equations 8 and 2, although the mechanism leads to a rate equation consistent with the experiment.

Acknowledgments.—The authors wish to thank Profs. R. Oda, S. Tanaka and M. Okano for their aid in performing these experiments.

KYOTO, JAPAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

The Kinetics of Solvolysis of Acyl Esters of Salicyclic Acid

BY EDWARD R. GARRETT

RECEIVED DECEMBER 28, 1956

The acid, neutral and alkaline hydrolysis of acetyl-, trimethylacetyl-, β-cyclopentylpropionyl- and diethylacetylsalicyclic acids were studied and the rate constants determined as functions of dissociation and of hydrogen and hydroxyl ion concentration. The Arrhenius parameters of entropy and heat of activation also were determined and mechanisms were considered in light of these values and the structures of the esters. Disagreement with values given in the literature was noted. An unusual increase in "spontaneous" rate was observed with increasing alcohol concentration whereas no such increase was noted with increasing dioxane content.

In order to determine the inhibition of hydrolysis of acyl salicylates by varying alkyl substitution on the acyl group, the acid and base hydrolysis of esters selectively chosen to scan substituent effects, acetyl-, trimethylacetyl-, β-cyclopentylpropionyl- and diethylacetyl salicylic acids were studied. A very complete study of the hydrolysis of acetyl salicylic acid (aspirin) had been made by Edwards.[1,2] However, since these papers had reported an unusually high alkaline hydrolysis heat of activation of 25 kcal./mole, whereas similar acyl phenates had activation energies of an order of magnitude of 12 kcal./mole,[3] the hydrolysis studies of aspirin were repeated and the Arrhenius parameters determined.

It was desired to carry out the hydrolysis studies in solutions as nearly aqueous as possible, but the inadequate water solubility of β-cyclopentylpropionyl- and diethylacetylsalicylic acids necessitated use of water–alcohol mixtures as solvents to maintain sufficient material in solution for spectrophotometric analysis. In order to place the hydrolysis studies of all these esters on comparative grounds, the hydrolysis of aspirin was studied in various water–alcohol mixtures. An unexpected increase in the hydrolysis rates of the anion in the *p*H-independent region was observed. This *p*H-independent hydrolysis of the completely ionized compound (as represented by the plateau of rate *vs.* *p*H at *p*H 5.5–9 in Fig. 1) had been ascribed by Edwards[1,2] to the water attack on the aspirin ion and would imply general acid–base catalysis.[4] In this light ethanol would have to be considered a more active base than water. However, Edwards[1] had also shown by studies in various concentrations of acetate buffers that the "spontaneous" hydrolysis was not subject to general acid–base catalysis.

The extraordinary magnitude of this "spontaneous" or water hydrolysis of aspirin has led to the formulation of cyclic mechanisms involving interaction of both carbonyls and their carbons in a rate-determining step.[5,6]

In order to clarify the anomalous enhancement of "spontaneous" hydrolysis with increasing alcohol content of the solvent and to determine if the rates were dependent on water content or were functions of dielectric constant, the "spontaneous" hydrolysis was studied in various dioxane–water mixtures. Surprisingly, there was small variation in hydrolysis rates.

(1) L. J. Edwards, *Trans. Faraday Soc.*, **46**, 723 (1950).
(2) L. J. Edwards, *ibid.*, **48**, 696 (1952).
(3) "Tables of Chemical Kinetics: Homogeneous Reactions," National Bureau of Standards Circular 510, U. S. Department of Commerce, Washington, D. C., 1951.
(4) J. L. Hockersmith and E. S. Amis, *Anal. Chim. Acta*, **9**, 101 (1953).
(5) J. D. Chanley, E. M. Gindler and H. Sobotka, THIS JOURNAL, **74**, 4347 (1952).
(6) K. Kangri, *ibid.*, **75**, 5984 (1953).

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TABLE I

TABULATION OF RATE CONSTANTS (k IN SEC.$^{-1}$, k_i IN L./MOLE/SEC.) FOR CALCULATION OF HYDROLYSIS OF ACYL ESTERS OF SALICYLIC ACID IN ACID AND NEUTRAL MEDIA[a]

Ester of salicylic acid	t, °C.	10^5k_b pH 1.10	10^5k_c pH 2.50	10^5k_d pH 5.05	10^5k_1	10^3k_4	$10^5k_5C_{H_2O}$
	25.0	2.24	0.562	3.63	25.0	1.02	3.72
Acetyl-	35.0	5.00	1.31	8.03	55.2	2.55	8.33
	50.3	20.5	4.83	35.3	237	7.13	36.3
	60.3	44.2	12.1	80.8	492	21.2	83.8
	25.0	0.113	0.0883	0.933	0.960	0.190	0.978
Trimethylacetyl-	35.0	0.273	.213	2.23	2.33	0.465	2.35
	50.3	1.13	.847	10.00	10.6	1.45	10.5
	60.3	2.77	2.02	25.5	27.8	2.80	26.8
		pH 1.10	pH 2.60	pH 5.30			
	25.0	0.922	0.207	3.62	10.3	1.80	3.95
β-Cyclopentylpropionyl-	35.0	2.15	0.462	8.05	24.3	3.97	8.80
	50.3	7.62	2.03	33.7	82.2	19.4	36.7
	60.3	17.8	5.12	80.0	188	51.6	87.5
	25.0	0.0262	0.0110	0.117	0.223	0.187	0.131
Diethylacetyl-	35.0	.0850	.0362	0.338	0.713	0.633	0.387
	50.3	.458	.215	1.64	3.53	4.00	1.82
	60.3	1.45	.662	4.38	11.2	12.5	4.92

[a] The acetyl- and trimethylacetylsalicyclic acids were studied in 0.5% ethanol; the β-cyclopentylpropionyl- and diethylacetylsalicylic acids were studied in 20% ethanol by volume. [b] The solutions were 0.0978 M in HCl, 0.0469 M in KCl. [c] The solutions were 0.534 M in acetic acid. [d] The solutions were 0.1091 M in acetic acid, 0.0785 M in NaOH.

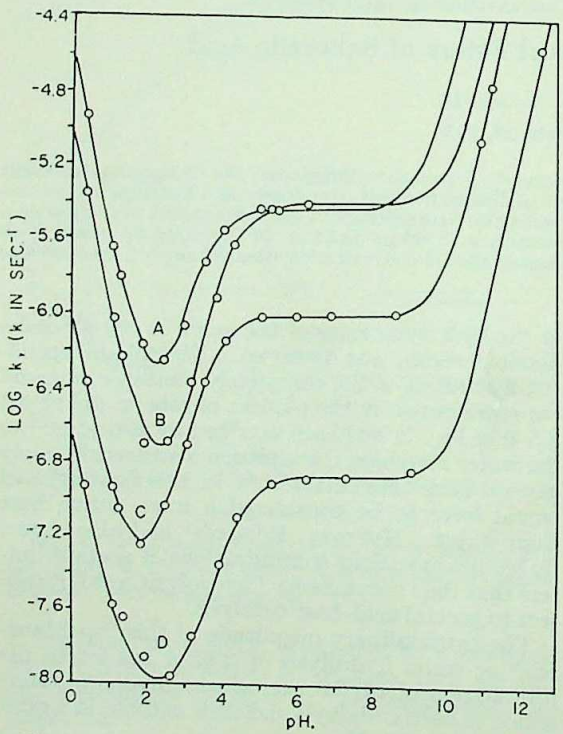

Fig. 1.—The pH profile of the logarithm of apparent first-order rate constants for hydrolysis. The points are experimental; the drawn lines are calculated.

Curve	Ester of salicylic acid
A	Acetyl-
B	β-Cyclopentylpropionyl-
C	Trimethylacetyl-
D	Diethylacetyl-

Calculations and Results

According to Edwards[1,2] the hydrolysis of aspirin, $C_6H_4(OOCCH_3)COOH$, may be expressed by

$$\begin{aligned} &d([C_6H_4(OOCCH_3)COOH] + [C_6H_4(OOCCH_3)COO^-])/dt \\ &= -k_1[H^+][C_6H_4(OOCCH_3)COOH] \\ &- (k_4[H^+] + k_5C_{H_2O} + k_6[OH^-])[C_6H_4(OOCCH_3)COO^-] \\ &= -k\{[C_6H_4(OOCCH_3)COOH] + \\ &\qquad [C_6H_4(OOCCH_3)COO^-]\} \quad (1) \end{aligned}$$

where

$$\begin{aligned} k &= k_1[H^+]/(1 + K'_a/[H^+]) \\ &+ (k_4[H^+] + k_2C_{H_2O} + k_6[OH^-])/(1 + [H^+]/K'_a) \quad (2) \end{aligned}$$

where K_a is the dissociation constant of aspirin and k is the pseudo first-order rate constant at a constant pH. The pseudo first-order rate constants obtained at pH values of 1.1, 2.5 and 5.1 and the determined K_a' values were used to calculate the k_1, k_4 and $k_5C_{H_2O}$ values for acetyl-, trimethylacetyl-, β-cyclopentylpropionyl- and diethylacetylsalicylic acids at 25.0°, 35.0°, 50.3° and 60.3°. These rate constants are given in Table I. The spectrophotometrically determined pK_a and pK_a' are given in Table II. Their relative significance is discussed in the Experimental section. The experimentally determined bimolecular rate constants, k_6, are in Table III.

TABLE II

DISSOCIATION CONSTANTS OF ESTERS OF SALICYLIC ACID

Ester of salicylic acid	% EtOH	pK'_a	pK_a
	0.5	3.62	3.69
	20	3.97	4.15
Acetyl-	30	4.26	4.47
	40	4.71	4.94
Trimethylacetyl-	0.5	3.74	3.87
β-Cyclopentylpropionyl-	20	4.26	4.36
Diethylacetyl-	20	4.35	4.45

t, °C.	K_w H₂O	K_w 20% EtOH
25	14.00	14.33
35	13.68	14.00
50	13.26	13.57
60	13.02	13.32

Actually, in these equations 1 and 2, $k_1 = k_1'f_{H^+}$ and $k_4 = k_4'f_{H^+}$, where the k_1' are true specific rate constants and f_{H^+} is the activity coefficient of hydrogen ion. The values actually used for $[H^+]$ were

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TABLE III

TABULATION OF BIMOLECULAR RATE CONSTANTS (k_6 IN L./MOLE/SEC.) FOR ALKALINE HYDROLYSIS[a] OF 5×10^{-4} M ACYL ESTERS OF SALICYLIC ACID AS DETERMINED AT VARIOUS INITIAL ALKALI CONCENTRATIONS, $[NaOH]_0$[b]

Ester of salicylic acid	T, °C., 25.3° $10^4[NaOH]_0$	25.3° 10^2k_6	35.0° $10^4[NaOH]_0$	35.0° 10^2k_6	50.3° $10^4[NaOH]_0$	50.3° 10^2k_6	60.3° $10^4[NaOH]_0$	60.3° 10^2k_6
Acetyl-[d]	100	11.3	50	20.2	20	53.8	10	95.0
	40	10.6	20	20.7	10	54.3	5	113[c]
	20	11.0						
	20	10.8						
Trimethylacetyl-	20	0.862	400	1.67	200	4.75	100	8.05
	10	0.867	200	1.66	100	4.50	50	7.70
β-Cyclopentylpropionyl-	200	4.03	100	8.05	50	14.7	30	26.8
	100	4.05	50	7.78	20	16.0	20	26.3
Diethylacetyl-	400	0.144	400	0.328	400	0.662	400	1.26
	200	0.139	200	0.297	200	0.638	200	1.18

[a] The acetyl- and trimethylacetylsalicylic acids were studied in 0.5% ethanol; the β-cyclopentylpropionyl- and diethylacetylsalicylic acids were studied in 20% ethanol. [b] The bimolecular rate constants were determined from pseudo first-order rate plots at $[NaOH]_0$ concentrations of 100×10^{-4} M and greater. [c] At this low concentration of alkali, it is expected that catalysis other than hydroxyl would be significant. Thus, the observed k_6 should be higher than the true k_6. [d] The apparent bimolecular rate constants (k_6) for alkaline hydrolysis were 0.116 and 0.114 l./mole/sec. in 20 and 40% ethanol by volume with 10×10^{-4} M [NaOH].

TABLE IV

OTHER ACID HYDROLYSIS[a] STUDIES OF ACYL ESTERS OF SALICYLIC ACID WITH ACTUAL pH[b] AND pH CALCULATED FROM $[H^+] = (k - k_4K_a)/k_1$; k IN SEC.$^{-1}$

Ester of salicylic acid T, °C.	Acetyl- 10^5k	Acetyl- Actual pH	Acetyl- Calcd pH	Trimethylacetyl- 10^5k	Trimethylacetyl- Actua pH	Trimethylacetyl- Calcd. pH	β-Cyclopentylpropionyl- 10^5k	β-Cyclopentylpropionyl- Actual pH	β-Cyclopentylpropionyl- Calcd. pH	Diethylacetyl- 10^5k	Diethylacetyl- Actual pH	Diethylacetyl- Calcd. pH
25.0	11.8	0.40[c]	0.34	0.415	0.32[c]	0.40	4.51	0.43[c]	0.36	0.116	0.50[c]	0.32
	1.57	1.30[d]	1.27	.0885	1.27[d]	1.25	0.593	1.36[d]	1.32	.0224	1.40[d]	1.20
35.0	6.88	0.86[e]	0.95	.347	0.93[e]	0.95	2.70	0.96[e]	0.99	.101	0.99[e]	1.00
50.3	26.9	.92[e]	.97	1.37	.95[e]	.98	9.40	1.03[e]	1.00	.556	.97[e]	0.97
60.3	199	.34[c]	.40	9.75	.34[c]	.48	28.2	0.67[f]	0.87	2.52	.71[f]	0.76

[a] The acetyl- and trimethylacetylsalicylic acids were studied in 0.5% ethanol; the β-cyclopentylpropionyl- and diethylacetylsalicylic acids were studied in 20% ethanol by volume. [b] pH was averaged from five samples taken at room temperature during the hydrolysis, the range in pH values was of the order of 0.1 pH. [c] 0.4708 M H_2SO_4. [d] 0.04708 M H_2SO_4. [e] 0.1178 M H_2SO_4. [f] 0.2354 M H_2SO_4.

the activities as related to the experimentally determined pH values. Anion and acid concentrations are defined in terms of K_a' experimentally derived from the spectrophotometric titrations. The rate constants k_5 and k_6 do not need activity corrections since they are based on anion concentrations similarly derived; the latter, k_6, is determined from hydroxyl concentration given in terms of molarity.

It should also be realized that Edwards' term, $k_4[H^+]$ [anion] is kinetically indistinguishable from k_4K_a' [acid].

The logarithmic profiles of pseudo first-order rate constants against pH at 25° for these esters of salicylic acid as calculated from the derived k_1, k_4, $k_5C_{H_2O}$, k_6 and K_a' values are drawn in Fig. 1. The plotted points are experimentally determined rate constants at their determined pH values and confirm the derived values. Similar profiles may be constructed for other temperatures using the proper autoprotolysis constant, K_w, of the solvent. Such values may be estimated from the literature.[7,8]

Several acid hydrolysis studies were run at the various temperatures and pH values and pseudo first-order rate constants were determined (Table IV). The experimental rate constant data were used to calculate the theoretical pH values determined on the basis of the previously derived k_1 and k_4 values, $[H^+] = (k - k_4K_a)/k_1$; the agreement of the actual and calculated pH values lends support to the validity of the data and methods of calculation.

The Arrhenius plots of the logarithm of the rate constants against the reciprocal of the absolute temperature as per

$$\log k = -(\Delta H_a/2.303R)(1/T) + \log P = S/T + \log P \quad (3)$$

are given in Fig. 2 for k_1, Fig. 3 for k_4, Fig. 4 for $k_5C_{H_2O}$ determined at pH 5.1 and Fig. 5 for k_6. The thermodynamic quantities derived from this function are given in Table V where $\Delta S^{\ddagger}$, the entropy of activation, is calculated from absolute reaction rate theory[9] as

$$\Delta S^{\ddagger} = 2.303R[\log P - \log (k_B T/h)] \quad (4)$$

where k_B is Boltzmann and h is the Planck constant.

The pseudo first-order rate constants for the hydrolysis of aspirin in various percentages by volume of 95% ethanol and dioxane in water mixtures, as well as the apparent pH values are given in Table VI.

Experimental[10]

Spectrophotometric Determination of Dissociation Constants.—The dissociation constants given in Table II of

(7) B. Gutbezahl and E. Grunwald, THIS JOURNAL, **75**, 565 (1953).
(8) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd Ed., Reinhold Publishing Corp., New York, N. Y., 1950, p. 485.
(9) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.
(10) The esters of salicylic acid were supplied by Mr. Maxton F. Hunter, Chemical Development Department, The Upjohn Co.

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TABLE V

THERMODYNAMIC QUANTITIES[a] FOR THE HYDROLYSIS[b] OF ESTERS OF SALICYLIC ACID

Ester of salicylic acid Rate constants	Acetyl- S	ΔH_a	log P	$\Delta S\ddagger$	β-Cyclopentylpropionyl- S	ΔH_a	log P	$\Delta S\ddagger$	Trimethylacetyl- S	ΔH_a	log P	$\Delta S\ddagger$	Diethylacetyl- S	ΔH_a	log P	$\Delta S\ddagger$
k at pH 1.10	3640	16.6	6.55	−28.8	3610	16.5	6.08	−30.7	3880	17.7	6.05	−31.2	4910	22.5	8.88	−17.9
k at pH 2.5	3700	17.0	6.17	−30.2	3880	17.8	6.40	−29.3	3860	17.7	5.90	−31.6	4980	22.8	8.74	−18.8
k_1	3690	16.7	7.78	−22.9	3560	16.3	6.93	−27.0	4130	18.9	7.80	−22.9	4710	21.6	9.16	−16.5
k_4	3590	16.4	9.05	−17.4	4150	19.0	11.14	− 7.8	3295	15.1	7.36	−24.7	5110	23.4	13.41	+ 2.7
$k_4C_{H_2O}$[c]	3840	17.6	7.45	−24.7	3820	17.5	7.40	−24.7	3980	18.2	7.34	−25.2	4420	20.2	7.95	−22.0
k_5	2730	12.5	8.18	−21.0	2480	11.3	6.89	−27.0	2730	12.5	7.08	−26.1	2700	12.4	6.21	−30.2

[a] The quantities are derived from the logarithmic form of the Arrhenius relation: $\log k = -(\Delta H_a/2.303R)(1/T) + \log P = -S/T + \log P$ where the k is in sec.$^{-1}$ and the k_i in l./mole/sec., the ΔH_a is the heat of activation in kcal./mole, R is the gas constant in cal./degree and T is the absolute temperature. The $\Delta S\ddagger$ entropy of activation is calculated from absolute reaction rate theory: $\Delta S\ddagger = 2.303R\,[\log P - \log (k_B T/h)]$ where k_B is the Boltzman constant and h is Planck's constant. [b] The acetyl- and trimethylacetylsalicylic acids were studied in 0.5% ethanol; the β-cyclopentylpropionyl- and diethylacetylsalicylic acids were studied in 20% ethanol by volume. [c] The values for $k_5C_{H_2O}$ are determined for the pseudo first-order rate constant of the presumed product in sec.$^{-1}$.

the various acyl esters of salicylic acid were determined at 26 ± 1° by a procedure similar to Edwards'[11] by the expression

$$pH = pK_a' - \log\{(a_{HA}C - A_t)/(A_t - a_A\text{-}C)\} = pK_a - \log\{(a_{HA}C - A_t)/(A_t - a_A - C)\} + fZ_1Z_2\sqrt{\mu} \quad (5)$$

where $a_{HA}C$ is the asymptotic absorbance in acid media, $a_A\text{-}C$ is the asymptotic absorbance in alkaline media, a_{HA} and a_A- are the molar absorptivities, respectively, of the undissociated and dissociated acid, μ is the ionic strength, fZ_1Z_2 is the coefficient of the ionic strength correction in the simple Debye–Hückel equation,[11] C is the total concentration of acid, *i.e.*, $C = [HA] + [A^-]$, and A_t is the total absorbance at any pH, *i.e.*, $A_t = a_A\text{-}(C - [HA]) + a_{HA}[HA]$.

The value of f in water is 0.51, but $f \propto 1/D^{3/2}$ where D is the dielectric constant so that $(D_{H_2O}/D_{\%\ Ethanol})^{3/2}\,0.51 = f_{\%\ Ethanol}$ where values of D for various percentages of ethanol at 25° are given in the literature.[12] The ionic strength of the acetate buffers in various ethanol concentrations also was calculated from the pK_a of acetic acid in aqueous alcohol.[13]

Sufficient acyl ester of salicylic acid was weighed in volumetric flasks, dissolved in the appropriate amounts of eth-

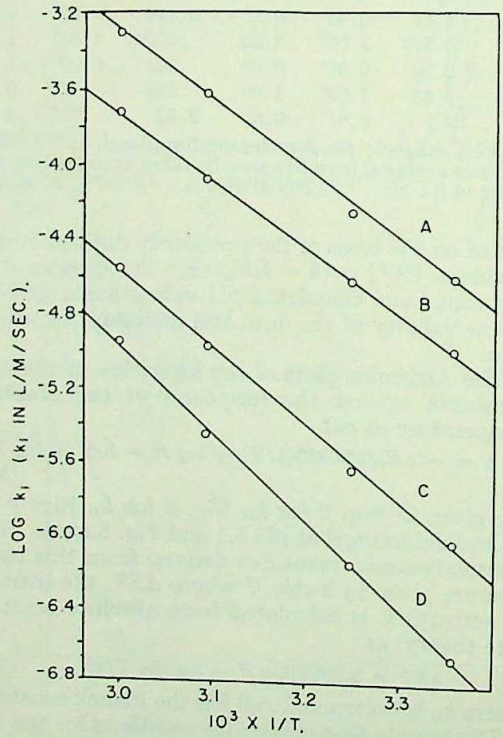

Fig. 2.—Arrhenius plots for acid hydrolysis of undissociated esters of salicylic acid (k_1 in l./mole/sec.).

Curve	Ester
A	Acetyl-
B	β-Cyclopentylpropionyl-
C	Trimethylacetyl-
D	Diethylacetyl-

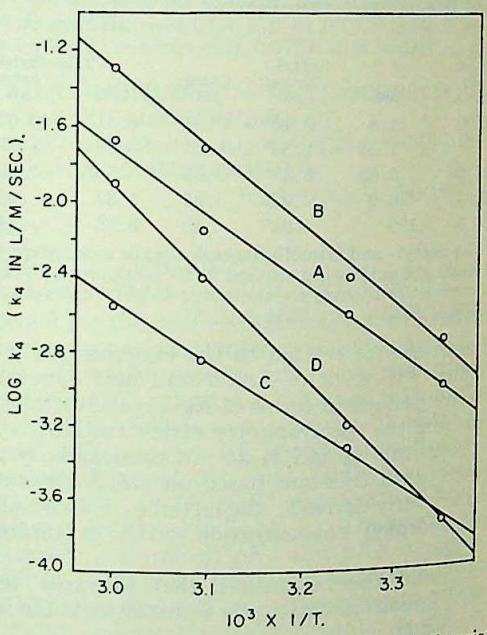

Fig. 3.—Arrhenius plots for acid hydrolysis of dissociated esters of salicylic acid (k_4 in l./mole/sec.).

Curve	Ester
A	Acetyl-
B	β-Cyclopentylpropionyl-
C	Trimethylacetyl-
D	Diethylacetyl-

(11) F. H. Getman and F. Daniels, "Outlines of Physical Chemistry," 7th Ed., John Wiley and Sons, Inc., New York, N. Y., 1945, pp. 667–670.

(12) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd Ed., Reinhold Publishing Corp., New York, N. Y., 1950, p. 118.

(13) I. M. Vandenbelt, C. H. Spurlock, M. Giffels and M. W. Eash, *Science*, **121**, 646 (1955).

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TABLE VI

EFFECT OF OTHER SOLVENTS ON PSEUDO FIRST-ORDER RATE CONSTANTS (k IN SEC.$^{-1}$) OF ASPIRIN HYDROLYSIS AT 25° (EACH COLUMN HAS THE SAME BUFFERS AND BUFFER CONCENTRATION.)

Volume % ethanol	10^5k	Apparent pH	10^5k	Apparent pH	10^5k	Apparent pH	10^5k	Apparent pH	10^5k	Apparent pH	10^5k	Apparent pH	10^5k	Apparent pH
0	(3.98)[a]	(8.65)	(3.69)[a]	(6.90)	3.62	6.00	0.560	2.45	0.672	1.90	2.24	1.10	1.18	0.40
20	5.19	8.42	5.02	7.28	4.86	6.25	.394	2.67	.536	1.94	1.94	1.19	2.71	1.04
40	9.54	8.83	9.10	7.74	9.10	6.71	.268	2.87	.395	2.07	1.60	1.21	1.98	1.21
60	14.4	9.36	14.1	8.19	14.4	7.91								
Volume % dioxane														
20	3.32	8.50	3.19	7.36	3.21	6.46								
40	3.42	9.15	3.34	8.00	3.41	7.11								
60	3.30	9.74	3.23	8.29	2.98	7.92								

[a] Estimated from Fig. 1

anol and diluted with water and concentrated buffer so that the final molarity in ester was 5×10^{-4} M at the desired alcohol concentration. The final buffer concentrations for dissociation constant determinations were similar to Edwards' first fourteen in his Table III.[1] The ester was dissolved in alcohol so that solubilization would be complete prior to the addition of buffer and the hydrolysis kept to a minimum before the immediate pH and spectrophotometric readings.

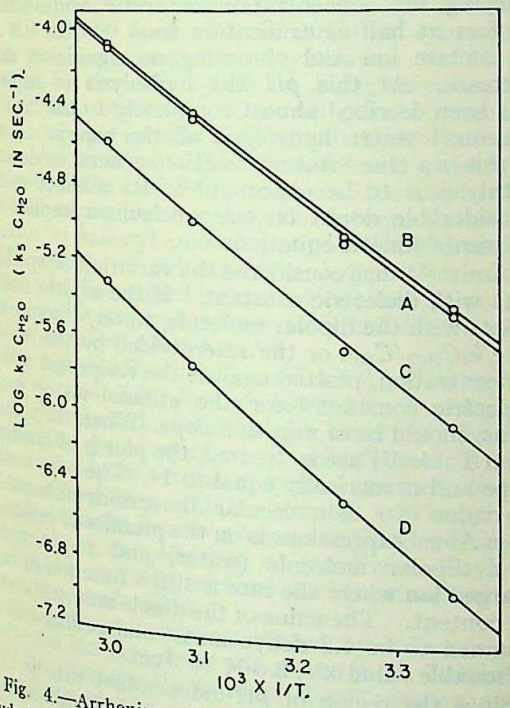

Fig. 4.—Arrhenius plots for so-called "spontaneous" hydrolysis of dissociated esters of salicylic acid ($k_5 C_{H_2O}$ in sec.$^{-1}$).

Curve	Ester
A	Acetyl-
B	Cyclopentylpropionyl-
C	Trimethylacetyl-
D	Diethylacetyl-

The pK_a' and pK_a were calculated for all buffers at wave lengths of 268, 272, 276, 280 and 284 mμ by equation 5. The calculated values at a given wave length whose log $[(a_{HA}C - A_t)/(A_t - a_{A^-}C)]$ lay within ±1 limits (usually four) were averaged. The results for the several wave lengths were again averaged to give the pK_a' and pK_a estimates of Table II. The pH-independent isosbestic point of salicylic acid on the Cary model 11 recording spectrophotometer was 300 mμ.

Determination of Rates of Alkaline Hydrolysis.—One-tenth of a millimole of the ester of salicylic acid was dissolved in 100 ml. of nitrogen-purged water (or aqueous alcohol) and maintained at the desired temperature. Twice the desired final alkali concentration was maintained at the same temperature in 50 ml. of water. Two different alkali concentrations were used. Fifty ml. of the acyl ester salicylic acid solution were added to each solution of alkali so that the final solution was 5×10^{-4} M in the acyl ester of salicylic acid and $5–400 \times 10^{-4}$ M in alkali; 5-ml. aliquots of the solutions were taken out at appropriate times and quenched in 5 ml. of HCl of sufficient concentration to neutralize the initial alkali content of the aliquot and with sufficient alcohol content to keep the free acid of the ester in solution. The sampling schedule was adjusted to include at

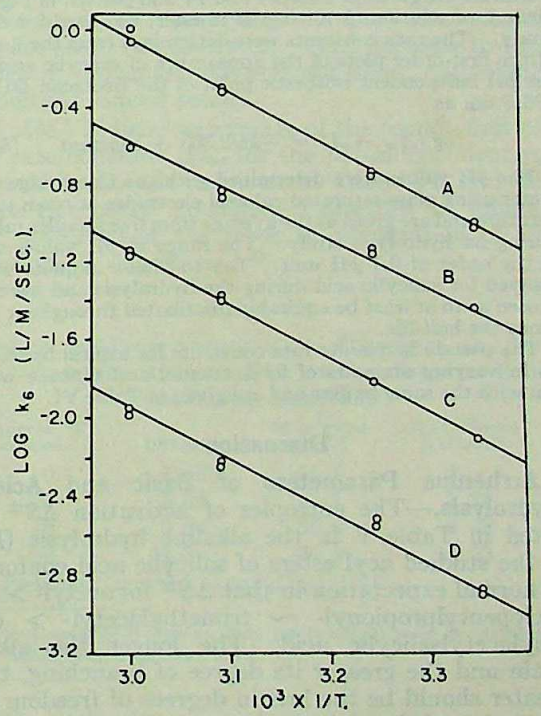

Fig. 5.—Arrhenius plots for alkaline hydrolysis of dissociated esters of salicylic acid (k_6 in l./mole/sec.).

Curve	Ester
A	Acetyl-
B	Cyclopentylpropionyl-
C	Trimethylacetyl-
D	Diethylacetyl-

least 1.5 times the half-life of the hydrolysis. These acidified aliquots were read at 296.5 mμ on a Beckman DU spectrophotometer for the appearance of salicylic acid. This previously had been determined as the isosbestic point for salicylic acid with absorbance independent of pH for this

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machine. The molar absorptivity was 354. The rate constants were determined from the slopes of the pseudo first-order plots of log $(A_\infty - A)$ *vs.* time for alkali concentrations $[NaOH]_0$ over $100 \times 10^{-4} M$ where A_∞ is the absorbance of salicyclic acid at total hydrolysis and A is the absorbance at any time t and

$$\log (A_\infty - A) = -k't = -k[NaOH]_0 t/2.303 \quad (6)$$

where

$$k = 2.303k'/[NaOH]_0$$

For lower alkali concentrations, the slopes of bimolecular rate plots were used

$$\log ([NaOH]/[Ester]) = k''t + \text{constant} = k([NaOH]_0 - [Ester]_0) \times t/2.303 + \text{constant} \quad (7)$$

where

$$k = 2.303k''/([NaOH]_0 - [Ester]_0)$$

and

$$[Ester] = [(A_\infty - A)/A_\infty] \times [Ester]_0$$

and

$$[NaOH] = [NaOH]_0 - [Ester]$$

The resultant rate constants and the alkali concentrations used in their determination are given in Table III.

Determination of Rates in Neutral and Acid Media.—The same buffer solutions as used in the determination of pK_a values were used in the determination of pseudo first-order rate constants. The buffer concentrations were 94% of Edwards' concentrations.[1] The experimentally determined constants are given in Tables I and IV and plotted in Fig. 1; 100 ml. of solution, $5 \times 10^{-4} M$ in ester, was used for each study. The rate constants were determined from the slopes of the first-order plots of the appearance of salicylic acid at the pH independent isosbestic point of the Beckman DU at 296.5 mμ as

$$\log (A_\infty - A) = -kt/2.303 + \text{constant} \quad (8)$$

The pH values were determined with the Cambridge pH meter using glass-saturated calomel electrodes at room temperature and are given as the average from five samples taken during an hydrolysis study. The range in pH values was of the order of 0.1 pH unit. Ten to fifteen aliquots were assayed for salicylic acid during the hydrolysis and were so chosen as to at least be equitably distributed throughout 1.5 times the half-life.

The pseudo first-order rate constants for aspirin hydrolysis in varying amounts of 95% ethanol and dioxane were run with the same buffers and are given in Table VI.

Discussion

Arrhenius Parameters of Basic and Acidic Hydrolysis.—The entropies of activation $\Delta S^\ddagger$ as listed in Table V in the alkaline hydrolysis (k_6) of the studied acyl esters of salicylic acid conform to normal expectation in that $\Delta S^\ddagger$ for acetyl- > β-cyclopentylpropionyl- ~ trimethylacetyl- > diethylacetylsalicylic acid. The longer the alkyl chain and the greater its degree of branching, the greater should be the loss in degrees of freedom in formation of the activated state and thus the more negative $\Delta S^\ddagger$.[14]

The heats of activation ΔH_a for the alkaline hydrolysis of aspirin and the other acyl esters of salicylic acid are of the magnitude of 12 kcal./mole which is consistent with the hydrolysis of similar acyl phenates.[3] Thus the more than twice this value reported previously[2] must be an artifact of the method of study.

The assumption of a common intermediate for acid-catalyzed esterification and hydrolysis permits comparison of substituent effects from both reactions.

Loening, *et al.*,[15] have tabulated the Arrhenius parameters for the acid-catalyzed esterifications of many aliphatic acids. The percentage increase in ΔH_a for acid esterification of trimethylacetic acid over acetic acid is 14% and for diethylacetic acid is 24%. The comparable activation values for acid hydrolysis (k_1) of the salicylic esters of these acids are similar percentages of 15% and 30%. Acid-catalyzed esterifications of solely β-disubstituted acids show no significant difference in ΔH_a over acetic acid. The ΔH_a's for the acid hydrolysis of acetyl- and β-cyclopentylpropionylsalicylic acid are also similar. The heats of activation are in the order appropriate to the effect of α-carbon substituents on the positivity of the carbonyl carbon,[16] acetyl- ~ β-cyclopentylpropionyl- < trimethylacetyl- < diethylacetylsalicylic acid.

Neutral Hydrolysis.—Edwards[1] has shown the absence of general acid–base catalysis[17] in the hydrolysis of aspirin at pH 4.7 in aqueous media by varying the concentration of acetic acid–acetate buffers at half-neutralization from 0.05 to 0.3 M in acetate ion and observing no significant rate increase. At this pH the hydrolysis of aspirin has been ascribed almost completely to the "spontaneous" water hydrolysis of the aspirin anion. If this is a true "water" reaction, general acid–base catalysis is to be expected.[4,17] Its absence casts considerable doubt on the mechanism implied in Edwards' kinetic equations.[1]

Amis[4,18,19] has considered the variation of specific rate with dielectric constant. If the aspirin anion reacts with the dipolar molecule, water, the specific rate $k_5 C_{H_2O}/C_{H_2O}$ or the rate divided by the water concentration, plotted against the reciprocal of the dielectric constant[12] for the ethanol–water solutions, should be of negative slope. When the values from Table VI are so treated, the plot is of positive slope and numerically equal to 14. The only sensible value of r of molecular dimensions obtainable from Amis' expressions is on the premise of reaction of a dipolar molecule (water) and a positively charged ion where the rate is still a function of water content. The value of the dipole moment μ was assumed to be 1.8 debye units[4] and resulted in a reasonable value of r, 2.6×10^{-8} cm.

Since the region of pH-independent rate is the region of the anionic form of aspirin, it is difficult to believe this happy result to be naught but fortuitous else the anion must react with two protons in a neutral solution before hydrolysis.

A more consistent mechanism for pH-independent hydrolysis where rate is not significantly affected by increasing dioxane concentration (Table VI) is one which does not involve water in the rate-determining step and may be due to an intramolecular rearrangement similar to the proposals sub-

(14) E. S. Amis, "Kinetics of Chemical Change in Solution," The Macmillan Co., New York, N. Y., 1949, p. 221.

(15) K. L. Loening, A. B. Garrett and M. S. Newman, THIS JOURNAL, **74**, 3929 (1952).

(16) S. Glasstone, K. J. Laidler and H. Eyring, ref. 9, p. 451.

(17) R. P. Bell, "Acid–Base Catalysis," Oxford University Press, London, 1941.

(18) E. S. Amis, *J. Chem. Ed.*, **29**, 337 (1952).

(19) E. S. Amis, *Anal. Chem.*, **27**, 1672 (1955).

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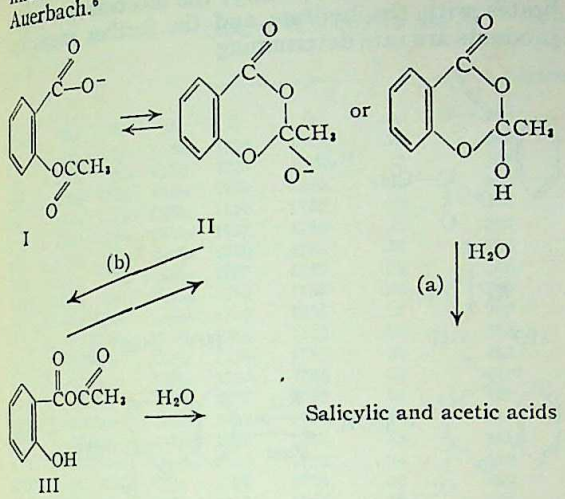
mitted by Chanley, *et al.*,[5,20,21] and Davidson and Auerbach.[6]



Salicylic and acetic acids

The presumed rate-determining step in these proposals is I to II and the subsequent route is either (a) or (b) to the final products. The presence of the anionic form of aspirin (I) is consistent with their argument that cyclization to II is favored by the carboxylate ion being more nucleophilic than carboxyl. The two possible mechanisms proposed for salicyl phosphate hydrolysis[5] are analogous to (a) and (b), the extremely quick hydrolysis of the cyclic intermediate II either in the anionic[5] or neutral form[6] or the intermediate formation of salicoyl phosphate (or salicoyl acetate (III)) which is subsequently hydrolyzed. The latter can be argued against since acetyl phosphate and benzoyl phosphate have half-life periods similar to salicyl phosphate.[5,22]

The higher ΔH_a for $k_5C_{H_2O}$ (Table V) of trimethylacetyl- and diethylacetyl- relative to β-cyclopentylpropionyl- and acetylsalicylic acids may be explained by pronounced steric interference in the formation of the activated cyclic intermediate II. In this closed form (II), the number and length of the alkyls on the β-carbon appears to hinder free rotation about the β-carbon as per Fisher–Taylor–Hirshfelder models and thus steric restrictions on activation are feasible.

The hydrolysis rate attributed by Edwards[1] to hydrogen ion attack on the anion (k_4 in Table V) may be alternatively considered as "spontaneous" hydrolysis of the undissociated acid (Edwards,[1] $k_2C_{H_2O} = k_4K_a$). It would appear that substitution on the fifth atom from the carbonyl oxygen, or Newman's six number,[15,23] raises the activation energy for this hydrolysis of the β-cyclopentylpropionyl- and diethylacetylsalicylic acids by sterically hindering the formation of an activated complex or transition state. However, this is also accompanied by a much smaller decrease in entropy, $\Delta S^{\ddagger}$. Chanley, *et al.*,[5] explain a similarly low $\Delta S^{\ddagger}$ in the hydrolysis of salicyl phosphate by the mutually hindering rotation of phosphate and carboxyl in the open form and thus little loss in degrees of freedom in the cyclic intermediate. Trimethylacetylsalicylic acid has no more restricted rotation of both carbonyls in the open form than does the diethylacetylsalicylic acid. The latter should have more internal energy to lose on activation and thus a more negative $\Delta S^{\ddagger}$.

This implies that the rate-determining step for k_4 or k_4K_a may not be in a step similar to the cyclization[6] (I to II) but in some other simultaneous or subsequent step where the rate-determining step is to a transition state with less restriction of rotation of β-substituted alkyls.[24]

pH-Independent Hydrolysis in Aqueous Ethanol.—The anomalous increase in rate with increasing ethanol content of the solvent in the pH-independent hydrolysis of aspirin is of interest (Table VI). Increase in alcohol content decreases acid-catalyzed hydrolysis as is expected, but the converse occurs in the neutral pH range over which rate is independent of pH. That this is not a dielectric phenomenon is apparent from the small changes in rate in varying dioxane–water mixtures. The alcohol must be specifically involved in the solvolytic mechanism. This is difficult to explain since for solvolysis in alcohol–water mixtures a paraphrase is apt: what alcohol can do, water can do better. Yet a decrease to 40% water in dioxane–water did not show any highly significant kinetic result.

Table VII lists the average of the pseudo first-order rate constant (k_{obs} for the pH-independent region of hydrolysis as given in Table VI and the more rigorously calculated molarities in ethanol and water when the mode of preparation of the solutions is considered).[25]

TABLE VII

AVERAGE pH-INDEPENDENT RATE CONSTANTS (k_{obs}[a] IN SEC.$^{-1}$) FOR THE HYDROLYSIS OF ASPIRIN ANION IN ETHANOL–WATER MIXTURES

Approx. % ethanol	10^6k_{obs}[a]	M in water [H_2O]	M in ethanol [C_2H_5OH]
0	3.65	55.5	0
20	5.02	45.7	3.33
40	9.24	35.9	6.66
60	14.3	24.1	10.29

[a] Previously referred to as $k_5C_{H_2O}$.

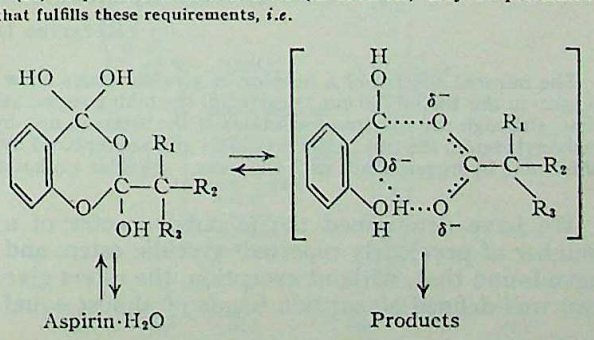
(20) J. D. Chanley and E. M. Gindler, THIS JOURNAL, **75**, 4035 (1953).

(21) J. D. Chanley and E. Feageson, *ibid.*, **77**, 4002 (1955).

(22) R. D. Birkenmeyer of The Upjohn Co. has succeeded in synthesizing salicoyl acetate (III), although in poor yield. This material decomposed in 24 hr. to an insoluble material and an oil.

(23) M. S. Newman, THIS JOURNAL, **72**, 4780 (1950).

(24) A possible transition state (in brackets) may be postulated that fulfills these requirements, *i.e.*



(25) "Handbook of Chemistry and Physics," 36th Ed., Chemical Rubber Publishing Company, Cleveland, Ohio, 1954, pp. 1932–1942.

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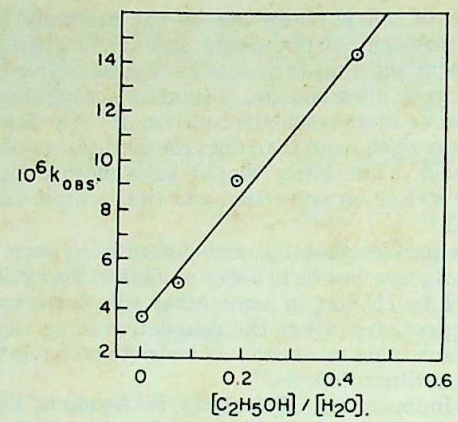
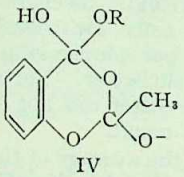


$$k_{OBS} = k_0 + k_{ROH}\,[ROH]/[H_2O].$$

Fig. 6.—Plot of the observed rate constant for *p*H-independent hydrolysis of aspirin anion at 25° against the molar ratio of ethanol to water. The postulated dependence of this plot is the equation $k_{obs} = k_o + k_{ROH}[ROH]/[H_2O]$.

If it is assumed that water and alcohol compete for aspirin anion ion II to form a reacting cyclic intermediate such as



IV

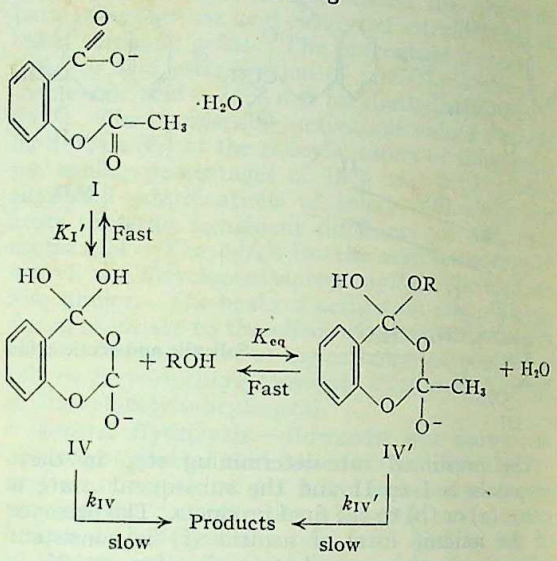
where R is H– or C_2H_5–, then

$$k_{obs} = k_a[H_2O] + k_b[ROH] \qquad (9)$$

However, the data of Table VII do not follow equation 9. At best, a linear representation is valid only for $[C_2H_5OH] > 3.33$ and

$$k_{obs} = 1.43 \times 10^{-6}[C_2H_5OH];\ k_a = 0 \qquad (10)$$

A possible explanation that best fits the data is that the cyclic intermediate in the hydrolysis of an aspirin anion II is formed stoichiometrically as the hydrate IV and $[IV] = K_{I'}[I']$ in a non-rate-determining step. Subsequently, the alcoholate equilibrates with the hydrate and the further steps to products are rate determining



On the basis of this mechanism, the rate expression can be formulated.

$$\begin{aligned} k_{obs}[I'] &= k_{IV}[IV] + k_{IV'}[IV'] \\ &= k_{IV}[IV] + k_{IV'}K_{eq}[IV][ROH]/[H_2O] \\ &= k_{IV}K_{I'}[I'] + k_{IV'}K_{eq}K_{I'}[I'][ROH]/[H_2O] \end{aligned} \qquad (11)$$

Thus

$$k_{obs} = k_0 + k_{ROH}[ROH]/[H_2O] \qquad (12)$$

Equation 11 best fits the data which are plotted accordingly in Fig. 6. The resultant quantitative equation is

$$k_{obs} = 3.65 \times 10^{-6} + 25.5 \times 10^{-6}[C_2H_5OH]/[H_2O] \qquad (13)$$

Acknowledgment.—The author is greatly indebted to Miss Kathryn G. Stimson for excellent technical assistance and to Mr. Maxton Murray for the supply of the esters.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

The Effect of Various Solvents on the Carbonyl Absorption Spectrum of Glycidic Esters

BY HORTON H. MORRIS[1] AND RAYMOND H. YOUNG, JR.

RECEIVED JANUARY 7, 1957

The infrared spectra of a number of glycidic esters show two well-defined absorption bands of approximately equal intensity in the 1800–1700 cm.$^{-1}$ carbonyl stretching region instead of the one to be expected. Of greater interest is the fact that, although the spectra of solutions of the esters in non-hydrogen bonding solvents show the two absorption bands in the carbonyl region, the two bands disappear and are replaced by a single band when the esters are dissolved in a solvent capable of forming hydrogen bonds with the ester. Possible explanations of these effects are advanced.

We have determined the infrared spectra of a number of previously reported[2] glycidic esters and have found that, without exception, the esters give two well-defined absorption bands of almost equal intensity in the 1800–1700 cm.$^{-1}$ carbonyl stretching region instead of the one expected band. The average position of the centers of the two bands for the esters studied are 1729 and 1753 cm.$^{-1}$.

Of even greater interest is the fact that the two bands disappear and are replaced by a single, rather broad band centering at about 1737 cm.$^{-1}$ when the

(1) Southern Clays, Inc., Gordon, Ga.

(2) H. H. Morris and R. H. Young, Jr., THIS JOURNAL, 77, 6678 (1955) and previous papers.

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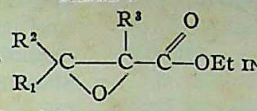
TABLE I

CARBONYL FREQUENCIES OF  IN CCl_4 AND IN $CHCl_3$

				CCl_4 solution							$CHCl_3$ solution		
No.	R_1	R_2	R_3	$\bar{\nu}_1$	$\bar{\nu}_2$	$\Delta\bar{\nu}$	$\epsilon_{\bar{\nu}_1}$	$\epsilon_{\bar{\nu}_2}$	$\frac{\epsilon_{\bar{\nu}_1}+\epsilon_{\bar{\nu}_2}}{2}$	A_{CCl_4}	$\bar{\nu}_3$	$\epsilon_{\bar{\nu}_3}$	A_{CHCl_3}
I	CH_3	CH_3	C_2H_5	1726	1748	22	246	231	239	13.2	1740	262	14.2
II	CH_3	CH_3	C_3H_7	1729	1756	27	292	258	275	18.4	1737	252	19.2
III	CH_3	CH_3	C_4H_9	1726	1752	26	273	221	247	16.1	1732	232	13.6
IV	CH_3	CH_3	C_5H_{11}	1729	1752	23	288	254	271	14.8	1736	251	16.5
V	CH_3	CH_3	C_6H_{13}	1727	1756	29	283	238	261	14.9	1737	251	13.6
VI	CH_3	CH_3	C_7H_{15}	1730	1753	23	286	242	264	15.5	1740	266	16.7
VII	CH_3	CH_3	C_8H_{17}	1727	1752	25	268	225	247	15.7	1735	254	17.4
VIII	CH_3	CH_3	C_9H_{19}	1729	1753	24	300	217	259	17.1	1730	278	18.4
IX	$-(CH_2)_5-$		CH_3	1729	1756	27	285	269	277	14.1	1740	304	14.2
X	$-(CH_2)_5-$		C_2H_5	1734	1760	26	238	216	227	13.9	1740	260	13.8
XI	$-(CH_2)_5-$		C_3H_7	1728	1751	23	292	218	255	17.5	1734	259	19.9
XII	$-(CH_2)_5-$		C_4H_9	1730	1756	26	317[b]	281[b]	299[b]	24.1[b]	1738	264[b]	26.6[b]
XIII	$-(CH_2)_5-$		C_5H_{11}	1727	1752	25	259	223	241	11.9	1739	260	14.5
XIV	$-(CH_2)_5-$		C_7H_{15}	1728	1754	26	249	202	226	14.4	1738	251	16.0
XV	$-(CH_2)_5-$		C_8H_{17}	1727	1755	28	268	201	235	14.3	1737	224	15.1
XVI	$-(CH_2)_5-$		$C_{10}H_{21}$	1726	1750	24	312	182	247	20.5	1732	235	17.8
XVII	C_6H_5	CH_3	CH_3	1726	1752	26	298	231	265	16.9	1739	261	15.5
XVIII	C_6H_5	H	CH_3	1732	1751	19	287	209	248	17.0	1741	268	17.2
XIX	C_6H_5	H	H	1736	1753	17	237	275	256	15.4	1739	293	15.1
Average values[a]				1729 ± 2	1753 ± 2	24.5 ± 2	276 ± 18	228 ± 19	252 ± 13	15.6 ± 1.5	1737 ± 3	259 ± 15	16.0 ± 1.6

[a] Average values calcd. from $\frac{\text{(observations)}}{\text{no. of observations}}$; average error = $\frac{\text{(absolute value of deviation)}}{\text{no. of observations}}$ [b] These values were excluded from calculation of averages.

esters are dissolved in a solvent capable of forming hydrogen bonds, while the spectra of the esters in a variety of non-hydrogen bonding solvents all show the two clearly defined absorption bands. Thus the two bands are present when the esters are dissolved in carbon tetrachloride, carbon disulfide, benzene, cyclohexane, 2-nitropropane, *n*-propyl mercaptan or dimethylaniline; but are replaced by a single band (often fairly broad) when solvents such as chloroform, *n*-butyl alcohol, aniline, methanol or *m*-cresol are used. In those solvents capable of hydrogen bonding with the ester there is a gradual shift of band center position to lower frequencies with increasing hydrogen bonding ability.

It is also of interest that the area under the curves of the esters in CCl_4 solution is found to be approximately equal to the area under the curve of chloroform solutions of the esters. The average value of the extinction coefficient, determined by taking one-half the sum of the extinction coefficients of each of the two bands observed in carbon tetrachloride solution, is approximately equal to that of the single band obtained when the esters are dissolved in chloroform. Thus the average molar extinction coefficient for the two bands in carbon tetrachloride solutions of the esters is 252, while the molar extinction coefficient for the single band given by the esters in chloroform solution is 259.

Table I lists the esters studied and gives the positions of the bands in the carbonyl region when the esters are dissolved in carbon tetrachloride ($\bar{\nu}_1$, $\bar{\nu}_2$) and when they are dissolved in chloroform ($\bar{\nu}_3$). No change in position or intensity of any other band in the spectra with change of solvent has been observed. Table I also gives the difference in frequency ($\Delta\bar{\nu}$) between the two bands, the molar extinction coefficients ($\epsilon_{\bar{\nu}_1}$, $\epsilon_{\bar{\nu}_2}$, $\epsilon_{\bar{\nu}_3}$) as determined for each band, the average molar extinction coefficient for the two bands observed in carbon tetrachloride solutions ($(\epsilon_{\bar{\nu}_1} + \epsilon_{\bar{\nu}_2})/2$) and the areas under the curves (A_{CCl_4}, A_{CHCl_3}) as determined between 1800 and 1600 cm.$^{-1}$ by means of a planimeter. Average values are given at the bottom of each column.

Figure 1 shows the appearance of the bands in the carbonyl region of ethyl α-*n*-propyl-β,β-dimethylglycidate dissolved in various solvents. The curves have been displaced upward for clarity.

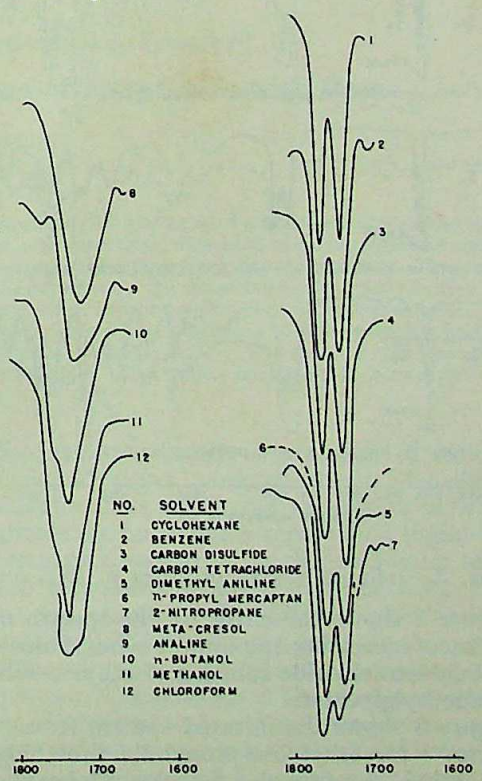


Fig. 1.—Ethyl α-*n*-propyl β,β-dimethylglycidate in various solvents.

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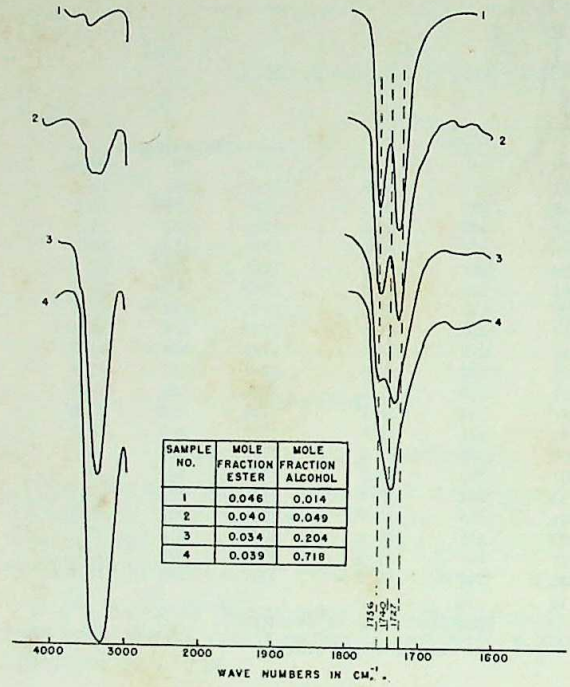
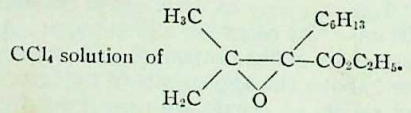


Fig. 2.—The effect of the addition of *n*-butyl alcohol to a CCl_4 solution of



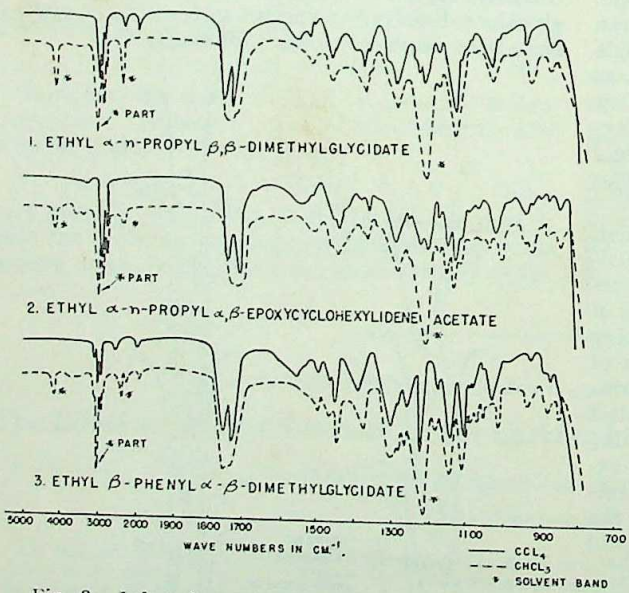


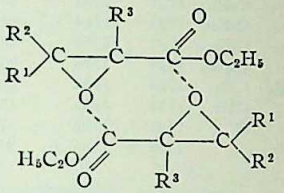
Fig. 3.—Infrared spectra of esters in CCl_4 and $CHCl_3$.

Figure 2 shows the effect on the spectra of the addition of increasing amounts of *n*-butyl alcohol to a carbon tetrachloride solution of ethyl α-*n*-hexyl-β,β-dimethylglycidate.

Figure 3 shows the infrared spectra from 5000–800 cm.$^{-1}$ for ethyl α-*n*-propyl-β,β-dimethylglycidate, ethyl α-*n*-propyl-α,β-epoxycyclohexylidene-acetate and ethyl β-phenyl-α,β-dimethylglycidate in CCl_4 and in $CHCl_3$. The spectra are representative of the types of glycidic esters herein discussed and the spectra of other members of the three homologous series differ only slightly from those shown.

Discussion

It may be possible to explain these observations by assuming dimer formation and hence a coupling between the characteristic stretching vibrations of the two ester carbonyl bonds to cause a frequency splitting, thus giving rise to a pair of absorption bands on either side of the unperturbed frequency. It seems reasonable to assume that two molecules of the ester could orient through dipole–dipole interaction as indicated in the diagram below to form bonds which are strong enough to allow coupling of the two ester carbonyl vibrations.



That the bonding is between the carbon of the ester carbonyl group and the oxygen of the oxirane ring may be indicated by the distance between the two absorption bands (average 24.5 cm.$^{-1}$) observed in CCl_4 solutions of the esters, since the split is a measure of the efficiency of the coupling.[3a] Davison[3b] has shown that in diacyl peroxides (two atoms separating the two carbonyl groups) the split between the two observed carbonyl absorption bands is about 25 cm.$^{-1}$, while anhydrides[4] show a similar pair of absorption bands with a split of about 65 cm.$^{-1}$ resulting from the shorter coupling link.

That the interaction does not involve a linear polymerization and is between two molecules only may be indicated by the fact that no change in the appearance of the two absorption bands occurs upon dilution—an effect to be expected with the type of bonding shown in the diagram, but not to be expected if the bonding were linear.[5]

Intensity measurements and determination of the area under the curves for the esters in CCl_4 and in $CHCl_3$ may also support the dimer picture. The data would seem to indicate that only the ester carbonyl stretching vibration is involved and that a splitting is occurring in non-hydrogen bonding solvents, rather than the juxtaposition of absorption bands caused by two different types of carbonyl vibrations.

The disappearance of the two absorption bands and the appearance of a single band centering approximately at the unperturbed frequency when a solvent capable of forming hydrogen bonds with the ester is added may be an indi-

(3) (a) Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., New York, N. Y., 1945, p. 199; (b) Davison, *J. Chem. Soc.*, 2456 (1951).

(4) Thompson, *ibid.*, 328 (1948); E. J. Modest and J. Szmuszkovicz, THIS JOURNAL, **72**, 577 (1950).

(5) J. R. Partington, "An Advanced Treatise on Physical Chemistry," Vol. V, Longmans, Green and Co., Ltd., London, 1954, p. 384.

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cation of the relative strength of the bonds involved in dimer formation.

That the frequency of the single band formed in hydrogen-bonding solvents appears to move toward lower frequencies with increasing hydrogen bonding ability of the solvent and that the appearance of the single band in hydrogen bonding solvents is concentration dependent (see Fig. 2) indicates a dissolution of the dimer and the formation of two molecules of the ester, each associated through hydrogen bonding with a solvent molecule.

The bonding which results in dimer formation, as postulated, must be very weak since molecular weight determinations by freezing point depression, as determined in benzene or cyclohexane, give the normal value for a monomeric unit.

It is of interest to note that Schotte[6] has recently recorded the infrared spectra of the diastereomers of $HO_2CCHEtCHMeCO_2H$, m.p. 177–178° (I) and 100–101° (II) and of $HO_2CCHEtCH_2CHMeCO_2H$, m.p. 104.5–5.5 (III) and 83.5–84.5° (IV), and has noted that II and III show a split peak for the carbonyl stretching frequency. He assumed these to have the racemoid configuration. I and IV showed no such split and were presumed to be the mesoid isomers.

Since the esters herein reported are all racemic mixtures, it may be that the proposed dimer is a racemic pair. Molecular models of such a racemic pair and of a pair having a single configuration indicate that the racemic pair may allow a closer approach of the ring oxygens to the carbonyl carbons because of less interference by the alkyl substituents.

The observations might be interpreted in a different way by assuming that two rotational isomers are present in which the carbonyl oxygen is on the same side of the molecule as the ring oxygen in one case and away from the ring oxygen in the other. Since this would represent an equilibrium mixture and since the extinction coefficients of the two observed bands are approximately equal in every case, the unlikely assumption must be made that equal numbers of molecules exist in each of the states for each of the esters. Since resonance splitting does seem to be indicated, we believe that dimer formation offers a better explanation of the data than the assumption of rotational isomerism.

(6) L. Schotte, *Arkiv. Kemi*, **9**, 397 (1956).

Experimental

The infrared spectra were measured with a Baird Associates model 4–55 recording infrared spectrometer employing sodium chloride optics. The same 0.029-mm. cell was used for all determinations. No reference cell was used. The accuracy of the wave length measurement is estimated to be ±5 cm.$^{-1}$ in the region discussed. Polystyrene bands at 1602.5 and 1594.7 cm.$^{-1}$ were recorded on each spectrum for calibration purposes.

Compounds XV, XVI, XVIII and XIX may contain small amounts of impurities. The other esters are considered to be quite pure (see reference 2).

Acknowledgment.—We wish to express our great appreciation for the financial aid and encouragement given us through a Cottrell grant from Research Corporation.

ORONO, MAINE

[CONTRIBUTION FROM THE FISHERY TECHNOLOGICAL LABORATORY[1]]

Liquid–Solid Countercurrent Distribution of Fatty Acids with Urea

BY W. N. SUMERWELL

RECEIVED FEBRUARY 7, 1957

The reaction of fatty acids with urea to form inclusion adducts has been used as the basis of a liquid–solid countercurrent distribution method for separating mixtures of fatty acids. The fatty acids and urea, dissolved in an appropriate solvent, served as the moving liquid phase while the precipitated reaction products served as the stationary solid phase. The character of the distribution curve obtained for a given mixture of fatty acids depends on the differences in the distribution coefficients for the individual fatty acids when they are distributed between solid inclusion adducts and organic solvent. The method was found to be effective in the separation of mixtures of fatty acids such as arachidic, stearic, palmitic and oleic acid as well as in the separation of a mixture of the *cis–trans* isomers, oleic and elaidic acids. The method also was applied to a mixture of highly unsaturated salmon egg oil fatty acids (iodine value 350). The results indicate that urea distribution may be a valuable tool in the separation of such unstable compounds.

Introduction

Studies on the formation of urea inclusion adducts as a means of fractionating marine oil fatty acids and their derivatives were begun in this Laboratory several years ago. A preliminary report of this work has been published.[2] The present paper describes the development of a liquid–solid countercurrent distribution procedure based on the differential binding of fatty acids by urea and its application to some synthetic and natural mixtures of fatty acids.

Subsequent to Craig's description of his two-phase liquid–liquid countercurrent distribution technique[3] and its use in the separation of organic compounds, he published a report on a liquid–solid countercurrent system.[4] By this technique, he distributed chrysene and anthracene between cyclohexane and alumina. He defined a coefficient A as the ratio of the weight of solute dissolved in the liquid phase to the weight of solute adsorbed on the solid phase. The position of the maximum concentration of a compound in the distribution system was then calculated by substituting the value of A

(1) A laboratory of the Branch of Commercial Fisheries, U. S. Fish and Wildlife Service, Seattle, Washington.

(2) C. Domart, D. T. Miyauchi and W. N. Sumerwell, *J. Am. Oil Chemists' Soc.*, **32**, 481 (1955).

(3) L. C. Craig, *J. Biol. Chem.*, **155**, 519 (1944).

(4) L. C. Craig, C. Golumbic, H. Mighton and E. Titus, *Science*,

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in the equation $N - n(A)/(A + 1)$ in the same way that the distribution coefficient is used to calculate the position of maximum concentration in a liquid–liquid countercurrent system.

A different approach to liquid–solid countercurrent distribution can be made if, instead of an adsorbent being used as the solid phase of the system, a precipitated reaction product, produced by a reaction involving the compounds to be distributed, is used. This precipitation reaction, however, must be of a special type in that the relative amounts of any compound in equilibrium between the liquid and solid phases of the system must be governed by a distribution coefficient instead of the solubility product which generally governs precipitation reactions of inorganic compounds. In other words, the solid phase of the system, made up of precipitated reaction products, must act as a solid solution. The requirement would most likely be met by products which are bound by only secondary bonds of the van der Waals and hydrogen bonding variety. Such products could be expected to resemble solutions in their behavior.

Consider a mixture of compounds A_1, A_2, A_3. . .A_j, each of which reacts with a compound B to form the solid reaction products (bound by secondary bonds) P_{A_1B}, P_{A_2B}, P_{A_3B}. . .P_{A_jB}. These reactions are represented by the general equation $A_i + B \rightarrow P_{A_iB}$.

In this system, A_i and B are present in solution in an appropriate solvent and as such constitute the liquid phase. The precipitated reaction products P_{A_iB} constitute the solid phase. From this reaction, distribution coefficients K_1, K_2, K_3 . . . K_j are defined by the general equation

$$K_i = \frac{[A_i \text{ liquid}]}{[A_i \text{ solid}]}$$

where the terms in brackets are the concentrations of A_i in liquid and solid phase, respectively.

It is evident that this equation will hold strictly true only when the volume of the liquid phase and the concentration of B in this phase are held constant. If the values of K_1, K_2, etc., differ sufficiently, then countercurrent distribution should effectively separate A_1, A_2, etc.

Since the binding forces existing between aliphatic compounds and urea are presumably van der Waals forces and in some cases hydrogen bonds, one might expect their adducts to act as solid solutions and to exhibit distribution coefficients. If such is the case, then it should be possible to develop a liquid–solid countercurrent method for the separation of fatty acids using urea, the fatty acids and a suitable solvent.

Preliminary Considerations

The reaction of a fatty acid with urea is represented by the equation xF.A. + yUrea $\rightleftarrows$ F.A.$_x$·Urea$_y$.[5]

In terms of the liquid–solid countercurrent distribution system, the inclusion adducts are the stationary solid phase, whereas the supernatant liquid is the moving phase.

(5) See H. Schlenk, "Progress in the Chemistry of Fats and Other Lipids," Vol. 2, Academic Press, Inc., New York, N. Y., 1952, p. 243, for a review of the urea inclusion compound literature.

To determine whether the amounts of fatty acid in equilibrium between the liquid and solid phases are governed by a distribution coefficient, quantitative measurements using pure palmitic acid as a reactant were made. The reactions were carried out at 30° at three different concentrations of palmitic acid, each in 100 ml. of methanol. In each solution, 19.2 g. of urea was dissolved, which is the amount required to saturate 100 ml. of methanol at 30°. Enough additional urea also was added to each solution to react with the weight of palmitic acid present at a ratio of 12.8 moles of urea per mole of fatty acid.[5] The solutions were held at 30° for 6 hr. Aliquots of the supernatant liquid were then removed and the palmitic acid in solution was extracted and weighed. The data and results of these experiments are given in Table I. It is evident that the palmitic acid does have a definite distribution coefficient in this system.[6]

TABLE I

DISTRIBUTION OF PALMITIC ACID IN A TWO-PHASE METHANOL–UREA SYSTEM

Wt. of palmitic acid, g.	Wt. of urea, g.	Distribution coefficient $K - C$ liquid
1.4200	23.45	0.013
0.6931	21.27	.014
0.3189	20.16	.012

To determine whether sufficient difference exists between the distribution coefficients of long-chain fatty acids to warrant investigation of the urea reaction as a countercurrent method, quantitative measurements employing palmitic, stearic and arachidic acids were made. The reactions were each carried out at 20° in a urea-saturated solution consisting of 70% methanol and 30% ethyl acetate. The K-values obtained were 0.016 for arachidic acid, 0.037 for stearic acid and 0.091 for palmitic acid. Although these values are small, they differ considerably in magnitude and, for this reason, studies on a countercurrent separation were begun.

The concentration of urea in solution at equilibrium should be constant throughout the countercurrent system. This condition can be met through the use of solvents that remain saturated with urea when the reaction has reached equilibrium. In addition, the distribution of different mixtures of fatty acids will, in general, require different concentrations of urea, from one system to another, depending on the chain length and degree of unsaturation of the component fatty acids. This requirement can be met by using a series of solvents with varying urea solubility characteristics.

In the separation of saturated fatty acids at or near room temperature, the solubility of urea can be effectively varied by the use of mixtures of methanol and ethyl acetate. Methyl alcohol when saturated with urea at 20° contains 16.5 g.

(6) The distribution of a fatty acid between solid urea and supernatant solution appears to be similar to the distribution of a compound between an ion exchange resin and supernatant solution. Helferich, THIS JOURNAL, 76, 5567 (1954), has defined the distribution coefficient of a substance in contact with resin as $\bar{c}/c$ where $\bar{c}$ is the concentration of substance in the pore liquid of the resin and c is the concentration in the supernatant solution.

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of urea per 100 ml. of solution. Ethyl acetate at 20° contains 0.35 g. of urea per 100 ml. of solution. By varying the proportions of methanol and ethyl acetate, it is possible to prepare saturated urea solutions of any desired concentration between the two limits. A solubility curve for urea in mixtures of methanol and ethyl acetate is shown in Fig. 1.

In the separation of unsaturated fatty acids at lower temperatures, methanol is used as the solvent although the solubility of urea in methanol in the temperature range of −10 to −30° is less than is desirable. Efforts are being made to find a better solvent for work in this range.

It has been found that the solubility of urea in methanol varies linearly with temperature in the range from 20 to −30°. The solubility equation is: $x = 10 + 0.32T$, where T is the centigrade temperature and x is the solubility (g. per 100 ml. of solution) of urea in methanol at that temperature. This equation is useful for computing the concentration of urea in methanol solution at any temperature at which a separation is to be made.

Experimental

Procedure.—Solutions of urea in methanol or a mixture of methanol and ethyl acetate, sufficient in volume for the number of stages (usually, 12 to 30) in the distribution system, were prepared so that the concentration of urea would be the same as that of a saturated solution at the temperature at which the distribution was to be performed.

The distribution was carried out in a series of 500-ml. erlenmeyer flasks, each fitted with a cork stopper holding a short air condenser. Each flask in the series was charged with 10 g. of dry urea (to maintain the solvent at saturation after complex formation). The sample of fatty acids to be distributed, weighing from 5 to 15 g., was placed in the first (0) flask. A 250-ml. volume of the urea solution was added and the mixture was heated until complete solution was obtained. The flask was then cooled to the desired temperature, either in a water-bath or in a refrigerated chest, and allowed to stand until the precipitation of the adducts was complete. The cooling of the reaction mixture should be carried out gradually. Rapid cooling results in less satisfactory separations.

After the reaction in flask 0 has reached equilibrium (about 2 hr.), the supernatant liquid was transferred into flask 1. In most cases, the adduct crystals were well-formed and the liquid layer was decanted easily. If the crystals were small, however, the liquid layer was filtered off with suction. In order that this operation could be accomplished without removing the solid phase from the reaction flask, a rubber stopper was inserted inside the filtering section of a No. 1 Coors büchner funnel. The stopper was ground so that it fitted snugly against the perforated face of the funnel and was bored so that the neck of an erlenmeyer flask fitted into it tightly. A very narrow slit was made on the inside of the stopper so that air could pass into the flask during the filtration. In operation, the stopper was fitted over the flask. The funnel, fitted with filter paper, was placed over the stopper. This assembly was then inverted and attached to a suction flask. In this way, the liquid layer was removed quickly, while the solid phase remained in the flask. Another 250-ml. volume of urea solution was added to flask 0. Flasks 0 and 1 were heated until complete solution was achieved, and they were then cooled to the desired temperature and held until the reaction had reached equilibrium.

The liquid layer in flask 1 was then transferred to flask 2, and the liquid layer in flask 0 was transferred to flask 1. Another 250-ml. volume of urea solution was added to flask 0, and the flasks were heated and then cooled.

This procedure was repeated until the fatty acids in the sample were distributed over the total number of flasks in the system.

To extract the fatty acids from the fractions, each fraction was transferred to a separatory funnel, and 300 ml. of warm water and 10 ml. of concd. HCl were added. The fatty acids were then extracted with 1:1 mixed ether and petroleum ether. The ether extract was dried over magnesium sulfate after which the ether was removed by distillation. Traces of solvent were removed by heating the residual fatty acid fractions in a vacuum oven at 40° for 30 min. The solid fatty acids were crystallized from acetone prior to the determination of their physical constants.

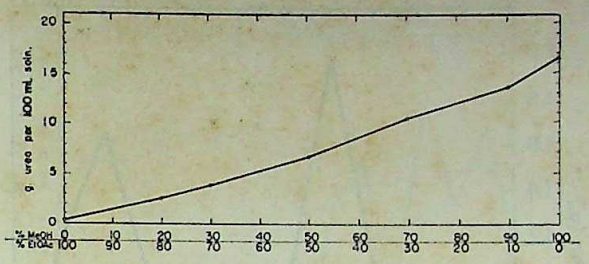

Fig. 1.—Solubility of urea in mixtures of methanol and ethyl acetate at 20°.

Results

1. Distribution of Mixed Stearic, Palmitic and Oleic Acids.—A mixture consisting of 5 g. each of technical-grade stearic, palmitic and oleic acid was distributed over 24 stages at 20° in a urea-saturated solvent made up of 70% methanol and 30% ethyl acetate. The results are shown in Fig. 2.

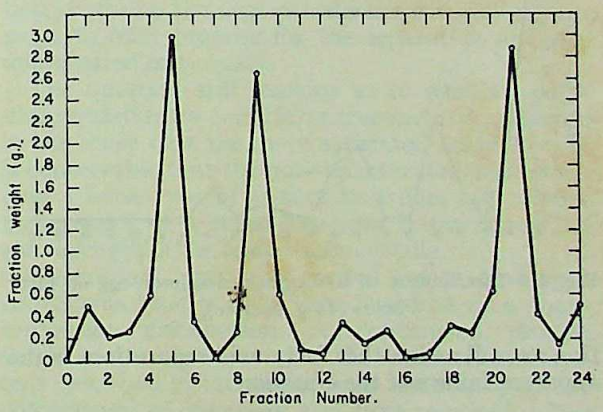

Fig. 2.—Distribution of a mixture of stearic, palmitic and oleic acids (5 g. each).

Fractions 0 through 15 were solids and the remaining fractions were oils. Stearic acid reached a maximum concentration in fraction 5; the physical constants of this fraction were m.p. 69.5°, I value 0.0 and $n^{72}D$ 1.4329. Palmitic acid was concentrated in fraction 9; the constants were m.p. 62.0°, I value 0.6 and $n^{70}D$ 1.4315. Oleic acid was concentrated in fraction 21; the constants were I value 89.5 and $n^{35}D$ 1.4545.

In addition to the major components, arachidic acid was concentrated in fraction 1; the constants of this fraction were m.p. 75.0°, I value 0.0, and $n^{80}D$ 1.4327. Fraction 13 apparently consists of myristic acid contaminated with an unsaturated fatty acid; the constants of this fraction were m.p. 50.5°, I value 2.3 and $n^{70}D$ 1.4305. Fractions 23 and 24 were considered to be largely dienoic fatty acid, owing to their respective refractive index values, $n^{35}D$ 1.4619 and $n^{35}D$ 1.4621.

One of the problems encountered in this separa-

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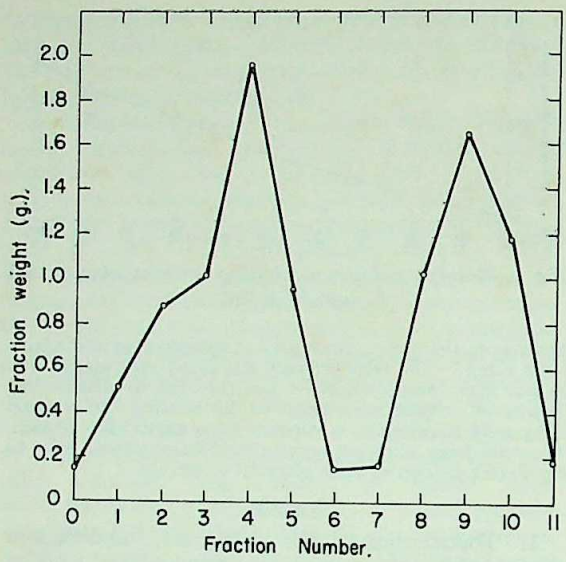

Fig. 3.—Distribution of a mixture of oleic and elaidic acids (5 g. each).

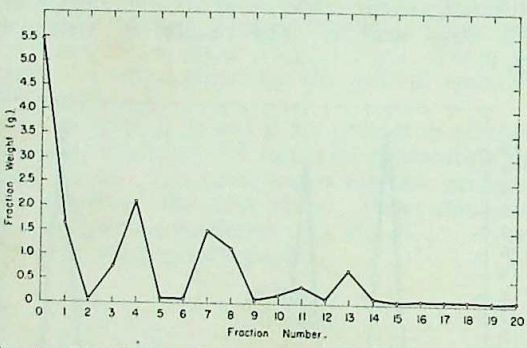

Fig. 4.—Distribution of hydrogenated salmon-egg oil fatty acids (15-g. sample).

tion as well as in other fatty acid separations is the apparent failure of the equation

$$N = n\,\frac{(K)}{K+1} \qquad (1)$$

to predict the point where the maximum of the distribution curve of a particular fatty acid will occur. In this equation, K is the distribution coefficient, N is equal to the number of flasks the maximal concentration has migrated from flask 0, and n is the total number of flasks used in the system. If $K/(K+1)$ is multiplied by 3.5, then the calculated values of N are in fair agreement with the experimental results. Possible explanations for this unexpected behavior might be: (1) large errors in the determined values of K, (2) failure of the reactions to completely reach equilibrium in the time allowed for each crystallization, (3) interaction between mixed fatty acids in the solution has a marked effect on the distribution coefficient of each individual fatty acid. It is felt that explanations 1 and 2 are unlikely to account for such a large discrepancy. Explanation 3, although of unknown significance, probably is the most likely one. The question is likely to remain unanswered until more detailed studies can be carried out. Some light may be thrown on the problem, by further experiments using pure fatty acids and their esters to avoid effects of interaction.

It is of interest to compare the results of urea countercurrent distribution of fatty acids with the results obtained by Ahrens and Craig[7] using a liquid–liquid system containing heptane, methanol, formamide and acetic acid. One difference is in the number of stages required to obtain a satisfactory separation. The liquid–liquid system required from 400 to 600 stages, depending on the nature of the fatty acid mixture, as compared to the 25 stages used for the urea system. The urea system permits larger amounts of fatty acids to be used per distribution as compared with either liquid–liquid countercurrent distribution or the various chromatographic methods which have been used.[8] It also does not require special equipment. However, operation of the urea system is very tedious and time consuming.

Distribution of the *cis–trans* Isomers, Oleic and Elaidic Acids.—It is a well-established fact that the formation of urea–fatty acid complexes is hindered by any distortion in the carbon chain of the fatty acid. It follows that the *cis* isomer of an unsaturated fatty acid should fit less readily in the urea crystal than the *trans* isomer. Thus, the urea countercurrent distribution technique may serve to separate *cis–trans* isomers, such as oleic and elaidic acids.

Elaidic acid was prepared from purified oleic acid by treatment with nitrous acid. The product was crystallized twice from petroleum ether.

A mixture made up of 5 g. each of oleic and elaidic acid was distributed over 12 stages at 20° in urea-saturated methanol. The results are shown in Fig. 3.

Fractions 0 through 5 were solid and the remaining fractions were liquid. Fraction 4 contained the maximum concentration of elaidic acid. The physical constants of this fraction were m.p. 45.5° and n^{70}D 1.4401. Fraction 9 contained the maximum concentration of oleic acid. The physical constants of this fraction were I value 89.3 and n^{35}D 1.4552. The elaidic acid distribution curve was skewed perhaps owing to the stearic acid present as an impurity in the system.

It appears from these results that urea countercurrent distribution may be an efficient method for separating a mixture of *cis–trans* isomers of the long-chain alkene type.

3. Distribution of Hydrogenated Salmon-Egg Oil Fatty Acids.[9]—Salmon-egg oil is characterized by a high content of poly-unsaturated C_{20}-, C_{22}- and C_{24}-fatty acids. Consequently, hydrogenated salmon-egg oil fatty acids should offer suitable raw material for the separation of C_{20} to C_{24} saturated fatty acids.

The hydrogenated sample (I value 6.7) was first separated into saturated and unsaturated fractions by treatment with acetone at −30°. Fifteen

(7) E. H. Ahrens, Jr., and L. C. Craig, *J. Biol. Chem.*, **195**, 299 (1952).

(8) R. T. Holman, "Progress in the Chemistry of Fats and Other Lipids," Vol. 1, Academic Press, Inc., New York, N. Y., 1952, p. 104.

(9) Kindly furnished by Mr. Robert Kyte of the Fishery Products Laboratory, Ketchikan, Alaska.

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grams of the saturated fraction was then distributed over 21 stages at 18° in a urea-saturated solvent consisting of equal volumes of methanol and ethyl acetate. The results are shown in Fig. 4. All of the fractions obtained from the distribution were solids except for the very small residues in fractions 17 through 20. Over one-third of the sample was found in fraction 0; the physical constants of this fraction were m.p. 73.8°, *I* value 0.0 and $n^{75}D$ 1.4341. Fraction 4, $n^{75}D$ 1.4322, was stearic acid; fraction 7, $n^{75}D$ 1.4302, was palmitic acid; and fraction 13, $n^{75}D$ 1.4285, was mainly myristic acid. Fraction 11, $n^{75}D$ 1.4292, was unidentified.

The results of this experiment suggest that the distribution of saturated fatty acids with more than 18 carbons could be done more successfully at temperatures above room temperature, probably in the range 30° to 35°.

4. **Distribution of Poly-unsaturated Fatty Acids.**—One of the difficult problems in oil chemistry is the separation of natural mixtures of unsaturated fatty acids containing 2 to 6 double bonds, such as those commonly found in marine oils. The preparation of highly unsaturated fatty acid concentrates from marine oils by the urea inclusion method has been reported.[1,10] The mild conditions inherent in the urea procedure are ideally suited for use in the separation of poly-unsaturated fatty acids, although the presence of double bonds in the chain greatly hinders the formation of urea–fatty acid adducts.

To determine whether poly-unsaturated fatty acids could be separated by the urea countercurrent technique, a 15-g. sample of unsaturated salmon-egg oil fatty acid (*I* value 350) was distributed over 18 stages at −30° in urea-saturated methanol. This experiment was exploratory and no attempt was made to characterize the products completely. The results are shown in Fig. 5. It appears from the curve that four fatty acids have been concentrated, one being in each of the fractions 7, 10, 12 and 14. Another fatty acid has perhaps been concentrated in fraction 9 but, if so, it is overshadowed by the large amount of material in fraction 10. The refractive indices of the fractions from this separation are given in Table II, together with the iodine numbers of the principal fractions. Fraction 15, after standing in a vacuum desiccator, was found to contain very fine, silky crystals, melting between 30–32°, in addition to oil. The crystals dissolved readily in the usual organic solvents.

TABLE II

Fraction	Wt., g.	Refractive Index $n^{30}D$	*I* value	Fraction	Wt., g.	$n^{30}D$	*I* value
0	0.000			9	1.503	1.4762	302
1	.020	....		10	1.771	1.4835	341
2	.030	....		11	0.961	1.4865	
3	.021	....		12	2.143	1.4874	364
4	.035	1.4667		13	1.514	1.4890	
5	.096	1.4573		14	2.018	1.4890	358
6	.219	1.4588		15	1.078	1.4912	
7	.747	1.4632	206	16	0.518	1.4924	
8	.531	1.4702		17	0.124	1.4928	

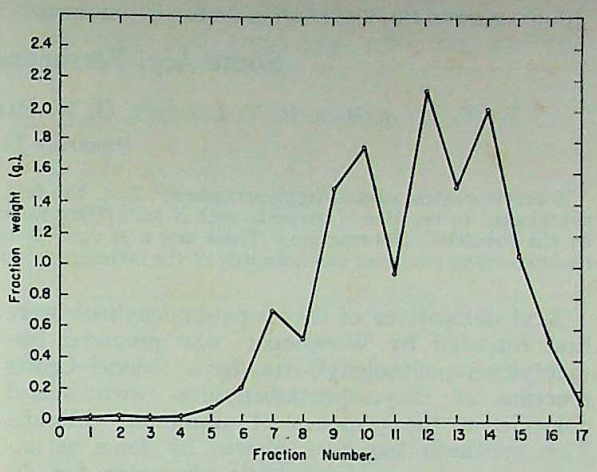

Fig. 5.—Distribution of unsaturated fatty acids from salmon-egg oil (15-g. sample).

The results of this distribution suggest that a larger number of stages should be used in future experiments. Although a considerable amount of work remains to be done toward improving the separation and also in characterizing the distribution products, the urea countercurrent method appears to offer promise for the separation of poly-unsaturated fatty acids.

The question still remains as to whether poly-unsaturated fatty acids form true inclusion adducts in the sense that the more saturated acids do. It is conceivable that the poly-unsaturated acids form only a loose type of adduct that does not require the creation of a crystalline urea lattice along the entire length of the fatty acid molecule.

Experiments are being carried out to develop a continuous type of separation based on urea countercurrent distribution. A continuous process would be greatly superior to the discontinuous system described in this paper from the standpoint of convenience of operation and time required. The experimental technique being used at present employs a 5.5 cm. × 45 cm. column packed with urea and maintained at a temperature suitable for the particular separation under study. The fatty acid sample dissolved in a suitable solvent is placed on the column, and the complexed fatty acids are then eluted with a non-polar solvent, such as hexane. The elution can be facilitated by raising the temperature of the column above the temperature used for forming the complexes.

In conclusion, it should be noted that the phenomenon of inclusion compound formation may become increasingly important in the future in the fields of organic chemistry and biochemistry.[7] In particular, the urea countercurrent technique could be applied to the problem of separating mixtures of petroleum hydrocarbons of the longer chain lengths as well as other types of aliphatic compounds.

Acknowledgment.—The author expresses his grateful appreciation to Mrs. Harriet Starr and Mr. Dave Wieg for their assistance in this work.

(10) A. M. Abu-Nasr, W. M. Potts and R. T. Holman, J. Am. Oil Chemists' Soc., 31, 16 (1954)

WASHINGTON, D. C.

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[CONTRIBUTION NO. 404 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO.]

Some Acyl Ferrocenes and their Reactions

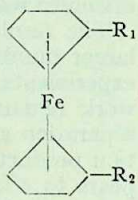
BY P. J. GRAHAM, R. V. LINDSEY, G. W. PARSHALL, M. L. PETERSON AND G. M. WHITMAN

RECEIVED JANUARY 10, 1957

Formylcyclopentadienyl-(cyclopentadienyl)-iron, the first ferrocene derivative bearing an aldehyde function, has been synthesized by reaction of ferrocene with N-methylformanilide. A number of new diacylferrocenes have also been prepared by the Friedel–Crafts reaction. These new acyl derivatives, as well as the known acetylferrocene and diacetylferrocene, undergo many reactions characteristic of the carbonyl group.

Acyl derivatives of dicyclopentadienyliron were first reported by Woodward[1] who prepared bis-(acetylcyclopentadienyl)-iron by a Friedel–Crafts reaction of dicyclopentadienyliron with acetyl chloride in the presence of aluminum chloride. This synthesis has been viewed by some as important evidence of aromatic character for dicyclopentadienyliron, though others have pointed out that acylation with Friedel–Crafts catalysts occurs with simple alicyclic compounds.[2]

DERIVATIVES OF DICYCLOPENTADIENYLIRON



R_1	R_2	
CHO	H	I
$COCH_3$	H	II
CH=NOH	H	III
CH_2OH	H	IV
$CH_2N(CH_3)_3I$	H	V
CN	H	VI
CH(OH)CN	H	VII
$CH{=}C(CN)CO_2H$	H	VIII
$CH(NH_2)CH_3$	H	IX
$CH_2C(=S)-[N(CH_2CH_2)_2O]$	H	X
CH_2CO_2H	H	XI
$CH_2CON(CH_2CH_2)_2O$	H	XII
$COCH_2CH_2CO_2H$	$COCH_2CH_2CO_2H$	XIII
$CHCH_2CH_2CO$ (O)	$CHCH_2CH_2CO$ (O)	XIV
$COCH_2CH_2CN$	$COCH_2CH_2CN$	XV
$(CH_2)_4NH_2$	$(CH_2)_4NH_2$	XVI
$CHOHCH_3$	$CHOHCH_3$	XVII
$COCH_2CH_2CO_2C_2H_5$	$COCH_2CH_2CO_2C_2H_5$	XVIII

Acetylcyclopentadienyl-(cyclopentadienyl)-iron (II) has been prepared by reaction of dicyclopentadienyliron with acetic anhydride in anhydrous hydrogen fluoride,[3] and in the presence of stannic chloride.[4] Pauson[5] interprets these results and his unpublished synthesis of the monoacetyl derivative with a boron trifluoride catalyst as evidence that dicyclopentadienyliron is more reactive than benzene. Some support is given this conclusion by our synthesis of formylcyclopentadienyl-(cyclopentadienyl)-iron from N-methylformanilide, dicyclopentadienyliron and phosphorus oxychloride, and by our preparation of acetylcyclopentadienyl-(cyclopentadienyl)-iron from dicyclopentadienyliron and acetic anhydride with phosphoric acid catalyst.

Diacyl derivatives of dicyclopentadienyliron reported herein were prepared by the Friedel–Crafts method. The acyl derivatives have been studied to determine effects of the dicyclopentadienyliron ring system on some reactions of the carbonyl group. In most cases, normal functionality was observed.

Formylcyclopentadienyl-(cyclopentadienyl)-iron; Dicyclopentadienylironcarboxaldehyde.—This aldehyde I was synthesized in 55% yield by the reaction of N-methylformanilide with dicyclopentadienyliron in phosphorus oxychloride at 50–55°.[5a] The new aldehyde formed such typical derivatives as a bisulfite addition product, a cyanohydrin, an oxime, an azine, a rhodanone and an acetal. It could be reduced to an alcohol and a hydrocarbon, and it underwent reductive amination. In other respects the aldehyde I displayed unexpected properties.

Under a polarizing microscope, formylcyclopentadienyl-(cyclopentadienyl)-iron was observed to undergo a sharp transition at 45° after which it was isotropic up to a temperature of 124.5°. Between these two temperatures, a liquid crystal region was observed and at 124.5° a sharp change in viscosity indicated the final melting point. Above the transition temperature of 45°, a sharp absorption peak characteristic of hydroxyl groups was observed in the infrared spectrum (Fig. 1). This unexplained hydroxyl absorption did not appear at the expense of carbonyl absorption and was observed only at temperatures above 45°. Chemically, the aldehyde was sensitive to oxidation either in dilute aqueous solutions or in concentrated anhydrous hydrocarbon solutions. The oxidation product, however, was not the carboxylic acid, since no acidic materials could be isolated from the typical amorphous brown oxidation product. When the aldehyde I was treated with Raney nickel and hydrogen at 50°, another unusual reaction was observed in its unexpected conversion to oxydimethylenebis-(dicyclopentadienyliron), $(C_5H_5FeC_5H_4CH_2)_2O$, instead of the expected alcohol, $C_5H_5FeC_5H_4CH_2OH$ (IV).

(1) R. B. Woodward, M. Rosenblum and M. Whiting, THIS JOURNAL, **74**, 3458 (1952).

(2) E. O. Fischer and R. Jira, *Z. Naturforsch.*, **86**, 1 (1953).

(3) V. Weinmayr, THIS JOURNAL, **77**, 3009 (1955).

(4) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and O. A. Nesmeyanova, *Doklady Akad. Nauk S.S.S.R.*, **97**, 459 (1954).

(5) P. L. Pauson, *Quart. Revs.*, **9**, No. 4, 391 (1955).

(5a) M. Rosenblum, *Chem. & Ind.*, No. 3, 72 (1957), disclosed the preparation of compound I by this route after this paper had been submitted for publication.

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Acetylcyclopentadienyl-(cyclopentadienyl)-iron.—A new method for the synthesis of acetylcyclopentadienyl-(cyclopentadienyl)-iron (II) has been discovered in which acetylation is accomplished with acetic anhydride at 90° with phosphoric acid catalyst. This suggests that dicyclopentadienyliron is more reactive toward electrophilic substitution than realized heretofore. Some reactions of the monoacetyl derivative II have already been described. These include oxidation to a monocarboxylic acid, conversion to an oxime and reduction to a monoethyl derivative.[6] Acetylcyclopentadienyl-(cyclopentadienyl)-iron has now been found to undergo reductive amination and the Willgerodt reaction. The Willgerodt reaction proceeded smoothly in morpholine to give a stable crystalline thiomorpholide (X) which could be hydrolyzed in methanolic potassium hydroxide to the carboxymethyl derivative XI, and the carboxamide XII. Both the amide and free acid were stable in crystalline form, but aqueous solutions of the acid rapidly turned blue on exposure to air.

Bis-[(3-carboxypropionyl)-cyclopentadienyl]-iron.—Dicyclopentadienyliron reacted with succinic anhydride in the presence of aluminum chloride catalyst to give a bis-(carboxyacyl) derivative (XIII). Attempts to perform a Wolff–Kishner or Clemmensen reduction on this diacyl derivative were unsuccessful. Catalytic reduction apparently stopped at the hydroxyl stage as evidenced by isolation of the corresponding dilactone XIV. The dilactone also was obtained by catalytic reduction of the diethyl ester of bis-[(3-carboxypropionyl)-cyclopentadienyl]-iron (XVIII).

Bis-[(4-aminobutyl)-cyclopentadienyl]-iron.—This new diamine XVI was prepared readily by catalytic reduction of bis-[(3-cyanopropionyl)-cyclopentadienyl]-iron (XV), obtained by reaction of bis-[(3-chloropropionyl)-cyclopentadienyl]-iron with potassium cyanide. The bis-(chloroacyl) derivative was obtained by the method of Woodward[1] from ferrocene and β-chloropropionyl chloride with aluminum chloride catalyst. Bis-[(4-aminobutyl)-cyclopentadienyl]-iron underwent the reactions characteristic of an aliphatic diamine.

Experimental

Formylcyclopentadienyl-(cyclopentadienyl)-iron (I).—A mixture of 112 g. (0.6 mole) of finely ground dicyclopentadienyliron and 107 g. (0.7 mole) of phosphorus oxychloride was heated to 50°, and 81 g. (0.6 mole) of N-methylformanilide was added dropwise with stirring in 1.25 hours. The reaction mixture was cooled slowly to room temperature and allowed to stand for three hours. The resulting mixture was poured onto ice (500 g.) and extracted with diethyl ether for 45 hours in a continuous extractor. The extract was washed with water, 5% aqueous sodium carbonate solution, and again with water. The washed extracts were dried with anhydrous magnesium sulfate and the ether removed by distillation. Crude aldehyde was obtained as a black oil that solidified on standing. It was sublimed at 70° (1 mm.) to give 85.4 g. (66% yield) of formylcyclopentadienyl-(cyclopentadienyl)-iron. A recrystallization from a mixture of *n*-heptane and methylene chloride (3 to 1), gave 71 g. (55% yield) of pure aldehyde as a reddish-brown crystalline solid.

Anal. Calcd. for $C_{11}H_{10}FeO$: C, 61.7; H, 4.71; Fe, 26.1; mol. wt., 214. Found: C, 61.9; H, 4.73; Fe, 26.3; mol. wt., 202.

(6) F. S. Arimoto and A. C. Haven, THIS JOURNAL, **77**, 6295 (1955).

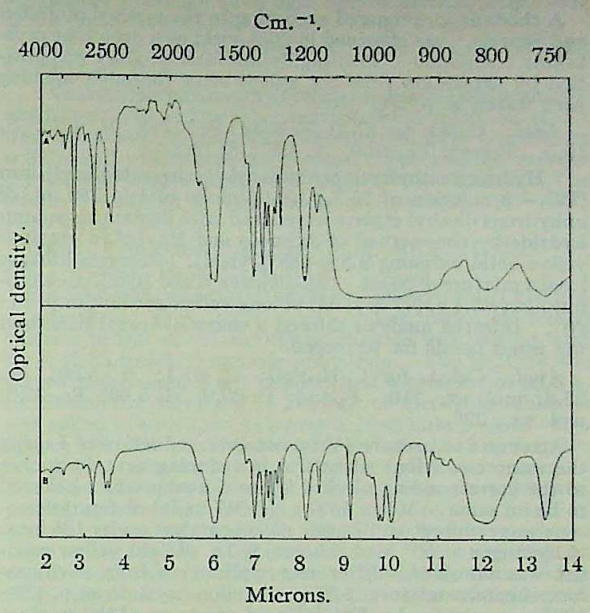

Fig. 1.—Infrared spectrum of formylcyclopentadienyl-(cyclopentadienyl)-iron above (A) and below (B) the transition temperature of 45°.

The aldehyde showed a sharp transition temperature at 45° under polarized light. True melting indicated by a sharp viscosity change occurred at 124.5°. The aldehyde was also prepared with dimethylformamide[7] as the formylating agent. This method required more vigorous conditions (85°, 3.5 hr.), produced considerable tar and gave only 23% yield of aldehyde I in 17% conversion.

Formylcyclopentadienyl-(cyclopentadienyl)-iron (10 g., 0.046 mole) was shaken vigorously with 100 g. of 40% aqueous sodium bisulfite and 15 ml. of ethyl alcohol to obtain 13.3 g. (90% yield) of a yellow bisulfite addition compound. The addition product could not be purified readily by recrystallization and was merely washed with cold water and with chloroform. The analyses indicated some impurities were still present in the product.

Anal. Calcd. for $C_{11}H_{11}FeNaO_4S$: C, 41.5; H, 3.5; Fe, 14.4; S, 10.1. Found: C, 34.7; H, 3.8; Fe, 16.2; S, 10.6.

An oxime III was prepared in 77% yield by reaction of hydroxylamine with I in aqueous methanol at 30°. The oxime was recrystallized from a 2:3 mixture of benzene and heptane, m.p. 133–135°. A transition temperature was noted at 98°.

Anal. Calcd. for $C_{11}H_{11}FeNO$: C, 57.6; H, 4.84; Fe, 24.4; N, 6.11. Found: C, 57.8; H, 5.08; Fe, 24.4; N, 6.37.

A semicarbazone was obtained in 58% yield by reaction of semicarbazide with I in aqueous ethyl alcohol at 60°. The purified semicarbazone, m.p. 203–204° dec., was obtained by recrystallization from a 5:4 mixture of ethyl alcohol and dimethylformamide.

Anal. Calcd. for $C_{12}H_{13}FeN_3O$: Fe, 20.6; N, 15.5. Found: Fe, 20.8; N, 15.5.

An isonicotinylhydrazone, prepared from I according to the method of Fox and Gibas,[8] was obtained in 39% yield after recrystallization from a mixture of isopropyl alcohol and ethyl alcohol (2:1), m.p. 212–213°.

Anal. Calcd. for $C_{17}H_{15}FeN_3O$: Fe, 16.7; N, 12.6. Found: Fe, 17.0; N, 12.5.

An azine, prepared by reaction of I with hydrazine hydrate in methanol at room temperature, was obtained in 47% yield as red-brown crystals after recrystallization from dimethylformamide, m.p. 245°.

Anal. Calcd. for $C_{22}H_{20}N_2Fe_2$: N, 6.61. Found: N, 6.65.

(7) F. Campaigne and W. L. Archer, *ibid.*, **75**, 989 (1953).
(8) H. Fox and J. T. Gibas, *J. Org. Chem.*, **18**, 994 (1953).

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A rhodanone, prepared according to the method of Julian and Sturgis,[9] was obtained in 70% yield as a deep blue crystalline compound. This highly insoluble product was purified by extraction with hot xylene after thorough washing with water, m.p. 245° dec.

Anal. Calcd. for $C_{14}H_{11}FeNO_2$: Fe, 17.0; N, 4.25; S, 19.5. Found: Fe, 16.9; N, 4.37; S, 19.2.

Hydroxymethylcyclopentadienyl-(cyclopentadienyl)-iron (IV).—A solution of 10.7 g. (0.05 mole) of I in 250 ml. of anhydrous diethyl ether was reduced with lithium aluminum hydride by the method of Arimoto and Haven[6] to obtain a yellow solid weighing 9.5 g. (88% yield). Recrystallization from a mixture of 60 ml. of Skellysolve B and 10 ml. of chloroform gave 5.4 g. (47% yield) of long yellow needles, m.p. 74–76°. Infrared analysis showed a sharp hydroxyl band and the usual bands for ferrocene.

Anal. Calcd. for $C_{11}H_{12}FeO$: C, 61.1; H, 5.60; Fe, 25.8; mol. wt., 216. Found: C, 60.9; H, 5.69; Fe, 26.0; mol. wt., 225.

Attempts to prepare IV by catalytic reduction of I using the same conditions successful in reducing acetylferrocene to the corresponding alcohol led to a new product believed to be an ether. When 10.0 g. (0.047 mole) of formylferrocene was reduced with Raney nickel catalyst under 135 atm. of hydrogen at 50° for 1.5 hours, 9.0 g. of light yellow product was obtained. After recrystallization from a chloroform–heptane mixture, 5.35 g. of yellow crystals, m.p. 129–130°, was obtained. The infrared spectrum of the product did not show hydroxyl or carbonyl absorption bands. The spectrum did show the presence of ether links, and a molecular weight determination supports the proposed ether structure, $(C_5H_5FeC_5H_4CH_2)_2O$, oxydimethylenebis-(dicyclopentadienyliron).

Anal. Calcd. for $C_{22}H_{22}Fe_2O$: C, 63.8; H, 5.35; Fe, 27.1; mol. wt., 414. Found: C, 63.7; H, 5.49; Fe, 27.4; mol. wt., 465.

Ferrocenylmethyltrimethylammonium Iodide (V).—A solution of 21.4 g. (0.1 mole) of I in 100 ml. of methanol was heated with 25 g. of dimethylamine in the presence of Raney nickel catalyst at 120° for three hours under 165 atm. pressure of hydrogen. The reaction mixture was filtered through charcoal, diluted with water and extracted with four 75-ml. portions of ether. The combined extracts were washed once with water, dried over magnesium sulfate and filtered. The clear filtrate was treated with a solution of 20 g. of methyl iodide in 50 ml. of anhydrous ether. The yellow precipitate that formed almost immediately was washed with dry ether and dried in a vacuum desiccator over phosphorus pentoxide. The finely divided yellow quaternary methiodide, m.p. 218° dec., weighed 29.1 g. (76% yield) and was readily soluble in water.

Anal. Calcd. for $C_{14}H_{20}FeIN$: C, 43.7; H, 5.23; Fe, 14.5; N, 3.63; I, 32.9. Found: C, 43.9; H, 5.30; Fe, 14.7; N, 3.55; I, 32.9.

This quaternary ammonium iodide was reported recently by Hauser and Lindsay[10] who prepared it by quaternization of dimethylaminoferrocene prepared from ferrocene, formaldehyde and dimethylamine.

Cyanocyclopentadienyl-(cyclopentadienyl)-iron (VI).—Acetic anhydride (40 ml.) was added to 20 g. of the oxime III at room temperature to give a deep red-brown solution. After about 30 minutes, the reaction mixture was poured onto 200 g. of ice, 10 g. of sodium carbonate added, and the red-orange oil that separated was extracted with methylene chloride. The combined extracts were washed with 100 ml. of 5% aqueous sodium carbonate followed by three washings with distilled water. The methylene chloride solution was dried over magnesium sulfate, filtered, and the solvent was evaporated at room temperature under a stream of nitrogen. The resulting viscous red oil decomposed slowly at room temperature to give acetic acid. Analysis indicated the oil was an acetate of the oxime III.

Anal. Calcd. for $C_{12}H_{12}FeNO_2$: Fe, 20.6. Found: Fe, 20.7.

The oxime acetate was placed in a vacuum desiccator over phosphorus pentoxide and pumped to remove the acetic acid produced by slow decomposition. After several days, the oil solidified. The solid residue was sublimed at 100° (1 mm.) for several days until no more brown sublimate was obtained. The crude product (10 g.) was recrystallized from 125 ml. of *n*-heptane to obtain 8.5 g. (46% yield) of pure cyanoferrocene, m.p. 103–104°.

Anal. Calcd. for $C_{11}H_9FeN$: C, 62.6; H, 4.30; Fe, 26.3; N, 6.64. Found: C, 62.6; H, 4.61; Fe, 26.7; N, 6.64.

1-Hydroxy-1-cyanomethylcyclopentadienyl-(cyclopentadienyl)-iron (VII).—The bisulfite addition compound of ferrocenecarboxaldehyde (I) was prepared by adding 21.4 g. (0.1 mole) of I in 35 ml. of ethyl alcohol to 20.8 g. (0.2 mole) of sodium bisulfite in 100 ml. of distilled water. To this slurry was added 9.8 g. (0.2 mole) of sodium cyanide in 100 ml. of water. The mixture was stirred for two hours at about 50°, cooled in ice and filtered. Extraction of the moist product (31 g.) with two 175-ml. portions of benzene and concentration of the extracts gave 17 g. of crude cyanohydrin. After recrystallization from benzene containing a trace of alcohol, 12.5 g. (52%) of cyanohydrin VII was obtained, m.p. 104°, slight decomposition, followed by sharp and complete decomposition at 125°.

It was not possible to prepare the cyanohydrin VII directly from ferrocenecarboxaldehyde and sodium cyanide. Successful preparations of VII were achieved only with the bisulfite addition compound as intermediate.

Anal. Calcd. for $C_{12}H_{11}FeNO$: C, 59.8; H, 4.60; Fe, 23.2; N, 5.81. Found: C, 59.6; H, 4.68; Fe, 23.5; N, 6.03.

2-Cyano-2-carboxyvinylcyclopentadienyl-(cyclopentadienyl)-iron (VIII).—A solution of 21.4 g. (0.1 mole) of I in anhydrous pyridine (50 ml.) was mixed at room temperature with a solution of 26 g. of cyanoacetic acid (0.3 mole) in 20 ml. of pyridine. The mixture was heated 2.5 hours on a steam-bath, cooled and allowed to stand for two days at room temperature. The mixture was diluted with 500 ml. of cold water, cooled in an ice-bath, and acidified with 150 ml. of 6 *N* sulfuric acid. The acidified mixture was extracted with four 150-ml. portions of methylene chloride and the combined extracts were washed three times with 200 ml. of water. The methylene chloride solution was dried with magnesium sulfate and evaporated to an oil which was treated with a solution of sodium carbonate monohydrate (20 g. in 200 ml. of water). The pastey mass that resulted was diluted with 100 ml. of water and filtered. The alkaline filtrate was cooled in an ice-bath and acidified with 6 *N* sulfuric acid to give 5.3 g. (19%) of a purple, gummy precipitate that crystallized on standing. Recrystallization from a mixture of chloroform and carbon tetrachloride gave 3.5 g. of pure VIII, m.p. 158.5–160° dec.

Anal. Calcd. for $C_{14}H_{11}FeNO_2$: C, 59.8; H, 3.95; Fe, 19.9; N, 4.98. Found: C, 59.8; H, 3.95; Fe, 19.7; N, 4.90.

The free acid VIII gave deep purple solutions in acetone or alcohol. Ultraviolet and visible spectra taken on the alcohol solution showed strongest absorptions at 2620, 3200 and 8300 Å.

Sodium Salt.—The solid remaining from the sodium carbonate extraction was dried over phosphorus pentoxide and extracted once with 150 ml. of chloroform to remove unreacted aldehyde. The residue was recrystallized from ethyl alcohol to give 9.4 g. (31% yield) of a dark red sodium salt of VIII.

Anal. Calcd. for $C_{14}H_{10}FeNNaO_2$: Fe, 18.4; Na, 7.59. Found: Fe, 17.9; Na, 8.02.

The sodium salt reacted readily with cupric acetate to give a red insoluble copper salt.

Hydantoin from Formylcyclopentadienyl-(cyclopentadienyl)-iron.—Moist bisulfite addition compound, prepared from 21.4 g. (0.1 mole) of ferrocenecarboxaldehyde (I), was slurried in 150 ml. of ethyl alcohol and added rapidly to a stirred mixture of 29.4 g. (0.45 mole) of potassium cyanide, 86.3 g. (0.9 mole) of ammonium carbonate, 150 ml. of distilled water and 50 ml. of ethyl alcohol. The reaction was stirred vigorously at 55° for 1.5 hours and cooled to room temperature. The alcohol was distilled from the mixture, and the residue was cooled and filtered to give 19 g. of an olive-brown hydantoin. The crude hydantoin was washed with hot benzene and hot methanol. The gray residue (11 g.) was purified by solution in 4% aqueous sodium hydroxide solution followed by filtration and acidification to give 9.0 g. (32% yield) of an olive product. One recrys-

(9) P. L. Julian and B. M. Sturgis, THIS JOURNAL, **57**, 1126 (1935).
(10) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **21**, 382 (1956).

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tallization from 1,2-dimethoxyethane and one from aqueous dimethylformamide afforded a pale yellow-brown crystalline product, m.p. 192–197° dec.

Anal. Calcd. for $C_{13}H_{12}FeN_2O_2$: C, 54.9; H, 4.26; Fe, 19.7; N, 9.86. Found: C, 54.3; H, 4.48; Fe, 19.7; N, 9.64.

5-Ferrocenylmethylenebarbituric Acid.—A solution of 6.4 g. (0.05 mole) of barbituric acid and 3.0 g. of anhydrous potassium acetate in 150 ml. of glacial acetic acid was filtered and heated to 95°. To it was added portionwise in about two minutes 10.7 g. (0.05 mole) of aldehyde I. The reaction mixture, which became deep blue immediately, was allowed to cool slowly to room temperature. The mixture was filtered and the crystalline violet precipitate was washed once with glacial acetic acid and three times with methanol. The washed product weighed 11.1 g. after drying over phosphorus pentoxide. An additional 2.0 g. of product (total yield 80%) was obtained by dilution of the filtrate with water to cause precipitation. After filtration, drying and sublimation of the residue, volatile impurities such as formylferrocene and ferrocene were removed by sublimation. The compound did not melt below 360°.

Anal. Calcd. for $C_{15}H_{12}FeN_2O_3$: C, 55.6; H, 3.73; N, 8.64. Found: C, 55.1; H, 3.76; N, 8.95.

Acetylcyclopentadienyl-(cyclopentadienyl)-iron (II).—A mixture of 93 g. (0.5 mole) of dicyclopentadienyliron, 250 ml. of acetic anhydride and 20 ml. of 85% phosphoric acid was heated at 100° for 10 minutes. The reaction mixture was cooled slightly and poured onto ice. After standing overnight, the mixture was neutralized with 200 g. of sodium carbonate monohydrate in 200 ml. of water. The resulting brown pasty mass was cooled in an ice-bath and filtered. The tan product was washed four times with 100-ml. portions of water and filtered. The granular product was dried in a vacuum desiccator over phosphoric anhydride. Sublimation of the crude product at 100° (1 mm.) gave 81.5 g. (71.4% yield) of an orange crystalline product II, m.p. 85–86° (lit.[3] 85–86°) after recrystallization from *n*-heptane.

1-Aminoethylcyclopentadienyl-(cyclopentadienyl)-iron (IX).—A mixture of 22.8 g. (0.1 mole) of the monoacetyl derivative II, 125 ml. of absolute ethyl alcohol, 30 g. of liquid ammonia and 10 g. of Raney nickel catalyst was heated for 3 hr. at 100° and 135 atm. hydrogen pressure. The red orange solution was mixed with 2 g. of Celite and filtered to remove catalyst. The filtrate was poured into 500 ml. of cold water and extracted with diethyl ether. About 600 ml. of extracts were combined, washed three times with water, and dried with anhydrous magnesium sulfate. The drying agent was removed by filtration, the filtrate was diluted with one liter of anhydrous ether, and the solution was treated with dry hydrogen chloride. After about 15 minutes, the pink amine hydrochloride was collected by filtration, washed with diethyl ether, partially air-dried, slurried with 100 ml. of chloroform at room temperature, and filtered. Further washing with chloroform on the büchner funnel gave a pale yellow solid weighing 5.9 g. after drying in a vacuum desiccator over phosphoric anhydride. Recrystallization from 75 ml. of anhydrous ethyl alcohol gave 3.3 g. of a lemon-yellow hydrochloride, m.p. 163–165° dec.

Anal. Calcd. for $C_{12}H_{16}ClFeN$: C, 54.2; H, 6.07; N, 5.27. Found: C, 54.4; H, 6.19; N, 5.37.

Thiomorphylamidomethylcyclopentadienyl-(cyclopentadienyl)-iron (X).—A mixture of 9.5 g. of the monoacetyl derivative II, 1.9 g. of sulfur and 5.2 ml. of morpholine was heated at 130° for 2.5 hours. The viscous black reaction mixture was extracted with hot methanol, and the extracts were diluted with water to give a dark brown precipitate of thioamide X. Successive recrystallizations from benzene–hexane and water–methanol mixtures gave orange needles, m.p. 128.5–129°, yield 4.5 g. (30%).

Anal. Calcd. for $C_{16}H_{19}FeNOS$: C, 58.3; H, 5.83; N, 4.26; S, 9.74. Found: C, 58.9; H, 6.01; N, 4.48; S, 9.79.

Carboxymethylcyclopentadienyl-(cyclopentadienyl)-iron (XI).—A solution of 5.0 g. of the thioamide X in 50 ml. of 10% methanolic potassium hydroxide was refluxed 17 hours. The reaction mixture was poured into 800 ml. of cold water and was thoroughly extracted with ether. Neutralization of the aqueous layer with concentrated hydrochloric acid gave a fine yellow precipitate. Recrystallization from decolorizing carbon and dilute methanol gave light yellow needles, m.p. 150–152°,[11] yield 2.5 g. (60%).

Anal. Calcd. for $C_{12}H_{12}FeO_2$: C, 59.1; H, 4.96. Found: C, 59.1; H, 5.17.

Carboxymorphilomethylcyclopentadienyl-(cyclopentadienyl)-iron (XII).—The ether extracts from synthesis of XI were combined, washed with water, dried over magnesium sulfate and evaporated to dryness. The residue was recrystallized from a mixture of benzene and hexane. The amide crystallized as fine yellow needles, m.p. 148–149°, yield 0.3 g. (6%).

Anal. Calcd. for $C_{16}H_{19}FeNO_2$: C, 61.3; H, 6.12; N, 4.47. Found: C, 61.1; H, 6.10; N, 4.57.

Bis-[(3-carboxypropionyl)-cyclopentadienyl]-iron (XIII).—A mixture of 96 g. (0.72 mole) of anhydrous aluminum chloride in 200 ml. of methylene chloride was treated with 36 g. (0.36 mole) of succinic anhydride. The mixture was stirred and shaken a few minutes and a solution of 33.3 g. (0.18 mole) of ferrocene in 200 ml. of methylene chloride was added in small portions over a 10-minute period. Hydrogen chloride gas was evolved and the heat of reaction brought the mixture to 35°. The dark violet, viscous solution was allowed to stand 7 hours at room temperature, poured onto ice, and filtered. The air-dried solid (yield 46 g.), was extracted once with 800 ml. of boiling water and twice with 150 ml. of boiling water. The combined extracts were cooled in an ice-bath and filtered to obtain 19.7 g. (38% yield) of crystalline bis-[(3-carboxypropionyl)-cyclopentadienyl]-iron, m.p. 164–166° dec.[11]

Anal. Calcd. for $C_{18}H_{18}FeO_6$: C, 56.0; H, 4.69; Fe, 14.5; neut. equiv., 193. Found: C, 56.3; H, 4.94; Fe, 14.9; neut. equiv., 193.

The acid XIII was converted to the corresponding diethyl ester XVIII by slowly distilling a solution of 21.3 g. of the acid, 1.5 g. of sulfuric acid, 200 ml. of ethyl alcohol and 250 ml. of toluene through a small still. After slow distillation for 4 hours, the remaining solution was cooled to room temperature and washed with 75 ml. of 10% aqueous sodium carbonate solution. The toluene solution was dried over magnesium sulfate, filtered and evaporated at room temperature to obtain 23 g. (94%) of red-brown crystals. Crystallization from ethyl alcohol gave 20.3 g. of shiny orange-brown platelets of bis-[3-carbethoxypropionyl)-cyclopentadienyl]-iron (XVIII), m.p. 134–136°.

Anal. Calcd. for $C_{22}H_{26}O_6Fe$: C, 59.7; H, 5.92; Fe, 12.6. Found: C, 59.8; H, 6.04; Fe, 12.8.

Bis-[(5-oxotetrahydro-2-furyl)-cyclopentadienyl]-iron (XIV).—A mixture of 17.1 g. (0.06 mole) of (XIII), 200 ml. of ethyl alcohol and 1 g. of ruthenium dioxide was heated for 3 hours at 85° under 165 atm. of hydrogen pressure. The reaction mixture was heated on a steam-bath and filtered through charcoal. Evaporation of the alcohol gave a tan, gummy residue that was converted to 7.5 g. of fine yellow powder by extraction with methanol. Recrystallization from 50 ml. of chloroform gave 4.3 g. of a yellow crystalline product. This was dissolved in 30 ml. of boiling chloroform, diluted with 25 ml. of methanol and evaporated until crystallization began. The mixture was cooled slowly to obtain 3.7 g. (17.5%) of golden yellow crystals of pure bis-[(5-oxotetrahydro-2-furyl)-cyclopentadienyl)-iron, m.p. at 165° dec.

Anal. Calcd. for $C_{18}H_{18}FeO_4$: C, 61.0; H, 5.12; Fe, 15.8. Found: C, 61.2; H, 5.12; Fe, 15.9.

The lactone also was obtained by hydrogenation of the ester XVIII with Raney nickel catalyst at 75° and 135 atm. of hydrogen pressure.

Bis-[(3-cyanopropionyl)-cyclopentadienyl]-iron (XV).—A solution of 10 g. of bis-[(3-chloropropionyl)-cyclopentadienyl]-iron (prepared by the method of Woodward[1] in 34% yield) and 4.0 g. of potassium cyanide in 150 ml. of ethyl alcohol was refluxed for 4 hours. The reaction mixture was filtered and the filtrate was cooled in an ice-bath to obtain 5.4 g. of an orange-red crystalline material, m.p. 118–121°. Recrystallization from toluene followed by recrystallization from ethyl alcohol gave orange crystals, m.p. 133–134°.

(11) Variations in decomposition temperatures have been noted in ferrocene derivatives having carboxyl functions. The decomposition temperature of bis-{(3-carboxypropionyl)cyclopentadienyl}-iron varies with heating rate. This may account for some discrepancy between [illegible] Reinhart, Curby and Sokol (p. 3420).

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Anal. Calcd. for $C_{18}H_{16}N_2O_2Fe$: C, 62.1; H, 4.63; Fe, 16.0. Found: C, 61.9; H, 4.83; Fe, 16.4.

Bis-[(4-aminobutyl)-cyclopentadienyl]-iron (XVI).—A solution of 8.2 g. (0.023 mole) of XV in 100 ml. of ethyl alcohol was hydrogenated over Raney nickel catalyst at 65° and 135 atm. of hydrogen pressure. The solution was filtered to remove catalyst, dried over magnesium sulfate and diluted with 500 ml. of ether. Dry hydrogen chloride gas was passed in to produce a dark red oil that slowly crystallized. The product was filtered, washed with ethyl alcohol and dissolved in 50 ml. of water. Addition of an aqueous solution of sodium carbonate precipitated 5.3 g. of an orange solid which was recrystallized from heptane to give fine orange crystals, m.p. 137–138°.

Anal. Calcd. for $C_{18}H_{28}N_2Fe$: N, 8.53; Fe, 17.0; neut. equiv., 164. Found: N, 8.87; Fe, 17.8; neut. equiv., 162.

Bis-[(1-hydroxyethyl)-cyclopentadienyl]-iron (XVII).—To a cooled solution of 3 g. of lithium aluminum hydride in 150 ml. of tetrahydrofuran, 30 g. of bis-(acetylcyclopentadienyl)-iron was added slowly. After the reaction was complete, 25 g. of ethyl acetate was added to the yellow solution. A mixture of ether, ethyl alcohol and the calculated quantity of water to destroy the aluminum complexes was added to the mixture. The solution was filtered with aid of Celite, and the filter cake was washed thoroughly with ether. Evaporation of the filtrates gave 27.8 g. (92%) of crude, yellow diol. Recrystallization from hexane gave yellow crystals, m.p. 69–71°.

Anal. Calcd. for $C_{14}H_{18}O_2Fe$: Fe, 20.4. Found: Fe, 20.6.

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

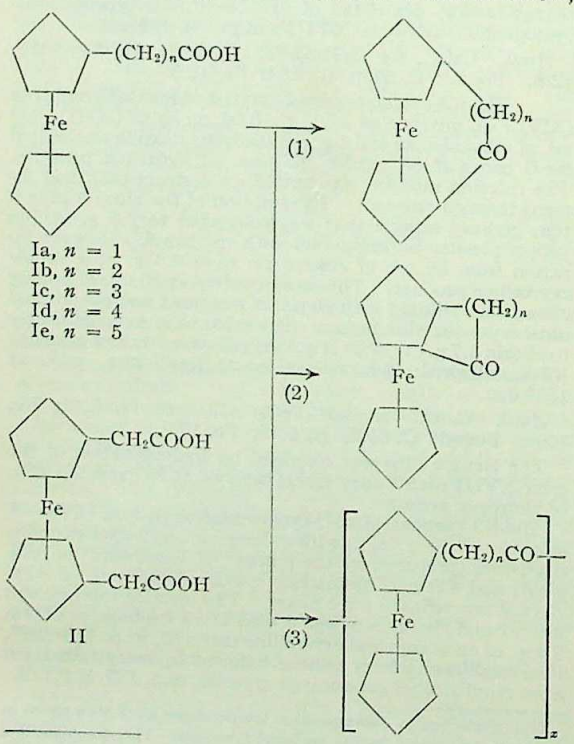
Organic Chemistry of Ferrocene. II. The Preparation of ω-Ferrocenyl Aliphatic Acids[1]

BY KENNETH L. RINEHART, JR., RONALD J. CURBY, JR., AND PHILLIP E. SOKOL

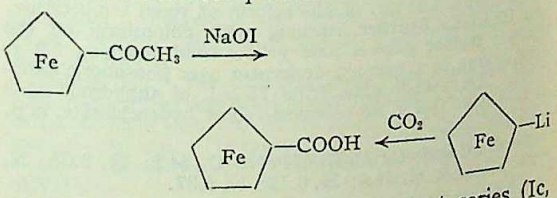
RECEIVED JANUARY 28, 1957

Five ω-ferrocenyl aliphatic acids have been synthesized; these are ferrocenylacetic acid, β-ferrocenylpropionic acid, γ-ferrocenylbutyric acid, δ-ferrocenylvaleric acid and ε-ferrocenylcaproic acid. Synthetic methods employed include the Willgerodt reaction of ferrocenyl ketones, carbethoxylation of acetylferrocene and Friedel–Crafts acylations of ferrocene.

As a portion of a general investigation of the spatial requirements for intramolecular reaction of substituted ferrocenes *vs.* intermolecular reaction by these compounds, a study has been undertaken of the relative tendency of ferrocene-substituted aliphatic acids (I) to undergo heteroannular and homoannular ring closure (routes 1 and 2 below, respectively) and polymer formation (route 3).[1,2] The present paper deals with the synthesis of the ω-ferrocenylmonocarboxylic acids ferrocenylacetic acid (Ia), β-ferrocenylpropionic acid (Ib), γ-ferrocenylbutyric acid (Ic), δ-ferrocenylvaleric acid (Id) and ε-ferrocenylcaproic acid (Ie) and the dicarboxylic acid 1,1′-ferrocenediacetic acid (II).



A number of substituted ferrocenecarboxylic acids (I, $n = 0$) have been previously prepared, both by the hypohalite oxidation of the corresponding acetylferrocenes[3–6] and by the carboxylation of ferrocenyllithium compounds.[7,8] As neither of these methods is readily applicable to the synthesis of the present acids, alternative routes have been investigated, adapted to the preparation of the individual compounds.



The higher homologs of the present series (Ic, Id, Ie) were easily prepared in sizable quantities by hydrogenation of the corresponding ω-keto acids (IIIa, IIIb, IIIc). The keto acids, in turn, were prepared by Friedel–Crafts acylation of fer-

(1) Presented in part at the 131st Meeting of the American Chemical Society, Miami, Florida, April 7 to 12, 1957; see Abstracts of Papers, p. 46-O.

(2) K. L. Rinehart, Jr., R. J. Curby, Jr., and Sung Moon, in preparation.

(3) K. L. Rinehart, Jr., K. L. Motz and S. Moon, THIS JOURNAL, **79**, 2749 (1957).

(4) R. B. Woodward, M. Rosenblum and M. C. Whiting, *ibid.*, **74**, 3458 (1952).

(5) M. Rosenblum, Ph.D. Thesis, Harvard University, August, 1953.

(6) V. Weinmayr, THIS JOURNAL, **77**, 3009 (1955).

(7) R. A. Benkeser, D. Goggin and G. Schroll, *ibid.*, **76**, 4025 (1954).

(8) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and L. G. Makarova, *Doklady Akad. Nauk., SSSR*, **97**, 459 (1954).

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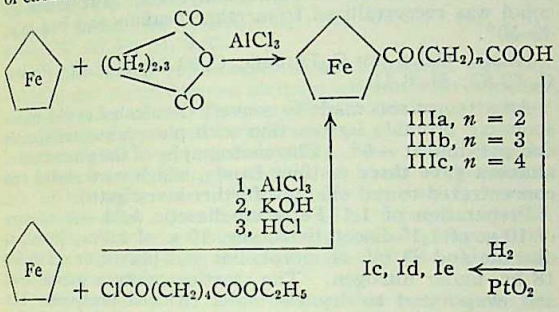
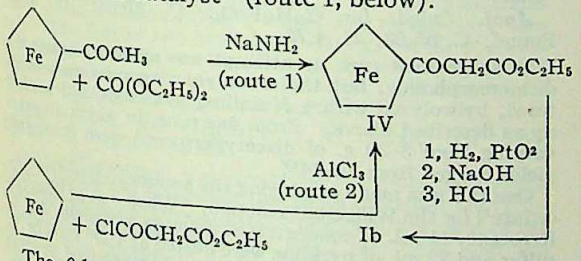
rocene with a limited amount of appropriate acid derivatives under conditions designed to give principally monoacylation.[3] Thus, ferrocene and succinic anhydride gave β-ferrocenoylpropionic acid (IIIa), and ferrocene and glutaric anhydride gave γ-ferrocenoylbutyric acid (IIIb), while ferrocene and δ-carbethoxyvaleryl chloride gave δ-ferrocenoylvaleric acid (IIIc). Yields from the anhydrides approximated 90%, while that from the half-ester acid chloride was 70%. Hydrogenation of each keto acid was effected in good yield.

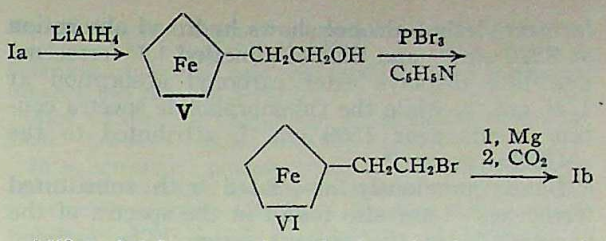


A similar procedure has been employed for the synthesis of β-ferrocenylpropionic acid by Woodward and Csendes,[9] who acylated ferrocene with carbethoxyacetyl chloride (route 2, below) to give the β-keto ester ethyl ferrocenoylacetate (IV) in good yield. Since carbethoxyacetyl chloride is inconvenient to prepare,[10] alternative routes have been investigated in the present study. The most convenient proved to be the carbethoxylation of acetylferrocene, employing diethyl carbonate and sodium amide catalyst[11] (route 1, below).

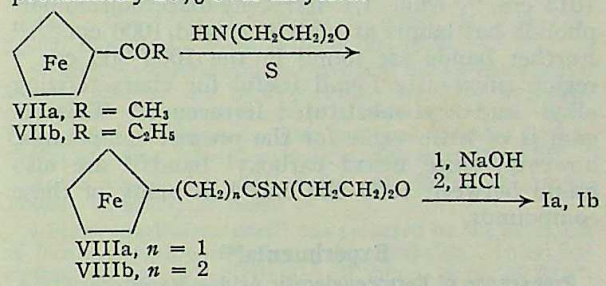


The β-keto ester IV was not isolated but was hydrogenated, then hydrolyzed directly to β-ferrocenylpropionic acid. No attempt was made to establish optimum conditions, but the ready availability of the starting materials render this approach particularly attractive.

Two alternative routes to β-ferrocenylpropionic acid were investigated but proved considerably less successful. One, the Willgerodt reaction of propionylferrocene, gave the acid, but in only very low yield, as described in the next paragraph. The second, below, was abandoned when the attempted conversion of β-ferrocenylethyl alcohol (V) to the corresponding bromide VI gave a complex mixture of products.



The Willgerodt reaction[12] was employed with success in the preparation of both ferrocenylacetic acid[13] and β-ferrocenylpropionic acid, from acetylferrocene (VIIa) and propionylferrocene (VIIb), respectively. The usual conditions[14] for the Kindler variation[15] of the Willgerodt reaction were modified slightly by the addition of dioxane to lower the reflux temperature, as the intermediate thiomorpholide was found to decompose at the normal reflux temperatures. Ferrocenylacetothiomorpholide (VIIIa) was obtained in 40% yield from one run and could be hydrolyzed in alkali to the corresponding acid. In other runs the thiomorpholide was not isolated, and the crude reaction mixture was hydrolyzed to give ferrocenylacetic acid in approximately 20% over-all yield.



No attempt was made to isolate β-ferrocenylpropionothiomorpholide (VIIIb), but the yield of β-ferrocenylpropionic acid from hydrolysis of the crude reaction mixture was only 4%, reflecting the usually lower yields of product obtained from higher alkyl aryl ketones compared to those from methyl aryl ketones.[12]

The dicarboxylic acid 1,1′-ferrocenediacetic acid was prepared by the same procedure in 13% over-all yield and was characterized as its dimethyl ester.

Infrared spectra are consistent with those anticipated for compounds of the structures given.[16] Thus, the spectra of the acids contain carboxyl carbonyl bands in the 1712–1705 cm.$^{-1}$ region, while those of the ketonic compounds, with carbonyl adjacent to the ferrocene nucleus, have bands between 1667–1663 cm.$^{-1}$.[17] The spectrum of

(9) R. B. Woodward and E. Csendes, personal communication.
(10) H. Staudinger and H. Becker, *Ber.*, **50**, 1016 (1917).
(11) R. Levine and C. R. Hauser, THIS JOURNAL, **66**, 1768 (1944).
(12) M. Carmack and M. A. Spielman in "Organic Reactions," Vol. III, R. Adams, ed., John Wiley and Sons, New York, N. Y., 1946, p. 83.
(13) Nesmeyanov has reported the isolation of ferrocenylacetothiomorpholide from the Willgerodt reaction of acetylferrocene, but has given no experimental details or physical properties (A. N. Nesmeyanov, XIVth International Congress of Pure and Applied Chemistry, Zurich, July 21–27, 1955; *cf.* Abstracts of Papers, p. 193).
(14) Reference 12, p. 97.
(15) K. Kindler, *Ann.*, **431**, 187 (1923).
(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.
(17) Exceptions to these values are found in the spectra of ferrocenylacetic acid and ε-ferrocenylcaproic acid, which show carboxyl carbonyl absorption at 1698 and 1694 cm.$^{-1}$, respectively, when determined in mulls. However, spectra of these compounds in chloroform solution have carboxyl bands at the normal positions. Also exceptional are the mull spectra of δ-ferrocenoylvaleric acid, which has two carboxyl bands, at 1723 and 1702 cm.$^{-1}$, and two ketone bands at 1658 and 1638 cm.$^{-1}$, and, to a lesser extent, the mull spectrum of β-ferrocenoylpropionic acid, with two ketone bands, at 1657 and 1640 cm.$^{-1}$. In these compounds, too, the abnormalities are absent from [illegible]

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ferrocenylethyl alcohol shows hydroxyl absorption at 3220 cm.$^{-1}$ and that of dimethyl 1,1′-ferrocenediacetate displays ester carbonyl absorption at 1740 cm.$^{-1}$, while the thiomorpholide spectra contain bands near 1500 cm.$^{-1}$, attributed to the —CSN= group.[18]

Bands previously associated with substituted ferrocenes[3,19] are also found in the spectra of the compounds in the present series. The carbon–hydrogen stretching band[19] is found between 3090 and 3040 cm.$^{-1}$, usually near 3060 cm.$^{-1}$, for every compound and carbon–hydrogen bending bands[19] in the narrow region 828–820 cm.$^{-1}$. All of the compounds with one unsubstituted cyclopentadienyl ring have bands near 1110 and 1005 cm.$^{-1}$ (9–10 μ rule),[20] although in some cases the 10 μ band is very weak. Thus the *absence* of *both* bands would be strong indication of substitution on both rings. However, the *presence* of one or more bands in these positions cannot be taken conclusively as proof of an unsubstituted ring. For example, in the present series dimethyl 1,1′-ferrocenediacetate has a band at 1015 cm.$^{-1}$, while 1,1′-ferrocene-diacetodithiomorpholide has bands at both 1111 and 1006 cm.$^{-1}$.[21] Further bands are found in the 1000–900 cm.$^{-1}$ region previously found useful for characterizing alkyl- and acyl-substituted ferrocenes.[3] This region is of little value for the present compounds, however, since broad carboxyl bands[22] are also found between 1000–900 cm.$^{-1}$ in many of these compounds.

Experimental[23]

Preparation of Ferrocenylacetic Acid.—A mixture of 20 g. of acetylferrocene, 7 g. of sulfur, 50 ml. of dioxane and 150 ml. of morpholine was heated at reflux for 18 hr. under nitrogen. The reaction mixture was filtered and evaporated to small volume under reduced pressure, then transferred to an alumina column and eluted in two fractions with benzene. From the first fraction was obtained 10.2 g. (35%) of **ferrocenylacetothiomorpholide**, m.p. 126–128°, and from the second fraction 1.0 g. (5%) of recovered acetylferrocene. Ferrocenylacetothiomorpholide, recrystallized from ether, had m.p. 130–131°.

Anal. Calcd. for $C_{16}H_{19}FeNOS$: C, 58.29; H, 5.80; N, 4.25. Found: C, 58.71, 58.52; H, 5.86, 5.75; N, 4.55.

The crude thiomorpholide was heated under reflux for 4 hr. with 2 *N* aqueous sodium hydroxide, then filtered, washed with ether and acidified with hydrochloric acid. The precipitated acid was extracted into ether, and the ether extracts were washed with water, dried and evaporated to small volume. Addition of pentane gave 5.5 g. (73% from the thiomorpholide) of precipitated ferrocenylacetic acid. The yellow acid, recrystallized from ether–pentane, darkened 125–135° and sintered 135–140°.

Anal. Calcd. for $C_{12}H_{12}FeO_2$: C, 59.05; H, 4.96. Found: C, 59.40; H, 5.34.

In subsequent runs the thiomorpholide was not isolated, but the reaction mixture from the Willgerodt procedure was filtered, then hydrolyzed directly with refluxing 4 *N* aqueous sodium hydroxide. The basic mixture was acidified and extracted with ether. The organic acid was extracted from ether with sodium carbonate and reprecipitated upon acidification. The ether–carbonate extraction sequence was repeated to give the pure acid; yields from six runs employing this procedure varied from 14 to 26%.

β-Ferrocenylethyl alcohol was prepared in quantitative yield from ferrocenylacetic acid by reduction at room temperature with lithium aluminum hydride. The yellow alcohol was recrystallized from ether–pentane and had m.p. 49–50°.

Anal. Calcd. for $C_{12}H_{14}FeO$: C, 62.64; H, 6.13. Found: C, 62.87; H, 6.41.

An attempt was made to convert the alcohol to the corresponding bromide by reaction with phosphorus tribromide and pyridine at −5°. Chromatography of the product over alumina gave three distinct bands, which were eluted and concentrated to red oils, not further investigated.

Preparation of 1,1′-Ferrocenediacetic Acid.—A mixture of 10 g. of 1,1′-diacetylferrocene, 10 g. of sulfur, 18 ml. of dioxane and 83 ml. of morpholine was heated at reflux for 18 hr. under nitrogen. The reaction mixture was filtered and evaporated to dryness under reduced pressure. The residue was dissolved in chloroform and reprecipitated with pentane. This process was repeated to give an analytical sample (0.32 g., 2%) of 1,1′-ferrocenediacetodithiomorpholide, which darkened 175–190°, sintered 200°.

Anal. Calcd. for $C_{22}H_{28}FeN_2O_2S_2$: C, 55.93; H, 5.96; N, 5.93. Found: C, 56.12; H, 6.10; N, 6.04.

The purified material was combined with the residue from the evaporated chloroform–pentane filtrates and hydrolyzed with sodium hydroxide as described above for the preparation of ferrocenylacetic acid. The yield of 1,1′-ferrocenediacetic acid was 1.4 g. (13%). The yellow acid, recrystallized from ether–pentane, darkened below 137° and sintered 140–143° with decomposition.

Anal. Calcd. for $C_{14}H_{14}FeO_4$: C, 55.64; H, 4.67. Found: C, 55.53; H, 4.75.

In subsequent runs no attempt was made to isolate the dithiomorpholide, but the crude reaction mixture was filtered, hydrolyzed with 4 *N* sodium hydroxide and worked up as described above. From five runs, in which amounts varying from 3–30 g. of diacetylferrocene were employed, yields ranged from 10–14%.

One run was made employing the ammonia–pyridine procedure[24] for the Willgerodt reaction. When 3 g. of diacetylferrocene, 11 ml. of concentrated aqueous ammonia, 4 g. of sulfur and 32 ml. of pyridine were heated at 165° for 4 hr. in a sealed tube, only 20 mg. of poorly characterized product could be obtained and the procedure was not further explored.

Dimethyl 1,1′-ferrocenediacetate was prepared in 75% yield by the reaction of 1,1′-ferrocenediacetic acid with diazomethane. The product was eluted from a Celite column with benzene and concentrated to the brown liquid diester. The infrared spectrum shows strong ester carbonyl absorption at 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{18}FeO_4$: C, 58.20; H, 5.49. Found: C, 58.43; H, 5.81.

Preparation of β-ferrocenylpropionic acid was effected *via* the β-keto ester obtained by carbethoxylation[11] of acetylferrocene. A solution of sodium amide[25] was prepared from 2.3 g. of sodium and 100 ml. of liquid ammonia. After the blue color had disappeared a solution of 10 g. of acetylferrocene in 100 ml. of absolute ether and 25 ml. of diethyl carbonate was added. The resulting mixture was stirred for 2 hr. under reflux, then poured over ice and acetic acid. The ether phase was washed with sodium carbonate, concentrated under reduced pressure and purified by elution with benzene from a Celite column. Benzene was removed in vacuum to give a red oil.

(18) Reference 16, p. 294.

(19) E. R. Lippincott and R. D. Nelson, THIS JOURNAL, **77**, 4990 (1955).

(20) This rule was proposed by Rosenblum,[3] who attributed sharp infrared bands at 9 and 10 μ to the presence of one or more unsubstituted cyclopentadienyl rings in the ferrocene molecule. Lippincott and Nelson[19] assign bands near 9 μ to ring breathing and bands near 10 μ to C–H bending parallel to the plane of the ring.

(21) It may be noted that 1,1′-dimethyl-2-ferrocenecarboxylic acid and the corresponding 3-carboxylic acid,[3] in which both rings are substituted, also have bands at 1104 cm.$^{-1}$.

(22) Reference 16, p. 148.

(23) Melting points are uncorrected. We are indebted to Mr. Jozsef Nemeth, Mrs. Maria Benassi, Mrs. Ruby Ju and Miss Claire Higham for microanalyses, and to Mr. James Brader, Mrs. Louise Griffing and Mr. Sy Portnow for infrared spectra. The spectra, which are on file in the Infrared Laboratory, were obtained for solids in Nujol mulls, for liquids as smears, with a recording Perkin–Elmer infrared spectrophotometer, model 21.

(24) D. F. DeTar and M. Carmack, THIS JOURNAL, **68**, 2025, 2029 (1946).

(25) K. W. Greenlee and A. L. Henne, *Inorg. Syntheses*, **2**, 128 (1946).

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A portion (4.0 g.) of the crude residue was dissolved in acetic acid and hydrogenated at four atmospheres pressure over 800 mg. of platinum oxide catalyst. After 48 hr. the mixture was filtered, diluted with water and extracted with ether. The ethereal solution was washed with sodium carbonate and concentrated. The residue was hydrolyzed with refluxing aqueous potassium hydroxide. The cooled basic solution was extracted with ether, then acidified to give crude β-ferrocenylpropionic acid, which was purified by passing the sodium salt through Celite, re-precipitation with acid and recrystallization from ether–pentane. A total of 1.73 g. was obtained of yellow-orange, crystalline β-ferrocenylpropionic acid, m.p. 115–116°,[26] together with an additional 340 mg. of less pure material.

Anal. Calcd. for $C_{13}H_{14}FeO_2$: C, 60.49; H, 5.47. Found: C, 60.44; H, 5.62.

The ether extract of the saponification mixture was concentrated and eluted from an alumina column with benzene. A small amount of ethylferrocene[27] was obtained, together with 580 mg. of recovered acetylferrocene.

A second portion of the crude β-keto ester was saponified with ethanolic potassium hydroxide at room temperature, then diluted with water. The orange aqueous layer was washed with ether, then acidified. The precipitated acid was extracted into ether, but apparently was decarboxylated readily as only acetylferrocene, m.p. 84–85°,[28] could be isolated from the ether solution.

A third portion of the crude β-keto ester was transferred to an alumina column. In addition to recovered acetylferrocene, a small amount of red oil[29] was obtained; the infrared spectrum of this material showed typical ferrocene bands at 3100 and 826 cm.$^{-1}$[19] and carbonyl absorption, consistent with that of a β-keto ester, at 1739 and 1665 cm.$^{-1}$.[30,31]

Propionylferrocene was prepared by the Friedel–Crafts acylation of ferrocene with propionic anhydride. To a mixture of 34.5 g. of aluminum chloride and 300 ml. of methylene chloride was added a solution of 44.3 g. of ferrocene and 15.6 g. of propionic anhydride in 300 ml. of methylene chloride. The mixture was stirred for 2 hr. at room temperature, then decanted over ice and worked up in the usual manner. The methylene chloride solution was concentrated and the residue dissolved in benzene and transferred to an alumina column, which was eluted with benzene. The first of two bands gave 21.4 g. (48%) of recovered ferrocene, while the second band yielded 15.3 g. (53%) of propionylferrocene as a red oil, which crystallized from pentane at Dry Ice temperature, m.p. 38–39°.

Anal. Calcd. for $C_{13}H_{14}FeO$: C, 64.49; H, 5.83. Found: C, 64.66; H, 6.08.

Propionylferrocene was converted to β-ferrocenylpropionic acid by the Willgerodt procedure described above for the preparation of ferrocenylacetic acid, but the yield of the substituted propionic acid was small (*ca.* 4%), and the material was impure (m.p. 112–114°). The infrared spectrum was, however, nearly identical with that of β-ferrocenylpropionic acid, obtained from the carbethoxylation sequence above.

β-Ferrocenoylpropionic acid[32] was prepared, by the procedure described above for the synthesis of propionylferrocene, from 7.4 g. of ferrocene, 2.0 g. of succinic anhydride and 5.8 g. of aluminum chloride.[33] The crude acid was extracted from methylene chloride with sodium carbonate, filtered through Celite and re-precipitated with dilute hydrochloric acid; yield 5.0 g. (87%). A sample of orange β-ferrocenoylpropionic acid, recrystallized from methanol–benzene, had m.p. 166.5–167.5°.

Anal. Calcd. for $C_{14}H_{14}FeO_3$: C, 58.78; H, 4.93; Fe, 19.52. Found: C, 58.74; H, 5.20; Fe, 19.24.

In an alternative procedure the order of addition of reagents was ferrocene (74.7 g.), aluminum chloride (58.8 g.), succinic anhydride (20.0 g.). Reaction was allowed to proceed for 20 hr. at room temperature. The yield of pure keto acid from this procedure was 11.8 g. (21%).

γ-Ferrocenylbutyric acid was prepared by hydrogenation of β-ferrocenoylpropionic acid, as described above for the preparation of β-ferrocenylpropionic acid. The diluted reaction mixture was extracted with ether, and the ether phase was in turn extracted with sodium carbonate. γ-Ferrocenylbutyric acid precipitated in yellow crystals on acidification of the carbonate extracts and was purified by repeated ether–carbonate extractions; yield 0.88 g. (93%, from 1.0 g. of keto acid), m.p. 115–116°.

Anal. Calcd. for $C_{14}H_{16}FeO_2$: C, 61.79; H, 5.93. Found: C, 61.79; H, 5.73.

γ-Ferrocenoylbutyric acid was prepared by the procedure described above for the preparation of β-ferrocenoylpropionic acid. From 33 g. of ferrocene, 10 g. of glutaric anhydride[34] and 26 g. of aluminum chloride the yield of γ-ferrocenoylbutyric acid was 24.1 g. (92%), m.p. 136–137°.

Anal. Calcd. for $C_{15}H_{16}FeO_3$: C, 60.05; H, 5.36; Fe, 18.59. Found: C, 59.75; H, 5.35; Fe, 18.52.

δ-Ferrocenylvaleric acid was prepared from γ-ferrocenoylbutyric acid by the hydrogenation procedure employed above for the preparation of γ-ferrocenylbutyric acid. From 1.0 g. of the orange keto acid was obtained 0.80 g. (84%) of yellow δ-ferrocenylvaleric acid, m.p. 109–110°.

Anal. Calcd. for $C_{15}H_{18}FeO_2$: C, 62.95; H, 6.34. Found: C, 62.69; H, 6.54.

δ-Ferrocenoylvaleric acid[32] was prepared by the acylation of ferrocene with δ-carbethoxyvaleryl chloride. Ethyl hydrogen adipate (b.p. 130–131° (2 mm.), m.p. 28–29.5°; lit.[35] b.p. 140–145° (2 mm.), m.p. 28–29°) was prepared by the procedure of Brown, *et al.*,[35] from diethyl adipate, adipic acid and ethanol and converted to the acid chloride (b.p. 70–73° (0.7 mm.); lit.[35] b.p. 120° (15 mm.)) by thionyl chloride.

Acylation was effected by the procedure described for the synthesis of propionylferrocene and employed 34.7 g. of δ-carbethoxyvaleryl chloride, 67.5 g. of ferrocene and 52.0 g. of aluminum chloride. After the reaction mixture had been worked up, the methylene chloride solution, containing ferrocene and keto ester, was allowed to stand for 60 hr. with 1 *N* ethanolic potassium hydroxide. Addition of water gave the sodium salt of δ-ferrocenoylvaleric acid in the aqueous layer. The orange acid precipitated on addition of glacial acetic acid and was extracted into ether, and recovered upon concentration; yield 43.5 g. (71%). An analytical sample, recrystallized from ether–pentane, had m.p. 83.5–84.5°.

Anal. Calcd. for $C_{16}H_{18}FeO_3$: C, 61.17; H, 5.78. Found: C, 61.48; H, 5.33.

In a second run the yield of keto acid was 65%.

ε-Ferrocenylcaproic acid[32] was prepared from δ-ferrocenoylvaleric acid by the hydrogenation procedure employed above for the preparation of γ-ferrocenylbutyric acid. From 5.0 g. of keto acid the yield of ε-ferrocenylcaproic acid was only 3.3 g. (70%) due to mechanical loss on bumping. The melting point behavior of ε-ferrocenylcaproic acid indicates polymorphism. Sharp yellow crystals, obtained from ether–pentane, had m.p. 92–93°; after re-solidification this material melted 85–86°. Microcrystals, obtained after grinding and prolonged drying, had m.p. 83–84°; after re-solidification this material melted 91.5–92.5°.

Anal. Calcd. for $C_{16}H_{20}FeO_2$: C, 64.03; H, 6.72. Found: C, 64.07; H, 6.57.

Acknowledgments.—The authors wish to express

(26) Woodward and Csendes[9] also have found m.p. 115–116° for this acid.

(27) K. L. Rinehart, Jr., Sung Moon and K. L. Motz, in preparation.

(28) The high degree of purity of this material [lit.[2] m.p. 86–87°] is in agreement with the formulation of the acidic product as ferrocenoylacetic acid.

(29) The oil did not yield readily to crystallization, presumably due to impurities. Woodward and Csendes[9] found ethyl ferrocenoylacetate to have m.p. 50–51°.

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URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL CORPS, CHEMICAL RESEARCH DIVISION, CHEMICAL WARFARE LABORATORIES]

Fluorocarbon Derivatives. I. Derivatives of Sulfur Hexafluoride[1]

BY FRIEDRICH W. HOFFMANN[2] AND THOMAS C. SIMMONS WITH R. B. BECK, H. V. HOLLER, T. KATZ, R. J. KOSHAR, E. R. LARSEN, J. E. MULVANEY, F. E. ROGERS, B. SINGLETON AND R. S. SPARKS

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The electrofluorination of dialkyl and cyclic sulfides and dialkyl disulfides in anhydrous hydrogen fluoride by the Simons process was investigated. Dialkyl sulfides were found to yield the corresponding di-perfluoroalkyl sulfur tetrafluorides, $(R_F)_2SF_4$ (I), together with degradation products. Dialkyl disulfides failed to give the corresponding di-(perfluoroalkyl) disulfur decafluorides, $(R_FSF_4)_2$, but yielded instead I and cleavage products.

Introduction

Direct as well as cobalt trifluoride fluorination of both methyl mercaptan and carbon disulfide result in the formation of trifluoromethyl sulfur pentafluoride, CF_3SF_5[3] (II). Clifford, El-Shemy, Emeleus and Haszeldine[4] obtained the same compound by electrochemical fluorination of dimethyl sulfide in anhydrous hydrogen fluoride (Simons process)[5] together with bis-(trifluoromethyl) sulfur tetrafluoride, $(CF_3)_2SF_4$ (III), the fully fluorinated analog of the starting material. II and III, which can be regarded as mono- and di-(perfluoroalkyl) derivatives of sulfur hexafluoride, respectively, seem to be the only representatives of these two classes of compounds reported in the literature.

The successful conversion of dimethyl sulfide to III and to the cleavage product II suggested that the relatively mild conditions prevailing in the Simons cell might permit the preparation of higher homologs of the two series of sulfur hexafluoride derivatives, $(R_F)SF_5$ (I) and $(R_F)_2SF_4$, (IV), respectively, from the corresponding dialkyl sulfides. Therefore, the behavior of several open-chain and cyclic sulfides and of three dialkyl disulfides during low-voltage electrolysis in anhydrous hydrogen fluoride was studied in the course of a program for the investigation of new sulfur- and nitrogen-containing fluorocarbon derivatives. This investigation resulted in the synthesis of several open-chain and one cyclic fluorocarbon derivatives of sulfur hexafluoride. The physical constants and analyses of these new compounds are listed in Table I.

After the Experimental part of our investigation had been completed, Severson, Brice and Coon[6] reported the preparation of $(C_4F_9)_2SF_4$ (X), $C_4F_9SF_5$ (IX) and $\overline{CF_2CF_2OCF_2CF_2SF_4}$ (XI) by the Simons process. These compounds also had been obtained in our study.

(1) Presented in part at the 130th Meeting of the American Chemical Society in Atlantic City, September 16–21, 1956.

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Experimental

Apparatus.—The large scale runs were performed in a cell of 3600-ml. capacity and a nominal rating of 50 amperes (cell A). The cell casing was constructed of nickel with an electrode pack of alternating anodes and cathodes (9 each, spaced 1/8 inch apart) of 8.9 × 17.8 × 0.16 cm. nickel sheeting and was provided at the bottom with a valve for the removal of insoluble liquid fluorinated product. Any gaseous reaction product, or low boiling materials entrained in the effluent hydrogen, were condensed in attached traps cooled with Dry Ice–acetone and liquid nitrogen. The effluent from the cell was passed through a low temperature reflux condenser and subsequently through a bed of sodium fluoride pellets in order to remove hydrogen fluoride from the gas stream before condensation in the attached cold traps.

Small cell runs were carried out in either of two nickel cells provided with Kel-F windows for observation of the electrolyte during the reaction. One of the cells (cell B), of 900-ml. capacity, had a cathode area of 250 sq. cm., the cell body served as the anode and the cell was rated at 10 amperes. The other small cell (cell C), of 1000-ml. capacity, was equipped with four anodes and four cathodes (14.0 × 12.7 × 0.16 cm. each) arranged alternatingly and was rated at 25 amperes. Cells A and C were provided with a mantle through which a refrigerant could be circulated. The coolant for the cell condensers and jacket was obtained from a Mayer Junior Chil-er (Mayer Refrigerating Engineers) model J-4, using a brine of ethylene glycol and water.

The power for cell A was supplied by a Sorenson Nobatron model E-6-100a and for cells B and C by a Mallory Rectopower, model 6RS25-1.

Materials.—The organic starting materials used in the electrofluorination were commercial products or were synthesized by conventional methods.

The hydrogen fluoride employed was commercial grade anhydrous hydrogen fluoride (Mathieson Chemical Corp. and Pennsylvania Salt Manufacturing Co.) which was distilled before use through a 122-cm. Monel column of 12.7 cm. inside diameter and packed with nickel Heli-pak (Podbielniak, Inc.).

The sodium fluoride pellets used for the removal of entrained hydrogen fluoride from the effluent gas stream were obtained as NaF·HF pellets (Harshaw Chemical Co.) and converted to NaF by the passage of dry air or nitrogen over the pellets at 450° for 10 hr.

Operation of the Cells.—Drying of the distilled anhydrous hydrogen fluoride (which contained approximately 0.5% of water) was accomplished by electrolyzing the cell charge of hydrogen fluoride at 5.5 to 6.0 volts. During the drying of the hydrogen fluoride some care had to be exercised to avoid undesirable explosions due to the formation of oxygen difluoride. The tendency for explosions was greatest during low flow rates of the effluent gases and could be prevented by increasing the gas flow with dry nitrogen.

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TABLE I

NEW COMPOUNDS

Compound	B.p., °C.	$n^{25}D$	d^{25}_{25}	Analyses, % Carbon Calcd.	Carbon Found	Fluorine Calcd.	Fluorine Found	Sulfur Calcd.	Sulfur Found	MR_D Calcd.[a]	MR_D Found[b]
$C_2F_4SF_5$ (V)	14										
$(C_2F_5)_2SF_4$[c] (VI)	70	1.2754	1.836	13.9	14.1	76.8	76.7	9.2	9.2	33.05	32.6
$C_4F_7SF_5$ (VII)	42	1.2594	1.801	12.1	12.8	76.8	76.5	10.8	11.2	28.15	26.87
$(C_4F_7)_2SF_4$[d] (VIII)	116	1.2856	1.865	16.1	16.1	76.7	76.8	7.18	7.18	42.29	42.75
$C_4F_9SF_5$[e] (IX)	70.5	1.2701	1.839	13.9	13.6	76.6	76.7	9.2	10.3	32.77	31.94
$(C_4F_9)_2SF_4$[f] (X)	154	1.2943	1.903	17.6	17.8	76.4	76.1	5.9	6.5	51.53	52.73
$OCF_2CF_2SF_4CF_2CF_2$ (XI)	80–80.5	1.3015	1.859	14.6	14.3	70.4	70.2	9.87	10.4	32.49	32.7
$(C_2F_5)_2NCF_2CF_2SF_5$[g] (XII)	124	1.2921	1.86	15.0	15.3			6.7	7.1	45.9	47.00

[a] The MR_D values were calculated using the following atomic refractions: S (in SF_4) 7.97, S (in SF_5) 7.69, F 1.10, C 2.42, N 2.84, -O- 1.64. [b] Calculated by the Lorentz–Lorenz equation. [c] Molecular weight, found 243, calculated 246. [d] Dielectric constant, liquid, 1.923. [e] Dielectric constant, liquid, 2.068. [f] Dielectric constant, liquid, 1.951. [g] *Anal.* Calcd.: N, 2.9; Found: N, 2.27.

The cells normally were operated at the reflux temperature of the electrolyte. However, cooling the cell charge was found to be desirable before addition of organic starting material, before emptying the cell after completion of a run, during temporary shut-downs over the week-ends, and in case of a leak or clogging of the exit gas lines. In general, the runs in cell A were carried out with 4 to 7 mole % of solute at 5.2–5.8 volts for extended periods on a 24-hr. day basis for 5 days per week with intermittent shut-downs of 65–70 hr. over the week-ends. If at all possible, cells B and C were also operated on this semi-continuous basis. During the course of all runs in cell A, hydrogen fluoride and organic starting materials were added intermittently in order to maintain an approximately constant concentration. Further addition of starting material was based on a measure of the hydrogen produced (as measured by a wet test meter) in the electrofluorination. The experimental data given in the original paper by Simons[5] on the electrofluorination process show that the replacement of one atom of hydrogen by fluorine proceeds with the consumption of two faradays and the formation of 1 mole of hydrogen with approximately 90% efficiency. In calculating the faradays required for fluorinating organic sulfur compounds and, thus, the hydrogen produced, it was assumed that the initial attack occurred at the sulfur atom and that this addition of fluorine would require only one faraday per fluorine atom. For example, the complete fluorination of one mole of dipropyl sulfide will require on this basis the passage of at least 32 faradays and result in the production of 358.4 liters of hydrogen (S.T.P.).

In runs performed in cells B and C the starting material was added in one portion to the hydrogen fluoride charge, and the electrofluorination was continued until the electrolyte was depleted of starting material.

Purification of Liquid Cell Products.—Liquid products obtained from the electrochemical cell were washed with water, dilute aqueous sodium bicarbonate solution and again with water. The heavy layer of insoluble, fluorinated product was separated and refluxed with 30–50% aqueous potassium hydroxide to remove hydrolyzable impurities. The insoluble fluorinated material was then washed with water, left in contact with Drierite or magnesium sulfate and the dried material was finally fractionated through a modified Todd column of approximately 40 plates. Center fractions of constant boiling point and refractive index were taken for analysis and determination of physical properties. The purity of the sample was checked by infrared and NMR analysis.

Gaseous products were passed over sodium fluoride pellets to remove entrained hydrogen fluoride and dried by passage over phosphorus pentoxide. If the gaseous cell effluents were found to attack mercury, they were purified further by passing through 30% aqueous potassium hydroxide solution. The purified gaseous material was then fractionally distilled in a low temperature column of approximately 25 plates. Molecular weights were determined by the vapor density method employing a gas density balance.[7]

Electrochemical Fluorinations.—The experimental conditions employed in the various runs are listed in Table II together with the weight-yields of the main products. In some of the runs, only portions of the cell products were worked up; in these cases, the amounts of products indicated in the table were calculated from the data obtained by fractionation of aliquots of the crudes.

Only the isolation of the major products from the insoluble, liquid cell drainings and the cold trap condensates is described in detail in the following for the various sulfur-containing starting materials.

Diethyl Sulfide.—The crude, liquid cell drainings (36.5 g.) were stabilized with aqueous alkali and refluxed under the column with overhead removal of the volatile material which was recondensed in an attached Dry Ice–acetone cold trap. Fractionation of the material remaining in the distillation flask yielded after a forerun of 5 g., b.p. 31–70.0°, 12.5 g. of di-(perfluoroethyl)-sulfur tetrafluoride (VI), b.p. 70.0–70.2°, $n^{25}D$ 1.2753.

The volatile material (14.5 g.) from the cell drainings was combined with the Dry Ice condensate (70 g.) from the cell effluents. The mixture was stabilized with alkali (89% recovery) and fractionated in a low temperature still to yield 20 g. of sulfur hexafluoride, b.p. −65 to −60°; 46 g. of pentafluoroethyl-sulfur pentafluoride (V), b.p. 13.5°, molecular weight 244 (calcd. 246); and 4 g. of pot residue. The identities of both V and VI were confirmed by nuclear magnetic resonance (NMR) analysis.

Di-*n*-propyl Sulfide.—The electrofluorination of 826 g. of di-*n*-propyl sulfide (Eastman Kodak, white label) gave during 215 hr. of operation 2052 l. of hydrogen at an average current of 23.5 amp. The run yielded 536 g. of HF-insoluble liquid product, 695 g. of Dry Ice–acetone trap condensate and 215 g. of condensate in the liquid nitrogen trap.

The combined Dry Ice and liquid nitrogen condensates were vaporized, passed over sodium fluoride, dried and separated into four arbitrary fractions: (1) b.p. −140 to −70°, approximately 200 g.; (2) b.p. −70 to 0°, 227 g.; (3) b.p. 0–25°, approximately 60 g.; (4) b.p. above 25°, 430 g.

Cut 1 was found to attack mercury. Therefore, a portion of 95 g. was passed through 30% aqueous potassium hydroxide solution to remove the reactive, unidentified contaminants; 59% of purified condensate was recovered. Low temperature distillation of the purified material yielded approximately 7 g. of crude carbon tetrafluoride, b.p. −140 to −80° (reported[8] b.p. 129°), molecular weight 78–86 (calcd. 88); 28 g. of crude sulfur hexafluoride, b.p. −80 to −60°, molecular weight 120–144 (calcd. 146) (identified by infrared analysis).[9]

Low temperature distillation of 219 g. of fraction 2 yielded 136.2 g. of sulfur hexafluoride, b.p. −62 to −57° (reported[10] b.p. −63.9°), molecular weight 138–147; and 52.8 g. of hexafluoropropane, b.p. −36 to −33° (reported[8] b.p. −38°) molecular weight 185 (calcd. 188). Fraction 3 of the original distillation did not yield any identifiable material.

Fraction 4 was stabilized with aqueous potassium hydroxide, dried with Drierite (88.4% recovery) and distilled to give the cuts: (4a) b.p. 27–42°, 42 g.; (4b) b.p. 42.0–

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TABLE II

EXPERIMENTAL CONDITIONS

Organic starting material	Mole % organic	Total organic used, g.	Potential applied, v.	Av. amp.	Cell used	Faradays	Products[a] Compound	Wt., g.
$(C_2H_5)_2S$	7.0	198	5.8	4.0	C	33	V	46
							VI	12.5
$(C_3H_7)_2S$	3.5	826	5.4	23.5	A	189	VII	312
							VIII	316
$(n\text{-}C_4H_9)_2S$	3.5	1746	5.4	24	A	472	IX	724
							X	695
$(n\text{-}C_4H_9S)_2$	4.0	1964	5.3	39.5	A	890	IX	838
							X	180
$(t\text{-}C_4H_9S)_2$	3.4	849	5.5	22.4	A	113.8	Liquid products[b]	178
							Gaseous products	825
$(t\text{-}C_4H_9S)_2$	3.0	713	4.5	12.7	A	171	Liquid products[b]	522
							Gaseous products	1051
$\ulcorner CH_2CH_2SCH_2CH_2 \urcorner$	3.0	100	5.4	4.0	B	17.2	Liq. product mixt.[c]	17.0
$\ulcorner CH_2CH_2OCH_2CH_2S \urcorner$	2.1	78	5.2	4.9	B	15.2	XI	19.0
$[(C_2H_5)_2NCH_2CH_2S]_2$	0.7	62	5.3	6.0	B	15.1	XII	30
$(C_4H_9)_2SO$	1.3	81	5.2	4.4	C	14.3	IX	3
							X	4

[a] Sulfur hexafluoride was obtained in all runs. [b] No effective separation was possible. [c] Mixture of XV, VI, IX and $C_3F_7SF_4CF_3$.

42.5°, $n^{25}D$ 1.2594, 312 g.; (4c) b.p. 43–46.0°, 21 g. Elemental and NMR analysis of cut 4b led to its identification as perfluoropropyl sulfur pentafluoride, $C_3F_7SF_5$ (VII), which was also the main component of the cuts 4a and 4c.

The fractionation of the purified cell drainings (493 g.) yielded after a forerun of 42 g. of material, b.p. 43–116°, 360 g. of di-(perfluoropropyl) sulfur tetrafluoride (VIII), colorless liquid, b.p. 116.0–116.5°, $n^{25}D$ 1.2856–1.2858; and 29.3 g. of less pure VIII, b.p. 117.0–118.0°, $n^{25}D$ 1.2868. An analytical cut of VIII, b.p. 116.0°, gave a NMR spectrum which confirmed its identity.

Di-*n*-butyl Sulfide.—From 1746 g. of di-*n*-butyl sulfide (Eimer & Amend, Highest Purity) were obtained 1530 g. of liquid cell products, 2330 g. of Dry Ice–acetone condensate and 600 g. of liquid nitrogen condensate.

Distillation of portions of the material condensed at −78° showed that its composition changed during the run and depended apparently on a variety of factors, such as cell voltage, flow rate of effluent gas and cell temperature. Dry Ice condensate (900 g.) collected during the first half of the run was separated into a gaseous and a liquid fraction (boiling above room temperature). A portion of 195 g. of the low boiling material (about 57% of the total amount of crude Dry Ice condensate) subjected to a low temperature distillation at 761 mm. gave 10.2 g. of unidentified product, b.p. −23 to −4°, average molecular weight 154; 173.3 g. of perfluorobutane, b. 1–3°, molecular weight 223–235 (calcd. 238); and 13.2 g. material, b. 3–15°. The weights of the three fractions correspond to 4.7, 88.4 and 6.3%, respectively, of the total charge.

A portion of 110 g. of low boiling material from the Dry Ice condensate collected at a later stage of the electrofluorination gave the following fractions: (1) b.p. 1–2°, 48.5 g., molecular weight 230–238; (2) b.p. 10–24°, 36.4 g., molecular weight 226–196; (3) b.p. above 24°, 20 g. The weights of the fractions 1 to 3 correspond to 44, 33.1 and 18.2%, respectively, of the total charge. The NMR spectrum indicated fraction 1 to be pure *n*-decafluorobutane (XIII), while fraction 2 gave a spectrum consistent with that expected for a mixture of nonafluorobutane (XIV) isomers (reported[11] C_4F_9H, b.p. 14–15°).

The higher boiling material from the various Dry Ice–acetone condensates was combined (1006 g.), and a portion of 268 g. was fractionated through an 18-in. heated column (packed with Heli-pak) to give after a forerun of 5.4 g., b.p. 61–68°, 95.1 g. of crude nonafluorobutyl sulfur pentafluoride (IX), b.p. 68–71°, $n^{20}D$ 1.2740–1.2728; and 25.0 g. of pot residue, $n^{20}D$ 1.2740. The NMR spectrum of the crude IX suggested the presence of approximately 25% of the cyclic compound perfluorothiophane tetrafluoride, $\ulcorner CF_2(CF_2)_2SF_4 \urcorner$ (XV), as a contaminant. One hundred thirty-seven grams of condensate was collected in a cold trap attached to the still. Redistillation of this material showed it to consist mainly of XIV isomers.

The total amount of mixture of IX and XV obtained by rectification of the Dry Ice condensate was 406 g. A separation of this mixture by careful redistillation was not possible.

Distillation of the purified liquid cell drainings (1416 g.) yielded 659 g. of bis-(nonafluorobutyl) sulfur tetrafluoride (X), b. 90.5–98.5° (100 mm.), $n^{25}D$ 1.2940–1.2948. A middle cut of this material was taken and redistilled at atmospheric pressure to give an analytical sample, b.p. 154.0°, $n^{25}D$ 1.2943. The lower boiling portion of the liquid cell product gave a cut of 318 g. of impure IX, b.p. 67–76°, $n^{25}D$ 1.2720–1.2709. An analytical cut, b.p. 70.5–70.7°, $n^{25}D$ 1.2709, gave a NMR spectrum similar to that for the mixture of IX and XV obtained from the Dry Ice condensate.

Low temperature distillation of the gaseous products condensed in the liquid nitrogen trap led to the identification of sulfur hexafluoride and XIII by infrared analysis.

Di-*n*-butyl Sulfoxide.—Rectification of the stabilized cell drainings (9.5 g. of crude material) yielded 3 g. of colorless distillate, b.p. 69.0–71.0°, $n^{25}D$ 1.2768–1.2770, identified by its NMR spectrum as impure IX, and 4 g. of colorless distillate, b. 155°, $n^{25}D$ 1.2945, identified as X. Low temperature distillation of the Dry Ice–acetone condensate (28 g.) led to the identification of sulfur hexafluoride and XIII.

Thiophane.—Fractionation of 60 g. of insoluble cell drainings, obtained from 100 g. of thiophane, b. 118–120°, gave 8 g. of forerun, b.p. up to 68.0°; 17.0 g. of colorless distillate, b. 68.0–72.5°, $n^{21.5}D$ 1.2768–1.2762; 11 g. of higher boiling material at 72.5–120°; and 16 g. of distillation residue. The material, b. 68.0–72.5°, was redistilled and a middle cut taken at 70.0°, $n^{25}D$ 1.2766, for analysis.

Anal. Calcd. for $C_4F_{12}S$: C, 15.59; F, 74.0; S, 10.41. Found: C, 15.4; F, 74.6; S, 10.0.

Although the analysis of this cut is in fair agreement with the values calculated for perfluorothiophane tetrafluoride (XV), its NMR spectrum showed considerable contamination with VI, IX and possibly $C_3F_7SF_4CF_3$. A cut, b.p. 72.5–73.5°, $n^{21.5}D$ 1.2758, of the higher boiling distillate showed the same NMR resonance peaks as the analytical samples of XV, but with variations in the intensities.

The pot residue was not further investigated.

Thioxane.—Electrofluorination of 78 g. of thioxane (Carbon & Carbide Chemicals Co.) yielded 55 g. of liquid

(11) A. F. Benning and J. D. McHard, U. S. Patent 2,519,760 (1950).

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cell drainings and 1 g. of Dry Ice–acetone condensate. Distillation of the liquid product gave in addition to 25.0 g. of lower boiling cuts 19.0 g. of colorless liquid, b.p. 78.2–78.8°, $n^{25}D$ 1.3019, and left 11 g. of residue. The main fraction was identified as perfluorothioxane tetrafluoride (XI), but infrared analysis indicated the presence of an acid fluoride impurity. The material, therefore, was refluxed for 3 hr. with excess ammonium hydroxide and redistilled to yield the pure XI, b.p. 80.0–80.5°, $n^{25}D$ 1.3015, as indicated by its infrared and NMR analysis. No identification of the Dry Ice condensate or of the lower boiling fractions was attempted.

Di-*n*-butyl Disulfide.—In this run, 1900 g. of HF-insoluble, liquid cell drainings, 2010 g. of Dry Ice condensate and 1044 g. of liquid nitrogen condensate were obtained from 1964 g. of di-*n*-butyl disulfide (Fisher, Highest Purity). Rectification of the stabilized liquid product gave after a forerun of 71.3 g., b. 45–70°, a fraction of 833 g. of crude IX, b. 70–72°, $n^{25}D$ 1.2704, and a fraction of 179.5 g. of X, b.p. 61–62° (21 mm.), $n^{25}D$ 1.2960. The NMR spectrum of the crude IX indicated 10–15% contamination with XV. A careful fractionation of the crude material gave a constantly boiling cut of IX, b.p. 70.5°, $n^{25}D$ 1.2701, which on the basis of its NMR spectrum was free from the cyclic compound XV.

A portion of the liquid nitrogen condensate was screened and found to contain approximately 60% of sulfur hexafluoride and 20% of decafluorobutane (XIII) together with products which attacked mercury and reacted with 20% aqueous potassium hydroxide solution. The remainder of this condensate was not investigated.

Careful rectification of the Dry Ice condensate gave a fraction of XIII, b.p. −12 to −11° (462 mm.), and a cut, b.p. 2–4° (462 mm.), consisting of a mixture of isomeric C_4F_9H (XIV). The NMR spectrum of the XIII showed it to contain approximately 15% of the isomeric decafluoroisobutane, $(CF_3)_3CF$ (XVI). The higher boiling portion of the −78° condensate consisted to a large extent of IX but was not processed further.

Di-*t*-butyl Disulfide.—Electrofluorination of 849 g. of di-*t*-butyl disulfide (Eastman Kodak, Practical Grade, b.p. 198–204°) gave 178 g. of HF-insoluble, liquid product, 502 g. of Dry Ice–acetone condensate and 323 g. of liquid nitrogen condensate. The rectification of the alkali-treated liquid product did not yield any constantly boiling fraction. NMR analysis of several arbitrary cuts indicated complex mixtures of fluorocarbons and derivatives of sulfur hexafluoride containing both normal and branched chains. Low temperature distillation of the gaseous products gave sulfur hexafluoride and decafluorobutane. The NMR analysis of the decafluorobutane fraction showed that the major component was XIII contaminated with 10–15% of XVI.

A second run with 713 g. of di-*t*-butyl disulfide at a lower voltage resulted in the formation of 522 g. of liquid cell drainings, 734 g. of Dry Ice condensate and 317 g. of condensate collected in the liquid nitrogen trap. In spite of the larger amount of liquid cell product from this run, we were unsuccessful in isolating any pure material. The results of the NMR analyses of several arbitrary cuts were similar to those obtained with the material from the run performed at 5.5–5.6 v.

Di-(β-diethylaminoethyl) Disulfide.—Di-(β-diethylaminoethyl) disulfide (62 g., 0.235 mole), b.p. 117° (35 mm.) to 119° (50 mm.), $n^{25}D$ 1.4977–1.4981, yielded 81 g. of liquid cell product and 16 g. of Dry Ice condensate which boiled above room temperature and gave upon fractionation a series of small, unidentified cuts in the range from 23 to 58°. Rectification of the liquid product gave after a forerun of 12.6 g., b.p. 60–120°, a fraction of 30 g. of $(C_2F_5)_2NCF_2CF_2SF_5$ (XII), b.p. 122–124°, $n^{25}D$ 1.2921, and left 15 g. of distillation residue which was not further investigated.

Small amounts of partly fluorinated tar-like products deposited in the cell in all runs. The tars isolated from the electrochemical fluorinations of di-*n*-butyl sulfide and di-*t*-butyl disulfide were analyzed and found to have the approximate compositions $C_{10}H_{11}F_{10}S$, $C_{11}H_6F_{10}S$ and $CH_2F_2S_2$, respectively.

Pyrolysis of Perfluorobutyl Sulfur Pentafluoride.—Perfluorobutyl sulfur pentafluoride (173 g., 0.3 mole) was passed at a rate of approximately 0.25 mole per hour through a metal tube packed with aluminum oxide–aluminum fluoride pellets heated to 650–700°. The effluent gases were condensed in attached Dry Ice–acetone and liquid nitrogen traps. Distillation of the combined condensate (147 g.) gave 44 g. of distillate, b.p. −130 to −75°; 74 g. of material boiling below 25°; and 29 g. of liquid, boiling above 25°. Further fractionation of the higher boiling liquid fraction yielded three distinct cuts: (1) b.p. 56–58°, $n^{20}D$ 1.2513, 3 g.; (2) b.p. 80–83°, $n^{20}D$ 1.2610, 3 g.; (3) b.p. 102–104°, $n^{20}D$ 1.2670, 4 g.; which were identified tentatively by their physical constants as perfluorohexane (reported[12] b.p. 57.23°, $n^{22}D$ 1.2515); perfluoroheptane (reported[13] b.p. 82.51°, $n^{20}D$ 1.26019) and perfluoroöctane (reported[14] b.p. 103.5°, $n^{25}D$ 1.2830) respectively.

Reaction of Perfluorodibutyl Sulfur Tetrafluoride with Aluminum Chloride.—Di-(perfluorobutyl) sulfur tetrafluoride (100 g., 0.183 mole) was cautiously added to 15 g. of anhydrous sublimed aluminum chloride in a 500-ml. flask equipped with stirrer. The temperature of the stirred mixture was slowly raised to 80° where a violent reaction occurred. When the reaction subsided, the material was heated to 100° and held at this temperature for 5 hr. Distillation of the reaction product after drying over Drierite gave 15 g. of a greenish yellow liquid, b.p. 96–97°, $n^{20}D$ 1.3489. Infrared analysis indicated that this material contained a C_4F_9-group and that its spectrum was very similar to that of $(C_4F_9)_2SF_4$ with some major differences in the long wave lengths. Elemental analysis gave 49.2% fluorine and 30.52% chlorine.

Summary of Results

The stability of alkyl sulfides and saturated cyclic sulfur compounds in anhydrous hydrogen fluoride makes these compounds suitable starting materials for conversion by the Simons process to the corresponding fully fluorinated analogs. Similarly to the behavior of dialkyl ethers the sulfides form in hydrogen fluoride more or less colored solutions which exhibit a high degree of conductivity. The conductivity of these sulfide solutions is undoubtedly the result of the formation of a salt-like addition compound between sulfide and hydrogen fluoride of the type $(R_2S—H)^+ F^-$, which ionizes readily in the liquid hydrogen fluoride.

While a considerable part of the sulfide is degraded with rupture of the sulfur–carbon and even the carbon to carbon bonds during the electrolysis, some of the starting material is converted without apparent change of the original skeleton to the fully fluorinated analog. The partial degradation of the starting material was observed in all electrolytic runs to varying degrees and was noticed to increase with increasing voltage; it is definitely responsible for the relatively low conversion of a given organic compound to the fully fluorinated analog.

The sulfur-containing fluorocarbon analogs obtained from dialkyl sulfides were in all runs of the types R_FSF_5, $(R_F)_2SF_4$ and $R_F'SF_4$, where R_F represents a C_nF_{2n+1} group and R_F' represents C_nF_{2n} and is part of a heterocyclic system incorporating the sulfur atom. In no case could any sulfur derivatives of a lower oxidation state be obtained. Although the absolute amount of bis-(heptafluoropropyl) sulfur tetrafluoride (VIII) was, in the run with dipropyl sulfide, larger than that of heptafluoropropyl sulfur pentafluoride (VII), the relative yield of VII on a molar basis was higher than that of VIII. In the runs starting with diethyl and di-*n*-butyl sulfide the yields of R_FSF_5 exceeded by far those of $(R_F)_2SF_4$, even on an absolute weight basis. Cleavage of the carbon–sul-

(12) V. E. Stiles and G. H. Cady, THIS JOURNAL, **74**, 3771 (1952).
(13) H. T. Milton and G. D. Owler, *ibid.*, **74**, 3951 (1952).
(14) R. N. Haszeldine and F. Smith, *J. Chem. Soc.*, 603 (1951).

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fur bonds was thus rather pronounced in all these runs. Whether this cleavage occurs by a rupture of one of the C–S bonds in the original or only partly fluorinated sulfide or whether it is the result of a degradation of the $(R_F)_2SF_4$ cannot be decided on the basis of our experiments; but the formation of partly fluorinated tar-like products in all cell runs might well be interpreted by an at-random attack on the carbon-to-sulfur and carbon-to-carbon bonds of the sulfide at any time during the electrolysis. Rupture of the C–S bond in the original sulfide should lead to gaseous monofluorohydrocarbon derivatives which, however, were not found, at least not in amounts sufficient for identification. The lack of solubility in the hydrogen fluoride and the great stability of the bis-(perfluoroalkyl) sulfur tetrafluorides argues against its degradation in the cell. The presence of the sulfur in its highest valence state in all products, except perhaps the cell tars, suggests that the oxidation of the sulfur occurs in the initial stages of the electrofluorination of the sulfides and disulfides before the fluorination of the carbon chain is completed. In contrast to this observation, Haszeldine and Nyman[15] were able to isolate from an electrofluorination run of thioglycolic acid in addition to $SF_5CF_2CO_2H$ the incompletely fluorinated product $SF_3CF_2CO_2H$ which demonstrates that in this case the substitution reaction on the carbon is completed before the oxidation of the sulfur atom is accomplished.

It was hoped that fluorocarbon derivatives of the type $(R_FSF_4)_2$, the symmetrical bis-(perfluoroalkyl) derivatives of disulfur decafluoride, S_2F_{10}, might be obtainable by the electrofluorination of dialkyl disulfides in hydrogen fluoride. However, in the runs performed with di-*n*-butyl disulfide and di-*t*-butyl disulfide, no indications for the formation of a derivative of S_2F_{10} were obtained. The results of these two runs were rather surprising insofar as in addition to the expected cleavage product, R_FSF_5, the second major, higher boiling reaction product was the SF_6 derivative of the type $(R_F)_2SF_4$. In the run starting with di-*n*-butyl disulfide, the main reaction product was identical with the compound obtained from di-*n*-butyl sulfide.

That the effect of the electrofluorination on a given carbon skeleton of an organic compound is far deeper reaching than that of a simple replacement of hydrogen by fluorine becomes obvious in the examination of the NMR spectra of the gaseous cleavage products from the runs with di-*n*-butyl and di-*t*-butyl disulfide. The decafluorobutane fraction, b.p. about 0°, was in both cases a mixture of the two possible isomers, *n*-C_4F_{10} and $(CF_3)_3CF$, containing 10–15% of the branched isomer. The observed rearrangement of a tertiary carbon arrangement as in $(C)_3{\equiv}C$ to a normal chain does not have a counterpart in the organic radical or carbonium ion chemistry and seems to be unique, but nevertheless general, in the chemistry of fluorocarbons. This type of rearrangement was also observed in the cleavage of substituted pyridines during electrochemical fluorination (see paper II of this series).[16] It is noteworthy that the ratio of normal to branched isomers seemed to be the same, regardless of the structure of the parent compound.

A unique side-reaction, involving an interesting cyclization, was demonstrated by the presence of 20–25% of an impurity in the $C_4F_9SF_5$ (IX) fraction (from di-*n*-butyl sulfide and disulfide) which was identified as perfluorothiophane tetrafluoride (XV) on the basis of the similarity of the additional peaks in the NMR spectrum of the crude IX with those expected and also found in the reaction product obtained from thiophane. A similar cyclization was observed previously[17] in the electrofluorination of $(C_2H_5)_2NCOF$ which resulted in the formation of perfluoro-3-ethyloxazolidine, $C_2F_5\overline{NCF_2CF_2OCF_2}$. It is interesting to note that the IX obtained by electrofluorination of di-*n*-butyl disulfide contained ony 10% of the cyclic impurity XV.

The NMR analysis of the higher boiling products from the electrofluorination of di-*t*-butyl sulfide indicated all of these fractions to be complex mixtures of normal and branched chain fluorinated compounds. Only a small part of the high boiling material consisted of sulfur-containing compounds, the majority was a mixture of fluorocarbons. The presence of fluorocarbons in these fractions, b.p. 70–85° (18 mm.), would require that these fluorocarbons contain at least six to twelve carbon atoms; in other words, they are coupling products of fragments of various chain lengths.

The fluorination of the cyclic 1,4-thioxane and thiophane indicates that a part of the starting material survives the electrolysis without cleavage of the original bonds. The NMR spectrum of the liquid product obtained in the electrofluorination of thiophane, on the other hand, showed absorption peaks which were attributed to the cyclic compound XV and the three possible cleavage products retaining the sulfur atom, *i.e.*, IX, VI and $C_3F_7SF_4CF_3$. The formation of these cleavage products demonstrates the susceptibility of each of the carbon–carbon bonds and of the sulfur-to-carbon bond toward cleavage. The stability of the various bonds in the five-membered ring system appears to be lower than in the six-membered ring of the 1,4-thioxane since the yield of the cyclic, completely fluorinated product is much higher from thioxane than from thiophane.

Since the electrofluorination runs carried out in the 10 and 25 ampere cells (B and C) employed relatively small amounts of starting materials, only the main products were obtained in amounts sufficiently large for identification. From the run with di-*n*-butyl sulfoxide, again only products with the sulfur in its highest oxidation state could be isolated. The products were identical with the two SF_6 derivatives obtained from di-*n*-butyl sulfide, and disulfide. The small-scale eletrofluorination of bis-(2-diethylaminoethyl) disulfide yielded a substantial amount of the perfluoroalkyl sulfur pentafluoride, $(C_2F_5)_2NCF_2CF_2SF_5$, formed by scission of the original S–S bond confirming, thus, the results from the runs with the isomeric dibutyl disulfides.

(15) R. N. Haszeldine and F. Nyman, *J. Chem. Soc.*, 2684 (1956).

(16) T. C. Simmons, F. W. Hoffmann and co-workers, THIS JOURNAL, **79**, 3429 (1957).

(17) T. C. Simmons and F. W. Hoffmann, *Ibid.*, **78**, 5637 (1956).

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The pyrolysis of IX at 650–700° gave small amounts of perfluoroöctane, perfluoroheptane and perfluorohexane with extensive decomposition of the starting material. Recent reports[6,18] on the pyrolysis of similar compounds under less drastic conditions demonstrated the possible free radical nature of these reactions.

The reaction of X with aluminum chloride was violent and could not be controlled effectively to obtain sufficient quantities of product for study.

A paper is in preparation by members of the Spectroscopy Group, Physical Measurements Branch, which will contain a more detailed discussion of the infrared spectra of the compounds reported in this paper. A study of the NMR spectra of these compounds was published recently by Muller, *et al.*[19]

Acknowledgments.—We are indebted to members of the Analytical Research Branch for the elemental analyses, the Spectroscopy Group for determination of the NMR and infrared spectra and to members of the Physical Measurements Branch for determination of some of the physical constants reported.

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[CONTRIBUTION FROM THE CHEMICAL CORPS, CHEMICAL RESEARCH DIVISION, CHEMICAL WARFARE LABORATORIES]

Fluorocarbon Derivatives. II.[1] Cyclic Nitrides

BY THOMAS C. SIMMONS AND FRIEDRICH W. HOFFMANN[2] WITH R. B. BECK, H. V. HOLLER, T. KATZ, R. J. KOSHAR, E. R. LARSEN, J. E. MULVANEY, K. E. PAULSON, F. E. ROGERS, B. SINGLETON AND R. E. SPARKS

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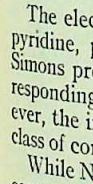
The electrofluorination of some secondary and tertiary cyclic amines in anhydrous hydrogen fluoride by the Simons process[3] was investigated. Pyridine, C-substituted pyridines and morpholine yielded the corresponding fully fluorinated, secondary cyclic nitrides, while N-substituted piperidines and 1-methylmorpholine gave the corresponding tertiary fluorocarbon nitrides. In all cases, considerable amounts of cleavage products also were formed; some of them were isolated in pure state and identified.

Introduction

The electrofluorination of cyclic amines, such as pyridine, piperidine and 1-alkylpiperidines by the Simons process has been reported to yield the corresponding cyclic fluorocarbon nitrides[4,5]; however, the information given in the literature on this class of compounds is rather scanty.

While N-alkyl-substituted piperidines and related compounds, such as N-substituted morpholines, will be converted by electrofluorination in anhydrous hydrogen fluoride to the corresponding, unreactive, cyclic tertiary nitrides (I with X = O or CF_2, and Y = C_nF_{2n+1}), unsubstituted pyridine, piperidine, morpholine, as well as their C-substituted derivatives, are expected to yield the corresponding secondary cyclic nitrides (I with X = O or CF_2, and Y = F). The secondary nitrides, by virtue of their NF group, may possibly undergo chemical reactions allowing thus the introduction of cyclic fluorocarbon nitride groups into other molecules.



I

Only two secondary cyclic fluorocarbon nitrides appear to have been described in the literature, *i.e.*, perfluoropiperidine, obtained either by electrofluorination of pyridine or piperidine[5] or by fluorination of pyridine with cobaltic fluoride[6] and perfluoro(2,6-dimethylpiperidine) prepared by Haszeldine[7] from 2,6-dimethylpyridine with cobalt trifluoride.

The purpose of this investigation was to study the general behavior of cyclic amines in the Simons cell and to characterize the resulting electrofluorination products. Pyridine, 4-alkyl-substituted pyridines and morpholine were chosen as starting materials for the preparation of secondary nitrides. N-methylmorpholine and 1,1′-dipiperidylmethane were expected to yield the corresponding tertiary fluorocarbon nitrides. The physical constants and analyses of the purified secondary and tertiary nitrides obtained in this study are listed in Table I.

Experimental

Electrochemical Fluorinations.—With the exception of N-methylmorpholine, which was electrofluorinated in the 10-amp. cell (B), all other runs were performed in the 50-amp. cell (A) in the manner described previously.[1] The experimental conditions for the electrochemical fluorination runs and the major reaction products are listed in Table II. The crude liquid and gaseous products were subjected to the same preliminary purification with alkali or sodium fluoride, as described for the runs using dialkyl sulfides and disulfides[1] as starting materials.

The hydrogen fluoride employed was commercial grade, anhydrous material (Mathieson Chemical Corp. and Pennsylvania Salt Manufacturing Co.) which was distilled and dried electrolytically[1] before use. The organic starting materials were commercial products with the exception of 1,1′-dipiperidylmethane, b.p. 77.0–79.5° (2.6–2.7 mm.), $n^{25}D$ 1.4810, which was prepared by the method of Knoevenagel[8] from piperidine and formaldehyde.

Only the isolation of the major reaction products from the HF-insoluble liquid cell drainings and the cold trap condensates is described in the following for the various runs employing nitrogen-containing heterocyclic compounds as

(1) Paper I of this series: F. W. Hoffmann and T. C. Simmons with co-workers, THIS JOURNAL, **79**, 3424 (1957).

(2) To whom inquiries about this paper should be directed: Chemical Research Division, Chemical Warfare Labs., Army Chemical Center, Maryland.

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(6) R. N. Haszeldine, *J. Chem. Soc.*, 1966 (1950).

(7) R. N. Haszeldine, *ibid.*, 1638 (1950).

(8) K. Knoevenagel, *B.*, **31**, 2585 (1898).

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TABLE I

FLUOROCARBON DERIVATIVES OBTAINED IN THE SIMONS CELL

Compound	B.p., °C.	$n^{25}D$	d^{25}_4	MR_D[a]	AR_F[b]	Analyses, % Carbon Calcd.	Carbon Found	Fluorine Calcd.	Fluorine Found	Nitrogen Calcd.	Nitrogen Found
Perfluoro-											
-piperidine (II)	49.5[c]	1.2752[d,c]	1.7043[c]	28.56	1.24			73.84	73.6	4.95	4.92
-dipiperidyl (III)	72 (51 mm.)	1.3022	1.870[e]	53.17	1.17	22.74	22.1	71.95	73.2	5.31	4.0
-1-methylpiperidine (IV)	66	1.2754[d]	1.7426	32.86	1.19	21.64	21.3	74.16	73.2	4.21	3.7
-4-propylpiperidine (V)	123.5	1.2965	1.8395	43.55	1.26	22.19	22.2	74.58	74.5	3.24	3.2
-3-ethylhexane (VI)	103	1.2744	1.809[e]	41.67	1.24	21.93	22.2	78.07	78.1		
-4-isopropylpiperidine (VII)	124.5	1.3010[d]	1.8461	43.74	1.27	22.19	22.5	74.58	74.5	3.24	3.3
-morpholine (VIII)	15 (356 mm.)					19.29	19.1	68.67	67.8	5.62	5.2
-1-methylmorpholine (IX)	51	1.2659	1.700[e]	29.43	1.17	20.08	20.1	69.89	69.8	4.68	3.9

[a] Calcd. by the Lorentz–Lorenz equation. [b] The AR_F values were calculated using the following atomic refractions: C, 2.42; N, 2.84; –O, 1.64. [c] B.p. 49–50°, $n^{25}D$ 1.279, d^{25}_4 1.738[6]; b.p. 48°, $n^{20}D$ 1.281, d^{20} 1.744.[5] [d] $n^{20}D$. [e] d^{25}_{25}.

TABLE II

EXPERIMENTAL CONDITIONS OF ELECTROCHEMICAL FLUORINATION RUNS AND PRODUCTS OBTAINED

Organic starting material	Amount used, g.	Concn. in HF, mole %	Volt	Amp. (av.)	Faradays	Products[a] Compound	g.
Pyridine (XII)	2370	4.5	5.5–5.6	26	483	NF_3	491
						II	888
						III	93
						X	2346
1,1′-Dipiperidylmethane (XIII)	1374	2.8	5.3–5.4	22.2	235	NF_3	260
						II	205
						IV	178
						X	1100
4-Propylpyridine (XIV)	1695	5.0	5.4	30.3	295	V	85.7
						VI	754
4-Isopropylpyridine (XV)	1452	5.0	5.4	32.8	299	VII	260
						C_8F_{18} isomers	582
Morpholine (XVI)	675	3.3	5.2	29.4	80.8	VIII	260
						XI	97
N-Methylmorpholine (XVII)	80	2.0	5.0–5.1	4.2	11.4	IX	33.7

[a] The amounts given are those of crude material.

starting materials. In runs where only portions of some of the cell crudes were worked up, the total weight of product given in Table II was calculated on the basis of the data obtained by processing the aliquots.

Pyridine XII.—The electrofluorination of 2370 g. of pyridine (Eastman Kodak, Karl Fischer Reagent) during 508 hr. of operation produced 5799 l. of hydrogen; 548 g. of liquid cell drainings; 3940 g. of Dry Ice–acetone condensate; and 698 g. of liquid nitrogen condensate.

The condensates collected at −78° throughout the run were combined and kept for removal of entrained hydrogen fluoride over sodium fluoride pellets in a refrigerator at about −15°. For distillation, this material was decanted from the sodium fluoride into a precooled round-bottom flask. A portion of 3759 g. was distilled in four batches through a 12-in. vacuum-jacketed column packed with nickel Heli-pak (Podbielniak, Inc.) and the following arbitrary cuts were taken: (1) b.p. up to 45°, 2774 g.; (2) b.p. 45–62°, 674 g.; (3) higher boiling residue, 69 g.

Fraction 1 consisted mainly of perfluoro-*n*-pentane (X). A portion of 681 g. of this fraction was distilled in a low temperature still at 486 mm. and yielded 526 g. of crude X, b. 17–23°, molecular weight 284–293 (calcd. 288). A higher boiling residue (1a) of 68 g. of liquid material remained in the flask; 14% loss during distillation and handling. Careful refractionation of the crude X at 460 mm. pressure gave an analytical sample, b.p. 16°, molecular weight 288 (reported b.p. 29.32°,[9] 29.3°)[10]; this sample melted at −128 to −124° with a plateau at −126 to −125° (reported[9] f.p. −125.65°).

Fraction 2 and the higher boiling residues 3 and 1a were combined (811 g.) and distilled through an 18-in. vacuum-jacketed column packed with nickel Heli-pak to give after 8.2 g. of forerun, b.p. 35–45°, 677.9 g. of crude perfluoropiperidine (II), b. 45–52.5°, and left 78 g. of higher boiling liquid. In an attached Dry Ice–acetone trap was collected 7.2 g. of low boiling material, presumably impure X which was discarded.

Careful refractionation of a 600-g. portion of the crude II through a modified Todd column of approximately 40 plates gave at atmospheric pressure after a small forerun of X and an intermediate fraction (b.p. up to 49.5°) 268.6 g. of pure II, b.p. 49.5–9.9°, $n^{20}D$ 1.2754–1.2759. Redistillation of a portion of this material furnished an analytical sample, b.p. 49.5°, $n^{20}D$ 1.2752, d_{25} 1.7043 (reported, b.p. 49–50°, $n^{25}D$ 1.279, d_{25} 1.738[6]; b.p. 48, $n^{20}D$ 1.281, d_{20} 1.744[5]).

All the material boiling above 52.5° from the previous rectifications was combined and the mixture (670 g.) was fractionated through the Todd column. A major fraction (306 g.), b.p. 67–71°, $n^{25}D$ 1.2756–1.2719, exhibited an infrared spectrum indicating the presence of residual hydrogen. This finding and the elemental analysis of the material suggest it to be a mixture of II and isomeric monohydrides of II.

Anal. Calcd. for $C_5F_{11}N$: C, 21.21; F, 73.82; N, 4.97. Found: C, 21.2; F, 72.1; N, 5.0. Calcd. for $C_5F_{10}HN$: C, 22.65; F, 71.68; N, 5.28.

Further distillation of the remaining material under reduced pressure yielded a constantly boiling fraction of 93 g. of a colorless, mobile liquid, b.p. 71–72° (51 mm.), which was tentatively identified by its analysis and nuclear magnetic resonance (NMR) spectrum as perfluoro-1,1′-dipiperidyl (III). The analytical sample was taken at 72° (51 mm.).

The liquid nitrogen trap condensate was evaporated and

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the gas passed successively through large drying tubes filled with sodium fluoride pellets and Drierite, respectively. The recondensed gas was then distilled in a low temperature still to yield 491 g. of nitrogen trifluoride contaminated with approximately 5% of carbon tetrafluoride, as determined by mass spectrometric analysis. This material boiled at −128 to −122° and showed a molecular weight range of 70 to 72 (calcd. 71) (reported for NF_3,[11] b.p. −129.07°).

1,1'-Dipiperidylmethane (XIII).—This run, performed in Cell A with an electrode pack of alternating iron cathodes and nickel anodes, yielded 130 g. of insoluble cell drainings; 1465 g. of Dry Ice–acetone condensate; and 260 g. of condensate in a liquid nitrogen trap. The latter condensate was screened and found to consist mainly of nitrogen trifluoride, b.p. −129 to −126°, molecular weight 74 (calcd. 71).

Distillation at atmospheric pressure of a portion of 136 g. of the Dry Ice condensate, after passing over sodium fluoride pellets, gave 69.3 g. of X, b. 28–30°, and left 62.1 g. of material boiling above 30°. In an attached cold trap was collected 7 g. of lower boiling material, presumably X, which was discarded. The remainder of the Dry Ice condensate was treated in the same manner. The material boiling above 30°, was combined with the liquid cell drainings and the mixture stabilized in the usual manner with aqueous potassium hydroxide. The dried, crude liquid product (470 g.) was then fractionated at atmospheric pressure to yield 97 g. of a mixture of X and II, b. 32–37.5°; 115 g. of II, b.p. 47.5–51°, $n^{20}D$ 1.2754; 75 g. of a mixture of II and perfluoro-1-methylpiperidine (IV); 143 g. of IV, b. 63–66°, $n^{25}D$ 1.2752–1.2754; and 21 g. residue (4% distillation loss). An analytical sample of IV was taken at 66°, $n^{25}D$ 1.2754, d_{25} 1.7426 (reported[4] 65–65.5° (730 mm.), $n^{24}D$ 1.275, d_{24} 1.760). The identity of IV was confirmed by its NMR spectrum.

4-*n*-Propylpyridine (XIV).—Commercial XIV (Reilly Tar & Chemical Corp.) was fractionated through a 3-ft. heated column packed with glass helices and the fraction b. 185.5–187.5° collected.

The electrofluorination of 1695 g. of XIV in cell A with an electrode pack of alternating nickel anodes and iron cathodes gave 1795 g. of liquid cell drainings, 295 g. of Dry Ice–acetone condensate, and 300 g. of liquid nitrogen condensate. The condensate in the liquid nitrogen trap consisted mainly of nitrogen trifluoride which was identified by its infrared spectrum.[12,13] The material condensed at −78° boiled in the range from −50 to +17° and might have contained C_3 and C_4 cleavage products; it was not investigated further.

The liquid cell drainings were stabilized in the usual manner and a 1237-g. portion of the dried material (1515 g., 84.4% recovery) was fractionated through the Todd column to give 15 g. of forerun, b.p. 35–58°, and 30 g. of a colorless liquid distillate, b.p. 58–59°, $n^{20}D$ 1.2578, possibly C_6F_{14} (reported for perfluoro-2-methylpentane,[14] b.p. 57.7°, $n^{25}D$ 1.2564). Further fractionation of the remaining crude product gave in addition to several intermediate, unidentified cuts 754 g. of perfluoro-3-ethylhexane (VI), b.p. 102–103°, and 85.7 g. of perfluoro-4-*n*-propylpiperidine (V), b.p. 121–124°; both yields are based on the total amount (1515 g.) of crude stabilized cell drainings.

The NMR spectrum of an analytical sample of VI, b.p. 103.0°, $n^{25}D$ 1.2744, confirmed its identity. A middle cut of V, b.p. 123.5°, was taken for elemental and NMR analysis.

4-Isopropylpyridine (XV).—Commercial XV (Reilly Tar & Chemical Corp.) was used without further purification as starting material in this run which yielded 1980 g. of HF-insoluble liquid product; 282.1 g. of Dry Ice–acetone trap condensate; and 280 g. of material condensed by liquid nitrogen. The condensate collected at −195° was mostly nitrogen trifluoride. No attempt was made to work up the Dry Ice condensate from this run.

A portion of 1538 g. of the crude, liquid cell product was stabilized in the usual manner and the dried recovered material (1378 g., 89.6% recovery) was fractionated at atmospheric pressure to yield the following main fractions: (1) crude perfluoroheptanes, colorless liquid, 74 g., $n^{20}D$ 1.2713; (2) crude VI, 452 g., b. 100–104°, $n^{20}D$ 1.2780; (3) colorless liquid, 305 g., b.p. 109–111°, $n^{20}D$ 1.2880; (4) crude perfluoro-4-isopropylpiperidine (VII), 226 g., b.p. 122–128°, $n^{20}D$ 1.3010; and 108 g. pot residue (4.2% distillation loss). The forerun, several intermediate cuts and the residue were not further investigated.

Fraction 1, which boiled in the range expected for perfluoroheptanes, is possibly a mixture of C_7F_{16} isomers (reported for perfluoro-2,2,3-trimethylbutane,[15] b.p. 82°, $n^{30}D$ 1.2676 with $\Delta n/\Delta t = -0.00045$, $n^{20}D$ 1.2712 calcd.).

The NMR spectrum of fraction 2 showed it to contain the expected perfluoro-2-methyl-3-ethylpentane only as a minor component; the major part of this fraction gave a spectrum identical with that of VI obtained by electrofluorination of XIV. The spectrum was taken on an analytical cut, b.p. 101.5°, $n^{25}D$ 1.2783. The calculated total yield of this material in the crude cell drainings was 582 g.

Fraction 3 could not be identified with certainty. The rather complex NMR spectrum seems to indicate the presence of a compound having the structure $(CF_3)_2CFCF(C_2F_5)CF_2CF_2NF_2$ or $(CF_3)_2CFCF(C_2F_5)CF_2NFCF_3$.

Anal. Calcd. for $C_8F_{19}N$: C, 20.4; F, 76.6; N, 2.97. Found: C, 22.1; F, 76.0; N, 1.8.

Analytical sample, b.p. 110°, $n^{20}D$ 1.2885, $n^{25}D$ 1.2864, d_{25} 1.8635, MR_D found 45.26, AR_F 1.22, MR_D calcd. 45.04 (using AR_F 1.22).

Fraction 4 (260 g. total yield) (analytical sample, b.p. 124.5°, $n^{20}D$ 1.3010) was identified by its NMR spectrum as VII.

Morpholine (XVI).—XVI (675 g.) (Eastman Kodak, Yellow Label) yielded 644 g. of condensate in the Dry Ice–acetone cooled trap and 93 g. of material condensed by liquid nitrogen. No HF-insoluble liquid cell drainings were obtained in this run.

The condensate collected at −78° was evaporated from the traps and the gas bubbled through 10% aqueous potassium hydroxide to remove small amounts of acidic impurities. The washed gas was passed successively through small columns of sodium fluoride pellets and granular Drierite, respectively, and recondensed with Dry Ice–acetone. Fractionation of the condensate through a low temperature still gave after a small forerun 96.9 g. of perfluorodiethyl oxide (XI), b.p. 3.0–4.5° (730 mm.) (reported[16] b.p. 1.0°), molecular weight 248 (calcd. 254), which was identified by its NMR spectrum. A subsequent cut, b.p. 4.5–30°, of 100 g. consisted of a mixture of XI and perfluoromorpholine (VIII). Further distillation of the remaining charge yielded 260 g. of a colorless liquid, b.p. 30.3–33.0° (730 mm.), b.p. 17–21° (455 mm.), molecular weight 248–253 (calcd. 249), which was identified by its analysis and NMR spectrum as VIII. No attempt was made to identify the contents of the liquid nitrogen trap.

1-Methylmorpholine (XVII).—XVII (80 g., 0.79 mole) (Eastman Kodak, Yellow Label) yielded 7 g. of HF-insoluble, liquid product and 55 g. of Dry Ice–acetone condensate which was found to boil above room temperature. No liquid nitrogen-cooled trap was attached to the cell in this run.

Fractional distillation of 55 g. of the combined products, after treatment with calcium sulfate and sodium fluoride, through a 25-cm. column packed with nickel Heli-pak gave 33.7 g. perfluoro-1-methylmorpholine (IX), b.p. 50.0–52.0°, $n^{25}D$ 1.2679–1.2659 (analytical sample, b.p. 51.1–51.3°, $n^{25}D$ 1.2659), which was identified by its elemental analysis and NMR spectrum. A small forerun and the column hold-up were not investigated further.

Summary of Results

The results of the electrochemical fluorination of the cyclic amines were comparable in many respects to those obtained in the electrofluorination of alkyl sulfides. The starting materials formed in the electrolyte colored solutions which exhibited a high degree of conductivity. These amine–hydrogen fluoride solutions showed boiling points considerably higher than anhydrous hydrogen fluoride al-

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lowing, in general, the cell temperatures to rise during the electrolysis to 25–35° and in some cases even to 40° (in the runs with XIV and XV).

The electrofluorination runs gave, with the exception of the run with dipiperidylmethane, the fully fluorinated analogs and in all cases fluorinated cleavage products of the organic starting materials. The electrochemical fluorination of pyridine (XII) yielded, as expected, perfluoropentane (X), nitrogen trifluoride contaminated with about 5% of carbon tetrafluoride and as the main product perfluoropiperidine (II). The formation of perfluoro-1,1′-dipiperidyl (III) from XII is noteworthy. Condensations of this type occur possibly in all electrofluorinations but, in general, the resulting products are not formed in small runs in amounts sufficient for isolation and identification.

The electrofluorination of 4-*n*-propylpyridine (XIV) yielded some of the fully fluorinated analog V which according to its NMR spectrum appeared to be free of isomers. The NMR analysis of the perfluoro-3-ethylhexane (VI) fraction which had been formed in this run by rupture of the two carbon-to-nitrogen bonds indicated the absence of isomers but showed contamination with a small amount of other impurities.

The isomeric 4-isopropylpyridine (XV) gave in an analogous manner perfluoro-4-isopropylpiperidine (VII) which, however, appeared to contain V as a contaminant. The NMR analysis of the cleavage product C_8F_{18} from this run indicated the major component to be VI with some perfluoro-2-methyl-3-ethylpentane, $(CF_3)_2CFCF(C_2F_5)_2$, present as an impurity. A similar conversion of a branched carbon skeleton to a straight chain has been observed in the electrochemical fluorination of *t*-butyl disulfide[1] which yielded as one of the cleavage products a perfluorobutane fraction consisting of approximately 85–90% of perfluoro-*n*-butane and 15–10% of perfluoroisobutane.

The only material which failed to give the perfluorinated analog was dipiperidylmethane (XIII). Only the cleavage products II, IV and X were obtained. It is interesting to note that in this run as well as in the electrofluorination of XIV, where the electrode pack consisted of alternating iron cathodes and nickel anodes, none, or at best only a relatively small yield, of the fully fluorinated analogs was formed. The amount of tarry materials obtained in the cells during these runs was correspondingly large. The electrochemical fluorination of XV employing an all-nickel electrode pack gave a larger yield of perfluorinated analog than the run with XIV using alternating iron and nickel electrodes (260 g. as compared to 85.7 g.). This observation was rather surprising since one might expect the more branched carbon skeleton of XV to be more susceptible to degradation than that of XIV.

The electrofluorination of morpholine (XVI) resulted in a relatively good yield of perfluoromorpholine (VIII) and a considerable amount of perfluorodiethyl oxide (XI) indicating extensive cleavage of the C–N bonds of the starting material. Similar results were obtained with 1-methylmorpholine (XVII) which yielded, as expected, the fully fluorinated analog IX and the cleavage product XI.

A detailed discussion of the NMR and infrared spectra of the various compounds obtained in this study will be published by members of the Spectroscopy Group, Physical Measurements Branch, of these laboratories in a forthcoming paper.

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[Contribution from the Department of Chemistry, University of California at Los Angeles]

Neighboring Carbon and Hydrogen. XXIX. $\rho-\sigma$ Analysis of Acetolysis of Substituted Neophyl Arylsulfonates

By R. Heck and S. Winstein

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In acetolysis of neophyl *p*-bromobenzenesulfonate, ionization is exclusively anchimerically assisted, only neighboring phenyl participating. Rates of aryl-assisted ionization of a series of substituted neophyl *p*-bromobenzenesulfonates have been measured and correlated with the aid of the Hammett $\rho-\sigma$ relation. Omitting the *p*-MeO group, log *k* of acetolysis is approximately linear in σ with a slope ρ of -3.65. The value of log *k* for the *p*-MeO substituent falls substantially above the line through the other points. By using σ^+-values of Brown and Okamoto which reflect a blend of inductive and resonance influences of the substituents more appropriate for an electron-demanding reaction, the *p*-MeO group may be treated along with the other substituents. The slope of the log *k* *vs.* σ^+ line is -2.96.

In connection with another investigation,[1] it became necessary to prepare *p*-benzhydrylneophyl alcohol (IX). The synthetic route employed involved preparation of the *p*-bromo- and *p*-carbomethoxyneophyl alcohols (III) and (V). Since these were available and the *p*-carbomethoxyneophyl alcohol was converted easily to the *p*-methyl analog, we were prompted to extend the previous study[2] of the effect of substituents on solvolysis rate of neophyl arylsulfonates. The results obtained and their analysis with the aid of Hammett's $\rho-\sigma$-relation[3] are given in the present article

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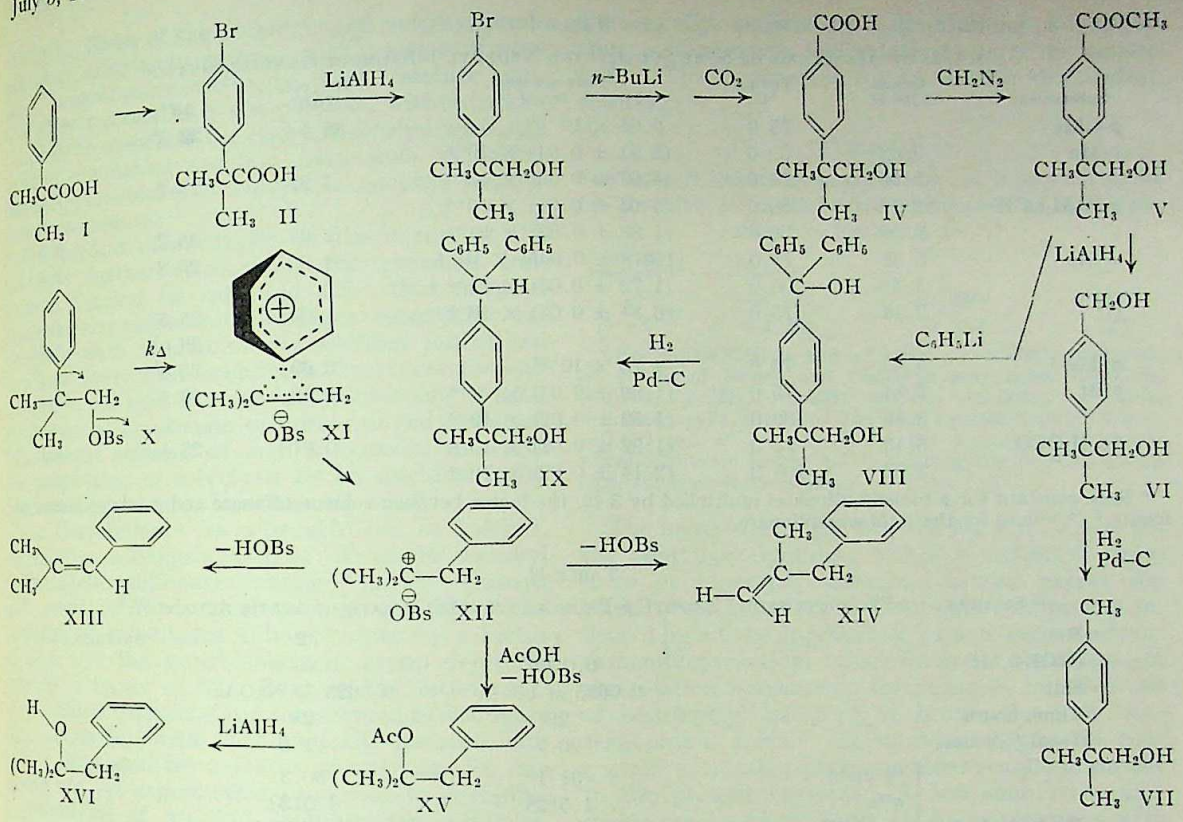

Substituted Neophyl Bromobenzenesulfonates.—All of the *p*-bromobenzenesulfonates required in the present study were prepared by the usual method from the corresponding alcohols. The preparation of several of the required alcohols began with the bromination of α,α-dimethylphenylacetic acid (I) which was available from the nitrile obtained by the alkylation of benzyl cyanide with sodamide and methyl iodide. From the bromination was obtained the α,α-dimethyl-*p*-bromophenylacetic acid (II). Lithium aluminum hydride reduction of the latter yielded *p*-bromoneophyl alcohol (III).

To confirm the *p*-position of the bromine atom in the brominated acid II and alcohol III, oxidation to *p*-bromobenzoic acid was carried out. Oxidation of the bromophenylisobutyric acid II with boiling alkaline potassium permanganate proceeded very slowly and yielded only a trace of pure *p*-bromobenzoic acid. However, much more satisfactory results were obtained by treatment of the bromoneophyl alcohol III with thionyl chloride and oxidizing the product with alkaline permanganate. Evidently, the reaction of the alcohol III with thionyl chloride proceeds with Wagner–Meerwein rearrangement, the aryl group migrating so that tertiary chloride and related olefins are produced. Oxidation of the whole crude reaction mixture gave a substantial yield of pure *p*-bromobenzoic acid.

p-Bromoneophyl alcohol (III) was converted to the aryllithium derivative, though in poor yield, by reaction with two equivalents of *n*-butyllithium in ether solution. Carbonation yielded *p*-carboxyneophyl alcohol (IV) which was converted to *p*-carbomethoxyneophyl alcohol (V) with diazomethane. Reduction of this ester with lithium aluminum hydride yielded *p*-hydroxymethylneophyl alcohol (VI). Hydrogenolysis of the latter over palladium-on-charcoal led to *p*-methylneophyl alcohol (VII).

The reaction of 3 equivalents of phenyllithium with *p*-carbomethoxyneophyl alcohol (V) gave *p*-diphenylhydroxymethylneophyl alcohol (VIII), hydrogenolysis of the latter leading to *p*-benzhydrylneophyl alcohol (IX).

The remaining new alcohol, *m*-methylneophyl alcohol, was prepared by the lithium aluminum hydride reduction of the corresponding acid. This acid, α,α-dimethyl-*m*-tolylacetic acid, was prepared by the hydrolysis of the nitrile which, in turn, was obtained by alkylating *m*-methylbenzyl cyanide with sodamide and methyl iodide.

Acetolysis.—All of the bromobenzenesulfonates investigated in the present work obeyed good first-order kinetics in acetolysis, the measured first-order rate constants being summarized in Table I, which also includes a comparison of the rates with those of three neophyl derivatives previously investigated.[2,4]

In order to verify[4,5] the course of acetolysis of the reference compound, neophyl *p*-bromobenzenesulfonate (X), the products of solvolysis of 0.05 *M* material in acetic acid, 0.06 *M* in lithium or sodium acetate, were investigated. Treatment of the reaction product with lithium aluminum hydride and

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TABLE I

RATES OF ACETOLYSIS OF SOME SUBSTITUTED NEOPHYL *p*-BROMOBENZENESULFONATES

Substituent	Concn., $10^2 M$	Temp., °C.	Rate constant, sec.$^{-1}$	Rel. rate 75.0°	ΔH^*_{75}	ΔS^*_{75}
p-OMe	..	75.0	6.05×10^{-3}[a]	88.5	23.2[b]	−4.4[b]
p-Me	3.02	50.0	$(2.91 \pm 0.04) \times 10^{-5}$			
	2.96	75.0	$(4.97 \pm 0.05) \times 10^{-4}$	7.27	24.7	−3.1
p-$(C_6H_5)_2CH$	2.16	50.0	$(1.01 \pm 0.01) \times 10^{-5}$			
	2.66	75.0	$(1.83 \pm 0.03) \times 10^{-4}$	2.68	25.2	−3.5
m-Me	3.32	75.0	$(1.318 \pm 0.005) \times 10^{-4}$	1.93	25.8	−2.4
	3.45	100.0	$(1.72 \pm 0.03) \times 10^{-3}$			
H[4]	2.14	75.0	$(6.84 \pm 0.03) \times 10^{-5}$	1.00	25.5	−4.6
					26.0[b]	−5.7[b]
m-MeO	3.42	75.0	4.75×10^{-5}[a]	0.69	25.4[b]	−8.1[b]
p-Br	2.84	75.0	$(1.09 \pm 0.01) \times 10^{-5}$	0.16	26.5	−5.4
	3.16	100.0	$(1.52 \pm 0.02) \times 10^{-4}$			
p-CH_3OCO	3.13	75.0	$(1.32 \pm 0.01) \times 10^{-6}$	0.019	28.1	−5.1
	2.82	100.0	$(2.14 \pm 0.02) \times 10^{-5}$			

[a] Rate constant for *p*-toluenesulfonate[2] multiplied by 3.42, the factor between toluenesulfonate and *p*-bromobenzenesulfonate.[4] [b] Values for the *p*-toluenesulfonate.

TABLE II

SUMMARY OF PRODUCTS FROM NEOPHYL *p*-BROMOBENZENESULFONATE IN ACETIC ACID AT 75°

Run		1	2	Average
(ROBs), *M*		0.0508[a]	0.0508	
Salt		0.0625 *M* LiOAc	0.0625 *M* NaOAc	
Time, hours		28	28	
Total % recov.		90.7	91.8	91.3
Product alcohol	% yield	31.1	30.3	30.7
	$n^{25}D$	1.5128	1.5120	
	m.p., °C.	25–26	24.5–25.5	
	b.p., °C. (mm.)	65–68 (1.5)	65–68 (2)	
	% neophyl	*ca.* 0.5–0.75	*ca.* 1	*ca.* 0.8
Product olefin	% yield	59.6	61.5	60.6
	$n^{25}D$	1.5207	1.5200	
	ϵ at $\lambda = 244$ mμ	6912	6880	
	% conjug. (XIII)	49,[b] 52[c]	52[c]	51
	% unconjug. (XIV)	51,[b] 48[c]	48[c]	49
Total product compn.	% olefin	65.7	66.9	66.3
	% rearr. alc.	34.1	32.8	33.4
	% neophyl alc.	0.2	0.3	0.3

[a] Three times recrystallized bromobenzenesulfonate was employed. [b] From the $n^{25}D$, using $n^{25}D$ 1.5364 for XIII and 1.5057 for XIV.[6] [c] From ultraviolet absorption, using ϵ 14,000 for XIII and 77 for XIV in isooctane.[6]

subsequent chromatography gave rise to olefin and alcohol fractions.

In quantitative hydrogenation, a sample of the olefin product consumed the correct quantity of hydrogen calculated for a mixture of β,β-dimethylstyrene (XIII) and 1-phenyl-2-methyl-2-propene (XIV). Also, the hydrogenation product proved to be pure isobutylbenzene, the infrared spectrum being identical with that of a pure standard. The analysis of the olefin product for conjugated and unconjugated components, XIII and XIV, respectively, could be based on either ultraviolet absorption spectrum or refractive index, both methods agreeing well. As summarized in Table II, the olefin proved to be 51% conjugated (XIII) and 49% unconjugated (XIV).

The alcohol product, m.p. 25–26°, was essentially pure rearranged tertiary alcohol XVI, the authentic synthetic material having m.p. 25.5–26.5°. There was some indication from the infrared spectrum of a trace of unrearranged material in the alcohol product. The alcohol product displayed an infrared spectrum nearly identical with that of authentic benzyldimethylcarbinol (XVI), except for the presence of slightly high absorption at 1000–1075 cm.$^{-1}$ and slightly low absorption at 1125–1250 cm.$^{-1}$. Since neophyl alcohol has a very strong band at 1030 cm.$^{-1}$ and is relatively transparent at 1125–1250 cm.$^{-1}$, it seems probable that a small amount of neophyl alcohol is present in the acetolysis product. By preparing a synthetic mixture containing 1.6% neophyl alcohol in the tertiary alcohol and comparing its spectrum with that of the solvolysis product, it was possible to estimate that the product alcohol contained 0.5–0.75% neophyl alcohol.

While the indications are that the over-all solvolysis product contains *ca.* 0.2% neophyl alcohol, it is not clear what its mode of formation is. Some of it may arise during lithium aluminum hydride treatment of the reaction product, since the latter would contain 0.1% of unreacted neophyl bromobenzenesulfonate after ten solvolysis half-lives

(6) S. J. Lapporte, unpublished work.

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(28 hr.). Some of the unrearranged neophyl product may arise from second-order reaction of neophyl bromobenzenesulfonate with acetate ion. For these reasons, it is not possible, without more controls, to associate the neophyl alcohol with any definite competing reaction path such as anchimerically unassisted solvolysis of neophyl bromobenzenesulfonate.

The present observations on the nature of the products further strengthens the previous conclusion,[2,5] based on rate and $\Delta S^{\ddagger}$, that neophyl bromobenzenesulfonate solvolyzes essentially exclusively with anchimerically assisted ionization. It seems likely that anchimerically unassisted solvolysis would lead to a product containing at least a substantial proportion of unrearranged material. The virtual absence of such a material indicates the proportion of solvolysis by an anchimerically unassisted route must be extremely small.

ρ-σ Correlation.—As is brought out in Table I, the relative solvolysis rates at 75° of the neophyl bromobenzenesulfonates studied in the present and previous[2] work cover a range of 4500. The *p*-methoxyl substituent enhances rate by a factor of 88.5 and the *p*-carbomethoxy group depresses rate by a factor of 52. Even in the latter case, aryl-assisted ionization can be assumed to dominate the acetolysis; with anchimerically assisted ionization depressed by a factor of only *ca.* 50, one would not yet expect other processes, so negligible in solvolysis of neophyl bromobenzenesulfonate, to be too serious. On this basis, one can expect sufficient uniformity of mechanism of solvolysis of the series of neophyl bromobenzenesulfonates to warrant application of the Hammett relation[3] (1) to the rate data.

As is clear from Fig. 1, the plot of log k *vs.* σ is roughly linear, with the point for *p*-OCH_3 lying

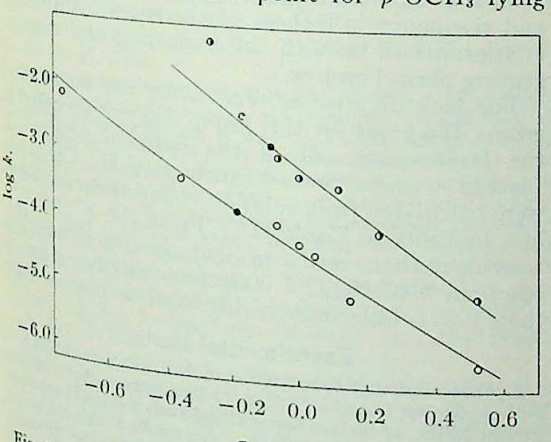

Fig. 1.—Plot of log k for acetolysis of neophyl *p*-bromobenzenesulfonates at 75° *vs.* σ: ◑, 1 + log k *vs.* σ; ○, log k *vs.* σ^+; ●, *p*-$(C_6H_5)_2CH$ group.

substantially above the line outlined by the other points. As summarized in Table III, after omitting the *p*-OCH_3 group, the remaining points fit the Hammett linear relation (1) with a slope ρ equal to −3.65, the probable error of the fit being 0.085 in log k. In line with the nature[5] of the anchimerically assisted rate-determining ionization step, ρ is negative and relatively large in magnitude. This is expected for an electron-demanding reaction.

TABLE III

SUMMARY OF LEAST SQUARES FITS OF LOG k OF ACETOLYSIS OF NEOPHYL *p*-BROMOBENZENESULFONATES TO THE HAMMETT ρ-σ RELATION AT 75°

Substit. constant[a,b]	log k^0	ρ	r^c
σ^{3b}	−4.037	−3.650	0.085[d]
σ^+	−4.281	−2.959	.125

[a] For *p*-$COOCH_3$, σ and σ^+ equal to +0.522 employed; σ^+ values of Brown and Okamoto were used: *p*-OCH_3, −0.764; *p*-CH_3, −0.306; *m*-CH_3, −0.0652; *m*-OCH_3, −0.0465; *p*-Br, 0.148. [b] The least squares lines yield σ = −0.082 and σ^+ = −0.184 for the *p*-$(C_6H_5)_2$ CH group. [c] Probable error in log k. [d] Omitting the *p*-OCH_3 group from the least-squares line.

The upward curvature of the log k *vs.* σ plot for the point corresponding to the *p*-methoxyl group is to be expected, since one cannot expect the blend[7-10] of inductive and resonance influences reflected by σ to be appropriate for a strongly electron-demanding reaction. Such failure of the Hammett ρ-σ-relation is common, for example, in solvolysis of benzhydryl halides[11] or brominolysis of benzeneboronic acids.[12] It is common also in connection with other rearrangement reactions similar to the present example. A few such rearrangements are listed in Table IV for comparison with the present work.

Table IV includes examples of aryl migration to carbon or oxygen, as well as a number of cases of migration to nitrogen. The latter include the Beckmann, Lossen, Hofmann and Stieglitz rearrangements, as well as Schmidt reactions of benzoic acids and 1,1-diarylethenes. Some of the applications of the Hammett relation are to rate data. When the substituent is in the migrating phenyl group, the Hammett relation is supposed to account for the modification of the inductive and anchimeric effects[5] of the phenyl group by the substituent. When the substituent is on a nonparticipating phenyl, the Hammett relation is supposed to account for the modification of the inductive and any conjugative effects[5] of the phenyl group.

Some of the applications of the Hammett relation in Table IV are to relative migration aptitudes. If we take anchimerically assisted ionization of 2,2-diphenylethyl[5,13] toluenesulfonates XV and XVI for illustration, the meaning of the plot of log of relative migration aptitude *vs.* σ may be clarified

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(8) P. B. D. de la Mare, *J. Chem. Soc.*, 4450 (1954).

(9) H. C. Brown and Y. Okamoto, Page 59-O of Abstracts, American Chemical Society meeting, Atlantic City, N. J., September 16–21, 1956.

(10) G. S. Hammond and F. T. Fang, Page 87-O of Abstracts, American Chemical Society meeting, Atlantic City, N. J., September 16–21, 1956.

(11) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 144.

(12) (a) H. G. Kuivila and A. R. Hendrikson, THIS JOURNAL, **74**, 5068 (1952); (b) ref. 11, p. 353.

(13) J. G. Burr, Jr., THIS JOURNAL, **75**, 5008 (1953); *Chemistry &*

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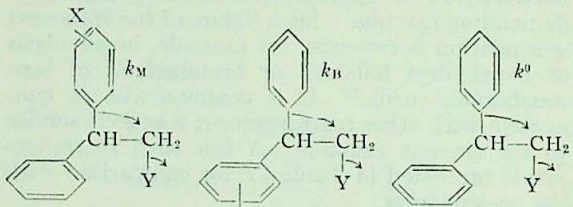
TABLE IV

SUMMARY OF APPLICATION OF HAMMETT'S RELATION TO CERTAIN REARRANGEMENTS

Reaction series	Ref.	$-\rho_M$	$-(\rho_M - \rho_B)$	$-\rho_B$
$XC_6H_4C(CH_3)_2CH_2OBs$, AcOH, 75.0°		3.7		
$XC_6H_4CH(C_6H_5)CH_2OTs$, AcOH, 99.5°	13	4.2		2.0
$XC_6H_4CH(C_6H_5)CH_2OH$, P_2O_5, xylene	14		2.3	
$XC_6H_4C(CH_3)_2OOCOC_6H_4NO_2$, AcOH, 25.0°	15	5.1		
$(XC_6H_4)(C_6H_5)C{=}NOC_6H_2(NO_2)_3$, CCl_4, 90.8°	16	4.3		1.9
$XC_6H_4CONHOCOC_6H_5$, aq. NH_3, 30°	17	2.6		
$XC_6H_4CONHBr$, aq. NaOH, 30°	18	2.5		
XC_6H_4COOH, HN_3, H_2SO_4, $Cl_2C{=}CHCl$, 40°	19a	2.0		
$XC_6H_4CN_2(C_6H_5)(CH_3)$, H_2SO_4, C_6H_6	20		2.8	
$(XC_6H_4)(C_6H_5)C{=}CH_2$, HN_3, H_2SO_4	19b		2.1	
$(XC_6H_4)(C_6H_5)_2CNHOH$, PCl_5, C_6H_6	21		1	

in the following way. To the extent that the Hammett relation will account successfully for the rates of the anchimerically assisted rate-determining ionizations, we may write relation (2) for k_M, where the substituent is in the migrating phenyl (XVM), and relation (3) for k_B, where the substituent is in the phenyl group which remains



XV M X XV B XVI

behind (XVB). In these relations, k^0 is half the rate constant of ionization of 2,2-diphenylethyl toluenesulfonate (XVI).

$$\log k_M = \log k^0 + \rho_M\sigma \quad (2)$$

$$\log k_B = \log k^0 + \rho_B\sigma \quad (3)$$

$$\log (k_M/k_B) = (\rho_M - \rho_B)\sigma \quad (4)$$

The relative migration aptitude of the substituted phenyl group, defined equal to the ratio k_M/k_B, is then given by relation 4. The latter is a linear relation between log of relative migration aptitude and σ, the proportionality constant being $(\rho_M - \rho_B)$. The situation is similar for cases where aryl does not participate in the rate-determining step but migrates at a later stage of the reaction. For such cases, k_M, k_B and k^0 are rate constants for the reaction steps involving aryl shift.

In most of the applications of the Hammett relation in Table IV, considerable tendency for curvature in the log k or log (k_M/k_B) *vs.* σ plot is evident. In such cases, the values of ρ listed are either for electron-withdrawing substituents or for a range of substituents including none more electron-supplying than p-CH_3. Within a factor of *ca.* 2, the various ρ_M values, some of them quite rough, are similar for all the rearrangements listed.

By choosing new σ values[7,9,10] which do reflect a blend of inductive and resonance influences more appropriate to electron-demanding reactions, one can hope to treat the present reactivity data more satisfactorily with relation 1. The set of σ values, labeled σ^+ values, which we have employed for this purpose is one derived by Brown and Okamoto[9,22] from rates of hydrolysis of substituted phenyldimethylcarbinyl chlorides in aqueous acetone. The plot of log k of acetolysis of the neophyl bromobenzenesulfonates *vs.* σ^+ is shown in Fig. 1, from which it is evident that the point for p-OCH_3 comes closer to fitting on the same line with the other substituents. The σ^+ value employed for p-OCH_3 somewhat over-corrects the present situation, since the p-OCH_3 point now falls below the line. The least-squares fit of the data to relation 1, including the p-OCH_3 point, is summarized in Table III. By using σ^+ values, the fit of the data including the p-OCH_3 point is comparable to that obtained using σ values but omitting p-OCH_3.

In principle, the fit of the other rearrangements in Table IV by the Hammett relation might be improved by the use of σ^+ instead of σ-values. However, the available data are too scanty in most cases to make a thorough recalculation worthwhile. In general, the σ^+ values seem to correct too far to account well for the p-OCH_3 group. If sufficient data were available, it would probably be desirable, in accounting for relative migration aptitudes, to use different σ values in equations 2 and 3, since it is unlikely that the same blend of inductive and resonance influences of the substituent group is appropriate in both the migrating and non-migrating phenyl groups.

For lack of σ or σ^+ values for the benzhydryl group, the point for this group was not included in the least-squares fit of the data to relation 1. Instead, σ and σ^+ values for the p-$(C_6H_5)_2CH$ group were calculated from relation 1, and these are listed in a footnote to Table III. From the σ^+ value, it is evident that, in the present electron-demanding reaction, p-$(C_6H_5)_2CH$ is electron-supplying, less so than p-CH_3 but considerably more so than m-CH_3.

Experimental Part

β-p-Bromophenylisobutyric Acid.—A mixture of 133 g. of β-phenylisobutyric acid, 135 g. of bromine and 0.2 g. of iron wire in 150 cc. of carbon tetrachloride was refluxed overnight. After being cooled, the solution was washed with cold dilute acid and then water. Finally, the product was extracted with a solution of 50 g. of sodium hydroxide in 500 cc. of water. Acidification of the basic extract and cooling gave rise to the crude acid. Four crystallizations from aqueous methanol yielded 118 g. of acid, m.p. 124–125.5°.

Anal. Calcd. for $C_{10}H_{11}O_2Br$: C, 49.40; H, 4.56. Found: C, 49.42; H, 4.79.

The oxidation of β-p-bromophenylisobutyric acid with boiling basic potassium permanganate solution proceeded very slowly, and only a trace of pure p-bromobenzoic acid was obtained.

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(15) K. Nelson, unpublished work.

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(18) C. R. Hauser and W. B. Renfrow, Jr., THIS JOURNAL, **59**, 121 (1937).

(19) (a) L. H. Briggs and J. W. Lyttleton, *J. Chem. Soc.*, 421 (1943); (b) W. E. McEwen and N. B. Mehta, THIS JOURNAL, **74**, 526 (1952).

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(21) M. S. Newman and P. M. Lee, *ibid.*, **76**, 4635 (1953).

(22) We are indebted to Professor H. C. Brown, who kindly made these σ^+ values available to us prior to publication.

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p-**Bromoneophyl Alcohol.**—A 46-g. quantity of the above acid in 200 cc. of ether was added slowly with stirring to 7.5 g. of lithium aluminum hydride in 500 cc. of ether. After the addition, the solution was refluxed for 1 hr., cooled and treated with cold dilute hydrochloric acid. The ether solution was washed with water and aqueous sodium bicarbonate. Then it was dried and concentrated. Distillation yielded 36.5 g. of crude alcohol, b.p. 120–123° (2.0 mm.), n^{25}D 1.5598. Recrystallization from pentane yielded 33.3 g. of material, m.p. 44–47°, m.p. 46–47.5° after a second crystallization.

Anal. Calcd. for $C_{10}H_{13}OBr$: C, 52.42; H, 5.72. Found: C, 52.46; H, 5.94.

A 1.0-g. quantity of the alcohol was refluxed 1 hr. with 10 cc. of thionyl chloride. The excess thionyl chloride was removed under vacuum, and the remaining oil was refluxed overnight with a solution of 4 g. of potassium permanganate and 2 cc. of 5% sodium hydroxide in 80 cc. of water. Cold dilute sulfuric acid was added and boiling was continued for 10 minutes. After the mixture was cooled to 0°, an excess of aqueous sodium bisulfite was added and the solid was filtered off. Recrystallization from benzene gave 0.30 g. (34%) of *p*-bromobenzoic acid, m.p. 248–250°, mixed m.p. 248–250°.

p-**Carboxyneophyl Alcohol.**—*n*-Butyllithium was prepared from 10.5 g. of lithium ribbon and 90 g. of butyl bromide in 300 cc. of ether at −10° as described by Gilman.[23] To this solution, cooled to 0°, was added a solution of 48 g. of *p*-bromoneophyl alcohol in 150 cc. of ether with stirring during *ca.* 10 min. The mixture was then stirred for 30 minutes at room temperature and poured onto an excess of Dry Ice. When the Dry Ice had disappeared and the solution had come to room temperature, cold dilute hydrochloric acid was added. The ether phase was separated and the aqueous solution was extracted with ether. The combined extracts were washed with water and the product was extracted with a solution of 30 g. of sodium bicarbonate in water. Acidification gave the crude acid. Two crystallizations from aqueous methanol yielded 5.8 g. of material, m.p. 155–157°. Another crystallization raised the m.p. to 158–159°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.80; H, 7.23.

p-Carbomethoxyneophyl alcohol was prepared from 7.0 g. of the above acid and an excess of ethereal diazomethane. The product, b.p. 135–140° (1.5 mm.), obtained by distillation, was recrystallized twice from ether–pentane to yield 5.0 g. of material, m.p. 42–43.5°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.25; H, 7.80.

p-**Diphenylhydroxymethylneophyl Alcohol.**—Phenyllithium was prepared from 1.4 g. of lithium ribbon and 15 g. of bromobenzene in 200 cc. of ether. To this stirred solution was added dropwise 5.0 g. of *p*-carbomethoxyneophyl alcohol in 50 cc. of ether. After the addition, the solution was refluxed for 2 hr. Then cold water was added with cooling. The aqueous phase was separated and extracted twice with ether. The combined ether solutions were washed with water, dried and concentrated. The residual oil crystallized on standing overnight. Two crystallizations from ligroin–benzene gave 6.0 g. of the glycol, m.p. 114–116.5°.

Anal. Calcd. for $C_{23}H_{24}O_2$: C, 83.10; H, 7.28. Found: C, 83.10; H, 7.25.

p-**Benzhydrylneophyl Alcohol.**—A solution of 6.0 g. of *p*-diphenylhydroxymethylneophyl alcohol in 50 cc. of pure methanol was shaken with 0.2 g. of 10% palladium-on-charcoal and 3 drops of 2 *N* hydrochloric acid under 35 p.s.i. of hydrogen for *ca.* 24 hr. The solution was filtered through Celite and poured into dilute aqueous sodium bicarbonate. The product was extracted with two portions of ether. The extracts were washed with water, dried and concentrated. The oil obtained was crystallized twice from ether–pentane. This gave 3.0 g. of alcohol, m.p. 75.5–77°.

Anal. Calcd. for $C_{23}H_{24}O$: C, 87.30; H, 7.64. Found: C, 87.17; H, 7.44.

p-**Hydroxymethylneophyl Alcohol.**—A solution of 4.5 g. of *p*-carbomethoxyneophyl alcohol in 50 cc. of ether was added cautiously to 3 g. of lithium aluminum hydride in 100 cc. of ether. A precipitate formed immediately. It was necessary to reflux the solution for 20 hr. in order to complete the reduction. Cold dilute sulfuric acid was added cautiously and the aqueous phase was separated and extracted with ether. The combined extracts were washed with water and aqueous sodium bicarbonate. The solution was dried and the ether was evaporated. The residue was recrystallized three times from ether–pentane. The product, 2.1 g., formed long colorless needles, m.p. 58–59°.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.39; H, 9.02.

p-**Methylneophyl Alcohol.**—The above glycol, 2.0 g., was dissolved in 25 cc. of pure methanol and hydrogenated at 35 p.s.i. using 0.2 g. of 10% palladium-on-charcoal as catalyst. The hydrogenation was complete in 3 hr. The resulting solution was filtered through Celite, and the filtrate was evaporated on a steam-bath. Vacuum distillation yielded 1.5 g. of alcohol, b.p. 87–88° (1.5 mm.), n^{25}D 1.5193.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.25; H, 9.84.

α,α-**Dimethyl-***m*-**methylbenzyl Cyanide.**—Sodamide was prepared in 500 cc. of liquid ammonia from 20 g. of sodium, ferric chloride being used as catalyst. The 500 cc. of dry benzene was added while the ammonia was evaporated. The benzene finally was boiled in order to expel the last traces of ammonia. To the warm solution, 48 g. of *m*-methylbenzyl cyanide[24] was added with stirring and slight cooling. A vacuum was applied to the warm solution to remove the ammonia formed. Then 130 g. of methyl iodide was added as rapidly as possible to the still warm, stirred solution, slight cooling being necessary to keep the reaction mixture from boiling too vigorously. The hot solution was stirred 10 minutes more and cooled. A little methanol was added to destroy any remaining sodamide and then ice-water. The benzene layer was separated, washed with water, cold dilute hydrochloric acid, water and finally with aqueous sodium bicarbonate. The solution was dried and concentrated. The dark brown product was fractionated under vacuum through a center-rod column (*ca.* 20 plates). The pure nitrile, 32 g., boiled at 119–120° (15 mm.).

Anal. Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.23. Found: C, 82.81; H, 8.20.

α,α-**Dimethyl-***m*-**tolylacetic Acid.**—The above nitrile, 15 g., was refluxed for 2 hr. with 12 g. of potassium hydroxide in 50 cc. of ethylene glycol. After being cooled, the solution was poured onto ice and hydrochloric acid. The oil which separated could be induced to crystallize, three crystallizations from pentane yielding 10.4 g. of material, m.p. 70.5–73°. Another crystallization raised the m.p. to 73–74°.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.86; H, 7.85.

m-**Methylneophyl Alcohol.**—The reduction of 8.0 g. of α,α-dimethyl-*m*-tolylacetic acid with 2.0 g. of lithium aluminum hydride in ether proceeded readily. The usual isolation yielded 7.0 g. of the pure alcohol, b.p. 91–94° (2.5 mm.), n^{25}D 1.5210.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.45; H, 9.56.

Bromobenzenesulfonates.—The *p*-bromobenzenesulfonates were prepared from the corresponding alcohols by the usual pyridine method. Most of the esters were recrystallized from benzene–ligroin. Table V summarizes the melting points and analyses of the five new *p*-bromobenzenesulfonates employed in the present work. The equivalent weights observed in acetolysis were close to the theoretical values except in the *p*-benzhydryl case, for which acetolysis indicated a purity of only 85%.

1,1-**Dimethyl-2-phenylethanol.**—This alcohol was prepared by the reaction between ethyl phenylacetate and methylmagnesium iodide. The crude alcohol was chromatographed carefully on alumina and recrystallized 4 times from pentane at −80°. The pure alcohol has the properties: m.p. 25.5–26.5°, n^{25}D 1.5128, b.p. 59–60° (1.5 mm.).

Acetolysis of Neophyl *p*-**Bromobenzenesulfonate.**—A solution of 50.0 cc. of 1.00 *M* lithium acetate and 750 cc. of dry acetic acid was heated to 75.0°, and 15.0 g. of the pure *p*-bromobenzenesulfonate,[4] m.p. 80.5–81.5°, three times recrystallized from ligroin, was added. The solvolysis solution was kept at 75.0° for 28 hr., and then it was

(23) H. Gilman, *et al.*, This Journal, 61, 109 (1939).

(24) Kanagar Collection, Chemical Sci., 514 (1926).

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TABLE V

PROPERTIES AND ANALYSES OF SUBSTITUTED NEOPHYL *p*-BROMOBENZENESULFONATES

Substituent	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
p-Br	116–117	$C_{16}H_{16}O_3SBr_2$	42.87	43.05	3.60	3.87
p-$COOCH_3$	117–118	$C_{18}H_{19}O_5SBr$	50.59	50.70	4.48	4.59
p-$(C_6H_5)_2CH$	112 dec.	$C_{29}H_{27}O_3SBr$	65.04	65.17	5.08	5.07
p-CH_3	91–92 dec.	$C_{17}H_{19}O_3SBr$	53.27	53.29	5.00	5.18
m-CH_3	89–90[a]	$C_{17}H_{19}O_3SBr$	53.27	53.15	5.00	4.89

[a] Mixed m.p. with *p*-isomer, 74–90°.

cooled and poured into water. The products were extracted with 5 portions of pentane, and the extracts were washed with water and aqueous sodium bicarbonate. The extract was dried and the solvent was distilled off carefully through a Vigreux column. The crude products were reduced with 1.5 g. of lithium aluminum hydride in ether. The products were isolated by adding water to the solution and decanting the ether solution from the insoluble salts. The solids were extracted several times with ether and the extracts were washed with water, dried and concentrated. Chromatography on 200 g. of alumina separated the products into olefin and alcohol. The olefins, 3.2 g. (59.6%), $n^{25}D$ 1.5207, were eluted with pentane and the alcohols, 1.90 g. (31.1%), $n^{25}D$ 1.5128, b.p. 65–68° (1.5 mm.), were eluted with ether.

The olefin fraction in isooctane displayed an ϵ 6912 at λ 244 mμ in ultraviolet absorption. A 0.8843-g. sample of the olefin product was hydrogenated in acetic acid at 27.5° and 752 mm., using 10% palladium-on-charcoal as catalyst. A total of 169 cc. of hydrogen (99%) was absorbed in 90 minutes. The hydrogenated product was isolated by pouring the acetic acid solution into water and extracting with pentane. The pentane extracts were washed with aqueous sodium bicarbonate and dried. The solvent was evaporated, and the residue was refluxed with sodium metal until the metal remained bright. A final distillation gave 0.45 g. of product, b.p. 172°, $n^{25}D$ 1.4837. The infrared spectrum of this material was identical with that of isobutylbenzene,[6] $n^{25}D$ 1.4841.

The alcohol fraction from the chromatography of the solvolysis product had m.p. 25–26°, mixed m.p. with 1,1-dimethyl-2-phenylethanol, 25–26°. The infrared spectrum indicated the presence of 0.5–0.75% of neophyl alcohol in the tertiary alcohol. Definite absorption was observed at 1000–1075 cm.$^{-1}$ where neophyl alcohol absorbs strongly, and slightly low absorption was observed at 1125–1150 cm.$^{-1}$ where neophyl alcohol is relatively transparent. The infrared spectrum of the solvolysis product was intermediate between a synthetic mixture containing 1.6% neophyl alcohol in the tertiary alcohol and the pure tertiary alcohol.

In a second solvolysis carried out as above with slightly less pure *p*-bromobenzenesulfonate, a 61.5% yield of olefin was obtained and a 30.3% yield of alcohol. The olefin fraction, $n^{25}D$ 1.5200, displayed ϵ 6880 at λ 244 mμ in ultraviolet absorption. The alcohol, m.p. and mixed m.p. 24.5–25.5°, b.p. 65–68° (2 mm.), $n^{25}D$ 1.5120, had an infrared spectrum consistent with the presence of more than 99% tertiary alcohol and *ca.* 1% neophyl alcohol.

In a control experiment, a solution of 1.5 g. of the tertiary alcohol, 1 cc. of acetic anhydride, 1 cc. of 1.00 *M* lithium acetate in dry acetic acid and 100 cc. of dry acetic acid was heated to 75.0° for 30 hr. The reaction mixture was worked up in the usual way, and the recovered product was reduced with 0.5 g. of lithium aluminum hydride in ether. The excess hydride decomposed with water, and the ether solution was decanted from the salts. The salts were extracted several times with fresh ether. The combined extracts were washed with water, dried and concentrated. Distillation gave 1.3 g. of product, b.p. 65° (1.5 mm.), $n^{25}D$ 1.5130, m.p. 24–25.5°. A comparison of the −OH band at 3350 cm.$^{-1}$ of the product with that of pure tertiary alcohol showed the product to contain a small amount of non-hydroxylic material, probably olefin. Otherwise, the infrared spectra of the two materials were very similar.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Mechanisms of Elimination Reactions. XVIII. Reactivities of Some 2,3-Norbornane Derivatives[1,2]

BY STANLEY J. CRISTOL AND ERHARD F. HOEGGER

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Rate constants have been determined for the second-order reaction of sodium 1-pentoxide in 1-pentanol with *endo-cis*- and *trans*-2,3-dichlorononorbornane at 101.3 and 116.2°, and with *exo*-2-*p*-toluenesulfonyl-*endo*-3-chlorononorbornane at 0 and at 12°. The relative reactivities toward elimination of the elements of hydrogen chloride from these boat-form cyclohexane rings have been interpreted on the basis of an elimination process involving a carbanion intermediate.

Elimination of the elements of hydrogen chloride from 11,12-dichloro-9,10-dihydro-9,10-ethanoanthracene with alkali has been shown[3] to be very sluggish and to be relatively non-stereospecific, *cis* elimination being preferred over *trans* by a factor of about 8, in contrast to the generally observed large preference of *trans* over *cis* elimination.[4] The striking lack of stereospecificity was rationalized[3] by the assumption that normal *trans* elimination (in acyclic systems or in cyclic systems without severe hindrance to rotation or ring conversion) utilizes a concerted *trans* coplanar transition state[4,5]; this transition state is forbidden to *cis* groups in ordinary small rings or to either *cis* or *trans* groups in bicyclo[2,2,2]octane derivatives without excessive torsional strain. Norbornane, or bicyclo[2,2,1]-heptane is locked by the 1,4-methano bridge in a boat-form cyclohexane ring in the same way as the 1,4-ethano bridge affects the cyclohexane ring in

(1) Previous paper in series: S. J. Cristol, F. R. Stermitz and P. S. Ramey, THIS JOURNAL, **78**, 4939 (1956).

(2) This work was reported at the 14th National Organic Chemistry Symposium at Lafayette, Indiana, June 13, 1955.

(3) S. J. Cristol and N. L. Hause, THIS JOURNAL, **74**, 2193 (1952).

(4) See, for example: (a) S. J. Cristol, *ibid.*, **69**, 338 (1947); (b) S. J. Cristol, N. L. Hause and J. S. Meek, *ibid.*, **73**, 674 (1951); (c) S. J. Cristol and W. P. Norris, *ibid.*, **76**, 3005 (1954).

(5) D. H. R. Barton and E. Miller, *ibid.*, **72**, 1066 (1950).

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TABLE I

DATA, REACTION RATE CONSTANTS AND QUANTITIES OF ACTIVATION FOR DEHYDROCHLORINATION WITH SODIUM 1-PENTOXIDE IN 1-PENTANOL

Compound	Temp., °C.	(Halide) *M*	(Base) *M*	*k*, l./sec./mole	$k_{110°}$	Eact., kcal./mole
endo-cis-2,3-Dichloronorbornane	116.2	0.022	0.42	4.9×10^{-6}	2×10^{-6}[a]	31
		.022	.31	5.0×10^{-6}		
			Av.	5.0×10^{-6}		
	101.3	.034	.19	1.05×10^{-6}		
		.034	.37	9.7×10^{-7}		
			Av.	1.01×10^{-6}		
trans-2,3-Dichloronorbornane[c]	116.2	0.011	.07	3.2×10^{-4}	1.7×10^{-4}[a]	32
		.034	.19	3.6×10^{-4}		
		.024	.14	3.3×10^{-4}		
			Av.	3.4×10^{-4}		
	101.2	.022	.23	6.7×10^{-5}		
		.022	.12	6.5×10^{-5}		
			Av.	6.6×10^{-5}		
exo-2-*p*-Toluenesulfonyl-*endo*-3-chloronorbornane	11.96	.0074	.0094	2.27×10^{-2}	1.2×10^{2}[b]	19
		.0075	.0141	2.05×10^{-2}		
			Av.	2.16×10^{-2}		
	0.00	.0075	.0236	4.85×10^{-3}		
		.015	.0236	4.97×10^{-3}		
			Av.	4.91×10^{-3}		

[a] Interpolated. [b] Extrapolated. [c] The initial halide concentrations recorded were corrected as described in the Experimental section.

the bicyclo[2,2,2]octane molecule. Accordingly, it would be anticipated that 2,3-dichloronorbornane isomers would be relatively inert and that *trans* elimination would not be markedly faster, and might be slower, than *cis* elimination. That this was true was observed in either a qualitative or a rough quantitative fashion in such compounds in three different laboratories.[6-8] In view of these results, it seemed worthwhile to get quantitative information about these isomers.

The preparations of *endo-cis*-2,3-dichloronorbornane and the *trans* isomer has been described,[7,8] and treatment with alkali has been shown to give 2-chloronorbornene.[7] We chose to use 1-pentanol as solvent for the kinetic study, and sodium 1-pentoxide as base, because of the moderately high temperatures involved. Appropriate details of the procedures used in determining rate constants are given in the Experimental section. The rate data are given in Table I for the reactions of these two isomers with sodium 1-pentoxide.

It may be noted from the data of the table that just as in the case of the dichlorodihydroethanoanthracenes, *cis*-dehydrochlorination is preferred over *trans*-dehydrochlorination in these rigid boat-form compounds where the eclipsed bonds cannot readily attain the requisite geometry for *trans* coplanar elimination. These data are not directly comparable with the data on the bicycloöctanes because of the different solvents used (ethanolic dioxane and *n*-amyl alcohol), but it may be fairly stated that in both cases, the favoring of *cis* elimination does not follow from factors increasing its rate, but rather from factors markedly decreasing the rate of *trans* elimination.[3] At the present time we are not in a position to discuss the preference of *cis* elimination over *trans* in the two systems, nor the differences in amount of this preference between the two systems. These may be the result of effects of solvent size and steric hindrance to solvation in the transition state of the various carbanions being formed, but discussion of speculations of this sort must await the accumulation of further data. It would also be desirable to have data on the *exo-cis*-dichloride, but this compound has not yet been described in the literature.

Two alternative processes have been suggested for bimolecular elimination in systems where the groups being eliminated cannot easily attain a *trans*-coplanar conformation. One suggestion has been made that the additional energy of activation required for the less favored process is used partly to twist the molecule more nearly into the requisite geometry and partly to force the mechanism against the still imperfect geometry,[9] but that the process is still concerted, removal of the proton by base being accompanied by formation of the multiple bond and loss of the anion. Unfortunately it seems difficult to define an experimental test for this postulate.

On the other hand, it has been suggested[4a] that a distinctly different mechanism is utilized by those compounds with geometry unfavorable to a *trans* coplanar transition state. This mechanism involves a first step in which the β-proton is transferred to the base to give a carbanion intermediate. The carbanion ultimately loses an anion to form the olefinic or acetylenic product. Energy calculations appear consistent with observed activation energies.[4b] The small amount of deuterium exchange observed in elimination with β-benzene hexachloride (*cis* elimination) was suggested as offering sup-

(6) H. Bluestone, R. E. Lidov and S. B. Soloway, private communication.

(7) J. D. Roberts, F. O. Johnson and R. A. Carboni, THIS JOURNAL, **76**, 5692 (1954).

(8) N. L. Hause, Ph.D. dissertation, University of Colorado, 1950.

(9) E. D. Hughes, C. K. Ingold and R. Pasternak, *J. Chem. Soc.*, 3832 (1953).

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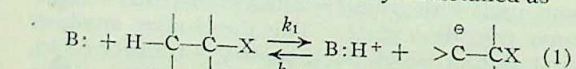
port to the postulated carbanion process.[10] Substantial amounts of deuterium exchange have been observed in treatment of trichloroethylene with alkali,[11] a fact consistent with a carbanion intermediate in elimination where the tendency to abstract a proton from solvent competes favorably with loss of chloride ion.

Another deduction from the dual mechanism theory is that substitution of electron-attracting substituents on the β-carbon atom would minimize the difference in reactivity and energy of activation between the two processes, as it appeared that the carbanion process (where a large negative charge was being developed on the β carbon atom in the transition state) would be more sensitive to the effect of such groups than the concerted process (where the negative charge was being distributed more widely). Such an effect has been observed.[4c,12]

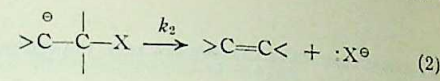
Such an electron-attracting group is a sulfone group, and it might be anticipated that such a group would stabilize the carbanion process markedly. This group (or any other electron-attracting group) might, for example, result in a situation where a stabilized carbanion process might be favored over an alternative concerted elimination process where no activation is present. Indeed, Bordwell and Kern[13] have shown that a *cis* hydrogen activated by the presence of a sulfone group on the same carbon atom will be removed in preference to a *trans* unactivated hydrogen in *trans*-2-*p*-toluenesulfonylcyclohexyl *p*-toluenesulfonate and the corresponding cyclopentyl compounds. In addition, Weinstock, Pearson and Bordwell[14] have shown that the sulfone group has a powerful activating influence in both *cis* and *trans* elimination, although they have not interpreted their data in terms of possible carbanion mechanisms.[15]

We were interested in how the sulfone group might affect elimination rates in boat-form cyclohexane rings and accordingly data were obtained on *exo*-2-*p*-toluenesulfonyl-*endo*-3-chloronorbornane,[16] and they are recorded in Table I. It may be noted that this compound is very reactive, rates being conveniently measurable at 0 and 12° as compared with 100–120° for the dichlorides, and with rates differing by six to eight orders of magnitude if the data on the chlorosulfone are extrapolated to 110°, or by ten to twelve orders of magnitude if the rates on the dichlorides are extrapolated down to 12°. Here we have a *cis* non-coplanar elimination proceeding at a very high rate, and with low activation energy, a result entirely consistent with predictions from the carbanion mechanism theory.

The carbanion mechanism may be detailed as



$$\mathrm{B:} + \mathrm{H{-}C{-}C{-}X} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{B{:}H^+} + \mathrm{{>}C^{\ominus}{-}CX} \quad (1)$$



$$\mathrm{{>}C^{\ominus}{-}C{-}X} \xrightarrow{k_2} \mathrm{{>}C{=}C{<}} + :X^{\ominus} \quad (2)$$

Some confusion apparently may exist as to when it may be experimentally distinguishable from the concerted process, where proton transfer, formation of the multiple bond and loss of halide ion occur simultaneously. It will not be distinguishable by deuterium-exchange studies or by studies of general base catalysis,[15] when $k_2 >> k_{-1}$. It will only be distinguishable when the sensitivities of the methods available for analysis of such results are consistent with the ratio k_{-1}/k_2. We see no reason to believe that it is more moderate[15] or conservative[9] to assume that all reactions in which substantial amounts of deuterium exchange are not observed or in which specific base catalysis is not found are concerted mechanisms, particularly in view of the body of evidence favoring a dual mechanism concept.

Acknowledgments.—The authors gratefully acknowledge support of this work by the Shell Development Company and by a contract between the University of Colorado and the Office of Naval Research. One of us (E.F.H.) is indebted to the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung and to the American-Swiss Foundation for Scientific Exchange, Inc., for travel grants.

Experimental

Materials Used.—*endo-cis*-2,3-Dichloronorbornane, m.p. 76–77°, and *trans*-2,3-dichloronorbornane, b.p. 43.5–44.5° (2.5 mm.), n^{20}D 1.5027, were prepared substantially as described by Roberts, Johnson and Carboni.[7] Our *trans* isomer was impure, however, and the kinetic work was performed with material that eliminated less than the theoretical amount of chloride ion under appropriate conditions. How this was corrected is described below under rate measurements. After all of the work had been completed, we succeeded in crystallizing the *trans* isomer, m.p. 5.5°. 2-*exo*-*p*-Toluenesulfonyl-3-chloronorbornane, m.p. 115–117°, was prepared by addition of *p*-toluenesulfenyl chloride to norbornene, followed by oxidation to the sulfone.[16]

1-Pentanol.—Commercial *n*-amyl alcohol contained significant amounts of chloride (1–2 mmoles/l.) even after distillation. For this reason *n*-amyl alcohol was treated with 1–2% of sodium and heated at reflux for 15 hours. It was then fractionally distilled and the fraction, b.p. 131–131.5° (630 mm.), was used. It showed no detectable halogen after this treatment.

Sodium 1-Pentoxide Solution.—About 11.5 g. of sodium, which had been cleaned first under toluene and then in 1-pentanol was dissolved in 1 liter of pure 1-pentanol. The solution was stored in a brown rubber-stoppered bottle and remained colorless for several months. Its titer was checked regularly and dropped slowly (less than 1% per month).

Measurements of Reaction Rates.—The rates at above 100° were run in sealed Corning 7280 alkali-resistant glass tubes, substantially as described previously,[3] except that the solvent was 1-pentanol. The thermostated baths appeared to hold constant temperature to ±0.05°, and temperatures recorded were checked against a National Bureau of Standards calibrated thermometer. The extent of reaction was followed by Volhard titration for chloride ion. Titration was accompanied by rapid stirring with a magnetic stirrer. This stirring helped in seeing the end-point clearly in the two-phase system. Calculations of rate were made in the usual graphical fashion,[3] and good lines (constant second-order rate constants) were obtained with the *endo*-*cis*-dichloride. However, the rate constants appeared to fall off rapidly with time with the *trans*-dichloride, and when study of this compound will be described in a paper by S. J. Cristol and C. D. Brindell.

(10) S. J. Cristol and D. D. Fix, This Journal, **75**, 2647 (1953).
(11) L. C. Leitch and H. J. Bernstein, *Can. J. Research*, **28B**, 35 (1950).
(12) S. J. Cristol and A. Begoon, This Journal, **74**, 5025 (1952).
(13) F. G. Bordwell and R. J. Kern, *ibid.*, **77**, 1141 (1955).
(14) J. Weinstock, R. G. Pearson and F. G. Bordwell, *ibid.*, **78**, 3468 (1956).
(15) J. Weinstock, R. G. Pearson and F. G. Bordwell, *ibid.*, **78**, 3473 (1956).
(16) The synthesis, proof of structure and examination of product

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the reaction was run for nine half-lives under pseudo first-order conditions (large excess of base), only 70–75% of the theoretical amount of chloride was produced. This amount did not appear to depend upon the concentration of alkali, so no base-insensitive transformation to a material which does not liberate chloride ion rapidly was involved. We suspect that our *trans* material was contaminated with the *cis-endo* isomer which, of course, is about 1/85 as reactive as the *trans* isomer. To correct for this, we attempted plots of our data feeding into our calculations various factors depending upon the percentage of *trans*-dichloride in the starting material. The data on all of the runs gave excellent straight lines when the value 71% was used to correct the initial concentration of dichloride and, of course, the extent of reaction as well. The rate constants in Table I are thus corrected.

As the solutions were made up at 20° and the reactions were run at 101 and 116°, the rate constants were further corrected for solvent expansion. The observed rate constants were multiplied by 1.09 and 1.11 at 101 and 116°, respectively.[17]

The rates at 12° were carried out in a thermostated water-bath in a room also held at 12°. Appropriate solutions of the chlorosulfone and base in 1-pentanol were equilibrated in the bath, were rapidly mixed in a volumetric flask, which was then filled to the mark with temperature-equilibrated 1-pentanol. The flask was shaken to mix the solution thoroughly and was then immersed in the bath. Samples were withdrawn every few minutes with a pipet having a tip which had been blown out to give rapid delivery, and these were run into an erlenmeyer flask containing 10 ml. of 2 *N* nitric acid. The runs at 0° were conducted in a water-ice bath in a room held at 5°. The pipets used for withdrawing samples were insulated by wrapping them with asbestos string and were stored in a long test-tube at 0°. In other respects the procedure followed was similar to that at the higher temperature.

BOULDER, COLORADO

(17) A. Zander, *Ann.*, **224**, 56 (1884).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Mechanisms of Elimination Reactions. XIX. Elimination and Solvolytic Reactivities in Some Bicyclo[2,2,1]heptane and Bicyclo[2,2,2]octane Derivatives[1,2]

BY STANLEY J. CRISTOL AND ROBERT P. ARGANBRIGHT

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A striking lack of stereospecificity in elimination reactions involving bonds held in the rigid eclipsed positions available in boat-form cyclohexane molecules has been noted in the reaction of sodium hydroxide with the *cis* and *trans* isomers of 11-*p*-toluenesulfonyl-12-chloro-9,10-dihydro-9,10-ethanoanthracene. Both compounds reacted rapidly with alkali at 0 and 12°, the *cis* compound (*trans* elimination) reacting about three times as fast as the *trans* isomer. These results compared with those reported earlier for 11,12-dichloro-9,10-dihydro-9,10-ethanoanthracene are well accommodated by the assumption that a carbanion is formed in the first step of the elimination reaction. Solvolysis rate constants for several β-chlorothioethers in bicycloheptane and bicyclooctane ring systems were determined in 85% ethanol at 116°. The extremely low reactivities and the minor difference in reactivity between *cis* and *trans* isomers demonstrate the lack of significant neighboring-group acceleration of solvolysis with groups held at rigid eclipsed bond angles.

Previous work[3] has shown that the normal preference for *trans* elimination disappears when groups are held rigidly in fixed positions such that *trans* coplanarity cannot be attained readily in the transition state for elimination. Evidence has been adduced to suggest that in these circumstances an alternative mechanism involving a carbanion is operative. It is the purpose of the present paper to supply further data in support of this postulate.

We have studied the rates of elimination of hydrogen chloride with sodium hydroxide from *cis*- (I) and *trans*-11-*p*-toluenesulfonyl-12-chloro-9,10-dihydro-9,10-ethanoanthracenes (II) to compare the rate constants and quantities of activation with those of the corresponding 11,12-dichlorides previously studied.[4] The rates were measured in a solvent consisting of 50% by volume of ordinary ethanol and 50% of dioxane. The rate data are given in Table I.

It will be noted that these compounds show extremely high reactivity toward elimination; the reactions proceed at quite rapid rates at 0 and 12°. These results may be contrasted with the results on the corresponding dichlorides,[4] which react at comparable rates at temperatures about 150° higher. If the data obtained on the dichlorides are extrapolated to 12°, the comparison of these values with the values given in Table I for the chlorosulfones indicate that substitution of a chlorine atom by a *p*-toluenesulfonyl group increases the rate of elimination by about 10 powers of 10. In addition, it should be noted that these compounds show little stereospecificity in the elimination reaction, *trans* elimination being favored over *cis* by a factor of only 3. It is of interest to note that in the two dichloride systems previously studied, that is, the dichlorodihydroethanoanthracenes[4] and the 2,3-dichloronorbornanes,[1] *cis* elimination was favored slightly over *trans*. In the present system, however, *trans* elimination is slightly favored over *cis*.

The striking lack of stereospecificity in this system, as well as in the systems previously studied, seems to us to be best explained on the basis that carbanion intermediates are involved and that a multiple-stage mechanism for elimination is utilized in these systems where bonds are rigidly held in eclipsed positions and a *trans* coplanar transition state is geometrically improbable. The tremendous increase in reactivity observed when an arenesulfonyl group replaces a chlorine atom in these systems may also be rationalized by the assumption that a carbanion mechanism is involved. We feel that the results given here lend additional support to the arguments given earlier.[1]

It should be noted that a comparison

(1) Previous paper in series: S. J. Cristol and E. F. Hoegger, THIS JOURNAL, **79**, 3438 (1957).

(2) This work was reported at the 130th meeting of the American Chemical Society in Atlantic City, New Jersey, September, 1956.

(3) References to previous work in this field are given in reference 1.

(4) S. J. Cristol and N. L. Hause, THIS JOURNAL, **74**, 2193 (1952).

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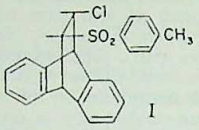
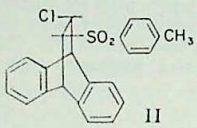
TABLE I

DATA AND SPECIFIC RATE CONSTANTS FOR THE REACTION OF β-CHLOROSULFONES AND SODIUM HYDROXIDE IN ETHANOLIC DIOXANE

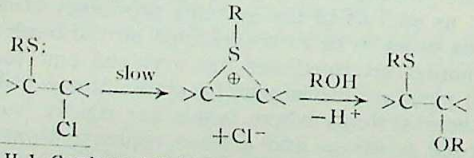
Compound	Temp., °C.	Halide, *M*	NaOH, *M*	*k*, l./mole/sec.	Av.	Dev., %	E_{act}, kcal./mole
 I	12.1	0.00192	0.00253	8.85	9.65	8.3	16.3
		.00189	.00209	10.46			
	0.0	.00194	.00211	2.84			
		.00189	.00211	2.61	2.65	7.0	
		.00199	.00211	2.51			
 II	12.1	.00524	.00421	2.83			
		.00612	.00419	3.01	3.10	7.8	
		.00225	.00253	3.47			
	0.0	.00389	.00422	0.926	0.920	0.6	15.6
		.00376	.00422	0.914			

of the rate data obtained on the dichlorides[1,4] with those data reported for *cis*- and *trans*-1,2-dichlorocyclohexane[5] is also consistent with the assumption that a carbanion intermediate is involved in systems which do not have favorable geometry for the concerted process.

Barton and Cookson[6] have recently discussed the effect of conformation upon neighboring-group participation in solvolytic reactions[7] and have pointed out the necessity for axial–axial relationships in providing neighboring-group assistance in chair-form cyclohexane derivatives. We were interested in a study of solvolysis rates for β-chlorosulfides which have the fixed eclipsed structures of boat-form cyclohexane molecules such as are present in bicycloheptanes and bicycloöctanes. Accordingly, solvolysis rates were studied in 85% ethanol with certain β-chlorothioethers, including *exo*-2-thiocresoxy-*endo*-3-chlorononbornane (III), *exo*-2-thiocresoxy-*endo*-3-chloro-5-norbornene (IV), and *cis*- (V) and *trans*-11-*p*-thiocresoxy-12-chloro-9,10-dihydro-9,10-ethanoanthracene (VI). The rate constants for the compounds studied are given in Table II.

It should be noted that all of the β-chlorosulfides reacted very slowly, even at 116°, the reactivities being roughly equivalent to those of bornyl chloride[8] (*endo* chlorine) or *endo*-norbornyl chloride.[9] No large difference was noted between the *cis* and *trans* isomers studied; the *trans* isomer reacted only four times as fast as the *cis* isomer. The relative inertness of our compounds may also be compared with the reactivity reported for *trans*-2-chlorocyclohexyl phenyl thioether.[10] This compound solvolyzes completely in 30 minutes at 100° in 80% ethanol.

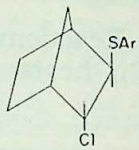
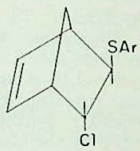
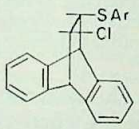
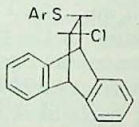
The normal mode of solvolysis of a β-chlorothioether may be presumed[11] to be



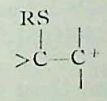
(5) H. L. Goering and H. H. Espy, THIS JOURNAL, **78**, 1454 (1956).
(6) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).
(7) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse, THIS JOURNAL, **74**, 1113 (1952).
(8) S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan and H. Marshall, *ibid.*, **74**, 1127 (1952).
(9) J. D. Roberts and W. Bennett, *ibid.*, **76**, 4623 (1954).
(10) H. L. Goering, D. I. Relyea and D. W. Larson, *ibid.*, **78**, 348 (1956).
(11) S. Winstein and E. Grunwald, *ibid.*, **70**, 828 (1948).

TABLE II

RATES OF SOLVOLYSIS OF SOME β-CHLOROTHIOETHERS IN 85% ETHANOL AT 116.5°

Compound[a] Ar = *p*-tolyl	Halide, *M*		*k*, sec.$^{-1}$
 III	0.009		2.5×10^{-5}
	.004		2.8×10^{-5}
		Av.	2.6×10^{-5}
 IV	0.005		6.3×10^{-6}
	0.004		7.0×10^{-6}
		Av.	6.6×10^{-6}
 V	0.003		1.2×10^{-6}
	0.003		0.9×10^{-6}
		Av.	1.1×10^{-6}
 VI	0.002		5.9×10^{-6}
	0.001		5.6×10^{-6}
		Av.	5.8×10^{-6}

with rate enhancement of about 10^7 over the corresponding simple alkyl halide due to neighboring-group participation of the β sulfur atom.[11] No such rate enhancement is noted in our compounds, and it therefore appears that the formation of the sulfonium intermediate cannot be a part of the rate-determining step, but rather that a simple carbonium ion of type



is being formed. The most reasonable explanation for these results appears to us to be a definite stereochemical requirement for *trans*-coplanarity in neighboring-group assistance of solvolysis and that this requirement cannot be met in the rigid geometry of these bicycloheptanes and bicycloöctanes.

It may be further noted that the norbornene chlorothioether was somewhat less reactive than the norbornane analog. This is consistent with observations made on the corresponding *endo* chlo-

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rides[9] and *endo*-*p*-bromobenzenesulfonates.[12] Rate data further indicate that there is little driving force toward solvolysis by participation of the π electrons of the benzene ring in solvolysis of the ethanodihydroanthracenes. Some participation might have been anticipated by analogy with the participation observed in *exo*-dehydronorbornyl systems, although the analogous bicyclo[2.2.2]octenyl systems have not been studied and may indeed show no such participation.[13]

Acknowledgments.—The authors are indebted to the Office of Naval Research, U. S. Navy, and to the National Science Foundation for support of this work.

Experimental

Preparation of Compounds.—The preparation of the materials used in these studies will be reported elsewhere. In general the chlorosulfides were prepared by addition of *p*-toluenesulfenyl chloride to the corresponding olefin or of thiocresol to the chloroölefin. The sulfones were prepared by oxidation of the chlorothioether with hydrogen peroxide.

Rate constants for elimination were measured as follows. A weighed amount of the β-chlorosulfone, from 0.1 to 0.8 mmole, was placed in a 100-ml. volumetric flask and 50 ml. of dioxane, measured at the temperature of the run, was added. About 40 ml. of 92.6% (by wt.) ethanol was then added, and the flask was placed in a 12.1° rate bath thermostatically controlled to a ±0.05°. After solution was complete and the contents had come to the temperature of the bath, a measured amount of ethanolic sodium hydroxide (normality calculated at 12.1°) was added followed by enough 92.6% ethanol (kept at 12.1°) to bring the volume up to the mark on the flask. The flask was removed from the bath and was shaken vigorously for several seconds. It was immediately replaced in the bath and, because the rates were fast, the first sample usually was taken almost immediately thereafter.

Since room temperature, in the case of the 12.1° runs, was about 20°, an asbestos-wrapped 10-ml. pipet was used for sampling. The samples were pipetted directly into 5 ml. of 3 *N* nitric acid contained in a 100-ml. erlenmeyer flask, the time being recorded the instant the sample started to flow from the pipet. The same pipet was used for all samples. The tip of the pipet was blown out to allow rapid drainage. The samples were analyzed for chloride ion by the Volhard procedure. Calculations of rate constants were made as described previously.[1,4]

The rate studies at 0° were run similarly except that an ice-water bath was employed in a room held at 2°.

Rate constants for solvolysis were measured as follows: A sample of the β-chlorothioether (about 0.2 mmole) was weighed into a 50-ml. volumetric flask and 50 ml. of 85% (by wt.) ethanol[14] was added at room temperature. After solution of the thioether had occurred, nine 5.5-ml. samples were removed and placed in 15 × 125 mm. Pyrex test-tubes which were then sealed. All tubes in any particular run were then placed in an oil-bath thermostatically maintained at 116.5 ± 0.05°. Tubes were removed at measured time intervals and were placed in a cold chest until the run was finished. The tubes were then opened and warmed to 20° and exactly 5 ml. was pipetted out of each into flasks for titration. Each sample was diluted with 25 ml. of ordinary ethanol, 2 drops of a mixed indicator (0.075% brom cresol green and 0.05% methyl red in ethanol) was added and the sample was titrated with aqueous 0.01 *N* sodium hydroxide. The first-order rate constants fell off with time, presumably due to reaction of ethanol with the hydrochloric acid produced in the solvolysis. The first-order plots were straight lines for the initial period of the reaction, however, and the straight-line portions were used to calculate the rate constants. It has been estimated that these results are accurate to ±30%.

BOULDER, COLORADO

(12) S. Winstein, H. M. Walborsky and K. Schreiber, THIS JOURNAL, **72**, 5795 (1950).

(13) For a discussion of the corresponding saturated systems, see H. M. Walborsky, *Experientia*, **9**, 209 (1953).

(14) This solvent was chosen, in place of the more customary 80% ethanol, in order to effect solubility of the difficultly soluble ethanoanthracene derivatives.

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORIES, HARVARD UNIVERSITY]

The Relative Stabilities of *cis* and *trans* Isomers. III. The Cyclodecenes

BY NORMAN L. ALLINGER[1,2]

RECEIVED FEBRUARY 18, 1957

The equilibrium constant for the reaction *trans*-cyclodecene ⇄ *cis*-cyclodecene has been determined to be >200 (25°). The dipole moments and other physical properties of the isomers were measured, and the relationships between these various quantities are discussed.

Introduction

It has long been a goal of organic chemists to be able to predict which of the various possible stereoisomeric structures exists in a given compound, either by a consideration of the reactions used to prepare the compound, or by an examination of its physical properties. Thus far no really general methods for accomplishing these purposes have been found. There have been evolved instead numerous rules for determining which of the various stereochemically possible products will result from a given reaction[3] and other rules which may be used to determine structure from physical properties.[4] Among the rules of the latter type, that of von Auwers was the earliest[4a] and it saw considerable service. It became clear at an early date however that exceptions to von Auwers rule existed,[5] nevertheless a great many structures were assigned using this rule some of which subsequently have been shown to be incorrect. When these incorrect assignments were uncovered several workers restated the rule in modified forms in an attempt to obtain a really useful

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(2) National Science Foundation Post-doctoral Fellow, 1955–1956.

(3) For a recent discussion of this subject see P. B. D. de la Mare in W. Klyne, "Progress in Stereochemistry," Butterworths Scientific Publications, London, 1954, pp. 90–125.

(4) (a) K. von Auwers, *Ann.*, **420**, 84 (1920); (b) L. H. Darling, A. K. Macbeth and J. A. Mills, *J. Chem. Soc.*, 1364 (1953); (c) S. Siegel, THIS JOURNAL, **75**, 1317 (1953); (d) W. E. Bachmann, A. Ross, A. S. Dreiding and P. A. S. Smith, *J. Org. Chem.*, **19**, 222 (1954); (e) F. R. Hewgill, P. R. Jefferies and A. K. Macbeth, *J. Chem. Soc.*, 699 (1954); (f) N. L. Allinger, *Experientia*, **10**, 328 (1954).

(5) (a) A. Skita, *Ber.*, **56**, 1014 (1923); (b) K. von Auwers and B.

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rule to which, within a precisely defined region of applicability, there would be no exceptions.[4b-f]

In the first paper in this series[4f] the physical properties of the *cis* and *trans* isomers of a great many compounds, including polysubstituted cyclohexanes and cyclopentanes, fused ring systems and olefins were examined, and these properties all seemed to be in agreement with the idea that the isomer of higher density, index of refraction, and boiling point was the less stable.[6] It was not clear at that time whether or not olefins were properly included with the other structures mentioned, since although a double bond is formally a two-membered ring, it is electronically quite different from the larger rings.[7] However, the experimental data available for monoölefinic hydrocarbons appeared without exception to fit the rule. On the other hand, at least one class of compounds, the α,β-unsaturated acids, were known not to be in agreement with the rule. For convenience in discussion, this rule will henceforth be referred to as the *conformational rule*. The existing forces of which this rule is a manifestation are not completely understood. Although the word steric has been used in this connection, it is clear that we are not here dealing with overlapping van der Waals radii, but rather with forces resulting from charge distribution between non-bonded atoms.[8] Whatever the nature of the forces involved, the existence of a conformational rule seems certain; it remains to state the rule correctly and define the region of its applicability.

It was suggested by van Arkel[9] that the boiling points of the *cis* and *trans* isomers of isomeric olefins were in fact determined by their dipole moments, both properties being greater for the same isomer.[10] For an olefin of the type ABC=CBA, where A and B are any substituents, the *cis* isomer would have the greater dipole moment, and consequently the higher boiling point. On the other hand, for an olefin of the type AHC=CHB, where A is any electron-attracting group and B is any electron-repelling group, the *trans* isomer has the greater dipole moment and, according to van Arkel's *dipole rule*, the higher boiling point. The dipole rule then predicts that with monoölefinic hydrocarbons the *cis* isomer will boil higher, but the reverse would be true with, for example, the α,β-unsaturated acid derivatives. These acid derivatives with their large dipole moments clearly obey the dipole rule, and they are in contrast to the predictions of the conformational rule. With the monoölefinic hydrocarbons the dipoles involved are quite small. With these compounds the same order of physical constants is predicted by both of the rules, and it is not certain which effect is in fact controlling the situation.

It seemed desirable at this point to disentangle the two rules by obtaining an isomeric pair of olefinic hydrocarbons in which the dipole rule and the conformational rule gave opposite predictions, so that the relative importance of these rules might be tested in a simple case. The *cis* and *trans* isomers of cyclodecene appeared to offer a suitable test case. Equilibrium studies appeared to indicate that the *cis* isomer had the lower free energy, and it also had the greater values of its physical constants, which facts suggested that perhaps in this case the dipole rule was the more important. However, there appeared to be some uncertainty as to just where the equilibrium point was for the reaction *trans*-cyclodecene $\rightleftarrows$ *cis*-cyclodecene. One of the earliest reported attempts at measurement of this equilibrium constant[11] indicated that $K < 1$ (at 175°), and this value was subsequently changed[12] to $\geqq 5.25$ (95°). Other workers have measured the value of this constant at various elevated temperatures,[13] and have indicated that it is "much greater" than 1. The temperatures at which the physical constants were measured were quite different from those at which the equilibrium constant was measured, the former being near room temperature. Inspection of models shows that the *cis* isomer has the greater entropy. Consequently, if the physical constants were related to the free energies, rather than the heat contents, none of the data mentioned above eliminates the possibility that the *cis* isomer has the more negative free energy at elevated temperatures, but that the free energies are reversed at room temperature because of the contribution of the entropy. There appears to be no reason to expect the physical constants to follow the free energies, either here or elsewhere, and in fact the data available in the literature are consistent only with the physical constants being related to the heat contents.[14] However, proof of the relationship appeared to be desirable in this case.

The dipole moments of the cyclodecenes could be calculated from bond moments. However, since the *trans* compound is obviously under some strain, the possibility that the normal planar sp^2 hybridization of the unsaturated carbons received a contribution from the tetrahedral sp^3 structure could not be dismissed. The latter type of hybridization, if it contributed to the actual structure of the molecule to any appreciable extent, would be expected to yield a very large dipole moment. Consequently the relative magnitudes of the dipole moments could not be unambiguously specified.

Results and Discussion

Pure samples of *cis*- and *trans*-cyclodecene were prepared by conventional methods, and their pu-

(6) Stable in this case refers to heat content rather than to free energy, but the distinction need be made only in certain rare cases.

(7) There is some evidence (M. T. Rogers and J. D. Roberts, This Journal, **68**, 843 (1946); R. H. Eastman, *ibid.*, **76**, 4115 (1954)) that a three-membered ring is somewhere between a saturated and an unsaturated compound electronically, and what is concluded here for olefins may prove of importance also with cyclopropane derivatives.

(8) (a) E. N. Lassettre and L. B. Dean, Jr., *J. Chem. Phys.*, **16**, 151 (1948); **17**, 317 (1949); (b) N. W. Luft, *Trans. Faraday Soc.*, **49**, 118 (1953).

(9) A. E. van Arkel, *Rec. trav. chim.*, **51**, 1081 (1932); **52**, 719, 733 (1933); **53**, 91, 246 (1934).

(10) It was also pointed out by van Arkel that from Kopp's rule the isomer with the higher boiling point would also have the greater density. By definition the same isomer has the smaller molecular volume. It will also in general have the greater refractive index but the smaller molar refractivity.

(11) A. T. Blomquist, R. E. Burge, Jr., and A. C. Sucsy, This Journal, **74**, 3636 (1952).

(12) A. T. Blomquist and A. Goldstein, *ibid.*, **77**, 1001 (1955).

(13) (a) V. Prelog, K. Schenker and H. H. Günthard, *Helv. Chim. Acta*, **35**, 1598 (1952); (b) A. C. Cope, D. C. McLean and N. A. Nelson, This Journal, **77**, 1628 (1955).

(14) N. L. Allinger, *J. Org. Chem.*, **21**, 915 (1956).

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rity was established by a comparison of their physical properties, including infrared spectra, with the published values. The indications in the literature were that it might be rather difficult to establish equilibrium at room temperature within a reasonable length of time, consequently it was decided to measure the refractive index of the compounds at elevated temperatures. It was found that plots of the refractive indices of the two isomers as functions of temperature from 11–60° were exactly parallel, the values being larger for the *cis* isomer, which indicated that while these quantities might be related to the heat contents they did not appear to be related to the free energies.

A quantitative value of the equilibrium constant was desired at as low a temperature as possible. The published method of isomerization (*p*-toluenesulfonic acid) proved to be too slow to be practical at room temperature; thus pure samples of each of the two isomers were each isomerized to a mixture containing not more than 1% of the other isomer after 24 hours. Since the difficulty seemed to be the mutual insolubility of the acid and the olefin, sulfuric acid was substituted for the solid sulfonic acid. In this case the isomerization proceeded smoothly and cleanly, equilibrium appeared to be reached in less than 120 hours at 25°. The equilibrated mixtures obtained from both isomers under the same conditions were analyzed by the infrared method, and it was found that the mixtures were indistinguishable from the pure *cis* isomer. As little as 1% of the *trans* isomer readily could be measured, and 0.5% could be detected under the conditions used. The amount of *trans* isomer present in the equilibrium mixture was thus less than 0.5%. When the equilibration was carried out in this manner, there was no trace of side reactions such as decalin formation which hampered the earlier investigations. From the equilibration described it can be calculated that for the reaction (at 25°) *trans*-cyclodecene → *cis*-cyclodecene, $-\Delta F \geqq 3.1$ kcal. Consequently, according to the conformational rule the *trans* isomer should have the greater values for its physical properties.[15]

Lastly, the dipole moments of the *cis*- and *trans*-cyclodecenes were determined in heptane solution. The atomic polarizations were neglected in the calculations. If it is assumed that no error is introduced thereby, the dipole moment of the *trans* isomer is indistinguishable from zero, the experimental value being $0.15\ ^{+0.06}_{-0.17} \times 10^{-18}$ e.s.u. The *cis* isomer, on the other hand, with the same qualification as above, was found to have a dipole moment of $0.44 \pm 0.03 \times 10^{-18}$ e.s.u. These values support the assumption that the atomic polarizations may be neglected since these dipoles are "normal," and they also indicate the absence of any detectable amount of unusual hybridization.

(15) Actually ΔH rather than ΔF should be used in this comparison (see ref. 14). Since the free energy change is so large, for ΔH to be opposite in sign from ΔF the entropy of the *cis* isomer would have to be greater than that of the *trans* by more than 11 e.u. This value is improbably large, and the use of ΔF in place of ΔH in this case seems justified. Subsequent to this work it was learned that the heats of hydrogenation of these compounds had been determined in the laboratories of Dr. R. B. Turner, and it was found that the *cis* isomer had the more negative heat content. The author wishes to thank Dr. Turner for making this data available in advance of publication.

Thus the *dipole rule* predicts that the *cis* isomer will have the greater values of its physical constants.

It is clear in the present case that the dipole moments rather than the heat contents are reflected by the physical constants even though the difference in the former is nearly the smallest non-zero value that is to be found in stereoisomeric organic compounds, and the difference in the latter is as large as the difference found between most pairs of stereoisomers. Thus it appears that the conformational rule is applicable to isomers which do not differ in dipole moment, while for isomers which do so differ, the dipole rule is to be applied.

All unstrained saturated hydrocarbons necessarily have zero dipole moments,[16] and among these hydrocarbons the conformational rule should invariably apply. There are, to the author's knowledge, no exceptions among these compounds. The conformational rule should also apply to monofunctional compounds (*e.g.*, the 2-methylcyclohexanols) since the two isomers do not differ in dipole moment. With difunctional compounds the situation is less simple. The *cis*- and *trans*-1,2- and 1,3-disubstituted cyclohexanes (ee and ea conformations) have, to a first approximation, the same angles between substituents and should not differ in dipole moment, hence the conformational rule should apply. If the substituents are 1,4- and if either both are electron withdrawing or both are electron repelling, the *cis* isomer will have a greater dipole moment. The conformational rule then leads to the correct prediction here, but probably fortuitously. A 1,4-disubstituted cyclohexane with one electron-withdrawing group and one electron-attracting group will be another test case as the dipole and conformational rules lead to opposite predictions, and in this case the dipoles are physically separated. There appear to be no dipole moments reported for such a pair of isomers, and it is planned to make such measurements in the future.

It now appears desirable to state the conformational rule in a more precise way than was previously possible: *For stereoisomers in cyclic systems which do not differ in dipole moment, the isomer which has the smaller molecular volume is the isomer which has the higher heat content.*[17]

Acknowledgment.—The author wishes to thank Professor Paul D. Bartlett for making it possible for him to spend the year in his laboratory at Harvard University.

Experimental

trans-**Cyclodecene.**—Sebacoin was prepared from di-

(16) See the discussion by L. E. Sutton in E. A. Braude and F. C. Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, p. 386.

(17) Several modifications have been incorporated in this statement of the rule relative to earlier versions,[4] and they require comment. First, the requirement of the same dipole moment seems clearly indicated by the present work. Second, the expression "smaller molecular volume" conveniently summarizes the nature of the densities, refractive indices, boiling points, molecular refractivities, and other less common properties (see ref. 4f for references to the experimental data). Lastly, the heat content is actually the quantity reflected in the physical properties. When the expression "relative stability" is used, there is some ambiguity as to whether heat content or free energy is indicated. It should be realized that for stereoisomers, differences in the latter are usually, but not necessarily, good approximations for differences in the former.

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methyl sebacate[18] and was reduced with zinc and hydrochloric acid to cyclodecanone.[19] The ketone had n^{25}D 1.4802, reported[13b] n^{20}D 1.4800. The oxime of the ketone was prepared in 95% yield, m.p. 78.5–79.5°, reported[20] m.p. 80°. Reduction of the oxime with sodium and ethanol[20] gave cyclodecylamine in 63% yield, b.p. 101–103° (17 mm.), reported[13b] b.p. 84–86° (4 mm.). Cyclodecyl dimethylamine was obtained by methylation in 86% yield and was in turn converted to the trimethylammonium iodide (94%).[13b] The iodide was then converted to the hydroxide, which was decomposed at 100–130° (20 mm.).[11] The crude distillate was purified and redistilled at a bath temperature of 100–130° (20 mm.) to yield pure *trans*-cyclodecene, n^{25}D 1.4795, yield 71%. The reported constants are[11] n^{20}D 1.4822, b.p. 68–70° (10 mm.). The infrared spectrum of the compound proved to be identical with those reported.[11,13a]

***cis*-Cyclodecene.**—Sebacoin was oxidized to 1,2-cyclodecanedione with bismuth oxide[21] in 89% yield, m.p. 39.7–41.4°, reported[11] m.p. 40–41°. The diketone was converted to the acetylene by mercuric oxide oxidation of the dihydrazone.[11] The yield of pure cyclodecyne was 16%. The infrared spectrum of the compound was identical with that reported. Hydrogenation of the acetylene to the pure *cis*-olefin proceeded cleanly, the hydrogen uptake being quantitative. The catalyst used for the hydrogenation was described earlier.[22] The yield of *cis*-cyclodecene was 75%, distilled at a bath temperature of 100–130° (20 mm.), n^{25}D 1.4835. The reported[11] constants are n^{20}D 1.4854 and b.p. 194–195° (740 mm.). The infrared spectrum was identical with those published.[11,13a]

TABLE I

REFRACTIVE INDICES OF THE CYCLODECENES (n_D)

t, °C.	*cis*	*trans*	t, °C.	*cis*	*trans*
11.0	1.4892	1.4852	40.0	1.4769	1.4730
20.0	1.4856	1.4818	50.0	1.4728	1.4688
25.0	1.4835	1.4795	60.0	1.4686	1.4646
30.0	1.4811	1.4773			

The refractometer was calibrated before use. The values of the refractive indices found are in good agreement with those reported by Blomquist, Burge and Suesy[11] (*cis* n^{20}D 1.4854, *trans* n^{20}D 1.4822), and that reported by Cope, McLean and Nelson[13b] (*trans* n^{25}D 1.4795), but these values differ significantly from the values reported by Prelog, Schenker and Günthard.[13a] Since this same deviation exists between the relative indices obtained by the latter group and the values obtained by others for other compounds and since it is consistent in both magnitude and direction, an instrumental error seems indicated.

Equilibration of the Cyclodecenes.—Three hundred milligrams of *trans*-cyclodecene and 20 mg. of concentrated sulfuric acid were allowed to stand at 25.0° for 120 hours with occasional shaking. The hydrocarbon layer was taken up in pure pentane, and the pentane layer was washed well with water. After removal of the solvent, the olefin was distilled at 20 mm. with a bath temperature of 100°. The same equilibration was then carried out starting with the *cis* isomer. The equilibrium mixtures were analyzed by the base line density infrared method,[12] using the pure *cis* and *trans* isomers as standards. It was found that the same mixture was obtained starting with either isomer, and it contained 97 ± 3% *cis* and not more than 0.5% *trans*. The equilibration experiments and analyses were then repeated as a check, and the results were identical.

(18) N. L. Allinger, "Organic Syntheses," Vol. 36, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 79.

(19) A. C. Cope, J. W. Barthel and R. D. Smith, *ibid*., p. 14.

(20) L. Ruzicka, M. Kobelt, O. Häfliger and V. Prelog, *Helv. Chim. Acta*, **32**, 544 (1949).

(21) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(22) D. J. Cram and N. L. Allinger, THIS JOURNAL, **78**, 2518 (1956).

Dipole Moments of the *cis*- and *trans*-Cyclodecenes.—The apparatus used for the dielectric constant measurements employed the heterodyne beat principle with a fixed frequency crystal oscillator at 100 kc. It has been described previously.[23] The dielectric constant cell held 60 ml. of solution and was thermostated in an oil-bath at 25.00 ± 0.02°. The general experimental procedure followed was that outlined by Smyth.[24] All weights were corrected to vacuum.

The molar polarization of the solute at infinite dilution was obtained following the method of Halverstadt and Kumler,[25] the pertinent relationship being

$$P_{2\infty} = [(\epsilon_1 - 1)/(\epsilon_1 + 2)][(1/d_1)][(M_2 - M_1\beta/d_1)] + [3M_1\alpha/(\epsilon_1 + 2)^2 d_1]$$

where $\epsilon_{12} = \epsilon_1 + \alpha N_2$, $d_{12} = d_1 + \beta N_2$, ϵ_1 = dielectric constant of the solvent; d_1, N_1 and M_1 are, respectively, its density, mole fraction in solution and molecular weight while the quantities with subscripts 2 and 12 have the same significance for the solute and solution, respectively. The data are summarized in Table II.

TABLE II

DIELECTRIC CONSTANTS OF CYCLODECENE SOLUTIONS IN *n*-HEPTANE

cis			*trans*		
N_2	d	ϵ	N_2	d	ϵ
0.020228	0.68406	1.0986	0.020273	0.68394	1.9100
.020228	.68406	1.9081	.011876	.68224	1.9065
.011116	.68207	1.9041	.005392	.68080	1.9054
.005820	.68092	1.9021	.000000	.67963	1.9025
.003482	.68041	1.9007			
.000000	.67963	1.8991			
α = 0.4596, β = 0.21844, $P_{2\infty}$ = 49.35 cc., ϵ_1 = 1.8992, d_1 = 0.67964			α = 0.328, β = 0.21330, $P_{2\infty}$ = 45.89 cc., ϵ_1 = 1.9028, d_1 = 0.67965		

The values of α and β were obtained in each case by the method of least squares. The calculation of the dipole moments from the molar polarizabilities made use of the Debye equation

$$\mu = 0.012181 \times 10^{-18}[(P_{2\infty} - R_D)T]^{1/2}$$

The molar refractivities were calculated from the refractive indices obtained in the present work (at 20°) and the densities reported by Blomquist and co-workers.[11] The values of R thus calculated are: *cis* 45.22, *trans* 45.43, which are in reasonable agreement with the theoretical value of 45.71.[26] The experimental rather than theoretical values for the molar refractivity were employed in the calculations, although use of the latter instead does not significantly affect the results.

The *trans* isomer was found to have a dipole moment of 0.15×10^{-18} e.s.u. The error in this value results almost entirely from the error in α, and it is estimated to be such that $\mu_{trans} = 0.15^{+0.06}_{-0.17} \times 10^{-18}$ e.s.u. The dipole moment of the *trans* isomer is hence indistinguishable from zero. For the *cis* isomer in a similar manner it is found that $\mu_{cis} = 0.44 \pm 0.03 \times 10^{-18}$ e.s.u.

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(23) (a) C. A. Brown and R. C. Osthoff, *ibid*., **74**, 2340 (1952); (b) R. C. Osthoff, Ph.D. Thesis, Harvard University, 1951.

(24) C. P. Smyth in A. Weissberger's "Physical Methods of Organic Chemistry," Vol. I, Part II, Second Edition, Interscience Publishers, Inc., New York, N. Y., 1949, p. 1611.

(25) I. F. Halverstadt and W. D. Kumler, THIS JOURNAL, **64**, 2988 (1942).

(26) J. A. Leermakers and A. Weissberger, in H. Gilman's "Organic Chemistry," Vol. II, Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 1751.

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[CONTRIBUTION FROM THE DIVISION OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF WISCONSIN]

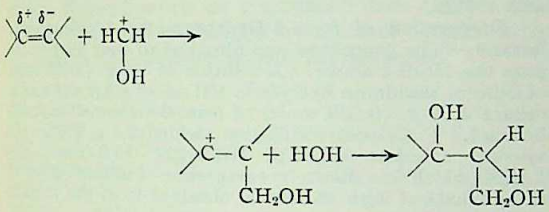
Stereochemistry of the Prins Reaction with Cyclohexene

BY EDWARD E. SMISSMAN AND ROBERT A. MODE

RECEIVED NOVEMBER 26, 1956

The reaction of formaldehyde with cyclohexene in acid media has been shown to give *trans*-2-hydroxymethyl-1-hydroxycyclohexane as the only 1,3-diol. No *cis*-diol was obtained.

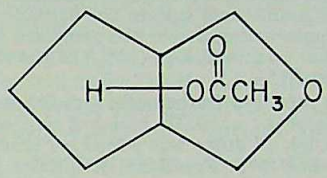
The mechanism of the Prins reaction has been reviewed and reported by Franzen and Krauch[1] to involve the initial protonation of formaldehyde followed by attachment of the hydroxymethyl carbonium ion to the double bond and finally solvolysis of the resulting carbonium ion. We have



investigated the stereochemistry of this reaction using cyclohexene and have found that only *trans*-diol is formed. Blomquist and Wolinsky[2] have studied this same reaction and have obtained the same results. We prepared the *cis*- and *trans*-2-hydroxymethyl-1-hydroxycyclohexane by reduction of 2-carbethoxycyclohexanone. Catalytic reduction gave predominantly *cis*-2-carbethoxycyclohexanol.[3] The *trans*-2-carboxycyclohexanol was obtained by epimerization of the *cis* compound in basic solution. The *cis*- and *trans*-2-carboxycyclohexanol esters were reduced to the corresponding 1,3-diols with lithium aluminum hydride. The *cis*-diol was shown to be a solid while the *trans*-diol and the product obtained from the Prins reaction were viscous liquids. Infrared spectra of *trans*-diol and the Prins reaction product were superimposable while the *cis*-diol spectra were found to differ markedly above the 8μ region.

The configuration has been shown to be *trans*. The exact mechanism of the reaction cannot be postulated until the conformational aspects have been studied. If the mechanism reported in the paper of Franzen and Krauch[1] was correct, a mixture of *cis*- and *trans*-diol should be obtained. If the initial attack of the hydroxymethylcarbonium ion is axial, then the resulting *trans*-diol must go to the flip conformation to produce the acetonide which we isolated. The conformational study would require a system incapable of undergoing a change in conformation once it is formed.

Other products are obtained during the Prins reaction, and these have been discussed by Olsen and Padberg[5] and more recently by Blomquist and Wolinsky.[2] One of the most important of these is hexahydrophthalanyl acetate, reported by Blomquist and Wolinsky to have the structure



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Experimental

Preparation of *trans*-2-Hydroxymethyl-1-hydroxycyclohexane by the Prins Reaction.[4]—Two hundred grams (2.22 moles) of trioxane, 1200 ml. of glacial acetic acid and 100 ml. of concentrated sulfuric acid were placed in a 2-l. three-necked flask. The mixture was heated (100–110°) until the trioxane depolymerized. The solution was allowed to cool to room temperature and 480 g. (5.84 moles) of freshly distilled cyclohexene was added dropwise over a period of 2 hr., the temperature being maintained between 45 and 65°. After completion of addition, the mixture was heated for 1.5 hr. at 65° and then stirred for 24 hr. at room temperature. One liter of water was then added to the mixture and the solution was extracted with three 750-ml. portions of ether. The ether was washed with water, saturated sodium bicarbonate solution until neutral and then with water. After concentration the crude product was fractionally distilled. The following higher boiling fractions containing the desired product were obtained: 1, b.p. 78–87° (0.80 mm.), 164 g.; 2, b.p. 88–93° (0.80 mm.), 179 g. Fraction 2 consisted, for the most part, of the diacetate of 2-hydroxymethyl-1-hydroxycyclohexane. Fraction 1 was found to contain only about 50% of the desired diacetate of the 1,3-glycol, the remainder consisting of the hexahydrophthalanyl acetate postulated by Olsen and Padberg.[5]

Fraction 2 (179 g.) was saponified with a solution of 94 g. of potassium hydroxide dissolved in 300 ml. of 6:1 aqueous alcohol. The solution was concentrated *in vacuo* and then extracted with ether. Fractional distillation gave a quantitative yield of a very viscous, water-clear, odorless glycol, b.p. 101–103° (0.96 mm.), n^{25}D 1.4840, bis-phenylurethan, m.p. 159–160°.

Saponification of fraction one (163.4 g.) yielded only 42 g. (49%) of the desired glycol. The remainder consisted of hexahydrophthalanol whose structure was postulated by Olsen and Padberg.[5]

The over-all yield of *trans*-2-hydroxymethyl-1-hydroxycyclohexane (configuration proved by infrared comparison with stereospecifically prepared *trans*-glycol) was found to be 150 g. (19.7%). Acid hydrolysis of the formaldehyde acetal of 2-hydroxymethyl-1-hydroxycyclohexane also yields the *trans*-glycol. This acetal is found in lower boiling fractions and is stable to base.

Preparation of 2-Carbethoxycyclohexanol.—Seventy-three and eight-tenths grams (0.433 mole) of 2-carbethoxycyclohexanone,[6] 70 ml. of absolute ethanol and 1.5 g. of Adams catalyst were placed in a hydrogenation apparatus.[7] The mixture was hydrogenated for 48 hr. at room temperature and five atmospheres pressure. The theoretical amount of

(1) V. Franzen and H. Krauch, *Chem. Ztg.*, **79**, 335 (1955).
(2) A. Blomquist and J. Wolinsky, THIS JOURNAL, in press.
(3) J. Pascual, J. Sistane and A. Regas, *J. Chem. Soc.*, 1943 (1949).
(4) J. Matti, *Bull. soc. chim. France*, **51**, 974 (1932).
(5) S. Olsen and H. Padberg, *Z. Naturforsch.*, **1**, 448 (1946).
(6) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 581.
(7) Reference 6, Coll. Vol. I, p. 61.

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hydrogen was consumed and on fractional distillation, 65 g. (87%), of *cis*-2-carbethoxycyclohexanol, b.p. 125–217° (27 mm.), $n^{25}D$ 1.4585 (lit.[3] 117–118° (17 mm.)).

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.94; H, 9.47.

Preparation of *cis*-2-Carboxycyclohexanol.—A mixture of 14.5 g. (0.08 mole) of 2-carbethoxycyclohexanol (95% *cis*) and 45 ml. of 25% aq. sodium hydroxide was stirred for 12 hr. The sodium salt of *cis*-2-carboxycyclohexanol acid separated and was filtered. It was dissolved in a small amount of water and the solution made acid to congo red with 10% hydrochloric acid. The aqueous solution was saturated with ammonium sulfate and extracted with ether. The ether-soluble material was recrystallized from a small amount of ether to give 5.4 g. (44%) of the *cis*-acid, m.p. 79–80° (lit.[3] 80–81°).

Preparation of *cis*-2-Carbomethoxycyclohexanol.—To a cooled solution of 5.1 g. (0.035 mole) of *cis*-2-carboxycyclohexanol in 25 ml. of ether was added an ether solution of diazomethane at 0–5°. Fractional distillation gave a quantitative yield of the desired ester, b.p. 87.5–88.5° (3 mm.), $n^{25}D$ 1.4647 (lit.[3] b.p. 105° (14 mm.), $n^{25}D$ 1.4645).

Preparation of *cis*-2-Hydroxymethyl-1-hydroxycyclohexane.—To a solution of 1.44 g. (0.038 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether, we added 5.4 g. (0.034 mole) of *cis*-2-carbomethoxycyclohexanol in an equal volume of ether at such a rate as to maintain slow refluxing. After addition was complete, the mixture was refluxed and stirred for an additional 1.5 hr. The excess lithium aluminum hydride was decomposed with moist ether followed by water and the metal alkoxides with cold dilute sulfuric acid. The aqueous solution was saturated with ammonium sulfate and extracted with ether. Distillation of the resulting glycol yielded a very viscous, colorless oil, b.p. 124° (2 mm.). On standing several hr. the glycol crystallized, m.p. 48–49° (lit.[8] 49–50°).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.65; H, 10.48.

The di-*p*-nitrobenzoate of *cis*-2-hydroxymethyl-1-hydroxycyclohexane was prepared by the usual procedure for these derivatives, m.p. 133.5–134 (lit.[9] 134°). The mono-*p*-nitrobenzoate, previously unreported, also was isolated, m.p. 95–96°.

Anal. Calcd. for $C_{14}H_{17}O_5N$: C, 60.28; H, 6.14; N, 5.02. Found: C, 59.60; H, 6.03; N, 5.00.

Preparation of *trans*-2-Carboxycyclohexanol.—The mother liquors from the preparation of *cis*-2-carboxycyclohexanol were concentrated *in vacuo* and refluxed with 7.5 *N* potassium hydroxide. The mixture was cooled, acidified to congo red with sulfuric acid and saturated with ammonium sulfate. The aqueous solution was extracted several times with ether. The *trans*-acid was recrystallized from ethyl acetate, m.p. 109–111° (lit.[3] m.p. 111°).

In a similar epimerization 12.1 g. (0.072 mole) of sodium *cis*-cyclohexanol-2-carboxylate was transformed into the *trans*-acid by refluxing with base. The yield was 5.6 g. (54%) of pure *trans*-acid.

Preparation of *trans*-2-Carbomethoxycyclohexanol.—The procedure was identical to that used for the *cis*-ester. Fractional distillation yielded a quantitative amount of the *trans*-methyl ester, b.p. 99.8–101.8° (2 mm.), m.p. 34–35°, $n^{25}D$ 1.4632.

Preparation of *trans*-2-Hydroxymethyl-1-hydroxycyclohexane.—The procedure was identical to that used to prepare the *cis*-diol above. A solution of 1.3 g. (0.032 mole) of lithium aluminum hydride in 100 ml. of ether was used to reduce 4.54 g. (0.029 mole) of *trans*-2-carbomethoxycyclohexanol. Fractional distillation yielded 2.4 g. (63%) of a viscous, colorless oil, b.p. 103.5–104° (0.9 mm.), $n^{25}D$ 1.4829, which was shown by comparison of infrared spectrum to be identical with the glycol obtained from the Prins reaction.

The acetonide of *trans*-2-hydroxymethyl-1-hydroxycyclohexane was prepared, b.p. 106–107° (30 mm.), 214–216° (740 mm.), $n^{25}D$ 1.4602.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.60; H, 10.75.

The bis-phenylurethan of *trans*-2-hydroxymethyl-1-hydroxycyclohexanol melted at 159–160.5° (lit.[5] m.p. 160–161).

(8) S. Siegel, THIS JOURNAL, **75**, 1317 (1953).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Epoxyethers. XI. O→O Acyl Migrations with α-Hydroxyacylals

BY CALVIN L. STEVENS AND BERNARD T. GILLIS[1,2]

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1,2-Epoxy-1-methoxy-2-methylpropane (X) was isolated in good yield from the reaction of α-haloisobutyraldehydes with dry sodium methoxide. This epoxyether X reacted with organic acids to form relatively stable α-hydroxyacylals XI (pseudoesters) which readily underwent O → O acyl migration with the loss of alcohol to give esters of α-hydroxyisobutyraldehyde (XIII). At 150°, the 3,5-dinitrobenzoate pseudoester XI eliminated 3,5-dinitrobenzoic acid to form the dioxane derivative IX.

The reaction of an organic acid with an epoxyether has been shown previously to give an α-ketoester. In one example, the intermediate α-hydroxyacylal could be isolated and was shown to undergo irreversible O→O acyl migration to form the α-ketoester and alcohol.[3] Acylals derived from aldehyde epoxyethers were found to be relatively more stable than those from ketone epoxyethers, one being distilled under reduced pressure without decomposition.[4] Since the O→O acyl migration is accompanied by formation of a carbonyl group in α-hydroxyacylals, these compounds provide unique and simple examples for the study of such migrations. The present work demonstrates that the more stable acylals from aldehyde epoxyethers can also be made to undergo acyl migration.

The aldehyde epoxyether chosen for this study was that from isobutyraldehyde. The starting α-chloroaldehyde I was prepared in 60% yield by direct chlorination of isobutyraldehyde using a modification of the method of Brown and Ash.[4,5]

(1) This work was supported by a research grant (A-769) from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

(2) Abstracted from the dissertation submitted by B. T. Gillis in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Wayne University, 1955.

(3) C. L. Stevens and S. Dykstra, THIS JOURNAL, **75**, 5975 (1953).

(4) C. L. Stevens, E. Farkas and B. Gillis, *ibid.*, **76**, 2695 (1954).

(5) H. C. Brown and A. B. Ash, *ibid.*, **77**, 4019 (1955).

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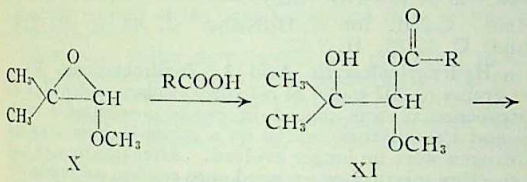
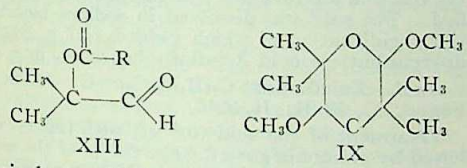
Direct bromination in the presence of calcium carbonate gave 35% of α-bromoisobutyraldehyde.[6,7] The α-haloisobutyraldehydes trimerized either in the presence of a trace of acid or during long standing. The monomeric haloaldehydes were regenerated from their trimers during distillation.

α-Chloroisobutyraldehyde and α-bromoisobutyraldehyde *gave the same* 2,4-dinitrophenylhydrazone when treated with the standard alcoholic 2,4-dinitrophenylhydrazine reagent. The α-chloroisobutyraldehyde derivative previously had been reported[8] to melt at 106°, that of α-bromoisobutyraldehyde at 116°.[9] In the present work, the derivative from both haloaldehydes, m.p. 116°, was found beyond doubt to be α-ethoxyisobutyraldehyde 2,4-dinitrophenylhydrazone. A negative Beilstein test, ultraviolet absorption spectra and carbon–hydrogen analyses supported this conclusion. Recent work of Ramirez[10] has shown that solvolysis of the α-halogen by alcohol occurs in the formation of 2,4-dinitrophenylhydrazones.



X XI



XIII IX

α-Chloroisobutyraldehyde (I) yielded 82% of α-hydroxyisobutyraldehyde dimethylacetal (II) when allowed to react with sodium methoxide in excess methanol for 1.5 hr. at 50°. The structure of II was proved by preparation of its solid 3,5-dinitrobenzoate derivative III, hydrolysis of the acetal to the aldehyde IV, followed by oxidation to the acid V. This acid was converted to an amide VI which was prepared independently from acetone cyanohydrin.

1,2-Epoxy-1-methoxy-2-methylpropane (X) was obtained in 37% yield from the reaction of α-chloroisobutyraldehyde and dry sodium methoxide in ether. The substitution of diethyl carbitol as solvent increased the yield to 53%, undoubtedly due to increased ease of isolation from the latter solvent.

The epoxyether X was identified by methanolysis to α-hydroxyisobutyraldehyde dimethylacetal in 57% yield. The infrared spectrum of the latter was superimposable on that of II obtained directly from α-chloroisobutyraldehyde. The 3,5-dinitrobenzoate derivatives of the two acetals showed no depression in melting point upon mixing.

When the epoxyether X was allowed to react with 3,5-dinitrobenzoic acid an α-hydroxyacylal XI was formed in 81% yield. The assignment of structure XI to the product of the reaction was based upon the fact that extraction of an ethereal solution with sodium carbonate solution permitted isolation of the acylal from the ether in 90% yield, proving that the acylal was not a complex of acid and epoxyether. An alternate structure, the methyl alcohol hemiacetal of α-hydroxyisobutyraldehyde 3,5-dinitrobenzoate, was eliminated since XI could be oxidized with concentrated nitric acid to give a 98% yield of 3,5-dinitrobenzoic and a 48% yield of α-hydroxyisobutyric acids; authentic α-hydroxyisobutyraldehyde 3,5-dinitrobenzoate gave 60% of α-hydroxyisobutyric acid 3,5-dinitrobenzoate under identical conditions. The fact that the Tollens test failed with XI and that methanol did not react with the aldehyde XIII to give XI provided further evidence against the hemiacetal structure. Spectral data showed the presence of hydroxyl and ester groups and together with the analytical data confirmed structure XI.

A 3,5-dinitrobenzoate acylal corresponding to XI but made from a ketone epoxyether has been shown to undergo O→O acyl migration smoothly at the melting point with the formation of an α-ketoester and alcohol.[3] This acyl migration also took place in an inert solvent at low temperatures.[3] Acylal XI behaved in a totally different manner. When heated above the melting point a change occurred and the resulting mixture partially solidified. The solid was not the aldehyde ester XIII but rather 3,5-dinitrobenzoic acid. When the pyrolysis was conducted under vacuum a second crystalline product could be isolated and shown to be the dioxane IX.

Parham[11] has shown recently that α-hydroxyacetals will undergo acetal interchange with the formation of dioxanes. Using this method IX was synthesized from α-hydroxyisobutyraldehyde dimethylacetal (II) and the crystalline isomer isolated shown to be identical in all respects with IX from the pyrolysis.

The O→O acyl migration of XI could be made to proceed smoothly at room temperature in ether solution with the aid of triethylamine catalyst. The structure of the resulting α-hydroxyisobutyraldehyde 3,5-dinitrobenzoate (XIII) was proved by oxidation to the corresponding acid and by synthesis from the α-hydroxyacetal II.

The epoxyether X reacted readily with acetic acid at 0° to give the acylal XI in which R is methyl in 58% yield. This liquid acylal could be distilled under reduced pressure without decomposition. However, when the acylal was heated in the presence of triethylamine catalyst, O→O acetyl migration proceeded smoothly with the evolution of methanol and the formation of α-acetoxyisobutyraldehyde in 79% yield.

Experimental

α-Chloroisobutyraldehyde (I).—In a 500-ml. flask equipped with a dropping funnel, stirrer and reflux condenser protected with a drying tube was placed 72.1 g. (1.0 mole) of isobutyraldehyde. To the aldehyde 135.0 g. (1.0 mole) of freshly distilled sulfuryl chloride was added slowly with agitation to maintain a temperature of 25–40°. After the addition was complete, the reaction was heated for 2 hr.

(6) H. Erlenmeyer and J. P. Jung, *Helv. Chim. Acta*, **32**, 35 (1949).
(7) I. Heilbron, E. R. H. Jones, R. W. Richardson and F. Sondheimer, *J. Chem. Soc.*, 737 (1949).
(8) A. Krattiger, *Bull. soc. chim. France*, 222 (1953).
(9) P. Z. Bedoukian, THIS JOURNAL, **66**, 1325 (1944).
(10) F. Ramirez and A. F. Kirby, *ibid.*, **76**, 1026 (1954).
(11) W. E. Parham, H. Wynberg and F. L. Ramp, *ibid.*, **75**, 2065 (1953); W. E. Parham and H. E. Reed, *ibid.*, **77**, 6391 (1955).

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and stirred for 4 hr., then flash distilled at 40 mm. pressure at a temperature of 80°. Final distillation through a 15-cm. Vigreux column gave 64 g. (60%) of α-chloroisobutyraldehyde,[8] b.p. 86–89°, $n^{25}D$ 1.4081, d^{25} 1.0199. The product contained 33.2% chlorine (calcd. 33.3%).

A 2,4-dinitrophenylhydrazone derivative of the α-chloroisobutyraldehyde was prepared by the method of Shriner and Fuson,[12] m.p. 116°, and corresponded to α-ethoxyisobutyraldehyde 2,4-dinitrophenylhydrazone, λ_{max} 357 mμ (95% alcohol).

Anal. Calcd. for $C_{12}H_{16}N_4O_5$: C, 48.64; H, 5.44. Found: C, 48.07; H, 5.49.

α-Chloroisobutyraldehyde (18 g., 0.168 mole) was added dropwise with stirring to an excess of concentrated nitric acid. After the evolution of nitrogen dioxide ceased, the remainder of the nitrogen dioxide was aerated from the mixture which then was extracted continuously with ether for 5 days. The ether was removed and the residue was refluxed with excess thionyl chloride for 3 hr. Distillation yielded 16 g. (68%) of α-chloroisobutyryl chloride,[13] b.p. 95–113°. Refractionation of the acid chloride gave a b.p. 111–112.5°, $n^{25}D$ 1.4313, d^{25} 1.1802.

The acid chloride could be converted in 77% yield to the known α-chloroisobutyramide,[14] m.p. 118–119°, and in 79% yield to the known α-chloroisobutyr-*p*-toluidide,[15] m.p. 68–69°.

The α-chloroisobutyraldehyde was trimerized by a trace of acid and the resultant solid trimer[16] melted at 106–107°. The monomeric α-chloroisobutyraldehyde could be regenerated from the trimer by heat and distillation.

α-Bromoisobutyraldehyde.—In a 1-l. flask equipped with condenser, drying tube, stirrer and dropping funnel was placed 150 g. (2.1 moles) of isobutyraldehyde, 200 ml. of carbon disulfide and 250 g. (2.5 moles) of calcium carbonate. Added slowly with agitation was 330 g. (2.06 moles) of bromine. Upon completion of the addition, the reaction mixture was stirred for 4 hr. and the excess bromine destroyed with sodium thiosulfate. The salts were removed by filtration and washed with carbon disulfide and the combined solution dried over anhydrous sodium sulfate. After filtration, the solution was distilled at atmospheric pressure through a 15-cm. Vigreux column to yield 106 g. (35%) of α-bromoisobutyraldehyde, b.p. 108–112°, $n^{25}D$ 1.4567. Redistillation gave b.p. 111–112°, d^{25} 1.4044, $n^{25}D$ 1.4500. The bromine content was 52.6% (calcd. 52.9).

The α-bromoisobutyraldehyde was trimerized in the same manner as the α-chloroisobutyraldehyde to yield a white solid,[17] m.p. 129–130°. The monomeric α-bromoisobutyraldehyde could be generated from the trimer by distillation.

A 2,4-dinitrophenylhydrazone derivative of the α-bromoisobutyraldehyde was prepared by the method of Shriner and Fuson[12] and melted at 116°. A mixture melting point determination with the derivative obtained from α-chloroisobutyraldehyde was undepressed.

α-Hydroxyisobutyraldehyde Dimethylacetal (II).—To 200 ml. of anhydrous methanol was added 6.5 g. (0.28 g. atom) of freshly cut sodium metal. After the sodium was completely dissolved, the sodium methoxide solution was cooled to 0° and 30 g. (0.282 mole) of α-chloroisobutyraldehyde was introduced over a period of 5 minutes. The reaction mixture was heated at 50° with stirring for 1.5 hr. The precipitated salt was removed by centrifugation and washed once with ether. The solutions were combined and distilled through a 30-cm. tubular column at atmospheric pressure to yield 31 g. (82%) of α-hydroxyisobutyraldehyde dimethylacetal, b.p. 148–149°, d^{25} 0.9694, $n^{25}D$ 1.4123.

Anal. Calcd. for $C_6H_{14}O_3$: C, 53.70; H, 10.51. Found: C, 53.42; H, 10.55.

α-Hydroxyisobutyraldehyde Dimethylacetal 3,5-Dinitrobenzoate (III).—To 8.36 g. (0.036 mole) of 3,5-dinitrobenzoyl chloride in excess anhydrous pyridine was added 4.88 g. (0.036 mole) of α-hydroxyisobutyraldehyde dimethylacetal. The reactants were heated and then poured onto cracked ice. A solid resulted which was filtered, dissolved in ether, extracted with sodium bicarbonate and saturated sodium chloride solution and then poured through anhydrous sodium sulfate. The ether was removed and 7.2 g. (61%) of α-hydroxyisobutyraldehyde dimethylacetal 3,5-dinitrobenzoate, m.p. 70–71°, was obtained. Recrystallization from a methanol–water mixture raised the melting point to 71–72°.

Anal. Calcd. for $C_{13}H_{16}N_2O_8$: C, 47.56; H, 4.91. Found: C, 47.81; H, 5.20.

α-Hydroxyisobutyraldehyde 3,5-Dinitrobenzoate (IV).—The acetal III (0.86 g., 0.0026 mole) and 14 ml. of concentrated hydrochloric acid were mixed and warmed. To this mixture was added 5 ml. of water and the reaction was heated 30 minutes on a steam-bath. The reaction mixture was then poured onto cracked ice from which 0.39 g. (53%) of α-hydroxyisobutyraldehyde 3,5-dinitrobenzoate, m.p. 140–142°, was isolated. An analytical sample melted at 143–144°.

Anal. Calcd. for $C_{11}H_{10}N_2O_7$: C, 46.81; H, 3.57. Found: C, 46.57; H, 3.58.

A 2,4-dinitrophenylhydrazone derivative of the aldehyde was prepared according to the directions of Shriner and Fuson,[12] m.p. 174–175° (dec).

Anal. Calcd. for $C_{17}H_{14}N_6O_{10}$: C, 44.16; H, 3.06. Found: C, 43.72; H, 3.42.

α-Hydroxyisobutyric Acid 3,5-Dinitrobenzoate (V).—Two grams (0.007 mole) of α-hydroxyisobutyraldehyde 3,5-dinitrobenzoate was placed in excess concentrated nitric acid and the mixture heated on a steam-bath until oxides of nitrogen were no longer evolved. After this time (3 hr.) the reaction mixture was poured onto cracked ice and solidified. The solid was dissolved in sodium bicarbonate solution, acidification of which yielded 1.27 g. (60%) of α-hydroxyisobutyric acid 3,5-dinitrobenzoate, m.p. 149–150°.

Anal. Calcd. for $C_{11}H_{10}N_2O_8$: C, 44.30; H, 3.38. Found: C, 43.94; H, 3.45.

Treatment of the acid (0.5 g.) with thionyl chloride followed by ammonia gave 0.40 g. (80%) of the α-hydroxyisobutyramide 3,5-dinitrobenzoate (VI), m.p. 177–178°.

Anal. Calcd. for $C_{11}H_{11}N_3O_7$: C, 44.44; H, 3.73. Found: C, 44.60; H, 3.97.

Acetone Cyanohydrin 3,5-Dinitrobenzoate.—Acetone cyanohydrin (5 g., 0.06 mole), 26.9 g. (0.117 mole) of 3,5-dinitrobenzoyl chloride and 10 ml. of anhydrous pyridine were mixed and heated on a steam-bath for 2 hr. From the reaction 14.88 g. (89%) of acetone cyanohydrin 3,5-dinitrobenzoate (VII), m.p. 125–126°, was isolated.

Anal. Calcd. for $C_{11}H_9N_3O_6$: C, 47.32; H, 3.25. Found: C, 46.86; H, 3.35.

Hydrolysis of 1.0 g. (0.00358 mole) of the above nitrile was accomplished in sulfuric acid solution to give 0.56 g. (53%) of α-hydroxyisobutyramide 3,5-dinitrobenzoate, m.p. 168–172°. Recrystallization from ethanol resulted in a solid, m.p. 178–179°, whose infrared absorption spectrum was superimposable with the amide obtained from the parent acid. A mixture melting point of the two amides was undepressed.

2,2,5,5-Tetramethyl-3,6-dimethoxy-*p*-dioxane (IX).—α-Hydroxyisobutyraldehyde dimethylacetal (12 g., 0.0894 mole) and a drop of sulfuric acid were heated to 100°. From the reaction 3.3 ml. of methanol, $n^{25}D$ 1.3270, was collected. The remaining material in the flask solidified at room temperature and amounted to 8.54 g. of 2,2,5,5-tetramethyl-3,6-dimethoxy-*p*-dioxane, m.p. 58–61°. The infrared spectrum of this compound had no hydroxyl or carbonyl absorption. A small sample sublimed at room temperature and 1 mm. pressure to give an analytical sample, m.p. 61–62°.

Anal. Calcd. for $C_{10}H_{20}O_4$: C, 58.79; H, 9.87. Found: C, 59.01; H, 9.54.

1,2-Epoxy-1-methoxy-2-methylpropane (X).—Two procedures were used. Procedure A was essentially the same as reported[4] for the reaction of α-chlorobutyraldehyde and sodium methoxide. From 25 g. of α-chloroisobutyraldehyde there was obtained 8.78 g. (37%) of 1,2-epoxy-1-methoxy-1-methylpropane, b.p. 93–94°, d^{25} 0.9036, $n^{25}D$ 1.3889.

Procedure B.—Dry sodium methoxide was prepared from

(12) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

(13) M. S. Kharasch and H. C. Brown, THIS JOURNAL, **62**, 298 (1940).

(14) C. L. Stevens, T. K. Mukherjee and V. Traynelis, *ibid.*, **78**, 2264 (1956).

(15) C. L. Stevens and J. C. French, *ibid.*, **76**, 4398 (1954).

(16) M. A. Brochet, *Ann. chim.*, [7] **10**, 352 (1897).

(17) A. Franke, *Monatsh.*, **21**, 200 (1900).

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11.5 g. (0.5 g. atom) of sodium. Diethyl carbitol was added to the dry finely powdered methoxide and the resulting slurry was cooled to 0°. To this slurry was added 39.5 g. (0.37 mole) of α-chloroisobutyraldehyde, and the reaction mixture was heated for 1.5 hr. at 50° with agitation. The product was distilled directly from the reaction mixture at 10 mm. pressure and 50° into a receiver cooled in a Dry Ice–acetone mixture. Final distillation through a 30-cm. tubular column at atmospheric pressure gave 19.97 g. (53%) of the epoxyether, b.p. 92–93°, $n^{25}D$ 1.3885.

When 28.5 g. (0.188 mole) of α-bromoisobutyraldehyde was treated with sodium methoxide following procedure B, 8.15 g. (42.5%) of the epoxyether was obtained, b.p. 91–96°, $n^{25}D$ 1.3884.

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.79; H, 9.87; OCH_3, 30.3. Found: C, 59.05; H, 10.04; OCH_3, 30.2.

To 3.65 g. (0.0357 mole) of the epoxyether in 20 ml. of anhydrous ether and 3.42 g. (0.107 mole) of anhydrous methanol at −30° was added a drop of hydrochloric acid. The reaction was then warmed slightly on a steam-bath. After cooling the flask to room temperature, the hydrochloric acid was neutralized with excess solid sodium carbonate. The reaction mixture was filtered and distilled. The α-hydroxyisobutyraldehyde dimethylacetal obtained amounted to 2.72 g. (57%), b.p. 63–64° (25 mm.), $n^{25}D$ 1.4122. The infrared spectrum of this material was superimposable on that of the acetal obtained from α-chloroisobutyraldehyde.

When 1.0 g. of the above acetal was permitted to react with 3,5-dinitrobenzoyl chloride in pyridine, 1.16 g. (48%) of the 3,5-dinitrobenzoate derivative was isolated, m.p. 70–71°. A mixture melting point determination with the authentic material obtained from α-chloroisobutyraldehyde was not depressed.

1-Methoxy-2-methylpropane-1,2-diol 1-(3,5-Dinitrobenzoate) (XI).—To 5.3 g. (0.052 mole) of epoxyether X in anhydrous ether was added 10.9 g. (0.052 mole) of 3,5-dinitrobenzoic acid in anhydrous ether. The reaction mixture was allowed to stand overnight. The ethereal solution was dried over anhydrous sodium sulfate and filtered. The ether was partially removed, the solution cooled to a sirup, a small amount of petroleum ether (30–60°) was added and upon scratching the product solidified to yield 13.18 g. (81%) of 1-methoxy-2-methylpropane-1,2-diol 1-(3,5-dinitrobenzoate), m.p. 84–85°.

Anal. Calcd. for $C_{12}H_{14}N_2O_8$: C, 45.86; H, 4.49; OCH_3, 9.87. Found: C, 45.46; H, 4.32; OCH_3, 9.99.

When 50 mg. of 1-methoxy-2-methylpropane-1,2-diol 1-(3,5-dinitrobenzoate) was placed in 50 ml. of ether and extracted with three 15-ml. portions of cold 5% sodium carbonate, no solid was obtained on acidification of the carbonate layer. Upon evaporation of the ether layer, addition of petroleum ether (30–60°) and cooling, there was obtained 45 mg. of the unchanged acylal, m.p. 81–83°. A mixture melting point with material melting 83–84° was not depressed.

Treatment of 7.74 g. (0.0246 mole) of the α-hydroxyacylal with excess nitric acid for 3 hr. on the steam-bath until oxides of nitrogen were no longer evolved gave two acids. The reaction mixture was poured onto cracked ice and filtered to give 5.10 g. (98%) of 3,5-dinitrobenzoic acid, m.p. 203–204°. The acidity of the remaining solution was reduced to *p*H 5, and the solution was continuously extracted with ether for 3 days. The ether was removed in part, the solution dried with anydrous sodium sulfate and product crystallized from a benzene–ether mixture to yield 1.22 g. (47.5%) of α-hydroxyisobutyric acid, m.p. 79°. A mixture melting point determination with the authentic hydroxy acid was undepressed. The infrared spectra of the two samples were superimposable.

Pyrolysis of 1-Methoxy-2-methylpropane-1,2-diol 1-(3,5-Dinitrobenzoate).—In a molecular still, 4.5 g. (0.014 mole) of the solid α-hydroxyacylal was placed under a pressure of 5 mm. and heated. The acylal melted cleanly and when the temperature reached 135°, vigorous bubbling occurred and the melt resolidified. After 0.5 hr. the solid residue dissolved in a bicarbonate solution and upon reacidification yielded 2.58 g. (85%) of 3,5-dinitrobenzoic acid, m.p. 203–204°. A mixture melting point determination with authentic acid showed no depression. The distillate from the pyrolysis amounted to 1.05 g. (73%) of semi-solid 2,2,5,5-tetramethyl-3,6-dimethoxy-*p*-dioxane, which probably contained both *cis* and *trans* isomers. Recrystallization from petroleum ether yielded an analytical sample, m.p. 61–62°. The infrared absorption of this compound and the compound obtained by pyrolysis of the α-hydroxyisobutyraldehyde dimethylacetal were identical.

Anal. Calcd. for $C_{10}H_{20}O_4$: C, 58.79; H, 9.87. Found: C, 58.60; H, 9.68.

Rearrangement of 1-Methoxy-2-methylpropane-1,2-diol 1-(3,5-Dinitrobenzoate).—To 5 g. (0.016 mole) of 1-methoxy-2-methylpropane-1,2-diol 1-(3,5-dinitrobenzoate) dissolved in ether was added a catalytic amount of triethylamine. After the solution remained at room temperature overnight, white crystals had formed. The solid was filtered and amounted to 4.08 g. (90%) of α-hydroxyisobutyraldehyde 3,5-dinitrobenzoate, m.p. 143–144°. A mixture melting point determination with authentic material from hydrolysis of α-hydroxyisobutyraldehyde dimethylacetal 3,5-dinitrobenzoate was not depressed.

Into a 10-ml. erlenmeyer flask was placed 0.5 g. (0.0016 mole) of the solid acylal in anhydrous benzene, and the solution was heated for 4 hr. Upon evaporating off the benzene an oil formed which was cooled, scratched and solidified. Ligroin and acetone were added and the solution was cooled to yield a white solid, 0.13 g. (29%), of the α-hydroxyisobutyraldehyde 3,5-dinitrobenzoate, m.p. 141–143°. A mixture melting point with the material above was not depressed, m.p. 142–143°.

1-Methoxy-2-methylpropane-1,2-diol 1-Acetate (XI).—Ten grams (0.0978 mole) of epoxyether was dissolved in 70 ml. of anhydrous ether, cooled to 0°, and 5.87 g. (0.0978 mole) of pure acetic acid in 20 ml. of anhydrous ether was added. The reaction mixture was stoppered, placed in a desiccator, and permitted to stand in the refrigerator overnight. The mixture was then extracted with three 20-ml. portions of cold saturated sodium bicarbonate and dried over anhydrous sodium sulfate. After filtration and removal of the ether under vacuum, the liquid acylal was distilled. The yield was 9.27 g. (58.4%) of 1-methoxy-2-methylpropane-1,2-diol 1-acetate, b.p. 84–85° (13 mm.), d^{25} 1.0454, $n^{25}D$ 1.4187.

Anal. Calcd. for $C_7H_{14}O_4$: C, 51.83; H, 8.70; OCH_3, 19.13. Found: C, 51.59; H, 8.97; OCH_3, 19.16.

Rearrangement of 1-Methoxy-2-methylpropane-1,2-diol 1-Acetate.—The liquid α-hydroxyacylal (5 g., 0.0308 mole) and 0.5 ml. of triethylamine were heated to 90° for 3 hr. The temperature was then raised to 105° and methanol and the triethylamine were collected until approximately the theoretical amount of methanol had been removed. The residue was then distilled at reduced pressure to yield 3.17 g. (79%) of α-acetoxyisobutyraldehyde, b.p. 79–81° (50 mm.), d^{25} 1.0155, $n^{25}D$ 1.4093.

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 54.86; H, 8.09.

A 2,4-dinitrophenylhydrazone derivative melted at 113–114°. *Anal.* Calcd. for $C_{12}H_{14}N_4O_6$: C, 46.44; H, 4.54. Found: C, 46.20; H, 4.82.

Acknowledgment.—The authors wish to thank Dr. J. M. Vandenbelt of Parke, Davis and Co. for determination of the ultraviolet spectra.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE HEBREW UNIVERSITY]

The Reaction of Acetals with Malonic Acid and its Derivatives. A Contribution to the Knowledge of the Knoevenagel–Doebner Reaction

BY J. KLEIN AND ERNST D. BERGMANN

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The acetals of aromatic aldehydes, cinnamic aldehydes and—with lower yields—also of aliphatic aldehydes react with malonic acid in the presence of pyridine and piperidine in the manner of a Knoevenagel reaction. The reaction does not proceed *via* the free aldehydes. Ethyl hydrogen malonate reacts with these acetals analogously in the absence of any catalyst, giving the corresponding ethyl hydrogen arylidene- and cinnamylidene-malonates. A reaction mechanism is proposed, invoking the formation of a hydrogen-bonded complex between the two components of the reaction mixture.

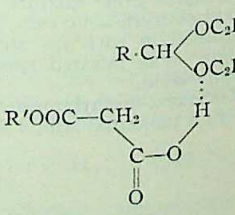
In a study to be published elsewhere, it was found that the acetals of 2-phenyl-1,2,3,6-tetrahydro- and 2-phenyl-hexahydrobenzaldehyde react with malonic acid in the presence of pyridine and piperidine in the manner of a Knoevenagel reaction, giving the corresponding hydrogenated 2-phenylcinnamic acids, with liberation of carbon dioxide. A systematic study of the reaction between dialkyl acetals of aldehydes and malonic acid led to the following conclusions: the diethylacetals of aromatic and of cinnamic aldehydes condense with malonic acid in quantitative yields. The aromatic aldehyde acetals thus give cinnamic acids. This is particularly noteworthy in the case of *p*-dimethylaminobenzaldehyde diethylacetal; this aldehyde is refractory in the Perkin reaction[1] but gives[2] by Doebner's method a yield of 85%. Bulky *o*-substituents (not, *e.g.*, *o*-methoxy) decrease the yield under the same operating conditions (to 50–60%); prolongation of the reaction time gives satisfactory yields also in these cases. It appears that these substituents decrease the rate at which condensation takes place. The acetals of aliphatic and hydroaromatic aldehydes react more slowly than those of aromatic ones, giving α,β-unsaturated monocarboxylic acids. The yields were low, but at least in a number of these cases the acetals have been recovered, so that not the yield but rather the conversion rates appear to be affected adversely.

The reaction between the acetals of cinnamic aldehydes and malonic acid leads to mixtures of the corresponding malonic and monocarboxylic acids; it has been shown that the former are decarboxylated only slowly, even in boiling pyridine.[3] Thus it must be assumed that the proximity of the aryl groups accelerates the decarboxylation. This assumption is supported by the observation that ethyl hydrogen (*p*-methylbenzylidene)-malonate (see below) is decarboxylated within a few minutes, when heated in boiling piperidine.

The mechanism of these reactions is not without interest. Under the experimental conditions employed, the acetals appear to condense directly and not *via* the aldehydes.[4,5] This point is emphasized by analogous experiments carried out with ethyl hydrogen malonate, which has been used before[6,7] in the Knoevenagel reaction with aromatic aldehydes, giving substituted ethyl cinnamates in the presence of pyridine and piperidine. Heated with the acetals of *p*-tolualdehyde and cinnamaldehyde in benzene without any addition of a catalyst, good yields (60 and 89% respectively) of ethyl hydrogen (*p*-methylbenzylidene)- and cinnamylidene-malonates were obtained. Under the same conditions, *free* *p*-tolualdehyde did not give appreciable amounts (6%) of ethyl hydrogen (*p*-methylbenzylidene)-malonate; also when an azeotropic trap was used to remove the water formed during the reaction, about the same yield (4%) of ethyl hydrogen (*p*-methylbenzylidene)-malonate was obtained.

Whilst in the reaction with the acetal of *p*-tolualdehyde only one of the possible stereoisomers was isolated, there is strong indication that with the acetal of cinnamaldehyde a mixture of two stereomeric compounds is formed, one of which has been isolated in pure form. The unresolved remaining mixture had the theoretically expected molecular weight and practically the same absorption spectrum as the pure isomer.

For an understanding of the reaction mechanism, it is of importance to note that diethyl malonate under the same conditions, *i.e.*, without catalyst, does not condense at all with *p*-tolualdehyde: at least one free carboxyl group is necessary for the reaction. Addition of piperidine caused the condensation to proceed with a yield of 2%, and alternative addition of *p*-toluenesulfonic acid led to about 5% of diethyl (*p*-methylbenzylidene)-malonate. In the latter case, incidentally, ethyl alcohol is liberated more quickly, but this is not followed by condensation. We believe, therefore, that the primary reaction is the formation of a complex between the acetal and the acid, based on a hydrogen bond



(1) H. Meyer and R. Beer, *Monatsh.*, **34**, 649 (1913).

(2) Ch. W. Shoppee, *J. Chem. Soc.*, 968 (1930).

(3) The relatively high stability of substances such as cinnamylidenemalonic acid has been commented upon before. See J. R. Johnson, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 210, especially p. 227.

(4) G. Charles (*Compt. rend.*, **242**, 2468 (1956)) has reported that benzophenoneimine reacts more quickly and with better yields with substances like malononitrile than benzophenone, even in the presence of catalysts.

(5) It is interesting to recall that originally W. A. Perkin (*J. Chem. Soc.*, **31**, 424 (1877); **49**, 317 (1886)) had suggested as the intermediate steps in the reaction of benzaldehyde and acetic anhydride the two compounds: $C_6H_5CH(OCOCH_3)_2$ and $C_6H_5(OCOCH_3)CH_2COOH$. However, this hypothesis has been refuted by the studies of F. Boeck, G. Lock and K. Schmidt, *Monatsh.*, **64**, 401 (1934).

(6) A. Calderbank, *Chem. News*, **173**, 376 (1946).

(7) K. Freudenberg and H. Schraube, *Ber.*, **88**, 16 (1955).

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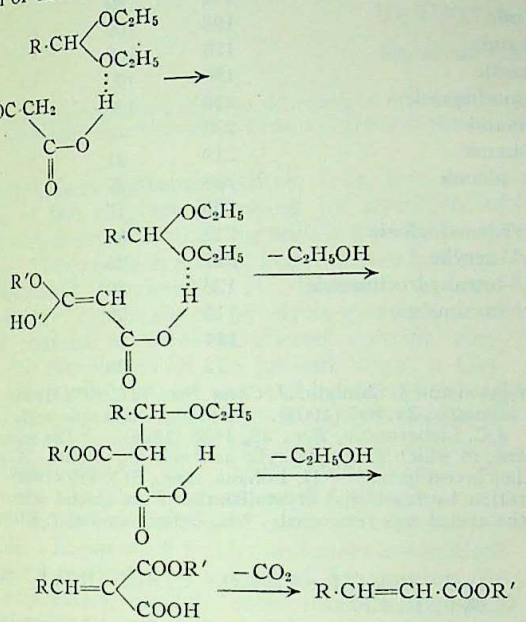
Thus the methylene group of the acid component is brought into the immediate vicinity of the central atom of the acetal molecule which then reacts



As in the case of the Knoevenagel reaction in the classical sense, the decarboxylation step requires the presence of pyridine,[8] whilst the elimination of ethanol from the ethoxydicarboxylic acid or its monoester appears to be spontaneous.

It is interesting to note that the cyclic acetal formed from benzaldehyde and ethylene glycol (2-phenyl-1,3-dioxolane) is capable of the same reaction with malonic acid as the diethylacetal, giving cinnamic acid. However, under comparable conditions, the yield is very much lower for the cyclic acetal. It seems likely that the oxygen atoms in the cyclic structure are less prone to form hydrogen bonds than those in an open acetal.

Whether this hypothesis really represents the facts can only be decided by kinetic measurements which will be reported in a later publication. The possibility that this condensation proceeds *via* the free cation $ArCH{\cdot}OC_2H_5^+$ which may be formed under the influence of the acid present in the reaction mixture is made improbable by the observation that when *p*-tolualdehyde diethylacetal was heated with diethyl malonate in the presence of equimolar amounts of *p*-nitrobenzoic or chloroacetic acids (these acids having approximately the same *pK* as hydrogen ethyl malonate), only 1–4% of the condensation product was obtained.

Experimental

Preparation of Diethylacetals. Method I.—The aldehyde (1 mole), ethyl orthoformate (1.1 mole) and anhydrous ethanol (three times the weight of the orthoformate) were kept for 12 hr. at room temperature, after a few drops of a saturated solution of hydrogen chloride in alcohol had been added. The mixture was stirred with an excess of solid sodium carbonate for 15 minutes, diluted with an equal volume of ether, filtered and distilled.

Method II.—Instead of hydrogen chloride, ammonium nitrate[9] (1 g.) was used as catalyst and the mixture refluxed for 30 minutes, cooled, treated with solid sodium carbonate and worked up as above. The properties of the diethylacetals are recorded in Table I.

Acetaldehyde dibutylacetal was prepared according to Weizmann, Bergmann and Sulzbacher,[10] b.p. 184°, and 2-phenyl-1,3-dioxolane according to Hibbert and Timm,[11] b.p. 134° (40 mm.).

Reaction of the Acetals with Malonic Acid.—The mixture of the acetal (0.1 mole), malonic acid (0.2 mole), pyridine (42 ml.) and piperidine (2 ml.) was heated at 100° for 3 hr. and at 140° for 30 minutes; it was then cooled and poured into a mixture of ice and concentrated hydrochloric acid. Crystalline products were filtered, oily ones isolated by extraction with ether. These ether extracts were treated with 5% sodium carbonate solution and the acidic products liberated with dilute acid and extracted again with ether. The results are summarized in Table II.

Reaction of *p*-Tolualdehyde Diethylacetal with Ethyl Hydrogen Malonate.—Ethyl hydrogen malonate was prepared according to Breslow, Baumgarten and Hauser.[12,13] (a) From a solution of 9.7 g. of the acetal in 65 ml. of benzene, 15 ml. of the solvent was distilled off, in order to remove

TABLE I

Aldehyde	Method of prepn.	Yield, %	B.p. °C.	Mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Benzaldehyde[a]	I	83	215–218					
p-Methylbenzaldehyde[b]	I	85	128–130	30				
p-Methoxybenzaldehyde[c]	I	95	140	16				
o-Methoxybenzaldehyde	I	83	155	30	68.6	68.8	8.6	8.2
p-Dimethylaminobenzaldehyde	I	90	155	3.5	70.0	70.6[d]	9.4	9.2
2,4-Dichlorobenzaldehyde	II	60	154–155	21	53.2	53.3	5.6	5.7
3,4-Dichlorobenzaldehyde	I	90	175	30	53.2	52.6	5.6	5.4
Cinnamaldehyde[e]	II	95	155	23				
o-Nitrocinnamaldehyde[e]	II	93	166–170	1.5	62.2	62.7	6.8	7.0
2-Phenyl-1,2,3,6-tetrahydrobenzaldehyde[f]	I	94	124	0.9				
2-Phenylhexahydrobenzaldehyde[g,f]		98	117	0.6				
Crotonaldehyde[e,h]	I	30	143–145					

[a] E. Fischer and G. Giebe, *Ber.*, **30**, 3053 (1897); **31**, 548 (1898). [b] H. W. Post, *J. Org. Chem.*, **5**, 244 (1940). [c] L. Claisen, *Ber.*, **31**, 1010 (1898). [d] The acetal is very prone to hydrolysis, which is the reason for the unsatisfactory analysis. [e] The quantity of ethanol used was only 40% of the weight of the ethyl orthoformate. [f] E. D. Bergmann and J. Klein, unpublished results. [g] Prepared by hydrogenation of the acetal of 2-phenyl-1,2,3,6-tetrahydrobenzaldehyde. [h] A. Wohl and F. Frank, *Ber.*, **35**, 1904 (1902).

(8) *Cf.* P. N. Kuriyan, K. C. Pande and V. R. Surange, *J. Indian Chem. Soc.*, **11**, 823 (1934) (*C. A.*, **29**, 3325 (1935)).

(9) See, *e.g.*, H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 514 (1935).

(10) Ch. Weizmann, E. Bergmann and M. Sulzbacher, *J. Org. Chem.*, **15**, 918 (1950).

(11) H. Hibbert and J. A. Timm, THIS JOURNAL, **46**, 1283 (1924); *cf.* M. Sulzbacher, E. Bergmann and R. Pariser, *ibid.*, **70**, 2827 (1948).

(12) D. S. Breslow, E. Baumgarten and Ch. R. Hauser, *ibid.*, **66**, 1286 (1944).

(13) *Cf.* K. Eisenbeis and H. F. Huebner, *Ber.*, **85**, 1181 (1952).

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TABLE II

Acetal of	Product, acid	M.p., °C.	Yield, %	Remarks
Benzaldehyde	Cinnamic	133	89	
p-Methylbenzaldehyde	*p*-Methylcinnamic	198	100	*a*
p-Methoxybenzaldehyde	*p*-Methoxycinnamic	173	100	*b*
o-Methoxybenzaldehyde	*o*-Methoxycinnamic	180	100	*c*
p-Dimethylaminobenzaldehyde	*p*-Dimethylaminocinnamic	216	100	*d*
2,4-Dichlorobenzaldehyde	2,4-Dichlorocinnamic	230	15	*e,f*
3,4-Dichlorobenzaldehyde	3,4-Dichlorocinnamic	218	31	*f*
Cinnamaldehyde	Cinnamylidene-malonic	208	27	*g*
	β-Styrylacrylic[h]	165	17	*i*
o-Nitrocinnamaldehyde	*o*-Nitrocinnamylidene-malonic	212	35	*k*
	β-(*o*-Nitrostyryl)-acrylic	217	25	*m*
2-Phenyltetrahydrobenzaldehyde	2-Phenyl-1,2,3,6-tetrahydrocinnamic	126	30[n]	*o*
2-Phenylhexahydrobenzaldehyde	2-Phenylhexahydrocinnamic	115	33[p]	*o*
Crotonaldehyde	Sorbic	134	20	
Acetaldehyde	Crotonic	72	20	

[a] V. Hanzlik and Al. Bianchi, *Ber.*, **32**, 1285 (1899). [b] R. Robinson and J. Shinoda, *J. Chem. Soc.*, **127**, 1973 (1925). [c] A. Reychler, *Bull. soc. chim. France*, [4] **3**, 552 (1927). [d] L. Weil, *Monatsh.*, **29**, 895 (1908). [e] From glacial acetic acid. [f] Ch. Walling and K. B. Wolfstirn, THIS JOURNAL, **69**, 852 (1947). [g] C. Liebermann, *Ber.*, **28**, 1438 (1895). [h] The separation was carried out by fractional crystallization from boiling benzene, in which β-styrylacrylic acid is easily soluble. A certain quantity of an acidic oil also was obtained, which was not further investigated. [i] H. Lohaus, *Ann.*, **513**, 219 (1934). [k] A. Einhorn and C. Gehrenbeck, *Ann.*, **253**, 348 (1889). [l] Separation by fractional crystallization from glacial acetic acid. [m] S. Diehl and A. Einhorn, *Ber.*, **18**, 2331 (1885). [n] 56% of the acetal was recovered. [o] E. Bergmann and J. Klein, unpublished results. [p] 55% of the acetal was recovered.

traces of water, and 7.3 g. of ethyl hydrogen malonate was added. The mixture was refluxed for 10 hr. and the volatile products were removed, ultimately at 150° in a vacuum of 20 mm. The residue solidified and was recrystallized from ligroin, whereupon it melted at 95–115° (yield 6 g.). Recrystallization from benzene raised the m.p. to 124–126° and finally 127°. Analysis indicated that the product was ethyl hydrogen (*p*-methylbenzylidene)-malonate.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.7; H, 6.0. Found: C, 67.1; H, 6.1.

When the same reaction was carried out using 8 g. of *diethyl malonate*, the starting materials were recovered unchanged, after 6 hr. at reflux temperature.

(b) When the same reaction was carried out in the presence of 3 drops of piperidine and the benzene solution was extracted with 5% sodium carbonate solution, acidification gave 7 g. of a product of m.p. 118–120°, which after two recrystallizations from benzene rose to 127°. The benzene solution contained 2.8 g. of an oil which, according to the boiling point and the ability to form a dinitrophenylhydrazone under acidic conditions, was unchanged acetal.

When the reaction was repeated with 8 g. of *diethyl malonate*, 0.4 g. of diethyl *p*-methylbenzylidene-malonate was obtained.

(c) The reaction was repeated, but 50 mg. of *p*-toluenesulfonic acid was added as catalyst. Alcohol was liberated very quickly. After 24 hr., the reaction mixture was washed with water, dried and distilled. A fraction amounting to 7.8 g. boiled between 90 and 110° (20 mm.) and 4.3 g. between 155 and 185° (1.5 mm.). The latter fraction solidified quickly. It was recrystallized from ligroin (1.5 g., m.p. 100–118°) and benzene, m.p. 124–125°.

When this reaction was repeated, using 8 g. of *diethyl malonate*, there was obtained after 6 hr. of refluxing 1 g. of diethyl (*p*-methylbenzylidene)-malonate which gave, after hydrolysis, *p*-methylbenzylidenemalonic acid, m.p. 214°, after recrystallization from butyl acetate.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.1; H, 4.9. Found: C, 63.9; H, 4.7.

(d) When 4 g. of *p*-tolualdehyde, 4.5 g. of ethyl hydrogen malonate and 30 ml. of benzene were refluxed for 10 hr., the work-up gave 2.8 g. of *p*-tolualdehyde, identified as dinitrophenylhydrazone and semicarbazone, and 0.5 g. of crude ethyl hydrogen (*p*-methylbenzylidene)-malonate, m.p. 112–120°.

(e) When 2.2 g. of ethyl hydrogen (*p*-methylbenzylidene)-malonate was refluxed for 30 minutes in 10 ml. of piperidine, 1.3 g. of ethyl *p*-methylcinnamate, b.p. 142° (1 mm.), was obtained. It was identified by analysis and ultraviolet spectrum.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4. Found: C, 76.1; H, 7.4; ultraviolet spectrum (in ethanol), 223 mμ (4.23), 285 mμ (4.27).

Reaction of Cinnamaldehyde Diethylacetal and Ethyl Hydrogen Malonate.—From 10.3 g. of the acetal, 7.3 g. of ethyl hydrogen malonate, 50 ml. of benzene and 3 drops of piperidine, which were refluxed together for 10 hr., there was obtained by the usual work-up 10.5 g. of an acidic, yellow product of m.p. 75–110°. Successive recrystallization from benzene and carbon tetrachloride gave pure ethyl hydrogen cinnamylidene-malonate of sharp m.p. 119–120°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.7. Found: C, 68.7; H, 5.6; ultraviolet spectrum, 315 mμ (log ε 4.51).

The mother liquors of the recrystallization left a solid product of m.p. 69–72°, which has a molecular weight corresponding to the above compound (calcd., 246; found, 243) and practically the same absorption spectrum; however, the extinction coefficient was somewhat lower: 315 mμ (log ε 4.34).

When the reaction was repeated in the presence of 50 mg. of *p*-toluenesulfonic acid as catalyst, the yield of the crude acid (m.p. 75–110°) was only 5 g.

JERUSALEM, ISRAEL

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[CONTRIBUTION NO. 231 FROM ORCHEM LABORATORIES E. I. DU PONT DE NEMORUS & COMPANY]

Cyclic Ethers Made by Pyrolysis of Carbonate Esters

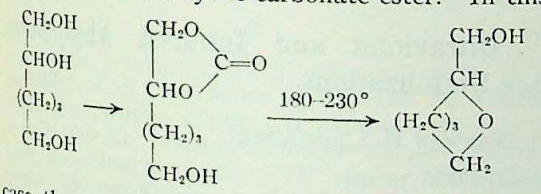
BY DEXTER B. PATTISON

RECEIVED JANUARY 17, 1957

Cyclic ethers containing three to six atoms in the ring are readily prepared in good yield by pyrolysis of the corresponding carbonate esters, if an activating hydroxyl group is present.

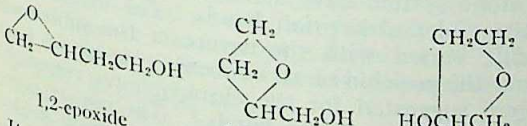
Cyclic ethers containing three, four, five or six atoms in the ring are prepared by pyrolysis of cyclic carbonate esters having one or two hydroxyl groups. The reaction is more general than has been demonstrated previously. H. Bruson[1] reported that glyceryl carbonate on pyrolysis gives glycidol, which contains a three-membered epoxide ring. Near the completion of the present work, a German patent application[2] was published describing the preparation of 3-ethyl and 3-methyloxetane-3-methanol by pyrolysis of the carbonate esters of trimethylolpropane and trimethylolethane, respectively. In the German work, phosgene was used to make the carbonate ester of trimethylolpropane. In our work a safer and more convenient laboratory method was employed for making the carbonate esters, namely, ester interchange with diethyl carbonate or ethylene carbonate.

A typical example of the formation of a six-membered oxide ring is the preparation of tetrahydropyran-2-methanol in 62% yield from 1,2,6-hexanetriol *via* the cyclic carbonate ester. In this



case the 1,5-epoxide was formed, and there was none of the 1,2- or the 1,6-epoxide. The structure was proved by the infrared spectrum which was identical with that of an authentic sample of tetrahydropyran-2-methanol.

A typical example of the formation of a five-membered ring is the synthesis of 3-hydroxytetrahydrofuran in 88% yield from 1,2,4-butanetriol *via* the cyclic carbonate ester. In this case the three possible structures of the product are shown below.



It was shown that the product was not a 1,2-epoxide because the material did not react at 100° with *n*-butylamine; and under these conditions glycidol, a 1,2-epoxide, is converted quantitatively to high boiling products, mainly 3-butylamino-1,2-propanediol. The compound had the same boiling point, refractive index and infrared spectrum as an authentic sample of 3-hydroxytetrahydrofuran[3] prepared by dehydration of 1,2,4-butanetriol using sulfuric acid as catalyst.

Four-membered oxide ring compounds which have been synthesized by this method are 3-ethyl-oxetanemethanol, 3-methyl-3-oxetanemethanol and 3,3-oxetanedimethanol.[4] They were made in yields of 87, 77 and 34%, respectively, from trimethylolpropane, trimethylolethane and pentaerythritol.

Cyclic carbonates containing no hydroxyl groups are much more stable than carbonate ester containing a hydroxyl group. For example a mixture of 2,2-diethylpropanediol and its cyclic carbonate ester can be distilled at 220° under slightly reduced pressure without decomposition, whereas the cyclic carbonate of trimethylolpropane decomposes rapidly at 180–200° to carbon dioxide and 3-ethyl-3-oxetanemethanol.

TABLE I

PREPARATION OF EPOXIDES BY PYROLYSIS OF CARBONATE ESTERS

Starting triol or tetrol	Alkyl carbonate	Product % Yield[a]	Product % Conversion[a]
1,2,6-Hexanetriol	Ethylene	62	78
1,2,4-Butanetriol	Diethyl	88	82
Trimethylolpropane	Ethylene	72	69
Trimethylolpropane	Diethyl	87	92
Trimethylolpropane	Dibutyl	83	93
Trimethylolethane	Diethyl	77	97
Pentaerythritol	Diethyl	34	100

[a] $\%\ \text{Yield} = \dfrac{\text{mol. wt. polyol}}{\dfrac{\text{g. product} \times \text{mol. wt. product}}{\text{g. polyol charged} - \text{g. polyol recovered}}} \times 100$

$\%\ \text{Conversion} = \dfrac{\text{g. polyol charged} - \text{g. polyol recovered}}{\text{g. polyol charged}} \times 100$

Experimental

Typical preparations employing ethylene carbonate or diethyl carbonate are described below. In Table I yield data are given, and in Table II physical properties and analytical data are recorded.

Tetrahydropyran-2-methanol from 1,2,6-Hexanetriol.—A mixture of 670 g. of 1,2,6-hexanetriol (5.0 moles) and 493 g. of ethylene carbonate (5.5 moles) was kept at 140–150°, and ethylene glycol (336 g.) was removed by distillation at 26–10 mm. pressure. The pot temperature was raised gradually to 250° and the pressure fell, due to carbon dioxide evolution.

Under full motor pump vacuum 510 g. of product was obtained. Part of this boiled at 100–130° under 30–130 mm. pressure, but near the end, when carbon dioxide evolution had ceased, the boiling point was 150–175° and the pressure was 2–10 mm. Redistillation through an efficient column gave 281 g. of tetrahydropyran-2-methanol, boiling at 57° at 4 mm. or 78° at 13 mm. and 150 g. of 1,2,6-hexanetriol, boiling at 174–180° at 6 mm.

(1) H. Bruson and R. Riener, THIS JOURNAL, **74**, 2100 (1952).

(2) German Application F 15046 (Jan. 5, 1956), W. Biedermann to Bayer.

(3) W. Reppe, *et al.*, *Ann.*, **596**, 80 (1956).

(4) F. Govaert and M. Beyaert, *C. A.*, **34**, 54152 (1940); *Proc. Acad. Sci. Amsterdam*, **42**, 720 (1939).

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TABLE II

PROPERTIES OF EPOXIDES CONTAINING HYDROXYL GROUPS

Compound	B.p., °C.	Press., mm.	$n^{25}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen % Calcd.	Hydrogen % Found	Hydroxyl No. Calcd.	Hydroxyl No. Found
Tetrahydropyran-2-methanol	57	4.2	1.4561	62.1	62.2	10.2	10.2	484	486
					62.1		10.6		487
							10.2		
3-Hydroxytetrahydrofuran	110	5.6	1.4493	54.6	54.6	9.1	9.0	638	629
					54.8		9.3		632
					54.9		9.3		
3-Ethyl-3-oxetanemethanol	84	2.8	1.4517	62.1	62.0	10.4	10.2	484	486
					62.4		10.4		483
3-Methyl-3-oxetanemethanol	80	4.0	1.4449	58.8	58.6	9.8	9.9		
					58.8		9.9	549	543
									546
3,3-Oxetanedimethanol	155	3.5	(Solid)	50.9	50.4	8.5	8.7	951	907
					50.5		8.8		906

3-Ethyl-3-oxetanemethanol from Trimethylolpropane.—A mixture of 268 g. of trimethylolpropane (2.0 moles), 236 g. of diethyl carbonate (2.0 moles) and 0.10 g. of potassium hydroxide dissolved in 5 ml. of absolute alcohol was refluxed until pot temperature was below 105° (15 minutes), and the mixture was distilled keeping the head temperature 76–78°. Distillation was continued until the pot temperature was 145°, and then the pressure was reduced gradually to 50 mm., maintaining the pot temperature at 140–150°. The weight of distillate was 179 g. (theory 184 g. alcohol). Upon heating above 180°, carbon dioxide evolution was rapid and most of the material distilled at 190–210° pot temperature, 90–140° head temperature and 50–90 mm. pressure. Near the end the pressure became 2–10 mm. and the head temperature rose. Redistillation through an efficient column gave: 13.4 g., b.p. 84–86° at 3.5 mm.; 136.6 g., b.p. 84–84.5 at 2.8 mm.; 24.4 g., b.p. 84.5–85.5 at 2.8 mm.; 26.1 g., residue.

The main fraction was analytically pure 3-ethyl-3-oxetanemethanol, and from the residue analytically pure trimethylolpropane was obtained by distillation.

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Endocyclic α,β-Unsaturated Ketones. VI.[1] Ultraviolet and Infrared Absorption Spectra and Resonance Stabilizations

BY RICHARD D. CAMPBELL[2] AND NORMAN H. CROMWELL[3]

RECEIVED MARCH 1, 1957

New data are presented for the ultraviolet absorption spectra of thirteen ketones. These compounds are members of three series, *viz.*, 1,1-dimethyl-2-keto-1,2-dihydronaphthalene (1,1-dimethyl-2(1*H*)-naphthalenone) (II), 4,4-dimethyl-1-keto-1,4-dihydronaphthalene (4,4-dimethyl-1-(4*H*)-naphthalenone) (I), and perinaphthenone-7 (1-(1*H*)-benzonaphthenone) (III). With previously reported data for eight related compounds, the spectra are discussed with respect to resonance stabilizations, effect of nature and position of substituents, and type of conjugation. New infrared spectral data are presented for twenty-one ketones in the three series. These results are discussed with respect to the same factors.

Ultraviolet Absorption Spectra Studies

Introduction.—Studies of ultraviolet absorption spectra of α,β-unsaturated ketones have mainly dealt with open chain systems, with some treatment of endocyclic series. The effect of conjugation of the unsaturated ketone system with phenyl groups has been studied, and chromophores assigned to ultraviolet absorption bands.[4,5] Absorption in the 2300–2500 Å. region was ascribed to the benzoyl or acrylophenone chromophore, and intense absorption from 2800 to 3500 Å. to the cinnamoyl chromophore. The effect of linear and crossed conjugation, and of endo- and exocyclic double bonds on the spectra of α,β-unsaturated ketones has been discussed.[6]

It was observed[4,7,8] that various substituents on the α- or β-carbon atom of the α,β-unsaturated ketone system have a bathochromic effect on the ultraviolet absorption bands. The extent of the shift varied with the nature of the substituent, and the position of attachment. Resonance forms were suggested for the chromophores responsible for the characteristic bands.[4] The importance of chelation in the β-hydroxy[7] and β-amino ketones was discussed.[4] Since such chelation or ionic interaction is impossible in the endocyclic series, it seemed of considerable interest to study these endocyclic compounds.

The compounds used in these studies are all of

(1) For paper No. V, see, N. H. Cromwell and R. D. Campbell, *J. Org. Chem.*, **22**, in press (1957).

(2) Du Pont Teaching Fellow, 1954–1955. Ph.D. Thesis, University of Nebraska, 1956.

(3) To whom inquiries regarding this article should be addressed.

(4) N. H. Cromwell and W. R. Watson, *J. Org. Chem.*, **14**, 411 (1949).

(5) W. B. Black and R. E. Lutz, *J. Am. Chem. Soc.*, **77**, 5970 (1955).

(6) H. S. French and L. Wiley, *ibid.*, **71**, 3702 (1949); H. S. French, *ibid.*, **74**, 514 (1952).

(7) K. Bowden, E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(8) A. L. Nussbaum, O. Mancera, R. Daniels, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3263 (1951).

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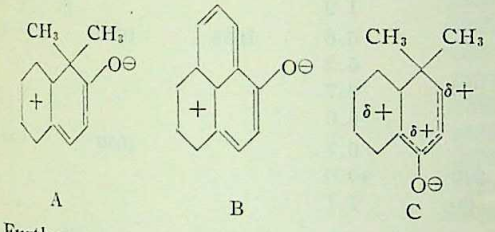
known structure. Their sources[9-17] are indicated in Table I. Since a detailed comparison of spectra needed to be made in order to study the effects of substituents on the spectra of the parent ketones, care was taken in imposing uniform conditions on the spectral determinations, with due regard to temperature, light exposure and solvent effects. Spectra used from the literature were checked for these conditions.

Discussion of Results.—In the three series of compounds studied, the parent endocyclic α,β-unsaturated ketones are 4,4-dimethyl-1-keto-1,4-dihydronaphthalene (I), 1,1-dimethyl-2-keto-1,2-dihydronaphthalene (II) and perinaphthenone-7 (III). In the order named, these compounds showed strong absorption bands at successively higher intensity and longer wave length. The same result was observed in the analogous open chain compounds,[4] ethylideneacetophenone, benzalacetone and chalcone. The aromatic ring on the β-carbon atom of the α,β-unsaturated carbonyl system carries the positive charge in the longest formally polarized (cinnamoyl) structures indicated by forms A and B, for ketones II and III.



A B C

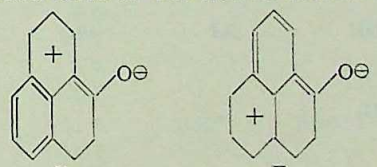
Further resonance stabilization of form B is possible. Canonical forms for III can be written with the positive charge on carbon atoms 1, 3, 4, 6, 7, 9 or 13. This accounts for the fact that the long wave length bands of III appear 500–800 Å. nearer the visible compared with the corresponding band (3000 Å.) of ketone II.

Although the extinction coefficients for the long wave length bands of II and III are nearly equal, the integrated intensity for this band of III is greater. This may be ascribed to the more extensive electronic system of III involved in the transition. Intensity of light absorption is related to the probability of the occurrence of the electronic transition, polarity of the excited state, and length of the conjugated system.[18]

The intense absorption bands below 2500 Å. for parent ketone I and its dihydro derivative IV may be attributed to the benzoyl polarization.[4,5] The vinyl ketone system of I also is responsible for absorption in this region. Absorption in the region 2300–2400 Å. is characteristic of vinyl ketones.[6] The weak bands in the region 2800–3000 Å. for I and IV also are attributed to the benzoyl polarization.[4,5] That this band for I is more intense than for IV is the expected result because I possesses a longer conjugated system.[18] This longer conjugated system is indicated by form C above. The simultaneous interaction of the double bond and the aromatic ring with the carbonyl group cannot be described by a single valence-bond structure. It is not apparent whether such simultaneous resonance interaction is impossible or the classical structures are inadequate for these cross-conjugated systems.

The intense band (3000 Å.) due to the long conjugated system of II is wiped out in the dihydro compound V in which the conjugated system is broken. The carbonyl group in V is insulated from the benzene ring. Only a weak isolated carbonyl band[19] remains in the 2600–2900 Å. region for V. The tetralin system also absorbs weakly in this region.[20]

The extensive resonance stabilization of III is decreased in the dihydro derivative VII. This is evident from the decreased intensity and hypsochromic shift (380–450 Å.) of the absorption band in the 3000–4000 A. region. The positive charge of the polarized form of VII can be carried by either



D E

aromatic ring, as forms D and E indicate. The two forms D are expected to be more stable due to the retention of the Kekule ring. In the three forms E the Kekule structure is absent. However, the long wave length band of VII is nearer the visible and more intense than the benzoyl band of IV or the principal band of the naphthalene nucleus.[20] Hence this band of VII must involve an important contribution from forms E, as well as forms D.

Further evidence for the nature of the resonance stabilizations possible in these three series of ketones (I, II and III) is revealed in the spectra of their α-bromo derivatives VIII, XII and XV, respectively. Introduction of the α-bromo substituent onto ketone II causes a bathochromic shift of 160 Å. for the long wave length band. The α-bromo substituent was reported[8] to cause a bathochromic shift of 80–120 Å. for α,β-unsaturated ketones. The shift indicates that the bromine atom lends more resonance stabilization to the excited state than to the ground state. In addition to forms indicated by A, forms F and G might be stabilizing the excited state by supporting part of the positive charge. One may consider two or more molecular orbitals simultaneously encompassing the systems described by A, F and G,

(9) (a) N. H. Cromwell, H. H. Eby and D. B. Capps, THIS JOURNAL, **73**, 1224 (1951); (b) **72**, 1230 (1951).
(10) N. H. Cromwell, D. B. Capps and S. E. Palmer, *ibid.*, **73**, 1226 (1951).
(11) R. T. Arnold, J. S. Buckley and J. Richter, *ibid.*, **69**, 2322 (1947).
(12) M. D. Soffer, *et al.*, *ibid.*, **72**, 3704 (1950).
(13) L. F. Fieser and L. W. Newton, *ibid.*, **64**, 919 (1942).
(14) L. F. Fieser and E. B. Hershberg, *ibid.*, **60**, 1658 (1938).
(15) L. F. Fieser and M. D. Gates, *ibid.*, **62**, 2335 (1940).
(16) A. M. Lukin, *Bull. Acad. Sci. U.R.S.S. Classe Sci. Chem.*, 695 (1941); *C. A.*, **37**, 2735 (1943).
(17) N. H. Cromwell and G. V. Hudson, THIS JOURNAL, **75**, 872 (1953).
(18) H. Gilman, "Organic Chemistry, an Advanced Treatise," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, Chapter 2.
(19) L. N. Ferguson, "Electronic Structures of Organic Molecules," Prentice-Hall, New York, N. Y., 1952, Chapter 9.
(20) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951.

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TABLE I

SUMMARY OF ULTRAVIOLET AND INFRARED ABSORPTION SPECTRA OF ENDOCYCLIC α,β-UNSATURATED KETONES

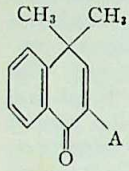
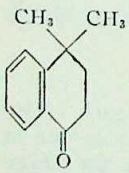
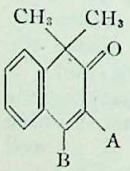
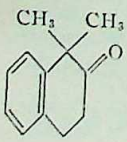
Structure	No.	Source[a]	Ultraviolet max.[b] λ(Å.)	Δλ[d]	× 10⁻³	Infrared C=O band[c] Wave number, cm.⁻¹ Nujol	CCl₄	Δν[d]
								
A = H	I	11	2300		10.7	1657	1665	..
			(2520)[e]		8.8			
			2870		2.2			
			2970		1.9			
A = Br	VIII	11	2250		5.0		1673	8
			2500	200	10.9			
			2560	260	11.0			
			(2680)		6.6			
			3010	50	1.8			
A = NC_4H_8O	IX	9b	2480	180	13.0		1662	− 3
			2890	20	2.6			
			2990	20	2.7			
			3250		1.9			
A = OCH_3	X	1	2200		6.6	1658	1670	5
			(2260)		5.2			
			2500	200	9.7			
			2810		6.0			
A = OH	XI	9b	2290		6.7		1649	−16
			2540	240	10.0			
			2930	60	7.7			
								
	IV	11	2430[i]		11.6		1685[l]	20
			2860	−10	1.4			
			2950	−20	1.1			
								
A = B = H	II	1	2300[h]		15.4	1658[g]	1662	..
			2360		15.8			
			2940		10.2			
			3000		10.1			
A = Br B = H	XII	1	2100		10.4		1678	16
			2350	50	11.7			
			2420	60	12.6			
			3160	160	13.2			
A = H B = NC_4H_8O	XIII	1	2200		9.1	1652	1670	8
			2450	90–150	15.0			
			3530	530	8.8			
A = H B = OH	XIV	1	2220		7.1	1642	1663	1
			2430	130	12.8			
			2510	150	14.5			
			3350	350	9.4			
								
	V	12, 1	2640[h]	−300	0.38	1710[g]	1712	50
			2720	−230	0.56			

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TABLE I (*Continued*)

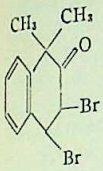
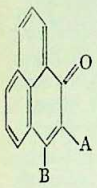
Structure	No.	Source[a]	Ultraviolet max.[b] λ(Å.)	Δλ[d]	ε × 10⁻³	Infrared C=O band[c] Wave number, cm.⁻¹ Nujol	CCl₄	Δν[d]
	VI	1	No max.			1714	1724	62
								
A = B = H	III	14	2450′		21.5	1636′	1646	..
			(2600)		9.5			
			(3400)		7.5			
			3550		11.5			
			3800		9.0			
A = Br	XV	16	2100		15.0	1640	1650	4
B = H			2200		10.6			
			(2420)		15.5			
			2520		20.1			
			2600		16.1			
			3260		4.1			
			3420	20	6.2			
			3570	20	10.7			
			3810	10	8.9			
			(3920)		8.7			
A = NC_4H_8O	XVI	10	2360[k]	− 90	21.0	1637[k]	1640	− 6
B = H			2680		15.0			
			2740		15.3			
			3360		4.7			
			3460	− 90	5.1			
			3620	−180	5.0			
			4520		5.2			
A = H	XVII	10	2400[k]		27.0	1633[k]	1640	−.6
B = NC_4H_8O			3440	−110	14.0			
			3660	−140	12.0			
A = OH	XVIII	10	2370[m]				1630	−16
B = H			(2510)					
			2590					
			(2700)					
			3160					
			3350	−200				
			3510	−290				
A = OH	XVIII	10	4200					
B = H			2100[f]		20.2			
			2380		17.8			
			(2530)		12.8			
			2600		14.0			
			(2700)		11.6			
			3290		5.7			
			3480	(− 70)	5.4			
			3630	(−170)	6.9			
			4260		5.3			
A = H	XIX	10	2110[f]		23.0	1626		−10
B = OH			2280		22.7			
			3330	−220	11.3			
			3520	−280	10.4			
			(3880)		4.5			

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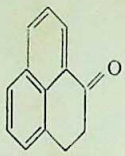
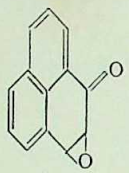
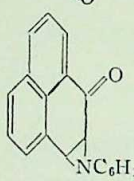
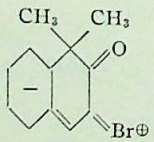
TABLE I (*Continued*)

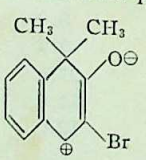
Structure	No.	Source[a]	Ultraviolet max.[b] λ(Å.)	Δλ[d]	ε × 10⁻³	Infrared C=O band[c] Wave number, cm.⁻¹ Nujol	CCl_4	Δν[d]
A = NHC_6H_{11}	XX	10	2400[k]		24.0	1632[k]	1622	−24
			2700		27.4			
			3300	−250	4.6			
			3700	−100	3.0			
			5000		5.5			
	VII	15	2400[j]	− 50	19.2	1677[j]	1690	44
			2450	−100	18.5			
			3170	−380	6.5			
			3310	−450	5.5			
	XXI	13	2430[j]		9.4	1676	1683	37
			2450		9.5			
			3200	−350	8.2			
			3350	−450	8.0			
	XXII	10	2470[j]		19.0	1685[j]	1683	37
			3200	−350	7.2			
			3350	−450	6.6			

[a] Numbers are literature references which appear throughout the article. All samples were freshly purified according to the literature directions. [b] The ultraviolet–visible spectra were determined using a Cary recording spectrophotometer, Model 11 MS, according to the manufacturer's directions. The sample solutions were freshly prepared using 2,2,4-trimethylpentane (Eastman Kodak spectra grade) in suitable concentration (10^{-3} to 10^{-5} *M*). [c] The infrared spectra were determined between 700 and 4000 cm.$^{-1}$ using a Perkin–Elmer Model 21 double-beam infrared spectrophotometer. The Nujol mulls (or pure liquid) were made up to give good resolution. The determinations using carbon tetrachloride solutions were carried out in 1.0 mm. or 0.1 mm. matched cells. The concentration of these solutions was 12 mg./ml. [d] The values for Δλ and Δν were calculated by subtracting the value for the parent ketone from that of the derivative for the corresponding band, and in corresponding medium where possible. [e] Values in parentheses are shoulders. [f] Solvent was absolute methanol. [g] Pure liquid. See footnote *c*. [h] Beckman DU spectrophotometer. [i] Data from ref. 9a. [j] Data from ref. 17. [k] Data from ref. 10. [l] Data from A. Hassner, Ph.D. Thesis, University of Nebr., 1956. [m] Satd. soln.

without conflict with the Pauli exclusion principle.



F



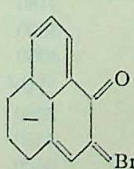
G

The bromine substituent contributes in some such indirect manner to the resonance stabilization of the excited state. It has been pointed out[8] that valence-bond structures such as A, F and G cannot be written to show the resonance contribution of the bromine atom to the polarized carbonyl system. This problem is present in any cross conjugated system.

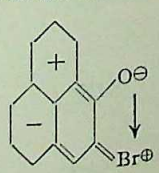
Introduction of the α-bromo substituent onto ketone I was reported[8] to give a bathochromic shift of 140 Å., using ethanol as solvent. The shift observed by us using isoöctane as solvent was 200 or 260 Å., depending on assignment of the split peak for VIII (2500, 2560 Å.). Only one peak was reported by Nussbaum, *et al.*,[8] for VIII at 2560 Å. in ethanol; the bands for I in ethanol and isoöctane are 2420 and 2300 Å., respectively. The solvent effect is as expected.[20] This solvent effect is greater with the parent ketone I than with the α-bromo derivative VIII. A generalization made by Nussbaum, *et al.*,[8] applies to these compounds: the α-bromo substituent causes a greater shift in the spectrum of phenyl vinyl ketones (*viz.*, I) than of β-styryl ketones (*viz.*, II), see Table I.

Introduction of the bromine atom onto the α-position of ketone III results in a bathochromic shift of 10–20 Å. of the long wave length bands (3300–4000 Å.). This indicates that the bromine atom hardly makes any more resonance contribution to the stability of the excited state than of the ground state. As indicated before, the positive charge of the polarized form B already is supported by extensive delocalization both in the ground state and in the excited state.

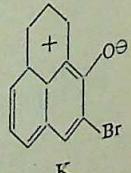
An additional triplet band (2300–2800 Å.) appears in the spectrum of XV. This triplet is characteristic of the α-substituted perinaphthenones to be mentioned later. Absorption in this region is characteristic of benzoyl polarizations stabilized by additional resonance interactions.[4,5,20] Canonical forms H, J and K, repre-



H



J



K

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sent such polarizations in XV. Although the two polarized molecular orbitals implied by J cannot interact by first-order conjugation, electrostatic interaction is expected to contribute some stabilization to the polar form. One might expect that the three forms K are of very nearly the same energy, *i.e.*, degenerate states. Under the electrostatic influence of polarization H (implied in J), the degeneracy of K gives rise to the triplet (Stark effect)[21] in the 2300–2800 Å. region.

The ultraviolet spectra of the derivatives of III with N-cyclohexylamino, morpholino and hydroxyl groups in the α-position (XX, XVI and XVIII, respectively) are nearly identical.[10] These substituents result in a considerable decrease in the intensity of absorption in the 3000–4000 Å. region, and a hypsochromic shift of 90–290 Å. for these absorption maxima. This may indicate resonance interaction and stabilization in the ground state to a greater extent than in the excited state.

Two bands appear in the spectrum of the α-substituted derivatives of III, and not in the spectrum of III. One of these, in the 2300–2800 Å. region, is the triplet discussed above, and attributed to chromophores described by forms H, J and K. The triplet was not resolved in the spectrum of XX. The other new band is a broad, low intensity absorption extending into the visible region (4200–5000 Å.). This low intensity band has been reported for similar ketones.[9b,4] The shoulder (3920 Å.) in the spectrum of XV might be considered to correspond to this band characteristic of α-substituted α,β-unsaturated ketones.

The absorption maxima for the α-substituted derivatives are lower than the corresponding maxima for the parent ketone III, in the longer wave length region. However, inspection of the spectral curves shows that the integrated intensity in the region 2500–5000 Å. is greater for the α-substituted ketones. Thus the longer, intensely absorbing chromophores of the parent ketone are broken into smaller chromophores (see H, J and K) by the α-substituent. The resonance effect of the substituents is seen as an increase in the absorption over the 2500–5000 Å. range, and not in individual bands.

Introduction of the hydroxy or morpholino groups into the β-position of ketone III results in a hypsochromic shift (110–280 Å.) of the bands in the 3300–4000 Å. region. This may indicate that the substituents contribute more resonance stabilization to the ground state than to the excited state. The shift is greater for the hydroxyl group. The β-substituents introduce no bands which did not appear in III, and some fine structure is lost.[20] The increase in intensity of absorption in the 3300–4000 Å. region may be attributed to the extension of the resonating system and the greater electrical moment involved.[4,18]

The imino and epoxy derivatives have been discussed elsewhere.[10,17] The three membered ring has a small effect on the resonance in this series which is unlike the effect of either the α- or β-substituents.

(21) H. S. Taylor and S. Glasstone, "A Treatise on Physical Chemistry," Vol. I, 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1942, p. 281.

Introduction of the morpholino, methoxy or hydroxy groups into the α-position of ketone I results in bathochromic shifts of 180, 200 and 240 Å., respectively, for the strong band (2300–2800 Å.), indicating resonance stabilization of the excited state with respect to the ground state.

The absorption band of I in the 2700–3100 Å. region is shifted 20–60 Å. to longer wave length (except in X) and increased in intensity by the α-substituents. The resonance stabilization of the excited state may be due to ionic forms described[4] for similar compounds. Since this is a cross-conjugated system, it is difficult to describe a polarization in which both the carbonyl oxygen and α-substituent simultaneously carry a charge, but some such interaction seems to occur.[4]

Since the electronic system of II is more closely related to benzalacetone, chalcone and ketone III than to I, the effects of substituents on the spectrum of II should follow this relationship. The β-morpholino and β-hydroxy groups cause bathochromic shifts (530 and 350 Å., respectively) of the cinnamoyl band of II. This is consistent with the effect observed in other series.[4,7,22,23] That the effect of the amino group is greater is consistent with its greater electromeric effect.[19] In those cases in which hydrogen bonding is possible[4,22,23] the effect of hydroxyl is greater. Intramolecular hydrogen bonding is not possible in XIV. One might predict that the unknown α-hydroxy derivative of II would have a cinnamoyl band shifted about 300 Å. to longer wave length from the corresponding band of II, and with little more than one-half of the intensity.[4,23] One might also expect a broad, low intensity band extending into the visible region.[9b,4]

The spectral studies in the three series, I, II and III result in the following conclusions:

1. The effects of substituents on α,β-unsaturated ketones vary widely not only with the nature of the substituent, but also with the position of the substituent in the molecule and the steric and electronic nature of the ketone system.
2. In the perinaphthenone-7 (III) system, extensive resonance interaction is indicated both in the ground state and excited state.
3. In the cross-conjugated system (I), the substituent effects are small.
4. In the linear conjugated system (II), the substituent effects are larger.

Infrared Absorption Spectra Studies

Introduction.—The infrared absorption by ketones due to the carbonyl stretching vibration has been intensively studied. Factors influencing the polarity of the carbonyl group, and thus the absorption frequency, have been discussed.[24] Most of the studies of such factors have dealt with the immediate environment of the carbonyl group, with some study of the farther-reaching resonance effects. Conjugation effects of aryl and olefinic groups in open chain compounds have been

(22) B. Eistert, F. Weygand and E. Csendes, *Ber.*, **84**, 763 (1951).

(23) T. M. Lowry, H. Moureu and C. A. H. MacConkey, *J. Chem. Soc.*, 3171 (1928).

(24) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, Chapter 9.

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studied.[24,25] Some substituent effects have been investigated,[25,26] but not with endocyclic α,β-unsaturated ketones. Hydrogen bonding effects have been observed.[24,27] Such effects might operate in α-substituted endocyclic α,β-unsaturated ketones but would be geometrically impossible in the β-derivatives.[4]

For some of the compounds involved in this study, infrared data have been determined using Nujol mulls. It has been pointed out[24,25] that intermolecular forces in condensed phases have an important influence on the infrared carbonyl absorption frequency. These forces can be minimized by using dilute solutions in carbon tetrachloride.

The discussion above, concerning the ultraviolet spectra of these compounds, dealt with some evidence for the effect of the various substituents on the ground state of the endocyclic α,β-unsaturated carbonyl system. It seemed of interest to obtain the more direct evidence of infrared spectra for these effects, and to study these spectra in relation to each other and to previous infrared data.[24]

Discussion of Results.—The physical state of the sample is important.[24] In dilute carbon tetrachloride solution the carbonyl band generally was found to be 10–20 cm.$^{-1}$ toward higher wave numbers than the carbonyl band observed in the condensed phase (*viz.*, liquid or Nujol mull). In some cases the difference was less, particularly in the perinaphthenone-7 (III) series. In the condensed phase, intermolecular effects might be expected to increase the polarity of the carbonyl group. Thus the solution data give a more reliable picture of the isolated molecule.[25] In the discussion which follows, references will be made almost exclusively to the solution data.

The carbonyl absorption frequency gives evidence of the polarity (single bond character) of the carbonyl group. The normal undisturbed carbonyl frequency is 1705–1725 cm.$^{-1}$ in aliphatic ketones.[24] Conjugation with an aryl group reduces the wave number to 1680–1700 cm.$^{-1}$. Phenyl vinyl ketones and β-styryl ketones absorb in the same range[25] (*viz.*, 1680 and 1690 cm.$^{-1}$, resp.).

Endocyclic ketones I and II absorb at 1665 and 1662 cm.$^{-1}$, respectively. This indicates that resonance interaction causes the carbonyl groups to be slightly more polar than in the corresponding open chain compounds.[25] The cyclic conjugated systems in I and II are held rigidly in position for maximum resonance interaction and polarization.[28]

Perinaphthenone-7 (III) shows even more extensive resonance interaction between the carbonyl group and the rest of the aromatic system. The carbonyl absorption frequency (1646 cm.$^{-1}$) indicates considerable polarity of the carbonyl group. Evidence for this extensive resonance interaction in the ground state of III and its derivatives was also noted in the ultraviolet spectra.

The dihydro derivatives in the three series exhibit carbonyl bands in the range expected. Ketone V has an aliphatic carbonyl group, and absorbs at 1712 cm.$^{-1}$. Ketones IV and VII are aryl ketones, and absorb at 1685 and 1690 cm.$^{-1}$, respectively. The α-bromine atom in VI shifts the absorption band 12 cm.$^{-1}$ to higher wave number, as expected.[24]

In all three series of unsaturated ketones, introduction of a bromine atom into the α-position caused a shift to higher wave numbers. This indicates that the strong inductive and coulombic field effects of bromine increase the double bond character of the carbonyl group. Several workers[24] have observed that the shift caused by an equatorial α-bromine was 20 cm.$^{-1}$ in saturated ketones, where only the inductive and coulombic field effects can operate. In the II, I and III series, the shift is progressively less (16, 8, and 4 cm.$^{-1}$, respectively). This indicates that the resonance and electrostatic dipolar interaction[29] of the bromine atom with the carbonyl group is progressively greater for the three series in the order named, and partly cancels the inductive and coulombic field effects, see Fig. 1. The resonance stabilization of the excited state for these compounds has been discussed above, in relation to the ultraviolet spectra.

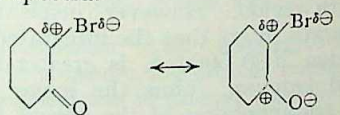
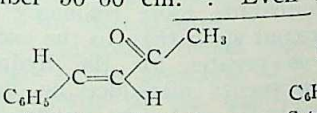
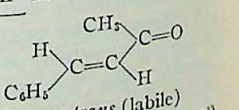


Fig. 1.—Coulombic field effect: equatorial bromine tends to suppress this indicated resonance in saturated cyclic ketones; see R. N. Jones, *et al.*, THIS JOURNAL, **74**, 2830 (1952).

The effect of the β-morpholino or β-hydroxyl group on the carbonyl band of open chain α,β-unsaturated ketones is varied. Where hydrogen bonding (resonance chelation)[24] is possible, the β-amino group[27] reduced the carbonyl band wave number 50–60 cm.$^{-1}$. Even in the absence of



S-*cis-trans* (labile) (C=O$_{CCl_4}$ band, 1699 cm.$^{-1}$)



S-*trans-trans* (labile) (C=O$_{CCl_4}$ band, 1678 cm.$^{-1}$)

The endocyclic ketone II might be expected to have its C=O band (1662 cm.$^{-1}$) nearer to that of the S-*trans-trans* form of benzalacetone than to that of the S-*cis-trans* comformation. Fuson, *et al.*, ref. 25, have reported C=O bands at 1700–1685 cm.$^{-1}$ and C=C bands at 1670–1662 cm.$^{-1}$ for various β-styryl ketones. We suggest that these lower frequency bands might best be assigned to the carbonyl group of the S-*trans-trans* forms of these compounds; see E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 3771 (1955). House, THIS JOURNAL, **78**, 4394 (1956); **79**, 1490 (1957), reported C=O bands for 2-benzalcyclohexanone-1 (an S-*cis-trans* structure) and 3-phenyl-2-cyclohexenone-1 (an S-*trans-trans* structure) at 1685 and 1660 cm.$^{-1}$, respectively.

(25) N. Fuson, M. L. Josien and E. M. Shelton, THIS JOURNAL, **76**, 2528 (1954).

(26) A. H. Soloway and S. L. Friess, *ibid.*, **73**, 5000 (1951).

(27) N. H. Cromwell, *et al.*, *ibid.*, **71**, 3337 (1949).

(28) In this Laboratory Prof. H. E. Baumgarten has recently measured the infrared spectrum of highly purified benzalacetone. Using Nujol mulls, bands were found at, 1688(V.S.); 1665(W); 1615–1605 (V.S.); 1585(S); 6 mg./ml. CCl_4 in 1.0 mm. matched cells, 1699 (79% abs.); 1678 (94% abs.); 1617 (92% abs.). We believe that a C=O band assignment should be made to both the 1688–1699 and 1665–1678 cm.$^{-1}$ bands. The strong 1617–1605 cm.$^{-1}$ bands are probably composite C=C and conjugated phenyl bands. The two C=O bands are apparently associated with two possible rotational isomers of *trans*-benzalacetone; see footnote *b*, Table I, N. H. Cromwell and R. J. Mohrbacher, THIS JOURNAL, **76**, 6251 (1953).

(29) See, for example, J. Jaffé, The indicated (↔) electrostatic interaction should aid resonance.

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chelation, the shift is approximately 30 cm.$^{-1}$ to lower wave number.[27] In the endocyclic compounds the chelation and dipolar[10] interaction effects are expected to be absent. In series II, the β-morpholino group effect seems anomalous, *i.e.*, it causes a shift of 8 cm.$^{-1}$ to higher wave number. It has been observed[27] that the resonance effect of the β-amino group is less in β-styryl ketones than in phenyl vinyl ketones. It would seem that in XIII the resonance effect of the morpholino group is less than its electron-withdrawing inductive effect.[30] The inductive effect of an α-bromine atom causes a shift in the same direction (see above). The β-hydroxyl group of XIV causes a shift of 1 cm.$^{-1}$ to higher wave length; again the expected[24] shift is to lower wave length. Here resonance and inductive factors are nearly balanced.

In the perinaphthenone-7 (III) series, the β-morpholino and β-hydroxyl groups cause shifts of the carbonyl band of 6 and 10 cm.$^{-1}$ to lower wave number. The shifts indicate that the carbonyl group has developed more single bond character through resonance interaction with the substituents, but the effect is smaller than in open chain compounds.[27] In XVII and XIX, intramolecular hydrogen bonding and dipolar[10] effects are not possible Also, the parent ketone system of III is extensively resonance stabilized, so the resonance effect of the substituents is less important.

Introduction of substituents into the α-position of parent ketone III results in shifts of the carbonyl band to lower wave numbers, indicating a more polar carbonyl group. The shifts for the α-morpholino, α-hydroxy and α-cyclohexylamino groups are −6, −16 and −24 cm.$^{-1}$, respectively. In the latter two (*viz.*, XVIII and XX), a five-atom chelate ring is possible. Intramolecular hydrogen bonding seems to increase the polarity of the carbonyl group in these compounds. The problem of direct resonance interaction between the carbonyl group and α-substituents has been discussed (see ultraviolet spectra discussion).

In series I, the effects of α-substitution on the polarity of the carbonyl group vary according to the nature of the substituent. It has been noted above and elsewhere,[24,27] that the inductive (electron withdrawing) effect of α-substituents decreases the polarity of the carbonyl group (shift to higher wave number), whereas the resonance effect and intramolecular hydrogen bonding give the opposite result. On the basis of electronegativity, and inductive effects,[31] the expected order of decreasing electron withdrawing (inductive) effect for the substituents is: bromo, hydroxy, methoxy and morpholino. The shifts caused by the α-substituents are: bromo, 8 cm.$^{-1}$; methoxy, 5 cm.$^{-1}$; morpholino, −3 cm.$^{-1}$; and hydroxy, −16 cm.$^{-1}$. For the bromo and methoxy substituents, the inductive effect is more important than the resonance effect. In the morpholino derivative IX the resonance effect is more important. Here the resonance effect may be aided in some manner by dipole interaction.[4] The hydroxyl group in XI seems to engage in intramolecular hydrogen bonding, thus increasing the polarity of the carbonyl group. In XI the resonance and hydrogen bonding effects of the substituent are considerably more important than the inductive effect on the polarity of the carbonyl group.

For the epoxy and imino derivatives of III, (XXI and XXII, respectively), the infrared spectra of Nujol mulls were reported[10,17] and discussed[17] in terms of the steric requirements of the three-ring for resonance interaction. It was suggested by N. Fuson[25] that data obtained in carbon tetrachloride solution would be necessary, to isolate the effect of the three-ring on the carbonyl frequency. Now these data are reported, and the previous conclusions[17] are essentially confirmed.

Acknowledgment.—This work was supported in part by a grant from the National Science Foundation, N.S.F., G-1091.

LINCOLN, NEBRASKA

(30) Resonance interaction of the morpholino group with the unsaturated ketone system may be somewhat inhibited sterically in this structure.

(31) C. K. Ingold "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 67.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Stereochemistry of Allylic Rearrangements. IX. The Solvolysis of *trans*-α,γ-Dimethylallyl Acid Phthalate in Aqueous Acetone[1]

BY HARLAN L. GOERING AND RICHARD W. GREINER[2]

RECEIVED JANUARY 14, 1957

The polarimetric (k_α) and titrimetric (k_t) rate constants for the solvolysis of *trans*-α,γ-dimethylallyl acid phthalate (I) in aqueous acetone have been determined. At concentrations up to 0.1 M both k_α and k_t are steady during the reaction and $k_\alpha > k_t$ under all conditions at which the two were compared. The greater rate of loss of optical activity than of formation of solvolysis products is due to partial racemization of the reactant, by an isomeric intramolecular (SNi′) allylic rearrangement, prior to solvolysis. The data are consistent with a picture involving the reversible formation of a symmetrical ion-pair intermediate which is irreversibly converted to solvolysis products.

In earlier papers in this series[3,4] it was pointed out that an intermediate (an "internal ion-pair" intermediate according to Winstein's classification[5]) is involved in the ionization–dissociation step of carbonium-ion reactions in allylic systems. This intermediate can return to the original allylic compound or its allylic isomer by internal return—presumably this represents the mechanism of the SNi′[6] rearrangement of allylic compounds[3]—or dissociate to the allylic cation and the accompanying anion. In non-reactive solvents, *e.g.*, non-hydroxylic solvents, the dissociated carbonium ion and anion recombine; however, in hydroxylic solvents this recombination is completely diverted by solvolysis.[3,4] Thus, in hydroxylic solvents the SNi′ rearrangement is cleanly isolated from an intermolecular isomeric rearrangement.

Optically active symmetrical allylic systems, *i.e.*, systems with similar α- and γ-alkyl substituents, are especially well suited for studying the SNi′ rearrangement (internal return) which accompanies solvolysis. In such systems the SNi′ rearrangement results only in the interconversion of enantiomers and thus does not disturb the first-order rate of product formation but results in a larger rate of loss of optical activity (polarimetric rate) than of product formation (titrimetric rate). The first-order rate constant for the conversion of one enantiomer to the other by the SNi′ rearrangement is $(1/2)(k_\alpha - k_t)$ and thus can be determined readily from the polarimetric (k_α) and titrimetric (k_t) rate constants.[3,4]

As described in earlier papers in this series, internal return is involved in the solvolysis of the isomeric 5-methyl-2-cyclohexenyl chlorides in ethanol and acetic acid[4] and the corresponding acid phthalates[3a] and *p*-nitrobenzoates[3b] in aqueous acetone. In the present work we have examined the solvolysis of α,γ-dimethylallyl acid phthalate in aqueous acetone to determine the importance of internal return in this acyclic symmetrical allylic system relative to that in the 5-methyl-2-cyclohexenyl system.

Results

The α,γ-dimethylallyl acid phthalate used in the present work was apparently the pure *trans* isomer. That the material was homogeneous was indicated by a rather sharp reproducible melting point (89–90.5°) which was unchanged by recrystallization. The infrared spectrum of α,γ-dimethylallyl alcohol obtained by reduction of the pure acid phthalate with lithium aluminum hydride had a strong absorption band at 10.4 μ and no bands above 14 μ, which is characteristic of *trans*-1,2-disubstituted ethylenes.[7] The neutral equivalents of the samples of racemic and optically active acid phthalate used in the kinetic experiments were within 0.3% of the theoretical value.

The first-order polarimetric (k_α) and titrimetric (k_t) rate constants for the solvolysis of *trans*-α,γ-dimethylallyl acid phthalate (I) in 70, 80 and 90% aqueous acetone are given in Table I. The data are arranged so that the polarimetric rate constants are for the same conditions as the preceding titrimetric rate constants.

The polarimetric constants were determined from the rate of loss of optical activity of solutions of (+)-I. In all cases solvolysis resulted in complete loss of optical activity, and the polarimetric constants were steady over the range that the reaction was followed (88 to 94% completion). The observed first-order rate constants were reproducible and most of the values for $k\alpha$ given in Table I are average values of two independent kinetic experiments. A typical kinetic experiment is included in the Experimental section.

The titrimetric constants (k_t) were determined from the rate of increase in acidity of solutions of racemic I. In all cases the observed initial titer, *i.e.*, the titer of freshly prepared solutions prior to heating, agreed well with the calculated value. The observed infinity titers, however, were found to be approximately 2% less than the calculated values (twice the initial titer). Evidently this discrepancy is due to conversion of about 1% of the phthalic acid to phthalic anhydride under the conditions of the solvolysis experiments. In a control experiment the titer of a 0.05 M solution of phthalic acid in 90% acetone at 100° was determined periodically. The titer of this solution decreased slowly and after a period of time, corresponding to infinity time for the solvolysis, the percentage difference between the initial and final titers was the same as between the observed and calculated infinity titers.

(1) This work was supported by the Office of Ordnance Research and by the Research Committee of the Graduate School with funds given by the Wisconsin Alumni Research Foundation.

(2) Socony-Mobil Co. Fellow, 1956–1957.

(3) (a) H. L. Goering and E. F. Silversmith, THIS JOURNAL, **77**, 1129 (1955); (b) **77**, 6249 (1955).

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TABLE I

POLARIMETRIC AND TITRIMETRIC RATE CONSTANTS FOR THE SOLVOLYSIS OF *trans*-α,γ-DIMETHYLALLYL ACID PHTHALATE IN AQUEOUS ACETONE

Acid phthalate, $10^2 M$	Method[b]	k,[c,d] 10^3 hr.$^{-1}$	$k\alpha/k_t$[e]
	90% (vol.[a]) acetone, 99.81°		
7.50	T	110 ± 6[f]	
10.0	T	117 ± 4	2.52 ± 0.16
10.0	P	295 ± 8[f]	
5.00	T	108 ± 4	2.69 ± 0.14
5.00	P	291 ± 4	
2.50	T	102 ± 2	2.83 ± 0.17
2.50	P	289 ± 11[f]	
5.00[g]	T	11.9 ± 0.6	2.50 ± 0.14
5.00[g]	P	29.8 ± 0.1	
5.00[h]	T	3.97 ± 0.16	2.43 ± 0.13
5.00[h]	P	9.66 ± 0.11	
	80% (vol.[a]) acetone, 79.58°		
5.00	T	52.9 ± 0.9	1.89 ± 0.05
5.00	P	100 ± 1	
	70% (vol.[a]) acetone, 79.58°		
5.00	T	142 ± 2	1.68 ± 0.03
5.00	P	238 ± 2	

[a] Based on volumes of pure components at 25° before mixing. [b] T = titrimetric and P = polarimetric. [c] These are values for k_α (polarimetric determinations) and k_t (titrimetric determinations). [d] These values are the average (and mean deviation) of two or more independent kinetic experiments, except as noted. [e] Indicated uncertainty determined from limiting values for k_α and k_t. [f] These values are the average (and mean deviation) of from seven to thirteen determinations within a kinetic experiment. [g] Temperature, 79.58°. [h] Temperature, 70.12°.

Because the conversion of phthalic acid to phthalic anhydride is slow, the calculated rather than the observed infinity titers were used to calculate the first-order titrimetric constants. The constants obtained in this way did not show any significant trends in reactions followed to 75–85% completion. With one exception the values for k_t in Table I are average values of two or more independent kinetic experiments. A typical kinetic experiment is included in the Experimental section.

In order to establish that the solvolysis of I in aqueous acetone involves alkyl–oxygen cleavage, the rate of solvolysis of the saturated analog, 2-pentyl acid phthalate, in 90% acetone at 100° was determined. The rate constant for this compound under these conditions is $7.4 \pm 0.4 \times 10^{-4}$ hr.$^{-1}$ or 1/45 of that for I. Since there is no apparent reason why an allylic ester should undergo acyl–oxygen cleavage more readily than the saturated analog, the observed factor of 145 appears to be compelling evidence that the solvolysis of I involves exclusive alkyl–oxygen cleavage.

As shown in the final column of Table I the polarimetric rate exceeds the titrimetric rate under all conditions where the two were compared. The polarimetric rate constants increase slightly as the initial concentration of acid phthalate is increased, and the titrimetric constants show a somewhat larger increase with increase in concentration. This increase in rate presumably is due to a slight increase in the ionizing power of the medium as the acid phthalate concentration is increased. Both $k\alpha$ and k_t show marked increases as the ionizing power of the solvent is increased; *cf.* rates in 70% and 90% aqueous acetone. The titrimetric rate is slightly more sensitive than the polarimetric rate to increase in ionizing power of the solvent. Thus $k\alpha/k_t$ decreases as the ionizing power increases. This behavior is similar to that observed previously for the solvolysis of *cis*-5-methyl-2-cyclohexenyl acid phthalate in aqueous acetone.[3a]

Excellent linear plots are obtained when log $k\alpha$ or log k_t is plotted against the Y values[8] of the solvents. The slopes of these plots, m,[8] are 0.542 for k_t and 0.454 for k_α. These values are similar to those calculated[8] for the solvolysis of *cis*-5-methyl-2-cyclohexenyl acid phthalate in aqueous acetone[3a] (m = 0.472 for k_t and 0.429 for $k\alpha$). Thus both k_α and k_t show about the same sensitivity to changes in the ionizing power of the solvent in the two systems.

The activation parameters for loss of optical activity ($k\alpha$), solvolysis (k_t) and racemization or SNi′ rearrangement ($k_\alpha - k_t$) in 90% acetone are given in Table II. These data were determined from least-square plots of log k *vs.* $1/T$.

TABLE II

ACTIVATION PARAMETERS FOR THE SOLVOLYSIS OF 0.05 M α,γ-DIMETHYLALLYL ACID PHTHALATE IN "90%" AQUEOUS ACETONE[a]

	E_a[b] kcal./mole	log A	$\Delta H^{\pm}$,[b,c] kcal./mole	$\Delta S^{\pm}$,[b,c] e.u.
$k\alpha$	29.1 ± 0.2	12.974	28.4 ± 0.2	−1.61 ± 0.51
k_t	28.3 ± 0.6	12.077	27.6 ± 0.6	−5.71 ± 1.79
$(k\alpha - k_t)$	29.8 ± 0.8	13.156	29.0 ± 0.8	−0.77 ± 2.0

[a] These values were calculated from the rate constants at 70, 80 and 100° given in Table I. [b] The indicated uncertainties were calculated from the limiting values of the rate constants at 70 and 100°. [c] These values were calculated for 100°.

The present system is a little more reactive than the 5-methyl-2-cyclohexenyl system. In 90% aqueous acetone at 100°, $k\alpha$, k_t and $k\alpha - k_t$ are larger for I than for the isomeric 5-methyl-2-cyclohexenyl acid phthalates by factors of about 5, 3 and 7, respectively.

Discussion

The solvolysis of α,γ-dimethylallyl acid phthalate (I) is similar to that of the isomeric 5-methyl-2-cyclohexenyl acid phthalates[3a] in that $k_\alpha > k_t$ in each case. It appears that the present data are consistent with the mechanism suggested previously[3,4] for the solvolysis and rearrangement of allylic compounds. According to this picture, which is illustrated below for the present system—the indicated rotations for the enantiomers of I have been chosen arbitrarily—an "internal ion-pair"[5] intermediate (II) is common to solvolysis and intramolecular (SNi′) rearrangement. The first-order rate constant for loss of optical activity is $k\alpha$. That for formation of phthalic acid, *i.e.*, the titrimetric rate constant (k_t) is $k_\alpha\, k_2/(2k_1 + k_2)$, and that for the conversion of one enantiomer to the other is $1/2\,(k_\alpha - k_t)$.

(8) A. H. Fainberg and S. Winstein, THIS JOURNAL, **78**, 2770 (1956).

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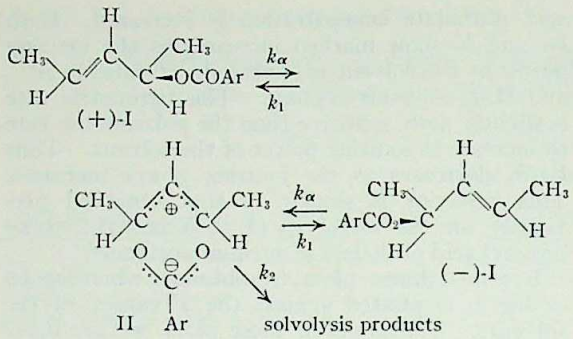

In the present system the intramolecular rearrangement results in the interconversion of enantiomers providing that the planar allylic moiety in II has the indicated configuration. The steady polarimetric and titrimetric rates suggest that I reacts *via* the conformation corresponding to the indicated configuration for II, *i.e.*, the configuration with the α- and γ-methyl groups *cis*. If II had the other configuration (*i.e.*, with the methyl groups *trans*) the SNi′ rearrangement would result in the conversion of optically active *trans*-acid phthalate to optically active *cis*-acid phthalate. This would likely disturb the polarimetric and possibly also the titrimetric rate. Scale models also indicate that the configuration indicated for the α,γ-dimethylallylcarbonium ion in II is the more stable one.[9]

It has been shown recently that in the intramolecular rearrangement of α-phenyl-γ-methylallyl[10a] and α-phenylallyl *p*-nitrobenzoate[10b] the carbonyl oxygen atom in the reactant becomes the alkyl oxygen atom in the product. This suggests that there is some covalent bonding between the allylic carbon atoms and the oxygen atoms in the symmetrical intermediate II. However, from the way in which k_α responds to changes in the ionizing power of the solvent, it appears that there must be considerable charge separation in the intermediate.

Experimental

Materials.—*trans*-α,γ-Dimethylallyl alcohol, b.p. 116–121°, n^{20}D 1.4280 (lit.[11] b.p. 116–121°, n^{20}D 1.4280) was prepared according to the previously described method.[11,12] The alcohol was converted[12] to *dl*-*trans*-α,γ-dimethylallyl acid phthalate, m.p. 89–90.5° (lit.[12] 90–90.5°); neut. equiv. found 233.9, calcd. 234.2. The acid phthalate was resolved according to the method of Kenyon, *et al.*[12] The (+)-*trans*-α,γ-dimethylallyl acid phthalate obtained in this way had a melting point of 78–83.6° and $[\alpha]^{25}$D 35.4° (*l* = 4, *c* 1.1, ethanol) (lit.[12] m.p. 82–84°, $[\alpha]$D 38.3° for optically pure material).

Reduction of α,γ-Dimethylallyl Acid Phthalate with Lithium Aluminum Hydride.—The ester was reduced according to the method of Doering and Zeiss.[13] α,γ-Dimethylallyl alcohol, b.p. 116–121°, was isolated in 66% yield. The infrared spectrum of this material was found to have a strong band at 10.4 μ.

Kinetic Experiments.—The kinetic runs were carried out as described previously.[3a] Typical kinetic experiments are summarized in Tables III and IV.

Table III

Titrimetric Rate of Solvolysis of 0.05 *M* *trans*-α,γ-Dimethylallyl Acid Phthalate in 90% Aqueous Acetone at 99.81°

t, hr.	NaOH, ml.	$10^3 k_{t,}$[a] hr.$^{-1}$
init.	4.745	..
0.00	4.910	..
0.75	5.240	100
1.50	5.580	105
3.00	6.205	111
4.50	6.690	109
6.00	7.150	112
7.50	7.530	113
9.00	7.800	111
10.50	8.060	111
12.10	8.310	112
13.50	8.470	111
15.00	8.600	109
Obs. ∞	9.300	..
Theor. ∞	9.490	..
		Av. 109 ± 3

[a] Calculated from theoretical infinity titer.

Table IV

Polarimetric Rate of Solvolysis of 0.05 *M* (+)-*trans*-α,γ-Dimethylallyl Acid Phthalate in 90% Aqueous Acetone at 99.81°

t, hr.	Obs.	$10^3 k_{\alpha,}$ hr.$^{-1}$
0.000	+1.955	..
0.500	+1.723	303
1.500	+1.363	296
3.083	+0.955	302
4.500	+ .751	291
6.000	+ .603	285
7.500	+ .497	287
∞	+ .308	..
Solvent	+ .305	
		Av. 294 ± 6

(9) The stereochemical relationship between the reactant and product for an SNi′ process in the *trans*-α,γ-dimethylallyl system has been discussed by W. G. Young, *et al.*, This Journal, **77**, 4182 (1955).

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[CONTRIBUTION FROM THE DIAMOND ORDNANCE FUZE LABORATORIES]

Synthesis of 2,2-Dialkylcyclopropane Nitriles[1]

BY EDWARD R. NELSON, M. MAIENTHAL, L. A. LANE AND A. A. BENDERLY

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The ditosylate of 2,2-dimethyl-1,3-propanediol reacted with potassium cyanide in ethylene glycol to give 2,2-dimethylcyclopropane nitrile in 63% yield. In a similar manner, the ditosylate of 2,2-diethyl-1,3-propanediol was converted to 2,2-diethylcyclopropane nitrile. The ditosylates of 1,3-propanediol and 2-methyl-1,3-propanediol failed to yield cyclopropane derivatives when treated under comparable conditions.

In a recent publication, Brown and van Gulick[2] described the synthesis of 2,2-dimethyl-4-methoxybutyronitrile by the treatment of 2,2-dimethyl-3-methoxypropyl tosylate with potassium cyanide in refluxing ethylene glycol. An attempt to adapt this procedure to the preparation of β,β-dimethylglutaronitrile from the ditosylate of 2,2-dimethyl-1,3-propanediol unexpectedly resulted in a cyclopropane nitrile. On hydrolysis, this nitrile gave 2,2-dimethylcyclopropane carboxylic acid, as shown by comparisons of the infrared spectrum of the corresponding amide with that of the amide of an authentic sample prepared by the method of Kishner.[3] Thus the original cyclopropane nitrile was identified as 2,2-dimethylcyclopropane nitrile.

The physical properties of the acid and amide described above corresponded closely to those reported by Kishner,[3] and also by Blanc,[4] for the same compounds prepared by different methods.

A survey of the methods of synthesizing cyclopropane compounds was compiled by Feldman[5] in 1940. Subsequently Schlatter[6,7] concluded that the most satisfactory method of obtaining cyclopropane nitrile involved the halogenation of 1,3-propanediol followed by reaction with sodium cyanide. This procedure resulted in only a 25% yield of the nitrile. Thus, the reaction of the ditosylate of 2,2-dimethyl-1,3-propanediol with potassium cyanide to give a cyclopropane ring structure appeared to be of interest because of the high yield of 2,2-dimethylcyclopropane nitrile (63%) and the ease of preparation of the ditosylate.

Reactions of potassium cyanide with the ditosylates of three other 1,3-glycols were then attempted in an effort to determine the general applicability of this method of ring closure. In the first experiments, treatment of the ditosylate of 2,2-diethyl-1,3-propanediol with potassium cyanide resulted in a 66% yield of 2,2-diethylcyclopropane nitrile. The infrared spectra of the acid and amide of this compound were similar to those obtained from the dimethylcyclopropanes. Presumably, other 2,2-dialkylcyclopropane nitriles could be prepared in a similar fashion.

The ditosylates of 2-methyl-1,3-propanediol and 1,3-propanediol, however, failed to yield cyclopropane derivatives under comparable conditions. This result probably is due to the absence of geminal alkyl groups and related steric effects in these two compounds. Such effects have been studied by Ingold[8] for the reaction of α-bromo-β-alkylglutaric acid with alkali.

None of the cyclopropane compounds prepared in this investigation had infrared bands in the region 1000 to 1020 cm^{-1} which is reported by Bellamy[9] to be a characteristic absorption band for cyclopropane compounds. However, all five compounds had bands of medium intensity nearby: 2,2-dimethylcyclopropane nitrile at 1034 $cm.^{-1}$, 2,2-dimethylcyclopropane carboxylic acid at 1037 $cm.^{-1}$, 2,2-dimethylcyclopropanecarboxamide at 1036 $cm.^{-1}$, 2,2-diethylcyclopropane nitrile at 1024 $cm.^{-1}$ and 2,2-diethylcyclopropane carboxamide at 1024 $cm.^{-1}$. In all likelihood the characteristic region for cyclopropane absorption should be broadened to 1000–1040 $cm.^{-1}$. This is supported by work of Cromwell and Mohrbacher[10] who reported bands in the region 1025–1036 $cm.^{-1}$.

Experimental

Ditosylate of 2,2-Dimethyl-1,3-propanediol.—A solution containing 286 g. (1.5 moles) of *p*-toluenesulfonyl chloride in 500 ml. of pyridine was held below 0°, and 52 g. (0.5 mole) of 2,2-dimethyl-1,3-propanediol in 100 ml. of pyridine was added. The mixture was stirred at 0° for 2 additional hours and then allowed to stand overnight at room temperature. The reaction mixture was poured into 1 liter of water and ice and the solid collected by filtering. The product was washed with water, dilute sulfuric acid, dilute sodium carbonate and again with water. There was obtained 194 g. of the ditosylate (94% yield) which, after two recrystallizations from a mixture of acetone and water, melted at 121–123°; reported 116–120° by Brown and van Gulick.[2]

Anal. Calcd. for $C_{19}H_{24}S_2O_6$: C, 55.3; H, 5.9; S, 15.5. Found: C, 55.4; H, 5.9; S, 14.9.

2,2-Dimethylcyclopropane Nitrile.—A mixture of 206 g. (0.5 mole) of the ditosylate of 2,2-dimethyl-1,3-propanediol and 97.6 g. (1.5 moles) of potassium cyanide in one liter of ethylene glycol was heated. The solids dissolved on warming and the reaction mixture turned dark when its temperature reached 70 to 90°. The distillation product, produced at 175°, consisted of a mixture of two liquids. Distillation of this mixture continued until a vapor temperature of 198° was reached. One-hundred-fifty ml. of a colorless two-phase system was obtained in about 2 hr. The top phase was separated and the lower phase, ethylene glycol, was extracted three times with 100 ml. of *n*-pentane which was combined with the top phase. The pentane was then removed by distillation and the final product, obtained in 63% yield, was a clear liquid with a very sharp boiling point, 154.5–155.5°, $n^{23}D$ 1.4261, and $d^{24.6}_{20}$ 0.8536. It slowly re-

(1) Presented at the Atlantic City Meeting of the American Chemical Society, September, 1956.

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duced a 2% potassium permanganate solution, indicating the presence of some unsaturated material.

Anal. Calcd. for C_6H_9N: C, 75.7; H, 9.5; N, 14.7. Found: C, 75.5; H, 9.7; N, 14.6.

2,2-Dimethylcyclopropane Carboxylic Acid.—The nitrile was hydrolyzed by refluxing with aqueous potassium hydroxide for 48 hr. The colorless acid was collected, b.p. 83–84° (5 mm.), 198–201° (1 atm.), $n^{20}D$ 1.4405 (78% yield); reported for 2,2-dimethylcyclopropane carboxylic acid, b.p. 100° (10 mm.), b.p. 198° (751 mm.),[4] n_D 1.4385.[3] This acid slowly reduced a 2% potassium permanganate solution, indicating the presence of some unsaturated material.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.1; H, 8.8. Found: C, 63.3, 62.8; H, 8.9, 9.0.

2,2-Dimethylcyclopropane Carboxamide.—The acid was converted into the amide *via* the acid chloride, by action of liquid ammonia upon the latter compound. The amide, after recrystallization from ethyl acetate, gave white needles, m.p. 177–177.5°; reported[4] m.p. 177°, yield 44%.

This amide did not reduce a dilute solution of potassium permanganate in acetone.

Anal. Calcd. for $C_6H_{11}NO$: C, 63.7; H, 9.8. Found: C, 63.7; H, 9.8.

A sample of this amide was hydrolyzed back to the acid using aqueous potassium hydroxide; this acid, $n^{20}D$ 1.4398, did not decolorize dilute potassium permanganate.

2,2-Dimethyl-1-isobutenylcyclopropane.—This synthesis was performed by a modification of methods described by Kishner[3] and Smith and Rogier.[11] To a mixture of 127.4 g. (0.92 mole) of phorone in 250 ml. of absolute ethanol, cooled in an ice-bath, there was added 93.3 g. (1.84 moles) of hydrazine hydrate in small amounts with stirring. After the reaction mixture had cooled, it was heated on a water-bath for an hour. The excess hydrate and ethanol were removed under 15 mm. pressure and a temperature of 80°.

The crude pyrazoline obtained from the above reaction was mixed with 6.2 g. of 5% platinum on asbestos and 14.0 g. of powdered potassium hydroxide, after which it was heated in an oil-bath. At a bath temperature of 175°, 2,2-dimethyl-1-isobutenylcyclopropane began to distil from the reaction mixture with evolution of nitrogen. The temperature of the bath was raised to 200° over a period of 2 hr. by which time the distillation had ceased. Upon redistillation, 69 g. (55% over-all yield) was obtained, b.p. 130–132°.

2,2-Dimethylcyclopropane Carboxylic Acid and its Amide.—A mixture of 25 g. (0.2 mole) of the above hydrocarbon and 63.2 g. (0.4 mole) of potassium permanganate in one liter of water was stirred at room temperature for 4 hr. The manganese dioxide was removed by filtration and the filtrate was made acid to litmus with dilute sulfuric acid. The acid was extracted with ether, and distillation of the ether solution gave 3.7 g. (8.1% yield) of 2,2-dimethylcyclopropane carboxylic acid, b.p. 95–98° (12 mm.). The infrared spectrum showed this material to be somewhat impure.

The amide of this sample was prepared by treating the acid with thionyl chloride and aqueous ammonium hydroxide according to the method of Shriner and Fuson.[12] The amide melted at 177° with sublimation. The spectrum of this amide was the same as that of the amide prepared from the acid originally obtained from the reaction of the 2,2-dimethyl-1,3-propanediol ditosylate and potassium cyanide.

Ditosylate of 2,2-Diethyl-1,3-propanediol.—To 66.1 g. (0.5 mole) of 2,2-diethyl-1,3-propanediol there was added 286 g. (1.5 moles) of *p*-toluenesulfonyl chloride in 600 ml. of pyridine. This synthesis was carried out in the same fashion as that used previously for 2,2-dimethyl-1,3-propanediol. The product was crystallized from acetone yielding 152.1 g. (69% yield), m.p. 109–110°.

Anal. Calcd. for $C_{21}H_{28}O_6S_2$: C, 57.2; H, 6.4. Found: C, 57.2; H, 6.5.

2,2-Diethylcyclopropane Nitrile.—This reaction was conducted in a fashion similar to that described previously for the ditosylate of 2,2-dimethyl-1,3-propanediol. A solution of 152 g. (0.34 mole) of the above ditosylate, 65.1 g. (1.0 mole) of potassium cyanide and a liter of ethylene glycol was heated. A codistillation took place at a vapor temperature of 188° giving a two-phase distillate. The lower phase was extracted with *n*-pentane, and the pentane extract was combined with the upper phase. The combined solution was washed with water, dried with calcium sulfate and distilled. It yielded 28.4 g. (66% yield) of 2,2-diethylcyclopropane nitrile, $n^{20}D$ 1.4422, b.p. 76–77° (8 mm.). The infrared spectrum was similar to that obtained with 2,2-dimethylcyclopropane nitrile.

Anal. Calcd. for $C_8H_{13}N$: C, 78.0; H, 10.6. Found: C, 77.8; H, 10.8.

2,2-Diethylcyclopropane Carboxylic Acid and Amide.—Thirty-five and five-tenths grams of 2,2-diethylcyclopropane nitrile was hydrolyzed by refluxing in an alcoholic solution of potassium hydroxide for 4.5 days. The resulting mixture was filtered and yielded 25 g. of the crude amide (61% yield), m.p. 133–135°. Recrystallization from a mixture of ethyl alcohol and water raised the melting point to 136–137° with sublimation. The amide did not react with dilute potassium permanganate solution in acetone.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.7. Found: C, 67.9; H, 10.6.

The filtrate from the above-described filtration of the amide was extracted with ether and acidified. The acid was extracted with ether. The ether extract was distilled, yielding 7.5 g. (18.2% yield) of 2,2-diethylcyclopropane carboxylic acid, b.p. 109–112° (6 mm.), $n^{25.5}D$ 1.4488.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.6; H, 9.9. Found: C, 67.6; H, 9.8.

Ditosylate of 1,3-Propanediol.—This synthesis also was conducted in a fashion similar to that described previously for the ditosylate of 2,2-dimethyl-1,3-propanediol. Thirty-eight g. (0.5 mole) of propanediol-1,3 was added to 286 g. (1.5 moles) of *p*-toluenesulfonyl chloride in 600 ml. of pyridine, and the product was recrystallized from acetone and water yielding 106 g. (55% yield), m.p. 94°; reported[13] 94°.

Reaction of Potassium Cyanide with the Ditosylate of 1,3-Propanediol.—This reaction was carried out in the same fashion as that described for the ditosylate of 2,2-dimethyl-1,3-propanediol. A solution of 152.1 g. (0.39 mole) of the ditosylate of propanediol-1,3, 77.4 g. (1.19 moles) of potassium cyanide and 750 g. of ethylene glycol was heated and distillation began at 199°. The distillation was stopped when 100 ml. of distillate was collected and found to contain only ethylene glycol.

2-Methylpropanediol-1,3.—To a slurry of 50.4 g. (1.33 moles) of lithium aluminum hydride in 1.5 liters of anhydrous ether, there was added, over a period of 2 hr., 231.9 g. (1.33 moles) of ethyl methylmalonate, b.p. 82–84° (13 mm.), which had been prepared by a method described in "Organic Syntheses."[14] After the addition was completed, the mixture was refluxed for an additional hour. Upon cooling, 25 ml. of 1-propanol was added followed by 250 ml. of saturated sodium chloride solution. After the salts were removed by filtration and the ether by evaporation, the solution was distilled through a two-foot-long vacuum Vigreux column, yielding 41.7 g. (46.3% yield) of 2-methylpropanediol-1,3, b.p. 106–109° (16 mm.), $n^{25}D$ 1.4433; reported[15] b.p. 107–109° (12 mm.); reported[16] n^4D 1.4499.

Ditosylate of 2-Methylpropanediol-1,3.—This synthesis was conducted in a fashion similar to that described for the ditosylate of 2,2-dimethyl-1,3-propanediol. To 45.06 g. (0.5 mole) of 2-methylpropanediol there was added 286 g. (1.5 moles) of *p*-toluenesulfonyl chloride in 600 ml. of pyridine. When the reaction mixture was poured into ice-water, there was obtained an oil which was difficult to crystallize. Recrystallization from methanol four times, and from ether and pentane twice, did not produce a material of sharp or constant melting point. Yield after six recrystallizations: 83.66 g. (42% yield) of white crystals, m.p. 78–83°. The infrared spectrum showed this material to be similar to the other ditosylates and free of hydroxyl groups.

Anal. Calcd. for $C_{18}H_{22}S_2O_6$: C, 54.3; H, 5.6. Found: C, 54.6; H, 5.8.

(11) L. I. Smith and E. R. Rogier, THIS JOURNAL, **73**, 3841 (1951).

(12) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948.

(13) I. Heilbron, "Dictionary of Organic Compounds," Revised Edition, Oxford Press, New York, N. Y., 1953.

(14) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943.

(15) J. Brewster, THIS JOURNAL, **73**, 368 (1951).

(16) R. Plummerer, *Ber.*, **75B**, 867 (1942).

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Reaction of Potassium Cyanide with the Ditosylate of 2-Methylpropanediol.—This reaction was also carried out in the same fashion as that described for the ditosylate of 2,2-dimethyl-1,3-propanediol. A solution of 83.6 g. (0.22 mole) of the ditosylate of 2-methylpropanediol and 43.0 g. (0.66 mole) of potassium cyanide in 600 ml. of ethylene glycol was heated. There was no distillate below the boiling point of ethylene glycol. Extraction of the 175 ml. of distillate with *n*-pentane, and evaporation of the pentane, yielded no product.

Acknowledgments.—The authors are indebted to these members of the National Bureau of Standards: J. Stewart for infrared spectroscopy and the suggestion that the region characteristic of cyclopropane absorption be broadened and R. Paulson and Miss Lorna Tregoning for the analyses.

WASHINGTON, D. C.

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Reaction of *t*-Butylethylene and 1-Hexene with Bromine in Methanol[1a]

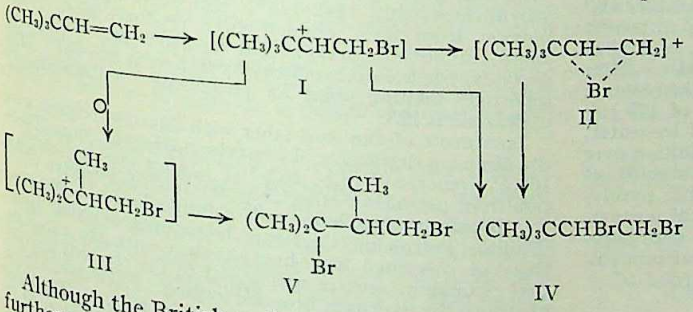
BY W. H. PUTERBAUGH[1b] AND MELVIN S. NEWMAN

RECEIVED JANUARY 23, 1957

The addition of bromine in methanol to *t*-butylethylene produces 1,2-dibromo-3,3-dimethylbutane (IV) and 2-bromo-1-methoxy-3,3-dimethylbutane (VI) in roughly equal amounts. The addition of bromine in methanol to 1-hexene produces about 31% of 1,2-dibromohexane and 59% of a mixture of 1-bromo-2-methoxyhexane and 2-bromo-1-methoxyhexane in the ratio four-to-one, respectively. The mechanism of these reactions is discussed.

The work herein described was undertaken to obtain qualitative evidence about the mechanism of addition of bromine to *t*-butylethylene in particular and to olefins in general. The interest in this work was aroused by the report that the rate of bromination of *t*-butylethylene was only slightly less than that of *n*-butylethylene[2] (0.70 to 1.05).

The rate-determining step undoubtedly involves the formation of a positively-charged bromine-containing intermediate since the rates are first order with respect to olefin and bromine.[2] If the first-formed intermediate is the carbonium ion I, the further reaction of I with the reaction medium might involve attachment of bromine directly to the internal carbon of I. Alternatively, compound I might rearrange to the cyclic bromonium ion II or to skeletally rearranged III. Both I and II would yield the dibromide IV, whereas III would yield the 1,3-dibromide V.



Although the British authors recognized that the further reaction of I would be expected to be slow[3] because of the neopentyl character of the intermediate, they did not go into any further discussion of how I forms final product nor did they prove the structure of the dibromide formed.

In our analysis of this problem we believed that if Compound I were formed directly, it would rearrange rapidly to II which would then be expected to react further at the terminal less hindered carbon to yield IV.[4] The noteworthy feature of this over-all reaction path is that *both bromine atoms enter the final molecule by attack at the terminal carbon*.[5,6]

In order to test this hypothesis, we have studied the reaction of *t*-butylethylene and of *n*-butylethylene with solutions of bromine in methanol, a reagent which adds bromo and methoxy groups to an olefin.[7]

The addition of a solution of bromine in methanol to *t*-butylethylene yielded about 45% of 1,2-dibromo-3,3-dimethylbutane (IV) and 44% of 2-bromo-1-methoxy-3,3-dimethylbutane (VI). The structure of IV was proved by debromination with zinc to yield *t*-butylethylene. The structure of VI was proved by dehydrobromination with sodium amide in liquid ammonia to an unsaturated ether VII, which on treatment with 2,4-dinitrophenylhydrazine reagent afforded the 2,4-dinitrophenylhydrazone of *t*-butylacetaldehyde in high yield. This result supports the hypothesis that both addenda enter the molecule by attack at the terminal carbon, although the first-formed species may be either I or II.

Although the accuracy of our experimental work does not exclude the possibility that small amounts of skeletally rearranged substances were formed, certainly the quantities were very small, if any. This finding is of interest in light of the fact that addition of hydro-

(1a) This work was supported by a grant from the National Science Foundation. (b) Thiel College, Greenville, Pennsylvania.

(2) P. W. Robertson, J. K. Heyes and B. E. Swedlund, *J. Chem. Soc.*, 1014 (1952). In this paper steric factors are ruled out on what seems to us inadequate grounds.

(3) However, if the formation of the bromine-containing intermediate I is the rate-determining step, the rate of further reaction of I would not affect the over-all rate.

(4) The stereochemistry of addition of bromine to *cis*- and *trans*-olefins demands an intermediate of type II. However, with *t*-butylethylene it is conceivable that an intermediate of type I could form first and then go into a type II intermediate.

(5) See M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 243.

(6) See also S. Winstein and L. Goodman, THIS JOURNAL, **76**, 4373 (1954), for an example of non-Markownikow addition of the elements of bromine and methoxyl to α,α-dimethylallyl alcohol.

(7) P. D. Bartlett and D. S. Tarbell, *ibid.*, **58**, 466 (1936).

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gen chloride to *t*-butylethylene gives from 60 to 65% of rearranged chloride, 2-chloro-2,3-dimethylbutane.[8] Furthermore, when neopentyl-type carbonium ions are formed from neopentyl halides and alcohols by bond cleavage, rearrangement almost always occurs to a large extent.

$$(CH_3)_3CCH{=}CH_2 \xrightarrow[CH_3OH]{Br_2} (CH_3)_3CCHBrCH_2OCH_3$$

$$(CH_3)_3CCHBrCH_2OCH_3 \xrightarrow[NaNH_2]{VI} (CH_3)_3CCH{=}CHOCH_3 \xrightarrow{VII} (CH_3)_3CCH_2CHO$$

For comparison we added bromine in methanol to 1-hexene and obtained about 31% of dibromide and 59% of methoxybromide.[9] The latter was shown to consist of about 4–5 parts of 1-bromo-2-methoxyhexane to 1 part of 2-bromo-1-methoxyhexane by dehydrobromination to a mixture of enol ethers VIII and IX. The composition of this mixture was estimated by crude separation of the 2,4-dinitrophenylhydrazones obtained therefrom and by hydrolysis to a mixture of 2-hexanone and hexanal which was analyzed by oxidation and titration of the hexanoic acid produced, as described in the Experimental part. Further work in this field is being carried out.

$$n\text{-}C_4H_9CH{=}CH_2 \xrightarrow[CH_3OH]{Br_2} \xrightarrow{NaNH_2} C_4H_9C(OCH_3){=}CH_2 + C_4H_9CH{=}CHOCH_3$$

$$C_4H_9C(OCH_3){=}CH_2 \xrightarrow{VIII} C_4H_9COCH_3 \qquad C_4H_9CH{=}CHOCH_3 \xrightarrow{IX} C_4H_9CH_2CHO$$

Experimental[10]

***t*-Butylethylene.**—To a stirred mixture of 12.6 g. (0.33 mole) of lithium aluminum hydride and 350 ml. of ether was added dropwise over 3.25 hr., 100 g. (1.00 mole) of pinacolone[11] in 125 ml. of ether. After stirring and refluxing for 45 minutes the mixture was cooled to room temperature and 163 g. (1.60 moles) of acetic anhydride added dropwise over 1.5 hr. The mixture was refluxed for 4 hr. and 84 g. (1.40 moles) of glacial acetic acid then added rapidly. After stirring overnight (12 hr.) at room temperature the reaction mixture was decomposed by adding a solution of 120 ml. of concentrated hydrochloric acid in 240 ml. of ice-water. The crude acetate was pyrolyzed by dropwise addition over 3 hr. to a pyrolysis tube heated to 510° under a constant stream of nitrogen as described previously.[12] The pyrolysate was taken up in toluene, washed with several portions of saturated sodium bicarbonate solution, once with saturated sodium chloride solution and dried over calcium sulfate. Distillation at atmospheric pressure afforded 57 g. (68%) of *t*-butylethylene, b.p. 40–42°.

Bromomethoxylation of *t*-Butylethylene.—To a stirred ice-cooled solution of 31 g. of *t*-butylethylene in 1 l. of absolute methanol protected from light was added dropwise over 3.5 hr. a solution of 60 g. of bromine in 300 ml. of methanol. After stirring for an additional 0.5 hr., the mixture was poured into 2 l. of ice-water containing 20.2 g. of sodium bicarbonate. The mixture was extracted with petroleum ether, b.p. 35–40° (Skellysolve F). Rectification of the washed and dried reaction products through a small packed column afforded 32 g. (44%) of methoxybromide IV, b.p. 81–82° at 30 mm., and 41 g. (45%) of dibromide III, b.p. 100–101° at 30 mm.

The methoxybromide fraction was redistilled to obtain an analytical sample of 1-methoxy-2-bromo-3,3-dimethylbutane (IV), b.p. 81° at 30 mm., $n^{20}D$ 1.4588, d^{27} 1.214.

Anal. Calcd. for $C_7H_{15}OBr$: C, 43.1; H, 7.8; Br, 41.0. Found: C, 43.0; H, 7.6; Br, 41.1.

The dibromide fraction also was redistilled to obtain an analytical sample of III,[13] b.p. 85° at 12 mm., $n^{20}D$ 1.5055, d^{27} 1.620.

Anal. Calcd. for $C_6H_{12}Br_2$: C, 29.5; H, 5.0; Br, 65.5. Found: C, 29.7; H, 5.1; Br, 65.3.

Debromination of III.—A solution of 40 g. of III in 40 ml. of alcohol was added dropwise with stirring to a mixture of 33 g. of zinc dust and 80 ml. of alcohol. After the exothermic reaction moderated, the mixture was heated and stirred for 90 minutes. There was isolated 6.6 g. (48%) of pure *t*-butylethylene, identical in physical properties and infrared spectrum to authentic *t*-butylethylene. No other olefin was found in appreciable amount.

Dehydrobromination of *t*-Butylethylene Methoxybromide (IV).—To a stirred suspension of sodium amide prepared from 5.2 g. (0.226 mole) of sodium and 450 ml. of liquid ammonia was added over 0.5 hr. 40 g. (0.205 mole) of IV in 100 ml. of ether. The mixture was stirred for 1.5 hr. in liquid ammonia until the ammonia evaporated, then refluxed for 0.5 hr. in ether. To the cooled mixture was added 100 ml. of ether followed by 75 ml. of water. The washed and dried reaction products on rectification yielded 12.7 g. (54%) of the enol ether, b.p. 100–106° at 750 mm., and 11.4 g. (28%) of recovered IV, b.p. 75–80° at 30 mm. The enol ether was redistilled to yield 11.5 g. (49%) of 1-methoxy-3,3-dimethyl-1-butene (VII), b.p. 103–106°.

After stirring with saturated sodium bisulfite solution, the enol ether was redistilled to give the analytical sample, b.p. 106° at 750 mm., $n^{20}D$ 1.4092.

Anal. Calcd. for $C_7H_{14}O$: C, 73.6; H, 12.4. Found: C, 73.7; H, 12.6.

Proof of Structure of VII.—To the reagent prepared from 1.7 g. of 2,4-dinitrophenylhydrazine, 3.5 ml. of concentrated hydrochloric acid and 35 ml. of 95% ethanol was added 1.0 g. of VII obtained as described above. An immediate precipitate formed which on cooling was filtered to yield 2.21 g. (92%) of *t*-butylacetaldehyde 2,4-dinitrophenylhydrazone, m.p. 142–146°. One recrystallization of a portion from 95% ethanol gave product, m.p. 147.5–148.0°, in 90% recovery. The reported[14] m.p. for *t*-butylacetaldehyde 2,4-dinitrophenylhydrazone is 146–147°. The reported[15] melting point for pinacolone 2,4-dinitrophenylhydrazone is 125°.

Treatment of the enol ether with dimedon reagent gave the dimedon derivative of *t*-butylacetaldehyde, m.p. 163.0–163.5° (reported[15] m.p. 162–163°), after one recrystallization from petroleum ether (b.p. 90–100°, Skellysolve C).

Bromo-methoxylation of *n*-Butylethylene.—Hexene-1 (Phillips Petroleum Co.) was bromo-methoxylated essentially as described for *t*-butylethylene with the exception that potassium acetate was added to the reaction mixture to absorb the hydrogen bromide formed. From the addition during 2 hr. of 119 g. (0.72 mole) of bromine in 450 ml. of methanol to 60 g. (0.714 mole) of hexene-1 and 74 g. (0.72 mole) of potassium acetate dissolved in 1300 ml. of methanol, there was obtained on distillation at 15 mm., 73 g. of methoxybromide, b.p. 75–78°; 20 g. of intermediate fraction, b.p. 78–88°, and 44 g. of dibromide, b.p. 88–90°. Assuming the intermediate fraction to consist of equal amounts of methoxybromide and dibromide, the yield of methoxybromide was 59% and of dibromide 31%.

Redistillation of the methoxybromide fraction gave an analytical sample, b.p. 68° at 10 mm., $n^{23}D$ 1.4495.

(8) G. G. Ecke, N. C. Cook and F. C. Whitmore, THIS JOURNAL, **72**, 1511 (1950).

(9) This proportion was obtained when potassium acetate was present. When no potassium acetate was present, a lower proportion of methoxybromide was obtained, but qualitatively the rate of bromine addition (decolorization) seemed about the same.

(10) Analyses by Galbraith Laboratories, Knoxville, Tenn. Melting points and boiling points uncorrected except where noted.

(11) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

(12) W. J. Bailey and H. R. Golden, THIS JOURNAL, **75**, 4780 (1953); W. J. Bailey, J. Rosenberg and L. J. Young, *ibid.*, **76**, 2928 (1954); W. J. Bailey and C. King, *ibid.*, **77**, 75 (1955).

(13) This compound has been reported previously (M. F. Claessens *Bull. soc. chim.*, [4] **5**, 113 (1909)), but the structure was not proved.

(14) Reported in U. S. Patent 2,481,157, Sept. 6, 1949.

(15) C. F. H. Allen, THIS JOURNAL, **52**, 2955 (1930).

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Anal. Calcd. for $C_7H_{15}OBr$: C, 43.1; H, 7.8; Br, 41.0. Found: C, 43.0; H, 7.9; Br, 41.2.

Dehydrobromination of *n*-Butylethylene Methoxybromide.—Treatment of 50 g. (0.256 mole) of the methoxybromide obtained from *n*-butylethylene with sodium amide prepared from 6.9 g. (0.3 mole) of sodium essentially as described above for *t*-butylethylene methoxybromide gave on distillation, 11.2 g. (38%) of enol ether, b.p. 120–126° (760 mm.), and 14.1 g. (28%) of recovered methoxybromide, b.p. 75–80° (20 mm.). There was also obtained 4.9 g. (23%) of hexyne-1, b.p. 60–64°. The enol ether fraction was redistilled to obtain an analytical sample, b.p. 122° at 750 mm.

Anal. Calcd. for $C_7H_{14}O$: C, 73.6; H, 12.4. Found: C, 73.5; H, 12.4.

Structure of Enol Ether Obtained from *n*-Butylethylene Methoxybromide.—To the 2,4-dinitrophenylhydrazine reagent prepared from 1.7 g. of 2,4-dinitrophenylhydrazine, 3.5 ml. of concentrated hydrochloric acid and 40 ml. of 95% ethanol was added 1 g. of the enol ether fraction, b.p. 120–126°, obtained as described above. The precipitate was filtered to yield 2.1 g. (89%) of a mixture of methyl *n*-butyl ketone and *n*-hexaldehyde 2,4-dinitrophenylhydrazones, m.p. 80–102°. Recrystallization of a 1.33-g. portion from 60 ml. of 95% ethanol gave as first crop, 0.88 g. (66%) of short orange crystals, m.p. 103.5–107°. The mixed m.p. with authentic methyl *n*-butyl ketone 2,4-dinitrophenylhydrazone (m.p. 107.5–108.5°) was 106–108°. Partial evaporation and freezing of the filtrate yielded 0.4 g. of yellow-orange crystals, m.p. 82–95°. From the latter it was possible to separate by hand a few long yellow needles, m.p. 105.5–107.5°, mixed m.p. with authentic *n*-hexaldehyde 2,4-dinitrophenylhydrazone (m.p. 105.5–107.5°) 106.0–107.5°. However, attempts to further separate the second crop quantitatively by recrystallization and chromatography were unsuccessful.

The amount of terminal enol ether in the enol ether mixture, which was shown above to be less than 34%, was estimated by conversion to a mixture of aldehyde and ketone, oxidation of the mixture with silver oxide and titration of the acid formed from oxidation of the aldehyde, as described below.

A mixture of 8.5 g. of enol ether, 2 ml. of concentrated hydrochloric acid, 6 ml. of water and 10 ml. of ethanol was refluxed 5 minutes. The mixture was diluted with water, taken up in ether, dried and distilled to yield 5 g. (67%), b.p. 124–125°, of a mixture of methyl *n*-butyl ketone and *n*-hexaldehyde. To a silver oxide reagent prepared from 3.40 g. of silver nitrate in 10 ml. of water and 2.40 g. of sodium hydroxide in 10 ml. of water was added 2.50 g. of the ketone–aldehyde mixture. After stirring for 30 minutes, the mixture was filtered with suction and extracted with ether. The aqueous layer was then carefully acidified, salted out and extracted with four 20-ml. portions of ether. The ether extracts were washed with saturated sodium chloride solution and dried. Removal of the solvent left an acidic residue, which on titration with standard base was shown to contain 4.7 mmoles (19%) of acid calculated as caproic acid. The acid isolated from this titration was refluxed with excess aniline for 2 hr. One recrystallization of the crude anilide from 95% ethanol gave *n*-caproanilide, m.p. 95.0–95.5° (reported[16] m.p. 96°). A duplicate run gave an acid yield of 15%. A check on the method with a mixture of 0.02 mole of methyl ethyl ketone and 0.005 mole of *n*-heptaldehyde gave on titration 0.0049 mole (98% of theory) of acid formed.

The enol ether formed from dehydrobromination of the methoxybromide obtained from *n*-butylethylene was thus shown by these methods to consist of approximately 80–85% of 2-methoxyhexene-1 and 15–20% of 1-methoxyhexene-1.

(16) A. Ludwig and S. Tache, *Bull. chim. soc. Romane chim.*, **39**, 87 (1937).

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE ROHM AND HAAS CO., REDSTONE ARSENAL RESEARCH DIVISION]

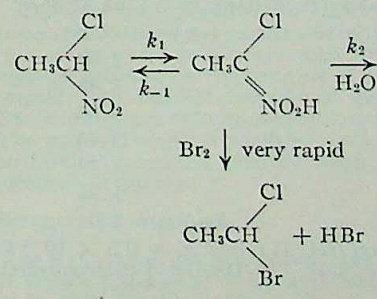
aci-Nitroalkanes. IV. The Mechanism of the Hydrolysis of 1-Chloronitroethane

BY M. FREDERICK HAWTHORNE AND R. DONALD STRAHM

RECEIVED FEBRUARY 11, 1957

In water at 35.0° and in independent first-order rate determinations, 1-chloronitroethane has been found to release chloride ion approximately one-third as rapidly as it absorbs bromine. 1-Deutero-1-chloronitroethane when examined in an identical manner showed approximately a twofold diminution in both measured rate constants. These facts prove that the hydrolytic release of chloride ion from 1-chloronitroethane is preceded by a tautomerization to the reactive *aci*-isomer and that return of the *aci*-isomer to reactant is kinetically important relative to the hydrolysis of the *aci*-isomer. The products of hydrolysis of 1-chloronitroethane have been found to be equivalent amounts of hydrogen chloride, acetic acid and a colorless gas which is probably nitrous oxide. Conductometric examination of the rate of hydrolysis of 1-chloronitroethane affords an instance in which the approach of a reaction system to a steady state situation may be observed.

It was recently reported by Pearson and Dillon[1] that 1-chloronitroethane hydrolyzed in aqueous solution at 34.9° to yield chloride ion at a rate equal to approximately one-half the rate at which the same nitroalkane ionized (absorbed bromine) under the same conditions. In view of the recent finding that the displacement of chloride ion from 1-chloronitroethane by nitrite ion is preceded by the tautomerization of the nitro compound to its *aci*-nitroisomer, it was proposed[2] that the hydrolysis of 1-chloronitroethane and the kinetic observations of Pearson and Dillon[1] could be explained on a similar basis if the rate of return of *aci*-1-chloronitroethane to its hydrolytically stable isomer were comparable to the rate of displacement of chloride ion from the reactive *aci*-isomeride by solvent water ($k_{-1} \sim k_2$).



Therefore

$$\frac{d[Cl^{\ominus}]}{dt} = \frac{k_1 k_2}{k_{-1} + k_2}[CH_3ClNO_2] \text{ and}$$

$$\frac{-d[Br_2]}{dt} = k_1[CH_3ClNO_2] \quad (1)$$

(1) R. G. Pearson and R. L. Dillon, THIS JOURNAL, **75**, 2439 (1953).

(2) M. F. Hawthorne, *ibid.*, **78**, 4980 (1956).

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Since both the rate of chloride ion release and the rate of bromination depend, according to this rationalization, upon the magnitude of the ionization rate constant, k_1, both reactions should show a kinetic primary isotope effect of equal magnitude when deuterium is substituted for protium on the carbon atom alpha to the nitro group.[2] This prediction has been confirmed within possible experimental error and the products of hydrolysis determined.

Results

1-Chloronitroethane was purified carefully by regeneration from its anion followed by fractional distillation[2] and 1-deutero-1-chloronitroethane was prepared by regeneration in deuterium oxide and fractionally distilled.[2]

The initial rates of ionization of these two materials in water at 35.0° were determined under zero-order conditions by the conductometric bromination method of Pearson and Dillon.[1] Table I summarizes the ionization rate constants of both the protium (k_{iH}) and deuterium (k_{iD}) compounds.

TABLE I

THE RATES OF IONIZATION OF 1-CHLORO- AND 1-DEUTERO-1-CHLORONITROETHANE IN WATER AT 35.0°

Init. concentrations, mole/l. $(Br_2) \times 10^2$	(CH_3CHNO_2Cl)	k_i,[a] min.$^{-1} \times 10^5$
1.53	0.0509	11.7
1.45	.102	12.7
2.06	.974	12.0
0.66	.040[b]	6.00
.71	.0772[b]	6.37
.10	.0795[b]	6.00
		$k_{iH}/k_{iD} \sim 2.0$

[a] Pearson and Dillon (ref. 1) report $k_i = 1 \times 10^{-4}$ min.$^{-1}$ at 34.9° for protium compound. [b] 1-Deutero-1-chloronitroethane.

Table II reports the initial first-order rate constants obtained for the hydrolytic release of chloride ion from both 1-chloronitroethane (k_{sH}) and its 1-deutero analog (k_{sD}) in water at 35.0°. These first-order rate constants were obtained by direct titration of released chloride ion and the rate runs were carried to approximately 25% completion in every case.

TABLE II

THE RATE OF CHLORIDE ION RELEASE BY 1-CHLORO- AND 1-DEUTERO-1-CHLORONITROETHANE IN WATER AT 35.0°

$[CH_3CHNO_2Cl]$, mole/l. $\times 10^2$	k_s,[a] min.$^{-1} \times 10^5$
0.97	3.50
1.99	3.49
3.48	3.56
3.56	3.45
0.88[b]	1.70
2.76[b]	1.75
	$k_{sH}/k_{sD} \sim 2.0$

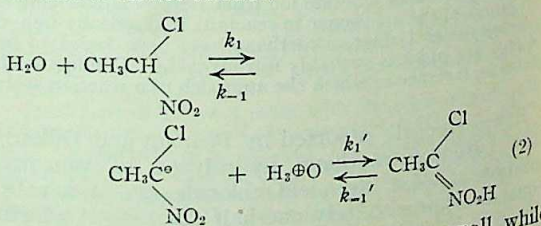
[a] Pearson and Dillon (ref. 1) report $k_s = 0.5 \times 10^{-4}$ for protium compound at 34.9°. [b] 1-Deutero-1-chloronitroethane.

The products of the hydrolysis of 1-chloronitroethane were accounted for in a quantitative fashion when the hydrolysis reaction was carried out in a sealed tube at 100°. These products consisted of one mole of hydrogen chloride and one mole of acetic acid per mole of 1-chloronitroethane consumed. The acetic acid was identified by conversion to its *p*-nitrobenzyl ester and by its characteristic potentiometric titration curve. Hydrogen chloride was determined by chloride ion analysis and by potentiometric titration of hydrogen ion. In addition to these products a considerable but undetermined amount of a colorless gas was produced which presumably was nitrous oxide. Nitrite ion was not present.

Discussion

Since the substitution of the 1-protium by deuterium produces an approximate twofold diminution in both rates of ionization and hydrolysis of 1-chloronitroethane at 35.0°, it may be concluded that the over-all hydrolysis reaction involves the breaking of a carbon–hydrogen bond prior to the expulsion of chloride ion. The near constant ratio of k_i to k_s which is equal to approximately 3.4 and which is obtained regardless of the isotopic nature of the reactant 1-chloronitroethane points up the fact that only a definite fraction of the molecules of 1-chloronitroethane which tautomerize to the *aci*-isomer react in such a manner as to produce chloride ion. All of these results are best rationalized in terms of the formulation (1) in which $k_{-1} \sim 2.4k_2$.

An additional piece of evidence also was obtained which indicates the correctness of this rationale. It was observed that freshly prepared aqueous solutions of 1-chloronitroethane initially gave only a very low rate of increase in conductance with time. However, this rate of increase of conductance increased as time progressed and finally became a linear function of time. Similarly, aqueous solutions of 1-chloronitroethane which had been employed in conductometric bromination rate determinations gave similar conductance *vs.* time curves following the consumption of the initially added bromine. These observations fit the proposed reaction scheme since the equilibria 2 are involved in the transformation of 1-chloronitroethane to its *aci*-isomer.



In these equilibria[3] k_1 and k_{-1} are small while k'_1 and k'_{-1} are large and k'_1/k'_{-1} may be of the order of 10^3. Thus, a solution which contains only very little *aci*-1-chloronitroethane will show a small initial conductance. However, as ionization (k_1 process) proceeds, the products of this ionization will be an equilibrium mixture of the solvolytically inert 1-chloronitroethane anion and the reactive *aci*-1-chloronitroethane. As a result of this situation, the first 1-chloronitroethane which ionizes will produce the electrolytes hydrogen ion and 1-chloronitroethane anion, but as these products accu-

(3) See D. Turnbull and S. H. Maron, THIS JOURNAL, 65, 212 (1943), for a discussion of similar equilibria.

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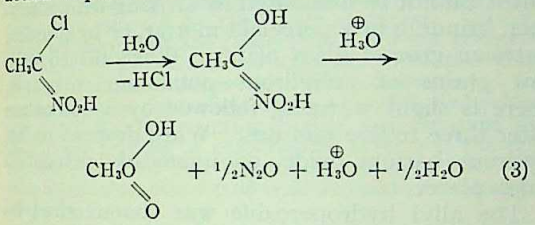
mulate the concentration of *aci*-1-chloronitroethane will increase and the rate of appearance of the products of the hydrolysis of this material will also increase. Since these products are hydrogen ion, chloride ion and dissociated acetic acid, an enhancement in the rate of increase of conductance will occur until the concentrations of 1-chloronitroethane anion and *aci*-1-chloronitroethane reach the steady state concentrations of the reaction system. The length of time required to reach the steady state condition was roughly inversely proportional to the initial concentration of substrate. Figure 1 illustrates this point.

The products of the hydrolysis of 1-chloronitroethane may be explained on the basis of the reaction sequence 3 in which the proposed reaction



takes the course of the nucleophilic displacement of chloride ion by water followed by a Nef reaction[4] of the resulting *aci*-1-hydroxynitroethane.

Experimental

Materials.—The 1-chloronitroethane was a portion of material which had been purified previously for another study.[2] The 1-deutero-1-chloronitroethane was similarly a portion of previously prepared material.[2]

The solvent water employed in the conductometric experiments gave an infinite resistance reading in the apparatus employed and had been prepared by the passage of distilled water through a commercial Deeminizer ion exchange column.

Rates of Bromination.—The rates of bromination were determined using low concentrations of bromine (1×10^{-4} to 2×10^{-3} *M*) and much greater concentrations of 1-chloronitroethane or 1-deutero-1-chloronitroethane in conductivity water at 35.00 + 0.01°. Resistance readings were obtained in a low resistance conductivity cell using a Leeds and Northrup conductivity apparatus and a General Electric Type ST-2A oscilloscope as a null point indicator.

An accurately measured small volume of a standard aqueous bromine solution was added to a known volume of a 1-chloronitroethane solution prepared from a weighed amount of nitroalkane at zero time. Both solutions were thermostated previous to the time of mixing. Resistance readings were taken at various time intervals and conductance plotted *vs.* time. Linear plots were obtained up to the time at which all of the added bromine was consumed. Beyond this point the conductance remained constant for a few moments and then began to rise at a progressively greater rate until a new linear conductance *vs.* time curve was established. The curves of Fig. 1 are similar to those obtained under these conditions. The time, *t*, required for the consumption of the known added bromine $[Br_2]_0$, was used along with the initial nitroalkane concentration, $[RNO_2]_0$, to calculate the first-order ionization rate constant, k_1.

$$k_1 t = [Br_2]_0/[RNO_2]_0$$

The deuterated substrate was treated in an identical fashion as were the experiments which were carried out in the absence of bromine.

(4) See M. F. Hawthorne, THIS JOURNAL, **79**, 2510 (1957), for a recent discussion of the mechanism of this reaction.

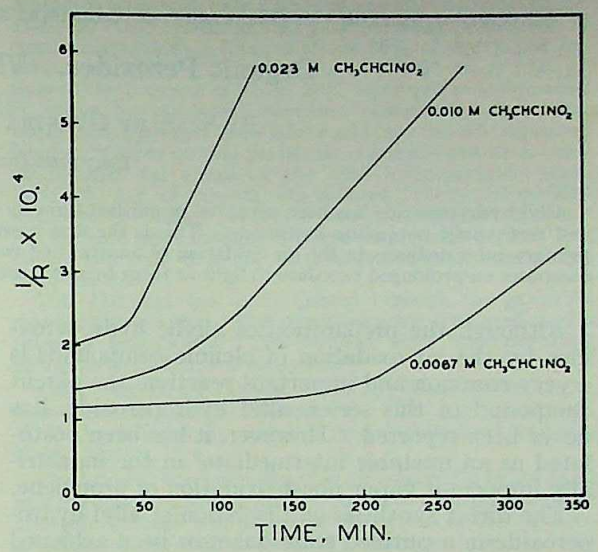


Fig. 1.—Conductivity *vs.* time curves for the hydrolysis of 1-chloronitroethane in water at 35.0°.

Rates of Hydrolysis.—Solutions of 1-chloronitroethane or 1-deutero-1-chloronitroethane were prepared in distilled water and thermostated at 35.00 ± 0.01°. Periodically, aliquots were withdrawn and chloride ion was titrated potentiometrically with 0.01 *N* standard silver nitrate solution using a Beckman model G *p*H meter with silver and calomel electrodes. The titration data were treated graphically and a correction was applied for the solubility of silver chloride. The reactions were carried to approximately 25% completion in every case and the first-order hydrolysis rate constants were obtained graphically from a plot of log [chloronitroethane] *vs.* time.

Product Analysis.—1-Chloronitroethane (1.180 g.) and 6 ml. of water were sealed in a glass tube and heated in a steam-bath for two weeks. The tube was then cooled to −80° and opened. A considerable quantity of colorless gas was released when the tube was opened. The contents were carefully washed into a 50-ml. volumetric flask and diluted to the mark with the distilled water.

A 10-ml. aliquot of the solution was titrated for chloride ion by the Mohr method after neutralizing with sodium hydroxide. The solution was found to be 0.215 *M* in chloride ion (99.7% of theoretical for complete hydrolysis). The concentration of hydrogen ion was found to be 0.427 *M* by the titration of another 10-ml. aliquot to a phenolphthalein end-point with standard sodium hydroxide.

A second acid titration was carried out on a 10-ml. aliquot using a Beckman *p*H meter. A break occurred at *p*H 3.1 indicating the solution to be 0.214 *M* in a strong acid. Another very sharp break occurred just beyond *p*H 7 giving a total hydrogen ion concentration of 0.427 *M*. A qualitative test for nitrite ion was negative.

The weak acid present in the reaction mixture was shown to be acetic acid by the partial neutralization of a 20-ml. portion of the reaction mixture with 10% sodium hydroxide solution followed by the addition of 0.5 g. of *p*-nitrobenzyl bromide and sufficient ethanol to give solution at reflux. The solution was refluxed several hours and cooled with ice. The material which crystallized melted at 72.5°[5] and gave an infrared spectrum identical with that of authentic *p*-nitrobenzyl acetate.

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(5) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1947, report the melting point of *p*-nitrobenzyl acetate to be 78°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Organic Peroxides. VI. Allyl Hydroperoxide[1]

BY STANLEY DYKSTRA AND HARRY S. MOSHER

RECEIVED OCTOBER 31, 1956

Allyl hydroperoxide has been prepared in purified form by the reaction of allyl methanesulfonate with hydrogen peroxide and methanolic potassium hydroxide. This is the first member of the series of allylic type hydroperoxides which are the primary intermediates in the air oxidation of unsaturated compounds. Allyl hydroperoxide detonates on heating and decomposes on prolonged exposure to light at room temperature but is relatively stable in the cold and dark.

Although the preparation of allylic hydroperoxides by the air oxidation of olefinic compounds is a very common and important reaction, the parent compound of this series, allyl hydroperoxide, has never been reported. However, it has been postulated as an unstable intermediate[2] in the industrially important vapor phase oxidation of propylene.

The direct synthesis and isolation of allyl hydroperoxide in a purified state has now been achieved by the action of hydrogen peroxide on allyl methane sulfonate by the method of Williams and Mosher.[3] Although the usual procedure[3] gave solutions indicating allyl hydroperoxide yields of 30–40% as measured by titration, considerable difficulty was experienced in isolation and purification because of its unstable nature. It underwent slow decomposition at 40–60° with the formation of an explosive polymeric residue. It detonated when heated rapidly in a capillary tube. The distilled but impure product, which was known to contain at least water and hydrogen peroxide, was very sensitive to light. Exposure to artificial room illumination for only ten minutes resulted in extensive destruction in some of the impure samples of allyl hydroperoxide as evidenced by the appearance of a carbonyl band at 5.95 μ in the infrared spectrum. Because of the decomposition of these crude preparations in the presence of light and heat, the preparation and purification of allyl hydroperoxide was conducted entirely in Pyrex low actinic glassware in the presence of artificial illumination from a photographic red light; initial purification was accomplished by evaporative distillation below 20°; final purification was by gas–liquid partition chromotography.[4] Samples so purified did not show this rapid decomposition on exposure to light.

The sensitivity to light must be dependent upon impurities and cannot be the result of enhanced absorption and photodissociation since the ultraviolet absorption spectrum of allyl hydroperoxide (log ϵ 0 at 312 mμ) shows only a slight bathochromic shift from that of *n*-butyl hydroperoxide (log ϵ 0 at 302 mμ) which is stable to ordinary light. Thus the amount of light which will pass through a Pyrex flask and be absorbed by allyl hydroperoxide must be extremely small.

Allyl hydroperoxide is extremely irritating to the mucous membrane of the nose. Even the slightest contact with the skin causes a prolonged burning sensation and blisters which persist for approximately one week. It detonates when heated, but it cannot be detonated by striking with a hammer, grinding in a porcelain mortar, or by grinding between ground glass plates. When placed on a few grains of anhydrous potassium carbonate, there is slight warming followed by a detonation after three to five minutes. When dropped on anhydrous barium oxide, an immediate detonation takes place.

The allyl hydroperoxide was characterized by carbon hydrogen analysis, active oxygen determination, infrared and ultraviolet spectra, positive reaction to bromine in carbon tetrachloride, solubility in cold dilute sodium hydroxide solution and reduction to propanol.

The starting material, allyl methanesulfonate, could not be made by the procedure of Sekera and Marvel.[5] The method which Hahn and Walter[6] developed for the preparation of allyl phenylsulfonate was also unsatisfactory, although it did result in a 20% yield of allyl methanesulfonate. The treatment of methanesulfonyl chloride and allyl alcohol in ether solution with powdered potassium hydroxide also gave very low yields. These findings correspond to those reported by Raphael and Sondheimer[7] in the preparation of 2-octyne-1-methanesulfonate. However, by the slow addition of methanesulfonyl chloride to an allyl alcohol–ether solution of sodium alloxide, yields up to 68% of allyl methanesulfonate were finally achieved.

Experimental

Allyl Methanesulfonate.—Sodium, 6.9 g. (0.3 mole), was allowed to dissolve in anhydrous allyl alcohol, 100 g., and the resulting solution was diluted with 100 ml. of anhydrous ether. This solution was cooled to 0° and rapidly stirred while methanesulfonyl chloride, 36 g. (0.31 mole), dissolved in 200 ml. of anhydrous ether, was added over a 2-hr. period. The reaction mixture was held at about −5° for 2 hr. and allowed to warm to room temperature overnight. The salt was removed by filtration, the filtrate was evaporated under 20 mm. pressure and the residue was distilled over a little potassium carbonate; b.p. 70–75° (3 mm.), 28 g. (68.5%), n^{20}D 1.4414.

Anal. Calcd. for $C_4H_8O_3S$: C, 35.30; H, 5.92. Found: C, 35.39; H, 5.78.

Lower yields were obtained when the allyl alcohol was not freshly distilled or when the methanesulfonyl chloride was added too rapidly with inefficient stirring. Yields from 55 to 68% were consistently obtained by the above procedure.

Allyl Hydroperoxide.—The following procedure was con-

(1) (a) Presented before the 126th Meeting of the American Chemical Society, New York, N. Y., Sept., 1954. (b) Previous paper in the series, *Anal. Chem.*, **27**, 517 (1955).

(2) V. Y. Shtern and S. S. Polynak, *Doklady Akad. Nauk, U.S.S.R.*, **85**, 161 (1952); *C. A.*, **46**, 9397 (1952).

(3) H. R. Williams and H. S. Mosher, THIS JOURNAL, **76**, 2984, 2987 (1954).

(4) M. Dimbat, P. E. Porter and F. H. Stross, *Anal. Chem.*, **28**, 90 (1956).

(5) V. C. Sekera and C. S. Marvel, THIS JOURNAL, **55**, 345 (1933).

(6) F. T. Hahn and H. Walter, *Ber.*, **54B**, 1531 (1921).

(7) R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 2100 (1950).

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ducted in Pyrex, low actinic, glassware in a room illuminated with a red photographic light bulb. Care was taken so that the reaction mixture never came into contact with metal such as nickel from a spatula, iron or rust from a metal stirrer, etc. At any point where the allyl hydroperoxide was being heated or concentrated by evaporation, the apparatus was surrounded by a safety shield and sand bags.

Allyl methanesulfonate, 10.8 g. (0.08 mole), was dissolved in methanol, 30 ml., and 30% reagent grade hydrogen peroxide, 44 g. (0.44 mole), was added after the temperature had reached 0° by cooling with an external ice–salt-bath. While the temperature was kept at 0°, 50% potassium hydroxide solution, 10.1 g. (0.09 mole), was added slowly dropwise with vigorous stirring over a fifteen-minute period. The mixture was stirred for 1 hr. at 0° and then allowed to warm to 20° over a 2-hr. period. The reaction mixture was cooled to 0°, made strongly basic with 50% potassium hydroxide solution, 10.1 g., and subjected to vacuum evaporation at 15° or below until 30 g. of distillate had been collected in the Dry Ice trap. Most of the methanol, some water and a small amount of hydrogen peroxide were removed by this latter operation. Care was taken to ensure that the concentration did not go beyond this point. The residue was extracted with two 15-ml. portions of ether to remove any non-volatile neutral substances and then neutralized at 0° with 15% hydrochloric acid to *p*H 6. The resulting solution was extracted with four 20-ml. portions of peroxide-free ether and the ether extracts were dried over anhydrous sodium sulfate. This ether solution contained 0.06 mole of total peroxide by titration.[8]

The major portion of the ether was removed below 15° at 150 mm. pressure through a 12-inch column packed with Pyrex helices. The residue was then evaporatively distilled at room temperature or below by progressively lowering the pressure to 6 mm. The fractions were collected in a series of traps kept at 0, −20 and −75°. The residue was about 0.5 g.[9] Each fraction was qualitatively analyzed by gas-liquid partition chromatography.[10] The −75° trap contained ether with only a trace of any allyl hydroperoxide. The −20° trap contained 0.93 g. which was estimated to be contaminated with a total of about 35% of water and hydrogen peroxide.[11] The contents of the 0° trap, 1.95 g., showed the presence of about 20% hydrogen peroxide and/or water by gas–liquid partition chromatography. The water and hydrogen peroxide could not be distinguished from each other on this particular column,[10] but both came off together far ahead of the allyl hydroperoxide peak. From 250 mg. of this cut was isolated 110 mg. of purified allyl hydroperoxide. Isolation was accomplished by passing the exit gases through a micro trap cooled in Dry Ice, during the time that the allyl hydroperoxide was exiting from the tube.[12]

This 110 mg. was again passed through the gas chromatography column. The partitionogram indicated only a trace of impurities.[13] The isolated allyl hydroperoxide, 58 mg., $n^{20}D$ 1.4200, was analyzed.[14]

Anal. Calcd. for $C_3H_6O_2$: C, 48.61; H, 8.16; O, 43.23; active oxygen, 21.58. Found: C, 47.87; H, 8.52; O, 43.61 (by difference); active oxygen (determined by titration[8]), 20.8%.

The infrared spectrum of a thin film showed a broad band at 3.0 μ characteristic of the O–H bond of the hydroperoxide molecule. There was moderate absorption at 6.15 μ characteristic of the double bond. This sample showed no discrete absorption at 5.8–6.0 μ indicating the absence of carbonyl impurities. There were strong peaks at 3.5, 7.09, 7.48, 10.12 (shoulder at 9.90), 10.74 and 12.28 μ. All primary hydroperoxides have shown this latter band.[1b] Weaker bands occurred at 5.38, 8.00, 8.70 and 11.64 μ. The latter is at the position assigned to the O–O stretching frequency of the peroxide bond.[1b]

Acknowledgment.—We are grateful to the California Research Corporation for a grant which made this investigation possible.

(8) C. D. Wagner, R. H. Smith and E. D. Peters, *Anal. Chem.*, **19**, 976 (1947).

(9) The amount of residue varied from slight, as in this experiment, to 3 g. if the distillation had been carried out slowly at a bath temperature of 50°. In every case this residue would detonate if a drop was heated in a test-tube over a free flame. Three drops were sufficient to shatter completely an eight-inch Pyrex test-tube. The explosive nature of this residue was lost slowly on standing. In one of the earlier experiments when the distillation was complete but the distillation flask containing the residue was still in an oil-bath at approximately 110°, a detonation occurred which completely destroyed the apparatus. The decomposition of allyl hydroperoxide and the nature of this polymer will be studied further.

(10) The column was a 100 × 0.6 cm. Pyrex tube packed with 60 mesh fire brick.[4] The fire brick had been digested with hydrochloric acid, followed by ammonium hydroxide treatment and thoroughly leached with distilled water, then dried and impregnated with G.E. SF-81 (40) silicone oil. The column was run at 38°, 8 p.s.i. with a helium through-put of 205 ml. min. Under these conditions the retention time for ether was 1.0 min., for allyl alcohol was 1.9 min., for benzene was 5.0 min. and for allyl hydroperoxide was 7.3 min. The samples were injected with an all-glass capillary pipet. The high flow rate was employed so that the temperature could be kept below 40°.

(11) Several previous experiments indicated that the water could not be separated satisfactorily by simple distillation. Successive dryings over anhydrous copper sulfate appeared to be the most efficient way to dry the product but led to extensive decomposition. Therefore anhydrous sodium sulfate was used as the drying agent although it did not appear to be too effective.

(12) Because of the very high flow rate of helium carrier gas during these isolations,[10] the recovery was very poor. On several calibration runs under approximately the same conditions, using allyl alcohol as a standard compound, a recovery of 45 to 50% was realized.

(13) The fact that a second passage of the main fraction through the gas–liquid partition chromatography column gave a partitionogram which indicated only traces of impurities establishes that insignificant decomposition of the allyl hydroperoxide was taking place on the column under the conditions used.[10]

(14) Carbon and hydrogen analyses by Microchemical Specialties Co., Berkeley, Calif. The samples were evaporated slowly and no unusual decomposition was observed during the combustion.

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[CONTRIBUTION NO. 1000 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Constitution of the Grignard Reagent

BY RAYMOND E. DESSY,[1] GEORGE S. HANDLER, JOHN H. WOTIZ AND C. A. HOLLINGSWORTH

RECEIVED JANUARY 12, 1957

The equilibria $Et_2Mg{\cdot}MgBr_2 \rightleftarrows Et_2Mg + MgBr_2 \rightleftarrows 2EtMgBr$ have been investigated by employing magnesium bromide labeled with radioactive magnesium. Only a small amount of exchange was noted between Et_2Mg and Mg^*Br_2. These results, in conjunction with the fact that the same species seems to be present in a solution of Et_2Mg and $MgBr_2$ as is present in the Grignard reagent prepared in the usual manner, indicate that the ethyl Grignard reagent is better represented by a complex $Et_2Mg{\cdot}MgBr_2$ than by EtMgBr.

Despite the fact that the Grignard reagent has been known and utilized for over fifty years, its structure, particularly in ether solution, is unknown. The most widespread hypothesis considers the equilibria[2]

$$R_2Mg{\cdot}MgX_2 \rightleftarrows R_2Mg + MgX_2 \rightleftarrows 2RMgX \quad (1)$$

The addition of dioxane to a Grignard solution results in the precipitation of virtually all of the halogen and part of the magnesium, leaving R_2Mg in the supernatant liquid.[2] It also has been shown[3,4] that equimolar mixtures of diethylmagnesium and magnesium bromide in ether yield almost instantaneously a solution having the same relative rate of reaction and kinetics in a reaction with a given substrate, hexyne-1, as does the Grignard reagent prepared in the normal manner from ethyl bromide and magnesium. This would seem to imply that the same species is/are present in the two solutions. Recalling these two pieces of information, it therefore seemed of interest to investigate equation 1 [R = ethyl, X = Br] employing radioactive magnesium as a tracer, using, for example, Mg^*Br_2.

Methods and Results

Radioactive magnesium (Mg^{28}, $t_{0.5}$ = 21.25 hr.) was prepared by a spallation reaction involving proton irradiation of potassium chloride. The magnesium, diluted with carrier, was separated as the oxinate and ignited to the oxide. The latter was converted to magnesium chloride, and exchange between this and elemental magnesium was accomplished by heating the mixture to 800°. The resulting labeled magnesium metal was then treated with bromine in dry ether to yield magnesium bromide. The specific activity of the magnesium in an aliquot was determined as a function of time. Table I lists the specific activities of the magnesium in the magnesium bromide used in two entirely separate experiments.

Equimolar amounts of this magnesium bromide and diethylmagnesium (prepared from ordinary magnesium) were dissolved in ether so as to give a solution 1.0 *M* in magnesium. The resulting solution was permitted to stand for ten minutes or 36 hr. and an excess of dioxane added, so as to precipitate the elements of magnesium bromide, leaving diethylmagnesium in the supernatant liquid. The specific activity of the magnesium in an aliquot of the diethylmagnesium solution was determined as a function of time. Table I also lists these specific activities, corrected to the same time of counting as the corresponding magnesium bromide sample and corrected for the small amount of magnesium bromide left unprecipitated by the dioxane.

TABLE I

RADIOACTIVITY EXCHANGE BETWEEN $(C_2H_5)_2Mg$ AND Mg^*Br_2

Run	Specific activity (counts/sec.-mg. Mg) Mg^*Br_2	Specific activity (counts/sec.-mg. Mg) Et_2Mg[a]	Contact time, min.	Activity ratio	% Migration	% Exchange (based on statistical exchange)
1	1.65	0.089	10	19:1	5	10
2a	13.05	.444	10	29:1	3	6
2b	4.20	.178	36 hr.	24:1	4	8

[a] The specific activity of the magnesium in the diethylmagnesium sample has been adjusted to the same counting time as that of the companion magnesium in the magnesium bromide sample by means of log (activity) *versus* time plots. It also takes into account the $MgBr_2$ present as a result of incomplete precipitation by the dioxane. This accounted for about 1% of the magnesium present in the sample.

Discussion

Assuming, on the basis of the rate data mentioned previously,[3,4] that an equimolar mixture of diethylmagnesium and magnesium bromide yields the same species as that to which we assign the name "ethyl Grignard" and considering equation 1, one would conclude that in a mixture of $(C_2H_5)_2Mg$ and Mg^*Br_2 there should be a 50% migration of the label (100% exchange). This would arise because of the fact that in the species C_2H_5MgBr we have an equilibrium partner in which all of the magnesium atoms are equivalent. The low percentage of exchange actually found[5] would seem to indicate that forms such as those represented by RMgX in equation 1 play little or no part in the constitution of the ethyl Grignard reagent. Although one is limited by the short

(1) Department of Chemistry, The Ohio State University, Columbus 10, Ohio.

(2) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954.

(3) J. H. Wotiz, C. A. Hollingsworth and Raymond E. Dessy, *J. Org. Chem.*, **21**, 1063 (1956).

(4) Raymond E. Dessy, J. H. Wotiz and C. A. Hollingsworth, THIS JOURNAL, **79**, 358 (1957).

(5) It is impossible at the present to explain why a low percentage of migration, rather than no migration at all was found. One possible explanation would be of course to assume that a very small amount of the species C_2H_5MgBr was present and that the disproportionation of this to the species $(C_2H_5)_2Mg$ and $MgBr_2$ occurs very slowly. However, it is also very likely that a considerable amount of precipitation exchange occurs, that is, migration occurring during the vigorous exothermic precipitation of the $MgBr_2$. The actual mechanism of this step is unknown.

The low percentage of exchange found is also most unexpected in view of the appreciable conductivity of ether solutions of $(C_2H_5)_2Mg$ and $MgBr_2$ (*cf.* Evans and Pearson, THIS JOURNAL, **64**, 2865 (1942)).

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half-life of the tracer, the fact that the activity ratios after a contact time of ten minutes or 36 hr. were sensibly the same indicates that equilibrium 2 is at most a very unimportant side

$$(C_2H_5)_2Mg + MgBr_2 \rightleftarrows 2C_2H_5MgBr \quad (2)$$

reaction with respect to the over-all picture. The results are compatible with an equilibrium of the type

$$(C_2H_5)_2Mg + MgBr_2 \rightleftarrows (C_2H_5)_2Mg\cdot MgBr_2 \quad (3)$$

Along the same lines it is interesting to note that the diethylcadmium–cadmium bromide system in tetrahydrofuran shows no exchange under similar conditions.[6]

A more comprehensive investigation of Grignard systems is being contemplated, employing stable isotopes as tracers.

Experimental

Diethylmagnesium.—The diethylmagnesium in ether was prepared by the action of dioxane on an ether solution of ethylmagnesium bromide,[7] followed by removal of the solvents and dissolution in ether.

Labeled Magnesium Bromide.—Mg^{28} was prepared by a spallation reaction involving proton irradiation of a one cc. single crystal of potassium chloride[8] for 1 hr. at a radius equivalent to 350 Mev. in the Synchrocyclotron of the Carnegie Institute of Technology. The crystal was permitted to stand for 2 hr. after it was dismounted from the probe to allow any short-lived material to decay, and it was then dissolved in 50 ml. of water, along with 100 mg. of $Al(NO_3)_3$ and 500 mg. of $MgBr_2$ to serve as carriers. The solution was heated to the boiling point and adjusted to *p*H 8 with ammonium hydroxide in order to precipitate aluminum hydroxide, which was filtered off. The filtrate was diluted to 125 ml. and heated to 60° and 35 ml. of 6 *N* ammonium hydroxide added. Then 30 ml. of 5% 8-hydroxyquinoline in 2 *N* acetic acid was added slowly. The suspension was brought to the boiling point and then permitted to settle for a few minutes. The oxinate of magnesium was collected by filtration and dried.

The greenish-yellow oxinate was mixed intimately with an equal volume of oxalic acid and placed in a fused silica crucible. Careful ignition with a blast burner yielded magnesium oxide as a fine white powder. The magnesium oxide was dissolved in concentrated hydrochloric acid and any excess acid destroyed by adding a few shavings of magnesium metal.

The solution of magnesium chloride was transferred to a graphite crucible enclosed in a Vycor capsule along with 10 g. of Dow atomized magnesium pellets. The capsule was then attached to a vacuum line and carefully pumped out. The capsule was then heated to 800° and kept at that temperature for 1 hr. in order to cause exchange between the Mg and Mg^*Cl_2. The contents of the crucible were permitted to cool, and the capsule was forced open. Under the conditions employed the Mg was obtained as a clean crystalline plug, which had distilled or sublimed from the hot furnace area of the crucible to cooler portions. This plug was crushed and added to 100 ml. of Mallinckrodt Anhydrous Ether in a three-necked flask equipped with a stirrer, addition funnel and Dry Ice–acetone condenser. Bromine was added slowly to the suspension until a considerable quantity of the magnesium had been utilized. Magnesium bromide and ether, in these concentrations, form a two-phase system.[9] The darker lower layer which contains 485 mg. of $MgBr_2$ per ml. at 25° was used.

Exchange Reactions.—The concentrated magnesium bromide solution and the concentrated diethylmagnesium solution were added to a sufficient volume of ether to yield a solution 0.5 molar in each component (1.0 molar in magnesium). This was permitted to stand for various time periods, and then 1.5 mole equivalents of 1,4-dioxane was added slowly over a 15-minute period with constant agitation. The suspension was agitated slowly for 15 minutes and then centrifuged at 2000 r.p.m. for five minutes. The supernatant solution was analyzed for basic magnesium using the technique described by Gilman[10] and was found to be approximately 0.5 *M* in magnesium. A potentiometric titration for halogen indicated that the supernatant liquid was approximately 0.01 *M* in bromine.[11]

Sampling and Counting.—A portion of the supernatant liquid was transferred to a glass planchet, air hydrolyzed, treated with concentrated hydrobromic acid and dried. A similar planchet was prepared from the original magnesium bromide solution.

The activity of the samples was determined using an Amperex Type 200 CB halogen filled Geiger tube. The activity of the samples was followed for 60 hr. A plot of log(activity) *versus* time indicated high radiochemical purity and a $t_{0.5}$ of 21.2 hr. The reported $t_{0.5}$ of Mg^{28} is 21.25 hr.[12]

Acknowledgment.—The authors are indebted to the staff and crew of the Carnegie Institute of Technology Synchrocyclotron at Saxonburg, Pennsylvania, for their aid and coöperation.

(6) A. B. Garrett, Arthur Sweet, Wm. L. Marshall, David Riley and Anis Touma, *Rec. Chem. Progr.*, **13**, 155 (1952).

(7) J. H. Wotiz, C. A. Hollingsworth and Raymond E. Dessy, THIS JOURNAL, **78**, 1221 (1956).

(8) M. Lindner, *Phys. Rev.*, **89**, 1150 (1953).

(9) W. E. Doering and C. R. Noller, THIS JOURNAL, **61**, 3436 (1939).

(10) H. Gilman, *ibid.*, **51**, 1576 (1929).

(11) It was very difficult to obtain reliable data on the halogen concentration in the solutions when only one-ml. samples were available. However, determinations made during blank runs which did not involve the radioactive tracer and hence could be run on a larger scale indicated similar results.

(12) G. Friedlander and J. W. Kennedy, "Nuclear and Radiochemistry," John Wiley and Sons, Inc., New York, N. Y., 1955.

PITTSBURGH, PENNA.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Condensation of Grignard Reagents with 3-Pyridyl and 3-Quinolyl Ketones

BY REYNOLD C. FUSON AND JOHN J. MILLER

RECEIVED JANUARY 18, 1957

Phenylmagnesium bromide was found to condense in the 1,4-manner with 3-benzoyl-, 3-mesitoyl- and 3-duroylpyridine and with 3-benzoyl- and 3-mesitoylquinoline. Benzylmagnesium chloride reacted in a similar way with the hindered pyridyl ketones, but gave the 1,2-addition product with 3-benzoylpyridine. The products with the phenyl reagents were the corresponding dihydro aromatic compounds; they were dehydrogenated readily with chloranil. 2-Azafluorenone (III) was produced when either 3-mesitoyl-4-phenylpyridine or 3-duroyl-4-phenylpyridine was treated with polyphosphoric acid. The action of polyphosphoric acid on 3-mesitoyl-4-phenylquinoline provided 3,4-benzo-2-azafluorenone (X).

In a search for diaryl ketones that might be unusually receptive to conjugate attack by Grignard reagents, attention was directed to the 3-pyridyl ketones. That these compounds would undergo condensation with organomagnesium halides in the 1,4-manner was indicated clearly by the

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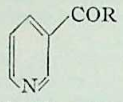
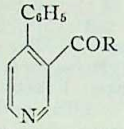
observation of Frank and Weatherbee,[1] that *n*-propylmagnesium bromide reacted with nicotinonitrile to give *n*-propyl 4-*n*-propyl-3-pyridyl ketone.

In the present work it was found that 3-duroylpyridine (Ia) reacted with phenylmagnesium bromide to yield a light yellow solid, the infrared spectrum of which indicates the presence of an >NH group, consistent with the structure of a dihydro phenyl substituted 3-duroylpyridine. The yield was 88% of theoretical. Dehydrogenation of the



Ia, R = Dur
b, R = Mes

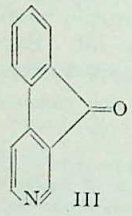


IIa, R = Dur
b, R = Mes

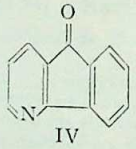
dihydro compound with chloranil gave 3-duroyl-4-phenylpyridine (IIa) in nearly quantitative yield.

Similar results were obtained with 3-mesitoylpyridine (Ib). The dihydro compound, isolated in a yield of 63%, underwent dehydrogenation smoothly with chloranil to give 3-mesitoyl-4-phenylpyridine (IIb).

The possibility existed that the products of the above reactions were pyridines phenylated in the 2- rather than the 4-position. That the materials were substituted in the 4-position was proved by the isolation of 2-azafluorenone (III) from the reaction of either phenylated ketone (IIa or IIb) with polyphosphoric acid.[2] 4-Azafluorenone (IV) would have been produced if the ketones had been phenylated in the 2-position.



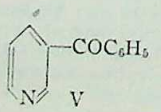
III



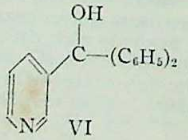
IV

It is assumed that the 2-azafluorenone (III) is obtained by cyclization of 4-phenylnicotinic acid, the product which would be expected from cleavage of the ketones with polyphosphoric acid.

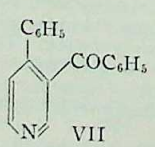
As might have been anticipated from the work of Frank and Weatherbee, conjugate addition was realized also with the unhindered ketone, 3-benzoylpyridine (V). Treatment of this material with phenylmagnesium bromide gave rise to diphenyl-3-pyridylcarbinol (VI), the 1,2-addition product, in 22% yield and to a dihydro 1,4-addition product in a yield of 45%. Dehydrogenation of this conjugate addition product gave 4-phenyl-3-benzoylpyridine (VII).



V

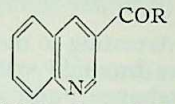


VI

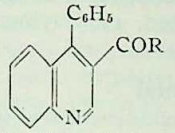


VII

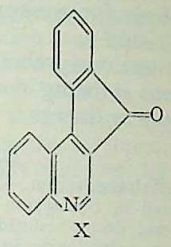
It was thought that conjugate addition to ketones in the quinoline series would be even more facile than to those in the pyridine series. This expectation was borne out by the addition of phenylmagnesium bromide to 3-benzoylquinoline (VIIIa). A dihydro derivative of 3-benzoyl-4-phenylquinoline was isolated in a yield of 90%. Dehydrogenation to 3-benzoyl-4-phenylquinoline (IXa) was accomplished with chloranil.



VIIIa, R = C_6H_5
b, R = Mes



IXa, R = C_6H_5
b, R = Mes



X

The addition of the phenyl reagent to 3-mesitoylquinoline (VIIIb) gave the expected dihydro derivative, which was aromatized to 4-phenyl-3-mesitoylquinoline (IXb) in excellent yield. Cleavage of this hindered ketone with polyphosphoric acid provided 3,4-benzo-2-azafluorenone (X).

The 3-pyridyl ketones were synthesized by the method of Friedel and Crafts. Nicotinyl chloride hydrochloride, prepared by the action of thionyl chloride on nicotinic acid,[3] was used with benzene and mesitylene, respectively, in the synthesis of 3-benzoyl- and 3-mesitoylpyridine. It was found necessary to employ free nicotinyl chloride[4] in tetrachloroethane as a solvent for the preparation of 3-duroylpyridine. 3-Benzoylquinoline, which has not been described previously, was obtained in 65% yield from the corresponding free acid chloride. 3-Mesitoylquinoline was prepared by treatment of the corresponding acid chloride hydrochloride with mesitylene and aluminum chloride in carbon disulfide.

The action of benzylmagnesium chloride on 3-benzoylpyridine proved interesting in that no conjugate addition product was isolated. It has been observed in many cases that the benzyl reagent brings about 1,2- rather than 1,4-addition even with hindered ketones.[5] With 3-mesitoylpyridine, the benzyl reagent produced a yellow solid, which, on the basis of infrared and combustion analyses, was assigned the structure of a dihydro-4-benzyl-3-mesitoylpyridine. Dehydrogenation of this material has not been accomplished. The position of the double bonds in this and other dihydro compounds has not been established definitely. The reaction of the benzyl reagent with 3-benzoylquinoline also proceeded in the conjugate manner.

Experimental[6]

3-Mesitoylpyridine (Ib).—To the nicotinyl chloride hy-

(1) R. L. Frank and C. Weatherbee, THIS JOURNAL, **70**, 3812 (1948).

(2) G. Nowlin, *ibid.*, **72**, 5754 (1950).

(3) F. J. Villani, M. S. King and D. Papa, *J. Org. Chem.*, **17**, 249 (1952).

(4) H. N. Wingfield, Jr., W. R. Harlan and H. R. Hammer, THIS JOURNAL, **75**, 4364 (1953).

(5) W. G. Young and J. D. Roberts, *ibid.*, **66**, 2131 (1944).

(6) All melting points are corrected.

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drochloride, produced by the action of excess thionyl chloride on 85.5 g. (0.7 mole) of nicotinic acid, was added 500 ml. of mesitylene. The mixture was cooled in an ice–salt-bath, and 348 g. (2.6 moles) of aluminum chloride was introduced in small amounts. The deep red solution was heated on a steam-bath for 6 hr. and then decomposed with ice and hydrochloric acid. Addition of an excess of sodium hydroxide to the aqueous layer caused the separation of a brown oil, which was extracted by shaking the mixture successively with five 100-ml. portions of chloroform. The chloroform extracts were combined, washed with water and dried over sodium sulfate. Evaporation of the solvent left a brown oil. Distillation of this material under reduced pressure gave 79 g. (50.5%) of 3-mesitoylpyridine, a light yellow oil, b.p. 96–98° (0.1 mm.).

Anal.[7] Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.13; H, 6.72; N, 6.32.

The infrared spectrum[8] of the oil supports the proposed structure. Absorption bands assignable to a hindered, conjugated carbonyl group (1675 cm.$^{-1}$) and to the mesitylene group (850 cm.$^{-1}$) are present.

The picrate of the ketone crystallized from ethanol in yellow needles, m.p. 167–168°.

Anal. Calcd. for $C_{21}H_{18}N_4O_8$: C, 55.51; H, 3.99; N, 12.33. Found: C, 55.79; H, 4.07; N, 12.36.

Dihydro-3-mesitoyl-4-phenylpyridine.—To the Grignard reagent prepared from 16.84 g. (0.1072 mole) of bromobenzene and 2.61 g. (0.1072 g. atom) of magnesium was added 12.08 g. (0.0536 mole) of 3-mesitoylpyridine. The addition was completed in 10 min. The yellow solid, which formed in the solution while the ketone was being added, changed to a brown gum as the reaction mixture was stirred for 10 min. Saturated ammonium chloride solution was introduced, and the yellow solid which separated was collected on a filter. Evaporation of the ether left additional yellow material, m.p. 174–181°. Recrystallization from ethanol gave 10.22 g. (63%) of a light yellow powder, m.p. 182–188°. Vacuum sublimation or recrystallization did not decrease the melting range.

An absorption band assignable to an N—H stretching frequency (3260 cm.$^{-1}$) is present in the infrared spectrum. The intensity of the carbonyl band (1668 cm.$^{-1}$) is extremely low. The structure proposed is a dihydro-3-mesitoyl-4-phenylpyridine.

Anal. Calcd. for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 82.90; H, 7.20; N, 4.43.

3-Mesitoyl-4-phenylpyridine (IIb).—Benzene solutions of 3.03 g. (0.01 mole) of dihydro-3-mesitoyl-4-phenylpyridine and 2.46 g. (0.01 mole) of chloranil were mixed in a 500-ml., round-bottomed flask. The mixture was heated at the reflux temperature for 8 hr. and then allowed to cool. Extraction of the solution with five 100-ml. portions of 10% aqueous sodium hydroxide removed 1.83 g. of tetrachlorohydroquinone. A brown oil (2.3 g.), which was left when the benzene was evaporated, was crystallized from an ethanol–water mixture. Vacuum sublimation of this crude material at 95° (0.05 mm.) gave white prisms, m.p. 94–95.2° (77% yield).

Anal. Calcd. for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.91; H, 6.20; N, 4.67.

The return of the carbonyl band (1668 cm.$^{-1}$) to normal intensity in the infrared spectrum is striking.

3-Duroylpyridine (Ia).—Nicotinyl chloride was prepared by the method of Wingfield, Harlan and Hammer[4] from 32.2 g. (0.2 mole) of potassium nicotinate and 25.2 g. (0.2 mole) of oxalyl chloride. Two hundred and fifty grams of tetrachloroethane was added to the acid chloride, and 22.8 g. (0.17 mole) of durene was then introduced. The mixture was cooled in an ice–salt-bath, and 50 g. (0.38 mole) of aluminum chloride was added in small portions. The solution was allowed to come to room temperature and was then heated on a steam-bath for 5 hr. The mixture was decomposed with ice and hydrochloric acid, and the organic layer was subjected to steam distillation to remove the tetrachloroethane. The ketone was extracted from the brown, tarry residue with low-boiling petroleum ether. The brown solution, after repeated treatment with decolorizing carbon and evaporation of the solvent, gave 3-duroylpyridine in the form of colorless plates. After recrystallization from low-boiling petroleum ether, the product weighed 13.93 g. (32% yield), m.p. 80.5–81.5°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.37; H, 7.15; N, 5.90.

The picrate was prepared and purified by recrystallization from ethanol, m.p. 183–185°.

Anal. Calcd. for $C_{22}H_{20}N_4O_8$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.66; H, 4.17; N, 11.92.

Dihydro-3-duroyl-4-phenylpyridine.—Phenylmagnesium bromide, prepared from 3.93 g. (0.025 mole) of bromobenzene and 0.608 g. (0.025 g. atom) of magnesium, was added to 2.99 g. (0.0125 mole) of 3-duroylpyridine. The subsequent procedure was similar to that described for the mesitoyl compound. The dihydro-3-duroyl-4-phenylpyridine, a yellow solid, m.p. 198–207°, was obtained in 88% yield.

Anal. Calcd. for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 82.97; H, 7.19; N, 4.34.

The infrared spectrum is similar to that of dihydro-3-mesitoyl-4-phenylpyridine; the carbonyl group absorption is again very weak.

3-Duroyl-4-phenylpyridine (IIa).—Treatment of 0.4 g. (0.0012 mole) of dihydro-3-duroyl-4-phenylpyridine with 0.295 g. (0.0012 mole) of chloranil provided 0.39 g. (99%) of the aromatized product, 3-duroyl-4-phenylpyridine, m.p. 168–169.5°.

Anal. Calcd. for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 83.51; H, 6.71; N, 4.29.

The picrate, m.p. 214–215°, was recrystallized from ethanol.

Anal. Calcd. for $C_{28}H_{24}N_4O_8$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.58; H, 4.52; N, 10.21.

3-Benzoylpyridine (V).—This ketone was prepared from nicotinic acid in a yield of 87.5% by the method of Villani, King and Papa.[3] The boiling point is 154–156° at 2.5–2.7 mm. **The picrate,** after recrystallization from ethanol, melted at 163–165°; reported 164–166°[3] and 161°.[9]

Dihydro-3-benzoyl-4-phenylpyridine and Diphenyl-3-pyridylcarbinol (VI).—The addition of 4 g. (0.022 mole) of 3-benzoylpyridine to the Grignard reagent prepared from 7.22 g. (0.046 mole) of bromobenzene and 1.09 g. (0.045 g. atom) of magnesium was followed in 20 min. by hydrolysis with saturated ammonium chloride solution. When the ethereal layer was concentrated, a yellow solid and a tan oil were obtained. Recrystallization of the solid from a large volume of ether gave 2.57 g. (45% yield) of dihydro-3-benzoyl-4-phenylpyridine, m.p. 142–148°. Vacuum sublimation of the yellow plates at 140° (0.1 mm.) provided a solid melting at 147–150°.

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.94; H, 6.07; N, 5.30.

The oil obtained from the reaction crystallized from ether. Recrystallization from ethyl acetate gave 1.27 g. (22% yield) of lustrous, white plates of diphenyl-3-pyridylcarbinol, m.p. 115–116°, reported[10] 115–116°.

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.74; H, 5.89; N, 5.37.

The melting point of the picrate of this carbinol, m.p. 195–197°, agrees with that reported.[10]

3-Benzoyl-4-phenylpyridine (VII).—Dehydrogenation of the corresponding dihydro compound with chloranil gave 3-benzoyl-4-phenylpyridine in a yield of 83%, m.p. 89.5–90°.

Anal. Calcd. for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.36; H, 5.08; N, 5.29.

The picrate, m.p. 203–205°, crystallized from ethanol.

Anal. Calcd. for $C_{24}H_{16}N_4O_8$: C, 59.02; H, 3.30; N, 11.47. Found: C, 59.11; H, 3.46; N, 11.23.

2-Azafluorenone (III).—A mixture of an excess of polyphosphoric acid and 0.5 g. of 3-mesitoyl-4-phenylpyridine was heated with stirring for 1.5 hr. at 185–200° (25 mm.) in a flask equipped for downward distillation. When the dark brown oil, produced in the reaction flask, was poured

(7) Microanalyses were performed by Mr. Joseph Nemeth, Mrs. R. Maria Benassi, Mrs. Lucy Chang, Mrs. Ruby Ju, Mr. Rollo Nesset and Miss Claire Higham.

(8) The infrared data were obtained and interpreted by Mr. James Brader, Mrs. Louise Griffing and Mr. Sy Portnoy.

(9) F. B. LaForge, THIS JOURNAL, **50**, 2477 (1928).

(10) L. C. Anderson and N. V. Seeger, *ibid.*, **71**, 343 (1949).

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on ice, an orange solution formed. The solution was filtered and neutralized with 5% sodium hydroxide. An orange solid, 2-azafluorenone, precipitated (48% yield). Vacuum sublimation of the solid gave yellow plates, m.p. 155.5–156.5°. The melting points reported for 2-azafluorenone are 156–158°[11] and 130°.[12]

The infrared spectrum of a Nujol mull of the material contains bands assignable to a carbonyl group of the fluorenone type (1707 cm.$^{-1}$) and to an *o*-disubstituted benzene ring (735 cm.$^{-1}$). The carbonyl band is at 1720 cm.$^{-1}$ in 5% chloroform solution.

Anal. Calcd. for $C_{12}H_7NO$: C, 79.55; H, 3.89; N, 7.73. Found: C, 79.46; H, 4.01; N, 7.88.

Treatment of 3-duroyl-4-phenylpyridine with polyphosphoric acid gave the same product.

3-Bromoquinoline.—Quinoline hydrobromide perbromide was pyrolyzed to 3-bromoquinoline hydrobromide in 36.5% yield according to the method of Claus and Collischon.[13] The amine was liberated quantitatively by treatment with base.

3-Quinolinecarboxylic Acid.—Treatment of 3-bromoquinoline with cuprous cyanide provided 3-cyanoquinoline, m.p. 106–107°, in a 60% yield.[14] Hydrolysis of the nitrile gave the acid, m.p. 272–273°, in 89% yield.[15]

3-Benzoylquinoline (VIIIa).—The potassium salt of 3-quinolinecarboxylic acid was treated with oxalyl chloride, and the acid chloride produced was condensed with benzene and aluminum chloride according to the method for the preparation of 3-duroylpyridine. 3-Benzoylquinoline, m.p. 76–77°, was isolated in 65% yield.

Anal. Calcd. for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.01. Found: C, 82.51; H, 4.70; N, 6.04.

The picrate, m.p. 216–218°, was recrystallized from ethanol.

Anal. Calcd. for $C_{22}H_{14}N_4O_8$: C, 57.15; H, 3.05; N, 12.12. Found: C, 57.01; H, 3.06; N, 12.02.

Dihydro-3-benzoyl-4-phenylquinoline.—The reaction of 1.81 g. (0.0078 mole) of 3-benzoylquinoline with phenylmagnesium bromide, prepared from 2.48 g. (0.0158 mole) of bromobenzene and 0.384 g. (0.0158 g. atom) of magnesium, gave 2.17 g. (90% yield) of dihydro-3-benzoyl-4-phenylquinoline, m.p. 201–204°.

Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50. Found: C, 84.58; H, 5.51; N, 4.44.

3-Benzoyl-4-phenylquinoline (IXa).—Dehydrogenation of 0.31 g. (0.001 mole) of dihydro-3-benzoyl-4-phenylquinoline with 0.25 g. (0.001 mole) of chloranil gave 0.23 g. (75% yield) of 3-benzoyl-4-phenylquinoline, m.p. 115–116°.

Anal. Calcd. for $C_{22}H_{15}NO$: C, 85.41; H, 4.89; N, 4.53. Found: C, 85.12; H, 5.19; N, 4.33.

3-Mesitoylquinoline (VIIIb).—3-Quinolinecarboxylic acid chloride hydrochloride was prepared from 3 g. (0.0173 mole) of 3-quinolinecarboxylic acid and excess thionyl chloride. After the excess thionyl chloride was removed by vacuum distillation, 150 ml. of carbon disulfide, 2.1 g. (0.0174 mole) of mesitylene and 4.62 g. (0.0346 mole) of aluminum chloride was introduced and the mixture was stirred at room temperature for 19 hr. Decomposition of the mixture was accomplished with ice and hydrochloric acid. The aqueous layer was made basic with sodium hydroxide and extracted with ether. Removal of the ether by distillation left 1.76 g. (37% yield) of a yellow-white solid, m.p. 87–91°. Vacuum sublimation gave white crystals of 3-mesitoylquinoline, m.p. 90.5–92°.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 83.06; H, 6.29; N, 5.07.

Dihydro-4-phenyl-3-mesitoylquinoline.—Treatment of 1 g. (0.0036 mole) of 3-mesitoylquinoline with the Grignard reagent prepared from 0.175 g. (0.0072 g. atom) of magnesium and 1.13 g. (0.0072 mole) of bromobenzene gave 1.07 g. (84.5% yield) of a dihydro-4-phenyl-3-mesitoylquinoline. A sublimed sample exhibited a melting range of 268–274°.

Anal. Calcd. for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96. Found: C, 84.78; H, 6.48; N, 3.95.

4-Phenyl-3-mesitoylquinoline (IXb).—Dehydrogenation of 0.75 g. (0.002 mole) of dihydro-4-phenyl-3-mesitoylquinoline was accomplished with 0.49 g. (0.002 mole) of chloranil to give 0.65 g. (92.5% yield) of 4-phenyl-3-mesitoylquinoline, m.p. 98.5–100°.

Anal. Calcd. for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.55; H, 5.97; N, 3.98.

3,4-Benzo-1-azafluorenone (X).—The procedure described for the preparation of 2-azafluorenone was followed. The ketone was obtained in 55.7% yield from 4-phenyl-3-mesitoylquinoline. Recrystallization from ethanol gave yellow needles, m.p. 223–224°, reported[16] 216–217°.

Anal. Calcd. for $C_{16}H_9NO$: C, 83.10; H, 3.92; N, 6.06. Found: C, 83.25; H, 3.74; N, 5.93.

The 2,4-dinitrophenylhydrazone of 3,4-benzo-2-azafluorenone, crystallized from ethanol, melted at 293° dec., reported[16] 290° dec.

Dihydro-4-benzyl-3-mesitoylpyridine.—A yellow solid, dihydro-4-benzyl-3-mesitoylpyridine, m.p. 169–172°, was obtained in 32% yield when 3-mesitoylpyridine was treated with benzylmagnesium chloride. The conditions employed were the same as those described in the other Grignard reactions. The infrared spectrum of the dihydro compound is similar to that of the corresponding phenyl compound.

Anal. Calcd. for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 82.71; H, 7.29; N, 4.67.

Benzylphenyl-3-pyridylcarbinol.—The introduction of 1.83 g. (0.01 mole) of 3-benzoylpyridine to a solution of benzylmagnesium chloride, prepared from 0.535 g. (0.022 g. atom) of magnesium and 2.77 g. (0.022 mole) of benzyl chloride, followed by hydrolysis with hydrochloric acid provided 1.5 g. of a colorless solid, m.p. 240–241° dec. The infrared spectrum contains a band at 2100 cm.$^{-1}$ which indicates the presence of a hydrochloride. A silver nitrate test confirmed the presence of halogen.

Anal. Calcd. for $C_{19}H_{18}ClNO$: C, 73.19; H, 5.82; N, 4.49. Found: C, 72.72; H, 5.55; N, 4.34.

Treatment of the hydrochloride with 5% aqueous sodium hydroxide gave almost quantitative liberation of benzylphenyl-3-pyridylcarbinol as white plates, m.p. 154–155°. The over-all yield was 48.5%.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.82; H, 6.32; N, 5.02.

Dihydro-4-benzyl-3-benzoylquinoline.—The action of the benzyl Grignard reagent, prepared from 1.34 g. (0.0106 mole) of benzyl chloride and 0.26 g. (0.0106 g. atom) of magnesium, on 1.23 g. (0.0053 mole) of 3-benzoylquinoline gave a brown oil from which 0.22 g. of a yellow solid, m.p. 195–200°, was obtained. The structure dihydro-4-benzyl-3-benzoylquinoline was assigned on the basis of the similarity of the infrared spectrum to that of dihydro-4-benzyl-3-mesitoylpyridine.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Metalation of 4-*t*-Butyldiphenyl Sulfone with *n*-Butyllithium[1]

BY DAVID A. SHIRLEY AND ERWIN A. LEHTO

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The metalation of 4-*t*-butyldiphenyl sulfone by *n*-butyllithium results in introduction of the lithium atom in the positions *ortho* to the sulfone group, 69% of the metalation occurring in the unsubstituted ring and 31% in the ring containing the *t*-butyl group. This orientation is due to the deactivating influence toward metalation exerted by the *t*-butyl group through its inductive effect.

A large amount of experimental data has accumulated on the position of metalation of aromatic and heterocyclic nuclei by organoalkali compounds. These results have been rather well correlated by a mechanistic picture of the reaction involving nucleophilic[2] or perhaps better "protophilic"[3] attack by the alkyl carbanion assisted by the metal cation. This picture further states that the principal factor controlling orientation and reactivity in the molecule being metalated is the inductive effect of substituents already present in the ring in increasing or decreasing the polarity of the carbon-to-hydrogen bonds at the various positions. Thus, such otherwise unrelated materials as trifluoromethylbenzene,[2] anisole,[4] diphenyl sulfone[5] and resorcinol dimethyl ether[6] all metalate in the position *ortho* to the substituent(s) present due to the inductive electron-withdrawing tendency of the substituents allowing maximum polarization at the adjacent C–H bond.

An important test of these ideas has been offered in the metalation of compounds containing electron-releasing alkyl substituents. Conflicting reports have appeared in the literature on the results of metalation of isopropylbenzene. Morton and co-workers[7,8] reported *ortho* and *para* metalation while Bryce-Smith[3] indicated *meta* and *para* attack. These workers[3,8] agree that *t*-butylbenzene metalates predominantly in the *p*-position and Bryce-Smith has shown by intermolecular competitive metalation that benzene is metalated in preference to *t*-butylbenzene.

It is the purpose of this paper to present some new evidence that the *t*-butyl group deactivates the ring to which it is attached. In order to do this we have adopted the technique used by Truce[5,9] involving an intramolecular competition reaction on a monosubstituted diphenyl sulfone, namely, 4-*t*-butyldiphenyl sulfone. The sulfone group activates strongly the adjacent rings toward metalation, and the ratio of metalation in the two rings reflects the influence of a substituent present in the *p*-position of one ring. Thus Truce[9] was able to demonstrate that the methyl group of phenyl *p*-tolyl sulfone caused a larger amount of metalation to occur in the unsubstituted ring. If the metalation reaction is under the control of the inductive effect of groups already present in the ring, then the *t*-butyl group should show a stronger deactivation of the ring to which it is attached than that shown by the methyl group.

The metalation of 4-*t*-butyldiphenyl sulfone (I) (0.024 mole) was carried out with 0.010 mole of *n*-butyllithium at 0° for 15 minutes. The mixture was carbonated and the resulting mixed carboxylic acids isolated without disturbing the isomer ratio by crystallization. Neutralization equivalents of the mixed metalation acids indicated no dicarboxylic acid to be present. It was necessary to carry out the metalation so as to avoid demetalation since: (1) separation of the dicarboxylic acid might involve some loss of monocarboxylic acid and (2) further metalation of the monometalated product would probably occur at different rates in the two isomers thus disturbing the isomer ratio. Construction of a melting point–composition diagram using synthetic samples of 4-*t*-butyl-2′-carboxydiphenyl sulfone (II) and 4-*t*-butyl-2-carboxydiphenyl sulfone (III) indicated the mixed monocarboxylic acids from metalation to consist of 69% II and 31% III. Thus metalation of I occurs somewhat more than twice as fast in the unsubstituted benzene ring and this substantiates the idea that the *t*-butyl group deactivates the ring to which it is attached. This deactivation is greater than that exhibited by a methyl group, since Truce and Norman[9] have shown that the metalation of 4-methyldiphenyl sulfone occurs 59% in the unsubstituted ring and 41% in the methyl substituted ring. It should be pointed out that these latter experiments were carried out so that at least 9 mole per cent. of dicarboxylic acid was formed and separated. The mixed monocarboxylic acids were subjected to crystallization before analysis, and no neutralization equivalent or other data were presented to show the ab-

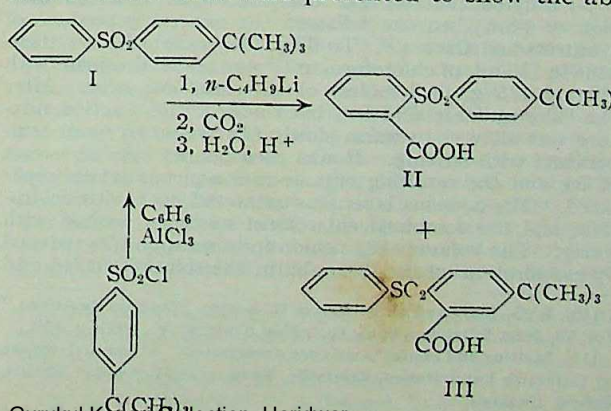

Fig. 1.

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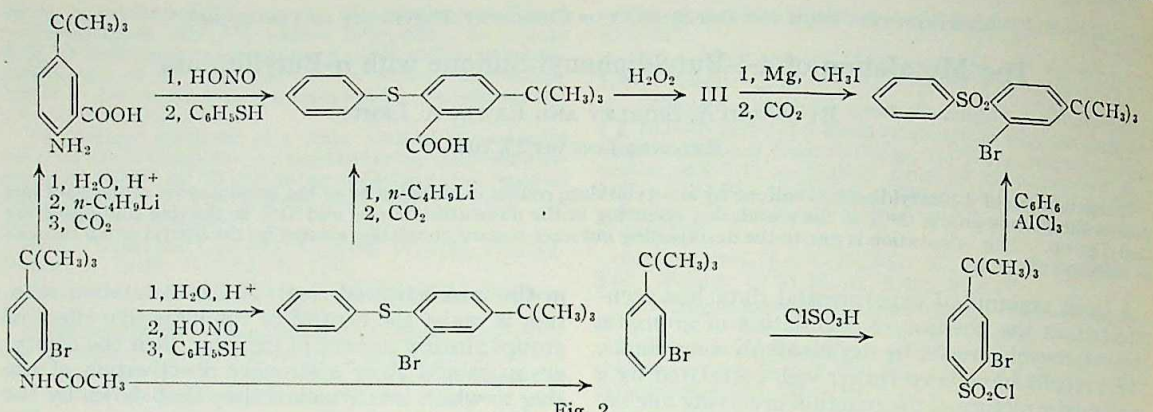

Fig. 2.

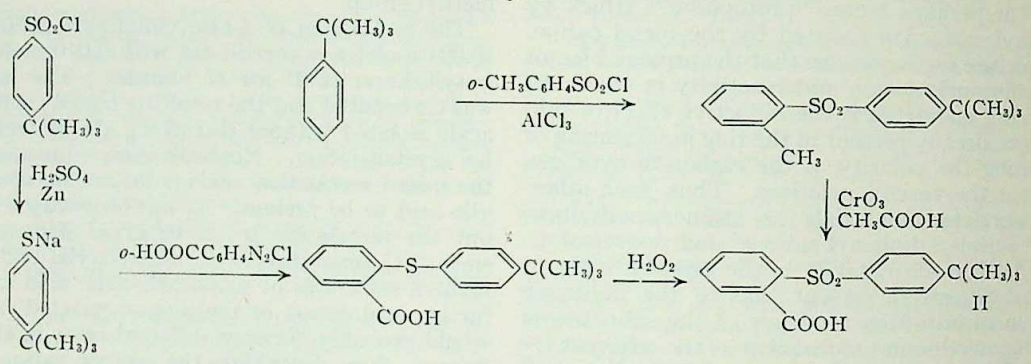

Fig. 3.

sence of some dicarboxylic acid in this fraction. Consequently, the results of our experiments and those of Truce and Norman[9] may not be strictly comparable.

The acid III was synthesized by three independent routes (Fig. 2) of which only the method starting from 2-bromo-4-*t*-butylaniline and proceeding through the halogen–metal interconversion reaction[10] of 2-bromo-4-*t*-butyldiphenyl sulfide and *n*-butyllithium gave the product in good yield. The isomeric acid II was prepared by two independent routes as indicated in Fig. 3. The route involving coupling of sodium *p*-*t*-butylthiophenolate with diazotized anthranilic acid was the better one.

The authors wish to express their appreciation to the Research Corporation of New York for financial support of this investigation.

Experimental[11]

p-t-Butylbenzenesulfonyl Chloride.—The chlorosulfonation of *t*-butylbenzene followed the general procedure of Huntress and Carten.[12] To 67 g. (0.5 mole) of *t*-butylbenzene in 150 ml. of chloroform at 0° was added dropwise with stirring 175 g. (1.5 moles) of chlorosulfonic acid. After the chlorosulfonic acid had been added, the reaction mixture was allowed to warm slowly (12 hours) to room temperature with stirring. It was then poured over an excess of ice and the resulting organic and aqueous layers separated. The aqueous layer was extracted once with chloroform and the combined chloroform solutions washed with water. The volume of the chloroform solution was reduced by evaporation on the steam-bath, the solution cooled and crystallization allowed to occur. The crystallized solid weighed 93.5 g. (81%) and melted at 78–80° after drying *in vacuo* over concentrated sulfuric acid. Another preparation carried out in a similar fashion resulted in a 77% yield of the sulfonyl chloride.

A small amount of the sulfonyl chloride was converted to the sulfonamide which melted at 135–136° after crystallization from aqueous ethanol. The reported[13] m.p. is 136–137°.

4-t-Butyldiphenyl Sulfone.—A solution of 58.1 g. (0.25 mole) of *p*-*t*-butylbenzenesulfonyl chloride in 300 ml. of benzene was placed in a 1-l. round-bottomed flask fitted with mechanical stirrer and reflux condenser. To this solution was added slowly with stirring 75 g. of anhydrous aluminum chloride. The reaction mixture was stirred at room temperature for one hour and then heated to reflux for two hours on the steam-bath. It was poured over an excess of ice and the unreacted benzene removed by steam distillation. The residue from the distillation, after two recrystallizations from methanol, weighed 49.2 g. (75%) and melted at 129–130°. Another run carried out in a similar manner resulted in a 68% yield.

Anal. Calcd. for $C_{16}H_{18}O_2S$: C, 70.07; H, 6.57. Found: C, 70.03, 69.84; H, 6.46, 6.76.

The method of preparation given above was found superior in yield of product to the Friedel–Crafts reaction of benzenesulfonyl chloride and *t*-butylbenzene.

Metalation of 4-t-Butyldiphenyl Sulfone.—To a well-stirred suspension of 6.7 g. (0.024 mole) of 4-*t*-butyldiphenyl sulfone in 250 ml. of dry ether at ice-bath temperature was added slowly 0.010 mole of an ethereal solution of *n*-butyllithium.[14] A nitrogen atmosphere was used. After the *n*-butyllithium had been added, the reaction mixture was stirred at ice-bath temperature for 15 minutes and then carbonated by the addition of crushed solid carbon dioxide directly into the reaction flask. After removal of the ether and carbon dioxide, the residue was treated with water and filtered. The insoluble material weighed 5.7 g. and was unreacted sulfone melting at 128–130°. The aqueous filtrate

(10) R. G. Jones and H. Gilman in R. Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 339.

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was extracted with ether and acidified with dilute hydrochloric acid. The resulting aqueous mixture was extracted with ether and the ether extract washed twice with water. The ether layer was extracted with dilute aqueous sodium carbonate and the sodium carbonate extract acidified with dilute hydrochloric acid. The precipitated colorless semi-solid was extracted with ether, the ether extract washed three times with cold water and dried over anhydrous sodium sulfate. After removal of the ether, the residue was dried *in vacuo* over anhydrous calcium chloride. After a short time, it partially crystallized. This material still possessed the odor of valeric acid and it was heated on the steam-bath with 200 ml. of water. The residue liquefied and on continued heating, a colorless solid separated. A further treatment with 200 ml. of water in a similar manner, followed by collection of the solid material, yielded 0.7 g. melting at 154–190°. A mixture melting point with a small amount of 2-carboxy-4-*t*-butyldiphenyl sulfone gave a final melting point of 196° and with 2-carboxy-4′-*t*-butyldiphenyl sulfone, 186°.

Anal. Calcd. for $C_{17}H_{18}O_4S$: C, 64.15; H, 5.66; neut. equiv., 318. Found: C, 64.01, 64.29; H, 5.77, 5.74; neut. equiv., 320.

The aqueous filtrates (from treatment of the acidic solid above) were concentrated to approximately 100 ml., filtered (no residue) and cooled. There was obtained by crystallization approximately 80 mg. of crystalline solid melting at 153–177°.

Anal. Calcd. for $C_{17}H_{18}O_4S$: C, 64.15; H, 5.66. Found: C, 64.33; H, 5.64.

Further concentration and cooling of the aqueous mother liquor yielded no solid material.

Treatment of the crude mixed acids with cold water was found not to effect complete removal of valeric acid.

Several other metalation conditions were tried in which a larger molar proportion of *n*-butyllithium to sulfone was used at longer reaction times. In all cases appreciable dimetalation resulted as indicated by low neutralization equivalents on mixed metalation acids free of valeric acid.

A melting point–composition diagram (Fig. 4) was constructed from samples of 2-carboxy-4-*t*-butyldiphenyl sulfone and 2-carboxy-4′-*t*-butyldiphenyl sulfone from the data shown in Table I.[15] The 0.7 g. of mixed acid, m.p. 154–190°, corresponds to a composition of 68% 2-carboxy-4′-*t*-butyldiphenyl sulfone and 32% of the 2,4-isomer. The 80 mg. isolated later, m.p. 153–177°, contains 74% of the 2,4-isomer II and 26% of the 2,4-isomer III. Addition of these fractions represents 69% of II and 31% of III. The data of Table I were collected by dissolving the weighed samples of acid in dry ether and evaporating the solvent. The melting range of the resulting mixture was determined on a Kofler hot-stage microscope. A plot of the data shows a smooth curve with a single eutectic at 20 mole per cent. 2-carboxy-4-*t*-butyldiphenyl sulfone (III).

2-*t*-Butylthioxanthone-5-dioxide.—Following the procedure described by Ullmann and Lehner,[16] 1.0 g. of a mixture of monocarboxylic acids from metalation was heated on the steam-bath with 10 ml. of concentrated sulfuric acid until solution was effected. The solution was heated between 190 and 200° for 15 minutes and then poured over an excess of ice. The precipitated solid, after collection and recrystallization from absolute ethanol, weighed 0.6 g. and melted at 109–110°.

Anal. Calcd. for $C_{17}H_{16}O_3S$: C, 68.00; H, 5.33. Found: C, 68.01; H, 5.01.

2-Bromo-4-*t*-butylbenzenesulfonyl Chloride.—*m*-Bromo-*t*-butylbenzene was prepared in general accordance with the procedure of Larner and Peters[17] by the sequence *p*-nitro-*t*-butylbenzene → *p*-*t*-butylaniline → *p*-*t*-butylacetanilide → 2-bromo-4-*t*-butylacetanilide → 2-bromo-4-*t*-butylaniline → *m*-bromo-*t*-butylbenzene.

To a well-stirred solution of 24.8 g. (0.12 mole) of *m*-bromo-*t*-butylbenzene in 200 ml. of chloroform was added slowly at room temperature 50 g. of chlorosulfonic acid. After the addition was complete, the reaction mixture was stirred at room temperature for two hours and then heated to reflux on the steam-bath for two hours. It was poured over an excess of ice and the resulting organic and aqueous layers separated. After removal of the chloroform from the organic layer, an oily residue remained which crystallized on standing. Recrystallization from petroleum ether yielded 25.1 g. (67%) of crystalline solid melting at 67–68°. Conversion of a small amount of the sulfonyl chloride to the corresponding sulfonamide in the usual manner[18] gave a crystalline solid, after recrystallization from dilute aqueous ethanol, melting at 109–110°.

Anal. Calcd. for $C_{12}H_{14}BrNO_2S$: C, 41.10; H, 4.79; N, 4.79. Found: C, 41.04; H, 4.68; N, 4.93.

2-Bromo-4-*t*-butylphenyl Sulfone.—A solution composed of 5.0 g. (0.016 mole) of 2-bromo-4-*t*-butylbenzenesulfonyl chloride and 50 ml. of benzene was warmed to 70° on the steam-bath. After removal from the bath, 10 g. of anhydrous aluminum chloride was added slowly with stirring. The reaction mixture was stirred at room temperature until the evolution of hydrogen chloride had ceased and then heated to reflux on the steam-bath for 30 minutes. The mixture was poured over an excess of ice and the excess benzene was removed by distillation with steam. Recrystallization of the solid residue from the distillation from 95% ethanol yielded 3.6 g. (63%) melting at 110–111°.

Anal. Calcd. for $C_{16}H_{17}BrO_2S$: C, 54.39; H, 4.82. Found: C, 54.43, 54.48; H, 4.74, 4.91.

2-Bromo-4-*t*-butyldiphenyl Sulfide.—The procedure followed for the preparation of this compound was in general that employed by Ziegler[19] for the preparation of 2-carboxydiphenyl sulfide. A solution of 19.0 g. (0.07 mole) of 2-bromo-4-*t*-butylanilinium hydrochloride in 200 ml. of water and 15 ml. of concentrated hydrochloric acid was diazotized in the usual manner at 0° by the slow addition (with stirring) of a solution of 4.8 g. of sodium nitrite in 30 ml. of water. After completion of diazotization, a solution of aqueous sodium acetate was added to neutralize the free acid.[20] The solution was filtered and added slowly to a solution of 8.4 g. (0.08 mole) of thiophenol and 30 g. of sodium hydroxide in 100 ml. of water kept at 70° on the steam-bath. After the addition was complete, the mixture was heated on the steam-bath for two hours, made acidic with concentrated hydrochloric acid, cooled and extracted with ether. The ether extract, after removal of the ether, was dissolved in a solution composed of 150 ml. of 95% ethanol and 30 ml. of concentrated hydrochloric acid. The solution was heated to boiling on the steam-bath and 35 g. of zinc dust was added at such a rate that the mixture was kept at vigorous ebullition. After the zinc had been added, the mixture was heated to reflux for 15 minutes and then filtered while hot. The filtrate was distilled with steam to remove any unreacted thiophenol and the residue from the distillation, after cooling, was extracted with ether. The ethereal extract was washed with dilute aqueous sodium hydroxide and water, and then dried over anhydrous sodium sulfate. After removal of the ether, there remained 5.2 g. of a yellow oil. This compound was characterized by its conversion to 2-carboxy-4-*t*-butyldiphenyl sulfide.

2-Carboxy-4-*t*-butyldiphenyl Sulfide. a. From 2-Bromo-4-*t*-butyldiphenyl Sulfide.—A solution of 5.2 g. (0.016 mole) of crude 2-bromo-4-*t*-butyldiphenyl sulfide in 100 ml. of dry ether was added slowly with stirring to an ethereal solution of 0.05 mole of *n*-butyllithium.[14] A nitrogen atmosphere was used and the reaction flask was immersed in an acetone–solid carbon dioxide bath kept between −50 and −60°. After the solution of *n*-butyllithium had been added, the reaction mixture was stirred at a bath temperature of −50 to −60° for 15 minutes. Carbonation was accomplished by pouring over a slurry of ether and crushed solid carbon dioxide. After the carbon dioxide had evaporated, water was added and the ethereal and aqueous layers were separated. The aqueous layer on acidification with concentrated hydrochloric acid yielded 2.1 g. of a light brown solid melt-

(15) Figure 4 and Table I have been deposited as Document No 5116 with the ADI Auxiliary Publication Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document No. and by remitting in advance $1.25 for photoprints or $1.25 for 35 mm. microfilm, by check or money order payable to the Chief.

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(18) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 186.

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ing at 174–201°. Recrystallization of this material from benzene gave 1.6 g. (35%) of an almost colorless crystalline solid melting at 205–206°.

Anal. Calcd. for $C_{17}H_{18}O_2S$: C, 71.33; H, 6.29. Found: C, 71.24, 71.09; H, 6.46, 6.41.

b. From 2-Bromo-4-*t*-butylaniline.—Following the procedure described by Gilman and Stuckwisch,[21] an ethereal solution of 0.32 mole of *n*-butyllithium was added slowly with stirring to a solution of 19.2 g. (0.08 mole) of 2-bromo-4-*t*-butylaniline in 200 ml. of dry ether at room temperature. An atmosphere of nitrogen was used. After the addition of *n*-butyllithium was complete, the reaction mixture was carbonated by pouring over a slurry of ether and crushed solid carbon dioxide. After the carbon dioxide had evaporated, excess water was added and the aqueous layer was extracted twice with ether and acidified with 1:1 hydrochloric acid until just neutral. This resulted in the separation of a light yellow solid which was collected by filtration and diazotized in the usual manner at 0°. After completion of diazotization, an aqueous solution of sodium acetate was added to neutralize the free acid[20] and the resulting solution was added to a solution of 4.8 g. of thiophenol and 25 g. of sodium hydroxide in 100 ml. of water kept at 70° on the steam-bath. The mixture was heated on the steam-bath for one hour and then filtered. The filtrate was acidified with concentrated hydrochloric acid and the precipitate collected by filtration. This material, after one crystallization from benzene, weighed 0.7 g. and melted at 194–201°. A recrystallization from methanol yielded 0.3 g. melting at 205–206°. A mixture melting point with the product obtained from 2-bromo-4-*t*-butyldiphenyl sulfide, melting point 205–206°, was 205–206°.

2-Carboxy-4-*t*-butyldiphenyl Sulfone (III). a. From 2-Bromo-4-*t*-butyldiphenyl Sulfone.—To 0.5 g. of magnesium turnings in 25 ml. of dry ether was added slowly with stirring 1.5 g. of 2-bromo-4-*t*-butyldiphenyl sulfone. There was no apparent reaction even on heating the mixture to reflux. A small amount of methyl iodide was added and the mixture heated once more to reflux. Presently reaction commenced and continued without the application of heat. When there was no further visible indication of reaction, crushed solid carbon dioxide was added to the mixture. After the removal of the ether and carbon dioxide, the residue was acidified with 20% sulfuric acid. When the magnesium had dissolved completely, the mixture was made alkaline by the addition of aqueous sodium hydroxide and the solution filtered. Acidification of the filtrate with 1:1 hydrochloric acid resulted in the precipitation of a tan-colored solid. It was collected by filtration and reprecipitated from an aqueous solution of sodium carbonate by means of dilute hydrochloric acid. This gave a small amount of colorless crystalline solid melting at 241–242°.

Anal. Calcd. for $C_{17}H_{18}O_4S$: C, 64.15; H, 5.66. Found: C, 64.00; H, 5.45.

b. From Oxidation of 2-Carboxy-4-*t*-butyldiphenyl Sulfide.—One and one-half grams (0.005 mole) of 2-carboxy-4-*t*-butyldiphenyl sulfide dissolved in 50 ml. of glacial acetic acid was heated to 80° on the steam-bath and then 15 ml. of 30% hydrogen peroxide was added slowly. The solution was heated on the steam-bath for one hour and, after the addition of another 10 ml. of 30% hydrogen peroxide, then to reflux for one hour. The reaction mixture was poured into an excess of water and the precipitated solid, weighing 0.8 g. (45%) and melting at 241–242°, was collected by filtration. A mixture melting point with the product obtained from 2-bromo-4-*t*-butyldiphenyl sulfone, melting at 241–242°, was 241–242°. The yield obtained from another preparation carried out in a similar manner was 55%.

2-Methyl-4′-*t*-butyldiphenyl Sulfone.—*o*-Toluenesulfonyl chloride (b.p. 143–145° at 25 mm.) was prepared in 75% yield in accordance with the procedure of Lee and Dougherty[22] for conversion of aromatic thiols to the corresponding sulfonyl chlorides. A solution of 38.0 g. (0.20 mole) of *o*-toluenesulfonyl chloride and 35 g. of *t*-butylbenzene was warmed to 70° on the steam-bath. After removal from the steam-bath, 50 g. of anhydrous aluminum chloride was added in small portions with vigorous stirring. Shortly after the addition was complete, the reaction mixture partially solidified and was poured immediately into an excess of cold water. The unreacted *t*-butylbenzene was removed by steam distillation. The water-insoluble residue was washed with petroleum ether and recrystallized twice from methanol, yielding 30.7 g. (52%) melting at 103–104°.

Anal. Calcd. for $C_{17}H_{20}O_2S$: C, 70.83; H, 6.94. Found: C, 70.76; H, 7.03.

Following in general the procedure described by Newell,[23] 14.4 g. (0.05 mole) of 2-methyl-4′-*t*-butyldiphenyl sulfone was dissolved in the minimum amount of glacial acetic acid and heated almost to boiling. Then a solution of 15 g. of chromium trioxide dissolved in the minimum amount of glacial acetic acid was added slowly with stirring. After the addition was complete, the reaction mixture was heated to reflux for 16 hours and then poured into an excess of cold water. The precipitated crystalline solid was collected by filtration, dissolved in aqueous sodium carbonate solution, the solution filtered and the filtrate acidified with dilute hydrochloric acid. The solid precipitate was recrystallized from benzene giving 0.3 g. of crystalline acid melting at 168–169°. This material is further characterized below.

***p*-*t*-Butylthiophenol.**—This compound was prepared according to the procedure given by Senear, Rapport and Koepfli[24] for the preparation of *p*-chlorothiophenol. To a mixture of 23.2 g. (0.10 mole) of *p*-*t*-butylbenzenesulfonyl chloride, 240 g. of ice and 50 ml. of concentrated sulfuric acid was added (30 minutes) with stirring 40 g. of zinc dust. The temperature of the reaction mixture was held at 0° throughout this operation and for two hours after the addition of the zinc. The mixture was then heated carefully to reflux and the resulting crystalline precipitate separated by filtration. The precipitate was suspended in a boiling mixture of 240 ml. of water and 45 ml. of concentrated sulfuric acid and then 40 g. of zinc was added in small portions. After the mixture had been steam distilled, the distillate was extracted with ether and the ether extract dried over anhydrous sodium sulfate. Removal of the ether left 9.8 g. (59%) of a colorless liquid. This compound was characterized by conversion to 2-carboxy-4′-*t*-butyldiphenyl sulfide.

2-Carboxy-4′-*t*-butyldiphenyl Sulfide.—Following the general procedure of Ziegler[19] and using some modifications reported by Hilbert and Johnson,[20] 8.1 g. (0.59 mole) of anthranilic acid was added to a solution of 60 ml. of water and 10 ml. of concentrated hydrochloric acid. The solution was diazotized at 0° by the slow addition of a solution of 5.6 g. of sodium nitrite in 25 ml. of water. After completion of diazotization, an aqueous solution of sodium acetate was added to neutralize the free acid. The solution of the diazonium salt was added to a solution (warmed to 70°) of 9.8 g. (0.059 mole) of *p*-*t*-butylthiophenol and 5.0 g. of sodium hydroxide in 30 ml. of water. After the addition was complete, the reaction mixture was heated on the steam-bath for one hour. The mixture was filtered and the filtrate acidified with concentrated hydrochloric acid. The precipitate was collected by filtration and, after one recrystallization from glacial acetic acid and one from benzene, there was obtained 4.6 g. (27%) of crystalline solid melting at 193–194°. Another run carried out in a similar manner resulted in a yield of 36%.

Anal. Calcd. $C_{17}H_{18}O_2S$: C, 71.33; H, 6.29; neut. equiv., 286. Found: C, 71.37, 71.45; H, 6.19, 6.14; neut. equiv., 288.

2-Carboxy-4′-*t*-butyldiphenyl Sulfone.—To a solution of 3.5 g. of 2-carboxy-4′-*t*-butyldiphenyl sulfide in 50 ml. of glacial acetic acid heated to 80° on the steam-bath was added slowly 15 ml. of 30% hydrogen peroxide. The resulting solution was heated on the steam-bath for 30 minutes and, after the addition of another 15 ml. of 30% hydrogen peroxide, for 30 additional minutes. The solution was heated to reflux for two hours and poured into an excess of cold water. The precipitated solid was collected by filtration and recrystallized from benzene, yielding 2.6 g. (67%) of a crystalline solid melting at 168–169°. A mixture melting point of this solid with the material obtained from chromic acid oxidation of 2-methyl-4′-*t*-butyldiphenyl sulfone, melting point 168–169°, was 168–169°.

(21) H. Gilman and C. G. Stuckwisch, THIS JOURNAL, **71**, 2934 (1949).

(22) S. W. Lee and G. Dougherty, [illegible] (1940).

(23) L. C. Newell, *Am. Chem. J.*, **20**, 302 (1898).

(24) A. E. Senear, M. M. Rapport and J. B. Koepfli, *J. Biol. Chem.*, **167**, 282 (1947).

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July 5, 1957

Anal. Calcd. for $C_{17}H_{18}O_4S$: C, 64.15; H, 5.66; neut. equiv., 318. Found: C, 64.08, 64.35; H, 5.63, 5.54; neut. equiv., 316.

KNOXVILLE, TENNESSEE

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Preparation of Some 10-Substituted Phenoxazines[1]

BY HENRY GILMAN AND LEONARD O. MOORE[2]

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An improved procedure for the synthesis and purification of phenoxazine has been developed which is applicable to the preparation of larger amounts than previously reported. Several 10-alkyl- and 10-arylphenoxazines have been prepared. Iodine has been shown to have little, if any, catalytic activity in the preparation of 10-arylphenoxazines from aryl bromides.

In the study of the chemistry of phenoxazine it was desired to use variously 10-substituted compounds for comparison of substitution reactions and also to use the aryl derivatives for testing as solutes in liquid scintillators.[3]

Phenoxazine was made first by Bernthsen[4] in 1887, and, though known for many years, has not had a systematic study made of its chemistry. Oxazine dyes, which are derivatives of phenoxazine, are widely used at present as biological stains.[5] They have been studied for staining brain tumors,[6] and as tuberculostatic agents.[7] In general the reactions of phenoxazine which have been studied have related directly to these dyes. The majority of reactions studied have been cyclization, oxidation–reduction to oxazonium salts, and some substitution of the oxazonium compounds.

Related heterocycles containing an N–H bond have been used quite extensively in reactions to prepare N-substituted compounds. Carbazole[8] and phenothiazine[9] both have had various alkyl and aryl groups substituted for the hydrogen on the nitrogen. Relatively few N-substituted derivatives of phenoxazine have been prepared. Morris and Snyder[10] prepared several 10-sulfolanyl- and 10-sulfolenylphenoxazines from phenoxazine and various sulfolene compounds in a basic solution. All other 10-substituted phenoxazines have been prepared by cyclization. Some 10-benzyl derivatives[11] were prepared for testing as tuberculostatic agents; some 10-(nitrophenyl)-phenoxazines[12] and one 10-methyl derivative[13] were prepared in studies of a cyclization mechanism.

We have studied the preparation of phenoxazine, varying the methods reported in the literature.[14] The best method for large amounts is to heat an equimolar mixture of *o*-aminophenol and *o*-aminophenol hydrochloride, allowing the water produced to distil. The completion of the reaction can be determined by measuring the amount of water produced. The addition of sea sand to facilitate extraction of the mass decreased the yield as also did heating the reaction for an extended length of time. The purification by chromatography was much less tedious than the methods reported in the literature. This procedure consistently gave 26 to 30% of a relatively pure product in runs of 0.5 to 2.5 moles.

In light of the patent by Waterman and Vivian[15] as well as their articles[16] on the preparation of phenothiazines and carbazoles from aromatic nitro compounds, attempts were made to produce phenoxazine from *o*-nitrophenyl phenyl ether. Heating this ether with powdered iron or ferrous oxalate yielded no phenoxazine.

The alkyl phenoxazines were prepared in liquid ammonia using 10-phenoxazylsodium, prepared from sodium amide and phenoxazine, with an alkyl iodide or a benzyl chloride.[17] Phenoxazine, similar to carbazole, is not acidic enough to condense with ethyl iodide in a refluxing acetone solution of potassium hydroxide, as do nitrocarbazoles.[18]

(1) This work was supported in part by the United States Atomic Energy Commission under Contract No. AT(11-1)-59.

(2) Du Pont Teaching Fellow, 1956–1957.

(3) F. Newton Hayes, *Intern. J. Applied Radiation Isotopes*, **1**, 46 (1956). Evaluation of these compounds for scintillator activity is being made by Wright N. Langham, F. N. Hayes and D. G. Ott of the Los Alamos Scientific Laboratory who will report the results later.

(4) A. Bernthsen, *Ber.*, **20**, 942 (1887).

(5) For a discussion of oxazine dyes see H. A. Lubs, ed., "The Chemistry of Synthetic Dyes and Pigments," Reinhold Publ. Corp., New York, N. Y., 1955, p. 259; and K. Venkataraman, "The Chemistry of Synthetic Dyes," Vol. II, Academic Press, Inc., New York, N. Y., 1952, p. 780.

(6) M. L. Crossley, P. F. Dreisbach, C. M. Hofmann and R. P. Parker, THIS JOURNAL, **74**, 573 (1952); M. L. Crossley, R. J. Turner, C. M. Hofmann, P. F. Dreisbach and R. P. Parker, *ibid.*, **74**, 578 (1952); M. L. Crossley, C. M. Hofmann and P. F. Dreisbach, *ibid.*, **74**, 584 (1952).

(7) R. A. Clapp, J. H. Clark, J. P. English, C. E. Fellows, R. E. Grotz and R. G. Shepherd, *ibid.*, **74**, 1989 (1952).

(8) See (a) W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," Interscience Publishers, Inc., New York, N. Y., 1954, p. 70; (b) W. Freudenberg in R. C. Elderfield, "Heterocyclic Compounds," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 291; and (c) N. Campbell and B. M. Barclay, *Chem. Revs.*, **40**, 359 (1947), for reviews on carbazole. Also more recently (d) H. Gilman and J. B. Honeycutt, Jr., *J. Org. Chem.*, **21**, 225 (1957).

(9) S. P. Massie, *Chem. Revs.*, **54**, 797 (1954).

(10) R. C. Morris and A. V. Snyder (to Shell Development Co.), U. S. Patent 2,530,070, Nov. 14, 1950; *C.A.*, **45**, 2988 (1951).

(11) B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1499, 1504 (1953).

(12) K. C. Roberts and C. G. M. de Worms, *ibid.*, 1309 (1935).

(13) K. C. Roberts and H. B. Clark, *ibid.*, 1312 (1935).

(14) S. Granick, L. Michaelis and M. P. Schubert, THIS JOURNAL, **62**, 7802 (1940); see also F. Kehrmann and A. A. Niel, *Ber.*, **47**, 3102, 3107 (1914).

(15) H. C. Waterman and D. L. Vivian, U. S. Patent 2,292,808, Aug. 11, 1942; *C.A.*, **37**, 892 (1943).

(16) H. C. Waterman and D. L. Vivian, *J. Org. Chem.*, **14**, 289 (1949); see also D. L. Vivian, J. L. Hartwell and H. C. Waterman, *ibid.*, **20**, 797 (1955), for other leading references.

(17) See refs. 9 and 10 for methods used for carbazole and phenothiazine.

(18) T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

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In the preparation of 10-ethylphenoxazine it was thought that perhaps 2,2′-dilithiodiphenyl ether[19] might react with ethyl dichloramide in the same way that other organometallic reagents do with haloamines[20] to give 10-ethylphenoxazine, but none of the desired product was obtained even though multiple fractional distillations were made in an attempt to isolate even a small amount.

The 10-aryl derivatives were prepared by heating phenoxazine and an aryl iodide or bromide with anhydrous potassium carbonate and a small amount of copper bronze powder as a catalyst. The aryl bromides required higher temperatures for reaction than did the aryl iodides, and even so did not usually give as good yields. Since iodine had been added in preparing some N-arylcarbazoles from aryl bromides, it was thought that perhaps iodine might act as a catalyst for the aryl bromides. But when 4,4′-dibromobiphenyl was heated with phenoxazine as described above with and without added iodine, it was found that the iodine had no observable effect on the yield. The effect of temperature, however, is very marked, since heating *p*-bromoiodobenzene with phenoxazine to 200° for 24 hr. gave a good yield of 10-(*p*-bromophenyl)-phenoxazine and no 1,4-bis-(10-phenoxazyl)-benzene; heating in the same manner except for a period of 30 min. at 300° gave 7% of the disubstituted compound.

Attempts to use nitrobenzene as a solvent were not successful. When used in the preparation of 10-phenylphenoxazine none of the expected product was found; in the preparation of 4,4′-bis-(10-phenoxazyl)-biphenyl only a 4% yield was obtained; and in the attempted preparation of 10-*p*-biphenylylphenoxazine an amino compound with a high nitrogen content was the only product isolated.

A comparison of the melting points of the derivatives prepared with the corresponding ones of carbazole and phenothiazine show no definite relationship but some trends. The methyl and ethyl derivatives melt much lower than those of the other heterocycles, but the benzyl and phenyl melt higher (see Table I).

TABLE I

MELTING POINTS OF N-SUBSTITUTED DERIVATIVES OF RELATED HETEROCYCLES, °C.

Substituted group	Phenothiazine[a]	Phenoxazine	Carbazole
H–	185	153–154	246–248
CH_3–	101–103	35–37	87[b]
CH_3CH_2–	103–104.5	46–47	70–72[b]
$C_6H_5CH_2$–	90–92	127.5–128	
C_6H_5–	94.5	138–139	91.5[b]
p-$C_6H_5C_6H_4$–		191–194	224–226[c]
Disub. *p*-C_6H_4–		249–250.5	320–322[c]
Disub. 4,4′-$C_6H_4C_6H_4$–		339–342	282.5–284[c]

[a] See ref. 6 for references to these derivatives. [b] See ref. 8a for references to these derivatives. [c] See ref. 8d.

Experimental[21]

Phenoxazine.—In a 2-l. round-bottom flask with a three-hole cork, through which was inserted a nitrogen inlet tube, a thermometer, and a short tube leading to a distilling condenser, were mixed 500 g. (4.59 moles) of *o*-aminophenol and 185 ml. (2.23 mole) of concentrated hydrochloric acid. This mixture was heated in a slow stream of nitrogen and water distilled off, first at a mass temperature of 115° for 4.33 hours; then, as a fine white solid began to sublime, the temperature rose slowly to 265° and was maintained at 265–290° for 4 hours or until the expected 180 ml. of water had distilled over. The mass was extracted with 1.5 l. of refluxing benzene for 48 hours and then with 1 l. more for 48 hours. The combined solution was chromatographed on a 50 × 450 mm. column of alumina with benzene as the eluent. There was collected 3 l. of solution which was distilled to 150 ml. and chilled. Filtration yielded 103 g. of light tan solid, m.p. 149–153°. From a fourth liter eluted there was obtained 7.1 g., m.p. 140–146°. The total represents a 26% yield. In several other runs, yields of 26 to 30% were obtained consistently. Sublimed white platelets had a m.p. 158–159°.

This compound formed a very dark green picrate, m.p. 141.5–142.0°.

Reaction of *o*-Nitrophenyl Phenyl Ether with Ferrous Oxalate.—In a 2-l. flask with air condenser 21.5 g. (0.1 mole) of *o*-nitrophenyl phenyl ether, 120 g. (0.40 mole) of ferrous oxalate dihydrate[22] and 250 g. of lead shot were heated to 370–400° for two hours.[23] Extraction by benzene and chromatography of the resulting solution on an alumina column with benzene as the eluent produced a red-brown oil, which was shown to be mainly *o*-nitrophenyl phenyl ether by the infrared spectrum.

Chromatography of a known mixture of phenoxazine and *o*-nitrophenyl phenyl ether with benzene showed that the *o*-nitrophenyl phenyl ether was the first eluted, but that the phenoxazine was washed off the column immediately after with only a relatively small amount of eluent.

Reaction of *o*-Nitrophenyl Phenyl Ether with Iron Powder.—In a thick wall flask with air condenser and solids trap at the top, were placed 200 g. of 20 mesh iron filings, 250 g. of hydrogen-reduced iron powder and 100 g. (0.47 mole) of *o*-nitrophenyl phenyl ether. These were heated slowly to 360° at which temperature fumes came off, first white then brown, with refluxing in the air condenser. Extraction with benzene and chromatography on an alumina column with benzene as eluent gave only red tars which could not be made to crystallize. The infrared spectrum indicated the presence of some N–H but had no other spectral bands indicative of phenoxazine. The major substance was the starting ether.

10-Ethylphenoxazine.—To 0.33 mole of sodium amide[24] in a 1-l. flask was added 54.96 g. (0.3 mole) of phenoxazine in small portions and this mixture stirred for 1 hour. Ethyl iodide (88.3 g., 0.57 mole) was added dropwise and the mixture allowed to stir while the ammonia evaporated. The residue was extracted with benzene, filtered and chromatographed on an alumina column. This gave a violet solution, from which the benzene was distilled and the residue distilled under reduced pressure, b.p. 138–143° (0.6 mm.). This gave 56.7 g. (89.4%) of a yellow liquid which solidified on chilling to give a yellow solid, m.p. 46–47°. If the liquid is not cooled below 20° nor seeded, then physical constants can be measured on the supercooled liquid, $n^{25}D$ 1.6445, d^{25}_{25} 1.1584; *MR* calcd. 63.6, found 66.0.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.65; N, 6.63. Found: C, 79.77, 79.79; H, 6.85, 6.96; N, 7.22, 7.15.

This compound formed a very dark green picrate, m.p. 93.5–94.0°.

The reaction of phenoxazine (9.16 g., 0.05 mole), ethyl iodide (14.7 g., 0.095 mole) and potassium hydroxide (5.7 g., 0.1 mole) in 250 ml. of refluxing acetone for 6 hours gave only phenoxazine (mixed melting point).

Reaction of 2,2′-Dilithiodiphenyl Ether with Ethyl Dichloramide.—To 0.17 mole of 2,2′-dilithiodiphenyl ether[19] in 1500 ml. of anhydrous ether was added with vigorous

(19) K. Oita and H. Gilman, THIS JOURNAL, **79**, 339 (1957).

(20) G. H. Coleman, *ibid.*, **55**, 3001 (1933); see also M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N.Y., 1954, pp. 1243–1248, for leading references.

(21) All melting points are uncorrected.

(22) W. Franke, *Ann.*, **491**, 30 (1931).

(23) Ferrous oxalate dehydrates at *ca.* 160° and decomposes above 300°; see P. L. Günther and H. Rehaag, *Z. anorg. allgem. Chem.*, **243**, 60 (1939).

(24) C. R. Hauser, F. W. Swamer and J. T. Adams, in R. Adams, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N.Y., 1954, p. 122.

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stirring an ether solution of ethyl dichloramide.[25] After stirring for 72 hours, Color Test I[26] was negative and the mixture was hydrolyzed, the layers separated, and the ether layer washed with water and 10% sulfuric acid until a sample on neutralization failed to become turbid. The ether was distilled and the residue distilled three times under reduced pressure using the fraction boiling nearest to that expected for 10-ethylphenoxazine. Physical constants on the liquid obtained from the last distillation did not indicate any 10-ethylphenoxazine. Infrared spectra of the various fractions indicated the product of the reaction to be mainly diphenyl ether, with some ethylaminodiphenyl ether, since there were some bands for the N–H bond and for the ethyl group, though these were weak. Neutralization of the sulfuric acid solution gave only a small amount of brown tarry material.

10-Methylphenoxazine.—Using the method described for 10-ethylphenoxazine for a 0.05-mole run, there was obtained 7.0 g. (71%) of a yellow liquid, b.p. 151–154° (3.0 mm.), which solidified on chilling to give a yellow solid, m.p. 35–37°.

Anal. Calcd. for $C_{13}H_{11}NO$: N, 13.14. Found: N, 13.20, 13.21.

This compound formed a dark green picrate, m.p. 101–102°.

10-Benzylphenoxazine.—Using the same method described for 10-ethylphenoxazine for a 0.05-mole run, there was obtained on distillation of the eluted solution 5.5 g. (40%) of white crystals, m.p. 126.5–128.0°. Recrystallization from 95% ethanol gave an analytical sample, m.p. 127.5–128.0°.

Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.54; N, 5.13. Found: C, 83.59, 83.30; H, 5.60, 5.72; N, 4.97, 5.02.

10-(*p*-Bromobenzyl)-phenoxazine.—Using the method described for 10-ethylphenoxazine for a 0.1-mole run, there was obtained on distillation of the eluted solution 8.0 g. (45.5%) of brown solid, melting range 73–111°. Recrystallization from petroleum ether (b.p. 60–70°) gave 3.49 g. of white needles, m.p. 113–114°.

Anal. Calcd. for $C_{19}H_{14}BrNO$: N, 3.98. Found: N, 4.25, 4.24.

10-Phenylphenoxazine.—In a 500-ml. flask were mixed 45.8 g. (0.25 mole) of phenoxazine, 68.3 g. (0.33 mole) of iodobenzene, 35 g. of potassium carbonate and 2.0 g. of copper bronze powder and this mixture heated to 200° for 48 hr. The mixture was extracted with 200 ml. of benzene, filtered and chilled to give 59.6 g. of white solid, m.p. 134.5–137.5°. Concentration of the filtrate gave 9.49 g. more of pale tan solid, m.p. 130–135°. This represents a crude yield of 81.5%. Recrystallization from benzene gave an analytical sample, m.p. 138–139°.

Anal. Calcd. for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.45; H, 5.13; N, 5.39.

10-(*o*-Bromophenyl)-phenoxazine.—*o*-Bromoiodobenzene was used in the procedure described for 10-phenylphenoxazine for a 0.05-mole run except that the reaction time was cut to 24 hr. The product was purified by chromatography on a column of alumina using benzene as the eluent. Concentration of the eluted solution gave 6.60 g. (39%) of light brown solid, melting range 159–187°, which was recrystallized from ethyl acetate to give 2.35 g. of white solid, m.p. 213–214°. Multiple recrystallizations gave an analytical sample, m.p. 214.5–215.5°.

Anal. Calcd. for $C_{18}H_{12}BrNO$: N, 4.14. Found: N, 4.21, 4.24.

10-(*p*-Bromophenyl)-phenoxazine.—Using the same method as described for the *o*-isomer, there was obtained 5.18 g. (61%) of a brown solid, m.p. 190–200°, which was recrystallized from benzene to give 2.63 g. of pale pink prisms, m.p. 200–202°.

Anal. Calcd. for $C_{18}H_{12}BrNO$: C, 63.92; H, 3.66; N, 4.14. Found: C, 63.96, 64.02; H, 3.53, 3.37; N, 3.83, 3.86.

The use of a higher temperature (same as above except for 30 min. at 300°) and addition of iodine gave 7% of *p*-bis-(10-phenoxazyl)-benzene.

10-(*p*-Biphenylyl)-phenoxazine. Method A.—This compound was prepared in the same manner as 10-phenylphenoxazine in a 0.03-mole run using 4-iodobiphenyl. The mass was extracted with benzene, concentrated to 75 ml. and chilled to give a tarry solid, m.p. 180–186°, which was recrystallized from toluene to give 4.38 g. (43.5%) of yellow needles, m.p. 191.5–193.0°. Further recrystallization raised the melting point to 191.5–194.0°.

Anal. Calcd. for $C_{24}H_{17}NO$: N, 4.18. Found: N, 4.23, 4.24.

Method B. (Attempted).—The use of 4-bromobiphenyl in the reaction as described for 9-(*p*-biphenylyl)-carbazole[5d] gave 0.38 g. (5%) of a white solid, m.p. 217–236°, which was recrystallized from benzene to give 0.16 g., m.p. 255.5–256.2°, of a product containing 8.14% nitrogen. This corresponds very nearly to an aniline-10-(*p*-biphenylyl)-phenoxazine. The infrared spectrum of this compound has bands for an N–H bond, and bands very similar to those of 10-(*p*-biphenylyl)-phenoxazine.

***p*-Bis-(10-phenoxazyl)-benzene.**—Using the procedure as for 10-(*o*-bromophenyl)-phenoxazine but substituting *p*-diiodobenzene for *p*-bromoiodobenzene, for a 0.02-mole run, there was obtained 10.05 g. (100%) of a tan solid, m.p. 215–240°, which was recrystallized several times from benzene to give only 17% of white needles, m.p. 249.0–250.5°.

Anal. Calcd. for $C_{30}H_{20}N_2O_2$: N, 6.36. Found: N, 6.38, 6.51.

4,4′-Bis-(10-phenoxazyl)-biphenyl.—In a 200-ml. flask 5.04 g. (0.0275 mole) of phenoxazine, 3.90 g. (0.0125 mole) of 4,4′-dibromobiphenyl, 7.6 g. of anhydrous potassium carbonate and 0.5 g. of copper bronze powder were heated to 300° for 23 hours. The mass was extracted with hot benzene, then with hot water and the water solution and solid were washed with benzene. The total of 175 ml. of benzene solution was chromatographed on a 35 × 350 mm. column of alumina using benzene as the eluent. There was collected 150 ml. of a forerun then 1000 ml. of yellow solution. Distillation of solvent and chilling gave 2.13 g. (33%) of pale yellow crystals, m.p. 332.0–335.5°.

In a second run, identical with the above except that 0.75 g. of iodine was added as a possible catalyst, there was obtained 2.09 g. (32.4%) of pale yellow crystals, m.p. 332.5–336.0°. The iodine appears to have no catalytic activity in this reaction.

Recrystallization of an analytical sample from benzene gave a solid, m.p. 339–342°.

Anal. Calcd. for $C_{36}H_{24}N_2O_2$: N, 5.42. Found: N, 5.30, 5.29.

Acknowledgment.—We are indebted to R. McCord and E. Miller Layton of the Ames Laboratory of the Atomic Energy Commission for assistance in the infrared spectra determinations.

AMES, IOWA

(25) Prepared by the method of G. H. Coleman, THIS JOURNAL, **55**, 5001 (1933). Attempts to use the method of J. Tscherniak, *Ber.*, **9**, 146 (1876), resulted in a vigorous, nearly explosive reaction.

(26) H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).

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[CONTRIBUTION FROM THE FRUIT AND VEGETABLE CHEMISTRY LABORATORY, WESTERN UTILIZATION RESEARCH BRANCH, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Chemical Composition of Lemon Oil. I. Isolation of a Series of Substituted Coumarins[1]

BY W. L. STANLEY AND S. H. VANNIER

RECEIVED DECEMBER 26, 1956

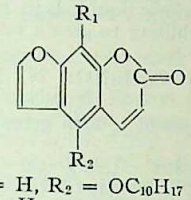
Seven substituted coumarin compounds have been isolated from domestic cold-pressed lemon oil by chromatographic separation on a column of powdered silicic acid. The identity of four of the compounds has been established, *viz.*, 5-geranoxypsoralen, 5,7-dimethoxycoumarin, 5-geranoxy-7-methoxycoumarin and byakangelicin. A fifth compound has been tentatively identified as 8-geranoxypsoralen, the geranyl group still being in doubt. The remaining two compounds were recovered in too small a quantity for analysis. However, they appear, from comparison of ultraviolet spectra, to be related to 5-geranoxypsoralen and 5-geranoxy-7-methoxycoumarin.

The presence of coumarin compounds in various citrus oils has been well established. Thus, for example, 5,7-dimethoxycoumarin, 5-methoxypsoralen, 5-hydroxypsoralen and 5-geranoxypsoralen have been isolated from oil of bergamot[2]; 5,7-dimethoxycoumarin, 5-geranoxy-7-methoxycoumarin and 5,8-dimethoxypsoralen from lime oil[3]; auraptene from orange oil[4]; and 7-hydroxycoumarin from grapefruit oil.[9] Also, 5,7-dimethoxycoumarin (limettin)[5,6] and an unidentified coumarin[7] have been reported in lemon oil.

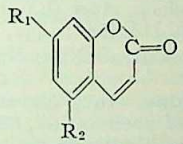
The present study was undertaken as part of a comprehensive investigation of the composition of lemon oil. By chromatography of whole cold-pressed lemon oil on a silicic acid column, seven crystalline solids were obtained. The ultraviolet spectra in neutral solution (Fig. 1)[3,8,9] and chemical properties indicated they were substituted coumarins. Furthermore, on addition of aluminum chloride and caustic soda to their cold alcoholic solution, there was no bathochromic shift in the spectral absorption. It was therefore apparent that the compounds did not contain free phenolic hydroxyl groups. All seven compounds gave a negative magnesium–hydrochloric acid test for flavones.

The spectra of II, IV and VI were closely similar to those of the 5,7-hydroxy and alkoxy coumarins (Fig. 1). Analyses of VI established the empirical formula $C_{11}H_{10}O_4$ and the presence of two methoxyl groups. The melting point, 146–147°, indicated the identity of this compound with the previously reported 5,7-dimethoxycoumarin. It was identical with material isolated from lime oil and oil of bergamot.

Compound II contained one methoxyl group. It was cleaved by mild acid treatment, indicating the presence of an allylic ether linkage. The phenol VIII thus produced was methylated with diazomethane and the product found to be identical with VI, 5,7-dimethoxycoumarin. The compound



I, R_1 = H, R_2 = $OC_{10}H_{17}$
III, R_1 = H, R_2 = OCH_2—CH = $C(CH_3)_2$(?)
V, R_1 = $OC_{10}H_{17}$; R_2 = H
VII, R_1 = OCH_2—CHOH—COH $(CH_3)_2$, R_2 = OCH_3
IX, R_1 = H; R_2 = OH
X, R_1 = H; R_2 = OCH_3
XI, R_1 = H; R_2 = $OCOCH_3$
XII, R_1 = OH; R_2 = H
XIII, R_1 = $OCOCH_3$; R_2 = H
XIV, R_1 = OCH_3; R_2 = H



II, R_1 = OCH_3; R_2 = $OC_{10}H_{17}$
IV, R_1 = OCH_3; R_2 = OCH_2—CH = $C(CH_3)_2$(?)
VI, R_1 = R_2 = OCH_3
VIII, R_1 = OCH_3; R_2 = OH

7-methoxy-5-geranoxycoumarin was then isolated from lime oil in the manner similar to that described by Caldwell and Jones[3] and found to be identical with II.

Compound IV was not isolated in amounts sufficient for elemental analysis. However, its ultraviolet spectrum suggested that it was also a 5,7-dialkoxycoumarin. Its R_f value, intermediate between that of II and VI, suggested that it is possibly a lower isoprene homolog of II, *viz.*, 5-γ,γ-dimethylallyloxy-7-methoxycoumarin. Such an allyl ether group is present in brayleyanin.[10]

The ultraviolet spectra of I and III were similar to the spectrum reported for 5-methoxypsoralen[9] (Fig. 1). Compound I did not contain a methoxyl group and was hydrolyzed readily with acids to give a phenol IX. This phenol gave a product X which was identical with authentic 5-methoxypsoralen.[11] Consideration of these data supported the identity of I with 5-geranoxypsoralen. This identity was confirmed by direct comparison of I

(1) Presented in part before the Symposium on Chemistry in the Citrus Fruit Industry at the Miami Meeting of the American Chemical Society, April, 1957.

(2) E. Späth and P. Kainrath, *Ber.*, **70B**, 2272 (1937).

(3) A. G. Caldwell and E. R. H. Jones, *J. Chem. Soc.*, 540 (1945).

(4) H. Böhme and G. Pietsch, *Ber.*, **72**, 773 (1939).

(5) H. E. Burgess, *Chem. Z.*, **25**, 602 (1901).

(6) E. Schmidt, *Apoth. Z.*, **16**, 619 (1901).

(7) G. Rodighiero, G. Caporale and E. Ragazzi, *Atti ist. veneto Sci. lettere ed arti, classe sci., mat. e nat.*, **III**, 125 (1952–1953); *C. A.*, **48**, 14116*h* (1954).

(8) R. H. Goodwin and B. M. Pollock, *Arch. Biochem. Biophys.*, **49**, 1 (1954).

(9) D. G. Crosby, Doctoral Thesis, 1954, Calif. Inst. of Technology.

(10) L. Anet, G. K. Hughes and E. Ritchie, *Austral. J. Sci.*, **A2**, 608 (1949).

(11) Samples of 5-methoxypsoralen and 8-γ,γ-dimethylallyloxypsoralen were kindly supplied by Dr. T. Soine, Univ. of Minnesota.

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with authentic 5-geranoxypsoralen isolated from oil of bergamot.[2,11]

An insufficient amount of III was isolated for analytical study. From chromatographic behavior and similarity of ultraviolet spectra with that of I, it may be a lower homolog of I.

Compound V was isomeric with I. It did not contain a methoxyl group. Acid hydrolysis of V gave a phenol XII, the acetate of which XIII had an ultraviolet spectrum closely similar to that of psoralen[9] (Fig. 2). Since Nakabayshi[12] has shown that the spectra of the acetates of phenolic coumarins resemble the spectrum of coumarin, it was apparent that V was probably a mono-ether of psoralen. This was confirmed by preparation of the mono-ether XIV of the phenol XII. Direct comparison of this methyl ether with 8-methoxypsoralen[13] showed them to be identical. Compound V is, therefore, an 8-alkoxypsoralen. The C_{10} allylic alkoxy group, by analogy with other compounds, is probably geranyl, but this has not been proved.

Compound VII, m.p. 119–123°, had an ultraviolet spectrum (Fig. 1) similar to that reported for 5,8-dimethoxypsoralen.[9] It was optically active, having an $[\alpha]^{25}D$ 25.61°, and did not migrate on chromatostrips with hydrophobic solvents. Noguchi[14] reported that the 5,8-diether of psoralen (byakangelicin) melts at 125°, forms a monohydrate melting at 117–118° and has an $[\alpha]^{25}D$ 24.62. Subsequently, direct comparison of VII with an authentic sample of byakangelicin[15] indicated they were identical.

Experimental

Chromatographic Fractionation of Lemon Oil.—A 300-g. sample of domestic cold-pressed lemon oil was added to a column of silicic acid 8 cm. in diameter and 25 cm. long prepared from a slurry in hexane.[16] When the oil had penetrated the column, hexane was added and the eluted solvent leaving the column was collected in a fraction cutter (about 20 ml. per tube). Every fifth tube from the fraction cutter was tested for unsaturation with chromatostrips[17] developed with 15% ethyl acetate in hexane and sprayed with a fluorescein-bromine test reagent.[18] When it was observed by this test that the mixture of unsaturated hydrocarbons (chiefly limonene) had passed through the column, a solution of 1% ethyl acetate in hexane was added, followed by gradually increasing amounts of ethyl acetate in hexane, and finally by a solution of 10% ethanol in ethyl acetate. After removal of the terpene hydrocarbons, the fractions were tested by development on chromatostrips containing small amounts of luminescent mineral phosphors. The developed strips were examined under ultraviolet light (maximum emission at 253 mμ) for fluorescent compounds and for compounds capable of absorbing the rays of the exciting illumination. These latter compounds appeared as purple shadows on a yellow background. Compounds II, IV and VI fluoresced a brilliant blue, and I, III, V and VII appeared as purple spots. The strips were also tested for carbonyl

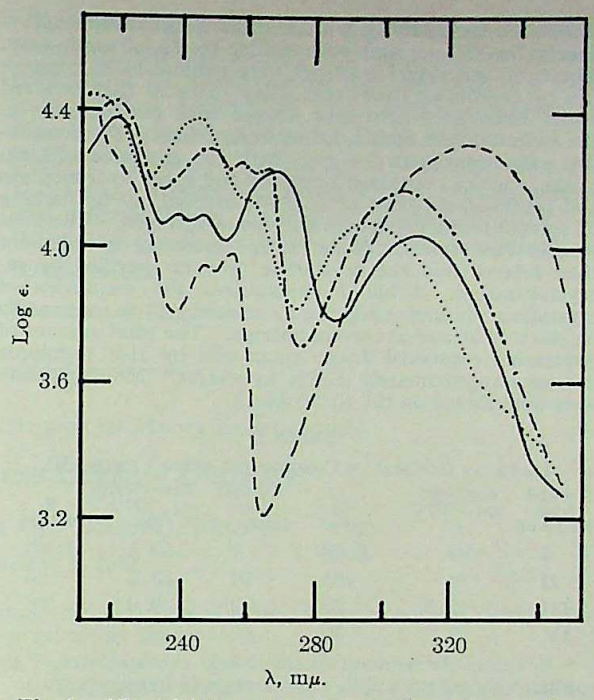

Fig. 1.—Ultraviolet spectra of coumarin compounds from lemon oil: –.–.–.–.–.–.–, 5-geranoxypsoralen (I) in absolute ethanol. Also characteristic for 5-geranoxypsoralen from oil of bergamot, 5-methoxypsoralen from oil of bergamot and synthetic from I, and unknown compound III. – – – – – – –, 5-geranoxy-7-methoxycoumarin (II) in absolute ethanol. Also characteristic for 5,7-dimethoxycoumarin (VI) and unknown IV. . . . . , 8-Geranoxypsoralen (V) in absolute ethanol. Also characteristic for 8-methoxypsoralen[13] and 8-γ,γ-dimethylallyloxypsoralen.[11] ————, Byakangelicin (VII). Also characteristic for 5,8-dimethoxypsoralen,[9] byakangelicol[14] and 5,8-dimethoxypsoralen from lime oil.

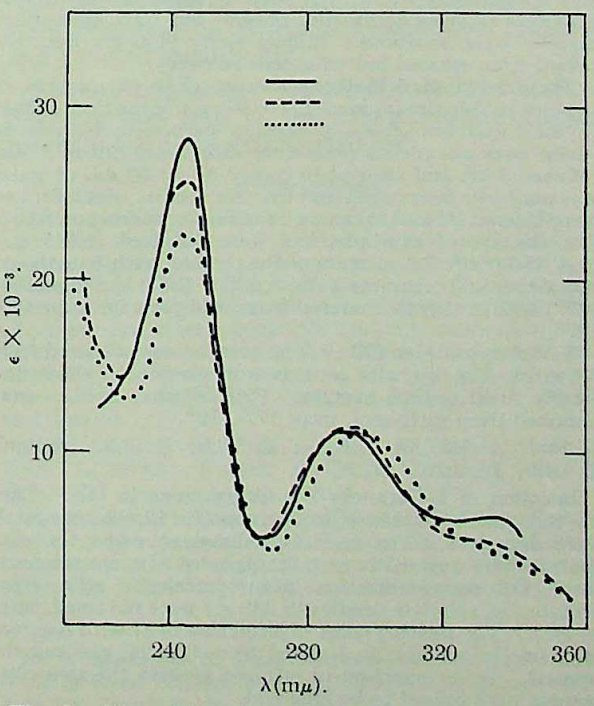

Fig. 2.—Ultraviolet absorption spectra in absolute ethanol: ————, psoralen; – – – – – – –, 8-acetoxypsoralen; 5-acetoxypsoralen.

(12) T. Nakabayashi, T. Tokoroyama, H. Miyazaki and S. Isono, *J. Pharm. Soc. Japan*, **73**, 669 (1953); *C. A.*, **47**, 10348e (1953).
(13) A sample of 8-methoxypsoralen was kindly supplied by Dr. H. E. Parker of the Paul D. Elder Co. who obtained it from the Egyptian Ammi Majus plant.
(14) T. Noguchi and M. Kawanami, *J. Pharm. Soc. Japan*, **59**, 755 (1939); *C. A.*, **34**, 2346 (1940).
(15) Samples of byakangelicin and byakangelicol were kindly supplied by Dr. D. G. Crosby of Carbide and Carbon Chemicals Co., who obtained his material from Dr. Noguchi.
(16) J. M. Miller and J. G. Kirchner, *Anal. Chem.*, **24**, 1480 (1952).
(17) J. M. Miller and J. G. Kirchner, *ibid.*, **26**, 2002 (1954).
(18) J. G. Kirchner, J. M. Miller and G. J. Keller, *ibid.*, **23**, 420 (1951).

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compound by spraying with acidified 2,4-dinitrophenylhydrazine in ethanol and *o*-dianisidine in glacial acetic acid. The 1,037 individual fractions were reduced to 25 composites by combining tubes containing material that behaved under ultraviolet light and reacted with test reagents in the same manner and had similar R_f values. The composites were reduced to 3–5 ml. (with the exception of composite 1 which contained limonene and other hydrocarbons and represented about 85% of the original oil) by flashing off solvent under vacuum in a stream of nitrogen. The composites were stored at 5° and those depositing crystals were then filtered and the crystalline products purified by recrystallization. Table I summarizes the recoveries of crystalline coumarins and the R_f values for these compounds on silicic acid coated chromatostrips. The total amount of coumarins recovered from lemon oils by this technique averages approximately 0.38% by weight. Melting points were determined on the Kofler block.

TABLE I

DATA ON COUMARIN COMPOUNDS FROM LEMON OIL

Compd. from lemon oil	Recovery, mg./100 g. oil	R_f value[a]	Compd. from lemon oil	Recovery, mg./100 g. oil	R_f value[a]
I	90	0.68	V	59.3	0.40
II	116	.64	VI	53.2	.25
III	2.5	.57	VII	9.0	.00
IV	3.0	.50			

[a] R_f values determined on silicic acid chromatostrips[15] by capillary ascent with 25% ethyl acetate in hexane (v./v.).

Isolation of 5-Geranoxypsoralen (I).—The product crystallizing from composite 10 at refrigerator temperatures (5°) was washed on a filter with cold petroleum ether and recrystallized from petroleum ether to yield the analytical sample (long needles) of 5-geranoxypsoralen, m.p. 53.5–54.5°.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.5; H, 6.55; MeO–, 0.0. Found: C, 74.5; H, 7.14; MeO–, 0.26.

5-Hydroxypsoralen (IX).—Two drops of sulfuric acid was added with stirring to a solution of 5-geranoxypsoralen (0.490 g.) in glacial acetic acid (5 ml.). A tan precipitate formed in a few minutes and the reagent solution turned light brown. The reaction mixture was stirred at room temperature for 1 hr., cooled to about 10° and filtered with suction. The melting point of the crude material (0.278 g.) was approximately 270°. A series of solvents was tried in attempts to recrystallize the phenol, but only amorphous nodules were produced. Minute shiny platelets were obtained from ethanol but with poor recovery.

Preparation of 5-Methoxypsoralen (X).—A solution of the crude 5-hydroxypsoralen (0.040 g.), dimethyl sulfate (1 ml.) and anhydrous potassium carbonate in acetone (dried over anhydrous potassium carbonate) (20 ml.) was refluxed 3 hr. and allowed to cool. About 50 ml. of water was added in increments and the fine needles which formed were filtered off and taken up in ethanol, whereupon frond-like clusters of thin platelets were obtained (0.011 g.), m.p. 185–192°. A mixture of the product with 5-methoxypsoralen from bergamot oil (m.p. 186.5–188°) had m.p. 186–187°, with authentic material from wild parsnip, m.p. 186–187°.[11]

5-Acetoxypsoralen (XI).—The acetate was prepared from 5-hydroxypsoralen with an excess of acetic anhydride and freshly fused sodium acetate. Fine colorless needles were obtained from methanol, m.p. 177–179°.

Anal. Calcd. for $C_{13}H_8O_5$: C, 63.9; H, 3.30. Found: C, 64.0; H, 3.30.

Isolation of 5-Geranoxy-7-methoxycoumarin (II).—During the removal of solvent from composite 12, white crystals were deposited. The crystals redissolved when the concentrate was warmed but again appeared at room temperature. On recrystallization from petroleum ether–ethyl acetate fine colorless needles (0.348 g.) were obtained, m.p. 86–87°. The melting point of a mixture of II with 5-geranoxy-7-methoxycoumarin isolated from lime oil was not depressed. By comparison of infrared spectra the two compounds were judged to be identical.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.15; H, 7.35; 1 MeO–, 9.4. Found: C, 72.7; H, 7.33; MeO–, 9.5.

7-Methoxy-5-hydroxycoumarin (VIII).—A sample of 7-methoxy-5-geranoxycoumarin (0.519 g.) was dissolved in glacial acetic acid (5 ml.), allowed to react with two drops of concentrated sulfuric acid with stirring for 1.5 hr. The product phenol (0.228 g.), m.p. 227–228°, gave, with ferric chloride, a yellow-green solution darkening with time, and with 1% sodium nitrate in concentrated sulfuric acid a bright yellow solution which turned orange-red when the solution was made alkaline with sodium hydroxide.

Preparation of 5,7-Dimethoxycoumarin.—To a methanol solution of 7-methoxy-5-hydroxycoumarin (0.065 g.) was added an ethereal solution of diazomethane. Recrystallized from acetone–hexane the product had m.p. 145–146°. The mixed melting point with compound VI (5,7-dimethoxycoumarin) was not depressed. Their infrared spectra were identical.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89; 2 MeO–, 30.10. Found: C, 63.5; H, 5.11; MeO–, 29.5.

Isolation of Compound III.—Composite 14 obtained from fractions 360 to 365 was concentrated under vacuum to about 1 ml. On standing overnight at about 5° the concentrate deposited crystals (7.5 mg.) which, on recrystallization from hexane–ethyl acetate (colorless blades), melted at 94–96°.

Isolation of Compound IV.—Composite 16 from fractions 380 to 405 was reduced to about 2 ml. under vacuum. On standing overnight at 5°, the concentrate deposited crystals (9 mg.). This material was recrystallized from hexane–ethyl acetate, yielding nodules, m.p. 90–92°.

Isolation of 8-Geranoxypsoralen (V).—Composite 17, made up of fractions 406 to 475, was reduced to about 5 ml. by flashing off solvent under vacuum in a stream of nitrogen. The concentrate was allowed to stand overnight at 5° whereupon a copious deposit of crystals was obtained (0.178 g.). Recrystallized from hexane–ethyl acetate this material (long blades) melted at 59–60°.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.5; H, 6.55; MeO–, 0.0. Found: C, 74.7; H, 6.75; MeO–, 0.32.

Preparation of 8-Hydroxypsoralen (XII).—A sample of 8-geranoxypsoralen (V) (0.275 g.) was dissolved in glacial acetic acid (4 ml.), and a drop of concentrated sulfuric acid was added with stirring. A precipitate began to appear within five minutes. Stirring was continued at room temperature for 1 hr. whereupon the solution was cooled to about 10°, the solid was filtered off and washed on the filter with a small amount of ethyl acetate followed by cold ethyl ether (product (0.115 g.).

Preparation of 8-Methoxypsoralen (XIV).—The methyl ether XIV of the phenol XII was prepared by the addition of an ethereal solution of diazomethane to a methanol solution of the phenol. Recrystallized from hexane–acetone solution the product (long hollow needles) had m.p. 145–146°. The melting point of a mixture with an authentic sample of 8-methoxypsoralen was not depressed.[13] A comparison of the infrared spectra of the two compounds indicated that they were identical.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.7; H, 3.73. Found: C, 66.5; H, 3.87.

Preparation of 8-Acetoxypsoralen (XIII).—A mixture of the 8-hydroxypsoralen (XII) (0.019 g.), acetic anhydride (1.0 ml.) and freshly fused sodium acetate (0.01 g.) was heated in a water-bath for 1 hr. The mixture was allowed to cool and water was gradually added with shaking until the acetic anhydride had hydrolyzed. The pale yellow solid that appeared was filtered off and dried *in vacuo* (0.014 g.). Recrystallized from methanol the pale yellow prisms melted at 177–180°.

Recovery of 5,7-Dimethoxycoumarin (VI).—Fractions 500 to 605 were composited (composite 18) and reduced under vacuum to about 6 ml. During concentration a crystalline solid appeared. The residue mixture was warmed, enough warm ethyl acetate added to dissolve the crystals and the clear solution was allowed to crystallize at room temperature. The product (0.160 g.) recrystallized from ethyl acetate had m.p. 146–147°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89; 2 MeO–, 30.10. Found: C, 64.0; H, 5.00; MeO–, 29.9.

Recovery of Byakangelicin (VII).—During the final development of the chromatogram with a solution of 10% (v./v.) ethanol in ethyl acetate, material appeared in the chromatostrip tests which indicated the possible presence of 2 coumarins. Fractions 937 to 1037 were composited

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(composite 25) and concentrated to about 3 ml. under vacuum. After storage at 5° a pale yellow crystalline product formed which was filtered off (0.027 g.). The material recrystallized from ethanol melted at 119 to 123° and had an $[\alpha]^{25}D$ of 25.61 in pyridine. A negative Molisch test for sugars and glycosides was obtained. In alcoholic solution the compound gave no coloration when warmed with a chip of magnesium turnings and concentrated hydrochloric acid (a negative test for flavones). The mixed melting point of VII with an authentic sample of byakangelicin[15] was not depressed, and a comparison of the infrared spectra of the two compounds indicated they were identical.

Anal. Calcd. for $C_{17}H_{18}O_7$: C, 61.1; H, 5.43; 1 MeO–, 9.3. Found: C, 61.6; H, 5.59; MeO–, 8.9.

Acknowledgments.—The authors wish to thank Leonard Jurd and R. W. Horowitz of this Laboratory and T. A. Geissman of the University of California in Los Angeles for their helpful suggestions. They are also indebted to Fred Stitt and Glen Bailey, Western Utilization Research Branch, U.S.D.A., Albany, California, for measurements and interpretation of infrared spectra and to L. M. White of the same laboratory for analytical determinations.

PASADENA 5, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH DIVISION OF ABBOTT LABORATORIES]

The Preparation of Some Organic Diazides

BY ARMIGER H. SOMMERS AND JAMES D. BARNES

RECEIVED FEBRUARY 9, 1957

The polymethylene diazides containing five to ten carbon atoms and examples of other classes of organic diazides have been prepared through displacement of halogen or arenesulfonoxy groups by the azide ion.

A recent review[1] of the literature on organic azides lists no diazidoalkanes other than 1,2-diazidoethane.[2] We have prepared a series of eight aliphatic diazides containing five to ten carbon atoms for pharmacologic testing as hypotensive agents. Examples of the oxa and aza analogs of these diazides were also synthesized, as was α,α'-diazido-*p*-xylene. Pharmacologic studies in these laboratories have shown that some of these diazides possess marked hypotensive action in normal animals.[3]

The treatment of polymethylene dibromides with sodium azide in aqueous methanol[4] generally gave the corresponding diazides in good yield.

$$Br{-}(CH_2)_n{-}Br + 2NaN_3 \rightarrow N_3{-}(CH_2)_n{-}N_3 + 2NaBr$$

Replacing one or both primary alkyl bromide groups in the reactant by secondary groups gave progressively lower yields of product. Table I summarizes the data obtained from these diazidoalkanes. α,α'-Diazido-*p*-xylene, in which an aromatic ring joins two azidoalkyl groups, was obtained in the same manner from α,α'-dichloro-*p*-xylene and sodium azide.

The displacement of an arenesulfonoxy group by azide ion, a method recently applied to the preparation of cyclohexyl azide,[5] is an effective alternate method of synthesis. The benzenesulfonic acid or *p*-toluenesulfonic acid esters of 1,6-hexanediol and 1,7-heptanediol were thus converted to the corresponding diazidoalkanes.

$$Ar{-}SO_3{-}(CH_2)_n{-}O_3S{-}Ar + 2NaN_3 \longrightarrow N_3{-}(CH_2)_n{-}N_3 + 2ArSO_3Na$$

Because 1,7-diazidoheptane possesses greater hypotensive potency than its homologs,[3] an isoster, di-3-azidopropyl ether, was prepared by the following reactions.

$$(ClCH_2CH_2CH_2)_2O + 2NaI \longrightarrow (ICH_2CH_2CH_2)_2O$$
$$(ICH_2CH_2CH_2)_2O + 2NaN_3 \longrightarrow (N_3CH_2CH_2CH_2)_2O$$

Treatment of N-methyl- and N-phenyl-N,N-bis-(β-chloroethyl)-amines with sodium azide gave the corresponding amino diazides, one of which was converted to a diazide quaternary ammonium salt.

$$RN(CH_2CH_2Cl)_2 + 2NaN_3 \longrightarrow RN(CH_2CH_2N_3)_2 \xrightarrow{CH_3I} [R(CH_3)N(CH_2CH_2N_3)_2]^+ I^-$$

No fires or explosions were experienced in working with these diazides. However, because of the reported sensitivity to heat of diazidoethane they were regarded as potentially explosive materials and handled accordingly.

Acknowledgment.—We are grateful to Mr. E. F. Shelberg and staff of the Microchemical Department for the analyses reported here.

Experimental

Dibromoalkanes.—With two exceptions these were commercially available. 1,7-Dibromoheptane and 1,8-dibromoöctane were made by the action of anhydrous hydrogen bromide[6] upon the corresponding glycols. The latter compounds were obtained by reduction of methyl or ethyl esters of pimelic and suberic acids with lithium aluminum hydride.[7] In the synthesis of diethyl pimelate from pimelonitrile using alcoholic hydrogen chloride there was obtained, along with the desired ester (75%), **ethyl pimelamate**, m.p. 76–77°, in 4% yield.

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; O, 25.64. Found: C, 58.29; H, 9.16; N, 7.47; O, 25.43.

Arenesulfonic Esters.—**1,6-Dibenzenesulfonoxyhexane**, prepared by a procedure described for alkyl esters,[8] decomposed upon attempted distillation and was purified by crystallization from alcohol which gave crystals melting at 58–60°.

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TABLE I

DIAZIDOALKANES N_3—CHR—$(CH_2)_n$—CHR_1—N_3

n	R	R_1	Yield, %	B.p. °C.	Mm.	$n^{25}D$	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
3	H	H	81	100	9	1.4729	$C_5H_{10}N_6$	38.95	39.43	6.54	6.34	54.51	54.80
4	H	H	80	119	12	1.4707	$C_6H_{12}N_6$	42.84	43.20	7.19	7.16	49.97	49.42
5	H	H	73	116	5	1.4700	$C_7H_{14}N_6$	46.14	46.36	7.74	7.75	46.12	45.77
6	H	H	75	129	5	1.4698	$C_8H_{16}N_6$	48.96	49.36	8.22	7.96	42.83	43.46
7	H	H	89	142	6	1.4685	$C_9H_{18}N_6$	51.40	51.59	8.63	8.68	39.97	39.91
8	H	H	72	105	0.2	1.4693	$C_{10}H_{20}N_6$	53.54	53.72	8.99	8.90	37.47	37.41
2	CH_3	H	66	88	8	1.4690	$C_5H_{10}N_6$	38.95	38.89	6.54	6.44	54.51	54.58
2	CH_3	CH_3	37	116	26	1.4642	$C_6H_{12}N_6$	42.84	43.31	7.19	6.86	49.97	50.04

Anal. Calcd. for $C_{18}H_{22}O_6S_2$: S, 16.09. Found: S, 16.29.

1,6-Di-*p*-toluenesulfonoxyhexane[9] **and 1,7-di-*p*-toluenesulfonoxyheptane** were obtained in yields of 87 and 71%, respectively, by Tipson's method.[10] The latter compound melted at 77–78° after crystallization from ethanol.

Anal. Calcd. for $C_{21}H_{28}O_6S_2$: C, 57.25; H, 6.41. Found: C, 57.54; H, 6.34.

Diazidoalkanes. From Dibromoalkanes.—To a solution of 0.1 mole of the dibromoalkane in 225 ml. of methanol, there was added a slurry of 16.3 g. (0.25 mole) of sodium azide in 15 ml. of water. The mixture was refluxed for 24 hr., the methanol removed and the residue diluted with 50 ml. of water. The resultant oil was extracted by 200 ml. of ether, dried over calcium chloride and distilled. Table I describes the diazidoalkanes obtained by this procedure.

1,7-Diazidoheptane was prepared also by the following method.[11] A solution containing 78 g. (1.2 moles) of sodium azide and 27 g. of sodium acetate in 270 ml. of water was added to a warm solution of 129 g. (0.5 mole) of 1,7-dibromoheptane in 460 ml. of absolute ethanol. The mixture was refluxed for 24 hr. on a steam-bath, and 375 ml. of alcohol was then distilled from the mixture. The residue was poured into 0.5 l. of water and shaken with three 200-ml. portions of benzene. Distillation of the extract gave 83 g. (95%) of the product, b.p. 80–81° at 0.3 mm., $n^{25}D$ 1.4698.

From Arenesulfonic Esters. 1,7-Diazidoheptane.—A mixture of 22 g. (0.05 mole) of 1,7-di-*p*-toluenesulfonoxyheptane, 9.8 g. (0.15 mole) of sodium azide, 150 ml. of acetone and 20 ml. of water was refluxed on a steam-bath for 24 hr. The condenser was removed and acetone was allowed to evaporate during 15 minutes. Water (100 ml.) was added and the oil which formed was extracted into benzene and distilled. There was obtained 8.5 g. (93%) of product, b.p. 72° at 0.2 mm., $n^{25}D$ 1.4701.

By this method the benzene- and *p*-toluenesulfonic acid diesters of 1,6-hexanediol were converted to 1,6-diazidohexane in yields of 74 and 83%.

α,α′-Diazido-*p*-xylene.—The general method described for the preparation of diazidoalkanes was applied to α,α′-dichloro-*p*-xylene. The product, a colorless oil, b.p. 82–83° at 0.1 mm., $n^{25}D$ 1.5590, was obtained in 90% yield.

Anal. Calcd. for $C_8H_8N_6$: N, 44.66. Found: N, 44.10.

Di-3-azidopropyl Ether. Di-3-iodopropyl Ether.—To a solution of 45 g. (0.3 mole) of sodium iodide in 250 ml. of acetone was added 20 g. (0.12 mole) of di-3-chloropropyl ether, and the mixture was refluxed for 19 hr. The salt was removed by filtering and the filtrate was concentrated and distilled. Redistillation of material (25 g.), b.p. 141–154° (10 mm.), gave 15 g. (36%) as a center cut, b.p. 134–142° (7 mm.), $n^{25}D$ 1.5638. This material was used for the next reaction without further purification.

Anal. Calcd. for $C_6H_{12}I_2O$: I, 71.70. Found: I, 69.10.

Di-3-azidopropyl Ether.—A mixture of 14.5 g. (0.04 mole) of di-3-iodopropyl ether, 6.5 g. (0.1 mole) of sodium azide, 75 ml. of ethanol and 15 ml. of water was heated to reflux for 25 hr. After the mixture had been diluted with 200 ml. of water, the oil which separated was extracted by benzene. Two distillations of the oil remaining after concentration of the extract gave 5 g. (68%) of product, b.p. 116–117° at 8 mm., $n^{25}D$ 1.4661.

Anal. Calcd. for $C_6H_{12}N_6O$: C, 39.12; H, 6.57; N, 45.63. Found: C, 38.99; H, 6.59; N, 45.47.

Diazido Amines. N,N-Bis-(β-azidoethyl)-aniline.—A mixture of 21.8 g. (0.1 mole) of N,N-bis-(β-chloroethyl)-aniline, 16.3 g. (0.25 mole) of sodium azide, 225 ml. of methanol and 15 ml. of water was refluxed for 24 hr. on the steam-bath. The methanol was removed under reduced pressure, and the residue was diluted with 225 ml. of water and shaken with 200 ml. of ether. The extract was dried over sodium sulfate and distilled to obtain 18 g. (79%) of product, b.p. 132–134° at 0.2 mm., $n^{25}D$ 1.5748. A redistilled sample was analyzed.

Anal. Calcd. for $C_{10}H_{13}N_7$: C, 51.93; H, 5.67; N, 42.40. Found: C, 52.66; H, 5.86; N, 41.09.

N,N-Bis-(β-azidoethyl)-methylamine.—A solution of 16.3 g. (0.25 mole) of sodium azide in 100 ml. of water was added to 39 g. (0.2 mole) of N,N-bis-(β-chloroethyl)-methylamine hydrochloride. After the mixture had stood 6 hr., it was warmed on the steam-bath and an additional 26 g. (0.4 mole) of sodium azide was added. The mixture was heated another hour, cooled and treated with 60 ml. of aqueous 25% sodium hydroxide. The oil was extracted by three 100-ml. portions of ether, dried over potassium hydroxide pellets and distilled. By redistillation of the material boiling at 97–100° at 5 mm., there was obtained 15 g. (44%) of product, b.p. 98–99° at 5 mm., $n^{25}D$ 1.4824.

Anal. Calcd. for $C_5H_{11}N_7$: C, 35.49; H, 6.55; N, 57.95. Found: C, 35.77; H, 6.65; N, 57.51.

Its oxalate, prepared in ether and recrystallized in isopropyl alcohol, melted at 95–97°.

Anal. Calcd. for $C_7H_{13}N_7O_4$: N, 37.83. Found: N, 37.17.

N,N-Bis-(β-azidoethyl)-dimethylammonium Iodide.—A solution of N,N-bis-(β-azidoethyl)-methylamine and methyl iodide in absolute ethanol was allowed to stand several days. Dilution with dry ether gave a small amount of white crystalline solid, m.p. 72–74°.

Anal. Calcd. for $C_6H_{14}IN_7$: C, 23.16; H, 4.54; N, 31.51. Found: C, 23.52; H, 4.58; N, 31.76.

NORTH CHICAGO, ILLINOIS

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF NORTHWESTERN UNIVERSITY]

The Free Radical Addition of Thiolacetic Acid to Some Cyclic Olefins

BY F. G. BORDWELL AND W. A. HEWETT[1]

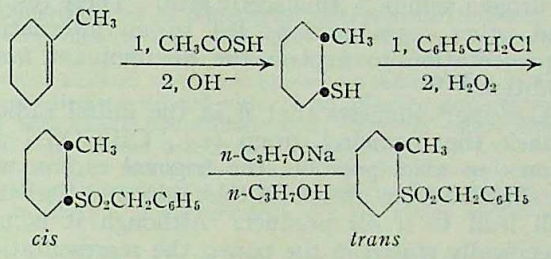
RECEIVED AUGUST 21, 1956

The free radical addition of thiolacetic acid to 1-methylcyclohexene gave about 85% of *cis*- and 15% of *trans*-2-methylcyclohexyl thiolacetate as judged from the composition of the thiol mixture obtained on hydrolysis. Under similar conditions 1-methylcyclopentene gave about 70% of *cis*- and 30% of *trans*-2-methylcyclopentyl thiolacetates. Radical addition of thiophenol to 1-methylcyclohexene also occurred predominantly in a *trans* manner. Addition of thiolacetic acid to camphene, β-pinene and α-pinene appears to have taken place with little or no rearrangement. However, two thiolacetates are formed with each of the pinenes.

As part of a program of synthesis of divalent sulfur compounds it was of interest to study the reaction of thiolacetic acid with several cyclic olefins including 1-methylcyclohexene, 1-methylcyclopentene, camphene, β-pinene and α-pinene.

The first free radical additions of thiolacetic acid to olefins were reported at about the same time by Holmberg[2] and by Ipatieff and Friedman.[3] Since that time similar additions to a large variety of olefins have been reported.[4] In this Laboratory preparation of thiolacetates has been found to provide an excellent general synthetic route to pure thiols, since yields are normally high and orientation is exclusively anti-Markownikoff.[5]

Addition of thiolacetic acid to 1-methylcyclohexene and 1-methylcyclopentene was of interest in connection with the stereoselectivity of free radical addition reactions, as well as for the preparation of the thiols. Cunneen[4b] reported the addition of thiolacetic acid to 1-methylcyclohexene, but did not attempt to decide the stereorelationships of the groups in the product. In the present work the additions were initiated at ordinary temperatures with the aid of light. Excellent yields of thiolacetates were obtained from 1-methylcyclohexene and from 1-methylcyclopentene. These were hydrolyzed with aqueous alcoholic alkali to the thiols. The crude thiols were converted to the corresponding benzyl sulfides and these were oxidized to the sulfones, which were purified by fractional crystallization. In each instance the sulfone formed could be isomerized almost completely by heating with sodium propoxide in *n*-propyl alcohol solution. It seems reasonable to suppose that the original sulfone had the *cis* structure, and was isomerized, by way of the carbanion, to the more stable *trans* isomer on heating with alkali. The sequence of reactions is shown for 1-methylcyclohexene.



Careful fractional distillation[6] separated each thiol into two fractions. For 2-methylcyclohexanethiol 17% of a lower boiling and 83% of a higher boiling fraction were collected. For 2-methylcyclopentanethiol the percentages of the lower and higher boiling materials were 29 and 71%.

The lower boiling 2-methylcyclohexanethiol and 2-methylcyclopentanethiol in each instance gave the more stable benzyl sulfone derivative. The higher boiling thiol was in each instance converted to the less stable benzyl sulfone, identical with that prepared from the crude thiol sample. It is clear, then, that thiolacetic acid gives predominantly *cis*-2-methylcyclohexyl and *cis*-2-methylcyclopentyl thiolacetates (*trans*-addition), but that this is by no means the exclusive product.

Allinger[7] in a restatement of von Auwers' rule states with respect to *cis* and *trans* isomers in cyclic systems: "That isomer which has the higher boiling point, higher index of refraction and higher density is the isomer which possesses the least stable configuration." Our assignment of *cis* and *trans* structures is consistent with this modified von Auwers rule.

Cunneen[4b] reported the addition of thiophenol to 1-methylcyclohexene and oxidation of the resulting sulfide to a sulfone. Reaction of *cis*-2-methylcyclohexanethiol with iodobenzene and oxidation of the resulting sulfide gave a sulfone identical with that prepared by the method of Cunneen. This sulfone was isomerized by heating with sodium propoxide in propyl alcohol, which indicates a *cis* structure. Therefore, thiophenol also adds to 1-methylcyclohexene primarily by *trans* addition.

Goering, Abell and Aycock[8] were first to observe that free radical addition to 1-substituted cyclohexenes occurs by stereoselective *trans* addition. They reported that free radical addition of hydrogen bromide to 1-bromocyclohexene and 1-methylcyclohexene was completely stereoselective (*i.e.*, stereospecific), and interpreted these data in terms of a bridged free radical intermediate. Our present results, which were announced several years

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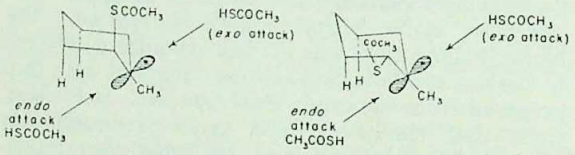
ago,[9] showed that the radical addition of thiolacetic acid to such systems is not stereospecific, since some *cis* addition occurs. This indicated that the concept of a bridged radical intermediate would not provide an entirely satisfactory explanation of the course of such additions. Recently Goering, Relyea and Larsen[10] have reported other examples of radical additions of this type which are not stereospecific. They have found that the degree of stereoselectivity increases with increased concentration for the addition of hydrogen sulfide, and varies with the reagent in the order thiophenol > hydrogen sulfide > thiolacetic acid. These results and other considerations led to an alternative representation to explain the predominant *trans* addition.[10,11]

Goering[10] suggests that if in the initial radical attack the incoming group (*e.g.*, CH_3COS–) assumes an axial position, the trigonal carbon will be shielded from attack on that side, and that this will lead to a *cis* product. Although it is not specifically stated in the paper, the representation given by Goering[10] implies a planar configuration, for the trigonal carbon. In terms of the diagram shown this would amount to *endo* attack by CH_3COSH on Ia. However, if a planar configuration is assumed for this carbon in the free radical inter-

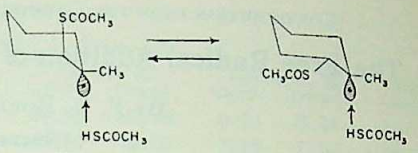


Ia Ib

Planar free radical intermediate

mediate, it does not necessarily follow that *endo* attack on Ia would be preferred. A closely analogous situation exists in the ketonization of enols, and here Zimmerman[12] has shown that due to the hindrance effect of the β-hydrogens (shown in Ia and Ib) *endo* attack of an acid HA is prohibited in an intermediate like Ib ($SCOCH_3$ equatorial). With the $SCOCH_3$ group axial (Ia) *exo* attack becomes less likely, but examination of models indicates that, unless it is assumed that the $SCOCH_3$ group is rotated so as to provide maximum hindrance, *exo* attack may still be favored over *endo*. If this is the correct picture, the *cis* product (predominant) would arise from *exo* attack on Ib rather than *endo* attack on Ia. It is difficult to account for the change in stereoselectivity with changing concentration[11] on this basis, however.

It is not at all certain that the carbon atom holding the odd electron does not maintain a tetrahedral rather than assume a planar configuration. If this carbon is tetrahedral the reaction would be represented as in IIa or IIb rather than as in Ia or Ib. If the methyl group assumes an equatorial



IIa IIb

Tetrahedral free radical intermediate

position, as seems logical, formation of the *cis* isomer would result from attack on IIa. The predominant, but not exclusive, *trans* radical additions to these systems would then be explained by assuming that the $-SCOCH_3$ group initially takes an axial position (IIa) and that conversion to IIb may occur to some extent. Steric hindrance to attack of CH_3COSH would not play an important role according to this mechanism. Increased stereoselectivity with increasing concentration[10] could result from less conversion of IIa to IIb.

No clear-cut choice between the mechanisms illustrated appears to be possible at present. A bridged radical intermediate[8] in these additions is made highly unlikely, however, by the failure of radical addition in non-cyclic alkenes to occur by stereoselective paths.[13]

The reactions of thiolacetic acid with camphene, β-pinene and α-pinene were carried out primarily to see whether or not free radical type rearrangements occur in these systems, which are notorious for their ease of carbonium ion rearrangements. Rearrangements during free radical additions are rare, one of the few well-established examples occurring in the addition of carbon tetrachloride to β-pinene.[14] Addition of thiolacetic acid to camphene followed by hydrolysis gave an over-all yield of 64% of a thiol, which appeared to be a single compound. Desulfurization yielded isocamphane, which indicates that no rearrangement occurred.

Addition of thiolacetic acid to β-pinene and hydrolysis gave a mixture of two thiols, as indicated by the isolation of two 2,4-dinitrophenyl sulfide derivatives. However, the original thiol mixture showed no band at 12.5 μ (characteristic of the olefinic band of Δ^1-*p*-menthene), which would be present if rearrangement of the type previously observed[14] had occurred (to give III). Infrared bands characteristic of norpinane were present, and it seems likely that no rearrangement of the carbon skeleton to III took place. The two thiols are probably *cis–trans* isomers (comparable to I and II) which are formed as a result of a partially stereoselective addition, as with 1-methylcyclohexene (I–III).

The infrared spectra of the 2,4-dinitrophenyl sulfide derivatives of these thiols were nearly identical, which shows a very close structural relationship. Addition of thiolacetic acid to α-pinene and hydrolysis also gave two thiols, as indicated by isolation of two 2,4-dinitrophenyl sulfide derivatives. These also are believed to be *cis–trans* isomers.

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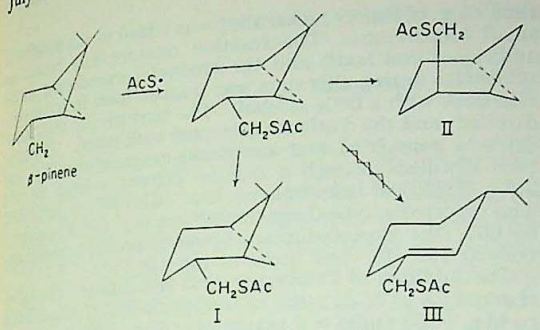

It has been shown by Seubold[15] that the life time of a radical under a particular set of conditions is an important factor in determining whether or not it will rearrange. The absence of rearrangement may be due to a very short half-life for the intermediate free radical. In this connection it is also of interest that carbon tetrachloride does not enter into the free radical chain of this type addition reaction, since chlorine was not incorporated into the product in an addition carried out in carbon tetrachloride solution, even when the ratio of carbon tetrachloride to thiolacetic acid was ten to one.

Experimental[16]

cis- and *trans*-2-Methylcyclohexanethiols.—2-Methylcyclohexyl thiolacetate was prepared by slowly adding 156 g. (2.0 moles) of practical grade thiolacetic acid to 164 g. (1.7 moles) of 1-methylcyclohexene while irradiating with a 100 watt bulb. Care must be taken as the reaction is highly exothermic and may have an induction period of several minutes. Distillation gave 250 g. (85%) of product, b.p. 110° (14 mm.), $n^{25}D$ 1.495. The reported boiling point of 2-methylcyclohexyl thiolacetate is 110° (14 mm.).[4b] (The thiolacetate is a mixture of *cis* and *trans* isomers.)

The thiolacetate (246 g., 1.43 moles) was hydrolyzed by refluxing for one hour in 2 l. of 10% aqueous alcoholic (50% by volume) potassium hydroxide. The solution was neutralized with glacial acetic acid and the non-aqueous phase separated. The aqueous portion was extracted three times with pentane and the pentane extracts were dried over anhydrous magnesium sulfate. The combined non-aqueous phase and pentane extracts were distilled giving 155 g. (82%) of 2-methylcyclohexanethiol, b.p. 71–72° (23 mm.); a b.p. of 165° was reported.[4b]

Careful fractionation[6] gave 16% of the charge as a fraction (*trans* isomer) boiling at 138.7° (300 mm.), $n^{20}D$ 1.4851, and 76% of the charge as a fraction (*cis* isomer) boiling at 143.4° (300 mm.), $n^{20}D$ 1.4937. Ignoring intermediate cuts the percentage of *trans* and *cis* isomers based on 92% of the charge are 17% and 83%, respectively.

The 2,4-dinitrophenyl sulfide derivatives of the pure thiols were prepared in the usual manner.[17]

Recrystallization of the derivative from the lower boiling fraction gave *trans*-2-methylcyclohexyl 2,4-dinitrophenyl sulfide, m.p. 140–140.5°.

Anal. Calcd for $C_{13}H_{16}O_4N_2S$: C, 52.69; H, 5.44. Found: C, 52.32; H, 5.65.

Recrystallization of the derivative from the higher boiling fraction gave *cis*-2-methylcyclohexyl 2,4-dinitrophenyl sulfide, m.p. 100–100.5°. This derivative also was obtained from the crude thiol prior to fractionation.

Anal. Calcd. for $C_{13}H_{16}O_4N_2S$: C, 52.69; H, 5.44. Found: C, 52.31; H, 5.31.

cis-2-Methylcyclohexyl Benzyl Sulfone.—The benzyl sulfide was prepared by dissolving the higher boiling thiol in 95% alcohol containing an equimolar quantity of sodium hydroxide and treating with an equimolar quantity of benzyl chloride. The solution was poured into water and the sulfide obtained by extraction with pentane. Oxidation of the crude sulfide, obtained by evaporation of the pentane, with a sixfold excess of 30% hydrogen peroxide in glacial acetic acid followed by addition of the reaction mixture to water gave the crude benzyl sulfone in 72% yield. One recrystallization from glacial acetic acid gave *cis*-2-methylcyclohexyl benzyl sulfone, m.p. 74–74.5°.

Anal. Calcd. for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99. Found: C, 66.50; H, 7.74.

This benzyl sulfone was also obtained from the thiol mixture prior to fractionation, but the melting point of the crude sulfone was low (58–65°), and repeated recrystallizations were necessary to raise the melting point to that of the pure *cis*-sulfone.

Isomerization of *cis*-2-Methylcyclohexyl Benzyl Sulfone.—The *cis*-sulfone (5.0 g., 0.02 mole) was dissolved in a solution of 1.6 g. (0.02 mole) of sodium *n*-propoxide in 30 ml. of *n*-propyl alcohol, and the solution was refluxed for 44 hr. The solution was diluted with 150 ml. of water and neutralized with dilute hydrochloric acid. The oil which separated was induced to crystallize by cooling with Dry Ice. After several recrystallizations from glacial acetic acid *trans*-2-methylcyclohexyl benzyl sulfone melting at 84–84.5° was obtained. A mixture with the *cis*-sulfone melted at 47–57°.

Anal. Calcd. for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99. Found: C, 66.57; H, 7.98.

The *trans*-sulfone also was obtained starting with the lower boiling thiol fraction using the method described above for the *cis*-sulfone.

2-Methylcyclopentyl Thiolacetate.—Starting with 1.9 moles of 1-methylcyclopentene and 2.1 moles of practical grade thiolacetic acid, 240 g. (80%) of 2-methylcyclopentyl thiolacetate, b.p. 98–101° (25 mm.), $n^{25}D$ 1.4900, was obtained by the procedure described above. This is a mixture of *cis* and *trans* isomers.

Anal. Calcd. for $C_8H_{14}OS$: C, 60.71; H, 8.92. Found: C, 61.05; H, 9.01.

cis- and *trans*-2-Methylcyclopentanethiols.—Hydrolysis of the thiolacetate as described above gave a mixture of *cis*- and *trans*-thiols in 96% yield, b.p. 146–148°.

Anal. Calcd. for $C_6H_{12}S$: C, 62.00; H, 10.41. Found: C, 62.37; H, 10.32.

Careful fractional distillation[6] gave 27% of the charge as a lower boiling fraction (*trans* isomer), b.p. 135.8° (590 mm.), $n^{20}D$ 1.4783, and 65% as a higher boiling fraction (*cis* isomer), b.p. 142.5° (590 mm.), $n^{20}D$ 1.4884. Based on 92% of the charge, 29% of *trans* isomer and 71% of *cis* isomer were obtained.

trans-2-Methylcyclopentyl 2,4-dinitrophenyl sulfide, prepared from the lower boiling fraction,[17] melted at 112.5–113° after crystallization from absolute alcohol.

Anal. Calcd. for $C_{12}H_{14}O_4N_2S$: C, 51.05; H, 5.00. Found: C, 51.02; H, 5.00.

cis-2-Methylcyclopentyl 2,4-dinitrophenyl sulfide, prepared from the higher boiling fraction,[17] melted at 99–100° after crystallization from absolute alcohol.

Anal. Calcd. for $C_{12}H_{14}O_4N_2S$: C, 51.05; H, 5.00; N, 9.93. Found: C, 50.52; H, 4.82; N, 10.02.

The 2,4-dinitrophenyl sulfide derivatives prepared from the thiol before fractionation melted at ranges between 70–90° despite repeated crystallizations from hexane. Carbon and hydrogen analysis of this mixture checked the theoretical for $C_{12}H_{14}O_4N_2S$, supporting the view that it is a mixture of the derivatives of the *cis*- and *trans*-thiols.

cis- and *trans*-2-Methylcyclopentyl Benzyl Sulfones.—These sulfones were prepared by the general method described above starting with the pure thiols. The *cis* isomer melted at 74.5–75° after crystallization from aqueous methanol or hexane.

Anal. Calcd. for $C_{13}H_{18}O_2S$: C, 65.51; H, 761. Found: C, 65.71; H, 7.41.

The *trans* isomer melted at 101–101.5° after recrystallization from methanol.

Anal. Calcd. for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61. Found: C, 65.75; H, 7.42.

The crude thiol mixture yielded a benzyl sulfone which was purified only with difficulty. Repeated recrystallizations

(15) F. H. Seubold, Jr., THIS JOURNAL, **75**, 2532 (1953).
(16) Microanalyses were by Miss Hilda Beck.
(17) R. W. Bost, J. O. Turner and R. D. Morton, THIS JOURNAL, **54**, 1985 (1932).

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from glacial acetic acid gave material melting sharply at 61–62°, but several additional recrystallizations from methanol gave the pure *cis* isomer, m.p. 74–74.5°. Carbon and hydrogen analysis of the material melting at 61–62° supported the conclusion that it was a mixture of *cis*- and *trans*-benzyl sulfones. A mixture of the *cis*- and *trans*-sulfones melted at 62–76°.

Isomerization of *cis*-2-Methylpentyl Benzyl Sulfone.—Treatment of either the pure *cis*-benzyl sulfone or the mixture of benzyl sulfones melting at 61–62° according to the method used to isomerize *cis*-2-methylcyclohexyl benzyl sulfone gave a 91% conversion to the *trans*-sulfone, m.p. 98–100°.

Attempts to isomerize the *cis*-thiol or *cis*-benzyl sulfide by this procedure were unsuccessful.

***cis*- and *trans*-2-Methylcyclohexyl Phenyl Sulfones.**—*cis*-2-Methylcyclohexylphenyl sulfide was prepared by heating a mixture of *cis*-2-methylcyclohexanethiol with iodobenzene and copper powder at 220° according to the procedure described by Cunneen.[4b] The sulfide also was prepared in 50% yield from 1-methylcyclohexene and thiophenol by heating on the steam-bath in the presence of *t*-butyl peroxide. Oxidation of each of these samples with 30% hydrogen peroxide in glacial acetic acid gave the same sulfone, m.p. 107–108° after recrystallization from methanol; Cunneen[4b] reports the melting point as 108°. Isomerization of the sulfone by the method described above gave an 85% yield of *trans*-**2-methylcyclohexyl phenyl sulfone** (m.p. 82–86°), which melted at 90–90.5° after recrystallization from methanol.

Anal. Calcd. for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61. Found: C, 65.40; H, 7.30.

A mixture of the *cis*- and *trans*-sulfones melted at 88–95°.

Addition of Thiolacetic Acid to 1-Hexene in Carbon Tetrachloride Solution.—Thiolacetic acid (28 g., 0.3 mole) was added slowly to a solution of 25 g. (0.3 mole) of 1-hexene in 461.5 g. (3 moles) of carbon tetrachloride under irradiation. The yield of *n*-hexyl thiolacetate, b.p. 88° (13 mm.), $n^{25}D$ 1.4591, was 83%; Wenzel and Reid[18] reported b.p. 205.8° (760 mm.), $n^{25}D$ 1.4591.

2-Mercaptomethyl-3,3-dimethylbicyclo[2,2,1]heptane.—Addition of 90 g. (1.2 moles) of thiolacetic acid to 136 g. (1 mole) of camphene in the usual manner gave 164 g. (77%) of 2-(S-thiolacetoxymethyl)-3,3-dimethylbicyclo[2,2,1]heptane, b.p. 93–95° (0.8–1.0 mm.); Behringer[4c] reports a boiling point of 147–148° (14 mm.). Alkaline hydrolysis gave 109 g. (83%) of 2-mercaptomethyl-3,3-dimethylbicyclo[2,2,1]heptane, b.p. 116° (20 mm.).

Anal. Calcd. for $C_{10}H_{18}S$: C, 70.52; H, 10.65. Found: C, 70.68; H, 10.64.

The 2,4-dinitrophenyl sulfide[17] of this thiol melted at 126–126.5° after crystallization from alcohol.

Anal. Calcd. for $C_{16}H_{20}O_4N_2S$: N, 8.33. Found: N, 8.33.

Isocamphane from the Desulfurization of 2-Mercaptomethyl-3,3-dimethylbicyclo[2,2,1]heptane.—Following the procedure of Papa, Schwenk and Ginsberg[19] a solution of 20 g. (0.117 mole) of thiol in 500 ml. of 10% aqueous sodium hydroxide and 40 ml. of alcohol was heated and stirred vigorously on a steam-bath for two hours, during which time 40 g. of Raney nickel alloy was added to the solution in small increments. The reaction mixture was heated an additional two hours and the product accumulating in the condenser during this time was washed back into the reaction flask with a little alcohol. The mixture was then steam distilled, and the distillate extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, and then distilled through a 3-plate Vigreux column to yield 3.5 g. (22%) of isocamphane, b.p. 163–164°, m.p. 54–56°. The reported physical constants[20] are b.p. 164.5° and m.p. 65–66° (the expected rearrangement product, camphane, boils at 160–161° and melts at 156–156.5°[20]).

The Addition of Thiolacetic Acid to β-Pinene.—The addition of 25.4 g. (0.33 mole) of freshly distilled thiolacetic acid to 45 g. (0.33 mole) of β-pinene gave 59 g. (84%) of thiolacetate, b.p. 91–92° (0.5 mm.), $n^{25}D$ 1.5090.

Anal. Calcd. for $C_{12}H_{20}OS$: C, 67.87; H, 9.49. Found: C, 68.00; H, 9.44.

Hydrolysis of 53 g. (0.25 mole) of the thiolester gave 40 g. (94%) of thiol, b.p. 124–125° (25 mm.), $n^{25}D$ 1.5100.

Anal. Calcd. for $C_{10}H_{18}S$: C, 70.52; H, 10.65. Found: C, 70.86; H, 10.52.

Neither the thiolacetate nor the thiol showed a band in the 12.5 μ region of the spectra, which indicates the absence of a RR′C=CHR″ type of double bond.

Recrystallization of the 2,4-dinitrophenyl sulfide derivative of the thiol from alcohol gave two different products. The first crop of crystals (compound A) melted at 141–143°, and this melting point was not changed by recrystallization from hexane. The second crop of crystals (compound B) melted at 121–122°, and recrystallization from alcohol did not raise the melting point. A mixture of the derivatives melted at 118–130°.

Anal. Calcd. for $C_{16}H_{20}O_4N_2S$: N, 8.33. Found: N, 8.40 (for A); N, 8.45 (for B).

Addition of Thiolacetic Acid to α-Pinene.—Addition of 22.8 g. (0.3 mole) of freshly distilled thiolacetic acid to 41 g. (0.3 mole) of α-pinene gave 43 g. (70%) of thiolacetate, b.p. 105° (3.2 mm.); Behringer[4c] reported the b.p. to be 135–137° (13 mm.). Hydrolysis of 42 g. of the thiolacetate gave 22 g. (64%) of thiol, b.p. 84° (7 mm.).

Anal. Calcd. for $C_{10}H_{18}S$: S, 70.52; H, 10.65. Found: C, 70.79; H, 11.07.

Crystallization of the 2,4-dinitrophenyl sulfide derivative[17] from alcohol gave two different products. The first crop (compound A′) melted at 154–160°, and recrystallization from hexane gave material melting at 158.5–164°. The second crop (compound B′) melted at 143–145°, and recrystallization from alcohol raised the melting point to 146–148°. A mixture of the two derivatives melted at 138–161°.

Anal. Calcd. for $C_{16}H_{20}O_4N_2S$: N, 8.33. Found: N, 8.40 (for A′); N, 8.53 (for B′).

Exhaustive attempts to purify the derivatives A, B, A′ and B′ were not made. It is probable that some or all might have higher melting points when purified further. A mixture of A (m.p. 141–143°) and B′ (146–148°) melted at 115–130°.

EVANSTON, ILLINOIS

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(19) D. Papa, R. Schwenk and H. F. Ginsberg, *J. Org. Chem.*, **14**, 723 (1949).

(20) J. L. Simonsen and I. N. Owen, "The Terpenes" (second edition), The University Press, Cambridge, England, Vol. 2, 1949, p. 272.

[CONTRIBUTION FROM THE RESEARCH AND BIOLOGICAL LABORATORIES OF AYERST, MCKENNA & HARRISON LIMITED]

New Analeptics. 1-Benzhydryl-2-alkyl-2-thiopseudoureas[1]

BY STANLEY O. WINTHROP, STELLA SYBULSKI, GREGORY GAVIN AND GORDON A. GRANT

RECEIVED JANUARY 30, 1957

The synthesis of a series of S-alkylated benzhydrylthioureas is reported. The lower members have shown analeptic properties.

During a search for new spasmolytic agents, 1-benzhydryl-2-methyl-2-thiopseudourea hydroiodide (I) was prepared. When tested in animals this compound showed an interesting central stim-

(1) This paper was presented before the Division of Medicinal Chemistry, American Chemical Society, Miami, Florida, April, 1957.

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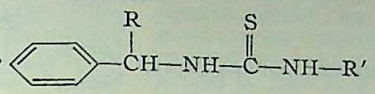
TABLE I

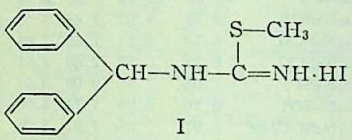
THIOUREAS,[b]



R	R′	M.p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
	H	172–173	99	$C_{14}H_{13}N_2SCl$					10.12	10.07	11.56	11.58
2-ClC_6H_4[c]	H	175–176	46	$C_{14}H_{13}N_2SCl$	60.74	60.89	4.73	4.67				
4-ClC_6H_4[d]	H	178–179	52	$C_{15}H_{16}N_2SO$	66.15	65.97	5.92	5.83			11.77	12.03
4-$CH_3OC_6H_4$[d]	CH_2CH_2OH	130–131	43	$C_{16}H_{18}N_2SO$	67.10	67.18	6.33	6.24	9.80	9.88	11.17	11.11
C_6H_5[c]	$CH_2CH_2N(C_2H_5)_2$	109–110	77	$C_{20}H_{27}N_3S$	70.34	70.52	7.97	7.94	12.30	12.01	9.39	9.57

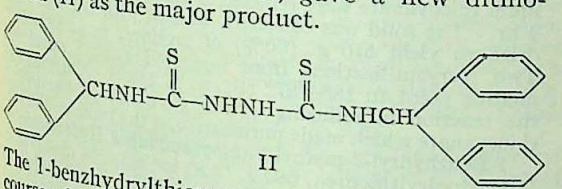
[a] Hydrochloride melts at 128–130°. Calcd. for $C_{20}H_{25}N_3SCl$: N, 11.12; S, 8.48; Cl, 9.39. Found: N, 11.22; S, 8.62; Cl, 9.02. [b] Other miscellaneous thioureas are included in the Experimental section of this paper. [c] Prepared from the appropriate benzhydryl isothiocyanate and amine. [d] Prepared from the appropriate benzhydrylamine hydrochloride and ammonium thiocyanate.

ulant activity. It appeared desirable therefore to prepare other compounds structurally related to I for pharmacological screening.



I

Schroeder[2] has described several methods for the preparation of thioureas. 1-Benzhydrylthiourea had previously been synthesized from benzhydryl isothiocyanate and ammonia.[3,4] It was found that 1-benzhydrylthioureas can also be conveniently prepared by fusing the benzhydrylamine hydrochloride and ammonium thiocyanate in the presence of an inert solvent. When benzhydryl isothiocyanate was allowed to react with a fivefold excess of hydrazine, a good yield of 4-benzhydrylthiosemicarbazide resulted. Equivalent amounts of these reactants, however, gave a new dithiobiurea (II) as the major product.



II

The 1-benzhydrylthioureas synthesized during the course of this investigation and not reported previously are listed in Table I. Other new miscellaneous thioureas are included in the Experimental section of this paper.

The thiopseudourea salts were prepared for the most part by refluxing an ethanol solution of the appropriate 1-benzhydrylthiourea and an alkyl halide. In the case of halides such as ethyl α-chloroacetate, α-chloroacetamide, α-chloroacetaldehyde and α-chloroacetone we were unable to isolate any thiopseudourea salt since these compounds so readily cyclized to thiazolidines. The cyclized compounds will be the subject of a later paper. When α-bromoacetic acid and 1-benzhydrylthiourea were brought together in an acetone–ether solution at room temperature, the desired thiopseudourea salt resulted. The same reactants gave a thiazolidine in ethanol. The thiopseudourea salts were stable, crystalline, high melting solids.

A thiopseudourea resulted when an aqueous methanolic solution of the thiopseudourea salt was treated with sodium carbonate. The 1-benzhydryl-2-alkyl-2-thiopseudoureas were easily isolated since they were considerably less soluble than their respective salts. In general, the thiopseudoureas were stable compounds. When 1-benzhydryl-2,3,3-trimethyl-2-thiopseudourea hydroiodide was treated with sodium carbonate in the usual manner for the preparation of a thiopseudourea, however, an appreciable amount of 1-benzhydryl-3,3-dimethylurea was obtained as a by-product. The characteristic odor of methyl mercaptan also was present.

Since the 1-benzhydryl-2-alkyl-2-thiopseudoureas appeared to be stable, it was of interest to investigate whether these compounds could be alkylated in the usual manner. There was also a question as to which of the two dissimilar nitrogens would be involved in the reaction. An acetone solution of 1-benzhydryl-2-methyl-2-thiopseudourea and methyl iodide was refluxed for 4 hr. Potassium carbonate was included to serve as the acid acceptor. The resulting product gave a hydroiodide which after purification was identical with 1-benzhydryl-2,3-dimethyl-2-thiopseudourea hydroiodide. This latter compound was prepared in an unambiguous manner from benzhydryl isothiocyanate by way of 1-benzhydryl-3-methyl-2-thiourea.

Pharmacological Acitivity.—Several of the 1-benzhydryl-2-alkyl-2-thiopseudourea salts were found to have central stimulant activity. The compounds were administered to rats and the degree of the stimulation recorded in activity cages.[5] The most active compound was the 1-benzhydryl-2-methyl-2-thiopseudourea hydroiodide. This activity decreased gradually with increasing size of the sulfur substituent. Substitution of a hydrogen atom from either nitrogen by a methyl group caused the activity to drop to about a tenth of its original level. Compounds with substituents on one of the phenyl rings had little or no activity. The other thiopseudourea salts were inactive when screened by this method.

This type of activity is not entirely unexpected in view of the report of some respiratory stimulation by 2-alkyl-2-thiopseudourea salts.[6] These ap-

(2) D. C. Schroeder, *Chem. Revs.*, **55**, 181 (1955).
(3) H. L. Wheeler, *Am. Chem. J.*, **26**, 353 (1901).
(4) I. A. Kaye, I. C. Kogon and C. L. Parris, THIS JOURNAL, **74**, 500 (1952).

(5) C. Chappel, G. A. Grant, S. Archibald and R. Paquette, to be published.
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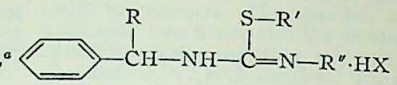
TABLE II

2-ALKYL-2-THIOPSEUDOUREA SALTS,[a]



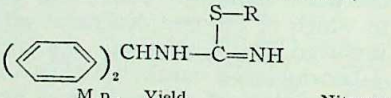
R	R	R″	X	Yield, %	M.p., °C.	Formula	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found	Halogen Calcd.	Halogen Found
C_6H_5	CH_3	H	I	92	178–180	$C_{15}H_{17}N_2SI$	7.29	7.17	8.33	8.39	33.07	33.13
C_6H_5	CH_2CH_3	H	I	73	145–147	$C_{16}H_{19}N_2SI$	7.04	7.04	8.05	8.17	31.88	32.38
C_6H_5	$CH_2CH_2CH_3$	H	I	74	150–151	$C_{17}H_{21}N_2SI$	6.79	6.86	7.78	8.21	30.81	30.79
C_6H_5	$CH(CH_3)_2$	H	I	63	185–186	$C_{17}H_{21}N_2SI$	6.79	6.77	7.78	7.95	30.81	30.68
C_6H_5	$CH_2CH_2CH_2CH_3$	H	I	75	160–161	$C_{18}H_{23}N_2SI$	6.57	6.67	7.52	7.78	29.74	29.67
C_6H_5	$CH_2C_6H_5$	H	Cl	77	168–172	$C_{21}H_{21}NSCl$	7.59	7.36	8.68	8.89	9.62	9.56
C_6H_5	CH_2CH_2OH	H	Br	71	179–182	$C_{16}H_{19}N_2SOBr$	7.63	7.63	8.73	8.78	21.76	21.88
C_6H_5	$CH_2CH_2CH_2OH$	H	Br	76	129–131	$C_{17}H_{21}N_2SOBr$	7.36	7.57	8.39	8.53		
C_6H_5	$CH_2CH_2OCH_2CH_3$	H	I	95	121–123	$C_{18}H_{23}N_2SOI$	6.33	6.48	7.25	7.36	28.69	28.10
C_6H_5	CH_2COOH	H	Br	97	162–163	$C_{16}H_{17}N_2SO_3Br$	7.36	7.32	8.42	8.53		
C_6H_5	$CH_2CH_2N(CH_3)_2$·HI	H	I	10	189–191	$C_{18}H_{23}N_3SI_2$	7.38	7.32	5.62	5.72	44.60	44.40
C_6H_5	$CH_2CH_2N(CH_2CH_3)_2$·HCl	H	Cl	50	176–178	$C_{20}H_{29}N_3SCl_2$	10.14	10.14	7.74	7.88	17.11	17.04
C_6H_5	$CH_2CH_2N(CH(CH_3)_2)_2$·HCl	H	Cl	74	205–208	$C_{22}H_{33}N_3SCl_2$	9.50	9.45	7.25	6.95	16.03	15.65
C_6H_5	CH_3	CH_3	I	97	172–173	$C_{16}H_{19}N_2SI$	7.03	6.98	8.05	8.34	31.86	31.64
C_6H_5	CH_3	CH_2CH_2OH	I	85	174–176	$C_{17}H_{21}N_2SOI$	6.54	6.75	7.48	7.67		
C_6H_5	CH_3	$CH_2CH_2N(C_2H_5)_2$·HCl	Cl	33	172–173	$C_{18}H_{18}N_3SI$	10.52	10.64	8.03	8.10		
2-ClC_6H_4	CH_3	H	I	90	156–157	$C_{21}H_{31}N_3SCl_2$	9.81	9.62	7.48	7.68	16.55	16.55
4-ClC_6H_4	CH_3	H	I	67	165–167	$C_{15}H_{16}N_2SClI$	6.78	6.53	7.65	7.69		
4-$CH_3C_6H_4$	CH_3	H	I	67	134–136	$C_{15}H_{16}N_2SClI$	6.78	6.57	7.65	7.91		
4-$CH_3OC_6H_4$	CH_3	H	I	63	133–134	$C_{16}H_{19}N_2SI$	7.03	7.36	8.06	8.28	31.85	31.81
4-ClC_6H_4	CH_2CH_2OH	H	I	93	152–153	$C_{16}H_{19}N_2SOI$	6.76	6.98	7.74	8.06	30.63	30.57
4-$CH_3C_6H_4$	CH_2CH_2OH	H	Br	68	140–141	$C_{16}H_{18}N_2SOClBr$	6.97	7.08	7.97	8.09		
4-$CH_3OC_6H_4$	CH_2CH_2OH	H	Br	69	108–110	$C_{17}H_{21}N_2SOBr$	7.35	7.33	8.39	8.50	20.90	20.81
H	CH_3	H	Br	60	119–120	$C_{17}H_{21}N_2SO_2Br$	7.05	6.94	8.09	7.67	20.10	20.12
H	CH_3	H	I	81	103–108	$C_9H_{13}N_2SI$	9.09	9.26	10.42	10.30		

[a] Other miscellaneous thiopseudourea salts are included in the Experimental section of this paper.

peared to be predominantly respiratory stimulants, however, which is not the case for the compounds in this present investigation.

TABLE III

1-BENZHYDRYL-2-ALKYL 2-THIOPSEUDOUREAS,



R	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	161–162	85	$C_{15}H_{16}N_2S$[a]	10.95	10.74
$CH_2CH_2CH_3$	75–77	89	$C_{17}H_{20}N_2S$	9.85	9.90
$CH_2CH_2CH_2CH_3$	77–79	98	$C_{18}H_{22}N_2S$	9.38	9.41
$CH_2C_6H_5$	94–97	55	$C_{21}H_{20}N_2S$	8.42	8.30
$CH_2CH_2CH_2OH$	107–108	64	$C_{17}H_{20}N_2SO$	9.33	9.33
$CH_2CH_2N(CH(CH_3)_2)_2$	Oil[b]	60	$C_{22}H_{31}N_3S$	11.37	11.48

[a] Calcd.: C, 70.25; H, 6.28; S, 12.52. Found: C, 70.34; H, 6.33; S, 12.59. [b] This compound could not be induced to crystallize. It was purified by repeated precipitations.

Acknowledgments.—The authors would like to thank Dr. C. I. Chappel of our laboratories for the pharmacological data, Mr. W. J. Turnbull for the analyses and Dr. Gilles Papineau-Couture and Mrs. J. Jachner for numerous infrared spectra.

Experimental[7]

Starting Materials.—*p*-Methylbenzophenone,[8] *p*-methoxybenzophenone,[8] *p*-chlorobenzhydrylamine,[8] benzhydrylamine,[8] benzhydryl chloride,[8] α,α-diphenylacetonitrile[9] and *o*-chlorobenzaldehyde[9] were available from commercial sources. The following were prepared but had been previously described in the literature: *o*-chlorobenzhydrol,[10] m.p. 64–66° (lit. m.p. 56–66°), *o*-chlorobenzhydryl chloride,[11] b.p. 150–155° at 2 mm., $n^{24}D$ 1.6020 (lit. b.p. 142–145° at 1.5 mm., $n^{21.5}D$ 1.6028); benzhydrylmethylamine hydrochloride,[11] m.p. 245–246° (lit. m.p. 238°); β,β-diphenylethylamine hydrochloride,[12] m.p. 256–257° (lit. m.p. 256°) *p*-methylbenzhydrylamine hydrochloride,[13] m.p. 256–260° (lit. m.p. 250°); *p*-methoxybenzhydrylamine hydrochloride,[14] m.p. 203° dec. (lit. m.p. 190° dec.); 1-benzylthiourea,[15] m.p. 160–162° (lit. m.p. 161–162°); 1-*p*-methylbenzhydrylthiourea,[16] m.p. 165–167° (lit. m.p. 162–163°); 1-benzhydryl-3-methyl-2-thiourea,[2] m.p. 156–157° (lit. m.p. 152–153°).

1-Benzhydrylthiourea.[3,4]—Benzhydrylamine hydrochloride, 780 g. (3.56 moles) and 300 g. (3.9 moles) of ammonium thiocyanate were refluxed in three liters of toluene for 4 hr. The solid was collected, washed with hot water and dried to yield 510 g. (60%) of product, m.p. 182–183°. Two recrystallizations from isopropyl alcohol raised the melting point to 186–187° (lit. m.p. 189°). Carrying out the reaction in refluxing xylene gave rise to benzhydryl thiocyanate which made purification of the product difficult.

1-Benzhydryl-2-methyl-2-thiopseudourea Hydroiodide.—1-Benzhydrylthiourea, 680 g. (2.83 moles), was dissolved in 12 liters of 1:1 acetone–ether, and 600 g. (4.15 moles) of methyl iodide was added. The reaction was considered complete after 1 hr. at room temperature. The solid was collected and dried to yield 800 g. (75%) of product melting at 175–178°. One recrystallization from isopropyl alcohol raised the melting point to 178–180° (see Table II).

1-Benzhydryl-2-methyl-2-thiopseudourea Hydrochloride.—1-Benzhydrylthiourea, 400 g. (1.67 moles), was dissolved in 2600 ml. of acetone, and 500 g. (10 moles) of methyl chloride was added. The solution was placed in a one-gallon pressure autoclave and heated at 80° for 16 hr. The product was then collected and dried to yield 376 g. (81%) melting at 192–195° dec. One recrystallization from ethanol-ether gave an analytical sample, m.p. 196–197° dec. This compound was also prepared by the addition of hydrogen chloride to an acetone solution of 1-benzhydryl-2-methyl-2-thiopseudourea. Calcd. for $C_{15}H_{17}N_2SCl$: C, 61.45; H, 5.85; N, 9.57; S, 10.94; Cl, 12.09. Found: C, 61.24; H, 5.65; N, 9.56; S, 10.74; Cl, 11.95.

1-Benzhydryl-2-methyl-2-thiopseudourea Methyl Bisulfate.—1-Benzhydrylthiourea, 12 g. (0.05 mole) and dimethyl sulfate, 3.15 g. (0.025 mole), were refluxed in 100 ml. of methanol for 3 hr. The methanol was then removed

(7) All melting points are uncorrected.
(8) Trubek Laboratories, East Rutherford, N. J.
(9) Eastman White Label.
(10) K. E. Hamlin, A. W. Weston, F. E. Fischer and R. J. Michaels, THIS JOURNAL, 71, 2731 (1949).
(11) E. Busch and F. Leefhelm, *J. prakt. Chem.*, 21, 77, 23 (1858), (1903).
(12) M. Freund and P. Immerwahr, *Ber.*, 23, 2845 (1891).
(13) H. Goldschmidt and H. Stocker, *ibid.*, 24, 2800 (1892).
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(15) A. E. Dixon, *J. Chem. Soc.*, 59, 555 (1865).
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in vacuo leaving an oil residue which crystallized on trituration with ether to yield 11 g. of solid, m.p. 110–118°. Two recrystallizations from isopropyl alcohol raised the melting point to 130–132°. Calcd. for $C_{16}H_{20}N_2S_2O_4$: C, 52.25; H, 5.48; N, 7.89; S, 18.06. Found: C, 52.65; H, 5.65; N, 7.83; S, 17.83.

1-Benzhydryl-2-methyl-2-thiopseudourea.—1-Benzhydryl-2-methyl-2-thiopseudourea hydroiodide, 46 g. (0.12 mole), was dissolved in aqueous methanol, and 10% sodium carbonate solution was added in excess. The thiopseudourea was filtered off, washed with water and recrystallized from benzene to yield 17 g., m.p. 160–161°. A second recrystallization raised the melting point to 161–162° (see Table III).

1-Benzhydryl-2-methyl-2-thiopseudourea Salts.—The following salts were prepared by addition of the appropriate acid to an acetone–ether solution of 1-benzhydryl-2-methyl-2-thiopseudourea: hydrobromide: m.p. 198–199°. Calcd. for $C_{15}H_{17}N_2SBr$: N, 8.31; S, 9.51; Br, 23.70. Found: N, 8.56; S, 9.59; Br, 23.76. Hydrogen sulfate: m.p. 202–203°. Calcd. for $C_{15}H_{18}N_2S_2O_4$: N, 7.91; S, 18.10. Found: N, 7.99; S, 18.35. Acetate: m.p. 144–145°. Calcd. for $C_{17}H_{20}N_2SO_2$: N, 8.86; S, 10.13. Found: N, 9.14; S, 10.32. Maleate: m.p. 164–165°. Calcd. for $C_{19}H_{22}N_2SO_4$: N, 7.48; S, 8.56. Found: N, 7.46; S, 8.80.

1-Benzhydryl-2-carboxymethyl-2-thiopseudourea Hydrobromide.—1-Benzhydrylthiourea, 4.8 g. (0.02 mole) and α-bromoacetic acid, 4.16 g. (0.03 mole), were dissolved in 100 ml. of a 1:1 acetone–ether mixture. On five minutes standing at room temperature, a solid started to separate out of solution. After ten minutes the precipitation appeared complete and the product was filtered off and dried to yield 7.3 g., m.p. 162–163° (see Table II).

1-Benzhydryl-2-(β-diethylaminoethyl)-2-thiopseudourea Dihydrochloride.—1-Benzhydrylthiourea, 8.0 g. (0.033 mole) and β-diethylaminoethyl chloride hydrochloride, 5.7 g. (0.033 mole) were refluxed in 150 ml. of isopropyl alcohol for 48 hr. The isopropyl alcohol was then removed *in vacuo* and the residue crystallized from an isopropyl alcohol–ether mixture to yield 6.9 g. of product, m.p. 164.5–165.6°. Three recrystallizations from a mixture of isopropyl alcohol and ether raised the melting point to 176–178° (see Table II).

o-Chlorobenzlhydryl Isothiocyanate.—*o*-Chlorobenzhydryl chloride, 92.5 g. (0.39 mole), and ammonium thiocyanate, 30 g. (0.39 mole), were refluxed in 75 ml. of benzene for five days. The solid material remaining was then collected and the benzene filtrate evaporated down *in vacuo* leaving a high boiling liquid residue. Vacuum distillation gave 46 g. (46%) of product boiling from 186–189° at 1.5 mm. Calcd. for $C_{14}H_{10}NSCl$: N, 5.39. Found: N, 5.60.

1-(o-Chlorobenzhydryl)-thiourea.—*o*-Chlorobenzhydryl isothiocyanate, 26 g. (0.1 mole), was dissolved in 500 ml. of an ethanol solution containing 37 ml. of concentrated ammonium hydroxide. The solution was brought to boiling and then allowed to stand at room temperature for 16 hr. Sufficient water was then added to ensure complete precipitation of the product which was collected, washed and dried to give a quantitative yield, 28 g. of crude product, m.p. 166–167°. Two recrystallizations from isopropyl alcohol raised the melting point to 172–173° (see Table I).

1,6-Dibenzhydryl-2,4-dithiobiurea.—Benzhydryl isothiocyanate, 34 g. (0.15 mole), was dissolved in 500 ml. of ethanol and 7.4 ml. of 85% aqueous hydrazine (0.20 mole) was added. An immediate reaction took place. The reaction was considered complete after 30 minutes. The ethanol was then removed *in vacuo* and the oil residue triturated with a little methanol to yield 22 g. of solid with m.p. 168–172°. Four recrystallizations from acetonitrile raised the melting point to 194–195° dec. Calcd. for $C_{28}H_{28}N_4S_2$: C, 69.75; H, 5.43; S, 13.28. Found: C, 69.55; H, 5.49; S, 13.14.

4-Benzhydrylthiosemicarbazide.[17]—The above procedure was repeated using a fivefold excess of hydrazine in order to increase the yield of product by keeping the formation of the dithiobiurea to a minimum. A solid came out of solution and was collected and dried to yield 32.3 g. (70%) of product, m.p. 150–152° dec. One recrystallization from acetonitrile did not raise the melting point (lit. m.p. 144°).

1-Benzhydryl-3,3-dimethyl-2-thiourea.—Benzhydryl isothiocyanate, 34 g. (0.15 mole), was dissolved in 500 ml. of ethanol, and 9.02 g. (0.2 mole) of dimethylamine (25% aqueous solution) was added. The solution was allowed to stand at room temperature for 70 hr. The ethanol was then removed *in vacuo* and the residue crystallized from isopropyl alcohol to yield 37.5 g. of product, m.p. 131–132°. One recrystallization from ethanol did not raise the melting point. Calcd. for $C_{16}H_{18}N_2S$: C, 71.06; H, 6.71; N, 10.36; S, 11.86. Found: C, 71.42; H, 6.94; N, 10.36; S, 12.11.

1-Benzhydryl-2,3,3-trimethyl-2-thiopseudourea Hydroiodide.—1-Benzhydryl-3,3-dimethyl-2-thiourea, 6.1 g. (0.023 mole), and 4.95 g. (0.035 mole) of methyl iodide were refluxed in 50 ml. of ethanol for 2 hr. On cooling and adding of ether, 8.3 g. of product, m.p. 148–150° dec., precipitated. One recrystallization from isopropyl alcohol did not raise the melting point. Calcd. for $C_{17}H_{21}N_2SI$: N, 6.80; S, 7.77; I, 30.78. Found: N, 6.97; S, 8.09; I, 30.78.

1-Benzhydryl-3,3-dimethyl-2-(α-acetonyl)-2-thiopseudourea Hydrochloride.—1-Benzhydryl-3,3-dimethyl-2-thiourea, 7.11 g. (0.03 mole) and α-chloroacetone, 4.2 g. (0.045 mole), were refluxed in 40 ml. of a 1:1 ether–acetone mixture for 2 hr. The acetone–ether was removed *in vacuo* and the residue crystallized from isopropyl alcohol to yield 6.8 g. of product, m.p. 133–144°. Two recrystallizations from an isopropyl–ether mixture followed by two recrystallizations from acetonitrile raised the melting point to 136–137°. Calcd. for $C_{19}H_{23}N_2SOCl$: N, 7.72; S, 8.84; Cl, 9.78. Found: N, 7.50; S, 8.78; Cl, 9.89.

1-Benzhydryl-2,3,3-trimethyl-2-thiopseudourea.—1-Benzhydryl-2,3,3-trimethyl-2-thiopseudourea hydroiodide, 21 g. (0.015 mole), was dissolved in 75 ml. of methanol, and 2.8 g. (0.052 mole) of sodium methoxide was added portionwise with cooling. On removal of about one-third of the methanol *in vacuo* at room temperature, a solid separated out, was filtered off and dried to yield 9 g. of product, m.p. 55–57°. An attempt at purification by recrystallizing from ethanol resulted in a poor recovery of material melting from 50 to 55° and the production of some methyl mercaptan whose presence was noticed by its characteristic odor. Calcd. for $C_{17}H_{20}N_2S$: C, 71.78; H, 7.08; N, 9.84; S, 11.30. Found: C, 72.19; H, 6.78; N, 9.92; S, 11.03.

On evaporating down the original methanol filtrate, additional 3.5 g. of material melting at 185–186° resulted. Two recrystallizations from ethanol raised the melting point to 194–195°. The infrared spectrum and analytical data indicated this compound was 1-benzhydryl-3,3-dimethylurea. Calcd. for $C_{16}H_{18}N_2O$: C, 75.50; H, 7.13; N, 11.02. Found: C, 76.15; H, 7.27; N, 11.05.

1-Benzhydryl-1-methyl-2-thiourea.—Benzhydrylmethylamine hydrochloride, 10 g. (0.043 mole), and ammonium thiocyanate, 3.6 g. (0.017 mole), were added to 100 ml. of xylene, and the reaction mixture was stirred and heated at 135° for 3 hr. On cooling, the solid material was collected, washed with hot water and dried to yield 3.1 g. of product, m.p. 186–189°. One recrystallization from isopropyl alcohol raised the melting point to 193–195°. Calcd. for $C_{15}H_{16}N_2S$: N, 10.92; S, 12.50. Found: N, 10.97; S, 12.42. The xylene filtrate was evaporated down to yield 5.6 g. of solid melting at 120–130° whose infrared spectrum suggested the benzhydrylmethylamine hydrothiocyanate salt.

1-Benzhydryl-1,2-dimethyl-2-thiopseudourea Hydroiodide.—The compound was prepared in the usual manner. It was recrystallized from an isopropyl alcohol-ether mixture to give an analytical sample melting at 175–176° dec. Calcd. for $C_{16}H_{19}N_2SI$: N, 7.03; S, 8.05; I, 31.86. Found: N, 6.81; S, 8.17; I, 31.92.

1-(β,β-Diphenylethyl)-thiourea.—β,β-Diphenylethylamine hydrochloride, 18.5 g. (0.079 mole), and ammonium thiocyanate, 6.7 g. (0.087 mole), were added to 350 ml. of xylene and stirred and heated at 135° for 6 hr. The xylene was then evaporated down *in vacuo* and the solid residue triturated with hot water, filtered and dried to yield 19.7 g. of product, m.p. 198–200°. One recrystallization from ethanol raised the melting point to 203–204°. Calcd. for $C_{15}H_{16}N_2S$: C, 70.30; H, 6.28; N, 10.92; S, 12.50. Found: C, 70.53; H, 6.42; N, 11.11; S, 12.65.

1-(β,β-Diphenylethyl)-2-methyl-2-thiopseudourea Hydroiodide.—The compound was prepared in the usual manner. Two recrystallizations from an isopropyl alcohol–ether mixture gave an analytical sample melting at 139–141°. Calcd. for $C_{16}H_{19}N_2SI$: N, 7.03; S, 8.05; I, 31.86. Found: N, 6.71; S, 8.06; I, 32.12.

(17) L. Braun and H. Deutch, *Ber.*, **45**, 2196 (1913).

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Alkylation of 1-Benzhydryl-2-methyl-2-thiopseudourea.—1-Benzhydryl-2-methyl-2-thiopseudourea, 7.68 g. (0.03 mole), and methyl iodide, 6.4 g. (0.045 mole), were refluxed in 100 ml. of acetone with 2 g. (0.015 mole) of potassium carbonate for 4 hr. Some inorganic material was filtered off and the acetone filtrate was evaporated down *in vacuo* at room temperature to leave a thick oil residue. The residue was taken up in chloroform and the chloroform solution filtered to remove more inorganic solids. The chloroform was then evaporated down *in vacuo* at room temperature and the residue taken up in a little isopropyl alcohol. Upon addition of dilute hydriodic acid to the isopropyl alcohol solution, 4.0 g. of a solid hydroiodide salt, m.p. 162–164°, precipitated. Two recrystallizations from an isopropyl alcohol–ether mixture gave a product, m.p. 173–174°, which was identical in every way with 1-benzhydryl-2,3-dimethyl-2-thiopseudourea hydroiodide.

MONTREAL, CANADA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

Reactions with Mercaptans. IV. Reaction of Aromatic Thiols with 3(2H)-Thianaphthenone-1,1-dioxides and 2-Benzylidene-3(2H)-thianaphthenone-1-1-dioxide

BY AHMED MUSTAFA AND SALAH MOHAMED ABDEL DAYEM ZAYED

RECEIVED NOVEMBER 19, 1956

The condensation reaction of 3(2*H*)-thianaphthenone-1,1-dioxides (I) with aromatic aldehydes has been investigated, *e.g.*, 3(2*H*)-thianaphthenone-1,1-dioxide condenses with benzaldehyde to give 2-benzylidene-3(2*H*)-thianaphthenone-1,1-dioxide (IIa). The latter undergoes an addition reaction with thiophenol, yielding the thiol adduct believed to have structure VI. Aromatic thiols react with 3(2*H*)-thianaphthenone-1,1-dioxides, in the presence of anhydrous zinc chloride and hydrogen chloride, to yield the corresponding unsaturated sulfides VII which are readily oxidized to the sulfone derivatives VIII.

Aldehyde condensation products of 3(2*H*)-thianaphthenone-1,1-dioxide (Ia) have not previously been prepared, although Ia has been known since 1912.[1] Weston and Suter[2] were unable to condense benzaldehyde with Ia in an alkaline medium.

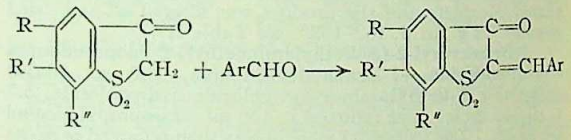
We obtained well-defined crystalline products by the reaction of benzaldehyde with Ia and by that of *p*-nitrobenzaldehyde with 7-methyl-3(2*H*)-thianaphthenone-1,1-dioxide (Id). The analytical data indicate that one molecule of aldehyde condenses with one molecule of the thianaphthenone-1,1-dioxide with the elimination of one molecule of water.

The structural assignments for these products are based on their participation in known reactions. When 2-benzylidene-3(2*H*)-thianaphthenone-1,1-dioxide (IIa) was treated with hydroxylamine hydrochloride, the corresponding oxime of 3(2*H*)-thianaphthenone-1,1-dioxide (IIIa)[3] was obtained.[4] The treatment of IIa with phenylhydrazine gave the hydrazone of 3(2*H*)-thianaphthenone-1,1-dioxide (IIIb).[5]

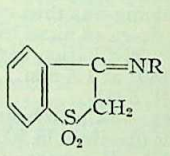
2-Benzylidene-3(2*H*)-thianaphthenone reacted with phenylhydrazine to give [10*H*]-thianaphtheno-[3,2-*b*]-indole (IV), *via* the Fischer indole ring closure of the resulting phenylhydrazone of 3(2*H*)-thianaphthenone.[5,6]

We have also studied the addition, *e.g.*, of benzenethiol, to the double bond at position 2 which is conjugated with the unsaturated group in 2-arylidene-3(2*H*)-thianaphthenone-1,1-dioxides.

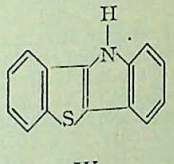
IIa, like the 2-arylideneindan-1,3-diones,[7] undergoes addition reaction with thiophenol in absence of a catalyst to give a colorless adduct which can be represented by V or VI.



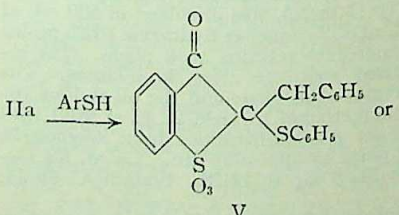
Ia, R = R′ = H
b, R = CH_3; R′ = R″ = H
c, R′ = CH_3; R = R″ = H
d, R″ = CH_3; R = R′ = H
e, R″ = Cl; R = R′ = H
IIa, R = R′ = R″ = H; Ar = C_6H_5
b, R = R′ = H, R″ = CH_3; Ar = $C_6H_4NO_2$-*p*



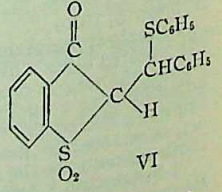
IIIa, R = OH
b, R = NHC_6H_5



IV



V



VI

In view of the well-established mechanism for the addition of thiols to analogous α,β-unsaturated

(1) M. Lanfry, *Compt. rend.*, **154**, 519 (1912).
(2) A. W. Weston and C. M. Suter, THIS JOURNAL, **61**, 389 (1939).
(3) D. H. Hartough, "Compounds with Condensed Thiophene Rings," Interscience Publishers, Inc., New York, N. Y., 1954, p. 166.
(4) This reaction is similar to that of hydroxylamine hydrochloride with 2-benzylideneindan-1,3-dione; *cf.* A. Mustafa and A. H. E. Harhash, THIS JOURNAL, **78**, 1649 (1956).
(5) E. W. McClelland and J. L. D'Silva, *J. Chem. Soc.*, 227 (1932).
(6) C. E. Dagliesh and F. G. Mann, *ibid.*, 653 (1947).
(7) A. Mustafa, *ibid.*, 1370 (1951).

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compounds,[8] structure VI is preferable. The fact that the adduct dissolves in cold aqueous sodium hydroxide solution with a yellow color and is liberated upon neutralization with ice-cold, dilute hydrochloric acid is also in accord with structure VI. When VI was heated above its melting point for a few minutes and then cooled, the styryl derivative IIa was regenerated. The ease of removal of the addend indicates that the substance is the result of simple addition and that no unexpected reaction has occurred. Attempts to oxidize VI with hydrogen peroxide in glacial acetic acid over a water-bath also led to the formation of IIa.[9]

Reaction of Aromatic Thiols with 3(2*H*)-Thianaphthenone-1,1-dioxides (I).—It is generally accepted that a ketone and a thiol react in the presence of an acid catalyst to form a mercaptal,[10] although scattered reports in the literature indicate that certain cyclic ketones, *e.g.*, 4-cholesten-3-one[11] and other ketosteroids,[12] yield unsaturated sulfides (enol thioethers).

Recently,[13] it was observed that 2-methyl-1-indanone and 2-methyl-1-tetralone react with thiophenol, under the conditions of the mercaptal reaction, to produce phenyl-2-methyl-3-indenyl sulfide and phenyl-2-methyl-3,4-dihydro-1-naphthyl sulfide, respectively.

We have investigated the reaction of aromatic thiols with 3(2*H*)-thianaphthenone-1,1-dioxides (I) in the presence of anhydrous zinc chloride and hydrogen chloride and have obtained colorless products, believed to have structure VII. Under these experimental conditions, 2-methyl-3(2*H*)-thianaphthenone-1,1-dioxide (IX) did not react with thiols.

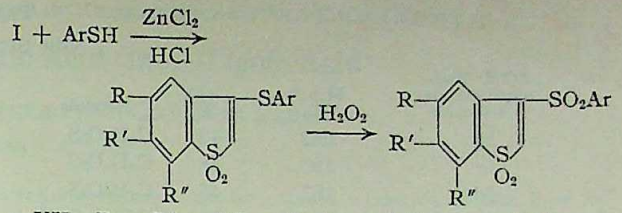
Desoxybenzoin[14] is known to form an unsaturated sulfide when treated with thiophenol. By analogy, a similar mechanism may be presented for the formation of VII, involving the addition of one mole of thiol to form a hemimercaptal followed by elimination of water to give the unsaturated sulfide VII.

The unsaturated sulfides VII, listed in Table II, are oxidized readily by hydrogen peroxide in glacial acetic acid to give the corresponding sulfones,[12] listed in Table III.

When VIIa was treated with aqueous sodium hydroxide and zinc dust, 2,3-dihydrothianaphthene-1,1-dioxide and thiophenol were obtained.[15]

Experimental

3(2*H*)-Thianaphthenone-1,1-dioxides.—The new 3(2*H*)-



VIIa, R = R′ = R″ = H; Ar = C_6H_5 VIII
b, R = CH_3; R′ = R″ = H; Ar = C_6H_5
c, R = CH_3; R′ = R″ = H; Ar = $C_6H_4CH_3$-*p*
d, R″ = CH_3; R = R′ = H; Ar = C_6H_5
e, R″ = CH_3; R = R′ = H; Ar = $C_6H_4CH_3$-*p*
f, R″ = Cl; R = R′ = H; Ar = C_6H_5
g, R″ = Cl; R = R′ = H; Ar = $C_6H_4CH_3$-*p*

thianaphthenone-1,1-dioxides listed in Table I were prepared from the corresponding 3(2*H*)-thianaphthenones which were obtained by known procedures.[16] A solution of 5 g. of the thianaphthenone in 30 ml. of glacial acetic acid was treated with 25 ml. of 30% hydrogen peroxide, and the reaction mixture was heated (steam-bath) for 1 hr., with the exception of 6-methyl- and 7-methyl-3(2*H*)-thianaphthenone, whereby oxidation was complete in 5 minutes. The reaction products, which separated on cooling, were crystallized from a suitable solvent as colorless crystals; they gave no color with concentrated sulfuric acid and a yellow color in alcoholic sodium hydroxide.

Condensation of: (a) 3(2*H*)-Thianaphthenone-1,1-dioxide (Ia) with Benzaldehyde.—A mixture of 1 g. of Ia[17] and 2 ml. of benzaldehyde was heated for 3 hr. over an oil-bath (140° temperature of bath). The reaction mixture was cooled to room temperature and triturated with 5 ml. of cold ethyl alcohol. The resulting pale yellow solid was crystallized from alcohol; m.p. 148° (yellow melt).

Anal. Calcd. for $C_{15}H_{10}O_3S$: C, 66.66; H, 3.70; S, 11.85. Found: C, 66.32; H, 3.61; S, 11.56.

This 2-benzylidene derivative IIa was soluble in benzene but difficultly soluble in ether, cold alcohol and acetic acid. It developed a yellow color in concentrated sulfuric acid.

A solution of 0.5 g. of IIa in 20 ml. of glacial acetic acid was treated with 2 g. of sodium acetate and 0.5 g. of hydroxylamine hydrochloride. The reaction mixture was refluxed for 3 hr., cooled and then poured into ice-cold water. The resulting substance was crystallized from dilute acetic acid (m.p. 245°) and identified as the oxime of 3(2*H*)-thianaphthenone-1,1-dioxide (IIIa)[3] by a mixed m.p. determination with a sample of IIIa, obtained by the reaction of hydroxylamine hydrochloride with Ia under similar experimental conditions.

(b) 7-Methyl-3(2*H*)-thianaphthenone-1,1-dioxide (Id) with *p*-Nitrobenzaldehyde.—A mixture of 1 g. of Id and 1 g. of the aldehyde was heated at 160° for 2 hr. The solid residue obtained after cooling was washed thoroughly with hot benzene and then crystallized from nitrobenzene as yellow crystals (IIb), m.p. 265°. IIb was difficultly soluble in most organic solvents and gave an orange solution in concentrated sulfuric acid.

Anal. Calcd. for $C_{16}H_{11}NO_5S$: C, 58.36; H, 3.34; N, 4.26; S, 9.72. Found: C, 57.97; H, 3.31; N, 4.03; S, 9.39.

Reaction of Thiophenol on IIa.—One g. of IIa was mixed with a slight excess over the calculated amount of the thiol in a test-tube, and the reaction mixture was heated at 100° for 3 hr. The cooled reaction mixture was triturated with boiling light petroleum (b.p. 30–50°, 50 ml.) when the oily reaction product turned into solid powder. It was filtered, washed with hot light petroleum and crystallized from benzene; m.p. 138°, yield *ca.* 88%.

Anal. Calcd. for $C_{21}H_{16}O_3S_2$: C, 66.31; H, 4.21; S, 16.84. Found: C, 66.77; H, 4.50; S, 16.49.

The thiol adduct formed colorless crystals, dissolved readily in hot benzene but was difficultly soluble in cold

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(10) E. Baumann, *Ber.*, **18**, 883 (1885).

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(13) E. Campaigne and R. D. Moss, *ibid.*, **76**, 1269 (1954).

(14) E. Campaigne and J. R. Leal, *ibid.*, **76**, 1272 (1954).

(15) *Cf.* the reduction of thianaphthene-1,1-dioxide by zinc dust and aqueous sodium hydroxide to yield 2,3-dihydrothianaphthene-1,1-dioxide; F. Challenger and P. H. Clapham, *J. Chem. Soc.*, 1615 (1948).

(16) 5-Methyl-: D. S. Tarbell, D. K. Fukushima and H. Dam, THIS JOURNAL, **67**, 1643 (1945); 6-methyl-: A. Mustafa and S. M. A. D. Zayed, *ibid.*, **78**, 6174 (1956); 7-methyl- and 7-chloro-: C. E. Dalgliesh and F. G. Mann, *J. Chem. Soc.*, 893 (1945); and 2-methyl-3(2*H*)-thianaphthenone: C. Hansch and W. A. Blondon, THIS JOURNAL, **70**, 1561 (1948).

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TABLE I

NEW SULFONES (I)

3(2*H*)-Thianaphthenone-1,1-dioxide	M.p.,[a] °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
Ib	202	42	$C_9H_8O_3S$	55.10	54.83	4.08	3.99	16.32	15.81
Ic	190	48	$C_9H_8O_3S$	55.10	55.30	4.08	4.02	16.32	16.01
Id	187	45	$C_9H_8O_3S$	55.10	54.73	4.08	4.09	16.32	15.88
Ie	227	56	$C_8H_5O_3SCl$[b]	44.34	43.82	2.31	2.31	14.78	15.06
IX[c]	Above 360	54	$C_9H_8O_3S$	55.10	54.92	4.08	4.01	16.32	16.03

[a] Melting points are uncorrected. [b] Calcd., Cl, 16.39; found, 16.01. [c] 2-Methyl-3(2*H*)-thianaphthenone-1,1-dioxide.

TABLE II

3-ARYLMERCAPTOTHIANAPHTHENE-1,1-DIOXIDES (VII)

3-Arylmercapto-deriv.	M.p.,[a] °C.	Yield, %	Color with concd. H_2SO_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
VIIa	128	81	Yellow	$C_{14}H_{10}O_2S_2$	61.31	61.01	3.65	3.57	23.36	23.12
VIIb	126	79	Orange	$C_{15}H_{12}O_2S_2$	62.50	62.39	4.16	4.00	22.22	21.98
VIIc	144	72	Deep red	$C_{16}H_{14}O_2S_2$	63.57	63.21	4.63	4.53	21.19	20.96
VIId	122	74	Yellow	$C_{15}H_{12}O_2S_2$	62.50	62.43	4.16	4.43	22.22	21.74
VIIe	124	71	Orange	$C_{16}H_{14}O_2S_2$	63.77	63.77	4.63	4.93	21.19	21.24
VIIf	134	82	Yellow	$C_{14}H_9O_2S_2Cl$[b]	54.46	53.91	2.91	3.16	20.74	20.25
VIIg	142	76	Orange	$C_{15}H_{11}O_2S_2Cl$[c]	55.81	55.47	3.41	3.31	19.84	19.43

[a] All melting points are uncorrected. [b] Calcd., Cl, 11.51; found, 10.95. [c] Calcd., Cl, 11.01; found, 10.82.

TABLE III

OXIDATION PRODUCTS OF 3-ARYLMERCAPTOTHIANAPHTHENE-1,1-DIOXIDE (VIII)

Oxidation products	M.p.,[a] °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
VIIIa	155	77	$C_{14}H_{16}O_4S_2$	54.90	54.63	3.27	3.12	20.91	20.28
VIIIb	184	68	$C_{16}H_{12}O_4S_2$	56.25	55.99	3.75	3.63	20.00	20.10
VIIIc	190	66	$C_{16}H_{14}O_4S_2$	57.48	17.09	4.19	4.00	19.16	19.76
VIIId	130	81	$C_{15}H_{12}O_4S_2$	56.25	55.98	3.75	3.66	20.00	19.67
VIIIe	158	78	$C_{16}H_{14}O_4S_2$	57.48	57.09	4.19	4.15	19.16	18.87
VIIIf	285	83	$C_{14}H_9O_4S_2Cl$[b]	49.34	48.97	2.64	2.54	18.79	17.97
VIIIg	210	75	$C_{15}H_{11}O_4S_2Cl$[c]	50.77	50.08	3.10	2.87	18.05	17.67

[a] All melting points are uncorrected. [b] Calcd., Cl, 10.42; found, 11.10. [c] Calcd., Cl, 10.01; found, 9.88.

ether, ethyl alcohol and acetic acid. It dissolved in aqueous sodium hydroxide (10%) with yellow color and gave an orange yellow solution in cold concentrated sulfuric acid.

Action of Heat on the Thiol Adduct VIII.—Two tenths g. of VIII was heated in a dry test-tube at 140° for 20 minutes (bath-temp.). The adduct melted and then turned into a somewhat solid substance. The cooled reaction mixture was crystallized from ethyl alcohol; m.p. 148° (identified as IIa, m.p. and mixed m.p.).

Reaction of Aromatic Thiols with 3(2*H*)-Thianaphthenone-1,1-dioxides. General Procedure.—To a solution of one gram of the sulfone derivative in the least amount of cold acetic acid, 1 g. of the thiol and 5 g. of powdered anhydrous zinc chloride are added. The reaction mixture was saturated with dry hydrogen chloride gas for 4 to 5 hr., stoppered and kept aside overnight at room temperature. It was poured into three times its volume of ice-cold water and extracted with benzene. The benzene layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The oily residue was treated with cold petroleum ether (b.p. 40–60°, *ca.* 60 ml.). The resulting solid was filtered and crystallized from a suitable solvent.

The 3-arylmercapto derivatives VII, listed in Table II, formed colorless crystals which were readily soluble in cold benzene and chloroform but sparingly soluble in alcohol, acetic acid and ether. When treated with concentrated sulfuric acid, they gave yellow solutions which changed to orange and finally violet on standing for a few minutes. VIIa in acetone solution decolorized potassium permanganate, and in chloroform solution it decolorized bromine dissolved in chloroform.

Oxidation of VII to the Sulfones VIII. General Procedure.—A suspension of 1 g. of the 3-arylmercapto derivative VII in 20 ml. of glacial acetic acid was treated with 4 ml. of 30% hydrogen peroxide and 5 ml. of acetic anhydride. The reaction mixture was heated on a boiling water-bath for 1 hr., cooled, poured into 100 ml. of ice-cold water and kept at room temperature overnight. The resulting solid was collected by filtration, washed with water, dried and crystallized from a suitable solvent.

The oxidation products VIII, listed in Table III, formed colorless crystals and gave no color when treated with cold sulfuric acid; they dissolved readily in glacial acetic but were sparingly soluble in ether and cold ethyl alcohol.

Reduction of 3-Phenylmercaptothianaphthene-1,1-dioxide (VII).—VIIa (0.7 g.) was treated with 50 ml. of aqueous sodium hydroxide (8%) and 10 g. of zinc dust according to the procedure described by Challenger.[15] The reaction mixture was refluxed for 2 hr., during which the solid VIIa changed into an oil. The cooled reaction mixture was diluted with water and extracted with benzene. After the benzene extract had been dried and evaporated, it was treated with cold petroleum ether (b.p. 40–60°, *ca.* 50 ml.) and the resulting solid crystallized from petroleum ether (b.p. 80–100°) as colorless crystals, m.p. 91°, which were identified as 2,3-dihydrothianaphthene-1,1-dioxide by mixed melting point determination.[16] The aqueous alkaline reaction mixture gave, on acidification, an oil which was proved to be thiophenol (m.p. and mixed m.p. determination with an authentic sample of phenyl thiobenzoate).

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[Contribution from the Research Laboratories of Farmochimica Cutolo-Calosi S.p.A.]

A New Synthesis of 6-Thioctic Acid (DL-α-Lipoic Acid)

By Augusto Segre, René Viterbo and Giovanni Parisi

Received January 16, 1957

6-Thioctic acid has been synthesized starting from 2-acetoxyethylcyclohexanone by peracid oxidation to the 1 → 6-lactone of 6-hydroxy-8-acetoxyoctanoic acid and reaction, with thiourea and a strong mineral acid, of this lactone, followed by alkaline hydrolysis of the isothiuronium salt and oxidation of the dithiol-acid thus formed. A preparation of 2-acetoxyethylcyclohexanone, starting from cyclohexanone, is also described.

The importance of 6-thioctic acid (VII) in biochemical processes is well known.[1] Thus its clinical application in the therapy of liver diseases[2] and its antitoxic activity combined with its low toxicity[3] have promoted many syntheses.[1,4] The synthetic method of preparation described in the present paper has the characteristics of starting from easily available raw materials, of using inexpensive reagents in simple reactions and of obtaining comparatively high yields.

The first object of a synthesis of 6-thioctic acid (VII) is to obtain a carboxylic acid with a normal chain of eight carbon atoms, with substituents at C_6 and C_8 suitable for the introduction of two thiol groups. The 1→6-lactone of 6-hydroxy-8-acetoxyoctanoic acid (V) is, in this sense, the required substance. Its preparation is a clear case for the application of the well known Baeyer–Villiger peracid ketone oxidation.[5] Indeed we have obtained the lactone V by peracetic acid oxidation of 2-acetoxyethylcyclohexanone (IVb).

The preparation of 2-hydroxyethylcyclohexanone (IVa) is already described,[6] but without mention of details and physical constants. We succeeded in the preparation of its acetate IVb by the following procedure.

Ethyl cyclohexanone-2-acetate (I) was obtained from cyclohexanone-pyrrolidine enamine and ethyl monobromoacetate by the method of Stork, *et al.*[7]; details of this preparation, not described so far, can be found in the Experimental part of this paper. Treatment of the keto-ester I with ethylene glycol yielded the ethylene ketal II. Both compounds I and II gave, as expected, the same 2,4-dinitrophenylhydrazone. The infrared spectrum of II showed presence of ketal[8] and ester bands, but absence of keto-carbonyl band. The ethylene-ketal II could be reduced either by lithium aluminum hydride in ether or, with similar yields, with sodium in ethanol to the ethylene ketal of 2-hydroxyethylcyclohexanone (IIIa). This compound gave a 2,4-dinitrophenylhydrazone corresponding to the derivative of 2-hydroxyethylcyclohexanone, and its infrared spectrum had the characteristic hydroxyl and ketal bands, but no carbonyl band. Direct acid hydrolysis[9] of the hydroxy-ketal IIIa failed to yield the expected ketoalcohol IVa and only mixtures of unsaturated cyclization compounds were obtained. This was avoided by first acetylating the hydroxy-ketal IIIa to the ketal-acetate IIIb, following with a mild hydrolysis to 2-acetoxyethylcyclohexanone IVb. The latter compound gave a 2,4-dinitrophenylhydrazone identical with the one obtained from the ketal-acetate IIIb and showed an infrared spectrum with acetate and keto bands.

The desired cyclohexanone derivative IVb thus obtained was smoothly oxidized by peracetic acid to the 1→6-lactone of 6-hydroxy-8-acetoxyoctanoic acid (V).[10] Its infrared spectrum had a very wide band at 1735 cm.$^{-1}$ and an acetate band at 1250 cm.$^{-1}$; it did not yield any 2,4-dinitrophenylhydrazone and, upon quantitative saponification, used up two equivalents of sodium hydroxide.

Although exceptions are known,[11] in general, lactones treated with thiourea in a strong mineral acid with alkaline hydrolysis of the isothiuronium salt thus obtained, yield thiol-acids.[12] In fact from our acetoxy-ε-lactone V in this way we easily obtained 6,8-dithioloctanoic acid (VI), which, after oxidation, gave 6-thioctic acid (VII) (19% over-all yield from cyclohexanone), with the same infrared spectrum of a sample of 6-thioctic acid synthesized by the method of Reed, *et al.*[13] The two samples, as well as their respective S-benzylisothiuronium salts,[14] did not give any melting point depression on admixture.

Acknowledgments.—The authors are indebted to Professor L. Ruzicka, Zurich, for the infrared spectra, to Professor G. Büchi, Cambridge, Mass., for a stimulating discussion and to the late Professor E. A. Braude, London, for the permission of reading his manuscript prior to publication.

(1) For references, see H. Grisebach, *Angew. Chem.*, **68**, 554 (1956); G. W. E. Plaut and J. J. Bethiel, *Ann. Rev. Biochem.*, **25**, 485 (1956); L. Fontanella, *Il Farmaco, ed. sci.*, **10**, 274 (1955).

(2) See, for example, P. Boni, F. Reduzzi, G. Bile and V. Galloro, *Clin. Terap.*, **9**, 129 (1955); F. Rausch, *Klin. Wschr.*, **34**, 737 (1956); F. Steigman and S. M. Canahuati, *Fed. Proc.*, **15**, 487 (1956).

(3) L. Donatelli, "Atti del Simposio Internazionale sull'Acido Tioctico," Università di Napoli, 1955, pp. 45–145.

(4) D. S. Acker, U. S. Patent 2,752,373 (June 26, 1956); D. S. Acker and C. W. Todd, U. S. Patent 2,752,374 (June 26, 1956); E. A. Braude, R. P. Linstead and K. R. H. Wooldridge, *J. Chem. Soc.*, 3074 (1956); M. W. Bullock and J. J. Hand, Abstracts of Papers, 127th Meeting of the A.C.S., Cincinnati, Ohio, March, 1955, p. 8N-9N; K. Makino and M. Koike, *Enzymologia*, **16**, 215 (1953); I. Nakano and M. Sano, *J. Soc. Pharm. Japan*, **25**, 1296 (1955).

(5) For a review of the mechanism of ketone oxidation by peracid, see V. Franzen and H. Krauch, *Chem. Zlg.*, **79**, 627, 845 (1955).

(6) W. Prichard, U. S. Patent 2,459,520 (April 17, 1951).

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(8) R. D. Bergmann and S. Pinchas, *Rec. trav. chim.*, **71**, 161 (1952).

(9) H. Schinz and G. Schäppi, *Helv. Chim. Acta*, **30**, 1493 (1947).

(10) E. A. Braude, *et al.*,[4] mention briefly in a footnote, as a by-product of their 6-thioctic acid synthesis, a compound having the same formula.

(11) A. Campbell, *J. Chem. Soc.*, 4218 (1955).

(12) *E.g.*, L. Schotte, *Arkiv Kemi*, **8**, 457 (1956).

(13) L. J. Reed and Ching-I Niu, This Journal, **77**, 416 (1955).

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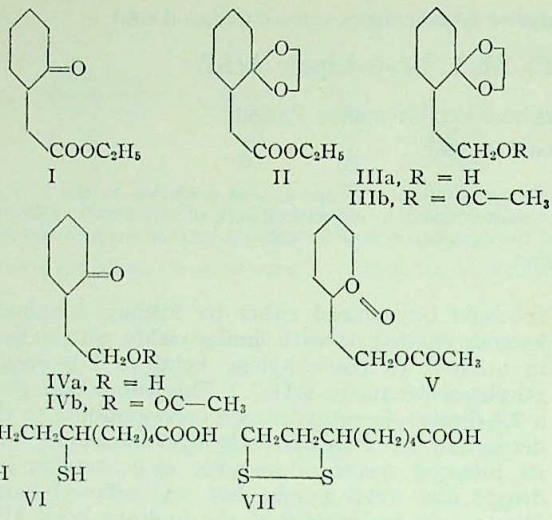

Experimental[15]

Ethyl Cyclohexanone-2-acetate (I).—In a round-bottomed flask fitted with a water separator, 29 g. of cyclohexanone, 85 g. of pyrrolidine and 200 ml. of dry benzene were refluxed for 1.5 hours. At this time the theoretical amount of water (6 ml.) had been separated and no more was evolved on longer heating. The solution was concentrated *in vacuo* to the oily residue of cyclohexanone-pyrrolidine enamine, so as to evaporate all the pyrrolidine in excess.

Thirty-seven and one-half grams of freshly distilled ethyl monobromoacetate was added dropwise to the boiling solution of the crude enamine in 150 ml. of dry benzene. Refluxing was then continued for another hour, the solvent and excess bromoester removed *in vacuo*, the thick residue refluxed for two hours, after addition of 100 ml. of methanol and 20 ml. of water. The solution was then concentrated at reduced pressure; the residue was treated with water and extracted with ether; the organic solution was washed successively with 2 *N* hydrochloric acid, sodium bicarbonate and water, dried over sodium sulfate and evaporated. The residue was fractionated twice *in vacuo* yielding 38.6 g. (71%),[16] b.p. 131–134° (13 mm.), $n^{23}D$ 1.4564; infrared spectrum bands at 1715 (keto-carbonyl), 1735 (ester-carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.43; H, 8.93.

2,4-Dinitrophenylhydrazone, m.p. 126°. *Anal.* Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.88; H, 5.55; N, 15.54.

Ethylene Ketal of Ethyl Cyclohexanone-2-acetate (II).—A solution of 38.5 g. of ethyl cyclohexanone-2-acetate (I), 14.5 g. of ethylene glycol and 50 mg. of *p*-toluenesulfonic acid in 100 ml. of dry toluene was refluxed in a round bottomed flask fitted with a water separator. After three hours, 4.5 ml. of water had been collected. The cooled toluene solution was washed with aqueous sodium bicarbonate and water, dried over sodium sulfate and evaporated. The residue was distilled twice at reduced pressure yielding 42 g. (88%), b.p. 145–147° (13 mm.), $n^{23}D$ 1.4630; infrared spectrum: bands at 1070 (ketal), 1735 (ester carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.02; H, 8.72.

Upon addition of 2,4-dinitrophenylhydrazine, the 2,4-dinitrophenylhydrazone of the ketoester I, m.p. 126°, was obtained. The mixture of the two samples did not give any melting point depression.

Ethylene Ketal of 2-Hydroxyethylcyclohexanone (IIIa).

a. By Lithium Aluminum Hydride Reduction.—A solution of 32 g. of ethylene ketal (II) in dry ether was added dropwise to a slurry of 4 g. of lithium aluminum hydride in 350 ml. of dry ether. The addition was completed after two hours and the mixture was refluxed for one hour longer. The excess reagent was destroyed with ethyl acetate and 2 *N* hydrochloric acid added. The organic layer, washed with aqueous sodium bicarbonate and water, dried over sodium sulfate, was evaporated. The residue was fractionated twice at reduced pressure yielding 25 g. (96%), b.p. 148–150° (13 mm.), $n^{23}D$ 1.4822; infrared spectrum bands at 1080 (ketal) and 3400 (hydroxyl) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.59; H, 9.90.

Addition of 2,4-dinitrophenylhydrazine yielded the expected 2,4-dinitrophenylhydrazone of 2-hydroxyethylcyclohexanone, m.p. 145–146.5°. *Anal.* Calcd. for $C_{14}H_{18}N_4O_6$: C, 52.17; H, 5.63; N, 17.38. Found: C, 52.01; H, 5.83; N, 17.37.

b. By Sodium–Ethanol Reduction.—To a boiling, well-stirred solution of 5 g. of ketal ester II in 25 ml. of absolute ethanol were added simultaneously 5 g. of sodium and 30 ml. of absolute ethanol over a period of a half-hour. Boiling was continued for two hours. After cooling and evaporating the solution almost to dryness, the residue was poured in ice-water and extracted with ether. The organic layer was washed to neutrality with water, dried over sodium sulfate and evaporated. The residue was distilled twice, yielding 3.7 g. (90%), b.p. 148–150° (13 mm.), identical with the product obtained by lithium aluminum hydride reduction, with the same constants and the same 2,4-dinitrophenylhydrazone.

Ethylene Ketal at 2-Acetoxyethylcyclohexanone (IIIb).—Two grams of hydroxy-ketal IIIa dissolved in 6 ml. of pyridine was acetylated with 2 ml. of acetic anhydride at room temperature for two hours. The solution was poured in iced water and extracted with ether. The organic layer was washed successively with 2 *N* hydrochloric acid, aqueous sodium bicarbonate and water, dried over sodium sulfate and evaporated to an oil, which, distilled twice at reduced pressure, yielded 2.1 g. (91%), b.p. 152° (13 mm.), $n^{27}D$ 1.4632; infrared spectrum 1090 (ketal), 1250 (acetate), 1740 (ester carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.15; H, 9.13.

Upon addition of 2,4-dinitrophenylhydrazine, the 2,4-dinitrophenylhydrazone of the acetoxy-ketone IVb, m.p. 109–111°, was obtained.

2-Acetoxyethylcyclohexanone (IVb).—A solution of 2 g. of ethylene ketal of 2-acetoxyethylcyclohexanone (IIIb) and 75 mg. of *p*-toluenesulfonic acid in 20 ml. acetone was refluxed for one hour. The solvent was removed *in vacuo*, keeping the bath temperature below 40°; the oily residue was dissolved in ether, washed with aqueous sodium bicarbonate and water, dried over sodium sulfate and evaporated. After two distillations at reduced pressure 1.55 g. (90%) was obtained, b.p. 142–146° (15 mm.), $n^{27}D$ 1.4565; infrared spectrum bands at 1250 (acetate), 1715 (keto-carbonyl), 1740 (ester carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.04; H, 8.82.

2,4-Dinitrophenylhydrazone, m.p. 109–111°. *Anal.* Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.79; H, 5.46; N, 15.28.

1→6-Lactone of 6-Hydroxy-8-acetoxyoctanoic Acid (V).—A solution of 4.7 g. of 2-acetoxyethylcyclohexanone (IVb) in 16.3 ml. of peracetic acid[17] (containing 28.0 mg. of active oxygen per ml.) was allowed to stand at room temperature for 24 hours; chloroform was added and the resulting solution was washed to neutrality with aqueous sodium bicarbonate. The organic layer, washed with water, dried over sodium sulfate, was evaporated and the residue distilled twice at reduced pressure; yield 3.3 g. (65%), b.p. 126–130° (0.5 mm.), $n^{23}D$ 1.4595, infrared spectrum bands at 1250 (acetate) and 1724–1750 (acetate and lactone) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05; mol. wt., 200.21. Found: C, 60.36; H, 8.21; equiv. wt., 105.0.

6,8-Dithioloctanoic Acid (VI).—A mixture of 2.2 g. of acetoxylactone V, 6.5 g. of thiourea and 8.66 g. of 57% hy-

(15) Melting points are uncorrected and determined in evacuated capillaries. Microanalyses and ultraviolet spectra from our Analytical Department (Drs. C. Ciriello and A. Costa).

(16) A. Dornow and E. Fleischmann, *Chem. Ber.*, **88**, 1340 (1955), obtained the same compound by another method starting from cyclohexanone with a yield of 48.8%.

(17) R. Criegee in "Methoden der organischen Chemie" (Houben-Weil), Band VIII, Sauerstoffverbindungen III, p. 41, Georg Thieme Verlag, Stuttgart, 1952.

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diiodic acid was refluxed for 36 hours and then hydrolyzed by adding 35 ml. of 30% aqueous potassium hydroxide and refluxing for 12 hours in the dark under nitrogen. The reaction mixture was extracted with ether, the aqueous layer separated, acidified with 2 *N* hydrochloric acid and extracted with chloroform. The chloroform solution, after washing to neutrality with water and drying over sodium sulfate, was concentrated and distilled *in vacuo* yielding 1.84 g. (80%) of 6,8-dithiooctanoic acid (VI), b.p. 180° (bath temperature) (1.5 mm.), $n^{22}D$ 1.5225; infrared spectrum 1285, 1235 (OH-carboxyl), 1710 (CO-carboxyl) cm.$^{-1}$.

Anal. Calcd. for $C_8H_{16}O_2S_2$: C, 46.12; H, 7.74. Found: C, 46.37; H, 7.74.

6-Thioctic Acid (DL-α-Lipoic Acid) (VII).—1.01 g. of dithiol-acid (VI) were dissolved in 2.3 ml. of 2 *N* sodium hydroxide, diluted with 17 ml. of water containing 3.5 mg. of iron trichloride hexahydrate, yielding a dark red solution, through which a slow stream of oxygen was bubbled for 10 hours. The resulting pale yellow solution was washed with chloroform. The aqueous layer, acidified with 2 *N* hydrochloric acid, was extracted with chloroform and this was washed to neutrality and evaporated to dryness. The yellow oily residue crystallized upon trituration with petroleum ether (boiling range 40–60°). After one crystallization from petroleum ether, 0.8 g. of pure 6-thioctic acid (DL-α-lipoic acid) (VII) (80%) was obtained, m.p. 61–62°; ultraviolet spectrum λ_{max}^{EtOH} 333 mμ (ε 147); infrared spectrum bands at 1285, 1235 (OH-carboxyl), 1700 (CO-carboxyl) cm.$^{-1}$.

Anal. Calcd. for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.68; S, 31.13. Found: C, 46.66; H, 6.90; S, 31.20.

S-Benzylisothiuronium salt, m.p. 153–154°[18] (from absolute methanol). *Anal.* Calcd. for $C_{16}H_{24}N_2O_2S_3$: C, 51.61; H, 6.45; N, 7.53; S, 25.79. Found: C, 51.53; H, 6.73; N, 7.56; S, 25.99.

NAPOLI, ITALY

(18) M.p. 132–134°[14] has been observed once. This discrepancy may be due to crystallization and drying conditions.

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Many-membered Carbon Rings. XIV. Transannular Ring Cleavage of Certain Cycloalkane Derivatives[1]

BY A. T. BLOMQUIST AND PETER R. TAUSSIG[2]

RECEIVED DECEMBER 4, 1956

Pyrolysis of cyclononyl acetate at 500° affords mainly 1,8-nonadiene (70%) together with *cis*-cyclononene (27%) and *trans*-cyclononene (1.5%). Thermal decomposition of cyclononyl S-methyl xanthate at various temperatures indicates that formation of 1,8-nonadiene occurs only at temperatures above 400°. Pure *trans*-cyclononene rearranges at 500° to 1,8-nonadiene (85%) and *cis*-cyclononene (15%) while pure *cis*-cyclononene, at 500°, yields only *ca.* 20% 1,8-nonadiene and 80% unchanged *cis*-cyclononene. Conformational analysis suggests two possible paths for the formation of the diene from cyclononyl acetate.

The discovery in recent years of transannular reactions[3,4] has done much to stimulate research in the chemistry of medium size rings. This has included several studies concerned with the course of elimination reactions of various derivatives of the cycloalkanes such as their amines, halides, acetates and xanthates.[5–7] This article presents studies of the thermal decomposition of the acetate and S-methyl xanthate of cyclononanol. In an earlier study of the pyrolysis of cyclodecyl acetate and cyclodecyl xanthate,[6] it was observed that a mixture of *cis*- and *trans*-cyclodecenes was produced rather than exclusively one stereoisomer as might have been expected. Further, it was noted that pyrolysis of cyclodecyl acetate gave, as a minor product, a low boiling "dienoid" substance. The latter was not fully characterized at that time.

Pyrolysis of cyclononyl acetate[8] at 500 ± 10° under the same conditions employed in the thermal decomposition of cyclodecyl acetate[6] afforded a pyrolyzate (78%) which interestingly contained only 30% of the expected mixture of *cis*- and *trans*-cyclononenes (IIa and IIb). The principal constituent (70%) of the pyrolyzate was found to be a low boiling compound analogous to the minor product formed in the thermal degradation of cyclodecyl acetate. This low boiling substance was readily identified as 1,8-nonadiene (I).

The structure of this hydrocarbon I was established as indicated below. Its properties agreed with those reported for 1,8-nonadiene by van Pelt[9] and by Everett.[10] Elementary analysis of I was in accord with the composition C_9H_{16} and quantitative catalytic hydrogenation of I indicated the presence of two double bonds. On oxidative ozonolysis I gave an acid (18%) which did not depress the melting point of an authentic sample of pimelic acid. Finally, the infrared absorption spectrum of I showed maxima at 10.07 and 10.97 μ, characteristic of a vinyl group, and was identical with the spectrum of 1,8-nonadiene obtained by pyrolysis of 1,9-nonanediol diacetate.

(1) (a) For the preceding paper in this series see A. T. Blomquist and P. R. Taussig, THIS JOURNAL, **77**, 6399 (1955). (b) Presented before the Division of Organic Chemistry at the National Meeting of the American Chemical Society at Miami, Florida, April 7–12, 1957.

(2) Du Pont Post-Graduate Teaching Fellow. The work reported here was abstracted from part of the dissertation presented by Peter R. Taussig in September, 1956, to the Graduate School of Cornell University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) V. Prelog and K. Schenker, *Helv. Chim. Acta*, **35**, 2044 (1952); V. Prelog, K. Schenker and W. Küng, *ibid.*, **36**, 471 (1953); V. Prelog, H. J. Urech, A. A. Bothner-By and J. Würch, *ibid.*, **38**, 1095 (1955); V. Prelog and V. Boarland, *ibid.*, **38**, 1776 (1955).

(4) A. C. Cope, S. W. Fenton and C. F. Spencer, THIS JOURNAL, **74**, 5884 (1952).

(5) A. T. Blomquist, R. E. Burge and A. C. Sucsy, *ibid.*, **74**, 3636 (1952).

(6) A. T. Blomquist and A. Goldstein, *ibid.*, **77**, 1001 (1955).

(7) A. C. Cope, R. A. Pike and C. F. Spencer, *ibid.*, **75**, 3212 (1953); A. C. Cope, D. C. McLean and N. A. Nelson, *ibid.*, **77**, 1628 (1955).

(8) M. Kobelt, D. Barman, V. Prelog and L. Ruzicka, *Helv. Chim. Acta*, **32**, 256 (1949).

(9) A. J. van Pelt, Jr., and J. P. Wibaut, *Rec. trav. chim.*, **60**, 55 (1941).

(10) J. L. Everett and C. A. R. Kon, *J. Chem. Soc.*, 3131 (1950).

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After completion of the characterization of I, it became apparent that the "dienoid" product formed in the pyrolysis of cyclodecyl acetate[6] was probably 1,9-decadiene (III). This was confirmed by preparing an authentic sample of III *via* pyrolysis of 1,10-decanediol diacetate and comparing the infrared absorption spectra of the two hydrocarbons. They were indistinguishable.

With the object of ascertaining, to some extent, the generality of this ring cleavage of cycloalkyl esters, the pyrolysis of cycloöctyl acetate[8] was examined. Here it was found that about 10% of the pyrolyzate had properties differing from the cycloöctenes but possessing an infrared absorption spectrum very similar to those of 1,8-nonadiene and 1,9-decadiene. All of the foregoing suggests that ring cleavage in the thermal degradation of medium sized cycloalkyl acetates is general, but it is a major reaction only for the nine-membered ring.

Estimation of the amount of *cis*- and *trans*-cyclononene (IIa and IIb, respectively) in the cyclononene fraction obtained in the pyrolysis of cyclononyl acetate was done by the quantitative infrared analysis method used previously for *cis*- and *trans*-cyclodecene.[1] The per cent. IIa in the mixture of cyclononenes was determined by noting the intensity of the absorption maximum at 13.16 μ with reference to a base line drawn from the minimum at 12.90 μ. The per cent. IIb was determined by measuring the intensity of the absorption maximum at 10.15 μ with reference to a base line drawn from the minimum at 10.60 μ. Application of the method to analyses of known mixtures of pure cyclononenes indicated that it was accurate to about $\pm 5\%$. Using the above method it was found that the cyclononene fraction resulting from the acetate pyrolysis comprised 90% IIa and 5% IIb.

In order to complement the pyrolysis study of cyclononyl acetate, it seemed desirable to examine the thermal decomposition of cyclononyl S-methyl xanthate (IV) at various temperatures. In these experiments (Table II) it was observed that the formation of I did not occur until the pyrolysis temperature was about 400°. At 500° the pyrolyzate from IV contained about 50% I. It was noted further that as the content of I increased in the pyrolyzate of IV, the per cent. IIb in the cyclononene fraction decreased.

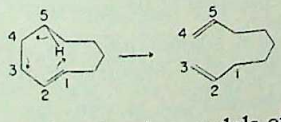
The foregoing suggested that perhaps cyclononenes were intermediates in the formation of I. Accordingly, both IIa and IIb were pyrolyzed under conditions similar to those used for the decomposition of the cyclononyl esters. The pure hydrocarbon IIa at 500° afforded a pyrolyzate comprising *ca.* 20% I, the remainder (80%) being unchanged IIa. The pure hydrocarbon IIb at 500° gave a product which contained 85% I and 15% of a mixture of IIa and IIb. The cyclononene in this latter mixture was very largely the *cis* isomer IIa (see Table I).

Discussion of Results

The observations presented in the foregoing can be accounted for by a careful conformational analysis of the nine-membered carbocycle. The most probable conformation for cyclononane itself would be that in which there is maximum distance between the non-bonded atoms. Stylized projection representations for two views of such a conformation derived from a Fisher–Hirschfelder–Taylor model is given in Fig. 1. According to this model (Fig. 1) there are eight *quasi-axial* hydrogens, attached to carbon atoms 1,2,3,4,5,2′,3′ and 4′, directed inward toward the center of the ring. Four of these are on the upper side of the ring and four below. The eight *quasi-equatorial* hydrogens attached to these carbon atoms and arranged about the periphery of the ring are directed outward and at an angle essentially perpendicular to the ring axis. The hydrogen atoms attached to the carbon labeled 1′ appear to be unique in that they extend away from the ring in a direction midway between the *quasi-axial* and *quasi-equatorial* hydrogens. On the basis of this model three principal conformations are theoretically possible for cyclononyl acetate. The acetoxy group may be *quasi-equatorial*, *quasi-axial* or at the intermediate position on C_1'. At 500° all of these should exist and their interconversion should be facile. From these conformations of the acetate the realization of the requisite transition state for 1,2-elimination of acetic acid, a planar six-membered ring arrangement of the atoms H–C–C–O—C=O,[11,12] would

appear to involve the least amount of "steric strain" under the circumstance that the hydrogen atom and acetoxy group on adjacent carbons both be in *quasi-equatorial* positions. Such a transition state would lead to IIb. Further, according to the models, the formation of *all* of those transition states which would lead to IIa is rendered more difficult because of steric factors. For the above reasons, IIb should be the principal product of the thermal 1,2-elimination of acetic acid from cyclononyl acetate.

The observations that (1) the pyrolyzate from cyclononyl acetate comprises principally I (70%) and IIa (*ca.* 30%) and (2) pyrolysis of the cyclononenes themselves affords I (*ca.* 20% from IIa and *ca.* 85% from IIb), suggests that the formation of I possibly involves two discrete steps. Initially, cyclononyl acetate affords, *via* 1,2-elimination of acetic acid, a mixture of cyclononenes containing mainly the *trans* isomer. Subsequently, the cyclononenes, especially the *trans* isomer, undergo transannular intramolecular rearrangement to the open-chain diene I. A possible path for this rearrangement is indicated in the diagram below. It involves a transannular shift of a *quasi-axial* hydrogen on carbon five to carbon one of the double bond with a concomitant redistribution of electrons.



Examination of molecular models of IIa and IIb indicates that the rearrangement should be particularly facile for IIb. In this olefin IIb the

(11) E. R. Alexander and A. Mudrak, THIS JOURNAL, **72**, 1810, 3194 (1950).

(12) W. Hückel, W. Tappe and G. Legutke, *Ann.*, **543**, 191 (1940).

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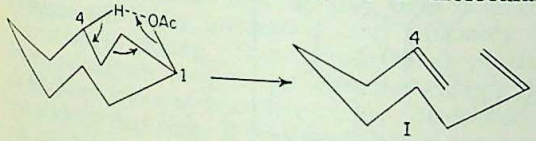
TABLE I

THERMAL DECOMPOSITION OF CYCLONONENES AT 500°

Cyclononene used		Pyrolyzate obtained			
Wt., g.	Compn.	Total yield in g. and %	Diene yield, g. and % of total	Cyclononone yield, g. and % of total	Compn.
7.7	100% *cis*	6.7 (87)	1.2 (18.5)	5.5 (81.5)	100% *cis*
3.4	95% *cis* 5% *trans*	2.7 (78)	0.5 (20)	2.2 (80)	100% *cis*
8.4	65% *cis* 35% *trans*	5.8 (69)	2.5 (44)	3.3 (56)	91.2% *cis* 3.7% *trans*
10.3	100% *trans*	7.9 (77)	6.7 (85)	1.2 (15)	93.4% *cis* 6.2% *trans*

quasi-axial hydrogen at position five appears to be easily within bonding distance of position one, and further the movement of this hydrogen from C_5 to C_1 is not obstructed by other *quasi-axial* hydrogen atoms. The situation with respect to IIa is quite different. The C_5-*quasi-axial*-hydrogen is at a greater distance from C_1 than in IIb, and also there are *quasi-axial* hydrogen atoms on C_3 and C_9 blocking the migration (see Fig. 2).

Although the above rationalizations appear to account satisfactorily for the experimental observations, the possibility of other operating mechanisms cannot be excluded. One of these was suggested in an earlier communication.[1] The proposed mechanism indicated the direct formation of the diene I from cyclononyl acetate by 1,4-transannular elimination of acetic acid *via* a six-membered cyclic transition state developed through interaction of the ethereal oxygen atom in *quasi-axial* cyclononyl acetate and the *quasi-axial* hydrogen atom on C_4. Examination of a molecular



I

model of *quasi-axial* cyclononyl acetate suggests that the requisite transition state could be realized easily.

Acknowledgments.—The authors are indebted to Professor R. M. Hexter for his aid in obtaining and interpreting the infrared spectra data used in these studies. Also, the authors wish to express their sincere appreciation to Dr. Yvonne C. Meinwald for her assistance in the preparation of this article.

Experimental[13]

Materials.—*cis*-Cyclononene (IIa) was obtained by hydrogenation of cyclononyne[14] using Lindlar catalyst following a procedure similar to that described for the preparation of *cis*-cyclodecene.[6] The IIa obtained (83% yield) had $n^{25}D$ 1.4780. *trans*-Cyclononene (IIb), $n^{25}D$ 1.4782, was obtained as described previously.[14] 1,8-Nonadiene (I), prepared by pyrolysis of 1,9-nonanediol diacetate at 500°, showed b.p. 136–138° (740 mm.), and $n^{25}D$ 1.4250.[9,10] 1,9-Decadiene b.p. 162–163° (740 mm.), and $n^{25}D$ 1.4316, was prepared similarly from 1,10-decanediol diacetate. Its properties were in good agreement with those reported for it by Everett and Kon.[10] The cyclononyl acetate used had b.p. 113–116° (12 mm.) and $n^{25}D$ 1.4629.

(13) All b.p.'s are uncorrected. Infrared absorption spectra were obtained by use of a Perkin–Elmer double beam infrared spectrophotometer, Model 21.

(14) A. T. Blomquist, L. H. Liu and J. C. Bohrer, THIS JOURNAL, **74**, 3643 (1952).

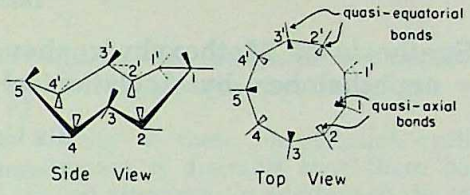
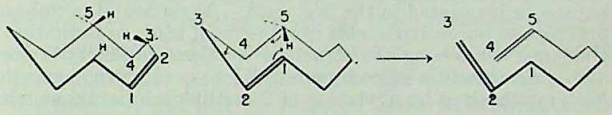


Fig. 1.—Conformation of cyclononane.



cis-Cyclononene *trans*-Cyclononene

Fig. 2.—Conformations of the cyclononenes.

Cyclononyl S-Methyl Xanthate.—This xanthate was prepared using the same method described for cyclodecyl S-methyl xanthate.[6] From 36.7 g. of cyclononanol 72 g. of crude xanthate was obtained. This crude xanthate was used in the pyrolyses described subsequently. An analytical sample of the xanthate was secured by chromatographing the crude product on alumina and eluting with pentane. It was obtained as a clear, slightly yellow oil.

Anal. Calcd. for $C_{11}H_{20}OS_2$: C, 56.87; H, 8.62; S, 27.62. Found: C, 56.62; H, 8.38; S, 27.40.

Thermal Decomposition of Cyclononyl Acetate.—The pyrolysis was carried out as described previously for the thermal decomposition of cyclodecyl acetate.[6] After the usual workup, the products were distilled through a 36-inch Podbielniak column to give two main fractions: (1) b.p. 140–144°, $n^{25}D$ 1.4260, d^{25} 0.748, which comprised 67–70% of the product, and (2) a mixture of *cis*- and *trans*-cyclononenes, b.p. 172–174°, $n^{25}D$ 1.4770, which comprised 33–30% of the product. The total yield of olefins amounted to 72–78%.

Analysis by infrared spectrophotometry indicated that fraction (2) consisted of 89–91% of IIa and 4–5% of IIb.

Thermal Decomposition of Cyclononenes (IIa and IIb).—The pyrolysis procedure used was identical with that employed in the cyclononyl acetate decomposition. The results are presented in Table I.

TABLE II

THERMAL DECOMPOSITION OF CYCLONONYL S-METHYL XANTHATE

Xanthate used, g.	Pyrolysis temp., °C.	Total, g. and %	Pyrolyzate % diene	% Cyclononenes	and compn.
12.0	120 − 130	2.2 (34.4)	0	100	60% *cis* 40% *trans*
14.0	360 ± 10	3.3 (44)	0	100	55% *cis* 45% *trans*
14.0	400 ± 10	2.9 (38)	Trace	99+	% 78% *cis* 19% *trans*
14.0	450 ± 10	3.4 (45)	10	90	80% *cis* 20% *trans*
14.0	500 ± 10	1.8 (24)	50	50	100% *cis*

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Thermal Decomposition of Cyclononyl S-Methyl Xanthate. (A) **Low Temperature Procedure.**—Crude cyclononyl S-methyl xanthate (12 g.) was pyrolyzed in a 100-ml. flask at 120–130° according to the procedure previously described.[6] The product, a yellow liquid, was distilled at 56–64° (15 mm.) and weighed 4.1 g. The yellow contaminant was removed by chromatography. Subsequent distillation through a Podbielniak column at atmospheric pressure yield 2.2 g. (34.4%) of II, b.p. 168–173°, $n^{25}D$ 1.4770. (B). **High Temperature Procedure.**—Crude cyclononyl S-methyl xanthate (14 g.) was dropped through a carborundum packed column heated to the desired temperature as described for the acetate pyrolysis. After completion of the pyrolysis, the column was cooled and washed with pentane. The combined pyrolyzate and washes were worked up as in the low temperature procedure.

The results of the pyrolyses at various temperatures are summarized in Table II.

ITHACA, NEW YORK

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Synthesis of Methoxyhydrophenanthrenes and Methoxyhydrocyclohepta[a]-naphthalenes by Acylation of Ketones with Homoveratric Anhydride

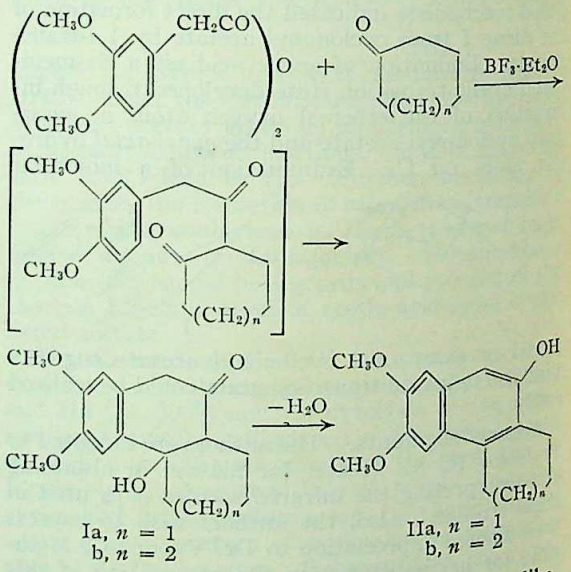
BY GORDON N. WALKER

RECEIVED JANUARY 24, 1957

Acylation of cyclohexanone and cycloheptanone with homoveratric anhydride in the presence of boron trifluoride etherate is accompanied by cyclization, giving, after dehydration, compounds IIa and IIb, respectively. An intermediate hydroxyketone Ia is isolated in the first case. Acylation of cyclohexanone and cycloheptanone with homoveratric anhydride in the presence of boron trifluoride in acetic acid leads to formation of 1-acetyl-2-naphthol derivatives, XIa and XIb, respectively. Evidence confirming the structures of these products is presented, notably oxidation of compounds II to quinones VIII, and hydrogenation of compounds XI to octahydrophenanthrenes, XII. Angular methyl compounds V and VI have also been synthesized by acylation of 2-methylcyclohexanone with homoveratric anhydride.

There are several methods for synthesizing phenanthrenes and hydrophenanthrenes from simple aromatic compounds, depending upon cyclization reactions of appropriate functional groups with benzene carbon–hydrogen. These methods include the classical Pschorr procedure[1] and its modifications, the Haworth method[2] and cyclizations first described by Bardhan and SenGupta[3] and independently by Bogert[4] and Cook[5] and their collaborators. The Pschorr synthesis,[6,7] and another approach, namely, closure of ring B after elaboration of the A/C system,[8,9] have been adapted to synthesis of methoxy tricyclic compounds incorporating seven-membered rings (colchicine relatives). Efforts to circumvent difficulties inherent in these approaches have now led to discovery of a new cyclodehydration[10] reaction, described in this paper,[11] which accomplishes in one step the synthesis of certain hydrophenanthrenes and their C-ring homologs.

Experimental work was begun, acting upon the premise that if cyclic ketones could be C-acylated with phenylacetic anhydrides, it should be possible to bring about cyclization of resulting β-diketones through interaction of the benzene ring and the cyclic ketone moiety under acid conditions. Exposure of mixtures of phenylacetic anhydride and cyclohexanone to boron trifluoride under various conditions failed to yield recognizable products, an observation which agrees with earlier data.[12] However, it seemed likely that C-acylation did occur, for infrared spectra of the (presumably polymeric) products showed ketone (5.8–5.9 μ) rather than enol ester (5.7 μ) bands. Experiments with homoveratric anhydride were then tried, and these proved to be successful, inasmuch as C-acylation did occur, as supposed, and cyclization of resulting diketones *in situ* took place as well.



Ia, $n = 1$
b, $n = 2$

IIa, $n = 1$
b, $n = 2$

(1) See P. H. Leake in *Chem. Revs.*, **56**, 27 (1956).

(2) R. D. Haworth, *et al.*, *J. Chem. Soc.*, 1125, 1784, 2248, 2717, 2720 (1932).

(3) J. C. Bardhan and S. C. SenGupta, *ibid.*, 2520, 2798 (1932).

(4) M. T. Bogert, *et al.*, *Science*, **77**, 289 (1933); *J. Org. Chem.*, **1**, 288, 300 (1936); THIS JOURNAL, **56**, 185, 959 (1934).

(5) J. W. Cook and C. L. Hewett, *Chemistry & Industry*, **52**, 451 (1933); *J. Chem. Soc.*, 1098 (1933).

(6) J. W. Cook, J. Jack and J. D. Loudon, *ibid.*, 1397 (1951), and preceding papers.

(7) H. Rapoport, *et al.*, THIS JOURNAL, **73**, 1414 (1951); **77**, 670 (1955).

(8) C. D. Gutsche and F. A. Fleming, *ibid.*, **76**, 1771 (1954).

(9) D. Ginsburg, *ibid.*, **76**, 3628 (1954).

(10) A term used by C. K. Bradsher, *Chem. Revs.*, **38**, 447 (1946), to describe formation of aromatic rings through reactions involving loss of water. The synthesis presented here may be considered to fall into this category.

(11) A preliminary report of this work appeared in THIS JOURNAL, **78**, 2340 (1956).

(12) J. C. Adkins and C. R. Hauser, *ibid.*, **67**, 284 (1954).

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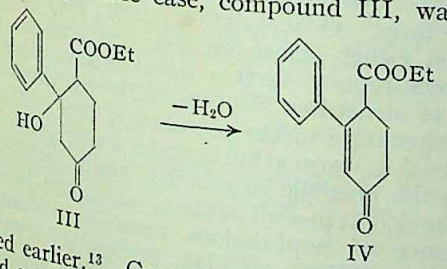
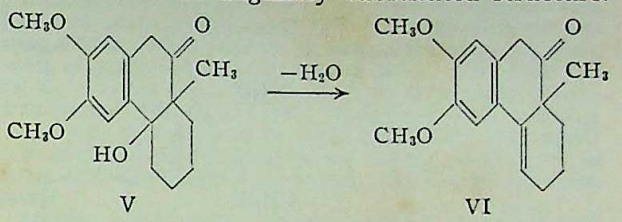
Compound Ia was obtained in 68% yield when a mixture of homoveratric anhydride, cyclohexanone and boron trifluoride etherate was allowed to stand at 0–10° for three days. Evidence leading to assignment of structure Ia and excluding other possibilities was obtained from analysis, spectra and further reactions. While the infrared spectrum of Ia showed only weak absorption at 2.8–2.9 μ, there was present a strong ketone band at 5.79 μ (chloroform solution) or 5.85 μ (mull). A hydroxymethylene derivative was prepared by reaction of Ia with ethyl formate (sodium methoxide), indicating that a methylene position adjacent to a ketone group was present. Attempts to acetylate Ia with acetic anhydride were fruitless, thus making it appear likely that a tertiary alcohol was at hand. As expected, compound Ia lost water rapidly in the presence of mineral acids, polyphosphoric acid being best for the purpose, and formed a β-naphthol, IIa. Infrared and ultraviolet spectra (see Experimental part) showed clearly that IIa was a naphthalene, and the structure was substantiated further by aromatization of IIa to 2,3-dimethoxy-9-phenanthrol in the presence of palladium. O-Acetates of IIa and the phenanthrol again had typical ultraviolet spectra, and the infrared spectra of these compounds disclosed, as anticipated, peaks at 5.70 μ.

Condensation of homoveratric anhydride with cycloheptanone in the presence of boron trifluoride etherate gave IIb directly, and Ib, though perhaps formed first in the reaction, could not be isolated. The fact that the presumed cycloheptanol intermediate Ib dehydrates more readily than does the cyclohexanol Ia is interesting and probably is due to steric effects. Data available at present do not permit an unequivocal statement about the stereochemistry of hydroxyketone Ia. However, it seems likely that rings B and C of Ia are arranged *cis*. A comparable case, compound III, was described earlier.[13] Compound III, in which a presumed equatorial hydroxyl group is located in the benzyl position, beta to a carbonyl group and *cis* with respect to hydrogen at carbon atom 4, is like Ia in being relatively resistant to dehydration, as well as to hydrogenolysis and acetylation. It has now been found that III, like Ia, loses water in the presence of polyphosphoric acid, giving IV.

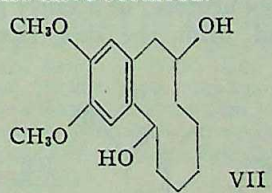


Another compound of the type shown in formula I was synthesized by condensation of homoveratric anhydride with 2-methylcyclohexanone in the presence of boron trifluoride etherate. Reasoning from some data available on methylene *versus* methinyl acylation,[14] it was felt that acylation of a 2-substituted cyclohexanone might as well take place at position 2 as at position 6 of the ketone. This in fact was the case, for the product isolated (63%) was compound V. Dehydration of V did not afford a naphthol, but rather an unsaturated ketone VI, a result readily explained only on the basis of an angularly substituted structure.



Thus it appears that the synthesis is applicable to preparation of angular-methyl compounds such as V or VI.

The novelty of these condensation–cyclization products makes it desirable that there be some proof of their structures in addition to the facts already presented. Attempts to convert Ia or IIa to a known compound, 2,3-dimethoxyphenanthrene,[15,16] were thwarted by the following events. Reduction of IIa under various conditions gave mixtures of products, and 2,3-dimethoxyphenanthrene could not be isolated after subsequent dehydration and aromatization. Hydrogenation of IIa may have taken place in ring A as well as in ring B, and in this connection some results obtained in hydrogenation of phenanthrene-9,10-quinone (see below) may be relevant. Compounds Ia, V and VI resisted catalytic hydrogenation in the presence of 10% palladium–charcoal. Lithium aluminum hydride (or sodium borohydride) reduction of Ia gave a diol, $C_{16}H_{24}O_4$, m.p. 147–149°, having two hydrogen atoms more than expected for a diol corresponding to Ia; it is thought at present that in this reduction reverse aldol reaction, leading to VII, or possibly some other type of cleavage may also have occurred.



A satisfactory demonstration of the correctness of structures II was achieved eventually in a rather unusual way. Although other oxidizing agents for the most part destroyed IIa and IIb, it was found that *ozone* oxidizes these compounds rapidly to corresponding *o*-quinones, VIIIa and VIIIb, respectively. Compound IIa is oxidized in this manner more rapidly than is IIb, and in the same vein quinone VIIIa appears to be somewhat less stable than VIIIb, although both compounds VIII are rather more stable than 1,2-naphthoquinone and 1,2,3,4 - tetrahydrophenanthrene - 9,10 - quinone. Preparation of quinoxaline derivatives IX from quinones VIII provided confirmation of structures VIII. There seemed to be no tendency toward formation of corresponding quinhydrones during oxidation of compounds II, an observation which

(13) G. N. Walker, THIS JOURNAL, **77**, 3664 (1955).
(14) C. R. Hauser and J. T. Adams, *ibid.*, **66**, 345 (1944).
(15) R. Pschorr and W. Buckow, *Ber.*, **33**, 1829 (1900).
(16) E. Mosettig and A. Burger, THIS JOURNAL, **52**, 2988 (1930).

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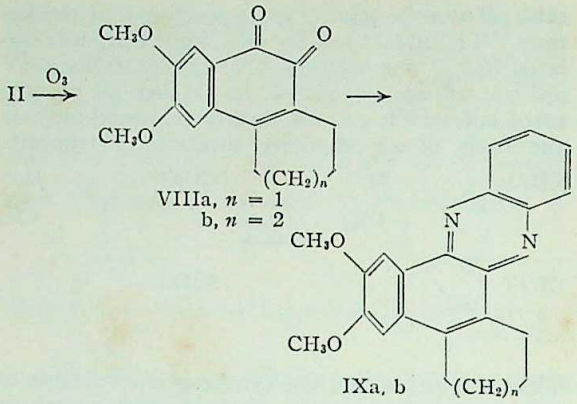
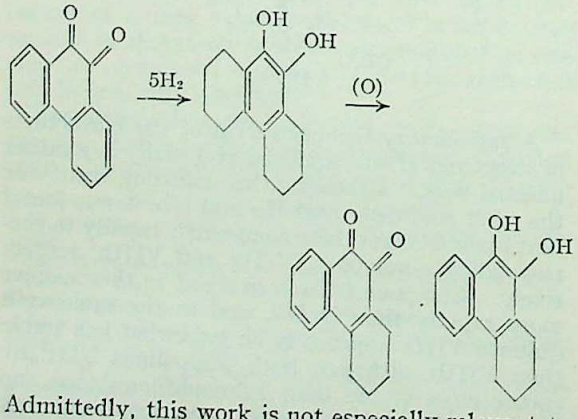
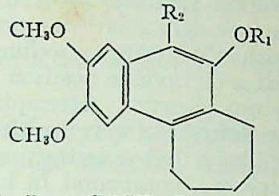


stood in contrast to a report concerning formation of the parent system, 1,2,3,4-tetrahydrophenanthrene-9,10-(quinone-hydroquinone).[17] Therefore, hydrogenation of phenanthrene-9,10-quinone was carried out in an effort to get more information about compounds in this category. After exhaustive hydrogenation of phenanthrene-9,10-quinone in the presence of 10% palladium–charcoal in ethyl acetate at 80°, a diol was obtained which, like the diol described by Skita,[17] oxidized very readily, even upon exposure to air, to tetrahydrophenanthrenequinhydrone. This oxidative transformation appeared at first to be analogous to oxidation of compounds II, and indeed a parallel could be drawn if the unstable reduction product obtained here were 1,2,3,4,9,10-hexahydrophenanthrene-9,-10-diol, as supposed earlier,[17] or 1,2,3,4,4a,9,10,10a-octahydrophenanthrene-9,10-diol, as seemed more likely from present analytical results. However, the diol evidently had neither of these structures but was instead 1,2,3,4,5,6,7,8-octahydrophenanthrene-9,10-diol. This conclusion was necessitated by the elementary composition and, more important, the properties, particularly infrared spectrum (5.70 μ, phenol acetate) of a fairly stable monoacetate obtained from the diol (see Experimental part).



Admittedly, this work is not especially relevant to other results presented here but is included because it has some novelty and represents one attempt to obtain a desired model compound, 1,2,3,4-tetrahydro-10-hydroxyphenanthrene.

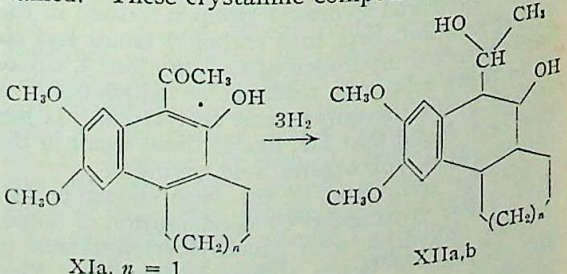
Some additional experiments with compound IIb were done in the interest of providing further evidence for the structure and exploring possible means of selectively opening ring B. The O-acetate Xa, methyl ether Xb and a bromo-derivative Xc were prepared by conventional reactions. Nitrous acid converted IIb to the nitroso-compound (quinone monoxime) Xd, catalytic reduction of which, followed by acetylation, provided Xe. Preliminary attempts to carry out inverse Beckmann rearrangement[7] of Xd, and other reactions



Xa, R_1 = $COCH_3$, R_2 = H
b, R_1 = CH_3, R_2 = H
c, R_1 = H, R_2 = Br
d, R_1 = H, R_2 = NO
e, R_1 = $COCH_3$, R_2 = $NHCOCH_3$

designed to selectively cleave the 5,6-double bond in IIb and its derivatives, have been unsuccessful.

Early in exploratory work, condensations of homoveratric anhydride with cyclohexanone and cycloheptanone were carried out using acetic acid, rather than ether, as solvent and complexing agent. The products when analyzed proved to be acetates of IIa and IIb, respectively, but were yellow rather than colorless compounds, gave strong ferric chloride tests and judging from ultraviolet spectra seemed to be C-acylnaphthalenes. The infrared spectra of the compounds lacked hydroxyl and ordinary carbonyl bands, as in spectra of other 1,3-keto-enols, and thus structures XIa and XIb, consistent with this evidence, were assigned to the compounds. Formation of XIa and XIb may have come about either by direct acetylation of IIa and IIb after cyclization or through Fries reaction[18] of O-acetates. O-Acetylation itself may have occurred either before or after cyclization. These matters require further examination. Confirmation of structures XIa and XIb was provided by hydrogenation in the presence of 10% palladium–charcoal in warm ethyl acetate, under which conditions the phenolic ring in XI was reduced as well as the 1,3-keto-enol system, as shown by disappearance of naphthalene ultraviolet absorption, and diols XIIa and XIIb, respectively, were obtained. These crystalline compounds appeared to



XIa, n = 1
b, n = 2

XIIa,b

(17) A. Skita and W. Rohrmann, *Ber.*, **63**, 1473 (1930).

(18) Boron trifluoride can expedite Fries reaction, according to A. H. Blatt, *Chem. Revs.*, **27**, 413 (1940); *cf.* H. Meerwein, *Ber.*, **66**, 411 (1933), and K. V. Auwers, H. Pötz and W. Noll, *Ann.*, **535**, 228 (1938). For rearrangement of 2-naphthyl acetate see K. Fries, *Ber.*, **54**, 709 (1921).

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consist of only one isomer in each case, and at present it seems likely that they are the all-*cis* isomers, formed by way of initial 1,4-addition, or perhaps even 1,6-addition, of hydrogen. Palladium-catalyzed hydrogenation of other 1,3-keto-enols such as *o*-hydroxyacetophenones,[19] dehydroacetic acids[19] and 2-acetylcyclohexanone (see Experimental part of this paper) under neutral conditions also results in reduction of the acetyl group in each case.

It should be mentioned that successful condensation–cyclization reactions of homoveratric anhydride with cyclopentanone and with 1-tetralone were not achieved, although with 2-tetralone a small amount of rather unstable ketone, $C_{20}H_{20}O_4$, was isolated. Even more disappointing was the failure to isolate any tricyclic compounds after reaction of 3,4,5-trimethoxyphenylacetic anhydride with cyclohexanone and cycloheptanone. The synthesis in its present form appears to be limited in practice to use of relatively simple 6- and 7-membered ring ketones and to use of phenylacetic anhydrides in which the benzene ring carbon atom (6) at which cyclization occurs is activated by suitably placed electron-releasing groups and is not hindered by a group at the adjacent position (5). Even with these limitations the method may prove to be useful in synthesizing a number of new polycyclic compounds, especially if improvements in experimental conditions can be found, and it is hoped to pursue further work in this direction.

Experimental[20]

3,4-Dimethoxyphenylacetic Anhydride.—A solution of 56.5 g. of 3,4-dimethoxyphenylacetic acid in 550 ml. of acetic anhydride was treated with 5.5 ml. of pyridine and was refluxed for 4 hr. The solution was evaporated on a steam-cone to a volume of 70 ml. The cooled residue was diluted with 300 ml. of ether and was stirred and chilled in ice until crystallization was complete. The product was collected and washed with 100 ml. of dry ether; first crop, 23 g., m.p. 79–82°. The filtrates were kept at ice temperature for a week, whereupon a second crop, 18 g., m.p. 77–80°, was obtained after trituration with ether. The yield of anhydride was 41 g. (76%). Recrystallization from ethyl acetate gave colorless crystals, m.p. 83–85°. The infrared spectrum (chf.) had an intense doublet, 5.48 and 5.70 μ.

Anal. Calcd. for $C_{20}H_{22}O_7$: C, 64.2; H, 5.92. Found: C, 64.5; H, 6.04.

2,3-Dimethoxy-4b-hydroxy-9-keto-4b,5,6,7,8,8a,9,10-octahydrophenanthrene (Ia).—A mixture of 10.1 g. (0.027 mole) of homoveratric anhydride and 7.3 g. (0.0745 mole) of redistilled cyclohexanone was treated with 74 ml. of ice-cold, commercial 47% boron trifluoride etherate. The mixture was swirled in an ice-bath for an hour until the solid material dissolved, and the dark solution was kept in an ice-box for 3 days. During this time a solid deposited slowly. The mixture was added to a solution of 60 g. of sodium acetate in 300 ml. of water, and this mixture was heated on a steam-cone and stirred for 15 minutes until the ether evaporated and the remaining dark oil began to crystallize. The mixture was chilled in ice and stirred until crystallization was complete. The crude product was collected and washed with two 50-ml. portions of water. The gummy crystals were triturated with three successive small portions of methanol, which removed dark, oily material and left 5.1 g. (68%) of light-brown crystals, m.p. 133–138°. Recrystallization from aqueous methanol (Norit) gave colorless crystals, m.p. 140–141°. Slow evaporation of solutions of this compound resulted in formation of large, rhombohedral crystals. The infrared spectrum (chf.) showed very weak absorption at 2.8–2.9 μ and an intense peak at 5.79 μ. The infrared spectrum in Nujol mull was devoid of hydroxyl bands, and in this medium the intense carbonyl peak was shifted to 5.85 μ, indicating hydrogen bonding. The ultraviolet spectrum (ethanol) had λ_{max} 232 and 285 mμ (log ϵ 3.88 and 3.57, respectively).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30; mol. wt., 276. Found: C, 69.55; H, 7.34; mol. wt. (Rast), 285.

Although the compound gave a transient positive test with 2,4-dinitrophenylhydrazine, attempts to prepare derivatives using this and other reagents were unsuccessful, apparently owing to decomposition or formation of IIa. The hydroxyketone was insoluble in dilute alkali and did not give a ferric chloride test. It was virtually unchanged after refluxing for an hour in acetic acid or acetic anhydride. Attempted hydrogenolysis in the presence of palladium–charcoal in acetic acid also resulted in recovery of most of the compound.

Another condensation of homoveratric anhydride and cyclohexanone was carried out as described above, except that the solution was allowed to stand at room temperature, rather than 0–10°, for 3 days. In this case the crude product contained very dark, sparingly soluble, gummy material. Compound Ia was isolated from this mixture in 20% yield by recrystallization from aqueous methanol.

The 10-hydroxymethylene derivative was prepared by reaction of 1.0 g. of Ia with excess ethyl formate in the presence of 0.5 g. of dry, freshly prepared sodium methoxide in 300 ml. of dry ether. The product was isolated as usual by acidification of an ether-washed, aqueous solution of the sodium salt. Trituration with ether gave 1.0 g. of pale yellow crystals, m.p. 131–135°. Recrystallization from ethyl acetate afforded 0.85 g. of colorless crystals, m.p. 159–161°. The infrared spectrum (chf.) had a band at 6.00 μ. The ultraviolet spectrum (ethanol) had λ_{max} 257, 288 and 309 mμ (log ϵ 4.05, 4.08 and 3.95, respectively). The compound was soluble in dilute sodium hydroxide solution and, like 1-hydroxymethylene-2-tetralone, gave a deep-blue color (changing to green) with ferric chloride.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.36; H, 6.87.

Efforts to dehydrate this compound with polyphosphoric acid resulted in formation of tars.

2,3-Dimethoxy-5,6,7,8-tetrahydro-9-phenanthrol (IIa).—A mixture of 1.4 g. of Ia and 18 g. of polyphosphoric acid was heated to 80° and stirred for 10 minutes, until a dark-brown solution was obtained. The chilled solution was treated with ice and water, and the resulting purple solid was extracted with ethyl acetate. The organic solution was washed with successive portions of water, sodium bicarbonate solution and water, and was dried over magnesium sulfate. Evaporation of the solvent and trituration of the crude product (0.8 g.) with methanol gave 0.6 g. (46%) of light-brown crystals, m.p. 211–218° dec. Recrystallization from methanol (Norit) gave colorless crystals, m.p. 219–221° dec. The infrared spectrum (chf.) had a peak at 2.76 μ. The ultraviolet spectrum[21] (ethanol) had $\lambda_{max.}$ 237, 272, 282, 293, 322 and 336 mμ (log ϵ 4.86, 3.60, 3.59, 3.46, 3.59 and 3.72, respectively).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.50; H, 7.09.

Dehydration of Ia also occurred in the presence of warm sulfuric–acetic acids mixture, as indicated by appearance of a deep-red color, but no crystalline product could be isolated after this reaction. Hydrogenation of IIa in the presence of 10% palladium–charcoal in ethyl acetate at 80° gave glassy material, the infrared spectrum of which showed absorption at 2.76 and 2.9–3.0 μ.

Acetylation of IIa with acetic anhydride (refluxed 2 hr.) gave the **O-acetate**, m.p. 170–171°, after recrystallization from methanol. The infrared spectrum (chf.) had a peak at 5.70 μ, and the ultraviolet spectrum (ethanol) had λ_{max} 235, 264, 273, 282, 293, 314 and 328 mμ (log ϵ 4.98, 3.68, 3.72, 3.71, 3.54, 3.49 and 3.69, respectively).

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.03; H, 6.69.

2,3-Dimethoxy-9-phenanthrol.—A mixture of 0.5 g. of IIa, 1.5 g. of 10% palladium–charcoal catalyst and 40 ml. of redistilled *p*-cymene was refluxed vigorously for 2.5 hr.

(19) G. N. Walker, THIS JOURNAL, 78, 3201 (1956).

(20) Melting points are corrected.

(21) See R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, Spectrum 238.

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The catalyst was filtered and was washed with 50 ml. of ethyl acetate. The yellow solution was evaporated to a small volume, and the residual material was taken up in 5 ml. of methanol. The solution was kept at ice temperature overnight, and the product was collected, washed with a small quantity of methanol and air-dried. There was obtained 0.2 g. of nearly colorless crystals, m.p. 244–248° dec. Recrystallization from methanol gave colorless crystals, m.p. 254–256° dec. The infrared spectrum (Nujol) had a strong peak at 2.81–2.87 μ. The ultraviolet spectrum (ethanol) had λ_{max} 241, 265, 282, 323, 338 and 362 mμ (log ϵ 4.62, 4.36, 4.23, 3.68, 3.64 and 3.28, respectively). The compound was first dried at 80° *in vacuo*.

Anal. Calcd. for $C_{16}H_{14}O_3 \cdot {}^1/_2H_2O$: C, 72.99; H, 5.74. Found: C, 73.17; H, 5.70.

When the material was dried at 100° *in vacuo*, it was obtained in anhydrous condition.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.67; H, 5.73.

Acetylation with acetic anhydride (4-hr. reflux) and recrystallization of the product from methanol gave the **O-acetate**, m.p. 197–199°. The infrared spectrum had an intense peak at 5.68 μ. The ultraviolet spectrum (ethanol) had λ_{max} 225, 246, 260, 278, 329, 339 and 355 mμ (log ϵ 4.42, 4.61, 4.59, 4.45, 3.44, 3.30 and 3.23, respectively).

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.68; H, 5.51.

2,3-Dimethoxy-6-hydroxy-8,9,10,11-tetrahydro-7H-cyclohepta[a]naphthalene (IIb).—A mixture of 41 g. (0.110 mole) of homoveratric anhydride and 21.7 g. (0.194 mole) of cycloheptanone was treated with 300 ml. of ice-cold boron trifluoride etherate (47%) in one portion. The solid material dissolved after stirring for 0.5 hr. The solution was allowed to stand at room temperature overnight, then was placed in an ice-box and allowed to stand (at 0–10°) for 24 hr. longer. The mixture was hydrolyzed with a solution of 260 g. of sodium acetate in 500 ml. of water, as described for Ia. Upon chilling the resulting oily mixture, the crude product crystallized. It was collected, washed with cold water and triturated with a small quantity of methanol. Two crops of crystalline product, total weight 8.7 g. (29%), m.p. 198–202°, were obtained. Recrystallization from methanol gave colorless crystals, m.p. 207–208°. The infrared spectrum (chf.) had a peak at 2.76 μ. The ultraviolet spectrum (ethanol) had λ_{max} 237, 274, 285, 296, 324 and 337 mμ (log ϵ 4.91, 3.61, 3.61, 3.49, 3.58 and 3.72, respectively).

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.93; H, 7.45.

Acetylation with boiling acetic anhydride (2 hr.) gave the **O-acetate, Xa**, m.p. 139–141°, after recrystallization from methanol or cyclohexane–ethyl acetate (Norit). The infrared spectrum showed an intense peak at 5.70 μ, and the ultraviolet spectrum (ethanol) had λ_{max} 238, 267, 276, 285, 296, 315 and 329 mμ (log ϵ 4.78, 3.54, 3.59, 3.58, 3.41, 3.28 and 3.48, respectively).

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.84; H, 7.06.

Methylation with excess dimethyl sulfate and potassium hydroxide afforded the **methyl ether Xb**, which, after recrystallization from methanol, was obtained as colorless crystals, m.p. 122–124°. The ultraviolet spectrum (ethanol) had λ_{max} 238, 272, 282, 321 and 330 mμ (log ϵ 4.92, 3.66, 3.62, 3.56 and 3.74, respectively).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.75. Found: C, 75.43; H, 7.72.

Treatment of IIb with bromine in chloroform at room temperature resulted in rapid consumption of the reagent, hydrogen bromide evolution and formation of **bromo-derivative Xc**. Evaporation of the solvent and recrystallization of the residue from methanol gave colorless crystals, m.p. 164–165°.

Anal. Calcd. for $C_{17}H_{19}O_3Br$: C, 58.13; H, 5.45; Br, 22.75. Found: C, 58.38; H, 5.49; Br, 22.86.

3-Phenyl-4-carbethoxycyclohex-2-ene-1-one (IV).—A mixture of 2 g. of crystalline ethyl benzoylacetate–methyl vinyl ketone adduct,[13] m.p. 127–129°, and 20 g. of polyphosphoric acid was heated on a steam-cone and stirred for 12 minutes. The solid dissolved rapidly and a deep carmine-red color appeared. Hydrolysis in the usual manner with ice and water and isolation of the neutral product in the usual way gave 1.5 g. of yellow oil, the infrared spectrum of which had intense peaks at 5.80 and 6.01 μ. **The 2,4-dinitrophenylhydrazone** was prepared in 95% yield from this crude product. Recrystallization from ethyl acetate gave red crystals, m.p. 169–171°, which did not depress the m.p. of a sample of the derivative prepared as described earlier.[13]

2,3-Dimethoxy-4b-hydroxy-8a-methyl-9-keto-4b,5,6,7,8,-8a,9,10-octahydrophenanthrene (V).—A mixture of 13.6 g. (0.0364 mole) of homoveratric anhydride and 9.9 g. (0.0883 mole) of 2-methylcyclohexanone was treated with 105 ml. of ice-cold, 47% boron trifluoride etherate (one portion). When the mixture was swirled in an ice-bath, the solid material dissolved gradually. The solution was allowed to stand in an ice-box for 5 days. Hydrolysis with a solution of 100 g. of sodium acetate in 350 ml. of water, as described for Ia, gave viscous, orange oil, which did not crystallize. The oil was extracted with ether, and the organic solution was washed with successive portions of water, sodium bicarbonate solution (excess) and water. Evaporation of the dried solution gave material which crystallized rapidly. Trituration with ether afforded 6.7 g. (63%) of pale-yellow crystals, m.p. 127–129°. Recrystallization from ethyl acetate gave colorless needles, m.p. 129–130°. The infrared spectrum (chf.) was very similar to that of Ia, showing weak hydroxyl band at 2.82–2.90 μ, and an intense carbonyl peak at 5.80 μ. The infrared spectrum in Nujol mull had no hydroxyl band and displayed the intense carbonyl peak at 5.82 μ. The ultraviolet spectrum (ethanol) had λ_{max} 231 and 283–287 mμ (log ϵ 3.89 and 3.58–3.59, respectively).

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.36; H, 7.45.

Like Ia, this compound was insoluble in dilute alkali, gave no ferric chloride test, was inert to acetic anhydride and did not form a 2,4-dinitrophenylhydrazone or semicarbazone. Sodium borohydride reduction (in methanol) gave glassy material, the infrared spectrum of which (chf.) showed fairly strong absorption at 2.7–2.75 and 2.8–2.85 μ, and no carbonyl peak. Attempts to dehydrate this reduction product resulted mainly in decomposition.

2,3-Dimethoxy-8a-methyl-9-keto-6,7,8,8a,9,10-hexahydrophenanthrene 2,4-Dinitrophenylhydrazone.—A mixture of 2.2 g. of V and 30 g. of polyphosphoric acid was heated on a steam-cone and stirred steadily for 7 minutes. The cooled, deep-red solution was hydrolyzed with ice and water, and the neutral product was isolated in the usual way. There was obtained 2.1 g. of bright-red, viscous oil which did not crystallize but on standing gradually became dark brown. The infrared spectrum (chf.) still had an intense peak at 5.80–5.83 μ but was rather different in other respects from the spectrum of V. The 2,4-dinitrophenylhydrazone was prepared in the usual way in approximately 70% yield. Recrystallization from ethyl acetate gave orange, small crystals, m.p. 221–223° dec.; λ_{max} (chf.) 365 mμ, 3.00 μ and 6.19 μ.

Anal. Calcd. for $C_{23}H_{24}N_4O_6$: C, 61.05; H, 5.35. Found: C, 61.25; H, 5.14.

Attempts to prepare other derivatives, for example the semicarbazone, from the crude dehydrated ketone were unsuccessful, apparently because of decomposition.

Lithium Aluminum Hydride Reduction of Ia.—Compound Ia (0.6 g.) was stirred with a mixture of 1.2 g. of lithium aluminum hydride and 500 ml. of dry ether at room temperature for 9 hr. Excess hydride and organic complex were then hydrolyzed by cautious addition of 5 ml. of water (stirring), and the suspension was filtered. Evaporation of the colorless ether solution and trituration of the residue with a few ml. of ethyl acetate gave 0.5 g. of colorless crystals, m.p. 147–149°, not raised after recrystallization from the same solvent. The infrared spectrum (chf.) had a moderately strong band at 2.77–2.86 μ. The ultraviolet spectrum (ethanol) had λ_{max} 232 and 282 mμ (log ϵ 4.07 and 3.59, respectively).

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.53; H, 8.73.

These analytical figures were obtained with a sample which had been dried at 100° in high vacuum for 5 hr., and thus the material evidently is not a hydrate. The same compound was obtained, although less pure and in lower yield, by reduction of Ia with sodium borohydride in methanol.

2,3-Dimethoxy-5,6,7,8-tetrahydrophenanthrene-9,10-quinone (VIIIa).—A rapid stream of air and ozone from a

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Welsbach ozonizer was passed into an ice-cold solution of 0.55 g. of IIa in 250 ml. of ethyl acetate. A bright-red color developed soon and did not appear to become any more intense after 3 minutes; the gas stream was discontinued after 4 minutes, and the solvent was evaporated as rapidly as possible. The partly crystalline residue was triturated with a small quantity of ethyl acetate. There was obtained 0.28 g. of deep-red needles. Neither this material nor that purified further by recrystallization from ethyl acetate had a sharp melting point but rather decomposed gradually when heated above 150°. The infrared spectrum of a purified sample (chf.) had a very sharp, intense peak at 6.01 μ with less intense shoulders at 5.94 and 6.07 μ.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.65; H, 6.23.

A small sample of VIIIa, when treated in warm acetic acid with a solution of *o*-phenylenediamine, gave compound IXa; yellow needles from ethyl acetate, m.p. 228–229°.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85. Found: C, 76.99; H, 6.00.

2,3-Dimethoxy-5,6-diketo-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]naphthalene (VIIIb).—Compound IIb was exposed to ozone as described in the preceding experiment, except that reaction time was increased to 30 minutes, in view of the fact that the red color developed more slowly. From 0.5 g. of IIb there was obtained 0.4 g. of red crystals, m.p. 140–145°. Recrystallization from ethyl acetate gave deep-red, lustrous needles, m.p. 146–148°. The infrared spectrum (chf.) had a sharp, intense peak at 6.06 μ with shoulders at 5.96 and 6.10 μ.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.35; H, 6.62.

Compound IXb was prepared as described for IXa; yellow crystals from ethyl acetate, m.p. 219–220°.

Anal. Calcd. for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19. Found: C, 76.85; H, 6.18.

Hydrogenation of 9,10-Phenanthrenequinone.—A mixture of 9.8 g. of 9,10-phenanthrenequinone, 6.5 g. of 10% palladium–charcoal and 450 ml. of ethyl acetate was shaken under hydrogen (40 lb.). Somewhat more than one mole of hydrogen was absorbed rapidly (5 minutes) at room temperature, representing, no doubt, reduction to the hydroquinone. Absorption then ceased and was not resumed until the system was heated to about 80°. Additional hydrogen (3–4 moles) was then absorbed slowly (7 hr.), and finally the consumption of hydrogen became extremely slow, whereupon the cooled contents of the bottle were filtered. The yellowish solution thus obtained became somewhat darker in color during evaporation of the solvent. The residue crystallized readily but continued to acquire a darker color; the exact yield of product could not be ascertained. By rapid, repeated crystallization of the crude material from ethyl acetate and then from cyclohexane, there were obtained colorless crystals, m.p. 127–128°. This material, **1,2,3,4,5,6,7,8-octahydrophenanthrene-9,10-diol**, appeared to be stable when purified and dried, but air-oxidized readily in the presence of solvents, especially if warmed above 70°. The infrared spectrum (chf.) had a fairly strong peak at 2.82 μ. The compound gave a positive ferric chloride test and deteriorated rapidly in the presence of aqueous alkali.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.92; H, 8.21.

Some of the original crude material from hydrogenation was treated with excess acetic anhydride (20 ml.) and ethyl acetate (200 ml.), and the solution was allowed to stand at room temperature overnight. Evaporation of solvent and excess reagent and recrystallization of the residue (cyclohexane–ethyl acetate) gave the **monoacetate** of the diol; colorless crystals, m.p. 169–171°. The infrared spectrum (chf.) had peaks at 2.80 and 5.70 μ. The compound did not give a ferric chloride test but was soluble in dilute sodium hydroxide solution.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.60; H, 7.51.

The remainder of the crude diol, upon standing exposed to air, acquired a red-purple color and finally, after a week, became almost black. Trituration with ethyl acetate then afforded (in rather good yield) greenish-black crystals. Recrystallization from the same solvent gave pure **1,2,3,4-tetrahydro-9,10-phenanthrenequinhydrone**[17]; green needles, m.p. 159–161°. Solutions and melts of this compound were deep purple. The infrared spectrum (chf.) had a moderately strong peak at 2.93 μ and a quintet of sharp peaks, 6.07, 6.14, 6.24, 6.29 and 6.40 μ.

Anal. Calcd. for $C_{28}H_{26}O_4$: C, 78.85; H, 6.14. Found: C, 79.12; H, 5.84.

1,2,3,4-Tetrahydrophenanthrenequinone, also prepared by Skita,[17] was found to consist of red-orange needles having no definite m.p. but rather decomposing gradually above 120°. The infrared spectrum of this quinone, after recrystallization from ethyl acetate, showed an intense peak at 6.02 μ with a less intense secondary peak at 5.90 μ.

2,3-Dimethoxy-5-nitroso-6-hydroxy-8,9,10,11-tetrahydro-7H-cyclohepta[a]naphthalene (Xd).—An ice-cold suspension of 1.4 g. of IIb and 2 g. of sodium nitrite in 100 ml. of methanol and 50 ml. of water was treated with 50 ml. of cold 50% sulfuric acid, in 10 portions, over a period of an hour. Additional sodium nitrite (1.5 g.) was added, and the mixture was kept in an ice-box for 4 days, during which time dark red crystals separated gradually. The product was collected and was washed with four 20-ml. portions of water and 20 ml. of methanol. After air-drying, there was obtained 1.4 g. of red crystals, m.p. 170–174°. Recrystallization from ethyl acetate raised the m.p. to 176–178°. The infrared spectrum (chf.), as expected in analogy with 1-nitroso-2-naphthol, showed no absorption near 3 μ and had a peak at 6.23 μ with a shoulder at 6.09–6.13 μ.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36. Found: C, 67.87; H, 6.52.

The corresponding **5-acetylamino-6-acetoxy** compound, Xe, was prepared by hydrogenation of 0.5 g. of Xd in the presence of 1 g. of 10% palladium–charcoal catalyst in ethyl acetate at room temperature for an hour. After filtration, the solution was treated immediately with 30 ml. of acetic anhydride and was allowed to stand at room temperature overnight. Evaporation then gave discolored crystals, trituration of which with ethyl acetate afforded 0.3 g. of product, m.p. 225–227°. Recrystallization from the same solvent gave colorless crystals, m.p. 228–228.5°.

Anal. Calcd. for $C_{21}H_{23}O_5N$: C, 67.91; H, 6.79; N, 3.77. Found: C, 68.11; H, 6.76; N, 3.73.

The infrared spectrum (chf.) displayed peaks at 2.96, 5.69, 5.97 and 6.03 μ.

2,3-Dimethoxy-5,6,7,8-tetrahydro-9-hydroxy-10-acetylphenanthrene (XIa).—Glacial acetic acid (50 ml.) was saturated with anhydrous boron trifluoride at ice temperature. There was added 9.6 g. (0.0257 mole) of homoveratric anhydride and 5.5 g. (0.0561 mole) of cyclohexanone. The mixture was stirred steadily and kept at 35–40° for 20 hr. During this time the anhydride dissolved, and later a brown solid separated. The mixture was treated with a solution of 32 g. of sodium acetate in 250 ml. of water, whereupon bright yellow crystals were formed. The material was collected and washed with two small portions of water. Trituration with methanol, in which the crystals were very sparingly soluble, afforded 3.2 g. of a complex, m.p. 239–241° dec., not changed by recrystallization from dry benzene. The complex was taken up in 100 ml. of methanol, and the suspension was boiled 1 hr. The resulting solution was reduced to 20-ml. volume and was cooled. The crystals which separated were collected, washed with a small portion of methanol and dried; 2.9 g. (38%) of yellow needles, m.p. 167–168°. Recrystallization from methanol did not improve this m.p. The infrared spectrum (chf.) showed no hydroxyl or ordinary carbonyl bands, although there was an intense peak at 6.25 μ with shoulders at 6.09 and 6.13 μ. The ultraviolet spectrum (ethanol) had λ_{max} 234, 294 and 340 mμ (log ϵ 4.80, 3.57 and 4.00, respectively). The compound gave a dark-green ferric chloride test.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.01; H, 6.75.

Aromatization of a sample of XIa in the presence of 3 parts by weight of 10% palladium–charcoal in *p*-cymene (refluxed 2.5 hr.) gave a small amount of **2,3-dimethoxy-9-hydroxy-10-acetylphenanthrene**, m.p. 161–162° (from methanol). The infrared spectrum (chf.) was similar to but not identical with the spectrum of XIa. The ultraviolet spectrum (ethanol) had λ_{max} 235, 254, 272, 316, 333, 346 and 378 mμ (log ϵ 4.47, 4.57, 4.31, 3.84, 3.80, 3.81 and 3.74, respectively).

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Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.4. Found: C, 72.70; H, 5.7.

2,3-Dimethoxy-5-acetyl-6-hydroxy-8,9,10,11-tetrahydro-7H-cyclohepta[a]naphthalene (XIb).—Condensation of 9.9 g. of homoveratric anhydride and 5.8 g. of cycloheptanone in the presence of 50 ml. of boron-trifluoride-saturated glacial acetic acid, as described in the preceding experiment, and hydrolysis with 33 g. of sodium acetate and 20 g. of sodium bicarbonate in 300 ml. of water (warmed on a steam-cone for 20 minutes) gave, after cooling the mixture, semi-solid brown oil. This material was washed with 2 small portions of water (decanting) and was triturated with a small amount of methanol. There was obtained 0.6 g. of yellow crystals, m.p. 155–157°. Additional product (0.3 g.) was obtained when the original aqueous solution was allowed to stand for a week, bringing the total yield to 0.9 g. (11%). Recrystallization from methanol gave yellow needles, m.p. 157–158°. The infrared spectrum (chf.) was similar to that of XIa, and the ultraviolet spectrum had λ_{max} 235, 291 and 345 mμ (log ε 4.84, 3.56 and 4.02, respectively). The compound gave a dark green ferric chloride test.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.64; H, 7.06.

2,3-Dimethoxy-9-hydroxy-10-(α-hydroxyethyl)-4b,5,6,7,-8,8a,9,10-octahydrophenanthrene (XIIa).—Compound XIa (0.3 g.) in 200 ml. of ethyl acetate with 1.5 g. of 10% palladium–charcoal was shaken under hydrogen (40 lb.) at 80° for 1.2 hr. Filtration of the catalyst and evaporation of the solvent gave viscous, pale yellow oil which crystallized rapidly in the presence of methanol. Recrystallization from cyclohexane–ethyl acetate gave 0.25 g. of colorless crystals, m.p. 167–170°. Further recrystallization gave pure material, m.p. 171–173°. The infrared spectrum (chf.) had a moderately strong doublet, 2.76 and 2.98 μ. The ultraviolet spectrum (ethanol) had λ_{max} 288 mμ (log ε 3.34) and an inflection point at 225 mμ (log ε 3.99).

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.50; H, 8.23.

Similar hydrogenation of the boron complex, m.p. 239–241°, of XIa afforded a monohydroxy compound, probably **2,3-dimethoxy-9-hydroxy-10-ethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthrene**, m.p. 151–152.5°, after recrystallization from cyclohexane–ether. The infrared spectrum (chf.) of this compound had a single, sharp peak at 2.73 μ, and the ultraviolet spectrum (ethanol) had λ_{max} 280 and 285 mμ (log ε 3.17 and 3.20, respectively).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.72; H, 9.12.

2,3-Dimethoxy-5-(α-hydroxyethyl)-6-hydroxy-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]naphthalene (XIIb).—Hydrogenation of 0.4 g. of XIb as described in the preceding experiment gave 0.35 g. of colorless crystals, m.p. 138–140°. Recrystallization from cyclohexane–ethyl acetate gave pure material, m.p. 142–144°. The infrared spectrum (chf.) had a doublet 2.76 and 2.99 μ, and the ultraviolet spectrum (ethanol) had λ_{max} 291 mμ (log ε 3.43) and a point of inflection at 227 mμ (log ε 3.98).

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.44; H, 8.75.

2-Ethylcyclohexanone.—A solution of 5 g. of 2-acetylcyclohexanone[22] in 250 ml. of ethyl acetate containing 4 g. of 10% palladium–charcoal was shaken under hydrogen (40 lb.) at 80° for an hour. Two moles of hydrogen were consumed in 0.5 hr., and then the reaction became very slow. Filtration of the catalyst and evaporation of the solvent gave nearly colorless oil. The infrared spectrum (chf.) had an intense peak at 5.87–5.89 μ and a very weak band at 2.90 μ (indicating presence of some hydroxylic material). The **2,4-dinitrophenylhydrazone** was prepared in *ca.* 80% yield from the crude product; recrystallization from ethanol gave orange needles, m.p. 160–161° (lit.[23] m.p. 159–161°).

Condensation of Homoveratric Anhydride with 2-Tetralone.—To a mixture of 7.4 g. of homoveratric anhydride and 4.2 g. of 2-tetralone was added 65 ml. of ice-cold 47% boron trifluoride etherate. The suspension was swirled in an ice-bath for 15 minutes until the anhydride dissolved and was kept in an ice-box for 2 days. Hydrolysis with a solution of 60 g. of sodium acetate in 350 ml. of water at 60–70° for 10 minutes gave oily material, which was extracted with ether–ethyl acetate. The organic solution was washed with successive portions of water, sodium bicarbonate solution (excess) and water and was dried over magnesium sulfate. The solvents were evaporated at 30°, and the residual oil (6.9 g.) was dissolved in 20 ml. of ether. Refrigeration of this solution overnight resulted in formation of 0.85 g. of gummy crystals. Trituration of the crystals with additional ether gave 0.5 g. of product, m.p. 189–192°. Recrystallization from methanol afforded colorless crystals, m.p. 194–195° dec. The infrared spectrum (chf.) showed a weak band at 2.82–2.86 μ and a moderately strong peak at 5.83 μ. The ultraviolet spectrum (ethanol) had λ_{max} 227, 275, 321 and 349 mμ (log ε 4.45, 4.61, 3.96 and 2.96, respectively).

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 74.05; H, 6.22. Found: C, 74.08; H, 5.90.

Efforts to dehydrate and acetylate this material as with Ia led to decomposition and formation of mixtures of products.

Acknowledgment.—I am indebted to Dr. William C. Alford and his staff for microanalytical data, and to Mr. H. Franklin Byers, Miss Catherine Monaghan and Miss Patricia Wagner for spectra.

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Further Research on Biphenyl, Stilbene and Diphenylethane Derivatives—Potential Anticholesterinemic, Antirheumatic Drugs. VII

BY G. CAVALLINI, E. MASSARANI, D. NARDI AND R. D'AMBROSIO

RECEIVED SEPTEMBER 21, 1956

Derivatives of biphenyl, stilbene and diphenylethane have been prepared with various substituents in the 4-position: alkylacetic acids; oxyacetic acid; and propionic, butyric, acrylic, pyruvic, crotonic, β-hydroxypropionic and γ-ethyl-β-hydroxybutyric acid.

In a previous paper[1] we prepared derivatives of biphenyl, stilbene and diphenylethane with various groups in the 4-position

$$-CH_2COOH,\ -\underset{\displaystyle C_2H_5}{\overset{\displaystyle |}{CH}}-COOH,\ -CH_2-CO-COOH$$

Some of these substances showed a marked anticholesterinemic activity, the most active among them being the 4-biphenylylethylacetic acid[2] which has been used therapeutically with satisfactory results.[3,4]

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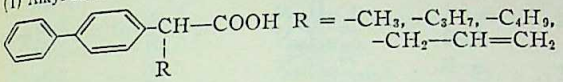
With the hope of finding substances having both anticholesterinemic and antirheumatic activity, we have prepared additional derivatives of biphenyl (and in a few cases of stilbene and diphenylethane) with the following acid groups in the 4-position:

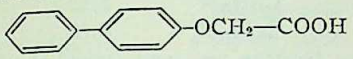
(1) Alkyl-substituted acetic acids



R = $-CH_3$, $-C_3H_7$, $-C_4H_9$, $-CH_2-CH=CH_2$

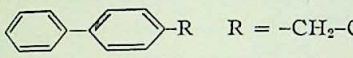
Diphenylethane, R = $-C_3H_7$

(2) Oxyacetic acid



Also stilbene and diphenylethane.

(3) 3 and 4 carbon acids



R = $-CH_2-CH_2-COOH$, $-CH_2-CH_2-CH_2-COOH$, $-CH=CH-COOH$, $-CH_2-CH=CH-COOH$, $-CH_2COCOOH$, $-CH(OH)-CH_2-COOH$, $-CH(C_2H_5)-CH(OH)-COOH$

Stilbene, R = $-CH=CH-COOH$

Diphenylethane, R = $-CH_2-CH_2-COOH$

4-Biphenylaldehyde, 4-biphenylylacetaldehydes and the 4-biphenylylalkylacetonitriles served as intermediates for the preparation of the acids. The 4-biphenylylalkylacetonitriles, obtained by alkylation[5] of 4-biphenylylacetonitrile, gave the corresponding acetic acids upon acid hydrolysis. Saponification of 4-biphenylylacetonitrile yielded 4-biphenylyloxyacetic acid; the oxyacetic acids of stilbene and diphenylethane were prepared in the same way. It was not possible to convert 4-biphenylyldiethylacetonitrile and 4-biphenylyl-*n*-octylacetonitrile to the corresponding acids as both the acid and alkaline hydrolyses were unsuccessful.

4-Biphenylaldehyde, which was obtained from 4-biphenylylmethyl chloride,[6] was used in the following preparations: (1) 2-phenyl-4-biphenylal-5-oxazolone which upon saponification yielded 4-biphenylylpyruvic acid; (2) 4-biphenylylacrylic acid by Knoevenagel's reaction[7]; the acrylic acid was reduced to the corresponding propionic acid; (3) 4-biphenylyl-β-hydroxypropionic acid which was obtained by the Reformatsky synthesis.[8]

4-Biphenylylacetaldehyde and the alkylacetaldehydes were prepared from the corresponding acid chlorides by Rosenmund's reaction.[9] The former was used for the synthesis of 4-biphenylylcrotonic acid which was subsequently reduced to the butyric acid.

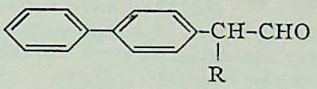
Experimental

The melting points are not corrected.

4-Biphenylaldehyde.—A mixture of 40.4 g. (0.2 mole) of 4-biphenylylmethyl chloride, 60.2 g. (0.44 mole) of hexamethylenetetramine and 90 ml. of 50% acetic acid was refluxed for 2 hours. It was then added to 200 ml. of water and extracted with ether. The organic layer was washed with saturated, aqueous sodium bicarbonate and with water, dried over sodium sulfate and concentrated. Distillation of the residue yielded 21 g. (60%) of 4-biphenylaldehyde b.p. 130° (0.5 mm.); m.p. 60°.[10]

4-Biphenylylacetaldehyde.—The following procedure was also used for the preparation of the 4-biphenylylalkylacetaldehydes. The data are reported in Table I. Thionyl chloride (59 g., 0.5 mole) was added dropwise to 10.56 g. (0.05 mole) of 4-biphenylylacetic acid. The mixture was stirred for one hour at room temperature and for one hour on a steam-bath. The thionyl chloride was then distilled at reduced pressure. The residue, dissolved in 100 ml. of dry toluene, was reduced by the procedure of Rosenmund.[9] The catalyst was filtered, and the solvent evaporated *in vacuo* at 40° under a stream of nitrogen. The residue yielded 4-biphenylylacetaldehyde which was characterized by its 2,4-dinitrophenylhydrazone.

TABLE I



R	Yield, %	M.p., °C.	2,4-Dinitrophenylhydrazone Solvent for cryst.[a]	Formula	N, % Calcd.	Found
–H	81	172	A	$C_{20}H_{16}O_4N_4$	14.88	14.94
$-CH_3$	78	177	A	$C_{21}H_{18}O_4N_4$	14.35	13.94
$-C_2H_5$	84	121–123	B	$C_{22}H_{20}O_4N_4$	13.85	13.94
$-C_3H_7$	82	117	A	$C_{23}H_{22}O_4N_4$	13.39	13.27

[a] A, acetic acid; B, ethanol.

4-Biphenylyl-*n*-propylacetonitrile.—The other 4-biphenylylalkylacetonitriles, which are reported in Table II, were prepared by this method.

A mixture of 19.30 g. (0.1 mole) of 4-biphenylylacetonitrile, 6 g. (0.15 mole) of sodium amide and 60 ml. of dry ether was refluxed for 1 hour. After the addition of 25.5 g. (0.15 mole) of propyl iodide dropwise with stirring, the reaction mixture was refluxed for 6 hours. Then it was cooled, cautiously diluted with water, acidified with dilute hydrochloric acid, and extracted with ether. The extract was washed with aqueous sodium thiosulfate. Drying and concentration gave an oil which upon distillation yielded 4-biphenylyl-*n*-propylacetonitrile.

4-Biphenylyl-*n*-propylacetic Acid.—This procedure is typical for the hydrolysis of the 4-biphenylylalkylacetonitriles to yield the corresponding acetic acids, which are listed in Table III. A mixture of 23.5 g. (0.1 mole) of 4-biphenylyl-*n*-propylacetonitrile, 103 g. (1 mole) of concentrated sulfuric acid, 100 ml. of water and 120 g. (2 mole) of acetic acid was refluxed for 36 hours and 1 liter of water added. The mixture was made alkaline with 40% NaOH, charcoal was added and the solution was filtered. Acidification with dilute hydrochloric acid gave a white precipitate, which was filtered, dried and recrystallized from ligroin.

Oxyacetic Acids and 4-Diphenylethane-*n*-propylacetic Acid.—A mixture of 26.3 g. (0.1 mole) of 4-diphenylethane-*n*-propylacetonitrile, 120 ml. of methanol and 120 ml. of 40% sodium hydroxide was refluxed until the evolution of ammonia was complete. After cooling and evaporation of solvent, water was added to the residue, which was extracted with ether. The aqueous layer was acidified with hydrochloric acid, cooled, filtered and crystallized from 70% acetic acid, ethanol or cyclohexane; yield 13.6 g. (48%), m.p. 95°.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.21; H, 7.73.

The oxyacetic acids of biphenyl, stilbene and diphenylethane were prepared by this method; see Table IV.

4-Biphenylylethylacetic Acid Ethyl Ester.—Thionyl chloride (11.9 g., 0.1 mole) was added dropwise to 2.40 g. (0.01 mole) of 4-biphenylylethylacetic acid. The mixture was stirred for 1 hour at room temperature and for 1 hour on a steam-bath. After distillation of the thionyl chloride at reduced pressure, 16 ml. of dry ethanol was added to the residue. The mixture was stirred for 1 hour at room temperature and for 2 hours over a steam-bath. Concentration gave an oil which, upon distillation, yielded 1.6 g. (64%) of

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(8) S. N. Reformatsky, *ibid.*, **20**, 1210 (1887).
(9) K. W. Rosenmund and F. Zetzche, *ibid.*, **54**, 436 (1921).

(10) For other syntheses of 4-biphenylaldehyde see L. Gattermann, *Ann.*, **347**, 381 (1906); C. L. Knowles, THIS JOURNAL, **43**, 897 (1921); D. H. Hey, *J. Chem. Soc.*, 2476 (1931); D. Worländer, *Ber.*, **68**, 435 (1935).

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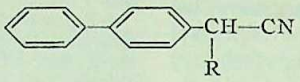
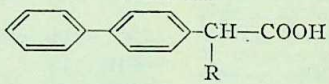
TABLE II



R	Yield, %	Boiling point °C.	Mm.	M.p., °C.	Solvent for cryst.[a]	Formula	Nitrogen, % Calcd.	Found
Methyl	63	155	1	54	A	$C_{15}H_{13}N$	6.76	6.55
n-Propyl	72	180	1	83	A	$C_{17}H_{17}N$	5.92	5.86
n-Butyl	84	158–160	0.5	58–59	A–B	$C_{18}H_{19}N$	5.61	5.60
Allyl	85	165–170	0.5	66–67	A–B	$C_{17}H_{15}N$	6.00	5.79
n-Amyl	85	160–168	1	72–73	A–B	$C_{19}H_{21}N$	5.31	5.08
n-Octyl	82	158–160	1	...	...	$C_{22}H_{27}N$	4.59	4.30
n-Propyl[b]	78	178–180	1	...	...	$C_{19}H_{21}N$	5.32	5.38
Diethyl[c]	80	167	0.5	87	A	$C_{18}H_{19}N$[d]	5.66	5.45

[a] A, Ethanol; B, water. [b] 4-Diphenylethane-*n*-propylacetonitrile. [c] Dry benzene was used instead of ether in the reaction mixture; the alkylating agent was ethyl bromide; and the extraction was made with benzene. [d] Calcd.: C, 86.70; H, 7.68. Found: C, 86.40; H, 7.71.

TABLE III[a]



R	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
Methyl[b]	70	145	...	...	...	...	...
n-Propyl[b]	69	117	...	...	...	...	...
n-Butyl[b]	30	107–108	...	...	...	...	...
n-Amyl	18	104	$C_{19}H_{22}O_2$	80.81	80.77	7.85	8.04
Allyl	15	117–118	$C_{17}H_{16}O_2$	80.96	80.99	6.38	6.26

[a] All products recrystallized from ligroin. Also prepared by F. F. Blicke and N. Grier, THIS JOURNAL, 65, 1725 (1943).

TABLE IV

R = $-O-CH_2-COOH$

	Yield, %	M.p., °C.	Solvent for cryst.[a]	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
Biphenyl[b]	90	189–190	A	...	...	...	...	...
Stilbene	95	208	A	$C_{16}H_{14}O_3$	75.55	75.77	5.55	5.69
Diphenylethane[c]	52	130	B	$C_{16}H_{16}O_3$	74.98	75.40	6.34	6.29

[a] A, acetic acid; B, benzene. [b] Prepared by E. Martin, M. E. Synerholm and P. W. Zimmerman, *Contr. Boyce Thomson Inst.*, 14, 91 (1945). [c] This product has been obtained also by the catalytic reduction of stilbeneoxyacetic acid in acetic acid with 0.5% of Pd on 10% C with a yield of 78%.

the ester; b.p. 161° (1 mm.). The crystals obtained from ethanol–water melted at 38°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 79.92; H, 7.50.

4-Biphenylyl-*n*-propylacetamide.—Thionyl chloride (11.9 g., 0.1 mole) was added dropwise to 2.54 g. (0.01 mole) of 4-biphenylyl-*n*-propylacetic acid. The mixture was stirred for 1 hour at room temperature and for 2 hours on a steam-bath. After distillation of the thionyl chloride at reduced pressure, 20 ml. of 15% ammonium hydroxide was added with shaking to the residue and vigorous stirring was continued for 3 hours at room temperature. The precipitate was filtered, washed with water and dried. Recrystallization from 70% acetone gave 2.4 g. (95%) of 4-biphenylyl-*n*-propylacetamide; m.p. 160°.

Anal. Calcd. for $C_{17}H_{19}ON$: N, 5.53. Found: N, 5.50.

4-Stilbenepyruvicacetamide was obtained by essentially the same procedure; m.p. 235°.

Anal. Calcd. for $C_{17}H_{15}O_2N$: N, 5.28. Found: N, 5.41.

2-Phenyl-4-(4′-biphenylal)-5-oxazolone.—A mixture of 3.64 g. (0.02 mole) of 4-biphenylaldehyde, 3.6 g. (0.02 mole) of hippuric acid, 3.2 g. (0.04 mole) of fused sodium acetate and 6.6 g. (0.6 mole) of acetic anhydride was stirred and heated for 4 hours on an oil-bath at 100°. After being cooled and standing overnight at room temperature, the mixture was filtered. The precipitate was washed with water and recrystallized from ethanol to give yellow crystals; yield 6 g. (92%); m.p. 182–183°.

Anal. Calcd. for $C_{22}H_{15}O_2N$: N, 4.30. Found: N, 4.29.

4-Biphenylylpyruvic Acid.—A mixture of 16.2 g. (0.05 [illegible] mole) of the above oxazolone and 1750 ml. of 6% aqueous sodium hydroxide was refluxed until the evolution of ammonia was complete. It was then cooled and filtered. The precipitate was suspended in water, boiled and acidified. The precipitate, which formed upon slow cooling, was crystallized from glacial acetic acid; yield 2 g. (17%); m.p. 220°.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.00; H, 5.03. Found: C, 74.52; H, 5.15.

***β*-4-Biphenylylacrylic Acid (I).**—A mixture of 3.64 g. (0.02 mole) of 4-biphenylaldehyde, 2.3 g. (0.022 mole) of malonic acid, 50 ml. of 95% ethanol and 0.5 ml. of pyridine was refluxed for 6 hours. After cooling the precipitate was filtered, washed with water and recrystallized from 95% ethanol. 4-Biphenylyl-γ-crotonic acid was prepared from the acetaldehyde by the same method. The data are listed in Table V.

4-Biphenylyl-*n*-propionic Acid (II).—4-Biphenylylacrylic acid (2.24 g., 0.01 mole), dissolved in 320 ml. of glacial acetic acid, was hydrogenated at normal pressure with 0.1 g. of a 10% Pd/C catalyst. Filtration followed by vacuum distillation gave a residue which was crystallized from 70% ethanol, see Table V.

4-Biphenylyl-β-hydroxypropionic Acid (III).—A Reformatsky reaction was carried out in the usual way with 3.64 g. (0.02 mole) of 4-biphenylaldehyde, 3.32 g. (0.02 mole) of ethyl bromoacetate, 1.3 g. (0.02 mole) of zinc dust in 50 ml. of benzene. After cooling the mixture was extracted with ether. The aqueous layer was acidified with hydrochloric acid and the resulting precipitate recrystallized from 50% acetic acid. 4-Biphenylyl-γ-ethyl-β-hydroxy-*n*-bu[illegible] same method; see Table V.

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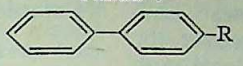
TABLE V



R	Starting product	Method	Yield, %	M.p., °C.	Solvent for cryst.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
-CH=CH-COOH[b]	4-Biphenylaldehyde	I	54	225	A	...	...	...	...	...
-CH_2-CH=CH-COOH	4-Biphenylylacetaldehyde	I	21	188	B	$C_{16}H_{14}O_2$	80.65	79.61	5.92	6.32
-CH_2-CH_2-COOH[c]	β-4-Biphenylacrylic acid	II	70	150	A–C	...	...	...	...	...
-CH_2-CH_2-CH_2-COOH[d]	γ-4-Biphenylyl crotonic acid	II	98	113–115	...	...	...	...	...	...
-CH(OH)-CH_2-COOH	4-Biphenylaldehyde	III	62	171	B–C	$C_{15}H_{14}O_3$	74.36	73.95	5.82	5.48
-CH(C_2H_5)-CH(OH)-CH_2-COOH	4-Biphenylylethylacetaldehyde	III	68	175–176	B	$C_{18}H_{20}O_3$	76.03	76.04	7.09	6.98

[a] A, ethanol; B, acetic acid; C, water. [b] Prepared also by D. H. Hey, *J. Chem. Soc.*, 2438 (1931); J. V. Brawn and J. Nelles, *Ber.*, 66, 1464 (1933). [c] R. W. Dodson and P. Sollman, THIS JOURNAL, 73, 4197 (1951). [d] C. Willgerodt and Th. Scholtz, *J. prakt. Chem.*, 81, 397 (1910); M. Weizmann, E. Bergmann and E. Bograchov, *Chemistry and Industry*, 402 (1940).

4-Stilbeneacrylic Acid.—This acid was prepared from 4-stilbenealdehyde in the following three ways: 1, procedure I, yield 65%, m.p. 256–258°.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64; O, 12.78. Found: C, 81.20; H, 5.89; O, 13.03.

2. Procedure II, yield 83%, m.p. 256–258°. This compound gave no depression of the melting point when mixed with the sample obtained above.

Anal. Found: C, 81.34; H, 5.90; O, 12.97.

3. A Perkin reaction[11] was carried out in the usual way with 4.16 g. (0.02 mole) of 4-stilbenealdehyde, 6.12 g. (0.06 mole) of acetic anhydride and 1.15 g. (0.014 mole) of fused sodium acetate. The mixture was added to water and filtered, and the residue recrystallized from glacial acetic acid; yield 1.1 g. (22%). The product gave no depression of melting point (256–258°) with the sample obtained above.

4-Diphenylethane-*n*-propionic Acid.—4-Stilbeneacrylic acid (2.50 g., 0.01 mole), dissolved in 2 liters of ethanol, was hydrogenated as described in (II). Filtration followed by vacuum distillation gave a residue which was crystallized from 80% acetic acid; yield 2.3 g. (92%), m.p. 170–172°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.57; H, 6.67.

MILANO, ITALY

(11) W. H. Perkin, *J. Chem. Soc.*, 21, 53 (1868).

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

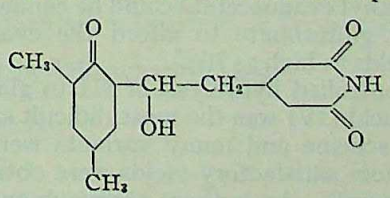
Actidione. I. The Synthesis of the Glutarimide Moiety

BY DONALD D. PHILLIPS,[1] MARIO A. ACITELLI[2] AND JERROLD MEINWALD

RECEIVED FEBRUARY 1, 1957

The synthesis of glutarimide-β-acetaldehyde (V) from acetone-dicarboxylic ester is described. The aldehyde is of interest as a possible intermediate in the total synthesis of actidione, an antifungal antibiotic produced by *Streptomyces griseus*.

The presence of an antifungal antibiotic in culture filtrates from streptomycin-producing strains of *Streptomyces griseus* was first reported in 1946.[3] The empirical formula $C_{27}H_{42}N_2O_7$ was originally assigned to the crystalline antibiotic[4] and the name "actidine" was proposed on the erroneous assumption that the compound was a diketone. The molecular formula was later corrected[5] to $C_{15}H_{23}NO_4$ and further investigations on the antibiotic indicated that it contained only one ketone group.[6] The total structure (I) for the antibiotic was established[7] in 1949, principally on the basis of the hydrolysis products obtained from I and the corresponding β-



I

diketone. To date, however, this assignment has not been verified by total synthesis.

Although the structure assigned to actidione (I) can hardly be in doubt, a total synthesis is of more than academic interest in view of the increasing importance of the antibiotic in plant disease control.[8]

(1) To whom inquiries regarding this article should be sent.

(2) From the dissertation presented by M.A.A. in partial fulfillment of the requirements for the degree of Doctor of Philosophy. This paper was delivered at the 131st Meeting of the A.C.S., Miami, Florida, April 7–12, 1957.

(3) A. J. Whiffen, N. Bohonos and R. L. Emerson, *J. Bacteriol.*, 52, 610 (1946).

(4) B. E. Leach, J. H. Ford and A. J. Whiffen, THIS JOURNAL, 69, 474 (1947).

(5) J. H. Ford and B. E. Leach, *ibid.*, 70, 1223 (1948).

(6) E. C. Kornfeld and R. G. Jones, *Science*, 108, 437 (1948).

(7) E. C. Kornfeld, R. G. Jones and T. V. Parke, THIS JOURNAL, 71, 150 (1949).

(8) I. M. Felber and C. L. Hamner, *Botan. Gaz.*, 110, 324 (1948); J. R. Vaughn and C. L. Hamner, *Proc. Am. Soc. Hort. Sci.*, 54, 435 (1949); H. W. Anderson and D. Gottlieb, *Econ. Botany*, 6, 294 (1952); C. Leben and G. W. Keitt, *J. Agr. Food Chem.*, 2, 234 (1954); P. W. Brian, *Chem. Products*, 17, 139 (1954); J. C. Dunegan, *J. Agr. Food Chem.*, 2, 1030 (1954); and W. J. Zaumeyer, *ibid.*, 3, 112 (1955).

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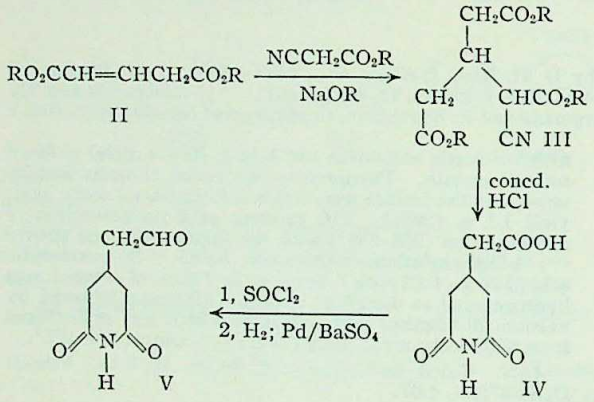
It has seen commercial application in the control of cherry leaf spot[9] and various turf diseases[10] and shows promise as a rodent repellent.[11] Moreover, its ability to prolong the life of leukemic mice[12] and its limited control of sarcoma 180[13] are of more than passing interest in cancer research.

We have approached the problem of total synthesis with the view that actidione (I) might be obtained from an aldol condensation between (+)-2,4-dimethylcyclohexanone and glutarimide-β-acetaldehyde (V). For this reason, we have synthesized the glutarimide moiety (V) and experiments designed to test our hypothesis are in progress.

The pertinent equations for the most satisfactory synthesis of the aldehyde are listed in Chart 1.

CHART 1



In the early stages of the problem, glutaconic ester (II) was prepared from chloroform and malonic ester,[14] but the yields were erratic and the reaction was difficult to control. A far superior method involved the catalytic reduction of acetone-dicarboxylic ester to dimethyl β-hydroxyglutarate which then could be dehydrated to II. This approach was particularly attractive in view of the recently announced commercial availability of dimethyl acetonedicarboxylate.[15] Although the corresponding hydroxy ester was surprisingly inert to a variety of dehydrating agents, good yields of glutaconic ester were obtained in the presence of phosphorus pentoxide. Under scrupulously anhydrous conditions, methyl cyanoacetate could be condensed with dimethyl glutaconate to afford the cyanotriester III in yields as high as 70%.

The controlled hydrolysis of III to glutarimide-β-acetic acid (IV) was the most difficult step in the reaction scheme and many variants were investigated before satisfactory yields were obtained (see Experimental). An indirect approach entailed the complete hydrolysis of III to methanetriacetic acid.

(9) D. Cation, *Am. Fruit Grower*, **74**, 29 (1954); T. T. McClure, *Phytopathology*, **42**, 14 (1952); J. M. Hamilton and M. Szkolnik, *Proc. N. Y. State Hort. Soc.*, 58 (1955).

(10) J. R. Vaughn, *Phytopathology*, **41**, 36 (1951); H. D. Wells and B. P. Robinson, *ibid.*, **44**, 509 (1954).

(11) J. F. Welch, *J. Agr. Food Chem.*, **2**, 142 (1954).

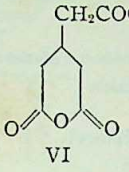
(12) J. C. Bateman and C. T. Klopp, *Proc. Am. Assoc. Cancer Research*, **1**, 3 (1953).

(13) H. C. Reilly, C. C. Stock, S. M. Buckley and D. A. Clark, *Cancer Research*, **13**, 684 (1953).

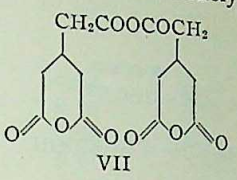
(14) E. P. Kohler and G. H. Reid, THIS JOURNAL, **47**, 2803 (1925).

(15) We are grateful to the Chas. Pfizer Co. of Brooklyn, N. Y., for generous samples of this ester.

It was anticipated that the corresponding anhydride VI would yield IV (or its amide) on ammonolysis,



VI



VII

but the only anhydride that could be isolated from methanetriacetic acid was VII and ammonolysis experiments on VII were inconclusive. The Guareschi imide synthesis was equally unsuccessful as no crystalline product could be obtained from the reaction between chloroacetaldehyde and methyl cyanoacetate. Moreover, the recently reported[16] hydrolysis of cyano esters to glutarimides in basic media resulted in the formation of intractable oils when applied to III (R = CH_3 and C_2H_5).

The preparation of the acid chloride from glutarimide-β-acetic acid (IV) presented no difficulties and a beautifully crystalline product (m.p. 129–130°) was obtained readily. When subjected to the conditions of the Rosenmund reduction, this acid chloride afforded good yields of the desired aldehyde, m.p. 122–123°, although it was found necessary to omit completely the catalyst poison often suggested.

Acknowledgment.—The antifungal and antibiotic properties of glutarimide β-acetaldehyde (V) and acid (IV) are being tested by the Upjohn Laboratories, Kalamazoo, Mich., through the courtesy of Dr. Alan J. Lemin. We are also indebted to the Upjohn Laboratories for generous samples of actidione.

Experimental[17]

Trimethyl α-Cyanomethanetriacetate (III, R = CH_3).[14]—To a flame-dried flask was added 50 ml. of methanol and 79.2 g. (0.8 mole) of methyl cyanoacetate (both of which had been dried by distillation from magnesium methoxide) followed by 63.2 g. (0.4 mole) of freshly distilled dimethyl glutaconate.[18] To this mixture was added 18 drops of freshly prepared sodium methoxide solution (from 0.9 g. of sodium and 30 ml. of absolute methanol). The reaction mixture, adequately protected from moisture by phosphorus pentoxide tubes, was heated under reflux for 12 hours with the addition of 18 drops of sodium methoxide solution every two hours to ensure alkalinity.

The reaction was allowed to stand overnight at room temperature after which time it was quenched by the addition of a few drops of acetic acid. Solvent methanol was removed at the water-pump and the residue was fractionally distilled to give 62 g. (60%) of the cyano ester as a colorless, viscous oil, b.p. 162–165° (2.5 mm.), $n^{25}D$ 1.4521.

Anal. Calcd. for $C_{11}H_{15}O_6N$: N, 5.44. Found: N, 5.50.

Complete Hydrolysis of III.—A stirred mixture of 5.5 g. (0.02 mole) of trimethyl α-cyanomethanetriacetate (III) and 50 ml. of concentrated hydrochloric acid was heated for three hours on the steam-bath. The volatile components were removed by distillation *in vacuo* and the residue was

(16) E. Tagmann, E. Sury and K. Hoffmann, *Helv. Chim. Acta*, **35**, 1235 (1952).

(17) Boiling points and melting points are both uncorrected. Analyses are by Schwarzkopf Microanalytical Labs., Woodside 77, N. Y.

(18) Prepared from dimethyl acetonedicarboxylate by catalytic hydrogenation followed by dehydration (phosphorus pentoxide) of the resultant dimethyl β-hydroxyglutarate (A. L. Lochte and P. L. Pickard, THIS JOURNAL, **68**, 721 (1946)). We are grateful to the Chas. Pfizer Co., Brooklyn, N. Y., for generous samples of dimethyl acetonedicarboxylate.

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taken up in 50 ml. of dry acetone. The ammonium chloride was removed by filtration and the acetone was evaporated to an oil. This oil was dissolved in ether and, on slow evaporation of the solvent, 1.9 g. (47%) of methanetriacetic acid precipitated, m.p. 115–118°. This material could not be recrystallized without large losses and was used directly in the next step.

(Glutaric Anhydride β-Acetic)-anhyride (VII).—Two grams of (0.02 mole) of acetic anhydride was added to 1.9 g. (0.01 mole) of methanetriacetic acid and the mixture was heated on the steam-bath for 15 minutes. Excess anhydride and acetic acid were removed by distillation *in vacuo* and the dark, residual oil was triturated with acetone. This induced the crystallization of needles that were recrystallized from acetone to give 0.6 g. of VII as colorless needles, m.p. 150–151°; λ_{max}^{KBr} 5.55, 5.60 and 5.70 μ.

Anal. Calcd. for $C_{14}H_{14}O_9$: C, 51.53; H, 4.32; neut. equiv., 54.4. Found: C, 51.45; H, 4.33; neut. equiv., 55.9.

Glutarimide-β-acetic Acid (IV).—A mixture of 30 g. (0.117 mole) of cyano ester III in 100 ml. of concentrated hydrochloric acid was stirred for one hour at room temperature. The reaction mixture was poured into 100 ml. of water and the resulting solution was evaporated on the steam-bath at a reduced pressure of approximately 50 mm. The yellow residual oil was taken up in 200 ml. of dry acetone leaving behind a small amount (*ca.* 10%) of ammonium chloride.

On concentration of the acetone to about 20 ml., colorless crystals were deposited. These were removed by filtration to yield 10 g. (50%) of the glutarimide, m.p. 168–170°. The analytical sample crystallized from acetone–hexane as colorless crystals, m.p. 172–173°, λ_{max}^{KBr} 5.82 and 6.00 μ.

Anal. Calcd. for $C_7H_9O_4N$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.15; H, 5.59; N, 7.89.

Yields in this reaction were subject to considerable variation because the hydrolysis conditions were difficult to duplicate, but usually they were in the range of 26–55%.

Glutarimide-β-acetyl Chloride. a. From the Sodium Salt of IV.—A solution containing 1.1 g. (0.008 mole) of glutarimide-β-acetic acid (IV) in 25 ml. of 95% alcohol was titrated to phenolphthalein with 1.0 *N* sodium hydroxide. The solvent was removed *in vacuo* and to the colorless solid was added 4.8 g. of thionyl chloride. The resulting slurry was heated on the steam-bath for 15 minutes and the excess thionyl chloride was removed by distillation under reduced pressure. The last traces were taken off by codistillation with dry benzene.

The dark red residue was taken up in warm benzene, filtered and the filtrate was concentrated to about 15 ml. On cooling there was deposited 0.5 g. (33%) of the acid chloride as colorless needles, m.p. 129–132°. A purified sample crystallized from acetone–hexane as colorless needles, m.p. 129–130°, λ_{max}^{KBr} 5.50 and 5.95 μ.

Anal. Calcd. for $C_7H_8O_3NCl$: C, 44.34; H, 4.25; Cl, 18.70. Found: C, 44.56; H, 4.39; Cl, 18.64.

The residue that did not dissolve in benzene was shown by infrared analysis to be a mixture of the acid and acid chloride. This mixture could be recycled so that the actual yield of acid chloride was probably higher than 33%.

b. From the Free Acid IV.—A slurry of 8.6 g. (0.05 mole) of the acid and 30 g. of thionyl chloride was heated under reflux for 30 minutes. The deep orange solution was cooled and the crystalline solid that precipitated was filtered rapidly, washed with dry acetone and stored immediately in a desiccator. The yield of impure acid chloride by this procedure was 6.3 g. (66%), m.p. 125–130°.

On some occasions the excess thionyl chloride was distilled under reduced pressure and the last traces were removed by codistillation with benzene. The orange residue then was triturated with cold acetone and dried. Yields of acid chloride, m.p. 126–131°, by this method were generally in the range of 50–55%. Repeated crystallizations of this impure material were seldom profitable and once-recrystallized acid chloride usually was employed in the Rosenmund reduction.

Glutarimide-β-acetaldehyde (V).—To a flask equipped with a gas inlet tube, stirrer and condenser were added 150 ml. of dry toluene, 3.4 g. (0.018 mole) of once-recrystallized glutarimide-β-acetyl chloride and 0.3 g. of 10% palladium-on-barium sulfate catalyst. The mixture was heated to reflux and hydrogen was passed through the system. The hydrochloric acid formed was titrated with standard alkali.

After three hours, 82% of the theoretical amount of acid had been titrated. The reaction was stopped and the hot toluene solution was filtered free of catalyst. On cooling, there was deposited long colorless needles of the aldehyde. These were removed and a second crop was obtained by concentrating the filtrate. In total, there was obtained 1.8 g. (64%) of the aldehyde, m.p. 121–123°. The analytical sample crystallized as colorless needles from acetone–hexane, m.p. 122–123°; λ_{max}^{KBr} 3.19, 3.73, 5.82 and 5.95 μ.

Anal. Calcd. for $C_7H_9O_3N$: C, 54.19; H, 5.84; N, 9.03. Found: C, 54.23; H, 5.47; N, 8.93.

The semicarbazone crystallized from dilute alcohol as colorless needles, m.p. 230–231°.

Anal. Calcd. for $C_8H_{12}O_3N_4$: N, 26.40. Found: N, 26.53.

When the catalyst was poisoned with quinoline and sulfur as suggested[19] in the literature, no aldehyde could be obtained in this reduction.

(19) E. B. Hershberg and J. Cason, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 627.

ITHACA, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Terpenes. VII.[1] The Structures of the Dieucarvelones

BY G. BÜCHI AND W. S. SAARI

RECEIVED JANUARY 21, 1957

The structures of the isomeric dieucarvelones obtained earlier by Wallach have been reinvestigated. β-Dieucarvelone was shown to be a mixture of the α- and ε-isomers. The γ- and ϑ-isomers described by this author never could be isolated but two new isomers, ε and ζ, were found. Two substances reported by Rupe from the reaction of eucarvone with magnesium and methyl iodide were shown to be identical with α- and β-dieucarvelone. Chemical and spectroscopic findings are in agreement with structure III for these isomers. The conjugate bimolecular reduction of eucarvone is discussed.

In 1899, and again in 1914, Wallach[2] reported that the reduction of eucarvone (I), with zinc in basic solution gave a series of compounds, $C_{20}H_{30}O_2$, which he named the dieucarvelones. Wallach found that these isomers could be separated by recrystallization from an acetic acid–water mixture into an α-isomer, m.p. 177°; β-isomer, m.p. 143°; γ-isomer, m.p. 128°; and a ϑ-isomer, m.p. 111°.

Because the α- and β-isomers only slowly decolorized a solution of bromine in acetic acid *with* liberation of hydrobromic acid and because they were not

(1) Paper VI, G. Büchi and David Rosenthal, THIS JOURNAL, **78**, 3360 (1956).

(2) O. Wallach, *Ann.*, **305**, 223 (1899); **403**, 96 (1914).

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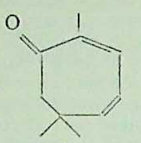
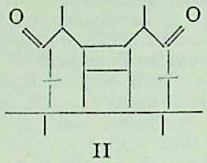
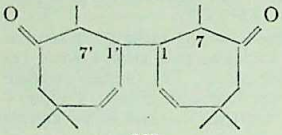
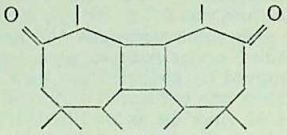
reducible over a palladium catalyst, he concluded that these compounds were saturated and proposed structure II for them. The γ-isomer, on the other


I


II



III


IV

hand, rapidly decolorized a solution of bromine in acetic acid with no liberation of hydrobromic acid. The unsaturated character of this isomer was furthermore ascertained by hydrogenation to a tetrahydro derivative over a palladium catalyst and structure III was proposed for the γ-isomer. The δ-isomer was isolated in such small yield that characterization was not possible.

In 1911, Rupe and Kerkovius[3] found that when eucarvone (I) was allowed to react with magnesium and methyl iodide two crystalline compounds for which they proposed structure IV ($C_{22}H_{36}O_2$) could be isolated in a total yield of 14%. They apparently did not realize that the melting points of their compounds and the corresponding oximes were identical with those of Wallach's α- and β-dieucarvelones.

The formation of both II and IV are mechanistically unsound in terms of present day theories and we therefore decided to reinvestigate these reactions. In this paper we describe work which shows that the dieucarvelones are most probably represented by III.

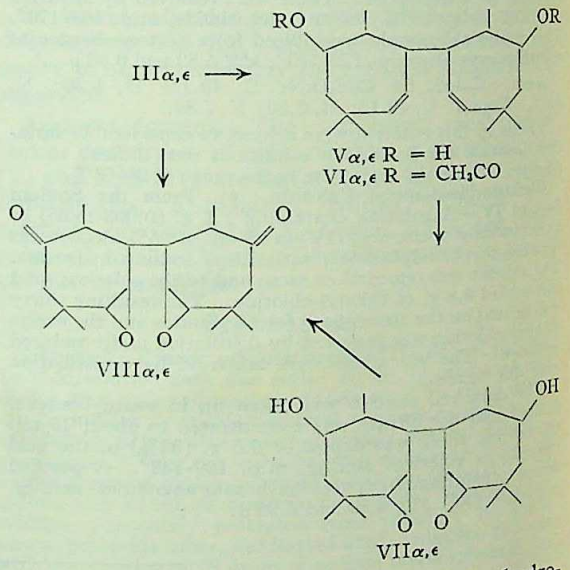
The α- and β-dieucarvelones were prepared easily by reduction of eucarvone with zinc dust in basic solution. Wallach's γ- and δ-isomers could never be isolated despite repeated recrystallization and chromatography of the crude reaction products, but two new isomers, ϵ- and ζ-dieucarvelone, were detected. Although the melting point of the ζ-isomer, 131°, is close to that of Wallach's γ-isomer, m.p. 128°, the two seem to differ markedly in their reactions with bromine in acetic acid solution.

When β-dieucarvelone, with a constant melting point of 142–144°, was chromatographed on active alumina, the α- and ϵ-isomers were obtained in yields of 23 and 77%, respectively. Both of these isomers were found to be stable to chromatography. Recombination of the α- and ϵ-isomers gave a mixture which was identical in all respects with the original β-dieucarvelone. Hence Wallach's β-dieucarvelone is not a pure compound but rather a mixture of the α- and ϵ-isomers. Confirmation was forthcoming from reduction of β-dieucarvelone with lithium aluminum hydride which yielded the α-glycol Vα in 23% yield and the ϵ-glycol Vϵ in 75% yield.

Repetition of Rupe and Kerkovius'[3] directions for the reaction of eucarvone with magnesium and methyl iodide gave two crystalline products in a total yield of 1% which appeared to be the compounds reported by them. These products were shown to be identical with α- and β-dieucarvelone by mixed melting point determinations.

Although none of the dieucarvelone isomers isolated decolorized a 5% solution of bromine in chloroform and all were saturated to tetranitromethane, we believe that they are in fact unsaturated since they all showed maxima in the infrared region at 3010, 1640 and 750 cm.$^{-1}$, characteristic of *cis*-disubstituted double bonds. Also the ultraviolet spectra of all the isomers exhibited strong end absorption at 210 mμ indicating unsaturation.

In order to further prove the unsaturated character of the dieucarvelone isomers, the α-glycol Vα obtained by a lithium aluminum hydride reduction of α-dieucarvelone (IIIα), was oxidized with perbenzoic acid. After seven days the α-glycol showed an uptake of peracid corresponding to 2.00 double bonds. Similarly the ϵ-glycol Vϵ derived from ϵ-dieucarvelone (IIIϵ) titrated for 1.96 double bonds after one day.



Furthermore we now have been able to hydrogenate the diacetate VIα, prepared from the α-glycol Vα, over Adams platinum catalyst in acetic acid solution to a tetrahydro derivative. The reduction is exceedingly slow and the fact that only this highly active catalyst is effective explains the negative results reported earlier by Wallach.[2] These findings as well as the inertness of α-dieucarvelone (IIIα) toward potassium permanganate (no reaction even in boiling pyridine) are only in agreement with the presence of two highly hindered double bonds in the molecule. It is significant that the three bands associated with the double bonds in the infrared spectra of the dieucarvelones are all present in every unsaturated derivative and disappear when any of the isomers, or their derivatives, are hydrogenated or converted to the epoxides. Contrary to Wallach's suggestion the dieucarvelones then must be bicyclic rather than tetracyclic.

Since α- and β-dieucarvelone can be recovered in

(3) H. Rupe and W. Kerkovius, *Ber.*, **44**, 2702 (1911). The analyses reported are also in agreement with $C_{11}H_{18}O$.

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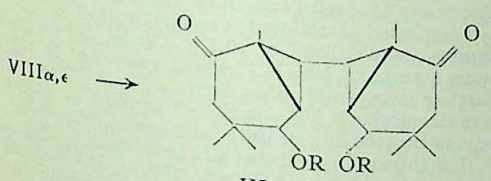
good yield from strenuous acid treatment, it is unlikely that they contain any three- or four-membered rings. This postulate is confirmed by the lack of significant absorption in the infrared in the regions usually associated with these groupings. Selenium dehydrogenation of the α-glycol Vα gave no aromatic compounds which could be detected spectroscopically and it is therefore unlikely that a six-membered ring is present in α-dieucarvelone. It is at any rate difficult to envision a change in the carbon skeleton of eucarvone under the conditions used in the preparation of III and structures containing two seven-membered rings seem much more plausible.

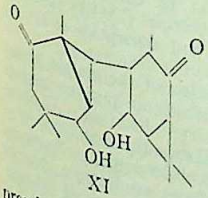
In agreement with structure III, α,α-dieucarvelone formed a hexadeutero derivative upon equilibration with alkaline deuterium oxide.

Oxidation of the α-diepoxyglycol VIIα with chromic acid in pyridine afforded α-diepoxydieucarvelone (VIIIα) which also could be obtained in good yield by epoxidation of α-dieucarvelone with trifluoroperacetic acid in the presence of a dibasic sodium hydrogenphosphate buffer. Similarly, ϵ-dieucarvelone (IIIϵ) yielded ϵ-diepoxydieucarvelone (VIIIϵ).

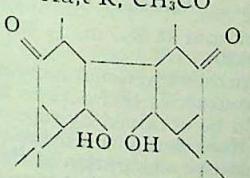
Treatment of α-diepoxydieucarvelone (VIIIα) with warm aqueous potassium hydroxide solution gave an isomeric compound which contained hydroxyl and carbonyl absorption in the infrared spectrum, a maximum in the ultraviolet spectrum at 216 mμ (ϵ 14,000) characteristic of cyclopropyl ketones,[4] was saturated to tetranitromethane and formed a diacetate (Xα). Only three structures (IX, XI and XII) fit these data. Since the dihydroxydiketone in question exchanged 3.76 hydrogens (after reconversion of –O–D to –O–H) upon equilibration with alkali in deuterium oxide, ex-



IXα,ϵ R, H
Xα,ϵ R, CH_3CO



XI

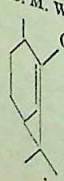


XII

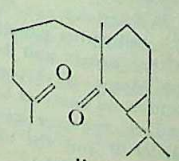
pression IXα must be the correct one.[5]

(4) R. H. Eastman and S. K. Freeman, THIS JOURNAL, **77**, 6642 (1955), and earlier references cited.

(5) Structures XI and XII have only three and two exchangeable hydrogens, respectively, because enols like i represent impossibly strained molecules. Similarly ii exchanged only five hydrogens (G. Büchi and D. M. White, THIS JOURNAL, **79**, in press (1957).



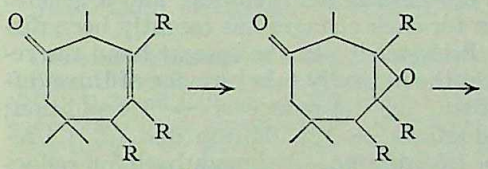
i



ii

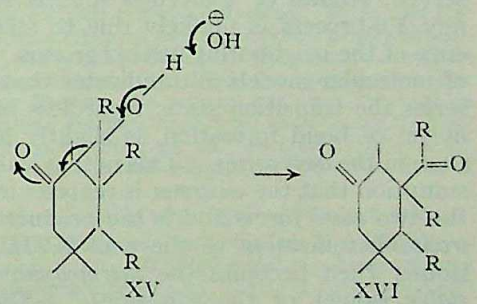
An analogous dihydroxydiketone (IXϵ) which exchanged 3.88 H on deuteration was prepared by the same sequence from ϵ-dieucarvelone (IIIϵ). The two compounds were clearly different.

The conversion of VIII to IX involves a transannular displacement reaction and is similar to the one observed by Barton and Lindsey[6] with an epoxycyclononanone derived from caryophyllene. Conversions of cycloheptanes to bicyclo[4,1,0]heptanes seem to occur generally with great ease and other reactions of this type recently have been discovered by Corey, *et al.*[7] The presence of a cyclopropane ring in IXα and IXϵ excludes partial structures XIII for these two dieucarvelones because the corresponding dihydroxydiketones would have to be represented by XV. Compounds of this type are known to be unstable to base and to undergo rapid retroaldol reactions[8] (*cf.* XV → XVI) a behavior not observed with IX. Furthermore the β,γ-unsaturated ketones XIII would be expected to rearrange at least partially to the corresponding α,β-unsaturated ketones in the presence of acids or bases but no such transformations have been observed in the present investigation.



XIII, R = second ring

XIV



XV XVI

A total of ten different isomers, namely, four *d,l*-pairs and two *meso* forms are possible from the parent structure III. Because α-dieucarvelone (IIIα) was not isomerized to any other isomer upon treatment with acid or base the methyl groups on C_7 and C_7' are already in the most stable configurations. The ϵ-isomer IIIϵ, on the other hand, was converted to an equilibrium mixture of the ϵ- and ζ-isomers on base-catalyzed isomerization. These facts clearly demonstrate that IIIα and IIIϵ cannot belong to the same (C_1, C_1', *syn* or *anti*) series and must have different configurations at C_1'. In agreement with this situation the α- and ϵ-isomers gave two different dihydroxydiketones (IXα and IXϵ).

Reduction of eucarvone (I) with zinc dust in the presence of ammonium chloride at 15° yielded only ϵ-dieucarvelone; under more strenuous conditions, however, a mixture of the ϵ- and α-isomers was

(6) D. H. R. Barton and A. S. Lindsey, *J. Chem. Soc.*, 2988 (1951).

(7) E. J. Corey and H. J. Burke, THIS JOURNAL, **78**, 174 (1956).

(8) M. S. Kharasch, T. Rudy, W. Nudenberg and G. Büchi, *J. Org. Chem.*, **18**, 1030 (1953).

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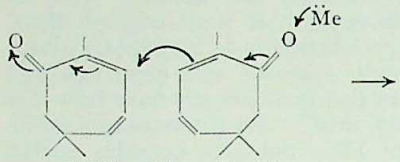
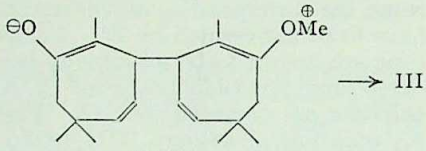
produced. This implies that the ϵ-isomer is formed through the transition state of lowest activation energy. We are inclined to believe that the formation of these "dimers" occurs *via* a concerted process involving reduction and Michael addition (*cf.* XVII → XVIII → III).



XVII Me = Zn, Mg



XVIII

There is ample precedent for such conjugate bimolecular reductions of α,β-unsaturated aldehydes[9] as well as α,β-unsaturated ketones[10] and a general mechanism for such changes has recently been discussed by Brewster.[11] In the case at hand the reaction could theoretically take any one of three different paths: (a) 1,4-reduction → 1,4-addition; (b) 1,6-reductions → 1,6-addition and (c) 1,4-reduction → 1,6-addition. Although both 1,6-reductions[12] and 1,6-Michael additions[13] have been observed, studies of molecular models suggest that any 1,6-process is unlikely due to steric interference of the neighboring methyl groups. Inspection of molecular models also indicates that in the *syn*-series the transition state, regardless of the mechanism of bond formation, is slightly less strained than in the *anti* series. This notion leads to the assumption that the ϵ-isomer is represented by one of the two *meso* forms and is the product of *rate controlled* ketonization of the enol XVIII.[14] The ζ-isomer then becomes the *thermodynamically most stable* isomer of the *syn*-series. α-Dieucarvelone thus is the most stable isomer in the *anti*-series. It must be pointed out though that an unambiguous assignment of configuration is by no means possible mainly because very little is known about the conformations of cycloheptenes. The configurational problem at hand is identical with the one of the isomeric perhydrodiphenic acids which has been solved so brilliantly by Linstead and Doering.[15] We have not yet had the courage to embark on a similar project to determine the configurations for the dieucarvelones.

Acknowledgment.—We are greatly indebted to Firmenich and Co., Geneva, for financial assistance and to the National Institutes of Health for a fellowship to W. S. S. Further, we should like to thank Mr. D. Shew for the preparation of dieucarvelone.

Experimental[16]

Eucarvone (I).—Eucarvone was prepared from carvone according to the directions of Corey and Burke[7] and was obtained as a yellow oil, b.p. 73–76° (5.0 mm.), $n^{25}D$ 1.5066 (lit.[7] $n^{21}D$ 1.5080), in a 45% yield.

Dieucarvelone Isomers.[2]—A solution of 68 g. (0.453 mole) of eucarvone in 700 ml. of 95% ethanol was added to a solution of 57 g. of potassium hydroxide in 250 ml. of water. After adding 57 g. (0.872 mole) of zinc dust, the mixture was heated under reflux for 3 hours with vigorous stirring and then allowed to stand at room temperature for 3.25 hours. One liter of ice-water was added and the precipitate filtered with suction. An additional liter of water was added to the filtrate and the solution extracted with ethyl ether which was then dried over anhydrous magnesium sulfate. After filtering, the solvents were removed *in vacuo* to give 2.6 g. (3.8%) of a yellow oil which could not be crystallized.

The filtered solids were extracted with chloroform and the solution dried over anhydrous sodium sulfate. After filtering, the solvent was removed *in vacuo* and the oily residue recrystallized from ethanol to give a total of 8.1 g. (12%) of α-dieucarvelone with a m.p. of 177–178° which was not raised upon further recrystallization. The sample did not decolorize a 5% solution of bromine in chloroform and was saturated to tetranitromethane in chloroform.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00; mol. wt., 302. Found: C, 79.42; H, 9.97; mol. wt., 300.

The infrared spectrum (KBr) contained maxima at 3008(w), 2955(s), 1699(s), 1640(w) and 752(s) cm.$^{-1}$. In chloroform, the carbonyl absorption was at 1692 cm.$^{-1}$.

The ultraviolet spectrum (EtOH) showed a maximum at 285 mμ (ϵ 115) with end absorption at 211 mμ (ϵ 1,700).

Continued fractional recrystallization of the mother liquors gave a total of 19.1 g. (28.3%) of β-dieucarvelone with a m.p. of 139–142° which was raised to 142–144° by further recrystallization from ethanol. The sample did not decolorize a 5% solution of bromine in chloroform and was saturated to tetranitromethane in chloroform.

The infrared spectrum (KBr) contained maxima at 2960(s) with a shoulder at 3020(w), 1691(s), 1647(w) and 752(m) cm.$^{-1}$. The carbonyl absorption in chloroform was at 1692 cm.$^{-1}$. The ultraviolet spectrum (EtOH) showed a maximum at 285 mμ (ϵ 68) with end absorption at 211 mμ (ϵ 2050).

Further fractional recrystallization of the mother liquors gave a series of fractions from which no pure compounds could be obtained by repeated recrystallization. All of the fractions were saturated to tetranitromethane and showed no significant absorption in the ultraviolet region. Fractional recrystallization of this mixture from an acetic acid–water mixture followed by repeated recrystallization of the fractions from ethanol gave no pure compounds. A total of 21.4 g. (31.5%) of this isomer mixture was obtained. Removal of the solvent *in vacuo* gave 12 g. (18%) of a yellow oil which would not crystallize even after chromatography on alumina, activity I.

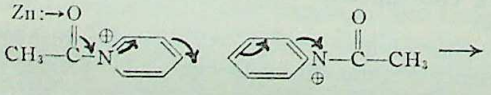
Isolation of ϵ- and ζ-Dieucarvelone from the Zinc and Base Reduction of Eucarvone.—One gram of the dieucarvelone isomer mixture (m.p. 112–125°) mentioned above was

(9) C. Glacet, *Ann. chim.*, **12**, 293 (1947), and earlier papers cited.

(10) C. Harries and F. Hubner, *Ann.*, **296**, 295 (1897); the reduction of the closely related carvone is described in ref. 1; J. F. J. Dippy and R. H. Lewis, *Rec. trav. chim.*, **56**, 1000 (1937); J. F. Wiemann and C. Glacet, *Compt. rend.*, **226**, 923 (1948); R. C. Fuson and co-workers, THIS JOURNAL, **77**, 3776 (1955), and many earlier papers.

(11) J. H. Brewster, *ibid.*, **76**, 6361 (1954).

(12) *E.g.*



N,N,-diacetyltetrahydro-4,4,-bipyridyl; O. Dimroth and F. Frister *Ber.*, **55**, 3693 (1922).

(13) A. Eschenomoser, J. Schreiber and S. A. Julia, *Helv. Chim. Acta*, **36**, 482 (1953); J. W. Rolls, THIS JOURNAL, **75**, 2123 (1953); Y. Abe, *et al.*, *ibid.*, **78**, 1416 (1956).

(14) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

(15) R. P. Linstead and W. von E. Doering, THIS JOURNAL, **64**, 2009 (1942), and earlier papers.

(16) Melting points and boiling points are uncorrected. Microanalyses by Mmes. N. Alvord and G. Kula and Dr. S. M. Nagy, M.I.T.; deuterium analyses by Mr. J. Nemeth, University of Illinois. The infrared spectra were measured on a Baird recording spectrophotometer model B and the ultraviolet spectra on a Cary recording spectrophotometer model [illegible].

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chromatographed in the usual manner on 100 g. of Merck acid-washed alumina, activity I. Elution with an 80% benzene–petroleum ether mixture gave a series of fractions one of which upon repeated recrystallization from ethanol gave γ-dieucarvelone, m.p. 131–132°, in a low yield. The infrared spectrum of this sample was identical with that of γ-dieucarvelone obtained by base isomerization of ϵ-dieucarvelone and there was no mixed melting point depression.

Several fractions were eluted with benzene which when recrystallized from ethanol gave α-dieucarvelone with a m.p. of 177–178°. No depression was observed upon mixed melting point with an authentic sample.

Elution with a 2–5% ethyl ether–benzene mixture gave a series of fractions which when recrystallized from ethanol gave ϵ-dieucarvelone with a m.p. of 151–152°. The infrared spectrum of this sample was identical with that of ϵ-dieucarvelone obtained from the chromatography of β-dieucarvelone and there was no mixed melting point depression.

Rupe and Kerkovius Grignard Reaction of Eucarvone (I).—To 1.1 g. (0.045 mole) of magnesium and a few drops of methyl iodide was added dropwise with stirring a solution of 6.0 g. (0.040 mole) of eucarvone and 6.4 g. (0.045 mole) of methyl iodide over a period of 2 hours. After the solution had been stirred at room temperature for 0.5 hour more, it was poured onto a mixture of 100 ml. of 10% sulfuric acid and ice. The reaction was extracted with ethyl ether which was then washed with water and dried over anhydrous magnesium sulfate. After filtering, the solvent was removed *in vacuo* and the oily residue chromatographed on 90 g. of alumina, activity I. Several of the fractions which were eluted with a 80% benzene–hexane mixture partially crystallized after standing overnight. These were combined and recrystallized from ethanol to give 0.04 g. (0.66%) of α-dieucarvelone with a m.p. of 178–179°. No depression was observed upon a mixed melting point with an authentic sample.

Later fractions of the recrystallization gave 0.02 g. (0.33%) of β-dieucarvelone with a m.p. of 142–143°. No depression was observed upon mixed melting point with an authentic sample.

Lithium Aluminum Hydride Reduction of α-Dieucarvelone (IIIα).—A solution of 1.7 g. (0.00563 mole) of α-dieucarvelone in 50 ml. of tetrahydrofuran was added over a period of 10 minutes to a slurry of 0.43 g. (0.0112 mole) of lithium aluminum hydride in 30 ml. of tetrahydrofuran with stirring. The mixture was then heated under reflux for 6 hours, cooled and the excess hydride decomposed with 15 ml. of ethyl acetate followed by 10 ml. of water. The reaction mixture was filtered and the residue washed with methylene chloride. The solvents were removed *in vacuo* and the crude product recrystallized from ethanol to give 0.775 g. (45%) of the α-glycol Vα with a m.p. of 246–248°. An analytical sample had a melting point of 249–249.4°. The infrared spectrum (KBr) contained bands at 3268(s), 2994(w), 2890(s), 1618(w) and 750(s) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.07; H, 11.31.

A perbenzoic acid titration of the α-glycol Vα proceeded as follows: after 1 day, it titrated for 0.94 double bonds 2 days, 1.45; 3 days, 1.75; 4 days, 1.94; 7 days, 2.00 double bonds.

The α-Diepoxyglycol VIIα.—A solution of 0.1 g. (0.000328 mole) of the α-glycol Vα in 20 ml. of chloroform containing 0.178 g. (0.077 mole) of perbenzoic acid was allowed to stand at room temperature for seven days. The chloroform solution was then washed with a saturated ferrous sulfate solution, water, a saturated sodium bicarbonate solution, water and then dried over anhydrous sodium sulfate. After filtering, the solvent was removed *in vacuo* and the oily residue recrystallized from methanol to give 0.08 g. (73%) of the diepoxide with a m.p. of 172–174° dec. Recrystallization from methanol gave an analytical sample with a m.p. of 175.4–176.0° dec. which was saturated to bromine and tetranitromethane in chloroform. The infrared spectrum (KBr) contained maxima at 3500 to 3200(s), 2958(s), 1255(m), 1235(m), 943(m), 933(m), 890(m), 860(m), 820(m), 795(w) and 775(m) cm.$^{-1}$, the bands at 2994, 1618 and 750 cm.$^{-1}$ which were present in the spectrum of the α-glycol Vα having disappeared.

Anal. Calcd. for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 71.19; H, 10.02.

The α-Diacetate VIα.—A solution of 0.375 g. (0.00123 mole) of the α-glycol Vα in 20 ml. of pyridine and 5 ml. (0.005 mole) of acetic anhydride was allowed to stand at room temperature overnight. The solvents were removed *in vacuo* and the residue chromatographed on 20 g. of acid-washed alumina, activity I to II. Elution with a 50% benzene–petroleum ether mixture gave a white solid which was recrystallized from methanol to give 0.356 g. (70%) of the α-diacetate with a m.p. of 199–201°. Recrystallization from methanol gave an analytical sample with a m.p. of 202.4–203.0°. The infrared spectrum (KBr) contained maxima at 2933(w), 2857(s), 1718(s), 1634(w), 1232(s) and 755(m) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.58; H, 9.74.

Reduction of the α-Diacetate VIα.—When 0.051 g. (0.000135 mole) of the α-diacetate was reduced with hydrogen in 8 ml. of glacial acetic acid, using 5 mg. of platinum oxide as a catalyst, the reduction was complete after 8 hours with the uptake of hydrogen equivalent to 2.07 double bonds. Filtration, evaporation of the solvent and crystallization of the residue from methanol yielded 0.030 g. (60%) of the α-tetrahydrodiacetate with a m.p. of 197.8–198.5°. The product was saturated to bromine and tetranitromethane in chloroform. A strong depression was observed upon mixed melting point with the α-diacetate VIα. The infrared spectrum (KBr) contained maxima at 2940(s), 1728(s) and 1240(s) cm.$^{-1}$, the bands at 2933, 1634 and 755 cm.$^{-1}$ present in the spectrum of the α-diacetate having disappeared.

Anal. Calcd. for $C_{24}H_{42}O_4$: C, 73.05; H, 10.73. Found: C, 72.75; H, 10.56.

Deuterium Exchange of α-Dieucarvelone.—A solution of 0.100 g. (0.00032 mole) of α-dieucarvelone in 4 ml. of 95% EtOD–D_2O and 0.05 ml. of 20% NaOD–D_2O was heated under reflux in an atmosphere of nitrogen for 15 minutes. After cooling, the solvents were removed *in vacuo*. Four ml. of a 95% EtOD–D_2O mixture and 0.05 ml. of deuterium oxide were added to the residue and the solution was heated under reflux in an atmosphere of nitrogen for 15 minutes, cooled and the solvents removed *in vacuo*. After this last exchange had been repeated two more times, deuterium oxide was added to the solid residue and the mixture extracted with ethyl ether which was then dried over anhydrous sodium sulfate. After filtering, the solvent was then removed *in vacuo*, the residue recrystallized from a 95% EtOD–D_2O mixture and then sublimed at 120° (0.1 mm.) to give 51 mg. (51%) of the deuterated α-dieucarvelone with a m.p. of 174–174.5°.

Anal. Calcd. for $C_{20}H_{24}D_6O_2$: D, 20.0. Found: D, 20.2.

Attempted Acid-catalyzed Isomerization of α-Dieucarvelone.—A solution of 0.5 g. (0.00166 mole) of α-dieucarvelone in 35 ml. of absolute ethanol and 10 ml. of 20% (vol.) sulfuric acid was heated under reflux for 5 hours. Ice-water was added to the solution and the product extracted with ether after saturating with sodium chloride. The ether solution was dried over anhydrous magnesium sulfate, filtered free from drying agent and the solvent removed *in vacuo*. The residue was recrystallized from ethanol and gave 0.32 g. (64%) of α-dieucarvelone with a m.p. of 177.5–178°. No depression was observed upon mixed melting point with an authentic sample.

Attempted Acid-catalyzed Isomerization of β-Dieucarvelone.—An identical experiment carried out with the β-isomer led only to recovered starting material (74%).

Oxidation of the α-Diepoxyglycol VIIα.—To a solution of 0.040 g. (0.000118 mole) of the α-diepoxyglycol in 5 ml. of pyridine was added 0.070 g. (0.00070 mole) of chromium trioxide. After the mixture had remained at room temperature for 2 days, water was added and the ketone extracted with chloroform. After drying over anhydrous sodium sulfate, the solution was filtered and the solvent removed *in vacuo* to give a dark brown solid. Recrystallization from a chloroform–methanol mixture gave 0.027 g. (69%) of crude α-diepoxydieucarvelone (VIIIα) with a m.p. of 285–290° dec. Further recrystallization raised the melting point to 295–296° dec. The infrared spectrum was identical with that of α-diepoxydieucarvelone obtained from epoxidation of α-dieucarvelone and there was no mixed melting point depression.

α-Diepoxydieucarvelone (VIIIα).—To 0.15 ml. (0.0053 mole) of 90% hydrogen peroxide in 1 ml. of methylene chloride was added slowly 0.9 ml. (0.0063 mole) of trifluoro-

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acetic anhydride. The mixture was kept in an ice-bath and allowed to remain cool until 5 minutes after the addition of the anhydride was complete. This solution was then added dropwise with stirring to a solution of 0.5 g. (0.00166 mole) of α-dieucarvelone in 10 ml. of methylene chloride with 3 g. of dibasic sodium hydrogen phosphate present as a buffer. The solution warmed to reflux temperature during the addition and was then allowed to stand at room temperature for 15 hours with stirring. The solution was filtered, washed successively with a saturated solution of ferrous sulfate, water, a saturated sodium bicarbonate solution, water and then dried over anhydrous magnesium sulfate. After filtering, the solvent was removed *in vacuo* and the residue recrystallized from a chloroform–ethanol mixture to give 0.3 g. (52%) of α-diepoxydieucarvelone with a m.p. of 294–296° dec. Recrystallization from chloroform gave an analytical sample with a m.p. of 296.5–298.5° dec. which did not decolorize a 5% solution of bromine in chloroform and was saturated to tetranitromethane. The infrared spectrum (KBr) contained maxima at 2960(s), 1690(s), 1405(w), 1290(m), 1265(m), 1245(m), 1200(m), 945(m), 915(m), 890(w), 840(s), 815(s), 785(w) and 775(m) cm.$^{-1}$, the bands at 3012, 1639 and 750 cm.$^{-1}$ present in the infrared spectrum of α-dieucarvelone having disappeared.

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.58; H, 9.14.

ε-Diepoxydieucarvelone (VIIIε).—This compound was prepared in 63% yield by the method described for the α-isomer. Recrystallization from ethanol gave an analytical sample with a m.p. of 176.5–177.5° which was saturated to bromine and tetranitromethane in chloroform. A strong depression was observed upon mixed melting point with α-diepoxydieucarvelone. The infrared spectrum (KBr) contained maxima at 2950(s), 1694(s), 1296(m), 1286(m), 1277(m), 1240(w), 1195(s), 940(m), 924(w), 902(w). 845(m), 820(m) and 809(m) cm.$^{-1}$, the bands at 3012, 1639 and 750 cm.$^{-1}$ present in the infrared spectrum of ε-dieucarvelone having disappeared. In chloroform solution the carbonyl absorption was at 1684 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.38; H, 9.04; mol. wt., 334. Found: C, 71.51, 71.63; H, 8.94, 9.09; mol. wt., 349.

Base Isomerization of α-Diepoxydieucarvelone (VIIIα).—A mixture of 0.33 g. (0.00099 mole) of α-diepoxydieucarvelone (VIIIα), 25 ml. of ethanol and 15 ml. of a 5% potassium hydroxide solution was heated under reflux with stirring. After 15 minutes solution was complete. The reaction mixture was then extracted with chloroform which was dried over anhydrous sodium sulfate. After filtering, the solvent was removed *in vacuo* and the residue recrystallized from chloroform to give 0.245 g. (74%) of the α-dihydroxydiketone IXα with a m.p. of 263–265°. Further recrystallization from chloroform gave an analytical sample with a m. p. of 265–266° which was saturated to tetranitromethane in chloroform and did not decolorize a 5% solution of bromine in chloroform.

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.58; H, 8.82.

The infrared spectrum (KBr) contained maxima at 2540(s and broad), 2945(s), 1660(s and broad), 1430(m) and 1012 (m) cm.$^{-1}$. The ultraviolet spectrum (EtOH) showed maxima at 216 mμ (ε 14,000) and 282 mμ (ε 328).

The diacetate was prepared in the usual manner with acetic anhydride in pyridine. Recrystallization of the crude product from methanol gave an analytical sample with a m.p. of 275.5–277°. The infrared spectrum ($CHCl_3$) contained maxima at 2960(m), 1728(s), 1686(s), 1240 to 1210(s) and 1015(m) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.86; H, 8.19. Found: C, 68.54; H, 8.17.

Deuterium Exchange of the α-Dihydroxydiketone (IXα).—A solution of 0.060 g. (0.00018 mole) of IXα, in 4 ml. of 95% EtOD–D_2O and 0.05 ml. of 20% NaOD–D_2O was heated under reflux in an atmosphere of nitrogen for 15 minutes. After cooling, the solvents were removed *in vacuo*. Four ml. of a 95% EtOD–D_2O mixture and 0.05 ml. of deuterium oxide were added to the residue and the solution was heated under reflux in an atmosphere of nitrogen for 15 minutes, cooled and the solvents removed *in vacuo*. After this last exchange had been repeated two more times, deuterium oxide was added and the solid recovered by suction and washed with 4 ml. of deuterium oxide. The residue was then dissolved in tetrahydrofuran and dried over anhydrous magnesium sulfate. After filtering, the solvent was removed *in vacuo* and the residue dissolved in methanol to exchange the hydroxyl deuteriums. The methanol was removed *in vacuo* and the crude product sublimed at 150° (0.1 mm.) to give 0.030 g. (50%) of the deuterated α-dihydroxydiketone with a m.p. of 262–263.5°. The infrared spectrum of the deuterated IXα showed no absorption in the –O–D region.

Anal. Calcd. for $C_{20}H_{26}D_4O_4$: D, 13.33. Found: D, 12.45.

Base Isomerization of ε-Diepoxydieucarvelone (VIIIε).—A mixture of 0.35 g. (0.00105 mole) of VIIIε and 40 ml. of a 5% potassium hydroxide solution was heated under reflux with stirring for 1.5 hours. After cooling, the solution was saturated with sodium chloride and extracted with chloroform which was then dried over anhydrous magnesium sulfate. Removal of the filtered solvent *in vacuo* and recrystallization of the residue from an ethanol–benzene mixture gave 0.245 g. (70%) of the ε-dihydroxydiketone IXε with a m.p. of 235–238°. Recrystallization from an ethanol–benzene mixture gave an analytical sample with a m.p. of 239–240.5° which was saturated to tetranitromethane and did not decolorize a 5% solution of bromine in chloroform.

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.52; H, 9.02.

The infrared spectrum (KBr) contained maxima at 3500(s and broad), 2945(s), 1682(s and broad), 1648(s), 1432(m) and 1005(m) cm.$^{-1}$. The ultraviolet spectrum (EtOH) showed maxima at 210 mμ (ε 11,200) and 280 mμ (ε 178).

The diacetate was prepared in the usual manner with acetic anhydride in pyridine. Recrystallization of the crude product from ethanol gave an analytical sample with a m.p. of 216.5–217.5°. The infrared spectrum ($CHCl_3$) contained maxima at 2980(m), 1275(s), 1686(s), 1250 to 1220(s) and 1013(m) cm.$^{-1}$.

Deuterium Exchange of the ε-Dihydroxydiketone IXε.—Using the method described above for the α-dihydroxydiketone IXα the deuterated ε-dihydroxydiketone, m.p. 237–239°, was obtained in 45% yield. The infrared spectrum of the deuterated IXε showed no absorption in the O–D region.

Anal. Calcd. for $C_{20}H_{26}D_4O_4$: D, 13.33. Found: D, 12.95.

Chromatography of β-Dieucarvelone. ε-Dieucarvelone (IIIε).—The chromatography of 60 mg. of β-dieucarvelone, with a constant melting point of 142–144°, on 6 g. of Merck acid-washed alumina, activity I, was carried out in the usual manner. Elution with benzene gave 14 mg. of a solid which when recrystallized from ethanol gave α-dieucarvelone with a m.p. of 177.0–177.8°. No depression was observed upon mixed melting with an authentic sample. A strong depression was observed upon mixed melting with β-dieucarvelone.

Elution of the column with a 5% ethyl ether–benzene mixture gave 45 mg. of a solid which when recrystallized from ethanol gave ε-dieucarvelone with a m.p. of 153.0–153.5°. The melting point was not raised upon further recrystallization. ε-Dieucarvelone did not decolorize a 5% solution of bromine in chloroform and was saturated to tetranitromethane in chloroform. No depression was observed upon mixed melting with β-dieucarvelone.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00; mol. wt., 302. Found: C, 79.64; H, 10.07; mol. wt., 288.

The infrared spectrum (KBr) showed maxima at 2980(s) with a shoulder at 3017(m), 1692(s), 1645(w) and 755(w) cm.$^{-1}$. The ultraviolet spectrum (EtOH) shows a maximum at 285 mμ (ε 68) with end absorption at 210 mμ (ε 1,260).

A mixture of equal amounts of α- and ε-dieucarvelone was recrystallized from methanol. Pure α-dieucarvelone was obtained from the first fractions. The later fractions gave β-dieucarvelone with a constant melting point of 141–143°. The infrared spectrum of this sample was identical with that of β-dieucarvelone isolated from the zinc dust–base reduction of eucarvone and no mixed melting point depression was obtained.

Trifluoroperacetic Acid Reaction of β-Dieucarvelone.—The oxidation was performed as described for α-dieucarvelone (VIIIα). The product was recrystallized from a chloroform–methanol mixture to give 0.25 g. (7.5%) of α

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diepoxydieucarvelone (VIIIα), with a m.p. 260–270° dec. The melting point was raised to 296–298° dec. by further recrystallization from chloroform. The infrared spectrum was identical with that of an authentic sample of VIIIα and no mixed melting point depression was observed.

Solvent was removed from the mother liquors and the oily residue recrystallized from ethanol to give 1.9 g. (57%) of ϵ-diepoxydieucarvelone (VIIIϵ) with a meltiug point of 167–171°. The melting point was raised to 176–177° by further recrystallization from ethanol. The infrared spectrum was identical with that of an authentic sample of VIIIϵ and no mixed melting point depression was observed.

Lithium Aluminum Hydride Reduction of β-Dieucarvelone.—A solution of 4.0 g. (0.0132 mole) of β-dieucarvelone in 100 ml. of tetrahydrofuran was added over a period of 20 minutes to a slurry of 0.86 g. (0.023 mole) of lithium aluminum hydride in 70 ml. of tetrahydrofuran with stirring. The mixture was then heated under reflux for 5 hours, cooled and the excess hydride decomposed with 10 ml. of ethyl acetate followed by 20 ml. of water. The reaction mixture was filtered and the residue placed in a Soxhlet extractor and extracted with chloroform. The solvents were removed *in vacuo* and the crude product recrystallized from methanol to give 0.9 g. (22.5%) of the α-glycol Vα with a m.p. of 248–249°. The infrared spectrum of this sample was identical with that of an authentic sample of the α-glycol and there was no depression upon mixed melting point.

Concentration of the mother liquors gave 3.0 g. (75%) of the ϵ-glycol Vϵ with a m.p. of 182–184°. Recrystallization from methanol gave an analytical sample with a m.p. of 182.6–183.8°. The infrared spectrum (KBr) contained bands at 3390(s), 3000(m), 2950(s), 1640(w), and 752(s) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.33; H, 11.19.

A perbenzoic acid titration of the ϵ-glycol Vϵ proceeded as follows: after 10 hours, the glycol titrated for 1.38 double bonds; 24 hours, 1.96 double bonds.

Attempted Base Isomerization of α-Dieucarvelone.—A solution of 0.69 g. (0.00229) mole of α-dieucarvelone and 0.3 g. of sodium in 100 ml. of absolute ethyl alcohol was allowed to stand at room temperature for 48 hours. A saturated sodium chloride solution was added and the mixture extracted with chloroform which was then dried over anhydrous magnesium sulfate. After filtering, the solvents were removed *in vacuo* and the solid residue recrystallized from ethanol. The first fractions, 0.500 g., had a melting point of 174–175° which was not lowered when melted with an authentic sample of α-dieucarvelone. The later fractions had a lower melting point and were chromatographed on 5 g. of alumina, activity I. A series of fractions was obtained (0.073 g.) which when recrystallized from ethanol had a m.p. of 177–178° which was not lowered when melted with an authentic sample of α-dieucarvelone. A total of 0.573 g. (83%) of α-dieucarvelone was recovered from the reaction mixture.

Base Isomerization of ϵ-Dieucarvelone (IIIϵ).—A solution of 0.700 g. (0.00232 mole) of ϵ-dieucarvelone and 0.15 g. of sodium in 50 ml. of absolute ethyl alcohol was allowed to stand at room temperature for 48 hours. A saturated sodium chloride solution was added and the mixture extracted with chloroform which was then dried over anhydrous magnesium sulfate. After filtering, the solvents were removed *in vacuo* and the solid residue chromatographed on 70 g. of Merck acid-washed alumina, activity I. Elution with benzene followed by a 10% chloroform–benzene mixture gave 0.377 g. (54%) of ζ-dieucarvelone which when recrystallized from ethanol gave an analytical sample with a m.p. of 131.0–132.0° which did not decolorize a 5% solution of bromine in chloroform and was saturated to tetranitromethane in chloroform.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00; mol. wt., 302. Found: C, 79.05: H, 9.86; mol. wt., 280.

The infrared spectrum (KBr) contained maxima at 3020 (m), 2930(s), 1700(s), 1640(w) and 755(m) cm.$^{-1}$. The ultraviolet spectrum (EtOH) showed a maximum at 290 mμ (ϵ 53) with end absorption at 210 mμ (ϵ 1,780).

Elution of the column with chloroform gave 0.285 g. (41%) of ϵ-dieucarvelone which when recrystallized from ethanol had a m.p. of 150–152°. Further recrystallization raised the melting point to 151.5–152.5° which was not lowered when melted with an authentic sample.

Zinc Reduction of Eucarvone (I).—A solution of 0.2 g. (0.00133 mole) of eucarvone and 1 g. of ammonium chloride in 10 ml. of an ethanol–water mixture was cooled to 10–15° with an ice-bath. Two grams of zinc dust was added and the slurry stirred vigorously at this temperature for 45 minutes. The mixture was then filtered and the filtrate extracted with ethyl ether which was dried over anhydrous magnesium sulfate. After filtering, the oily residue was recrystallized from methanol to give 0.025 g. (12.5%) of ϵ-dieucarvelone with a m.p. of 150.5–152.0°. The infrared spectrum of this sample was identical with that of an authentic sample and no mixed melting point depression was observed. Only uncrystallizable oils could be obtained from the mother liquors.

CAMBRIDGE 39, MASS.

[JOINT CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY AND THE INSTITUTO DE QUIMICA DE LA UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO]

Terpenoids. XXVIII.[1] The Triterpene Composition of the Genus Myrtillocactus[2]

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All known species of the genus *Myrtillocactus* have been examined. While no alkaloids were encountered, seven triterpenes have been isolated of which only two have been found outside the cactus family. Cochalic acid, chichipegenin and myrtillogenic acid seem to be particularly characteristic of this genus and attention is called to possible taxonomic implications of these results.

The main purpose of our chemical investigations of giant cacti has been the isolation and structure proof of new alkaloids and triterpenes.[4] It was felt desirable to study, as far as possible, all species of a given genus which contained alkaloids or triterpenes since such results could be of biogenetic and taxonomic interest. Some fruitful conclusions already have been reached from examinations of the genera *Lemaireocereus*,[4,5] *Machaerocereus*,[6] and *Lophocereus*[7] and we should now like to report on a

(1) Paper XXVII, C. Djerassi and H. G. Monsimer, THIS JOURNAL, **79**, 2501 (1957).

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(4) For a summary see "Cactus Triterpenes," by C. Djerassi in "Festschrift Arthur Stoll," Birkhäuser, Basel, 1957, pp. 830–852.

(5) See C. Djerassi, A. Bowers, S. Burstein, H. Estrada, J. Grossman, J. Herrán, A. J. Lemin, A. Manjarrez and S. C. Pakrashi, THIS JOURNAL, **78**, 2312 (1956), and earlier papers.

(6) C. Djerassi, L. H. Liu, E. Farkas, A. E. Lippman, A. J. Lemin, L. E. Geller, R. N. McDonald and B. J. Taylor, *ibid.*, **77**, 1200 (1955).

(7) C. Djerassi, S. K. Figdor, J. M. Bobbitt and F. X. Markley, *ibid.*, **79**, 2499 (1957), and earlier papers.

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detailed investigation of the genus *Myrtillocactus*.

Britton and Rose[8] have assigned four species—*M. geometrizans*, *M. cochal*, *M. schenckii* and *M. eichlamii*—to this genus, which is indigenous to Mexico and Guatemala. *Myrtillocactus grandiareolatus* is usually considered a synonym[9] for *M. geometrizans*, but our chemical results indicate a distinct difference. Through the coöperation of Mr. Howard E. Gates (Corona, California), Don Mariano Pacheco (Guatemala, C.A.) and Dr. Alberto Sandoval (Instituto de Quimica, Mexico, D.F.) it has been possible to secure specimens of all five species, which were investigated in the customary manner[4] for alkaloids and triterpenoid glycosides. All of these plants were rich in glycosides but did not contain any alkaloids, in agreement with earlier results among the *Cactaceae*[4] as well as other plant families[10] that glycosides and alkaloids usually do not occur in the same plant. In three instances, the non-glycosidic, neutral fraction was saponified[11] and was found to contain small amounts of triterpenes which were present in esterified form.

Myrtillocactus cochal (Baja California, Mexico) proved to be particularly rich in triterpenes. Acid hydrolysis of the glycosides yielded a neutral and an acidic fraction. The former consisted of essentially one triterpene which could be purified by direct crystallization and was found to be a new triterpene tetrol ($C_{30}H_{50}O_4$). With one exception (*M. schenckii*) this tetrol has proved to be the principal triterpene of all *Myrtillocactus* species and it has been encountered subsequently in only one species of another genus, namely, *Lemaireocereus chichipe*. We have named the substance chichipegenin and its structure elucidation[12] is being undertaken jointly with Dr. Alberto Sandoval and collaborators. The acidic portion consisted chiefly of one acid, cochalic acid, the structure (Ia) of which recently has been established.[13] Methylation of the mother liquors and chromatography gave in addition to methyl cochalate the methyl ester of a new trihydroxy triterpene acid which has now been named myrtillogenic acid and whose structure has been shown[1] to be IIa. Saponification of the oily, neutral, non-glycosidic constituents of this cactus furnished a small amount of longispinogenin (IIIa).[14] The co-occurrence of cochalic acid (Ia) and longispinogenin (IIIa), two triterpenes which differ only in the oxidation state of C-28, suggested that myrtillogenic acid (IIa) and the new tetrol chichipegenin might bear the same relationship to each other. This possibility was eliminated, however, when it was found that the lithium aluminum hydride reduction product (IVa) of myrtillogenic acid (II) was different from chichipegenin.

Myrtillocactus geometrizans (Central Mexico) exhibited qualitatively the same triterpene composition as *M. cochal* thus confirming the close botanical relationship of these two species. The common structural feature among its three triterpenes of known structure—cochalic acid (Ia), myrtillogenic acid (IIa) and longispinogenin (IIIa)—is the fact that they are oxygenated at positions 3, 16 and 28. Whether this also applies to the main constituent, chichipegenin, will have to be determined by degradation experiments which are now in progress.[12]

Myrtillocactus eichlamii is the only species of this genus which grows in Guatemala and it also contained chichipegenin, cochalic acid (Ia), myrtillogenic acid (IIa) and longispinogenin (IIIa), the latter being present in the non-glycosidic portion. In addition, there was encountered oleanolic acid (Va) (from the glycosidic fraction) and maniladiol (VI) (present in esterified form). The isolation of the latter is of interest since it has so far been found only in *manila elemi* resin[15] and in the cactus *Escontria chiotilla*.[5] Structurally, it fits nicely into the cactus triterpene pattern[4] according to which oxygenation is observed only in rings D and E aside from C-3.

The remaining two Mexican species *M. grandiareolatus* and *M. schenckii* yielded only two triterpenes.[16] The principal constituent of the former was the above-mentioned chichipegenin accompanied by some oleanolic acid (Va) while the latter contained oleanolic acid (Va) and stellatogenin (VIIa).[17]

From these studies it can be concluded that chichipegenin is the most characteristic triterpene (followed by cochalic and myrtillogenic acids) of this genus since it has been isolated in large amounts from four species. The only species which did not contain it, *M. schenckii*, yielded triterpenes which are characteristic[4] of the genus *Lemaireocereus*, while the only species outside the genus *Myrtillocactus* where chichipegenin has been encountered has been *Lemaireocereus chichipe*.[12] It would appear that a botanical reinvestigation of these two species is in order and in view of the considerable taxonomic difficulties among the *Cactaceae* chemical criteria (such as triterpene content) might be used to good advantage.

Britton and Rose[4] have pointed out that botanically the genus *Myrtillocactus* has no close relatives and it has been placed next to *Lophocereus* only because plants of both genera show several flowers at each areole. Chemically these two genera are completely distinct[4] since all *Lophocereus* species are rich in alkaloids but do not contain any triterpenoid glycosides in marked contrast to the above described *Myrtillocactus* species.

(8) N. L. Britton and J. N. Rose, "The Cactaceae," Carnegie Institution of Washington, Washington, D. C., 1920, Vol. II, pp. 178–181.

(9) H. Bravo, "Las Cactaceas de Mexico," Imprenta Universitaria, Mexico, D.F., 1937, pp. 308–314.

(10) *Cf.* M. E. Wall, C. R. Eddy, J. J. Willaman, D. S. Correll, B. G. Schubert and H. S. Gentry, *J. Amer. Pharm. Assoc.*, **43**, 503 (1954).

(11) The observation that cactus triterpenes may sometime also be present in esterified form was first made by Dr. Alberto Sandoval working with *Lemaireocereus chichipe*.

(12) To be published.

(13) C. Djerassi, G. H. Thomas and H. G. Monsimer, THIS JOURNAL, **77**, 3579 (1955).

(14) C. Djerassi, R. N. McDonald and A. J. Lemin, *ibid.*, **75**, 5940 (1953); C. Djerassi, L. E. Geller and A. J. Lemin, *ibid.*, **76**, 4089 (1954).

(15) R. Morice and J. C. E. Simpson, *J. Chem. Soc.*, 795 (1940).

(16) The neutral, non-glycosidic fraction was not investigated in this case.

(17) C. Djerassi, E. Farkas, L. H. Liu and G. H. Thomas, THIS JOURNAL, **77**, 5330 (1955).

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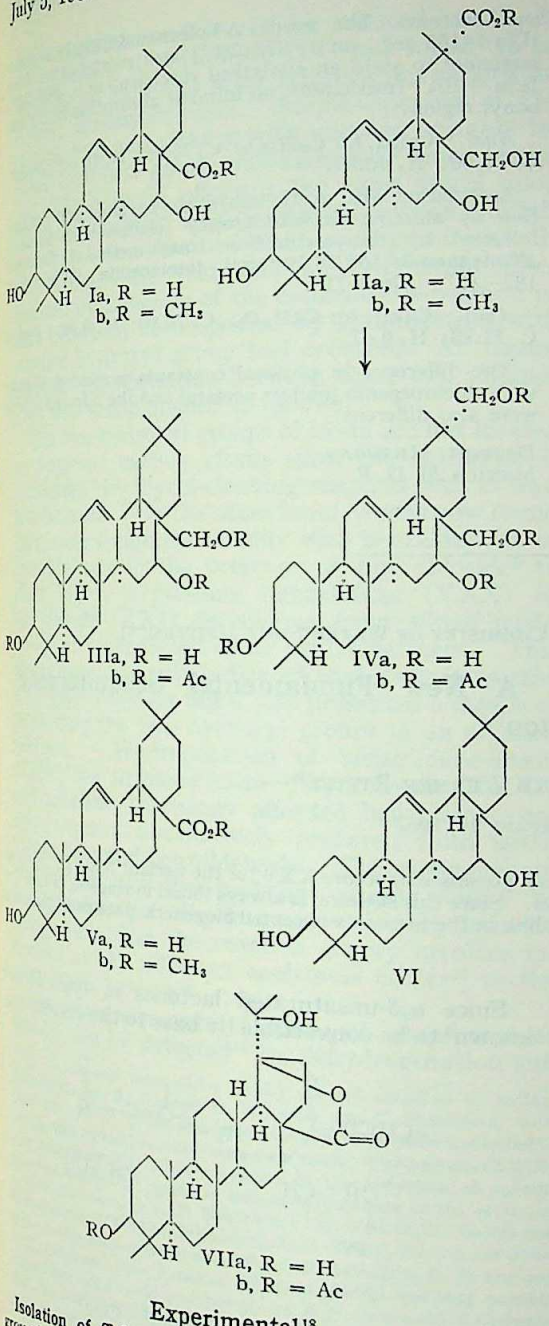

Experimental[18]

Isolation of Triterpenes from *M. cochal*.[19]—Dried and ground plant (1.6 kg.) from 21 kg. of fresh cactus (furnished by Mr. Howard E. Gates, Corona, California) was extracted continuously for 4 days with ethanol in a Soxhlet extractor and the solvent removed to yield 475 g. of extract. This was washed thoroughly with ether to remove non-glycosidic material (see below) and then hydrolyzed by heating under reflux for 4 hours with 450 cc. of concd. hydrochloric acid and 800 cc. of ethanol. After reducing the volume to one-half, much water was added and the precipitate was collected and dried. Continuous extraction of this solid with ether in a Soxhlet apparatus (4 days) and cooling of the ether solution furnished 25.5 g. of crude **chichipegenin**, m.p. 278–285°, raised to 320–325° after two recrystallizations from ethanol. The ether filtrate was washed thoroughly with 5% potassium hydroxide solution (see below for isolation of acids), water, dried and evaporated, leaving 34 g. of neutral semi-solid. Extraction of this fraction with benzene left 14 g. of insoluble residue which after recrystallization from methanol–acetone yielded an additional 12 g. of chichipegenin (m.p. 304–310°). Chromatography of the benzene solution on 400 g. of acetic acid-deactivated alumina and elution with ether gave 2.0 g. of chichipegenin to raise the total yield to 39.5 g. (2.47% based on dry plant). The analytical sample was obtained from methanol–acetone and exhibited m.p. 322–325°, $[\alpha]D$ +60° (methanol).

Anal. Calcd. for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. Found: C, 75.56; H, 10.93.

Acetylation of a sample with acetic anhydride–pyridine at room temperature overnight followed by recrystallization from methanol–chloroform led to **chichipegenin tetraacetate**, m.p. 278–280, $[\alpha]D$ +30°.

Anal. Calcd. for $C_{38}H_{58}O_8$: C, 70.99; H, 9.09. Found: C, 70.78; H, 9.17.

The above alkali washes were combined and acidified. Extraction with ether gave *ca.* 40 g. of acidic residue, which upon crystallization from acetone yielded 15 g. of **cochalic acid** (Ia), m.p. 300–302°.[13] The filtrate was evaporated, methylated overnight with excess diazomethane in methanol solution and then chromatographed on 800 g. of alumina deactivated with 10 cc. of 10% acetic acid. Elution with 8:2 benzene–ether provided 5.0 g. of crude methyl cochalate (Ib) (m.p. 175–180°)[13] raising the total yield of this triterpene to 1.25%.

Washing of the column with ether gave 3.1 g. (0.19%) of **methyl myrtillogenate** (IIb), m.p. 232–236°. Recrystallization from methanol–acetone provided the analytical sample, m.p. 248–250°, $[\alpha]D$ +87°.

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03. Found: C, 74.24; H, 9.98.

Acetylation with acetic anhydride–pyridine and recrystallization from methanol gave the corresponding **triacetate**, m.p. 147–149°, $[\alpha]D$ +76°.

Anal. Calcd. for $C_{37}H_{56}O_8$: C, 70.67; H, 8.98. Found: C, 70.56; H, 9.11.

The ether washings of the original ethanolic cactus extract were evaporated and the dark green oil (25 g.) was heated under reflux overnight with 25 g. of potassium hydroxide and 250 cc. of methanol. Concentration, dilution with water and extraction with ether furnished 6.5 g. of a semi-solid which was chromatographed on 80 g. of acetic acid-deactivated alumina. All crystalline eluates were combined and recrystallized from acetone to give 2.5 g. (0.157%) of **longispinogenin** (IIIa), m.p. 241–245°. Purification was best accomplished *via* its **triacetate** (m.p. 219–222°, $[\alpha]D$ +69°) which was shown to be identical with an authentic sample[14] by mixture melting point determination and infrared comparison.

Isolation of Triterpenes from *M. geometrizans*.[20]—The isolation was carried out exactly as above and the results differed only quantitatively from those observed with *M. cochal:* chichipegenin (0.62%), methyl cochalate (Ib) (0.25%), methyl myrtillogenate (IIb) (0.14%) and longispinogenin (IIIa) (0.0025%).

Isolation of Triterpenes from *M. eichlamii*.—The cactus was collected by Don Mariano Pacheco near Guatemala City and sun dried before being shipped to Detroit. From 1720 g. of dried, ground cactus, there was obtained 430 g. of ethanol extract which upon thorough washing with ether led to 319 g. of solid, tan-colored glycoside and 77 g. of neutral, non-glycosidic material.

Acid cleavage of the glycosides yielded 0.90% of chichipegenin, while chromatography of the methylated acid fraction gave 0.16% of **methyl oleanolate** (Ib) (m.p. 199°, $[\alpha]D$ +72°), 0.037% of **methyl cochalate** (Ib) and 0.028% of **methyl myrtillogenate** (IIb).

Saponification of the non-glycosidic fraction followed by chromatography of the neutral fraction gave some **β-sitosterol** (m.p. 138–140°, $[\alpha]D$ −37°; **acetate**, m.p. 125–128°, $[\alpha]D$ −44°), 0.14% of **maniladiol** (VI) (m.p. 215–217°, $[\alpha]D$ +67°, identified by direct comparison with a sample prepared[14] from gummosogenin) and 0.83% of **longispinogenin** (IIIa).

Isolation of Triterpenes from *M. grandiareolatus*.—This

(18) Melting points are uncorrected. Unless noted otherwise, rotations were measured in chloroform solution. We are indebted to Mrs. Theodora Phillips for the infrared spectra and to Dr. A. Bernhardt (Mülheim, Germany) for the microanalyses.

(19) A preliminary investigation was carried out by Dr. G. H. Thomas (see ref. 13).

(20) Collected at km. 205, of the Mexico–Laredo highway near the town of Zimapán.

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cactus was collected near Zapotitlán on the road from Tehuacán Puebla to Huajuapan de León and from the glycosidic fraction there was obtained nearly 1% of chichipegenin and 0.2% of methyl oleanolate (Vb).

Isolation of Triterpenes from *M. schenckii*.—A 1.54-kg. sample (dry) of cactus collected near Diaz Ordaz, Oaxaca, yielded only 55 g. of glycosidic material after alcohol extraction and ether washing. Acid hydrolysis and chromatography of the neutral fraction gave 0.052% of stellatogenin (VIIa)[17] (m.p. 311–314°, $[\alpha]_D$ +40°; acetate VIIb, m.p. 323–326°, $[\alpha]_D$ +49°), identified by infrared comparison with an authentic sample,[6] while methylation of the acids and chromatography led to 0.136% of methyl oleanolate (Vb) (m.p. 197–199°).

Lithium Aluminum Hydride Reduction of Triacetyl Methyl Myrtillogenate.—Methyl myrtillogenate (IIb) triacetate (196 mg.) was heated under reflux for 12 hours with 1 g. of lithium aluminum hydride in 100 cc. of ether and was then processed in the manner described earlier[21] for oleanolic acid lactone. The crude Δ^{12}-oleanen-3β,16β,28,29-tetrol (IVa) (155 mg., m.p. 275–280°) was recrystallized from methanol to yield an analytical specimen, m.p. 280–283°, $[\alpha]_D$ +101° (methanol), no infrared absorption in the carbonyl region.

Anal. Calcd. for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. Found: C, 76.00; H, 10.52.

Acetylation with acetic anhydride–pyridine and purification by alumina chromatography (elution with benzene) followed by recrystallization from methanol furnished Δ^{12}-oleanen-3β,16β,28,29-tetrol tetraacetate (IVb), m.p. 182–183°, $[\alpha]_D$ +71°.

Anal. Calcd. for $C_{38}H_{58}O_8$: C, 70.99; H, 9.09. Found: C, 71.23; H, 9.47.

The difference in physical constants precluded identity with chichipegenin (and its acetate) and the infrared spectra were also different.

DETROIT, MICHIGAN
MEXICO 20, D. F.

(21) C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins and F. Walls, THIS JOURNAL, **76**, 2969 (1954).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Terpenoids. XXIX.[1] Iresin (Part 2).[2] A New Fundamental Sesquiterpene Skeleton[3,4]

BY CARL DJERASSI AND WERNER RITTEL[5]

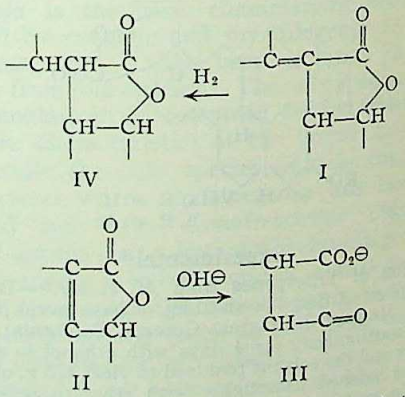
RECEIVED FEBRUARY 14, 1957

By means of various degradations, it has been shown that iresin possesses structure XXV (or the variant XXXII) based on a skeleton (XIII or XIV) which is unique among sesquiterpenes. Since this skeleton is always found in rings A, B and C of the higher (di- and tri)-terpenes, iresin represents an important link in the presently accepted biogenetic pattern of the lower and higher terpenes.

Recently,[2] there has been described the isolation and characterization of a novel sesquiterpene ($C_{15}H_{22}O_4$) which was named iresin. We should now like to record the salient experiments which led to the elucidation of the skeletal structure of this substance and which suggest that iresin occupies a unique position in terpene chemistry. Future papers will deal with various transformations of the functional groups of iresin and with its stereochemistry.

The nature of the four oxygen atoms already has been elucidated in the first paper[2] of this series and they were shown to be present as two reactive hydroxyl groups and as an α,β-unsaturated, five-membered lactone ring. The latter could, *a priori*, be of two types—the double bond being exocyclic (I) or endocyclic (II) with respect to the lactone ring—and it seemed important to differentiate between these two possibilities before initiating more drastic degradations.

Since α,β-unsaturated lactones of type II are known[6] to be convertible by base to the corresponding keto acids III, iresin was subjected to such treatment and was recovered unchanged (after acidification) even when heated with potassium *t*-butoxide. We conclude that the unsaturated lactone system of iresin is of type I and direct chemical proof for this supposition was afforded by ozonization experiments described below. The only double bond present in iresin is that conjugated with the



(1) Paper XXVIII, C. Djerassi, S. Burstein, H. Estrada, A. J. Lemin, A. E. Lippman, A. Manjarrez and H. G. Monsimer, THIS JOURNAL, **79**, 3525 (1957).

(2) Part 1, C. Djerassi, P. Sengupta, J. Herran and F. Walls, *ibid.*, **76**, 2966 (1954).

(3) Announced in part in a preliminary communication (C. Djerassi, W. Rittel, A. L. Nussbaum, F. W. Donovan and J. Herran, *ibid.*, **76**, 6410 (1954)).

(4) We are grateful to the Rockefeller Foundation for financial support.

(5) Ciba Ltd., Basel, Switzerland. Postdoctorate research fellow, 1953–1954.

(6) *Cf.* W. D. Paist, E. R. Blout, F. C. Uhle and R. C. Elderfield, *J. Org. Chem.*, **6**, 273 (1941); L. C. McKean and F. S. Spring, *J. Chem. Soc.*, 1989 (1954); J. B. Stenlake and W. D. Williams, *ibid.*, 2114 (1955).

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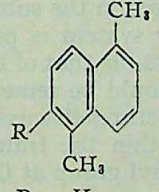
lactone system and it can be reduced readily.[2,7] The resulting dihydroiresin (IV) was found[2] to be unstable to base and after acidification yielded an isomer, isodihydroiresin. Simple opening of the lactone ring and closure with another, suitably located hydroxyl group was excluded,[2] since iresin[8] and dihydroiresin afforded the same tetrol upon lithium aluminum hydride reduction while a different tetrol was obtained from isodihydroiresin. It follows that base treatment of dihydroiresin either resulted in inversion of the enolizable α-position or that inversion accompanied by lactonization with another hydroxyl group had occurred. An unambiguous differentiation between these two alternatives was accomplished as follows.

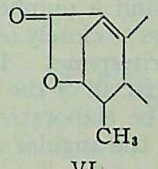
The two hydroxyl groups of iresin are not located on adjacent carbon atoms since the substance is unaffected[2] by glycol-cleaving reagents such as lead tetraacetate. On the other hand, it was now found that iresin condensed readily with benzaldehyde or acetaldehyde in the presence of zinc chloride[9] to yield highly crystalline benzylidene (XXX) or acetylidene (XXI) derivatives from which iresin could be regenerated after acid treatment. This observation not only indicated that iresin possessed a 1,3-glycol system but it also presented a means of protecting the two hydroxyl groups in an alkaline medium. Hydrogenation of benzylidene–iresin (XXX) led to benzylidene–dihydroiresin (XXXI) and alkaline treatment afforded benzylidene–isodihydroiresin, alternatively prepared from isodihydroiresin and benzaldehyde. This circle demonstrates that the two hydroxyl groups cannot be implicated in the dihydroiresin → isodihydroiresin change and that the reaction simply involves inversion at the adjacent enolizable center[10] to the more stable isomer.[11]

The gross structural features of sesquiterpenes usually can be detected[12] by dehydrogenation and identification of the resulting aromatic products. When iresin was heated with palladized charcoal catalyst near 300°, two crystalline dehydrogenation products were obtained. These were identified as 1,5-dimethylnaphthalene (Va)[13] and 1,5-dimethyl-2-naphthol (Vb)[14] and it should be noted that while both substances had been described in the literature,[13,14] neither one had ever been encountered as a characteristic sesquiterpene dehydrogenation product.[12] This constituted the first indication that iresin might represent a novel sesquiterpene type, a supposition which was shown in the sequel to be correct.

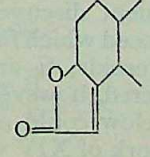
The two naphthalene derivatives (Va, Vb) account for 12 out of the 15 carbon atoms of iresin. Since angular or *gem*-substituents as well as actual or potential carboxyl groups are lost during dehydrogenations,[12] it can be assumed that the loss of three carbon atoms involved the carboxyl group of the lactone ring as well as one (ethyl or oxygenated ethyl) or two (methyl or oxygenated methyl) angular (or *gem*) alkyl groups. Obviously the more significant dehydrogenation product was the naphthol Vb since the surviving oxygen atom automatically labeled one of the three hydroxylic functions of iresin. *A priori*, the phenol could have arisen from either the two alcoholic substituents of iresin or from the hydroxyl group incorporated in the lactone ring. The latter possibility, however, could be ruled out since an α,β-unsaturated five-membered lactone moiety involving that oxygen atom (and furnishing Vb upon dehydrogenation) would lead to partial structures VI or VII. The former would violate Bredt's rule while the latter does not follow the earlier mentioned prerequisite (*cf.* I) that the double bond be exocyclic to the lactone ring.



Va, R = H
b, R = OH
c, R = C_6H_5COO



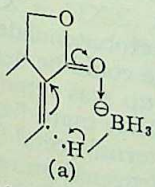
VI



VII

It follows, therefore, that the phenolic hydroxyl group of 1,5-dimethyl-2-naphthol (Vb) originated from one of the two alcoholic groups, which are very easily acylated and saponified.[2] Since this chemical behavior excludes tertiary hydroxyl functions and since they must be part of a 1,3-glycol system (condensation with aldehydes), partial structures VIII and IX (R = H or alkyl) are the only permissible ones insofar as the two hydroxyl groups are concerned. The survival of an alcohol under the drastic dehydrogenation conditions is reminiscent of the 3-hydroxy-4,4-dimethyl system of the pentacyclic triterpenes (*e.g.*, β-amyrin (X)), since dehydrogenation[15] of such compounds leads in part to phenolic products (*e.g.*, XI, XII) in which the orig-

(7) Unsaturated butenolides usually are not attacked by sodium borohydride (*cf.* R. Richter, O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **37**, 76 (1954), and references cited) but iresin was found to be converted by this reagent in very good yield to dihydroiresin (XXIX) (see Experimental). While examples of the reduction of α,β-unsaturated ketones by means of sodium borohydride to the saturated alcohols are known (*e.g.*, F. Sondheimer, M. Velasco, E. Batres and G. Rosenkranz, *Chemistry & Industry*, 1482 (1954)), the sole reduction of the double bond appears unusual (*cf.* H. Schechter, D. E. Ley and E. B. Roberson, THIS JOURNAL, **78**, 4984 (1956)) and may possibly proceed through a cyclic intermediate (*cf.* R. E. Lutz and J. S. Gillespie, *ibid.*, **72**, 2002 (1950)) which would be favored by the *cisoid* unsaturated carbonyl system (a).



(a)

(8) In this case the double bond was also reduced.

(9) Cf. K. Freudenberg, H. Toepffer and C. C. Andersen, *Ber.*, **61**, 1758 (1928).

(10) As is to be expected on mechanistic grounds, inversion appears to occur prior to opening of the lactone ring since some isodihydroiresin can be extracted from the alkaline solution without acidification.

(11) The stereochemistry of these compounds will be discussed in a subsequent paper.

(12) Cf. J. Simonsen and D. H. R. Barton "The Terpenes," Vol. III, Cambridge University Press, 1952, and A. J. Haagen-Smit in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. XII, Springer, Vienna, 1955, pp. 1–43.

(13) A. S. Bailey, K. C. Bryant, R. A. Hancock, S. H. Morrell and J. C. Smith, *J. Inst. Petroleum*, **33**, 503 (1947).

(14) L. Ruzicka and E. Rey, *Helv. Chim. Acta*, **26**, 2136 (1943).

(15) For pertinent review, see O. Jeger in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. VII, Springer, Vienna, 1950, p. 10.

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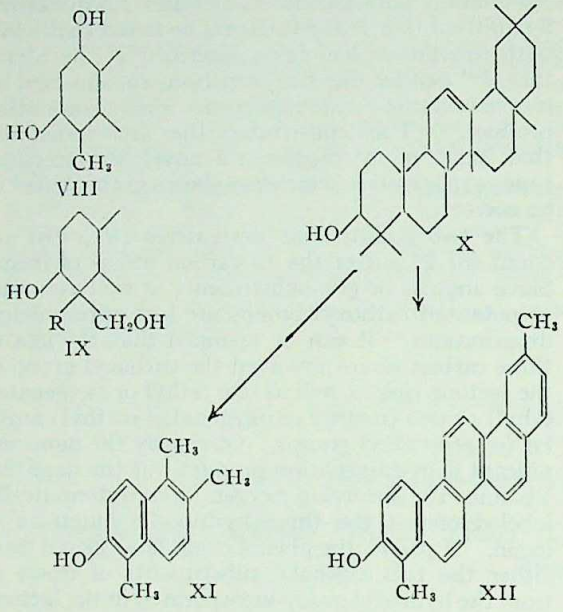
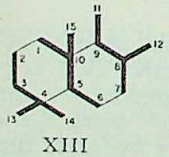
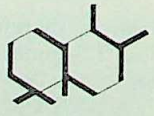
inal alcoholic group is retained. Such an analogy would tend to support partial structure IX (R = alkyl) for iresin and direct chemical proof will be described below.

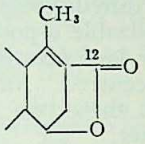


On the assumption that iresin obeys the isoprene rule, only two carbon skeletons need to be considered. The first one (XIII) (1x-y2, 2x-y3)[16] follows both the isoprene and farnesol rules (head-to-tail attachments of isoprene units) and is thus suggestive of rings A, B and C of the di- and triterpenes, while structure XIV (1x-x2, 2y-y3)[16] involves an irregular attachment of isoprene units. For the sake of brevity, only XIII will be used in the subsequent discussion and a numbering system is proposed which follows as closely as possible that of the steroids, di- and triterpenes. It should be remembered, however, that all of the structures discussed below could also be elaborated within the framework of XIV with the angular methyl group at C-5 instead of C-10.

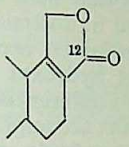

XIII


XIV

If a skeleton based on XIII or XIV is provisionally accepted for iresin, then the attachment of the lactone ring follows rigorously. The carboxyl carbon atom of the lactone ring is lost during dehydrogenation to 1,5-dimethylnaphthalene (V) and hence can only be represented by C-12, C-13 (or C-14) or C-15. Since iresin possesses a double bond which is in conjugation with the potential carboxyl group, only C-12 is left for consideration. This, *ipso facto*, also locates the hydroxyl group involved in lactone formation since of the three possible attachments of a five-membered, α,β-unsaturated lactone moiety originating at C-12 (of XIII or XIV), XV violates Bredt's rule and XVI possesses a double bond endocyclic to the lactone ring (II rather than the required I). This leaves XVII (or the variant with the angular methyl group at C-5) as the only reasonable expression for iresin, the remaining hydroxyl group occupying either position 1 (*cf.* VIII) or 13 (or 14) (*cf.* IX). Experimental proof for this structural proposal was provided by various oxidations.



XV



XVI

The key experiment proved to be the ozonolysis of iresin, which was expected to lead to rupture of the double bond and the introduction of two extra carbonyl groups ($C_{15}H_{22}O_4 \rightarrow C_{15}H_{22}O_6$). In point of fact, only one oxygen atom was added and the two hydroxyl groups originally present in iresin had disappeared. The ozonization product ($C_{15}H_{20}O_5$) gave a color with ferric chloride solution and exhibited an ultraviolet absorption maximum at 240 mμ (as compared to 224 mμ for iresin) which was shifted to 274 mμ in alkaline solution. Acetylation produced a monoacetate (subsequently shown to be XIXb) which had an ultraviolet absorption maximum at 218 mμ and which could be saponified to the original compound. These spectral properties are in excellent agreement with those predicted for an α-ketobutenolide[17] (XVIIIa) (and its enol acetate XVIIIb), which would be formed by ozonolysis of XVII. This would also explain the disappearance of the two hydroxyl groups in the ozonization product since if structure XVII (hydroxyl group at C-1 or C-13) were indeed correct, then the intermediate aldehyde XVIIIa would be perfectly located for internal acetal closure. On that basis, the final product should be represented by XIXa or XXa, depending upon the location of the second hydroxyl group (VIII or IX) in iresin and either structure is strain-free as well as fully compatible with the analytical, spectroscopic and chemical data. Complete confirmation for these views was provided by the observation that ozonolysis[18] of acetylidene iresin (XXI or XXIII)—the two hydroxyl groups now being blocked—afforded a crystalline product (XXII or XXIV) in which the presence of an α-ketobutenolide system as well as that of an aldehyde could be demonstrated. When the protecting group was removed by acid treatment, the intermediate immediately cyclized to the above described internal acetal (XIX or XX).

While the dehydrogenation results (formation of 1,5-dimethyl-2-naphthol (Vb)) favor locating the second hydroxyl group at C-13 or C-14 (IX) and consequently structures XIX, XXI and XXII, more conclusive evidence had to be provided concerning this important constitutional point.

Chromium trioxide oxidation of iresin in pyridine

(16) For symbolism see W. Klyne, *Chemistry & Industry*, 725 (1954); ref. 3c.

(17) *Cf.* A. Rossi and H. Schinz, *Helv. Chim. Acta*, **31**, 473 (1948); T. A. Geissman, THIS JOURNAL, **75**, 4008 (1953).

(18) This experiment was carried out by Dr. A. L. Nussbaum (see

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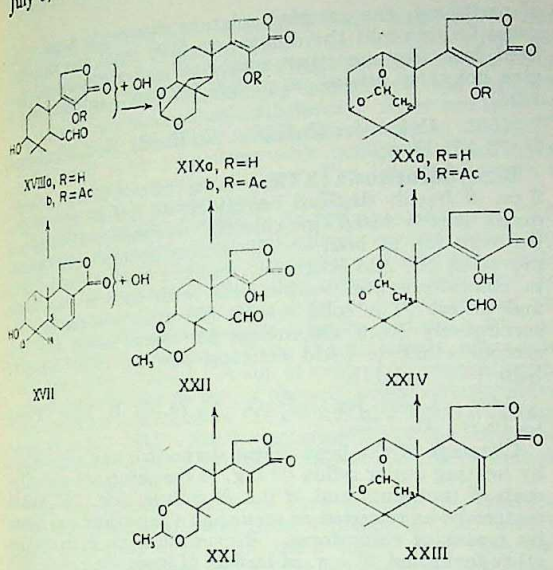
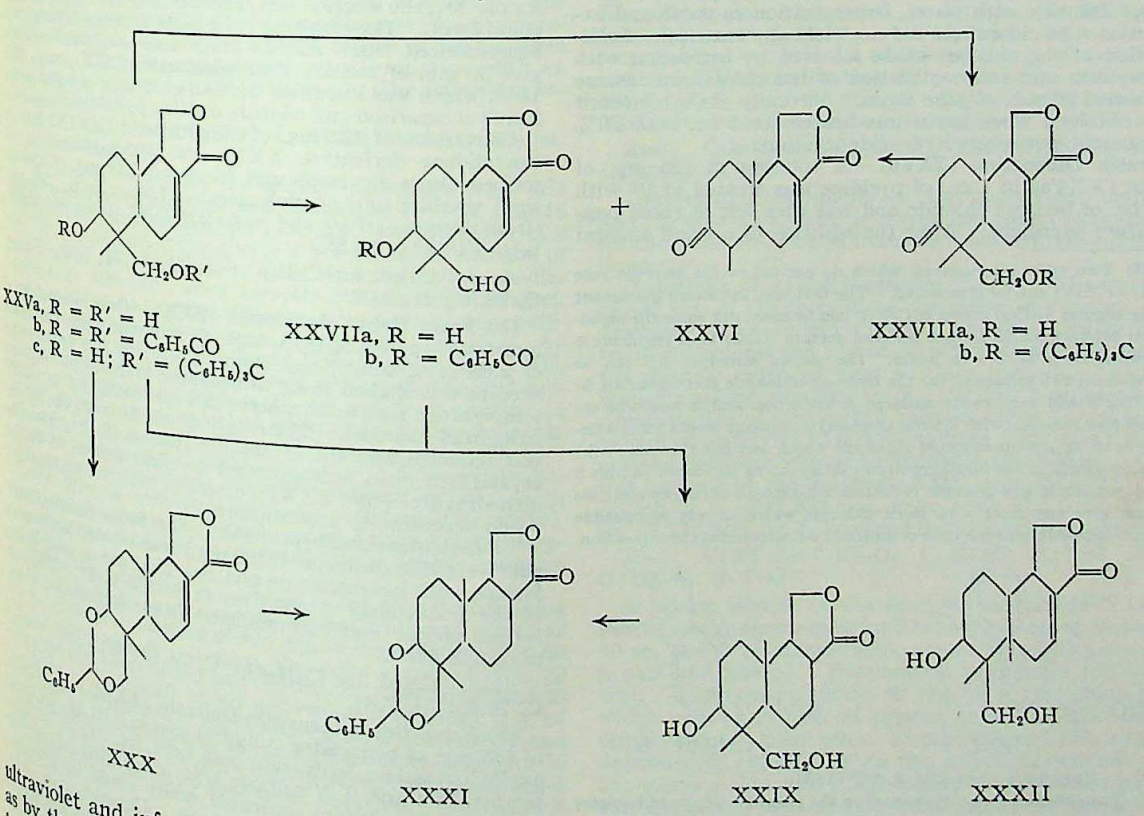


solution[19] led to two products which could be separated chromatographically. The analysis of the less polar substance indicated the loss of CH_4O, which would only be compatible with a 13-nor-3-keto structure (XXVI). The presence of the unchanged α,β-unsaturated butenolide system and of an isolated keto group was demonstrated by the nor-ketone (XXVI) can be rationalized only *via* an intermediate β-keto aldehyde or β-keto acid and consequently requires the presence of a primary hydroxyl group in iresin (XXVa), thus eliminating the alternate formulation with a hydroxyl group at C-1 (VIII). The more polar product, although not giving a Tollens reaction, was shown to be the hydroxy-aldehyde XXVIIa rather than the corresponding hydroxy-ketone (XXVIIIa). The substance did not give formaldehyde upon base treatment, as would be expected[21] from the hydroxy ketone XXVIIIa upon retroaldolization, and did not form a trityl ether. On the other hand, it did yield a crystalline benzoate (XXVIIb) as well as a 2,4-dinitrophenylhydrazone, the ultraviolet absorption maximum of which was typical[20] ($\lambda_{max}^{CHCl_3}$ 354 mμ) of an aldehyde and produced dihydroiresin (XXIX) upon reduction with sodium borohydride.[7,8]

A related approach by another series of transformations[22] led to the same conclusion and involved conversion of iresin (XXVa) to its trityl ether XXVc followed by chromium trioxide–pyridine oxidation[19] to the keto-alcohol trityl ether XXVIIIb. Acid cleavage of the trityl ether was accompanied by reverse aldol condensation with formation of formaldehyde (isolated as the dimedone derivative) and the nor-ketone (XXVI).



ultraviolet and infrared spectroscopic data as well as by the formation of a yellow 2,4-dinitrophenylhydrazone ($\lambda_{max}^{CHCl_3}$ 364 mμ[20]). The formation of a

The above-described degradations are only compatible with structures XXV or XXXII for iresin, the single uncertainty being the location of the

(19) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(20) *Cf.* E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 498 (1945); J. D. Roberts and C. Green, THIS JOURNAL, **68**, 214 (1946); C. Djerassi and E. Ryan, *ibid.*, **71**, 1000 (1949).

(21) *Cf.* D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 887 (1953).

(22) These three experiments were carried out by Dr. F. W. Donovan (see ref. 3) and will be published in part 3 of this series, together with other reactions of the glycol system of iresin.

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angular methyl group[23] which could be at C-10 (XXV) or at C-5 (XXXII). Experiments are under way to settle this point but from a biogenetic standpoint, either structure would be acceptable since XXXII would almost certainly have arisen by methyl migration of a plant precursor based on structure XXV. It should be noted that iresin is the first sesquiterpene which follows an isoprene pattern found so far only among the higher terpenes (di- and triterpenes). In fact, the conspicuous absence of such a skeleton in the sesquiterpene series (prior to the isolation of iresin) led Ruzicka[24] to the plausible assumption that "this appears to indicate that the biogenesis of the steroids, diterpenes and triterpenes differs in some fundamental detail from that of the monoterpenes and sesquiterpenes." The present demonstration that iresin possesses such a structure makes this assumption unnecessary and to that extent iresin can be considered a missing link in terpene biogenesis.[25] Its importance in the terpene series has encouraged us to study its chemistry in detail and future papers will deal with additional transformations as well as with its relative[26] and absolute configuration.

Experimental[27]

Stability of Iresin toward Alkali.—A solution of 100 mg. of iresin and 0.45 g. of potassium in 20 cc. of dry *t*-butyl alcohol was heated under reflux for 16 hr. in an atmosphere of nitrogen. Dilution with water, concentration *in vacuo* and extraction with chloroform did not yield any material. Acidification of the aqueous phase followed by extraction with chloroform and recrystallization of the chloroform residue furnished 86 mg. of pure iresin. Virtually the same result was obtained when iresin was heated for 5 hr. with 20% methanolic potassium hydroxide solution.

Iresin Dibenzoate (XXVb).—A solution of 100 mg. of iresin (XXVa) in 1 cc. of pyridine was treated at 0° with 0.5 cc. of benzoyl chloride and was then left at room temperature overnight. After the addition of a small amount of methanol, the reaction mixture was worked up in the usual fashion and the dibenzoate (190 mg.) was recrystallized from acetone–ether, methanol and methanol–ether to give colorless prisms, m.p. 209.5–210.5°, $[\alpha]^{22}D$ −52° (*c* 1.07).

Anal. Calcd. for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37. Found: C, 73.47; H, 6.36.

Benzylideneiresin (XXX).—A mixture of 50 mg. of iresin, 2 cc. of freshly distilled benzaldehyde and 80 mg. of powdered, freshly fused zinc chloride[9] was shaken at room temperature for 14 hours. The excess benzaldehyde was removed at 60° and 0.01 mm., and the residue was taken up in chloroform and washed well with sodium bicarbonate and water. The solid residue (66 mg.) was recrystallized successively from chloroform–petroleum ether and from acetone–ether to yield colorless needles, m.p. 242–244°, $[\alpha]D$ +70° (*c* 1.11).

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.48; H, 7.52.

Cleavage of the benzylidene derivative was accomplished by heating under reflux 30 mg. of the substance with 20 cc. each of methanol and of 0.1 *N* sulfuric acid. All volatile material was removed *in vacuo* and the product was isolated by means of chloroform. Recrystallization from acetone–ether furnished 16 mg. of leaflets of iresin (m.p. 133–135°), identified by infrared comparison.

Benzylidenedihydroiresin (XXXI). (a) **From Dihydroiresin (XXIX).**—The required dihydroiresin (XXIX) could be prepared by hydrogenation[2] as well as by sodium borohydride[7] reduction of iresin in the following manner.

A solution of 40 mg. of iresin, 8 mg. of sodium borohydride and 6 cc. of 95% ethanol was kept for 6 hr. at room temperature and then acidified with dilute sulfuric acid to *p*H 3. After addition of 10 cc. of water and heating to 60° for one hr., the solution was concentrated and extracted with chloroform. The resulting crystalline residue (38 mg.) was recrystallized from acetone–ether and methanol–ether to give 30 mg. of needles of **dihydroiresin (XXIX)**, m.p. 142–145°, which was identified with an authentic sample[2] by infrared comparison and mixture melting point determination.

Conversion of 125 mg. of dihydroiresin (XXIX) into its benzylidene derivative XXXI was accomplished as described above for iresin and furnished 123 mg. of the desired product as two polymorphic forms, m.p. 188–191° (from acetone–ether) and m.p. 204–206° (from methanol), $[\alpha]D$ +19.5° (*c* 1.15).

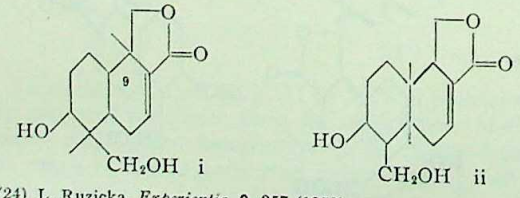
Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.64; H, 8.09.

(b) **From Benzylideneiresin (XXX).**—One equivalent of hydrogen was taken up within 40 minutes when a solution of 2.66 g. of benzylideneiresin (XXX) in 250 cc. of ethyl acetate was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure with 1.5 g. of 5% palladized charcoal. The catalyst was filtered, the solvent was removed and the crystalline residue (2.51 g.) was recrystallized from acetone–ether to yield prisms of benzylidenedihydroiresin (XXXI), identical with the material prepared according to procedure (a).

Benzylideneisodihydroiresin. (a) **From Isodihydroiresin.**[18]—Isodihydroiresin[2,28] (60 mg.) was treated in the usual fashion with benzaldehyde and zinc chloride to give 51 mg. of the benzylidene derivative, m.p. 236–239°. The analytical sample was recrystallized from methanol–acetone, m.p. 238–240°.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.30; H, 7.88.

(b) **From Benzylidenedihydroiresin (XXXI).**—A solution of 185 mg. of benzylidenedihydroiresin in 8 cc. of 5% methanolic potassium hydroxide was kept for 24 hr. at room temperature and 2 *N* sulfuric acid was added followed by water. A precipitate separated which could be extracted only with difficulty with chloroform. Concentration of the washed and dried chloroform extract yielded colorless needles (153 mg.) which were filtered. This rather insoluble material gave an acid reaction toward litmus and its solubility increased during recrystallization attempts. It appears,



(23) Two other alternatives, which do not follow the isoprene rule (XIII or XIV) can be eliminated. The first one, involving placement of the angular methyl group at C-9 (i) can be ruled out since the ozonization product XIXa formed an enol acetate XIXb thus requiring a hydrogen atom at C-9 in iresin. The second structure (ii) can be excluded on two grounds: (a) the hydroxy-aldehyde corresponding to XXVIIa would very easily undergo dehydration and it would be expected that reaction with 2,4-dinitrophenylhydrazine would yield a derivative of an α,β-unsaturated aldehyde which was not the case. (b) In experiments in the isodihydroiresin series (to be published in part 3 of this series), it was possible to isolate a 3-keto-13-aldehyde and this did not give any color with ferric chloride which is only compatible with a β-ketoaldehyde which is completely substituted at the α-position.

(24) L. Ruzicka, *Experientia*, **9**, 357 (1953).

(25) The substance may be formed in the plant by a type of farnesol (or its equivalent) cyclization for which there exists experimental precedent (for leading references see G. Stork and A. W. Burgstahler, THIS JOURNAL, **77**, 5068 (1955)).

(26) In this connection it may be pertinent to mention that the formation of the cyclic acetal XIX is of considerable significance since this requires that the C-3 hydroxyl group, the carbon atom bearing the primary hydroxyl function and the 5–6 bond must all be *cis*.

(27) Melting points are uncorrected. Unless noted otherwise, rotations were determined in chloroform solution in 1 dcm. tubes. The microanalyses were carried out by Geller Laboratories (Hackensack, N. J.) and by Mr. Joseph F. Alicino (Metuchen, N. J.).

(28) Mr. Sumner Burstein has observed that when the alkaline isomerization of dihydoiresin is conducted in the earlier described manner (ref. 2) approximately 10–15% of isodihydroiresin can be extracted from the alkaline solution prior to acidification (*cf.* ref. 10).

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therefore, that this was the open hydroxy acid which relactonized slowly. Crystallization from ethanol–ether furnished two fractions, a low melting material (50 mg., m.p. 183–200°) probably representing impure starting material, and 40 mg. of a more soluble substance. After one more recrystallization, this latter substance melted at 235–238°, undepressed upon admixture with benzylideneisodihydroiresin prepared according to (a). The infrared spectra of the two samples were identical.

Dehydrogenation of Iresin.—An intimate mixture of 1.04 g. of iresin and 2.0 g. of 5% palladized charcoal was heated for 2 hr. at 280–300° in an atmosphere of nitrogen. After cooling, the reaction mixture was extracted first with hot petroleum ether and then with ether and each extract was washed with sodium carbonate solution and with 20% sodium hydroxide solution. From the petroleum ether fraction there was obtained 118 mg. of neutral oil, no carbonate-soluble material and 45 mg. of phenolic solid (after acidification and ether extraction of the sodium hydroxide washings) with m.p. 150–164°. Similar examination of the ether fraction produced 90 mg. of hydrocarbon and 150 mg. of phenolic solid, m.p. 158–165°.

The two phenolic fractions were pooled, recrystallized twice from chloroform and then sublimed at 125° and 14 mm., whereupon a m.p. of 163.5–164.5° was observed. Identity was established by mixture melting point determination and infrared comparison with a specimen (m.p. 164–165°) of **1,5-dimethyl-2-naphthol (Vb)**[14] which was prepared by saponification of a sample of authentic benzoate Vc kindly furnished by Prof. O. Jeger, E.T.H., Zurich.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.74, 83.63; H, 7.00, 7.01.

A 31-mg. sample of the phenol Vb was benzoylated in the manner described above for iresin dibenzoate (XXXVb) and purified by chromatography on neutral alumina.[29] The crystals (20 mg.) eluted with hexane–benzene (4:1) were recrystallized from methanol to afford prisms of the **benzoate Vc**, m.p. 152–153°, undepressed upon admixture with an authentic specimen[14] of the same m.p. The infrared spectra were identical.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.29; H, 5.99.

The neutral oils from the original petroleum ether and ether extracts were pooled and distilled at 80–100° and 16 mm. The colorless distillate (122 mg.) was dissolved in 2 cc. of ethanol and treated with a hot ethanolic solution of 150 mg. of trinitrobenzene. The resulting yellow needles melted at 120–150° after recrystallization from ethanol, but could not be purified effectively by further recrystallization and the complex was decomposed, therefore, by passing a hot pentane solution of it through alumina. The regenerated hydrocarbon was partially crystalline and several recrystallizations from methanol and from pentane at −80° gave 6 mg. of colorless leaflets of **1,5-dimethylnaphthalene (Va)**, m.p. 77–79°. The undepressed (78–81°) mixture melting point with authentic[13] 1,5-dimethylnaphthalene (m.p. 81–81.5°), kindly provided by Dr. A. S. Bailey (Dyson Perrins Laboratory, Oxford University), and the coincidence of the infrared and ultraviolet absorption spectra established the identity of the dehydrogenation product.

Ozonolysis of Iresin.—A stream of dry oxygen containing 1.5% of ozone (flow rate *ca.* 180 cc./minute) was passed at −80° through a solution of 490 mg. of iresin dissolved in 60 cc. of ethyl acetate. A faint blue color appeared after 20 minutes and ozonization was continued for an additional 10 minutes. The excess ozone was removed *in vacuo*, 2 g. of 5% palladium–calcium carbonate catalyst was added and the mixture was shaken in an atmosphere of hydrogen for 15 minutes whereupon no more hydrogen was consumed and a starch–iodide test was found to be negative. The catalyst was filtered, the ethyl acetate solution was washed with sodium carbonate solution, dried, evaporated and crystallized (acetone–ether) yielding 160 mg. (31%)[30] of solid, m.p. 210–220°. Recrystallization from acetone–ether and from methanol–ether furnished colorless prisms of the **acetal XIXa** showing the following properties: m.p. 230–233°, $[\alpha]D$ −26° (*c* 0.56); $\lambda_{max}^{CHCl_3}$ 2.82, 3.00, 5.69 and 5.95 μ; λ_{max}^{EtOH} 240 mμ, log ϵ 3.90; $\lambda_{max}^{0.01\ N\ KOH}$ 274 mμ, log ϵ 4.03; bluish-gray color with alcoholic ferric chloride solution, negative Tollens (room temperature) and Schiff reactions.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; mol. wt., 280. Found: C, 64.08, 64.22; H, 7.38, 7.06; neut. equiv. (titration with 0.1 *N* sodium hydroxide), 263.

Acetylation with acetic anhydride–pyridine and recrystallization from acetone–ether and from methanol–ether gave needles of the **enol acetate XIXb**, m.p. 149–151°, $[\alpha]D$ −20° (*c* 0.53), λ_{max}^{EtOH} 218 mμ, log ϵ 4.02, no free hydroxyl absorption in the infrared.

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88; acetyl, 13.35. Found: C, 63.46; H, 6.72; acetyl, 13.75.

A 40-mg. sample of the above enol acetate dissolved in 5 cc. of 80% aqueous methanol containing 50 mg. of potassium bicarbonate was kept at room temperature for 4 days. The methanol was removed under reduced pressure and the remaining aqueous phase was extracted with chloroform. Evaporation of the washed and dried chloroform extract left 36 mg. of crystals which melted at 232–234° after recrystallization from methanol–ether and were shown to be identical with the acetal XIXa by the usual criteria.

Acetylideneiresin (XXI).—A mixture of 2.66 g. of iresin, 100 cc. of acetaldehyde and 2.5 g. of freshly fused zinc chloride was set aside at room temperature overnight. During this time, large, well-formed prisms separated which were filtered (1.74 g., m.p. 272–275°) and washed with ether. The filtrate was evaporated to dryness, the residue was taken up in ethyl acetate, washed, dried, evaporated and recrystallized to yield an additional 0.5 g. of satisfactory material. Recrystallization from methanol, chloroform–ethyl acetate and from acetone afforded large prisms, m.p. 283° (with variable, earlier sintering), $[\alpha]D$ + 64° (*c* 1.0).

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.96; H, 8.25.

The relative insolubility of the acetylidene derivative and the ease with which it crystallizes would recommend it for the isolation of iresin from crude concentrates or mother liquors.

Ozonolysis of Acetylideneiresin (XXI).[18]—The ozonolysis of 825 mg. of the acetylidene derivative was carried out as described above for iresin itself except that a mixture of 50 cc. of chloroform and 250 cc. of ethyl acetate was used and the reaction extended over a 1.5-hr. period. The crude, semi-crystalline product (m.p. 140–210°) obtained upon concentration of the reaction mixture (after filtration of the palladium catalyst) was recrystallized from ethyl acetate–acetone and from acetone–methanol to give 275 mg. of colorless crystals of the **aldehyde XXII**, m.p. 222–225°, λ_{max}^{Nujol} 5.72–5.75 μ, λ_{max}^{EtOH} 233 mμ, log ϵ 3.92; $\lambda_{max}^{0.01\ N\ KOH}$ 272 mμ, log ϵ 3.72; positive Tollens and ferric chloride reactions.

Anal. Calcd. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.76; H, 7.47.

A 53-mg. sample of the acetylidenealdehyde XXII was heated on the steam-bath for 3 hr. with 30 cc. of dioxane and 10 cc. of 0.2 *N* sulfuric acid, neutralized with barium carbonate and filtered. Evaporation to dryness and isolation with chloroform furnished 50 mg. of a crystalline residue which yielded 22 mg. of prisms, m.p. 230–234° after recrystallization from ethyl acetate–ether. The m.p. was depressed to 195–210° when this substance was mixed with the starting aldehyde XXII but remained unchanged when the compound was mixed with the cyclic acetal XIXa. Infrared spectral examination confirmed the identity.

Chromium Trioxide–Pyridine Oxidation of Iresin.—Iresin (3.8 g.) was added at 0° to the complex[19] derived from 4.0 g. of chromium trioxide and 100 cc. of pyridine and the mixture was kept at room temperature for 6 hr. whereupon 15 cc. of methanol was added. After 3 hr., the mixture was evaporated to dryness at 40° and 1 mm. and the dark red residue was extracted with ethyl acetate. The latter was

(29) All of the alumina used in this work was freed of alkali and reactivated (*cf.* J. v. Euw, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **27**, 1292 (1944)) in the following manner. Commercially available alumina (Alcoa, grade F-20), which showed a strongly alkaline reaction, was heated under reflux for 24 hr. with ethyl acetate, filtered and dried at 110°. The alumina was then washed continuously (Soxhlet extractor) for 48 hr. with hot water and then for 24 hr. with methanol. After drying at 110°, the alumina was reactivated at 180–190° for 30 minutes whereupon it exhibited activity I–II (H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941)) and was found to be neutral.

(30) On a larger scale (*e.g.*, 2.90 g. of iresin), the yield was reduced to 22%.

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washed with dilute sulfuric acid, 10% sodium bicarbonate solution, water, dried and evaporated. The resulting gum (2.76 g.) was chromatographed on 85 g. of alumina[29] and led to two crystalline products.

Elution with benzene produced 350 mg. of solid (m.p. 127–137°) which was recrystallized successively from methanol, benzene–ether and ethanol to give colorless plates of the **13-nor-3-ketone XXVI**, m.p. 146–148°, $[\alpha]D$ +74° (*c* 0.43); λ_{max}^{EtOH} 224 mμ, log ε 4.11; $\lambda_{max}^{CHCl_3}$ 5.65 (lactone), 5.82 (ketone) and 5.90 μ (double bond[2]).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.71, 71.87; H, 7.74, 7.76.

The 2,4-dinitrophenylhydrazone of the nor-ketone XXVI, prepared by the acetic acid method,[31] was purified by chromatography on alumina and eluted with benzene–chloroform (1:1). Recrystallization from acetic acid and from ethanol gave fine yellow needles, m.p. 188–191°, $[\alpha]D$ +178° (*c* 0.80); $\lambda_{max}^{CHCl_3}$ 364 mμ,[20] log ε 4.34; $\lambda_{max}^{CHCl_3}$ 3.00 (NH), 5.67 (lactone) and 5.90 μ (double bond[2]).

Anal. Calcd. for $C_{20}H_{22}N_4O_6$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.93; H, 5.34; N, 13.48.

The later benzene and benzene–chloroform (9:1) eluates from the original chromatogram furnished 725 mg. of crystals (m.p. 150–160°) which were subjected to recrystallization from acetone–ether, methanol and finally acetone. The resulting small prisms of the **hydroxy-aldehyde XVIIa** exhibited m.p. 164–166°, $[\alpha]D$ +39° (*c* 0.79); λ_{max}^{EtOH} 224 mμ, log ε 3.90; $\lambda_{max}^{CHCl_3}$ 2.82, 5.65, 5.82 and 5.90 μ, did not give a Tollens reaction at room temperature and did not form a trityl ether under conditions where iresin readily forms a monotrityl ether (XXVc).[22] No formaldehyde was produced under the basic conditions employed successfully with icterogenin,[21] thus excluding structure XXVIIIa.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.74; H, 7.73.

A small sample (21 mg.) of the hydroxy-aldehyde XXVIIa was treated with 4 mg. of sodium borohydride[7] in ethanol solution and was then processed as described above in the reduction of iresin. Recrystallization from acetone–ether led to 16 mg. of dihydroiresin (XXIX),[2] m.p. 142–146°, diacetate,[2] m.p. 208–210°.

The presence of the alcoholic function in the hydroxy-aldehyde XXVIIa was demonstrated by the formation of the **benzoate XXVIIb**, which was recrystallized from methanol and from acetone–ether, m.p. 193–195°, $[\alpha]^{16}D$ −45° (*c* 0.96).

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.95; H, 6.53.

The hydroxy aldehyde was converted into the **2,4-dinitrophenylhydrazone** by the acetic acid procedure[31] and crystallized from ethanol as orange-yellow prisms, m.p. 274–278° dec., $[\alpha]D$ +19° (*c* 0.95), $\lambda_{max}^{CHCl_3}$ 354 mμ,[20] log ε 4.12, $\lambda_{max}^{CHCl_3}$ 3.00, 5.67 and 5.90 μ.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.74; H, 5.44; N, 12.61. Found: C, 56.76; H, 5.59; N, 12.86.

DETROIT, MICHIGAN

(31) C. Djerassi, THIS JOURNAL, **71**, 1003 (1949).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF S. B. PENICK AND CO. AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

Constitution of Samidin, Dihydrosamidin and Visnadin[1]

BY ERIC SMITH, NORMAN HOSANSKY, W. G. BYWATER AND EUGENE E. VAN TAMELEN

RECEIVED OCTOBER 22, 1956

Analytical and degradative evidence have been obtained which indicate the structure XIII for samidin (R = —CH=C-$(CH_3)_2$), dihydrosamidin (R = —$CH_2CH(CH_3)_2$) and visnadin (R = $CH(CH_3)CH_2CH_3$), potent vasodilatory agents isolated from the "visnagan" fraction of *Ammi visnaga*.

Ammi visnaga L. (bishop's weed), a plant indigenous to the Mediterranean regions, has been used in Egypt for centuries as a home remedy and spasmolytic. That the seeds contain biologically active substances other than the chromones khellin and visnagin[2] has been shown by Samaan,[3] whose "visnagan" fraction (the oil remaining after removal of all crystalline material) evidenced considerable vasodilatory activity. Visnagan was subsequently investigated by Cavallito and Rockwell,[4] who obtained, through chromatography on silica, a glassy solid to which the formula $C_{22}H_{26}O_7$ was ascribed. In repeating the chromatographic procedure, Smith, Pucci and Bywater[5] were able to secure two crystalline substances, designated as RI-778 (visamminol)[6] and RI-832. More recently,[5b] refined chromatographic techniques allowed isolation from the visnagan fraction of six crystalline components, of which RI-860, the so-called "yellow body," and visamminol did not possess biological activity in the test employed. The three remaining substances, all colorless and optically active, were strongly vasodilatory and consequently chemical investigations were initiated.

Elemental analyses indicated the molecular formula $C_{21}H_{22}O_7$ for substance RI-870 (m.p. 134–5°), which has been given the name *samidin*. RI-832 (m.p. 85–8°), called *visnadin*, and dihydro-RI-870 (m.p. 111–13°) are isomers possessing the formula $C_{21}H_{24}O_7$. The relationship between samidin and dihydro-RI-870 is more than empirical: the former substance absorbed one mole of hydrogen over platinum, giving rise to the latter. Therefore, dihydro-RI-870 may be properly designated *dihydrosamidin*.

The ultraviolet absorption spectra of all three substances (Table I) coincide at the maximum 323–324 mμ and at the minimum 264 mμ and are otherwise similar except that samidin absorbs strongly at lower wave lengths.

Comparison of ultraviolet curves with those of authentic chromones and coumarins provided at the outset strong evidence for the presence of a 7-oxygenated coumarin chromophore, an assignment

(1) Described preliminarily in *Chemistry & Industry*, 718 (1956).

(2) E. Spaeth and W. Gruber, *Ber.*, **71B**, 106 (1938); **74**, 1549 (1941).

(3) K. Samaan, *Quart. J. Pharm. Pharmacol.*, **4**, 14 (1931); **6**, 12 (1933); **18**, 83 (1945).

(4) C. G. Cavallito and H. E. Rockwell, *J. Org. Chem.*, **15**, 820 (1950).

(5) (a) E. Smith, L. A. Pucci and W. G. Bywater, *Science*, **115**, 520 (1952); (b) E. Smith, N. Hosansky and W. G. Bywater, Abstracts of the Medicinal Division, 24N, 126th Meeting of the American Chemical Society, New York, N. Y., September, 1954.

(6) W. Benzce and H. Schmid, *Experientia*, **10**, 81 (1954).

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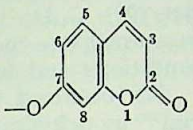
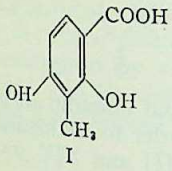
TABLE I

Substance	λmax, mμ	log ε	λmin, mμ	log ε
Samidin	324	4.17	264	3.27
Dihydrosamidin	323	4.12	264	3.16
Visnadin	323	4.14	264	3.29
7-Methoxycoumarin	323	4.12	260	3.08
Dihydroxanthotoxin	330	4.01	274	3.45

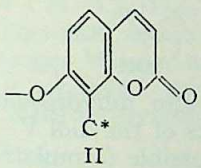
supported by the alkaline fusion results described below.[7]



Maintenance of a samidin-alkali melt at 230° for 30 minutes led to the formation of a substance $C_8H_8O_4$, m.p. 213–214° dec., which, yielding 2-methylresorcinol on thermal decarboxylation, subsequently was identified by infrared spectral comparison as 3-methyl-β-resorcylic acid (I).[8] Since samidin itself is not an acid, the carboxyl group present in the methylresorcylic acid must be masked, and, by incorporating the lactone moiety known to be present, the only logical[9] skeleton which emerges is II, where the starred carbon represents the actual or potential methyl group of the basic fusion product.



I



II

In order to continue the structural argument, it is necessary to describe certain hydrolysis operations and the study of the resulting products. In titration experiments, two equivalents of alkali were consumed by each of the coumarins at room temperature, whereas at reflux, three equivalents were used up. Apparently one equivalent is required for opening of the lactone ring; the remaining two serve to liberate volatile carboxylic acids, all of which were isolated and identified At the higher temperature, samidin surrenders senecioic acid, whereas *l*-methylethylacetic acid and isovaleric acid are obtained from visnadin and dihydrosamidin, respectively. In addition, one mole of acetic acid accompanies, in each case, the five-carbon acid. These findings, it may be mentioned in passing, define the structural difference between samidin and dihydrosamidin.

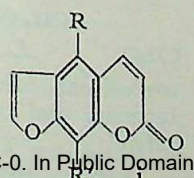
It seemed most likely, in light of the above results, that the trio of new natural products were diesters, and isolation of a glycol with the anticipated composition $C_{14}H_{14}O_5$ was indicated as a logical move. When a solution of samidin or visnadin in *ethanolic* potassium hydroxide was refluxed, an optically active substance III formed which gave, however, an analysis corresponding to the formula $C_{16}H_{18}O_5$. This same product resulted from the action of ethanolic hydrochloric acid on the parent material. Moreover, when the basic hydrolysis was carried out in *methanolic* base, a different product IV, having the composition $C_{15}H_{16}O_5$, was obtained; *and it became clear that solvent had been incorporated into the system during the saponification step.* Neither samidin nor visnadin shows the presence of alkoxyl in the Zeisel determination, and the fact that III and IV possess one ethoxyl and one methoxyl, respectively, confirms this interpretation.

The desired C_{14}-diol (V) was obtained in two ways. Either aqueous alkaline hydrolysis of samidin or ether cleavage of III with concentrated hydriodic acid afforded the crystalline, optically active product, the glycol nature of which was confirmed by the preparation of a diacetate. The hydriodic acid step is very facile in that it is completed in a matter of minutes at room temperature, and the preparation of the diol by this means is preferable to the direct, aqueous alkaline hydrolysis.

The ultraviolet spectra of all these transformation products were similar to those of the parent coumarins, indicating that the chromophores had been unmodified in any major respect during the hydrolysis steps.

Sufficient evidence for a unique structure assignment was provided by a more detailed chemical investigation of the ethanolysis product III, which appears to be identical with the "ethylkhellactone" obtained by Spaeth, *et al.*,[10a] through alkaline hydrolysis of crude *Ammi visnaga* extracts. The analogous "methylkhellactone" and "khellactone" (diol V) were studied more recently by Schmid, *et al.*[10b] Although the latter group of investigators did not advance definite structures for the naturally occurring parent coumarins, they did establish the same structures independently deduced by us for the products III, IV, V and XI. Presented below are our experimental findings and an abbreviated version of the arguments which led to the structural assignments.

First of all, none of the coumarins secured in the entirety of this investigation gave a coloration with ferric chloride and consequently none is phenolic. Substance III was expected to be the monoether of a glycol, and this presumption was confirmed by the preparation of a monoacetate. Since the fifth oxygen in III did not reveal itself by any detectable reactivity and since the parent coumarins bear no small alkyl group attached to oxygen, the members of this group must be *cyclic ethers*, a conclusion which, in view of the apparent absence of an excess of double bonds over those in the coumarin ring



1

(7) The observation that each of the three substances dissolves on warming in alcoholic alkaline solution with the formation of a deep yellow color is in keeping with the coumarin formulation (E. Spaeth and H. Schmid, *Ber.*, **73B**, 1309 (1940)).

(8) The authors are indebted to Dr. J. W. Hinman, The Upjohn Co., for supplying the 3-methyl-β-resorcylic acid and 2-methylresorcinol.

(9) Xanthotoxin (i, R = H, R′ = OCH_3), on basic fusion, affords pyrogallol-4-carboxylic acid (H. Thoms, *Ber.*, **44**, 332 (1911)); bergapten (I, R = OCH_3; R′ = H) is reported to yield phloroglucinol (C. Pomeranz, *Monatsh.*, **12**, 379 (1891)).

(10) (a) E. Spaeth, W. Gruber and O. Matzke, *Canadian J. Chem.*, **31**, 715 (1953); (b) W. Benzce, O. Halpern and H. Schmid, *Experientia*, **12**, 137 (1956); (c) a similar finding was reported by Schmid, *et al.* (ref. 10b).

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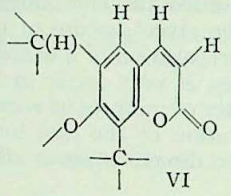
(*vide infra*), agrees with the demands of the molecular formulas. Finally, none of these substances gives indication of aldehydic or ketonic properties, hence they are probably not hemiacetals or hemiketals.

The nature of three additional carbon atoms became apparent when it was observed that alkaline permanganate oxidation of ether III yielded acetone—a $(CH_3)_2C-O-$ grouping is necessarily present.[10c]

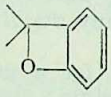
Hydrogenation of III by means of palladium-on-charcoal in glacial acetic acid led to the *dihydro product*, the ultraviolet spectrum of which indicated saturation of the 3,4-double bond of the coumarin ring. The new substance was oxidized with fuming nitric acid; succinic acid was identified as one of the products, a finding which indicates lack of substitution at the 3- and 4-positions of the parent ring system.[11]

By utilizing these results we see that partial structure II may now be expanded to VI, which is potentially tricyclic.[12]



VI

Now, any four-membered ether of the type VII is untenable because, being a benzyl ether, ring cleav-

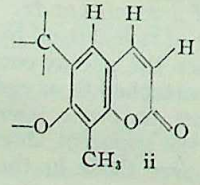


VII

age by hydrogen iodide during the conversion of III to V would be expected; on this basis the diol should be phenolic, but it is not. Also, 3-hydroxy-2,3-dihydrobenzofurans may be excluded from consideration, since they have been reported[13] to dehydrate spontaneously and give the benzofuran. Finally, by taking into account the observation that the diol consumes in an acidic medium just one mole of periodate[10c] without liberation of volatile aldehydes, we find that only one formulation, namely, IX, serves suitably as the structure of the diol.

(11) The spectral character of the natural coumarins offered no evidence for oxygenation at either of these positions, and it is apparent that hydroxyl attachment is excluded. Because of the number of oxygens which must therefore be placed on the few carbon atoms remaining after allowance is made for those in the coumarin ring and those in the $(CH_3)_2C-O-$ portion, the two methylene groups of the succinic acid *cannot* arise from any portion of the molecule other than the 3- and 4-positions of dihydro-III.

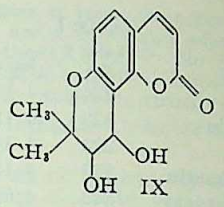
(12) Partial structure ii, which is the one following most naturally



ii

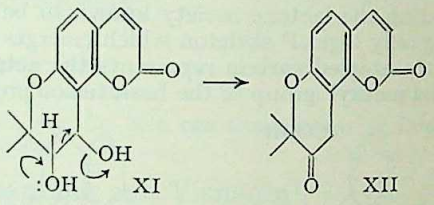
from the basic fusion results, can be dismissed at this stage in that it is not possible to develop from it a structure for diol V which has no more than one hydroxyl or ethereal oxygen per carbon atom.

(13) R. Stoermer and W. Koenig, *Ber.*, **39**, 1496 (1906).



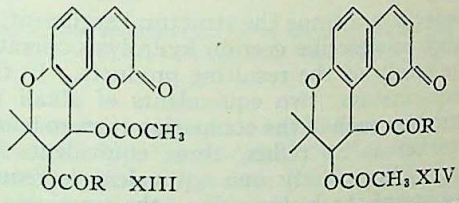
IX

Spaeth, Gruber and Matzke[10a] reported that the monoethyl ether III yielded, through the action of phosphorus pentoxide or hydrogen bromide in acetic acid, a substance (X), $C_{14}H_{12}O_4$, which was optically inactive, consumed two moles of hydrogen under catalytic conditions and formed a *p*-nitrophenylhydrazone. We obtained what appears to be the same material[10c] by dehydrating the diol V in hydrobromic–acetic acid and noted in addition that compound X gives no aldehyde or phenol color tests and displays an ultraviolet absorption which is very similar to that of its precursor. These observations provide support for the proposal IX, in that XII, a completely satisfactory expression for ketone X, arises logically from the diol structure by the process (XI → XII).[14]



XI XII

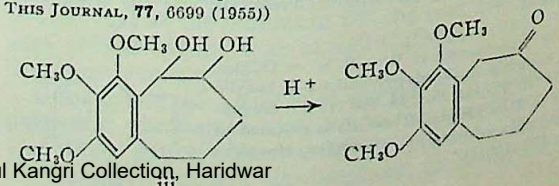
Samidin, dihydrosamidin and visnadin are mixed diesters of the diol V. In order to distinguish the two possible formulations XIII and XIV, we con-



XIII XIV

sider now the selective solvolysis of a representative, samidin. When subjected to the action of excess potassium hydroxide in ethanol *at room temperature*, this substance was converted to a new product (XV), $C_{21}H_{24}O_6$, which must have arisen through loss of acetic acid and incorporation of solvent into the molecule. The general nature of the change was confirmed by Zeisel determination (one $-OC_2H_5$), the apparent absence of alcoholic hydroxyl in XV and the liberation of senecioic acid on refluxing XV with alcoholic alkali. The incorporation of ethoxyl during hydrolysis becomes clear with the development of the diester structures pictured above. It is well recognized that certain *benzyl esters* suffer O-alkyl cleavage in either basic or

(14) Glycol iii rearranges to the β-benzsuberone (G. N. Walker, THIS JOURNAL, **77**, 6699 (1955))



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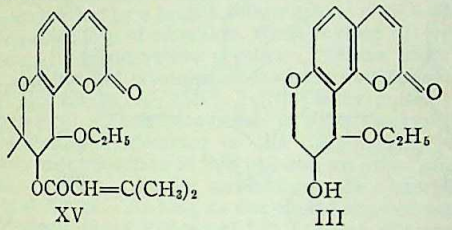
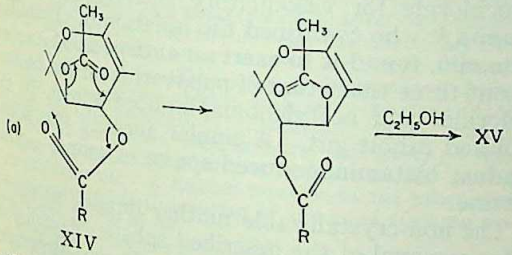
acidic alcohol solution. Although not observed with esters of benzyl alcohol itself, such cleavage is facilitated by alkyl substitution on the benzyl carbon, attachment of the benzyl oxygen to a ring (*e.g.*, α-tetralol) and the presence of *o*- or *p*-electron-donating groups on the aromatic ring.[15] All three of these features are present in the structural type under consideration. *If* the loss of acetoxyl involves *simple* replacement by ethoxyl, structure XIII (R = CH=C(CH$_3$)$_2$) must represent samidin, and dihydrosamidin and visnadin may be assigned the structure XIII (R = CH(CH$_3$)C$_2$H$_5$), respectively. The partial solvolysis product XV of samidin and the monoether III may then be represented by the formulas

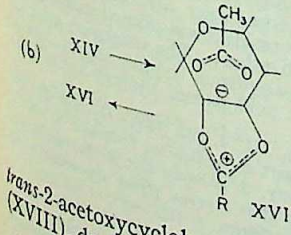


XV III

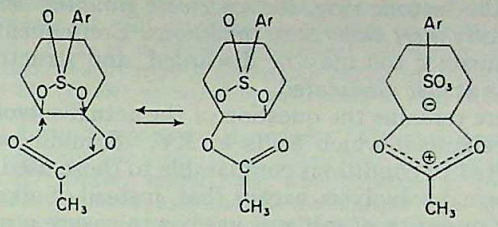
However, before considering the structural question settled, we must examine the possibility that the monoester XV might have come, not from XIII, but—by way of over-all acyl migration—from the alternate structure XIV (R = CH=C(CH$_3$)$_2$) for the parent natural product. There are several distinct mechanisms by which such a change might be realized. In the first (a), a concerted, twofold migration is envisioned which leads to inversion at



both asymmetric centers and interchange of the acetyl and the senecioyl groups. Mechanism b, in which starting diester XIV is transformed to the ion pair XVII and then collapses to the isomeric diester, is similar to (a) and may be indistinguishable from it. In connection with the possible contributions of *either* mechanism a or b, it is pertinent that a closely similar case has been investigated in some detail. Winstein and Heck,[16] studying *d*-

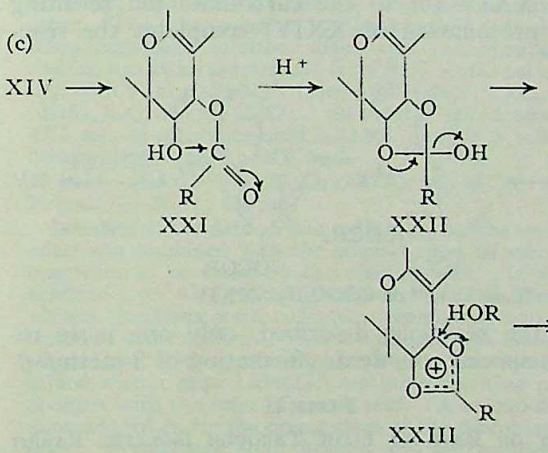


trans-2-acetoxycyclohexyl *p*-toluenesulfonate (XVIII), demonstrated the absence of any internal rearrangement phenomenon during solvolysis, thereby vitiating the case for the process (XIX → XVIII) or (XVIII ⇄ XX); the absence of this type of change[17] was considered as due to "the



special nature of the neighboring acetoxy group."[16] Application of these findings to the case under consideration seems direct and convincing; we therefore consider mechanisms a and b inoperative.

Still a third route can be envisioned for the hypothetical change XIV → XV. In (c), a selective removal of acetyl from XIV yields initially the monoester XXI which then cyclizes, as the first stage in an acyl migration, to XXII. The latter intermediate could advance to the isomeric mono-



ester, which in itself would be incapable of yielding an ether, or it could undergo alcoholysis, possibly *via* the mesomeric cation XXIII, and finally afford structure XV. The solvolysis rate data on samidin can be marshalled so as to exclude convincingly path c. Bearing in mind that the ester group in XV and the acetate substituent in XIV would possess the same steric environment, one concludes that the rate difference in hydrolysis of both ester functions should approximate that between simple esters of acetic acid and senecioic acid. Although this specific information apparently has not been recorded, rough calculations, using accessible rate data,[18] show that ethyl acetate and ethyl crotonate differ in basic hydrolysis rate by a factor of only about ten.

The difference between the cases XIV and XV should be of the same order of magnitude. However, this expectation is contrary to fact, in that samidin, in the presence of excess alcoholic alkali, consumes

(15) A. G. Davies and J. Kenyon, *Quart. Revs.*, **9**, 203 (1955).
(16) S. Winstein and R. Heck, THIS JOURNAL, **74**, 5584 (1952).
(17) The reality of ion pairs in other cases where either tosylate or acetate is the leaving group has been demonstrated (D. J. Cram, *ibid.*, **74**, 2129 (1952); S. Winstein and K. C. Schreiber, *ibid.*, **74**, 2165 (1952)).
(18) P. Heinanen, *Ann. Acad. Sci. Fennicae*, Ser. A, II, Chemica, No. 9, 3 (1943).

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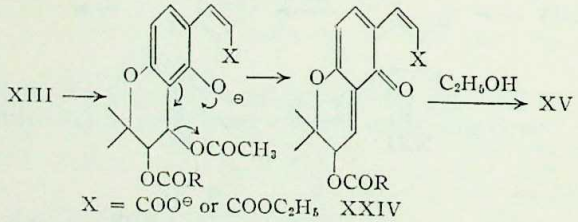
at room temperature almost two moles of base in six minutes without further uptake after 4 hr. These are the conditions used to prepare XV; therefore, the two moles are used to discharge acetoxyl and to open the lactone ring, *the senecioate grouping being essentially inert under these conditions*. Consequently mechanism c too may be discarded, and structure XIII is at last vindicated.

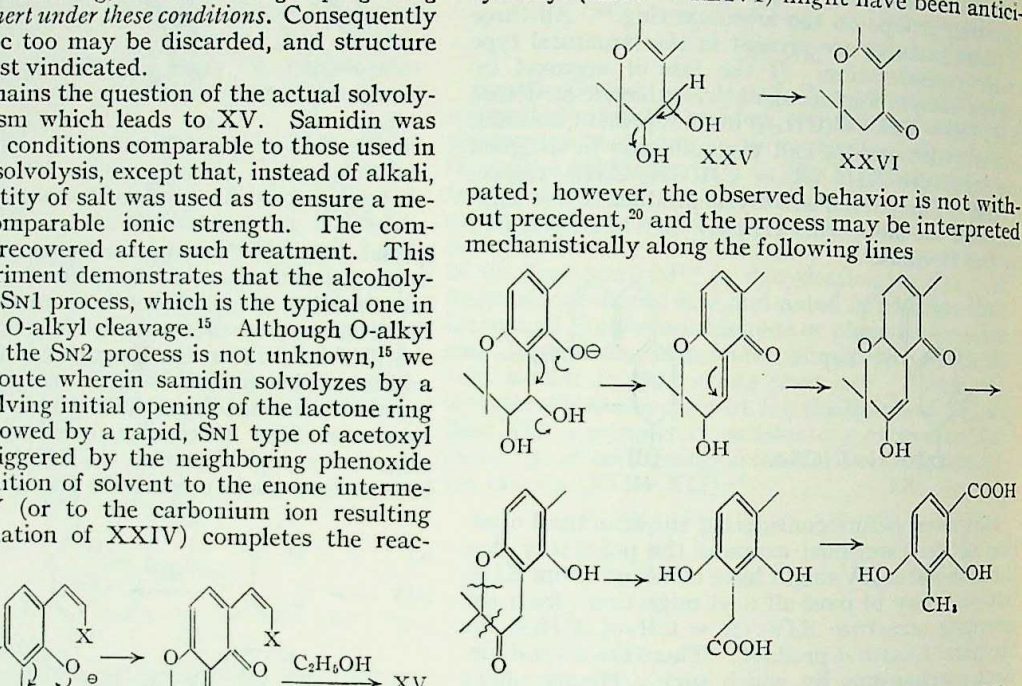
There remains the question of the actual solvolysis mechanism which leads to XV. Samidin was subjected to conditions comparable to those used in the normal solvolysis, except that, instead of alkali, such a quantity of salt was used as to ensure a medium of comparable ionic strength. The compound was recovered after such treatment. This simple experiment demonstrates that the alcoholysis is not an SN1 process, which is the typical one in benzyl ester O-alkyl cleavage.[15] Although O-alkyl cleavage by the SN2 process is not unknown,[15] we prefer the route wherein samidin solvolyzes by a process involving initial opening of the lactone ring by base, followed by a rapid, SN1 type of acetoxyl expulsion triggered by the neighboring phenoxide anion. Addition of solvent to the enone intermediate XXIV (or to the carbonium ion resulting from protonation of XXIV) completes the reaction.[19]



X = $COO^{\ominus}$ or $COOC_2H_5$ XXIV

Of the reactions described, only one more requires special comment: formation of 3-methyl-β-resorcylic acid in the basic fusion of samidin, an unusual result in that *a partially oxidized carbon atom is converted to methyl*.

Base-catalyzed dehydration with β-elimination of hydroxyl (XXV → XXVI) might have been anticipated; however, the observed behavior is not without precedent,[20] and the process may be interpreted mechanistically along the following lines



Pharmacology.—Visnadin and dihydrosamidin were compared with khellin and papaverine hydrochloride for vasodilatory activity (Table II). Gomes,[21] who confirmed the isolation of crystalline visnadin, found it to exert an antispasmodic action about three times that of papaverine on the barium chloride- and acetylcholine-induced spasm of the isolated rabbit gut. A similar activity was found against histamine-induced spasm of guinea pig intestine.

The non-crystallizable mother liquors remaining after removal of the described substances still contained considerable activity. Their ultraviolet spectra, which were identical with those of the compounds described above, show that this activity probably was derived from material of similar chemical structure. These mother liquors are being investigated further.

TABLE II

EFFECT ON RATE OF FLOW THROUGH ISOLATED RABBIT HEART[a]

Compound	Concentration	Rate of flow Control, ml./2 min.	Sample ml./2 min.	Increase, %	Relative potency
Khellin	1:60,000	26.5	37	40	1
Visnagan	1:150,000	30.7	43	41	2.5
Khellin	1:30,000	28.0	39.7	41.8	1
Visnadin	1:60,000	21.0	49.1	131.6	
Visnadin	1:300,000	28.5	39.7	39.2	10
Khellin	1:30,000	26.5	37.0	39.6	1
Visnadin Mother Liquors	1:240,000	23.5	30.8	31.2	App. 8
Khellin	1:15,000	24.7	45.6	84.6	1
Dihydrosamidin	1:75,000	24.7	45.0	82.2	5
Khellin	1:15,000	29.2	47.7	63.2	1
Papaverine HCl	1:75,000	27.2	37.2	36.7	2.5

[a] Hazleton Laboratories, Falls Church, Virginia.

Experimental[22]

Purification of Visnagan.—About 10 lb. of visnagan prepared according to Samaan[3] was mixed with 6 gal. of pentane and this solution extracted repeatedly with 80% alcohol, using 6, 2 and 2 gallons, respectively. The alcoholic layers were separated, washed once with pentane and concentrated *in vacuo*. The residue was diluted with 2 gal. of water and extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered and gaseous hydrochloric acid passed through the solution

(19) The arguments leading to structure XIII render untenable the structures of samidin, dihydrosamidin and visnadin proposed earlier by E. Smith, N. Hosansky and W. G. Bywater.[5b] The stereochemistry of XIII is not known but is arbitrarily designated on account of its kinship to *trans* (*e.g.*, XVI).

(20) D. Sontag, *Ann. chim.*, [11] **1**, 359 (1934), reported that stilbene glycol is converted in part by potassium hydroxide at 250° to 1,2-diphenylethane; L. Palfray, S. Sabetay and D. Sontag, *Compt. rend.*, **193**, 941 (1931), state that styrene glycol apparently yields some toluene under similar conditions.

(21) F. P. Gomes, *Compt. rend. soc. biol.*, **147**, 1836 (1953).

(22) Microanalyses and molecular weight determination by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The rotational measurements were run in U.S.P. alcohol. Intensities are expressed as log ϵ.

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under cooling as long as oxonium salts precipitated. The ether solution was filtered, washed acid-free with sodium carbonate solution, then washed with water, dried over anhydrous sodium sulfate and concentrated; 160 g. of clear brown oil remained. This fraction had an optical activity of +22°.

Chromatography of Visnagan.—Seven pounds of the refined oil was diluted with 5 lb. of ether and mixed into 7 lb. of Filter-cel. The mix was air-dried, put through a screen and then added to a column containing 127 lb. of silica (J. F. Smith) which had previously been covered with pentane. The column was developed and cut, according to the following scheme: (1) Fifteen gallons of pentane which eluted 690 g. of oil not further investigated; (2) fifty gallons of an ether-pentane mixture containing 10 to 20% ether. This eluted 59 g. of a non-crystalline oil with an optical activity of +55°. The oil, rubbed up with alcohol, gave 24 g. (RI-860) of crystals which, after repeated recrystallizations from alcohol, melted at 285–287°, $[\alpha]_D$ +69°. This fraction was followed by a bright yellow eluate which on concentration gave 113 g. of oil which, when rubbed up with ether, gave 10 g. of bright yellow crystals ("yellow body") melting, after repeated crystallizations from methanol, at 176–178°, λ_{max} 293 mμ (E^1_1 1580). (3) Thirty gallons of ether pentane (1:3). The eluate began to show the typical ultraviolet absorption spectrum of the dihydrofurocoumarins; an absorption minimum at 268 mμ and an absorption maximum at 320 mμ. At the same time, the absorption was taken at 220 mμ. As long as the eluate showed an absorption ratio of 322 mμ:222 mμ of 1–1.7:1 and 322 mμ:262 mμ of 2–4:1, it was collected for the preparation of *visnadin*. A total throughput of 75 gal. was collected, concentrated to 5 gal. and allowed to crystallize for a week in the ice-box. There were thus obtained 236 g. of crude visnadin, melting at 75–78° and having an optical activity of +12°, and 190 g. of oil with an optical activity of +10°. (4) The next fraction was collected until the ratio 322 mμ:220 mμ had risen to about 6:1. This fraction eluted *samidin*. It required about 30 gal. of ether–pentane (1:3) and 40 gal. of ether–pentane (3:7). The combined eluates were concentrated to 6 gal. and allowed to crystallize; 320 g. of crude samidin, with a melting point 127–135° and an optical activity of +20°, and 220 g. of a non-crystallizable oil were recovered from this fraction. (5) At this point the ultraviolet absorption spectrum of the eluate showed a distinct shift of the minimum from 262 to 270 mμ and of the maximum from 320 to 300 mμ. Further elution with ether–pentane (1:1) resulted in the isolation of *visamminol*. Fifty gallons of eluate was needed for total removal and gave, on concentrating to 5 gal., 215 g. of visamminol and 200 g. of non-crystallizable oil. A further increase in the ether concentration resulted in the elution of 110 g. of *visnagin* and an additional 270 g. of oil.

Visnadin.—The crude fraction (236 g.) was dissolved in 500 ml. of ether, charcoaled, 600 ml. of hexane was added; the solution was concentrated to 600 ml. and allowed to crystallize. The 200 g. of visnadin so obtained was once more crystallized and gave 160 g. of white needles, m.p. 84–86°, $[\alpha]_D$ +9° (*c* 2.0) and +38° (*c* 1.0 in dioxane). In a volatile acid determination, 46.0 mg. yielded an amount of acid equivalent to 11.29 ml. of 0.02 *N* sodium hydroxide; calcd. for two acids, 11.75 ml.

Anal. Calcd. for $C_{21}H_{24}O_7$: C, 64.95; H, 6.23. Found: C, 65.04; H, 6.19.

Dihydrosamidin.—The mother liquors of the visnadin recrystallizations were concentrated to half-volume and an additional small amount of impure visnadin was isolated. They were then taken down to dryness and rubbed up with 20 ml. of ether and allowed to crystallize in the ice-box; 6 g. of crystals was obtained which, when recrystallized from 90% methanol, gave 5 g. of pyramids, m.p. 117–119°, $[\alpha]_D$ +19° (*c* 1.0) and +63° (*c* 1.0 in dioxane). On volatile acid determination, 84.8 mg. used 22.08 ml. of 0.02 *N* sodium hydroxide; calcd. for two acids 21.86 ml.

Anal. Calcd. for $C_{21}H_{24}O_7$: C, 64.95; H, 6.23. Found: C, 64.91; H, 6.09.

Samidin.—The 320 g. of crude samidin was repeatedly crystallized from alcohol to give 250 g. of pure material as cubes, m.p. 135–137°, $[\alpha]_D$ +26° (*c* 1.0) and +100° (*c* 1.0 in dioxane). In a volatile acid determination, 40.6 mg. used 9.99 ml. of 0.02 *N* sodium hydroxide; calcd. for two acids 10.51 ml.

Anal. Calcd. for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74. Found: C, 65.21; H, 5.53.

Hydrogenation of Samidin.—Twenty grams of samidin was dissolved in 200 ml. of alcohol and hydrogenated with 200 mg. of platinum oxide. After 1 mole of hydrogen was consumed, the hydrogenation was interrupted, the catalyst filtered off, and the alcoholic solution concentrated to 20 ml., 12 g. of substance crystallized out which, on recrystallization from 90% methanol, melted at 115–117°, $[\alpha]_D$ +16° (*c* 1.0); no mixed m.p. depression with natural dihydrosamidin.

Room Temperature Hydrolysis. Titration Experiments.—Samidin (59.8 mg., 0.154 mmole) and visnadin (45.6 mg., 0.117 mmole), respectively, were dissolved in 10.0 ml. of 0.25 *N* sodium hydroxide in alcohol and after time, *t*, at room temperature a 1.0-ml. aliquot was removed, diluted with 10 ml. of CO_2-free water and titrated with 0.025 *N* sulfuric acid, using phenolphthalein as indicator. A blank consisting of the alcoholic alkaline solution was titrated at the same time. After t = 6, 80 and 230 min., the moles of alkali consumed were for samidin 1.73, 2.23 and 2.19, and for visnadin 1.78, 2.10 and 2.11. The remainder of the solutions were then refluxed for 1 hr., cooled and again titrated as above. The total mole uptake for samidin was 3.06, for visnadin 3.25.

Samidin (5 g.) was dissolved in 45 ml. of ethanol and 45 ml. of 1 *N* sodium hydroxide in ethanol was added. The solution was allowed to stand at room temperature and its rotation taken every 10 min. The rotation increased for about 45 min., after which the solution was diluted with 1 l. of water, acidified with sulfuric acid and extracted with ether. The ether solution was backwashed with dilute sodium carbonate solution, dried and concentrated. The residue was twice crystallized from 80% methanol and gave 3 g. of XV, m.p. 91–93°, $[\alpha]_D$ +99° (*c* 0.9); λ_{max} 326 mμ (4.16), $\lambda_{min.}$ 264 mμ (3.42). On volatile acid determination 47.7 mg. of substance used 5.92 ml. of 0.02 *N* sodium hydroxide; calcd. for 1 acid 6.4 ml.

Anal. Calcd. for $C_{21}H_{24}O_6$ (372.4): C, 67.73; H, 6.50. Found: C, 67.81; H, 6.51.

Isolation of the Acid.—The sodium carbonate wash of the ether was combined with the original aqueous solution and concentrated *in vacuo* on the alkaline side. It was then acidified with 5 *N* sulfuric acid and steam distilled. Ten 100-ml. fractions were collected, neutralized and concentrated *in vacuo* to 50 ml. A 5-ml. aliquot was taken for the preparation of the *p*-phenylphenylacyl ester which was obtained with a m.p. 110–111°, no mixed melting point depression with the ester of acetic acid. A second 5-ml. aliquot was taken for the preparation of the *p*-bromophenacyl ester. Crystallized from hexane and recrystallized from aqueous alcohol, the ester melted at 84–86° and showed no mixed m.p. depression with authentic ester prepared from acetic acid.

Hot Ethanolic Alkaline Hydrolysis.—Twenty-five grams of samidin in ethanol was refluxed with 165 ml. of 2 *N* alcoholic sodium hydroxide for 1.5 hr. The orange colored solution was cooled, diluted with water, concentrated *in vacuo* to remove alcohol, acidified with concentrated sulfuric acid and extracted with ether. The ether was backwashed with sodium bicarbonate solution, dried and concentrated. Pentane was added to the concentrated solution to slight turbidity, whereupon crystallization occurred. The 7.4 g. (40% of theory) of III so obtained was repeatedly recrystallized from an ether–pentane mixture; m.p. 161–162°; $[\alpha]_D$ −59° (*c* 0.9), λ_{max} 325 mμ (4.15), $\lambda_{min.}$ 266 mμ (3.18). The same compound was obtained when either XV or visnadin or dihydrosamidin was used as starting material.

Anal. Calcd. for $C_{16}H_{18}O_5$ (290.3): C, 66.19; H, 6.25; OC_2H_5, 15.52. Found: C, 66.20; H, 6.11; OC_2H_5, 16.00.

Isolation of Acid.—The sodium bicarbonate wash of the ether solution was combined with the original water solution and concentrated on the alkaline side *in vacuo*, acidified and extracted thoroughly with ether. The ether was concentrated, after drying, to give a yellow, oily residue which distilled at 20 mm. at 160–180°. The distillate crystallized and was redistilled at atmospheric pressure. The fraction coming over at 190–193° was recrystallized from water; m.p. 68–69° (lit.[23] for senecioic acid 68–70°).

The *p*-toluidide was prepared over the acid chloride; m.p. 107–108° (lit.[23] 106–107°). *Anal.* Calcd. for C_{12}-

(23) R. B. Wagner, THIS JOURNAL, 71, 3214 (1949).

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$H_{15}ON$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.20; H, 7.88; N, 7.26.

The *p*-phenylphenacyl ester was prepared in the usual way; m.p. 144.5–146°. *Anal.* Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.17. Found: C, 77.54; H, 5.76.

On hydrogenation with platinum oxide, the acid consumed 1 mole equivalent of hydrogen. The *p*-phenylphenacyl ester of the hydrogenated acid had a m.p. 76–77°; no depression on admixture with the ester of isovaleric acid. *Anal.* Calcd. for $C_{19}H_{20}O_3$: C, 76.98; H, 6.87. Found: C, 77.00; H, 6.49.

The acid isolated in the same manner from visnadin gave a *p*-phenylphenacyl ester melting at 69–70° (lit. for 1-α-methylbutyric acid, 70–71°)[24] and a *p*-bromphenacyl ester, m.p. 54–55° (lit.[24] 55°).

Acetate of III.—On acetylation with acetic acid anhydride in pyridine, 392 mg. of III gave, after crystallization from aqueous methanol, 385 mg. of monoacetate, m.p. 170–172°, $[\alpha]_D$ −40.8° (*c* 0.6%), λ_{max} 325 mμ (4.16), $\lambda_{min.}$ 264 mμ (3.22).

Anal. Calcd. for $C_{18}H_{20}O_6$ (332.3): C, 65.05; H, 6.07. Found: C, 65.23; H, 6.03; mol. wt. by Rast, 332.

Oxidation of III.—III (1.16 g.) was dissolved with slight warming in 1% sodium hydroxide solution. To the cooled solution a saturated solution of permanganate was added until the violet color persisted. After acidification the solution was steam distilled and the distillate precipitated with *p*-nitrophenylhydrazine. The hydrazone obtained (240 mg.) melted, after recrystallization, at 147–149°; no depression on admixture with *p*-nitrophenylhydrazone prepared from acetone.

Hydrogenation and Oxidation of III.—III (4 g.) was hydrogenated in 40 ml. of glacial acetic acid with 400 ml. of palladium-on-charcoal. The uptake was very slow, one mole equivalent being taken up after 9 hr. The catalyst was filtered off, the filtrate diluted with water and extracted with ether. The ether was backwashed with sodium carbonate solution, dried and concentrated. The residue was crystallized twice from ethyl acetate–hexane (1:2) to give 3.56 g. of the reduced product, m.p. 125–127°, $[\alpha]_D$ −11°, dissolving colorless in alcoholic alkali; λ_{max} 287 mμ (3.36), $\lambda_{min.}$ 261 mμ (2.81).

One gram of this substance was dissolved in ice-cold fuming nitric acid (d. 1.4) and allowed to stand at room temperature for 12 hr. The yellow solution was then heated on the steam-bath for 8 hr. and taken down to dryness. The residue was dissolved in dilute ammonia, the *p*H adjusted to 5.5 and the oxalic acid precipitated from the boiling hot solution with calcium chloride. The precipitate was filtered off and the filtrate concentrated *in vacuo*, acidified and extracted in a liquid–liquid extractor with ether. The ether deposited crystals on concentrating, which were collected and then sublimed *in vacuo*. The sublimate melted at 187–188° and did not give a m.p. depression on admixture with succinic acid; 25.6 mg. of substance used 21.2 ml. of 0.02 *N* sodium hydroxide; calcd. for succinic acid, 21.6 ml.

Hot Methanolic Alkaline Hydrolysis.—Twenty grams of samidin in 85 ml. of methanol was refluxed with 85 ml. of 2 *N* methanolic sodium hydroxide for 1.5 hr. The solution was then concentrated *in vacuo*, diluted with water, acidified and extracted with ether. The ether was backwashed with dilute sodium carbonate solution, water, dried and concentrated. The residue was crystallized from ether–pentane to give 6.48 g. (44%) of IV, m.p. 158–159°, $[\alpha]_D$ +14° (*c* 1.04), λ_{max} 328 mμ (4.18), $\lambda_{min.}$ 267 mμ (3.21).

Anal. Calcd. for $C_{15}H_{16}O_5$ (276.3): C, 65.19; H, 5.84; OCH_3, 11.23. Found: C, 65.46; H, 5.76; OCH_3, 11.17.

On acetylation, 400 mg. of IV gave, after recrystallization from methanol, 318 mg. of the monoacetate, m.p. 147–149°, $[\alpha]_D$ +18.4° (*c* 1.29), λ_{max} 324 mμ (4.17), $\lambda_{min.}$ 265 mμ (3.19).

Anal. Calcd. for $C_{17}H_{18}O_6$ (318.31): C, 64.14; H, 5.70. Found: C, 64.12; H, 5.83.

The same alcohol and acetate were obtained when the hydrolysis was conducted with methanolic hydrochloric acid.

Preparation of Diol V.—Eight hundred and eighty-four mg. of III was dissolved in 5 ml. of hydriodic acid (d. 1.70). After about 20 min., crystalline material began to separate out and was collected after standing 1 hr. After several crystallizations from acetone, 400 mg. of V was obtained, m.p. 180–182°, $[\alpha]_D$ +13° (*c* 0.7), λ_{max} 328 mμ (4.17), $\lambda_{min.}$ 265 mμ (3.16).

Anal. Calcd. for $C_{14}H_{14}O_5$ (262.3): C, 64.11; H, 5.38. Found: C, 64.16; H, 5.37.

V, acetylated in the usual way, gave after recrystallization from methanol, the diacetate, m.p. 161–163°, $[\alpha]_D$ −27° (*c* 0.69), λ_{max} 323 mμ (4.14), $\lambda_{min.}$ 263 mμ (3.21).

Anal. Calcd. for $C_{18}H_{18}O_7$ (346.3): C, 62.42; H, 5.24. Found: C, 62.54; H, 5.07; mol. wt., 344.8 (Rast).

The same substance was obtained when samidin was refluxed with aqueous sodium hydroxide. From 20 g., 7.7 g. of oil was recovered, which was chromatographed over alumina. The eluate obtained by developing with ether crystallized to give, after repeated crystallization from methanol, 2 g. of V, m.p. 183–184°, $[\alpha]_D$ +11°, no mixed m.p. depression with V prepared from III.

Anal. Found: C, 64.07; H, 5.40.

Dehydration of V.—V (200 mg.) was refluxed with 0.5 ml. of acetic acid and 0.5 ml. of concd. hydrobromic acid for 15 min. The solution was cooled, diluted with water and extracted into ether. The ether, after washing with sodium bicarbonate and water, was dried, evaporated to dryness and the residue crystallized from ethyl acetate. The product XII, after several crystallizations, melted at 156–157°, $[\alpha]_D$ 0 (*c* 2.0), λ_{max} 321 mμ (4.11), $\lambda_{min.}$ 263 mμ (3.45).

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.86; H, 4.95. Found: C, 68.54; H, 4.95.

Alkaline Fusion of Samidin.—Three and two-tenths grams of samidin was added in small portions to a sodium hydroxide–potassium hydroxide melt kept at 150–160°. The temperature was then raised slowly to 230° and kept at that temperature until the melt cleared. After cooling, the melt was dissolved in water, filtered, chilled in ice and acidified with concentrated hydrochloric acid. Insoluble flocculent material was filtered off and the filtrate extracted with ether. The ether gave, on concentration, 1.5 g. of amorphous residue.

This material was chromatographed on 20 g. of silica with benzene. The first benzene eluates gave, on concentration, 910 mg. of crystalline material, m.p. 213–214° with evolution of gas, λ_{max} 262 mμ (4.14), λ 297 mμ (3.65). Its infrared spectrum was indistinguishable from that of 3-methyl-β-resorcylic acid.

Anal. Calcd. for $C_8H_8O_4$ (168.1): C, 57.14; H, 4.80. Found: C, 56.92; H, 5.11; mol. wt. (Rast), 163.3.

Preparation of 2-Methylresorcinol.—One hundred and sixteen mg. of the acid was melted in a sealed tube at 220° and kept at that temperature until gas evolution stopped. The cooled contents were dissolved in benzene and chromatographed on silica. From the first benzene eluates 76 mg. of crystals was isolated, sublimed in high vacuum at 60–70° to give pure material melting at 117–119°. Its infrared spectrum was identical with that of authentic 2-methylresorcinol.

Anal. Calcd. for $C_7H_8O_2$ (124.1): C, 67.73; H, 6.50. Found: C, 68.00; H, 6.42; mol. wt. (Rast), 131.

Periodate Oxidation of V.—Twelve and nine-tenths mg. (0.049 mmole) of diol V was dissolved in 5.0 ml. of 0.098 molar periodic acid in 80% methanol (distilled from zinc–sodium hydroxide). The analysis was standard, excess arsenite being titrated by 0.00946 molar iodine.

Time, hr.	HIO_4 consumed, mole
0.17	0.35
0.50	0.40
2.50	0.65
12.50	1.00
17.00	0.98
21.00	1.00

Dimedon was employed to detect any volatile aldehyde. However, apart from a small amount of amorphous material, no derivative was obtained.[25]

MADISON, WISCONSIN

(24) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 191.

(25) The authors are grateful to Dr. John Dyer for these determinations.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

The Preparation of Glycamines[1]

BY FRED KAGAN, M. A. REBENSTORF AND RICHARD V. HEINZELMAN

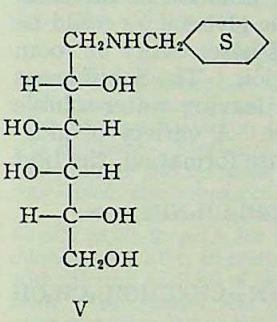
RECEIVED FEBRUARY 8, 1957

Large quantities of pure glycamines were conveniently prepared by the reductive alkylation of ammonia or by the hydrogenolysis of N-benzylglycamines. To ensure high quality products, purification of the glycamines from either process should be carried out through their Schiff bases.

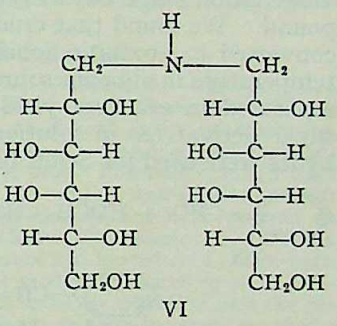
Although 1-amino-1-deoxy sugars, the glycamines, have been known for over fifty years, a good preparative method which is practical for the synthesis of large quantities of high purity material is not available. The need for large quantities of galactamine of greater than 95% purity as a resolving agent in a synthesis of pantothenic acid[2] prompted us to reinvestigate the preparation of this class of compounds.

Glycamines previously have been prepared by the chemical reduction of sugar oximes,[3-5] by electrolytic, chemical and catalytic reduction of glycosylamines[5] and by the reductive alkylation of ammonia with a sugar.[6-8] The chemical and electrolytic reduction methods were of little interest because they were not readily adaptable to large-scale operations. The Flint and Salzburg[7] method yielded impure sirups unsuitable for our purposes. Wayne and Adkins[8] prepared glucamine in low yield by the reduction of glucose in methanolic ammonia. Holly and co-workers[9] synthesized glycamines of approximately 80% purity by the reductive alkylation of liquid ammonia with sugars. None of these methods was suitable for the large-scale production of pure sugar amines.

One route to glycamines which we investigated involved the hydrogenolysis of an N-benzylglycamine. For example, N-benzylgalactamine (III), prepared in 64% yield by the reductive alkylation of benzylamine with galactose, gave galactamine (IV) in 77% yield when hydrogenolyzed in the presence of palladium-on-charcoal. An attempt to simplify the process by carrying out the two hydrogenations consecutively in the same vessel without isolating the intermediate N-benzylgalactamine yielded an impure product, a major constituent of which proved to be cyclohexylmethylgalactamine (V). Structure assignment was made on

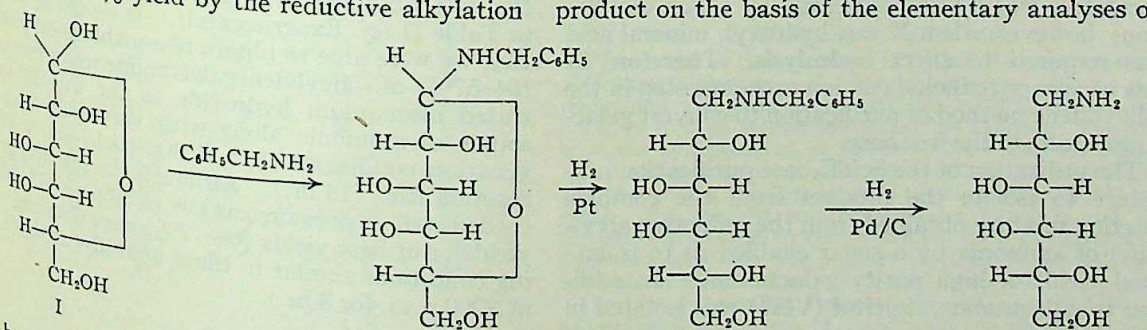


V



VI

the basis of elementary analysis (6 more hydrogens than N-benzylgalactamine), the absence of characteristic phenyl absorption in the ultraviolet and by the neutral equivalent. One attempt to carry out the reductive alkylation and hydrogenolysis steps simultaneously in the presence of a mixed catalyst (platinum and palladium-on-charcoal) yielded another new sugar amine, didulcitylamine (VI). The structure VI has been assigned tentatively to the product on the basis of the elementary analyses of both the free base and the hydrochloride and on the basis of the neutral equivalent.



I II III IV

In several experiments, the glycamines obtained by the hydrogenolysis procedure were difficult to purify. It seems likely that didulcitylamine and cyclohexylmethylgalactamine, were the main contaminants. To ensure a high quality product, it is recommended that the crude hydrogenolysis mixture be purified through either the benzylidene or salicylidene derivative as described below.

Although the hydrogenolysis of an N-benzylglycamine was a satisfactory low pressure laboratory procedure for the preparation of glycamines, cata-

(1) Presented in part before the 129th Meeting of The American Chemical Society, Dallas, Texas, April, 1956.
(2) F. Kagan, R. V. Heinzelman, D. I. Weisblat and W. Greiner, THIS JOURNAL, **79**, 3545 (1957).
(3) L. Maquenne and E. Roux, *Compt. rend.*, **132**, 980 (1901).
(4) E. Roux, *ibid.*, **135**, 691 (1902).
(5) C. Neuberg and F. Marx, *Biochem. Z.*, **3**, 539 (1907).
(6) A. R. Ling and D. R. Nanji, *J. Chem. Soc.*, 1682 (1922).
(7) R. B. Flint and P. L. Salzburg, U. S. Patent 2,016,962, Oct. 8, 1935; *C. A.*, **29**, 8007 (1935).
(8) W. Wayne and H. Adkins, THIS JOURNAL, **62**, 3314 (1940).
(9) F. W. Holly, E. W. Peel, R. Mozingo and K. Folkers, *ibid.*, **72**, 5416 (1950).

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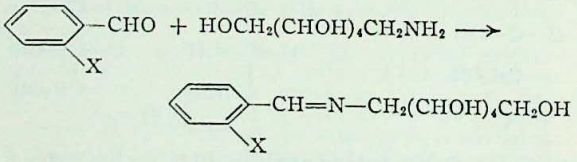
lyst costs and the multiplicity of steps made it unattractive for large-scale preparative work.

Roux[2] has reported the preparation of benzylideneglucamine and its hydrolysis by steam distillation. He suggested that this procedure could be used for the purification of glucamine; however, no experimental details were given. Wayne and Adkins[3] prepared benzylideneglucamine by heating glucamine with benzaldehyde at 180–190° They obtained a dark reaction mixture from which the benzylidene derivative was isolated by fractional crystallization. The low over-all yield of glucamine in this case may have been due in part to the vigorous conditions used in the isolation of the product. These investigators stated that in their opinion the difficulty in obtaining glucamine was not in the hydrogenation stage but in the isolation of the compound. We found that crude glycamines could be converted to aromatic Schiff bases easily at room temperature in aqueous solution. The Schiff bases separated in excellent yield leaving water-soluble sugar derivatives in solution. A variety of aldehydes were used for Schiff base formation, the best



being salicylaldehyde, benzaldehyde, cinnamaldehyde, furfural, 2-hydroxy-3-methoxybenzaldehyde and anisaldehyde. Vanillin and 2,4-dihydroxybenzaldehyde condensed sluggishly with galactamine and yielded only small amounts of Schiff bases. The ease of hydrolysis of the Schiff bases depended to a great extent upon the nature of the substituent X. When X was hydrogen, the benzylidene derivative was hydrolyzed easily by steam distillation; however, when X was hydroxyl, mineral acid was required to effect hydrolysis. Therefore, it was necessary to include an ion exchange step in the salicylidene method of purification to convert galactamine salts to the free base.

The utilization of the Schiff-base purification procedure to isolate the product from the complex reaction mixture obtained from the reductive alkylation of ammonia by a sugar enabled us to isolate good yields of high purity galactamine. In addition to galactamine, dulcitol (VIII) was isolated in up to 12% yield by ion exchange treatment of crude reaction mixtures. It is of interest that even in the presence of a large excess of liquid ammonia a significant portion of the original sugar remained in the aldehyde form and was reduced to dulcitol during the hydrogenation. Didulcitylamine (VI) was also isolated; however, the yields were generally less than 10% when liquid ammonia was used as solvent during the hydrogenation. When concentrated aqueous ammonia was used as solvent, the yield of VI was variable, being as high as 20% in one case. Compound VII, 1,2-dideoxydiaminodulcitol was not isolated as such; however, its presence in some of our products was inferred from potentiometric titration data. In addition to the inflections for galactamine (pK_a' in water, 9.4) and didulcitylamine (pK_a' in water, 8.9), a basic group (in small amounts) with a pK_a' of 5.9 was identified. The pK_a' of this group is typical of what one would expect from the neutralization of the second amino group in VIII; however, in addition to the titration behavior, we have further justification for assigning the vicinal diamine structure to VII. Careful purification of the salicylidenegalactamine obtained from crude hydrogenation mixtures yielded a salicylidene derivative, m.p. 126–128°, in very low yield (<3%). This material was hydrolyzed to an amine hydrochloride whose infrared spectrum was identical to that of ethylenediamine dihydrochloride. This material could have formed by cleavage of the carbon chain after the formation of a vicinal diamine or by cleavage to ethanolamine followed by conversion to ethylenediamine. In view of the titration data, which indicated the presence of a diamine, we prefer the former hypothesis.

We investigated many sets of conditions for the reductive alkylation of ammonia with a sugar. Since most of our work was done with galactamine, the data obtained with this sugar are summarized in Table II (*cf.* Experimental). It should be noted that we were able to obtain reasonably good yields (54–57%) of salicylidenegalactamine using concentrated ammonium hydroxide as the solvent and source of ammonia along with very mild hydrogenation conditions (55° at 200 p.s.i.) and a long reaction time (16 hr.). Although the reaction proceeded well at pressures as low as 50 p.s.i. (48–52% yields), our best yields (66–77%) were obtained using conditions similar to those of Holly, *et al.*[8] (85° at 2000 p.s.i. for 3 hr.).

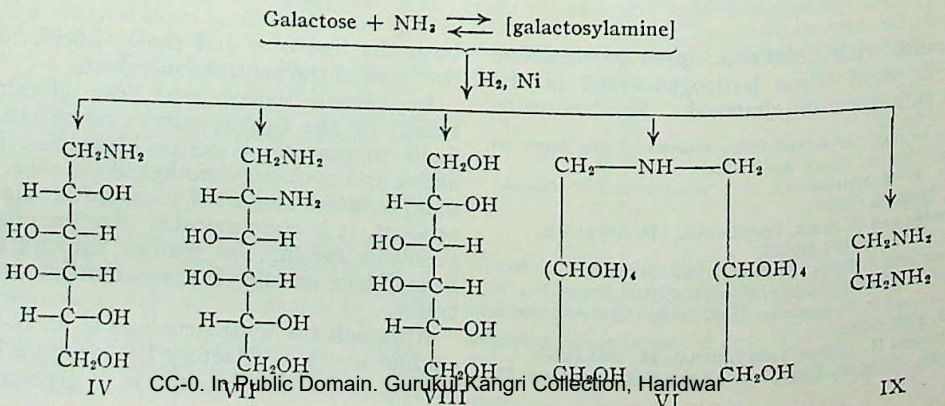


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TABLE I[a]

SALICYLIDENE GLYCAMINES OBTAINED BY THE HYDROGENOLYSIS OF N-BENZYLGLYCAMINES

$$\text{Sugar} \xrightarrow[(2)\ H_2,\ Pt]{(1)\ C_6H_5CH_2NH_2} \text{N-Benzylglycamine} \xrightarrow[(2)\ \text{Salicylaldehyde}]{(1)\ \text{Hydrogenolysis}} \text{Salicylideneglycamine}$$

Sugar	N-benzylglycamine Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Salicylideneglycamine Overall yd., %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
L-Arabinose	64	122–123	$C_{12}H_{19}NO_4$	59.73	59.74	7.94	8.11	5.81	5.77	60	187–188	$C_{12}H_{17}NO_5$	56.46	56.35	6.71	6.47	5.49	5.76
D-Galactose	64[b]	157–159	$C_{13}H_{21}NO_5$	57.55	57.23	7.80	7.59	5.16	5.05		200–202	$C_{13}H_{19}NO_6$	54.73	54.94	6.71	7.09	4.91	4.75
D-Glucose	68[c]	138–139	$C_{13}H_{21}NO_5$	57.55	57.59	7.80	8.03	5.16	5.00									
D-Ribose	46	102–103	$C_{12}H_{19}NO_4$	59.73	59.58	7.94	8.21	5.81	5.71	25	126–128	$C_{12}H_{17}NO_5$	56.46	56.18	6.71	6.30	5.49	5.56
D-Xylose	Oil									26	131–133	$C_{12}H_{17}NO_5$	56.46	56.57	6.71	6.65	5.49	5.63

[a] The experiments on L-arabinose, D-ribose and D-xylose were carried out by R. D. Birkenmeyer of these laboratories. [b] Crude yield, m.p. 151–157°. [c] Crude yield, m.p. 132–135°.

TABLE II

CONDITIONS USED FOR THE ALKYLATION OF AMMONIA WITH GALACTOSE

No.	Catalyst	Time, hr.	Temp., °C.	Pressure, p.s.i.	Product[c] and yield, %
1	Ni (R)[a]	3	85	1500–2000	S, 66–77
2	Ni (R)[a]	1	100	2000	S, 43
3	Co (R)[a]	3	85	1500	B, 65
4	Ni (R)[a]	4	50	500[d]	B, 28
5	Ni (R)[a]	16	50	500[d]	B, 59
6	Ni (R)[b]	16	55	200[d]	B, 54–57
7	Ni (R)[b]	16	55	50[d]	B, 48–52
8	Ni (R)[b]	7	55	50[d]	B, 43

Solvent: [a] Liquid ammonia containing 3% by weight of water. [b] 28–30% ammonium hydroxide. [c] S = salicylidenegalactamine; B = benzylidenegalactamine. Under comparable conditions, the yield of benzylidenegalactamine was consistently about 5% less than that of the salicylidene derivative. [d] Constant.

Experimental[10]

N-Benzylgalactamine (III).—Galactose (50 g., 278 millimoles), benzylamine (30 g., 280 millimoles) and 15 ml. of water were heated on a steam-bath at 60° until solution was complete. Methanol (50 ml.) was added and the reaction mixture was set aside to cool. Platinum oxide (3.2 g.) was added, the volume of the solution was adjusted to 500 ml. with methanol and the mixture was hydrogenated at 40–50° at 50–20 p.s.i. for 15 hr. The reaction mixture was diluted with 1.5 l. of methanol and heated on a steam-bath with stirring until all of the product appeared to be in solution. The catalyst was removed by filtration and the filtrate was allowed to cool slowly to room temperature as the product separated from solution. N-Benzylgalactamine (48 g., 64%, m.p. 151–157°) was obtained in three crops. An analytical sample was prepared by recrystallization from methanol, m.p. 157–159°, $[\alpha]_D$ −6°.

Anal. Calcd. for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.23; H, 7.59; N, 5.05.

N-Benzylglucamine.—The procedure for the preparation of N-benzylglucamine was similar to that for N-benzylgalactamine. The yield of crude product, m.p. 132–135°, was 67.5%. Recrystallization from ethanol to a constant melting point, 138–139°, produced an analytical sample.

Anal. Calcd. for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.59; H, 8.03; N, 5.00.

Preparation of Galactamine (IV). (a) Hydrogenolysis of N-Benzylgalactamine.—N-Benzylgalactamine (30 g., 111 millimoles) was suspended in 250 ml. of 95% ethanol and 5.0 g. of 10% palladium-on-charcoal was added. The mixture was hydrogenated at 50° and 50–30 p.s.i. for 1.5 hr. The reaction mixture was diluted to 500 ml. with methanol and heated on a steam-bath until the supernatant liquid was clear. The catalyst was removed by filtration and the filtrate was allowed to cool overnight in a refrigerator at approximately 3°. The product (14.1 g., 77% yield) was removed by filtration, m.p. 143–145°, $[\alpha]_D$ −1°.

(b) Liquid Ammonia Process.—D(−)-Galactose (150 g., 833 millimoles), 400 ml. of liquid ammonia and 4 teaspoonfuls of Raney nickel were hydrogenated in a stainless steel autoclave equipped with a mechanical stirrer at 1800 p.s.i. at 85° for 4 hr. The contents of the reactor were removed with hot water and the purple reaction mixture was filtered to remove the catalyst The filtrate was concentrated under reduced pressure until the odor of ammonia was no longer apparent. The concentrate was diluted to 750 ml. with water, transferred to a 3-necked, creased flask equipped with a mechanical stirrer and a nitrogen inlet. Salicylaldehyde (103 g., 833 millimoles) was added with stirring and the mixture was stirred vigorously for 10 minutes while being cooled in an ice-bath. The yellow solid which precipitated was removed by filtration, washed on the filter by slurrying with water and dried in a vacuum oven at 50° to yield 192 g. of salicylidenegalactamine (81% yield), m.p. 189–195°.

The crude salicylidene derivative (159 g.) was suspended

(10) All melting points were taken in capillaries and are uncorrected. Rotations were measured in water at 23° at a concentration of 1–4% in a 2-decimeter tube.

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in 400 ml. of ether, and the mixture was stirred vigorously for 5 minutes. The salicylidene derivative was washed onto a filter with an additional 250 ml. of ether and air-dried under a heat lamp to yield 146 g. (74% over-all) of purified material, m.p. 196–198°. A nicely crystalline solid (2.5 g.), m.p. 123–125.5°, was isolated from the ether solution by concentrating and cooling. This material proved to be N,N′-bis-salicylideneethylenediamine (*cf.* below for proof of structure).

An analytical sample of salicylidenegalactamine was prepared by recrystallization from methanol, m.p. 200–202°.

Anal. Calcd. for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.94; H, 7.09; N, 4.75.

The purified salicylidenegalactamine (145.5 g., 0.51 mole), m.p. 196–198°, was suspended in a solution of 1 l. of water and 90 ml. of concentrated hydrochloric acid, and the mixture was heated on a steam-bath for 15 minutes with vigorous stirring. After being cooled to room temperature the reaction mixture was extracted three times with 125-ml. portions of methylene chloride to remove salicylaldehyde. The aqueous phase was concentrated to dryness, the residual galactamine hydrochloride was dissolved in 2 l. of water and the solution was passed through a bed of IR-410 anion exchange resin ($1^5/_8'' \times 31''$) (OH^- cycle). The column was rinsed with water until the *p*H of the effluent was 7–8. The effluent was concentrated under reduced pressure (20 mm.) to a volume of 200 ml., 800 ml. of ethanol was added and the solution was cooled at 3° overnight. The galactamine which crystallized was removed by filtration (78 g., 85% over-all from salicylidenegalactamine), m.p. 145–148°, $[\alpha]D$ −1°. The over-all yield of galactamine from galactose was 63%.

Anal. Calcd. for $C_6H_{15}NO_5$: C, 39.77; H, 8.34; N, 7.73; Van Slyke N, 7.73; neut. equiv., 181. Found: C, 39.43; H, 8.65; N, 7.29; Van Slyke N, 8.0; neut. equiv., 183.

The Isolation of Galactamine through the Benzylidene Derivative.—The procedure for the preparation of benzylidenegalactamine was similar to that used for the salicylidene derivative. From a hydrogenation mixture which yielded 66% of pure salicylidenegalactamine, we obtained a 61% yield of benzylidenegalactamine, m.p. 192–193° (analytical sample, m.p. 191.5–193°). The benzylidenegalactamine was hydrolyzed by steam distillation in a nitrogen atmosphere to yield galactamine in 91% yield (based on the benzylidene derivative), m.p. 146–148°, $[\alpha]D$ −1°.

Anal. Calcd. for $C_6H_{15}NO_5$: Van Slyke N, 7.7; neut. equiv., 181. Found: Van Slyke N, 7.72; neut. equiv., 182.

Hydrogenolysis of N-Benzylglucamine. The Preparation of Glucamine.—The procedure in this preparation was similar to that employed for the hydrogenolysis of N-benzylgalactamine. The yield was 62% of material melting at 124.5–130°. Recrystallization of the crude product from absolute ethanol showed that a considerable amount of a high melting impurity was present which proved very difficult to separate by fractional crystallization. The Schiff base procedure was not developed at the time this experiment was done.

Proof of Structure of N,N′-Bis-salicylidenegalactamine.—The ether-soluble salicylidene derivative isolated above had a melting point after recrystallization from ethanol of 126–128°. The literature melting point of N,N′-bis-salicylidenegalactamine is 125–126°.[11]

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 72.10; H, 6.42; N, 10.94; ash, 0.24.

A sample of the salicylidene derivative was hydrolyzed with dilute hydrochloric acid to yield salicylaldehyde and an amine hydrochloride melting over 250°. The infrared spectrum of the latter was identical to that of an authentic sample of ethylenediamine dihydrochloride.

Isolation of Cyclohexylmethylgalactamine (V) from a Preparation of Galactamine by Hydrogenolysis of N-Benzylgalactamine.—Galactose (54 g., 300 millimoles), benzylamine (32.1 g., 300 millimoles) and 16.5 ml. of water were heated at 60° for 20 minutes, and the reaction mixture was stored at room temperature overnight. The resulting viscous solution was diluted with 360 ml. of methanol and hydrogenated in a stainless steel autoclave in the presence of 3.5 g. of platinum oxide for 5 hr. at 50° and 30 p.s.i. The hydrogen in the reactor was displaced with nitrogen, the head was removed and 15 g. of 10% palladium-on-charcoal, slurried in 150 ml. of 95% ethanol, was added. Hydrogenation was continued at 50° and 30 p.s.i. for 3 hr. The product was washed from the autoclave with 250 ml. of water and the resulting suspension was heated to 60°, filtered, and the filtrate was concentrated under reduced pressure until a solid began to separate. After cooling to 3°, a white solid was isolated (6.1 g., 11.3%), m.p. 148–152°. The mother liquor was concentrated to an oil which crystallized when triturated with methanol yielding 35 g. (65%) of a white solid, m.p. 120–127°, $[\alpha]D$ +2°, neut. equiv., 244.

The first crop of crystals was recrystallized from water yielding a 38% recovery of a new sugar amine, m.p. 132–135°. Recrystallization of this material four times from water yielded an analytical sample of N-cyclohexylmethylgalactamine, m.p. 135–136°, $[\alpha]D$ −6°. The ultraviolet spectrum showed no evidence for the presence of a phenyl group.

Anal. Calcd. for $C_{13}H_{27}NO_5$: C, 56.29; H, 9.81; N, 5.05; neut. equiv., 277. Found: C, 56.45; H, 9.68; N, 4.95; neut. equiv., 279.

D(−)-Didulcitylamine (VI).—A mixture of galactose (54 g., 300 millimoles), benzylamine (33 g., 308 millimoles) and water (16.5 ml.) was heated on a steam-bath at 60° with occasional swirling until homogeneous. The reaction mixture was diluted with alcohol (54 ml.) and set aside for 17 hr. Further dilution with 500 ml. of alcohol was followed by the addition of 3.5 g. of platinum oxide and 15 g. of 10% palladium-on-charcoal. The mixture was then hydrogenated at 50° and 10 p.s.i for 6 hr. The reaction mixture was heated to 65°, filtered and diluted to 1 l. with water. The white solid that separated was removed by filtration (10.3 g., 20%), m.p. 195–197°. A second crop was obtained by concentrating under reduced pressure to a white paste-like mass which was diluted to 500 ml. with methanol and filtered. The solid which was obtained (21.0 g., 40%) melted at 169–173°. A third crop of solid was obtained after storage of the filtrate at 3° for 5 days (8.6 g., 16.7%), m.p. 93–100°.

Recrystallization of the first crop of solid three times from water yielded an analytical sample of D-(−)-didulcitylamine, m.p. 202–204°, $[\alpha]D$ −9°.

Anal. Calcd. for $C_{12}H_{27}NO_{10}$: C, 41.73; H, 7.88; N, 4.06; neut. equiv., 345. Found: C, 42.00; H, 7.71; N, 4.08; neut. equiv., 352.

A crystalline hydrochloride salt of this amine melted at 240–241°.

Anal. Calcd. for $C_{12}H_{28}ClNO_{10}$: C, 37.75; H, 7.39; N, 3.67; Cl, 9.29. Found: C, 38.05; H, 7.34; N, 3.95; Cl, 9.24.

Acknowledgments.—The authors are grateful to Dr. E. R. Garrett for potentiometric titration data, to Dr. J. L. Johnson and Mrs. G. S. Fonken for infrared spectra and to Mr. W. A. Struck and his associates for optical rotations and microanalyses.

KALAMAZOO, MICHIGAN

(11) A. T. Mason, *Ber.*, **20**, 271 (1887).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

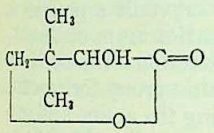
A Novel Resolution of Pantolactone—The Synthesis of D(+)-Calcium Pantothenate[1]

BY FRED KAGAN, RICHARD V. HEINZELMAN, DAVID I. WEISBLAT AND WARD GREINER

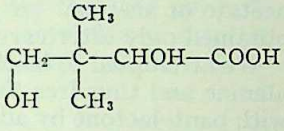
RECEIVED FEBRUARY 8, 1957

D(−)-Galactamine, a novel resolving agent, was used to resolve pantolactone, a key intermediate in the synthesis of D(+)-calcium pantothenate. Pantolactone reacted with D(−)-galactamine to yield a pair of diastereoisomeric N-D-dulcityl-2,4-dihydroxy-3,3-dimethylbutyramides. Fractional crystallization yielded (+)-N-D-dulcityl-D-2,4-dihydroxy-3,3-dimethylbutyramide in 70% yield (98% optical purity) and the (−)-diastereoisomer in 80% yield (93–98% optical purity). D(−)-Pantolactone and D(−)-galactamine were recovered from the (+)-diastereoisomer in 94 and 96% yields, respectively, by acid hydrolysis. The calcium salt of β-alanine was coupled with D(−)-pantolactone in methyl Cellosolve at 25–30° to yield crystalline D(+)-calcium pantothenate in 94% yield based on pantolactone.

Pantolactone (I), a key intermediate in the synthesis of pantothenic acid, previously has been resolved by conversion to diastereoisomeric salts of the corresponding 2,4-dihydroxy acid (II)[2–6] by



I



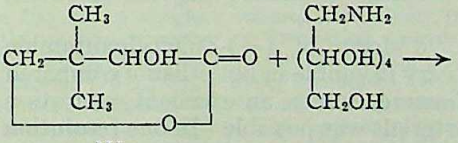
II

conversion of the secondary hydroxyl group to a half-ester followed by salt formation[7–9] and through the formation of molecular complexes with brucine.[7]

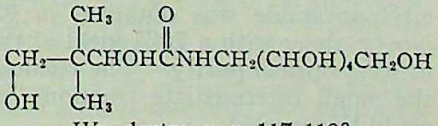
With the exception of the pyridinium diacetyl tartrate resolution,[7] each of the above schemes utilized a relatively expensive alkaloid[2–4,7–9] or a synthetic material which itself had to be resolved before use.[5,6] Our initial objective was to find an optically active base useful in the resolution of pantolactone and sufficiently inexpensive so that its near quantitative recovery would not be a critical factor in the successful operation of a commercial process. To achieve such an objective, one must necessarily prepare the resolving agent from inexpensive, naturally occurring, optically active materials. Since certain sugars are the least expensive of the pure optically active organic compounds available to the chemist, it seemed desirable to use a sugar or one of its derivatives for resolution work. The benzimidazole base formed by D-*gluco*-D-*gulo*-heptonolactone and *o*-phenylenediamine has been used successfully to resolve tartaric acid[10]; however, no report has yet appeared on the use of a simple basic sugar derivative such as a glycamine as a resolving agent. Since the glycamines appeared to meet our requirements for a readily available, inexpensive resolving agent, we undertook a program aimed at determining their applicability to the resolution of pantolactone.

Glucamine, potentially the least expensive of the glycamines, was prepared by the hydrogenolysis of N-benzylglucamine.[11] Galactamine was prepared by the method of Flint and Salzberg[12] as modified by Holly and co-workers.[13] The crude product obtained by the latter method was not suitable for resolution work. It was purified through the salicylidene or benzylidene derivatives to yield a material which was essentially pure galactamine.[11]

Glucamine failed to form crystalline derivatives with pantolactone; however, galactamine condensed smoothly with the lactone to form crystalline diastereoisomeric forms of N-D-dulcityl-2,4-dihydroxy-3,3-dimethylbutyramide (IV), hereafter referred to as dulcitylpantamide. The reaction occurred readily in refluxing ethanol or by fusion at 100–125°. N-Substituted glycamines such as N-methylglucamine and N-benzylglucamine failed to react with pantolactone in refluxing ethanol, refluxing pyridine or by fusion.



III



IVa, dextro, m.p. 117–118°
b, levo, m.p. 122–123°

In contrast with glucamine, galactamine proved to be a very satisfactory resolving agent. Early experiments in which this agent was used to resolve pantolactone yielded dextrorotatory dulcitylpantaamide (IVa), m.p. 117–118°, and the levo diastereoisomer IVb, m.p. 122–123°. Solubility studies in ethanol at 25° indicated that the dextro diastereoisomer was about 30% more soluble than the levo form. During resolution, the first compound to crystallize from the reaction mixture was the unexpected, more soluble dextro compound. As the initial dextro enriched crops crystallized from solution, the composition of the mother liquor became

(1) Presented in part at the 129th Meeting of The American Chemical Society, Dallas, Texas, April, 1956.

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(6) F. D. Pickel and S. Chodroff, U. S. Patent 2,460,240 (Jan. 25, 1949); *C. A.*, **43**, 3448 (1949).

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(8) J. Finkelstein, U. S. Patent 2,328,000 (Aug. 31, 1943); *C. A.*, **38**, 527 (1944).

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(12) R. B. Flint and P. L. Salzberg, U. S. Patent 2,016,962 (Oct. 8, 1935); *C. A.*, **29**, 8007 (1935).

(13) F. W. Holly, E. W. Peel, R. Mozingo and K. Folkers, THIS JOURNAL, **72**, 5418 (1950).

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predominantly levo until a 5–10% enrichment was reached. At this point, levo isomer was deposited until the composition of the mother liquor again approached that of a racemate. This behavior was then repeated in a cyclic fashion. Since an appreciable displacement of the composition of the mother liquor from that of a racemate was impossible, and, furthermore, since optical purity appeared to be inversely related to the size of the crops which were isolated, this method of resolution of pantolactone was tedious.

In one of the galactamine resolution experiments a new material was obtained which melted 40° higher than either of the previously isolated dulcitylpantamides (IVa and IVb). Potentiometric titration showed that the compound was not a dulcitylammonium salt of 2,4-dihydroxy-3,3-dimethylbutyric acid. Since acid hydrolysis yielded galactamine hydrochloride and L(+)-pantolactone, it appeared that the new material was a polymorphic form of *l*-dulcitylpantamide. A mixed melting point between the previously isolated *l*-dulcitylpantamide (m.p. 122–123°, IVb) and the new material (m.p. 162.5–165°, IVc) was not depressed, and the specific rotations of the two materials in water were identical. The new polymorph, synthesized from D(−)-galactamine and L(+)-pantolactone by the methods which had previously yielded the low melting material, was designated the "β"-form of (−)-dulcitylpantamide. In resolution work in these laboratories, the "α"-form (IVb) had been used for several years with no apparent instability. Samples stored at room temperature in screw-cap vials remained unchanged; however, attempts to recrystallize existing samples of "α"-(−)-dulcitylpantamide have thus far yielded only the "β"-form (IVc).

Since the "β"-form of (−)-dulcitylpantamide proved to be very insoluble in hot ethanol compared to the (+)-diastereoisomer, an excellent separation of the two materials was possible. In one resolution of 100 g. of pantolactone, an 80% yield of (−)-dulcitylpantamide was obtained in 93–98% optical purity along with a 70% yield of the D(+)-isomer in 96% optical purity. The residual material and the small intermediate fractions of lesser purity could be recycled.

(+)-Dulcitylpantamide was hydrolyzed with dilute hydrochloric acid to give a 94% yield of D-(−)-pantolactone based on the starting amide and a practically quantitative yield of galactamine hydrochloride. The latter was converted to the free base by passage of an aqueous solution through a bed of anion exchange resin. The over-all yield of recovered galactamine was 96% from (+)-dulcitylpantamide. This material was suitable for further resolution work with no additional purification.

The biologically inactive L(+)-pantolactone was easily racemized by the procedure of Stiller and co-workers,[14] by fusing with trisodium phosphate at 160° or by merely heating to 195° in the presence of soft glass. The soft-glass method is similar to that of Klein and Kapp[15] in which they used alkali metal silicates as their catalyst. Both trisodium phosphate and the soft-glass procedures convert L(+)-pantolactone to the racemic form in over 95% yield.

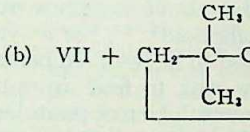
The final step in the synthesis of pantothenic acid is the coupling of β-alanine or one of its salts with pantolactone. If β-alanine is used, a temperature of about 180°[16] is necessary to effect reaction, presumably because the zwitterion form of the amino acid is relatively inactive toward attacking the carbonyl group of pantolactone. The procedures in which salts of β-alanine are used in the coupling with pantolactone are often carried out in refluxing anhydrous alcohol[17] and in aqueous solution.[18,19] These methods are usually complicated since the product, a salt of pantothenic acid, is first isolated as an amorphous hygroscopic solid by precipitation from alcoholic solution by the addition of ethyl acetate or acetone. A pure crystalline product is obtained only after crystallization from methanol.

We attempted to block zwitterion formation in β-alanine and thus free the amino group for reaction with pantolactone by adsorbing the amino acid on a strongly basic anion exchange resin (IR-410) to form the resin salt VII. Coupling with pantolactone was then carried out to form the resin pantothenate (VIII). The product was then displaced from the resin by calcium chloride solution. In addition to D(+)-calcium pantothenate (15% yield), we obtained a material (49% yield) which melted at 226–230° dec., approximately 30° higher than calcium pantothenate. Microbiological assay of this material with *lactobacillus arabinosus* indicated a D(+)-calcium pantothenate activity of 67%. The microbiological assay, the analytical data and the infrared spectrum indicated that the product was a mixed salt of pantothenic acid and 2,4-dihydroxy-3,3-dimethylbutyric acid (X).

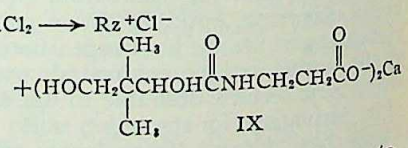
We found that the reaction of D(−)-pantolactone with the calcium salt of β-alanine proceeded

(a) $NH_2CH_2CH_2COOH + Rz^+OH^- \longrightarrow Rz^+ {}^-OOCCH_2CH_2NH_2$

VII, Rz = Resin

(b) VII +  $\longrightarrow$

$Rz^+ {}^-OOCCH_2CH_2NHCCHOHCCH_2OH$ (VIII)

(c) VIII + $CaCl_2 \longrightarrow Rz^+Cl^-$ + 

IX

(14) E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy and K. Folkers, THIS JOURNAL, **62**, 1785 (1940).

(15) H. C. Klein and R. Kapp, U. S. Patent 2,688,027 (Aug. 31, 1954); *C. A.*, **49**, 13289 (1955).

(16) M. B. Moore, U. S. Patent 2,234,680 (March 11, 1941); *C. A.*, **35**, 4041 (1941).

(17) F. D. Pickel and H. H. Weinstock, U. S. Patent 2,442,143 (May 25, 1948); *C. A.*, **42**, 5174 (1948).

(18) S. H. Babcock, Jr., U. S. Patent 2,375,885 (May 15, 1945); *C. A.*, **39**, 3399 (1945).

(19) S. H. Babcock, Jr., U. S. Patent 2,441,949 (May 25, 1948); *C. A.*, **42**, 7788 (1948).

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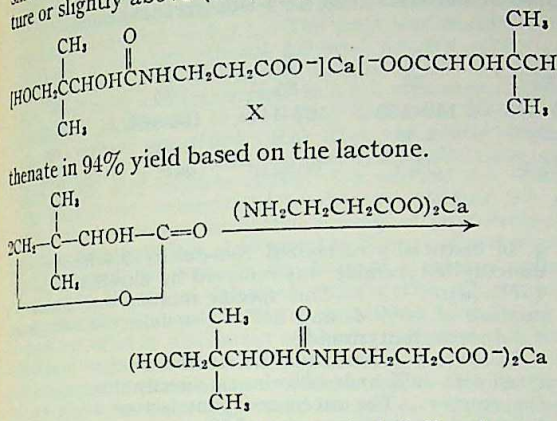
smoothly in methyl Cellosolve at room temperature or slightly above (35°) to yield calcium pantothenate in 94% yield based on the lactone.



The attractive aspect of using methyl Cellosolve as the solvent in this reaction was that the product, D(+)-calcium pantothenate, crystallized directly from the reaction mixture in excellent yield in an analytically pure condition.

Experimental[20]

(+)-N-D-Dulcityl-D-2,4-dihydroxy-3,3-dimethylbutyramide (IVa).—D(−)-Galactamine (0.585 g., 3.2 millimoles) and 0.763 g. (5.9 millimoles, 81% excess) of D(−)-pantolactone were fused in a test-tube on a steam-bath for 4 hr. The hard glass which formed on cooling was pulverized and triturated with 5 ml. of absolute ethanol. The residual solid was dissolved in 12 ml. of hot ethanol, filtered and stored in a refrigerator overnight. The copious white solid which precipitated was removed by filtration, washed with ethanol and dried, yielding 0.68 g. (68%) of IVa, m.p. 115–116°. Recrystallization from hot absolute ethanol yielded 0.56 g. of (+)-N-D-dulcityl-D-2,4-dihydroxy-3,3-dimethylbutyramide, m.p. 117–118°, $[\alpha]_D$ +11°.

Anal. Calcd. for $C_{12}H_{25}NO_8$: C, 46.29; H, 8.09; N, 4.50. Found: C, 46.28; H, 8.12; N, 4.66.

(−)-N-D-Dulcityl-L-2,4-dihydroxy-3,3-dimethylbutyramide (IVb).—D(−)-Galactamine (1.4 g., 78 millimoles), 1.4 g. (10 millimoles, 34% excess) of L(+)-pantolactone and 75 ml. of absolute ethanol were heated to reflux with stirring for 12 hr. The resulting yellow reaction mixture was clarified by centrifugation and was stored at room temperature overnight. The solid which separated was removed by centrifugation. Recrystallization from ethanol yielded an analytical sample, m.p. 122–123°, $[\alpha]_D$ −33°.

Anal. Calcd. for $C_{12}H_{25}NO_8$: C, 46.29; H, 8.09; N, 4.50. Found: C, 46.63; H, 8.10; N, 4.24.

The Resolution of Pantolactone with D(−)-Galactamine. (a) Typical Resolution Involving "α"-(−)-Dulcitylpantamide (IVb). The Isolation of "β"-(−)-Dulcitylpantamide (IVc).—Pantolactone (17.4 g., 0.134 mole), 11.2 g. (0.062 mole) of D(−)-galactamine and 200 ml. of absolute ethanol were heated to reflux with vigorous stirring in a nitrogen atmosphere for 7 hr. The cloudy reaction mixture was filtered yielding a clear pale yellow filtrate (*p*H 8). The ethanol was removed under reduced pressure and the residual sirup was dissolved in 40 ml. of hot water. The excess pantolactone was removed by extraction with five 40-ml. portions of methylene chloride, and the aqueous solution was concentrated under reduced pressure to a viscous pale yellow sirup which was dried by repeated distillation of absolute ethanol. The dried residue was dissolved in 65 ml. of hot ethanol, seeded with "α"-(−)-dulcitylpantamide and stored at 3°. Five crops of crystals were removed over a period of two weeks. The pertinent data for these crops are summarized in Table I. After the removal of the fifth crop, the mother liquor was concentrated to a sirup which was dissolved in 25 ml. of water and extracted well with methylene chloride. The aqueous solution was evacuated at 15 mm. to remove residual methylene chloride and was filtered through a column of Darco–Celite (1:2) (5 cm. × 1 cm.). The golden yellow solution was decolorized effectively by this treatment. The filtrate was concentrated under reduced pressure to a viscous sirup which was dissolved in 18 ml. of hot ethanol. The solution was seeded with (+)-dulcitylpantamide and stored at 3°. After two days, a white crystalline solid, crop 6, was removed by filtration, 2.0 g. (11%), m.p. 149–152°, $[\alpha]_D$ −25°. This material melted about 30° higher than any crop previously isolated in the resolution of pantolactone with galactamine. Crop 6 was recrystallized three times from ethanol–water to yield an analytical sample of "β"-(−)-dulcitylpantamide, m.p. 162.5–165°.

TABLE I

SUMMARY OF CROPS REMOVED FROM THE RESOLUTION IN WHICH "β" (−)-DULCITYLPANTAMIDE WAS ISOLATED

Crop	1	2	3	4	5	6
Weight, g.	6.7	1.4	2.1	0.5	1.0	2.0
Theor. amides, %	35	7	11	3	5	11
M.p., °C.	107–112	100–110	111–117	115–122	92–102	149–152
$[\alpha]_D$ (°)	−2	−20	−28	−29	0	−25
Major component,[a] %	71% D	71% "α"-L	89% "α"-L	91% "α"-L	75% D	82% "β"-L

[a] (+)-Dulcitylpantamide is designated D and (−)-dulcitylpantamide L.

Anal. Calcd. for $C_{12}H_{25}NO_8$: C, 46.29; H, 8.09; N, 4.50. Found: C, 46.46; H, 8.32; N, 4.37.

(b) Resolution Involving "β"-(−)-Dulcitylpantamide.—Pantolactone (100 g., 0.769 mole, 99% excess) was dissolved in 500 ml. of absolute ethanol, and about 100 ml. of the ethanol was removed by distillation to dry the lactone. The solution was cooled below the boiling point, D(−)-galactamine (70 g., 0.387 mole) was added and the suspension was stirred vigorously at the reflux temperature in a nitrogen atmosphere for 17.5 hr. The reaction mixture (*p*H 7) was cooled to room temperature, and the solid which was present was removed by filtration, 47.2 g. (29% of the theoretical amides), m.p. 161.5–163.5°, $[\alpha]_D$ −30°. The filtrate was concentrated under reduced pressure to a sirup which was taken up in 200 ml. of warm water. The aqueous solution was extracted six times with 125 ml. portions of methylene chloride, the combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to a semi-solid (50 g., 100%) recovered pantolactone. The aqueous solution was concentrated under reduced pressure to a burnt orange colored sirup which was dried by distillation of 100 ml. of absolute ethanol and dissolved in 200 ml. of hot alcohol. It was seeded with "β"-(−)-dulcitylpantamide and stored at 30° for 4 hr. The white crystalline solid which separated was removed by filtration, washed with absolute ethanol and dried in a vacuum oven at 50°, (34.1 g., 28%) of the theoretical amides, m.p. 112–115°, $[\alpha]_D$ +9°. It is surprising that practically pure (+)-dulcitylpantamide was obtained in this crop in spite of the fact that the solution was seeded with the L(−)-isomer. After removal of two intermediate crops totaling 12.5 g. (10%), an additional crop of pure D(+)-diastereoisomer was isolated, 7.5 g. (6%), m.p. 103–111°, $[\alpha]_D$ +9°. A summary of the crystalline crops isolated in this resolution is presented in Table II.

Hydrolysis of N-D-Dulcityl-2,4-dihydroxy-3,3-dimethylbutyramide. Proof of Structure of the "β"-(−)-Enriched Form.—"β"-(−)-N-D-Dulcityl-L-2,4-dihydroxy-3,3-dimethylbutyramide (6.6 g., 0.0212 mole, m.p. 160–162.5°, $[\alpha]_D$ −30°, 93% (−)-diastereoisomer) was heated on a steam-bath with 40 ml. of 6% by volume hydrochloric acid

[20] All melting points are uncorrected. Specific rotations were taken in water at 23°, at a concentration of 1–4% in a 2-decimeter tube.

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TABLE II

RESOLUTION OF PANTOLACTONE WITH D(−)-GALACTAMINE INVOLVING "β"-(−)-DULCITYLPANTAMIDE

Crop							
Weight % of theor. amides	39	28	6	5	6	1	12
Cum. weight, %	39	67	73	78	84	85	97
M.p., °C.	161–163	112–115	120–135	149–153	103–111	162–164	Sirup
$[\alpha]_D$ (°)	−30	+9	−7	−23	+9	−32	.....
Major component, %	93% L	96% D	59% D[a]	77% L[a]	96% D	98% L	*ca.* 63% D[a]

[a] Can be recycled.

for 3 hr. The resulting solution was extracted with five 25-ml. portions of methylene chloride and the combined extracts were dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure afforded 2.3 g. (83%) of pantolactone which was purified for analysis by sublimation ($[\alpha]_D$ +43°, equivalent to 93% of the L(+)-enantiomorph). From another experiment in which the starting material to be hydrolyzed melted at 148–151°, the pantolactone which was obtained melted at 86.6–90°, $[\alpha]_D$ +16° [66% L(+)].

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.45; H, 7.61.

The aqueous phase was concentrated under reduced pressure to a white crystalline solid which was further dried by distillation of absolute ethanol, reslurried in ethanol and filtered to yield galactamine hydrochloride in 97% yield, m.p. 158–161°.

Anal. Calcd. for $C_6H_{16}ClNO_5$: Cl, 16.29. Found: Cl, 16.66.

A mixed melting point with an authentic sample of galactamine hydrochloride was not depressed and the infrared spectra of the two samples were identical.

(b) D(+)-Form.—(+)-N-D-Dulcityl-D-2,4-dihydroxy-3,3-dimethylbutyramide (31.0 g., 99.7 millimoles) was hydrolyzed by the above procedure to yield 12.2 g. (94% yield) of D-(−)-pantolactone ($[\alpha]_D$ −48°, 98% D(−)-enantiomorph). The galactamine hydrochloride was dissolved in 500 ml. of deionized water and the resulting solution was passed through a ¾″ × 18″ column of Rohm and Haas IR-410 anion exchange resin in the hydroxide cycle at the rate of 5 ml. per minute. The column was washed with water until the *p*H of the effluent was 7.5. The aqueous solution of galactamine was then concentrated to dryness under reduced pressure in a nitrogen atmosphere. The white crystalline residue was dried by repeated distillation of absolute ethanol and finally by evacuation with an oil-pump to yield 17.3 g. of galactamine (96%), m.p. 142–146°.

Anal. Calcd. for $C_6H_{15}NO_5$: neut. equiv., 181.2. Found: neut. equiv., 188.

This material when treated with D(−)-pantolactone yielded (+)-dulcitylpantamide in 90% yield in one crop of crystals. The mother liquor was not worked up further for additional crops.

The Racemization of L(+)Pantolactone. (a) **Trisodium Phosphate Procedure.**—L(+)-Pantolactone [19.2 g., 0.148 mole, $[\alpha]_D$ +45° (H_2O)] was fused with 0.96 g. of trisodium phosphate decahydrate with stirring at 160° for 18 hr. The product was then flash-distilled to yield 18.5 g. (95.4%) of racemic pantolactone, $[\alpha]_D$ +1°.

(b) **Soft-glass Procedure.**—L(+)-Pantolactone (10 g.) was fused at 195° with 2.1 g. of powdered soft glass with stirring for 16 hr. The lactone was then flash-distilled at 15 mm. to yield 9.7 g. (97%) of racemic pantolactone, $[\alpha]_D$ 0°.

Racemization of L(−)-N-D-Dulcityl-L-2,4-dihydroxy-3,3-dimethylbutyramide.—Sodium metal (0.5 g., 0.022 gram atom) was dissolved in absolute methanol in a stainless steel autoclave with careful exclusion of moisture. L(−)-N-D-Dulcityl-2,4-dihydroxy-3,3-dimethylbutyramide (5.0 g., 0.165 mole) was added, and the reaction mixture was heated at 100° for 2 hr. The methanol was removed under reduced pressure and the residue was taken up in 125 ml. of water. The aqueous solution was passed through a bed of Rohm and Haas IR-120 cation exchange resin in the hydrogen cycle (1 cm. × 17 cm.) to remove caustic. The effluent solution was concentrated to a sirup under reduced pressure yielding 4.1 g. of residue (82%) which was dissolved in 20 ml. of absolute ethanol and stored at 3°. After 3 days 1.4 g. of essentially racemized N-D-dulcityl-2,4-dihydroxy-3,3-dimethylbutyramide was removed by filtration, m.p. 127–137°, $[\alpha]_D$ −13°. This specific rotation corresponds to a mixture of 46% *d*- and 54% *l*-N-D-dulcityl-2,4-dihydroxy-3,3-dimethylbutyramide.

In another experiment the reaction mixture was hydrolyzed with 10% hydrochloric acid directly after removal from the reactor. The racemized pantolactone which was isolated had a specific rotation of 0°.

The Coupling of β-Alanine and D(−)-Pantolactone. The Synthesis of D(+)-Calcium Pantothenate. (a) **Calcium Metal in Methyl Cellosolve.**—In a 3-necked, round-bottomed flask equipped with a stirrer and a condenser fitted with a drying tube were placed 3.5 g. (87.3 millimoles) of calcium turnings and 200 ml. of methyl Cellosolve. The methyl Cellosolve was heated to the reflux temperature under nitrogen with stirring for 1 hr. After cooling, the flask was immersed in a constant temperature bath at 35°, and 15.6 g. (0.175 mole) of β-alanine was added and stirring was continued for 1 hr. D(−)-Pantolactone (25.2 g., 0.194 mole, 10% excess) was then added and stirring was continued at 35° for about 2 hr. Celite (1.0 g.) was added to the black solution, and it was filtered through a pressure filter in a nitrogen atmosphere to remove the black coloration. The filtrate was transferred to another 3-necked flask equipped with a mechanical stirrer and a nitrogen inlet and the flask was placed in a 35° constant temperature bath. The clear solution was seeded with D(+)-calcium pantothenate and stirred in a nitrogen atmosphere for 7 hr. The white solid which separated was removed by filtration and washed on the filter with 300 ml. of methyl Cellosolve. The product was dried in a vacuum desiccator over concentrated sulfuric acid for two days; however, this treatment did not remove the methyl Cellosolve completely. The residual solvent was removed in a vacuum oven at 50° (24 hr.). The yield of D(+)-calcium pantothenate was 36.0 g. (87%), m.p. 193.5–195°, $[\alpha]_D$ +27°. A second crop, 0.38 g. (1%), was obtained by stirring the mother liquor further at 35°, m.p. 193.5–195°.

Anal. Calcd. for $C_{18}H_{32}CaN_2O_{10}$: C, 45.36; H, 6.77; N, 5.88; Ca, 8.41. Found: C, 45.64; H, 6.85; N, 6.21; Ca, 8.23; bioassay (*Lactobacillus arabinosus*), 100%.

The filtrates were concentrated under reduced pressure to remove methyl Cellosolve. The residue was taken up in 60 ml. of 10% hydrochloric acid, and the solution was heated on a steam-bath for 4 hr. After cooling, the aqueous solution was extracted with chloroform (*ca.* 150 ml.), and the chloroform solution was dried over anhydrous sodium sulfate. The chloroform was removed under reduced pressure leaving 4.0 g. of recovered pantolactone. An aliquot of the recovered lactone, after sublimation, had a specific rotation of −48°. The yield of D(+)-calcium pantothenate based on pantolactone was 94%.

The methyl Cellosolve used in this reaction must be distilled before use to eliminate heavy metal contamination of the final product. From one lot of methyl Cellosolve which was shipped from the manufacturer in a one-gallon metal container, a 100-ml. aliquot yielded 80 mg. of residue on evaporation. After ignition, the 60 mg. of ash which was obtained contained magnesium, calcium, lead, silicon and a trace of iron. D(+)-Calcium pantothenate which was prepared in this lot of methyl Cellosolve contained 5000 p.p.m. of heavy metals whereas the U.S.P. allowable limit is 20 p.p.m.[21]

(b) **Ion Exchange Resin.**—A solution of 10 g. of β-alanine (0.113 mole) in 1000 ml. of deionized water was passed through a column of IR-410 anion exchange resin

[21] "The National Formulary," 10th Edition, Edwards Brothers, Inc., Ann Arbor, 1955, p. 122.

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(OH^- cycle) ($^3/_4'' \times 18''$). The column was washed with 500 ml. of water, and the effluent was concentrated to dryness to determine the amount of β-alanine that came through the column (residue = 0 g.). The resin was washed with 1000 ml. of absolute ethanol followed by dry ether. A vacuum was then applied to the column to dry the resin. The dried resin was transferred to a 1-l. erlenmeyer flask, and 32.5 g. (0.25 mole) of D(−)-pantolactone in 200 ml. of absolute ethanol was added. The flask was gently shaken for 67 hr. at 25°. The resin was removed by filtration and washed well with absolute ethanol followed by dry ether. The filtrate was concentrated to dryness yielding 9.0 g. (50% recovery of the theoretical excess) of pantolactone. Calcium chloride (6.2 g., 0.56 mole) in 200 ml. of water was passed through the resin (in the form of a column again) followed by 500 ml. of deionized water. The effluent was concentrated to dryness yielding a sirup-like residue, 31.7 g., which was dried by distillation of absolute ethanol. It was dissolved in hot methanol, seeded with a trace of D(+)-calcium pantothenate and set aside at room temperature overnight. The white solid that formed on standing was removed by filtration, 13.0 g. (49% yield), m.p. 226–230° dec., $[\alpha]_D$ +21°. A bioassay with *L. arabinosus* indicated that this material was 67% D(+)-calcium pantothenate.

Anal. Calcd. for calcium pantothenate, $C_{18}H_{32}CaN_2O_{10}$: C, 45.36; H, 6.77; N, 5.88; Ca, 8.41. Found: C, 44.56; H, 6.85; N, 3.97; Ca, 9.57.

From the bioassay and the analytical data, it was obvious that the product was not D(+)-calcium pantothenate but was instead a mixed salt, calcium pantothenate-pantoate. Calcd. for $C_{15}H_{27}CaNO_9$: C, 44.43; H, 6.71; N, 3.46; Ca, 9.89. Found: C, 44.56; H, 6.85; N, 3.97; Ca, 9.57. The calcium pantothenate portion of the molecule represents about 64% of its total weight, in good agreement with the 67% activity determined in the bioassay.

A second crop of solids (4.1 g., 15.4%) was obtained after storage for an additional 24 hr. which proved to be D(+)-calcium pantothenate, m.p. 193–196°. Bioassay with *l. arabinosus* indicated a purity of 90%.

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KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Pyridine-1-oxides. III. Oxidative Coupling of 4-Nitro-3-picoline-1-oxide[1]

BY E. C. TAYLOR, A. J. CROVETTI[2] AND N. E. BOYER

RECEIVED NOVEMBER 7, 1956

4-Nitro-3-picoline-1-oxide (I) undergoes a facile oxidative coupling upon treatment in alkaline medium with oxygen, sodium nitrite or *n*-butyl nitrite to give 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl (II). Several reactions of II are discussed.

In the course of an investigation of the chemistry of pyridine-1-oxides, 4-nitro-3-picoline-1-oxide (I) was prepared and utilized as a key intermediate for the preparation of derivatives of nicotinic acid[3] and for a new synthesis of the alkaloid ricinine.[4] In the hope of extending further the usefulness of this versatile intermediate, an attempt was made to prepare 4-nitro-3-pyridyl aldehyde *via* the corresponding oxime by treatment of 4-nitro-3-picoline-1-oxide with *n*-butyl nitrite in the presence of a molar quantity of sodium ethoxide in ethanol. This method is similar to that reported by Lapworth[5] for the conversion of *o*-nitrotoluene to its oxime. Upon mixing the reactants at 0°, a rapid and pronounced color change from green-blue to red-brown took place with the simultaneous separation of a yellow, alkali-insoluble product (A). The same product was also obtained, although in lower yield, when a suspension of I in water containing an excess of sodium nitrite and a molar quantity of sodium hydroxide was shaken at room temperature or when oxygen was passed through a mixture of I in aqueous sodium hydroxide or in sodium ethoxide in ethanol.

The anticipated oxime structure for the product A was immediately suspect on the basis of its insolubility in alkali. Microanalytical values were almost identical with those calculated for I, but a molecular weight determination revealed that the product A was actually a "dimer" of I. An oxidative coupling had thus taken place to give 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl (II) (A) under conditions reminiscent of the oxidative coupling of *o*- and *p*-nitrotoluenes to the corresponding bibenzyls.[6–14] It is noteworthy that treatment of 4-nitropyridine-1-oxide with sodium nitrite and sodium hydroxide leads only to reduction to the corresponding azo compound,[15] and treatment of 4-nitro-2-picoline-1-oxide with sodium alkoxides results in normal nucleophilic displacement of the nitro group.[16]

It is curious that the formation of II from 4-nitro-3-picoline-1-oxide (I) has not been noted previously. Thus, Katritzky[17] treated I with sodium benzylate in benzyl alcohol and noted the formation of an intense green coloration (similar to that

(1) This work was supported in part by grants from the Smith, Kline and French Foundation and from the National Science Foundation.

(2) Parke, Davis and Co. Fellow, 1954–1955.

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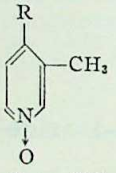
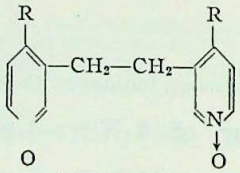
observed here with sodium ethoxide), but no product was isolated from the reaction. Using similar conditions, Itai and Ogura[18] isolated 4-benzyloxy-3-picoline-1-oxide in 21.5% yield; it seems possible that the low yield of product may have been due to concomitant formation of the "dimer" II.

A careful examination of the reaction of I with sodium ethoxide in the presence of oxygen revealed that, in addition to the predominant formation of II, 4,4′-diethoxy-1,1′-dioxy-3,3′-dipicolyl (III, 0.72% yield), 4-ethoxy-3-picoline-1-oxide (IV, 2.9% yield) and a red solid (V, ~5% yield when pure) were formed. By addition of I and *n*-butyl nitrite to a solution of sodium ethoxide in ethanol, the yield of III could be raised to 19% without concomitant formation of II. Since II could not be converted to III with sodium ethoxide in ethanol, even under strenuous conditions, it would appear that III must arise by oxidative coupling of IV initially formed by the reaction of I with sodium ethoxide.



I, R = $-NO_2$
IV, R = $-OC_2H_5$

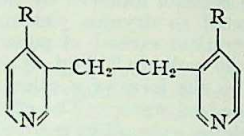


II, R = $-NO_2$
III, R = $-OC_2H_5$
VI, R = $-OH$
VII, R = $-Cl$
VIII, R = $-NHOH$

Formation of the red solid V also was noted in the other preparations of 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl (II), and it could be formed directly from II by hydrogenation in dimethylformamide solution in the presence of palladium-on-carbon catalyst. It was a highly deliquescent material which proved difficult to purify; microanalysis of both V and its picrate indicated a probable empirical formula of $C_{12}H_{11}N_3O_3$, in which one nitrogen atom appears to have been lost from the "dimer" II, perhaps by cyclization across the 4,4′-positions. However, no definitive structure for this compound can be advanced at this time.

Hydrolysis of 4,4′-diethoxy-1,1′-dioxy-3,3′-dipicolyl (III) with two molar equivalents of aqueous potassium hydroxide yielded the dipotassium salt of 4,4′-dihydroxy-1,1′-dioxy-3,3′-dipicolyl (VI); hydrolysis with barium hydroxide yielded the corresponding barium salt, from which VI could be obtained by treatment with sulfuric acid. Attempts to prepare VI directly from II either with alkali or with alkaline hydrogen peroxide were unsuccessful. Somewhat surprisingly, III failed to react with liquid ammonia or with a mixture of sodium amide and liquid ammonia.

Although II failed to react with sodium alkoxides (a reaction typical of 4-nitropyridine-1-oxides),[15] it reacted readily with acetyl chloride to give 4,4′-dichloro-1,1′-dioxy-3,3′-dipicolyl (VII). The chlorine atoms in VII proved to be amazingly inert toward nucleophilic displacement. Thus, VII was recovered unchanged after refluxing in glacial acetic acid for 6 hr., after treatment with liquid ammonia at atmospheric pressure for 30 hr. or after refluxing in concentrated ammonium hydroxide. When VII was heated in a sealed steel bomb with liquid ammonia at 150° for 6 hr., 4,4′-dichloro-3,3′-dipicolyl (IX) was formed, and no displacement of chlorine was observed. This unusual deoxygenation reaction was confirmed by an independent preparation of IX involving catalytic reduction of VII in aqueous hydrochloric acid.



IX, R = $-Cl$
X, R = $-NH_2$

Catalytic reduction of II in aqueous hydrochloric acid led to the exclusive formation of 4,4′-dihydroxylamino-1,1′-dioxy-3,3′-dipicolyl (VIII). Further reduction to the corresponding diamine could not be achieved in this medium. When the reduction was carried out in glacial acetic acid as solvent, 4,4′-diamino-3,3′-dipicolyl (X) was formed, in which the N-oxide functions had also been reduced.

The possibility of utilizing these intermediates for the preparation of condensed heterocyclic systems containing large rings is under investigation.

Experimental[19]

4,4′-Dinitro-1,1′-dioxy-3,3′-dipicolyl (II). Method A.—One hundred and twenty grams (0.78 mole) of 4-nitro-3-picoline-1-oxide was dissolved in 3 l. of absolute ethanol by heating on a steam-bath and the resulting solution was chilled in an ice-bath. To it was added 86 g. (0.83 mole) of cold (0°) *n*-butyl nitrite, followed by the slow addition of a cold (0°) solution of 18 g. (0.78 mole) of sodium in 500 ml. of absolute ethanol. During the addition the reaction mixture was stirred continuously and maintained at 0° by means of a salt–ice-bath. The color of the mixture turned from red to green to blue-green; ten minutes after addition of the sodium ethoxide solution was complete, the color changed to dark brown. The reaction mixture was stirred at 0° for 6 hr. and then poured into 5 l. of ice-cold water. The precipitated yellow solid was collected by filtration, dissolved in concentrated hydrochloric acid and reprecipitated by the addition of water; yield 63 g. (53%), m.p. 240° dec. An analytical sample, m.p. 242° dec., was prepared by repetition of the above procedure.

Anal. Calcd. for $C_{12}H_{10}N_4O_6$: C, 47.1; H, 3.3; N, 18.3; mol. wt., 306.2. Found: C, 47.2; H, 3.2; N, 18.2; mol. wt., 317.0.

Method B.—To a solution of 1.3 g. of sodium hydroxide in 200 ml. of water was added 5.0 g. of 4-nitro-3-picoline-1-oxide. Oxygen was bubbled through the mixture at room temperature (35°) for a total of 3 hr.; a reaction commenced within the first ten minutes. The suspended solid was then filtered, washed with water and dried to yield 1.92 g. (39%) of the "dimer," m.p. 240° dec. The same material was formed in 24% yield when sodium nitrite was used as the oxidizing agent.

Method C.—A solution of 4.60 g. (0.20 mole) of sodium in 250 ml. of absolute ethanol was added slowly to a suspension of 30.8 g. (0.20 mole) of 4-nitro-3-picoline-1-oxide in 1.5 l. of absolute ethanol maintained at 0°. The solution acquired a blue-green color upon the addition of the first few drops of the base; the color soon changed to red. Oxygen was bubbled through the solution for 10 hr.; the temperature was maintained at 0° for the first 2 hr. and then allowed to warm up to 20°. Oxygen was again bubbled through the reaction mixture for 1 hr. after it had stood overnight at room temperature. Filtration then yielded 21 g. of a crude solid product and a dark green filtrate (see below). The solid was extracted with three 400-ml. portions of boiling chloroform, dissolved in concentrated hydrochloric acid and reprecipitated by the addition of ice-water to give 11.5 g.

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(19) All melting points are corrected. The microanalyses were performed by Dr. Joseph F. Alicino, Metuchen, N. J.

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(38%) of 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl, m.p. 240° dec.

4,4′-Diethoxy-1,1′-dioxy-3,3′-dipicolyl (III).—By evaporation of the chloroform extracts above and fractional crystallization of the residue from chloroform, there was obtained 0.22 g. (0.72%) of pale yellow prisms, m.p. 237°. Recrystallization from ethanol raised the m.p. to 245–246° dec.

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.1; H, 6.6; N, 9.2. Found: C, 63.0; H, 6.6; N, 9.2.

By modification of the conditions of the "dimerization" reaction, the yield of this product could be significantly improved. Thus, to a solution of 15 g. (0.65 mole) of sodium in 200 ml. of absolute ethanol was added a solution of 50 g. (0.32 mole) of 4-nitro-3-picoline-1-oxide and 40 g. (0.39 mole) of *n*-butyl nitrite in 1.8 l. of absolute ethanol. The resulting blue-green solution was stirred at 0° for 2 hr. and then at room temperature for an additional 2 hr. Filtration of the solid product and fractional crystallization from ethanol yielded as the least soluble fraction 9.40 g. (19%) of 4,4′-diethoxy-1,1′-dioxy-3,3′-dipicolyl, m.p. 245–246° dec. No 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl was formed in this reaction, and no 4-nitro-3-picoline-1-oxide could be recovered.

4-Ethoxy-3-picoline-1-oxide (IV).—The dark green ethanolic filtrate (method C above) was concentrated to a small volume under reduced pressure to give a brownish-yellow solid and a very dark filtrate. Treatment of the solid with absolute ethanol yielded a small amount (2 g.) of unreacted 4-nitro-3-picoline-1-oxide. The dark filtrate was evaporated to dryness and the residue extracted several times with small portions of ether. Evaporation of the ether extracts yielded 0.9 g. (2.9%) of colorless crystals, m.p. 135–136°. Recrystallization from absolute ethanol raised the melting point to 139–140°. The melting point of this compound has been reported previously as 134–135°.[16]

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.7; H, 7.2; N, 9.2. Found: C, 62.6; H, 7.2; N, 9.2.

Red Side Product (V).—The residue obtained in the above isolation of 4-ethoxy-3-picoline-1-oxide was a red, deliquescent solid. A similar solid was obtained by concentration of the filtrates from methods A and B. It was extracted with boiling chloroform and the red chloroform extracts evaporated to dryness under reduced pressure. Suspension of the residue in ethanol, filtration and recrystallization of the remaining solid from dry chloroform yielded a bright red solid, m.p. 242° dec., which was extremely hygroscopic.

Anal. Calcd. for $C_{12}H_{11}N_3O_3 \cdot 1.5H_2O$: C, 52.9; H, 5.2; N, 15.4. Found: C, 52.1; H, 5.1; N, 15.6.

Addition of picric acid to an aqueous solution of this material yielded a yellow picrate, m.p. 161° dec., which was recrystallized from water.

Anal. Calcd. for $C_{12}H_{11}N_3O_3 \cdot C_6H_3N_3O_7 \cdot {}^1/_2H_2O$: C, 44.7; H, 3.1; N, 17.4. Found: C, 44.7; H, 3.4; N, 16.9.

The same material was obtained from 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl as follows: a mixture of 320 ml. of dimethylformamide, 9.19 g. of 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl and 1.50 g. of 5% palladium-on-carbon catalyst was hydrogenated at 80° and 3 atmospheres pressure for 18 hr. The reaction mixture was then filtered to remove the catalyst and unreacted "dimer," and the red filtrate was concentrated to give 5.5 g. of a red, hygroscopic solid. Conversion of this material to its picrate (m.p. 161°) showed it to be identical with the red compound obtained above.

4,4′-Dihydroxy-1,1′-dioxy-3,3′-dipicolyl (VI).—A mixture of 9.13 g. (0.03 mole) of 4,4′-diethoxy-1,1′-dioxy-3,3′-dipicolyl, 3.37 g. (0.06 mole) of potassium hydroxide and 70 ml. of water was heated under reflux for 20 hr., cooled to room temperature and diluted with a 1:1 mixture of ethanol and acetone. The voluminous, yellow solid which separated was recrystallized from water; yield 6.74 g. (69%), m.p. 355° dec.

Anal. Calcd. for $C_{12}H_{10}N_2O_4K_2$: C, 44.4; H, 3.1; N, 8.6. Found: C, 44.4; H, 3.2; N, 8.6.

By dissolving the dipotassium salt in water and adding palladium chloride, the dipalladium salt of 4,4′-dihydroxy-1,1′-dioxy-3,3′-dipicolyl was obtained as red-brown crystals, m.p. 175–180°.

The barium salt was obtained conveniently by direct hydrolysis of 4,4′-diethoxy-1,1′-dioxy-3,3′-dipicolyl with an equivalent amount of aqueous barium hydroxide. The salt separated from the reaction solution in quantitative yield upon cooling.

Decomposition of the barium salt with sulfuric acid yielded 4,4′-dihydroxy-1,1′-dioxy-3,3′-dipicolyl as a pale yellow solid, m.p. 165–166°, which readily could be recrystallized from water. A satisfactory analytical sample could not be obtained from this material, however, because of its tenacious retention of small amounts of inorganic ions. It is best identified as its dipotassium salt as described above.

4,4′-Dichloro-1,1′-dioxy-3,3′-dipicolyl (VII).—To 90 ml. of cold (0°) acetyl chloride was added 9.19 g. of 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl and the mixture heated under reflux on a steam-bath for 2 hr. The reaction mixture was then poured on 450 g. of crushed ice, the solution adjusted to *p*H 6 with sodium carbonate and extracted several times with chloroform. The combined extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The solid residue was triturated with cold water containing a little sodium carbonate and then recrystallized from ethanol to give 6.02 g. (70%) of white needles, m.p. 212–214° dec. Recrystallization from water raised the melting point to 219° dec.

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2O_2$: C, 50.5; H, 3.5; N, 9.8. Found: C, 50.5; H, 3.8; N, 9.7.

This compound was converted to its dihydrochloride salt, m.p. 245° dec., by recrystallization from 10% aqueous hydrochloric acid.

Anal. Calcd. for $C_{12}H_{12}Cl_4N_2O_2$: C, 40.3; H, 3.4; N, 7.9. Found: C, 40.6; H, 3.6; N, 8.2.

4,4′-Dichloro-3,3′-dipicolyl (IX). Method A.—A mixture of 100 ml. of liquid, anhydrous ammonia and 2.73 g. of 4,4′-dichloro-1,1′-dioxy-3,3′-dipicolyl was sealed in a steel reaction vessel and heated with shaking at 150° for 6 hr. The bomb was then cooled, the excess ammonia bled off and the solid residue recrystallized from aqueous ethanol to give colorless crystals, m.p. 110–111°. The product was further purified by sublimation at 100° (0.02 mm.); m.p. 115–115.5°.

Anal. Calcd. for $C_{12}H_{10}N_2Cl_2$: C, 56.9; H, 4.0; N, 11.1. Found: C, 57.0; H, 4.0; N, 10.5.

Recrystallization of this material from a mixture of dilute hydrochloric acid and ethanol gave the dihydrochloride salt, m.p. 291° dec., which could be sublimed readily at 200° (0.05 mm.).

Anal. Calcd. for $C_{12}H_{12}N_2Cl_4$: C, 44.2; H, 3.7; N, 8.6. Found: C, 44.4; H, 3.7; N, 8.5.

Treatment of 4,4′-dichloro-3,3′-dipicolyl in aqueous ethanol with picric acid yielded a yellow crystalline picrate, m.p. 228° dec., which was purified readily by sublimation at 200° (0.005 mm.).

Anal. Calcd. for $C_{12}H_{10}N_2Cl_2 \cdot 2C_6H_3N_3O_7$: C, 40.5; H, 2.3; N, 15.8. Found: C, 40.5; H, 2.2; N, 15.7.

Method B.—A solution of 2.26 g. of 4,4′-dichloro-1,1′-dioxy-3,3′-dipicolyl in a mixture of 100 ml. of water and 10 ml. of concentrated hydrochloric acid containing 0.8 g. of 5% palladium-on-carbon catalyst was hydrogenated at 3 atmospheres pressure and at room temperature until hydrogen absorption ceased. The catalyst was removed by filtration and the acid filtrate was evaporated to dryness under reduced pressure. Recrystallization of the residue from a mixture of dilute hydrochloric acid and ethanol yielded the dihydrochloride of 4,4′-dichloro-3.3′-dipicolyl, m.p. 291° dec., identical in all respects with the sample prepared above. Likewise, a sample of the free base (m.p. 115°) was also identical with the authentic sample prepared above.

4,4′-Dihydroxylamino-1,1′-dioxy-3,3′-dipicolyl (VIII).—Hydrogenation of 8.42 g. of 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl in 300 ml. of absolute ethanol containing 6 ml. of concentrated hydrochloric acid in the presence of 5% palladium-on-carbon catalyst at 50° under 3 atmospheres pressure was carried out until hydrogen absorption ceased. The reaction mixture was then concentrated to about half its volume, cooled and filtered, and the resulting solid was recrystallized from aqueous hydrochloric acid to give 8.51 g. (88%) of long, colorless prisms, m.p. 228° dec.

Anal. Calcd. for $C_{12}H_{16}N_4O_4Cl_2$: C, 41.0; H, 4.6; N, 16.0. Found: C, 41.0; H, 4.4; N, 15.9.

The dihydrochloride could be converted readily to the yellow free base, m.p. 295–300° dec., by dissolving in water

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and precipitating with ammonium hydroxide. This material proved to be difficult to purify, however, because of its sparing solubility in organic solvents and its tendency to decompose slowly in high boiling solvents such as dimethylformamide. It is best purified and characterized as its dihydrochloride as described above.

4,4′-Diamino-3,3′-dipicolyl (X).—To a suspension of 6.12 g. of 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl in 200 ml. of glacial acid was added 4.5 g. of 5% palladium-on-carbon catalyst, and the mixture was hydrogenated at 3 atmospheres pressure and at 50° until hydrogen absorption ceased (about 5 hr.). The hydrogenation mixture was heated to 70° and filtered from the catalyst, and the filtrate was cooled and diluted with ether. The voluminous white solid which separated was collected by filtration and recrystallized from acetic acid to give 6.68 g. (100%) of 4,4′-diamino-3,3′-dipicolyl diacetate as colorless crystals, m.p. 115–116°.

Anal. Calcd. for $C_{16}H_{22}N_4O_4$: C, 57.5; H, 6.6; N, 16.8. Found: C, 57.2; H, 6.8; N, 16.9.

The free base was prepared in 75% yield by addition of aqueous sodium hydroxide to a saturated aqueous solution of the above diacetate. Recrystallization of the precipitated solid from ethanol–acetone yielded colorless prisms, m.p. 250–251°.

Anal. Calcd. for $C_{12}H_{14}N_4$: C, 67.3; H, 6.6; N, 26.2. Found: C, 67.2; H, 6.5; N, 26.3.

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TULANE UNIVERSITY]

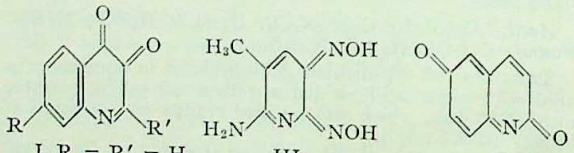
Azaquinones. I. Oxidation of Certain Hydroxy- and Aminopyridones[1]

BY J. H. BOYER AND S. KRUGER

RECEIVED JANUARY 26, 1957

Hydroxylation at unsubstituted α-positions during oxidation of aminopyridones, V and VI (R = H, CH_3), or 3-hydroxypyridone-2 with manganese dioxide, chromium trioxide or potassium bromate (preferred) brought about the formation of tautomeric hydroxyazaquinones (VII ⇄ VIII, R = H, CH_3), isolated as quinhydrones. Reductive acetylation produced 2,3,6-triacetoxypyridine (X, R = H). Attempts to prepare 4-azabenzoquinone were unsuccessful.

Kudernatsch introduced azaquinones to the chemical literature by an oxidation of 2,3-dihydroxypyridine.[2] More recently 4-azanaphthquinone-1,2 (I)[3] as an impure yellow powder, its 3-hydroxy-6-methyl- derivative (II)[4] as light yellow needles and the dioxime (III) of 3-aza-4-amino-5-methylbenzquinone-1,2[5] as red needles have been reported. Derivatives of 1-azanaphthquinone-2,6 (IV) were considered as intermediates in the oxidation of derivatives of 6-hydroxycarbostyril into red carbostyril-5,6-quinones.[6]



I, R = R′ = H
II, R = CH_3, R′ = OH

III

IV

Two general methods for the preparation of azaquinones were selected for preliminary investigations. The oxidation of certain aminopyridones is reported here; the transformation of azaquinone dioximes into quinones is under investigation.

Satisfactory oxidations of aminopyridones (V, VI, R = H, CH_3) were carried out in cold sulfuric acid with deficient amounts of manganese dioxide, chromium trioxide or potassium bromate (preferred). Bromate oxidation of 5-aminopyridone-2 (VI, R = H) occurred at a convenient rate at 0° whereas 3-aminopyridone-2 (V, R = H) required cooling to −20° for control of the reaction. Attempts to oxidize 3-aminopyridone-4 with deficient amounts of bromate even at −50° led to the formation of intractable tars. From each of 3- and 5-aminopyridone-2 and from 3-hydroxypyridone-2, a deep purple solid was obtained and was separated into two fractions by Soxhlet extraction with ethanol.

Oxidation of V (R = CH_3) and VI (R = CH_3) was successful at higher temperatures (*ca.* 25°); however, to avoid decomposition a deficient amount of bromate again was necessary. The deeply colored products appeared to be quinhydrones (VIII · VI and VII · V, R = CH_3). A condensation product from VII · V (R = CH_3) and phenylhydrazine was identified with a reported product from phenylhydrazine and XI.[7] This established the occurrence of hydroxylation at unsubstituted α-positions during the oxidation of V, VI (R = CH_3). Hydroxylation of a pyridine ring had previously been observed in the oxidation of 2-hydroxy-7-methylquinoline,[4] in the oxidation of 1,4-dihydroxyisoquinoline into yellow phthalonimide (X)[8a] and in the permanganate oxidation of 3,4-dihydroxypyridine-6-carboxylic acid into 2,3,4-trihydroxypyridine-6-carboxylic acid.[8b]

Elemental analyses and reductive acetylation demonstrated that hydroxylation, presumably at an α-position, had also occurred during the oxidation of V, VI (R = H) into hydroxyazabenzquinones (VII ⇄ VIII, R = H) and their quinhydrones with 2,3,6-trihydroxypyridine. The trihydroxypyridine was an expected product of the reversible oxidation–reduction between an aminopyridone and an hydroxyazaquinone. Impure quinhydrones, VII·V or VIII·VI (R = H), were apparently obtained in certain experiments. At-

(1) Partial support of this work under a National Institutes of Health Grant No. RG-4210 is gratefully acknowledged. Presented at the 129th American Chemical Society National Convention, Dallas, Texas, April, 1956.

(2) R. Kudernatsch, *Monatsh.*, **18**, 613 (1897); O. v. Schickh, A. Binz and A. Schulz, *Ber.*, **69**, 2593 (1936). In the present series, azaquinone designates nitrogen as a member of the quinone ring.

(3) M. Passerini, T. Bonciani and N. Di Gioia, *Gazz. chim. ital.*, **61**, 959 (1931).

(4) O. Kruber and L. Rappen, *Ber.*, **81**, 483 (1949).

(5) J. H. Boyer and W. Schoen, THIS JOURNAL, **78**, 423 (1956).

(6) R. R. Holmes, J. Conrady, J. Guthrie and R. McKay, *ibid.*, **76**, 2400 (1954).

(7) S. Ruhemann, *Ber.*, **27**, 1272 (1894).

(8) (a) S. Gabriel and J. Colman, *ibid.*, **35**, 2421 (1902); (b) T. Kotalen, *J. prakt. Chem.*, [2] **24**, 286 (1881); *Ber.*, **14**, 2692 (1881).

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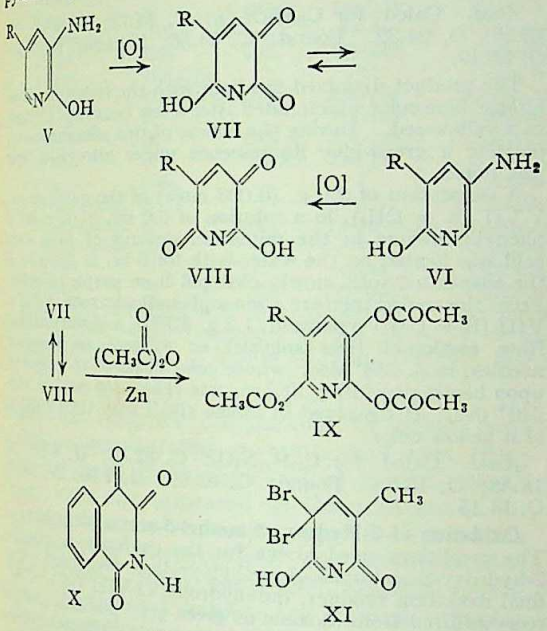
tempts to repeat Kudernatsch's preparation of 3-azabenzquinone-1,2, a brown-violet powder, from 3-hydroxypyridone-2 and manganese dioxide[2] resulted, instead, in the formation of hydroxyazaquinones or their quinhydrones, identical with the oxidation products from the corresponding aminopyridone. Unidentified material was obtained upon refluxing samples of the oxidation product in acetic anhydride; however, reductive acetylation produced the previously unknown, 2,3,6-triacetoxypyridine (IX, R = H) in good yield.



Experimental[9]

Reduction of Nitropyridones.—According to a method described by Crowe for the reduction of 3-nitro-4-hydroxypyridine,[10] 3-nitropyridone-2[11] and 5-nitropyridone-2[11] were reduced by tin and hydrochloric acid to 3-aminopyridone-2 hydrochloride and 5-aminopyridone-2 hydrochloride in 85–90% yields.

Oxidation of 2-Hydroxy-5-aminopyridine.—A suspension of 3.0 g. (0.02 mole) of the amine hydrochloride in 25 ml. of concentrated sulfuric acid was warmed gently until hydrogen chloride evolution had ceased. The mixture was cooled and poured onto 50 g. of ice. A solution of 1.1 g. (0.0066 mole; 0.010 mole required for oxidation to the hydroquinone, $C_{10}H_8N_2O_6$; 0.0134 mole for the quinone, $C_5H_3NO_3$) of potassium bromate in 25 ml. of water was then rapidly added with stirring. The temperature of the reaction was not allowed to rise above 5°. The reaction mixture remained for several hours at 3–5° as a purple precipitate slowly separated. This was isolated by filtration, washed with ice-water and dried. A Soxhlet extraction of the dried solid with absolute ethanol was extended over a one-week period; however, several hours were sufficient for the extracting liquid portions to become colorless. After several recrystallizations from N,N-dimethylformamide and from molten acetanilide, the Soxhlet insoluble fraction separated as purple-brown micro-crystals with a metallic green sheen, 0.80 g. (47%).[12] It was very insoluble in all common organic solvents and had an indefinite decomposition range above 300°.

Anal. Calcd. for $C_5H_3NO_3$: C, 47.99; H, 2.42; N, 11.20. Calcd. for $C_{10}H_8N_2O_6$: C, 47.62; H, 3.20; N, 11.11. Found: C, 48.14, 48.16; H, 2.83, 2.70; N, 11.61, 11.99.

Upon concentration and cooling, the alcohol solution obtained from the Soxhlet extraction afforded red-brown leaflets, 0.40 g. (23%, total yield 70%).[12] This fraction was slightly soluble in common solvents and recrystallized from ethanol or methanol as purple-brown rhombs with indefinite decomposition above 300°. With the exception of ethanol solubility these two fractions appeared to be identical.

Anal. Calcd. for $C_5H_3NO_3$: C, 47.99; H, 2.42; N, 11.20. Calcd. for $C_{10}H_8N_2O_6$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.86, 47.65; H, 2.72, 3.31; N, 11.50, 11.15.

Attempts to carry out the oxidation with the theoretical amount of potassium bromate (at least 0.50 mole per mole of aminopyridone) led to excessive decomposition of organic material. The oxidation was also carried out with chromium trioxide in sulfuric acid.

Both the soluble and insoluble fractions of oxidation product dissolved in alkali. The formation of an intense blue color faded rapidly as decomposition progressed with the absorption of oxygen and evolution of ammonia. The alkaline solutions finally became red-yellow and fluoresced in ultraviolet light.

Oxidation of 2-Hydroxy-3-aminopyridine.—A suspension of 1.0 g. (0.0066 mole) of 2-hydroxy-3-aminopyridine hydrochloride in 10 ml. of concentrated sulfuric acid was warmed until evolution of hydrogen chloride gas had ceased. The solution was then maintained at −20° as 0.3 g. (0.003 mole; 0.0066 mole required for oxidation to the hydroquinone $C_{10}H_8N_2O_6$; 0.010 mole for the quinone, $C_5H_3NO_3$) of chromium trioxide in 5 ml. of concentrated sulfuric acid was added with stirring. The mixture was held at −20° for an additional 2 hr., slowly warmed to room temperature, poured onto ice and filtered. The purple precipitate (0.25 g., 62%)[12] was identical with the oxidation product obtained from 2-hydroxy-5-aminopyridine and separated into soluble and insoluble fractions upon Soxhlet extraction with absolute ethanol.

Reductive Acetylation.—A mixture of 0.1 g. (0.8 mmole) of either the ethanol-soluble or the ethanol-insoluble fraction of the above oxidation product obtained from the oxidation of either 2-hydroxy-3-aminopyridine or 2-hydroxy-5-aminopyridine and 0.5 g. zinc dust in 3 ml. of acetic anhydride was heated at water-bath temperature until all solid material had dissolved and the solution became pale yellow. A pale blue fluorescence to ultraviolet light developed during the reaction. The hot solution was filtered and excess solvent was removed *in vacuo*. Upon recrystallization from ethanol the residue separated as pale yellow crystals, 0.15 g. (75%), m.p. 135–140°. Further purification of a chloroform solution of the product by chromatographic separation on an alumina column easily was followed by the compound's characteristic blue fluorescence to ultraviolet light. The product upon additional recrystallization from ethanol produced pale cream platelets, m.p. 159°, of 2,3,6-triacetoxypyridine (X, R = H).

Anal. Calcd. for $C_{11}H_{11}NO_6$: C, 52.15; H, 4.38; N, 5.53; O, 37.94. Found: C, 52.58; H, 4.30; N, 5.78; O, 36.90.

Samples of 2,3,6-triacetoxypyridine obtained from each hydroxyazaquinone fraction obtained from each of the isomeric aminopyridones were identical as established by m.p. and mixture m.p. determinations.

Oxidation of 2,3-dihydroxypyridine by either Kudernatsch's procedure using manganese dioxide or by the present method using potassium bromate led to the formation of the ethanol-soluble and -insoluble fractions obtained above. A trace amount of an unidentified light yellow solid, m.p. >300° dec., was slowly collected over a period of two days upon attempted sublimation of a sample of the insoluble fraction at 250–280° (10^{-4} mm.) (*Anal.* Found: C, 47.62; H, 3.20; N, 11.11). In agreement with the previous results both fractions were transformed by reductive acetylation into 2,3,6-triacetoxypyridine, m.p. 159°.

Attempts to oxidize **3-amino-4-hydroxypyridine hydrochloride**[13] were unsuccessful and led to the formation of intractable red tars even with insufficient amounts of oxidizing agent at −50°.

(9) Analyses by Micro-tech Laboratories, Skokie, Ill.; Alfred Bernhardt, Mikroanalytisches Laboratorium, Max-Planck Institute, Mulheim (Ruhr), Germany; Midwest Microlab Inc., Indianapolis, Ind. Melting points are uncorrected.

(10) W. M. Crowe, *J. Chem. Soc.*, **127**, 2028 (1925).

(11) W. T. Caldwell and E. O. Kornfeld, THIS JOURNAL, **64**, 1695 (1942).

(12) The yield is based upon the oxidizing agent ($KBrO_3$ or CrO_3) and assumes the product to be a quinhydrone, $C_{10}H_8N_2O_6$.

(13) S. Kruger and F. G. Mann, *J. Chem. Soc.*, 2755 (1955).

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Preparation of 3-Nitro-4-azidopyridine.—A solution of 3.2 g. (0.02 mole) of 3-nitro-4-chloropyridine and 2.6 g. (0.04 mole) of sodium azide in 23 ml. of methanol and 2 ml. of water was warmed to 35–40° for 10 minutes. The solution was filtered and concentrated to half its volume. Upon cooling, the azide separated as pale yellow crystalline rods, 2.55 g. (76.5%), m.p. 89° dec.

Anal. Calcd. for $C_5H_3N_5O_2$: C, 36.36; H, 1.83; N, 42.42. Found: C, 36.28; H, 2.03; N, 41.94.

Upon warming slightly above 90° for a few seconds decomposition occurred with a violent evolution of gas and formation of a yellow oil which changed rapidly into a dark-colored insoluble solid residue which neither melted nor decomposed under 300°.

Aminomethylpyridones.—Nitration of 2-amino-5-methylpyridine[14] followed by diazotization and hydrolysis afforded 2-hydroxy-3-nitro-5-methylpyridine, m.p. 253–255°, in 38% yield. To a suspension of 30.8 g. (0.2 mole) of this nitro compound in 400 ml. of 2% acetic acid, an excess of iron filings was added. The mixture was warmed on the water-bath with occasional stirring until the yellow color of the nitro compound had disappeared. The mixture was then neutralized with calcium carbonate, filtered while hot and the precipitate was washed several times with hot water. An excess of acetic anhydride was added with stirring to the filtrate, externally cooled in an ice-bath. The isolated precipitate was recrystallized from ethanol from which 2-hydroxy-3-acetamido-5-methylpyridine separated as rhombic leaflets, m.p. 253° (with slight sublimation), 22.2 g. (67%). A change in crystalline form from rhombic leaflets into needles occurred around 220°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.03; N, 16.87. Found: C, 57.89; H, 6.05; N, 17.14.

Nitration of 2-amino-3-methylpyridine[14] followed by diazotization and hydrolysis brought about the formation of 2-hydroxy-3-methyl-5-nitropyridine in 71% yield.[15] According to the above directions it was reduced and acetylated in 69% yield. Upon recrystallization from ethanol, 2-hydroxy-3-methyl-5-acetamidopyridine separated as colorless needles, m.p. 247°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.03; N, 16.87. Found: C, 57.44; H, 6.36; N, 16.45.

Oxidation of 2-Hydroxy-3-acetamido-5-methylpyridine.—A suspension of 3.0 g. (0.018 mole) of 2-hydroxy-3-acetamido-5-methylpyridine in 50 ml. of 16% (by volume) sulfuric acid was heated at 95–100° for 5 minutes. Longer heating at this stage diminished the final yield. The pale yellow solution was cooled to 25°, and 1.0 g. (0.006 mole) of potassium bromate in 25 ml. of water was added in one portion. The solution turned purple immediately and was cooled externally so that the temperature was held under 40°. A marked decrease in yield was observed if the temperature at this stage was allowed to reach 50–55°. A violet-brown precipitate separated from a blue solution upon standing at room temperature for 2 hr. and in the refrigerator for 24 hr. The crude product, 0.7 to 1.0 g. (29 to 42%), was washed with cold water and dried. An increase in the molar ratio of bromate resulted in nearly complete destruction of this product. Recrystallization from methanol allowed the separation of thin birefringent green-gray leaflets of impure quinhydrone, V·VII (R = CH_3), indefinite decomposition above 300°, from a deep purple supernatant liquid.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 54.73; H, 4.98; N, 15.96; O, 24.32. Found: C, 54.56; H, 4.94; N, 14.99; O, 25.49.

The product dissolved in alkali with the formation of an intense blue color which faded after a few hours and changed to a yellow-red. During the course of this alkaline decomposition a green-blue fluorescence under ultraviolet light was noted.

A suspension of 2.0 g. (0.008 mole) of the quinhydrone, V VII (R = CH_3), in a solution of 5.0 ml. (0.05 mole) of phenylhydrazine in the minimum amount of 10% acetic acid was heated on the water-bath for 6 hr. as the color of the suspended solid slowly changed from purple to brown. From the cooled mixture a monophenylhydrazone of VII ⇄ VIII (R = CH_3) separated, 1.2 g. (67%), and recrystallized from methanol (less soluble) or ethanol as brown-red needles, m.p. 254° dec., whose color changed to yellow-red upon heating to 210°; lit.[7] reports yellow-red needles, m.p. 240° dec. It dissolved in dilute alkali with the formation of a yellow color.

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.85; N, 18.38; O, 13.89. Found: C, 62.69; H, 4.90; N, 18.11; O, 14.15.

Oxidation of 2-Hydroxy-3-methyl-5-acetamidopyridine.—The conditions used above for the oxidation of isomeric 2-hydroxy-3-acetamido-5-methylpyridine were used. The final oxidation product, quinhydrone VI·VIII (R = CH_3), recrystallized from dioxane as green-gray platelets and decomposed above 300°. The deep purple dioxane solutions of this product were stable for short times only and soon became red-yellow in color with the simultaneous formation of a green-blue fluorescence to ultraviolet light. It was also soluble in alkali with decomposition and with the development of a green-blue fluorescence.

Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.73; H, 4.98; N, 15.96; O, 24.32. Found: C, 55.02; H, 4.88; N, 15.07; O, 24.63.

NEW ORLEANS, LOUISIANA

(14) Obtained from Reilly Tar and Chemical Co., Indianapolis, Ind.

(15) G. F. Hawkins and A. Roe, *J. Org. Chem.*, **14**, 328 (1949).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

The Pyridylethylation of Indole and Related Reactions

BY ALLAN P. GRAY AND WESLEY L. ARCHER

RECEIVED JANUARY 19, 1957

Pyridylethylation of indole and 1-substituted indoles in refluxing glacial acetic acid smoothly yielded 3-indolylethylpyridine derivatives. In ethanol containing a catalytic amount of sodium ethoxide, indole added to 4-vinylpyridine to provide 4-(1-indolylethyl)-pyridine. Under alkaline conditions indene yielded monopyridylethylated products which are tentatively formulated as 3-indenyl derivatives. Indole and 1-methylindole readily condensed with pyridinecarboxaldehydes in glacial acetic acid at room temperature to give relatively unstable di-indolylmethylpyridine products. Fischer cyclization in polyphosphoric acid of the phenylhydrazones of 3- and 4-acetylpyridine afforded the corresponding 2-indolylpyridines. The methobromide of 4-(2-indolyl)-pyridine gave no evidence of anhydronium base formation. Catalytic hydrogenation of the methobromides of many of the indolyl-substituted pyridines yielded the 1-methylpiperidine derivatives.

A general interest in pyridine derivatives with relatively large substituents[1] prompted this investigation. Although primary concern in the present paper is with a study of the reactions of indole and its 1-substituted derivatives with vinylpyridines and pyridinecarboxaldehydes, preparations of some related bases also are discussed.

Pyridylethylation.—The experiments of Doering and Weil[2] established 2- and 4-vinylpyridine as

(1) *E.g.*, A. P. Gray, W. L. Archer, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **79**, July 20 (1957).

(2) W. E. Doering and R. A. N. Weil, *ibid.*, **69**, 2461 (1947).

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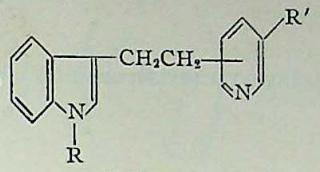
TABLE I

INDOLYLETHYLPYRIDINES



	Vinylpyridine	R	Salt	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, %[b] Calcd.	Halogen, %[b] Found	Nitrogen, %[c] Calcd.	Nitrogen, %[c] Found
	4-Vinyl-	H	..	149–151	$C_{15}H_{14}N_2$							6.30	6.32
I	4-Vinyl-	H	HCl	260–262	$C_{15}H_{15}ClN_2$	69.62	69.78	5.84	5.78	13.70	13.71		
	4-Vinyl-	H	CH_3Br	211–213	$C_{16}H_{17}BrN_2$	60.57	60.64	5.40	5.36	25.19	25.11		
	4-Vinyl-	CH_3	..	96–98	$C_{16}H_{16}N_2$							5.93	5.99
II	4-Vinyl-	CH_3	HCl	152–153	$C_{16}H_{17}ClN_2$	70.45	70.85	6.28	5.87	13.00	13.09		
	4-Vinyl-	$C_6H_5CH_2$	..	[d]	$C_{22}H_{20}N_2$							4.48	4.51
III	4-Vinyl-	$C_6H_5CH_2$	HCl	199–200	$C_{22}H_{21}ClN_2$	75.74	75.47	6.07	5.96	10.16	9.95		
	4-Vinyl											6.30	6.41
IV	2-Vinyl-	H	..	118–120	$C_{15}H_{14}N_2$								
	2-Vinyl-	H	HCl	157–159	$C_{15}H_{15}ClN_2$	69.62	69.65	5.84	6.07	13.70	13.58		
	2-Vinyl-	H	CH_3Br	226–227	$C_{16}H_{17}BrN_2$	60.57	60.67	5.40	5.45	25.19	25.17		
V	2-Vinyl-	CH_3	..	[f]	$C_{16}H_{16}N_2$							5.93	6.12
VI	2-Vinyl-5-ethyl	H	..	112–113	$C_{17}H_{18}N_2$							5.60	5.61
	2-Vinyl-5-ethyl	H	HCl	164.5–165.5	$C_{17}H_{19}ClN_2$	71.19	70.96	6.68	6.54	12.36	11.94		
VII	2-Vinyl-5-ethyl	CH_3	..	[g]	$C_{18}H_{20}N_2$							5.30	5.57
VIII	4-Vinyl-	[d]	..	41–45	$C_{15}H_{14}N_2$							6.30	6.31
	4-Vinyl-	[d]	HCl	206–208	$C_{15}H_{15}ClN_2$	69.62	69.46	5.84	5.45	13.70	13.83		

[a] Most of the salts melt with decomposition. [b] Ionic halogen determinations. [c] Basic nitrogens by acetous–perchloric titration. [d] The 1-indolyl isomer of I; (*i.e.*, R = H; R and the 4-pyridylethyl moiety are interchanged). [e] Thick oil, b.p. 220–230° (0.3 mm). [f] Yellow oil, b.p. 170–185° (0.5 mm.), $n^{25}D$ 1.6140. [g] Yellow oil, b.p. 175–185° (0.4 mm.), $n^{25}D$ 1.5957.

electrophilic reagents comparable to other conjugated α,β-unsaturated systems, and this reactivity has been much exploited in recent years.[3] Reports have also appeared on the addition of indole and its derivatives to conjugated olefins such as acrylonitrile,[4] nitroethylene[5] and to substituted acrylic acids.[6] Under controlled alkaline conditions, N-substituted indoles are formed, whereas acid catalysis, high temperatures or use of a Grignard reagent directs reaction to the 3-position. Although Reich and Levine[3] have 2-pyridylethylated pyrrole at the 1-position under alkaline conditions, no report of the pyridylethylation of indole has come to our attention.

In the present work main interest centered on the preparation of 3-substituted indole derivatives. Acetic acid was found to provide an excellent solvent-catalyst for this purpose. Thus, refluxing a glacial acetic acid solution of indole and 4-vinylpyridine smoothly afforded 4-(3-indolylethyl)-pyridine (I) in approximately 70% yield. The 2-indolylethylpyridines II through VII, listed in Table I, were prepared in similar fashion. On the other hand, when indole was 4-pyridylethylated in an ethanol solution containing small amounts of sodium ethoxide and copper sulfate (polymer inhibitor), 4-(1-indolylethyl)-pyridine (VIII) was obtained in 57% yield.

Although an ample basis already exists for the structural assignments, a few points may be worthy of mention. In this connection may be noted the infrared spectrum[7] of I which exhibits an intense absorption band in the N–H stretching region. The spectrum of VIII, however, possessed a very weak band in the same region, suggesting the contamination of this compound by a small amount of I. (This is not too surprising in view of the long appreciated difficulties in obtaining *pure* 1-alkylated indole derivatives.) Catalytic hydrogenation of the methobromide of 2-(3-indolylethyl)-pyridine (IV) readily provided 2-(3-indolylethyl)-1-methylpiperidine (XI), the melting point of which agreed with that of the compound obtained by the catalytic hydrogenation of the condensation product from 3-indolecarboxaldehyde and 2-picoline methohalide (see footnote *d*, Table II). Finally, as is apparent from Table I, 1-methyl- and 1-benzylindole also smoothly afforded pyridylethylated derivatives in hot glacial acetic acid.

The 1-substituted indoles, as anticipated,[8] were more sluggish than indole in the acetic acid catalyzed reaction, albeit comparable yields of the products were obtained after more prolonged refluxing. It is interesting to note that acetic acid solutions of 1-methylindole (but not indole) developed an emerald green color on warming. Although this is suggestive of the formation of the indolenine salt, it probably has no mechanistic bearing on the reaction. Indeed, the only logical path for acid catalysis would seem to be *via* protonation of the vinylpyridine, thus polarizing the molecule and lowering the transition state energy.[9] Yields obtained from 4-vinylpyridine were somewhat better than from the 2-isomer and markedly

(3) See (among others): V. Boekelheide and J. H. Mason, *ibid.*, **73**, 2356 (1951); H. E. Reich and R. Levine, *ibid.*, **77**, 4913 (1955); G. Magnus and R. Levine, *ibid.*, **78**, 4127 (1956); A. P. Phillips, *ibid.*, **78**, 4441 (1956).

(4) I. G. Farbenind. A. G., British Patent 457,621 (1936) [*C.A.*, **31**, 3098 (1937)]; A. P. Terent'ev, A. N. Kost, and V. A. Smit, *Zhur. Obshchei Khim.*, **26**, 557 (1956) [*C. A.*, **50**, 13871*h* (1956)]; H. Erdtman and A. Jönsson, *Acta Chem. Scand.*, **8**, 119 (1954) [*C. A.*, **49**, 13963*a* (1955)].

(5) W. E. Noland and P. J. Hartman, THIS JOURNAL, **76**, 3227 (1954).

(6) H. R. Snyder and J. A. MacDonald, *ibid.*, **77**, 1257 (1955).

(7) Infrared spectra were determined by the Sadtler Research Laboratories, Philadelphia, Pa.

(8) *Cf.* H. R. Snyder and E. L. Eliel, THIS JOURNAL, **70**, 1703 (1948); A. P. Gray, *ibid.*, **75**, 1252 (1953).

(9) *Cf.* Phillips, and Reich and Levine (ref. 3). These authors, whose papers on the acetic acid catalyzed additions of amines to vinylpyridines appeared after the present work was completed, seem to envision the role of acid as acting in ways which should not affect the rate of reaction.

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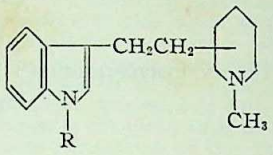
TABLE II

INDOLYLETHYLPIPERIDINES

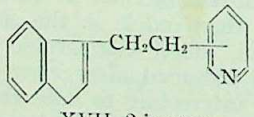


	Position of attachment to piperidine	R	Salt	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, %[b] Calcd.	Chlorine, %[b] Found	Nitrogen, %[b] Calcd.	Nitrogen, %[b] Found
IX	4	H	..	171–173	$C_{16}N_{22}N_2$							5.78	5.70
	4	H	HCl	206–208	$C_{16}H_{23}ClN_2$	68.92	69.23	8.31	8.06	12.72	12.37		
X	4	CH_3	..	158–160	$C_{17}H_{24}N_2$							5.46	5.73
	4	CH_3	HCl	143–145	$C_{17}H_{25}ClN_2$	69.72	68.99	8.61	8.66	12.11	11.56		
XI	2	H	..	137–138[d]	$C_{16}H_{22}N_2$							5.78	5.64
	2	H	HCl	170–173	$C_{16}H_{23}ClN_2$	68.92	69.19	8.31	7.85	12.72	12.51		
							68.90		8.05		12.62		
XII	2	CH_3	..	[e]	$C_{17}H_{24}N_2$							5.46	5.59
	2	CH_3	HCl	187–188	$C_{17}H_{25}ClN_2$	69.72	69.72	8.61	8.53	12.11	11.87		

[a,b,c] See corresponding footnotes of Table I. [d] J. Finkelstein and J. Lee, U. S. 2,695,290 (1954), reported m.p. 138–140°; A. M. Ackerman and H. Veldstra, *Rec. trav. chim.*, **73**, 629 (1954), gave m.p. 141° for this compound prepared by a different method. [e] Low melting solid, b.p. 165–167° (0.5 mm.).

better than from 2-vinyl-5-ethylpyridine (see Experimental part); this, however, could have been a result of differences in ease of isolation of the products.

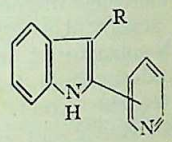
In connection with this program, indene was added, under alkaline conditions, to both 2- and 4-vinylpyridine. Catalysis with either sodium ethoxide or sodamide furnished rather modest yields of monopyridylethylated indene products accompanied by considerable tar. Optimum yields were obtained when excess indene was used. Increasing the proportion of vinylpyridine lowered the yield of mono-derivative, although no pure poly-pyridylethylated materials were isolated. In comparison, cyanoethylation using Triton B affords tris-(cyanoethyl)-indene.[10] Although no experimental evidence as to structure was obtained, these products are tentatively formulated as 3-indenylethylpyridines in view of the facile isomerization of 1-substituted into the presumably more stable 3-substituted indenes under very mild alkaline conditions.[11]



XVII, 2-isomer
XVIII, 4-isomer

Pyridinecarboxaldehyde Reactions.—Indole has long been known to condense readily with carbonyl compounds, *e.g.*, under acid or Grignard conditions. This nucleophilic reactivity has been fruitfully exploited in the Mannich reaction and in the preparation of arylidene and diindolylmethyl derivatives.[12] The corresponding reactions of indole and of 1-methylindole with the pyridinecarboxaldehydes proceeded exothermically in glacial acetic acid at room temperature to provide fair yields (50–75%) of the diindolylmethylpyridine derivatives described in Table III. As has been previously noted for diindolylmethyl derivatives,[12] these products were relatively unstable and underwent disproportionation and air oxidation to highly colored materials.

XIX, 3-isomer, R = H
XX, 4-isomer, R = H



Related Derivatives.—3- and 4-(2-indolyl)-pyridine were prepared by the Fischer indole synthesis from the phenylhydrazone of the corresponding acetylpyridine. Although a few (3-alkyl-2-indolyl)-pyridines have been prepared[13] by Fischer cyclization from the appropriate pyridyl ketone, apparently none of the *unsubstituted* 2-indolylpyridines have been obtained previously. In this context it is noteworthy that attempted cyclization of the phenylhydrazone of 4-acetylpyridine under the conditions successfully employed[13] for the preparation of the 2- and 3-isomers of XIX in which R = methyl or ethyl (*i.e.*, hydrogen chloride in refluxing ethanol) resulted in almost quantitative recovery of the starting phenylhydrazone. Even hydrogen chloride in refluxing glacial acetic acid gave back only starting material (80% recovery). XIX and XX were satisfactorily (55–65% yield) obtained, however, by somewhat harsher treatment with polyphosphoric acid.[14] The markedly

It might be noted in passing that in attempted Mannich reactions of indole with *substituted* aldehydes in place of formaldehyde (benzaldehyde, *p*-dimethylaminobenzaldehyde) and dimethylamine in aqueous acetic acid at room temperature, good yields of phenyldiindolylmethane and *p*-dimethylaminophenyldiindolylmethane (respectively) were obtained as the only products (unpublished results from this Laboratory).

(10) H. A. Bruson, THIS JOURNAL, **64**, 2457 (1942).

(11) See E. H. Rodd, "The Chemistry of Carbon Compounds," Vol. IIIB, Elsevier Publishing Co., 1956, pp. 1257–1259, for an authoritative account.

(12) See P. L. Julian, E. W. Meyer and H. C. Printz in Elderfield, "Heterocyclic Compounds," Vol. III, John Wiley and Sons, Inc., New York, N. Y., pp. 93–95.

Also see H. v. Dobeneck and J. Maas, *Chem. Ber.*, **87**, 455 (1954); A. Treibs and E. Herrmann, *Hoppe-Seyler's Z. Physiol. Chem.*, **289**, 168 (1955) [*C. A.*, **50**, 943i (1956)]; K. Dahlbom and A. Misiorny, *Acta Chem. Scand.*, **9**, 1074 (1955) [*C. A.*, **50**, 13869i (1956)].

(13) F. B. LaForge, THIS JOURNAL, **50**, 2477 (1928); R. M. Anderson, G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 2962 (1954); Yeeson, *ibid.*, 2865 (1955).

(14) H. M. Kissman, D. W. Farnsworth and B. Witkop, THIS JOURNAL, **74**, 3948 (1952).

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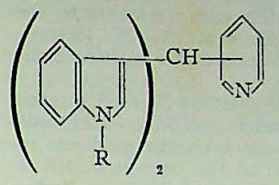
TABLE III

DIINDOLYLMETHYLPYRIDINES

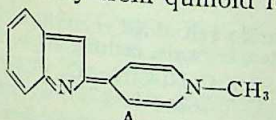


	Position of attachment to pyridine	R	Salt	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, %[b] Calcd.	Halogen, %[b] Found	Nitrogen, %[c] Calcd.	Nitrogen, %[c] Found
XIII	4	H	..	152–155	$C_{22}H_{17}N_3$							4.33	4.09
	4	H	HCl	204–205	$C_{22}H_{18}ClN_3$	73.43	73.70	5.04	5.45	9.85	9.30		
	4	H	CH_3Br	239–240	$C_{23}H_{20}BrN_3$	66.03	66.32	4.82	5.01	19.10	18.83		
XIV	4	CH_3	..	186–188	$C_{24}H_{21}N_3$	82.02	82.25	6.02	5.94				
	4	CH_3	HCl	224–225	$C_{24}H_{22}ClN_3$	74.31	74.59	5.72	5.47	9.14	8.74		
XV	3	H	..	162–163	$C_{22}H_{17}N_3$							4.33	3.96
	3	H	HCl	214–215	$C_{22}H_{18}ClN_3$	73.43	73.29	5.04	5.15	9.85	9.04		
XVI	2	H	..	208–210	$C_{22}H_{17}N_3$							4.33	4.23
	2	H	HCl	218–220	$C_{22}H_{18}ClN_3$	73.43	73.31	5.04	4.91	9.85	9.68		

[a] These compounds melt with decomposition. [b,c] See corresponding footnotes of Table I.

greater stability of the phenylhydrazones of methyl *vs.* methylene ketones to acid is well known and presumably can be ascribed to the relative stabilities of the respective carbonium ions (prim. *vs.* sec.). Reaction of the phenylhydrazone of 3-acetylpyridine in polyphosphoric acid was decidedly less violent than that of the 4-isomer, the product was obtained in poorer yield and accompanied by more tar.

Of incidental interest is the fact that the methobromide of XX (or XIX) gave no indication of anhydronium base formation in aqueous alcohol by titration with 0.1 *N* NaOH.[15] In contrast to the carboline anhydronium bases, the properties of which seemed to correspond more closely to the charge-separated structures,[15] the present information points up the importance of resonance contributions to stability from quinoid forms; *i.e.*, A



A

should contribute very little to over-all stabilization.[16]

Catalytic hydrogenation of the methobromides of a number of the indolyl-substituted pyridines readily yielded the corresponding 1-methylpiperidines; most of these are listed in Table II.

NOTES ADDED IN PROOF.—After this paper had been accepted for publication, the abstract of an article [S. Sugasawa, M. Terashima and Y. Kanaoka, *Pharm. Bull.* (Japan), 4, 16 (1956) [*C. A.*, 51, 3593*d* (1957)]] appeared describing the preparation of 2-, 3-, and 4-(2-indolyl)-pyridine by essentially the same procedure (polyphosphoric acid cyclization) employed here. Physical properties of the products and derivatives are in good agreement. It is recognized, as mentioned in a private conversation with Dr. W. E. Noland at the Miami meeting, that pure 3,3′-diindolylmethylpyridines should be colorless. The analytical data and the fact that the compounds are all monoacidic bases argue against formulation of the materials as the rosindole oxidation products. This question is being further investigated.

Acknowledgment.—The authors are grateful to Dr. C. J. Cavallito for continued interest and encouragement. Ionic halogens and basic nitrogens were determined by Mr. Dean F. Cortright.

Experimental[17]

Intermediates.—1-Methylindole, b.p. 114–115° (14 mm.), $n^{25}D$ 1.6038, was obtained in 80–85% yield by the reaction of indole with sodamide and dimethyl sulfate in dry toluene[18] at steam-bath temperatures. 1-Benzylindole, b.p. 145–147° (0.3 mm.), m.p. 43°, was prepared essentially as described by Plieninger.[18] The vinylpyridines were obtained from the Reilly Tar and Chemical Corp. and the pyridinecarboxaldehydes from the Aldrich Chemical Co. Dr. F. Cislak of Reilly kindly supplied samples of 3- and 4-acetylpyridine.

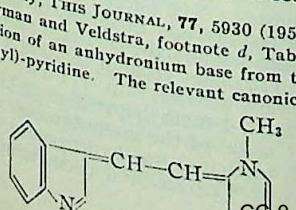
Pyridylethation at the 3-Position of the Indole Nucleus.—These reactions were run in hot glacial acetic acid, usually with approximately equimolar proportions of the reactants. Frequently the vinylpyridine was freshly distilled prior to use, although the commercial product (containing inhibitor) gave perfectly satisfactory results. The products were purified either by recrystallization (I, IV, VI), *via* the hydrochloride (II), or by distillation (III, V, VII). Yields averaged 65–75% with 4-vinylpyridine, 50–65% with 2-vinylpyridine and only 25–30% with 2-vinyl-5-ethylpyridine.

A. 4-(3-Indolylethyl)-pyridine (I).—A solution of 26.0 g. (0.25 mole) of 4-vinylpyridine (undistilled) and 23.4 g. (0.2 mole) of indole in 100 ml. of glacial acetic acid was refluxed (oil-bath) for 3 hr. The solution was concentrated *in vacuo* and the residue made weakly basic with dilute alkali. The resultant crystalline precipitate was recrystallized from aqueous isopropyl alcohol to yield 30.6 g. (69%) of I, m.p. 149–151°.

B. 4-(1-Methyl-3-indolylethyl)-pyridine (II).—To a refluxing (emerald green) solution of 1965 g. (15 moles) of 1-methylindole in 4.5 liters of glacial acetic acid was added, dropwise with stirring, 1590 g. (15 moles) of 4-vinylpyridine. After 22 hr. refluxing the solution was concentrated under reduced pressure. The residue was dissolved in dilute hydrochloric acid, the solution was filtered and then treated with concentrated hydrochloric acid in order to precipitate the hydrochloride salt of the product. (This step removed tarry, polymeric basic materials which were otherwise diffi-

(15) Cf. A. P. Gray, THIS JOURNAL, 77, 5930 (1955).

(16) Cf. Ackerman and Veldstra, footnote *d*, Table II, who report the facile formation of an anhydronium base from the methiodide of 2-(3-indolylethenyl)-pyridine. The relevant canonical form is



(17) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill. Melting points are corrected for stem exposure.

(18) *Cf.* H. Plieninger, *Chem. Ber.*, 87, 127 (1954). Toluene was found to be a more convenient solvent for the methylation reaction than liquid ammonia and ether.

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cult to separate.) The collected salt was dissolved in water and the solution was made alkaline with ammonia to precipitate 2580 g. (73% yield) of II, m.p. 91–93°. Recrystallization from aqueous acetone raised the melting point to 96–98°.

C. **2-(1-Methyl-3-indolylethyl)-pyridine (V).**—A solution of 30 g. (0.23 mole) of 1-methylindole and 25 g. (0.24 mole) of 2-vinylpyridine in 100 ml. of glacial acetic acid was refluxed for 18 hr. After removal of the solvent under reduced pressure, the residue was dissolved in dilute hydrochloric acid, the aqueous solution was washed with ether, made alkaline and extracted with ether. Concentration of the dried extract left an oil which was distilled to yield 26.3 g. (49%) of V, b.p. 170–185° (0.5 mm.), $n^{25}D$ 1.6140.

4-(1-Indolylethyl)-pyridine (VIII).—To 50 ml. of ethanol containing 0.5 g. of sodium and 0.5 g. of cupric sulfate was added 29.2 g. (0.25 mole) of indole and 52.4 g. (0.5 mole) of 4-vinylpyridine. The reaction mixture was heated in a sealed tube for 4 hr. at 140–150° (oil-bath temperature), allowed to cool to room temperature, filtered and the filtrate was concentrated *in vacuo*. The residue was taken up in ether, extracted with acid, the acid solution was made alkaline and extracted with ether. Drying and removal of the ether left a red oil which was distilled *in vacuo*. Redistillation afforded 31.7 g. (57% yield) of VIII as an oil which crystallized on standing, b.p. 160–165° (0.1 mm.), m.p. 41–45°. A weak absorption band in the N–H stretching region of the infrared indicated that this product was contaminated by a little of the 3-isomer.

4-(3(?)-Indenylethyl)-pyridine (XVII).—A mixture of 50.0 g. (0.43 mole) of freshly distilled indene and 1 g. of metallic sodium dissolved in 5 ml. of ethanol was heated to 80°, and 23.0 g. (0.22 mole) of 4-vinylpyridine (undistilled) was added dropwise with stirring. Stirring was continued and the reaction mixture was heated for 5 hr. at 80°. The ethylene dichloride extract of the cooled mixture was washed with water, dried over sodium sulfate and distilled. A fraction which immediately crystallized, b.p. 145–170° (0.3 mm.), was charcoaled and recrystallized from Skellysolve B to give 16.6 g. (34% yield) of XVII, m.p. 96–97°. The picrate melted at 176° dec. after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{15}N$: N, 6.33. Found: N (basic), 6.52.

The methobromide of XVII, recrystallized from ethanol, melted at 210–212° dec.

Anal. Calcd. for $C_{17}H_{18}BrN$: C, 64.56; H, 5.74; Br, 25.27. Found: C, 64.66; H, 5.50; Br (ionic), 25.27.

2-(3(?)-Indenylethyl)-pyridine (XVIII).—To 116 g. (1.0 mole) of indene and 2.0 g. of powdered sodamide in 300 ml. of dry toluene, stirred and brought to reflux in an oil-bath, was added, dropwise, 52.5 g. (0.5 mole) of 2-vinylpyridine in 50 ml. of toluene. Stirring was continued and the reaction mixture was refluxed for 5 hr. The solution was separated from considerable tarry material and distilled *in vacuo*. Redistillation afforded 33.0 g. (30% yield) of XVIII, b.p. 145–155° (0.4 mm.), $n^{25}D$ 1.5987.

Anal. Calcd. for $C_{16}H_{15}N$: N, 6.33. Found: N (basic), 6.39.

The hydrochloride formed colorless crystals from isopropyl alcohol–ether, m.p. 148–150° dec.

Anal. Calcd. for $C_{16}H_{16}ClN$: C, 74.55; H, 6.26; Cl, 13.76. Found: C, 74.25; H, 6.19; Cl (ionic), 13.58.

3-(2-Indolyl)-pyridine (XIX).—To the polyphosphoric acid prepared from 36 g. of phosphorus pentoxide and 20 g. of 85% phosphoric acid was added 30.8 g. of the crude, powdered phenylhydrazone of 3-acetylpyridine (m.p. 139–141°[19]). The mixture was stirred by hand with a thermometer and gradually heated in an oil-bath until the internal temperature reached 125–130°. At this point a vigorous reaction ensued. The reaction flask was immediately removed from the oil-bath as the temperature shot rapidly to >230°. After the reaction had subsided (in 3–4 minutes), the flask was cooled under a cold water tap to an internal temperature of about 90° and diluted with water. The tarry, aqueous mixture was washed with ethyl acetate, made alkaline with a saturated solution of sodium carbonate and exhaustively extracted with chloroform. The chloroform extract was dried over a mixture of anhydrous sodium sulfate and sodium carbonate and concentrated to dryness. The crystalline residue was charcoaled in ethanol, the solution was diluted with water, decanted from the initial tarry precipitate and diluted with more water to yield, after refrigeration, 15.6 g. (55%) of crude product, m.p. 166–173°. Further recrystallization (with charcoaling) from ethanol–water afforded XIX as almost colorless platelets, m.p. 173–175°.

Anal. Calcd. for $C_{13}H_{10}N_2$: N (basic), 7.21. Found: N (basic), 6.86.

The hydrochloride salt of XIX formed pale yellow crystals from methanol–ether, m.p. 259–261° dec.

Anal. Calcd. for $C_{13}H_{11}ClN_2$: C, 67.68; H, 4.81; Cl, 15.37. Found: C, 68.02; H, 4.96; Cl (ionic), 15.03.

The methiodide crystallized from methanol–ethyl acetate in clusters of small, yellow, prismatic needles, m.p. 248–250° dec.

Anal. Calcd. for $C_{14}H_{13}IN_2$: C, 50.02; H, 3.90. Found: C, 50.18; H, 3.79.

The methobromide, recrystallized from methanol–ether, melted at 266–268° dec.

Anal. Calcd. for $C_{14}H_{13}BrN_2$: C, 58.14; H, 4.53; Br, 27.64. Found: C, 57.94; H, 4.65; Br (ionic), 27.43.

4-(2-Indolyl)-pyridine (XX).—This compound was prepared similarly to the 3-isomer. The reaction was considerably more vigorous, however, and afforded a cleaner product in better yield. An intimate mixture of polyphosphoric acid (60 g. of phosphorus pentoxide and 32 g. of 85% phosphoric acid) and 51.2 g. of the crude, powdered phenylhydrazone of 4-acetylpyridine (m.p. 143–146°[20]) was stirred with a thermometer and gradually heated until the internal temperature reached 115–120°. The flask was removed from the bath as a violent reaction accompanied by considerable fuming took place. The temperature rose to 280–285° in less than five minutes. When the reaction had subsided (in an additional 2–3 minutes), the mixture was cooled under a cold water tap, taken up in water and washed with ethyl acetate. The mixture of water and solid was made alkaline with excess saturated sodium carbonate and triturated until all of the insoluble salts had been converted to base. The solid precipitate was collected, exhaustively extracted with hot ethanol and the solution charcoaled. XX crystallized from the refrigerated ethanol solution in cream-colored plates, m.p. 208–209°; the yield was 30.6 g. (65%).

Anal. Calcd. for $C_{13}H_{10}N_2$: N (basic), 7.21. Found: N (basic), 7.21.

The hydrochloride salt of XX crystallized from methanol–ether in pale yellow crystals, melting above 285°.

Anal. Calcd. for $C_{13}H_{11}ClN_2$: C, 67.68; H, 4.81; Cl, 15.37. Found: C, 67.62; H, 4.77; Cl (ionic), 15.25.

The methiodide formed tiny, orange cubes from methanol–ethyl acetate, melting with decomposition at 260°.

Anal. Calcd. for $C_{14}H_{13}IN_2$: C, 50.02; H, 3.90. Found: C, 49.99; H, 3.71.

The methobromide, crystallized from methanol–ether, showed m.p. 272–274° dec.

Anal. Calcd. for $C_{14}H_{13}BrN_2$: C, 58.14; H, 4.53; Br, 27.64. Found: C, 58.76; H, 4.60; Br (ionic), 27.37.

Catalytic Hydrogenation of Indolyl-pyridine Methobromides.—The following are representative examples. Crude salts were used in those cases in which no methobromide is listed in Table I.

A. **4-(3-Indolylethyl)-1-methylpiperidine (IX).**—A solution of 8.0 g. (0.025 mole) of the methobromide of I dissolved in 100 ml. of analytical grade methanol containing 0.5 g. of platinum oxide (Adams catalyst; added under nitrogen) was hydrogenated in an Adams–Parr apparatus at 40 p.s.i. and room temperature. Hydrogen absorption ceased in 20 minutes. The filtered solution was evaporated to dryness, the residue was dissolved in warm water, the solution made alkaline and the resultant precipitate was recrystallized from aqueous ethanol to yield 4.3 g. (69%) of IX as fine, colorless needles, m.p. 171–173°.

B. **3-(2-Indolyl)-1-methylpiperidine (XXI).**—A solution of 6.1 g. (0.021 mole) of the methobromide salt of XIX in 200 ml. of 75% methanol was hydrogenated over 0.5 g. of Adams catalyst at 45 p.s.i. and room temperature. Hy-

(19) C. Engler and W. Kiby, *Ber.*, **22**, 598 (1889).

(20) A. Pinner, *ibid.*, **34**, 4250 (1901).

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drogenation was complete in less than 1 hr. The filtered solution was evaporated to a thick resin which was taken up in water, treated with alkali and extracted into ether. The dried ether extract was concentrated to a crystalline residue. Recrystallization from aqueous ethanol and then from benzene–Skellysolve B afforded 2.55 g. (56% yield) of XXI, m.p. 118–120°.

Anal. Calcd. for $C_{14}H_{18}N_2$: N (basic), 6.54. Found: N (basic), 6.24.

XXI hydrochloride showed m.p. 204–206° dec. after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64. Found: C, 66.89; H, 7.27.

C. **4-(2-Indolyl)-1-methylpiperidine (XXII).**—Similarly, 18.8 g. of XX methobromide was hydrogenated to yield, after recrystallization from ethanol, 9.2 g. (67%) of XXII in the form of colorless prisms, m.p. 183–187°.

Anal. Calcd. for $C_{14}H_{18}N_2$: N (basic), 6.54. Found: N (basic), 6.57.

XII hydrochloride formed glistening plates from aqueous methanol–acetone, m.p. 259–260° dec.

Anal. Calcd. for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64; Cl, 14.14. Found: C, 66.85; H, 7.73; Cl (ionic), 13.89.

Condensation of Indoles with Pyridinecarboxaldehydes.—These reactions were carried out in acetic acid at room temperature. The products were relatively unstable, rapidly oxidizing in air to highly colored materials and were stored under nitrogen.

A. **4-(3,3′-Diindolylmethyl)-pyridine (XIII).**—To a solution of 32.1 g. (0.3 mole) of 4-pyridinecarboxaldehyde in 150 ml. of glacial acetic acid, cooled in an ice-bath, was added 70.2 g. (0.6 mole) of indole. The mixture was allowed to warm to room temperature. As the indole dissolved, a moderately exothermic reaction took place, and the resultant solution developed a deep purple color. After standing for 18 hr., the solution was diluted with aqueous hydrochloric acid to precipitate a purple hydrochloride salt which was recrystallized from ethanol–ether. Addition of aqueous alkali to an ethanol solution of the hydrochloride precipitated the base. This was crystallized from benzene–ethanol with the addition of Skellysolve B to provide 73 g. (75% yield) of yellow-orange crystals of XIII, m.p. 152–155° dec.

B. **4-[Bis-(1-methyl-3-indolyl)-methyl]-pyridine (XIV).**—Some heat was evolved on dissolving 5.0 g. (0.047 mole) of 4-pyridinecarboxaldehyde and 12.2 g. (0.094 mole) of 1-methylindole in 50 ml. of glacial acetic acid at room temperature. After standing for 21 hr. the deep purple solution was worked up as described above. The isolated base was recrystallized from benzene–Skellysolve B, affording 8.9 g. (54% yield) of flesh-colored crystals of XIV, m.p. 186–188° dec.

DECATUR, ILLINOIS

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some Chlorinated 4-Indanols: Preparation and Proof of Structures[1]

BY J. S. BUCK,[2] R. A. CUTLER, F. C. NACHOD, R. G. POWLES, R. RAKOCZY, T. J. SLAUSON AND B. F. TULLAR

RECEIVED FEBRUARY 2, 1957

Chlorination of 4-indanol with sulfuryl chloride yields 5-chloro-4-indanol and 7-chloro-4-indanol. The structure assignment has been carried out by analysis of the infrared spectra as well as by unambiguous synthesis. It is shown that the OH stretching frequencies of the two isomeric chloro-4-indanols coincide with the corresponding frequencies of *o*-chloro- and *p*-chlorophenol. Chemical structure proof starts with *p*-chlorophenyl β-chloropropionate which rearranges with $AlCl_3$ to 5,β-dichloro-2-hydroxypropiophenone which in turn cyclizes to form 4-chloro-7-hydroxy-1-hydrindone. The latter compound is reduced with Zn in HCl to the corresponding 7-chloro-4-indanol.

The recent availability of 4-indanol[3] (I) from the coal hydrogenation process prompted us to investigate some of its chlorinated derivatives as potential antiseptic agents. The reaction of one equivalent of sulfuryl chloride on 4-indanol yielded a mixture from which two white crystalline products were isolated. The more abundant of the two melted at 91.0–93.7° and was assumed to be 7-chloro-4-indanol (III). This assumption was later proved correct by infrared studies and by synthesis by another route as outlined below (V → VI → VII → III). From the filtrates of the chlorination mixture there was obtained a smaller amount of a substance melting at 70.4–73.1° which appeared to be 5-chloro-4-indanol (II). Actual proof of this structure was supplied by infrared spectral analyses.

The reaction of 4-indanol (I) with two equivalents of sulfuryl chloride yielded a mixture from which a solid was isolated melting at 54.5–56.8°. That this product was indeed 5,7-dichloro-4-indanol (IV) was proved by showing that treatment of either 5-chloro- (II) or 7-chloro-4-indanol (III) with sulfuryl chloride yielded this same material.

Physicochemical Data.—The spectra of the two isomeric chloroindanols (II and III) and the unchlorinated starting material I in CS_2 solution are sufficiently different to permit differential assays. The 7-chloro-4-indanol (III) has a strong band at 12.35 μ while the 5-chloro analog II does not absorb in this region, which is used to estimate the former compound. In the 9.5 to 10.5 μ region both compounds show doublets, the 7-chloro-4-indanol absorbing at 9.98 and 10.11 μ and the 5-chloro-4-indanol at 9.98 and 10.05 μ. The intensity of the first and second maximum are reversed with respect to the pair. Distortion (in the case of 0.4 to 0.6 mole fraction of the 7-chloro compound) or peak ratio assays (in the case of 0.8 to 1.0 mole fraction of the 7-chloro compound) establish their relative concentration. Unchlorinated starting material shows a doublet at 12.97 and 13.12 μ where neither of the monochloro derivatives absorbs.

Structure Assignment of 5- and 7-Chloro-4-indanol *via* Infrared Spectra.—The two isomeric indanols can be compared with *o*- and *p*-chlorophenol with respect to the geometry of their substituents. The trimethylene bridge of the indanol should not influence the position of the OH stretching frequency to any extent just as it would not exert any marked effect upon the dipole moment of the molecule. Dipole-dipole interaction, *viz.*,

(1) Presented before the Division of Organic Chemistry at the 131st meeting of the American Chemical Society, Miami, Fla., April, 1957.
(2) Deceased.
(3) Samples of 4-indanol were kindly supplied by Carbide and Carbon Chemicals Co.

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mixed (Cl···H–O) hydrogen bonding, should reduce the OH frequency for 5-chloro-4-indanol as it does for *o*-chlorophenol. The OH absorption maxima found were identical for the respective pairs of chlorophenol and chloroindanol; *p*-chlorophenol and 7-chloro-4-indanol in CS_2 solution absorb sharply at 2.786 μ while *o*-chlorophenol and 5-chloro-4-indanol under the same conditions absorb sharply at 2.823 μ. The damping of the OH frequency does indeed shift the absorption maximum to a longer wave length as postulated.

Acknowledgments.—The authors are indebted to Messrs. M. E. Auerbach and K. D. Fleischer and staff for the microanalyses and to Miss C. M. Martini and Mrs. M. Becker for assistance in the spectroscopical aspects of the work.

Experimental[4]

4-Chloro-7-indanol (III). Method A.—To a stirred solution of 194 g. (1.45 moles) of 4-indanol[5] and a small crystal of iodine in 100 ml. of glacial acetic acid was added 123 ml. (1.52 moles) of sulfuryl chloride over a period of ten minutes. External cooling was applied to keep the temperature below 55°. After an additional hour of stirring, the yellowish-orange solution was poured onto ice and made neutral to litmus with 35% sodium hydroxide solution. The solid which separated amounted to 230 g. (1.37 moles) (95%) and melted at 50–65°. Two recrystallizations from hexane, including treatment with charcoal in the first, gave 115 g. (47%) of white needles, m.p. 91.0–93.7°.

Anal. Calcd. for C_9H_9ClO: C, 64.10; H, 5.38; Cl, 21.03. Found: C, 64.59; H, 5.35; Cl, 20.90.

Method B (Chlorination without Solvent).—In a flask equipped with stirrer, thermometer, dropping funnel and gas vent, 469 g. (3.5 moles) of 4-indanol was melted by warming to 60°. After addition of a small crystal of iodine, 340 ml. (560 g., 4.2 moles) of sulfuryl chloride was added dropwise within 10 min. After an initial temperature surge to 75° the rate was such that it reached a level of about 65°. After complete addition, stirring and heating (70–75°) were continued for 1 hr. At that point 1.5 liters of water was added and heating and stirring (70–75°) were continued for an additional half hour. Slow cooling to 40° produced solidification of the mixture, and the product was filtered at room temperature and washed with cold water. Drying in a vacuum oven overnight yielded 583 g. of crude product (99%).

Infrared analyses (*vide infra*) indicated 88% of 7-chloro-4-indanol (III), 11% of 5-chloro-4-indanol (II) and 1% of unreacted starting material I. Recrystallization of this mixture from hexane gave a 75%[6] yield of 7-chloro-4-indanol, m.p. 90–92° (uncor.).

Isolation of 5-Chloro-4-indanol (II).—The solvent was removed by distillation from the hexane filtrates remaining after the purification of the 7-chloro-4-indanol (method A) to give 85 g. of dark oil. The latter was distilled at 2.5 mm. and four fractions of colorless oil collected. Crystallization of the first two fractions [b.p. range of 72–101° (uncor.)] from hexane yielded 12 g. of 5-chloro-4-indanol which melted at 70.4–73.1° after an additional recrystallization from hexane.

Anal. Calcd. for C_9H_9ClO: C, 64.10; H, 5.38; Cl, 21.03. Found: C, 64.02; H, 5.58; Cl, 20.75.

Crystallization of the third and fourth fractions from hexane gave additional amounts of 7-chloro-4-indanol.

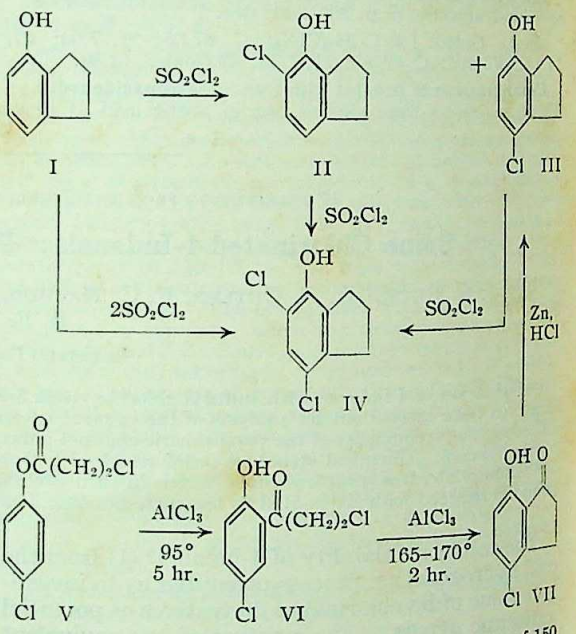
5,7-Dichloro-4-indanol (IV).—A stirred solution consisting of 40.5 g. (0.3 mole) of 4-indanol and a small crystal of iodine dissolved in 100 ml. of acetic acid was treated with 52 ml. (0.64 mole) of sulfuryl chloride and worked up similar to Method A above. A crude yield of 62 g. of low melting solid was obtained which gave 23 g. of pure 5,7-dichloro-4-indanol after two recrystallizations from pentane; m.p. 54.5–56.8°.

Anal. Calcd. for $C_9H_8Cl_2O$: Cl, 34.92; neut. equiv., 203.06. Found: Cl, 34.60; neut. equiv., 201.8.

The same product was obtained by the action of sulfuryl chloride on an acetic acid solution of either 7-chloro-4-indanol (III) or 5-chloro-4-indanol (II) according to the procedure outlined in Method A.

Chemical Proof of Structure of 7-Chloro-4-indanol (III),[7] *p*-Chlorophenyl β-Chloropropionate (V).—Molten *p*-chlorophenol was stirred and treated dropwise with an equimolecular amount of β-chloropropionyl chloride. After the addition was complete, the reaction mixture was allowed to stir for 3 hr. at room temperature and then heated for 1 hr. on a steam-bath. Distillation of the resulting oil gave a 90% yield of the desired product boiling at 152–156° (uncor.) at 11 mm., $n^{25}D$ 1.5306.

Anal. Calcd. for $C_9H_8Cl_2O_2$: Cl, 32.38. Found: Cl, 32.4.



4-Chloro-7-hydroxy-1-indanone (VII).[8]—A mixture of 150 g. (0.69 mole) of chlorophenyl β-chloropropionate with 350 g. of anhydrous aluminum chloride was heated 5 hr. at 95° and then 1 hr. at 160–170°. The mixture was quenched with ice and water. The product which separated was collected on a filter and washed well with water. Recrystallization from isopropyl alcohol, including treatment with charcoal, gave 45 g. (0.246 mole) (35.7%) of 4-chloro-7-hydroxy-1-indanone, m.p. 118–122° (uncor.).[9] By increasing the heating time at 165–170° to 2 hr., the yield of crude indanone (VII) was raised to 70% and none of the intermediate VI was recovered.

After recrystallization from ethyl acetate pure 4-chloro-

(4) All melting points are corrected unless otherwise specified.

(5) M.p. 45–47°.

(6) The increased yield over that of Method A is due mainly to the excess of sulfuryl chloride (20% employed.) When the reaction was run with no solvent and only a 5% excess of chlorinating agent was used, the yield was comparable to that obtained in Method A. Infrared analyses of the resulting crude product indicated that about 5% of it consisted of unchlorinated 4-indanol (I).

(7) The over-all procedure employed in this structure proof is similar to that used by R. A. Barnes, E. R. Kraft and L. Gordon, THIS JOURNAL, 71, 3523 (1949), for the preparation of 7-bromo-4-indanol.

(8) F. Mayer, H. Phillipps, F. W. Ruppert and A. T. Schmitt, *Ber.*, **61B**, 1966 (1928), prepared this same compound (m.p. 122°) by the action of $AlCl_3$ on β-(2-chloro-5-methoxyphenyl)-propionyl chloride.

(9) From the liquors 30 g. of somewhat impure 5,β-dichloro-2-hydroxypropiophenone (VI) was recovered; m.p. 75–78° (uncor.). A 96% yield of this same compound was obtained by heating the *p*-chlorophenyl β-chloropropionate with one and one half times its weight of $AlCl_3$ at 120° for 20 minutes. After quenching in ice and two recrystallizations of the resulting solid from hexane the pure rearranged product VI was obtained as coarse white crystals; m.p. 89.8–90.8°. *Anal.* Calcd. for $C_9H_8Cl_2O_2$: C, 49.36; H, 3.68; Cl, 32.38. Found: C, 49.67; H, 4.17; Cl, 32.4.

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7-hydroxy-1-indanone (VII) was obtained, m.p. 119.7–121.4°.

Anal. Calcd. for $C_9H_7ClO_2$: C, 59.20; H, 3.86; Cl, 19.42. Found: C, 59.16; H, 3.99; Cl, 19.50.

7-Chloro-4-indanol (III from VII).—A mixture of 450 g. (0.247 mole) of 4-chloro-7-hydroxy-1-indanone in 2 liters of toluene with 2 liters of acetic acid and 1500 g. of freshly amalgamated zinc (10 mesh) was heated with strong mechanical stirring under reflux at 90°, and 5 liters of hydrochloric acid was added during 4 hr. The heating and stirring were continued another 4 hr. with occasional additions of hydrochloric acid to a total of 7 liters.

The mixture was cooled and separated from undissolved zinc. The water layer was separated and washed with one liter of toluene. The combined toluene extracts were concentrated *in vacuo*. The residue was crystallized from 1 liter of "Skellysolve C" after decolorizing with charcoal yielding a 300 g. first crop of 7-chloro-4-indanole, m.p. 90–92°. By concentration and cooling and recrystallization a second crop of 35 g. was collected melting at the same point; total yield 335 g. (81%).

After recrystallization from 1.5 liters of ethylene dichloride, 310 g. of pure 7-chloro-4-indanol (II) was obtained, m.p. 91.2–92.8°.

Anal. Calcd. for C_9H_9ClO: Cl, 21.03. Found: Cl, 21.0.

A mixture melting point with the original sample of 7-chloro-4-indanol prepared by Method A was not depressed.

RENSSELAER, N. Y.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

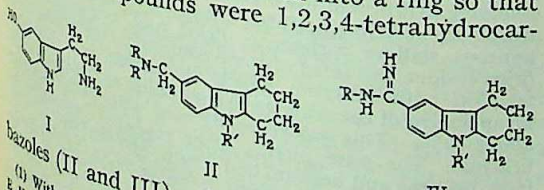
Indole Carboxamidines and Aminomethylindoles as Antimetabolites of Serotonin

BY E. SHAW AND D. W. WOOLLEY[1]

RECEIVED JANUARY 30, 1957

A number of antimetabolites of serotonin have been synthesized and studied in both isolated smooth muscles and in normal animals. These compounds were 1,2,3,4-tetrahydrocarbazoles (dialkylindoles) with $-CH_2-NR_2$ or $-C(=NR)-NH_2$ in the 6-position. Some had a benzyl group attached to the indole nitrogen as well. Methods for the synthesis of these compounds are described.

The early studies of the structural changes necessary to convert the hormone serotonin (I) into a specific antimetabolite of it had shown that one good way was to move the amino group from its position in the side chain of the hormone to position 5 in the indole nucleus.[2,3] The 5-amino-indoles, with alkyl groups in positions 3 (or 2 and 3) were active antiserotonins. However, they possessed the disadvantage that they were destroyed readily in living mammals. This defect apparently resided in the fact that they were substituted *p*-phenylenediamines which are liable to attack by some of the cytochrome-containing enzyme systems.[4] Since a basic group seemed to be needed somewhere in the molecule to confer high activity, the idea arose that the amino group of the aminoindoles might be protected from enzymic attack by placing a carbon atom between it and the indole nucleus. To test this postulate some 5-indolecarboxamidines and some 5-aminomethylindoles were synthesized and examined biologically for antiserotonin activity. These compounds contained either a $-C(=NH)-$ or a $-CH_2-$ between the basic nitrogen and the indole ring. For convenience in the practical syntheses, the alkyl groups in positions 2 and 3 were incorporated into a ring so that all of the compounds were 1,2,3,4-tetrahydrocarbazoles (II and III). Some of them proved to be relatively potent antimetabolites which were effective even in whole animals. Previous work had shown[5] that this was a rather rare property among antagonists of this hormone. The majority of existing antiserotonins were only effective on isolated tissues.



I II III

Experimental Part[6]

1,2,3,4-Tetrahydrocarbazole-6-carboxamide.—*p*-Aminobenzamide (7.0 g.) dissolved in water (55 ml.) and concentrated hydrochloric acid (20 ml.), was diazotized at −5° with sodium nitrite solution (3.5 g. in 25 ml. water). The filtered diazonium solution was poured into a cold solution of stannous chloride dihydrate (25 g.) in concentrated hydrochloric acid (25 ml.). After 15 minutes the tin complex was collected by suction filtration and converted to the hydrazine by treatment of a cold suspension in water (50 ml.) with 40% aqueous sodium hydroxide (20 ml.). *p*-Hydrazinobenzamide so obtained was combined with cyclohexanone in aqueous acetic acid in the usual manner. The crude hydrazone was refluxed in concentrated hydrochloric acid (20 ml. per g.) for 30 minutes. The resultant oil was dissolved in ethyl acetate which was washed with dilute alkali, dried and concentrated. The product crystallized in a yield of 45% (for the cyclization step) and had m.p. 217–219°.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.89; H, 6.59; N, 13.08. Found: C, 73.41; H, 6.41; N, 12.83.

The intermediate hydrazine and hydrazone were too unstable to purify profitably.

1,2,3,4-Tetrahydrocarbazole-6-carboxhydrazide.—1,2,3,4-Tetrahydrocarbazole-6-carboxylic acid[7] was converted to the ethyl ester when refluxed for six hours with ten volumes of 2 *N* ethanolic hydrogen chloride. After recrystallization from ethanol, a 75% yield of ester, m.p. 117–119°, was obtained.

The ethyl ester (11.4 g.) was then refluxed in absolute alcohol (85 ml.) and 100% hydrazine hydrate (56 ml.) for 21 hours. The solution was concentrated in an air stream until crystals appeared; water was added and the product was filtered, washed with 50% aqueous alcohol and desiccated *in vacuo*. The material so obtained, 10.0 g. (93%), m.p. 197–199°, was used in the next step. An analytical sample crystallized from ethanol had m.p. 201–203°.

(1) With the technical assistance of C. Carter, G. Schaffner and E. van Winkle.

(2) D. W. Woolley and E. Shaw, THIS JOURNAL, **74**, 2948 (1952).

(3) D. W. Woolley and E. Shaw, *J. Biol. Chem.*, **203**, 69 (1953).

(4) D. W. Woolley and E. Shaw, *J. Pharmacol. Exper. Therap.*, **108**, 97 (1953).

(5) E. Shaw and D. W. Woolley, *ibid.*, **116**, 164 (1956).

(6) M.p.'s are uncorrected. Analyses were performed by S. Theodore Bella.

(7) W. H. Gray and S. G. Powell, *J. Chem. Soc.*, 808 (1926).

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Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.09; H, 6.59; N, 18.33. Found: C, 68.51; H, 6.38; N, 18.94.

1,2,3,4-Tetrahydrocarbazole-6-carboxylic Acid Dimethylamide.—1,2,3,4 - Tetrahydrocarbazole - 6 - carboxhydrazide (10 g.) in glacial acetic acid (150 ml.) was treated with aqueous sodium nitrite solution (3.5 g. in 10 ml. water) at 15°. The reaction mixture was then partitioned between ether (700 ml.) and water (200 ml.). After the ether layer had been washed with successive portions of aqueous bicarbonate, it was dried briefly with anhydrous sodium carbonate and filtered. A slow stream of dimethylamine was passed into the ethereal azide solution for six hours. Finally the mixture was evaporated to dryness in an air stream and the residue stirred with water and filtered. After recrystallization from ethyl acetate, 8.0 g., m.p. 188–190°, was obtained, a yield of 75%. In earlier runs a different crystalline modification was isolated with m.p. 150–151°. It could be converted to the higher melting form if its solutions were seeded with the latter.

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.47; H, 7.51; N, 11.64.

Amidation of the ester with dimethylamine failed.

6-Dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole.—The preceding N,N-dimethylamide (5.7 g.) was stirred overnight with a suspension of lithium aluminum hydride (2.5 g.) in dry ether (750 ml.). The excess hydride was cautiously decomposed in the usual way with aqueous sodium potassium tartrate and the product extracted from the ether layer with several 50-ml. portions of 0.5 *N* hydrochloric acid. The base was precipitated by addition of alkali to the acid extracts and was recrystallized from ethanol in a yield of 70%, m.p. 161–163°.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.91; H, 8.83; N, 12.27. Found: C, 78.72; H, 8.82; N, 12.35.

6-Aminomethyl-1,2,3,4-tetrahydrocarbazole Hydrochloride.—1,2,3,4-Tetrahydrocarbazole-6-carboxamide (2.0 g.) was reduced with lithium aluminum hydride (1.0 g.) in dry ether (250 ml.) as in the preceding example. The product was extracted from the ether solution with 0.5 *N* HCl (3 × 30 ml.). When the acid extracts were made alkaline, the base crystallized, 0.65 g., m.p. 142–145°. For convenience, it was converted to the hydrochloride, m.p. 255–257° dec.

Anal. Calcd. for $C_{13}H_{17}N_2Cl$: C, 65.95; H, 7.23. Found: C, 65.54; H, 6.93.

9-Benzyl-6-dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole Hydrochloride.—A solution of 1,2,3,4-tetrahydrocarbazole-6-N,N-dimethylcarboxamide (10 g.) in benzene was added to a suspension of sodium hydride (1.5 g.) in benzene (400 ml.) in an atmosphere of nitrogen. The mixture was refluxed for one-half hour. Benzyl chloride (5.2 ml.) was added and the refluxing was continued overnight. To decompose excess hydride, absolute ethanol (10 ml.) was introduced. The benzene layer was washed with water, dried and evaporated to dryness. The benzylated amide was not crystallized. Instead the residue was taken up in anhydrous ether and added to a suspension of lithium aluminum hydride (4.0 g.) in ether (1 liter). After the mixture had been stirred for two days, the excess hydride was decomposed in the usual way with aqueous sodium potassium tartrate and the product was extracted from the ether layer with *N* hydrochloric acid (2 × 100 ml.). The hydrochloride of the product which had crystallized immediately in the acid extracts was filtered, washed with dilute hydrochloric acid, and desiccated *in vacuo* with moistened pellets of sodium hydroxide. The hydrochloride thus isolated always had a characteristic m.p. of 84–87° but was hydrated to a variable degree in different preparations. After recrystallization from water, lustrous flakes, 7.0 g., of the same m.p. were obtained. After drying for several hours at 65° and 1 mm. this material was analytically pure as anhydrous hydrochloride[8] and represented a yield of 50% for the two steps. Recrystallization from absolute alcohol gave a product with a m.p. of 198–199°.

Anal. Calcd. for $C_{22}H_{27}N_2Cl$: C, 74.45; H, 7.67; N, 7.89. Found: C, 74.34; H, 7.48; N, 7.98.

This anhydrous high melting form was reconverted to the form melting at 84–87° by recrystallization from water.

This same compound was prepared by direct benzylation of 6-dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole in liquid ammonia in the presence of sodamide. The yield was 46%.

***p*-Hydrazinobenzamidine Dihydrochloride.**—*p*-Aminobenzamidine dihydrochloride was prepared by low pressure hydrogenation of *p*-nitrobenzamidine[9] in ethanol with palladized charcoal. The filtrate was concentrated to a small volume and the product precipitated by the addition of concentrated hydrochloric acid. Yields of 85%, m.p. 290–291°, resulted. Although lit. m.p. is 320° cor.,[10] the material obtained was analytically pure.

Anal. Calcd. for $C_7H_{11}N_3Cl_2$: Cl^-, 34.1; N, 20.19. Found: Cl^-, 34.4; N, 20.44.

Diazotization of *p*-aminobenzamidine dihydrochloride (5.0 g.) in 2 *N* hydrochloric acid (80 ml.) was carried out at −10° with a solution of sodium nitrite (1.75 g.) in water (5 ml.). A cold solution of stannous chloride dihydrate (25 g.) in concentrated hydrochloric acid (25 ml.) was added. After 20 minutes, the tin complex was filtered with suction and washed with ice-water. The precipitate in water (125 ml.) was treated with hydrogen sulfide and the filtrate concentrated to a small volume with reduced pressure until the appearance of crystals. After refrigeration, the product was collected. It was recrystallized from water (15 ml.) by the addition of *N* ethanolic HCl (60 ml.) in the form of long needles, m.p. 269–270° dec., 2.9 g.

Anal. Calcd. for $C_7H_{12}N_4Cl_2$: C, 37.68; H, 5.42; N, 25.11. Found: C, 37.80; H, 5.34; N, 25.14.

1,2,3,4-Tetrahydrocarbazole-6-carboxamidine Hydrochloride.—*p*-Hydrazinobenzamidine dihydrochloride (3.0 g.) in water (90 ml.) was treated with cyclohexanone (2 ml.). The yellow solution was made strongly alkaline with 6 *N* sodium hydroxide whereupon the hydrazone separated as an oil which crystallized. After the mixture was chilled, the product was filtered, washed with water and desiccated *in vacuo*. The crude hydrazone melted at 225–226° dec. Purification proved unprofitable.

The hydrazone (2.2 g.) was refluxed for 30 minutes in concentrated hydrochloric acid (22 ml.). The hydrochloride of the product which formed as an oil crystallized on standing. It was dissolved in hot water (20 ml.). The solution was cooled for four hours, filtered from an insoluble impurity and crystallized from the filtrate by addition of 6 *N* hydrochloric acid (2 ml.) to yield 1.6 g. (44%), m.p. 193–195°. It was recrystallized from hot 0.5 *N* hydrochloric acid.

Material dehydrated at 100° *in vacuo* was hygroscopic; satisfactory analyses were obtained on anhydrous material allowed to hydrate in a moist atmosphere until no further gain in weight occurred. The uptake indicated a monohydrate.

Anal. Calcd. for $C_{13}H_{16}N_3Cl \cdot H_2O$: C, 58.30; H, 6.72; N, 15.69. Found: C, 58.93; H, 6.71; N, 15.88.

The free base was obtained as a gum by treatment of the hydrochloride with aqueous NaOH. In some preparations, this gum was obtained crystalline by solution in ethanol and partial evaporation of the solvent. Occasionally the gum could not be induced to crystallize. The free base melted at 171–173°.

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.20; H, 7.09; N, 19.70. Found: C, 73.16; H, 6.75; N, 19.52.

6-Cyano-1,2,3,4-tetrahydrocarbazole.—The hydrazone from cyclohexanone and *p*-cyanophenylhydrazine[11] formed in the usual manner (m.p. 174–175°) was refluxed in concd. hydrochloric acid (15 ml. per g.) for 15 minutes. Longer refluxing hydrolyzed the nitrile. The precipitated gum was dissolved in ethyl acetate which was then washed with aqueous sodium carbonate, dried and evaporated. The dried residue was freed of some contaminating amide by extraction with ether in which the amide was insoluble. Evaporation of the ether gave crystalline nitrile in a yield of about 70%. This was generally used without further purification. The pure nitrile, after repeated crystallization from benzene and hexane, had a m.p. of 117–119°.

Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.24; H, 6.31; N, 14.23.

Attempts to convert the nitrile to an imino ether in ether

(8) The m.p. of this anhydrous material was considerably lower than that of the anhydrous material obtained by crystallization from alcohol.

(9) A. Pinner and F. Gradenwitz, *Ann.*, **298**, 47 (1897).

(10) A. P. T. Easson and F. L. Pyman, *J. Chem. Soc.*, 2991 (1931).

(11) A. Weissburger, H. P. Porter and W. A. Gregory, THIS JOURNAL, **66**, 1854 (1944).

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or chloroform resulted only in the formation of a hydrochloride of the starting material. Amidines were therefore prepared by alternate routes.

9-Benzyl-6-cyano-1,2,3,4-tetrahydrocarbazole.—6-Cyano-1,2,3,4-tetrahydrocarbazole (2.0 g.) in benzene (75 ml.) was converted to a sodium salt with sodium hydride (0.25 g.) followed by dimethylformamide (5 ml.). Benzyl chloride (1.2 ml.) was then introduced and the reaction mixture was refluxed for two hours. After decomposition of unreacted hydride with ethanol the benzene solution was washed, dried and concentrated. The residue in a small volume of benzene was applied to a column of alumina (3.4 × 30 cm.) and eluted with the same solvent containing 2% ethanol. The first fraction which emerged crystallized on removal of the solvent. The crystals were thinned with alcohol and water for filtration and provided 1.6 g., 56% of product melting at 117–118°. The analytical sample obtained from the same solvents had m.p. 120–121°.

Anal. Calcd. for $C_{20}H_{18}N_2$: C, 83.87; H, 6.34; N, 9.78. Found: C, 84.02; H, 6.38; N, 9.99.

1,2,3,4-Tetrahydrocarbazole-6-N-phenylcarboxamidine Hydrochloride.[12]—6-Cyano-1,2,3,4-tetrahydrocarbazole (3.1 g.) and aniline *p*-toluenesulfonate (4.3 g.) were heated for one hour at 220° and the cooled melt was partitioned between chloroform and *N* sodium hydroxide. The chloroform layer was washed with water followed by 3 *N* hydrochloric acid which precipitated the amidine hydrochloride as a gum. The latter was either crystallized from 80% ethanol or, with smaller losses, purified as the picrate, m.p. 258–259°, in a yield of 49%. The hydrochloride had a m.p. of 266–267°.

Anal. Calcd. for $C_{19}H_{20}N_3Cl$: C, 70.04; H, 6.18; N, 12.90. Found: C, 70.33; H, 6.05; N, 12.63.

9-Benzyl-1,2,3,4-tetrahydrocarbazole-6-N-phenylcarboxamidine Hydrochloride.[12]—9-Benzyl-6-cyano-1,2,3,4-tetrahydrocarbazole (1.5 g.) was heated with aniline *p*-toluenesulfonate (1.4 g.) for one hour at 200° and worked up as in the preceding example. Saturated sodium chloride solution was added to help break emulsions in the extraction step. When the chloroform layer was shaken with *N* hydrochloric acid (20 ml.) the product remained dissolved in the chloroform layer as the hydrochloride. The chloroform was dried and concentrated to a small volume whereupon the product crystallized. After recrystallization from alcohol and ether, the hydrochloride was obtained in a yield of 50%, m.p. 272–273°.

Anal. Calcd. for $C_{26}H_{26}N_3Cl$: C, 75.09; H, 6.30; N, 10.10. Found: C, 74.85; H, 6.03; N, 10.44.

Pharmacological Results

Antiserotonin Activity as Measured on Artery Rings.—The method of Woolley and Shaw[3] was used, which depended on the measurement of the concentration of the analog required to overcome the contraction caused in ring-shaped segments of carotid arteries by a fixed amount of serotonin. The results of these tests are shown in Table I where it can be seen that most of the analogs possessed activity. The increased potency of the dimethylaminomethyl over the aminomethyltetrahydrocarbazole was noteworthy. One would expect the latter to be deaminated readily, and this may explain partly the observed difference.

Antiserotonin Activity on Isolated Rat Uterus.—The method introduced by Erspamer[13] was used in the manner previously described from this Laboratory.[5] The results of these tests are also shown in Table I. The variation in relative potency of a single compound on the two tissues is noteworthy. Clearly, most of the analogs were antimetabolites on the uterus as well as on the carotid artery.

Antiserotonin Activity as Measured against the

(12) Cf. general method of Oxley and Short, *J. Chem. Soc.*, 147 (1946).

(13) V. Erspamer, *Ricerca Sci.*, **22**, 1568 (1952).

TABLE I

ANTISEROTONIN ACTIVITIES OF THE ANALOGS AS MEASURED WITH ISOLATED TISSUE IN VITRO

1,2,3,4-Tetrahydrocarbazoles	Inhibition index in sheep arteries[a]	Inhibition index in rat uterus[b]
6-Carboxamidine	6	25
6-N-Phenylcarboxamidine[c]	200	50
6-Aminomethyl	20	..
6-N,N-Dimethylaminomethyl	2	10
9-Benzyl 6-N,N-dimethylaminomethyl[c]	..	300

[a] These values represent the number of mg. of analog required to antagonize the contracting action of 1 mg. of serotonin creatinine sulfate and were determined from the point of half maximal effect. The concentration of serotonin in the bath was 0.2 γ/ml. [b] Inhibition index has the same connotation as above. The amount of serotonin in the bath was 0.05 γ/ml. The analog was left in contact with the tissue for two minutes before addition of serotonin. [c] These analogs endowed the tissues with an insensitivity to serotonin that persisted long after washing. The acetyl choline response was not affected by them.

Pressor Action in Dogs.—The compounds were examined according to the methods previously described.[4,5] When given by the intravenous route two of the compounds (the dimethylaminomethyltetrahydrocarbazole and the tetrahydrocarbazole N-phenylcarboxamidine) proved to be quite effective. Data are summarized in Table II. By the oral route, however, the former was without demonstrable antiserotonin action on dogs. Daily doses of 45 mg. per kg. for 4 days failed to protect against the pressor effect of serotonin. In fact this compound given orally potentiated serotonin. The N-phenylcarboxamidine fed at 3.5 and 7.5 mg. per kg. per day partially protected 2 dogs but in one the effect was slight.

Hypotension Caused by the 1,2,3,4-Tetrahydrocarbazole 6-N-Phenylcarboxamidine in Dogs.—When given intravenously in doses of 2–7 mg. per kg. to anesthetized dogs the tetrahydrocarbazole 6-N-phenylcarboxamidine caused a sharp fall in arterial blood pressure (usually about 20 mm. of Hg). In two of five animals, however, the hypotension was very severe, and in one of these the pressure fell to zero with 9 mg. per kg. Sometimes the hypotension persisted for an hour or more. This kind of action has been rare among antiserotonins, but was noted recently with the benzyl analog of bufotenin.[14]

Behavioral Changes Caused by 9-Benzyl-6-dimethylaminomethyl - 1,2,3,4 - tetrahydrocarbazole.—Although the dimethylaminomethyltetrahydrocarbazole did not cause any noticeable behavioral changes when fed to normal dogs or mice, the corresponding benzyl derivative, *viz.*, 9-benzyl-6-dimethylamino-methyl-1,2,3,4-tetrahydrocarbazole brought about an alteration which might be called a psychosis. Dogs fed daily 25 mg. per kg. of this analog mixed with their food ate it readily for 3 or 4 days. They then developed a most pronounced aversion to the taste of it, whereas in the first days they did not object at all. This aversion was so great that the animals refused to touch any food containing the drug. At the time that this distaste arose, the attitude and behavior

(14) E. Shaw and D. W. Woolley, *Proc. Soc. Exptl. Biol. Med.*, **93**, 617 (1956).

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TABLE II

AMOUNTS OF ANALOGS REQUIRED BY THE INTRAVENOUS AND BY THE ORAL ROUTE TO PROTECT DOGS FROM THE PRESSOR ACTION OF SEROTONIN

1,2,3,4-Tetrahydrocarbazoles	No. of dogs	I.V. dose,[a] mg./kg. Av.	Extreme range	Oral dose, mg./kg./day
6-Carboxamidine	1	No effect at 6	.....	.....
6-N-Phenylcarboxamidine	4	0.4[b]	0.14–0.5	.....
	2	..	.....	Some protection at 3.5 and 7.5 but not complete
6-N,N-Dimethylaminomethyl	4	1.6	0.7–2.7	.....
	2	..	.....	No protection at 45[c]
9-Benzyl 6-N,N-dimethylaminomethyl	1	..	Less than 2.5	.....
	4	..	....	Partial at 25[d]

[a] Amount required to reduce to half the pressor response of the standard dose of serotonin (usually 50 gamma per kg.). [b] Complete protection was not achieved in some of the dogs with doses ten times this amount, although partial protection was always seen. [c] Both dogs showed an increase in the pressor effect of serotonin after eating this compound. [d] Two dogs showed only slight protection; one showed good protection; and one showed no protection but instead there was augmentation of the pressor response

of the animals became quite changed. Some raced around the room excitedly and without obvious purpose. One animal was so distracted that in running constantly about the room he would bump into articles of furniture. The behavioral changes varied from animal to animal, but of the 4 dogs tested all showed the slow onset and the delayed development of distaste for food mixed with the analog. In all, the symptoms could be summarized as marked excitement. A further sign was seen in all, *viz.*, constant slow movement of the head from side to side in a horizontal plane. This motion was continued regularly for hours.

When dogs exhibiting the influence of this compound were anesthetized with Nembutal, the sleeping time was always prolonged so that they would not awaken for about 24 hours. When ingestion of the compound was stopped, the behavior of the animals returned to normal within a few days.

In mice, the intraperitoneal injection of this compound (30 mg. per kg.) brought about neurological changes similar to those seen in dogs. Chief of these were the excitement, and the turning of the head from side to side regularly and rhythmically. In a mouse it is not as easy to recognize behavioral changes which can be called psychotic with any assurance, and none which could be so labeled were observed. The walking backwards as seen in mice given lysergic acid diethylamide[15] was never seen. However, just as in dogs, the sleeping time caused by a standard dose of Nembutal was markedly increased.

Curious Prolonged Action of 9-Benzyl-6-dimethylaminomethyl - 1,2,3,4 - tetrahydrocarbazole as an Antipressor Agent in Dogs.—When dogs were fed this compound for 4 days (25 mg. per kg. per day) and then tested for their protection against the pressor effects of serotonin, the results were not dramatic. Only partial protection could be found (*cf.* Table II). When the feeding of the compound was then stopped, and the dogs were challenged at long intervals thereafter, their protection was sometimes found to have lasted or even increased. This effect was noticeable for periods ranging (in various dogs) from a few days to many weeks. The dimethylaminomethyltetrahydrocarbazole which lacked the benzyl group did not cause this prolonged and progressive effect.

Discussion

Although a basic group seems to be necessary in a serotonin analog for it to show marked antiserotonin activity, the results of the present study illustrate the degree of freedom which may be enjoyed in the location of this group. The insertion of a carbon atom between the indole ring and the basic nitrogen has resulted in the attainment of compounds which are much more potent than the corresponding aminoindoles.

The fact that these new antimetabolites were relatively inactive as antipressor agents when fed, or at least, were not as active as when injected intravenously, should be borne in mind. The reason why this should be so is unknown. Compounds such as 6-dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole have had incorporated in them the features designed to protect them from destruction by deamination or from a variety of oxidative enzyme systems, and yet they failed to act by the oral route. Perhaps they may have been excreted too rapidly, or may have been destroyed in unsuspected ways.

The pronounced effects of 9-benzyl-6-dimethylaminomethyl-1,2,3,4- tetrahydrocarbazole are noteworthy for 2 reasons. Firstly, the abnormal behavior which it caused lends support to the idea first proposed by Woolley and Shaw[16] that serotonin plays a role in mental processes.

The second point of interest about this compound was that 6-dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole, which differed from it only in lacking the benzyl group, did not call forth the abnormal behavior. Neither did it exhibit the curious delayed and prolonged action as an antipressor agent. Recently, the conferment of striking properties on another antiserotonin by introduction of a benzyl group has been illustrated by comparison of BAS with the corresponding unbenzylated analog.[5,17] In both cases prolonged action and increased potency resulted from introduction of the benzyl group.

NEW YORK 21, N. Y.

(15) D. W. Woolley, *Proc. Natl. Acad. Sci.*, **41**, 338 (1955).

(16) D. W. Woolley and E. Shaw, *ibid.*, **40**, 228 (1954).

(17) D. W. Woolley and E. Shaw, *Science*, **124**, 34 (1956).

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, SETON HALL UNIVERSITY]

Preparation and Reactions of 2-Nitropyridine-1-oxides

BY ELLIS V. BROWN

RECEIVED FEBRUARY 7, 1957

2-Nitropyridine-1-oxide and a number of its homologs have been prepared by the action of mixtures of fuming sulfuric acid and 27.5% hydrogen peroxide on the corresponding aminopyridine-1-oxides. Displacement of nitro by chloro has given the 2-chloropyridine-1-oxides, and these were identified where possible by means of their 4-nitro derivatives.

Because of the many reactions which it undergoes, the importance of 4-nitropyridine-1-oxide is well established,[1] and it is of interest to compare its behavior with that of the 2-isomer; however, attempts to prepare 2-nitropyridine-1-oxide by the oxidation of 2-nitropyridine have been unsuccessful.[2] We wish to report the synthesis of compounds of this class by the oxidation of 2-aminopyridine-1-oxides. Starting with the commercially available 2-aminopyridine and its homologs, we acetylated, oxidized to the corresponding N-oxides with peracetic acid (20%) and then hydrolyzed with sodium hydroxide. All of these compounds except the 4,6-dimethyl were prepared by us as the hydrochlorides and reported in another connection.[3] The aminopyridine-1-oxide and the 6-methyl-2-aminopyridine-1-oxide subsequently were reported by Adams and Miyano.[4]

The free aminopyridine-1-oxides listed in Table I were then oxidized using a mixture of 30% fuming H_2SO_4 and 27% hydrogen peroxide at 10–20°. The reaction mixture was poured onto the ice, neutralized to congo red paper with ammonium hydroxide, extracted with ether or butyl alcohol and evaporated to give the product. The yields and melting points of the 2-nitropyridine-1-oxides so prepared are listed in Table II.

TABLE I

2-AMINOPYRIDINE-1-OXIDES

Substituent	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
3-Methyl-	68	164–165				
4-Methyl-	65	128–129	58.06	58.18	6.45	6.50
5-Methyl-	72	130–132	58.06	58.13	6.45	6.35
6-Methyl-	75	150–151	58.06	57.92	6.45	6.60
4,6-Dimethyl-	78	153–154				
	70	149–150	60.87	60.90	7.25	7.40

TABLE II

2-NITROPYRIDINE-1-OXIDES

Substituent	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
3-Methyl-	50	85–86	42.86	42.64	2.86	2.90
4-Methyl-	55	110–111	46.75	46.85	3.90	3.85
5-Methyl-	52	118–119	46.75	46.90	3.90	3.97
6-Methyl-	45	112–113	46.75	46.68	3.90	3.88
4,6-Dimethyl-	57	120–121	46.75	46.71	3.90	3.98
	40	108–109	50.00	50.12	4.76	4.90

We have proved the structure of these new compounds by two reactions. The first is reduction of the N-oxide function to give the corresponding nitropyridines. All of these except the 4,6-dimethyl-2-nitropyridine have been made by Wiley and Hartman[5] by the oxidation of the aminopyridines with the fuming sulfuric acid–hydrogen peroxide mixture following the original preparation of 2-nitropyridine by Kirpal.[6] The new 4,6-dimethyl-2-nitropyridine we have prepared using the same procedure. Ochiai[1] had previously shown that 4-nitropyridine-1-oxide could be reduced to 4-nitropyridine by warming with phosphorus trichloride. By this same means we have prepared the 2-nitropyridines from the 2-nitropyridine-1-oxides and compared the compounds by melting points and mixed melting points.

A second proof was the complete reduction by catalytic hydrogenation of the 2-nitropyridine-1-oxides back to the original 2-aminopyridines. These were compared by melting points and mixed melting points and found to be identical.

When one reduces 4-nitropyridine-1-oxide with palladium at low hydrogen pressure, 4-aminopyridine-1-oxide is prepared. We have not been able to realize this reaction since complete reduction of the 2-nitro compound occurs. The 2-aminopyridine-1-oxides prepared as indicated previously are stable to air, the 4-aminopyridine-1-oxides can usually only be isolated as the hydrochlorides since they oxidize in air to the azo compound.

The nitro group in the 4-nitropyridine-1-oxides is readily replaced by chlorine using acetyl chloride, and we have displaced the nitro group in our 2-nitropyridine-1-oxides in the same manner thus preparing the corresponding 2-chloropyridine-1-oxides. For comparison it was necessary to prepare these compounds by the oxidation of the chloropyridines. Some of these chloropyridines have been prepared by previous workers. We used the method of Siede[7] in preparing all of the compounds listed in Table III. His method consists of simply diazotizing the available aminopyridines in concentrated hydrochloric acid at 0° and allowing the mixture to warm, neutralizing with ammonium

TABLE III

2-CHLOROPYRIDINE-1-OXIDE HYDROCHLORIDE

Substituent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
.....	138–142	36.14	36.58	3.01	2.78
3-Methyl-	146–150	39.78	39.42	3.87	3.80
4-Methyl-	121–125	39.78	39.35	3.87	3.65
5-Methyl-	125–128	39.78	40.02	3.87	3.57
6-Methyl-	155–160	39.78	39.92	3.87	3.60
4,6-Dimethyl-	144–148	43.30	43.01	4.64	4.50

(1) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).
(2) E. Ochiai, E. Hayashi and M. Katada, *J. Pharm. Soc. Japan*, **67**, 79–81 (1947).
(3) R. W. Paessinger and E. V. Brown, Abstracts of the Buffalo meeting of the A.C.S., March, 1951.
(4) R. Adams and S. Miyano, THIS JOURNAL, **76**, 2735 (1954).
(5) R. H. Wiley and J. L. Hartman, *ibid.*, **73**, 494 (1951).
(6) A. Kirpal and W. Bohm, *Ber.*, **64**, 767 (1931).
(7) O. Siede, *ibid.*, **57**, 791 (1924).

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hydroxide, extracting with ether and distilling. Although the 2-bromopyridine-1-oxides have been prepared previously, the corresponding chloro compounds have not. We oxidized all of the chloropyridine homologs with 20% peracetic acid in the usual manner and the 2-chloropyridine-1-oxide hydrochlorides were compared by melting point and mixed melting point and appear to be identical, although the rather wide melting range of these salts was somewhat unsatisfactory. We therefore nitrated them with nitric–sulfuric acid mixture to give the 4-nitro-2-chloropyridine-1-oxides, and these are listed in Table IV. After nitrating the products from the acetyl chloride reaction, comparison of melting points and mixed melting points established their identity.

TABLE IV

2-CHLORO-4-NITROPYRIDINE-1-OXIDES

Substituent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
.....	152–153	34.38	34.51	1.72	1.88
3-Methyl-	145–146	38.19	38.23	2.65	2.50
5-Methyl-	154–155	38.19	38.31	2.65	2.69
6-Methyl-	106–107	38.19	38.14	2.65	2.81

Although no quantitative data have been obtained, there was a very obviously faster rate of reaction of acetyl chloride with 2-nitropyridine-1-oxide than with 4-nitropyridine-1-oxide in the cold, nitrogen dioxide being evolved rapidly.

Experimental

Preparation of 2-Aminopyridine-1-oxides.—All of the compounds listed in Table I were prepared from commercially available 2-aminopyridine and its homologs in the same manner. One mole of aminopyridine was refluxed 1 hr. with 100 ml. of acetic anhydride, and the acetylaminopyridine was isolated by distillation at reduced pressure or crystallization in the usual manner. The acetylaminopyridine so prepared was oxidized by a mixture of 150 ml. of glacial acetic acid and 125 ml. of 40% peracetic acid.[8] In the beginning the temperature was moderated by a cooling bath, and then the temperature was held at 70° for 3 hr. Evaporation *in vacuo* and crystallization from toluene completed the preparation of the acetylaminopyridine-1-oxides. For the hydrolysis, 72 g. of acetylaminopyridine-1-oxide was refluxed in 500 ml. of water containing 60 g. of sodium hydroxide for 3 hr. At the end of this time, the solution was acidified and evaporated under reduced pressure. The free aminopyridine-1-oxides were then isolated from the residue by crystallization from absolute ethanol (Table I).

Preparation of 2-Nitropyridine-1-oxides.—The compounds listed in Table II were prepared by oxidation of the free amino compounds listed in Table I. To a mixture of 100 ml. of fuming sulfuric acid (30%) and 50 ml. of 27.5% hydrogen peroxide[8] prepared below 20° was added a solution of 9 g. of the aminopyridine-1-oxide in 50 ml. of concd. sulfuric acid. The temperature was held at 10–15° during the addition and then maintained at 25° for 24 hr. The reaction mixture was poured onto cracked ice, neutralized with concd. ammonium hydroxide and extracted with ether, butanol or both. Evaporation of the solvent under reduced pressure and temperature not exceeding 50° gave the crude products which were recrystallized from absolute ethanol (Table II).

Reduction of the N-Oxide Function.—Following the procedure of Ochiai,[1] 1 g. of 2-nitropyridine-1-oxide was refluxed in 20 ml. of chloroform with 2 ml. of phosphorus trichloride, cooled, neutralized with sodium hydroxide and the chloroform evaporated to dryness. Crystallization from petroleum ether afforded the nitropyridines which showed no depression in melting point when mixed with the products prepared by the method of Wiley and Hartman.[5] 2-Nitro-4,6-dimethylpyridine was prepared from the commercially available 2-amino-4,6-dimethylpyridine by the method of Wiley and Hartman[5] and melted at 59–60°. The yield was 50%. *Anal.* Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.26. Found: C, 55.32; H, 5.30. The product from reduction of the N-oxide function of 2-nitro-4,6-dimethylpyridine-1-oxide showed no depression of melting point when mixed with this nitropyridine.

Catalytic Reduction of 2-Nitropyridine-1-oxides.—One gram of the nitropyridine-1-oxide was dissolved in 50 ml. of absolute ethanol, treated with 0.5 g. of 5% palladium-on-charcoal in a Parr low pressure hydrogenator at 45 lb. per sq. inch of hydrogen pressure. When no more hydrogen was absorbed, the catalyst was filtered, the solvent evaporated and the product identified as the aminopyridine in each case.

Replacement of Nitro Group by Chloro.—Two grams of the 2-nitropyridine-1-oxide was treated with 20 ml. of acetyl chloride. A violent reaction evolving nitrogen oxides took place at once. The reaction mixture was refluxed for 0.5 hr., evaporated to dryness and the 2-chloropyridine-1-oxides isolated as the hydrochlorides by recrystallization from butanol (Table III).

Preparation of the 2-Chloropyridine-1-oxides.—All of the 2-chloropyridines were prepared by the method of Siede.[7] To a mixture of 500 ml. of concd. hydrochloric acid and 36 g. of the aminopyridine cooled to 0° was added 35 g. of sodium nitrite in the usual manner. The reaction mixture was allowed to come to room temperature overnight and was then steam distilled and fractionated *in vacuo*. Two tenths mole of the 2-chloropyridines was treated with 25 ml. of glacial acetic acid and 22 ml. of 40% peracetic acid. The temperature was moderated to 70° then held at 70° for 3 hr. A slight excess of concd. hydrochloric acid was added, and the solvent was removed at reduced pressure. The chloropyridine-1-oxide hydrochlorides were recrystallized from butanol (Table III).

Nitration of the 2-Chloropyridine-1-oxides.—To a mixture of 2.2 g. of the above hydrochloride dissolved in 3 ml. of concd. sulfuric acid was added a mixture of 2.5 ml. of fuming HNO_3 (sp. gr. 1.50) and 5 ml. of concd. sulfuric acid. The reaction mixture was heated on a steam-bath for 4 hr., neutralized with sodium carbonate and extracted with benzene. Evaporation of the benzene left practically quantitative yields of crude nitro compounds which were recrystallized from absolute ethanol (Table IV).

Acknowledgment.—We are grateful to the Lasdon Foundation for a grant-in-aid of this project.

SOUTH ORANGE, NEW JERSEY

(8) We are grateful to the Buffalo Electrochemical Company for a generous supply of 40% peracetic acid and 27.5% hydrogen peroxide.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Phosphorus Compounds. I. Reduction of Benzylphosphonium Compounds with Lithium Aluminum Hydride[1]

BY WILLIAM J. BAILEY AND SHELDON A. BUCKLER[2]

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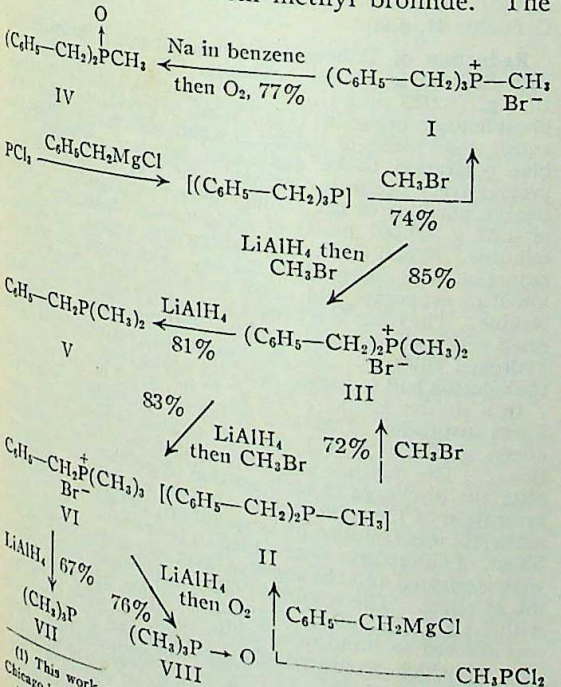
Lithium aluminum hydride in tetrahydrofuran was employed to remove a benzyl group from a benzylphosphonium compound in high yield to produce a tertiary phosphine. Reduction followed by alkylation of the resulting phosphine was shown to be a very excellent method for the replacement of a benzyl group with an alkyl group. This procedure can conveniently be used for the stepwise synthesis of a variety of tertiary phosphines. Thus tribenzylmethylphosphonium bromide (I), prepared in a 74% yield from phosphorus trichloride, was reduced with lithium aluminun hydride, and the product was alkylated to produce dibenzyldimethylphosphonium bromide (III) in an over-all yield of 85%. III, in turn, was reduced and the phosphine was alkylated in a similar manner to produce benzyltrimethylphosphonium bromide (VI) in an over-all yield of 83%. Further reduction of VI with lithium aluminum hydride produced trimethylphosphine in a 67% yield.

The reductive cleavage of benzyl groups bonded to nitrogen, oxygen and sulfur is a well-known phenomenon and has received considerable study. It recently has been the subject of a comprehensive review.[3] Reductions have been effected by both catalytic and chemical means, and the chief utility of this reaction has been to remove, under relatively mild conditions, benzyl groups which had served as blocking agents in some preliminary reactions. This is a report of the extension of this reductive cleavage to benzyl-containing phosphonium compounds, accomplished most effectively by lithium aluminum hydride.

Tribenzylmethylphosphonium bromide (I) was used for the preliminary study of the reductive cleavage of benzyl groups. The bromide I was readily prepared in a 74% yield by the reaction of 3 moles of benzylmagnesium chloride with phosphorus trichloride, followed by direct treatment of the ethereal extracts with methyl bromide. The intermediate tribenzylphosphine was not isolated because of the facile air oxidation of benzyl-containing phosphines.



Benzylammonium compounds have been reduced by hydrogen with palladium catalyst[4] and sodium amalgam[5]; the latter method has had the widest applicability. For example, Emde[5a] found that dibenzyldimethylammonium chloride was reduced to benzyldimethylamine in 91% yield by sodium amalgam in aqueous solution.

Attempts to reduce I by hydrogen and palladium were unsuccessful, even at elevated temperature and pressure. An initial success was realized by the use of sodium in liquid ammonia. When small pieces of sodium were added to a slurry of the phosphonium compound I in this medium, discharge of the blue coloration was observed until four equivalents of sodium had been consumed. No further reduction occurred. A distinct phosphine odor was present after the ammonia had been removed by evaporation, but no product corresponding to the removal of the two benzyl groups could be isolated. When the experiment was repeated with only two equivalents of sodium, the product corresponding to the removal of one benzyl group, dibenzylmethylphosphine (II), was formed. Since II was oxidized easily in air, it was not isolated but was converted to its methyl bromide derivative, dibenzyldimethylphosphonium bromide (III), which was isolated in a 29% over-all yield. When this experiment was performed without a nitrogen atmosphere, the phosphine was converted directly to its oxidation product, dibenzylmethylphosphine oxide (IV), which was isolated in a 39% over-all yield.

Reduction of the benzylphosphonium compound I by means of sodium in warm ethanol was also successfully carried out. Again, the product was isolated as the oxide IV, in a 64% over-all yield. The I also was debenzylated by means of sodium in refluxing benzene; 77% of the theoretical amount of IV was isolated in this case. However, lithium aluminum hydride in tetrahydrofuran proved to be the most convenient as well as the most effective debenzylating agent for all the benzylphosphonium compounds studied. When a slurry of finely pow-

(1) This work was done on a subcontract with the University of Chicago in fulfillment of a contract with the Chemical Corps.

(2) Member of the Armed Forces assigned to the Army Chemical Corps.

(3) W. H. Hartung, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 263.

(4) L. Birkofer, *Ber.*, **75**, 429 (1942).

(5) (a) H. Emde, *Arch. Pharm.*, **247**, 314, 351, 369 (1909); (b) H. Emde and H. Schellbach, *ibid.*, **249**, 111, 118 (1911); (c) W. H. Perkin, Jr., *Chem. Soc., Trans.*, **105**, 815 (1914); (d) R. H. F. Manske, L. Marion and A. E. Ledingham, THIS JOURNAL, **64**, 1659 (1942).

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dered I was heated under reflux in a tetrahydrofuran solution of the hydride for 5.5 hr., the reduction product was obtained as its methyl bromide derivative III in an 85% over-all yield. No appreciable amount of reduction was observed, however, when diethyl ether was used as the solvent.

A similar study of the conditions required for debenzylation was carried out on the dibenzyldimethylphosphonium bromide (III). An alternative preparation of III was carried out in a 72% yield by the reaction of 2 moles of benzylmagnesium chloride with methyldichlorophosphine, followed by treatment of the resulting phosphine II with methyl bromide. In contrast to the work of Emde[5a] with dibenzyldimethylammonium compounds, III was not reduced with sodium amalgam. When the phosphonium derivative III was treated with this same reagent, no phosphine was detected and no other evidence of reduction was observed. Stannous chloride in acidic solution proved to be equally ineffectual as a reducing agent. In spite of the fact that sodium in liquid ammonia, in warm ethanol or in refluxing benzene produced some debenzylation of I, none of these combinations was at all successful for the reduction of III. Apparently the lower solubility of III, compared to I, could account for this difference. However, when the dibenzylphosphonium derivative III was reduced with lithium aluminum hydride in tetrahydrofuran, the debenzylated product, benzyldimethylphosphine (V), was isolated in an 81% yield. When the ethereal extracts from a similar reaction were treated directly with methyl bromide, benzyltrimethylphosphonium bromide (VI) was obtained in an 83% yield. VI also was successfully reduced by lithium aluminum hydride. The product, trimethylphosphine (VII), was isolated in a 67% yield by slow distillation of the reducing mixture without preliminary hydrolysis. The true yield was probably greater, and the amount obtained reflects the difficulty in the separation of a small amount of VII from the tetrahydrofuran, which boils only 27° higher. That this was the case was shown by the introduction of a slow stream of air through a solution of crude VII combined with the higher boiling tetrahydrofuran fraction. Trimethylphosphine oxide (VIII) was obtained in a 76% over-all yield.

The action of lithium aluminum hydride has thus been shown to be a very effective method for debenzylating phosphonium compounds containing one, two or three benzyl groups. All these reactions proceeded smoothly and in reasonably high yields. The reaction is thought to proceed selectively in the sense that only one benzyl group is removed at a time, since even if a large excess of lithium aluminum hydride was used, the products corresponding to the removal of one benzyl group were the only ones isolated. The reaction can be envisioned as proceeding by hydride attack on a benzyl carbon atom, followed by ejection of the neutral tertiary phosphine with its free pair of electrons. The formal positive charge on the phosphorus atom, even though partially neutralized in a complex, probably furnishes the driving force for the reaction. The tertiary phosphine formed probably does not react further because of the absence of a positive charge or because of the necessity for the development of a negative charge on the phosphorus atom during the reduction.

The over-all result of the alkylation of a benzylphosphine, followed by reductive cleavage of the product, is the replacement of a benzyl group by an alkyl group. The extension of these observations to the synthesis of unsymmetrical, tertiary phosphines will be reported separately.

Experimental[6]

Except where otherwise noted, all phosphines, solutions of phosphines and Grignard reagents were prepared and handled in an atmosphere of nitrogen purified by passage through basic pyrogallol traps.

Tribenzylmethylphosphonium Bromide (I).—Benzylmagnesium chloride, prepared in the usual way from 12.2 g. (0.5 mole) of magnesium, 63.3 g. (0.5 mole) of freshly distilled benzyl chloride and 400 ml. of anhydrous ether, was diluted with 100 ml. of additional ether and cooled in a salt–ice bath. A solution of 22.0 g. (0.16 mole) of phosphorus trichloride in 100 ml. of ether was added over a period of 1.5 hr. with cooling and stirring. After the stirring was continued for an additional 30 minutes, the mixture was hydrolyzed by the addition of 150 ml. of water, followed by 200 ml. of a saturated ammonium chloride solution, at a rate such that gentle refluxing ensued. Stirring was stopped, the solids were allowed to settle and most of the ether solution was removed through a glass tube by the application of an excess nitrogen pressure. After 250 ml. of chloroform was added and the mixture was stirred, the layers were separated. The organic layers were combined, cooled in an ice-bath and treated with 30.4 g. (0.32 mole) of methyl bromide. The mixture was allowed to stand under a Dry Ice condenser for 40 hr. The precipitated crystalline salt was then removed by filtration and was washed thoroughly with ether to give 47.5 g. (74%) of slightly impure tribenzylmethylphosphonium bromide (I), m.p. 222–226°. Two recrystallizations from the minimum quantity of ethanol gave 41.0 g. (64%) of pure material, m.p. 229–229.5°.

Anal. Calcd. for $C_{22}H_{24}BrP$: C, 66.17; H, 6.06. Found: C, 66.00; H, 5.90.

Reduction of Tribenzylmethylphosphonium Bromide (I) with Sodium in Liquid Ammonia.—To a stirred slurry of 10.0 g. (0.025 mole) of finely powdered tribenzylmethylphosphonium bromide (I) in 100 ml. of liquid ammonia were added small pieces of sodium at a rate sufficient to allow the blue coloration to be discharged between additions. (A progressively deepening orange color was observed as successive portions of the sodium were discharged.) A total of 2.32 g. (0.101 mole) of sodium was consumed in 265 minutes. When additional sodium was added, no further reduction was observed in 2.5 hr. The ammonia was allowed to evaporate and water and ether were added to the residue. The ether layer (with a strong phosphine odor) was dried with sodium sulfate and was saturated with anhydrous hydrogen chloride. No precipitate was formed even after the solution had remained at 0° for a long time.

In a similar fashion, 20.0 g. (0.05 mole) of the bromide I was suspended in 200 ml. of liquid ammonia and was reduced with 2.30 g. (0.1 mole) of sodium (added in six portions). The mixture was stirred vigorously for 10 minutes after the discharge of each portion of sodium to ensure saturation of the solvent with starting material. After the ammonia was removed by evaporation, 100 ml. of water and 50 ml. of chloroform were added to the residue. The layers were separated and the aqueous layer was extracted with 100 ml. of ether. The combined organic solutions were treated with 7.1 g. (0.075 mole) of methyl bromide, and the mixture was allowed to stand in a tightly stoppered flask for 40 hr. The oil which separated was removed and it crystallized when it was stored at −20°. Recrystallization from methylisobutylcarbinol yielded 4.45 g. (29%) of dibenzyldimethylphosphonium bromide (III), m.p. 138–141°. Further recrystallization from methylisobutylcarbinol–petroleum ether produced analytically pure III, m.p. 141–142°.

(6) The authors are grateful to Dr. Mary Aldridge and Kathryn Gehlman for the analyses. All melting points and boiling points are corrected.

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Anal. Calcd. for $C_{16}H_{20}BrP$: C, 59.45; H, 6.24; Br, 24.73; P, 9.59. Found: C, 59.23; H, 6.37; Br, 24.61; P, 9.43.

In a similar experiment conducted without a nitrogen atmosphere, dibenzylmethylphosphine oxide (IV) was obtained in a 39% yield by the removal of the ammonia by evaporation after reduction, followed by the addition of water and the subsequent removal of the white solid thus obtained. Recrystallization from benzene–petroleum ether gave white needles of the phosphine oxide IV, m.p. 133.5–134.0°.

Anal. Calcd. for $C_{15}H_{17}OP$: C, 73.75; H, 7.02; P, 12.68. Found: C, 73.71; H, 6.75; P, 12.61.

Reduction of I with Sodium in Alcohol.—To a solution of 5.0 g. (0.0125 mole) of tribenzylmethylphosphonium bromide (I) in 40 ml. of warm anhydrous ethanol was added 0.58 g. (0.025 mole) of sodium in three portions. After all the sodium had reacted, 150 ml. of water was added and the resulting solution was extracted with two 150-ml. portions of ether. The organic solution was dried with Drierite, and the ether and ethanol were removed by evaporation. The oily residue gradually solidified when it was exposed to air. This material was recrystallized from benzene-petroleum ether to give 1.95 g. (64%) of dibenzylmethylphosphine oxide (IV) as white needles, m.p. 133.5–134.0°. This sample of IV showed no depression of melting point upon admixture with the oxide IV obtained from the sodium in liquid ammonia reduction described above.

Reduction of I with Sodium in Benzene.—A suspension of 5.0 g. (0.0125 mole) of tribenzylmethylphosphonium bromide (I) and 0.58 g. (0.025 mole) of sodium in 100 ml. of anhydrous benzene was heated under reflux for 5 hr. Since a few specks of sodium were unreacted, 10 ml. of anhydrous ethanol was then added. When all the sodium was consumed, 100 ml. of water was added. A solid, which was insoluble in either the aqueous or organic layer, was removed by filtration and was proved to be starting material, m.p. 228.5–229.5° (no depression with an authentic sample). The benzene layer was separated and the aqueous layer was extracted with ether. The combined organic solutions were concentrated by evaporation to give an oil which solidified when it was exposed to air. The solid was recrystallized from benzene–petroleum ether to give 1.85 g. (77% yield, when corrected for the amount of starting material recovered) of dibenzylmethylphosphine oxide (IV), m.p. 133.5–134.0°. This sample of IV showed no depression of melting point upon admixture with the substance obtained from sodium in liquid ammonia reduction described previously.

Dibenzyldimethylphosphonium Bromide (III). A. By Reduction of Tribenzylmethylphosphonium Bromide (I) with Lithium Aluminum Hydride.—To a suspension of 10.0 g. (0.025 mole) of finely powdered tribenzylmethylphosphonium bromide (I) in 125 ml. of dry tetrahydrofuran was added 0.6 g. (0.0158 mole) of lithium aluminum hydride, and the mixture was heated under reflux for 5.5 hr. Most of the tetrahydrofuran was then removed by distillation, and the residue was treated cautiously with 100 ml. of commercial ether and 80 ml. of 20% sodium potassium tartrate solution. The layers were separated and the aqueous layer was extracted with 75 ml. of ether. The combined ether extracts were placed in a pressure bottle with 10 ml. of methyl bromide, and the mixture was allowed to stand at room temperature for 48 hr. The crystalline solid which was deposited was removed by filtration and recrystallized from methylisobutylcarbinol–petroleum ether to give 6.90 g. (85% over-all yield) of dibenzyldimethylphosphonium bromide (III), m.p. 141–142°. There was no depression of the melting point when this material was mixed with an authentic sample of III. When diethyl ether was used as a solvent, the phosphonium compound I did not gradually dissolve (as was observed when tetrahydrofran was used) and only a slight phosphine odor was detected after the reaction mixture was heated under reflux for 24 hr.

B. From Methyldichlorophosphine.—Benzylmagnesium chloride was prepared from 24.3 g. (1.0 mole) of magnesium, 126.6 g. (1.0 mole) of freshly distilled benzyl chloride and 900 ml. of anhydrous ether. The reagent was cooled in an ice-bath while 53.8 g. (0.46 mole) of freshly distilled methyldichlorophosphine, b.p. 77–79°, (Army Chemical Center, Maryland) in 200 ml. of ether was added over a 2-hr. period with stirring. The mixture was stirred for an additional hour and then was hydrolyzed with 200 ml. of water and 300 ml. of a saturated ammonium chloride solution. The layers were separated and the aqueous layer was extracted with 200 ml. of ether. To the combined ether solutions was added 87.4 g. (0.92 mole) of methyl bromide, and this mixture was allowed to stand at room temperature in a stoppered flask for 48 hr. The solid was then collected by filtration and recrystallized from methylisobutylcarbinol–petroleum ether to yield 107 g. (72%) of dibenzyldimethylphosphonium bromide (III), m.p. 141–142°.

Attempted Catalytic Reduction of III.—To a solution of 5.0 g. (0.016 mole) of dibenzyldimethylphosphonium bromide (III) in 35 ml. of acetic acid (distilled from potassium permanganate) was added 2.5 g. of a freshly prepared 25% palladium-on-charcoal catalyst. The mixture was shaken in a hydrogen atmosphere at 100° and 900 lb./sq. inch for 15 hr. No uptake of hydrogen was observed and 92% of the starting material was recovered in pure form. Similar low pressure experiments with either III or tribenzylmethylphosphonium bromide (I) were unsuccessful.

Benzyldimethylphosphine (V).—A mixture of 45.0 g. (0.14 mole) of finely powdered dibenzyldimethylphosphonium bromide (III), 2.4 g. (0.063 mole) of lithium aluminum hydride and 300 ml. of dry tetrahydrofuran was heated under reflux for 5 hr. Most of the tetrahydrofuran was then removed by distillation and 300 ml. of commercial ether and 250 ml. of 20% sodium potassium tartrate solution were added cautiously. The layers were separated and the aqueous layer was extracted with two 100-ml. portions of ether. The combined ether solutions were dried with magnesium sulfate and the ether was removed by distillation through a 12-inch Vigreux column. The residue was fractionated through the same column to yield 17.1 g. (81%) of benzyldimethylphosphine (V), b.p. 87–89° (10 mm.), $n^{20}D$ 1.5416 [reported[7] b.p. 93–96° (12 mm.)].

Benzyltrimethylphosphonium Bromide (VI).—When 45.0 g. (0.14 mole) of dibenzyldimethylphosphonium bromide (III) was reduced by the exact procedure described above, the ether extracts were not distilled but were treated directly with an excess of methyl bromide in a stoppered flask for 48 hr. The solid was removed by filtration and recrystallized from methylisobutylcarbinol–petroleum ether to yield 28.6 g. (83% over-all yield) of benzyltrimethylphosphonium bromide (VI), m.p. 223–225° (reported[8] m.p. 222°).

Reduction of Benzyltrimethylphosphonium Bromide (VI) with Lithium Aluminum Hydride.—To a suspension of 18.0 g. (0.073 mole) of finely powdered benzyltrimethylphosphonium bromide (VI) in 100 ml. of dry tetrahydrofuran was added 1.52 g. (0.04 mole) of lithium aluminum hydride, and the mixture was heated under reflux for 3 hr. The reaction mixture was slowly fractionated through a 12-inch Vigreux column at a reflux ratio of 17:1. A total of 3.73 g. (67%) of trimethylphosphine, b.p. 40–43° (reported[9] b.p. 37.8°), was collected.

Distillation was then continued to collect all material boiling below 65°. This crude material was combined with the lower boiling fraction of pure trimethylphosphine (VII) and the mixture, dissolved in 100 ml. of anhydrous ether, was placed in a flask equipped with a gas-inlet tube and Dry Ice condenser. Dry air was bubbled through the solution for 5 hr., and the crystalline trimethylphosphine oxide (VIII) which formed was removed by filtration. The solid was dried in a vacuum desiccator to give 5.10 g. (76% yield based on VI) of slightly impure trimethylphosphine oxide (VIII), m.p. 135–137° (sealed capillary). Recrystallization of this crude material from tetrahydrofuran–ethyl acetate produced the pure oxide VIII, m.p. 137–138° (reported[10] m.p. 137.5–138.5°).

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[CONTRIBUTION FROM THE CHEMICAL CORPS, CHEMICAL RESEARCH DIVISION, CHEMICAL WARFARE LABORATORIES]

Organic Phosphorus Compounds. I. The Conversion of the Chloroaluminate Complexes, $[RPCl_3][AlCl_4]$, to Alkyl Alkylphosphonochloridates and Dialkyl Alkylphosphonates

BY FRIEDRICH W. HOFFMANN,[1] THOMAS C. SIMMONS AND LOUIS J. GLUNZ III

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Phosphorus trichloride can be converted in methylene chloride solution in good yields by a simple one-batch procedure with alkyl chloride and aluminum chloride to the intermediate chloroaluminate complexes, $[RPCl_3][AlCl_4]$ (I) or $[RPCl_3][Al_2Cl_7]$, and by alcoholysis further to alkyl alkylphosphonochloridates or dialkyl alkylphosphonates. It is shown that the complexes I are converted by alcoholysis stepwise to $[RP(O)Cl][AlCl_4]$, $[RP(O)OR'][AlCl_4]$ and finally to $[RP(O)(OR')_2 \cdot AlCl_3]$, all of which can be decomposed with water to yield $RP(O)Cl_2$, $RP(O)(OR')Cl$ and $RP(O)(OR')_2$, respectively, and hydrated aluminum salts.

Introduction.—The various methods described in the literature for the preparation of phosphonic acids and their derivatives[2] have been supplemented recently by a simple general procedure which utilizes the ready formation of complexes of the type $[RPCl_3][AlCl_4]$ (I) from equimolar amounts of alkyl chloride, aluminum chloride and phosphorus trichloride.[3-5]

Treatment of the complexes I in methylene chloride solution with 7–11 mole equivalents of water gives the corresponding alkylphosphonyldichloridates, $RP(O)Cl_2$ (II), generally in good yields.[3-5] Perren and Kinnear[5] also demonstrated by one example that the I can be converted directly with ethanol to the corresponding diethyl alkylphosphonate, in their example the ethylphosphonate, $C_2H_5P(O)(OC_2H_5)_2$ (III).

The mechanisms proposed by Clay[3] and by Kinnear and Perren[4] for the formation of the dichlorides II differ with regard to the first step of the reaction. While Clay assumes that the first mole equivalent of water attacks the cation of the complex I forming by hydrolytic cleavage a $[RP(O)Cl]^+$ cation and thus a new ionic complex $[RP(O)Cl][AlCl_4]$ (IV), the British authors believe the first step of the hydrolysis to be a hydrolytic cleavage of the ionic complex I into $H[AlCl_4]$ and $RPCl_3 \cdot OH$. The intermediate, having an unstable electron decet around the phosphorus atom, is then stabilized by elimination of HCl resulting in the formation of II.

Since ethanolysis of the complex $[C_2H_5PCl_3][AlCl_4]$ (V) is reported[5] to give III in 92% yield, while its hydrolysis resulted in the isolation of 82% of $C_2H_5P(O)Cl_2$ (VI), it appears that the complexes I can be utilized, at least in some cases, directly as starting materials for the synthesis of valuable organic phosphorus derivatives without the intermediate isolation of the dichlorides II. Clarification of the mechanism of the solvolysis of I would allow a proper selection of suitable conditions for the conversion to products other than II. Therefore, a study of the stepwise alcoholysis of I was undertaken. The results of this investigation enabled us to devise a useful method for the synthesis of alkyl alkylphosphonochloridates and dialkyl alkylphosphonates directly from the appropriate alkyl halides.

Summary of Results.—The complex $[CH_3PCl_3][AlCl_4]$ (VII), suspended in methylene chloride solution, deposited upon treatment with one mole equivalent of absolute methanol at 25° the less soluble crystalline complex $[CH_3P(O)Cl][AlCl_4]$ (VIII), the composition of which was established by independent synthesis and by analysis. The high thermal stability of the distillable complex VIII indicates strong complexing of its components.

The postulated breakdown of the complexes I into II and $H[AlCl_4]$ by which Kinnear and Perren[4] explain the hydrolysis to II seems to be disproved by the formation of the complex VIII from its components. The tendency of II to enter into complex formation with aluminum chloride is much too high to allow its coexistence with the weak complex $H[AlCl_4]$ in a solution. If the products II and $H[AlCl_4]$ existed at any time in the reaction mixture, complex formation to IV would occur with the elimination of hydrogen chloride. In other words, the first step of the hydrolysis appears to proceed in the fashion suggested by Clay[3] with the formation of IV.

The treatment of complex VII with two mole equivalents of methanol resulted in the formation of another complex with the elimination of hydrogen chloride. This new complex analyzes for a composition of an adduct of methyl methylphosphonochloridate, $CH_3P(O)(OCH_3)Cl$, and aluminum chloride and may possibly be formulated as $[CH_3P(O)OCH_3][AlCl_4]$. The reaction of VII with an additional, *i.e.*, with three, mole equivalent of methanol gave again a complex which could be isolated as a stable solid from the reaction mixture. The resulting product had the approximate composition $CH_3P(O)(OCH_3)_2 \cdot AlCl_3$.

Conclusive evidence for the stepwise alcoholysis of I to new complex intermediates was obtained by ethanolysis of V in methylene chloride solution with one, two and three mole equivalents of absolute ethanol. The nuclear magnetic resonance (NMR) spectra of the resulting products were identical for all practical purposes with the spectra of the complexes prepared in methylene chloride solution from anhydrous aluminum chloride and VI, $C_2H_5P(O)(OC_2H_5)Cl$, (IX) and III, respectively. The chemical shift (δ) values for the various complexes prepared by alcoholysis of V and by direct synthesis from the components, and also for the

(1) To whom inquiries about this paper should be directed.

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phosphorus-containing components of the complexes are listed in Table I.

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA[6]

P^{31} RESONANCE

Compound	Chemical shift, δ[a,b]
$[C_2H_5PCl_3][AlCl_4]$ (V)	−128.6
$[C_2H_5PCl_3][Al_2Cl_7]$ (XVI)	−128.6
$C_2H_5P(O)Cl_2$[c] (VI)	−53.0
$[C_2H_5P(O)Cl][AlCl_4]$ (X)[d]	−75.8
$[C_2H_5P(O)Cl][AlCl_4]$ (X)[e]	−77.4
$[C_2H_5P(O)OC_2H_5][AlCl_4]$[f]	−53.8
$[C_2H_5P(O)OC_2H_5][AlCl_4]$[g]	−54.5
$C_2H_5P(O)(OC_2H_5)Cl$ (IX)	−45.0
$[C_2H_5P(O)(OC_2H_5)_2\cdot AlCl_3]$[h]	−31.0
$[C_2H_5P(O)(OC_2H_5)_2\cdot AlCl_3]$[i]	−31.0
$C_2H_5P(O)(OC_2H_5)_2$ (III)	−32.8

[a] Chemical shift, $\delta = (H \text{ sample} - H_{H_3PO_4}) \times 10^6/H_{H_3PO_4}$; the operating radio frequency for these measurements was 17 megacycles. [b] The spectra were taken in methylene chloride solution except where stated otherwise. [c] Without solvent. [d] From V and one mole of absolute ethanol. [e] From VI and $AlCl_3$. [f] From V and two moles of absolute ethanol. [g] From IX and $AlCl_3$. [h] From V and three moles of absolute ethanol. [i] From III and $AlCl_3$.

That VI is not formed by alcoholysis of V with one mole equivalent of ethanol is clearly demonstrated by the differences of the chemical shift values between VI and its complex with aluminum chloride, $[C_2H_5P(O)Cl][AlCl_4]$ (X). The presence of VI in quantities of more than 2–3% of the total amount of phosphorus in the solution of the alcoholysis product of V with one mole of ethanol and of the product from VI and aluminum chloride would have been observed in the spectra of the two samples of complex X.

The chemical shifts of −53.8 and −54.5 observed for the solvolysis product of V with two mole equivalents of ethanol and for the reaction product of IX with aluminum chloride, respectively, again prove the identity of the reaction products. The smaller shift of −45.0 shown by IX seems to indicate that the conversion of a covalent P–Cl bond to an ionic bond results in a larger chemical shift. The same observation is made in the conversion of VI to X. The NMR spectrum of the reaction product of V with three moles of ethanol was identical with that of the synthetic complex obtained from III and aluminum chloride. The absence of a chemical shift to a more negative value upon complexing III can be regarded, on the basis of the foregoing observations, as indicative for the absence of a conversion of a covalent P–O bond to an ionic bond and can best be explained by the non-ionic structure $[C_2H_5P(O)(OC_2H_5)_2\cdot AlCl_3]$ for the complex.

None of the conversion complexes formed by alcoholysis of I can be broken by the usual techniques, such as treatment with sulfuryl chloride, phosphorus oxychloride, triethylamine or fusion with sodium chloride, but requires hydration of the $[AlCl_4]^-$ anion to aluminum chloride hydrate and hydrogen chloride.

(6) The NMR spectra reported in this paper were measured and interpreted by Messrs. Harold Finegold and G. F. Svatos employing the same instrumentation and technique as described by Messrs. F. C. Lauterbur and Jerome Goldenson, THIS JOURNAL, 78, 3557 (1956). The authors gratefully acknowledge this valuable help.

The reaction scheme involved in the alcoholysis, synthesis and cleavage of the various complexes is illustrated in Fig. 1.

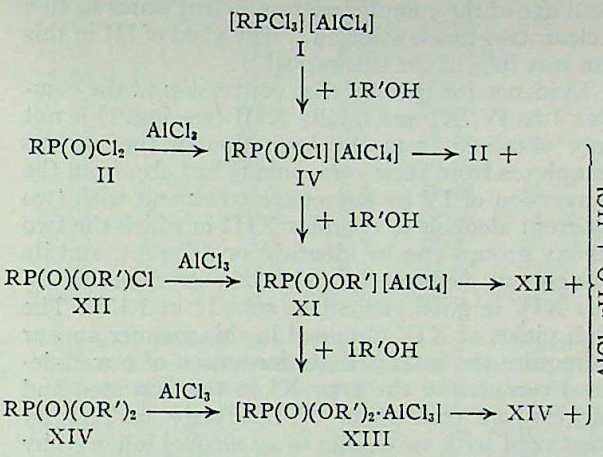

Fig. 1.

The first step of the alcoholysis of I (as well as of the hydrolysis) is the conversion to IV with the replacement of two chlorine atoms by one oxygen atom and the formation of alkyl chloride and hydrogen chloride. This reaction takes place in all probability by a nucleophilic displacement of a chloride ion on the phosphorus by the alkoxide ion followed by elimination of alkyl halide. A repetition of the nucleophilic displacement reaction on the cation of IV leads to the formation of the cation $[RP(O)OR']^+$ (XV). The conversion of IV to XI corresponds to the reaction of II with one mole equivalent each of an alcohol and a base leading to the chloridate XII. The role of the base is taken over in the system IV–R'OH by the displaced chloride ion which removes the proton as undissociated HCl. A similar situation prevails for the further alcoholysis of XI to XIII, except that here the nucleophilic attack of the alkoxide ion on the phosphorus atom of the cation XV results in a neutral molecule XIV, which forms an un-ionized complex with aluminum chloride. The chloride ion liberated from the anion $[AlCl_4]^-$ by the complexing is taken up by the proton originating from the alcohol.

Clay[3] and Kinnear and Perren[4] demonstrated that further treatment of the complex IV with one to fourteen moles of water (depending on the nature of the alkyl group) gives the corresponding II in good yields. The direct conversion of complex V with absolute ethanol until no further reaction occurred, followed by treatment with water,[5] showed that the isolation of the II is unnecessary for the synthesis of the phosphonates XIV. While the formation of XIV from II in acceptable yields requires the presence of two mole equivalents of a base as an acceptor for the liberated hydrogen chloride, no base is necessary in the conversion of I to XI and further to XIV. Complex V treated in methylene chloride solution with seven moles of ethanol (see run 5) and water added dropwise to the reaction mixture until the original gelatinous precipitate dissolved gave an 80% yield of III.

That not more than three mole equivalents of alcohol are actually required for the formation of III is demonstrated clearly by a run (no. 2) in which a

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solution of V in methylene chloride was at first treated for conversion to $C_2H_5P(O)(OC_2H_5)_2 \cdot AlCl_3$ with three mole equivalents of ethanol and then for cleavage of the complex with sufficient water to give a clear, two-phase solution. The yield of III in this run was 76% of the theoretical.

Evidence for the stepwise conversion of the complex I to IV, XI and finally XIII (see Fig. 1) is not only obtained from the formation of the various complexes from their components but also from the conversion of IV by successive treatment with two different alcohols to complex XIII in which the two alkoxy groups can be identical or different, and its subsequent cleavage to yield the corresponding esters XIV in good yields (see runs 11 and 13). The high yields of XIV obtained in this manner appear to require the intermediate formation of a well-defined complex of the type XI in the first step and suggest the conversion of I directly to XII by treatment with two moles of an alcohol followed by cleavage of the intermediate complex XI with a limited amount of water. This reaction sequence permits the conversion of phosphorus trichloride through the readily obtainable complexes I in a simple one-batch method to the valuable alkylphosphonochloridates XII (see runs 14–17) in acceptable yields.

Since the first mole of alcohol in the reaction with the complex I serves merely the purpose of replacing two chlorine atoms of the cation by an oxygen atom, any inexpensive alcohol, such as methanol or ethanol, can be employed in the first step of the alcoholysis. For the preparation of phosphonochloridates or phosphonates, the introduction of the desired alkoxy group or groups on the phosphorus atom can then be accomplished by means of the appropriate alcohol. The feasibility of this procedure is, in principle, demonstrated by run 13 in which the complex $[iso\text{-}C_3H_7PCl_3][AlCl_4]$ was first treated with ethanol (20% deficiency) and then with isopropyl alcohol (20% excess) and finally hydrolyzed with a limited amount of water to yield 62% of di-isopropyl isopropylphosphonate.

The methods of Clay[3] and of Kinnear and Perren[4] for the preparation of the II use the complexes I which are prepared in solid form. It was found, however, that the I also are formed readily in dry methylene chloride and that the resulting solutions can be converted further without the actual isolation of the complexes I. This procedure had in some cases the added advantage that discoloration of the reaction mixture which is observed in the formation of the I from isopropyl chloride can be avoided entirely. In general the complexes I are formed readily by adding the appropriate alkyl chloride slowly to a stirred solution of phosphorus trichloride in the solvent containing the equivalent amount of anhydrous aluminum chloride in suspension. Completion of the complex formation is indicated by the disappearance of the aluminum chloride.

While the reaction products from equimolar quantities of phosphorus trichloride, aluminum chloride and alkyl chloride gave generally the solvolysis products of the I in good yields, it was observed that similar runs with ethyl chloride led consistently to yields below 50% of the theoretical (see run 3). A methylene chloride solution of the complex V (prepared from the components without solvent), on the other hand, could be converted in 62% yield to IX (run 15) and in 80% yield to III (run 5). When a solution of the complex from ethyl chloride (prepared in methylene chloride) was evaporated under reduced pressure, the residue was not the solid complex I. The ratio of PCl_3: C_2H_5Cl:$AlCl_3$ was 1:1:2 in the residual viscous oily product. The same liquid material also was obtained by shaking a mixture of the reactants in the molar ratio 1:1:2 without solvent in a pressure bottle until the aluminum chloride had dissolved.

The formation of 1:1:2 complexes is described by Perren and Kinnear[5] without indicating the physical state of the resulting products. However, these authors make the general statement that the amount of complex-forming agent is not critical in determining the course of the reaction but is of importance to ensure the formation of liquid complexes.

The structure of the liquid complex of the composition $[C_2H_5Cl \cdot PCl_3 \cdot 2AlCl_3]$ can be either $[C_2H_5PCl_3][Al_2Cl_7]$ (XVI) or $[C_2H_5PCl_2]^{++}[2AlCl_4]^{--}$ (XVII). Since the complexes V and XVI have the same cation in common, identical NMR spectra are to be expected if the 1:1:2 complex possesses structure XVI. A structure of the type XVII, however, would result in a different chemical shift of the phosphorus resonance as compared to complex V. The δ-value of -128.6 for both, the 1:1:1 and the 1:1:2 complex, rules out formula XVII.

The formation of the complexes I from the components seems to proceed through the intermediate complexes $[RPCl_3][Al_2Cl_7]$ which react further with one mole equivalent of phosphorus trichloride and alkyl halide. A mixture of equal molar quantities of methyl chloride, phosphorus trichloride and anhydrous aluminum chloride mixed at Dry Ice temperature forms, when allowed to come to room temperature in a sealed Pyrex tube, in an exothermic reaction a clear, colorless liquid which solidifies on further shaking spontaneously within a few seconds to a solid crystal cake consisting of VII.[7] A similar observation was made in the preparation of the complex V, except that here the further conversion of the primarily formed XVI to V required heating to 60° or continued shaking overnight.

While the higher alkyl chlorides form the complexes I readily in methylene chloride as a reaction medium, the reaction of ethyl chloride in solution with phosphorus trichloride and aluminum chloride led only to XVI. This accounts for the low yield of III from ethyl chloride in run 3, when calculated on the basis of complex V instead of XVI as actually required.

For preparative purposes, the alcoholysis of I with absolute ethanol was preferable to that with other alcohols because of the solubility of the intermediate complexes in methylene chloride. When methanol was used instead of ethanol for the alcoholysis reactions, white crystals separated from the solutions and subsequent decomposition of the in-

[7] In the reaction of methyl chloride a very violent explosion occurred. In the preparation of the complex VII, the sealed tube should always be encased in a heavy steel pipe closed at the ends with steel screw caps.

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TABLE II

ELEMENTAL ANALYSES OF NEW PHOSPHORUS COMPOUNDS

Compound	Calcd. C	H	P	Cl	Found C	H	P	Cl
	Analyses, %							
i-$C_3H_7P(O)(OC_2H_5)_2$	46.66	9.51	17.19	...	46.5	9.5	16.85	...
i-$C_4H_9P(O)(OC_2H_5)_2$	49.47	9.86	15.95	...	49.6	9.9	...	...
$C_6H_{11}P(O)(OC_2H_5)_2$[a]	54.43	9.89	13.95	...	54.2	9.6	14.05	...
i-$C_3H_7P(O)(OCH_3)_2$	39.47	8.61	20.36	...	38.9	8.3	20.36	...
i-$C_3H_7P(O)(OC_2H_5)OCH(CH_3)_2$	49.47	9.86	15.95	...	49.1	10.1	16.31	...
i-$C_3H_7P(O)[OCH(CH_3)_2]_2$	51.91	10.17	14.88	...	50.3	10.1	15.64	...
$CH_3P(O)(OC_2H_5)Cl$	25.28	5.65	21.74	24.88	24.6	5.6	21.58	25.97
$C_2H_5P(O)(OC_2H_5)Cl$	30.68	6.44	19.79	22.65	29.9	6.3	19.90	21.76
i-$C_3H_7P(O)(OC_2H_5)Cl$	35.20	7.10	18.16	20.78	34.8	7.2	18.57	20.02
$CH_3P(O)(OC_3H_7)Cl$	30.68	6.44	19.79	22.65	30.9	6.5	19.69	21.61

[a] Diethyl cyclohexylphosphonate, previously prepared by R. Graf, *Chem. Ber.*, **85**, 9 (1952), b. 148° (1.5 mm.).

termediate complexes with excess water resulted in the formation of gelatinous precipitates, insoluble in more water or acid, which had to be separated by centrifugation.

The yields of chloridates or dialkyl esters obtained in the various alcoholysis runs (see Tables III, IV and V) are not representative of optimum results but can be improved without doubt. It is interesting to note that, although the I from *t*-butyl chloride and from carbon tetrachloride can be hydrolyzed to give the corresponding II in good yields,[4,8] the alcoholysis of the *t*-butyl complex with excess ethanol followed by hydrolytic cleavage gave only *t*-butylphosphonodichloridate, while that of the trichloromethyl complex resulted in the formation of intractable products.

The analytical values of the new phosphorus compounds obtained in this investigation are listed in Table II.

Acknowledgment.—We are indebted to the personnel of the Analytical Research Branch, Chemical Research Division, for the performance of all elemental analyses reported in this paper.

Experimental

Preparation of the Chloroaluminate Complexes.—The solid complexes $[CH_3PCl_3][AlCl_4]$ (VII) and $[C_2H_5PCl_3][AlCl_4]$ (V) were prepared by the method of Kinnear and Perren.[4] Thus, 0.55 mole of anhydrous aluminum chloride and 0.50 mole of phosphorus trichloride was charged to a Pyrex glass pressure bottle of 350-cc. capacity and cooled in a Dry Ice–acetone-bath. To the cooled mixture was then added 0.60 mole of precooled methyl or ethyl chloride. The sealed pressure container was shaken mechanically overnight, during which time the reaction mixture solidified to a colorless crystal cake. The preparation of V was speeded up by shaking the mixture of the reactants for approximately 1 hr. until the aluminum chloride had dissolved and then heating for another hour to 60°.

The liquid complex $[C_2H_5PCl_3][Al_2Cl_7]$ (XVI) was prepared in a similar fashion by shaking a mixture of 0.5 mole of phosphorus trichloride, 1.0 mole of anhydrous aluminum chloride and 70 cc. of ethyl chloride in a pressure bottle at room temperature until a clear solution was obtained.

All complexes of type I with alkyl groups higher than ethyl were prepared in methylene chloride as the reaction medium. The preparation of the complex from isopropyl chloride, representative of the general procedure, is described in detail.

Dry methylene chloride (200 cc.) was placed in a 1-l., three-neck, round-bottom flask equipped with dropping funnel, mercury-sealed stirrer, pot thermometer and reflux condenser. The system was protected against atmospheric moisture by a drying tube charged with anhydrous calcium chloride. Phosphorus trichloride (68.5 g., 0.5 mole) and 64 g. (0.5 mole) of powdered, anhydrous aluminum chloride (Baker and Adamson, reagent grade, sublimed) were added successively to the solvent. The aluminum chloride remained undissolved in the mixture. The contents of the flask was then cooled to 0° and 44 g. (0.55 mole) of isopropyl chloride was added to the vigorously stirred mixture dropwise at such a rate as to maintain the temperature between 5 and 15°. Throughout the entire addition, the reaction vessel was immersed in an ice–water-bath. As the reaction progressed, the aluminum chloride went slowly into solution. The resulting colorless solution of $[(CH_3)_2CHPCl_3][AlCl_4]$ was allowed to warm to room temperature and used for further reactions.

Alcoholysis of the Chloroaluminate Complexes.—In general, a solution of the appropriate complex in dry methylene chloride (prepared either as described in the preceding paragraph or by dissolving the solid I in methylene chloride) was stirred vigorously and the desired amount of the alcohol was added without external cooling dropwise at such a rate as to keep the mixture refluxing gently. After the addition of the alcohol was completed, the mixture was refluxed for a period of 2–8 hr. and then cooled. The resulting solutions were treated further with vigorous stirring with water or dilute hydrochloric acid in order to break up the conversion complexes formed by alcoholysis.

Method A.—The hydrolytic cleavage of the intermediate complexes was accomplished by adding sufficient water to the methylene chloride solution at 10–20° to dissolve the gelatinous precipitate which was formed initially. The resulting liquid layers were separated and the heavy methylene chloride layer concentrated in a Rinco evaporator[9] under reduced pressure. The residual liquid product was fractionated under reduced pressure.

Method B.[10]—In an alternate procedure for the hydrolytic decomposition of the conversion complexes, water was added at −25° with vigorous stirring or with shaking in a separatory funnel to the complex solution (cooled occasionally by adding Dry Ice pellets) in an amount just sufficient to coagulate the initially formed, gelatinous aluminum salt. The resulting granular precipitate was filtered on a büchner funnel from the clear supernatant solution, and the filtrate was concentrated in a Rinco evaporator. The product was isolated by distillation of the liquid residue under reduced pressure.

Because of the sensitivity of the phosphonochloridates toward water, the complexes of type XI were cleaved exclusively by method B. The hydrolytic decomposition of complexes of type XIII can be carried out by either one of the two methods.

Preparation of Ethyl Isopropylphosphonochloridate.—The following procedure illustrates the general method for the conversion of alkyl halides to alkyl alkylphosphonochloridates.

Isopropyl chloride (0.55 mole) was added in the usual manner to 0.5 mole of phosphorus trichloride and 0.5 mole of anhydrous aluminum chloride in 700 cc. of methylene

(8) K. C. Kennard and C. F. Hamilton, *J. Org. Chem.*, **20**, 1711 (1955).

(9) Rinco Instrument Co., Greenville, Ill.

(10) This method is an adaptation of the method described by W. T. Dye, Jr., THIS JOURNAL, **70**, 2595 (1948), for the processing of reaction mixtures containing hydrocarbons, aluminum chloride and phosphorus trichloride.

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chloride. To the resulting solution of the complex $[(CH_3)_2CHPCl_3][AlCl_4]$ was added dropwise with stirring over a period of 1 hr. 46 g. (1 mole) of absolute ethanol. Refluxing of the resulting colorless solution was continued with stirring for an additional period of 6 hr. After cooling to −25°, the solution was treated with water, in portions of approximately 5 cc., and shaken vigorously in a separatory funnel for several minutes after the addition of each portion. The addition of water was continued until the gelatinous precipitate, first formed, had coagulated to give a readily removable, granular mass. A total of 85 cc. of water was required in this operation. The methylene chloride solution was filtered rapidly from the coagulated aluminum salt through a Büchner funnel and the filter cake washed three times on the filter with 50-cc. portions of methylene chloride. The solvent was removed from the combined filtrates under reduced pressure and the residue distilled *in vacuo* to yield 67.4 g. (79%) of ethyl isopropylphosphonochloridate, b.p. 51–53° (1.9 mm.) (see Table III).

TABLE III

CONVERSION OF $[RPCl_3][AlCl_4]$ TO $RP(O)(OR')Cl$[a]

Run	R	R′	B.p. °C.	B.p. Mm.	$n^{25}D$	Yield calcd. on PCl_3, %
14	CH_3[b]	C_2H_5	33	0.9	1.4320	47.5
15	C_2H_5[c]	C_2H_5	55	2.4	1.4345	62
16	i-C_3H_7[d]	C_2H_5	53	1.9	1.4357	79
17	CH_3[e]	n-C_3H_7	46	1.0	1.4332	32.5

[a] All runs were carried out by alcoholysis of the appropriate complex I with two mole equivalents or less of the suitable alcohol and working up the reaction mixture by method B. [b] VII (0.5 mole) suspended in 1500 cc. of methylene chloride was treated with 41 g. (0.9 mole) of absolute ethanol during 1.5 hr., refluxed for a period of 6 hr. and finally hydrolyzed at −30° with 110 cc. of water. [c] V (0.3 mole) was dissolved in 750 cc. of methylene chloride, treated with 25.8 g. (0.56 mole) of absolute ethanol and the mixture stirred 2 days at room temperature and finally treated at −20° with 60 cc. of water. [d] This run is described in detail in the Experimental section. [e] To VII (0.5 mole) suspended in 1300 cc. of methylene chloride was added at 10–15° 60 g. (1 mole) of 1-propanol and the mixture refluxed for 1 hr. and treated at −30° with 110 cc. of water. A liquid distillation residue of 13.9 g. decomposed upon attempted distillation under high vacuum to form a gelatinous semi-solid.

Similar conversions of I to phosphonochloridates were performed with the complexes V and VII under varying conditions. The results of these runs are listed in Table III. No attempt was made to establish optimum conditions in the various runs.

Preparation of Diethyl Isopropylphosphonate.—The complex $[(CH_3)_2CHPCl_3][AlCl_4]$ was prepared by the general procedure in 400 cc. of methylene chloride from 1.1 moles of isopropyl chloride and 1.0 mole each of phosphorus trichloride and anhydrous aluminum chloride. Absolute ethanol (322 g., 7 moles) was added dropwise with stirring to the resulting solution of the complex at such a rate that gentle refluxing was maintained. After the alcohol addition was completed, the mixture was refluxed with stirring for an additional period of 3 hr. The colorless solution was then cooled to 20°, and 500 cc. of water was added slowly with stirring. During the addition, the temperature was maintained below 25° by cooling with ice-water. At the beginning of the addition of the water, a white solid precipitated from the reaction mixture. This precipitate, however, dissolved gradually upon further water addition and had completely disappeared after approximately 400 cc. of water had been added. The two colorless layers of the reaction mixture were separated, and the upper aqueous layer was extracted with three 50-cc. portions of methylene chloride. The combined methylene chloride layer and washings were evaporated under reduced pressure at room temperature and the liquid residue was distilled to yield 127.8 g. (71%) of diethyl isopropylphosphonate, b.p. 56° (1.8 mm.) to 58° (2.25 mm.), $n^{25}D$ 1.4161.

In the same fashion were prepared the diethyl alkylphosphonates listed in Table IV.

Preparation of Ethyl Isopropyl Isopropylphosphonate.—The complex $[(CH_3)_2CHPCl_3][AlCl_4]$ (0.5 mole) was prepared from isopropyl chloride and aluminum chloride in 250 cc. of methylene chloride in exactly the same manner as described for the preparation of diethyl isopropylphosphonate. The resulting solution was diluted with 500 cc. of dry methylene chloride and treated dropwise with 46 g. (1 mole) of absolute ethanol. The reaction mixture was then refluxed for a period of 4 hr. and subsequently treated in the usual manner with 60 g. (1 mole) of isopropyl alcohol. Refluxing of the reaction mixture was continued for a period 8 hr. Subsequent dropwise addition of 300 cc. of water precipitated a white solid which was brought back into solution by the addition of 50 cc. of concentrated hydrochloric acid. Separation of the methylene chloride layer and processing in the usual manner yielded 77% of ethyl isopropyl isopropylphosphonate (see run 11, Table V).

TABLE IV

CONVERSION OF $[RPCl_3][AlCl_4]$ TO $RP(O)(OC_2H_5)_2$[a,b]

Run	R	B.p. °C.	B.p. Mm.	$n^{25}D$	Yield, calcd. on PCl_3, %
1	CH_3[c]	44	1.5	1.4119[o]	83.5
2	C_2H_5[d]	54	1.6	1.4148[p]	76
3	C_2H_5[e]	45	0.93	1.4146	46
4	C_2H_5[f]	40	.75	1.4146	70
5	C_2H_5[g]	44	.9	1.4148	80
6	i-C_3H_7[h]	56	1.8	1.4159	71
7	i-C_3H_7[i]	51	0.65	1.4152	80
8	i-C_4H_9[k]	55	.7	1.4212	68
9	C_6H_{11}[l,m,n]	87	.8	1.4538	49

[a] Except where stated otherwise (runs 1 and 2), the alcoholysis of the I solution was carried out with 7 mole equivalents of absolute ethanol. [b] The solutions of the alcoholyzed complex were worked up by method A; all runs were performed in methylene chloride solution. [c] VII (0.25 mole) suspended in 500 cc. of methylene chloride was treated with 6 mole equivalents (1.5 moles) of absolute ethanol and the mixture refluxed for 3 hr. and decomposed with 200 cc. of water. [d] V (0.3 mole) in 150 cc. of methylene chloride was treated with 0.9 mole of absolute ethanol, refluxed for 8 hr. and hydrolyzed with 100 cc. of water. [e] Phosphorus trichloride (1 mole) and 1 mole of powdered, anhydrous aluminum chloride was treated at −10° with approximately 70 cc. of ethyl chloride, the mixture stirred for 2 hr. without cooling, treated with 420 cc. of absolute ethanol, refluxed for 8 hr. and decomposed with 60 cc. of concentrated hydrochloric acid in 400 cc. of water. [f] XVI from 0.5 mole of phosphorus trichloride, 1 mole of anhydrous aluminum chloride and 70 cc. of ethyl chloride in 300 cc. of methylene chloride was used. [g] Solid V (0.3 mole) dissolved in 150 cc. of methylene chloride; reflux time 3 hr.; decomposed with 100 cc. of water. [h] Described in detail in the Experimental section. [i] $[(CH_3)_2CHPCl_3][AlCl_4]$ (0.25 mole) was prepared in 150 cc. of methylene chloride from n-propyl chloride (see ref. 4); the final hydrolysis was carried out with 20 cc. of concentrated hydrochloric acid in 100 cc. of water. The infrared spectrum of the product was identical with that obtained of the product from run 6. [k] n-Butyl chloride (0.27 mole) (see ref. 4), 0.25 mole each of phosphorus trichloride and 100 cc. of solvent were employed; the final decomposition was performed with 100 cc. of water. [l] Cyclohexyl. [m] The complex I was prepared from 0.5-mole quantities each of cyclohexyl chloride, phosphorus trichloride and aluminum chloride in 200 cc. of solvent, treated with 3.8 moles of absolute ethanol, refluxed for 3 hr. and decomposed with 200 cc. of water. [n] See footnote *a* of Table II. [o] A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947); b.p. 64° (4 mm.), $n^{16}D$ 1.4210. [p] B.p. 62° (2 mm.), $n^{15}D$ 1.4172 (Ford-Moore and Williams, ref. *o*).

Reaction of $[CH_3PCl_3][AlCl_4]$ with One Mole of Methanol.—To a vigorously stirred suspension of 107 g. (0.33 mole) of VII in 300 cc. of methylene chloride, maintained at 25° by cooling with water, was added dropwise in the course of 2 hr. a mixture of 10.6 g. (0.33 mole) of absolute methanol and 50 cc. of methylene chloride. After the addition of approximately one-half of the methanol–solvent mixture, the solid complex was completely dissolved. About 30 minutes after the methanol addition was complete, the clear, pale yellow solution became turbid and small colorless crystals began to precipitate. The mixture was stirred for an additional 3 hr. and was allowed to stand at room temperature

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TABLE V

CONVERSION OF $[(CH_3)_2CHPCl_3][AlCl_4]$ (XVIII) TO $(CH_3)_2CHP(O)(OR')_2$[a]

Run	R'	B.p. °C.	Mm.	$n^{25}D$	Yield, calcd. on PCl_3, %
10	CH_3[b]	71	5.5	1.4179	40
11	i-C_3H_7 and C_2H_5[c]	47	0.7	1.4138	77
12	i-C_3H_7[d]	38.5	0.25	1.4129	21
13	i-C_3H_7[e]	44	0.35	1.4148	62

[a] XVIII (0.5 mole) was prepared in all runs in the usual manner from isopropyl chloride in methylene chloride solution. [b] To XVIII (0.5 mole) in 150 cc. of solvent was added dropwise 64 g. (2 moles) of absolute methanol. After the addition of about 0.5 mole of methanol, a white solid began to precipitate. The alcoholysis mixture was refluxed for 4 hr. after the addition of the methanol was completed. The addition of 300 cc. of water to the mixture resulted in the formation of a gelatinous emulsion which was broken by centrifuging. [c] Described in detail in the Experimental part. [d] XVIII in 200 cc. of solvent was refluxed for 6 hr. with 2 moles of isopropyl alcohol. The white solid precipitate, formed upon the addition of 300 cc. of water, was dissolved by adding 100 cc. of concentrated sulfuric acid. In addition to the product, 33 g. of liquid distillation residue was obtained; on attempted distillation of the residue, decomposition occurred. [e] XVIII in 600 cc. of solvent was first treated with 18.4 g. (0.4 mole) of absolute ethanol in 50 cc. of solvent, refluxed for 1 hr., treated with 80 g. (1.33 moles) of isopropyl alcohol, refluxed for an additional 5 hr. and hydrolyzed at −10° with 110 cc. of water by method B. overnight. About 200 cc. of the solvent was then removed by distillation at atmospheric pressure; the remainder was evaporated under reduced pressure, leaving a pale yellow, crystalline mass which weighed 93.5 g. The product which did not fume in air was pulverized to a light, crystalline powder. Recrystallization from methylene chloride after decolorizing with Norit yielded the complex VIII as a white, microcrystalline powder, m.p. 140–150° (not sharp). The complex VIII could be distilled without decomposition at a pressure of 5 mm.; at 242–245° a liquid distilled which solidified immediately in an attached air condenser.

Anal. Calcd. for CH_3AlCl_5OP: C, 4.5; H, 1.1; Al, 10.1; Cl, 66.6; P, 11.6. Found: C, 5.0; H, 1.6; Al, 9.6; Cl, 63.0; P, 11.6.

Reaction of Methylphosphonyldichloride with Aluminum Chloride.—To a solution of 25 g. of methylphosphonyldichloride in 150 cc. of methylene chloride was added 25 g. of aluminum chloride in portions. A vigorous exothermic reaction occurred keeping the solvent refluxing. After the initial reaction had subsided, the mixture was refluxed for an additional 30 minutes. The light brown solution was filtered to remove a small amount of solid and the filtrate was refrigerated overnight. The resulting deposit of fine, colorless crystals was filtered off, washed on the filter with a small amount of cold methylene chloride and dried in a vacuum desiccator; 93.9% yield.

Anal. Calcd. for CH_3AlCl_5OP: Al, 10.1; Cl, 66.6; P, 11.6. Found: Al, 10.3; Cl, 66.6; P, 12.8.

Reaction of $[CH_3PCl_3][AlCl_4]$ with Two Moles of Methanol.—To a suspension of 107 g. (0.33 mole) of VII in 250 cc. of methylene chloride was added dropwise in the course of 3 hr. a mixture of 21.0 g. (0.66 mole) of absolute methanol and 50 cc. of methylene chloride. After standing overnight, the solvent was removed from the clear, pale yellow solution under reduced pressure leaving 89.5 g. of a pale yellow, crystalline residue. The solid material was kept in a vacuum desiccator for 65 hr.; the loss of weight during this time was 9.5 g. The remaining 80 g. (91.9%) of product was recrystallized from methylene chloride to yield the complex $[CH_3P(O)OCH_3][AlCl_4]$ as colorless crystals.

Anal. Calcd. for $C_2H_6AlCl_4O_2P$: C, 9.2; H, 2.3; Al, 10.3; Cl, 54.2; P, 11.8. Found: C, 9.0; H, 2.4; Al, 10.4; Cl, 52.3; P, 11.9.

Preparation of Samples for NMR Spectra.—Solid V (0.3 mole) was dissolved with stirring at room temperature in 150 cc. of methylene chloride and a 2-cc. aliquot removed for determination of the NMR spectrum. The bulk of the solution was then treated with 13.8 g. (0.3 mole) of absolute ethanol in the usual fashion and refluxed for a period of 6 hr. The mixture, containing complex X, was cooled and another 2-cc. sample of the solution removed for NMR analysis. The alcoholysis was continued in two steps by adding each time a 0.3-mole portion of absolute ethanol and withdrawing at each step a sample for spectral analysis.

The solution used for the determination of the NMR spectrum of the complex $[C_2H_5P(O)(OC_2H_5)_2 \cdot AlCl_3]$ was prepared in the following manner. To a solution of diethyl ethylphosphonate (37 g., 0.22 mole) in 100 cc. of methylene chloride was added, after cooling to −78°, 30 g. (0.22 mole) of anhydrous aluminum chloride in two portions. An exothermic reaction took place upon each addition, but the temperature of the reaction mixture was maintained below 0° by cooling. The mixture was stirred below 0° until the aluminum chloride was dissolved and the stirring continued for an additional 2 hr. at room temperature. The trace amounts of insoluble material were allowed to settle by standing undisturbed overnight and an aliquot of the clear supernatant solution of the desired complex was removed for NMR analysis.

The spectra of III, VI, IX and the liquid complex XVI were determined without solvent.

Table I contains the chemical shifts exhibited by the various ethyl complexes and their phosphorus-containing components.

ARMY CHEMICAL CENTER, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

Monoesters and Ester-amidates of Aromatic Phosphonic Acids

BY ALFRED BURGER AND JAMES J. ANDERSON[1]

RECEIVED JANUARY 30, 1957

Reaction of phosphonic acids with dicyclohexylcarbodiimide yields pyrophosphonic acids, $[RPO(OH)]_2O$, which with alcohols or phenol furnish the respective alkyl or phenyl hydrogen phosphonate esters. These in turn with dicyclohexylcarbodiimide give dialkyl pyrophosphonates, $[RPO(OR)]_2O$, which react with amines to render alkyl N-substituted phosphonamidates. The monoesters and ester-amidates of *p*-aminophenylphosphonic acid exhibited only negligible bacteriostatic activity. The biological observations are discussed in the light of ionization theories of analogous bacteriostatically active sulfanilamide derivatives.

In the course of their studies about the dependence of bacteriostatic activity of sulfanilamide derivatives on the relative negative character of the SO_2 group in these compounds, Bell and Roblin[2] expressed the view that the principles outlined by them should apply to any substance of the type p-$H_2NC_6H_4XO_2R$, provided its activity is inhibited by *p*-aminobenzoic acid. If the properties of the aromatic amino group are constant, activity in such compounds should be expressed by the negativity

(1) Virginia-Carolina Chemical Corporation Fellow, 1955–1956.

(2) P. H. Bell and R. O. Roblin, Jr., THIS JOURNAL, 64, 2905 (1942).

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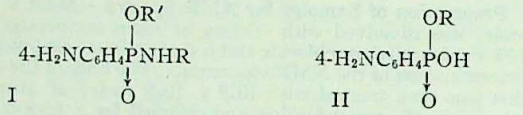
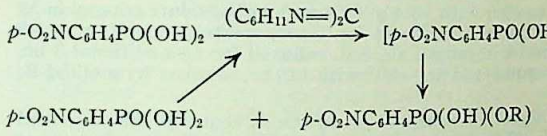
of the XO_2 group. Among compounds predicted to conform with this hypothesis were substances where X is phosphorus.

Since phosphanilic[3,4] and *p*-aminobenzenephosphonous acid[5] as well as phosphanilamide[4] show bacteriostatic activity and the effect of the first two compounds is antagonized by *p*-aminobenzoic acid,[3,5,6] Bell and Roblin's prediction seems to be borne out for these compounds. Moreover, several diamides of phosphanilic acid [$H_2NC_6H_4PO(NHR)_2$] are more highly bacteriostatic than the parent acid,[7] and here the inductive effect of the PO should be equally divided between both NHR groups. It appeared promising to synthesize alkyl N^1-substituted P-(4-aminophenyl)-phosphonamidates (I)[8] because the ionization of the hydrogen of the NHR group could be altered by a change in the electronegativity of one or both R radicals, and this would permit the design of variants with a



range of pK_a values and activities as predicted by Bell and Roblin. In the related, more strongly acidic alkyl hydrogen 4-aminophenylphosphonates (II), acid strength might be manipulated to some extent by varying the structure of the ester group.

Only few monoesters of phosphonic acids have been reported. The methods for their preparation[9–15] include such procedures as the partial alcoholysis of phosphonochloridates or the partial alkaline hydrolysis of dialkyl phosphonate esters and are not generally applicable.[12] The reaction of pyrophosphonic acids [$RPO(OH)]_2O$ with alcohols or phenols should lead to monoesters, but little is known about such anhydrides.[13] It has now been found that the method of Khorana and Todd[16] for the preparation of esters of diphosphoric acids can be extended to the synthesis of alkyl- and arylpyrophosphonic acids. Dehydration of phosphonic acids with one-half molar equivalent of dicyclohexylcarbodiimide in tetrahydrofuran solution quickly furnishes a precipitate of insoluble dicyclohexylurea, and the filtrate contains the desired anhydride. Several phosphonic acids were treated with dicyclohexylcarbodiimide; *n*-hexylphosphonic acid yielded a crystalline pyrophosphonic acid, $[C_6H_{13}PO(OH)]_2O$, while other anhydrides were obtained as viscous oils which we were unable to crystallize. Nevertheless, the tetrahydrofuran solution of the pyrophosphonic acids reacted smoothly with primary or secondary alcohols, or with phenol, to furnish the corresponding monoesters, $RPO(OH)OR'$. Inevitably, one-half of the phosphonic acid used was recovered from this step, and its separation from the acidic monoester proved difficult. In the case of 4-nitrophenylphosphonic acid, which is obtained by a relatively laborious process,[17] the unavoidable recovery of valuable starting material posed the need of recycling in order to increase the yield of monoesters. These obstacles were overcome by dissolving the phosphonic acid and the alcohol or phenol in tetrahydrofuran and slowly adding *one molar* equivalent of dicyclohexylcarbodiimide. The phosphonic acid recovered from the alcoholysis of the resulting pyrophosphonic acid was thus reconverted to the anhydride *in situ*, and the latter was recycled to more monoester. Excellent yields of monoesters were realized by this procedure (Table I).



When dicyclohexylcarbodiimide was added slowly to a solution of an alkyl hydrogen *p*-nitrophenylphosphonate and an amine, the latter was converted to the corresponding N,N′-dicyclohexyl-N″-alkylguanidine derivative [$C_6H_{11}NHC(NH)=NC_6H_{11}$]. Although the addition of amines to carbodiimides had been known,[18,19] the failure of phosphonate monoesters to form anhydrides which in turn could react with amines was surprising, since in an analogous case the addition of dicyclohexylcarbodiimide to a cold solution of two amino acids yielded peptides.[20] The synthesis of alkyl P-(*p*-nitrophenyl)-N-substituted phosphonamidates did succeed when the alkyl hydrogen *p*-nitrophenylphosphonates were converted to the corresponding dialkyl pyrophosphonates, $[p\text{-}O_2NC_6H_4PO(OR)]_2O$, dicyclohexylurea was filtered, and the filtrate containing the anhydride was heated with an amine. The resulting ester-amidates (Table II) could be separated readily from the salts of the monoesters by extraction into ether.

The alkyl or aryl N-substituted P-(*p*-nitrophenyl)-phosphonamidates as well as the alkyl hydrogen *p*-nitrophenylphosphonates were hydrogenated over Raney nickel catalyst to the corresponding *p*-amino derivatives in good yields.

Experimental[21]

Materials.—4-Nitrophenylphosphonic acid was prepared according to Doak and Freedman.[17] Dicyclohexylcarbodi-

(3) R. Kuhn, E. F. Möller, G. Wendt and H. Beinert, *Ber.*, **75**, 711 (1942).

(4) G. O. Doak and L. D. Freedman, THIS JOURNAL, **55**, 4825 (1955); *cf.* U. K. Kanitkar and B. V. Bhide, *Current Sci. (India)*, **16** 223 (1947).

(5) I. M. Klotz and R. T. Morrison, THIS JOURNAL, **69**, 473 (1947).

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TABLE I

MONOESTERS OF PHOSPHONIC ACIDS

$RPO(OH)(OR')_{R'}$ R	R'	Yield, %[a]	M.p., °C. (cor.)	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
C_6H_5	C_6H_5[b]	82	70–72	$C_{12}H_{11}O_3P$	61.54	4.74	61.69	4.54
	C_2H_5	60	B.p. 147–149° (1 mm.)	$C_8H_{15}O_3P$	43.47	9.10	43.28	9.02
n-C_4H_9	C_6H_5	82	139–141	$C_{12}H_{10}NO_5P$	51.62	3.61	51.57	3.48
p-$O_2NC_6H_4$	C_2H_5	83	111–112.5	$C_8H_{10}NO_5P$	41.57	4.36	41.21	4.40
					N, 6.10		N, 5.98	
	CH_3	60	129–131	$C_7H_8NO_5P$	38.72	3.71	38.63	4.06
	CF_3CH_2[c]	77	115–117	$C_8H_7F_3NO_5P$	33.71	2.48	33.54	2.70
	cyclo-C_6H_{11}	91	123–125	$C_{12}H_{16}NO_5P$	50.53	5.65	50.83	5.49

[a] These yields were also realized if batches up to 0.15 mole were run. [b] Previously prepared by A. Michaelis[14] who reported m.p. 57°. [c] Calcd.: neut. equiv., 285.03. Found: neut. equiv., 283.7.

TABLE II

ESTER-AMIDATES OF *p*-NITROPHENYLPHOSPHONIC ACID

p-$O_2NC_6H_4PO(NHR)(OR')$ R	R'	Yield, %	M.p., °C. corr.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$C_6H_5CH_2$–	C_2H_5[a]	80	81.5–82.5	$C_{15}H_{17}N_2O_4P$	56.25	5.35	56.20	5.37
2-Thiazolyl-	CH_3[b,c]	77	135–136.5	$C_{10}H_{10}N_3O_4PS$	40.14	3.37	40.02	2.87
	C_2H_5[b,d]	85	138–139	$C_{11}H_{12}N_3O_4PS$	42.17	3.86	42.17	4.11
					N, 13.42		N, 13.02	
	C_6H_5[d,e]	67	172–174	$C_{15}H_{12}N_3O_4PS$	49.86	3.35	50.20	3.83
	CF_3CH_2[b,d]	81	143–145	$C_{11}H_9F_3N_3O_4PS$	35.97	2.47	36.06	2.42
2-Pyridyl-	CH_3[e]	55	113–115	$C_{12}H_{12}N_3O_4P$	49.15	4.13	48.97	4.03
	C_2H_5[e]	90	92–94	$C_{13}H_{14}N_3O_4P$	50.82	4.59	50.46	4.59
2-Pyrimidyl-	C_2H_5[b]	50	192–193	$C_{12}H_{13}N_4O_4P$	46.75	4.25	47.25	4.17
2-(5-Methylpyridyl)-	C_2H_5[b,f]	75	142–144	$C_{14}H_{16}N_3O_4P$	52.33	5.02	52.50	5.02

[a] Recrystallized from isopropyl ether. [b] Recrystallized from ethanol–isopropyl ether. [c] Bright yellow. [d] Pale yellow. [e] Recrystallized from butanone–isopropyl ether. [f] Picrate, m.p. 179–180°. Calcd. for $C_{20}H_{19}N_6O_{11}P$: C, 43.64; H, 3.48. Found: C, 43.53; H, 3.48.

imide was obtained by the directions of Schmidt, *et al.*,[22] except that commercial 5.25% sodium hypochlorite solution was used. The compound distilled at 117–120° (0.5 mm.) and melted at 34–35°.

2-Aminopyridine, 2-aminothiazole and 2-aminopyrimidine were supplied generously by Dr. Gilmer T. Fitchett, American Cyanamid Co. 3,4-Dimethyl-5-aminoisoxazole was donated by Hoffmann–LaRoche Co.

General Directions. (a) **Monoesters of Phosphonic Acids.**—A solution of 0.01 mole of the phosphonic acid and 0.01 mole of phenol, or the respective alcohol, in 25 ml. of dry tetrahydrofuran was heated to boiling, and a solution of 0.011 mole of dicyclohexylcarbodiimide in 10 ml. of the same solvent was added over a period of 2.5–3 hr. N,N′-Dicyclohexylurea separated out and was filtered after the mixture had been heated for another 8–10 hr. and allowed to stand at 37° for several hours. The solvent was evaporated under reduced pressure, the resulting pale-brown viscous oil was dissolved in 25 ml. of warm 1 *N* ammonium hydroxide, the solution was filtered and acidified with 6 *N* hydrochloric acid. The viscous oily esters crystallized on scratching to colorless solids which were recrystallized from mixtures of butanone and isopropyl ether, except phenyl hydrogen phenylphosphonate which crystallized from dilute ethanol.

t-Butyl alcohol did not react by this procedure. Data on the monoesters are collected in Table I.

(b) **Ester-amidates of 4-Nitrophenylphosphonic Acid.**—A solution of 22 mmoles of dicyclohexylcarbodiimide in 10 ml. of dry tetrahydrofuran was added slowly with stirring to a solution of 20 mmoles of the respective monoester of 4-nitrophenylphosphonic acid in 40 ml. of dry tetrahydrofuran at 25°. N,N′-Dicyclohexylurea precipitated out immediately. After the mixture was allowed to stand for 30 minutes, the N,N′-dicyclohexylurea was filtered, the filtrate heated to boiling and 22 mmoles of the respective amine was added. Refluxing was continued for 10 hr., and the solvent then evaporated under reduced pressure. The residual light brown tar was extracted with 75 ml. of boiling ether. The undissolved crystalline amine salt of the starting ester was filtered and the ether removed. When the remaining oil was taken up in the minimum amount of ethanol and the solution was diluted with a little water, a viscous oil precipitated which crystallized on scratching. The crude ester-amidates crystallized from isopropyl ether, or from mixtures of isopropyl ether and ethanol or butanone. Data on ester-amidates are listed in Table II. 3,4-Dimethyl-5-aminoisoxazole did not react by this procedure.

(c) **Monoesters and Ester-amidates of 4-Aminophenylphosphonic Acid.**—The derivatives of *p*-nitrophenylphosphonic acid (0.01 mole) were dissolved in 100 ml. of absolute methanol and hydrogenated with the aid of Raney nickel catalyst at 3 atm. and 25° in 2–3 hr. The catalyst was filtered, the solvent evaporated under reduced pressure, the crystalline or viscous residue was taken up in butanone and treated with isopropyl ether. In some cases a sparingly soluble amino compound precipitated during the hydrogenation; it had to be dissolved by addition of a few drops of ammonium hydroxide before the catalyst could be filtered, and the amine was reprecipitated by adjustment of the filtrate to *p*H 5–6. The colorless amino compounds obtained by this procedure are recorded in Table III.

P,P′-(Di-*n*-hexyl) Dihydrogen Pyrophosphonic Acid.—A solution of 1.13 g. (0.055 mole) of dicyclohexylcarbodiimide in 5 ml. of dry ether was added slowly with stirring to a solution of 1.66 g. (0.01 mole) of *n*-hexylphosphonic acid in 50 ml. of dry ether. N,N′-Dicyclohexylurea precipitated immediately and quantitatively. It was filtered and the filtrate concentrated to 5 ml. On cooling, 1 g. (65%) of colorless crystals precipitated which after recrystallization from ligroin melted at 64–66°.

Anal. Calcd. for $C_{12}H_{28}O_5P_2$: C, 45.85; H, 8.98. Found: C, 45.57; H, 9.11.

Determination of pK_a Values.—The apparent pK_a values for the compounds listed in Table IV were determined by measuring the *p*H of a solution containing equimolar concentrations of the acidic material and its salt, prepared by adding 0.2–0.7 mmole of the compound to 50–100 ml. of water followed by addition of the exact amount of standard base to neutralize one-half of the acidic substance.

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TABLE III

MONOESTERS AND ESTER-AMIDATES OF PHOSPHANILIC ACID

p-H2NC6H4PO(Y)(OR) Y	R	Yield, %	M.p., °C. corr.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
OH	CH_3[a]	90	196.5–197	$C_7H_{10}NO_3P$	44.92	5.39	44.48	5.67
OH	C_2H_5[a]	80	208–210	$C_8H_{12}NO_3P$	47.76	6.01	47.70	6.09
OH	C_6H_5[b]	74	245.5–246	$C_{12}H_{12}NO_3P$	57.83	4.86	57.70	5.14
OH	cyclo-C_6H_{11}	77	236–238	$C_{12}H_{18}NO_3P$	56.46	7.11	56.44	7.43
2-Pyridylamino-	CH_3[c]	80	162–164	$C_{12}H_{14}N_3O_2P$	54.75	5.36	54.69	5.75
	C_2H_5[c]	75	167–169	$C_{13}H_{16}N_3O_2P$	56.31	5.82	56.82	5.60
2-Thiazolylamino-	CH_3[c]	79	162–163	$C_{10}H_{12}N_3O_2PS$	44.60	4.49	44.34	4.68
	C_2H_5[c]	80	163–165	$C_{11}H_{14}N_3O_2PS$	46.64	4.98	46.59	4.76
	CF_3CH_2[d]	76	145–147	$C_{11}H_{11}F_3N_3O_2PS \cdot {}^1/_2C_6H_{14}O$	43.30	4.67	42.94	4.91
							43.42	4.76
	C_6H_5[c]	91	209–211 d.	$C_{15}H_{14}N_3O_2SP$	54.37	4.26	53.67	4.29
2-Pyrimidylamino-	C_2H_5[c]	75	171–173	$C_{12}H_{15}N_4O_2P$	51.80	5.43	52.14	5.42
$C_6H_5CH_2NH$–	C_2H_5[a]	75	91– 93	$C_{15}H_{19}N_2O_2P$	62.06	6.60	62.43	6.47

[a] Recrystallized from methanol. [b] Purified by reprecipitation from dilute hydrochloric acid. [c] Recrystallized from butanone. [d] Recrystallized from butanone–isopropyl ether, dried at 110° (1 mm.). The presence of 0.5 mole of isopropyl ether of crystallization is based on the analytical values only, since infrared absorption shows all major peaks for ether oxygen where NH_2 may be expected to absorb. The compound contained nitrogen, phosphorus, sulfur and fluorine (small amounts in qualitative test) and exhibited a strong absorption band at 3 μ in the infrared.

A Beckman model G *p*H meter equipped with a glass electrode in conjunction with a saturated calomel electrode was used. From control experiments with known acids, the accuracy was judged to be ±0.1 for pK_a values of 4 to 10, while for higher values a drift of 0.1–0.3 was observed. For values below 3.8, see Table IV.

TABLE IV

pK_a VALUES OF SOME DERIVATIVES OF 4-NITRO- AND 4-AMINOPHENYLPHOSPHONIC ACID

R	p-RC6H4PO(R′)(OR″) R′	R″	pK_a[a]	pK_a of sulfonamide analog RC6H4-SO2R′2
NO_2	OH	C_2H_5	2.5	
NO_2	OH	C_6H_5	2.5	
NO_2	OH	CF_3CH_2	2.5	
NO_2	OH	cyclo-C_6H_{11}	2.6	
NH_2	OH	CH_3	3.8	
NH_2	OH	C_2H_5	3.9	
NH_2	OH	C_6H_5	4.0	
NH_2	OH	cyclo-C_6H_{11}	3.9	
NO_2	2-Thiazolylamido-	CF_3CH_2	8.3	
NO_2	2-Thiazolylamido-	CH_3	8.6	
NO_2	2-Thiazolylamido-	C_2H_5	8.7	
NO_2	2-Thiazolylamido-	C_6H_5	8.9	
NO_2	2-Pyridylamido-	CH_3	10.2	
NO_2	2-Pyridylamido-	C_2H_5	10.4	
NH_2	2-Thiazolylamido-	CF_3CH_2	8.7	7.2
NH_2	2-Thiazolylamido-	CH_3	9.2	7.2
NH_2	2-Thiazolylamido-	C_2H_5	9.3	7.2
NH_2	2-Thiazolylamido-	C_6H_5	9.7	7.2
NH_2	2-Pyridylamido-	CH_3	10.4	8.43
NH_2	2-Pyridylamido-	C_2H_5	10.5	8.43
NH_2	2-Pyrimidylamido-	C_2H_5	10.4	7.86
NH_2	$C_6H_5CH_2$–	C_2H_5	10.7	..

[a] For pK_a values below 3.8 the accuracy is 0.2. Calculated by equation (252), S. Glasstone, "Textbook of Physical Chemistry," 2nd Ed., Van Nostrand Co., Inc., New York, N. Y., 1946. The other values were calculated by the Henderson equation.

Infrared Absorption Spectra.—Major assigned characteristic absorptions of *p*-nitro- and *p*-aminophenylphosphonic acid monoesters and ester-amidates were observed as follows: CF_3 at 9.2 μ[23]; NH_2 at 2.9 and 2.98 μ[23]; *p*-disubstituted phenyl at 12.1 μ[23]; NO_2 at 7.4 μ[23]; thiazole at 6.12 and 6.6 μ[24]; P–O–C aliphatic at 9.7–9.9 μ[25]; P=O at 7.8 μ.[25] In addition, all these compounds absorbed in the region of 10.2–10.4 μ which may be considered characteristic for many phosphorus compounds including phosphonates.[25]

The infrared data indicate that the ester-amidate derivatives of phosphanilic acid contain a free amino group and most probably do not exist as zwitterions. Thus the pK_a values should express the dissociation of the phosphonamidate group. In the case of monoalkyl hydrogen phosphanilates, no bond appears in the region of 3 μ. This implies that the amino group is associated and the pK_a values of these compounds represent probably the dissociation of the inner salt, p-$H_3N^+C_6H_4P(O)(OR)O^-$.

Discussion of Bacteriostatic Activity

The *in vitro* bacteriostatic activities of ethyl N¹-(2-pyridyl)-P-(*p*-aminophenyl)-phosphonamidate, the corresponding N¹-(2-pyrimidyl) and N¹-(2-thiazolyl) derivatives and the lower methyl N¹-(2-thiazolyl) homolog, as well as those of methyl and ethyl N¹-(2-pyridyl)- and N¹-(2-thiazolyl)-P-(*p*-nitrophenyl)-phosphonamidates were measured by the agar diffusion method in the Microbiology Section of Smith, Kline and French Laboratories. Also included in this series were methyl and ethyl hydrogen *p*-nitrophenylphosphonate and methyl hydrogen *p*-aminophenylphosphonate. The organisms employed were *Pseudomonas sp.*, *Escherichia coli*, *Micrococcus pyogenes* var. *aureus*, *Mycobacterium smegmadis*, and *Diplococcus pneumoniae* Type I. Only *D. pneumoniae* was inhibited slightly by all but two of the compounds tested in a 2 × 10^{-4} % solution, and *M. aureus* responded equally slightly to the four *p*-nitrophenylphosphonamidates. The relatively most active derivative, ethyl N¹-(2-pyridyl)-P-(*p*-aminophenyl)-phosphonamidate, did not protect mice against pneumococcus infection at 100 and 800 mg./Kg.

These disappointing findings are not easily fitted into the framework of the Bell and Roblin theory. The lack of correlation between bacteriostatic values and acid dissociation data points to

(23) H. Gilman, "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, Chapter 2.

(24) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determinations of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949.

(25) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, Chapter 18.

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the influence of other factors which are not so pronounced in the sulfonamide series. Apparently the SO_2 and PO groups cannot compete equally for the negative charge left by the dissociation of the proton of the amide. In the bacteriostatically ineffective alkyl hydrogen *p*-aminophenylphosphonates the PO_2^- carries a formal negative charge as does the CO_2^- in the *p*-aminobenzoate ion, and the pK_a (3.8 to 4.0) of these esters approaches that of PABA (4.68). The effects of solubility, steric influences, etc., may outweigh those of acid dissociation; alkyl N^1-heterocyclically substituted P-(*p*-aminophenyl)-phosphonamidates are uniformly more soluble in base than the corresponding sulfonamide drugs. The valence requirements of the phosphonamidates place an alkyl group on one of the oxygens whereas this is absent in the sulfonamides. While it is conceivable that the extra group could interfere with the fit at an essential receptor site, the bacteriostatic activity of *p*-aminophenylphosphonamidates containing two relatively bulky substituents in the amidate group[7] cannot readily be reconciled with this view.

CHARLOTTESVILLE, VIRGINIA

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

Synthesis of Peptides of Arginine Related to Arginine-vasopressin[1]

BY DUANE T. GISH[2] AND VINCENT DU VIGNEAUD

RECEIVED MARCH 7, 1957

The preparation of L-prolyl-L-arginylglycinamide dihydrobromide and S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide dihydrobromide, peptides containing sequences that are found in arginine-vasopressin, is described.

As a result of degradation studies on purified preparations of arginine-vasopressin, the principal pressor and antidiuretic hormone of the beef posterior pituitary gland, the sequence of amino acids in arginine-vasopressin was obtained[3] and a structure was postulated.[4,5] For the purpose of investigating synthetic routes to arginine-vasopressin, the peptides L-prolyl-L-arginylglycinamide dihydrobromide (I) and S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide dihydrobromide (II) were desired. The preparation of these peptides and their intermediates are described in this paper.

N^{α}-*p*-Nitrobenzyloxycarbonyl-L-arginylglycinamide hydrochloride (III) was prepared by the method of Gish and Carpenter[6] and the peptide derivative was isolated as the crystalline picrate IV. The picrate IV was cleaved with acetic acid saturated with hydrogen bromide to give L-arginylglycinamide dihydrobromide (V) as an amorphous solid. The dipeptide amide V was characterized as its crystalline dipicrate VI. The dihydrobromide V was converted to the monohydrobromide and the monohydrobromide was condensed with carbobenzoxy-L-proline by the tetraethyl pyrophosphite method[7] to give carbobenzoxy-L-prolyl-L-arginylglycinamide hydrobromide (VII). The tripeptide amide derivative VII was purified by countercurrent distribution and then treated with acetic acid saturated with hydrogen bromide to give L-prolyl-L-arginylglycinamide dihydrobromide (I). The amorphous product was converted to the crystalline diflavianate for characterization.

S-Benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteine was converted to its acid chloride and then condensed with proline benzyl ester to give S-benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-proline benzyl ester (VIII) and with proline methyl ester to give the corresponding methyl ester IX. The esters VIII and IX were obtained as oils, but could be converted to the crystalline hydrazide in high yield. Saponification of these esters yielded S-benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-proline (X). Yields of 50–85% were obtained on various runs of the saponification of the benzyl ester of the *p*-nitrobenzyloxycarbonyl derivative of this dipeptide, whereas a yield of 52% was obtained in the saponification of the methyl ester. Saponification of S-benzyl-N-carbobenzoxy-L-cysteinyl-L-proline methyl ester (XI), prepared in a manner similar to that used for the preparation of IX, gave consistent yields of about 85%. No difficulties had been encountered previously during the saponification of *p*-nitrobenzyloxycarbonyl derivatives of peptides.[6,8] The dipeptide derivative X was condensed with L-arginylglycinamide monohydrobromide by the tetraethyl pyrophosphite method to give the S-benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-prolyl-L-arginylglycinamide hydrobromide (XII). The crude product was purified by countercurrent distribution and the tetrapeptide amide derivative was characterized as its crystalline picrate XIII. Treatment of the purified tetrapeptide amide derivative XII with acetic acid saturated with hydrogen bromide gave S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide dihydrobromide (II) as an amorphous solid. Countercurrent distribution of this material in the system 2-butanol–0.1% acetic acid revealed a single peak and the tetrapeptide amide dihydrobromide

(1) This work was supported in part by grants from the National Heart Institute, Public Health Service, Grant H-1675, and Lederle Laboratories Division, American Cyanamid Co. A preliminary report of part of this work has appeared [V. du Vigneaud, D. T. Gish and P. G. Katsoyannis, THIS JOURNAL, **76**, 4751 (1954)].

(2) Lilly Postdoctoral Fellow in the Natural Sciences administered by the National Research Council, 1953–1955.

(3) E. A. Popenoe and V. du Vigneaud, *J. Biol. Chem.*, **206**, 353 (1954).

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(8) F. H. Carpenter and D. T. Gish, *ibid.*, **74**, 3818 (1952).

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was generally used for further work directly following the cleavage in acetic acid–hydrogen bromide without further purification except for precipitation from methanol with ether in order to remove acetic acid and excess hydrogen bromide.

Experimental[9,10]

Nα-*p*-Nitrobenzyloxycarbonyl-L-arginylglycinamide Picrate.—Nα-*p*-Nitrobenzyloxycarbonyl-L-arginyl chloride hydrochloride was prepared as previously described[6] from 3.53 g. (0.01 mole) of Nα-*p*-nitrobenzyloxycarbonyl-L-arginine. To the acid chloride was added a cold solution of 1.11 g. (0.01 mole) of glycinamide hydrochloride[11] and 3.0 ml. (0.0215 mole) of triethylamine in 15 ml. of dimethylformamide. The mixture was stirred for one hour in the cold. The precipitate of triethylamine hydrochloride was filtered off, washed with a few ml. of cold dimethylformamide and the washings were added to the filtrate. The product was precipitated with chloroform and the sticky solid was collected on a Buchner funnel and washed with chloroform. The material was dissolved in 25 ml. of warm water and 2.6 g. (1.1 moles) of picric acid dissolved in 25 ml. of warm ethanol was added. The crystalline picrate separated as the solution cooled to room temperature. The mixture was not cooled below room temperature since further cooling caused the separation of an oily product. The picrate was collected, washed with 50% ethanol and dried over P_2O_5 *in vacuo*. The yield was usually 60–65%, m.p. 148–158°. For further work the material was twice recrystallized from 50% ethanol to give an over-all yield of 50%, m.p. 165–168°. For analysis a sample was further recrystallized from 50% ethanol, m.p. 165–168°, and dried over P_2O_5 *in vacuo* at 75°; $[\alpha]^{22}D$ −3.8° (*c* 1, acetone–water (4:1)).

Anal. Calcd. for $C_{16}H_{23}O_6N_7 \cdot C_6H_3O_7N_3$: C, 41.38; H, 4.10; N, 21.94. Found: C, 41.40; H, 4.17; N, 21.82.

Sometimes during crystallization of this material a crystalline product of m.p. 110–120° was obtained. This was presumably a hydrate and could be converted to the material of m.p. 165–168° by seeding a warm solution with crystals of m.p. 165–168°.

L-Arginylglycinamide Dihydrobromide.—Nα-*p*-Nitrobenzyloxycarbonyl-L-arginylglycinamide picrate (10 g.) was suspended in 75 ml. of acetic acid which had been saturated with hydrogen bromide in the cold. The mixture was warmed to 50–55° for 1.25 hours. Ether was then added to the cooled mixture to precipitate the dihydrobromide as a white amorphous solid. The material was collected and washed with ether. To free the product from excess hydrogen bromide and acetic acid it was precipitated several times from methanol with ether. The yield was quantitative. The product was easily soluble in water, alcohol and dimethylformamide and insoluble in the usual organic solvents. The material was hygroscopic. Titration of a sample with standard alkali, using the Model G Beckman *p*H meter, gave the expected titration curve, showing the absence of any free carboxyl group and the presence of an α-amino group with a pK' of 7.3. The electrodes used did not permit titration of the guanido group. For titration of the α-amino group, 0.0620 g. requires 1.58 ml. of 0.0998 *N* NaOH. Found: 1.56 ml.

In order to characterize this hygroscopic compound it was converted to its crystalline dipicrate. The dihydrobromide (0.94 g., 2.4 mmoles) was dissolved in 5 ml. of warm water and 1.32 g. (20% excess) of picric acid dissolved in 10 ml. of hot ethanol was added. The crystalline dipicrate separated from the cooled mixture; yield 1.21 g., m.p. 206–207°. The material was recrystallized from water–ethanol (8:1), m.p. 209–210°; $[\alpha]^{24}D$ +15.9° (*c* 1, acetone–water (1:1)). A sample was dried *in vacuo* over P_2O_5 at 56° for analysis.

Anal. Calcd. for $C_8H_{18}O_2N_6 \cdot 2C_6H_3O_7N_3$: C, 34.89; H, 3.51; N. 24.42. Found: C, 34.95; H, 3.62; N, 24.31.

S-Benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteine.—This was prepared from 21.13 g. (0.1 mole) of S-benzyl-L-cysteine[12] according to procedure A previously described.[13] The yield was 34.75 g. (89%), m.p. 127–133°. One recrystallization from 1600 ml. of 50% acetic acid gave 31.5 g., m.p. 134–135°. Further recrystallization did not raise the melting point. For analysis a sample was dried *in vacuo* over P_2O_5 at 75°; $[\alpha]^{22}D$ −47.0° (*c* 1, 95% ethanol).

Anal. Calcd. for $C_{18}H_{18}O_6N_2S$: C, 55.37; H, 4.65; N, 7.18; S, 8.21. Found: C, 55.42; H, 4.88; N, 7.19; S, 8.08.

S-Benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-proline Benzyl Ester.—S-Benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteine (7.8 g., 0.02 mole) was suspended in 100 ml. of dry absolute ether and the mixture was cooled in an ice-salt bath. To the mixture was added 4.6 g. (10% excess) of phosphorus pentachloride and the mixture was stirred for 1.25 hours. The solution was filtered free of excess phosphorus pentachloride and the ether was evaporated at reduced pressure, with a bath temperature less than 20°. The acid chloride crystallized from the concentrated solution. The product was washed with cold hexane by decantation and then collected on a Buchner funnel and washed on the funnel with cold hexane. The acid chloride was added to 100 ml. of cold ether (almost all dissolved) and a cold solution of proline benzyl ester, prepared from 5.8 g. (0.024 mole) of proline benzyl ester hydrochloride,[14] and 2.8 ml. of triethylamine in ether was added. (The free ester was prepared by dissolving the hydrochloride in 30 ml. of chloroform, adding 3.4 ml. of triethylamine and evaporating the solution to a small volume. Dry ether (75 ml.) was added, triethylamine hydrochloride was filtered off, washed with ether and the washings were added to the filtrate. The ethereal solution of the free ester was kept cold until used and triethylamine equivalent to the acid chloride was added just before use.) The reaction mixture was stirred in the cold for about 15 minutes and then at room temperature for 1.5 hours. The triethylamine hydrochloride was removed by filtration and washed with ethyl acetate, the washings being added to the filtrate. The solution was washed successively with *N* hydrochloric acid, water, *N* sodium bicarbonate and saturated sodium chloride and dried over magnesium sulfate. The solvent was removed *in vacuo* and the oil was washed with hexane and then dried *in vacuo* over concentrated sulfuric acid and paraffin. The yield varied from 89–98%. This compound could not be crystallized.

S-Benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-proline.—The ester was saponified by stirring a dioxane solution with a 5% excess of *N* sodium hydroxide for 2–3 hours. The mixture was acidified and the product was extracted into ethyl acetate–ether (1:1). The organic solution was washed with *N* hydrochloric acid and water and the product was then extracted into *N* sodium bicarbonate. The bicarbonate solution was washed with ethyl acetate–ether and acidified and extracted with ethyl acetate. The organic solution was washed with *N* hydrochloric acid, water and saturated sodium chloride and dried over magnesium sulfate. The solvent was removed *in vacuo* and the oil was dried over concentrated sulfuric acid *in vacuo*. The yield generally varied from 50–85% and gave a product with a neutral equivalent within a few per cent. of the calculated value.

S-Benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-proline Methyl Ester.—This compound was prepared in the same manner as that described for the benzyl ester. The yield varied from 73 to 80%.

Saponification of the methyl ester, carried out as described for the benzyl ester, gave, in a yield of 52%, a product with a neutral equivalent within 3% of the calculated value.

S-Benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-proline Hydrazide.—The conversion of both the methyl and benzyl ester to the hydrazide was slow and required more drastic conditions than usually employed. The methyl ester (5.54 g.) was refluxed for one hour with 15 ml. of ethanol and 1.5 ml. of hydrazine hydrate (99–100%). The solution was then stored at about 37° for three weeks. The solution was filtered and crystallization was then induced. The hydrazide was filtered from the cooled mixture and

(9) Corrected capillary melting points are reported.

(10) The analyses were performed by Mr. Joseph Albert of this Laboratory.

(11) Prepared essentially as described by Yang and Rising (THIS JOURNAL, **53**, 3183 (1931)) using glycine ethyl ester hydrochloride as the starting material; yield 40%, m.p. 195–200° with decomposition.

(12) J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, **130**, 109 (1939).

(13) D. T. Gish and F. H. Carpenter, THIS JOURNAL, **75**, 950 (1953).

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washed with cold ethanol. The yield was 5.06 g. (91%), m.p. 149–151°. Recrystallization was from ethanol, m.p. 150–151°; $[\alpha]^{24}D$ −51.6° (*c* 1, dimethylformamide). A sample was dried *in vacuo* over P_2O_5 at 75° for analysis.

Anal. Calcd. for $C_{23}H_{27}O_6N_5S$: C, 55.08; H, 5.43; N, 13.96; S, 6.39. Found: C, 55.16; H, 5.57; N, 13.64; S, 6.30.

S-Benzyl-N-carbobenzoxy-L-cysteinyl-L-proline Methyl Ester.—This preparation was carried out in the same manner as that used for the preparation of the *p*-nitrobenzyloxycarbonyl derivative. The yield was 69%.

S-Benzyl-N-carbobenzoxy-L-cysteinyl-L-proline.—The saponification was carried out as described above for the *p*-nitrobenzyloxycarbonyl derivative except that 1.5 hours was required for complete saponification. The yield was 85%. Neutral equivalent: Calcd. for $C_{23}H_{26}O_5N_2S$: 442.5. Found: 450.

S-Benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-prolyl-L-arginylglycinamide Hydrobromide.—L-Arginylglycinamide dihydrobromide (1.18 g., 0.003 mole) was dissolved in 5 ml. of dimethylformamide, 0.47 ml. of triethylamine was added, the mixture was stirred for a few minutes and the monohydrobromide was then precipitated by addition of chloroform. The gummy material was washed with chloroform, then ether, and was dried over P_2O_5 *in vacuo*. The material was dissolved in 5 ml. of diethyl phosphite, 1.46 g. (0.003 mole) of S-benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-proline and 1.55 g. (100% excess) of tetraethyl pyrophosphite were added and the mixture was heated at 100° with stirring for 30 minutes. The mixture was cooled and the product, along with unreacted L-arginylglycinamide, was precipitated by the addition of ethyl acetate. The amorphous solid was collected on a Buchner funnel, washed with ethyl acetate and ether and dried *in vacuo* over P_2O_5 and sodium hydroxide pellets. The crude material weighed 1.78 g. The material was purified by countercurrent distribution in the system 2-butanol–0.1% acetic acid. One hundred and twenty transfers were sufficient to obtain complete separation of the tetrapeptide (K = 1.1) from unreacted dipeptide (K = 0.2). The distribution curves were obtained by use of the Sakaguchi reaction.[15] The solvent from the tubes containing the tetrapeptide was concentrated on the flash evaporator[16] and lyophilized to yield a white amorphous solid, weight 1.38 g. (59%). The material was easily soluble in water, alcohol and dimethylformamide and insoluble in the usual organic solvents. For the purpose of characterization the amorphous tetrapeptide was converted to its crystalline picrate. The purified tetrapeptide (175 mg.) was dissolved in 5 ml. of warm water and 55 mg. of picric acid in 5 ml. of warm ethanol was added. The picrate crystallized from the cooled solution; yield 184 mg. (88%), m.p. 155–160°. Recrystallization from 50% ethanol gave 153 mg., m.p. 181.5–184.5°; $[\alpha]^{22}D$ −47.7° (*c* 1, acetone–water (4:1)). A sample was dried over P_2O_5 *in vacuo* at 75° for analysis.

Anal. Calcd. for $C_{31}H_{41}O_8N_9S \cdot C_6H_3O_7N_3$: C, 47.84; H, 4.77; N, 18.10. Found: C, 47.78; H, 4.95; N, 17.73.

S-Benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide Dihydrobromide.—The cleavage of the *p*-nitrobenzyloxycarbonyl derivative was carried out in the same manner as for N^{α}-*p*-nitrobenzyloxycarbonyl-L-arginylglycinamide picrate except that warming was at 50° for 45 minutes. The product was freed from excess hydrogen bromide and acetic acid as before. The yield was nearly quantitative. The white amorphous solid was hygroscopic and was easily soluble in water, alcohol and dimethylformamide and insoluble in the usual organic solvents. The tetrapeptide amide dihydrobromide was titrated using the Model G Beckman *p*H meter. No free carboxyl group was detectable. The pK' of the α-amino group was 6.7. For titration of the α-amino group, 0.035 g. requires 0.52 ml. of 0.100 *N* NaOH; found, 0.52 ml. When subjected to countercurrent distribution up to 200 transfers in the system 2-butanol–0.1% acetic acid this material gave a single peak. The distribution constant was about 0.2 but varied with concentration. As a result the distribution curve (the Sakaguchi reaction was used as before) was sharp on the leading edge but skewed to the rear, as expected.[17]

Carbobenzoxy-L-prolyl-L-arginylglycinamide Hydrobromide.—Carbobenzoxy-L-proline[18] (0.5 g., 0.002 mole, m.p. 74.5–76.5°), L-arginylglycinamide monohydrobromide, prepared from 0.78 g. (0.002 mole) of the dihydrobromide as described above, 3 ml. of diethyl phosphite and 1.0 g. (100% excess) of tetraethyl pyrophosphite were heated at 100° for 30 minutes with stirring. Ether was added to the cooled mixture to precipitate the product along with unreacted arginylglycinamide. The amorphous solid was collected, washed with ether and dried over P_2O_5 and sodium hydroxide pellets. The crude material was purified by countercurrent distribution in the system 2-butanol–0.1% acetic acid. One hundred and fifty transfers were sufficient for complete separation. The distribution constant of the tripeptide was 0.6. The Sakaguchi reaction was used for preparation of the distribution curve. From concentration and lyophilization of the solvent containing the tripeptide was obtained 0.80 g. (74%) of a white amorphous solid. Yields from other preparations varied from 65–75%.

L-Prolyl-L-arginylglycinamide Dihydrobromide.—The carbobenzoxy group was removed by warming the carbobenzoxy derivative in acetic acid saturated with hydrogen bromide for one hour at 40–45°. The white amorphous product was freed from excess hydrogen bromide and acetic acid in the manner described for L-arginylglycinamide dihydrobromide. The yield of the hygroscopic dihydrobromide varied from 80–84%. It was easily soluble in water, alcohol and dimethylformamide and insoluble in the usual organic solvents. The pK' of the imino group was 8.5. To characterize this compound it was converted to its crystalline diflavianate. The dihydrobromide (0.36 g., 0.74 mmole) was dissolved in 2 ml. of warm water and 0.51 g. of flavianic acid in 1.5 ml. of warm water was added along with 0.5 ml. of ethanol. The diflavianate crystallized from the cooled mixture; yield 0.58 g. (80%), m.p. 173° (opaque melt). After recrystallization from water–ethanol (3:1) the diflavianate hydrate was allowed to dry in air for analysis, m.p. 180° (forms opaque melt), $[\alpha]^{24}D$ −18.2° (*c* 1, acetone–water (1:1)).

Anal. Calcd. for $C_{13}H_{25}O_3N_7 \cdot 2C_{10}H_6O_8N_2S \cdot 1^1/_2H_2O$: C, 40.32; H, 4.10; N, 15.68; H_2O, 2.75. Found: C, 40.63; H, 4.16; N, 15.38; H_2O, 2.43.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELHI]

Acetylium Perchlorate-catalyzed Preparation of Ketones. The Use of Sodium Perchlorate–Acetyl Chloride Mixture in the Ring Acetylation of Phenol Ethers

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Sodium perchlorate and acetyl chloride taken in glacial acetic acid together work as satisfactorily as acetylium perchlorate or perchloric acid for ring acetylations. In the presence of acetic anhydride and using the above mixture certain monohydric, dihydric and trihydric phenol ethers have been found to undergo catalytic ring acetylations. A 30–50% conversion of the ethers into the acetophenones can generally be brought about at 40–60° in 4–6 hr., depending on the reactivity of the ethers. The acetyl group enters a position *para* to the ether grouping and, when this is not free, *ortho* substitution also can occur. Except for anisole, the perchlorate-catalyzed acetylations with various phenol ethers have been studied for the first time.

Several workers have studied the ring acetylations of aromatic hydrocarbons and phenol ethers in the presence of catalysts, *e.g.*, trifluoroacetic acid[1a] or its anhydride[1b], chloroacetic acid at high temperatures,[1c] phosphorus pentoxide,[1d] polyphosphoric acid,[1e] sulfuric acid[1f,10b] and sundry other inorganic substances[1g,3a] all of which are different from the usual catalysts of the Friedel and Crafts type.[2a–c,8a] In this connection the use by Burton and Prail[3a] of perchloric acid or of acetylium perchlorate seems to be of greater practical importance.[3b] Thus, acetylium perchlorate, acetic acid, anisole and acetic anhydride when used in the molecular proportion 1:2:4:3 or 1:8:4:3 easily give 1.46 and 1.02 moles of *p*-methoxyacetophenone,[3c] respectively. It is, however, found that solvation with larger proportions of acetic acid or using larger proportions of acetic anhydride seriously lowers the yield of the ketone. The above workers minimized the side reactions, *e.g.*, formation of a certain amount of phenol, diketones, colored pyrrilium salts and tar by keeping the temperature low (0–5°) and limiting the reaction time to 45 minutes. Remarkably *p*-methoxyacetophenone is said to be obtainable in identical yields[4] whether acetylium perchlorate or perchloric acid be used as the catalyst. No systematic study, however, has so far been made of the perchlorate-catalyzed acetylations of phenol ethers other than anisole. Even in the latter case Burton and Prail's own work[3a] was directed more to the elucidation of reaction mechanism. In the present investigation the acetylations of the above type of some monohydric, dihydric and trihydric phenol ethers have been undertaken from a preparatory point of view and by a modified technique.

The modification relates to the use of an equivalent amount of anhydrous sodium perchlorate and acetyl chloride in glacial acetic acid solution, and this solution has been found to work as satisfactorily as acetylium perchlorate or perchloric acid. The amount of acetic acid used as the solvent is limited to what will not cause much of its harmful effect on the yield of the ketones. In the first instance four acetylation mixtures containing sodium perchlorate, acetyl chloride, acetic acid, the phenol ether and acetic anhydride in the mol. proportion 1:1:8:*x*:3 (x = 1, 2, 3 or 4) have been examined with anisole. It is seen (*vide* Table III) that a greater conversion of the ether to the ketone takes place when only one or two (x = 1, 2) mol. proportions of it are used. But in these cases losses—mechanical, as well as those due to side reactions[3a]—are proportionately greater than when acetylation is done with a mixture of composition 1:1:8:4:3. The latter has, therefore, been chosen for acetylation because in most cases it is easy to remove the unchanged ether by vacuum distillation at low temperatures. However, in those cases where the separation is not so easy and the ethers are reactive, acetylation with a 1:1:8:2:3 or even 1:1:8:1:3 mixture may be done. Using the acetylation mixtures (x = 4 or 2), the ethers listed in Table I have been successfully acetylated to give in each case an acetophenone

$$(CH_3O)_nRH + \frac{(CH_3CO)_2O}{NaClO_4,\ CH_3COCl,\ CH_3COOH} (CH_3O)_nRCOCH_3 + CH_3COOH$$

n = 1, 2 or 3

in which the acetyl group is found to be present in a position *para* to the ether grouping. When the *para* position is not free, the acetyl group enters the *ortho* position but the yields then are poor.

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(2) (a) *Cf.* C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941, Chapter VI and pp. 302–341; (b) C. R. Noller and R. Adams, THIS JOURNAL, **46**, 1889 (1924); (c) N. M. Cullinane, S. J. Chord and D. M. Layshon, *J. Chem. Soc.*, 376 (1952).

(3) (a) H. Burton and P. F. S. Prail, *J. Chem. Soc.*, 2036 (1950), and earlier and later papers; (b) *cf.* also R. E. Foster, U. S. Patent 2,496,786; *C. A.*, **44**, 4930c (1950); (c) it is, however, also reported[3b] that the perchloric acid-catalyzed acetylation of anisole results in the formation of both *o*- and *p*-methoxyacetophenone, the yield of the *o*-isomer being half as much (7.3%) as that of the *p*-isomer (14.7%).

(4) It is suggested[3a] that in these reactions, acetylium ions CH_3CO^+, or their solvated form $(CH_3CO)_2OH^+$, are mainly concerned in bringing about acetylation. The reaction becomes catalytic if acetic anhydride is also present, the whole mechanism in the case, *e.g.*, of acetylium perchlorate and anisole is then represented thus:

$$AgClO_4 + CH_3COCl \longrightarrow CH_3CO^+ClO_4^- + AgCl \quad (i)$$

$$CH_3CO^+ClO_4^- \rightleftharpoons CH_3CO^+ + ClO_4^- \quad (ii)$$

$$CH_3CO^+ + C_6H_5OCH_3 \longrightarrow CH_3CO\cdot C_6H_4\cdot OCH_3 + H^+ \quad (iii)$$

$$H^+ + (CH_3CO)_2O \longrightarrow CH_3CO^+ + CH_3COOH \quad (iv)$$

When perchloric acid is the catalyst, the hydrogen ion available from this strong acid is supposed to initiate the reaction iv after which reactions iii and iv occur in sequence as above.

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TABLE I

YIELDS OF THE KETONES UNDER OPTIMUM CONDITIONS

Phenol ether	Moles	No.	Ketone[c] formed	Yield, Mol.[a] prop.	Yield, Per cent.[b]
Anisole	4	1	4-Methoxyacetophenone	2.0	50
o-Cresol methyl ether	4	2	3-Methyl-4-methoxyacetophenone	1.8	45
m-Cresol methyl ether	4	3	2-Methyl-4-methoxyacetophenone	2.2	55
p-Cresol methyl ether	4	4	3-Methyl-6-methoxyacetophenone	0.68	17
Phenetole	4	5	4-Ethoxyacetophenone	1.83	45.8
1-Naphthol methyl ether	4	6	1-Acetyl-4-methoxynaphthalene	1.76	44
2-Naphthol methyl ether	4	7	1-Acetyl-2-methoxynaphthalene	1.48	37
Methylenedioxybenzene	4	8	3,4-Methylenedioxacetophenone	1.2	30
Pyrogallol trimethyl ether	4	9	2,3,4-Trimethoxyacetophenone	0.67	16.8
Phloroglucinol trimethyl ether	2	10	2,4,6-Trimethoxyacetophenone	0.68	34
Phloroglucinol dimethyl ether	4	11	2-Hydroxy-4,6-dimethoxyacetophenone	0.64	16
Catechol dimethyl ether	2	12	3,4-Dimethoxyacetophenone	1.02	50.6
Resorcinol dimethyl ether	2	13	2,4-Dimethoxyacetophenone	1.23	62
Hydroquinone dimethyl ether	2	14	2,5-Dimethoxyacetophenone	0.58	30

[a] Moles of ketone formed per 4 or 2 moles of the ether. [b] Calculated on the ether used. [c] Obtainable in a fair degree of purity even by the first distillation; the ketones 1, 5–8 and 10–13 also have been obtained in the pure solidified forms, in spite of the low m.p. of some of them.

In separating the ketones no earlier[3b,3c] or later ketonic fraction containing the acetyl group in a position different from the above has been obtained. Considering the purity of the ketones and the homogeneity of their derivatives, there does not seem to be any possibility of isomeric ketones present in the recovered ketone fractions either. As regards the yields, it will be noted from Table I that any one of the two acetylation mixtures chosen, a 30–50% conversion of the ether to the ketone generally occurs under optimum conditions, though it may be less in an ether of low reactivity. An idea about the reactivities of the ethers can be obtained from Table II in which results for the extent of acetylation undergone by some of the representative phenol ethers at 40° in 2 hr. are compiled together. *m*-Cresol methyl ether, 1-naphthol methyl ether can thus be considered to be very reactive; phenetole, *o*-cresol methyl ether, anisole fairly reactive and pyrogallol trimethyl ether, *p*-cresol methyl ether, methylenedioxybenzene, 2-naphthol methyl ether less reactive. In the case of the reactive ethers the maximum yield of the ketones (*vide* Tables IV and V) can be obtained by heating at 40–45° for 4 hr. and in those of medium or low reactivity by heating at 60° for 4–6 hr. Higher temperatures (*cf.* expt. on *p*-cresol methyl ether at 70°) or a longer time of reaction (*cf.* expt. on 2-naphthol methyl ether for 8 hr.) either produce more residue or because of side reactions do not improve the yield of the ketone materially.

TABLE II

EXTENT OF KETONE FORMATION AT 40° IN 2 HOURS

Ether	Ketone formed mol. proportion	
m-Cresol methyl ether	1.88	Very reactive
1-Naphthol methyl ether	1.76	
Phenetole	1.05	Reactive
o-Cresol methyl ether	0.83	
Anisole	0.44	
Pyrogallol trimethyl ether	0.67 (4 hr.)	Less reactive
p-Cresol methyl ether	0.40	
Methylenedioxybenzene	0.20 (4 hr.)	
2-Naphthol methyl ether	Traces	
o-Bromoanisole	Nil	

At low temperatures (0–5°) very little acetylation is found to occur in the case of anisole. With ethers more reactive than anisole, yields comparable to those obtained by heating at 40–60° are had by keeping the reaction mixture at room temperature (15–22°) for 24 hr. or more. In fact, acetylation in the cold is the better procedure for the preparation of 3,4-dimethoxy- and 2,4-dimethoxyacetophenones from catechol and resorcinol dimethyl ethers. Remarkably for a 50% conversion to the ketones, resorcinol dimethyl ether requires only 0.75 hr., whereas catechol dimethyl ether takes 24 hr. at room temperature.

Partial methyl ethers of polyhydric phenols can be acetylated too. Phloroglucinol dimethyl ether gives 2-hydroxy-4,6-dimethoxyacetophenone. But resorcinol monomethyl ether gives a mixture of 2-hydroxy-4-methoxyacetophenone and 2-methoxy-4-hydroxyacetophenone. Here acetylation seems to have occurred both *para* and *ortho* to the methoxy group. This is rather unusual as in all other cases only one product has been isolated, *i.e.*, the one in which the acetyl group comes *para* or *ortho* to the ether group.

In connection with the identification of the various ketones, 2,3,4-trimethoxyacetophenone (gallacetophenone trimethyl ether) has also been characterized by its oxidation to 2,3,4-trimethoxybenzoic acid by the iodoform reaction. The semicarbazone and picrate of 1-acetyl-2-methoxynaphthalene have been described for the first time. The m.p. of the picrate of 1-acetyl-4-methoxynaphthalene has been corrected.

As for the mode of working of the acetylation mixture, an initial change, *e.g.*

$$CH_3COCl + NaClO_4 \longrightarrow CH_3CO^+ClO_4^- + NaCl$$

can be visualized to occur first in the acetic acid solution[5a,b] after which through the suggested se-

(5) (a) Potassium perchlorate does not work for acetylations, and its inability to do so has been traced to its insolubility in acetic acid. (b) We have tried a different modification also, *viz.*, using perchloric acid liberated *in situ* by mild heating of equivalent amount of sodium perchlorate and concd. sulfuric acid together. This modification, however, does not seem to be as expedient and efficient as using the sodium perchlorate–acetyl chloride mixture.

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quence of changes involving acetylium ion,[4] the ketone formation would occur. However, it is found that by using lesser proportions of the catalyst mixture, proportionately lesser yields of 4-methoxyacetophenone are obtained. The catalyst mixture therefore acts like acetylium perchlorate or perchloric acid only in the sense that a given amount of the mixture can enable the acetylation of more phenol ether than is stoichiometrically possible on the amount of the perchlorate used.

Compared to the Friedel and Crafts reactions, where possibilities of side reactions and dealkylations in the ketone formed are greater,[2a,b,12b,13a,18b] acetylations of phenol ethers have been found to go smoothly by the use of sodium perchlorate–acetyl chloride mixture as the catalyst. The latter technique is also superior to the use of perchloric acid or acetylium perchlorate—obtainable from the hygroscopic silver perchlorate, in that the sodium salt is convenient to handle and its purity can be depended upon. A further advantage is that the reaction conditions do not require excessive cooling or heating. The sodium perchlorate–acetyl chloride mixture can be used successfully for the ring acetylation of phenol ethers.

Experimental

Anhydrous sodium perchlorate was obtained by heating the monohydrate at 135–140° for 4 hr. It was found to be appreciably soluble in warm acetic acid (24 g. in 100 g. of acetic acid at 60°). Potassium perchlorate, however, was insoluble even in hot acetic acid and was ineffective as a catalyst.

Acetic acid, acetyl chloride and acetic anhydride were Merck pure reagents. Anisole, *p*-cresol methyl ether, *m*-cresol methyl ether, *p*-cresol methyl ether and phenetole were used from stock. 2-Naphthol methyl ether, methylenedioxybenzene, pyrogallol trimethyl ether, catechol dimethyl ether, resorcinol dimethyl ether, hydroquinone dimethyl ether and phloroglucinol trimethyl ether were prepared by standard methods described in literature. Phloroglucinol dimethyl ether, b.p. 185° (16 mm.), and resorcinol monomethyl ether, b.p. 240–242°, were obtained as reported by Robinson, *et al.*[6] The m.p. or b.p. of the ethers stated in Tables IV and V are those recorded in literature and were also checked. 2-Naphthol methyl ether was found to have b.p. 132–134° (10 mm.). 1-Naphthol methyl ether could be obtained better by methylation of 1-naphthol with dimethyl sulfate and alkali.

The following account is given as typical of the process of acetylation, being done with anisole under optimum conditions.

Acetylation of Anisole, Taking Sodium Perchlorate, Acetyl Chloride, Acetic Acid, Anisole and Acetic Anhydride in the Molecular Proportion 1:1:8:4:3.—Anhydrous sodium perchlorate (3.1 g., 0.025 mole) was dissolved at 60° in acetic acid (12 g., 0.2 mole) and, when cold, acetyl chloride (2.0 g., 0.025 mole) was added. Slight turbidity was produced. Anisole (10.8 g., 0.1 mole) and acetic anhydride (7.7 g., 0.75 mole) were then added and the reaction mixture warmed under reflux at 60° for 4 hr. There was gradual development of color which became deep brown toward the end. The reaction mixture was then poured over crushed ice. The aqueous liquor which contained the oily reaction product was extracted with ether (50 ml., thrice). The ether layer, separated from the aqueous layer,[7a] still contained a suspension of an orange-red solid and was therefore filtered. The filtered ether extract was washed successively with aq. sodium carbonate, 2 *N* caustic soda solution and finally with water. The residue from the dried (Na_2SO_4) ether extract was fractionally distilled. Unchanged anisole (3.5 g.) admixed with little of the ketone came over at 45–47° (6–8 mm.). The ketone fraction came over at 119–120° (6–8 mm.) and solidified upon refrigeration giving m.p. 37° (4-methoxyacetophenone is reported[3b] to have b.p. 117° (6 mm.) and m.p. 37°); 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 221°[7b]; oxime,[8a] m.p. and mixed m.p. 88°; yield 7.5 g. (moles of ketone formed per 4 moles of the ether, *i.e.*, mol. prop. = 2); non-volatile residue, 1.7 g. The amount of the ketone formed corresponds to 50% conversion of the ether into 4-methoxyacetophenone. The latter could be obtained in equivalent yields by using hydrated sodium perchlorate $NaClO_4 \cdot H_2O$; the proportion of the sodium perchlorate, acetyl chloride, acetic acid, anisole and acetic anhydride then was 1:1:6:4:4.

When in these experiments acetyl chloride was not included in the acetylation mixture no acetylation took place, but when the acetic anhydride was omitted, there was some acetylation—4-methoxyacetophenone being obtained in poor yields (1.7 g. at 40° in 4 hr.). The results of acetylation of anisole, using different amounts at 60° in 4 hr., as well as those for the yield of the ketone at different temperature and time and with decreasing amount of the catalyst are incorporated in Table III.

TABLE III

ACETYLATION OF ANISOLE UNDER DIFFERENT CONDITIONS

Temp., 60° $NaClO_4$:AcCl:AcOH:Anisole:Ac_2O Mol. proportion	Anisole used, g.	Time, 4 hours Yield[a] 4-methoxyacetophenone, %	Ether recovd., g.
1:1:8:1:3	2.7	60	0.25
1:1:8:2:3	5.4	58	0.75
1:1:8:3:3	8.1	52	1.90
1:1:8:4:3	10.8	52[b,c]	3.50
1:1:8:4:4	10.8	48[d]	3.40

[a] Calculated on the anisole used. [b] At other temperatures and time the amount of the ketone formed was: 0–5°/72 hr. or 45°/4 hr., 3 g.; at 40°/2 hr., 1.7 g. (mol. prop. with anisole, 0.44). [c] AcOH, anisole and Ac_2O remaining the same (8:4:3), at diminished mol. concentration of the catalyst mixture ($NaClO_4$ + AcCl), the amount of the ketone was: 0.25 mole/1.9 g., 0.5 mole/3.4 g., 0.75 mole/5.0 g., the first figures being those for the catalyst mixture. [d] With concentrations greater than 3 moles, Ac_2O is utilized more in promoting side reactions (ref. 3a).

Acetylation of Various Phenol Ethers.—Further experiments were conducted with other ethers at different temperature and time in the manner described for anisole. The results are listed in Tables IV and V. Experiments relating to the ketones a–f in Table IV and c and d in Table V were conducted with an acetylation mixture of composition 1:1:8:4:3 and those for e–h in Table V with one of composition approximating 1:1:8:2:3. The actual amount of the ether is mentioned in the first column, the amount of the other constituents being adjusted accordingly. Distillation of the final reaction products under reduced pressure (as indicated) gave a forerun composed of the unchanged ether and containing also, in some cases, a little of the ketone fraction. After a sudden rise of 40–65°, the main ketone fraction came later at temperatures stated in the tables. Only in a few cases was a second distillation necessary to improve the purity of the ketones. The latter have been characterized through suitable derivatives (*vide* literature cited, Tables IV and V). In the case of 1-acetyl-4-methoxy- and 1-acetyl-2-methoxynaphthalene, their identity has been further confirmed by comparison with authentic samples of the ketones and of their derivatives. The purification of 2,4,6-trimethoxyacetophenone (phloroacetophenone trimethyl ether) was done by crystallization. In all cases, losses entailed during the working of the reaction mixture as well as those due to side reactions were inevitable, but considering together the weights of the ketone fraction, forerun and residue (*cf.*

(6) R. Robinson, *et al.*, *J. Chem. Soc.*, **125**, 193 (1924); **127**, 945 (1926).

(7) (a) The filtered aqueous layer after repeated evaporation on the water-bath left a residue which did not contain an appreciable amount of the chloride. (b) Burton and Prail (ref. 3a) obtained m.p. 223°. Vogel ("Practical Organic Chemistry," Longmans, Green & Co., London, 1956, p. 743) gives m.p. 220°. Hartmann and [illegible] Barthenheier, *Ann.*, **553**, 250 (1942), report the m.p. to be 232–234°.

(8) (a) K. v. Auwers, M. Lechner and H. Bundesmann, *Ber.*, **58**, [illegible] (1925); (b) G. Stadnikoff and A. Baryschewa, *ibid.*, **61**, 1997 (1928).

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TABLE IV

ACETYLATION OF MONOHYDRIC PHENOL ETHERS

Phenol ether	Reaction Temp., °C.	Reaction Time, hr.	Ketone fraction B.p., °C. (6–8 mm.)	Ketone fraction Yield, %	Forerun Temp., °C. (6–8 mm.)	Forerun G.	Residue, g.
			3-Methyl-4-methoxyacetophenone[a]				
o-Cresol methyl ether, b.p. 55.5° (9 mm.), 12.2 g., 0.1 mole	15	24	132–134	15	78–80	..	..
	40	2		20.8		6.5	2.1
	60	4		45		1.6	2.0
			2-Methyl-4-methoxyacetophenone[b]				
m-Cresol methyl ether, b.p. 56.5° (9 mm.), 12.2 g., 0.1 mole	15	24	133–135	30	80–82	6.0	..
	40	2		47		3.4	0.7
	45	4		55		2.3	1.2
			3-Methyl-6-methoxyacetophenone[c]				
p-Cresol methyl ether, b.p. 56.2° (9 mm.), 12.2 g., 0.1 mole	20	24	120–122	5	75–78	..	..
	40	2		10		9.8	1.0
	60	4		17		8.7	0.6
	70	2		23		6.7	2.3
			4-Ethoxyacetophenone[d]				
Phenetole, b.p. 60° (9 mm.), 12.2 g., 0.1 mole	15	24	124–125	20.8	55–60	7.5	..
	40	2		26.3		6.6	0.6
	50	4		45.8		3.6	1.8
			1-Acetyl-4-methoxynaphthalene[e]				
1-Naphthol methyl ether,[g] b.p. 134–135° (9.5 mm.), 7.9 g., 0.05 mole	25	24	192–195	44	136–140	2.9	..
	40	2		44		2.4	..
			1-Acetyl-2-methoxynaphthalene[f]				
2-Naphthol methyl ether,[g] b.p. 132–134° (10 mm.), 7.9 g., 0.05 mole	28	70	174–178	Nil	132–134	7.5	..
	40	4		Traces		7.5	..
	60	6		37		4.0	..
	60	8		35		4.5	..

[a] Reported[8a] b.p. 145–146° (14 mm.); oxime, m.p. 101–102°, reported[8a] 101–102.5°; semicarbazone, m.p. 206–207°, reported[8b] 206–207°. [b] Reported[8a] b.p. 140–141° (14 mm.); semicarbazone, m.p. 194–196°, reported[8a] 194–195°. [c] Reported[2b] b.p. 120.5° (7 mm.); oxime m.p. 89–91°, reported[8a] 89–90°; semicarbazone, m.p. 176–177°, reported[8b] 176–177°. [d] Reported[1d] b.p. 131° (6 mm.). After redistillation and refrigeration solidified, m.p.[9a] 36–37°. Upon oxidation[9b] (with $KMnO_4$ and aq. K_2CO_3) gave *p*-ethoxybenzoic acid, m.p. 195–196°. [e] Reported[10a] b.p. 224–225° (15 mm.). Solidified on keeping. Crystals (from alcohol and then petroleum ether) gave m.p. and mixed m.p. with authentic sample[10b] 70–71°. Semicarbazone, m.p. and mixed m.p. 221–222°. (*Anal.* Calcd. for $C_{14}H_{15}N_3O_2$: N, 16.34. Found: N, 15.91.) Picrate, m.p. and mixed m.p. 129–130° (*Anal.* Calcd. for $C_{19}H_{15}N_3O_9$: C, 53.14; H, 3.49. Found: C, 53.2; H, 3.6). Schneider and Kunau[10b] had reported m.p. of the picrate to be 119–121°. [f] Reported[2b] b.p. 158° (2 mm.). Solidified on keeping to give crystals m.p. and mixed m.p. with authentic sample[2b] 59–60°. Semicarbazone, m.p. and mixed m.p. 234–235°. (*Anal.* Calcd. for $C_{14}H_{15}N_3O_2$: N, 16.34. Found: N, 16.64.) Picrate m.p. and mixed m.p. 134–135°. (*Anal.* Calcd. for $C_{19}H_{15}N_3O_9$: C, 53.1; H, 3.19. Found: C, 52.7; H, 3.57.) [g] Fractionation in the case of the reaction products from these two ethers was done under 8–10 mm. pressure.

Tables IV and V), these losses are not found to be more than 1.5–2.5 g. With 0.1-mole quantities of the ethers, this weight might account for the fate of 15–25% of the phenol ether used.

Acetylation of Resorcinol Monomethyl and Phloroglucinol Dimethyl Ether.—Resorcinol monomethyl ether (12.4 g., 0.1 mole) was acetylated at 60° for 4 hr. using the acetylation mixture of composition 1:1:8:4:3. The reaction mixture was made alkaline and refluxed for 1 hr. to hydrolyze the O-acetyl group if any. It was then acidified and extracted with ether. The ether layer was filtered from suspended matter (0.5 g.) and the ether removed. The residual liquid mass was steam distilled till no more emulsion came over. The steam distillate upon ether extraction yielded an oil (5 g.) which did not solidify but contained 2-hydroxy-4-methoxyacetophenone (peonol); semicarbazone, m.p. 219–221°, reported[17a] 221–222°. Four tenths gram of the oil gave 0.13 g. of semicarbazone, indicating it to contain 25–30% peonol (total *ca.* 1.3 g.), the rest being the unused ether. The colored solid left behind after steam distillation was extracted with ether, the extract treated with animal charcoal and filtered. After removing the ether and crystallizing the residue (1 g., m.p., crude, 120–125°) from alcohol, pure 2-methoxy-4-hydroxyacetophenone (isopeonol) was obtained, m.p.[17b] 137–138°; 2,4-dinitrophenylhydrazone, m.p. 219–220°, reported[17c] 216–217°.

The experiment with phloroglucinol dimethyl ether (7.7 g., 0.05 mole) was done in the same way. The steam distillate gave 2-hydroxy-4,6-dimethoxyacetophenone (1.6 g., mol. prop. 0.64); m.p. and mixed m.p. 84–85° with an authentic sample of m.p. 85°. The m.p.'s of this ketone are variously reported, *e.g.*, 80°,[13a] 85–88°,[18b] 86–87°,[18a] etc. The sample gave with nitric acid[12b] a blue color turning green on making alkaline and an intense violet color with ferric chloride in alcoholic solution.[18b]

Acetylations Using Perchloric Acid Liberated *in situ*.—Anhydrous sodium perchlorate (1.54 g., 0.0125 mole) and concd. sulfuric acid (1.22 g., 0.0125 mole) were heated together at 100–110° for 0.5 hr. The heated mass was cooled and extracted with glacial acetic acid (2 g., 0.034 mole). The extract was filtered through glass wool which was pressed to squeeze out the extract. Acetic anhydride (4.1 g., 0.0 mole) and anisole (5.4 g., 0.05 mole) were then added. This mixture was maintained at 50° for 4 hr. The reaction

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(10) (a) S. Ruheman and S. I. Levy, *ibid.*, **53**, 270 (1920); (b) beside W. Schneider and F. Kunau, *ibid.*, **54**, 2304 (1921).

(11) (a) C. Ciamician and P. Silber, *Ber.*, **24**, 2989 (1891); (b) F. Mauthner, *J. prakt. Chem.*, **116**, (ii) 324 (1927); (c) T. Posner, *Ann.*, **389**, 67 (1912).

(12) (a) C. Mannich and F. Hahn, *Ber.*, **44**, 1551 (1911); (b) W. H. Perkin and C. Weizmann, *J. Chem. Soc.*, **89**, 1654 (1906); (c) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds,"

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TABLE V

ACETYLATION OF DI- AND TRIHYDRIC PHENOL ETHERS

Phenol ether	Reaction Temp., °C.	Reaction Time, hr.	Ketone fraction B.p., °C. (8–10 mm.)	Ketone fraction Yield, %	Forerun Temp., °C. (8–10 mm.)	Forerun G.	Residue, g.
			3,4-Methylenedioxyacetophenone[c]				
Methylenedioxybenzene,[a] b.p. 55–56° (9 mm), 6.1 g., 0.05 mole	40	4	138–140	5	56–58	..	..
	70	4		30		1.0	1.0
			2,3,4-Trimethoxyacetophenone[d]				
Pyrogallol trimethyl ether,[a] b.p. 241°, 8.4 g., 0.05 mole	20	24	156–158	Traces	116–118	..	..
	40	4		16.8		..	..
	50[b]	4		16.8		5.0	..
			2,4,6-Trimethoxyacetophenone[e]				
Phloroglucinol trimethyl ether, m.p. 52°, 7.5 g., 0.045 mole	22	24		34		..	..
			3,4-Dimethoxyacetophenone[f]				
Catechol dimethyl ether, b.p. 205–206°, 6.5 g., 0.047 mole	15	24	160–161	46.1	93–94	..	..
	22	60		50.6		..	..
			2,4-Dimethoxyacetophenone[g]				
Resorcinol dimethyl ether,[i] b.p. 207–208°, 6.5 g., 0.047 mole	15	0.5	165–167	27	96–98	..	..
	5–10	0.75		49.4		2.1	1.1
	22	0.75		62		1.4	0.7
			2,5-Dimethoxyacetophenone[h]				
Hydroquinone dimethyl ether,[i] b.p. 109° (20 mm.), 6.5 g., 0.047 mole	50	4	156–158	22.4	120–121	..	..
	60	4		30		..	..

[a] Composition of the acetylation mixture was 1:1:8:4:3, in others it was 1:1:8:2:3. [b] Perchloric acid, from $NaClO_4$ + H_2SO_4 (*v. infra*), was the catalyst. [c] Solidified upon refrigeration. After recrystallization from benzene, m.p.[11a,b] 87°; oxime, from hydroxylamine hydrochloride and sodium acetate, m.p. 155–156°, reported[11c] 156–157°; phenylhydrazone, m.p. 115°, reported[11a] 114°. Semicarbazone, m.p. 238–240°, reported[11b] 241–242°. [d] The ketone fraction did not solidify; reported[12a] m.p. 14–15°, b.p. 165° (12 mm.). Semicarbazone, m.p. 168–169°. (*Anal.* Calcd. for $C_{12}H_{17}N_3O_4$: N, 15.73. Found: N, 15.49.) Oxidation with iodine and alkali[12c] gave iodoform, m.p. 119°, and 2,3,4-trimethoxybenzoic acid, m.p. 98° (reported 100°). [e] The reaction product was first decolorized with animal charcoal in 20% alcohol (40 ml.) at 80° and the extract filtered. The residue was then further extracted with alcohol (10 ml. thrice). The combined extracts on concentration and cooling deposited the crude product (3.2 g.), representing a 34% conversion of the ether. The crude product upon recrystallization from alcohol gave crystals, m.p.[13a,13b] 99–100°. The latter gave a blue color with nitric acid.[13b] In a similar experiment, using 5.7 g. of ether and doing the acetylation at 70° for 4 hr., the yield of the crude ketone was 2.4 g., showing 33% conversion of the ether. [f] Reported[14a] b.p. 158° (9 mm.). After redistillation and refrigeration, m.p.[14b] 48–49°; oxime,[14a] m.p. 140°; semicarbazone,[14a] m.p. 211°. [g] Reported[2b] b.p. 157.5° (7 mm.) and[15a] 163–165° (12 mm.). After redistillation and refrigeration solidified to give m.p.[15a] 40°; oxime,[15b] m.p. 125°. At higher reaction temperature considerable colored and tarry material was also produced. [h] Reported[16a] b.p. 156–158° (11 mm.); semicarbazone,[16b] m.p. 181–182°. [i] Fractionation was done under 10–12 mm. pressure.

mixture was then worked as described before for anisole. 4-Methoxyacetophenone isolated weighed 2 g. The amount was 2.5 g. by the sodium perchlorate–acetyl chloride method. The yields of ketones obtained from *m*-cresol methyl ether and pyrogallol trimethyl ether when sodium perchlorate–sulfuric acid was used approached the yields obtained using the sodium perchlorate–acetyl chloride method (*cf.* Table V). In other cases (*e.g.*, phenetole, 1-naphthol methyl ether, phloroglucinol dimethyl ether) the yields were less. Similar results were obtained when the experiments were conducted at room temperatures.

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[CONTRIBUTION FROM THE FULMER CHEMICAL LABORATORY, THE STATE COLLEGE OF WASHINGTON]

Cortical Steroid Analogs. II. The Synthesis of Open-chain Dihydroxyacetones from 2,3-Butanedione[1]

BY GARDNER W. STACY, RICHARD A. MIKULEC, STEPHEN L. RAZNIAK AND LAURENCE D. STARR[2]

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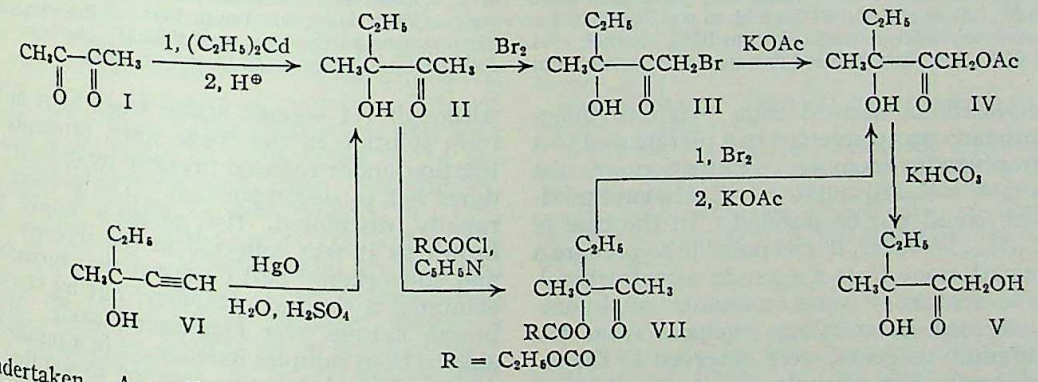
The synthesis of 1,3-dihydroxy-3-methyl-2-pentanone (V), an open-chain or acyclic dihydroxyacetone derivative which had resisted prior attempts at synthesis, has been accomplished. The synthetic scheme employed appears to have rather general potentialities for the preparation of a series of such dihydroxyacetone derivatives with 2,3-butanedione (I) as the starting point. It has been demonstrated that from I it is possible to prepare conveniently by reaction with appropriate organocadmium reagents a number of representative acetylcarbinols similar to II, these latter substances being key compounds in the synthesis of dihydroxyacetones. Biological evaluation of V and its corresponding 1-acetate IV has revealed that neither substance has significant anti-inflammatory or glucocorticoid activity.

Syntheses of alicyclic analogs of cortisone have been reported,[3] and studies in the same direction also have been carried out in this Laboratory.[1,4] It now has been decided to investigate the synthesis and possible biological activity of open-chain (acyclic) analogs because of the number of compounds of lesser structural complexity that might possibly be synthesized. A survey of the literature revealed that apparently no acyclic dihydroxyacetone derivatives with a tertiary hydroxyl group had been prepared previously, although an attempted synthesis of such compounds had been reported by Diels and Johlin.[5]

A synthetic scheme, similar to that attempted by Diels and Johlin[5] and employed more recently with success in respect to steroid[6] and analog syntheses,[3] was undertaken. Accordingly, this resulted in the successful preparation of 1,3-dihydroxy-3-methyl-2-pentanone (V), one of the compounds that Diels and Johlin[5] previously had failed to obtain and a representative example of the type of acyclic analog that may be derived from 2,3-butanedione (I).

Acetylcarbinols such as II are the key intermediates for the synthesis of acyclic analogs (V) in respect to the scheme outlined. A method of readily obtaining a series of such acetylcarbinols, where one alkylcarbinol substituent remained constant as a methyl group, suggested itself. It seemed quite possible to derive such a series from 2,3-butanedione (I) by reaction of this substance with an appropriate organometallic reagent. The use of Grignard reagents appeared to be unsatisfactory, for it had been reported that such a reaction results in bis addition to the very reactive twin carbonyl grouping of I to yield pinacols.[7] Although Lapkin and Golovkova[8] more recently had observed that Grignard reagents involving radicals of large size will react under the proper conditions to give acetylcarbinols, a procedure more general in scope was desired for the present application. Since it had been noted that organocadmium reagents, which are relatively unreactive with isolated carbonyl groups, react readily with the twin carbonyl group of α-keto esters to form α-hydroxy esters,[9] it appeared likely that a similar reaction would occur in the case of organocadmium reagents and 2,3-butanedione. This hope was indeed realized, and a number of acetylcarbinols were prepared in yields of 38–70% (Table I). It was found that a 0.5 equivalent excess of organocadmium reagent in respect to the 2,3-butanedione gave optimum results. For example, when an equivalent amount of diethylcadmium was used in the preparation of II, a 28% yield was obtained; however, when the excess was used the yield was 68%. With one exception, the acetylcarbinols were characterized as semicarbazones (Table II).



(1) Presented in part before the Division of Organic Chemistry at the 128th Meeting of the American Chemical Society, Minneapolis, Minn., Sept. 15, 1955; Paper I, G. W. Stacy and R. A. Mikulec, THIS JOURNAL, **76**, 524 (1954).

(2) In part abstracted from a thesis submitted by Laurence D. Starr in partial fulfillment of the requirements for the degree of Doctor of Philosophy, the State College of Washington, June, 1955.

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TABLE I

ACETYLCARBINOLS $CH_3C(OH)(R)-C(=O)CH_3$

R	Yield, %	B.p., °C.	Mm.	$n^{25}D$	d^{25}_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-C_6H_{13}[a]	38	102–103	14	1.4333	0.8998	$C_{10}H_{20}O_2$	69.72	69.66	11.70	11.45
n-C_8H_{17}	39	132–133	14	1.4378	.8799	$C_{12}H_{24}O_2$	71.95	72.11	12.07	12.13
n-$C_{10}H_{21}$	43	160–162	15	1.4425	.8902	$C_{14}H_{28}O_2$	73.63	73.80	12.35	12.15
n-$C_{12}H_{25}$	39	141–142	1.5	1.4453	.8799	$C_{16}H_{32}O_2$	74.94	75.20	12.58	12.68
$C_6H_5CH_2CH_2$	41	101–105	1	1.5103	1.0289	$C_{12}H_{16}O_2$	74.96	75.16	8.39	8.30

[a] In addition to the new compounds listed in the table, the following known acetylcarbinols were prepared: R = C_6H_5, 44% yield, b.p. 48–50° (0.1 mm.), $n^{25}D$ 1.5133; J. Wegmann and H. Dahn, *Helv. Chim. Acta*, 29, 101 (1946), reported b.p. 132° (10 mm.). R = 1-$C_{10}H_7$, 34% yield, b.p. 120–135° (0.15–0.25 mm.), $n^{25}D$ 1.6071; Lapkin and Golovkova (ref. 8) reported b.p. 155–156° (3 mm.). R = C_2H_5, 68% yield, b.p. 74–75° (50 mm.), $n^{25}D$ 1.4195; J. Kapron and J. Wiemann, *Bull. soc. chim. France*, [5] 12, 945 (1945), reported b.p. 52° (17 mm.), $n^{19}D$ 1.4230. R = n-C_4H_9, 70% yield, b.p. 81–84° (20 mm.), $n^{25}D$ 1.4274, d^{25}_4 0.9075; L. Leers, *ibid.*, [4] 39, 423 (1926), reported b.p. 74° (10 mm.), d^0_4 0.931.

TABLE II

SEMICARBAZONES OF ACETYLCARBINOLS

R	Yield,[a] %	M.p.,[b] °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
n-C_6H_{13}[c]	80	132–133	$C_{11}H_{23}N_3O_2$	57.61	57.54	10.11	9.85	18.32	18.00
n-C_8H_{17}	79	131.5–132.5[d]	$C_{13}H_{27}N_3O_2$	60.66	60.76	10.58	10.74	16.33	16.50
n-$C_{10}H_{21}$	82	123–126	$C_{15}H_{31}N_3O_2$	63.12	62.91	10.95	10.80	14.72	14.75
n-$C_{12}H_{25}$	98	125–128	$C_{17}H_{35}N_3O_2$	65.13	65.15	11.25	11.22	13.41	13.44
n-$C_{16}H_{33}$	91	129–130[e]	$C_{21}H_{43}N_3O_2$	68.24	68.43	11.73	11.97	11.37	11.42
$C_6H_5CH_2CH_2$	94	185–186[f]	$C_{13}H_{19}N_3O_2$	62.63	62.67	7.68	7.95	16.86	16.87

[a] Yields were based on the weight of crude product. [b] M.p. of analytical sample. All samples were recrystallized from aqueous ethanol unless otherwise stated. [c] In addition to the derivatives listed in the table, the following known semicarbazones were prepared for purposes of comparison: R = C_6H_5, 82% yield, m.p. 187°; Wegmann and Dahn (ref. *a*, Table I) reported m.p. 183–184°. R = C_2H_5, 69% yield, m.p. 150.5–151°; Kapron and Wiemann (ref. *a*, Table I) reported m.p. 148.5–149.5°. R = n-C_4H_9, 63% yield, m.p. 152–153°; Leers (ref. *a*, Table I) reported m.p. 152°. [d] Recrystallized from aqueous acetone. [e] Recrystallized from 95% ethanol. [f] In this instance purification was difficult; the crude product, m.p. 93.5–114°, was recrystallized five times, twice from aqueous ethanol and three times from 2-propanol.

The acetylcarbinol derived from 1-naphthylmagnesium bromide was converted to a picrate and to a 2,4-dinitrophenylhydrazone. Extension of the study to R = n-$C_{16}H_{33}$ and R = n-$C_{18}H_{37}$ gave products which could not be purified. In the case of R = n-$C_{16}H_{33}$, however, it was possible to prepare a pure semicarbazone from the crude acetylcarbinol.

In some instances small amounts of hydrocarbons, formed as coupling products from the organocadmium reagents, were observed in the reaction mixture. For example, eicosane and tetracosane were isolated from the reaction mixtures involving the C_{10}- and C_{12}-organocadmium reagents, respectively. To confirm the structure of the acetylcarbinols obtained from I by the method just described, II was prepared by hydration of the ethynylcarbinol (VI). The identity of these compounds prepared by the two different methods was established through comparison of semicarbazones by a mixture melting point determination. As a result of the study of this procedure involving the reaction of organocadmium reagents with 2,3-butanedione, it is to be concluded that it constitutes a useful supplement to the ethynylcarbinol hydration for the preparation of acetylcarbinols, particularly where the prerequisite ethynylcarbinols are not readily available.

In continuation of the description of the synthesis of the dihydroxyacetone derivative V, the intermediate bromo ketone III was obtained in yields of about 60% by addition of bromine to a chloroform solution of the acetylcarbinol II. Although III seemed stable when kept in chloroform solution in the crude state, attempts at distillation under reduced pressure by ordinary procedures led to decomposition. The product always rapidly discolored, the colorless liquid turning brown as it was collected in the receiver. Catch and co-workers[10] had observed that bromoacetone exhibited a similar instability, but by storing this bromo ketone over magnesium oxide, they were able to keep samples indefinitely in a purified state. Application of this principle led to solution of the distillation problem just described, and our bromo ketone was obtained as a colorless liquid when it was distilled from magnesium oxide into a receiver containing magnesium oxide. Although the bromo ketone III failed to yield typical carbonyl derivatives, a solid derivative in the form of a 2-naphthyl ether could be prepared in low yield.

The intermediate acetate IV was formed by a modification of the procedure of Rosenkranz, *et al.*,[11] in yields ranging from 24 to 33%, as based on the acetylcarbinol II (it was unnecessary to isolate and purify the unstable bromo ketone). Finally, the desired dihydroxyacetone derivative V was obtained in yields of 41–43% by the reaction of IV with methanolic potassium bicarbonate. A molecular distillation of this substance gave a colorless product, which reduced both Benedict

(10) J. R. Catch, D. F. Elliott, D. H. Hey and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

(11) G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin and C. Djerassi, *J. Am. Chem. Soc.*, 72, 4081 (1950).

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solution and Tollens reagent. The infrared absorption spectrum was compatible with a dihydroxy ketone structure. There was no sign of an absorption band corresponding to the carbon–hydrogen stretching frequency that might be related to an aldehyde group. Therefore, an aldose type structure isomeric with V did not seem probable for the product obtained. Attempts to characterize V by solid derivatives were not at first successful. Using standard procedures, we were unable to prepare common carbonyl derivatives (semicarbazone, thiosemicarbazone, phenylhydrazone, osazone, 2,4-dinitrophenylhydrazone, *p*-nitrophenylhydrazone, or oxime). By way of comparison, it was interesting to note that the very similar acetylcarbinol II formed a semicarbazone easily in excellent yield. The timely appearance of an article by Reich and Samuels[12] on the preparation of derivatives of dihydroxyacetone resolved the difficulty. When the procedures of these authors were employed, it was possible to prepare both a 2,4-dinitrophenylhydrazone and a 2,4-dinitrophenylosazone of V, although the yields of pure derivative in each instance were relatively low.

In relation to bromination of acetylcarbinols, one is confronted with difficulties which may detract from the yield of the desired bromo ketone. In addition to the well-known ease of reaction of a tertiary hydroxyl group with hydrobromic acid, tertiary alcohols react with bromine to form dibromides.[13] It was thought that such problems might be advantageously circumvented by proceeding through an intermediate where the tertiary hydroxyl group was protected by conversion to an ester. One type of ester that was of particular interest was an oxalate because of the prospective ease with which this group might be reconverted to the hydroxyl group under mild conditions. Accordingly, the ethoxalyl derivative VII was obtained in a 72% yield by reaction of II with ethoxalyl chloride in the presence of pyridine. A bromination product was obtained in a 62% yield, and it was interesting to note that the bromo ketone obtained showed a much lesser tendency to discolor on standing than III. In the treatment of the bromo ketone with potassium acetate in acetone, not only was the bromo group displaced by an acetate group but also the ethoxalyl group was removed to give the acetate IV in a 31% yield. These experiments demonstrated the ease with which the ethoxalyl group is removed and its possible use in analog synthesis as a protective device for the hydroxyl group. However, the method has not yet proved to be advantageous from the standpoint of over-all yield.

Biological Evaluation.—1,3-Dihydroxy-3-methyl-2-pentanone (V) and the corresponding 1-acetate (IV) were investigated for possible biological activity. These compounds revealed no significant anti-inflammatory activity in the granuloma pouch assay[14] in rats; the compounds were applied locally at a level of 1 mg. In comparison, hydrocortisone is very active at a level of 300 μg., so that the activity, if any, is less than 20% of hydrocortisone.

In the glycogen deposition assay for glucocorticoid activity,[15] these compounds were inactive at levels of 300 mg./kg. subcutaneously in fasted, adrenalectomized rats, and even at higher dosage levels of 1 g./kg., no increase in the weight of liver glycogen over the controls was to be observed.

Experimental[16]

Preparation of Acetylcarbinols.—The procedure for the preparation of the acetylcarbinol where R = *n*-$C_{12}H_{25}$ will serve to illustrate the general method used in all cases. Di-*n*-dodecylcadmium was obtained by reaction of a Grignard reagent, prepared from 7.30 g. (0.30 gram atom) of magnesium turnings in 200 ml. of absolute ether and 74.8 g. (0.30 mole) of *n*-dodecyl bromide in 50 ml. of absolute ether, with 27.5 g. (0.15 mole) of anhydrous cadmium chloride in 100 ml. of absolute ether.[17] After formation of the organocadmium reagent was shown to be complete by a negative Gilman test, 17.2 g. (0.20 mole) of 2,3-butanedione in 50 ml. of absolute ether was added dropwise.[18] After the addition was complete, the reaction mixture was heated under reflux with vigorous stirring for 11 hr. The complex then was decomposed by the slow addition of cold 1 *N* hydrochloric acid. The water phase was separated and in turn was extracted with four 100-ml. portions of ether. The ether extracts and the original ether phase were combined and washed with a saturated sodium bicarbonate solution and then with a saturated sodium chloride solution. The ether solution was dried over anhydrous sodium sulfate. The ether was removed under reduced pressure, and as the solution cooled during the evaporation of the ether, material, which by melting point appeared to be tetracosane, crystallized from solution. As much of the substance as possible was removed by filtration, the remainder of the ether was removed and the residue was fractionally distilled to yield 20.1 g. (39%) of the acetylcarbinol (Table I). The residue, remaining after the distillation had been completed, crystallized and was combined with the material previously removed by filtration. This was recrystallized from toluene–ethanol to give 4.45 g., m.p. 48–50° (tetracosane is reported[19] to melt at 51°).

Semicarbazones (Table II) were prepared according to standard procedures.[20]

3-Hydroxy-3-(1-naphthyl)-2-butanone 2,4-Dinitrophenylhydrazone.—This derivative was prepared[20] from 500 mg. (2.3 mmoles) of the corresponding acetylcarbinol. Two recrystallizations from an ethanol–water–ethyl acetate mixture gave 430 mg. (47% yield) of orange needles, m.p. 193.5–194.5° (uncor.).

Anal. Calcd. for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21. Found: C, 61.14; H, 4.69; N, 14.05.

3-Hydroxy-3-(1-naphthyl)-2-butanone Picrate.—This picrate was prepared from 100 mg. (0.46 mmole) of the acetylcarbinol, dissolved in 1 ml. of ethanol, and 3 ml. of a saturated ethanolic solution of picric acid.[20] The product was recrystallized twice from 95% ethanol and washed with a small amount of anhydrous ether to yield fine yellow needles, m.p. 133–135°.

Anal. Calcd. for $C_{20}H_{17}N_3O_9$: C, 54.18; H, 3.86; N, 9.48. Found: C, 54.20; H, 4.00; N, 9.45.

(12) H. Reich and B. K. Samuels, *J. Org. Chem.*, **21**, 68 (1956).

(13) L. J. Andrews and R. M. Keefer, THIS JOURNAL, **75**, 3557 (1953).

(14) A. Robert and J. E. Nezamis, *Acta Endocrinol.*, **17**, 173 (1954).

(15) R. O. Stafford, L. E. Barnes, B. J. Bowman and M. M. Meinzinger, *Proc. Soc. Exp. Biol. Med.*, **89**, 371 (1955).

(16) All melting points are corrected unless otherwise stated, and boiling points are uncorrected. The microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn., and Weiler and Strauss Laboratories, Oxford, England. Infrared absorption spectra were determined on pure liquid samples using a Perkin-Elmer double beam infrared spectrometer, model 21.

(17) For a more detailed procedure for the preparation of organocadmium reagents see ref. 9a.

(18) Since the reaction mixture many times becomes viscous and difficult to stir, it is advisable to use a heavy-duty stirrer and motor for this operation. We used a Hershberg-type stirrer constructed from one-quarter-inch nickel rod and No. 15 chromel wire and a "Power-Stir" motor, manufactured by Eberbach and Son Co., Ann Arbor, Mich.

(19) K. Ziegler, F. Dersch and H. Wollthan, *Ann.*, **511**, 13 (1934).

(20) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 218, 219, 229, 244.

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3-Hydroxy-3-methyl-2-pentanone (II) from VI.[21]—To a mixture of 380 ml. of water, 16 ml. of concd. sulfuric acid and 10 g. of red mercuric oxide[21] heated to 60° was added dropwise 78.5 g. (0.80 mole) of 3-hydroxy-3-methyl-1-pentyne[22] over a 1-hr. period. The product was distilled through a 20-cm. column packed with glass helices to give 79.5 g. (86%) of II, b.p. 74–78° (50 mm.), $n^{25}D$ 1.4205 (see footnote, Table I).

The infrared absorption spectrum showed bands that were assignable to OH stretching frequency (3450 cm.$^{-1}$, s), *t*-OH (1350 cm.$^{-1}$, s; 1170 cm.$^{-1}$, s) and C=O (1705 cm.$^{-1}$, s).

A mixture melting point determination of a semicarbazone prepared from this material and that derived from the organocadmium procedure showed no depression.

1-Bromo-3-hydroxy-3-methyl-2-pentanone (III).—To a solution of 20.0 g. (0.17 mole) of II in 800 ml. of chloroform was added dropwise over a 3.5-hr. period 28.9 g. (0.18 mole) of bromine in 400 ml. of chloroform. The reaction mixture was washed with 190 ml. of ice-cold 5% sodium hydroxide solution and two 100-ml. portions of water. The organic layer was separated and dried over 100 g. of anhydrous sodium sulfate, to which had been added 0.1 g. of magnesium oxide.[10] After the solvent had been removed, the product was fractionally distilled under nitrogen from magnesium oxide using as short a pathway of distillation as possible (fraction cutter directly attached to distilling flask). Seven fractions were collected amounting to 20.4 g. (61%), b.p. 49–56° (0.1–0.15 mm.), $n^{25}D$ 1.4790–1.4847. The first four fractions distilled as a colorless liquid and turned tan to brown as collected. The third fraction was subjected to molecular distillation at 43–45° (oil-bath temperature) (0.005 mm.) from magnesium oxide and collected in a receiver containing magnesium oxide.[23] The sample submitted for analysis ($n^{25}D$ 1.4831) was stored over magnesium oxide.

Anal. Calcd. for $C_6H_{11}BrO_2$: C, 36.94; H, 5.69; Br, 40.97. Found. C, 36.75; H, 5.84; Br, 41.20.

The infrared absorption spectrum showed bands that were assignable to OH stretching frequency (3485 cm.$^{-1}$, s), *t*-OH (1375 cm.$^{-1}$, s; 1175 cm.$^{-1}$, s) and C=O (1720 cm.$^{-1}$, s).

A 2-naphthyl ether[20] was prepared from 2.00 g. (0.01 mole) of III, which had been obtained by a molecular distillation. One recrystallization from petroleum ether (b.p. 90–120°) gave 330 mg. (13%) of fine colorless needles, m.p. 114.5–115°.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.27; H, 7.12.

1,3-Dihydroxy-3-methyl-2-pentanone 1-Acetate (IV).—A mixture of 54.3 g. of glacial acetic acid and 86.2 g. of potassium bicarbonate in 516 ml. of acetone was heated under reflux with stirring for 30 minutes.[11] Crude III, obtained from 20.0 g. (0.17 mole) of II, in 70 ml. of acetone was added dropwise with stirring to the acetone–potassium acetate suspension. The resulting mixture was heated under reflux for 12 hr. and then was allowed to stand for 2 days. The reaction mixture was cooled for 1 hr. in an ice-bath to precipitate dissolved potassium acetate, filtered and dried over 50 g. of anhydrous potassium carbonate. After the acetone had been removed, the residue was distilled under nitrogen through a 15-cm. Vigreux column to give four fractions of IV amounting to 10.0 g. (33%), b.p. 75–77° (0.1 mm.), $n^{25}D$ 1.4400–1.4410. A portion of a middle fraction was subjected to molecular distillation[23] at 55–60° (oil-bath temperature) (0.025 mm.) to give a colorless analytical sample, which was stored under nitrogen; $n^{25}D$ 1.4403, d_4^{25} 1.0933.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10; *M*D, 42.34. Found: C, 55.32; H, 8.25; *M*D, 42.02.

The infrared absorption spectrum showed bands that were assignable to OH stretching frequency (3470 cm.$^{-1}$, s), *t*-OH (1355 cm.$^{-1}$, s; 1165 cm.$^{-1}$, m) and C=O (1725 cm.$^{-1}$, s).

A semicarbazone was prepared from 1.00 g. (5.7 mmoles) of IV. Recrystallization from water afforded 690 mg. (52%) of colorless needles, m.p. 174.5–175.5°.

Anal. Calcd. for $C_9H_{17}N_3O_4$: C, 46.75; H, 7.40; N, 18.17. Found: C, 46.95; H, 7.30; N, 18.24.

1,3-Dihydroxy-3-methyl-2-pentanone (V).—A mixture of 12.6 g. (0.072 mole) of IV and 52.7 g. of potassium bicarbonate in 275 ml. of methanol was stirred under nitrogen for 48 hr. at room temperature.[3b] The mixture was filtered and was concentrated by distilling the solvent under reduced pressure through a 20-cm. Vigreux column. The residual mixture was dissolved in 500 ml. of water, which then was saturated with sodium chloride. The solution was continuously extracted with ether for 2 days. Then the ether phase was separated and dried over 100 g. of anhydrous sodium sulfate. After the ether was removed by distillation, the residue was fractionally distilled through a 15-cm. Vigreux column to give three fractions of product; yield 4.20 g. (44%), b.p. 51–58.5° (0.1–0.25 mm.), $n^{25}D$ 1.4548. Molecular distillation[23] of a small portion of this material at 25° (0.005 mm.) gave a colorless, analytical sample, $n^{25}D$ 1.4537, d^{25}_4 1.0998.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.52; H, 9.16; *M*D, 32.97. Found: C, 54.48; H, 9.19; *M*D, 32.52.

The infrared absorption spectrum showed bands that were assignable to OH stretching frequency (3400 cm.$^{-1}$, s), *t*-OH (1350 cm.$^{-1}$, m; 1160 cm.$^{-1}$, s) and C=O (1710 cm.$^{-1}$, s).

A 2,4-dinitrophenylhydrazone was prepared[12] by heating under reflux for 22 hr. a mixture of 132 mg. (1.0 mmole) of V, 200 mg. (1.0 mmole) of 2,4-dinitrophenylhydrazine and 5 ml. of absolute ethanol. The reaction mixture was concentrated to a small volume from which was obtained 42 mg. (13%) of product, m.p. 140.5–144°. Two recrystallizations from aqueous ethanol gave 22 mg. (7%) of yellow needles, m.p. 147.5–148°.

Anal. Calcd. for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.32; H, 5.02; N, 17.74.

A 2,4-dinitrophenylosazone also was prepared[12] by heating under reflux for 1 hr. a mixture of 132 mg. (1.0 mmole) of V, 790 mg. (4.0 mmoles) of 2,4-dinitrophenylhydrazine and 200 ml. of 2 *N* hydrochloric acid. The reaction mixture was allowed to stand overnight; yield 412 mg. (84%), m.p. 256–258° dec. Six recrystallizations from ethylene chloride gave 168 mg. (34%) of bright-red, microscopic prisms, m.p. 269.5–270° dec.

Anal. Calcd. for $C_{18}H_{18}N_8O_9$: C, 44.08; H, 3.70; N, 22.85. Found: C, 44.18; H, 3.50; N, 22.74.

3-Ethoxaloxy-3-methyl-2-pentanone (VII).—To a mixture of 81.3 g. (0.70 mole) of II and 119.5 g. (0.875 mole) of ethoxalyl chloride[24] in 140 ml. of absolute ether was added 69.2 g. (0.875 mole) of anhydrous pyridine in 140 ml. of absolute ether with stirring at such a rate as to produce moderate reflux (85 minutes). The reaction mixture was stirred for an additional 10 minutes, was allowed to cool and was filtered. The filter cake (pyridine hydrochloride) was washed with three 70-ml. portions of anhydrous ether. The combined ether filtrates were washed with two 50-ml. portions of saturated sodium chloride solution and were dried over sodium sulfate. The ether was removed under reduced pressure through a 15-cm. helices-packed column, and the residue was distilled; yield 108.1 g. (72%), b.p. 102–106° (3 mm.), $n^{25}D$ 1.4342, d^{25}_4 1.0859.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46; *M*D, 51.71. Found: C, 55.32; H, 7.35; *M*D, 51.88.

1,3-Dihydroxy-3-methyl-2-pentanone 1-Acetate (IV) from VII.—A solution of 21.6 g. (0.10 mole) of VII in 320 ml. of chloroform was treated with 0.6 ml. of 30% hydrobromic acid in acetic acid. The mixture was heated to 50° and, with stirring, a solution of 16.8 g. (0.105 mole) of bromine in 120 ml. of chloroform was added dropwise over a period of 2.5 hr. After the solvent was removed under reduced pressure, the residue was distilled through a 15-cm. Vigreux column to give 18.4 g. (62%) of an intermediate bromo ketone, b.p. 94–98° (0.07 mm.), $n^{25}D$ 1.4645–1.4740.

To a solution of 17.9 g. of the crude bromo ketone in 630 ml. of acetone was added 143 mg. of potassium iodide, 40.0 g. of potassium acetate and 6.3 ml. of glacial acetic acid.[25]

(21) This preparation is similar to one previously reported for 1-acetylcyclopentanol (ref. 1). A modification of the original procedure which was employed here to advantage involved sprinkling the mercuric oxide on the surface of the sulfuric acid solution with stirring; this greatly facilitated the dissolving of the material.

(22) Generously furnished by Reilly Tar and Chemical Corporation, Indianapolis, Ind.

(23) A micro distilling apparatus was employed.

(24) P. L. Southwick and L. L. Seivard, THIS JOURNAL, 71, 2532 (1949).

(25) Compare Organic Reactions, Hardwar, 76, 546 (1954).

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The mixture was heated under reflux with stirring for 16 hr., filtered and the filter cake washed well with acetone. The acetone was removed by distillation, and the dark-brown residue was distilled through a 15-cm. Vigreux column; yield 5.17 g. (31%), b.p. 79–105° (0.2–0.5 mm.), $n^{25}D$ 1.4422–1.4435.

A sample of semicarbazone of this substance was prepared in a 48% yield, m.p. 174.5–175.5°, and when admixed with a sample of semicarbazone as derived above (III→IV), no depression in melting point was observed.

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PULLMAN, WASHINGTON

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

Preparations of Synthetic Estrogens. VIII.[1a] New Syntheses of 1,1,2-Tri-*p*-anisylethylene and Diethylstilbestrol

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1,1,2-Tri-*p*-anisylethylene (VI) has been obtained by the condensation of α-chloro-*p*-methoxyacetophenone (I) with 2 moles of anisole in the presence of titanium tetrachloride. A similar condensation of α-chloroacetophenone (VII) with 2 moles of anisole gave 1,2-di-*p*-anisyl-1-phenylethylene (VIII). When these condensations were carried out with sulfuric acid or aluminum chloride as a catalyst, 1,1,1,2- and 1,1,2,2-tetra-*p*-anisylethanes as well as 1,1-di-*p*-anisylethylene were obtained instead of triarylethylenes. 2,3-Di-*p*-anisylbutene-2 (X) and diethylstilbestrol dimethyl ether (XII) were prepared by the condensation of 3-chlorobutanone (IX) and 4-chlorohexanone-3 (XI) with 2 moles of anisole in the presence of titanium tetrachloride.

In the previous paper[1a] it was reported that the treatment of *p*-methoxy-α,α-di-*p*-anisylacetophenone with phosphorus pentachloride effected simultaneous chlorination and dehydrochlorination giving 1,1,2-tri-*p*-anisyl-2-chloroethylene. The usual preparation[2] of 1,1,2-tri-*p*-anisyl-2-chloroethylene is the chlorination of tri-*p*-anisylethylene (VI) with chlorine in carbon tetrachloride. Recent studies in this Laboratory have given a new preparation of the key intermediate, tri-*p*-anisylethylene (VI), using a Grignard reaction between α-chloro-*p*-methoxyacetophenone (I) and *p*-anisylmagnesium bromide.[1] It has now been discovered that the condensation of α-chloro-*p*-methoxyacetophenone (I) with 2 moles of anisole in the presence of titanium tetrachloride gives tri-*p*-anisylethylene (VI) in a 53% yield. This method, in which the use of a Grignard reaction is avoided, seems to be suitable for large scale preparation.

The condensation of α-haloketones with phenol in the presence of an acidic catalyst has been studied by Lippmann.[3] Zaheer, *et al.*,[4] have reported recently that the reaction between chloroacetone and phenol or its ether in the presence of sulfuric acid or aluminum chloride as a catalyst gives 4,4′-dihydroxy- or -dialkoxy-α-methylstilbene, respectively. They have reported further that the similar condensation of 4-chlorohexanone-3 (XI) with anisole gives 3,3,4-tri-*p*-anisylhexane in addition to 1,1-di-*p*-anisyl-2-ethylbutene-1, and that phenol reacts with 1,3-dichloroacetone only at its carbonyl group to give 1,3-dichloro-2,2-di-*p*-hydroxyphenylpropane.[5] It was observed in the present experiments, in which sulfuric acid or aluminum chloride was used, that anisole reacted with α-chloro-*p*-methoxyacetophenone (I) to give various condensation products, among which, however, the desired tri-*p*-anisylethylene (VI) could not be found. The treatment of the chloroketone I with 2 moles of anisole in the presence of concentrated sulfuric acid in glacial acetic acid solution resulted in almost quantitative recovery of the starting materials. Essentially the same result was obtained in a reaction without the solvent, but further experiments in which the chloroketone I was dissolved in a large excess of anisole gave 1,1,1,2-tetra-*p*-anisylethane (III) and 1,1,2,2-tetra-*p*-anisylethane (IV).

$$\underset{\text{I}}{\text{ClCH}_2\text{COC}_6\text{H}_4\text{OCH}_3\text{-}p} + \underset{\text{II}}{3\text{C}_6\text{H}_5\text{OCH}_3} \xrightarrow{\text{concd. } H_2SO_4} p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{C}(\text{C}_6\text{H}_4\text{OCH}_3\text{-}p)_3 + (p\text{-CH}_3\text{OC}_6\text{H}_4)_2\text{CHCH}(\text{C}_6\text{H}_4\text{OCH}_3\text{-}p)_2$$

III IV

As to the mechanism of the initial step of the condensation of chloroketone with phenol, Zaheer, *et al.*, postulated either a Friedel–Crafts type removal of the chlorine atom involving combination of phenol at that position,[4a] or an addition of one mole of phenol at the carbonyl group and a subsequent rearrangement involving a dehydrochlorina-

(1) (a) Previous paper: K. Sisido, K. Okano, T. Isida and H. Nozaki, THIS JOURNAL, **77**, 6580 (1955). (b) Department of Chemistry, Cornell University, Ithaca, N. Y.

(2) R. S. Shelton, M. G. Van Campen, Jr., D. F. Meisner, S. M. Parmerter, E. R. Andrews, R. E. Allen and K. K. Wyckoff, THIS JOURNAL, **75**, 5491 (1953).

(3) E. Lippmann, *Ber.*, **45**, 2489 (1912).

(4) (a) P. M. Bhargava and S. H. Zaheer, *Nature*, **171**, 746 (1953); (b) V. D. N. Sastri, N. S. Rao and S. H. Zaheer, *Current Sci. (India)*, **22**, 338 (1953); C. *A.*, **48**, 6984h (1954); (c) S. H. Zaheer, V. Singh, B. Bhushan, P. M. Bhargava, I. K. Kacker, K. Ramachandran, V. D. N. Sastri and N. S. Rao, *J. Chem. Soc.*, 3360 (1954).

(5) S. H. Zaheer, B. Singh, B. Bhushan, I. K. Kacker, K. Ramachandran and N. S. Rao, *ibid.*, 1706 (1955).

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tion and a migration of an aromatic nucleus.[4b] The latter mechanism seems to be more plausible, as they suggested,[4c] since in the chloroketone the chlorine atom is attached firmly by the effect of the electron-attracting carbonyl group and the Friedel–Crafts type reaction, in which the chlorine atom must be taken off as an anion, would not be expected to occur.

In either route, however, desoxyanisoin may be formed at the first step of this reaction, being followed by attacks of second and third molecules of anisole to give 1,1,1,2-tetra-*p*-anisylethane (III) *via* 1,1,2-tri-*p*-anisylethanol. The unsymmetrical tetraanisylethane may partly be isomerized to the symmetrical one because of excessive crowding in III.

When the chloroketone I was treated with a large excess of anisole in the presence of aluminum chloride as a catalyst, 1,1-di-*p*-anisylethylene (V) and a resinous product were obtained. The mechanism of the production of this material is presumed to involve the removal of the chlorine atom by means of the reducing action of aluminum chloride at the first step and the subsequent addition of one mole of anisole at the carbonyl group followed by a dehydration. Similar removal of the chlorine atom has been observed in the reaction of acetyl chloride and cyclohexene in the presence of aluminum chloride.[6] It seems that 1-acetyl-2-chlorocyclohexane

$$\text{I} + \text{II} \xrightarrow{AlCl_3} CH_2{=}C(C_6H_4OCH_3\text{-}p)_2$$

$$\text{I} + \text{II} \xrightarrow{TiCl_4} p\text{-}CH_3OC_6H_4CH{=}C(C_6H_4OCH_3\text{-}p)_2$$

$$\underset{\text{VII}}{ClCH_2COC_6H_5} + \text{II} \xrightarrow{TiCl_4} p\text{-}CH_3OC_6H_4CH{=}\underset{\text{VIII}}{C(C_6H_5)C_6H_4OCH_3\text{-}p}$$

is formed at the first step of the reaction but is reduced to acetylcyclohexane by means of aluminum chloride.

This specificity of catalytic action of individual Lewis acids in this condensation stimulated the trial of titanium tetrachloride, which was reported[7] recently to be an advantageous catalyst in Friedel–Crafts reactions. When the chloroketone I was treated with a large excess of anisole in the presence of 2 moles[7a] of titanium tetrachloride at 35–37°, 1,1,2-tri-*p*-anisylethylene (VI) was obtained in a 53% yield. Higher reaction temperature decreased the yield of VI, *i.e.*, 35% at 50° and only resinous product resulted above 60°. Treatment of the reaction mixture at 0–35° gave 1,1,1,2-tetra-*p*-anisylethane (III) besides a small quantity of 1,1,2-tri-*p*-anisylethylene (VI). If carbon disulfide was used as a solvent instead of an excess of anisole, only starting materials were recovered, and if chloroacetyl chloride was used as a reactant instead of I, 1,1,2-tri-*p*-anisylethylene (VI) and I were obtained in very poor yield.

It was found furthermore that the condensation of α-chloroacetophenone (VII) with 2 moles of anisole in the presence of titanium tetrachloride at 0° gave two forms of 1,2-di-*p*-anisyl-1-phenylethylene (VIII), m.p. 105.5–107° and 92–94°[8] in 61% yield. Prolonged reaction time decreased the yield of VIII and phenyl-tri-*p*-anisylethane was obtained as a by-product.

Attempted condensations with stannic chloride or polyphosphoric acid failed. Thus treatment of the α-chloro-*p*-methoxyacetophenone (I) with anisole in the presence of these Lewis acids afforded only a non-crystallizable resin.

In addition to these reactions, it was also discovered that the condensations of 3-chlorobutanone (IX) and 4-chlorohexanone-3 (XI) with 2 moles of anisole in the presence of titanium tetrachloride at 0° gave 2,3-di-*p*-anisylbutene-2 (X) and 3,4-di-*p*-anisylhexene-3 (XII), so-called diethylstilbestrol dimethyl ether, in 32 and 19% yields, respectively. As described above, Zaheer, *et al.*,[5] were unable to prepare 3,4-di-*p*-anisylhexene-3 (XII) by the condensation of 4-chlorohexanone-3 (XI) with anisole in the presence of sulfuric acid or aluminum chloride. It was found that the reaction with titanium tetrachloride gave an oil, presumably the *cis* form of 3,4-di-*p*-anisylhexene-3 (XII), in a 51% yield, and that when the oil was treated with iodine in chloroform solution[9] the stilbestrol ether (XII) was obtained in crystalline form.

$$\underset{\text{IX}}{CH_3COCHClCH_3} + 2CH_3OC_6H_5 \xrightarrow{TiCl_4} \underset{\text{II}}{} p\text{-}CH_3OC_6H_4C(CH_3){=}\underset{\text{X}}{C(CH_3)C_6H_4OCH_3\text{-}p}$$

$$\underset{\text{XI}}{C_2H_5COCHClC_2H_5} + 2CH_3OC_6H_5 \xrightarrow{TiCl_4} \underset{\text{II}}{} p\text{-}CH_3OC_6H_4C(C_2H_5){=}\underset{\text{XII}}{C(C_2H_5)C_6H_4OCH_3\text{-}p}$$

An attempted condensation of 4-chlorohexanone-3 (XI) with phenol under the same conditions, however, failed to afford 3,4-di-*p*-hydroxyphenylhexene-3. A considerable quantity of starting materials besides a small amount of tar was recovered.

Experimental[10]

Tetra-*p*-anisylethane (III and IV).—To a solution of 10.0 g. (0.054 mole) of α-chloro-*p*-methoxyacetophenone (I) in 150 g. of anisole (II), 100 g. of concentrated sulfuric acid was added dropwise with stirring. The addition required about 40 minutes, during which the temperature was maintained below 0°. The stirring was continued for an additional six hours at 20° and the mixture was allowed to stand overnight. Ice-cold water was then added and the product was extracted with benzene. The benzene solution was washed with dilute sodium hydroxide solution and water. After distilling off the solvent the residue was subjected to steam distillation in order to remove excess anisole. The residue was taken up in benzene, dried over anhydrous sodium sulfate, the solvent was removed on a water-bath, and the residue was recrystallized from ethanol. Distillation of the crystals gave 2.4 g. of unchanged chloroketone I and 1.9 g. of 1,1,2,2-tetra-*p*-anisylethane (IV) boiling at 265–272° (3 mm.), which melted at 190°[11] after a single recrystallization from glacial acetic acid.

(6) C. D. Nenitzescu and E. Ciorănescu, *Ber.*, **69**, 1820 (1936).

(7) (a) N. M. Cullinane, S. J. Chard and D. M. Leyshon, *J. Chem. Soc.*, 376 (1952); (b) 4106 (1952); (c) B. M. Cullinane and D. M. Leyshon, *ibid.*, 2942 (1954).

(8) E. C. Dodds, L. Goldberg, W. Lawson and R. Robinson, *Proc. Roy. Soc.* (London), **B127**, 140 (1939), reported m.p. of 105–106° and 92–93°, respectively.

(9) F. v. Wessely, E. Kerschbaum, A. Kleedorfer, F. Prillinger and E. Zajic, *Monatsh.*, **73**, 127 (1940).

(10) All temperatures are uncorrected.

(11) E. Bergmann and S. Fujise, *Ann.*, **483**, 65 (1930), reported a

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Anal. Calcd. for $C_{30}H_{30}O_4$: C, 79.27; H, 6.65. Found: C, 79.14; H, 6.78.

On the other hand, distillation of the mother liquor of the recrystallization gave 1.3 g. of I and 1.8 g. of 1,1,1,2-tetra-*p*-anisylethane (III) boiling at 265–275° (3 mm.) which melted at 149–150°[12] after several recrystallizations from glacial acetic acid.

Anal. Calcd. for $C_{30}H_{30}O_4$: C, 79.27; H, 6.65. Found: C, 79.15; H, 6.52.

1,1-Di-*p*-anisylethylene (V).—To a solution of 10.0 g. (0.054 mole) of α-chloro-*p*-methoxyacetophenone (I) in 150 g. of anisole (II), 14.6 g. (0.109 mole) of anhydrous aluminum chloride was added below 10° in small portions, and the mixture was heated at 92–94° for five hours, during which time a vigorous evolution of hydrogen chloride was observed. After cooling, the reaction mixture was poured into ice-cold dilute hydrochloric acid. The product was taken up as usual and the distillation gave 1 g. of 1,1-di-*p*-anisylethylene (V) boiling at 167–180° (4 mm.) and 3 g. of a brown resinous product boiling at 261–263° (4 mm.). The former product melted at 139–141° after several recrystallizations from ethanol and showed no depression when admixed with an authentic specimen.[13] The latter fraction could not be crystallized.

1,1,2-Tri-*p*-anisylethylene (VI).–A solution of 10.0 g. (0.054 mole) of α-chloro-*p*-methoxyacetophenone (I) in 150 g. of anisole (II) was cooled with an ice–salt-bath and 20.9 g. (0.110 mole) of titanium tetrachloride was added dropwise with stirring at a rate sufficient to maintain the temperature at about −3°. After the addition was completed, the mixture was heated at 35–37° for five hours. An evolution of hydrogen chloride took place in the initial stage of the reaction. The dark-brown sticky product was poured into a mixture of 200 g. of crushed ice and 20 ml. of concentrated hydrochloric acid and the precipitated oil was extracted with benzene. The benzene solution was washed with dilute sodium hydroxide solution and water. After distilling off the solvent the residue was subjected to steam distillation. The residue was taken up in benzene and dried over calcium chloride. After removing the solvent, distillation of the residue gave 2.5 g. of unchanged chloroketone I followed by the product boiling at 245–260° (4 mm.) which was crystallized from glacial acetic acid. A single recrystallization from glacial acetic acid gave 10.0 g. (53%) of 1,1,2-tri-*p*-anisylethylene (VI), m.p. 97–99°,[14] which showed no depression when admixed with the product prepared by the Grignard reaction in the previous paper.[1]

When this reaction mixture was treated at 0–35° for 6 hours, the evolution of hydrogen chloride was not vigorous and 2.0 g. of 1,1,1,2-tetra-*p*-anisylethane (III) boiling at 260–275° (4 mm.) was obtained, which melted at 149° after a single recrystallization from glacial acetic acid. In addition 0.8 g. of 1,1,2-tri-*p*-anisylethylene (VI) also was isolated from the mother liquor of the recrystallization.

1,2-Di-*p*-anisyl-1-phenylethylene (VIII).—To a solution of 10.0 g. (0.065 mole) of α-chloroacetophenone (VII) in 150 g. of anisole (II), 24.7 g. (0.130 mole) of titanium tetrachloride was added dropwise below 0°. The addition required about 40 minutes, after which time the mixture was immediately poured into ice-cold dilute hydrochloric acid. The product was taken up as usual, and the distillation gave 15.5 g. of a resinous product boiling at 235–243° (4 mm.), which was crystallized to yield 12.4 g. (61%) of 1,2-di-*p*-anisyl-1-phenylethylene (VIII) by the treatment with ethanol. Fractional recrystallization from ethanol gave nearly the same quantity of two crystalline products which were considered to be *cis* and *trans* isomers. The less soluble one melted at 105.5–107° (VIIIa), while the substance isolated from the mother liquor melted at 92–94° (VIIIb).[8] Each mixed melting point with the products prepared by the use of the Grignard reaction between α-chloroacetophenone (VII) and *p*-anisylmagnesium bromide showed no depression.

When the stirring was continued for an additional 2.5 hr. at 0° after the addition was completed, 8.2 g. (40%) of 1,2-di-*p*-anisyl-1-phenylethylene (VIII) boiling at 230–240° (5 mm.) and 4.0 g. of 1,1,2-tri-*p*-anisyl-1- or -2-phenylethane boiling at 245–260° (5 mm.), which melted at 113–114° after a single recrystallization from ethanol, were obtained.

Anal. Calcd. for $C_{29}H_{28}O_3$: C, 82.05; H, 6.65. Found: C, 82.23; H, 6.64.

2,3-Di-*p*-anisylbutene-2 (X).—To a stirred mixture of 5.3 g. (0.050 mole) of 3-chlorobutanone (IX)[15] and 10.8 g. (0.100 mole) of anisole (II), 19.0 g. (0.100 mole) of titanium tetrachloride was added dropwise during 1.5 hr. at 0–5°, and the mixture was allowed to stand for five hours at the same temperature. The product was poured into ice-cold hydrochloric acid and was extracted with ether. The extract was washed with dilute sodium hydroxide solution and water and dried over anhydrous sodium sulfate. Distillation gave 4.3 g. (32%) of 2,3-di-*p*-anisylbutene-2 (X) boiling at 180–200° (5 mm.), which melted at 129–130° after a single recrystallization from methanol and the mixed m.p. with an authentic sample[16] showed no depression.

3,4-Di-*p*-anisylhexene-3 (XII).—To a mixture of 17.5 g. (0.15 mole) of propionoin and 18.0 g. (0.15 mole) of dimethylaniline, 18.3 g. (0.15 mole) of thionyl chloride was added at 0–5° with vigorous stirring. The addition required about 1.5 hr., during which the mixture almost solidified. The mixture was slightly heated until the semi-solid was dissolved, poured into water and extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate. Distillation gave 8.0 g. (39%) of 4-chlorohexanone-3 (XI) boiling at 42–43° (8 mm.).

A mixture of 8.0 g. of (0.059 mole) of 4-chlorohexanone-3 (XI) and 12.8 g. (0.118 mole) of anisole (II) was treated with 22.6 g. (0.119 mole) of titanium tetrachloride below 0° in the manner described above and the product was worked up as usual. Distillation gave 9.0 g. (51%) of yellow viscous oil boiling at 196–200° (8 mm.) which could not be crystallized. When the oil was treated with 1.0 g. of iodine in 190 ml. of chloroform,[9] 3.3 g. (19%, based on XI) of 3,4-di-*p*-anisylhexene-3 (XII) was obtained. A single recrystallization from petroleum ether gave colorless plates melting 123–124°, which showed no depression when admixed with an authentic specimen.[16]

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(12) E. Ziegler and K. Gitschthaler, *Österr. Chem.-Ztg.*, **53**, 208 (1952); *C. A.*, **48**, 6404c (1954), reported a m.p. of 151°.

(13) Prepared according to L. Gattermann, *Ber.*, **22**, 1129 (1889), who reported a m.p. of 140°.

(14) The recorded m.p. is 97–98.5° (ref. 1).

(15) The compound prepared by the method of G. Korschun, *Ber.*, **38**, 1125 (1905), was used.

(16) K. Sisido and H. Nozaki, THIS JOURNAL, **70**, 776 (1948).

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

D-Homo Rearrangement of 11-Oxygenated 17α-Hydroxy-20-ketosteroids

BY EUGENE P. OLIVETO, CORINNE GEROLD, RICHARD RAUSSER AND E. B. HERSHBERG

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Reaction of 11-oxygenated 17α-hydroxy-20-ketopregnanes with refluxing acetic anhydride was found to produce D-homo rearrangement products rather than the expected 17α-acetoxy-20-ketosteroids.

Two methods are claimed to be satisfactory for the preparation of 17α-acetates from a 17α-hydroxy-20-ketone: reaction of the ketol with an acylating agent and an acid catalyst at room temperature,[1,2] or with refluxing acetic anhydride alone.[2]

By this last procedure 3α-acetoxy-17α-hydroxypregnane-11,20-dione (II) was reported to be converted into its diacetate XIV in good yield.[2] We attempted to prepare the same compound XIV from 3α,17α-dihydroxypregnan-11,20-dione (I). The use of acetic anhydride, either redistilled or not, gave no isolable XIV but a different compound. This was identified as a D-homo rearrangement product, since it was identical with the compound obtained from I upon reaction with boron trifluoride in acetic acid–acetic anhydride. With the 3-acetate II and refluxing acetic anhydride, however, we did obtain the expected 3,17-diacetate but in lower yield than the previous workers. The diacetate also was obtained from II if the acetic anhydride contained acetic acid.

Our studies were then extended to other 11-oxygenated 17α-hydroxy-20-ketosteroids. Both 3α,-11β,17α-trihydroxypregnan-20-one 11-acetate (III) and 3α,11α,17α-trihydroxypregnan-20-one 3,11-diacetate (IV) were converted to D-homo rearrangement products VI and X identical with those obtained by reaction with boron trifluoride. With all three starting materials, acetic anhydride gave at least as good yields as boron trifluoride.

The rearrangement products were all submitted to lithium aluminum hydride and sodium–alcohol reductions. Reaction of X with either reducing agent gave the same tetrol XIII. Reduction of IX and VI with lithium aluminum hydride gave two different tetrols (which we formulate as XI and XII) while reduction of IX with sodium gave the same tetrol XIII which had been obtained from X. These results suggest that the D-ring structures of IX and X are similar, while those of IX and VI are different. Unfortunately the yields in most of the reduction experiments were too low to permit positive conclusions to be drawn. However, further evidence was obtained from a study of the Zimmerman reaction on VI, IX and X, and by a comparison of molecular rotation differences.

The Zimmerman test for active methylene groups[3] was strongly positive with compound VI (derived from III) and essentially negative with IX (from I) and X (from IV),[4] indicating that IX and X have the 17a keto structures. In addition, the molecular rotation changes (ΔM_D) for the transformations II → IX and IV → X are in good agreement with the values reported by Fukushima[3] for the conversion of a 17α-hydroxy-20-ketosteroid to a 17α-hydroxy-17a-keto-D-homo-steroid, and the molecular rotation change for the transformations XV → VIII and III → VII are also in fair agreement with the expected value. However, the ΔM_D for the change XV → VI is far from the published figure (Table I).

TABLE I

MOLECULAR ROTATION DIFFERENCES

	$[\alpha]_D$	M_D	ΔM_D
3α,17α-Dihydroxypregnane-11,20-dione 3-acetate (II)	+50.3	+196	+276
3α,17α-Diacetoxy-17β-methyl-D-homoetiocholane-11,17a-dione (IX)	+109.4	+472	
ΔM_D (17α-OH,20-C=O → 17-OAc,17a-C=O) ~ + 290			
3α,11α,17α-Trihydroxypregnan-20-one 3,11-diacetate (IV)	− 7.7	− 33	+128
3α,11α,17α-Triacetoxy-17β-methyl-D-homoetiocholan-17a-one (X)	+19.9	+ 95	
ΔM_D (17α-OH, 20-C=O → 17-OH,17a-C=O) ~ + 135			
3α,11β,17α-Trihydroxypregnane-20-one 11-acetate (III)	+35.6	+140	− 15
11β-Acetoxy-3α,17aα-dihydroxy-17aβ-methyl-D-homoetiocholan-17-one (VII)	+32.5	+125	
3α,11β,17α-Trihydroxypregnane-20-one 3,11-diacetate (XV)	+62.6	+271	− 35
3α,11β-Diacetoxy-17aα-hydroxy-17aβ-methyl-D-homoetiocholan-17-one (VIII)	+54.2	+235	
ΔM_D (17α-OH,20-C=O → 17a-OH,17-C=O) ~ −70			
3α,11β-17α-Trihydroxypregnane-20-one 3,11-diacetate (XV)	+62.6	+271	−271
3α,11β,17aα-Triacetoxypregnane-17aβ-methyl-D-homoetiocholan-17-one (VI)	0.0	0	
ΔM_D (17α-OH,20-C=O → 17a-OAc,17-C=O) ~ + 40			

No simple explanation is immediately apparent to explain the fact that I, III and IV give D-homo products, and II the normal diacetate.[5] Pending

(1) R. Turner, THIS JOURNAL, 75, 3489 (1953).

(2) Huang-Minlon, E. Wilson, N. Wendler and M. Tishler, *ibid.*, 74, 5394 (1952).

(3) *Cf.* D. Fukushima, S. Dobriner, M. Heffler, T. Kritchevsky, F. Herling and G. Roberts, *ibid.*, 77, 6585 (1955).

(4) The 12-methylene group of IX adjacent to the 11-ketone is apparently sufficiently hindered so that only a faint color is obtained in the Zimmerman reaction. The same faint color is obtained with I.

(5) It is, of course, quite possible that *mixtures* of D-homo and normal products are obtained which we have made no particular attempt to separate. However, one would presume that the fastest reaction of I with hot acetic anhydride would be formation of the 3-acetate II, and that therefore I and II should give the same isolable

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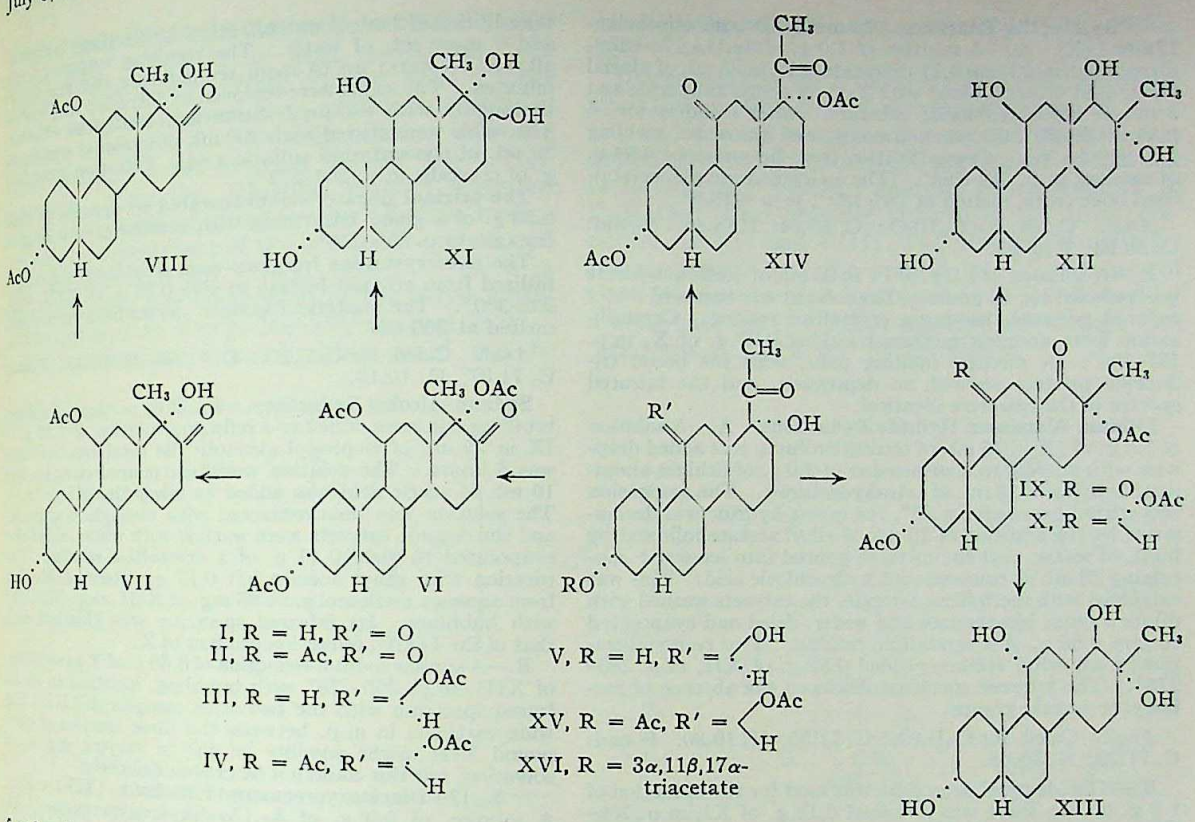

further investigation, it would seem that the use of refluxing acetic anhydride to prepare 17α-acetates is not as satisfactory as room temperature acylations with an acid catalyst.

Experimental[6]

3α,11β,17aα-Triacetoxy-17aβ-methyl-D-homoetiocholan-17-one (VI). A.—A solution of 1.0 g. of 3α,11β,17α-trihydroxypregnan-20-one-11-acetate (III) in 35 ml. of acetic acid, 2 ml. of acetic anhydride and 2 ml. of boron trifluoride–ether complex was allowed to stand overnight at 25°. The mixture was poured into water, the solid removed by filtration and triturated with ether to give 0.08 g. of VI, m.p. 235–255°. One crystallization from methanol raised the m.p. to 258–262°.

B.—A solution of 10.0 g. of 3α,11β,17α-trihydroxypregnan-20-one in 100 ml. of C.P. acetic anhydride was refluxed for 12 hours. The solvent was removed under reduced pressure, and the crystalline residue sludged with 75 ml. of ether to yield 4.96 g. of VI, m.p. 260–263°. Two crystallizations from methanol raised the m.p. to 267–268°, $[\alpha]_D$ 0.0°.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.82; H, 8.62.

The use of acetic anhydride which had been freshly distilled through a glass-packed column gave the same compound, but in somewhat lower yield (0.2 g. from 1 g.). The infrared spectra of the two compounds prepared in (A) and (B) were identical, and did not match the spectrum of 3α,11β,17α-triacetoxypregnan-20-one. Both also gave strong Zimmerman tests.

11β-Acetoxy-3α,17aα-dihydroxy-17aβ-methyl-D-homoetiocholan-17-one (VII).—A mixture of 1.0 g. of VI, 0.5 g. of potassium carbonate, 40 ml. of C.P. methanol and 4 ml. of water was refluxed for 2.5 hours. The excess carbonate was then neutralized with acetic acid, the methanol removed under reduced pressure, and the residue diluted with water to precipitate 0.79 g. of crude material, m.p. 131–143°. The analytical sample, crystallized twice from ether–hexane, melted at 173–174°, $[\alpha]_D$ +32.5°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.47; H, 9.31.

3α,11β-Diacetoxy-17aα-hydroxy-17aβ-methyl-D-homoetiocholan-17-one (VIII).—A solution of 130 mg. of VII in 4 ml. of pyridine and 1 ml. of acetic anhydride was allowed to stand 17 hours at 25°. The solution was then poured into ice and water containing excess hydrochloric acid to give 120 mg. of solid. Crystallization from ether–pentane gave 70 mg. of VIII, m.p. 197–201°, $[\alpha]_D$ +54.2°.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.85; H, 8.54.

3α,17α-Diacetoxy-17β-methyl-D-homoetiocholane-11,17a-dione (IX). A.—A solution of 1.0 g. of 3α,17α-dihydroxypregnane-11,20-dione (I) in 35 ml. of acetic acid, 2 ml. of acetic anhydride and 2 ml. of boron trifluoride–ether complex was allowed to stand overnight at 25°. Addition of water precipitated 1.15 g., m.p. 105–145°. Trituration with ether, followed by recrystallization from aqueous methanol, gave 0.38 g., m.p. 169–171°; lit.[7] m.p. 167–168.5°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.62; H, 8.54.

B.—A solution of 1.0 g. of I in 25 ml. of C.P. acetic anhydride was refluxed for 12 hours. The solvent was removed under reduced pressure, the residue taken up in methylene chloride, the organic layer washed with dilute sodium carbonate solution, twice with water, dried and evaporated to yield 1.24 g. of a pale yellow resin which crystallized on the addition of methanol. Trituration with ether, followed by recrystallization from aqueous methanol, gave 0.51 g. of IX, m.p. 163–167°, $[\alpha]_D$ +109.4°. The use of acetic anhydride freshly distilled through a glass-packed column gave the same compound in slightly lower yield.

The infrared spectra of either sample was identical with that of the compound obtained by means of boron trifluoride, and was not identical with the spectrum of 3α,17α-diacetoxy pregnane-11,20-dione.

Treatment of 3α,11β,17α-triacetoxypregnan-20-one or 3α,17α-diacetoxypregnane-11,20-dione with refluxing acetic anhydride for 12 hours as described above resulted in almost quantitative recovery of starting material in both cases.

(6) All m.p.'s are corrected. All rotations were taken in a one dm. tube in chloroform at a concentration of *ca.* 1% and at 25°. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

(7) N. Wendler, D. Taub, S. Dobriner and D. Fukushima, THIS JOURNAL, 78, 5027 (1956).

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3α,11α,17α-Triacetoxy-17β-methyl-D-homoetiocholan-17a-one (X). A.—A solution of 1.0 g. of 3α,11α,17α-trihydroxypregnan-20-one 3,11-diacetate (IV) in 35 ml. of glacial acetic acid was combined with 2 ml. of acetic anhydride and 2 ml. of boron trifluoride etherate. After standing for 16 hours at 30–35°, the reaction was poured into water, yielding 1.07 g. of a gel. Crystallization from hexane gave 0.94 g. of needles, m.p. 184–186°. The analytical sample, crystallized once more, melted at 186–189°, $[\alpha]_D$ +19.9°.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.23; H, 8.82.

B.—A solution of 1.0 g. of IV in 25 ml. of acetic anhydride was refluxed for 12 hours. The solvent was removed under reduced pressure, leaving a crystalline residue. Crystallization from aqueous methanol yielded 0.93 g. of X, m.p. 187–190°. A mixture melting point with the boron trifluoride product showed no depression, and the infrared spectra of the two were identical.

Lithium Aluminum Hydride Reductions. A.—A solution of 1.0 g. of IX in 45 ml. of tetrahydrofuran was added dropwise with stirring to a suspension of 2.0 g. of lithium aluminum hydride in 15 ml. of tetrahydrofuran. The suspension was stirred overnight at 25°, the excess hydride was decomposed by the addition of 10 ml. of ethyl acetate followed by 5 ml. of water, and the mixture poured into ice-water containing 25 ml. of concentrated hydrochloric acid. This was extracted with methylene chloride, the extracts washed with dilute sodium bicarbonate and water, dried and evaporated to give 0.65 g. of a crystalline residue. Two recrystallizations from ethyl acetate yielded 0.22 g. of XII, m.p. 260–275°. The infrared spectrum disclosed the absence of carbonyl or acetate groups.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.29; H, 10.65.

B.—The identical procedure was used for the reduction of 1.0 g. of VI; there was obtained 0.12 g. of XI, m.p. 260–270°. This material also did not possess any acetate or carbonyl groups, but its infrared spectrum was not identical with that of XII.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.52; H, 10.62.

C.—A solution of 1.0 g. of X in 30 ml. of tetrahydrofuran was added dropwise to a stirred suspension of 2.0 g. of lithium aluminum hydride in 50 ml. of anhydrous ether. The mixture was refluxed for 17 hours, then allowed to stand with stirring at room temperature for 48 hours. The reaction was cooled in an ice-bath, and the excess reagent destroyed by the addition of 2 ml. of water, 2 ml. of 15% sodium hydroxide and 6 more ml. of water. The resulting suspension was allowed to warm up to room temperature and stir for 20 minutes. The solids were removed by filtration and washed thoroughly with tetrahydrofuran and methylene chloride. The solids were stirred with 200 ml. of ice-water containing 20 ml. of concentrated sulfuric acid. Filtration gave 0.27 g. of crystals, m.p. 265–272°.

The original filtrate was evaporated to dryness to yield 0.50 g. of a gum; triturating with acetone gave 0.29 g. of crystals, m.p. 235–275°.

The two crystalline fractions were combined and recrystallized from ethanol–hexane to give 0.34 g. of XIII, m.p. 292–300°. The analytical sample, crystallized once more, melted at 300–307°.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.37; H, 10.13.

Sodium–Alcohol Reductions. A.—Ten portions of sodium totalling 2 g. were added to a refluxing solution of 0.50 g. of IX in 75 ml. of isopropyl alcohol; the total reaction time was 5 hours. The solution was then poured onto ice and 10 ml. of acetic acid was added to lower the *p*H to *ca.* 7. The solution was then extracted with methylene chloride, and the organic extracts were washed with water, dried and evaporated to yield 0.45 g. of a crystalline residue. Trituration with ethyl acetate left 0.17 g. Recrystallization from aqueous methanol gave 85 mg. of XIII, m.p. 230–237° with bubbling. Its infrared spectrum was identical with that of the $LiAlH_4$ reduction product of X.

B.—A similar sodium reduction of 0.50 g. of X gave 95 mg. of XIII, m.p. 265–278° with bubbling, identical in its infrared spectrum with the two other samples of XIII. The wide variation in m.p. between the three samples of compound XIII might possibly be due to varying degrees of solvation, but this could not be proven definitely.

3α,17α-Diacetoxypregnane-11,20-dione (XIV). A.—A solution of 2.0 g. of 3α,17α-dihydroxypregnane-11,20-dione-3-acetate (II) in 40 ml. of C.P. acetic anhydride was refluxed for 12 hours. The excess anhydride was decomposed at reflux by the slow addition of water, the solution poured into ice and water and the resulting precipitate filtered and dried: 1.67 g., m.p. 160–180°. Crystallization from methanol yielded 0.66 g., m.p. 195–199°, and 0.20 g. m.p. 192–197°.

B.—Repetition of the above experiment, with 1.2 g. of acetic acid added, gave 0.80 g. of XIV, m.p. 196–199°, $[\alpha]_D$ +50.4°; lit.[2] m.p. 203–204°, $[\alpha]_D$ +46.7° ($CHCl_3$).

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

Some Transformation Products of Cortisone Acetate

BY EUGENE P. OLIVETO, CORINNE GEROLD AND E. B. HERSHBERG

RECEIVED JANUARY 22, 1957

Addition of HOBr to cortisone acetate, followed by treatment with potassium acetate, gave the 4,5α- and 4,5β-epoxides III and IV. Reaction of either of these with HBr, or warming the intermediate bromohydrins with acetic acid, gave 4-bromocortisone acetate (V). 4-Chlorocortisone acetate (VI) was prepared by the action of HCl on the β-epoxide. Compound VI was also the main product from the addition of HOCl to cortisone acetate. Opening the β-epoxide with acid gave the 4,5-glycol IX.

Relatively simple changes in the structure of cortisone have resulted in marked increase in corticoid activity. For example, introduction of a 9α-fluorine atom increases the glucocorticoid activity by a factor of about 9 with an even greater enhanced mineralocorticoid activity.[1] Even more startling, the introduction of an added double bond to produce 1-dehydrocortisone enhances the glucocorticoid activity three- to fourfold, without increasing the salt-retaining properties.[2] It seemed desirable, therefore, to prepare other simple derivatives of cortisone.

Addition of hypobromous acid (N-bromoacetamide and perchloric acid) to the 4,5-double bond of cortisone acetate, followed by treatment with potassium acetate, resulted in the formation of two epoxides: The major one had m.p. 224–227°, $[\alpha]_D$ +142°, and the minor product, m.p. 248–255°, $[\alpha]_D$ +34.9°. In order to help assign configurations, 4-cholesten-3-one was converted to its two epimeric epoxides; the β-epoxide[3] had $[\alpha]_D$

(1) J. Fried and E. Sabo, THIS JOURNAL, **76**, 1455 (1954).

(2) H. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. Perlman and M. Pechet, *Science*, **121**, 335 (1955).

(3) P. Plattner, H. Heusser and A. Kulkarni, *Helv. Chim. Acta*, **31**, 1823 (1948).

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$+123.8°$, and the α-epoxide (prepared from cholestenone with H_2O_2 and an acid resin) had $[\alpha]D$ $-33.4°$. The lower-melting epoxide with a more positive rotation derived from cortisone acetate is therefore assigned the β-configuration, and the higher-melting, lower-rotation epimer the α-configuration. Recently, Ringold, *et al.*,[4] prepared the $4\alpha,5\alpha$-epoxide of cortisone by alkaline hydrogen peroxide treatment of the 3-keto-Δ^4-system and reported m.p. 235–237°, $[\alpha]D$ $-13°$. This is in agreement with our assignment of the α-configuration to our acetate of m.p. 248–255°, $[\alpha]D$ $+34.9°$.

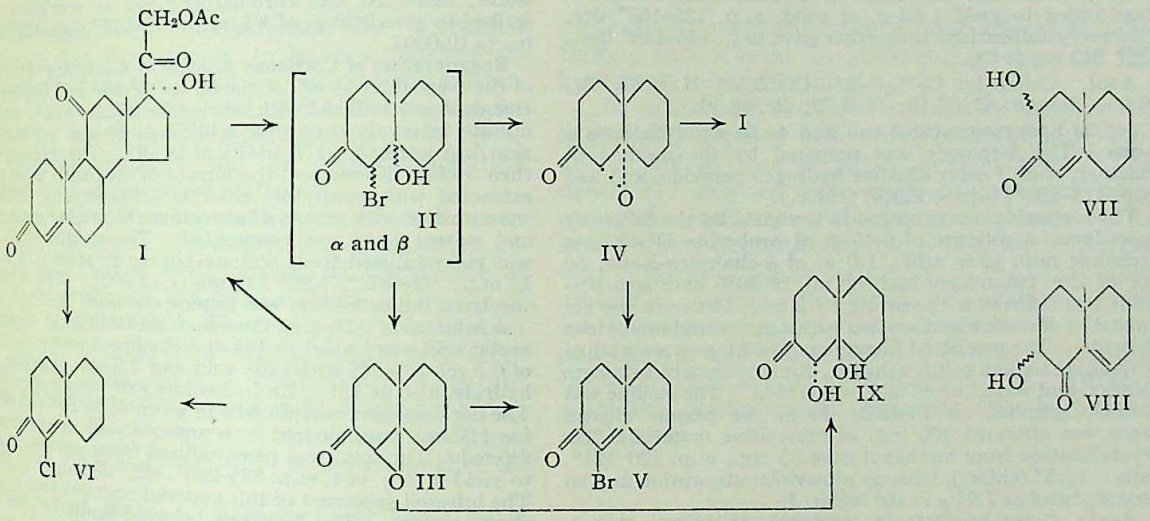
The intermediate bromohydrins could not be isolated in pure state, but treatment of the crudes with hydrogen bromide in acetic acid at room temperature, or warming with acetic acid alone, produced 4-bromocortisone acetate, λ_{max}^{EtOH} 260 mμ (ϵ 11,200). This latter compound could be prepared from either epoxide by reaction with hydrogen bromide in acetic acid. Debromination by vigorous treatment with zinc and acetic acid regenerated cortisone acetate.

Addition of hypochlorous acid (N-chlorosuccinimide and perchloric acid) to cortisone acetate, followed by potassium acetate treatment, gave, as the main product, 4-chlorocortisone acetate (VI) rather than either epoxide. Compound VI was also prepared readily by the action of hydrogen chloride in acetic acid on the β-epoxide.

Reaction of either epoxide with hydriodic acid in acetic acid readily regenerated cortisone acetate. Zinc dust treatment of the β-epoxide also gave cortisone acetate but in an impure state.

Opening of the β-epoxide with aqueous perchloric or trifluoroacetic acid gave a glycol, which, if our formulation of the epoxide is correct, must be the $4\alpha,5\beta$-diol. The α-epoxide, however, on treatment with trifluoroacetic acid failed to react. These results differ from those obtained with the two epoxides derived from testosterone.[5] In this latter case, the β-epoxide with dilute sulfuric acid in acetone rearranged to 2α-hydroxytestosterone, while the α-epoxide with the same reagent gave the $4\beta,5\alpha$-diol.

In one reaction with the β-epoxide and perchloric acid, the reaction time was extended from 18 to 72 hr., and a small amount of a second product was obtained with an ultraviolet maximum at 236 mμ (ϵ 13,200) and with an analysis corresponding to $C_{23}H_{30}O_7$. Two possible structures for this compound are VII and VIII: The first might arise by rearrangement and the second by dehydration of the 5-hydroxyl with a hydrogen at C-6, followed by a keto–enol shift. Unfortunately, not enough material was available for further study.



Experimental[6]

$4\beta,5\beta$-Epoxypregnane-17α,21-diol-3,11,20-trione 21-Acetate (IV) and $4\alpha,5\alpha$-Epoxyallopregnane-17α,21-diol-3,11,20-trione 21-Acetate.—A suspension of 20.0 g. of cortisone acetate (I) in 1 liter of tetrahydrofuran and 100 ml. of water was chilled in an ice-bath, and 100 ml. of 1 *N* aqueous perchloric acid and 13.8 g. of N-bromoacetamide were added. The ice-bath was removed after the reaction was homogeneous (*ca.* 1 hr.) and then stirred and protected from light for 72 hr. at 25°. At the end of this time, a starch–iodide test was either negative or very weak. The solution was diluted with water containing a small amount of sodium sulfite and extracted with methylene chloride. The combined organic extracts were washed with dilute sodium bicarbonate solution and water, dried over magnesium sulfate and concentrated to dryness under reduced pressure. The resinous residue was taken up in 1 liter of acetone, 40 g. of potassium acetate added and the mixture refluxed with stirring for 5 hr. Water was added, the mixture extracted with methylene chloride, and the organic extracts were washed with water, dried and concentrated under reduced pressure. The crystalline residue was reacetylated by reaction with 100 ml. of pyridine and 15 ml. of acetic anhydride for 1 hr. The excess anhydride was destroyed by the addition of 40 ml. of water and the mixture poured into excess dilute sulfuric acid and ice, then extracted with methylene chloride. The residue obtained from the organic extracts was chromatographed on Florisil. Elution with 50% methylene chloride–benzene yielded a crystalline mixture of the α- and β-epoxides.

Crystallization from acetone–hexane yielded 2.32 g. of α-epoxide, m.p. 240–247°; concentration of the mother liquor yielded 4.40 g. of β-epoxide, m.p. 224–229°. The former was purified by three additional crystallizations from acetone, m.p. 248–255°, $[\alpha]D$ $+34.9°$ (chlor.).

(4) H. Ringold, E. Batres, O. Mancera and G. Rosenkrantz, *J. Org. Chem.*, **21**, 1432 (1956).

(5) B. Camperino, B. Patelli and A. Vercellone, THIS JOURNAL, **78**, 3540 (1956).

(6) All m.p.'s are corrected. All rotations were taken in a 1-dm. tube at a concentration of *ca.* 1% at 25°. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry De-

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Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.15; H, 7.33.

The β-epoxide was crystallized from acetone–hexane, m.p. 224–227°, $[\alpha]D$ +142.2° (chlor.).

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.74; H, 7.16.

Further elution of the Florisil column with methylene chloride, and methylene chloride–methanol gave fractions having increasing ultraviolet absorption at 238 mμ.

Instead of perchloric acid, either trifluoroacetic acid or Amberlite IR-120 ion exchange resin (free acid form) could be used.

The intermediate bromohydrins could not be obtained pure, because of their instability and the ease with which they were converted to 4-bromocortisone acetate. The resinous bromohydrin from the addition of HOBr to 1 g. of cortisone acetate was dissolved in ether, and pentane was then added to yield 1.02 g. of solid, m.p. 125–150° dec. Two recrystallizations from ether gave m.p. 145–148° dec., λ_{max}^{EtOH} 242 mμ (ε 73).

Anal. Calcd. for $C_{23}H_{31}O_7Br$: C, 55.31; H, 6.26; Br, 16.00. Found: C, 56.18; H, 6.72; Br, 16.16.

4β,5β-Epoxycoprostan-3-one and 4α,5α-Epoxycholestan-3-one.—The β-epoxide was prepared by the method of Plattner, *et al.*,[3] using alkaline hydrogen peroxide, and had m.p. 118–120°, $[\alpha]D$ +123.8° (chlor.).

The α-epoxide was prepared in low yield by the following procedure: A mixture of 0.45 g. of Amberlite IR-120 ion exchange resin (free acid), 1.0 g. of 4-cholesten-3-one, 50 ml. of C.P. chloroform and 3.0 ml. of 30% hydrogen peroxide was refluxed with stirring for 3 hr. The resin was removed by filtration and washed with acetone and methylene chloride. The combined filtrate and washings were washed with dilute sodium sulfite solution, dilute sodium bicarbonate solution and water, dried and evaporated. The residue was chromatographed on Florisil. From the hexane eluates there was obtained 100 mg. of crystalline material. Recrystallization from methanol gave 35 mg., m.p. 120–121°, $[\alpha]D$ −42.5° (chlor.), with no ultraviolet absorption and an epoxide band at 7.91 μ in the infrared.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.62; H, 10.98.

4-Bromocortisone Acetate (V).—The crude bromohydrins obtained from 1 g. of cortisone acetate were dissolved in 10 ml. of acetic acid and heated on the steam-bath for 30 minutes. Dilution with water gave crystals contaminated with a dark oil. The mixture was extracted with methylene chloride, the organic extracts washed with dilute sodium bicarbonate and water, dried and evaporated. The residue was reacetylated in the usual manner, and the resulting 1.02 g. of crystalline material was chromatographed on Florisil. The material eluted with 50% benzene–methylene chloride was recrystallized from acetone–hexane to give 0.22 g. of V, m.p. 170–173° dec., $[\alpha]D$ +196.2° (diox.), λ_{max}^{EtOH} 260 mμ (ε 10,400). Two crystallizations from acetone–hexane gave a m.p. of 178–181° dec.

Anal. Calcd. for $C_{23}H_{29}O_6Br$: Br, 16.60. Found: Br, 16.20.

The crude bromohydrins also could be converted to V by treatment with hydrogen bromide. The resin from the addition of HOBr to 2.5 g. of cortisone acetate was dissolved in 25 ml. of acetic acid, and 5 ml. of acetic acid saturated with hydrogen bromide added. After standing for 1 hr. at 25°, the reaction was diluted with water, extracted and chromatographed in the usual way to give 0.46 g., m.p. 183–185° dec., λ_{max}^{EtOH} 260 mμ (ε 11,200).

Reaction of either epoxide III or IV with HBr in acetic acid by the following procedure also gave V.

A mixture of 0.3 g. of III in 10 ml. of acetic acid was combined with 0.6 ml. of 4 *N* hydrogen bromide in acetic acid. After 1 hr. at 25°, water was added, the precipitated solids were removed by filtration, dried and recrystallized from acetone–hexane to yield 0.23 g. of V, m.p. 189–191° dec. All samples of V were identical in their infrared spectra. The reported[3,7] ultraviolet absorption for 3-keto-Δ⁴-4-bromo-steroids is λ_{max} 258–261 mμ (ε 10–12,000).

4-Chlorocortisone Acetate (VI).—A solution of 0.20 g. of the β-epoxide III in 5 ml. of glacial acetic acid was combined with 1 ml. of glacial acetic acid saturated with hydrogen chloride. The solution was allowed to stand for 1 hr. at 25° and was then poured into water. The resulting white gel (0.18 g.) was recrystallized from acetone–hexane to yield 0.13 g. of VI, m.p. 227–231° dec., $[\alpha]D$ +223.8° (chlor.), λ_{max}^{MeOH} 253 mμ (ε 11,200); lit.[8] m.p. 232–234° dec., $[\alpha]D$ +214° (diox.), λ_{max} 253 mμ (ε 12,900).

The same product, 4-chlorocortisone acetate, was obtained *via* the addition of hypochlorous acid to cortisone acetate. This compound formed with such great ease that it was impossible to obtain any reasonably pure epoxide on potassium acetate treatment of the supposed chlorohydrin. The reaction of 1 g. of cortisone acetate and N-chlorosuccinimide (instead of N-bromoacetamide) gave, after potassium acetate treatment and chromatography, 0.3 g. of VI, m.p. 218–224° dec., λ_{max}^{EtOH} 252 mμ (ε 8,500).

The crude "chlorohydrin" from another 1-g. reaction was taken up in 20 ml. of glacial acetic acid and heated for 30 minutes on the steam-bath. The mixture was diluted with water, extracted and chromatographed as previously described to give 0.26 g. of VI, m.p. 210–222° dec., λ_{max}^{EtOH} 253 mμ (ε 10,000).

Regeneration of Cortisone Acetate.—A mixture of 0.15 g. of the β-epoxide, 15 ml. of glacial acetic acid and 150 mg. of zinc dust was refluxed with stirring for 30 minutes.[9] At 10-minute intervals thereafter additional 80-mg. portions of zinc dust were added (5 additions in all). The mixture was then cooled, filtered and the filtrate diluted with water and extracted with methylene chloride. The organic extracts were washed with water, dilute sodium bicarbonate solution and water, dried and evaporated. The residue (0.13 g.) was recrystallized from acetone–hexane to yield 0.07 g. of I, m.p. 196–202°, λ_{max}^{EtOH} 238 mμ (ε 12,500). The infrared spectrum indicated this was impure cortisone acetate.

A solution of 0.20 g. of the α-epoxide IV in 5 ml. of glacial acetic acid was cooled to 15° and combined with a mixture of 0.5 ml. of 48% hydriodic acid and 2.3 ml. of acetic anhydride, also at 15°. An immediate iodine color appeared. The dark solution was allowed to warm up to 25° and stand for 1.5 hr., then poured into aqueous sodium sulfite and filtered. The solid was recrystallized from acetone–hexane to yield 0.14 g. of I, m.p. 235–240°, λ_{max}^{EtOH} 238 mμ (ε 14,800). The infrared spectrum of this material matched that of cortisone acetate. The β-epoxide behaved similarly with hydriodic acid.

A solution of 0.20 g. of 4-bromocortisone acetate (V) in 20 ml. of ethanol and 5 ml. of glacial acetic acid was brought to reflux with stirring, and eight portions of zinc (200 mg. each) were added, one every 15 minutes. The solids were removed by filtration and washed with methylene chloride. The combined washings and filtrate were diluted with water and the organic extract washed with dilute sodium bicarbonate solution and water, dried and evaporated. Recrystallization of the residue from acetone–hexane yielded 0.12 g. of cortisone acetate (I), m.p. 225–231°, λ_{max}^{MeOH} 238 mμ (ε 13,000), identical in its infrared spectrum with an authentic sample.

4α,5β,17α,21-Tetrahydroxypregnane-3,11,20-trione 21-Acetate (IX).—A solution of 0.50 g. of the β-epoxide, 25 ml. of acetone, 5 ml. of water and 5 drops of trifluoroacetic acid was allowed to stand for 18 hr. at 25°. The solution was diluted with water and extracted with methylene chloride. The combined extracts were washed with dilute sodium bicarbonate solution and water, dried and evaporated. Crystallization of the residue from acetone–hexane gave 0.34 g. of IX, m.p. 228–234°. The analytical sample, crystallized twice more, had m.p. 230–235°, $[\alpha]D$ +203.0° (chlor.).

Anal. Calcd. for $C_{23}H_{32}O_8$: C, 63.28; H, 7.39. Found: C, 63.34; H, 7.12.

An 18-hr. run using perchloric acid as the catalyst and chromatographing the crude reaction product gave the same result. However, a 72-hr. run with perchloric acid followed by chromatography gave, besides the expected glycol, 50 mg. (from 0.50 g. of III) of a second product. Crystallization from acetone yielded 35 mg., m.p. 265–270°, λ_{max}^{MeOH} 236 mμ (ε 13,200). Compounds VII and VIII are possible structures.

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.91; H, 7.11.

BLOOMFIELD, NEW JERSEY

(7) D. Kirk, D. Patel and V. Petrow, *J. Chem. Soc.*, 627 (1956).

(8) D. Kirk, D. Patel and V. Petrow, *ibid.*, 1184 (1950).

(9) *Cf.* H. Heusser, G. Saucy, R. Anliker and O. Jeger, *Helv. Chim.*

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[CONTRIBUTION NO. 759 FROM THE DEPARTMENT OF CHEMISTRY OF INDIANA UNIVERSITY]

The Effects of Deuterium Substitution on the Rates of Organic Reactions. V. Hydrolysis of α-Deutero Ketals[1]

BY V. J. SHINER, JR., AND SALLY CROSS

RECEIVED FEBRUARY 28, 1957

A study of the effect of deuterium substitution in the α-positions on the rates of hydrolysis of the diethyl ketals of acetone, methyl ethyl ketone, methyl isopropyl ketone and phenoxyacetone has been made. It has been found that the magnitude of the effect is solvent dependent and varies according to the nature of the substituents on the α-carbon atom. This is in general agreement with the results previously obtained for secondary deuterium isotope rate effects on the solvolysis of tertiary alkyl halides, although the rate effects are smaller in the present case. The results are interpreted as indicating that the assumption of Kreevoy and Taft, that the hyperconjugative release of electrons by a C–H bond is independent of the nature of the other substituents on the C-atom, is not quite correct.

The substitution of deuterium for β-situated hydrogen has been shown to have a marked retarding effect on the solvolysis rates of certain tertiary alkyl chlorides and related compounds. This effect has been explained tentatively in terms of hyperconjugation[2] and of hyperconjugation assisted by β-hydrogen solvation.[3]

It has further been shown that the effect is cumulative as the degree of β-deuterium substitution increases and that it is dependent on the nature of the other groups on the carbon which is the site of isotopic substitution.[3] For example, substitution of a deuterium atom for a secondary hydrogen atom in an ethyl group gives a smaller effect than obtains when the tertiary atom of an isopropyl group is replaced. Replacement of a primary hydrogen atom of a methyl group leads to a still smaller effect.

The recent work of Kreevoy and Taft[4] gives some of the best evidence in the literature for the effect of hyperconjugation on reaction rates. These authors were able to correlate the hydrolysis rates of a number of diethyl acetals and ketals with the Taft equation in the form $\log k/k_0 = \rho^*\Sigma\sigma^* + (n-6)h$, where k refers to the hydrolysis rate of any of the ketals or acetals studied, k_0 refers to the hydrolysis rate of diethyl acetonal, ρ^* is a reaction constant, σ^* is a substituent constant characteristic of the substituent on the ketal linkage, n is the number of α-C–H bonds in the acetal or ketal and h is a constant characteristic of the acceleration of the solvolysis rate due to the hyperconjugative effect of one C–H bond. The important thing to note for purposes of the present discussion is that the equation rather successfully correlates a large number of rate constants differing in magnitude over a wide range, with the assumption that each α-C–H bond hyperconjugates the same amount regardless of the nature of its environment in the molecule. Since this leads to a conclusion different from that obtained from the secondary deuterium isotope rate effects, *if* one assumes that the *variations* noted in the latter are due to variations in hyperconjugation, it was of interest to us to locate the apparent discrepancy more precisely by measuring the isotope effects of deuterium substitution in different groups on the hydrolysis rates of ketals.

The deuterated ketals were made by treating the deuterated ketones with ethyl orthoformate, ethanol-*d* and a trace of strong acid catalyst. The deuterated ketones were made by repeated base-catalyzed exchange with deuterium oxide. The ketones were deuterated in the α-position to the extent of 95–97% before being used in the ketal preparation. During the ketal preparations some spurious exchange apparently lowered the deuterium content and the deuterated ketals were not of the same high degree of isotopic purity. Table I gives the deuterium analyses for the deuterated ketals used.

TABLE I

DEUTERIUM ANALYSES OF KETALS

Ketal of	D, %	Atoms D/mole	Deut. of α-pos., %
Acetone	30.56	4.88	81.3
Methyl ethyl ketone	22.46	4.04	80.8
Methyl isopropyl ketone	13.23	2.65	66.2
Phenoxyacetone	21.19	4.24	84.8

The rates of hydrolysis of the ketals of acetone, methyl ethyl ketone and their deuterated analogs were first measured in an acetic acid–sodium acetate buffer in 50% (by weight) aqueous dioxane, the solvent used by Kreevoy and Taft. In order to make the isotope rate effects as large as possible, subsequent measurements on all of the compounds were done in 90% dioxane–10% water solution. The phenoxyacetone ketal hydrolyses were catalyzed by dilute hydrochloric acid and the others by a dichloroacetic acid–sodium acetate buffer.

The rate measurements were mainly made with a dilatometer, although several constants obtained in this way were checked using a spectrophotometric method. The rate constants were calculated by the statistical method for first-order reactions described by DeTar.[5] Fifty to seventy points were used in calculating the results for each run. The computation was programmed for an IBM 650 Magnetic Drum Data Processing Machine. The program yielded the rate constant, the constants a and b and the standard deviations for each. It is important to note that the statistical method successfully overcomes difficulties in reproducing rate constants which are associated with errors in

(1) (a) Abstracted from the thesis submitted by Sally Cross to the Graduate School of Indiana University in partial fulfillment of the requirements for the M.A. degree. (b) Presented at the Southwide Chemical Conference in Memphis, Tennessee, December 6, 1956. (c) Supported by a grant from the National Science Foundation.

(2) R. S. Lewis and C. E. Boozer, THIS JOURNAL, **76**, 791 (1954).

(3) V. J. Shiner, Jr., *ibid.*, (a) **75**, 2925 (1953); (b) **76**, 1603 (1954).

(4) M. M. Kreevoy and R. W. Taft, Jr., *ibid.*, **77**, 5590 (1955).

(5) D. F. DeTar, *ibid.*, **78**, 3911 (1956).

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the zero and infinity readings. As a result the variations in the same rate constants from run to run are of the same order as the standard errors in a given run. The hydrolysis rate for each compound was measured in from two to five different runs and several times with different preparations of the ketals. With a few exceptions all of the reactions in a given solvent type were carried out with solvent from the same master batch. The common impurities encountered in the ketals, the hydrolysis products, ethyl formate and ethyl orthoformate do not affect the observed rates if they are present in only small amounts. Ethyl formate hydrolyzes too slowly and ethyl orthoformate too rapidly. However, the impurities would affect the deuterium analyses, so care was taken to obtain pure compounds. Gas chromatography analyses showed that the deuterated ketals were about 95 mole % pure. More than half of the impurities was accounted for as hydrolysis products which would not strongly affect the deuterium analyses. The constants obtained are summarized in Tables II and III.

Table II

Hydrolysis Rates of Ketals in 90% Dioxane–10% Water at 25°

Diethyl ketal of	k_1, 10^{-4} sec.$^{-1}$	Std. error	No. of runs
Acetone[a]	3.67	0.01	3
Acetone-d_6[a]	3.27	.01	5
Methyl ethyl ketone[a]	2.73	.02	3
Methyl ethyl ketone-d_5[a]	2.37	.01	2
Methyl isopropyl ketone[a]	3.20	.02	3
Methyl isopropyl ketone-d_4[a]	2.89	.01	3
Phenoxyacetone[b]	3.52	.03	3
Phenoxyacetone[b,c]	3.52	.02	2
Phenoxyacetone-d_5[b]	2.80	.01	2

[a] Solution 0.05 N in dichloroacetic acid and 0.02 N in sodium acetate. [b] Solution 0.00786 N in hydrogen chloride. [c] Measured spectrophotometrically.

Table III

Hydrolysis Rates of Ketals in 50% Dioxane–50% Water at 25°

Diethyl ketal of	k_1[a]	[H$^+$]	k_2, l./mole/sec. This work	Ref. 4[b]
Acetone[c]	2.31	3.04×10^{-7}	7.60×10^2	7.52×10^2
Acetone-d_6[c]	2.09	3.04×10^{-7}	6.87×10^2	
Methyl ethyl ketone[c]	2.34	3.04×10^{-7}	7.70×10^2	7.2×10^2
Methyl ethyl ketone-d_6[c]	2.12	3.04×10^{-7}	6.96×10^2	
Phenoxyacetone[d]	4.04	1.28×10^{-3}	0.315	0.350

[a] Units of 10^{-4} sec.$^{-1}$; std. errors are all about 0.01. [b] Data of Kreevoy and Taft, ref. 4. [c] Measured dilatometrically in buffer solutions 0.02 N in sodium acetate and 0.01 N in acetic acid, [H$^+$] calculated by method of Kreevoy and Taft. [d] Measured spectrophotometrically because of low solubility of ketal; solution 0.001283 N in $HClO_4$.

Table III shows that the rate constants obtained in this work for diethylacetonal and diethylbutanonal dilatometrically and for diethylphenoxyacetonal spectrophotometrically agree reasonably well with those obtained spectrophotometrically by Kreevoy and Taft for these compounds. Table II also shows agreement between hydrolysis rate constants obtained in this work for diethylphenoxyacetonal by the spectrophotometric and dilatometric methods. Table IV gives a summary of the isotope rate effects observed for the different compounds in 90% dioxane–10% water at 25°. The observed rate ratios, the changes in free energy of activation due to the amount of deuteration actually obtained (calculated by the formula $\Delta\Delta F_a = RT \ln k_H/k_D$) and the predicted free energy of activation change due to complete deuteration of the α-positions are given. These last figures were obtained from the observed free energy differences and the deuterium analyses given in Table I by a proportional extrapolation.

Table IV

Summary of Isotope Rate Effects Due to α-Deuteration on Hydrolysis of Ketals at 25°

Diethyl ketal of	K_H/K_D (obs.)	$\Delta\Delta F_a$ (obsd.)	$\Delta\Delta F_a$ (cor.)[a]
Acetone[b]	1.12	67.2	82.5
Acetone[c]	1.10		
Methyl ethyl ketone[b]	1.15	83.0	102.6
Methyl ethyl ketone[c]	1.10		
Methyl isopropyl ketone[b]	1.11	61.9	93.5
Phenoxyacetone[b]	1.25	132.0	156.0

[a] Corrected to represent complete α-deuteration; units are calories. [b] In 90% dioxane–10% water. [c] In 50% dioxane–50% water.

Table V shows how the data in the last column of Table IV may be broken down to give the isotope rate effects due to deuteration of the α-position of each group and due to each deuterium atom substituted. This separation is based on the assumption that the free energy of activation effects of deuteration are linearly accumulative and that the methyl group shows a constant effect (for a given reaction) from compound to compound. The available data, obtained in the study of secondary deuterium isotope rate effects on the hydrolysis of tertiary alkyl halides,[3] which test these two assumptions, indicate that they are at least approximately correct. The first three entries in Table V show that the isotope rate effect per α-deuterium atom increases in the series of groups methyl (14 cal.), ethyl (30 cal.), isopropyl (51 cal.) in about the same way that it does in these three groups in the hydrolysis of tertiary alkyl halides where the free energy of activation effects per deuterium atom are, in order, 56, 96 and 156 calories. Thus the two cases are strikingly similar. The isotope effects are smaller in the hydrolysis of ketals because the carbon atom to which the groups are attached develops a smaller degree of unsaturation in the ketal hydrolysis transition state, which forms a carbonium–oxonium ion, than it does in the alkyl chloride solvolysis transition state, which forms a carbonium ion.

Table V

Isotope Rate Effects in Ketal Hydrolyses Due to α-Deuteration of Different Groups

Group deuterated	$\Delta\Delta F_a$/group[a]	$\Delta\Delta F_a$/D atom[a]
Methyl	42.3	14
Ethyl	61.3	30
Isopropyl	51.2	51
Phenoxymethyl	115.0	57

[a] Units are calories.

The last entry in Table V summarizes the data which contribute our present knowledge of the effects

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of substituents on secondary isotope rate effects to include the interesting example of the phenoxy group. This substituent increases the isotope rate effect of deuteration more than do two methyl groups. Since the methyl group is an inductive electron releaser while the phenoxy group is an inductive electron attractor, it would seem that the similar effects of the two groups on the isotope rate effect would be related to their conjugative electron-releasing powers which operate in the same direction for both but to a greater extent in the phenoxy group. Thus the group effects on the isotope rate effect might be attributed to the extra stabilization of hyperconjugative canonical forms by resonance (conjugation and hyperconjugation). These effects are viewed as being intrinsically similar to second-order hyperconjugation which shows up, for example, in the alternation effect.[6]

The isotope effects were observed to be larger in 90% dioxane–10% water than in 50% dioxane–50% water. This trend is in the same direction as that already observed for solvent effects on secondary isotope rate effects in the solvolysis of organic halides.[2,3,7]

Using the Taft–Hammett equation and the rate constants obtained in this work for acetonal, methyl ethyl ketone ketal and phenoxyacetonal, values for ρ^* and h can be calculated for the reaction in each of the two solvents used. The calculated value for h is appreciably larger in the less polar solvent, so h and the isotope rate effect apparently show the same gross dependence on solvent composition. Unexpectedly, ρ^* turned out to be slightly smaller in the less polar solvent, but the difference was small and apparently within the experimental error. These values are not given because they are not calculated as averages for a representative number of points and their absolute magnitude is not very significant, but they should be accurate enough to show the correct relationship between the parameters for the two solvents.

In conclusion, it seems that the apparent discrepancy noted in the introduction between the interpretation of the substituent effects on secondary deuterium isotope rate effects as being due to variations in hyperconjugation and the use of the Taft h parameter as a measure of hyperconjugation is inherent in the methods themselves and not in the reaction systems studied. It appears that the Kreevoy–Taft assumption of a constant value of h characteristic of every C–H bond may be an approximation and that the value obtained by the statistical method used is an average one which smooths out the variations among the different cases. Perhaps the remaining deviations of the points from the line are due to variations in h values.

It is not considered that the secondary deuterium isotope rate effects are a direct relative measure of hyperconjugation.[8] At least two other factors, not yet fully investigated, are recognized as influencing the magnitude of these secondary isotope rate effects. The first of these is the solvent effect[3,7] and the second is the isotope effect on the frequency factor of the Arrhenius equation. Carbon–hydrogen bond stretching, presumably resulting from increased hyperconjugation in the transition state, shows up most directly in the activation energy term of the isotope rate effect. The observed rate effect is of course a combination of the activation and frequency factor effects. In the cases where the Arrhenius parameters of the secondary isotope rate effects have been measured, it has turned out that the activation energy effect was present and affected the rate ratios, in the temperature range in which they were observed, in the direction observed. However, this effect was, in each case, partly cancelled by a frequency factor effect in the opposite direction. This suggests that at some temperature the frequency factor and activation energy effects would cancel and no isotope rate effect would be observed. At a higher temperature a negative rate effect would be found. This "cross-over" temperature might be different in different reaction systems. The most fundamental (but more difficulty obtained) experimental quantity is the isotope activation energy effect. In each of the cases that have been measured thus far this has paralleled the isotope rate effect at the temperatures used. This relationship, which will not always hold, is a necessary condition for the isotope rate effects to be relative measures of hyperconjugation. However, in comparing closely related reactions in the same solvent at the same temperature it seems that the isotope rate effect variations are most reasonably attributed to variations in hyperconjugation.

Experimental

Purification of Commercial Chemicals.—The following compounds were purified by distillation through an 88 × 1.9 cm. column packed with $^1/_{32}$″ glass helices: ethyl orthoformate, b.p. 143–144° (740 mm.); methyl ethyl ketone, b.p. 78.5° (740 mm.); and methyl isopropyl ketone, b.p. 92.3° (740 mm.). Dioxane was purified according to the method of Fieser[9] and fractionated through the 88 × 1.9 cm. column. Absolute alcohol was obtained by distilling added benzene from commercial absolute ethanol through a packed column. The ternary azeotrope (b.p. 64.9°), the ethanol–benzene azeotrope (b.p. 68.2°) and a foreshot of ethyl alcohol (b.p. 78.5°) were removed before the material to be used was collected.

Deuterium Oxide.—The deuterium oxide was obtained from the Stuart Oxygen Co. and was specified to be 99.5% isotopically pure.

Phenoxyacetone.—This compound was prepared according to the method of Hurd and Perletz[10] and vacuum distilled. It was then fractionally distilled through a spinning band column and the product collected at 125° (18 mm.), over-all yield 48%. The semicarbazone derivative gave m.p. 175–176°, reported[11] 173°.

Deuteration of Ketones.—Deuteroacetone was made by repeated potassium carbonate catalyzed exchange with deuterium oxide. The deuteroacetone was separated from each exchange by distillation. Methyl ethyl ketone was exchanged by refluxing the ketone with deuterium oxide and a little potassium carbonate for 24 hr. The deuterated methyl ethyl ketone–water azeotrope was separated from the deuterium oxide each time by distillation. Methyl isopropyl ketone was exchanged by refluxing with deuterium

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(7) V. J. Shiner, Jr., and C. J. Verbanic, THIS JOURNAL, **79**, 373 (1957).
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(9) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, pp. 369.
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(11) R. Stoermer, *Ann.*, **312**, 273 (1900).

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oxide and a little potassium carbonate for three days. Deuterated methyl isopropyl ketone was separated from the deuterium oxide by separation of the layers after cooling. Phenoxyacetone was exchanged by refluxing for 24 hr. with a deuterium oxide–dioxane solution to which had been added several drops of triethylamine. Enough dioxane was used so that all of the deuterium oxide could be distilled from the mixture as the dioxane azeotrope and separation was thus accomplished. The exchanges were carried out each time with 5.0 g. (0.25 mole) of deuterium oxide and enough ketone so as to have an equivalent number of exchangeable (alpha) hydrogen atoms. Several successive ketone samples were run through the same sequence of deuterium oxide samples to increase the efficiency of deuterium transfer. The exchanges were continued until the completely α-deuterated ketones were 95–97% isotopically pure as shown by combustion analysis.

Preparation of Ketals.—The method of Carswell and Adkins[12] was used for the preparation of the ketals. These materials had to be distilled carefully at reduced pressures to prevent decomposition to the enol ethers which was apparently promoted by higher temperatures. The Carswell and Adkins procedure which involves the treatment of the ketone with ethyl orthoformate, ethyl alcohol and a little hydrochloric acid had to be modified for the preparation of the deuterated ketals, to include ethanol-*d* instead of ethanol to prevent loss of the deuterium from the deuterated ketones by exchange. This was accomplished as described in the following procedure for the preparation of deuterated phenoxyacetone ketal. The other deuterated ketals were prepared in a similar way. A 39 × 1.0 cm. fractionating column packed with $^1/_{16}$″ glass helices was cleaned and dried by refluxing ethyl orthoformate through it and removing the low-boiling material. In a 100-ml. round-bottomed flask were placed 57 ml. (0.35 mole) of ethyl orthoformate, 3.9 ml. (0.21 mole) of deuterium oxide and one drop of concentrated hydrochloric acid. The flask was attached to the cleaned column, and 17.2 g. of material was distilled out until the temperature reached 76°; theoretical yield of ethyl formate, 15.8 g. The flask was allowed to cool and 15.75 g. (0.10 mole) of deuterated phenoxyacetone and one drop of concentrated hydrochloric acid were added. The mixture was shaken and allowed to stand at room temperature for 11 days and then distilled through a dry spinning band column. Ethyl formate was distilled over at atmospheric pressure and the ethanol-*d* was distilled at 100 mm. Deuterated phenoxyacetone ketal, 19.5 g. (0.087 mole), was collected at 69–71° (0.1 mm.), yield 87%. Combustion deuterium analysis showed the material to contain an average of 4.24 deuterium atoms per molecule.

The yields of the other deuterated ketals varied from 45 to 65%. The boiling points of methyl isopropyl ketone ketal and ethyl orthoformate are very close together so the product obtained in the preparation of the former compound was subjected to partial hydrolysis with deuterium oxide catalyzed by a drop of glacial acetic acid. Enough deuterium oxide was added to hydrolyze about 33% of the material. This hydrolysis should have preferentially removed any ethyl orthoformate impurity. The hydrolysis reaction mixture was redistilled in the spinning band column. Gas chromatography analysis showed the distillate to be 95 mole % or more pure.

Dioxane–Water Solution.—Solutions 90% dioxane–10% water and 50% dioxane–50% water (by weight) were prepared from the dioxane purified as mentioned above and deionized distilled water. The following solutions were made from the 50% dioxane, placed in brown glass-stoppered bottles and stored in an ice-box for use as needed: (1) 0.02 *N* sodium acetate and 0.01 *N* acetic acid, (2) 0.001283 *N* perchloric acid. The following solutions were made from the 90% dioxane solution and similarly stored: (1) 0.02 *N* sodium acetate and 0.05 *N* dichloroacetic acid, (2) 0.00786 *N* hydrogen chloride.

Deuterium analyses were done using the method previously described.[13]

Kinetic Equipment.—The dilatometer consisted of a 125-ml. spherical mixing chamber connected by a long-handled stopcock to a 100-ml. reaction chamber in the shape of a U-tube approximately 34 cm. long and 15 mm. in diameter. The other end of the U-tube was connected to a precision bore capillary tube 30 cm. long and approximately 0.6 mm. inside diameter. The runs were done in a constant temperature water-bath kept in a room at 22° and heated intermittently by an infrared lamp. The temperature was set at 25.00 ± 0.001° with a Beckman thermometer calibrated against a platinum resistance thermometer. The temperature variations were of the order of ±0.002°.

Kinetic Procedure.—The dilatometer was placed in the 25.00° bath, and 105 ml. of solvent was placed in the mixing chamber. After the solvent had come to the temperature of the bath, approximately 1 ml. of the ketal was pipetted into the solution which was then stirred and degassed. Degassing was accomplished by reducing the pressure in the mixing chamber until the solution boiled. Then the reaction mixture was run into the reaction chamber and allowed about 15 minutes to come to temperature. The meniscus was then allowed, by slow opening of the stopcock, to rise into the bottom part of the capillary tube, and readings by a cathetometer of the meniscus heights with time were begun. The reaction half-lives were of the order of 45 min., and readings were taken through the second half-life or longer. The total capillary rise was usually in the range of 5 to 10 cm.

The rate of hydrolysis of phenoxyacetone ketal was measured in several experiments using a spectrophotometric method based on the change in absorption at 295 mμ which accompanies the reaction. The run was done in a flask in the 25.00° bath, and 3-ml. samples were withdrawn periodically and their optical densities measured at 295 mμ in a Beckman DU spectrophotometer.

Calculation of Rate Constants.—The rate constants were calculated by the statistical method described by DeTar.[4] The basic equation which applies is

$$h_i = a + be^{-kt_i}$$

where k is the first-order hydrolysis rate constant, h_i is the cathetometer reading at time t_i, a is equal to the cathetometer reading at infinity and b is equal to the cathetometer reading at zero time minus the infinity reading. The data are fitted to the equation treating a, b and k as disposable parameters chosen so that $\Sigma(h_i \text{ (observed)} - h_i \text{ (calculated)})^2$ is a minimum. This treatment avoids difficulties in reproducing first-order constants which have traditionally been associated with errors in zero and infinity readings. The solution was programmed for an IBM 650 Magnetic Drum Data Processing Machine. The programming was done in the Bell Laboratories interpretive system. The data, consisting of a series of height and a series of corresponding time readings along with an estimate of the infinity height reading, is fed into the machine on punched cards. The machine calculates a trial rate constant and then calculates corrections for the trial constant and for a and b. It then tests these for size, and if the corrections are 0.1% or more, it recycles to calculate another correction. When the correction is small enough, it then calculates the standard errors, punches a, b and k and their standard errors on output cards and takes in the data for the next run. The program for a seventy point run usually takes five to ten minutes machine time depending on the number of successive corrections (usually two to four) it must calculate. This compares with DeTar's estimate of 4 hr. used by an experienced operator to calculate a single set of corrections and the standard errors for a ten point run using a desk calculator. These calculations would not be practical for runs involving many points without an electronic computing machine.

Gas Chromatography Analyses.—The deuterated ketals used were analyzed for impurities using a Fisher–Gulf Partitioner equipped with an 8 ft. column packed with Carbowax supported on powdered firebrick. The column was thermostated at 100°. Elution times for the ketones and ketals (except phenoxyacetone ketal which was not run) were less than 15 minutes. Ethyl orthoformate seemed to decompose a little on the column but gave a characteristic elution pattern. The deuterated ketals were all 95 or more mole % pure with most of the impurities being accounted for as the ketal hydrolysis products.

Acknowledgment.—The authors are indebted to Professor L. L. Merritt for his help in programming the calculations for the computer.

(12) H. E. Carswell and H. Adkins, THIS JOURNAL, **50**, 236 (1928).
(13) V. J. Shiner, Jr., *ibid.*, **74**, 5285 (1952).

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COMMUNICATIONS TO THE EDITOR

THE CLEAVAGE OF 3-TROPANYL CHLORIDE WITH POTASSIUM CYANIDE

Sir:

When 3-tropanyl chloride[1] (I) was treated with potassium cyanide in alcohol solution a sharp-boiling (b.p. 68–70°, 0.2 mm.) mixture of isomers was obtained whose analysis agreed with the formula $C_9H_{14}N_2$ (I); (*Anal.* Calcd. for $C_9H_{14}N_2$: N, 18.65, N_{AP},[2] 9.33. Found: N, 18.35; N_{AP},[2] 9.38).

The infrared spectrum[3] was characterized by the presence of two cyanide bands at 4.50 μ and an intense band at 6.08 μ. When this oil was treated with phenylmagnesium bromide a liquid (b.p. 69–70°, 0.1 mm.), presumably a mixture of isomers also, was obtained, the analysis of which was compatible with the formula $C_{14}H_{19}N$ (III); (*Anal.* Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.70; H, 9.81; N, 6.84). The infrared spectrum showed that bands due to the aromatic ring system and the 6.08 μ band were present but the absorption at 4.50 μ had disappeared. This displacement of a nitrile function by the radical of a Grignard reagent is manifested by α-dialkylaminoacetonitriles.[4] The band at 6.08 μ is indicative of a terminal vinyl group (confirmatory bands at 11.00 μ + 3.27 μ). Catalytic hydrogenation resulted in the uptake of one mole of hydrogen and the bases IV (b.p. 111–113°, 0.4 mm.). (*Anal.* Calcd. for $C_{14}H_{21}N$: N, 6.86. Found: N, 6.90) were isolated. The band at 6.08 μ had disappeared. Structures I–IV illustrate the course of the reactions. The mixtures which persisted throughout were due to the formation of *cis* and *trans* pyrrolidine nitriles in the first step.

The bases (IV) were converted to a mixture of methiodides (V), m.p. 126–130°, the most readily purified of which melted at 173–174° after crystallization from acetone (*Anal.* Calcd. for $C_{15}H_{20}IN$: I, 36.1. Found: I, 36.0). Hofmann degradation of the bases corresponding to V furnished an oil VI (b.p. 125–128°, 0.4 mm.). (*Anal.* Calcd. for $C_{15}H_{23}N$: N, 6.46. Found: N, 6.44) which showed typical styrene absorption, $\lambda_{max}^{95\%\ EtOH}$ 253 (log ϵ 4.07).

Reduction in the presence of Adams catalyst furnished 4-dimethylamino-1-phenylheptane, which was independently synthesized from 1-phenyl-4-heptanone via oximation, reduction and methylation. The picrates from both samples melted at 92.5–94° (*Anal.* Calcd. for $C_{21}H_{28}N_4O_7$: N, 12.49. Found: N, 12.23) and were otherwise identical in all respects. The 1-phenyl-4-heptanone (b.p. 96–98°; 0.1 mm.; *Anal.* Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.07; H, 9.43) required for this synthesis was prepared from γ-phenylbutyronitrile and propylmagnesium iodide.

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RECEIVED MAY 29, 1957

(1) M. Polonovski and M. Polonovski, *Bull. soc. chim.*, [IV] **45**, 365 (1929).

(2) Acetic–perchloric acid titration of basic nitrogen. Analyses were carried out under the supervision of Mr. K. D. Fleischer.

(3) We are indebted to Miss C. M. Martini for determination of the spectra reported here.

(4) P. Bruylants, *Bull. soc. chim. Belg.*, **33**, 467 (1924); *Chem. Abs.*, **19**, 288 (1925).

THYMIDINE INCORPORATION INTO DEOXYRIBONUCLEIC ACID OF RAT LIVER HOMOGENATES

Sir:

The incorporation of radioactive thymidine into DNA[1] of cell-free extracts of *E. coli* was reported in 1956.[2] Attempts to demonstrate thymidine incorporation in homogenates of chick embryo were unsuccessful,[3] although rabbit thymus nuclei have been reported to be active in this respect.[4] In normal or regenerating rat liver homogenates which actively incorporate radioactive orotic acid into RNA, no radioactivity was found in DNA.[5] The availability[6] of very high specific activity tritium labeled thymidine encouraged us to re-examine DNA synthesis in rat liver homogenates. Our experiments have met with some success, and will be described briefly herein.

(1) These abbreviations are used: DNA, deoxyribonucleic acid; RNA, ribonucleic acid; ATP, adenosine triphosphate; and Tris, tris-(hydroxymethyl)-aminomethane.

(2) A. Kornberg, I. R. Lehman and E. S. Simms, *Federation Proc.*, **15**, 291 (1956).

(3) M. Friedkin, D. Tilson and D. Roberts, *J. Biol. Chem.*, **220**, 627 (1956).

(4) M. Friedkin and H. Wood, *ibid.*, **220**, 639 (1956).

(5) E. Herbert, V. R. Potter and L. I. Hecht, *ibid.*, **225**, 659 (1957).

(6) From Schwarz Laboratories, Inc., Mount Vernon, N. Y. Specific activity of the thymidine is reported to be 390 μc./μM., labeled in position 4; radiochemical purity 100%.

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Previous work[7] demonstrated that following hepatectomy, no DNA is synthesized or labeled by orotic acid for the first 18 hours following the operation. An experiment was therefore designed in which homogenates were prepared from lobes removed at partial hepatectomy, as well as from liver allowed to regenerate 15 hours, and 24 hours and incubated in the presence of radioactive thymidine. The results presented in Table I show the incorporation observed in these preparations.

TABLE I

INCORPORATION OF THYMIDINE INTO DNA OF RAT LIVER HOMOGENATES

Each 50-ml. flask contained: 2 ml. of 25% rat liver homogenate; approximately 3×10^6 c.p.m. (3 micrograms) of thymidine[b]; 20 μM. each of K fumarate, K glutamate and K pyruvate; 5 μM. disodium ATP; 100 μM. nicotinamide; 12 μM. $MgSO_4$; 12 μM. K phosphate, *p*H 7.6; 10 μM. KCl; 20 μM. Tris:HCl buffer, *p*H 8; and 500 μM. of sucrose in a final volume of 2.55 ml.; incubation, for one hour with shaking, 38°, O_2 in the gas phase. Reaction was stopped by placing the flasks in an ice-bath. Sodium nucleates extracted and DNA purified as described previously.[7] A trace of radioactivity associated with RNA is attributed to slight degradation of radioactive DNA during the mild alkaline hydrolysis required to remove RNA.

Rat no.	Homogenate from	C.p.m./plate (actual[a])	DNA[c] mg./plate	Sp. act.[a] c.p.m./mg. DNA
1	Lobes removed at partial hepatectomy	350	0.35	1,000
2	Lobes removed at partial hepatectomy	270	.32	840
1	Liver 15 hours after operation	360	.30	1,200
2	Liver 24 hours after operation	12,300	.28	44,000
3	Liver 24 hours after operation	4,400	.26	16,900[c]

[a] Tritium was assayed in windowless flow counters. Since approximately the same amount of DNA was placed on each plate no correction has been made for self-absorption. Crude self absorption curves for tritium, using DNA as absorber, indicate a correction of about 2-fold could be applied to the DNA samples. [b] Colorimetric analysis using the Dische diphenylamine reagent. [c] This homogenate aged for 2 hours at 0° before incubation. All others incubated immediately after preparation.

It is apparent that a low level of incorporation is present in the zero hour and 15 hour regenerated preparations, and that the 24 hour regenerating liver shows about a 50-fold increase (Rat no. 2) in ability to incorporate thymidine into DNA. Thus the results with the homogenates are in agreement with previous studies with orotic acid *in vivo*[7] and in rat liver slices.[8]

It is our opionion that the marked incorporation seen in the 24-hour livers and the low incorporation in other samples argues against simple exchange reactions, since in all cases the same amount of tissue was incubated with the labeled precursor under identical conditions. The distribution of tritium in the isolated DNA was examined by hydrolysis with 98% formic acid for 2 hours at 165° and chromatography of the bases in 2-propanol:HCl on S. and S. no. 589 filter paper. The chromatogram showed only one radioactive spot, coincident with an ultraviolet quenching spot, with R_f and spectrum of thymine.[9]

(7) L. I. Hecht and V. R. Potter, *Cancer Res.*, **16**, 988 (1956).

(8) L. I. Hecht and V. R. Potter, *Fed. Proc.*, **15**, 271 (1956).

(9) *Cf.* G. R. Wyatt in E. Chargaff and J. N. Davidson, "The Nucleic Acids," Vol. I, Academic Press, New York, N. Y., 1955, pp. 243–265.

(10) Postdoctoral Fellow of the National Cancer Institute. This investigation was also supported by a grant (No. C-646) from the National Cancer Institute, National Institutes of Health, Public Health Service.

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RECEIVED MAY 24, 1957

FORMATION OF L-XYLULOSE FROM L-GULONOLACTONE IN RAT KIDNEY

L-Xylulose, a sugar excreted by patients with essential pentosuria, is present normally in urine of man,[1] guinea pig[1] and rat.[2] Conversion of D-glucuronolactone to L-xylulose occurs in man[1,3] and guinea pig.[1] L-Gulonic acid, which is formed from D-glucuronolactone in the rat and guinea pig,[4] has been postulated to be an intermediate in this reaction.[1] This communication reports the presence of an enzyme system in rat kidney which catalyzes the formation of L-xylulose from L-gulonolactone. It has been shown previously that L-gulonolactone is converted to L-ascorbic acid in rats.[5–7]

Carboxyl labeled and uniformly labeled L-gulonolactone[8] were incubated with the soluble fraction of rat kidney (Table I).[9] Carboxyl labeled L-gulonolactone yielded 30 to 60% of the added C^{14} in CO_2.[10] Uniformly labeled L-gulonolactone yielded about one-sixth the amount of C^{14} in CO_2.

TABLE I

DECARBOXYLATION OF L-GULONOLACTONE IN RAT KIDNEY

Expt.	% of added C^{14} found in CO_2[a] Carboxyl labeled L-gulonolactone	Uniformly labeled L-gulonolactone
1	30	4.9
2	51	7.8
3	..	4.6
4	..	7.6
5	60	..
6	35	..

[a] 2.0 mg. of either carboxyl labeled L-gulonolactone (0.05 μc./mg.) or uniformly labeled L-gulonolactone (0.20 μc./mg.) was incubated under air at 37° for 90 minutes in 6.0 ml. of a high speed supernate fraction (100,000 × *g*) equivalent to 600 mg. of tissue, *p*H 7.0, 0.1 *M* phosphate buffer. Cofactor additions were the same as used by Rabinowitz and Sall.[9] The methods used in preparation and assay of samples for C^{14} have been described.[5]

(1) O. Touster, R. M. Hutcheson and L. Rice, *J. Biol. Chem.*, **215**, 677 (1955).

(2) S. Futterman and J. H. Roe, *ibid.*, **215**, 257 (1955).

(3) M. Enklewitz and M. Lasker, *ibid.*, **110**, 443 (1935).

(4) J. J. Burns, THIS JOURNAL, **79**, 1257 (1957).

(5) J. J. Burns and C. Evans, *J. Biol. Chem.*, **223**, 897 (1956).

(6) M. ul Hassan and A. L. Lehninger, *ibid.*, **223**, 123 (1956).

(7) J. J. Burns, P. Peyser and A. Moltz, *Science*, **124**, 1148 (1956).

(8) The authors are grateful to Dr. Peter Dayton for carrying out the syntheses of these labeled compounds.

(9) This system is similar to that described for decarboxylation of D-glucuronolactone, J. L. Rabinowitz and T. Sall, *Biochim. Biophys. Acta*, **23**, 289 (1957).

(10) Parallel experiments with carboxyl labeled L-gulonic acid show that this compound is oxidized similarly to CO_2.

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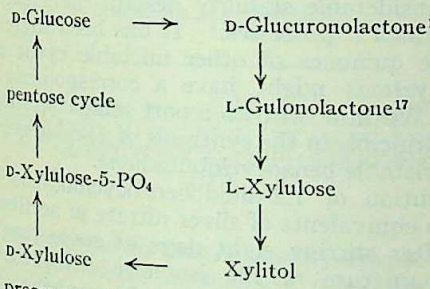
These results indicate that L-gulonolactone is decarboxylated in this system.

Evidence was found for the conversion of at least 15% of the uniformly labeled L-gulonolactone to labeled L-xylulose as follows:[11] 400 mg. of carrier L-xylulose[12] was added to the trichloroacetic acid extract of the incubation mixture and the solution was passed through an Amberlite IR-4B (acetate) column. L-Xylulose, in the effluent, was converted to L-ascorbic acid by the procedure described previously.[13] In brief, this method involved oxidizing L-xylulose to L-xylosone which was converted to imino-L-ascorbic acid by cyanide addition. After hydrolysis, the resulting L-ascorbic acid was purified by ion-exchange chromatography and converted to its 2,4-dinitrophenylosazone derivative which was recrystallized to constant specific activity.[5,14] This procedure does not distinguish between L-xylulose and L-xylose since both isomers are oxidized to L-xylosone. However, identification of the labeled pentose as L-xylulose was established and it was quantitatively determined by the cysteine-carbazole method[15] and a specific enzyme assay.[16]

Finding that L-gulonolactone is converted to L-xylulose suggests the following cyclic pathway for glucose metabolism in animals



The presence of enzyme systems in mammalian tissues for all these steps has been reported by others,[6,18–24] except the conversion of L-gulonolactone to L-xylulose. Evidence for occurrence *in vivo* of such an alternate pathway of glucose metabolism in animals will be presented elsewhere.

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RECEIVED APRIL 27, 1957

(11) A carrier dilution procedure[5] showed less than 0.2% of the added C^{14} present as L-ascorbic acid at the end of incubation.

(12) Carrier L-xylulose was kindly furnished by Dr. Gilbert Ashwell. In some experiments L-xylose was used as carrier instead of L-xylulose.

(13) L. L. Salomon, J. J. Burns and C. G. King, THIS JOURNAL, **74**, 5161 (1952).

(14) Repeated recrystallization of the 2,4-dinitrophenylosazone removes any labeled D-ascorbic acid osazone originating from D-xylulose. This was shown in control experiments with samples of osazone prepared from non-radioactive L-ascorbic acid which contained a trace amount of D-ascorbic acid-1-C^{14}; P. G. Dayton and J. J. Burns, to be published.

(15) Z. Dische and E. Borenfreund, *J. Biol. Chem.*, **192**, 583 (1951).

(16) L-Xylulose was determined by measuring the decrease in absorption of reduced triphosphopyridine nucleotide at 340 mμ in the presence of a purified xylitol dehydrogenase prepared from guinea pig liver. The authors are grateful to Dr. Gilbert Ashwell for carrying out the enzymatic and colorimetric assays for L-xylulose.

(17) It is not known at present whether the lactone or acid form of each compound is the intermediate in this scheme.

(18) J. L. Strominger, H. M. Kalckar, J. Axelrod and E. S. Maxwell, THIS JOURNAL, **76**, 6411 (1954).

(19) O. Touster, V. H. Reynolds and R. M. Hutcheson, *J. Biol. Chem.*, **221**, 697 (1956).

(20) S. Hollmann and O. Touster, THIS JOURNAL, **78**, 3544 (1956).

(21) S. Hollmann and O. Touster, *J. Biol. Chem.*, **225**, 87 (1957).

(22) J. Hickman and G. Ashwell, THIS JOURNAL, **78**, 6209 (1956).

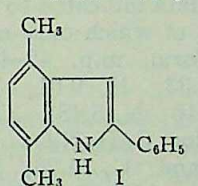
(23) B. L. Horecker, J. Hurwitz and P. Z. Smyrniotis, *ibid.*, **78**, 692 (1956).

(24) P. A. Srere, J. R. Cooper, V. Klybas and E. Racker, *Arch. Biochem. Biophys.*, **59**, 535 (1955).

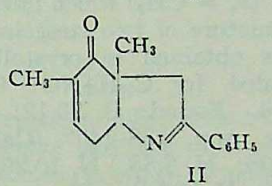
EVIDENCE FOR A HIGH ENERGY INTERMEDIATE IN THE FISCHER INDOLE SYNTHESIS. A NEW CLASS OF HYDROINDOLES

Sir:

When acetophenone 2,6-dimethylphenylhydrazone was heated at 130° in nitrobenzene solution with anhydrous zinc chloride for one hour, five products were isolated, among which 2-phenyl-4,7-dimethylindole (I), 4% yield, and 3a,4,7,7a-tetrahydro-2-phenyl-3a,5-dimethyl(3H)pseudoindolone-4 (II), 33% yield, were the most significant.



I



II

The structure of I, m.p. 65.5–66.5°, (calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.38; N, 6.33. Found: C, 86.69; H, 7.17; N, 6.24) was established by its independent synthesis from acetophenone 2,5-dimethylphenylhydrazone. The structure of II was proven by degrading it to 2-(β-phenylethyl)-2,6-dimethylcyclohexanone (VI), b.p. 143° (1–2 mm.), $n^{20}D$ 1.5205, (Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.20; H, 9.66. Oxime, m.p. 115–116°, calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.51; H, 9.28; N, 5.64) which was synthesized by treating 2,6-dimethylcyclohexanone with sodamide and then with β-phenylethyl bromide. The infrared spectra of the two samples of VI were identical, and their oximes had the same m.p. and gave no mixed m.p. depression.

Crystalline II, m.p. 92–101°, was obtained as a hemihydrate (Calcd. for $C_{16}H_{17}NO \cdot {}^1/_2H_2O$: C, 77.39; H, 7.31; N, 5.64. Found: C, 77.46; H, 7.31; N, 5.68.), but the oxime, m.p. 230° (dec.), (Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.42; H, 7.25; N, 11.20), picrate, m.p. 224° (dec.), (Calcd. for $C_{22}H_{20}N_4O_8$: C, 56.41; H, 4.30: N, 11.96. Found: C, 56.19; H, 4.02; N, 12.20.), and hydrochloride, m.p. 214° (dec.) (Calcd. for $C_{16}H_{17}NO \cdot HCl$: C, 69.68; H, 6.58; N, 5.08. Found: C, 69.74; H, 6.49; N, 5.16) all crystallized without bound water. The infrared spectrum ($CHCl_3$) of II featured bands at 2.72 μ (water), 6.02 μ (conj. C=O); 6.22 μ (conj. C=N, conj. phenyl) which split into two bands at

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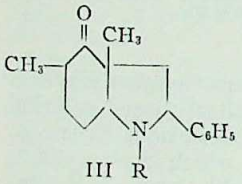
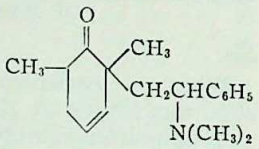
6.12 μ and 6.24 μ in acid solution. The ultraviolet absorption spectrum in ethanol showed a major band at 242 mμ (ϵ, 21,500) which split into two bands in acid solution (λ_1 242 mμ; ϵ_1 10,500; λ_2 273 mμ; ϵ_2, 16,500). Both the infrared and the ultraviolet spectra are characteristic of the conjugated carbonyl and conjugated imine chromophores.[1]

Hydrogenation of II over Adams catalyst in acetic acid afforded stereoisomeric forms of III (R = H), m.p. 56.5–58° and 92.5–93.5° (Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.01 and 78.94, resp.; H, 8.80 and 8.86, resp.; N, 5.67 and 5.60, resp.). Oximes, m.p. 162–164° and 177–179°, resp. (Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.44 and 74.32, resp.; H, 8.40 and 8.39, resp.; N, 10.74 and 10.83, resp.)

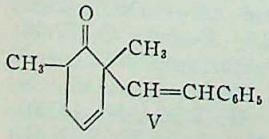


III R

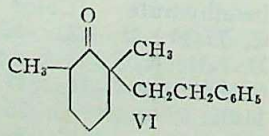


IV

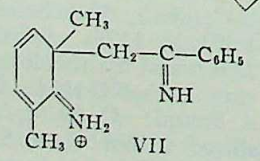
Formaldehyde and formic acid converted either stereoisomeric form of III (R = H) to the same III (R = CH_3) which infrared data indicated to be a mixture of two stereoisomers of which only one was obtained in crystalline form, m.p. 42–44° (Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.12; H, 9.16; N, 5.48). Oxime, m.p. 138–140° (Calcd. for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.29. Found: C, 75.26; H, 8.89; N, 10.18). The methiodide of III (R = CH_3) (Calcd. for $C_{18}H_{26}NOI$: C, 54.14; H, 6.56; N, 3.51. Found: C, 54.27; H, 6.65; N, 3.61) was converted to the methohydroxide by passage of its water solution through a column of the hydroxide form of Amberlite IRA-400. Heating the methohydroxide at 120° (1μ) afforded IV (methiodide, m.p. 158–213° (dec.), Calcd. for $C_{19}H_{28}NOI$: C, 55.21; H, 6.83; N, 3.39. Found: C, 55.33; H, 7.18; N, 3.26). Action of 30% hydrogen peroxide on IV gave the amine oxide (picrate, m.p. 133–134.5°, Calcd. for $C_{24}H_{28}N_4O_9$: C, 55.81; H, 5.46; N, 10.85. Found: C, 56.13; H, 5.56; N, 10.95) which decomposed[2] at 100° (15–20 mm.) to V, not obtained analytically pure, (Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 83.60; H, 7.71). Hydrogenation of V in absolute methanol over Adams catalyst yielded VI.



V



VI



VII

(1) B. Witkop, *Experientia*, **10**, 420 (1954).

(2) A. C. Cope, T. T. Foster and P. H. Towle, THIS JOURNAL, **71**, 3929 (1949).

The formation of both I and II can be rationalized in terms of a single intermediate VII, an analog of the kind of intermediate shown to take part in the *para* Claisen rearrangement[3] and also an analog of intermediates postulated in the Fischer reactions of acetophenone 2,6-dihalogenphenylhydrazones.[4] A more complete account of the degradation of II to VI, with the properties of this new group of hydroindole derivatives, and a mechanism to account for the formation of I and II through VII will be forthcoming.

(3) H. Conroy and R. A. Firestone, *ibid.*, **78**, 2290 (1956); D. Y. Curtin and H. W. Johnson, *ibid.*, **78**, 2611 (1956).

(4) R. B. Carlin and G. W. Larson, *ibid.*, **79**, 934 (1957).

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RECEIVED JUNE 10, 1957

BENZOCYCLOBUTADIENOQUINONE

Sir:

Although no stable cyclobutadiene has yet been found, the monophenyl derivative of cyclobutadienoquinone has been prepared and appears to have considerable stability despite the great ring strain which it possesses.[1] It has been suggested[1] that the quinones of other unstable cyclic polyolefin systems might have a corresponding stability. We now wish to report some confirmation of this principle in the synthesis of a stable quinone of the unstable benzocyclobutadiene.[2]

A solution of 1,2-diiodobenzocyclobutene[2a] (I) and two equivalents of silver nitrate in acetonitrile gave, after stirring eight days at room temperature, a mixture of the isomeric *cis*-benzocyclobutene-1,2-diol dinitrate (II) and *trans*-benzocyclobutene-1,2-diol dinitrate (III), separable by crystallization from methanol. Isomer A:[3] m.p. 110°. *Anal.* Calcd. for $C_8H_6N_2O_6$: C, 42.48; H, 2.67; N, 12.39. Found: C, 42.50; H, 2.59; N, 12.42. Isomer B:[3] m.p. 55.5–56.5°. *Anal.* Found: C, 42.24; H, 2.88; N, 12.29. Either isomer, when refluxed one hour with 1:1 methylene chloride–triethylamine gave, in 75% yield, the pale yellow 1,2-diketobenzocyclobutene, or benzocyclobutadienoquinone (IV), m.p. 132.5°. *Anal.* Calcd. for $C_8H_4O_2$: C, 72.73; H, 3.05. Found: C, 72.77; H, 3.08; λ_{max}^{EtOH} 271 mμ (log E = 3.45), 277 mμ (log E = 3.83). In the infrared (CS_2 solution), the strained carbonyls absorbed as a doublet at 5.51 and 5.61 μ.

The quinone IV was quite stable thermally and sublimed unchanged at 100° (0.2 mm. pressure). It reacted rapidly with *o*-phenylenediamine (V) to give the first known heterocyclic biphenylene analog, 1,4-diaza-benzo[b]biphenylene (VI), m.p. 238–239°. *Anal.* Calcd. for $C_{14}H_8N_2$: C, 82.33; H, 3.95; N, 13.72. Found: C, 82.21; H, 3.84; N, 13.83.

(1) E. J. Smutney and J. D. Roberts, THIS JOURNAL, **77**, 3420 (1955).

(2) (a) M. P. Cava and D. R. Napier, *ibid.*, **79**, 1701 (1957); (b) M. P. Cava and J. F. Stucker, *ibid.*, **79**, 1706 (1957).

(3) The configurations of isomers A and B remain unassigned as yet.

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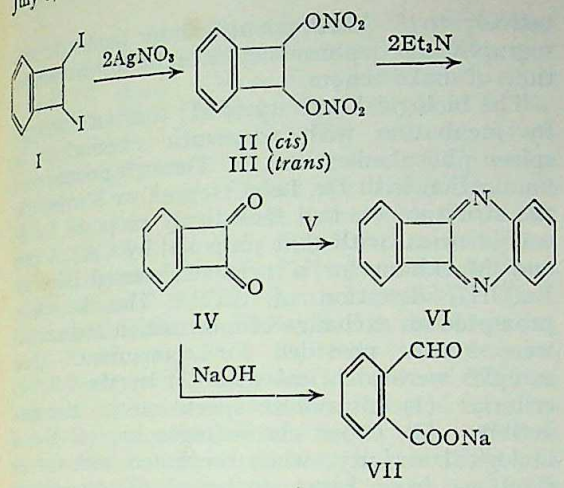

The quinone IV was oxidized rapidly and quantitatively by peracetic acid to phthalic acid.

A dilute solution of IV in 5% aqueous methanolic sodium hydroxide was decolorized completely after five hours at 25°, the sodium salt of phthalaldehydic acid (VII) being produced in 94% yield.

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Received May 25, 1957

THE FORMATION OF A CYCLIC DIANHYDRODIADENYLIC ACID (I) BY THE ALKALINE DEGRADATION OF ADENOSINE-5′-TRIPHOSPHORIC ACID (II)[1]

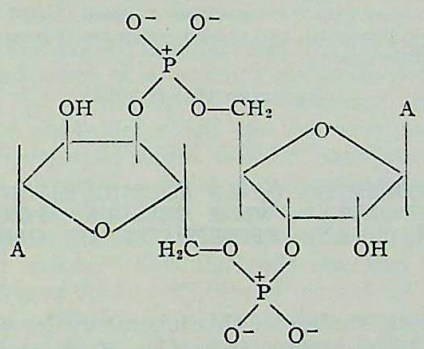
Sir:

It has been shown that barium hydroxide hydrolysis of (II) yields adenosine-5′-phosphoric acid (III) and inorganic pyrophosphate.[2] Hock and Huber[3] recently demonstrated that at least one other product is formed in this reaction.

Experiments in this laboratory show that the degradation of (II) by barium hydroxide is complex and that a number of previously unreported products are formed. One of these (I) exhibits sufficiently unexpected properties to merit description, particularly since it appears to be identical with a recently isolated, naturally-occurring compound.[4] In the preparation of (I), 250 mg. of (II)[5] and 3 ml. of 0.4 *N* barium hydroxide were heated for 30 min. at 100° and then the barium ion was precipitated. The solution was chromatographed on paper using 70% 2-propanol-ammonia as the developing solvent.[6] The fastest-moving substance is adenosine and this is closely followed by (I) (yield *ca.* 5–10%[7]).

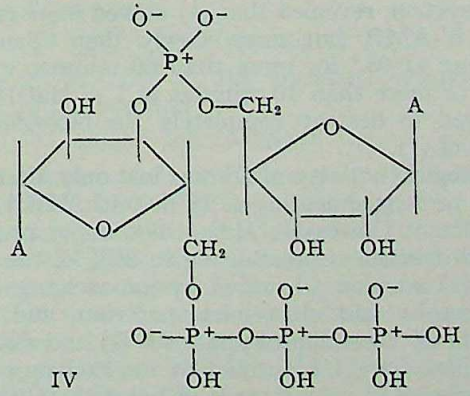
The new compound (I) has the following properties: (1) the molar ratio of adenine:phosphorus is unity; (2) adenosine is slowly formed from it by the action of *Crotalus adamanteus* venom; (3) it is not attacked by prostate phosphomonoesterase; (4) it is not oxidized by periodate; (5) it is deaminated by nitrite to the inosine analog, which also has been prepared from inosine-5′-triphosphoric acid; (6) its electrophoretic mobility on paper[8] relative to (III) is 1.2 at *p*H 3.5 (formate), 0.57 at *p*H 7.2 (phosphate) and 0.49 at *p*H 9.2 (borate); and (7) it is eluted from a Dowex-2 formate column by ammonium formate (*p*H 5.0) after all four known adenine-containing monoribonucleotides and just prior to adenosine-5′-pyrophosphoric acid.

A structural formula for (I) which is in accord with the above data is (A = adenine-9 residue)



There is no evidence at present to indicate that the phosphate ester bonds involve only the 3′, in addition to the 5′, carbon atoms. A study of models indicates, however, that this is the most likely phosphate diester structure and explains the surprising stability of (I) toward alkali. The positions of the phosphorus atoms in (I) are such that the formation of a 2′,3′ cyclic phosphate ester is hindered. The compound also is exceptionally stable toward acid hydrolysis.

The formation of (I) may take place by one of two paths. Two molecules of (II) suitably oriented may react simultaneously at two sites to give (I) directly, or (IV)



and inorganic pyrophosphate may form followed by intramolecular cyclization to give (I). Alternatively, (IV) could yield equivalent amounts of adenosine and 3′(or 2′)-phosphoadenosine-5′-phosphoric acids. The latter, which we have tenta-

(1) This research was supported in part by the U. S. Atomic Energy Commission.

(2) K. Lohmann, *Biochem. Z.*, **233**, 460 (1931); S. E. Kerr, *J. Biol. Chem.*, **139**, 131 (1941).

(3) A. Hock and G. Huber, *Biochem. Z.*, **328**, 44 (1956).

(4) E. W. Sutherland and T. W. Rall, This Journal, **79**, 3608 (1957).

(5) We wish to thank Pabst Laboratories for the gift of a generous sample of (II).

(6) R. Markham and J. D. Smith, *Biochem. J.*, **52**, 552 (1952).

(7) Low yields of (I) also are obtained by the action of barium hydroxide on adenosine-5′-pyrophosphoric acid or by trifluoroacetic anhydride on (III).

(8) R. Markham in K. Paech and M. V. Tracey, "Modern Methods of Plant Analysis," Springer-Verlag, Berlin, 1955, Vol. IV, p. 278.

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tively identified in our hydrolyzates, may be the product NF observed by Hock and Huber.

It is interesting to note that the reactions leading to the formation of (I) are similar in character to two of the enzymatic reactions involved in polynucleotide synthesis.[9,10]

Recently Khorana, *et al.*,[11] described a thymidine derivative analogous to (I) which they prepared by an entirely different procedure.

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DAVID LIPKIN
ROY MARKHAM[12]

(9) M. Grunberg-Manago and S. Ochoa, THIS JOURNAL, **77**, 3165 (1955).

(10) A. Kornberg, I. R. Lehman, M. J. Bessman and E. S. Simms, *Biochim. Biophys. Acta*, **21**, 197 (1956).

(11) H. G. Khorana, *et al.*, THIS JOURNAL, **79**, 1002 (1957).

(12) On leave from the Agricultural Research Council Virus Research Unit, Cambridge, and wishes to thank the Wellcome Foundation for a travel grant.

RECEIVED MAY 6, 1957

THE PROPERTIES OF AN ADENINE RIBONUCLEOTIDE PRODUCED WITH CELLULAR PARTICLES, ATP, Mg^{++}, AND EPINEPHRINE OR GLUCAGON

Sir:

Previous studies in this laboratory have shown that a heat-stable factor (formed by particulate fractions of liver homogenates in the presence of ATP, Mg^{++}, and epinephrine or glucagon) stimulated the formation of phosphorylase in supernatant fractions of homogenates.[1] This factor was isolated by ion-exchange chromatography and proved to be an adenine ribonucleotide (I).[1] Similar or identical compounds have been isolated from heart, skeletal muscle and brain. Crystals formed when 2×10^{-2} *M* aqueous solutions of (I) were chilled at acid *p*H. (I) was not attacked by several monoesterases[1] and upon titration with alkali exhibited no buffering capacity between *p*H 5 and *p*H 8. Descending paper chromatography, using an ethanol–ammonium citrate (*p*H 4.4) solvent system, revealed that (I) moved more rapidly than 5′-AMP, but more slowly than adenosine. Heating at 98° for more than 60 minutes in 1 *N* HCl, or more than 40 minutes in 1 *N* NaOH, was required to destroy completely the biological activity of (I).

Biological activity of (I) was lost only after relatively prolonged heating at 98° in 0.05 *N* HCl in the presence of Dowex-50 (H^+). The major products of such treatment, amounting to 85% of the total, were (1) adenine, identified by ion-exchange chromatography and ultraviolet spectrum, and (2) a mixture of ribose-3-phosphate (60%) and ribose-2-phosphate (40%), identified by ion-exchange chromatography in the presence of borate.[2] However, the biological activity of (I) was lost rapidly on incubation with crude or fractionated extracts of heart or brain. In the presence of a partially purified enzyme from heart, (I) was converted quantitatively to 5′-AMP, identified by paper chromatography and dephosphorylation by low concentrations of snake venom.

The biological activity of (I) was not destroyed by incubation with pancreatic ribonuclease or spleen phosphodiesterase.[3] Through private communication with Dr. Leon Heppel, we learned that the structure we had tentatively proposed for (I) was identical with that proposed by Cook, Lipkin and Markham for a product isolated from the $Ba(OH)_2$ digestion of ATP.[4] This knowledge prompted an exchange of information and samples were kindly provided for comparison.[5] These samples were identical with (I) by the following criteria: (1) ultraviolet spectrum, (2) biological activity, (3) paper chromatography, (4) loss of biological activity, when incubated with enzyme fractions from heart or brain, (5) quantitative conversion to 5′-AMP on incubation with a partially purified enzyme from heart, and (6) conversion to adenosine on prolonged incubation with large amounts of *Crotalus adamanteus* venom (although, as reported,[1] moderate amounts of Russell's viper venom did not attack (I)).[6]

(1) T. W. Rall, E. W. Sutherland and J. Berthet, *J. Biol. Chem.*, **224**, 463 (1957).

(2) J. X. Khym and W. E. Cohn, THIS JOURNAL, **75**, 1158 (1953).

(3) We thank Dr. Leon Heppel of the National Institutes of Health, Bethesda, Maryland, for supplying a sample of purified spleen phosphodiesterase, and for the information regarding the similarity of (I) with the compound reported in the accompanying paper by W. H. Cook, D. Lipkin and R. Markham.

(4) W. H. Cook, D. Lipkin and R. Markham, THIS JOURNAL, **79**, 3607 (1957).

(5) We thank Dr. Roy Markham for sending these samples and for furnishing a sample of *Crotalus adamanteus* venom.

(6) This investigation was supported (in part) by a research grant No. H-2745 from the National Heart Institute of the Public Health Service.

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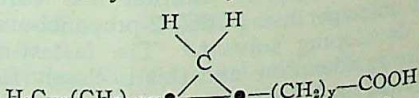
T. W. RALL

RECEIVED MAY 13, 1957

UNEQUIVOCAL SYNTHESES OF DL-*cis*-9,10-METHYLENEOCTADECANOIC ACID (DIHYDROSTERCULIC ACID) AND DL-*cis*-11,12-METHYLENEOCTADECANOIC ACID[1]

Sir:

The recent interest regarding the structure of sterculic acid[2-7] prompts us to record at this time an unequivocal synthesis of DL-*cis*-9,10-methyleneoctadecanoic acid (I) and the demonstration of its complete identity with dihydrosterculic acid.[2,8]



(I) x and $y = 7$; (VI) $x = 5$; $y = 9$

(1) Supported by grants from the American Cancer Society, recommended by the Committee on Growth of the National Research Council, and by the U. S. Public Health Service.

(2) J. R. Nunn, *J. Chem. Soc.*, 313 (1952).

(3) J. P. Verma, B. Nath and J. S. Aggarwal, *Nature*, **175**, 84 (1955).

(4) P. K. Faure and J. C. Smith, *J. Chem. Soc.*, 1818 (1956).

(5) D. G. Brooke and J. C. Smith, *Chem. and Ind.*, 49 (1957).

(6) B. A. Lewis and R. A. Raphael, *ibid.*, 50 (1957).

(7) V. V. Narayanan and B. C. L. Weedon, *ibid.*, 394 (1957).

(8) K. Hofmann, O. Jucker, W. R. Miller, A. C. Young, Jr., and F. Stussi, THIS JOURNAL, **76**, 1799 (1954).

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The addition of dibromocarbene to 1,4-cyclohexadiene[9] afforded 7,7-dibromonorcar-3-ene (II), m.p. 36.8–37.0°; *Anal.* Calcd. for $C_7H_8Br_2$: C, 33.5; H, 3.2; Br, 63.3. Found: C, 33.0; H, 3.5; Br, 63.0. Oxidation converted (II) into *cis*-3,3-dibromocyclopropane-1,2-diacetic acid (III), m.p. 179.4–181.2°; *Anal.* Calcd. for $C_7H_8O_4Br_2$: C, 26.8; H, 2.5; Br, 50.5; neut. equiv., 158. Found: C, 26.5; H, 2.2; Br, 50.5; neut. equiv., 159. Hydrogenolysis of (III) gave *cis*-cyclopropane-1,2-diacetic acid (IV), m.p. 131–133°; *Anal.* Calcd. for $C_7H_{10}O_4$: C, 53.3; H, 6.4; neut. equiv., 79.4. Found: C, 53.0; H, 6.2; neut. equiv., 79.6. The monomethyl ester chloride of (IV) on treatment with *n*-hexylcadmium followed by alkaline hydrolysis afforded DL-*cis*-6-keto-3,4-methylene-dodecanoic acid which was reduced[10] to DL-*cis*-3,4-methylenedodecanoic acid (V), b.p. 153–154° at 3 mm.; *Anal.* Calcd. for $C_{13}H_{24}O_2$: C, 73.7; H, 11.4; neut. equiv., 213. Found: C, 73.6; H, 11.3; neut. equiv., 208. Conversion of (V) into DL-*cis*-9,10-methyleneoctadecanoic acid (I) was effected by procedures previously described,[8,11] m.p. 38.6–39.6°; *Anal.* Calcd. for $C_{19}H_{36}O_2$: C, 77.0; H, 12.2; neut. equiv., 296. Found: C, 77.0; H, 12.2; neut. equiv., 298. Amide, m.p. 86.4–87.6°; *Anal.* Calcd. for $C_{19}H_{37}ON$: C, 77.2; H, 12.6; N, 4.7. Found: C, 77.0; H, 12.3; N, 5.0. Mixed melting point determinations and comparison of the infrared absorption spectra and X-ray diffraction patterns of (I) and dihydrosterculic acid demonstrated the complete identity of these compounds. The X-ray diffraction patterns of the amide of (I) and of dihydrosterculamide were identical also, and admixture of the amides did not result in a depression of the melting point. These findings establish the structure of dihydrosterculic acid.[12]

In connection with studies on the structure of lactobacillic acid, we have converted *cis*-cyclopropane-1,2-diacetic acid (IV) into DL-*cis*-11,12-methylene-octadecanoic acid (VI), m.p. 31.0–33.6°; Found: C, 76.5; H, 12.0; neut. equiv., 294. Amide, m.p. 84.0–85.2°; Found: C, 77.0; H, 12.6; N, 4.8. Although exhibiting an identical infrared absorption spectrum, the synthetic specimen differed from lactobacillic acid in melting point and X-ray diffraction pattern. The non-identity of lactobacillic acid (which has been shown to represent one of the stereoisomeric forms of 11,12-methyleneoctadecanoic acid[13]) with either *cis*- or *trans*-DL-11,12-methyleneoctadecanoic acids demonstrates clearly that lactobacillic acid must be a distinct optical isomer. Synthetic DL-*cis*-11,12-methyleneoctadecanoic acid exhibits approximately one-half the growth promoting activity of natural lactobacillic acid for *Lactobacillus delbrueckii*. DL-*trans*-11,12-Methyleneoctadecanoic acid fails to support growth of this organism under identical experimental conditions.[14] These observations point to either D- or L-*cis*-11,12-methyleneoctadecanoic acid as the structure for lactobacillic acid.

(9) W. von E. Doering and A. K. Hoffmann, THIS JOURNAL, **76**, 6162 (1954).

(10) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(11) S. Stallberg-Stenhagen, *Archiv Kemi Mineral. Geol.*, **A22**, No. 19, 1 (1946).

(12) We wish to express our sincere appreciation to Professor G. A. Jeffrey, Department of Chemistry, University of Pittsburgh, for the X-ray studies. Details of this work will be presented in THIS JOURNAL.

(13) G. J. Marco and K. Hofmann, *Federation Proc.*, **15**, 308 (1956).

(14) K. Hofmann and C. Panos, *J. Biol. Chem.*, **210**, 687 (1954).

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SALVADOR F. OROCHENA
CLAYTON W. YOHO

RECEIVED MAY 16, 1957

OXIDATIONS AT MERCURY HALIDE ANODES

Sir:

It is well known in polarography that the anodic potential range of a mercury electrode is severely limited by oxidation of the mercury itself. A mercury electrode which can be used at highly anodic potentials might well be considered a significant advance in polarographic practice. Such an electrode has been developed as a result of chronopotentiometric studies at a mercury pool in chloride media. This electrode operates through formation of an "inert" film of mercurous chloride prior to oxidation of electroactive species in the bulk of solution. This phenomena has not been observed previously since conventional polarography at the dropping mercury electrode does not allow sufficient time for the proper film formation.

The theory of chronopotentiometry has been thoroughly reviewed by Delahay.[1] The equipment used in the present study was conventional in all respects. The background electrolyte was a solution 0.3 M in potassium chloride and 2×10^{-3} M in hydrochloric acid (pH 2.7). The anodic chronopotentiogram of this solution (Hg pool area 1.47 cm.^{2}, current 350 microamperes) shows four small waves at *ca.* +0.07, 0.5, 0.8, and 1.2 v. *vs.* S.C.E. The first wave is due to formation of mercurous chloride. The variation of $E_{1/4}$ for this wave follows closely

$$E_{Hg} = E^0 - 0.059 \log [Cl^-]/2$$

where $E^0 = 0.022$ v., the standard potential vs. S.C.E. of the reaction

$$2Hg^0 + 2Cl^- = Hg_2Cl_2 + 2e^-$$

Further interpretation of these potential–time patterns will be reported in the near future.

The chronopotentiogram of a 2×10^{-3} M solution of N,N′-dimethyl-p-phenylenediamine (DPP) in the same background electrolyte shows an identical first wave for mercurous chloride formation. It is followed by a clearly defined wave for the oxidation of DPP. The $E_{1/4}$ of DPP (*ca.* +0.4 v.) wave is identical with that obtained at a platinum electrode under the same pH conditions. A plot of $\tau^{1/2}$ *vs.* concentration shows excellent linearity between 4×10^{-4} to 3×10^{-3} M DPP.

The anodic oxidations of aniline, *o*-phenylenediamine and hydroquinone, which take place at

(1) P. Delahay, "New Instrumental Methods in Electrochemistry," Interscience Publishers, Inc., New York, N. Y., 1954.

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considerably more positive potentials, also have been studied. Again, plots of $\tau^{1/2}$ *vs.* concentration show the expected linearity for a chronopotentiometric reaction which is proceeding independent of any previous electrode process. Oxidation reactions with potentials as high as +1.0 v. appear possible with the mercury chloride electrode.

The electrode can also be operated in a more conventional polarographic sense. The halide film is formed by application of an anodic potential for a short period of time. The compound to be oxidized is then introduced and the voltage scanned in an increasing anodic direction using a Leeds and Northrup Electrochemograph. With DPP and ferrocyanide, typical quiet pool polarograms[2] are obtained whose peak heights are proportional to concentration. Investigations are in progress to evaluate the effect of stirring and changing scan rate on peak currents as well as application of the technique to the hanging drop electrode.

A detailed report of this work will be published shortly.

(2) C. A. Streuli and W. D. Cooke, *Anal. Chem.*, **25**, 1691 (1953).

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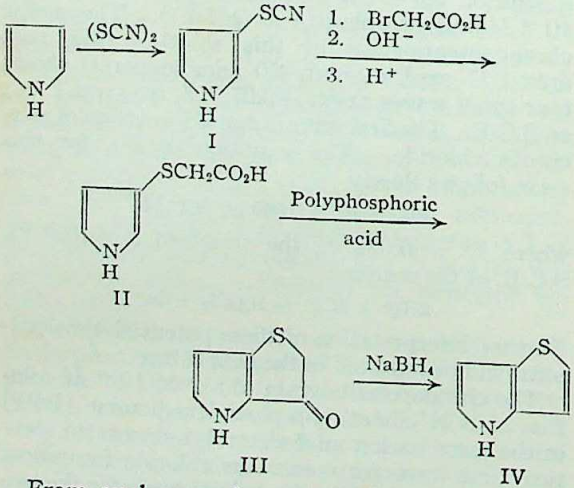
RECEIVED MAY 20, 1957

A PRACTICAL SYNTHESIS OF THIENO[3,2-*b*]PYRROLE

Sir:

We have synthesized thieno[3,2-*b*]pyrrole (IV) from pyrrole in four steps. The new synthesis makes this isostere of indole readily available for conversion to various derivatives of biological interest.



From analogous electrophilic substitutions and resonance theory,[1] thiocyanation of pyrrole was expected to occur preferentially at the 2-position. However, recent molecular orbital calculations[2] indicate that the orientation of substitution in the pyrrole nucleus cannot be predicted unambiguously; π-electron localization energy favors 2-substitution but π-electron densities favor 3-substitution. When the reaction was carried out by rapidly mixing cold (−75°) methanolic solutions of pyrrole and thiocyanogen (prepared at −60° from potassium thiocyanate and bromine), the product collected after pouring the reaction mixture onto ice and salt, and amounting to 50% yield after recrystallization from methylene chloride–methylcyclohexane, was 3-thiocyanopyrrole (I), m.p. 40–44°. *Anal.* Calcd. for $C_5H_4N_2S$: C, 48.36; H, 3.25; N, 22.55. Found: C, 48.72; H, 3.15; N, 22.80.

Treatment of a cold methanolic solution of I and bromoacetic acid with an excess of potassium hydroxide in aqueous methanol furnished in 90% yield (3-pyrrolylthio)-acetic acid (II), characterized as the ammonium salt which crystallized when anhydrous ammonia was introduced into a methylene chloride solution of the acid. The salt melted at 127–133° (dec.). *Anal.* Calcd. for $C_6H_{10}N_2O_2S$: C, 41.35; H, 5.78; N, 16.08. Found: C, 41.59; H, 5.73; N, 15.77. Addition of a dilute methylene chloride solution of II over 1 hr. to vigorously stirred polyphosphoric acid at 125°, followed by dilution of the mixture with water, extraction with ethyl acetate and sublimation of the product, yielded 36% of 2H,3H-thieno[3,2-*b*]-pyrrol-3-one (III), m.p. 183–188.5°. The analytical sample, m.p. 187–190°, was prepared by a series of recrystallizations and resublimations. *Anal.* Calcd. for C_6H_5NOS: C, 51.78; H, 3.62; N, 10.07. Found: C, 52.04; H, 3.82; N, 10.14. The infrared spectrum of III (Nujol) contained strong bands at 1635 (C=O) and 3150 cm.$^{-1}$ (NH). The structure of III was proved by desulfurization with Raney nickel catalyst to 2-acetylpyrrole, shown to be identical with an authentic sample[3] by infrared spectra (chloroform), m.p. and mixture m.p. Treatment of III with sodium borohydride in methanol yielded 62% of sublimed thieno[3,2-*b*]-pyrrole (IV), m.p., after further purification, 25–28°. *Anal.* Calcd. for C_6H_5NS: C, 58.50; H, 4.09; N, 11.38. Found: C, 58.60; H, 4.27; N, 11.32. The infrared spectrum of IV (smear) was identical with that[4] of a less pure sample prepared[5] unequivocally from thiophene, except for bands due to a carboxylic acid present as an impurity in the latter sample.

(1) R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 300–301.
(2) R. D. Brown, *Australian J. Chem.*, **8**, 100 (1955).
(3) (a) B. Oddo, *Ber.*, **43**, 1012 (1911); (b) structure proof of 2-acetylpyrrole, G. Ciamician and P. Silber, *ibid.*, **20**, 2594 (1887).
(4) J. F. Zack, Ph.D. Thesis, University of Illinois, 1956.
(5) H. R. Snyder, L. A. Carpino, J. F. Zack and J. F. Mills, THIS JOURNAL, **79**, 2556 (1957).
(6) National Science Foundation Predoctoral Fellow, 1954–1957.

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DONALD S. MATTESON[6]
H. R. SNYDER

RECEIVED MAY 6, 1957

STUDIES IN THE SYNTHESIS OF THE ANTIRACHITIC VITAMINS. IV. THE SYNTHESIS OF A BIOLOGICALLY ACTIVE VITAMIN D HOMOLOG

Sir:

We wish to report the synthesis of 1-cholestanyli-

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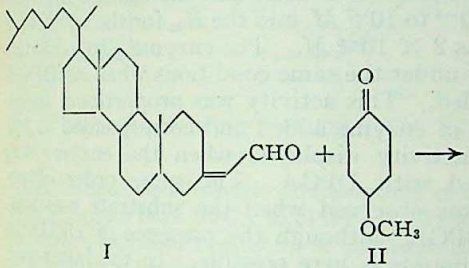
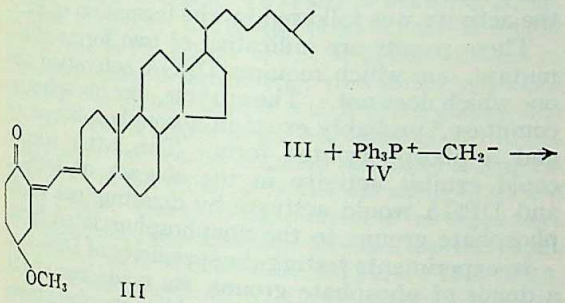
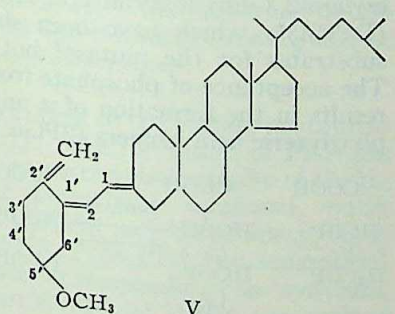
dene)-ethane (V), a homolog of vitamin D, which is biologically active. Following the scheme outlined in previous publication,[1] 7.54 g. of 2-cholestanylideneethan-1-al (I) [m.p. 114–115°. *Anal.* Calcd. for $C_{29}H_{48}O$: C, 84.39; H, 11.72. Found: C, 84.00; H, 11.82; ϵ (244.5 mμ), 30,250 (ethanol); $[\alpha]^{25}D$ −9.38° (chloroform)] was condensed in the dark with 4.7 g. of 4-methoxycyclohexanone (II) in a liter of *t*-butanol containing 4 g. of sodium hydroxide and 10 cc. of water. The mixture was stirred under nitrogen in the dark for 24 hr. A yellowish-brown amorphous product (7.4 g.) was isolated from this reaction and chromatographed in the dark using alumina (Act. III) from which was obtained two fractions: one



I II



III



V

the 2,1′-*trans*-dienone (10%), m.p. 221–224° (dec.). *Anal.* Calcd. for $C_{36}H_{58}O_2$: C, 82.70; H, 11.18. Found: C, 82.73; H, 11.33; ϵ (309 mμ), 30,600 (ethanol); infrared α,β-conjugated >C=O band at 1674 cm.$^{-1}$; $[\alpha]^{25}D$, +86.8° (chloroform). Semicarbazone, m.p. 220–222°. *Anal.* Calcd. for $C_{37}H_{62}N_3O_2$: C, 76.50; H, 10.76; N, 7.23. Found: C, 76.72; H, 10.95; N, 6.94. The other fraction was the 2,1′-*cis*-dienone (12%), m.p. 186°. *Anal.* Calcd. for $C_{36}H_{58}O_2$: C, 82.70; H, 11.18; |═, 2.00. Found: C, 82.71; H, 11.07; |═, 1.85 (Pd.); ϵ (307 mμ), 12,200 (ether); infrared α,β-conjugated >C=O band at 1675 cm.$^{-1}$; $[\alpha]^{25}D$, +40.3° (chloroform).

Reaction of the 2,1′-*cis*-dienone (III) with triphenylphosphinemethylene (IV) in a pressure bottle gave an amorphous solid (23%), m.p. 193° (dec.); ϵ (265 mμ), 20,200 (ether). This was further purified by chromatography in a nitrogen atmosphere and in the dark giving again an amorphous product which had the following analyses.[2] *Anal.* Calcd. for $C_{37}H_{60}O$: C, 85.34; H, 11.61. Found: C, 84.22; 11.55; $[\alpha]^{25}D$, −10.6°; ϵ (267 mμ), 31,300 (ether); principal infrared bands[3] for =CH_2: 3100R, 1641W, 892S cm.$^{-1}$. Principal infrared bands for =CH_2 of vitamin D_3: 3100R, 1645M, 892M cm^{-1}.

An exploratory biological test of this homolog was carried out by Professor Robert S. Harris of the Nutritional Biochemical Laboratories of M.I.T. and he reports that the group of rachitic rats which was fed this homolog showed nearly the same degree of healing as the group which was fed vitamin D_2 at approximately the same concentration. These preliminary results do make it possible to estimate exactly the potency of the 2,1′-*cis*-homolog (V) but indicate quite definitely that its activity may approach that of vitamin D_2.

The 2,1′-*trans*-homolog was also synthesized from the 2,1′-*trans*-dienone and had an ϵ (272 mμ), 34,700 (ether). The *trans*-homolog also was found to be biologically active but very much less so than the *cis*-homolog. Details of this work will be published elsewhere.

Acknowledgment.—The authors are indebted to Dr. Nagy and his associates for all the analyses, to Dr. Nelson and Miss Cassie for the infrared spectra, to Prof. Robert S. Harris for the biological results and to Research Corporation–Milas–M.I.T. Fund for financial support of this investigation.

(1) N. A. Milas, L. C. Chiang, C. P. Priesing, A. A. Hyatt and J. Peters, THIS JOURNAL, **77**, 4180 (1955).

(2) This substance is highly sensitive to air oxidation and in spite of extensive precautions the carbon was always low.

(3) R = shoulder, W = weak, S = strong, M = medium.

DEPARTMENT OF CHEMISTRY NICHOLAS A. MILAS
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RECEIVED JUNE 6, 1957

A NEW SYNTHESIS OF THE CHROMIUM HEXACARBONYL

Sir:

We wish to report a new synthesis of chromium hexacarbonyl starting from easily available chromium compounds which appear to have been converted now for the first time, into the hexacarbonyl.

At present the only well described method for this synthesis is the "Grignard method" discovered by Job and Cassal[1] and substantially improved by Owen and co-workers.[2] Recently Fischer and Hafner[3] synthesized the carbonyl starting from chromium bis-cyclopentadienyl (no yield reported). Both these valuable methods suffer from some disadvantages such as the unsatisfactory over-all yields,[4] or the requirement of a rather

(1) A. Job and A. Cassal, *Compt. rend.*, **183**, 392 (1926).

(2) B. B. Owen, J. English, Jr., H. G. Cassidy and C. Vanderbilt Dundon, THIS JOURNAL, **69**, 1723 (1947).

(3) E. O. Fischer and W. Hafner, *Z. Naturf.*, **10b**, 140 (1955).

(4) W. H. Cumming, J. A. Horn and P. O. Ritchie, *J. Appl. Chem.*,

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involved procedure for preparing the suitable starting material.

We have now observed[5] that chromic acetylacetonate, chromic and chromous salts of organic acids such as acetic and 2-ethylhexanoic can be reduced easily and converted into the hexacarbonyl under high pressure of carbon monoxide if pyridine or related bases are employed as a reaction medium.

Our method consists in dissolving (or suspending) any one of the above compounds in pyridine, containing catalytic amounts of halogens or halogenated substances. The mixture is then treated at 80–170° with an excess of powdered magnesium or zinc and 100–300 atm. of carbon monoxide. When soluble chromium compounds are employed the yields are as high as 80–90%.

We believe the base to play an essential role in the synthesis because intermediate pyridine-containing complexes are formed in the course of the reaction.

It is also noteworthy that the hexacarbonyl as such is still present in substantial quantities in the end-products of the reaction. This seems not to happen in the synthesis by the Grignard method, the hexacarbonyl, in this case, being produced uniquely after the hydrolysis of the reaction mixtures.[4]

Experimental.—Chromium acetylacetonate (17.5 g.), magnesium (4.5 g.) and 80 g. of a 2% solution of iodine in dry pyridine are charged in a stainless steel oscillating autoclave of 500-ml. capacity. After removal of air, oscillation is started and pure oxygen-free carbon monoxide is compressed into the vessel up to a pressure of 190 atm. The autoclave is then warmed to 160° within one hour and maintained at this temperature (± 2°) for six hours, while pressure drops from 325 to 285 atm. After cooling and venting, the hexacarbonyl and the other reaction products are quantitatively transferred into a 3-liter two-necked distillation flask with the aid of a large amount of water. On distillation of the mixture, the white hexacarbonyl is drained off. The distillate is filtered, washed with chilled methanol and paper dried. Sublimation of the powder at 70–75° at 15 mm. affords 9.0 g. of pure chromium hexacarbonyl in coarse crystals (yield 82%).

(5) Italian Patent Application No. 671, February 4, 1957 (to Montecatini S.p.A.).

DEPARTMENT OF INDUSTRIAL CHEMISTRY
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RECEIVED MAY 4, 1957

PHOSPHATE TRANSFER CATALYZED BY PHOSPHOGLYCERIC ACID MUTASE

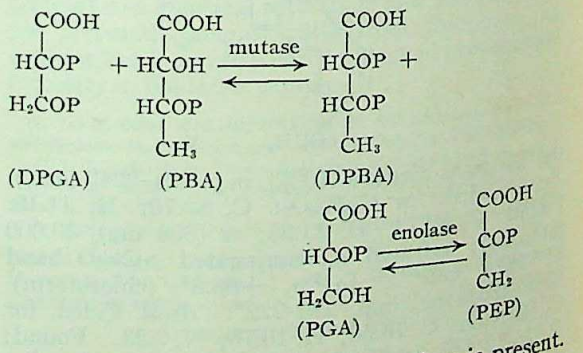
Sir:

The activation of partially purified muscle phosphoglyceric acid mutase by diphosphoglyceric acid (DPGA) was reported by Sutherland, *et al.*,[1] and we have undertaken the further study of this process with the crystalline enzyme, which was obtained from purified muscle enzyme[2] by employing the conditions found by Rodwell, *et al.*,[3] for the crystallization of the yeast mutase. In order to eliminate the possibility of DPGA contamination of the monophosphate substrate, synthetic phosphoenolpyruvate (PEP)[4] recrystallized as the cyclohexylamine salt[5] was used, and 2-phosphoglyceric acid (2PGA) was generated from it with crystalline enolase. Mutase activity was detected by its effect on the absorbance at 240 mμ of the equilibrated mixture, (PEP $\overset{\text{enolase}}{\rightleftharpoons}$ 2PGA $\overset{\text{mutase}}{\rightleftharpoons}$ 3PGA).

Synthetic DPGA[6] activated the mutase over the range 10^{-4} to 10^{-7} M, and the K_m for the conditions used was 2×10^{-6} M. The enzyme also exhibited activity under the same conditions when no DPGA was added. This activity was proportional to the amount of enzyme added and corresponded to 5% of the activity displayed when the enzyme was saturated with DPGA. The same order of activity was observed when the substrate was synthetic 3PGA,[7] although the presence of DPGA in trace amounts is here possible. In the latter case the activity was followed by the formation of PEP.

These results are indicative of two forms of the mutase, one which requires DPGA activation and one which does not. The enzyme, like phosphoglucomutase,[8] probably exists in a nonphosphorylated and a phosphorylated form. The latter species could exhibit activity in the absence of DPGA, and DPGA would activate by donating one of its phosphate groups to the nonphosphorylated form.

In experiments testing the specificity of DPGA as a donor of phosphate groups, we made use of the *erythro*-2,3-dihydroxybutyric acid monophosphates (DPBA)[9]; which have been shown to be active substrates for the mutase[2] but not for enolase.[5] The acceptance of phosphate from DPGA by PBA results in the formation of a mixture of the phosphoglyceric acid isomers (2PGA and 3PGA) which



are in part converted to PEP if enolase is present.

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(2) R. W. Cowgill and L. I. Pizer, *ibid.*, **223**, 885 (1956).

(3) V. W. Rodwell, J. C. Towne, and S. Grisolia, *Biochim. et Biophys. Acta*, **20**, 394 (1956).

(4) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **180**, 145 (1949).

(5) F. Wold and C. E. Ballou, *ibid.*, in press.

(6) E. Baer, *ibid.*, **185**, 673 (1950).

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(9) C. E. Ballou, THIS JOURNAL, **79**, 984 (1957).

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In this experiment the formation of PGA from DPGA occurs only in the presence of PBA (Fig. 1, lines Ia, b) to an extent dependent on DPGA concentration if PBA is in excess (Fig. 1, lines IIa, b),

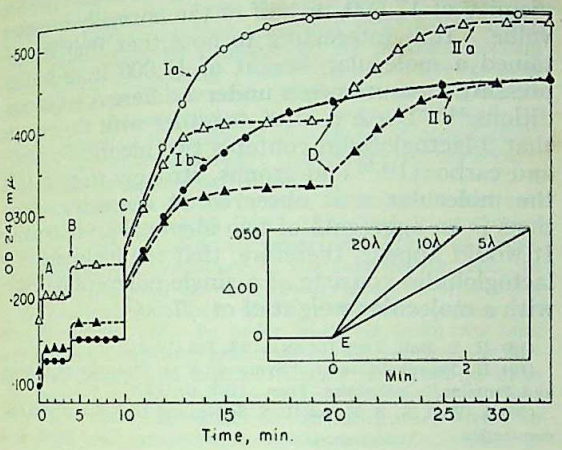

Fig. 1.—Spectrophotometric demonstration of the transfer of phosphate from DPGA to 2PBA and 3PBA: each 1 cm. cuvette contained 1 ml. of 0.1 *M* imidazole–HCl buffer, *p*H 7.0, 0.015 *M* in $MgCl_2$. To Ia and Ib was added 0.2 ml. of 0.015 *M* DPGA; to IIa was added 0.1 ml. of 0.15 *M* 2PBA; and to IIb, 0.1 ml. of 0.15 *M* 3PBA. At time A, enolase was added to each cuvette; then mutase was added at time B. At time C, 0.1 ml. of 0.15 *M* 2PBA was added to Ia, and 0.1 ml. of 0.15 *M* 3PBA was added to Ib. At the same time, 0.1 ml. of 0.015 *M* DPGA was added to both IIa and IIb. A further 0.1 ml. of DPGA was added to IIa and IIb at time D. Insert: Demonstration of the dependence of rate on mutase concentration. Cuvettes contain: 1 ml. of buffer, 0.1 ml. of 0.015 *M* DPGA, 0.1 ml. of 0.15 *M* 2PBA, 0.02 ml. of enolase and 1.76 ml. of H_2O. At E the quantities of mutase indicated on the curves were added and the 240 mμ adsorbance followed with the energy recording adaptor to the Beckman DU spectrophotometer.

and at a rate proportional to the mutase concentration, (Fig. 1, insert). The formation of PEP has been confirmed by paper chromatography of the reaction mixture in 2-propanol, ammonia, water (70:10:20). With the acid molybdate spray, spots corresponding to PEP, PGA-PBA (no separation) and a diphosphate corresponding to synthetic DPBA[10] are found. Synthetic DPBA can replace DPGA as a mutase activator, although ten times the concentration is required for comparable activity.

This series of reactions independently supports the conclusion[1] that DPGA donates one of its phosphate groups during its role in the enzymatic interconversion of the two monophosphoglyceric acid isomers. To show that DPGA donates directly to the enzyme would require the demonstration of phosphorus on the enzyme in equilibrium with the phosphorus on the substrate, but as the formation of a phosphate diester (between DPGA and PGA) as an intermediate in the phosphate transfer appears unlikely,[11] the series of reaction (a) and (b) satisfactorily explains the results.

(10) C. E. Ballou, unpublished.
(11) W. H. Harrison, P. D. Boyer and A. B. Falcone, *J. Biol. Chem.*, **218**, 303 (1955).

$$\text{(a)}\quad \text{DPGA} + \text{E} \rightleftharpoons \text{PE} + \text{PGA} \xrightleftharpoons{\text{enolase}} \text{PEP}$$

$$\text{(b)}\quad \text{PE} + \text{PBA} \rightleftharpoons \text{E} + \text{DPBA}$$

$$\text{(a)} + \text{(b)}\quad \text{DPGA} + \text{PBA} \rightleftharpoons \text{DPBA} + \text{PGA} + \text{PEP}$$

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Received June 4, 1957

THE MOLECULAR WEIGHT OF β-LACTOGLOBULIN

Sir:

The generally accepted molecular weight of β-lactoglobulin is in the vicinity of 35,000.[1,2,3,4] In the course of a detailed study of the association properties of this protein as a function of *p*H, it has been found that the weight of its disperse units is strongly dependent on *p*H.[5,6,7] In the *p*H regions below 3.5 and above 7.5, its sedimentation constant, measured at a protein concentration of 10 g./l., decreases from a value of $S_{20,w} = 2.85$ to $S_{20,w} = 2.25$, indicating that there occurs either a decrease in molecular weight or an expansion of the molecule, as in the case of serum albumin.[8,9,10,11,12]

In order to clarify this question, light scattering measurements were carried out on β-lactoglobulin as a function of *p*H. These show[7] that below *p*H 3.5 the molecule of β-lactoglobulin dissociates into units smaller than 35,000, probably into two portions of equal weight. These data are in qualitative agreement with the results of Rands and Tanford,[13] who also observed a similar decrease in the molecular weight of this protein at low *p*H. Because of the rapid re-equilibration of the dissociation with dilution, however, the light scattering data curve strongly upward in the low concentration range, and it is not possible to extrapolate them to a reliable value of the weight average molecular weight. As a result, ultracentrifugal determinations of the molecular weight were carried out by the Archibald technique,[14,15,16] under conditions of strong dissociation.

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(5) A. G. Ogston and J. M. A. Tilley, *Biochem. J.*, **59**, 644 (1955).
(6) R. Townend and S. N. Timasheff, *Arch. Biochem. and Biophys.*, **63**, 482 (1956).
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(16) S. M. Klainer and G. Kegeles, *J. Phys. Chem.*, **59**, 952 (1955).

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TABLE I

pH	Temp., °C.	Speed	Prot. concn., g./l.	Concn. at menisicus, g./l.	$\frac{1}{cx}\frac{dc}{dx}$ extrapd.	Mol. wt.
1.64	24.8	42,040	10.7	0.25	3.30 ± 0.20	16,900 ± 1000
				0.1	3.49 ± .20	17,900 ± 1000
2.01	23.7	39,460	13.2	2.8	3.75 ± .30	20,300 ± 1600
				0.36	3.23 ± .20	17,500 ± 1100
				0.1	3.22 ± .10	17,400 ± 500
2.08	25.0	20,410	12.1	5.4	1.047 ± .02	22,700 ± 500
				4.7	1.054 ± .03	22,900 ± 700

Solutions of β-lactoglobulin were prepared under the desired conditions of *p*H and ionic strength, and centrifuged in a Spinco Model E analytical ultracentrifuge. In each case, the protein solution was centrifuged in one Kel-F cell, while pure solvent was centrifuged in an identical cell used in place of the counterbalance. The menisci of the two were made to coincide by weighing in the proper amount of liquid into each cell, as suggested by Singer.[17] In this manner, the correct base line was obtained directly on each ultracentrifugal pattern. The weight average molecular weight at the meniscus was calculated at various times late in the run, so that the equilibrium be close to total dissociation. Some of the results obtained in a 0.1 Γ/2 NaCl-HCl medium are presented in the table.

These data show that the molecular weight of the dissociated species of β-lactoglobulin is in the vicinity of 17,500, or half of the normally accepted value. It is interesting to note that Bull has obtained a molecular weight of 17,000 from surface pressure measurements under a different set of conditions.[18] These results, together with the reports that β-lactoglobulin contains two identical amino[19] and carboxyl[19,20] end groups, strongly suggest that the molecular unit observed at isoelectric conditions is an aggregate of two identical protein units. It would appear, therefore, that the molecule of β-lactoglobulin consists of a single polypeptide chain with a molecular weight of *ca.* 17,500.

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RECEIVED MAY 16, 1957

BOOK REVIEWS

Biochemical Problems of Lipids. Proceedings of the Second International Conference held at the University of Ghent 27–30 July, 1955, organized with the collaboration of the "Vlaamse Chemische Vereniging" of Belgium, under the presidency of Professor R. Ruyssen. Editors, G. POPJÁK and E. LE BRETON. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1956. xvi + 509 pp. 16 × 25.5 cm. Price, $10.75.

This volume contains about 80 papers including a discussion of the nomenclature of the enzymes concerned in fatty acid metabolism. The languages used were English, French and German. There were present about 250 scientists representing 20 nationalities.

The papers are arranged in four sections as they were presented at the meetings: (1) physical and chemical properties of the lipids—methods of separation, structure; (2) metabolism and biosynthesis, enzyme systems; (3) phospholipids and transport; (4) miscellaneous problems.

An excellent outline of the work covered is given in the introduction by President R. Ruyssen. Among his comments are remarks about the complex chemical constitution of the lipids and their behavior as amphophilic substances. The knowledge of structure and composition of the natural phospholipids has much increased due almost entirely to new methods of separation and identification, such as countercurrent distribution, chromatography and spectrophotometry. Knowledge of the enzyme systems and their isolation as discussed in the conference puts us now in position to describe precisely most of the reactions in the fatty acid cycle. The part taken by the phospholipids in the transport of the fatty acids is now due for a reconsideration. Also thereby, new light has been thrown on fat absorption, [illegible] quantities of thermal power either exothermic or endother-

It would be impossible in a brief outline to mention the topics presented and their discussion by the attending members. It is sufficient to say that practically every phase of lipid structure, behavior and metabolism has been brought out and examined so that a reader gets a comprehensive picture of the present state of the problems connected with the lipids. A fact which detracts a little from the book as a publication is the repetition of the last three papers of section (1) together with an occasional extra page. Of course, this does not affect the value of the material from a scientific point of view.

The book will be of interest, not only to the purely lipid chemists, but since the lipids in nature combine with most known biochemical substances, forming aggregates of great size and complexity, it should interest all biochemists as well as those whose main interest is in the huge molecules which constitute living matter.

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Microcalorimétrie. Applications Physico-Chimiques et Biologiques. By E. CALVET, Professeur à la Faculté des Sciences de Marseille, and H. PRAT, Professeur a l'Université de Montréal. Masson et Cie., Editeurs, 120, Boulevard Saint-Germain, Paris-6e, France. 1956. viii + 395 pp. 17 × 25 cm. Price, Broché, 4.500 fr. Cartonné toile, 5.200 fr.

Microcalorimetry comprises the measurement of small

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mic as produced in chemical reactions. In the apparatus developed by Calvet, Prat and co-workers the sensitivity has been increased to the point where the incredibly small power of 0.2 microwatt (1.5 cal./yr.) can be recognized. The fundamental idea which makes this possible was originally proposed by A. Tian in Marseille in 1923 (whose apparatus was used by Calvet for his doctoral research). Tian suggested that the heat generated or adsorbed in the reaction under study be compensated by electrical cooling (Peltier Effect) or heating (Joule Effect). The present authors over a period of twenty years have developed the apparatus to the sensitivity mentioned above and by means of ingenious innovations as well as of sound theoretical analyses of error brought the science of microcalorimetry to a high state of perfection.

The book has been written in three sections, the first two by Calvet and the third by Prat. The first on apparatus and methods gives detailed mathematical analyses of errors, heat leaks, thermal unbalance in the calorimeter, etc., as well as a description of the calorimeter, methods of forming the thermocouple junctions, electrical circuits (which are relatively simple), etc. In order to avoid unknown heat losses due to temperature gradients along the exterior surface of calorimeter and interior surface of jacket (a difficulty commonly overlooked by many calorimetrists), Calvet covers nearly the whole surface of the calorimeter with thin silver plates each connected to a thermocouple. Thus in his calorimeter heat leaks are magnified, but controlled and measured. This is perhaps the outstanding feature of his technique. It would be interesting to know how such a scheme works at high temperatures where heat exchange by radiation becomes dominant.

The second part describes the special methods and results of calorimetric studies of heats of solution, dilution, mixing, gelatinization, esterification, hydrolysis, saponification, immersion, decomposition and hydration (especially of cements). A large and important part of this section is devoted to the description not only of total heats but also of kinetic heat effects. The apparatus can also be used for specific heat and thermal conductance measurements although in these two fields the special advantages of the Tian-Calvet calorimeter are not so marked.

The final part describes chiefly Prat's work on biological systems such as heat effects of germination and respiration of seeds, bacteria, tissues, invertebrates and vertebrates. Of especial interest here are the kinetic heat effects which make it possible to recognize and measure quantitatively different stages in growth cycles as well as the effects produced on the organisms by herbicides, hormones, variations of temperature and humidity, etc.

The authors make no attempt to review the whole subject of microcalorimetry, their purpose in writing this book being to expound their own techniques. A general bibliography is given as well as indices and a table of contents. F. D. Rossini in his capacity of President of the Commission of Chemical Thermodynamics of the I. U. P. A. C. generously contributed an appreciative preface.

DEPARTMENT OF CHEMISTRY
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MALCOLM DOLE

Treatise on Inorganic Chemistry. Volume II. Sub-Groups of the Periodic Table and General Topics. By H. REMY, Professor of Inorganic Chemistry, University of Hamburg, (Germany). Translated by J. S. Anderson, F.R.S., Professor of Inorganic Chemistry, University of Melbourne (Australia), Formerly Deputy Chief Officer, Atomic Energy Research Establishment, Harwell (England). Edited by J. KLEINBERG, Professor of Inorganic Chemistry, University of Kansas, Lawrence, Kansas (U.S.A.). D. Van Nostrand Co., Inc., 126 Alexander Street, Princeton, New Jersey. 1956. xxviii + 800 pp. 18 × 25.5 cm. Price, $17.75.

The English translation of this famous German textbook by Professor Remy is a welcome addition to the number of treatises in inorganic chemistry which have appeared in the last few years. Professor Anderson who has translated this book has been successful in keeping basic objectives of Professor Remy intact.

As the title indicates, a large part of this book pertains to the treatment of the various groups in relation to their position in the periodic table. However, several chapters have been added which treat subjects of great present interest.

The first chapter is a discussion of the metals and the intermetallic phases emphasizing the theoretical and practical aspects of this subject. Chapters 2, 3, 4, 5 and 6 discuss the first five periods of the transition elements. Chapter 7 discusses the 8th sub-group divided into the metals of the iron series and the metals of the platinum series. This division, unfortunately, produces a loss of some of the significance of the electronic structure in the sub-groups of group VIII. Chapters 8 and 9 discuss the 1st and 2nd subgroup of the periodic system and chapter 10 discusses the Lanthanum group.

Chapters 2 through 10 start with a general discussion of the groups such as their valence, basicity of the hydroxides, oxides and salts, properties of the metals, alloys, etc. Much of this discussion is of the type which still adheres to the memory type discussion which was so typical of German treatises. The other parts of the chapter consist of the discussion of the physical and chemical properties of the metals and their compounds including their analytical chemistry. Energy relationships which are so important in discussion of trends in the groups are unfortunately not included for most groups. In many cases certain aspects of a group are discussed in great detail whereas other parts are just barely mentioned. Some compounds are discussed as Werner type complexes although this has not been fully established.

The rest of the chapters consider general phenomena important in inorganic chemistry. Chapter 11, for example, considers radioactivity and isotopes, and chapter 12, isotopes of the stable elements; chapter 13, artificial radioactivity in nuclear chemistry and chapter 14, the Transuranic elements in general. This discussion covers about 150 pages and is quite well organized and presented. Chapter 15 considers geochemistry in general and could possibly be included in this group.

Chapter 16 discusses colloids and surface; chapter 17, catalysis and reaction kinetics; chapter 18, reactions in nonaqueous solutions and chapter 19, reactions of solid substances. These chapters are well organized but consider phenomena which can, because of space limitation, be only discussed superficially. In such a case, naturally, the specific interest of the author determines the treatment of the subject matter.

In general, this second volume of Remy's Treatise on Inorganic Chemistry is a very welcome addition to the shelf of general reference books in inorganic chemistry. The author, the translator and the American editor are to be congratulated for having undertaken to make this reference book available to those research chemists in inorganic chemistry who are not too familiar with the German language.

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HANS B. JONASSEN

Organic Analysis. Volume III. Editorial Board: JOHN MITCHELL, JR., I. M. KOLTHOFF, E. S. PROSKAUER and A. WEISSBERGER. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1956. viii + 546 pp. 16 × 23.5 cm. Price, $11.50.

This latest publication in the series "Organic Analysis" marks another forward step in the projection originally set forth by its editors of consolidating and critically evaluating the extensive and widely scattered literature of the field. It is gratifying to note in this connection that the contributors to Volume III have completed their assignments with distinction.

The book contains six chapters, the first four of which deal with functional group analyses (1. Organic Acids, 2. Organic Anhydrides, 3. Amines and Amides, and 4. Olefinic Unsaturation), the fifth with a relatively new instrumental technique, analytical mass spectrometry, and the sixth with synthetic organic resin coatings. The chapters are all of uniformly high quality, their treatment showing ample evidence of both painstaking scholarly care and of broad

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practical experience with the subject matter in hand. The coverage of the many and varied chemical and instrumental techniques pertinent to the above mentioned functional groups is inclusive and well documented: there is a generous selection of proven methods accompanied by procedural details and tabular surveys of compounds to which the methods apply. The chapter on olefinic unsaturation, certainly the largest undertaking in the book, is probably unique in its breadth and excellence, and is one which will be welcomed by organic chemists generally. The fifth chapter opens with a clear and concise theoretical discussion of mass spectrometry, but appropriately limits its treatment of specific applications to those of interest to the structural organic chemist. Because of the expensive equipment which this method entails this chapter is addressed unfortunately to a rather restricted audience. The last chapter is a survey of a variety of separation procedures and determinations which have been applied successfully in the field of resin coatings. As such the information in it will no doubt find daily use in the laboratories engaged in the field, and will definitely come as a boon to the analyst who is confronted with a problem in it only occasionally. In summary, this is a useful volume indeed, and is highly recommended as an addition to the library of the organic analyst.

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Rheology. Theory and Applications. Volume I. Edited by Frederick R. Eirich, Polytechnic Institute of Brooklyn, Brooklyn, New York. Academic Press, Inc., Publishers, 111 Fifth Avenue, New York 3, N. Y. 1956. xiii + 761 pp. 16.5 × 23.5 cm. Price, $20.00.

The importance of rheology to the chemist is constantly growing, with both the variety of materials available for various purposes and the demands of the applications in which these materials are put to use. Rheology, originally the science of flow, has become the science of the response of materials or objects to many kinds of steady or cyclical stresses. Its subject matter ranges from the viscosities of very dilute polymer solutions through the behavior of lubricating oils, paints, printing inks, doughs, plastics, fibers and rubbers, to the deformation of metals and the behavior under stress of soil and concrete.

The chief cause of this increase in practical importance has been the extensive development of the science of rheology itself, particularly during the last ten or fifteen years. The science is in need of systematization and of standardization of terminology and nomenclature. There is need for books, both systematic introductions and also advanced expositions of the progress of the science on its many fronts. This present book is in the latter category; it might well be called a source book of theoretical and applied rheology. Many of the scientists who have contributed most heavily to the recent development of the science have written chapters summarizing their special fields.

After an introduction by Professor Eirich, Volume I contains chapters by M. Reiner and by William Prager on the mathematical analysis of rheological behavior; by D. C. Drucker on plastic behavior in metals; by G. J. Dienes on "Crystal Properties and Imperfections"; by J. M. and W. G. Burgers on "Dislocations in Crystals"; and by J. Fleeman and G. J. Dienes on "Mechanical Properties of Metals." Next is a chapter by R. B. Dow on rheological behavior under high pressures. A. Bondi then writes on "Theories of Viscosity." R. S. Rivlin summarizes the mathematical theory of large plastic strains, chiefly his own work. There then follow five chapters dealing chiefly with the rheology of high polymers: by T. Alfrey, Jr., and E. F. Gurnee ("Dynamics of Viscoelastic Behavior"); T. G. Fox, Serge Gratch and S. Loshaek ("Viscosity Relations for Polymers in Bulk and in Concentrated Solution"); J. Riseman and J. G. Kirkwood ("The Statistical Mechanical Theory of Irreversible Processes in Solutions of Macromolecules"); H. L. Frisch and R. Simha ("The Viscosity of Colloidal Suspensions and Macromolecular Solutions"); and A. Peterlin ("Streaming and Stress Birefringence"). Finally come a mathematical study by [illegible]

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Newtonian liquids, by J. G. Oldroyd, and a brief chapter by R. B. Lindsay on "Acoustics and the Liquid State." The announced contents of Volumes II and III lists roughly as many chapters for each of these volumes, with the chapters somewhat more specialized and, in Volume III, of a more applied nature.

The chapters of Volume I differ considerably among themselves in plan, in thoroughness and in level of difficulty. This reviewer was more at home in the chapters on polymers and found some of them quite useful. With the many additional chapters announced for the subsequent volumes the coverage of polymer rheology will be relatively complete. In contrast the treatment of metals appears not to be extended into later volumes. The chapters on metals in the first volume appear to be of high quality, though outside this reviewer's field of competence.

In view of the nature, scope and price of this volume, and of the set, this reviewer considers that it can be recommended particularly for purchase by libraries of universities and of colleges strong in technical work and by industrial libraries in a large segment of chemical and related industry. The case is somewhat different for the individual chemist. Those working actively in applications of rheology, having considerable knowledge of the field, may find this compilation of authorative summaries of great value. For the beginning worker in the field, or the chemist in another field wanting orientation in rheology, the work has several drawbacks—its length, the thoroughness and comparative difficulty of some of the treatments, the lack of correlation between the chapters with consequent repetition and variation in terminology, notation and viewpoint, and a lack of unity and coherence in the work as a whole which is an unavoidable consequence of this type of authorship.

American Viscose Corporation
Marcus Hook, Pennsylvania M. T. O'Shaughnessy

An Investigation on Promoted Iron Catalysts for the Synthesis of Ammonia. Second Edition. By Anders Nielsen. Jul. Gjellerups Forlag, Copenhagen, Denmark. 1956. 233 pp. 16 × 24 cm. Price, paper bound, 28.00 Danish Kroner; cloth bound, 33.00 Danish Kroner.

During the past five decades the synthesis and decomposition of ammonia on the surface of solid catalysts has been of intense interest to fundamental and applied scientists. Some of the complexities of heterogeneous catalysis have been resolved, and the industrial development of the ammonia synthesis has been accelerated. Nielsen's book presents data of major importance in the rational design of industrial equipment as well as data and discussions pertinent to an understanding of the mechanism and kinetics of the synthesis. A brief introduction outlining the subject matter and purposes of the book is in Chapter I. The second chapter contains thermodynamic data on the equilibrium concentration of ammonia in $3H_2 + 1N_2$ as a function of pressure and temperature, on the heat of reaction at 500° and various pressures, on compressibility of $3H_2 + 1N_2$ at 10° and 100–400 atmospheres, on the solubility of H_2, N_2, A and CH_4 in liquid NH_3 and on the vapor phase composition of $3H_2 + N_2$ equilibrated with liquid NH_3 at various temperatures and pressures. After a brief description of laboratory catalyst pretesting apparatus in Chapter 3, the following chapter presents data on the per cent. conversion, the efficiency factor (ratios of actual partial pressure of NH_3 to equilibrium partial pressure of NH_3), and space–time–yield as a function of temperature, pressure, space velocity. Chapter 4 also contains data on the effect of the ratio of H_2 to N_2, the partial pressures of inert gases, the per cent. of NH_3 in the feed gas; and includes discussion of the differences between laboratory and industrial converters particularly with respect to temperature gradients and turbulence, and the effect of particle size of catalyst with regard to the extent of reduction and the limitation of reaction velocity by diffusion to and from the surface of the catalyst.

The great utility and limitations of Temkin and Pyshev's equation for the rate of the synthesis are demonstrated in Chapter 5 by an analysis of the variation in rate constants with pressure and temperature. The limitations encountered when the NH_3 partial pressure is low, when diffusion

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into and out of the catalyst granule is rate determining, and the decrease in the rate constants with increasing pressure and with decreasing H_2 to N_2 ratio, are of particular significance. The magnitude of the change in the rate constants with pressure in is not the same for all catalysts, being lowest for the doubly promoted Al_2O_3–K_2O–Fe_3O_4 catalyst.

In Chapter 6 are presented the properties of various catalysts which are of industrial importance such as temperature stability, effect of promoters, the characteristics of reversible poisoning by O_2, H_2O, CO, CO_2 and more permanent poisoning by S, As; the optimum reduction procedures, and the effect of particle size on activity and on pressure-drop in industrial reactors. The extent of reduction is of critical importance to the activity of the catalyst. Virtually complete reduction is desirable because of the poisoning action of H_2O, and it is obtained by the use of very high space velocities of the reducing gas and the highest temperatures consistent with minimum deterioration of the catalyst by sintering. Promoters such as Al_2O_3, CaO and K_2O markedly lower the rate of reduction of Fe_3O_4.

X-Ray diffraction patterns of various catalysts before and after reduction are presented and discussed in Chapter 7. The distribution of Al_2O_3 in the spinel lattice of Fe_3O_4 is uniform and this accounts for the structural promotion of Al_2O_3. Whether CaO, or MgO are "dissolved" in the Fe_3O_4 is not yet determined. K_2O remains largely on the surface of the reduced catalysts, and its promotional activity probably is related to its effect on the thermionic work function of the surface and consequently on the rate and extent of activated adsorption of nitrogen (the rate determining step in the synthesis).

Chapters 8 and 9 are concerned with the details of the reaction mechanism as determined by critical experiments on surface properties, the energetics of chemisorption of H_2 and N_2 and measurements of the rates of nitrogen isotope exchange reactions. The data and discussion are of critical importance to an understanding of heterogeneous catalytic reactions. Although structural heterogeneity of catalyst surfaces exists and is effective in the selectivity of certain catalysts, and although surface interaction of chemisorbed molecules and atoms also contributes to energetics of the surface reactions, nevertheless neither of these factors is adequate to explain the changes in heat of adsorption with extent of surface coverage. Boudart's calculations of the influence of the electrical double layer which is formed on a catalyst surface by a fully or partially ionized adsorptive bond show large changes in thermionic work-function and adequately large decreases in heat of adsorption with increase in the fraction of the surface covered.

Nielsen's book is a valuable one for both scientists and engineers who are interested in heterogeneous catalysis.

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H. H. Storch

Organo-metallic Compounds. By G. E. Coates, M.A., D.Sc., F.R.I.C., Professor of Chemistry in the University of Durham. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 1956. viii + 197 pp. 13 × 19 cm. Price, $2.50.

This little book deals with organometallic compounds, defined as substances containing a metal to carbon bond. Alkoxides and other compounds in which metal atoms are bonded to organic systems *via* oxygen, nitrogen or sulfur, and which are often referred to as organometallic compounds, are excluded. A further restriction on the scope of the book is the entire omission of the organic chemistry of silicon, phosphorus and arsenic, on the reasonable grounds that their inclusion in a book of this size would impair the treatment of the other elements.

The author deals with the compounds of the alkali metals, and of the elements of Groups II, III and IV, of antimony and bismuth, and of the transition elements. Whilst the book is written in a rather terse style and is not particularly readable, it is, however, well worth close study, since it contains a wealth of information and the large numbers of references to the original literature given at the end of the chapters, although not exhaustive, are most useful.

In addition to the preparations, properties and reactions of compounds, the structural side is quite adequately dealt with considering the scope of the book. There are but few errors and, although the views expressed in some sections now need modification, the book is fairly well up to date—almost an impossibility in this field at the present time. The final section on cyclopentadienyl compounds is one of the weakest, and the discussion of bonding in ferrocene and similar compounds is far from illuminating. Metal–benzene derivatives are mentioned only in a footnote.

On its information content alone this book is a worthwhile addition to one's library and it has the additional merit of being handy for the pocket.

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Chimie Physique Nucléaire Appliquée. By Jacques Errera, Professeur a l'Universite de Bruxelles. Masson et Cie., Éditeurs, Librairies de l'Academie de Medecine. 120 Boulevard Saint-Germain, Paris VI, France. 1956. 226 pp. 16.4 × 24.8 cm. Price, 2.100 fr.

This little book covers applications of radioisotopes to areas where physico-chemical methods are common. The contents of the several chapters (and their lengths in pages) are approximately as follows: the atom and the nucleus (14); nuclear reactions (19); fission, reactors, nuclear power (36); fusion reactions (3); military applications of nuclear energy (4); fields of application for nuclear reactions (4); detection of nuclear radiations (20); units of radioactivity (4); preparation of radioisotopes (5); comparison of usefulness of stable and radioactive tracers (2); health protection (9); applications to pure and applied science (81); list of elements and table of useful radioisotopes (4). The text is written on a semi-technical level.

Of the 150-odd references and illustration credits in the book, 2 are to British journals, 2 to a Belgian article, 1 to a recent British compendium, and the remainder to current American textbooks, monographs and journals. The book seems to be largely a collection of review and summary material published elsewhere. The book can be recommended to students who are preparing for their pre-doctoral French examinations.

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Peter E. Yankwich

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PHYSICAL AND INORGANIC CHEMISTRY

[CONTRIBUTION NO. 92 FROM THE CRYOGENIC LABORATORY OF THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Palladium Hydride. I. The Thermodynamic Properties of Pd_2H between 273 and 345°K.[1]

BY DONALD M. NACE AND J. G. ASTON

RECEIVED FEBRUARY 13, 1957

The 30° absorption isotherm for hydrogen dissolved in a highly active palladium black has been measured and found to agree very closely with an equilibrium desorption isotherm obtained previously by Gillespie and Hall. Partial molar heats of desorption for the system palladium–hydrogen have been calculated from the isotherms. Partial molar heats of absorption and desorption of hydrogen from palladium hydride also have been measured in an adiabatic calorimeter. These values are used to calculate the free energy and the entropy change associated with the formation of Pd_2H from the elements at 30°. Agreement between the calorimetric heats and those calculated from the temperature coefficient of the equilibrium pressure establishes a reasonable criterion of equilibrium for the system.

Introduction

Palladium is a rapid exothermic absorber of large volumes of hydrogen. Although this phenomenon has been the subject of many previous investigations,[2,3] no entirely satisfactory explanation of the nature of the bonding force has been established. The phase equilibria of the hydrogen–palladium system have been extensively investigated for different forms of palladium (wire, foil, sponge and black). Hysteresis effects have been quite evident in all the isotherms, especially those for temperatures below 160°.

By using a special heat treatment technique, Gillespie and Hall[4] obtained, at temperatures as low as 0 and 30°, apparently true equilibrium isotherms which are located between the usually different absorption and desorption curves. The equilibrium isotherm is interpreted as indicating two solid solutions; one is a hydrogen-poor solution (α-phase), the other is a hydrogen-rich solution (β-phase) of approximate composition Pd_2H. For both α- and β-phases X-ray analysis identifies the palladium atom array as being face-centered cubic, the α-phase having a parameter of 3.886 Å., and the β a parameter of 4.020 Å.[5]

The data presented in this paper were compiled for the purpose of calculating the entropy for the system Pd_2H at near room temperature. Such a value is needed in order to determine the absolute entropy of Pd_2H at 0°K. from a third law study. It is best that this be determined on the sample used for the third law study. Therefore, a series of equilibrium pressure and heat of absorption measurements have been made on a *very active* palladium black between 273 and 345°K.

Materials.—The palladium used is a special grade of palladium black obtained from Baker and Company, Newark, New Jersey. This extremely active palladium is made for their own research purposes, so the method of preparation is not available. The purity is given as 99.9%. Although the density of bulk palladium is 12.0 g./cc., the packed density of this black powder is only 0.6 g./cc. One sample, weighing 34.277 g., was sealed into a gold calorimeter and used for all of the experimental work. The sample was never heated over 100° because the material supposedly sinters at higher temperatures. Any possible oxide of palladium was reduced initially by adding hydrogen to the sample and then degassing at 98°. Following this reduction, the sample was exposed only to very pure helium, nitrogen and hydrogen.

High purity hydrogen made by electrolysis and purified by liquefying and then compressing into a high pressure cylinder was used throughout. All portions of the hydrogen allowed to react with the palladium were first passed through a trap packed with activated charcoal and immersed in a liquid nitrogen-bath.

(1) Aided in part by contract N6onr-269, T. O. III of the Office of Naval Research. Reproduction in whole or in part is permitted for any purposes of the United States government.

(2) A complete bibliography of the literature up to 1947 is given by D. P. Smith in the book "Hydrogen in Metals," University of Chicago Press, Chicago, Ill., 1948.

(3) (a) P. Wright, *Proc. Phys. Soc.* (London), **63A**, 727 (1950); (b) R. E. Norbert, *Phys. Revs.*, **86**, 745 (1952).

(4) L. J. Gillespie and F. P. Hall, THIS JOURNAL, **48**, 1207 (1926).

(5) R. Kruger and G. Gehm, *Ann. Physik*, [5] **16**, 174 (1933).

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Apparatus.—The container for the palladium black sample is a closed gold cylinder fitted at the top with a gold inlet tube and having an internal volume of 55.6 cc. Connection between the gold calorimeter and a glass vacuum system is made through a platinum–rhodium tube which has an inside diameter of 0.0292 in. and which is gold welded inside the calorimeter inlet tube. The calorimeter contains a 2.5 in. long re-entrant well which is gold welded in the center of the cylinder bottom. The re-entrant well is designed for insertion of a platinum resistance thermometer.

Volumes of gas are measured in a calibrated 3-liter Pyrex bulb set up inside a 50-gallon insulated stirred water-bath which is kept at room temperature. Mercury from a storage tank immersed in the water-bath can be raised into or lowered from the 3-liter bulb in order to transfer the gas to the calorimeter. The system is patterned after one described by Giauque and Johnston.[6] The temperature of the water is measured on a mercury thermometer which has been calibrated against a platinum resistance thermometer. The pressure of the gas is measured using a 13 mm. bore, copper cased, mercury manometer. The mercury levels and meniscus heights were referred to a stainless steel, calibrated meter bar by means of a Gaertner Scientific Corporation M901 cathetometer.

The calorimeter vessel was immersed in the inner bath of a double constant temperature bath for the isothermal pressure–composition study and the pressure–temperature studies at fixed composition. The inner bath consists of a 1000-cc. insulated Pyrex beaker equipped with a Transite lid and provided with a stirrer, a calibrated platinum resistance thermometer, an uncalibrated platinum resistance thermometer, and a six-watt light bulb. The uncalibrated resistance thermometer was used to control the temperature by means of a Wheatstone bridge arrangement in which any unbalance of the bridge resulting from a temperature change in the bath of 0.001° or more is detected by a type R galvanometer. A light beam reflected from the galvanometer mirror activates a photocell relay circuit which turns on or off the six-watt bulb. Glycerol was used as the medium in both inner and outer baths. The outer bath was controlled by means of a mercury thermostat at a few tenths of a degree below the temperature of the inner bath. Measured fluctuations of temperature in the inner bath amounted to ±0.002°.

Heats of absorption and desorption were measured in the same gold calorimeter vessel after it had been incorporated in an assembly designed for adiabatic operation with high vacuum insulation. This adiabatic assembly is described in the following paper.[7] Temperatures are measured with a strain-free platinum resistance thermometer, Pt-G-5, based on the International Temperature Scale. The calorimeter was held adiabatic during the addition of gas and until equilibrium was established, or in many cases, until pressure and temperature changes were small enough to allow extrapolation to an approximate equilibrium. The heat of absorption per mole of hydrogen is calculated from the same expression used for heats of adsorption, namely[8]

$$q = \frac{C_p \Delta T}{n} - \frac{V_{cal} \Delta P}{n} \qquad (1)$$

where ΔT is the temperature rise, n is the number of moles of hydrogen absorbed, ΔP is the change in pressure during absorption and V_{cal} is the dead space volume of the calorimeter. The calorimeter was cooled between increments of hydrogen added so that the mean temperature for each rise was about 30°. The mean heat capacity of the system before and after absorption of hydrogen, C_p, was interpolated to the mean temperature for the temperature rise. The measured heat capacities have been corrected for the heat of desorption, which is assumed to be equal in magnitude to the measured heat of absorption but negative in sign, and the heat of compression. The equation for making these corrections to the measured values is

$$C_p = C_m - \frac{(-q)}{\Delta T}(\Delta n) + \frac{V_{cal} \Delta P}{\Delta T} \qquad (2)$$

where C_m is the measured heat capacity and Δn is the increase in the number of moles of gas in the dead space.

After each measurement of heat evolved by a given quantity of gas, the calorimeter was cooled to the initial temperature and one or two heat capacity measurements were made between the initial and final temperatures of the heat of absorption measurement. The heat of absorption was calculated by a series of reiterations of eq. 1 and 2 since q and C_p appear in both equations.

The Absorption Isotherm.—A 30° isotherm for the absorption of hydrogen in palladium black was determined in the isothermal apparatus. The isotherm is shown as the solid curve in Fig. 1 where it is compared with the 30° isotherm obtained by Gillespie and Hall.[4] Since the Gillespie and Hall isotherm is a desorption isotherm brought to equilibrium by the use of a 360° heat treatment prior to each pressure measurement, the similarity between these isotherms indicates that true equilibrium has also been reached in the absorption isotherm of this paper. Equilibrium, as revealed by the constant pressure portion of the isotherm, has never reportedly been obtained for the absorption of hydrogen in palladium below 160° without a heat treatment. The reason for the lack of hysteresis in the present investigation is undoubtedly inherent in the extremely finely divided state of the palladium black used. Pressure equilibrium for the isotherm was obtained in two to six hours after addition of a hydrogen increment. Three of the experimental points of the isotherm were obtained after allowing the pressure to come to equilibrium overnight, but the pressure increased only 0.02 mm. after the second hour. The pressure during the horizontal portion of the isotherm varies only ±0.20 mm. from an average of 17.35 mm. This value is 1.45 mm. (ΔF = 51 cal.) below the value obtained by Gillespie and Hall.

After sufficient hydrogen had been absorbed in the palladium to pass the second break in the isotherm, about 12% of the hydrogen was desorbed. The pressure fell to a low value quite rapidly, and the calorimeter had to be heated to 80° in order to desorb such a large quantity of hydrogen. This desorption curve, as shown in Fig. 1, is identical with that obtained by Gillespie and Hall on desorption of hydrogen where the 360° heat treatment was not previously applied.[4] No increase in pressure occurred over a period of four days after desorption of hydrogen. By heating the system again and holding it at 80° for 24 hours, the pressure after the system was cooled to 30° differed from that before the second heat treatment by only 0.10 mm. Reabsorption of hydrogen raises the pressure to a point where it coincides with the original absorption isotherm. A second set of desorption and reabsorption isotherms is shown in Fig. 1.

Isosteric Heats of Desorption.—The palladium hydride at a composition of about 0.40 atom of hydrogen per atom of palladium was heated to 45° and pressures were measured at a series of temperatures from 45 to 75°. The temperature was controlled with an accuracy of ±0.002° and

(6) W. F. Giauque and H. L. Johnston, THIS JOURNAL, 51, 2300 (1929).

(7) Donald M. Nace and J. G. Aston, *ibid.*, 79, 3623 (1957).

(8) G. L. Kington and J. G. Aston, *ibid.*, 73, 1929 (1951). In equation 1 a term, due to temperature rise, has been neglected since this term is insignificant. This is the term $n_g R(\partial T/\partial n_g)s$ in eq. 14 of this reference.

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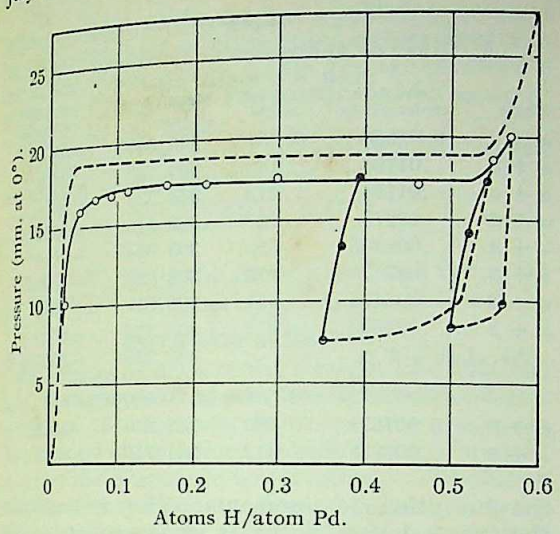

Fig. 1.—Isotherm at 30° for hydrogen in palladium: solid curves, data of present investigation; open circles, absorption; half-filled circles, desorption; filled circles, absorption following desorption; dashed curve, data of Gillespie and Hall.

pressures determined within ±0.04 mm. A plot of $\log p$ *vs.* $1/T$ for the equilibrium pressure data over this 30° temperature range is shown in Fig. 2 (open circles). On a large scale plot no curvature is evident. The slope of this line corresponds to a heat of desorption of 8870 cal./mole of hydrogen, which agrees very closely with the value of 8860 cal./mole obtained by Gillespie and Hall[4] from their 30 and 80° equilibrium values (line with no points in Fig. 2). However, it was found that on decreasing the temperature from 75 to 45°, the pressure values did not fall on the same straight line but established a new straight line (filled circles). The palladium hydride was heated again, and the equilibrium pressure was measured at several temperatures between 45 and 75° (half-filled circles). Pressures also were measured at several temperatures on cooling to 50°. All points obtained after the first 75° heating lay on the second straight line. The 14 experimental points from 55 to 75° were least squared to fit a straight line. The heat of desorption calculated is 9440.8 cal./mole of hydrogen. The most probable error in the experimental data corresponds to ±0.1 mm. pressure at 75° or ±0.5 mm. at 55°. The probable error in the heat of desorption is ±0.9 cal./mole of hydrogen if equilibrium could be assumed.

In the process of measuring heats of absorption and heat capacities in the adiabatic calorimeter, additional pressure–temperature data were observed. Log p *vs.* $1/T$ plots of the data obtained are shown in Fig. 3. The sample of palladium hydride had been completely degassed prior to these measurements and hydrogen added until the final composition corresponded to 0.487 atom H per atom Pd (open circles). It was during this addition of hydrogen that calorimetric heats of absorption also were measured. The isosteric heat calculated on the basis of the slope of this line is 9330 cal./mole. After a period of two months

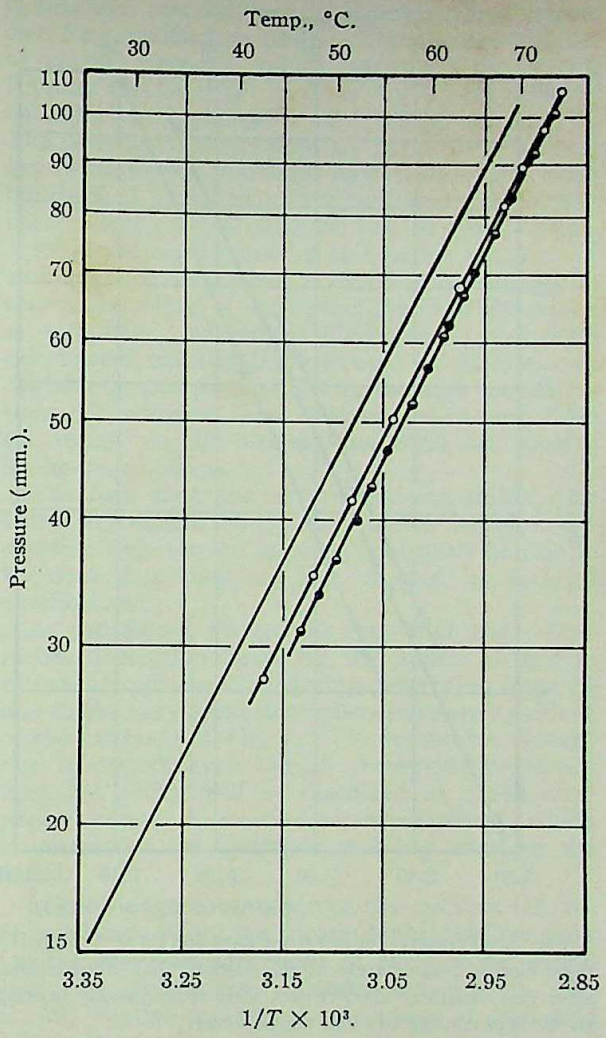

Fig. 2.—Pressure–temperature data for Pd + 0.2 H_2: open circles, preheated to 35° only; filled circles, preheated to 75° and temperature lowered to point; half-filled circles, preheated to 75°, cooled to 45°, and then raised to point; line without points, data of Gillespie and Hall.

during which time the sample was subjected to temperatures from 15 to 300°K., pressures were again measured from 12 to 73° (half-filled circles). The plot of these data gives an isosteric heat of 9640 cal./mole. However, after heating to 73° and cooling to room temperature (filled circles), the corresponding isosteric heat is 10,300 cal./mole.

This variation of the isosteric heats must be due to lack of internal equilibrium.

Calorimetric Heats of Absorption and Desorption.—Heats of absorption were measured calorimetrically at 30° at various concentrations of hydrogen. Heats of desorption of hydrogen from palladium hydride were measured at 68°. The heat determinations are listed in Table I.

The heat of absorption of hydrogen remained constant over the entire mixed phase region of palladium hydride. The average value of the heat is −9605 cal./mole at an average temperature of 30.195°. The average deviation of the heat of absorption is ±45 cal./mole and of the temperature is ±0.146°.

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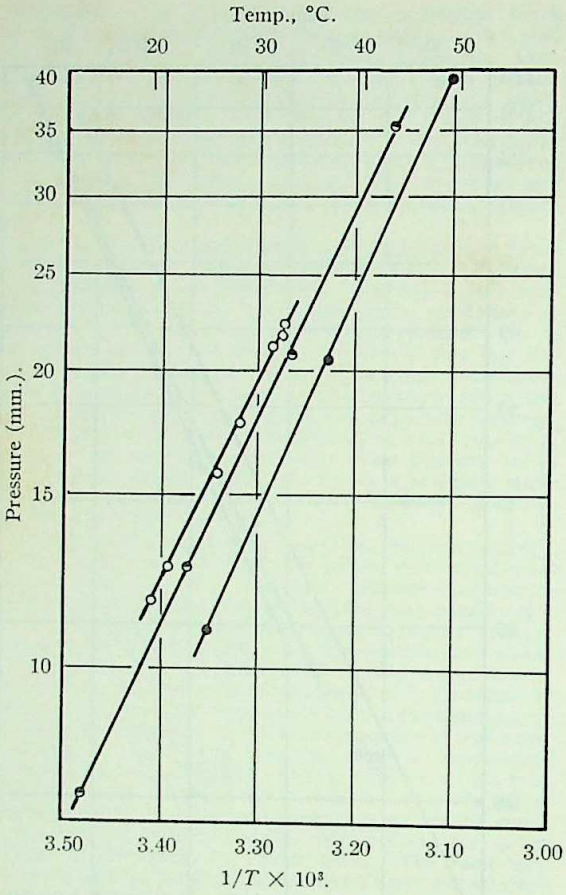

Fig. 3.—Pressure–temperature data for Pd + 0.2435 H_2: open circles, immediately after addition; half-filled circles, after two months; filled circles, after subsequently heating to 73° and cooling to room temperature.

The heats of desorption do not agree well with those of absorption or with each other; this is due undoubtedly to a great lack of equilibrium during desorption, whereas there is good equilibrium for the absorption.

The heat of the reaction

$$4Pd + H_2\,(1\text{ atm.}) = 2Pd_2H \qquad (3)$$

is the total heat of absorption of hydrogen from pure palladium to the composition of Pd_2H based on a mole of hydrogen. The one determination of the α-phase heat evolution resulted in a value of 8948 cal./mole; the average heat evolution during formation of β-phase Pd_2H is 9605 cal./mole. Since the α-phase heat evolution, which occurs up to the atomic ratio 0.125, corresponds to one-quarter of the over-all reaction to form Pd_2H, the value of $\Delta H°$ corresponding to equation 3 is given by

$$\Delta H° = {}^1/_4(-8948) + {}^3/_4(-9605) = -9440 \pm 45\text{ cal./mole} \qquad (4)$$

Since the heats of absorption are measured directly, lack of thermodynamic equilibrium should not greatly affect them, particularly when the equilibrium during absorption is as good as it was in these measurements. The fact that the isosteric heats are even close to the measured values is an indication of relatively good equilibrium in

TABLE I

A. HEAT OF ABSORPTION OF HYDROGEN AT 30°

1 cal. = 4.1833 int. joules

Phase	Change in moles of H_2	Mean ratio H/Pd	Mean temp. T_m, °K.	ΔH, cal. mole^{-1}
α	0.01653	0.052	305.685	−8948
$\alpha + \beta$	.01198	.140	303.638	−9643
$\alpha + \beta$	.01134	.212	303.335	−9554
$\alpha + \beta$	.01273	.287	303.519	−9562
$\alpha + \beta$	.009905	.358	303.664	−9564
$\alpha + \beta$	.007176	.412	303.223	−9665
$\alpha + \beta$	.005464	.451	303.617	−9583
$\alpha + \beta$	.002800	.477	303.382	−9665
Av. of all $\alpha + \beta$			303.355	−9605 ± 45

B. HEAT OF DESORPTION OF HYDROGEN AT 68°

$\alpha + \beta$	0.007878	0.460	341.270	10280
$\alpha + \beta$	.007851	.412	341.753	9304

the absorption measurements. Thus we emphasize that the calorimetric heats of absorption are the only ones that need be considered. Their internal consistency is an excellent confirmation of the estimated accuracy.

Free Energy and Entropy for Formation of Pd_2H.—The change in the standard free energy for reaction 3 can be calculated from the pressure–composition relation during the course of the reaction in which

$$\Delta F° = 2F°_{Pd_2H} - F_{H_2}° - 4F°_{Pd} = 2F°_{Pd_2H} \qquad (5)$$

Since reaction 3 represents a solution of hydrogen in palladium with the two limits being pure palladium and pure Pd_2H, the entire process can be treated thermodynamically using the conventional method for handling solutions; that is, the partial molar free energies of the components are considered

$$F°_{Pd_2H} = 2(\bar{F}_{Pd})_{Pd_2H} + 1(\bar{F}_H)_{Pd_2H} \qquad (6)$$

The free energy in the standard state of Pd_2H (which is, of course, pure Pd_2H) is thus relative to those of pure palladium and hydrogen in the ideal gas state at 1 atm. pressure. Since the hydrogen in Pd_2H is in equilibrium with hydrogen gas at the equilibrium pressure, P_{H_2}, the partial molar free energy of hydrogen in palladium hydride is given by

$$(\bar{F}_H)_{Pd_2H} = {}^1/_2F_{H_2(p)} = 0.5RT \ln p_{H_2(Pd_2H)} \qquad (7)$$

Using the Gibbs-Duhem equation, one obtains

$$(\bar{F}_{Pd})_{Pd_2H} = -0.5RT \int_{x=0}^{x=0.5} x\,d \ln p_{H_2(Pd_2H)} \qquad (8)$$

where x stands for n_H/n_{Pd}. Since the square root of the pressure follows a straight line relationship with composition at the very low concentrations of hydrogen, the integral is best evaluated in two parts: the integral of $x\,dp^{1/2}/p^{1/2}$ at low concentrations, *i.e.*, an upper limit of $x = 0.04$, and the integral $x\,d \ln p$ for the higher hydrogen concentrations. The experimental pressure–composition data used in the evaluation of the integral are taken from the isotherm of Fig. 1 which is extrapolated at low concentrations of hydrogen to coincide with the isotherm of Gillespie and Hall. Graphical integration of eq. 8 produced a value of $(\bar{F}_{Pd})_{Pd_2H} = -18.7$ cal./mole. The standard molar free energy of Pd_2H is then evaluated from eq. 6 and 7 to be $F°_{Pd_2H} = -1153 \pm 6$ cal./mole. The hydrogen

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lation was taken as the average equilibrium pressure for the seven heat of absorption measurements in the mixed phase region. This average pressure is 18.78 ± 0.91 mm. From eq. 5, $\Delta F°_{303.16°} = -2306 \pm 12$ cal./mole.

According to the second law of thermodynamics, the entropy change for reaction 1 is

$$\Delta S° = \frac{\Delta H° - \Delta F°}{T} \qquad (9)$$

At 303.16°K., using the above calculated values for $\Delta H°$ and $\Delta F°$, $\Delta S°_{303.16°} = -23.50 \pm 0.19$ e.u.

Discussion of Results

The change of slope of the straight line obtained from the pressure–temperature relationship after heating to 75° obviously involves some change in the structure of palladium hydride which is brought about by the increase in temperature. The change is apparently permanent since the desorption energy is fixed according to the highest temperature to which the hydride has been heated. The most surprising aspect of this effect is that only 10% of the hydrogen in the palladium had not previously been heated to 80°. Most of the hydrogen in the hydride had been heated to 80° when the two desorption experiments illustrated in Fig. 1 were accomplished. This indicates that the hydrogen pressure is determined by a relatively small quantity of hydrogen which probably is located in the surface lattices of the metal and which is not in all cases in internal equilibrium with the hydrogen in the interior of the metal. This fact is explained in the third paper of this series. The fact that equilibrium pressures are indicative of only the surface hydride concentration invalidates the use of isosteric heats at low temperatures for absolute values of the heat of desorption.

Heats of absorption have been measured twice before calorimetrically, both times at 0°.[9] The ice calorimeter apparatus used in both investigations is useful only in measuring fairly rapid heats of reaction, certainly not in observing heat effects over long equilibrium times. The average of a set of almost constant values measured by Mond, Ramsay and Shields[9a] at 0° is −9362 cal. mole^{-1}. Gillespie and Ambrose[9b] found −9283 cal. mole^{-1}. The palladium blacks used by both these investigators are known to exhibit hysteresis effects when hydrogen is absorbed at low temperatures so that these values are probably too low on this account.

From the experiments of this paper, the heat of absorption in the α-phase is found to be lower than the constant heat of absorption found in the mixed α- + β-phase. Although Gillespie and Ambrose's[9b] calorimetric investigation detected no difference in the heat of absorption at low and at high concentrations of hydrogen, their isosteric heats were 6000 cal. mole^{-1} in the α-phase and 8860 cal. mole^{-1} in the mixed phases.

The fact that the several investigations give better agreement for the calorimetric heats of adsorption than for the isosteric ones must be due to the fact that they are less affected by lack of equilibrium.

As mentioned above, the fact that the calorimetric desorption heats for the mixed α- and β-phases are not constant during desorption must be due to the very great desorption hysteresis evident in the isotherm of Fig. 1. The reason for desorption hysteresis, even though absorption hysteresis does not occur, will be discussed in a following paper[10] because it involves a new mechanism which is postulated for hydrogen mobility through the metal.

Acknowledgments.—One of the authors (D. M. N.) wishes to thank the Socony Mobil Oil Company for the generous provisions of the Socony Mobil Incentive Fellowship. Thanks are due to Mr. C. W. Brouse for the construction of the gold calorimeter and to Dr. R. G. Ascah for the construction and help in the calibration of the platinum resistance thermometer.

(9) (a) L. Mond, W. Ramsay and J. Shields, *Trans. Roy. Soc. (London)*, **A186**, 657 (1895); (b) L. J. Gillespie and H. A. Ambrose, *J. Phys. Chem.*, **35**, 3105 (1931).

(10) Donald M. Nace and J. G. Aston, THIS JOURNAL, **79**, 3627 (1957).

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[CONTRIBUTION NO. 93 FROM THE CRYOGENIC LABORATORY OF THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Palladium Hydride. II. The Entropy of Pd_2H at 0°K.[1]

BY DONALD M. NACE AND J. G. ASTON

RECEIVED FEBRUARY 13, 1957

The heat capacity contribution due to the absorbed hydrogen atoms in palladium hydride at a composition of nearly Pd_2H was measured in a newly constructed adiabatic calorimeter over small temperature intervals from 16 to 340°K. A residual entropy of 0.59 ± 0.18 e.u. has been calculated from experimental data to exist at 0°K. It is concluded that Pd_2H does not approach a completely ordered state at low temperatures and so is not a true compound. The shape of the heat capacity curve indicates the probability of covalently bound hydrogen at low temperatures with a dissociation process occurring as the temperature is varied. More evidence for this model is to be given in the succeeding paper.

Introduction

If Pd_2H were a true compound, and there were no hydrogen bonding as in ice, the entropy at 0°K. should be zero. This principle has been used by Hildenbrand and Giauque[2] to establish that at low temperatures ammonium oxide and ammonium hydroxide are true compounds. By using calori-

(1) Aided in part by Contract N6onr-269 T. O. III of the Office of Naval Research. Reproduction in whole or in part is permitted for any purposes of the United States government.

(2) D. L. Hildenbrand and W. F. Giauque, THIS JOURNAL, **75**, 2811 (1953).

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metric heat capacities measured as a function of temperature, they calculated the absolute entropy of a system from

$$S_T = \int_0^T C_p \, d \ln T + S_0 \qquad (1)$$

where S_0 is the entropy at absolute zero. According to the third law of thermodynamics, S_0 of any substance whose atomic arrangement and quantum states correspond to a unique lowest energy state at the absolute zero is zero. In the preceding paper[3] the entropy change for the reaction at 303.16°K., $4Pd + H_2 = 2Pd_2H$, is determined as

$$\Delta S_{303.16°} = 2S_{Pd_2H} - 4S_{Pd} - S_{H_2} = -23.50 \pm 0.19 \text{ e.u.} \qquad (2)$$

The experimental heat capacities measured in this investigation were those of the gold calorimeter containing pure palladium black before and after absorption of sufficient hydrogen to form about 98% Pd_2H. Since both sets of heat capacities include the heat capacity of the gold calorimeter, only the difference between the heat capacity of the calorimeter with pure palladium and the calorimeter with palladium hydride has any real significance. If this difference in heat capacity is expressed on a molar basis of hydrogen absorbed, $\Delta C_p'$ per mole of hydrogen added can be stated to be

$$\Delta C'_p = C_p(2Pd_2H) - C_p(4Pd) \qquad (3)$$

If the entropy at 0°K. of pure palladium is zero, eq. 2 can be expressed as

$$\Delta S_{303.16°} = \int_0^{303.16°} \Delta C'_p \, d \ln T - S_{303.16°}(H_2) + S_0(2Pd_2H) \qquad (4)$$

The absolute entropy of gaseous hydrogen in the standard state has been published[4] and is 31.34 e.u. at 303.16°K. Rearranging eq. 4 and inserting the known values, the entropy of Pd_2H at 0°K. is

$$S_0(Pd_2H) = {}^1/_2(-23.50 \pm 0.19 + 31.34 - \int_0^{303.16°} \Delta C'_p \, d \ln T) \qquad (5)$$

The zero point entropy of Pd_2H can thus be calculated from the results of a study of the heat capacity contribution of a mole of hydrogen to the heat capacity of palladium when palladium hydride is formed.

If the hydrogen atoms in Pd_2H are randomly distributed at room temperature, the system on cooling under equilibrium conditions will approach a unique lowest energy state corresponding to the most ordered arrangement of the atoms. Frequently the lowest energy state is degenerate, in which case a residual entropy $k \ln O$ is retained in which O is the number of equal energy orientations possible and k is the Boltzmann constant. If the energy differences between possible arrangements are small, a residual entropy of δ will be found at the absolute zero when the temperature is lowered to a point where thermal motions are unable to orient atoms into the completely ordered arrangement. Such a situation exists for carbon monoxide, nitrous oxide and nitric oxide.

(3) Donald M. Nace and J. G. Aston, THIS JOURNAL, **79**, 3619 (1957).

(4) H. W. Wooley, R. B. Scott and F. G. Brickwedde, *J. Natl. Bur. Standards*, **41**, 379 (1948).

The shape of the heat capacity *vs.* temperature curve necessary for the third law entropy study also serves as a clue to the origin of thermal energies in the solid. The energy content of a solid at low temperatures arises from vibrations of the atoms in the crystal, but molecules have the opportunity to increase their energy in other degrees of freedom, such as rotation of a molecular unit or vibration of atoms within a molecule, as the temperature is increased.

Apparatus.—The heat capacity measurements were carried out in a newly constructed adiabatic calorimeter designated as Calorimeter J. The gold calorimeter and the sample of palladium black which it contains are described in the preceding paper.[3] A strain-free platinum resistance thermometer inserted into this calorimeter carries the designation Pt-G-5. It was calibrated between 11.5 and 92.6°K. by comparison under adiabatic conditions with two platinum resistance thermometers which are primary standards of The Pennsylvania State University temperature scale. The two primary standards, Pt-G-8 and PT-G-12, had been calibrated against the helium gas thermometer.[5] A total of 20 resistance measurements were made in this comparison calibration. Thermometer Pt-G-5 was calibrated on the International Scale by a similar comparison against the two primary standards involving 13 resistance measurements from 92.6 to 300°K. in addition to a precise determination of the ice point resistance. The value of such a calibration on the International Scale made by comparison measurements against a primary standard is that the chance need not be taken of thermally affecting the platinum wire during calibration at the boiling point of sulfur, one of the fixed points on the International Temperature Scale. The scale below 90°K. corresponds to 90.154°K. for the boiling point of oxygen,[6] whereas the value chosen to establish the International Temperature Scale was originally 90.19°K. In this case the value 90.154°K. was used for the boiling point of oxygen and proper adjustments made.

The low temperature cryostat and adiabatic shield arrangement were designed basically like those previously described.[7-9] Details are given in a thesis.[10] Above the shield, inside the cryostat the entering gas is passed through a temperature controlled heat exchanger to bring it to the same temperature as the calorimeter. This was for use in heat of absorption measurements.

Materials.—The palladium sample and hydrogen have been described in the preceding paper.[3]

Results

It was possible to maintain perfectly adiabatic conditions for Calorimeter J above 18°K. The average time necessary for thermal equilibrium was five minutes in the liquid hydrogen region, 15 minutes in liquid nitrogen, and 20 to 30 minutes above 200°K. For 55 experimental heat capacities of the calorimeter containing pure palladium, the average deviation of the points from a smooth curve is shown in Table I.

TABLE I

15 to 50°K.	±0.13%
50 to 100	.08
100 to 250	.05
250 to 300	.08
300 to 350	.15

(5) G. W. Moessen, J. G. Aston and R. G. Ascah, *J. Chem. Phys.*, **22**, 2096 (1954).

(6) J. G. Aston and G. W. Moessen, *ibid.*, **21**, 1948 (1953).

(7) J. G. Aston and G. J. Szasz, THIS JOURNAL, **69**, 3108 (1947).

(8) J. A. Morrison and G. J. Szasz, *J. Chem. Phys.*, **16**, 280 (1948).

(9) J. G. Aston, H. L. Fink, G. J. Janz and K. E. Russell, THIS JOURNAL, **73**, 1939 (1951).

(10) D. M. Nace, Ph.D. dissertation, Penn. State Univ., University Park, Penna., 1956.

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At the conclusion of all the experimental heat capacity measurements for palladium and palladium hydride, the heat capacity of the degassed calorimeter was again determined in the region from 35 to 95°K. These ten heat capacity determinations have an average deviation of ±0.05% from the new curve but on the average are 0.06% below the original heat capacity smoothed curve.

The heat capacities of the calorimeter containing first palladium black and later palladium hydride at the composition at which the atomic ratio H/Pd is 0.487 were measured from 16 to 303°K. The experimental data are given in Tables II and III. The heat capacity contribution of one mole of hydrogen to four moles of palladium, ΔC_p, is plotted against temperature in Fig. 1. The heat capacity anomaly which occurs between 30 and 100°K. is illustrated on an enlarged scale in Fig. 2. The repeated heat capacity determinations of the degassed calorimeter are also plotted on Fig. 2 as deviations from the original empty calorimeter heat capacity curve, and the deviations have been multiplied by the same factor used to convert the palladium hydride experimental heat capacity difference to a molar basis of hydrogen. The purpose of showing these remeasured heat capacities is to illustrate that the hump cannot be due to any permanent change undergone by the palladium.

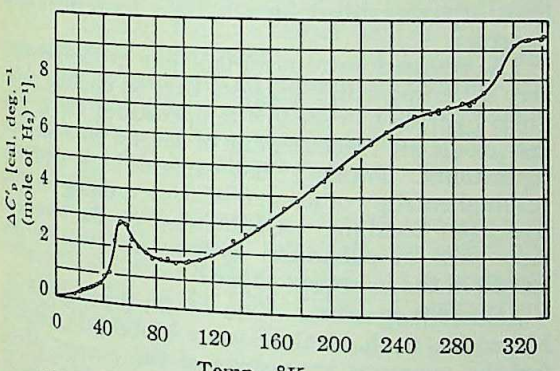

Fig. 1.—Heat capacity due to 1 mole H_2 in Pd_2H.

The heat capacities in all the temperature regions are quite reproducible for palladium hydride. The agreement among several overlapping series of runs is demonstrated in both Figs. 1 and 2. Obviously, any rearrangement of structure on change of temperature, if such occurs, proceeds rapidly since the heat capacities are reproducible regardless of the initial temperature to which the calorimeter is cooled. Based on the average deviations of the experimental heat capacities, the probable error of the $\Delta C'_p$ is about 10% at 15°K., and about 3% between 25 and 50°K., decreasing to 2% above 200°K. On integration to give entropies, the percentage error probably is decreased.

The heat capacity curve for palladium hydride above 290°K. shows a sudden rise. Heat capacities in this range are corrected for the heat of desorption of hydrogen evolved into the dead space of the calorimeter and filling line, the heat of compression of gas in the calorimeter dead space, and the change in concentration of hydrogen in the palladium. The heat of desorption for the quantities of hydrogen desorbed was assumed to be equal, but negative in sign, to the calorimetrically measured heat of absorption, −9605 cal./mole of hydrogen.

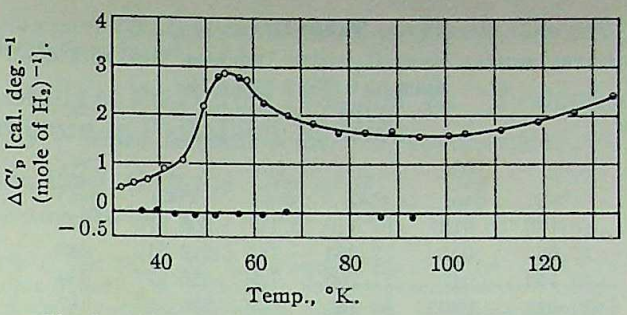

Fig. 2.—Heat capacity due to hydrogen in palladium (4 atoms): open circle, system cooled to 14°K.; half-filled circle, system cooled to 50°K. only; completely filled circles, after long pumping to remove the absorbed H_2.

TABLE II

HEAT CAPACITY OF CALORIMETER J CONTAINING 0.3212 MOLE PALLADIUM AT ROUNDED TEMPERATURES

0°C. = 273.16°K., 1 cal. = 4.1833 int. joules

T (°K.)	C_p (cal./deg.)	T (°K.)	C_p (cal./deg.)	T (°K.)	C_p (cal./deg.)	T (°K.)	C_p (cal./deg.)
15	0.444	68	6.569	185	10.52	305	11.71
16	.516	71	6.802	190	10.58	300[a]	11.68
17	.604	75	7.104	195	10.65	305	11.70
18	.703	80	7.440	200	10.71	310	11.73
19	.808	85	7.745	205	10.78	315	11 75
20	.919	90	8.024	210	10.83	320	11.78
22	1.165	95	8 260	215	10.88	325	11.81
24	1.426	100	8.476	220	10.93	330	11.84
26	1.691	105	8.674	225	10.98	335	11.87
28	1.967	110	8.866	230	11.03	840	11.90
30	2.241	115	9.038	235	11.08	345	11.93
32	2.521	120	9.202	240	11.13		
34	2.799	125	9.346	245	11.17		
36	3.078	130	9.483	250	11.22	36.203[a]	3.110
38	3.349	135	9.609	255	11.27	39.413	3.540
41	3.743	140	9.730	260	11.32	43.157	4.017
44	4.128	145	9.848	265	11.38	47.316	4.524
47	4.494	150	9.952	270	11.43	51.760	5.029
50	4.840	155	10.05	275	11.48	56.662	5.539
53	5.166	160	10.14	280	11.53	61.638	6.016
56	5.477	165	10.22	285	11.58	66.639	6.453
59	5.775	170	10.30	290	11.62	86.418	7.819
62	6.052	175	10.37	295	11.65	92.865	8.150
65	6.316	180	10.45	300	11.68		

[a] Heat capacities at this and the following temperatures were measured after degassing of the calorimeter following all heat capacity measurements on Pd_2H.

Table IV contains a summary of the entropy change found by evaluating the integral in eq. 5. The zero point entropy can now be stated to be

$$S_0(Pd_2H) = \tfrac{1}{2}(-23.50 \pm 0.19 + 31.34 - 6.66 \pm 0.16)$$
$$= +0.59 \pm 0.18 \text{ e.u.}$$

The entropy of Pd_2H thus approaches a value of 0.59 ± 0.18 e.u. at the absolute zero of temperature. This discrepancy from an entropy of zero must be due to some degree of randomness in the arrangement of hydrogen atoms in the metal.

Discussion

The combination of bonding potentialities of unfilled inner shells of palladium and the observed exothermic release of energy when hydrogen is absorbed in palladium would certainly lead one to consider chemical bonding of some sort between

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TABLE III

EXPERIMENTAL HEAT CAPACITY INCREASE DUE TO PRESENCE OF 0.07819 MOLE H_2

H/Pd = 0.4869

0°C. = 273.16 °K., 1 cal. = 4.1833 int. joules;

T (°K.)	ΔC_p (cal./deg.)	T (°K.)	ΔC_p (cal./deg.)	T (°K.)	ΔC_p (cal./deg.)
16.178	0.012	67.110	0.157	206.972	0.391
17.661	.015	72.353	.145	216.515	.435
19.153	.017	77.702	.128	226.277	.454
20.613	.020	83.135	.130	236.387	.487
22.218	.025	88.674	.132	246.783	.506
24.318	.029	94.315	.123	254.982	.531
26.637	.032	100.385	.125	265.553	.537
28.997	.036	103.758	.128	270.130	.545[b]
31.619	.039	111.187	.133	271.201	.535
34.376	.047	118.784	.148	277.257	.549
37.385	.052	126.149	.162	286.208	.561
40.847	.072	134.105	.189	294.254	.568
44.896	.084	142.658	.206	291.877	.557
49.312	.171	151.002	.223	301.383	.592
53.849	.224	159.665	.246	311.302	.647
58.472	.214	168.646	.281	321.318	.717
52.478[a]	.220	177.938	.300	331.269	.731
56.870	.217	187.552	.333	340.930	.742
61.946	.217	195.721	.354	328.407	.731
		198.271	.376	339.544	.732

[a] Cooled to 50.5°K. [b] This and following data corrected for heat of desorption and heat of compression.

TABLE IV

CALORIMETRIC ENTROPY CHANGE

0–15.85°K.	Debye extrapolation = 0.05 ± 0.01	e.u.
15.85–28.19	$\int \Delta C'_p \, d \ln T$ = 0.16	.01
28.19–118.85 (hump)	.83	.02
28.19–118.85 (without hump)	1.38	.04
118.85–303.16	4.24	.08
0–303.16°K	$\int_0^{303.16°} \Delta C'_p \, d \ln T$ = 6.66 ± 0.16	e.u.

palladium and hydrogen atoms as the probable explanation for the absorption process. If such bonding does occur, the character of the metallic bond between palladium atoms is undoubtedly involved in a resonating system probably involving hydrogen bridge bonds as suggested by Rundle.[11]

The heat capacity curves of Figs. 1 and 2, in general, rise rapidly with temperature. In addition, an anomaly exists at 55°K. which is of the type commonly attributed to the beginning of molecular rotation in a covalent molecule. The 55°K. anomaly is similar to that of $(NH_4)_2O$ at about the same temperature as recently reported,[2] NH_4Cl, NH_4NO_3, $(NH_4)_2SO_4$ and CH_4 (references given in ref. 2). Rotation of the tetrahedral NH_4^+ ion and CH_4 molecule is commonly regarded as responsible for the increased energy absorption in the neighborhood of the anomaly. In the case of pure compounds, the anomaly is of the λ type, indicating that the potential barrier to rotation depends on the degree to which neighboring molecules are rotating. In cases where the coöperative interaction between neighboring molecules is not very great, the anomaly becomes less sharp. The effect of reducing the cooperation between neighboring molecules of methane is shown when methane is diluted with krypton. The λ-type anomaly[12] for pure methane is converted to a broad rounded hump for the methane in dilute solid solution with krypton.[13]

At temperatures above 55°K., the heat capacity contribution of hydrogen rises continuously at a rapid rate up to room temperature. The absence of a leveling off of the heat capacity indicates vibrational degrees of freedom present in the hydride which could be associated with molecular vibrations of covalently bound atoms. The heat capacity of pure palladium and of molecular hydrogen, or even of free protons if such could be present in the palladium lattice, would reach a constant classical limit at temperatures much lower than room temperature.

The residual entropy of 0.59 e.u. at the absolute zero of temperature suggests that on cooling palladium hydride to very low temperatures the hydrogen atoms are frozen in one of several possible configurations. Pauling[14] has explained the 0.82 e.u. residual entropy of ice at 0°K. by assuming random hydrogen bonding. A somewhat similar situation may exist in palladium hydride and will be discussed in the following paper.[15]

Acknowledgments.—One of the authors (D. M. N.) wishes to thank the Socony Mobil Oil Company for the generous provisions of the Socony Mobil Incentive Fellowship. The help of Mr. L. F. Shultz, who produced all of the refrigerants and aided in the assembly of the apparatus, was invaluable.

UNIVERSITY PARK, PA.

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[CONTRIBUTION NO. 94 FROM THE CRYOGENIC LABORATORY OF THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Palladium Hydride. III. Thermodynamic Study of Pd_2D from 15 to 303°K. Evidence for the Tetrahedral PdH_4 Structure in Palladium Hydride[1]

BY DONALD M. NACE AND J. G. ASTON

RECEIVED FEBRUARY 13, 1957

The heat capacity of Pd_2D has been measured from 15 to 152°K. and 280 to 300°K. for comparison with that of Pd_2H to verify a theoretical conclusion based on the shape of the lambda transition in the latter. For completeness certain points in the isotherm and partial molal heats of absorption of deuterium in palladium have been measured. The heat capacities of Pd_2H have been analyzed. Reasonable barrier heights and frequencies have been calculated to fit for a model based on PdH_4·7Pd at low temperatures. To explain the heat capacities above 120°K., a dissociation process is postulated which involves a decrease in the average number of hydrogen bonds as the temperature is raised. Hydrogen diffusion through palladium is conceived as a movement of hydrogen atoms by a continuous combination of (1) rotation about a parent palladium atom and (2) bonding to, and subsequent rotation about, a neighboring palladium atom. A new theory has been developed to explain the phase separation and hysteresis in the absorption isotherm.

Introduction

This is a continuation of the work reported in the two previous papers.[2,3] A lambda transition was found in the heat capacity curve of Pd_2H which is reminiscent of the type found for solutions of methane in krypton and for ammonium compounds. The effect on the lambda transition of substituting all the hydrogen in methane by deuterium has been studied by Clusius, Popp and Frank.[4] Due to the smaller zero point energy of deuterium as compared to hydrogen, the temperature of the lambda transition for CD_4 is shifted to a higher temperature. It also is split into two peaks. A comparison of the heat capacity anomaly of palladium hydride and palladium deuteride to see whether the equivalent shift and splitting occur is thus desirable. The heat capacity of Pd_2D has therefore been studied from 15 to 152°K.

As will be seen presently, it was necessary to conclude from the results that Pd_2H was essentially PdH_4·7Pd at the low temperatures. It is necessary to assume that as the temperature is raised reactions of the type

$$PdH_{2x} + Pd = 2PdH_x \qquad (A)$$

occur, giving a contribution to the heat capacity. Such reactions are essentially reactions of migrations. To substantiate this, the heat capacity of Pd_2D also was studied in the postulated temperature region of migration. In this paper, a calculation of the heat capacity curve for palladium hydride is made on the basis of this proposed PdH_4 model and correlated with the experimental data. The way in which the model explains other phenomena associated with the palladium–hydrogen system at high temperatures will be discussed.

Experimental

The adiabatic calorimeter and sample of palladium used for the heat capacity and calorimetric heat measurements is described in the preceding papers.[2,3] The deuterium used was obtained from the Cryogenic Laboratory at Boulder, Colorado (National Bureau of Standards), and reportedly contains 99.4 to 99.7% deuterium, the remaining fraction being HD.

Absorption of Deuterium by Palladium.—Seven increments of deuterium were absorbed at 30° in the palladium black sample, and the heat released by each increment was measured under adiabatic conditions. Deuterium was much slower than hydrogen in coming to pressure equilibrium during the heat of absorption measurements. In the case of hydrogen absorption, pressure equilibrium generally was reached in three to four hours, but, with deuterium, the pressure was decreasing at a rate of over 1 mm. per hour as much as seven hours after absorption. The heats, which are listed in Table I, were calculated on the basis of the temperature change after four hours of adiabatic conditions, at which time the rate of temperature change was never greater than 0.0003° per minute.

TABLE I

A. HEAT OF ABSORPTION OF DEUTERIUM AT 30°

Phase	Change in moles of D_2	Mean ratio D/Pd	Mean temp. T_m, °K.	ΔH
α	0.007436	0.023	302.434	−7497
$\alpha,\alpha+\beta$	.008436	.072	302.303	−8184
$\alpha+\beta$	.013593	.141	303.263	−8336
$\alpha+\beta$	.014085	.227	303.334	−8342
$\alpha+\beta$	.015513	.319	303.274	−8406
$\alpha+\beta$	.017687	.422	303.761	−8434

B. HEAT OF DESORPTION OF DEUTERIUM AT 30°

$\alpha+\beta$	0.005873	0.458	303.775	9536
$\alpha+\beta$	.004874	.425	299.733	8873

The average heat of absorption of deuterium in the mixed phase region is −8379 cal. mole^{-1} at an average temperature of 30.248°. These heats show a definite increase for each increment of gas added throughout the mixed phase region. The pressure over palladium deuteride also increased with each addition of deuterium. One month after the heats of absorption measurements were made, the equilibrium pressure over the final composition of palladium deuteride was measured, and at 35° was found to be 100 mm. instead of the value of 230 mm. observed several hours after addition. This amazingly slow equilibrium obviously has an effect on the accuracy of the heats of absorption for deuterium. The high heats of desorption compared to those of absorption shown in Table I correspond to a similar situation for palladium hydride.[3]

The temperature coefficient of the pressure of deuterium over palladium deuteride was measured

(1) Aided in part by Contract N6onr-269, T. O. III of the Office of Naval Research. Reproduction in whole or in part is permitted for any purposes of the United States government.
(2) D. M. Nace and J. G. Aston, THIS JOURNAL, **79**, 3619 (1957).
(3) D. M. Nace and J. G. Aston, *ibid.*, **79**, 3623 (1957).
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from 0 to 33° a month after the deuterium had been absorbed by the palladium. Figure 1 is a plot of log p *versus* $1/T$ at a D:Pd ratio of 0.479. The isosteric heat calculated from this straight line is 8635 cal. mole^{-1}.

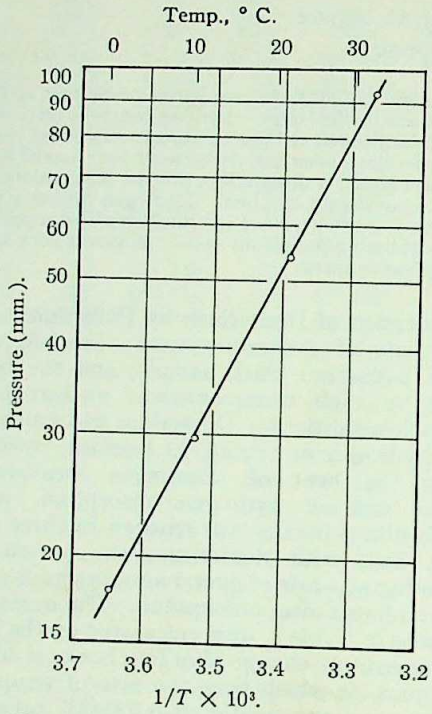

Fig. 1.—Pressure–temperature data Pd_2D.

Although calorimetric determinations of the heat of deuterium absorption in palladium never have been reported in the literature, isosteric heats above 200° have been determined before. The isosteric heat for deuterium desorption in the mixed phase region from the pressure–temperature relation of Gillespie and Downs[5] at an average temperature of 215° is 7760 cal. mole^{-1}. It is interesting to compare the isosteric heats obtained for palladium hydride and for palladium deuteride from this and the investigations of others.[5,6] The ratio of the isosteric heat, $\Delta H(Pd_2H)/\Delta H(Pd_2D)$, at 200° from the results of Gillespie and collaborators is 1.11. From this investigation, the same ratio at 30° is 1.12. The ratio of the equilibrium pressure over palladium deuteride to the pressure over palladium hydride shows an increase as the temperature is lowered. From the data of Gillespie the ratio is 2.1 at 270°, 2.4 at 250° and 2.9 at 200°. From this investigation the ratio is 4.6 at 30° and 4.8 at 20°.

The Heat Capacity Curve for Palladium Deuteride.—The heat capacities of the calorimeter containing palladium deuteride at a deuterium concentration corresponding to an atomic ratio D:Pd of 0.479 were measured from 15 to 152°K., and from 279 to 301°K. Because the time for this investigation was limited, it was not considered essential to cover the region from 152 to 279°K. The increase in heat capacity due to the deuterium is listed for each temperature in Table II. The data are plotted in Fig. 2 and Fig. 3. Agreement among overlapping runs is again evident as it was in the case of palladium hydride. The anomalous hump is again present, the temperature corresponding to the maximum value at the peak having shifted from 55.0°K. for palladium hydride to 57.5°K. for palladium deuteride. This is a 4.6% increase, while the shift from 20.4°K. for CH_4 to 21.4°K. for the first peak of CD_4 represents a 4.9% temperature increase. Although a second peak is not immediately evident in the case of palladium deuteride, the heat capacity decreases only slightly after the peak, and the two peaks may be combined in the general shape of the curve. The peak of the palladium deuteride curve is higher than that of the palladium hydride curve.

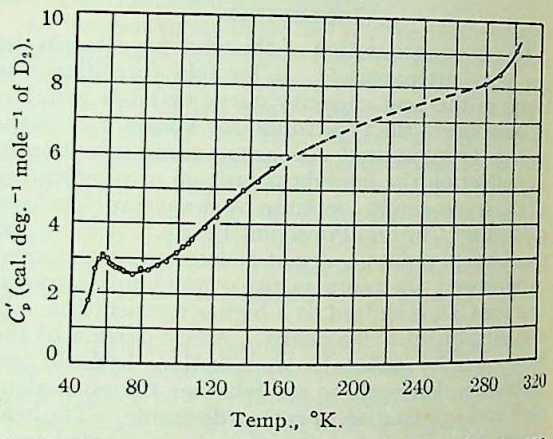

Fig. 2.—Heat capacity increase of palladium due to one mole of deuterium.

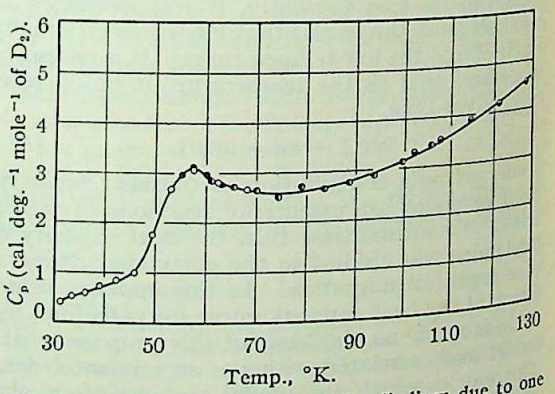

Fig. 3.—Heat capacity increase of palladium due to one mole of deuterium: open circles, cooled to 15°K.; half-filled circles cooled to 59°K., only completely filled circles, cooled to 53°K.

The second rise in the heat capacity of palladium hydride above room temperature following a leveling off of the curve also finds its analogy in the palladium deuteride curve, the temperature of the rise being considerably lower.

Theoretical Heat Capacity Curve at Low Temperatures Based on $PdH_4 \cdot 7Pd$ and $PdD_4 \cdot 7Pd$.—On the basis of the probable covalent bonding between palladium and hydrogen atoms, and the striking resemblance of the heat capacity anomaly to the cooperative rotational transition found in tet-

(5) L. J. Gillespie and W. R. Downs, THIS JOURNAL, 61, 2496 (1939).

(6) L. J. Gillespie and L. S. Galstaun, *ibid.*, 58, 2565 (1936).

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TABLE II

EXPERIMENTAL HEAT CAPACITY INCREASE DUE TO PRESENCE OF 0.07692 MOLE D_2

D/Pd = 0.4790; 1 cal. = 4.1833 int. joules; 0°C. = 273.16°K.

T (°K.)	ΔC_p (cal./deg.)	T (°K.)	ΔC_p (cal./deg.)
15.389	0.015	74.360	0.194
17.358	.022	78.928	.211
18.928	.024	83.527	.206
20.546	.024	88.409	.215
22.183	.020	93.664	.224
23.915	.026	99.390	.243
25.981	.019	105.535	.268
28.118	.014	55.209[b]	.229
30.979	.031	57.464	.243
33.388	.041	60.017	.231
36.009	.047	63.044	.216
38.957	.057	101.951	.258
42.153	.067	107.659	.274
45.759	.079	114.204	.301
49.299	.138	121.053	.324
53.004	.207	128.179	.359
57.402	.237	136.022	.383
62.363	.217	144.119	.403
67.838	.208	152.485	.432
61.061[a]	.220	278.895	.624
65.268	.211	289.324	.643
69.810	.206	300.514	.701

[a] Cooled to 59.0°K. [b] Cooled to 53.3°K.

rahedral NH_4^+ ions and CH_4 molecules, a starting hypothesis for the molecular unit is PdH_4.

In comparing the experimental data with those calculated from any model, the former must be expressed on the basis used in the theoretical calculations. Accordingly, the experimental heat capacities from Fig. 1 of the preceding paper[2] must be calculated on the basis of one mole of PdH_4, and this can be done simply by adding the known molar heat capacity of one gram atom of pure palladium[7] to the experimental heat capacity contribution of four hydrogen atoms in palladium hydride in units of cal. per mole of PdH_4, if the theoretical calculation also neglects the excess palladium.

It now remains to define the details of the model more precisely. At the over-all composition of Pd_2H, one out of every eight palladium atoms would have four hydrogen atoms covalently bound to it according to the PdH_4 model. Also, in order to have the hydrogen atoms present in Pd_2H uniformly distributed throughout the lattices of the metal, two hydrogen atoms must be present in each palladium lattice cube since each face centered cubic palladium lattice contains the equivalent of four palladium atoms. The hydrogen atoms can satisfy both these requirements if PdH_4 molecules replaced palladium atom on four corners of each palladium lattice. If the hydrogen atoms of each PdH_4 molecule are tetrahedrally arranged about their central palladium atom, they can be directed toward the center of four different palladium lattice cubes. The two hydrogen atoms which are oriented toward the center of each cube lie at a point at which each hydrogen atom is equidistant from four tetrahedrally surrounding palladium atoms. The coöperative aspect of rotation of hydrogen atoms around adjacent corner palladium atoms is obvious. Rotation must be in phase so that only two hydrogen atoms occupy a minimum energy position in a cube at the same time. Figure 4 shows one possible arrange-

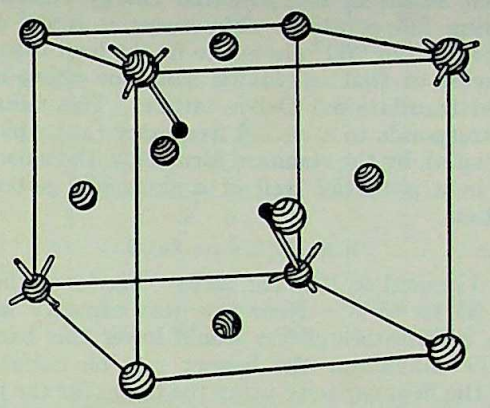

Fig. 4.—One possible arrangement of PdH_4 molecules in the palladium lattice: open circles, Pd atoms; black circles, H atoms.

ment of four PdH_4 molecule on corners of a palladium lattice cube. At the composition Pd_2H, each cube has attained this capacity of two hydrogen atoms. Based on this model and the crystallographic dimensions of the expanded palladium lattice in the β-phase, the Pd–H bond distance is 1.72 Å. and the moment of inertia of the spherical top molecule PdH_4 is 13.0×10^{-40} g. cm.^{2}.

A theoretical heat capacity curve can now be drawn for the hypothetical molecule PdH_4. This curve is drawn in Fig. 5 as the solid curve and superimposed on the experimental heat capacity data (open circles) expressed on the basis of PdH_4. The theoretical curve is composed of five contributions to the heat capacity. Curve A is the contribution of three translational degrees of freedom in the crystal based on Debye $\theta(\theta_t)$ of 275°, the value for

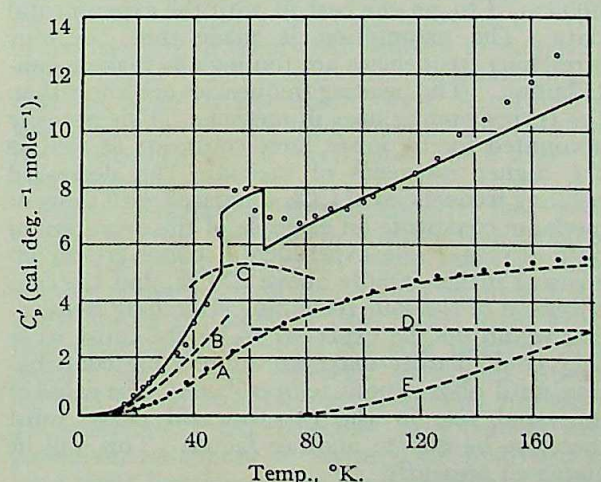

Fig. 5.—Theoretical contribution to the heat capacity of PdH_4: curve A, Debye translation; curve B, Debye torsional modes; curves C and D, rotation; curve E, Einstein modes; solid curve, A + (B, C, or D) + E; open circles, experiment for PdH_4; filled circles, experimental atomic heat capacities of palladium.

(7) K. Clusius and L. Schachinger, Z. Naturforsch., Publ. Domain. Courtesy Banaras Hindu University Varanasi Collection. CC-0.

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pure Pd. The filled circles are the experimental value for pure palladium.[7] Curve B represents the contribution of the additional three rotational degrees of freedom which would be present in the PdH_4 molecule, representing oscillations of the hydrogen atoms in the potential energy barrier restricting full rotation. The curve is based on a Debye $\theta(\theta_r)$ of 200° chosen to fit the heat capacity in excess of that calculated from the above-mentioned translational Debye lattice. This value of θ_r corresponds to a cut-off frequency (ν_m) which is associated, by the standard formula, with an oscillation in a potential well of a sinusoidal potential function.

$$V = V_0(1 - \cos 3\varphi)/2 \qquad (1)$$

with V_0 equal to 1600 cal. mole^{-1} barrier in the region 35 to 45°K. Near the heat capacity maximum coöperative effects would lower this barrier. At the maximum the barrier can be calculated from the heat capacity using the tables for the thermodynamic functions for molecules with restricted internal rotation. Curve C then represents the heat capacity curve due to a restricted rotor with V_0 equal to 390 cal. calculated from these tables. By considering that rotation becomes essentially free of hindering effects above the transition peak, the heat capacity contribution from the three rotational degrees of freedom must approach the classical limit of 3/2 R, represented in Fig. 5 as line D. Since the experimental heat capacity curve for PdH_4 increases sharply above 90°K., additional contributions must come from the nine remaining vibrational degrees of freedom in the molecule. Curve E is the vibrational contribution based on five bending frequencies, empirically set equal to 500 cm.$^{-1}$ to get the best fit with the experimental data. The assumption is made that the four stretching frequencies are too high to make a contribution. The bending frequencies are lower than the corresponding ones in methane. This is easily accounted for by lower force constants as well as the higher moments of inertia. The decreased bending frequencies of CCl_4 compared with those of methane constitute an example of the operation of both effects. The experimental curve is still increasing rather rapidly above 120°K., but the contribution of the four remaining stretching frequencies would not be expected to be the cause since they could hardly make an appreciable contribution until above room temperature. The cause of the rapid rise in the experimental curve must therefore be due to another factor. This will be discussed presently.

A corresponding treatment of the results with deuterium can be made in the same way. The results are shown in Fig. 6 which corresponds exactly to Fig. 4. The barrier to give the best fit at the peak is 475 cal. mole^{-1}, whereas the θ_r value for the torsional vibration to obtain the best fit below the peak is 235° corresponding to a ν_m of 164 cm.$^{-1}$. The value of V_0 calculated from the value of ν_m is 4480 cal. mole^{-1}. The agreement between this frequency and the 139 cm.$^{-1}$ value for ν_m for palladium hydride is illusory since the reduced mass is greatly increased with deuterium. The contribution of the five internal bending modes [illegible] arbitrarily made because once the average frequency has been set at 500 cm.$^{-1}$ for PdH_4 the value of PdD_4 is determined. The Teller–Redlich rule states that for a heavy central atom replacement of all the hydrogen by deuterium changes the frequencies inversely as the square root of two. This rule predicts quite closely the results of replacing the four hydrogens of methane by deuterium.[8]

On this basis the frequency for PdD_4 is 355 cm.$^{-1}$, and this was used in calculating the theoretical curve in Fig. 6. Inspection of Fig. 8 shows that the experimental points deviate considerably from the calculated curve on the high temperature side of the peak in a manner quite different from that of methane. The palladium hydride fits because the average frequency of the bending modes was chosen to obtain a fit, but obviously no reasonable frequency could be chosen to fit the deuterium results. The contribution for the vibration frequencies is negligible at temperatures immediately above that of the peak for any physically real frequency.

There are two *a priori* factors which would predict a higher heat capacity contribution. One of them is the possibility of a second peak in the rotational heat capacity on the high temperature side of the anomaly as has been mentioned above (as with deuteromethane); the other is that the dissociation process causing the deviation of the measured curve from the theoretical curve for palladium hydride above 120°K. is shifted to a much lower temperature. The higher barrier for palladium deuteride is most naturally attributed to its lower zero point energy.

High Temperature Model of Palladium Hydride.—The only previous heat capacity study of a transition metal hydride at low temperatures was made on tantalum containing small amounts of hydrogen.[9] The tantalum hydrides (in the α-phase) have about the same heat capacity as pure tantalum up to 100°K.; then the heat capacity rises considerably and reaches a peak at a temperature that is determined by the concentration of hydrogen. After the peak is reached, the heat capacity rapidly falls to the heat capacity of pure tantalum. The height of each peak is the same regardless of the concentration of hydrogen present if the heat capacity is expressed on a molar basis for the hydrogen. The peak occurs at 220°K., for an atomic H:Ta ratio of 0.0284; at 255°K., for a ratio of 0.0676; and at 265°K., for a ratio of 0.0958. The peaks form an envelope which is the heat capacity curve for the highest H:Ta ratio.

The rapid rise in heat capacity of palladium hydride up to room temperature in place of an expected leveling out above 150°K. may be analogous to Kelly's broad heat capacity peak. Kelly believes this anomaly is due to ordering of the dissolved hydrogen atoms (which are assumed to be free protons) as the temperature is lowered. Recent X-ray diffraction studies[10] on tantalum hydrides at low temperatures indicate that Ta_2H begins to pre-

(8) G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., Inc., New York, N. Y., 1945, pp. 235 and 307.

(9) K. K. Kelly, *J. Chem. Phys.*, **8**, 316 (1940).

(10) T. R. Waite, W. E. Wallace and R. S. Craig, *ibid.*, **24**, 634 (1956).

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cipitate from a homogeneous α-phase hydride when the temperature is lowered below room temperature. In view of this discovery, the energy taken up by palladium hydride as the temperature is raised probably is due to heat of dissociation. The dissociation process involves a disordering migration of hydrogen atoms from the low energy position in $PdH_4 \cdot 7Pd$ to more random arrangements throughout the lattice. Such reactions can be symbolized by

$$PdH_{2x} + Pd = 2PdH_x \qquad (A)$$

In the case of palladium hydride, the second rise in heat capacity occurring at about 290°K. may well be the stage in which reaction (A) becomes

$$PdH_2 + Pd = 2PdH \qquad (B)$$

Evidently the second rise in heat capacity near room temperature due to this cause is shifted down the temperature scale on replacement of hydrogen by deuterium. Therefore a corresponding effect would be expected for the abnormal rise just above 120°K. It is apparently this effect which is at least in part responsible for the different behavior of palladium deuteride in the high temperature side of the peak.

The Diffusion Mechanism of Hydrogen through Palladium.—The disordering process that occurs when $PdH_4 \cdot 7Pd$ is heated is thus taken to involve a redistribution of hydrogen bonds among various palladium atoms in each lattice cube. The stability of the hydrogen bond itself most likely is due to resonance forms involving hydrogen atoms which lie midway between two or more palladium atoms. The bonds themselves may be similar to the "half bonds" which Rundle proposed[11] for electronically deficient compounds. He predicted that in the case of great electron deficiency, such as occurs in transition metals, four or more atomic orbitals may be combined to give a single bond orbital of lower energy than the single atomic orbital. After it has settled into a hydride configuration, the rotating PdH_4 molecule (or lower hydrides such as PdH_2) may be thought of as being in a higher energy state with the hydrogens bonded to only one palladium atom. If rotation of the hydrogen atoms in a PdH_4 molecule (or a lower hydride) occurs, it is feasible for a hydrogen atom bridging two palladium atoms to be rotated about the second palladium atom with which it shares a common orbital. The availability of rotational energy allows a translation of hydrogen atoms from one palladium lattice to another by a combination of hydrogen atoms being first shared with and then rotated about neighboring palladium atoms.

This concept of hydrogen transfer through the metal differs from previous theories in which inexplicably free protons drift at random in the metal. The proposed mechanism is supported by two recently published discoveries. Results of a neutron diffraction study of palladium hydride at room temperature show that the most probable positions for the hydrogen atoms are on the edges of the palladium lattice cube, mid-way between the corner palladium atoms, and at the center of the cube (coördinator $\frac{1}{2}a,0,0; 0,\frac{1}{2}b,0; 0,0,\frac{1}{2}c$; and $\frac{1}{2}a,\frac{1}{2}b,\frac{1}{2}c$, respectively).[12] In the model of palladium hydride proposed in this paper, each palladium atom in the lattice is a revolving sphere with a high hydrogen probability on the surface. Four of these spheres nearly intersect at the center of the cube and at points on the edges midway between the corners; therefore, maximum intensity should be found at these positions in the neutron diffraction patterns. The nuclear magnetic resonance studies[13] of palladium hydride at room temperature by Norberg have revealed line widths which indicate rapid proton motion within the lattice. The activation energy for diffusion necessary to explain his result in terms of the free proton theory led Norberg to propose a "short circuit" diffusion mechanism consisting of diffusion along lattice imperfections. According to the present theory, the "short circuit" is formed by the resonance-rotation mechanism which arises in a natural fashion.

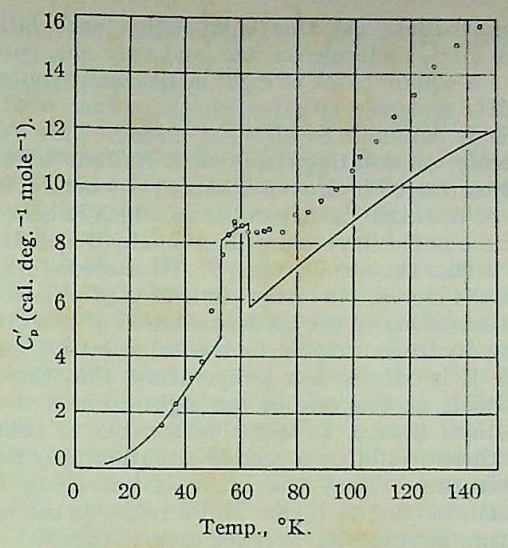

Fig. 6.—Theoretical heat capacity of PdD_4: open circles, experimental PdD_4 points; solid line, total of Debye translation, Debye torsion, rotation and Einstein modes.

Phase Separation Hysteresis.—It has been pointed out that, because the lattice is face centered cubic, for the composition Pd_2H the maximum number of hydrogen atoms that can be present in a palladium lattice cube is two. This presupposes that each hydrogen atom lies at a position equidistant from four different palladium atoms. At high temperatures where absorption isotherms are measured, PdH_4 molecules have reacted with palladium neighbors to share their hydrogen or form lower hydrides. The same number of hydrogen atoms per unit cell, on an average, are demanded by the configuration. The average is maintained by the rotation (*not necessarily free*) of each hydrogen atom around a parent palladium atom in phase with the other hydrogen atoms. At low temperatures the hydrogen atoms cluster as PdH_4 molecules on corners of the palladium lattice. This leads to the prediction of the first break in the absorption isotherm at a composition Pd_8H (H:

(11) R. E. Rundle, *J. Chem. Phys.*, **17**, 671 (1949); *J. Am. Chem. Soc.*, **70**, 1769 (1948); **69**, 1719 (1947); **70**, 99 (1948); **69**, 1379 (1947); **69**, 1327 (1947); **69**, 1980 (1947); **69**, 1719

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Pd = 0.125). At this composition each lattice has a PdH_4 molecule on one, and only one, corner site. A square block of eight lattice cubes contains a PdH_4 molecule situated on the corner position which is common to all eight cubes. This PdH_4 molecule, on rotating, can orient its four tetrahedrally arranged hydrogen atoms at any instant into four of the eight lattice cubes to which it belongs. No cube could have more than one hydrogen atom in it unless the atomic ratio H:Pd exceeded 0.125. Thus the increase in lattice dimension (β-phase) has its *raison d'etre* in the accommodation of two interacting hydrogen atoms in the same lattice cube. While it is only at low temperatures that there is one PdH_4 at this one of the eight corners of the palladium lattice, it seems reasonable to believe that there would be a related situation near room temperature. Thus the break is not sharp but gradual, moving to higher H:Pd ratios as the temperature increases as observed experimentally.

From the evidence given in the first paper[2] in this series, the absorption isotherm (as distinct from the desorption process) for hydrogen in palladium black is convincingly an equilibrium isotherm. Hydrogen must be able to penetrate into all the lattices of the palladium sample, and the β-phase which is formed must be uniformly distributed. This is not true for many isotherms which have been published, such as is shown in Fig. 7

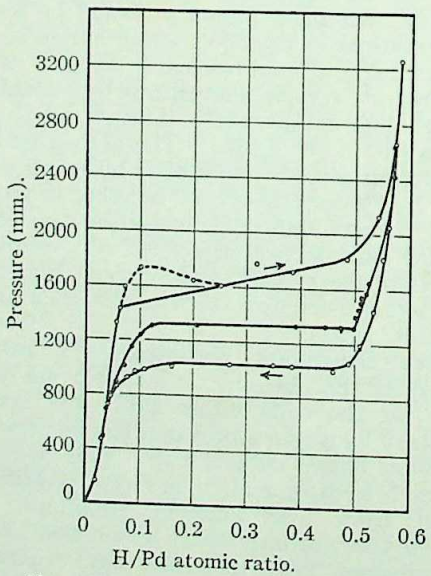

Fig. 7.—Absorption, desorption and equilibrium isotherms at 160° for hydrogen on palladium: open circles, absorption and desorption; filled circles, equilibrium.

where the hysteresis involved in a 160° isotherm[14] is contrasted with the isotherm of Gillespie and Hall at 160°.[15] The diffusion of hydrogen into palladium proceeds rapidly and without hysteresis to a composition approximately Pd_8H. Additional hydrogen absorption must form β-phase expanded lattices on the surface of the metal. The process of forming an internal β-phase expanded lattice cannot occur spontaneously by diffusion of hydrogen atoms from the surface β-phase lattices into an unexpanded α-phase cube because energy must be absorbed in order to expand the lattice. The mechanism for the formation of internal expanded β-phase lattice must involve an unstable active state and probably one in which three hydrogen atoms are present in one of the already expanded external lattices. Such a process is then followed by the rapid release of the third hydrogen atom into a neighboring α-phase lattice. Obviously the farther from the surface this process must proceed, the slower will be the approach to equilibrium.

The proposed mechanism presupposes that the condition of the surface lattices determines the hydrogen pressure over the hydride. If this is so, desorption of hydrogen from surface β-phase lattices should produce α-phase surface lattices over which the equilibrium pressure of hydrogen is abnormally low. Experimentally this is always observed, even in the case of the two true equilibrium isotherms in Fig. 1 of the first paper[2] in this series. The rapid drop in pressure on desorbing hydrogen implies that surface β-phase lattices have been depleted of hydrogen and become α-lattices. A pressure is soon reached at which a steady state is established in which hydrogen can be desorbed without further lowering of pressure. Since internal lattices must also be undergoing desorption, hydrogen atoms from internal β-phase lattices pass to β-phase lattices near the surface at a rate depending on the hydrogen concentration gradient in the internal lattice. During this rapid flow of hydrogen, the β-lattices near the surface must of necessity have an excess of hydrogen atoms in order that they may pass hydrogen on to α-lattices in the surface. When the pumping of hydrogen from the palladium hydride sample is stopped, the rate of desorption of hydrogen from surface lattices to the gas phase falls to zero. The external hydrogen pressure in equilibrium with the surface lattices will remain fixed at a value depending on the hydrogen concentration which lies entirely in α-phase surface lattices. No sort of β-lattice is possible on the surface unless the pressure is raised to that of the flat part of the isotherm, or as Gillespie and Hall have done, the temperature of the system is raised to a high enough temperature (360°) to equilibrate the system internally.

By the addition of hydrogen, partially desorbed palladium hydride can be brought back to an equilibrium condition with a pressure of hydrogen in contact with it which is again on the true equilibrium isotherm. This is in accord with the theory. Not even the total amount desorbed need be added in order to return the pressure to the equilibrium value of the two-phase region because the pressure is established by the surface lattices. This fact is a striking confirmation.

The model has been shown to be consistent with the two isotherm breaks which occur at the compositions Pd_8H and Pd_2H. The initial break in the isotherm of Gillespie and Hall[15] occurs at Pd_8H in the range 160 to 250°. The fact that the break occurs at somewhat lower hydrogen concentrations at lower temperatures can only be due to lack of

(14) H. Bruning and A. Sieverts, *Z. physik. Chem.*, **163A**, 409 (1933).

(15) L. J. Gillespie and F. P. Hall, This Journal, **48**, 1205 (1926).

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internal equilibrium. Gillespie and Perry[16] have in fact observed several abnormal 0° isotherms for which no break at all occurs.

The second isotherm break occurs at Pd_2H from 80 to 200°. The break occurs at higher hydrogen concentrations at lower temperatures possibly because of hydrogen adsorption in structural rifts and defects caused by the independent expansion of each lattice cube.

Significance of the Entropy of Pd_2H at 0°K.—In the preceding paper[2] a residual entropy of 0.59 e.u. at 0°K. was compared to the residual entropy of 0.82 e.u. for ice on the basis that random hydrogen bonding can occur in both. In ice, each oxygen atom is surrounded by four tetrahedrally arranged hydrogen atoms. In $PdH_4 \cdot 7Pd$, only some of the palladium atoms are surrounded by four tetrahedrally arranged hydrogen atoms. For ice, however, only two hydrogen atoms are covalently bound at one time to an oxygen atom while all four hydrogen atoms can be covalently bound to the central palladium atom. Just as random distribution of hydrogen atoms in ice is frozen into a false equilibrium at low temperatures, the arrangement in Pd_2H is subject to a similar circumstance. In building a model of $PdH_4 \cdot 7Pd$, many different arrangements of the PdH_4 molecules on corner lattice sites can be constructed. Actually there are five possible arrangements for the distribution in an independent lattice cube, but the cubes are not independent in the metal. The arrangement of PdH_4 molecules in one cube partially determines the arrangement in the neighboring cubes. The system is too complex to lend itself to a numerical calculation of the total number of arrangements as can be done in the case of ice. However, since each cube is equivalent to two Pd_2H molecules, the experimental value of 0.59 e.u. allows the choice of two arrangements for the PdH_4 molecules in each cubic lattice because

$$S_0 = k \ln 2^{N/2} = {}^1/_2 R \ln 2 = 0.69 \text{ e.u.} \qquad (2)$$

Comparison with Free Proton Theory.—It must be remembered that the degree of hydrogen bonding in palladium hydride is changing with temperature as indicated by the heat capacity curve. It is apparent that the covalently bonded hydrogen model at high temperatures becomes a model of interstitial hydrogen atoms vibrating and rotating relative to the palladium lattice. This assembly of hydrogen atoms, even though the hydrogen atoms share electrons with individual palladium atoms, would be indistinguishable from the model of free protons assembled in regular monolayers as considered by Lacher.[17] The straight line relation in the α-phase between hydrogen concentration and the square root of hydrogen pressure applies equally to a PdH covalently bound hydrogen model or to a free proton model. In other words, much that has been explained in the past on the basis of free protons can also be explained by the covalently bound hydrogen. Additional investigations, particularly of neutron diffractions, will have to be conducted at temperatures well below room temperature in order that the covalently bound hydrogen model be further verified.

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(16) L. J. Gillespie and J. H. Perry, *J. Phys. Chem.*, **35**, 3367 (1931).

(17) J. R. Lacher, *Proc. Roy. Soc.* (*London*), **161**, 525 (1937).

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[Contribution No. 1008 from the Department of Chemistry, University of Pittsburgh]

Magnesium–Cadmium Alloys. VIII. Heat Capacities of Mg_3Cd and $MgCd_3$ between 20 and 290°. The Standard Heats, Free Energies and Entropies of Formation and the Residual Entropies[1,2]

By W. V. Johnston, K. F. Sterrett, R. S. Craig and W. E. Wallace

Received March 23, 1957

Heat capacities of $MgCd_3$ and Mg_3Cd have been measured between 25 and 270° using a new adiabatic calorimeter permitting a precision of 0.1 to 0.2% in the measurements. Experiments were performed using an intermittent heating technique in order that equilibrium heat capacities might be obtained. The data reveal a specific heat anomaly of the customary type for alloys undergoing order–disorder transitions, with peak values at 83.8 and 150.6° for $MgCd_3$ and Mg_3Cd, respectively. With the aid of the heat capacity data, the standard heats, free energies and entropies of formation of the alloys at 270°, which were reported earlier, have been corrected to 25°. The residual entropy of Mg_3Cd has been found to be 0.03 ± 0.04 e.u./g. atom and the corresponding quantity for $MgCd_3$ has been found to be 0.16 ± 0.04. The latter is in good agreement with the quantity 0.17 ± 0.01 e.u. computed statistically under the assumption that there is a random distribution of the observed number of Schottky defects over the lattice sites. Attention is directed to the large errors which can occur when the conventional continuous heating technique is used with systems undergoing configurational changes.

In Paper VII of this series heat capacity data for Mg_3Cd and $MgCd_3$ between 12 and 320°K. were presented.[3] Entropies of formation of these two substances at 270° had been determined[4] earlier by the electrochemical cell method and in

(1) This work was supported by a grant from the U. S. Atomic Energy Commission.

(2) From a thesis submitted by W. V. Johnston in partial fulfillment of the requirements for the Ph.D. degree at the University of Pittsburgh, August, 1955.

(3) L. W. Coffer, R. S. Craig, C. A. Krier and W. E. Wallace, This Journal, **76**, 241 (1954).

(4) F. A. Trumbore, W. E. Wallace and R. S. Craig, *ibid.*, **74**, 132 (1952).

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paper VII the two sets of data were used to evaluate the residual entropy of the compound $MgCd_3$. The required thermal data above 320°K. were taken from the literature. A similar calculation for Mg_3Cd was not possible at that time because of the unreliability of the heat capacity data for it above 320°K. In fact the calculation for $MgCd_3$ was not entirely satisfactory since the existing data extended only to 430°K. and an extrapolation over an interval of 110° had to be made. To permit a satisfactory evaluation of the residual entropies of these substances a new calorimeter has been built and used to determine their heat capacities between 20 and 290°. The data obtained are of additional interest in that (1) they permit reliable evaluations of the heats, free energies and entropies of formation of the two compounds at 25° and (2) they indicate for the first time the temperature dependence of the *equilibrium* heat capacities in the region where these substances exhibit thermal anomalies due to order–disorder transformations. Previous studies have consistently involved the continuous heating technique yielding *non-equilibrium* heat capacities, which for these materials differ at some temperatures appreciably from the equilibrium values.

Experimental

Apparatus.—Since full descriptions of the calorimetric equipment used may be found elsewhere,[5,6] only a brief account will be given here. The calorimeter assembly was essentially of the Southard–Brickwedde design.[7] A few departures from conventional practice were necessary because of the higher temperatures involved. Wires were insulated with glass braid (instead of Nylon) impregnated with either Teflon or a silicone resin. The sample container was very similar to that which has been used[3] in this Laboratory for several years in the study of intermetallic compounds at low temperatures. It was sealed off using a solder consisting of Pb with 5% Ag added. This proved to be more satisfactory mechanically than pure Pb which was originally used. The sample was sealed off in an enclosed container which permitted the soldering to be done under reduced pressure. About 0.1 atm. pressure of helium exchange gas was introduced. Temperatures were measured with a capsule type platinum resistance thermometer that had been calibrated by the National Bureau of Standards. Its fundamental interval was periodically redetermined during the course of the work.

Materials Used.—The samples employed were the same as had been used in the earlier work.[3] They had been stored under an atmosphere of helium while not in use. Compositions were 74.98 ± 0.04 and 24.98 ± 0.04 atomic % cadmium for $MgCd_3$ and Mg_3Cd, respectively. The masses of sample employed were: $MgCd_3$, 582.207 g. or 6.4425 g. atoms; Mg_3Cd, 252.092 g. or 5.4418 g. atoms.

Method of Measurement.—$MgCd_3$ and Mg_3Cd undergo order–disorder transitions in the temperature range covered at about 85 and 150°, respectively. Most of the heat capacity data for alloys in the order–disorder region have been obtained using the continuous heating technique. It appears that such results may in certain regions of temperature be seriously in error (10% or more) due to the failure to maintain equilibrium in the sample. Disordering requires a redistribution of atoms over the positions in the lattice and this may fail to keep pace with the changing temperature when continuous heating is used. In this event the measured heat capacity is a non-equilibrium value and is therefore not suitable for entropy calculations.

The intermittent heating technique has been employed in the present study. The sample is heated for a carefully measured interval of time of 5 to 15 minutes duration resulting in a temperature increment of roughly 5°. Temperature was then followed until it became constant,[8] if this occurred in a reasonable length of time. This was not feasible with Mg_3Cd from 35 to 60° and with $MgCd_3$ from 31 to 95°. In these ranges the temperature continued to fall for many hours after the heat input was stopped, indicating that disorder in the sample was continuing to increase. In some instances the course of the temperature–time curve was followed for 20 hr. and the sample had not reached configurational equilibrium. In these cases an extrapolated final temperature was found under the assumption that the temperature tends exponentially toward the equilibrium value, an assumption which has been justified by recent kinetic studies[9] of the order–disorder transformation in $MgCd_3$.

With Mg_3Cd the extrapolations were short and errors introduced from this source were slight. The extrapolations were not short, however, for temperatures near the order–disorder Curie point for $MgCd_3$. Equilibration was so sluggish that errors of several per cent. were possible at temperatures between 70 and 80°. Accordingly three determinations were made of the total change in enthalpy for $MgCd_3$ on heating it from 50 to 100°. It was carefully maintained at the lower temperature for a long period of time to establish equilibrium initially. Near 100° equilibration occurred in a short period of time so that ΔH for the 50° interval of temperature could be established quite reliably. The individual heat capacity determinations were then used to construct a provisional curve of C_p *vs.* T. That curve was then adjusted upward proportionally so that the integrated heat effect obtained from the curve agreed with the directly measured ΔH for the 50 to 100° interval.

Results

The data for Mg_3Cd were obtained in 10 series of measurements involving a total of 81 determinations. For $MgCd_3$ there were 11 series and a total of 71 individual measurements. It was of course necessary to have the sample at equilibrium before and after each measurement. The treatment of the sample in the after-period has been described above. The details of the thermal conditioning of the samples prior to initiating a series of measurements are too numerous to relate here.[10] In general the thermal treatment was such that the sample was as near to equilibrium as could be achieved experimentally before measurements were begun. In some instances the treatment involved a very considerable amount of time and care. For example, with $MgCd_3$ below 80° it proved necessary to maintain the sample at temperature for roughly a week for it to come to equilibrium.

Smoothed values for the heat capacities are given in Table I. Excluding the regions of slow equilibration, the precision of the measurements is 0.1 to 0.2% as judged from the scatter of points from a smooth curve.

Residual Entropies.—Entropies of formation of magnesium–cadmium alloys were reported earlier based on measurements made using the electrochemical cell method.[4,11] The entropies of formation of $MgCd_3$ and Mg_3Cd at 270° were

(5) W. V. Johnston, Ph.D. Thesis, University of Pittsburgh, August, 1955.

(6) W. E. Wallace, R. S. Craig and W. V. Johnston, U. S. Atomic Energy Commission Report No. NYO-6328, Oct., 1955. This document is available from the U. S. Government Printing Office.

(7) J. C. Southard and F. G. Brickwedde, THIS JOURNAL, **55**, 4378 (1933).

(8) Absolute constancy is of course never achieved. In practice because of stray voltages in the thermocouple circuits temperatures will steady off until there is a drift of 10^{-5} to 5×10^{-5} deg./min. With experience an operator can ascertain when a proper final state of the system has been reached.

(9) R. A. Flinn, R. S. Craig and W. E. Wallace, *J. Phys. Chem.*, **61**, 236 (1957).

(10) The details of the thermal preconditioning are given in ref. 5.

(11) F. A. Trumbore, THIS JOURNAL, **76**, 6417 (1954).

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TABLE I

HEAT CAPACITIES OF $MgCd_3$ AND Mg_3Cd

T, °K.	C_p, cal./deg. g. atom $MgCd_3$	C_p, cal./deg. g. atom Mg_3Cd	T, °K.	C_p, cal./deg. g. atom $MgCd_3$	C_p, cal./deg. g. atom Mg_3Cd
298.16	7.06	6.01	415	6.88	16.68
300	7.10	6.01	420	6.89	19.98
310	7.39	6.10	423.8	..	27.35
320	8.01	6.90			(max.)
330	9.05	7.00	425	6.89	18.02
340	10.88	7.16	430	6.90	7.40
345	12.41	7.25	440	6.91	7.10
350	13.95	7.35	450	6.93	7.03
355	16.28	7.47	460	6.95	6.99
357.0	21.04	..	470	6.98	6.96
	(max.)		480	7.00	6.94
360	9.19	7.59	490	7.02	6.93
365	7.46	7.72	500	7.04	6.94
370	6.98	7.87	510	7.07	6.97
380	6.90	8.23	520	7.10	6.93
390	6.88	8.70	530	7.13	6.94
400	6.88	9.41	540	7.17	6.98
405	6.88	9.91	543.16	7.18	6.99
410	6.88	12.23			

found to be 1.04 and 0.91 e.u., respectively.[12] Using the heat capacity data for the pure metals reported in the following paper[13] together with earlier data from this Laboratory for the low temperature region[14] one computes entropies at 270° to be 11.56 e.u. for Mg and 16.28 e.u. for Cd. From these data one calculates the entropies of $MgCd_3$ and Mg_3Cd to be 16.14 and 13.65 e.u., respectively. The data in the present paper together with previously published results[3] permit the calculation of $S_{270°} - S_{0°K.}$ for the two compounds. These entropy increments are found to be 13.54 e.u. for Mg_3Cd and 15.96 e.u. for $MgCd_3$, from which one computes the residual entropies to be 0.11 and 0.18 e.u. for the respective compounds.

For reasons which shall now be indicated the quantities so computed represent that which may be called the uncorrected values. The compounds are formed upon cooling the corresponding magnesium–cadmium solid solution, the solution being the stable form at high temperatures. Since the transitions are second order and are spread out over a temperature range, progressive reduction of the temperature of the systems results in an accompanying configurational change. For the present purpose the configuration of the system can be represented by the Bragg–Williams[15] order parameter s. As temperature approaches 0°K., s tends to unity corresponding to the situation in which each magnesium atom occupies a magnesium site in the lattice and each cadmium atom, a cadmium site. However, in practice mobility is lost before perfect configurational order is achieved, s is frozen-in at some value slightly less than unity and the compound is left with a residual entropy.

The heat capacity data for Mg_3Cd show this freezing-in of the configuration in a very striking way (Fig. 1). The C_p values rise with temperature as if they will reach the Dulong–Petit limit at about 300°K. However, at about 310°K. there is a sudden rise in C_p followed by a small maximum, after which the heat capacity rises steadily until the λ point is reached. These results indicate that on cooling the order parameter becomes frozen-in at about 310°K. On warming back up configurational changes begin to occur at that temperature and there is a sudden rise in the heat capacity. The small maximum in C_p is undoubtedly a kinetic effect. Some of the configurational contribution which should have appeared at a slightly lower temperature has been displaced upward on the curve due to the slowness of atomic redistributions at the lower temperature. This point of view is supported by the results obtained by Welber, Webeler and Trumbore[16] using the continuous heating technique. Their results obtained with a heating rate of 4 deg./min. are also shown in Fig. 1. They find a small maximum at about 370°K. and their C_p values from 325 to 355°K. are about 10% lower than the present results. It seems clear that their technique delayed full development of the configurational contribution to C_p until temperatures in excess of 360°K. were reached at which point the mobility in the solid had increased to the point that the accumulated deficit in C_p could be realized. This gave rise to their maximum in C_p.

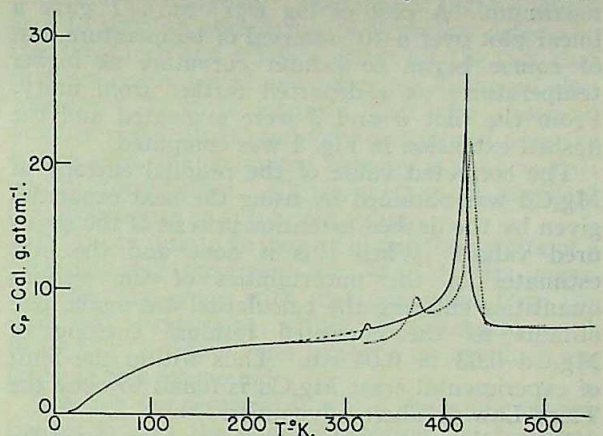

Fig. 1.—Heat capacity of Mg_3Cd: ———, this study; - - - - - -, present results corrected for frozen-in disorder (see text); ....., data of Welber, Webeler and Trumbore (ref. 16).

The dashed extension of the experimental curve in Fig. 1 shows the behavior to be expected if s had not become frozen-in. This extension has been constructed using results of theoretical treatments of order–disorder phenomena. The Bragg–Williams theory was used since results computed from their theory when s approaches unity do not differ from those obtained using more refined treatments. As s approaches unity, the configurational heat capacity C_p^c is given by the expression

$$C_p^c = \frac{\alpha}{T^2} e^{-\beta/T}$$

(12) Data are expressed throughout this paper on a per gram atom basis. These data therefore refer to the entropy change accompanying the formation of one gram atom of alloy from the component metals.

(13) W. G. Saba, K. F. Sterrett, R. S. Craig and W. E. Wallace, THIS JOURNAL, **79**, 3637 (1957).

(14) R. S. Craig, *et al.*, *ibid.*, **76**, 238 (1954).

(15) W. L. Bragg and E. J. Williams, *Proc. Roy. Soc.* (*London*), **145A**, 699 (1934).

(16) B. Welber, R. Webeler and F. A. Trumbore, *Acta Met.*, **1**, 374 (1953).

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where α and β are constants. C_p^s was estimated by extending linearly the curve below the sharp rise at 310°K. so as to join the curve at 530°K. and then subtracting data taken from this curve from the experimental results above the small maximum. A plot of log $C_p^s T^2$ *vs.* $1/T$ gave a linear plot over a 40° interval of temperature, but of course began to exhibit curvature at higher temperatures as s departed farther from unity. From the plot α and β were evaluated and the dashed extension in Fig. 1 was computed.

The corrected value of the residual entropy of Mg_3Cd was obtained by using the heat capacities given by the dashed extension instead of the measured values. When this is done and the best estimates of the uncertainties of the various quantities entering the calculation are made, one obtains as the corrected residual entropy of Mg_3Cd 0.03 ± 0.04 e.u. Thus within the limit of experimental error Mg_3Cd is found to obey the Third Law of Thermodynamics.

When the unsmoothed heat capacity data[3] for $MgCd_3$ were examined, it was found that there is a sharp rise and a small maximum at about 200°K. These are smaller than the ones shown in Fig. 1 for Mg_3Cd and had escaped notice at the time of the original publication. A procedure similar to that which was used for Mg_3Cd was applied to $MgCd_3$. The frozen-in disorder corresponded to 0.02 e.u., which leads to a corrected value for the residual entropy of 0.16 ± 0.04 e.u. for $MgCd_3$. The probable origin of this entropy will be considered in a later section of this paper.

Standard Heats, Free Energies and Entropies of Formation at 25°.—Values for all of these quantities have been reported earlier[4,11] for 270°. Using the present heat capacity data it is possible to calculate values for these quantities for 25°. Results of such calculations are shown in Table II. For Mg_3Cd the results pertain to the hypothetical state in which there is the equilibrium value of the order parameter s. In other words for this material the heat capacities used below 310° were not the data obtained experimentally but those taken from the dashed extension in Fig. 1. Although this is the way the calculations were made, the actual data might have been employed without incurring errors exceeding the listed uncertainties. Those uncertainties are rough estimates based upon the uncertainties in the various measured quantities employed in making the calculations. The principal contribution to the uncertainty in ΔH_f and ΔF_f is the uncertainty in the value of these quantities as measured at 270°. The uncertainties in the heat capacity data make a negligible contribution to uncertainty of those quantities but account for about half of the uncertainty in the ΔS_f values.

TABLE II

STANDARD HEATS, FREE ENERGIES AND ENTROPIES OF FORMATION OF $MgCd_3$ AND Mg_3Cd AT 25°

	$MgCd_3$		Mg_3Cd	
ΔH_f (cal./g. atom)	−1130	± 60	−1330	± 50
ΔF_f (cal./g. atom)	−1177	± 55	−1286	± 45
ΔS_f (e.u./g. atom)	+ 0.16	± 0.02	+ 0.15	± 0.03

Buck, Wallace and Rulon measured ΔH_f for these substances at 25° using a differential solution calorimetric technique.[17] They obtained −1595 and −775 cal./g. atom of compound for $MgCd_3$ and Mg_3Cd, respectively. These data are in poor agreement with the quantities given in Table II. The present data are undoubtedly more reliable. There are two reasons for believing that this is the case. First, as was pointed out earlier,[17] the directly determined ΔH_f's are extremely sensitive to experimental error. An error of 0.001 in mole fraction leads to an error of 180 cal./g. atom in ΔH_f and a weighing error of only 0.1 mg. affected ΔH_f to the extent of 450 cal. Second, there is a better appreciation now of the care which must be taken to establish equilibrium in the samples at 25°. It is possible that in the earlier study there was a considerable amount of frozen-in disorder in the samples of Mg_3Cd accounting for the large discrepancy in that case. The present results should be free of this difficulty since the electrochemical cell work was carried out at temperatures ranging from 270 to 300° where configurational equilibrium is quickly and easily established. Furthermore, sufficient attention was given to maintaining equilibrium during the heat capacity work that it is felt that no significant errors are introduced from this source into the data in Table II.

Discussion of Results

Heat Capacities.—The heat capacities reported in this paper join smoothly with the results obtained earlier[3] for the low temperature region. In addition to the work of Welber, *et al.*, referred to earlier, Nagasaki, Hirabayashi and Nagusa[18] and more recently Rosenbaum and Welber[19] have studied alloys with compositions fairly near to Mg_3Cd. The continuous heating technique was used in these studies. Their results resemble qualitatively the behavior exhibited in Fig. 1 except that the low temperature peak does not appear. However, because of the composition difference a detailed quantitative comparison seems unwarranted. Khomyakov, Kholler and Troshkina[20] have measured the heat capacity of a magnesium–cadmium alloy with composition which is stated to be 75.15 atomic % cadmium, also using continuous heating. Their results agree within about 3% with the present results up to 75°. Their specific heats reached a maximum at 77.7° whereas the present results continue to rise and reach a peak 25% higher at 83.9°. At 160°, the highest temperature reached by Khomyakov, *et al.*, the results again agree within a few per cent. The discrepancy between the temperatures at which C_p peaks in these two cases is in the wrong direction to be ascribed to kinetic factors. It must arise because the composition of the sample studied by Khomyakov deviated from 75.0 atomic % cadmium by

(17) T. M. Buck, Jr., W. E. Wallace and R. M. Rulon, THIS JOURNAL, **74**, 136 (1954).

(18) M. Hirabayashi, S. Nagasaki, H. Maniwa and H. Nagusa, *J. Jap. Inst. Met.*, **13**, 1 (1949).

(19) B. M. Rosenbaum and B. Welber, *J. Chem. Phys.*, **24**, 485 (1956).

(20) K. G. Khomyakov, V. A. Kholler and V. A. Troshkina, *Vestnik Moskov. Univ., No. 6, Ser. Fiz-Mat. i Estest Nauk*, No. 4, 5, 43 (1950).

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more than the published composition would indicate, since Stepanov and Kornilov[21] have shown that the transformation point is maximal for the composition $MgCd_3$ and falls away for alloys whose cadmium contents are either greater or less.

The present study serves to emphasize the great care which must be exercised to obtain equilibrium heat capacities in systems which are undergoing atomic rearrangements. It is clear that the conventional continuous heating technique may in these cases lead to results which are seriously in error. Only if diffusion is exceptionally rapid, such as in beta brass, will the results be meaningful. For reasons which have been set forth earlier spurious heat capacity maxima can appear. (This to a lesser degree may also happen with the intermittent heating procedure.) Furthermore the heat capacity distribution under the λ-point for the continuously heated sample may be seriously distorted from its equilibrium shape. Thus, some aspects of the intense theoretical work of the 1930's dealing with order–disorder phenomena seems like effort misplaced. Much theoretical work was done in attempts to account for the exact temperature dependence of experimental configurational heat capacities, when due to the experimental method employed, the results obtained are now open to question.

Residual Entropy of $MgCd_3$.—As was shown earlier, even after allowing for frozen-in disorder associated with interchanged Mg and Cd atoms, $MgCd_3$ has a residual entropy of 0.16 e.u./g. atom of alloy. It is suggested that this entropy originates with vacant lattice sites (Schottky defects) which persist in this system down to the lowest temperatures studied. The density of $MgCd_3$ has been found[22] to be 1.7% less than that computed[23] from the unit cell dimensions. This density discrepancy has been attributed to the fact that an average of 1.7% of the lattice sites are unoccupied in $MgCd_3$. The special factors which lead to such an abundance of Schottky defects in this substance and which account for the fact that they are not removed on cooling are discussed elsewhere.[24,25] If it is assumed that the observed number of defects is randomly distributed over the lattice sites, the computed entropy is 0.17 ± 0.01 e.u./g. atom of alloy. This is, of course, in excellent agreement with the observed value.

It is appropriate to inquire about the results of a corresponding treatment for Mg_3Cd. Its measured density agrees with that computed from the unit cell dimensions within experimental error (0.2%). Therefore, one expects no residual entropy in this compound.

The low temperature at which the configuration freezes in and the small correction for frozen-in disorder for $MgCd_3$ are both suggestive of extensive vacancies in this substance at low temperatures. Atomic interchanges most likely occur through a mechanism involving a series of interchanges with a vacancy. The persistence of mobility to such low temperatures and low amounts of disorder is consistent with the notion that extensive vacancies exist in this system at low temperatures.

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PITTSBURGH 13, PA.

[CONTRIBUTION NO. 1009 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Heat Capacities of Magnesium and Cadmium between 20 and 270°[1]

BY W. G. SABA, K. F. STERRETT, R. S. CRAIG AND W. E. WALLACE

RECEIVED MARCH 23, 1957

Heat capacities of magnesium and cadmium are reported for the temperature interval 20 to 270°. Measurements were made using an adiabatic calorimeter. Results are compared with previous determinations in the same temperature range. Deviations from the values accepted in the compilations by Kelley and Stull and Sinke are substantial for magnesium. For cadmium they are smaller but still appreciable. Results are in good agreement with the data obtained at lower temperatures by Craig, *et al.*

In making the thermodynamic calculations reported in the preceding paper[2] it was necessary to know the heat capacities of magnesium and cadmium in the temperature interval 25 to 270°. Values obtainable from the literature were not sufficiently precise, particularly for the residual entropy calculations, and so it became necessary to redetermine these quantities. The results of those redeterminations are reported in this paper.

Experimental Details

The apparatus employed and method of measurement have been described elsewhere.[3-5] The procedure employed in the present work differed from that used in the study of the magnesium–cadmium compounds only in that for some of the measurements on magnesium the individual determinations covered somewhat larger temperature intervals

(1) This work was supported by a grant from the Atomic Energy Commission.

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(10°). This was possible because the heat capacities were almost linear with temperature. In contrast with the behavior observed when the compounds were being studied the calorimeter came to thermal equilibrium in the normal length of time (about 30 min.) throughout the temperature range covered.

The samples employed were portions of samples used in the study of the low temperature specific heats of these metals published earlier.[6] The masses of the samples used were: magnesium, 127.613 g. or 5.2472 g. atoms; cadmium, 639.451 g. or 5.6886 g. atoms.

Results

For magnesium thirty-seven determinations were made covering the range 20 to 275°. The data for cadmium consisted of 39 measurements extending from 27 to 280°. The smoothed heat capacities obtained are given in Table I. The average deviation from a smooth curve drawn through all the points was 0.12 for magnesium and 0.08 for cadmium, indicating a precision of about 0.1%. Of the 76 results only 9 deviated from the smooth curve by more than 0.2%. The maximum deviations were 0.4% and 0.35% for magnesium and cadmium, respectively.

TABLE I

HEAT CAPACITIES OF MAGNESIUM AND CADMIUM

T, °K.	C_p, cal./deg. g. atom Magnesium	Cadmium	T, °K.	C_p, cal./deg. g. atom Magnesium	Cadmium
298.16	5.941	6.212	430	6.314	6.556
300	5.948	6.218	440	6.339	6.586
310	5.982	6.239	450	6.363	6.616
320	6.013	6.259	460	6.386	6.652
330	6.042	6.283	470	6.414	6.692
340	6.072	6.307	480	6.440	6.728
350	6.104	6.334			
360	6.134	6.361	490	6.467	6.769
370	6.163	6.390	500	6.493	6.814
380	6.189	6.416	510	6.517	6.869
390	6.216	6.443	520	6.541	6.927
400	6.241	6.470	530	6.561	6.988
410	6.266	6.499	540	6.583	7.054
420	6.289	6.527	543.16	6.591	7.076

It is of interest to compare the present data with results obtained in earlier studies. Kelley[7] and Stull and Sinke[8] have reviewed existing heat capacity data for these two elements and have accepted certain values as the best representation of their heat capacities for the above room temperature range. Their accepted values coincide for cadmium but differ appreciably for magnesium. Both accepted values for magnesium deviate on the average from the present results by about a per cent.; Kelley's equation leads to a result which is very much too low at the low temperature limit (4% at 300°K.). Agreement with the present data is somewhat better for cadmium. Between 300 and 500°K. the deviations average 0.22%, but above 500°K. the differences rapidly increase until at 540°K. the accepted results computed from Kelley's equation are low by 2.4%. Examination of the original literature, and limiting consideration to the last 25 years, reveals that cadmium has been studied by Bronson and Wilson[9] (−80 to 120°) and magnesium has been studied by Jaeger and Poppema[10] (0 to 550°) and Seekamp[11] (18 to 500°). As was the case in the earlier study of cadmium at lower temperatures the results of Bronson and Wilson are in good agreement with those obtained in this Laboratory. Over the 90° interval of temperature common to both series of determinations the maximum deviation is 0.22% and the average deviation is 0.15%, Bronson and Wilson's results being consistently higher by this amount. Seekamp's data for magnesium scatter about the present results; the deviations average about 0.8% and rise to a maximum of 1.1%. Jaeger and Poppema's results are consistently lower than those reported in this paper by about 0.7% but the difference in no case exceeds 0.9%.

Low temperature heat capacities of magnesium and cadmium were determined[6] in this Laboratory several years ago covering the range 12 to 320°K. In the 20 degrees of overlap it is found that the present results are consistently about 0.2% lower than the previous results. Since the two sets of data were obtained using entirely different instruments, this difference is perhaps indicative of the combined systematic error present in the measurements. Considering the deviations normally observed between independently determined heat capacities, this close agreement between the two sets of data is gratifying.

The rather rapid rise of the heat capacities of cadmium above the equation of Kelley for temperatures in excess of 500°K. has been mentioned above. This appears to be the beginning of a heat capacity anomaly associated with premelting, or heterophase fluctuations,[12] such as have been observed for the alkali metals.[13] Khomyakov, *et al.*,[14] have studied pure cadmium in the immediate vicinity of the melting point. They find a sharp rise in the heat capacity curve and claim that more than one third of the normally reported latent heat of fusion is associated with this premelting heat capacity anomaly. The rapidly increasing slope in the curve obtained in this study for cadmium above 500°K. represents perhaps the faint beginnings of the more pronounced effects observed by Khomyakov, *et al.*, above 570°K. In contrast, the curve for magnesium near the upper limit of the present study appears to be leveling off, which is not surprising since this substance is still so far removed from its melting point that any influence of heterophase fluctuations on its heat capacity is expected to be slight.

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[CONTRIBUTION FROM THE MINERALS THERMODYNAMICS EXPERIMENT STATION, REGION II, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

Heats of Formation of Crystalline Silicates of Strontium and Barium

BY R. BARANY, E. G. KING AND S. S. TODD

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Heats of formation from the component oxides at 298.15°K. were obtained for strontium metasilicate, strontium orthosilicate, barium metasilicate, barium orthosilicate, dibarium trisilicate and barium disilicate by measuring heats of reaction of the silicates and oxides with hydrofluoric acid.

This paper presents heats of formation of two crystalline strontium silicates ($SrSiO_3$ and Sr_2SiO_4) and four crystalline barium silicates ($BaSiO_3$, Ba_2SiO_4, $Ba_2Si_3O_8$ and $BaSi_2O_5$). Previous papers from this Laboratory by Torgeson and Sahama[1] and King[2] contained corresponding data for some magnesium and calcium silicates.

Materials and Method

The silicates were prepared by repeated, prolonged sintering of stoichiometric mixtures of reagent-grade strontium or barium carbonate and pure quartz. In each instance several heats were required, with intervening grinding, mixing, analysis and adjustment of composition, to obtain a satisfactory product.

In preparing strontium metasilicate the total heating time was 246 hr. between 1000 and 1350°, of which 32 hr. were above 1200°. The product gave an X-ray diffraction pattern agreeing virtually perfectly with that reported by Carlson and Wells.[3] Chemical analysis gave 63.26% strontium oxide, 36.66% silica and 0.12% iron and aluminum oxides (theoretical analysis, 63.30% strontium oxide and 36.70% silica).

Strontium orthosilicate required four heats totaling 35 hr. at 1200–1300°, which were conducted in a platinum vessel. X-Ray diffraction of the product gave no evidence of uncombined oxides, but the pattern disagreed with that of O'Daniel and Tscheischwili,[4] who may have had a different crystalline variety. Analysis gave 77.51% strontium oxide, 22.47% silica and 0.03% sodium oxide (theoretical analysis, 77.52% strontium oxide and 22.48% silica).

The stoichiometric mixture for the preparation of barium metasilicate was pelletized and heated nine times for a total of 247 hours between 1000 and 1410°, of which 48 hours were above 1200°. Silverman and co-workers[5] list two crystalline varieties of barium metasilicate. Austin[6] obtained the X-ray diffraction pattern of one variety, but that of the other has not been reported in the literature. The pattern for the present material showed no evidence of uncombined oxides but disagreed with that of Austin, indicating that it probably is the variety labeled "$BaO{\cdot}SiO_2$(II)" by Silverman and co-workers. Analysis gave 71.95% barium oxide and 28.17% silica, as compared with the theoretical 71.85 and 28.15%.

Barium orthosilicate was prepared in a nickel crucible; the stoichiometric mixture was heated five times for a total of 10 days at 1000–1150° and 16 hours at 1150–1300°. There was some attack of the crucible, making it necessary to discard the surface layer after each heat. The cleaned product gave no visible precipitate of nickel glyoxime from a 1-g. sample. The X-ray diffraction pattern agreed with that reported by Austin.[6] Analysis showed 83.78% barium oxide and 16.39% silica, as compared with the theoretical 83.62 and 16.38%.

The preparation of dibarium trisilicate required many days at 1050°, 78 hr. at 1200°, 24 hr. at 1250°, and 6 hr. at 1300°. The product gave an X-ray diffraction in excellent agreement with that of Austin.[6] Chemical analysis showed 63.00% barium oxide, 37.05% silica, and 0.01% iron and aluminum oxides (theoretical analysis, 62.98% barium oxide and 37.02% silica).

The stoichiometric mixture for preparing barium disilicate was pelletized and heated for a total of 100 hr. at 1100° and 30 hr. at 1300°. The X-ray diffraction pattern obtained immediately after the last heat checked that in the ASTM Catalog. However, the pattern changed slowly with time on standing at room temperature, indicating the compound to be unstable. In using this substance in the subsequently reported measurements, it was reheated to 1300° and quenched to room temperature immediately before each run. Chemical analysis gave 56.05% barium oxide and 43.92% silica, as compared with the theoretical 56.06 and 43.94%.

Strontium oxide was prepared from reagent-grade strontium carbonate by first repeatedly boiling in water and filtering and then heating to 1400° until decomposition was essentially complete. Analysis gave 99.75% strontium oxide and less than 0.1% carbon dioxide. The substance was kept in sealed glass bulbs before use in the measurements.

Barium oxide was prepared from reagent-grade barium hydroxide. The latter was dissolved in water and treated with hydrogen peroxide to precipitate hydrated barium peroxide. The precipitate was dried, heated *in vacuo* to 1300° to decompose it to the normal oxide, and sealed in glass bulbs for preservation. Analysis of the product showed 0.15% water, 0.02% silica and 0.05% barium carbonate as impurities.

The heats of formation were determined by measuring the heats of reaction of the silicates and their constituent oxides with 20.1% hydrofluoric acid at 73.7°. In all instances 940.1 g. of the acid was employed. The masses of the silicates, strontium oxide and barium oxide conformed stoichiometrically in each instance with 0.7420 g. of quartz, which was adopted as a basis. The samples were contained in gelatin capsules for dropping from room temperature (measured and correction made to 25°) into the calorimeter. Correction for the capsules was made from separate measurements of the heat of solution of gelatin under the same calorimetric conditions.

The various compounds that were run picked up small amounts of water in handling. In each instance the amount of this water was determined by weight loss on ignition and correction was applied for it.

It was found expedient to mix about 0.1 g. of barium carbonate per capsule with the barium compounds to prevent clumping and therefore to obtain complete reaction with the acid. The heat of reaction of barium carbonate with the acid was determined as −31.5 cal./g. in separate experiments, and proper correction was applied. The heat of reaction of the barium carbonate was between 0.5 and 2% of the total heat evolved, depending upon the substance under study.

The calorimetric apparatus was that described by Torgeson and Sahama[1] with the modifications reported by King.[2]

Measurements and Results

All values are in terms of the defined calorie (1 cal. = 4.1840 abs. joules). All weighings were reduced to vacuum, and all molecular weights accord with the 1954–55 Report on Atomic Weights.[7]

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TABLE I

HEATS OF REACTION (CAL./MOLE)

	Reaction	No. of detns.	ΔH	Uncertainty
(1)	SiO_2(c, 25°) + 6HF(sol, 73.7°) → H_2SiF_6(sol, 73.7°) + $2H_2O$(sol, 73.7°)	7	−33,290	80
(2)	SrO(c, 25°) + 2HF(sol, 73.7°) → SrF_2(p, 73.7°) + H_2O(sol, 73.7°)	5	−65,290	80
(3)	2SrO(c, 25°) + 4HF(sol, 73.7°) → $2SrF_2$(p, 73.7°) + $2H_2O$(sol, 73.7°)	5	−131,070	100
(4)	BaO(c, 25°) + 2HF(sol, 73.7°) → BaF_2(p, 73.7°) + H_2O(sol, 73.7°)	11	−73,040	120
(5)	2BaO(c, 25°) + 4HF(sol, 73.7°) → $2BaF_2$(p, 73.7°) + $2H_2O$(sol, 73.7°)	11	−146,080	240
(6)	$SrSiO_3$(c, 25°) + 8HF(sol, 73.7°) → SrF_2(p, 73.7°) + H_2SiF_6(sol, 73.7°) + $3H_2O$(sol, 73.7°)	6	−67,340	110
(7)	Sr_2SiO_4(c, 25°) + 10HF(sol, 73.7°) → $2SrF_2$(p, 73.7°) + H_2SiF_6(sol, 73.7°) + $4H_2O$(sol, 73.7°)	6	−114,320	200
(8)	$BaSiO_3$(c, 25°) + 8HF(sol, 73.7°) → BaF_2(p, 73.7°) + H_2SiF_6(sol, 73.7°) + $3H_2O$(sol, 73.7°)	6	−68,300	90
(9)	Ba_2SiO_4(c, 25°) + 10HF(sol, 73.7°) → $2BaF_2$(p, 73.7°) + H_2SiF_6(sol, 73.7°) + $4H_2O$(sol, 73.7°)	6	−114,890	110
(10)	$Ba_2Si_3O_8$(c, 25°) + 22HF(sol, 73.7°) → $2BaF_2$(p, 73.7°) + $3H_2SiF_6$(sol, 73.7°) + $8H_2O$(sol, 73.7°)	6	−165,530	80
(11)	$BaSi_2O_5$(c, 25°) + 14HF(sol, 73.7°) → BaF_2(p, 73.7°) + $2H_2SiF_6$(sol, 73.7°) + $5H_2O$(sol, 73.7°)	3	−98,340	150

Each heat of formation is the resultant of measurements of a series of reactions for which skeleton equations are given in Table I. The precision uncertainties were calculated according to the methods of Rossini and Deming.[8]

The experimental data are given in Table I which shows the reactions, numbers of determinations, average heat values, and precision uncertainties. In this table, "c" denotes a crystalline substance, "sol" denotes a substance in solution, and "p" denotes a precipitate.

The heat of reaction 1 is from the paper of King,[2] who employed the same equipment and calorimetric conditions as in the present work.

Each of reactions 2 to 5 were conducted in solutions identical in composition with the final solution from reaction 1. Each of reactions 6 to 11 were conducted in fresh acid, without previous additions. This procedure is necessary to produce the exact material balance in the summation of the reaction heats to obtain the desired heats of formation of the silicates from their constituent oxides.

The heat of reaction 3 is nearly 500 cal. more than twice that of reaction 2, showing that there is a considerable concentration effect. On the other hand, the concentration effect for reactions 4 and 5 was negligible. Eleven determinations were made of the heat of reaction of barium oxide with acid containing the proper amount of dissolved silica. The samples of barium oxide were varied in size to cover the composition range necessary to conform stoichiometrically with compounds ranging from $BaSi_2O_5$ to Ba_2SiO_4. No significant dependence of the heat of reaction on sample size was noted, and so the same molal value is used in obtaining the heats of formation of all the barium silicates.

Measurement of the heat of reaction 11 was difficult because of the previously mentioned instability of barium disilicate. Even though the samples were heated to 1300° and quenched to room temperature, the results were uncertain. The three best values obtained are −98,220, −98,470 and −98,330 with a mean of −98,340 ± 150 cal.

Table II illustrates the use of the data in Table I for obtaining heats of formation of the silicates from their constituent oxides.

(8) F. D. Rossini and W. E. Deming, *J. Wash. Acad. Sci.*, **29**, 416 (1939).

TABLE II

HEAT OF FORMATION OF $SrSiO_3$ (CAL./MOLE)

	Reaction	ΔH	Uncertainty
(1)	SiO_2(c, 25°) + 6HF(sol. 73.7°) → H_2SiF_6(sol. 73.7°) + $2H_2O$(sol. 73.7°)	−33,290	80
(2)	SrO(c, 25°) + 2HF(sol. 73.7°) → SrF_2(p, 73.7°) + H_2O(sol. 73.7°)	−65,290	80
(6)	$SrSiO_3$(c, 25°) + 8HF(sol. 73.7°) → SrF_2(p. 73.7°) + H_2SiF_6(sol. 73.7°) + $3H_2O$(sol. 73.7°)	−67,340	110
(12)	SrO(c, 25°) + SiO_2(c, 25°) → $SrSiO_3$(c, 25°) $\Delta H_{12} = \Delta H_1 + \Delta H_2 - \Delta H_6$	−31,240	160

As the final solution after conducting reactions 1 and 2 consecutively in the same acid solution is identical in composition with the solution after conducting reaction 6 in fresh acid, it follows that the reactions and heats may be added as indicated to obtain the heat of formation of strontium metasilicate at 25° from its constituent oxides.

The heats of formation of the crystalline strontium and barium silicates, obtained in this manner, appear in Table III. Because of the before mentioned difficulty of measurement, it is recommended that the value for barium disilicate be interpreted as setting an upper limit (algebraic) to the heat of formation, rather than as clearly defining its value.

TABLE III

HEATS OF FORMATION FROM THE OXIDES (KCAL./MOLE)

Substance	$\Delta H_{298.16}$	Substance	$\Delta H_{298.16}$
$SrSiO_3$	−31.24 ± 0.16	Ba_2SiO_4	−64.48 ± 0.28
Sr_2SiO_4	−50.04 ± .24	$Ba_2Si_3O_8$	−82.42 ± .35
$BaSiO_3$	−38.03 ± .17	$BaSi_2O_5$	−41.28 ± .25

Related Thermal Data.—The heats of formation of the meta- and orthosilicates of magnesium, calcium, strontium and barium are assembled for comparison in Table IV. The values for the magnesium and calcium compounds are from the work of Torgeson and Sahama[1] and King,[2] except for $Ca_2SiO_4(\gamma)$, which was derived from unpublished data of Coughlin and O'Brien of this Laboratory.

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Rossini and co-workers[9] list values leading to the following heats of formation from the oxides (kcal./mole): −24.7 for strontium metasilicate, −33.0 for strontium orthosilicate, −20.7 for barium metasilicate, and −24.6 for barium orthosilicate, based upon older thermochemical work. The present values are considered much superior. It is of interest to note that the new values become increasingly negative in going from magnesium to barium in both the meta- and ortho-series whereas the solder work indicated a reversal in this trend.

TABLE IV

HEATS OF FORMATION FROM THE OXIDES AT 298.15°K. (KCAL./MOLE)

Substance	ΔH	Substance	ΔH
$MgSiO_3$[a]	− 8.69 ± 0.15	Mg_2SiO_4[c]	−15.12 ± 0.21
$CaSiO_3$[b]	−21.25 ± .13	$Ca_2SiO_4(\beta)$	−30.19 ± .23
$SrSiO_3$	−31.24 ± .16	$Ca_2SiO_4(\gamma)$	−32.7
$BaSiO_3$	−38.03 ± .17	Sr_2SiO_4	−50.04 ± .24
		Ba_2SiO_4	−64.48 ± .28

[a] Clinoenstatite. [b] Wollastonite. [c] Forsterite.

The heats of formation of the silicates from the oxides may be converted to heats of formation from the elements by means of available data for the oxides. In this connection, the heat of formation of quartz (−210.26 kcal./mole) obtained by Humphrey and King[10] and the recent value of Huber and Holley[11] for calcium oxide (−151.79 kcal./mole) are adopted. Shomate and Huffman[12] and Holley and Huber[13] have obtained values of the heat of formation of magnesium oxide that differ by only 140 cal./mole; the mean, −143.77 kcal./mole, is adopted. Values for strontium oxide (−141.1 kcal./mole) and barium oxide (−133.4 kcal./mole) are from NBS Circular 500.[9] These values lead to the heats of formation from the elements listed in Table V, which also brings up-to-date the values given by Torgeson and Sahama[1] and King.[2]

TABLE V

HEATS OF FORMATION FROM THE ELEMENTS AT 298.15°K. (KCAL./MOLE)

Substance	ΔH	Substance	ΔH
$MgSiO_3$	−362.7	$SrSiO_3$	−382.6
Mg_2SiO_4	−512.9	Sr_2SiO_4	−542.5
$CaSiO_3$	−383.3	$BaSi_2O_5$	−595.2
$Ca_2SiO_4(\beta)$	−544.0	$Ba_3Si_2O_8$	−980.0
$Ca_2SiO_4(\gamma)$	−546.5	$BaSiO_3$	−381.7
Ca_3SiO_5	−692.6	Ba_2SiO_4	−541.5

(9) F. D. Rossini, D. D. Wagman, W. H. Evans, S. Levine and I. Jaffe, Natl. Bur. Standards Circular 500, Feb. 1, 1952.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SYRACUSE UNIVERSITY]

Low Temperature Heat Capacities of Magnesium Diboride (MgB_2) and Magnesium Tetraboride (MgB_4)

BY ROBINSON M. SWIFT AND DAVID WHITE[1]

RECEIVED FEBRUARY 14, 1957

The heat capacities of magnesium diboride (MgB_2) and magnesium tetraboride (MgB_4) were measured in the temperature range 18 to 305°K. The values of heat capacity, entropy, enthalpy and free energy function have been tabulated at integral values of temperature. The entropy at 298.16°K. of MgB_2 is 8.60 ± 0.04 cal. deg.$^{-1}$ mole^{-1}, that of MgB_4 is 12.41 ± 0.06 cal. deg.$^{-1}$ mole^{-1}. The heat capacity of these compounds at the lowest temperatures measured do not exhibit at T^2 relationship characteristic of some substances having a layer structure.

Introduction

The existence of magnesium borides with formulas MgB_2[2,3] and $MgBr_4$[2] has been shown by X-ray diffraction studies and chemical analysis. The diboride has a layered structure in which hexagonal nets of boron atoms are separated by layers of magnesium atoms. The structure of the tetraboride is not known. Recent studies have shown that in crystalline substances with layer structures, such as graphite[4] and gallium,[5] the heat capacity at low temperatures follows a T^2 law, rather than the Debye T^3 law. However, for CdI_4, a compound having a layered structure, it has been found that neither the T^2 nor T^3 relationship was followed at low temperatures.[6] The pronounced anisotropy characteristic of the graphite and gallium structures does not prevail in CdI_4 which may account for the lack of a T^2 relationship in the latter case.

The layer structure of MgB_2 is more closely related to that of CdI_4 than that of graphite from the standpoint of anisotropy. However, in the case of MgB_4, if the hexagonal boron network is retained, the interactions between the layers may be sufficiently diminished so as to lead to a T^2 dependence in the heat capacity at relatively low temperatures.

Apparatus and Procedure

Calorimeter.—The Nernst type vacuum calorimeter which was used for the measurements was similar to that described by Johnston and Kerr[7] with only minor changes being made in the calorimeter assembly and vacuum system.

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The calorimeter itself had a capacity of about 60 ml. Its cylindrical surface was wound with AWG 40, formex-insulated gold–0.15% silver wire. This served as both resistance thermometer and heater and its resistance at room temperature was about 300 ohms. The winding was covered with gold foil cemented with General Electric Adhesive No. 7031. The calorimeter assembly was inserted directly into a Collins helium cryostat.

Electrical Circuits.—A White double potentiometer with a 100,000 microvolt range was used for the resistance thermometer and energy measurements together with suitable standard resistors calibrated by the National Bureau of Standards. A Wenner potentiometer with a 10,000 microvolt range was used to measure the thermocouple electromotive forces. A 30,000:100 ohm voltage divider was used in the energy circuit.

Timing.—The timing of the energy input was done by a clutch-operated Standard Electric Timing Company timing clock which read directly to 0.01 sec. This clock was driven by the amplified output of a General Radio Company precision fork and was actuated by a single master switch which also controlled the energy input.

Temperature Scale.—The thermodynamic temperature scale for this Laboratory was established by comparison of a copper–constantan thermocouple against a standard thermocouple obtained from the Ohio State University Cryogenic Laboratory, and calibrated there against a primary standard, No. 80.[8] Absolute temperatures are probably accurate to within ±0.05°. The uncertainties in the measured temperature differences of the heat capacity runs are no greater than ±0.005°.

Data Computation.—The calculations were made as outlined by Giauque[9] and Johnston.[7] Corrections were made to the measured heat capacities for the energy lost in the potential divider and leads, heat leaks, calorimeter surface superheating during energy input, drifts in block temperatures, radiation to the calorimeter from the blocks, potentiometer battery drifts, and heat generated in the leads connecting the calorimeter winding with the block terminals. The same corrections were applied to the empty calorimeter calculations. Helium gas was introduced into the calorimeter after filling with solid and before sealing to reduce superheating. Corrections were made for this and for the other impurities as listed in Table I, assuming that the heat capacities of the individual substances were completely independent and additive.

Preparation of the Magnesium Borides.—Magnesium diboride was prepared by heating together in a helium atmosphere at 900 ± 25° for three hours stoichiometric quantities of the elements. The magnesium was a commercial grade analyzing 99.9%. The boron was obtained by vacuum sublimation at 1500° of Fisher Scientific Company "purified amorphous boron." After our further purification the residue analyzed 99.70 ± 0.25% boron by sodium hydroxide–mannitol titration of the oxidized product. The MgB_2 product included gross impurities as given in Table I and spectroscopic impurities totalling less than 0.1% and consisting principally of iron, aluminum, manganese, silicon and calcium.

The magnesium tetraboride was made by treating the magnesium diboride with somewhat more than two equivalents of purified boron at 1050 ± 25° for four hours in an argon atmosphere. Higher temperatures favored production of a colored magnesium boride thought to be MgB_6; lower temperatures and shorter times gave lower yields of MgB_4 and larger amounts of unreacted MgB_2. The latter, together with other soluble impurities, was removed by treatment with warm dilute hydrochloric acid and subsequent washing with water. Considerable free boron remained with the MgB_4.

X-Ray diffraction studies identified the substances present and chemical analysis established the amounts in each of the two boride preparations. The analysis for each is given in Table I.

Results and Discussion

The calculated molal heat capacity of magnesium diboride is shown in Table II and that of magnesium tetraboride in Table III. These results have been corrected for the impurities listed in Table I.[10] They are listed in the order done. Temperature increments may be inferred from the mean temperatures. They never exceeded 10% of the temperature scale or 10°, whichever was smaller. Computed thermodynamic functions for these compounds are given in Tables IV and V. The ice point was taken as 273.16°K. and the results are expressed in calories equal to 4.1840 absolute joules.

The heat capacities of MgB_2 and MgB_4 do not follow the Debye T^3 law at low temperatures; hence, a graphical extrapolation was made to absolute zero to determine the entropy and other

Table I

Composition of Samples of Magnesium Borides

Substance	MgB_2, wt. %	MgB_4, wt. %
MgB_2	93.90	...
MgB_4	1.08	89.42
B	3.69	10.32
Mg	0.46	...
MgO	0.73	...
Spectroscopic impurity (as SiO_2)	0.14	0.25
Wt. of sample in calorimeter (g.)	62.685	43.946

Table II

Molal Heat Capacity of Magnesium Diboride (MgB_2)

Mol. wt. 45.96; 1.2808 moles

Mean temp., °K.	C_p, cal. deg.$^{-1}$	Mean temp., °K.	C_p, cal. deg.$^{-1}$
18.28	....	140.35	5.070
21.12	0.010	154.92	5.911
23.05	.022	173.53	6.864
25.06	.034	194.73	7.973
27.19	.046	219.27	9.096
29.66	.053	236.77	9.857
32.41	.074	238.63	9.728
34.92	.103	246.14	10.111
37.75	.134	253.63	10.581
41.37	.163	259.61	10.694
45.43	.248	266.88	10.872
54.12	.450	274.04	11.134
57.42	.554	286.69	11.414
60.99	.661	298.81	11.492
65.42	.849		
70.26	1.108	26.44	0.058
75.60	1.355	128.41	4.398
81.29	1.684	145.03	5.366
85.52	1.871	160.29	6.266
91.29	2.188	183.37	7.414
97.04	2.485	208.21	8.593
102.83	2.786	248.39	10.196
108.58	3.155	279.19	11.251
114.13	3.421	300.14	11.410
119.20	3.767		
124.40	4.043	237.71	10.032
129.79	4.319	238.69	9.882
		254.87	10.409
293.42	11.419	287.69	11.370
		304.22	11.435
136.05	4.823	304.06	11.424

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TABLE III

MOLAL HEAT CAPACITY OF MAGNESIUM TETRABORIDE (MgB_4)

Mol. wt. 67.60; 0.5813 mole

Mean temp., °K.	C_p, cal. deg.$^{-1}$	Mean temp., °K.	C_p, cal. deg.$^{-1}$
187.17	10.130	47.81	0.944
265.74	15.177	53.71	1.247
271.52	15.423	78.84	2.744
276.60	15.712	86.28	3.236
		94.01	3.750
20.29	0.071	103.08	4.288
25.83	.050	112.87	4.889
28.72	.243	121.84	5.553
31.45	.296	130.84	6.169
36.82	.449	139.20	6.740
149.05	7.430	188.99	10.215
155.81	7.971	201.24	11.161
162.66	8.438	212.85	11.995
169.74	8.873	225.01	12.647
177.27	9.320		
235.27	13.318	20.56	0.067
242.98	13.765	22.66	.028
251.01	14.298	24.38	.076
257.37	14.611	26.26	.155
267.17	15.215	29.82	.237
284.62	16.340	69.03	2.032
		75.69	2.489
17.34	0.110	154.62	7.799
52.96	1.175	179.64	9.298
58.32	1.509	220.17	11.902
62.81	1.717	225.11	13.044
68.65	2.011	281.27	16.536
75.11	2.522	283.39	15.017
		295.49	16.681
17.52	0.015	299.53	16.824
20.73	.033		
27.94	.167	280.31	15.939
34.55	.387	285.36	16.283
38.53	.502	290.41	16.438
42.77	.628		

TABLE IV

THERMODYNAMIC FUNCTIONS FOR MAGNESIUM DIBORIDE (MgB_2)

Temp., °K.	C_p, cal. deg.$^{-1}$ mole^{-1}	S^0, cal. deg.$^{-1}$ mole^{-1}	$(H^0 - H^0_0)/T$, cal. deg.$^{-1}$ mole^{-1}	$-(F^0 - H^0_0)/T$, cal. deg.$^{-1}$ mole^{-1}
20	0.014	0.005	0.0004	0.004
25	.036	.010	.005	.005
30	.060	.015	.008	.007
35	.095	.027	.019	.008
40	.150	.045	.033	.012
45	.222	.070	.053	.017
50	.337	.102	.076	.026
60	.630	.183	.141	.042
70	1.094	.318	.246	.072
80	1.595	.491	.379	.112
90	2.125	.711	.540	.171
100	2.670	.962	.729	.233
110	3.241	1.238	.938	.300
120	3.823	1.549	1.147	.402
130	4.43	1.872	1.372	.500
140	5.05	2.231	1.618	.613
150	5.63	2.65	1.859	.731
160	6.20	2.98	2.120	.862
170	6.72	3.37	2.365	1.001
180	7.24	3.77	2.632	1.141
190	7.74	4.18	2.876	1.300
200	8.22	4.59	3.126	1.462
210	8.68	4.99	3.382	1.612
220	9.11	5.41	3.645	1.768
230	9.53	5.82	3.90	1.92
240	9.95	6.24	4.15	2.09
250	10.34	6.65	4.38	2.27
260	10.71	7.07	4.61	2.46
270	11.01	7.48	4.84	2.64
280	11.26	7.89	5.07	2.82
290	11.39	8.27	5.28	2.99
298.16	11.43	8.60	5.45	3.15
300	11.44	8.67	5.49	3.18

TABLE V

THERMODYNAMIC FUNCTIONS FOR MAGNESIUM TETRABORIDE (MgB_4)

Temp., °K.	C_p, cal. deg.$^{-1}$ mole^{-1}	S^0, cal. deg.$^{-1}$ mole^{-1}	$(H^0 - H^0_0)/T$, cal. deg.$^{-1}$ mole^{-1}	$-(F^0 - H^0_0)/T$, cal. deg.$^{-1}$ mole^{-1}
20	0.030	0.022	0.018	0.004
25	.107	.046	.037	.009
30	.225	.077	.063	.014
35	.370	.119	.093	.026
40	.540	.175	.130	.045
45	.746	.242	.184	.058
50	.978	.339	.259	.080
60	1.520	.559	.413	.146
70	2.15	.831	.622	.209
80	2.80	1.155	.852	.303
90	3.45	1.52	1.111	.413
100	4.12	1.92	1.370	.546
110	4.88	2.34	1.648	.688
120	5.45	2.79	1.93	.856
130	6.12	3.26	2.23	1.031
140	6.80	3.73	2.53	1.202
150	7.49	4.23	2.84	1.39
160	8.20	4.73	3.15	1.58
170	8.90	5.25	3.47	1.78
180	9.61	5.78	3.80	1.98
190	10.33	6.32	4.13	2.19
200	11.06	6.86	4.46	2.40
210	11.74	7.42	4.79	2.63
220	12.40	7.98	5.12	2.86
230	13.01	8.55	5.45	3.10
240	13.61	9.12	5.78	3.34
250	14.20	9.68	6.10	3.58
260	14.78	10.75	6.42	3.83
270	15.34	10.82	6.74	4.08
280	15.88	11.39	7.06	4.33
290	16.40	11.95	7.37	4.58
298.16	16.81	12.41	7.63	4.78
300	16.90	12.52	7.68	4.84

thermodynamic functions. The entropy of the MgB_2 at 298.16°K. is 8.60 ± 0.04 cal. deg.$^{-1}$ mole^{-1}, with 0.013 (0.15%) being obtained by the extrapolation. For MgB_4, the entropy at 298.16°K. is 12.41 ± 0.06 cal. deg.$^{-1}$ mole^{-1}, with 0.062 (0.50%) being obtained by the extrapolation.

Since the X-ray diffraction studies[1,2] had shown layered structures for at least one of these compounds, MgB_2 plots of log C_p *versus* log T were made to determine whether a region of T^2 dependency existed. A linear relationship was found for MgB_2 from 20 to 80°K. with slope of 3.5 and for MgB_4 from 30 to 70°K. with slope of 2.6.

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SYRACUSE, N. Y.

[CONTRIBUTION NO. 95 FROM THE CRYOGENIC LABORATORY OF THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Heat Capacity and Magnetic Susceptibility of Copper(II) Tetrammine Sulfate Monohydrate from 1.3 to 24°K.

BY J. J. FRITZ AND H. L. PINCH

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The heat capacity and magnetic susceptibility of copper tetrammine sulfate have been investigated between 1.3 and 29°K. The results indicate strong interactions between copper ions, leading to a transition, of order higher than the second, with a maximum in the heat capacity of 0.75 cal. mole^{-1} deg.$^{-1}$ at 3.0°K. The magnetic susceptibility is nearly constant between 1 and 4°K., and thereafter falls gradually; the maximum value of the molar susceptibility is 0.04. It is believed that the interaction is directly related to the coördination with ammonia.

Introduction

The magnetic behavior of crystalline salts of cupric ion varies considerably from salt to salt. The Tutton salt, $CuSO_4 \cdot K_2SO_4 \cdot 6H_2O$, is one of the most ideal of all paramagnetic salts, and has been used in the attainment of temperatures far below 1°K.[1] The ordinary hydrated sulfate, $CuSO_4 \cdot 5H_2O$, has a magnetic transition[2] in the vicinity of 1°K., the exact nature of which is not clear. The hydrated chloride, $CuCl_2 \cdot 2H_2O$, has a lambda-type transition at about 4.2°K. below which the salt becomes anti-ferromagnetic.[3] The acetate, $Cu(C_2H_3O_2)_2 \cdot H_2O$, becomes diamagnetic at about 50°K.[4]

With the exception of the acetate, the properties of all the salts described above may be explained in terms of the effect of crystalline environment on a substantially free copper ion. The ground state of free cupric ion is $^2D_{5/2}$. At temperatures above the magnetic transitions, the typical copper salts behave almost as ^2S states; their magnetic susceptibilities are but slightly higher than the "spin-only" values.

Copper tetrammine sulfate differs formally from $CuSO_4 \cdot 5H_2O$ only in the replacement of four of the water molecules by ammonia molecules. In the crystal the basic unit is $Cu(NH_3)_4^{++}$, rather than $Cu(H_2O)_4^{++}$; due to differences in crystal structure, the less near neighbors of the copper ion are different in the two salts. At the outset of this research, it was expected that the ammine salt would behave in the same general fashion as the hydrate, so that comparison of the two would show the effect of the ammonia and in addition shed further light on the behavior of the ordinary hydrate.

Experimental

The experimental procedures were substantially the same as those employed by Fritz and Pinch in the investigation of vanadium ammonium alum,[5] and will not be described in detail. The ellipsoidal sample container had an internal volume of 31.13 cm.^{3}, and contained 32.64 g. of the salt. The weight of the container was 19.56 g. The carbon thermometer had a resistance at room temperature of about 6000 ohms. At low temperatures its sensitivity was decidedly higher than that of the thermometer previously described,[5] but it was also considerably less stable.

The specimen used in the investigation was prepared by addition of C.P. ammonium hydroxide to a solution of C.P. copper sulfate according to the method of Walton.[6] The crystalline salt was obtained by cooling of the resulting hot solution. The crystals used were ground to a powder; the portion selected for use passed through a 20-mesh screen, but failed to pass through a 100-mesh screen. The irregular particles were stored for a time under a saturated solution of the salt and then dried manually.

A sample for analysis was withdrawn during the filling of the sample tube. Its copper content was determined electrolytically to be 25.92% (theoretical 25.87%); the ammonia–copper ratio was determined by titration to be 3.92 to 1.

Measurements of heat capacity and magnetic susceptibility were made in the manner previously described.[5] For the low temperature susceptibility measurements, the coil constants were obtained with the specimen near 70°K., after the coils had been cooled by liquid helium or hydrogen. The effect of the sample at 70°K., upon the coils was determined in a separate experiment in which the specimen was cooled from room temperature to 70°K. The susceptibilities were thus based upon the room temperature susceptibility of the salt. The molar susceptibility at 290°K. is 1.40 $\times 10^{-3}$, according to Bhatnage, Lessheim and Khanna.[7] An independent check on our specimen by the Gouy method gave a result of 1.35×10^{-3}. (For the purpose of the correction this susceptibility is required only to about 20%.)

Results

The heat capacity of the salt was measured between 1.3 and 24°K. The observed measurements were corrected for the heat capacity of 19.56 g. of Pyrex as previously described.[5] At the highest temperatures, this represented 1/4 of the observed heat capacity. In view of the unusual behavior of the heat capacity between 12 and 20°K., this region was investigated in three separate sets of experiments; the results of the several sets were consistent. The heat capacity measurements are given

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in Table I. The accuracy of the heat capacity measurements below 20°K. is estimated as 1%; above 20°K., the errors are probably 2–3%, due to uncertainty in thermometer calibration.

TABLE I

MOLAR HEAT CAPACITY OF COPPER TETRAMMINE SULFATE MONOHYDRATE

Temp., °K.	Heat capacity, cal. deg.$^{-1}$ mole^{-1}	Temp., °K.	Heat capacity cal. deg.$^{-1}$ mole^{-1}
1.355	0.405	8.99	0.662
1.417	.418	10.01	.797
1.530	.432	10.77	.934
1.662	.491	13.17	1.56
2.323	.701	14.44	1.96
2.638	.721	14.89	2.05
2.910	.732	15.35	2.16
3.223	.732	15.72	2.16
3.579	.714	16.36	2.43
3.950	.685	16.42	2.51
4.336	.661	17.30	2.67
4.792	.614	17.72	2.74
5.325	.579	18.88	3.32
5.86	.566	19.09	3.26
6.44	.558	20.61	3.79
6.99	.551	22.06	3.90
7.58	.576	23.68	4.49
8.23	.585		

The magnetic susceptibility was measured between 1.2 and 20.2°K. The results are shown in Fig. 1, where the molar susceptibility is plotted against the temperature. Because of the small magnitude of the susceptibility, the error is estimated as 5%, although (as will be seen from Fig. 1) the internal consistency of the measurements was better than this. The results indicate a slight maximum near 4°K., but the diminution below 4° is within the accuracy claimed; accordingly the curve is drawn with the maximum at the lowest temperature. The results between 11 and 20°K. are represented by the formula

$$\chi_M = 0.53/(T + 5.3)$$

Upon adiabatic magnetization of the salt at 1.4°K., the temperature remained constant within 0.002°K.

Discussion

The nature of the heat capacity of the salt was unexpected and remarkable. There is a maximum at 3.0°K. which evidently is due to a magnetic transition. The height of the maximum is very nearly half that required for a transition from a single lower state to a doubly degenerate upper state. (In this connection, it is interesting to note that for $CuSO_4 \cdot 5H_2O$ Giauque and Geballe[2] obtained a maximum which was half that required for a transition between two singly degenerate states.) Moreover, the heat capacity between 1 and 6°K., after correction for the small lattice heat capacity, may be represented within several per cent. by a function

$$C/R = 0.975(\delta/kT)^2 e^{-\delta/kT}(1 - 2e^{-\delta/kT})^{-2}$$

with $\delta/k = 7.9$°K. (The lattice heat capacity may be estimated as about 0.006 cal. mole^{-1} deg.$^{-1}$ at 2.5°K. and about 0.08 cal. mole^{-1} deg.$^{-1}$ at 6°K.)

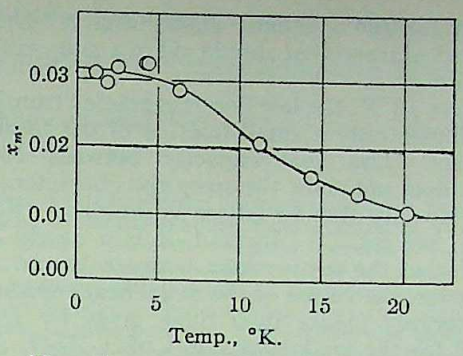

Fig. 1.—Magnetic susceptibility of copper tetrammine sulfate monohydrate.

In view of the fit of the Schottky function given above, it is tempting to view the basic unit in the salt (at low temperatures) as a pair of ions with their spins coupled. In this view, the state observed is the "triplet" state of the pairs, with total spin of unity. Such a state would have three magnetic energy levels, just as in vanadium alum,[5] and would give rise to the observed heat capacity below 6°K. There are two serious arguments against such specific "pairing" of ions. First, if the ions are paired, there should be both the "triplet" state and a "singlet" state, the latter with total spin of zero. This state of affairs has been observed with copper acetate[8]; both states are observed, with the singlet having the lower energy. In the present case, there is no evidence for a low-lying singlet level; on the other hand, it would be surprising to find it at an energy well above the ground state. Second, the crystal structure of copper tetrammine sulfate at room temperature[9] gives no evidence of pairing of copper ions. On the other hand, in copper acetate the crystal structure[10] indicates clearly the grouping of copper ions by pairs. A change in structure so as to bring copper ions together by pairs would require a substantial change in crystal structure below room temperature.

Actually it is not necessary to assume a coupling mechanism as specific as pair-formation to explain the observed results. The crystal structure of the tetrammine salt indicates that the copper ions are arranged in zig-zag chains parallel to the 100 planes of the crystal, with the units linked together by coordination with water molecules. Strong exchange interactions (with energy of the order of that given above as δ) along the chains will give rise to the same general behavior as the pairing considered above.[11] In chemical terms this mechanism corresponds to a weak bonding along the chains $Cu(NH_3)_4$–H_2O–$Cu(NH_3)_4$–H_2O——. The microwave results at room temperature[12] show the single transition typical of single electron spins, but the line is abnormally narrow; this narrowing previously has been attributed to strong exchange coupling between copper ions.

Either of the coupling (exchange) mechanisms suggested will give rise to the sort of behavior ob-

(8) B. Bleaney and K. D. Bowers, *Proc. Roy. Soc.* (*London*), **A214**, 451 (1952).

(9) F. Mazzi, *Acta Cryst.*, **8**, 137 (1955).

(10) J. F. Niekirk and F. R. L. Schoening, *ibid.*, **6**, 227 (1953).

(11) We thank Dr. Julian Eisenstein for suggesting this possibility.

(12) K. Kang, *Phys. Rev.*, **94**, 314 (1954).

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served for the magnetic susceptibility. Detailed theoretical treatment should aid in a more exact description.

Above 10°K. the low lying magnetic "transition" contributes only a small fraction of the total heat capacity. The heat capacity between 10 and 20°K. does not show the steep rise characteristic of heat capacity due to lattice vibrations. (For example, see ref. 5.) Instead, it is a nearly linear function of the temperature between 12 and 24°K. Moreover, the values of the molal heat capacity are considerably higher than those given by Duyckaerts[13] for the analogous salt, $CuSO_4 \cdot 5H_2O$. Comparison of the data for the two salts shows that the difference between the heat capacities reaches a maximum near 20°K. and diminishes at higher temperatures. Any other reasonable assignment for the lattice heat capacity gives a similar broad maximum in the heat capacity due to other causes. It is possible that the excess heat capacity is due to a second magnetic "transition." There is no evidence of a sharp rise in the heat capacity such as might be associated with a coöperative transition. Complete examination of this "transition" will require additional measurements above 20°K.

Magnetic Behavior of Copper Tetrammine Sulfate.—The unquestionably large coupling between copper ions in the tetrammine sulfate was surprising, particularly in view of the observed crystal structure. It is possible that this coupling is an accident of the structure, but we think this quite unlikely in view of the rather large distance between copper ions. In the tetrammine, the smallest distance between copper ions is 5.3 Å. compared with 5.7 Å. in $CuSO_4 \cdot 5H_2O$, 3.5 Å. in $CuCl_2 \cdot 2H_2O$, and 2.6 Å. in $Cu(C_2H_3O_2)_2 \cdot H_2O$. The chloride displays large exchange interactions, leading to the previously cited transition to antiferromagnetism at 4.2°K. However, the minimum Cu–Cu distance is much smaller than in the tetrammine, and there are in fact two other pairs of copper ions within only 5.5 Å. of each ion. The exchange interactions in the tetrammine are much larger than would be expected by comparison.

We believe that the (comparatively) large exchange interactions are no accident, but are probably enhanced greatly by the presence of the ammonia molecules. Ammonia is well known to coordinate with copper (and some other iron group ions) much more strongly than does water or the sulfate ion. (Copper acetate is a special case, in that in crystalline copper acetate adjacent copper ions in a pair are at a distance almost equal to the Cu–Cu separation in metallic copper.[10] Thus it is almost certain that the very strong exchange interactions in the acetate occur because of directly coupling between adjacent copper ions.[8]) To our knowledge, the present case is the first where extensive low temperature investigation has been made of a cupric salt in which the copper was coordinated with species other than water, halide ions or oxygenated anions. The latter species are notoriously poor coördinating agents for copper ion, and it is not surprising that the introduction of stronger coördinating agents might enhance interactions between the cupric ions.

(13) G. Duyckaerts, *Soc. Roy. Sci. Liege*, **14**, 284 (1941).

Conclusions

The heat capacity and magnetic susceptibility of copper tetrammine sulfate below 20°K. indicate that there is strong interaction between cupric ions. This coupling may be simply of the exchange variety, or may occur as a result of a low temperature crystal transition. It will be highly desirable to carry out both X-ray and microwave investigations on this salt below 90°K. There is evidence of a transition (not first order) in the salt starting about 10°K. We propose to investigate this transition further by other means, and plan for the future a complete Third Law study of the salt. In addition we strongly recommend investigations of copper salts containing strong coördinating and chelating agents. One such investigation is already in progress.

Acknowledgments.—We wish to thank Dr. S. Seki and Mr. R. G. Taylor for assistance with the experimental measurements, and Mr. L. F. Shultz for aid in production of refrigerants. We thank E I. du Pont de Nemours and Company and the Office of Naval Research for financial aid in the early stages of the experiments, and the National Science Foundation for aid during their completion. We gratefully acknowledge the provision of funds for the iron-free solenoid magnet by the Research Corporation and the Westinghouse Electric Company.

University Park, Pa.

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[CONTRIBUTION FROM THE RESEARCH AND ENGINEERING DIVISION, MONSANTO CHEMICAL COMPANY]

The Mechanism of Formation of Sodium Triphosphate from Orthophosphate Mixtures[1]

BY JAMES W. EDWARDS AND ARNO H. HERZOG

RECEIVED FEBRUARY 13, 1957

The condensation reactions which take place when mixtures of sodium orthophosphates, having a mole ratio Na_2O/P_2O_5 of 5/3, are heated to higher temperatures have been investigated by means of thermal analysis, X-ray diffraction, chromatographic analysis and wet-chemical analysis coupled with dehydration studies. Intimate equimolar mixtures of $NaH_2PO_4 \cdot Na_2HPO_4$ and $Na_2HPO_4 \cdot 2H_2O$, obtained as polycrystalline granules by drying of aqueous solutions, lose 3/2 moles of constitutional water when heated to 210° and change to a mixture of crystalline $Na_4P_2O_7$, and an amorphous phase. The amorphous phase is shown by combined X-ray and chromatographic analysis to be a mixture of ortho-, pyro-, tri-, ring meta-, and longer chain polyphosphates. Further heating at somewhat higher temperatures results in evolution of more water and consumption of equivalent amounts of $Na_4P_2O_7$ and the amorphous phase to give $Na_5P_3O_{10}$ (I), the high temperature form, which then changes to the low temperature form II. A mechanism is proposed which involves diffusion of only small cations and water through the amorphous phase to support the reaction. Mobile equilibrium between water and condensed phosphate ions maintains a level of orthophosphate to support the reaction $HPO_4^{2-} + HP_2O_7^{3-} \rightarrow P_3O_{10}^{5-} + H_2O$, which occurs at the growing crystal face of $Na_5P_3O_{10}$.

Introduction

Sodium triphosphate, $Na_5P_3O_{10}$, can be prepared[2] by thermal dehydration and/or fusion of various mixtures of any variety of phosphates having an over-all mole ratio, Na_2O/P_2O_5, of 5/3; however, the most efficacious method employs intimate mixtures of orthophosphates prepared *in situ* by drying appropriate solutions. Thermal dehydration of such an *in situ* mixture at temperatures between *ca.* 300 and *ca.* 600° then gives good yields of $Na_5P_3O_{10}$ without fusion of the entire mass.

$Na_5P_3O_{10}$ is bimorphic; it has low and high temperature modifications, II and I, respectively, that have, according to thermal analysis, high temperature microscopy and quench studies, a transition temperature of *ca.* 500°. This is an erratic transformation and the existence of $Na_5P_3O_{10}$-I in preparations which were never heated higher than *ca.* 400° were interpreted to mean that the transition point was considerably below 500°.

Heating of ortho mixtures to constant weight at successively higher temperatures[3] points to a mechanism involving initial condensation of pyrophosphate salts with subsequent condensation and/or reorganization to give form II. This is shown by the following equations which describe preliminary studies[3] on the thermal decomposition of some crystalline phosphates

$$2Na_2HPO_4 \cdot 2H_2O \xrightarrow{200°} Na_4P_2O_7 + 5H_2O \quad (1)$$

$$2(NaH_2PO_4 \cdot Na_2HPO_4) \xrightarrow{200°} Na_2H_2P_2O_7 + Na_4P_2O_7 + 2H_2O \quad (2)$$

$$2Na_4P_2O_7 + Na_2H_2P_2O_7 \xrightarrow{250°} 2Na_5P_3O_{10} + H_2O \quad (3)$$

In eq. 3, it should be noted that three dimeric molecules, in crystalline state as derived from reactions 1 and 2, react to give two trimeric molecules. Obviously many complex intermediate steps must be involved. It has been observed[3] that the pyrophosphates obtained *via* the reaction given in eq. 2 give much poorer yields at, say 350°, than the direct, uninterrupted heating of the ortho mixture at the same temperature.

$$NaH_2PO_4 \cdot Na_2HPO_4 + Na_2HPO_4 \cdot 2H_2O \longrightarrow Na_5P_3O_{10} + 4H_2O \quad (4)$$

It appeared then that the two-step conversion might have a different mechanism from that of the direct conversion, hence a new approach was made in which techniques of thermal-, X-ray diffraction, chromatographic- and chemical-analyses of quenched, partly reacted mixtures were combined with dehydration studies.

Experimental

Starting Materials.—In most of the experiments below the ortho mixture used was prepared by drum-drying an aqueous sodium orthophosphate solution which had a mole ratio Na_2O/P_2O_5 = 1.686 as determined by *p*H titration analysis, total P_2O_5 content of 51.98% and an ignition loss of 14%. X-Ray diffraction analysis of this mixture showed it to consist of $NaH_2PO_4 \cdot Na_2HPO_4$, $Na_2HPO_4 \cdot 2H_2O$ and anhydrous Na_2HPO_4.[4] The drum-dried mixture had the form of coarse polycrystalline aggregates ranging from less than 1 mm. to about 8 mm. Some particles were thin and flake-like while others were dense and roughly spherical.

Thermogravimetric Analysis.—A thermogravimetric apparatus was constructed in which both sample weight and temperature could be observed simultaneously and continuously during the reaction. Three or four gram samples of the orthophosphate mixture, contained in a small porcelain crucible, were suspended by a three mil tungsten wire from one arm of a chainomatic analytical balance. The suspension wire passed through the floor of the balance and through the top of a high table. A pot furnace, 3 in. in diameter by 5 in. deep, was mounted beneath the table so that it could be raised into position around the sample. The furnace could then be closed with a split cover containing a small hole through which the suspension and thermocouple wires could pass without contact. This thermocouple, made of 3 mil Pt and Pt + 10% Rh wire, was placed with its hot junction in the middle of the sample and the extension leads brought out along the suspension wire and over to a fixed support at right angles to the suspension wire. The sensitivity of the balance was about 0.3 mg. with these wires in place. The temperature was recorded continuously on a 2.5 millivolt recording potentiometer. The sample weight was obtained manually by one observer at intervals of about 5 mg. weight change, with the corresponding time in seconds being recorded by another observer. The zero of time was taken when the pre-heated furnace was raised into position around the

(1) Presented at the 130th meeting of the American Chemical Society, Atlantic City, Sept., 1956.

(2) (a) B. Topley, *Quart. Rev.*, **3**, 345 (1948); (b) E. P. Partridge, V. Hicks and G. W. Smith, THIS JOURNAL, **63**, 454 (1941).

(3) Unpublished results, Monsanto Chemical Co.

(4) R. P. Langguth and J. W. Edwards, Monsanto Chemical Co., unpublished results. *In situ* mixtures of sodium orthophosphates, having Na_2O/P_2O_5 ratios of 5/3, made by rapid drying on steam heated flaking rolls, have been shown to consist of $NaH_2PO_4 \cdot Na_2HPO_4$ and Na_2HPO_4 (dihydrate and anhydrous) in substantial agreement with the phase diagram published by Wendrow and Kobe, *Ind. & Chem.*, **44**, 1091 (1952).

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TABLE I

X-RAY ANALYSIS OF REACTION MIXTURES

$Na_2HPO_4 + NaH_2PO_4 \cdot Na_2HPO_4 \xrightarrow{250°}$

Time in furnace, min.	Composition, wt. % Na_2HPO_4	$NaH_2PO_4 \cdot Na_2HPO_4$	$Na_4P_2O_7$	$Na_5P_3O_{10}$ (I)	$Na_5P_3O_{10}$ (II)
0	34	66	..	..	..
15	8	13	49	..	..
20	..	..	66	..	..
30	..	..	51	25	..
45	..	..	26	48	2
60	..	..	19	54	26
120	..	..	8	15	63

pletion of the reactions of eq. 1 and 2, but with no crystalline $Na_2H_2P_2O_7$ except in mixtures heated for long periods near 200°.

Thermal analysis curves made in an attempt to determine the beginning of the reaction of eq. 3 on the assumption that 1 and 2 were completed before formation of the triphosphate failed to shed light on this particular part of the problem because no breaks due to triphosphate formation were detectable, as can be seen by examination of the upper curve in Fig. 1.

In a further effort to find the reaction temperature, the thermal analysis experiments were expanded to thermogravimetric analysis, thus obtaining a simultaneous record of the temperature and weight of the sample with respect to heating time. Several runs were made with typical data as shown in Fig. 1. Breaks in the thermal curve show incongruent melting of $Na_2HPO_4 \cdot 2H_2O$ at 82° and boiling of the saturated solution at 109°. The strong break at 210° indicates the first loss of constitutional water. No other breaks could be discerned at higher temperatures. The weight *vs.* time curve reflects the corresponding losses of water without any particular effect being evident in the neighborhood of point B, a point calculated to represent the weight loss corresponding to completion of reactions in eq. 1 and 2.

TABLE II

COMPOSITION OF MIXTURE AT VARIOUS STAGES OF REACTION; FURNACE AT 250°

Sample	Water loss, moles	X-Ray anal., % of total P_2O_5 as: Ortho	Pyro	Tri	Chromatographic anal., % of total P_2O_5 as: Ortho	Pyro	Tri	Long chain[b]	Mol ratio ortho to amor. pyro
A	0.75	46	39	..	49.9	50.0	0.0	0.0	..
B[a]	1.50	0	63	0	9.3	86.4	3.1	1.0	0.80
C	1.55	0	62	8	6.7	86.3	6.6	0.4	.56
D	1.70	0	49	33	5.7	63.9	27.9	2.5	.72
E	1.95	0	11	83	0.4	18.6	81.0	0.1	..
F[c]	2.00	0	6	94	0.4	6.9	92.6	0.1	..

[a] According to the chromatographic analysis sample B contained 0.15% P as trimeta, an amount barely above the detection limit. [b] "Long chain" is principally tetrapoly-, containing some pentapolyphosphate. [c] F heated to constant weight at 400°.

sample. This furnace contained a large heavy-walled stainless steel crucible which surrounded the sample and thus reduced thermal gradients. The furnace was temperature controlled and kept at a fixed temperature throughout each experiment.

Prior to the construction of the thermogravimetric apparatus, thermal analysis curves on the orthophosphate mixtures were made using the same furnace but without suspending the sample from a balance.

X-Ray Diffraction Analysis.—All of the X-ray diffraction work was done using a Geiger-counter recording X-ray diffractometer (G. E. XRD-3). The X-ray analyses were made using the diffraction maxima recommended by Mabis and Quimby[5]; however, their detailed procedure was not used and therefore the results are considered semi-quantitative in nature. The accuracy is estimated to be within ±10% of the absolute value. Cu Kα radiation was used.

Chromatographic Analyses.—The products from some of the dehydration experiments were also analyzed by paper chromatography[6] using both the one- and two-dimensional techniques. The comparison of these analyses with the X-ray diffraction results helps to characterize the noncrystalline components in the samples. These chromatographic analyses are believed to be accurate to 0.5%, with a sensitivity of detection of 0.1%.

Results and Discussion

The steps involved in the thermal conversion of an orthophosphate mixture ($Na_2O/P_2O_5 = 1.686$) to sodium tripolyphosphate were first determined by analysis of quenched two-gram portions that had been heated for various periods of time at several different temperatures. Typical X-ray diffraction data, showing the variation of composition with time in the temperature range 225 to 300°, are illustrated by the results at 250° given in Table I. These data clearly indicate that $Na_4P_2O_7$ and $Na_5P_3O_{10}$ (I), both crystalline, rise in concentration successively and then diminish as they are consumed by subsequent reactions. In other similar experiments both of these compounds have been observed in even higher amounts, the highest for $Na_4P_2O_7$ approaching the theoretical for com-

In order to identify the actual chemical species in the mixture at points A, B, C, D, E and F in Fig. 1, identical thermogravimetric runs were made which were then stopped short at these points of weight and the samples quickly removed and cooled by immediately grinding them in a large mortar. The results of these experiments are recorded in Table II. The X-ray diffraction analysis gives the crystalline components only, with Na_2HPO_4 and $NaH_2PO_4 \cdot Na_2HPO_4$ accounting for the ortho-, $Na_4P_2O_7$ being the only pyro- compound, while both forms I and II triphosphate were observed. Note that the crystalline orthophosphates fell rapidly below the detection limit (*ca.* 1%) even though appreciable amounts of ortho- remained in the mixture for samples B, C, and D as shown in the chromatographic analyses. This leaves most of the ortho- in the amorphous phase. Similar comparison shows the amorphous phase to contain a large amount of pyrophosphate. It is believed that the triphosphate in B is in the amorphous phase since strong diffraction maxima of form I, which subsequently appears first, would be detectable if present in excess of about 1%. The data

(5) A. J. Mabis and O. T. Quimby, *Anal. Chem.*, **25**, 1814 (1953).
(6) Editha Karl-Kroupa, *ibid.*, **28**, 1091 (1956).

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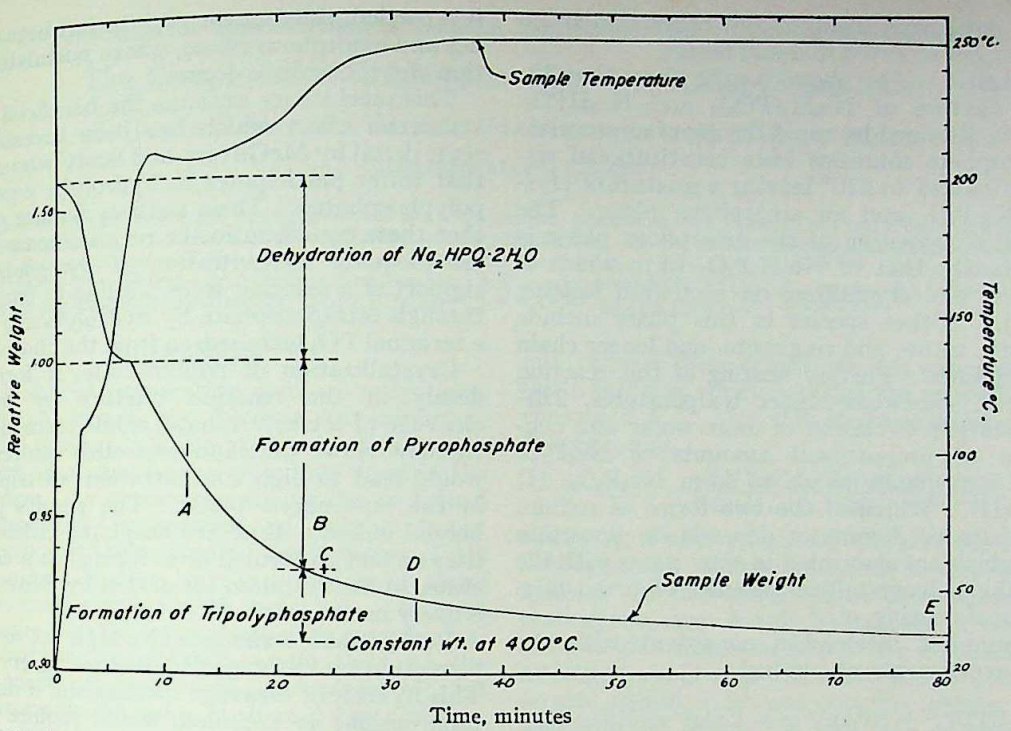

Fig. 1.—Thermogravimetric curves for dehydration of an orthophosphate mixture to sodium triphosphate.

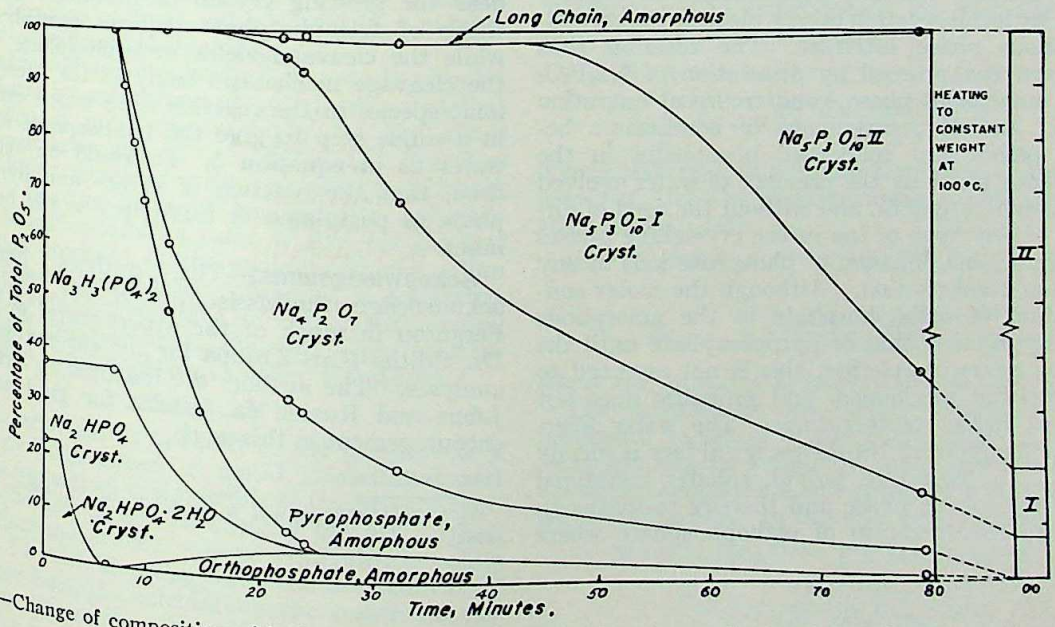

Fig. 2.—Change of composition with time during thermal dehydration of an orthophosphate mixture to sodium triphosphate.

do not permit firm conclusions about amorphous triphosphate in subsequent samples although the preponderance of high X-ray results suggest that the amorphous phase contains at most only a low concentration of triphosphate. Analytical results for long chains are erratic for unknown reasons; however, the trend in the data suggests that long chains build up to a maximum concentration and then decline. The long chain polyphosphates were mostly tetrapolyphosphate.

The results given in Fig. 1 and Table II have been combined to construct Fig. 2, a cumulative plot of the change of composition with time for the reaction mixture heated at 250°. The boundaries have been drawn in on the basis of the various analyses while the weight loss data were used for interpolation of several curves. For example, the boundary between $Na_4P_2O_7$ and $Na_5P_3O_{10}$ is established by analytical data at the points shown by circles while the curve from 32 to 79 min. was interpolated on the assumption that for this region triphosphate formation is directly proportional to the amount of water evolved. The curve between the two forms of $Na_5P_3O_{10}$ was sketched in on the

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basis of data from Table I and other similar experiments not reported in detail herein.

Mechanism.—The above results show that the *in situ* mixture of $Na_3H_3(PO_4)_2$ and Na_2HPO_4-(0–2)H_2O, obtained by rapid drying of appropriate orthophosphate solutions loses constitutional water when heated to 210° leaving a mixture of crystalline $Na_4P_2O_7$ and an amorphous phase. The elemental composition of the amorphous phase is approximately that of $Na_2H_2P_2O_7$ (into which it transforms and crystallizes on prolonged heating at 200°).[3] Other species in this phase include ortho-, tri-, tetra-, and ring meta- and longer chain polyphosphates. Further heating of this reaction mixture at somewhat higher temperatures, 225–400°, results in evolution of more water and consumption of proportional amounts of $Na_4P_2O_7$ and the amorphous phase to form $Na_5P_3O_{10}$ (I) and/or (II). Which of the two forms of sodium triphosphate predominates depends on uncertain factors which are associated in some cases with the size of the polycrystalline granules of ortho mixture, rate of heating, etc.[3]

The simplest mechanism consistent with the various experiments above has

$$HPO_4^{2-} + HP_2O_7^{3-} \longrightarrow P_3O_{10}^{5-} + H_2O \quad (5)$$

as the primary reaction for formation of triphosphate, with this reaction taking place at the crystal-amorphous phase interface. The reaction thus conceived can proceed by dissolution of $Na_4P_2O_7$ in the amorphous phase, countercurrent migration of Na^+ and H^+, sustenance of equilibrium between ortho- and condensed phosphates in the amorphous phase by the presence of water evolved in the reaction (eq. 5), and without the need of diffusion of any type of ion in the crystalline phases nor appreciable diffusion of phosphate ions of any degree of condensation. Although the molar concentration of orthophosphate in the amorphous phase approaches that of pyrophosphate until the reaction nears completion, this is not essential to the proposed mechanism and probably does not occur at higher temperatures. The water liberated at the growing $Na_5P_3O_{10}$ crystal face is ideally situated to hydrolyze polyphosphates contained in the amorphous phase and thereby maintain an adequate concentration of orthophosphate where it is needed, that is, near the interface between product and amorphous phase, where postulated formation of triphosphate occurs.

This mechanism explains the beneficial effect of water, an effect which has been investigated in some detail by McGilvery and Scott[7] who suggested that water participates in hydrolytic equilibria of polyphosphates. These authors further suggested that these equilibria in the reaction mass maintain an adequate concentration of *pyrophosphate* for support of a reaction series leading to triphosphate through tetraphosphate by hydrolytically cleaving a terminal PO_4 tetrahedron from the chain.

Crystallization of triphosphate, if formed randomly in the reaction mixture by hydrolytic cleavage of tetraphosphate, would seem to be an extremely slow, diffusion-controlled process which would lead to high concentrations of triphosphate in the amorphous phase. The results presented herein indicate that triphosphate either crystallizes as fast as formed or is formed in a crystalline state, so that random formation by cleavage is not a likely mechanism.

Rather than a random cleavage, let us consider formation by cleavage at the growing crystal face. This hydrolytic cleavage mechanism, if diffusion of large anions is excluded, would require synthesis and subsequent cleavage of tetraphosphate ions near the growing crystal of product. The synthesis of tetraphosphate requires pyrophosphate while the cleavage yields orthophosphate. Thus the cleavage mechanism leads to the presence of ionic species in the reaction zone which can react in a single step to give the triphosphate ion and water as in equation 5. It would be expected, then, that the reaction of ortho- and pyrophosphate as postulated in this paper would be dominant.

Acknowledgments.—The authors gratefully acknowledge the assistance of Mr. Ralph R. Ferguson in much of the experimental work and Dr. Editha Karl-Kroupa for the chromatographic analyses. The authors are indebted to Drs. I. B. Johns and Russell L. Jenkins for guidance and encouragement in this work.

DAYTON 7, OHIO

(7) J. D. McGilvery and A. E. Scott, *Can. J. Chem.*, **32**, 1100 (1954).

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[CONTRIBUTION FROM MCPHERSON CHEMICAL LABORATORY, THE OHIO STATE UNIVERSITY]

The Complexes of Triphosphate Ion with Alkali Metal Ions[1]

BY JAMES I. WATTERS, SHELDON M. LAMBERT AND E. DAN LOUGHRAN

RECEIVED MARCH 6, 1957

The stabilities of the complexes of triphosphate ion with sodium, potassium and lithium ions have been calculated from the pH lowering during titrations of triphosphate ion with hydrogen ion. In one M tetramethylammonium chloride at 25°, formulas of the complexes and the values of their formation constant are: $KP_3O_{10}^{4-}$, $10^{1.39 \pm 0.06}$; $NaP_3O_{10}^{4-}$, $10^{1.64 \pm 0.06}$; $LiP_3O_{10}^{4-}$, $10^{2.87 \pm 0.06}$. Sodium and lithium ions also form acidic complexes with $HPO_3O_{10}^{4-}$, having the following formulas and values for their formation constants: $Na(HPO_3O_{10})^{3-}$, $10^{0.77 \pm 0.06}$; and $Li(HP_3O_{10})^{3-}$, $10^{0.88 \pm 0.06}$.

Introduction

Since Huber's[2] preparation and investigations, sodium triphosphate has become an important commercial product. Triphosphate ion forms complexes with most metal ions including those of the alkali group. As a consequence of the biological and commercial importance of triphosphates, several authors[3-5] have studied the lowering of pH of triphosphate buffers by the addition of alkali and particularly alkaline earth metal ions. In most of the studies the effect was ascribed to complex formation, but no quantitative evaluations of the stability constants were made. Recently, Martell and Schwarzenbach[6] have evaluated the stability constants of magnesium and calcium complexes with triphosphate by treating the data obtained in the titration of triphosphoric acid in a manner similar to that used in this study.

Schendewolf and Bonhoeffer[7] in a study of polyphosphates by membrane potentials observed that the order of increasing stability for the alkali metal complexes was $K^+ < Na^+ < Li^+$ and that the stability increased with polyphosphate chain length. On the basis of conductivity measurements Monk[8] obtained a value of $10^{2.5}$ for the first formation constant of the sodium complex. Van Wazer and Campanella[9] obtained a somewhat smaller complexity constant for sodium with several condensed polyphosphate glasses. They also investigated the complexes of other metal ions.

Theoretical

If an acid can be titrated in the presence of a relatively large excess of metal ion without precipitate formation, it is possible to investigate complex formation by the lowering of the pH. When the inflections at the various equivalence points persist for the stepwise addition or removal of hydrogen ions, the calculations are greatly simplified. In this case, it is evident that each ligand adds one hydrogen ion in a stepwise manner even though the ligand may also be bound to a metal ion. Under these conditions it is expedient to define a function which is called the apparent acidity constant,[6] $K_5'_{-n}$, for this stepwise addition of hydrogen ion as

$$K'_{5-n} = \frac{[H^+]\Sigma q(M_m(H_nP_3O_{10})_q^{(5q-nq-m)-})}{\Sigma q(M_m(H_{n+1}P_3O_{10})_q^{(4q-nq-m)-})} \quad (1)$$

where m, n and q indicate the number of metal, hydrogen and triphosphate ions in any particular species. In this paper parentheses indicate concentrations and brackets indicate activities. n has a single value from zero to five if the addition of hydrogen ion is stepwise while m and q may have several values if several complex species and the uncomplexed ligand, as well, are in equilibrium. The general equation for the stepwise addition of hydrogen ion to triphosphate ion and the corresponding acidity constant are

$$H^+ + H_nP_3O_{10}^{(5-n)-} \rightleftharpoons H_{n+1}P_3O_{10}^{(4-n)-} \quad (2)$$

$$K_{5-n} = \frac{[H^+](H_nP_3O_{10}^{(5-n)-})}{(H_{n+1}P_3O_{10}^{(4-n)-})}$$

The general equation for the formation of any complex ion and the corresponding complexity constant, $\beta_{M_mH_nL_q}$, are

$$mM^+ + qH_nP_3O_{10}^{q(5-n)-} \rightleftharpoons M_m(H_nP_3O_{10})_q^{(5q-nq-m)-} \quad (3)$$

$$\beta_{M_mH_nL_q} = \frac{(M_m(H_nP_3O_{10})_q^{(5q-nq-m)-})}{(M^+)^m(H_nP_3O_{10}^{(5-n)-})^q}$$

where the subscript L indicates the ligand $P_3O_{10}^{5-}$.

The calculations are further simplified if the maximum values of m and q are unity. This assumption can be tested by calculations based on varied concentrations and ratios of metal ion and triphosphate ion. In this case eq. 3 reduces to

$$M^+ + H_nP_3O_{10}^{(5-n)-} \rightleftharpoons MH_nP_3O_{10}^{(4-n)-} \quad (4)$$

$$K_{MH_nL} = \frac{(MH_nP_3O_{10}^{(4-n)-})}{(M^+)(H_nP_3O_{10}^{(5-n)-})}$$

A high concentration of an essentially non-complexing electrolyte such as tetramethylammonium chloride and relatively low concentrations of metal ion and triphosphate ion are used in order to minimize the effect of the varied concentrations of the reacting species on the various activity coefficients. Under these conditions a lowering of the pH in the titration curve indicates complex formation since the presence of metal ion in an acid enhances its acidity. In regions where no pH lowering occurs, one may conclude that complex formation does not occur to an appreciable extent. Since no pH lowering occurred in the triphosphate curves for n values larger than 2, when the concentrations of the reactants were relatively small

(1) Presented before the Division of Physical and Inorganic Chemistry, 131st Meeting of the American Chemical Society, Miami, Florida, 1957.

(2) H. Huber, *Angew. Chem.*, **50**, 323 (1937).

(3) L. Frankenthal, THIS JOURNAL, **66**, 2124 (1944).

(4) H. Rudy, *Angew. Chem.*, **54**, 447 (1941).

(5) M. Bobtelsky and S. Kertes, *J. Appl. Chem.* (*London*), **4**, 419 (1954).

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(9) J. R. Van Wazer and D. Campanella, THIS JOURNAL, **72**, 655 (1950).

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the following equations were derived by substituting equations having the forms of (2) and (3) into (1) with m and q equal to unity in the metal complex.

$$K'_4 = \frac{[H^+][(HP_3O_{10}^{4-}) + (MHP_3O_{10}^{3-})]}{(H_2P_3O_{10}^{3-})} = K_4 + K_{MHL}K_4(M^+) \quad (5)$$

$$K'_5 = \frac{[H^+][(P_3O_{10}^{5-}) + (MP_3O_{10}^{4-})]}{(HP_3O_{10}^{4-}) + (MHP_3O_{10}^{3-})} = \frac{K_5 + K_{ML}K_5(M^+)}{1 + K_{MHL}(M^+)} \quad (6)$$

K_4 and K_5 are the acidity constants of triphosphoric acid, while K_{ML} and K_{MHL} are the formation constants of the form in eq. 4 for the complexes $M(P_3O_{10})^{4-}$ and $M(HP_3O_{10})^{3-}$.

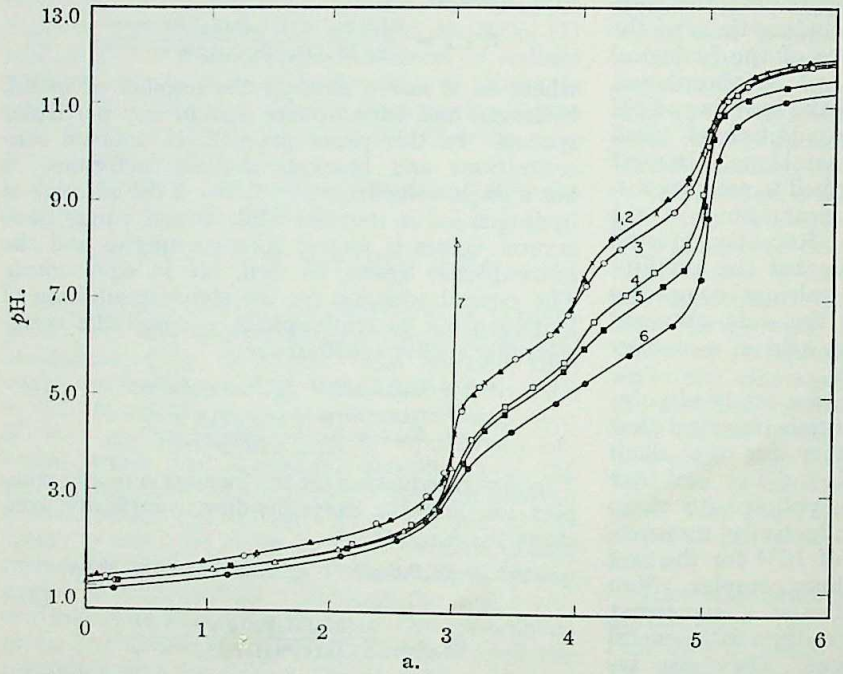

Fig. 1.—A comparison of the effects of potassium, sodium and lithium ions on titration curves of triphosphoric acid with tetramethylammonium hydroxide: curve 1, 0.0393 M $H_5P_3O_{10}$ titrated with 0.1326 N $(CH_3)_4NOH$; curve 2, 0.0396 M $H_5P_3O_{10}$ with 0.0868 N $(CH_3)_4NOH$, μ = 1.0 M with $(CH_3)_4NCl$; curve 3, 0.0399 M $H_5P_3O_{10}$ with 0.1108 N KOH; curve 4, 0.0396 M $H_5P_3O_{10}$ with 0.0961 N KOH, μ = 1.0 M with KNO_3; curve 5, 0.0379 M $H_5P_3O_{10}$ with 0.1194 N NaOH, μ = 1.0 M with $NaNO_3$; curve 6, 0.0415 M $H_5P_3O_{10}$ with 0.0960 N KOH, μ = 1.0 M with $LiNO_3$; curve 7, 0.1162 M HCl with 0.1004 N $(CH_3)_4NOH$, μ = 1.0 M with $(CH_3)_4NCl$.

From these equations it follows that the apparent acidity constants are constants if the concentration of unbound metal ion is constant, provided precautions are taken to avoid changes in activity coefficients. The apparent constants can be calculated by the following form of eq. 1 for the titration of the triphosphate ion with hydrogen ion

$$K'_{5-n} = \frac{[H^+][(n + 1 - a)C_p - K_w/[H^+]f + [H^+]/f]}{(a - n)C_p + K_w/[H^+]f - [H^+]/f} \quad (7)$$

where "a" is the number of moles of hydrogen added per mole of triphosphate ion present in any form. The symbol f indicates the activity coefficient of a univalent ion. If the acid is not too dilute pK'_{5-n} has the same value as the pH at $a = n + 1/2$.

Experimental

The sodium triphosphate, tetramethylammonium chloride and tetramethylammonium hydroxide were prepared according to a procedure described in a previous paper.[10] Carbonate-free potassium and sodium hydroxide solutions were prepared from Baker Analyzed pellets and stored in paraffin-lined bottles. All water used in preparing solutions and washing the columns was demineralized, doubly distilled, and purged with nitrogen to remove the dissolved carbon dioxide. Mallinckrodt reagent grade salts were used.

The potassium and lithium triphosphate solutions were prepared by passing a 0.03 M solution of the recrystallized sodium salt[10] through a 90 cm. by 2 cm. column filled to a height of 50 cm. with Dowex 50-x12 cation-exchange resin, 100–200 mesh, low porosity, supported on a Pyrex glass wool plug. The resin was in the potassium or lithium form, depending upon the triphosphate salt desired. The column was fitted with a Pyrex water jacket, 4 cm. in diameter, through which ice-water was circulated constantly. The column resembled a Liebig condenser, differing in that it had a stopcock on the lower end and a rubber stopper fitted with an ascarite bulb and a tube to facilitate the entry of nitrogen at the top. The eluted solution was warmed to 25 ± 0.1°, diluted to the desired concentration and immediately titrated with standardized hydrochloric acid containing the same concentration of triphosphate as the solution titrated. The inclusion of the triphosphate in both solutions eliminated the dilution of the triphosphate during the titration.

In order to prevent any hydrogen ion leakage, the resin which was originally in the acidic form was charged with potassium or lithium ions by passing through it a 10% solution of KCl or LiCl containing enough KOH or LiOH to make the solution slightly basic. Then a 15% solution of KCl or LiCl was passed through the column which was finally rinsed with water. The titrations were performed in a stoppered Berzelius beaker, placed in a water thermostat at 25 ± 0.1°, with a stream of nitrogen flowing over the solution. pH measurements were made with the Beckman model G pH meter with the Beckman All Purpose Glass electrode and the Beckman reference electrode inserted directly in the solution.

Results and Discussion

Figure 1 illustrates the pH lowering effect due to the presence of large concentrations of sodium, potassium and lithium nitrate in the titration of approximately 0.04 M $H_5P_3O_{10}$ with approximately 0.1 N $(CH_3)_4NOH$. Curve 1 was obtained in the absence of extraneous electrolytes while curves 2 and 3 were obtained with sufficient $(CH_3)_4NCl$ to produce an ionic strength of 1.0. Curve 3 was obtained for the titration of 10 ml. of 0.0339 M triphosphoric acid with 0.1108 N potassium hydroxide. At "a" values below 4 this curve coincides with curve 1 for the titration using tetramethyl-

(10) J. D. Watters, D. D. Loughran and S. M. Lambert, This Journal, 78, 4855 (1956).

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ammonium hydroxide in the absence of metal ions. Above this "a" value the pH is lower, indicating the presence of a complex ion since any activity coefficient effect should have appeared at lower "a" values also. Curves 4, 5 and 6 illustrate the effect of one M potassium, sodium and lithium nitrate on the titration curve for triphosphoric acid. At "a" values below 3 there is a small pH decrease due to the different effects of the various alkali salts on the activity coefficients. At "a" values above 3 the pH drop is much larger due to complex formation. The increasing complex stability in the order $K^+ < Na^+ < Li^+$ is quite evident from curves 4, 5 and 6 of Fig. 1. The necessity of using a constant large concentration of a non-complexing electrolyte and relatively low concentrations of complexing species is evident from these curves for there is a pH lowering when the mean number of bound hydrogen ions exceeds 2 where no complex formation occurs. This conclusion was based on results such as those in Fig. 2. The effect did not occur for $n > 2$ with lower total concentrations but the same ratios of triphosphate and metal ion with sufficient tetramethylammonium chloride present to adjust the ionic strength to unity.

Curve 1, Fig. 2, was obtained for the titration of 0.00919 M $((CH_3)_4N)_5P_3O_{10}$ with a solution containing 0.0543 M HCl and exactly the same concentration of $H_5P_3O_{10}$ as the solution titrated. Curves 2, 3, 4 and 5 were obtained in titrations of solutions containing approximately 0.01 M $Na_5P_3O_{10}$ and different concentrations of NaCl. The acid solution contained approximately 0.05 M HCl and the same concentrations of NaCl and triphosphate as the solution titrated. Since no complex formation was observed between any of the metal ions and triphosphate ions containing two or more hydrogen ions, eq. 5, 6 and 7 were sufficient to calculate the formation constants. The data and results are given in Table I.

TABLE I

DATA AND RESULTS FOR THE TITRATION OF TRIPHOSPHATE ION WITH HYDROGEN ION IN THE PRESENCE OF VARIOUS ALKALI METAL IONS

The heading "a" is the number of moles of hydrogen ion added per mole of triphosphate ion, $C_L \times 10^3$ is the total triphosphate concentration and $C_M \times 10^3$ is the total concentration of metal ion. The ionic strength was adjusted to unity with $(CH_3)_4NCl$, 25°.

Metal ion	"a"	pH	$C_L \times 10^3$	$C_M \times 10^3$	log K
Potassium					log K_{KL}
	0.50	8.69	2.274	13.87	1.43
	.50	8.61	2.274	28.87	1.36
	.50	8.52	2.274	33.87	1.38
	.50	8.45	2.274	58.87	1.38
				Av.	1.39 ± 0.06
Sodium					log K_{NaL}
	0.50	8.51	10.20	51.00	1.65
	.50	8.30	9.940	99.70	1.64
	.50	8.75	1.040	5.20	1.66
	.50	8.46	2.500	50.00	1.62
				Av.	1.64 ± 0.06
					log K_{NaHL}
	1.50	5.72	10.20	51.00	0.76
	1.50	5.63	9.970	99.90	.77
	1.50	5.42	10.10	250.0	.78
				Av.	.77 ± 0.06
Lithium					log K_{LiL}
	0.50	8.01	3.208	31.04	2.84
	.50	8.24	2.623	13.12	2.84
	.50	8.01	2.223	28.12	2.86
	.50	7.89	3.208	46.04	2.90
	.50	7.87	2.623	42.12	2.89
				Av.	2.87 ± 0.06
					log K_{LiHL}
	1.50	5.29	3.208	31.04	1.90
	1.50	5.19	3.208	46.04	1.87
	1.50	5.13	3.208	61.04	1.86
				Av.	1.88 ± 0.06

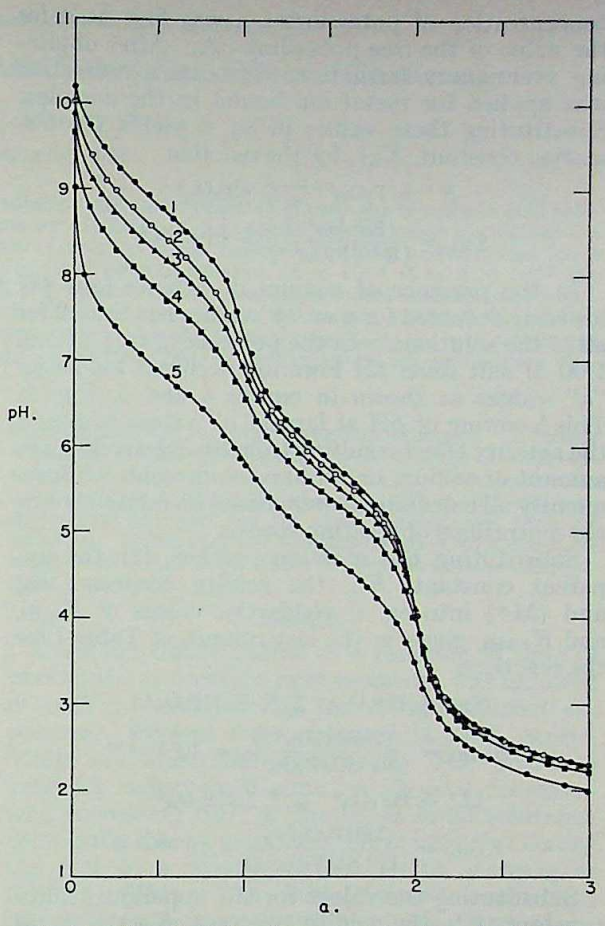

Fig. 2.—The effect of various concentrations of sodium ion on titration curves for the titration of triphosphate ion with hydrochloric acid: curve 1, 0.00919 M $((CH_3)_4N)_5P_3O_{10}$ titrated with a solution 0.0543 M in HCl and 0.00919 M in $H_5P_3O_{10}$. All solutions adjusted to $\mu = 1$ with $(CH_3)_4NCl$. Curve 2, similar to curve 1 but 0.05 M in Na^+; curve 3, 0.10 M in Na^+; curve 4, 0.25 M in Na^+; curve 5, 1.00 M in Na^+.

In the presence of potassium ion a lowering of the pH occurred only for "a" values less than unity proving the absence of detectable concentrations of potassium hydrogen triphosphate complexes, so eq. 6 reduced to the form

$$K'_5 = K_5 + K_{KL}K_5(K^+) \qquad (8)$$

The apparent constant, K'_5, is equal to the pH at the corresponding "a" value of $1/2$. The values for the acidity constants of triphosphoric acid in 1 M $(CH_3)_4NCl$ at 25° taken from the previous paper were $10^{-5.53}$ for K_4 and $10^{-8.81}$ for K_5. The total

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concentration of potassium ion was first used for the value of the free potassium ion. After obtaining preliminary formation constants a correction was applied for metal ion bound in the complex. Substituting these values in eq. 6 yields the formation constant, K_{KL}, for the reaction

$$K^+ + P_3O_{10}^{5-} \rightleftharpoons KP_3O_{10}^{4-}$$

$$K_{KL} = \frac{(KP_3O_{10}^{4-})}{(K^+)(P_3O_{10}^{5-})} = 10^{1.39 \pm 0.06}$$

In the presence of sodium or lithium ions pH lowering occurred for n or "a" values less than 2 for all of the solutions. In the presence of 0.25 M and 1.00 M salt some pH lowering occurred for larger "a" values as shown in curves 4 and 5, Fig. 2. This lowering of pH at larger "a" values is due to the activity effect resulting from the relatively large amount of sodium or lithium ion present. Consequently all calculations were based on relatively low concentrations of reacting species.

Substituting the individual values for the apparent constant, K'_4, the acidity constant, K_4, and (M^+) into eq. 5 yields the values of K_{LiHL} and K_{NaHL} given in the last column of Table I for the reactions

$$Na^+ + HP_3O_{10}^{4-} \rightleftharpoons NaHP_3O_{10}^{3-}$$

$$K_{NaHL} = \frac{(NaHP_3O_{10}^{3-})}{(Na^+)(HP_3O_{10}^{4-})} = 10^{0.77 \pm 0.06}$$

$$Li^+ + HP_3O_{10}^{4-} \rightleftharpoons LiHP_3O_{10}^{3-}$$

$$K_{LiHL} = \frac{(LiHP_3O_{10}^{3-})}{(Li^+)(HP_3O_{10}^{4-})} = 10^{1.88 \pm 0.06}$$

Substituting the values for the apparent acidity constant, K'_5, the acidity constant, K_5, the metal concentration, (M^+), and the above metal–hydrogen formation constants into eq. 6 yields the values of the metal formation constant given in the last column of Table I for the reactions

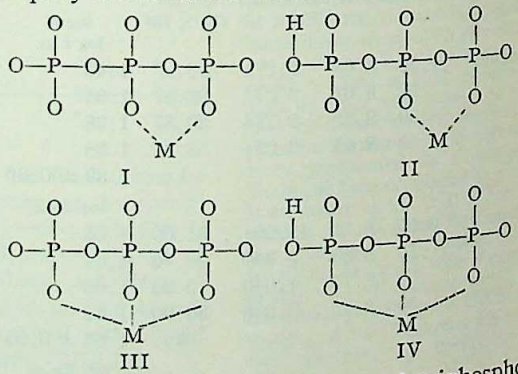
$$Na^+ + P_3O_{10}^{5-} \rightleftharpoons NaP_3O_{10}^{4-}$$

$$K_{NaL} = \frac{(NaP_3O_{10}^{4-})}{(Na^+)(P_3O_{10}^{5-})} = 10^{1.64 \pm 0.06}$$

$$Li^+ + P_3O_{10}^{5-} \rightleftharpoons LiP_3O_{10}^{4-}$$

$$K_{LiL} = \frac{(LiP_3O_{10}^{4-})}{(Li^+)(P_3O_{10}^{5-})} = 10^{2.87 \pm 0.06}$$

These results establish moderately stable complex formation between triphosphate ion and these alkali metals which should be considered in calculating the stabilities of other complexes of triphosphate ions. It is probable that the metal ions are members of at least one chelate ring containing two phosphorus and three oxygen atoms, structure I, as suggested by Kolthoff and Watters[11] for the manganese(III) complex with pyrophosphate and by Van Wazer[9] and his co-workers for complexes of higher phosphates since no complexes were observed in similar experiments with orthophosphate. In these structures the three resonating double bonds and the ionic charges are omitted. It is possible that, in the acidic complexes, the hydrogen ion is bound in the same way. However, the strong bonding of the last hydrogen ion in phosphoric acid relative to its bonding in higher phosphates indicates that the hydrogen ion may be bonded to a single phosphate tetrahedron as shown in structure II. In the next paper of this series it will be shown that the acid triphosphate complexes of lithium are slightly less acidic than the acidic pyrophosphate complexes. This evidence supports a structure for the acidic complex in which the metal ion is not bonded to the same phosphate tetrahedron as the hydrogen ion. Accordingly, structure II seems feasible for the acidic complex. Hydrogen bonding in the same or adjacent tetrahedron probably occurs. Martell and Schwarzenbach[6] have proposed that the triphosphate ion may be tridentate, structures III and IV, in the corresponding complexes with calcium and magnesium. Their structure III for triphosphate is supported by similar experiments with pyrophosphate. These studies indicate that the pyrophosphate complexes with the alkali metals are somewhat less stable than the triphosphate complexes. Hirshfelder–Taylor models indicate that bonding of the metal ion to the two terminal phosphate tetrahedra and to the center tetrahedron as well can occur without strain. However, the bonding with alkali metals is probably essentially electrostatic rather than covalent in nature so the exact position of the metal ion as part of any particular chelate ring may be more a function of field strength than of bonding direction. On this basis it is probable that neither structure I or III uniquely describes the actual situation.



The last four acidity constants of triphosphoric acid and the four acidity constants of ethylenediaminetetraacetic acid are somewhat similar. It is of interest that this similarity persists in the sodium and lithium complexes of these ligands.

Acknowledgment.—The authors wish to acknowledge financial assistance to E. D. L. by a grant from the Ohio State Alumni Development Fund and to S. M. L. by a Kettering Foundation Fellowship.

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[CHEMISTRY DIVISION, OAK RIDGE NATIONAL LABORATORY[1]]

Photoreduction of Ceric Ion in Sulfuric Acid Solutions. Effect of Thallous Ion[2a]

BY THOMAS J. SWORSKI[2b]

RECEIVED MARCH 14, 1957

Evidence has been obtained for the OH radical as an intermediate in the photoreduction of ceric ion in sulfuric acid solutions. The observed chemical reaction in the photolysis of ceric ion–thallous ion mixtures is the oxidation of thallous ion by ceric ion. The initial quantum yield (ΦCe^{+++}) for reduction of ceric ion in the absence of initially added cerous ion is markedly enhanced by thallous ion but is independent of the thallous ion concentration (2×10^{-4} M to 2×10^{-2} M). At any particular initial cerous ion concentration, the initial ΦCe^{+++} decreases with decreasing initial thallous ion concentration. These data obtained in 0.4 M sulfuric acid are quantitatively interpreted by a mechanism in which thallous ion competes with cerous ion for reaction with OH radical. The measured value of 42 for $k_{Tl^+, OH}/k_{Ce^{+++}, OH}$ is in agreement with the value of 38 previously determined in 0.4 M sulfuric acid for the radiolysis of ceric ion–cerous ion–thallous ion mixtures with cobalt-60 γ-radiation.

Introduction

When ceric ions in perchloric acid solution absorb ultraviolet radiation, oxygen is evolved with concomitant reduction of ceric ions to cerous ions.[3,4] Weiss and Porret[4] postulated the formation of an OH radical in the photochemical primary process. This assumption has been a subject of controversy.[5,6]

Photoreduction of ceric ions also occurs[7] in sulfuric acid solutions in disagreement with the observations of Weiss and Porret.[4] Although no definitive evidence was presented, the OH radical was also postulated[7] as an intermediate in sulfuric acid solutions. This paper reports the results of a kinetic study of the photolysis of ceric ion–cerous ion–thallous ion mixtures in 0.4 M sulfuric acid. These results, when compared with those reported[8] for the radiolysis of ceric ion–cerous ion–thallous ion mixtures with cobalt-60 γ-radiation also in 0.4 M sulfuric acid, yield supporting evidence for the intermediate formation of OH radical in the photoreduction of ceric ion in sulfuric acid solutions.

Experimental

The source of ultraviolet radiation was a G. E. 4-watt germicidal lamp operating from a Sola Electric constant voltage transformer. The light was used without collimation, the solutions being reproducibly placed several centimeters from the light source. The light flux incident upon the solutions was measured with an equal volume of actinometer solution.[9] The light absorbed from this source by the uranyl actinometer is reported[10] to be almost entirely 253.7 mμ. The quantum efficiency for oxalate oxidation was observed to be constant up to 65% of completion.

Solutions of 50-ml. volume were contained in a silica vessel of 3 cm. diameter. The ceric ion solutions in 0.4 M sulfuric acid were prepared in the same manner as previously reported[8] for the radiolysis of ceric ion–cerous ion–thallous ion mixtures with cobalt-60 γ-radiation. Ceric ion concentrations were determined spectrophotometrically with a Cary model 11 recording spectrophotometer. A molar extinction coefficient for ceric ion at 320 mμ of 5580 was used for 0.4 M sulfuric acid solutions.[11] Molar extinction coefficients of 2440 at 370 mμ and 1020 at 395 mμ were determined and used for the more concentrated ceric ion solutions. Cerous ion and thallous ion have no measurable effect on these molar extinction coefficients at the concentrations employed.

Results

Ceric ion concentration as a function of time of photolysis, at constant light intensity, was followed in each solution through use of intermittent exposures. Typical data obtained in such experiments are illustrated by Fig. 1. The quantum yield for reduction of ceric ion ($\Phi_{Ce^{+++}}$) decreased with increasing time of photolysis in all solutions, principally due to an internal filter action of cerous ion and to a smaller extent to an increase in $(Ce^{+++})/(Tl^+)$. The initial $\Phi_{Ce^{+++}}$ could not, therefore, be measured with any high degree of accuracy or reproducibility. The initial $\Phi_{Ce^{+++}}$ obtained under a variety of experimental conditions in air-saturated 0.4 M sulfuric acid are listed in Table I.

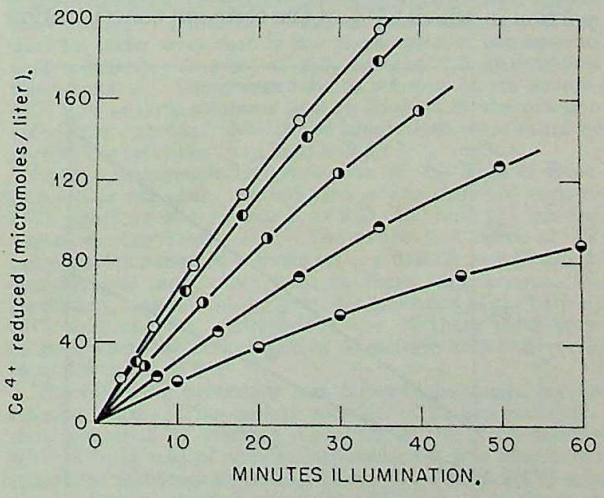

Fig. 1.—Effect of variation in initial thallous ion concentration on the rate of photoreduction of ceric ion at constant initial ceric and cerous ion concentrations. Initial cerous ion concentration in all solutions was 10^{-2} M. Initial ceric ion concentration in all solutions was 3.64×10^{-4} M. Initial thallous ion concentrations were: ○, 10^{-2} M; ◐, 10^{-3} M; ◑, 4×10^{-4} M; ◒, 2×10^{-4} M; ◓, 10^{-4} M.

(1) Operated by Union Carbide Nuclear Company for the Atomic Energy Commission.

(2a) Paper presented before the Division of Physical and Inorganic Chemistry, 131st Meeting of the American Chemical Society at Miami, Fla., April 7–12, 1957.

(2b) Sterling Forest Nuclear Center, Union Carbide Nuclear Company, Union Carbide Corporation, New York, N. Y.

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TABLE I

EFFECT OF CERIC, CEROUS AND THALLOUS ION CONCENTRATIONS ON THE QUANTUM YIELD FOR PHOTOREDUCTION OF CERIC ION[a]

(Ce^{4+}), μmoles/l.	(Ce^{+++}), moles/l.	(Tl^{+}), mole/l.	Initial $\Phi_{Ce^{+++}}$
242	0	5×10^{-3}	0.200
478	0	5×10^{-3}	.205
962	0	5×10^{-3}	.201
1907	0	5×10^{-3}	.200
460	0	2×10^{-2}	.204
460	0	5×10^{-3}	.204
460	0	2×10^{-4}	.212
325	0	2×10^{-2}	.199
325	0	2×10^{-3}	.212
325	0	2×10^{-4}	.206
325	2×10^{-2}	2×10^{-2}	.0292
325	2×10^{-2}	2×10^{-3}	.0263
325	2×10^{-2}	8×10^{-4}	.0197
325	2×10^{-2}	4×10^{-4}	.0158
325	2×10^{-2}	2×10^{-4}	.00947
364	10^{-2}	10^{-2}	.0490
364	10^{-2}	10^{-3}	.0400
364	10^{-2}	4×10^{-4}	.0313
364	10^{-2}	2×10^{-4}	.0204
364	10^{-2}	10^{-4}	.0146

[a] Quantum yields are based on total light absorbed by the solutions.

The chemical change which occurs during photolysis is oxidation of thallous ion by ceric ion. This was experimentally established by two different methods. (I) In a solution containing initially 10^{-3} M ceric ion and 2.67×10^{-4} M thallous ion, the rate of photoreduction markedly decreased when 5.40×10^{-4} mole/l. of ceric ion had been reduced. (II) For a solution containing initially 10^{-3} M ceric ion and 2.67×10^{-3} M thallous ion, equal volumes of either the original solution or a portion in which 85% of the ceric ion concentration had been photochemically reduced oxidized equal amounts of ferrous ion.

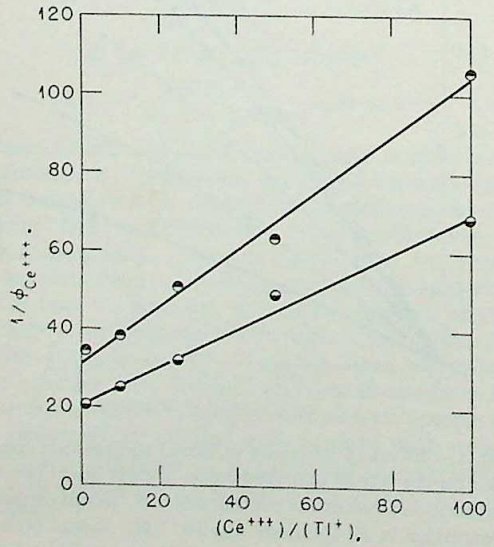

Fig. 2.—Effect of $(Ce^{+++})/(Tl^{+})$ ratio on the initial rate of photoreduction of ceric ion in air-saturated 0.4 M sulfuric acid solutions. Initial cerous ion concentrations were: ◓, 2×10^{-2} M and ◒, 10^{-2} M. Initial ceric ion concentrations were: ◓, 3.25×10^{-4} M; ◒, 3.64×10^{-4} M.

In ceric ion–thallous ion mixtures, the initial $\Phi_{Ce^{+++}}$ is independent of the ceric ion concentration (2.4×10^{-4} M to 1.9×10^{-3} M). This indicates that essentially all the incident light is absorbed by these solutions. These results in sulfuric acid solutions differ markedly with those obtained in perchloric acid solutions by Heidt and Smith[5] where $\Phi_{Ce^{+++}}$ increases with increasing ceric ion concentration.

The initial $\Phi_{Ce^{+++}}$ is also independent of thallous ion concentration (2×10^{-4} M to 2×10^{-2} M) but only in the absence of initially added cerous ion. At any particular initial cerous ion concentration, the initial $\Phi_{Ce^{+++}}$ decreases with decreasing thallous ion concentration. Since cerous ion acts as an internal filter, dependence of initial $\Phi_{Ce^{+++}}$ on $(Ce^{+++})/(Tl^{+})$ was investigated at constant concentration of ceric and cerous ions.

Discussion

The reactions of ceric and cerous ions with radicals in aqueous solution have been elucidated by recent studies in radiation chemistry. $G(Ce^{+++})$[12] in the radiolysis of sulfuric acid solutions containing ceric ions was postulated[13] to be equal to $2G_{H_2O_2} + G_H - G_{OH}$. The following radical reactions were assumed

$$Ce^{4+} + H \longrightarrow Ce^{+++} + H^{+} \quad (1)$$

$$Ce^{+++} + OH \longrightarrow Ce^{4+} + OH^{-} \quad (2)$$

This mechanism was confirmed[14] by a demonstration of ceric ion reduction with concomitant oxidation of radioactive cerous ion.

Thallous ion increases[15] $G(Ce^{+++})$ to $2G_{H_2O_2} + G_H + G_{OH}$ according to the reaction mechanism

$$Tl^{+} + OH \longrightarrow Tl^{++} + OH^{-} \quad (3)$$

$$Ce^{4+} + Tl^{++} \longrightarrow Ce^{+++} + Tl^{+++} \quad (4)$$

A value of 38 was measured[8] for the ratio k_3/k_2 in 0.4 M sulfuric acid.

If the postulate is correct that an OH radical is formed in the primary photochemical process in sulfuric acid solutions

$$Ce^{4+} + H_2O \xrightarrow{h\nu} Ce^{+++} + H^{+} + OH \quad (5)$$

then the experimental data should be fully described by a reaction mechanism containing only reactions 5, 2, 3 and 4. From this reaction mechanism, the following kinetic relationship can be derived

$$\frac{1}{\Phi_{Ce^{+++}}} = \frac{1}{2\Phi_{OH}} + \frac{k_2(Ce^{+++})}{2\Phi_{OH}k_3(Tl^{+})}$$

Φ_{OH} is the quantum yield for the OH radicals formed in the primary photochemical process.

A linear relationship does exist between $1/\Phi_{Ce^{+++}}$ and $(Ce^{+++})/(Tl^{+})$ as shown in Fig. 2. Treatment of the data by the method of least

(12) In the decomposition of water by ionizing radiation, 100 e.v. yields of the intermediates H, OH, H_2 and H_2O_2 are denoted by G_H, G_{OH}, G_{H_2} and $G_{H_2O_2}$. The 100 e.v. yield of any measurable product in radiolysis of aqueous solutions is denoted by G(product).

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(14) G. E. Challenger and B. J. Masters, THIS JOURNAL, **77**, 1063 (1955).

(15) T. J. Sworski, *ibid.*, **77**, 4689 (1955).

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squares yields the equations

$$1/\Phi_{Ce^{+++}} = 31.2 + 0.730(Ce^{+++})/(Tl^{+}) \quad (I)$$

$$1/\Phi_{Ce^{+++}} = 20.5 + 0.495(Ce^{+++})/(Tl^{+}) \quad (II)$$

Equation I is obtained from the data with 2×10^{-2} M cerous ion solutions while eq. II is obtained from the data with 10^{-2} M cerous ion solutions.

From eq. I and II, k_3/k_2 is evaluated by division of the intercept by the slope. From eq. I, k_3/k_2 is equal to 31.2/0.73 or 42.7. From eq. II, k_3/k_2 is equal to 20.5/0.495 or 41.4. The average value of 42 is in excellent agreement with the value of 38 measured[8] for the radiation chemistry of the same chemical system using cobalt-60 γ-radiation.

This comparison of the photochemistry with the radiation chemistry of ceric ion–cerous ion–thallous ion mixtures thus yields convincing evidence for the postulated formation of OH radical in the photoreduction of ceric ion in sulfuric acid solutions.

Let us assume that OH is an intermediate in perchloric acid and that OH radical can reduce[6] ceric ion in perchloric acid. Then, the following kinetic relationship can be derived

$$\frac{1}{\Phi_{Ce^{+++}}} = \frac{1}{x\Phi_{OH}} + \frac{k_2(Ce^{+++})}{x\Phi_{OH}k_y(Ce^{4+})}$$

The value of x would be either 2 or 4 and k_y would be either k_6 or k_7 depending whether ceric ion oxidized OH radical according to reaction 6 or reaction 7

$$Ce^{4+}\cdot H_2O + OH \longrightarrow Ce^{+++} + H^{+} + H_2O_2 \quad (6)^{6}$$

$$Ce^{4+} + OH \longrightarrow Ce^{+++} + H^{+} + {}^1/_2O_2 \quad (7)$$

Heidt and Smith[5] report that for 1.1×10^{-2} M ceric ion solutions in perchloric acid $1/\Phi_{Ce^{+++}} = 5 + 670(Ce^{+++})$. Thus, k_y/k_2 would have a value of 0.68. Whether reaction 6 or reaction 7 occurs could be determined if Φ_{OH} were known. This would have required a study of the effect of added solutes, such as reported here, which was not investigated by Heidt and Smith.[5]

OAK RIDGE, TENN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TOLEDO]

A Study of the Kinetics of the Reaction between Oxalate Ion and Cerium(IV) in Aqueous Sulfuric Acid Solution

BY VANCE H. DODSON AND ARTHUR H. BLACK

RECEIVED FEBRUARY 7, 1957

The kinetics of the reaction between cerium(IV) and oxalate ion, bioxalate ion and oxalic acid in aqueous sulfuric acid has been studied over the temperature range of 19 to 35°. The reaction appears to be second order, and the rate of the reaction is dependent upon the concentration of sulfuric acid. The experimental energy of activation is 16.5 ± 0.4 kcal./mole in 0.5, 1.0 and 2.0 M sulfuric acid solutions.

Kinetic studies of the reactions between cerium(IV) and tin(II),[1] arsenic(III)[2] and oxalic acid[3] have been reported in the literature. In a recent examination of the reaction between cerium(IV) and oxalate ion[4] in aqueous sulfuric acid, it was noted that the rate of the reaction decreased as the concentration of the sulfuric acid was increased. Since the previously published work[3] merely established the order of the reaction, it was of interest to re-examine the kinetics of the reaction and attempt to establish a mechanism for it.

Experimental Part

Equipment and Reagents.—Reaction rates were determined by using a Bausch and Lomb Spectronic 20 colorimeter. The solutions were kept in a constant temperature bath, then mixed and immediately transferred to the cell and placed in the instrument. In all of the experiments conducted, the cell and its contents were never in the instrument longer than one minute. Over the temperature range of 19 to 35° this short exposure to the heat of the exciter lamp produced no deviations greater than ±0.1° in the reaction mixtures.

The reagents were prepared by dissolving anhydrous cerium(IV) acid sulfate (G. Frederick Smith Chemical Co.) and C.P. Special Grade anhydrous sodium oxalate (Baker Chemical Co.) in aqueous sulfuric acid of known molarity. The cerium(IV) solutions were standardized with iron(II). Ferrous o-phenanthroline was used as the indicator. The concentrations of the oxalate solutions were checked against the cerium(IV) solutions. Reagent grade sulfuric acid and distilled water were used in the preparation of the aqueous acid solutions. A series of 2.0, 1.0 and 0.5 M solutions was prepared. These were used as solvents in the cerium(IV) and oxalate solutions and as diluents in the reaction rate measurements. No special precautions were taken to protect the solutions from light and air.[5]

Spectrophotometric Determination of the Rate of Reaction.—The per cent. transmission of the standard cerium(IV) solutions was measured at 425, 450 and 475 mμ and found to obey Beer's law. The calibration curve at 450 mμ over the range of concentrations 0.0055 to 0.00025 M was the one most often used in these experiments. No significant variation in per cent. transmission of the cerium(IV) solutions was observed at any of these three wave lengths when the concentration of sulfuric acid was varied from 0.5 to 2.0 M.[6]

The following procedure was followed in measuring the reaction rates. The oxalate solution of known concentration, prepared by diluting a portion of the stock solution with sulfuric acid of appropriate molarity, was placed in a stoppered wide-mouth conical flask. The cerium(IV) solution of known concentration (in sulfuric acid of the same molarity as that in the oxalate solution) was placed in a stoppered soft glass test-tube whose bottom had been blown to form a thin-walled bulb. Both the bulb and flask were then placed in the constant temperature bath. At time zero the bulb of cerium(IV) solution was broken in the conical flask and the solutions were mixed by rapid swirling. A portion of the reaction mixture was immediately transferred to the colorimeter cell and per cent. transmission readings were taken at various time intervals.

(1) C. H. Brubaker, Jr., and A. J. Court, THIS JOURNAL, **78**, 5530 (1956).
(2) J. S. Yates and H. C. Thomas, *ibid.*, **78**, 3950 (1956).
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The time required by the experimenters to mix the solutions and place them in the instrument varied from eight to ten seconds. The number of readings taken per experiment ranged from three to seven in number. The concentration of unreacted cerium(IV) at the various time intervals was then determined from a plot of the logarithm of per cent. transmission *versus* concentration that had been predetermined from the standard solutions.

Results

The initial concentration of the oxalate ion, bioxalate ion or oxalic acid was varied from 0.007 to 0.005 *M* in the experiments, while that of the cerium(IV) was approximately 0.01 *M*. The reaction was observed to be second order, first order each in cerium(IV) and oxalate, bioxalate or oxalic acid. A graphical treatment of the results of several typical experiments is shown in Fig. 1.

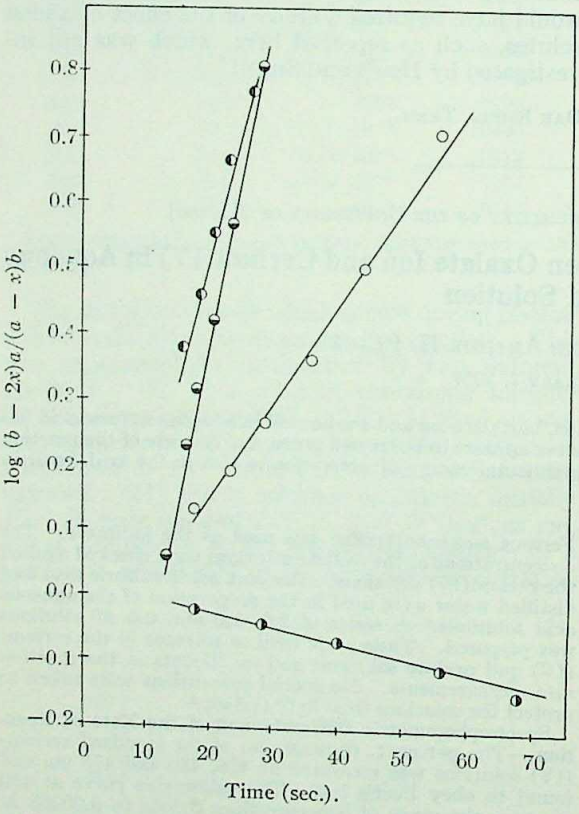

Fig. 1.—Typical second-order rate plots: ◐, $a = 0.01045$ *M* Ce(IV), $b = 0.00613$ *M* oxalate, in 1.0 *M* H_2SO_4 at 27°; ◒, $a = 0.01045$ *M* Ce(IV), $b = 0.00750$ *M* oxalate, in 1.0 *M* H_2SO_4 at 19°; ○, $a = 0.01050$ *M* Ce(IV), $b = 0.00693$ *M* oxalate, in 2.0 *M* H_2SO_4 at 25°; ◑, $a = 0.01050$ *M* Ce(IV), $b = 0.00495$ *M* oxalate, in 2.0 *M* H_2SO_4 at 25°.

The second-order rate constants that are reported in Table I were calculated from the slopes of plots similar to those of Fig. 1 and represent the average of several experiments. The deviations reported in Table I are average deviations.

The plots of log *k versus* $1/T$, shown in Fig. 2, for the reactions carried out in the three different concentrations of sulfuric acid have approximately the same slope. The activation energies calculated from the slopes of these plots are 16.9 kcal./mole (in 0.5 *M* acid), 16.7 kcal./mole (in 1.0 *M* acid)

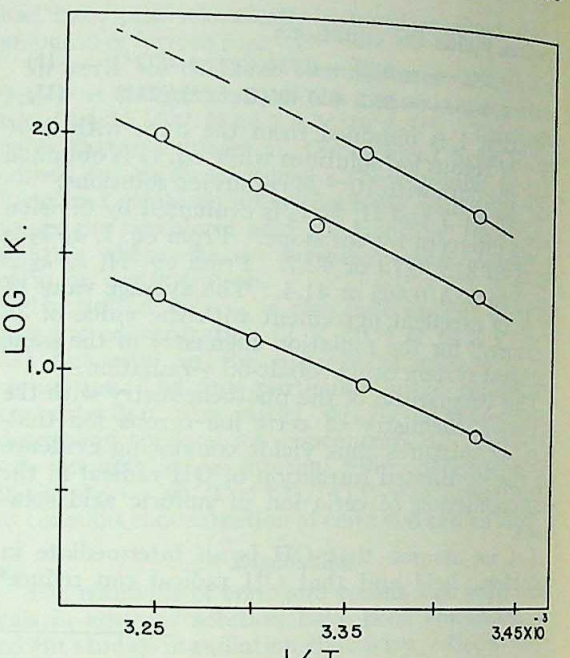

Fig. 2.—Arrhenius plot: upper curve, reactions in 0.5 *M* H_2SO_4; middle curve, reactions in 1.0 *M* H_2SO_4; lower curve, reactions in 2.0 *M* H_2SO_4.

TABLE I

RATE CONSTANTS FOR THE OXIDATION OF OXALATE BY CERIUM(IV) AT VARIOUS TEMPERATURES IN AQUEOUS SULFURIC ACID

No. of exp.	Concn. of H_2SO_4, *M*	Temp., °C. ±0.1°	$k_{av.}$, l. × mole^{-1} × sec.$^{-1}$
7	0.5	19.0	49.7 ± 8.7
8		25.0	87.6 ± 7.2
9	1.0	19.0	22.6 ± 0.9
10		27.0	42.8 ± 4.0
10		30.0	62.9 ± 4.3
4		35.0	97.0 ± 10.5
8	2.0	19.0	5.45 ± 0.26
9		25.0	9.02 ± 0.27
6		30.0	13.7 ± 0.7
6		35.0	20.9 ± 1.6

and 15.8 kcal./mole (in 2.0 *M* acid) and average 16.5 ± 0.4 kcal./mole.

Discussion and Conclusions

The total ionic strength of each of the reaction mixtures examined in this work is extremely large in comparison with that of the reactants; and, as might be expected, the deviations in the reaction rates with changes in concentration of the reactants are not significant. Had there been a noticeable variation, an interpretation would not be entirely justified in view of the high ionic strength of the solutions.[7]

A plot of log k − log k_0 *versus* $\sqrt{\mu}$ is shown in Fig. 3. In this graph, log k_0 is the rate constant at infinite dilution with respect to sulfuric acid, k is the average measured rate constant (Table I), and μ is the total ionic strength of the hydrogen, bisulfate and sulfate ions in solution. The concentrations

(7) S. Glasstone, "Textbook of Physical Chemistry," 2nd Ed., D. Van Nostrand Co., New York, N. Y., 1946, Chap. 13.

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of these ions were roughly estimated from the dissociation constants of oxalic acid and bisulfate ion.[8] Molar concentrations were converted to molalities and ionic strengths were derived from these latter values. The graph in Fig. 3 shows that the differences between log k and log k_0 over the temperature range 19 to 35° are approximately the same for solutions of similar ionic strength (with respect to sulfuric acid). This same conclusion can be reached by comparing the slopes of the curves in Fig. 2. The data plotted in Figs. 2 and 3 indicate that the same species of reactants are involved in the rate-determining step, regardless of the acidity of the reaction medium.

There is considerable evidence that the cerium(IV) ion exists primarily as the trisulfato complex ion in sulfuric acid solutions. This is especially true in acid concentrations such as those employed in this work.[6,9] It is also reasonable to assume that in these strongly acid solutions the oxalate is present mainly as oxalic acid with smaller amounts of bioxalate ion and only traces of oxalate ion. The rate-determining step must then be either (I) or (II)

$$2Ce(SO_4)_3^{-2} + HC_2O_4^{-1} \longrightarrow 2Ce^{+3} + 2CO_2 + 5SO_4^{-2} + HSO_4^{-1} \quad (I)$$

$$2Ce(SO_4)_3^{-2} + H_2C_2O_4 \longrightarrow 2Ce^{+3} + 2CO_2 + 4SO_4^{-2} + 2HSO_4^{-1} \quad (II)$$

Since both reactions I and II produce bisulfate ions, they might be expected to respond to a change in acid concentration. The presence of excess sulfate ions in the reaction medium would also tend to reduce the rate of the reaction. From the standpoint of the concentration of the reactants, an increase in acid concentration would tend to slow down reaction I and speed up reaction II. However, as the concentration of the sulfuric acid solutions is increased from 0.5 to 2.0 M, the concentration of bioxalate ion and oxalic acid remains fairly constant. Therefore, the noted effect of the acid on the reaction rates must be due to the excess sulfate, bisulfate and hydrogen ions in solution.

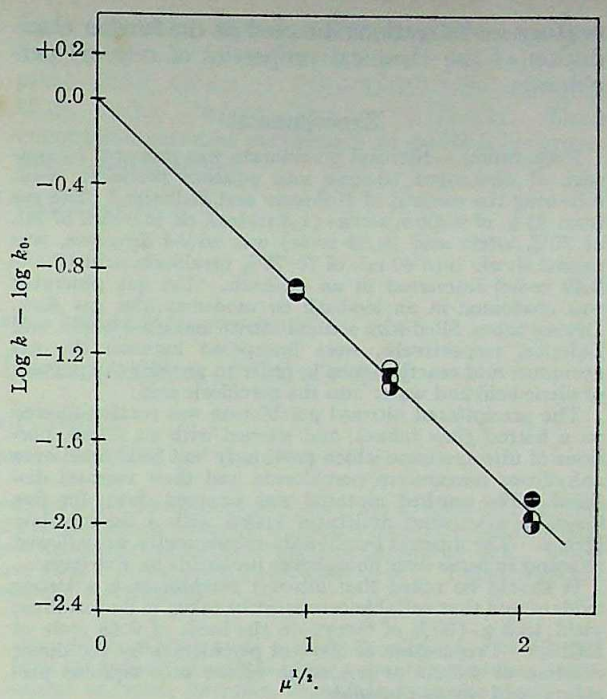

Fig. 3.—Relationship between measured second-order rate constants and ionic strength of acid medium: ◒, 19°; ◓, 25°; ◐, 30°; ◑, 35°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL ENGINEERING AND FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

The Chemical Properties of Nitrosyl Perchlorate: The Neutralization Equivalent

BY MEYER M. MARKOWITZ, JOHN E. RICCI, RICHARD J. GOLDMAN AND PAUL F. WINTERNITZ

RECEIVED MARCH 5, 1957

The quantitative preparation of nitrosyl perchlorate from dinitrogen trioxide and perchloric acid is limited by the subsequent hydrolysis of the product below a minimum acid concentration. The neutralization equivalent weight of nitrosyl perchlorate under defined conditions is $NOClO_4/2$. Some aspects of the thermal behavior of the salt are treated briefly.

Introduction

Interest in the nitric oxide molecule stems from the diversity of bond types into which the group may enter.[1-3] Previous studies concerning nitrosyl perchlorate ($NOClO_4$), as representative of a compound containing a nitric oxide cation (NO^+), have dealt with the electrolytic behavior in anhydrous nitromethane,[4] the Raman spectrum in perchloric acid,[5] the crystallographic structure,[6] the heat of formation,[7] and the thermal decomposition.[8] The material to follow presents lab-

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oratory investigations directed at the further elucidation of the chemical properties of nitrosyl perchlorate.

Experimental

Preparation.—Nitrosyl perchlorate was prepared by passage of dinitrogen trioxide into aqueous perchloric acid, following the method of Hofmann and Zedtwitz.[9] The gas from 89 g. of sodium nitrite (1.3 moles), on to which 57 ml. of 70% nitric acid (0.89 mole) was added dropwise, was passed slowly into 40 ml. of 70–72% perchloric acid (0.47–0.49 mole) immersed in an ice-bath. The gas generator was contained in an ice-bath to moderate the gas flow. Drying tubes, filled with sodium nitrite and glass beads, and Drierite, respectively, were interposed between the gas generator and reaction tube in order to prevent the passage of nitric acid and water into the perchloric acid.

The precipitated nitrosyl perchlorate was suction-filtered on a fritted glass funnel, and washed with six 20-ml. portions of nitromethane which previously had been dried over anhydrous magnesium perchlorate and then vacuum distilled. The washed material was pumped down for five hours in a vacuum desiccator sealed with a fluorocarbon grease. The nitrosyl perchlorate subsequently was allowed to stand *in vacuo* over phosphorus pentoxide for five days.

It should be noted that nitrosyl perchlorate is a strong oxidant and that suitable care must be taken in its handling; yield 18.3 g. (30% of theory on the basis of 0.48 mole of $HClO_4$). Preparation of nitrosyl perchlorate by the direct reaction of sodium or potassium nitrite with aqueous perchloric acid was not possible.

Analytical Methods.—Analyses for chlorine were performed by admixture of the product with anhydrous sodium carbonate in a platinum crucible, addition of water dropwise to allow for conversion to sodium perchlorate, oven-drying at 90°, and ignition over a blast lamp for decomposition of the perchlorate to chloride.[10] Chlorine was then determined gravimetrically as silver chloride.

Direct determination of the nitrosyl group was afforded by suspension of the salt (0.5 g.) in concentrated sulfuric acid (100 ml.), and slow addition, accompanied by constant stirring, of excess potassium permanganate (0.2 *N*).[11,12] The permanganate solution must be added below the surface of the acid to avoid any loss of sample by hydrolysis. The excess permanganate was titrated with acidified ferrous sulfate solution (0.2 *N*).

Anal. Calcd. for $NOClO_4$:Cl, 27.39; nitrosyl group, 23.17. Found: Cl, 27.28; nitrosyl group, 23.16.

Hydrolysis of Nitrosyl Perchlorate.—The low yield obtained may, in part, be traced back to the ready hydrolysis of ionic nitrosyl compounds.[1,13] Solution of dinitrogen trioxide in strong, concentrated acids yields the nitrosyl ion.[14,15] Thus, with perchloric acid, the following reaction must occur

$$N_2O_3 + 3HClO_4 \longrightarrow 2NO^+ + 3ClO_4^- + H_3O^+$$

As the addition of dinitrogen trioxide is continued, nitrosyl perchlorate will precipitate and the concentration of the water will rise. However, precipitation can only proceed to the point at which hydrolysis of the product ensues because of the augmenting water concentration. Hydrolysis will yield nitrous acid as per

$$NOClO_4 + H_2O \longrightarrow HNO_2 + HClO_4$$

which may, in turn, decompose according to the disproportionation reaction

$$3HNO_2 \longrightarrow HNO_3 + 2NO + H_2O$$

Titration with sodium hydroxide of the filtrate obtained from the above-described preparation of nitrosyl perchlorate showed that the alkali titer, expressed as equivalents of base per 1000 g. of solution, had changed from the value of 7.10 for the original perchloric acid (71.4%) to a final value of 6.18 after precipitation.

Nitrosyl perchlorate placed in 51.7% perchloric acid at 25.0° (5.14 equivalents per 1000 g. of dilute acid) decomposed until the alkali titer of the acid plus nitrosyl perchlorate decomposition products reached 5.44. These data indicate that nitrosyl perchlorate will hydrolyze in perchloric acid solutions of less than about 55% concentration.

The Neutralization Equivalent of Nitrosyl Perchlorate.—Previous studies of the alkali titers of nitrosyl compounds suggest neutralization equivalent weights dependent upon the reaction conditions which would determine the extent of the nitrous acid disproportionation reaction.[7,16] Cruse, *et al.*,[7] reported the reaction of nitrosyl perchlorate with 0.5 *N* sodium hydroxide to be given by

$$9NOClO_4 + 16NaOH \longrightarrow 9NaClO_4 + 6NaNO_2 + NaNO_3 + 2NO + 8H_2O$$

In order to determine the neutralization equivalent under conditions such that the disproportionation reaction would be minimized, a series of titrations with sodium hydroxide was carried out at 0°. 0.25–0.30 g. of nitrosyl perchlorate contained in a small vial was dropped into a flask containing 25 ml. of water and 45–50 ml. of 0.1 *N* sodium hydroxide. The flask was stoppered quickly, shaken vigorously, and allowed to stand for three minutes whereupon the contents were titrated with 0.1 *N* sulfuric acid to a phenolphthalein end-point. Of ten such determinations, an average titer corresponding to 98.82% nitrosyl perchlorate (average deviation, 2.3 parts/1000) on the basis of a neutralization equivalent weight of $NOClO_4/2$ was obtained. This substantiates the neutralization reaction to be

$$NOClO_4 + 2OH^- \longrightarrow NO_2^- + ClO_4^- + H_2O$$

No appreciable variations in the alkali titer were found in performing the titrations at higher temperatures, *i.e.*, 25 and 30°, indicating that the neutralization reaction under the described conditions is sufficiently rapid to avoid a significant amount of interference from nitrous acid disproportionation. At 25°, the average value of six titrations was 98.54% (average deviation, 2.1 parts/1000), and at 35°, for three determinations, 98.40% (average deviation, 2.8 parts/1000). This titration method thus affords a convenient means for the analysis of nitrosyl perchlorate-containing materials.

Nitrosyl perchlorate was found to deteriorate on exposure to and handling in the open air because of the extreme hygroscopicity of the substance. This was seen in a lower alkali titer from a subsequent series of experiments at 0°. The average value for seven experiments on such a treated sample corresponded to 98.14% nitrosyl perchlorate (average deviation, 1.0 part/1000).

Thermal Behavior of Nitrosyl Perchlorate.—Nitrosyl perchlorate is thermally unstable,[8] yielding volatile decomposition products as per the equations

$$2NOClO_4 \longrightarrow 2ClO_2 + {}^1/_2O_2 + N_2O_5 \text{ and}$$

$$2NOClO_4 \longrightarrow N_2O_4 + 3O_2 + Cl_2$$

It was determined in the present work that at 92°, under vacuum (3–5 mm.), weight losses of 27, 61, 94 and 100% occurred with a 0.5-g. sample after 3, 6, 9 and 12 hr., respectively. Losses at 100°, under similar conditions, were 65, 80 and 99%, after 3, 6 and 9 hr., respectively.

Unlike ammonium perchlorate and the alkali metal perchlorates,[17] nitrosyl perchlorate undergoes no crystallographic transition before the onset of rapid decomposition. This was determined by thermal analyses[18] of the compound (5-g. samples), performed over the range from 0 to 100° at heating rates of 5 and 10° per minute. Because nitrosyl perchlorate is isomorphous with ammonium perchlorate,[6] it may be supposed that the normal rhombic structure of the latter is retained by nitrosyl perchlorate at least up to 100°.

Miscellaneous Reactions.—Because the nitrosyl group contains an unshared pair of electrons about the nitrogen atom,

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attempts were made to obtain coördinate bond formation between nitrosyl perchlorate and oxygen (to yield nitronium perchlorate), boron trifluoride and dinitrogen tetroxide, respectively. Nitrosyl perchlorate was thus brought in contact with a rapid stream of gaseous oxygen at room temperature, heated with nitrosyl fluoborate, and treated with liquid dinitrogen tetroxide at 0°, all without any indications of compound formation.

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NEW YORK 53, N. Y.

[CONTRIBUTION FROM THE BALLISTICS RESEARCH LABORATORIES]

The Nitronium Ion Catalyzed Decomposition of Caro's Acid

BY LESTER P. KUHN

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Caro's acid in strong sulfuric acid is catalytically decomposed by small amounts of nitronium ion to yield sulfuric acid and oxygen. The kinetics of the reaction have been studied and a mechanism is presented which is compatible with the data. An unusual feature of the reaction is that both the rate and the order depend upon the strength of the sulfuric acid. Below 91% sulfuric acid the reaction is −1 order in peroxide and above 95% acid, the order in peroxide is +1. Throughout the entire range studied, from 85 to 98% acid the reaction is second order in nitric acid.

Aqueous solutions of Caro's acid, H_2SO_5, are relatively unstable; the kinetics and mechanism of their decomposition recently has been reported.[1] Solutions of Caro's acid in concentrated sulfuric acid, on the other hand, are quite stable and may be stored for days at room temperature without change of peroxide titer. It has been found that the addition of a very small amount of nitric acid to such solutions produces a reaction in which oxygen is evolved and the Caro's acid is converted completely to sulfuric acid. The nitric acid is recovered unchanged. A study of the kinetics of this reaction

$$H_2SO_5 \xrightarrow[H_2SO_4]{HNO_3} H_2SO_4 + {}^1/_2O_2$$

and a mechanism which is compatible with the data are presented in the succeeding paragraphs.

Experimental

The reaction was followed by measuring the rate of gas evolution. The gas was collected in inverted graduated cylinders over water which had previously been saturated with oxygen. The reactions were run in a 125-ml. erlenmeyer flask containing a sidearm which was connected through a gas bubbler containing concentrated sulfuric acid to the inverted cylinders. The mouth of the flask was closed with a rubber stopper which held a buret that was calibrated in 0.05 ml. The flask was held in a constant temperature bath that was constant to ±0.05°. The reaction mixture was stirred with a magnetic stirrer, the motor of which was below the constant temperature bath. Two sets of stock solutions were made up, one for reactions in the more concentrated acid, and the other for the less concentrated acid region. The latter was J. T. Baker C.P. concentrated sulfuric acid, and the former was made by mixing 75 parts by volume of concentrated acid with 25 parts of 20% fuming sulfuric acid. Nitric acid stock solutions approximately 0.05 *M* were made by dissolving 98% nitric acid or potassium nitrate in each of the sulfuric acid stock solutions. The stock solutions were saturated with oxygen. In a typical run a volume of the sulfuric acid stock solution, such that after the addition of the peroxide and nitric acid stock solution flask and the stirrer started. The appropriate amount, usually 0.5 to 1 ml. of 90% hydrogen peroxide was then added and the flask was stoppered and allowed to stand in the constant temperature bath for 40 minutes to allow for temperature equilibration. The reaction was started by the addition of the nitric acid stock solution, 1 to 10 ml., from the buret. Readings of gas volumes were taken at 30-second or longer intervals, depending upon the rate. Immediately after each run two 10-ml. samples were pipetted from the reaction mixture and, after dilution with distilled water in 500-ml. volumetric flasks, titrated with standard base to give the normality of the reaction mixture. Before each run the glassware which was to come in contact with the sulfuric acid was washed with distilled water, rinsed with alcohol and dried at 130° for several hours. Every effort was made to minimize the exposure of the sulfuric acid solutions to atmospheric moisture. In those experiments in which water was required to obtain the desired acid strength, the appropriate amount of water was added prior to the peroxide.

Results and Discussion

One of the most interesting features of this reaction is the profound effect that water has on both the rate and the order of the reaction. In the region below 91% sulfuric acid the reaction is −1 order in peroxide, above 95.5% acid, the order in peroxide is +1, and in a very narrow region at about 93% acid the reaction is zero order in peroxide. In the regions of about 91–92.5% and 93.5–95.5% acid one observes no integral order. Over the entire range studied, from 85 to 98% acid the reaction is second order in nitric acid. The rate constants in the region below 91% acid will be called k_{-1} and those for the region above 95.5% acid will be designated as k_1. These constants were obtained graphically from the relationships

$$k_1 = \frac{2.303\Delta \log (1 - V_t/V_f)}{\Delta t\ (HNO_3)^2}$$

$$k_{-1} = \frac{\Delta(1 - V_t/V_f)^2 C_0^2}{2\Delta t (HNO_3)^2}$$

Concentration is in moles per liter, time is in seconds, C_0 is the initial concentration of peroxide, V_t is the volume of gas given off at time t and V_f is the total volume of gas given off. Typical curves from which the k's were calculated are shown in Fig. 1. Straight lines were generally obtained for at least 60% of the reaction. Values of k's from runs using different initial concentrations of peroxide and nitric acid are shown in Table I. As will be shown shortly, the values of the k's are extremely

(1) D. L. Ball and J. O. Edwards, THIS JOURNAL, 78, 1125 (1956).

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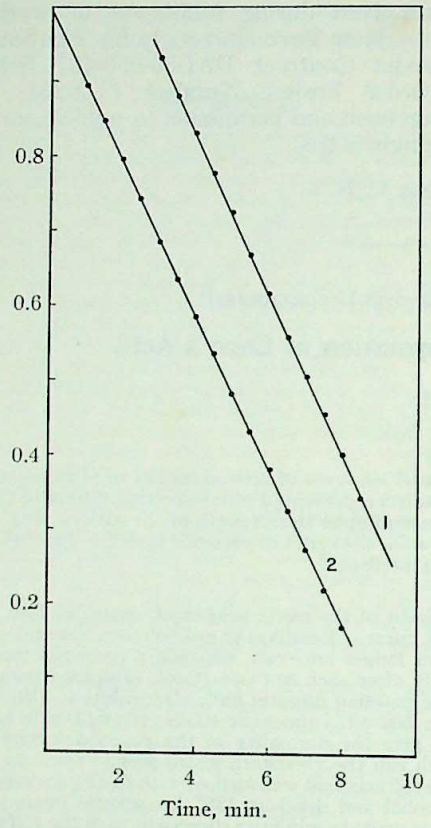

Fig. 1.—Curve 1, first-order reaction, log $(1 - V_t/V_f)$ *vs.* time, run no. 23; curve 2, -1 order reaction, $(1 - V_t/V_f)^2$ *vs.* time, run no. 11. Experimental conditions given in Table I. Curve 1 displaced along time axis.

sensitive to the amount of water present. For this reason, in order to obtain constant values for the k's, it is necessary to compare runs in which the acid strength is as constant as possible. Since duplicate runs are not always of the same acidity because of the hygroscopic nature of sulfuric acid, and since varying the initial concentration of peroxide at the same time varies the acidity, it was necessary to make a great number of runs in order to get enough comparable curves to yield the data shown in Table I.

The rate of the reaction is very sensitive to the strength of the sulfuric acid, it being at a maximum at 93 to 94% acid. In Fig. 2 are plotted k_1 and k_{-1} as a function of the acid strength. The addition of water increases k_1 and decreases k_{-1}. The effect of the addition of potassium or ammonium bisulfate is qualitatively the same as that of water.

Some miscellaneous experiments were performed which have a bearing on the reaction mechanism. Substitution of potassium nitrite for potassium nitrate as the catalyst, or substitution of potassium persulfate for hydrogen peroxide as the source of Caro's acid produces no change in the course of the reaction or its kinetics. To determine whether free radicals are intermediates in the reaction, a run was made in the presence of *m*-dinitrobenzene (nitrobenzene was nitrated under our reaction conditions, and thus could not be used). No change in the yield of oxygen or the kinetics was observed.

Table I

Rate Constants, k_1 and k_{-1}, for the Decomposition of Caro's Acid at Various Acid Strengths; T = 303.0°K.

No.	Acid, N	(N)[a]	(P)[b]	k_1
4	36.50	0.01	0.21	30.8
12	36.47	.01	.42	32.4
14	36.48	.005	.42	31.5
10	36.40	.01	.42	36.0
13	36.36	.01	.21	38.1
23	35.93	.005	.42	156.8
24	35.91	.005	.21	165.6
				k_{-1}
5	32.75	0.0015	0.420	17.9
11	32.76	.0030	.435	17.7
6	32.70	.0045	.437	16.5
8	32.90	.0030	.372	20.6
9	32.86	.0030	.704	19.3
16	32.90	.0030	1.070	20.7

[a] Initial concentration of nitric acid in moles/l. [b] Initial concentration of peroxide in moles/l.

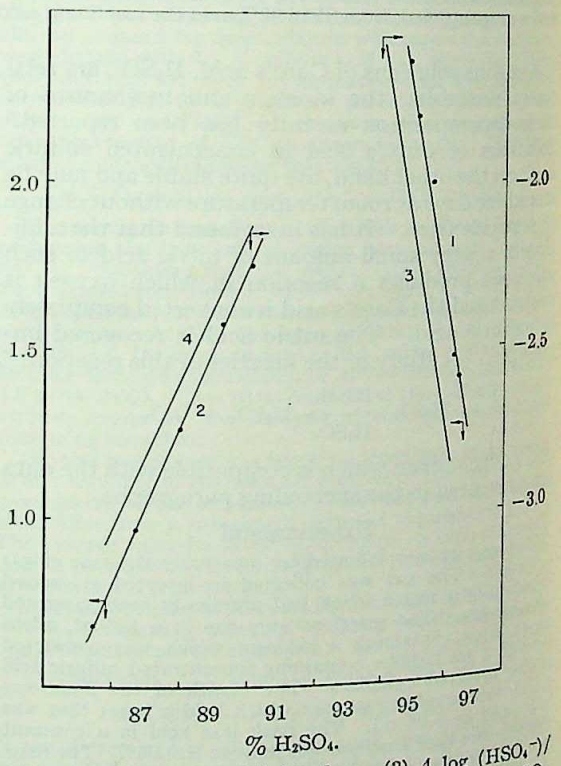

Fig. 2.—(1) log k_1; (2) log k_{-1}; (3) 4 log $(HSO_4^-)/(H_2SO_4)$; (4) $2 + 2\log (H_2SO_4)/(HSO_4^-)$; each *vs.* % H_2SO_4.

In another run the reaction mixture was irradiated with ultraviolet light from a mercury vapor lamp. Again no effect was observed, indicating that free radicals are probably not involved. To determine whether the reaction of hydrogen peroxide or potassium persulfate with the solvent to yield Caro's acid is kinetically important, several runs were made in which solutions of either of these were allowed to stand 18 hours before the addition of the nitric acid. The results were identical with those in which the nitric acid was added after 30 minutes.

The following reasonable mechanism is compatible with the experimental data. The following reversible equilibria are rapidly established

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$$H_2O_2 + 2H_2SO_4 \overset{K_1}{\rightleftharpoons} H_3O^+ + HSO_4^- + H_2SO_5$$

$$H_2SO_5 + HSO_4^- \overset{K_2}{\rightleftharpoons} HSO_5^- + H_2SO_4$$

$$HSO_5^- + NO_2^+ \overset{K_3}{\rightleftharpoons} HSO_5NO_2$$

$$HSO_5NO_5 + HSO_4^- \overset{K_4}{\rightleftharpoons} SO_5NO_2^- + H_2SO_4$$

$$H_2SO_4 + H_2SO_5 \overset{K_5}{\rightleftharpoons} H_2O + H_2S_2O_8$$

$$HNO_3 + 2H_2SO_4 \overset{K_6}{\rightleftharpoons} NO_2^+ + H_3O^+ + 2HSO_4^-$$

$$H_2O + H_2SO_4 \overset{K_7}{\rightleftharpoons} H_3O^+ + HSO_4^-$$

The first equilibrium represents the formation of Caro's acid from the reaction between hydrogen peroxide and sulfuric acid.[2] The fact that identical kinetics are observed when either hydrogen peroxide or potassium persulfate are used gives further support to this equilibrium. The product of the third equilibrium is the mixed anhydride of nitric and Caro's acids. Although this anhydride has never been reported its existence is not unreasonable. Peracids have a strong tendency to form mixed anhydrides with ordinary acids, *e.g.*, acetyl peroxide, benzoyl peroxide and peroxydisulfuric acid, $H_2S_2O_8$. The other equilibria require no comment.

The total amount of nitric acid present in all forms will be designated by N and the total amount of peroxide will be designated by P.

$$(N) = (HNO_3) + (NO_2^+) + (NO_2HSO_5) + (NO_2SO_5^-) \quad (1)$$

$$(P) = (H_2SO_5) + (HSO_5^-) + (NO_2HSO_5) + (NO_2SO_5^-) + (H_2S_2O_8) \quad (2)$$

Since the measurements were made under conditions such that $(P)/(N)$ is in the range of 25 to 500

$$(NO_2HSO_5) + (NO_2SO_5^-) << (H_2SO_5) + (HSO_5^-) + (H_2S_2O_8)$$

and eq. 2 can be replaced by

$$(P) = (H_2SO_5) + (HSO_5^-) + (H_2S_2O_8) \quad (3)$$

From the above equilibria and eq. 1 and 3 the following relationships can be derived

$$(NO_2^+) = \frac{K_6K_7Z(N)}{K_4K_7Z + K_7(H_3O^+)X^2Z + K_2K_3K_6X^2(H_3O^+)(P)(1 + K_4X)} \quad (4)$$

$$(NO_2SO_5^-) = \frac{K_2K_3K_4K_6X^3(H_3O^+)(N)(P)}{K_4K_7Z + K_7(H_3O^+)X^2Z + K_2K_3K_6X^2(H_3O^+)(P)(1 + K_4X)} \quad (5)$$

Where $X = (HSO_4^-)/(H_2SO_4)$ and $Z = K_2X(H_2O) + (H_3O) + K_5(H_2SO_4)$.

The reaction proceeds in two steps

$$NO_2 + NO_2SO_5^- \xrightarrow{\text{slow}} NO^+ + NO_2^+ + SO_4^{--} + O_2$$

$$NO^+ + HSO_5^- \xrightarrow{\text{fast}} NO_2^+ + HSO_4^-$$

The rate of the reaction is given by the equation

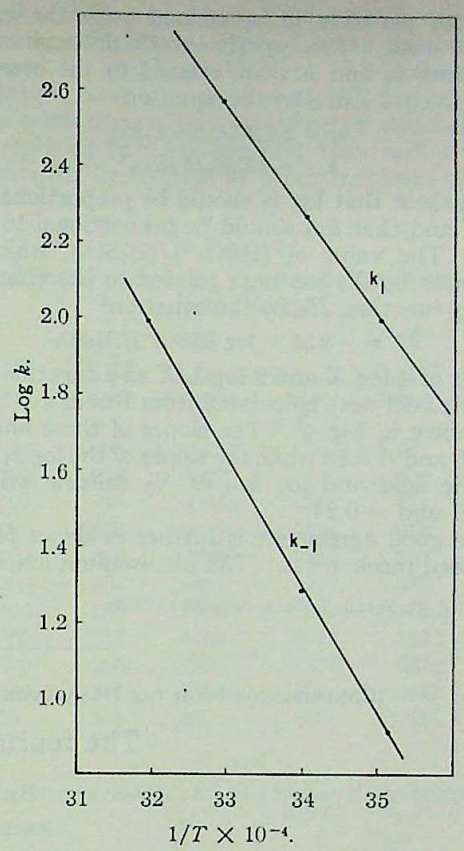

Fig. 3.—Temperature dependence of k_1 and k_{-1}. The acid concentrations were 95.8% acid for k_1 and 88.9% for k_{-1}.

$$r = k(NO_2^+)(NO_2SO_5^-) = \frac{kK_2K_3K_4K_6^2X^3Z(H_3O^+)PN^2}{[K_6K_7Z + K_7ZX^2(H_3O^+) + K_2K_3K_6(P)X^2(H_3O^+)(1+K_4X)]^2} \quad (6)$$

Since peroxy acids are weaker than the corresponding non-peroxidic acids, K_2 and K_4 must be smaller than one. We shall assume then that $K_4X << 1$ and that $K_5(H_2SO_4) >> (H_2O) + K_2X(H_2O)$. The first assumption means that $(NO_2SO_5^-) << (NO_2SO_5H)$ and the second assumption means that the peroxide is predominantly in the form of $H_2S_2O_8$ in the acid range we have used. Therefore $Z = K_5(H_2SO_4)$.

Since addition of water increases X and decreases Z at acid strength greater than 95% the first term in the denominator of eq. 6 is much larger than the second and third terms and the equation reduces to

$$r = kK_2K_3K_4X^3(H_3O^+)PN^2/K_5K_7^2(H_2SO_4)$$

Since (H_3O^+) is approximately equal to (HSO_4^-) this may be written as

$$r = kK_2K_3K_4PN^2X^4/K_5K_7^2 \quad (7)$$

At acid strength below 91% acid the last term in the denominator of eq. 6 becomes large compared to the first two terms and the equation reduces to

$$r = kK_4N^2Z/K_2K_3(P)X(H_3O^+) = kK_4K_5N^2/K_2K_3PX^2 \quad (8)$$

According to eq. 7 the reaction in strong acid is second order in nitric acid and first order in peroxide whereas in more dilute acid eq. 8 requires that the reaction be second order in nitric acid and −1

(2) N. V. Sidgwick, "The Chemical Elements and their Compounds," Oxford Press, New York, N. Y., 1950, p. 939.

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order in peroxide in agreement with the experimental data. The experimentally determined rate constants k_1 and k_{-1} are related to the constants given in eq. 7 and 8 by the equations

$$k_1 = kK_2K_3K_4X^4/K_6K_7^2 \quad (9)$$

$$k_{-1} = kK_4K_5/K_2K_3X^2 \quad (10)$$

which show that log k_1 should be proportional to 4 log X and that k_{-1} should be proportional to 2 log $1/X$. The value of $(HSO_4^-)/(H_2SO_4)$, which we designate by X, has been related to the Hammett acidity function, H_0, by the equation[3]

$$H_0 = -8.36 + \log (HSO_4^-)/(H_2SO_4)$$

Values of 4 log X and 2 log $1/X$ as a function of % sulfuric acid were calculated from Brand's data and are shown in Fig. 2. The slopes of these lines are -0.58 and $+0.23$ while the slopes of the log k_1 *vs.* % sulfuric acid and log k_{-1} *vs.* % sulfuric acid are -0.59 and $+0.24$.

The good agreement is further evidence for the proposed mechanism. The nitrosonium ion, NO^+, which is formed in the rate-determining step, is rapidly oxidized to NO_2^+ by a persulfate ion. Since potassium nitrite yields the nitrosonium ion in sulfuric acid, it is just as effective a catalyst as potassium nitrate or nitric acid.

The temperature dependence of k_1 and k_{-1} is shown in Fig. 3, the former being determined in 95.8% sulfuric acid and the latter in 88.9% acid. From the slopes of these lines the activation energy of k_1 is 13.3 kcal. per mole, and of k_{-1}, 15.3. Since K_3 and X have negative temperature coefficients and since these appear in the numerator in the equation for k_1 and in the denominator for k_{-1}, the temperature dependence and hence the activation energy of k_1 would be expected to be lower than that of k_{-1}.

The rate-determining step shown above is probably a sequence of steps which may be formulated as

$$NO_2^+ + SO_5NO_2^- \longrightarrow O_2N\text{–}O\text{–}O\text{–}SO_2\text{–}ONO_2$$

$$O_2N\text{–}O\text{–}O\text{–}SO_2\text{–}ONO_2 \longrightarrow NO_3^+ + SO_4^{--} + NO_2^+$$

$$NO_3^+ \longrightarrow NO^+ + O_2$$

ABERDEEN PROVING GROUND, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CLARKSON COLLEGE OF TECHNOLOGY]

The Ionization of Sulfuric Acid[1]

BY MILTON KERKER

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The method of Sherrill and Noyes, based on conductance and transference number, has been used to calculate the ionization of sulfuric acid at 18 and 50° from data in the literature and to extend the results at 25° to higher concentrations. The results have been compared with those obtained by other methods. The effect of the nature of the counterion on the equivalent conductance of sulfate and hydrogen ion has been examined. The equivalent conductance of bisulfate ion has been calculated at 18, 25 and 50°.

The ionization of sulfuric acid has been studied by electromotive force,[2] colorimetry,[3,4] kinetics,[5] Raman spectra[6–8] and a combination of conductance and transference number.[9] Sherrill and Noyes employed transference number as well as conductance data because of the unavailability of the equivalent conductance of the bisulfate ion. Assuming the first hydrogen is completely ionized, they developed the equations

$$\alpha = (\Lambda + \Lambda T - \Lambda_H)/(\Lambda_H + \Lambda_{SO_4}) \quad (1)$$

$$\Lambda_{HSO_4} = (\Lambda - \Lambda T - \alpha\Lambda_{SO_4})/(1 - \alpha) \quad (2)$$

where

α	fraction of HSO_4^- dissociated
Λ	equivalent conductance of H_2SO_4
Λ_H	equivalent conductance of H^+ in the H_2SO_4
Λ_{SO_4}	equivalent conductance of SO_4^- in the H_2SO_4
Λ_{HSO_4}	equivalent conductance of HSO_4^- in the H_2SO_4
T	stoichiometric transference number

In solving the above equation, Sherrill and Noyes used values of Λ_H and Λ_{SO_4} obtained from the conductance and transference number of hydrochloric acid and potassium sulfate at the ionic strength prevailing in the sulfuric acid solution under consideration. However, they did recognize that this "ionic strength principle" could not be justified theoretically. Since the ionic strength in the sulfuric acid is given by $m(1 + 2\alpha)$, eq. 1 had to be solved by a series of successive approximations.

The results of Sherrill and Noyes are confined to 25° because of the limited data for T available at that time.[10] In this paper we extend their calculations to 18 and 50° using data which have since appeared in the literature. We have also carried the 25° calculations to higher concentrations.

The stoichiometric transference number, T, which appears in the above equations is related to the individual ionic transference number,[11] t, by

$$T = t_H - t_{HSO_4} \quad (3)$$

where

$$t_H = c_H\Lambda_H/c\Lambda \quad (4)$$

$$t_{HSO_4} = c_{HSO_4}\Lambda_{HSO_4}/c\Lambda \quad (5)$$

and c_H, c_{HSO_4} and c are the normalities of H^+, HSO_4^- and H_2SO_4, respectively. In the Hittorf

(1) This work has been supported by the Atomic Energy Commission, Contract No. AT (30-1)-1801.

(2) (a) W. J. Hamer, THIS JOURNAL, **56**, 860 (1934); (b) C. W. Davies, H. W. Jones and C. B. Monk, *Trans. Faraday Soc.*, **48**, 921 (1952).

(3) I. M. Klotz, Thesis, University of Chicago, 1940.

(4) C. R. Singleterry, Thesis, University of Chicago, 1940.

(5) W. C Bray and H. A. Liebhafsky, THIS JOURNAL, **57**, 51 (1935).

(6) N. R. Rao, *Indian J. Phys.*, **14**, 143 (1940).

(7) H. M. Smith, Thesis, University of Chicago, 1949.

(8) L. F. Maranville, Thesis, University of Chicago, 1949.

(9) M. S. Sherrill and A. A. Noyes, THIS JOURNAL, **48**, 1861 (1926).

(10) O. F. Tower, *ibid.*, **26**, 1039 (1904).

(11) M. Spiro, *J. Chem. Educ.*, **33**, 464 (1956).

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method T is equal to the number of equivalents of sulfuric acid transferred from anode to cathode region per faraday of electricity passed when electrodes reversible to sulfate ion (*e.g.*, Ag, Ag_2SO_4; Hg, Hg_2SO_4) are used. With the galvanic cell method T is obtained from

$$T = dE_T/dE \qquad (6)$$

E is the electromotive force of the sulfuric acid concentration cell without transference in which the anode is reversible to hydrogen ion and the cathode to sulfate ion. E_T is the electromotive force of the sulfuric acid concentration cell with transference in which both electrodes are reversible to sulfate ion.

Hamer[12] has determined T for sulfuric acid over a wide range of concentration and temperature by the galvanic cell method. He found that T remained constant in the range from 0.05 to 0.2 m and then dropped rapidly with increasing concentration, falling to about 0.5 in concentrated sulfuric acid. Using the Onsager equation, he calculated the variation of t_H with concentration in the infinitely dilute range where the sulfuric acid is completely ionized. Since in this range T would be expected to increase with concentration he suggested that the constancy of T in his dilute solutions was actually a manifestation of a flat maximum and that at concentrations lower than 0.05 m, T would decrease. Hamer's work is discussed by Harned and Owen.[13] Kanning and Waltz[14] extended the work of Hamer to solutions of sulfuric acid in anhydrous methanol at 25°. Ferguson and France[15] had made an earlier study of the same cell as Hamer at 25° for one pair of concentrations.

We have used Hamer's extensive values of T to calculate the dissociation of sulfuric acid at 18 and 50° by the method of Sherrill and Noyes and to extend their results at 25° to higher concentrations. The equivalent conductance of HSO_4^- also has been calculated.

Values of Λ_H were obtained from the equivalent conductance[16,17] and transference number[18,19] of HCl. For Λ_{SO_4} we used the equivalent conductance[20,21] and transference number[22,23] of K_2SO_4. For the equivalent conductance of H_2SO_4 we used the data of Noyes,[20] Kohlrausch,[21] Campbell,[24] and Roughton.[25]

Our results are presented in Tables I, II and III. The equilibrium quotient K_2' for the second ionization of sulfuric acid extrapolates to the ionization constant K_2, at infinite dilution. The values of the ionization constant at 18 and 50°, as calculated from conductance and transference number data, are reported here for the first time and are compared with the results of other methods in Table IV.

TABLE I

IONIZATION OF H_2SO_4 AND EQUIVALENT CONDUCTANCE OF HSO_4^- AT 18°

Molality of H_2SO_4	Fraction HSO_4^- ionized	Ionic strength	Equilibrium quotient	Quotient of activity coefficients	Equiv. conductance of HSO_4^-
0			0.0124	1	43.6
0.0005	0.936	0.00144	.0141	0.851	
.0010	.888	.00275	.0150	.800	
.0025	.790	.00645	.0168	.714	
.0050	.696	.01196	.0194	.619	40.1
.0100	.600	.0220	.0240	.500	38.7
.0250	.461	.0481	.0312	.385	35.4
.0500	.333	.0835	.0333	.360	32.6
.1000	.317	.1634	.0614	.195	
.2500	.298	.399	.1377	.0871	
.5000	.295	.795	.271	.0443	
1.133	.405	2.05	1.083	.0111	

TABLE II

IONIZATION OF H_2SO_4 AND EQUIVALENT CONDUCTANCE OF HSO_4^- AT 25°

Molality of H_2SO_4	Fraction HSO_4^- ionized	Ionic strength	Equilibrium quotient	Quotient of activity coefficients	Equiv. conductance of HSO_4^-
0			0.0102	1	51.2
0.00025	0.959	0.0007295	.0118	0.864	
.0010	.874	.002648	.0130	.785	
.0050	.667	.01167	.0169	.604	46.8
.0125	.523	.02558	.0209	.488	45.3
.0250	.417	.04568	.0253	.403	39.8
.0500	.336	.08357	.0338	.302	38.7
.1000	.266	.1532	.0459	.222	
.250	.267	.3841	.1185	.0861	
.526	.311	.853	.311	.0328	
.933	.362	1.608	.722	.0141	
1.15	.436	2.16	1.28	.00797	
1.80	.73	4.43	8.31	.00123	

TABLE III

IONIZATION OF H_2SO_4 AND EQUIVALENT CONDUCTANCE OF HSO_4^- AT 50°

Molality of H_2SO_4	Fraction HSO_4^- ionized	Ionic strength	Equilibrium quotient	Quotient of activity coefficients	Equiv. conductance of HSO_4^-
0			0.0053	1	73.3
0.00100	0.764	0.00253	.0057	0.93	
.00500	.493	.00993	.0073	.73	66.5
.00625	.456	.01195	.0076	.70	65.4
.02506	.259	.0376	.0110	.48	59.4
.04016	.214	.0573	.0133	.40	57.5
.05025	.200	.0704	.0151	.35	55.8

Harned and Owen[26] have pointed out the necessity for re-examining the methods of computing ionization constants from electromotive forces for acids as strong as HSO_4^-. They give no weight to

(12) W. J. Hamer, THIS JOURNAL, **57**, 662 (1935).
(13) H. S. Harned and B. B. Owen "Physical Chemistry of Electrolytic Solutions," 2nd Ed., Reinhold Publ. Corp., New York, N. Y., 1950, pp. 442–443.
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(15) A. L. Ferguson and W. G. France, *ibid.*, **43** 2150 (1921).
(16) T. Shedlovsky, *ibid.*, **54**, 1411 (1932).
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(19) L. G. Longsworth, *ibid*, **54**, 2741 (1932).
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(21) F. Kohlrausch and L. Holborn, "Das Leitvermögen der Elektrolyte," B. G. Teubner, Leipzig and Berlin, 1916.
(22) L. G. Longsworth, THIS JOURNAL, **57**, 1185 (1935); **60**, 3070 (1938).
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(24) A. N. Campbell, E. M. Kartzmark, D. Bisset and M. E. Bednis, *Can. J. Chem.*, **31**, 303 (1953).
(25) J. E. Renghton, *J. Appl. Chem.* (*London*), **1**, Suppl. Issue No. 2, S.141 (1951).
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TABLE IV

DISSOCIATION CONSTANT OF HSO_4^- × 10^2

Temp., °C.	From conductance and transference no.	From electromotive force Hamer Hamer[25]	Hamer recalcd. by Davies[25]	Davies[25]	From spectrophotometry, Klotz[3] and Singleterry[4]
18	1.24	1.30	1.14	1.26	1.26
25	1.02	1.20	1.02	1.03	1.02
50	0.53	0.79	0.69	0.50	0.48

Hamer's electromotive force results, citing instead those of Klotz[3] and Singleterry[4] obtained by a colorimetric method. The temperature dependence of their ionization constants leads to heats of ionization which are in accord with the accepted values, while those of Hamer are in gross disagreement. Klotz and Singleterry report that the error in their results is probably less than 2%. Davies, Jones and Monk[2] have recalculated Hamer's data, introducing correct values of activity coefficients and bringing them into slightly better agreement with the colorimetric work. They have, furthermore, carried out electromotive force measurements in a cell which minimizes the ion association, obtaining results in good agreement with Klotz and Singleterry. The ionization constants calculated from the data of Sherrill and Noyes at 25° and by us at 18 and 50° are also in agreement with the colorimetric work.

Although Sherrill and Noyes recognized that ionic conductivities are not determined by ionic strength, they formally used an ionic strength principle in estimating the equivalent conductance of the sulfate and hydrogen ions in sulfuric acid, and we have followed their heuristic procedure.

We have used the data for potassium sulfate in estimating the equivalent conductance of sulfate ion because they are available over a wide range of conditions. In Tables V and VI there is compiled the equivalent conductance of sulfate ion at several ionic strengths at 18 and 25° as obtained from a number of other salts. For the bi-bivalent salts, where ion association is appreciable, the equivalent conductance of the sulfate ion is calculated from the product of the anion transference number and the equivalent conductance of the salt, divided by the degree of dissociation. The correction for ion association is not so easily made for the uni-bivalent salts but even a rough approximation indicates it is small enough to be neglected. The equivalent conductance of sulfate at 0.1 ionic strength obtained from sodium and potassium sulfate differs from that obtained from thallium sulfate in the direction that would be expected from the greater ion association in the latter.

TABLE V

EQUIVALENT CONDUCTANCE OF SULFATE AT 18° FROM CONDUCTANCE AND TRANSFERENCE NUMBER OF VARIOUS SALTS[27-30]

Ionic strength	Na_2SO_4	K_2SO_4	$CdSO_4$	$CuSO_4$	$MgSO_4$
0.002	63.0	63.4	64.7	66.0	63.5
.010	59.0	59.6	60.0	60.5	58.2
.050	53.8	54.2	54.1	..	..
.100	50.4	51.3	51.8	..	..

TABLE VI

EQUIVALENT CONDUCTANCE OF SULFATE AT 25° FROM CONDUCTANCE AND TRANSFERENCE NUMBER OF VARIOUS SALTS[20-23,27-30]

Ionic strength	Na_2SO_4	K_2SO_4	Tl_2SO_4	$ZnSO_4$	$CdSO_4$
0.002	76.1	76.0	76.0	76.1	76.0
.010	71.2	71.3	70.0	71.1	70.4
.050	63.4	63.4	59.7	..	63.8
.100	58.9	59.0	53.4	..	61.2

Although the equivalent conductance of the sulfate ion does depend to some extent upon the nature of the cation, the agreement among the results is quite good, especially in view of the uncertainties involved in the ion association of the solutions. Even at 0.1 ionic strength, the fraction ionized would differ by only 1.5% if the equivalent conductance of 53.4 derived from the thallium sulfate data had been used instead of 59.0 derived from the potassium sulfate data.

The fraction ionized α is not very sensitive to the equivalent conductance of sulfate ion since in eq. 1 it is added to the much larger equivalent conductance of the hydrogen ion. This simply transfers the onus of the method to the determination of the equivalent conductance of the hydrogen ion. In Table VII we have compared the values of Λ_H obtained from several monobasic acids at comparable ionic strengths. It is apparent that the anion effect is small. We should like to call attention to the agreement between the hydrochloric and iodic acid results where the available conductance and transference number data are quite accurate. What is especially striking about the agreement is that iodic acid is only partially dissociated so that the equilibrium data have also entered into the calculation much as in the case for the bi-bivalent salts treated above.

TABLE VII

EQUIVALENT CONDUCTANCE OF HYDROGEN ION AT 25° FROM CONDUCTANCE AND TRANSFERENCE NUMBER OF VARIOUS ACIDS

Ionic strength	HCl[16-19]	HNO_3[21,27]	HI[27]	HIO_3[27,31]
0.01	339.9	340	..	339.3
.05	330.9	330	331	330.0
.10	325.5	325	326	...
.20	320.4	..	316	...

The quotient of activity coefficients γ_R is defined by

$$\gamma_R = (\gamma_H)(\gamma_{SO_4^-})/\gamma_{HSO_4^-} \quad (7)$$

and

$$K_2 = K_2'\gamma_R \quad (8)$$

where K_2 and K_2' are the ionization constant and equilibrium quotient, respectively, and γ_{H^+}, $\gamma_{SO_4^-}$ and $\gamma_{HSO_4^-}$ are ionic activity coefficients. Young and Blatz[32] have compared the values of γ_R at 25° obtained in dilute solutions by the conductance and transference number method of Sherrill and Noyes

(27) "International Critical Tables," McGraw-Hill Book Co., Inc., New York, N. Y., 1929.

(28) B. B. Owen and R. W. Gurney, THIS JOURNAL, **60**, 3074 (1938).

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and the kinetic method of Bray and Liebhafsky with those obtained in more concentrated solutions by Rao[6] using Raman spectra. Later, Smith[7] and Maranville[8] obtained more accurate Raman spectral data. Since we have extended the values of γ_R at 25° to the concentration range used in the kinetic and Raman spectral studies, it is of interest to compare results again, especially in the overlapping region. Figure 1 is a curve of γ_R at 25° *versus* the square root of the ionic strength. The agreement among the three methods is excellent up to an ionic strength somewhat greater than 1. This agreement is remarkable, especially at the higher ionic strengths. Our only justification for extending the 25° calculations to these high concentrations has been this unexpected agreement among the three methods.

A comment on the work of Bray and Liebhafsky is in order. There was considerable scatter in their results. In plotting a function of γ_R against the square root of the ionic strength, they drew a smooth curve which they presumed was an extrapolation of Sherrill and Noyes conductance and transference number results but which obviously was not the best representation of their own data. Previous workers[7,8,32] have used these smoothed data but we find, despite the scatter, that the actual data of Bray and Liebhafsky give better agreement with both our calculations and the Raman spectral results. In Fig. 1, points representing both their actual and smoothed results are shown.

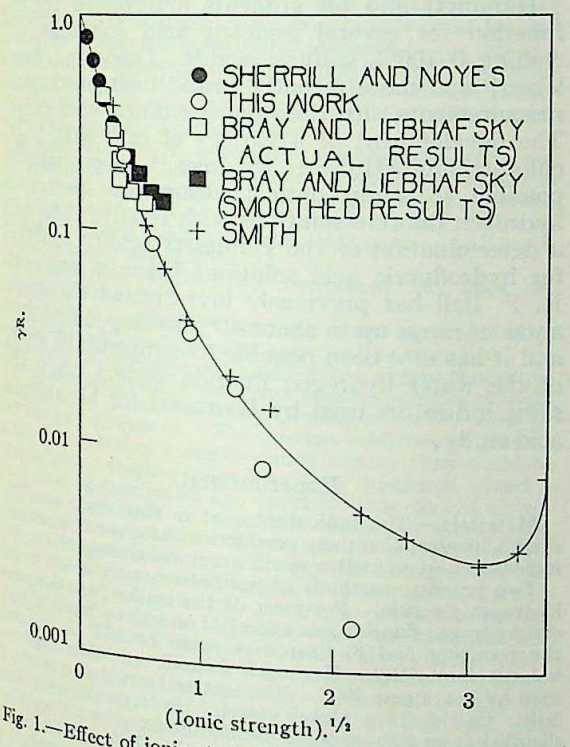

Fig. 1.—Effect of ionic strength on the quotient of activity coefficients, γ_R, of HSO_4^- at 25°.

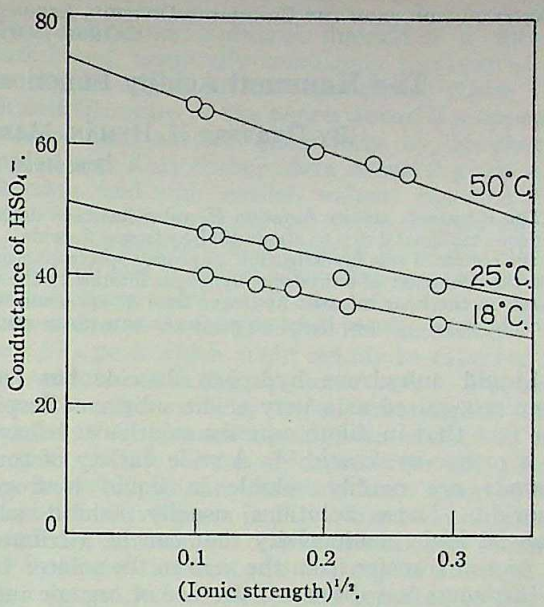

Fig. 2.—Equivalent conductance of HSO_4^-. Circles are computed from conductance and transference number data. Lines are drawn with slope from limiting Onsager law.

The conductance data at 50° do not extend to sufficiently high concentrations to compare γ_R with those from Raman spectra at that temperature.

In Tables I, II and III is also found the equivalent conductance of the bisulfate ion as calculated by eq. 2. In Fig. 2, the equivalent conductance of bisulfate ion is extrapolated to infinite dilution using the limiting Onsager slope for a uni-univalent electrolyte. Since the slope itself is dependent on the intercept, it had to be determined by a series of successive approximations.

POTSDAM, N. Y.

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[CONTRIBUTION FROM THE CHEMISTRY DIVISION, ARGONNE NATIONAL LABORATORY, AND THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

The Hammett Acidity Function H_0 for Hydrofluoric Acid Solutions[1]

BY HERBERT H. HYMAN, MARTIN KILPATRICK AND JOSEPH J. KATZ

RECEIVED FEBRUARY 28, 1957

The Hammett acidity function H_0 value has been determined for hydrogen fluoride in the concentration range from anhydrous material down to about 40% hydrogen fluoride. The dryest hydrogen fluoride prepared had an H_0 value of −10.2. In the course of this investigation, improved spectrophotometric cells were developed for handling hydrofluoric acid solutions and the spectrum of anhydrous hydrogen fluoride in the near infrared was determined. The effect of sodium fluoride and water on the near infrared hydrogen fluoride spectrum was investigated and an analytical method for water in hydrogen fluoride was developed based on measurements of the water absorption at 1.95 μ.

Liquid anhydrous hydrogen fluoride has long been recognized as a very acidic substance despite the fact that in dilute aqueous solution it behaves as a rather weak acid.[2,3] A wide variety of compounds are readily soluble in liquid hydrogen fluoride. These solutions usually exhibit substantial ionic conductivity that can be attributed to proton transfer from the acid to the solute.

Hammett has discussed the use of organic indicators for the determination of relative acidity and suggested an acidity scale based on the relative concentration of protonated and non-protonated species in the medium under investigation.[4]

Paul and Long[5] recently have reviewed the determination and use of the H_0 function. In particular, the acidity of any solution on the H_0 scale is determined by the fraction of the neutral indicator which is converted from an uncharged molecule to a protonated species. Hammett also discussed the H_- and H_+ scales in which the original indicator was an anion or cation rather than a neutral molecule.

For practical use of the H_0 acidity functions, it is defined by the equation

$$H_0 = pK_a^I + \log (C_I/C_{IH^+})$$

$$pK_a^I = -\log \frac{C_{H^+} C_I}{C_{IH^+}} - \log \frac{f_{H^+} f_I}{f_{IH^+}}$$

for the indicator, I, is determined by a series of intercomparisons with indicators of decreasing pK_a^I. The activity coefficient term for a constant charge type is supposed to be independent of the medium or indicator, and H_0 approaches pH in dilute aqueous solution.

Paul and Long have reviewed previous intercomparisons and extrapolations and suggest a best value for each indicator which has been studied. As they point out, these values are not entirely self-consistent within the expected limit of error. Different indicators will give different values for the same solution. Other workers[6] have questioned the general applicability of the H_0 concept, or sought more satisfying acidity functions.[7] In spite of this, the H_0 function is very useful in correlating and predicting for different media properties such as solubility or catalytic effects which depend on acidity. In the highly acid, high dielectric solvents, such as those considered here, it is probably fair to assume that a medium which shows a more negative H_0 value for a specific indicator is the more acidic medium.

Hammett and his students determined the H_0 function for several aqueous acid solutions, including 0–100% sulfuric acid.[8,9] Lewis and Bigeleisen[10] and more recently Brand[11] extended these measurements into the fuming sulfuric acid range. The development of a variety of cells with polychlorotrifluoroethylene windows,[12] now make it possible to study optical absorption spectra in hydrogen fluoride solutions with relative ease, and a determination of the Hammett acidity function for hydrofluoric acid solutions becomes practical. R. P. Bell has previously investigated the dilute aqueous range up to about 40% hydrogen fluoride[13] and it has now been possible to complete the study of the water–hydrogen fluoride system using the same indicators used by Hammett for his sulfuric acid study.

Experimental

Materials.—The indicators used in this work were Aldrich Chemical Company products sold for use as Hammett indicators and no further purification was attempted.

Two separate methods of purification were used for the hydrogen fluoride. For most of the earlier runs commercial hydrogen fluoride was absorbed on sodium fluoride, and the resulting $NaHF_2$ heated *in vacuo* at 150° to remove volatile impurities. Hydrogen fluoride was then regenerated by heating at 300°. The material was stored over cobaltic fluoride in a nickel vessel. Hydrogen fluoride was distilled from this vessel as needed directly into a conductivity cell or an optical absorption cell. Hydrogen fluoride purified in this way showed conductivities in the range 4 to 6×10^{-4} ohm^{-1} cm.$^{-1}$ at 0° indicating a water content of 0.01% or less. More recently a better quality acid has been obtained. As suggested by Runner, Balog and Kilpatrick, the hydrogen fluoride was purified by fractional distillation in an efficient column.[14] The product was collected and handled entirely in polychlorotrifluoroethylene and gold lined fittings thus avoiding contact with base metal (nickel). Under these conditions, batches of acid have been obtained with conductivities below 10^{-5} ohm^{-1} cm.$^{-1}$. Measurably higher acidities (more negative H_0 values) were found for

(1) Based on work performed under the auspices of the U. S. Atomic Energy Commission.

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(3) L. Pauling, *J. Chem. Ed.*, **33**, 16 (1956).

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(10) G. N. Lewis and J. Bigeleisen, *ibid.*, **65**, 1144–50 (1943).

(11) J. C. D. Brand, *J. Chem. Soc.*, 997 (1950).

(12) J. J. Katz and H. H. Hyman, *Rev. Sci. Instr.*, **24**, 1066 (1953).

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(14) M. E. Runner, G. Balog and M. Kilpatrick, THIS JOURNAL, **78**, 5183 (1956).

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hydrogen fluoride purified by distillation than for the earlier material.

Sodium fluoride was reagent grade material and was dried before use.

Optical Equipment.—The optical cells employed polychlorotrifluoroethylene bodies and windows. The cells were made vacuum and pressure tight with external metal fittings but no metal was in contact with the solution. At the beginning of the work the cells were fitted with small metal valves of the bellows type; however, a polythene tubing and pinch clamp arrangement was found more convenient and made it possible completely to eliminate base metal from contact with the solution.

The absorption cells are connected to a vacuum line through the polythene tubing. After evacuating and filling the cell, the tubing is pinched shut, and the cell removed from the line.

For highly absorbing solutions, variable spacer cells of the type described by Quarterman, Hyman and Katz[15] were employed. These could be closed down to useful thicknesses of 50 μ with sapphire windows and 10 μ with selected polychlorotrifluoroethylene windows. These cells have nickel bodies, some of which have been gold plated, and because of the difference of expansion between the window and body cannot be subjected to severe temperature changes without leaking. This problem introduces minor changes in filling procedure. For example, hydrogen fluoride must be condensed in a separate vessel and transferred to the cell as a liquid, rather than condensed directly in the cell. However, if severe temperature changes are avoided these cells may be evacuated, filled and emptied, and the optical path changed repeatedly without incident.

A Beckman DK-1 automatic spectrophotometer was equipped with a secondary container to prevent damage in case of leaky cells. With the exception of this precaution, the instrument was used in a conventional way. The instrument was in a constant temperature room and all measurements were made at 25 ± 2°.

The electrical conductivity equipment has been described elsewhere.[15]

Solution Preparation.—Solutions were prepared in a variety of ways, usually using vacuum line technique. In most cases the indicator was made up to a known concentration in benzene and a measured volume pipetted directly into the cell. The solution was frozen, cooled to below 0° and the cell evacuated. The benzene sublimed off leaving a known amount of indicator much smaller than could be conveniently weighed directly. The hydrogen fluoride could then be distilled in, and water or other diluent added. Additions were made to a partially filled cell without significant loss or exposure of the contents to the atmosphere. This was accomplished by pinching the tubing shut, and making the addition to the length of tubing above the closure. After capping the cell, the pinch clamp was opened and the solution mixed. In other cases, the indicator was dissolved in dilute hydrofluoric acid whose concentration was determined by titration with standard base. The indicator concentration in this stock solution was usually determined optically. A known weight of this acid was added to the cell and anhydrous hydrogen fluoride distilled in to yield the desired concentration.

Hydrofluoric acid concentrations were determined by titration below 50% and by direct weighing in the cell in the 50 to 98% region. Above 98% the most convenient determination of water content was found to be that based on optical absorbancy at 1.95 μ described below.

The solutions of indicator as prepared were all stable for at least 24 hours. In preliminary experiments where optical cells with nickel bodies were employed, the nitro aromatic indicators were decolorized slowly on standing, presumably by reduction of the nitro group. Indicators in the acid form usually could be destroyed by heating the solution, yielding in most cases deeply colored compounds, that did not behave as indicators at least in similar acidity ranges. The composition or nature of these colored materials was not investigated further. Solutions of the basic form of the aniline type indicators used appear to be stable indefinitely when stored in all plastic containers.

The Spectrum of Anhydrous Hydrogen Fluoride.

—Anhydrous hydrogen fluoride is a water-white liquid, essentially completely transparent in the visible region of the spectrum. While the infrared spectrum in the region above 2 μ appears to have been studied adequately by Maybury, Gordon and Katz,[16] their data below 2 μ are not adequate and the earlier values reported by Safari[17] for this region appear to be entirely incorrect. A portion of Safari's curve is drawn with a dotted line and it is not clear that any significant measurements were made by him below 2 μ. There seems to be no doubt about the existence of the 1.45 μ peak which might readily be expected as the overtone of the 2.9 μ polymer peak. The 0.98 μ overtone is shown by Safari, but slightly displaced and with much too high an extinction coefficient. While we cannot account for the difference between our spectrum and that reported by Safari, the curve given in Fig. 1 has been obtained repeatedly on a number of different samples of purified hydrogen fluoride. In the region above 2 μ, Fig. 1 agrees perfectly with data reported by Maybury, Gordon and Katz for different samples, with different cells using silver fluoride rather than polychlorotrifluoroethylene windows, using a Perkin–Elmer spectrophotometer rather than a Beckman DK.

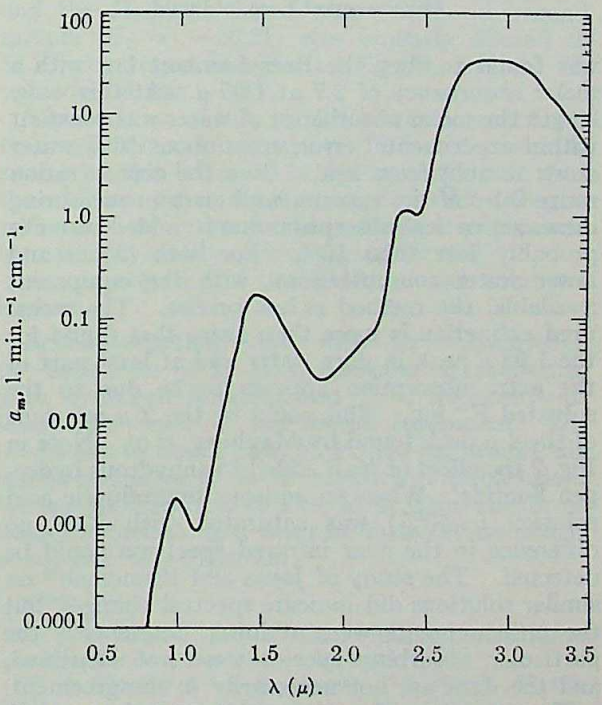

Fig. 1.—Near infrared absorption spectrum of anhydrous liquid hydrogen fluoride.

The Effect of Water and Sodium Fluoride on the Hydrogen Fluoride Spectrum.

—These observations are summarized in Fig. 2. Since water has a significant absorption peak near 1.9 μ where hydrogen fluoride is relatively transparent, it appeared reasonable to develop an analytical method for water content based on this difference in behavior. This proved to be possible, since water as a solute

(15) L. A. Quarterman, H. H. Hyman and J. J. Katz, to be published.

(16) R. H. Maybury, S. Gordon and J. J. Katz, *J. Chem. Phys.*, **23**, 1277 (1955).

(17) E. Safari, *Ann. Physik*, **9**, 203 (1954).

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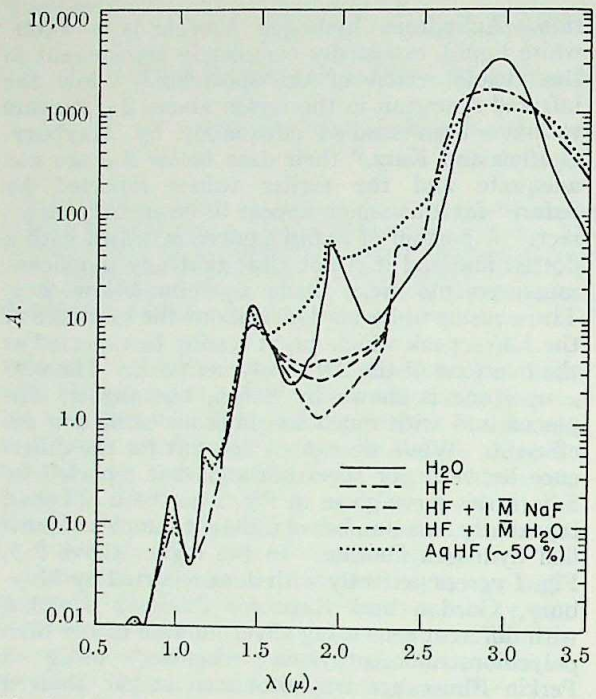

Fig. 2.—Near infrared spectrum of some fluoride solutions. Absorbancy of 1 cm. of liquid.

was found to obey the Beer–Lambert law with a molar absorbancy of 2.7 at 1.95 μ. At this wave length the molar absorbancy of water was constant within experimental error, from about 50% water down to anhydrous acid. Over the concentration range 0.1–2M the experimental error in measuring increased optical absorption due to added water is probably less than 10%. For both higher and lower water concentrations, with the equipment available, the method is less precise. The measured extinction is more than twice that found for the 1.92 μ peak in pure water and at least part of the extra absorption appears to be due to the solvated F^- ion. This could be the 2 μ overtone of the 4 μ peak found by Maybury, *et al.* Note in Fig. 2 the effect of NaF added to anhydrous hydrogen fluoride. When an aqueous hydrofluoric acid solution (~50%) was saturated with NaF, no difference in the near infrared spectrum could be detected. The study of Jones and Penneman[18] on similar solutions did indicate spectral changes, but the measurements were at lower frequencies, the particular absorbing species were not identified, and the data are not necessarily in disagreement.

The Acidity Function.—All solutions were scanned in the visible region and the percentage of acid or basic form calculated in the usual way from the optical density near the peak of the colored species.

The measured H_0 values are summarized in Tables IA and B. In Fig. 3 these values are combined with those of Bell to give the H_0 values for 0–100% hydrofluoric acid and compared with the sulfuric acid values. All of the hydrogen fluoride points plotted were selected from indicator measurements in the 10% acid to 10% basic range (± 1 H_0 unit).

TABLE IA

THE H_0 FUNCTION FOR HYDROFLUORIC ACID SOLUTIONS

Concn. wt. %	HF in H_2O mole %	H_0	Concn. wt. %	HF in H_2O mole %	H_0
39.6	37.2	−2.07[a]	83.5	82.0	−7.65[d]
42.6	40.1	−2.53[a]	87.8	86.6	−7.94[d]
45.4	43.8	−2.94[a]	90.2	89.2	−8.17[d]
48.7	46.1	−3.55[a]	92.3	91.5	−8.27[d]
55.3	52.7	−5.04[b]	93.9	93.3	−8.39[d]
61.4	58.8	−6.30[c]	97.0	96.7	−8.54[d]
71.0	68.8	−6.79[c]	100	100	−10.0[d]
80.9	79.2	−7.52[d]			

[a] Indicator used: p-nitrodiphenylamine, $pK = -2.50$. [b] Indicator used: 2,6-dinitro-4-methylaniline, $pK = -4.44$. [c] Indicator used: 6-bromo-2,4-dinitroaniline, $pK = -6.71$. [d] Indicator used: anthraquinone, $pK = -8.27$.

TABLE IB

THE H_0 FUNCTION FOR HYDROFLUORIC ACID SOLUTIONS

Concn. H_2O in HF, mole/l.[a]	Concn. wt. %	HF in H_2O mole %	H_0[b]
<0.001			−10.2
< .01	100.0	100.0	−9.96
.12	99.78	99.76	−9.59
.38	99.29	99.22	−9.47
.50	99.07	98.97	−9.31
.63	98.83	98.70	−9.34
.83	98.48	98.31	−9.12
.87	98.40	98.23	−9.09
.89	98.38	98.20	−9.11
1.03	98.13	97.93	−8.86

[a] Concentration determined by optical absorption at 1.95 μ. [b] The indicator used in this set of measurements was 2,4,6-trinitroaniline, $pK = -9.41$.

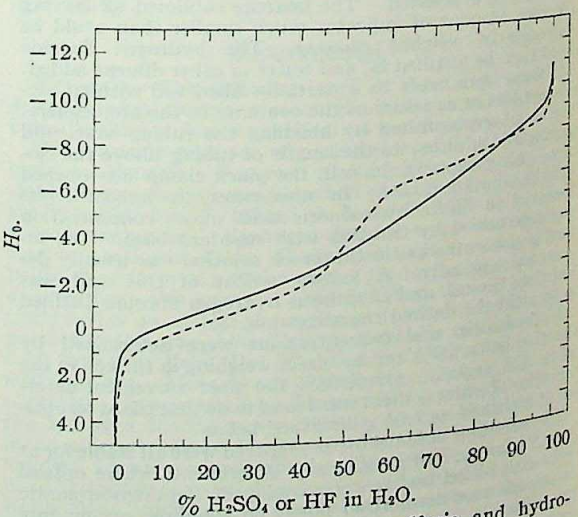

Fig. 3.—The H_0 function for aqueous sulfuric and hydrofluoric acids: ———, H_2SO_4; - - - - - - - -, HF.

On the whole hydrogen fluoride is a weaker acid than sulfuric. The dryest hydrogen fluoride obtainable by us had an H_0 value of −10.2 while 100% sulfuric acid has an H_0 value of −11.0. Due to the lower molecular weight of hydrogen fluoride, however, a 60–80% hydrogen fluoride solution in water is more acid than a similar weight

(18) L. H. Jones and R. A. Penneman, *J. Chem. Phys.*, **22**, 781 (1954).

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% H_2SO_4 solution, although on an equivalent concentration basis, sulfuric acid is always stronger.

Neither gram nor moles of hydrogen fluoride per unit volume are satisfactory units for plotting hydrogen fluoride concentration in aqueous solutions. The density increases rapidly as water is added to hydrogen fluoride to a maximum near 75% hydrogen fluoride.[19] This is reflected in a maximum in the molar hydrogen fluoride concentration well below 100%.

A plot of acidity *vs.* weight or mole % hydrogen fluoride rises steadily and shows no such maximum. However it is not a smooth continuous curve from pure water to pure HF. In fact there appear to be several separate regions in this plot. In dilute aqueous solutions, the actual acidic species present is H_3O^+, according to the equation

$$HF + H_2O \rightleftarrows H_3O^+ + F^-$$

Even for infinitely strong acids, the acidity of a solution in which the concentration of H_2O molecules exceeds that of the acid molecule cannot exceed a value fixed by the inherent acidity of H_3O^+. In this region, hydrofluoric acid solutions are significantly less acid than equal concentrations of any of the group of strong acids studied by Hammett but the acidity rises more rapidly with concentration. Of these strong acids, only sulfuric acid has been studied by anyone in the range where there are fewer water molecules than acid molecules. In hydrogen fluoride, as the 1-1 point is approached the acidity rises sharply, then increases steadily until a region close to 100% acid, where it again rises sharply.

Bell[13] has discussed the rise in acid strength below 50 mole % in terms of increasing concentration of HF_2^-, $H_2F_3^-$, and even longer chains as the HF concentration is increased. Several authors have commented on the occurrence of such polymeric ions.[18,20] Presumably as the 1-1 point is passed, the much more acidic species HF_2^+ appears, and acidity then increases regularly with concentration. At the high hydrogen fluoride end of the scale a further sharp rise in acidity is encountered which may also be correlated with the occurrence of polymer chains stabilized by ionization. In this case, however, the increase in chain length serves to decrease the acidity.

As water is added to hydrogen fluoride, the acidity of the solution is reduced by substituting H_3O^+ for H_2F^+. The equilibria involved may be represented as

$$H_2O + nHF \rightleftarrows H_3O^+ + F^-(HF)_{(n-1)}$$

$$HF + nHF \rightleftarrows H_2F^+ + F^-(HF)_{(n-1)}$$

The relative effect of H_2O is enhanced beyond its molar concentration as n is increased. The observed anomalous density behavior of hydrofluoric acid solutions mentioned above may well be correlated with this hypothesis. We hope to discuss the subject more fully elsewhere.

The effect of water on acidity is probably not specific since sodium fluoride is a slightly stronger base as is shown in Table II.

TABLE II

H_0 VALUE FOR HF–NaF SOLUTION

Solution	H_0
100% HF	−10.13
0.447% NaF = 0.103 $\bar{M}$	−9.62
4.32% NaF = 1.0 $\bar{M}$	−8.4

Qualitatively other reagents such as ethyl alcohol similarly yield the basic form of trinitroaniline when added in small amounts to a solution of this indicator in anhydrous hydrogen fluoride.

The addition of liquid SO_2 has little effect. Anhydrous hydrogen fluoride ($H_0 = -10.25$) was diluted to 82.3% hydrogen fluoride, 17.7% SO_2 and the H_0 value found was −9.98. A second sample ($H_0 = -10.21$) was similarly diluted to 81.7% hydrogen fluoride, 18.3% SO_2 and the H_0 value found was −9.93.

The addition of SO_3 to 100% sulfuric acid leads to a regular increase in acidity. There is no simple analog of this behavior in hydrogen fluoride, but the addition of fluoride ion acceptors such as boron trifluoride or antimony pentafluoride might well increase the acidity of hydrogen fluoride.[21–23]

An investigation of the acidity of such solutions is planned.

Acknowledgment.—We wish to acknowledge the assistance of L. A. Quaterman in preparing pure hydrogen fluoride, and J. R. Pickhardt in fabricating much of the special equipment. We would like to thank Prof. R. P. Bell for making his results available to us in advance of publication. We are also indebted to Drs. M. A. Paul and F. A. Long for furnishing a draft of their review article in advance of publication.

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[CONTRIBUTION FROM THE CHEMISTRY DIVISION, ARGONNE NATIONAL LABORATORY]

Isotopic Exchange Reactions of Neptunium Ions in Solution. V. The Np(V)–Np(VI) Exchange in D_2O[1]

BY J. C. SULLIVAN, DONALD COHEN AND J. C. HINDMAN

RECEIVED DECEMBER 3, 1956

From studies in mixed electrolyte systems the conclusion is drawn that the perchlorate ion does not participate in the Np(V)–Np(VI) exchange reaction. The data do indicate that there are two possible reaction paths, one acid dependent and the other acid independent. The substitution of deuterium for hydrogen decreases the rate of the acid independent path, indicating that hydrogen atoms are involved in the mechanism for the exchange process. The hydrogen ion dependent path probably involves specific hydronium ion catalysis.

Previous communications[2-4] have reported the results of investigations of various factors affecting the rate of the Np(V)–Np(VI) isotopic exchange reaction. It has been demonstrated that the rate of the reaction is negligibly affected by the variation of the macroscopic dielectric constant in perchlorate media containing ethylene glycol or sucrose.[4] Although these results demonstrate the inapplicability of the model for exchange by electron tunneling, for the present system, in the form presented by Marcus, Zwolinski and Eyring,[5,6] they do not conclusively show that the exchange proceeds by a mechanism other than direct electron transfer.

It has been suggested for the present reaction and for similar reactions[7,8] that the exchange in perchlorate solution proceeds by a mechanism involving hydrogen atom transfer. In principle this can be demonstrated by examination of the isotope effect, *e.g.*, by carrying out the reaction in a D_2O solution. Hudis and Dodson[9] have used this technique to gain support for the view that a hydrogen atom transfer mechanism is probable for the Fe(II)–Fe(III) system. Similar measurements are reported here for the Np(V)–Np(VI) system.

In addition, evidence was sought that would indicate whether or not there was a possibility that perchlorate ion might be involved as a bridging group in the activated complex. In principle, if perchlorate enters the complex one would expect to find a dependence of the rate of the reaction with perchlorate ion concentration at constant ionic strength. Anion effects of this nature were reported by Olson and Simonson[10] for a number of reactions in dilute solution. On the other hand, in perchlorate solutions at higher ionic strengths, Silverman and Dodson[11] found that the rate of the Fe(II)–Fe(III) exchange was unaffected by the anion concentration as long as the ionic strength was unchanged. Recently, Sutcliffe and Weber,[12] working at comparable ionic strengths, obtained results that led them to postulate that the perchlorate ion was involved in the oxidation–reduction reaction between Ce(III) and Co(III).

Experimental

The salt solutions were prepared as follows; sodium perchlorate solutions were made by dissolution of the carbonate in perchloric acid. Magnesium and lanthanum perchlorate solutions were prepared by addition of an excess of the respective oxides to perchloric acid. The filtered solutions had a final *p*H of approximately 5. The authors wish to thank Miss I. Fox of the Analytical Group for performing the analyses of these solutions.

Deuteroperchloric acid was prepared in the following manner: first, deuterosulfuric acid was prepared by dissolution of anhydrous SO_3 in D_2O (99.25%). The sulfate was removed from the approximately 13 *M* D_2SO_4 by addition of barium perchlorate and centrifugation of the precipitated barium sulfate. The deuteroperchloric acid (99 ± 0.3% deuterium content) was purified by vacuum distillation. Only the center fraction of the constant boiling mixture was used for preparation of the dilutions.

Stock solutions of Np(V) and Np(VI) were prepared in $DClO_4$. The exchange reactions were carried out in solutions containing a maximum of 99% deuterium. The authors are grateful to Dr. H. Crespi for the determination of the isotopic content of the deuterated solvent solutions.

The majority of the experiments were performed at a temperature of 5.00°, employing the experimental techniques and procedures previously described.[2-4] Solvent extraction separation of the Np(VI) from Np(V) was done using theonyltrifluoroacetone in toluene for the extractant in 0.1 *M* acid and tributyl phosphate for the extractant at higher acid concentrations.

Results and Discussion

The exchange reaction previously has been found to be bimolecular.[2,3] The rate of the exchange may be expressed by the equation

$$R = k[\mathrm{Np(V)}]\,[\mathrm{Np(VI)}] \qquad (1)$$

The specific rate constant, k, is determined from the exponential rate law for a radioactive exchange written as

$$t = \frac{\ln (1 - F)}{([\mathrm{Np(V)}] + [\mathrm{Np(VI)}])k} \qquad (2)$$

where F is the fraction exchanged at time, t. Details of the method of treatment of the data are given in an earlier communication.[2]

The Influence of Ionic Strength and Hydrogen Ion Concentration.—The effect of ionic strength is depicted graphically in Fig. 1. Table I shows the effect of varying the hydrogen ion at constant

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ionic strength. The following conclusions may be drawn from these data: first, the invariance of the rate at constant ionic strength in the sodium, magnesium and lanthanum perchlorate solutions, up to $\mu = 3$, indicates that the perchlorate ion participates neither in an equilibrium prior to the rate-determining step nor in the activated complex. In this respect the results are similar to those observed for the Fe(II)–Fe(III) system by Silverman and Dodson.[11] Second, the data in Fig. 1 suggest that an alternate exchange path involving hydrogen ion becomes increasingly important at high acidities. In an earlier communication observations at lower temperatures also suggested this possibility.[3] The results shown in Table I strongly support this hypothesis. The observed rates can be reproduced by a rate law of the form

$$k_{obsd} = k_1 + k_2[H^+] \quad (3)$$

TABLE I

THE EFFECT OF HYDROGEN ION CONCENTRATION ON THE EXCHANGE RATE AT $\mu = 3.0$, $t = 4.5°$

H^+ moles/l.	k_{obsd} (l. mole^{-1} sec.$^{-1}$)	k_{calcd} (l. mole^{-1} sec.$^{-1}$)
0.1	75	75
1.0	86	88.5
1.55	90	96.5
2.17	109	106
3.00	118	118.5

where k_1 is the specific rate constant for the acid independent path and k_2 the specific rate constant for the acid dependent path. At 4.5°, $k_1 = 73.5$ and $k_2 = 15$. From the earlier data[3] at 0° we would estimate $k_1 = 50$ and $k_2 = 10$. Calculation yields a value of 12 ± 5 (95% confidence level) for the activation energy of the acid independent path and 15 ± 7 kcal. for the acid dependent path. There is the implicit assumption in these calculations that the ionic strength data given in Fig. 1 can be interpreted to mean that the activity coefficients remain essentially constant at ionic strengths up to 3.0 M with changes in the medium composition.

The Effect of Deuterium Concentration.—Table II summarizes the data on the effect of deuterium

TABLE II

SUMMARY OF RELATIVE RATES OF REACTION AND ENERGIES OF ACTIVATION FOR THE EXCHANGE IN H_2O AND D_2O SOLUTIONS

$t = 5°$, $[Np(V)] = [Np(VI)] = 2 \times 10^{-5}$ M

H^+ (mole/l.) (μ)	k_{H^+}/k_{D^+}	E_{expt} ($HClO_4$) (kcal./mole)	E_{expt} ($DClO_4$)[a] (kcal./mole)
0.1	1.4 ± 0.1	11.6 ± 0.8	12.1 ± 1.6
1.0	1.3 ± .1	10.6 ± .8	11.6 ± 1.0
3.0	1.2 ± .1	10.6 ± .8	

[a] 99 ± 0.7% deuterium content.

on the rate of the reaction under different conditions. Table III shows the effect of varying the deuterium content for the 0.1 M acid solutions, where the effect of replacing $[H^+]$ by $[D^+]$ is maximal. The uncertainties given are for the 95% confidence level. The fact that the rate of the exchange is slower by a factor of 1.4 in the 0.1 M acid solutions in the presence of deuterium we interpret as evidence for the participation of hydrogen in the

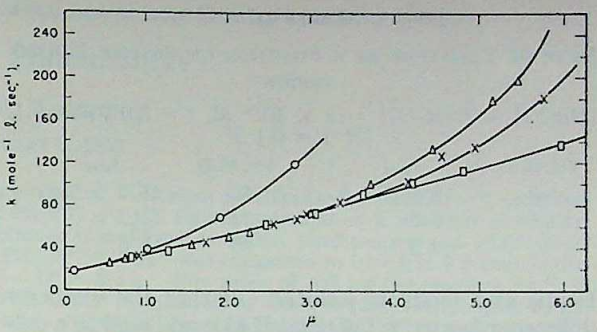
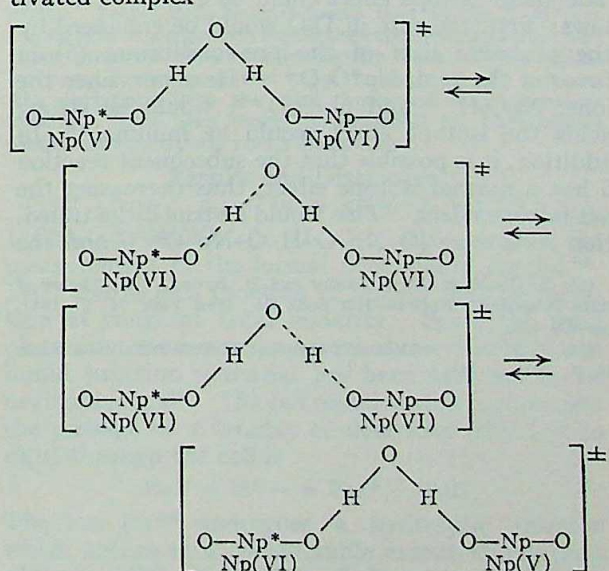


Fig. 1.—The effect of ionic strength and hydrogen ion concentration on the Np(V)–Np(VI) exchange. $[Np(V)] = [Np(VI)] \cong 2 \times 10^{-5} M$; t, 5.00°: O, $[H^+]$; $[H^+]$ 0.1 M and Δ, $NaClO_4$, × $Mg(ClO_4)_2$, □ $La[ClO_4]_3$.

exchange process for the acid independent reaction path. Various suggestions for hydrogen transfer processes involving participation of the solvent have been made.[7,8,13] All involve some kind of group transfer. The isotope factor observed for the present case is minimal for a process involving transfer of hydrogen atoms and corresponds to the situation where the bonding in the activated complex is as strong as in the reactants or to the case where a new bond is formed as the old bond is broken.[14] This suggests that we might visualize the electron transfer process through a water bridge as one which does not involve group transfer but only a stretching of bonds. One possible representation of such a process is depicted schematically as

$$Np^*O_2^+ + NpO_2^{++} + H_2O \rightleftharpoons [X^{+3}]^\ddagger \longrightarrow NpO_2^+ + Np^*O_2^{++} + H_2O \quad (4)$$

where the electron transfer could be considered as involving the internal rearrangements in the activated complex



The dotted lines indicate stretching of bonds to conform to the transfer of an electron to a proton to approach the configuration of a hydrogen atom.

In their discussion of the interpretation of the deuterium effect on the Fe(II)–Fe(III) exchange,

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TABLE III

RATE OF EXCHANGE AS A FUNCTION OF VOLUME % DEUTERIUM

$[Np(V)] = [Np(VI)] = 2 \times 10^{-5}\ M$, $t = 5.0°$, $\mu = 0.1$, $[H^+] = 0.1\ M$

Vol. % D	k_{obsd}	Vol. % D	k_{obsd}
0	18.3 ± 1.2	50	15.5 ± 1.2
5	16.0	75	14.7
10	16.2	99	13.5

Hudis and Dodson[9] pointed out that the viscosity difference between D_2O and H_2O could lead to a collision frequency difference of about 20%. However, for reactions involving activation energies of the order of magnitude under consideration diffusion cannot be the rate-determining step, hence viscosity differences will be of little importance.[15] This view is supported in the present case by the experimental results in mixed solvent systems.[4] In these systems, despite much larger viscosity differences the rate was not affected.

The decrease in the k_{H^+} to k_{D^+} ratio with increasing acid concentration indicates a difference in the isotope effect between the acid independent and acid dependent reaction paths. The rate of the reaction for the acid dependent path appears to be more rapid in D_2O solution ($k_{D^+}/k_{H^+} \sim 1.1$). This result suggests that this reaction path involves specific hydronium ion catalysis.[14,16] A reasonable mechanism would involve the two step process

$$Np^*O_2^+ + H^+ \rightleftarrows Np^*O_2H^{++} \qquad (5)$$

and

$$NpO_2^{++} + Np^*O_2H^{++} \rightleftarrows [X^{+4}]^\ddagger \longrightarrow Np^*O_2^{++} + NpO_2H^{++} \qquad (6)$$

The small isotope effect could be explained as follows: first, the rate in D_2O would be enhanced by the probable shift of the pre-equilibrium (5) in favor of the acid, $Np^*O_2D^{++}$. However, since the ions, NpO_2H^{++} and NpO_2D^{++}, would be strong acids the isotope effect would be minimal.[14] In addition, it is possible that the subsequent reaction 6 has a normal isotope effect, thus decreasing the net isotope effect. This would be true if the transition state were $[O–Np–O–H–O–Np–O^{4+}]^\ddagger$ and the exchange process involved the transfer of a hydrogen atom.

Virtues of the mechanism as written are: (1) the transition state is symmetrical. (2) The formation of the transition state would involve the minimum of rearrangement of configuration for the reacting ions. (3) The products of the reaction are the same as the reactants. It should also be pointed out that the normal isotope effect could be small for the mechanism as written since a simultaneous making and breaking of bonds could occur. The net isotope effect would require that the normal isotope effect be small if the isotope effect on the pre-equilibrium (5) is minimal.

A different interpretation has been advanced by Duke and Pinkerton[17] to explain the isotope effect on the rate of the U(V) disproportionation, a reaction similar to that under discussion. A k_{D^+}/k_{H^+} ratio of 1.7 was found. They attribute the enhanced rate in D_2O to a shift in the equilibrium

$$UO_2^+ + H^+ \rightleftarrows UO_2H^{++} \qquad (5a)$$

They consider, however, that the transfer of a proton is unlikely and that the reaction more probably involves a hydroxyl atom transfer

$$O–U–OH^{++} + O–U–O^+ \rightleftarrows [X^{+3}]^\ddagger \longrightarrow O–U^{++} + H–O–U–O_2^+ \qquad (7)$$

If we consider the possibility of hydroxyl atom transfer for the present reaction we have

$$O–Np^*–OH^{++} + O–Np–O^{++} \rightleftarrows [X^{+4}]^+ \longrightarrow O–Np^*–OH^{+3} + O–Np–O^+ \qquad (8)$$

Examination of reaction 8 reveals that OH cannot be transferred in the exchange process. Basically the reaction would have to be considered as an electron transfer through a bridging hydroxyl ion. Little or no isotope effect might be expected in this step. To have a OH transfer in the present case we would have to assume the formation of the less probable species of Np(VI), $O–Np–OH^{+3}$, in the pre-equilibrium step and the reaction

$$O–Np–O–H^{+3} + O–Np^*–O^+ \rightleftarrows [X^{+4}]^\ddagger \rightleftarrows O–Np^{+3} + H–O–Np^*–O_2^+ \qquad (9)$$

This mechanism would involve the breaking of a Np–O bond. In view of the great stability of the O–Np–O structure this is considered a highly unlikely process.

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[CONTRIBUTION FROM THE UNIVERSITY OF CALIFORNIA, LOS ALAMOS SCIENTIFIC LABORATORY]

The Hydrolysis of Plutonium(IV)[1]

BY SHERMAN W. RABIDEAU

RECEIVED FEBRUARY 8, 1957

The hydrolysis quotient, $(PuOH^{+++})(H^+)/(Pu^{+4})$, has been evaluated in lithium perchlorate–perchloric acid solutions at a constant total molarity of two from measurements of the Pu(III)–Pu(IV) formal potential as a function of acidity. The temperature dependence of this hydrolysis quotient was obtained from formal potential measurements at 14.88, 25.00 and 34.35°; the value of ΔH for the reaction $Pu^{+4} + H_2O \rightleftarrows PuOH^{+++} + H^+$ was computed to be 7.3 ± 0.5 kcal./mole. At 25° the value of ΔF is 1.73 ± 0.01 kcal./mole; hence, ΔS = 19 ± 2 e.u. The value of ΔH for the reaction $Pu^{+3} + H^+ \rightleftarrows Pu^{+4} + {}^1/_2H_2$, in 2 *M* perchloric acid at 25° was found to be 13.3 ± 0.5 kcal./mole which is very nearly equal to the value obtained previously for this reaction in molar perchloric acid. Virtually identical Pu(III)–Pu(IV) formal potentials were obtained in those cases in which sodium perchlorate was used to replace lithium perchlorate as the added salt to maintain an ionic strength of two in the solutions. Thus, it would appear that the concentration of the perchlorate ion plays a more significant role than the sodium or lithium ion in determining the value of the activity coefficient ratio $\gamma^5_{\pm Pu(ClO_4)_4}/\gamma^4_{\pm Pu(ClO_4)_3}\ \gamma^2_{\pm HClO_4}$.

Introduction

In the study of the isotopic exchange between Pu(III) and Pu(IV) Keenan[2] observed that his results indicated that the hydrolyzed species of Pu(IV), $PuOH^{+++}$ appeared to be involved in the reaction mechanism. The present work was directed toward the evaluation of this hydrolysis quotient in the media in which the exchange experiments were performed, *i.e.*, lithium perchlorate–perchloric acid mixtures, and the determination of some of the thermodynamic quantities applicable to the hydrolysis reaction, $Pu^{+4} + H_2O \rightleftarrows PuOH^{+++} + H^+$. The hydrolysis of Pu^{+4} has been studied previously[3-5] by spectrophotometric and potentiometric methods at ionic strengths ranging from 0.5 to 1.1. However, none of these previous studies included measurements of the temperature coefficient of the hydrolysis quotient. Hindman[6] has considered the evaluation of the degree of hydrolysis of some trivalent and tetravalent ions, including plutonium, from a theoretical point of view in which an attempt is made to calculate the electrostatic free energy involved in the hydrolytic reaction. However, this treatment appears to be semi-quantitative in scope.

Experimental

The experimental apparatus has been described previously.[7] The Pu^{+3} solutions were prepared by dissolving weighed quantities of oxide-free metal in Mallinckrodt Analytical Reagent grade 70% perchloric acid, then diluting with water redistilled from alkaline permanganate. The lithium perchlorate was prepared by neutralizing C.P. lithium carbonate with perchloric acid followed by recrystallization of the salt from water as the trihydrate. This salt was analyzed for perchlorate content by precipitation with tetraphenylarsonium chloride, and for water content by heating to about 160° to form the anhydrous salt. Electrolytic grade hydrogen was purified by passing the gas through a uranium furnace heated to 600°. The gas was saturated with the cell solution in a bubbler maintained at the temperature of the cell; then the gas was passed into the hydrogen electrode compartment. Dual hydrogen and bright platinum electrodes were used and intercompared to assure proper electrode behavior. The plutonium solutions of known (Pu(IV))/(Pu(III)) ratio were prepared by adding weighed aliquots of a standard potassium dichromate solution to the Pu^{+3} solutions. The same acid–salt concentration was used in both the dichromate and Pu^{+3} solutions to maintain the ionic strength at two during the potentiometric titration. The temperature of the plutonium solutions was maintained at ±0.01° during the course of an experiment and was obtained from measurements of the resistance of a type 20D Western Electric thermistor which was calibrated against a platinum resistance thermometer certified by the National Bureau of Standards. A voltage of 1.0000 was impressed upon the thermistor by using a voltage divider and Mallory type 302157 mercury batteries to maintain the resistance–temperature calibration over a period of several months.

To correct the hydrogen electrode for the partial pressure of hydrogen gas, the vapor pressure of the lithium perchlorate–perchloric acid solutions was required. Since it appeared that the vapor pressure data required had not been published previously, the vapor pressures of the acid–salt solution were measured between 5 and 25° by using a high vacuum line and a mercury manometer. The air was removed from the solutions during repeated freezing–melting cycles. Pearce and Nelson[8] found that in the 2 *M* perchloric acid concentration region the experimentally observed vapor pressures differed only slightly from the theoretical fractional lowering of the vapor pressure of the solvent. The deviations from the ideal theoretical vapor pressure lowerings have been found to be small for the lithium perchlorate–perchloric acid solutions also.

Results and Discussion

The cell Pt; Pu^{+3}, Pu^{+4}, $HClO_4(c_1)$, $LiClO_4(c_2)$; $LiClO_4(c_2)$, $HClO_4(c_1)$; H_2, Pt was used in the measurement of the formal potential of the Pu^{+3}–Pu^{+4} couple as a function of acidity and temperature at constant total molarity. Since the total plutonium concentrations were about 8×10^{-3}, the liquid junction potential has been assumed to be negligibly small. The cell reaction that occurs upon the passage of a faraday of electricity from left to right through the cell is

$$Pu^{+3} + H^+ \longrightarrow Pu^{+4} + {}^1/_2H_2$$

The ion Pu^{+4} undergoes a hydrolytic reaction which occurs to a considerable extent in solutions of low acidity (*ca.* 35% hydrolyzed in 0.1 *M* perchloric acid at 25°, *vide infra*)

$$Pu^{+4} + H_2O \rightleftarrows PuOH^{+3} + H^+$$

The concentration quotient, K, for this hydrolysis reaction is

$$K = (PuOH^{+3})(H^+)/(Pu^{+4})$$

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The formal potential of the Pu^{+3}–Pu^{+4} couple is given by the expression

$$E^{0\prime} = E_{cell} + RT/F \ln \Sigma Pu(IV)/Pu(III) + RT/F \ln p_{H_2}^{1/2}/(H^+)$$

This formal potential is related to the concentration quotient, K, by the formula

$$E^{0\prime} = E^0 - RT/F \ln [(H^+)/\{(H^+) + K\}] - RT/F \ln \frac{\gamma^5_{\pm Pu(ClO_4)_4}}{\gamma^4_{\pm Pu(ClO_4)_3}\gamma^2_{\pm HClO_4}}$$

If it is assumed that the activity coefficient ratio $\gamma^5_{\pm Pu(ClO_4)_4}/\gamma^4_{\pm Pu(ClO_4)_3}\gamma^2_{\pm HClO_4}$ is constant in perchloric acid–lithium perchlorate solutions of constant ionic strength, the value of the concentration quotient, K, can be evaluated from a plot of the formal potential of the Pu^{+3}–Pu^{+4} couple *versus* log $[(H^+)/(H^+) + K]$. This plot should result in a straight line relation with a slope of $-2.303RT/F$ if the assumption with reference to the constancy of the activity coefficient ratio is valid. It appears that this assumption is justified since reasonably good straight lines do result from plots of the formal potentials *versus* log $[(H^+)/(H^+) + K]$.

In Table I are given the formal potentials of the Pu^{+3}–Pu^{+4} couple in lithium perchlorate–perchloric acid solutions as a function of temperature and of acidity at a total constant molarity of two.

The uncertainty of the formal potentials is about ±0.0002 volt. The values of the hydrolysis quotients were obtained as shown in Fig. 1 by adjusting the value of K in the plot of $E^{0\prime}$ *vs.* log $[(H^+)/(H^+) + K]$ until the theoretical slope of $-2.303RT/F$ was obtained. The values of K are considered to have an uncertainty of ±0.001.

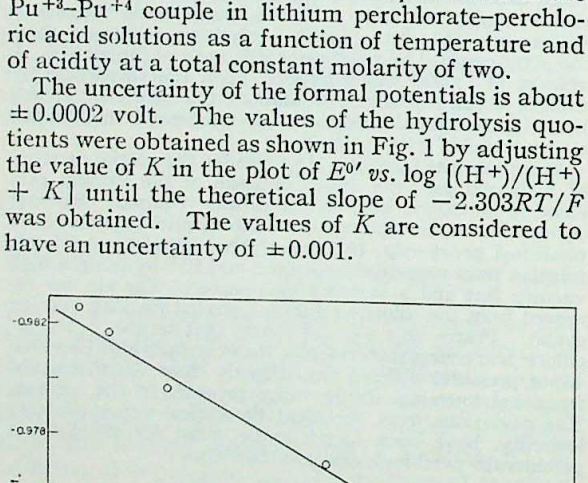

Fig. 1.—Evaluation of hydrolysis quotient of plutonium(IV) from potentiometric measurements in lithium perchlorate–perchloric acid solutions at 25° and at an ionic strength of two.

From the temperature coefficient of the hydrolysis quotient a value of +7.3 ± 0.5 kcal./mole was obtained for ΔH. Since at 25° the value of ΔF equals 1.73 ± 0.01 kcal./mole, the increase in entropy accompanying the hydrolysis of Pu^{+4} is +19 ± 2 e.u. The data given in Table II were used in the evaluation of the heat of the hydrolysis reaction. It is of interest to compare the thermodynamic quantities for the hydrolysis of Pu^{+4} with those reported[9,10] for U^{+4}. With spectrophotometric methods these authors obtained values which were in essential agreement. Values of ΔH = 11.0 kcal./mole and ΔS = 33 e.u. were obtained for the reaction $U^{+4} + H_2O \rightleftarrows UOH^{+3} + H^+$. These values refer to the hydrolysis reaction at zero ionic strength whereas in the hydrolysis of Pu^{+4} the ionic strength of two was used.

TABLE I

TEMPERATURE AND ACIDITY DEPENDENCE OF Pu(III)–Pu(IV) FORMAL POTENTIALS IN LITHIUM PERCHLORATE–PERCHLORIC ACID SOLUTION AT AN IONIC STRENGTH OF TWO

T, °K.	(H^+), moles/l.	$E^{0\prime}$, volt	$[(H^+)/(H^+) + K]$	log $[(H^+)/(H^+) + K]$	K
288.05	2.000	−0.9681	0.98087	−0.00839	
	1.000	.9657	.96246	.01662	
	0.500	.9651	.92764	.03262	0.039
	.200	.9620	.83682	.07737	
	.150	.9611	.79365	.10037	
	.100	.9587	.71942	.14302	
298.16	2.000	−0.9826	0.97371	−0.01157	
	1.000	.9817	.94877	.02284	
	0.500	.9797	.90253	.04454	0.054
	.200	.9771	.78740	.10380	
	.150	.9748	.73529	.13354	
	.100	.9719	.64935	.18752	
307.51	2.000	−0.9944	0.95785	−0.01871	
	1.000	.9891	.91912	.03663	
	0.500	.9879	.85034	.07041	0.088
	.200	.9818	.69444	.15837	
	.150	.9795	.63025	.20048	
	.100	.9733	.53191	.27416	

TABLE II

DETERMINATION OF ΔH FOR HYDROLYSIS OF Pu(IV)

T, °K.	$1/T \times 10^3$	K	log K
288.05	3.472	0.039	−1.409
298.16	3.354	.054	−1.263
307.51	3.252	.088	−1.056

The value of ΔH for the reaction $Pu^{+3} + H^+ \rightleftarrows Pu^{+4} + {}^1/_2H_2$ also was determined since values of the formal potential of the Pu^{+3}–Pu^{+4} couple in 2 M perchloric acid as a function of temperature were measured. From a plot of $E^{0\prime}/T$ *vs.* $1/T$ a value of 13.3 ± 0.5 kcal./mole was computed for ΔH for this reaction at 25°. This value is very nearly equal to the value reported[11] for this reaction in molar perchloric acid.

A point of interest was examined in connection with changes in activity coefficient ratios in mixed electrolytes at constant ionic strength as sodium perchlorate is substituted for lithium perchlorate. In Table III are given the formal potentials of the Pu^{+3}–Pu^{+4} couple as a function of acidity in the presence of either sodium or lithium perchlorate.

Thus, as evident from a comparison of the formal potentials of the Pu^{+3}–Pu^{+4} couple in sodium or lithium perchlorate–perchloric acid solutions, the alteration of the hydrolysis quotient with the change in added salt is very small. It would seem that the activity coefficient ratio $\gamma^5_{\pm Pu(ClO_4)_4}/\gamma^4_{\pm Pu(ClO_4)_3}\gamma^2_{\pm HClO_4}$ is not very sensitive to the substitution of lithium ions for hydrogen ions, or to

(9) K. A. Kraus and F. Nelson, THIS JOURNAL, 77, 3721 (1955).
(10) R. H. Betts, *Can. J. Chem.*, 33, 1775 (1955).
(11) S. W. Rabideau and H. D. Cowan, *ibid.*, 77, 6145 (1955).

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TABLE III

EFFECT OF TYPE OF ADDED SALT UPON Pu^{+3}–Pu^{+4} FORMAL POTENTIALS AT CONSTANT IONIC STRENGTH AND 25°

(H^+), moles/l.	$(NaClO_4)$, moles/l.	$(LiClO_4)$, moles/l.	$E^{0\prime}$, volts
2.000	0.000	0.000	−0.9826
0.500	.000	1.500	− .9797
.500	1.500	0.000	− .9791
.200	0.000	1.800	− .9771
.200	1.800	0.000	− .9768
.100	0.000	1.900	− .9719
.100	1.900	0.000	− .9728

the substitution of sodium ions for lithium ions in these solutions of constant ionic strength.

It might have been predicted from the treatment of Robinson and Stokes[12] that the above activity coefficient ratio would be significantly altered in the solution of mixed electrolytes since the osmotic coefficients and the hydration numbers of sodium perchlorate and lithium perchlorate are appreciably different. However, it appears that this difference is not observed experimentally in view of the small changes noted in the formal potentials of the Pu^{+3}–Pu^{+4} couple.

(12) R. A. Robinson and R. H. Stokes, "Electrolytic Solutions," Butterworths Publications, Ltd., London, 1955, p. 443.

LOS ALAMOS, NEW MEXICO

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Composition and Formation of Cobalt Complexes with 1-Nitroso-2-naphthol

BY I. M. KOLTHOFF AND EINAR JACOBSEN

RECEIVED MARCH 7, 1957

Controversial statements are found in the literature on the composition and the mode of formation of the complex which precipitates upon addition of a solution of 1-nitroso-2-naphthol (HR) to a cobalt(II) solution in an acetate buffer. The precipitate is soluble in benzene and acetonitrile (AN). From its polarographic properties in AN, from amperometric titrations in water and AN, and from gravimetric studies it was concluded that the complex has the formula $Co(III)\,R_3{\cdot}H_2R'$, $H_2R\cdot$ being the semiquinone obtained by a one-electron reduction of HR. $H_2R\cdot$ is unstable in a vacuum at 110°. $H_2R\cdot$ is soluble in 40% acetic acid; the precipitate obtained from this medium has the composition $Co(III)R_3$. It is proposed that $Co(II)R_2$ is the first reaction product which, in acid medium, decomposes rapidly according to the equation: $2Co(II)R_2 \rightarrow Co(III)R_3 + H_2R\cdot + Co(II)$. A precipitate of $Co(II)R_2$ is obtained from neutral and slightly alkaline aqueous medium. When dissolved in AN which contains acid, the reaction products of the disproportionation are found in the solution. The polarographic properties of some other metal–HR complexes have been determined.

Ilinsky and v. Knorre[1] reported in 1885 that upon addition of excess cobalt(II) to a neutral aqueous solution of the sodium salt of 1-nitroso-2-naphthol (designated in this paper as HR) a brown-red precipitate is formed. By addition of acid to the mixture and heating, the precipitate is transformed to a purple-red compound. The purple complex is also obtained when the precipitation is carried out in acid medium. The percentage of cobalt in the complexes was determined and the formulas CoR_2 and CoR_3 for the brown-red and purple-red complexes were suggested.

During this century HR has been recommended by a number of investigators for the determination of cobalt. The precipitate has been reported to be of variable composition, and for this reason is ignited to and weighed as Co_3O_4 or the oxide is reduced with hydrogen to the metal.[2,3]

Mayer and Feigl[4] suggest that divalent cobalt is partly oxidized by the reagent to the trivalent state and claim that the precipitate formed by addition of HR to an acid solution of divalent cobalt is not a pure compound but contains both divalent and trivalent cobalt. In order to obtain all cobalt in the trivalent form they first convert cobalt(II) into cobaltic hydroxide by addition of hydrogen peroxide and sodium hydroxide. The hydroxide is dissolved by heating in a fairly concentrated solution of acetic acid to yield a complex trivalent cobalt acetate. After dilution the cobalt(III) is precipitated with the reagent and the precipitate weighed as $CoR_3{\cdot}2H_2O$. It is not realized by these authors that on heating of a cobalt(III) solution in aqueous acetic acid reduction to cobalt(II) occurs.

Kolthoff and Langer[5] titrated divalent cobalt in acetate buffer amperometrically with HR. The ratio of cobalt to HR in the purple-red precipitate was found to be 1:4 and they suggested the formula $CoR_2{\cdot}2HR$.

In a discussion of these results Feigl[6] suggested that HR reacts with cobalt(II) salts to form an inner complex containing trivalent cobalt. He suggests that the precipitate is composed of the trivalent cobalt complex with one molecule of coördinated reagent. No experimental evidence however was presented and no simple reaction mechanism would account for this suggestion.

From the above review it is evident that the composition of the red cobalt complex and its mode of formation are not yet clear. In the present paper experiments are described which establish the composition of the red precipitate and the reactions leading to its formation.

It was observed that some of the metal complexes with HR, which are precipitated from aqueous medium, are soluble in benzene and acetonitrile (designated in this paper as AN). In AN as solvent or in mixtures of AN with benzene well-de-

(1) M. Ilinski and G. von Knorre, *Ber.*, **18**, 699 (1885).
(2) P. Slawik, *Chem. Z.*, **38**, 514 (1914); *C. A.*, **8**, 2541 (1914).
(3) H. Willard and D. Hall, THIS JOURNAL, **44**, 2210 (1922).
(4) C. Mayer and F. Feigl, *Z. Anal. Chem.*, **80**, 15 (1930).
(5) I. M. Kolthoff and A. Langer, THIS JOURNAL, **62**, 3172 (1940).
(6) F. Feigl, "Chemistry of Specific, Selective and Sensitive Reactions," Academic Press, New York, N. Y., 1949, pp. 252–262; *Anal. Chem.*, **21**, 1383 (1949).

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fined polarographic waves of the metal complexes were obtained. A polarographic study of the cobalt complexes indicated that cobalt is present in the trivalent form. Evidence is presented that cobalt(II) reacts in an acetate buffer or in other acid medium with RH to form $Co(II)R_2$ which rapidly is transformed into $Co(III)R_3$ and $H_2R{\cdot}H_2R{\cdot}$ having properties of a semiquinone. In dilute acetic acid medium $H_2R{\cdot}$ precipitates quantitatively with the red compound, which has the overall composition $CoR_3{\cdot}H_2R{\cdot}$. At higher concentrations of acetic acid the semiquinone is soluble and the precipitate is composed of CoR_3. This interpretation was supported by gravimetric and amperometric experiments.

Experimental

Materials Used.—C.P. chemicals were used unless otherwise stated. Standard solutions of HR were prepared and standardized as recommended by Kolthoff and Langer.[5] Unless otherwise stated, 0.1 *M* sodium perchlorate prepared from the anhydrous salt served as supporting electrolyte in AN as solvent.

Technique.—The conventional type of dropping mercury electrode and of electrolysis cell were used. Current–voltage curves were recorded with a Sargent Recording Polarograph Model XXI. Oxygen was eliminated from the solutions by bubbling pure nitrogen through the cell for 10 min. and passing it over the solution during the electrolysis. Further details on the polarographic technique in AN are found in a recent paper.[7]

Results

Polarography.—Irreproducible and poorly defined current–voltage curves of the reagent and its metal complexes in AN were obtained in acid-free solutions of sodium perchlorate. By addition of acetic acid or perchloric acid well-defined and reproducible polarograms were observed.

Current–voltage curves of 10^{-3} *M* HR in AN of different acidity are plotted in Fig. 1. The diffusion current was found not to be affected by concentration and kind of acid present and to be proportional to concentration of HR, the value of $i_{d/c}$ being equal to 16.0 μa./mmole HR/liter. By assuming a reasonable value for the diffusion coefficient of HR, it was inferred that its reduction involves four electrons. This corresponds to a reduction of the nitroso group to the amine. The half-wave potential is shifted to more positive values with increasing concentration of acetic acid, while the stronger acid perchloric in 0.1 *M* solution has a much greater effect than 1.5 *M* acetic acid. Identical waves were obtained when the reagent was extracted with benzene from aqueous acetic acid solution and the benzene solution diluted with AN which contained the appropriate amount of acid and salt.

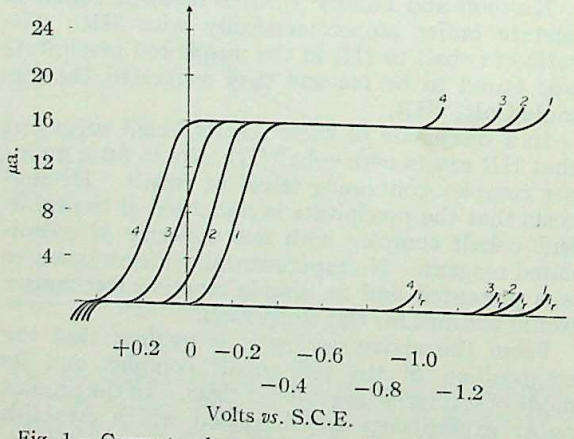

Fig. 1.—Current-voltage curves of 10^{-3} *M* HR in 0.1 *M* sodium perchlorate in acetonitrile: (1) 0.1 *M*; (2) 0.5 *M*; (3) 1.5 *M* in acetic acid; (4) 0.1 *M* in perchloric acid.

Complexes of various metals with HR were prepared by adding a known volume of the reagent in 60% acetic acid to aqueous 0.2 *M* sodium acetate solutions containing an excess (50 to 100%) of the metal salts. The precipitates formed were extracted with benzene and an aliquot part of the extract diluted with AN, which was 0.5 *M* in acetic acid and 0.1 *M* in sodium perchlorate, shortly before recording the polarograms. Current–voltage curves of the metal complexes are plotted in Fig. 2. Diffusion currents and $E_{1/2}$ values are reported in Table I.

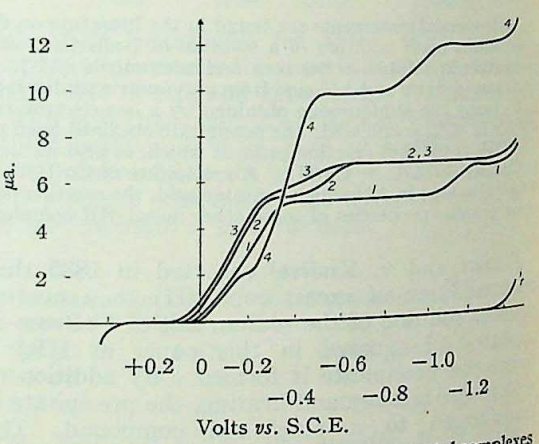

Fig. 2.—Current-voltage curves of various metal complexes with HR in AN (0.5 *M* in acetic acid and 0.1 *M* in $NaClO_4$): 1) 2×10^{-4} *M* $Fe(II)R_2$; (2) 2×10^{-4} *M* $Ni(II)R_2$; (3) 2×10^{-4} *M* $Cu(II)R_2$; (4) 2×10^{-4} *M* $Co(III)R_3{\cdot}R$.

Solutions of the metal complexes also were prepared by mixing together equivalent amounts of the metal perchlorates and the reagent in acetonitrile which was 0.5 *M* in acetic acid. Current–voltage curves of these solutions were identical with those in Fig. 2 and the i_d values were proportional to the concentration of the respective complexes.

The polarograms of copper(II), nickel(II) and the iron(II) complexes exhibit two waves. The first wave corresponds to reduction of the reagent in the complex, the second wave to reduction of the metal ion to amalgam. The half-wave potentials of the second wave of the nickel and ferrous iron complexes are practically identical with the observed $E_{1/2}$ value of the corresponding metal/perchlorates in the same medium (Table I). The $E_{1/2}$ value of the second wave of the copper complex is close to that of copper(I) to copper amalgam. The copper(II) in the complex is held firmly and cannot be reduced until all the reagent is destroyed, whereupon the reduced reagent also

(7) I. M. Kolthoff and J. F. Coetzee, THIS JOURNAL, 79, 870 (1957).

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TABLE I

DIFFUSION CURRENTS AND $E_{1/2}$ VALUES OF 2×10^{-4} M META . COMPLEXES WITH HR IN ACETONITRILE

Complex	Color	i_{d1}	i_{d2}	Ratio i_{d2}/i_{d1}	$E_{1/2}$ 2nd wave	$E_{1/2}$ of Me(ClO_4)$_2$	
NiR_2	Brown	5.30	1.30	1:4.1	−0.54	Ni(II)–Ni(0)	−0.55
FeR_2	Green	5.20	1.30	1:4.0	−1.12	Fe(II)–Fe(0)	−1.11
CuR_2	Brown	5.40	1.35	1:4.0	−0.42	Cu(I)–Cu(0)	−0.40
$CoR_3 \cdot R\cdot$	Purple-red	9.85	1.96	1:5.0	−0.93	Co(II)–Co(0)	−0.68

stabilizes the copper(II). Considering that the reduction of one molecule of reagent involves 4 electrons and that of one metal(II) 2 electrons, the ratio i_{d_2}/i_{d_1} should be 1:4 for MR_2. As seen from Table I, this ratio is found experimentally.

The polarogram of the cobalt complex differs from the others. The half-wave potential of the second wave was found to be 0.25 volt more negative than the $E_{1/2}$ for reduction of uncomplexed cobalt(II) ions in the same medium. This difference might be attributed to complex formation of cobalt with the reduced reagent. If the complex had the composition $CoR_2 \cdot 2HR$, the ratio of i_{d_2}/i_{d_1} should be 1:8, while the ratio should be 3:16 or 1:5.33 if the formula were $CoR_3 \cdot HR$. Actually, a ratio of 1:5.00 was found, which corresponds to a formula $Co(III)R_3 \cdot R\cdot$, in which $R\cdot$ is the semiquinone of HR, which would require 3 electrons per molecule for its reduction. From Fig. 2 it is seen that the reagent wave of the cobalt complex is composed of two waves, the first wave being about 2 μa., and the second wave 7.9 μa. According to the formula $Co(III)R_3 \cdot R\cdot$ the ratio of the waves should be 1:5.0, which is actually found.

In order to get further information on the formation and composition of the cobalt complex several amperometric titrations and gravimetric determinations have been carried out.

The Amperometric Titrations.—Cobalt(II) chloride in 0.2 M aqueous acetate buffer was titrated amperometrically with HR dissolved in 60% acetic acid. The diffusion current of the reagent was measured at an applied potential of −0.6 volt *vs.* S.C.E. The titration curve is plotted in Fig. 3 curve 1. In agreement with Kolthoff and Langer[5] the ratio Co:R in the precipitate at the end-point was found to be exactly 1:4.00. When the titration was carried out in 40% acetic acid, a current passed immediately upon addition of reagent, this current increased linearly with the volume of reagent added until the end-point. After the end-point the increase in current became much greater (curve 2, Fig. 3). Again, the end-point was found at a ratio of Co:R of 1:4.00.

Several titrations were carried out by first precipitating the cobalt as cobaltic hydroxide and dissolving the precipitate in hot acetic acid solution according to Mayer and Feigl's[4] procedure for preparation of the trivalent cobalt acetate. In agreement with Kolthoff and Langer[5] the results were found somewhat variable; in several titrations the ratio Co:R in the precipitate at the end-point varied between 1:3.70 and 1:3.90, indicating that most of the cobalt(III) was reduced to the divalent

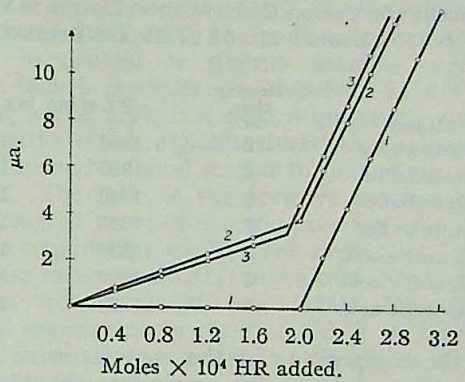

Fig. 3.—Amperometric titration of cobalt with 0.1 M HR in 60% acetic acid at −0.60 volt: (1) 5×10^{-5} M cobalt(II) in 50 ml. of acetate buffer; (2) in 50 ml. of 40% acetic acid; (3) 5×10^{-5} M "cobalt(III)" in 50 ml. of 35% acetic acid.

form upon dissolution in 40% acetic acid. A typical titration curve is plotted in Fig. 3, curve 3.

Amperometric titrations of the reagent with cobalt(II) perchlorate were carried out in AN which was 1 M in acetic acid and 0.1 M in sodium per-

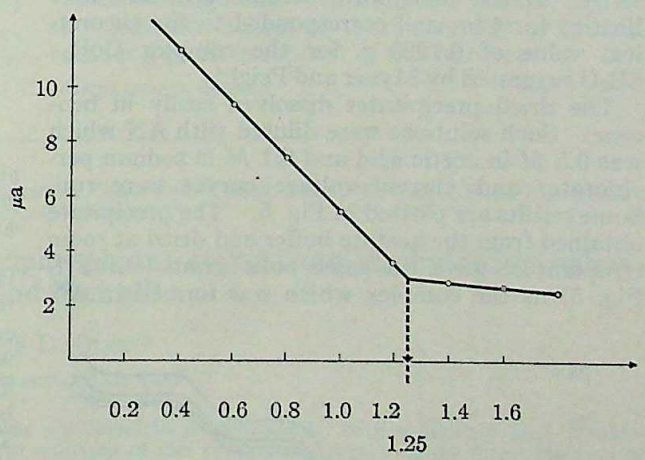

Fig. 4.—Titration of 5×10^{-5} M HR in 50 ml. of acetonitrile which was 1.0 M in acetic acid with 10^{-2} M $Co(ClO_4)_2$ in acetonitrile. Measured at −0.16 volt *vs.* S.C.E.

chlorate. The titrations were carried out at −0.16 volt at which potential the free reagent yields a diffusion current, and the reagent in the complex a very small current only (compare Figs. 1 and 2). A typical titration line is given in Fig. 4. The end-point corresponded again to a ratio of Co:HR of 1:4.00

Gravimetric Determinations.—Several gravimetric determinations were carried out in which cobalt(II) in acetate buffer was partially precipi-

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tated with a 0.1 *M* solution of HR. One hundred per cent. excess of cobalt was present in all experiments. The precipitate was filtered, washed with distilled water, and dried in a vacuum oven at 110°. The weight of the precipitate decreased with time of heating. The results of two experiments are reported in Table II.

TABLE II

WEIGHT OF THE COBALT COMPLEX UPON DRYING IN VACUUM OVEN AT 110°, USING 8 ML. 0.1 *M* HR AND EXCESS COBALT (II)

Medium	Heating time, hr.	Wt. of ppt. in g. a	b
Acetate buffer	2	0.1366	0.1370
Acetate buffer	4	.1350	.1352
Acetate buffer	6	.1340	.1341
Acetate buffer	8	.1325	.1323
40% acetic acid	2	.1226	.1228
40% acetic acid	4	.1222	.1223
40% acetic acid	6	.1223	.1222

If the composition of the complex were $CoR_2 \cdot 2HR$, the weight of the precipitate should be 0.1499 g. assuming quantitative precipitation of HR. If 4 moles of the reagent react with 1 mole cobalt(II) to give a complex of the form $CoR_3 \cdot 2H_2O$, the weight of the complex should be 0.1223 g. As seen from Table II the final weight of the precipitate was between these two values.

The precipitation also was carried out in 40% acetic acid as solvent. The precipitate was filtered and washed with 40% acetic acid. The weight of the precipitate became constant after heating for 4 hr. and corresponded to the theoretical value of 0.1223 g. for the complex $CoR_3 \cdot 2H_2O$ suggested by Myaer and Feigl.[4]

The dried precipitates dissolved easily in benzene. Such solutions were diluted with AN which was 0.5 *M* in acetic acid and 0.1 *M* in sodium perchlorate, and current–voltage curves were run. Some results are plotted in Fig. 5. The precipitate obtained from the acetate buffer and dried at room temperature gave the same polarogram (curve 1, Fig. 5) as the complex which was formed in AN

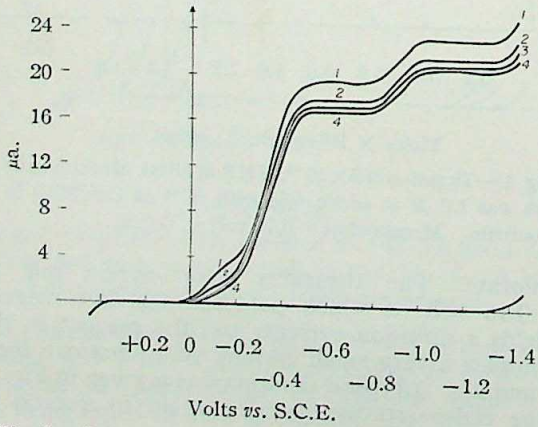

Fig. 5.—Current–voltage curves of 4×10^{-4} *M* Co-complex in acetonitrile which was 0.1 *M* in $NaClO_4$ and 0.5 *M* in acetic acid: (1) precipitate dried at room temperature; (2) dried 2 hr.; (3) 4 hr.; (4) 8 hr.

(Fig. 2). However, on drying, the first wave of the reagent wave decreased markedly. The decrease of the height of the total reagent wave corresponded to the decrease of the prewave. The ratio i_{d_2}/i_{d_1} decreased from 1:4.99 (air-dried) to 1:4.33 after 8 hr. drying at 110°.

The current–voltage curve of the dried complex prepared in 40% acetic acid is plotted in Fig. 6, curve 2. This polarogram does not exhibit a prewave. The ratio i_{d_2}/i_{d_1} was found to be 1:4.02, indicating that the composition of the complex corresponds to $Co(III)R_3$. After precipitation in 40% acetic acid the filtrate was shaken out with benzene and the extract diluted with AN. The polarogram of this solution is plotted in curve 3 of Fig. 6. The height of this wave was 3.8 μa. while the height of the reagent wave in $Co(III)R_3$ was 15.9 μa. (curve 2). The sum of the two is 19.7 μa. and exactly equal to the total height of the total reagent wave in the complex prepared in dilute acetate buffer (curve 1). This agreement, combined with the

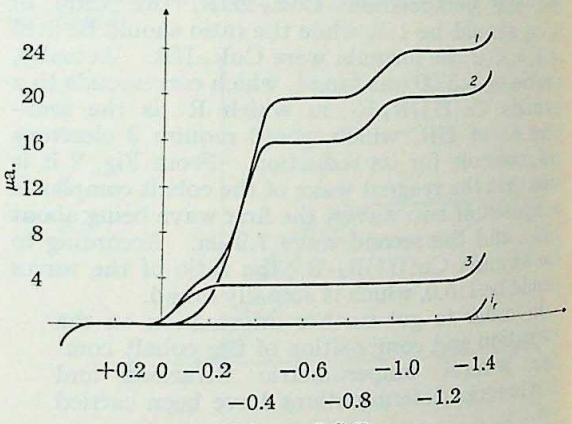

Fig. 6.—(1) Current–voltage curves of 4×10^{-4} *M* Co-complex in acetonitrile; (0.5 *M* in acetic acid and 0.1 *M* in sodium perchlorate); (2) of 4×10^{-4} *M* complex, prepared in 40% acetic acid; (3) of extract of the 40% acetic acid filtrate.

fact that the wave in curve 3 occurs in the same potential region as the prewave in curve 1, allows the conclusion that the prewave is given by the species which is soluble in 40% acetic acid. This was confirmed by preparing a complex from dilute acetate buffer and extracting it with hot 40% acetic acid. The resulting complex now gave a polarogram identical with that in curve 2 (Fig. 6) instead of that in curve 1, while the soluble species after extraction gave a wave identical with curve 3.

Composition and Formation of Cobalt Complexes with HR.—On the basis of the experimental results presented in the previous section it is possible to present the equations of formation and the composition of cobalt complexes with HR. The precipitate obtained from an acetate buffer is evidently not a pure compound and contains some "coprecipitated reagent." This "coprecipitated reagent" is soluble in warm 40% acetic acid. After extraction of the precipitate with 40% acetic acid its formula is $Co(III)R_3$. This compound is obtained directly when the precipitation is carried out in 40% acetic acid as was

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indicated by the results of polarographic and gravimetric experiments and amperometric titrations.

The precipitate obtained from dilute acetate buffer contains cobalt and reagent in the molecular ratio 1:4.00. After extraction with 40% acetic acid this ratio becomes 1:3.00 ($Co(III)R_3$). The extracted reagent requires only 3 electrons per molecule in its reduction, while HR requires 4 electrons. This is strong evidence that the extra molecule of reagent is a free radical, denoted as $H_2R\cdot$, which is an intermediate and stable product formed in the reduction of HR

$$HR + H^+ + e^- \longrightarrow H_2R\cdot$$

It is not plausible to assume that the precipitate in dilute acetate buffer is formed by the sequence of reactions

$$Co(II) + HR \longrightarrow Co(III) + H_2R\cdot \quad (1)$$

$$Co(III) + 3HR \longrightarrow Co(III)R_3 + 3H^+ \quad (2)$$

$$Co(III)R_3 + H_2R\cdot \longrightarrow CoR_3\cdot H_2R\cdot \quad (3)$$

In amperometric titrations of cobalt(II) with the reagent in acetate buffer and in the reverse titration it was found that at any stage of the titration before and after the end-point the over-all composition of the precipitate corresponded to 1:4.00. In 40% acetic acid the reaction ratio in both types of titration also was at any stage 1:4.00, although the precipitate had the composition $Co(III)R_3$. Finally, from the identical polarographic behavior in AN of the precipitate formed from dilute acetate buffer and of the reaction product obtained by mixing cobalt(II) and HR in AN, and also from amperometric titrations in AN it appears impossible that the formation of the final reaction product occurs by the sequence of reactions 1 and 2. It is postulated that this sequence of reactions accounts for the observed results

$$Co(II) + 2HR \longrightarrow Co(II)R_2 + 2H^+ \quad (4)$$

$$2Co(II)R_2 \longrightarrow Co(III)R_3 + H_2R\cdot + Co(II) \quad (5)$$

The cobalt(II) complex formed according to eq. 4 is transformed rapidly in acid medium. In dilute acetate buffer $H_2R\cdot$ is insoluble and coprecipitates with $Co(III)R_3$. In 40% acetic acid $H_2R\cdot$ is soluble and only $Co(III)R_3$ precipitates. In AN both $Co(III)R_3$ and $H_2R\cdot$ are soluble.

As stated by Ilinski and v. Knorre[1] and confirmed in this Laboratory $Co(II)R_2$ precipitates on mixing cobalt(II) with the sodium salt of the reagent in neutral or slightly alkaline medium. When such a precipitate is dissolved in AN containing acetic acid, it should disproportionate according to eq. 5. Qualitatively the polarogram should be and is found similar to that of curve 1 in Fig. 6. The ratio of the prewave to that of the total reagent wave minus the prewave was found 1:4, as required by eq. 5. The ratio of i_{d_2} (cobalt wave, in this case Co(III) and Co(II)) to i_{d_1} (total reagent wave) should be 1:3.00. Actually in several experiments a ratio of 1:2.97 ± 0.03 was found, in excellent agreement with the postulated interpretation.

The gravimetric data (Table II) and Fig. 5 indicate that coprecipitated $H_2R\cdot$ can be volatilized more or less completely in a vacuum oven at 110°. The reason why Mayer and Feigl[4] could obtain such good results is not because they first oxidized cobalt from the divalent to trivalent state, but because they carried out the precipitation in fairly concentrated acetic acid medium in which $H_2R\cdot$ is soluble.

Acknowledgment.—Appreciation is expressed to the Graduate School of the University of Minnesota for a grant in support of this research.

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM RESEARCH AND DEVELOPMENT DEPARTMENT, WESTVACO CHLOR-ALKALI DIVISION, FOOD MACHINERY AND CHEMICAL CORPORATION]

The Synthesis of Tetrakis-(dichloromethylphosphine)-nickel from Methyldichlorophosphine and Nickel[1a]

BY LOUIS D. QUIN[1b]

RECEIVED FEBRUARY 23, 1957

The reaction of bulk nickel with methyldichlorophosphine was found to proceed readily to give high yields of tetrakis-(dichloromethylphosphine)-nickel. This represents the first synthesis of this type of compound by the direct reaction of nickel and a trivalent phosphorus compound. A small amount of a black unidentified solid adhering to the residual nickel is also formed. Similar conditions were not effective for causing phosphorus trichloride or phenyldichlorophosphine to react with nickel. The properties of tetrakis-(dichloromethylphosphine)-nickel were in general similar to those of related compounds.

Several compounds of the type $Ni(PY_3)_4$ have been prepared in recent years by the reaction of nickel tetracarbonyl[2-5] or other $Ni(PY_3)_4$ compounds[2,3] with trivalent phosphorus compounds. Their preparation by the direct reaction of nickel with phosphorus compounds has not yet been successful, although evidence of a reaction has been obtained with phosphorus trichloride.[2] Phosphorus trifluoride showed no reaction with nickel.[3,6] We now wish to report the facile synthesis of the new compound tetrakis-(dichloromethylphosphine)-nickel, $Ni(CH_3PCl_2)_4$ (I), by the reaction of methyldichlorophosphine and elemental nickel.

The reaction has been affected by several tech-

(1) (a) Portions of this paper report work done under contract with the Chemical Corps, U. S. Army, Washington 25, D. C. (b) Department of Chemistry, Duke University, Durham, N. C.
(2) J. W. Irvine, Jr., and G. Wilkinson, *Science*, **113**, 742 (1951).
(3) G. Wilkinson, THIS JOURNAL, **73**, 5501 (1951).
(4) G. Wilkinson, *Z. Naturforsch.*, **9b**, 446 (1954).
(5) L. Malatesta and A. Sacco, *Ann. chim.*, **44**, 134 (1954).
(6) J. Chatt and A. A. Williams, *J. Chem. Soc.*, 3061 (1951).

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niques, the best of which involves refluxing methyldichlorophosphine through a column packed with bulk nickel as turnings or wire. Under these conditions, the reaction proceeds relatively rapidly, as large surface area of nickel can be exposed to the methyldichlorophosphine. The product is very soluble in methyldichlorophosphine and accumulates in the pot; it is isolated by vacuum distillation of the unreacted methyldichlorophosphine and recrystallization of the residue. The pot temperature provides a good indication of the extent of reaction; the operation has generally been stopped when the temperature has risen from the boiling point of pure methyldichlorophosphine (81–82°) to 102–104°. Beyond this point, the solution becomes so concentrated in I that its crystallization commences; any material deposited on the walls of the flask is decomposed on continued heating. The conversion of methyldichlorophosphine to I at the usual stopping point is about 60–70%; the yields based on either consumed methyldichlorophosphine or nickel exceed 90%. With equipment properly sized for a charge of 250 g. of methyldichlorophosphine, a production rate of I of 40–50 g. per hour has been obtained. This rate is dependent primarily on the amount of nickel in the column.

Another technique for conducting this reaction involves merely refluxing methyldichlorophosphine in a flask containing nickel. In this case the reaction of a given amount of methyldichlorophosphine is considerably slower than that in the column. The product of this reaction appears to be less pure than that obtained by the column reaction. We have also found that Raney nickel will react with methyldichlorophosphine at room temperature to produce I, but this method of preparation has not been explored in detail.

In the preparation of I, bulk nickel slowly acquired a light powdery coating of an unidentified black by-product II which contains Ni, Cl and P (and probably C and H). There was no evidence of this coating decreasing the rate of production of I. That II was not an intermediate in the formation of I was shown by the fact that a small residue of II remained when a sample of nickel was completely consumed by prolonged refluxing with methyldichlorophosphine.

Compound I was found to be attacked readily by oxygen. When solutions of I were exposed to air or oxygen, precipitation of tan solids commenced immediately. These solids have not yet been sufficiently investigated to permit their identification. A report[2] on $Ni(PCl_3)_4$ implies instability of its solutions on exposure to air also.

Compound I reacted readily with phenyldichlorophosphine to affect replacement of all CH_3PCl_2 groups. The $Ni(C_6H_5PCl_2)_4$ so produced was of high purity; it melted at a temperature slightly higher than that previously reported.[5] In general other properties of I were similar to those of related compounds and are described in the Experimental section.

Attempts were made to apply the most favorable conditions for preparing I to the direct synthesis of $Ni(PCl_3)_4$ and $Ni(C_6H_5PCl_2)_4$. After prolonged refluxing of phosphorus trichloride and phenyldichlorophosphine through nickel-packed columns, there was no indication of a reaction and not a trace of the corresponding nickel complex could be isolated. The reduced availability of the electron pair on the phosphorus atom in these cases may be of importance in interpreting their lack of reactivity. Further study of the structural requirements of trivalent phosphorus compounds for undergoing the reaction with elemental nickel is contemplated.

Experimental[7]

Preparation of $Ni(CH_3PCl_2)_4$ (I).—A 1.8 cm. i.d. heated column with a 37-cm. section packed with 258 g. of chopped nickel turnings of average size 0.4 mm. × 5 mm. × 6 mm. was attached to a flask containing 274 g. (2.34 moles) of CH_3PCl_2. The top of the column was fitted with a reflux condenser. The system was flushed with nitrogen before the reaction and protected from the atmosphere thereafter. The CH_3PCl_2 was then boiled (81–82°) at a rate slightly below that causing flooding in the column. A yellow color developed in the pot after a few minutes; the nickel was noticeably blackened after 1–2 hr. operation. The pot temperature rose slowly at first and then rapidly as the relative change in content of solute (I) with respect to solvent (CH_3PCl_2) became greater. After 6 hr., the pot temperature had reached 100° and the reaction was stopped. On cooling, large crystals of I formed in the pot. The residual CH_3PCl_2 was removed by vacuum distillation. The crude I so obtained weighed 198 g. (0.376 mole). The conversion from CH_3PCl_2 charged was 64.3%. In the distillation there was recovered 88.2 g. (0.754 mole) of CH_3PCl_2; the yield of I from CH_3PCl_2 consumed was therefore 94.6%. The nickel packing was found to have lost 24.5 g. (0.417 mole); the yield of I based on this value was 90%. The crude I was recrystallized from dry diethyl ether or *n*-pentane at about −50° in the absence of air.

Anal. Calcd. for $C_4H_{12}Cl_8NiP_4$: C, 9.13; H, 2.30; Cl, 53.89; Ni, 11.2; P, 23.5. Found: C, 8.77; H, 2.35; Cl, 54.46; Ni, 11.2; P, 23.7.

Isolation and Properties of Black Ni–CH_3PCl_2 Product (II).—The nickel from an experiment such as that above was washed twice with dry, air-free *n*-pentane to remove residual I and CH_3PCl_2. The nickel was dried in a stream of nitrogen and transferred to a bottle. The bottle was shaken vigorously to cause detachment of the black coating on the nickel. The powder so obtained was removed through a sieve. Analysis of two different samples of II gave the following inconclusive data: Cl, 26.0 and 33.1; Ni, 49.1 and 33.8; P, 12.9 and 18.0, respectively. II was insoluble in all solvents investigated. It had no melting point but released a small amount of a volatile substance above 100°. No attempt has yet been made to identify this substance other than to ascertain that it is not CH_3PCl_2. II did not react with CH_3PCl_2 on prolonged refluxing in the presence or absence of nickel, indicating it not to be an intermediate in the formation of I. II has occasionally shown ferromagnetic properties, but this is possibly due to the presence of some elemental nickel.

Properties of $Ni(CH_3PCl_2)_4$. (a) **Thermal Stability.**—At room temperature, I appeared relatively stable when protected from the atmosphere, although it developed a strong CH_3PCl_2 odor. In a capillary, I slowly blackened over the range 170–185°; no melting point was observed. A 6.8-g. sample of I was heated to 240° in 15 minutes. There distilled 4.5 g. of dark blue liquid, which was redistilled to remove the trace of colored impurities. The liquid was found to be almost pure CH_3PCl_2 (74% yield) by its infrared spectrum. The pyrolysis flask was partially mirrored with nickel. The rest of the residue was a black powder, partly soluble in water.

(b) **Solubility.**—I was very soluble in organic solvents. The solutions were relatively stable at room temperature when protected from the atmosphere; at elevated temperatures, decomposition generally occurred to give dark brown or green mixtures. I was insoluble in cold water, though a slow reaction occurred over a period of several days to give a green solution. With boiling water, a green

(7) All melting points are uncorrected.

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solution rapidly resulted; no solid separated on cooling. Similarly, the lower alcohols appeared to dissolve I with reaction on boiling. Hot sodium hydroxide (2 *N*) and ammonium hydroxide (concd.) rapidly gave dark brown mixtures with I.

(c) **Reaction with Oxygen.**—Most solutions of I deposited a light tan solid unless carefully protected from oxygen. When air was purposely passed for one hour through a solution of 1.49 g. of I in 25 ml. of *n*-pentane at room temperature, precipitation of the solid commenced immediately and a thick slurry resulted. The solid was recovered by filtration and washed with benzene. It weighed 0.30 g. Reliable analytical data have not yet been obtained for this compound. It was soluble in water (solution strongly acid) and alcohols and insoluble in organic solvents. It did not melt but darkened at a high temperature. Pentane-soluble products of the oxidation were not examined. Exposure of solid I to the atmosphere results in partial conversion to a pentane-insoluble solid which may be similar to the material described above.

(d) **Reaction with Phenyldichlorophosphine.**—A solution of 6.0 g. (0.0114 mole) of I in 40 g. (0.22 mole) of phenyldichlorophosphine was agitated at 70–80° at 35 mm. for 3 hr. CH_3PCl_2 replaced and volatilized was collected in a trap chilled by a bath of Dry Ice and trichloroethylene. The trap was found to contain 5.1 g. of pure CH_3PCl_2. This recovery represented 96% of theory. Excess phenyldichlorophosphine was removed by vacuum distillation of the orange reaction product, leaving an oil which readily crystallized. This residue was washed with *n*-pentane to remove residual phenyldichlorophosphine and then recrystallized from diethyl ether. The recovery of bright yellow product was rather low (57% yield) due to its great solubility in the solvent. It is believed the true yield of $Ni(C_6H_5PCl_2)_4$ was nearly quantitative. The product melted at 91–94°; since the reported value is 86.5°,[5] the solid was recrystallized again. It then melted at 93–94° after sintering at 91–92°. Analysis indicated it to be high purity $Ni(C_6H_5PCl_2)_4$.

Anal. Calcd. for $C_{24}H_{20}Cl_8NiP_4$: Cl, 36.6; Ni, 7.58; P, 16.0. Found: Cl, 36.4; Ni, 7.40; P, 15.9.

Acknowledgment.—The assistance of Donald C. Frokjer and Charles H. Rolston in performing some of the experimental work is acknowledged. Analyses were performed by Dr. Raymond Annino and his associates, of this Laboratory, and by the Schwarzkopf Microanalytical Laboratory, Woodside, New York.

[Contribution from the Department of Chemistry, The University of Texas]

Kinetic Studies of Thiourea Derivatives. II. The Dimethylthioureas[1]

By William H. R. Shaw and David G. Walker

Received February 11, 1957

unsym-Dimethylthiourea isomerizes in aqueous solutions at elevated temperatures to form dimethylammonium thiocyanate. Experimental first-order rate constants for this reaction under a variety of conditions have been obtained. The isomerization is *p*H independent over a wide range and no effect of ionic strength was observed. At high *p*H, however, a complicating parallel reaction takes place. The behavior of *sym*-dimethylthiourea also has been examined. This compound decomposes to form methylamine and methyl isothiocyanate as primary products. Additional reactions by the product species occur. Rate constants and Arrhenius parameters for the isomerization of *unsym*-dimethylthiourea and for the decomposition of the symmetrical derivative are reported. All of the findings are discussed in terms of a possible mechanism.

Introduction

A few papers[2,3] on the chemistry of the dimethylthioureas have recently become available, but no work concerned with the kinetic behavior of these compounds could be found in the literature. Since data on both symmetrical and unsymmetrical dimethylthiourea would be of obvious value in any theoretical interpretation of the relative reactivity of thiourea derivatives, the present[4–7] study was undertaken.

Experimental

Apparatus and Technique.—The apparatus and technique used in the kinetic runs have been described in detail in earlier publications.[5–7]

Analytical Methods.—Ammonium, methylammonium and dimethylammonium ions were separated from the reaction mixture by passing the experimental solution through a cation-exchange column as previously described. Elution was effected by 20 ml. of 0.1 *N* NaOH, at the usual flow rate. This slight modification was necessary to ensure quantitative elution of the dimethylamine. After elution aliquots of the neutralized elutriate were used to determine ammonia,[5] methylamine[7] and dimethylamine[8] by spectrophotometric analyses described in detail elsewhere.

The ammonia analysis was not affected by dimethylamine in the concentrations encountered. As previously reported, however, methylamine exerted a moderate interference but suitable corrections could be made.

The methylamine analysis was unaffected by the ammonia and dimethylamine concentrations prevailing in the reaction mixtures. The dimethylamine analysis was similarly uninfluenced by ammonia and methylamine.

Thiocyanate ion was determined spectrophotometrically as before.[6] No significant interference by ammonia, methylamine, dimethylamine or the dimethylthioureas was encountered.

The average deviation of a set of 12 analyses of 0.3 m*M* dimethylamine was 7.0%. The average deviations for the other analyses have been reported in earlier work.

Compounds.—*sym*-Dimethylthiourea (1,3-dimethyl-2-thiourea) was prepared by the addition of methylamine to methyl isothiocyanate.[9] The product was separated as an oil from water solution twice and then finally crystallized, m.p. 64° (lit.[10] 61°) from benzene which had been partially distilled to remove the last traces of moisture.

Anal. Calcd. for $C_3H_8N_2S$: C, 34.6; H, 7.79; N, 26.9. Found: C, 34.8; H, 7.78; N, 27.0.

unsym-Dimethylthiourea (1,1-dimethyl-2-thiourea) was prepared by the addition of H_2S to dimethylcyanamide.[11]

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(1) Presented before the Division of Physical and Inorganic Chemistry, 131st National Meeting of the American Chemical Society held in Miami, Florida, April, 1957.

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(4) Related work from this Laboratory on urea (ref. 5), thiourea (ref. 6) and methylthiourea (ref. 7) has been reported previously.

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(9) E. C. Horning, Ed., "Organic Syntheses," Coll. Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1955, pp. 617–618.

(10) M. Freund and E. Asbrand, *Ann. Chem. Justus Liebigs*, **285**, 170 (1895).

(11) C. Willgerodt, *ibid.*, **34**, 1899 (1899).

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The product was twice crystallized from water solution, m.p. 158° (lit.[11] 159°).

Anal. Calcd. for $C_3H_8N_2S$: C, 34.6; H, 7.79; N, 26.9. Found: C, 34.5; H, 7.78; N, 26.6.

Results

The rates of formation of four possible reaction products: (1) thiocyanate ion, (2) ammonia, (3) methylamine, and (4) dimethylamine were followed; corresponding empirical first-order rate constants: k_1, k_2, k_3 and k_4 were calculated by the initial rate equation presented before.[7]

The decomposition of *sym*-dimethylthiourea in water solution at elevated temperatures gave methylamine as one reaction product. Carbon oxysulfide also was formed. No thiocyanate, ammonia or dimethylamine could be detected by our rather sensitive analytical techniques. If these products were formed at all, the empirical constants: k_1, k_2 and k_4 characterizing their rate of formation at 100° must be less than: 10^{-10} sec.$^{-1}$, 10^{-9} sec.$^{-1}$ and 10^{-9} sec.$^{-1}$, respectively. Consequently the only rate constants reported for this compound are based on the rate of methylamine formation divided by two. At 100.0 ± 0.1° for reaction times varying from 6.75 to 24.0 hr. the numerical value for k_3 was found to be $2.50 \pm 0.16 \times 10^{-7}$ sec.$^{-1}$. This value was obtained with average *sym*-dimethylthiourea concentrations ranging from 19.4 to 992 mM in solutions that were also 0.005 M in H_2SO_4. Thus, in acidic media, the empirical first-order constant, k_3, was found to be independent of average *sym*-dimethylthiourea concentration, $\bar{u}$, and reaction time, t. Consequently the decomposition of this compound can be regarded as a first-order reaction producing methylamine and carbon oxysulfide as ultimate products in acid solution.

In neutral and alkaline media more complex behavior was observed (Fig. 1), and a faint precipitate of mercuric sulfide was detected at *p*H 9.1 by our usual test. The amount of precipitate increased with increasing *p*H. These findings are analogous to results reported with methylthiourea.[7] Thus the *p*H dependence of k_3 in basic solutions can be rationalized by postulating the occurrence of a significant amount of reverse reaction (synthesis of reactant from products); and the formation of sulfide can be explained by assuming the onset of a base-catalyzed parallel reaction (see Discussion).

Runs were also made at different temperatures (Table IA) and in acid media of varying ionic strength. Samples initially 40 mM in *sym*-dimethylthiourea and 12 mM in H_2SO_4 were subjected to a reaction time of 16.8 hr. at 100°. These samples also contained added sodium sulfate ranging in concentration from 0.00 to 0.50 M. No salt effects were encountered.

unsym-Dimethylthiourea was studied in a similar fashion. Two reaction products: thiocyanate and dimethylamine were found in all reaction mixtures. The empirical constants k_1 and k_4 based on these products were independent of $\bar{u}$, t and *p*H (Fig. 2) over a wide range. These findings are in sharp contrast to results noted above with *sym*-dimethylthiourea. The behavior of k_1, however, is similar to that of analogous constants obtained with methylthiourea and thiourea. No conversion of thiocyanate to ammonia was observed in the low *p*H range. This conversion has been noted before; but, because the increased reactivity of *unsym*-dimethylthiourea made a shorter reaction time possible, this reaction was not important in the present work. No methylamine was detected in any of the experimental solutions. At *p*H 12.6, however, ammonia was observed ($k_2 = 38 \times 10^{-7}$ sec.$^{-1}$), the rate of dimethylamine production increased ($k_4 = 54 \times 10^{-7}$ sec.$^{-1}$), and a strong positive test for sulfide ion was obtained. Neither ammonia nor sulfide ion was detected in solutions of lower *p*H. All of these results point, as in previous work, to the onset of a base-catalyzed parallel reaction that produces ammonia and dimethylamine in equimolar amounts.[12] In acid media, neutral solutions, and solutions up to *p*H 11.4, however, k_1 and k_4 were extremely well behaved constants. At 100 ± 0.1° the numerical values for k_1 and k_4 were: $16.7 \pm 1.5 \times 10^{-7}$ sec.$^{-1}$ and $16.9 \pm 1.20 \times 10^{-7}$ sec.$^{-1}$, respectively. The fact that $k_1 = k_4$ within experimental error over this wide range of conditions established the stoichiometry of the reaction rather rigidly. Moreover, a neutral 42.6 mM solution of *unsym*-dimethylthiourea when heated for 90 hours at 127° gave the

TABLE I

RATE CONSTANTS[c,d] OBTAINED AT VARIOUS TEMPERATURES

Temp., °C. ±0.1	$\bar{u}$[a]	t[b]	$k_1 \times 10^7$, sec.$^{-1}$
A. *sym*-Dimethylthiourea soln. 0.015 M in HNO_3			
99.6	307	2.93	1.90
100.0	90.8	6.55	2.23
110.0	45.5	6.17	8.10
110.0	93.3	3.07	7.88
120.0	22.7	4.58	28.8
120.0	31.0	2.98	30.1
130.0	9.08	3.62	91.1
130.1	9.33	2.85	108
140.0	9.08	2.78	246
140.0	4.67	2.67	210
B. *unsym*.-Dimethylthiourea soln.			$k_1 \times 10^7$, sec.$^{-1}$
79.5[e]	199.3	12.6	1.44
80.0	99.9	5.83	1.52
90.0[e]	24.9	6.00	5.16
90.0	99.4	6.15	5.68
100.0[e]	24.8	2.90	17.4
100.0	29.4	5.97	20.3
109.5[e]	24.4	2.78	57.2
109.6	9.3	5.85	69.3
119.9	4.35	3.78	230
120.0[e]	9.11	2.40	227

[a] $\bar{u}$ is the average concentration of the dimethylthiourea (mmoles/liter). [b] t is reaction time in hours. [c] The constant k_2 is based on the rate of production of methylamine divided by two. The constant k_1 is based on the rate of production of thiocyanate. [d] For the least squares Arrhenius analysis values representing an average of all data available at 100.0° were substituted for the values at 100° in the above table. [e] These runs were made in 0.015 M HNO_3 solution.

thiourea when heated for 90 hours at 127° gave the

(12) This reaction is probably a fairly complex hydrolytic reaction that involves *unsym*-dimethylurea and/or dimethylcyanamide as intermediates. A related reference is cited below.[13]

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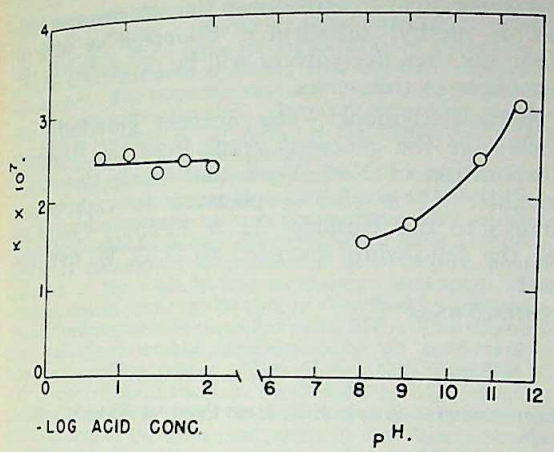
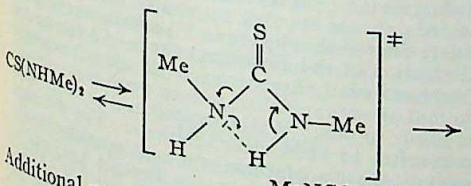


Fig. 1.—Empirical first-order rate constant obtained with *sym*-dimethylthiourea as a function of acid concentration. The constant k_3 is based on the rate of formation of methylamine divided by two. Runs above *p*H 7 were made in buffered 0.071 *M* borax solutions. Results recorded below *p*H 7 were made in H_2SO_4 solutions. All solutions were initially 0.040 *M* in *sym*-dimethylthiourea. Reaction times were 16.83 hours for the high *p*H run and 24.0 hours for the low *p*H run. All measurements were made at 100°.

following analysis: thiocyanate, 42.3 ± 0.5 m*M*; dimethylamine, 39 ± 3 m*M*. Thus, like thiourea, the synthesis of the parent compound from the decomposition products in aqueous media must be very slight. In the absence of solvent, however, equilibrium mixtures of *unsym*-dimethylthiourea and dimethylammonium thiocyanate have been reported[13] to contain 16.9% *unsym*-dimethylthiourea and 80.4% dimethylammonium thiocyanate at 130°. In summary, then, the decomposition of *unsym*-dimethylthiourea is a first-order reaction producing dimethylammonium thiocyanate. The decomposition[14] is not catalyzed by hydrogen or hydroxide ions and is unaffected by ionic strength. Rate constants for this reaction at different temperatures also were obtained (Table I).

Discussion

By analogy to previous work[6] a plausible reaction mechanism for *sym*-dimethylthiourea can be written as



$$MeNCS + MeNH_2 \quad (1)$$

Additional reactions by the products include

$$MeNCS + H_2O \longrightarrow MeNH_2 + COS\uparrow \quad (2)$$

$$MeNH_2 + H^+ \rightleftharpoons MeNH_3^+ \quad (3)$$

$$MeNCS + MeNH_2 \longrightarrow CS(NHMe)_2 \quad (4)$$

In acid solution the experimental rate constant, k_3, is presumably the result of reaction 1 followed quickly by reactions 2 and 3. Reaction 4 does not occur, being suppressed by the rapid occurrence

(13) H. Salkowski, *Ber.*, **26**, 2497 (1893).

(14) The hydrolytic reaction[12,15] is, however, catalyzed by hydrogen ions.

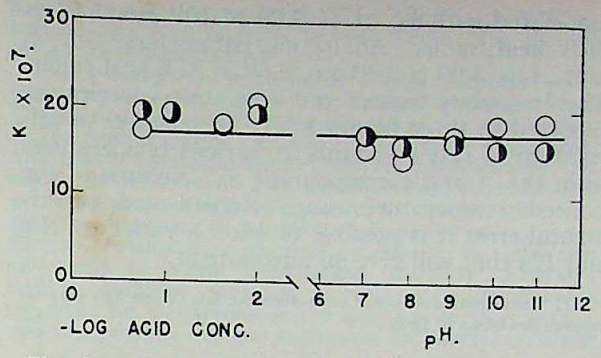
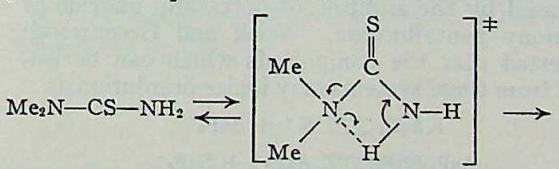


Fig. 2.—Empirical first-order rate constants obtained with *unsym*-dimethylthiourea as a function of acid concentration. The constants k_1 (O) and k_4 (◑) are based on the rate of formation of thiocyanate and dimethylamine, respectively. Runs above *p*H 7 were made in buffered 0.008 *M* borax solutions. Results recorded below *p*H 7 were made in HNO_3 solutions. An initial concentration of 42.7 m*M* *unsym*-dimethylthiourea was used with reaction times of 5.47 hours on the acid side and 4.17 hours on the high *p*H side. All data were collected at 100°.

of reactions 2 and 3. In neutral and basic solutions, however, reaction 4 does take place. In alkaline media, a parallel base-catalyzed reaction, producing H_2S and an unstable fragment[15] which further decomposes to yield methylamine, is also present.

A similar mechanism for *unsym*-dimethylthiourea would predict two primary reaction products produced in equimolar amounts



$$Me_2NH + HNCS \quad (5)$$

Also

$$HNCS \longrightarrow H^+ + NCS^- \quad (6)$$

$$Me_2NH + H^+ \rightleftharpoons Me_2NH_2^+ \quad (7)$$

No significant synthesis (reverse of reaction 5) is possible in aqueous media since HNCS is a strong acid. The rate constants (Fig. 2) are, consequently, *p*H independent.

The absence of methylamine in *unsym*-dimethylthiourea reaction mixtures and the lack of dimethylamine in *sym*-dimethylthiourea reaction solutions is strong experimental proof that the methyl groups do not migrate during reaction. Thus all products can be predicted by assuming intramolecular hydrogen transfer and dissociation of the activated complex as indicated (reactions 1 and 5).

Over the temperature range studied, the rate constants for the decompositions of the dimethylthioureas follow the simple Arrhenius relationship. A least squares analysis of the data presented in Table I gave the following Arrhenius parameters[16]

(15) Perhaps a carbodiimide is formed which undergoes further reaction with the solvent. See for example: H. G. Khorana, *Chem. Revs.*, **53**, 145 (1953).

(16) These parameters will reproduce the rate constants in Table IA within the average deviation at 3%.

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associated with k_3: $A = 3.69 \times 10^{14}$ sec.$^{-1}$, $E = 36.3$ kcal./mole. Analogous parameters[17] for k_1 are: $A = 3.90 \times 10^{14}$ sec.$^{-1}$, $E = 34.6$ kcal./mole. The frequency factors and activation energies are reported to three figures solely for purposes of calculation of rate constants at various temperatures from the A and corresponding E. Because of the limited temperature range studied and experimental error it is possible to select a variety of A's and E's that will give an adequate fit.

(17) These parameters will reproduce the k_1's (Table IB) with an average deviation of 10%.

A theoretical discussion of the relative reactivities of methyl substituted thioureas as well as other thiourea derivatives will be presented in the last paper of this series.

Acknowledgment.—The authors gratefully acknowledge the generous grant from the Research Corporation of New York that made this study possible. It is also a pleasure to express our thanks to the Humble Oil & Refining Company for the fellowship awarded to D. G. W. this past year.

AUSTIN, TEXAS

[CONTRIBUTION NO. 409 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND COMPANY]

Fluoroarsenites

BY E. L. MUETTERTIES AND W. D. PHILLIPS

RECEIVED MARCH 21, 1957

The interactions of several inorganic fluorides with arsenic trifluoride were examined and a physical characterization of some of these systems was made. Some monovalent fluorides formed solids of the composition $MAsF_4$. The stability of these fluoroarsenites appeared to be inversely related to the polarizing power of the cation. Dissociation of the fluoroarsenites was very high in the fused state, and in arsenic trifluoride solution they underwent rapid fluorine exchange. The existence of the tetrafluoroarsenite anion in melts and in solution could therefore not be established by n–m–r data. A bridged structure is suggested for the antimony pentafluoride complex: $F_4Sb(F)_2AsF_2$.

Introduction

The conductivity of arsenic trifluoride is greatly increased by the addition of potassium fluoride or antimony pentafluoride. Woolf and Greenwood[1] suggested that the compounds which can be isolated from these systems may ionize in solution as

$$KAsF_4 \rightleftharpoons K^+ + AsF_4^-$$

$$AsF_3 \cdot SbF_5 \rightleftharpoons AsF_2^+ + SbF_6^-$$

This present study was undertaken to gain a more general understanding of the behavior of arsenic trifluoride toward inorganic fluorides and an attempt also was made to determine the structure of the complex fluorides obtained from some of these systems.

Experimental

Materials and Apparatus.—Arsenic trifluoride was stored in contact with sodium fluoride and was distilled (b.p. 60.3° (760 mm.)) prior to use. Commercial samples of the alkali metal and thallous fluorides were used. These fluorides all totaled at least 98% metal and fluorine after vacuum drying at 100–250°. Baker and Adamson antimony pentafluoride was distilled before use. Matheson tank boron trifluoride was stored over sodium fluoride to remove any traces of hydrogen fluoride.

Dissociation pressures were determined in an isoteniscope. With this apparatus, cathetometer readings of the manometer had a precision of ±0.5 mm. which proved to be much better than the reproducibility of the actual dissociation pressures of various samples. The fluorine magnetic resonance spectra were obtained using a Varian high resolution n–m–r spectrometer and electromagnet[2] at a frequency of 30 Mc. and a magnetic field of 7,500 gauss. Spectra were calibrated in terms of displacements in cycles per second (c.p.s.) from the fluorine resonance of CF_3COOH. Positive frequency displacements indicate resonances occurring at lower fields than the fluorine resonance of CF_3COOH. Calibration was accomplished by superimposing an audio-frequency on the sweep field to produce side band peaks to the CF_3COOH resonance.[3]

Preparation of Fluoroarsenites.—The fluorides of potassium, rubidium, cesium and thallium all reacted spontaneously and quite exothermally with arsenic trifluoride. Because the products of these reactions had limited solubility in arsenic trifluoride, the fluoroarsenites were prepared in pressure vessels at 80° to ensure complete reaction. Three hour reaction periods proved satisfactory for quarter-mole quantities of the metal fluoride; a 300% excess of arsenic trifluoride was used. The products, which were slurries, were filtered and the solids were recrystallized from arsenic trifluoride.

Anal. Calcd. for $KAsF_4$: K, 20.6; As, 39.4; F, 40.0. Found: K, 19.91; As, 39.21; F, 39.45. Calcd. for $CsAsF_4$: Cs, 46.8; As, 26.4; F, 26.8. Found: Cs, 47.3; As, 26.96; F, 27.06. Calcd. for $TlAsF_4$: Tl, 57.6; As, 21.1; F, 21.4. Found: Tl, 57.61; As, 21.59; F, 20.61.

Lithium and sodium fluorides did not react with arsenic trifluoride. Treatment of these fluorides with liquid arsenic trifluoride at temperatures up to 160° in pressure vessels yielded only the starting materials. Analyses of the solid products showed that less than 1% arsenic was present.

Characterization of the Fluoroarsenites.—All the fluoroarsenites were extremely hygroscopic: 30 seconds exposure to fairly humid air was sufficient to turn tenth-gram quantities of the solids to oils. Water reacted exothermally with the fluoroarsenites to yield clear solutions. The F^{19} magnetic resonance spectra of these solutions consisted solely of a rather broad resonance in the fluoride ion region. There was no evidence for a fluoroarsenite ion, *e.g.*, AsF_4^- or $AsOF_2^-$, in aqueous solution, but such an ion could be present in very low concentration and in equilibrium with fluoride and arsenite ions.

Saturated solutions of the fluoroarsenites in arsenic trifluoride at 30° contained 2% K, 6% Rb, 8% Cs and 11% Tl, respectively. Such solutions had a F^{19} magnetic resonance spectrum that consisted of a single resonance, shifted slightly from that of arsenic trifluoride toward a position denoting higher shielding: δ for AsF_3 = 1050 c.p.s. and δ for $KAsF_4$ in AsF_3 = 1025 c.p.s. The absence of two or

(1) A. A. Woolf and N. N. Greenwood, *J. Chem. Soc.*, 2200 (1950).

(2) Varian Associates, Palo Alto, California.

(3) J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).

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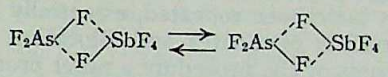
more resonances indicated that fluorine exchange was taking place in this system. (Exchange phenomena of sufficiently high frequency have been shown capable of collapsing a two-line spectrum into a single, concentration-dependent resonance.[4]) The exchange rate was too fast to be "frozen out" by cooling the solutions. It was therefore not possible to establish whether F^- or AsF_4^- is the major conducting species in arsenic trifluoride solution.[5]

The F^{19} magnetic resonance spectrum of a melt of $KAsF_4$ consisted of a single rather broad resonance at +940 c.p.s. The tetrafluoroarsenite anion is isoelectronic with selenium tetrafluoride and thus may be expected to have a trigonal bipyramid structure. The absence of structure in the spectrum of the melt is due to fluorine exchange. The exchange mechanism may be simply described by a dissociation of the fluoroarsenite into AsF_3 and MF. This dissociation was demonstrated tensimetrically at temperatures below the melting points. The dissociation pressures at 100° ranged from 0.18 atm. for $KAsF_4$ to 0.07 atm. for $CsAsF_4$. Equilibria were attained slowly. Because of slight etching of the glass equipment by the fluoroarsenites at 100°, the dissociation pressures are considered to be approximate values.

Covalent Fluorides.—Nuclear magnetic resonance spectra of binary systems of covalent fluorides and arsenic trifluoride were examined in an attempt to gain structural information. Samples were prepared by condensing the fluorides in 5 mm. o.d. Pyrex tubes which were then sealed. Approximately equimolar quantities of the fluorides were used except where excess arsenic trifluoride was necessary to prevent solid formation.

Although boron trifluoride slightly increases the conductivity of arsenic trifluoride, no evidence for interaction of these two liquids was obtained at temperatures up to ~ −10° or between liquid arsenic trifluoride and gaseous boron trifluoride up to 30°. The characteristic resonances of the components were observed. Woolf and Greenwood[1] have suggested the possibility of an unstable $AsF_2^+BF_4^-$ compound in such mixtures but the n–m–r data give no support to this suggestion.[6]

The F^{19} magnetic spectrum of arsenic trifluoride–antimony pentafluoride consisted of a single resonance peak. The position of the peak was between the resonance positions of the pure fluorides and was concentration dependent. Any type of compound formed between the antimony and arsenic fluorides would have non-equivalent fluorines and would present two or more peaks in the fluorine spectrum. Absence of structure in the spectrum is attributed to a rapid fluorine exchange (low temperature did not slow the rate sufficiently to permit a structural analysis). Although lacking conclusive evidence, a bridge-type structure is suggested for this system in the liquid state since such a structure provides a simple mechanism for fluorine exchange



A bridge structure is supported by related data. Bridge-type structures have been cited as intermediates for fluorine exchange in halogen fluorides.[7] Antimony pentafluoride appears to have bridge-bonding[8] and a bridge intermediate has been proposed for chlorine exchange between antimony (III) and antimony(V).[9] It should be noted that a simple coördination complex $F_5Sb–AsF_3$ is not acceptable as an intermediate for exchange since dissociation of such a complex would not involve cleavage of As–F or Sb–F bonds.

(4) H. S. Gutowsky and A. Saika, *J. Chem. Phys.*, **21**, 1688 (1953).

(5) Although the fluoroarsenites are undoubtedly composed of M^+ and AsF_4^- aggregates in the solid state, it does not necessarily follow that the tetrafluoroarsenite anion is the major anion in AsF_3 solution. The equilibrium for AsF_4^-(soln) ⇌ AsF_3 + F^-(soln) may be far to the right.

(6) It should be noted that an $AsF_2^+BF_4^-$ intermediate could be present to concentrations involving approximately 5% of the total fluorine and not be detected. However, if this intermediate is present, rapid equilibration between the components and the intermediate does not occur. Rapid equilibration would yield a single F^{19} resonance rather than the observed, non-perturbed resonances of the components.

(7) E. L. Muetterties and W. D. Phillips, This Journal, **79**, 322 (1957).

(8) E. L. Muetterties and W. D. Phillips, manuscript in preparation.

(9) H. M. Neumann and H. Brown, This Journal, **78**, 1843 (1956).

Wilmington 98, Del.

[Contribution from the University of California, Los Alamos Scientific Laboratory]

Di-*t*-butylberyllium and Beryllium Hydride[1]

By E. L. Head, C. E. Holley, Jr., and S. W. Rabideau

Received December 6, 1956

Methods are described for the preparation of pure di-*t*-butylberyllium and for the preparation of beryllium hydride (approx. 80 wt. %) by the pyrolysis of both pure di-*t*-butylberyllium and its etherate. Pure di-*t*-butylberyllium is a clear, colorless, mobile liquid with a density of 0.65 g./cc. and a freezing point of −16°. When freshly prepared it has a vapor pressure of about 35 mm. at 25°; on standing it undergoes slow decomposition at room temperature with the evolution of isobutene. Beryllium hydride prepared by pyrolysis of di-*t*-butylberyllium has a density of about 0.57 g./cc., evolves hydrogen slowly at 190 to 200° and rapidly at 220°, is relatively inert to laboratory air, and reacts slowly with water and rapidly with acid. It was analyzed by chemical and microscopic methods. It gave no X-ray pattern.

Introduction

The preparation of beryllium hydride has been announced by a number of workers. In view of the apparently tenuous nature of some of the published results, the present authors, with others,[2] have investigated these procedures in considerable detail. Attempts to prepare beryllium hydride by heating beryllium in atomic hydrogen by the method of Pietsch[3] were unsuccessful. A surface reaction between excess lithium hydride and beryllium chloride in ether solution was observed as described by Wiberg and Bauer,[4] but separation of the product, which contained organic material, from the excess lithium hydride could not be accomplished and analysis was not possible. There seems to be little direct evidence for identifying this material as beryllium hydride.

(1) This work was done under the auspices of the Atomic Energy Commission.

(2) Some 30 staff members of this Laboratory have contributed to the program to a greater or lesser extent. In addition to procedures mentioned here, preparation of beryllium hydride was attempted by many other methods, including direct combination of the elements under various conditions, reduction of inorganic salts and reduction of beryllium alkyls with various reducing agents. Los Alamos Scientific Laboratory report LA-1660, "The Preparation of the Hydrides of Magnesium and Beryllium," by C. E. Holley, Jr., and J. F. Lemons, April 1, 1954.

(3) E. Pietsch, *Z. Elektrochem.*, **39**, 577 (1933).

(4) E. Wiberg and R. Bauer, *Z. Naturforsch.*, **6b**, 171 (1951).

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Experiments on the reaction between lithium aluminum hydride and dimethylberyllium in diethyl ether essentially confirm the results of Schlesinger and co-workers.[5] Our best product, out of some 30 preparations, contained 60+% BeH_2,[6] and was contaminated with several per cent. each of lithium hydride and aluminum hydride, or possibly lithium aluminum hydride, and ether, which was the major impurity.

Recently Coates and Glockling[7] reported the preparation of beryllium hydride by the pyrolysis of di-*t*-butylberyllium etherate to give a product containing 71% BeH_2 (96.5 mole %). These experiments have been repeated, essentially confirming the results of Coates and Glockling, and by modifications of the procedure a purer product was obtained. Also, a method for the preparation of ether-free di-*t*-butylberyllium has been developed. These latter experiments are described below along with the results of the determination of some of the properties of the beryllium hydride thus obtained.

Preparation of Di-*t*-butylberyllium Etherate.—The di-*t*-butylberyllium etherate was prepared from *t*-butylmagnesium chloride and beryllium chloride in diethyl ether solution following the directions of Coates and Glockling[7] as closely as possible. The product was analyzed by hydrolysis and found to contain 51 to 52 mole % di-*t*-butylberyllium, the remainder being ether, as compared to 55.4 mole % obtained by Coates and Glockling.

Preparation of Ether-free Di-*t*-butylberyllium.—Attempts to increase the di-*t*-butylberyllium content to higher values according to the directions of Coates and Glockling were unsuccessful. An investigation was then made of the effect on the etherate of etherphilic substances such as $AlCl_3$, BF_3 and $BeCl_2$. The first two gave complicated reactions but treatment with anhydrous beryllium chloride was successful in giving pure di-*t*-butylberyllium. A typical preparation is described below.

In an inert atmosphere (N_2), approximately 7.5 g. of anhydrous $BeCl_2$ and a glass-enclosed iron stirring bar were put into a reaction flask fitted with a stopcock and ground joint for attaching to the vacuum line, and a seal-off constriction and ground joint for introducing the di-*t*-butylberyllium etherate, the latter joint plugged with a rubber stopper. After connecting the flask to the vacuum line, the rubber stopper was removed and the ground joint on the end of a glass ampoule containing approximately 24 g. of di-*t*-butylberyllium etherate (15 g. di-*t*-butylberyllium) was inserted. (These quantities correspond to a 50% excess of $BeCl_2$ if each $BeCl_2$ molecule accepts two ether molecules.) The flask was then evacuated, the stopcock closed, the break-off seal in the end of the ampoule broken, and the di-*t*-butylberyllium allowed to drain into the flask onto the beryllium chloride, the last portion being driven into the reaction flask by heating the ampule with a hair dryer. Upon completion of the transfer the flask was cooled with liquid nitrogen and the ampule and ground joint removed by sealing at the seal-off. This procedure permitted a transfer without exposure to the atmosphere with the possibility of weighing by difference the amount of di-*t*-butylberyllium etherate used.

The contents of the flask were stirred magnetically for several hours at room temperature, usually overnight, after which the stopcock was opened and the contents exposed at room temperature to a −80° trap followed by a −195° trap to collect the volatile constituents. In addition to di-*t*-butylberyllium, some isobutane and isobutene were formed, which were soluble in it but which could be separated from it and collected in the −195° trap by alternate freezing and thawing. Some of this gas may have been present in the original di-*t*-butylberyllium etherate, but some probably was formed during the reaction with beryllium chloride or by subsequent slow decomposition of the ether-free di-*t*-butylberyllium.

The yield of ether-free di-*t*-butylberyllium was about 40% of the amount expected on the basis of the di-*t*-butylberyllium content of the starting material.

A by-product of the treatment with beryllium chloride was a volatile white solid which melted at about 50° and sublimed under vacuum at temperatures just below this. From analysis it was apparently *t*-butylberyllium chloride etherate but it was not otherwise characterized.

Some Properties of Di-*t*-butylberyllium and its Etherate.—Di-*t*-butylberyllium etherate containing 51 to 52 mole % of di-*t*-butylberyllium is a clear, colorless liquid with a density of 0.78 g./cc. Its vapor pressure is a few millimeters at room temperature, and it gave no evidence of decomposition.

The freshly prepared ether-free material is a clear, colorless, mobile liquid with a density of 0.65 g./cc.; and a freezing point of −16°. The freshly prepared material had a vapor pressure of about 35 mm. at 25°. A reliable figure could not be obtained since at room temperature the compound decomposed slowly with the liberation of isobutene and apparently with the polymerization of the remaining liquid. After standing for seven weeks under its own vapor, it could not be distilled quantitatively.

Pyrolysis of Di-*t*-butylberyllium and its Etherate.—When the pyrolysis of di-*t*-butylberyllium etherate was carried out as described by Coates and Glockling,[7] using a closed vessel up to a temperature of 150° and a vacuum at higher temperatures, considerable amounts of ethane were formed and a product containing only 40% BeH_2 was obtained. The pyrolysis was repeated using a vessel equipped with a cold finger maintained at −20°. The di-*t*-butylberyllium was refluxed under vacuum by means of an oil-bath which was slowly raised to 200°. The volatile decomposition products were collected in a liquid nitrogen cold trap and thus prevented from possible reaction with beryllium hydride. The product analyzed 80% BeH_2, the remainder being mostly ether. This is equivalent to 97 mole %, assuming ether to be the only impurity. Between 190 and 200° the loss of hydrogen from the product was detectable, but negligible in 1 hr.; at 220° the hydrogen loss was rapid.

Pyrolysis of ether-free di-*t*-butylberyllium could not be carried out in this apparatus because of its high volatility. Since no ether was present to react with the beryllium hydride, it could be pyrolyzed, first in a closed system until its volatility became negligible, and then under vacuum. In this way a product was obtained which again contained about 80% BeH_2, the impurity probably being unreacted *t*-butyl groups, however, instead of ether.

Vapor phase pyrolysis of pure di-*t*-butylberyllium was attempted by passing it repeatedly through a hot tube. This was not successful. At temperatures between 150 and 210° most of the material passed through the tube and condensed as a liquid of low volatility, and above 210° the beryllium hydride decomposed rapidly.

Analyses.—Samples of di-*t*-butylberyllium and its pyrolysis products were hydrolyzed, and the resulting gases were measured and analyzed with the mass spectrometer. The solutions from the hydrolyses were analyzed for beryllium and chlorine and in the case of the di-*t*-butylberyllium etherate, for magnesium also. A combustion analysis for carbon and hydrogen also was carried out on some of the pyrolysis products using the method of Head and Holley.[8]

Some typical analytical results with a possible interpretation follow.

1. **Hydrolysis of Di-*t*-butylberyllium Etherate.**—A typical sample (weighing approximately 0.6 g.) on hydrolysis was found to contain 36.1% ether, and isobutane and isobutene (4:1 molar ratio) equivalent to 61.7% di-*t*-butylberyllium, or a total of 97.8% of the original sample.

(5) G. D. Barbaras, C. Dillard, A. E. Finholt, T. Wartik, K. E. Wilzbach and H. I. Schlesinger, THIS JOURNAL, **73**, 4585 (1951).

(6) All percentages in this paper refer to per cent. by weight unless otherwise stated.

(7) G. E. Coates and F. Glockling, *J. Inorg. & Nuclear Chem.*, **2**, 253 (1956).

(8) E. L. Head and C. E. Holley, Jr., *Anal. Chem.*, **28**, 1172 (1956).

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Analysis of the hydrolysis solution showed beryllium equivalent to 66.6% di-*t*-butylberyllium or, including the ether, a total of 102.7% of the original sample. On a molar basis the sample was about 51% di-*t*-butylberyllium.

Several points deserve comment. First, isobutene was always evolved on hydrolysis. If its origin is the decomposition of di-*t*-butylberyllium, a corresponding amount of hydrogen should be observed. Although hydrogen was occasionally found, it was not observed in this instance. Second, the discrepancies in material balance are probably within experimental error, since the individual analyses are accurate, at best, to only 1%. It was observed in each of five different preparations that the ether content was slightly less than 50 mole %.

2. **Hydrolysis of Beryllium Hydride Prepared by the Pyrolysis of Di-*t*-butylberyllium Etherate.**—A sample (approximate weight 19 mg.) of the best preparation of beryllium hydride from di-*t*-butylberyllium etherate was found on hydrolysis to liberate hydrogen equivalent to 81% BeH_2. Analysis of the hydrolysis solution showed beryllium equivalent to 79% BeH_2. The check between the beryllium found and the hydrogen observed is within the expected analytical error, so the major impurity is not a beryllium compound and is probably ether. In this sample the hydrolysis gases were not analyzed for ether and isobutane. In other samples both ether and isobutane in varying ratios were found in addition to the hydrogen. The purity of most preparations was between 76 and 80%.

3. **Combustion Analysis of Beryllium Hydride Prepared by the Pyrolysis of Di-*t*-butylberyllium Etherate.**—A sample (weight 33 mg.) on combustion gave CO_2 equivalent to an ether content of 21%. The hydrogen (determined as water) in excess of the stoichiometric amount required for ether corresponded to a BeH_2 content of 76%. Analysis of this material by the hydrolysis procedure also indicated a BeH_2 content of 76%. The ether and BeH_2 calculated in this manner account for 97% of the original sample weight.

4. **Hydrolysis of Di-*t*-butylberyllium.**—Hydrolysis of a sample of the best di-*t*-butylberyllium (weight 225.2 mg.) gave isobutane and isobutene (molar ratio 60:1) equivalent to 101% di-*t*-butylberyllium. (Half as much hydrogen was observed as isobutene.) Analysis of the hydrolysis solution showed an equivalent amount of beryllium (17.5 mg. found, 16.8 mg. expected).

5. **Hydrolysis of Beryllium Hydride Prepared by Pyrolysis of Di-*t*-butylberyllium.**—A sample weighing 17.9 mg. gave, on hydrolysis, hydrogen equivalent to 80.5% BeH_2 and isobutane equivalent to 17.8% di-*t*-butylberyllium, giving a total of 98.3% of the sample. Analysis of the hydrolysis solution showed beryllium equivalent to 99% of the beryllium calculated from the gas analysis (the di-*t*-butylberyllium contributes a minor amount of beryllium to the solution). This is the best sample of beryllium hydride prepared by pyrolysis of ether-free di-*t*-butylberyllium.

Properties of Beryllium Hydride.—The density of the product was estimated from the fact that it sank in liquid ethane at −110°, but floated at lower temperatures. The density of ethane is 0.561 g./cc. at −100°,[9] and the density of the product is estimated to be 0.57 ± 0.02 g./cc. at −110°. Since the product is 97 mole % BeH_2, it is probable that the density of pure BeH_2 would not differ significantly.

Beryllium hydride prepared by pyrolysis is relatively inert to laboratory air. A 26-mg. sample containing 76% BeH_2 gained 0.8 mg. on exposure to laboratory air for eight days and the BeH_2 content decreased to 72%. The product reacts slowly with water but vigorously with dilute mineral acid.

The product prepared from ether-free reagent was not altered by treatment with ethereal $LiAlH_4$.

A microscopic examination of the product prepared from the etherate showed it to be heterogeneous, consisting of optically isotropic grains, with refringence near 1.58, which contained optically anisotropic inclusions with much lower refringence, densely but non-uniformly distributed. The grain size of the inclusions was several tenths of a micron. The two constituents appeared to be present in approximately equal amounts.

X-Ray examination of the product prepared from di-*t*-butylberyllium gave no lines attributable to BeH_2.

Acknowledgments.—The authors wish to express their appreciation to J. F. Lemons for his encouragement and helpful suggestions; C. Apel, A. W. Mosen, and G. Warren for chemical analyses; F. H. Ellinger for X-ray analyses; E. Staritzky for microscopic analyses; and P. Fain, R. Kandel and E. D. Loughran for mass spectrometric analyses.

(9) "Handbook of Chemistry and Physics," 30th ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1948, p. 790.

LOS ALAMOS, N. M.

[CONTRIBUTION FROM THE NATIONAL RESEARCH COUNCIL OF CANADA]

Electrolyte Catalysis. III. The Cleavage of Benzyl Phenyl Ether by Hydrogen Bromide in Nitrobenzene, Chloroform and Carbon Tetrachloride

BY A. V. DRUMMOND AND A. M. EASTHAM

RECEIVED AUGUST 27, 1956

The kinetics of the cleavage of benzyl phenyl ether by hydrogen bromide in nitrobenzene and chloroform have been determined and the effects of five substituted ammonium bromides on the rate of reaction in these solvents examined. The rate of cleavage in carbon tetrachloride solution is negligibly small but is subject to heterogeneous catalysis by several solid salts. Mechanisms are suggested for the cleavage and its catalysis by electrolytes.

Earlier work in this Laboratory[1,2] showed that several reactions involving the cleavage of a C–O bond were catalyzed by electrolytes in non-aqueous solvents. The salts had considerable specificity in their catalytic powers and it was suggested that the electrolyte facilitated the charge transfers which occurred during the reaction.

In order to obtain more information about this type of catalysis, the cleavage of ethers by hydrogen bromide has now been studied. Walvekar, *et al.*,[3] have reported that this reaction is catalyzed by amine salts in carbon tetrachloride and *n*-hexane. It was first necessary to establish the kinetics of the uncatalyzed reaction for, although the similar cleavage by hydrogen iodide is widely used, little work has been done on the mechanism of this type of reaction.[4]

Since cleavage of ethers by hydrogen bromide is much slower than that by hydrogen iodide, benzyl

(1) A. M. Eastham, *J. Chem. Soc.*, 1936 (1952).

(2) A. M. Eastham, E. L. Blackall and G. A. Latremouille, THIS JOURNAL, **77**, 2182 (1955); E. L. Blackall and A. M. Eastham, *ibid.*, **77**, 2184 (1955).

(3) S. P. Walvekar, N. L. Phalnikar and B. V. Bhide, *J. Ind. Chem. Soc.*, **20**, 131 (1943).

(4) R. L. Burwell, *Chem. Revs.*, **54**, 689 (1954).

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phenyl ether was used throughout the work in order to obtain a convenient rate of reaction. The solvents nitrobenzene and chloroform were chosen for their widely different dielectric constants and good solvent properties. The salts used as catalysts were necessarily all bromides in order to avoid uncertainty as to the acid species present.

Experimental

Materials.—Technical nitrobenzene was steam distilled from 2 *N* sulfuric acid, washed with water and dried over calcium chloride. After standing for 12 hr. over phosphorus pentoxide it was filtered and distilled rapidly at *ca.* 10 mm. pressure. The distillate was shaken with dry activated alumina for 8 hr. and filtered before carefully fractionally distilling at *ca.* 5 mm. The product was pale yellow and did not darken on standing over phosphorus pentoxide for 24 hr., $n^{25}D$ 1.5499–1.5500.

C.P. chloroform was shaken with a large amount of calcium chloride. After filtering, it was refluxed over phosphorus pentoxide in an atmosphere of dry nitrogen for 2–3 hr. and was allowed to cool with nitrogen bubbling through. It was then decanted on to fresh phosphorus pentoxide and, after flushing out very thoroughly with nitrogen, was fractionally distilled. The pure chloroform was collected and stored in blackened vessels under nitrogen. The infrared and mass spectra showed no trace of ethanol. After removing the ethanol present in C.P. chloroform it is essential to keep the liquid out of contact with air; accordingly, all vessels were thoroughly flushed out with dry nitrogen before being used with chloroform solutions.

C.P. carbon tetrachloride was passed down silica and alumina columns and was fractionally distilled.

Anhydrous hydrogen bromide was obtained both from a cylinder (The Matheson Co.) and by dropping bromine into dry tetralin. It was stored in solution or in a cold trap at −180°. Benzyl phenyl ether (m.p. 38.9°) was prepared in the usual way[5] from reagent grade phenol and benzyl chloride.

Pyridinium bromide was prepared as previously described.[1] Tri-*n*-butylamine hydrobromide and tetra-*n*-butylammonium bromide were recrystallized from ethyl acetate (m.p. 75.2–75.9° and 117–118°, respectively). Tetra-*n*-propylammonium bromide was recrystallized from ethyl acetate containing 10% absolute ethanol. (*Anal.* Calcd. for $C_{12}H_{28}NBr$: C, 54.15; H, 10.53; N, 5.26; Br, 30.06. Found: C, 54.10; H, 10.58; N, 5.31; Br, 30.09.) Tetraethylammonium bromide was recrystallized from absolute ethanol. (*Anal.* Calcd. for $C_8H_{20}NBr$: C, 45.73; H, 9.59; N, 6.66; Br, 38.03; Found: C, 45.65; H, 9.61; N, 6.70; Br, 38.05.)

Analytical Methods.—Samples of solutions of hydrogen bromide in organic solvents were taken from a buret with the tip held under the surface of 30–40 ml. of aqueous alcohol (60–70% ethanol). They were titrated with standard alkali (brom cresol green indicator) or silver nitrate solution (Ag/AgCl electrode; Fisher Titrimeter). In the latter method alcohol was added during the titration to prevent separation of the solvent. The alkali titration was not affected by small amounts of phenol but the bromide estimation was the more reliable in the presence of appreciable amounts of amine salts.

Kinetics Measurements.—The kinetics of the reaction were determined by measuring the initial rate of consumption of hydrogen bromide. The reaction vessel consisted of a 25-ml. buret fitted with a jacket through which water circulated from a thermostat controlled to within ±0.005°. This buret was sealed to a capillary tube and glass joint with reduced ends, so that it could be filled from the mixing vessel.

Reaction mixtures (30 ml.) were made up in a small flask fitted with a ground joint to take the buret, the solution of ether being in a small sealed bulb. This flask was attached to the elongated buret tip by the ground joint, zero time was taken on breaking the sealed bulb and, after stirring magnetically, the solution was forced up into the reaction buret by nitrogen pressure.

Samples were taken by running out 2 ml. of the solution from the buret. Immediately before sampling, 0.5 ml. of solution was run out and discarded to ensure that the sample came from the main thermostated body of the solution. The first reading was taken after 5 min. and a total of 9 samples was analyzed during the first 5–10% reaction. The initial concentration of hydrogen bromide [HBr] was determined by extrapolating the (straight) line through the experimental points back to zero time. The slope of this line was taken as the initial rate of reaction.

In some experiments in carbon tetrachloride solution a solid salt was placed between two plugs of glass wool at the bottom of the reaction buret. When filling the reaction vessel, all the solution came in contact with the salt. By withdrawing a sample normally, solution which had been standing in contact with the salt was obtained while discarding 2.5 ml. of solution before sampling gave a solution which had had only a short time of contact with the salt. For other experiments with this solvent, the flask in which the reactants were mixed was modified to permit filtering the reaction mixture through sintered glass while forcing it into the buret.

In order to test the quantitative nature of the reaction 22.9 g. of benzyl phenyl ether in nitrobenzene (2.38 *M*) was saturated with hydrogen bromide and left 3 weeks. The solution was extracted with alkali and the phenol estimated by bromide–bromate titration; 6.7 g. of phenol (equivalent to 13.1 g. ether) was found. The organic layer was distilled under reduced pressure yielding 3 fractions: (a) mainly nitrobenzene, (b) 7.9 g. of benzyl phenyl ether, (c) 2.1 g. of high boiling residue. 21 g. (92%) of the original ether was thus found and the remainder was presumed to be in fraction (c). Phenol was therefore formed essentially quantitatively. The other expected product, benzyl bromide, which was detected by its lachrymatory effects, would have distilled in fraction (a) and was not estimated.

Vapor Pressure Measurements.—A modification of the apparatus of Howland, Miller and Willard[6] was used. An all-glass system which could be thoroughly evacuated was constructed and hydrogen bromide was supplied from a cold trap. The solvent was stirred magnetically and surrounded by a water-bath at 10.0 ± 0.06°.

Samples were taken into a sealed, evacuated trap which was attached to the solvent flask by a ground joint. This trap had a calibrated stem in which the volume of solution was measured. The solvent and hydrogen bromide were frozen in liquid nitrogen, the trap removed and excess standard alkali was placed over the sample. After melting, the hydrogen bromide was determined by back titration.

Results

The Reaction in Nitrobenzene at 25.0°.—At least in its initial stages the cleavage of benzyl phenyl ether is second order with respect to the concentration of hydrogen bromide and first order with respect to the concentration of ether. The kinetics of the reaction are expressed by the equation

$$-\frac{d[HBr]}{dt} = k[HBr]^2[C_6H_5OCH_2C_6H_5]$$

in which, at 25°, $k = 0.058 \pm 0.002$ l.^{2} mole^{-2} min.$^{-1}$.

Figure 1 shows the vapor pressure of hydrogen bromide at 10.0° over pure solvent and over solutions of pyridinium, tetra-*n*-propyl- and tetra-*n*-butylammonium bromides. A stable complex MBr·HBr is formed with each salt and these complex salts have distinct "salting-in" effects on the "free" hydrogen bromide in the solution. Within the limits of experimental error, the vapor pressure of hydrogen bromide over solutions of benzyl phenyl ether (up to 0.25 *M*) is the same as that over pure solvent. The salt complex, MBr·HBr, in the ab-

(5) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., London, 1950, p. 67.

(6) J. J. Howland, R. B. Miller and J. E. Willard, This Journal, 63, 2807 (1941).

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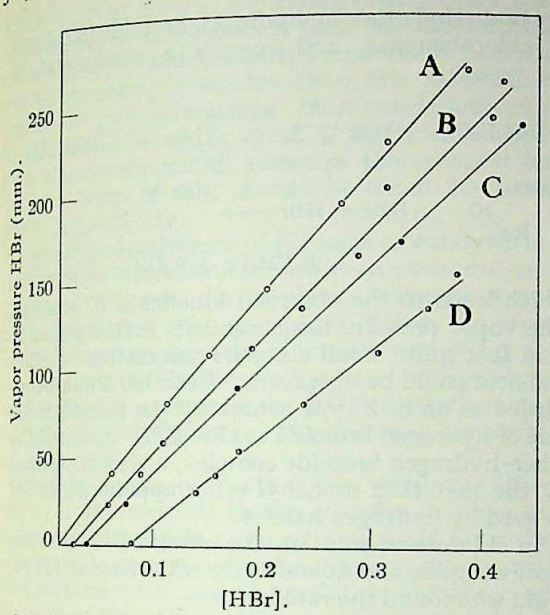

Fig. 1.—Vapor pressure of HBr over nitrobenzene: B, 0.018 *M* tetra-*n*-propylammonium bromide; C, 0.031 *M* pyridinium bromide; D, 0.075 *M* tetra-*n*-butylammonium bromide; A, no added salt.

sence of free HBr reacts only very slowly, if at all, with the ether.

At constant salt concentration the kinetics of the catalyzed cleavage of the ether have the same form as before, *i.e.*

$$-\frac{d[HBr]}{dt} = k'[HBr]^2[C_6H_5OCH_2C_6H_5]$$

where [HBr] is taken as the concentration of hydrogen bromide, outside the MBr·HBr complex. The dependence of k' on the electrolyte concentration is shown in Fig. 2. The catalytic effects of the five salts increase in the order: $C_5H_5NHBr \cong n\text{-}Bu_3NHBr < n\text{-}Bu_4NBr < n\text{-}Pr_4NBr < Et_4NBr$.

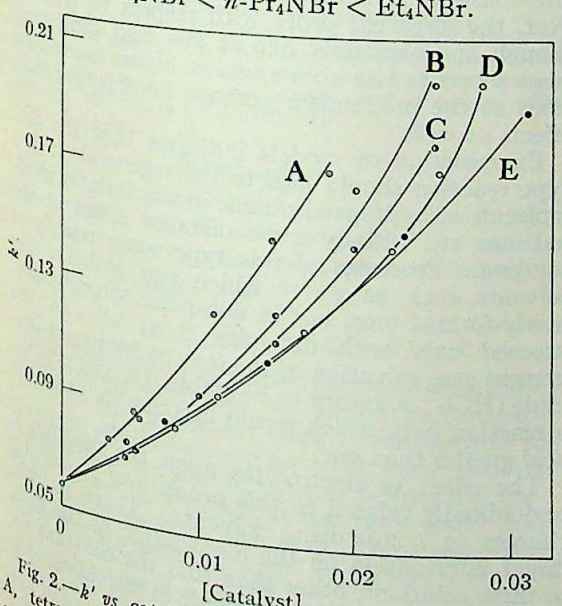

Fig. 2.—k' *vs.* catalyst in nitrobenzene; ether = 0.35 *M*: A, tetra-ethylammonium bromide; B, tetra-*n*-propylammonium bromide; C, tetra-*n*-butylammonium bromide; D, tri-*n*-butylammonium bromide; E, pyridinium bromide.

Water, ethanol and phenol also catalyze the reaction. Phenol, a product of the reaction, is less active than the other compounds and did not cause significant error in the initial rate measurements.

Reaction in Chloroform at 40.0°.—The cleavage is much slower in chloroform than in nitrobenzene and experiments were therefore done at a higher temperature. Initial rates for the uncatalyzed reaction were again first order with respect to the concentration of ether but showed a complex dependence of the initial rate upon the initial concentration of hydrogen bromide. It was impossible, with the experimental method used, to maintain a fixed and reproducible initial concentration of hydrogen bromide, so the initial rates were corrected to a chosen standard concentration of hydrogen bromide. The corrections, which very rarely exceeded 5–10%, were made on the basis of curve A in Fig. 3. The "standard" concentration

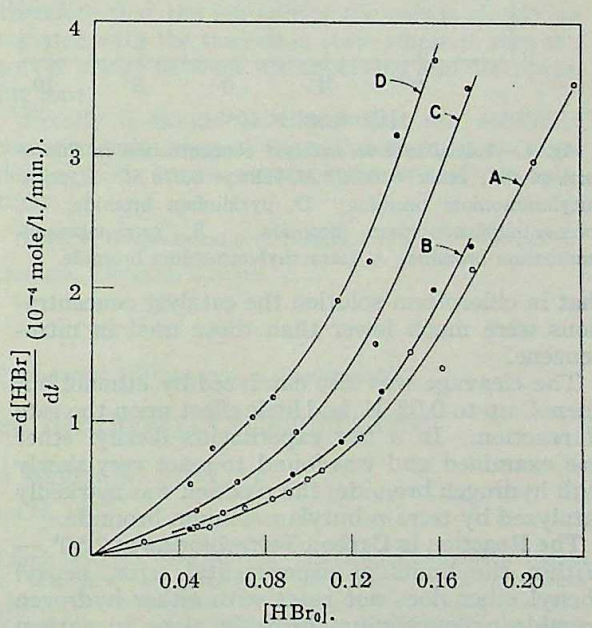

Fig. 3.—Initial rate *vs.* HBr concentration in chloroform; ether = 0.367 *M*, all salts 3.03×10^{-4} *M*: A, no added salt; B, tri-*n*-butylammonium bromide; C, pyridinium bromide; D, tetra-*n*-propylammonium bromide.

of hydrogen bromide was chosen to lie in the most accurate region of the rate *vs.* [HBr] curve. Similar corrections were applied to the results of Fig. 4 on the basis of the experiments of Fig. 3.

In the presence of a constant amount of a catalyst the cleavage is again a complex function of the concentration of hydrogen bromide as is shown by curves B, C and D of Fig. 3. Experiments in which the concentration of hydrogen bromide was varied also were performed using constant amounts of tetraethylammonium and tetra-*n*-butylammonium bromides as catalysts but the results were too close to those for tetra-*n*-propylammonium bromide to be shown on the graph. At a fixed concentration of hydrogen bromide the initial rate of reaction varies linearly with the amount of catalyst up to 10^{-3} *M* (Fig. 4). The five salts increased in catalytic activity in the order *n*-Bu_3NHBr < PyHBr < *n*-Bu_4NBr < *n*-Pr_4NBr < Et_4NBr. It may be noted

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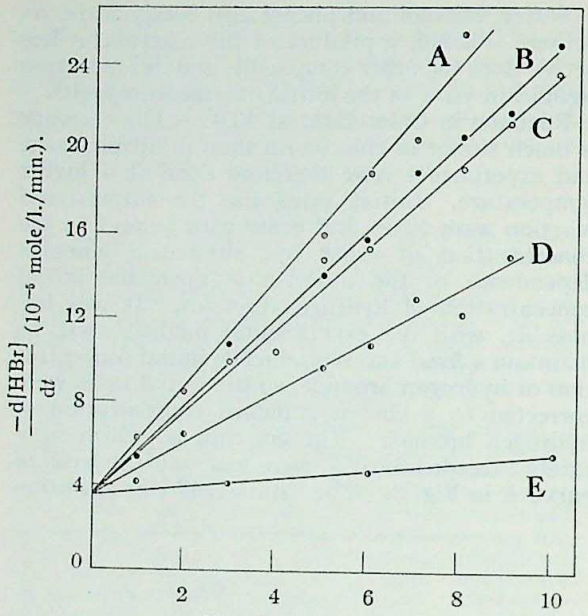

Fig. 4.—Initial rate *vs.* catalyst concentration in chloroform at 40°; ether = 0.367 *M*, HBr = 0.076 *M*: E, tri-*n*-butylammonium bromide; D, pyridinium bromide; C, tetra-*n*-butylammonium bromide; B, tetra-*n*-propylammonium bromide; A, tetraethylammonium bromide.

that in chloroform solution the catalyst concentrations were much lower than those used in nitrobenzene.

The cleavage was also catalyzed by ethanol but phenol, up to 0.02 *M*, had little effect upon the rate of reaction. In a few experiments diethyl ether was examined and was found to react very slowly with hydrogen bromide; the reaction was markedly catalyzed by tetra-*n*-butylammonium bromide.

The Reaction in Carbon Tetrachloride at 2.50°.—Within the limits of experimental error, benzyl phenyl ether does not react with either hydrogen bromide or pyridinium bromide alone in carbon tetrachloride. However, solid pyridinium bromide, which is insoluble in carbon tetrachloride solutions of hydrogen bromide or of benzyl phenyl ether, catalyzes the cleavage of the ether by hydrogen bromide. After stirring a solution of ether and hydrogen bromide with pyridinium bromide for $^1/_2$ hr. and then filtering, the filtrate did not react further but a considerable amount of the hydrogen bromide had reacted during the stirring. The insoluble salts LiBr, NaBr, KBr, NH_4Br, Me_4NBr, LiCl, NaCl, KCl, Na_2SO_4 and K_2SO_4 behave similarly to pyridinium bromide but glass surfaces do not act catalytically. Very finely divided sodium chloride (*ca.* 15 m.²/g.) is a more powerful catalyst than an ordinarily ground specimen. There can be little doubt that in all these experiments in carbon tetrachloride the cleavage of the ether occurred on the surface of the solid salt.

Discussion

The results obtained in nitrobenzene are in agreement with those of Mayo, *et al.*,[7] for the cleavage of diethyl ether by hydrogen bromide in toluene or chlorobenzene, and suggest a mechanism of the type

$$R_1CH_2OR_2 + HBr \overset{K}{\rightleftharpoons} R_1CH_2(R_2)O\cdots\cdots HBr \quad (1)$$

$$R_1CH_2(R_2)O\cdots\cdots HBr + HBr \xrightarrow{k_1} R_1CH_2Br + R_2OH + HBr \quad (2)$$

which leads to the observed kinetics if K is small. The vapor pressure measurements indicate that K is in fact quite small since no association of ether and acid could be observed. Reaction 2 can be regarded as an S_N2 type attack by the second molecule of hydrogen bromide at the $-CH_2-$ group of the ether–hydrogen bromide complex, a view supported by the fact that diphenyl ether apparently is not cleaved by hydrogen halides.[8]

In chloroform solution the observed kinetics are more complex and do not agree with those of Mayo, *et al.*, who found the rate law

$$-\frac{d[HBr]}{dt} = k[HBr]^{3/2}[ether]^{1/2}$$

for the cleavage of diethyl ether. In the present work the apparent order with respect to acid increases with concentration, an effect not due to polymeric molecules of hydrogen bromide since Henry's law is obeyed.[6]

One must suppose that the mechanism suggested for reaction in nitrobenzene would also apply to some extent in chloroform. It seems possible, however, that the ether–hydrogen bromide complex may also decompose in a unimolecular fashion since Hart and Eleuterio[9] have observed retention of configuration in the cleavage of α-phenylethyl phenyl ether by hydrogen chloride in solvents of low dielectric constant and high acid concentration. However, the apparent order with respect to HBr although approximately one at low acid concentrations seems to rise above two at higher concentrations so the mechanism perhaps involves medium effects as well.

Examination of models indicates that the S_N2 type reaction should lead to the regeneration of a molecule of hydrogen bromide in which the individual ions are initially some distance apart in the solution. Processes of this type occur readily in solvents such as water which can stabilize the newly-formed ions, but in non-polar solvents they proceed only with difficulty if at all. In the present case solvation of the ions by hydrogen bromide (HCl_2^- is known to be stable[10]) might provide a reaction path which would account for orders in acid greater than one.

The effect of electrolytes upon the reaction is undoubtedly related to this problem of separating charges in non-ionizing solvents. There is little direct information on the dissociation of the salts in these solutions, other than that the constant for tetra-*n*-butylammonium bromide in nitrobenzene is

(7) F. R. Mayo, W. B. Hardy and C. G. Schultz, This Journal, **63**, 426 (1941).

(8) W. Hoffmeister, *Ber.*, **3**, 347 (1870).

(9) H. Hart and H. S. Eleuterio, This Journal, **76**, 1379 (1954).

(10) H. C. Brown, T. Dickenson and J. Weinstein, *ibid.*, **76**, 4046 (1954).

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1.6×10^{-2} at 25°.[11] By analogy with other systems, however, it is apparent that the constants for tetra-*n*-propyl- and tetraethylammonium bromide will be successively smaller than this value while those for pyridinium and tri-*n*-butylammonium bromides will be of the order of 10^{-4}. In chloroform the corresponding values of the constant for the two types of salts should be about 10^{-9} and 10^{-14}, respectively.

Since the effectiveness of the salts as catalysts increases with decreasing dissociation constant and dielectric constant, the catalysis probably is not due to free ions in solution. Also, it does not seem to result from an increase in the activity of the reactants since the "salting in" of the hydrogen bromide indicates a decrease in activity which is not likely to be outweighed by an increase in the activity of the ether.

The equilibrium of reaction 1 in which the ether and hydrogen bromide form a complex involves an increase in the dipole moment associated with the HBr and the presence of other ions and dipoles will tend to increase K and so accelerate the observed cleavage of the ether. However, it is doubtful if such an increase in K would account for more than a small part of the catalysis. Walvekar, *et al.*,[12] found no correlation between the values of K for different ethers and their rates of cleavage as measured by Ghaswalla and Donnan.[13] However, the very slow cleavage of diethyl ether in chloroform is markedly catalyzed by tetra-*n*-butylammonium bromide. Since diethyl ether certainly forms an oxonium complex much more readily than benzyl phenyl ether, it must be stage 2 of the reaction, cleavage of the complex, which is significantly affected by the catalyst.

It seems then that the catalysis is due to the ion pairs in solution accelerating the rate of cleavage of the C–O bond, a process which probably is closely related to the heterogeneous catalysis observed in carbon tetrachloride. The catalysis by ionic crystals is of such a general nature that it must be due primarily to the electrical inhomogeneity of the crystal surface but in solution specific ion effects must be of considerable importance because the catalytic activities of the salts do not seem to be related to the dipole moments. It seems probable therefore that the ion pair of the salt is closely associated with the transition state where it acts as a sort of bridge between the appearing and disappearing ions.

Finally it should be noted that our solubility measurements suggest that Walvekar, *et al.*, were dealing with heterogeneous systems and not solutions.

(11) C. R. Witschonke and C. A. Kraus, THIS JOURNAL, **69**, 2472 (1947).

(12) S. P. Walvekar, N. L. Phalnikar and B. V. Bhide, *J. Univ. Bombay*, **11A**, Pt. 5, 69 (1943).

(13) R. P. Ghaswalla and F. G. Donnan, *J. Chem. Soc.*, 134 (1936).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Studies of Some Methyl-substituted Benzhydryl Carbonium Ions

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The behavior of the following methylbenzhydrols in 100% sulfuric acid has been studied: 2,2′,3,4,5,6-hexamethylbenzhydrol, 2,2′,4,6-tetramethylbenzhydrol and 3-methylbenzhydrol. The first two compounds gave fairly stable carbonium ions; the last gave a less stable and more reactive carbonium ion. The properties were investigated utilizing *i*-factors, ultraviolet and near-visible spectra, titration studies, and chemical studies, all using sulfuric acid. Evidence for the steric effect of three *ortho*-methyl groups and the "buttressing" effect of methyl groups in the 3- and 5-positions of the hexamethylbenzhydryl carbonium ion is discussed.

Introduction

It has been shown that many benzhydrols[1-4] ionize in 100% sulfuric acid to give stable carbonium ions. The ionization can be represented as

$$(C_6H_5)_2CHOH + 2H_2SO_4 \longrightarrow (C_6H_5)_2\overset{+}{C}H + 2HSO_4^- + H_3O^+ \quad (1)$$

Actually benzhydrol is rather unstable in sulfuric acid and undergoes rapid polymerization and sulfonation.[1] In the present work it was desired to find out the effect of certain methyl-substitutions on the formation and stabilization of benzhydryl carbonium ions. In addition, it had been noted that benzhydryl carbonium ions with two or less *ortho*-methyl substituents formed benzhydryl ethers, while those with four *ortho*-methyl substituents formed benzhydrols when poured into water. It was therefore of interest to ascertain the behavior of such ions when three *ortho*-methyl substituents were present.

(1) C. M. Welch and H. A. Smith, THIS JOURNAL, **72**, 4748 (1950).
(2) M. S. Newman and N. C. Deno, *ibid.*, **73**, 3644 (1951).
(3) V. Gold and F. L. Tye, *J. Chem. Soc.*, 2172 (1952).
(4) H. A. Smith and R. G. Thompson, THIS JOURNAL, **77**, 1778 (1955).

Results

i-Factors.—Table I gives the *i*-factors as extrapolated to zero time for the compounds studied. For the hexamethyl and tetramethyl compounds, solution was rapid, and the first *i*-factors could be determined within 10 or 15 minutes after addition of the benzhydrol to the sulfuric acid. The freezing points slowly changed as sulfonation took place. The *i*-factor of approximately 4.0 obtained by extrapolation to zero solution time is that expected for ionization according to eq. 1. For 3-methylbenzhydrol, however, solution in the sulfuric acid was very slow, for an insoluble polymer was formed which dissolved slowly as sulfonation occurred

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TABLE I

CHARACTERISTICS OF BENZHYDROLS IN SULFURIC ACID

Benzhydrol	Color in sulfuric acid	Initial i-factors (extrapolated)	% Yield Methyl ether	M.p., °C.[a]	Methyl ether analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2,2′,3,4,5,6-Hexamethyl	Red-brown	3.9	65[c]	69.5–70.1	85.05	85.60	9.28	9.12
2,2′,4,6-Tetramethyl-	Red-purple (iridescent)	3.9–4.0	64[d]	61.7–62.2	84.99	84.94	8.72	8.69
3-Methyl-	Red-brown (with polymer)	5.0–5.1[e]	0	(Polymer; no methyl ether isolated)				

[a] Melting points were taken on an aluminum melting point block and are uncorrected. [b] Analyses were done by Galbraith Microanalytical Laboratories, Knoxville, Tennessee. [c] Based on the crude compound. [d] Based on the purified product; the crude product was an oil and not weighed. [e] Obtained by extrapolation of the slow sulfonation curve.

After five or six hours, complete solution was achieved, and i-factors could be determined. Extrapolation of these slowly increasing values to zero solution time gave the figure of 5.0 recorded in Table I. Polymerization gives lower values and sulfonation gives larger values. The polymerization reaction can be represented for benzhydrol as

$$(n + 2)(C_6H_5)_2CHOH + (n + 3)H_2SO_4 \longrightarrow C_6H_5\overset{+}{C}HC_6H_4[CH(C_6H_5)C_6H_4]_n\ CH(C_6H_5)_2 + (n + 2)H_3O^+ + (n + 3)HSO_4^- \quad (2)$$

The i-factor would be $(2n + 6)/(n + 2)$ for dissolved polymer if no sulfonation occurred. For dimerization, $n = 0$, and $i = 3.0$. For dimerization and monosulfonation of two rings the i-factor would be 5.0. After this sulfonation complete solution should be achieved, with further sulfonation occurring rather slowly. Higher polymers with more extensive sulfonation could also give i-factors around five.

Chemical Studies. Methyl Ether Preparations.—The preparation of alkyl ethers from benzhydryl carbonium ions, as described later, is not only an important synthetic method, but gives excellent confirmation that the sulfuric acid solutions actually contain carbonium ions. The ordinary acid-catalyzed etherification of a highly methylated carbinol would yield essentially no ether in the reaction times used.

The yields are given in Table I for the methyl ethers prepared. Both polymethylated-benzhydrols gave the methyl ethers. However only a polymeric material melting at 150–160° and a small amount melting at 200–210° could be obtained from the 3-methylbenzhydrol.

Reactions of Carbonium Ions with Water.—It has been demonstrated that four *ortho*-methyl groups on a benzhydryl carbonium ion are sufficient to prevent the formation of the bis ether.[1,4] Both hexamethyl- and tetramethylbenzhydrol have three *ortho*-methyl groups and therefore are sterically hindered so that formation of the bis ether is prevented. The original carbinol is obtained when the sulfuric acid solution is added to water.

A solution obtained by adding 0.25 g. of 2,2′,3,4,5,6-hexamethylbenzhydrol to 18 g. of 100% sulfuric acid and stirring for one minute was poured into an ice–water mixture. A 96% yield of the original carbinol (identified by mixed melting point) was obtained. The solution of the same benzhydrol which had stood for 21 hours in the process of cryoscopic determinations was also poured into an ice–water mixture to give a product which was completely water soluble and was not identified.

A solution obtained by the addition of 0.25 g. of 2,2′,4,6-tetramethylbenzhydrol to 18 g. of 100% sulfuric acid was stirred for one minute and then poured into an ice–water mixture to give a 100% yield of the original carbinol which was identified by mixed melting point. The solution from a 24-hr. cryoscopic run was poured into water to give an essentially clear solution.

Six solutions of 3-methylbenzhydrol in 100% sulfuric acid solution (generally in the ratio of 1 g. of benzhydrol per 100 g. of acid) were allowed to stand for times of from 10 seconds to 15 minutes and subsequently poured into ice–water mixtures. Yellow gums with different melting ranges between 130 and 250° were obtained. For one gum, some softening was noted at 50° which is close to the melting point of 3-methylbenzhydrol. The solution from a 27 hour cryoscopic run when poured into an ice–water mixture gave a clear solution. Yields of 46–90% for the gums indicate that rapid sulfonation must have occurred to give water-soluble products. This material probably gives a protonated species initially, but this undergoes a rapid reaction with undissolved benzhydrol to give a polymer which is not very soluble in sulfuric acid. Subsequently, the polymer is slowly sulfonated and is finally completely dissolved. No conditions were found where any bis ether was obtained when the sulfuric acid solution was poured into ice-water. Only polymeric materials and the original carbinol were found in the water-insoluble products. The yellow polymeric gums could be separated into two portions by extraction with ligroin, methanol or ethanol. A small fraction of insoluble, brittle material melted over the range of 180–250°, while the large fraction of soluble material melted between 130–160°.

Titrations to Form Carbonium Ions.—Titrations of the compounds dissolved in an inert solvent and water mixture using 96% sulfuric acid were made to obtain the relative stabilities from the minimum

TABLE II

TITRATION TO FORM CARBONIUM IONS WITH SULFURIC ACID

Compound	Wt. of cpd., g.	Min. % acid for visible color
2,2′,3,4,5,6-Hexamethylbenzhydrol	0.05	62.4
2,2′,4,6-Tetramethylbenzhydrol	.05	65.0
	.05	68.7
3-Methylbenzhydrol	.05	71.2
Benzhydrol	.05	72.0
Benzhydrol	.01	65.6
Benzhydrol	.25	47.7
2,2′,4,4′,6,6′-Hexamethylbenzhydrol	.05	

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percentage of sulfuric acid necessary for the permanent appearance of the characteristic carbonium ion color. The procedure has been described previously.[4] It was found in the present work that a suitable choice of concentration is needed to achieve satisfactory reproducibility. Reducing the concentration of the carbinol one-fifth did not affect the results appreciably whereas increasing the concentration fivefold gave very low results. Temperature control during titration is also necessary. Titration results are shown in Table II.

Experimental

Factors.—The apparatus, technique and solvent for the cryoscopic measurements have been described previously.[1,5] Trial runs using triphenylcarbinol as the solute gave values of 4.02 and 3.96. Since the rates of possible side reactions, such as sulfonation, increase with increasing temperature, it is very important that the temperature of the solutions used remain as low as possible. The range actually encountered was 7–14°. Also the maintenance of a fairly constant temperature minimizes the amount of moist air drawn into the cryostat through the silicone-lubricated sleeve and stirring stem.

For the run with 3-methylbenzhydrol the polymer formed was very slow to dissolve, and the freezing point measurements were not commenced until the compound was dissolved. The cryostat, with a ground glass stopper, was fitted with an outside rubber stopper which was inserted into the container of a motor-driven shaker. Powdered solid carbon dioxide and crushed ice were added to the bottom of the shaker container to maintain a small amount of frozen solvent and to ensure that the temperature was held essentially constant. After five hours of shaking at 180–200 c.p.m., the Beckmann thermometer was inserted and the freezing run was begun.

Preparation of Methyl Ethers.—A 0.25-g. sample of carbinol was dissolved in approximately 18 g. of 100% sulfuric acid, and the solution was added immediately to 100 ml. of absolute methanol. This solution was then poured into 125 g. of an ice–water mixture and extracted quickly with two 100-ml. portions of ether. After drying the ether extracts over Drierite, evaporation of the ether gave the methyl ether which was then purified by recrystallization from ethanol.

Reactions of Carbonium Ions with Water.—A sample of carbinol was dissolved in 100% sulfuric acid. After a definite reaction time the solution was poured into an ice–water mixture and extracted with several portions of ether. After drying the ether extracts with solid sodium hydroxide pellets, evaporation of the ether gave the products. The solid was purified by recrystallization from ethanol. The polymers were extracted with methanol, ethanol or ligroin in the attempt to separate any bis ether which might have been formed. No bis ether was indicated in the products.

Titrations to Form Carbonium Ions.—The carbinol was dissolved in 10 ml. of carbon tetrachloride and this solution added to 50 ml. of water. This mixture was then titrated to the barely visible carbonium ion end-point with 96% sulfuric acid. The acid was added very slowly with constant stirring of the mixture which was maintained at approximately room temperature. From the volume of acid required, the percentage of acid necessary for visible carbonium ion formation in the aqueous layer was determined.

Spectra.—The ultraviolet and near-visible spectra were obtained using a Beckman DU spectrophotometer and quartz cells 1 cm. thick. A hydrogen discharge lamp was used for the range 250–350 mμ; a tungsten filament lamp was used for the range 350–600 mμ. For 3-methylbenzhydrol a solution in cyclohexane was prepared and added to sulfuric acid contained in a volumetric flask. The cyclohexane was evaporated under the vacuum produced with a water aspirator while the flask was swirled to effect extraction of the compound into the sulfuric acid layer. The flask was then filled to the mark with sulfuric acid. By this procedure solid polymer did not form and the spectrum could be measured. The reference solvent was treated exactly as just described. The spectra are shown in Fig. 1.

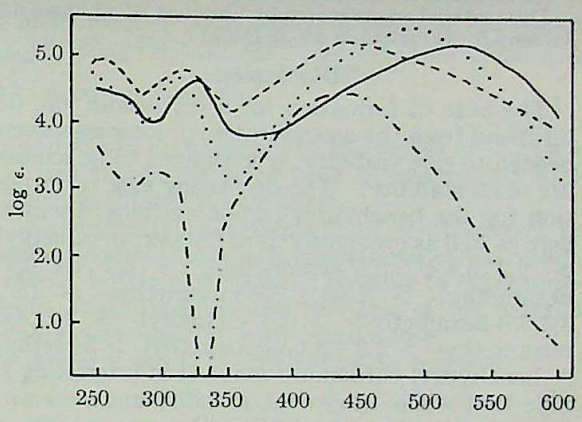

Fig. 1.—Absorption spectra of benzhydryl carbonium ions in 100% sulfuric acid: — · —, 3-methyl; . . . ., 2,2′,4,6-tetramethyl; ———, 2,2′,4,4′,6,6′-hexamethyl; – – – –, 2,2′,3,4,5,6-hexamethyl.

Preparation of Compounds. 2,2′,3,4,5,6-Hexamethylbenzophenone.—This compound was prepared by the reaction of pentamethylbenzene and 2-methylbenzoyl chloride in the presence of anhydrous aluminum chloride; carbon disulfide was used as the solvent. After the addition of the acid chloride to the reaction mixture, the mixture was refluxed for two hours before hydrolysis. The ketone was purified by recrystallization from ethanol. A yield of 80.3% was obtained of white crystals very soluble in benzene; soluble in ether, ethanol and acetone; and slightly soluble in carbon disulfide. The compound melted at 155.5–155.7°.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.73; H, 7.61. Found: C, 85.44; H, 7.58.

2,2′,3,4,5,6-Hexamethylbenzhydrol.—The hexamethylbenzophenone was reduced for two hours using a fourfold excess of ethereal lithium aluminum hydride. After hydrolysis of the complex with 10% hydrochloric acid, and separation of the ether layer, evaporation gave a white solid in 99.3% yield which melted at 132.7–133.0°. Using excess lithium aluminum hydride to reduce a sterically hindered ketone evidently gives excellent yields of the carbinol. A less sterically hindered ketone, 4,4′-dimethylbenzophenone, gave an unsatisfactory yield of the carbinol but the bis ether was obtained in 70% yield.[4]

Anal. Calcd. for $C_{19}H_{24}O$: C, 84.95; H, 8.39. Found: C, 84.73; H, 8.19.

2,2′,4,6-Tetramethylbenzophenone.—This ketone was prepared in 48% yield by the reaction of 2-methylbenzoyl chloride with mesitylene in the presence of anhydrous aluminum chloride; carbon disulfide was used as the solvent. After addition of the acid chloride to the reaction mixture, the mixture was refluxed for two hours, before hydrolysis. Evaporation of the carbon disulfide layer gave the ketone which was purified by recrystallizations from ethanol. The melting point was 111.9–112.2°. A melting point of 111° has been reported.[6]

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 8.32. Found: C, 85.44; H, 8.50.

2,2′,4,6-Tetramethylbenzhydrol.—The tetramethylbenzophenone was reduced for two hours using a four-fold excess of ethereal lithium aluminum hydride. A white solid melting at 123.5–124.5° was obtained. The yield was 99.2%. This compound is sterically hindered also and is obtained in an excellent yield with no bis ether impurities.

Anal. Calcd. for $C_{17}H_{20}O$: C, 85.02; H, 9.01. Found: C, 85.01; H, 9.16.

3-Methylbenzhydrol.—This compound was prepared by the Grignard reaction using *m*-tolylmagnesium bromide and

(5) L. P. Hammett and A. J. Deyrup, This Journal, **55**, 1900 (1933); H. P. Treffers and L. P. Hammett, *ibid.*, **59**, 1708 (1937).

(6) J. Coops, W. Nauta, M. Ersting and A. Faber, *Rec. trav. chim.*, **59**, 1102 (1940).

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benzaldehyde. The compound melted at 53.0–53.3° and was obtained in 80% yield. The literature gives melting points of 53°[7] and 61°.[8] In this work the higher melting compound could not be obtained.

Anal.[9] Calcd. for $C_{14}H_{14}O$: C, 84.82; H, 7.11. Found: C, 84.75; H, 7.29.

2,2′,4,4′,6,6′-Hexamethylbenzhydrol (Dimesitylcarbinol).—This material was prepared by "Method B" of Fuson and Jackson.[10] It melted at 150.6–151.4°.

Discussion

The ease of formation for a carbonium ion, determined from the concentration of ionizing solvent needed to give visibility, is considered to be a measure of its stability. The decreasing ease of formation for the benzhydryl carbonium ions discussed here as well as previously[1] is as follows: decamethyl- > 2,2′,3,4,4′,5,6,6′-octamethyl- > 2,2′,4,4′,6,6′-hexamethyl- > 2,3,4,4′,5,6-hexamethyl- > 2,2′,-3,4,5,6-hexamethyl- > 4,4′-dimethyl- > 2,2′,4,6-tetramethyl- > 2,3,4,5,6-pentamethyl- > 3-methyl- > benzhydryl carbonium ion. It is interesting to note that while, in general, stability increases with increasing methyl substitution, the accumulation of methyl groups is not so effective when all substituents are on one ring as when they are distributed over both rings.

Another interesting comparison involves compounds which should show the "buttressing effect."[11] According to Newman and Deno[12] resonance in the mesityldimethylcarbonium ion is sterically hindered by the introduction of methyl groups in the 3- and 5-positions to form the pentamethylphenyldimethylcarbonium ions. A similar effect should be found when methyl groups are introduced into the 3- and 5-positions of the 2,2′,4,6-tetramethylbenzhydrylcarbonium ion and into the 3,5- and 3′,5′-positions of the dimesitylcarbonium ion. These introductions should give for the relative ease of formation the following orders: 2,2′,-4,6-tetramethyl- > 2,2′,3,4,5,6-hexamethyl- and 2,2′,4,4′,6,6′-hexamethyl- > 2,2′,3,4,4′,5,6,6′-octamethyl- > decamethylbenzhydryl carbonium ions. Exactly the reverse order is noted. One must conclude that the "buttressing" effect is not of considerable importance in these ions. It is possible that steric hindrance is not as great when methyl groups are substituted in the *ortho* positions of the benzhydryl carbonium ions as is found for similar substitution in the benzyldimethyl carbonium ions studied by Newman and Deno. However scale models indicate little difference.

When one studies the absorption spectra of these ions, the opposite conclusions concerning the "buttressing effect" can be drawn. The order of increasing extinction coefficient should be decamethyl- < 2,2′,3,4,4′,5,6,6′-octamethyl- < 2,2′,-4,4′,6,6′-hexamethyl- and also 2,2′,3,4,5,6-hexamethyl- < 2,2′,4,6-tetramethyl. This is the observed order. One might also anticipate that λ_{max} would be shifted toward shorter wave lengths as resonance is hindered by the 3,5-methyl substituents, but the decamethylbenzhydryl carbonium ion has the largest rather than the smallest value.

Gold and Tye[3] attach theoretical significance to the intensity of the second absorption occurring at about 320–340 mμ as compared with the intensity of the principal band for several benzhydryl and α-substituted benzhydryl carbonium ions. They predict greater stability for smaller values of the intensity difference. The differences in the logarithms of the intensities between the principal and secondary bands for 2,2′,4,4′,6,6′-hexamethylbenzhydryl, 2,2′,3,4,5,6-hexamethylbenzhydryl, tetramethylbenzhydryl, methylbenzhydryl and benzhydryl carbonium ions are 0.57, 0.64, 0.87, 1.18 and 1.32, respectively. This order of decreasing stability is in agreement with the titration results.

2,2′,3,4,5,6-Hexamethylbenzhydrol and 2,2′,4,6-tetramethylbenzhydrol gave fairly stable carbonium ions which did not polymerize. The solutions as initially formed reacted with water to give the original carbinol and with methanol to give the methyl ether. These results are explained best by the existence of carbonium ions. Carbonium ions in sulfuric acid when poured into water usually give the bis ether but evidently three as well as four *ortho*-methyl groups prevent this reaction and permit regeneration of the original benzhydrol.

From the cryoscopic runs the rate of sulfonation of the hexamethylbenzhydryl carbonium ion appears to be somewhat faster than that of the tetramethylbenzhydryl carbonium ion. The factors that contribute to carbonium ion stability also increase the tendency for sulfonation as previously noted.[4] It appears that monosulfonation presumably in the unsubstituted ring takes place readily. Further sulfonation, if any, is very slow. Sulfonation of one ring for all molecules is also suggested from the fact that the contents of the cryostat when poured into an ice–water mixture after the cryoscopic run gave a clear solution indicating no unsulfonated material.

The "*i*" value of 5.0 listed in Table I for 3-methylbenzhydrol is believed to correspond to dimerization with monosulfonation in one ring of each unit in the dimer. Obviously the fast initial reaction was polymerization which caused insolubility until sulfonation had occurred. Formation of a trimer followed by sulfonation in each unit would give an "*i*" factor of 4.67. Further sulfonation is apparently quite slow, for the slope in the plot of freezing point *vs.* time after complete solution was less than 0.002° per hour.

KNOXVILLE, TENNESSEE

(7) P. J. Montagne and J. M. van Charante, *Rec. trav. chim.*, **31**, 348 (1912).

(8) W. D. Cohen, *ibid.*, **38**, 118 (1919).

(9) Analysis was done by Weiler and Strauss Microanalytical Laboratory, Oxford, England.

(10) R. C. Fuson and H. L. Jackson, THIS JOURNAL, **72**, 351 (1950).

(11) G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 212.

(12) M. S. Newman and N. C. Deno, THIS JOURNAL, **73**, 3650 (1951).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF OREGON]

Kinetics of the Homogeneous Reaction of NO and H_2[1]

BY WENDELL M. GRAVEN

RECEIVED FEBRUARY 4, 1957

An examination of the kinetics of the reaction of NO and H_2 within the temperature interval of 850–1060° has resulted in information which may be represented by the rate expression $\frac{\Delta H_2O}{\Delta t} = \frac{2.2 \times 10^9 \exp(-41000/RT)[NO]^2[H_2]^{1/2}}{1-3.0\,[H_2]^{1/2}}$. A chain mechanism has been found to be in partial agreement with the experimental data.

Introduction

In each of the gaseous molecular reactions which have been demonstrated kinetically to be of third order nitric oxide is one of the participants.

The interaction of NO and H_2 differs from most of the other reactions in that its rate constant has a higher activation energy and a larger pre-exponential factor.[2] This fact caused Taylor and Tanford[3] to reject the mechanism proposed by Hinshelwood and Mitchell,[4] which involved ternary molecular collisions as well as collisions of molecules with "binary collision complexes." Believing the reaction mechanism to be more complex and probably to involve hydrogen atoms they undertook an investigation of the mercury-photosensitized NO–H_2 reaction. Quite understandably, a different dependence of reaction rate on H_2 and NO pressures was observed.

In view of recent interest in the high temperature behavior of NO–H_2 flames[5,6] a re-examination of the kinetics of the NO–H_2 reaction has been considered to be appropriate.

Before a comprehensive kinetic investigation was initiated an approximate dependence of the rate upon reactant concentrations was determined by a simple and rapid technique which will be described.

For a binary system, the reaction rate of which is ith order in reactant A and jth order in reactant B, the initial rate, R_N, may be expressed in terms of the mole fraction, N, of component A and a pressure-dependent rate constant, k, according to eq. 1

$$R_N = kN^i(1-N)^j \qquad (1)$$

Elimination of k by taking the ratio of the initial rate at mole fraction N to that at some other composition, say the equi-molar mixture, enables one to define the relative rate ratio, R, by means of eq. 2.

$$R = R_N/R_{1/2} = 2^{i+j}N^i(1-N)^j \qquad (2)$$

Equation 2 is applicable to all two-component reaction systems at constant temperature and pressure, provided that the extent of reaction is not greater than several per cent.

A plot of R against N results in a family of curves corresponding to the selected values of the exponents, i and j. Figure 1 shows such a plot in which i and j have been limited to the values of $1/2$, 1 and 2, and the curves have been terminated at mole fractions 0.1 and 0.9 for clarity.

Experimental measurement of R at several reactant compositions and comparison of the results with a master plot makes it possible to determine i and j, and therefore the rate law of the reaction under consideration, with relative ease.

Application of this method to the reaction

$$NO + H_2 = H_2O + {}^1/_2N_2 \qquad (3)$$

yielded results which have been plotted as individual points in Fig. 1, where N represents the mole fraction of NO. It may be observed that the

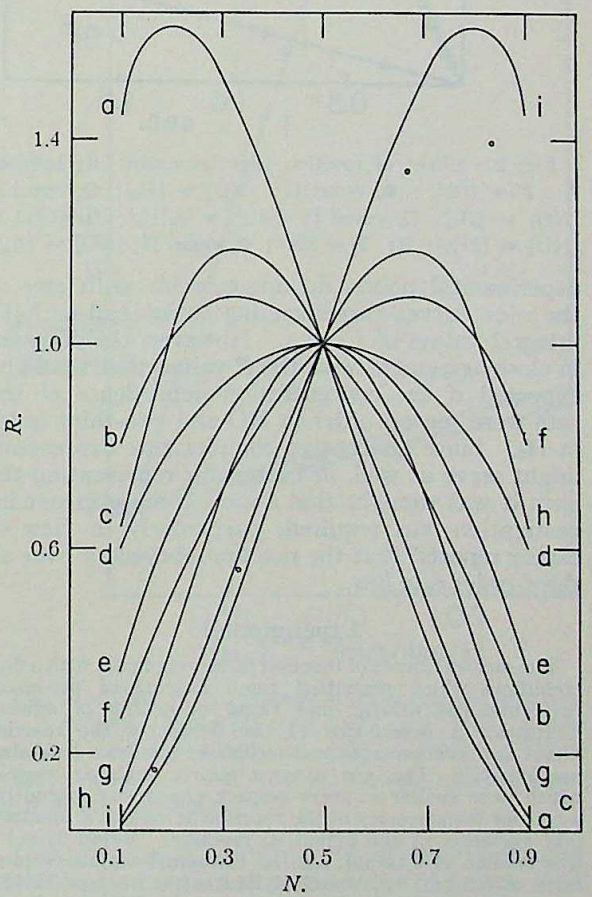

Fig. 1.—Effect of composition of binary systems on initial rate ratio: R, initial reaction rate relative to that of equimolar mixture; N, mole fraction of component with ith order concentration dependence; a, $i = 1/2, j = 2$; b, $i = 1/2, j = 1$; c, $i = 1, j = 2$; d, $i = 1/2, j = 1/2$; e, $i = 1, j = 1$; f, $i = 1, j = 1/2$; g, $i = 2, j = 2$; h, $i = 2, j = 1$; i, $i = 2, j = 1/2$; O, R (experimental) NO + H_2; $T = 1025°$; 0.3–3.0% reaction.

(1) Financial support for this research was obtained from the Graduate School of University of Oregon and Research Corporation.
(2) C. N. Hinshelwood and T. E. Green, *J. Chem. Soc.*, 730 (1926).
(3) H. A. Taylor and C. Tanford, *J. Chem. Phys.*, **12**, 47 (1944).
(4) C. N. Hinshelwood and J. W. Mitchell, *J. Chem. Soc.*, 378 (1936).
(5) G. K. Adams, W. G. Parker and H. G. Wolfhard, *Disc. Faraday Soc.*, **14**, 97 (1953).
(6) A. I. Rozlovskil, *Zhur. Fiz. Khim.*, **30**, 912 (1956).

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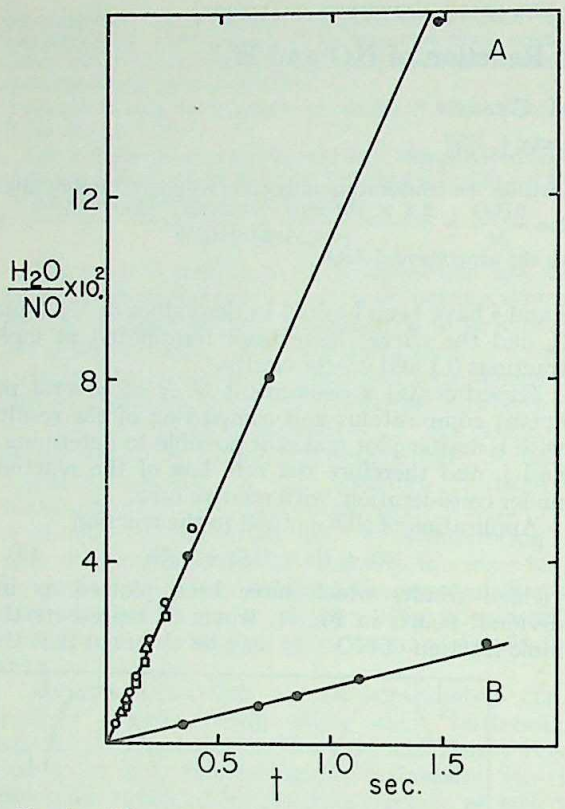

Fig. 2.—Effect of reaction time on extent of reaction. A: $T = 1025°$; ●, vessel II; $[NO] = [H_2]$; ○, vessel I; $[NO] = [H_2]$; □, vessel I; $[NO] = \frac{1}{2}[H_2]$; △, vessel I; $[NO] = [2H_2]$; B: $T = 850°$; ●, vessel II; $[NO] = [H_2]$

experimental points do not coincide with any of the nine curves corresponding to integral or half-integral values of i and j. However, the data are in close agreement with the R values that would be expected if the concentration dependence of the rate were second order in NO and two-third order in H_2. Since alternative complex rate expressions might serve as well, or better, for representing the data it was thought that a more comprehensive investigation was required, particularly in view of earlier reports[2] that the reaction obeyed an over-all third-order rate law.

Experimental

The measurements of reaction rates were made with a flow technique which permitted rapid heating of pre-mixed reactants and diluent and rapid quenching of effluent mixtures. A description of the design of the reaction vessel and the experimental technique has been published previously.[7,8] The use of two quartz reaction vessels, which were similar in every respect except size, permitted a test for homogeneity of the reaction as well as a hundred-fold variation of the extent of reaction. Vessel I had a free volume of 5.60 ml. and an estimated surface/volume ratio of 5.6 cm.$^{-1}$. Vessel II had a free volume of 42.6 ml. and an estimated surface/volume ratio of 2.3 cm.$^{-1}$.

Reaction rates were determined by absorption of water vapor in calcium chloride. Gravimetric measurement of the amount collected during an appropriate time interval permitted a precise estimate of the steam content of the effluent mixture.

Calibrated capillary tube flowmeters facilitated measurement and control of the flow rates of reactants and diluent. Mixing was accomplished with tangential jet mixing chambers.

Mass spectrometric analyses of the compressed N_2, H_2 and He gases showed that the principal impurity (H_2O, N_2, O_2 or CH_4) did not exceed a few tenths of a per cent. Each gas was dried and freed of O_2 by standard catalytic methods. Compressed NO gas which had been passed through ascarite absorbent showed no evidence of NO_2, an amount of N_2O which did not exceed a few tenths of a per cent., and N_2 in an amount that exceeded the maximum impurity stated by the supplier.

The temperature at the center of the reaction vessel, which was situated in an electric furnace, was maintained constant within one degree with a modified "Simplytrol" pyrometer-relay furnished by Assembly Products, Inc. Temperature measurements along the major axis of the larger vessel with a Pt, Pt–Rh thermocouple, which had been calibrated by the Bureau of Standards, indicated a temperature gradient of 11° between the entrance and the center.

The total pressure of the reactant mixture was approximately 77 or 80 cm., depending upon which vessel was being used.

With the use of helium as a diluent to maintain a constant total flow rate it was possible to vary the reactant concentrations independently of one another without changing the reaction time. A total flow rate of 1.5 l./min., which corresponded to a reaction time of about 0.05 sec. in vessel I and 0.4 sec. in vessel II, resulted in about one and 5% reaction, respectively, at the maximum temperatures. Consequently, in all runs except those in which the reaction time was increased deliberately initial rates were being measured and a differential rate law, together with initial reactant concentrations, could be employed in computing rate constants.

Results

Adjustment of the total flow rate permitted a wide variation in the residence time of the gases within the vessel. This was extended further by the use of two vessels with different volumes. Figure 2 shows the results of rate measurements in both vessels at two temperatures with three different compositions of reactants. In each case a linear relationship exists between per cent. reaction and reaction time. Curve A, in which the variation of t covers a 40-fold range, indicates that the linearity persists nearly to 15% conversion. Moreover, the close fit to a single curve of data from two vessels, one having 2.5 times the surface/volume ratio of the other, argues against any significant contribution of heterogeneous reaction.

That N_2 takes no part in that portion of the reaction mechanism which is rate-determining may be seen from the data in Fig. 3. Reaction rates were obtained from runs in which NO and H_2 concentrations remained invariant while N_2 replaced He as diluent at two temperatures with the use of both reaction vessels. The greater scatter of the points in curve A is due in part to the ten-fold magnification of error that arises from the division of product concentrations by the reaction time.

In Fig. 4 the reaction rates obtained from runs at constant H_2 concentration with varying NO concentration have been plotted against the square of the corresponding NO concentrations. Data obtained at three temperatures with both vessels give straight lines over ten-fold variations in NO concentration, thus demonstrating a second-order dependence.

The dependence of the reaction rate upon H_2 concentration was found by preliminary experiments, Fig. 1, to be non-integral and less than first order. By plotting a number of trial functions it

(7) W. M. Graven and F. J. Long, THIS JOURNAL, **76**, 2602 (1954).
(8) W. M. Graven, *ibid.*, **78**, 3297 (1956).

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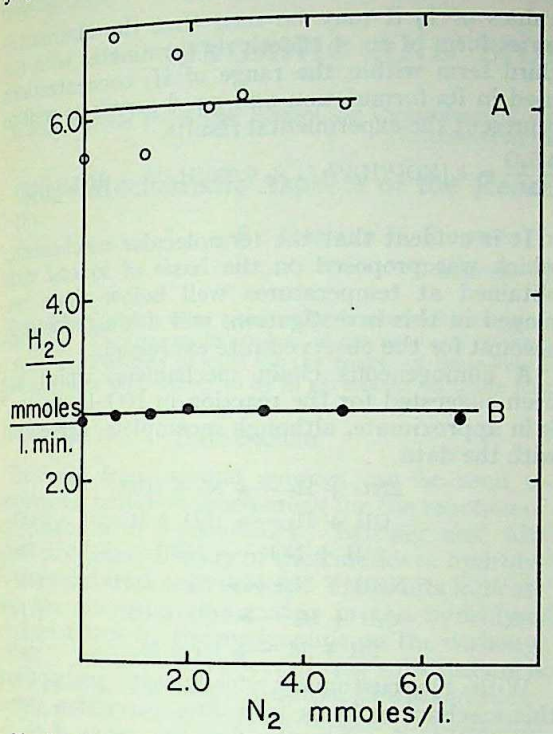

Fig. 3.—Effect of N_2 concentration on rate of reaction. A: $T = 1060°$; vessel I; $t = 0.0469$ sec.; $[NO] = [H_2] = 2.33$ mmoles/l.; B: $T = 1025°$; vessel II; $t = 0.391$ sec.; $[NO] = 1.98$, $[H_2] = 1.32$ mmoles/l.

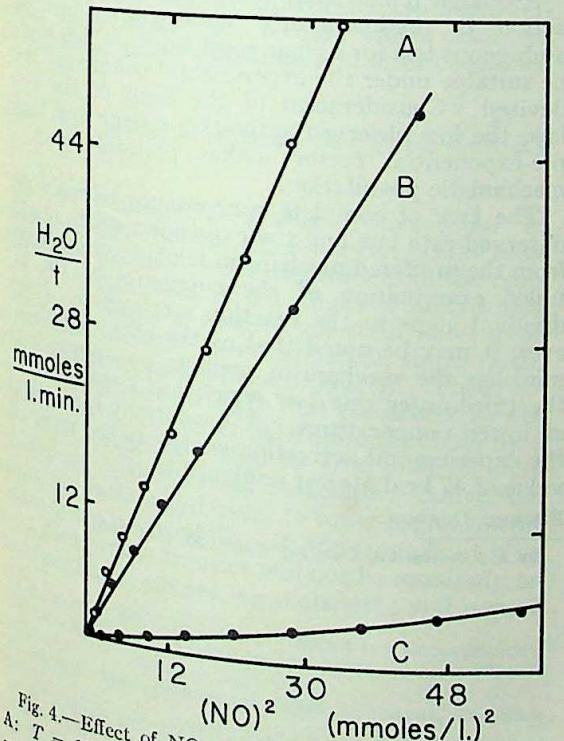

Fig. 4.—Effect of NO concentration on rate of reaction. A: $T = 1060°$; vessel I; $t = 0.0469$ sec.; $[H_2] = 3.49$ mmoles/l.; B: $T = 1025°$; vessel II; $t = 0.391$ sec.; $[H_2] = 3.31$ mmoles/l.; C: $T = 850°$; vessel II; $t = 0.452$ sec.; $[H_2] = 3.79$ mmoles/l.

was ascertained that for runs at constant NO and varying H_2 concentrations a plot of the reciprocals of the reaction rates against the reciprocals of the square roots of corresponding H_2 concentrations yielded a straight line. Figure 5 shows three such plots which span ten-fold variations in H_2 concentration and include data procured at three temperatures with the use of both reaction vessels.

Sufficient information has been provided for the formulation of a tentative rate law which may be expressed in the incremental form

$$\frac{\Delta H_2O}{\Delta t} = \frac{k_1[NO]^2[H_2]^{1/2}}{1 + k_2[H_2]^{1/2}} \qquad (4)$$

The two parameters of eq. 4, k_1 and k_2, can be evaluated from the slopes and intercepts, respectively, of the curves in Fig. 5. It may be observed that k_2 is singular by virtue of being negative and nearly independent of temperature. Thus, at 1025° it is found to be -0.095 (l./mmole)$^{1/2}$, while at 850° where the experimental uncertainty is greater a value of -0.08 is computed.

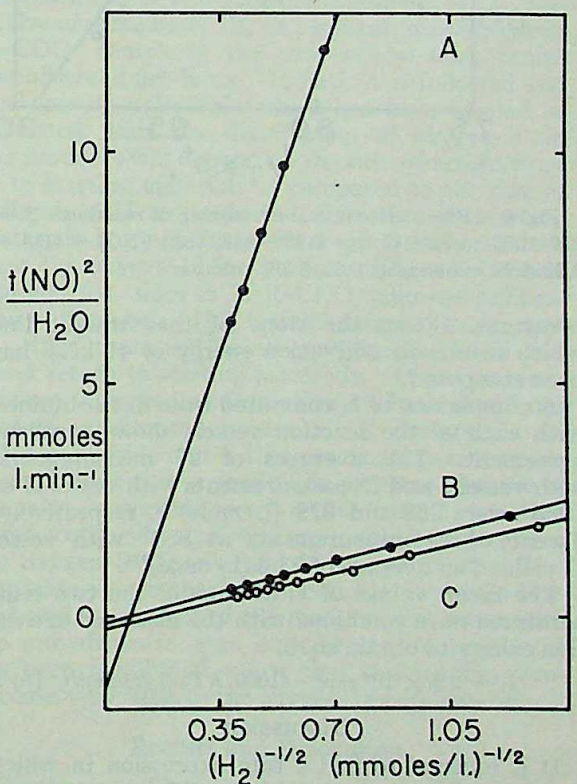

Fig. 5.—Effect of H_2 concentration on rate of reaction. A: $T = 850°$; vessel II; $t = 0.678$ sec.; $[NO] = 4.45$ mmoles/l.; B: $T = 1025°$; vessel II; $t = 0.391$ sec.; $[NO] = 3.31$ mmoles/l.; C: $T = 1060°$; vessel I; $t = 0.0469$ sec.; $[NO] = 3.49$ mmoles/l.

Calculations of k_1 for individual runs were made with the assumption that the value of k_2 was -3.0 (l./mole),$^{1/2}$ independent of temperature. Therefore, the observed temperature dependence of the over-all reaction rate was assigned to k_1.

Rate measurements were made with the larger vessel using an equi-molar reactant mixture and extended over a 200° temperature interval. The data appear in Fig. 6 as a plot of the logarithms of the ratios of k_1 to the square roots of corresponding temperatures against the reciprocals of the tem-

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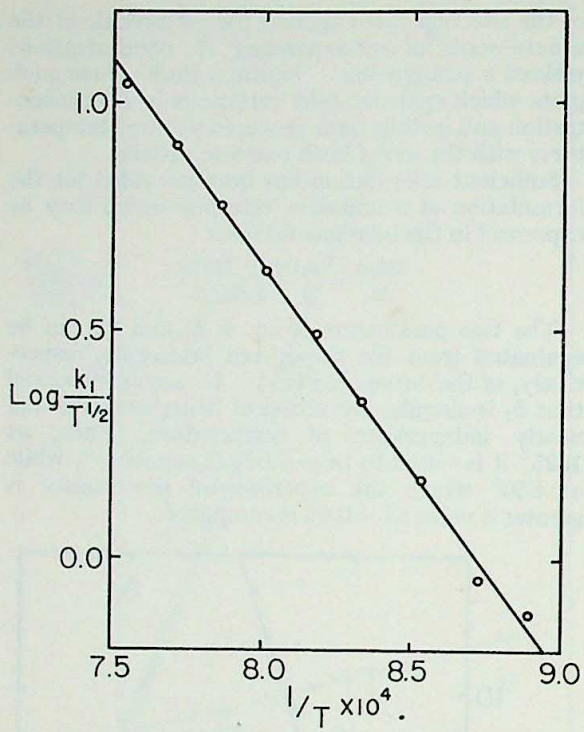

Fig. 6.—Effect of temperature on rate of reaction. T = 850–1053°; vessel II; t = 0.383–0.452 sec.; [NO] = [H_2] = 3.23–3.79 mmoles/l.; 0.33–3.3% reaction.

peratures. From the slope of the straight line which results an activation energy of 41 kcal. has been computed.

A comparison of k_1 computed from data obtained with each of the reaction vessels shows excellent agreement. The averages of 27 measurements with vessel I and 28 measurements with vessel II at 1025° were 268 and 279 (l./mole)$^{1/2}$, respectively. Twenty-three measurements at 850° with vessel II yielded an average of 23.2 (l./mole)$^{1/2}$.

The mean values of k_1 at each of the two temperatures were combined with the observed activation energy to obtain eq. 5.

$$k_1 = 2.2 \times 10^9 \exp(-41000/RT)\ (\text{l./mole})^{1/2} \quad (5)$$

Discussion

It is unusual to find a rate expression in which the denominator consists of the difference between two terms, associated with a non-detonating reaction. However, if use is made of the experimental values of k_2 it may be seen that the alternative series form of eq. 4 effectively terminates with the third term within the range of H_2 concentrations used in its formulation and eq. 6 serves as well to represent the experimental results.

$$\frac{\Delta H_2O}{\Delta t} = k_1[NO]^2[H_2]^{1/2}(1 + 0.095[H_2]^{1/2} + 0.0090\,[H_2]) \quad (6)$$

It is evident that the termolecular mechanism,[2] which was proposed on the basis of kinetic data obtained at temperatures well below those employed in this investigation, will not satisfactorily account for the observed rate expression.

A homogeneous chain mechanism, which has been suggested for the reaction in NO–H_2 flames,[9] is in approximate, although incomplete, agreement with the data.

$$2NO + H_2 \longrightarrow N_2 + 2OH \quad (7)$$
$$OH + H_2 \longrightarrow H_2O + H \quad (8)$$
$$H + NO \longrightarrow NOH \quad (9)$$
$$NOH + NO \longrightarrow N_2 + O_2H \quad (10)$$
$$O_2H + H_2 \longrightarrow H_2O + OH \quad (11)$$
$$2H + M \longrightarrow H_2 + M \quad (12)$$

With the customary steady-state assumptions this mechanism leads to a rate expression corresponding in form to the first two terms of eq. 6, which, it may be observed, account for 95% of the experimental rate of reaction at the highest H_2 concentration employed in this investigation.

Although it has been demonstrated that the reaction is predominantly homogeneous no unambiguous test for a chain mechanism, which would be suitable under the experimental conditions, was devised. Consideration of the form of the rate law, the low observed activation energy and large pre-exponential factor makes plausible such a mechanistic postulation.

The lack of complete concordance between the observed rate law and the expression which results from the proffered mechanism tends to vitiate a detailed examination of the energetics of the individual steps in the reaction mechanism. However, it may be noted that as the chain length diminishes the mechanism predicts an approach to the third-order rate law which has been observed at lower temperatures. A concurrent increase of the experimental activation energy to the reported value of 47 kcal.[4] is not implausible.

EUGENE, OREGON

(9) A. I. Rozlovskiĭ, *Zhur. Fiz. Khim.*, **30**, 1444 (1956).

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ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY AND THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Some Mechanistic Aspects of the Reaction of Anhydrides with Nucleophiles[1]

BY DONALD B. DENNEY AND MICHAEL A. GREENBAUM[2]

RECEIVED JANUARY 19, 1957

Anhydrides, which were specifically labeled with oxygen-18, have been treated with various nucleophiles under several conditions. The oxygen-18 content of the products of these reactions coupled with data from the literature can be utilized to define a multi-step process for the course of these reactions. Several reactions have been devised to test this mechanism and have been shown to be in agreement with the postulate.

Introduction

Evidence from several sources can be used to construct a tentative mechanism for the reaction of anhydrides with nucleophiles. Berliner and Altschul[3] have made a study of the kinetics of hydrolysis of several aroyl anhydrides. Their data indicate that the rate-determining step in the hydrolysis involves attack by the nucleophile on the carbonyl carbon. The observed effect of ring substituents is in accord with this view. Bunton, Lewis and Llewellyn[4] have shown by using an oxygen-18 tracer that an intermediate $C_6H_5-C(OH)_2-\overset{\overset{O}{\|}}{C}-C_6H_5$ must be in equilibrium with the starting materials in the aqueous hydrolysis of benzoic anhydride. Gold and Jefferson[5] have studied the tertiary amine catalyzed hydrolysis of acetic anhydride and have concluded that the reactive species is $[CH_3-\overset{\overset{O}{\|}}{C}-\overset{+}{N}(R)_3\ \ {}^{O}_{\|}\ CH_3-C-O^-]$ although rigorous evidence for its formation was not obtained. Emery and Gold[6] have studied the product ratios obtained from the reaction of anilines with mixed aliphatic anhydrides. They have found a marked effect of solvent on these ratios as well as an apparent steric factor which alters the ratio of the products.[7] These observations indicate strongly that the attack by the nucleophile, :NH, on an anhydride proceeds by a slow rate-determining step to give I which is in equilibrium with starting materials. Conversion of I to products will depend to some degree on the nature of the nucleophile. If, for example, it is an anion then proton transfer will not be required; on the other hand, amines, alcohols, etc., will require that a proton be transferred before the products are formed. It is the latter situation which is of concern here. There are two attractive paths for the formation of products from I. Path A involves an ionization of I to give the fragments of II. Reaction of some base, :B, *i.e.*, solvent, nucleophile or $R-COO^-$ completes the process and one obtains the observed products. If Path A is followed and one uses an anhydride which has been labeled as indicated, then the distribution of oxygen-18 in the products will depend on the rate of return from II to starting materials as compared to the rate of collapse of II to products.[8] If return to starting materials is much faster than product formation, then the oxygen-18 in the anhydride will become equilibrated, since in II $R-COO^-$ allows equilibration of the label. If k_4 is much larger than k_{-1} and k_{-2}, then there will be no equilibration, as II will never return to starting materials. It can be readily seen that product formation by Path B will not lead to equilibrated products. If one uses a labeled anhydride and if these two paths are the ones being followed, it is possible to get some measure of the relative importance of return from II as compared to the non-equilibrating routes by measuring the oxygen-18 distribution in the products. Unfortunately, a further complication arises since benzoic acid, a product of the reaction, can react with the anhydride to give equilibrated material. It has been possible to show that this reaction contributes very little to the oxygen-18 equilibration.

Results and Discussion

Synthesis.—The preferred method of preparing the monocarbonyl labeled benzoic anhydride is to allow silver benzoate to react with labeled benzoyl chloride. This reaction affords good yields of specifically labeled anhydride. It was by this procedure that IV was converted *via* the acid chloride to VII (see Table I). Another method used for preparing the monolabeled anhydride was to allow sodium benzoate in water to react with labeled benzoyl chloride (from III) in chloroform. Using this procedure VI was prepared; however, because of the unpredictableness of the method, it cannot be recommended. When labeled benzoic acid, V, was allowed to react with benzoyl chloride and pyridine in ether, an excellent yield of VIII was obtained.

(1) A portion of this work has been reported as a Communication. D. B. Denney and M. A. Greenbaum, THIS JOURNAL, **78**, 877 (1956).

(2) Alfred P. Sloan Postdoctoral Fellow at Rutgers, The State University.

(3) E. Berliner and L. H. Altschul, THIS JOURNAL, **74**, 4110 (1952).

(4) C. Bunton, T. Lewis and D. Llewellyn, *Chem. and Ind.*, 1154 (1954).

(5) V. Gold and E. Jefferson, *J. Chem. Soc.*, 1409 (1953).

(6) A. Emery and V. Gold, *ibid.*, 1443 (1950).

(7) A study in this Laboratory of the ratio of products obtained from mixed aroyl anhydrides as yet has not led to the large solvent effects found by Emery and Gold. Further discussion of the points raised by these experiments will be deferred until a later paper as they do not affect the arguments advanced in this paper.

(8) The reasoning which is being applied here depends upon the fact that the products are not in equilibrium with the starting materials; that this is the case is abundantly demonstrated by qualitative organic chemical data.

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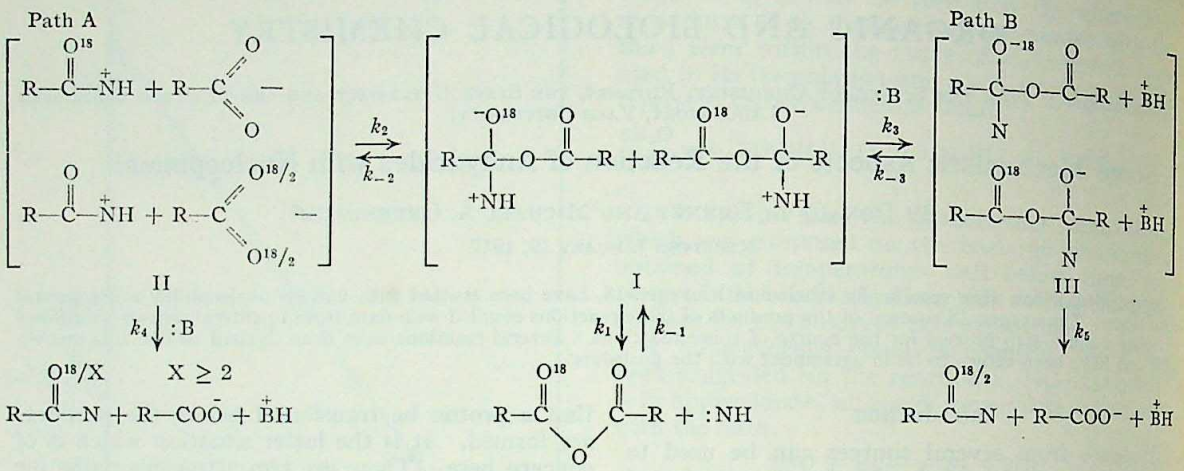


It was shown that VIII was partially equilibrated with respect to its oxygen-18, and therefore this method is unreliable.

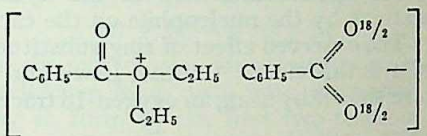
TABLE I

Compound	Atom % O^{18} in labeled position
Benzoic anhydride (VI)	1.32; 1.30
Benzoic anhydride (VII)	1.00; 0.99
Benzoic anhydride (VIII)	1.19; 1.19
Benzoic acid (III)	1.32; 1.31
Benzoic acid (IV)	1.02; 1.01
Benzoic acid (V)	1.19; 1.18
p-Nitrobenzoic anhydride (IX)	1.13; 1.11

Position of Label.—The distribution of oxygen-18 in these anhydrides was elucidated by allowing them to react with ammonia at −33°. The oxygen-18 content of the benzamides and benzoic acids derived from VI and VII indicated that all of the excess oxygen-18 was incorporated in the carbonyl groups. The methods of synthesis limit this excess oxygen-18 to only one of the carbonyls. When VIII was treated in this manner, the results showed that VIII was about 35% equilibrated. This equilibration presumably occurred during the preparation of the anhydride.

The reaction of these anhydrides with ammonia proceeds without any equilibration; therefore, Path B must be operating or no return from II is taking place. Such a finding is not unexpected since the excess ammonia will make the conversion of II to products and of I to III very rapid, thereby eliminating return. It is very interesting to note that at −78° the reaction of the anhydrides with ammonia leads to completely equilibrated products. At this temperature ammonia apparently exists as rather tightly hydrogen bonded oligmers. Diffusion of these large groups to the reaction site will be slow compared to the reaction at −33°, and therefore return from II can compete effectively with the non-equilibrating processes.

Equilibration Paths.—When the labeled anhydrides were allowed to react with aniline in ether, the products showed complete equilibration of the oxygen-18. If the anhydride interacts very rapidly with the ether to give an ion pair, X, then collapse of X to the starting material would lead to equilibration. It has been shown that the equilibration does not take place through X since anhydride which had been dissolved in ether gave the same oxygen-18 distribution as untreated material when they were allowed to react with aniline in water–acetone.



X

Another possible path for the equilibration involves a rapid attack by the benzoic acid being formed in the reaction on unreacted anhydride. That this path contributes little to the equilibration has been shown by allowing molar ratios of benzoic anhydride, aniline, dimethylaniline and benzoic acid-C^{14} to react in ether. The benzanilide contained 15% of the possible carbon-14 calculated on the basis of complete exchange of all benzoyl species. This figure represents an unreal maximum since the concentration of benzoic acid under the normal reaction conditions is much lower than that used here. In the absence of aniline the amount of exchange was considerably higher, 46%.

The other path which can lead to equilibration involves return from II. In order to test this possibility, a molar ratio of anhydride to aniline of 2:1 was allowed to react in ether. The unreacted anhydride was recovered and treated with ammonia. The benzamide contained 38% of the excess oxygen-18 and the benzoic acid 58%. These figures correspond to about 69% equilibration and amply demonstrate that equilibration of the starting materials is taking place.

Effect of Basic Solvent.—An inspection of the proposed reaction scheme shows that in all paths some base :B is required before the products can be formed. In Path A benzoate ion can function as the base and, since it is intimately associated with the cation, it should have ample opportunity to remove the proton. It also has the opportunity to function as a nucleophile and cause return to I. If the benzoate ion acts primarily as a base, then one would expect to find non-equilibrated products, which is not the case in most of the examples studied. The prime function of the benzoate ion therefore appears to be that of a nucleophile, and it attacks on the cation to give return to I.

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TABLE II[a]

Reactants and conditions	Amide or ester-O^{18}	Benzoic acid-O^{18}	% Equilibration	Dev. from total O^{18}
VI + NH_3 at −33°	0.86, 0.85	0.66, 0.65	0	0.00
VII + NH_3 at −33°	.57, .57	0.40	0	− 0.02
VIII + NH_3 at −33°	0.85	1.03	35	− 0.06
VII + NH_3 at −78°	0.46, 0.46	0.46	100	− 0.01
VI + C_6H_5–NH_2 in ether	.64, .64	0.64, 0.64	100	0.00
VII (after $C_6H_5NH_2$ in ether) + NH_3	0.50	0.43	69	− 0.03
VI + C_6H_5–NH_2 acetone/H_2O(1:2)	0.81, 0.80	0.55, 0.56	23	0.00
VII + cyclo-$C_6H_{11}NH_2$ in C_6H_5–$N(CH_3)_2$	0.51	0.44	62	0.00
VII + cyclo-$C_6H_{11}ND_2$ in C_6H_5–$N(CH_3)_2$	.46	.47	100	+ 0.01
VII + CH_3OH	.46	.47	100	+ 0.01
IX + C_6H_5–NH_2 in ether	.67		74	
VII + cyclo-C_6H_{11}–NH_2 in acetonitrile	.47	.46	100	+ 0.01
VII + CH_3OH in acetonitrile	.46	.45	100	− 0.03
VII + C_6H_5–NH_2 in acetonitrile	.47	.47	100	+ 0.02
VII + C_6H_5–NH_2 in DMF	.46	.45	100	− 0.03

[a] Analyzed by the method of W. E. Doering and E. Dorfman, THIS JOURNAL, 75, 5595 (1953), as slightly modified by D. B. Denney and M. A. Greenbaum, *ibid.*, 78, 979 (1957). In the case of the anhydrides and products the observed oxygen-18 values appear to be good to ±0.01 atom % oxygen-18. In general, in work of this sort the tendency is to obtain low values for the oxygen-18 content since any dilution or exchange causes a decrease in oxygen-18 content. The deviation from the expected total oxygen-18 content of the products has been listed in the table, and in all cases but one it is equal to or less than ±0.03. These values represent the sum of the errors over three positions. The calculated per cent. equilibration is accurate to about ±8%, in the case of products from VII. In the case of products from VI it is about ±5%. The reason for the difference between VII and VI is because of the greater oxygen-18 content of VI.

The presence of added base in the reaction mixture should lead to a net decrease in equilibration, all other things being equal. This will arise since the rate of conversion of II to products will be increased as will the rate of formation of III. The reaction in ammonia demonstrates the importance of base concentration in controlling the amount of equilibration. In order to find other examples of this behavior, the labeled benzoic anhydride was allowed to react with aniline in acetone–water (1:2). Analysis of the products showed that 23% equilibration had occurred. Under these conditions the water is functioning as a base and therefore decreases the rate of return from II. II is also probably much more stable in this solvent mixture than in solvents of lower dielectric constant, and the ions should therefore be much more loosely bound. Any diffusion away from the cation by benzoate ion will lead to a lowering in the rate of return from II to I.

Prof. Philip A. Vaughan (Rutgers) has derived an equation which relates the ratio of the rate of return from II to the rate of those processes which lead to products, *i.e.*, k_4 and Path B. This equation only applies to those situations in which an effective base is present in excess throughout the course of the reaction. The equation is

$$V = 0.333 + \frac{0.166}{0.75r + 1}$$

where V = the observed excess oxygen-18 content in the product benzoyl species normalized to a starting value of 1.00.

r = the ratio of the rate of return from II to product formation by all paths, and r is also equal to the average number of returns from II.

Using this equation r can be calculated for the reaction in acetone/water and it is 0.22. This result is indicative of the delicate balance of rates between return and product formation.

It was deemed desirable to have an example of the reaction in a basic organic solvent. The choice of such a solvent is rather difficult since they can in general react with the anhydride to cause equilibration. It was found that the reaction of cyclohexylamine with labeled anhydride in dimethylaniline afforded products which were 62% equilibrated. In this example at least some of the equilibration may have been caused by the dimethylaniline. A calculation of r for the above reaction shows it to be 1.4. In this case it is interesting to note that although dimethylaniline is a stronger base than water, more equilibration takes place than occurred in the aqueous solution. At least a part of this effect is due to the lower dielectric constant of dimethylaniline which will cause II to be "tighter" and will facilitate return. When methanol was used as the solvent as well as the nucleophile, the products contained completely equilibrated oxygen-18. Since methanol is a weaker base than either water or dimethylaniline and since its dielectric constant is rather low as compared to water, it is not surprising that one finds complete equilibration in the reaction.

Effect of Deuterium Substitution.—Inspection of the proposed reaction scheme indicates that any diminution in the rate of conversion of II to products or in the rate of Path B should lead to increased oxygen-18 equilibration. Deuterium substitution for hydrogen to give :N–D will lead to intermediates containing deuterium and presumably to a diminution in rate of hydrogen transfer since the energy required to transfer the deuteron will be larger than that required for the proton. When cyclohexylamine–ND_2 was allowed to react with labeled anhydride in dimethylaniline, the products showed complete equilibration of the label. These results are to be compared with the undeuterated material in which the amount of equilibration was 62%. Clearly there is an isotope effect which leads to the predicted behavior.

Effect of Substituent.—When *p*-nitrobenzoic benzoic anhydride-*p*-nitrobenzoyl-*carbonyl*-O^{18} (IX)

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was allowed to react with aniline in ether, the *p*-nitrobenzanilide contained 52% of the excess oxygen-18. Several factors can contribute to the difference found between the amount of oxygen-18 equilibration in the substituted and unsubstituted cases. One difference is that in the substituted case one can isolate product containing only the original labeled position, *i.e.*, *p*-nitrobenzanilide. In this manner the dilution factor which was present in the symmetrical case is removed. The presence of the *p*-nitro group will enhance the rate of attack at the carbonyl adjacent to the ring bearing the *p*-nitro group. Increased attack at this position causes a slower equilibration than an equal number of statistical attacks. There are considerable complications attendant with any attempt to calculate the number of returns from II in this case, since II now consists of two different ion pairs which are formed at different rates and which have different k_{-1}'s, etc. It is possible to make a very naive calculation if several assumptions are made. It has been assumed that the ratio of the rate of attacks at the substituted benzoyl moiety as compared to the benzoyl is 3:1. This assumption is based on the product ratio, there being 75% *p*-nitrobenzanilide to 25% benzanilide. It is also necessary to assume that k_4 and k_3 are zero until the proper degree of equilibration is reached and then become infinite. Such an assumption leads to a value for the number of returns (the ratio of the rates is not being calculated here) that is smaller than the actual value. The equation used in this calculation is one that arose during the derivation of the equation reported above. It is

$$P_N = \frac{1}{3} + \frac{{}^2/_3 g_2 - {}^1/_6 - {}^1/_2 x}{g_2 - g_1} g_1 N + \frac{{}^1/_6 + {}^1/_2 x - {}^2/_3 g_1}{g_2 - g_1} g_2 N$$

where P_N = observed excess oxygen-18 in the benzoyl product normalized to a starting value of 1.0.

x = probability of attack at the labeled position here ${}^3/_4$.

$$g_1 = \frac{1 + \sqrt{1 - 3x + 3x^2}}{2} \qquad g_2 = \frac{1 - \sqrt{1 - 3x + 3x^2}}{2}$$

N = number of returns, with the limitations discussed above

Calculation of N for the reaction of the *p*-nitrobenzoic benzoic anhydride gives a value between four and five. This average value is low since the rate of formation of product has been ignored.

Effect of Solvent.—The reaction of the labeled anhydride with aniline in dimethylformamide, acetonitrile and ether have been investigated. In all of these cases the products were completely equilibrated. In going from ether to dimethylformamide and acetonitrile, the dielectric constant of the solvent has changed from 4.34 to 37.5. An increase in dielectric constant of the solvent should markedly increase k_1 and decrease k_{-1}. An increase in k_2 should also be observed if, as seems likely, the charges in II are separated farther apart than in I. If such is the case, one would expect k_2 to decrease. The effect of increased dielectric on k_4 should be a slight decrease since in the transition state leading from II to products, *i.e.*, the proton transfer, there will be a dispersal of positive charge. In Path B k_3 should increase and k_{-3} decrease if the charge separation in III is greater than in II. The effect on k_5 should be relatively slight. The predicted over-all effect of increased dielectric constant is less equilibration of the oxygen-18, since the large decrease in k_{-1} relative to the changes of the other constants should make return a slower process. Since in all of the non-basic solvents studied to date the products have been equilibrated, it is impossible to test this prediction. Future experiments using monolabeled *p*-nitrobenzoic benzoic anhydride should give a quantitative measure of the solvent effect in this reaction.

Effect of Nucleophile.—Cyclohexylamine in ether and methanol in acetonitrile were allowed to react with the labeled anhydride. In both of these cases the products contained completely equilibrated oxygen-18. These findings are not unexpected since the controlling factors for these reactions do not appear to involve the rate of formation of I which will be affected markedly by a change in the power of the nucleophile.

Acknowledgment.—We wish to thank the Esso Research Corporation for making available the mass spectrometer used in this work.

Experimental

Benzoic Anhydride (V).—A solution of 6.70 g. (0.048 mole) of benzoyl chloride-O^{18} (from III) in 30 ml. of chloroform was shaken intermittently over a 48-hr. period with a solution of 6.00 g. (0.050 mole) of benzoic acid and 2.00 g. (0.050 mole) of sodium hydroxide in 50 ml. of water. The chloroform solution was dried and concentrated *in vacuo* to afford material which after two crystallizations from petroleum ether had m.p. 41.5–42°; yield 5.80 g. (55%).

Benzoic Anhydride (VII).—To an ice-cold stirred suspension of 40.0 g. (0.175 mole) of silver benzoate and 25 g. of glass beads in 250 ml. of dry ether was added 24.0 g. (0.171 mole) of benzoyl chloride-O^{18} (from IV) in 25 ml. of ether. The mixture was stirred at 0° for 12 hr. The ether solution was evaporated to give 31.5 g. of crude anhydride which after crystallization from hexane afforded 26.4 g. (68%) of VII, m.p. 43–43.5°.

Benzoic Anhydride (VIII).—To a stirred solution of 43.8 g. (0.312 mole) of benzoyl chloride in 60 ml. of ether was added over 15 minutes a solution of 38.0 g. (0.312 mole) of benzoic acid-O^{18} (V) and 24.7 g. (0.312 mole) of pyridine in 100 ml. of ether. The solution was washed with water, 10% hydrochloric acid and 10% sodium bicarbonate solution. After drying the ether, it was evaporated to afford 67.0 g. of crude VIII. The crude material was crystallized from hexane–benzene to afford 61.0 g. (86%) of VIII, m.p. 41–42°.

Reactions and Reagents.—In general the solvents and reagents were purified by standard methods. The products in all cases were isolated easily in high yield with a minimum amount of effort. All of the products were purified before analysis. Table III contains the experimental data.

Cyclohexylamine-ND$_2$.—A solution of 5.0 g. of cyclohexylamine in 25 ml. of ether was shaken with 3 ml. of deuterium oxide followed by four 1-ml. washes. The ether layer was dried over magnesium sulfate and evaporated to yield the deuterated amine. The infrared spectrum of this material indicated the presence of deuterium in the molecule. The amine was used as such in the reaction with the anhydride.

***p*-Nitrobenzoic Benzoic Anhydride-*p*-nitrobenzoyl Carbonyl-O^{18} (IX).**—The labeled anhydride was prepared as described by Denney and Greenbaum.[9]

Reaction of VI in the Presence of Benzoic Acid-C^{14}.[10]—To a solution of 0.465 g. (0.005 mole) of aniline, 0.61 g. (0.005 mole) of benzoic acid-C^{14}, activity 4.07 mμc./mg. C and

(9) D. B. Denney and M. A. Greenbaum, THIS JOURNAL, 79, 979 (1957).

(10) The authors wish to thank Dr. A. P. Wolf of the Brookhaven National Laboratory for his kind assistance in carrying out these experiments.

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TABLE III

Reactants[a]	Temp., °C.	Solvent	% Yield C_6H_5–CO–	% Yield C_6H_5–COOH
VI[b] + NH_3	−33	Ammonia, 25 ml.	70	65
VII + NH_3	−33	Ammonia, 25 ml.	93	86
VII + NH_3	−78	Ammonia, 25 ml.	91	85
VI + C_6H_5–NH_2	25	Ether, 30 ml.	80	70
VI + C_6H_5–NH_2	25	Acetone/H_2O, 20 ml.	81	75
VII + cyclo-C_6H_{11}–NH_2	25	Dimethylaniline, 25 ml.	85	80
VII + CH_3OH	25	Methanol, 25 ml.	92	80
VII + CH_3OH	25	Acetonitrile, 30 ml.	25[c]	21
VII + cyclo-C_6H_{11}–NH_2	25	Acetonitrile, 35 ml.	89	92
VII + C_6H_5–NH_2	25	Acetonitrile, 40 ml.	86	82
VII + C_6H_5–NH_2	25	Dimethylformamide, 40 ml.	86	90

[a] Unless otherwise specified the quantities of reactants used were 0.01 mole. [b] 0.0018 mole of VI used. [c] A large recovery of starting material indicated that this reaction was not completed.

0.61 g. (0.005 mole) of dimethylaniline in 50 ml. of anhydrous ether was added 1.13 g. (0.005 mole) of benzoic anhydride. After standing 1 hr., 10 ml. of 10% hydrochloric acid was added and the ether was evaporated. The heterogeneous mixture was treated with chloroform to dissolve the solid. The chloroform was washed with 10% sodium carbonate solution and water. The dried chloroform was evaporated to afford 1.01 g. of benzanilide which was recrystallized from methanol–water to afford 0.70 g. (71%) of material, m.p. 162.2–163.4°. The basic extracts were acidified to yield crude benzoic acid which was recrystallized from hexane to afford 0.90 g. (74%) of benzoic acid, m.p. 121–122°.

The recovered benzoic acid had an activity of 2.02 mμc./mg. C and the benzanilide showed 0.093 mμc./mg. C. These data indicate that 15% of the theoretical amount of C^{14} has been incorporated into the benzanilide.

When benzoic anhydride was allowed to stand under the same conditions but in the absence of aniline, the recovered benzoic anhydride had 0.63 mμc./mg. C which corresponds to 46% equilibration of the C^{14}.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Electronic Effects in Elimination Reactions. I. Pyrolysis of Acetates[1]

BY C. H. DEPUY AND R. E. LEARY

RECEIVED FEBRUARY 8, 1957

Pyrolytic eliminations of some acetates of substituted 1,3-diphenyl-2-propanols lead to the formation of that olefin which also predominates when the possible olefins are equilibrated and not to the olefin which would be formed by loss of the most acidic hydrogen. It is suggested that in the transition state for acetate pyrolysis reactions, a large amount of double bond character has been developed.

Although the Saytzeff and Hofmann rules—which allow the position of the double bond in unsymmetrical elimination reactions to be predicted—have been formulated for nearly a century, the underlying steric and electronic effects which determine this position still are not fully understood. The most generally accepted interpretation of the rules is that of Hughes and Ingold.[2] According to their view, in the Hofmann elimination (elimination from trialkylammonium or dialkylsulfonium salts with base) the most acidic hydrogen is removed and the direction of elimination is determined by this factor. In the Saytzeff elimination (elimination of halogen or other neutral anions), the stability of the resulting olefinic product is the more important factor and controls the direction of elimination. Hyperconjugative factors were postulated to be of primary importance. Recently Brown and co-workers[3] have demonstrated the importance of steric effects in directing eliminations.

A priori, an elimination of the type I might be imagined to have a whole spectrum of transition

$$H\text{–}C\text{–}C\text{–}X \longrightarrow H^+ C{=}C\ X^- \qquad (I)$$

states available to it, depending upon the nature of the group X, the particular mechanism of the elimination, the type of solvent and a host of other factors. As one extreme, a case might be imagined in which the carbon–hydrogen bond is completely broken before the C–X bond has even started to rupture, II. At the other extreme, both the C–H

$$H\cdots\overset{|}{C}\text{—}\overset{|}{C}\text{—}X \qquad (II)$$

and C–X bonds might be very much broken in the transition state, III. Other situations may be imagined. An understanding of the structural

$$H\cdots\overset{|}{C}\cdots\overset{|}{C}\cdots X \qquad (III)$$

factors that affect the transition state configuration could allow more control over the nature of the product to be expected in eliminations and the amount of olefin being formed in competing reac-

(1) This work was supported by a grant from the Research Corporation.

(2) For a general discussion of elimination reactions and for the conclusions of Ingold and co-workers about the Hofmann and Saytzeff rules, see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 420–472.

(3) H. C. Brown and I. Moritani, THIS JOURNAL, 78, 2203 (1956), and preceding papers.

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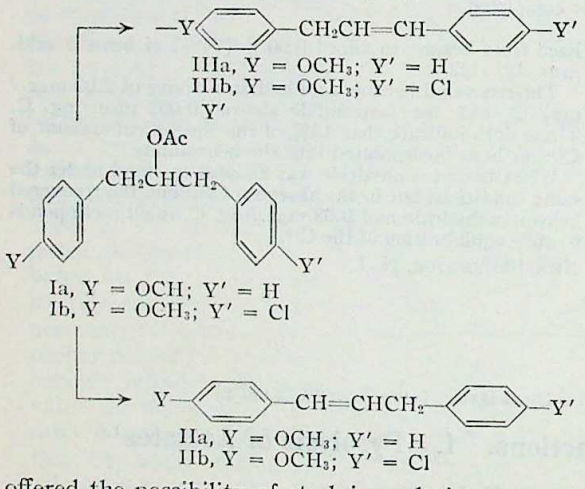
tions. To this end we have begun a general investigation of the effect of various electronic factors on the rate of several elimination reactions.

In studying elimination reactions, we wished to choose a system in which we could readily determine both the acidity of the hydrogens being removed and the relative stability of the olefins being formed. In addition, we desired a system in which base-catalyzed eliminations could be followed kinetically, and at the same time eliminations could be studied in which kinetic data would be either difficult to obtain (pyrolytic eliminations) or of no value (first-order eliminations). For this investigation we have chosen compounds of the type I. These 1,3-diphenyl-2-propyl compounds



offered the possibility of studying relative rates of eliminations where actual rate measurements were not possible. Thus, in a pyrolytic elimination of acetic acid the rate for a substituted benzene ring could be compared to the rate for an unsubstituted ring by analyzing the olefin mixture for the relative amounts of olefins II and III. Variations in the nature of the substituent would allow a Hammett σ–ρ treatment to be carried out. Concurrently a straight kinetic investigation of base-catalyzed eliminations in the simpler but analogous β-phenyl ethyl system was begun.

If the system I appeared satisfactory from the standpoint of kinetics, it also seemed attractive for the investigation of both the stabilities of the resultant olefins and the acidities of the hydrogens. Thus, Ingold and Shoppee[4] had shown that olefins of this type could be equilibrated in base and, of course, the proportion at equilibrium would reflect the relative thermodynamic stabilities of the two olefins. The relative hydrogen acidities could be estimated from the Hammett σ-values of the substituent groups and, if more precise data were deemed necessary, a study of the *rates* of the equilibration of the olefins would be indicative. Two other advantages of this system made its selection propitious. First the absence of selective steric effects served to simplify the interpretation of results, and secondly the ease of analysis of the mixture of products, as will be discussed below, offered the possibility of studying a number of different eliminations with the same system.

(4) C. K. Ingold and C. W. Shoppee, *J. Chem. Soc.*, 447 (1929).

Synthesis.—For reasons that will become apparent in the discussion of the analytical method, it was felt desirable to have Y = OCH_3. In order to make the rate differences as large as possible, the presence of a *p*-chloro group seemed desirable. In base-induced eliminations where hydrogen acidity is important, the presence of a *p*-chloro group favors the elimination by a factor of nearly ten.[5] On the other hand, a *p*-methoxyl group conjugates well with a double bond[3] and would be expected to accelerate those reactions in which the relative stability of the olefin played a dominant role. For this reason Ia and Ib were synthesized. The synthesis of the requisite alcohols are summarized in Charts I and II. These paths had the advantage over other imaginable paths of providing the olefins for equilibration and analysis studies.

Analytical Method.—In the pyrolysis of the acetates the two possible olefins would be obtained together with varying amounts of unreacted acetate. Other contaminants were to be anticipated when these compounds were applied to the study of other elimination reactions. While spectral analysis would probably be possible in this system, it appeared to be extremely difficult to make general. In choosing these particular compounds for the study, we planned to make use of the well-known variation in the reactivity of substituted benzyl compounds.[6] The mixture of olefins was converted to a mixture of benzyl bromides with HBr in methylene chloride under conditions where the initial acetate was unreactive. These solutions were made up to a known volume with absolute acetone and, after the addition of a small amount of water, the bromides allowed to solvolyze. The *p*-methoxybenzyl bromides formed by addition of HBr to olefins IIa and IIb solvolyzed very rapidly as compared to either the unsubstituted (from IIb) or *p*-chloro bromides (from IIc), and titration of the liberated acid after about 40 minutes at 25° gave the amount of this bromide present. Solvolysis at higher temperatures with more water added, or reaction with silver nitrate solution, was used to get the total halide and from this the amount of unsubstituted or *p*-chlorobenzyl bromide. By this method known mixtures could be determined to within 3%. It should be pointed out that the large differences in solvolysis rate which were utilized in these experiments are not necessary for the analytical method to be useful. Differences of a factor of three or less are sufficient if more kinetic points are taken.

Results and Discussion

Acetate pyrolysis reactions have been extensively investigated by Bailey and co-workers[7] in an effort to determine the direction of elimination. In three aliphatic cases the Hofmann rule was obeyed exclusively, that is, the hydrogen was abstracted from a CH_3 group in preference to a CH_2 group and from a CH_2 group in preference to a C–H group. This preference for the methyl hydrogen

(5) C. H. DePuy and D. H. Froemsdorf, THIS JOURNAL, **79**, 3710 (1957).

(6) J. K. Kochi and G. S. Hammond, *ibid.*, **75**, 3445 (1953).

(7) W. J. Bailey and C. King, *ibid.*, **77**, 75 (1955); W. J. Bailey and J. Nichols, *J. Org. Chem.*, **21**, 883 (1956).

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CHART I

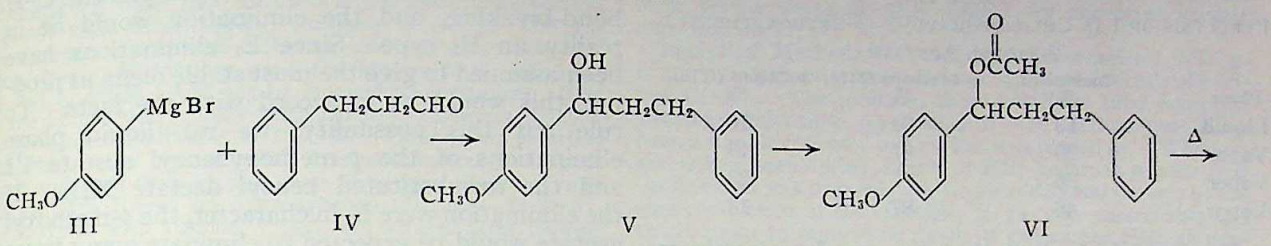
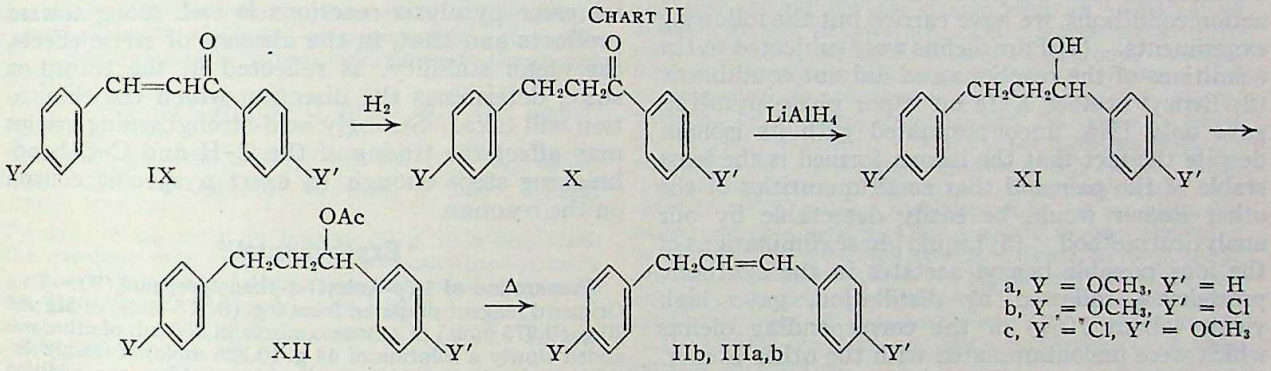


CHART II



a, Y = OCH_3, Y′ = H
b, Y = OCH_3, Y′ = Cl
c, Y = Cl, Y′ = OCH_3

was observed again in the pyrolysis[8] of 1-methoxy-2-propyl acetate and in 1-dimethylamino-2-propyl acetate. However, in compounds containing a benzene ring, Hofmann control was less complete. In 1-phenyl-1-propyl acetate, 75% of the resultant olefin was conjugated to the benzene ring; and this rose to 100% in the case of 1,1-diphenyl-2-propyl acetate.[9] Compounds containing nitro[10] and ester[9] groups also have given products not in accordance with the Hofmann rule.[11] In these cases the olefin formed was found to be conjugated with the unsaturated group. Bailey has interpreted these results to mean that the acidity of the hydrogen being removed is primarily responsible for determining the direction of elimination. Since our system gave a means of checking this conclusion where the various electronic influences were determinable and since, in addition, steric factors were the same for the competing eliminations, we decided to investigate the electronic effects in acetate pyrolyses as the first case in our general study of elimination reactions.

From the standpoint of its electronic effects, a *p*-methoxyl group appeared to be a desirable substituent. From its σ-value (-0.268)[12] it could be predicted to have the effect of decreasing the acidity of the benzyl hydrogens and so of making eliminations slower which depended on this acidity.[5] Ingold and Shoppee[4] have measured the position of equilibrium of the olefins IIa and IIIa and had found that IIa, in which the olefin was conjugated to the methoxyl group, predominated at equilibrium by a factor of 2.3. As a consequence, olefin IIa is the more stable of the two and should predominate in the pyrolysis if olefin stability is the more important effect in the transition state.

The results of a number of pyrolyses of acetate Ia under different conditions are summarized in Table I. Under all conditions investigated, the more thermodynamically stable of the two possible olefins is formed in the elimination. In fact, the olefin proportion is the same, within experimental error, as that which would result from equilibration.

TABLE I

PYROLYSIS OF 1-PHENYL-3-*p*-METHOXYPHENYL-2-PROPYL ACETATE

Phase	Conversion, %	*p*-Methoxy (IIa), %	Hydrogen (IIIa), %
Liquid	47	70	30
Vapor	46	75	25
Vapor	20	73	27
Vapor	..	70	30
Liquid	11	75	25

We next investigated a compound in which the difference in hydrogen acidity would be even larger than was the case in Ia. Replacement of the *p*-hydrogen with a chlorine ($\sigma = +0.227$) gave Ib in which the benzyl hydrogen acidity was greatly enhanced. On the other hand, our equilibration experiments showed that at equilibrium the *p*-methoxyl olefin should still predominate. The results of these pyrolyses, summarized in Table II, again indicate that the stability of the olefin being formed is controlling the direction of the elimination.

(8) W. J. Bailey and L. Nicholas, *J. Org. Chem.*, **21**, 648 (1952).
(9) W. J. Bailey and C. King, *ibid.*, **21**, 858 (1956).
(10) M. H. Gold, *ibid.*, **68**, 2544 (1946).
(11) Bailey[8] appears to have misconstrued the results of Paul and Tchelitcheff, *Compt. rend.*, **233**, 1116 (1951), on the pyrolysis of an acetylenic acetate.
(12) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapt. VII.

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TABLE II

PYROLYSIS OF 1-(*p*-CHLOROPHENYL)-3-(*p*-METHOXYPHENYL)-2-PROPYL ACETATE

Phase	Conversion, %	*p*-Methoxy (IIb), %	*p*-Chloro (IIIb), %
Liquid	13	84	16
Vapor	20	87	13
Vapor	26	77	23
Vapor	46	87	13

Because of the fact that the pyrolysis products and the equilibrium products were the same, it had to be demonstrated that the actual products isolated were those arising directly from the elimination and not being formed by equilibration of an initially formed mixture of a different composition. To establish that the products are stable to the reaction conditions, we have carried out the following experiments. (1) Pure olefins were subjected to the conditions of the reactions and did not equilibrate. (2) Benzyl acetate XIIa on vapor phase pyrolysis gave only IIIa, uncontaminated with its isomer, despite the fact that the isomer formed is the least stable of the pair and that small quantities of the other isomer would be easily detectable by our analytical method. (3) Liquid phase eliminations of the four possible benzyl acetates in the synthetic procedures, followed by distillation, gave high yields (about 70%) of the corresponding olefins which were uncontaminated with the other isomer. We believe that these control experiments establish the absence of post-equilibration to a high degree of probability.

Our results demonstrate that the relative stabilities of the olefins being formed are instrumental in determining the rate of eliminations and that, at least in our system, relative hydrogen acidity is not of importance. In compounds with very acidic hydrogens, as in the nitro and carbethoxy cases, it may be that resonance stabilization of anions is important; but our data make it unlikely that hydrogen acidity is important in the simple aliphatic systems. It seems more probable that steric factors are playing an important role in determining the course of the reaction[13] in these cases and that only when steric factors are canceled out, or the electronic effects become overpowering, do non-Hofmann products arise.

A transition state whose structure is rather close to that of the olefin seems a reasonable one for the acetate pyrolysis. Both the leaving group (–OOCCH$_3$) and the base (O=C) are weak, and simultaneous breaking of both the C–H and C–O bonds would be expected. The elimination would be anticipated to be much less exothermic than the E$_2$ reaction of the corresponding halides, and hence the transition state would occur well along the reaction coördinates.[14] This would lead to appreciable double bond character in the carbon–carbon bond, and interactions between this developing double bond and the aromatic substituents would parallel the interaction found in the olefinic products.

An alternative mechanism for these pyrolytic eliminations appeared possible. In this mechanism the C–O bond-breaking would precede C–H bond-breaking, and the elimination would be in reality an E$_1$ type. Since E$_1$ eliminations have been assumed to give the most stable olefin as product, this would be in accord with the facts. To rule out this possibility, we ran liquid phase eliminations of the *p*-methoxybenzyl acetate VI and the unsubstituted benzyl acetate XIIa. If the elimination were E$_1$ in character, the *p*-methoxyl acetate would be expected to eliminate many times faster than the unsubstituted acetate. However, the actual differences in rate were small and consistent with the view that differences in stability of the olefins being formed in the two cases were responsible for the differences in rates.

It seems probable then that the transition state for ester pyrolysis reactions is well along toward products and that, in the absence of steric effects, the olefin stability, as reflected in the transition state, determines the direction which the elimination will take. Strongly acid-strengthening groups may affect the timing of the C–H and C–O bond-breaking steps enough to exert a specific control on the reaction.

Experimental[15]

Preparation of 1-(*p*-Anisyl)-3-phenylpropanol (V).—To a Grignard reagent prepared from 9 g. (0.375 mole) of Mg and 70 g. (0.375 mole) of *p*-bromoanisole in 250 ml. of ether was added slowly a solution of 44 g. (0.328 mole) of freshly distilled hydrocinnamaldehyde in ether. After the addition was complete, the mixture was heated at reflux for 0.5 hr. and decomposed by the addition of 450 ml. of a cold, saturated solution of ammonium chloride. After washing and drying, the ether was removed and the oily residue distilled. The product (56.5 g., 71% yield, b.p. 175–180° (0.5 mm.)) crystallized upon scratching. Recrystallization from hexane gave needles, m.p. 46–48°. Several times during distillations, spontaneous elimination occurred giving the olefin IIa directly.

Preparation of 1-(*p*-Anisyl)-3-phenylpropene (IIa).—The olefins could best be prepared in a pure form by liquid phase pyrolysis of the acetates. The alcohol V was acetylated with pyridine and acetic anhydride to give 1-(*p*-anisyl)-3-phenylpropyl acetate (VI), b.p. 170–175° (1 mm.), n^{18}D 1.5458. The acetate (10 g.) was placed in a small distilling flask equipped with a short column and a graduated centrifuge tube as a receiver. The liquid was heated with a soft bunsen flame until acetic acid began to distil. Heating was continued at such a rate that the acetic acid distilled rapidly and until the calculated amount had been collected. The residue was then cooled, taken up in methylene chloride and washed free of any excess acid. Distillation gave 5.5 g. (70% yield) of olefin, b.p. 160° (1 mm.).

Anal. Calcd. for C$_{16}$H$_{16}$O: C, 85.68; H, 7.19. Found: C, 85.80; H, 7.04.

Preparation of Hydroxybenzoate VII.—A cold mixture of the olefin IIa (45 g., 0.2 mole) and 24 g. (0.2 mole) of benzoic acid in 240 ml. of methylene chloride was added over 0.5 hr. to a cold solution of 30 g. (0.23 mole) of perbenzoic acid in methylene chloride. The solution was stirred and kept below 5° with an ice-bath during the addition. After the solution stood overnight at 4°, the excess acid was removed by extraction and the methylene chloride removed. The crystalline hydroxybenzoate which remained could be used in the next step without further purification. A sample crystallized from aqueous alcohol gave m.p. 98–99°.

Anal. Calcd. for C$_{23}$H$_{22}$O$_4$: C, 76.22; H, 6.12. Found: C, 75.94; H, 6.06.

Preparation of 1-(*p*-Anisyl)-3-phenylpropanol-2 (Ia).—A solution of 40 ml. of concd. H$_2$SO$_4$, 40 ml. of water and 250 ml. of alcohol was added to 40 g. of the hydroxybenzoate

(13) But see T. D. Nevitt and G. S. Hammond, THIS JOURNAL, **76**, 4124 (1954), for an all-aliphatic case where product stability may be important.

(14) G. S. Hammond, *ibid.*, **77**, 334 (1955).

(15) The use of the Baird infrared spectrophotometer of the Institute of Atomic Research, Ames, Iowa, is hereby gratefully acknowledged.

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and the mixture heated at reflux for 3.5 hr. After cooling the mixture, water (200 ml.) was added and the ketone extracted with three 150-ml. portions of ether. The extracts were washed with carbonate and water and the solution dried. Distillation gave the ketone (b.p. 160–170° (1 mm.)) which could not be induced to crystallize. The crude ketone was reduced with lithium aluminum hydride to give, after distillation at 175–180° (1.5 mm.), a colorless oil which soon crystallized. Recrystallization from pentane and then from alcohol gave Ia as long needles; yield 20 g., 71% (based on hydroxybenzoate), m.p. 48–48.5°. Admixtures with alcohols V and XIa showed large depressions in melting points.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.68; H, 7.49. Found: C, 79.50; H, 7.50.

The acetate, prepared in the usual manner, had b.p. 188–190° (0.5 mm.). *Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.10; H, 7.18.

Preparation of 1-Phenyl-3-(*p*-anisyl)-1-propene (IIIa).—*p*-Anisaldehyde and acetophenone were condensed and reduced catalytically according to the method of reference 16 to give 1-phenyl-3-(*p*-anisyl)-1-propanone (Xa), m.p. 65–66°. Lithium aluminum hydride reduction gave the alcohol XIa, m.p. 64–65°.

Anal. Calcd. for $C_{16}H_{18}O_2$: C. 79.68; H, 7.49. Found: C, 78.95; H, 7.20.

Acetylation gave the acetate, b.p. 166–170° (0.7 mm.).

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.20; H, 6.95.

Pyrolysis of the ester by heating 30 g. in a pear flask with a free flame until approximately the calculated amount of acetic acid distilled and distillation of the residue gave the olefin, b.p. 147–148° (0.3 mm.), $n^{24}D$ 1.5948.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.90; H, 7.20.

Addition of HBr in methylene chloride to a sample of this olefin and subsequent solvolysis showed it to be uncontaminated with the other isomer.

Preparation of 1-(*p*-Anisyl)-3-(*p*-chlorophenyl)-1-propanol (XIc).—This alcohol, prepared by $LiAlH_4$ reduction of the corresponding ketone Xc,[15] was distilled at 196–200° (1 mm.). It could not be induced to crystallize.

Preparation of 1-(*p*-Anisyl)-3-(*p*-chlorophenyl)-2-propanol.—This alcohol was synthesized using the same procedure as above. In this series the hydroxybenzoate failed to crystallize, but the oily product was used directly to furnish crystalline ketone, m.p. 42–44°. Lithium aluminum hydride reduction of this ketone gave the alcohol, m.p. 69–69.5° after recrystallization first from hexane and then from alcohol–water.

Anal. Calcd. for $C_{16}H_{17}O_2Cl$: C, 69.43; H, 6.19; Cl, 12.85. Found: C, 69.60; H, 6.43; Cl, 12.70.

The acetate, prepared in the usual manner, had m.p. 64–65°. *Anal.* Calcd. for $C_{18}H_{19}O_3Cl$: C, 67.81; H, 6.01; Cl, 11.12. Found: C, 68.09; H, 6.09; Cl, 11.15.

Pyrolysis.—The pyrolyses were carried out by two different methods. In the liquid phase experiments the pure liquid acetates, together with a crystal of a polymerization inhibitor, were heated in a small flask until approximately 50% of the calculated amount of acetic acid was collected. The residue was taken up in ether or methylene chloride and washed free of acetic acid. The solvent was then removed and the residue analyzed. In the vapor phase experiments pure liquid acetate was added dropwise to the top of a vertical glass pyrolysis tube, electrically heated and equipped with a thermocouple. The tube was heated to 500°. Glass beads and glass helices gave identical results when used as packing for the tube. To minimize carbonization, eliminations were carried out to 20–50% conversion. The products were collected in a Dry Ice trap, an aliquot was removed and analyzed for acetic acid and the remainder was washed free of acid, dried and the solvent was removed. Samples of the residue were analyzed for the olefin proportions and other samples for unreacted acetate and total olefin.

Analytical Methods.—In a typical experiment 1.0746 g. of the pyrolysis mixture of Ia was dissolved in 5 ml. of purified CH_2Cl_2. The solution, in a centrifuge tube equipped with a gas inlet tube, was cooled to −10° and gaseous HBr, from a sample collected in Dry Ice, was passed in. When an excess had been added, fumes of HBr began to appear and the addition was stopped. After an additional minute to ensure completion of the reaction, N_2 gas was passed through the solution to remove as much of the excess HBr as possible. The solution was transferred to a 50-ml. volumetric flask and diluted to 50 ml. with anhydrous acetone. A 5-ml. aliquot was removed and the excess HBr was determined by titration with triethylamine in acetone. The sample required 0.09 ml. of 0.1 *N* base. Water (2 ml.) was added and the flask was placed in a constant temperature bath at 25°; 5-ml. samples were removed periodically and titrated. After 40 minutes, 1.80 ml. of amine was required, and this amount did not change after an additional 30 minutes at this temperature. This corresponds to 0.160 meq. of bromide conjugated to the *p*-anisyl group. Another 5-ml. sample of the solution was added to 5 ml. of standard aqueous silver nitrate solution, and the excess silver was determined by titration with standard thiocyanate. Silver (0.213 meq.) was used. Therefore, the olefin was 75% IIa and 25% IIIa. The sample contained 46% olefin. Titration of the acetic acid liberated in the pyrolysis had indicated that 47% reaction had taken place. A saponification equivalent on a sample of the pyrolysis product showed it to contain 51% unreacted acetate. Hence, 97–98% of the product was accounted for. At higher conversions the percentage of the product which could be accounted for by this method dropped off, presumably because of polymerization of the olefinic products, and olefin proportions from these runs are not reported.

Equilibration of Olefins.—The procedure was that of Ingold and Shoppee[4] except that the olefins were analyzed by the reaction with HBr described above. In the case of the IIa–IIIa equilibrium Ingold and Shoppee reported a 70–30 mixture and our results confirmed this. In the case of IIb–IIIb we found 85% IIb and 15% IIIb.

Control Experiments.—1-Phenyl-3-(*p*-anisyl)-1-propyl acetate (XIIa) was pyrolyzed over both glass beads and glass helices at 550°. The product was analyzed in the usual manner. In three runs with conversions up to 42% no easily solvolyzable bromide could be detected and the olefin was completely non-equilibrated. Samples of the pure olefins were passed through the pyrolysis tube and subsequently analyzed for olefin proportion. They were free of detectable amounts of the other isomer. Olefins prepared in the synthetic scheme by liquid phase pyrolysis were analyzed and shown to be uncontaminated with the isomers.

A sample of the pure 2-propylacetates Ia and Ib were subjected to the conditions of the analytical procedure. No detectable solvolyzable bromide was formed, nor was any silver bromide precipitated. In the cases of the benzyl acetates, XII, HBr was absorbed to form presumably the benzyl bromides.

Solvents and Reagents.—The acetone was purified by refluxing with potassium permanganate and drying with Drierite. It was then distilled through a 50-plate column. The triethylamine was refluxed over sodium for 0.5 hr. and then distilled through a 50-plate column; b.p. 88.0°. The indicator was a mixture of brom cresol green and methyl red.[5]

Competitive Pyrolyses of Benzyl Acetates.—Two grams of 1-(*p*-anisyl)-3-phenyl-1-propyl acetate (V), and 1-phenyl-3-(*p*-anisyl)-1-propyl acetate (XIIa), were placed in separate test-tubes and simultaneously placed in a Woods metal-bath at 320° for three minutes. The samples were removed at the same time and analyzed for olefin by reaction in methylene chloride solution with a standard solution of perbenzoic acid. Under these conditions V developed 74% olefin and XIIIa developed 20%.

AMES, IOWA

(16) "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941, p. 101.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Electronic Effects in Elimination Reactions. II. The E_2 Reaction[1a,b]

BY C. H. DEPUY AND D. H. FROEMSDORF

RECEIVED FEBRUARY 8, 1957

The base-promoted elimination reaction of substituted β-phenylethyl halides, tosylates and sulfonium salts has been studied as a function of substituents. Good fits to a Hammett $\sigma-\rho$ plot were obtained, indicating that the acidity of the hydrogen being removed is controlling the direction of elimination. In contrast to their reactivity in solvolysis and displacement reactions, tosylates are eliminated very slowly as compared to bromides and iodides.

In connection with a general study of electronic effects in elimination reactions,[1b] we were led to an investigation of the electronic effects in the E_2 reaction, both because of the interest in the reaction for its own sake[2] and because such a study would serve as a reference for our investigation in the similar 1,3-diphenylpropyl system. Surprisingly, no comprehensive investigation of substituent effects on E_2 eliminations has been reported[3] except for some polyhalo compounds[4] and for a few β-phenylethyl chlorides.[5] Quantitative data on E_2 tosylate eliminations are likewise unavailable.[6]

Our data for the elimination of β-phenylethyldimethylsulfonium iodide, β-phenylethyl bromide, iodide and tosylate are summarized in Tables I and II. For the sulfonium salts $\rho = 2.75 \pm 0.21$, the highest value of ρ for the series. For the bromides $\rho = 2.14 \pm 0.15$ and for the iodides $\rho = 2.07 \pm 0.09$. Omitting the point for the *p*-methoxy group, $\rho = 2.50 \pm 0.06$ for the tosylates. A high positive value for ρ implies that in the transition state of the reaction a large amount of negative charge has developed, and those groups which make a negative charge more stable speed up the reaction.[7]

It has been suggested that the Saytzeff rule is a consequence of a transition state in which the stability of the incipient double bond is the dominant characteristic.[2a,8] Our results indicate that when the hydrogen being removed is on a carbon adjacent to a benzene ring, the stability of the product being formed is not of importance,[9] for if it were the *p*-methoxystyrene should be formed most rapidly.[1b,10] The fact that the sulfonium salts, bromides and iodides, and to a major extent the tosylates,[9] all show a good correspondence of rate with a measure of hydrogen acidity is to be contrasted with our results with acetate pyrolysis reactions in which a good correlation with product stability was observed[1b] in an analogous system. In these two cases we have demonstrated the extremes of transition state structural variation, from one in which double bond development is too small to be significant (E_2) to one in which the stability of the double bond being formed determines the rate of elimination.

TABLE I

RATES OF THE ELIMINATION REACTION OF $XC_6H_4CH_2CH_2Y$ at 30.10°

X	Y	k	Olefin, %	k_{E2}
H	Br	4.10×10^{-4}	100	4.10×10^{-4}
p-Cl	Br	1.88×10^{-3}	100	1.88×10^{-3}
p-OCH_3	Br	1.73×10^{-4}	100	1.73×10^{-4}
m-Br	Br	3.71×10^{-3}	100	3.71×10^{-3}
H	I	2.66×10^{-3}	100	2.66×10^{-3}
p-Cl	I	1.05×10^{-2}	100	1.05×10^{-2}
p-OCH_3	I	9.56×10^{-4}	100	9.56×10^{-4}
m-Br	I	2.03×10^{-2}	100	2.03×10^{-2}
H	OTos	1.18×10^{-4}	33	3.92×10^{-5}
p-Cl	OTos	2.93×10^{-4}	47	1.38×10^{-4}
p-OCH_3	OTos	8.61×10^{-5}	20	1.69×10^{-5}
m-Br	OTos	5.53×10^{-4}	67	3.69×10^{-4}
H	$S(CH_3)_2I^-$	3.79×10^{-3}	100	3.79×10^{-3}
p-Cl	$S(CH_3)_2I^-$	2.18×10^{-2}	100	2.18×10^{-2}
p-CH_3	$S(CH_3)_2I^-$	9.13×10^{-4}	100	9.13×10^{-4}

TABLE II

	ρ (method of least squares)	log k_0 (calcd.) Intercept
Tosylates (omitting *p*-methoxy)	2.50 ± 0.06	−4.427
Tosylates (including *p*-methoxy)	2.04 ± .47	−4.280
Bromides	2.14 ± .15	−3.260
Iodides	2.07 ± .09	−2.497
Sulfonium salts	2.75 ± .21	−2.330

The fact that the ρ-value for the sulfonium salts is larger than that for the bromides and iodides implies that the transition state for Hofmann eliminations has significantly more carbanionic character than that for the elimination of iodides or bromides. Whether this difference would be enough to account for some of the differences in direction of halide and 'onium salt eliminations in strictly aliphatic systems[2] cannot yet be said with certainty.

(1) (a) Supported by a Grant-in-Aid from the Monsanto Chemical Co. Presented in part at the 130th Annual Meeting of the American Chemical Society, Atlantic City, N. J., September 16–21, 1956. (b) Paper I in this series, C. H. DePuy and R. E. Leary, THIS JOURNAL, **79**, 3705 (1957).

(2) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, p. 420; (b) W. H. Saunders and R. A. Williams, THIS JOURNAL, **79**, 3712 (1957).

(3) At the time of our preliminary announcement of some of these results, we were informed by Dr. W. H. Saunders of the results of some excellent work that was being done in his laboratory along similar lines.[2b] The existence of these data, more complete than our own in terms of the temperature range studied but confined to two leaving groups, has influenced the presentation of our data. We shall be content to point out a few conclusions pertinent to our main interests and to refer the reader to the report of Dr. Saunders for much of the background. We are grateful to Dr. Saunders for interesting discussions and for data on the extinction coefficients of some of the olefins.

(4) S. J. Cristol, N. L. Hause, A. J. Quant, H. W. Miller, K. R. Eilar and J. S. Meek, THIS JOURNAL, **72**, 3333 (1952).

(5) M. Simonetta and G. Favini, *J. Chem. Soc.*, 1840 (1954).

(6) *Cf.* R. P. Linstead, L. N. Owen and R. F. Webb, *ibid.*, 1218 (1953).

(7) See R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 556, for a discussion of the mechanistic interpretation of ρ.

(8) H. C. Brown and I. Moritani, THIS JOURNAL, **78**, 2203 (1956).

(9) See, however, the discussion of the deviation of the *p*-methoxyl tosylate.

(10) C. K. Ingold, E. H. Ingold and C. W. Shoppee, *J. Chem. Soc.*, 447 (1929).

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Perhaps the most surprising result of this investigation is the very slow rate of elimination of the tosylates. For the unsubstituted cases, $k_I/k_{Tos} = 68$ and $k_{Br}/k_{Tos} = 10$. In the case of direct displacement reactions, sulfonic acid esters appear to be more reactive than either bromides or iodides,[11] although admittedly the data are meager. This slowness in the elimination reaction has a synthetic as well as a theoretical value. From Table I it can be seen that the percentage olefin in the product varies from 20 to 67% for the tosylate eliminations. In all other cases of leaving groups studied, the olefin yield was close to 100%. Hence, while the E_2 reaction is slow, apparently the S_N2 reaction remains fast. For this reason the tosylate can be useful in preparing the corresponding ethers or amines[12] when the iodides and bromides lead only to olefin. The meagerness of available data makes a firm theoretical conclusion hazardous, and we shall discuss in subsequent papers the results of a more detailed study of tosylate elimination. The *p*-methoxy tosylate eliminates significantly faster than would be predicted on the basis of the ρ-value of the reaction. This may imply that, in this relatively unactivated case, some effect of the olefin stability is being felt in the transition state.

Experimental

Preparation of 2-Arylethanols. 2-(*m*-Bromophenyl)-ethanol.—*m*-Bromoacetophenone was prepared by bromination of acetophenone in the presence of excess anhydrous aluminum chloride.[13] This was transformed into *m*-bromophenylacetic acid by heating under reflux for 16 hr. 103 g. of the ketone with 68 g. of morpholine and 25 g. of sulfur. The resulting thiomorpholide was hydrolyzed by boiling with 10% potassium hydroxide for 18 hr. and then acidifying. The precipitated *m*-bromophenylacetic acid weighed 78.7 g. (70.7% yield) and had m.p. 99–100° (lit.[14] m.p. 100°). Lithium aluminum hydride reduction of the ethyl ester gave the alcohol, b.p. 107–110° (1 mm.).

2-(*p*-Chlorophenyl)-ethanol was prepared by refluxing *p*-chlorobenzyl cyanide with 95% ethanol and concentrated sulfuric acid[15] to yield the ethyl ester of *p*-chlorophenylacetic acid. Reduction with lithium aluminum hydride gave the alcohol (75.5% yield), b.p. 98–100° (1 mm.) (lit.[16] b.p. 110° (0.5 mm.)).

2-(*p*-Methoxyphenyl)-ethanol was prepared from *p*-methoxyacetophenone by the same method[17] as the 2-(*m*-bromophenyl)-ethanol, b.p. 110–113° (1 mm.) (lit.[18] 148° (19 mm.)).

2-Phenylethanol was Eastman Kodak Co. White Label.

Preparation of Tosylates.—The tosylates were prepared from the corresponding alcohol by Tipson's procedure.[19]

2-(*m*-Bromophenyl)-ethyl-*p*-toluenesulfonate, m.p. 43–44°. *Anal.* Calcd. C, 50.75; H, 4.26; S, 9.02. Found: C, 51.05; H, 4.54; S, 9.44.

2-(*p*-Chlorophenyl)-ethyl *p*-toluenesulfonate, m.p. 79.3–80.3°. *Anal.* Calcd. C, 58.00; H, 4.87; S, 10.32. Found: C, 58.00; H, 4.76; S, 10.69.

2-(*p*-Methoxyphenyl)-ethyl *p*-toluenesulfonate, m.p. 58.6–59.6°. *Anal.* Calcd. C, 62.72; H, 5.92; S, 10.46. Found: C, 62.86; H, 5.82; S, 10.60.

2-Phenylethyl *p*-toluenesulfonate, m.p. 38.5–39°. *Anal.* Calcd. C, 65.20; H, 5.84; S, 11.60. Found: C, 65.45; H, 5.77; S, 11.25.

Preparation of 2-Arylethyl Bromide.—The bromides were prepared by addition of the appropriate tosylate to a solution of anhydrous lithium bromide in acetone[20] and careful fractionation of the resultant bromides: 2-(*m*-bromophenyl)-ethyl bromide, b.p. 98–100° (1 mm.); 2-(*p*-chlorophenyl)-ethyl bromide, b.p. 79° (0.5 mm.); 2-(*p*-methoxyphenyl)-ethyl bromide, b.p. 79° (0.5 mm.); 2-phenylethyl bromide was Eastman Kodak Co. White Label which was redistilled, b.p. 65° (2 mm.).

Preparation of 2-Arylethyl Iodides.—The iodides were prepared by addition of the appropriate tosylate to a solution of anhydrous sodium iodide in acetone[20] and fractionation: 2-(*m*-bromophenyl)-ethyl iodide, b.p. 105–110° (1 mm.); 2-(*p*-chlorophenyl)-ethyl iodide, b.p. 115–117° (1 mm.); 2-(*p*-methoxyphenyl)-ethyl iodide, b.p. 117–119° (1 mm.); 2-phenylethyl iodide was Eastman Kodak Co. White Label which was redistilled, b.p. 95° (3 mm.).

Preparation of Sulfonium Salts.—The sulfonium salts were prepared by treating the appropriate iodide with sodium methylmercaptide[8]; this gave the sulfide. The sulfide was then treated with methyl iodide[8] in acetonitrile which gave the dimethylsulfonium iodide: 2-(*p*-chlorophenyl)-ethyldimethylsulfonium iodide, m.p. 127–128°; 2-(*p*-methoxyphenyl)-ethyldimethylsulfonium iodide, m.p. 118–119°; 2-phenylethyldimethylsulfonium iodide, m.p. 124–125°.

Procedure for Kinetics.—The reactions were carried out in 100-ml. volumetric flasks. About 0.06 mole of the desired compound was placed in the volumetric flask and weighed accurately. Then 0.12 *N* sodium ethoxide in absolute ethanol, previously equilibrated thermally with the bath, was added to the calibration mark of the volumetric flask. After adequate agitation, the flask was placed in the bath and allowed to come to thermal equilibrium. Aliquots were then withdrawn periodically with a calibrated automatic pipet.

A modification of this method was necessary for the sulfonium salts because of their slow rate of dissolution. The weighed sulfonium salt was dissolved in 50 ml. of absolute ethanol and 0.24 *N* sodium ethoxide in absolute ethanol added so the total volume was 100 ml.

Olefin Determinations.—The reactions were allowed to go to completion, and 25-ml. aliquots were poured into water and extracted with carbon tetrachloride (3 × 10 ml.), the extract washed with water and the amount of olefin determined by bromination with standard bromide–bromate solution.[21] Duplicate runs agreed to within 1%.

In the bromination of the *p*-methoxystyrene it was necessary to modify the above method by adding the bromide–bromate solution in 1-ml. aliquots until a color remained to the solution. This was necessary to minimize substitution by avoiding an excess of bromine. In the case of sulfonium salts it was necessary to wash the carbon tetrachloride layer twice with saturated mercuric chloride solution to extract dimethyl sulfide.

AMES, IOWA

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(16) G. Baddeley and G. M. Bennett, *J. Chem. Soc.*, 1819 (1935).
(17) U. V. Solmssen and E. Wenis, THIS JOURNAL, **70**, 4200 (1948).
(18) G. M. Bennett and M. Hafaz, *J. Chem. Soc.*, 652 (1941).
(19) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).
(20) H. C. Brown and O. H. Wheeler, THIS JOURNAL, **78**, 2199 (1956).
(21) Sidney Siggia, "Quantitative Organic Analysis *via* Functional Groups," 2nd Ed., John Wiley & Sons, Inc., New York, N. Y., 1954, p. 68.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF ROCHESTER]

Mechanisms of Elimination Reactions. II. Rates of Elimination from Some Substituted 2-Phenylethyl Bromides and 2-Phenylethyldimethylsulfonium Bromides[1]

BY WILLIAM H. SAUNDERS, JR., AND RICHARD A. WILLIAMS[2]

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A series of *p*-substituted 2-phenylethyl bromides and 2-phenylethyldimethylsulfonium bromides has been prepared. The rates of their reactions with sodium ethoxide in ethanol were determined over a range of temperatures and the enthalpies and entropies of activation calculated. All of the compounds studied gave quantitative yields of the corresponding styrenes. The data fit the Hammett equation satisfactorily, giving $\rho = +2.15$ for the bromides and $+2.64$ for the sulfonium salts when the substituents are *p*-methoxyl, *p*-methyl, hydrogen and *p*-chloro. The substituents *p*-acetyl and *p*-nitro require the use of σ-values derived from the reactions of phenols and anilines. Factors affecting the balance and timing of the bond-making and bond-breaking processes in E2 eliminations are discussed, and some applications of these ideas to previous results are made.

Recent studies of base-promoted elimination reactions have suggested the need for revision of some commonly accepted ideas. For instance, the usual marked preference for *trans* elimination may be greatly reduced when electron-withdrawing substituents are present on the β-carbon atom[3] or when the four centers involved (H–C–C–X) cannot achieve coplanarity.[4] Reactivities of diastereomeric 1,2-diphenyl-1-propyl derivatives show that the degree of eclipsing in the transition state may be greatly modified by changes in the leaving group, the solvent and the base.[5] The absence of an appreciable sulfur isotope effect in eliminations from 2-phenylethyldimethylsulfonium bromide has been taken as indicating a transition state possessing considerable carbanion character.[1]

These and other results provide evidence that many E2 eliminations may depart rather widely from the conventional picture of a synchronous *trans* process. Recent evidence that steric[6] as well as electronic factors may be important in elimination reactions also calls for a reconsideration of former concepts. We felt that a systematic study of electronic influences on rates of eliminations might shed further light on these problems. Consequently, the preparation of a series of *p*-substituted 2-phenylethyl bromides and 2-phenylethyldimethylsulfonium bromides was undertaken and the rates of their reactions with sodium ethoxide in absolute ethanol were determined. It was anticipated that the direction and magnitude of substituent effects would lead to information on the electron distribution in the transition state.

Syntheses of the desired compounds were accomplished by conventional procedures. The reactions employed in most cases are summarized in Fig. 1. A considerable number of the intermediates and products were unknown prior to this investigation. Details on these and other aspects of the synthetic approach are given under Experimental. Some departures from the general scheme were necessary. Direct acetylation[7] of IIIa and IVa yielded IIIe and IVe, respectively. Nitration[7] of IIIa gave IIIf. Attempts to prepare Vf were unsuccessful and were abandoned when it became apparent that the reaction of Vf with base would be too fast to measure.

The compounds examined in the kinetic studies were IIIa-f in the bromide series and Va-d in the sulfonium bromide series. The corresponding styrenes (VI) were, for the most part, obtained by treatment of the sulfonium salts with aqueous sodium hydroxide, followed by isolation and careful distillation of the styrenes. The ultraviolet absorption spectra of the styrenes were determined in absolute ethanol. Extinction coefficients at the maxima used for analysis are recorded in Table I. These values were used in the calculation of olefin yields in the kinetic experiments.

TABLE I

ULTRAVIOLET ABSORPTION OF *p*-SUBSTITUTED STYRENES IN 95% ETHANOL

Cpd.[a]	λ_{max}, mμ	Molar extinction $\times 10^{-4}$
VIa	248	1.38[b]
VIb	252	1.69
VIc	258	1.92
VId	253	1.97
VIe	280	2.07[c]
VIf	300	1.37[d]

[a] See Fig. 1 for numbering of compounds. [b] Lit.[1] 1.35 $\times 10^4$. [c] G. Baddeley, E. Wrench and R. Williamson, *J. Chem. Soc.*, 2110 (1953), give 2.15×10^4. [d] M. J. Kamlet and D. J. Glover, THIS JOURNAL, 77, 5696 (1955), give 1.39×10^4.

The rates of the reactions of III and V with sodium ethoxide in absolute ethanol were followed acidimetrically. Olefin yields were calculated from the ultraviolet absorption of the reaction mixtures at the appropriate maxima. Rate constants and olefin yields are collected in Table II. The olefin yields are obviously within experimental error of 100% and thus the rate constants are attributable entirely to elimination.[8] The reactions were all

(1) Paper I in this series: W. H. Saunders, Jr., and S. Ašperger, THIS JOURNAL, 79, 1612 (1957).

(2) American Cyanamid Fellow, 1955–1956; Beaunit Mills Fellow, Summer, 1956.

(3) J. Weinstock, R. G. Pearson and F. G. Bordwell, THIS JOURNAL, 78, 3468 (1956).

(4) S. J. Cristol and N. L. Hause, *ibid.*, 74, 2193 (1952); S. J. Cristol and R. P. Arganbright, Abstracts of Papers, 130th Meeting of the American Chemical Society, Atlantic City, N. J., September 16–21, 1956.

(5) D. J. Cram, F. D. Greene and C. H. DePuy, THIS JOURNAL, 78, 790 (1956).

(6) H. C. Brown and I. Moritani, *ibid.*, 78, 2203 (1956), and preceding papers.

(7) E. L. Foreman and S. M. McElvain, *ibid.*, 62, 1435 (1940).

(8) The styrene yield from IIIa is reported to be 94.6% by E. D. Hughes, C. K. Ingold, S. Masterman and B. J. McNulty, *J. Chem. Soc.*, 899 (1940). The sulfonium iodide corresponding to Va is reported to give 89.4% olefin by E. D. Hughes, C. K. Ingold and G. A. Maw, *ibid.*, 2072 (1948). Our analyses employed the bromine-addition

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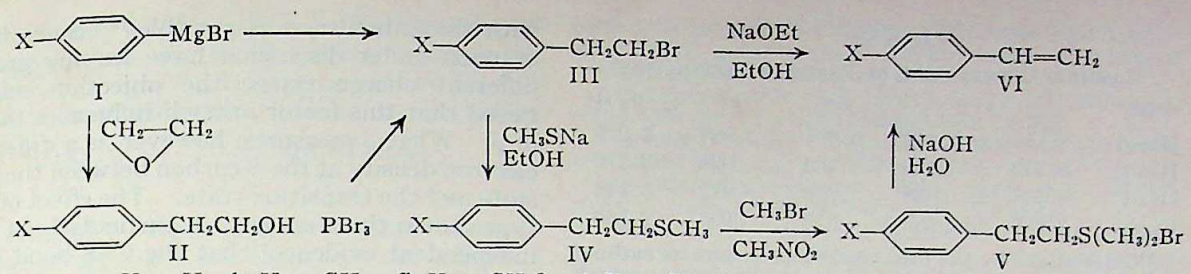

a, X = H; b, X = CH_3; C, X = CH_3O; d, X = Cl; e, X = CH_3CO; f, X = NO_2

Fig. 1.—Synthetic scheme.

cleanly second order and the constants were steady to a precision of 1–2% in practically all cases. The data were fitted to log k *vs.* $1/T$ plots by the method of least squares and the enthalpies and entropies of activation calculated. These values are recorded in Table III.

TABLE II

RATE CONSTANTS AND OLEFIN YIELDS FOR ELIMINATIONS FROM 2-ARYLETHYL BROMIDES AND 2-ARYLETHYLDIMETHYLSULFONIUM BROMIDES WITH SODIUM ETHOXIDE IN ABSOLUTE ETHANOL

Cpd.[a]	T, °C.	$k_2 \times 10^5$, l. mole^{-1} sec.$^{-1}$[c]	Olefin yield, %[c]
IIIa	59.40	814 ± 9.4	99.7 ± 0.3
IIIa	50.20	342 ± 4.3	99.5 ± .3
IIIa	40.75	133 ± 2.1	99.6 ± .4
IIIa	30.05	41.7 ± 0.66	99.6 ± .1
IIIb	59.40	494 ± 6.0	100.1 ± .2
IIIb	50.20	202 ± 3.3	99.6 ± .4
IIIb	40.75	75.0 ± 1.14	100.0 ± .1
IIIb	30.05	22.8[b]	.....
IIIc	59.40	378 ± 4.7	99.3 ± 0.4
IIIc	50.20	151 ± 1.5	100.5 ± .3
IIIc	40.75	52.8 ± 0.71	99.8 ± .3
IIIc	30.05	16.2[b]	.....
IIId	50.20	1410 ± 22	99.1 ± 0.5
IIId	40.75	585 ± 11.9	99.4 ± .4
IIId	30.05	191 ± 3.3	99.0 ± .1
IIIe	30.05	3720[b]	.....
IIIe	20.10	1340 ± 27	100.4 ± 0.3
IIIe	10.35	464 ± 5.1	100.0 ± .2
IIIe	0.0	135 ± 2.4	100.2 ± .1
IIIf	30.05	74200[b]	.....
IIIf	10.35	9140 ± 280	99.0 ± 0.7
IIIf	0.0	2680 ± 24	99.4 ± .5
Va	40.75	1970 ± 26	99.4 ± .2
Va	30.05	500 ± 7.5	99.4 ± .3
Va	20.10	133 ± 1.1	99.4 ± .2
Vb	40.75	1000 ± 12	99.5 ± .4
Vb	30.05	232 ± 2.3	99.9 ± .3
Vb	20.10	55.1 ± 0.69	100.2 ± .2
Vc	40.75	484 ± 3.6	99.5 ± .4
Vc	30.05	111 ± 1.4	99.3 ± .2
Vd	30.05	2440 ± 38	99.0 ± .2
Vd	20.10	680 ± 12	99.2 ± .3
Vd	10.35	177 ± 3.8	99.0 ± .1

[a] See Fig. 1 for numbering of compounds. [b] Extrapolated from the Arrhenius plot of data at other temperatures. [c] Deviations listed are average deviations.

Inspection of the rate constants shows that the elimination reaction in both series is strongly accelerated by electron-withdrawing substituents. Activation enthalpies for the sulfonium salts run 3–5 kcal. higher than for the bromides, but the reactions of the sulfonium salts are actually faster because of a compensating difference in entropies of activation. The much larger entropies of activation for the sulfonium salts probably can be ascribed mainly to entropies of solvation. Since the reaction is between oppositely charged ions, solvent molecules should be released on going to the transition state. The variation in entropy of activation among the bromides (except IIIf) appears to be within experimental error. The difference for IIIf may have mechanistic significance, but we cannot exclude the possibility of systematic errors in the rate constants aggravated by the high speed of the reaction. Entropies of activation for the sulfonium salts are spread over a wider range (*ca.* 5 e.u.), and there is a tendency for high $\Delta S^{\ddagger}$ to be associated with high $\Delta H^{\ddagger}$.[9]

TABLE III

ENTROPIES AND ENTHALPIES OF ACTIVATION FOR ELIMINATIONS FROM 2-ARYLETHYL BROMIDES AND 2-ARYLETHYLDIMETHYLSULFONIUM BROMIDES

Cpd.	T, °C.[a]	$\Delta H^{\ddagger}$,[b] kcal.-mole^{-1}	$\Delta S^{\ddagger}$,[c] cal.-mole^{-1}, °C.$^{-1}$
IIIc	50	20.8	−7.3
IIIb	50	20.3	−8.2
IIIa	45	19.6	−9.2
IIId	40	18.7	−9.2
IIIe	20	17.6	−7.0
IIIf	5	17.7	−0.8
Vc	45	25.4	11.6
Vb	30	25.0	12.2
Va	30	23.3[d]	7.7
Vd	20	22.2	7.2

[a] Mid-point of the temperature range of the data. [b] Calculated from the slope (method of least squares) of a log k *vs.* $1/T$ plot and the equation $\Delta H^{\ddagger} = E_a - RT$. [c] Calculated from the intercept (method of least squares) of a log k *vs.* $1/T$ plot. [d] lit.[8] reports E_a = 23.9 kcal., which is equivalent to $\Delta H^{\ddagger}$ = 23.3 kcal.

Rate constants at 30° (some extrapolated from data at other temperatures) for the *p*-substituents methoxyl, methyl, hydrogen and chlorine in each series were fitted to the Hammett equation[10] by the method of least squares, using the σ-values tabulated by Jaffé.[10b] Table IV records the results of these calculations. Reaction constants for the entire series of bromides IIIa to IIIf are also tabulated. It is evident that the calculations employ-

(9) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955), discusses such relationships and quotes many examples.

(10) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chap. VII; (b) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

method. The reasons for the discrepancies are not entirely clear, but chances of loss of product should be greater in the chemical than in the spectrophotometric analyses.

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TABLE IV

HAMMETT CORRELATION OF RATES OF ELIMINATION[a]

Cpd.	ρ	s^e	r^f	$-\log k_0^g$
IIIa-d	2.154 ± 0.242[d]	0.091	0.987	3.269
IIIa-f[b]	2.342 ± .115	.154	.996	3.270
IIIa-f[c]	3.505 ± .338	.308	.982	3.148
Va-d	2.639 ± .157	.059	.996	2.365

[a] Calculations by the least squares procedure as outlined in ref. 10b. [b] Using σ^*-values for *p*-nitro and *p*-acetyl. [c] Using ordinary σ-values for *p*-nitro and *p*-acetyl. All σ-values are from ref. 9b. [d] Standard deviation of ρ. [e] Standard deviation of experimental points from the least squares line. [f] Correlation coefficient. [g] Calculated value of the intercept.

ing σ^*-values[10b] (those derived from the reactions of phenols and anilines) give a far better fit with the *p*-acetyl and *p*-nitro groups. Figure 2 shows that the use of ordinary σ-values for these two substituents produces marked curvature.[11]

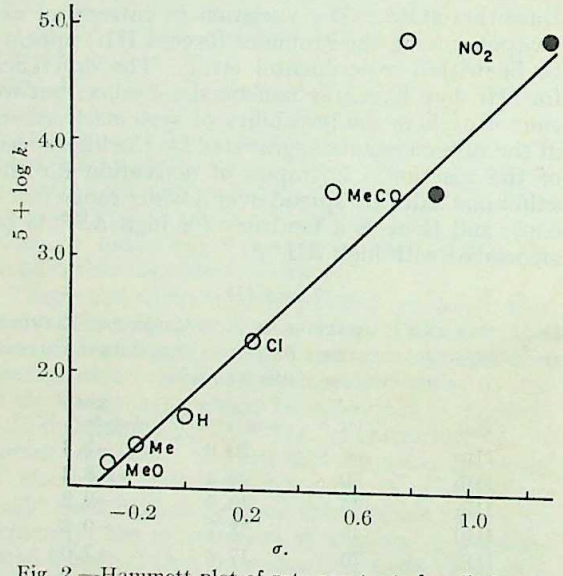
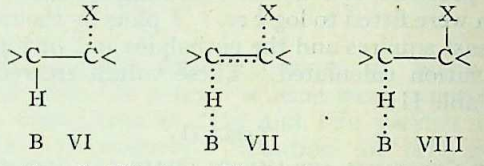


Fig. 2.—Hammett plot of rate constants for eliminations from *p*-substituted 2-phenylethyl bromides. The straight line is constructed from data given in line 2, Table IV. Open circles, ordinary σ-values; solid circles, σ^*-values.

The results of the Hammett correlation clearly show that eliminations from the sulfonium salts are more sensitive to electronic effects than are eliminations from the bromides. The rather large positive values of ρ suggest that the carbon atom adjacent to the ring (the β-carbon) acquires considerable negative charge in the transition state[12] and that this increase in charge density is greater for the sulfonium salts than for the bromides. Further support for this view is found in the necessity of using σ^*-values for *p*-nitro and *p*-acetyl, since these are derived from cases where strong resonance interaction of a negative charge or an unshared pair with the substituent is possible.[13] Since the two systems under discussion have leaving groups of different charge types, the objection might be raised that this factor in itself influences the value of ρ. What ρ measures, however, is a *difference* in electron density at the β-carbon between the ground state and the transition state. The effect of charge type should therefore cancel, particularly in view of independent evidence[1] that the C–S bond is little disturbed on going to the transition state.

The nature of the transition state in E2 eliminations can be discussed best in terms of the structures VI–VIII.[5] In this representation VII is the



conventional E2 transition state. Appropriate changes in reaction variables could, however, shift the mechanism either toward the E1 (VI) or the E1cb (VIII) end of the scale. The manner in which the solvent, the base and the nature of the group "X" affect the transition state already has been discussed by Cram.[5]

The larger ρ-value for the sulfonium salts than for the bromides is in harmony with the greater ease of heterolysis of a C–Br bond than a C–$\overset{+}{S}R_2$ bond.[14] The positive charge on sulfur would also increase the ease of heterolysis of the C–H bond *via* an electrostatic effect. Both of these factors would increase the contribution of VIII. Our evidence leads to the somewhat surprising conclusion that even with the bromides the transition state is closer to VIII than to VII. If simple alkyl halides are assumed to react *via* a transition state similar to VII, this means that a β-phenyl group shifts the mechanism toward the E1cb end of the scale. Comparison of our results with those of Cram[5] suggests that an α-phenyl group has the opposite effect.[15] It should be remembered, however, that the *p*-substituents themselves probably affect the nature of the transition state. The calculated ρ thus represents an average over the range of compounds studied and is not necessarily a good measure of electron distribution in the unsubstituted case. The systems studied by Weinstock, Pearson and Bordwell[3] probably react *via* a carbanion-like transition state because of the strongly electron-withdrawing β-sulfone grouping. The low preference for *trans* over *cis* elimination supports this view, since a transition state with a large contribution from VIII and only a small contribution from VII would not be very dependent on a *trans–anti* arrangement of the β-hydrogen and the leaving group. Another example of an electron-withdrawing group reducing the preference for *trans* elimination has been given by Cristol and Norris.[16]

(11) The compound Ve was also examined kinetically at 0 and 10°. The extrapolated rate constant appeared to fit the σ^*-value better, but the measured constants were very imprecise due to the high speed of reaction. Discussion will therefore be reserved until contemplated studies in aqueous solution are completed.

(12) See C. G. Swain and W. P. Langsdorf, Jr., THIS JOURNAL, **73**, 2813 (1951), for an excellent discussion of the reasoning in this interpretation of reaction constants.

(13) The σ^*-values also apply to activated nucleophilic aromatic substitution. Here, too, ability to delocalize a negative charge should be important. See J. F. Bunnett, F. Draper, Jr., P. R. Ryason, P. Noble, Jr., R. G. Tonkyn and R. E. Zahler, *ibid.*, **75**, 642 (1953).

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There are only a few examples in the literature of other applications of the Hammett equation to elimination reactions.[17] Eliminations from IX and X have been studied with sodium hydroxide in

Ar_2CHCCl_3 $Ar_2CHCHCl_2$

IX X

92.6% ethanol.[18] Recalculation of these data at our temperature (30°) and using only our substituents (*p*-methoxyl, *p*-methyl, hydrogen and *p*-chloro) gives $\rho = 2.43$ for IX and 2.26 for X. These ρ-values are larger than for the phenylethyl bromides. The result is not unexpected, since both the additional β-aryl group and the substitution of chlorine for bromine as the leaving group should increase the carbanion character of the transition state. Comparison of our results with the data of Simonetta and Favini[19] on the 2-arylethyl chlorides is more difficult because they used different temperatures (60 and 70°), different substituents (*p*-methoxyl, *m*-methoxyl and hydrogen) and a much more aqueous solvent (2:1 ethanol–water). Since variations in the kind and number of substituents alone may change ρ considerably (*cf.* Table IV), conclusions would be unwise.

Finally, the present results provide additional support for the Hughes–Ingold explanations of the empirical rules of orientation in elimination reactions. In their interpretation the Hofmann rule is a consequence of electrostatic influences on the acidity of the β-hydrogen,[20] while the Saytzeff rule is a consequence of hyperconjugative stabilization of the partial double bond in the transition state.[21] An increased contribution to the transition state from VIII would result in an increased sensitivity to electrostatic effects. Since there should be a concomitant decrease in the contribution of VII, a decreased sensitivity to hyperconjugative effects is also expected. Our evidence shows that sulfonium salts, which follow the Hofmann rule, are more sensitive to electrostatic effects than bromides, which follow the Saytzeff rule.

No mention of steric effects has been made in this discussion, because our results provide neither positive nor negative information on their possible importance. Undoubtedly there are many situations where such effects are important. It should be noted, however, that Brown's[6] arguments are based on VII as a model for the transition state and may therefore require some modification.

Experimental[22]

Preparation of 2-Arylethanols.—The appropriate arylmagnesium bromide was treated with ethylene oxide according to the general procedure of Houston and Agett,[23] using a 10% molar excess of ethylene oxide. Compounds prepared by this procedure are listed below.

2-(*p*-Tolyl)-ethanol: 65% yield, b.p. 110–111° (10 mm.), $n^{24}D$ 1.5279 (lit.[24] b.p. 105° (4 mm.), $n^{21}D$ 1.5275).

2-(*p*-Anisyl)-ethanol: 76% yield, b.p. 142–145° (15 mm.), $n^{25}D$ 1.5397 (lit.[25] b.p. 148° (19 mm.)).

2-(*p*-Chlorophenyl)ethanol: 50% yield, b.p. 77–78° (0.5 mm.), $n^{25}D$ 1.5482 (lit.[26] b.p. 110° (0.5 mm.)).

Preparation of 2-Arylethyl Bromides.—The arylethanol was treated with phosphorus tribromide, using a procedure similar to that of Rupe.[27] The bromides obtained by this and other procedures are as follows.

2-(*p*-Tolyl)-ethyl bromide: 81% yield, b.p. 43.5° (0.3 mm.), $n^{22}D$ 1.5490 (lit.[28] b.p. 103.5–105° (11 mm.)).

2-(*p*-Anisyl)-ethyl bromide: 50% yield, b.p. 63° (0.15 mm.), $n^{21}D$ 1.5595 (lit.[29] b.p. 147–149° (22 mm.)).

2-(*p*-Chlorophenyl)-ethyl bromide: 61% yield, b.p. 86.5° (1.6 mm.), $n^{25}D$ 1.5697.

Anal. Calcd. for C_8H_8BrCl: C, 43.76; H, 3.67. Found: C, 43.82; H, 3.75.

2-Phenylethyl bromide was redistilled commercial material of b.p. 66° (2 mm.), $n^{26}D$ 1.5542 (lit.[30] $n^{24}D$ 1.5549).

2-(*p*-Acetylphenyl)-ethyl bromide was obtained by the acetylation of 2-phenylethyl bromide with acetyl chloride in the presence of aluminum chloride.[8] The product, obtained in 71% yield, had b.p. 111–112° (0.3 mm.), $n^{24}D$ 1.5722 (lit.[7] b.p. 117–118° (0.1 mm.), $n^{25}D$ 1.5724).

2-(*p*-Nitrophenyl)-ethyl Bromide.—The nitration of 2-phenylethyl bromide with nitric acid in acetic anhydride[7] gave 33% of a product of m.p. 69–69.5° (lit.[7] 69–70°).

Preparation of Methyl 2-Arylethyl Sulfides.—The 2-arylethyl bromides were converted to methyl 2-arylethyl sulfides by treatment with a solution of methyl mercaptan in ethanolic sodium hydroxide according to a procedure given by Fehnel and Carmack[31] for ethyl 2-phenylethyl sulfide. The sulfides prepared are described below.

Methyl 2-phenylethyl sulfide: 95% yield, b.p. 70–71° (11 mm.), $n^{24.5}D$ 1.5494 (lit.[32] b.p. 111° (12 mm.)).

Methyl 2-(*p*-tolyl)-ethyl sulfide: 93% yield, b.p. 49–50° (0.3 mm.), $n^{21}D$ 1.5450. *Anal.* Calcd. for $C_{10}H_{14}S$: C, 72.23; H, 8.49. Found: C, 72.24; H, 8.54.

Methyl 2-(*p*-anisyl)-ethyl sulfide: 83% yield, b.p. 102–103° (2 mm.), $n^{25}D$ 1.5522. *Anal.* Calcd. for $C_{10}H_{14}OS$: C, 65.89; H, 7.74. Found: C, 65.70; H, 7.84.

Methyl 2-(*p*-chlorophenyl)-ethyl sulfide: 87% yield, b.p. 83–85° (0.6 mm.), $n^{25}D$ 1.5630. *Anal.* Calcd. for $C_9H_{11}SCl$: C, 57.90; H, 5.97. Found: C, 57.82; H, 6.12.

Methyl 2-(*p*-Acetylphenyl)-ethyl Sulfide.—Methyl 2-phenylethyl sulfide was acetylated by the procedure of Foreman and McElvain,[7] using 2 moles of aluminum chloride per mole of sulfide. The product (88% yield) had b.p. 131–132° (1.0 mm.), $n^{24}D$ 1.5670.

Anal. Calcd. for $C_{11}H_{14}OS$: C, 67.99; H, 7.26. Found: C, 67.69; H, 7.23.

Preparation of 2-Arylethyldimethylsulfonium Bromides.—The sulfide was treated with methyl bromide in nitromethane solution[8b] and the product recrystallized from ethanol–ether.

2-Phenylethyldimethylsulfonium bromide: 70% yield, m.p. 135–135.5° dec. (cor.) (lit.[1] m.p. 135.5°).

2-(*p*-Tolyl)-ethyldimethylsulfonium bromide: 65% yield, m.p. 106.5–107° dec. (cor.). *Anal.* Calcd. for $C_{11}H_{17}SBr$: C, 50.57; H, 6.56. Found: C, 50.80; H, 6.66.

2-(*p*-Anisyl)-ethyldimethylsulfonium bromide: 50% yield, m.p. 133–133.5° dec. (cor.). *Anal.* Calcd. for $C_{11}H_{17}OSBr$: C, 47.65; H, 6.18. Found: C, 47.81; H, 6.34.

2-(*p*-Chlorophenyl)-ethyldimethylsulfonium bromide: 63% yield, m.p. 126–126.5° dec. (cor.). *Anal.* Calcd.

(17) We learned recently that Dr. C. H. DePuy is engaged in studies similar to ours. We thank Dr. DePuy for information in advance of publication and for several helpful discussions. See C. H. DePuy and D. H. Froemsdorf, Abstracts of Papers, 130th Meeting of American Chemical Society, Atlantic City, N. J., September 16–21, 1956; C. H. DePuy and D. H. Froemsdorf, THIS JOURNAL, **79**, 3705 (1957).

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for $C_{10}H_{14}SClBr$: C, 42.64; H, 5.01. Found: C, 42.74; H, 5.27.

2-(*p*-Acetylphenyl)-ethyldimethylsulfonium bromide: 74% yield, m.p. 121–121.5 dec. (cor.). *Anal.* Calcd. for $C_{12}H_{17}OSBr$: C, 49.82; H, 5.92. Found: C, 49.53; H, 5.82.

Preparation of Styrenes.—The sulfonium bromide was dissolved in water, treated with 10% sodium hydroxide solution and the mixture warmed gently on the steam-bath. The cessation of methyl sulfide evolution indicated completion of the reaction. The styrene was decanted, dried over Drierite and fractionated in the presence of a small amount of *p-t*-butylpyrocatechol.

Styrene: 87% yield, b.p. 38° (15 mm.), $n^{25}D$ 1.5433 (lit.[33] $n^{25}D$ 1.5433).

***p*-Methylstyrene**: 87% yield, b.p. 50° (13 mm.), $n^{26}D$ 1.5395 (lit.[34] $n^{25}D$ 1.5402).

***p*-Methoxystyrene**: 92% yield, b.p. 85° (14 mm.), $n^{23}D$ 1.5595 (lit.[35] $n^{20}D$ 1.5608).

***p*-Chlorostyrene**: 93% yield, b.p. 38° (2.2 mm.), $n^{20}D$ 1.5650 (lit.[36] $n^{20}D$ 1.5648).

***p*-Acetylstyrene**: 88% yield, m.p. 33–33.5° (lit.[37] m.p. 33°).

***p*-Nitrostyrene** was obtained by treating 2-(*p*-nitrophenyl)-ethyl bromide with warm alcoholic sodium hydroxide for 15 min. The mixture was poured into a saturated salt solution and the organic layer taken up in ether and dried. Removal of the ether left a solid which was recrystallized from petroleum ether. There was obtained 70% of *p*-nitrostyrene, m.p. 29° (lit.[38] m.p. 28°).

Styrene Analysis.—Ultraviolet absorption spectra of the freshly distilled styrenes in 95% ethanol solution were determined on a Cary recording spectrophotometer. The optical densities at the maxima used for analysis (around 250 mμ) were then carefully determined on a Beckman DU spectrophotometer. Molar extinction coefficients at these maxima are listed in Table I. Beer's law was obeyed over the concentration ranges used, and the solutions underwent no changes in concentration over a period of at least 48 hr.

Samples of the reaction mixtures at "time infinity" were appropriately diluted and optical densities determined, from which the olefin concentrations were calculated. In some of the slower reactions there appeared to be a slow depletion of the styrene, so the determinations were made on aliquots taken after one or two half-lives. Under the conditions of the measurements the styrene precursors (bromides or sulfonium bromides), sodium ethoxide, sodium bromide and methyl sulfide did not contribute appreciably to the observed ultraviolet absorption. Olefin yields in Table II are averages of two or three analyses with indicated average deviations.

Kinetic Measurements.—Reactions were carried out in a 100-ml. volumetric flask to which was attached, above the calibration mark, a side-arm bearing a 10-ml. bulb sealed with a rubber ampoule-stopper. This could be covered with a ground-glass cap so that the entire vessel could be immersed in the constant-temperature bath. Runs were carried out in a thermostat with temperature control to ±0.05°. Runs at 0° were performed in a well-stirred ice–water slurry.

For the bromides (mostly liquids), 50.0 ml. of *ca.* 0.2 *M* sodium ethoxide in absolute ethanol (at bath temperature) was diluted to 99.0 ml. with thermally equilibrated absolute ethanol. To this was added a weighed portion of the bromide (0.005 mole, *ca.* 1 ml.). The reactor was agitated in the bath for two minutes following the addition. Aliquots were withdrawn periodically with a calibrated 5-ml. hypodermic syringe and delivered into excess aqueous hydrochloric acid. The quenched sample was diluted fivefold with water and titrated to the phenolphthalein end-point with standard sodium hydroxide. The sodium ethoxide solution was sampled at bath temperature and standardized before each run.

A weighed quantity of a sulfonium salt (*ca.* 0.005 mole) was dissolved in slightly less than 50 ml. of absolute ethanol and the solution allowed to equilibrate thermally. To this solution was added by pipet 50.0 ml. of thermally equilibrated ethoxide solution, the volume adjusted to 100 ml. and the vessel agitated for 1 minute. Sampling and analysis were carried out as with the bromides.

Compounds used had the physical constants indicated under their preparation. Absolute ethanol was obtained by the procedure of Smith as modified by Manske.[39] All solutions were frequently restandardized to ensure that rate constants would be comparable. Each run consisted of at least 10 points and the rate constants from the integrated second-order equation were arithmetically averaged. Values recorded in Table II are the averages of two or more runs with average deviations. Whenever there was a departure from the usual concentrations, ionic strength was maintained with added sodium bromide. Most runs covered two or three half-lives and no serious drifts were noted.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, BROOKHAVEN NATIONAL LABORATORY]

The Chemical Consequences of the $N^{14}(n,p)C^{14}$ Reaction in the Acetamide System and the Implications of Nuclear Recoil as a Tool for Synthesis[1]

BY ALFRED P. WOLF, CAROL S. REDVANLY AND R. CHRISTIAN ANDERSON

RECEIVED FEBRUARY 18, 1957

Acetic acid-1,2-C_1^{14} and propionic acid-1,2,3-C_1^{14} have been prepared from acetamide irradiated in a nuclear reactor. The distribution of activity in acetic acid averages 62% in the carbonyl carbon and 38% in the methyl carbon. For propionic acid obtained by basic hydrolysis of the amide we found 24% in the carbonyl carbon, 24% in the methylene carbon and 52% in the methyl carbon. These results are interpreted in terms of chemical mechanisms being the determining factors in the labeling process. The formation of acetone-1,2-C_1^{14} with 80% of the activity in the methyl groups and 20% of the activity in the carbonyl group is also reported. Acetonitrile as a product of the radiation chemistry of the system is mentioned. The implication of this work with regard to using nuclear recoil as a tool for the synthesis of labeled compounds is discussed.

The consequences of nuclear recoil in organic nitrogen-containing systems irradiated with neutrons have been the subject of an increasing number of studies.[2] The carbon-14 as it is born receives a recoil energy of about 40,000 e.v. This kinetic energy imparted to the carbon atom causes it to break its chemical bonds and to move into its surroundings. Energy loss occurs by coulomb scattering, collision with other atoms and other processes. When the carbon-14 has been slowed sufficiently to be able to react with its environment, it finds itself a considerable distance from its birthplace,[3-5] the estimates varying from 10 to 3000 Å. The fragmentation and recombination process caused by the recoil atom results in a complex mixture of products. While only one labeled product can result from each event, the amount of energy available for chemical reaction at the site of entrapment of the carbon-14 allows a large variety of compounds to be formed. This is reflected in the diversity of products obtained in an irradiation.

Numerous approaches to this problem are possible. A complete product analysis may conceivably be done. Investigation of specific products and the degree of labeling found in them can be carried out. Compounds with structural features of interest can be investigated in terms of what changes can be made to occur on exposures to carbon recoils. External influences on the products, such as temperature and pressure, might yield useful information. The effect of phase on product distribution is also of interest.

Our studies have been directed toward the elucidation of the mechanism of this process, which in turn should provide the necessary information for the intelligent use of the recoil method in labeling organic compounds. A consideration of the factors enumerated should yield this end.

Constancy of specific activity is the basic criterion for the purity of any product obtained by the recoil method. While chemical purity usually is achieved readily, radiochemical purity, in most cases, is obtained with inordinate difficulty. It became increasingly evident from our work on this and other systems that this difficulty was possibly due to *synthesis*[6] products. It must be kept in mind that these *synthesis* products are formed in microgram amounts or less (with one carbon-14 per molecule), distributed in tens of grams of irradiated material. The presence of these compounds, whose chemical behavior is sufficiently similar to the parent compound to make their separation quite difficult, makes purification a challenging task. Their detection and removal from the parent compound can be effected by carrier methods. Substitution of nitrogen or carbon in the parent compound by carbon-14 results in a *re-entry*[7] product. This product is also removed by carrier methods where applicable.

Results

Acetamide was irradiated in the Brookhaven reactor. Our approach has been to center attention on *re-entry* and *synthesis* products and further to center attention on activity distribution in the compounds themselves. Thus, the *re-entry* product, acetamide-1,2-C_1,[14] and the *synthesis* product, propionamide-1,2,3-C_1,[14] were investigated, and the extent of incorporation of carbon-14 in each position was determined. Both propionic acid and propionamide were added as carriers on the assumption that the synthesized, excited three carbon fragment might in some cases collapse to give propionic acid. The reactions are given in equations 1 and 2.

The hydrolysis was carried out both in acid and in base to investigate possible differences in state of the irradiated material. The hydrolysis in base was carried out on two independently irradiated samples. The results of these runs are listed in Tables I and II. Hydrolysis in acid yielded the results listed in Table III.

(1) Research performed under the auspices of the U. S. Atomic Energy Commission.

(2) (a) R. Edwards, A.C.S. Sixth Southwest Regional Meeting, San Antonio, Texas, 1949. (b) G. Giacomello, *La Ricerca Scientifica*, **21**, 1211 (1951). (c) U. Croatto, G. Giacomello and A. G. Maddock, *ibid.*, **21**, 1598 (1951). (d) M. Zifferero and I. Masi, *Annali di Chim.*, **44**, 551 (1954). (e) M. Zifferero, *ibid.*, **44**, 555 (1954). (f) G. Giacomello and M. Zifferero, *ibid.*, **44**, 558 (1954). (g) M. Zifferero, *ibid.*, **44**, 563 (1954). (h) M. Zifferero and D. Sordelli, *La Ricerca Scientifica*, **26**, 1194 (1956). (i) A. P. Wolf and R. C. Anderson, THIS JOURNAL, **77**, 1608 (1955). (j) A. P. Wolf, C. S. Redvanly and R. C. Anderson, *Nature*, **176**, 831 (1955). (k) A. P. Wolf, B. Gordon and R. C. Anderson, THIS JOURNAL, **78**, 2657 (1956). (l) A. G. Schrodt and W. F. Libby, *ibid.*, **76**, 3100 (1954). (m) A. G. Schrodt and W. F. Libby, *ibid.*, **78**, 1267 (1956).

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(6) By *synthesis* product we mean any product formed which has *one carbon more* than the parent compound, *exclusive* of the carbon analog of the parent compound; *cf.* reference 21.

(7) We prefer *re-entry* to retention in describing this process in order to avoid the implication that the molecule undergoing nuclear transformation is the same molecule which then contains the C^{14} in its skeleton.

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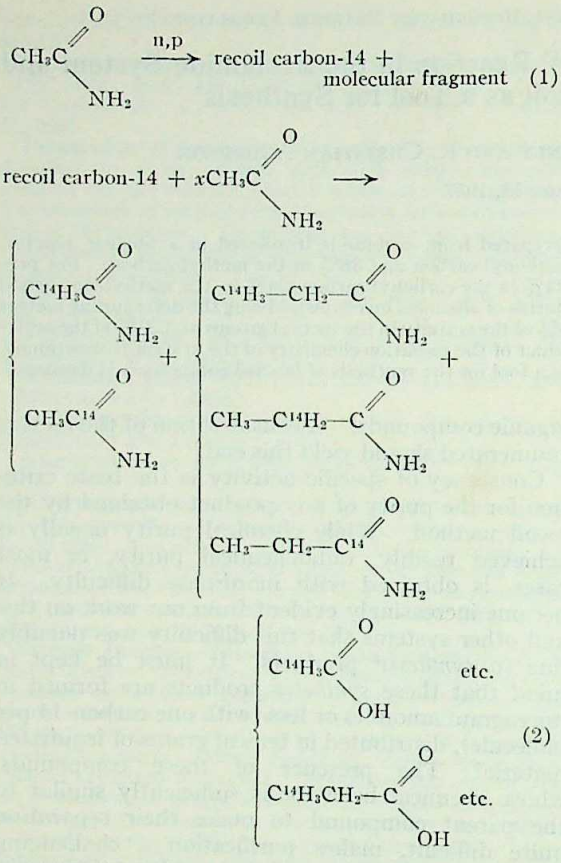

While it is clear from these results that synthesis does take place, it becomes evident that the reaction to give "propionamide" involves processes other than a simple replacement of hydrogen.

TABLE I

ACETAMIDE, BASIC HYDROLYSIS, A SERIES

	$CH_3—COOH^a$		$CH_3—CH_2—COOH^b$		
1. Specific activity, assay on compd., mμc./mg. C.	0.715		2.18		
2. Activity relative to total activity in irradiated sample in per cent.	6.44		6.52		
3. Specific activity, by position, mμc./mg. C.	0.536	0.840	3.30	1.44	1.49
4. Percentage of summed activity by position	38.9	61.0	52.9	23.1	23.9
5. Activity accounted for by degradation	96.2		95.4		

[a] Neat. [b] Carrier material.

TABLE II

ACETAMIDE, BASIC HYDROLYSIS, D SERIES

	$CH_3—COOH^a$		$CH_3—CH_2—COOH^b$		
1. Specific activity, assay on compd. mμc./mg. C.	0.811		0.886		
2. Activity relative to total activity in irradiated sample in per cent.	6.83		6.15		
3. Specific activity by position, mμc./mg. C.	0.608	0.991	1.32	0.646	0.644
4. Percentage of summed activity by position	38.0	61.9	50.6	24.7	24.6
5. Activity accounted for by degradation	98.5		98.2		

[a] Neat. [b] Carrier material.

TABLE III

ACETAMIDE, ACIDIC HYDROLYSIS, C SERIES

	$CH_3—COOH^a$		$CH_3—CH_2—COOH^b$		
1. Specific activity, assay of compd., mμc./mg. C.	1.24		1.00		
2. Activity relative to total activity in irradiated sample in per cent.	8.12		4.86		
3. Specific activity by position, mμc./mg. C.	0.888	1.52	1.46	0.764	0.583
4. Percentage of summed activity by position	36.8	63.1	52.1	27.1	20.7
5. Activity accounted for by degradation	97.1		93.7		

[a] Neat. [b] Carrier material.

Discussion

A number of hypotheses have been suggested to account for the results of reactions activated by the n,γ-process. Notable among these are the "billiard ball collision–epithermal collision" hypothesis of Libby[8] and the "random fragmentation–brush heap" hypothesis of Willard.[9]

Yankwich[5] has published a stimulating article on the $N^{14}(n,p)C^{14}$ system in particular. He has provided a rationale for ionic crystal work based mainly on the Seitz and Koehler[10] description of the displacement of atoms during irradiation.

We have considered the formation of labeled species in terms of three steps, each of which may affect product distribution. *The first of these is the slowing down of the carbon-14 and its localization in a reactive site by elastic and inelastic processes. The second step involves the imposition of chemical considerations leading to a variety of intermediate chemical species depending on the structural features of the site and on the energy available for chemical reaction at the entrapment site. The third step involves the collapse of the intermediates to stable compounds or the collapse of reactive fragments, which lead to stable compounds, during the chemical operations carried out on the material subsequent to the irradiation.* Each step involves several factors. The first step is thought of as involving: (1) the energy of the recoil fragment just prior to entrapment in a site, where its motion becomes essentially diffusive in character; (2) the structural features of the fragment during this period and just prior to reaction; (3) the probability of interaction with a particular bond, atom or molecule. The second step is concerned with the chemical considerations which affect the nature of the final product. Involved are: (1) the probability of formation of any of a number of intermediates; (2) the probability that such an intermediate will lead to a stable product; (3) the effect of the surroundings on product distribution. Step three involves essentially three considerations: (1) the probability that a given intermediate will collapse to a compound stable in its surroundings; (2) whether or not the compound will be isolable under the reac-

(8) See reference 3; *cf.* M. S. Fox and W. F. Libby, *J. Chem. Phys.*, **20**, 487 (1952).

(9) "Annual Review of Nuclear Science," Annual Reviews, Inc., Stanford, Cal., 1953, see J. E. Willard, pp. 193–217.

(10) F. Seitz and D. Turnbull, "Solid State Physics," Academic Press, Inc., New York, N. Y., 1956; see F. Seitz and J. S. Koehler, pp. 305–448.

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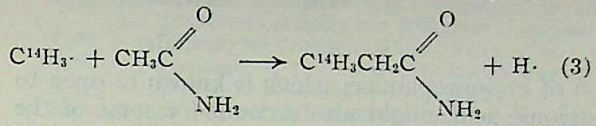
tion conditions; (3) the influence of the isolation method on product distribution.

In theory, a rigorous evaluation of these various factors should allow accurate prediction of product distribution in any given system. The complexity of product distribution from the $N^{14}(n,p)C^{14}$ reaction carried out in relatively simple systems such as ionic crystals has been demonstrated by Yankwich.[11] The greatly increased complexity resulting in an organic system, in which the $Br^{81}(n,\gamma)Br^{82}$ reaction was carried out and in which attention necessarily was centered on the organically bound bromine only, was elegantly investigated by Evans and Willard.[12] These results imply an almost staggering complexity for the product distribution in a system where a recoiling carbon comes to rest in an organic matrix. The complexity of product distribution is certainly evidenced by the work of Schrodt and Libby.[2m]

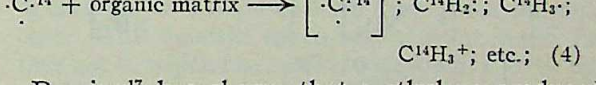
By centering attention on *re-entry* and *synthesis* products and, further, by centering attention on activity distribution in the compounds themselves, it becomes abundantly clear that chemical forces do indeed play a role in both *re-entry* and *synthesis*. Random distribution is not observed in the *re-entry* product, acetamide-1,2-C_1^{14}, and exclusive hydrogen substitution is not observed in the *synthesis* product, propionamide-1,2,3-C_1^{14}. This is a primary consideration with regard to using the recoil method as a means for preparing labeled compounds. The specificity observed in acetamide probably reflects the effects of factors 1 and 2 in step 2. The higher activity yield of labeled acetic acid from the acid hydrolysis of irradiated material may again reflect these same factors and in addition be a function of factors 1 and 3 of step 3. It may be suggested that the reactive fragment containing carbon-14 will react with its surroundings to give labeled malonic acid. The acid hydrolysis isolation procedure would augment the activity finally assayed as acetic acid since the malonic acid would readily decarboxylate to give acetic acid. It cannot be overemphasized that the nature of the product isolated reflects the structure of the active moiety in the organic matrix only insofar as there is an allowable chemical pathway from the moiety in the matrix to the compound finally isolated. It is not a necessary condition that the active fragment be isolable as a stable chemical entity, nor is it necessary that the final product observed is the result of sequential chemical steps identified with *one* starting moiety.[13]

A number of mechanisms can be suggested to account for the distribution of the activity in the propionamide. It is noteworthy that there is *synthesis* and that there is specificity for replacement of a methyl hydrogen. It is, however equally significant that in addition to the 3-position, the 1- and 2-positions are also labeled.

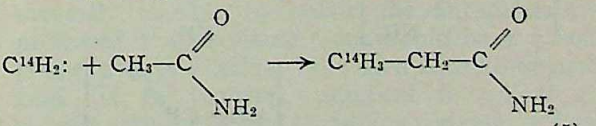
It seems reasonable to assume that the energy associated with the terminal "hot spot" where the recoiling carbon-14 is finally trapped will be of the order of 25–50 e.v.[15,10,14] Clearly then,[15] sufficient energy will be available to allow reaction 3 to occur even though the reaction indicated by equation



3 is endothermic in the ordinary sense. This "inversion" reaction is different from that of Hornig, Levey and Willard[16] in that the assemblage after collision need not have sufficient energy to cause bond rupture in the subsequent steps necessary to reduce it to thermal energies. It does not seem likely that such a reaction can take place in the high energy region, since, although the collisions can be between atoms of almost equal mass, the residual energy left, on the average, in such a hot spot will be so high as to allow complete rupture of many bonds, thus resulting in the destruction of any chemical coherence in the center of the spot.[10] The recoiling carbon-14 is an extremely active radical and can react with its surroundings, particularly when its motion becomes essentially diffusive, to give a variety of molecular species such as are indicated in equation 4.



Doering[17] has shown that methylene produced by the photolysis of diazomethane reacts indiscriminately with the carbon–hydrogen bonds in its surroundings. The reaction given by equation 5 is analogous to Doering's cases, particularly in that a methylene produced from a recoiling carbon can



(5)

certainly have an energy equal to or in considerable excess of the energy of a photolytically produced methylene. Although Doering observed no reaction with carbon–carbon bonds, such a reaction may be possible with a more energetic methylene. Propionamide might therefore be formed by the insinuation of methylene between the two carbons

(11) (a) P. E. Yankwich and J. D. Vaughan, THIS JOURNAL, **76**, 5851 (1954); (b) P. E. Yankwich and W. R. Cornman, Jr., *ibid.*, **77**, 2096 (1955); (c) **78**, 2908 (1956).

(12) J. B. Evans and J. E. Willard, *ibid.*, **78**, 2908 (1956).

(13) A. G. Maddock and N. Sutin, *Trans. Faraday Soc.*, **51**, no. 2, 184 (1955), discuss the effect of the isolation technique on the distribution of activities obtained by neutron irradiation of triphenylarsine and triphenylstibine.

(14) "Reports on Progress in Physics," The Physical Society, London, England, 1955; see G. H. Kinchin and R. S. Pease, pp. 1–51.

(15) The maximum energy transmittable for a collision between two entities is given by

$$E_M = \frac{4M_1M_2}{(M_1 + M_2)^2} E_I$$

where E_I is energy of the incident particle of mass M_1. M_2 is the mass of the struck entity. On the average, the energy transmitted equals $\frac{1}{2}E_M$. The maximum fraction of the kinetic energy of the struck entity which is then available as internal energy is given by

$$E_{Int} = \frac{M_2}{M_1 + M_2} E_T$$

where E_T is the energy transmitted.

(16) J. F. Hornig, G. Levey and J. E. Willard, *J. Chem. Phys.*, **30**, 1556 (1952).

(17) W. von E. Doering, R. G. Buttery, R. G. Laughlin and N. Chaudhuri, THIS JOURNAL, **78**, 3224 (1956).

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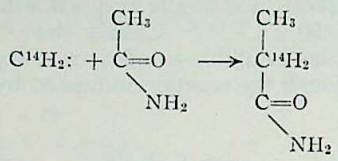
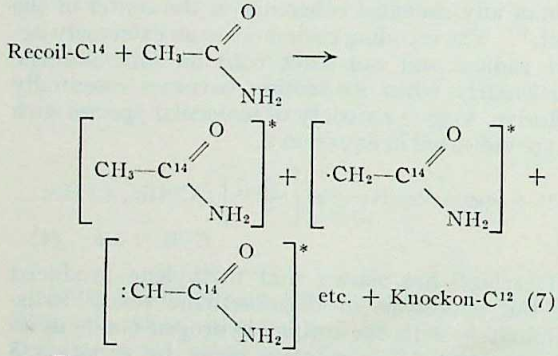
of acetamide as given in equation 6. The formation of cyclopropanone, which is known to open to propionic acid, might also account for some of the labeled acid.



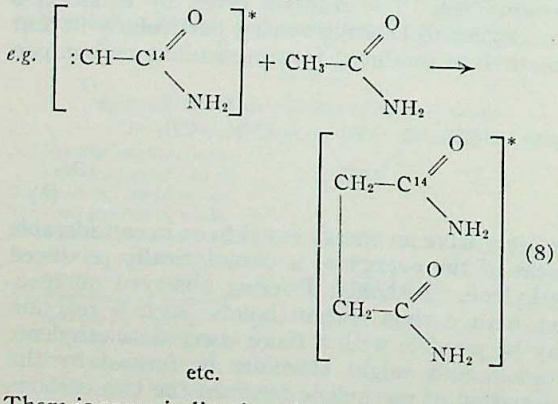
(6)

Activity in the carbonyl group might be the result of the formation of an intermediate which can then undergo skeletal rearrangement and shifting of the oxygen. An intermediate which becomes stripped of oxygen and is then reoxidized is also a possibility.

Here as with acetamide, the formation of an intermediate which subsequent chemistry can transform to propionic acid is a possibility. The case of carbonyl labeling is indicated by equations 7 and 8.



(7)

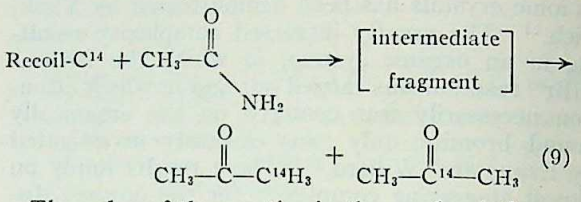


etc.

There is some indication that succinic acid may decarboxylate to give small amounts of propionic acid when in the presence of base and traces of heavy metal salts. Alternatively the excited succinamide might break a methylene to carboxamide bond to give a radical which would then abstract a hydrogen from its surroundings.

Experiments which will distinguish between these various mechanisms are in progress at the present time.

Acetone-1,2-$C_1{}^{14}$.—In our work on the acridine–anthracene[2] system it was shown that the ratio of activity as acridine to activity as anthracene averaged 18/1. A completely random *re-entry* would result in a ratio of 13/1. Muxart[18] has obtained an average ratio of 19/1 in the 5,6-benzacridine–5,6-benzanthracene system where the statistical ratio is 17/1. The activity as acetone in the carrier material was found to be 0.13% of the total activity produced. A ratio of 49/1 was found, whereas the statistical ratio for acetone is 2/1. The reaction is given by equation 9.



(9)

The value of these ratios in the mechanistic sense probably has real meaning when the molecules formed by *re-entry* do not have fundamentally different chemical stabilities. We also need to assume that the excited *re-entered* molecules will behave similarly in their surroundings in the chemical sense. For example, the excited states of acridine and anthracene are sufficiently similar that we might expect the *re-entered* acridine and the active anthracene from nitrogen replacement to have roughly equal probabilities of being reduced intact to thermal energies. Acridine which might be lost by the formation of biacridine might be mirrored by bianthracene formation from anthracene. Once formed, the chemical stabilities and their stability to radiation damage are nearly equal in terms of total product destroyed. This parallel behavior then lends validity to the conclusions one can draw from the statistical nature of the replacement.

The applicability of these hypotheses is supported by the results with acetone. Here the intermediates leading to acetone and *re-entered* acetamide probably bear no relationship. Further the radiation stabilities of these two materials, once formed, are markedly different. The deviation from statistical behavior is then a reflection of the chemistry of the system after *re-entry* has occurred, emphasizing the fact that a purely physical picture of the chemical results from a system containing recoil fragments is not sufficient.

In addition, the degree of labeling by position in acetone, being 20% in the carbonyl carbon and 80% in the indistinguishable methyl carbons, is significant in that it necessitates a mechanism involving not only *re-entry* but also rearrangement of the species after *re-entry*.

Acetonitrile.—The rate of energy absorption by the system due to the recoiling carbons is about 2.7×10^{15} e.v./sec./gram of acetamide and is about 3.5×10^{16} e.v./sec./gram of acetamide for the ejected protons. A crude calculation based on the "Dosimetry of Reactor Radiations" work by Richardson, Allen and Boyle[19] indicates that about 1.2×10^{17} e.v./sec./gram of acetamide are being dissipated in the sample due to pile irradiation. Since only 1.7% of the energy absorbed by the sample can be attributed to the recoil fragment,[20]

(18) R. Muxart, *Compt. rend.*, **242**, 2457 (1956).

(19) "Proceedings of the International Conference on the Peaceful Uses of Atomic Energy," Vol. XIV, United Nations, New York, N. Y., 1956; see D. M. Richardson, A. O. Allen and J. W. Boyle, pp. 209–212.

(20) Additional reactions such as $C^{13}(n,\gamma)C^{14}$ play an insignificant part in the

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it seems unlikely that acetonitrile formation is a specific effect caused by the knockons from carbon-14. It is, however, interesting to speculate whether or not acetonitrile is a specific product of knockons by fast neutrons, ejected protons, and by recoil fragments or whether it is formed by means of the gross radiation the sample receives.[21]

Use of Nuclear Recoil as a Method for Labeling Organic Compounds.—Several factors must be evaluated in using nuclear recoil as a labeling method. The level of activity desired in the compound, the degree of labeling by position and the ease with which the labeled compound may be prepared by conventional methods must be considered.

It is necessary first to decide on the source of the required nitrogen. In many of the cases reported, the compound serves as its own nitrogen source. If the compound to be labeled contains no nitrogen, it may be mixed with a nitrogen source which will form a homogeneous solution[22] with the compound. This source must provide a high nitrogen to carbon ratio, be radiation stable and be easily removable from the desired compound. Derivatization of the compound with nitrogen-containing compound is a third possibility.

The optimum irradiation time is based on minimization of radiation damage such that a sensible amount of chemically pure material can be recovered. This must be coupled with maximization of activity produced. A review by Collinson and Swallow[23] on the radiation chemistry of organic substances can serve as a guide for the qualitative evaluation of the expected radiation damage. For example, acridine,[2i] after 20 days of pile irradiation, is 76% recoverable, whereas L-alanine[24] is only 22% recoverable after a six-day irradiation.

Calculation of the total activity produced during the irradiation can be carried out easily.[2i] The fraction of the total activity found in the *re-entry* product depends strongly on the nature of the compound to be *re-entered*. We have observed a wide range of values: *e.g.*, 0.2% in alanine,[24] ~ 1% in ethylpyridine,[24] 1.5–2% in benzene[2j,k] (not corrected for dilution by the nitrogen source), 3.5% in acridine, to 8.0% in acetic acid from the acid hydrolysis of acetamide. These percentages are corrected for the material lost by radiation damage. Higher *re-entry* figures have been reported for some organic compounds, but they do not serve as a basis for calculation in the absence of rigorous proof of constancy of the specific activities observed.

The specific activity obtainable is then given by equation 10.

$$S.A._x = \frac{A_T \times P_T}{M_C \times 100} \qquad (10)$$

$S.A._x$ = estimated specific activity expected in compound x in activity per milligram of carbon
A_T[25] = total activity produced during irradiation
P_T[26] = percentage of the total activity produced expected to be found in compound x
M_C = milligrams of carbon in total sample of compound x

This calculation assumes no radiation damage in evaluating M_C and thereby gives a common basis for comparison between compounds. Clearly the specific activity is the same for any compound derived from the compound irradiated provided the derived compound has the same number of carbons per mole and provided no carbons were exchanged.

The actual chemical yield of *re-entry* product is dependent on the amount not destroyed by radiation damage. After the material is shown to be chemically and radiochemically pure, it can be diluted as desired, depending on the detection limits of the assay method used. With our present assay equipment the acetic acid produced from the acid hydrolysis of acetamide (1.24 mμc./mg. C) could have been diluted 500-fold without appreciably changing[27] the precision of assay.

It must be remebered that the degree of labeling in each position *is not* uniform throughout the molecule. This must be taken into account in any further use to which the labeled compound is to be put.

The *re-entry* product resulting from replacement of nitrogen in the original compound, provided it acts as its own nitrogen source, and all *synthesis* products present a different picture. In theory, compounds with extremely high specific activity could be produced in this way. If it were experimentally feasible to isolate the anthracene-C_1^{14} produced from acridine,[28] we would have a compound with one carbon-14 in each anthracene molecule. It is, however, practical to adjust the specific activity desired by adding a greater or lesser amount of carrier at the end of the irradiation. Again the percentage of the total activity to be expected in the N-replacement and *re-entry* and/or *synthesis* products is estimated and sufficient carrier added to give the desired specific activity. For example, the specific activity of the propionic acid in the experiments reported here could have been increased by a factor of ten in any series by a corresponding decrease in the amount of added carrier. By the choice of a proper system and a high N/C

(21) Production by knockons would necessarily proceed with very high efficiency since an estimate of the energy deposited by "knockons" (total) alone indicates it to be a borderline possibility at best. This question might be resolved by comparing acetonitrile production from pile irradiation (at maximum fast neutron flux) with acetonitrile production from irradiation in a cobalt-60 source under conditions of identical total energy deposition.

(22) In labeling benzene,[2k] a mixture of benzene and 2-methylpyrazine was used; *cf.* 2a,l,m. We have used liquid ammonia without notable success because of the difficulty in finding appropriately soluble materials. Heterogeneous mixtures are not suitable because of the comparatively short range of the recoiling carbon-14. The percentage of carbon recoils reaching organic material in a mixture such as finely ground ammonium nitrate and anthracene is too small to make the method feasible.

(23) E. Collinson and A. J. Swallow, *Chem. Revs.*, **56**, 471 (1956).

(24) A. P. Wolf and C. S. Redvanly, unpublished work.

(25) While this is the value calculated, it should be noted (*cf.* ref. 33) that the activity produced experimentally is usually higher than the calculated value. Thus the value obtained as SA is a minimum in most cases. In no case that we have observed has the experimental value been greater than $1.8A_T$. An average of our published and unpublished work is $1.3A_T$. This variation from theoretical may be due to the primitive technology involved in carrying out these irradiations. An accurate value for the slow neutron flux integrated over the whole irradiation is not as yet available.

(26) As indicated in the text the value for P_T varies rather widely. A judicious guess based on the published work[2i] is required in order to evaluate P_T. We assume a value of 3% in lieu of any other information.

(27) D. R. Christman and A. P. Wolf, *Anal. Chem.*, **27**, 1939 (1955).

(28) A twenty day irradiation of 24 grams of acridine at a flux of 3×10^{13} neutrons/cm.^{2} sec. produces about 0.6 microgram of anthracene-C_1^{14} dispersed in the acridine.

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ratio, it may be possible to obtain a *synthesis* or N-replacement product carrier free.

As with the *re-entry* product, it must be remembered that the labeling is not specific. In the cases observed to date, the majority of the label is found in the expected position in the N-replacement product, and in the *synthesis* products: methyl group in acetone; methyl group in propionamide; methyl group in toluene.[2k] The percentage found in the expected position is not, however, the same in all compounds. Again the application to which the compound is to be put is the determining factor.

The quantities of materials that can be produced are subject to the geometry of the facility available. The water-cooled facility with maximum available flux in the Brookhaven reactor can accommodate about 80 grams (assumed density = 1) of a liquid sample per irradiation. About 100 grams of tightly packed solid can be irradiated in the same facility. Radiation times range from 4 to 30 days.

It is hoped that this outline based on work to date will aid in deciding whether or not the method is applicable to the compound in question. The complexity of the purification is usually the deciding factor. With the advent of vapor phase chromatography, however, labeled liquid alkanes, aromatics, alcohols, acids, etc., can be prepared easily and quickly. Carrier-free materials may also be within reach.[29] It is clear that adequate fractionation techniques hold the key to the application of nuclear recoil as a labeling method.

The elucidation of the mechanisms involved in these reactions is the continuing interest of the authors. The investigation of the effect of structure and phase on *re-entry* and *synthesis* is being pursued.

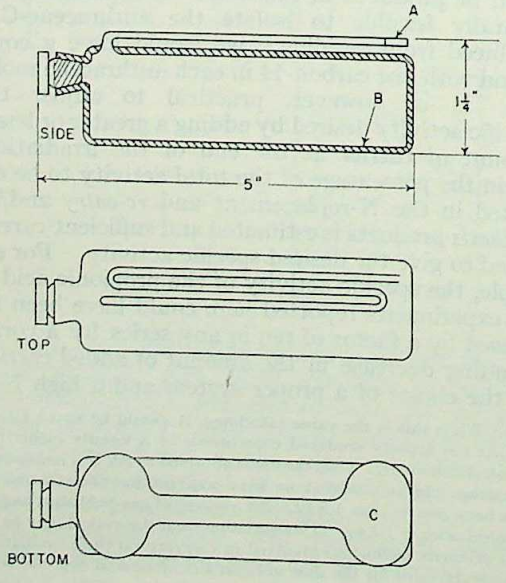

Fig. 1.—A, 0.5 mm. i.d. quartz capillary; B, 25 mm o.d. quartz tubing; C, ends blown flat and then ground for stability in boat.

(29) *Cf.* R. M. Lemmon, F. Mazzetti, F. L. Reynolds and M. Calvin, THIS JOURNAL, **78**, 6414 (1956). This case is closely analogous to the recoil method.

Experimental[30]

Irradiation.—The samples were irradiated in the Brookhaven reactor at an approximate flux of 4×10^{12} neutrons/cm.^{2} sec. The fast neutron flux was $\geqq 10^{12}$ neutrons/cm.^{2} sec. The gamma exposure was $\geqq 2 \times 10^6$ r./hr. In order to correct approximately for fluctuations in neutron density during irradiation, an integrated value for the total irradiation is reported in megawatt hr.[31] All irradiations were carried out in a facility operating at 30°. After irradiation, at least ten days were allowed for the decay of short lived activities in the quartz containers.

Packaging.—The type of container used is pictured in Fig. 1. The plug is held in place with Kronig cement. The capillary aids in reducing the amount of air in continuous contact with the sample, while still allowing the gases formed during the irradiation to escape. Appreciable gas pressures build up on irradiation of many aliphatic compounds. Closed systems are contra-indicated for pile irradiation of these samples. Safe irradiation of samples evolving gases can be accomplished in closed systems if necessary.[32]

Fisher Certified Reagent acetamide, m.p. 80–81°, was used for all irradiations.

Anal. Calcd. for C_2H_5ON: C, 40.7; H, 8.5. Found: C, 41.1; H, 8.4.

Processing of Acetamide-C_1^{14}. Addition of Carriers. A Series.—Two samples of acetamide (1, 21.077 g.; 2, 23.662 g.) received an irradiation of 4965 megawatt hours; acetamide survival 74 ± 4% (average both samples).

Sample 1.—*Anal.* Calcd. for C_2H_5ON: C, 40.7; H, 8.5. Found: C, 39.0 ± 0.9; H, 8.2; 12.06 ± 0.93 mμc./mg. C.[33]

Sample 2.—*Anal.* Found: C, 40.1 ± 1.2; H, 8.4; 10.27 ± 0.51 mμc./mg. C.[33]

Samples one and two were combined before carrier material was added. A weighted average for the carbon value and the carbon-14 activity is given; C, 39.6 ± 1.5; 11.11 ± 1.06 mμc./mg. C. The total activity for the irradiated sample was based on the carbon value before irradiation multiplied by the specific activity value obtained by assay. The total activity produced was 0.202 mc.

Transfer of 35.999 g. of the mixture to a bulb which could be connected to a vacuum line was carried out. Carriers were added to the bulb as follows: (1) 5.117 g. of propionamide, (2) 5.13 g. of acetone, (3) 4.806 g. of propionic acid. The vacuum bulb was capped and raised to a temperature of 70°. Copious gas evolution occurred during the melting and dissolution process. The liquid was resolidified in an ice-bath.

Acetone-1,2-C_1^{14}.—The vacuum bulb containing the resolidified homogenate was evacuated through two liquid N_2 traps connected to a high vacuum system. A vacuum

(30) Microanalyses on inactive samples were performed by F. Schwarzkopf, Woodside 77, N. Y. Radioassays were performed by P. R. Hansell and D. R. Christman of this Laboratory. The method of D. R. Christman, N. E. Day, P. R. Hansell and R. C. Anderson, *Anal. Chem.*, **27**, 1935 (1955), was used. A minimum of two assays were performed on each compound. The standard deviation for any given assay is 1–2% ($\sigma = \sqrt{\text{total counts}} \times 100/\text{total counts}$). The root mean square error encompassing all errors inherent in the analysis is not greater than 5%.

(31) Reference 2i explains the method of calculation used.

(32) A. P. Wolf and A. Oltmann, Brookhaven National Laboratory Report No. 2811.

(33) The deviations given here are average deviations calcd. from the experimental data. Data was based on 9 determinations for sample 1 and 7 determinations for sample 2. It has been our observation on all but the most radiation-stable compounds that precise C, H data and precise radioassays are difficult to obtain on the unprocessed pile material. Various factors such as inhomogeneity of the sample and the presence of other radioactive species have been investigated as possible causes for these effects. Negative results have been obtained. In particular the CO_2 from combustions has been purified both by cycling through $BaCO_3$ and by passing the CO_2 through a Vapor Phase Chromatographic (V.P.C.) column. No significant improvement in statistics was noted. The disparity between samples 1 and 2 is due to their location in the pile during the irradiation, the former having been close to the position of maximum flux. It should be noted that the megawatt hour reading serves mainly as an approximate irradiation value.

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transfer of the added acetone and other volatile constituents was effected. A negligible amount of the propionic acid was transferred. An 8.21-g. sample was obtained. The sample was separated into four fractions by distillation. Fractionation in an 8-inch glass helix packed column served to further purify the acetone fraction. Material boiling at 56° was converted to the semicarbazone. The semicarbazone was recrystallized twice from H_2O, m.p. 186°.

Anal. Found: 0.0674 mμc./mg. C., cor. for inactive carbon. The bisulfite addition product was prepared. *Anal.* Found: 0.069 mμc./mg. C.

Iodoform was prepared from the acetone using the procedure described by Meinwald.[34] *Anal.* Found: 0.082 mμc./mg. C.

Acetic Acid-C_1^{14}.—After vacuum transfer of the volatile constituents of the vacuum bulb had been effected, the residue, 40.0 g., was transferred to a r.b. flask. The mixture was hydrolyzed with 50 g. of sodium hydroxide in 200 cc. of H_2O. The solution was taken to *p*H 2 with sulfuric acid. The precipitate formed on neutralization was removed and washed with water. The combined aqueous solutions were continuously extracted with ether. The ether was removed through a Vigreux column. An acid fraction, 35.2 g., obtained on continued heating was used to charge the pot of a 12 mm. i.d. by 380 mm. long, $^3/_{32}$'' glass helix packed column. Mesitylene was used as a chaser.

A center cut of acetic acid was used for all derivative preparations. The cut was contaminated with a trace of mesitylene. *Anal.* Found: 0.721 mμc./mg. C.; b.p. 117–118.5°.

The *p*-toluidide of acetic acid was prepared, m.p. 145.5–146°. *Anal.* Calcd. for $C_9H_{11}ON$: C, 72.5; H, 7.4. Found: C, 72.8; H, 7.6; 5th recrys., 0.155 mμc./mg. C.; 7th recrys, 0.157 mμc./mg. C.; 0.702 mμc./mg. C., cor. for inactive carbon.

Acetic acid was converted to the thallous salt[35] for purification. Carbon dioxide free solutions of thallous hydroxide were prepared from thallous hydroxide obtained from Varlacoid.[36] The acid was carefully titrated to a phenolphthalein end-point. Care had to be taken to eliminate any excess of thallous hydroxide by back titration with an inorganic acid. A slight excess of thallous hydroxide makes subsequent purification more troublesome. After vacuum evaporation of the aqueous solution, the residue was triturated with absolute ethanol. The alcohol solution usually was treated with Darco and again taken to dryness. Thallous acetate can be recrystallized readily from absolute ethanol. It comes out of solution in shining platelets, m.p. 126.5–127.5°. The ease of preparation and purification coupled with the non-hygroscopic nature of this salt makes it ideal as a derivative and as a source of acetic acid in degradation procedures.

Anal. Calcd. for $TlC_2H_3O_2$: C, 9.1; H, 1.2. Found: C, 9.2; H, 1.2; 3rd recrys., 0.723 mμc./mg.C.

Propionic-C_1^{14} Acid.—The carrier propionic acid–propionamide was isolated as propionic acid during the fractionation described under acetic-C_1^{14} acid. The propionic acid fraction contained considerable mesitylene. The *p*-toluidide of propionic acid was prepared, m.p. 123.5–125°.

Anal. Calcd. for $C_{10}H_{13}ON$: C, 73.6; H, 8.0. Found: C, 73.5; H, 8.1; 3rd recrys., 0.675 mμc./mg. C.; 5th recrys., 0.654 mμc./mg. C.; 2.21 mμc./mg. C., cor. for inactive carbon.

Thallous propionate was prepared, m.p. 190–190.5°.[37] *Anal.* Calcd. for $TlC_3H_5O_2$: C, 13.0; H, 1.8. Found: C, 13.1; H, 1.8; 2.20 mμc./mg. C.

A further fractionation of 6 g. of this material was carried out in a 50-plate concentric tube column. Propionic acid boiling at 141.2° was used for analysis and degradation. A small trace of mesitylene still contaminated the sample.

Anal. Found: 2.13 mμc./mg. C. (cor. for trace of mesitylene).

Degradation of Acetic Acid-1,2-C_1^{14}.—The method used was an adaptation of the method of Phares[38] based on the Schmidt reaction. *Anal.* Found: CO_2, 0.840 mμc./mg. C. (2 runs).

The methylamine produced was converted to N-phenyl-N′-methylthiourea, m.p. 113–113.5°. *Anal.* Calcd. for $C_8H_{10}N_2S$: C, 57.8; H, 6.1. Found: C, 57.8; H, 6.1; 0.536 mμc./mg. C., cor. for inactive carbon.

Degradation of Propionic Acid-1,2,3-C_1^{14}.[39]—*Anal.* Found: CO_2, 1.49 mμc./mg. C. (4 runs).

The ethylamine produced from one of the runs was converted to N-phenyl-N′-ethylthiourea. *Anal.* Calcd. for $C_9H_{12}N_2S$: C, 60.0; H, 6.7. Found: C, 60.2; H, 6.7; 2.39 mμc./mg. C., cor. for inactive carbon (1 run).

The ethylamine was also converted to acetic acid by the method of Phares and degraded further. *Anal.* Found: CO_2, 1.44 mμc./mg. C. (2 runs).

The methylamine produced was converted to N-phenyl-N′-methylthiourea. *Anal.* Found: 3.30 mμc./mg. C. corr. for inactive carbon (3 runs).

Acetonitrile.—A higher boiling fraction obtained from the fractionation of the carrier acetone sample was shown to be infrared spectroscopically identical with authentic acetonitrile.

Processing of Acetamide-C_1^{14}; Addition of Carriers. C Series.—A sample of acetamide (32.745 g.) received an irradiation of 6254 megawatt hours. Acetamide survival 46% (estimated). *Anal.* Found: 15.27 ± 0.25 mμc./mg. C.[40] Total activity produced, 0.203 mc. The carriers (9.928 g. of propionamide, 9.663 g. of propionic acid) were added directly to the quartz irradiation vessel containing the remaining acetamide (31.825 g.). The contents of the vessel were homogenized by melting.

Acetic Acid-C_1^{14}.—The contents of the quartz vessel were transferred (48.768 g.) to a round-bottom flask containing 200 g. of sulfuric acid and 200 cc. of water. After boiling for 16 hr. the solution was distilled. The distillate was treated with 0.88 g. of potassium permanganate to remove the sulfite ion present. The solution was continuously extracted with ether for 24 hr. Removal of the ether left 59.53 g. of an acid–water mixture. A center cut, b.p. 118–118.5°, obtained by fractionation as previously described under Acetic acid-1,2-C_1^{14}, A series (no mesitylene chaser was used), was used for all derivative preparations. *Anal.* Found: 1.22 mμc./mg. C.

The *p*-bromophenacylacetate was prepared, m.p. 83–84.5°. *Anal.* Found: 1.26 mμc./mg. C., cor. for inactive carbon.

Thallous acetate was prepared as previously described. *Anal.* Found: 5th recrys., 1.23 mμc./mg. C., 7th recrys., 1.23 mμc./mg. C.

Acetic acid from this cut was purified by vapor phase chromatography (V.P.C.) on a 1.2 cm. × 250 cm. column containing crushed firebrick, Johns–Manville C-22, 80–100 mesh; 50% by weight of 90% Dow Corning (D.C.) 710 plus 10% stearic acid constituted the liquid phase. The column temperature was 120°. The heart cut of the acetic acid fraction was converted to the thallous salt. The dissolved salt was treated with Darco and subsequently recrystallized. *Anal.* Found: 1.24 mμc./mg. C.

Propionic Acid-C_1^{14}.—Propionic acid from the fractionation described under acetic acid-C_1^{14} was analyzed. *Anal.* Found: 1.02 mμc./mg. C.

Thallous propionate was prepared as previously described. *Anal.* Found: 1.00 mμc./mg. C.

Propionic acid was converted to methyl propionate by treatment with diazomethane. The ester was purified by V.P.C. on a column such as described under acetic acid-C_1^{14}. The liquid phase was Dow–Corning 710. After hydrolysis of the ester fraction with base, the solution was acidified and then extracted with ether. The thallous salt was prepared from the ether solution. Analysis of the salt followed its treatment with Darco and subsequent recrystallization. *Anal.* Found: 0.982 mμc./mg. C.

Degradation of Acetic Acid-1,2-C_1^{14}.[38]—*Anal.* Found: CO_2, 1.52 mμc./mg. C. (3 runs).

The methylamine produced was assayed as N-phenyl-

(34) J. Meinwald, THIS JOURNAL, **77**, 1617 (1955).
(35) R. Walter, *Ber.*, **59**, 962 (1926).
(36) 116 Broad Street, New York 4, N. Y.
(37) *Cf.* preparation of thallous acetate and reference 35.
(38) E. F. Phares, *Arch. Biochem. Biophys.*, **33**, 173 (1951). Our modification will be published in a forthcoming article in *Anal. Chem.*

Counting tubes were filled with the CO_2 produced in the Schmidt reaction. The assays were carried out using both the neat acid and the thallous salt as starting material.

(39) *Cf.* degradation of acetic acid-C_1^{14}. The assays were carried out using both the neat acid and the thallous salt as starting material.

(40) Average deviation of experimental data.

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N′-methylthiourea. *Anal.* 0.888 mμc./mg. C., cor. for inactive carbon (3 runs).

Degradation of Propionic Acid-1,2,3-C_1^{14}.[39]—*Anal.* Found: CO_2, 0.583 mμc./mg. C. (4 runs).

The ethylamine produced from one of the runs was converted to N-phenyl-N′-ethylthiourea. *Anal.* Found: 1.10 mμc./mg. C., cor. for inactive carbon.

Acetic acid made from the ethylamine was degraded. *Anal.* Found: CO_2, 0.764 mμc./mg. C.

The methylamine produced was assayed as N-phenyl-N′-methylthiourea. *Anal.* Found: 1.46 mμc./mg. C., cor. for inactive carbon.

Processing of Acetamide-C_1^{14}; Addition of Carrier D Series.—A sample of acetamide (37.150 g.) received an irradiation of 5174 megawatt hours; acetamide survival, 65 ± 3%. *Anal.* Found: 11.86 mμc./mg. C. Total activity produced, 0.179 mc. The carriers (9.0128 g. of propionamide, 9.0413 g. of propionic acid) were added to 26.428 g. of irradiated acetamide. The mixture was homogenized by liquefaction.

Acetic Acid-C_1^{14}.—Hydrolysis of the mixture with base, isolation of the acids and fractionation of the acids was carried out as previously described under Acetic acid-C_1^{14}, A series (no mesitylene chaser was used).

Acetic acid, b.p. 118.5–119.5°, was further purified by V.P.C. The column previously described was used. The liquid phase was 90% D.C. 710 plus 10% stearic acid. A heart cut of the acetic acid was taken. This material was converted to thallous acetate and subsequently purified. *Anal.* Found: 0.811 mμc./mg. C.

Propionic Acid-C_1^{14}.—Propionic acid, b.p. 140.5–141.1°, from the fractionation of the acid fraction was purified by V.P.C. as described under acetic acid-1,2-C_1^{14}. The heart cut of this material was converted to thallous propionate and subsequently purified. *Anal.* Found: 0.886 mμc./mg. C.

Degradation of Acetic Acid-1,2-C_1^{14}.—The thallous salt was degraded. *Anal.* Found: CO_2, 0.991 mμc./mg. C.

The methylamine was assayed as N-phenyl-N′-methylthiourea. *Anal.* Found: 0.608 mμc./mg. C., cor. for inactive carbon.

Degradation of Propionic Acid-1,2,3-C_1^{14}.—The thallous salt was degraded. *Anal.* Found: CO_2, 0.644 mμc./mg. C.

The ethylamine was assayed as N-phenyl-N′-ethylthiourea. *Anal.* Found: 0.959 mμc./mg. C., cor. for inactive carbon.

Acetic acid made from the ethylamine was degraded. *Anal.* Found: CO_2, 0.646 mμc./mg. C.

The methylamine produced was assayed as N-phenyl-N′-methylthiourea. *Anal.* Found: 1.32 mμc./mg. C., cor. for inactive carbon.

UPTON, NEW YORK

[CONTRIBUTION FROM THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

The Rate of Hydration of Methylenecyclobutane and the Effect of Structure on Thermodynamic Properties for the Hydration of Small Ring Olefins[1]

BY PETER RIESZ, ROBERT W. TAFT, JR., AND ROBERT H. BOYD

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The effects of small ring structure on the position of equilibrium in hydration of olefins to *t*-carbinols have been found to be of substantial magnitude and in the directions predicted by Brown's I-strain rules. The relatively small effects of ring size on the rates of hydration which are found indicate that there is no appreciable covalent bonding of a water molecule to carbon in the reaction transition state. It is concluded from the observed effects of structure on the rate of hydration that the π-complex provides a more suitable model for the molecular structure (nuclear arrangement) of the transition state than does the classical carbonium ion. The transition state exhibits the property of possessing carbonium ion character with respect to electronic, but not molecular, structure. This property is attributed to more sluggish nuclear than electronic rearrangements in attaining the transition state.

The rates of hydration of gaseous methylenecyclobutane and 1-methyl-1-cyclobutene to 1-methylcyclobutanol in aqueous nitric acid solution have been determined by measuring the rate of drop in the saturated vapor pressure of olefin over the solution in which the reaction occurs.[2]

Demjanow and Dojarenko have shown that methylenecyclobutane is converted to 1-methylcyclobutanol by treatment with 66% H_2SO_4.[3] We find no evidence that rearranged products are formed during the hydration.

Rates and equilibria in the hydration of the small ring olefins have been investigated in order to provide critical evidence concerning the reaction mechanism. Taft has proposed that the rate-determining step in the aqueous acid-catalyzed aliphatic olefin–*t*-carbinol interconversion involves the isomerization of π-complex and carbonium ion intermediates.[4] Several criteria of mechanism indicate that the same mechanism is involved for the small ring as for the open chain olefins.[4,5]

By combining the results of the present research with those of previous investigations, we have obtained data on the effect of structure on the thermodynamic equilibrium and rate properties for the hydration of small ring olefins relative to that for corresponding open chain olefins. This information provides new evidence in support of Taft's mechanism.

Experimental

Methylenecyclobutane.—The zinc reduction of pentaerythrityl tetrabromide[6] was carried out in a manner similar to that described by Roberts and Sauer.[7] In order to separate the olefins in the crude product from spiropentane, the reaction product was extracted several times with almost saturated aqueous silver nitrate solution and the olefin was regenerated by warming the solution.[8] The crude olefin product was fractionated through a 40-inch column packed

(1) The work reported herewith was carried out as Project NR055-295 between the Office of Naval Research and The Pennsylvania State University. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) J. B. Levy, R. W. Taft, Jr., D. Aaron and L. P. Hammett, THIS JOURNAL, **73**, 3972 (1951).

(3) I. N. Demjanow and M. Dojarenko, *J. Russ. Phys. Chem. Soc.*, **45**, 176 (1913); *Chem. Zentr.*, **84**, I, 2026 (1913); *C. A.*, **7**, 2226 (1913).

(4) (a) R. W. Taft, Jr., THIS JOURNAL, **74**, 5372 (1952); (b) R. W. Taft, Jr., E. L. Purlee, P. Riesz and C. A. DeFazio, *ibid.*, **77**, 1584 (1955).

(5) (a) J. B. Levy, R. W. Taft, Jr., and L. P. Hammett, *ibid.*, **75**, 1253 (1953); (b) E. L. Purlee and R. W. Taft, Jr., *ibid.*, **78**, 5807 (1956).

(6) *Org. Syntheses*, **31**, 82 (1951).

(7) J. D. Roberts and C. W. Sauer, THIS JOURNAL, **71**, 3925 (1949).

(8) Cf. M. L. Moyer and H. H. Stevenson, *ibid.*, **66**, 812 (1944).

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with glass helices. The material used for the kinetic work had a b.p. 40.8–41.0° (737 mm.), n^{20}D 1.4206. Literature values[9] for these constants are b.p. 41.4° (750 mm.), n^{20}D 1.4210. The infrared spectrum of the gaseous olefin sample was taken in a 10-cm. gas cell at a pressure of 5 cm. and corresponded closely to that reported by Cleveland, Murray and Galloway.[10]

1-Methyl-1-cyclobutene.—A mixture of this olefin and methylenecyclobutane was prepared following a procedure of Shand, Schomaker and Fischer.[9] Methylenecyclobutane was treated with HI and the resulting 1-methyl-1-cyclobutyl iodide was dehydrohalogenated with alcoholic KOH. The earlier workers obtained a sample containing 1-methyl-1-cyclobutene in a ratio of 2 to 1 to its exo isomer.[9] Our sample contained more nearly equivalent amounts of the two olefins (*cf.* Kinetic Procedure). The infrared spectrum of the gaseous mixture showed only the peaks reported for the two olefins.[10]

1-Methyl-1-cyclobutanol.—This carbinol was prepared in over 80% yield by the hydration of methylenecyclobutane with a 1:1 (by volume) mixture of aqueous sulfuric acid.[11] The crude product was dried over calcium hydride and fractionated through a 10-inch Vigreux column, b.p. 115–116° (uncor.) at 730 mm., n^{20}D 1.4343. Literature values[9,16b] for these constants are b.p. 115–118° (at 747 mm.), n^{24}D 1.4333. There was no evidence of the formation of other products such as cyclobutanemethanol (b.p. 142–143.5°, n^{20}D 1.4450; H. Pines, H. G. Rodenberg and V. N. Ipatieff, This Journal, **75**, 6065 (1953)) or 1-methylcyclopropane methanol (b.p. 128° at 750 mm., n^{20}D 1.4308; S. Siegel and C. G. Bergstrom, This Journal, **72**, 3815 (1950)—*cf.* further comment on reaction product from kinetic experiments).

Kinetic Procedure for Methylenecyclobutane.—The apparatus and the hydration procedures are those described in the study of the hydration of 1-methyl-1-cyclopentene.[12] The rate of hydration, k_p, of gaseous methylenecyclobutane at unit pressure in the gas phase by an aqueous nitric acid is given by the expression[2]

$$k_p = \left(\frac{r}{RT} + h\right)(s - k_{-1})$$

where

$$s = \frac{-\mathrm{d} \ln (P - P^e)}{\mathrm{d}t}$$

P = partial pressure of gaseous olefin at any time t
P^e = partial pressure of olefin when reaction has reached equilibrium
k_{-1} = rate of dehydration of aqueous alcohol at unit concentration (negligible in the present case)
r = ratio of volume of gas phase to volume of acid solution
h = distribution constant of olefin between liquid and gas phase

Since the distribution constant, h, was determined by separate experiments, it was possible to determine a k_p value from a single kinetic run. In general, four kinetic runs were made with values of r/RT ranging from 0.05 to 0.150 and the average k_p calculated. The probable errors given in Table III are based upon deviations from the mean. Distribution constants in acid solutions were estimated[13] from the value obtained in water, h_0, by using the Setschenow equation

$$\log (h_0/h) = KC$$

The value of the Setschenow parameter, K, at 25.17° was obtained from the value of h_0 (Table IV) and the value of h obtained indirectly in 3 M nitric acid. Nine hydration experiments in 3 M acid at varying values of r/RT were made (results are listed in Table I). Use was then made of the relationship[2]

$$\frac{RT}{rs} = \frac{1}{k_p} + \frac{hRT}{k_p r}$$

From the least squares calculation a value of $h = 22.6 \pm 2.0 \times 10^{-3}$ mole-l.$^{-1}$ atm.$^{-1}$ is obtained. Accordingly, $K = -0.056 \pm 0.013$.

Table I

Hydration of Methylenecyclobutane in 2.995 M Nitric Acid at 25.17°

$r/RT \times 10^3$	33.71	46.38	49.94	60.23	79.51
$s \times 10^2$	7.68	6.52	6.60	5.60	4.39
$r/RT \times 10^3$	142.0	151.7	152.2	158.9	
$s \times 10^2$	2.70	2.45	2.60	2.50	

The equilibrium pressures obtained in the hydration of methylenecyclobutane were not equal to the solvent pressures but slightly larger. This difference was independent of a variation of r/RT from 0.05 to 0.150 and independent of temperature, both of which would have a large effect if the residual pressure were due to reversibility. In all experiments this residual corresponded to about 3% of the amount of original olefin introduced. No drift was noted in the equilibrium pressures after 10 half-lives and no systematic deviation from linearity could be detected in any of the rate plots which were followed to as much as 95% of complete reaction. It was therefore concluded that 3% of an inert impurity was present in the methylenecyclobutane. It has been shown previously that the presence of a small amount of inert gas (air) does not affect the measurements when the hydration is irreversible.[2] The infrared spectrum of a gas sample enriched in this impurity was obtained by "hydrating out" methylenecyclobutane. The spectrum shows large absorption peaks at 10.07 and 12.57 μ which were barely noticeable in the original sample. The enrichment factor of both peaks was comparable. The absorption peak at 10.07 μ is identical in position and appearance with that from a spiropentane sample.[10]

Kinetic Procedure for 1-Methyl-1-cyclobutene.—The rates of hydration of gaseous 1-methyl-1-cyclobutene and methylenecyclobutane were determined simultaneously in 2.52 M nitric acid solution at 25.0°. The procedure used is that given previously,[12] and the olefin mixture used was that obtained from the dehydrohalogenation of 1-methyl-1-cyclobutyl iodide. The methylenecyclobutane reacts so much faster (about seven times) than its endo isomer that no difficulty was encountered in precisely resolving a plot (Fig. 1 is a typical example) of log P *vs.* t into the two first-

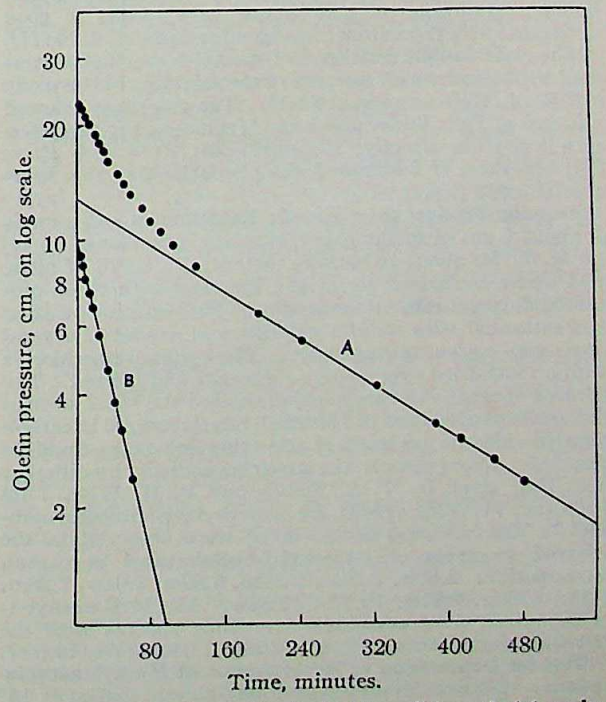

Fig. 1.—Parallel first-order hydration of 1-methyl-1-cyclobutene (A) and methylenecyclobutane (B).

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(10) F. F. Cleveland, M. J. Murray and W. S. Galloway, *J. Chem. Phys.*, **15**, 742 (1947).
(11) For details of this preparation, see P. H. Williams, Ph.D. Thesis, The Pennsylvania State College, 1941.
(12) R. W. Taft, Jr., J. Levy, D. Aaron and L. P. Hammett, This Journal, **74**, 4735 (1952).
(13) R. W. Taft, Jr., E. L. Purlee and P. Riesz, *ibid.*, **77**, 899 (1955).

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order components using conventional procedure.[14] The plot becomes precisely linear after about 75% of the original olefin has reacted, and the resulting slope, $s/2.303$, used in the equation, $k_p = (r/RT + h)(s)$, provides a value of k_p for the slower reacting olefin. Typically the k_p value is based upon the pressure drop from about 6 to 2 cm. with an initial pressure of 20 to 25 cm. The partial pressure due to the slower reacting olefin was calculated from the first-order rate law and subtracted from the observed pressure to obtain the partial pressure of the faster reacting isomer. These pressures followed precisely a first-order rate law (*cf.* Fig. 1) from which, in turn, the k_p value for the faster reacting olefin was obtained. Intercepts in the log P *vs.* t plots indicate that the composition of the olefin sample is approximately 45% in the latter olefin. Table II lists results obtained in several experiments.

TABLE II

SIMULTANEOUS HYDRATION OF 1-METHYL-1-CYCLOBUTENE AND METHYLENECYCLOBUTANE IN 2.523 *M* NITRIC ACID AT 25.0°

r/RT	k_p, 10^4 moles-l.$^{-1}$-atm.$^{-1}$-min.$^{-1}$ 1-Methyl-1-cyclobutene	Methylene-cyclobutane	Intercept ratio
0.1078	4.77	33.0	1.3
.1165	4.62	32.6	1.3
.1167[a]	4.60		4.3
.1325[b]	4.70	32.1	1.3
.1498	4.76	30.3	1.2
Mean value	4.64	32.0	

[a] Experiment with enriched 1-methyl-1-cyclobutene sample. [b] Concentration of acid 2.55 *M*.

The mean value of k_p identifies the faster reacting olefin as methylenecyclobutane. The rate of hydration of this olefin has not previously been determined in 2.52 *M* HNO_3 but has been shown to follow the equation log $k_p = (-1.29)H_0 - 3.53$ for the range 0.973 to 4.94 *M* HNO_3.[4b] The observed value agrees substantially with that calculated from this equation. Combined with the earlier data, the hydration rates for methylenecyclobutane are best fitted by the equation log $k_p = (-1.27)H_0 - 3.49$.

In order to check the above results, methylenecyclobutane was "hydrated out" of the original olefin sample, giving a sample which by kinetic analysis (ratio of intercepts) and by infrared analysis contained 80–85% of 1-methyl-1-cyclobutene. Hydration of this sample gave results in good agreement with those from the original sample (*cf.* Table II).

The olefin sample enriched in 1-methyl-1-cyclobutene was used to obtain a rough measure of the solubility of this olefin in 2.52 *M* HNO_3 solution at 25.0°. The procedure followed was that of Taft, Purlee and Riesz[13] (equation 1 of this reference is given incorrectly; it should read: $P^0 = P + \rho(t - t')$); the value of h obtained using equation 3 of this reference is 0.010 mole-l.$^{-1}$.

Reaction Product from Kinetic Experiments.—A sample of about 1 ml. of methylenecyclobutane was allowed to react at 45° for about 10 half-life periods with 0.973 *M* nitric acid under conditions essentially identical with those prevailing during a rate measurement. The resulting solution was saturated with sodium chloride and extracted several times with carbon tetrachloride. The carbon tetrachloride solution was dried over sodium carbonate and filtered. The infrared spectrum of this solution showed the same absorption peaks as a solution of 1-methyl-1-cyclobutanol in carbon tetrachloride and no trace of any other substance could be detected. (For example, the spectrum is distinctly different from that given by V. A. Slabey and P. H. Wise, THIS JOURNAL, 71, 3252 (1949), for α-methylcyclopropanemethanol.) The following peaks (in μ) were observed in the infrared spectrum of 1-methyl-1-cyclobutanol in carbon tetrachloride: 2.80w, 3.04w, 3.40m, 6.89m, 7.01w, 7.28m, 7.95s, 8.49m, 9.81w, 10.47s, 10.89w. Liquid 1-methyl-1-cyclobutanol gives essentially the same spectra with the following modifications: 2.80 missing, 3.04s, 8.49s, 14.00w.

Test for Deuteration or Isomerization of Methylenecyclobutane.—Gaseous methylenecyclobutane was shaken at 45° with 0.973 *M* nitric acid in 60% deuterated water under the conditions of a rate experiment until the pressure had fallen to half of the initial value. The residual olefin was then removed and its infrared absorption observed in the gaseous state with a path length of 10 cm. at a pressure of 5 cm. Comparison of this spectrum and that of the original olefin showed that no detectable deuteration or isomerization of the olefin occurs during the hydration reaction.

Dehydration of 1-Methylcyclobutanol.—The gaseous material obtained as indicated in the Results section gave the following infrared peaks (in μ) which were used to characterize isoprene (we are indebted to Professor J. D. Roberts for suggesting this assignment): 6.25m, 10.08m, 11.04s and 11.20s. Peaks at 5.96 (w), 7.00 (w) and 11.40 (s) characterize methylenecyclobutane. 1-Methyl-1-cyclobutene was identified by peaks appearing at 6.90 (m), 7.80 (w), 11.40 (s), 11.68 (s) and 3.68 (m). The quantitative analysis of the olefin mixture was based upon the following peaks: 1-methyl-1-cyclobutene, 13.68 μ; isoprene, 6.25, 10.08 and 11.04 μ; methylenecyclobutane, 5.96 and 11.40 μ. The analysis given has been rounded off to the nearest 5% and is estimated to be accurate within this limit.

Results

Rate Data.—Measurements of the rate of hydration of methylenecyclobutane in 0.972 *M* nitric acid have been made for the temperature range 25 to 45°. In this temperature range the hydration is, within the precision of measurement, completely irreversible. Table III lists the rate constants, k_p, obtained.

TABLE III

RATE CONSTANTS, k_p, FOR THE HYDRATION OF GASEOUS METHYLENECYCLOBUTANE IN 0.972 *M* NITRIC ACID IN 10^4 MOLES-L.$^{-1}$-ATM.$^{-1}$-MIN.$^{-1}$

Temp., °C.	25.17	34.58	45.15
k_p	3.97	9.47	22.75
Probable error	0.036	0.072	0.15

A plot of log k_p against $1/T$ is linear essentially within the precision of measurement. Thus the value of 10^4 k_p in 0.972 *M* nitric acid at 34.58° calculated on the basis of this linearity from the value at 25.17° is 9.31 ± 0.06, compared with the observed value 9.47 ± 0.07.

From equations 8 and 9 of reference 3, we calculate the best values of the enthalpy of activation, $\Delta H_p^{\ddagger}$, to be 15.83 ± 0.11 kcal. and the entropy of activation, $\Delta S_p^{\ddagger}$, to be −28.81 ± 0.34 cal./deg. These quantities represent the difference in enthalpy and entropy between the activated state in solution on the one hand and the gaseous olefin and aqueous acid on the other.

The rate constants, k_p, obtained for 1-methyl-1-cyclobutene and methylenecyclobutene in 2.52 *M* nitric acid at 25.0° are 4.69×10^{-4} and 3.20×10^{-3} mole-l.$^{-1}$-atm.$^{-1}$-min.$^{-1}$, respectively. The value of k_p for 1-methyl-1-cyclobutene in 0.973 *M* nitric acid at 25.0° may be estimated as 6.8×10^{-5} mole-l.$^{-1}$atm.$^{-1}$-min.$^{-1}$ by the relationship: log $(k^2/k^1) = (-1.25)(H^2_0 - H^1_0)$.[4b]

Solubility Measurement.—The distribution constant, h, for methylenecyclobutane between gas phase and water has been measured over a temperature range from 15 to 45°. The results are recorded in Table IV.

A plot of log h against $1/T$ is linear to a reasonable precision. Thus the value of 10^3h at 34.95° calculated on the basis of this linearity from the value at 25.17° is 11.04 ± 0.08; the observed value is 10.95 ± 0.14.

(14) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 199.

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TABLE IV

DISTRIBUTION CONSTANT, h, FOR METHYLENECYCLOBUTANE BETWEEN GAS PHASE AND WATER AS A FUNCTION OF TEMPERATURE IN 10^3 MOLES-L.$^{-1}$-ATM.$^{-1}$

Temperature, °C.	16.02	19.95	25.17	30.11	34.95	45.13
h	21.56	18.99	15.49	12.63	10.85	8.01
Probable error	0.20	0.29	0.20	0.10	0.14	0.02

The heat and entropy of solution of methylenecyclobutane in water were calculated from the slope of the appropriate least squares lines. The value of the enthalpy of solution, ΔH_{sol}, is -6.43 ± 0.12 kcal. and that of the entropy of solution, ΔS_{sol} is -29.5 ± 0.4 cal./deg. The standard state is hypothetical one molal.

The rate constant for dissolved olefin at unit concentration, k_c (in units of min.$^{-1}$), is obtained from the relationship[2]: $k_c = k_{p/h}$. Using the value of h (0.010 mole-l.$^{-1}$-atm.$^{-1}$) obtained for 1-methyl-1-cyclobutene in 2.52 M nitric acid at 25.0° and the Setschenow equation with an estimated K value of 0.074,[4b] an h value for 0.973 M nitric may be estimated as 0.008 mole-l.$^{-1}$-atm.$^{-1}$. This value together with the estimated k_p value (6.8×10^{-5} mole-l.$^{-1}$-atm.$^{-1}$) gives $k_c = 9 \times 10^{-3}$ min.$^{-1}$. In a similar fashion from the data given above, the k_c value for methylenecyclobutane in 0.973 M nitric acid at 25.0° is calculated to be 2.3×10^{-2} min.$^{-1}$.

The relative enthalpies and entropies of activation, $\Delta\Delta H_c^{\ddagger}$ and $\Delta\Delta S_c^{\ddagger}$, respectively, for dissolved olefins at unit concentration (in 0.973 M HNO_3) can be obtained from the equations

$$\Delta\Delta H_c^{\ddagger} = \Delta\Delta H_p^{\ddagger} - \Delta\Delta H_{sol} \quad (1)$$

$$\Delta\Delta S_c^{\ddagger} = \Delta\Delta S_p^{\ddagger} - \Delta\Delta S_{sol} \quad (2)$$

The use of these equations in this manner involves the assumption that the relative enthalpies and entropies of solution, $\Delta\Delta H_{sol}$ and $\Delta\Delta S_{sol}$, respectively, are the same in one molar acid as in water. This assumption has been confirmed to a good approximation by direct measurements with isobutene and trimethylethylene.[15]

Hydration Equilibrium.—In the temperature range 25 to 45° the hydration of methylenecyclobutane was found to proceed to completion within the precision of pressure measurement. None of the olefins previously studied under comparable equilibrium conditions has been found to hydrate to this degree at 45°. It was therefore clear that the ring size of the olefin has an appreciable effect on the value of the equilibrium constant. The remarkable stability of 1-methyl-1-cyclobutanol toward dehydration has interested previous investigators.[16]

We have been able to estimate a maximum value for the equilibrium constant at 70° for the reaction

methylenecyclobutane (g) + H_2O(l) $\rightleftharpoons$ 1-methyl-1-cyclo-butanol(aq)

Using a one molar (nearly saturated) solution of the carbinol in 0.0973 M perchloric acid at 70°, a steady olefin pressure of about 0.7 cm. developed with long standing. Assuming, in accord with the experimental results given below, that not more than 20% of the generated olefin is methylenecyclobutane, an equilibrium constant, $K_p = C_a^e/p_0^e$, of greater than 500 moles-l.$^{-1}$-atm. is obtained.

A solution 0.9 M in 1-methyl-1-cyclobutanol and 0.3 M in $HClO_4$ was heated at reflux temperature for several hours, during which time a stream of nitrogen was swept through the system and the exit vapors were passed into a liquid nitrogen trap. The olefin sample collected was analyzed by infrared spectra in a 10-cm. gas cell at a pressure of 4.9 cm. The analysis indicated the decomposition product to be a mixture of approximately 45% 1-methyl-1-cyclobutene, 35% isoprene and 20% methylenecyclobutane. The formation of isoprene readily is pictured in the dehydration of 1-methyl-1-cyclobutanol in terms of a Whitmore β-cleavage of a C–C bond of the cyclobutane ring.

An estimate of the relative thermodynamic stability of the endo and exo isomers may be made from the present results. Assuming the composition of the dehydration product given above to provide a rough measure of the relative rates of formation of the two olefins from aqueous carbinol solution at 25°,[17] one may calculate from this and the relative hydration rates, k_p, that the free energy of formation of gaseous 1-methyl-1-cyclobutene is on the order of 1,5000 cal./mole more negative than that for methylenecyclobutane. Turner and Garner have recently reported results indicating that in 5- and 6-membered rings the 1-methyl-1-cycloalkene is also more stable than its methylenecycloalkane isomer.[18]

Discussion

By combining the data of the present research with that of previous investigations,[19] the effects of ring size on the rates, equilibria and thermodynamic properties given in Tables V and VI are obtained. The standard of comparison is isobutylene which apparently possesses properties reasonably typical of open-chain olefins leading to *t*-carbinols. Thus, the rates of hydration relative to isobutylene are: 2-methyl-2-butene, 0.67; 2-methyl-1-butene, 1.30; 2,3,3-trimethyl-1-butene, 1.20. The rates of dehydration relative to *t*-butyl alcohol are: *t*-amyl alcohol, 10 (to give 2-methyl-2-butene) and 2.0 (to give 2-methyl-1-butene); and dimethyl-*t*-butylcarbinol, 15. These relative rates and those given in Tables V and VI apply to dissolved reactants at unit concentration in one molar nitric acid solution at 30°.

The equilibrium data of Table V indicate that the formation of carbinol from olefin is favored ($K/K_0 >> 1$) by a very substantial factor when the carbon atom forming the C–O bond is in a 4-membered ring, but the reverse ($K/K_0 << 1$) is true for the 5-membered ring. A factor of greater than four powers of ten favors the hydration equilibrium constant for methylenecyclobutane compared to

(15) E. L. Purlee, R. W. Taft, Jr., and C. A. De Fazio, THIS JOURNAL, **77**, 837 (1955).

(16) (a) Reference 10; (b) H. C. Brown and M. Borkowski, *ibid.*, **74**, 1894 (1952).

(17) If, as seems less likely, the composition of the dehydration product is equilibrium controlled, then the figure for the estimated difference in the free energy of formation of the two isomers should instead be about 500 cal./mole (favoring the endo compound). It is probable that the correct figure lies between 500 and 2000 cal./mole.

(18) R. B. Turner and R. H. Garner, THIS JOURNAL, **79**, 253 (1957).

(19) References 2, 4, 5, 12, 13, 15 and unpublished data of C. A. De Fazio.

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TABLE V

EFFECT OF RING SIZE ON HYDRATION OF OLEFINS

Olefin	Reaction equilibria			Reaction rates		
	K/K_0 at 30°	$\Delta\Delta H°_c$, kcal.	$\Delta\Delta S°_c$, e.u.	k/k_0 at 30°	$\Delta\Delta H^{\ddagger}_c$, kcal.	$\Delta\Delta S^{\ddagger}_c$, e.u.
Isobutene	(1.00)	(0.0)	(0.0)	(1.00)	(0.00)	(0.00)
1-Methyl-1-cyclopentene	0.0073	3.7 ± 0.7	2.9 ± 1.6	2.29	-1.2 ± 0.6	-2.3 ± 1.4
Methylenecyclobutane	>200	.....	.....	0.60	1.5 ± 0.3	4.4 ± 0.8
1-Methyl-1-cyclobutene	>30	.....	.....	0.2	.....	.....

TABLE VI

EFFECT OF RING SIZE ON DEHYDRATION OF CARBINOLS

Carbinol	Reaction equilibria			Reaction rates		
	K/K_0 at 30°	$\Delta\Delta H_{-1}$, kcal.	$\Delta\Delta S_{-1}$, e.u.	k/k_0 at 30°	$\Delta\Delta H^{\ddagger}_{-1}$, kcal.	$\Delta\Delta S^{\ddagger}_{-1}$, e.u.
t-Butyl alcohol	(1.00)	(0.0)	(0.0)	(1.00)	(0.0)	(0.00)
1-Methyl-1-cyclopentanol	140	-3.7 ± 0.7	-2.9 ± 1.6	315	-4.9 ± 0.4	-5.2 ± 1.0
1-Methyl-1-cyclobutanol	<0.005[a]	.....	.....	<0.003[a]	.....	.....

[a] Based on dehydration to methylenecyclobutane.

that for 1-methyl-1-cyclopentene. The results are in accord with the I-strain hypothesis of Brown.[20] According to this hypothesis increasing the coördination number of the carbon atom of the 4-membered ring from three to four (olefin to alcohol) is favorable because of the release of some ring strain. That is, constraint of the carbon valences to 90° involves less strain in the normally tetrahedral than in the trigonal state. Further, the unfavorable effect resulting from the increase from three to four of the coördination number of the carbon atom of the 5-ring system is explained on the basis of increased eclipsing of ring hydrogen atoms.

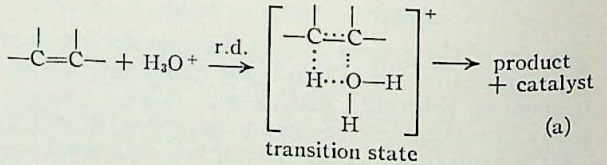
The rate of hydration (Table V) shows no such dependence on structure. In general there is relatively little effect of structure on the hydration rate. The maximum factor of one power of ten in the hydration rate involves exactly the opposite relationship to structure as that shown by the equilibria; namely, the 5-ring olefin, 1-methyl-1-cyclopentane, hydrates about ten times faster than the 4-ring olefin, 1-methyl-1-cyclobutene.

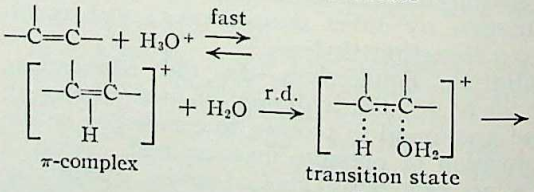
It is striking to note that in each case where temperature coefficients of rate or equilibrium have been determined (*cf.* Tables V and VI) the effects of structure on the relative free energy changes are accompanied by even larger effects in the same direction on the enthalpy changes.

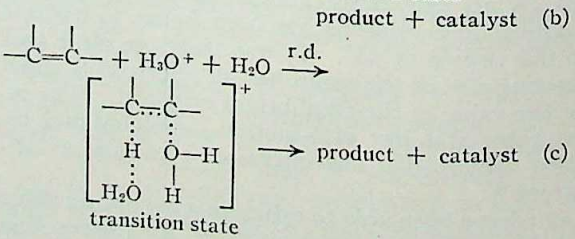
We conclude that there is no appreciable covalent bonding of a water molecule to carbon in the hydration transition state. The argument is based upon the proposition that if the transition state resembled the carbinol (with appreciable covalent C–O bond interaction), the effect of structure on the hydration rate and on the equilibrium would be in the same direction and of similar magnitude. That is, similar effects from increasing the coördination number of the ring carbon atom would result from the formation of either the transition state or the carbinol from the olefin. The relationships expected on this basis are not observed.

On the other hand, the formation of both the transition state and the olefin from the carbinol are similarly affected (in direction and in magnitude) by structure (compare corresponding values of K/K_0 and k/k_0 of Table VI). The direction of the observed effects are those expected according to the I-strain hypothesis for the decrease in coördination number of the ring carbon atom from four (carbinol) to three (olefin or transition state). In other words, the closely similar effects of structure on the rate and equilibrium of carbinol dehydration indicate that the water present in the conjugate acid of the carbinol is lost from carbon in the formation of either the olefin or the transition state. A similar conclusion has been reached earlier based upon the entropies of activation and reaction for olefin hydration and carbinol dehydration.[4]

The present results, therefore, exclude such mechanisms as the following (as well as those rigorously excluded by earlier results[5])







The results in Tables V and VI are consistent with, and lend further support to, the mechanism of Taft (given below) which pictures no appreciable covalent interaction between oxygen (of H_2O) and carbon (of olefin) in the proposed transition state.

Apparently the only alternate mechanism which is consistent with the present results is a rate-determining proton transfer from hydronium ion to olefin. This mechanism is considered to be of low probability on the basis of observed isotope effects on the hydration rate.[6]

(20) (a) Reference 17b; (b) H. C. Brown, R. S. Fletcher and R. B. Johannesen, THIS JOURNAL, **73**, 212 (1951); (c) H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

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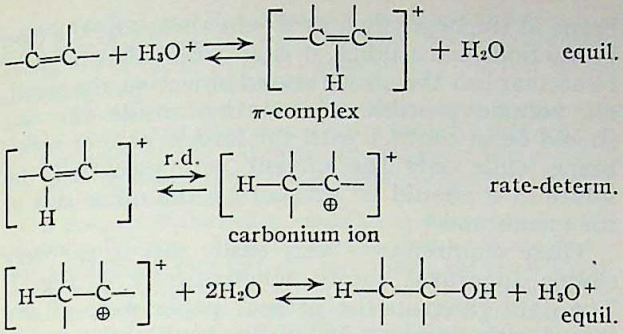
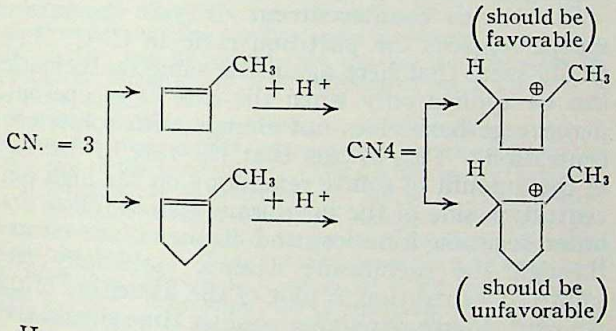


Application of the I-strain hypothesis to the relative rates of olefin hydration listed in Table V provides further evidence of importance concerning the structure of the transition state. If the positions occupied by the nuclei in the reaction transition state were those expected of a classical carbonium ion (in which the added H has formed a conventional C–H bond), then by arguments paralleling those used above, the rate of hydration of the cyclobutene should be favored and the cyclopentene retarded relative to the open chain olefins



However, as noted above, exactly the opposite order of rates is observed. We conclude therefore that the transition state does not possess the nuclear arrangement of a classical carbonium ion. On the other hand, the transition state is stabilized by those structural features which by electronic shifts (inductive or hyperconjugative electron-release) stabilize carbonium ions, as witnessed by the many powers of ten increase in rate in the series: ethylene << propylene << isobutylene.[21] The olefin hydration transition state may thus be ascribed the property of possessing carbonium ion character with respect to electronic but not with respect to molecular structure (nuclear arrangement). This property bears a striking similarity to the well-known Franck–Condon principle and, by analogy, leads to the proposal that the property results from more sluggish nuclear than electronic rearrangements in attaining the transition state.

It is a corollary of our conclusions that the transition state cannot be said (as frequently implied in discussions) to possess a fixed fractional character of the products and reactants of the rate-determining step, but this assessment, if it is to be generally useful, must be made with respect to both electronic and nuclear rearrangements.

Since the effects of structure on hydration rates shown in Table V are relatively small (compared to the effects on dehydration rates shown in Table VI), the π-complex appears to provide a suitable model for the molecular structure of the transition state. According to the structure proposed from the π-complex,[22] its formation from olefin should not require notable nuclear rearrangements.

(21) This is in contrast to the formation constants of the Ag^+ complexes of these olefins which show relatively little dependence on structure; *cf.* F. R. Hepner, K. N. Trueblood and H. J. Lucas, THIS JOURNAL, **74**, 1333 (1952).

(22) (a) M. J. S. Dewar, *J. Chem. Soc.*, 406 (1946); (b) C. C. Price, "Mechanisms of Reactions at the Carbon–Carbon Double Bond," Interscience Publishers, Inc., New York, N. Y., 1946, p. 46; (c) E. L. Purlee and R. W. Taft, Jr., THIS JOURNAL, **78**, 5807 (1956); (d) L. G. Cannell and R. W. Taft, Jr., *ibid.*, **78**, 5812 (1956).

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Dialysis Studies. II. Some Experiments Dealing with the Problem of Selectivity

BY LYMAN C. CRAIG, TE PIAO KING AND ALFRED STRACHER[1]

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A convenient cellophane dialysis cell for quantitatively studying dialysis rates is described. A series of proteins of increasing molecular weight up to 45,000 have been studied. The rate of dialysis for each protein has been shown to fall in the order of increasing molecular weight but the membrane becomes more selective as the solute size approaches the membrane pore size. The method may offer a simple means for detecting a change in shape or size during certain types of transformation and for studying homogeneity with respect to size.

In the first paper[2] of this series an experimental approach for fractional dialysis with cellophane was described which permitted multiple fractional separations to be made in a manner entirely analogous to that accomplished with a few stages of countercurrent distribution.[3] Evidence of unanticipated selectivity was encountered at that time which was sufficient to make the procedure as it was described of practical use for the preliminary fractionation of complex mixtures of solutes differing widely in size. It seemed likely that the overall selectivity of the method could be improved either by enhancing the inherent selectivity at each stage or by some mechanical systematization so that many stages could be applied with a minimum of labor as was done in countercurrent distribution.

This latter is made difficult by the fact that for each unit in a stage the dilute dialyzate must be concentrated in some way to one tenth or less of its volume before being transferred to the inside of the next unit in the series. Before attempting to

(1) Fellow of the National Foundation for Infantile Paralysis.

(2) L. C. Craig and T. P. King, THIS JOURNAL, **77**, 6620 (1955).

(3) L. C. Craig, *J. Biol. Chem.*, **155**, 519 (1944).

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design a physical set up for accomplishing the larger number of stages it seemed wise to make a more thorough study of some of the factors which could contribute to the inherent and unexplained selectivity possible in each membrane. The present paper will describe certain experiments along this line.

The results already published and other experiments soon showed that the inherent membrane selectivity was a function of many different factors such as the type of membrane, the solvent, the nature of the solute, the temperature, etc. The proper evaluation of each of these factors is made difficult by the fact that they are all more or less interdependent.

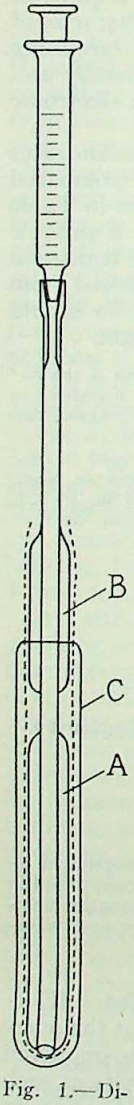

Fig. 1.—Dialysis cell.

In spite of such interdependence it was obvious from the data published[2] and from other preliminary data that the major factor governing selectivity, at least with cellophane membranes, and similar types of solutes, was primarily the size of the solute. Moreover, the effect of size appeared much greater than would be expected on the basis of difference in rates of diffusion in free solution. Apparently the membrane not only prevents mixing due to convection but in addition exerts a selective action of its own in inhibiting the diffusion of the larger molecules through it to a greater degree than the smaller ones. If this is true then it might be expected that relatively higher selectivity with a given membrane would be found for those molecules which due to their size are barely able to pass through the membrane.

Rather than search for a membrane which would slowly pass only small solutes or try to decrease the permeability of one already available it seemed more profitable first to study the passage of larger molecules through the commercial membranes already available to everyone.

In order to pursue this line of attack it seemed advisable first to consider some arrangement for shortening the time of passage of the more sluggish solutes through the membrane both in the interest of saving time and in minimizing the chance of transformation due to bacterial growth. The desired arrangement should not alter the inherent permeability of the membrane in any way such as stretching of the membrane by hydrostatic pressure. This point will be discussed later.

As might be expected, the net total rate of passage of solute caused solely by a concentration gradient of that solute across a membrane is directly proportional to the effective area of the membrane. When the rate is considered in terms of per cent. of the total solute included in the membrane at the beginning, as would always be the case in fractionation studies, it is apparent that in order to accomplish the above stated objective, the smallest volume possible of solution inside the sac should be in contact with the largest area of membrane while only the solvent with essentially no solute in it should be present on the other side of the membrane.[4]

These requirements were easily met in the very simple apparatus shown schematically in Fig. 1. The data given in the present paper were all obtained with a dialysis cell of this type.

Rather early in the development of the method of countercurrent distribution,[5] it was realized that the simple calculations of the binomial theorem could be applied only when the partition isotherms of the solutes were essentially linear, *i.e.*, the partition ratios for a given system did not shift with a change in solute concentration. This ideality proved to be best also from the standpoint of overall separation although non-linear isotherms often permitted better resolution of one component at the expense of the purity of the others.

Since with countercurrent dialysis the rate of escape replaces the partition ratio in C. C. D., it would seem that here again the same mathematics can be applied only when the rate of escape on a percentage basis does not change with solute concentration. This means that the rate of decrease of the amount of solute remaining on the high concentration side of the membrane should follow first order reaction kinetics, and if the solute escapes through the membrane against essentially zero solute concentration, a plot of the logarithm of the per cent. solute remaining against time should give a straight line. In countercurrent dialysis such a straight line behavior is analogous to a linear partition isotherm in C. C. D. Departure from linearity in the dialysis process would be expected to have an effect similar to that already so familiar in C. C. D.

Experimental

The simple apparatus shown in Fig. 1 is constructed easily by an amateur glass blower. A Pyrex glass tube of outside diameter slightly smaller than the diameter of the extended cellophane tubing is chosen and a 6 mm. tube sealed inside it is shown with the lower end of the smaller tube left open. The smaller tube passes through a ring seal at the upper end of the larger tube, A, and at distance of about one cm. from this ring seal into a second section, B, of the larger tubing. This second section of the larger tubing is approximately 0.5 mm. larger in diameter than the lower section, A, and approximates 4 cm. in length. After passing through the upper ring seal of the upper section, the 6 mm. tube is joined to the appropriate part of a standard Becton–Dickinson adapter so that a 2-ml. syringe can be fitted to it.

The dialysis casing to be used is soaked for a few moments in water and one end is tied off with a single knot exerting care not to stretch in any way the part of the membrane above the knot which will later serve as the dialysis membrane. The knot can be tightened adequately by holding the initial loosely formed knot with two fingers while it is pulled tight with the short piece extending below the knot. The extension is then cut off with scissors. The tubing is cut to form a sac of such length that most of section B will be covered when it is pulled over A. This can be done by slowly rotating the wet glass part while the wet membrane

(4) R. E. Stauffer in Weissberger, "Technique of Organic Chemistry," Vol. III, 2nd edition, Interscience Publishers, New York, N. Y., 1956, p. 79.

(5) L. C. Craig, C. Gehrke, H. Mighton and E. Titus, *J. Biol. Chem.*, **161**, 321 (1945).

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is gently pulled over it. That part of the membrane covering A is kept immersed in water but that over B is permitted to dry. The latter almost immediately contracts in air sufficiently to fix the membrane in place.

Even though kept wet the membrane around A contracts slightly and a small allowance must be made for this in fixing the membrane to B. Likewise, allowance for this contraction must be made in the initial choice of the tube to give the correct outside diameter of A.

C is the part of the cell to contain the solvent into which the solute dialyzes. It is of such size that a volume of solvent 10–20 times that initially used inside the sac will provide a level as high as the upper part of A. The rim of C is heated above the melting temperature and permitted to collapse sufficiently so that A and B will barely pass through. This contracted opening later rests against B and serves to center the upper part of A in the cell C. When in use the unit is supported by a clamp gripping it just below the ground joint but C rests on the table. The lower end of A can then be centered in C by a small shift of the latter on the table. A small spout is made in the rim of C to facilitate pouring.

Before the solution to be dialyzed is inserted, a small hole is punched with a needle through the membrane at a point well above the top of A and just below the bottom of B. This is to avoid pressure when the solution is forced into the sac. The membrane is washed several times with portions of the solvent both inside and out. For the inside wash, the solvent is added through the ground joint. Depression of the plunger of the syringe attached to the top forces the liquid out around the annular space inside the membrane. The solution can be moved into the inside tube again by raising the plunger and then withdrawn by a pipet or a second syringe.

A second small syringe fitted to a plastic tube is most convenient for placing and withdrawing solutions from the lower end of the inside tube. The flexible plastic tube can be of polyethylene or better yet of "Kel F." It is attached to a standard Becton–Dickinson adapter with the end drawn out to a size slightly larger than the inside diameter of the plastic tube. If the tubing is forced over the prepared tip while it is kept hot in a steam jet it will remain firmly fixed in place. The other end of the glass adapter carries the ground joint for attachment to the syringe.

After withdrawing all the wash solution from the inside, the solution to be dialyzed is inserted and gently forced out into the annular space with the syringe. The solution must be of such volume that when the upper level in the annular space inside the membrane reaches the top of A none of it will remain in the glass tube inside A but all will be essentially in intimate contact with the membrane. In the case of the 20/32 and 18/32 membranes the volume inside was 0.6 ml. In these cells the outside diameter of A was 14.8 mm.

Since the annular space between the glass and the membrane only provides for a thin film of solution it is important that the distribution be uniform. This can be ensured by gentle manipulation of the membrane with freshly washed finger tips and by drawing the solution back and forth into the glass tube inside A with the plunger of the syringe.

After satisfactory adjustment the unit is hung in the solvent in C to a height so that the levels of liquid inside the membrane and outside are equal. The time is then recorded.

After an arbitrary interval the outside solution is changed and the first solution set aside for analysis. At each change of outside solution the solution inside the membrane is drawn back into the glass tube by moving the plunger of the syringe and redistributed over the membrane.

At the end of the dialysis experiment each change of solution is analyzed as well as the solution remaining inside the sac so that the rate of escape can be calculated on the basis of total recovery of the solute. The recovery may be slightly greater or less than the material taken, but too great a divergence serves to indicate analytical errors.

At the beginning of a dialysis run when the concentration of solute is highest inside the sac, water will tend to flow into the sac due to osmotic pressure. This dilution will become progressively less as the solute moves out. The effect of the dilution is included in the escape rates indicated by the plot of the decrease of solute against time. No attempt to correct for this effect has been made. The increase in volume inside the sac is usually not more than 20 to 50% but with certain proteins may be much greater. When the latter is the case the escape rate is seldom linear and may indicate strong association.

The cellophane tubing used thus far has steadily given off a small amount of solute absorbing in the range of 280 mμ in spite of the preliminary washing treatment. This absorption has amounted to about 0.010 to 0.015 density unit in the 1-cm. cell at the beginning. That it was not due to an analytical error was confirmed in a 10-cm. cell but has not been of sufficient amount to give a weighable residue in the weight analysis procedure when 1.0 ml. was evaporated.

The bacitracin used in this study was the A fraction obtained by countercurrent distribution. The salmine came from the Nordisk insulin laboratories in Denmark and the "protamine" from GBI. Cytochrome C from horse heart was obtained from Sigma. Subtilin was obtained from the Western Regional laboratories. Ribonuclease and lysozyme were obtained from Armour. The pituitary lactogenic hormone was a sample considered pure by C. C. D. and obtained from Dr. R. D. Cole. We take this opportunity to thank him and Dr. C. H. Li for it. The insulin was a fraction obtained by C. C. D. of a sample of Boots beef insulin. The other proteins were obtained from Worthington.

Results and Discussion

If a single pure solute behaves ideally in that it does not associate to form larger molecules, or be adsorbed appreciably by the membrane, it should be possible to set up experimental conditions for dialysis so that the net rate of passage of solute per unit area of membrane would be proportional only to the concentration gradient across the membrane.[4] That this has been achieved can be shown best experimentally by frequent replacement of dialyzate with fresh solvent. A plot of the logarithm of the per cent. of the original solute remaining in the sac against time then should give a straight line.

Actual experiments with a number of pure solutes in distilled water or dilute acid in the dialysis cell described above have given experimental results which adhered to a straight line to a remarkable degree over a wide concentration range. The solutes studied have included glucose, sucrose, leucine, tryptophan, aspartic acid, bacitracin, subtilin and others. Curves of escape rates for aspartic acid and for bacitracin already have been published.[6] A representative experiment is that made with a good preparation of the polypeptide subtilin and shown in Fig. 2. The result for bacitracin with the same membrane is also shown. As mentioned in the introduction this represents "ideal" behavior as far as fractionation is concerned. However, not all preparations studied were found to give straight lines and it was soon concluded that deviation from a straight line could arise from causes other than impurity as discussed later.

The membranes most used in the studies reported in this paper were Visking 20/32 dialysis tubing selected for dialysis work and 18/32 Visking seamless cellulose tubing. In a cell of the type described the former was found to pass solutes dissolved in 0.01 *N* acetic acid even up to the size of ovalbumin, mol. wt. 45,000, at an appreciable rate. Table I gives the 50% escape time[2] for a number of readily available proteins differing in molecular weight from 5743 to 45,000, plus a few smaller solutes for comparison. The 20/32 membrane is not the most suited for the smaller solutes as ex-

(6) L. C. Craig and T. P. King, THIS JOURNAL, 78, 4171 (1956).

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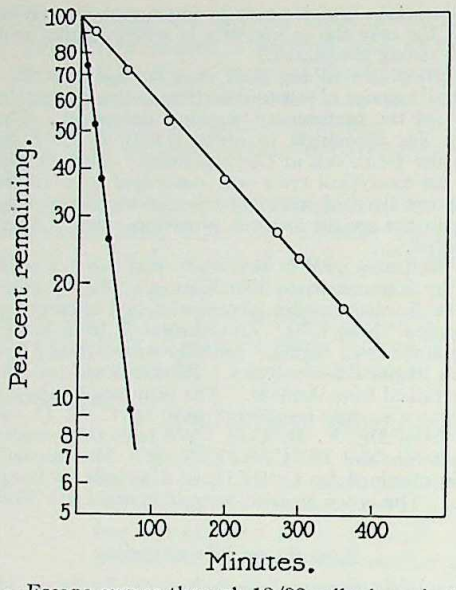

Fig. 2.—Escape curves through 18/32 cellophane in 0.01 *N* acetic acid: ●, bacitracin; ○, subtilin.

plained below. The cells used in gathering these data provided approximately 45 sq. cm. of dialyzing surface with a volume of solution inside the membrane of 0.6 ml. at the start of the dialysis. Each dialysis experiment required from 5 to 20 mg. of solute. A temperature of 25° was used throughout.

TABLE I

COMPARATIVE ESCAPE RATES OF A SERIES OF POLYPEPTIDES AND PROTEINS

Solute	Mol. wt.	50% escape time, min. 0.1 *N* HAc 20/32	0.01 *N* HAc 20/32	0.01 *N* HAc 18/32
Tryptophan	204	.....	4	6
Bacitracin	1,422	.....	15	21
Salmine	2000–8000	.....	40	150
Subtilin	3,300	.....	54	138
Insulin	5,733	1.5 hr.	..	Will not pass
Cytochrome C	12,000	.....	60	
Ribonuclease	13,600	3.5 hr.	2 hr.	
Lysozyme	14,000	3.5 hr.	2.3 hr.	
Trypsin	20,000	.....	4 hr.	
Trypsinogen	20,000	.....	6.5 hr.	
Chymotrypsin	24,500	.....	5 hr.	
Chymotrypsinogen	25,000	12 hr.	9 hr.	
Pit. lact. hormone	26,000	.....	13 hr.	
Gliadin	27,000	.....	29 hr.	
Ovomucoid	28,000	.....	35 hr.	
Pepsin	35,500	.....	80 hr.	
Ovalbumin	45,000	.....	More slowly than pepsin	

About half the solutes listed in Table I showed more or less of a tendency to deviate from straight line behavior—an indication of impurity, association or unexplained membrane effect of some kind. In these cases analysis of the escape rate by several different analytical methods as discussed below did not clearly reveal size inhomogeneity for the ones listed. However, the results from a number of preparations studied were thrown out on this basis and not listed.

In spite of the deviation it is worth comparing the 50% escape times with the latest accepted molecular weight values somewhat arbitrarily selected from the more recent literature. The values for most of the molecular weights of the proteins appear to be subject to a certain amount of revision (except for insulin and ribonuclease) and should not be considered as too exact. Certainly the 50% escape times should not be interpreted too strictly at this time. In spite of such uncertainties the correlation between molecular weight and escape rate is very striking. Only cytochrome C (granting its molecular weight range to be correct) would appear to be appreciably out of line. It is a strongly basic protein with a high isoelectric point (10.65) and contains many lysine residues. Earlier work[2] had indicated that strongly basic peptides with a high proportion of basic amino acids such as the polymyxins would show a higher escape rate in acetic acid solution than would otherwise be expected from their molecular size. The result given here could indicate that cytochrome C is a more tightly coiled molecule than has been suspected and thus of smaller molecular size than its molecular weight would indicate.

The proteins in Table I include ones with widely differing isoelectric points ranging from pepsin to lysozyme and cytochrome C. Yet they fall in the proper order according to size which indicates that charge does not play a very significant role in determining escape rate under the conditions chosen. It seems justifiable to conclude that molecular size is by far the most important factor in determining escape rate in a given cell, solution and membrane.

Tryptophan is one sixth the size of bacitracin but its 50% escape time approximates one fourth that of the latter. Ribonuclease is a little larger than one half the size of chymotrypsinogen yet its 50% escape time is also of the order of one fourth that of chymotrypsinogen.[7] The selectivity of the membrane obviously increases as the molecular size approaches the limit passed by the membrane. This is confirmed by comparison of the escape rates of bacitracin and subtilin in the 20/32 and 18/32 membranes.

It would now appear on the basis of these data, those in the previous paper, and other data still being accumulated in this Laboratory, that the relative molecular size of solutes up to molecular weights of 45,000 probably can be approximated by very simple, controlled dialysis experiments with considerable reliability. The reliability of the size derived for an unknown would of course depend on the assumption that the substance is reasonably globular in shape as are all proteins thus far studied. The deviation from spherical shape of the proteins listed in Table I as indicated by their published frictional ratios[8] is not sufficient to upset the relationship of molecular weight to 50% escape time.

Although considerable caution should be taken in interpreting the meaning of an escape rate until wider experience has been gained, there would appear to be no difficulty as far as the duplication of an experiment is concerned. The escape rates given in Table I for several of the proteins were checked by different workers at different times on more than one preparation and with membranes

(7) The value reported in (6) for chymotrypsinogen is a misprint.

(8) J. T. Edsall in "The Proteins," Neurath and Bailey, Vol. IB, Academic Press, Inc., New York, N. Y., 1953, p. 634.

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prepared from rolls of cellophane purchased at different times. Apparently, within a given size the membrane is a remarkably uniform product as far as this type of test is concerned. The 50% escape times for check runs at different times have agreed to well within 10%.

It is of interest that trypsin gives a considerably smaller 50% escape time than trypsinogen. Although not shown to be significantly smaller by direct molecular weight determination heretofore, it is known that the activation of trypsinogen to trypsin involves a type of proteolytic splitting,[9] with loss of at least a hexapeptide.

Similarly chymotrypsin gives a significantly shorter 50% escape time than chymotrypsinogen. Again the former is formed from the latter by proteolysis[9,10] with loss of a peptide moiety.

In both pairs the enzyme is formed from the zymogen by loss of probably something less than 10% of its original weight. The difference in escape rate noted must therefore arise from a significant change in shape. That the transition from zymogen to active enzyme does involve a change in shape has been indicated strongly by the studies of Neurath, Rupley and Dreyer.[11] They found that the changes in optical rotation and viscosity produced by reversible urea denaturation were such as to indicate the active enzyme to be more tightly coiled or folded than the zymogen but capable of being unfolded to the same degree by urea.

Further information on the changes involved in the activation of trypsinogen and chymotrypsinogen is given by Neurath and Dreyer[12] who consider the molecular weights to be 23,800 and 23,000, respectively.

The foregoing and Table I have been presented to enable some rough over-all correlations to be drawn. Obviously, it is of equal importance to consider the finer details of the individual behavior of each substance or preparation.

For instance, a commercial protamine sample did not give a straight line. Its escape curve was characterized by two distinct breaks in the curve as shown in Fig. 3, curve 1. Since it has already been shown[6] by a curve of the escape rate of an artificial mixture of aspartic acid and bacitracin that a rather sharply breaking curve will be given by a mixture of two solutes provided their individual escape rates are sufficiently different, it is only natural to deduce from curve 1 that this sample of protamine is a mixture with at least three or more different molecular sizes present.

Further experience with the method, however, showed that such a conclusion could not be drawn unless the diffusion behavior of each pure solute with the same membrane under identical conditions was known already. Indeed, a few pure solutes have been found not to give a straight line with the 20/32 membrane. Thus tyrosine repeatedly gave a curve indicating two components. Histidine and threonine similarly did not give a straight line. Obviously a greater tendency to deviate from ideality is to be expected with these solutes, perhaps, due to some form of association between like molecules or with the membrane surface. These are the amino acids with substituents which would most likely permit some form of hydrogen bonding.

If a reversible association complex of dimers, trimers, etc., were formed, dilution would favor the monomeric form and it would be expected that the rate of escape would increase with dilution. This should lead to a deviation from a straight line as shown in the hypothetical case of the curve of Fig. 4. However, a striking deviation of this type has thus far not been observed and it seems most likely that the type noted in actual practice with the small solutes could be caused by a membrane effect of some sort. That it was not a concentration effect was established by beginning the dialysis with different amounts of solute. There is the unlikely possibility that those solutes with strong associating tendencies form dimers which pass through the membrane more rapidly than their monomers due to a different degree of adsorption on the membrane surface.

A further suggestion that the deviation stems from a particular membrane was obtained from the finding that the amino acids mentioned above gave a straight line when Visking 18/32 seamless cellulose tubing was substituted for the 20/32 membrane. The former gives a slower rate of escape and in fact will not permit any of the proteins thus far studied including insulin to pass in appreciable amount. It could be that the time interval was too short in this experimental set up for the small solutes to behave ideally in the 20/32 membrane.

Irrespective of the basic cause of such deviations it is not difficult to differentiate a divergence due to this phenomenon from that due to the presence of a mixture of molecular sizes. Thus the solute which has passed through until the time of the first break can be recovered and run again. If the original comprised a mixture of sizes, the escape rate of the re-run would then more nearly approximate a straight line, or at least show a faster escape rate than the original. Such a re-run of the first 20% of the sample of protamine gave curve 3 in Fig. 3.

In evaluating whether or not a mixture of sizes is present in a preparation it is helpful to analyze the different portions of the dialyzate with several analytical techniques. These could include weight analysis,[13] optical density, ninhydrin,[14] Folin–Ciocalteau,[15] acid or alkali titration, biological assay, etc.

If a single molecular size is present in the sample, the same curve will be obtained regardless of the analytical method used for determination of the escape curve. When it is possible to use direct weight analysis[13] this is the most reliable from the

(9) J. S. Fruton and M. J. Mycek, *Ann. Rev. Biochem.*, **25**, 63 (1956).

(10) B. Meedom, *Acta Chem. Scand.*, **10**, 881 (1956).

(11) H. Neurath, J. A. Rupley and Wm. J. Dreyer, *Arch. Biochem. Biophys.*, **65**, 243 (1956).

(12) H. Neurath and Wm. J. Dreyer, *Dis. Faraday Soc.*, **20**, 32 (1955).

(13) L. Craig and D. Craig, in Weissberger, "Technique of Organic Chemistry," Vol. III, Part I, 2nd Ed., Interscience Publishers, New York, N. Y., 1956, p. 321.

(14) S. Moore and W. H. Stein, *J. Biol. Chem.*, **211**, 907 (1954).

(15) O. H. Lowry, N. J. Rosebrough, L. A. Farr and R. J. Randall, *ibid.*, **193**, 265 (1951).

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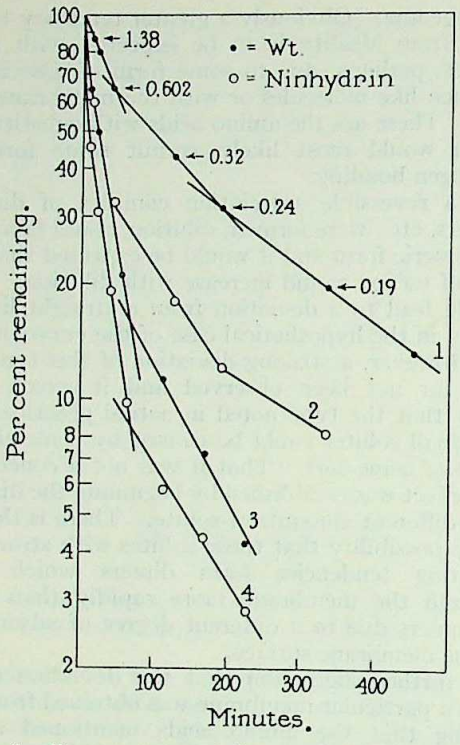

Fig. 3.—Escape curves of "protamine" through 18/32 cellophane in 0.01 *N* acetic acid: 1, weight curve of original; 2, ninhydrin curve of original; 3, weight curve of re-run; 4, ninhydrin curve of re-run.

standpoint of interpretation since it gives the per cent. escape rate based on total solute. The contrast of this with that based on one of the other selective methods then may be very enlightening as can be seen from curves 2 and 4 of Fig. 3 which are based on ninhydrin. As would be expected, the weight curve and ninhydrin curve more nearly agree on the re-run. Since the total solids in each dialyzate fraction is known, the change of ninhydrin color yield per mg. along the curve can be determined. The numbers given above curve 1 of Fig. 3 refer to leucine microequivalents of ninhydrin per mg. for the corresponding dialyzate. It is evident from these data that there is a steady partial resolution of molecular size since the smaller molecular sizes would be expected to give higher ninhydrin values per mg. of solute. It is also evident that further fractionation will be required.

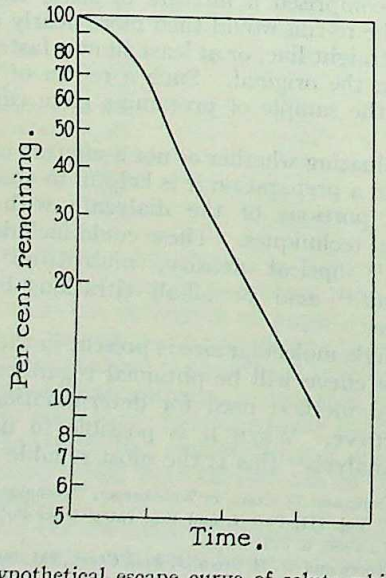

Fig. 4.—Hypothetical escape curve of solute which shows association–dissociation.

Figure 5 gives the comparative weight curves for the protamine mixture in the 20/32 and 18/32 membrane. The latter gives a much more distinct break in the curve indicating greater selectivity. It also shows a second break not revealed by the first. This again confirms the deduction from Table I that the selectivity becomes greater as the solutes approach the limit of size which will pass through the membrane.

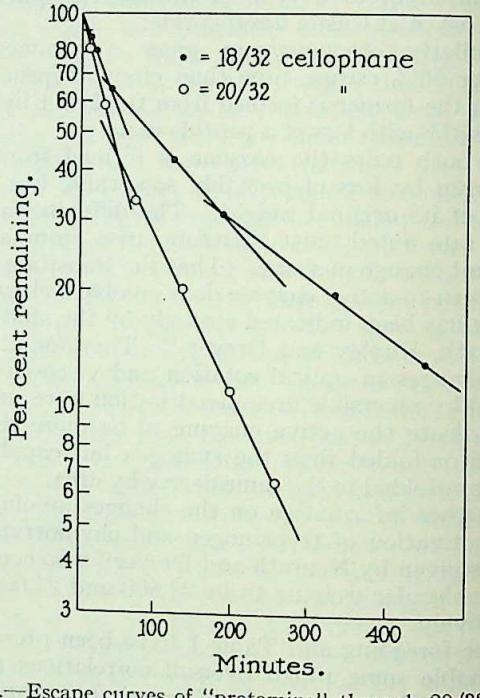

Fig. 5.—Escape curves of "protamine" through 20/32 and 18/32 cellophane in 0.01 *N* acetic acid.

The results in the case of insulin are interesting since more is known about the properties and structure of it than for any other protein. It is an unusually stable protein. These considerations make it a good model for basic studies.

A sample of beef insulin purified by extensive fractionation by countercurrent distribution[16] gave the lower curve in Fig. 6. The experiment was made with 12 mg. of insulin in 0.1 *N* acetic acid. Straight line adherence was observed until 85% of the solute had passed through the membrane. It should be pointed out that a result of this type is on a logarithm scale which has the effect of magnifying the relative importance of the last part of the solute to escape. Actually almost 99% of the insulin had passed through the membrane by 21 hours time.

This result contrasted sharply to that shown in the upper curve of Fig. 6, which was obtained with

(16) E. J. Harfenist and L. C. Craig, THIS JOURNAL, **74**, 3083 (1952).

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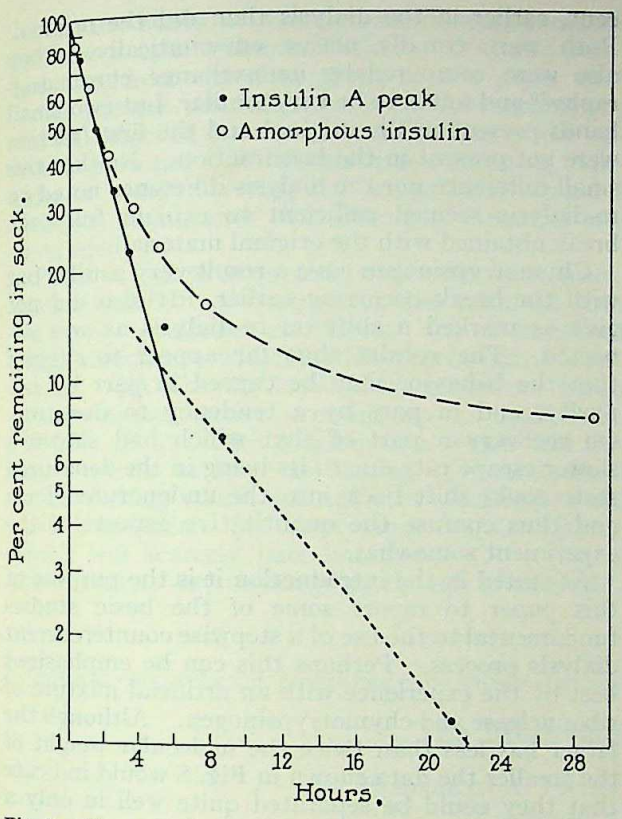

Fig. 6.—Escape curves of insulin through 20/32 cellophane in 0.1 *N* acetic acid.

an amorphous commercial sample. The latter was known by countercurrent distribution to be of the order of 70% pure.

Insulin is known to associate in the neutral *p*H range to a size with six or more sub-molecules in a particle. It also can form fibrils at acid *p*H ranges.[17] This tendency suggests that the deviation noted even in the lower curve could be due to associated molecules which do not return rapidly to the monomeric form.

Irrespective of the truth of this speculation it was found experimentally that a sample of insulin brought into solution in water with a minimum of dilute ammonia would not pass through the 20/32 membrane in appreciable amount after several hours in the standard cell when distilled water was used outside the membrane. During this time the original *p*H of the insulin solution had dropped from about 8 to 6. Ribonuclease (mol. wt. 13,600) readily passed under these same conditions.

In the first paper[2] of this series it was noted that the solvent had considerable influence on the rate of passage of smaller molecules through cellophane. Distilled water nearly always permitted the fastest rate. This appears to be even more true for the larger protein type molecules. All salt solutions thus far studied irrespective of the salt used have had a definite retarding effect as compared to distilled water when they were present in ionic strength greater than 0.01. The effect increased with increasing salt concentration to a certain salt concentration above which there was little effect.

(17) D. F. Waugh, in "Internal Secretions of the Pancreas," Ciba Foundation Symposia, Vol. IX, Little, Brown & Co., Boston, Mass., 1956, p. 122.

The *p*H also was found to have an effect but somewhat complicated by interrelationship with the salt effect. The data in Table I show that with several proteins studied 0.01 *N* acetic acid permitted a faster escape rate than 0.1 *N* acetic acid. The former permitted a rate not significantly different from distilled water.

With the larger molecules part of the experimental work has involved a search for conditions which would permit the most rapid dialysis without loss of selectivity. The use of distilled water or 0.01 *N* acetic acid as a solvent and with the 20/32 membrane has been uniformly the best thus far found. Fortunately, these conditions also have been those providing the nearest adherence to straight line escape rates. A straight line adherence until approximately 84% of the ribonuclease had escaped was noted, Fig. 7, if no salt was present in the solvent. Even somewhat better adherence was found when the solvent was distilled water alone. Here, although the main part of the curve coincided with that noted with 0.01 *N* acetic acid, a break in the curve was not observed until 93% of the solute had passed the membrane as shown by the dashed curve.

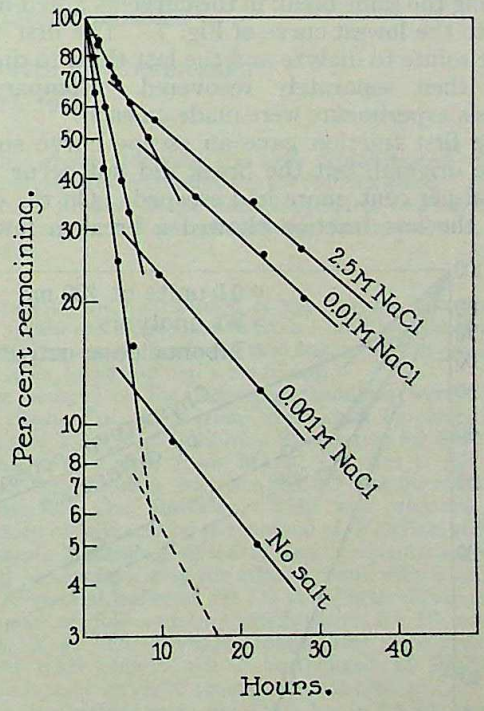

Fig. 7.—Escape curves of ribonuclease through 20/32 cellophane in 0.01 *N* acetic acid at various salt concentrations and in distilled water- - -.

The effect of various concentrations of sodium chloride in the 0.01 *N* acetic acid can be seen from Fig. 7. The salt effect is more pronounced up to 0.01 molar after which there is less increase in effect.

When the effect of *p*H was studied a marked influence other than that due to the salt effect of the buffer was not noted until a rather high *p*H was reached. The escape rate for 0.01 *N* ammonia was much less than for 0.01 *N* acetic acid.

The effect of urea also was studied. With insulin in 0.01 *N* acetic acid and six molar with re-

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spect to urea, the 50% escape time was increased from 1.5 to 5 hr. Straight line adherence was noted until about 70% of the solute had escaped but the remainder appeared to dialyze very slowly.

Similarly ribonuclease dialyzed very slowly through the 20/32 membrane in 6 molar urea, 0.01 *N* acetic acid. Here straight line behavior was not found, perhaps an indication of progressive denaturation or transformation of some sort.

Since conditions favoring denaturation appeared always to result in a much slower escape rate, it seemed likely that the deviations from straight line behavior even in 0.01 *N* acetic acid might be due to a tendency toward denaturation. However, before this could be considered the question of size inhomogeneity in the samples used should be considered.

With ribonuclease this question was studied in the following way. A standard run was made, but the escape rate was determined by weight determination, ninhydrin, optical density and quantitative enzymatic activity.[18] With the latter a reproducibility of the values of ±10% was found in several experiments. All of these gave a curve superimposable within the experimental error, but showing the same break in the curve as noted in the next to the lowest curve of Fig. 7. The first third of the solute to dialyze and the last third to dialyze were then separately recovered. Comparative dialysis experiments were made on each.

The first fraction gave an escape curve similar to the original, but the break did not occur until several per cent. more had escaped. On the other hand the last fraction showed a break a few per cent. earlier in the dialysis than did the original. Both were equally active enzymatically. They also were compared by ion-exchange chromatography[19] and found to be very similar, but two small bands present in the original and the first fraction were not present in the last fraction. Neither this small difference nor the dialysis difference noted on re-dialysis seemed sufficient to explain fully the break obtained with the original material.

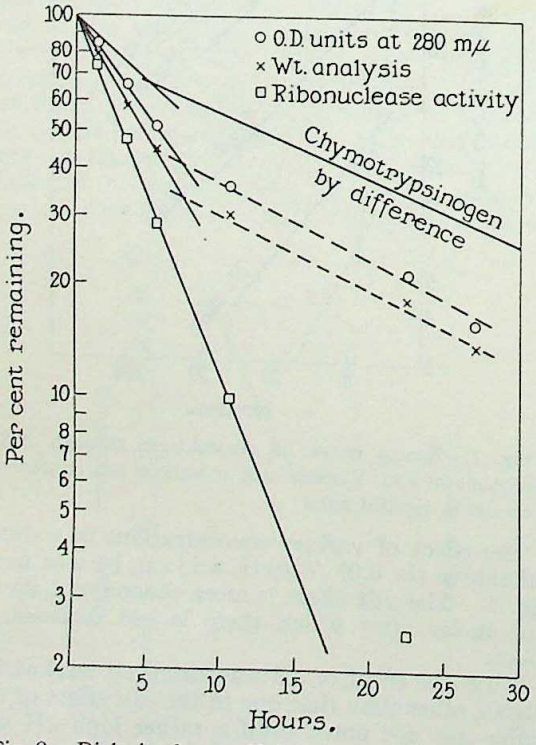

Fig. 8.—Dialysis of an artificial mixture of equal parts of ribonuclease and chymotrypsinogen through 20/32 cellophane in 0.01 *N* acetic acid.

Chymotrypsinogen gave a result very similar but with the break occurring earlier. It also did not give as marked a shift on re-dialysis as was expected. The results thus far appear to suggest that the behavior may be caused in part by impurity, and in part by a tendency to denature. On recovery a part of that which had shown a slower escape rate due to its being in the denatured state could shift back into the undenatured form and thus confuse the quantitative aspects of the experiment somewhat.

As stated in the introduction it is the purpose of this paper to report some of the basic studies fundamental to the use of a stepwise countercurrent dialysis process. Perhaps this can be emphasized best by the experience with an artificial mixture of ribonuclease and chymotrypsinogen. Although the larger has less than twice the molecular weight of the smaller the data shown in Fig. 8 would indicate that they could be separated quite well in only a few dialysis stages.[2] It so happens that these proteins are separated easily by other methods and Fig. 8 is of value only for an example.

Our studies thus far have shown that selectivity can be improved by choice of a membrane which will pass the solutes of interest only slowly under favorable conditions. For certain mixtures the selectivity can be improved by doubling the membrane.[6] It can be varied by choice of the solvent[2] and by substitution of the solutes, for instance, as by preparation of DNP derivatives of amino acids or peptides.[2]

A given roll of cellophane can be made considerably more porous by placing it under hydrostatic pressure. Thus 20/32 Visking will withstand a hydrostatic pressure of 200 mm. of Hg, but will stretch from a diameter of 15 to 24 mm. After release of the pressure the diameter will return to 21 mm. A cell made from this membrane will now pass larger proteins than the unstretched membrane. A brief treatment with sodium hydroxide also makes the membrane more porous.[4]

On the other hand acetylation of the membrane appears to make it less porous. A preliminary experiment with the 20/32 membrane has given a membrane which would not pass subtilin, but would permit bacitracin to pass slowly (50% escape time = 2.8 hr.). It readily passed tryptophan (50% escape time = 11 min.). Acetylation of 18/32 Visking gave an even less porous membrane which would scarcely permit bacitracin to pass although it gave a 50% escape time of 15 minutes for tryptophan. These findings with modified membranes are again in line with the thesis that size is the primary factor governing an escape rate for a given membrane and solution.

(18) M. Kunitz, *J. Biol. Chem.*, **164**, 563 (1946).

(19) C. H. W. Hirs, S. Moore and W. H. Stein, *ibid.*, **200**, 493 (1953).

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A closer study of modified membranes must be left for a later communication. It is apparent, however, from the data given in this paper that much greater over-all selectivity for separations can be achieved by use of a membrane of the optimum pore size. When mixtures containing molecules of widely differing size are to be separated a series of membranes with different porosities will be needed.

From our data at present with cellophane membranes and 0.01 *N* acetic acid five standard sizes are easily available as follows. (1) A stretched 20/32 membrane which readily passes native ovalbumin. (2) The 20/32 Visking cellophane which readily passes native proteins up to ovalbumin. (3) The 18/32 Visking cellophane which will not pass proteins as large as insulin. (4) Acetylated 20/32 Visking which will not pass subtilin but will pass bacitracin. (5) Acetylated 18/32 Visking which will scarcely pass bacitracin. A study of the optimum way to integrate the use of these different sizes with the countercurrent approach is in progress.

The porosity of the membrane does not correlate with the thickness as can be seen from the data in Table II, which gives five sizes of cellophane studied with insulin. The thickness given is that found with a micrometer on the dry membrane before use.

TABLE II

COMPARISON OF THICKNESS, SIZE AND POROSITY OF SEVERAL SIZES OF VISKING TUBING

Size	Thickness, mm.	Result with insulin
8/32	0.064	Slowly passes
18/32	.0175	Does not pass
20/32	.020	Rapidly passes
23/32	.0275	Does not pass
27/32	.025	Passes less rapidly than with 20/32

NEW YORK, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE]

The Methylation of Deoxyuridine[1]

BY ELIZABETH A. PHEAR AND DAVID M. GREENBERG

RECEIVED JANUARY 15, 1957

The methylation of deoxyuridine, with formaldehyde as the methyl group precursor, has been demonstrated with cell-free preparations from various tissues. The most active of the extensively studied tissues was the thymus gland. Employing a Dowex-1-Cl^--treated, dialyzed rat thymus preparation, the primary product of the reaction appeared to be thymidylic acid, which was then partially converted to thymidine. Tetrahydrofolic acid, reduced phosphopyridine nucleotide, adenosine triphosphate and Mg^{++} were required as cofactors for the reaction.

Friedkin and Roberts[2] showed that deoxyuridine (UDR)[3] was incorporated into DNA-thymine and free TDR by suspensions of chick embryo and by rabbit and chick bone marrow. They concluded that the TDR was formed by a folic acid-dependent methylation. Reichard[4] also showed that deoxyuridine was incorporated into DNA-thymine. The observations of Friedkin and Wood[5] suggested that CDR also may be incorporated into DNA-thymine by the same or a similar reaction.

This paper describes studies of the methylation of UDR with $H_2C^{14}O$ in a cell-free preparation of rat thymus gland, and a survey of the distribution of this enzyme system in various other tissues.

Experimental

Materials.—Thymus glands from 1 month old Long-Evans rats were used for most of the work. In the determination of the distribution of the enzyme in various tissues, spleen and bone marrow from 1 month old rabbits, and marrow from pork, lamb and veal bones,[6] and thymus glands from steer, lamb and pig[7] were tested.

The sources of the following chemicals were: DPNH from Sigma Co., ATP from Nutritional Biochemical Co., UDR and TDR from California Foundation for Biochemical Research, folic acid from Mann, CF was a gift of the Lederle Laboratories, and the $H_2C^{14}O$ was purchased from the Bio-Rad Co., Berkeley. THF was prepared by the reduction of folic acid by the method of O'Dell, *et al.*[8]

Enzyme Methods.—Cell-free tissue preparations were obtained by homogenizing the minced tissue with 9 volumes of 0.05 *M* veronal buffer at *p*H 7.6 in a Potter–Elvehjem glass homogenizer, followed by centrifugation for 10 minutes at 20,000 × *g*. The thymus preparations were then batch-treated with Dowex-1-Cl^-,[9] centrifuged at 59,000 × *g*, and dialyzed overnight against veronal buffer.

The incubations were run for 2 hr. in 25-ml. beakers at 37° under nitrogen in a Dubnoff shaking metabolic incubator. Each vessel contained 2 ml. of enzyme (5–20 mg. protein) and substrates and cofactors at the following levels: $H_2C^{14}O$, 5 μmoles (98,400 c.p.m. per μmole); UDR, 10 μmoles; carrier TDR, 1.2 μmoles; ATP, 10 μmoles; DPNH, 2 μmoles; $MgSO_4$, 10 μmoles; THF 500 μg. The total volume was 2.7 ml. and when any of the above constituents was omitted the volume was made up with buffer; 0.05 *M* veronal buffer at *p*H 7.6 was used throughout unless otherwise indicated. Carrier thymidylic acid was added after incubation, since it inhibited the reaction, but the addition

(1) Aided by research grants from the National Cancer Institute (CY-2915 and 3175), National Institutes of Health, U. S. Public Health Service and the Cancer Research Funds of the University of California.

(2) M. Friedkin and D. Roberts, *Federation Proc.*, **14**, 215 (1955); *J. Biol. Chem.*, **220**, 653 (1956).

(3) Other abbreviations employed: TDR, free thymidine; TA, "thymidylic acid"—see Analytical Methods section; TTC, total acid-soluble compounds yielding thymine on hydrolysis; CDR, deoxycytidine; CF, citrovorum factor, leucovorin; ATP, adenosine triphosphate; DPN, DPNH, oxidized and reduced diphosphopyridine nucleotide; TPN, TPNH, oxidized and reduced triphosphopyridine nucleotide; TCA, trichloroacetic acid; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; THF, tetrahydrofolic acid.

(4) P. Reichard, *Acta Chem. Scand.*, **9**, 1275 (1955).

(5) M. Friedkin and H. Wood, IV, *J. Biol. Chem.*, **220**, 689 (1956).

(6) Kindly supplied by Swift and Co., San Francisco.

(7) These were a gift from James Allen and Sons, 3rd Street, San Francisco.

(8) B. L. O'Dell, J. M. Vandenbelt, E. S. Bloom and J. J. Pfiffner, THIS JOURNAL, **69**, 250 (1947).

(9) B. E. Wright and T. C. Stadtman, *J. Biol. Chem.*, **219**, 863 (1956).

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of carrier TDR before incubation had no effect on the reaction, and counteracted breakdown of TDR.[10] The incubations were run in pairs, with UDR added to one member of the pair only. The TDR, TA and TCC formed from the UDR were deduced from the difference in activity of these compounds isolated from the two incubations.

The reaction was stopped by adding TCA to give a final concentration of 10%. The precipitate was washed with 5% TCA, and the supernatant and washings combined.

Analytical Methods. Total Thymine-containing Compounds (TTC).[11]—These were estimated in the incubation extract after removal of the TCA with ether. The liquid was dried and hydrolyzed for 15 min. with 0.2 ml. of 12% perchloric acid, and the latter removed with KCl. To eliminate amino acids and salts, the preparation was adjusted to *p*H 2.3 and eluted from a Dowex-50-H^+ column with water at *p*H 3. The eluate was neutralized with NH_4OH, dried and chromatographed on Whatman No. 1 paper with butanol–water (86:14) as solvent. After 18 hr. of diffusion, the thymine spots were located by ultraviolet light. These, together with paper blanks, were cut out, weighed and eluted with warm water at *p*H 3. The concentration and purity of the samples was estimated photometrically, by use of their absorption densities at 250, 260 and 280 mμ in acid solution.

Thymidine (TDR) was measured in the presence of 1.2 μmoles of carrier. Samples of the dried, TCA-free acid-soluble residues after incubation were streaked onto Whatman No. 1 paper and chromatographed for 18 hr. in butanol–water (86:14). The thymidine spots were eluted, dried and rechromatographed for 5 hr. in 0.1 *M* borate buffer at *p*H 9.3. The spots (located with ultraviolet light) together with paper blanks were cut out, weighed, and the concentration of thymidine estimated from its absorption density at 260 mμ.

"Thymidylic Acid" (TA).—The majority of counts were present in a substance which behaved similarly to, and moved together with thymidylic acid on chromatography in isopropyl alcohol–HCl (isopropyl alcohol 17 ml., concentrated HCl 41 ml., water 39 ml.), isobutyric acid–NH_3 (10 vol. isobutyric acid, 6 vol. 0.5 *N* NH_4OH), 0.1 *M* borate at *p*H 9.3, and butanol–water. However it was not possible to isolate and characterize this compound as thymidylic acid. It was estimated by chromatography in butanol–water in the presence of 5.6 μmoles of carrier thymidylic acid. The immobile area in this solvent was eluted, and rechromatographed in isopropyl alcohol–HCl. The TA spot was eluted, hydrolyzed, passed through a Dowex-50-H^+ column, eluted with water at *p*H 3, chromatographed on Whatman No. 1 paper in butanol–water, and estimated spectrophotometrically as thymine. The sum of the activity of *Thymidine and "Thymidylic acid"* (Table I) was obtained after chromatography of the TCA-free residue from incubations in isopropyl alcohol–HCl in the presence of carriers. The spot which contained both these compounds was eluted, hydrolyzed and estimated, after chromatography on Dowex-50-H^+, and on paper in butanol–water, as thymine. Radioactivity was measured in duplicate, on infinitely thin samples dried on polythene planchets, to 5% accuracy with a gas flow counter. $H_2C^{14}O$ activity was estimated after its conversion to the dimedon derivative.[12] Protein was estimated with the biuret reagent.[13]

It was shown that TTC formation was proportional to the protein concentration over the range 3–20 mg. protein per incubation, so results have been expressed as μmoles of TTC, TA and TDR formed per mg. protein.

The activity of the TTC formed in the absence of added UDR in Dowex-treated samples varied from 0–8% of that formed in its presence. Results using the paired incubation method for TTC estimation agree to within 10% of those obtained using 2-C^{14}-uridine prepared by the method of Friedkin and Roberts.[2]

Table I shows that of the total activity in TTC, most was present in the TA fraction, with about 10% in the TDR. As the work was concerned primarily with the methylation of UDR, TTC only was usually measured.

Results

A test for the incorporation of UDR and $H_2C^{14}O$ into the purine and pyrimidine bases of DNA and RNA was performed following an incubation by isolating the nucleic acids according to the method of Schmidt and Thannhauser.[14] After hydrolysis free bases were isolated by the method of Cohn.[15] In confirmation of the results of Friedkin and Wood,[5] only DNA-thymine contained significant activity. TTC was more active than the DNA-thymine, so further studies were confined to this fraction.

Substrate Specificity.—UDR was found to be a better substrate than CDR or deoxycytidylic acid for TTC formation, and thus was used throughout the work. In one experiment in which 10 μmoles of these bases were compared as substrates, a thymus preparation, formed 22.2×10^{-4} μmole of TTC per mg. protein from UDR and only 2.2×10^{-4} and 3.2×10^{-4} μmole from CDR and cytidylic acid, respectively.

TABLE I

DISTRIBUTION OF RADIOACTIVITY BETWEEN TTC, TA AND TDR

Thymine activity estimated as	μmoles formed per mg. protein $\times 10^4$
TTC	19.5
TDR	1.7
TA	16.8
TA and TDR	20.1

Occurrence of the Enzyme System.—Table II shows that cell-free preparations of spleen were more active enzymatically than bone marrow preparations from various sources. The comparative activity of other tissues was investigated in the rat, and the results are shown in Table III. An immature rat (100 g. wt.) was used in this experiment, since the tissues of young animals were found to be more active than those of older animals.

TABLE II

DISTRIBUTION OF METHYLATING ENZYME SYSTEM IN VARIOUS SPLEEN AND MARROW PREPARATIONS

Differences from standard incubation medium: 0.77 μmole $H_2C^{14}O$ per incubation, and 0.15 *M* KCl–$KHCO_3$ buffer, *p*H 7.4.

Source		μmoles TTC formed per mg. protein $\times 10^5$
Spleen	Rat	34.0
	Rabbit	17.0
Bone marrow	Pork	8.2
	Lamb	7.2
	Rabbit	3.8
	Veal	0.1

The high activity found in the thymus gland led to a survey of the activities of thymus glands of various species. The results are shown in Table IV. Preparations of sheep, steer and hog thymus were made from adult animals. Probably prepara-

(10) L. A. Manson and J. O. Lampen, *Federation Proc.*, **8**, 224 (1949).

(11) Total acid-soluble compounds yielding thymine on hydrolysis with perchloric acid: which could include thymidine, thymidylic acid and other acid-soluble nucleotides.

(12) L. P. Vernon and S. Aronoff, *Arch. Biochem.*, **29**, 179 (1950).

(13) T. E. Weichselbaum, *Am. J. Clin. Path. Tech. Sect.*, **10**, 40 (1946).

(14) G. Schmidt and S. J. Thannhauser, *J. Biol. Chem.*, **161**, 83 (1945).

(15) W. E. Cohn, *ibid.*, **159**, 377 (1949).

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tions from young animals would have had greater activity.

TABLE III

DISTRIBUTION OF METHYLATING ENZYME SYSTEM IN TISSUES OF THE RAT

Tissue	μmoles TTC formed per mg. protein × 10^4
Submaxillary gland	185.0
Thymus	95.1
Liver	6.9
Spleen	2.6
Lung	2.6

TABLE IV

DISTRIBUTION OF METHYLATING ENZYME SYSTEM IN VARIOUS THYMUS PREPARATIONS

Source	μmoles TTC formed per mg. protein × 10^4
Hog	34.2
Rat	24.4
Steer	6.5
Sheep	2.8

Preparations homogenized and centrifuged in 0.25 *M* sucrose exhibited less enzymic activity than those prepared in 0.05 *M* veronal buffer at *p*H 7.4. Acetone powders, and preparations frozen either before or after dialysis were completely inactive.

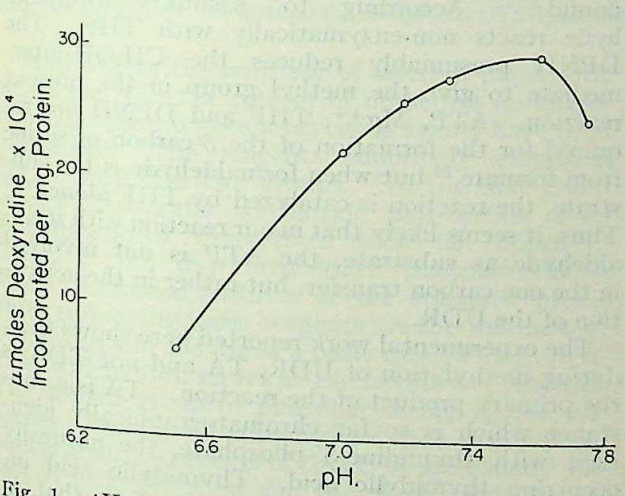

Fig. 1.—*p*H–activity curve for formation of acid-soluble thymine derivatives from deoxyuridine.

Attempts at fractionation of the enzyme system with $(NH_4)_2SO_4$ in 0.05 *M* veronal buffer at *p*H 7.4 were unsuccessful. If nucleic acids were first removed with protamine sulfate or $MnCl_2$,[16] and the $(NH_4)_2SO_4$ fractionation performed in 0.15 *M* KCl–$KHCO_3$ at *p*H 7.4, most of the enzyme activity was precipitated between 33 and 50% saturation. However, both the protamine sulfate and the $MnCl_2$ caused loss of activity. Moreover, recombination of the fraction containing most of the activity with that not precipitated at 60% $(NH_4)_2SO_4$ saturation, which alone had no activity, led to enhanced activity.

Dowex-1-Cl^- treatment and overnight dialysis caused no loss of activity, decreased the radioactivity of the TTC in the control vessel and facilitated the study of cofactor requirements. This is the only purification so far achieved with the enzyme system.

Cell-free preparations of rabbit bone marrow were more active in 0.05 *M* veronal than in 0.15 or 0.05 *M* tris-(hydroxymethyl)-aminomethane, glycylglycine or KCl–$KHCO_3$ buffers at *p*H 7.4. No enzyme activity was obtained in phosphate buffer. In veronal buffer the *p*H optimum was 7.4–7.7 (Fig. 1).

Conversion of Thymidylic Acid to Thymidine.—1.2 μmoles of TDR was added to a series of incubations of rat thymus preparation, containing 20 mg. protein per incubation. In these, the initial thymidylic acid carrier content varied from 0–5.6 μmole. The remainder, to give a total of 5.6 μmoles in each vessel, was added at the end of the experiment. Recovery of carrier thymidylic acid decreased serially from 2.9 μmoles in the incubation to which thymidylic acid had all been added after incubation, to 2.3 μmoles in the sample to which it had all been added initially. The TDR recovery varied inversely from 0.7–1.5 μmoles. This experiment shows qualitatively, since recoveries were low, that the TDR increases, and the thymidylic acid decreases in concentration during incubation. Some of the thymidylic acid may have been converted into acid-insoluble compounds, but some must have given rise to TDR. From the results obtained from studies of the relative activities of TA and TDR (*cf.* Table I and V), it seems that about 10% of the TA is converted to TDR during incubation under the present conditions in rat thymus preparations.

Cofactor Requirements.—The results obtained in a study of TA and TDR formation by a Dowex-1-treated, dialyzed rat thymus preparation are shown in Table V. Essentially similar results were obtained for TTC formation by rat thymus, rat spleen and rabbit bone marrow preparations. Table V shows that ATP, DPNH, THF and Mg^{++} are required for the formation of the methyl group of thymine compounds from UDR and formaldehyde.

THF was more effective than CF as the cofactor in this reaction, and other experiments (not given in the table) showed that folic acid at levels of 500 or 250 μg. was without effect.

In this table the need for DPNH in the presence of 500 μg. of THF was not clearly demonstrated. Paper chromatography of samples to which DPNH had not been added revealed the presence of DPN, which had presumably remained attached to the protein in the preparation. THF reduces DPN,[17] and the residual DPN is probably present in its oxidized form at the end of the manipulations prior to incubation. If the amount of THF is reduced to 166 μg., Table V shows that added DPNH definitely stimulated the reaction. Presumably at the higher level, the THF acts both as a reducing agent for the residual DPN in the preparation, and as cofactor, while at the lower level it functions mainly as a co-factor.

The requirement for DPNH also was shown in an experiment in which 6 ml. of rat thymus prepa-

(16) S. Korkes, A. del Campillo, I. C. Gunsalus and S. Ochoa, *J. Biol. Chem.*, **193**, 721 (1951).

(17) I. C. Gunsalus, *Biochim. Biophys. Acta*, **17**, 588 (1955).

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ration was passed through a 6 × 1 cm. Dowex-1-Cl^- column at *p*H 7.2 before centrifugation, dialysis and incubation. 15.0 and 21.1 × 10^{-4} μmoles of TTC were then formed in the absence and presence of added DPNH, respectively, when 500 μg. of THF (which gave a maximum yield of TTC) was added. Presumably the column had been more effective in removing DPN than the usual batch treatment. Another possible explanation for the small effect of added DPNH could be that formaldehyde itself might reduce the THF-formaldehyde complex, and in so doing yield an equimolar quantity of HCOOH. To test this possibility, HCOOH was estimated by the method of Sakami.[18] It was found that it was formed in amounts comparable to the TTC, but that its formation was not dependent on the presence of UDR, so that it must have been produced by an independent reaction. Table V does not show clearly a requirement for DPN or TPNH, and shows that TPN is inhibitory. Table VI gives results of an experiment in which only TTC was measured. ATP, Mg and THF were present in all incubation flasks. This experiment shows that DPN is less effective than DPNH as a cofactor. TPN alone or in the presence of DPN was inhibitory. Addition of TPNH increased the yield of TTC only slightly. The requirement for TPNH has not been demonstrated clearly in any experiment, but experiments such as those described above do demonstrate clearly the need for DPNH has not been met with TPNH. Possibly, therefore, this is not a TPNH linked reaction, or possibly residual DPN in the preparation masks the effect of this added cofactor. Thus from the data a requirement for TPNH has not been demonstrated, but reduction can occur by a DPNH linked reaction.

TABLE V

COFACTOR REQUIREMENTS FOR METHYLATING ENZYME SYSTEM

Cofactors were added at the following levels: ATP, 10 μmoles; $MgSO_4$, 10 μmoles; DPNH, 2 μmoles; DPNH,[a] 0.67 μmole; TPNH, TPN and DPN, 0.67 μmole; CF, 500 μg.; THF 500 μg.; THF,[b] 166 μg., 1 μmole carrier thymidylic acid added initially and 4.6 μmoles after incubation.

Cofactors added	μmoles TA formed per mg. protein × 10^4	μmoles TDR formed per mg. protein × 10^6
Mg	0.0	0.0
Mg and DPNH	.1	.3
Mg and ATP	.0	.8
Mg and THF	.1	.0
Mg, THF and DPNH	.4	.8
Mg, THF and ATP	27.0	24.2
Mg, THF, ATP and DPNH	31.7	29.9
THF, ATP and DPNH	12.8	10.7
Mg, ATP and THF[b]	11.4	8.2
Mg, ATP, THF[b] and DPNH	21.5	21.6
Mg, ATP, THF and DPNH[a]	24.0	22.6
Mg, ATP, THF and DPN	21.5	20.7
Mg, ATP, THF, and TPNH	18.4	21.8
Mg, ATP, THF and TPN	0.8	0.7
Mg, ATP, DPNH and CF	3.9	17.6

(18) W. Sakami, *J. Biol. Chem.*, **187**, 369 (1950).

Discussion

From the experimental work reported here it is concluded that the methylation of UDR with formaldehyde is dependent on the presence of THF, ATP, Mg^{++} and DPNH. These same cofactors serve in the biosynthesis of the methyl group of methionine in a system containing formaldehyde and homocysteine.[19]

TABLE VI

EFFECT OF PYRIDINE NUCLEOTIDES ON THE METHYLATING ENZYME SYSTEM

Pyridine nucleotide added 0.28 μmole	μmoles TTC formed per mg. protein 10^4
...	48.3
DPNH	75.2
TPNH	54.5
DPN	62.6
TPN	11.6
DPN and TPN	15.8

THF has been shown to be the most effective folic acid derivative in the transfer of one carbon units to form the β-carbon of serine.[20,21] It is evidently more closely related to the active cofactor than either CF[21,22] or folic acid.[19]

It has been proposed that "active formaldehyde" is N_{10}-CH_2OH·THF or a closely related compound.[22,23] According to Kisliuk[24] formaldehyde reacts non-enzymatically with THF. The DPNH presumably reduces the CH_2OH-intermediate to give the methyl group in the present reaction. ATP, Mg^{++}, THF and DPNH are required for the formation of the β-carbon of serine from formate,[22] but when formaldehyde is the substrate, the reaction is catalyzed by THF alone.[21,22] Thus, it seems likely that in our reaction with formaldehyde as substrate, the ATP is not involved in the one carbon transfer, but rather in the activation of the UDR.

The experimental work reported here shows that, during methylation of UDR, TA and not TDR is the primary product of the reaction. TA is a substance which is so far chromatographically identical with thymidine-5′-phosphate, the naturally occurring thymidylic acid. Thymidylic acid inhibits methylation of UDR, suggesting that it may be involved in the reaction, and in our system both TA (chromatographic material) and thymidylic acid are partially converted to TDR. Thus it seems probable that, since ATP is necessary for the reaction, a phosphorylated derivative and not UDR itself is the natural substrate for the reaction. In support of this, Friedkin and Kornberg[25]

(19) A. Nakao and D. M. Greenberg, THIS JOURNAL, **77**, 6715 (1955).

(20) R. L. Blakely, *Biochem. J.*, **58**, 448 (1954).

(21) N. Alexander and D. M. Greenberg, *J. Biol. Chem.*, **214**, 821 (1955); **220**, 775 (1956).

(22) R. L. Kisliuk and W. Sakami, THIS JOURNAL, **76**, 1456 (1954); *J. Biol. Chem.*, **214**, 47 (1955).

(23) G. R. Greenberg, L. Jaenicke and M. Silverman, *Biochim. Biophys. Acta*, **17**, 589 (1955).

(24) R. L. Kisliuk, *Federation Proc.*, **15**, 289 (1956).

(25) M. Friedkin and A. Kornberg, "Symposium on the Chemical Basis of Heredity," Johns Hopkins Press, Baltimore, Md., 1957, p. 609, quoted by Cohen, *et al.*[26]

(26) S. S. Cohen, M. Green and H. D. Barner, *Biochim. Biophys. Acta*, **22**, 210 (1956).

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have found that deoxyuridylic acid is converted to thymine nucleotides by bacteria. It has been suggested recently[27] and partially supported by experimental evidence[26] that the methylation of pyrimidine derivatives may involve first an aldol condensation of the CH_2OH-THF compound with the pyrimidine derivative and then formation of the 5-CH_2OH-dihydro-pyrimidine compound. This is followed by removal of water, yielding the methylene derivative, and finally there is a shift of the double bond. These steps also could possibly involve ATP.

ADDENDUM:—Friedkin and Kornberg[25] and Friedkin[28] have shown that deoxyuridine-5′-phosphate is the substrate for methylation. They postulate a direct condensation of $HOCH_2$·THF with the deoxyuridylic acid, with the splitting out of water, and subsequent cleavage to yield the methyl group. Presumably this would lead to an oxidation of THF to dihydrofolic acid. The function of the reduced phosphopyridine nucleotide might then be to reconvert the latter to THF.

(27) R. L. Hamill, R. L. Herrmann, R. U. Byerrum and J. L. Fairley, *Biochim. Biophys. Acta*, **21**, 394 (1956).

(28) M. Friedkin, *Federation Proc.*, **16**, 183 (1957).

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF THE BRITISH COLUMBIA RESEARCH COUNCIL]

Carbodiimides. VII.[1] Tetra-*p*-nitrophenyl Pyrophosphate, a New Phosphorylating Agent

BY J. G. MOFFATT AND H. G. KHORANA

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Tetra-*p*-nitrophenyl pyrophosphate, prepared *in situ* by the reaction of di-*p*-nitrophenyl hydrogen phosphate with di-*p*-tolyl carbodiimide in anhydrous dioxane, has been found to phosphorylate alcohols at room temperature without basic catalysis and, therefore, constitutes a powerful phosphorylating agent. A number of tertiary di-*p*-nitrophenyl phosphate esters were thus prepared in excellent yields. The nitrophenyl groups may be removed by hydrogenolysis in the presence of platinum or by alkaline treatment. Very mild alkaline hydrolysis results in the quantitative formation of alkyl mono-*p*-nitrophenyl hydrogen phosphates. Some other interesting properties of the neutral di-*p*-nitrophenyl phosphate esters have been recorded. A method for the large scale preparation of di-*p*-nitrophenyl hydrogen phosphate is detailed.

Methods for the synthesis of esters of phosphoric acid have been the subject of numerous investigations and several phosphorylating agents have been introduced. The reagents commonly employed fall broadly into two groups. To the first group belong phosphorus oxychloride[2] and certain of its monofunctional derivatives such as diphenyl,[3] dibenzyl[4] and di-*p*-nitrobenzyl[5] phosphorochloridates. Common features of the standard procedures employing these reagents are the mildness of conditions and the use of a basic catalyst, *e.g.*, pyridine, which often serves as the medium of reaction. The second group of phosphorylating agents embraces a number of anhydrides[6,7] such as polyphosphoric acid. Reagents of this type are usually employed in large excess and the phosphorylation reactions, which are carried out in the absence of a base, proceed under relatively drastic conditions.[8] Although lacking in elegance, reagents of the second type offer advantages of ready accessibility and simplicity in operation and have proved useful in certain cases.[9]

While the successful application of the existing methods of phosphorylation to a variety of synthetic problems has been recorded, inert hydroxyl functions are sometimes encountered whose phosphorylation in a satisfactory yield presents difficulties. One specific example is that of 2′,3′-*O*-isopropylidene guanosine, the phosphorylation of which formed a part of our studies in the nucleotide field. In connection with this problem and our broader interest in developing new and improved methods for the synthesis of phosphate esters of biological interest it was considered desirable to devise a method of phosphorylation which would utilize a mono-functional, powerful and yet mild reagent and which would not require basic catalysis. The present communication describes a method which meets the above requirements and, therefore, combines the desirable features of the two aforementioned types of procedures. The application of this method to a satisfactory synthesis of guanosine 5′-phosphate is recorded in the following communication.[10]

A convenient and efficient method for the synthesis of the symmetrical esters of pyrophosphoric acid

(1) Paper VI. C. A. Dekker and H. G. Khorana, THIS JOURNAL, **76**, 3522 (1954).

(2) See *e.g.*, E. Fischer, *Ber.*, **47**, 3193 (1914); P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **106**, 113 (1934).

(3) (a) K. Zeile and H. Meyer, *Z. physiol. Chem.*, **256**, 131 (1938); (b) P. Brigl and H. Muller, *Ber.*, **72**, 2121 (1939); (c) H. Bredereck, E. Berger and J. Ehrenberg, *ibid.*, **73**, 269 (1940).

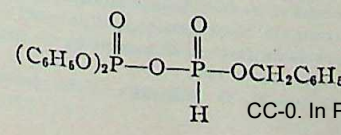
(4) F. R. Atherton, H. T. Openshaw and A. R. Todd, *J. Chem. Soc.*, 382 (1945) and subsequent papers.

(5) L. Zervas and I. Dilaris, THIS JOURNAL, **77**, 5354 (1955).

(6) Broadly speaking all phosphorylating agents are anhydride in character. The above classification serves to emphasize the different types of procedures used in phosphorylation reactions.

(7) For references to earlier literature see G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, New York, N. Y., 1950.

(8) The reagent *O*-benzyl phosphorus *O,O*-dibenzylphosphoric anhydride



developed by N. S. Corby, G. W. Kenner and A. R. Todd, *J. Chem. Soc.*, 3669 (1952), for the preparation of mixed secondary phosphites is more akin to the phosphoric acid chlorides in that it is used under mild conditions in the presence of a tertiary base.

(9) See *e.g.*, A. N. Wilson and S. A. Harris, THIS JOURNAL, **73**, 4693 (1951); J. E. Seegmiller and B. L. Horecker, *J. Biol. Chem.*, **192**, 175 (1951); R. H. Hall and H. G. Khorana, THIS JOURNAL, **77**, 1871 (1955).

(10) R. W. Chambers, J. G. Moffatt and H. G. Khorana, *ibid.*, **79**, 3747 (1957).

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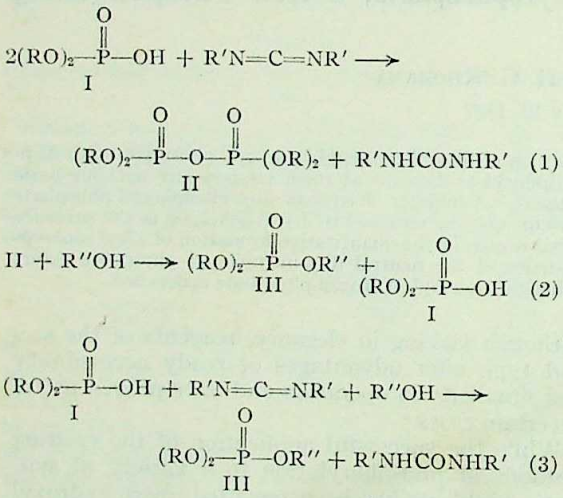
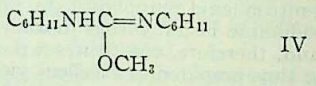
(II) is now available[11] (equation 1), and our first aim in the present work was to utilize a suitable compound of the type II for the phosphorylation of an alcohol according to equation 2. Since the liberated acid I would be expected to react again with the carbodiimide reagent to form II, the over-all reaction would be represented by equation 3. The fully protected pyrophosphate we chose to study as a phosphorylating agent was tetra-*p*-nitrophenyl pyrophosphate[11] (II, R = *p*-nitrophenyl). The choice of this ester was influenced by certain observations recorded by Todd and co-workers in their studies of the reactivity of the various fully protected pyrophosphates[12] and by a consideration of the ease of the subsequent removal of the protecting groups from the resulting esters of the type III



In the initial experiments, therefore, a mixture of di-*p*-nitrophenyl hydrogen phosphate (1 equiv.) and methyl alcohol (1.5 equiv.) was brought into reaction at room temperature in anhydrous dioxane with dicyclohexyl or di-*p*-tolyl carbodiimide (1 equiv.). In these experiments, varying amounts of the desired di-*p*-nitrophenyl methyl phosphate[13] were formed but side reaction(s) occurred. Thus when dicyclohexyl carbodiimide was used, a highly crystalline side product could be isolated, which from its elemental analysis was concluded to be the di-*p*-nitrophenyl phosphoric acid salt of N,N′-dicyclohexyl-*O*-methylisourea (IV). This conclusion was confirmed by the isolation and elemental analysis of the basic isourea (IV) itself from the salt. The latter could, subsequently, be prepared in quantitative yield by the addition of dicyclohexyl carbodiimide to an anhydrous methyl alcoholic solution of di-*p*-nitrophenyl hydrogen phosphate. A similar acid-catalyzed addition[14] of methyl alcohol to di-*p*-tolyl carbodiimide would be expected to occur, although the analogous compound was not isolated.

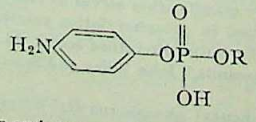
While the above experiments demonstrated the feasibility of the new approach, the side reaction observed precluded quantitative phosphorylation according to the scheme originally intended (equation 3) and it was therefore decided to add the alcohol to the preformed pyrophosphate, II (R = *p*-nitrophenyl), and to realize phosphorylation only according to equation 2 (the reaction mixture would thus contain no free carbodiimide). Because of the greater insolubility and consequent ease of removal of the resulting di-*p*-tolylurea, di-*p*-tolyl carbodiimide was preferred as the reagent.

Tetra-*p*-nitrophenyl pyrophosphate[15] was prepared *in situ* in anhydrous dioxane by the instantaneous reaction of di-*p*-tolyl carbodiimide with di-*p*-nitrophenyl hydrogen phosphate[11] and methyl alcohol was added. On working up (see Experimental) after a reaction period of some 15 hours, pure di-*p*-nitrophenyl methyl phosphate (III, R = *p*-nitrophenyl; R‴ = CH_3) was obtained in over 90% yield (based on equation 2). The generality of the



technique was established by the preparation of a number of simple alkyl di-*p*-nitrophenyl phosphate esters. By the same method, the primary hydroxyl groups in 2′,3′-*O*-isopropylidene uridine and 2′,3′-*O*-isopropylidene guanosine[10] were phosphorylated to give 90–95% yields of the corresponding di-*p*-nitrophenyl phosphate esters. (The phosphorylation of 1,2-*O*-isopropylidene D-xylofuranose by this reagent has been recorded elsewhere.[16])

An important consideration in the use of a method of phosphorylation, clearly, is the ease and selectivity with which one and/or both of the protecting groups may be removed from the initial products of phosphorylation. In this respect, obviously, the new reagent is akin to the well-established reagent diphenyl phosphorochloridate,[3] and, by analogy, the *p*-nitrophenyl groups may be removed by the platinum-catalyzed hydrogenolysis of the di-*p*-nitrophenyl phosphate esters. However, the presence of an acid (*e.g.*, hydrochloric acid) is necessary for removing both the protecting groups since otherwise hydrogenolysis does not proceed beyond the formation of the mono-*p*-aminophenyl esters of the type V. *p*-Aminophenyl methyl hydrogen phosphate (V, R = CH_3) was thus isolated as the crystalline free acid. Examples of the mono alkyl di-hydrogen phosphates prepared by the hydrogenolytic removal of the *p*-nitrophenyl groups are given in the Experimental section.



(11) H. G. Khorana and A. R. Todd, *J. Chem. Soc.*, 2257 (1953).

(12) N. S. Corby, G. W. Kenner and A. R. Todd, *ibid.*, 1234 (1952). The reactivity (phosphorylating power) of symmetrical pyrophosphates of the type II is, as expected, a function of the acid strength of the parent acid.

(13) J. A. A. Ketelaar and H. R. Gersmann, THIS JOURNAL, **72**, 5777 (1950).

(14) For base- and metal ion-catalyzed additions of alcohols to carbodiimides see H. G. Khorana, *Can. J. Chem.*, **32**, 231 (1954); E. Schmidt and F. Moosmüller, *Ann.*, **597**, 235 (1955).

(15) The isolation and storage of this substance, which is extremely susceptible to moisture, is unnecessary and is not recommended. Instead, it may be prepared, immediately prior to use, from the stable highly crystalline starting materials.

(16) J. G. Moffatt and H. G. Khorana, THIS JOURNAL, **79**, in

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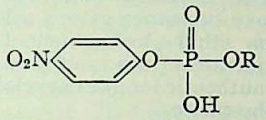
A characteristic and frequently useful feature of the neutral di-*p*-nitrophenyl phosphate esters of the type III (R = *p*-nitrophenyl) is the extreme ease with which one of the *p*-nitrophenyl groups may be removed under mildly alkaline conditions. This hydrolytic reaction, which may be followed conveniently by paper chromatography or by measuring spectrophotometrically the liberation of *p*-nitrophenol, occurs rapidly at room temperature in 0.01 to 0.1 *N* alkali and results in the quantitative formation of alkyl *p*-nitrophenyl hydrogen phosphates of the type VI. A number of diesters of this type were prepared in a crystalline state (see Experimental). Heating esters of the type VI at 100°



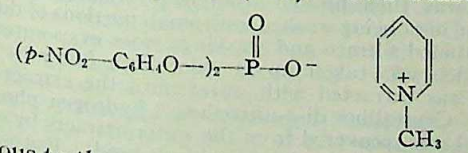
VI

in 1 *N* alkali for a few hours was necessary to remove the second *p*-nitrophenyl group. This alkaline hydrolysis[17] is useful as an alternative method for the removal of the protecting groups where platinum-catalyzed hydrogenolysis cannot be used (see for example the preparation of guanosine 5′-phosphate[10]).

Some other properties of the model substance di-*p*-nitrophenyl methyl phosphate may be briefly mentioned. As expected, in the presence of sodium benzoxide it underwent a rapid transesterification reaction to yield dibenzyl methyl phosphate. The latter substance was monodebenzylated with aqueous acetic acid[18] and the resulting benzyl methyl hydrogen phosphate was isolated as the crystalline cyclohexylammonium salt.

On heating di-*p*-nitrophenyl methyl phosphate in 50% acetic acid hydrolysis[19] occurred to give both di-*p*-nitrophenyl hydrogen phosphate and methyl *p*-nitrophenyl hydrogen phosphate; the proportions of the two products were, respectively, 77 and 23%. Hydrolysis in a mixture of 1 *N* hydrochloric acid and dioxane appeared to follow the same pattern.

An anhydrous pyridine solution of di-*p*-nitrophenyl methyl phosphate on standing for a few hours at room temperature deposited a highly crystalline material which from its elemental analysis, paper-chromatographic and paper-electrophoretic behavior was identified as N-methylpyridinium di-*p*-nitrophenyl phosphate (VII). This reaction is



VII

analogous to the quaternization reactions of neutral phosphate esters, especially, dibenzyl alkyl phosphates, which have been studied extensively by Todd and co-workers.[20] The great ease with which the reaction occurred in the present case, clearly, is a consequence of the strongly electron-withdrawing nitro groups since diphenyl *n*-propyl phosphate is apparently unaffected by refluxing in 4-methylmorpholine for three hours.[21]

Methods for the large scale preparation of di-*p*-nitrophenyl hydrogen phosphate have been examined in detail, since from the practical standpoint it was important that this starting material[22] in the described method of phosphorylation be readily available. The two step procedure involving (a) preparation of tri-*p*-nitrophenyl phosphate[23] from phosphorus oxychloride and (b) alkaline hydrolysis to the desired diester[24] (see Experimental) has given consistently an over-all yield of over 80% on a preparative scale. Initially, however, we prepared the diester by the reaction of phosphorus oxychloride with *p*-nitrophenol in pyridine according to Corby, Kenner and Todd.[12] The yields obtained in different runs varied and were rather unsatisfactory. Furthermore, in some runs the only crystalline product isolated was a low-melting (90–91°) substance. The nature of this interesting compound may be discussed in some detail. The substance, which was strongly acidic, was indistinguishable from authentic di-*p*-nitrophenyl hydrogen phosphate in its behavior on paper chromatograms developed in six solvent systems and, further, formed a crystalline cyclohexylammonium salt which was identical with that from di-*p*-nitrophenyl hydrogen phosphate (m.p., mixed m.p. and infrared spectrum). The possibility that the low-melting substance was a hydrate or an isomorphic form of di-*p*-nitrophenyl hydrogen phosphate was ruled out by the analytical data and the ultraviolet absorption spectrum. The latter, in fact, proved to be particularly informative; while it was practically identical with that of di-*p*-nitrophenyl hydrogen phosphate in the region 280–320 mμ, there was slightly increased absorption in the range 230–270 mμ. This evidence taken together with the observation that the low-melting substance was also encountered in the experiments in which aqueous pyridine was used for the hydrolysis of tri-*p*-nitrophenyl phosphate indicated that pyridine was present in the substance. Confirmatory evidence was provided by treating an aqueous solution of the 90–91° melting substance with an excess of Dowex-2-formate resin (removal of di-*p*-nitrophenyl phosphate ions) and determining the ultraviolet absorption spectrum of the clear supernatant. The "difference spectrum" was identical with that of pyridine. A quantitative determination of the pyridine content and of the neutralization equivalent, and the elemental analysis of the low-melting substance have led us to conclude that it represents a complex consisting of two molecules of di-*p*-nitrophenyl hydrogen phosphate and one molecule, each, of pyridine and water.

Finally, the preparation of the crystalline pyrophosphate VIII is recorded. This substance was prepared in order to test its use as a phosphorylat-

(17) The removal of phenyl groups from neutral phosphate esters by alkaline hydrolysis is well known. See *e.g.*, ref. 3c; and J. Baddiley and E. M. Thain, *J. Chem. Soc.*, 1610 (1953).

(18) J. Baddiley and A. R. Todd, *ibid.*, 648 (1947).

(19) For a recent detailed discussion of the hydrolysis of organic phosphates see P. W. C. Barnard, C. A. Bunton, D. R. Llewellyn, K. G. Oldham, B. L. Silver and C. A. Vernon, *Chemistry and Industry*, 760 (1955).

(20) J. Baddiley, V. M. Clark, J. J. Michalski and A. R. Todd, *J. Chem. Soc.*, 815 (1949).

(21) J. Lecocq and A. R. Todd, *ibid.*, 2381 (1954).

(22) Di-*p*-tolyl carbodiimide, the second starting material, may be readily prepared in quantity (ref. 14).

(23) M. Rapp, *Ann.*, **225**, 156 (1884).

(24) S. Yoshida, *J. Biochem. (Japan)*, **34**, 23 (1941).

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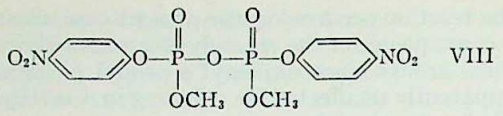

VIII

ing agent, in model experiments on the synthesis of unsymmetrical diesters of phosphoric acid. Preliminary experiments showed that basic catalysis was necessary for the phosphorylation of an alcohol by this pyrophosphate.

Experimental[25]

Paper chromatography was used extensively as an analytical tool. The two solvent systems which proved most useful were: *n*-butyl alcohol–acetic acid–water (4:1:5, v./v.)[26] (solvent A) and isopropyl alcohol–ammonia–water (7:1:2, v./v.)[27] (solvent B). In both solvent systems the R_f's of different types of esters followed the order: tertiary esters of phosphoric acid > diesters > monoesters. Some particularly relevant R_f's are mentioned in the text.

Sodium *p*-Nitrophenoxide.—Sodium hydroxide (110 ml. of 10 *N*) was added with stirring to a suspension of *p*-nitrophenol (150 g.) in boiling water (700 ml.). To the resulting clear solution was added a further volume (100 ml.) of 10 *N* alkali and the mixture rapidly cooled. The yellow sodium salt which separated was collected by filtration and washed three times with 50-ml. portions of ice-water. After drying thoroughly at 110° and pulverization the anhydrous salt was obtained as a red powder (165 g., 95%).

Tri-*p*-nitrophenyl Phosphate.—Rigorously dried, finely powdered sodium *p*-nitrophenoxide (112 g.) was added slowly to an anhydrous ethereal solution (400 ml.) of freshly distilled phosphorus oxychloride (16 ml.), with exclusion of moisture. The mixture was stirred mechanically at room temperature for 30 minutes and then refluxed for two hours. The resulting mixture of orange and white solids was collected by filtration and washed repeatedly with cold water (total volume, 1500 ml.) until the washings were colorless. The white crystalline residue of tri-*p*-nitrophenyl phosphate was dried *in vacuo* over phosphorus pentoxide. The yield was 76.6 g. (96%) and the m.p. 153–155° which was raised to 155–156° upon one recrystallization from ethyl acetate or acetone. The recrystallization was unnecessary for the next step.

Di-*p*-nitrophenyl Hydrogen Phosphate.—Tri-*p*-nitrophenyl phosphate (80 g.) was dissolved in warm dioxane (800 ml.) and the solution quickly cooled. To the solution were added 125 ml. of 4 *N* lithium hydroxide and sufficient water to give a homogeneous solution. The yellow solution was kept for 30 minutes and then neutralized by the portionwise addition of IR-120(H^+) resin. The resin was removed by filtration, washed with small portions of water and the combined filtrate evaporated to dryness under reduced pressure. The resulting sirup was dissolved in water (400 ml.) and the *p*H of the solution adjusted to 4 by the further addition of the acidic resin. The resin was removed and washed and the filtrate extracted repeatedly with ether until an extract produced no yellow color with aqueous alkali. The aqueous solution was then heated to 80° and strongly acidified by the slow addition (*ca.* 5 minutes) of concentrated hydrochloric acid.[28] The oil which initially separated solidified on cooling and scratching. The crystalline material was collected by filtration, dissolved in the minimum volume of boiling water and the solution kept at 0°. Di-*p*-nitrophenyl hydrogen phosphate (51 g.) separated as white needles and was collected by filtration. A further amount (2 g.) was recovered from the mother liquor by the addition of concentrated hydrochloric acid (2 ml.); total yield 53 g. (90%), m.p. after drying at 100° *in vacuo*, 175–175.5° (reported m.p. 176–178,°[12] 175°[29]).

Preparation of the Compound with M.P. 90–91°.—Tri-*p*-nitrophenyl phosphate (7 g.) was dissolved in dry, boiling pyridine (20 ml.) and an equal volume of water was added to the resulting colorless solution. The clear yellow solution now obtained was refluxed for 30 minutes. The solvent was then evaporated under reduced pressure and the oily residue taken up in water (100 ml.). The *p*H of the solution was adjusted to 5 with acetic acid and the resulting suspension was extracted with ether until an extract gave no yellow color with alkali. The clear aqueous solution was concentrated to 25 ml. and strongly acidified with concentrated hydrochloric acid. The light colored oil which separated, crystallized on trituration, was collected by filtration and recrystallized from ethyl acetate. The chunky crystals thus obtained (5.1 g.) had m.p. 90–91°, which remained unchanged upon further recrystallization. *Anal.* Calcd. for $C_{29}H_{23}N_5O_{16}P_2 \cdot H_2O$: C, 44.90; H, 3.24; N, 9.02; neut. equiv., 388. Found: C, 45.17; H, 3.27; N, 9.24; neut. equiv., 389.

Addition of excess cyclohexylamine to an acetonitrile solution of the above substance gave a salt which after recrystallization from ethyl alcohol melted at 188–188.5°. This material was identical (m.p., mixed m.p., and infrared spectrum) with an authentic sample of cyclohexylammonium di-*p*-nitrophenyl phosphate.

Forty grams of the substance with m.p. 90–91° was converted to the cyclohexylamine salt as described above and a hot suspension of the salt was treated with an excess of IR-120(H^+) ion-exchange resin. The strongly acidic solution was filtered from the resin and evaporated to give di-*p*-nitrophenyl hydrogen phosphate (35 g.) with m.p. 173–174° after crystallization from ethyl acetate.

Identification of Pyridine in the Compound with M.P. 90–91°.—The substance (5.81 mg.) with m.p. 90–91° and authentic di-*p*-nitrophenyl hydrogen phosphate (5.71 mg.) were each dissolved in 5-ml. portions of water and the solutions stirred with 1-ml. portions of freshly washed Dowex-2 (formate form) resin. The resin was removed and washed thoroughly with water until the optical density of the washings were zero. The two combined filtrates were diluted to 100 ml. with water and the ultraviolet absorption spectrum of the solution from the 91° melting substance was determined using the solution obtained from di-*p*-nitrophenyl phosphate as the blank. The spectrum was found to be identical with that of pyridine in 10^{-4} *M* formic acid solution. From the optical density of the above solution at 256 mμ and using a figure of 5400 as E_{max} for pyridine at this wave length, the pyridine content of the 91° melting substance could be calculated to be 10.07%. This corresponds to a monohydrate of a molecular compound of two moles of di-*p*-nitrophenyl phosphate and one mole of pyridine. This is in agreement with the elemental analysis recorded above.

Di-*p*-nitrophenyl Methyl Phosphate.—Di-*p*-nitrophenyl hydrogen phosphate (1 g., 2.94 mmoles) was dissolved in anhydrous dioxane (8 ml.) by warming with exclusion of moisture. The solution was cooled quickly to room temperature and di-*p*-tolyl carbodiimide (330 mg., 1.49 mmoles) was added. Di-*p*-tolylurea began to separate immediately and after ten minutes at room temperature anhydrous methyl alcohol (0.063 ml., 1.56 mmoles) was added. The stoppered flask was kept in a desiccator overnight and the solution was then filtered from di-*p*-tolylurea (335 mg., 94%), the urea being washed with small portions of dioxane. The combined filtrate and washings were evaporated to a sirup which was taken up in chloroform (10 ml.). The solution was extracted with water until the extracts were neutral. Crystalline di-*p*-nitrophenyl hydrogen phosphate (475 mg.) was recovered from the water extracts by acidification with concentrated hydrochloric acid. Evaporation of the chloroform solution gave a dry white residue which was crystallized from aqueous ethyl alcohol to give di-nitrophenyl methyl phosphate[13] (490 mg., 90%) as white needles, m.p. 142–143°, identical with that of a sample prepared according to Ketelaar and Gersmann.[13] (No depression in m.p. on admixture of the two samples.) *Anal.* Calcd. for $C_{13}H_{11}N_2O_8P$: C, 44.08; H, 3.13; N, 7.90. Found: C, 44.25; H, 3.07; N, 7.98.

Benzyl di-*p*-nitrophenyl phosphate was prepared in 96% yield by the phosphorylation of benzyl alcohol; m.p. 101–102° after crystallization from carbon tetrachloride. *Anal.* Calcd. for $C_{19}H_{15}N_2O_8P$: C, 53.00; H, 3.51; N, 6.51. Found: C, 53.17; H, 3.51; N, 6.36.

Cyclohexyl di-*p*-nitrophenyl phosphate was similarly pre-

(25) Melting points are uncorrected. Analyses recorded were performed by Mr. W. Manser, Zürich, Switzerland.

(26) S. M. Partridge, *Biochem. J.*, **42**, 238 (1948).

(27) R. Markham and J. D. Smith, *ibid.*, **52**, 552 (1952); D. M. Brown and A. R. Todd, *J. Chem. Soc.*, 2040 (1953).

(28) The lithium salt may coprecipitate with the free acid if hydrochloric acid is added all at once or in the cold.

(29) J. M. A. Hoeflake, *Rec. trav. chim.*, **36**, 24 (1916).

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pared in 85% yield; m.p. 81–82° after crystallization from alcohol. *Anal.* Calcd. for $C_{18}H_{19}N_2O_8P$: C, 51.19; H, 4.54; N, 6.64. Found: C, 51.17; H, 4.70; N, 6.75.

2′,3′-*O*-isopropylidene Uridine 5′-Di-*p*-nitrophenyl Phosphate.—Di-*p*-nitrophenyl hydrogen phosphate (2.85 g.) was dissolved in anhydrous dioxane (15 ml.) by warming with exclusion of moisture. The solution was cooled to room temperature, di-*p*-tolyl carbodiimide (900 mg.) added and the mixture kept for ten minutes. Dry 2′,3′-*O*-isopropylidene uridine[30] (1.0 g.) was added and the sealed reaction mixture kept overnight at room temperature. Di-*p*-tolylurea (880 mg.) was removed by filtration and washed with small portions of dioxane. The combined filtrate was evaporated to dryness, the residue taken up in chloroform (25 ml.) and the solution extracted with water until an extract was neutral. Evaporation of chloroform gave 2′,3′-*O*-isopropylidene uridine 5′-di-*p*-nitrophenyl phosphate (1.916 g.) including the residual di-*p*-tolylurea (96 mg.). The material was used directly in the subsequent steps described later. A sample was crystallized from ethyl alcohol to give white needles with m.p. 118.5–120.5°. *Anal.* Calcd. for $C_{24}H_{23}N_4O_{13}P$: C, 47.53; H, 3.82; N, 9.24. Found: C, 47.34; H, 3.84; N, 9.03.

Methyl *p*-Nitrophenyl Hydrogen Phosphate.—To an acetonitrile (50 ml.) solution of di-*p*-nitrophenyl methyl phosphate (4.5 g.) was added 1 *N* aqueous lithium hydroxide solution (38 ml.) and the resulting yellow solution was kept for 30 minutes at room temperature. It was then partly evaporated to remove acetonitrile and the remaining aqueous solution adjusted to *p*H 5 with acetic acid. *p*-Nitrophenol was extracted with ether until an extract gave no yellow color with alkali. The residual solution was concentrated to 15 ml., and freed from lithium ions by passage through a 2.5 × 15 cm. column of IR-120(H^+) resin. The effluent and washings were evaporated to dryness under reduced pressure leaving free methyl *p*-nitrophenyl hydrogen phosphate as a colorless oil which crystallized on prolonged evacuation. The substance was recrystallized from a mixture of benzene and petroluem ether to give stout white needles (2.77 g., 94%) with m.p. 121–123°. One further recrystallization raised the m.p. to 123.5–124.5°. *Anal.* Calcd. for $C_7H_8NO_6P$: C, 36.09; H, 3.46; N, 6.01. Found: C, 36.27; H, 3.46; N, 5.91. The crystalline cyclohexylamine salt was prepared by adding an excess of cyclohexylamine to an acetonitrile–ether solution of the free acid. After recrystallization from benzene it melted at 150.5–151.0°. *Anal.* Calcd. for $C_{13}H_{21}N_2O_6P$: C, 47.00; H, 6.37; N, 8.44. Found: C, 47.18; H, 6.23; N, 8.44.

Other alkyl mono-*p*-nitrophenyl hydrogen phosphates prepared by the alkaline hydrolysis of the neutral esters are mentioned below.

Benzyl *p*-nitrophenyl hydrogen phosphate was prepared as the crystalline cyclohexylammonium salt in 90% yield; m.p. 168–169° after crystallization from benzene. *Anal.* Calcd. for $C_{19}H_{25}N_2O_6P$: C, 55.88; H, 6.17; N, 6.86. Found: C, 55.64; H, 6.17; N, 6.95.

Cyclohexyl *p*-nitrophenyl hydrogen phosphate was prepared as the cyclohexylammonium salt in 85% yield; m.p. 202–203° after crystallization from acetonitrile. *Anal.* Calcd. for $C_{18}H_{29}N_2O_6P$: C, 54.00; H, 7.30; N, 7.00. Found: C, 54.03; H, 7.50; N, 7.03.

***n*-Hexyl *p*-nitrophenyl hydrogen phosphate** also was prepared as the cyclohexylammonium salt in 85% yield; m.p. 109–110° after crystallization from acetonitrile. *Anal.* Calcd. for $C_{18}H_{31}N_2O_6P$: C, 53.90; H, 7.79; N, 6.97. Found: C, 54.08; H, 7.37; N, 7.00.

Uridine 5′-*p*-Nitrophenyl Hydrogen Phosphate.—To an acetonitrile (30 ml.) suspension of 2′,3′-*O*-isopropylidene uridine 5′-di-*p*-nitrophenyl phosphate (1.22 g.) was added lithium hydroxide solution (6.5 ml.) and water (15 ml.), and the yellow mixture shaken for 30 minutes. Paper chromatography at this stage showed that removal of one of the nitrophenyl groups was complete; R_f's of 2′,3′-*O*-isopropylidene uridine 5′-*p*-nitrophenyl hydrogen phosphate were: solvent A, 0.54; solvent B, 0.62. Most of the acetonitrile then was removed by evaporation under reduced pressure and the residual solution brought to *p*H 5 with acetic acid. The slight suspension of di-*p*-tolylurea was removed and the aqueous solution extracted with ether until an extract gave no yellow color with alkali. The *p*H of the solution was then adjusted to 2.7 by the addition of glacial acetic acid and the acidic solution heated in a boiling water-bath for 90 minutes. The solution was then evaporated to dryness, last traces of acetic acid being removed by co-evaporation with dioxane. The oily residue was dissolved in water and the solution passed slowly through a Dowex 50(H^+) column (10 cm. × 2 cm.), the column being washed thoroughly with water. The total acidic effluent was concentrated to about 5 ml. and the concentrate neutralized with aqueous barium hydroxide to *p*H 4.0. A trace of insoluble material was removed by centrifugation and the supernatant concentrated to an oil which solidified on trituration with ethyl alcohol. The amorphous barium salt (746 mg., 67%) was collected by centrifugation, washed with acetone and ether and dried under a vacuum at room temperature. Paper chromatography revealed a single strong spot; R_f's: solvent A, 0.25; solvent B, 0.45. *Anal.* Calcd. for $C_{15}H_{16}N_3O_{11}PBa^1/_2 \cdot 2H_2O$: C, 32.75; H, 3.66; N, 7.64. Found: C, 33.34; H, 3.75; N, 7.19.

A kinetic study of the degradation of this substance by snake venom diesterase has been carried out by Dr. C. A. Dekker and Miss M. L. Dirksen and will be reported by these authors elsewhere.

***p*-Aminophenyl Methyl Hydrogen Phosphate.**—A solution of di-*p*-nitrophenyl methyl phosphate (1 g.) in ethyl alcohol (200 ml.) was hydrogenated at room temperature in the presence of Adams platinum catalyst (200 mg.). After four hours, when hydrogen uptake (624 ml.) ceased, the catalyst was removed, washed with ethyl alcohol, and the combined filtrate evaporated to a colorless oil which was taken up in water (10 ml.). The aqueous solution was passed through a column (10 × 1 cm.) of IR-120(H^+) resin and the column washed until the effluent was neutral. The total effluent, which slowly turned brown in air, was evaporated to dryness under reduced pressure giving a brown solid (442 mg.), which was washed three times with ether. (Addition of cyclohexylamine to the ethereal extracts gave a small amount (27 mg.) of bis-cyclohexylammonium monomethyl phosphate). The ether-insoluble residue (m.p. 205–208°) was dissolved in hot aqueous ethyl alcohol, the solution decolorized with charcoal and allowed to cool. *p*-Aminophenyl methyl hydrogen phosphate (300 mg., 53%) was obtained as white needles of m.p. 212–213°. *Anal.* Calcd. for $C_7H_{10}NO_4P$: C, 41.62; H, 5.57; N, 6.90. Found: C, 41.62; H, 5.57; N, 6.93.

Benzyl Methyl Hydrogen Phosphate.—A freshly prepared solution of sodium benzoxide (from 200 mg. of sodium and 10 ml. of benzyl alcohol) was added to a benzyl alcohol (5 ml.) solution of di-*p*-nitrophenyl methyl phosphate (1 g.). The resulting orange solution was kept overnight, then filtered from some crystalline sodium *p*-nitrophenoxide which had separated, and evaporated under a high vacuum at 50°. The oily residue was dissolved in ether and the ethereal solution extracted repeatedly with 0.01 *N* alkali until the extracts were colorless. Evaporation of the ethereal solution gave an oil[31] which was treated with 35% acetic acid (30 ml.) at 100° for one hour. The acetic acid solution was then evaporated to dryness and the residue equilibrated with water (20 ml.) at *p*H 8. The aqueous solution was freed from the insoluble oil by extraction with ether. The clear aqueous solution was passed through a column (10 cm. × 1 cm.) of IR-120(H^+) resin, the column being washed with water until the effluent became neutral. The acidic solution was evaporated, the residual colorless oil (288 mg.) taken up in ether (5 ml.) and an excess of cyclohexylamine was added. On adding light petroleum and keeping the mixture at 0° cyclohexylammonium benzyl methyl phosphate (400 mg., 50%) crystallized; m.p. 99–101°, raised after one recrystallization from ether to 100–101.5°. *Anal.* Calcd. for $C_{14}H_{24}NO_4P \cdot 1H_2O$: C, 52.85; H, 8.21; N, 4.39. Found: C, 53.10; H, 8.14; N, 4.58.

Methyl Dihydrogen Phosphate from Di-*p*-nitrophenyl Methyl Phosphate: (1) By Alkaline Hydrolysis.—Aqueous lithium hydroxide (9 ml. of 1 *N*) was added to a dioxane (10 ml.) solution of di-*p*-nitrophenyl methyl phosphate (1 g.), and the yellow solution shaken for 30 minutes. The solution was neutralized with acetic acid and evaporated to a gum which was heated in 1 *N* lithium hydroxide (15 ml.) in a polyethylene tube at 100°. Paper chromatography in the solvent system butyl alcohol–acetic acid–water (4:1:5,

(30) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, 106, 113 (1934).

(31) The oil was very much in excess of the expected dibenzyl methyl phosphate and contained a large proportion of another substance, presumably dibenzyl ether.

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v./v.) showed that methyl *p*-nitrophenyl hydrogen phosphate (R_f, 0.55) had disappeared completely after three hours, only two spots corresponding to *p*-nitrophenol (R_f, 0.93) and methyl dihydrogen phosphate (R_f, 0.11) being present. The *p*H of the alkaline solution was then adjusted to 5 with acetic acid and the solution extracted with ether until an extract gave no yellow color with alkali. The colorless aqueous solution was then passed through a column (15 cm. × 1.5 cm.) of IR-120(H^+) resin and the acidic effluent and washings were evaporated to dryness, the last traces of acetic acid being removed by repeated evaporation in presence of dioxane. The oily residue was dissolved in water (5 ml.), the solution neutralized to *p*H 8.5 with cyclohexylamine and then evaporated. The white solid residue was crystallized from ethyl alcohol giving bis-cyclohexylammonium methyl phosphate (790 mg., 90%) as colorless needles, which on heating decomposed at 195–198°. The sample was dried *in vacuo* at room temperature.[32] *Anal.* Calcd. for $C_{13}H_{31}N_2O_4P \cdot 1H_2O$: C, 47.54; H, 10.13; N, 8.53. Found: C, 47.53; H, 10.13; N, 8.64.

(2) **By Catalytic Hydrogenation.**—Di-*p*-nitrophenyl methyl phosphate (500 mg.) was hydrogenated in ethyl alcohol (200 ml.) containing one ml. of concentrated hydrochloric acid in the presence of Adams platinum catalyst (100 mg.). After four hours, when hydrogen uptake ceased, the catalyst was removed by filtration and the alcoholic solution evaporated. The white solid was dissolved in water (5 ml.) and the solution passed through a column (10 cm. × 1 cm.) of IR-120(H^+) resin. The effluent was evaporated to dryness and converted to the bis-cyclohexylammonium salt as described above. The product (345 mg., 78%) was identical with that obtained above by alkaline hydrolyses.

Benzyl dihydrogen phosphate[33] was prepared in 94% yield from benzyl di-*p*-nitrophenyl phosphate by alkaline hydrolysis as described above; m.p. 94–96° after crystallization from ether–petroleum ether (reported[33] m.p., sharp but varying between 85 and 113°, depending upon rate of heating). *Anal.* Calcd. for $C_7H_9O_4P$: C, 44.70; H, 4.82. Found: C, 44.84; H, 4.87. The bis-cyclohexylammonium salt prepared by the addition of excess of cyclohexylamine to an ethereal solution of the acid had m.p. 232–234° (Chase, *et al.*,[33] quote 233–235°). *Anal.* Calcd. for $C_{19}H_{35}N_2O_4P$: C, 59.02; H, 9.12; N, 7.25. Found: C, 58.91; H, 8.91; N, 6.96.

***n*-Hexyl dihydrogen phosphate** was prepared in 91% yield from the corresponding di-*p*-nitrophenyl ester by hydrogenolysis in the presence of acid and was characterized as the bis-cyclohexylammonium salt. M.p. of the salt was 195–196° after crystallization from ethyl alcohol. *Anal.* Calcd. for $C_{18}H_{41}N_2O_4P$: C, 56.81; H, 10.86; N, 7.36. Found: C, 56.77; H, 11.01; N, 6.95.

Bis-cyclohexylammonium cyclohexyl phosphate also was prepared in 85% yield by hydrogenolysis of the corresponding ester; m.p. 218–219° after crystallization from a mixture of benzene and ethyl alcohol. *Anal.* Calcd. for $C_{18}H_{39}N_2O_4P$: C, 57.15; H, 10.38; N, 7.40. Found: C, 57.31; H, 10.38; N, 7.46.

N-Methylpyridinium Di-*p*-nitrophenyl Phosphate.—An anhydrous pyridine (5 ml.) solution of di-*p*-nitrophenyl methyl phosphate (1 g.) was kept at room temperature with exclusion of moisture. The highly crystalline N-methylpyridinium di-*p*-nitrophenyl phosphate which separated was collected by filtration after 18 hours; yield 1.06 g. Evaporation of the mother liquor afforded a further amount (100 mg.) of the same product; m.p. 134–135°, unchanged after recrystallization from ethyl acetate–ethyl alcohol. *Anal.* Calcd. for $C_{18}H_{16}N_3O_8P$: C, 49.89; H, 3.72; N, 9.70. Found: C, 49.87; H, 3.74; N, 9.72.

Paper chromatography and paper electrophoresis (*p*H 4) of the crystalline compound showed two ultraviolet absorbing spots; one, corresponding to di-*p*-nitrophenyl phosphate ion, and the second corresponding to N-methylpyridinium ion (identical in electrophoretic mobility and ultraviolet absorption spectrum to this ion prepared from dimethyl sulfate and pyridine in ether).

Acidic Hydrolysis of Di-*p*-nitrophenyl Methyl Phosphate.—To an acetic acid (2 ml.) solution of di-*p*-nitrophenyl methyl phosphate (40 mg.), maintained at 100°, slowly was added two ml. of water so as to maintain a homogeneous solution. Duplicate five microliter aliquots were removed at intervals and applied to Whatman No. 1 paper. Paper chromatography in solvent A showed the formation of spots corresponding to di-*p*-nitrophenyl hydrogen phosphate (R_f, 0.73) and methyl *p*-nitrophenyl hydrogen phosphate (R_f, 0.55). The percentages of the two products were ascertained by elution of the spots and determination of the optical density at 285 mμ. These were found to be: di-*p*-nitrophenyl hydrogen phosphate, about 77%; methyl *p*-nitrophenyl hydrogen phosphate, about 23%. The amounts of these products reached a maximum after three hours and then slowly decreased, with the concomitant formation of mono-*p*-nitrophenyl and monomethyl dihydrogen phosphates.

O-Methyl-N,N′-dicyclohexylisourea.[14]—Dicyclohexyl carbodiimide (310 mg.) was added to an anhydrous methyl alcoholic solution (5 ml.) of di-*p*-nitrophenyl hydrogen phosphate (500 mg.) and the solution kept at room temperature for four hours. The solvent was then evaporated and the residue crystallized from dioxane to give the di-*p*-nitrophenyl phosphate salt of *O*-methyl-N,N′-dicyclohexylisourea (IV) (710 mg., 84%) as colorless needles of m.p. 153–153.5°. *Anal.* Calcd. for $C_{26}H_{35}N_4O_9P$: C, 54.00; H, 6.10; N, 9.70. Found: C, 54.20; H, 6.30; N, 9.91.

A warm aqueous ethyl alcoholic solution of the salt (500 mg.) was well stirred with freshly washed IRA 400($O\bar{H}$) resin. The resin was removed by filtration, washed twice with ethyl alcohol and the total filtrate evaporated to dryness. The residual colorless oil was distilled in a short path apparatus to give O-methyl-N,N′-dicyclohexylisourea (185 mg., 90%) as a colorless mobile liquid; b.p. 90° (0.1 mm.). *Anal.* Calcd. for $C_{14}H_{26}N_2O$: C, 70.45; H, 11.00. Found: C, 70.10; H, 11.08.

P^1P^2-Di-*p*-nitrophenyl P^1P^2-Dimethyl Pyrophosphate (VIII).—To a solution of methyl *p*-nitrophenyl hydrogen phosphate (466 mg.) in anhydrous acetonitrile (5 ml.) was added di-*p*-tolyl carbodiimide (240 mg.) and the mixture, which deposited di-*p*-tolylurea immediately, was kept at room temperature for one hour. The urea was then removed by filtration in a dry box and the filtrate evaporated to an oil. It was suspended in ether (5 ml.) and acetonitrile gradually added until a clear solution resulted. On keeping at 0°, the solution deposited the pyrophosphate VIII as colorless stout crystals (350 mg., 78%); m.p. 81–83°, unchanged on recrystallization from the same solvents. *Anal.* Calcd. for $C_{14}H_{14}N_2O_{11}P_2$: C, 37.50; H, 3.15; N, 6.25. Found: C, 37.31; H, 3.21; N, 6.35.

Acknowledgment.—This work has been carried out under Defence Research Board of Canada, grant number 2020-23, Project D52-20-20-23.

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(32) Drying at higher temperatures results in some loss of cyclohexylamine. All the bis-cyclohexylammonium salts reported herein were therefore dried only at room temperature.

(33) B. H. Chase, G. W. Kenner, A. R. Todd and R. F. Webb, *J. Chem. Soc.*, 1371 (1956).

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[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF THE BRITISH COLUMBIA RESEARCH COUNCIL]

Nucleoside Polyphosphates. IV.[1] A New Synthesis of Guanosine 5′-Phosphate

BY ROBERT WARNER CHAMBERS,[2] J. G. MOFFATT AND H. G. KHORANA

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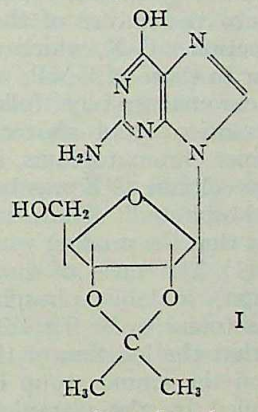
The previously recorded phosphorylation of 2′,3′-*O*-isopropylidene guanosine with phosphorus oxychloride in a mixture of pyridine and dimethylformamide has been re-examined. While some guanosine 5′-phosphate was produced, large amounts of the nucleoside always remained unreacted and phosphorus-containing side products, tentatively identified as guanosine 5′-di- and triphosphates, were formed. Guanosine 5′-phosphate was synthesized in a good (*ca.* 70%) yield by using tetra-*p*-nitrophenyl pyrophosphate as the phosphorylating agent. The steps were: 2′,3′-*O*-isopropylidene guanosine → 2′,3′-*O*-isopropylidene guanosine 5′-di-*p*-nitrophenyl phosphate $\xrightarrow{\bar{O}H}$ 2′,3′-*O*-isopropylidene guanosine 5′-mono-*p*-nitrophenyl phosphate $\xrightarrow[\text{snake venom or } \bar{O}H]{}$ 2′,3′-*O*-isopropylidene guanosine 5′-phosphate $\xrightarrow{H^+}$ guanosine 5′-phosphate. Some interesting properties of 2′,3′-*O*-isopropylidene guanosine 5′-di-*p*-nitrophenyl phosphate are recorded. An improved procedure for the preparation of 2′,3′-*O*-isopropylidene guanosine is described.

Nucleoside 5′-mono-, di- and triphosphates corresponding to all the four naturally occurring ribonucleosides were first demonstrated to be present in certain tissues by Potter and co-workers[3] and subsequent work reported from different laboratories has established the widespread occurrence[4] and biological importance[5] of these substances. In this Laboratory, attention has been devoted during the last several years to the development of methods for the chemical synthesis of nucleoside polyphosphates and related compounds. It was hoped that in addition to providing synthetic confirmation of structures, our studies might lead to new and improved procedures which would make some of the difficultly accessible members of this group readily available in a pure state. In continuing these studies,[6] we undertook the problems of the synthesis of guanosine 5′-mono-, di- and triphosphates. Chemical work in this series was anticipated to be particularly difficult, for the reasons which will become clear from the sequel,[7] and it was therefore considered that these problems would provide stringent tests for the synthetic methods which have been developed in this Laboratory. The present communication describes our work on the synthesis of guanosine 5′-phosphate (GMP) while the synthesis of the higher phosphates is reported in the following communication.[7] A brief account of a part of this work has already appeared.[8]

While highly satisfactory syntheses of a number of nucleoside 5′-phosphates[1,9,10c] have been recorded, previous attempts at the phosphorylation of guanosine derivatives[10] have met with only very limited success. In particular, the 5′-hydroxyl group in 2′,3′-*O*-isopropylidene guanosine (I) is



I

uniquely inert and resists phosphorylation[11] by the well-known phosphorylating agents, dibenzyl and diphenyl phosphorochloridates.[10] Michelson and Todd[10c] have, however, recorded the preparation of guanosine 5′-phosphate in 20% yield by using phosphorus oxychloride as the phosphorylating agent, and since at the time this work was undertaken this was the only applicable method,[12] we undertook a re-examination of this synthesis.

In the first experiments, Michelson and Todd's procedure was repeated exactly (addition of 1.1 equiv. of phosphorus oxychloride to a cold solution of 2′,3′-*O*-isopropylidene guanosine in a mixture of dimethylformamide and pyridine). Using paper chromatography, electrophoresis and ion-exchange analysis as analytical tools, two phosphorus-con-

(1) Paper III. R. H. Hall and H. G. Khorana, THIS JOURNAL, **77**, 1871 (1955).

(2) Life Insurance Medical Research Post-doctoral Fellow, 1954–1956.

(3) H. Schmitz, R. B. Hurlbert and V. R. Potter, *J. Biol. Chem.*, **209**, 11 (1954).

(4) R. Bergkvist and A. Deutsch, *Acta Chem. Scand.*, **8**, 1880, 1889 (1954); H. Schmitz, *Naturwiss.*, **5**, 120 (1954); *Biochim. Z.*, **325**, 555 (1954); P. Ayengar, D. M. Gibson, C. H. L. Peng and D. R. Sanadi, *J. Biol. Chem.*, **218**, 521 (1956).

(5) Some selected references are: A. Munch-Petersen, H. M. Kalckar, E. Cutols and E. E. B. Smith, *Nature*, **172**, 1036 (1953); E. P. Kennedy and S. B. Weiss, THIS JOURNAL, **77**, 250 (1955); D. R. Sanadi, D. M. Gibson, P. Ayengar and M. Jacob, *J. Biol. Chem.*, **218**, 505 (1956); M. Grunberg-Manago, P. J. Ortiz and S. Ochoa, *Biochem. Biophys. Acta.*, **20**, 269 (1956); A. Kornberg, I. R. Lehman, M. J. Bessman and E. S. Simms, *ibid.*, **21**, 197 (1956).

(6) H. G. Khorana, THIS JOURNAL, **76**, 3517 (1954); R. H. Hall and H. G. Khorana, *ibid.*, **76**, 5056 (1954).

(7) R. W. Chambers and H. G. Khorana, *ibid.*, **79**, 3752 (1957).

(8) R. W. Chambers, J. G. Moffatt and H. G. Khorana, *ibid.*, **77**, 3416 (1955).

(9) J. Baddiley and A. R. Todd, *J. Chem. Soc.*, 648 (1947) and the references cited therein.

(10) (a) H. Bredereck and E. Berger, *Ber.*, **73**, 1124 (1940); (b) J. M. Gulland and G. I. Hobday, *J. Chem. Soc.*, 746 (1940); (c) A. M. Michelson and A. R. Todd, *ibid.*, 2476 (1949).

(11) It should be pointed out that 2′,3′-*O*-isopropylidene guanosine is highly insoluble in pyridine. In the procedure reported by Michelson and Todd,[10c] a mixture of dimethylformamide and pyridine was used in order to obtain a homogeneous reaction mixture. The situation may be complicated by the reaction of phosphorylating agents with dimethylformamide. See, *e.g.*, H. K. Hall, Jr., THIS JOURNAL, **78**, 2717 (1956).

(12) The simple phosphorylating agent consisting of a mixture of phosphoric acid and phosphorus pentoxide which is satisfactory for the phosphorylation of the suitably protected pyrimidine nucleosides[1] was useless in the present case. 2′,3′-*O*-isopropylidene guanosine undergoes extensive degradation.

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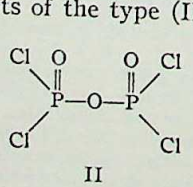
taining substances, in addition to guanosine 5′-phosphate, were detected as products. Further, about 50% of the starting material remained unreacted. The use of an approximately threefold excess of the phosphorylating agent caused no significant increase in the yield of the phosphorylated products. The results of the quantitative ion exchange analysis are recorded in the Experimental Section (Table II), the side products being designated as G-X and G-Y. As can be seen, GMP was formed in yields varying between 17 and 31%. However, the isolation of this desired substance was complicated by the presence of large amounts of inorganic phosphate and the yield of the pure product never exceeded 15% by this method of synthesis.

The phosphorus-containing side products (G-X and G-Y), both, had ultraviolet absorption spectra identical with that of guanosine 5′-phosphate and from their behavior on ion-exchange columns appeared to be polyphosphates. They were investigated more closely with the hope of obtaining some insight into the nature of the above phosphorylation reaction. G-X, which was present in amounts similar to those of GMP, was purified by ion-exchange chromatography followed by absorption and elution from charcoal. From its behavior on paper chromatograms, ionograms and an ion-exchange column, G-X was believed to be a "guanosine diphosphate." The evidence adduced below suggested that the product was guanosine 5′-diphosphate. (1) The ratio of guanosine (ultraviolet absorption) to labile phosphorus to total phosphorus was found to be 0.9:1.0:2.0. It may be mentioned that the location of the labile phosphoryl group on the amino group in the guanine ring was excluded by the ultraviolet absorption spectrum and the fact that the substance had survived the acidic treatment used to remove the isopropylidene group. (2) Crude snake venom degraded G-X to guanosine and inorganic phosphate. (3) The vicinal hydroxyl groups in the ribose moiety were intact as shown by the periodate–benzidine spray.

G-Y was only a very minor product and the availability of only a very small amount of the purified sample precluded a rigorous examination. However, experiments along the lines described above suggested that G-Y probably was guanosine 5′-triphosphate.

The formation of guanosine 5′-di- and triphosphates as side products suggests that linear phosphorylating agents of the type (II) are present in



II

the above reaction mixtures. (Inorganic pyro- and polyphosphates were also detected as reaction products.) These polyphosphorylating agents[13] could arise by the reaction of phosphorus oxychloride with traces of water present in the reaction mixture, although all possible precautions to exclude moisture were taken.[14]

The above experiments would appear to demonstrate conclusively the inertness of the 5′-hydroxyl group in I, since large amounts of the nucleoside always were recovered.[15] More recently, Hayes, Michelson and Todd[16] have also remarked on the inertness of the hydroxyl groups in 2′-deoxyguanosine derivatives. A possible explanation of this inertness is that the 5′-hydroxyl group is involved in hydrogen bonding with the 2-amino group in the guanine ring, a situation unique to this nucleoside.

The unsatisfactory results obtained above and the virtual failure of the other known phosphorylating agents led us to conclude that the phosphorylation of 2′,3′-*O*-isopropylidene guanosine (I) could be best accomplished with a powerful, monofunctional reagent which would not require basic catalysis. Tetra-*p*-nitrophenyl pyrophosphate, which is described in detail in the preceding communication,[17] was found to meet these requirements. The reagent was allowed to react with I in the presence of one equivalent of the free di-*p*-nitrophenyl hydrogen phosphate and, after a reaction period of 15 hours at 20°, 2′,3′-*O*-isopropylidene guanosine 5′-di-*p*-nitrophenyl phosphate (III) was isolated in a nearly quantitative yield. This successful phosphorylation in acidic medium would appear to support the belief that the 5′-hydroxyl group acquired "normal" reactivity when the 2-amino group in I was protonated.

As recorded in the preceding communication[17] the removal of one of the *p*-nitrophenyl groups from the neutral esters of the type III may be accomplished by very mild alkaline treatment; IV was thus obtained in a nearly quantitative yield, as estimated by spectrophotometric measurement of the liberated *p*-nitrophenol. The removal of the second *p*-nitrophenyl group was conveniently effected by digestion with crude rattlesnake venom, which is known to have a relatively unspecific and potent phosphodiesterase activity.[18]

(13) M. Viscontini and K. Ehrhardt, *Ang. Chem.*, **66**, 717 (1954).

(14) It also is possible that the polyphosphates are formed during decomposition of the excess of phosphorus oxychloride with aqueous pyridine (see Experimental).

(15) It might be argued that the free nucleoside found in the reaction products arose from the breakdown of an acid-labile phosphorylated derivative, *e.g.*, N^2-phosphate, during the acidic removal of the isopropylidene group. Thus, Levene and Tipson (*J. Biol. Chem.*, **121**, 131 (1937)) have recorded the isolation of an adenosine diphosphate after treatment of 2′,3′-*O*-isopropylidene adenosine with 2.2 equivalents of phosphorus oxychloride. Since one of the two phosphate groups in the above product was acid-labile, Levene and Tipson formulated the substance as adenosine N^6,5′-diphosphate. If N-phosphorylation were also to occur in the guanosine series, then by using an excess of phosphorus oxychloride N^2,O5′-diphosphate would have been obtained, which after mild acidic treatment would have afforded guanosine 5′-phosphate. In other words, an increase in the amount of the phosphorylating agent should have resulted in an increase in the yield of guanosine 5′-phosphate. Actually, this was found not to be the case. Furthermore, when the phosphorylation mixture was examined by paper chromatography *before* any acidic treatment, a large proportion of isopropylidene guanosine was found to be present.

(16) D. H. Hayes, A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 808 (1955).

(17) J. G. Moffatt and H. G. Khorana, THIS JOURNAL, **79**, 3741 (1957).

(18) For a recent review see G. Schmidt, "Enzymes Attacking Nucleic Acids," in "The Nucleic Acids," Vol. I, Academic Press, Inc., New York, N. Y., 1955, p. 483.

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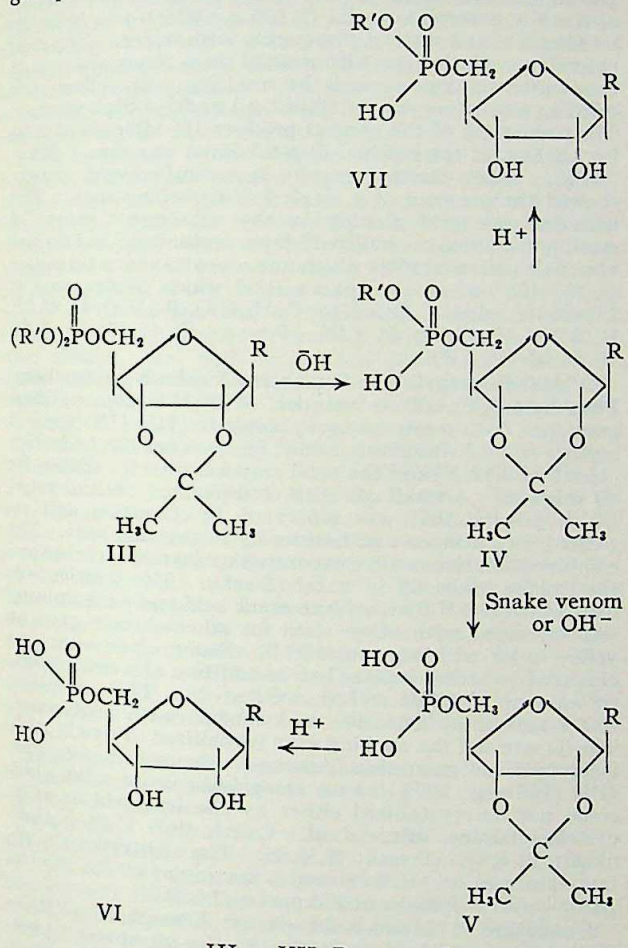
Treatment of the resulting V with dilute acid furnished guanosine 5′-phosphate which was isolated in yields of 65–75% based on isopropylidene guanosine. As was expected, the 5′-nucleotidase, which is also present in the crude snake venom, was inactive toward V, since the 3′-hydroxyl group[19] was protected by the isopropylidene

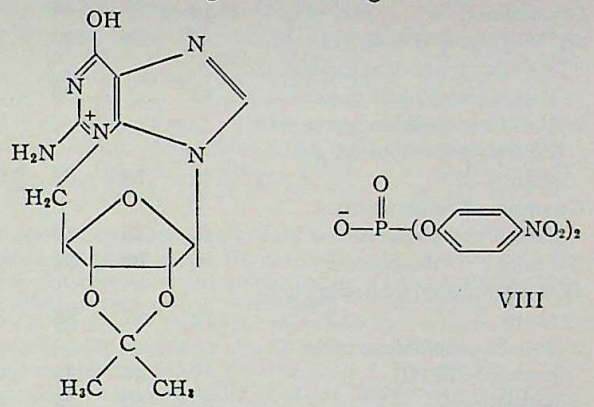


III → VII, R = guanine
III, IV and VII, R′ = *p*-nitrophenyl

group. However, it was fully active against guanosine 5′-phosphate (VI). Therefore, the removal of the protecting groups in the order IV → V → VI enabled the use of the crude snake venom.

The removal of the *p*-nitrophenyl group from IV also was accomplished by treatment with 1 *N* lithium hydroxide at 100° for about three hours. Some concomitant hydrolysis to inorganic phosphate also occurred under these conditions, but the product could be purified by fractional precipitation of the barium salt. The yield of guanosine 5′-phosphate prepared by alkaline hydrolysis was about 60%.

Two observations made during the course of the work on the neutral III may be mentioned. On heating its acetonitrile solution a new high-melting isomeric substance was produced. The product was concluded to be a quaternary ammonium salt of di-*p*-nitrophenyl phosphate, its formation being analogous to the quaternization reaction undergone by 2′,3′-*O*-isopropylidene adenosine 5′-*p*-toluenesulfonate.[20] While the structure VIII is tentatively advanced for this substance, the alternative possibility of cyclization with the 2-amino group in the guanine ring cannot be ignored.



Cyclization, instead of transesterification,[17] was also the preferred reaction when III was treated with sodium benzoxide in benzyl alcohol. Analogy for this reaction may again be found in the work of Brown, Todd and Varadarajan[21] who have recorded quaternization reactions of *p*-toluenesulfonic acid esters of uridine derivatives in methyl alcohol–ammonia.

Finally, the preparation of 2′,3′-*O*-isopropylidene guanosine, the starting material, by the published procedure[10c] was tedious and gave in our hands unsatisfactory yields. A simpler method of isolation which utilizes an ion-exchange resin for the removal of zinc ions is described in the Experimental Section. The procedure gave consistently 70–80% yields.

Experimental

Methods.—Paper chromatography was carried out with Whatman No. 1 paper, using mostly the descending technique. The solvent systems employed were: (1) *n*-butyl alcohol–acetic acid–water (4:1:5, v./v.)[22] (solvent I); (2) sopropyl alcohol–ammonia–water (7:1:2)[23] (solvent II); (3) isopropyl alcohol–1% ammonium sulfate solution (2:1, v./v.)[24] (solvent III); (4) pyridine–isoamyl alcohol–water (7:7:6, v./v.)[25] (solvent IV); (5) potassium dihydrogen phosphate solution (5%)–isoamyl alcohol[26] (solvent V); (6) isopropyl alcohol (75 ml.)–water (25 ml.)–trichloroacetic acid (5 g.)–ammonia (0.25 ml., sp. gr. 0.9)[27] (solvent VI); (7) isobutyric acid (100 ml.)–1 *N* ammonium hydroxide (60 ml.)–0.1 *M* ethylenediaminetetraacetic acid disodium salt[28] (1.6 ml.) (solvent VII). The R_f's of various compounds are given in Table I.

For paper electrophoresis, five inch strips of Whatman No. 3 MM paper were washed first with 2 *N* formic acid,[29] then with water and dried in air. The spots were applied and dried and the papers then sprayed with 0.02 *M* citrate buffer, *p*H 4.4, and then subjected to a potential of 12 volts/cm.

(19) The 5′-nucleotidase is inactive when the 3′-hydroxyl group is substituted. Thus, adenosine 3′,5′-diphosphate (A. Kornberg and W. E. Pricer, Jr., *J. Biol. Chem.*, **186**, 557 (1950)) is not attacked by the snake venom.

(20) V. M. Clarke, A. R. Todd and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

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TABLE I

PAPER CHROMATOGRAPHY OF GUANOSINE DERIVATIVES

Compound	R_f's in solvent systems I	II	III	IV
Guanine	0	0.24	0.30	0.85
Guanosine	0.18	.27	.44	.85
2′,3′-*O*-Isopropylidene guanosine	.63	.60	.70	.70
2′,3′-*O*-Isopropylidene guanosine 5′-di-*p*-nitrophenyl phosphate	.95	..	.95	..
2′,3′-*O*-Isopropylidene guanosine 5′-mono-*p*-nitrophenyl phosphate	.48	.58	.68	.64
Guanosine 5′-mono-*p*-nitrophenyl phosphate	.15	.35	.50	.41
Guanosine 5′-phosphate	0	.03	.31	0
Di-*p*-nitrophenyl hydrogen phosphate	.73	.87	.85	.83
2′,3′-*O*-Isopropylidene cycloguanosine (VIII)	.47	.47	.49	.46
p-Nitrophenol	.89	.69	.83	.91

for two hours. The apparatus employed was a modification of Paigen's design,[30] in that the starch troughs were replaced by a glass baking dish (13.5″ × 8.5″ × 2″) filled with carbon tetrachloride. The paper strips were immersed in this bath during the run.

Spots were located on paper chromatograms by their ultraviolet absorption and by spraying the chromatograms with the molybdate–perchloric acid spray[31] and subsequently irradiating with ultraviolet light.[32] Total phosphorus determination was carried out by King's method,[33] while inorganic phosphate was determined by the method of Lowry and Lopez.[34]

Preparation of 2′,3′-*O*-Isopropylidene Guanosine.—Zinc chloride (56 g. of a freshly fused, anhydrous sample) was dissolved in anhydrous acetone (350 ml.). Twenty-two grams of guanosine (dried previously *in vacuo* at 100° over phosphorus pentoxide) was added and the mixture heated overnight under reflux with exclusion of moisture. The clear solution was then evaporated to a thick sirup and 8 *N* ammonium hydroxide was added until the initially formed precipitate redissolved and a clear solution resulted. Amberlite IR-120-ammonium form (100 ml.) was added and if a precipitate formed, it was dissolved by the gradual addition of concd. ammonia. The mixture was stirred for 15 minutes. The resin was then removed by filtration and washed twice with 50-ml. portions of very dilute ammonia. This whole process was repeated four times using 100–125 ml. portions of the wet resin each time. The total volume of the final filtrate was about 1000 ml. On evaporation of ammonia, either by keeping the solution in an open vessel for several days or by heating on a water-bath and then allowing the solution to cool, 2′,3′-*O*-isopropylidene guanosine crystallized. It was collected by filtration, washed with water and dried in air to give 15.2 g. of a crystalline, pure sample. The mother liquor was concentrated and retreated twice with 100-ml. portions of IR-120-ammonium form resin. A further amount (4.2 g.) of pure material was thus obtained; total yield 19.4 g., m.p. 296° (resolidification) (reported[10c] m.p. 299° dec.). This material could be recrystallized from hot water with negligible loss. Paper chromatography in four solvent systems (Table I) showed a single strong spot; guanosine could not be detected.

2′,3′-*O*-Isopropylidene Guanosine 5′-Di-*p*-nitrophenyl Phosphate (III).—Di-*p*-nitrophenyl phosphate[35] (4.2 g., *ca.* 12.4 mmoles) was dissolved in warm anhydrous dioxane (20 ml.) and the solution cooled to room temperature under running cold water with exclusion of moisture. Di-*p*-tolyl carbodiimide (1.10 g., 4.97 mmoles) was added, and the stoppered reaction flask was kept at room temperature for ten minutes. 2′,3′-*O*-Isopropylidene guanosine[35] (1.0 g., 3.1 mmoles) was quickly added and the sealed flask stored overnight in a desiccator. Di-*p*-tolylurea (1.080 g., theory 1.190 g.) was then removed by filtration and washed three times with 3-ml. portions of dioxane. The filtrate and the washings were evaporated and the resulting oil shaken with a mixture of chloroform (30 ml.) and 1 *M* lithium acetate buffer (*p*H 6.5, 10 ml.). The chloroform layer was separated and further extracted three times with the same buffer. During the extractions a part of the product III separated as a white amorphous solid (1.106 g.) which was collected by filtration and washed thoroughly with water. The clear chloroform solution was also washed three times with water, evaporated to dryness and the resulting pale yellow resin dried to a constant weight (0.982 g.) under a high vacuum. The total yield of the neutral product III after accounting for 110 mg. of the residual di-*p*-tolylurea was thus 1.898 g. (95%). Paper chromatography in several solvent systems showed the presence of a single fast-travelling spot. This material was used directly in the subsequent steps. A small portion was crystallized[36] from acetonitrile and formed very pale yellow needles which underwent a sharp transition at 161–163° to an amorphous solid which decomposed at 263–264°. *Anal.* Calcd. for $C_{25}H_{24}N_7O_{12}P\cdot 1H_2O$: C, 45.28; H, 3.95; N, 14.80; P, 4.68. Found: C, 45.57; H, 4.45; N, 15.00; P, 4.80.

2′,3′-*O*-Isopropylidene Guanosine 5′-Mono-*p*-nitrophenyl Phosphate (IV).—To a solution of 2′,3′-*O*-isopropylidene guanosine 5′-di-*p*-nitrophenyl phosphate (III) (180 mg.) in acetone (6 ml.) was slowly added aqueous barium hydroxide (16 ml. of 0.12 *N*) and the total reaction mixture shaken for 30 minutes. A small quantity of unreacted neutral ester, which precipitated, was separated by filtration and retreated with acetone and barium hydroxide as above. The combined solutions were evaporated to dryness *in vacuo* and the residue taken up in water (5 ml.). The solution was neutralized to *p*H 5 with dilute acetic acid and *p*-nitrophenol was extracted with ether until an ether extract gave no yellow color with aqueous alkali. Barium ions were precipitated as barium sulfate by the addition of a stoichiometric amount of dilute sulfuric acid at 0°. The precipitate was removed by filtration and washed with cold water. The filtrate and the washing were lyophilized to give 2′,3′-*O*-isopropylidene guanosine 5′-mono-*p*-nitrophenyl phosphate (IV) (155 mg., 85%) as an amorphous white solid which could not be crystallized either as the free acid or as its cyclohexylamine salt. *Anal.* Calcd. for $C_{19}H_{21}N_6O_{10}P\cdot 6H_2O$: P, 4.89. Found: P, 4.88. The ultraviolet absorption spectrum at *p*H 2 showed a maximum at 258 mμ (ϵ_{258} 15,100) with a shoulder at 276 mμ (ϵ_{276} 14,000).

Guanosine 5′-Mono-*p*-nitrophenyl Phosphate (VII).—2′,3′-*O*-Isopropylidene guanosine 5′-di-*p*-nitrophenyl phosphate (180 mg.) was hydrolyzed with barium hydroxide in aqueous acetone as above. After extraction of the *p*-nitrophenol with ether, the aqueous solution was adjusted to *p*H 2.7 with acetic acid and held in a boiling water-bath for 1.5 hours. Barium was removed with sulfuric acid and the aqueous solution lyophilized to give guanosine 5′-mono-*p*-nitrophenyl phosphate (VII) as a fluffy white solid (145 mg., 90%) which could not be crystallized. *Anal.* Calcd. for $C_{16}H_{17}N_6O_{10}P\cdot 5H_2O$: P, 5.38. Found: P, 5.34.

Guanosine 5′-Phosphate.—2′,3′-*O*-Isopropylidene guanosine (1.0 g.) was phosphorylated as described above to give the di-*p*-nitrophenyl phosphate ester III in 96% yield. This product was suspended in dioxane (25 ml.), lithium hydroxide (12 ml. of 1 *N*) was added and the suspension was shaken for ten minutes. More water (12 ml.) was added and the shaking was continued for 30 minutes. The yellow solution was neutralized with hydrochloric acid to *p*H 7–8, a little di-*p*-tolylurea was removed by filtration and the clear solution evaporated under reduced pressure. The residue was treated in either of the following two ways to remove the second *p*-nitrophenyl group.

(a) **Enzymatic Hydrolysis.**—The residue was dissolved in 25 ml. of tris[37]-buffer (0.1 *M*, *p*H 8.8) and filtered to remove a final trace of di-*p*-tolylurea. Magnesium acetate (25 ml. of 0.3 *M*) was added and the total volume brought to 150 ml. with the buffer solution. Crude rattlesnake

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(35) Dried at 110° *in vacuo* over phosphorus pentoxide.

(36) Prolonged heating must be avoided during crystallization since this results in the formation of the cyclonucleoside salt VIII (see below).

(37) Tris(hydroxymethyl)-aminomethane.

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venom[38] (62 mg.) was added and the solution was incubated at 37° for three hours.[39] The solution was cooled to room temperature, adjusted to *p*H 5 with glacial acetic acid and stirred for 20 minutes with 25 ml. of IR-120 ion-exchange resin (ammonium form) to remove magnesium ions. The resin was removed by filtration and washed thoroughly with water (the final volume of the filtrate was 260 ml.). Glacial acetic acid (28 ml.) was added and the solution adjusted to *p*H 2.7 (*p*H meter) by the dropwise addition of concentrated hydrochloric acid. The solution was heated in a boiling water-bath for 1 hour, cooled to room temperature and extracted seven times with 70-ml. portions of ether to remove *p*-nitrophenol. The aqueous solution was then evaporated to dryness under reduced pressure. The residue was taken up in water and adjusted to *p*H 8.5 with 4 *M* lithium hydroxide (total volume of solution *ca.* 25 ml.). Four ml. of 2 *M* barium acetate solution was added and the solution allowed to stand at room temperature for 1 hour. Barium phosphate was removed by centrifugation and the sediment washed with water. To the combined supernatants were added two volumes of 95% ethyl alcohol and the precipitation of the product was completed at −10° (1.5 hours). The barium salt of guanosine 5′-phosphate was collected by centrifugation, washed twice with cold 70% ethyl alcohol, then with 95% ethyl alcohol, acetone and finally ether. It was dried *in vacuo* over phosphorus pentoxide for several hours. The yield of this product which contained 8 moles of water of hydration varied between 1.263 and 1.377 g. (64–75%, based on 2′,3′-*O*-isopropylidene guanosine). *Anal.* Calcd. for $C_{10}H_{12}N_5O_8P\cdot Ba^{++}\cdot 8H_2O$ (mol. wt., 642.7): C, 18.69; H, 4.39; P, 4.82. Found in a reprecipitated sample: C, 18.59; H, 3.55; P, 4.67. A sample (117.48 mg.) of this material was dried overnight *in vacuo* at 100° over phosphorus pentoxide. The weight loss was 25.79 mg., corresponding to 7.8 moles of water. Paper chromatography in several solvent systems, paper electrophoresis (see above) and ion-exchange chromatography showed the sample to be homogeneous. R_f's in solvent systems not mentioned in Table I were as follows: solvent V, 0.63; solvent VI, 0.35; solvent VII, 0.28. Electrophoretic mobility under the conditions described above, 8.2 cm.

The above preparation has been carried out on three times the above scale and has given a 66% yield based on isopropylidene guanosine.

(b) **Alkaline Hydrolysis.**—The residue obtained above after mild alkaline hydrolysis of III was taken up in water (15 ml.), a final trace of di-*p*-tolylurea was removed by filtration and the solution evaporated again. The gummy residue was dissolved in 20 ml. of 1 *N* lithium hydroxide, the solution transferred to a polyethylene tube and heated in a boiling water-bath for 2.5 hours. The solution was cooled, adjusted to *p*H 2.7 with concentrated hydrochloric acid and heated in a boiling water-bath for 1.5 hours to remove the isopropylidene group. After cooling, the acidic solution was extracted repeatedly with ether until an extract gave no yellow color with alkali. The *p*H of the aqueous solution was then brought up to 8.5 with 4 *N* lithium hydroxide and the volume adjusted to *ca.* 25 ml. Four ml. of 2 *M* barium acetate was added and the precipitate (mixture of barium phosphate and some product) was collected by centrifugation and washed with water. Two volumes of ethyl alcohol were added to the combined supernatants and the precipitation was completed by storing at 0° for one hour. The white precipitate was collected by centrifugation, washed twice with 70% ethyl alcohol, once with 95% ethyl alcohol, then acetone and ether and dried at room temperature *in vacuo* over phosphorus pentoxide to give 1.00 g. of barium guanosine 5′-phosphate. Recovery of more product from the first precipitate was tedious, but could be accomplished as follows. The mixture of barium phosphate and guanosine 5′-phosphate was suspended in ice-water, cold hydrochloric acid was added until a clear solution resulted and the acidic solution was again neutralized to *p*H 8.5 with lithium hydroxide. The resulting precipitate was collected and again processed in the manner described above. Addition of two volumes of ethyl alcohol to the combined supernatants gave 163 mg. of an essentially pure product; total yield 1.163 g. (59%). Inorganic phosphate determination showed that this product contained 2.7% barium phosphate. One further reprecipitation gave a pure sample of barium guanosine-5′-phosphate (octahydrate); λ_{max} at *p*H 2, 256 mμ; ϵ_{max} 12,400; λ_{max} at *p*H 12, 260 mμ; ϵ_{max}, 12,100.

Quaternization of 2′,3′-*O*-Isopropylidene Guanosine 5′-Di-*p*-nitrophenyl Phosphate (III) to (VIII). (a) **By Heating the Neutral Ester III.**—2′,3′-*O*-Isopropylidene guanosine 5′-di-*p*-nitrophenyl phosphate (III) (45 mg.) was dissolved in acetonitrile (10 ml.) and heated under reflux for three hours. On cooling, very fine needles (30 mg.) separated and evaporation of the mother liquor gave more of the same material (10 mg., total yield 90%). This substance decomposed at 261–263°. *Anal.* Calcd. for $C_{25}H_{24}N_7O_{12}P$: C, 46.51; H, 3.75; N, 15.20. Found: C, 46.13; H, 4.10; N, 14.99.

Paper chromatography in four solvent systems (Table I) showed, as expected for the salt VIII, the presence of two spots, one corresponding to di-*p*-nitrophenyl phosphate and the other corresponding, presumably, to the cycloguanosine (R_f's in Table I). The ultraviolet absorption spectrum of the slower moving spot after elution from paper showed a single broad maximum (245–260 mμ) at *p*H 2. The spectra at *p*H 6.8 and 10.7 were essentially identical, there being strong end absorption (below 230 mμ) and a maximum at 266–267 mμ. Paper electrophoresis of VIII at *p*H 3.4 revealed the presence of the anion corresponding to di-*p*-nitrophenyl phosphate and a cation. Electrophoresis at *p*H 7.6, showed the presence of di-*p*-nitrophenyl phosphate ion and a second spot close to the origin and identical in behavior with guanosine, indicating the loss of a proton from the cation of cycloguanosine (VIII).

(b) Sodium benzoxide (40 mg. of sodium in 3 ml. of dry benzyl alcohol) was added to a solution of 2′,3′-*O*-isopropylidene guanosine 5′-di-*p*-nitrophenyl phosphate (300 mg.) in benzyl alcohol (2 ml.) and the resulting orange solution set aside for 15 minutes. Glacial acetic acid (0.15 ml.) was then added to the solution and benzyl alcohol removed under a high vacuum. The oily residue was taken up in 5% aqueous acetic acid, a trace of insoluble material removed by filtration and the solution extracted with ether until an extract gave no yellow color with alkali. Spectrophotometric analysis of the ethereal extracts showed that only 8 mg. of *p*-nitrophenol was present. Paper chromatography of the aqueous solution showed two major spots corresponding to the products obtained above in (a).

Phosphorylation of 2′,3′-*O*-Isopropylidene Guanosine with Phosphorus Oxychloride. (a) **Using One Equivalent of Phosphorus Oxychloride.**—The phosphorylation was carried out exactly as described by Michelson and Todd[10c] using 1.1 g. of 2′,3′-*O*-isopropylidene guanosine (one-fifth the scale used by the above authors). After the addition of water to the reaction mixture, the *p*H was brought to 9 with 4 *N* lithium hydroxide and the solvent was removed under reduced pressure. The residue was taken up in 50 ml. of 10% acetic acid and the *p*H of the solution adjusted to 2.7 (*p*H meter) by the addition of a little concentrated hydrochloric acid. The clear solution was heated for one hour in a boiling water-bath and then evaporated under reduced pressure. The white gel which resulted was dissolved in 30 ml. of water and the solution was lyophilized to a dry, light yellow powder (2.6 g.). This is designated as Product A.

(b) **Using 2.6 Equivalents of Phosphorus Oxychloride.**—Dry 2′,3′-*O*-isopropylidene guanosine (0.97 g., 3 mmoles) was dissolved in 15 ml. of freshly distilled dimethylformamide and 7 ml. of dry pyridine (distilled over calcium hydride) was added. The solution was cooled to −20° in an ice-salt bath and 0.72 ml. (7.8 mmoles) of freshly distilled phosphorus oxychloride was added in one batch, the temperature of the reaction mixture being maintained between −10 and −20°. Five-ml. aliquots were removed at intervals of 1 and 2 hours. These two aliquots and the remaining reaction mixture (after three hours reaction time) were worked up as described above in (a). These products of one, two and three hour reaction periods are designated as Products B, C and D, respectively.

Analysis of Products. (a) **Paper Chromatography and Paper Electrophoresis.**—Paper chromatography of Product A in solvents III and V showed the presence of five ultraviolet absorbing components. Three of these components were identified as guanine, guanosine and guanosine 5′-phosphate. The two other phosphorus-containing products corresponded in their R_f values to guanosine 5′-di- and tri-

(38) *Crotalus adamanteus*, Ross Allen's Reptile Farm, Silver Springs, Florida.

(39) Spectrophotometric estimation (440 mμ) of the liberated *p*-nitrophenol indicated 96% hydrolysis.

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phosphates.[7] The ultraviolet spectra (obtained by eluting the spots with 0.01 *N* hydrochloric acid) of these products were identical with that of guanosine 5′-phosphate. Hydrolysis with 0.1 *N* hydrochloric acid at 100° for 10 minutes gave, in both cases, guanine.

Paper electrophoresis of Product A revealed the presence of six ultraviolet-absorbing components. Three of these components were identified as guanine, guanosine and guanosine 5′-phosphate. The other three spots had mobilities relative to guanosine 5′-phosphate of 0.6, 1.2 and 1.7, the higher mobilities corresponding to those of guanosine 5′-di- and triphosphate,[7] respectively.

(b) **Ion-exchange Analysis.**—The following standard procedure was employed for quantitative analysis of the products obtained above. A 15-mg. sample of the lyophilized material was dissolved and the solution, after adjusting the *p*H to 8.5 with 1 *N* ammonium hydroxide, was applied to the top of a Dowex 2-chloride form (200–325 mesh) column (3 cm. × 0.8 cm. diameter). The column was washed first with water and then with 0.003 *N* hydrochloric acid to remove guanine and guanosine. Elution was then carried out using the linear gradient technique.[7] Five-ml. fractions were collected, using an automatic fraction cutter, and the optical density of the individual fractions at 260 mμ was determined using a Beckman spectrophotometer, model DU. The two peaks which emerged from the column after guanosine 5′-phosphate (GMP) were designated as G-X and G-Y. These two peaks corresponded in their positions to guanosine 5′-di- and triphosphate,[7] respectively. The results of these analyses are shown in Table II.

TABLE II

ION-EXCHANGE ANALYSIS OF PRODUCTS OF PHOSPHORYLATION OF 2′,3′-*O*-ISOPROPYLIDENE GUANOSINE WITH PHOSPHORUS OXYCHLORIDE

Product	% of total topical density at 260 mμ				
	Guanine	Guanosine	Guanosine 5′-phosphate	G-X	G-Y
A	1	49	31	14	5
B	3	61	17	18	1
C	4	55	23	17	1
D	4	52	19	16	9

Isolation of G-X and G-Y.—One gram of the lyophilized solid (Product A, see above) was triturated twice with 15-ml. portions of methyl alcohol to remove most of the inorganic salt (lithium chloride). The residual solid was dissolved in 25 ml. of water, adjusted to *p*H 8.5 with 1 *N* ammonium hydroxide and applied to a column (4 cm. × 2.2 cm. diameter) of Dowex-2 chloride form. The procedure used was as described in the preparation of guanosine 5′-di- and triphosphates.[7] The following fractions were obtained: guanosine 5′-phosphate; with 0.003 *N* HCl + 0.015 *M* NaCl (1,100 ml., 3,077, O.D. units at 260 mμ); G-X, with 0.003 *N* HCl + 0.1 *M* NaCl (1,000 ml., 1,674, O.D. units); G-Y, with 0.003 *N* HCl + 0.2 *M* NaCl (700 ml., 504, O.D. units). G-X was isolated as the barium salt (78 mg.) as described for guanosine 5′-diphosphate.[7] Since this product was found to be contaminated by inorganic pyrophosphate, purification was carried out as follows. Forty milligrams of the barium salt was shaken with Dowex-50-sodium form until it dissolved. The resin was removed by filtration and washed with water. The total solution (10 ml.) of sodium G-X was adjusted to *p*H 2.7 and stirred with 100 mg. of Darco-G-60 charcoal[40] (95% of the optical density was absorbed). The charcoal was washed with 3 portions of 0.003 *N* HCl to remove the last traces of pyrophosphate and then with three 5-ml. portions of ethyl alcohol–ammonia–water[41] to elute G-X. The ammoniacal solution was evaporated under reduced pressure and the product was precipitated as its barium salt at *p*H 7 from its aqueous solution. One reprecipitation was carried out by dissolving the barium salt in 0.5 ml. of 0.5 *N* HCl at 0° and adding ethyl alcohol.

Characterization of G-X.—(1) The above sample was converted to the sodium salt as described above and examined by paper chromatography and paper electrophoresis. Only one ultraviolet absorbing spot, corresponding to guanosine 5′-diphosphate,[7] could be detected. (2) The guanosine (ultraviolet absorption) to labile phosphorus to total phosphorus was found to be 0.9:1.0:2.0. (3) Tris-buffer (*p*H 7.5) and rattlesnake venom[38] were added to a small portion of the sodium salt solution. The mixture was incubated for 6 hours at 37° and then subjected to chromatography in solvent system III. The original spot of G-X (R_f, 0.12) had completely disappeared and a new spot corresponding to an authentic sample of guanosine (R_f, 0.44) had appeared. (4) The periodate–benzidine spray[42] gave a positive test for vicinal hydroxyl groups in both standard guanosine 5′-diphosphate and G-X.

G-Y was isolated by dissolving the solid obtained by lyophilization of the last ion-exchange fraction in 40 ml. of water and absorbing the nucleotide component on 100 mg. of charcoal (Darco-G-60) in two 50-mg. portions. The charcoal was collected by filtration through Celite, washed as above, and the nucleotidic material then eluted with four 5-ml. portions of 5% aqueous pyridine. The barium salt was prepared in the usual manner. Paper chromatography and paper electrophoresis indicated the presence of a major component, resembling guanosine 5′-diphosphate in behavior and a minor component which behaved like guanosine 5′-triphosphate.[7] Phosphorus analysis gave a ratio of labile to total phosphorus of 2:4.6; theory for guanosine 5′-triphosphate, 2:3.

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[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF THE BRITISH COLUMBIA RESEARCH COUNCIL]

Nucleoside Polyphosphates. V.[1] Syntheses of Guanosine 5′-Di- and Triphosphates

BY ROBERT WARNER CHAMBERS[2] AND H. G. KHORANA

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The syntheses of guanosine 5′-di- and triphosphates by the reaction of guanosine 5′-phosphate and 85% phosphoric acid with dicyclohexyl carbodiimide are reported.

The condensation of an unprotected nucleoside 5′-monophosphate with orthophosphoric acid in the presence of a carbodiimide forms the basis of a simple method for the synthesis of nucleoside 5′-polyphosphates. The application of this method to the preparation of ADP, ATP,[3,4] UDP and

(1) Paper IV. R. W. Chambers, J. G. Moffatt and H. G. Khorana, THIS JOURNAL, **79**, 3747 (1957).

(2) Life Insurance Medical Research Fund Post-doctoral Fellow, 1954–1956.

(3) The following abbreviations are used: ADP, adenosine 5′-diphosphate; ATP, adenosine 5′-triphosphate; UDP, uridine 5′-diphosphate; UTP, uridine 5′-triphosphate; GMP, guanosine 5′-monophosphate; GPD, guanosine, 5′-diphosphate; GTP, guanosine 5′-triphosphate; DCC, dicyclohexyl carbodiimide.

(4) H. G. Khorana, THIS JOURNAL, **76**, 3517 (1954).

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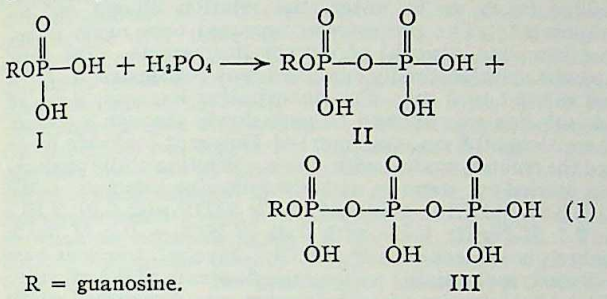
UTP[3,5] has been recorded previously. In view of the increasing biochemical interest in the naturally occurring ribo- and deoxyribonucleoside 5′-polyphosphates[6] it was considered desirable to test further the generality of the method. Attention was turned, therefore, to the synthesis of guanosine 5′-di- (II) and triphosphate (III) from guanosine 5′-monophosphate[1] (I) (eq. 1)



R = guanosine. (1)

In order to determine the optimum conditions for the formation of GDP[3] and GTP[3] it was necessary to have a convenient and reliable method for analyzing the reaction mixtures. For this purpose, ion-exchange chromatography using a linear gradient elution apparatus, similar to that described by Paar,[7] proved satisfactory. Analytical columns, using Dowex-2 (chloride form) resin, were routinely run overnight and gave well separated sharp peaks of the various components. Use of the more expedient techniques of paper chromatography and paper electrophoresis was investigated in some detail but it was not possible to find a system which would separate GTP from higher guanosine polyphosphates.

The previous work on the condensation of nucleoside monophosphates with phosphoric acid has shown that in aqueous pyridine homogeneous reaction mixtures are not obtained. Since all of the reagent (DCC) must be present in the upper aqueous pyridine phase, this is the reaction phase. The lower "sirupy" phase contains a large proportion of the phosphoric acid as well as varying amounts of the nucleoside monophosphate, depending upon the pyridine–water ratio and the solubility of the nucleotide in pyridine. In this solvent system the rate of condensation was found to be, as expected, a function of the solubility of the nucleotide in the upper phase. Thus, UMP is soluble in anhydrous pyridine and the synthesis of uridine polyphosphates occurs rapidly even when the pyridine–water ratio is as high as fifteen. AMP, on the other hand, has a very low solubility in pyridine and, consequently, the formation of adenosine polyphosphates is much slower even when the pyridine–water ratio is as low as seven.

In the present work, GMP was found to be even less soluble in aqueous pyridine than AMP and, consequently, the rate of polyphosphate formation was very slow. Attempts, therefore were made to find an alternative solvent system. Freshly distilled dimethylformamide was found to give a homogeneous reaction mixture and the condensation was then, as expected, very rapid. Several experiments were performed using varying proportions of GMP, phosphoric acid and DCC. The results obtained in a typical experiment by removing aliquots from the reaction mixture at suitable time intervals are shown in Table I (Experimental Section). These experiments, as may be seen from the data, were disappointing in that GDP and/or GTP could not be obtained as major products of the reaction. Higher guanosine polyphosphates, which have not been investigated further, were formed rapidly after an initial lag period and accounted for more than 50% of the total nucleotidic material.

The lack of specificity in effecting condensation is a disadvantage of the carbodiimide method for the synthesis of nucleoside polyphosphates and this fact necessitates the use of a large excess of orthophosphoric acid. Therefore, large amounts of inorganic polyphosphates are concomitantly formed. As the reaction proceeds the concentration of these substances increases[8] leading to a complicated kinetic situation. Qualitatively, the above results are perhaps not surprising since the condensation of inorganic pyrophosphate, which may form quite rapidly in the homogeneous system, with either GDP or GTP, would lead directly to higher guanosine polyphosphates.

In view of these unsatisfactory results[9] the aqueous pyridine solvent system was investigated in more detail. As in previous work, many experiments were performed in which the proportion of the reactants, pyridine–water ratio and reaction time were varied. The results of three selected experiments are shown in Table I. In no experiment was a completely satisfactory yield of GDP and GTP[10] obtained. The best yield was about 25% each of GDP and GTP, representing a total of about 50% conversion of GMP to the desired products. These conditions were used on a preparative scale.[11]

The main problem in isolating nucleoside di- and triphosphates synthesized by the present method is the separation of the nucleotides from the inorganic polyphosphates. In the adenosine series, ADP and ATP were precipitated as mercury salts with Lohmann reagent. In the uridine series, the removal of the inorganic phosphates was accomplished by repeated precipitation of the free nucleotides from alcohol–ether mixtures. Neither of

(5) R. H. Hall and H. G. Khorana, THIS JOURNAL, **76**, 5056 (1954).
(6) For selected references see ref. 1.
(7) C. W. Paar, *Biochem. J.*, **56**, xxvii (1954).

(8) This will be so, especially, when homogeneous reaction mixtures are employed. In aqueous pyridine, the higher polyphosphates are, probably, removed from the reaction phase (see above) because of their greater insolubility.

(9) Attempts were also made to hydrolyze partially the higher guanosine 5′-polyphosphates to GDP and GTP by heating the reaction mixture at *p*H 4.5 and 100° as described by Lieberman [THIS JOURNAL, **77**, 3373 (1955)]. However, large amounts of GMP were formed and the yields were only slightly better than in the unhydrolyzed reaction mixture. The polyphosphates appeared to be stable on heating in 0.5 *N* sodium hydroxide at 100° for 1 hour.

(10) The optimum reaction time appeared to be 67–72 hours. Long reaction periods were also found necessary by Kennedy for the synthesis of cytidine diphosphate choline and related compounds [E. P. Kennedy, *J. Biol. Chem.*, **222**, 185 (1956)]. This also is due probably to the low solubility of the phosphate esters in the pyridine phase.

(11) The aqueous pyridine system required longer reaction time and much larger quantities of DCC than dimethylformamide reaction mixtures. However, the aqueous pyridine system was selected for the preparative scale since difficulty was experienced in obtaining clean ion-exchange separation of the products from the dimethylformamide runs (see Experimental).

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these methods was completely satisfactory, however, since they were attended by large losses of the nucleotides. A mild and general method for the above purpose utilizes the selective adsorption of the nucleotides by charcoal. The use of charcoal for the separation of nucleotides from salts and inorganic phosphates has previously been recorded by a number of workers[12] and the method was used successfully in the present work.[13] However, some irreversible adsorption of the nucleotides occurred and best recoveries, after trials with different kinds of charcoal and eluting agents, were about 65%.

Using charcoal purification in conjunction with ion-exchange chromatography, pure samples of GDP and GTP were obtained in about 10% overall yield, representing a 20% conversion of GMP to the desired compounds. The ultraviolet absorption spectra of the synthetic samples and their behavior on paper chromatography, paper electrophoresis and ion-exchange chromatography were identical with samples of GDP and GTP isolated from yeast.[14] Furthermore, both samples were biologically active in the assay system developed by Ayengar, *et al.*[14] Elemental analysis indicated that GDP, precipitated as the barium salt at an acidic *p*H, was best represented by the formula GDP·$Ba_{1/2}$·$3H_2O$ while dibarium GTP appeared to be the hexahydrate.[15]

While the yields of GDP and GTP were somewhat disappointing this work represents the first chemical synthesis of these newly discovered nucleoside polyphosphates. Furthermore the present experiments together with the independent work reported from other laboratories[16] serve to illustrate the general scope of the carbodiimide method in the synthesis of biologically important "anhydrides." It also seems clear that one limitation of the technique is the contrasting solubility properties of DCC, on the one hand, and the nucleotides and related compounds on the other, in aqueous pyridine. Nevertheless this is the only solvent system which has proved satisfactory so far. It might be expected that the situation would be improved in some cases by using a water-soluble carbodiimide. Experiments on the use of such reagents will be reported in a forthcoming communication.[13b]

Experimental

The Reaction of GMP and Phosphoric Acid with DCC. (a) In Dimethylformamide.—A series of experiments was carried out as follows: GMP (5 mg. of the free acid)[17] was dissolved in 0.4 ml. of freshly distilled dimethylformamide and the solution cooled to 0°. Five microliters (*ca.* 5 equiv.) of 85% phosphoric acid and 58 mg. of DCC were added and the resulting clear solution allowed to stand at 0° for various lengths of time. The reaction was stopped by the addition of water. Dicyclohexylurea was removed by filtration, washed three times with small portions of water and the combined filtrate adjusted to *p*H 8 with ammonium hydroxide. The solution was evaporated under reduced pressure, the residue taken up in water, the solution filtered and re-evaporated. The process was repeated once again to ensure complete removal of dimethylformamide. The clear aqueous solution finally obtained was readjusted to *p*H 8 and diluted to 5 ml. For quantitative analysis, 2 ml. of this solution was allowed to pass slowly through a column (2 cm. long, 0.8 cm. diameter) of Dowex 2 (chloride form) and the column washed with water. Elution of the products was carried out stepwise with the following solutions: GMP with 0.01 *N* HCl + 0.015 *M* NaCl; GDP with 0.01 *N* HCl + 0.1 *M* NaCl; GTP with 0.01 *N* HCl + 0.2 *M* NaCl; higher phosphates with 2 *N* HCl. Five-ml. fractions were collected, maintaining an average flow rate of 0.5 ml./min. The optical density of each fraction was determined at 260 mμ. The results of these experiments are shown in Table I.

TABLE I

REACTION OF GMP AND PHOSPHORIC ACID WITH DCC

Conditions				Products[a]			
Solvent	H_3PO_4[b]	DCC[b]	Time (hr.)	GMP	GDP	GTP	Higher phosphates
DMF	5	20	0.5	58	18	17	7
DMF	5	20	0.75	13	17	30	42
DMF	5	20	1.0	7	14	23	55
Pyridine–water ratio							
4:1[c]	5	50[e]	24	64	14	13	9
6:1[d]	12	60	49	48	25	17	10
10:1	5	100[f]	67	28	26	25	20

[a] Expressed as percentages of the total optical density recovered from the column. [b] Equivalents based on GMP used. [c] Homogeneous reaction mixture. [d] These conditions are identical to those reported for the preparation of ADP and ATP (experiment 5, Table II[4]). [e] 10 equiv. at first, 10 equiv. each after 2, 4, 7 and 9 hours. [f] 40 equiv. at first, 40 equiv. DCC + 0.1 ml. water after 24 hours; 20 equiv. DCC + 0.1 ml. H_2O after 48 hours.

(b) In Aqueous Pyridine. General Method.—Monopyridinium[18] GMP (63 mg.)[19] was dissolved in an appropriate amount of water and enough pyridine was added to bring the solution to the desired pyridine–water ratio. The final volume of the solvent was 7 ml. in all of the reactions. Orthophosphoric acid (85%) and DCC were added as indicated in Table I and the mixture was shaken vigorously for the specified length of time. The reaction mixture was worked up as described above for the dimethylformamide reactions. Aliquots (0.3 ml.) were analyzed on the same size ion-exchange columns as described above, but using a linear gradient elution technique.[7,20,21] The mixing flask contained 500 ml. of 0.003 *N* hydrochloric acid while the reservoir contained an equal volume of 0.5 *M* sodium chloride solution in 0.003 *N* hydrochloric acid.

The results of the experiments using aqueous pyridine are given in Table I.

Isolation of GDP and GTP.—Monopyridinium GMP (635 mg.) was dissolved in 6 ml. of water and 60 ml. of py-

(12) (a) G. A. LePage and G. C. Mueller, *J. Biol. Chem.*, **180**, 775 (1949); (b) E. Cabib, L. F. Leloir and C. E. Cardini, *ibid.*, **203**, 1055 (1953); (c) R. K. Crane and F. Lipman, *ibid.*, **201**, 235 (1953); (d) D. Lipkin, P. T. Talbert and M. Cohn, THIS JOURNAL, **76**, 2871 (1954).

(13) The method also has been used successfully in subsequent work on the synthesis of nucleoside polyphosphates: (a) A. Kornberg, unpublished work on thymidine polyphosphates; (b) M. Smith and H. G. Khorana, unpublished work on the use of water-soluble carbodiimides in the synthesis of nucleoside polyphosphates.

(14) P. Ayengar, D. M. Gibson, C. H. Lee Peng and D. R. Sanadi, *J. Biol. Chem.*, **218**, 521 (1956). We are grateful to Dr. Sanadi for the enzymatic tests on our synthetic samples and for the gift of a sample of GTP isolated from yeast.

(15) Since GTP was contaminated by a small amount of GDP, the assignment of the exact degree of hydration cannot be conclusive.

(16) (a) E. P. Kennedy (footnote 10); (b) F. M. Huennekens and G. L. Kilgour, THIS JOURNAL, **77**, 6716 (1955); (c) P. T. Talbert and F. M. Huennekens, *ibid.*, **77**, 4671 (1956); (d) P. Berg, unpublished work on the synthesis of α-aminoacyladenylic acids.

(17) Prepared by shaking the barium salt with Dowex-50 (H^+), removing the resin by filtration, lyophilizing to a dry powder and washing the solid three times with anhydrous ether.

(18) Prepared by shaking an aqueous suspension of the barium salt with pyridinium Dowex-50, removing the resin by filtration and lyophilizing to a dry powder.

(19) Small scale reactions such as described using dimethylformamide as the solvent, were not satisfactory because of the difficulty in maintaining vigorous agitation of the heterogeneous reaction mixtures.

(20) See also R. M. Bock and N. Ling, *Anal. Chem.*, **26**, 1543 (1954), for a description of the apparatus.

(21) The gradient elution technique did not give satisfactory results with dimethylformamide–water mixtures.

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ridine was added, followed by phosphoric acid (0.5 ml. of 85%) and DCC (11.6 g.). The two phase reaction mixture was agitated vigorously using a mechanical shaker. After 24 hours, 11.6 g. of DCC and 1 ml. of water were added and the shaking was continued. A final addition of DCC (5.8 g.) and water (1 ml.) was made after 50 hours. After a total reaction time of 72 hours, the mixture was worked up as described above for the small scale experiments except that the filtrate and washings obtained after removal of the dicyclohexylurea were extracted twice with ether to remove a small amount of unchanged DCC. The clear aqueous solution (50 ml.; total optical density in 0.003 *N* hydrochloric acid at 260 mμ, 13,800 units) was adjusted to *p*H 2.8 (*p*H meter) with hydrochloric acid and to it were added five 0.5-g. portions of charcoal,[22] the solution being stirred for three minutes after each addition. After the final addition, the suspension was stirred for ten minutes and the charcoal was then collected by filtration through Celite. The total filtrate (optical density, 2570 units at 260 mμ) was treated in a similar manner with five 0.2-g. portions of charcoal and the charcoal collected again on the first filter bed. The filtrate (1000 optical density units) was retreated with 2 × 0.1 g. of charcoal. The final filtrate contained 200 optical density units and was discarded (total absorption, 97%). The total charcoal was washed free of inorganic phosphates by suspending it three times in 100-ml. portions of 0.003 *N* hydrochloric acid.[23] The total acidic filtrate (1640 optical density units) was treated twice with 0.3-g. portions of charcoal and the filtration and washing repeated. The nucleotidic material was recovered by batchwise elution of the charcoal with an ethyl alcohol–ammonia–water mixture.[12b] The combined eluates were concentrated using a Craig flash evaporator at bath temperature below 30°. The concentrated solution was filtered to remove a small amount of charcoal and some insoluble material. The *p*H of the filtrate (63 ml., containing 8760 optical density units; 64% recovery) was adjusted to 8.5 with ammonium hydroxide and the solution passed through a Dowex-2 (chloride form, 200–325 mesh) column (7 cm. high, 2.2 cm. diameter) at a flow rate of 1 ml./min. The column was washed with water (flow rate 4 ml./min.) until the optical density of the effluent dropped below 0.200 (total water wash, 180 ml. containing 35 optical density units). The nucleotides were eluted in a stepwise manner as follows. One hundred ml. fractions were collected and immediately adjusted to *p*H 7. Eluents were changed when the optical density of the effluent fell below 0.2. GMP with 0.003 *N* HCl + 0.015 *M* sodium chloride (1500 ml. containing 2460 optical density units; 28% of the total optical density applied to the column); GDP with 0.003 *N* HCl + 0.1 *M* sodium chloride (900 ml. containing 2182 optical density units, 25%); GTP with 0.003 *N* HCl + 0.2 *M* sodium chloride (1400 ml. collected, after discarding the first 500 ml., total optical density recovered, 2058 units, 23%); higher phosphates with 2 *N* HCl (800 ml. containing 1649 optical density units, 19%). Recovery of the optical density from the column was quantitative.

GDP and GTP fractions were concentrated to about 30 ml. using a flash evaporator (bath temperature, under 30°), the concentrate readjusted to *p*H 7 and lyophilized.

(22) Nuchar C was treated as described by D. Lipkin, P. T. Talbert and M. Cohn, THIS JOURNAL, **76**, 2871 (1954), for Darco G-60 except that drying was carried out at 60–70° for 48 hours.

(23) Washing with water caused excessive losses of ultraviolet absorbing material.

GDP was isolated as its barium salt by the procedure described by Hall and Khorana[5] for UDP except that 0.5 ml. of 2 *M* barium acetate was used. The product[24] after drying over phosphorus pentoxide *in vacuo* weighed 70 mg. A second crop (11 mg.) was obtained from the mother liquor by the addition of ethyl alcohol. Fifty milligrams of the first crop was dissolved in 0.7 ml. of 0.5 *N* hydrochloric acid at 0°, a small amount of insoluble material was removed by centrifugation and the *mono* barium salt was precipitated by the addition of ethyl alcohol. The product was dried over phosphorus pentoxide *in vacuo* (30 mg.) and then equilibrated with air before analysis. *Anal.* Calcd. for $C_{10}H_{14}N_5O_{11}P_2Ba_{1/2}\cdot 3H_2O$ (564.94): C, 21.26; H, 3.57; P, 10.97. Found: C, 21.30; H, 3.87; P, 11.12. The ratio of guanosine (using 12.4 × 10^3 as the E_{max} at 257 mμ): labile phosphorus:total phosphorus was 1:1:2. Paper chromatography in the four solvent systems mentioned above, paper electrophoresis (Table II) and ion-exchange chromatography showed a single ultraviolet absorbing component.

TABLE II

CHROMATOGRAPHIC AND ELECTROPHORETIC DATA

Compound[a]	R_f's in solvents III	V	VI	VII	Electrophoretic mobility[b]
GMP	0.24	0.63	0.35	0.28	8.2
GDP	.10	.75	.14	.18	14.9
GTP	.06	.78	.13	.15	16.2

[a] All the data recorded are on sodium salts prepared by shaking the barium salts with Dowex-50 sodium form and spotting the supernatant. [b] Centimeter movement toward anode in 2 hours. (For details see preceding paper.[1])

GTP was isolated as its barium salt, as described by Hall and Khorana[5] for the isolation of barium UTP, and dried over phosphorus pentoxide; 97 mg. *Anal.* Calcd. for $C_{10}H_{12}N_5O_{14}P_3Ba_2\cdot 6H_2O$ (902.02): C, 13.31; H, 2.68; P, 10.30. Found: C, 13.37; H, 3.30; P, 10.47. The ratio of labile phosphorus to total phosphorus was 2:3.

Paper chromatography, paper electrophoresis (Table II) and ion-exchange chromatography showed that the main ultraviolet absorbing component corresponded to GTP isolated from yeast.[14] A trace spot corresponding to GDP also was present. The ultraviolet spectra of synthetic GDP and GTP in 0.01 *N* hydrochloric acid were identical with that of GMP under the same conditions.

Paper Chromatography and Paper Electrophoresis.—Paper chromatography and paper electrophoresis were carried out as described in the preceding paper.[1] The solvent systems designated as III, V, VI and VII proved suitable in the present work. The R_f values and electrophoretic mobilities are listed in Table II.

Acknowledgment.—We wish to thank the National Research Council and the National Cancer Institute of Canada for grants in aid of this work.

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(24) Recovery of GDP from the salt cake was only about 60% and the material remaining on the cake could not be freed easily from the salt.

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[Contribution from the Department of Chemistry and Chemical Engineering, Stanford University]

The Beckmann Rearrangement of β-Dihydroumbellulone Oxime[1]

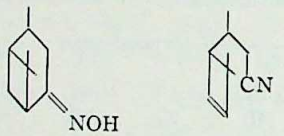
By W. Dickinson Burrows[2] and Richard H. Eastman

Received March 9, 1957

The course of the Beckmann rearrangement of the oxime of a bicyclic ketone having an α-carbon atom which is quaternary, a bridge-head and part of a cyclopropane ring system has been ascertained. The rearrangement proceeds in the usual fashion to produce a lactam, with the cyclopropyl group migrating.

Introduction

As a rule, bicyclic ketoximes having a bridge-head α-carbon atom yield, under the conditions of the Beckmann rearrangement, an unsaturated nitrile rather than the usual lactam.[3,4] One case of many[5] which is specially pertinent here is that of verbanone oxime (I)[6] which gives a poor yield of an unsaturated nitrile, presumably II.



I II

On a purely analogical basis, β-dihydroumbellulone oxime (III) might be expected to yield the cyclopropenyl nitrile IV. It gives, in fact, only the lactam V or products derived therefrom in excellent yield under a variety of rearrangement conditions.

The Structure of the Lactam.—That the product of the rearrangement was a bicyclic lactam and not an unsaturated nitrile was evident immediately from its saturated character and its infrared absorption spectrum (3.12 μ (NH), 6.04 μ (CO)), characteristic of a six-membered lactam.[7] However, the data permitted no unequivocal choice between the alternatives V and VI.[8] Accordingly the degradation of the lactam was undertaken. The attachment of the nitrogen atom to the cyclopropane ring was revealed when hydrolysis of the lactam in 50% sulfuric acid gave a nitrogen-free, saturated, *keto* acid of ten carbon atoms (V → VIII). When the keto acid was found to be 5-oxo-3,4,6-trimethylheptanoic acid (VIII) by study of its properties and further degradation, the structure assignment V to the lactam became unequivocal.

The keto acid VIII was obtained as a crystalline, dextrorotatory solid of m.p. 49.5–50°, $[\alpha]^{27}D$ +50°. In accord with the assigned structure which contains one labile (a) and one stable (b) asymmetric carbon atom, it underwent rapid mutarotation (+50° → −23°) on being dissolved in 10% potassium hydroxide solution. Furthermore, when oximation of the crystalline keto acid was carried out in pyridine a single oximino acid of m.p. 156° was obtained,[9] but when carried out in aqueous potassium hydroxide a mixture of stereoisomeric oximino acids was obtained that was separated into forms melting at 134° and 156°, the latter being identical with that from the reaction in pyridine. Oximation of the oily residue from the crystallization of the acid of m.p. 49.5–50° gave the oximino acid of m.p. 134°.

The relationship of the ketone and carboxyl groups in the keto acid VIII was demonstrated by preparation of the enol lactone IX which showed bands at 5.72 and 5.93 μ characteristic of a six-membered enol lactone,[10] yet no bands corresponding to =C—H out-of-plane deformation.[7] Permanganate oxidation of the enol lactone IX produced a keto γ-lactone assigned structure X on the basis of analysis, infrared spectrum and solubility properties. As a by-product of the oxidation, isobutyric acid was evident, and the integrity and position of the isopropyl group in the keto acid VIII was established by isolation of isobutyric acid and isopropylamine from the hydrolysis of the Beckmann rearrangement product of the aforementioned oximino acid derived from VIII.

One property of the keto acid VIII which is not at first glance in accord with its structure is its ability to produce bromoform in significant amounts in the haloform reaction. It is proposed that under the strongly alkaline conditions of the reaction, acetic acid is eliminated in a reverse Michael reaction, producing a double bond between carbon atoms a and b in formula VIII, and that the resulting α,β-unsaturated ketone, $(CH_3)_2CHCOC(CH_3)=CHCH_3$, provides acetaldehyde for the haloform reaction through retrograde aldol condensation.[11]

(1) Reported in part at the Meeting of the American Chemical Society, Dallas, Texas, April 10, 1956, Abstracts, 37N.

(2) Taken from the Doctoral Dissertation of W. D. Burrows in the Department of Chemistry, Stanford University.

(3) A. H. Blatt, *Chem. Revs.*, **12**, 218 (1933).

(4) It is to be noted that the α-carbon atom involved need not be at a bridge-head since menthone oxime gives both unsaturated nitrile and normal lactam depending on conditions [O. Wallach, *Ann.*, **277**, 157 (1893); **312**, 197 (1900)].

(5) For some other examples see A. Weiner and A. Piquet, *Ber.*, **37**, 4308 (1904); O. Wallach, *Ann.*, **315**, 289 (1901); W. H. Glover, *J. Chem. Soc.*, **93**, 1299 (1908).

(6) H. Wienhaus and P. Schumm, *Ann.*, **439**, 38 (1924.)

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 176.

(8) The preparation of the *p*-toluenesulfonate and *p*-bromobenzenesulfonate derivatives of the oxime III and their conversion to the lactam indicated structure V if it was assumed that bulk considerations required a *trans* orientation of the sulfonate group and the bridge-head connection, and that the rearrangement proceeded by the usual migration of *trans*-oriented groups.

(9) The oximino acid of m.p. 156° was found to be identical in rotatory power and infrared absorption with an oximino acid (m.p. 154°) reported earlier (R. H. Eastman and J. C. Selover, This Journal, **76**, 4118 (1954)) as an anomalous product of the nitrosation of β-dihydroumbellulone.

(10) G. I. Fujimoto and J. Prager, *ibid.*, **75**, 3259 (1953).

(11) Reversal of the aldol condensation under the conditions of the haloform test has been observed for pulegone which gives a similar anomalous positive result in the test [O. Wallach, *Ann.*, **289**, 337 (1896)]. As precedent for the retrograde Michael condensation may be cited the formation of tanacetophorone from α-tanacetonedicarboxylic ester ["The Terpenes," R. H. Eastman and C. R. Noller in Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, Vol. IV, p. 632].

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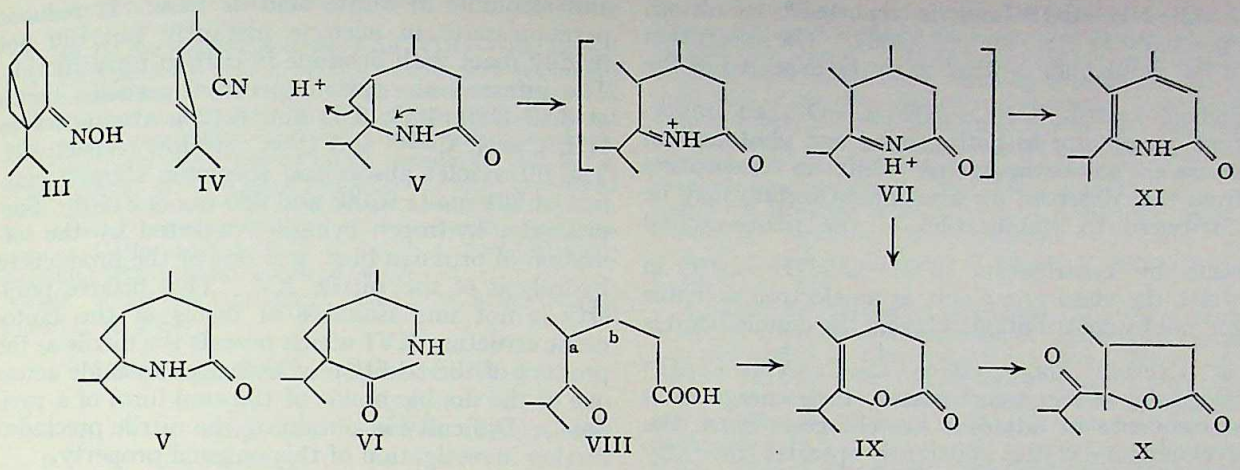
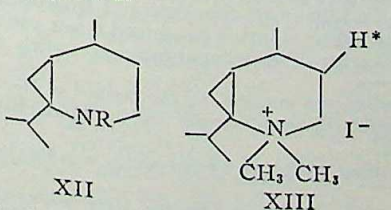


Products Derived from the Lactam.—The smooth hydrolytic degradation of the lactam V to the keto acid VIII came only at the end of a series of unsuccessful degradations whose course became clear with the structure of the lactam established. Some observations on the properties of the compounds prepared are of interest.

When the lactam V, dihydroumbellulone oxime (III) or its *p*-toluenesulfonate were heated at the steam-bath in concentrated sulfuric acid, sulfur dioxide was evolved and the pyridone XI was produced in good yield, presumably through oxidation by the sulfuric acid of the intermediate VII. In accord with the structure assigned, the pyridone (m.p. 220°) was optically inactive, weakly basic, inert to neutral permanganate and had ultraviolet maxima at 232 mμ (ε 6020), and 308 mμ (ε 6620) similar to those reported for 2-pyridone.[12] It showed one active hydrogen by the Zerevitinov method, was not reduced by lithium aluminum hydride and could be distilled through zinc dust intact.

Lithium aluminum hydride reduction of the lactam V proceeded smoothly to the bicyclic amine XII (R = H) which was cleanly methylated by the formic acid–formaldehyde method, then quaternized to XIII with methyl iodide. The ultraviolet absorption spectrum of the tertiary amine XII (R = CH_3) showed λ_{max}^{alc} 213 mμ (ε 1450) comparable to that reported[13] for 1-methylpiperidine, λ_{max}^{alc} 213 mμ (ε 1600), to be contrasted with that for 1-ethyl-2-methyl-Δ^2-tetrahydropyridine,[13] λ_{max}^{alc} 231 mμ (ε 5100), and further indicative[9] of the inability of the cyclopropane ring to act as an electron acceptor as does a vinyl group[14] in establishing a chain of conjugation.



Surprisingly, and in contradistinction to the behavior of cyclopropyltrimethylammonium hydroxide which yields cyclopropene under the conditions of the Hofmann elimination,[14a] the methiodide XIII reverted to the tertiary amine XII (R = CH_3) with loss of methanol. Failure of β-elimination to occur is not rationalized readily on steric grounds, for a nearly coplanar four-center transition state involving the starred hydrogen atom in XIII can be obtained with an approximate model of the system. The situation parallels that found for the quaternary salt of tetrahydroquinoline which also eliminates methanol under the conditions of the Hofmann degradation.[15] The two systems have in common an electron-rich, highly polarizable group attached to the quaternary nitrogen which may so diffuse the positive pole on the nitrogen as to reduce the acidity of the starred proton on the β-carbon below the level required for elimination.[16]

As a base, the secondary amine XII (R = H) (pK_B' 4.9) was 1.6 pK_B' units weaker than piperidine (pK_B' 3.3)[17] and comparable in strength with cyclopropylamine (pK_B' 5.34).[18] The low basic strength of the amine XII (R = H) relative to piperidine can as well be attributed to the base-weakening effect of the cyclopropane ring attachment[18] and a decrease in solvation of the ammonium ion on account of blocking by the isopropyl group as to any specific interaction of the bicyclic system.[19]

The lactam V, absorbing maximally at 211 mμ (ε 5190), showed only a moderate exaltation over ε-caprolactam, absorbing maximally at 208 mμ (ε 3700), definitely not of the magnitude found for the unsaturated lactam, 7-oxo-3,5,5-trimethyl-Δ^2-tetrahydroazepine which contains the system

(12) H. Specker and H. Gawrosch, *Ber.*, **75B**, 1342 (1942).
(13) N. I. Leonard and D. M. Locke, THIS JOURNAL, **77**, 438 (1955).
(14) See, however, R. J. Mohrbacher and N. Cromwell, *ibid.*, **79**, 401 (1957), for arguments to the contrary.
(14a) M. J. Schlatter, *ibid.*, **63**, 1733 (1941).
(15) H. Embde, *Ann.*, **391**, 92 (1912).
(16) E. D. Hughes and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941).
(17) The pK_B' values are apparent values obtained by titration of the amines in 50% by volume ethanol using a Beckman pH meter standardized against aqueous buffers in the manner of Roberts and Chambers (ref. 18).
(18) J. D. Roberts and Vaughan C. Chambers, THIS JOURNAL, **73**, 5031 (1951).
(19) A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1293 (1949). The difference of 1.6 in pK_B' values between the amine XII (R = H) and piperidine is only slightly greater than that of 1.0 pK_B' unit between dimethylcyclopropylamine (pK_B' 6.3) and cyclopropylamine (pK_B' 5.3) (ref. 18). The small increment may be attributed to less hindrance to solvation in the dimethyl compound than that encountered in XII (R = H).

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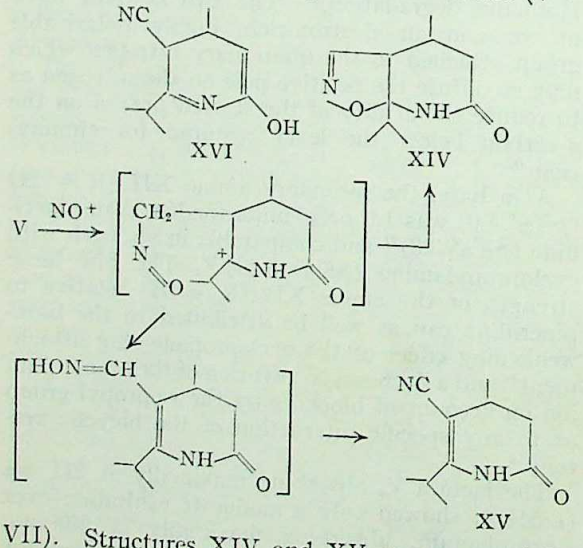
C=C—NH—COR and is reported[20] to absorb maximally at 218.5 mμ (ε 10,700). The absorption of the vinylamide is what might be expected of the dienoid system, $C{=}C{-}\overset{+}{N}H{=}C{-}O^{-}$, an important contributor to both ground and photoexcited states. The bathochromic shift in absorption from that observed for a saturated lactam may be attributed to stabilization of the photo-excited state by contribution of $\overset{-}{C}{-}C{=}\overset{+}{N}H{-}C{=}O$ in which the vinyl group acts as an electron acceptor but not by contributions wherein the double bond is an electron donor, since $\overset{+}{C}{-}C{=}\overset{+}{N}H{-}\overset{-}{C}{-}O^{-}$ would be of disproportionately high energy as a consequence of adjacent like-charges. Since the cyclopropane system apparently operates efficiently only as a donor of electrons[21] to adjacent unsaturated centers, the small shift observed is not unexpected.

Nitrosation of the lactam V either by the use of nitrogen tetroxide or nitrosyl chloride failed to produce an N-nitrosoamide for rearrangement with nitrogen elimination to the corresponding lactone according to the method of White,[22] but gave instead products resulting from attack of the nitrosating agent on the cyclopropane ring in the same sense as that envisioned for the attack of a proton in the sulfuric acid hydrolysis of the lactam (V→



VII). Structures XIV and XV are proposed for two of the products on the basis of properties and spectroscopic data. The substance assigned structure XIV was a colorless solid, m.p. 164°, which was optically active, insoluble in dilute acid or base, not readily oxidized by permanganate in acetone, and of ultraviolet absorption essentially identical with that of the lactam V. The infrared absorption spectrum showed bands characteristic[7] of the NH (3.12, 3.22), amide carbonyl (5.94) and C=N (6.21) groups.

The compound assigned structure XV was a white solid, m.p. 156°, which was optically active and insoluble in dilute acid or base. It reduced permanganate in acetone instantly but did not readily react with bromine in carbon tetrachloride. The infrared absorption spectrum revealed bands at 3.12–3.22, 4.53, 5.92 and 6.12 μ attributed[7] to NH, C≡N, C=O and C=C groups, respectively. The ultraviolet absorption spectrum showed maxima at 261 mμ (ε 9200) and 280 mμ (ε 8150). Surprisingly, hydrogen cyanide, detected by the formation of prussian blue, was one of the products of hydrolysis of the nitrile XV. This bizarre property is not unreasonable in terms of the tautomeric structure XVI which reveals the nitrile as the product of the addition of hydrogen cyanide across one of the double bonds of the enol form of a pyridone. Difficulty in obtaining the nitrile precluded further investigation of this unusual property.

Acknowledgment.—We wish to express our sincere appreciation to the Eli Lilly Co. and the Nichols Fellowship donor for their generous aid to W. D. B. during this investigation.

Experimental

The Beckmann Rearrangement of Dihydroumbellulone Oxime: Preparation of 5-Methyl-1-isopropyl-2-azabicyclo-[4.1.0]heptanone-3 (V).—Dihydroumbellulone oxime[23] (III) (14.4 g.) was dissolved in 30 ml. of dry pyridine, cooled to 0°, and added to a chilled solution of 25 g. of *p*-toluenesulfonyl chloride (or *p*-bromobenzenesulfonyl chloride), in 30 ml. of dry pyridine. The mixture was allowed to stand one hour, then heated on a steam-bath. After 20 min. of heating the mixture turned dark red and began boiling. Heating was continued another 10 min., and the reaction mixture was allowed to stand at room temperature about two hours, after which it was poured on a mixture of 25 ml. of sulfuric acid and 120 g. of ice. The product solidified in two hours and was separated and washed with cold water, leaving 10.3 g. of white, crystalline material with a soapy odor. Ether extraction of the filtrate and washings yielded another 2.7 g. The product melted at 102.2–102.7°[24] after recrystallization from cyclohexane and had $[\alpha]^{27}D$ +60 ± 1° (*l* 0.5, *c* 4, 95% ethanol); spectra[25]: λ_{max}^{alc} 211 mμ, ε 5190; λ_{max}^{mull} 3.12, 6.04 μ.

Anal.[26] Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.92; H, 10.14; N, 8.48.

Dihydroumbellulone Oxime *p*-Toluenesulfonate.—Two grams of oxime III was dissolved in 5 ml. of dry pyridine. The solution was cooled to 0° and added to a chilled solution of 4.0 g. of toluenesulfonyl chloride in 5 ml. of pyridine. After standing at room temperature for four hours the mixture was poured into 50 ml. of 3 *N* sulfuric acid, chilled and extracted with ether. Recrystallization of the product from medium boiling petroleum ether yielded 1.0 g. of white solid melting at 84.6–85.3°.

Anal. Calcd. for $C_{17}H_{23}NO_3S$: C, 63.52; H, 7.21; N, 4.36; S, 9.97. Found: C, 63.31; H, 7.41; N, 4.52; S, 10.18.

When the oxime toluenesulfonate was heated with dry pyridine a slow decomposition to tarry products was the result. The addition of concentrated hydrochloric acid to the heated pyridine solution produced a fair yield of the lactam V. Heating the toluenesulfonate with aqueous or

(20) R. S. Montgomery and G. Dougherty, *J. Org. Chem.*, **17**, 823 (1952).

(21) See refs. 9, 14 and R. H. Eastman and S. K. Freeman, This Journal, **77**, 6642 (1955).

(22) E. H. White, *ibid.*, **77**, 6008, 6014 (1955).

(23) The oxime was prepared by the method of H. Wienhaus and K. T. Todenhöfer, *Schimmel's Report*, 285 (1929), and had m.p. 72–73° (reported 72°).

(24) All melting points were observed on a calibrated Kofler hot-stage.

(25) Ultraviolet absorption spectra were observed on alcohol solutions unless otherwise noted, using a Beckman DU instrument. The instrument was balanced by varying the slit width, readings were taken at no greater than 5-mμ intervals and the photomultiplier attachment was used below 220 mμ. Infrared absorption spectra were obtained using the Perkin–Elmer model 21 instrument equipped with the rock-salt prism.

(26) Analyses by Microtech Laboratories, Skokie, Ill., and Chas. Campbell Specialties, Berkeley, Calif.

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ethanolic potassium hydroxide produced dihydroumbellulone as the major product.

5-Oxo-3,4,6-trimethylheptanoic Acid (VIII).—The lactam V (10.0 g.) dissolved in 60 g. of 50% sulfuric acid was heated on a steam-bath for six hours. The reaction mixture was poured on ice, made basic with sodium hydroxide, extracted with ether, reacidified, and extracted with chloroform. The chloroform was removed under vacuum leaving 9.0 g. of pale-yellow, odorless oil, about 25% of which crystallized when diluted with one volume of hexane and chilled to −10°. The material melted at 49.5–50° after recrystallization from hexane; $[\alpha]^{27}D$ +50 ± 0.5° (*l* 0.5, *c* 4, 95% ethanol); spectrum: λ_{max}^{mull} 5.82 (sh.), 5.85, 6.04 (sh.) μ.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.47; H, 9.75. Found: C, 64.71; H, 9.89.

MUTAROTATION OF THE KETO ACID VIII

Time, hr.	Base	Concn. of XIII, g./100 ml.	$[\alpha]D$ (28–30°)
0	5% $NaHCO_3$	4	58°
0.5	11% KOH	4.5	− 7.5
2	11% KOH	4.5	−20
24	11% KOH	4.5	−23

The oxime was prepared by refluxing 0.25 g. of the crystalline keto acid, 0.25 g. of hydroxylamine hydrochloride, 2 ml. of dry pyridine and 2 ml. of absolute alcohol two hours on a steam-bath. The solvents were evaporated in a current of air, and the residue was stirred with 5 ml. of cold water until the oxime crystallized. After recrystallization from 50% ethanol–water, the oxime melted at 154–156° and had $[\alpha]^{26}D$ +6.9 ± 0.1° (*l* 0.5, *c* 4, 95% ethanol). The liquid portion of the lactam hydrolysate similarly treated yielded an oxime melting at 132–134° after repeated recrystallizations. The latter was submitted for combustion analysis.

Anal. Calcd. for $C_{10}H_{19}NO_3$: C, 59.66; H, 9.52. Found: C, 59.88; H, 9.60.

To 5.0 g. of a mixture of both oximes of VIII dissolved in 15 ml. of dry pyridine was added a chilled solution of 6.0 g. of toluenesulfonyl chloride in 15 ml. of pyridine. The resulting solution was allowed to stand 45 min., then heated 30 min. on a steam-bath, after which it was poured on a mixture of 25 g. of concentrated sulfuric acid and ice. Extraction with ether and evaporation of the solvent left 4.5 g. of very thick, red sirup, which was hydrolyzed, without purification, by boiling it with 50% sulfuric acid for 4 hours. The hydrolysis mixture was extracted with ether, the aqueous portion was set aside and the ether extract was distilled at atmospheric pressure, then redistilled at 20 mm. into two fractions. The low-boiling fraction was shown to be isobutyric acid by its odor, infrared spectrum and index of refraction. The high-boiling fraction was not characterized.

The aqueous portion from the hydrolysis was made strongly basic with 50% sodium hydroxide and was immediately steam distilled into 10% hydrochloric acid, about 50 ml. of distillate being collected. The distillate was evaporated to dryness, leaving 0.5 g. of red, hygroscopic solid. This material was decolorized with Norit in absolute ethanol and left in a drying pistol two hours at 100° and 20 mm. The dry, colorless solid melted at 136–139° dec. in a sealed capillary and was thereby identified as isopropylamine hydrochloride.

2-Oxo-4,5-dimethyl-6-isopropyl-3,4-dihydropyran (IX).—Two grams of the keto acid VIII was refluxed for five hours with 6 ml. of acetic anhydride. The acetic acid and most of the acetic anhydride were then distilled off, and the residue was dissolved in ether and extracted with sodium carbonate solution. The ether solution was evaporated and the residual oil was distilled at 15–20 mm. with bath temperature near 125°, yielding 1.2 g. of colorless, fragrant oil. The oil, purified by liquid–vapor partition chromatography, had $n^{24}D$ 1.4583; spectrum, λ_{max}^{film} 5.72, 5.93 μ.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.49; H, 9.42.

One gram of enol lactone IX was suspended in 25 ml. of water with 2 g. of sodium bicarbonate in a 100-ml. r.b. flask equipped with a mechanical stirrer, and 1.25 g. of potassium permanganate was added in small portions. The color produced by 0.1 g. of additional permanganate was not dispelled after one hour of stirring. The reaction mixture was filtered through Celite and the manganese dioxide cake was washed with water. Filtrate and washings were acidified to *p*H 1 with sulfuric acid, resulting after 20 min. in the separation of an oil. The oil was extracted with chloroform and the extract was distilled at 20 mm. with bath temperature near 125° to yield 0.5 g. of colorless oil with a camphor-like odor. The product, purified by liquid–vapor partition chromatography, had $n^{20.2}D$ 1.4519, and is assigned the structure of β,γ-dimethyl-γ-isobutyryl-γ-butyrolactone (X); spectrum, λ_{max}^{film} 5.65, 5.86 μ.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.84; H, 8.67.

4,5-Dimethyl-6-isopropyl-2-pyridone (XI).—Five grams of lactam V was dissolved in 25 ml. of concentrated sulfuric acid and heated on a steam-bath one hour. The reaction mixture was poured on 100 g. of ice and extracted with ether to remove acidic and neutral material. The aqueous portion was diluted with water to 250 ml., made basic with sodium carbonate, and continuously extracted four days with ether. Most of the product crystallized out on the sides of the ether reservoir, and by evaporation of the solvent there was obtained 1.63 g. of white, crystalline solid melting at 219–220° with rapid sublimation and having $[\alpha]D$ 0.0 ± 0.2° (*l* 0.5, *c* 4, chloroform); spectra, λ_{max}^{alc} 232 mμ (ε 5190), 308 mμ (ε 6620); λ_{max}^{mull} 3.20 (sh.), 6.03, 6.50 μ.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.70; H, 9.15. Found: C, 72.98; H, 9.08.

Dihydroumbellulone oxime (III), treated with sulfuric acid as described above for the lactam V, gave a 12% yield of the pyridone.

5-Methyl-10-isopropyl-2-azabicyclo[4.1.0]heptane (XII, R = H).—To 20 g. of lactam V in 750 ml. of absolute ether was added in small portions 12 g. of lithium aluminum hydride. The mixture was refluxed gently for five hours, then allowed to stand at room temperature 12 hours, and finally decomposed with 100 ml. of ethanol followed by 100 ml. of water. The ether was decanted and the residual hydroxides were washed with several hundred milliliters of absolute ether. The ethereal portions were combined, evaporated on a steam-bath, and the residual product was distilled, yielding 11.1 g. of colorless oil with an odor like crushed geraniums, boiling at 35–35.5° at 2–3 mm., $[\alpha]^{24}D$ +108.5 ± 0.5° (*l* 0.5, neat), d^{20}_4 0.864, $n^{20}D$ 1.4561.

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.35; H, 12.50; N, 9.15. Found: C, 78.44; H, 12.31; N, 9.18.

The picrate, m.p. 164.5–166.5° (Found: C, 50.42; H, 5.91), and the benzenesulfonamide, m.p. 98.8–99.8° (Found: C, 65.58; H, 7.86), were prepared in the usual ways.

2,5-Dimethyl-1-isopropyl-2-azabicyclo[4.1.0]heptane (XII, R = CH_3).—To 4.8 g. of reduced lactam (XII, R = H) were added, with cooling, 4.5 g. of 85% formic acid and 3.0 g. of 36–38% formaldehyde. The solution was allowed to stand overnight, then heated two hours on a steam-bath, after which 3 ml. of concentrated hydrochloric acid was added. The mixture was evaporated on a steam-bath to remove excess formaldehyde and formic acid. The residue was diluted with several volumes of water, made strongly basic with 20% sodium hydroxide, and steam distilled. The distillate was made strongly basic with solid potassium hydroxide, extracted with ether, and the extract was distilled without ebullator to give in about 50% yield a colorless oil boiling at 57–59° at 7 mm., $[\alpha]^{24}D$ +34.4 ± 0.1° (*l* 0.5, neat), d^{27}_4 0.867, $n^{20}D$ 1.4578.

Anal. Calcd. for $C_{11}H_{21}N$: C, 78.96; H, 12.65; N, 8.38. Found: C, 78.86; H, 12.40; N, 8.44.

The picrate, m.p. 160–165° dec., was prepared by adding the amine to a hot, saturated solution of picric acid in ethanol.

The methiodide XIII was prepared by refluxing 0.51 g. of XII, R = CH_3, with a fivefold excess of methyl iodide. The product (0.58 g.), recrystallized from methanol, decomposed above 280° and had $[\alpha]^{25}D$ −29.2 ± 0.4° (*l* 0.5, *c* 5, methanol).

Anal. Calcd. for $C_{12}H_{24}NI$: C, 46.60; H, 7.82. Found: C, 46.49; H, 7.96.

The Hofmann elimination was attempted by boiling this methiodide (0.10 g.) under reflux with 10 ml. of 50% sodium hydroxide solution for 10 minutes followed by steam dis-

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tillation of the oil which had separated. The oily layer from the steam distillate was identical in infrared absorption characteristics with the tertiary amine XII, R = CH_3.

Nitrosation of the Lactam V with Nitrogen Tetroxide.—Five grams of lactam dissolved in 25 ml. of glacial acetic acid was chilled to 0° and saturated with dry nitrogen tetroxide. After standing one hour at room temperature the solution was poured on 100 g. of ice. A yellow solution resulted which turned red-brown when made basic with 50% sodium hydroxide. The basic solution was extracted with ether and the aqueous portion was set aside. In the best run, evaporation of the ether extract left about 0.25 g. of white, crystalline solid melting at 162–164° after recrystallization from ethyl acetate. The solid had $[\alpha]^{26}D$ +288 ± 5° (*l* 0.5, *c* 4, 95% ethanol), and is assigned structure XIV; spectrum, λ_{max}^{mull} 3.12, 3.22, 5.94, 6.21 μ.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22. Found: C, 61.33; H, 8.33.

The aqueous portion from the extraction was acidified with concentrated sulfuric and extracted with ether. The extract was evaporated on a steam-bath to remove ether, then under reduced pressure to remove acetic acid. A black tar remained that slowly crystallized to yield 0.75 g. of white needles melting at 155–156° after recrystallization from ethanol–water; $[\alpha]^{26}D$ −104 ± 5° (*l* 0.5, *c* 4, 95% ethanol). This compound is assigned structure XV; spectra: λ_{max}^{alc} 261 mμ (ϵ 9200), 280 mμ (ϵ 8150); λ_{max}^{mull} 3.12, 4.52, 5.92, 6.12 μ.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.71; H, 7.88; N, 15.55.

When the nitrile XV (0.20 g.) was warmed for 15 minutes with 10 ml. at 10% sodium hydroxide a colorless solution was obtained. Acidification of the hydrolysis mixture caused an oil to separate and when this oil was dissolved in dilute sodium bicarbonate solution, carbon dioxide and hydrogen cyanide, detected by the formation of prussian blue, were evolved.

STANFORD, CALIF.

[CONTRIBUTION FROM THE RESEARCH CENTER, HERCULES POWDER CO.]

Synthesis of Poly-β-alanine from Acrylamide. A Novel Synthesis of β-Alanine[1]

BY DAVID S. BRESLOW, GEORGE E. HULSE AND ALBERT S. MATLACK

RECEIVED MARCH 15, 1957

Poly-β-alanine has been prepared by the base-catalyzed polymerization of acrylamide. By fractionation samples with weight-average molecular weights as high as about 80,000 have been prepared. Acid hydrolysis of the polymer constitutes a simple preparation of β-alanine in yields of 90% starting with acrylamide. Substituted acrylamides and analogous sulfonamides yield polymers of much lower molecular weight. An unusual mechanism for the polymerization is proposed.

Poly-β-alanine has been prepared previously by the elimination of HX from a β-alanine derivative, $H_2NCH_2CH_2COX$, where X is NH_2,[2] OC_2H_5,[3] Cl[4] or OH,[5] or by the elimination of thiophenol and carbon dioxide from N-carbothiophenyl-β-alanine.[6] It is questionable whether any of these methods give high molecular weight polymers.[7] Poly-β-alanine has now been prepared by the base-catalyzed polymerization of acrylamide, a readily available compound.

Preparation of Polymers.[9]—Poly-β-alanine formed a mixture of water-soluble and water-insoluble polymers when acrylamide, usually in an inert diluent, was contacted with a strong base in the presence of an inhibitor for radical-induced polymerization. The technique of polymerization was similar in most cases, typical examples being given in the Experimental section.

The effects of certain variables on the polymerization are shown in Table I.

The highest molecular weight water-insoluble polymer was obtained in pyridine. The largest amount of water-insoluble polymer was formed in the absence of solvent. Phenyl-β-naphthylamine was superior to hydroquinone as a radical inhibitor, presumably because hydroquinone acted as a chain terminator for basic polymerization. It was possible to carry out small-scale preparations without an inhibitor, but in larger runs the presence of an inhibitor was advantageous. Sodium *t*-butoxide in *t*-butyl alcohol appeared to be the best catalyst; apparently the alcohol did not terminate polymer chains. Dilution lowered the yield and molecular weight of water-insoluble polymer somewhat.

Properties of Poly-β-alanine.—Each polymerization yielded a spectrum of products with fractions soluble in pyridine, fractions soluble in water and fractions soluble only in solvents such as formic acid being obtained. The pyridine-soluble material consisted largely of monomer and dimer, the latter analyzing reasonably well for CH_2=CH-$CONHCH_2CH_2CONH_2$. This polymerized much like acrylamide itself on addition of base.

Both the water-soluble and the water-insoluble polymers were highly crystalline, melting at about 325° and about 340°, respectively, with considerable decomposition. Both gave the same well-defined X-ray diffraction pattern, the water-insoluble polymer being somewhat more crystalline than the water-soluble. The lattice spacings of 4.6, 3.9 and 3.55 Å. had relative intensities of 60, 10 and 100, respectively, for the water-insoluble polymer.

The water-insoluble polymer showed typical polyamide solubility. Thus, it was soluble in for-

(1) Presented at the 131st Meeting of the American Chemical Society, Miami, Florida, April, 1957.

(2) A. P. N. Franchimont and H. Friedman, *Rec. trav. chim.*, **25**, 80 (1906).

(3) E. Abderhalden and F. Reich, *Z. physiol. Chem.*, **178**, 169 (1928).

(4) M. Frankel, Y. Liwschitz and A. Zilkha, *Experientia*, **9**, 179 (1953); THIS JOURNAL, **76**, 2814 (1954).

(5) J. S. Chirtel and A. M. Mark, U. S. Patent 2,691,643 (1954).

(6) J. Noguchi and T. Hayakawa, THIS JOURNAL, **76**, 2846 (1954).

(7) Noguchi and Hayakawa reported a molecular weight of 43,500 for their sample of poly-β-alanine. However, their intrinsic viscosity of 0.063 in formic acid is remarkably low for this molecular weight. Recently Weymouth[8] has shown that several polypeptides made by this procedure have relatively low molecular weights, of the order of 1000–5000.

(8) F. J. Weymouth, *Chem. & Ind.*, Brit. Inds. Fair Rev., April, 1956, R34.

(9) D. S. Breslow, British Patent 736,461 (1955); U. S. Patent 2,749,331 (1956).

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TABLE I

THE BASE-CATALYZED POLYMERIZATION OF ACRYLAMIDE[a]

Solvent	Catalyst	Inhibitor[b]	Temp., °C.	Yield, % Sol.	Yield, % Insol.	Specific viscosity[c] Sol.	Specific viscosity[c] Insol.
t-Butanol	*t*-C_4H_9ONa[d]	HQ	83	39	8	0.307(P)	
						.202(W)	
Acetonitrile	CH_3ONa[e]	HQ	82	67	19	.150(A)	0.193(A)
Benzene	CH_3ONa[f]	HQ	80	48		.171(W)	
Dioxane	*t*-C_4H_9ONa[d]	HQ	100	28	13	.222(P)	0.293(A)
						.210(A)	
Quinoline	*t*-C_4H_9ONa[d]	HQ	200		55		0.234(A)
							.151(F)
Pyridine	*t*-C_4H_9ONa[d]	HQ	100	28	39	.196(P)	.316(P)
Pyridine	*t*-C_4H_9ONa[d]	DBHQ	100	70	0		
Pyridine	*t*-C_4H_9ONa[d]	PBNA	100	36	48		1.03(A)
							0.658(F)
Pyridine	*t*-C_4H_9ONa[d]	Q	100	69	17		0.91(A)
Pyridine	*t*-C_4H_9ONa[d]	None	100	48	29		1.03(A)
Dioxane	Na[f]	PBNA	100	30	4		0.88(A)
Pyridine	$NaNH_2$[g]	PBNA	100	44	12		.63(F)
None	*t*-C_4H_9ONa[h]	PBNA	[k]		65		.242(F)
Pyridine[i]	*t*-C_4H_9ONa[d]	PBNA	100		47		.636(F)
Pyridine[j]	*t*-C_4H_9ONa[d]	PBNA	100		21		.567(F)

[a] Runs were made with 10 g. of acrylamide in 100 ml. of solvent for 18 hr. [b] 0.1% hydroquinone (HQ), 0.2% phenyl-β-naphthylamine (PBNA), 0.2% di-*t*-butylhydroquinone (DBHQ) and 0.2% quinone (Q) were used. [c] Determined as 1% solutions in phenol at 100° (P) or at 25° in 90% formic acid (F), anhydrous formic acid (A) or water (W). [d] 0.46 g. [e] 0.5 g. [f] 0.1 g. [g] 0.2 g. [h] 0.1 g. of sodium in 10 ml. of *t*-butyl alcohol, then solvent removed *in vacuo*. [i] 40 ml. [j] 300 ml. [k] Uncontrolled reaction.

mic acid, dichloroacetic acid, phenol containing 11% water and concentrated aqueous salt solutions. It was also soluble in phenol at 100°, in boiling ethylene glycol and in boiling glycerol. Viscosities were higher in anhydrous formic acid than in 90% formic acid; this behavior has been observed with other polyamides.[10]

Poly-β-alanine has been prepared with weight-average molecular weights of about 80,000 (by light scattering in 90% formic acid). The molecular weight of the water-insoluble polymer could be raised by solution and reprecipitation. Thus, a sample of molecular weight 58,000, corresponding to a 1% specific viscosity of 0.500 and an intrinsic viscosity of 0.416 (both in 90% formic acid), after solution in formic acid and precipitation by water, had a molecular weight of 76,000, corresponding to a specific viscosity of 0.639.

Structure of Poly-β-alanine and the Mechanism of Polymerization.—Acrylamide might polymerize with base in a manner analogous to that of methacrylonitrile[11]; the product would then be polyacrylamide. That the polymer was essentially linear poly-β-alanine was proved by hydrolysis of the polymer with 50% sulfuric acid. This constitutes a convenient synthesis of β-alanine from acrylamide, a readily available starting material, in essentially one step, since it is only necessary to heat acrylamide with a base and hydrolyze the reaction mixture. Yields of about 90% based on acrylamide can be obtained.[12]

The presence of an olefinic double bond as an end group in poly-β-alanine was shown by both hydrogenation and polarographic reduction. However, in the absence of data on the number-average molecular weight of these polymers, the presence of some alkoxy end groups cannot be ruled out entirely. The presence of a $-CONH_2$ end group was shown by carrying out a hydrolysis with hydrochloric acid and determining the ammonium chloride formed.

Two alternative modes of initiation must be considered for the base-catalyzed polymerization of acrylamide.

$$CH_2{=}CHCONH_2 + B^- \rightleftharpoons CH_2{=}CHCONH^\ominus + BH \quad (1)$$

$$CH_2{=}CHCONH_2 + B^- \rightleftharpoons B{-}CH_2\overset{\ominus}{C}HCONH_2 \rightleftharpoons B{-}CH_2CH_2CONH^\ominus \quad (2)$$

Equation 1 is preferred as the major source of initiation for several reasons. One is the olefinic end group found in the polymer. More important, however, is the isolation of the unsaturated dimer from the reaction mixture. If initiation were by equation 2, B-$CH_2CH_2CONH_2$ should be present and none was found. It must be admitted, however, that the unsaturated dimer could be formed from equation 2 by a scheme such as the following, the proton migrating in a *quasi* six-membered ring.

$$B{-}CH_2CH_2CONH^\ominus + CH_2{=}CHCONH_2 \longrightarrow B{-}CH_2{-}CHCO(NH)\ (H^\ominus)\ H_2NOC{-}CH{-}CH_2 \longrightarrow CH_2{=}CHCONHCH_2CH_2CONH_2 + B^- \quad (3)$$

Two possible methods of growth must be considered, too. One would involve a continuation of the process depicted in the first part of reaction sequence 3, the anion transferring its charge from carbon to nitrogen as shown in equation 2, and

(10) J. R. Schaefgen and C. F. Trivisonno, THIS JOURNAL, 73, 4580 (1951).
(11) R. G. Beaman, *ibid.*, 70, 3115 (1948).
(12) A. S. Matlack, U. S. Patent 2,672,486 (1954).

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TABLE II

BASE-CATALYZED POLYMERIZATION OF OTHER MONOMERS[a]

Monomer	Solvent	Inhibitor[b]	Yield, %[c]	% N in end group	Specific viscosity[d]	Physical properties, m.p., °C.
Methacrylamide[e]	*t*-Butanol	HQ	9	0.28		
Methacrylamide[e]	Dioxane	HQ	36	0.81	0.100(A)	257 d.
Methacrylamide[f]	None	PBNA	39		.092(A)	
Crotonamide[g]	Pyridine	HQ	69	1.32	.072(F)	
Crotonamide[f]	None	PBNA	55		.066(F)	>300 d.
3,4,5,6-Tetrahydrobenzamide[h]	None	PBNA	100	4.28		Brown resin
Methylenebisacrylamide[i]	Pyridine	PBNA	100			Insol., infus.
Ethylenesulfonamide[f]	None	PBNA	85		.079(D)	Soft. 100–160
2-Propene-1-sulfonamide[j]	None	PBNA	39		.060(D)	Soft. 130
Ethylenesulfonanilide[k]	None	PBNA	57		.022(D)[k]	270 d.
p-Acrylamidobenzenesulfonamide[l]	Pyridine	PBNA	44		.038(D, 100°)	255–300
Acrolein oxime[m]	Dioxane	PBNA	25		.06(F)	>300 d.

[a] Polymerization of 10 g. of monomer in 100 ml. of solvent, 0.1 g. of sodium as catalyst, overnight at 100°, except as noted. [b] 0.01 g. of hydroquinone (HQ) or 0.02 g. of phenyl-β-naphthylamine (PBNA). [c] Of water insoluble-polymer. [d] Of 1% solutions in anhydrous formic acid (A), 90% formic acid (F) or dimethylformamide (D) at 25°. [e] Five days at 100°. [f] Exothermic reaction allowed to subside. [g] Two days at 100°. [h] Mixture heated gradually to 220°, then cooled; it was not fractionated. [i] Sodium methoxide catalyst (5%). [j] Heated 6 hr., purified by ether extraction. [k] Sodium catalyst (5%), polymer extracted with hot ethanol, viscosity of 0.5% solution at 150°. [l] 25% solution. [m] Polymer extracted with hot acetone.

growth continuing on the amide part of the chain. This could be initiated by the anion shown in equation 1 in exactly the same manner. Chain termination would involve reaction of the growing chain with BH, regenerating the base B^-, or with any other active hydrogen compound present. This mechanism differs from the usually accepted mechanism for the base-catalyzed polymerization of acrylates[11] only in the necessity for a proton migrating from nitrogen to carbon for each addition. A second possibility exists, however, for the initiating species shown in equation 1. This involves essentially a chain transfer reaction in each growth step, as shown in reaction sequence 4.

$$CH_2{=}CHCONH^{\ominus} + CH_2{=}CHCONH_2 \longrightarrow CH_2{=}CHCONHCH_2\overset{\ominus}{C}HCONH_2 \quad (4)$$

$$CH_2{=}CHCONHCH_2\overset{\ominus}{C}HCONH_2 + CH_2{=}CHCONH_2 \longrightarrow CH_2{=}CHCONHCH_2CH_2CONH_2$$

$$+ CH_2{=}CHCONH^{\ominus} \longrightarrow CH_2{=}CHCONHCH_2\overset{\ominus}{C}HCO(NHCH_2CH_2CO)_nNH_2$$

Although the sequence has been depicted with the growing anion chain abstracting a proton from acrylamide, it could abstract a proton from any acidic species present, such as the unsubstituted amide end group of an already formed polymer chain[13]; the chain could grow, therefore, from either end. This unusual polymerization is in essence an addition polymerization which should have all the attributes of a condensation polymerization[14]; the polymerization should be relatively slow and the molecular weight should increase with conversion. Our preference for this mode of polymerization is at present based on only one observation. It would appear to us highly unlikely that, in any usual type of polymerization, one could isolate both a dimer and a high molecular weight polymer from the same reaction mixture. If chain transfer were so prevalent as to form a dimer, a high molecular weight polymer should not be found. Inasmuch as both were isolated, the molecular weight distribution must be unusually broad, and it seems that at least the major amount of polymer must be formed by this chain-transfer route.

Other Polymers.—The polymerization of several other monomers containing both an active hydrogen and an activated double bond is summarized in Table II. Any substituent in the acrylamide molecule decreased both the rate and degree of polymerization, a substituent on the nitrogen showing the greatest effect, on the β-carbon next and on the α-carbon least. The sulfonamides appeared to give lower molecular weight polymers than their carbon analogs. A factor influencing the molecular weight of all these polymers may be the inherent reversibility of addition reactions of α,β-unsaturated systems.

Experimental[15]

Materials.—Acrylamide (American Cyanamid Co.) was sublimed *in vacuo* before use. Methacrylamide was obtained from Rohm and Haas Co. The following compounds were prepared by described procedures: crotonamide,[16] 3,4,5,6-tetrahydrobenzamide,[17] 2-propene-1-sulfonamide,[18] ethylenesulfonanilide[19] and acrolein oxime.[20] The synthesis of ethylenesulfonamide will be reported elsewhere.

To prepare *p*-acrylamidobenzenesulfonamide a solution of 5.0 g. of sulfanilamide hydrochloride (Matheson Co.) in 70 ml. of water at 50° was treated with 4.0 g. of acrylic anhydride[21] and a solution of 2.05 g. of sodium acetate in 12 ml. of water. The mixture was stirred for 20 minutes at 65°, cooled to 0° and the product collected by filtration; the yield was quantitative. After two recrystallizations from aqueous ethanol (containing a trace of phenyl-β-naphthyl-

(13) Since alkyl groups are electron-donating, the hydrogen on a terminal amide group should be more acidic than one on a substituted amide group in the chain. If this were not so, a highly branched polymer would result. N-Substituted acrylamides have been found to polymerize much less readily under these conditions.

(14) Flory would actually classify this as a condensation polymerization (P. J. Flory, "Principles of Polymer Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 37–40).

(15) Analyses were carried out by the Analytical and Physical Chemistry Divisions of the Research Center.

(16) R. Stoermer and H. S. Stockmann, *Ber.*, **47**, 1786 (1914).

(17) A. Einhorn, *ibid.*, **26**, 451 (1893).

(18) A. Lambert and J. D. Rose, *J. Chem. Soc.*, 46 (1949).

(19) A. A. Goldberg, *ibid.*, 465 (1945).

(20) K. H. W. Tuerck and H. J. Lichtenstein, U. S. Patent 2,417,024 (1947).

(21) W. Reppe, *et al.*, *Ann.*, **582**, 1 (1953).

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amine) at 60°, colorless needles melting at 215° were obtained.

Anal. Calcd. for $C_9H_{10}SO_3N_2$: C, 47.77; H, 4.46. Found: C, 47.70; H, 4.55.

Polymerization of Acrylamide in Pyridine.—Acrylamide (10 g.) was added with stirring at 100° to a solution of 0.02 g. of phenyl-β-naphthylamine in 100 ml. of pyridine (dried over barium oxide). When the acrylamide had dissolved, a solution of 0.1 g. of sodium in 10 ml. of *t*-butyl alcohol was added. Polymer began to form on the walls in 4 minutes. After heating for 16 hr., the polymer was removed by filtration, extracted with boiling water for an hr. and dried *in vacuo* at 80° (4.8 g.). After neutralization with acetic acid, the aqueous extract was evaporated to dryness. The residue (3.6 g.) was purified by pouring an aqueous solution into methanol; 2.6 g. of polymer was isolated.

After the addition of phenyl-β-naphthylamine (0.02 g.) the mother liquor was evaporated to dryness *in vacuo*. On sublimation of the residue at 0.1 mm., acrylamide (0.4 g., m.p. 81–83°) was obtained, leaving behind 1.2 g. of solid.

Anal. Calcd. for $C_6H_{10}O_2N_2$: H_2 absorption, 1.42; NH_3, 12.0. Found: H_2 absorption, 1.18; NH_3, 12.5.

Application of the above polymerization procedure to this dimer fraction converted it into a mixture of polymer fractions similar to the one described.

Bulk Polymerization of Acrylamide.—To a solution of 0.4 g. of sodium in 15 ml. of *t*-butyl alcohol was added 40 g. of acrylamide and 0.04 g. of hydroquinone. The alcohol was removed *in vacuo* at 40°, and the residue was cautiously heated (while being stirred with a thermometer) to form a homogeneous melt. In a short time the temperature began to rise rapidly as a vigorous exothermic reaction set in. After polymerization was complete (three minutes), the solid foam was extracted with boiling water for 1 hr., yielding 26 g. of water-insoluble polymer with a specific viscosity of 0.23 (1% in anhydrous formic acid).

β-Alanine.—A solution of 30 g. of crude polymer prepared by bulk polymerization (before water extraction) in 120 ml. of 50% sulfuric acid was refluxed for 4 hr. The cooled solution was diluted with water and adjusted to *p*H 7 with hot aqueous barium hydroxide. After removal of the barium sulfate by filtration, the filtrate was evaporated to dryness. The residue (34 g., 90.5% yield based on acrylamide) melted at 191–193°. One recrystallization from aqueous methanol raised the melting point to 195–196°; a mixed melting point with authentic β-alanine showed no depression. The compound was further identified by conversion to the β-naphthalenesulfonamide derivative, m.p. 136–137° (lit.[22] m.p. 135.5–136.5°).

Polymerization of 2-Propene-1-sulfonamide.—A mixture of 2-propene-1-sulfonamide (1.30 g.), phenyl-β-naphthylamine (0.01 g.) and sodium (0.03 g.) was heated overnight at 100°. The product, a brittle resin, was extracted with 2% acetic acid, taken up in acetone and poured into ether. After drying overnight *in vacuo* the polymer weighed 0.50 g.

(22) H. H. Weinstock, H. K. Mitchell, E. F. Pratt and R. J. Williams, THIS JOURNAL, **61**, 1421 (1939).

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE RESEARCH DIVISION, RIKER LABORATORIES, INC.]

Alkaloids of *Rauwolfia Canescens* Linn. IV.[1] The Structure of Pseudoreserpine

BY M. W. KLOHS, F. KELLER, R. E. WILLIAMS AND G. W. KUSSEROW

RECEIVED MARCH 20, 1957

The isolation and characterization of pseudoreserpine ($C_{32}H_{38}O_9N_2$), a new alkaloid possessing hypotensive and sedative activity, is reported. On methanolysis pseudoreserpine yielded methyl 3,4,5-trimethoxybenzoate and a new alkamine designated methyl pseudoreserpate, which has been shown to be methyl 17-nor-reserpate by conversion to the 17,18-diacetyl derivative of methyl 17-nor-3-isoreserpate and through the conversion of reserpine to methyl pseudoreserpate.

A continuation of our investigation of the crude reserpine fraction obtained from the roots of *Rauwolfia canescens* Linn. has resulted in the isolation of **pseudoreserpine,** a new reserpine-like alkaloid, possessing hypotensive and sedative activity.

Further development of the chromatogram which had previously yielded deserpidine and reserpine[2] afforded an additional fraction from which crystalline pseudoreserpine was obtained. As a test for homogeneity, this compound was submitted to a 24-plate countercurrent distribution between 5% acetic acid and chloroform–methyl-chloroform (60:40) and gave a single peak which corresponded well with the theoretical curve for a single substance.

The analyses of pseudoreserpine and its derivatives, as well as equivalent weight determinations, were in accord with the empirical formula $C_{32}H_{38}O_9N_2$. The infrared spectrum of pseudoreserpine showed certain similarities to the spectrum of reserpine in exhibiting ester carbonyl absorption at 5.86 μ and a band at 6.13 μ, attributed to polarization of an indole nucleus by a methoxyl group in the 6-position.[3] The region of >NH, –OH absorption showed two discrete bands at 2.81 and 2.90 μ, one of which could be attributed to an indole >NH, and the other to the possible presence of a hydroxyl group. The existence of the latter group was further demonstrated by the formation of an O-acetyl derivative. The ultraviolet spectrum of pseudoreserpine was identical to that of reserpine and indicated that it also contained the 3,4,5-trimethoxybenzoyl and 6-methoxyindole chromophores.

On treatment with sodium methoxide, pseudoreserpine yielded methyl 3,4,5-trimethoxybenzoate and a new alkamine, methyl pseudoreserpate. The analysis of this new base was in agreement with the empirical formula $C_{22}H_{28}O_5N_2$ and showed the presence of two methoxyl groups. The infrared spectrum of methyl pseudoreserpate revealed a single strong broad band in the >NH, –OH region (2.95 μ) indicative of hydrogen bonding, ester carbonyl absorption at 5.74 μ, and the 6-methoxyindole band at 6.10 μ. The ultraviolet spectrum was identical to that of methyl reserpate, the alkamine of reserpine.

Lithium aluminum hydride reduction of pseudoreserpine afforded the corresponding triol which

(1) A preliminary report of this investigation appeared in a previous communication; *cf.* M. W. Klohs, F. Keller, R. E. Williams and G. W. Kusserow, *Chemistry & Industry*, 187 (1956).

(2) M. W. Klohs, F. Keller, R. E. Williams and G. W. Kusserow, THIS JOURNAL, **77**, 4084 (1955).

(3) N. Neuss, H. E. Boaz and J. W. Forbes, *ibid.*, **76**, 2463 (1954).

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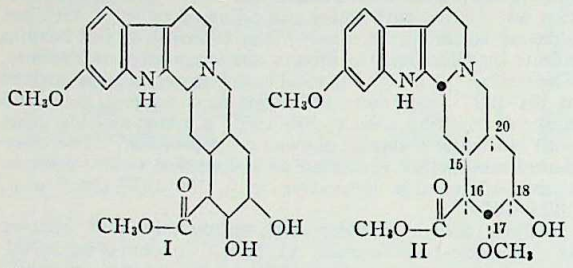
was transparent in the carbonyl region of the infrared spectrum.

The above data and biogenetic considerations suggested that the basic structure of methyl pseudoreserpate was closely related to that of methyl reserpate (II) and differed by the presence of a hydroxyl, rather than a methoxyl group at the C-17 position in ring E, as shown in structure I.



Since the structure of methyl reserpate has been proven conclusively by degradation[4] and synthesis[5] it was desirable, in order to obtain experimental evidence in support of the above hypothesis, to attempt the conversion of these two compounds to a common degradation product. The 17,18-diacetyl derivative of methyl 17-nor-3-isoreserpate was chosen as the intermediate for this purpose, since its formation would appear to follow a straight forward path and permit the bulk of the work to be carried out on the more abundant starting material, reserpine. The first step toward this objective was the preparation of methyl 17-nor-3-isoreserpate (IV) through the demethylation and concomitant C-3 epimerization[6] of reserpine (III) with aqueous hydrobromic acid followed by methylation with diazomethane.

A comparison of the physical and spectral properties of methyl pseudoreserpate and methyl 17-nor-3-isoreserpate showed them to be dissimilar[7] which was not unexpected; however, since it was presumed, in view of the biological activity of pseudoreserpine,[8] that methyl pseudoreserpate possessed the less stable β-oriented hydrogen at C-3. For this reason, methyl pseudoreserpate was treated under conditions known to effect epimerization at C-3, *i.e.*, by extended refluxing in acetic anhydride[6] to yield the epimeric diacetyl derivative. A comparison of this compound with the diacetyl derivative of methyl 17-nor-3-isoreserpate showed them to be identical on the basis of their physical and spectral properties. Conclusive evidence was thus available for the assignment of the basic ring system in methyl pseudoreserpate, as well as the location of its functional groups as shown in structure I.

After establishing this portion of the structure for methyl pseudoreserpate, the stereochemical implications of the above transformations on the six asymmetric centers at C-3, C-15, C-16, C-17, C-18 and C-20 remained to be considered. The assignment of a *cis* relationship for the hydrogen atoms at C-15, C-16 and C-20 as in methyl reserpate seemed unambiguous, but the chemical evidence in favor of the β-configuration at C-3 could not be considered conclusive in view of the possibility that inversion at C-17 and C-18 by epoxide formation and opening, rather than a simple isomerization at C-3, might have occurred during the prolonged treatment of methyl pseudoreserpate with acetic anhydride. It was, therefore, deemed advisable to obtain additional experimental evidence prior to the definite assignment of configuration at these centers.

Further work by direct chemical methods was hindered at this stage by the exhaustion of our supply of pseudoreserpine; however, the opportune report of the conversion of 3-isoreserpine to reserpine[9] by oxidation with mercuric acetate followed by reduction with zinc in aqueous acetic acid afforded a facile route through which methyl 17-nor-3-isoreserpate could be converted to methyl pseudoreserpate and thereby clarify the stereochemical ambiguities in question. By this procedure, methyl 17-nor-3-isoreserpate (IV) was converted to methyl pseudoreserpate which was identified by comparison with an authentic sample prepared through the methanolysis of pseudoreserpine. The lithium aluminum hydride reduction product of VII was also identical with that obtained through the reduction of pseudoreserpine. With these data at hand, it is now possible to assign configurations to the asymmetric centers of methyl pseudoreserpate and thus postulate its complete structure as VII.

Conclusive evidence is not available to place the site of attachment of the 3,4,5-trimethoxybenzoyl linkage on methyl pseudoreserpate in forming pseudoreserpine; however, by analogy with the other members of this series, reserpine, rescinnamine and deserpidine, we favor C-18 VI.

Pharmacology.—Pharmacological studies show that the cardiovascular and sedative effects of pseudoreserpine are very similar to, but weaker than, those of reserpine.[10]

Experimental[11]

The Isolation of Pseudoreserpine.—The crude reserpine fraction (100 g.) obtained from the roots of *Rauwolfia canescens* Linn. as previously described,[12] was chromatographed on a 3-inch column, using Merck acid-washed alumina (3 kg.) as the adsorbent. The column was developed with benzene–chloroform (3:1) and the percentage of chloroform was increased until straight chloroform and finally mixtures of chloroform–methanol were used as eluting solvents, the progress of the column being followed by spot testing the

(4) (a) C. F. Huebner, H. B. MacPhilliamy, E. Schlitter and A. F. St. André, *Experientia*, II, 303 (1955); (b) E. E. van Tamelen and P. D. Hance, THIS JOURNAL, **77**, 4692 (1955), and references cited therein.

(5) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *ibid.*, **78**, 2023 (1956).

(6) H. B. MacPhillamy, C. F. Huebner, E. Schlitter, A. F. St. André and P. R. Ulshafer, *ibid.*, **77**, 4335 (1955).

(7) In our previous communication[1] we noted the more negative molecular rotation of methyl pseudoreserpate as compared to methyl 17-nor-3-isoreserpate and made mention of this as being contrary to that observed for C-3 isomers of reserpine and its derivatives. Dr. C. F. Huebner has kindly pointed out, in a private communication, that while there is a negative shift in going from reserpine to 3-isoreserpine, the opposite holds true for methyl reserpate and its C-3 isomer; thus the change in rotation observed for methyl 17-nor-3 isoreserpate was to be expected for this derivative.

(8) It has been shown previously[4] that reserpine loses its characteristic physiological activity upon epimerization at the C-3 center.

(9) Frank L. Weisenborn and Patrick A. Diassi, THIS JOURNAL, **78**, 2022 (1956).

(10) S. Rothman and I. M. Tockes, to be published.

(11) All melting points were taken in evacuated capillaries, unless otherwise noted.

(12) M. W. Klohs, M. D. Draper, F. Keller and F. J. Petracek, THIS JOURNAL, **76**, 4538 (1954).

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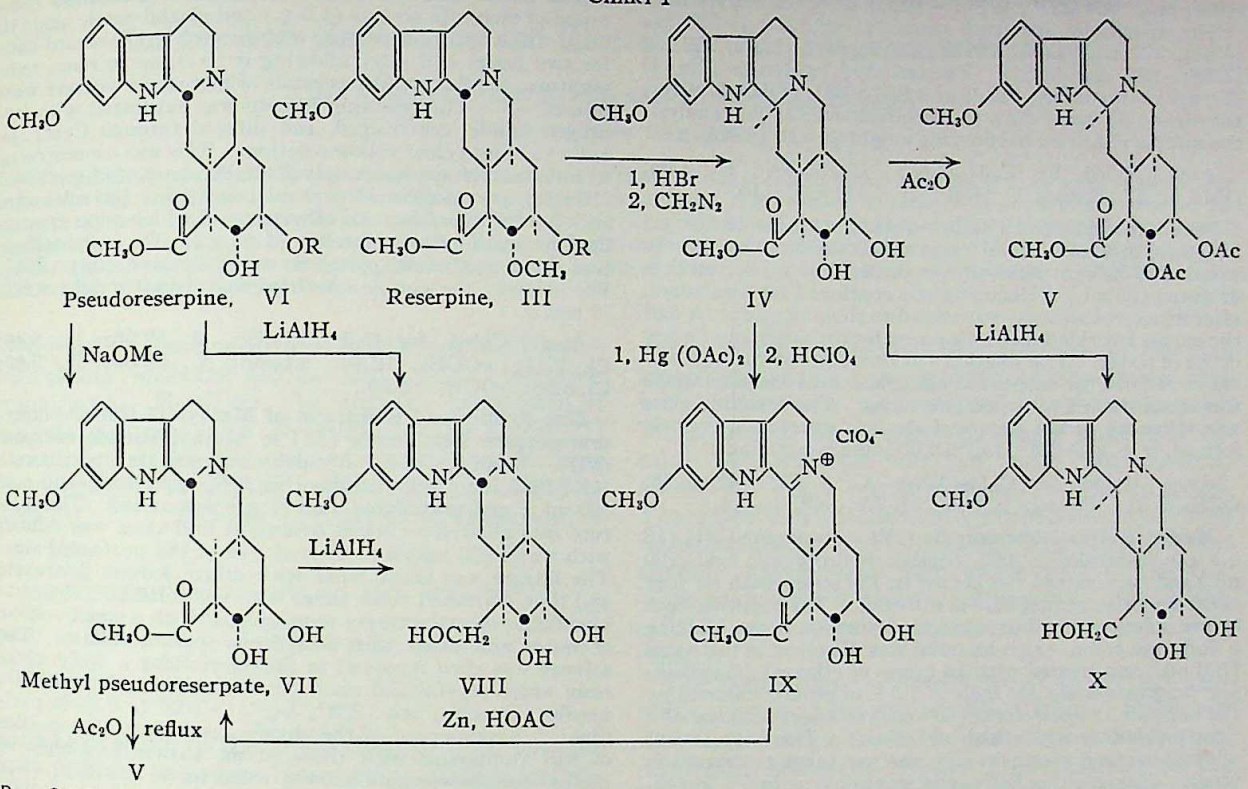
CHART I



R = 3,4,5-trimethoxybenzoyl

eluents with Frohde reagent and by the use of infrared spectra. Deserpidine was obtained from the fraction eluted with benzene–chloroform (1:1); on reaching the solvent system chloroform–methanol (99:1) a new alkaloid was encountered in trace amounts, m.p. 152–154°, $[\alpha]^{24}D$ −187° in $CHCl_3$. Further elution of the column with chloroform–methanol (95:5) yielded reserpine, followed by a fraction which behaved like reserpine on crystallization and spot tests, but showed differences in its infrared spectrum. This compound was further purified as described below.

Pseudoreserpine.—The crude resin fraction obtained above (1.2 g.) on dissolving in methanol (10 ml.) yielded crystalline pseudoreserpine; after several recrystallizations from dilute acetone, pseudoreserpine melted at 257–258°, $[\alpha]^{24}D$ −65 ± 2° (*c* 1.0 in $CHCl_3$). A 24-plate countercurrent distribution in a Craig glass apparatus between 5% aqueous acetic acid and chloroform–methylchloroform (60:40), gave a single band (K = 0.85) which corresponded with the theoretical curve for a single substance. The ultraviolet spectrum showed: λ^{alc}_{max} (log ϵ) 218 mμ (4.76), 268 mμ (4.22), 296 mμ (4.02); λ^{alc}_{min} (log ϵ) 246 mμ (3.98), 288 mμ (3.99). The infrared spectrum (Nujol) showed well defined and characteristic bands at 2.81 μ, 2.90 μ (>NH, OH); 5.86 μ (ester carbonyl); 6.13 μ (6-methoxyindole); 6.26 and 6.63 μ (aromatic). For analysis the sample was dried to constant weight at room temperature (2 mm.).

Anal.[13] Calcd. for $C_{32}H_{38}O_9N_2$: C, 64.63; H, 6.44; N, 4.71; 5-OCH_3, 26.10; mol. wt., 594.64. Found: C, 64.36; H, 6.44; N, 4.63; $-OCH_3$, 26.34; equiv. wt.,[14] 598.

On diluting the methanol mother liquors obtained above with water, an additional crystalline alkaloid was obtained which was purified further by recrystallization from dilute methanol. On the basis of its physical constants and spectral data, the compound appeared to be identical with rauvoscine.[15]

Pseudoreserpine Nitrate.—Pseudoreserpine (50 mg.) was suspended in methanol (2 ml.) and the solution was made acid with concentrated nitric acid. The addition of acid solubilized the suspended pseudoreserpine; however, on standing, fine needles separated. The crystals (35 mg.) were collected by filtration, washed with water and dried to constant weight at room temperature (2 mm.), m.p. 253–255°.

Anal. Calcd. for $C_{32}H_{38}O_9N_2 \cdot HNO_3$: C, 58.44; H, 5.97; N, 6.39. Found: C, 58.32; H, 6.03; N, 6.16.

Acetylpseudoreserpine.—Pseudoreserpine (100 mg.) was dissolved in anhydrous pyridine and acetic anhydride (1 ml.) was added; the solution, after standing overnight under anhydrous conditions, was concentrated to dryness under vacuum. The resulting light colored residue was dissolved in chloroform (25 ml.) and extracted with equal portions of dilute sodium carbonate and then water. The chloroform solution was filtered through anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The product was crystallized first from dilute methanol and then from dilute acetone as clusters of platelets (80 mg.), m.p. 150–154°. The infrared spectrum (Nujol) showed well defined bands at 3.0 (>NH), 5.78, 5.81 (ester carbonyl), 6.18 (6-methoxyindole) and 6.30 and 6.70 μ (aromatic). For analysis the sample was dried to constant weight at room temperature (2 mm.)

Anal. Calcd. for $C_{34}H_{40}O_{10}N_2$: C, 64.14; H, 6.33; N, 4.40; acetyl, 6.83. Found: C, 64.12; H, 6.46; N, 4.48; acetyl, 6.80.

Methanolysis of Pseudoreserpine to Methyl 3,4,5-Trimethoxybenzoate and Methyl Pseudoreserpate.—Pseudoreserpine (0.85 g.) was suspended in anhydrous methanol (50 ml.) to which sodium (0.15 g.) had previously been added. The mixture was refluxed for two hours. At the end of this time, the clear solution was concentrated *in vacuo* to a volume of approximately 5 ml. and water was added (50 ml.). The solution was made acid to congo red paper by the addition of concentrated hydrochloric acid and was then extracted two times with ether (50-ml. portions.) The dried ether extracts (sodium sulfate) yielded crystals of methyl 3,4,5-trimethoxybenzoate upon being taken to dryness *in vacuo* (identified by comparison with an authentic sample).

The aqueous layer obtained above was made basic with ammonium hydroxide and extracted three times with chloroform (50-ml. portions). The combined chloroform extracts were dried over anhydrous sodium sulfate and upon removal of the solvent *in vacuo*, a fluffy resin was obtained. This material was quite difficult to crystallize and only yielded a small quantity of needles upon treatment with

(13) All microanalyses by H. V. Tashinian, Microchemical Specialties Co., Berkeley 3, Calif.
(14) By titration with perchloric acid in glacial acetic acid solution.
(15) N. Hosansky and E. Smith, *J. Am. Pharm. Assn., Sci. Ed.*, **44**, 639 (1955).

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ether; m.p. 234–237°, $[\alpha]^{24}D$ −102 ± 3° (*c* 0.5 in pyridine).

The ultraviolet spectrum showed: λ_{max}^{alc} (log ε) 228 mμ (4.54), 270 mμ (3.68), 298 mμ (3.79); λ_{min}^{alc} (log ε) 252 mμ (3.56), 282 mμ (3.60). The infrared spectrum (Nujol) showed characteristic bands at 2.95 (>NH, –OH), 5.74 (ester carbonyl) and 6.20 μ (6-methoxyindole). For analysis the sample was dried to constant weight at 100° (2 mm.).

Anal. Calcd. for $C_{22}H_{28}O_5N_2$: C, 65.98; H, 7.05; OMe, 15.5. Found: C, 65.67; H, 7.31; OMe, 15.7.

Pseudoreserpinediol (VIII).—Pseudoreserpine (0.244 g.) in tetrahydrofuran (25 ml.) was added slowly to a refluxing solution of lithium aluminum hydride (0.25 g.) in tetrahydrofuran (35 ml.). Refluxing was continued for four hours, after which the solution was cooled to room temperature and the excess hydride was decomposed by the addition of a few drops of water. The solution was then filtered through Celite to remove the suspended aluminum salts and the filtrate was concentrated to dryness *in vacuo*. The resulting glass was taken up in hot isopropyl alcohol, whereupon crystals formed, m.p. 230–231°, $[\alpha]^{24}D$ 0.0° (*c* 0.5 in pyridine).

Anal. Calcd. for $C_{21}H_{28}O_4N_2$: C, 67.72; H, 7.58; OCH_3, 8.33. Found: C, 68.0; H, 7.9; $-OCH_3$, 8.4.

Methyl 17-Nor-3-isoreserpate (IV).—Reserpine (III) (18 g.) was suspended in 48% aqueous hydrobromic acid (100 ml.) and the mixture was heated on the steam-bath for four hours under an atmosphere of nitrogen. The resulting light brown solution was then taken to dryness *in vacuo*, yielding a fluffy tan resin. This material was dissolved in methanol (100 ml.) and treated with an excess of ethereal diazomethane (approximately one mole in 1.5 l. of ether), followed by the addition of chloroform (100 ml.) to effect solution of a light precipitate which had settled out. The mixture was allowed to stand overnight and then was taken to dryness *in vacuo*. The resulting fluffy resin was taken up in 5% methanol in chloroform and applied to a chromatographic column containing 500 g. of Merck acid-washed alumina. The initial eluates consisted mainly of methyl 3,4,5-trimethoxybenzoate identified by comparison with an authentic sample. The fractions immediately following this, and those eluted with 10% methanol in chloroform, yielded a light fluffy resin which crystallized from methanol yielding needles (2.75 g.), m.p. 265–266°, $[\alpha]^{24}D$ −69° (*c* 0.5 in pyridine). For analysis the sample was dried to constant weight at 100° (2 mm.).

Anal. Calcd. for $C_{22}H_{28}O_5N_2$: C, 65.98; H, 7.05; $-OCH_3$, 15.50. Found: C, 65.82; H, 7.10; $-OCH_3$, 15.54.

17,18-Diacetyl Methyl-17-nor-3-isoreserpate (V).—Methyl 17-nor-3-isoreserpate (IV) (200 mg.) was dissolved in anhydrous pyridine (20 ml.) and acetic anhydride (6 ml.) was added. The mixture was refluxed for one hour under anhydrous conditions and then concentrated to dryness *in vacuo*. The amorphous residue was dissolved in chloroform (25 ml.) and the solution was extracted with equal portions of dilute ammonium hydroxide and then with water; the chloroform layer was dried over anhydrous sodium sulfate and then evaporated to dryness *in vacuo*. On addition of methanol to the residue, a white powder (191 mg.) was obtained which was recrystallized from dilute acetone, m.p. 290–291°, $[\alpha]^{24}D$ −88.2° (*c* 0.5 in $CHCl_3$). For analysis the sample was dried to constant weight at 100° (2 mm.).

Anal. Calcd. for $C_{26}H_{32}O_7N_2$: C, 64.45; H, 6.66; O-acetyl, 17.8. Found: C, 64.62; H, 6.57; O-acetyl, 17.4.

Acetylation and Epimerization of Methyl Pseudoreserpate.—Methyl pseudoreserpate (VII) (275 mg.) was refluxed for six hours with acetic anhydride (10 ml.) under anhydrous conditions. The reaction mixture was then worked up as described above for V to yield an amorphous residue. On addition of methanol, a white powder was obtained (57 mg.) which on recrystallization from dilute acetone, melted at 292–293°, $[\alpha]^{24}D$ −86.9° (*c* 0.5 in $CHCl_3$). A mixture melting point with the diacetyl derivative of methyl 17-nor-3-isoreserpate obtained above gave no depression; a comparison of their infrared and ultraviolet spectra showed them to be identical.

Methyl 17-Nor-$\Delta^{3,4}$-dehydroreserpate Perchlorate (IX).—Methyl 17-nor-3-isoreserpate (IV) (1.2 g.), dissolved in glacial acetic acid (10 ml.), was added to a solution composed of mercuric acetate (1.3 g.) and glacial acetic acid (10 ml.). The resulting mixture was warmed on the steam-bath for two hours and after allowing it to come to room temperature, the flaky white crystals of mercurous acetate were filtered off. The resulting filtrate was saturated with hydrogen sulfide, centrifuged, and filtered through Celite, finally yielding a clear yellow solution. This was concentrated to a volume of approximately 2 ml. *in vacuo*, and methanol (10 ml.), perchloric acid (0.6 ml.) and ether (30 ml.) were added in that order. An oil separated which soon crystallized as small yellow platelets (1.48 g.). On recrystallization from methanol, platelets were obtained, m.p. 258°. For analysis, the sample was dried to constant weight at 60° (2 mm.).

Anal. Calcd. for $C_{22}H_{27}O_9N_2Cl$: C, 52.96; H, 5.46; Cl, 7.11; $-OCH_3$, 12.44. Found: C, 52.66; H, 5.65; Cl, 6.98; $-OCH_3$, 12.35.

Zinc–Acetic Acid Reduction of Methyl 17-Nor-$\Delta^{3,4}$-dehydroreserpate Perchlorate (IX) to Methyl Pseudoreserpate (VII).—Methyl 17-nor-$\Delta^{3,4}$-dehydroreserpate perchlorate (IX) (285 mg.) was dissolved in 50% aqueous acetic acid (20 ml.), and granulated zinc (1 g.) was added. The mixture was allowed to stand overnight and then was diluted with water (50 ml.) and filtered free of the unreacted zinc. The filtrate was made basic with dilute sodium hydroxide and then extracted three times with chloroform. The combined chloroform extracts were washed with a small volume of water and dried with anhydrous sodium sulfate. The solvent was then removed *in vacuo*, yielding a fluffy white resin which crystallized upon the addition of ether as white needles (70 mg.), m.p. 228°, $[\alpha]^{26}D$ −100° (*c* 0.29 in pyridine). A comparison of the physical and spectral properties of this compound with those of an authentic sample of methyl pseudoreserpate showed them to be identical. For analysis the material was dried to constant weight at 100° (2 mm.).

Anal. Calcd. for $C_{22}H_{28}O_5N_2$: C, 65.98; H, 7.05. Found: C, 65.82; H, 7.29.

Lithium aluminum hydride reduction of this compound was carried out as reported above for pseudoreserpinediol and yielded needles, m.p. 233°. A mixture melting point with pseudoreserpinediol obtained by reduction of pseudoreserpine gave no depression and the infrared spectra of the two preparations were identical. The optical rotations also agreed, $[\alpha]^{26}D$ 0.0° (*c* 0.3 in pyridine).

3-Isopseudoreserpinediol (X).—Methyl 17-nor-3-isoreserpate (IV) (107 mg.) was dissolved in tetrahydrofuran (25 ml.) and added to a refluxing solution of lithium aluminum hydride (100 mg.) in tetrahydrofuran (25 ml.). The solution was kept at reflux for four hours and then the reaction mixture was worked up as for pseudoreserpinediol. White needles (46 mg.) were obtained, which were recrystallized several times from isopropyl alcohol, m.p. 286–287°, $[\alpha]^{27}D$ −107° (*c* 0.2 in pyridine). This material easily formed solvates and did not lose all of its solvent of crystallization even when dried at 120° (2 mm.).

Anal. Calcd. for $C_{21}H_{28}O_4N_2 \cdot {}^1/_2H_2O$: C, 66.12; H, 7.66. Found: C, 65.43; H, 7.82.

Treatment of Pseudoreserpine with Mercuric Acetate.—Pseudoreserpine (50 mg.) was dissolved in glacial acetic acid (4 ml.), and mercuric acetate (50 mg.) in glacial acetic acid (4 ml.) was added. The mixture was heated on the steam-bath for 0.5 hour and at the end of this time the solution remained clear. In contrast 3-isoreserpine gave a copious precipitate of mercurous acetate within three to five minutes. Reserpine itself gave a precipitate only on prolonged warming, presumably because of isomerization occurring at C-3.

Acknowledgment.—We wish to express our thanks to Messrs. C. H. Stimmel and A. Shimamura and Miss M. Roper in the Analytical Section, Research Division, Riker Laboratories, for the optical rotations, spectral data and equivalent weight determinations.

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[CONTRIBUTION FROM THE NEW YORK STATE AGRICULTURAL EXPERIMENT STATION, CORNELL UNIVERSITY]

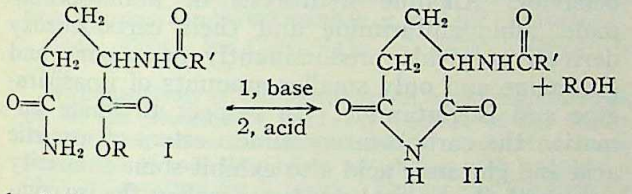
Imides from Asparagine and Glutamine. II. α-Aminoglutarimide[1]

BY ERNEST SONDHEIMER AND ROBERT W. HOLLEY

RECEIVED FEBRUARY 7, 1957

Hydrogenolysis of carbobenzoxy-DL-α-aminoglutarimide in the presence of hydrochloric acid yields DL-α-aminoglutarimide hydrochloride. Some of the properties of this compound are described. With weaker bases than those previously employed, the cyclization of carbobenzoxy-L-glutamine methyl ester gives carbobenzoxy-α-aminoglutarimide with partial retention of configuration. Treatment of the methyl esters of carbobenzoxy-L-glutamine and carbobenzoxy-L-isoglutamine with aqueous sodium hydroxide followed by hydrogenolysis gives mixtures of partially racemized glutamine and isoglutamine. This reaction was studied quantitatively.

Normally, treatment of N-acylamino acid esters with alkali yields the alcohol and a salt of the acylamino acid. However, the alkaline hydrolysis of N-acylasparagine and N-acylglutamine esters (I) is complicated by the ease of cyclization of these compounds to succinimide and glutarimide derivatives (II).[2-4] Alkaline hydrolysis of these imides



leads to opening of the imide rings in both possible ways. Thus, the over-all process of alkaline hydrolysis gives mixtures of products and is, in the case of the glutamine derivative, further complicated by racemization.[2,3] Because of the possible significance of these reactions during peptide synthesis and the cleavage of peptide chains,[3] studies of the reactions and of the properties of the imides are of importance.

As reported earlier,[2] hydrogenolysis of carbobenzoxy-DL-α-aminoglutarimide does not give pure α-aminoglutarimide. The hydrogenolysis product turns violet when exposed to air and becomes more intensely colored during storage at room temperature after evaporation of the solvent. That an aqueous solution of this mixture still contained large amounts of unchanged aminoglutarimide could be shown by paper chromatography. The solution had one broad absorption band in the visible region with a peak at 560 mμ, $E_{1cm}^{1\%}$ 60. The solution could be decolorized by catalytic hydrogenation or by treatment with sodium hydrosulfite. It seems likely that the pigment is a conversion product of aminoglutarimide, possibly formed by aerobic oxidation.

When the hydrogenolysis of the carbobenzoxy-DL-α-aminoglutarimide was carried out in the presence of a slight excess of hydrochloric acid, colorless, crystalline, water-soluble DL-α-aminoglutarimide hydrochloride was obtained. The hydrochloride has much less of a tendency to give the violet material and is not as readily hydrolyzed in water to glutamine and isoglutamine as the free aminoglutarimide. Hydrolysis of the imide with hot hydrochloric acid yielded DL-glutamic acid. When heated on a micro-hot-stage aminoglutarimide hydrochloride did not melt, but changed above 220° to a violet material which sublimed. The imide can be chromatographed on paper with water-saturated phenol, R_f 0.9, and with *n*-butyl alcohol, acetic acid and water (4:1:5), R_f 0.2. With ninhydrin it gives a salmon-red color, which exhibits an absorption maximum at 523 mμ in 95% ethanol.

The conditions previously used[2] to prepare carbobenzoxy-α-aminoglutarimide from carbobenzoxy-L-glutamine methyl ester gave completely racemized material. Since the formation of the imide from carbobenzoxyglutamine methyl ester does not involve direct reaction on the asymmetric carbon atom, it seemed possible that ring closure might be effected without racemization, if cyclization were catalyzed by the weakest base possible. No imide formation could be detected with triethylamine as the base. But by using equivalent amounts of ester and sodium methoxide in methanol at 0°, optically active carbobenzoxy-α-aminoglutarimide, $[\alpha]^{24}D$ −24.6° (*c* 1, methanol), was obtained. Imide with somewhat higher rotation, $[\alpha]^{24}D$ −35.3° (*c* 1, methanol), could be prepared by the addition of an equivalent amount of N-methylacetamide to the sodium methoxide. This effect of N-methylacetamide is attributed to its ability to lower the base strength. On the other hand, with excess sodium methoxide in methanol the optical rotation of the imide was lower, $[\alpha]^{24}D$ −10.7° (*c* 1, methanol). By hydrogenolysis of carbobenzoxy-α-aminoglutarimide which had a rotation of $[\alpha]^{24}D$ −35.3° (*c* 1, methanol) optically active α-aminoglutarimide hydrochloride was obtained, $[\alpha]^{24}D$ −53.5° (*c* 1, methanol). Acid hydrolysis to glutamic acid showed that approximately 40% of the material has been converted to the racemic form. The purity of these optically active preparations was checked chromatographically and by analysis.

We have shown earlier that treatment of carbobenzoxy-L-glutamine methyl ester and carbobenzoxy-L-isoglutamine methyl ester with aqueous sodium hydroxide does not lead to the isolation of an imide.[2] However, evidence for intermediate imide formation was obtained since alkaline hydrolysis followed by hydrogenolysis gave a mixture of glutamine and isoglutamine from either ester. In order to determine what fraction of the ester was hydrolyzed by way of the imide, the ratio of glutamine

(1) Journal Paper No. 1060, New York State Agricultural Experiment Station. This investigation was supported in part by a research grant, H-2104 and H-2104 (c) from the National Institutes of Health, Public Health Service. For Part *T*, see ref. 2.

(2) E. Sondheimer and R. W. Holley, THIS JOURNAL, **76**, 2467 (1954).

(3) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955).

(4) D. W. Clayton, G. W. Kenner and R. C. Sheppard, *ibid.*, 371 (1956).

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TABLE I

PRODUCTS FROM ALKALINE HYDROLYSIS FOLLOWED BY HYDROGENOLYSIS

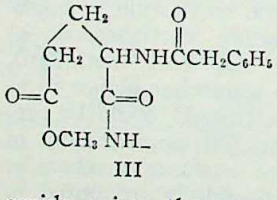
	Yield glutamine Mg.	σ	Yield isoglutamine Mg.	σ	Ratio glutamine/ isoglutamine	Hydrolysis through the imide, %	Racemization, %
Carbobenzoxy-DL-α-aminoglutarimide[a]	10.52[c]	1.54	2.24	0.84	4.7:1	..	..
Carbobenzoxy-L-glutamine methyl ester[b]	10.60[d]	0.97	2.25	.71	4.7:1	100	53
Carbobenzoxy-L-isoglutamine methyl ester[b]	8.34[e]	1.40	4.17	.58	2.0:1	80	43

[a] From 26.2 mg. of imide. [b] From 29.4 mg. of ester. [c] Mean of 14 determinations. [d] Mean of 23 determinations. [e] Mean of 11 determinations. σ Standard deviation. By the use of Student's *t* test it could be shown that the yields of glutamine and isoglutamine from carbobenzoxy-L-glutamine methyl ester and carbobenzoxy-DL-α-aminoglutarimide were not significantly different and that yields of the products from carbobenzoxy-L-isoglutamine methyl ester were different at the 99% level from those obtained with the other two compounds.

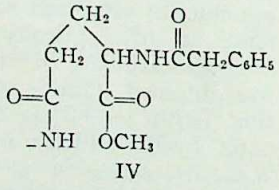
to isoglutamine, obtained after alkaline hydrolysis and hydrogenolysis, was determined by quantitative paper chromatography. By comparing these values to the ratio of glutamine to isoglutamine obtained on alkaline hydrolysis and hydrogenolysis of carbobenzoxy-DL-aminoglutarimide, the contribution that imide formation makes to the total hydrolysis of the esters could be calculated. Information on the extent of racemization during aqueous alkaline hydrolysis was also obtained. The results are summarized in Table I.

The hydrolysis and hydrogenolysis of carbobenzoxyaminoglutarimide yielded predominantly glutamine. This was the expected result since the lower electron density of the carbonyl group closest to the carbobenzoxyamido group favors attack by the hydroxyl ions at that site.[5]

The greater participation of the imide in the total de-esterification of carbobenzoxy-L-glutamine methyl ester as compared with carbobenzoxy-L-isoglutamine methyl ester is most likely due to differences in the nucleophilic character of the amide anions III and IV. The more nucleophilic the



III



IV

amide anion, the greater the extent of imide formation,[6] since competition between the anion and hydroxyl ion determines the proportion of hydrolysis through the imide for each ester. The location of the carbobenzoxyamido group would be expected to make III less nucleophilic than IV and therefore imide formation would be favored with IV.

De-esterification of the two esters with aqueous sodium hydroxide is accompanied by partial racemization. Of the various species present it would appear most likely that only the intermediate carbobenzoxy-α-aminoglutarimide is subject to racemization. This assumption is in accord with the experimental data. From Table I it is seen that the percentage hydrolysis through the imide is 20% greater for carbobenzoxy glutamine methyl ester than for the iso compound and that the extent of racemization is increased by an almost identical amount, 19%.

A comparison of the properties of the imides from glutamine and asparagine shows a number of similarities but also pronounced differences in behavior. Alkaline hydrolysis of aminosuccinimide, aminoglutarimide and their carbobenzoxy derivatives yields predominantly asparagine and glutamine and only smaller amounts of isoasparagine and isoglutamine. In respect to imide formation the carbobenzoxy amido esters of aspartic acid and glutamic acid also exhibit some similarity since with the normal amides as well as the iso compounds, imide formation was favored over normal saponification.

In common with the unsubstituted 5- and 6-membered cyclic imides[7] α-aminoglutarimide is much more rapidly hydrolyzed in alkali than aminosuccinimide. This difference in the rate of hydrolysis is explained by the generalization of Brown, Brewster and Schechter[8] that 6-membered rings with exo double bonds appear to be generally less stable and more susceptible to ring opening than 5-membered rings of this kind. Another striking difference in the behavior of the imides from asparagine and glutamine derivatives is that carbobenzoxy-α-aminoglutarimide is much more easily racemized than carbobenzoxyaminosuccinimide. This observation also seems to be in accord with the above generalization[8] since enolization should be favored in the 6-membered ring.

Another difference in the behavior of the two imides is that pigment formation has been observed only with aminoglutarimide and not with the 5-membered analog. Possibly this is also related to differences in the ring size since dehydrogenation of aminoglutarimide could lead to 2,6-dihydroxypyridine derivatives, compounds known to be oxidized to colored products.[9]

It seemed of interest to obtain some information on the growth response of a biological system to aminoglutarimide. The utilization of DL-α-aminoglutarimide by *Lactobacillus plantarum* var. *arabinosus* in glutamic acid-free, synthetic medium was therefore investigated. The growth response obtained was somewhat similar to that of glutamine. However, the amount of cell growth obtained per microgram imide was much less than that given by an equivalent quantity of glutamine. It was

(5) Similar results were obtained by Clayton, Kenner and Sheppard[4] who reported that the alkaline hydrolysis of the imide from benzoyl-DL-glutamylglycine cyclohexylamide yielded 85% of the γ-isomer and 13% of the α-compound.

(6) Differences in the electrophilic character of the carbomethoxy groups of the two esters might be expected to have little effect on the extent of de-esterification through saponification or imide formation, since both these processes are competing for the same carbomethoxy group.

(7) S. S. G. Sircar, *J. Chem. Soc.*, 600, 1252 (1927).

(8) H. C. Brown, J. H. Brewster and H. Schechter, THIS JOURNAL, 76, 467 (1954).

(9) G. Ciamician, *Ber.*, 31, 1241 (1898).

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found, though, that cell growth could be increased somewhat by increasing the initial *p*H of the medium, by increasing its buffer capacity or by adding the imide to the medium several hours before inoculation. Since *L. plantarum* produces acids during growth these observations indicate that hydrolysis precedes utilization of the imide. It was therefore concluded that DL-α-aminoglutarimide is not utilized as such, that it is not a potent growth inhibitor and that the observed growth is due to non-enzymatic hydrolysis of the imide to glutamine and isoglutamine.

Experimental[10]

Reaction of Carbobenzoxy-DL-α-aminoglutarimide with Ammonia.—To 100 mg. of carbobenzoxy-DL-α-aminoglutarimide was added with shaking 2 ml. of 28% aqueous ammonia. The product started to precipitate before all the starting material had dissolved. The mixture was filtered after overnight storage at room temperature. The yield of carbobenzoxy-DL-glutamic acid diamide was 77 mg. (71%), m.p. 181–183°, m.p. was unchanged by recrystallization from aqueous dimethylformamide or from 95% ethanol.

Anal. Calcd. for $C_{13}H_{17}N_3O_4$: N, 15.05. Found: N, 14.8.

Hydrogenolysis of Carbobenzoxy-DL-α-aminoglutarimide. (a) In the Absence of Acid.—A mixture of 200 mg. of carbobenzoxy-DL-α-aminoglutarimide in 5 ml. of methanol and 50 mg. of palladium black was shaken with hydrogen at room temperature for 2 hours. During the filtration the solution turned violet. Evaporation of the solvent in vacuum yielded crystals which were tinted violet at the surface, m.p. approximately 120° with decomposition to a violet solid. Storage of the hydrogenolysis product at room temperature caused a measurable increase in the color intensity. The amount of pigment could be increased further by periodically dissolving the material in water and evaporating the solvent in vacuum. In 13 days $E^{1\%}_{1\,cm.}$ at 560 mμ in water increased from 0.75 to 60. However, the preparation still consisted predominantly of unchanged aminoglutarimide. An aqueous solution of this mixture could be decolorized by hydrogenation with palladium black at room temperature and atmospheric pressure, with nitrous acid, and with sodium hydrosulfite. Cupric nitrate precipitates the colored material. DL-α-Aminoglutarimide hydrolyzes slowly at room temperature in aqueous solution to a mixture of glutamine and isoglutamine.

(b) In the Presence of Hydrochloric Acid.—Hydrogen was bubbled at room temperature and atmospheric pressure through a mixture of 1.05 g. of carbobenzoxy-DL-α-aminoglutarimide in 4.1 ml. of 0.99 *N* hydrochloric acid and 15 ml. of methanol in the presence of 200 mg. of palladium black. Sufficient water was added during the hydrogenolysis to keep the product in solution. After 1.5 hours the mixture was filtered and the filtrate concentrated in vacuum below 50° to 5 ml. On the addition of 20 ml. of *n*-propyl alcohol and storage overnight at 0° the product crystallized, yielding 0.565 g. (86%) of DL-α-aminoglutarimide hydrochloride. The latter was recrystallized in 70% yield on the addition of 15 ml. of propanol to the filtrate from 0.550 g. of crude product in 3.5 ml. of water. The compound, which does not melt, is changed to a violet, water-insoluble material above 220°. The hydrochloride is optically inactive and forms no more than traces of violet material on storage at room temperature for 12 months; the amino group has a pK_a 6.8 in water.

Anal. Calcd. for $C_5H_8N_2O_2 \cdot HCl$: C, 36.49; H, 5.51; N, 17.02; neut. equiv., 164.6. Found: C, 36.75; H, 5.87; N, 16.75; neut. equiv., 166.

Preparation of Optically Active Carbobenzoxy-α-aminoglutarimide.—Under the previously described conditions for cyclization[2], sodium methoxide in benzyl alcohol, only racemized imide was obtained. Therefore the cyclization was attempted under milder conditions.

Refluxing 294 mg. of carbobenzoxy-L-glutamine methyl ester with 5 ml. of triethylamine for 2 hours yielded only unchanged starting material. Since the ester was only partially soluble in the hot triethylamine, the cyclization attempt was repeated with a mixture of 1,4-dioxane and triethylamine. Again only unchanged ester was obtained after reflux.

Optically active imide was obtained by adding at 0°, 294 mg. of carbobenzoxy-L-glutamine methyl ester to a solution of 1.5 ml. of methanol containing sodium methoxide from 23.0 mg. of sodium. After 15 minutes at 0°, 0.1 ml. of acetic acid was added followed by 10 ml. of water. The mixture was stored at 0° overnight, yielding 230 mg. (84%) of carbobenzoxy-α-aminoglutarimide, m.p. 134–136° (transition 121°), $[\alpha]^{24}D$ −24.6° (*c* 1, methanol).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.33; N, 10.7. Found: C, 59.15; H, 5.19; N, 10.3.

Under similar conditions the addition of one equivalent of N-methylacetamide to this system gave imide with a somewhat higher rotation, $[\alpha]^{24}D$ −35.3° (*c* 1, methanol).

Preparation of Optically Active α-Aminoglutarimide Hydrochloride.—Hydrogen was bubbled at room temperature and atmospheric pressure for two hours through a mixture of 80 mg. of carbobenzoxy-α-aminoglutarimide, $[\alpha]^{24}D$ −35.3° (*c* 1, methanol), in 5 ml. of methanol and 0.5 ml. of 1 *N* hydrochloric acid plus 30 mg. of palladium black. The mixture was filtered, the catalyst washed with methanol and the combined washings and filtrate concentrated in vacuum. The yield of crystalline α-aminoglutarimide hydrochloride was 44.7 mg., 87% of the theoretical yield, $[\alpha]^{24}D$ −53.5° (*c* 1, methanol). By chromatographic analysis the material was shown to be indistinguishable from the racemized product and was practically free of glutamine and isoglutamine. It was recrystallized from aqueous solution by the addition of *n*-propyl alcohol for analysis.

Anal. Calcd. for $C_5H_8N_2O_2 \cdot HCl$: C, 36.49; H, 5.51; N, 17.02. Found: C, 36.76; H, 5.66; N, 17.2.

A solution of 68.3 mg. of the above α-aminoglutarimide hydrochloride in 2 ml. of 6 *N* hydrochloric acid was refluxed 3 hours, cooled and the volume adjusted to 5 ml. with 6 *N* hydrochloric acid. The resulting glutamic acid solution had a specific rotation of $[\alpha]^{24}D$ +18.4° (*c* 1.2 in 6 *N* hydrochloric acid), indicating approximately 40% conversion to the racemic form.

Alkaline Hydrolysis of Carbobenzoxy-L-glutamine Methyl Ester, Carbobenzoxy-L-isoglutamine Methyl Ester and Carbobenzoxy-DL-α-aminoglutarimide.—The addition of 1.1 ml. of 0.97 *N* sodium hydroxide to 29.4 mg. of ester or 26.2 mg. of imide (0.1 millimole) caused the compounds to go rapidly into solution. After storage at room temperature for 2 hours the solution was acidified with 1.15 ml. of 0.97 *N* hydrochloric acid, 15 mg. of palladium black was added and hydrogen was bubbled through the mixture at room temperature for one hour. The mixture was filtered, the catalyst washed with water and the combined washings and filtrate made up to 10 ml. Aliquots of 5, 10 and 20 microliters were chromatogramed on Whatman No. 1 paper for 16 hours with *n*-butyl alcohol, acetic acid and water (4:1:5). The papers were dried at room temperature. The amino acid spots were detected by spraying with a 1% ninhydrin solution in 95% ethanol containing 2% collidine–lutidine mixture (1:3) and developed for one hour in a 40° cabinet through which water-saturated air was passed. Immediately after development the spots were cut out and the pigment was extracted with 50% ethanol. After storage in the dark for one hour the optical density at 570 mμ was determined. Chromatograms with known concentrations of glutamine and isoglutamine were run with each unknown and these served for the construction of calibration curves. The only products detected were glutamine and isoglutamine. The absence of glutamic acid could be shown by chromatograming with water-saturated phenol. Hydrogenolysis of carbobenzoxyglutamine and carbobenzoxyisoglutamine gave only glutamine and isoglutamine, respectively.

Estimation of the Extent of Racemization of Carbobenzoxy-L-glutamine Methyl Ester and Carbobenzoxy-L-isoglutamine Methyl Ester during Alkaline Hydrolysis.—To 294 mg. (1 millimole) of the carbobenzoxy esters 1.2 ml. of 1 *N* sodium hydroxide was added and the solution stored at room temperature overnight. After acidification with 2 ml. of concentrated hydrochloric acid, the mixture was refluxed eight hours, cooled and extracted with benzene to remove benzyl alcohol. The aqueous phase was diluted

(10) All melting points were determined on a microscope hot-stage and are corrected. Analyses are by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

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with 20 ml. of water and passed over a column of 5 g. of Dowex 2 in the hydroxide form (20–50 mesh). The column was washed with water until the effluent was neutral. The glutamic acid was eluted with 0.25 *N* hydrochloric acid. Five-ml. fractions were collected and the fractions giving a positive ninhydrin test (usually fractions 5 through 9) were combined, the solvent was evaporated in vacuum and the crystalline residue was freed from excess hydrochloric acid by repeated additions and evaporations of 5-ml. portions of water. After drying in a vacuum desiccator over phosphorus pentoxide and potassium hydroxide the material was weighed and the optical rotation in 6 *N* hydrochloric acid determined. In order to show that the decrease in the specific rotation of the glutamic acid was caused by the alkaline treatment of the esters, hydrolysis to glutamic acid was also brought about by refluxing carbobenzoxy-L-glutamine methyl ester without prior treatment with alkali. The yields of glutamic acid averaged 93%. The glutamic acid obtained from alkaline de-esterification of carbobenzoxy-L-glutamine methyl ester had a specific rotation of $[\alpha]^{24}D$ +14.2° (*c* 1 in 6 *N* hydrochloric acid) and, from carbobenzoxy-L-isoglutamine methyl ester, $[\alpha]^{24}D$ +17.1° (*c* 1 in 6 *N* hydrochloric acid). Acid hydrolysis of carbobenzoxy-L-glutamine methyl ester yielded glutamic acid with a specific rotation of $[\alpha]^{24}D$ +30.0° (*c* 1 in 6 *N* hydrochloric acid) and carbobenzoxy-DL-α-aminoglutarimide, $[\alpha]^{24}D$ 0° (*c* 1 in 6 *N* hydrochloric acid).

Growth Response of *Lactobacillus plantarum* to DL-Aminoglutarimide.—The general procedure used has been described previously.[11] In the synthetic medium DL-aminoglutarimide was substituted for L-glutamic acid. A lag phase of from 4 to 6 hours was observed. This is similar to that obtained with L-glutamine.[11] The maximum amount of growth obtained with DL-α-aminoglutarimide at *p*H 6.1 was only 20–30% of that given by an equivalent amount of L-glutamine. A small increase in the maximum amount of growth could be obtained with the imide, by raising the *p*H of the growth medium, by increasing its buffering capacity, or by storing the growth medium at 35° prior to inoculation.

Acknowledgment.—We wish to thank Mrs. Carole B. Karash for technical assistance and Dr. R. S. Shallenberger for the statistical analysis.

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GENEVA, NEW YORK

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

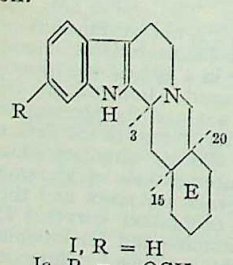
New Total Synthesis of *dl*-Alloyohimbane and *dl*-Epialloyohimbane and their 11-Methoxy Derivatives

BY RICHARD T. RAPALA, EDWARD R. LAVAGNINO, EDWIN R. SHEPARD AND EUGENE FARKAS

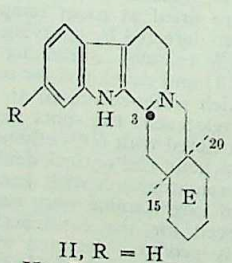
RECEIVED FEBRUARY 20, 1957

Racemic alloyhimbane and epialloyohimbane and the 11-methoxy analogs have been prepared by a series of facile reactions. The key bicyclic (ring DE) intermediate, a *cis*-fused decahydroisoquinoline-3-carboxylic acid, was obtained by hydrogenation of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid using rhodium-on-alumina catalyst.

This paper describes a convenient synthesis of *dl*-allo- and epialloyohimbane (I and II) and the corresponding 11-methoxy derivatives (Ia and IIa). The starting point for this synthesis was 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid which constitutes the potential D and E rings of the pentacyclic bases. Since these pentacyclic ring systems occur as the nuclei of reserpine,[1a] deserpidine[1b] and related alkaloids, it is important to be able to prepare such systems by a general unequivocal method capable of producing ring E substituted derivatives for pharmacological evaluation.



I, R = H
Ia, R = —OCH_3



II, R = H
IIa, R = —OCH_3

Previously the pentacyclic bases *dl*-alloyohimbane (I) (C_3, C_{15}, C_{20} *cis*) and its isomer epialloyohimbane (II) (C_3 *trans*; C_{15}, C_{20} *cis*) have been obtained through total synthesis by Stork and Hill[2] and through partial synthesis by Wenkert and Liu[3] as well as by LeHir, Janot and Goutarel.[4] Racemic 11-methoxyalloyohimbane (Ia) has been prepared by E. E. van Tamelen, *et al.*,[5a] and Huebner, *et al.*[1b] Huebner[5b] has shown that prolonged acid treatment of this allo isomer provides *dl*-11-methoxyepialloyohimbane as the major product.

Our approach to a general synthesis depended upon the unambiguous preparation of suitably substituted *cis*-decahydroisoquinolines which would serve as the D and E rings of the pentacyclic ring skeleton. Previous attempts[6] toward the preparation of these *cis* ring systems indicated that the reduction of hydroxyisoquinolines with noble metals in acetic acid proceeded to the *cis*-decahydroisoquinolines but with concomitant loss of the hydroxyl group. Hydrogenations of similar compounds over Raney nickel catalyst yielded mixtures of the stereoisomeric decahydroisoquinolines.[7]

In the present work the desired *cis* isomer was obtained by catalytic hydrogenation of a selected tetrahydroisoquinoline using rhodium-on-alumina catalyst. That this substance possessed the *cis* configuration in the bicyclic form was evidenced by its conversion through a series of reactions to the

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(3) E. Wenkert and L. Liu, *Experientia*, **11**, 302 (1955).

(4) A. LeHir, M. Janot and R. Goutarel, *Bull. soc. chim.*, 1091 (1952).

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(6) R. B. Woodward and W. E. Doering, THIS JOURNAL, **67**, 865 (1945).

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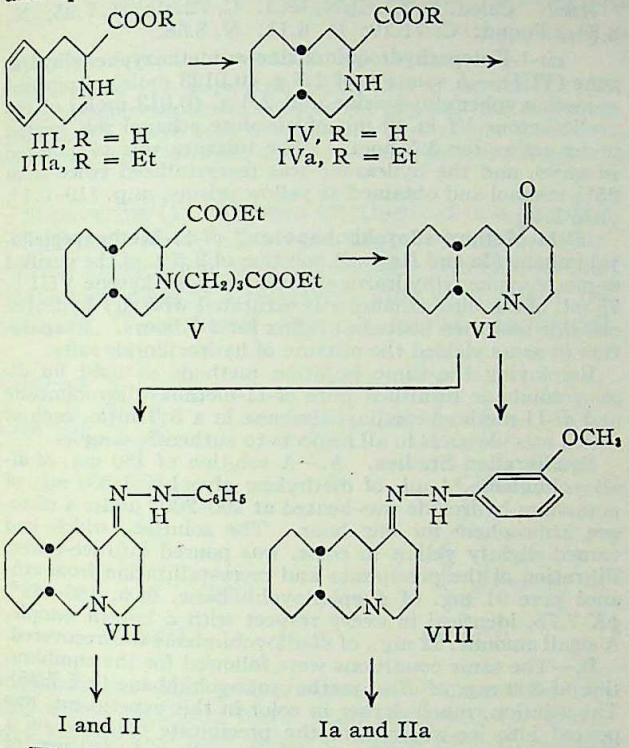
known *dl*-allo- and epialloyohimbanes. This same procedure, with slight modifications, was employed for the facile synthesis of *dl*-11-methoxyallo- and epialloyohimbane.



When 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid[8] was hydrogenated over 5% rhodium-on-alumina catalyst at 50°, three moles of hydrogen was consumed, and the crystalline *cis*-decahydroisoquinolinecarboxylic acid IV was isolated in 41% yield.

The substituents on the tetrahydroisoquinoline molecule have a great influence on the outcome of the rhodium-on-alumina reduction, for when the corresponding ester IIIa is employed, the alcohol results and no ring reduction occurs. However, preliminary evidence shows that tetrahydroisoquinolines substituted in the aromatic portions of the molecule are reduced in the desired manner and the substituents are retained.

By a series of reactions, analogous to those employed by Swan[9] for the synthesis of yohimbone, the ethyl ester IVa was alkylated with ethyl γ-bromobutyrate yielding the diester V. Dieckmann cyclization with sodium hydride in toluene, followed by acid hydrolysis and decarboxylation, converted the diester to the tricyclic ketone, *cis*-1-keto-perhydroquinolizine (VI). The reaction of VI with phenylhydrazine and subsequent treatment of the hydrazone VII with hot ethanolic hydrochloric acid furnished the desired *dl*-allo- and epialloyohimbane (I and II) as a mixture of hydrochlorides. Basification and chromatographic separation of the mixed bases yielded the pure isomers, the allo predominating. Under Huang-Minlon reduction conditions,[10] this allo isomer was epimerized to a large extent to epialloyohimbane. The interconversion of these isomers can be explained by the acidic and basic equilibration studies of Wenkert and Liu[3] which indicate that mixtures of bases can be expected.

The *m*-methoxyphenylhydrazone, which formed readily upon treatment of the ketone VI with *m*-methoxyphenylhydrazine, underwent the Fischer indole reaction giving *dl*-11-methoxyallo- and epialloyohimbane (Ia and IIa) as a mixture of hydrochlorides. The free bases were obtained by neutralization and chromatographic separation, the major portion, as before, being the allo isomer. Again, this allo isomer under alkaline conditions was epimerized to the epiallo isomer.

The successful applications of this method to the synthesis of the pentacyclic bases are encouraging and experiments are in progress to determine the generality of this procedure for obtaining derivatives substituted at various positions in these ring systems.

During these investigations *l*-yohimbane was required for comparison studies. The ethanedithiol derivative of *l*-yohimbone was formed readily, and upon treatment with freshly prepared W-7 Raney nickel catalyst in dioxane was converted to *l*-yohimbane. Previous attempts to desulfurize *l*-yohimbone ethanethiol were reported to be unsuccessful.[11]

Acknowledgments.—We gratefully acknowledge valuable assistance by: Messrs. G. M. Maciak, W. L. Brown, H. L. Hunter and Miss G. Beckmann, elemental analysis; Dr. H. E. Boaz, Messrs. P. W. Landis, R. C. Reed and Miss M. Hofman, physicochemical measurements; Dr. H. A. Rose and Miss A. Van Camp, X-ray data.

Experimental

3-Carboxy-1,2,3,4-tetrahydroisoquinoline (III).—The modified procedure of Julian[8] was followed for the condensation of phenylalanine with formaldehyde to furnish the isoquinolinecarboxylic acid in 70% yield. The corresponding ethyl ester IIIa was prepared by the method of Archer.[12]

***cis*-3-Carboxydecahydroisoquinoline (IV).**—A mixture of 20 g. 3-carboxy-1,2,3,4-tetrahydroisoquinoline in 300 ml. of 50% ethanol and 5 g. of 5% rhodium-on-alumina catalyst (J. T. Baker Chemical Co.) absorbed three moles of hydrogen at 50–100° and 15 atmospheres. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo*. The product was recrystallized three times from ethanol, m.p. 256–257°, yield 8.2 g. (41%).

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.55; N, 7.64. Found: C, 65.45; H, 9.35; N, 7.46.

The hydrochloride salt was crystallized from ethanol–ether, m.p. 235–236°.

Anal. Calcd. for $C_{10}H_{17}NO_2 \cdot HCl$: C, 54.67; H, 8.26; N, 6.38. Found: C, 54.66; H, 8.49; N, 6.10.

3-Hydroxymethyl-1,2,3,4-tetrahydroisoquinoline.—A solution of 20.3 g. (0.1 mole) of ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate in 50 ml. of absolute ethanol was hydrogenated over 5 g. of rhodium-on-alumina catalyst at 50° and 50 atmospheres for 17 hours. The product was isolated by distillation followed by crystallization from benzene as colorless plates, m.p. 82–83.5°, yield 6.0 g. (36%).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.72; H, 8.22; N, 8.49.

The hydrochloride salt was crystallized from ethanol–ether, m.p. 185–188°.

Anal. Calcd. for $C_{10}H_{13}NO \cdot HCl$: C, 60.15; H, 7.07; N, 7.02. Found: C, 59.84; H, 7.29; N, 6.78.

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Ethyl *cis*-Decahydroisoquinoline-3-carboxylate Hydrochloride (IVa).—By the procedure of Brenner and Huber,[13] 1.3 ml. of thionyl chloride in 10 ml. of absolute ethanol was allowed to react with 2.0 g. of *cis*-decahydroisoquinoline-3-carboxylic acid. Recrystallization from benzene–ether gave 1.5 g. (56%) of ester as colorless solid, m.p. 166–168°.

Anal. Calcd. for $C_{12}H_{21}NO_2 \cdot HCl$: C, 58.65; H, 9.02; N, 5.70. Found: C, 58.42; H, 8.99; N, 5.48.

Ethyl 2-(γ-Carbethoxypropyl)-*cis*-decahydroisoquinoline-3-carboxylate (V).—A mixture of 100 g. (0.475 mole) of the above ester, 92.5 g. (0.475 mole) of ethyl γ-bromobutyrate and 65.5 g. (0.475 mole) of anhydrous potassium carbonate was heated with stirring for 27 hours. The mixture was cooled, poured onto crushed ice and the mixture extracted with ether. The residue obtained on evaporation of the ether was distilled, b.p. 168–172° (0.75 mm.), $n^{25}D$ 1.4768, yield 110.6 g. (75.5%).

Anal. Calcd. for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.26; H, 9.57; N, 4.57.

***cis*-1-Ketoperhydroquinolizine (VI).**—To a suspension of 4.8 g. (0.2 mole) of sodium hydride in 25 ml. of dry toluene was added dropwise a solution of 32.5 g. (0.1 mole) of diester V in toluene over a period of 45 minutes. Following the addition, the reaction mixture was heated at reflux for 5 hours. To the stirred, cooled mixture was added cautiously 10 ml. of ethanol followed by 10 ml. of water. Concentrated hydrochloric acid (200 ml.) was then introduced, and the reaction mixture was heated under reflux for 17 hours. The mixture was evaporated to dryness *in vacuo*, the residue dissolved in 50 ml. of water and then basified with solid potassium carbonate. Ether extraction followed by drying and evaporation of the solvent left a residue which crystallized as colorless needles from absolute ethanol, m.p. 103–104°, yield 10.6 g. (51%).

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.31; N, 6.76. Found: C, 74.86; H, 10.33; N, 6.57.

The hydrochloride salt was crystallized from ethanol–ether, m.p. 208–210°.

Anal. Calcd. for $C_{13}H_{21}NO \cdot HCl$: C, 64.05; H, 9.10; N, 5.75. Found: C, 63.71; H, 9.23; N, 5.52.

***cis*-1-Ketoperhydroquinolizinephenylhydrazone (VII).**—A solution of 1.1 g. (0.01 mole) of purified phenylhydrazine and 2.0 g. (0.0096 mole) of tricyclic ketone VI in 10 ml. of absolute ethanol was heated under reflux for 2.5 hours. The mixture was evaporated *in vacuo*, and the residue was recrystallized twice from absolute ethanol–ether and obtained as yellow prisms, m.p. 127–129°, yield 1.4 g.

***dl*-Alloyohimbane and *dl*-Epialloyohimbane (I and II).**—A solution of 1.4 g. of the recrystallized phenylhydrazone of the tricyclic ketone VII in 75 ml. of absolute ethanol was saturated with dry hydrogen chloride and then heated at reflux for 3 hours. The mixture of hydrochloride salts was obtained by evaporation *in vacuo*. Careful neutralization with sodium hydroxide solution followed by ether extraction and chromatography of the residue on alumina furnished the pure *dl*-alloyohimbane and *dl*-epialloyohimbane in about a 5:1 ratio. Each of these were identical in all respects (X-ray, infrared and ultraviolet spectra, and melting points) to previously prepared bases.[14]

The allo isomer hydrochloride was obtained directly from the mixed hydrochlorides by several recrystallizations from aqueous ethanol, m.p. 294–297°.

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot HCl$: C, 72.01; H, 7.95; N, 8.84. Found: C, 71.79; H, 8.11; N, 8.68.

***cis*-1-Ketoperhydroquinolizine-*m*-methoxyphenylhydrazone (VIII).**—A solution of 1.7 g. (0.0123 mole) of purified *m*-methoxyphenylhydrazine and 2.6 g. (0.013 mole) of tricyclic ketone VI in 10 ml. of absolute ethanol was heated under reflux for 2.5 hours. The mixture was evaporated *in vacuo*, and the hydrazone was recrystallized twice from 95% ethanol and obtained as yellow prisms, m.p. 119–121°, yield 1.4 g.

***dl*-11-Methoxyalloyohimbane and *dl*-11-Methoxyepialloyohimbane (Ia and IIa).**—A solution of 2.5 g. of the purified *m*-methoxyphenylhydrazone of the tricyclic ketone VIII in 75 ml. of absolute ethanol was saturated with dry hydrogen chloride and then heated at reflux for 2.5 hours. Evaporation *in vacuo* yielded the mixture of hydrochloride salts.

Employing the same isolation methods as used for *dl*-alloyohimbane furnished pure *dl*-11-methoxyalloyohimbane and *dl*-11-methoxyepialloyohimbane in a 5:1 ratio, each of which was identical in all respects to authentic samples.

Equilibration Studies. A.—A solution of 180 mg. of *dl*-alloyohimbane, 4 ml. of diethylene glycol and 500 mg. of potassium hydroxide was heated at 190–200° under a nitrogen atmosphere for one hour. The solution, which had turned slightly yellow in color, was poured into ice-water. Filtration of the precipitate and recrystallization from ethanol gave 91 mg. of *dl*-epialloyohimbane, m.p. 186–188°, *pK* 7.75, identical in every respect with a known sample. A small amount, 22 mg., of *dl*-alloyohimbane was recovered.

B.—The same conditions were followed for the equilibration of 300 mg. of *dl*-11-methoxyalloyohimbane (*pK* 7.35). The solution, much darker in color in this experiment, was poured into ice-water, and the precipitate collected on a filter. After recrystallization from methanol, 110 mg. of *dl*-11-methoxyepialloyohimbane was obtained, m.p. 203–205°, *pK* 7.90. In this case also, a small amount of starting material was obtained.

***l*-Yohimbone Ethanedithiol.**—Dry hydrogen chloride was bubbled into a cold solution of 1.0 g. of *l*-yohimbone and 5 ml. of ethanedithiol in 40 ml. of glacial acetic acid for 15 minutes, and the reaction mixture was allowed to remain at room temperature overnight. The product was removed by filtration, added to water and basified with ammonium hydroxide solution to liberate the free base as a colorless solid, m.p. 158–161°, yield 1.03 g.

Anal. Calcd. for $C_{21}H_{26}N_2S_2$: N, 7.56. Found: N, 7.27.

***l*-Yohimbane.**—A mixture of 200 mg. of the ethanedithiol derivative, 50 ml. of purified dioxane and 2 ml. of a dense Raney nickel suspension (freshly prepared W-7) was stirred and heated at reflux for 16 hours. The catalyst was removed by filtration, and the filtrate evaporated *in vacuo*. Chromatography of the residue on alumina furnished 60 mg. of *l*-yohimbane, m.p. 207–208°, identical with material obtained by Huang-Minlon reduction conditions on *l*-yohimbone.

INDIANAPOLIS, INDIANA

(13) M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953).

(14) Authentic samples were kindly supplied by Drs. E. Wenkert and E. van Tamelen.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

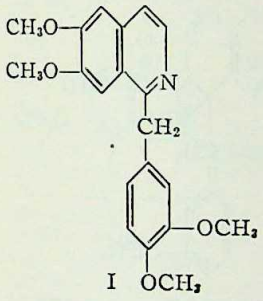
Syntheses of Papaverine, Papaverinol and Papaveraldine from Reissert Compounds

BY FRANK D. POPP AND WILLIAM E. MCEWEN

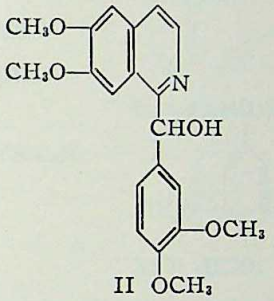
RECEIVED JANUARY 21, 1957

Papaverine (I), papaverinol (II) and papaveraldine (III) have been synthesized from 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) as the key starting material. Improved methods for the preparation of 6,7-dimethoxyisoquinoline (V) have been developed. Several new Reissert compounds have been prepared and subjected to characteristic acid-catalyzed hydrolysis and base-catalyzed condensation, displacement or rearrangement reactions.

Papaverine (I) has been synthesized in a number of different ways, all of the reported methods requiring application of a ring-closure reaction as one of the last steps of a relatively long sequence of reactions.[1] There are several known industrial methods for the preparation of papaverine (I), and these methods have been reviewed by Burger,[2] Dickenson[3] and Wahl.[4] Since procedures are known[5-15] for the interconversion of papaverine (I), papaverinol (II) and papaveraldine (III), syntheses of the latter two compounds may also be considered equivalent to syntheses of papaverine (I).[16,17]



I



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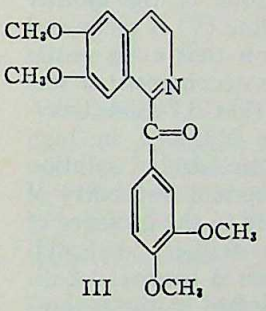
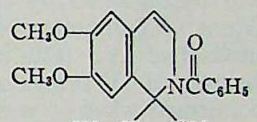
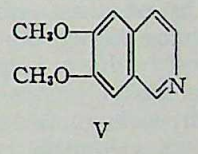


III



IV



V

Owing to a number of recently discovered reactions of Reissert compounds,[18] it appeared likely that papaverine (I), papaverinol (II) and papaveraldine (III) could all be synthesized quite readily from 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV)[19] as the key starting material. The first requirement, however, was to develop a convenient method of synthesis of 6,7-dimethoxyisoquinoline (V), from which the Reissert compound IV may be prepared.[19]

On the basis of reports in the literature it appeared that 6,7-dimethoxyisoquinoline (V) could be prepared from homoveratrylamine (VI) in about 35% yield by a Bischler–Napieralski reaction of the N-formyl derivative of VI, followed by catalytic dehydrogenation of the resulting dihydro derivative of V.[20-24] 6,7-Dimethoxyisoquinoline (V) also has been prepared in 19% yield by oxidative cyclization of veratrylaminoacetal (VII) with arsenic pentoxide and sulfuric acid.[25,26] It was stated[25] that veratrylideneaminoacetal (VIII) would not undergo a normal Pomeranz–Fritsch reaction. By appropriate modifications of the previously reported[20-24] procedures it has now been found that 6,7-dimethoxyisoquinoline (V) may be prepared in about 70% yield by the Bischler–Napieralski ring-closure and catalytic dehydrogenation route. Also, by use of a mixture of polyphosphoric acid and phosphorus oxychloride as the cyclizing agent, veratrylideneaminoacetal (VIII) has been converted to 6,7-dimethoxyisoquinoline (V) in about 55% yield. Other workers have found that Pomeranz–Fritsch ring-closure reactions may sometimes be effected by use of polyphosphoric acid when the usual sulfuric acid method fails.[27]

By reaction of 6,7-dimethoxyisoquinoline (V), benzoyl chloride and aqueous potassium cyanide, Haworth and Perkin[19] obtained a 35% yield of

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(17) D. Guthrie, A. W. Frank and C. B. Purves, *Canadian J. Chem.*, **33**, 729 (1955).
(18) W. E. McEwen and R. L. Cobb, *Chem. Revs.*, **55**, 511 (1955).
(19) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **127**, 1434 (1925).
(20) E. Spath and H. Epstein, *Ber.*, **59**, 2791 (1926).
(21) E. Spath and N. Polgar, *Monatsh.*, **51**, 190 (1929).
(22) G. A. Swan and D. Wright, *J. Chem. Soc.*, 1549 (1956).
(23) J. S. Buck and W. Ide, THIS JOURNAL, **60**, 2101 (1938).
(24) W. M. Whaley and M. Meadow, *J. Chem. Soc.*, 1067 (1953).
(25) L. Rugheimer and P. Schon, *Ber.*, **42**, 2374 (1909).
(26) R. Forsyth, C. Kelly and F. Pyman, *J. Chem. Soc.*, **127**, 1659 (1925).
(27) W. E. McEwen and J. Tsai, THIS JOURNAL, **75**, 5122 (1953).

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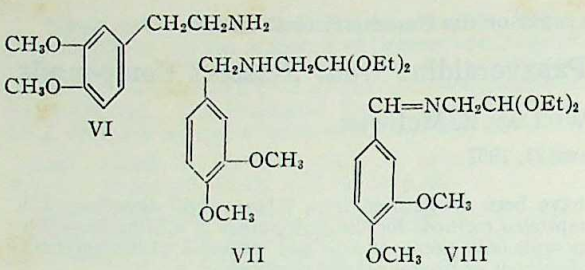
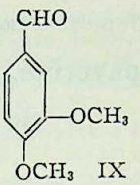
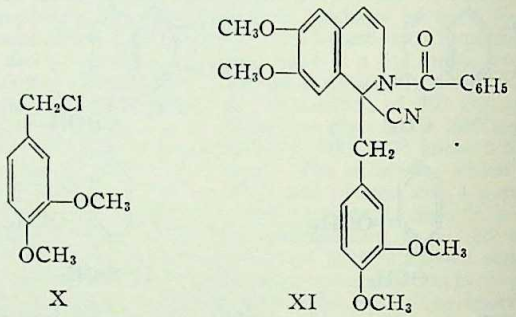


crude 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV). We have found that crude material can be obtained in as high as 90% yield, but that purification of the product by recrystallization from ethanol leads to a marked diminution of the yield. Furthermore, no Reissert compound can be obtained by concentration of the mother liquor; 6,7-dimethoxyisoquinoline (V) is recovered instead of IV. The implication that even gentle heating of IV brings about its decomposition was confirmed when it was found that 6,7-dimethoxyisoquinoline picrate could be obtained in high yield by warming pure IV in an alcohol solution containing picric acid. The thermal instability of IV must be due in large measure to the presence of the methoxyl groups because neither 2-benzoyl-1,2-dihydroisoquinaldonitrile nor 1-benzoyl-1,2-dihydroquinaldonitrile gave a picrate of the heterocyclic base upon being warmed in an alcohol solution containing picric acid. The lithium salt of IV, prepared by a metal–hydrogen exchange reaction of IV and phenyllithium, proved to be even less stable than the Reissert compound itself. Even at −10°, the characteristic red color of the lithium salt in ether–dioxane solution rapidly disappeared. However, at a temperature of −20°, the red color persisted for an appreciable period of time.

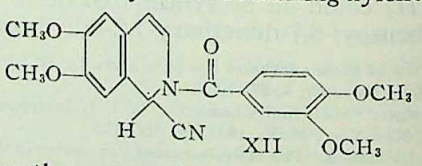
In view of the thermal instability of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) and its lithium salt, it was felt that a synthesis of papaverine (I) or one of its derivatives could best be effected by use of reactions which occur at low temperatures. A recent finding,[28] namely, that the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile would react with benzaldehyde at an initial temperature of −20° to give eventually the benzoate of phenyl-1-isoquinolylcarbinol, suggested a method for the synthesis of papaverinol (II). The lithium salt of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile, prepared by metalation of IV with phenyllithium in ether–dioxane solution, was caused to condense with one equivalent of veratraldehyde (IX) at an initial temperature of −20°. Alkaline hydrolysis of the resultant product afforded papaverinol (II) in 67% yield. When the lithium salt of IV was treated with an excess of veratraldehyde (IX) and the reaction mixture later refluxed with aqueous alcoholic potassium hydroxide solution, papaveraldine (III) rather than papaverinol (II) was obtained in 67% yield. Evidently the excess veratraldehyde (IX) functions as an oxidizing agent for the conversion of II to III in a strongly alkaline medium.

Owing to the fact that 3,4-dimethoxybenzylchloride (X) is highly reactive in nucleophilic displacement reactions, it was felt that an alkylation reaction similar to that reported by Boekelheide and co-workers[29−31] might be carried out at a low temperature. Treatment of the lithium salt of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) with X at an initial temperature of −20° gave the condensation product, XI, which was not purified; alkaline cleavage of crude XI afforded papaverine (I) in 22% yield.





Due to the relatively high temperature required to bring about the base-catalyzed rearrangement of a Reissert compound to the α-acyl derivative,[29,32,33] it did not seem likely that papaveraldine (III) could be synthesized by application of such a method. This proved to be the case. 2-(3,4-Dimethoxybenzoyl)-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (XII) was prepared in 73% yield by the Grosheintz and Fischer method,[34] but no papaveraldine (III) was obtained on treatment of XII with sodium hydride in refluxing xylene.



During the course of these studies, a number of new Reissert compounds were prepared and some of their characteristic reactions investigated. In addition to XII, the new compounds included 2-(3,4-dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile, 2-cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile and 2-anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile. Papaverinol (II) could be obtained from the latter two compounds in the same manner as described earlier for the preparation of II from 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV). All four Reissert compounds gave aldehydes in high yield upon acid-

(28) L. R. Walters and W. E. McEwen, unpublished results.

(29) V. Boekelheide and J. Weinstock, THIS JOURNAL, **74**, 66 (1952).

(30) V. Boekelheide and J. Godfrey, *ibid.*, **75**, 3679 (1953).

(31) V. Boekelheide and A. Seig, *J. Org. Chem.*, **19**, 587 (1954).

(32) W. E. McEwen, J. V. Kindall, R. N. Hazlett and R. H. Glazier THIS JOURNAL, **73**, 4591 (1951).

(33) A. P. Wolf, W. E. McEwen and R. H. Glazier, *ibid.*, **78**, 861 (1956).

(34) J. M. Grosheintz and O. L. Fischer, *ibid.*, **63**, 2021 (1941).

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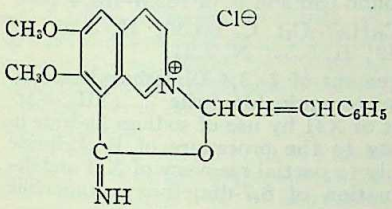
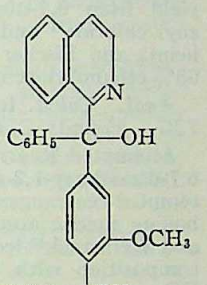
catalyzed hydrolysis. By reaction of 2-cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile with anhydrous hydrogen chloride, there was obtained a red solid of molecular formula $C_{21}H_{21}N_2O_4Cl$. This corresponds to the monohydrate of the salt of structure XIII (or a tautomer), the type of intermediate anticipated on the basis of the mechanism recently proposed[35] for the acid-catalyzed hydrolysis of Reissert compounds. Although 2-(3,4-dimethoxybenzoyl) - 1,2 - dihydroisoquinaldonitrile would not undergo reaction with sodium hydride to form 1-(3,4-dimethoxybenzoyl)-quinoline, reaction with phenyllithium gave phenyl-3,4-dimethoxyphenyl-1-isoquinolylcarbinol (XIV), proving that a rearrangement reaction could be effected under the right conditions.



XIII



XIV

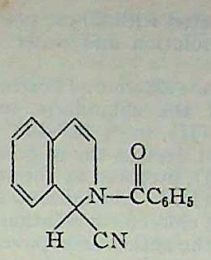
Prior to the reactions cited earlier, those leading to the preparation of papaverine (I), papaverinol (II) and papaveraldine (III), some model reactions were carried out with the readily available[36] Reissert compound, 2-benzoyl-1,2-dihydroisoquinaldonitrile (XV). Reaction of the lithium salt of XV with one equivalent of veratraldehyde (IX) gave the benzoate XVI of 3,4-dimethoxyphenyl-1-isoquinolylcarbinol XVII in 86% yield, whereas reaction of the lithium salt of XV with an excess of veratraldehyde (IX), with subsequent alkaline hydrolysis of the crude product, gave a mixture of XVII and 1-(3,4-dimethoxybenzoyl)-quinoline (XVIII). Alkylation of the lithium salt of XV with 3,4-dimethoxybenzyl chloride (X), with subsequent alkaline cleavage of the initially formed product, gave 1-(3,4-dimethoxybenzyl)-isoquinoline (XIX) in 53% yield.

Acknowledgment.—This investigation was supported by a research grant, H-2155, from the National Heart Institute of the National Institutes of Health, Public Health Service.

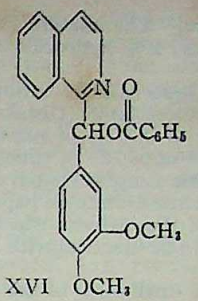
Experimental[37]

6,7-Dimethoxy-3,4-dihydroisoquinoline.—This compound was prepared in 97% yield from homoveratrylamine (VI) by the same procedure used by Haworth[38] to prepare 5,6-dimethoxy-3,4-dihydroisoquinoline from β-(2,3-dimethoxyphenyl)-ethylamine. Its picrate melted at 207–208° (reported[39] m.p. 206–208°).

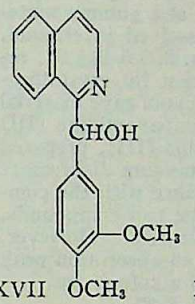
6,7-Dimethoxyisoquinoline (V).—To a solution of 10.3 g. (0.054 mole) of crude 6,7-dimethoxy-3,4-dihydroisoquinoline in 31.5 cc. of decalin was added 5.7 g. of 10% palladium-on-charcoal catalyst, and the mixture was refluxed for 1.5 hr. The suspension was extracted with 15% hydrochloric acid, the acid solution filtered, made alkaline and extracted with ether. Distillation of the ether afforded 8.34 g. (82%) of crude 6,7-dimethoxyisoquinoline (V); picrate, m.p. 222–224° (reported m.p. 218–220°,[25] 226–227°[21]). Distillation of 37.3 g. of crude material gave 33 g. of purified 6,7-dimethoxyisoquinoline (V), b.p. 152–158° (0.8–0.9 mm.).



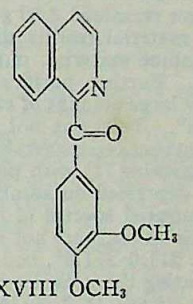
XV



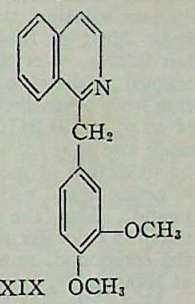
XVI



XVII



XVIII



XIX

Preparation of 6,7-Dimethoxyisoquinoline (V) by the Pomeranz–Fritsch Method.—Veratrylideneaminoacetal (VIII) was prepared in quantitative yield from veratraldehyde (IX) and aminoacetal by the method of Forsyth, Kelly and Pyman.[26] To a solution of 25 g. of phosphorus oxychloride in 160 g. of polyphosphoric acid maintained at 23–26° was added with stirring during a 10-minute period 25 g. (0.087 mole) of veratrylideneaminoacetal (VIII). The mixture was stirred for an additional 2 hr. at 23–26°, then added to ice-water. The acid solution was washed with ether, made alkaline and extracted with chloroform. Distillation of the chloroform left a dark, viscous oil, which was extracted with ether. Distillation of the ether afforded 8.25 g. (53%) of crude 6,7-dimethoxyisoquinoline (V); picrate, m.p. 220–221°.

2-Benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV).—To an ice-cold mixture of 5.3 g. (0.081 mole) of potassium cyanide, 30 cc. of water and 5.1 g. (0.027 mole) of 6,7-dimethoxyisoquinoline (V) was added with stirring 7.6 g. (0.054 mole) of benzoyl chloride during a period of seven minutes. The mixture was stirred for an additional 1.7 hr. at room temperature, then the aqueous solution was decanted from an orange solid. After having been washed with water, 10% hydrochloric acid, water again and ether, and dried, the solid weighed 8.0 g. and had a m.p. of 130–135°. One crystallization from absolute ethanol gave 2.66 g. (31%) of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV), m.p. 153–155° (reported[19] m.p. 164°). This material was sufficiently pure to be used in the reactions to be described below.

In another run, the anhydrous method of Grosheintz and Fischer[34] was employed. From a mixture of 37.84 g. (0.20 mole) of 6,7-dimethoxyisoquinoline (V), 10 cc. of liquid hydrogen cyanide and 14.06 g. (0.10 mole) of benzoyl chloride in anhydrous benzene there was obtained 27.0 g. of gummy material. One crystallization from absolute ethanol gave 6.05 g. (19%) of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV), m.p. 156–157°.

Reaction of the Lithium Salt of 2-Benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile with 1.16 Equivalents of Veratraldehyde (IX).—To a solution of 2.00 g. (0.0062 mole) of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) in 15 cc. of anhydrous ether and 25 cc. of anhydrous dioxane was added slowly an ether solution of phenyllithium prepared from 1.62 g. of bromobenzene, the solution being stirred and maintained at a temperature of −20° and under a nitrogen atmosphere during this and the subsequent operation. To the deep red solution was added slowly 1.20 g. (0.0072 mole) of veratraldehyde (IX). The mixture was stirred for 1 hr. at −20° and then for 12 hr. at room tem-

(35) R. L. Cobb and W. E. McEwen, THIS JOURNAL, **77**, 5042 (1955).
(36) J. Padbury and H. Lindwall, *ibid.*, **67**, 1268 (1945).
(37) Analyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. All m.p.'s are corrected.
(38) R. D. Haworth, *J. Chem. Soc.*, 2281 (1927).
(39) F. Pyman, *ibid.*, **95**, 1610 (1909).

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perature. The mixture was extracted with 20-cc. portions of water, 2% hydrochloric acid solution and water once again.

The aqueous acid solution was made alkaline and extracted with chloroform. Distillation of the chloroform left a residue of 0.77 g. of papaverinol (II), m.p. 137–138° (reported[13] m.p. 137°), which did not depress the m.p. of an authentic sample of papaverinol (II), prepared by the action of mercuric acetate on papaverine (I).[13] The infrared spectrum of the material was taken in chloroform solution and found to be identical with that of the authentic papaverinol (II).

After distillation of the solvents from the original ether–dioxane solution, there remained 2.80 g. of a gummy material. Most of this material readily dissolved in ethanol, but 0.30 g. of crystalline material, m.p. 209.5–211.0°, remained undissolved. Further purification by crystallization from a relatively large amount of ethanol gave material of m.p. 211.0–211.8°. This was not papaveraldine (III) since the m.p. of authentic papaveraldine (III), prepared by oxidation of papaverine (I) with potassium dichromate in acetic acid,[7] was depressed on admixture with the compound. Also, the infrared spectra of the two compounds, taken in chloroform solution, were not identical. However, the compound, m.p. 211.0–211.8°, had an absorption peak at 1650 cm.$^{-1}$, indicating the presence of a keto group.

Anal. Found: C, 68.80; H, 5.39; N, 8.37.

A solution of 0.88 g. of potassium hydroxide in 50 cc. of water was added to the ethanol solution of the gummy material cited above and the mixture was refluxed for 1.7 hr. The ethanol was distilled *in vacuo* and the aqueous solution extracted with chloroform. Evaporation of the chloroform gave 0.72 g. of papaverinol (II), m.p. 133–135°. The total yield of papaverinol (II) was 1.49 g. (67%).

Reaction of the Lithium Salt of 2-Benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile with an Excess of Veratraldenyde (IX).—A reaction was carried out with the lithium salt prepared from 2.70 g. (0.0084 mole) of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) and 6.50 g. (0.039 mole) of veratraldehyde (IX) in the same manner as described above. After the washing operation with water and 2% hydrochloric acid (no organic material obtained on making the acid wash alkaline), the solvent was distilled from the organic layer. The residual oil was added to a solution of 1.17 g. of potassium hydroxide in 60 cc. of 33% ethanol, and the resulting mixture was refluxed for 1 hr. Most of the alcohol was removed by distillation *in vacuo*, and the residual mixture was extracted with chloroform. The chloroform solution was extracted with 10% hydrochloric acid, then the aqueous acid solution was made alkaline and extracted with fresh chloroform. Removal of the chloroform by distillation gave 1.99 g. (67%) of papaveraldine (III), m.p. 195–200° (reported[8,9] m.p. 210°). Recrystallization from absolute ethanol gave material of m.p. 208–209°, which did not depress the m.p. of authentic papaveraldine (III).[7] The infrared spectrum of the compound was taken in chloroform solution and found to be identical with that of the authentic material.

3,4-Dimethoxybenzyl Chloride (X).—This compound, m.p. 49–51°, was prepared in 73% yield by the method of Kindler and Gehlhaar.[40]

Synthesis of Papaverine (I).—To a solution of 3.20 g. (0.01 mole) of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) in 25 cc. of anhydrous ether and 30 cc. of anhydrous dioxane maintained at −20° was added with stirring an ether solution of phenyllithium prepared from 1.93 g. of bromobenzene. The solution was maintained under an atmosphere of pure nitrogen during this and the subsequent operation. To the exchange mixture was added a solution 2.33 g. (0.0125 mole) of 3,4-dimethoxybenzyl chloride in 5 cc. of ether. The reaction mixture was stirred at −20° for 2 hr., then at room temperature for 12 hr. The mixture was washed with 25-cc. portions of water, 0.5 *M* hydrochloric acid and water once again. Distillation of the solvent gave 5.63 g. of gummy material. Upon addition of ethanol to this material, 0.33 g. of starting material, 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV), m.p. 159.5–161.0°, crystallized and was collected by filtration. To the filtrate was added a solution of 1.40 g. of potassium hydroxide in 60 cc. of water, and the resulting mixture was refluxed for 1.5 hr. Most of the alcohol was removed by distillation *in vacuo*, and the residue was extracted with ether. Distillation of the ether gave 3.62 g. of gummy solid. This was dissolved in chloroform, extracted with 10% hydrochloric acid and the acid solution made alkaline by addition of sodium bicarbonate. Extraction of the alkaline mixture with benzene afforded 2.06 g. of gummy material. Trituration of this material with absolute ethanol gave as the residue 0.68 g. (22%) of papaverine (I), m.p. 140–144°, reported[15] m.p. 146–147°. Recrystallization from ethanol gave material of m.p. 145–147° which did not depress the m.p. of an authentic sample of papaverine (I). The infrared spectrum of the material was taken in chloroform solution and found to be identical with that of authentic papaverine (I).

Addition of picric acid to the alcohol solution from the trituration step caused 0.46 g. of the picrate of 6,7-dimethoxyisoquinoline (V) to precipitate. The m.p. was found to be 225–226°, also in admixture with authentic V.

2-(3,4-Dimethoxybenzoyl)-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (XII).—The compound was prepared in 73% yield from 6,7-dimethoxyisoquinoline, 3,4-dimethoxybenzoyl chloride[41] and liquid hydrogen cyanide by the Grosheintz and Fischer method.[34] After recrystallization from 95% ethanol the compound had a m.p. of 152.0–152.4°.

Anal. Calcd. for $C_{21}H_{20}N_2O_5$: C, 66.30; H, 5.30; N, 7.37. Found: C, 66.49; H, 5.53; N, 7.21.

Attempted Rearrangement of 2-(3,4-Dimethoxybenzoyl)-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (XII).—Attempted rearrangement of XII by use of sodium hydride in boiling xylene according to the procedure of Boekelheide and Weinstock[29] led only to partial recovery of XII and decomposition with formation of 6,7-dimethoxyisoquinoline (V).

2-(3,4-Dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile.—To a mixture of 13.5 g. (0.207 mole) of potassium cyanide, 80 cc. of water and 8.90 g. (0.069 mole) of isoquinoline was added with stirring 26.2 g. (0.138 mole) of freshly prepared 3,4-dimethoxybenzoyl chloride[41] during a period of 15 minutes. The mixture was stirred for an additional 50 minutes. A solid material which had formed was collected by filtration and washed with water, 10% hydrochloric acid and ether. This treatment provided 16.16 g. (73%) of crystalline 2-(3,4-dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile, m.p. 193.5–196.5°. Recrystallization from glacial acetic acid, then absolute ethanol gave pure material, m.p. 202.3–202.6°.

Anal. Calcd. for $C_{19}H_{16}O_3N_2$: C, 71.24; H, 5.04; N, 8.75. Found: C, 71.02; H, 5.26; N, 8.80.

2-Cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile.—The compound was prepared in 68% yield from 6,7-dimethoxyisoquinoline (V), cinnamoyl chloride and liquid hydrogen cyanide by the Grosheintz and Fischer method.[34] Upon recrystallization from absolute ethanol there was obtained yellow crystalline material of m.p. 164.8–165.4°.

Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 73.05; H, 5.21; N, 7.91.

2-Anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile.—Prepared in 78% yield by the Grosheintz and Fischer method,[34] the compound was crystallized from absolute ethanol, giving material of m.p. 156.4–157.2°.

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.69; H, 4.95; N, 8.16.

Acid-catalyzed Hydrolysis of the Reissert Compounds.—Each of the Reissert compounds was subjected to acid catalyzed hydrolysis in a hydrochloric acid solution of 2,4-dinitrophenylhydrazine as previously described.[42] From 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) there was obtained an 84% yield of benzaldehyde 2,4-dinitrophenylhydrazone; from 2-(3,4-dimethoxybenzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (XII), 87% of veratraldehyde 2,4-dinitrophenylhydrazone; from 2-(3,4-dimethoxybenzoyl-1,2-dihydroisoquinaldonitrile, 91% of veratraldehyde 2,4-dinitrophenylhydrazone; from 2-cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile, 98% of cinnamaldehyde 2,4-dinitrophenylhydrazone; and from 2-anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile, 89% of anisaldehyde 2,4-dinitrophenylhydrazone.

(40) K. Kindler and E. Gehlhaar, *Arch. Pharm.*, **274**, 377 (1936).

(41) H. Ryan and M. Walsch, *Sci. Proc. Roy. Dublin Soc. (N.S.)*, **15**, 113 (1916).

(42) W. E. McEwen, R. H. Terss and I. W. Elliott, THIS JOURNAL, **74**, 3605 (1952).

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Reaction of 2-Cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile with Anhydrous Hydrogen Chloride.—When anhydrous hydrogen chloride was passed into a pure chloroform solution of 2-cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile at 0° and in an atmosphere of pure nitrogen, the solution first turned yellow, then orange and finally a red solid precipitated. This was washed with ether and dried over calcium chloride *in vacuo*. It is thought that the substance is a monohydrate of XIII or its tautomer. The substance decomposed at 190–192°.

Anal. Calcd. for $C_{21}H_{21}N_2O_4Cl$: C, 62.92; H, 5.28; N, 6.99; Cl, 8.85. Found: C, 61.92; H, 5.18; N, 6.84; Cl, 9.53.

Preparation of Papaverinol (I) from 2-Anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile and from 2-Cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile.—The condensation reactions with veratraldehyde (IX) were carried out in the same manner as described above for the reaction of the lithium salt of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) with 1.16 equivalents of veratraldehyde (IX). The yields of papaverinol (I) were about the same as when IV was employed.

Base-catalyzed Rearrangement of 2-(3,4-Dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile.—Only starting material was recovered after an attempt to prepare 1-(3,4-dimethoxybenzoyl)-isoquinoline by treatment of 2-(3,4-dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile with sodium hydride in boiling xylene according to the procedure of Boekelheide and Weinstock.[29]

To a solution of 5.12 g. (0.016 mole) of 2-(3,4-dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile in 18 cc. of anhydrous dioxane and 5 cc. of anhydrous ether maintained at −10° and in an atmosphere of nitrogen, there was slowly added with stirring an ether solution of phenyllithium prepared from 3.70 g. of bromobenzene. The deep red reaction mixture was stirred for an additional 15 minutes at −10°, for 3.5 hr. at room temperature, for 15 minutes at 100°, then allowed to stand at room temperature for 12 hr. The mixture was washed with water, then extracted with 10% hydrochloric acid. The acid solution was made alkaline, and ether extraction provided 1.76 g. of very crude phenyl-3,4-dimethoxyphenyl-1-isoquinolylcarbinol (XIV). This material was converted to the picrate, m.p. 172.5–173.5° after several recrystallizations from ethanol.

Anal. Calcd. for $C_{30}H_{24}N_4O_{10}$: C, 60.00; H, 4.03; N, 9.33. Found: C, 60.25; H, 4.02; N, 9.25.

The picrate was decomposed with lithium hydroxide solution and extracted with chloroform. From the chloroform extract there was obtained phenyl-3,4-dimethoxyphenyl-1-isoquinolylcarbinol (XIV), m.p. 135–136° after recrystallization from ethanol.

Anal. Calcd. for $C_{24}N_{21}NO_3$: C, 77.60; H, 5.70; N, 3.77. Found: C, 77.73; H, 5.82; N, 3.84.

Concentration of the organic layer remaining after the extraction with hydrochloric acid gave 2.27 g. of a viscous oil. Sublimation at 0.4 mm. afforded 0.5 g. of isoquinaldonitrile, m.p. 86–87° after recrystallization from petroleum ether (reported[36] for isoquinaldonitrile, m.p. 89.0–89.5°). This product did not depress the m.p. of a sample of authentic isoquinaldonitrile. The infrared spectrum of the material was taken in chloroform solution and found to be identical with that of authentic isoquinaldonitrile.

Condensation of 2-Benzoyl-1,2-dihydroisoquinaldonitrile (XV) with Veratraldehyde (IX).—To a solution of 10.41 g. (0.04 mole) of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XV) in 60 cc. of anhydrous dioxane and 20 cc. of anhydrous ether, maintained at −15° and under an atmosphere of nitrogen, was added slowly with stirring an ether solution of phenyllithium prepared from 7.22 g. of bromobenzene. To the deep red exchange mixture there was added slowly 6.65 g. (0.04 mole) of veratraldehyde (IX). The mixture was stirred at −15° for 2 hr., then at room temperature for 12 hr. The reaction mixture was washed with successive 25-cc. portions of water, 0.5 *M* hydrochloric acid and water. Distillation of the solvent left a residue of viscous oil. Addition of ethanol caused 13.76 g. (86%) of 3,4-dimethoxyphenyl-1-isoquinolylcarbinyl benzoate (XVI) to precipitate, m.p. 121–130°. Recrystallization from ethanol gave material of m.p. 134–135°.

Anal. Calcd. for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.06; H, 5.07; N, 3.77.

In a second run, a fourfold excess of veratraldehyde (IX) was employed. The benzoate XVI was isolated in 45% yield upon addition of ethanol to the residual oil as described above. The alcohol mother liquor was diluted to 40 cc. by addition of fresh ethanol, and then a solution of 3.2 g. of potassium hydroxide in 75 cc. of water was added. The mixture was refluxed for 5.5 hr. Ether extraction provided an oil, which was dissolved in chloroform and extracted with 10% hydrochloric acid. The acid solution was made alkaline and extracted with chloroform. Distillation of the chloroform gave an oil which was probably a mixture of 3,4-dimethoxy-1-isoquinolylcarbinol (XVII) and 1-(3,4-dimethoxybenzoyl)-isoquinoline (XVIII), since the infrared spectrum showed a characteristic carbinol peak at 3335 cm.$^{-1}$ and a characteristic ketone peak at 1685 cm.$^{-1}$.

Saponification of 3,4-Dimethoxyphenyl-1-isoquinolylcarbinyl Benzoate (XVI).—To a solution of 5.00 g. of the benzoate XVI in 50 cc. of ethanol was added a solution of 1.75 g. of potassium hydroxide in 100 cc. of water, and the mixture was refluxed for 6 hr. Ether extraction, followed by removal of the solvent gave 3.32 g. (90%) of 3,4-dimethoxyphenyl-1-isoquinolylcarbinol (XVII), m.p. 89–90°. The m.p. was not changed by recrystallization of the solid from ethanol or petroleum ether.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.00; H, 5.91; N, 4.86.

The picrate, m.p. 100–101°, was crystallized from ethanol.

Anal. Calcd. for $C_{24}H_{20}N_4O_{10}$: C, 54.96; H, 3.84; N, 10.68. Found: C, 54.77; H, 3.99; N, 10.45.

Acidification of the alkaline solution remaining from the ether extraction gave benzoic acid in quantitative yield.

When the benzoate XVI was mixed with an equal weight of veratraldehyde, then saponified, there was obtained a mixture of carbinol XVII and ketone XVIII, as indicated by the presence of absorption peaks at 3335 and 1680 cm.$^{-1}$ in the infrared spectrum.

Preparation of 1-(3,4-Dimethoxybenzyl)-isoquinoline (XIX).—When the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XV) was treated with 3,4-dimethoxybenzyl chloride (X) and the reaction mixture worked up in the same manner as described for the preparation of papaverine (I), there was obtained crude 1-(3,4-dimethoxybenzyl)-isoquinoline (XIX), an oil, in 53% yield. The picrate melted at 165.0–165.5° after crystallization from ethanol.

Anal. Calcd. for $C_{24}H_{20}N_4O_9$: C, 56.69; H, 3.97; N, 11.02. Found: C, 56.92; H, 3.89; N, 10.93.

LAWRENCE, KANSAS

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Xanthinin. II. The Structures of Xanthinin and Xanthatin

BY PETER G. DEUEL AND T. A. GEISSMAN

RECEIVED FEBRUARY 11, 1957

Xanthinin, $C_{17}H_{22}O_5$, and xanthatin, $C_{15}H_{18}O_3$, have been found to be α-methylenic lactones containing a single carbocyclic ring. Evidence is presented for the nature of all of the structural elements, and complete structures are proposed. The compounds are formulated as sesquiterpenoid lactones related to the known azulenogenic guaianolides.

In the first paper of this series[1] were described the isolation and characterization of xanthinin from *Xanthium pennsylvanicum*, and its conversion into xanthatin. Xanthinin is an acetoxy ketolactone which loses the elements of acetic acid with the formation of an α,β–γ,δ-dienone (xanthatin). The composition of xanthatin, $C_{15}H_{18}O_3$, indicated that the compound possessed, in addition to the keto and lactone carbonyl groups, the lactone ring, and the two carbon–carbon double bonds, a total of two additional rings or double bonds.

Hydrogenation and quantitative bromination studies indicated that of these two remaining structural elements, one was a double bond, and that xanthinin and xanthatin were monocarbocyclic compounds. Hydrogenation of xanthinin resulted in the uptake of amounts of hydrogen (about 3 moles) that suggested that both addition and hydrogenolysis were occurring. Hydrogenolysis could be accounted for, since the easily eliminated acetoxy group was probably in a position allylic to one of the double bonds; and indeed it was found that acetic acid is present in the solutions after hydrogenation. However, under conditions in which hydrogenation was allowed to proceed to completion no crystalline products could be isolated.

When hydrogenation was allowed to proceed to the uptake of one mole of hydrogen only, and then interrupted, crystalline dihydroxanthinin was isolated. The formation of dihydroxanthinin did not involve the saturation of the double bond that eventually becomes part of the dienone system of xanthatin, since by the removal of acetic acid from dihydroxanthinin, dihydroxanthatin, having an ultraviolet absorption spectrum nearly identical with that of xanthatin, was formed. It was thus apparent that a double bond hitherto unrecognized had been disclosed, and that xanthinin and xanthatin each contained but one carbocyclic ring.

That the double bond that is reduced in the formation of dihydroxanthinin is present in an exocyclic methylene group was shown by the presence in the dihydro compound of an additional carbon-linked methyl group (Table III, Experimental part) over those present in xanthinin itself. This was confirmed by the isolation of formaldehyde (as the dimedone derivative) by ozonization of xanthinin, and by other experiments described herein.

An examination of the infrared absorption spectrum of xanthinin failed to reveal the characteristic absorption of the aliphatic $>C=CH_2$ grouping at about 890 cm.$^{-1}$ [2] despite the clear indication, reinforced by subsequent observations, of the presence of this group. It seemed probable that the behavior of the methylene group was altered by its presence in a situation other than that of a simple 1,1-disubstituted olefin, and that it might exist in conjugation with the lactone carbonyl group. This expectation was borne out by an examination of the ultraviolet absorption spectra of xanthinin and the dihydro compound.

Xanthinin possesses no prominent ultraviolet absorption until the low wave length region is reached, when strong end absorption is observed in the 220–210 mμ region. This is characteristic of α-methylenic γ-lactones,[3,4] and distinguishes them from α,β-unsaturated γ-lactones in which the double bond is intracyclic. In the latter case, absorption maxima near 215–225 mμ are observed.[3,5] Dihydroxanthinin and dihydroxanthatin lack the pronounced end absorption of their unreduced counterparts, an indication that the reduction of an α-methylenic γ-lactone to an α-methyl lactone has occurred (Table I).

TABLE I

EXTINCTION COEFFICIENTS OF XANTHININ AND DERIVATIVES

Compound	Molar extinction coefficient, ϵ In 95% ethanol 220 mμ	In 95% ethanol 215 mμ	In water 220 mμ	In water 215 mμ
Xanthinin	5974	9037	8823	12193
Dihydroxanthinin	401	925	2031	3332
Xanthinin-pyrazoline	..	2500	..	...

The presence of the conjugated exocyclic methylene group was further established by the reaction of xanthinin with diazomethane, with the formation of a pyrazoline.[4,6] The pyrazoline showed the same loss of end absorption, compared with xanthinin, as did the dihydro compound, again showing that the α,β-ethylenic linkage had disappeared in its formation.

Diazomethane also added to xanthatin with the formation of a compound that still retained the characteristic ultraviolet absorption maximum (276 mμ) of xanthatin itself. This substance, therefore, is the pyrazoline analogous to that derived from xanthinin, and resulted from the addition of diazomethane to the methylene group of the lactone. When the reaction of diazomethane with xanthinin or xanthatin was carried out in methanol–ether, rather than in dry ether alone, two molecules of diazomethane were added with the formation from either xanthinin or xanthatin of the same compound. It is apparent that elimination of acetic acid took place in the reaction with xanthinin. The bis-pyrazoline possesses a markedly different ab-

(1) T. A. Geissman, Peter Deuel, E. K. Bonde and F. A. Addicott, THIS JOURNAL, **76**, 685 (1954).

(2) N. Sheppard and D. M. Simpson, *Quart. Revs.*, **6**, 1 (1952).

(3) E. E. van Tamelen, C. E. Osborn, Jr., and S. R. Bach, THIS JOURNAL, **77**, 4625 (1955).

(4) E. E. van Tamelen and S. R. Bach, *ibid*, **77**, 4683 (1955).

(5) W. G. Dauben and P. D. Hance, *ibid.*, **75**, 3352 (1953).

(6) K. E. W. Hansen, *Ber.*, **64**, 943 (1931).

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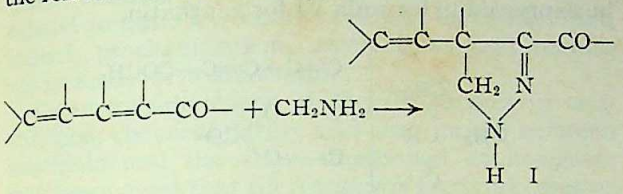
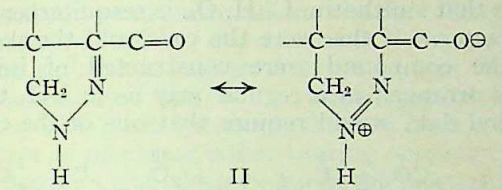
sorption spectrum from that of xanthatin, having a principal maximum at 314 mμ. This suggests that the relevant structural fragment (I) is formed



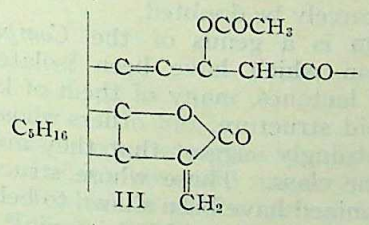
and that the 314 mμ absorption maximum is the result of participation of such contributing forms as II

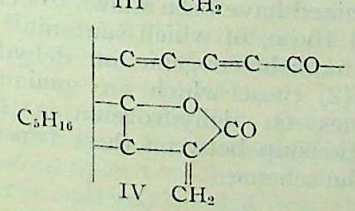


Dihydroxanthinin, as would be expected from these conclusions regarding the structure of the lactone moiety, was recovered unchanged after treatment with diazomethane in ether solution. In methanol, however, a monopyrazoline having the spectral characteristics (λ_{max} 314 mμ) of the bis-pyrazoline of xanthatin is formed.

The formulation of the lactone ring as 5-membered derives from a consideration of the infrared absorption spectra (Table II). The carbonyl absorption of the lactone, recurring in the spectra of xanthinin, xanthatin and their derivatives, is found at 1755–1765 cm.$^{-1}$, typical of γ-lactones and different from that (about 1740 cm.$^{-1}$) characteristic of 6-membered lactones. The observation that the lactone carbonyl frequency does not change materially or systematically upon removal of the α,β-unsaturation by hydrogenation or diazomethane addition is not unusual.[4,5]

The foregoing observations can be summarized in the following partial structures for xanthinin (III) and xanthatin (IV)





Evidence regarding the nature of the five carbon atoms not specified as to structure in III and IV is found in the results of oxidation procedures. These were of two kinds: hypoiodite oxidation and chromic acid oxidations under conditions that were essentially those of the Kuhn–Roth carbon-linked methyl group determination.

Both xanthinin and xanthatin, when treated with sodium hypoiodite, give iodoform and xanthatic acid, $C_{14}H_{16}O_4$. This confirms the presence of the grouping $-COCH_3$, and spectral data indicate that the conjugated system in xanthatin is C=C–C=C–$COCH_3$. The formation of xanthatic acid from xanthinin under these alkaline conditions is accompanied by the loss of acetic acid in a reaction analogous to that in which xanthatin is formed from xanthinin.

Table II

Infrared Spectral Data for Xanthinin and Derivatives

Compound	Absorption peaks in cm.$^{-1}$ Lactone CO	Other CO and C=C	$R_2C=CHR$[d]
Xanthinin[a]	1765	1720	814
Xanthatin[a]	1766	1660, 1609, 1590	812
Dihydroxanthinin[b]	1757	1720	807
Dihydroxanthatin[b]	1760	1653, 1606, 1587	820
Xanthatic acid[c]	1756	1670, 1608	827
Dihydroxanthatic acid[c]	1765	1677, 1613	815
Methyl xanthate-pyrazoline[b]	1770	1715sh, 1700, 1618	834

[a] Film. [b] Chloroform. [c] Potassium bromide disk. [d] For six olefins of the type $R_2C=CHR$, where the substituents are simple alkyl groups, Sheppard and Simpson[2] give 801, 812, 823, 824, 825 and 833 cm.$^{-1}$.

Xanthatic acid shows an absorption maximum at 252 mμ (ethanol) (ε 21,400), in good agreement with the value reported for sorbic acid (254 mμ, ε 24,800),[7] and indicates that xanthatic acid is an α,γ-dienoic acid whose derivation from xanthatin may be represented as

C=C–C=C–$COCH_3$ ⟶ C=C–C=C–COOH

That the lactone grouping of xanthatin is preserved in xanthatic acid is shown by the positive hydroxamic test and by titration experiments. Xanthatic acid can be titrated in ethanol solution to a sharp end-point with the consumption of exactly one equivalent of alkali. When excess alkali is added and the solution is heated, back-titration shows that two equivalents of base are consumed.

Dihydroxanthatic acid was prepared in two ways: by catalytic hydrogenation of xanthatic acid, or by hypoiodite oxidation of dihydroxanthinin. Dihydroxanthatic acid has an absorption maximum at 252 mμ (ε 22,400) and thus possesses the same conjugated system as xanthatic acid. The C-methyl values are in harmony with these observations: xanthatic acid shows 0.54 and dihydroxanthatic acid 1.39 C-methyl groups. Moreover, xanthatic acid shows a greater absorption in the short wave length region than does the dihydro acid, the values for Δε being 7304 (220 mμ) and 9080 (215 mμ).[8]

When xanthatic acid was treated with diazomethane in ether, a nitrogen-containing compound was formed. This substance is the pyrazoline formed by the addition of diazomethane to the α,β-unsaturated system of the lactone, with concomitant esterification of the carboxyl group; it displays an ultraviolet absorption maximum at 262 mμ (ε 25,700), in agreement with its formulation as the

(7) A. E. Gillam and R. E. Stearn, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," E. Arnold, London, 1955.

(8) The value Δε is the difference between the molar extinction coefficients of the unsaturated acid and the dihydro acid at the indicated wave length.

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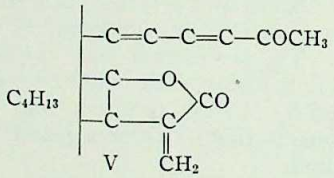
methyl α,γ-dienoate. The very low absorption of the pyrazoline in the 210–220 mμ region, like that of dihydroxanthinin, shows again that the addition of diazomethane is accompanied by the loss of the α,β-unsaturation in the lactone grouping.

Both xanthatic and dihydroxanthatic acids show infrared absorption curves that confirm the above conclusions. The lactone carbonyl bands of 1755 cm.$^{-1}$ for xanthatic acid and 1765 cm.$^{-1}$ for the dihydro acid are in agreement with their formulation as γ-lactones. Xanthatic acid shows a weak absorption at 1410 cm.$^{-1}$ which is assigned to in-plane $=CH_2$ deformations[9]; this band is absent from the spectrum of dihydroxanthatic acid.

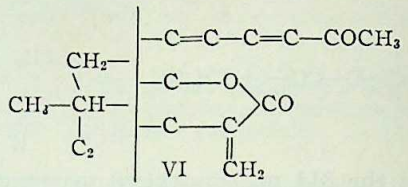
Since xanthatin can now be formulated as V, the remaining questions concern the nature of the residual four-carbon fragment and the manner in which the structural elements shown are assembled.



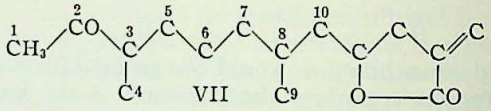
Since the C-methyl determination on xanthatin shows value of 1.44, the presence of two methyl groups is suggested. One of these is in the $-CO-CH_3$ grouping and would be expected to give nearly the theoretical amount of acetic acid. The other, from which only about 0.5 mole of acetic acid is formed, is probably present in a secondary, saturated location. In a very illuminating study of the Kuhn–Roth oxidation, Eisenbaum, McElvain and Aycock[10] have demonstrated that certain simple substances are remarkably resistant to the conditions of this method, and suggested that such acids as succinic, glutaric and adipic may be end-products of the degradation of more complex substances. Model studies were carried out in the course of the present investigation, and it was found that succinic, glutaric and adipic acids could be isolated from proline, cyclopentanone and cyclohexanone, respectively, after simulated C-methyl determinations on these compounds.

The oxidation of xanthinin with a chromic–sulfuric acid mixture gave a 29% yield of methylsuccinic acid. This compound was identified by analysis of it, its monoanilide and the *l*-quinine salt, and by mixed melting point determinations using the latter and an authentic sample. Melting point data on the acid and its anilide were inconclusive, probably because the "natural" acid was a mixture of racemic and active forms. Markownikov[11] reported the isolation of partially racemized (+)-methylsuccinic acid from oxidations of several terpene derivatives. Ladenburg[12] has stated that the *l*-quinine salt formed from *rac*-methylsuccinic acid is that of the dextrorotatory form. In the present experiments the *l*-quinine salt of the "natural" and synthetic samples of methylsuccinic acid were identical in melting point and behavior.

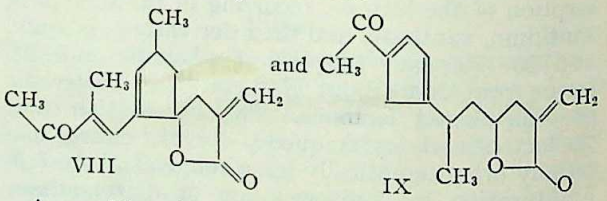
These data allow the structural information to be expressed in formula VI for xanthatin



The presence of the α-substituted lactone grouping and an additional methyl group strongly suggests that xanthatin, $C_{15}H_{18}O_3$, is sesquiterpenoid in character. If this were the case, and the skeleton of the compound were constructed of isoprene units arranged in a regular way as in VII, the C-methyl data would require that one of the carbon

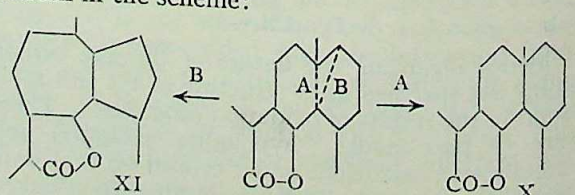


atoms 4 and 9 be utilized in ring formation. Now the ultraviolet absorption maximum of xanthatin is 276 mμ, which corresponds best to a dienone system that is linear and bears two alkyl substituents, or that contains a ring of at least six members in which the γ,δ-double bond is found.[13] Such structures as VIII and IX for xanthatin fail on one or the other of these requirements.



A consideration of biogenetical relationships allows the proposal of a structure that not only accommodates all of the experimental evidence but relates these lactones to others to which their kinship can scarcely be doubted.

Xanthium is a genus of the *Compositae*, the family from which have been isolated a large number of lactones, many of them of known, sesquiterpenoid structure, and others whose empirical formulas strongly suggest that they are members of the same class. Those whose structures have been determined have been shown to belong to two groups: (1) those, of which santonin[14] is typical, which are naphthalenogenic on dehydrogenation (X); and (2) those which are guaianolides and give azulenes on dehydrogenation (XI). The formal relationship between these two classes can be seen in the scheme:



(9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954.

(10) E. J. Eisenbaum, S. M. McElvain and B. F. Aycock, THIS JOURNAL, **76**, 607 (1954).

(11) W. Markownikov, *Chem. Zentr.*, **74**, II, 288 (1903).

(12) A. Ladenburg, *Ber.*, **31**, 525, 937 (1898).

(13) R. B. Woodward, THIS JOURNAL, **63**, 1123 (1941).

(14) J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol. 3, 2nd Ed., Cambridge University Press, Cambridge, Mass., 1952.

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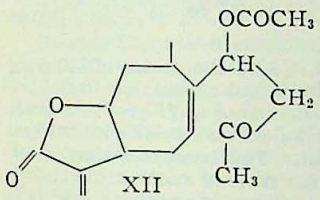
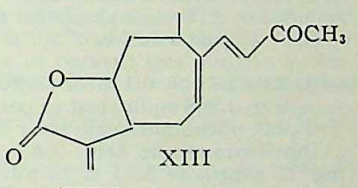
It is further to be noted that xanthinin, a C_{17}-compound, is related to xanthatin as prochamazulene,[15] tenulin,[16] pyrethrosin[17] and isotenulin[16] are related to basic C_{15}-sesquiterpenoid lactones; and, indeed, prochamazulene, pyrethrosin and tenulin are isomeric with xanthinin.

These considerations of the similarities in constitution, chemical nature and plant origin between xanthinin and the above-mentioned azulenogenic lactones suggest that the *Xanthium* lactone possesses a structure which, while not constructed on an azulene skeleton, is a monocarbocyclic congener of this type of compound. Structures XII and XIII are proposed for xanthinin and xanthatin. They accommodate all of the experimental evidence, possess the same basic carbon skeleton (except for the open 5-membered ring) as the known guaianolides, and may be regarded as being derived from a common type of precursor either by ring opening or by the failure of a ring-closing step in the biosynthesis.

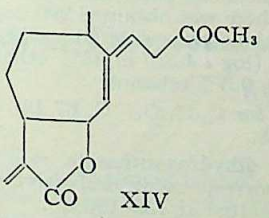


XII



XIII

An alternative structure (XIV, given for xanthatin) cannot be excluded from consideration, and indeed bears a closer analogy in respect to the position of oxygenation of the ring to the known guaianolides than do structures XII and XIII. However, the position of oxygenation of the ring in XII



XIV

and XIII finds its counterpart in tenulin and helenalin,[18] both of which bear two ring-oxygenated positions, one of which is at the carbon shown oxygenated in XII and XIII. Indeed, in the formula advanced for helenalin the lactone ring is constructed as it is in XII and XIII.

The present preference for structure XII for xanthinin rather than the corresponding derivative of XIV is based upon two observations: (1) while methylsuccinic acid was isolated from the oxidation of xanthinin and xanthatin, no α-methylglutaric acid could be found. Since α-methylglutaric acid appears to be nearly as stable as methylsuccinic acid to the oxidizing conditions used,[10] it would have been expected as a product from XIV, but not from XIII. (2) There was no evidence of the presence of an acidic compound, other than acetic acid, among the products of hydrogenation of xanthinin—a result that suggests that the lactone oxygen atom is not attached in the allylic position shown in XIV, in which it would be subject to hydrogenolysis.

With the structures XII and XIII for xanthinin and xanthatin in consideration, supporting evidence was found upon further scrutiny of the infrared spectral data. In the spectra of all of the compounds examined in this study is observed a prominent band in the neighborhood of 820 cm.$^{-1}$ (Table II). This band corresponds to the hydrogen-deformation frequency characteristic of trisubstituted olefins of the type $R_1R_2C{=}CHR_3$,[2] and is excellent confirmatory evidence for the presence in the compounds of a carbon–carbon double bond of the kind shown in XII and XIII (and XIV) as a part of the seven-membered ring.

The structures proposed for the xanthium lactones accommodate all the experimental evidence that is at hand, and in addition allow the reconciliation of some negative results. Numerous experiments aimed at the formation of naphthalene or azulene derivatives by dehydrogenation failed to yield any products of these types.

Further evidence will be required to establish structures XII and XIII, and studies of these and related lactones of the *Compositae* are continuing.

Experimental

Xanthinin was isolated from *Xanthium pennsylvanicum* in the manner described in the first paper in this series.[1]

Xanthatin was prepared by a method that is superior to that first used.[1] A solution of 1.24 g. of xanthinin and 2.3 g. of sodium acetate in 20 ml. of ethanol was refluxed for 40 minutes, 10 ml. of alcohol being allowed to distil from the solution during this period. The mixture was made slightly acid (litmus) with hydrochloric acid and water was added until the sodium chloride had dissolved. Xanthatin (0.96 g., 96%) crystallized on cooling, m.p. 114.5–115.5° after recrystallization from absolute ethanol.

Catalytic Hydrogenation of Xanthinin and Xanthatin.—In attempts to prepare reduction products of xanthinin, experiments were performed in which the extent of hydrogen uptake was determined. (a) Reduction of 55.2 mg. of xanthinin in glacial acetic acid with 8.8 mg. of platinum oxide resulted in the absorption of 2.95 moles of hydrogen per mole of xanthinin. In a repetition of this experiment, 3.17 moles was absorbed. (b) In ethanol, with platinum oxide, 2.90 moles of hydrogen was absorbed. (c) Xanthatin absorbed 3.14 moles of hydrogen in glacial acetic acid and 2.87 moles in ethanol. In none of these experiments could a crystalline hydrogenation product be obtained. The oily materials that resulted gave no indication of acidic character.

Dihydroxanthinin.—A solution of 1.50 g. of xanthinin in 35 ml. of absolute ethanol was hydrogenated at atmospheric pressure in the presence of 27 mg. of platinum oxide. The reaction was interrupted when the amount of hydrogen corresponding to 1.0 mole had been absorbed (about 2 hours), and after removal of the catalyst the filtrate was concentrated and cooled. The yield of dihydroxanthinin from a series of runs using a total of 15.03 g. of xanthinin was 8.02 g. (45%). Dihydroxanthinin forms colorless crystals (from ethanol), m.p. 117–118°.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.13; H, 7.80.

The combined mother liquors from the first crystallizations of dihydroxanthinin were evaporated and the residue dissolved in ether. This solution was found to contain 2.64

(15) V. Herout and F. Šorm, *Coll. Czech. Chem. Comm.*, **18**, 854 (1953); **19**, 792 (1954); Z. Cěkan, V. Herout and F. Šorm, *ibid.*, **19**, 798 (1954).

(16) E. P. Clark, THIS JOURNAL, **61**, 1836 (1939); **62**, 597, 2154 (1940); D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 142 (1956).

(17) Thoms, *Pharm. Ztg.*, 503 (1891); W. G. Rose and H. L. Haller, *J. Org. Chem.*, **2**, 484 (1937).

(18) R. Adams and W. Herz, THIS JOURNAL, **71**, 2553 (1949); G. Büchi and D. Rosenthal, *ibid.*, **78**, 3860 (1956).

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meq. of titratable acid (compared to 49.05 millimoles of xanthinin reduced), and from it, by appropriate manipulations, 1.17 millimoles of *p*-bromophenacyl acetate was obtained, m.p. 83–85°.

Dihydroxanthatin.—To a solution of 0.53 g. of dihydroxanthinin in 15 ml. of boiling absolute ethanol was added 0.60 g. of sodium bicarbonate. The mixture was refluxed for one hour, filtered and acidified with dilute hydrochloric acid. Colorless crystals of dihydroxanthatin formed at once. Recrystallized from ethanol, the compound forms colorless leaflets, m.p. 138–140°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.47; H, 8.14.

Ozonization of Xanthinin: Isolation of Formaldimedon.—A solution of 0.152 g. of xanthinin in 30 ml. of methylene chloride was ozonized at Dry Ice-acetone temperature for 105 minutes. The reaction solution was added to the contents of a water trap used on the outlet from the ozonization flask and the mixture was refluxed for 20 minutes. The water layer was separated and distilled into an ice-cooled receiver.

An aliquot of 60 ml. of the total 200 ml. of distillate was added to a hot solution of 300 mg. of dimedon in 30 ml. of water. The formaldimedon that separated weighed 11.0 mg. (0.254 mole CH_2O per mole xanthinin), and melted at 190–190.5°. There was no depression on mixing with an authentic sample, m.p. 189°.

Another 60-ml. aliquot of the distillate was analyzed for formic acid by Harper's method.[19] The result showed that 0.112 mole of formic acid was formed per mole of xanthinin.

Reaction of Xanthinin and Xanthatin with Diazomethane. (A).—The diazomethane generated from 3.9 g. of nitrosomethylurea was added to a solution of 1.24 g. of xanthinin in a total of 500 ml. of dry ether. The solution was kept at room temperature for an hour and at 3° for 25 hours, and then evaporated until the diazomethane had been removed and the solution was colorless. The crystalline product that separated on cooling weighed 1.26 g. (90%) and melted at 130–132° with gas evolution. The reaction also was carried out in dioxane–ether; the yield was 0.18 g. from 0.24 g. of xanthinin.

Anal. Calcd. for $C_{18}H_{24}O_5N_2$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.02; H, 6.94; N, 8.17.

(B).—When dihydroxanthinin was treated with diazomethane in dioxane–ether solution, no adduct could be isolated, and 84% of (recrystallized) starting material was recovered.

(C).—From 79 mg. of xanthatin and excess diazomethane in dioxane–ether was obtained the pyrazoline, m.p. 144.5–146° after recrystallization from methanol.

Anal. Calcd. for $C_{16}H_{20}O_3N_2$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.66; H, 6.90; N, 9.92.

The compound had a λ_{max} at 276 mμ, showing that the dienone chromophore of xanthatin was unaltered.

(D).—An ethereal solution of diazomethane was added to a solution of 0.30 g. of xanthinin in absolute methanol (10 ml.). After 20 hours at room temperature the solution was evaporated, affording 0.10 g. of product, yellow crystals, m.p. 170–73° with gas evolution. This compound no longer gives the purple-red color with hydrochloric acid that is characteristic of xanthinin and xanthatin; λ_{max} 314 mμ (95% ethanol).

Anal. Calcd. for $C_{17}H_{22}O_3N_4$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.52; H, 6.70; N, 16.77.

(E).—The same "dipyrazoline" was obtained from xanthatin and diazomethane in methanol–ether solution.

Anal. Found: C, 61.67; H, 7.06; N, 17.28.

(F).—Dihydroxanthinin (0.30 g.) in 10 ml. of methanol was treated with excess ethereal diazomethane. After 6 hours the ether was removed by distillation, and the product allowed to crystallize. The yield was 14.1 mg. of slightly yellowish needles, m.p. 139–142° dec., λ_{max} 314 mμ (95% ethanol).

Anal. Calcd. for $C_{16}H_{22}O_3N_2$: C, 66.18; H, 7.64. Found: C, 66.01; H, 7.48.

Xanthatic Acid.—To a solution of 12.5 g. of iodine in 125 ml. of 20% potassium iodide solution was added 10% aqueous sodium hydroxide until the color of the iodine was discharged. The resulting solution was added to 5.0 g. of xanthinin and, while stirring, sodium hydroxide was added until the solution of the xanthinin was complete. After 30 minutes the solution was acidified carefully until iodine reappeared, then made basic and the precipitated iodoform collected by filtration. The reaction required 24 hours to go to completion. Acidification yielded 3.82 g. of crude xanthatic acid; 4.0 g. of iodoform was obtained, and was identified by melting point and mixed melting point with authentic material.

After three recrystallizations from absolute ethanol, 1.36 g. of xanthatic acid, m.p. 300° dec., was obtained.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.37; H, 6.52.

Xanthatic acid gives a positive hydroxamic acid test, but does not give a red color with concentrated hydrochloric acid. It had λ_{max} 252 mμ (log ϵ 4.33) in 95% ethanol, 260 mμ (log ϵ 4.33) in 9.5% ethanol.

***p*-Nitrobenzyl Xanthatate.**—A solution of 105 mg. of xanthatic acid in 0.7 ml. of 4% sodium hydroxide solution was brought to slight acidity (litmus) with hydrochloric acid and added to a solution of 96 mg. of *p*-nitrobenzyl bromide in 3 ml. of ethanol. After one hour of refluxing, the volume of the solution was reduced by distillation and cooled. The product (59.5 mg.) formed colorless crystals from ethanol, m.p. 140–142°.

Anal. Calcd. for $C_{21}H_{21}O_6N$: C, 65.78; H, 5.52. Found: C, 65.74; H, 5.71.

Titration of Xanthatic Acid. (A).—A solution of 110.5 mg. of xanthatic acid in 5 ml. of ethanol containing 10.0 ml. of 0.118 *N* sodium hydroxide was heated at 75° for 20 minutes and titrated to the phenolphthalein end-point with 2.75 ml. of 0.102 *N* hydrochloric acid. The base consumed corresponded to 2.00 equivalents per mole of xanthatic acid.

(B).—A cold solution of 235.8 mg. of xanthatic acid in 50 ml. of ethanol was titrated to a phenolphthalein end-point with 8.24 ml. of 0.115 *N* sodium hydroxide. This corresponds to 0.998 equivalent of base per mole of xanthatic acid. The pink phenolphthalein color faded after about 5 minutes.

Dihydroxanthatic Acid. (A).—The hydrogenation of 167 mg. of xanthatic acid in 15 ml. of ethanol (with platinum oxide, 7.6 mg.) was stopped after 20.0 ml. (0.81 mole) of hydrogen had been taken up. The solution was filtered and concentrated, and yielded on cooling 21.4 mg. of dihydroxanthatic acid, m.p. 232–239° (crude product).

(B).—The oxidation of 0.89 g. of dihydroxanthinin with an alkaline solution of 2.21 g. of iodine was carried out as described for the preparation of xanthatic acid. The crude dihydroxanthatic acid weighed 450 mg. After several recrystallizations there was obtained 296 mg., m.p. 240–243°; iodoform (0.51 g.) also was isolated. Dihydroxanthatic acid had λ_{max} 252 mμ (log ϵ 4.35) in 95% ethanol, and λ_{max} 260 mμ (log ϵ 4.35) in 9.5% ethanol.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.06; H, 7.53.

***p*-Nitrobenzyl dihydroxanthatate** was prepared as described for the corresponding derivative of xanthatic acid. The compound melted at 135–136.5°.

Anal. Calcd. for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02. Found: C, 65.61; H, 6.09.

Chromic Acid Oxidations.—An oxidizing solution was prepared by dissolving 33.6 g. of chromium trioxide in 200 ml. of water and 20 ml. of concentrated sulfuric acid. When 600 mg. of succinic acid was refluxed with 100 ml. of this solution for 1.5 hours, 47% of the succinic acid was recovered. From 1.5 g. of cyclohexanone and 150 ml. of the oxidizing solution (2 hours), 1.21 g. (73%) of adipic acid was isolated; from 1.0 g. of cyclopentanone and 100 ml. of the oxidizing solution (2 hours), 1.14 (73%) of glutaric acid was isolated; and from 1.53 g. of proline and 100 ml. of oxidizing solution, 0.11 g. (8%) of succinic acid was isolated.

Methylsuccinic Acid. (A).—A solution of 1.95 g. of xanthinin in 140 ml. of the oxidizing solution was refluxed for 2.25 hours. The excess chromic acid was reduced with 40% formaldehyde and the aqueous solution extracted continuously with ether. After evaporation of the ether, the residual oily material was dissolved in hot benzene and allowed to cool. The product weighed 0.25 g., melted at 109–111° (reported[19] m.p. 111°), and after recrystallization from water melted at 115–117°. Mixed with *dl*-methylsuccinic acid (m.p. 115–117°) the m.p. was 103–113°. The variation in melting point (recrystallized from carbon tetrachlo-

(19) S. H. Harper, *J. Chem. Soc.*, 595 (1942).

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ride the sample melted at 104–106°) appears to be due to the fact that the compound is a mixture of the active and racemic acids.[11]

Anal. Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10. Found: C, 45.30; H, 6.26.

(B).—Oxidation of xanthatin under the above conditions gave an 18% yield of methylsuccinic acid, m.p. 112–114°; mixed with *dl*-methylsuccinic acid the m.p. was 105–114°.

Monoanilide of Methylsuccinic Acid (from Xanthinin).—A solution of 85 mg. of methylsuccinic acid in 0.75 ml. of thionyl chloride was refluxed for 45 minutes. The excess thionyl chloride was removed and to the residue was added a solution of 0.5 g. of aniline in 5 ml. of benzene. After 5 minutes refluxing a precipitate appeared. This was collected, washed with dilute hydrochloric acid, dissolved in 5% sodium hydroxide solution, and reprecipitated with dilute acid. Recrystallized from ethanol–benzene, the anilide melted at 150–151.5°.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.85; H, 6.59; N, 6.74.

Authentic *dl*-methylsuccinanilic acid was prepared, and had m.p. 147–149° (reported 148–149°,[20] 147°[21]), and a mixture of the two melted at 140–144°. Again, the presence of a mixture of active and racemic forms in the product derived from xanthinin is probably responsible for the differences in melting point.

Quinine Salt of *d*-Methylsuccinic Acid (from Xanthinin).—To a hot aqueous solution of 0.114 g. of the methylsuccinic acid from the oxidation of xanthinin was added an equivalent amount of *l*-quinine. On cooling, the solution deposited the crystalline salt, m.p. 168–169.5°. The quinine salt derived from authentic *dl*-methylsuccinic acid was made in the same way, and melted at 168–169.5° (reported[12,22] 169–171°). The two samples showed no depression in melting point on mixing.

The quinine salt crystallizes with water and after drying at room temperature over phosphorus pentoxide (16 hours) melted at 184–186° and analyzed for the monohydrate.

Anal. Calcd. for $C_{20}H_{24}N_2O_2 \cdot C_5H_8O_4 \cdot H_2O$: C, 67.65; H, 7.32. Found: C, 67.63; H, 7.30.

After drying at 138° (P_2O_5, 27 hours) the salt melted at 188–190° and was anhydrous.

Anal. Calcd. for $C_{20}H_{24}N_2O_2 \cdot C_5H_8O_4$: C, 69.20; H, 7.23. Found: C, 68.97; H, 7.27.

The salt from the synthetic acid, treated in the same way, formed the monohydrate (m.p. 182–184°; found: C, 67.64; H, 7.48) and the anhydrous form (m.p. 188–189°; found: C, 69.11; H, 7.36).

Carbon-linked methyl groups were determined by the use of the procedure of Barthel and LaForge.[23] In Table III are collected the C-methyl values for the compounds analyzed.

TABLE III

Compound	C-Methyl groups
Xanthinin	2.45
Xanthatin	1.44
Dihydroxanthinin	2.96
Dihydroxanthatin	1.95
Xanthinin-pyrazoline	2.55
Xanthatin-pyrazoline	1.47
Xanthatin-dipyrazoline	1.42
Xanthatic acid	0.53
Dihydroxanthatic acid	1.39
Methyl xanthatate pyrazoline	0.64

Ultraviolet absorption spectra were determined with a Beckman model DU spectrophotometer.

Infrared absorption spectra were determined with a Perkin–Elmer model 21 recording spectrophotometer equipped with a sodium chloride prism. Samples were in chloroform solution, as a film, or in a potassium bromide disk as noted in Table II.

(20) W. A. Bone and C. H. G. Sprankling, *J. Chem. Soc.*, **75**, 839 (1899).

(21) D. Vorländer, P. Weissheimer and F. Sponnagel, *Ann.*, **345**, 232 (1906).

(22) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Eyre and Spottiswoode, Ltd., London, 1953.

(23) W. F. Barthel and F. B. LaForge, *Ind. Eng. Chem., Anal. Ed.*, **16**, 434 (1944).

LOS ANGELES 24, CALIFORNIA

[CONTRIBUTION OF THE DEPARTMENT OF RESEARCH AND DEVELOPMENT, U. S. NAVAL POWDER FACTORY]

The Reaction of Thiopseudoureas with 1,3-Diamino-2,2-bis-(hydroxymethyl)-propane[1]

BY L. S. HAFNER AND ROBERT EVANS

RECEIVED DECEMBER 14, 1956

The reaction of 1,3-diamino-2,2-bis-(hydroxymethyl)-propane with the salts of 2-methyl-2-thiopseudourea or with 1-nitro-2-alkyl-2-thiopseudourea formed the following products: the salt of 1,3-bis-(guanidino)-2,2-bis-(hydroxymethyl)-propane, the salt of 1-guanidino-3-amino-2,2-bis-(hydroxymethyl)-propane, 1,3-bis-(nitroguanidino)-2,2-bis-(hydroxymethyl)-propane, 2-nitrimino-5,5-bis-(hydroxymethyl)-1,3-diazacyclohexane and 2-imino-5,5-bis-(hydroxymethyl)-1,3-diazacyclohexane, which may have formed from the nitrimino compound by a secondary reaction involving the addition of ammonia and the elimination of nitramide. These compounds when nitrated yielded 1,3-bis-(nitroguanidino)-2,2-bis-(nitroxymethyl)-propane and 2-nitrimino-5,5-bis-(nitroxymethyl)-1,3-diazacyclohexane. The 1,3-diamino-2,2-bis-(hydroxymethyl)-propane was prepared from the diacetate of 1,3-dibromo-2,2-bis-(hydroxymethyl)-propane by the Gabriel synthesis.

Both straight chain and cyclic guanidine and nitroguanidine derivatives of 2,2-bis-(hydroxymethyl)-1,3-propanediol have been prepared by the reaction between 1,3-diamino-2,2-bis-(hydroxymethyl)-propane and 1-nitro-2-alkyl-2-thiopseudoureas[2] or the salts of 2-methyl-2-thiopseudoureas.[3–5] The 1,3-diamino-2,2-bis-(hydroxymethyl)-propane used in the synthesis of these compounds was prepared from the diacetate of 1,3-dibromo-2,2-bis-(hydroxymethyl)-propane by the Gabriel synthesis. 1,3-Bis-(phthalimido)-2,2-bis-(hydroxymethyl)-propane could not be prepared from 1,3-dibromo-2,2-bis-(hydroxymethyl)-propane. The recovery of over 50% of the potassium phthalimide used in this reaction as phthalimide indicated that hydrogen bromide had split from the 1,3-dibromo-2,2-bis-(hydroxymethyl)-propane with the probable formation of an oxacyclobutane ring. Phthalimide would then be formed by the reaction between hydrogen bromide and potassium phthal-

(1) Published with permission of the Bureau of Ordnance, Navy Department. The opinions and conclusions are those of the authors.

(2) L. Fishbein and J. A. Gallaghan, THIS JOURNAL, **76**, 1877 (1954).

(3) B. Rathke, *Ber.*, **17**, 297 (1884).

(4) H. L. Wheeler and G. S. Jamieson, *J. Biol. Chem.*, **1**, 111 (1905).

(5) W. Schoeller and H. Schotte, U. S. Patent 1,805,889 (1931).

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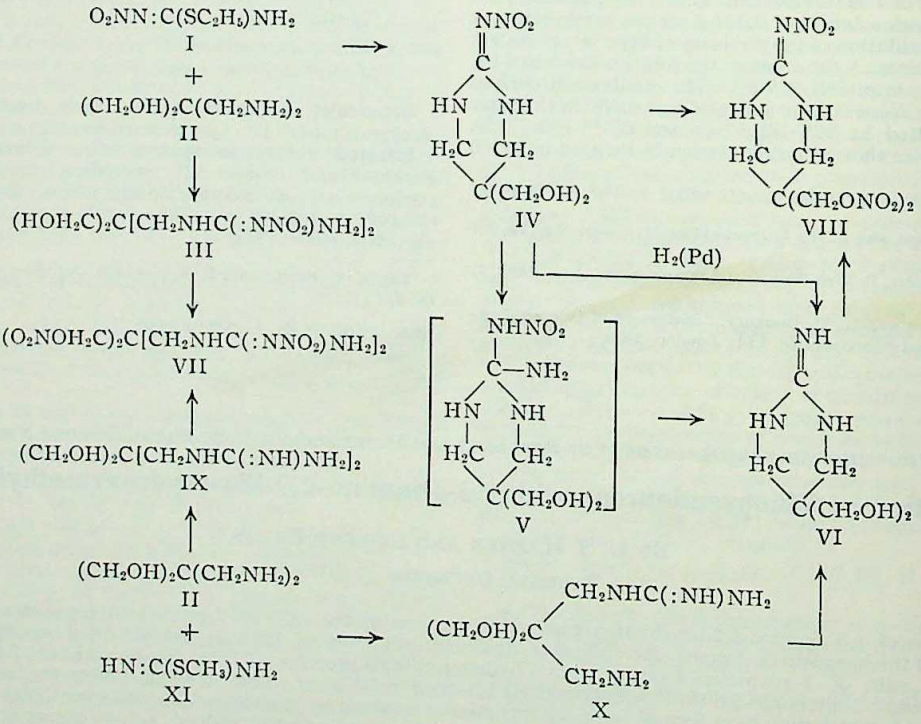
imide. Phthalimide formation was greatly reduced by the acetylation of the hydroxyl groups of the 1,3-dibromo-2,2-bis-(hydroxymethyl)-propane, and by this method a 60% yield of the phthalimido compound was obtained. The hydrolysis of the phthalimido compound with hydrogen bromide was unsatisfactory due to a partial bromination of the hydroxyl groups. However, with aqueous hydrazine,[6] 1,3-diamino-2,2-(hydroxymethyl)-propane was obtained in 45% yield. Slight variations in the hydrazinolysis procedure led to the formation of alcohol-soluble sirups that were difficult to process. Under the conditions used, however, the hydrochloride and nitrate salts of the amine were obtained readily in the crystalline state and were not hygroscopic. Govaert and Beyert,[7] who prepared the amine by the ammonolysis of 1,3-dibromo-2,2-bis-(hydroxymethyl)-propane, stated that these salts were deliquescent and difficult to obtain in a pure state, and elemental analyses were not reported.

uct VI also was prepared by the hydrogenolysis of the cyclic nitrimino compound in the presence of a palladium catalyst.

The reaction between 55% of the molar quantity of 1-nitro-2-methyl-2-thiopseudourea and II produced 26% of the cyclic imino compound VI, 20% of the cyclic nitrimino compound IV and none of the bis-(nitroguanidino) compound III. 2-Nitrimino-5,5-bis-(nitroxymethyl)-1,3-diazacyclohexane (VIII) was prepared from either the cyclic nitrimino compound IV or the nitrate salt of the cyclic imino compound VI by the selection of the proper nitrating conditions.

The free base II reacted with 60% of the molar quantity of the nitrate salt of 2-methyl-2-thiopseudourea (XI) to form the dinitrate salts of both 1,3-bis-(guanidino)-2,2-bis-(hydroxymethyl)-propane (IX, 13%) and 1-amino-3-guanidino-2,2-bis-(hydroxymethyl)-propane (X, 21.5%). The reaction between II and a 20% molar excess of XI gave a 52% yield of the bis-(guanidino) compound



Three compounds were isolated from the reaction between 1-nitro-2-ethyl-2-thiopseudourea (I) (20% molar excess) and 1,3-diamino-2,2-bis-(hydroxymethyl)-propane (II). The principal product was 1,3-bis-(nitroguanidino)-2,2-bis-(hydroxymethyl)-propane (III, 26% yield). The other two products were 2-nitrimino-5,5-bis-(hydroxymethyl)-1,3-diazacyclohexane (IV) (6.3%) and 2-imino-5,5-bis-(hydroxymethyl)-1,3-diazacyclohexane (VI, 20%). The cyclic imino compound VI probably was not an initial reaction product. Possibly it resulted from the elimination of nitramide from an addition compound V formed when the ammonia liberated as IV was produced added to IV.[8] Product IX. By selecting the proper conditions, either the bis-(nitroguanidino) compound III or the nitrate salt of the bis-(guanidino) compound IX could be nitrated to form 1,3-bis-(nitroguanidino)-2,2-bis-(nitroxymethyl)-propane (VII). The free base 1-amino-3-guanidino-2,2-bis-(hydroxymethyl)-propane (X) was converted to the cyclic imino compound VI (20% yield) in refluxing methanol.

Experimental[9]

1,3-Bis-(phthalimido)-2,2-bis-(hydroxymethyl)-propane Diacetate.—The conditions employed for this preparation were a modification of those used by Sheehan and Bolhofer[10] to prepare dimethyl α,δ-diphthalimidoadipate. A solution

(6) A. F. Child, *et al.*, *J. Chem. Soc.*, 2174 (1948).

(7) F. Govaert and M. Beyert, *Proc. Koninkl. Akad. Wetenschap. Amsterdam*, **42**, 641 (1939).

(8) A. F. McKay, *Chem. Revs.*, **51**, 301 (1952).

(9) All melting points were measured on a Kofler micro hot-stage.

(10) J. C. Sheehan and W. A. Bolhofer, THIS JOURNAL, **72**, 2786

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of 1,3-dibromo-2,2-bis-(hydroxymethyl)-propane diacetate (194 g., 0.561 mole) in 675 ml. of dimethylformamide was placed in a 2-liter flask equipped with a stirrer, condenser and thermometer. The temperature was maintained at 152° with stirring, while seven portions (24.4 g. each) of potassium phthalimide were added at 10-minute intervals. The temperature was then lowered to 144°, and two more portions of potassium phthalimide were added at 20-minute intervals. The mixture was heated for an additional 4.3 hr. at 144°. The reaction was then cooled to approximately 100° and the sodium bromide removed by filtration. The filtrate was allowed to stand at room temperature overnight, and the precipitate that formed was removed and washed in turn with dimethylformamide, ethanol, water and hot ether. The crude product, 164 g. (62%), was used for the preparation of 1,3-diamino-2,2-bis-(hydroxymethyl)-propane. A pure sample prepared by recrystallizing three times from benzene melted at 199.5–200.5°.

Anal. Calcd. for $C_{25}H_{22}O_8N_2$: C, 62.75; H, 4.64; N, 5.86. Found: C, 62.78; H, 4.64; N, 5.82.

1,3-Diamino-2,2-bis-(hydroxymethyl)-propane Dihydrochloride.—The phthalimido compound was converted to the diamine by the method of Child and co-workers.[6] 1,3-Bis-(phthalimido)-2,2-bis-(hydroxymethyl)-propane diacetate, 153.8 g. (0.324 mole), and 358 ml. of ethanol were placed in a flask equipped with a condenser, stirrer and dropping funnel. The mixture was heated to the reflux temperature, with stirring, and 38.9 g. of aqueous hydrazine (61%, 0.741 mole) was added over a period of 10 minutes. After stirring at the reflux temperature for 15 minutes, the heat was removed, and the mixture was stirred for an additional 50 minutes. At the end of this interval, 55 ml. of concentrated hydrochloric acid was added and the solution stirred for an additional 35 minutes. Concentrated hydrochloric acid (18 ml.) was added to the reaction mixture which was then heated and the ethanol–ethyl acetate azeotrope removed by distillation. Four hundred ml. of additional alcohol was put in as required. The alcoholysis was complete in about 2 hr. The phthalyl hydrazide and undissolved reaction products were then filtered, washed with ethanol and with water and the combined filtrates and wash solutions concentrated under vacuum to a sirup. This sirup was washed twice with absolute ethanol and once with ether, dissolved in water (60 ml.) and filtered. The filtrate was agitated for 1 hr. with salicylaldehyde to remove excess hydrazine. The insoluble material was removed, and the filtrate, after extracting with ether to remove excess salicylaldehyde, was concentrated under vacuum to a sirup. The sirup was washed twice in a Waring blender with absolute ethanol. Recrystallization from ethanol gave 30.8 g. (45.8%) of product with a melting point of 246–247°.

Anal. Calcd. for $C_5H_{16}O_2N_2Cl_2$: C, 28.99; H, 7.79; N, 13.53; Cl, 34.24. Found: C, 29.25; H, 8.02; N, 13.55; Cl, 34.58.

1,3-Diamino-2,2-bis-(hydroxymethyl)-propane Dinitrate Salt.—This compound was prepared from the dipicrate salt of the diamine and after recrystallization from ethanol melted at 117–118°.

Anal. Calcd. for $C_5H_{16}O_8N_4$: C, 23.08; H, 6.20; N, 21.53. Found: C, 23.19; H, 5.99; N, 21.46.

1,3-Bis-(phthalimido)-2,2-bis-(hydroxymethyl)-propane Monoacetate.—A solid sometimes separated from the alcoholic solution remaining after the insoluble phthalyl hydrazide was removed. After purification by crystallizing from methanol, dissolving in chloroform and precipitating with *n*-heptane and crystallizing again from methanol, the compound melted at 142–143°.

Anal. Calcd. for $C_{23}H_{20}O_7N_2$: C, 63.29; H, 4.62; N, 6.42. Found: C, 63.30; H, 4.77; N, 6.58.

1,3-Bis-(phthalimido)-2,2-bis-(hydroxymethyl)-propane.—The attempt to hydrolyze the diacetyldiphthalimido compound to the diamino compound with dilute hydrochloric acid was unsuccessful. The product after crystallization from benzene melted at 220.5–222.0°.

Anal. Calcd. for $C_{21}H_{18}O_6N_2$: C, 63.95; H, 4.60; N, 7.11. Found: C, 64.09; H, 4.44; N, 7.37.

Reaction of 1-Nitro-2-methyl-2-thiopseudourea with an Excess of 1,3-Diamino-2,2-bis-(hydroxymethyl)-propane.—The free base of the diamine was prepared by the reaction between the dihydrochloride and sodium ethoxide. To 3.743 g. (0.0279 mole) of the free base in a 50-ml. flask was added 3.957 g. (0.0293 mole) of the thiopseudourea in small portions over a period of about 15 minutes. The well stirred reaction mixture became warm, and ammonia and methyl mercaptan were evolved. At the end of the addition period, the flask was evacuated with a water aspirator (about 30 mm.) for 15 minutes. Fourteen ml. of absolute ethanol was added, and the flask was evacuated for an additional 15 minutes. The reaction product was filtered and washed with absolute ethanol. The precipitate, which weighed 1.4 g. and melted at 185–193° dec., was set aside. The filtrate was treated with a picric acid–methanol solution. The precipitate that formed (7.3 g.) was dissolved in 500 ml. of ethanol, and, by taking off successive fractions, two products were obtained. The first, consisting of 2.8 g. (17%), was determined to be the dipicrate of the original diamine. The second picrate, 3.9 g. (36.2%), after two crystallizations from ethanol melted at 179–180° and by proof outlined in the discussion was determined to be the picrate of 2-imino-5,5-bis-(hydroxymethyl)-1,3-diazacyclohexane VI.

Anal. Calcd. for $C_{12}H_{16}O_9N_6$: C, 37.12; H, 4.15; N, 21.64. Found: C, 37.10; H, 4.46; N, 21.64.

This picrate was converted to the nitrate salt which, after two crystallizations from absolute ethanol, melted at 114–115°.

Anal. Calcd. for $C_6H_{14}O_6N_4$: C, 32.46; H, 6.36; N, 25.24. Found: C, 32.64; H, 6.22; N, 25.40.

The crude alcohol-insoluble reaction product was dissolved in water and fractionated by slow evaporation. The fractions which melted at 203–207° dec. and weighed 1.01 g. (18.8%) were combined. Crystallization from alcohol and then from water raised the melting point to 207.5–208.5° dec. This product was 2-nitrimino-5,5-bis-(hydroxymethyl)-1,3-diazacyclohexane (IV).

Anal. Calcd. for $C_6H_{12}O_4N_4$: C, 35.29; H, 5.93; N, 27.46. Found: C, 35.43; H, 6.05; N, 27.02.

The nitrimino compound IV was converted to the imino compound VI by hydrogenolysis in the presence of palladium black by the following procedure. The nitrimino compound IV (0.469 g., 0.00296 mole) was added to 50 ml. of 15% acetic acid solution containing 0.06 g. of palladium black in a modified Skita[11] hydrogenation apparatus and agitated, slightly above atmospheric pressure, for 20 hr. The catalyst was removed, the filtrate treated with picric acid and the picrate (57% yield) after crystallization from methanol melted at 179–180°. A mixed melting point with the picrate of compound VI was not depressed.

Reaction of an Excess of 1-Nitro-2-ethyl-2-thiopseudourea with 1,3-Diamino-2,2-bis-(hydroxymethyl)-propane.—A solution of 3.214 g. (0.02175 mole) of the thiopseudourea in 11 ml. of tetrahydrofuran was added to 1.2075 g. (0.009 mole) of the diamine. The mixture was stirred for 25 minutes, the tetrahydrofuran removed under a vacuum, 10 ml. of absolute ethanol added and the stirring continued for 2.5 hr. The solid material was removed and washed with absolute ethanol and then with ether. The filtrate was treated with picric acid. The only product isolated was the picrate of 2-imino-5,5-bis-(hydroxymethyl)-1,3-diazacyclohexane (VI, 20.1%). The insoluble reaction product weighed 1.14 g. and melted at 158–160° dec. Washing with water, alcohol and finally ether reduced the weight to 0.83 g. and increased the melting point to 164–168° dec. This material was dissolved in concentrated hydrochloric acid, filtered and precipitated by dilution with water. The product, compound III (26%), melted at 200–201° dec.

Anal. Calcd. for $C_7H_{16}O_6N_8$: C, 27.23; H, 5.23; N, 36.35. Found: C, 27.43; H, 5.28; N, 36.24.

The material recovered by the evaporation of the diluted hydrochloric acid solvent and by the evaporation of the water wash of the crude material was crystallized from ethanol. The product was the nitrimino compound IV (6.3%). A mixed melting point with an authentic sample of IV was not depressed.

Reaction of 1,3-Diamino-2,2-bis-(hydroxymethyl)-propane with an Excess of the Nitrate Salt of 2-Methyl-2-thiopseudourea.—To a stirred solution of 2.459 g. (0.0183 mole) of the diamine in 2 ml. of water was added a 10% excess of the nitrate salt of 2-methyl-2-thiopseudourea, 6.184 g.

(11) A. Skita and W. A. Meyer, *Ber.*, **45**, 3589 (1912).

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(0.0403 mole), dissolved in 8 ml. of water. The reaction was stirred for 5.5 hr. at room temperature, allowed to stand overnight and then stirred for an additional 5 hr. with a current of air blowing over the surface of the liquid to remove methyl mercaptan and ammonia. The reaction mixture was filtered, the precipitate washed with absolute ethanol and all the filtrates combined and treated with picric acid. The reaction precipitate was dissolved in warm water (60°) and successive fractions of crystals collected by slow evaporation of the water. A total of 3.27 g. (51.8%) of material was recovered. After recrystallizing twice from water, the product, the dinitrate salt of compound IX, melted at 196–198° dec.

Anal. Calcd. for $C_7H_{20}O_8N_8$: C, 24.41; H, 5.86; N, 32.55. Found: C, 24.59; H, 5.98; N, 32.33.

The dipicrate was prepared from the nitrate salt and after crystallization from methanol melted at 257–259° dec.

Anal. Calcd. for $C_{19}H_{24}O_{16}N_{12}$: C, 33.74; H, 3.58; N, 24.85. Found: C, 33.81; H, 3.68; N, 24.85.

The picrates from the filtrate could not be separated. Conversion to the nitrate salts and extraction with acetone gave a small amount of the nitrate salt of the starting material, 2-methyl-2-thiopseudourea (XI).

Reaction of the Nitrate Salt of 2-Methyl-2-thiopseudourea with an Excess of 1,3-Diamino-2,2-bis-(hydroxymethyl)-propane.—To the diamine (2.951 g., 0.022 mole) dissolved in 2 ml. of water was added 3.719 g. (0.0275 mole) of the thiopseudourea salt in 2 ml. of water. The mixture was stirred for 5.5 hr., absolute ethanol added and the insoluble material removed and washed with absolute ethanol. This product was crystallized from water, and its properties indicated that it was the dinitrate salt of compound IX (13% yield).

The filtrate was heated with picric acid, and the picrates were collected and converted to the nitrate salts. Fractional crystallization from ethanol gave 1.43 g. (21.4%) of product X which melted at 128–129°.

Anal. Calcd. for $C_6H_{18}O_8N_6$: C, 23.84; H, 6.00; N, 27.80. Found: C, 24.50; H, 5.63; N, 27.49.

The dipicrate was prepared from the purified nitrate and after crystallization from methanol melted at 209.5–211.5° dec.

Anal. Calcd. for $C_{18}H_{12}O_{16}N_{10}$: C, 34.20; H, 3.51; N, 22.10. Found: C, 34.18; H, 3.42; N, 21.93.

It was found that 1-amino-2-guanidino-2,2-bis-(hydroxymethyl)-propane (X) could be cyclized to VI by the following procedure. The salt (0.365 g.) was converted to the free base with sodium ethoxide, dissolved in methanol and refluxed for 1.2 hr. The product was neutralized with dilute nitric acid and concentrated in a current of air. Absolute ethanol was then added and 0.163 g. of sodium nitrate removed. The filtrate was treated with picric acid and the picrate removed. After crystallization from water the product weighed 0.093 g. (20%) and melted at 179–180°. A mixed melting point with an authentic sample of the picrate of VI was not depressed.

2-Nitrimino-5,5-bis-(nitroxymethyl)-1,3-diazacyclohexane (VIII).—The nitrate salt of the imino compound VI (0.7 g., 0.0032 mole) was added to a nitration mixture consisting of 1.29 g. of 99% nitric acid and 2 ml. of 98% sulfuric acid at −15°. The mixture was kept below 10° for 12 minutes and then allowed to warm and stand at room temperature (21°) for 1.7 hr. It was then poured over 30 g. of crushed ice and the precipitate collected on a medium sintered-glass funnel. The product VIII (0.61 g., 65.9%) after crystallization from ethanol melted at 214–215° dec.

The nitrimino compound IV (0.465 g., 0.0023 mole) was added to 5 g. of 99% nitric acid at −10°. The solution was held at 10–15° for 30 minutes, poured over 30 g. of crushed ice, filtered and the precipitate washed with cold water. The product VIII (0.601 g., 89%) after crystallization from water melted at 214–215° dec.

Anal. Calcd. for $C_5H_{10}O_8N_6$: C, 24.49; H, 3.43; N, 28.57. Found: C, 24.56; H, 3.28; N, 28.63.

1,3-Bis-(nitroguanidino)-2,2-bis-(nitroxymethyl)-propane (VII).—The dinitrate salt of IX (1.008 g., 0.0029 mole) was nitrated by the procedure used to produce the nitrate salt of VI except that the holding time at room temperature was increased to 2.7 hr. The product VII (0.613 g., 53%) after crystallization from water melted at 158.5–160° dec.

The nitroguanidino compound III (0.39 g., 0.00129 mole) was nitrated in 4 ml. of 99% nitric acid using the same procedure as for the cyclic nitrimino compound IV. The product VII weighed 0.4393 g. (85.5%) and melted at 158–160° dec.

Anal. Calcd. for $C_7H_{14}O_{10}N_{10}$: C, 21.11; H, 3.54; N, 35.17. Found: C, 21.37; H, 3.66; N, 34.82.

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INDIAN HEAD, MARYLAND

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

2,2-Disubstituted-1,3-propanediamines and Related Diurethans, Diureides and Hexahydropyrimidin-2-ones

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2,2-Disubstituted-1,3-propanediamines have been prepared and converted to diurethans, diureides and hexahydropyrimidin-2-ones. A practical synthesis of 5-alkyl-5-phenylhexahydropyrimidin-2-ones has been the major achievement. As a cyclization reagent diphenyl carbonate was superior to diethyl carbonate.

Since the replacement of carbonyl by methylene at position 2 in 5-ethyl-5-phenylbarbituric acid gave a compound[1] which still possessed anticonvulsant properties, it seemed of interest to prepare analogs with methylene groups at positions 4 and 6 in the ring. Our experimental work was practically complete when there appeared a paper[2] describing the preparation of one of these compounds (Table III) by reduction of the corresponding barbituric acid derivative.

Our syntheses depend upon the preparation of the 2,2-disubstituted-1,3-propanediamines. The method involving the condensation of ketones[3] with nitromethane generally gave poor yields when both radicals were larger than ethyl. In the case of propiophenone none of the intermediate dinitro compound was obtained.

The 2-alkyl-2-phenyl-1,3-propanediamines were therefore prepared from phenylcyanoacetamide[4] which was alkylated[5] and then reduced to the di-

(1) W. R. Boone, H. C. Carrington and C. H. Vasey, *C. A.*, **46**, 6162a (1952).

(2) F. J. Marshall, THIS JOURNAL, **78**, 3696 (1956).

(3) (a) H. B. Hass and J. F. Bourland, U. S. Patent 2,343,256 (1944); (b) M. S. Larrison and H. B. Hass, U. S. Patent, 2,383,603 (1945).

(4) J. C. Hessler, *Am. Chem. J.*, **32**, 120 (1904).

(5) T. J. Thompson, H. L. Bedell and G. M. Buffet, THIS JOURNAL, **47**, 875 (1925).

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amine. The use of lithium aluminum hydride gave incomplete reduction, partial cleavage to 2-phenylbutylamine and a poor yield of the diamine when tested in the case of ethylphenylcyanoacetamide. The 2-phenylbutylamine was identical with that from 2-phenylbutyronitrile. Equimolar quantities of aluminum chloride[6] and the hydride afforded a good yield of the diamine and almost completely eliminated cleavage to the monoamine. The yields of VII, VIII, IX and X (Table I) all refer to this improved procedure.

Table I

2,2-Disubstituted-1,3-propanediamines, $RR'C(CH_2NH_2)_2$

	R	R′	B.p. °C.	Mm.	n^tD	t, °C.	d^t_4	t, °C.	Nitrogen, % Calcd.	Found	Yield, %
II	CH_3	i-C_4H_9	90–92	13	1.4626	20	0.8664	27	19.4	18.9	51
III	CH_3	n-C_5H_{11}	120–121.5	24	1.4621	20	.8573	30.2	17.7	17.9	39
IV	C_2H_5	C_2H_5	88–89	16	1.4651	25	.8851	22	21.5	21.9	77
V	C_2H_5	n-C_4H_9	123–125	31	1.4662	20.1	.8711	26.2	17.7	17.6	15
VI	i-C_4H_9	i-C_4H_9	130–132	20	1.4642	20	.8671	20	15.0	15.7	43
VII	CH_3	C_6H_5	108–109	0.75	1.5535	20	1.0247	20	17.06	16.94	80
VIII	C_2H_5	C_6H_5	113–114	0.65	1.5469	25	1.0132	25	15.72	15.71	74
IX	n-C_3H_7	C_6H_5	120.5–121	0.65	1.5412	20	0.9984	20	14.57	14.47	64
X	i-C_3H_7	C_6H_5	122.5–123	0.65	1.5487	20	1.0135	20	14.57	14.48	68

2,2-Dimethyl-1,3-propanediamine (I) when refluxed 4 days with 5 moles of diethyl carbonate until the theoretical amount of alcohol had distilled gave almost twice as many moles of diurethan XI as the hexahydropyrimidin-2-one XX (Table II). The identical diurethan prepared from ethyl chloroformate, when heated at 240–245°, gave diethyl carbonate and XX. In contrast to the action of diethyl carbonate on the diamine, diphenyl carbonate gave good yields of the hexahydropyrimidin-2-one (Table III) in 8 hr. XI was also converted to the diamine I by acid hydrolysis. The diureide XVI was thermally decomposed to the hexahydropyrimidin-2-one XXVIII. Finally, the hexahydropyrimidin-2-one XX was hydrolyzed to I by refluxing with sulfuric acid.

Table II

Diurethans and Diureides, $RR'C(CH_2NHCOZ)_2$

No.	Z	R	R′	M.p., °C.	Nitrogen, % Calcd.	Found	Yield, %
XI	OEt	CH_3	CH_3	62–64[a]	11.37	11.41[b]	87
XII	OEt	CH_3	C_6H_5	68–70	9.09	9.10	90
XIII	OEt	C_2H_5	C_6H_5	90–91	8.69	8.72	89
XIV	OEt	n-C_3H_7	C_6H_5	86–87	8.33	8.36	95
XV	OEt	i-C_3H_7	C_6H_5	99–100	8.33	8.36[c]	88
XVI	NH_2	CH_3	C_6H_5	204–205	22.39	22.30	84
XVII	NH_2	C_2H_5	C_6H_5	188–189	21.20	21.23	81
XVIII	NH_2	n-C_3H_7	C_6H_5	194–195	20.13	20.12	80
XIX	NH_2	i-C_3H_7	C_6H_5	112–113	18.91[d]	18.93	85

[a] B.p. 138–141° (0.65 mm.). [b] Calcd. for $C_{11}H_{22}N_2O_4$: C, 53.6; H, 9.0. Found: C, 53.8; H, 9.1. [c] Calcd. for $C_{18}H_{28}N_2O_4$: C, 64.3; H, 8.4. Found: C, 64.8; H, 8.3. [d] Calcd. as monohydrate for $C_{14}H_{24}N_4O_3$: C, 56.73; H, 8.16. Found: C, 56.91; H, 7.91.

Preliminary pharmacological tests[7] indicate that the diurethans and hexahydropyrimidin-2-ones possess hypnotic and anticonvulsant activity while the diureides have little or no activity.

Experimental

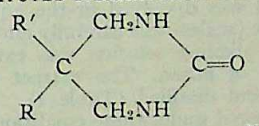
2,2-Dialkyl-1,3-dinitropropanes.—These compounds were prepared by condensation of nitromethane[8] with the corresponding ketone. 2,2-Diisobutyl-1,3-dinitropropane is new. Diisobutyl ketone (427 g.), diethylamine (880 g.), nitromethane (735 g.) and Drierite (200 g.), allowed to react one week at ice temperature, gave 86.5 g. (11.7%) of the desired product, b.p. 153° (3.4 mm.).

Anal. Calcd. for $C_{11}H_{22}O_4N_2$; N, 11.34. Found: N, 11.24.

Reduction of 2,2-Dialkyl-1,3-dinitropropanes to Diamines.—2,2-Diethyl-1,3-dinitropropane (0.20 mole) in 100 cc. of alcohol with 15 g. of Raney nickel[8] at an initial pressure of 1000 p.s.i. of hydrogen was allowed to react in a rocking bomb at 50–65° until there was no further drop in pressure (2 hr.). In addition to the desired product (20 g., 77%), diethylmalonamide (1.5 g., m.p. 219–219.5°) and low boiling cleavage products were formed.

Table III

5,5-Disubstituted Hexahydropyrimidine-2-ones



No.	R	R′	M.p., °C.	Nitrogen, % Calcd.	Found	Yield, %
XX	CH_3	CH_3	255–257	21.9	21.8	89
XXI	CH_3	C_2H_5	221–222	19.7	19.4	87
XXII	CH_3	i-C_4H_9	191–192	16.5	16.7	77
XXIII	CH_3	n-C_5H_{11}	200–202	15.2	14.9	86
XXIV	C_2H_5	C_2H_5	224–225	17.9	17.5	88
XXV	C_2H_5	n-C_4H_9	147–148	15.2	15.0	63
XXVI	n-C_3H_7	n-C_3H_7	147–148	15.2	15.2	58
XXVII	i-C_4H_9	i-C_4H_9	157–158	13.2	13.3	59
XXVIII	CH_3	C_6H_5	217–219	14.73	14.77	78
XXIX	C_2H_5	C_6H_5	198–200[a]	13.72	13.74	82
XXX	n-C_3H_7	C_6H_5	171–173	12.83	12.82	55
XXXI	i-C_3H_7	C_6H_5	240–241	12.83	12.88	80

[a] This compound (m.p. 195–197°) has been made by the reduction of phenobarbital and was reported after our product had been prepared; ref. 2.

The remaining dialkyldinitropropanes were reduced to II, III, V and VI, respectively, by iron and hydrochloric acid. The reduction procedure of Senkus[9] was followed except that alcohol was added to the reaction mixture to aid in the separation of the diamine from the voluminous precipitate of iron hydroxide. Thus the reaction mixture from 20.4 g. (0.100 mole) of 2-isobutyl-2-methyl-1,3-dinitropropane, 44.8 g. (0.800 mole) of iron turnings, 21 cc. of hydrochloric acid (sp. gr. 1.19), 100 cc. of water and 150 cc. of alcohol required 20 g. of sodium hydroxide to cause separation of the iron hydroxide so that the clear supernatant liquid could be decanted. The iron hydroxide was washed by decantation with small portions of alcohol. Sodium hydroxide was dissolved in the combined decantate and washings until two layers separated. The upper alcohol layer was removed and the lower aqueous layer was extracted with three 30-cc. portions of alcohol. The com-

(6) R. F. Nystrom, This Journal, **77**, 2544 (1955).
(7) By Merck, Sharp and Dohme, West Point, Pennsylvania.
(8) (a) L. W. Covert and H. Adkins, This Journal, **54**, 4116 (1932); (b) M. Senkus, U. S. Patent 2,418,237 (1947).
(9) M. Senkus, *Ind. Eng. Chem.*, **40**, 506 (1948).

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bined alcohol layer and extracts were dried over sodium sulfate. The alcohol was distilled and enough water was added to dissolve the residual sodium hydroxide. The supernatant liquid was removed and the water layer was extracted with four 20-cc. portions of ether. The combined liquid and extract were dried over sodium sulfate. II was obtained by distillation (Table I).

2-Alkyl-2-phenylcyanoacetamides.—Phenylcyanoacetamide was prepared by the action of aqua ammonia on phenylcyanoacetic ester[4] in yields of 75–80%. This was alkylated according to the method of Thompson, *et al.*[5] The methyl derivative does not appear to have been reported. In this case the temperature of the reaction mixture was lowered to 50° before the methyl iodide was added; yield 70%, m.p. 113–114°.

Anal. Calcd. for $C_{10}H_{10}ON_2$: N, 16.08. Found: N, 15.82.

2-Alkyl-2-phenyl-1,3-propanediamines.—To a well-stirred mixture of 20.0 g. (0.528 mole) of lithium aluminum hydride and 150 cc. of absolute ether was added rapidly through the dropping funnel a solution of 70.5 g. (0.528 mole) of aluminum chloride[6] in 350 cc. of ether. Five minutes later a solution of 0.100 mole of the 2-alkyl-2-phenylcyanoacetamide in 150 cc. of absolute ether and 60 cc. of anhydrous tetrahydrous tetrahydrofuran was added dropwise to the stirred refluxing mixture. Refluxing was continued 18–24 hr. during which the color changed from light tan to dark gray.

The excess hydride was decomposed by the dropwise addition of 20 cc. of water to the cooled mixture. After careful addition of 700 cc. of 6 *N* hydrochloric acid and 500 cc. of water, the mixture was allowed to stand overnight. The ether layer was separated and the aqueous layer was extracted with four 100-cc. portions of ether. Potassium tartrate (380 g.) was dissolved in the aqueous layer and sodium hydroxide (scales) was carefully added until no solid remained. The alkaline solution was extracted with six 200-cc. portions of ether. The extract was dried over sodium sulfate and distilled (Table I). The amount of monoamine produced under these conditions was negligible in all cases.

Reduction to a Monoamine with $LiAlH_4$.—A mixture of 20 g. (0.528 mole) of the hydride and 300 cc. of dry ether (or tetrahydrofuran) was refluxed for 6 hr. To this was added dropwise a solution of 18.8 g. (0.100 mole) of 2-ethyl-2-phenylcyanoacetamide in 100 cc. of tetrahydrofuran. The mixture was refluxed 14 hr. and after cooling was decomposed with 20 cc. of water followed by 430 cc. of 9 *N* hydrochloric acid. Most of the solvent was distilled and the aqueous layer was extracted with ether. The aqueous layer was treated carefully with 300 g. of sodium hydroxide and then extracted with six 100-cc. portions of ether. The ether extract was dried over sodium sulfate and distilled: (1) b.p. 108–112° (20 mm.), 2.6 g. (18%); (2) b.p. 159–163° (20 mm.), 3.7 g. (21%). The combined products from three preparations were redistilled. Fraction 1: b.p. 109–109.5° (20 mm.)[10]; $n^{25}D$ 1.5162, d^{25} 0.9317. Calcd. for $C_{10}H_{15}N$: *MR*, 48.21; neut. equiv., 149. Found: *MR*, 48.39; neut. equiv., 151.

The hydrochloride was precipitated from a dry ether solution of the monoamine, m.p. 168–169° (lit.[10] 156°). An authentic sample of 2-phenylbutylamine (b.p. 108–110° (20 mm.), $n^{25}D$ 1.5163) prepared by reduction of 2-phenylbutyronitrile with $AlCl_3$ and $LiAlH_4$ (see above) gave a hydrochloride which, after crystallization from ligroin (b.p. 90°) containing enough alcohol to dissolve it at the boiling point, had m.p. and mixed m.p. 168–169°.

Anal. Calcd. for $C_{10}H_{16}NCl$: Cl, 19.09. Found: Cl, 19.10.

Redistilled fraction 2 had b.p. 162–164° (18 mm.). *Anal.* Calcd. for $C_{11}H_{14}(NH_2)_2$: neut. equiv., 89. Found: neut. equiv., 95.

Reaction of Diethyl Carbonate with 2,2-Dimethyl-1,3-propanediamine (I).—A mixture of 20.4 g. (0.200 mole) of I and 118 g. (1.00 mole) of diethyl carbonate was refluxed four days in a flask fitted with a small condenser (protected from air by Ascarite) and a small fractionating column. From time to time the alcohol from the reaction was distilled while the condenser was closed; yield of alcohol 17.7 g. (96%). The solid in the cooled residue was filtered with suction. One crystallization from alcohol gave XX, m.p. 255–257°, soluble in hot water and insoluble in ether. The filtrate was distilled to give 19.9 g. (41%) of the diurethan XI, b.p. 138–141° (0.6–0.7 mm.). The product crystallized on standing and was purified by crystallization from ligroin, m.p. 62–64°, identical with XI from the action of ethyl chloroformate on the diamine.

A mixture of 1.6 g. of XI, 6.6 g. of hydrochloric acid (37%) and 1.6 g. of glacial acetic acid was refluxed two days to yield 1.0 g. of the dihydrochloride[11] which had m.p. 256–257° (from alcohol). The m.p. of this salt varies greatly with the rate of heating. It was identical with an authentic sample prepared from the diamine.

Preparation of the Diurethans.—In a typical adaptation of a well known procedure,[12] 5.1 g. (0.050 mole) of I and 10.9 g. (0.100 mole) of ethyl chloroformate gave 10.7 g. (87%) of product which crystallized from ligroin to yield pure XI.

Conversion of the Diurethan to the Hexahydropyrimidin-2-one.—XI (2.5 g., 0.10 mole) was heated 1 hr. at 240–245° and 1 hr. at 265–275° during which 0.90 g. (76%) of diethyl carbonate (b.p. 124–126°) distilled. The cooled solid residue, after washing with ether, weighed 0.70 g. (55%). Crystallization from alcohol gave XX, m.p. 255–257°, identical with that obtained from the action of diethyl carbonate on I.

2-Alkyl-2-phenyl-1,3-propanediureides.—In a typical experiment 6.6 g. (0.040 mole) of VII was dissolved in 13 cc. of water and 6.6 cc. (0.080 mole) of hydrochloric acid (sp. gr. 1.19). To this solution was added rapidly with stirring a solution of 6.8 g. (0.084 mole) of potassium cyanate in 12 cc. of water. The mixture was heated on the steam-bath for 15 min. (5 for the isopropyl derivative) with occasional stirring. After standing at room temperature the mixture was cooled in ice. The crystalline XVI was filtered, crystallized from hot water and dried *in vacuo*.

Conversion of the Diureide to the Hexahydropyrimidin-2-one.—XVI (1.0 g.) was heated 30 min. at 210–215° and then 15 min. at 255–260°. The cooled material was dissolved in hot alcohol and filtered from a small amount of insoluble matter. The filtrate was evaporated to a small volume, mixed with two volumes of hot water and cooled. The crystals were recrystallized twice from 2:1 water–alcohol; yield of XXVIII, 0.32 g. (42%), m.p. 217–219°, identical with the product from the diamine (mixed m.p.).

Preparation of 5,5-Disubstituted Hexahydropyrimidin-2-ones.—In a typical case 13.5 g. (0.063 mole) of diphenyl carbonate was mixed portionwise with 9.8 g. (0.060 mole) of VII. The mixture was then heated in a bath at 160–170° for 8 hr. in an apparatus protected by a tube filled with Ascarite. After distillation of the phenol under diminished pressure, the cooled residue was triturated with ether. The crystalline material was filtered and crystallized from a 2:1 mixture of alcohol and water to give XXVIII (Table III).

Hydrolysis of 5,5-Dimethylhexylhydropyrimidin-2-one (XX).—XX (2.6 g., 0.020 mole) was refluxed in 20 cc. of sulfuric acid (40%) with the addition of 2.2-cc. portions of sulfuric acid (sp. gr. 1.84) at intervals until carbon dioxide was detected at the outlet. The resulting 60% solution was refluxed for 4 days. The deliquescent salt of the diamine was precipitated by 14 volumes of acetone. The solution of the salt in 40 cc. of water was treated with an excess of sodium hydroxide and extracted with six 10-cc. portions of ether. The organic base was identified as I by conversion to the diurethan XI (yield 53%, m.p. and mixed m.p. 62–64°).

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(10) Lit. 110° (13 mm.); P. Rampart and P. Amagat, *Ann. chim.*, **8**, 263 (1927).

(11) J. Rockett and F. C. Whitmore, THIS JOURNAL, **71**, 3249 (1949).

(12) W. W. Hartman and M. R. Brethen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 278.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

The Structure of Novobiocin[1,2]

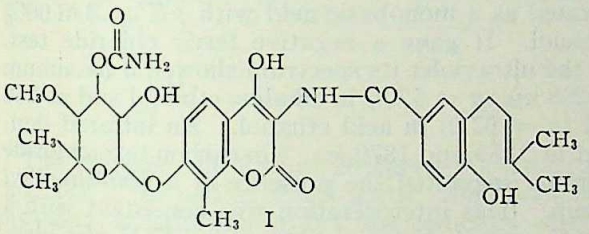
BY J. W. HINMAN, E. LOUIS CARON AND HERMAN HOEKSEMA

RECEIVED JANUARY 24, 1957

The antibiotic novobiocin[2] has been shown to be 7-[4-(carbamoyloxy)-tetrahydro-3-hydroxy-5-methoxy-6,6-dimethyl-pyran-2-yloxy]-4-hydroxy-3-[4-hydroxy-3-(3-methyl-2-butenyl)-benzamido]-8-methylcoumarin (I).

Novobiocin, elaborated by *Streptomyces niveus*, is a crystalline, acidic antibiotic of the composition $C_{31}H_{36}N_2O_{11}$. Studies on the fermentation,[3-4] extraction, purification and properties,[5,6] biological activity[7] and clinical usefulness[8] have been reported.

Because of its interesting antibacterial action and its clinical efficacy, the structure of novobiocin is of particular significance. Evidence is presented in this paper to show that novobiocin possesses structure I.



I

General Characteristics.—Novobiocin crystallized in two polymorphic modifications, one melting at 174–178° and the other at 152–156°.[5-6] The dibasic acid properties of the compound were indicated by the preparation of both acid and neutral salts. Potentiometric titrations and ultraviolet spectral shifts confirmed these observations and showed novobiocin to be a dibasic acid with pK'_a values of 4.3 and 9.1 in aqueous solution. The ultraviolet spectra in acid, neutral and alkaline solutions are given in Fig. 1. The ultraviolet spectra showed a characteristic hypsochromic shift of the phenolindophenol type in going from acid to alkaline solution. Isosbestic points linked the curves for acid to acid salt and acid salt to neutral salt transitions. Infrared spectra indicated the presence of a monosubstituted amide, hydroxyl groups, ether linkages, conjugate C=C unsaturation and possible isopropylidene and urethan groups. One methoxyl and at least two C-methyl groups were detected by analytical group determinations.

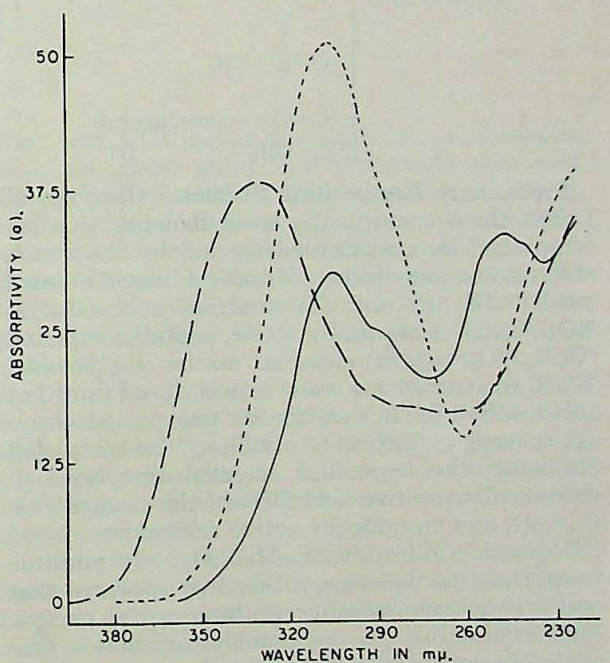


Fig. 1.—Ultraviolet spectra of novobiocin, solvents: ———, 70% ethanolic 0.01 *N* phosphate buffer, *p*H 7.5; - - - - - -, alkaline ethanol; – – – – –, acid ethanol.

Investigation of the polarographic behavior of novobiocin revealed no groups reducible below −1.5 v. *vs.* S.C.E. in acid solution or below −2.0 v. *vs.* S.C.E. in neutral on alkaline solution. These findings virtually eliminated the possible presence of nitro groups, aromatic aldehyde or keto groups, conjugate unsaturation other than an aromatic system and conjugated aliphatic acid groups.

On reaction with one mole of diazomethane the stronger acid group was neutralized with the formation of a methyl derivative whose ultraviolet spectrum closely resembled the alkaline curve of novobiocin and which did not alter appreciably with change of *p*H. This observation, considered with the absence of carboxylate absorption in the infrared, indicated that the pK'_a 4.1 function was enolic. The pK'_a value of the other acid function was in the range for a phenol, although novobiocin failed to

(1) Novobiocin. IV. The investigations upon which this paper is based were first reported in a series of preliminary communications. (a) (THIS JOURNAL, **77**, 6710 (1955); (b) **78**, 1072; (c) **78**, 2019 (1956)). These findings are in agreement with those reported independently by the Merck group (d) (*ibid.*, **78**, 1770 (1956)).

(2) The Upjohn Co. Registered Trademark for novobiocin is Albamycin. Our former generic name, streptonivicin, has been abandoned.

(3) C. G. Smith, A. Dietz, W. T. Sokolski and G. M. Savage, *Antibiotics and Chemotherapy*, **6**, 135 (1956).

(4) H. Wallick, D. A. Harris, M. A. Reagan, M. Ruger and H. B. Woodruff, *Antibiotics Annual*, 909 (1955–1956).

(5) H. Hoeksema, M. E. Bergy, W. G. Jackson, J. W. Shell, J. W. Hinman, A. E. Fonken, G. A. Boyack, E. L. Caron, J. H. Ford, W. H. DeVries and G. F. Crum, *Antibiotics and Chemotherapy*, **6**, 143 (1956).

(6) E. A. Kaczka, F. J. Wolf, F. Rathe and K. Folkers, THIS JOURNAL, **77**, 6404 (1955).

(7) (a) J. R. Wilkins, C. Lewis and A. R. Barbiers, *Antibiotics and Chemotherapy*, **6**, 149 (1956); (b) R. M. Taylor, W. T. Sokolski, G. M. Savage and M. J. Vander Brook, *ibid.*, **6**, 157 (1956); (c) E. J. Larson, N. D. Connor, O. F. Swoap, R. A. Runnells, M. C. Prestrud, T. E. Eble, W. A. Freyburger, W. Veldkamp and R. M. Taylor, *ibid.*, **6**, 226 (1956); (d) B. M. Frost, M. E. Valiant, L. McClelland, M. Solotorovsky and A. C. Cuckler, *Antibiotic Annual*, 918 (1955–1956); (e) W. F. Verwey, A. K. Miller and M. K. West, *ibid.*, 924 (1955–1956); (f) M. Finland, *ibid.*, 929 (1955–1956).

(8) (a) Feng-Kai Lin and L. L. Coriell, *ibid.*, 634 (1955–1956); (b) W. J. Martin, F. R. Heilman, D. R. Nichols, W. E. Wellman and J. E. Geraci, *Proc. Staff Meetings Mayo Clinic*, **30**, 540 (1955); (c) N. A. David and P. R. Burgner, *Antibiotic Medicine*, **2**, 219 (1956); (d) G. Lubash, J. Van Der Meulen, C. Berntsen, Jr., and R. Tompsett, *ibid.*, **2**, 233 (1956); (e) R. L. Nichols and M. Finland, *ibid.*, **2**, 241 (1956); (f) B. M. Limson and M. J. Romansky, *ibid.*, **2**, 277 (1956); (g) M. B. Milberg, R. D. Schwartz and J. N. Sifontes, *ibid.*, **2**, 286 (1956).

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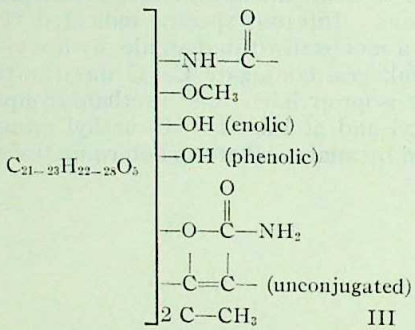
give a typical ferric chloride reaction for an unhindered phenol. Elemental analyses and molecular weight determinations on the intact molecule gave variable results because of solvation. For this reason only an approximate formula of $C_{30-31}H_{38-42}N_2O_{11}$ was established prior to degradation studies. Mild catalytic hydrogenation of I yielded a dihydro-derivative (II) whose ultraviolet and infrared spectra were almost identical with those of I indicating saturation of an unconjugated double bond. Dihydronovobiocin was found to be fully as active as novobiocin both *in vitro* and *in vivo*. The tentative findings on the intact molecule may be summarized by III.

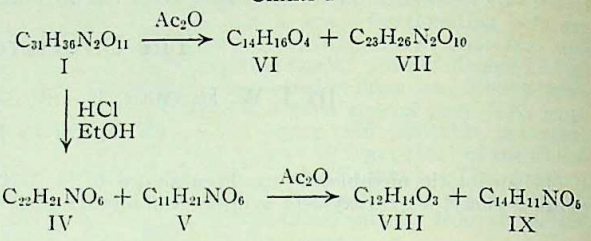


III

Preliminary Degradation Studies.—Cleavage of I into three conveniently sized moieties was accomplished by acid alcoholysis and by the action of hot acetic anhydride. Heating I in acid ethanol yielded IV, an optically inactive acid ($C_{22}H_{21}NO_6$),[9] and V, an optically active, neutral compound ($C_{11}H_{21}NO_6$) which appeared to be a glycoside. When an attempt was made to acetylate I using hot acetic anhydride in pyridine, an unexpected cleavage occurred. Instead of obtaining the acetylated antibiotic, two crystalline acetates were isolated: an optically inactive acid (VI) of the composition $C_{14}H_{16}O_4$ and an optically active neutral compound (VII) with the formula $C_{23}H_{26}N_2O_{10}$. In addition to splitting the molecule, it therefore appeared that acetic anhydride introduced three acetyl groups. Further study of the reaction showed that it proceeded in acetic anhydride alone but not with pyridine alone or with pyridine in combination with water, hydrochloric acid or glacial acetic acid. Carbon dioxide was not a product of the reaction. When the acid alcoholysis product, IV, was heated with acetic anhydride and pyridine, a similar cleavage and acetylation reaction took place to yield VIII ($C_{12}H_{14}O_3$), an optically inactive acid, and neutral IX ($C_{14}H_{11}NO_5$). These findings are summarized in Chart I.

Considering the composition of the various degradation products, VI through IX, and the methods by which they were obtained, the $C_{31}H_{36}N_2O_{11}$ formula for I was indicated. It also seemed likely that there were three main moieties in the molecule. Thus if I were represented by ABC, acetic anhydride cleaved the A–B linkage, and acid–ethanol the B–C linkage. The general properties of the degradation products indicated that those related to the A moiety were substitued benzoic acids, those related to B, an aromatic heterocyclic compound, and those related to C, some type of sugar.

CHART I



The Substituted Benzoic Acid.—Because of their apparent simplicity, the acetic anhydride degradation products VI and VIII were investigated first. The latter, a $C_{12}H_{14}O_3$ compound, m.p. 181–183°, titrated as a monobasic acid with pK'_a 6.3 in 66% ethanol. It gave a negative ferric chloride test. In the ultraviolet its spectrum showed a maximum at 258 mμ (a = 57.9) in alkaline ethanol and at 269 mμ (a = 67.2) in acid ethanol. An infrared doublet at 1385 and 1370 cm.$^{-1}$ in carbon tetrachloride solution suggested the presence of a *gem*-dimethyl group. This interpretation was consistent with a low C-methyl analysis. Compound VIII was identified as 2,2-dimethyl-6-carboxychroman[12] by comparison with an authentic sample.

Compound VI, the $C_{14}H_{16}O_4$ acid obtained directly from I by the action of hot acetic anhydride, titrated as a monobasic acid with pK'_a 5.67 in 50% ethanol. The infrared spectrum, similar to that of acetylsalicylic acid, contained bands which could be accounted for by carbonyl, ester, ethylenic and C–O linkages. The ferric chloride test was negative, but hydrolysis with 0.5 *N* sodium hydroxide deacetylated it to a dibasic acid (XI) with pK'_a values of 6.2 and 11.0 in 66% ethanol. In the ultraviolet XI exhibited maxima at 260 mμ (a = 68.2) in acid ethanol and 288 mμ (a = 76.2) in alkaline ethanol characteristic of *p*-hydroxybenzoic acids (see Fig. 2). An infrared band at 842 cm.$^{-1}$ indicated the presence of an isopropylidene group. With ferric chloride XI gave a red-brown color suggesting steric hindrance of the phenolic hydroxyl. Successive oxidations of VI with osmium tetroxide and sodium periodate yielded acetone as a major product. The side-chain was shown therefore to be the pentenyl group. Its position on the aromatic ring was determined when XI was heated in 4 *N* hydrochloric acid in 70% ethanol and cyclized to 2,2-dimethyl-6-carboxychromane (VIII) *via* the ethyl ester.

Under mild hydrogenation conditions VI consumed one mole of hydrogen to yield X, $C_{14}H_{18}O_4$. This compound, with absorption spectra very similar to those of VI, was also obtained by the action of acetic anhydride on dihydronovobiocin (II). This conveniently established the site of hydrogenation in novobiocin. Thus, the structure 4-acetoxy 3-(3-methyl-2-butenyl)-benzoic acid was assigned

(9) Although first described by this Laboratory,[1a] this compound was named *cyclonovobiocic acid* and synthesized later by the Merck group.[10,11]

(10) C. F. Spencer, C. H. Stammer, J. O. Rodin, E. Walton, F. W. Holly and K. Folkers, THIS JOURNAL, **78**, 2655 (1956).

(11) E. A. Kaczka, C. H. Shunk, J. W. Richter, F. J. Wolf, M. M. Gasser and K. Folkers, *ibid.*, **78**, 4125 (1956).

(12) A. M. Lauer and O. Moe, *ibid.*, **65**, 289 (1943). We gratefully acknowledge receipt of a sample of this compound used for identification of VIII.

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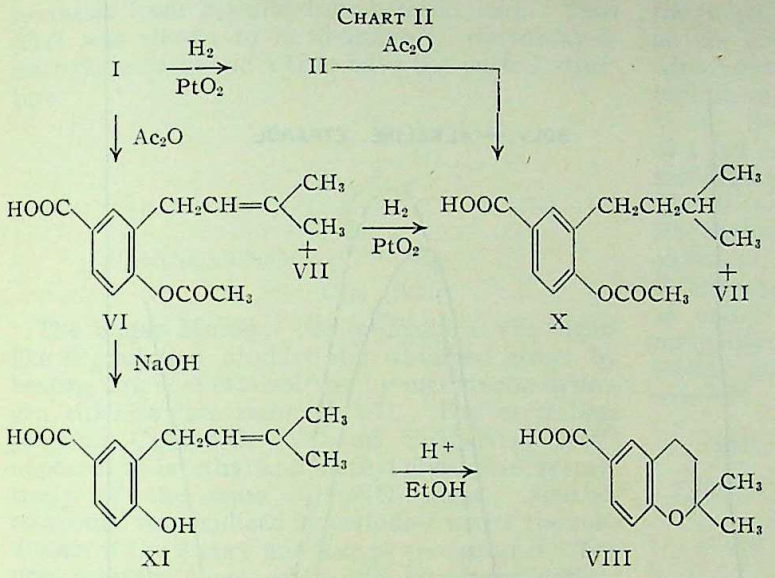
to VI, 4-acetoxy-3-(3-methylbutyl)-benzoic acid to X and 4-hydroxy-3-(3-methyl-2-butenyl)-benzoic acid to XI (see Chart II).

CHART II



The Heterocyclic Center Moiety.—As indicated in Chart I, the action of hot acetic anhydride on I provided, in addition to VI, an optically active, neutral compound, VII. This compound, m.p. 168–172°, solvated readily, especially when crystallized from acetone, but its composition was determined finally as $C_{23}H_{26}N_2O_{10}$. Its ultraviolet spectra showed characteristic fine structure between 280 and 340 mμ in neutral and acid solution and gave evidence of irreversible degradation in alkaline solution. Sodium methoxide in boiling methanol caused removal of one acetyl group with formation of another neutral compound, $C_{21}H_{24}N_2O_9$ (XII), m.p. 276–280°. The ultraviolet absorption was essentially the same as that of VII. Hot methanolic hydrogen chloride cleaved both VII and XII to optically inactive, amphoteric XIII and neutral, optically active XIV. These reactions are summarized in Chart III. The two methanolysis products were separated by fractional crystallization, XIII being the less soluble.

Compound XIII was isolated as the hydrochloride, but recrystallization from water or aqueous ethanol gave a halogen-free zwitterion-like material which decomposed above 200°. Both the hydrochloride and the free base gave a pink color with ferric chloride, a positive Benedict test, and an intense blue color with ninhydrin in pyridine. The ultraviolet spectra showed maxima at 238 mμ (a = 57.8) and 301 mμ (a = 34.5) and 347 mμ (a = 104.5) in alkaline ethanol. This same amphoteric material was obtained from IX (see Chart I) by acid hydrolysis (see Chart IV).

CHART III

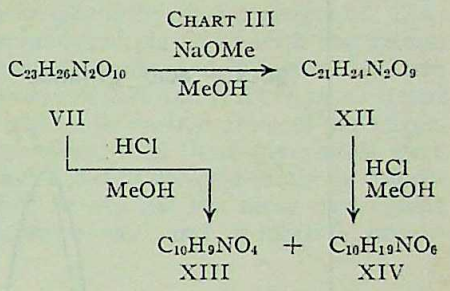
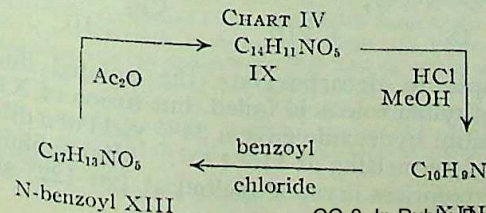
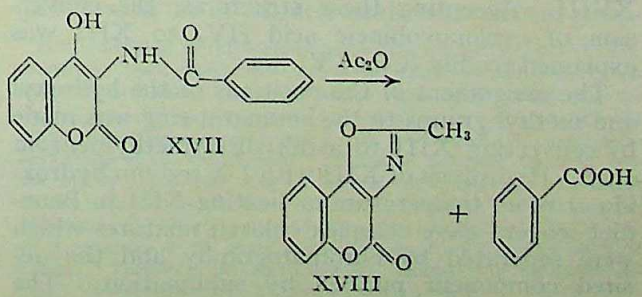


CHART IV



Benzoylation of XIII under Schotten–Baumann conditions gave an acidic monobenzoyl derivative of the composition $C_{17}H_{13}NO_5$. It appeared, therefore, that XIII had an aromatic nucleus substituted with an amino group and a strongly acid enol. Group analyses indicated the presence of one C-methyl group. Elemental analyses and ultraviolet absorption spectra indicated the presence of a neutral or phenolic hydroxyl group. On reaction with nitrous acid, XIII formed a yellowish diazo compound, $C_{10}H_7N_2O_4$ (XV). The diazo group was detected by intense infrared absorption at 2165 cm.$^{-1}$. The properties and reactions of XIII suggested a close resemblance to 3-amino-4-hydroxycoumarin[13] (XVI). The latter, generously supplied by Professor K. P. Link and also prepared according to his procedure,[13] served as a useful model compound.

Benzoylation of XVI provided 3-benzamido-4-hydroxycoumarin (XVII) whose ultraviolet spectra and other properties were similar to those of the unknown benzoyl derivative of XIII. Actually the spectra of 3-benzamido-4-hydroxycoumarin, which has no phenolic hydroxyl, exhibited the same unusual hypsochromic shift in going from acid to alkaline solution as did novobiocin itself. With the model compound the maxima occurred at 305 mμ in alkaline ethanol and at 320 mμ in acid ethanol *vs.* 308 and 333 mμ, respectively, for novobiocin. On heating with acetic anhydride, the model benzamido compound XVII yielded benzoic acid and a cyclized derivative whose properties and reactions



[13] K. P. Link, THIS JOURNAL, **67**, 99 (1945).

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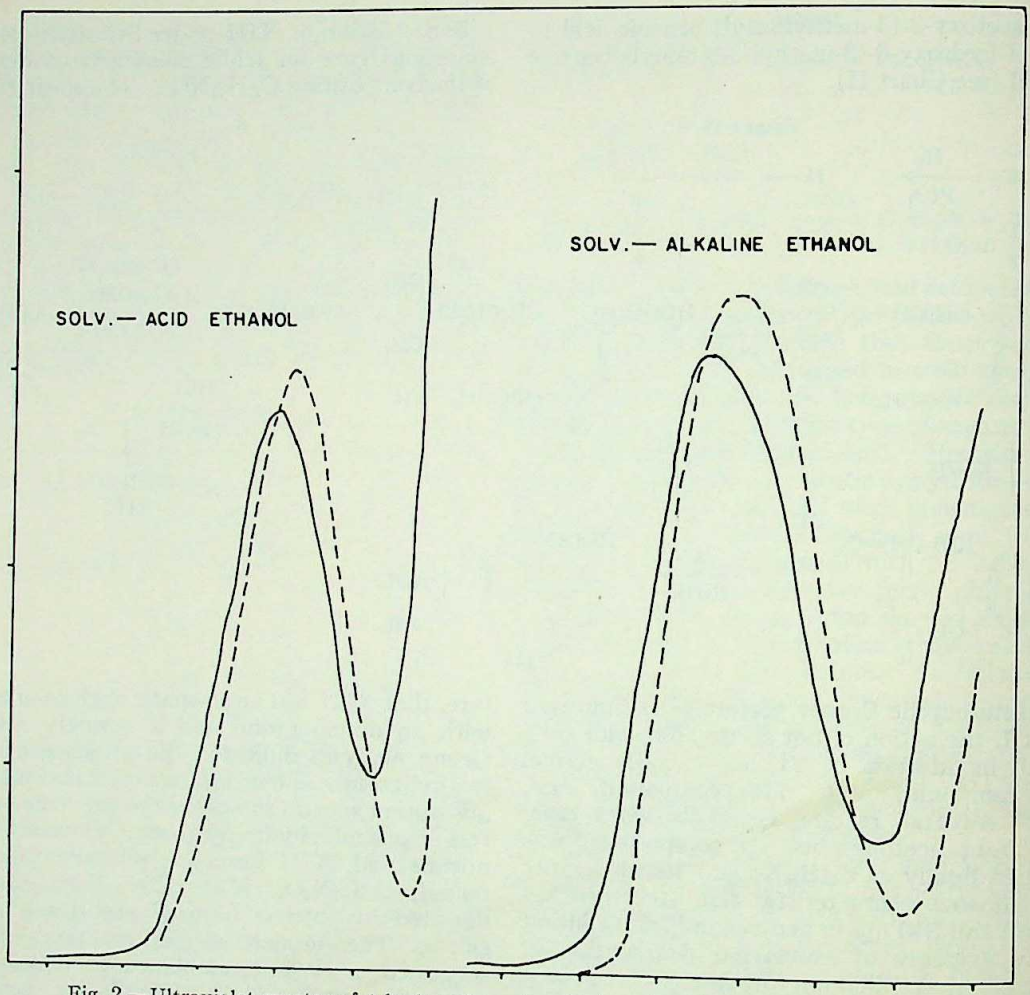
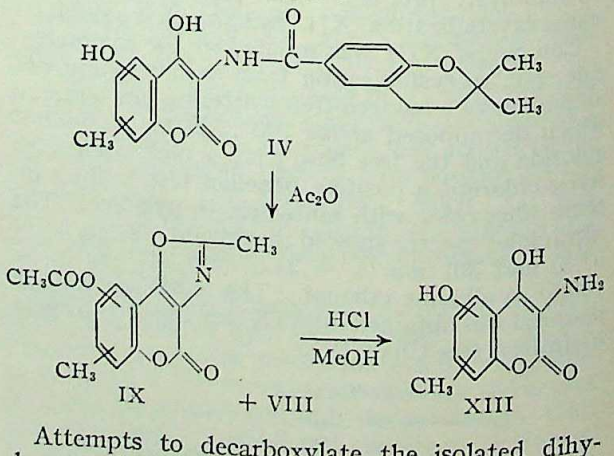


Fig. 2.—Ultraviolet spectra of *p*-hydroxybenzoic acid (- - - -) and compound XI (———).

showed it to be 2-methyl-4H[1]benzopyrano[3,4-d]oxazol-4-one (XVIII). The ultraviolet spectrum of XVIII in neutral and acid solution exhibited the same characteristic fine structure and irreversible destruction by alkali as did the spectra of the acetic anhydride products VII and IX (Fig. 3). Furthermore, treatment of N-benzoyl XIII with acetic anhydride caused elimination of benzoic acid and reformation of IX. This ready replacement of the benzoyl group by acetyl and cyclization to the oxazole derivative provided an explanation for the somewhat unexpected course of the acetic anhydride cleavage of I. It was concluded, therefore, that XIII was a hydroxyl- and methyl-substituted 3-amino-4-hydroxycoumarin and that IX was the acetoxy- and methyl-substituted analog of XVIII. Accepting these structures, the conversion of cyclonovobiocic acid (IV) to XIII was explained readily (Chart V).

The assignment of the positions of the hydroxyl and methyl groups to the coumarin ring was made by converting XIII to a dihydroxymethylbenzoic acid. Hydrolysis of XIII with 1 *N* sodium hydroxide at room temperature or heating XIII in Benedict reagent gave complex colored mixtures which were separated by chromatography and the desired component purified by sublimation. The crystalline acid, obtained in 15–20% yields, melted with sublimation at 210–225°, gave a bluish-purple ferric chloride test and analyses indicated a formula of $C_8H_8O_4$ with one C–CH_3 group. Ultraviolet absorption studies indicated the presence of two phenolic hydroxyl groups.

CHART V



Attempts to decarboxylate the isolated dihydroxymethylbenzoic acid failed, but fusion of XIII in potassium hydroxide gave a 34% yield of a dihydroxytoluene melting at 115–120°. After sublimation, the colorless crystals melted at 120–122° and

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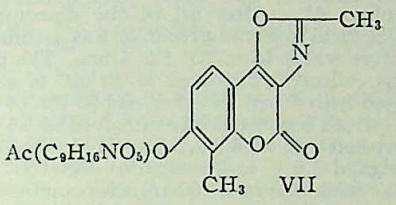
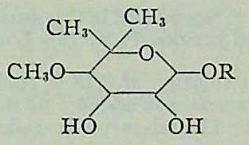
were identified as 2-methylresorcinol.[14] The identity of the isolated acid was confirmed as 2,4-dihydroxy-*m*-toluic acid by melting point and infrared comparison with an authentic sample[15] obtained by synthesis from 2,4-dihydroxybenzoic acid. Thus XIII was shown to be 3-amino-4,7-dihydroxy-8-methylcoumarin and VII to have the partial structure.



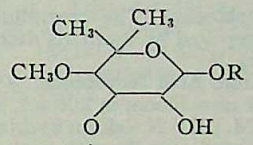
VII

The Sugar Moiety.—An optically active sugar-like degradation product was obtained either by heating I in acid ethanol[16] or by methanolic hydrogen chloride treatment of VII. The crystalline products $C_{11}H_{21}NO_6$ (V) and $C_{10}H_{19}NO_6$ (XIV) appeared to be ethyl and methyl glycosides, respectively, of the same $C_9H_{16}NO_6$ sugar. Neither compound was oxidized by periodate under the conditions of the Fleury and Lange procedure.[17] The preparation of monoacetate and monomesyl derivatives indicated the presence of one free hydroxyl group in V and XIV. The presence of one methoxyl in addition to the glycosidic alkoxyl was shown by analysis. A low C-methyl analysis (about 30% of the value calculated for one C-methyl) suggested the possibility of a *gem*-dimethyl group. A doublet at 1382 and 1366 cm.$^{-1}$ in the infrared spectra of these compounds supported this contention. Hydrolysis of XIV with hot aqueous acid caused loss of the nitrogen as ammonium chloride. This eliminated an acylamino group as a possibility for the nitrogen-containing function. When heated under reflux in methanolic hydrogen chloride, XIV yielded (in addition to ammonium chloride) a crystalline sugar derivative, $C_{10}H_{16}O_6$ (XIX), whose infrared spectrum showed a complete absence of OH/NH absorption and a strong band at 1785 cm.$^{-1}$ suggestive of a carbonate ester carbonyl. Upon treatment with barium hydroxide at room temperature, XIX gave nearly the theoretical yield of barium carbonate and a new glycoside, $C_9H_{18}O_5$ (XX). Repetition of this reaction with XIV and extending the reaction time somewhat gave ammonia, barium carbonate and a $C_9H_{18}O_5$ glycoside (XXI) as the products. These reactions and the physical-chemical data provided conclusive evidence for the presence of a carbamate group and further indicated the carbamate to be located on a carbon atom adjacent to the free hydroxyl group.

The isomeric methyl glycosides XX and XXI were shown to be anomers by hydrolysis to the same sugar aldehyde XXII. Both XX and XXI consumed one mole of periodate[17] cleanly and on oxidation with chromic acid gave acetone in 46% yield as the dinitrophenylhydrazone. This latter finding furnished confirmatory chemical evidence for the presence of the *gem*-dimethyl group. Analyses on the crystalline sugar aldehyde XXII were in agreement for the formula $C_8H_{16}O_5$ indicating retention of one methoxyl group under acid conditions. Positive reactions were obtained with Benedict and 2,4-dinitrophenylhydrazine reagents. Consumption of two moles of periodate with the formation of two moles of formic acid indicated the two free hydroxyl groups of XX and XXI to be adjacent to the no. 1 or glycosidic carbon atom of the sugar. It appeared, therefore, that these glycosides were α- and β-methyl 2,3-dihydroxy-4-methoxy-5,5-dimethylpyranoside or—to use the more convenient trivial nomenclature—α- and β-methyl novioside.[1c,18]

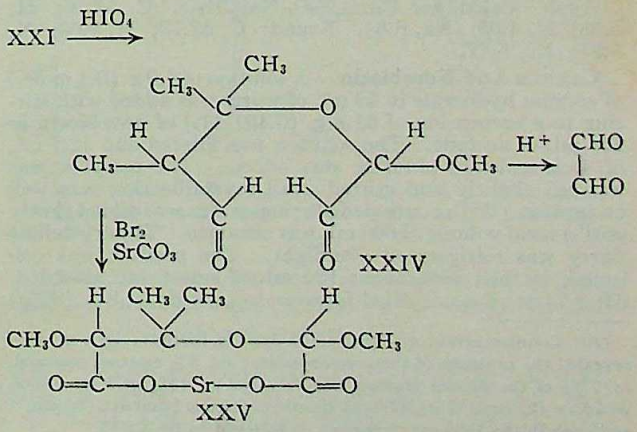


XX, XXI, R = Me
XXII, R = H



V, R = Et
XIV, R = Me
XXIII, R = H

Additional support for this structure was obtained by studying the oxidation products of XXI. Mild acid hydrolysis of the periodate oxidation product of XXI yielded glyoxal which was isolated as the 2,4-dinitrophenylosazone. Oxidation of the dialdehyde XXIV with bromine in the presence of strontium carbonate according to the method of Jackson and Hudson[19] gave the expected crystalline strontium salt XXV.



Hydrolysis of methyl 3-*O*-carbamylnovioside (XIV) with 0.5 *N* sulfuric acid removed the glyco-

(14) E. T. Jones and A. Robertson, *J. Chem. Soc.*, 1690 (1932).
(15) R. C. Shah and M. C. Laiwalla, *ibid.*, 1828 (1938).
(16) When Compound I was heated under reflux in alcohol with one mole of acetyl chloride or hydrogen chloride, the major products of the reaction were the glycoside (*i.e.*, V or XIV depending on the alcohol used) and 4,7-dihydroxy-3-[4-hydroxy-3-(3-methyl-2-butenyl)-benzamido]-8-methylcoumarin. For the latter we propose the trivial name *novobiocic acid*. Its structure was established by acetic anhydride cleavage to IX and 4-acetoxy-3-(3-methyl-2-butenyl)-benzoic acid (VI).
(17) P. F. Fleury and J. Lange, *J. pharm. chim.*, **17**, 107, 196 (1933).
(18) According to the Merck nomenclature,[1d] which evolved independently, these compounds would be called α- and β-methyl 4-methylnovobioside. This name seems undesirable because (1) the *biose* ending erroneously indicates the sugar to be a disaccharide and (2) precedent favors overwhelmingly the inclusion of the stable methoxyl group in the trivial name. This point has been discussed with the Merck group and they agree that the trivial name *novobiose* should be abandoned in favor of *noviose*. Recently the configuration of L-lyxose has been assigned to this sugar (E. Walton, J. O. Rodin, C. H. Stammer, F. W. Holly and K. Folkers, THIS JOURNAL, **78**, 5454 (1956)). Therefore, the glycosides in question may be named α- and β-methyl 4-*O*-methyl-5,5-dimethyl-L-lyxoside.
(19) E. L. Jackson and C. J. Hudson, *ibid.*, **59**, 994 (1937).

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sidic methyl group to give 3-*O*-carbamylnoviose (XXIII) in 77% yield.[20] The carbamate group was assigned to the 3-position of the sugar because XXIII consumed one mole of periodate with the formation of one mole of formic acid. Since the type and position of the linkages between the three major moieties were established in cyclonovobiocic acid (IV) and degradation product VII, structure I could be assigned to novobiocin.

Acknowledgments.—The authors are indebted to Drs. J. L. Johnson, E. C. Olson, Mrs. G. S. Fonken and Mr. J. E. Stafford for certain physico-chemical determinations, and to Mr. W. A. Struck and his associates for micro-analytical work. Appreciation is expressed to Drs. M. Calvin, H. E. Carter, D. J. Cram, W. G. Jackson, M. S. Newman and D. I. Weisblat for their interest and assistance.

Experimental[21]

Novobiocin.—The crystalline novobiocin used in this study was prepared by methods described previously by this Laboratory.[3,5]

Sodium Acid Novobiocin.—To a solution of 6.18 g. (0.01 M.) of novobiocin in 200 ml. of acetone was added 1.67 ml. (0.01 M.) of 6 *N* sodium hydroxide. The mixture was seeded and stirred rapidly with a magnetic stirrer for 16–18 hr. at 30–40°. During this time the suspended alkali dissolved and crystalline sodium acid novobiocin separated. The crystals were collected, washed with acetone and dried to yield 5.9 g. (90%), m.p. 210–215° dec., $[\alpha]_D^{25}$ −34° (*c* 1.081 in water). The crystalline salt had a potency of approximately 1000 mcg./mg. by the *K. pneumoniae* novobiocin bioassay.[3]

Anal. Calcd. for $C_{31}H_{35}N_2O_{11}Na \cdot H_2O$: C, 57.05; H, 5.72; N, 4.29. Found: C, 57.04; H, 5.93; N, 4.06.

Disodium Novobiocin.—To a suspension of 10 g. (0.0162 M.) of novobiocin in 100 ml. of water was added slowly 32.4 ml. (0.0324 M.) of 1.0 *N* sodium hydroxide. The novobiocin dissolved during this treatment and the resulting solution was dried by evaporation from the frozen state. This white amorphous salt had a potency of about 960 mcg./mg. by the *K. pneumoniae* novobiocin assay.[3]

Anal. Calcd. for $C_{31}H_{34}N_2O_{11}Na_2 \cdot 2H_2O$: C, 53.76; H, 5.53; N, 4.05; Na, 6.64. Found: C, 53.73; H, 5.63; N, 3.97; Na, 6.77.

Calcium Acid Novobiocin.—A solution of 4.0 g. (0.1 mole.) of sodium hydroxide in 50 ml. of water was added with stirring to a suspension of 61.8 g. (0.101 M.) of novobiocin in 250 ml. of acetone. The solution was filtered and 12.7 ml. of 4 *M* calcium chloride was added. The solution was warmed slightly and stirred until crystallization was well underway. With continued stirring, water was added slowly until a total volume of 600 ml. was obtained. The crystalline slurry was refrigerated overnight. The product was collected, washed with about 100 ml. of water and air-dried. After 24 hr. the salt dried *in vacuo* to provide 54.8 g. (86%) of nearly white microcrystalline powder. On the Kofler micro-hot-stage the crystals lost birefringence above 240° but did not melt up to 325°.

Anal. Calcd. for $C_{31}H_{35}N_2O_{11}Ca/2 \cdot H_2O$: C, 57.31; H, 5.74; N, 4.31. Found: C, 57.12; H, 5.88; N, 4.21.

Diazomethane Methylation of Novobiocin.—The diazomethane from 6.9 g. (0.032 M.) of N-methyl-N-nitroso-*p*-toluenesulfonamide was distilled into a stirred suspension of 10 g. (0.016 M.) of novobiocin in 40 ml. of ether and 10 ml. of methanol at 4°. After all of the diazomethane was added (a 60% yield from the precursor was assumed), the reaction mixture was held at 25° for 4 hr. The precipitated product was collected, dissolved in 30 ml. of acetone then reprecipitated with 30 ml. of ether and 60 ml. of Skellysolve B. The oil which separated was dissolved in 35 ml. of acetone and precipitated with 6 volumes of Skellysolve B. The product weighed 2.6 g. and melted at 158–160° dec. This material was subjected to a 200-transfer countercurrent distribution analysis using the solvent system 20% water, 30% ethanol, 32.5% ethyl acetate and 17.5% cyclohexane. It was found to contain 5% unchanged novobiocin, but the remainder was homogeneous by this method. The peak fraction was isolated for analysis and physical constants. Its ultraviolet spectra showed maxima in basic ethanol at 314 mμ (a = 58.6) and in acid ethanol at 310 mμ (a = 27.2) and 290 mμ (a = 27.5).

Anal. Calcd. for $C_{32}H_{38}N_2O_{11}$: N, 4.47; OCH_3, 9.90. Found: N, 4.39; OCH_3, 9.61.

Dihydronovobiocin.—A solution of 40 g. (0.0654 M.) of novobiocin in 400 ml. of warm absolute ethanol was hydrogenated using 10 g. of Adams catalyst and 40 p.s.i.g. of hydrogen pressure for 1 hr. at 25–40°. The mixture was filtered through Celite, and 1400 ml. of water was added to the vigorously stirred filtrate. Addition of 20 ml. of 1 *N* hydrochloric acid to the resulting emulsion caused a white precipitate to form. This was collected and dried *in vacuo* to yield 36 g. (90%), m.p. 163–165° dec.

Anal. Calcd. for $C_{31}H_{40}N_2O_{11}$: C, 60.38, H, 6.54; N, 4.54. Found: C, 59.96; H, 6.44; N, 4.49.

Sodium Acid Dihydronovobiocin.—A solution of 4.0 g. (6.45 mM.) of dihydronovobiocin in 90 ml. of acetone was dried 30 minutes over magnesium sulfate. To the filtered solution was added 350 mg. (6.4 mM.) of sodium methoxide. The mixture was stirred 24 hr. at 25°. As the sodium methoxide dissolved, sodium acid dihydronovobiocin crystallized. The product was collected, washed with 90 ml. of dried acetone and dried at 25° *in vacuo* to yield 3.35 g. (81%), m.p. 225–235° dec.

Anal. Calcd. for $C_{31}H_{37}N_2O_{11}Na \cdot H_2O$: C, 56.87; H, 6.01; N, 4.28. Found: C, 56.98; H, 5.95; N, 4.47.

Calcium Acid Dihydronovobiocin.—To a solution of 250 g. (0.47 M.) of dihydronovobiocin in 1 l. of acetone was added 1200 ml. (0.47 M.) of a 0.00039 *N* sodium hydroxide solution. The solution was treated with 29.7 g. (0.20 M.) of calcium chloride dihydrate in 50 ml. of water and stirred 3 hr. The crystalline precipitate was washed with acetone and dried *in vacuo* at 25° to yield 190 g. (75%) of white crystals, m.p. 225–250° dec.

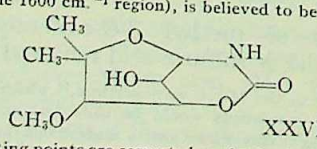
Anal. Calcd. for $(C_{31}H_{37}N_2O_{11})_2Ca \cdot 6H_2O$: C, 54.14; H, 6.30; N, 4.07; Ca, 2.91. Found: C, 54.57; H, 6.49; N, 4.24; Ca, 3.14.

Hydrolysis of Novobiocin in Acid Ethanol. A. Preparation of Cyclonovobiocic Acid (IV).—A solution of 10 g. (16.2 mM.) of novobiocin in 100 ml. of ethanol was heated to boiling. Concentrated hydrochloric acid (50 ml.) was added over a period of 7 minutes. The mixture was heated under reflux for about 30 minutes, then cooled. The solid (6.1 g., 95%) was collected, washed with water and recrystallized from 400 ml. of 1-butanol to yield 5.4 g. of IV. After a second recrystallization from ethanol the pale yellow crystals melted at 288–291°. In 75% DMF the compound titrated as a monobasic acid with pK'_a 6.3. Absorption maxima were observed at 252 mμ (a = 84.7) and 328 mμ (a = 68.2) in alkaline ethanol. In acid ethanol the intensity of the 252 mμ maximum was greatly diminished and the 328 mμ peak shifted to 331 mμ (a = 61.0).

Anal. Calcd. for $C_{22}H_{21}NO_6$: C, 66.82; H, 5.35; N, 3.54; 2 C-CH_3, 7.60. Found: C, 67.18; H, 5.40; N, 3.70; C-CH_3, 3.67.

B. Preparation of 3-*O*-Carbamyl-4-*O*-methyl-5,5-di-

(20) Countercurrent distribution analysis of the hydrolysis mixture revealed the presence of three components: *ca.* 8% starting material, *ca.* 77% of the desired product (XXIII) and *ca.* 15% of a substance, which on the basis of its infrared spectrum (strong band at 1695 cm.$^{-1}$ and none in the 1600 cm.$^{-1}$ region), is believed to be XXVI.



XXVI

(21) All melting points are corrected as obtained with a Kofler micro-hot-stage. Specific rotation values were determined using a 2-decimeter tube. All ultraviolet spectra were obtained using Cary model 11 recording spectrophotometers; infrared measurements, with Perkin–Elmer recording spectrophotometers. With reference to solvents used for ultraviolet measurements, the term *acid ethanol* means 70% ethanol 0.01 *N* with respect to its sulfuric acid content, and *alkaline ethanol* means 70% ethanol 0.01 *N* with respect to its potassium hydroxide content. The abbreviation *a* (absorptivity) is the density of a 1-g./l. solution. The abbreviations M. and mM. are used for mole and millimole, respectively.

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methyl-L-lyxoside (V).—The acid mother liquor from the above experiment was neutralized with 6 *N* sodium hydroxide and concentrated at reduced pressure to a small volume. The precipitated sodium chloride was removed and the filtrate was taken to dryness. The residue was extracted with acetone and the extract diluted with Skellysolve B to yield 316 mg. of ethyl 3-*O*-carbamyl-4-*O*-methyl-5,5-dimethyl-L-lyxoside (V), m.p. 172–176°. Recrystallization from acetone–Skellysolve B gave a 72% recovery of material melting at 173–175°, $[\alpha]_D^{25}$ −36° (*c* 1.0 in ethanol).

Anal. Calcd. for $C_{11}H_{21}NO_6$: C, 50.18; H, 8.04; N, 5.32; OCH_3, 11.79; OEt, 17.11. Found: C, 50.68; H, 8.16; N, 5.25; OCH_3, 11.71; OEt, 17.01.

Cleavage of Novobiocin to Novobiocic Acid and Ethyl 3-*O*-Carbamyl-4-*O*-methyl-5,5-dimethyl-L-lyxoside (V).—To a solution of 10 g. (0.0162 M.) of novobiocin in 100 ml. of boiling absolute ethanol was added slowly 1.1 g. (0.014 M.) of acetyl chloride. After 2 hr. of heating under reflux the solution was cooled, then treated with 300 ml. of water to precipitate 6.0 g. (94% yield) of crystalline 4,7-dihydroxy-3-[4-hydroxy-3-(3-methyl-2-butenyl)-benzamido]-8-methylcoumarin (novobiocic acid). This product was recrystallized from acetone, then purified in a 424-transfer countercurrent distribution in a solvent system containing ethyl acetate, ethanol, water and cyclohexane. The main peak fraction, representing 63% of the reaction product, was recovered and analyzed. Prolonged heating *in vacuo* at 100° was necessary to remove solvent of crystallization.

Anal. Calcd. for $C_{22}H_{21}NO_6$: C, 66.82; H, 5.35; N, 3.50. Found (average of three analyses): C, 66.47; H, 5.66; N, 3.50.

The filtrate from the reaction mixture was distilled *in vacuo* to a volume of 100 ml., then neutralized with 1*N* sodium hydroxide. The distillation was continued until the volume was 25 ml. This was then chilled to precipitate 3.0 g. of crude crystalline V, which was recrystallized from a acetone–Skellysolve B solution to yield 1.14 g. (27%) of ethyl glycoside identical with that described above.

Cleavage of Novobiocic Acid with Acetic Anhydride to VI and IX.—A solution containing 2 g. (0.005 M.) of novobiocic acid, 20 ml. of pyridine and 4 g. (0.039 M.) of acetic anhydride was heated under reflux 4 hr. It was cooled to 4°, diluted with 25 ml. of water and acidified to *p*H 2 with 22 ml. of concentrated hydrochloric acid. The resulting precipitate was filtered and dried to yield 2.6 g. of material. This was leached three times with 30 ml. of ether. The residue (1.5 g.) was crystallized from ethanol and water and the crystalline product dried *in vacuo* to yield 0.75 g. (55%). Its melting point, ultraviolet and infrared spectra were identical with those of IX.

The ether leachings were combined and evaporated to dryness to yield 0.9 g. of solid. This was crystallized from ethanol and water to yield 0.72 g. (57%) of white crystalline product which was identified as VI by its ultraviolet spectra and melting point.

Reaction of Novobiocin with Acetic Anhydride: Preparation of VI and VII.—A solution of 100 g. (0.162 M.) of novobiocin in 1 l. of pyridine and 216 g. (2.14 M.) of acetic anhydride was heated under reflux 4 hr. The solution was cooled to 5°, 1500 ml. of water and 1030 ml. of 12 *N* hydrochloric acid were added. The precipitate which formed was collected, washed with water and dried to yield 110 g. of partially crystalline solid. This was extracted with ether and the extract was evaporated to yield crude VI. After recrystallization from 400 ml. of ethanol and 600 ml. of water, 26 g. (60%) of VI, m.p. 100–113°, was obtained. The ether-insoluble fraction (51 g.) was recrystallized from 750 ml. of ethanol and 200 ml. of water to yield 46.5 g. (65%) of VII, m.p. 167–172°. Recrystallization from boiling acetone gave solvated crystals which melted at 150–170°. Another recrystallization from ethanol and water gave material which melted at 169–172°.

Compound VI, an optically inactive acid (pK_a' 5.67 in 50% ethanol), exhibited absorption maxima at 235 mμ (a = 51.6), 275 mμ (a = 5.35) and at 285 mμ (a = 4.65) in acid ethanol. In ethanolic base an irreversible shift of the maximum to 288 mμ (a = 63.2) occurred.

Optically active, $[\alpha]_D^{25}$ −94.4 (*c* 2% in DMF), VII titrated as a neutral compound which appeared to be unstable in alkali. Its ultraviolet absorption spectrum in neutral or acid ethanol showed characteristic peaks at 292 mμ (a = 25.3), 315 mμ (a = 39.7), 238 mμ (a = 33.6), 321 mμ (a = 35.0) and 329 mμ (a = 32.3). In alkaline ethanol the spectrum was irreversibly changed to end absorption with inflection points at about 240, 290 and 340 mμ.

Anal. Calcd. for $C_{14}H_{16}O_4$ (VI): C, 67.72; H, 6.50; acetyl, 17.3; 2 C–CH_3, 12.08; equiv. wt., 248.27. Found: C, 67.75; H, 6.56; acetyl, 16.3; C–CH_3, 8.84; equiv. wt., 254. Calcd. for $C_{23}H_{26}N_2O_{10}$ (VII): C, 56.33; H, 5.35; N, 5.71. Found: C, 56.65; H, 5.44; N, 5.74.

Subsequent experiments showed that this cleavage does not occur in pyridine, aqueous pyridine, pyridine with hydrochloric acid or with pyridine and glacial acetic acid. No carbon dioxide was formed during the reaction.

Reaction of Cyclonovobiocic Acid (IV) with Acetic Anhydride: Formation of VIII and IX.—A solution of 10 g. (0.025 M.) of IV in 80 ml. of pyridine and 10 ml. (0.10 M.) of acetic anhydride was heated under reflux for 3 hr. After addition of 2 ml. of water to the hot solution, it was cooled to 5° and acidified to *p*H 2 with 80 ml. of 12 *N* hydrochloric acid. The precipitate was dissolved in 400 ml. of hot 97% ethanol. On cooling, 4.3 g. of crude IX separated. The filtrate was diluted with 800 ml. of water to precipitate VIII (4.6 g.). Both compounds were recrystallized twice from ethanol. Compound VIII, m.p. 184°, was obtained in 90% yield and was identified as 2,2-dimethyl-6-carboxychromane by comparison with an authentic sample.[12] Compound IX, m.p. 203–206°, obtained in 62% yield, was neutral, optically inactive and unstable in alkali. Its ultraviolet spectrum is given in Fig. 3.

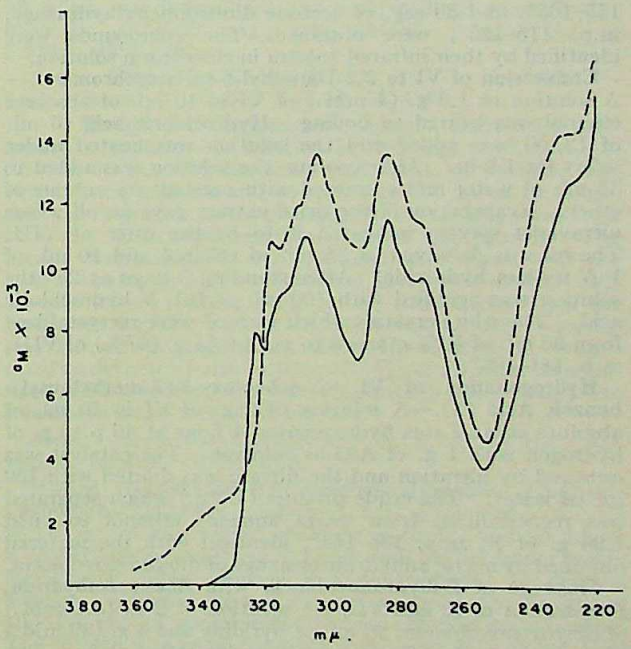

Fig. 3.—Ultraviolet spectra of 2-methyl-4H-[1]benzopyrano [3,4-d]oxazol-4-one (XVIII) (———) and compound IX (- - - - -); solvent and acid ethanol.

Anal. Calcd. for $C_{12}H_{14}O_3$ (VIII): C, 69.88; H, 6.84. Found: C, 69.80; H, 6.71. Calcd. for $C_{14}H_{11}NO_5$ (IX): C, 61.54; H, 4.06; N, 5.13. Found: C, 61.59; H, 3.77; N, 5.06.

Deacetylation of VI; Preparation of 4-Hydroxy-3-(3-methyl-2-butenyl)-benzoic Acid (XI).—A solution of 0.5 g. (2 mM.) of VI, 20 ml. of 1 *N* sodium hydroxide and 50 ml. of ethanol was allowed to stand at 25° for 3 hr. After acidification to *p*H 2 with 6 *N* hydrochloric acid, the solution was distilled at reduced pressure to an aqueous concentrate. This was extracted with ether, the extract dried and evaporated. The residue was crystallized from acetone and water by rapid evaporation of the acetone to yield 350 mg. (85%) of XI, m.p. 103–106°; ultraviolet spectra are given in Fig. 2.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; 2 C–CH_3, 14.6; equiv. wt., 206.23. Found: C, 69.89; H, 6.94; C–CH_3, 6.94; equiv. wt., 208.

Osmium Tetroxide–Sodium Periodate Oxidation of VI.—To a solution of 3 g. (12.1 mM.) of VI in 60 ml. of ether (dried by distillation from methylmagnesium iodide) was

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added 3 g. (11.8 mM.) of osmium tetroxide in 20 ml. of dry ether at 0°. A heavy green precipitate formed immediately. The mixture was allowed to warm slowly to 24° and was stored for 3 days at this temperature. The precipitate was separated, the ethereal solution evaporated and the residue and precipitate combined. The solid was added to 100 ml. of ethanol, 80 ml. of water and 18 g. of sodium sulfite and the mixture heated under reflux for 30 minutes. The mixture was filtered, the precipitate washed with 200 ml. of hot ethanol and the washings added to the filtrate. The latter was evaporated to 25 ml. of aqueous solution, acidified with hydrochloric acid to *p*H 2 and extracted with ether. The dried ether extract was evaporated to yield 1.82 g. of hygroscopic solid. The ultraviolet spectra were similar to those of the unsaturated starting material, but the infrared absorption showed greatly increased hydroxyl content. A 1.72-g. quantity of this solid was dissolved in 17.2 ml. of methanol, and 1.5 g. of sodium metaperiodate in 30 ml. of water was added. After 1.5 hr. at 25° the solution was neutralized to *p*H 6.0 with sodium hydroxide and distilled as rapidly as possible into ethanolic 2,4-dinitrophenylhydrazine to yield 200 mg. of a mixture of products. This material (90 mg.) was chromatographed using a 1″ × 40″ silicic acid column (dry-packed) which was developed with a Skellysolve B–ether mixture (the ether content progressively increased from 2 to 6%). The column was dried, extracted, cut into fractions and the products isolated by elution with chloroform. After recrystallization from ethanol and water 40 mg. of formaldehyde 2,4-dinitrophenylhydrazone, m.p. 155–165°, and 30 mg. of acetone dinitrophenylhydrazone, m.p. 115–125°, were obtained. The compounds were identified by their infrared spectra in chloroform solution.

Conversion of VI to 2,2-Dimethyl-6-carboxychromane.—A solution of 1.0 g. (4 mM.) of VI in 10 ml. of absolute ethanol was heated to boiling. Hydrochloric acid (5 ml. of 12 *N*) was added and the solution was heated under reflux for 1.5 hr. After cooling, the solution was added to 35 ml. of water and extracted with one-half its volume of ether. Evaporation of the dried extract gave an oil whose ultraviolet spectra indicated it to be the ester of VIII. The oil was dissolved in 35 ml. of ethanol and 10 ml. of 1 *N* sodium hydroxide. After standing 3 days at 25° the solution was acidified with 100 ml. of 0.1 *N* hydrochloric acid. The white crystals which formed were recrystallized from 20 ml. of 50% ethanol to yield 0.55 g. (67%) of VIII, m.p. 181–183°.

Hydrogenation of VI to 4-Acetoxy-3-(3-methylbutyl)-benzoic Acid (X).—A solution of 2 g. of VI in 50 ml. of absolute ethanol was hydrogenated 1 hour at 40 p.s.i.g. of hydrogen with 1 g. of Adams catalyst. The catalyst was removed by filtration and the filtrate was diluted with 150 ml. of water. The crude product (1.3 g.) which separated was recrystallized from warm aqueous ethanol to yield 1.06 g. of X, m.p. 136–144°, identical with the material obtained by acetic anhydride cleavage of dihydronovobiocin.

Cleavage of Dihydronovobiocin with Acetic Anhydride; Preparation of X and VII.—A solution of 2 g. (3.2 mM.) of dihydronovobiocin, 20 ml. of pyridine and 4 g. (39 mM.) of acetic anhydride was heated under reflux 3 hr. The solution was diluted with 25 ml. of water, chilled to 5°, brought to *p*H 1 with 20 ml. of 12 *N* hydrochloric acid and extracted with three 50-ml. portions of ether. The combined extracts were washed with 150 ml. of water, dried and evaporated to a residue. Crystallization from 150 ml. of 30% ethanol yielded 0.32 g. of X, m.p. 135–144°. The ultraviolet spectra were similar to those of VI.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.45; H, 6.93.

The material which was not extracted with ether was separated by filtration, crystallized and recrystallized from ethanol to yield 0.68 g. of VII identical with that obtained from novobiocin.

Deacetylation of VII.—A suspension of 2.0 g. (4 mM.) of VII in 50 ml. of commercial anhydrous methanol and 1 *N* sodium methoxide in methanol was heated under reflux for 30 minutes. During this time all of the original solid dissolved and the product separated as white crystals (1.43 g.), m.p. 268–272°. For analysis a portion of the material was recrystallized from a large volume of boiling acetone. This material (XII) was neutral, non-reducing, ferric chloride and ninhydrin negative and exhibited ultraviolet spectra qualitatively identical with those of VII.

Anal. Calcd. for $C_{21}H_{24}N_2O_9$: C, 56.34; H, 5.40; N, 6.25. Found: C, 56.07; H, 5.54; N, 6.25.

Methanolysis of XII; Preparation of 3-Amino-4,7-dihydroxy-8-methylcoumarin (XIII) and Methyl 3-*O*-Carbamyl-4-*O*-methyl-5,5-dimethyl-L-lyxoside (XIV).—A suspension of 2.0 g. (4.45 mM.) of XII (VII could also be used) in 400 ml. of methanol and 100 ml. of 3.15 *N* methanolic hydrogen chloride was heated under reflux with frequent swirling. After about 2 hr. all of the crystals dissolved and the colorless solution was cooled, filtered and concentrated *in vacuo*. The two products, XIII and XIV, crystallized and were separated by fractional crystallization from methanol and ether to yield 1.9 g. of XIII as the hydrochloride and 435 mg. of XIV. The former, less soluble in methanol, decomposed above 200°, gave a pink color with ferric chloride and a strong positive reaction with ninhydrin in pyridine in the cold.

Anal. Calcd. for $C_{10}H_{10}NO_4Cl$: C, 49.49; H, 4.15; N, 5.77; Cl, 14.61. Found: C, 48.52; H, 4.79; N, 5.44; Cl, 12.06.

Recrystallization of XIII hydrochloride from water or aqueous ethanol yielded the free-base or zwitterion compound.

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.99; H, 4.38; N, 6.77. Found: C, 57.69; H, 4.32; N, 6.25.

Final purification of XIV was accomplished by recrystallization from acetone and Skellysolve B. The colorless platelets were neutral, ninhydrin-negative, showed only end absorption in the ultraviolet and melted at 194–195°, $[\alpha]_D^{25}$ − 24.7° (*c* 1 in 95% ethanol).

Anal. Calcd. for $C_{10}H_{19}NO_6$: C, 48.19; H, 7.68; N, 5.62. Found: C, 48.11; H, 7.71; N, 5.61.

Reaction of IX with Methanolic Hydrogen Chloride. Preparation of 3-Amino-4-hydroxy-8-methylcoumarin Hydrochloride (XIII).—A solution of 2 g. (7.3 mM.) of IX in 100 ml. of 3.5 *N* methanolic hydrogen chloride and 400 ml. of methanol was heated under reflux 3 hr., then stored at 24° 16 hr. Concentration of the solution to 100 ml. by distillation *in vacuo* and chilling to −10° yielded 1.5 g. of white precipitate. Recrystallization from 100 ml. of absolute ethanol and 200 ml. of ether gave 1.15 g. which decomposed over the range 240–310°. This material was ninhydrin-positive in the cold and gave a transient pink color with ferric chloride.

Anal. Calcd. for $C_{10}H_{10}NO_4Cl$: C, 49.49; H, 4.15; N, 5.77. Found: C, 49.88; H, 5.30; N, 5.18.

Recrystallization of this hydrochloride from hot 30% ethanol gave XIII free base identical with that obtained from XII.

3-Benzamido-4,7-dihydroxy 8-methylcoumarin (N-Benzoyl XIII).—Benzoyl chloride (0.6 ml.) was added portionwise and with vigorous shaking to a solution of 0.46 g. of XIII in 30 ml. of 1 *N* sodium hydroxide at 0–5°. After 2 hr., the solution was filtered free of a trace of insoluble material and acidified with 2 *N* hydrochloric acid. The orange precipitate which formed was filtered off, washed with water and dried. The crude product was extracted with four 30–40-ml. portions of boiling Skellysolve B to remove benzoic acid then recrystallized from 95% ethanol using Darco G-60 for decolorization. The yield of pale yellow product was 0.39 g., m.p. 309–310°. For analysis, a sample was recrystallized again from ethanol.

Anal. Calcd. for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.63; H, 4.19; N, 4.42.

Conversion of N-Benzoyl-XIII to IX by the Action of Acetic Anhydride.—A solution of 515 mg. of 3-benzamido-4,7-dihydroxy-8-methylcoumarin in 45 ml. of pyridine and 15 ml. of acetic anhydride was held at 25° for 1 hr. and heated under reflux for 2 hr. After cooling, water and solid potassium bicarbonate were added and the solution taken to dryness *in vacuo*. The residue was taken up in water and chloroform. After shaking, the layers were separated and the aqueous phase extracted several times with chloroform. The combined, dried extracts were evaporated and the residue crystallized from aqueous ethanol to yield 100 mg. of nearly colorless crystals, m.p. 201–203°. Comparison with IX obtained by the other route by means of ultraviolet and infrared spectra and mixed melting point established the identity.

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Anal. Calcd. for $C_{14}H_{11}NO_6$: C, 61.54; H, 4.06; N, 5.13. Found: C, 61.84; H, 3.80; N, 5.12.

3-Benzamido-4-hydroxycoumarin (XVII).—Using the same procedure as employed for the benzoylation of XIII, 1.0 g. of 3-amino-4-hydroxycoumarin[13] was benzoylated with benzoyl chloride in 1 *N* sodium hydroxide at 5°. The benzoic acid-free product was recrystallized from ethanol to yield 700 mg. of benzamide, m.p. 207–208° dec.

Anal. Calcd. for $C_{16}H_{11}NO_4$: C, 68.48; H, 3.94; N, 4.98. Found: C, 68.31; H, 4.04; N, 4.88.

2-Methyl-4H-[1] benzopyrano[3,4-d]oxazol-4-one (XVIII).—A solution of 200 mg. (0.14 mM.) of 3-benzamido-4-hydroxycoumarin in 2 ml. of pyridine was heated under reflux for 3 hr. with 5.0 g. (50 mM.) of acetic anhydride. After addition of 0.4 ml. of water and cooling, the solution was diluted with one volume of water and acidified to *p*H 2 with hydrochloric acid. The precipitate was filtered, washed with water and dried. The crude product was washed with ether and recrystallized from absolute ethanol to yield 80 mg. of white crystals, m.p. 195° dec. The ultraviolet spectrum was almost identical with that of IX (see Fig. 3).

Anal. Calcd. for $C_{11}H_7NO_3$: C, 65.67; H, 3.51; N, 6.96. Found: C, 65.83; H, 3.55; N, 6.94.

3-Diazo-7-hydroxy-8-methyl-2,4-chromandione (XV).—To an ice-cold solution of 200 mg. of XIII in 20 ml. of glacial acetic acid and 15 ml. of water was added 200 mg. of sodium nitrite. The solution was stirred until the nitrite crystals dissolved. After 1.5 hr. the solution was allowed to warm to room temperature and was taken to dryness *in vacuo*. The oily yellow residue was triturated with water and the product crystallized. The crude crystals (80 mg.) were recrystallized from ethanol and water using Darco G-60 to yield 60 mg. of peach-colored crystals which melted at 195–197° with explosive decomposition. The infrared spectrum showed a prominent band at 2165 cm.$^{-1}$ for the diazo group. Ultraviolet maxima occurred at 250 mμ (a = 46.2) and 312 mμ (a = 69.9) in acid ethanol and at 260 mμ (shoulder) (a = 37.8) and 366 mμ (a = 95.0) in alkaline ethanol.

Anal. Calcd. for $C_{10}H_7N_2O_4$: C, 54.79; H, 3.22; N, 12.78. Found: C, 55.28; H, 3.19; N, 12.91.

2,4 Dihydroxy-*m*-toluic Acid from 3-Amino-4,7-dihydroxy-8-methylcoumarin (XIII).—A solution of 0.50 g. (2.05 mM.) of XIII hydrochloride in 30 ml. of 1 *N* sodium hydroxide was allowed to stand at 25° for 4 days. The dark solution, which smelled of ammonia, was acidified with 2 *N* hydrochloric acid. Following the vigorous evolution of carbon dioxide, the solution was extracted several times with ether. The combined, dried extract was evaporated to yield 0.21 g. of red-brown solid. This material was dissolved in ethanol, stirred with Darco G-60 and the filtered solution evaporated to dryness. Most of the residue dissolved in saturated aqueous bicarbonate. The solution was filtered, acidified and extracted with ether. After drying, the ether extract was concentrated to a volume of about 10 ml. and passed through a $^3/_8'' \times 10''$ column of Florisil (Upjohn 6565a) previously dry-packed and wet-down with ether. As the column was developed with ether, most of the colored impurities were held near the top. The ferric chloride-positive material passed through with little or no adsorption. Fractions of 15–20 ml. were collected and evaporated. The residues from the first two fractions were crystallized from ether and Skellysolve B to provide 65.8 mg. (20%) of pale yellow acid which melted with sublimation at 210–215°. Final purification by sublimation at 200–220° and atmospheric pressure gave 50.4 mg. of colorless plates, m.p., with sublimation, 210–215°. In ethanol solution the spectrum showed maxima at 262.5 mμ (a_M = 12,950) and 298 mμ (a_M = 4,175); in acid ethanol, 264 mμ (a_M = 14,300) and 298 mμ (a_M = 4,250); and in alkaline ethanol, 237 mμ (a_M = 12,350) and 282 mμ (a_M = 14,375). This substance was identified as 2,4-dihydroxy-*m*-toluic acid by direct comparison with a synthetic sample.[15]

Anal. Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.80; C–CH_3, 8.93. Found: C, 57.28; H, 5.24; C–CH_3, 8.16.

2-Methylresorcinol from 3-Amino-4,7-dihydroxy-8-methylcoumarin (XIII).—Three grams (12.3 mM.) of XIII hydrochloride was added to 20 g. of molten potassium hydroxide with stirring and continued heating on the hot-plate. The mixture became very dark and bubbled vigorously as ammonia evolved. After 30 minutes the reaction mixture was cooled to room temperature. Water (35 ml.) was added to the dark solid and the mixture was stirred until a uniform gelatinous slurry was obtained. The coal-black slurry was acidified with concentrated hydrochloric acid and extracted several times with ether. After drying over magnesium sulfate, the solvent was evaporated and the residue crystallized from benzene. Two crops totaling 0.52 g. (34%) of yellow crystals, m.p. 115–120°, were obtained. Part of this material was sublimed at *ca.* 125° and atmospheric pressure to yield colorless crystals which melted at 120–122°. When dissolved in ethanol and treated with 1% aqueous ferric chloride, little or no color change was noted. In aqueous solution alone (*i.e.*, no ethanol) a fleeting purple color was observed. This is in agreement with the properties recorded by Jones and Robertson,[14] for 2-methylresorcinol. When mixed with tolu-*p*-quinol, the m.p. was depressed to 100–105°.

Anal. Calcd. for $C_7H_8O_2$: C, 67.73; H, 6.49; C–CH_3, 12.1. Found: C, 67.89; H, 6.21; C–CH_3, 9.18.

Methyl 2-*O*-Acetyl-3-*O*-carbamyl-4-*O*-methyl-5,5-dimethyl-L-lyxoside.—A solution of 201 mg. (0.8 mM.) of XIV in 2.0 ml. of pyridine and 0.5 ml. of acetic anhydride was allowed to stand at 25° for 48 hr. The solution was cooled in an iced bath and diluted with 10 ml. of water. After 10–15 minutes the reaction mixture was extracted twice with an equal volume of chloroform. The dried, pooled extracts were evaporated to yield 230 mg. of colorless oil which was crystallized and recrystallized from Skellysolve B; yield 202 mg., m.p. 44–48°, $[\alpha]_D^{24}$ −14.0 (c 1.136 in 95% ethanol).

Anal. Calcd. for $C_{12}H_{21}NO_7$: C, 49.47; H, 7.27; N, 4.81. Found: C, 49.67; H, 7.49; N, 4.96.

Methyl 3-*O*-Carbamyl-2-*O*-mesyl-4-*O*-methyl-5,5-dimethyl-L-lyxoside.—A solution of 916 mg. (3.67 mM.) of XIV in 15 ml. of chloroform and 3 ml. of pyridine was chilled in an ice-bath and swirled with 0.3 ml. of methanesulfonyl chloride. After standing in a glass-stoppered flask at 4° for 22 hr., the reaction mixture was filtered. The filtrate was cooled to 0–5°, shaken with water and the layers separated. The chloroform layer was washed with ice-cold 0.5 *N* sulfuric acid, water, saturated sodium bicarbonate solution and finally with water. After drying over anhydrous magnesium sulfate, the solution was evaporated to dryness to yield 610 mg. (61%) of oil which crystallized quite readily. On recrystallization from water, the colorless crystals melted at 149–151°.

Anal. Calcd. for $C_{11}H_{21}NO_8S$: S, 9.79; OCH_3, 19.0. Found: S, 9.82; OCH_3, 18.5.

Methyl 4-*O*-Methyl-5,5-dimethyl-L-lyxoside 2,3-Cyclic Carbonate (XIX).—A solution of 1.03 g. (4 mM.) of XIV in 175 ml. of commercial absolute methanol and 40 ml. of 3 *N* methanolic hydrogen chloride was heated under reflux for 3.5 hr. The solution was concentrated to dryness *in vacuo*. The residue was slurried in 10–12 ml. of acetone, and 98.4 mg. of insoluble ammonium chloride was removed. The filtrate was evaporated to 5 ml. and 245 mg. of XIV recovered. The filtrate was concentrated to dryness under nitrogen and the remaining hydrogen chloride dispelled by vacuum drying. The residue was extracted with 15 ml. of hot water. As the solution cooled colorless crystals formed, 109 mg., m.p. 122–128°. After sublimation at 120° and 20–25 mm. the carbonate ester melted at 132–132.5°, $[\alpha]^{25}D$ +117.7° (c 0.998 in 95% ethanol).

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.95; OCH_3, 26.7. Found: C, 51.97; H, 6.91; OCH_3, 27.6.

Methyl 4-*O*-Methyl-5,5-dimethyl-L-lyxoside (XX).—Three ml. of saturated aqueous barium hydroxide solution was added to a solution of 76 mg. (0.328 mM.) of XIX in 12 ml. of carbon dioxide-free water. A white precipitate of barium carbonate separated immediately. After 2 hr. the precipitate (58.25 mg., 90%) was removed and the filtrate was neutralized with solid carbon dioxide. Again the barium carbonate was removed and the filtrate was concentrated *in vacuo* to a colorless sirup (48.26 mg., 71%). Crystallization and recrystallization from Skellysolve B gave colorless platelets, m.p. 61–68°, $[\alpha]^{25}D$ +113.8° (c 1.0 in water).

Anal. Calcd. for $C_9H_{18}O_5$: C, 52.41; H, 8.80. Found: C, 52.42; H, 8.57.

Preparation of Anhydric Methyl 4-*O*-Methyl-5,5-di-

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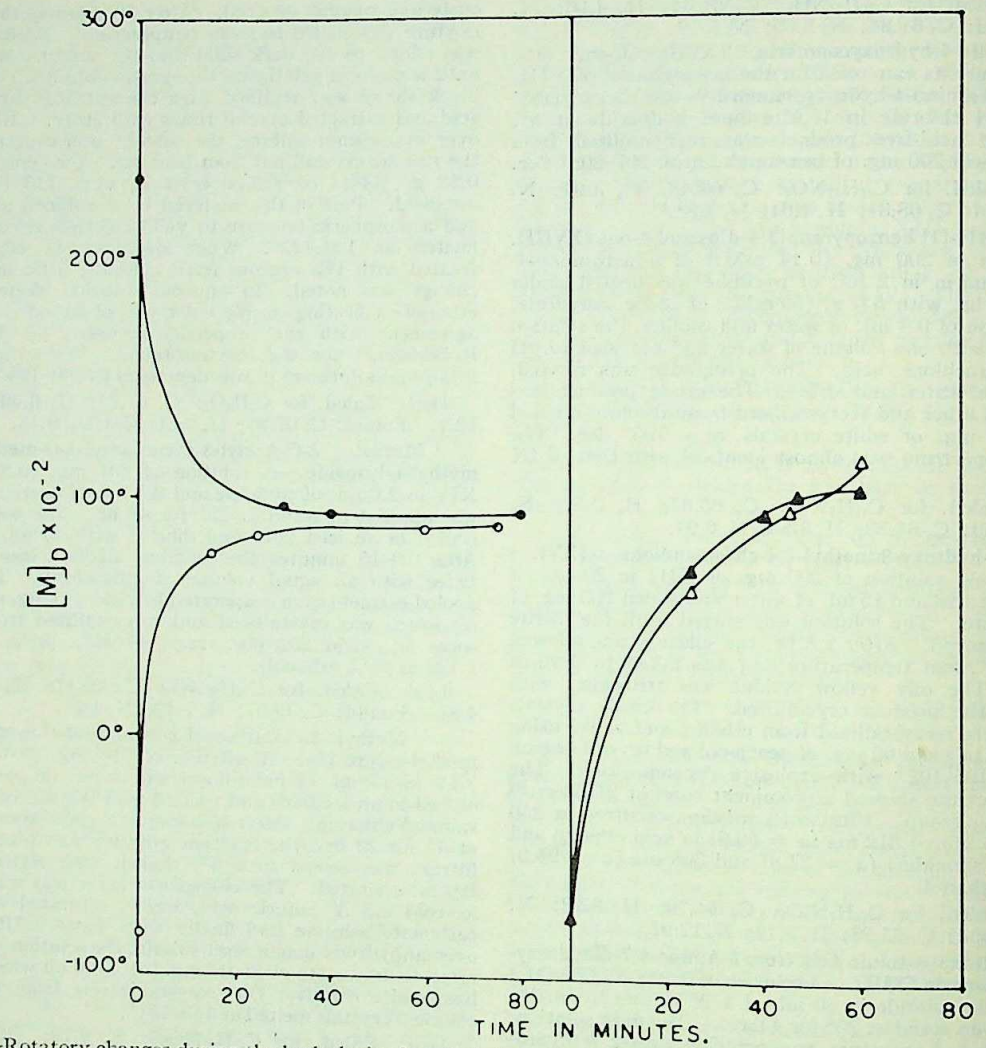

Fig. 4.—Rotatory changes during the hydrolysis of methyl glycosides in 0.5 *N* sulfuric acid at *ca.* 80°: ●, methyl novioside, anomer XXI; ○, methyl novioside, anomer XX; ▲, methyl 3-*O*-carbamylnovioside, 30 ml. of solution; ○, methyl 3-*O*-carbamylnovioside, 250 ml. of solution.

methyl-L-lyxoside (XXI) from XIV.—A solution of 2.0 g. (8 mM.) of XIV in 75 ml. of water was treated with 55 ml. of a saturated solution of barium hydroxide and allowed to react at 25° for 16 hr. The precipitate of barium carbonate was removed by filtration through a pad of Celite, and the filtrate (which smelled strongly of ammonia) was neutralized with carbon dioxide. The second precipitate was removed in the same fashion and the filtrate was taken to dryness *in vacuo*. The residue was dissolved in ether, filtered free of the last traces of barium carbonate and the solution evaporated to yield 1.6079 g. of a clear oil, which crystallized on standing. After recrystallization from Skellysolve B the dense, colorless rods melted at 65–70° and depressed the m.p. of XX. The infrared spectrum of XXI was very similar to that of XX but not identical, $[\alpha]^{24}D$ −63.6° (*c* 0.621 in 95% ethanol), −63.6° (*c* 1.0 in water).

Anal. Calcd. for $C_9H_{18}O_5$. C, 52.41; H, 8.80; OCH_3, 30.0; C–CH_3, 14.7. Found: C, 52.67; H, 8.88; OCH_3, 29.9; C–CH_3, 2.17.

Methyl 2,3-Di-*O*-acetyl-4-*O*-methyl-5,5-dimethyl-L-lyxoside.—Using the procedure described for the acetylation of XIV, 201.58 mg. (0.975 mM.) of XXI was acetylated using 3 ml. of pyridine and 1 ml. of acetic anhydride. The product was crystallized and recrystallized from Skellysolve B to yield 217 mg. of dense rods, m.p. 62–64°, $[\alpha]^{24}D$ −20.4° (*c* 0.973 in 95% ethanol).

Anal. Calcd. for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64; OAc, 29.66. Found: C, 54.16; H, 7.59; OAc, 28.07.

4-*O*-Methyl-5,5-dimethyl-L-lyxose (XXII).—A solution of 840 mg. (4.07 mM.) of methyl novioside (XXI) in 84 ml. of 0.5 *N* sulfuric acid was heated on the steam-bath at 80–85° for 1.25 hr. Previous studies had shown that this was sufficient time for completion of the reaction as indicated by the change in rotation (see Fig. 4). The solution was cooled and stirred with an excess of barium carbonate. The neutralized mixture was filtered free of insoluble salts and concentrated *in vacuo* to dryness. The residue was dissolved in absolute ethanol and the solution filtered to remove traces of salts. Evaporation of the filtrate gave a nearly quantitative yield of noviose as a colorless sirup which crystallized on standing. After recrystallization from ethanol–ether, acetone–Skellysolve B and finally from ethyl acetate, the fine colorless needles melted at 128–130°, $[\alpha]^{24}D$ +19.9° (*c* 0.950 in 50% ethanol).

Anal. Calcd. for $C_8H_{16}O_5$: C, 49.99; H, 8.39; OCH_3, 16.15. Found: C, 49.71; H, 8.50; OCH_3, 16.23.

Noviose, identical with the above, was obtained by similar treatment of XX. This proved the α-, β-methyl glycoside relationship between XX and XXI.

Chromic Acid Oxidation of Methyl 4-*O*-Methyl-5,5-dimethyl-L-lyxoside (Methyl Novioside).—To 300 mg. (1.45 mM.) of XXI was added 10 ml. of a solution containing 7.5 ml. of 5 *N* chromic acid and 2.5 ml. of concd. sulfuric acid. The solution was distilled rapidly into ethanolic 2,4-dinitrophenylhydrazine. Two additional 5-ml. portions of the oxidizing mixture and 15 ml. of water were added during the distillation. The yield of re-

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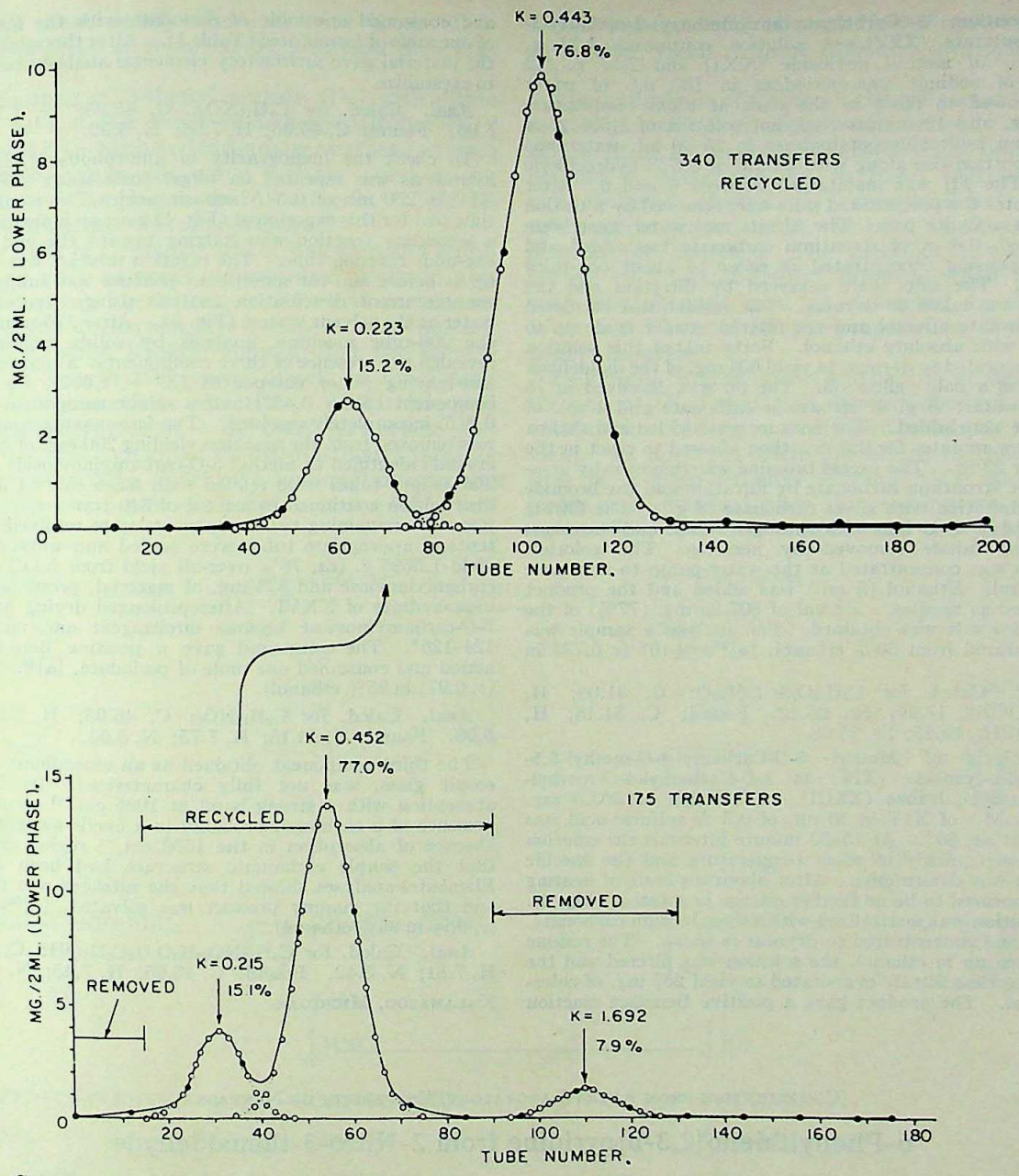

Fig. 5.—Countercurrent distribution analysis of methyl 3-*O*-carbamylnovioside hydrolysate; ●, observed; O, calculated.

crystallized acetone 2,4-dinitrophenylhydrazone was 160 mg. (46%), m.p. 125–127°. The sample was further identified by infrared comparison with authentic acetone 2,4-dinitrophenylhydrazone.

Quantitative Periodate Oxidation Studies.—Using the procedure of Fleury and Lange,[17] 0.1-mM. quantities of each compound were oxidized with sodium metaperiodate in aqueous solution in the dark at room temperature. Formic acid was determined by potentiometric titration, conversion of mercuric chloride to calomel[22] or by isolation as the water-soluble but alcohol-insoluble strontium formate. Results for pertinent compounds are given in Table I.

Glyoxal from Periodate Oxidation of Methyl Novioside (XXI).—To 249 mg. of XXI in 50 ml. of water was added 25 ml. of a 50 mg./ml. solution of sodium metaperiodate. After 2 hr. in the dark at 25°, the iodate and excess periodate were precipitated with barium hydroxide (*p*H 7). The neutral solution was evaporated *in vacuo* to 25 ml. and sodium bicarbonate added to precipitate the remaining barium ions. The filtrate was evaporated to dryness at reduced pressure and the residue extracted with ethanol. Removal of the solvent left a residue of 225 mg. which was dissolved in 10 ml. of 0.5 *N* hydrochloric acid. The solution was heated at 80° for 15 minutes then added to a hot solution of 730 mg. of 2,4-dinitrophenylhydrazine, 1 ml. of concd. hydrochloric acid and 100 ml. of ethanol. This mixture was boiled 5 minutes and an additional 5 ml. of 2 *N* hydrochloric acid was added. On cooling, 400 mg. of glyoxal dinitrophenylosazone (m.p. 345°) separated. Its identity was confirmed by infrared comparison with an authentic

TABLE I

Compound	M·IO_4^- consumed per M. cpd. 30 min.	60 min.	100 min.	M. formic acid formed per M. cpd.
Methyl 3-*O*-carbamylnovioside (XIV)	0.0	0.0	0.0	0
Methyl novioside (XX)	0.98	0.98	..	0
Methyl novioside (XXI)	0.96	0.98	0.99	0
Noviose (XXII)	1.87	1.96	1.98	1.9
3-*O*-Carbamylnoviose (XXIII)	0.95	0.97	0.98	0.8

(22) L. Ahlen and O. Samuelson, *Anal. Chem.*, 24, 1838 (1952).

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Strontium 3-(Carboxymethoxymethoxy)-2-methoxy-3-methylbutyrate (XXV).—A solution containing 1.24 g. (6 mM.) of methyl novioside (XXI) and 2.57 g. (12 mM.) of sodium metaperiodate in 150 ml. of water was allowed to react in the dark at room temperature for 1 hr. and 10 minutes. A hot solution of 1.595 g. of strontium hydroxide octahydrate in 25–30 ml. water was added portionwise along with 24 ml. of 0.5 *N* hydrochloric acid. The *p*H was maintained between 5 and 6. After 30 minutes the precipitated salts were removed by filtration through a Celite pad. The filtrate and water wash were combined, 0.4 g. of strontium carbonate was added and the suspension concentrated *in vacuo* to about one-third volume. The salts were removed by filtration and the filtrate was taken to dryness. The residue was extracted with absolute ethanol and the filtered extract made up to 50 ml. with absolute ethanol. Forty ml. of this solution was evaporated to dryness to yield 694 mg. of the dialdehyde XXIV as a pale yellow oil. The oil was dissolved in 75 ml. of water; 8 g. of strontium carbonate and 1 ml. of bromine were added. The mixture was swirled and shaken every few minutes for 0.5 hr., then allowed to react in the dark for 23 hr. The excess bromine was removed by aeration, the strontium carbonate by filtration and the bromide by precipitation with silver carbonate (8 g.). The filtrate was freed of silver ions with hydrogen sulfide and the excess hydrogen sulfide removed by aeration. The colorless solution was concentrated at the water-pump to a volume of 3–4 ml. Ethanol (5 ml.) was added and the product separated as needles. A total of 807.23 mg. (77%) of the crystalline salt was obtained. For analysis a sample was recrystallized from 50% ethanol, $[\alpha]^{24}D$ +10° (*c* 0.734 in water).

Anal. Calcd. for $C_9H_{14}O_7Sr \cdot 1.5H_2O$: C, 31.00; H, 4.91; OCH_3, 17.39; Sr, 25.12. Found: C, 31.18; H, 5.07; OCH_3, 19.65; Sr, 25.68.

Hydrolysis of Methyl 3-*O*-Carbamyl-4-*O*-methyl-5,5-dimethyl-L-lyxoside (XIV) to 3-*O*-Carbamyl-4-*O*-methyl-5,5-dimethyl-L-lyxose (XXIII).—A solution of 303.5 mg. (0.928 mM.) of XIV in 30 ml. of 0.5 *N* sulfuric acid was heated at *ca.* 80°. At 15–30 minute intervals the solution was cooled quickly to room temperature and the specific rotation was determined. After about an hour of heating there appeared to be no further change in rotation (Fig. 4). The solution was neutralized with excess barium carbonate, filtered and concentrated to dryness *in vacuo*. The residue was taken up in ethanol, the solution was filtered and the clear, colorless filtrate evaporated to yield 257 mg. of colorless glass. The product gave a positive Benedict reaction and consumed one mole of periodate with the formation of one mole of formic acid (Table I). After thorough drying the material gave satisfactory elemental analyses but failed to crystallize.

Anal. Calcd. for $C_9H_{17}NO_6$: C, 45.95; H, 7.29; N, 5.96. Found: C, 45.95; H, 7.66; N, 5.92.

To check the homogeneity of amorphous XXIII, the hydrolysis was repeated on larger scale using 2.50 g. of XIV in 250 ml. of 0.5 *N* sulfuric acid. The rotation *vs.* time plot for this experiment (Fig. 4) gave an indication that a secondary reaction was starting toward the end of the one-hour reaction time. The reaction mixture was worked up as before and the amorphous product was subjected to countercurrent distribution analysis using 1-butanol and water as the solvent system (Fig. 5). After 175 transfers in the 200-tube machine, analysis by solids measurement revealed the presence of three components: a well-resolved, fast-moving minor component (K = 1.692), the major component (K = 0.452) and a minor component (K = 0.215) incompletely resolved. The fast-moving component was removed from the machine yielding 200 mg. of colorless crystals identified as methyl 3-*O*-carbamylnovioside (XIV). The empty tubes were refilled with fresh solvent and the distribution continued to a total of 340 transfers. At this point the remaining two components were resolved. Contents of appropriate tubes were pooled and worked up to yield 1.5595 g. (*ca.* 76% over-all yield from XIV) of 3-*O*-carbamylnoviose and 336 mg. of material, presumably the monohydrate of XXVI. After prolonged drying *in vacuo*, 3-*O*-carbamylnoviose became birefringent and melted at 124–126°. The compound gave a positive Benedict reaction and consumed one mole of periodate, $[\alpha]^{26}D$ +45.3° (*c*, 0.971 in 95% ethanol).

Anal. Calcd. for $C_9H_{17}NO_6$: C, 45.95; H, 7.29; N, 5.96. Found: C, 46.15; H, 7.75; N, 5.63.

The third component obtained as an amorphous, hygroscopic glass, was not fully characterized. Its infrared absorption with a strong band at 1695 cm.$^{-1}$ assured the presence of a carbonyl, probably in a cyclic system. The absence of absorption in the 1600 cm.$^{-1}$ region indicated that the simple carbamate structure had been altered. Elemental analyses showed that the nitrogen was retained and that the gummy product was solvated, $[\alpha]^{26}D$ +63° (*c*, 0.96 in 95% ethanol).

Anal. Calcd. for $C_9H_{15}NO_5 \cdot H_2O \cdot {}^1/_2C_2H_5OH$: C, 46.50; H, 7.81; N, 5.42. Found: C, 46.95; H, 7.45; N, 5.61.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

6-Phenylthieno[2,3-b]pyridine from 2-Nitro-3-thenaldehyde

BY WILLIAM J. RAICH[1] AND CLIFF S. HAMILTON

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3-Methylthiophene was converted to 3-thenyl acetate which on nitration gave a mixture of 2- and 5-nitro-3-thenyl acetates. The readily isolated 2-isomer was hydrolyzed to the alcohol, nitric acid oxidation of which gave 2-nitro-3-thenaldehyde. The aldehyde condensed readily with malonic acid and with acetophenone. The product from the latter reaction was reduced and cyclized to 6-phenylthieno[2,3-b]pyridine.

Recently, an interest developed in the synthesis of compounds containing fused thiophene rings of the C_4N–C_4S or C_4S–C_5N systems in which the sulfur and nitrogen atoms are in the peri position. Of particular interest as an intermediate was 2-nitro-3-thenaldehyde (I) which by analogy to *o*-nitrobenzaldehyde would be a satisfactory starting material for the preparation of a number of the desired type compounds. Using commercially available 3-methylthiophene (VI), 2-nitro-3-thenaldehyde (I) was prepared in an over-all yield of 5%. The aldehyde was converted *via* the condensation product with acetophenone to 6-phenylthieno[2,3-b]-pyridine (XII), the thiophene analog of 2-phenylquinoline.

3-Methylthiophene (VI) was treated with N-bromosuccinimide as described by Campaigne and Tuller[2] to give 3-thenyl bromide which without isolation was converted immediately to 3-thenyl acetate (IV) in 58% over-all yield. The small amount of 2-bromo-3-methylthiophene formed in the bromination step was removed readily from the ester by distillation. The physical properties of the ace-

(1) Parke, Davis Fellow, 1952–1955. The Dow Chemical Company, Midland, Michigan.

(2) E. Campaigne and B. F. Tuller, *Org. Syntheses*, **33**, 96 (1953).

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tate IV were nearly identical with those of 2-thenyl acetate as reported by Emerson and Patrick.[3]

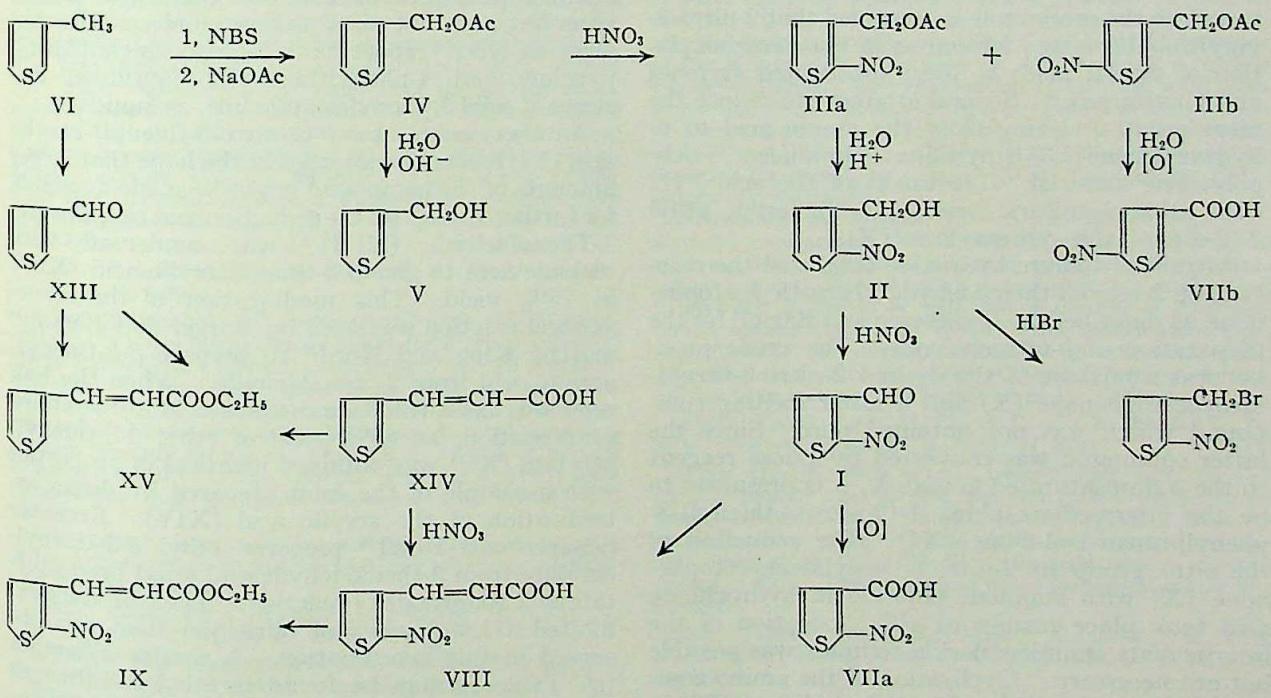
Hydrolysis of 3-thenyl acetate (IV) with dilute alkali gave a fair yield of 3-thenyl alcohol (V).[4] 3-Thenyl N-α-naphthylcarbamate synthesized from the alcohol gave the same melting point as reported by Campaigne and Bourgeois.[4] The N-phenylcarbamate was also prepared.

The work of Grimaux[5] and of Beilstein and Kuhlberg[6] as well as some unpublished work in this Laboratory on the nitration of benzyl acetate indicated the acetoxymethyl group to be *ortho-para* directing, while Rinkes[7] showed that the methyl group in 3-methylthiophene directs to the 2-position predominantly in nitration. With nitric acid in acetic anhydride at −10° 3-thenyl acetate (IV) gave a 30% yield of 2-nitro-3-thenyl acetate (IIIa) plus a 53% yield of a low-melting mixture of 2-nitro-and 5-nitro-3-thenyl acetates (IIIa and IIIb).

3-thenyl acetate (IV) to a solution of acetyl nitrate gave lower yields of more difficultly purified product.

The hydrolysis of 2-nitro-3-thenyl acetate (IIIa) to the alcohol II proceeded satisfactorily only in acid solution because of the sensitivity of both compounds to decomposition in base. Although 2-nitro-3-thenyl alcohol (II) recrystallized easily, sublimation proved to be the best means of purification for analysis. The alcohol II was converted to 2-nitro-3-thenyl bromide when treated with hydrobromic acid as described by Norris, Watt and Thomas[8] for the preparation of *o*-nitrobenzyl bromide.

Helferich, Streeck and Gunther[9] have described the uncontrolled oxidation of *o*-nitrobenzyl alcohol with nitric acid to give *o*-nitrobenzaldehyde in 85% yield. In applying their procedure to the oxidation of 2-nitro-3-thenyl alcohol (II) maximum yields were obtained when the reaction was carried out at 35°. At this temperature the yield of 2-



Attempts to obtain the 5-nitro isomer pure by fractional crystallization failed. Chromatography of the isomer mixture on alumina gave a small amount of pure 5-nitro-3-thenyl acetate (IIIb) due mainly to decomposition of the 2-isomer in the process. By projecting the results of the chromatographic experiment it was estimated that nitration of 3-thenyl acetate (IV) in the 2-position is favored 4:3 over nitration in the 5-position. No evidence of the existence of the third possible isomer, 4-nitro-3-thenyl acetate, was found although small amounts may have been present. The addition of nitro-3-thenaldehyde (I) remained nearly constant at 54% over a 15 to 30 minute reaction time. With shorter reaction periods larger amounts of 2-nitro-3-thenyl alcohol (II) were recovered while reactions of longer duration yielded increasing amounts of 2-nitro-3-thenoic acid (VIIa). The aldehyde I was isolated from the crude reaction mixture by steam distillation and further purified by sublimation in the dark. The phenylhydrazone and thiosemicarbazone of 2-nitro-3-thenaldehyde (I) were prepared most conveniently by appropriate treatment of the filtrate from the steam distillate.

The structure of 2-nitro-3-thenoic acid (VIIa) had been established earlier by Rinkes.[7] The iso-

(3) W. S. Emerson and T. M. Patrick, *J. Org. Chem.*, **14**, 790 (1949).

(4) E. Campaigne and R. C. Bourgeois, THIS JOURNAL, **76**, 2445 (1954), obtained this alcohol from the lithium aluminum hydride reduction of some halo-3-thenoic acids and refer to its previous preparation by W. C. McCarthy at the University of Indiana.

(5) E. Grimaux, *Compt. rend.*, **65**, 211 (1867).

(6) F. Beilstein and A. Kuhlberg, *Ann.*, **147**, 339 (1868).

(7) I. J. Rinkes, *Rec. trav. chim.*, **53**, 1083 (1934).

(8) J. F. Norris, M. Watt and R. Thomas, THIS JOURNAL, **38**, 1070 (1916).

(9) B. Helferich, R. Streeck and E. Gunther, *J. prakt. Chem.*, **151**, 249 (1938).

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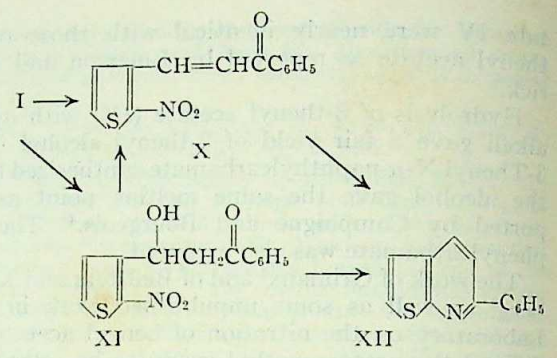
lation of this acid from the oxidation reaction substantiated the structures of the 2-nitro aldehyde I, alcohol II and acetate IIIa. The acid VIIa was converted to the previously unreported 2-nitro-3-thenamide without isolation of the intermediate acid chloride. The structure of 5-nitro-3-thenyl acetate (IIIb) was proved by hydrolysis and oxidation to the known 5-nitro-3-thenoic acid[4,7] (VIIb). Although the yield in the oxidation step was poor, only one acid was isolated. As a further check the acid VIIb was converted to 5-nitro-3-thenamide identical in melting point with that reported by Campaigne and Bourgeois.[4]

Besides forming the usual derivatives of the carbonyl group 2-nitro-3-thenaldehyde (I) underwent typical condensations with active methyl or methylene groups. With malonic acid in pyridine it reacted to form β-(2-nitro-3-thienyl)-acrylic acid (VIII). On heating the acrylic acid decomposed with the evolution of carbon dioxide; a reproducible melting point was obtained only when approached rapidly. Although no attempt was made to isolate the product, it is presumed that 2-nitro-3-vinylthiophene was formed as in the decarboxylation of similar acids to form substituted styrenes and vinylfurans.[10] Several attempts to reduce the nitro group and ring close the amino acid to 6-hydroxythieno[2,3,-b]pyridine produced only polymeric material. Treatment of the acid VIII with ethanol–sulfuric acid gave the ester, ethyl β-(2-nitro-3-thienyl)-acrylate (IX).

A trace of sodium hydroxide catalyzed the reaction of 2-nitro-3-thenaldehyde (I) with acetophenone as described by Tanesescu and Bacic[11] for the preparation of *o*-nitrochalcone. The crude product was a mixture of the desired 2-nitro-3-thenylideneacetophenone (X) and a lower melting compound which was not obtained pure. Since the latter compound was converted by Lucas reagent to the α,β-unsaturated ketone X, it is presumed to be the intermediate aldol, 1-(2-nitro-3-thienyl)-3-phenylpropan-1-ol-3-one (XI). The reduction of the nitro group in 2-nitro-3-thenylideneacetophenone (X) with stannous chloride in hydrochloric acid took place readily at 40°. Isolation of the intermediate stannic chloride complex was possible but not necessary. Cyclization of the amino compound to 6-phenylthieno[2,3,-b]pyridine (XII) in 66% yield occurred spontaneously when the crude reduction mixture was added to an excess of cold potassium hydroxide solution. It was found that both the impure aldol XI and the crude acetophenone condensation product gave only slightly lower yields of the fused ring compound under the same conditions.

Only four other thieno[2,3-b]pyridines have been reported in the literature. Two of these, the parent compound[12] and the 4,6-dimethyl derivative,[13] were prepared from 2-aminothiophene while the other two were synthesized from pyridine derivatives.



6-Phenylthieno[2,3-b]pyridine (X) is a solid quite similar in odor and appearance to 2-phenylquinoline. Of the compounds prepared in this work only the thienopyridine (XII) and β-(2-nitro-3-thienyl)-acrylic acid (VIII) exhibit melting points below those of the analogous benzene compounds. The similarity in physical properties between corresponding thiophene and benzene compounds is quite evident with the simple derivatives but may not exist among more complex analogs as Herz[14] reports both 7-phenylthieno[2,3-c]-pyridine and 4-phenylthieno[3,2-c]pyridine, isosteres of solid 1-phenylisoquinoline, as liquids.

Another route to β-(2-nitro-3-thienyl)-acrylic acid (VIII) was investigated in the hope that larger amounts of the compound might be made available for further studies on the reduction and ring closure. 3-Thenaldehyde (XIII)[15] was condensed with malonic acid to give β-3-thienylacrylic acid (XIV) in 78% yield. This modification of the Knoevenagel reaction was used by Barger and Easson[16] and by King and Nord[17] to prepare β-2-thienylacrylic acid from 2-thenaldehyde. When the half ester was substituted for malonic acid in the above condensation, an 86% yield of ethyl β-3-thienylacrylate (XV) was obtained identical in properties with a sample of the ester prepared by direct esterification of the acrylic acid (XIV). Recently Schuetz and Houff[18] prepared ethyl β-3-thienylacrylate from 3-thenaldehyde and ethyl bromoacetate in a Reformatsky reaction. Their product exhibited a lower index of refraction than was observed in this investigation. A similar difference (*cf.* Table I) may be found in ethyl β-2-thienylacrylate prepared by the Claisen and the Reformatsky methods.

TABLE I

REFRACTIVE INDICES OF ETHYL THIENYLACRYLATES

Ethyl ester	Method of preparation	(n_D, °C.)
β-(3-Thienyl)-acrylate	Reformatsky[a]	1.5562 (25)
	Knoevenagel[b]	1.5796 (25)
β-(2-Thienyl)-acrylate	Reformatsky[c]	1.5573 (30)
	Claisen[d]	1.5868 (20)

[a] Ref. 18. [b] Present work. [c] R. E. Miller and F. F. Nord, *J. Org. Chem.*, 15, 89 (1950). [d] Ref. 17.

Since the nitration of cinnamic acid has been re-

(10) R. H. Wiley and N. R. Smith, THIS JOURNAL, **72**, 5198 (1950).

(11) I. Tanesescu and A. Bacic, *Bull. soc. chim. France* [5], **4**, 1742 (1937).

(12) W. Steinkopf and G. Lutzkendorf, *Ann.*, **403**, 45 (1914).

(13) W. S. Emerson, F. W. Holly and L. H. Klemm, THIS JOURNAL, **63**, 2569 (1941).

(14) W. Herz, *ibid.*, **73**, 351 (1951).

(15) E. Campaigne, R. C. Bourgeois and W. C. McCarthy, *Org. Syntheses*, **33**, 93 (1953).

(16) G. Barger and A. P. T. Easson, *J. Chem. Soc.*, 2100 (1938).

(17) W. J. King and F. F. Nord, *J. Org. Chem.*, **14**, 405 (1949).

(18) R. L. Schuetz and W. H. Houff, THIS JOURNAL, **77**, 1836 (1955).

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ported[19] to yield predominantly *o*- and *p*-nitrocinnamic acids, it was hoped that the nitration of β-3-thienylacrylic acid (XIV) would yield useful quantities of the desired 2-nitro isomer VIII. In practice the separation of the isomers formed proved formidable. However, a small amount of the desired isomer was obtained by repeated crystallizations. The work was hampered by the low solubility of the acids and the difficulty in reproducing the melting or decomposition points. The 5-nitro derivative presumably present could not be obtained pure enough for characterization.

Experimental[20]

3-Thenyl Acetate (IV).—3-Methylthiophene (VI) (109 g. 1.1 moles) was brominated with N-bromosuccinimide (178 g., 1.0 mole) as described by Campaigne and Tuller.[2] The benzene solution of crude 3-thenyl bromide remaining after removal of succinimide was added to a flask containing 90 g. (1.1 moles) of freshly fused sodium acetate. While stirring to prevent bumping the benzene was removed by distillation and replaced simultaneously with acetic anhydride until the temperature of the mixture reached 120°. Heating and stirring at this temperature continued for 8 hours. The salt removed from the mixture by filtration was dissolved in water and extracted twice with chloroform. The combined extracts and organic filtrate were washed with water and dried before removal of the solvent under reduced pressure. The dark residue was distilled through a six-inch Vigreux column to give a small forerun containing 2-bromo-3-methylthiophene and 90.1 g. (58%) of colorless 3-thenyl acetate (IV), b.p. 98–107° (17 mm.), $n^{25}D$ 1.5169. Two fractionations through a Podbielniak column[21] gave analytical material, b.p. 105.5° (16 mm.), $n^{25}D$ 1.5138, d^{20}_4 1.174.

Anal. Calcd. for $C_7H_8O_2S$: C, 53.83; H, 5.17. Found: C, 53.93; H, 5.39.

3-Thenyl Alcohol (V).—One-tenth mole of 3-thenyl acetate (IV) was heated under reflux for 3 hours with 200 ml. of 2 *N* sodium hydroxide containing a trace of synthetic detergent. After cooling the organic layer was separated with the aid of benzene, washed and dried. Following removal of the benzene, the material was distilled through a six-inch Vigreux column to give 6.6 g. (58%) of impure 3-thenyl alcohol (V), b.p. 106–115° (20 mm.), $n^{25}D$ 1.5609 (Campaigne and Bourgeois[4] reported b.p. 88–90° (10 mm.))

With phenyl isocyanate the alcohol V formed 3-thenyl N-phenylcarbamate, m.p. 73.5–74.0° (c), after recrystallization from cyclohexane.

Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.01. Found: C, 61.68; H, 4.88; N, 6.02.

3-Thenyl N-α-naphthylcarbamate was found to melt at 132–133° as reported by Campaigne and Bourgeois.[4]

2-Nitro-3-thenyl Acetate (IIIa).—Fuming nitric acid (10 ml., 0.24 mole, sp. gr. 1.51) was added *cautiously* drop by drop to a stirred solution of 31.2 g. (0.2 mole) of 3-thenyl acetate (IV) in 60 ml. of acetic anhydride cooled to below −10° with a Dry Ice–acetone bath. Stirring was continued for 3 hours while the temperature was allowed to rise slowly to 10°. The mixture was poured into about 1 liter of ice-water and stirred until crystallization of the oil was complete. The solid was washed twice with cold water by decantation, then was collected on a büchner funnel with the aid of 100 ml. of cold 50% methanol. Three rapid recrystallizations from minimum amounts of boiling 95% ethanol gave 12.0 g. (30%) of 2-nitro-3-thenyl acetate (IIIa) as yellow platelets, m.p. 88–91°.

Anal. Calcd. for $C_7H_7NO_4S$: C, 41.78; H, 3.51; N, 6.96. Found: C, 41.95; H, 3.56; N, 6.86.

The combined ethanolic filtrates from the above recrystallizations were cooled and diluted slowly with water until crystallization was complete. After drying in a vacuum desiccator over phosphorus pentoxide, the collected solid mixture of 2- and 5-nitro-3-thenyl acetates weighed 21.4 g. (53%) and melted below 55°.

5-Nitro-3-thenyl Acetate (IIIb).—Three grams of the low melting isomer mixture obtained above was dissolved in ether and placed on a chromatographic column prepared from 300 g. of alumina (Merck). Development and elution were carried out with ether. A light yellow band moved rapidly down the column and was collected to give 2.2 g., m.p. 59–61°. After recrystallization from ethyl acetate–petroleum solvent (b.p. 89–98°) and from isopropyl ether the material melted at 65.0–65.5° (c). This was shown below to be 5-nitro-3-thenyl acetate (IIIb).

Anal. Calcd. for $C_7H_7NO_4S$: C, 41.78; H, 3.51; N, 6.96. Found: C, 41.59; H, 3.39; N, 6.94.

A dark red band had formed and moved slowly down the column in a diffuse manner. When fractions containing this material were evaporated, only a brown oil was obtained. An ether solution of 2-nitro-3-thenyl acetate (IIIa) placed on a similar column could not be eluted as such but produced a similar dark oil.

A 2.0-g. sample of 2-nitro-3-thenyl acetate (IIIb) was heated with 35 ml. of 10% sulfuric acid for 1.5 hours, then filtered with an acetic acid wash to remove some carbonaceous material present. A saturated solution of 3 g. (1.5 oxidation equivalents) of sodium dichromate dihydrate in water was added slowly over an hour at 30–35°. After an additional hour at 50°, the mixture was thoroughly cooled and the dark green solid, wt. 0.3 g., collected. Extraction of the filtrate with ether gave an additional 0.2 g. of less colored material. Recrystallization of the first solid from water and from benzene (charcoal) gave colorless prisms of 5-nitro-3-thenoic acid (VIIb), m.p. 147° (reported[4,7] as 147° and 145–146°). The acid VIIb was converted to 5-nitro-3-thenamide, m.p. 162–163° as reported by Campaigne and Bourgeois.[4]

2-Nitro-3-thenyl Alcohol (II).—A mixture of 10 g. of 2-nitro-3-thenyl acetate (IIIa) and 150 ml. of 10% sulfuric acid was heated under reflux until solution was complete (about 2 hours), filtered with charcoal while hot, and cooled to give 6.8 g. (86%) of pale yellow needles of 2-nitro-3-thenyl alcohol (II), m.p. 88–91°. An additional 0.6 g., m.p. 65–72°, was extracted from the filtrate with ether. The colorless alcohol II melted at 90–91.5° after recrystallization from water and sublimation at 55° (300 μ).

Anal. Calcd. for $C_5H_5NO_3S$: C, 37.73; H, 3.17; N, 8.80. Found: C, 37.88; H, 3.16; N, 8.85.

When treated with concd. hydrobromic acid at 75° for 1.5 hours,[8] the alcohol was converted to 2-nitro-3-thenyl bromide, m.p. 58–61°, in 71% yield. After recrystallizations from ethanol–water and from benzene–petroleum ether (b.p. 30–60°) the pale yellow crystals melted at 62°. The compound was a lachrymator and skin irritant.

Anal. Calcd. for $C_5H_4NO_2SBr$: C, 27.04; H, 1.81; N, 6.31; Br, 35.99. Found: C, 27.32; H, 1.78; N, 6.19; Br, 35.96.[22]

2-Nitro-3-thenaldehyde (I).—A stirred solution of 4 g. of 2-nitro-3-thenyl alcohol (II) in 8 ml. of concd. nitric acid was warmed to 30° until an exothermic reaction and the evolution of nitrogen oxides began. Cooling was applied as necessary to keep the temperature at 35° until no further heat effects were noted (about 20 min.). The green mixture was poured onto 20 g. of ice and the yellow solid which formed collected by filtration. The material was distilled with steam, and from 500 ml. of cold distillate there was obtained 1.5 g. (37%) of yellow needles of 2-nitro-3-thenaldehyde (I), m.p. 52–54°. For analysis the aldehyde I was recrystallized from ether–petroleum ether (b.p. 30–60°) and then sublimed at 30–35° (150 μ); m.p. 54–55°.

Anal. Calcd. for $C_5H_3NO_3S$: C, 38.21; H, 1.92; N, 8.92. Found: C, 38.28; H, 1.83; N, 8.77.

By treatment of the filtrate from the steam distillate with phenylhydrazine–acetic acid solution, 2-nitro-3-thenaldehyde phenylhydrazone was obtained in amount corresponding to an additional 0.6 g. (17%) of the aldehyde. The phenylhydrazone crystallized from absolute ethanol as dark red platelets, m.p. 213–215° dec.

(19) W. Davey and J. R. Gwilt, *J. Chem. Soc.*, 204 (1950).

(20) Melting points are uncorrected unless marked (c).

(21) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1950, p. 212.

(22) Analysis for bromine by the Parr bomb method was performed

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Anal. Calcd. for $C_{11}H_9N_3O_2S$: N, 16.99. Found: N, 17.08.

Similar treatment of the filtrate with an aqueous solution of thiosemicarbazide gave 2-nitro-3-thenaldehyde thiosemicarbazone, m.p. 243–244° dec., which could not be crystallized without decomposition.

Anal. Calcd. for $C_6H_6N_4O_2S_2$: N, 24.33. Found: N, 24.26.

Evaporation of the ether extract of the filtrate from the diluted reaction mixture gave 1.1 g. of yellow solid which after two recrystallizations from benzene proved to be 2-nitro-3-thenoic acid (VIIa), m.p. 156–157° (Rinkes[7] reported 155–156°). The acid was converted through the acid chloride to 2-nitro-3-thenamide, m.p. 184–185°, as yellow needles from hot water.

Anal. Calcd. for $C_5H_4N_2O_3S$: N, 16.28. Found: N, 16.28.

β-(2-Nitro-3-thenyl)-acrylic Acid (VIII) and Ethyl Ester (IX).—A mixture of 1.5 g. of 2-nitro-3-thenaldehyde (I), 2.0 g. of malonic acid and 5 ml. of dry pyridine containing two drops of piperidine was heated under reflux for 1 hour. The cooled, red mixture was diluted with two volumes of ice-water and acidified with hydrochloric acid. The dark solid was collected by filtration, washed with water, and dried in air to give 1.5 g. (79%), m.p. 217–219° dec. with rapid heating, of β-(2-nitro-3-thienyl)-acrylic acid (VIII). Recrystallization from hot water (charcoal) was accompanied by considerable loss but gave nearly colorless needles of the acid, m.p. 220–222° dec.

Anal. Calcd. for $C_7H_5NO_4S$: C, 42.21; H, 2.53; N, 7.03. Found: C, 42.21; H, 2.54; N, 6.92.

Decomposition of the β-(2-nitro-3-thienyl)-acrylic acid began as low as 175° as noted when the melting point was approached slowly. The evolution of carbon dioxide was shown by allowing the decomposition gas to bubble through a faintly pink, dilute phenolphthalein solution.

Ethyl β-(2-nitro-3-thienyl)-acrylate (IX) was prepared by treating the above acid VIII with absolute ethanol containing a trace of sulfuric acid. After recrystallization from ether–petroleum ether (b.p. 30–60°) and from ethanol–water, the ester IX melted at 73–74°.

Anal. Calcd. for $C_9H_9NO_4S$: C, 47.57; H, 3.99; N, 6.16. Found: C, 47.46; H, 3.93; N, 6.19.

Condensation of 2-Nitro-3-thenaldehyde (I) with Acetophenone.—Four ml. of a 1% solution of sodium hydroxide in 95% ethanol was added to a cold solution of 1.40 g. of 2-nitro-3-thenaldehyde (I) and 1.08 g. of acetophenone in 9 ml. of ether. The reaction mixture immediately darkened and became warm enough to boil away most of the ether. After 30 minutes the mixture was cooled, acidified with acetic acid and diluted with 20 ml. of water. Filtration gave 1.45 g. of brown solid, m.p. 116–130°. Extraction of this material with 50 ml. of boiling 95% ethanol left 0.85 g., (36%) m.p. 165–181°, which, after two recrystallizations from absolute ethanol, was obtained as long, light yellow needles, m.p. 181–182°, of 2-nitro-3-thenylideneacetophenone (X).

Anal. Calcd. for $C_{13}H_9NO_3S$: C, 60.22; H, 3.50; N, 5.40. Found: C, 60.24; H, 3.69; N, 5.47.

From the original filtrate and the ethanol extract of the reaction product, 0.54 g. of material melting below 130° was obtained by evaporation and dilution with water. Fractional crystallization of the material, from ethanol by the addition of water, gave material melting 131–134°. No further improvement of the melting point could be obtained. Concentrated hydrochloric acid–zinc chloride solution (Lucas reagent) converted the material to 2-nitro-3-thenylideneacetophenone (X). The material was presumed to be the aldol, 1-(2-nitro-3-thienyl)-3-phenylpropan-1-ol-3-one (XI).

6-Phenylthieno[2,3-b]pyridine (XII).—2-Nitro-3-thenylideneacetophenone (X) (0.26 g., 0.001 mole) was suspended in a solution of 1.80 g. (0.008 mole) of stannous chloride dihydrate in 5 ml. of concd. hydrochloric acid and 5 ml. of 95% ethanol. Cooling was applied as necessary to keep the reaction temperature at 40°. After no further evidence of reaction was noted, the resulting solution was allowed to stand at 35° for two hours. The entire reaction mixture was added dropwise with stirring to 25 ml. of aqueous 50% potassium hydroxide cooled below 10°. Evaporation of the ether extract of the alkaline mixture and crystallization of the residue from ethanol–water gave 0.14 g. (66%) of 6-phenylthieno[2,3-b]pyridine (XII) as orange platelets, m.p. 74–76°. Additional crystallizations from ethanol–water gave colorless material, m.p. 77–78° (c).

Anal. Calcd. for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63. Found: C, 74.01; H, 4.34; N, 6.70.

Nearly identical yields of 6-phenylthieno[2,3-b]pyridine (XII) were obtained when the low melting by-product or the crude reaction product from the acetophenone condensation were reduced and cyclized under the above conditions.

Fusion of 6-phenylthieno[2,3-b]pyridine (XII) with an equal weight of picric acid gave the picrate, m.p. 149–150° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{13}H_9NS \cdot C_6H_3N_3O_7$: N, 12.72. Found: N, 12.78.

β-(3-Thienyl)-acrylic Acid (XIV) and Ethyl Ester (XV).—3-Thenaldehyde[16] (XIII) (11.2 g., 0.1 mole) was condensed with 20.4 g. (0.2 of mole) of malonic acid as described by King and Nord[17] for the preparation of β-(2-thienyl)-acrylic acid. The crude solid, wt. 16.0 g., m.p. 141–149°, was obtained pure in 78% yield after a single recrystallization from 30% ethanol, m.p. 153–153.5° (c). Recrystallization from petroleum solvent (b.p. 89–98°) for analysis gave β-(3-thienyl)-acrylic acid (XIV) with no change in m.p.

Anal. Calcd. for $C_7H_6O_2S$: C, 54.53; H, 3.93. Found: 54.53; H, 3.72.

By substituting ethyl hydrogen malonate for malonic acid in the above procedure and isolating the liquid ester by ether extraction, an 86% yield of ethyl β-(3-thienyl)-acrylate (XV) was obtained after distillation through a six-inch Vigreux column; b.p. 147–152° (14 mm.), $n^{20}D$ 1.5755. For analysis the ester was fractionated in a Podbielniak column,[21] b.p. 154–155° (17 mm.), $n^{20}D$ 1.5819, $n^{25}D$ 1.5796, d^{20}_4 1.163 (Schuetz and Houff[18] reported $n^{25}D$ 1.5562).

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.33; H, 5.71.

Ethyl β-(3-thienyl)-acrylate (XV), b.p. 148° (14 mm.), $n^{25}D$ 1.5790, was obtained from the esterification of β-(3-thienyl)-acrylic acid (XIV) with absolute ethanol containing a trace of sulfuric acid.

Nitration of β-(3-Thienyl)-acrylic Acid (XIV).—Fuming nitric acid (2.1 ml., 0.05 mole, sp. gr. 1.51) was added slowly to a stirred mixture of 4.6 g. (0.03 mole) of β-(3-thienyl)-acrylic acid (XIV), 10 ml. of acetic acid and 15 ml. of acetic anhydride cooled below 5°. Stirring at 0° was continued for 1 hour after completion of the addition, then the temperature was allowed to rise slowly to 15°. The "mushy" yellow mixture was filtered, and the solid washed and dried; wt. 4.7 g., m.p. 187–197°. An additional 0.5 g., m.p. 177–195°, was obtained from the diluted filtrate. By repeated fractional crystallization from absolute ethanol in which the material was moderately soluble, 0.1 g. of β-(2-nitro-3-thienyl)-acrylic acid (VIII), m.p. 219–222° dec., was obtained. The mixed m.p. with a sample of the acid prepared from the condensation of 2-nitro-3-thenaldehyde (I) with malonic acid was not depressed. No other acid of constant melting point was obtained. The decomposition and dependence of the melting point on rate of heating added to the difficulty of separating any isomers present.

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Bis-Ammonium Salts. Unsymmetric Derivatives of Substituted Pyridine Bases that Are Potent and Selective Hypotensive Agents[1]

BY ALLAN P. GRAY, WESLEY L. ARCHER, ERNEST E. SPINNER AND CHESTER J. CAVALLITO

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In continuation of earlier work, a series of unsymmetric bis-quaternary salts has been prepared in which the large head is derived from a substituted pyridine (or piperidine) base. Variations in size and point of attachment of the substituent(s) have been introduced. Among the derivatives have been found compounds that are remarkably potent *and selective* hypotensive agents. Structure–activity relationships as well as certain implications of the biological findings are discussed.

Reports from these laboratories have described several series of unsymmetric bis-quaternary salts in which hypotensive and peripheral autonomic blocking activity could be independently varied.[2] A central component of action was implicated.[2,3] In our earlier reports, requirements for biological activity had been quite sharply delineated with respect to size of the small cationic head, distance between charged nitrogens, charge distribution and degree of ionization. Although the limitations as to size, shape and polarity of the large cationic head had been somewhat less clearly defined, it had been established that pyridine[2] and N-methylpiperidine[4] were too small to provide active derivatives.[5a,b]

In continuing these studies, many facets of the problem of structure–activity relationships have been explored. One approach to a more detailed examination of the structural limits imposed on the large head has been, logically enough, to determine the effects on pharmacological properties of attaching a variety of substituents at different points on a pyridine or piperidine nucleus. This has led not only to further clarification of the question but also to some remarkably potent and pharmacologically selective hypotensive agents. The present paper deals with a selected group of these unsymmetric bis-quaternary salts which are described in Tables I and II.

The route to most of the bis-ammonium salts—*i.e.*, quaternization of the appropriate pyridine (or piperidine) base with bromopropyltrimethylammonium bromide—has become more or less standard in these laboratories[2] and requires no further comment here. The preceding paper[6] describes the preparation of some indolyl- and indenyl-substituted pyridine bases, derivatives of which have been prominent in this study. IV, VII and XIII (Table I) were prepared by the base-catalyzed condensation[7] of benzaldehyde, 1-naphthaldehyde and 3-indolecarboxaldehyde (respectively) with trimethylene-1-(4-picolinium)-3-trimethylammonium dibromide (II).

4-Benzyl-1-methylpiperidine readily was obtained by the catalytic hydrogenation of 4-benzylpyridine methobromide. Hydrogenation of 4-benzylpyridine at room temperature over Adams catalyst proceeded slowly in aqueous acetic acid but provided 4-benzylpiperidine in good yield and without evidence of any concomitant saturation of the benzene ring.[8] XXIV (Table II) was prepared by alkylation of 4-benzylpiperidine with dimethylaminoethyl chloride followed by bis-quaternization of the product with methyl iodide.

Pharmacological Activity.—Of principal interest are the marked hypotensive activity of a number of these compounds and the lack of relationship between hypotensive and ganglionic blocking action. The present series confirms and extends more dramatically previously discussed hypotheses.[2] In order to facilitate comparisons, activities are expressed in potencies relative to unity for hexamethonium bromide.[9] The figures attempt to take into consideration the factors of dosage and intensity and duration of action. It is apparent that whereas ganglionic blocking action varies within a rather narrow range, there is a spread of two orders of magnitude in hypotensive activity.[10]

Inasmuch as the effects of variations in chain length and in the small head were established earlier, these factors are here kept essentially constant. In regard to the large head, the present report more clearly defines the requirement of a bulky, lipophilic, cationic moiety. This may be seen by comparing activities in the series of salts derived from: pyridine (I), N-methylpiperidine (XXIII) and picoline (II) (practically inert); 4-benzylpyridine (III) (comparable to hexamethonium); and 4-diphenylmethylpyridine (V) (more active). Although sufficient size is a minimal requirement for an effective large head, there are

(1) Presented in part before the Division of Medicinal Chemistry at the 131st National Meeting of the American Chemical Society, April 7–12, 1957.

(2) A. P. Gray, W. L. Archer, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **77**, 3536 (1955), and references cited therein; T. B. O'Dell, C. Luna and M. D. Napoli, *J. Pharmacol. Exptl. Therap.*, **114**, 317 (1955).

(3) For more recent support of this thesis, see H. E. Lape, D. J. Fort and J. O. Hoppe, *ibid.*, **116**, 462 (1956).

(4) W. L. Archer, C. J. Cavallito and A. P. Gray, THIS JOURNAL, **78**, 1227 (1956).

(5) (a) Recent publications from other laboratories have described additional groups of unsymmetric bis-quaternary hypotensive agents. It is difficult, however, to glean much information from these pertaining to structure–activity relationships. See L. M. Rice, C. H. Grogan and E. E. Reid, *ibid.*, **77**, 616 (1955); L. M. Rice and C. H. Grogan, Abstracts of Papers, 129th Meeting of the American Chemical Society, Dallas, Texas, April 8–13 (1956), p. 24M; A. J. Plummer, J. H. Trapold, J. A. Schneider, R. A. Maxwell and A. E. Earl, *J. Pharmacol. Exptl. Therap.*, **115**, 172 (1955); D. W. Adamson, J. W. Billinghurst, A. F. Green and S. Locket, *Nature*, **177**, 523 (1956). (b) Just prior to the submission of this manuscript, J. Fakstorp, J. G. A. Pedersen, E. Poulsen and M. Schilling, *Acta Pharmacol. Toxicol.*, **13**, 52 (1957), reported on the ganglionic blocking activity of a series of bis-quaternary salts which can in a way be considered as bridging the gap between symmetric and unsymmetric classes of agents.

(6) A. P. Gray and W. L. Archer, THIS JOURNAL, **79**, 3554 (1957).

(7) See A. P. Phillips, *J. Org. Chem.*, **14**, 302 (1949).

(8) *Cf.* W. L. C. Veer and St. Goldschmidt, *Rec. trav. chim.*, **65**, 793 (1946).

(9) The pharmacology of these compounds will be described in detail by T. B. O'Dell, *et al.*, *J. Pharmacol. Exptl. Therapy*, in press.

(10) Unless otherwise qualified, the term activity in this discussion will refer to hypotensive activity.

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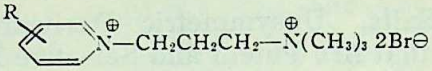
TABLE I

SUBSTITUTED PYRIDINE SALTS

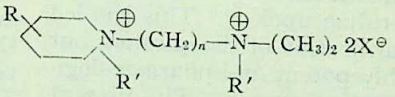


	R	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Bromine, %[b] Calcd.	Bromine, %[b] Found	Relative[c,e] hypotensive activity	Relative[d,e] ganglionic blockade
I	Hydrogen	[f]								<0.1	
II	4-Methyl	244–245	$C_{12}H_{22}Br_2N_2$	40.69	41.08	6.27	6.50	45.12	44.63	<0.1	
III	4-Benzyl	172–174	$C_{18}H_{26}Br_2N_2$	50.25	50.32	6.09	6.38	37.15	36.72	1	
IV	4-Phenylethenyl	150	$C_{19}H_{26}Br_2N_2$	51.59	51.94	5.94	6.05	36.14	35.50	0.5	
V	4-Diphenylmethyl	145–150	$C_{24}H_{32}Br_2N_2O$[g]	54.97	54.59	6.16	5.69	30.48	30.74		
					H_2O	3.44	2.12[g]			3	0.5
VI	2-(1-Naphthylethyl)	170–171	$C_{23}H_{30}Br_2N_2$	55.88	56.15	6.12	6.36	32.33	31.58	100	2
VII	4-(1-Naphthylethenyl)	178	$C_{23}H_{28}Br_2N_2$	56.11	55.77	5.73	6.25	32.47	31.90	5	
VIII	2-(3-Indenylethyl)	188–190[h]	$C_{22}H_{30}Br_2N_2$	54.78	54.44	6.27	6.42	33.14	32.68	40	1
IX	4-(3-Indenylethyl)	195–197	$C_{22}H_{30}Br_2N_2$	54.78	54.52	6.27	6.48	33.14	33.05	15	1
X	2-(3-Indolylethyl)	201–203	$C_{21}H_{29}Br_2N_3$	52.18	52.23	6.05	6.17	33.07	32.82	50	3
XI	4-(3-Indolylethyl)	218–219	$C_{21}H_{29}Br_2N_3$	52.18	52.74	6.05	6.25	33.07	33.05	20	3
XII	4-(1-Indolylethyl)	223–225	$C_{21}H_{29}Br_2N_3$	52.18	51.79	6.05	5.87	33.07	32.63	150	2
XIII	4-(3-Indolylethenyl)	275	$C_{21}H_{27}Br_2N_3$	52.40	53.06	5.66	5.32	33.21	33.02	4	1
XIV	2-(1-Methyl-3-indolylethyl)	139–140	$C_{22}H_{31}Br_2N_3$	53.13	53.26	6.28	5.96	32.14	31.83	25	1
XV	4-(1-Methyl-3-indolylethyl)	133	$C_{22}H_{31}Br_2N_3$	53.13	52.83	6.28	6.47	32.14	31.98	80	1
XVa	4-(1-Methyl-3-indolylethyl)[i]	195	$C_{22}H_{31}Cl_2N_3$					17.36[j]	17.30[j]		
XVI	4-(1-Benzyl-3-indolylethyl)	193–194	$C_{28}H_{35}Br_2N_3$	58.64	58.36	6.15	5.95	27.87	27.34	10	
XVII	2-(1-Methyl-3-indolylethyl)-5-ethyl	173–174	$C_{24}H_{35}Br_2N_3$	54.86	54.21	6.72	6.53	30.42	30.28	120	0.5
XVIII	3-(2-Indolyl)	235–237	$C_{19}H_{25}Br_2N_3$	50.12	50.06	5.54	5.49	35.11	34.96	0.5	
XIX	4-(2-Indolyl)	236–238	$C_{19}H_{25}Br_2N_3$	50.12	50.73	5.54	5.30	35.11	34.51	10	
XX	4-(3,3′-Diindolylmethyl)	220	$C_{29}H_{32}Br_2N_4$	57.54	57.43	5.52	5.63	27.35	26.72	5	
XXI	4-(Phthalimidoethyl)	204	$C_{21}H_{27}Br_2N_3O_2$	49.14	49.46	5.30	5.32	31.14	30.89	2	

[a] Most of the salts melt with decomposition. Melting points are corrected for stem exposure. [b] Either volumetric or gravimetric determination of ionic halogen. [c] Intravenously in anesthetized dogs; relative activities are primarily weighted on the basis of duration at about the same per cent. maximum fall. [d] Superior cervical ganglion in the cat; relative activities are primarily weighted on the basis of duration of about the same degree of block. [e] On this scale hexamethonium = 1. The slopes of the dose-response curves for these compounds vary; for purposes of approximation, however, the compounds are compared at doses equivalent (in potency) to 2 mg./kg. of hexamethonium bromide. [f] See Gray, *et al.*, ref. 2. [g] Monohydrate; Karl Fischer titration for water. [h] Sealed tube. [i] Dichloride salt. [j] See ref. 4.

TABLE II

SUBSTITUTED PIPERIDINE SALTS



	R	R′	n	X	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, %[b] Calcd.	Halogen, %[b] Found	Relative hypotensive activity[c,e]	Rel. ganglionic blockade[d,e]
XXII	Hydrogen	CH_3	3	Br	[i]									
XXIII	4-Benzyl	CH_3	3	Br	237–238	$C_{19}H_{34}Br_2N_2$	50.67	50.58	7.61	7.73	35.49	35.03	<0.1	
XXIV	4-Benzyl	CH_3	2	I	217–219	$C_{18}H_{32}I_2N_2$	40.77	41.05	6.08	5.96	47.87	47.34	5	
XXV	4-Benzyl	H	2	Cl	>270	$C_{16}H_{28}Cl_2N_2$	60.18	60.50	8.84	8.71	22.21	22.11	5	0.5

[a] See footnotes, Table I.

quite evidently other factors (*e.g.*, shape or configuration and, possibly, flexibility) which determine the influence of this size on activity. Differences in activity between corresponding 2- and 4-substituted pyridine isomers are not consistent, and both types may be very active (X, XI, XIV, XV). However, very marked differences exist among a group of derivatives of approximately the same mass (V–IX). The greater potencies of VI, VIII and IX than of the less flexible and non-planar V should be principally related to the arrangement of bulk-contributing structures (*cf.* also XVIII and XIX). The lower activities of VII and IV, possessing planar heads with completely conjugated systems (compare VI and VII; *cf.* also the indole derivatives, XI and XIII), might be ascribable to more rapid biological destruction as well as to more diffuse distribution of the positive charge. A reasonably good example of the influence of polar structures is provided by a comparison of XI and XXI (although stability also may be a factor). These observations emphasize the difficulties in controlling individual variables in the course of structural modification (note that V and XIII can yield neutralized large heads by the loss of a proton).

That there is an upper limit on size of the large head is perhaps best demonstrated by comparison of XV[11] and XVI. Apparently XVI has a larger head than that which appears to be approximately optimum (as exemplified in XV and XII). It is of interest that the indole N-methylated derivatives XIV and XV show reduced ganglionic blocking action in comparison with X and XI, but this effect is unrelated to changes in hypotensive activity. This could be a result of elimination of the bonding capacity of the indole N–H as well as of a reduction in polarity.

Providing that the compounds have minimal

(11) This compound, bearing the laboratory designation IN 391, is the subject of extensive clinical investigations. Intravenously in the anesthetized dog, a dose of 0.025 mg./kg. lowers the blood pressure 50% for more than 1 hr.

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structural features, the relative intensities of the measured responses will be influenced by the distribution of the compounds among responsive receptors and the many non-specific adsorption sites throughout the organism.[12] Several of the present compounds have been observed to be more active in barbiturate anesthetized than in unanesthetized dogs. Since these are relatively lipophilic substances, the potentiation by anesthetics could well be the result of competition at sites of loss.[13]

The broad class of short chain, unsymmetric diquaternary salts include compounds of much greater hypotensive activity than the early C_{5-6} symmetric bis-onium types. If we assume that the compounds of both groups act as specific acetylcholine antagonists, hypotheses of spatial relationships of receptor structures formulated on the basis of the earlier blocking agents will require reconsideration. The active C_{5-6} compounds can assume configurations in which the two onium groups are separated by distances equivalent to those in the C_{2-3} unsymmetric analogs. This would make possible bonding at two adjacent anionic sites or, quite possibly, ion pair formation of the bis-onium moiety with a single anionic function in the low dielectric region of the receptor surface.[14] The non-ionic portion of the diquaternary salt would influence the relative distribution of the compound among adsorption sites and also the stability of the cation–receptor complex.

Experimental[15]

Preparation of Intermediates.—Indolyl- and indenyl-substituted pyridine bases are described in an accompanying paper[6]; the method used for the preparation of 3-bromopropyltrimethylammonium bromide has appeared earlier.[16] 2-(1-Naphthylethyl)-pyridine, hydrochloride salt, m.p. 174.5–175.5°, was obtained by the alkylation of α-picoline with 1-chloromethylnaphthalene using sodamide in liquid ammonia.[17] 4-Diphenylmethylpyridine was supplied by the Reilly Tar and Chemical Corp.

4-Phthalimidoethylpyridine.—This compound was prepared in a manner similar to that described for the 2-isomer.[18] A mixture of 14.7 g. (0.1 mole) of phthalimide, 15.9 g. (0.15 mole) of freshly distilled 4-vinylpyridine and 1 ml. of piperidine was refluxed for 5 hr. at an oil-bath temperature of 190–200°. The cooled, solid reaction mixture was dissolved in 10% hydrochloric acid. The acid solution was filtered, made alkaline and the resultant tan precipitate recrystallized from aqueous isopropyl alcohol to yield 16.5 g. of light tan needles, m.p. 157–158°.[19]

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N (basic), 5.55. Found: C, 71.68; H, 4.79; N (basic), 5.71.

The hydrochloride melted at 220° dec. *Anal.* Calcd. for $C_{15}H_{13}ClN_2O_2$: C, 62.39; H, 4.54; Cl, 12.28. Found: C, 62.81; H, 4.70; Cl, 12.27.

The methobromide, prepared in ethanol and recrystallized from ethanol–ether, showed m.p. 204.5–205.5° dec. *Anal.* Calcd. for $C_{16}H_{15}BrN_2O_2$: C, 55.34; H, 4.35. Found: C, 55.38; H, 4.25.

4-Benzyl-1-methylpiperidine.—4-Benzylpyridine was converted to its methobromide salt, m.p. 84–87°. A solution of 15 g. of the recrystallized salt in 100 ml. of methanol was hydrogenated over 0.5 g. of Adams platinum oxide at 40 p.s.i. and room temperature. The reduction was complete in about 20 minutes. After removal of the solvent *in vacuo*, the residue was distilled to yield 7.2 g. (66%) of 4-benzyl-1-methylpiperidine, b.p. 100–103° (3.5 mm.), $n^{25}D$ 1.5189[20]; picrate, m.p. 185–186°, after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{19}N$: N, 7.40. Found: N (basic), 7.34.

4-Benzylpiperidine.—A solution of 51.0 g. (0.3 mole) of 4-benzylpyridine in a mixture of 100 ml. of purified glacial acetic acid and 50 ml. of water was hydrogenated over 1.0 g. of Adams catalyst at room temperature and 50 p.s.i. Hydrogen absorption was complete in 72 hr. The filtered solution was concentrated *in vacuo*, the residue was treated with excess 20% sodium hydroxide and extracted with ether. After washing with water and drying, the organic layer was distilled to yield 44.5 g. (85%) of 4-benzylpiperidine, b.p. 90–92° (0.6 mm.), $n^{25}D$ 1.5357; picrate, m.p. 192–193° dec.[21]

Anal. Calcd. for $C_{12}H_{17}N$: N, 7.99. Found: N (basic), 7.96.

1-Dimethylaminoethyl-4-benzylpiperidine.—A stirred mixture of 28.0 g. (0.16 mole) of 4-benzylpiperidine, 34.6 g. (0.24 mole) of dimethylaminoethyl chloride hydrochloride and 50 g. of anhydrous, powdered sodium carbonate in 200 ml. of 1-butanol was refluxed (oil-bath) for 24 hr. The cooled, filtered solution was concentrated *in vacuo* and the residue was extracted with ether. Drying and removal of the ether and distillation of the residual oil afforded 12.3 g. (31% yield) of the product, b.p. 135–140° (0.5 mm.), $n^{24}D$ 1.5167.

Anal. Calcd. for $C_{16}H_{26}N_2$: N, 11.37. Found: N (basic), 11.22.

The dihydrochloride XXV, recrystallized from wet methanol, melted above 270°.

The dimethiodide XXIV, prepared in ethanol and recrystallized from methanol–ethyl acetate, showed m.p. 225–226° dec.

Preparation of Bis-salts by Quaternization with 3-Halopropyltrimethylammonium Halides. A. Trimethylene-1-(4-picolinium)-3-(trimethylammonium) Dibromide (II).—An ethanol solution of 9.3 g. (0.1 mole) of γ-picoline and 26.1 g. (0.1 mole) of 3-bromopropyltrimethylammonium bromide was refluxed on the steam-bath for 15 hr. The crystalline precipitate that formed upon refrigeration of the solution was recrystallized from ethanol to yield 21.8 g. (62%) of colorless crystals of II, m.p. 244–245° with gas evolution.

B. Trimethylene-1-[2-(3-indolylethyl)-pyridinium]-3-(trimethylammonium) Dibromide (X).—To 130.5 g. (0.5 mole) of 3-bromopropyltrimethylammonium bromide dissolved in 600 ml. of acetonitrile was added 111 g. (0.5 mole) of 2-(3-indolylethyl)-pyridine, and the solution was refluxed for 30 hr. The precipitate was recrystallized from ethanol to yield 120 g. (63%) of pale yellow crystals of X, m.p. 201–203°.

C. Trimethylene-1-[4-(1-methyl-3-indolylethyl)-pyridinium]-3-(trimethylammonium) Dibromide (XV).—A solution of 1420 g. (6 moles) of 4-(1-methyl-3-indolylethyl)-pyridine and 1570 g. (6 moles) of 3-bromopropyltrimethylammonium bromide in 4.5 liters of acetonitrile was refluxed, with stirring, for 18 hr. Recrystallization of the resultant precipitate from isopropyl alcohol afforded a yield of 2390

(12) In a recent review, Veldstra, *Pharmacol. Rev.*, **8**, 339 (1956), refers to these as "sites of loss."

(13) A similar relationship recently has been demonstrated with another type of acetylcholine blocking agent (C. J. Cavallito, J. G. Arrowood and T. B. O'Dell, *Anesthesiology*, **17**, 547 (1956)).

(14) See O. V. Brody and R. M. Fuoss, *J. Phys. Chem.*, **60**, 156 (1956), and earlier papers of Fuoss, *et al.*, for physical chemical evidence of this type of association; S. A. Rice, THIS JOURNAL, **78**, 5247 (1956); *cf.* F. Bergmann and R. Segal, *Biochem. J.*, **58**, 692 (1954).

(15) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill.

(16) A. P. Gray, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **77**, 3648 (1955).

(17) F. W. Bergstrom, T. R. Norton and R. A. Seibert, *J. Org. Chem.*, **10**, 452 (1945).

(18) F. K. Kirchner, J. R. McCormick, C. J. Cavallito and L. C. Miller, *ibid.*, **14**, 388 (1949).

(19) E. Profft, *J. prakt. Chem.*, [4] **4**, 19 (1956), recently reported this compound (impure), m.p. 143–146°

(20) F. J. Villani, M. S. King and D. Papa, *J. Org. Chem.*, **17**, 249 (1952), report b.p. 129–130° (8 mm.), $n^{26}D$ 1.5295, for this compound prepared by sodium and ethanol reduction of benzylpyridine followed by Eschweiler–Clarke methylation. The high refractive index they report would appear to be a further indication of the difficulty of effecting complete reduction of the pyridine ring with sodium and alcohol.

(21) W. L. C. Veer and St. Goldschmidt[3] report b.p. 150–152° (17 mm.), picrate m.p. 187–188°, for this compound prepared by

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g. (79%) of XV as hygroscopic, light tan crystals, m.p. 133° dec.

D. Dichloride Salt of XV (XVa).—A solution of 600 g. of XV in 12 liters of distilled water was passed through a column of Amberlite anion exchange resin, IRA 401 (regenerated with aqueous sodium chloride), and the column was washed with fresh water. The eluate was concentrated *in vacuo* and the residue was crystallized from ethanol–acetone to yield 425 g. (86%) of the dichloride salt, XVa, m.p. 195° dec.

Two alternative routes to XVa have been found quite satisfactory: 1. A solution of 4-(1-methyl-3-indolylethyl)-pyridine and 3-chloropropyltrimethylammonium bromide[22] in dimethylformamide was heated at 120–125° (oil-bath temperature) for 24 hr. and the crude mixed halide product passed through a column of Amberlite IRA 401. 2. A dimethylformamide solution of the pyridine base and 3-chloropropyltrimethylammonium chloride[23] was heated at 120° (oil-bath) for 24 hours, thus directly affording a 55% yield of XVa.

Condensation of II with Aldehydes. A. Benzaldehyde. The Preparation of IV.—To a solution of 6.3 g. (0.018 mole) of II and 3.8 g. (0.036 mole) of freshly distilled benzaldehyde in 50 ml. of methanol was added 1 ml. of piperidine. After 4 hr. reflux on the steam-bath, the deep purple solution was cooled, diluted with ether and the purple precipitate was recrystallized from ethanol to provide 4.3 g. (54% yield) of IV, melting with decomposition and gas evolution at 150°.

B. 1-Naphthaldehyde. The Preparation of VII.—Refluxing a solution of 4.4 g. (0.028 mole) of 1-naphthaldehyde and 10 g. (0.028 mole) of II in 50 ml. of ethanol containing 1 ml. of piperidine for 3 hr., diluting with ether and crystallizing the resultant purple, oily precipitate from ethanol–ether yielded 9.6 g. (69%) of VII, m.p. 178° dec.

C. 3-Indolecarboxaldehyde. The Preparation of XIII.—In similar fashion, 3-indolecarboxaldehyde[24] was condensed with II to yield, after recrystallization from methanol–ethyl acetate, 56% of bright orange crystals of XIII, melting with decomposition and gas evolution at 275°.

Acknowledgments.—The authors wish to thank Mrs. Dorothy Schlieper for assistance with some of the synthetic work and Mr. Dean F. Cortright for the ionic halogen and basic nitrogen determinations.

(22) This salt was prepared from trimethylene chlorobromide and trimethylamine, m.p. 204–206°.

(23) Prepared from 3-chloropropyltrimethylammonium bromide by passage over the anion exchange resin, m.p. 202° dec.

(24) Prepared as described by F. T. Tyson and J. T. Shaw, THIS JOURNAL, **74**, 2273 (1952), from indole and dimethylformamide with phosphorus oxychloride.

DECATUR, ILLINOIS

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Quinone Imides. XLIV. The Orientation of Groups in Addition Reactions to Substituted p-Quinonedibenzimides

BY ROGER ADAMS AND HARRY J. NEUMILLER, JR.[1]

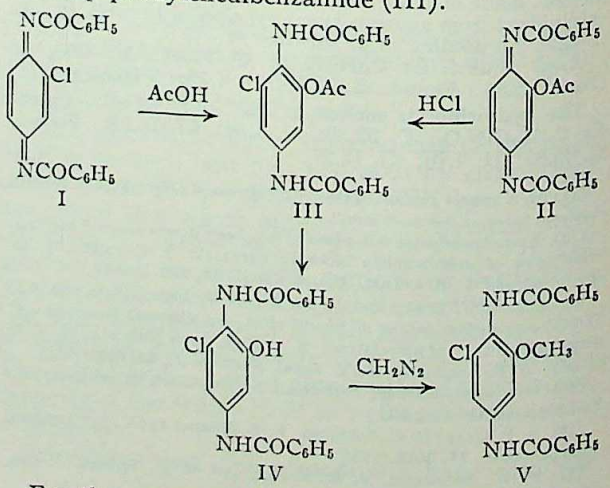
RECEIVED FEBRUARY 1, 1957

The acetoxychloro-*p*-phenylenedibenzamide isomer, which results both from the addition of acetic acid to 2-chloro-*p*-quinonedibenzimide and from the addition of hydrogen chloride to 2-acetoxy-*p*-quinonedibenzimide, has been identified as 2-acetoxy-6-chloro-*p*-phenylenedibenzamide. The oxidation of 2-methoxy-*p*-phenylenedibenzamide with lead tetraacetate affords 2-methoxy-*p*-quinonedibenzimide which adds hydrogen chloride to give a mixture of 2-chloro-5-methoxy- and 2-chloro-6-methoxy-*p*-phenylenedibenzamides, both identified by unequivocal syntheses.

In a recent paper[2] the orientation of groups in the adducts of 2-substituted *p*-quinonedibenzenesulfonimides and 2-substituted *p*-quinonedibenzimides was summarized. 2-Chloro-*p*-quinonedibenzenesulfonimide adds hydrogen chloride to afford a mixture of 2,3- and 2,5-dichloro-*p*-phenylenedibenzenesulfonamides. The addition of hydrogen chloride and a number of other reagents to 2-methoxy-*p*-quinonedibenzenesulfonimide results in substituted *p*-phenylenedibenzenesulfonamides having exclusively the 2,5-orientation.

In contrast to the foregoing, the addition of hydrogen chloride to 2-chloro-*p*-quinonedibenzimide (I) affords 2,6-dichloro-*p*-phenylenedibenzamide; the addition to 2-methyl-*p*-quinonedibenzimide yields exclusively 6-chloro-2-methyl-*p*-phenylenedibenzamide. The 2-phenylmercapto analog gives 3-chloro-2-phenylmercapto-*p*-phenylenedibenzamide and the 2-benzenesulfonyl derivative gives a mixture of 2-benzenesulfonyl-3-chloro- and 2-benzenesulfonyl-6-chloro-*p*-phenylenedibenzamides.

Previous investigators demonstrated that both the addition of acetic acid to 2-chloro-*p*-quinonedibenzimide (I) and the addition of hydrogen chloride to 2-acetoxy-*p*-quinonedibenzimide (II) yielded the same acetoxy-chloro-*p*-phenylenedibenzamide isomer as the sole product of each reaction.[3] The product has now been identified as 2-acetoxy-6-chloro-*p*-phenylenedibenzamide (III).



For the purpose of its identification, III was hydrolyzed with dilute aqueous sodium hydroxide to

(1) An abstract of a thesis submitted by Harry J. Neumiller, Jr., to the Graduate College of the University of Illinois, 1956, in partial fulfillment of the requirements for the Degree of Doctor of Philosophy; Minnesota Mining and Manufacturing Fellow, 1952–1954; University of Illinois Fellow, 1953 and 1954–1955.

(2) R. Adams and M. D. Nair, THIS JOURNAL, **78**, 5927, 5932 (1956).

(3) R. Adams and D. F. Miller, *ibid.*, **74**, 3657 (1952).

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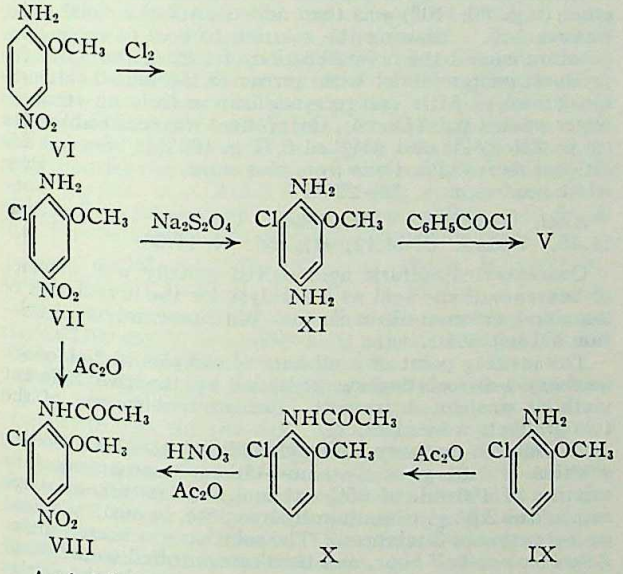
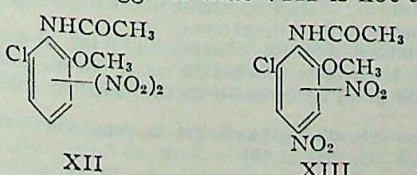
2-chloro-6-hydroxy-*p*-phenylenedibenzamide (IV), and this was methylated with diazomethane to give 2-chloro-6-methoxy-*p*-phenylenedibenzamide (V). The unequivocal synthesis of V was then accomplished through the following steps. 2-Amino-5-nitroanisole (VI) was chlorinated to 2-amino-3-chloro-5-nitroanisole (VII). The position of the chlorine atom in this compound was established by its acetylation to afford 2-chloro-6-methoxy-4-nitroacetanilide (VIII); the same compound resulted from a sequence involving acetylation of 2-amino-3-chloroanisole (IX) to 2-chloro-6-methoxyacetanilide (X) followed by nitration to VIII. Compound VIII is the only possible common product of these two reaction sequences. By reduction with sodium hydrosulfite, VII was converted to 2-chloro-6-methoxy-*p*-phenylenediamine (XI), which was then benzoylated to the desired 2-chloro-6-methoxy-*p*-phenylenedibenzamide (V). Through comparison of infrared spectra and melting points, the compound prepared in this manner was shown to be identical with the sample of V obtained from 2-chloro-*p*-quinonedibenzimide (I).

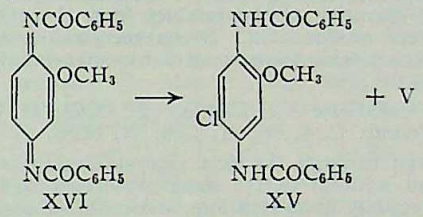


An initial attempt was made to prepare V through 2′-chloro-6′-methoxy-4′-nitrobenzanilide, the benzoyl derivative of VII. Benzoylation of VII was difficult and was achieved only by a long period of refluxing with benzoyl chloride in pyridine and subsequent separation of the benzoyl derivative from unreacted amine by chromatography.

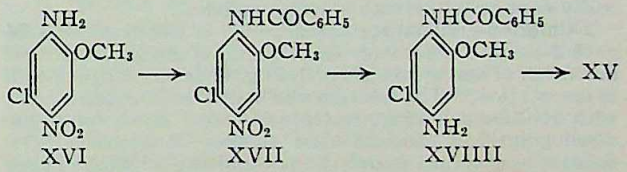
While studying the conditions under which X could best be mononitrated to VIII, it was found that 2-chloro-6-methoxyacetanilide (X) was dinitrated (XII) by means of a mixture of cold concentrated sulfuric and nitric acids. When 2-chloro-6-methoxy-4-nitroacetanilide (VIII), prepared from 2-amino-3-chloro-5-nitroanisole, was nitrated in a similar fashion a different dinitro compound XIII resulted. This suggests that VIII is not an intermediate in the formation of the dinitro derivative of X.



2-Methoxy-*p*-quinonedibenzimide (XIV) could not be isolated in a crystalline state, but treatment of the solution in which it was prepared with hydrogen chloride resulted in a mixture of chloromethoxy-*p*-phenylenedibenzamide isomers. The mixture was cleanly separated by chromatography on a column of aluminum oxide into 2-chloro-5-methoxy-*p*-phenylenedibenzamide (XV) and 2-chloro-6-methoxy-*p*-phenylenedibenzamide (V). The unequivocal synthesis of the latter of these two



isomers already has been described. The former was synthesized through the following sequence: 2-Amino-4-chloro-5-nitroanisole (XVI) was benzoylated to 5′-chloro-2′-methoxy-4′-nitrobenzanilide (XVII), reduced to 4′-amino-5′-chloro-2′-methoxybenzanilide (XVIII) and benzoylated to XV.



Acknowledgment.—The authors are indebted to Mr. Joseph Nemeth, Mrs. Lucy Chang, Mrs. Esther Fett and to Mr. R. Maria Benassi for the microanalyses, and to Mr. James Brader, Mrs. Louise Griffing and Miss Helen Miklas for the determination and interpretation of the infrared spectra.

Experimental

All melting points are corrected. The infrared spectra were run in Nujol mulls, using a Perkin–Elmer model 21 double beam spectrophotometer.

2-Acetoxy-6-chloro-*p*-phenylenedibenzamide.—A solution of 0.52 g. of 2-chloro-*p*-benzoquinonedibenzimide[4] in 10 ml. of glacial acetic acid was prepared by gentle warming. The red solution was allowed to stand at room temperature for 14 hours. The addition of 20 ml. of petroleum ether (b.p. 80–110°) did not cause the precipitation of the product, as previously reported,[3] and most of the petroleum ether was retained as an upper layer. As much as possible of the petroleum ether was therefore removed *in vacuo*, and 25 ml. of water was added, causing the precipitation of the very crude product. After one recrystallization from benzene (Darco) it weighed 0.24 g. (39%). Two more recrystallizations from benzene (Darco) afforded small white lustrous crystals, m.p. 179.5–181° dec. (lit.[3] m.p. 181–182°).

2-Chloro-6-hydroxy-*p*-phenylenedibenzamide.—A suspension of 0.08 g. of 2-acetoxy-6-chloro-*p*-phenylenedibenzamide in 25 ml. of 5% aqueous sodium hydroxide was allowed to stand at room temperature for 7.5 hours. The solid went slowly into solution during the course of this period. The mixture was filtered, and the filtrate was made acidic to congo red with concentrated hydrochloric acid, causing the precipitation of the very crude product. After one recrystallization from an ethyl acetate–petroleum ether (b.p. 80–110°) solvent pair, it weighed 0.03 g. (43%). Further recrystallization from the same solvent pair (Darco) gave white needles, m.p. 240–243° (lit.[3] m.p. 246–246.5°).

(4) R. Adams and J. L. Anderson, THIS JOURNAL, **72**, 5154 (1950).

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2-Amino-3-chloro-5-nitroanisole.—Into a stirred suspension of 8.40 g. of 2-amino-5-nitroanisole in 200 ml. of concentrated hydrochloric acid and 100 ml. of glacial acetic acid, maintained at a temperature of 5–15°, was passed a stream of chlorine gas (dried by passage through concentrated sulfuric acid) at a moderate rate until the increase in the weight of the mixture was 5.8 g. (45 minutes). The mixture was filtered through a sintered-glass funnel and the precipitate was stirred with 200 ml. of 10% aqueous sodium bisulfite for *ca.* 20 minutes. The product was then collected by suction filtration, washed with water, and recrystallized once from 95% ethanol, after which it weighed 3.76 g. Concentration of the ethanolic mother liquors afforded an additional 1.42 g. of the product, and thus the total crude yield was 5.18 g. (51%). Attempts to obtain an additional quantity of the product from the chlorination liquors were unsuccessful. Seven recrystallizations from carbon tetrachloride gave small flat orange-yellow prisms, m.p. 122–124°.

Anal. Calcd. for $C_7H_7ClN_2O_3$: C, 41.49; H, 3.48; N, 13.83. Found: C, 41.66; H, 3.28; N, 13.86.

The steps through the first recrystallization should be carried out without delay, since unrecrystallized product darkened rapidly upon standing, and could subsequently be purified only with great loss. In runs in which concentrated hydrochloric acid was used as the solvent for chlorination a very impure grade of product was obtained. The use of dimethylformamide resulted in the formation of an uncrystallizable tarry product. When glacial acetic acid, or a hydrochloric acid–glacial acetic mixture containing a relatively large proportion of the latter substance, was used as the solvent the chlorination was incomplete, and the product was badly contaminated with starting material.

2-Chloro-6-methoxyacetanilide.—To a solution of 1.58 g. of 2-amino-3-chloroanisole[5] in 10 ml. of glacial acetic acid and 3 ml. of water was added 1.23 g. of acetic anhydride all in one portion. The solution was boiled for 10 minutes and, with continued boiling, water was added slowly until the cloud point was attained after another 40 minutes. The solution was cooled under the tap and the oil which began to form was scratched with a glass rod to initiate crystallization. After the resulting mixture had cooled to room temperature, filtration gave 1.64 g. of crystalline product, m.p. 145–146.5° with sintering at 144°. By concentration of the filtrate and further addition of water an additional 0.06 g. of the product was obtained and thus the total yield was 1.70 g. (85%). Three recrystallizations from water followed by two recrystallizations from a benzene–petroleum ether solvent pair afforded small lustrous white prisms, m.p. 145.5–147°, with sintering at 144.5°.

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.19; H, 5.09; N, 6.70.

This compound was reported by Meldola and Eyre[6] as melting at 147–148°, with softening between 115 and 125°, and by Hodgson and Kershaw[5] as melting at 123°. Furthermore, the latter investigators reported that 2-chloro-N,N-diacetyl-6-methoxyaniline melted at 145.5°. The infrared spectrum of the compound prepared by the method described above showed N–H stretching absorption at 3195 cm.$^{-1}$, and a single amide C=O band at 1664 cm.$^{-1}$. These data, together with the composition of the compound, leave no doubt that it is the desired monoacetyl derivative of 2-chloro-6-methoxyaniline. In one attempt to monoacetylate 2-chloro-6-methoxyaniline, the amine was heated with acetic anhydride on the steam-bath for 1.5 hours, in accordance with the procedure described by Hodgson and Kershaw[5] for the preparation of the monoacetyl derivative. After the subsequent addition of water to decompose the acetic anhydride, the precipitate, m.p. *ca.* 100–123°, was repeatedly recrystallized from petroleum ether (b.p. 80–110°), water, and petroleum ether again, giving small white plates, m.p. 123–125°, in very low yield. This material was apparently the diacetyl derivative of the amine, since a mixture of it and the previously described monoacetyl derivative melted at 107–111°. Thus, the melting points as reported by Hodgson and Kershaw[5] for the monoacetyl derivative and the diacetyl derivative should be reversed. The compound reported by Meldola and Eyre[6] was undoubtedly the monoacetyl derivative.

(5) H. H. Hodgson and A. Kershaw, *J. Chem. Soc.*, 191 (1928).
(6) R. Meldola and J. V. Eyre, *ibid.*, **81**, 988 (1902).

2-Chloro-6-methoxy-4-nitroacetanilide. Method A.—A suspension of 0.33 g. of 2-chloro-6-methoxyacetanilide in 3.0 ml. of acetic anhydride was cooled to −10° by the direct addition of Dry Ice. While maintaining the temperature below 0°, a cooled solution of 0.12 g. of fuming nitric acid (sp. gr. 1.5) in 1.0 ml. of acetic anhydride was added, with constant agitation, over a period of 5 minutes. Agitation was continued for a period of 20 minutes during which the temperature was permitted to rise rapidly to 10° and was then held at 10–15°. All of the suspended solid went into solution during the period in which the temperature was rising. The solution was poured into 10 ml. of water and the resulting mixture was shaken until all of the acetic anhydride had decomposed. After allowing the mixture to stand overnight, 0.09 g. (22%) of the crystalline product was obtained by filtration. Dilution of the filtrate with water and subsequent concentration did not afford more product. The product was recrystallized three times from an ethanol–water solvent pair (Darco), giving white needles, m.p. 223.5–225°.

Anal. Calcd. for $C_9H_9ClN_2O_4$: C, 44.19; H, 3.71; N, 11.45. Found: C, 44.17; H, 3.45; N, 11.47.

Method B.—To a boiling solution of 1.01 g. of 2-amino-3-chloro-5-nitroanisole in 75 ml. of dry benzene was added a solution of 0.61 g. of acetic anhydride in 5 ml. of dry benzene, followed by several mg. of benzenesulfonic acid. The solution was allowed to continue to boil and evaporate until the volume had been reduced to *ca.* 20 ml. Petroleum ether (b.p. 80–110°) was then added until the cloud point was reached. Allowing the solution to cool to room temperature caused the crystallization of 1.02 g. (84%) of the product, contaminated with unreacted 2-amino-3-chloro-5-nitroanisole. After one recrystallization from an ethanol–water solvent pair (Darco), the product was reasonably pure (m.p. 221–224°) and weighed 0.77 g. (63%). Several additional recrystallizations from this same solvent pair gave white needles, m.p. 224–226°.

Anal. Calcd. for $C_9H_9ClN_2O_4$: C, 44.19; H, 3.71; N, 11.45. Found: C, 44.12; H, 3.54; N, 11.66.

Concentrated sulfuric acid served equally well in place of benzenesulfonic acid as a catalyst for the acetylation of 2-amino-3-chloro-5-nitroanisole. With no catalyst acetylation did not occur.

The melting point of a mixture of samples of 2-chloro-6-methoxy-4-nitroacetanilide prepared by the two different methods was not depressed. The infrared spectra of the two products were identical.

2-Chloro-6-methoxy-*p*-phenylenediamine.—To a boiling solution of 1.01 g. of 2-amino-3-chloro-5-nitroanisole in a mixture of 100 ml. of 95% ethanol and 100 ml. of water was added 2.65 g. of sodium hydrosulfite, in small portions over a period of 3 minutes. The solution was heated under reflux for one-half hour, and then concentrated to the cloud point on the hot-plate. Subsequent storage in the refrigerator at 0–5° for 3 hours caused the crystallization of 0.53 g. (62%) of the diamine. One recrystallization from a benzene–petroleum ether (b.p. 80–110°) solvent pair gave medium brown needles, m.p. 97–99.5° dec. The product deteriorated upon standing, and it was used in the following experiment without further characterization.

2-Chloro-6-methoxy-*p*-phenylenedibenzamide. Method A.—A solution of 0.28 g. of 2-chloro-6-methoxy-*p*-phenylenediamine and 0.56 g. of benzoyl chloride in 20 ml. of pyridine was heated under reflux for 2 hours. After cooling to room temperature it was poured into 200 ml. of 10% hydrochloric acid containing 75 g. of ice, causing the precipitation of 0.45 g. (74%) of light gray solid. Four recrystallizations from benzene (Darco) gave the pure compound; white needles, m.p. 224–225.5°.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36. Found: C, 66.15; H, 4.43; N, 7.36.

Method B.—The method used for the preparation of the ethereal solution of diazomethane in the following experiment was the one described in reference 7.

To a mixture of 30 ml. of ether and 9 ml. of 40% aqueous potassium hydroxide, cooled to *ca.* 5° in an ice-bath, was added 3.00 g. of α-nitroso-α-methylurea[8] in small portions

(7) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc. New York, N. Y., 1943, p. 165.
(8) Reference 7, p. 442.

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over a period of 3 minutes. The ether layer was decanted from the mixture and slowly added, with constant swirling, to a suspension of 0.15 g. of 2-chloro-6-hydroxy-*p*-phenylenedibenzamide in 15 ml. of methanol, cooled to *ca.* 5° in an ice-bath. Slight effervesence occurred, and the diamide went into solution. The solution was allowed to stand in the ice-bath for one-half hour, and 25 ml. of glacial acetic acid was then added to destroy excess diazomethane. The solvents were removed by means of a current of dry air, and the resulting residue was dissolved in 50 ml. of hot acetone. The hot solution was treated with Darco and filtered, and 0.07 g. (45%) of crystalline product was precipitated from the filtrate by the addition of water. Four recrystallizations from benzene gave white needles, m.p. 224–225.5°.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36. Found: C, 66.35; H, 4.78; N, 7.46.

The melting point of a mixture of samples of 2-chloro-6-methoxy-*p*-phenylenedibenzamide prepared by the two different methods was not depressed. The infrared spectra of the two products were identical.

2-Chloro-x,y-dinitro-6-methoxyacetanilide.—A solution of 0.28 g. of 2-chloro-6-methoxyacetanilide in 1.00 ml. of concentrated sulfuric acid was prepared by the slow addition of the solid to the acid. The solution was agitated and maintained at a temperature of 12–18°, and a solution of 0.18 g. of concentrated nitric acid (sp. gr. 1.42) in 0.25 ml. of concentrated sulfuric acid was added over a period of 5 minutes. The mixture was agitated at 12–15° for an additional 30 minutes, and was then allowed to stand at room temperature for 40 minutes. The mixture was poured onto 10 g. of ice, causing the precipitation of a yellow solid which was washed with water, 60 ml. of 5% aqueous sodium carbonate, and then with water again. It weighed 0.24 g. and melted at *ca.* 150–190° dec. Repeated fractional crystallization of this material from 95% ethanol gave 0.07 g. (24%, based on the amount of nitric acid employed) of white needles, m.p. 215.5–216.5° with simultaneous bubbling. For analysis, the compound was sublimed at 1.5–1.8 mm. pressure, which did not alter the melting point.

Anal. Calcd. for $C_9H_8ClN_3O_6$: C, 37.33; H, 2.78; N, 14.51. Found: C, 37.51; H, 3.07; N, 14.31.

The infrared spectrum showed N–H stretching absorption at 3190 cm.$^{-1}$, an amide C=O band at 1683 cm.$^{-1}$, and $-NO_2$ bands at 1537 cm.$^{-1}$ and 1350 cm.$^{-1}$.

2-Chloro-4,z-dinitro-6-methoxyacetanilide.—A solution of 0.49 g. of 2-chloro-6-methoxy-4-nitroacetanilide in 1.50 ml. of concentrated sulfuric acid was prepared by adding the solid to the acid over a period of 4 minutes. The solution was agitated and maintained at a temperature of 10–13°, and a solution of 0.23 g. of concentrated nitric acid (sp. gr. 1.42) in 0.30 ml. of concentrated sulfuric acid was added over a period of 4 minutes. The mixture was agitated at 10–16° for an additional 25 minutes, and was then allowed to stand at room temperature for 55 minutes. The mixture was poured onto 10 g. of ice, causing the precipitation of the product. Sufficient water was added to bring the volume to 25 ml., and the precipitate was collected by filtration and washed with water. After one recrystallization from an ethanol–water solvent pair it weighed 0.27 g. (47%). Five more recrystallizations from this same solvent pair (Darco) afforded white needles. The substance behaved in a peculiar fashion in the melting point determination: A sample inserted into the melting-point bath at room temperature melted at 221–223°, with slight decomposition, after previously softening at 213.5°, while a sample inserted at 217° immediately melted completely, with frothing and moderate decomposition. It is possible that the compound was contaminated to some extent with an isomer.

Anal. Calcd. for $C_9H_8ClN_3O_6$: C, 37.33; H, 2.78; N, 14.51. Found: C, 37.43; H, 2.83; N, 14.29.

The infrared spectrum had an amide C=O band at 1674 cm.$^{-1}$. The N–H stretching region contained two bands of only medium intensity, one at 3140 cm.$^{-1}$ and the other at 3060 cm.$^{-1}$.

A mixture of the 2-chloro-4,z-dinitro-6-methoxyacetanilide and the 2-chloro-x,y-dinitro-6-methoxyacetanilide described in the immediately preceding experiments melted at 180–195°.

2′-Chloro-6′-methoxy-4′-nitrobenzanilide.—A solution of 1.01 g. of 2-amino-3-chloro-5-nitroanisole and 0.84 g. of benzoyl chloride in 20 ml. of pyridine was heated under reflux for 21 hours. The bright red solution was allowed to cool to room temperature and then poured into 200 ml. of 10% hydrochloric acid containing 75 g. of ice, causing the precipitation of an orange-brown gum. After having been washed with water, the gum was dissolved in 150 ml. of carbon tetrachloride, and the solution was passed through a 1.7 × 32.8 cm. column of aluminum oxide (Merck, Reagent Grade). The column was eluted with *ca.* 275 ml. of chloroform. The eluate was collected in 25-ml. fractions, and each fraction was evaporated to dryness. Fractions 1–6 contained nothing, fraction 7 contained 0.05 g. of impure 2-amino-3-chloro-5-nitroanisole, fraction 8 contained 0.16 g. of the same substance, fairly pure, fraction 9 contained 0.07 g. of a mixture of 2-amino-3-chloro-5-nitroanisole and the product, and fractions 10–16 contained 0.68 g. of the product desired. Further elution afforded only colored amorphous material. The yield of the product, based on fractions 10–16, and corrected for reusable starting material recovered (fraction 8), was 53%. Several recrystallizations from carbon tetrachloride gave small white needles, m.p. 176.5–178°.

Anal. Calcd. for $C_{14}H_{11}ClN_2O_4$: C, 54.82; H, 3.62; N, 9.14. Found: C, 54.95; H, 3.47; N, 9.42.

A complete separation of the product from the unreacted starting material was obtained by using a mixture of equal parts by volume of carbon tetrachloride and chloroform as an initial elutant in the chromatogram. The process was considerably slower than the one described above, and the given procedure is more convenient from a preparative standpoint.

Reaction of 2-Methoxy-*p*-quinonedibenzimide with Hydrogen Chloride: 2-Chloro-5-methoxy-*p*-phenylenedibenzamide (Method A) and 2-Chloro-6-methoxy-*p*-phenylenedibenzamide (Method C).—A suspension of 0.87 g. of 2-methoxy-*p*-phenylenedibenzamide[9] and 1.14 g. of lead tetraacetate in 50 ml. of dry, thiophene-free benzene was stirred and heated under gentle reflux for 50 minutes. The mixture was allowed to cool to room temperature and filtered to remove the insoluble material, and 100 ml. of petroleum ether (b.p. 80–110°) was added to the orange-yellow filtrate.[10] Hydrogen chloride gas was passed into the solution at a moderate rate for 10 minutes, causing rapid bleaching of the color to light greenish-yellow and the concomitant formation of a precipitate. The solvents were removed *in vacuo* and the resulting residue was dissolved in a mixture of 300 ml. of carbon tetrachloride and 150 ml. of chloroform. This solution was passed through a 1.7 × 35.5 cm. column of aluminum oxide (Merck, Reagent Grade). The eluate was collected in 50-ml. fractions. The first 8.5 fractions resulted from the addition of the original solution; during the collection of the succeeding 16.5 fractions, 2:1 by volume carbon tetrachloride and chloroform was used as the elutant; and during the collection of the remaining fractions, chloroform was used as the elutant. The rate of elution ranged from 4.5 ml. per minute to 6.3 ml. per minute. The fractions were evaporated to dryness, and the following results were observed: Fractions 1–9 contained nothing, fractions 10–13 contained 2-chloro-5-methoxy-*p*-phenylenedibenzamide, fractions 14–19 contained unidentified traces of residues which melted over large ranges, fraction 20 contained nothing, fraction 21 contained a trace of residue which melted over a large range, fractions 22–27 contained 2-chloro-6-methoxy-*p*-phenylenedibenzamide, and fractions 28 and 29 contained only faint traces of residue.

The residues from fractions 10–13 were combined and recrystallized once from benzene (Darco), giving 0.22 g. (23%) of small lustrous white prisms, m.p. 225.5–226.5°. Two more recrystallizations from benzene did not alter the melting point.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36. Found: C, 66.46; H, 4.51; N, 7.11.

The melting point of a mixture of this product and the authentic 2-chloro-5-methoxy-*p*-phenylenedibenzamide, to be described, was not depressed. The infrared spectra of the two samples were identical.

(9) R. Adams and D. S. Acker, THIS JOURNAL, **74**, 5872 (1952).

(10) If the mixture was now cooled in a Dry Ice–methanol-bath, a yellow crystalline solid separated which became a brownish-orange viscous oil upon warming to room temperature after removing the solvent. The diimide turned darker on standing and was not obtained in a pure crystalline form.

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The residues from fractions 22–27 were combined and recrystallized once from benzene (Darco), affording 0.22 g. (23%) of crystalline product, m.p. 225–226°, with slight sintering at 223°. Two more recrystallizations from benzene gave white needles of 2-chloro-6-methoxy-*p*-phenylenedibenzamide, m.p. 225–226.5°.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36. Found: C, 66.24; H, 4.51; N, 7.23.

The melting point of a mixture of this product and the previously described authentic 2-chloro-6-methoxy-*p*-phenylenedibenzamide was not depressed. The infrared spectra of the two samples were identical.

The total yield of chloro-methoxy-*p*-phenylenedibenzamide isomers from the addition of hydrogen chloride to 2-methoxy-*p*-quinonedibenzimide was thus 0.44 g. (46%), based on the quantity of 2-methoxy-*p*-phenylenedibenzamide employed.

Although the two isomers melted at essentially the same point, the melting point of a mixture was depressed. The infrared spectra of the compound were different. The 2,5-isomer was more soluble in benzene than the 2,6-isomer.

5′-Chloro-2′-methoxy-4′-nitrobenzanilide.—To a solution of 0.72 g. of 2-amino-4-chloro-5-nitroanisole[11] in 10 ml. of pyridine was added 1.00 g. of benzoyl chloride. The reaction mixture was allowed to stand for 12 minutes and then boiled for 2 minutes, cooled to room temperature, and poured into 100 ml. of 10% hydrochloric acid containing 50 g. of ice. An oil precipitated which rapidly solidified. The solid was collected by filtration, washed with water, and recrystallized once from carbon tetrachloride, after which it weighed 0.79 g. (73%). A subsequent recrystallization from an acetic acid–water solvent pair (Darco) gave pinkish-yellow needles, m.p. 138–143° (lit.[12] m.p. 142°). Further recrystallization improved the melting point only very slowly.

4′-Amino-5′-chloro-2′-methoxybenzanilide.—To a boiling solution of 0.58 g. of 5′-chloro-2′-methoxy-4′-nitrobenzanilide in 35 ml. of ethanol, water was added until the cloud point was attained. To the still boiling solution was slowly added 1.01 g. of sodium hydrosulfite, followed by water until the cloud point was again attained. The solution was cooled, caused the crystallization of 0.28 g. of the product, m.p. 151.5–153°, which was collected by filtration. By dilution of the filtrate with water, followed by heating and recooling, an additional 0.02 g. of crystals was obtained, thus bringing the total yield to 0.30 g. (58%). The product was recrystallized once from an ethanol–water solvent pair, giving lustrous creamish needles, m.p. 152–154° (lit.[12] m.p. 152.5°).

2-Chloro-5-methoxy-*p*-phenylenedibenzamide. Method B.—To a solution of 0.11 g. of 4′-amino-5′-chloro-2′-methoxybenzanilide in 1.0 ml. of pyridine, cooled in an ice-bath, was added a solution of 0.07 g. of benzoyl chloride in 1.0 ml. of pyridine. The solution was allowed to stand at room temperature for 10 minutes, then boiled for 2 minutes, and finally cooled and allowed to stand at room temperature for another 5 minutes. The solution was poured into 20 ml. of 10% hydrochloric acid containing 5 g. of ice, causing the precipitation of 0.14 g. (93%) of the product, which was collected by filtration and washed with water. Two recrystallizations from benzene gave small lustrous white prisms, m.p. 225.5–226.5°.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36. Found: C, 66.24; H, 4.58; N, 7.31.

(11) Aktien-Gesellschaft für Anilin-Fabrikation, German Patent 137,956 (December 1, 1902); *Chem. Zentr.*, **74**, I, 112 (1903); T. E. Young, Thesis Doctor of Philosophy, University of Illinois, 1952.

(12) N. Kizhner and V. Krasnova, *Anilinokrasochnaya Prom.*, **3**, 179 (1933); *Chem. Zentr.*, **105**, I, 2354 (1934); *C. A.*, **27**, 5319 (1933).

URBANA, ILLINOIS

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The Synthesis and Antibiotic Activity of Analogs of Citrinin and Dihydrocitrinin

BY HAROLD H. WARREN,[1] GREGG DOUGHERTY AND EVERETT S. WALLIS

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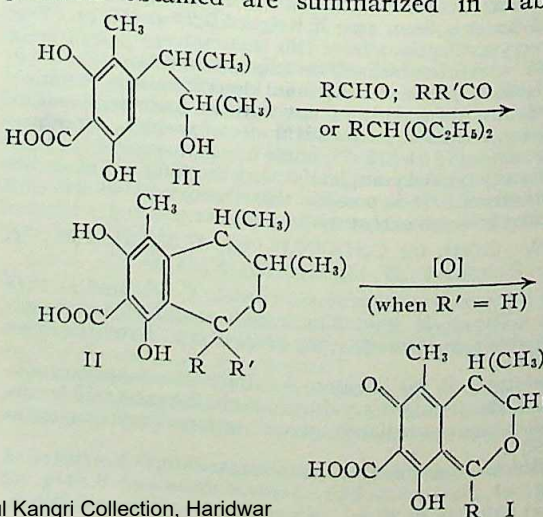
A method has been developed for the preparation of 1-substituted dihydrocitrinin derivatives (II) by the cyclization of the carboxylic acid derivative of Compound A (III) with acetals, aldehydes and ketones, and the conversion of the dihydro derivatives to the corresponding 1-substituted citrinin derivatives (I) by oxidation. Assay of the antibiotic activity of the compounds prepared indicated that the 1-methyl-, 1-ethyl- and 1-phenylcitrinin derivatives possess considerably less activity than the parent compound. The 1-methyl-, 1-ethyl-, 1-phenyl- and 1,1-dimethyldihydrocitrinin derivatives are inactive as is dihydrocitrinin, while the 1-benzyl derivative shows moderate activity.

In a previous article[2] we reported a partial synthesis of citrinin[3] (I, R = H) involving the cyclization of the carboxylic acid derivative of Raistrick's Compound A[4] (III) with methylal to give dihydrocitrinin[5] (II, R = H; R′ = H) and the oxidation of the latter with bromine to citrinin. The purpose of the present work was to extend this synthesis to the preparation of dihydrocitrinin and citrinin derivatives bearing alkyl and aryl substituents at the 1-position and to determine the effect of such structural variation on their antibiotic activity.

It has been found that aldehydes, acetals and ketones will condense with the carboxylic acid derivative of Compound A in a fashion analogous to that of methylal. The reactants used and the products obtained are summarized in Table I.



(1) Thompson Chemical Laboratory, Williams College, Williamstown, Mass.

(2) H. H. Warren, G. Dougherty and E. S. Wallis, THIS JOURNAL, **71**, 3422 (1949).

(3) 4,6-Dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-3H-2-benzopyran-7-carboxylic acid.

(4) 4-(2-Hydroxy-1-methylpropyl)-3-methyl-γ-resorcylic acid.

(5) 6,8-Dihydroxy-3,4,5-trimethyl-7-isochromancarboxylic acid.

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The cyclization occurs readily at room temperature with zinc chloride or anhydrous hydrogen chloride as the catalyst. In the case of acetone and phenylacetaldehyde, both reagents are required to give a reasonably rapid reaction. Although the carboxylic acid derivative is only slightly soluble in benzene, the reaction occurs readily in that solvent, and its progress can be followed easily by observing the disappearance of the suspended material.

TABLE I

CONDENSATION PRODUCTS OF CARBONYL COMPOUNDS WITH THE CARBOXYLIC ACID DERIVATIVE OF COMPOUND A

Reactant	Product	Yield, %	M.p., °C.[a]
Acetal	1-Methyldihydrocitrinin (II, R = CH_3; R′ = H)	28	152.0–153.0
Propionaldehyde (or its acetal)	1-Ethyldihydrocitrinin (II, R = C_2H_5; R′ = H)	9	170.0–171.4
Acetone	1,1-Dimethyldihydrocitrinin (II, R = CH_3; R′ = CH_3)	31	166.5–167.5
Benzaldehyde	1-Phenyldihydrocitrinin (II, R = C_6H_5; R′ = H)	23	168.5–169.5
Phenylacetaldehyde	1-Benzyldihydrocitrinin (II, R = $CH_2C_6H_5$; R′ = H)	24	172.5–173.5

[a] Decomposition occurred at the melting point in all cases.

Purification of the products by recrystallization resulted in considerable loss and was complicated by the fact that, while the dihydrocitrinin derivatives crystallize most readily from halogenated hydrocarbon solvents or mixed solvents containing them, the products are contaminated by solvent of crystallization which cannot be removed completely by prolonged drying under vacuum at elevated temperature.

The smallness of the reported yields is due largely to the losses involved in the preparation of samples of analytical purity. Yields of crude material were ample (50–80%).

All of the dihydrocitrinin derivatives are readily soluble in dilute sodium bicarbonate and give the characteristic deep blue color with dilute alcoholic ferric chloride.

The oxidation with bromine in chloroform of the substituted dihydrocitrinins to the corresponding citrinin derivatives proved less satisfactory than in the case of dihydrocitrinin itself. Small but adequate yields of light lemon-yellow crystals of 1-methylcitrinin and orange crystals of 1-phenylcitrinin were obtained, but all attempts to oxidize 1-ethyldihydrocitrinin and 1-benzyldihydrocitrinin with this reagent produced brominated products, and in the case of the latter compound a small amount of a non-brominated lemon-yellow substance which did not possess the characteristic properties of citrinin derivatives.

1-Ethyldihydrocitrinin was oxidized successfully to 1-ethylcitrinin by means of red mercuric oxide in benzene, but this method failed when applied to the 1-benzyl derivative.

In an attempt to develop a more satisfactory method for carrying out the conversion, the catalytic dehydrogenation of dihydrocitrinin was investigated. It was found that a 50% yield of citrinin can be obtained by heating dihydrocitrinin with 30% palladium–charcoal in nitrobenzene through which oxygen is slowly passed. All attempts, however, to adapt this procedure to the dehydrogenation of 1-benzyldihydrocitrinin failed. The only product that could be isolated was a small amount of material which had all the properties of citrinin and which did not depress the melting point of an authentic sample of citrinin, indicating that under the conditions of the reaction the benzyl group is eliminated more readily than hydrogen.

All the citrinin derivatives prepared give the deep red color with dilute alcoholic ferric chloride characteristic of citrinin and are soluble in dilute sodium bicarbonate but with increasing difficulty as the size of the substituent group is increased.

The agar-streak technique of Waksman and Reilly[6] was chosen as a rapid and convenient method for comparing the antibiotic activity of the synthetic derivatives to that of citrinin and dihydrocitrinin.

At the highest concentration tested, 3000 dilution units (ml. of nutrient agar/g. of test compound), of all the synthetic derivatives only four compounds show any inhibition of growth of the test organisms used. The results are summarized in Table II. As expected, none of the compounds shows activity toward the gram-negative organisms, *E. coli*.

It is apparent that introduction of an alkyl or aryl group into citrinin greatly reduces the antibiotic activity of the compound compared to the parent compound. On the other hand, the potency of dihydrocitrinin, itself inactive at the highest concentration tested, is greatly enhanced by the presence of the benzyl group.

Work is under way to determine the effect of increasing the chain length of the alkyl substituent on the antibiotic activity of citrinin derivatives and to determine whether the effect of the benzyl group on the activity of dihydrocitrinin is due merely to its size or to a specific function of that group.

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Experimental[7]

Starting Materials.—Citrinin was produced by the growing of *Aspergillus candidus* on a modified Czapek–Dox medium according to the method of Wyllie.[8] The hydrolysis of citrinin to Compound A and the preparation of the carboxylic acid derivative of compound A (III) by the carboxylation of Compound A have been described previously.[2] Ethyl acetate proved to be the most effective solvent for the purification of the carboxylic acid derivative. Dihydrocitrinin was prepared by the reduction of citrinin with Raney nickel according to the method of Schwenk, Schubert and Stahl.[9] The zinc chloride used was J. T. Baker, reagent grade.

1-Methyldihydrocitrinin (6,8-Dihydroxy-1,3,4,5-tetramethyl-7-isochromancarboxylic Acid).—To a suspension of 2.0 g. of the carboxylic acid derivative of Compound A (III) in 16 ml. of benzene was added 6.0 ml. of acetal and

(6) S. A. Waksman and H. C. Reilly, *Anal. Chem.*, **17**, 556 (1945).
(7) All melting points are corrected.
(8) J. Wyllie, *Can. J. Pub. Health*, **36**, 477 (1945).
(9) E. S. Schwenk, M. Schubert and E. Stahl, *Arch. Biochem.*, **20**, 230 (1949).

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TABLE II

ANTIBIOTIC POTENCY OF CITRININ AND ITS DERIVATIVES

Compound	*S. aureus* Ml. agar/g. cpd. for Partial inhib.	*S. aureus* Ml. agar/g. cpd. for Complete inhib.	*B. mycoides* Ml. agar/g. cpd. for Partial inhib.	*B. mycoides* Ml. agar/g. cpd. for Complete inhib.	*B. subtilis* Ml. agar/g. cpd. for Partial inhib.	*B. subtilis* Ml. agar/g. cpd. for Complete inhib.
Citrinin	70,000	40,000	70,000	40,000	70,000	50,000
Dihydrocitrinin	....[a]	....	....	....	....	....
1-Methylcitrinin	3,000	....	3,000	....	6,000	....
1-Ethylcitrinin		3,000		3,000	6,000	3,000
1-Phenylcitrinin	3,000	....	3,000	....	3,000	....
1-Benzyldihydrocitrinin	10,000	6,000	10,000	6,000	10,000	6,000

[a] .... indicates no inhibition at highest concentration tested.

1.0 g. of zinc chloride. The mixture was allowed to stand at room temperature with frequent shaking for 15 minutes during which most of the suspended material dissolved. After standing for 2 hr. the clear orange solution was washed twice with dilute hydrochloric acid, once with water and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded a red tar which was taken up in warm ethylene dibromide. Addition of petroleum ether and vigorous stirring initiated the formation of white crystals. After five recrystallizations from ethylene dibromide and petroleum ether followed by two from 1:10 toluene–ligroin, the product melted at 152.0–153.0° dec., yield 0.62 g. (28%).

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.12; H, 6.81. Found: C, 63.32; H, 6.83.

1-Methylcitrinin (4,6-Dihydro-8-hydroxy-1,3,4,5-tetramethyl-6-oxo-3H-2-benzopyran-7-carboxylic Acid).—To a solution of 0.20 g. of 1-methyldihydrocitrinin in 10 ml. of chloroform was added 3.0 ml. of 0.5 *M* bromine in chloroform. The solution was allowed to stand at room temperature for 15 minutes and then was washed with 5% sodium bisulfite solution, with water, dried over anhydrous sodium sulfate and evaporated to a red tar which crystallized when stirred with a small amount of ether. The product was filtered and recrystallized twice from chloroform–petroleum ether and once from absolute ethanol. The yield of lemon-yellow crystals was 0.03 g. (15%) melting at 259.2–260.0° dec. A sample introduced into the melting point apparatus preheated to 170° melted immediately, resolidified and remelted at the higher temperature.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.60; H, 6.10. Found: C, 63.45; H, 6.30.

The product could be purified readily by recrystallization from absolute ethanol, but it underwent decomposition in aqueous ethanol or aqueous methanol, forming a deep green solution and a deposit of dark green tar. This was the only citrinin derivative to exhibit such behavior.

1-Ethyldihydrocitrinin (1-Ethyl-6,8-dihydroxy-3,4,5-trimethyl-7-isochromancarboxylic Acid).—Dry halogen chloride was passed for 30 seconds through a suspension of 1.0 g. of the carboxylic acid derivative of Compound A (III) in 10 ml. of benzene and 3.0 ml. of propionaldehyde. The mixture was allowed to stand at room temperature for 2 hr. during which time the suspended material rapidly dissolved followed by spontaneous crystallization of the product. The mixture was diluted with sufficient ether to dissolve the crystalline deposit and was extracted twice with 5% sodium bicarbonate. The aqueous extract was acidified with excess dilute hydrochloric acid, and the resulting insoluble oil was extracted with ether. After drying over sodium sulfate, the ethereal solution was evaporated to a yellow oil which crystallized when stirred with benzene and cooled thoroughly. Recrystallization of the product once from amyl acetate and once from acetone yielded 0.10 g. (9%) of white crystals melting at 170.6–171.4° dec.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 63.97; H, 7.01.

The diethyl acetal of propionaldehyde was found to react in exactly the same fashion as the free aldehyde.

1-Ethylcitrinin (1-Ethyl-4,6-dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-3H-2-benzopyran-7-carboxylic Acid).—A mixture of 0.20 g. of 1-ethyldihydrocitrinin, 3.0 g. of red mercuric oxide, 1.0 g. of anhydrous magnesium sulfate in 10 ml. of benzene was refluxed for 45 minutes. After cooling, sufficient dilute hydrochloric acid was added to dissolve the sludge. The organic layer was separated, washed with dilute hydrochloric acid, once with water and then dried over sodium sulfate. Evaporation of the solvent yielded an orange oil which crystallized readily from dilute ethanol. Two recrystallizations of the product from the same solvent yielded 10 mg. (5%) of lemon-yellow crystals melting at 139.0–139.8°, resolidifying and remelting at 263.0–267.0° dec.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.86; H, 6.57.

1,1-Dimethyldihydrocitrinin (6,8-Dihydroxy-1,1,3,4,5-pentamethyl-7-isochromancarboxylic Acid).—To a suspension of 0.5 g. of the carboxylic acid derivative of Compound A (III) in 6.0 ml. of benzene and 1.5 ml. of acetone was added 0.1 g. of zinc chloride, and dry hydrogen chloride was bubbled through for 10 seconds. Within 10 minutes the suspended material had dissolved. After standing at room temperature for 4 hr. the nearly colorless solution was washed once with dilute hydrochloric acid and twice with water, dried over sodium sulfate and evaporated to a colorless oil which crystallized spontaneously. The product was recrystallized once from *p*-cymene and once from cyclohexane–carbon tetrachloride, yielding 0.18 g. (31%) of white crystals melting at 166.5–167.5° dec.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.26; H, 7.03.

1-Phenyldihydrocitrinin (6,8-Dihydroxy-3,4,5-trimethyl-1-phenyl-7-isochromancarboxylic Acid).—Four-tenths of a gram of zinc chloride was added to a suspension of 1.5 g. of the carboxylic acid derivative of Compound A (III) in a solution of 3.0 ml. of benzaldehyde and 15 ml. of benzene at room temperature. The suspended material completely dissolved within 30 minutes. After standing for 4 hr. the solution was washed with dilute hydrochloric acid and with water, dried over sodium sulfate and evaporated to a yellow oil which crystallized readily from carbon tetrachloride. The product was recrystallized once by dissolving it in 2 ml. of methanol, adding 15 ml. of hot carbon tetrachloride and cooling. A second recrystallization from 1:5 methyl ethyl ketone–ligroin yielded 0.57 g. (23%) of white crystals melting at 168.5–169.5° dec.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.49; H, 6.14. Found: C, 69.23; H, 6.30.

1-Phenylcitrinin (4,6-Dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-1-phenyl-3H-2-benzopyran-7-carboxylic Acid).—To a solution of 0.20 g. of 1-phenyldihydrocitrinin in 5.0 ml. of chloroform at room temperature was added slowly 0.7 ml. of 1.0 *M* bromine in chloroform. After standing for five minutes the orange solution was evaporated to an oil and then vacuum desiccated. The resulting glass crystallized when dissolved in hot ethanol to which water was cautiously added. Three recrystallizations of the product from dilute ethanol yielded 10 mg. (5%) of orange crystals melting at 249.5–251.5° dec. Though no shrinkage occurred at a lower temperature, a sample introduced into the apparatus preheated to 200° melted, resolidified and remelted at the higher temperature. The color of the pure product remained orange as compared to the lemon-yellow of most citrinin derivatives.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.94; H, 5.56. Found: C, 69.77; H, 5.43.

1-Benzyldihydrocitrinin (1-Benzyl-6,8-dihydroxy-3,4,5-trimethyl-7-isochromancarboxylic Acid).—Dry hydrogen chloride was bubbled for 15 seconds through a suspension of 1.0 g. of the carboxylic acid derivative of Compound A

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(III) and 0.2 g. of zinc chloride in a solution of 13 ml. of benzene and 2.0 ml. of freshly distilled phenylacetaldehyde. After standing at room temperature for 4 hr. the resulting yellow solution was washed with three portions of water, dried over sodium sulfate and evaporated to an oil which crystallized when stirred with petroleum ether. The product was recrystallized once from ethylene bromide and petroleum ether, once from *p*-cymene and three times from xylene yielding 0.34 g. (24%) of white crystals melting at 172.5–173.5° dec.

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.15; H, 6.48. Found: C, 70.28; H, 6.39.

Catalytic Dehydrogenation of Dihydrocitrinin.—Oxygen was bubbled slowly through a mixture of 0.10 g. of dihydrocitrinin and 0.05 g. of 30% palladium–charcoal in 1.0 ml. of nitrobenzene. After 23 minutes the solution gave a red color with ferric chloride indicating complete conversion of the dihydro compound. The solution was cooled, diluted to a convenient volume with ether, filtered to remove the catalyst and extracted with 5% sodium bicarbonate solution. Acidification of the aqueous extract with dilute sulfuric acid produced an orange-yellow crystalline precipitate. One recrystallization from hot ethanol yielded 0.05 g. (50%) of lemon-yellow crystals melting at 171.0–171.5° dec. No depression of the melting point was noted when this product was mixed with an authentic sample of citrinin.

The reaction proceeded in the absence of oxygen, but a longer reaction time was required, and the yield was considerably less.

Attempted Catalytic Dehydrogenation of 1-Benzyldihydrocitrinin.—The reaction was carried out using the same quantities and conditions given above for dihydrocitrinin. Heating was continued for 45 minutes before the blue ferric chloride test due to the dihydro compound became negative and a brown color was obtained. No appreciable product could be isolated by extraction of the reaction mixture.

The reaction was repeated using successively higher temperatures. At 150° a reaction time of nine minutes was required. Extraction of the solution yielded 0.02 g. of a yellow crystalline material which after one recrystallization from ethanol melted at 165.0–168.0° dec. A mixture of this product with citrinin melted at 166.0–169.0° dec.

Assay for Antibiotic Activity.—The comparison of the antibiotic activity of the synthetic derivatives to that of citrinin and dihydrocitrinin was made by the agar-streak method of Waksman and Reilly[6] using four organisms, *E. coli*, *S. aureus*, *B. mycoides* and *B. subtilis*. Stock solutions of the compounds to be tested were made up by dissolving the appropriate amount of substances (usually 5.0, 10.0 or 20.0 mg.) in three drops of acetone and three drops of 5% sodium bicarbonate and diluting to a volume of 10.0 ml. In no case did the latter reagents, at a concentration equal to the maximum present in the test cultures, inhibit the growth of control cultures. The stock solutions were used immediately after preparation to avoid decomposition of the sample in the slightly basic solution. A maximum concentration of test substance corresponding to 3,000 dilution units was used. The test cultures were examined after incubation for 20 hr. at 28°. The results for all compounds showing any inhibition of bacterial growth are summarized in Table II.

WILLIAMSTOWN, MASS.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Ethylenimine Ketones. XII. Stereoisomerism of 1-Cyclohexyl-2-(*o*-nitrophenyl)-3-benzoylethylenimine. Quinoline Syntheses

BY NORMAN H. CROMWELL AND GERALD D. MERCER

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A *trans* configuration has been assigned to the low melting form of 1-cyclohexyl-2-(*o*-nitrophenyl)-3-benzoylethylenimine which results from the reaction of 2-nitrochalcone with iodine and cyclohexylamine. Both the *cis* and *trans* forms are obtained in nearly equal amounts from 2,3-dibromo-3-(*o*-nitrophenyl)-propiophenone. The assignment of configuration is based upon the diagnostic phenylhydrazine reaction and absorption spectra studies. The catalytic hydrogenation of either the *cis*- or *trans*-ethylenimine ketone to 3-cyclohexylamino-2-phenylquinoline provides a new method of synthesis of such materials not readily available by conventional means. The course of this reaction is considered and the ultraviolet and infrared spectra of several 2-phenylquinolines are discussed.

Several pairs of *cis*- and *trans*-arylaroylethylenimines[1] and one pair of *cis*- and *trans*-alkylaroylethylenimines[2] have been prepared by the reaction of primary amines with α,β-dibromoketones. These isomeric pairs have been separated by fractional recrystallization or by chromatographic means and characterized by chemical and physical methods.

To study the sterical and electrical effects of the *o*-nitro group on the β-aryl ring of these ketones and to investigate certain synthetic possibilities, we have now prepared the *cis* and *trans* forms of 1-cyclohexyl-2-(*o*-nitrophenyl)-3-benzoylethylenimine. A comparable study in the epoxyketone series has been reported.[3]

The reaction of cyclohexylamine with 2,3-dibromo-3-(*o*-nitrophenyl)-propiophenone[4] in benzene solution gave an 89% yield of a nearly 50–50 mixture of the *cis* (Ia) and *trans* (Ib) forms of the ethylenimine ketone. These racemic geometrical isomers were separated by column chromatography.[2] The higher-melting *cis* isomer (Ia) in this series was the more strongly absorbed on the alumina. This appears to be a general property of the *cis* forms of the ethylenimine ketones.[2,5]

The low-melting *trans* form (Ib) also was prepared in 64% yield from 2-nitrochalcone,[4] cyclohexylamine and iodine in benzene solution, using a procedure similar to that outlined by Southwick and Christman[6] for a related reaction.

The configurations of Ia and Ib were assigned by methods which have been described previously for analogous compounds.[1–3] The high-melting ethylenimine ketone isomer (Ia) reacted with phenylhydrazine in the presence of acetic acid in an alcohol–chloroform mixture to produce an 85% yield of 1,3-diphenyl-5-(*o*-nitrophenyl)-pyrazole (II).[3] Under similar conditions the low-melting isomer (Ib) gave what appeared to be, from elemental analysis

(1) (a) N. H. Cromwell, *et al.*, THIS JOURNAL, **73**, 1044 (1951); (b) N. H. Cromwell and M. A. Graff, *J. Org. Chem.*, **17**, 414 (1952).

(2) N. H. Cromwell and R. J. Mohrbacher, THIS JOURNAL, **75**, 6252 (1953).

(3) N. H. Cromwell and R. A. Setterquist, *ibid.*, **76**, 5752 (1954).

(4) R. Sorge, *Ber.*, **35**, 1065 (1902); W. Dilthey, L. Neuhaus and W. Schommer, *J. prakt. Chem.*, **123**, 235 (1930); I. Tanasescu and A. Georgescu, *ibid.*, **139**, 189 (1934).

(5) N. H. Cromwell, R. P. Cahoy, W. E. Franklin and G. D. Mercer, THIS JOURNAL, **79**, 922 (1957).

(6) J. F. Southwick, Jr., and R. Christman, *ibid.*, **74**, 1886 (1952).

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and ultraviolet spectral studies,[1a] see Fig. 1, a mixture of the pyrazole II and 1,3-diphenyl-4-cyclohexylamino-5-(*o*-nitrophenyl)-pyrazoline (III). This mixed material gave a positive Knorr test[7] for pyrazolines.

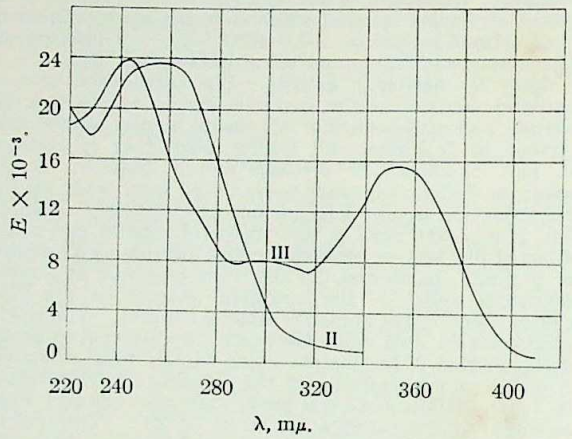

Fig. 1.—Ultraviolet absorption spectra in 95% ethanol of 1,3-diphenyl-5-(*o*-nitrophenyl)-pyrazole (II) and impure (contaminated with II) 1,3-diphenyl-4-cyclohexylamino-5-(*o*-nitrophenyl)-pyrazoline (III).

Attempts to separate the pyrazoline from the pyrazole by chromatographic adsorption on alumina led to conversion of all of the material to the pyrazole. The pyrazoline readily loses cyclohexylamine to produce the pyrazole, probably because the electron attraction of the *o*-nitro group on the phenyl ring at position-5 of the pyrazoline ring allows the proton to be lost readily from this carbon atom-5.

The aminopyrazolines with an unsubstituted phenyl group in position-5, which have been obtained from other *trans*-ethylenimine ketones,[1] are considerably more stable. The *trans*-arylaroyl ethylenimines are expected to produce aminopyrazolines while the *cis* isomers have been found to give only the pyrazoles.[1,2] The ultraviolet and infrared absorption spectra studies further confirmed the configurations assigned to Ia and Ib; see Absorption Spectra Discussion.

Hydrogenation of the isomeric ethylenimine ketones (Ia and Ib) using W-2 Raney nickel catalyst produced 3-cyclohexylamino-2-phenylquinoline (IV) isolated as its picrate. The isomeric 4-cyclohexylamino-2-phenylquinoline (IX) readily was prepared in good yield from 4-chloro-2-phenylquinoline by reaction with cyclohexylamine.

Colonna and Passerini[8] have prepared 3-arylamino-2-phenylquinolines by applying the Pfitzinger reaction[9] using isatin and ω-arylaminoacetophenones to obtain the 3-arylamino-2-phenyl-4-cinchonic acids, which were readily decarboxylated. Using ω-cyclohexylaminoacetophenone and isatin we obtained a good yield of 3-cyclohexylamino-2-phenyl-4-cinchonic acid (V). This acid was decarboxylated by heating alone to give 3-cyclohexylamino-2-phenylquinoline (IV), the picrate of which was identical with that obtained from the product of the catalytic hydrogenation of Ia and Ib.

When the cinchonic acid (V) was heated with 85% phosphoric acid or concd. sulfuric acid, dealkylation as well as decarboxylation occurred and the known 3-amino-2-phenylquinoline (VI) was produced.

3-Bromo-2-phenylquinoline (VIII) was obtained by a chemical reduction of α-bromo-2-nitrochalcone (VII) which was prepared by dehydrobromination of 2,3-dibromo-3-(*o*-nitrophenyl)-propiophenone. Attempts to replace the 3-bromo group in VIII with the cyclohexylamino group were unsuccessful.

The catalytic hydrogenation of 2-nitrochalcone produced 2-phenylquinoline in 82% yield while reduction with hydroiodic acid[10] gave the same compound in 31% yield.

3-(*o*-Nitrophenyl)-propiophenone (X) and 3-(*p*-nitrophenyl)-propiophenone (XI) were prepared by a Friedel–Crafts synthesis employing the acid chlorides of *o*-nitrohydrocinnamic acid and *p*-nitrohydrocinnamic acid. These acids were obtained in good yields from the nitration of hydrocinnamic acid using a procedure similar to that outlined by Buckles and Bellis[11] for the nitration of cinnamaldehyde.

Reduction of 3-(*o*-nitrophenyl)-propiophenone with hydroiodic acid produced a 30% yield of 2-phenylquinoline, but catalytic hydrogenation gave a 40% yield of 1,2,3,4-tetrahydro-2-phenylquinoline, isolated as its hydrochloride XIII.

The formation of the 3-cyclohexylamino-2-phenylquinoline from both the *cis*- and *trans*-ethylenimine ketones (Ia and Ib) undoubtedly involves the reduction of the nitro group to the amino group as the first step. The electron-releasing effect of the *o*-amino group would be expected to facilitate a cleavage of the β-carbon-to-nitrogen bond in the ethylenimine ring. This cleavage could lead to a rearrangement of both the *cis* and *trans* forms of the intermediate 1-cyclohexyl-2-(*o*-aminophenyl)-3-benzoylethylenimine (A) to α-cyclohexylamino-2-aminochalcone (B). This latter compound would be expected to undergo a facile ring closure to produce the quinoline IV. A similar mechanism has been suggested[3] to explain the formation of 3-hydroxy-2-phenylquinoline from the catalytic hydrogenation of both *cis*- and *trans*-2-nitrochalcone oxide.

An expanded study of these and related methods of synthesis for 3-amino-2-phenylquinolines will be described in a forthcoming paper.

Absorption Spectra Discussion.—The *cis*- and *trans*-ethylenimine ketones Ia and Ib show ultraviolet maxima midway between those of the parent saturated and unsaturated ketones, with the *trans* form exhibiting the stronger absorption. The *trans* form is expected to have a higher degree of three-ring carbonyl hyperconjugation.[1] The 2-nitrochalcone, which is probably the *trans* form, shows a maximum to be expected for the vinyl-benzoyl chromophore. The steric effect of the *o*-nitro group seems to inhibit conjugation sufficiently to exclude maxima to be associated with either the nitrostyryl or ni-

(7) L. Knorr, *Ann.*, **238**, 200 (1887).
(8) M. Colonna and R. Passerini, *Gazz. chim. ital.*, **78**, 778 (1948).
(9) W. Pfitzinger, *J. prakt. Chem.* [2] **33**, 100 (1886).
(10) A. Jancish, *Ber.*, **56**, 2448 (1923).
(11) R. E. Buckles and M. P. Bellis, *Org. Syntheses*, **33**, 60 (1953).

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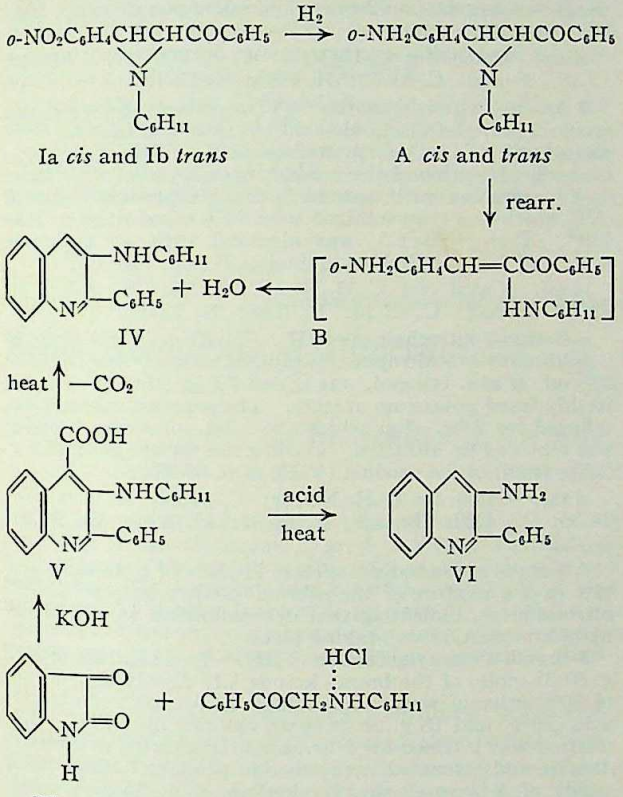
trocinnamoyl grouping.[12] The ethylenimine ketone Ib showed a carbonyl stretching vibration infrared band at lower frequencies than did Ia, further confirming that the former is undoubtedly the *trans* form, with three-ring carbonyl hyperconjugation making a greater contribution to the ground state than is the case for the *cis* form Ia.



The α-bromo-2-nitrochalcone showed two ultraviolet maxima at 220 and 261 mμ, again indicating that the steric effect of the *o*-nitro group inhibits conjugation and excludes the maxima which might be associated with either the nitrostyryl or nitrocinnamoyl groupings.[12] The relatively high value of 1681 cm.$^{-1}$ for the carbonyl bond stretching frequency in the infrared for this compound VII as compared with the value 1671 cm.$^{-1}$ for 2-nitrochalcone indicates an increase in double bond character for the C=O group in the ground state. This shift may be associated with a decrease in conjugation between the benzoyl and bromovinyl group as well as with the inductive and coulombic field effects of the α-bromo group.[13]

The 2-phenylquinolines show strong ultraviolet absorption between 254 and 265 mμ. In general[14] the 3-amino-2-phenylquinolines absorb at shorter wave lengths and/or lower intensities than the 4-amino-2-phenylquinolines in this range of the spectrum, possibly because of steric crowding between the 2-phenyl group and the space-demanding N-substituted 3-amino groups. In general[14] N-substituted 3-amino-2-phenylquinolines absorb at higher wave lengths above 300 mμ but at lower intensities than the isomeric 4-amino derivatives. The 3-cyclohexylamino-2-phenylquinoline has a third high intensity band at 221 mμ.

All of the 2-phenylquinolines studied showed two moderately strong infrared bands between 1540 and 1620 cm.$^{-1}$. The assignment of bands in this range of the spectrum, where those to be associated with conjugated phenyl, phenyl, C=C, C=N and N—H (B) bending are expected, is difficult and often uncertain.

Summary of Absorption Spectra

Compound	No.	Ultraviolet max.[a] λ, mμ	ε × 10^{-3}	Infrared bands[b] Bond	Wave no.	Approx. % abs.
1-Cyclohexylamino-2-(*o*-nitrophenyl)-(*cis*) 3-benzoylethylenimine (*trans*)	IA	254	17.9	C=O	1687	70
	IB	254	21.5	C=O	1675	64
2-Nitrochalcone (*trans*)[d]	..	262	17.5	C=O	1671	64[c]
					1650	46
α-Bromo (*trans*)	VII	220	13.9	C=O	1681	95[e]
		261	16.7			
3-(*o*-Nitrophenyl)-propiophenone[d]	X	244	15.8	C=O	1690	80
1,3-Diphenyl-5-(*o*-nitrophenyl)-pyrazole	II	257	23.9			
2-Phenylquinoline	..	256	46.7	C=N	1620	15[f]
		322	9.0	C_6H_5	1600	30
3-Bromo	VIII	255	50.8	C=N	1611	20[g]
		323	10.5	C_6H_5	1593	40
3-Amino-	VI	254	34.6	N—H	3480	10[h]
		355	7.4	N—H	3395	14
				C=N	1618	40
				N—H (B)	1545	43
3-Cyclohexylamino-	IV	221	29.0	N—H	3418	20[i]
		258	29.7	C=N	1604	30
		371	5.9	N—H (B)	1560	4
4-Cyclohexylamino-	IX	265	33.6	N—H	3428	50
		332	11.1	C=N	1583	78
				N—H (B)	1555	68
1,2,3,4-Tetrahydro-2-phenylquinoline hydrochloride	XIII	250	12.4			
		300	3.8			

[a] The ultraviolet spectra were determined in the range of 220–450 mμ in 95% ethanol using 10^{-4} molar solutions with a Cary model 11 spectrophotometer. [b] The infrared spectra were determined over the range of 4000–600 cm.$^{-1}$ at 25° using 1.0-mm. matched NaCl cells with a Perkin–Elmer model 21 instrument; the solutions were 6 mg./ml. CCl_4 unless otherwise indicated. [c] Concn. was 12 mg./ml. CS_2. [d] See ref. 3. [e] Concn. was 12 mg./ml. CCl_4. [f] In 0.1-mm. cells. [g] Concn. was 21 mg./ml. CCl_4 in 0.1-mm. cells. [h] Concn. was 37 mg./ml. CCl_4 in 0.1-mm. cells. [i] Concn. was 30 mg./ml. CCl_4 in 0.1-mm. cells.

Acknowledgment.—This work was supported in part by a grant from the National Science Foundation, N.S.F. G-1091.

Experimental

***cis*- and *trans*-1-Cyclohexyl-2-(*o*-nitrophenyl)-3-benzoylethylenimines (Ia and Ib).**—To a well-stirred suspension of 50 g. (0.121 mole) of 2,3-dibromo-3-(*o*-nitrophenyl)-propiophenone[4] in 150 ml. of dry benzene, cooled to 5°, was added dropwise 36.2 g. (0.376 mole) of cyclohexylamine. The mixture was stirred for 3 hr. and then placed in the refrigerator for 16 hr. The solid cyclohexylamine hydrobromide was removed by filtration and the filtrate concentrated to a thick sirupy residue under vacuum. This residue was taken up in benzene and three successive crops of crystals removed by addition of petroleum ether (b.p. 30–60°); wt. 35.5 g. (89% yield), m.p. 98–120°. This mixed product was separated by column chromatography, using aluminum oxide, into nearly equal amounts of the *cis* isomer Ia, m.p. 130–131°, and the *trans* form Ib, m.p. 114–115°. The total recovery of material was 98% and the *trans* isomer was

(12) See W. B. Black and R. E. Lutz, This Journal, **77**, 5134 (1955), who studied the *p*-nitrochalcones.

(13) R. D. Campbell and N. H. Cromwell, *ibid.*, **79**, 3456 (1957).

(14) In a forthcoming article the absorption spectra of a considerable number of N-substituted 3-amino- and 4-amino-2-phenylquinolines will be discussed.

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the first to be eluted from the column by the benzene–alcohol mixture.

trans-1-Cyclohexyl-2-(*o*-nitrophenyl)-3-benzoylethylenimine (Ib).—A 11.4-g. (0.045 mole) sample of 2-nitrochalcone[4] and 17.9 g. (0.181 mole) of cyclohexylamine dissolved in 125 ml. of dry benzene was treated with a solution of 11.4 g. (0.045 mole) of iodine in 125 ml. of dry benzene with stirring and external cooling. The product, isolated as before, weighed 10.2 g. (64.6% yield), m.p. 114–115°, identical with Ib described above.

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found for Ia; C, 72.32; H, 6.56; N, 8.00. For Ib: C, 72.14; H, 6.28; N, 8.18.

Reaction of the Ethylenimine Ketones Ia and Ib with Phenylhydrazine.—The *cis isomer* Ia (2.1 g., 0.006 mole) was dissolved in 25 ml. of a 2:3 alcohol–chloroform mixture and to this solution was added 0.75 g. (0.006 mole) of phenylhydrazine and 0.75 g. (0.012 mole) of glacial acetic acid. The solution was warmed to about 40° for 30 minutes and then allowed to stand at room temperature for 45 hr. The product was isolated by cooling the reaction mixture and recrystallizing the crude product from methanol to yield 2.2 g. (85.7% yield) of 1,3-diphenyl-5-(*o*-nitrophenyl)-pyrazole (II), m.p. 178–179°, identical with the product previously prepared in this Laboratory.[3]

The *trans* isomer Ib (2.1 g., 0.006 mole) was treated in a similar manner, but without warming, and found to yield after 14 hr., 0.70 g. of 1,3-diphenyl-5-(*o*-nitrophenyl)-pyrazole.[3] Evaporation of the reaction filtrate produced an additional 1.01 g. of a solid material, m.p. 126–142°. Recrystallization of this product from alcohol gave material melting at 137–147°. Attempts at purification of this mixed product by chromatographic means gave only the pure pyrazole II. The 137–147° melting material gave a positive Knorr[7] pyrazoline test. This mixed product was undoubtedly a mixture of 1,3-diphenyl-4-cyclohexylamino-5-(*o*-nitrophenyl)-pyrazoline (III) and the pyrazole II.

Anal. Calcd. for $C_{27}H_{22}N_4O_2$: C, 73.61; H, 6.41; N, 12.72. Found: C, 73.29; H, 5.46; N, 12.33.

2-Phenyl-3-cyclohexylaminoquinoline (IV) from Ethylenimine Ketones Ia and Ib. (a) **From the *trans* isomer Ib.**—A 4.1-g. sample of Ib was dissolved in 20 ml. of ethyl acetate and shaken under 45 lb./in.^{2} of hydrogen in the presence of 0.50 g. of W-2 Raney nickel catalyst for 2 hr. Filtration and evaporation left an oil which could not be crystallized from ethanol. Treatment of the ethanol solution of the oil with picric acid produced 3.1 g. (50% yield) of the picrate of 2-phenyl-3-cyclohexylaminoquinoline, m.p. 203–205°, identical with the authentic compound described below.

b. **From the *cis* Isomer Ia.**—In a similar experiment, using 30 ml. of ethanol as solvent, after 3 hr. of hydrogenation 3.5 g. of Ia produced 2.69 g. (56% yield) of the picrate, m.p. 203–205°, identical with the one obtained in (a).

ω-Cyclohexylaminoacetophenone Hydrochloride.[15]—To 88.5 g. (0.894 mole) of cyclohexylamine in 200 ml. of ethyl ether and 132 ml. of dry benzene, held to 14°, slowly was added 88 g. (0.443 mole) of ω-bromoacetophenone dissolved in 160 ml. of ethyl ether and 55 ml. of dry benzene. The reaction mixture was stirred an additional hour. The by-product cyclohexylamine hydrobromide was removed and the product isolated as the hydrochloride by passing dry hydrogen chloride gas into the solution; wt. 60 g. (54% yield), m.p. 250–252° dec., recrystallized from abs. ethanol.

Anal. Calcd. for $C_{14}H_{20}NOCl$: Cl, 13.97. Found: Cl, 13.98.

3-Cyclohexylamino-2-phenyl-4-cinchonic Acid (V).—A solution of 25 g. (0.171 mole) of isatin in aqueous potassium hydroxide (400 g. in 500 ml. of water) was added to a hot solution of 43.5 g. (0.171 mole) of ω-cyclohexylaminoacetophenone hydrochloride in 800 ml. of 95% ethanol. The mixture was heated under reflux for 5 hr. and then 800 ml. of solvent removed by distillation. The residual solution was cooled to precipitate the potassium salt which was removed by filtration and converted to the yellow colored acid in hot water, acidified with glacial acetic acid. This product was recrystallized from 95% ethanol to give 38 g. (64% yield) of 3-cyclohexylamino-2-phenyl-4-cinchonic acid (V), m.p. 198–200° dec.

Anal. Calcd. for $C_{22}H_{22}N_2O_2$: C, 76.27; H, 6.40; N, 8.08. Found: C, 76.43; H, 6.53; N, 7.87.

3-Cyclohexylamino-2-phenylquinoline (IV).—A 6.92-g. sample of the cinchonic acid V was heated at its melting point (200°) for 30 minutes and then distilled under vacuum (pot temp. 240°, 300 μ pressure). A pale yellow oil (IV) was collected, 3.2 g. (51% yield). The spectra of this material was determined without further purification. A sample of this oil was treated with the picric acid to produce the 3-cyclohexylamino-2-phenylquinoline picrate, m.p. 204–205°, in a 95% yield.

Anal. Calcd. for $C_{27}H_{25}N_5O_7$: C, 61.01; H, 4.74; N, 13.18. Found: C, 61.36; H, 4.83; N, 13.47.

3-Amino-2-phenylquinoline (VI).—When 3-cyclohexylamino-2-phenyl-4-cinchonic acid (V) was heated with 85% phosphoric acid or concd. sulfuric acid at 200°, a gas was evolved. Isolation of the product upon dilution with water and basification with sodium hydroxide produced a solid (VI) which was recrystallized from 95% ethanol; m.p. 118–119°. This product V was identical with an authentic sample of 3-amino-2-phenylquinoline,[16] m.p. 118–119°.

Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 82.13; H, 5.68; N, 12.34.

α-Bromo-2-nitrochalcone (VII).—To 31 g. (0.075 mole) of 2,3-dibromo-3-(*o*-nitrophenyl)-propiophenone,[4] suspended in 300 ml. of abs. ethanol, was added 7.5 g. (0.0754 mole) of freshly fused potassium acetate. The reaction mixture was refluxed for 2 hr. after which the solid potassium bromide was removed by filtration. Cooling the filtrate gave 22.3 g. (93% yield) of the product (VII), m.p. 85–86°.

Anal. Calcd. for $C_{15}H_{10}NO_3Br$: C, 54.24; H, 3.03; Br, 24.06; N, 4.22. Found: C, 54.39; H, 3.15; Br, 23.81; N, 4.26.

Attempts to use sodium acetate in place of potassium acetate gave a mixture of the α-bromo-2-nitrochalcone and 2-nitrochalcone, indicating that debromination as well as dehydrobromination was taking place.

3-Bromo-2-phenylquinoline (VIII).—To a solution of 3.22 g. (0.01 mole) of the bromo ketone VII dissolved in 50 ml. of 50% ethanol–water, was added 50 ml. of hydrobromic acid (29%) and 18 g. of stannous chloride dihydrate. The mixture was warmed for 2 hr., made basic with sodium hydroxide and extracted with ether to produce 0.82 g. (30% yield) of 3-bromo-2-phenylquinoline, m.p. 85–86°, corresponding to that reported by John[17]; mixed m.p. with starting material, 60–65°.

Treatment of a sample of 3-bromo-2-phenylquinoline with cyclohexylamine in a sealed tube by the procedure used for the preparation of the 4-position isomer IX resulted in the recovery of the starting material.

4-Cyclohexylamino-2-phenylquinoline (IX).—A 1.2-g. sample of 4-chloro-2-phenylquinoline was heated in a sealed tube[17] at 200° for 10 hr. with 0.90 g. (an excess) of cyclohexylamine. The product was recrystallized from 95% ethanol; 1.35 g. (89% yield), m.p. 128–129°.

Anal. Calcd. for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33; N, 9.27. Found: C, 83.26; H, 7.43; N, 9.12.

3-(*o*-Nitrophenyl)-propiophenone (X) and 2-(*p*-Nitrophenyl)-propiophenone (XI).—*o*-Nitro- and *p*-nitrohydrocinnamic acid were prepared by the nitration of hydrocinnamic acid using the procedure described by Buckles and Bellis[11] for cinnamaldehyde. The *o*- and *p*-isomers were obtained in an over-all yield of 69%; 64% of the product was the *o*-isomer. They were separated by fractional crystallization from hot water and alcohol; *o*-isomer, m.p. 111–112°[18]; *p*-isomer, m.p. 161–163°.[18]

o-Nitrohydrocinnamoyl chloride was prepared by treating 14.3 g. of the acid with thionyl chloride. A Friedel-Crafts reaction was carried out with the crude acid chloride and benzene, using aluminum chloride as the catalyst. Hydrolysis of the product complex gave 12.2 g. (66% yield) of 3-(*o*-nitrophenyl)-propiophenone; recrystallized from benzene and petroleum ether, m.p. 58–59°; Janeish[10] reported m.p. 68–69°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13. Found: C, 70.60; H, 5.12.

(15) This compound was first prepared in this Laboratory by E. A. Nielsen, M.S. thesis, 1950, Univ. of Nebraska.

(16) Prepared in this Laboratory by Dr. H. E. Baumgarten by the reduction of 3-nitro-2-phenylquinoline.

(17) H. John, *J. prakt. Chem.*, **118**, 303 (1927); **131**, 350 (1932).

(18) J. Koněk and E. Pacsu, *Ber.*, **51**, 855 (1918).

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Using the above procedure, 35 g. of *p*-nitrohydrocinnamic acid produced 31.1 g. (69% yield) of 3-(*p*-nitrophenyl)-propiophenone, m.p. 94–96°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13. Found: C, 70.73; H, 5.24.

2-Bromo-3-(*p*-nitrophenyl)-propiophenone (XII).—A 25.5-g. sample of 3-(*p*-nitrophenyl)-propiophenone was dissolved in 100 ml. of glacial acid and warmed to 50°. To this solution was added 16 g. of bromine in 50 ml. of glacial acetic acid. The temperature of the reaction mixture was maintained at 50° for 1 hr., cooled and poured into 500 ml. of cold water. The oily solid residue was crystallized from ethanol; wt. 32.23 g. (96% yield), m.p. 100–101°.

Anal. Calcd. for $C_{15}H_{12}NO_3Br$: C, 53.91; H, 3.62; Br, 23.92. Found: C, 54.08; H, 3.62; Br, 24.32.

2-Phenyl-1,2,3,4-tetrahydroquinoline Hydrochloride (XIII).—A 3.0-g. sample of 3-(*o*-nitrophenyl)-propiophenone was dissolved in 50 ml. of ethyl acetate and shaken with 45 lb./in.^{2} of hydrogen in the presence of 0.5 g. of W-2 Raney nickel catalyst for 3 hr. at room temperature. The oily product isolated from the reaction mixture was converted to its hydrochloride salt upon passing dry hydrogen chloride gas into a dry ether solution of it; wt. 1.15 g. (40% yield), m.p. 220–225°, recrystallized from abs. ethanol.

Anal. Calcd. for $C_{15}H_{16}NCl$: Cl, 14.67. Found: Cl, 14.43.

2-Phenylquinoline.—A 2.0-g. sample of 2-nitrochalcone was dissolved in 60 ml. of ethyl acetate, and hydrogenated in the presence of W-2 Raney nickel as outlined above to produce 1.3 g. (82% yield) of 2-phenylquinoline, m.p. 81–82°. This product was identical with samples prepared by (a) refluxing *o*-nitrochalcone for 16 hr. with 48% hydroiodic acid (31% yield) or (b) by refluxing 3-(*o*-nitrophenyl)-propiophenone with the same reagent for 20 hr. (30% yield).[10]

LINCOLN, NEBRASKA

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Amino Derivatives of Nitrochalcones. I. Synthesis, Structure Studies and Absorption Spectra

BY NORMAN H. CROMWELL AND GERALD D. MERCER[1]

RECEIVED MARCH 16, 1957

2,3-Dibromo-3-(*o*-nitrophenyl)-propiophenone and the corresponding α-bromo-2-nitrochalcone react with morpholine, piperidine or dimethylamine to produce the expected 2,3-diamino-3-(*o*-nitrophenyl)-propiophenones, while secondary amines with greater steric requirements, such as diethylamine and N-methylcyclohexylamine, react to produce β-amino-2-nitrochalcones. The corresponding bromine derivatives of 3-nitro and 4-nitrochalcone react with both classes of secondary amines in the normal manner to produce 2,3-diamino-3-nitrophenylpropiophenones and/or α-aminonitrochalcones. The structures of the amino chalcones were established by acid hydrolysis studies. A discussion of the ultraviolet and infrared absorption spectra of these and related compounds is given.

The reactions of secondary amines with α,β-dibromoketones and α-bromo-α,β-unsaturated ketones have been the subject of numerous investigations reported from this Laboratory[2] and from others.[3]

The reaction of 2,3-dibromo-3-(*o*-nitrophenyl)-propiophenone[4] with morpholine, piperidine and dimethylamine produced the corresponding α,β-diamino ketones I, II and III. Only one of the two possible racemates was isolated in each case in at least 75% yield, and it was not possible to isolate either α-amino- or β-amino-α,β-unsaturated ketones from the highly colored reaction mixtures. These same products I, II and III also were obtained in slightly lower yields from α-bromo-2-nitrochalcone.[5]

When 2,3-dibromo-3-(*o*-nitrophenyl)-propiophenone was allowed to react with secondary amines having higher steric requirements, yellow colored products were produced which analysis, absorption spectra studies and acid hydrolysis showed were β-amino-*o*-nitrochalcones. Thus β-diethylamino- (IV) and β-(N-methylcyclohexylamino)-2-nitrochalcone (V) were produced in good yields using the corresponding amines. These same products were obtained in nearly the same yields from α-bromo-2-nitrochalcone.

The unsaturated amino ketones IV and V were difficult to hydrolyze, but long heating with dilute sulfuric acid produced the known *o*-nitrodibenzoylmethane which readily gave a copper chelate. This 1,3-diketone reacted with phenylhydrazine to give the known 1,3-diphenyl-5-(*o*-nitrophenyl)-pyrazole.[5,6]

In contrast with the *o*-nitro compound, both 2,3-dibromo-3-(*m*-nitrophenyl)-propiophenone and 2,3-dibromo-3-(*p*-nitrophenyl)-propiophenone reacted with diethylamine to produce the corresponding α-diethylamino-3-nitrochalcone (XI) and α-diethylamino-4-nitrochalcone (X), respectively. The structures of these products X and XI were established by analysis, absorption spectra studies and their acid hydrolysis to the corresponding 1,2-diketones. Compound X was hydrolyzed to *p*-nitrobenzylphenyl diketone (XII) which produced 2-(*p*-nitrobenzyl)-3-phenylquinoxaline (XIII) on heating with *o*-phenylenediamine. The α-amino-α,β-unsaturated ketone XI produced the corresponding 1,2-diketone which was converted to the known 2-(*m*-nitrobenzyl)-3-phenylquinoxaline on warming with *o*-phenylenediamine.

2,3-Dibromo-3-(*p*-nitrophenyl)-propiophenone reacted with morpholine to give a mixture of 2,3-di-(N-morpholino)-3-(*p*-nitrophenyl)-propiophenone (VI) and α-(N-morpholino)-4-nitrochalcone (VIII), which were separated readily by fractional recrystallization. Piperidine behaved in a similar

(1) Standard Oil Co. (of Indiana) Fellow, 1955–1956.

(2) See N. H. Cromwell, *Chem. Revs.*, **38**, 83 (1946), and ref. cited therein.

(3) (a) R. Lutz, *et al.*, *J. Org. Chem.*, **14**, 982 (1949); (b) **16**, 1442 (1951).

(4) R. Sorge, *Ber.*, **35**, 1065 (1902); W. Dilthey, L. Neuhaus and W. Schommer, *J. prakt. Chem.*, **123**, 235 (1930); I. Tanasescu and A. Georgescu, *ibid.*, **139**, 189 (1934).

(5) N. H. Cromwell and G. D. Mercer, THIS JOURNAL, **79**, 3815 (1957).

(6) N. H. Cromwell, R. A. Setterquist, *ibid.*, **76**, 5752 (1954).

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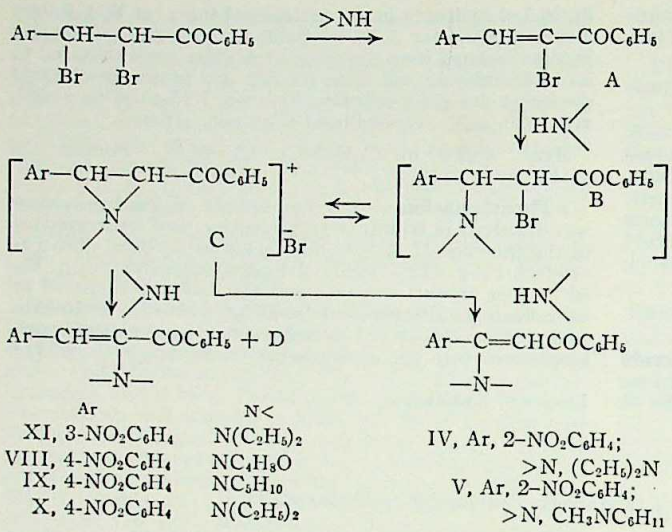


Ar	N<
XI, 3-$NO_2C_6H_4$	$N(C_2H_5)_2$
VIII, 4-$NO_2C_6H_4$	NC_4H_8O
IX, 4-$NO_2C_6H_4$	NC_5H_{10}
X, 4-$NO_2C_6H_4$	$N(C_2H_5)_2$

IV, Ar, 2-$NO_2C_6H_4$; >N, $(C_2H_5)_2N$

V, Ar, 2-$NO_2C_6H_4$; >N, $CH_3NC_6H_{11}$

manner to produce the corresponding α,β-di-(N-piperidino) ketone VII and the α-(N-piperidino)-α,β-unsaturated ketone IX.

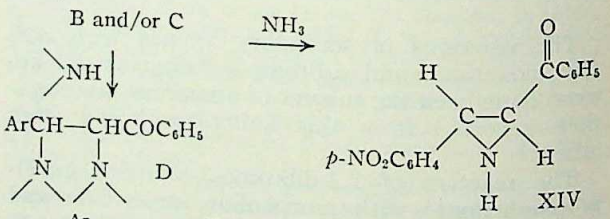
With anhydrous ammonia, 2,3-dibromo-3-(*p*-nitrophenyl)-propiophenone produced *trans*-2-(*p*-nitrophenyl)-3-benzoylethylenimine (XIV), previously prepared by Wieland[7] but assigned a piperizine structure without further investigation. A molecular weight determination and the measurement of absorption spectra (infrared and ultraviolet) clearly established the structure of this ethylenimine ketone.

Discussion of Reactions.—It has been shown[2] that α-bromochalcone or 2,3-dibromo-3-phenylpropiophenone reacts with secondary amines to produce either mixtures of α-amino-α,β-unsaturated ketones and α,β-diaminoketones (*i.e.*, morpholine and piperidine) or only the α-amino-α,β-unsaturated ketone (*i.e.*, diethylamine). An endocyclic α,β-unsaturated ketone, 8-bromoperinaphthenone-7, was found to react with secondary amines (*i.e.*, morpholine and piperidine) to produce either α-amino- or β-amino-α,β-unsaturated ketones, depending upon the conditions employed.[8] Recently it has been reported that 3-bromo-1,-1-dimethyl-2-keto-1,2-dihydronaphthalene reacts with morpholine to give a β-amino-α,β-unsaturated ketone.[9]

It seems probable that the first step in the reaction of amines with each of the 2,3-dibromo-3-arylpropiophenones (*o*-nitro, *m*-nitro and *p*-nitro) involves the loss of hydrogen bromide to produce the corresponding α-bromonitrochalcone (A). The second step in the presence of excess reagent is the addition of the amine to produce the reactive 2-bromo-3-amino-3-nitrophenylpropiophenones (B). With primary amines[5,10] or ammonia the last step in the sequence of reactions in all three series involves a ring closure to produce the ethylenimine ketone. Both the *m*-nitrophenyl and *p*-nitrophenyl series of bromo ketones react with diethylamine, morpholine and piperidine in the normal[2] manner to produce the expected results, *via* the intermediate quaternary ethylenimmonium ion, since α-amino-α,β-unsaturated ketones are included in the products.

The presence of an electron-attracting nitro group on the 3-aryl group in the 2,3-dibromo-3-(nitrophenyl)-propiophenones would be expected to activate the hydrogen atom in the 3-position and thus facilitate the loss of hydrogen bromide from the intermediate 2-bromo-3-amino-3-(nitrophenyl)-propiophenones (B) to produce β-aminonitrochalcones. However, since only the 2,3-dibromo-3-(*o*-nitrophenyl)-propiophenone behaved in this manner, it seems possible that a steric effect as well as the electrical effect of the *o*-nitro group is involved in determining the course of these reactions to produce the β-amino α,β-unsaturated ketones (IV) and (V). It is possible (but not certain) that the intermediate formation of the usual ethylenimmonium bromides[2] is not involved in the loss of hydrogen bromide from the intermediate 3-diethylamino- and 3-(N-methylcyclohexylamino)-2-bromo-3-(*o*-nitrophenyl)-propiophenones.

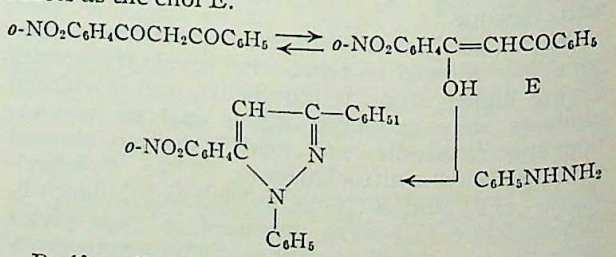
Steric controls[11] which are expected to operate in the formation of the 3-amino-2-bromo-3-arylpropiophenones suggest that the main products to be expected from the reactions involving ammonia are the *trans*-2-aryl-3-benzoylethylenimines (*i.e.*, XIV).



Ar	N<
I, *o*-$NO_2C_6H_4$	NC_6H_8O
II, *o*-$NO_2C_6H_4$	NC_5H_{10}
III, *o*-$NO_2C_6H_4$	$N(CH_3)_2$

Ar	N<
VI, *p*-$NO_2C_6H_4$	NC_4H_8O
VII, *p*-$NO_2C_6H_4$	NC_5H_{10}

It was of interest to find that *o*-nitrodibenzoylmethane reacted with phenylhydrazine to produce the known 1,3-diphenyl-5-(*o*-nitrophenyl)-pyrazole. This result implies that *o*-nitrodibenzoylmethane reacts as the enol E.



Bodforss[12] came to a similar conclusion with regard to the reaction of *m*-nitrodibenzoylmethane and phenylhydrazine. Although the course of the reaction suggested by Bodforss has been disputed by Barnes and Dodson,[13] we are inclined to

(7) H. Wieland, *Ber.*, **37**, 1150 (1904).

(8) N. H. Cromwell, D. B. Capps and S. E. Palmer, THIS JOURNAL, **73**, 1226 (1951).

(9) N. H. Cromwell and R. D. Campbell, *J. Org. Chem.*, **22**, 520 (1957).

(10) N. H. Cromwell, THIS JOURNAL, **69**, 258 (1947).

(11) N. H. Cromwell, W. Franklin and R. P. Cahoy, *ibid.*, **79**, 922 (1957).

(12) S. Bodforss, *Ber.*, **49**, 2795 (1916).

(13) H. L. Barnes and D. Dodson, THIS JOURNAL, **65**, 1585 (1943).

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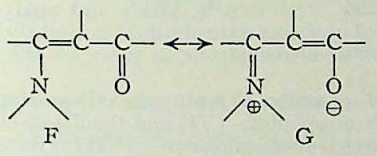
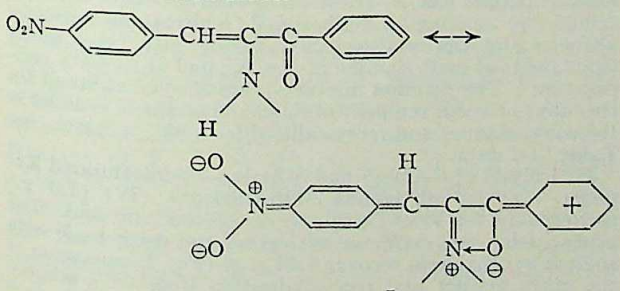
believe that Bodforss' description of these reactions is correct. The fact that 2,3-dibromo-3-phenyl-*m'*-nitropropiophenone reacts with a mixture of potassium hydroxide and phenylhydrazine to produce the same pyrazole[13] as does *m*-nitrodibenzoylmethane[12] cannot be taken as conclusive evidence for the structure of the pyrazole. The dibromide may have undergone an initial reaction with potassium hydroxide to produce *m*-nitrodibenzoylmethane. We believe that Bodforss' assignment of the 1,3-diphenyl-5-(*m*-nitrophenyl)-pyrazole structure to this derivative is correct.

Discussion of Absorption Spectra.—2-Nitrochalcone[5,6] has been shown to have only one maximum in the ultraviolet at 262 mμ, which is to be associated with the vinyl–benzoyl chromophore. The β-amino-2-nitrochalcones (IV) and (V) both showed benzoyl absorption in the range of 243–247 mμ and a new intense maximum at 340 mμ. Both of these β-amino-α,β-unsaturated ketones have carbonyl stretching frequencies near 1635 cm.$^{-1}$ in the infrared. As has been suggested previously,[14,15] such results indicate that the resonance implied by (F) ⟷ (G) makes an important contribution to both the ground and excited states of β-amino-α,β-unsaturated ketones.



F G

The α-amino-α,β-unsaturated ketones (VIII) and (IX) also showed vinyl–benzoyl absorption at 255 mμ and moderately strong bands near the visible-ultraviolet boundary of the spectrum, 390–425 mμ. These longer wave length bands may be ascribed[14] to chromophores involving the whole molecule, and resonance implied by H ⟷ J is suggested as making a considerable contribution to the excited state.



J

It is important to observe that the presence of the nitro group in the *p*-position, which would be expected to support a negative charge through interaction with the benzene ring, greatly enhances light absorption in this part of the spectrum. Although α-diethylamino-3-nitrochalcone (XI) also has an ultraviolet absorption band at 400 mμ, the intensity is much lower than for the α-amino-4-nitrochalcones. Resonance interaction of the *m*-nitro group with the benzene ring is, of course, not expected. Ketone XI also shows a moderately strong nitrocinnamoyl band at 313 mμ. The infrared carbonyl stretching frequencies of all of these α-aminochalcones were between 1677 and 1682 cm.$^{-1}$. This shift to higher frequencies with respect to the carbonyl values for nitrochalcones (1671 cm.$^{-1}$ or less)[5,6] indicates that the resonance H ⟷ J makes little or no contribution to the ground state and that instead the inductive and coulombic field effects[16] of the α-amino groups increase the double bond character of the carbonyl group in the α-aminochalcones.[15] This shift in carbonyl frequency also may be associated with a steric inhibition of conjugation between the benzoyl and vinyl groups caused by the presence of the α-amino group.[5]

3-(*p*-Nitrophenyl)-propiophenone shows benzoyl absorption in the ultraviolet at 246 mμ and a slightly less intense band at 274 mμ, possibly to be associated with the nitrophenyl grouping. The ethylenimine derivative XIV showed similar absorption characteristics with an increase in wave length and intensity for the benzoyl and nitrophenyl bands. The infrared carbonyl stretching frequency of the ethylenimine ketone XIV was found at 1680 cm.$^{-1}$ as compared with a value of 1686 cm.$^{-1}$ for 3-(*p*-nitrophenyl)-propiophenone. These ultraviolet and infrared studies imply that hyperconjugation of the three-ring with the carbonyl and *p*-nitrophenyl groups makes a small contribution to both the ground and excited states of XIV, and that it has a *trans* configuration.[5]

The infrared spectrum for the copper chelate XV of *o*-nitrodibenzoylmethane showed the characteristics to be expected of such materials.[17]

Acknowledgment.—This work was supported in part by a grant from the National Science Foundation, N.S.F. G-1091.

Experimental

2,3-Di-*sec*-amino-3-(*o*-nitrophenyl)-propiophenones.—The 2,3-di-N-morpholino- (I), the 2,3-di-N-piperidino- (II) and the 2,3-bis-dimethylamino-3-(*o*-nitrophenyl)-propiophenone (III) were prepared by stirring a suspension of 10 g. (0.0242 mole) of 2,3-dibromo-3-(*o*-nitrophenyl)-propiophenone[4] in 50 ml. of abs. ethanol with 0.097 mole of the corresponding amine for 15 minutes with ice-bath cooling. These reaction mixtures were allowed to stand in the refrigerator for 24 hr. The yellow-orange colored solids were removed by filtration and the filtrates concentrated to yield several more crops. These crude materials were combined in each run, washed with water and recrystallized from benzene–alcohol mixtures using charcoal to decolorize the solutions; see Table I for yields, anal. and m.p. Attempts to isolate α-amino or β-amino α,β-unsaturated ketones from these three reaction mixtures were unsuccessful. These products, I, II and III, also were obtained in slightly lower yields from α-bromo-2-nitrochalcone.[5]

Several attempts to prepare 2-bromo-3-morpholino-3-(*o*-nitrophenyl)-propiophenone by mixing α-bromo-2-nitrochalcone with one molar equiv. of morpholine in dry ether produced only small amounts of the diamino ketone I. Treatment of 2-nitrochalcone with N-bromomorpholine using Southwick's[18] procedure failed to give the α-halo-β-amino ketone in this case, and only small amounts of I could be isolated.

β-Diethylamino-(IV) and β-(N-Methylcyclohexylamino)-2-nitrochalcone (V).—The dibromoketone (0.05 mole) was

(14) N. H. Cromwell and W. R. Watson, *J. Org. Chem.*, **14**, 411 (1949).

(15) N. H. Cromwell, *et al.*, THIS JOURNAL, **71**, 3337 (1949).

(16) R. D. Campbell and N. H. Cromwell, *ibid.*, **79**, 3456 (1957).

(17) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 126.

(18) P. L. Southwick and W. L. Walsh, THIS JOURNAL, **77**, 405 (1955).

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TABLE I

PHYSICAL AND ANALYTICAL DATA

Amino ketones	No.	Yield, %	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3-(*o*-Nitrophenyl)-propiophenone										
2,3-Di-(N-morpholino)-	I	78	182–183	$C_{23}H_{27}N_3O_5$	64.92	6.40	9.88	65.27	6.51	10.19
2,3-Di-(N-piperidino)-	II	77	159–160	$C_{25}H_{31}N_3O_5$	71.23	7.41	9.97	71.31	7.40	9.89
2,3-Bis-(dimethylamino)-	III	75	144–145	$C_{19}H_{23}N_3O_5$	66.84	6.79	12.31	66.69	6.56	12.59
2-Nitrochalcone										
β-Diethylamino-	IV	76	112–113	$C_{19}H_{20}N_2O_3$	70.35	6.22	8.64	70.59	6.30	8.56
β-(N-Methylcyclohexylamino)-	V	63	145–146	$C_{22}H_{24}N_2O_3$	72.50	6.64	7.69	72.86	6.92	7.55
3-(*p*-Nitrophenyl)-propiophenone										
2,3-Di-(N-morpholino)-	VI	43	183	$C_{23}H_{27}N_3O_5$	64.92	6.40	9.88	65.31	6.23	9.76
2,3-Di-(N-piperidino)-	VII	26	165–166	$C_{25}H_{31}N_3O_3$	71.23	7.41	9.97	71.39	7.37	9.95
4-Nitrochalcone										
α-(N-Morpholino)-	VIII	30	159–160	$C_{19}H_{18}N_2O_4$	67.44	5.36	8.28	67.63	5.49	8.64
α-(N-Piperidino)-	IX	52	106–107	$C_{21}H_{21}N_2O_3$	71.41	5.99	8.33	71.62	6.29	8.51
α-Diethylamino-	X	99	102–103	$C_{19}H_{20}N_2O_3$	70.35	6.22	8.64	20.37	6.20	8.49
3-Nitrochalcone										
α-Diethylamino-	XI	90	92–93	$C_{19}H_{20}N_2O_3$	70.35	6.22	8.64	70.62	6.26	8.54

TABLE II

SUMMARY OF ULTRAVIOLET AND INFRARED SPECTRA

Compound	No.	Ultraviolet max.[a] λ, mμ	ε × 10⁻³	Infrared bands[b] Band	Wave no.	Rel. % abs.
2-Nitrochalcone	IV	247	16.4	C=O	1635	83
β-Diethylamino-		340	23.6	C=C	1618	57
				Ar	1600	50
β-(N-Methylcyclo-	V	243	16.4	C=O	1636	88
hexylamino)-		340	24.3	C=C	1620	69
				Ar	1600	60
4-Nitrochalcone (*trans*)		316	28.8[c]	C=O	1650	23[d]
				C=C	1605	25
				Ar	1593	27
α-[N-Morpholino]-	VIII	255	19.5	C=O	1682	15
		390	12.5	ArC=C	1593	26
α-[N-Piperidino]-	IX	255	19.5	C=O	1677	40
		413	13.8	ArC=C	1587	68
α-Diethylamino-	X	258	19.5	C=O	1677	35
		425	15.7	ArC=C	1597	37
3-Nitrochalcone	XI	256	22.3	C=O	1677	31
α-Diethylamino-		313	17.2	ArC=C	1595	45
		400	2.5			
2-(*p*-Nitrophenyl)-	XIV	255	20.5	N—H	3300	9[e]
3-Benzoylethylen-		279	19.4	C=O	1680	26
imine (*trans*)				Ar	1612	21
3-(*p*-Nitrophenyl)-		246	12.3	C=O	1686	75
propiophenone		274	10.7	Ar	1597	36
Bis-[1-(*o*-nitrophenyl)-	XV			Ar	1600	45[d]
3-phenyl-1,3-pro-				C=O	1560	60
panedione]copper				C=C	1530	65

[a] The ultraviolet spectra were determined with a Cary model 11 spectrophotometer in the range of 220–450 mμ in 95% ethanol using 10^{-4} molar solutions. [b] The infrared spectra were determined over the range of 4000–600 cm.$^{-1}$ at 25° using 0.10-mm. matched cells with a Perkin–Elmer model 21 instrument and 12–20 mg./ml. CCl_4 solutions, unless otherwise indicated. [c] See W. Black and R. Lutz, THIS JOURNAL, 77, 5134 (1955). [d] Determined as a Nujol mull. [e] Determined with a satd. soln. in CCl_4.

suspended in 100-ml. amounts of abs. ethanol and treated with 0.21 mole of diethylamine and 0.15 mole of N-methylcyclohexylamine, respectively. These reaction mixtures were allowed to stand in the dark at room temperature for two days. The solvent was removed under reduced pressure and the oil–solid residues mixed with 400 ml. of ether. The ether solutions were filtered to remove the by-product amine hydrobromides, washed with water and dried over anhyd. magnesium sulfate. Concentration of these ether solutions by evaporation followed by the addition of petroleum ether, b.p. 30–60°, caused the crystallization of the crude products which were recrystallized from 95% ethanol; see Table I for m.p.'s, yields and analyses. These yellow colored products were obtained in slightly lower yields using α-bromo-2-nitrochalcone in place of the dibromoketone.

2,3-Di-*sec*-amino-3-(*p*-nitrophenyl)-propiophenones.—The 2,3-di-N-morpholino- (VI) and the 2,3-di-N-piperidino-3-(*p*-nitrophenyl)-propiophenone (VII) were prepared by stirring at room temperature for 3 hr., suspensions of 12.39 g. (0.030 mole) of 2,3-dibromo-3-(*p*-nitrophenyl)-propiophenone in 250 ml. of abs. ethanol with 0.120 mole of the corresponding amine. The working up of these reaction mixtures in the usual manner produced both the diamino ketones VI and VII and the corresponding α-amino-α,β-unsaturated ketones, **α-morpholino-*p*-nitrochalcone (VIII) and α-piperidino-*p*-nitrochalcone (IX)**; these products were recrystallized from 95% ethanol, see Table I for yields, m.p.'s and analytical data.

α-Diethylamino-4-nitrochalcone (X) and α-Diethylamino-3-nitrochalcone (XI).—These orange-red products were obtained by mixing 2,3-dibromo-3-(*p*-nitrophenyl)-propiophenone and the *m*-nitrophenyl analog with three molar equivalents of diethylamine in abs. ethanol at ice-bath temperature. The reaction mixtures were allowed to stand for two days at room temperature and the products isolated in the usual manner and recrystallized from 95% ethanol; see Table I for data.

Hydrolysis of β-Amino and α-Amino-α,β-unsaturated Ketones.—(a) **β-Diethylamino-2-nitrochalcone (IV)** (1.0 g.) was refluxed for 16 hr. in 20 ml. of 15% sulfuric acid. The acid solution was extracted with ether and made basic with sodium hydroxide to recover 0.49 g. of IV. Evaporation of the ether extract and recrystallization from 95% ethanol produced 0.090 g. (22% yield) of *o*-nitrodibenzoylmethane,[19] m.p. 115–116°. This product gave a deep-red color with alcoholic ferric chloride.

A 0.05-g. sample of *o*-nitrodibenzoylmethane was dissolved in 10 ml. of 50% acetone–water and treated with a saturated solution of cupric acetate in 50% acetone–water. **The bis-[1-(*o*-nitrophenyl)-3-phenyl-1,3-propanedione]-copper** was filtered from the solution and recrystallized from dioxane and benzene; m.p. 287–288°, wt. 0.045 g. (80% yield).

Anal. Calcd. for $C_{31}H_{21}N_2O_8Cu$: Cu, 10.58. Found: Cu, 10.69.

A 0.025-g. sample of *o*-nitrodibenzoylmethane was dissolved in 5 ml. of 1:1 alcohol–chloroform and one molar equivalent of phenylhydrazine and a drop of gl. acetic acid added. The mixture was warmed and allowed to stand at

(19) S. Sugasawa and T. Kikkawa, *Ber.*, **54B**, 1613 (1921).

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room temperature for a day. The yellow crystalline product was recrystallized from 95% ethanol, 0.02 g. (63% yield), m.p. 178–180°. This product was identical with an authentic sample of 1,3-diphenyl-5-(*o*-nitrophenyl)-pyrazole.[6]

(b) β-(N-Methylcyclohexylamino)-2-nitrochalcone (V) was hydrolyzed in a similar manner, as in (a), to produce a 47% yield of *o*-nitrodibenzoylmethane. Almost half of the starting material was recovered after 12 hr. of reflux with 15% sulfuric acid.

(c) α-Diethylamino-4-nitrochalcone (X) (1.0 g.) was refluxed for 6 hr. with 20 ml. of 15% sulfuric acid and the reaction mixture cooled and extracted with ether. Evaporation of the ether extract produced an oily solid which was recrystallized from 95% ethanol after decolorizing with charcoal; m.p. 119–120°, wt. 0.70 g. (84.5% yield), *p-nitrobenzylphenyl diketone* (XII).

Anal. Calcd. for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12. Found: C, 67.09; H, 4.34.

A 0.027-g. (0.001 mole) sample of XII was heated for a few minutes with 0.108 g. (0.001 mole) of *o*-phenylendiamine in 5 ml. of abs. ethanol. Cooling the mixture produced 2-(*p*-nitrobenzyl)-3-phenylquinoxaline (XIII); recrystallized from 95% ethanol, m.p. 124–125°, wt. 0.292 g. (86% yield).

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 74.09; H, 4.29; N, 12.78.

(c) α-Diethylamino-3-nitrochalcone (XI) (1.0 g.) was refluxed with 20 ml. of 15% sulfuric acid for 3 hr., cooled and extracted with ether. Evaporation of the ether gave an oil which was dissolved in 5 ml. of abs. ethanol and warmed with 0.329 g. of *o*-phenylenediamine. Cooling produced 2-(*m*-nitrobenzyl)-3-phenylquinoxaline,[12] recrystallized from 95% ethanol, m.p. 120–121.5°, wt. 0.83 g. (78% yield).

2-(*p*-Nitrophenyl)-3-benzoylethylenimine (XIV).—A 4.13-g. (0.010 mole) sample of 2,3-dibromo-3-(*p*-nitrophenyl)-propiophenone was suspended in 50 ml. of abs. ethanol and the mixture saturated with anhydrous ammonia and allowed to stand in the dark at room temperature for one week. The dibromide dissolved in about three days. The solvent was removed under reduced pressure and the residue mixed with water and extracted with ether. Evaporation of the ether and recrystallization of the oily residue from 95% ethanol produced 2.23 g. (78% yield) of XIV, m.p. 142–143°. This product appears to be identical with that reported by Wieland[7] as either the ethylenimine ketone or a dimer having a piperazine structure, which he preferred. A mol. wt. determination by the cryoscopic method showed the structure of this product actually to be XIV.

No other identifiable products could be isolated from this reaction mixture.

LINCOLN, NEBRASKA

[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE[1]]

meso-Dihydroguaiaretic Acid and its Derivatives[2]

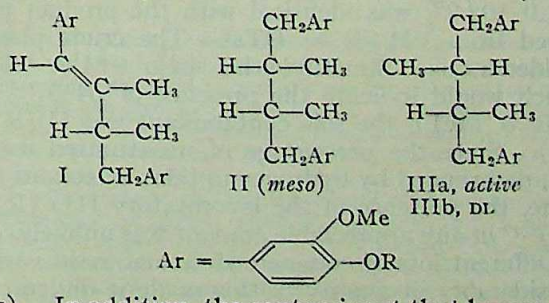
BY ANTHONY W. SCHRECKER

RECEIVED FEBRUARY 28, 1957

The contaminant of crude guaiaretic acid (I, R = H) has been identified as *meso*-dihydroguaiaretic acid (II, R = H). II (R = Me) and its DL-isomer have been synthesized by a stereospecific method. The infrared spectra of diastereoisomers in this series are discussed.

Guaiaretic acid (I, R = H), a key compound in the elucidation of the absolute configuration of lignans,[3] occurs in *Guaiacum officinale* L.[4] together with a number of related compounds.[5] Its isolation has, however, been complicated by the presence of a contaminant, which lowers the optical rotation of the crude product and from which it is not readily separated. Schroeter, who was the first to obtain pure I (R = H) (m.p. 99–100.5°, $[\alpha]_D$ −94° in ethanol),[6] informed Haworth[7] that his crude material was contaminated with an optically active (IIIa, R = H) and an inactive dihydro derivative of I (R = H), both of which occurred naturally in Guaiac resin; however, he never published these findings. He had previously prepared the dimethyl ethers of these dihydro compounds by reduction of I (R = Me) and assigned the *meso* configuration (II, R = Me) to the inactive ether, m.p. 100–101°, because of its mode of formation and because its diamino derivative could not be resolved.[6] Haworth,[7] however, prepared the same compound, m.p. 101–102°, by reduction of synthetic (DL)-I (R = Me) and named it "*dl*-dihydroguaiaretic acid dimethyl ether." He and Cartwright[8] later isolated I (R = Ac) and one of its dihydro derivatives from Guaiac resin after acetylation, but reported no optical rotations.[9]

Although it is generally assumed[4] that Schroeter's inactive dimethyl ether does possess the *meso* rather than the DL-configuration, confirmatory proof was desired. This was accomplished by a stereospecific synthesis of both II and IIIb (R = Me). In addition, the contaminant that lowers the rotation of crude I (R = H) was identified as its



(1) National Institutes of Health, Public Health Service, U. S. Department of Health, Education and Welfare.

(2) Presented in part at the XIVth International Congress of Pure and Applied Chemistry in Zurich, Switzerland, July 22, 1955; *cf.* Congress Handbook, p. 45.

(3) A. W. Schrecker and J. L. Hartwell, *J. Org. Chem.*, **21**, 381 (1956); THIS JOURNAL, **79**, 3827 (1957).

(4) For leading references, see (a) H. Erdtman in Paech and Tracey, "Modern Methods of Plant Analysis," Vol. III, Springer–Verlag, Berlin, 1955, p. 428; (b) W. M. Hearon and W. S. MacGregor, *Chem. Revs.*, **55**, 957 (1955).

(5) F. E. King and J. G. Wilson, Congress Handbook, XVIth International Congress of Pure and Applied Chemistry, Paris, 1957; *J. Chem. Soc.*, to be published.

(6) G. Schroeter, L. Lichtenstadt and D. Ireneu, *Ber.*, **51**, 1587 (1918).

(7) R. D. Haworth, C. R. Mavin and G. Sheldrick, *J. Chem. Soc.*, 1423 (1934).

(8) N. J. Cartwright and R. D. Haworth, *ibid.*, 948 (1947).

(9) Inactive dihydroguaiaretic acid dimethyl ether, m.p. 102–103°, was also obtained by methylation of nordihydroguaiaretic acid, isolated from *Larrea divaricata*: *cf.* C. W. Waller and O. Gisvold, *J. Am. Pharm. Assoc., Sci. Ed.*, **34**, 78 (1945).

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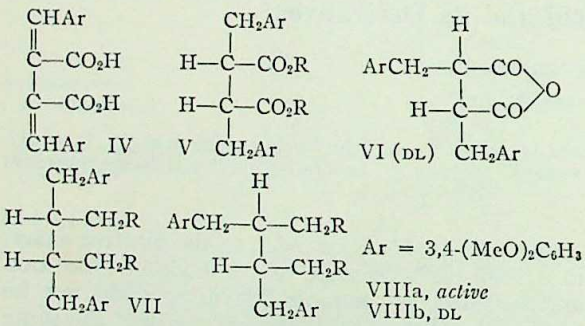
meso-dihydro derivative II (R = H), while none of the diastereoisomeric IIIa (R = H) could be detected. The present paper deals with these findings.

Haworth and Woodcock[10] have shown that reduction of diveratrylidenesuccinic acid (IV) afforded *meso*-diveratrylsuccinic acid (V, R = H), which was converted to DL-diveratrylsuccinic anhydride (VI) by heating with acetic anhydride. The configurational assignments are correct because careful saponification of VI yielded an acid which was different from V (R = H) and which could be resolved.[10] *meso*-2,3-Diveratryl-1,4-butanediol (VII, R = OH), previously obtained[11] by lithium aluminum hydride reduction of isomataireresinol dimethyl ether, has now been prepared from V (R = H or Me) by the same method. Following the procedure employed in the synthesis of IIIa (R = Me),[12] the ditosylate VII (R = OTs) was converted to II (R = Me), which melted at 101.5–102° and was identical with the known inactive dihydroguaiaretic acid dimethyl ether. Therefore, the latter is definitely *meso*. VI was converted similarly, *via* VIIIb (R = OH and OTs), to DL-dihydroguaiaretic acid dimethyl ether (IIIb, R = Me), m.p. 70.4–71.2°.



The preparation of guaiaretic acid from Guaiac resin *via* the sodium salt by Schroeter's procedure[6] led to a product, m.p. 83–86°, $[\alpha]_D$ −48 to −51° (ethanol), from which pure I (R = H), m.p. 100.8–101.3°, $[\alpha]_D$ −91°, was obtained in low yield by repeated recrystallizations from ethanol. Attempts to separate the mixture by chromatography on silica or alumina failed. *meso*-Dihydroguaiaretic acid (II, R = H), m.p. 87–88°, was isolated by recrystallizing the crude sodium salt repeatedly from dilute ethanol; its dimethyl ether, m.p. 101.9–102.2°, was identical with the product prepared from VII (R = OTs). The crude phenol yielded a mixed dimethyl ether, $[\alpha]_D$ −51 to −54°, which would indicate the presence of 54–57% of I (R = Me) if the sole contaminant was II (R = Me). Since the percentage of unsaturated material, determined by hydrogen uptake, was about the same, the presence of the levorotatory IIIa (R = Me)[6,12] in any appreciable amount was unlikely.

Different lots of commercial Guaiac resin varied considerably in quality[4a]; this made it difficult to obtain reproducible results. In subsequent experiments, therefore, *Guaiacum* heartwood was extracted by King and Wilson's[5] procedure. Pure I (R = H), identical in its properties with the compound isolated from the resin, was obtained by fractional recrystallization of the crude phenol. Pure II (R = Me or Ac, resp.), devoid of optical activity, was isolated by methylating or acetylating the material remaining in the mother liquors, then oxidizing the residual I. Saponification of II (R = Ac) afforded II (R = H), m.p. 87.8–88.6°. No trace of any derivative of IIIa could be detected.[13] This demonstrates the presence of II (R = H) in *Guaiacum officinale* L. and shows that it is the contaminant of crude guaiaretic acid.[14]

Infrared Spectra.—Solutions of diastereoisomers, as contrasted with those of enantiomers, generally do not possess identical infrared spectra.[17] The diastereoisomeric dihydrosmilagenin and dihydrosarsasapogenin, chloroform solutions of which exhibit essentially identical spectra,[18] are an exception to this rule. Similarly, the infrared spectra of II (R = Me), its dibromo and dinitro derivative,[19] and of the ditosylate VII (R = OTs) in chloroform solution differ from those of the corresponding diastereoisomers by only one or two minor bands (Fig. 1).[21] Interaction of the polar hydroxyl groups in the diols VII and VIII (R = OH) leads to somewhat larger differences. In all these compounds, free rotation between the asymmetric centers is possible. When free rotation is prevented by cyclization, the infrared spectra show pronounced differences in the 9–12.5 μ region, as in the case of the tetrahydrofurans VII and VIII (RR = O).

Experimental[22]

Veratrylidenesuccinic acid, prepared in 51–53% yield according to Horning and Walker,[23] melted at 172.5–173.5° dec. (lit. 169–171.5°,[23] 175°[24]). The dimethyl ester was obtained[25] by refluxing 30 g. of the acid with 450 ml. of

(10) R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 154 (1939).
(11) R. D. Haworth and L. Wilson, *ibid.*, 71 (1950).
(12) A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **77**, 432 (1955).
(13) This negative evidence renders the presence of (−)-dihydroguaiaretic acid (IIIa, R = H) (*cf.* ref. 7) unlikely, but does not exclude it definitively.
(14) The "guaiaretic acid" isolated by Doebner[15] and Herzig[16] was probably impure II (R = H); this follows from their methods of isolation and from the melting points of the substance and its derivatives.
(15) O. Doebner and E. Lücker, *Arch. Pharm.*, **234**, 590 (1896).
(16) J. Herzig and F. Schiff, *Monatsh.*, **18**, 714 (1897); *Ber.*, **30**, 378 (1897).
(17) F. A. Miller in Gilman, "Organic Chemistry," Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1953, p. 136.
(18) I. Scheer, R. B. Kostic and E. Mosettig, THIS JOURNAL, **77**, 641 (1955).
(19) The positions of the substituents in the dibromo and dinitro derivatives (Fig. 1) are postulated by analogy with the known bromination and nitration products of 3,4-dimethoxytoluene and 3,4-dimethoxypropylbenzene.[20]
(20) H. Thoms, *Ber.*, **36**, 854 (1903); T. G. H. Jones and R. Robinson, *J. Chem. Soc.*, **111**, 903 (1917).
(21) Only the 9–12.5 μ region is illustrated because the spectra of the *meso* compounds and the corresponding diastereoisomers were entirely identical in the 2–9 μ region. As expected,[17] the solution spectra of the optically active and DL-isomers were completely identical, while the Nujol mull spectra of the *meso* compounds were quite different from those of their diastereoisomers.
(22) Melting points were determined in Pyrex capillaries and are corrected. Infrared spectra were obtained with a Perkin–Elmer model 21 spectrometer; 0.1-mm. sodium chloride cells were used for chloroform solutions. Optical rotations were measured with 1.5% solutions in ethanol, unless specified otherwise.
(23) E. C. Horning and G. N. Walker, THIS JOURNAL, **74**, 5147 (1952).
(24) H. Stobbe and K. Leuner, *Ann.*, **380**, 75 (1911).
(25) Gordon N. Walker, unpublished procedure.

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methanol and 18 ml. of concd. sulfuric acid for 6 hr. and removing 360 ml. of the solvent by distillation. The chilled residue was treated with ether and ice-water, and the ether phase was washed with water and sodium carbonate solution, dried and evaporated. Distillation yielded 26.4 g. (80%) of pale yellow oil, b.p. 188–192° (0.5 mm.).

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17; OCH_3, 42.18. Found: C, 61.39; H, 6.47; OCH_3, 42.22.

Diveratrylidenesuccinic Acid (IV).—The published procedure[24] resulted in a very low yield, while other attempts[10] to isolate the compound failed. The following method gave reproducible results. A suspension of 21.4 g. of 93.6% sodium methoxide in 100 ml. of dry ether was treated with stirring in an ice-bath with a mixture of 46.1 g. of veratraldehyde, 24.2 g. of ethyl succinate and 150 ml. of ether dropwise during 1 hr., stirred in the ice-bath for another hour and kept at room temperature overnight. Ether was then distilled off while 300 ml. of absolute ethanol was added gradually to maintain the volume of liquid. Distillation was continued, with removal of 400 ml. of solvent, while 150 ml. of water was added in portions. The solution was cooled, diluted with water to about 300 ml. and neutralized to *p*H 7 with hydrochloric acid. Dark impurities were extracted with chloroform, and the solution was made strongly acid. The yellow gum was extracted repeatedly with boiling water until it became crystalline, in order to remove monoveratrylidenesuccinic acid. Digesting the dried solid with 150 ml. of boiling ethyl acetate and cooling provided 15.2 g. (26%) of yellow solid, m.p. 213–215° dec. A similar run yielded 22% of material, m.p. 217–219° dec. (lit.[24] 220°).

IV also was obtained from 12.95 g. of veratraldehyde, 22.9 g. of dimethyl veratrylidenesuccinate and 4.77 g. of sodium in 110 ml. of ethanol by the general method of Horning and Walker.[23] The reaction mixture was neutralized with 26 ml. of 2 *N* hydrochloric acid, extracted with chloroform and made strongly acid. The yellow solid, digested with 150 ml. of boiling ethyl acetate, yielded 26.1 g. (81%) of IV, m.p. 217° dec. Refluxing the acid with acetyl chloride[24] gave **diveratrylidenesuccinic anhydride**, yield 92%, orange-red plates from benzene, m.p. 172–173° (lit.[24] 172–173°).

***meso*-Diveratrylsuccinic acid (V, R = H)**, previously obtained[10] by sodium-amalgam reduction of a reaction mixture containing IV, was prepared more conveniently by reducing 10.76 g. of IV in 320 ml. of 10% sodium hydroxide with 32 g. of Raney nickel–aluminum alloy at 90°.[26] The crude acid was redissolved in dilute sodium hydroxide and reprecipitated by stirring the solution into dilute hydrochloric acid; yield 10.78 g. (99%), m.p. 198–215°. Recrystallization from glacial acetic acid afforded 6.14 g. (57%) of colorless needles, m.p. 222–223° dec. (lit.[10] 223–224°).

V was also prepared by hydrogenating 15.1 g. of IV in 78 ml. of *N* sodium hydroxide with 3 g. of W-7 Raney nickel catalyst[27] at 80° and 1000 p.s.i. for 18 hr. The filtrate was acidified and the precipitate recrystallized from glacial acetic acid; yield 9.37 g. (62%), m.p. 221–222° dec.

Dimethyl *meso*-Diveratrylsuccinate (V, R = Me).—A suspension of 3.12 g. of V (R = H) in 30 ml. of acetone and 30 ml. of methanol was treated with ethereal diazomethane (distilled from 8.2 g. of nitrosomethylurea), kept for 24 hr., evaporated and the residue dissolved in chloroform. The solution was washed with aqueous sodium bicarbonate and sodium chloride, dried and concentrated with addition of ethanol to yield 3.06 g. (92%) of colorless needles, m.p. 142.2–143.5°. A sample, chromatographed on neutral alumina, eluted with chloroform and recrystallized from ethanol, melted at 143.2–143.7°.

Anal. Calcd. for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77; OCH_3, 41.70. Found: C, 64.61; H, 6.85; OCH_3, 41.60.

DL-Diveratrylsuccinic anhydride (VI)[10] crystallized from benzene–hexane in rosettes of colorless prisms, m.p. 111–113° (lit.[10] 110–112°).

***meso*-2,3-Diveratryl-1,4-butanediol (VII, R = OH)** was prepared by the procedure employed for analogous diols,[12] except that the diacid (V, R = H) (2.0 g.) or the diester (V, R = Me) (2.8 g.) was added directly to an ice-cold suspension of lithium aluminum hydride (2.0 g.) in tetrahydrofuran, which was then stirred at room temperature for 3 hr., refluxed in the case of the acid for 0.5 hr. and decomposed as usual.[12] The residue obtained from the combined filtrate and ethanol extract was dissolved in ethyl acetate and the solution washed with water, dried, concentrated and diluted with hexane. Scratching caused slow separation of colorless rhombic plates; yields 62 and 75%, m.p.'s 90–92° and 91–93°, respectively, from V (R = H) and V (R = Me). Recrystallization from ethyl acetate–hexane afforded a product, m.p. 93.1–94.0°, unchanged after further recrystallization. Haworth and Wilson[11] report prisms, m.p. 94–95° for the same compound, prepared by reduction of isomatairesinol dimethyl ether.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.68; H, 7.53.

Heating the diol with potassium hydrogen sulfate[11] gave ***meso*-3,4-diveratryltetrahydrofuran (VII, RR = O)**, which

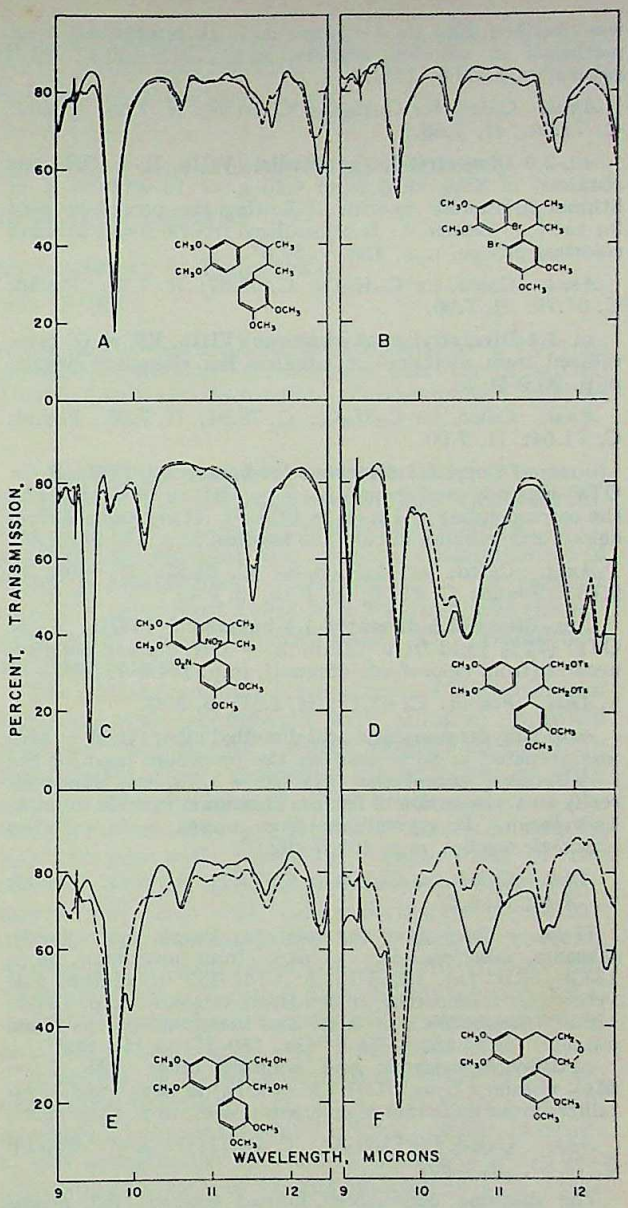

Fig. 1.—Infrared absorption spectra in chloroform of the optically active (————) and *meso* (— — —) isomers of: A, dihydroguaiaretic acid dimethyl ether; B, dibromo-A; C, dinitro-A; D, ditosyl-2,3-diveratryl-1,4-butanediol; E, 2,3-diveratryl-1,4-butanediol; F, 3,4-diveratryltetrahydrofuran.

(26) E. Schwenk, D. Papa, B. Whitman and H. F. Ginsberg, *J. Org. Chem.*, **9**, 175 (1944).
(27) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 176.

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was purified like its (−)-isomer.[12] It crystallized from methanol in colorless leaflets, m.p. 120.0–120.4° (lit.[11] prisms, m.p. 114–115°).

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.14; H, 7.68.

DL-2,3-Diveratryl-1,4-butanediol (VIIIb, R = OH) was obtained in 88% yield from 4.10 g. of VI and 3.1 g. of lithium aluminum hydride, following the procedure used for the (−)-isomer.[12] It crystallized from benzene in small colorless prisms, m.p. 128.7–129.6°.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.79; H, 7.96.

DL-3,4-Diveratryltetrahydrofuran (VIIIb, RR = O) crystallized from methanol in colorless flat elongated prisms, m.p. 90.0–90.5°.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.04; H, 7.90.

meso-Ditosyl-2,3-diveratryl-1,4-butanediol (VII, R = OTs) was prepared from VII (R = OH) in 96% yield like the corresponding VIIIa (R = OTs).[12] It crystallized from chloroform–ethanol in colorless needles, m.p. 140.5–141.0°.

Anal. Calcd. for $C_{36}H_{42}O_{11}S_2$: C, 61.87; H, 6.06; S, 9.18. Found: C, 61.76; H, 6.15; S, 9.46.

DL-Ditosyl-2,3-diveratryl-1,4-butanediol (VIIIb, R = OTs) (77% yield from VIIIb, R = OH) formed colorless needles (from chloroform–ethanol), m.p. 174.5–175.5°.

Anal. Found: C, 62.12; H, 6.17; S, 8.83.

meso-Dihydroguaiaretic acid dimethyl ether (II, R = Me) was prepared in 83% yield by the procedure used for the (−)-isomer,[12] except that VII (R = OTs) was added directly to a suspension of lithium aluminum hydride in tetrahydrofuran. It crystallized from methanol in colorless prismatic needles, m.p. 101.5–102.0°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.74; H, 8.62.

II (R = Me) gave the following known derivatives[19]: **dibromo**, colorless silky needles (from methanol), m.p. 133.3–133.9° (lit. 130.5–131.5°,[6] 131–132°[7]); **dinitro**, pale yellow flat transparent prisms (from ethanol), m.p. 138.2–138.9° (metastable), or cubic and hexagonal prisms (from ethanol), m.p. 152.9–153.6° (lit. 150–151°,[6] 151–152°[7]).

DL-Dihydroguaiaretic acid dimethyl ether (IIIb, R = Me), obtained from VIIIb (R = OTs) in 81% yield, crystallized from methanol in colorless prisms, m.p. 70.4–71.2°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.83; H, 8.30.

The dibromo derivative[19] formed colorless flat prisms (from methanol), m.p. 104.0–104.8°.

Anal. Calcd. for $C_{22}H_{28}Br_2O_4$: C, 51.18; H, 5.47; Br, 30.96. Found: C, 51.16; H, 5.35; Br, 30.91.

The dinitro derivative,[15] pale yellow flat prisms from chloroform–ethanol, melted at 181.1–181.9°.

Anal. Calcd. for $C_{22}H_{28}N_2O_8$: C, 58.92; H, 6.29; N, 6.25. Found: C, 58.75; H, 6.07; N, 6.05.

The following known derivatives were prepared from (−)-dihydroguaiaretic acid dimethyl ether[12] (IIIa, R = Me) and recrystallized from methanol: dibromo, colorless shiny flat prisms, m.p. 122.5–123.0° (lit.[6] 121–122°); dinitro, lemon-yellow flat prisms, m.p. 124.0–124.8° (lit.[6] 122–123°).

Guaiaretic Acid (I, R = H). (a) From Guaiac Resin.—The sodium salts (60–61 g.), obtained from 450 g. of resin[28] by Schroeter's procedure,[6] were suspended in 300 ml. of hot methanol and treated with 30 ml. of glacial acetic acid. The mixture was filtered (Celite) and the residue washed with 100 ml. of methanol. The filtrate and washings, diluted with 250 ml. of water, abandoned 34–35 g. of colorless flakes, m.p. 83–86°, $[\alpha]^{20}D$ −48 to −51°.[29] This crude phenol (11 g.), recrystallized thrice from ethanol, afforded 1.3 g. of I (R = H), m.p. 100.8–101.3° (lit. 100–101°,[5] 99–100.5°[6]), $[\alpha]^{20}D$ −91° (lit. −91°,[5] −94°[6]).

(b) From the Heartwood.[5]—The material soluble in both hot hexane and methanol (278 g.)[30] from 45.4 kg. of *Guaiacum officinale* L. wood chips was treated with 800 g. of 5% sodium hydroxide. The precipitate was collected after 64 hr. and additional sodium salt obtained by increasing the alkali concentration to 7%. The salts were washed with 7% sodium hydroxide and acetone, suspended in water and decomposed with carbon dioxide. The mixed phenols (120 g.) were recrystallized first from 3.5 l. of hexane (yield 87 g., $[\alpha]D$ −61°), then from 65% methanol (by vol.) (yield 75 g., $[\alpha]D$ −67°) and finally several times from 1.3 vol. of ethanol (thorough chilling, systematic recrystallization of second and third crops). The yield of pure I (R = H), m.p. 100.8–101.4°, $[\alpha]^{22}D$ −91°, was 29 g.

Methylation[6] of I (R = H), followed by chromatography on alumina, elution with chloroform and crystallization from ethanol, provided **guaiaretic acid dimethyl ether** (I, R = Me), colorless prismatic needles, m.p. 92.3–92.8° (lit.[6] 94–95°), $[\alpha]^{22}D$ −94° (*c* 1.00) (lit.[5,6] −92°).

Refluxing 1.0 g. of I (R = H) with 5 ml. of acetic anhydride and 1 g. of sodium acetate for 1 hr. and treating the mixture with water yielded 1.23 g. (98%) of **diacetylguaiaretic acid** (I, R = Ac), m.p. 83–85°, which after chromatography as above and recrystallization from aqueous methanol formed colorless prisms, m.p. 84.0–85.0° (lit.[8] 86–87°), $[\alpha]^{20}D$ −66°.

Anal. Calcd. for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.89; H, 7.04.

meso-Dihydroguaiaretic Acid (II, R = H). **(a) From the Resin.**—The mixed sodium salts[6] (24.6 g.) were recrystallized thrice from aqueous ethanol, decomposed with acetic acid in methanol, and the product (5.4 g.) was recrystallized from 60% methanol (by vol.) to yield 4.2 g. of colorless rectangular plates, m.p. 87–88°, $[\alpha]^{20}D$ −0.1 ± 0.1°.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.44; H, 7.86.

Methylation[6] and chromatography afforded **II (R = Me)**, colorless prismatic needles (from methanol), m.p. 101.9–102.2°, no depression with a sample prepared from VII (R = OTs).

(b) From the Wood.—The hexane, aqueous methanol and ethanol mother liquors from the purification of I (R = H) were evaporated, and a portion of the residual mixed phenols was methylated. The mixed dimethyl ethers were treated with peracetic acid in acetic acid at room temperature to oxidize I (R = Me). The solution was diluted with water, extracted with benzene, and the extract was washed with alkali, dried and chromatographed on alumina. Elution with benzene and crystallization from aqueous methanol afforded II (R = Me), m.p. 101.4–102.1° (no depression with a sample prepared from VII, R = OTs), $[\alpha]^{22}D$ +0.1 ±0.1° (*c* 8.0, chloroform). No IIIa (R = Me) ($[\alpha]D$ −31° in chloroform[12]) could be detected.

Another portion of the residual phenols was acetylated and the product dissolved in benzene and treated with osmium tetroxide and pyridine.[3] The mixture was chromatographed on alumina, which retained preferentially the black osmate complex formed from I (R = Ac). Elution with benzene and crystallization from ethanol provided ***meso*-diacetyldihydroguaiaretic acid** (II, R = Ac), m.p. 115.2–116.0° (lit.[8] 112°), $[\alpha]^{19}D$ −0.04 ± 0.05° (*c* 4.0, chloroform). No other compound could be detected in the mother liquor.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.46; H, 7.05.

Saponification of II (R = Ac) with potassium hydroxide in 50% ethanol afforded II (R = H) as small elongated plates (from 60% methanol), m.p. 87.8–88.6°.

Acknowledgments.—The author is greatly indebted to Dr. Frederick E. King of British Celanese Ltd., London, for a summary of his procedure[5] in advance of publication and other valuable suggestions, and to Dr. E. F. Woodward of S. B. Penick & Co., New York, for his collaboration in

(28) Glassy Select Guaiac Gum N.F., S. B. Penick & Co., New York, N. Y.

(29) Other lots gave much lower yields. Methylation[6] of the crude phenol provided a mixed dimethyl ether, m.p. 93.5–94.5°, $[\alpha]^{20}D$ −51 to −54° (*c* 1).

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the extraction of Guaiac wood. Miss Mary M. Trail carried out a portion of the experimental procedures and the determination of rotations and spectra. Microanalyses were performed by Dr. W. C. Alford and his staff.

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE[1]]

The Absolute Configuration of Lignans[2]

BY ANTHONY W. SCHRECKER AND JONATHAN L. HARTWELL

RECEIVED FEBRUARY 16, 1957

Guaiaretic acid dimethyl ether (I) has been correlated stereochemically with L-3,4-dihydroxyphenylalanine (VI) *via* (−)-4-(3,4-dimethoxyphenyl)-3-methyl-2-butanone (II), (−)-3,4-dimethoxy-α-methylhydrocinnamic acid (III, X = OH) and (−)-3,4-dimethoxy-α-methylphenethylamine (IV). I, II, III and IV belong to the D-series. This establishes the absolute configuration of a number of naturally-occurring lignans.

The stereochemical correlation of guaiaretic acid dimethyl ether[3] (I)[4] with (−)-3,4-dimethoxy-α-methylhydrocinnamic acid[7] (III, X = OH) has been reported in a preceding communication.[8] The enantiomer of III (X = OH) has the same sign and about the same magnitude of rotation as (+)-α-methylhydrocinnamic acid,[7,9] which by the Curtius degradation[7,10,11] yields the same (+)-α-methylphenethylamine that has been obtained[12,13] from D-phenylalanine. This led us to postulate that III, and hence I, possess the absolute D-configuration.[14]

A more rigorous demonstration than this proof by analogy has now been accomplished by correlating III with L-3,4-dihydroxyphenylalanine (VI), a natural amino acid, the absolute configuration of which is established.[17] The object of the present report is to present these new findings and the experimental details missing from our preliminary communication.

The osmate complex formed from I with osmium tetroxide was decomposed with alkaline mannitol solution,[18] a procedure which proved to be more satisfactory than reductive decomposition with alkaline formaldehyde.[19] The crude diol thus obtained, presumably a mixture of diastereoisomers, was cleaved with periodate. Separation of the oily (−)-4-(3,4-dimethoxyphenyl)-3-methyl-2-butanone (II), $[\alpha]_D$ −35° (chloroform), from veratraldehyde was accomplished with Girard reagent. A number of pilot experiments showed that this treatment did not cause any detectable racemization.[20] II was characterized by its semicarbazone, m.p. 159.5–160°, $[\alpha]_D$ −48° (chloroform).

Reaction of (−)-3,4-dimethoxy-α-methylhydrocinnamoyl chloride[7] (III, X = Cl) with a nearly equivalent amount of methylmagnesium bromide at low temperature afforded a mixture from which the semicarbazone of II was isolated in 17% yield. The product rotated −47.5° (chloroform) and proved to be identical with the semicarbazone obtained from I. The optical antipode of II, again isolated as the semicarbazone, $[\alpha]_D$ + 47°, was similarly derived from the enantiomer of III (X = Cl). Reaction of the acid chloride with dimethylcadmium,[21] while affording better yields (up to 46%), was always accompanied by partial racemization.

The Curtius degradation of III (X = Cl) to (−)-3,4-dimethoxy-α-methylphenethylamine[7] (IV) proves[11] that IV and III (and hence I and II) have identical configurations. IV and VI were corre-

(1) National Institutes of Health, Public Health Service, U. S. Department of Health, Education and Welfare.

(2) Presented in part before the Biological Chemistry Division of the American Chemical Society at Miami, Florida, April 8, 1957; *cf.* Abstracts of Papers, **131**, 19-C (1957).

(3) G. Schroeter, L. Lichtenstadt and D. Ireneu, *Ber.*, **51**, 1587 (1918); A. W. Schrecker, THIS JOURNAL, **79**, 3823 (1957).

(4) The projection formulas, which are drawn according to Klyne,[5] conform to the Fischer convention and represent absolute configurations.[5,6]

(5) J. A. Mills and W. Klyne in Klyne, "Progress in Stereochemistry," Academic Press, Inc., New York, N. Y., 1954, p. 178; W. Klyne in Braude and Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, p. 74.

(6) J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, *Nature*, **168**, 271 (1951).

(7) A. W. Schrecker, *J. Org. Chem.*, **22**, 33 (1957).

(8) A. W. Schrecker and J. L. Hartwell, *ibid.*, **21**, 381 (1956).

(9) (a) F. S. Kipping and A. E. Hunter, *J. Chem. Soc.*, **83**, 1005 (1903); (b) R. H. Pickard and J. Yates, *ibid.*, **95**, 1011 (1909).

(10) L. W. Jones and E. S. Wallis, THIS JOURNAL, **48**, 169 (1926).

(11) Retention of configuration in the Curtius rearrangement is well established; *cf.* C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, p. 500.

(12) P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).

(13) Retention of configuration in lithium aluminum hydride reductions has been demonstrated by D. S. Noyce and D. B. Denney, THIS JOURNAL, **72**, 5743 (1950).

(14) The assignment of the D-configuration to I, II, III, IV and V conforms to the convention proposed by Klyne and by McCasland,[15] according to which formulas are drawn so that the lower-numbered end of the chain[16] is at the top. The prefix "D" then refers to the fact that the reference group[15b] is to the right. VI, VII, VIII, IX and X are L in agreement with the nomenclature conventionally[5] used for amino acids and their derivatives. The shift from L to D in the conversion of X to V does not represent an actual change of configuration but is simply a matter of nomenclature. In X, the NHTs group is the reference group,[15b] while it becomes the chief function[16] and CH_3 becomes the reference group in V. Formula V (first series of formulas) is derived from V (second series) by a double interchange of substituents; therefore, both formulas represent an identical configuration.

(15) (a) W. Klyne, *Chemistry & Industry*, 1022 (1951); (b) G. E. McCasland, "A New General System for the Naming of Stereoisomers," Chemical Abstracts, Columbus, Ohio, 1953.

(16) The *Chem. Abstracts* numbering system gives the smallest number for the chief function (determined from the "order of precedence"), then for double bonds; *cf. C. A.*, **46**, 1211 (1952).

(17) E. Waser and M. Lewandowski, *Helv. Chim. Acta*, **4**, 657 (1921); E. Waser and E. Brauchli, *ibid.*, **7**, 740 (1924). *Cf.* A. Neuberger, *Advances in Protein Chem.*, **4**, 319 (1948); J. P. Greenstein, *ibid.*, **9**, 124 (1954); W. Klyne, ref. 5, pp. 184 and 88, resp.

(18) R. Criegee, B. Marchand and H. Wannowius, *Ann.*, **550**, 99 (1942).

(19) H. Reich, M. Sutter and T. Reichstein, *Helv. Chim. Acta*, **23**, 170 (1940).

(20) Under different conditions, purification of optically-active ketones with Girard reagent may lead to extensive racemization; *cf.* K. Mislow and J. Brenner, THIS JOURNAL, **75**, 2319 (1953); R. B. Turner, *ibid.*, **72**, 878 (1950).

(21) A. Campbell and J. Kenyon, *J. Chem. Soc.*, 25 (1946).

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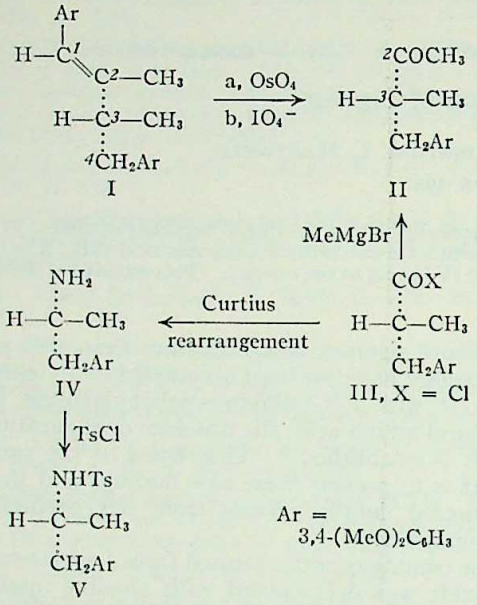
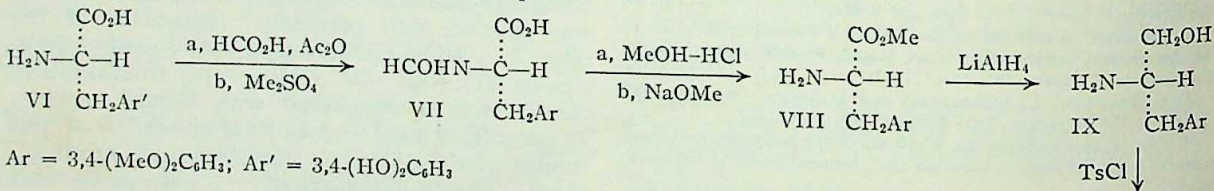
lated by a series of steps adapted from analogous reactions used in the phenylalanine and tyrosine series. Formylation[22] and methylation[23] of VI



provided *N*-formyl-L-3,4-dimethoxyphenylalanine (VII), m.p. 125–126°, $[\alpha]_D$ +72° (ethanol). Simultaneous[24] removal of the formyl group and



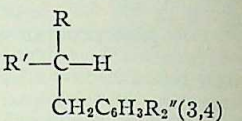
Ar = 3,4-$(MeO)_2C_6H_3$; Ar′ = 3,4-$(HO)_2C_6H_3$

esterification by means of methanolic hydrogen chloride yielded L-3,4-dimethoxyphenylalanine methyl ester (VIII) hydrochloride, m.p.158 –159° dec., $[\alpha]_D$ +7° (methanol). Reduction of VIII with lithium aluminum hydride[13,25] afforded L-3,4-dimethoxyphenylalaninol (IX), m.p. 79–80°, $[\alpha]_D$ −21.5° (ethanol), the *O,N*-ditosylate X, $[\alpha]_D$ −58° (ethanol), of which was further reduced[12] to *N*-tosyl-D-3,4-dimethoxy-α-methylphenethylamine[14] (V), m.p. 75.6–76.6°, $[\alpha]_D$ −29° (ethanol). Since IV yielded by direct tosylation the same levorotatory tosylate V, its absolute D-configuration,[14] and hence that of III, II and I is demonstrated unequivocally.

This result confirms the configurations previously[8] derived from rotational values. The assumption that introduction of phenolic ether groups into a benzene ring not directly attached to the asymmetric center would not greatly influence the sign and value of the optical rotation is in agreement with Tchúgaeff's rule.[26] Comparative rotational data on several phenyl and 3,4-dimethoxyphenyl derivatives, the configuration of which is pertinent to the present investigation, are shown in Table I.

TABLE I

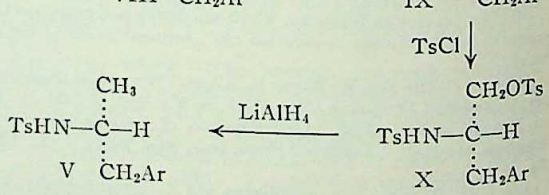
SPECIFIC AND MOLECULAR ROTATIONS OF COMPOUNDS OF THE TYPE



R	R′	$[\alpha]_D$, degrees R″ = H	$[\alpha]_D$, degrees R″ = OMe	$[M]_D$, degrees R″ = H	$[M]_D$, degrees R″ = OMe	Solvent
CO_2H	NHCHO	+75[a]	+72	+145	+181	Ethanol
CO_2Me	NH_2·HCl	+17	+ 7	+ 37	+ 19	Methanol
CH_2OH	NH_2	− 4[b]	−21	− 6	− 45	Ethanol
CH_2OTs	NHTs	−51[c,d]	−58	−232	−301	Ethanol
CH_3	NH_2	−34[c,e]	−32[g]	− 47	− 62	Ethanol
CH_3	CO_2H	−28[c,f]	−28	− 46	− 63	Chloroform

[a] Ref. 22. [b] Ref. 25. [c] Calculated from the reported rotation of the enantiomer. [d] Ref. 12. [e] W. Leithe, *Ber.*, **65**, 660 (1932). [f] Ref. 9b. [g] Ref. 7.

Discussion of the stereochemistry of I is not complete without mentioning the arrangement of the substituents about the ethylenic linkage. The *trans* configuration of sphingosine has been proved[27] by application of Bruni's rule.[28] By a similar reasoning it appears very likely that the hydrogen at C_1 and the methyl group at C_2 are *trans* in I. Indeed, *meso*-dihydroguaiaretic acid dimethyl ether[3] and I are isomorphous, as shown in Fig. 1, and hence the shape of their molecules should be very similar.



The relative configuration of a number of naturally-occurring lignans,[29] especially diarylbutanes (matairesinol, hinokinin, savinin) and 4-aryltetralins (conidendrin, podophyllotoxin, desoxypodophyllotoxin, α- and β-peltatin, galbulin), is now established; in addition it has been demonstrated that they possess the same configuration at C_3 as I.[30] The present findings, therefore, establish their absolute configuration.[31] The configuration

(22) E. Fischer and W. Schoeller, *Ann.*, **357**, 1 (1907); *cf.* V. du Vigneaud and C. E. Meyer, *J. Biol. Chem.*, **98**, 295 (1932).

(23) N. Izumiya and A. Nagamatsu, *Bull. Chem. Soc. Japan*, **25**, 265 (1952); *C. A.*, **48**, 3929*i* (1954).

(24) S. G. Waley, *Chemistry & Industry*, 107 (1953).

(25) P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

(26) L. Tchúgaeff, *Ber.*, **31**, 360 (1898); *cf.* ref. 5, pp. 204 and 78, resp.

(27) G. Fodor and J. Kiss, *Nature*, **171**, 651 (1953).

(28) G. Bruni and F. Gorni, *Atti reale accad. Lincei*, [5] **8, I**, 454 (1899); [5] **13, I**, 626 (1904); *Chem. Zentr.*, **70, II**, 4 (1899); **75, II**, 412 (1904).

(29) *Cf.* W. M. Hearon and W. S. MacGregor, *Chem. Revs.*, **55**, 957 (1955); H. Erdtman in Paech and Tracey, "Modern Methods of Plant Analysis," Vol. III, Springer–Verlag, Berlin, 1955, p. 428.

(30) A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **77**, 432 (1955); *cf.* J. L. Hartwell, A. W. Schrecker, J. Leiter and W. L. Shilling, *Abstracts of Papers, Am. Chem. Soc.*, **125**, 11M (1954).

(31) The formulas previously published by us[30] to show the relative configurations of a number of lignans also happen to represent their absolute configurations. These formulas were drawn according to Linstead's "black dot" convention,[32] in which a black dot indicates that the hydrogen atom is above (or in front of) the molecule. In the Klyne and McCasland convention,[15] rings are drawn edgewise, so that the right side (numbered 1, 2, 3, 4) represents the front edge; the configuration at an asymmetric atom is then D, if the reference group[15b] is to the right. Thus a "black dot" indicates a D-configuration at the corresponding asymmetric center.[33]

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of tetrahydrofuran derivatives, such as lariciresinol and pinoresinol, is not yet known in all the details, but that at two of their asymmetric carbon atoms also has been correlated with I[30,34] and now can also be expressed in absolute terms. Thus the stereochemistry of another important class of natural products has largely been elucidated.

Experimental[36,37]

D-(−)-4-(3,4-Dimethoxyphenyl)-3-methyl-2-butanone (II). (a) From Guaiaretic Acid Dimethyl Ether[3] (I).—A solution of 2.80 g. of I, m.p. 92.3–92.8°, $[\alpha]^{22}D$ −94° (*c* 1.00, ethanol), in 75 ml. of dry ether and 1.4 ml. of dry pyridine[18] was kept with 2.08 g. of osmium tetroxide in 75 ml. of dry ether for 24 hr. at room temperature and the supernatant decanted from the black resin. Vacuum-evaporation provided a small amount of additional complex. The combined residues in 40 ml. of methylene chloride were shaken with 16 g. of mannitol and 5.33 g. of potassium hydroxide in 160 ml. of water for 1.5 hr., and the organic layer was washed with 0.5 *N* sulfuric acid, 0.5 *N* sodium hydroxide, then worked up.[37] The yellow gum, presumably a mixture of diastereoisomeric glycols, could not be crystallized. Its solution in 40 ml. of methanol was kept with 2.52 g. of sodium metaperiodate and 0.71 ml. of glacial acetic acid in 60 ml. of water at room temperature during 2 hr., diluted with more water and extracted with chloroform four times. The extracts were washed with aqueous sodium bicarbonate and evaporated.[37] The residual yellow oil (3.06 g.) was refluxed with 8.0 g. of Girard reagent P,[38] 8.0 ml. of glacial acetic acid and 106 ml. of methanol for 1 hr., the solution cooled, poured into an ice–water slurry (about 570 ml.) containing 6.66 g. of sodium carbonate and extracted twice with ether. The aqueous phase was then treated with 100 ml. of 8 *N* sulfuric acid, covered with 200 ml. of ether and kept with frequent shaking during 0.5 hr. It was then extracted twice with additional ether (150 + 100 ml.), and the extracts were washed with 0.5 *N* sulfuric acid and sodium bicarbonate.[37] The pale oil thus obtained (1.87 g., 107%) was further purified by repeating the treatment with Girard reagent P.[39] Distillation in a bulb tube assembly[40] provided 1.51 g. (86.5%) of colorless oil, b.p. 95° (air-bath temperature) (0.005 mm.), $n^{20}D$ 1.5252, $[\alpha]^{20}D$ −35.3° (*c* 4.30, chloroform).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.43, 70.10; H, 8.14, 8.10.

The semicarbazone was prepared by heating 1.0 g. of the ketone in 15 ml. of 30% methanol with 1 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate for a short time. Chilling yielded 1.19 g. (95%) of colorless solid, m.p. 158–159°, which after recrystallization from 30% methanol formed shiny scales, m.p. 159.5–160.0°, $[\alpha]^{20}D$ −48.0° (*c* 2.00, chloroform).

Anal. Calcd. for $C_{14}H_{21}N_3O_3$: C, 60.19; H, 7.58; N, 15.04. Found: C, 60.05; H, 7.57; N, 15.08.

II also was obtained in low yield by stirring 3.4 g. of I in 5 ml. of methylene chloride with 25 ml. of hydrogen peroxide–*t*-butyl alcohol reagent,[41] 20 mg. of vanadium pentoxide[42] and 5 g. of anhydrous sodium sulfate magnetically during 1 hr., keeping for 64 hr., and evaporating the filtrate *in vacuo*. Treatment with Girard reagent, then with semicarbazide provided 0.15 g. of impure semicarbazone, m.p. 155–156.5°, $[\alpha]^{20}D$ −45° (chloroform).

(b) From D-(−)-3,4-Dimethoxy-α-methylhydrocinnamic Acid[7] (III, X = OH).—The acid chloride (III, X = Cl), prepared by refluxing 1.95 g. of the acid with 2.25 ml. of oxalyl chloride for 1 hr., evaporating *in vacuo* and re-evaporating twice after addition of dry benzene, was dissolved in 14 ml. of dry ether. The solution was stirred magnetically with exclusion of moisture and treated dropwise at −74° during 10 minutes with 12.1 ml. of 0.7 *M* ethereal methylmagnesium bromide, stirred at −74° for another hour and allowed to come to −10° over a period of 45 minutes. It was then treated dropwise at −10° with water and 2 *N* sulfuric acid. The aqueous phase was extracted with additional ether, and the ether solutions were washed with 0.5 *N* sulfuric acid and bicarbonate, then worked up as usual.[37] The residual oil, treated with semicarbazide, provided 0.41 g. (17%) of the **semicarbazone**, which recrystallized thrice from 30% methanol melted at 159.3–160.0° (no depression with material prepared under (a)) and had $[\alpha]^{20}D$ −47.5° (*c* 1.99, chloroform).

A few other runs, carried out without any change in procedure, led to a considerably racemized product.

L-(+)-4-(3,4-Dimethoxyphenyl)-3-methyl-2-butanone semicarbazone, obtained in 17% yield from L-(+)-3,4-dimethoxy-α-methylhydrocinnamic acid,[7] had m.p. 156.5–157.5°, $[\alpha]^{21}D$ +47° (*c* 2.00, chloroform), and an infrared spectrum identical with that of the (−)-semicarbazone prepared above under (a). It was also prepared, although partially racemized, by treating the acid chloride with dimethylcadmium. In a representative run, 18.2 ml. of 0.65 *M* methylmagnesium bromide was stirred and refluxed with 1.19 g. of cadmium chloride (precipitated from its aqueous

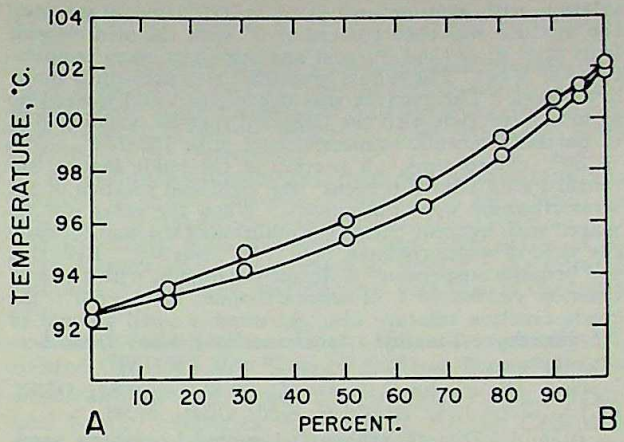

Fig. 1.—Initial and final melting temperatures of mixtures of: A, guaiaretic acid dimethyl ether (I), and B, *meso*-dihydroguaiaretic acid dimethyl ether (ref. 3), as determined by the method of H. Rheinboldt, *J. prakt. Chem.*, 111, 242 (1925).

(32) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, THIS JOURNAL, **64**, 1985 (1942).

(33) While the "black dot" convention has primarily been employed for cyclic compounds, it was also used in our previous paper[30] to illustrate the configuration of open-chain lignans, in order to show their relation to the aryltetralin derivatives. Examination of a three-dimensional model demonstrates the equivalence of our previous formula XIII[30] and the present formula I. The aryltetralins were all numbered as 4-aryl derivatives so as to illustrate more clearly their relationship to guaiaretic acid. This numbering system is correct for derivatives of 4-aryl-2-naphthoic acid (*e.g.*, conidendrin), but it does not conform to standard nomenclature[16] for compounds like podophyllotoxin (our previous formula IV[30]), which are named more correctly as derivatives of 1-aryl-2-naphthoic acid. The configuration of podophyllotoxin, expressed previously[8] as 1D,2L,3D,4D[15a] (aryl at 4), then becomes 1L,2L,3D,4L or L(1,2,4)A[15b] (aryl at 1). This change is, of course, merely a matter of nomenclature and does not affect the true spatial relationships.

(34) The (−)-diol which was reduced to the (−)-dihydro derivative of I[30] could be obtained by hydrogenolysis[35] of lariciresinol and pinoresinol dimethyl ethers.

(35) R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 1054 (1939).

(36) Melting points are corrected and were determined in Pyrex capillaries with the Hershberg apparatus. Optical rotations were measured in 4-dm. tubes.

(37) Extracts were washed with dilute acid and base (if so specified), then with dilute sodium chloride solution, dried with sodium sulfate and evaporated *in vacuo* at room temperature, using a rotating evaporator (Rinco Instrument Co., Greenville, Ill.).

(38) Arapahoe Chemicals, Inc., Boulder, Colo.

(39) The ketone, after the first purification with Girard reagent, had $[\alpha]D$ −31° (chloroform) and still appeared to contain veratraldehyde, as indicated by the yield, the low rotation and by a low C analysis. In the second purification, 4.0 g. of Girard reagent was used, and the solution diluted with 285 ml. of water (sodium carbonate and extraction of non-ketonic materials omitted) and made 0.5 *N*, instead of *N*, with sulfuric acid.

(40) A. W. Schrecker, *Anal. Chem.*, 20, 1015 (1948).

(41) N. A. Milas and S. Sussman, THIS JOURNAL, **58**, 1302 (1936).

(42) N. A. Milas, *ibid.*, **59**, 2342 (1937).

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solution with acetone and dried at 110°) for 40 minutes; the mixture was then treated at 0° with the acid chloride from 2.03 g. of the (+)-acid and stirred at room temperature for 3 hr. The whole procedure was performed under dry argon. The mixture was decomposed and worked up as in the reaction with the Grignard reagent, yielding 46% of partially racemic semicarbazone, m.p. 155–156°, $[\alpha]^{21}D$ + 36° (chloroform). A portion of the crude ketone was purified with Girard reagent; the yield and rotation of the semicarbazone were unchanged. When the ether was replaced with benzene before the addition of the acid chloride, the yield of semicarbazone, $[\alpha]D$ +26°, was 8%. Refluxing the benzene suspension of dimethylcadmium with the acid chloride yielded 33% of semicarbazone, $[\alpha]D$ +5.5°; the crude reaction mixture also deposited a small amount of **5,6-dimethoxy-2-methyl-1-indanone** as needles from benzene–hexane, m.p. 132–133° (lit.[43] m.p. 129–130°).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; OCH_3, 30.10. Found: C, 70.05; H, 6.66; OCH_3, 29.93.

DL-4-(3,4-Dimethoxyphenyl)-3-methyl-2-butanone semicarbazone, prepared by cocrystallizing the enantiomers from 30% methanol, formed small rectangular plates, m.p. 164.4–164.7°.

***N*-Formyl-L-3,4-dimethoxyphenylalanine (VII).**—A solution of 10.0 g. of L-3,4-dihydroxyphenylalanine (VI), $[\alpha]^{22}D$ −12.2° (*c* 1, *N* hydrochloric acid),[44] in 90 ml. of 90% formic acid was stirred and treated with 30 ml. of acetic anhydride (temperature rise to 63°), allowed to stand for 0.5 hr., evaporated *in vacuo* below 70° with magnetic stirring (Teflon-coated stirring bar) and re-evaporated several times after addition of water. The residual gummy *N*-formyldihydroxyphenylalanine, which could not be crystallized, was dissolved in about 15 ml. of water and treated, under argon and with magnetic stirring, with 15 ml. of 10 *N* sodium hydroxide, then with four 9.5-ml. portions of methyl sulfate at 20-minute intervals. The temperature was maintained at 35° and the *p*H kept at 7–8 by the dropwise addition of 29 ml. of 10 *N* sodium hydroxide. Finally, 0.5 hr. after all the methyl sulfate had been added, the solution was treated with another 2 ml. of 10 *N* sodium hydroxide, stirred for an additional 0.5 hr., chilled and acidified with 16 ml. of 8 *N* sulfuric acid. The mixture was extracted with ether continuously for 20 hr., and the partly gummy solid which separated from the extract was crystallized from ethyl acetate to give 7.69 g. of colorless solid, m.p. 123–126°. An additional 0.41 g., m.p. 124–126°, was isolated from the mother liquor, bringing the yield to 63%. A sample, recrystallized from ethyl acetate, formed colorless elongated prisms, m.p. 125–126°, $[\alpha]^{24}D$ +71.6° (*c* 2.00, ethanol).

***N*-Formyl-DL-3,4-dimethoxyphenylalanine**, prepared similarly from DL-3,4-dihydroxyphenylalanine in 77% yield, formed small colorless prisms, m.p. 134–135.5°.

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.99; H, 5.95; N, 5.52.

L-3,4-Dimethoxyphenylalanine Methyl Ester (VIII).—A solution of 8.06 g. of VII in 80 ml. of methanol was saturated with dry hydrogen chloride, refluxed for 1 hr. and evaporated *in vacuo*. The residual oil, digested with ether, gave a gum. Recrystallization from ethanol–ether (1:3) provided the **hydrochloride** as colorless needles, which were dried in a vacuum-desiccator over solid potassium hydroxide; yield 4.58 g., m.p. 151–155° dec. An additional 1.95 g., m.p. 142–152°, was isolated from the mother liquor, bringing the yield to 75%. A sample, recrystallized from ethanol–ether, had m.p. 158–159° dec. and $[\alpha]^{20}D$ +6.8° (*c* 2.00, methanol).

Anal. Calcd. for $C_{12}H_{18}ClNO_4$: Cl, 12.86. Found: Cl, 12.74.

The free base was obtained by treating a magnetically stirred solution of 2.17 g. of the hydrochloride in 10 ml. of methanol at −30° with 0.181 g. of sodium in 4.5 ml. of methanol, then with 10 ml. of ether. The mixture was stirred at −30° for 15 minutes, filtered and the filtrate evaporated *in vacuo;* the residue was dissolved in methylene chloride, the solution refiltered, re-evaporated and evaporated again after addition of dry benzene. The residue, dried in a high vacuum, formed a yellowish oil; yield 1.74 g. (92%).

DL-3,4-Dimethoxyphenylalanine Methyl Ester.—**The hydrochloride**, obtained in 76% yield, formed colorless needles, m.p. 185–186° dec.

Anal. Calcd. for $C_{12}H_{18}ClNO_4$: Cl, 12.86. Found: Cl, 12.86.

The free base was obtained in 85% yield with sodium methoxide as above but in 42% yield only by treating an aqueous solution of the hydrochloride with potassium carbonate and extracting with ether.

L-Phenylalanine methyl ester hydrochloride, prepared analogously from L-phenylalanine[45] *via* the *N*-formyl derivative,[22] crystallized from methanol–ether in colorless needles, m.p. 159–160° dec., $[\alpha]^{20}D$ +17.2° (*c* 2.00, methanol), $[\alpha]^{20}D$ −4.5° (*c* 4.00, water).[46]

Anal. Calcd. for $C_{10}H_{14}ClNO_2$: Cl, 16.44. Found: Cl, 16.19.

L-3,4-Dimethoxyphenylalaninol (IX).—A magnetically stirred suspension of 0.828 g. of lithium aluminum hydride in 22 ml. of dry ether was treated during 15 minutes with 1.74 g. of VIII in 23 ml. of ether, refluxed for 1.5 hr., cooled in ice, treated dropwise with 6.1 ml. of ethanol in 12 ml. of ether, then with 4.7 ml. of saturated sodium chloride solution and filtered through Celite. The residue was extracted with about 80 ml. of hot ethanol, and the combined filtrate and extract were evaporated *in vacuo*. The residue was dissolved in benzene, filtered from inorganic salts and re-evaporated to yield 1.47 g. of dark yellow oil, which was dissolved in hot ethanol and treated with 0.438 g. of oxalic acid dihydrate in a little water. **The neutral oxalate**, yield 1.32 g. (69.5%), was recrystallized from water–ethanol; colorless scales, m.p. 210–211.5° dec., $[\alpha]^{20}D$ −16.8° (*c* 3.96, water).

Anal. Calcd. for $2C_{11}H_{17}NO_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$: C, 55.27; H, 7.15; N, 5.37; H_2O, 1.73. Found: C, 55.25; H, 6.93; N, 5.35; wt. loss at 139°, 1.59.

The oxalate (1.12 g.) was treated with 10 *N* sodium hydroxide, the mixture extracted with benzene continuously for 19 hr. and the extract evaporated *in vacuo* to yield 0.90 g. (99%) of the **free base** as a colorless oil, which crystallized on standing, m.p. 78–79°. Recrystallization from methylene chloride–pentane afforded long needles, m.p. 79–80°, $[\alpha]^{20}D$ −21.5° (*c* 7.99, ethanol).

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.80; H, 8.39; N, 6.54.

DL-3,4-Dimethoxyphenylalaninol.—**The neutral oxalate** formed colorless micro-crystals, m.p. 228–229° dec.

Anal. Calcd. for $2C_{11}H_{17}NO_3 \cdot C_2H_2O_4$: C, 56.24; H, 7.88; N, 5.47. Found: C, 56.19; H, 7.03; N, 5.70.

The free base, recovered from the oxalate, melted at 63–64.5° and was not recrystallized. It was very soluble in water.

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.69; H, 8.30; N, 6.03.

***O,N*-Ditosyl-L-3,4-dimethoxyphenylalaninol (X).**—A solution of 0.70 g. of IX and 2.1 g. of tosyl chloride in 5.7 ml. of dry pyridine was prepared at 0°, kept at room temperature for 24 hr., treated with ice and water, kept 15 minutes and extracted with chloroform. The extract was washed with 21 ml. of 4 *N* hydrochloric acid and with sodium bicarbonate solution, then worked up.[37] The residual yellow gum, which could not be crystallized, was dried at 80° (0.05 mm.), yield 1.65 g. (96%), $[\alpha]^{24}D$ −58° (*c* 1.99, ethanol).

Anal. Calcd. for $C_{25}H_{29}NO_7S_2$: C, 57.78; H, 5.63; S, 12.34. Found: C, 58.29; H, 5.79; S, 11.14.

***O,N*-Ditosyl-DL-3,4-dimethoxyphenylalaninol.**—The washed and dried chloroform extract was diluted with four volumes of hexane to yield 71% of pale yellow crystals, m.p. 133–135°. Recrystallization from chloroform–pentane provided small colorless prisms, m.p. 135.5–136.0°.

Anal. Calcd. for $C_{25}H_{29}NO_7S_2$: C, 57.78; H, 5.63; S, 12.34. Found: C, 57.72; H, 5.41; S, 12.15.

(43) F. Šorm, J. Gut and J. Krupička, *Chem. Listy*, **45**, 240 (1951); *C. A.*, **47**, 8702*i* (1953).

(44) Supplied by California Foundation for Biochemical Research, Los Angeles, Cal.

(45) Kindly supplied by Dr. Jesse P. Greenstein.

(46) B. F. Erlanger, H. Sachs and E. Brand, THIS JOURNAL, **76**, 1806 (1954), reported $[\alpha]^{25}D$ +3.9° (*c* 2.67, water) (calcd. as free ester) for the isomer prepared by direct esterification of D-phenylalanine.

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N-Tosyl-D-3,4-dimethoxy-α-methylphenethylamine[14] (V). (a) From X.—The gummy ditosylate (1.64 g.) in 58 ml. of dry purified[30] tetrahydrofuran was added dropwise during 15 minutes with magnetic stirring to a suspension of 0.82 g. of lithium aluminum hydride in 33 ml. of tetrahydrofuran. The mixture was stirred at room temperature for 0.5 hr., refluxed for 3 hr., chilled, treated with water and 4 *N* hydrochloric acid and extracted with chloroform. The extract was washed with sodium chloride and potassium carbonate solutions, dried with potassium carbonate, concentrated, chromatographed on neutral alumina and the product eluted with chloroform. Evaporation and crystallization from ether–pentane yielded 0.93 g. (84%) of colorless elongated prisms arranged in rosettes, m.p. 74.5–76.0°. Recrystallization from ether–pentane provided material, m.p. 75.6–76.6°, $[\alpha]^{20}D$ −29.3° (*c* 2.00, ethanol), $[\alpha]^{20}D$ −10.0° (*c* 2.00, chloroform).

(b) From D-(−)-3,4-Dimethoxy-α-methylphenethylamine[7] (IV).—A solution of 1.00 g. of IV and 3 g. of tosyl chloride in 15 ml. of dry pyridine was kept at room temperature for 1 hr. and poured into a slurry of ice, water and 20 ml. of concd. hydrochloric acid. The oil, which crystallized on standing in the refrigerator, was washed with water, then chromatographed and recrystallized as above; yield 1.20 g. (67%), m.p. 75.6–76.6° (no depression with a sample prepared under (a)), $[\alpha]^{20}D$ −28.9° (*c* 2.26, ethanol), $[\alpha]^{21}D$ −9.8° (*c* 2.00, chloroform). Samples prepared under (a) and (b) had identical infrared spectra.

Anal. Calcd. for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01; S, 9.18. Found: C, 61.86; H, 6.42; N, 4.12; S, 8.96.

N-Tosyl-L-3,4-dimethoxy-α-methylphenethylamine, prepared from L-(+)-3,4-dimethoxy-α-methylphenethylamine[7] in 59% yield, formed rosettes of colorless elongated prisms, m.p. 76.2–77.2°, $[\alpha]^{20}D$ +29.4° (*c* 2.00, ethanol), $[\alpha]^{20}D$ +10.6° (*c* 2.01, chloroform).

N-Tosyl-DL-3,4-dimethoxy-α-methylphenethylamine was obtained by mixing the enantiomers or (in 68% yield) by reduction of ditosyl-DL-3,4-dimethoxyphenylalaninol. It was crystallized with difficulty by slow evaporation of its ether solution at 3° and melted at 63–67°. Its infrared spectrum in chloroform was identical with that of the D-isomer.

Acknowledgments.—The authors are greatly indebted to Dr. W. Klyne of the Postgraduate Medical School of London for very valuable advice and to Dr. Frederick E. King of British Celanese Ltd., London, for suggesting an improved method for the isolation of guaiaretic acid. Miss Mary M. Trail carried out a large portion of the experimental procedures, including determination of the melting point diagram and of the optical rotations. Microanalyses were performed by Dr. W. C. Alford and his staff.

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

Reaction of Steroids with Diazomethane[1]

BY ALEXANDER L. NUSSBAUM AND FLORENCE EMILIE CARLON

RECEIVED FEBRUARY 18, 1957

The action of diazomethane in ether–methanol upon certain steroids has been investigated. This reagent not only saponifies acetate groups at C-21 but also causes homologation of the side chain. Evidence is presented that the new compounds are homologous 20,22-epoxides. A model compound possessing this structure was prepared and correlated with a known compound.

The recent report on the use of diazomethane as a catalyst in transesterification[2] led us to investigate that method in the hydrolysis of the 21-acetates of a number of physiologically active steroids, since the usual methods of saponification cause concomitant side reactions.[3]

When 17α,21-dihydroxy-Δ[1,4]-pregnadiene-3,11,-20-trione 21-acetate[4] (Ia) was exposed to the action of an excess of diazomethane in ether–methanol solution, the ester group was lost, but the resulting product was not identical with the predicted hydrolysate Ib. Although its melting point was similar to that of 17α,21-dihydroxy-Δ[1,4]-pregnadiene-3,11,20-trione[4] (Ib) and no depression of this melting point was observed upon admixture with the new material, the two compounds were definitely not identical, as shown by their infrared spectra, optical rotations and migration rates in paper chromatography. The same material could also be obtained directly from non-acetylated 17α,21-dihydroxy-Δ[1,4]-pregnadiene-3,11,20-trione (Ib). Elemental analysis indicated that the new substance was a homolog of its alcohol precursor. It could be monoacetylated and resaponified.

The new material possessed a high intensity maximum at 239 mμ in the ultraviolet. This could arise from either the original dienone or a newly formed enone chromophore. However, survival of the dienone system was indicated by the characteristic absorption doublet in the infrared at 6.16 and 6.22 μ[4] and by polarographic data.[5] Failure of diazomethane to attack the ring system was not entirely unexpected, since the work of Wettstein[6] and that of Djerassi and Scholz[7] has shown that the double bond of a steroidal Δ[4]-3-ketone is resistant to that reagent.[8]

(1) Part of the results reported in this paper were published in a communication to the editor of *Chemistry & Industry*, 1313 (1956); other parts were presented before the Miami Meeting of the American Chemical Society, April 7–12, 1957.

(2) H. Bredereck, R. Sieber and L. Kamphenkel, *Chem. Ber.*, **89**, 1169 (1956).

(3) See, for instance, N. L. Wendler and R. P. Graber, *Chemistry & Industry*, 549 (1956).

(4) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, in press (1957).

(5) Peter Kabasakalian and James McGlotten, THIS JOURNAL, **78**, 5032 (1956). We are indebted to Mr. T. Coniglio of these laboratories for his kind assistance in the measurement of the polarographic reductions.

(6) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).

(7) Carl Djerassi and C. R. Scholz, *J. Org. Chem.*, **14**, 661 (1949).

(8) Addition of diazomethane to α,β-unsaturated ketones was first described by E. Azzarello, *Gazz. chim. ital.*, II, **36**, 50 (1906). The validity of the statement[7] that the addition of diazomethane to steroidal α,β-unsaturated ketosteroids is characteristic of the Δ[16]-20-one-moiety has received further support from the failure of 3,17-diketo-Δ[1]-androstene to add diazomethane: Carl Djerassi and Alexander L. Nussbaum, unpublished experiment performed at Wayne University.

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Oxidative degradation of the new substance with chromic acid[9] gave 3,11,17-triketo-$\Delta^{1,4}$-androstadiene(III).[10] It could be concluded, therefore, that the methylene group had entered into the side chain. This was supported by the observation that the original dihydroxyacetone grouping had not survived the reaction. The new substance failed to give a purple color with 2,3,5-triphenyltetrazolium chloride,[11] and the carbonyl band in the infrared spectrum of the starting material attributable to the interaction of the C_{21}-acetate with the C_{20}-ketone at 5.80 μ gave way to a simple acetate band at 5.74 μ[12] in the acetate of the new substance. The C_{20}-carbonyl seemed to be involved in the new transformation. In order to facilitate interpretation of the infrared spectrum, the reaction was carried out on prednisolone where there was no ketone function at C-11 which would complicate absorption in the carbonyl region. When 11β,17α,21-trihydroxy-$\Delta^{1,4}$-pregnadiene-3,20-dione 21-acetate (Ic) was exposed to the action of diazomethane in ether–methanol, there was again obtained a new homolog, which did not exhibit any infrared absorption typical of saturated ketones. Furthermore, sodium bismuthate[13] treatment of the new compounds failed to cleave the side chain, indicating the absence of a dihydroxyacetone group.

All these facts were in agreement with the view that a methylene group had added to the side chain carbonyl with the formation of an epoxide, a reaction often observed in diazomethane chemistry.[14] Thus, the reaction products of Ia (or b) and Ic were formulated as IIa and IIc, respectively. This formulation was supported by the fact that the free alcohols of these reaction products (see following) showed a new band in the infrared near 8.05 μ which can be attributed to the epoxide grouping.[15]

Their migration rates in a paper chromatographic system[16] were slightly greater than those of the parent substances, indicating a slight decrease in polarity expected from the proposed transformation. An analogous reaction has been observed by Prins and Reichstein[17] who obtained a 20,21-epoxide from the reaction of 17α-formyltestosterone.

An investigation of the scope of this reaction showed that, under the conditions used, only those steroids possessing the complete dihydroxyacetone side chain undergo the transformation described to any appreciable extent. In addition to Ia (or b) and Ic, the following compounds were submitted to the reaction: cortisone acetate (Id), Δ^6-cortisone (Ie)[18] and Compound S (If). The corresponding bisnorcholane-epoxides are formulated in Chart I. Desoxycorticosterone (IV), lacking a hydroxyl group at C-17, failed to react as smoothly as the preceding steroids of the cortisone type: only small amounts of the homolog V could be isolated after careful chromatography.

Also submitted to the reaction were 17-hydroxyprogesterone, 21-hydroxypregnenolone and allopregnanolone acetate. None of these compounds underwent the reaction here discussed; in each case starting material was recovered in high yield. A slight degree of acetate hydrolysis was observed in the case of allopregnanolone acetate (4%).

The new substances show uniform negative molecular rotation differences (see Table I). Their physical (especially spectral) properties are in agreement with the arguments here outlined.

TABLE I

MOLECULAR ROTATION DIFFERENCES

Starting material (1)	M_D of (1) (2)	M_D of product (alcohol) (3)	ΔM_D (3) − (2) (4)
Prednisone acetate (Ia)	617	402	−215
Prednisolone acetate (Ic)	364	82	−282
Cortisone acetate (Id)	754	519	−235
Δ^6-Cortisone (Ie)	932	723	−209
Compound S (If)	423	195	−228
Desoxycorticosterone acetate (IV)	589	328	−261
3β,17α,21-Trihydroxy-Δ^5-pregnen-20-one 3,21-diacetate	−106	−213	−107

In order to confirm the course of the proposed reaction, it was carried out on 3β,17α,21-trihydroxy-Δ^5-pregnen-20-one 3,21-diacetate (VIa)[19] (Chart II). The expected 3β,17α,21-trihydroxy-Δ^4-bisnorcholene-20 ξ,22-epoxide 3-acetate (VIIa) was obtained. Reduction of the diacetate VIIb with lithium aluminum hydride gave a mixture of tetrols (VIIIa), from which, upon acetylation, a homogeneous 3,21-diacetate (VIIIb) could be isolated in moderate yield. The same mixture of tetrols had been prepared previously[19] by a Grignard reaction on VIa, and upon repetition of this work, followed by acetylation, we were able to isolate the same diacetate (VIIIb) as had been obtained from the model compound. While this method of synthesis does not give any knowledge concerning the stereochemistry at C-20, it does establish the structure of the carbon skeleton.

Preliminary biological studies indicate compounds IIa, IIc and IId to be essentially devoid of eosinopenic, anti-inflammatory and glycogen-depositing activity. The homolog of desoxycorticosterone (V) appeared to have lost all of its sodium-retaining characteristics. We are indebted to Drs. S. Tolksdorf and P. Perlman of our laboratories for these data.

(9) A. S. Meyer, *J. Biol. Chem.*, **203**, 469 (1953).

(10) H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto and E. B. Hershberg, THIS JOURNAL, **77**, 4781 (1955).

(11) R. B. Burton, A. Zaffaroni and E. H. Keutmann, *J. Biol. Chem.*, **188**, 763 (1951).

(12) R. Norman Jones, P. Humphries, F. Herling and Konrad Dobriner, THIS JOURNAL, **74**, 2820 (1952).

(13) C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(14) C. D. Gutsche, "The Reactions of Diazomethane and its Derivatives," in R. Adams, ed., "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 364 *et seq.* We are indebted to Dr. D. Gould of these laboratories for first suggesting the epoxide as a possibility.

(15) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

(16) U. S. Patent 2,658,023.

(17) D. A. Prins and T. Reichstein, *Helv. Chim. Acta*, **24**, 945 (1941).

(18) V. R. Mattox, E. L. Worosh, G. A. Fleischer and E. C. Kendall, *J. Biol. Chem.*, **197**, 261 (1952). The additional double bond in ring B again failed to add diazomethane.[8]

(19) H. G. Fuchs and T. Reichstein, *Helv. Chim. Acta*, **24**, 804 (1941).

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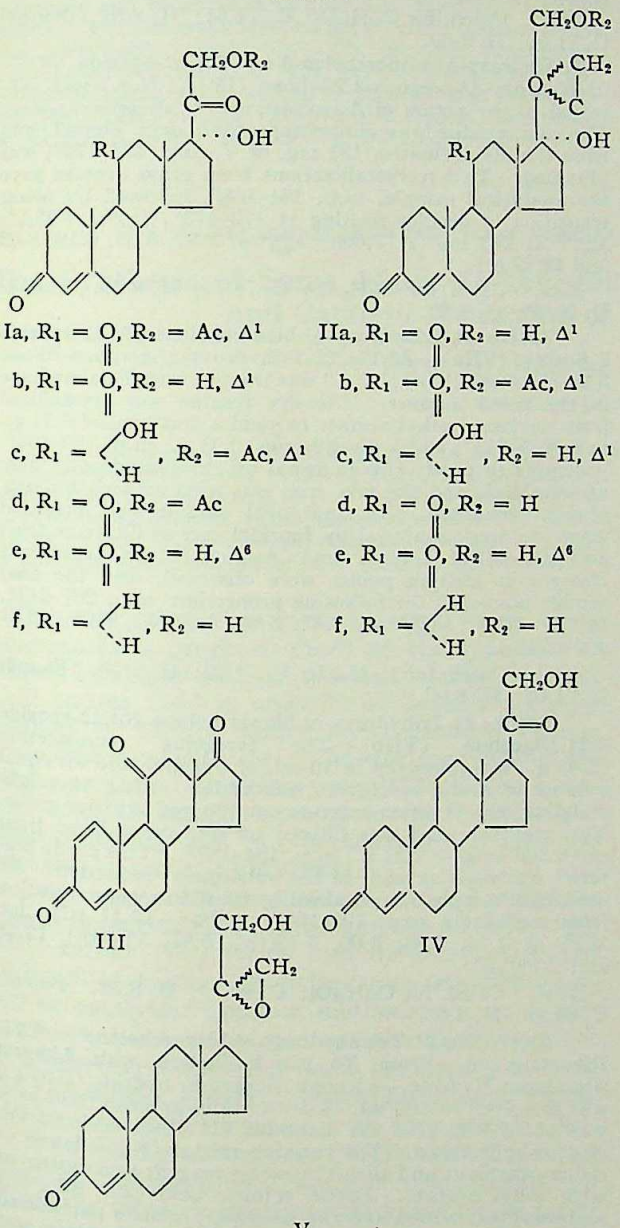
CHART I



Experimental[20]

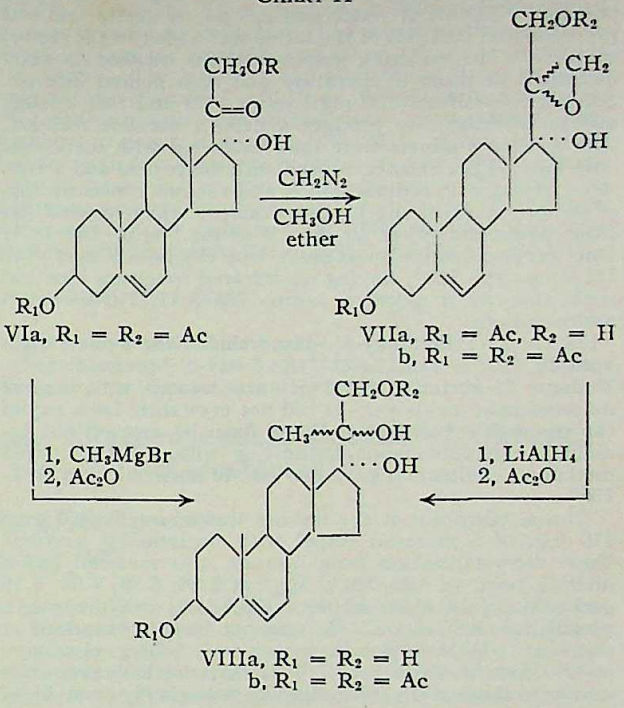
17α,21-Dihydroxy-Δ1,4-bisnorcholadiene-3,11-dione-20ξ,22-epoxide (IIa).—The following procedure is typical of all subsequent preparations of the homologs: 17α,21-Dihydroxy-Δ1,4-pregnadiene-3,20-dione 21-acetate (Ia) (600 mg.) was dissolved in 20 ml. of methanol, and into this solution was filtered another solution of *ca.* 1.2 g. of diazomethane in 60 ml. of ether,[21] and the mixture was allowed to stand for a period of five days at room temperature.[22]

(20) All melting points were taken on a Kofler block. Rotations were carried out in a 1-dm. tube at a concentration of *ca.* 1% in dioxane, unless otherwise specified. Analyses and spectral data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

(21) *Cf.* Th. J. de Boer *et al.*, *Org. Syntheses*, **34**, 2496 (1954).

(22) A subsequent study by paper chromatographic methods showed an optimum reaction time of 50 hr.

CHART II



The small amount of "polymethylene" which had appeared was then filtered off, the solution was concentrated to dryness under vacuum, and the crystalline residue was dissolved in methanol, treated with charcoal and recrystallized from the same solvent. A first crop of 420 mg., m.p. 226–231°, was obtained. Fourfold recrystallization from methanol gave the analytical sample, m.p. 239–241°, $[\alpha]^{25}D$ +108.2°, λ_{max}^{MeOH} at 239 mμ (ε 15,600); λ_{max}^{Nujol} at 3.03, 5.85, 5.99, 6.16, 6.22 and 8.03 μ.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.90; H, 7.79.

17α,21-Dihydroxy-Δ1,4-bisnorcholadiene-3,11-dione-20ξ,22-epoxide 21-Acetate (IIb).—A sample of relatively crude free alcohol IIa (200 mg.) was dissolved in 1 ml. of pyridine, 1 ml. of acetic anhydride was added and the resulting solution allowed to stand overnight. It was then poured into ice, filtered and air-dried to give 185 mg. of a product melting 195–198°. Recrystallization from methylene chloride–ether gave 145 mg., m.p. 210–212°. A further wasteful recrystallization from acetone gave the analytical sample, m.p. 213–215°, $[\alpha]^{25}D$ +113.2; λ_{max}^{Nujol} at 2.97 5.74(sh), 5.85, 6.03, 6.16, 6.23 and 8.12 μ.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.52; H, 7.30. Found: C, 69.50; H, 7.00.

Saponification[23] of IIb.—The foregoing acetate (60 mg.) was suspended in 3 ml. of methanol and placed in an atmosphere of nitrogen. To this solution 0.2 ml. of a stock solution of 0.67 g. of sodium methylate in 15 ml. of methanol was added and the reaction was allowed to proceed at room temperature for 18 minutes. All of the material was observed to dissolve after 5 minutes, but some solid reappeared after 10 minutes. Aqueous methanol (0.06 ml. of a solution containing 3 ml. of methanol and 0.2 ml. of water) was then added and the reaction time extended another 6 minutes. Finally, 2 ml. of ice-water was added, and the mixture was concentrated under vacuum at 35°. A few pieces of ice were added, and the resulting suspension filtered with suction. The solid was washed well with water and air-dried to give 49.5 mg., m.p. 220–235°. One recrystallization from methanol gave paper chromatographically pure free alcohol IIa, m.p. 235–239°, identified by its infrared spectrum.

3,11,17-Triketo-Δ1,4-androstadiene (III).—17α,21-Dihydroxy - Δ1,4 - bisnorcholadiene - 3,11 - dione - 20ξ,22-epoxide (117.5 mg.) was dissolved in 6.6 ml. of glacial acetic acid previously distilled over chromium trioxide.

(23) U. S. Patent 2,634,277 in *C. A.*, **48**, 1448c (1954), and **49**, 14093 (1955).

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An oxidizing solution consisting of 300 mg. of chromium trioxide, 0.36 ml. of water and 3.6 ml. of acetic acid was prepared and 0.91 ml. of the latter was added to the steroid solution. The resulting suspension was allowed to react overnight at room temperature and then poured into ice. Sodium thiosulfate (100 mg.) was added and then enough sodium hydroxide to produce a definite alkaline reaction. The neutral products were then extracted with methylene chloride and the extract washed with dilute acid and water. After drying over sodium sulfate and vacuum concentrating, a yellow oil (51.6 mg.) was obtained, which crystallized from petroleum ether to give 26.5 mg., m.p. 158–187°. One recrystallization from methylene chloride–hexane gave III, m.p. 187–193°, having an infrared spectrum identical with that of a genuine sample of 3,11,17-triketo-$\Delta^{1,4}$-androstadiene.

11β,17α,21-Trihydroxy-$\Delta^{1,4}$-bisnorcholadiene-3-one-20ξ,22-epoxide (IIc).—11β,17α-21-Trihydroxy-$\Delta^{1,4}$-pregnadiene-3,-20-dione 21-acetate (Ic) (3 g.) was treated with 6 g. of diazomethane as above. It did not crystallize from any of the common solvents but did so from its own oil and remained crystalline upon trituration with a little ice-cold methanol. Filtration gave 880 mg. of material, m.p. 135–150°.

Chromatography of the mother liquors on Florisil gave 110 mg. of a material eluted with benzene–5% acetone. Upon recrystallization from acetone, this material had a melting point of 192–220°; λ_{max}^{Nujol} at 2.86, 5.86, 6.04, 6.19 and 6.24 μ (not identical with 11β,17α,21-trihydroxy-$\Delta^{1,4}$-pregnadiene-3,20-dione). It was not further examined at this time. With 30% acetone-benzene, 1.62 g. of a more polar eluate was obtained. This material had properties similar to those of the substance which originally crystallized from the crude reaction mixture. Like the latter, it was impossible to recrystallize from the common solvents, but eventually it was found to form a crystalline solvate with methylene chloride. One recrystallization from methanol–methylene chloride gave 960 mg., transition point with partial melting 135–150°, definite m.p. 213–222°. Two more recrystallizations from the same solvent gave the analytical sample, transition range 136–152°, definite m.p. 215–219°; λ_{max}^{MeOH} at 244 mμ (ϵ 15,000), $[\alpha]^{25}D$ +17.3°; λ_{max}^{Nujol} at 2.98, 6.04, 6.21, 6.26 and 8.05 μ.

Anal. Calcd. for $C_{22}H_{30}O_5 \cdot CH_2Cl_2$: C, 60.13; H, 7.02. Found: C, 60.25; H, 7.33.

An acetate was prepared in the usual manner and was found to have the following properties: m.p. 240–243°, λ_{max}^{MeOH} at 243 mμ (ϵ 15,000); λ_{max}^{Nujol} at 2.85(sh), 2.94, 5.74, 6.03 and 6.19 μ.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.55; H, 7.98.

17α,21-Dihydroxy-Δ^4-bisnorcholene-3,11-dione-20ξ,22-epoxide (IId).—17α,21-Dihydroxy-Δ^4-pregnene-3,11,20-trione 21-acetate (Id) (1.5 g.) was treated with 3 g. of diazomethane as described. Chromatography on Florisil gave 510 mg. of product, m.p. 210–232°. Several recrystallizations from methanol failed to improve the sharpness of the melting point, and eventually the following properties were measured from a sample that had been recrystallized four times: m.p. 225–245°,[24] $[\alpha]^{25}D$ +138.1°, λ_{max}^{MeOH} at 238 (ϵ 15,400); λ_{max}^{Nujol} at 2.92, 5.89, 6.12 and 8.05 μ.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.54; H, 8.08.

17α,21-Dihydroxy-$\Delta^{4,6}$-bisnorcholadiene-3,11-dione-20ξ,22-epoxide (IIe).—17α,21-Dihydroxy-$\Delta^{4,6}$-pregnadiene-3,11,-20-trione 21-acetate (Ie) (1 g.) was treated with the usual excess of diazomethane in the manner described. Crystallization from methanol gave 354 mg. of a product with m.p. 230–270°. Two recrystallizations from methanol gave the analytical sample, transition range 220–230°, m.p. 280–286, $[\alpha]^{25}D$ +194.2°, λ_{max}^{MeOH} at 280.5 (ϵ 24,700); λ_{max}^{Nujol} at 2.98, 5.84, 6.10, 6.19, 6.31 and 8.14 μ.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.87; H, 7.33.

17α,21-Dihydroxy-Δ^4-bisnorcholen-3-one-20ξ,22-epoxide (IIf).—17α,21-Dihydroxy-Δ^4-pregnene-3,20-dione (If) (1.5 g.) was converted as usual. Crystallization from methanol gave 830 mg., m.p. 223–236°. Two recrystallizations from methanol gave the analytical sample, (vacuum capillary) m.p. 245–246°, $[\alpha]^{25}D$ +54.0°, λ_{max}^{MeOH} at 242 mμ (ϵ 16,800); λ_{max}^{Nujol} at 2.97, 5.99, 6.21(w) and 8.05 μ.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.16; H, 8.95.

Preparation of an acetate in the usual manner gave a product with m.p. 217–220°, $[\alpha]^{25}D$ +78.5°, λ_{max}^{MeOH} at 242 (ϵ 15,800); $\lambda_{max}^{CHBr_3}$ at 5.74, 6.01, 6.19 and 8.13 μ.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.60; H, 8.69.

21-Hydroxy-Δ^4-bisnorcholen-3-one-20ξ,22-epoxide (V).—21-Hydroxy-Δ^4-pregnen-3,20-dione (IV) (1.5 g.) was subjected to the action of diazomethane, as described above. The oily residue was chromatographed over Florisil, and from the ether eluates, 181 mg. of V, m.p. 166–172°, was obtained. Two recrystallizations from ethyl acetate gave the analytical sample, m.p. 164–168°, followed by phase transition to needles melting at 172–173°, $[\alpha]^{25}D$ +95.1°, λ_{max}^{MeOH} at 242 mμ (ϵ 17,000); λ_{max}^{Nujol} at 2.97, 6.09, 6.19, 8.02 and 12.22 μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.96; H, 9.26.

3β,17α,21-Trihydroxy-Δ^5-bisnorcholene-20ξ,22-epoxide 3-Acetate (VIIa).—3β,17α,21-Trihydroxy-Δ^5-pregnen-20-one 3,21-diacetate (VIa) (7.5 g.) was treated with diazomethane in the usual manner. The dry residue was crystallized from methanol–ethyl acetate to yield a first crop of 3.51 g., m.p. 205–211°, and a second crop, 0.51 g., m.p. 180–195°. Attempts to purify this material by chromatography were unsuccessful, and the first crop was used as such for subsequent reactions. An analytical sample was prepared from the crude material by fourfold recrystallization from acetone, ethyl acetate and methanol. No significant changes in melting points were observed, and the final sample possessed the following properties: m.p. 207–213°, $[\alpha]^{25}D$ −52.9°; $\lambda_{max}^{CHBr_3}$ at 2.87, 5.81, 6.03(sh), 8.02, 12.31 and 12.48 μ.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 71.25; H, 8.97. Found: C, 71.09; H, 8.92.

3β,17α,21-Trihydroxy-Δ^5-bisnorcholene-20ξ,22-epoxide 3,21-Diacetate (VIIb).—The foregoing monoacetate (2.43 g.) was dissolved in 10 ml. of pyridine and an equal volume of acetic anhydride was added. After overnight standing, the reaction mixture was poured into ice-water. The resulting solid was filtered off and crystallized from methanol to give 2.21 g., m.p. 164–182°. This crude material was used as such in the subsequent reduction. An analytical sample was obtained by fourfold recrystallization from methanol: m.p. 190–196°, $[\alpha]^{24}D$ −13.1° ($CHCl_3$); $\lambda_{max}^{CHBr_3}$ at 2.76, 2.86, 3.00, 5.73(sh), 5.81, 5.94(sh), 12.28 and 12.50 μ.

Anal. Calcd. for $C_{26}H_{36}O_6$: C, 69.93; H, 8.58. Found: C, 69.88; H, 8.45.

3β,17α,20ξ,21-Tetrahydroxy-Δ^5-bisnorcholene 3,21-Diacetate. A. From Xb *via* Reduction with Lithium Aluminum Hydride.—Lithium aluminum hydride (2.00 g.) was dissolved in 100 ml. of dry tetrahydrofuran, and to it was added 2.03 g. of the diacetate VII dissolved in 75 ml. of tetrahydrofuran. The reaction mixture was allowed to reflux overnight and then the excess reagent was destroyed with ethyl acetate. Dilute sulfuric acid (200 ml., 5% aqueous) was added and the reaction products partitioned between water and ethyl acetate. The organic phase was washed with sodium bicarbonate and water and eventually dried and concentrated. Crystallization of the residue from ethyl acetate gave 500 mg. of a product, m.p. 185–215°, which did not show absorption in the carbonyl region of the infrared spectrum. The material was dissolved in 5 ml. of pyridine, and an equal volume of acetic anhydride was added. The solution was allowed to stand overnight and was then poured into ice-water. The resulting crude (m.p. 145–170°) was crystallized from ethyl acetate to give 267 mg. of VIIIb, m.p. 217–230°. After three recrystallizations from methanol, there remained 127.2 mg. of an analytical sample, m.p. 228–235°, $[\alpha]^{24}D$ −70.1°; λ_{max}^{Nujol} at 2.84, 5.76, 5.82, 5.98(sh) and 8.02 μ.

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.57; H, 8.85.

B. **From VIa *via* Grignard Reaction.**—Methylmagnesium bromide was prepared in the usual manner by allowing 15 ml. of methyl bromide to react with 5.7 g. of magnesium

(24) A capillary melting point, however, was 217–223°, as previously reported.

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turnings in 350 ml. of anhydrous ether. A solution of 5 g. of 3β,17α,21-trihydroxy-Δ⁶-pregnen-20-one 3,21-diacetate (VIa) was then added dropwise and the resulting reaction mixture was allowed to reflux overnight. The suspension was cooled, and 500 ml. of 5% sulfuric acid was added. After 2 hr. of agitation, the two phases were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic fractions were washed with sodium bicarbonate and water to neutrality and dried over sodium sulfate. Vacuum concentration gave a crude product which was acetylated immediately. (In another experiment, methylation of 2.18 g. of VIa gave a crude which was crystallized from ethyl acetate to give 790 mg. with m.p. 214–248°. This material, in spite of the great discrepancy of the melting point, possessed an infrared spectrum very like that of the lithium aluminum hydride reduction product of VIIa. However, like the latter, it could not be purified by conventional techniques.) The entire residue was dissolved in 50 ml. of pyridine, and 50 ml. of acetic anhydride was added. The solution was allowed to stand at room temperature overnight and then poured into ice-water. The resulting solid was filtered and recrystallized from methanol to give 1.12 g., m.p. 185–202°. Three recrystallizations from ethyl acetate followed by two from methanol gave an analytical sample, 250 mg., m.p. 225–232°, no depression upon admixture of the diacetate from the lithium aluminum hydride reduction of VIIa, infrared spectrum identical with that of the latter, $[\alpha]^{25}_{D}$ −64.9°.

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

The Synthesis of Some 14-Iso-11-ketosteroids. Stereochemical Course of Chemical and Catalytic Reduction of a 14β-Δ⁸-11-Ketosteroid[1,2]

BY CARL DJERASSI AND G. H. THOMAS[3]

RECEIVED JANUARY 17, 1957

The lithium–ammonia reduction product of Δ⁸-22a,25a,5α,14β-spirosten-3β-ol-11-one (IVa) was shown to be 22a,25a,5α,-14β-spirostan-3β-ol-11-one (VIa) by converting the latter to the known 14β,17α-allopregnan-3β-ol-20-one acetate (XIb). With a reference compound (VI) of known stereochemistry now being available, application of conformational analysis leads to the assignment of the 8α,9α-orientation (V) to the *catalytic hydrogenation* product of IV. The elucidation of the stereochemistry of the *chemical reduction* product (VI) has a bearing on the evaluation of conformational factors involved in the metal–ammonia reduction of unsaturated ketones.

Recently, there has been undertaken in these laboratories a program aimed at the synthesis of steroid hormones with an abnormal configuration at C-8[4] and/or C-14 in order to evaluate the consequences of such a minor stereochemical change upon biological activity. The starting material for all the projected syntheses was Δ⁸-22a,25a,5α-spirosten-3β-ol-11-one (I)[5] since it is readily available[6] from diosgenin and can be transformed into the various C-8 and C-14 isomers.

Treatment of the unsaturated ketone I with base effects isomerization at C-14[6] and the resulting 14β-Δ⁸-11-ketone (IV) yields two different saturated 14-iso(β)-11-ketones depending upon whether chemical or catalytic reduction methods are employed. It already has been pointed out[6] that in the absence of a reference compound (as is the case with II in the 14α-series), a stereochemical assignment in the 14β-series is difficult since of the four possible isomers (V–VIII), all but one (VIII) can exist in an all-chair conformation.[7] Since precise information about the stereochemistry of these reduction products was necessary in order that the subsequent transformation to steroid hormone isomers be of stereochemical value, correlation of one of the reduction products of IV with a steroid of known configuration was attempted. The results of this work and its bearing upon certain aspects of carbanion reduction processes[8] form the subject of this paper.

The lithium–ammonia reduction product of Δ⁸-22a,25a,5α,14β-spirosten-3β-ol-11-one (IVa), now shown to be 22a,25a,5α,14β-spirostan-3β-ol-11-one (VIa), was transformed by a modified Wolff–Kishner reduction[9] and subsequent acetylation to 22a,-25a,5α,14β-spirostan-3β-ol acetate (IXb).[10] Con-

(1) We are indebted to the American Cancer Society through the Committee on Growth of the National Research Council for a research grant.

(2) A portion of this material has been described in a preliminary communication (C. Djerassi and G. H. Thomas, *Chemistry & Industry*, 1228 (1954).

(3) Postdoctorate research fellow, 1953–1955.

(4) *Cf.* C. Djerassi, A. J. Manson and A. Segaloff, *J. Org. Chem.*, **21**, 490 (1956); C. Djerassi, H. Bendas and A. Segaloff, *ibid.*, **21**, 1056 (1956); C. Djerassi, A. J. Manson and H. Bendas, *Tetrahedron*, 1, 22 (1957).

(5) For nomenclature see C. Djerassi, T. T. Grossnickle and L. B. High, THIS JOURNAL, **78**, 3166, ref. 10 (1956).

(6) C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, *ibid.*, **75**, 3496 (1953).

(7) See Table I in ref. 6.

(8) *Cf.* D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954), and references cited.

(9) D. H. R. Barton, A. A. J. Ives and B. R. Thomas, *ibid.*, 2056 (1955). We are indebted to Prof. Barton for providing us with the experimental details prior to publication.

(10) The argument might be raised that even though the saturated 11-ketone was found to be stable to base, it could still have been represented by the 8β,9β-11-ketone VII and that IX (8β,9α) is produced in the Wolff–Kishner reduction by a "kinetic inversion" *via* the 8β,9α-ketone VI similar to the observed (ref. 5) reduction of the alkali-stable 14-iso(β)-digitogenone to gitogenin (14α). Such a kinetic inversion would require a considerable difference in the reactivity of the carbonyl groups in VI and VII which cannot be determined experimentally since only one isomer is known. However, two arguments can be offered against such an assumption: (a) the good yield in the Wolff–Kishner reduction (VI → IX) in contrast to the poor one observed in the digitogenin series (ref. 5); (b) conformational analysis which would suggest that VI should be more stable than VII in spite of the fact that both can exist in all-chair conformations. Not only is the 9–11 bond axial in VII, but there exists also a 1,3-diaxial interaction between the 7–8 and 13–17 bonds which is not found in VI. In any event, none of the other stereochemical assignments made in this paper are affected by this question since the 8β-orientation has been proved rigorously by conversion to XI.

It should be noted that in the 14α-series the 8β,9β-isomer can be isomerized with base to the natural 8β,9α-derivative (P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. W. Wood, J. Elks, R. M. Evans, E. E. Hathway, J. F. Oughton and G. H. Thomas, *J. Chem. Soc.*, 2921 (1953)), but on the other hand the conformational difference between the two isomers is a much more striking one (see Table I in ref. 6 and A. Crawshaw, H. B. Henbest, E. R. H. Jones and A. A. Woolland, *ibid.*, 3420 (1955)) as compared to the 14β-series.

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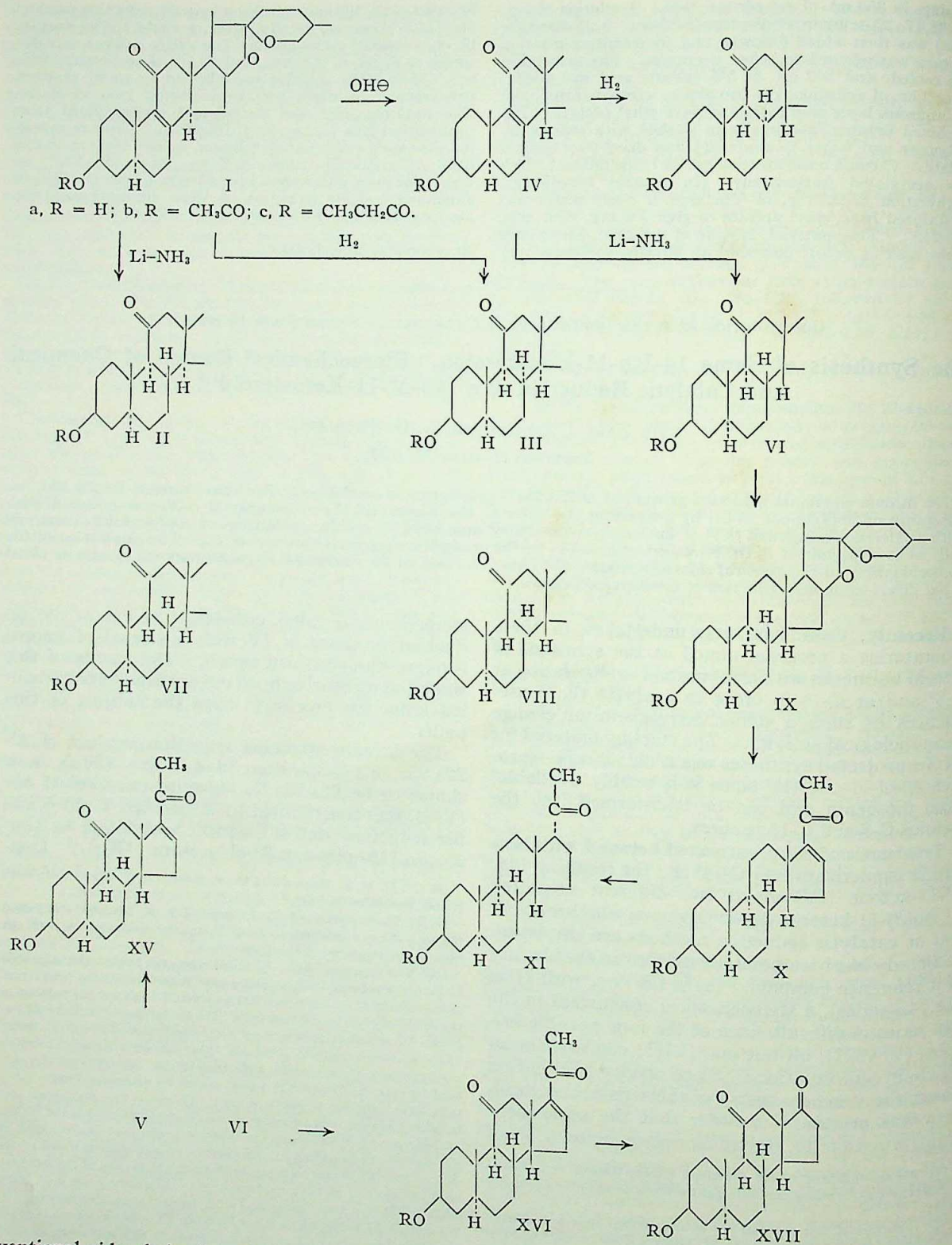

a, R = H; b, R = CH_3CO; c, R = CH_3CH_2CO.

ventional side chain degradation yielded Δ^{16}-14β-allopregnen-3β-ol-20-one acetate (Xb), and catalytic hydrogenation led in good yield to 14β,17α-allopregnan-3β-ol-20-one acetate (XIb), which had been obtained[11] previously by catalytic hydrogenation of $\Delta^{14,16}$-allopregnadien-3β-ol-20-one acetate.[12]

The above correlation with a 14β-steroid (XI) of

(11) P. A. Plattner, L. Ruzicka, H. Heusser and E. Angliker, *Helv. Chim. Acta*, **30**, 385 (1947); P. A. Plattner, H. Heusser and A. Segre, *ibid.*, **31**, 249 (1948).

(12) While C-8 and possibly even C-9 could have been involved (*via* the enol) in the preparation and reduction of the $\Delta^{14,16}$-dien-20-one, this has been excluded by a correlation with a 14β-androstane derivative where participation of C-8 and C-9 need not be considered (A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica and O. Wintersteiner, THIS JOURNAL, **74**, 5506 (1952)).

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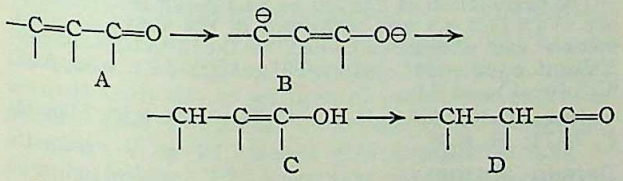
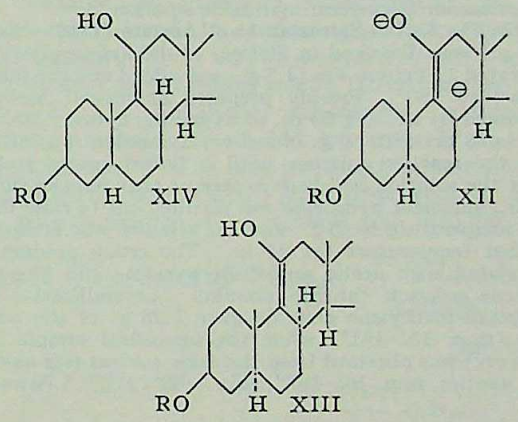
known configuration at C-8 and C-9 establishes[10] the stereochemistry of the *chemical reduction product* (VI) of the 14β-Δ^8-11-ketone IV and thus offers an important reference compound. The plausible criterion[8,13] that chemical reduction of an α,β-unsaturated ketone (under equilibration conditions) gives the thermodynamically more stable product could, *a priori*, not have been applied easily to the present case (IV) since the energy differences are probably small. While VIII is surely the least favored (ring B present as boat),[7] analysis by Johnson's method[14] —determination of number of equatorial and axial bonds by which the central ring is joined to its two neighbors—shows only a difference of one axial bond in favor of the all-chair 8β,9α-isomer VI over the all-chair 8α,9α-isomer V.[15]

The present chemical proof that the lithium–ammonia reduction product is represented by the 8β,9α-11-ketone VI offers also a means of establishing the stereochemistry of the *catalytic hydrogenation* product of the 14β-Δ^8-11-ketone IV. Since the hydrogenation product was stable to heating with alkali,[6] the 8β,9β-isomer VII is excluded since it would have led to the chemical reduction product VI, which was also unaffected by base. This leaves only 22a,25a,5α,8α,14β-spirostan-3β-ol-11-one (Va) as the appropriate structure for the hydrogenation product since it (all-chair conformation) would not be expected to be isomerized to the *trans*-isomer VIII (requiring ring B as a boat).[7]

It has been suggested[8] that reduction of α,β-unsaturated ketones A by metals in liquid ammonia proceeds *via* the dianion B which is protonated to the enol C and then furnishes the saturated ketone D. This implies that the controlling factor for the eventual stereochemistry of the saturated ketone D is the protonation step of the β-carbon atom, since the more stable orientation at the enolizable α-position (*cf.* C) will be governed by it.[16]



The above course of the reaction (A → D) is in accordance with all the reductions reported so far[8,13] for unsaturated alicyclic ketones and in each instance protonation of the β-position resulted in a *trans* or *anti* relationship with respect to hydrogen or methyl at the γ-carbon atom. The presently investigated reduction of the 14β-Δ^8-11-ketone IV demonstrates clearly that this need not be the case. Rather than indicating that protonation at the β-carbon atom does not occur first, the *syn* configuration for the present case provides good support for the conclusion that metal–ammonia reduction will give the more stable stereoisomer insofar as the β-position is concerned.[16,17] Conformational analysis suggests that the same factor[15] favoring the ketone VI (8β,9α) over V (8α,9α) also applies to the enols XIV (8β) and XIII (8α) and that consequently the *syn*-stereochemistry (XIV) is produced.



With the stereochemistry of the 11-oxygenated sapogenins (V and VI) established, these compounds can now serve as standard starting materials for the synthesis of 11-oxygenated steroids with abnormal configuration. Side chain degradation of V and VI led respectively to Δ^{16}-8α-14β-allopregnene-11,20-dione-3β-ol acetate (XVb) and Δ^{16}-14β-allopregnene-11,20-dione-3β-ol acetate (XVIb), which could represent key intermediates for the synthesis of 14-iso and 8-iso-14-iso 11-oxygenated cortical hormones. In the case of Δ^{16}-14β-allopregnene-11,20-dione-3β-ol acetate (XVI) it was also attempted to synthesize the corresponding 17-ketone XVIIb by Beckmann rearrangement of its oxime,[18] and while it was possible to isolate the desired substance, the yield was sufficiently poor to discourage further transformations.[19]

Experimental[20]

Δ^8-22a,25a,5α,14β-Spirosten-3β-ol-11-one Acetate (IVb). —Since only the propionate IVc had been described earlier,[6] a sample of the alcohol IVa[6] was acetylated with acetic anhydride–pyridine overnight and recrystallized from ether–hexane, m.p. 188–190°, $[\alpha]_D$ +86°; $\lambda_{max}^{CHCl_3}$ 5.76, 5.98, 6.18 (weak) and 8.0 μ.

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 74.33; H, 9.29.

(13) Leading references are given by H. Heusser, M. Roth, O. Rohr and R. Anliker, *Helv. Chim. Acta*, **38**, 1178 (1955).

(14) W. S. Johnson, *Experientia*, **7**, 315 (1951); THIS JOURNAL, **75**, 1498 (1953).

(15) The important factor to be considered is the nature of the non-bonded interaction produced by the additional axial linkage. In point of fact, this is rather serious in the 8α,9α-11-ketone V since ring C is now present in a different chair conformation (not possible in the 14α-series because of the *trans* C/D ring juncture) with an equatorial C-13 angular methyl group, whereby there is produced a 1,3-diaxial interaction between the C-10 angular methyl group and the 8–14 bond. No such interaction is present in the 8β,9α-isomer.

(16) Provided the reaction mixture is worked up under equilibration conditions. H. E. Zimmerman (THIS JOURNAL, **78**, 1168 (1956)) and A. J. Birch, H. Smith and R. E. Thornton (*J. Chem. Soc.*, 1339 (1957)) have called attention to the fact that under non-equilibrium conditions the unstable isomer (at the α-position) may be formed.

(17) An exception to this statement has been presented recently in the decahydrochrysene series in the reduction of a styrene double bond by W. S. Johnson, J. Ackerman, J. F. Eastham and H. A. De Walt (THIS JOURNAL, **78**, 6302 (1956)). However, a complicating factor was the presence of a hydroxyl group at the ring juncture which may have directed attack to the opposite side of the molecule because of electrostatic repulsion.

(18) G. Rosenkranz, O. Mancera, F. Sondheimer and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956).

(19) Originally, it had been planned to prove the stereochemistry of 22a,25a,5α,14β-spirostan-3β-ol-11-one (VIa) *via* XVI and XVII followed by Clemmensen reduction to 14β-androstan-3β-ol.

(20) Melting points are uncorrected. Rotations were measured in chloroform solution in 1-dcm. tubes. The microanalyses were performed by Geller Laboratories, Hackensack, N. J.

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22a,25a,5α,14β-Spirostan-3β-ol-11-one (VIa).—The earlier reported reduction[6] (of the propionate IVc) was carried out in slightly modified form (with the acetate IVb) on a larger scale. A solution of 6.0 g. of the above acetate IVb in 50 cc. of dry ether was added with stirring at −40° to a solution of 400 mg. of lithium in 500 cc. of liquid ammonia. After stirring for 4 min., the excess metal was decomposed by the addition of ammonium chloride, the ammonia was allowed to evaporate and the residue was treated with 5% methanolic potassium hydroxide for 1 hr. with occasional warming. Isolation with ether yielded 5.2 g. of solid (m.p. 216–220°) which was chromatographed on 200 g. of alumina. Elution with benzene–ether and recrystallization from ether–hexane furnished 3.01 g. of the saturated ketone VIa[6] as needles, m.p. 236–239°. The substance was recovered unchanged after being heated under reflux for 20 hr. with 5% ethanolic potassium hydroxide solution.

22a,25a,5α,14β-Spirostan-3β-ol Acetate (IXb).—Sodium (2.0 g.) was dissolved in 200 cc. of diethylene glycol, the saturated 11-ketone VIa (1.5 g.) was added and the solution heated to 180°. Freshly prepared anhydrous hydrazine (obtained by heating 50 cc. of hydrazine hydrate under reflux for 3 hr. with 50 g. of sodium hydroxide) was distilled into the reaction mixture until it boiled gently at 180°. After the solution had been heated at that temperature for 18 hr., sufficient hydrazine was distilled out to raise the reflux temperature to 210°, and the mixture was maintained at that temperature for 24 hr. The crude product was acetylated with acetic anhydride–pyridine and filtered in benzene solution through alumina. Crystallization from methanol–methylene chloride gave 1.25 g. of the acetate IXb (m.p. 155–161°) while the analytical sample (85% recovery) was obtained from the same solvent pair as colorless needles, m.p. 165–167°, $[\alpha]_D$ −38°, $\lambda_{max}^{CHCl_3}$ 5.79 and 8.0 μ.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 76.11; H, 10.05.

Δ16-14β-Allopregnen-3β-ol-20-one Acetate (Xb).—The above sapogenin IXb (1.5 g.) was heated in 10 cc. of acetic anhydride in a sealed tube for 9 hr. at 195°. The cooled reaction mixture was poured onto ice and the product was isolated with ether. Chromium trioxide (0.9 g.) in 10 cc. of 90% acetic acid was added dropwise to a solution of the furosten in 35 cc. of 80% acetic acid and 24 cc. of ethylene dichloride, the solution then being stirred for 2 hr. at room temperature. Extraction with ether yielded a gum which was adsorbed on 60 g. of basic alumina in benzene solution. After standing for 1 hr., the product was eluted with benzene and 1:1 benzene–ether and recrystallized from methanol; yield 0.33 g., m.p. 167–170°. Further recrystallization from methanol gave the analytical sample with the following constants: m.p. 170–172°, $[\alpha]_D$ +74°; λ_{max}^{EtOH} 242 mμ, log ε 3.95; $\lambda_{max}^{CHCl_3}$ 5.79, 5.99, 6.21 (weak) and 8.0 μ.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.16; H, 9.71.

14β,17α-Allopregnan-3β-ol-20-one Acetate (XIb).—The Δ16-20-ketone Xb (250 mg.) in 50 cc. of ethyl acetate was shaken with 10% palladized charcoal (70 mg.) in an atmosphere of hydrogen for 1 hr. The uptake of hydrogen was rapid and the crude reduction product showed no significant ultraviolet absorption at 242 mμ. Crystallization from aqueous methanol yielded the saturated ketone (XIb) as laths (185 mg.), m.p. 109–110°, $[\alpha]_D$ +7°; $\lambda_{max}^{CHCl_3}$ 5.79, 5.85 and 8.0 μ. Identity with authentic specimens,[11,12] kindly provided by Dr. H. Heusser (E. T. H., Zurich) and Dr. H. B. MacPhillamy (Ciba Pharmaceutical Products, Summit, N. J.), was established by mixture melting point determination and by infrared comparison.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.71; H, 10.10.

Δ16-14β-Allopregnene-11,20-dione-3β-ol Acetate (XVIb).—The side chain degradation of 1.3 g. of 22a,25a,5α,14β-spirostan-3β-ol-11-one (VIa) was carried out exactly as described above for the 11-desoxo compound and yielded 470 mg. of crude, crystalline ketone (λ_{max}^{EtOH} 235 mμ, log ε 3.89). Recrystallization from aqueous acetone furnished 390 mg. of the analytical sample as needles, m.p. 182–184°, $[\alpha]_D$ +34°; λ_{max}^{EtOH} 235 mμ,[21] log ε 3.90; $\lambda_{max}^{CHCl_3}$ 5.80, 5.84, 5.98, 6.15 (weak) and 8.0 μ.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.57; H, 9.03.

14β-Androstane-11,17-dione-3β-ol Acetate (XVIIb).—The Δ16-11,20-diketone XVIb (390 mg.) in ethanol (2 cc.) and pyridine (0.5 cc.) was heated under reflux with 170 mg. of hydroxylamine hydrochloride for 30 min. No solid separated on leaving the solution at 20° for 18 hr. Accordingly, the oxime was precipitated with water, collected and dried *in vacuo* over phosphorus pentoxide.

The crude oxime was dissolved in 2 cc. of pyridine, cooled to 0° and a solution of *p*-acetamidobenzenesulfonyl chloride (0.5 g.) in 2 cc. of pyridine was added. The solution was kept at 20° for 2 hr. during which time a considerable amount of discoloration occurred. On addition of water a black gum separated which could not be induced to solidify. Sulfuric acid (5.5 cc. of 10%) was added and the reaction mixture was heated on the steam-bath for 2 hr. The residual solid was collected and extracted several times with benzene. Evaporation of the combined extracts afforded 90 mg. of a gummy solid which was crystallized from methanol to give 40 mg. of the 11,17-diketone XVIIb as needles, m.p. 248–253°. The analytical specimen was sublimed at 160° and 0.005 mm. and exhibited m.p. 251–255°; $\lambda_{max}^{CHCl_3}$ 5.75, 5.79–5.84 (broad) and 8.0 μ.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 73.02; H, 8.94.

It should be noted that no difficulty was encountered in duplicating the recorded yield[17] in a model experiment with Δ5,16-pregnadien-3β-ol-20-one acetate.

Δ16-8α,14β-Allopregnene-11,20-dione-3β-ol Acetate (XVb).—The degradation of 22a,25a,5α,8α,14β-spirostan-3β-ol-11-one (Va)[6] (1.2 g.) was performed in the above described manner and afforded 200 mg. of the Δ16-11,20-diketone XVb, m.p. 131–132°, $[\alpha]_D$ +99°; $\lambda_{max}^{CHCl_3}$ 5.81, 5.85, 5.98, 6.13 (weak) and 8.0 μ.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.74; H, 8.58.

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(21) A similar bathochromic shift due to the 11-ketone has been observed in the 14α-series (E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951); C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *ibid.*, **74**, 3634 (1952)).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

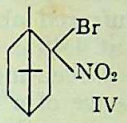
Structure of the Anhydrobromonitrocamphanes

BY EUGENE E. VAN TAMELEN AND JOSEPH E. BRENNER[1]

RECEIVED JANUARY 30, 1957

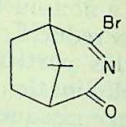
Structures I and II are proposed for anhydrobromonitrocamphane-I and -II, first prepared in 1899 by acid treatment of 2-bromo-2-nitrocamphane.[2]

During the course of his investigations dealing with the preparation and properties of (−)-2-bromo-2-nitrocamphane (IV), Forster[2] subjected

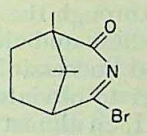


IV

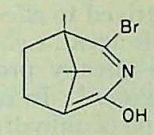
the substance to the action of concentrated sulfuric acid at 0° and found that there was formed, in addition to some 2-bromo-*p*-cymene, a crystalline *monodehydration product* (I). The same author noted further that hot, aqueous mineral acid induced the transformation of this anhydride into a well-defined *isomer* (II).[2] A similar pair of products was secured from 2-chloro-2-nitrocamphane,[3] although 2-nitro- and 3-bromo-2-nitrocamphane were indifferent to the acid reagent.[4] Following additional study,[4] Forster in 1901 suggested for I (referred to herein as "anhydrobromonitrocamphane-I") an *N-acyliminobromide structure* (V or VI), which Ginnings and Noyes[5] later adopted in



V



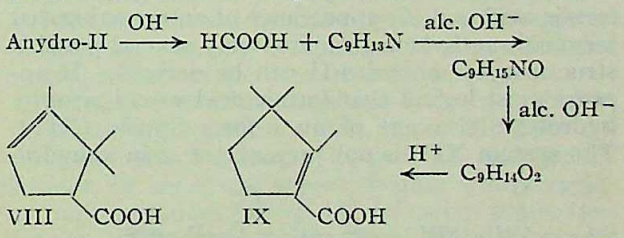
VI



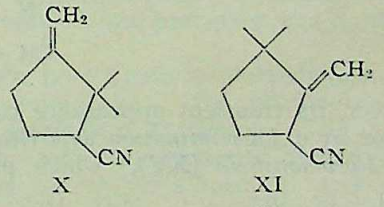
VII

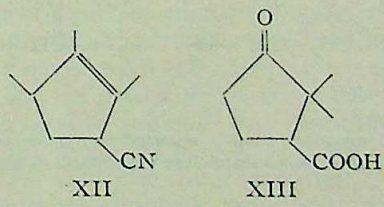
their *enol formulation* (VII) for the isomer II ("anhydrobromonitrocamphane-II"). For several, readily apparent, reasons the proposal VII can be dismissed. Moreover, Forster's structure hardly accords with the experimental facts; for example, mineral acid treatment of a compound possessing structure V or VI should give camphoric acid or camphorimide. The ineptness of the bromonitrocamphane structure for accommodating a dehydration reaction,[4] we, as did Forster, found arresting; consequently we took up the matter, which seemingly had lain unattended since 1922.[5]

Since there has been recorded more chemical information about anhydro-II, this isomer appeared better suited for initial study. Forster reported that, in addition to hot hydrochloric acid, various mild bases such as hydroxylamine, phenylhydrazine and alcoholic ammonia served to convert anhydro-I to -II,[4] and we have observed that the change can be brought about by heat alone. It is recorded that anhydro-II melts at 240° and is optically inactive. The substance was negative in the Liebermann nitroso reaction and was stable to bromine, permanganate and zinc dust and acetic acid. A benzoyl derivative resulted from treatment with benzoyl chloride. But by far the most provocative and valuable of Forster's observations is the change engendered by refluxing dilute aqueous alkali: *anhydro-II, as well as anhydro-I, was cleaved to formic acid and a liquid nitrile possessing the formula* $C_9H_{13}N$.[2] The latter substance, on hydrolysis with alcoholic alkali, led successively to the amide and acid.[6] The end product, isomeric with α-campholytic acid (VIII) and isolauronolic acid (IX), was transformed by mineral acid into the lat-



ter of these two previously known substances. Of the structures for the C_9-nitrile which can accommodate these results (*e.g.*, X-XII), 2,2-dimethyl-3-





methylenecyclopentanecarbonitrile (X) has been established as correct, in that ozonization led to formaldehyde and the known 2,2-dimethyl-3-ketocyclopentanecarboxylic acid (XIII).[7,8] The

(1) Wisconsin Alumni Research Foundation Research Assistant.
(2) M. O. Forster, *J. Chem. Soc.*, **75**, 1141 (1899).
(3) M. O. Forster and W. Robertson, *ibid.*, **79**, 1003 (1901).
(4) M. O. Forster, *ibid.*, **79**, 653 (1901).
(5) P. M. Ginnings with W. A. Noyes, THIS JOURNAL, **44**, 2567 (1922).
(6) M. O. Forster, *J. Chem. Soc.*, **79**, 108 (1901).
(7) Experimental result obtained in this Laboratory and also reported as an undocumented item by J. L. Simonsen "The Terpenes," Vol. II, Cambridge University Press, Cambridge, 1949, p. 367.
(8) Before obtaining the new C_9-acid corresponding to the C_9-nitrile, Forster erroneously believed[2] that he had in hand the previously unknown nitrile (and amide) of α-campholytic acid (VIII). Later G. Blanc (*Bull. soc. chim.*, **23**, 695 (1900)) reported that sodium and alcohol reduction of Forster's nitrile afforded α-aminocampholene, identical with the product of hypohalite degradation of α-campholenamide, which at that time Blanc believed to possess structure i. The α-campholenamide structure was soon revised to ii, however; and Forster, on the basis of Blanc's experimental finding, therefore assigned[6] structure iii to his nitrile ("infracampholenonitrile"). Forster was then compelled to "revise" the structure for campholytic acid which is now known to be correct, and he regarded it as best represented by iv. With the structures of all these substances now estab-

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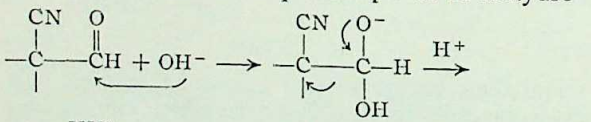
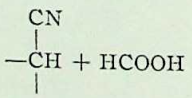
structure assignment was in agreement with the ultraviolet spectrum, showing no selective absorption, and the infrared spectrum, which revealed the nitrile function (4.48 μ) and the terminal methylene grouping (6.08 and 11.27 μ).

The nature of the reactive centers in anhydrobromonitrocamphane-II was clarified by means of its infrared spectrum: well-defined peaks at 2.80 and 4.48 μ definitely indicated the presence of hydroxyl and nitrile functions. Furthermore, the anhydro compound was virtually transparent in the ultraviolet, and infrared bands indicative of a terminal methylene grouping were absent; thus it appeared that this molecule was saturated. Forster's conversion of anhydro-II to a benzoyl derivative (absorption at 4.48 and 5.82 μ) also points to a hydroxyl substituent, and this conclusion has been supported further by the preparation of a methanesulfonate.

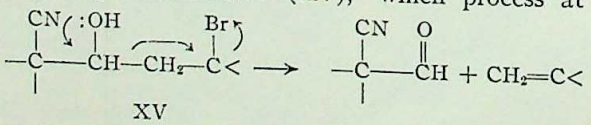
By incorporating the above information into a mechanistic scheme which satisfactorily accounts for (1) the conversion by base to the C_9-nitrile and formic acid and (2) appearance of an unconjugated terminal methylene grouping, only several possible structures for anhydro-II can be derived. It appears most logical that formic acid would arise by hydrolytic cleavage of an α-formylnitrile (XIV). The system XIV is not present *per se* in anhydro-



XIV

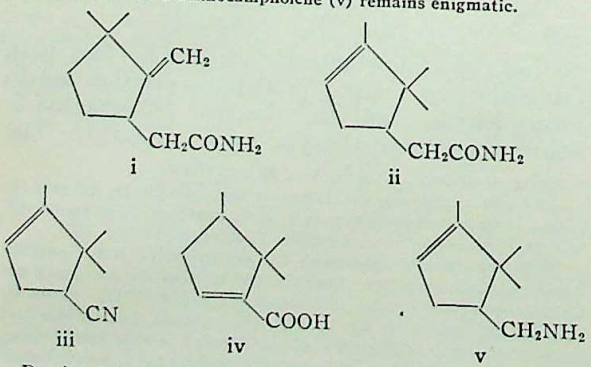


II; however, its transient appearance can be accounted for by *a 1,4-elimination with cleavage of a β-hydroxy-δ-bromonitrile* (XV),[9] which process at



XV

lished beyond question, Blanc's reported conversion of "infracampholenonitrile" to α-aminocampholene (v) remains enigmatic.

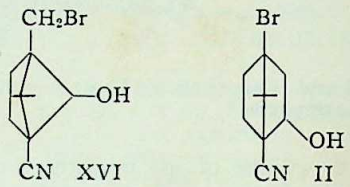


i ii iii iv v

Despite the conflicting and insufficient evidence, structure X has been assumed to represent Foster's nitrile (Beilstein's "Handbuch der Organischen Chemie," Vol. IX, Julius Springer, Berlin, 1926, p. 61; E. Josephy and F. Radt, Elsevier's "Encyclopedia of Organic Chemistry," *Ser. III*, Vol. 12A, Elsevier Publishing Co., Inc., New York, N. Y., 1948, p. 600).

(9) C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955).

the same time generates the required olefinic linkage. Application to the case under consideration leads to the formulations XVI and II for anhydro-II. Now, chromic acid oxidation afforded a crys-

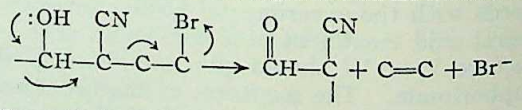


XVI II

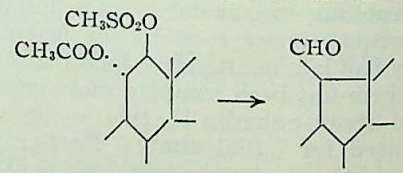
talline ketone, m.p. 237°, which regenerated anhydro-II in high yield on reduction with sodium borohydride. The infrared absorption of the ketone featured bands at 4.48 μ—indicating that the nitrile portion had not been modified—and at 5.71 μ, revealing the presence of a cyclopentanone system, a result at variance with that anticipated for structure XVI. Apart from this, the indifference of anhydro-II toward hot silver nitrate is difficult to accommodate on the basis of XVI; II, however, bears a bridgehead halogen, well-recognized for its inertness under SN1 conditions.[10]

Although II (2-hydroxy-4-bromoapocamphane-1-carbonitrile) remains as the solely acceptable structure for anhydro-II, independent confirmation of the proposal was sought. The carbon–oxygen system of camphor is, of course, present, and it seemed that conversion to some appropriate member of that family would serve admirably as a structural proof. In that regard we faced hydrogenolytic removal of the bridgehead halogen, which we contrived to effect through the use of a non-nucleophilic agent, *e.g.*, sodium and alcohol, a reducing device already proved successful for this particular purpose.[11] In order to obviate the elimination reaction of anhydro-II, an almost certain consequence of employing the basic reducing agent, the hydroxyl group was protected by conversion to the tetrahydropyranyl ether (XVII).[12] Hydrogenolysis and

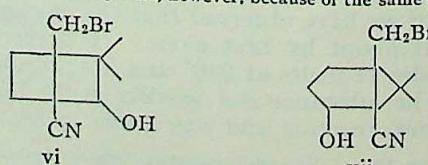
(10) In a related, but less likely, process, a β-cyano-δ-bromo alcohol eliminates, accompanied by bond migration from the alcoholic carbon



(Witness the base-induced rearrangement observed in the steroid



series (N. L. Wendler, R. F. Hirschmann, H. L. Slates and R. W. Walker, THIS JOURNAL, **77**, 1632 (1955)). The implied structures vi and vii are unacceptable, however, because of the same considerations



vi vii

which allow elimination of XVI.

(11) G. Komppa and T. Hasselstrom, *Ann.*, **496**, 164 (1932).

(12) W. E. Parham and E. L. Anderson, THIS JOURNAL, **70**, 4187 (1948).

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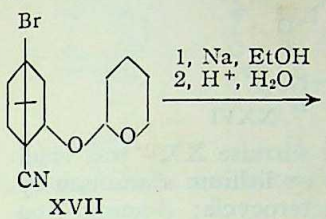
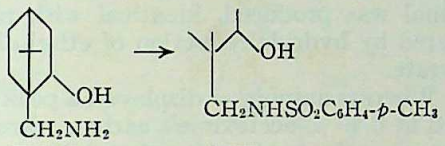
reduction of the nitrile to a primary amino group were effected simultaneously; and the intermediate ether was hydrolyzed without isolation to the free aminoalcohol XVIII, which in turn was converted

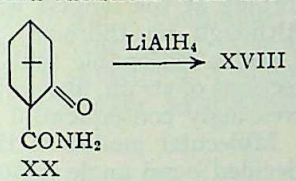


XVII



XVIII XIX

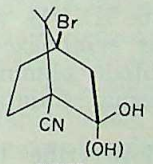
directly to the crystalline *p*-toluenesulfonamide XIX, m.p. 165–166°. This same sulfonamide was found to be derivable from the well-known ketopinic acid.[13] Preparation of ketopinamide (XX) was followed by lithium aluminum hydride reduction; the *p*-toluenesulfonamide of the resulting aminoalcohol was found identical with the corresponding



XX

derivative secured from anhydro-II. The sulfonamide was characterized by chromic acid oxidation to a crystalline ketone, which displayed carbonyl absorption in the infrared at 5.8 μ.

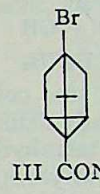
The stereoelectronic demands of the elimination reaction leading to the C_9-nitrile are satisfied by the proposed structure—halogen as well as carbons 2, 3 and 4 describe a plane, as illustrated in XXI.



XXI

Although the carbon–oxygen bond cannot lie in this plane, its geomtery is probably not critical for the elimination[14]; conversely, no conclusion regarding the configuration of the hydroxyl can be drawn from the elimination result.

During the period when we were gathering evidence bearing on the structure of anhydrobromonitrocamphane-I (*vide infra*), its reconstitution from anhydro-II was attempted. Concentrated sulfuric acid, acting for three days at room temperature on the stabler anhydride, did indeed bring about a change, although examination of the product showed it to be a *new isomer* (m.p. 201–202°), which was designated as *anhydrobromonitrocamphane-III*. Simple diagnostic tests revealed the substance to be neutral, and stable to bromine, chromium trioxide or permanganate in the Baeyer test; and infrared spectral analysis led to the conclusion that a primary amide (6.08 and 6.41 μ) grouping was present. Confirmation of this structural feature was found by conversion with nitrous acid to a carboxylic acid which, as its methyl ester, was reduced by lithium aluminum hydride to an alcohol, characterized as a 3,5-dinitrobenzoate. The chemistry described is well accommodated by the structure III for anhydro-III, which arises by



III

controlled nitrile hydrolysis accompanied by 2,6-dehydration with formation of a cyclopropane ring.[15] The formulation III (4-bromotricyclenamide) is strengthened by the persistence throughout the series of a strong band at *ca.* 10 μ, attributable to the presence of the three-membered ring.

Anhydrobromonitrocamphane-I is a colorless substance which does not melt, but at 210–220° decomposes and rearranges in part to anhydro-II. Forster, in his initial report dealing with this dehydration product,[2] listed the following properties: negative Liebermann nitroso test; stability to cold concentrated nitric acid, hot concentrated sulfuric acid, boiling pyridine and bromine in chloroform; oxidation by permanganate in dilute sulfuric acid. Like anhydro-II, the precursor was optically inactive.

Our own investigations started, again, with a spectral examination: the ultraviolet spectrum showed a single band at 225 mμ (ϵ 2300); in the infrared there was no evidence of hydroxyl or nitrile absorption but rather a medium peak at 6.40 μ, suggestive of a carbon–nitrogen double bond.

Since anhydro-I is transformed readily to -II (or products derived from -II[4]), acquisition of chemical evidence for the structure of the former under as mild conditions as possible was desirable. Reduction seemed most promising, and we accordingly studied the catalytic hydrogenation, as well as lithium aluminum hydride reduction, of the parent anhydride. The hydride reaction, carried out under normal conditions, provided a mixture of products, from which were separated two crystalline materials. One of these, isolated in about 20% yield, was indicated by analysis to be a dihydroanhydro-I, which was not investigated further. The second product, a base formed in 60% yield, was readily recognized as a tetrahydroanhydro-I and was characterized by conversion to N-toluenesulfonyl and N-benzoyl derivatives. The catalytic reduction of anhydro-I in ethanol–sulfuric acid proceeded to give a tetrahydro product, isolated as the sulfate salt, which was converted directly to an N-benzoyl derivative identical with that secured from the hydride reduction. This amine appeared to be a *bona fide* reduction product of anhydro-I, in that

(13) P. D. Bartlett and L. H. Knox, THIS JOURNAL, **61**, 3184 (1939).

(14) Pointed out by Professor John D. Roberts, California Institute of Technology.

(15) *Cf.* the dehydration of 2-hydroxyapocamphane-1-carboxylic acid to apocamphane-1-carboxylic acid (R. Lipp, *Ann.*, **402**, 343 (1902)).

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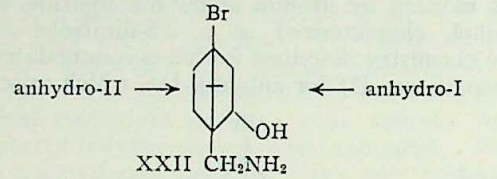
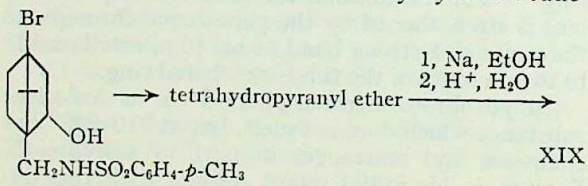
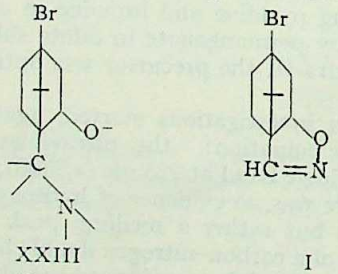
the latter remained unaltered when subjected, in the absence of hydrogen, to the catalytic hydrogenation conditions used. Structure assignment to the tetrahydro compound was made possible by the finding that *this same base resulted from lithium aluminum hydride or catalytic reduction of anhydro-II*—only the aminoalcohol formulation XXII is reasonable. This assignment was confirmed by relating the amine to one of already demonstrated structure. The sulfonamide of the tetrahydro compound, after conversion to the tetrahydropyranyl ether, was reductively debrominated by sodium and alcohol; mild acid hydrolysis then yielded the sulfonamide XIX of the same amine secured by hydride reduction of ketopinamide. These findings led to the important conclusion that *anhydro-I and -II possess the same carbon–oxygen–nitrogen skeleton* (*XXIII*).

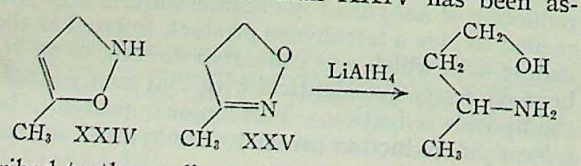




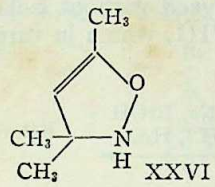


Moreover, the molecular formula requirement, taken together with the absence of –NH, –OH and –CN stretching absorption in the infrared region, invalidate all sterically possible structures for anhydrobromonitrocamphane-I but one: *the isoxazoline* (I).

In order to consolidate the evidence bearing on this proposal, we set about to gather, from model compounds, information which would impart significance to the spectral properties of anhydro-I. Unfortunately, there appeared to be no information available on the spectral behavior of oxime-O-ethers, and the literature seemed wanting in examples of purely aliphatic Δ^2-isoxazolines to which structures had not been assigned arbitrarily or on the basis of meager evidence. For example, the structure XXV rather than XXIV has been ascribed to the cyclic product obtained by the interaction of hydroxylamine with 2-methyl-*p*-chlorostyryl



ketone[16]; contrarily, elsewhere the inorganic reagent is claimed[17] to convert mesityl oxide to the Δ^4-isoxazoline XXVI. The surmise XXV was vindicated in this Laboratory by lithium aluminum hydride reduction of the heterocycle; 3-amino-1-butanol was produced, identical with material prepared by hydride reduction of ethyl *dl*-β-aminobutyrate.

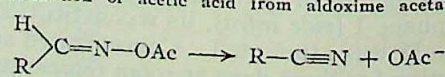


Whereas anhydro-I displayed a peak in the infrared at 6.40 μ, acetoxime's carbon–nitrogen stretching was reflected by a band at 6.01 μ and that of 3-methyl-Δ^2-isoxazoline (XXV), at 6.17 μ. In the ultraviolet region, acetoxime-O-acetic acid[18] absorbed in the shorter wave length region without indication of a peak; the isoxazoline, however, possesses a band at 212 mμ (ϵ 2830). Thus the models and anhydro-I constitute, in both the infrared and ultraviolet regions, a short graded series with the terpenoid absorbing at the longest wave length in each case. Although no thorough analysis was carried out, it seems reasonable that the observed values are reflections of strain, absent in the acyclic cases, but increasingly consequential in the cycles XXV and I. Molecular models of the last structure showed decided bond angle distortion, apparently relieved by electronic displacement and thus accounting for the lower energy requirements for absorption in the ultraviolet. At the same time, the infrared values cited parallel those recorded for cycloalkenes and cyclic imines of medium ring size.[19]

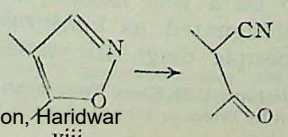
Justification of structure I, insofar as rational conversion to anhydro-II is concerned, offers no great problem. The acid-catalyzed process may be represented by scheme XXVII, whereas the change initiated by base is symbolized by the process XXVIII.[20] Undoubtedly elimination is facilitated by release of the internal strain afflicting the starting isomer.

Inspection of models verifies that an isoxazoline I utilizing an *endo* bond for attachment of oxygen is almost impossibly strained. Accordingly the stereochemistry of anhydro-I can be depicted by

(16) E. E. Blaise and M. Maire, *Compt. rend.*, **142**, 216 (1899).
(17) C. Harries and L. Jablonski, *Ber.*, **31**, 1376 (1898).
(18) The 6μ region of acetoxime-O-acetic acid is uninformative, because of the broad carbonyl base.
(19) B. Witkop, THIS JOURNAL, **78**, 2873 (1956).
(20) Elimination of acetic acid from aldoxime acetates yields



nitriles, and many isoxazoles (viii) isomerize to the ketonitriles (W. S. Johnson and W. E. Shelberg, *ibid.*, **67**, 1745 (1945)). Both processes are brought about by base.



viii

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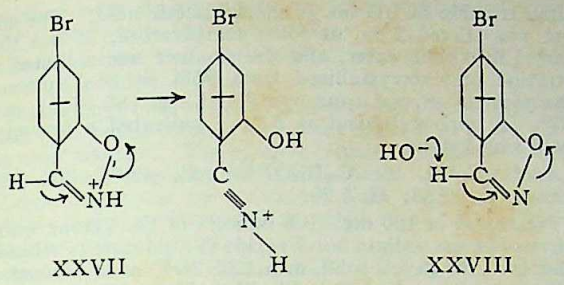
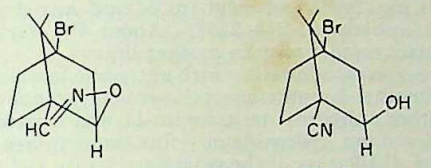


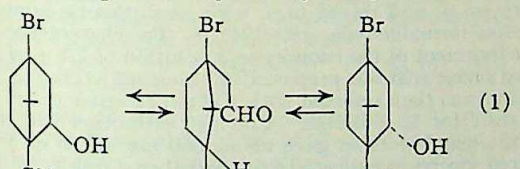
XXVII XXVIII

formula XXIX, *i.e.*, involving fusion of the hetero-



XXIX XXX

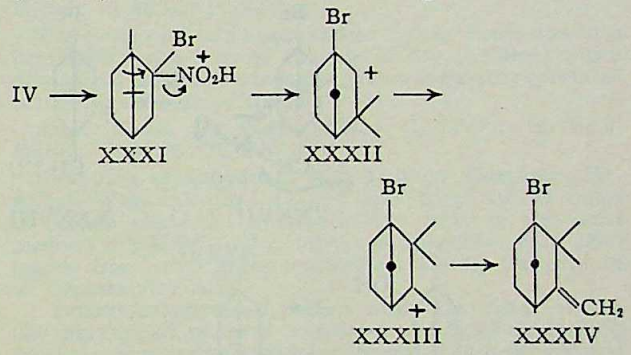
cyclic ring to the camphane system through an *exo* bond, an arrangement still implying definite distortion. The stereochemistry of anhydro-II cannot be disposed of so easily. If, in proceeding from I to II, we assume that no change other than that described by the mechanism considered above (XXVII or XXVIII) occurs, the stereochemical integrity of the hydroxyl group will be maintained, and the configurational assignment XXX is automatic. On the other hand, a subsequent equilibrium system (1) involving the bicyclic hydroxynitrile and the



XXX (1)

monocyclic aldehydronitrile is conceivable and would provide for conversion of the *exo* (less stable[21]) configuration of XXX to the *endo*. The regeneration of anhydro-II through sodium borohydride reduction of the corresponding ketone, a reaction which parallels the lithium aluminum hydride reduction of camphor to isoborneol,[22] also implies, in the simplest interpretation, the *exo* configuration. However, the case is again weakened by the same equilibrium consideration. A secure stereochemical assignment is made possible by reference to the hydrogenation results already detailed. Both anhydro compounds yield the same tetrahydro isomer, which is no longer epimerizable at C-2; since the hydrogenation conditions used are not likely to effect inversion at some intermediary stage,[23] oxygen attachment is *exo* (XXX) in anhydro-II, as in -I. Corollarially, the aldo-type equilibrium (1) considered above cannot intervene to the extent that any detectable amount of the more stable *endo* isomer of anhydro-II accumulates. Further, the hydride reduction of the ketones in this series must then, as in the camphor case, provide the less stable of the possible diastereoisomeric alcohols.

Associated with the structural clarification of anhydro-I is the more fundamental problem of its formation, a change involving a seemingly random reshuffling of non-skeletal atoms. Some order can be gained by considering, first of all, a series of Wagner–Meerwein shifts initiated by attachment of a proton to the nitro group of the starting material (XXXI). Nitrous acid, or its equivalent, is expelled and may remain associated with the cation, although its sphere of activity in these early stages is obscure. Production of the isocamphane skeleton involves a migration of methyl (XXXII → XXXIII) followed by elimination of a proton to give 4-bromocamphene (XXXIV). ω-Nitrosation ensues, yielding XXXV or XXXVI, and this recombination is followed by a second skeletal rearrangement, as expressed by the formulas (XXVI → XXVII). Closure (XXVII) of the isoxazoline ring (which one would anticipate to give the stabler form (*exo*) of I) completes the sequence.[24]



XXXI XXXII XXXIII XXXIV

Earlier it was noted that both I and II are optically inactive. This property can be best accounted for by assuming 2,6-hydrogen transfer at the stage XXXVII, resulting in racemization, either through simple enantiomer production (XXXVII → XXXVIII) or by way of a symmetrical cation.[25,26]

It is possible that reactions in the terpene series similar to those described above have been carried out but gone unrecognized. For example, Konovalov,[27] in 1902, recorded the conversion of camphene by dilute nitric acid at 100° to an oxidation product $C_{10}H_{15}NO$ (m.p. 266–267°). The substance was said to be stable in the bromine and permanganate tests but susceptible to the action of sodium and alcohol. More drastic acid conditions effected transformation to tricyclenic acid (XXXIX). These data, admittedly scanty, are interpretable

(21) Borneol (*endo*) is more stable than isoborneol (*exo*); J. L. Simonsen, "The Terpenes," Vol. II, Cambridge University Press, Cambridge, 1949, pp. 351–353.

(22) W. G. Brown, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 475.

(23) This same reaction cannot, in fact, be operative since the same aminoalcohol is secured from anhydro-II tetrahydropyranyl ether (XVII), which is not susceptible to the heavy-metal catalyzed, oxidation–reduction equilibrium necessary for inversion under these conditions.

(24) Certain features of this over-all change find analogy in, *e.g.*, the formation of β-camphor dichloride (J. Houben and E. Pfankuch, *Ann.*, **501**, 219 (1933)) and camphor-10-sulfonic acid (E. Wedekind, D. Schenk and R. Stusser, *Ber.*, **56**, 633 (1923)) from camphor.

(25) J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., This Journal, **76**, 4501 (1954).

(26) The most recent publication[5] dealing with anhydro-I or -II describes the action of methylmagnesium iodide on -I. The intermediate ($C_{11}H_{18}ONBr$) was reported to undergo hydrolysis with alkali, affording 1,2,2-trimethyl-3-acetylcyclopentanecarboxylic acid. However, the final product was not compared with authentic material, nor was an analysis reported; consequently, we do not believe that this claim need be reconciled with the findings and conclusions reported in this contribution.

(27) K. Konovalov, *J. Russ. Phys. Chem. Soc.*, **34**, II, 43 (1902).

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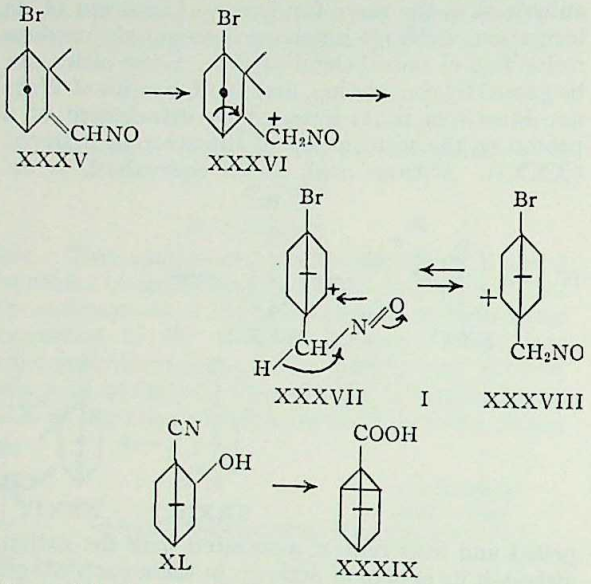
in terms of the structure XL, arising along lines considered above. Konovalov further states that, on treatment with fuming nitric acid, the $C_{10}H_{15}NO$ compound gave rise to a product $C_{10}H_{14}N_2O_3$, which regenerates the starting material on reduction with



tin and hydrochloric acid. A similar pair of reactions characterizes anhydrobromonitrocamphane-II,[2] and the infrared behavior indicates that the nitro derivative is merely the O-nitrate. This explanation is of course equally applicable to the Konovalov case.

Experimental[28]

Anhydrobromonitrocamphane-I.—A solution of 43 g. (0.16 mole) of bromonitrocamphane in 100 ml. of petroleum ether was dropped slowly into a vigorously stirred mixture of 300 g. of concentrated sulfuric acid and 50 ml. of petroleum ether held at −5°. After the addition was complete, the mixture was stirred an additional 0.5 hr., then poured on crushed ice. In order to obtain even fairly good crude material, it was found necessary to wash the precipitated product with dilute ammonia as it was being filtered, since it turned dark brown otherwise. This is in contrast to the experience of Ginnings and Noyes,[5] who state that the product precipitates "as a slightly yellow flocculent solid in nearly quantitative yield, pure enough for most purposes." Recrystallization from ethanol gave in general 18–25 g. of crude product (46–60%).

Anhydrobromonitrocamphane-II.—Refluxing a solution of 10 g. of anhydro-I in 30 ml. of 95% ethanol containing 5 ml. of 12 *N* hydrochloric acid gave anhydro-II essentially quantitatively; m.p., after recrystallization from ethanol–water, 244–245°.[2]

Treatment of II with methanesulfonyl chloride in dry pyridine gave a mesylate as needles from benzene–petroleum ether, m.p. 101–102°.

Anal. Calcd. for $C_{11}H_{16}O_3NSBr$: C, 41.00; H, 5.01. Found: C, 41.06; H, 4.75.

Heating II with fuming nitric acid for 10 minutes on the steam-bath gave a nitrate ester as needles from ethanol, m.p. 99–100°. Infrared bands at 6.07, 7.80 and 11.5 μ could be assigned to the nitrate grouping.

Anal. Calcd. for $C_{10}H_{13}O_3N_2Br$: C, 41.54; H, 4.53. Found: C, 41.59; H, 4.49.

Anhydro-II Ketone.—Anhydro-II (2.4 g., 0.01 mole) was dissolved in 50 ml. of glacial acetic acid and was added with stirring to a cooled mixture of 1.0 g. (0.01 mole) of chromium trioxide in 100 ml. of glacial acetic acid. The mixture was stirred 2 hr. at room temperature; it was then poured into cold water, and the product was collected by filtration and recrystallized from 95% ethanol (prisms). The yield in several runs was 2.1–2.3 g. (85–95%), m.p. 237°. A carbonyl band at 5.71 μ indicated a five-membered ring ketone.

Anal. Calcd. for $C_{10}H_{12}ONBr$: C, 49.55; H, 4.99. Found: C, 49.83; H, 5.20.

Treatment of 120 mg. (0.5 mmole) of the ketone with a slurry of excess sodium borohydride in a mixture of ethanol–ether for 1 hr. gave a solid, m.p. 235–238°, after decomposition of the excess hydride with dilute hydrochloric acid and the usual work-up. One recrystallization from ethanol gave 110 mg. (92%) of solid, m.p. and mixed m.p. with authentic anhydro-II 244–245°. About 4% starting material was recovered from the mother liquors, m.p. 235–237° (no depression on admixture with authentic ketone).

2,2-Dimethyl-3-methylenecyclopentanecarbonitrile (X).—When either anhydro-I or anhydro-II was treated with excess 30% sodium hydroxide at reflux temperature for 1 to 2 hr., steam distillation of the reaction mixture and extraction of the distillate with ether followed by the usual drying and distillation afforded *ca.* 40% of a sweet-smelling, mobile oil, b.p. 81° (16 mm.), $n^{25}D$ 1.4620.[2]

Ozonolysis of X.—A moderate excess of ozone was passed into a solution of 1.1 g. of nitrile X (0.00815 mole) in 50 ml. of cooled glacial acetic acid. Half this solution was poured into a 250-ml. flask containing 50 ml. of water and 2 g. of zinc dust; the mixture was steam distilled under nitrogen until 110 ml. of distillate was collected. Half of this was refluxed for 10 minutes with 1.0 g. of dimedon, 20 ml. of ethanol and 3 drops of pyridine and allowed to stand overnight in the cold. The other half was treated with 50 ml. of dimedon reagent, neutralized with 5 ml. of 5% hydrochloric acid and also allowed to stand in the ice-box overnight. The combined yield of adduct was 0.365 g., 25% of theory, m.p. and mixed m.p. with an authentic sample of dimedon–formaldehyde 189–191°.[29] To characterize the other fragment of the ozonolysis, a solution of 1.1 g. of X in glacial acetic acid was prepared and ozonized as above. The solution was then refluxed with 100 ml. of water and 4 g. of zinc dust for 15 minutes. Cooling, extraction with ether and the usual workup gave about 650 mg. of an oil whose infrared spectrum indicated a five-membered ring ketonitrile. This oil was refluxed with 20 ml. of 25% sodium hydroxide until the oil disappeared. The solution was cooled, acidified and extracted repeatedly with ether. Drying and evaporation of the ether yielded about 200 mg. of a glass which solidified on rubbing with cold methanol. It sublimed readily at 0.3 mm. on the steam-bath to give XII, m.p. 104–105°.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.95; H, 7.93.

The material was characterized by the preparation of an oxime, m.p. 195°, and a semicarbazone, m.p. 219–220°. Perkin and Thorpe[30] gave the following melting points for 2,2-dimethyl-3-ketocyclopentanecarboxylic acid: acid, 108–109°; oxime, 198°; semicarbazone, 215°. A mixed melting point of our material with authentic ketoacid XII was undepressed.[31] The infrared spectra were identical.

Anhydrobromonitrocamphane-III.—When anhydro-II was allowed to stand three days at room temperature in concentrated sulfuric acid, a product was obtained on pouring the sulfuric acid solution into cold water and recrystallizing the precipitate from ethanol. A sample recrystallized from ethanol for analysis melted at 201–202° (prisms).

Anal. Calcd. for $C_{10}H_{14}ONBr$: C, 49.18; H, 5.74. Found: C, 49.32; H, 5.81.

This material was further characterized as follows: treatment of a solution of the amide in dry chloroform in the presence of anhydrous sodium carbonate with nitrogen dioxide,[32] followed by acidification, drying and evaporation of the solvent, gave an acid. This acid was quantitatively

(28) Infrared spectra were taken on a Baird recording infrared spectrophotometer. Ultraviolet spectra were measured with a Cary spectrophotometer, on samples dissolved in ethanol.

(29) P. Karrer and J. Kebrle, *Helv. Chim. Acta*, **35**, 863 (1952).

(30) W. H. Perkin, Jr., and J. F. Thorpe, *J. Chem. Soc.*, **85**, 138 (1904).

(31) C. S. Gibson, K. V. Hariharan and J. L. Simonsen, *ibid.*, 3009 (1927).

(32) E. White, This Journal, **76**, 4497 (1954).

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esterified with diazomethane in ether solution to give a methyl ester, m.p. 69° (sublimed).

Anal. Calcd. for $C_{11}H_{15}O_2Br$: C, 50.98; H, 5.84. Found: C, 50.64; H, 5.80.

This methyl ester was converted to the alcohol by treatment with excess lithium aluminum hydride in dry ether in the usual manner. The product (feathery needles from ethanol) melted sharply at 160° (87% yield). Conversion to a 3,5-dinitrobenzoate by treatment with the corresponding chloride in dry pyridine gave material, m.p. 124–125° (leaflets from ethanol–water).

Anal. Calcd. for $C_{17}H_{17}O_6N_2Br$: C, 48.01; H, 4.03. Found: C, 48.46; H, 4.19.

Conversion of Anhydro-II to 2-Hydroxy-10-aminocamphane (XVIII).—Anhydro-II, 2.0 g. (0.0082 mole), was dissolved in 20 ml. of alcohol-free chloroform. To this was added 1.0 g. of dry, redistilled dihydropyran followed by four drops of concentrated hydrochloric acid and approximately 1 g. of anhydrous sodium sulfate.[12] The mixture was stirred 3 hr. at room temperature, then shaken with two 10-ml. portions of 30% sodium hydroxide. Ether was added and the organic layer washed with water. The usual work-up gave 2.3 g. of tetrahydropyranyl ether (XVII), m.p. 120–130°, star-shaped clusters of needles from hexane (89% yield).

The ether (1.76 g., 0.0054 mole) was dissolved in 75 ml. of refluxing absolute ethanol and 5 g. of sodium added in small pieces over a period of 2 hr. The solution was made acid to congo red with concentrated hydrochloric acid in ethanol (cooling), concentrated *in vacuo* on the steam-bath; the residue was taken up in water and extracted with ether. The aqueous layer was made basic with 10% sodium hydroxide and thoroughly extracted with ether. Drying and evaporation of the ether gave about 350 mg. of a slightly greenish oil. The yield is 39%. The material readily was converted with tosyl chloride in pyridine (or with 20% sodium hydroxide) to a sulfonamide (XIX), m.p. 165–166°, leaflets from ethanol–water. A sample was recrystallized from ethyl acetate for analysis (prisms).

Anal. Calcd. for $C_{17}H_{25}O_3NS$: C, 63.14; H, 7.79. Found: C, 63.45; H, 7.56.

Oxidation of XIX.—The sulfonamide (140 mg., 0.41 mmole) was dissolved in 10 ml. of glacial acetic acid, and 50 mg. (0.5 mmole) of chromic anhydride was added in small portions. The mixture was stirred magnetically at room temperature for an hour, then poured onto ice and extracted with ether. The usual workup gave 86 mg. of ketone, m.p. 130–133° (62% yield). After recrystallization from ethanol–water and then ethyl acetate, it melted at 144–146° (short rods).

Anal. Calcd. for $C_{17}H_{23}O_3NS$: C, 63.53; H, 7.21. Found: C, 63.66; H, 7.31.

Conversion of Ketopinic Acid to XVIII.—Ketopinamide was prepared by treatment of an ether solution of the acid chloride with a stream of anhydrous ammonia.[33] After evaporation of the ether and excess ammonia, the residue was treated with hot ethyl acetate. Inorganic material was removed by filtration, and the solution was evaporated to dryness, taken up in benzene and evaporated to dryness again. On trituration with petroleum ether, a nicely crystalline product was obtained, m.p. 190–194°, 4.6 g., 92% from 5.0 g. of acid. The amide is extremely soluble in cold water. Ketopinamide (1.50 g., 0.00825 mole) was dissolved in 25 ml. of dry tetrahydrofuran and added to a slurry of 2 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The mixture was refluxed with stirring under nitrogen for 2 hr. The usual workup gave about 1.2 g. of a slightly yellow oil. This was not purified but treated immediately with 25 ml. of 20% sodium hydroxide and 2 g. of tosyl chloride. The originally oily mixture solidified, on warming, after 10 minutes. After all excess tosyl chloride had decomposed, the precipitate was filtered, washed and dried to yield 2.25 g. of crude tosylamide, m.p. 153–156° (85%). On recrystallization from ethanol–water and then ethyl acetate, the m.p. was raised to 165–166°, and a mixed melting point with II gave no depression. The infrared spectra of the compounds were identical.

Anal. Calcd. for $C_{17}H_{25}O_3NS$: C, 63.14; H, 7.79. Found: C, 62.94; H, 7.86.

(33) E. Wedekind, *Ber.*, **57**, 664 (1924).

Oxidation with chromic anhydride in glacial acetic acid yielded a ketone, m.p. 144–145° after recrystallization from ethanol–water, identical (mixed m.p., infrared) with the corresponding ketone prepared from authentic XIX (see above).

Tetrahydroanhydro-II (XXII).—Anhydro-II (1.076 g., 0.00441 mole) was hydrogenated at atmospheric pressure in the presence of *ca.* 0.2 g. of prereduced platinum oxide in 95% ethanol; 93% of 2 moles of hydrogen was absorbed in 11 hr. (For no apparent reason, the reaction was sometimes complete, on approximately the same amounts of material, in 5 hr.) Workup yielded 980 mg. of an amine, m.p. after recrystallization from ethyl acetate–petroleum ether, 183–184°.

Anal. Calcd. for $C_{10}H_{18}ONBr$: C, 48.39; H, 7.31. Found: C, 48.15; H, 7.22.

The compound was characterized by the formation of a benzamide (with benzoyl chloride in dry pyridine) which crystallized as thin, rectangular plates from ethyl acetate–petroleum ether, m.p. 219–220°.

Anal. Calcd. for $C_{17}H_{22}O_2NBr$: C, 57.96; H, 6.29. Found: C, 57.70; H, 6.37.

Reduction of Anhydro-II with Lithium Aluminum Hydride.—When anhydro-II (1.5 g.) was reduced with an excess of lithium aluminum hydride in dry ether in the usual manner, it yielded 1.44 g. (95%) of an amine, m.p. 184° (plates from ethyl acetate–petroleum ether), identical in all respects with XXII.

Tetrahydroanhydro-II Sulfate from Anhydro-I.—When 900 mg. (0.0037 mole) of anhydro-I was dissolved in 95% ethanol containing an equimolar amount of sulfuric acid and the mixture hydrogenated as above (cooling), 2 moles of hydrogen were absorbed in 1 hr. The crude amorphous product crystallized as small plates from a mixture of ethanol and water containing a little sulfuric acid, m.p. *ca.* 318° (with vigorous decomposition).

Anal. Calcd. for $C_{20}H_{38}O_6N_2Br_2S$: C, 40.42; H, 6.44. Found: C, 40.35; H, 6.40.

To check the possibility that anhydro-I might have isomerized under the conditions of the reduction, 244 mg. (1 mmole) was stirred with 1 mmole of sulfuric acid in 25 ml. of 95% ethanol containing 50 mg. of platinum oxide for 3 hr. at room temperature. The usual workup and one recrystallization from ethanol gave material which was apparently pure anhydro-I according to its infrared. It showed characteristic anhydro-I behavior on melting.

Treatment of Anhydro-I with Lithium Aluminum Hydride.—Reduction of 2.03 g. of anhydro-I with excess lithium aluminum hydride in ether yielded, after the usual workup, 1.91 g. of crude amorphous product, m.p. 110–130°. This was chromatographed with chloroform on silicic acid to yield 75% of XXII and 25% of another compound, which was neutral and analyzed as a *dihydro derivative*, m.p., after several recrystallizations from ethyl acetate, 185–187°.

Anal. Calcd. for $C_{10}H_{18}ONBr$: C, 48.79; H, 6.55. Found: C, 48.90; H, 6.79; infrared spectrum (KBr disk), 3.03, 3.24 sharp, 6.18, 6.40 μ.

Conversion of Tetrahydroanhydro-II to XVIII.—Tetrahydroanhydro-II (160 mg., 0.65 mmole) was treated with tosyl chloride in pyridine; the usual workup gave 180 mg. of tosylamide, m.p. 163–165°, needles from ethanol–water (68% yield). The tetrahydropyranyl ether of this material was prepared by stirring the above with 42 mg. of dihydropyran (0.5 mmole, 0.05 ml.) in 10 ml. of alcohol-free chloroform containing two drops of concentrated hydrochloric acid and a little anhydrous sodium sulfate. After 1 hr., the mixture was poured into cold 10% sodium hydroxide and shaken thoroughly to remove all traces of acid. The crude ether weighed 100 mg., after recrystallization from ethanol. It was then dissolved in absolute ethanol and treated with sodium as previously described. Acidification and the usual workup gave about 50 mg. (80%) of material which, after passage through a silicic acid column and two recrystallizations from benzene–petroleum ether, melted at 165–166° and did not depress the melting point of an authentic sample of XIX. The infrared spectra in chloroform were essentially identical.

Lithium Aluminum Hydride Reduction of 3-Methyl-Δ^2-isoxazoline.—The isoxazoline (6.5 g.) was dissolved in 25 ml. of dry tetrahydrofuran and added to a magnetically-stirred slurry of 1.0 g. of lithium aluminum hydride in 50 ml.

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of tetrahydrofuran under nitrogen. The mixture was held at 65° for 0.5 hr., then allowed to stand at room temperature for another hour. Ethyl acetate was added to decompose the excess hydride, followed by saturated sodium potassium tartrate. The solvents were separated from sludge by decantation, the latter extracted with hot alcohol, combined with the former, dried and distilled to give 18% of crude starting material (b.p. 48–53° (8 mm.), $n^{25}D$ 1.4435) and 2.48 g. of 3-amino-1-butanol, b.p. 73–74° (7 mm.) (reported[34] b.p. 82–85° (19 mm.)), $n^{25}D$ 1.4532–1.4543, 48% yield (based on unrecovered isoxazoline). A sample was distilled twice for analysis, precautions being taken to exclude water vapor and carbon dioxide.

Anal. Calcd. for $C_4H_{11}NO$: C, 53.89; H, 12.44. Found: C, 54.15; H, 11.97.

Reduction of Ethyl *dl*-β-Aminobutyrate.—Ethyl β-aminobutyrate (5.0 g., 0.0038 mole), prepared from 3-acetamidocrotonic ester[35] by reduction of the latter according to Skita with platinum oxide in ethanol containing a few drops of concentrated hydrochloric acid, followed by hydrolysis and re-esterification,[36] was reduced with lithium aluminum hydride in ether for 15 minutes according to Karrer.[37] Workup yielded an oil which was rectified in vacuum to give 2.11 g. of an aminoalcohol, b.p. 73° (7 mm.), $n^{25}D$ 1.4534–1.4543 (62%). The infrared of this material (neat) and that from isoxazoline showed little resolution but were superimposable, broad bands centered at 3.15, 6.29, 9.05, 9.40 μ. Samples of both amino alcohols were converted to identical bis-*p*-nitrobenzoyl derivatives, m.p. 155–156°, separately and on admixture. An analytical sample was recrystallized from ethanol (balls of tiny needles, m.p. 157°).

Anal. Calcd. for $C_{18}H_{17}N_3O_7$: C, 55.81; H, 4.42. Found: C, 55.91; H, 4.56.

The aminoalcohol was further characterized as the bis-benzoyl derivative, leaflets from ethanol–water, m.p. 112–112.5°.

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.40. Found: C, 72.36; H, 6.37.

(34) Bayer and Co., German Patent 247,144; *Chem. Zentr.*, **83**, 159 (1912).

(35) A. Skita and C. Wulff, *Ann.*, **453**, 206 (1927).

(36) E. Fischer and C. Roeder, *Ber.*, **34**, 3755 (1901).

(37) P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

MADISON, WISCONSIN

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

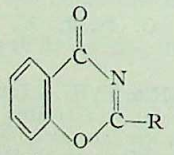
Experiments with 2-Aryl-1,3-benzoxaz-4-ones and with 2-Phenyl-2,3-dihydro-1,3-benzoxaz-4-one. A New Type of Thermochromic Compounds

BY AHMED MUSTAFA AND ALAA ELDIN ABDEL AZIZ HASSAN

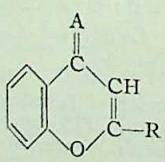
RECEIVED FEBRUARY 5, 1957

A number of new thermochromic di-(2-aryl)-1,3-benzoxaz-4-ylidenes (IVa-c) now have been prepared. Fission of the central ethylene linkage in IVa-c is brought about by the action of sulfur at 250° to yield the corresponding benzoxaz-4-thione derivatives (Va-c), respectively, and by the action of thionyl chloride followed by water in the case of IVa to give 2-phenyl-1,3-benzoxaz-4-one (Ia). The two new benzoxaz-4-one derivatives (Ib-c), needed in this investigation, have been synthesized. Whereas Ia, Ic, Va and/or Vc react with hydroxylamine hydrochloride in the presence of pyridine to give the corresponding oxime derivatives, they react with hydrazine hydrate to yield the corresponding 1,2,4-triazole derivatives (VIa-b), respectively. Treatment with organomagnesium compounds brought about addition to the carbonyl group in the case of Ic and cleavage of the hetero ring in the case of 2-phenyl-2,3-dihydro-1,3-benzoxaz-4-one (X).

2-Aryl-1,3-benzoxaz-4-ones (Ia-c) bear a structural resemblance to flavone (IIa), the former having in the hetero ring the system —CR=N— in place of CR=CH— in the latter. This has stimulated us to investigate the analogy between I and II in their chemical reactions.

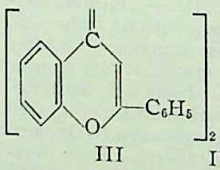


Ia, R = C_6H_5
b, R = $C_6H_4CH_3$-*p*
c, R = $C_6H_4OCH_3$-*p*

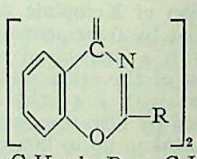


IIa, A = O; R = C_6H_5
b, A = S; R = C_6H_5

Diflavylene (III) shows remarkable physical and chemical properties; it forms light yellow crystals at the temperature of liquid air, at room temperature they are yellow, the melt is ruby-red and the color of the hot solutions varies from orange-red to deep red depending on concentrations.[1] Under pressure, it shows piezochromic properties,[2] changing from yellow to dark red. We now have found that di-(2-aryl)-1,3-benzoxaz-4-ylidenes (IVa-c) show thermochromic properties: dilute solutions of IVa in ethyl benzoate and/or in diphenyl ether are yellow at 0° and orange-red at the boiling point of the solvent; the phenomenon is reversible. Strong thermochromic effects also were observed with powdered solid IVa (yellow at 0° ⟷ deep red at 260°).



III



IVa, R = C_6H_5; b, R = $C_6H_4CH_3$-*p*;
c, R = $C_6H_4OCH_3$-*p*

III shows remarkable behavior toward thionyl chloride, followed by the action of water[3] and toward the action of elementary sulfur[4]; fission of the central ethylene bond occurs and IIa and IIb are formed, respectively. We now have found that IVa behaved analogously; fission of the central ethylene linkage in IVa-c is brought about by the action of sulfur at 250° to yield the corresponding benzoxaz-4-thione derivatives (Va-c), respectively, and by the action of thionyl chloride followed by the action of water in the case of IVa to give Ia.

Whereas IIa reacts with hydroxylamine hydrochloride to give the corresponding oxazole deriva-

(1) A. Schönberg and S. Nickel, *Ber.*, **64**, 2325 (1931).

(2) A. Schönberg, A. F. A. Ismail and W. Asker, *J. Chem. Soc.*, 442 (1946).

(3) A. Schönberg and W. Asker, *ibid.*, 272 (1942).

(4) A. Schönberg, *Ber.*, **58**, 1793 (1925).

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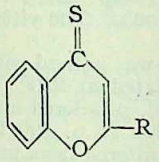
tive,[5] Ia and Ic react readily with the same reagent, under the same conditions, to give the corresponding oxime derivatives. The latter are also formed by the action of the same reagent on the thione derivatives (Va and Vc, respectively).[6]

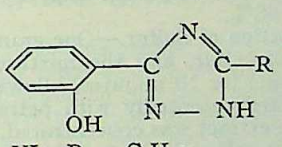
Phenylhydrazine reacts with flavone to form the pyrazole derivative,[5] but 2,4-dinitrophenylhydrazine reacts with flavone in acid solution to give the corresponding hydrazone derivative.[7] We now have found that Ia reacts readily with phenylhydrazine to give the hydrazone derivative.

It has been established that the action of hydrazine on 2-methylchromone[8] and on chromone itself[5b] leads to the formation of pyrazole derivatives and not hydrazones of the chromones in question as previously described.

We now have investigated the action of hydrazine hydrate on Ia and on Va and believe, by analogy, that the reaction product is the 1,2,4-triazole derivative VIa. Similarly, VIb is obtained upon treatment of Ic with the same reagent. VIa-b are colorless compounds, soluble in aqueous sodium hydroxide solution and give violet color with ferric chloride.

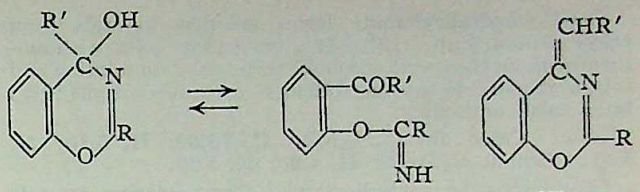


Va, R = C_6H_5;
b, R = $C_6H_4CH_3$-*p*;
c, R = $C_6H_4OCH_3$-*p*



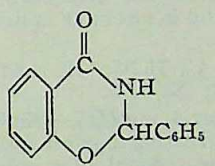
VIa, R = C_6H_5;
b, R = $C_6H_4OCH_3$-*p*

Recently, Mustafa and co-workers[9] have shown that in contrast to 2-phenyl-3,1-benzoxaz-4-one, which underwent hetero ring opening with phenylmagnesium bromide, Ia reacted with the same reagent to yield 2,4-diphenyl-4-hydroxy-1,3-benzoxazine (VIIa) which could also be present in equilibrium with the open form VIIIa. 2-Phenyl-4-benzal-1,3-benzoxazine (IXa) was obtained when Ia was treated with benzylmagnesium chloride. Similar results now have been obtained when 2-(*p*-methoxyphenyl)-1,3-benzoxaz-4-one (Ic) was allowed to react with phenylmagnesium bromide and with benzylmagnesium chloride, followed by hydrolysis, yielding 2-(*p*-methoxyphenyl)-4-phenyl-4-hydroxy-1,3-benzoxazine (VIIb), which could also be present in equilibrium with the open form VIIIb, and 2-(*p*-methoxyphenyl)-4-benzal-1,3-benzoxazine (IXb), respectively. That VIIb and IXb are not identical in structure is indicated by the analytical results; furthermore, VIIb is colorless and contains an active hydrogen atom, while IXb is yellow and contains no active hydrogen atom. The behavior of Ia and Ic toward Grignard reagents is comparable to that of flavone.[10]

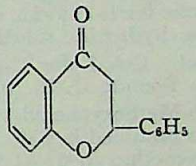


VIIa, R = R′ = C_6H_5 VIII IX
b, R = $C_6H_4OCH_3$-*p*; R′ = C_6H_5

In this connection, we have also investigated the behavior of 2-phenyl-2,3-dihydro-1,3-benzoxaz-4-one (X), which bears structural resemblance to flavanone (XI), toward the action of organomagnesium compounds. Thus, whereas XI reacts with both aliphatic[11] and aromatic Grignard reagents[12] to form chromanols which can be dehydrated to α-chromenes, X undergoes hetero ring

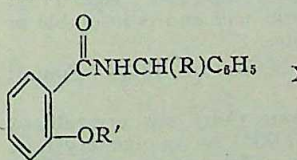


X



XI

opening with phenylmagnesium bromide and with methylmagnesium iodide to yield colorless products, believed to have structures like XIIa-b, respectively. XIIa-b are soluble in aqueous sodium hydroxide solution and give violet color with alcoholic ferric chloride. They form insoluble acetyl derivatives (XIIc-d) in aqueous sodium hydroxide solution when allowed to react with acetic anhydride. When an acetic acid solution of XIIa is boiled with hydrochloric acid, salicylamide was obtained.



XIIa, R = C_6H_5; R′ = H
b, R = CH_3; R′ = H
c, R = C_6H_5; R′ = $COCH_3$
d, R = CH_3; R′ = $COCH_3$

Methods of Preparation.—The new 2-aryl-1,3-benzoxaz-4-ones (Ib-c) now have been obtained after the procedure of Titherley[13] by treatment of O-*p*-methylbenzoyl- and O-*p*-methoxybenzoylsalicylamides, respectively, with hydrogen chloride gas in boiling anisole.

IVa-c have been obtained by the action of copper bronze on the corresponding 2-aryl-1,3-benzoxaz-4-thiones[14] (Va-c), respectively, which may be prepared by treating Ia-c with phosphorus pentasulfide.[15] IVa also has been obtained by the action of copper bronze[14] on the product resulting by treatment of Ia with thionyl chloride.

Experimental

2-Aryl-1,3-benzoxaz-4-ones (Ib-c). O-Aroylsalicylamides.—O-*p*-Toluoyl- and O-*p*-methoxybenzoylsalicylamides were obtained by treating a solution of 5 g. of salicylamide in 20 ml. of dry pyridine with 5.5 g. of *p*-toluoyl chloride and with 6 g. of *p*-methoxybenzoyl chloride, respectively. The reaction mixture was heated on a steam-bath for 1 hr., poured into ice-cold water and the resulting solids (yield 85, 89%, respectively) collected and worked up as follows:

(5) (a) W. Baker and V. S. Butt, *J. Chem. Soc.*, 2142 (1949); (b) W. Baker, J. B. Harborne and W. D. Ollis, *ibid.*, 1303 (1952).
(6) *Cf.* the formation of flavone oxime by the action of hydroxylamine hydrochloride on thioflavone in presence of pyridine (ref. 5b).
(7) R. Mozingo and H. Adkins, THIS JOURNAL, **60**, 669 (1938).
(8) E. Koenigs and J. Freund, *Ber.*, **80**, 143 (1947).
(9) A. Mustafa, W. Asker, M. Kamel, A. F. A. Shalaby and A. E. A. E. Hassan, THIS JOURNAL, **77**, 1612 (1955).
(10) E. R. Watson, K. B. Sen and V. R. Medhi, *J. Chem. Soc.*, **107**, 1477 (1915); I. M. Heilbron, D. H. Hey and A. Lowe, *ibid.*, 1380 (1936).
(11) K. v. Auwers and F. Krollpfeiffer, *Ber.*, **47**, 2591 (1914).
(12) A. Lowenbein, *ibid.*, **57**, 1517 (1924).
(13) A. W. Titherley, *J. Chem. Soc.*, **97**, 200 (1910).
(14) A. Schönberg, O. Schütz and O. Nickel, *Ber.*, **61**, 1375 (1927).
(15) O. Stolcenberg and T. Hervici, *ibid.*, **50**, 787 (1917).

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O-*p*-Toluoylsalicylamide forms colorless crystals from ethyl alcohol, m.p. 213°. It gives yellow color with sulfuric acid, no color with alcoholic ferric chloride solution and is insoluble in cold aqueous sodium hydroxide solution (10%) but soluble on boiling.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.59; H, 5.10; N, 5.48. Found: C, 70.32; H, 4.90; N, 5.60.

O-*p*-Methoxybenzoylsalicylamide forms colorless crystals from dilute ethyl alcohol, m.p. 198°. It gives greenish-yellow color with sulfuric acid and behaves similarly toward ferric chloride and sodium hydroxide solutions.

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.80; N, 5.17. Found: C, 66.23; H, 4.72; N, 5.15.

2-*p*-Tolyl-1,3-benzoxaz-4-one (Ib) was obtained in 72% yield by treating a clear solution of 5 g. of O-*p*-toluoylsalicylamide in 30 ml. of freshly distilled anisole with a stream of dry hydrogen chloride for a few minutes after the procedure described by Titherley[13] for the preparation of Ia. Ib forms colorless crystals from a mixture of petroleum ether (b.p. 80–100°), m.p. 113°. It does not give color with alcoholic ferric chloride solution and is insoluble in aqueous sodium hydroxide solution.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.95; H, 4.64; N, 5.90. Found: C, 76.10; H, 4.52; N, 5.56.

2-*p*-Methoxyphenyl-1,3-benzoxaz-4-one (Ic).—Similarly, Ic was obtained in 68% yield by treating a solution of 5 g. of O-*p*-methoxybenzoylsalicylamide in 40 ml. of anisole with a stream of hydrogen chloride as described above. Ic forms colorless crystals from ethyl alcohol, m.p. 168°. It is insoluble in aqueous sodium hydroxide solution and gives no color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.35; N, 5.53. Found: C, 70.88; H, 4.14; N, 5.41.

2-Aryl-1,3-benzoxaz-4-thiones (Va-c). General Procedure.—The thiones were prepared by refluxing a benzene solution of 1 g. of each of Ia-c with 1 g. of phosphorus pentasulfide for 3 hr. The reaction mixture was filtered while hot, the benzene was evaporated and the oily residue was washed several times with cold light petroleum (b.p. 40–60°). The solidified mass was then worked up as follows: 2-phenyl-1,3-benzoxaz-4-thione (Va) was crystallized from petroleum ether as orange crystals, m.p. 128°, yield 71%. It gives orange color with sulfuric acid and is insoluble in aqueous sodium hydroxide solution.

Anal. Calcd. for $C_{14}H_9NOS$: N, 5.81; S, 13.38. Found: N, 5.72; S, 13.58.

2-*p*-Tolyl-1,3-benzoxaz-4-thione (Vb) was crystallized from petroleum ether (b.p. 60–90°) as orange crystals, m.p. 155°, yield 78%. It gives yellow color with sulfuric acid.

Anal. Calcd. for $C_{15}H_{11}NOS$: C, 71.14; H, 4.35; N, 5.53; S, 12.65. Found: C, 70.78; H, 4.15; N, 4.92; S, 12.34.

2-*p*-Methoxyphenyl-1,3-benzoxaz-4-thione (Vc) formed orange crystals from petroleum ether (b.p. 60–90°), m.p. 148°, yield 62%. It gives orange-red color with sulfuric acid.

Anal. Calcd. for $C_{15}H_{11}NO_2S$: N, 5.20; S, 11.90. Found: N, 4.99; S, 11.72.

Di-(2-aryl)-1,3-benzoxaz-4-ylidenes (IVa-c). General Procedure.—These were obtained by refluxing a solution of 1 g. of each of Va-c in 40 ml. of dry xylene with 1 g. of copper bronze for 6 hr. The reaction mixture was filtered off, concentrated and cooled. The crystals that separated out were collected. No molecular weight determination could be carried as the compounds (IVa-c) are difficultly soluble. Di-2-phenyl-1,3-benzoxaz-4-ylidene (IVa) was crystallized from xylene, as yellow crystals, m.p. 269°, yield *ca.* 68%. It gives yellow color with sulfuric acid.

Anal. Calcd. for $C_{28}H_{18}N_2O_2$: C, 81.16; H, 4.35; N, 6.76. Found: C, 80.92; H, 4.16; N, 6.95.

Di-2-(*p*-tolyl)-1,3-benzoxaz-4-ylidene (IVb) formed yellow-orange crystals, m.p. 288°, yield *ca.* 71%. It gives yellow color with sulfuric acid and is insoluble in aqueous sodium hydroxide solution.

Anal. Calcd. for $C_{30}H_{22}N_2O_2$: C, 81.45; H, 4.98; N, 6.33. Found: C, 81.24; H, 4.76; N, 6.25.

Di-2-(*p*-methoxyphenyl)-1,3-benzoxaz-4-ylidene (IVc) was crystallized from xylene as orange-yellow crystals, m.p. 282°, yield *ca.* 61%. It gives yellow color changing to violet with sulfuric acid.

Anal. Calcd. for $C_{30}H_{22}N_2O_4$: C, 75.94; H, 4.64; N, 5.91. Found: C, 75.74; H, 4.26; N, 5.67.

IVa also was obtained by the following procedure: one gram of Ia was treated with 15 ml. of freshly distilled thionyl chloride on a steam-bath for 20 hr.; the excess of thionyl chloride was distilled off. The residue was dissolved in 30 ml. of dry xylene and refluxed with 1 g. of copper bronze for 6 hr. The xylene solution was filtered hot and concentrated; on cooling IVa (*ca.* 0.42 g.) separated out. It was filtered off and recrystallized from xylene, m.p. 269°; identified as IVa (m.p. and mixed m.p.).

Experiments with Thermochromic Substances.—The color changes, which are all reversible, were obtained in layers of solution 1 cm. in depth. The solutions were heated nearly to the boiling point (heating lasted only for a few seconds) and then cooled immediately. The expansion of the volume of the solutions with temperature was taken into consideration.

Ethyl benzoate (Schering–Kahlbaum) was purified by shaking it with sodium carbonate for 24 hr., followed by filtration and distillation.

Action of Thionyl Chloride.—One gram of IVa was refluxed with 30 ml. of thionyl chloride for 6 hr.; the excess of thionyl chloride was distilled off completely (pump) and the residual oil was dissolved in benzene and shaken with water at 30° for 30 minutes. The benzene layer was evaporated and the residual oil was solidified on scratching and crystallized from petroleum ether, m.p. 106°; identified as Ia (m.p. and m.p. determination). The yield was *ca.* 68%.

Action of Sulfur.—One gram of IVa was ground with 0.5 g. of sulfur, and the mixture was heated at 250° (bath-temp.) for 10 minutes, allowed to cool, powdered and extracted repeatedly with petroleum ether (b.p. 100–120°). The extract was concentrated, cooled, filtered from precipitated sulfur and was concentrated further and cooled. Va was obtained; identification was carried out by m.p. and m.p. determination with an authentic specimen (see above).

Behavior of 2-Aryl-1,3-benzoxaz-4-ones toward: (a) Hydroxylamine Hydrochloride.—A solution of 1 g. of each of Ia and Ic in 40 ml. of ethyl alcohol was treated with 0.3 g. of hydroxylamine hydrochloride and five drops of freshly distilled pyridine for 4 hr. (steam-bath). The cooled reaction mixture was poured into ice-cold water, acidified with dilute hydrochloric acid; the deposit formed was filtered (*ca.* 0.75 g., 0.64 g., respectively), and crystallized from alcohol as colorless crystals.

2-Phenyl-1,3-benzoxaz-4-one oxime melts at 135°, gives no color with alcoholic ferric chloride and is soluble in aqueous sodium hydroxide solution.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.20; N, 11.76. Found: C, 70.26; H, 4.05; N, 11.92.

The above oxime derivative was similarly prepared by the action of hydroxylamine hydrochloride on Va, as described above, in almost quantitative yield. Identification was carried out by m.p. and mixed m.p. determination.

2-(*p*-Methoxyphenyl)-1,3-benzoxaz-4-one oxime formed colorless crystals (*ca.* 0.73 g.), m.p. 140°. Its behavior toward ferric chloride and sodium hydroxide simulates that of the oxime of Ia.

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.47; N, 10.45. Found: C, 66.92; H, 4.31; N, 10.55.

(b) Phenylhydrazine.—A mixture of 1 g. of Ia and 1 g. of phenylhydrazine and 40 ml. of absolute ethyl alcohol was refluxed for 3 hr. Working up the reaction mixture gave colorless crystals from ethyl alcohol (*ca.* 0.67 g.) of 2-phenyl-1,3-benzoxaz-4-one phenylhydrazone derivative, m.p. 130°. It is insoluble in aqueous sodium hydroxide solution and gives no color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{20}H_{15}N_3O$: C, 76.69; H, 4.79; N, 13.42. Found: C, 76.36; H, 4.38; N, 13.21.

(c) Hydrazine Hydrate.—A solution of 1 g. of each of Ia and Ic in 50 ml. of absolute ethyl alcohol was treated with 0.30 g. of hydrazine hydrate. The reaction mixture was heated (steam-bath) for 15 minutes and kept aside overnight at room temperature. It was diluted with water and the colorless crystals, so obtained, were collected.

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3-(*o*-Hydroxyphenyl)-5-phenyl-1,2,4-triazole (VIa) formed colorless crystals from benzene, m.p. 204°, yield *ca.* 82%. VIa is soluble in aqueous sodium hydroxide solution and gives violet color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.88; H, 4.64; N, 17.72. Found: C, 70.61; H, 4.42; N, 17.90.

VIa was similarly prepared by the action of hydrazine hydrate on 1 g. of Va, as described above, in an almost quantitative yield. Identification was carried out by m.p. and mixed m.p. determination.

3-(*o*-Hydroxyphenyl)-5-(*p*-methoxyphenyl)-1,2,4-triazole (VIb) formed colorless crystals from ethyl alcohol, m.p. 186°, yield *ca.* 79%. It behaves in a similar manner to VIa toward ferric chloride and sodium hydroxide solutions.

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.87; N, 15.73. Found: C, 67.52; H, 4.65; N, 15.80.

Action of Grignard Reagents on Ic. (a) Phenylmagnesium Bromide.—To a solution of phenylmagnesium bromide (prepared from 0.9 g. of magnesium and 9 g. of bromobenzene in 50 ml. of dry ether) was added a solution of 1.5 g. of Ic in 50 ml. of dry benzene. The ether was evaporated and the reaction mixture heated for 3 hr. on a steam-bath. After the mixture had stood overnight at room temperature, it was poured slowly into 100 ml. of saturated aqueous ammonium chloride solution and extracted with ether. The precipitate which separated from the ether–benzene mixture was crystallized from benzene–light petroleum as colorless crystals, m.p. 122°, yield *ca.* 0.89 g.

Anal. Calcd. for $C_{21}H_{17}NO_3$: C, 76.13; H, 5.13; N, 4.23; active H, 0.30. Found: C, 75.68; H, 4.96; N, 4.15; active H, 0.27.

2-(*p*-Methoxyphenyl)-4-phenyl-1,3-benzoxazine (VIIa) is easily soluble in benzene and hot ethyl alcohol, difficultly soluble in light petroleum and insoluble in cold aqueous sodium hydroxide solution. It gives red color with sulfuric acid. The alcoholic solution of VIIb does not become colored when treated with alcoholic ferric chloride solution.

(b) Benzylmagnesium Chloride.—To a Grignard solution of benzylmagnesium chloride (prepared from 0.8 g. of magnesium, 5.5 g. of benzyl chloride and 50 ml. of dry ether) was added a solution of 1 g. of Ic in 40 ml. of benzene. The reaction mixture was worked up in the usual manner. The oily product, obtained upon evaporation of the ethereal extract, solidified after working with light petroleum. 2-(*p*-Methoxyphenyl)-4-benzal-1,3-benzoxazine (IXb) was obtained as yellow crystals from petroleum ether, yield 0.68 g., m.p. 126°.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.73; H, 5.20; N, 4.28. Found: C, 80.62; H, 4.91; N, 4.05.

IXb is easily soluble in chloroform and benzene, difficultly soluble in cold petroleum ether and insoluble in cold aqueous sodium hydroxide solution; it gives an orange red color with sulfuric acid.

Action of Grignard Reagents on X. (a) Phenylmagnesium Bromide.—To a solution of phenylmagnesium bromide was added 1 g. of X[13] in 30 ml. of dry benzene. The reaction mixture was worked up as described above. The oily residue, obtained on evaporation of the ethereal extract, solidified on scratching and cooling. N-Benzohydrylsalicylamide (XIIa) was crystallized from petroleum ether (b.p. 100–120°) as colorless crystals, m.p. 140°, yield 0.64 g.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.21; H, 5.61; N, 4.62. Found: C, 79.20; H, 5.46; N, 4.32.

XIIa is easily soluble in benzene and hot alcohol, difficultly soluble in light petroleum and soluble in cold aqueous sodium hydroxide; it gives an orange-red color with alcoholic ferric chloride solution.

Acetylation.—A solution of 0.5 g. of XIIa in 30 ml. of acetic anhydride was refluxed for 2 hr. The reaction mixture was poured into cold water, and the solid, so obtained after cooling, was filtered off, washed thoroughly with water and crystallized from alcohol as colorless crystals (*ca.* 0.39 g.), m.p. 148°. The acetyl derivative XIIc is insoluble in cold aqueous sodium hydroxide solution and gives no color with ferric chloride. It gives an orange-red color with sulfuric acid.

Anal. Calcd. for $C_{22}H_{19}NO_3$: C, 76.52; H, 5.51; N, 4.06. Found: C, 76.50; H, 5.34; N, 3.82.

Action of Hydrochloric Acid on XIIa.—A solution of 1 g. of XIIa in 40 ml. of glacial acetic acid was treated with 5 ml. of concentrated hydrochloric acid. The reaction mixture was refluxed for 3 hr., cooled, poured into ice-cold water and neutralized with sodium carbonate. It was extracted with ether, dried and evaporated. The solid residue was crystallized from ethyl alcohol as colorless crystals (*ca.* 0.41 g.), m.p. 136°; identified as salicylamide (m.p. and mixed m.p.).

Anal. Calcd. for $C_7H_7NO_2$: C, 61.31; H, 5.10; N, 10.21. Found: C, 61.42; H, 4.96; N, 10.12.

(b) Methylmagnesium Iodide.—A solution of 1 g. of XIIa in 40 ml. of dry benzene was added to methylmagnesium iodide (prepared from 0.9 g. of magnesium, 3.6 g. of methyl iodide and 50 ml. of dry ether); the reaction mixture was refluxed on a steam-bath for 3 hr., allowed to stand overnight at 25° and worked out as usual. N-(α-Phenylethyl)-salicylamide (XIIb) was crystallized from light petroleum as colorless crystals, m.p. 103°, yield 0.51 g.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.68; H, 6.22; N, 5.81. Found: C, 74.46; H, 5.98; N, 5.85.

XIIb is easily soluble in benzene and hot alcohol, difficultly soluble in light petroleum and soluble in cold aqueous sodium hydroxide solution; it gives yellow color with sulfuric acid. The alcoholic solution of XIIb gives violet color with alcoholic ferric chloride solution.

Acetylation.—The acetyl derivative XIId was similarly prepared as previously described in the case of XIIc. It was obtained in colorless crystals from chloroform–light petroleum mixture, m.p. 98°, yield 82%. It was insoluble in aqueous sodium hydroxide solution and gives no color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.00; N, 4.94. Found: C, 71.78; H, 5.82; N, 5.00.

GIZA, CAIRO, EGYPT

[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

Relative Reactivities of Polynuclear Aromatic Systems. The Solvolysis of α-Arylethyl Chlorides[1]

BY ERNST BERLINER AND NAN SHIEH

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The rates of reaction, activation energies and entropies were determined for the SN1 solvolysis of 13 different α-arylethyl chlorides, $ArCHClCH_3$, in 80% or 90% aqueous acetone. The relative reactivities, referred to 25° and 80% aqueous acetone, correlate satisfactorily with various theoretical parameters, but compounds with an "α-naphthalene-like" structure react slower than predicted.

Although polynuclear aromatic hydrocarbons have played an important part in organic chemical theories, an experimental knowledge of the relative reactivities of polycyclic aromatic systems is very scanty. This is in contrast to the theoretical treatment accorded these systems, particularly in

(1) Taken from a dissertation submitted by Miss Nan Shieh to the Graduate School of Bryn Mawr College in partial fulfillment of the requirements for the Ph.D. degree, June, 1957.

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TABLE I

KINETIC DATA FOR THE SOLVOLYSIS OF α-ARYLETHYL CHLORIDES

Ar– in ArCHClCH₃	Solvent, % acetone	Temperature, °C. 25.00 $k \times 10^5$ sec.$^{-1}$	32.00	40.00	45.00	E, kcal.	log A	ΔS^* e.u.
			$k \times 10^5$, sec.$^{-1}$					
2-Phenanthryl	80	3.31	0.843	2.14	3.76	22.9 ± 0.2	11.3 ± 0.2	−8.75
		3.29		2.18	3.77			
2-Naphthyl	80	4.71	1.13	2.92	5.28	22.6 ± .1	11.3 ± .1	−8.96
		4.81	1.16	2.98	5.26			
9-Phenanthryl	80	5.83	1.45	3.85	6.86	23.2 ± .1	11.8 ± .1	−6.53
		5.85	1.42	3.85	6.83			
4-Biphenylyl	80	7.45	1.76	4.59	7.91	22.25 ± .1	11.2 ± .1	−9.35
		7.46	1.85	4.56	7.89			
3-Phenanthryl	80	8.96	2.20	5.77	10.4	22.8 ± .1	11.7 ± .1	−6.99
		9.31	2.23	5.76	10.3			
		9.20						
1-Naphthyl	80	11.7	2.75[a]	6.94[b]	12.1	22.3 ± .15	11.4 ± .1	−8.30
		11.7	2.71	6.81	12.5			
			2.74		12.4			
2-Chrysenyl	80	24.8	6.05	15.6	27.1	22.8 ± .1	12.1 ± .1	−5.04
		24.0	6.05	15.8	27.9			
	90	2.30	0.564	1.40	2.41	22.0 ± .2	10.5 ± .1	−12.5
		2.31		1.37	2.39			
2-Anthryl	90	2.69	0.629	1.56	2.62	21.5 ± .1	10.2 ± .1	−13.9
		2.69	0.623	1.54	2.61			
1-Anthryl	90	5.65			5.50	21.4	10.4	−12.9
		5.77						
2-Fluorenyl	90	31.6	6.98	15.9	26.7	20.1 ± .1	10.2 ± .1	−13.7
		31.5	6.87	16.2	26.7			
		Temperature, °C. 0.00	12.00	18.00	25.00			
2-Fluorenyl	80	19.7	9.60	20.5	47.7	20.6 ± .1	11.8 ± .1	−6.51
		19.6	9.67	20.1	47.6			
				21.0				
3-Pyrenyl	90	26.0	10.8	21.6	44.0	18.5 ± .1	10.2 ± .1	−14.0
		25.5	10.7	21.4	44.3			
9-Anthryl	90	89.5	33.2			17.0	9.57	−16.7
		87.5	33.0					
		Temperature, °C. 45.00	55.00	65.00	70.00			
Phenyl	80	7.23	2.12	5.83	9.47[c]	22.2 ± .1	10.1 ± .1	−14.2
		7.29	2.09	5.68	9.39			

[a] $T = 32.13°$. [b] $T = 39.70°$. [c] Values of 9.04 (titrimetric) and 10.0 (polarimetric) are reported by E. D. Hughes, C. K. Ingold and A. D. Scott, ref. 8.

the last decades. Various parameters arising out of modern theories, such as free valences, atom- and bond-localization energies, charge densities, molecular diagrams and others, have made it possible to predict relative reactivities at various positions within the same molecule, as well as differences among different molecules.[2]

Two lines of approach suggest themselves for a collection of data by which relative reactivities of polynuclear aromatic systems can be ascertained. One is a kinetic study of an electrophilic substitution reaction, the other a study of a suitable side-chain reaction. The latter was chosen for a preliminary survey because a definite position in the polynuclear aromatic compound can be studied without the complicating factor of isomer distribution or polysubstitution.

Most of the older quantitative data refer to various side-chain reactions and dissociation constants in the benzene and naphthalene series, but some extend to biphenyl, anthracene and phenanthrene.[3] In direct electrophilic substitution, there is abundant qualitative information, based usually on preparative ease of substitution, that the reactivity is anthracene > phenanthrene > naphthalene > benzene for the most reactive positions.[4] Systematic quantitative data were practically completely missing, until Dewar, Mole and Warford recently demonstrated an excellent correlation between theoretical parameters and relative rates of nitration for polynuclear aromatic hydrocarbons.[5]

(2) For general discussions see, for instance, L. Pauling, "The Nature of the Chemical Bond," 2nd Ed., Cornell University Press, Ithaca, N. Y., 1944; G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955; C. A. Coulson, "Valence," Oxford University Press, London, 1952; B. Pullman and A. Pullman, "Les Theories electroniques de la Chimie organic," Masson and Co., Paris, 1952; M. J. S. Dewar, THIS JOURNAL, **74**, 3341 ff. (1952); M. J. S. Dewar in J. W. Cook, "Progress in Organic Chemistry," Vol. II, Academic Press Inc., New York, N. Y., 1953, p. 1.

(3) Some of the older literature has been reviewed by E. A. Braude and J. S. Fawcett, *J. Chem. Soc.*, 800 (1950).

(4) For instance, see the discussion in L. F. Fieser and M. Fieser, "Organic Chemistry," 3rd Ed., Heath and Co., Boston, 1956, Ch. 31, 32.

(5) M. J. S. Dewar, T. Mole and E. W. T. Warford, *J. Chem. Soc.*, 3581 (1956); also, M. J. S. Dewar and T. Mole, *ibid.*, 342 (1957).

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Relative reactivites in free radical reactions (methyl or trichloromethyl affinities and others)[6] correlate well with free valence numbers or the atom localization energies.[6,7] Since the point of attack in these reactions is not known with certainty, the assumption is always made that the attack occurs at the position predicted to be the most reactive.

The side-chain reaction chosen for the present study is the SN1 solvolysis of α-arylethyl chlorides, $ArCHClCH_3$, in aqueous acetone, partly because the mechanism of the reaction and the nature of the transition state are fairly well understood[8] and partly because of the similarity of the transition state, as far as electronic effects are concerned, to the transition state in aromatic substitution. Since this work was initiated, two very similar studies on the solvolysis of arylmethyl chlorides, $ArCH_2Cl$, have been reported by Fierens, *et al.*,[9] and by Dewar and Sampson.[10] The aim of these papers was the same as the present one, and the results are very similar. A study has also been reported on the reaction of polynuclear amines with 2,4-dinitrochlorobenzene.[11]

Results and Discussion

The kinetic data for the solvolysis of 13 compounds, most of them studied at four different temperatures, are collected in Table I. Because of a considerable spread in reactivity and solubility it was not possible to compare all compounds in the same solvent mixture or at the same temperature. Four compounds were studied in 90% aqueous acetone and all the others in 80% acetone. Two compounds, 2-fluorenyl and 2-chrysenyl, were investigated in both solvents, and the results obtained were used to refer all compounds to 80% aqueous acetone. This was not wholly satisfactory, because, as expected, the factors thus obtained differed for the two standard compounds, but the uncertainty introduced by taking an average value was probably not too serious, and in no case was a reactivity order inverted. Where necessary, rate constants were extrapolated to 25° by means of the Arrhenius equation. The only kinetic complication was experienced with the 9-anthryl compound. The first-order rate constants fell within one run, and the data could be analyzed very well for two concurrent first-order reactions by the method of Brown and Fletcher.[12] But neither the crystalline solid starting material nor the products revealed the presence of two compounds. A more likely explanation is that this compound, the fastest of all, is subject to a mass law effect by the chloride ion.[13] When analyzed on this assumption, a smooth curve was obtained on plotting the apparent k_1 against time, which was extrapolated to zero time, to give the rate constants recorded in Table I.

In Table II are listed all rate constants referred to 80% by volume aqueous acetone at 25°. A number of relevant theoretical parameters are also listed. In Fig. 1 the logarithms of the rate constants ($\log k/k_0$) are plotted against the atom-localization energies ($E_0 - E$), where k_0 and E_0 refer to benzene. The atom-localization energies (in units of β) are those obtained by Dewar by a simplified molecular orbital treatment.[14] These values were used rather than those obtained by the more rigorous method[15] because they easily can be extended to a wide variety of alternant hydrocarbons;[16] the results of the plots are identical. Although atom-localization energies refer strictly to the π-electron energy difference between the initial and the transition state in aromatic substitution, *i.e.*, for a direct attack on the nucleus, rather than the side-chain, they were chosen as the most general ones for a possible future comparison. Also, the various parameters are interrelated, and from a general knowledge of carbonium ion stability, one would expect a relation between the power of conjugation of Ar– with a carbonium ion, and hence the stabilizing effect of Ar–, and some of the

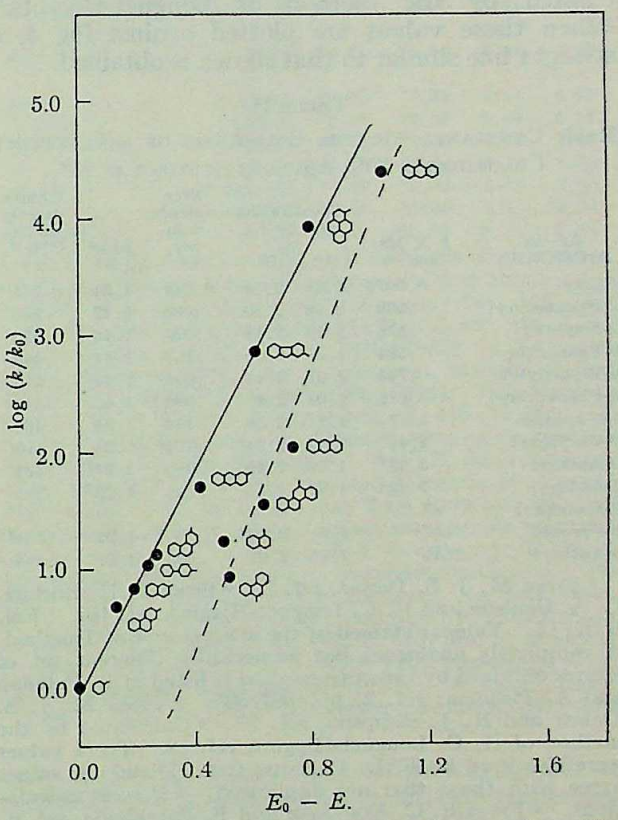

Fig. 1.—A plot of log k against localization energies. The point corresponding to the 2-fluorenyl compound was obtained from the line.

(6) M. Levy and M. Szwarc, THIS JOURNAL, **77**, 1949 (1955); J. Smid and M. Szwarc, *ibid.*, **78**, 3322 (1956); M. Szwarc and F. Leavitt, *ibid.*, **78**, 3590 (1956); E. C. Kooyman and E. Farenhorst, *Trans. Faraday Soc.*, **49**, 58 (1953); J. R. Dunn, W. A. Waters and I. M. Roitt, *J. Chem. Soc.*, 580 (1954).

(7) C. A. Coulson, *ibid.*, 1435 (1955); P. M. G. Bavin and M. J. S. Dewar, *ibid.*, 164 (1956).

(8) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Ch. 7; S. Winstein, E. Grunwald and H. W. Jones, THIS JOURNAL, **73**, 2700 (1951); E. D. Hughes, C. K. Ingold and A. D. Scott, *J. Chem. Soc.*, 1201 (1937).

(9) P. J. C. Fierens, H. Hannaert, J. Van Rysselberge and R. H. Martin, *Helv. Chim. Acta*, **38**, 2009 (1955).

(10) M. J. S. Dewar and R. J. Sampson, *J. Chem. Soc.*, 2789 (1956).

(11) F. L. J. Sixma, *Rec. trav. chim.*, **74**, 168 (1955).

(12) H. C. Brown and R. S. Fletcher, THIS JOURNAL, **71**, 1845 (1949).

(13) C. K. Ingold, ref. 8.

(14) M. J. S. Dewar, ref. 2.

(15) F. H. Burkitt, C. A. Coulson and H. C. Longuet-Higgins, *Trans. Faraday Soc.*, **47**, 553 (1951).

(16) See, for instance, P. M. Gore, *J. Chem. Soc.*, 3166 (1954).

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parameters referring to ArH.[17] In their more strict treatment, Dewar and Sampson[10] have plotted rate constants against the parameters $2a_{or}$, which are related to the energy difference between $ArCH_2X$ and $ArCH_2^+$. When our data were plotted against these quantities, a plot similar to Fig. 1 is obtained. Another readily available quantity is the charge density on the exocyclic carbon atom in the carbonium ion, which can be calculated by the method of Longuet-Higgins.[18] When these values are plotted against log k, a straight line similar to that shown is obtained.

TABLE II

RATE CONSTANTS FOR THE SOLVOLYSIS OF α-ARYLETHYL CHLORIDES IN 80% AQUEOUS ACETONE AT 25°

Ar– in $ArCHClCH_3$	$k \times 10^5$, sec.$^{-1}$	Localization energy E_A (β) A[a]	B[b]	Free valence number, N[c]	$2a_{or}$[d] (β)	Charge density on Ar-CH_2+, q[e]
Phenyl	0.0679	2.31	2.54	0.081	1.51	0.571
2-Phenanthryl	.330	2.18	2.50	.086	1.47	.543[f]
2-Naphthyl	.476	2.12	2.48	.086	1.46	.529
9-Phenanthryl	.584	1.79	2.30	.133	1.34	.446
4-Biphenylyl	.746	2.07	2.44	.094	1.44[f]	.516
3-Phenanthryl	.916	2.04	2.41	.089	1.43	.511[f]
1-Naphthyl	1.17	1.81	2.30	.134	1.34	.450
2-Chrysenyl	2.44	1.67	2.24[g]	.139[h]	1.28[f]	.410[f]
2-Anthryl	3.45[i]	1.89	2.40	.090	1.37[f]	.471
1-Anthryl	7.33[i]	1.57	2.25	.141	1.23[f]	.381
2-Fluorenyl	47.7					
3-Pyrenyl	567[i]	1.51	2.19[g]	.151[h]	1.21	.364[f]
9-Anthryl	1640[i]	1.26	2.01	.202	1.07	.286

[a] From M. J. S. Dewar, ref. 2. [b] From F. H. Burkitt, C. A. Coulson and H. C. Longuet-Higgins, ref. 15. [c] Ref. b and 15. Values obtained by the molecular orbital method. A completely analogous but numerically different set of figures obtained by the same method is listed in B. Pullman and A. Pullman, ref. 2, pp. 587–589. [d] From M. J. S. Dewar and R. J. Sampson, ref. 10. [e] Calculated by the method of H. C. Longuet-Higgins, ref. 18. These values were also used by F. L. J. Sixma (ref. 11) and our values agree with those that are duplicated. [f] Present calculations. [g] From E. C. Kooyman and E. Farenhorst, ref. 6. [h] G. Berthier, C. A. Coulson, H. H. Greenwood and A. Pullman, *Compt. rend.*, 226, 1906 (1948). [i] Value extrapolated from kinetic data in 90% aqueous acetone.

In general, high reactivity corresponds to low values for the localization energies, the $2a_{or}$ parameters and the charge densities, and high values for the maximum free valence numbers.[9] On a more quantitative comparison, a very satisfactory agreement and a good linear relation is obtained when the compounds are classed in two groups. The lower curve in Fig. 1, which defines a line of lower reactivity than predicted and which is practically parallel to the first line, contains without exception compounds which have the substituent in an α-naphthalene-like structure, next to a *peri*-hydrogen. The same was observed by the other two groups of workers ("α-naphthalene effect") and has been ascribed by them to a steric effect.[9,10] This is the most reasonable explanation that can be offered, and it shows that the SN1 solvolysis of α-arylethyl chlorides is subject to steric hindrance toward either coplanarity or solvation, even by the somewhat remote *peri* grouping. That the lower reactivity might be due to a theoretical value which is uniformly too high for just these compounds is unlikely and can be ruled out by the observation that it is not observed in cases where no hindrance might be expected, such as in direct nitration[5] or free radical attack.[6,7]

The slope of the straight line in Fig. 1, which is measured in terms of the resonance integral β, has a least square value of 4.82 ± 0.16. It has a meaning similar to Hammett's ρ-value,[19] and the magnitude of the slope should make it possible to draw conclusions about the susceptibility of various reactions to changes in hydrocarbon structure. Particularly, in direct aromatic substitution it should be related to the activity of the substituting agent.[20] A more detailed discussion of the significance of the slopes in both side-chain and substitution reactions has been given by Dewar, *et al.*,[5,7,10] who has pointed out that β, obtained from the slope,[21] should not be considered the usual universal constant, but a variable parameter dependent on the particular reaction. In a plot of our rate constants (log k_1) against $2a_{or}$ the slope has the value 12.6 ± 0.31, and β is 17.1 kcal. as compared to 30 kcal. obtained for β in the SN1 solvolysis of arylmethyl chlorides, $ArCH_2Cl$, in moist formic acid.[10] In the interpretation of Dewar and Sampson, this means that the transition state of α-arylethyl chloride solvolysis in 80% aqueous acetone has not progressed as far in free carbonium ion character as that of arylmethyl chloride solvolysis in moist formic acid. Viewed differently, the carbonium ion formed from $ArCHClCH_3$ is more stable than that formed from $ArCH_2Cl$ and therefore the reaction less "selective,"[20] giving rise to a smaller slope.

If it is accepted that the results group themselves into two classes of compounds and if each class is considered separately, only one pair of compounds shows an inverted order: 9-phenanthryl should be faster than 1-naphthyl but is slower. Both are less reactive than predicted, and an additional steric effect may possibly be operative in the 9-position of phenanthrene. Such an additional effect should then also be operative in 9-anthryl, where it is not observed, but the value for 9-anthryl is probably the least accurate because it was obtained by several extrapolations. Also, the 3-pyrenyl compound should by analogy fall on the low reactivity line but does not. It is gratifying that certain observed orders of reactivity, which could not easily have been predicted on the basis of preparative reactivities, agree with the theory. For instance, the 4-biphenylyl and 2-naphthyl compounds fall within the 2- and 3-phenanthryl derivatives. Other orders, found and predicted by the various theoretical parameters are, for instance, 9-anthryl > 3-pyrenyl > 1-anthryl > 2-anthryl, or 2-chrysenyl > 1-naphthyl > 2-naphthyl, etc. To the extent to which the deviations from the least square lines can be taken as a measure of agreement between theoretical and ex-

(17) For instance, see C. A. Coulson and H. C. Longuet-Higgins, *Proc. Royal Soc. (London)*, **195**, 188 (1948); R. Daudel, C. Sandorfy, C. Vroelant, P. Yvan and O. Chalvet, *Bull. soc. chim.*, 66 (1950); also ref. 9.

(18) H. C. Longuet-Higgins, *J. Chem. Phys.*, **18**, 265 ff. (1950).

(19) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Ch. 7.

(20) H. C. Brown and K. L. Nelson, THIS JOURNAL, **75**, 6292 (1953).

(21) The slope is equal to $E_A/2.303RT$.

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TABLE III

PREPARATION OF α-ARYLETHYL CHLORIDES AND INTERMEDIATES[a]

Ar–	Ketone	°C. (mm.) M.p. or b.p. Carbinol	Chloride	Formula	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Phenyl		69.0–70.0 (1.3–1.7)[c]	41.0–42.0 (0.9–1.0) 39–40 (0.5)[d]					
1-Naphthyl	[e]	62.4–63.5 (66[e])	133–134 (7)[f] 128–129 (4)					
2-Naphthyl	[e]	71.3–72.1 (72)[g]	66.4–67.3 (62–63)[h]					
4-Biphenylyl	[e,i] 120.5 (121)[k]	96.4–97.6 (97)[k]	52.6–53.7	$C_{14}H_{13}Cl$	77.59	77.38	6.05	5.97
2-Phenanthryl	145 (143)[l]	131.5–132.2 (131–131.5; 134–135)[m,n]	80.5–81.5[o]	$C_{16}H_{13}Cl$	79.83	79.70	5.44	5.49
3-Phenanthryl	71.0–72.0 (72)[l]	77.8–80.0 (79–81; 76–78; 83–83.5)[p,o,n]	85.5–86.5	$C_{16}H_{13}Cl$	79.83	79.81	5.44	5.57
9-Phenanthryl	74.0–74.5 (73–74)[q]	134.5–135.5 (134–135)[r]	93.5–94.5	$C_{16}H_{13}Cl$	79.83	79.89	5.44	5.53
1-Anthryl	109.4–109.8[s] (103–105)[t]	107.2–108.0[u]	60.0–61.1	$C_{16}H_{13}Cl$	79.83	79.97	5.44	5.47
2-Anthryl	186–187[s] (183–185;[t] 188)[v]	162.8–163.3[w]	177.3–178.8 d.	$C_{16}H_{13}Cl$	79.83	79.98	5.44	5.47
9-Anthryl	73.0–74.5 (75–76)[x]	124.0–125.0 (124–125)[y]	75.5–77.0	$C_{16}H_{13}Cl$	79.83	79.94	5.44	5.33
2-Fluorenyl	129.0–130.0 (128–129)[z]	134.0–135.6 (139–140)[aa]	90.5–92.0	$C_{15}H_{13}Cl$	78.77	79.06	5.73	5.80
3-Pyrenyl	89.0–90.0 (89–90)[bb]	112.0–113.2 (112–112.5)[bb]	98.5–99.5 d.	$C_{18}H_{13}Cl$	81.66	81.66	4.95	5.04
2-Chrysenyl	141.5–142.7 (142–143)[dd]	159.0–160.5[cc]	149.0–150.0 d.	$C_{20}H_{15}Cl$	82.61	82.89	5.20	5.04

[a] Values in parentheses are literature values. The melting points of the chlorides and the new carbinols are corrected. [b] Carbon and hydrogen analyses of all new chlorides by Galbraith Laboratories, Knoxville, Tenn. [c] Commercial. [d] G. Baddeley, J. Chadwick and H. T. Taylor, *J. Chem. Soc.*, 2405 (1954). [e] R. H. Pickard and J. Kenyon, *ibid.*, 105, 1126 (1914). [f] Reported in the patent literature without physical constants; French Patent 724,105 (*Chem. Zentr.*, 104, I, 505 (1933)). [g] H. Lund, *Ber.*, 70, 1520 (1937). [h] W. Gerrard and B. D. Shepherd, *J. Chem. Soc.*, 2069 (1953). [i] We are indebted to Dr. D. T. Mowry of the Monsanto Chemical Co., Dayton, Ohio, for a generous sample of this compound. [k] W. F. Huber, M. Renoll, A. G. Rossow and D. T. Mowry, THIS JOURNAL, 68, 1109 (1946). [l] E. Mosettig and J. van de Kamp, *ibid.*, 52, 3704 (1930). [m] W. E. Bachmann and W. S. Struve, *J. Org. Chem.*, 5, 416 (1940). [n] E. Mosettig and J. van de Kamp, THIS JOURNAL, 55, 3442 (1933). [o] A different compound is obtained when the carbinol is treated with pyridine and thionyl chloride; C. C. Price and B. D. Halpern, *ibid.*, 73, 818 (1951). [p] W. E. Bachmann and J. M. Chemerda, *J. Org. Chem.*, 6, 36 (1941). [q] J. E. Callen, C. A. Dornfeld and G. H. Coleman, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 26. [r] W. E. Bachmann, THIS JOURNAL, 56, 1363 (1934). [s] The 1- and 2-acetylanthracenes were separated by chromatography over alumina in benzene–ligroin mixtures [t] German Patent 492,247 (*C. A.*, 24, 2472 (1930)). [u] *Anal.* Calcd. for $C_{16}H_{14}O$: C, 86.46; H, 6.35. Found: C, 86.42; H, 6.27. Recrystallized from ligroin; all other new carbinols were crystallized from benzene. Analysis, footnote *b*. The analytical sample was obtained by hydrolysis of the pure chloride. [v] Ng. Ph. Buu-Hoi and P. Cagniant, *Rec. trav. chim.*, 62, 713 (1943). [w] *Anal.* Calcd. for $C_{16}H_{14}O$: C, 86.46; H, 6.35. Found: C, 86.26; H, 6.59. Analysis by Geller Laboratories, Hackensack, N. J. [x] C. Merritt, Jr., and C. E. Braun, footnote *q*, Vol. 30, 1950, p. 1. [y] E. L. May and E. Mosettig, THIS JOURNAL, 73, 1301 (1951). [z] F. E. Ray and G. Rieveschl, Jr., footnote *q*, p. 23. [aa] D. T. Mowry, M. Renoll and W. F. Huber, THIS JOURNAL, 68, 1105 (1946). [bb] W. E. Bachmann and M. Carmack, *ibid.*, 63, 2494 (1941). [cc] *Anal.* Calcd. for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.46; H, 6.21. Analysis by N. S. [dd] W. Carruthers, *J. Chem. Soc.*, 3486 (1953).

perimental values, the experimental values agree almost equally well with any of the theoretical parameters. The localization energies (A and B), the $2a_{or}$ constants and the charge densities (Table II) give straight lines with probable errors of 3.3, 4.5, 2.5 and 2.4%, respectively, but the error is larger (12.4%) when the maximum free valence numbers are plotted.[22]

No theoretical value is available for 2-fluorenyl, but it is very reactive, and the effect of the 5-membered ring and the methylene group raises the reactivity greatly over that of 4-biphenylyl. Forced coplanarity and hyperconjugation may be a contributing factor.

The most desirable situation would obtain if the localization energies could be compared directly with the experimental activation energies. Although the errors obtained for the activation energies are small, and logarithms of rate constants at four different temperatures fall virtually on a straight line when plotted against $1/T$, the differences among the activation energies for the various compounds are not sufficiently large or regular to be usable in place of the rate constants.[23] In a very approximate way, rate differences appear to be determined by differences in activation energies. The log A factors are of the same order of magnitude for reaction in the same solvent, and the activation entropies are, as expected, negative. Some of the deviations from the straight line may be due to variations in activation entropy, because one of the assumptions made in calculating the theoretical parameters is that the entropies remain constant. It is also noted that the differences in rate on going from the more to the less aqueous solvent is due almost exclusively to a lowering of the activation entropies in the less aqueous solvent. This is expected for reactions where ions are formed from neutral molecules.[24]

(22) Not only is the error small when the parameters $2a_{or}$ are plotted, but the "low reactivity" line is almost exactly parallel; the slopes of the two lines are 12.61 and 12.21, respectively, and 4.82 and 6.05 when the localization energies are used. In either case, however, the low reactivity line contains rate constants that were obtained by several extrapolations and are probably not as accurate as those of the other line.

(23) See also ref. 9, and the relevant discussion in ref. 10.

Experimental

Materials.—All chlorides were prepared by passing a stream of HCl gas, in the presence of calcium chloride, into the cold ethereal solutions of the carbinols[25]; yields of crude product were 80–90%. For the phenyl and the two naphthyl compounds, thionyl chloride was used.[26] After evaporation of the solvent, the chlorides were repeatedly recrystallized from 60–70° ligroin (petroleum ether in the case of 9-anthryl), until the melting point remained constant. The phenyl and the two naphthyl compounds were distilled *in vacuo*. The carbinols were made by aluminum isopro-

(24) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, Ch. 7.

(25) E. D. Hughes, C. K. Ingold and N. A. Taher, *J. Chem. Soc.*, 949 (1940). The treatment with anhydrous sodium carbonate was omitted.

(26) G. Baddeley, J. Chadwick and H. T. Taylor, *ibid.*, 2405 (1954).

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poxide reduction of the corresponding ketones (yields of crude product usually 80–90%); lithium aluminum hydride was used for the reduction of 2- and of 9-anthryl methyl ketone (87 and 85%), as well as of 2-chrysenyl methyl ketone (85%). The 1-anthryl methyl ketone was reduced by both reagents, but aluminum isopropoxide proved superior (70%). All the ketones were made by methods described in the literature, usually involving a Friedel and Crafts acylation of hydrocarbons, which had been purified by recommended procedures. The physical properties of all compounds and the carbon, hydrogen analyses of the new compounds are listed in Table III.[27]

Kinetic Runs.—Purified acetone[28] and boiled-out distilled water were thermostated at 25° and the necessary volumes, measured in 2-l. volumetric flasks (for instance 8 l. of acetone and 2 l. of water), were mixed in a 5 gal. Pyrex bottle. Enough of the 80 and the 90% aqueous acetone was prepared to last throughout the entire investigation. Kinetic runs below 25°, and some at 25°, were conducted in a 100-ml. volumetric flask, and 10-ml. samples were withdrawn at appropriate time intervals. Most runs at 25°, and all runs above 25°, were run in sealed tubes, prepared from 15-mm. Pyrex tubing. For these runs, an exactly weighed amount of chloride was made up to volume in a 100-ml. volumetric flask at room temperature, the mixture was cooled and eight approximately 12-ml. samples were pipetted into the ampules, sealed at ice-bath temperature and placed in the thermostat. When the tubes had reached the temperature of the thermostat, one ampule was opened and a 10-ml. sample was withdrawn and titrated for the zero titer. The contents of one sealed tube were allowed to react for at least 10 half-life times, in order to get the infinity reading. All samples, including the one for the infinity reading, were withdrawn at the reaction temperatures, which were maintained at ±0.02°. The 10-ml. samples were allowed to run into 60–80 ml. of ice-cold acetone and were titrated with a NaOH solution contained in a 5-ml. microburet graduated in hundredths; a 0.5% alcoholic lacmoid solution was used as an indicator. Initial concentrations of chloride were usually around 0.01 *M*, except for the less soluble 2-anthryl (0.006–0.007 *M*) and 2-chrysenyl (0.005 *M* in 80% acetone) compounds. A check with the 2-fluorenyl compound at a 0.01 and 0.005 *M* concentration showed that the rates were not affected by the initial concentrations. Reactions were conducted to at least 60% completion, and usually more. Isolation runs were conducted with all compounds, except the phenyl, 1-naphthyl and 4-biphenylyl compounds, and the only products that were isolated were the corresponding carbinols, whose identity was checked by mixed melting points. The purity of the chlorides was obtained from infinity readings at 25°; all titrated for 99–100% purity except for the 1-naphthyl compound which was only 84% pure. This was undoubtedly due to some decomposition which was noticeable during vacuum distillation, but runs conducted with samples of various chloride content (60–84%) gave identical results.

Rate constants were calculated from the integrated form of the first-order rate equation. All runs were conducted at least in duplicate, all runs being listed in Table I. The average deviations within one run were 1–2%; some runs had a slight upward drift. The errors quoted for the activation energies and log *A* factors are probable errors obtained from least square calculations, rounded off to the values shown in Table I. The results of two typical runs are recorded in Table IV.

TABLE IV

THE HYDROLYSIS OF α-(2-FLUORENYL)-ETHYL CHLORIDE IN 80% AQUEOUS ACETONE AT 12.00°
Concn., 0.01002 *M*

Time, sec.	NaOH[a] ml.	$k \times 10^5$, sec.$^{-1}$
0	0.501	..
1290	.855	9.58
2600	1.168	9.51
4010	1.470	9.55
5870	1.820	9.67
7985	2.140	9.68
10870	2.481	9.67
14490	2.784	9.56
∞	3.546	..

[a] 0.02803 *N*.

THE HYDROLYSIS OF α-(4-BIPHENYLYL)-ETHYL CHLORIDE IN 80% AQUEOUS ACETONE AT 40.00°
Concn., 0.01017 *M*

Time, sec.	NaOH[a] ml.	$k \times 10^5$, sec.$^{-1}$
0	0.306	.
2370	.639	4.51
5970	1.100	4.63
9570	1.460	4.52
13170	1.790	4.56
16290	2.030	4.56
23970	2.494	4.57
∞	3.594	..

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BRYN MAWR, PENNA.

(27) We are indebted to Miss N. Pearson, who prepared most of the ketones and the known carbinols during her tenure of a fellowship at Bryn Mawr College.

(28) J. B. Conant and W. R. Kirner, THIS JOURNAL, **46**, 232 (1924).

[CONTRIBUTION NO. 2173 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

On Some *cis*-Forms of Phenylundecapentaenal

BY CH. GANSSER AND L. ZECHMEISTER

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All-*trans*-11-phenyl-2,4,6,8,10-undecapentaenal (I) can be rearranged to give four *cis* isomers, termed I–IV. The pertinent experimental conditions, relative thermo- and photostabilities and certain interconversions are described. Some connected spectroscopic phenomena are discussed and tentative configurational assignments are made.

While the stereoisomerization of some α,ω-diphenylpolyenes,[1] $C_6H_5(CH{=}CH)_nC_6H_5$, and symmetrical azines,[2] $C_6H_5(CH{=}CH)_nCH{=}N{-}N{=}CH(CH{=}CH)_nC_6H_5$, was studied earlier, *cis* forms of phenylpolyene aldehydes, $C_6H_5(CH{=}CH)_nCHO$, containing a rather high number of conjugated double bonds in an unbranched chain, do not seem to be known.

All-*trans*-11-phenylundecapentaenal ($n = 5$) was first obtained by Kuhn and Wallenfels,[3] then by Schmitt[4] who used a modified procedure. Theoretically, the molecules of this unsymmetrically built compound may assume 32 spatial configurations, the all-*trans* form included.[1e] We find

(1) (a) Diphenylbutadienes: F. Straus, *Ann.*, **342**, 190 (1905); C. Kelber and A. Schwarz, *Ber.*, **45**, 1946 (1912); E. Ott and R. Schröter, *ibid.*, **60**, 624 (1927); A. Sandoval and L. Zechmeister, THIS JOURNAL, **69**, 553 (1947); J. H. Pinckard, B. Wille and L. Zechmeister, *ibid.*, **70**, 1938 (1948). (b) Diphenylhexatrienes: K. Lunde and L. Zechmeister, *ibid.*, **76**, 2308 (1954). (c) Diphenyloctatetraenes: L. Zechmeister and A. L. LeRosen, *ibid.*, **64**, 2755 (1942); L. Zechmeister and J. H. Pinckard, *ibid.*, **76**, 4144 (1954). (d) Biphenylene derivatives: E. F. Magoon and L. Zechmeister, *ibid.*, **77**, 5642 (1955). (e) Survey articles: L. Zechmeister, *Chem. Revs.*, **34**, 267 (1944); *Experientia*, **10**, 1 (1954).

(2) J. Dale and L. Zechmeister, THIS JOURNAL, **75**, 2379 (1953).

(3) R. Kuhn and K. Wallenfels, *Ber.*, **70**, 1331 (1937).

(4) R. L. Schmitt, Collection, Haridwar (1941).

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that when the all-*trans* aldehyde is submitted to some thermic or photochemical treatments, upon subsequent chromatographic resolution of the stereoisomeric mixture, four *cis* zones appear, all located below the *trans* zone. They were termed *cises* I-IV, in the sequence of decreasing adsorption affinities. As will be indicated in the Experimental Part, this resolution is successful only on a specially prepared adsorbent, because of the rather difficult separation of the isomers and the sensitivity of the aldehyde group.[5]

In all experiments, regardless of the method, the main product of the *trans* → *cis* rearrangement was *cis*-II, while IV appeared only in traces. The *cises* II and III have been obtained as crystals but I and IV only as chromatographically homogeneous solutions. Each *cis* form yielded, upon iodine catalysis, (in part) the all-*trans* compound that was chromatographically inseparable from, and spectroscopically identical[6] with, the synthetic product.

With reference to relative stabilities the following observations were made (Tables I–II).

TABLE I

RATIO OF STEREOISOMERS OBTAINED BY TREATMENT OF ALL-*trans*-PHENYLUNDECAPENTAENAL AND OF ITS *cis*-II AND III FORMS

Treatment	Ratio, all-*trans*:*cis*-I:*cis*-II:*cis*-III (in the recovered substance)	Irreversible loss (% of starting material)[g]
(A) Starting material, all-*trans*:		
(Mostly 15 mg. substance were dissolved in 15 ml. of benzene. The ratios are based on observed extinction of the iodine catalyzed eluates of the respective zones.)		
Refluxing in darkness (30 min.)[a]	100:0:0:0	7
Standing in diffuse daylight (2 hr.)[b]	61:3:32:4	5
Insolation (2 hr.)[c]	62:6:25:7	25
Irradiation (2 hr.)[d]	58:6:32:4	10
Iodine catalysis, in light (30 min.)[e]	84:1:5:10	6
Melting crystals (90 sec.)[f]	72:1:27:0	31
(B) Starting material, *cis*-II:		
(Mostly 0.5 mg. substance in 5 ml. of benzene)		
Refluxing in darkness (30 min.)[a]	1:0:99:0	2
Standing in diffuse light (2.5 mg. in 50 ml.) (2 hr.)[b]	47:3:45:5	10
Insolation (2 hr.)[c]	61:5:27:7	39
Irradiation (2 hr.)[d]	54:2:39:5	22
Iodine catalysis, in light (30 min.)[e]	82:3:5:10	15
Melting crystals (90 sec.)[f]	69:3:28:0	40
(C) Starting material, *cis*-III:		
Refluxing in darkness (1 mg. in 50 ml.) (30 min.)[a]	10: trace:1:89	4
Standing in darkness (1 mg. in 5 ml.). (75 min.)[a]	0.5:trace:0:99.5	1
Insolation (5 mg. in 5 ml.) (20 sec.)[c]	9:0:4:87 (and traces of *cis*-IV)	1
Iodine catalysis, in light (4 min.)[e]	48:1:13:38	1

[a] A slow stream of nitrogen is recommended. [b] Intense diffuse light in the open (shade). [c] Intense morning sunshine (summer); end temp., 35°. [d] Three Photoflood bulbs from 10 cm. distance; end temp., 35–40°. [e] At 60 cm. distance from the light source. [f] 1–2 mg. substance in an evacuated capillary tube at about 190°, then cooled in iced water, extracted, and chromatographed. [g] These figures are based on the loss in extinction of iodine-catalyzed mixtures obtained from aliquots before and after the treatment but preceding chromatographic resolution.

TABLE II

RATIOS OF STEREOISOMERIC PHENYLUNDECAPENTAENALS OBTAINED UPON EXPOSURE TO WEAK DIFFUSE LIGHT[a] AT 20–25° FOR 4 MIN. (2.5 MG. IN 5 ML. BENZENE)

The ratios are based on observed extinctions of the iodine catalyzed eluates of the respective zones.

Isomer treated	Ratio, all-*trans*:*cis*-I:*cis*-II:*cis*-III (in recovered substance)	Irreversible loss (% of starting material)[b]
all-*trans*	95:1:3:1	1
cis-II	12:traces:76:12	1
cis-III	48:1:13:38	1

[a] Light intensity corresponding to f/5.6–1/100 sec.; (10 ASA) (Metraphot photometer). [b] *Cf.* footnote g to Table I.

When benzene solutions were refluxed in darkness for 0.5 hr., the all-*trans* compound remained sterically unaltered, while, respectively, 1 and 10% of the *cis* forms II and III were converted into the all-*trans* form.[7]

Like the diphenylbutadienes, the stereoisomeric phenylundecapentaenals show marked stereolability when exposed to intense scattered daylight. Under the conditions defined in Table I, roughly half of the all-*trans* and *cis*-II molecules were thus rearranged, while the *cis*-III configuration practically disappeared. Upon short exposure to weak daylight the data given in Table II were obtained. Likewise, in direct intense sunshine the photolability of the *cis*-III configuration surpasses that of the other isomers.

Under the usual conditions of the iodine catalysis (in light, in quartz cells) the rearrangement rates in this set are not significantly higher than in the absence of the catalyst (*cf.* the similar behavior of C=N bonds in azines).[2]

The spectral curves of the individual isomers, taken in the visible and ultraviolet regions,[8] appear in Figs. 1–3. The Figs. 1 and 2 also demonstrate the strong dependence of the fine structure on the solvent. Furthermore, while *trans* → *cis* rearrangements depressed the extinction values at λ_{max} con-

(5) *Cf.* J. F. Thomas and G. Branch, *J. Org. Chem.*, **18**, 1753 (1953).

(6) However, for some reason, our *trans ex cis* preparations showed a moderate band at 5.8 μ that was missing or present with much lower intensity in the spectra of synthetic all-*trans* samples.

(7) No reliable data are available for *cis*-I, since this isomer undergoes, while being rechromatographed, a partial structural alteration, whereby a beige-colored new zone appears on the column, much above the *cis*-I zone. The adsorption affinity of this pigment surpasses that of all-*trans*-phenylundecapentaenal; λ_{max} in benzene at 421 mμ, *versus* 425 mμ for all-*trans*-phenyltridecahexaenal.[5] Considering these observations, the spectral data listed in the Experimental Part and represented for this isomer in Fig. 4 are given with some reservation.

(8) Considering the photosensitivity of our substances, the unchanged steric homogeneity of the solutions was checked chromatographically each time after ultraviolet or infrared spectra had been taken. Qualitative curves of (probably not chromatographed) all-*trans*-phenylundecapentaenal samples had been given earlier by Thomas and Branch.[5] Quantitative spectrum of the all-*trans*-*p*- [illegible] and M. C. Whiting, *J. Chem. Soc.*, 4082 (1956).

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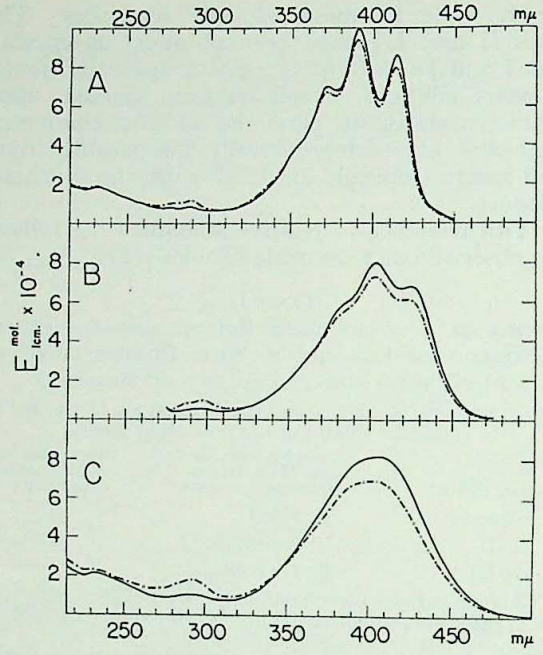

Fig. 1.—Molecular extinction curves of all-*trans*-phenylundecapentaenal: ———, fresh solution, and –·–·–·, mixture of the stereoisomers after iodine catalysis: A, in hexane; B, in benzene; and C, in methanol.

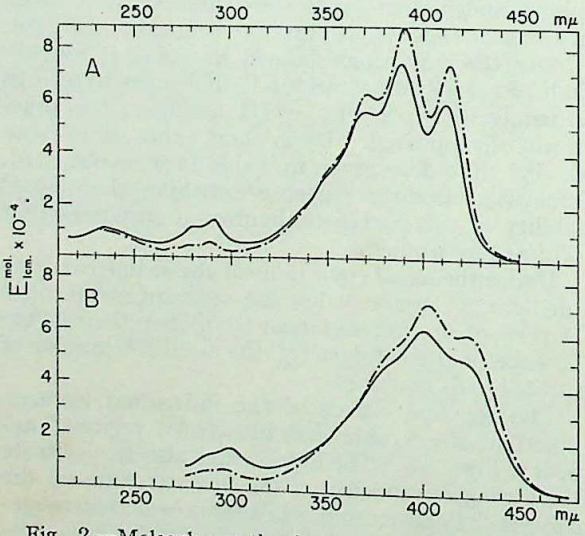

Fig. 2.—Molecular extinction curves of *cis*-II-phenylundecapentaenal: ———, fresh solution; and –·–·–·, mixture of stereoisomers after iodine catalysis: A, in hexane; and B, in benzene.

siderably, the position of the latter on the wave length scale was shifted by a few millimicrons only (Table III). In the *cis*-peak region the all-*trans*, *cis*-I and *cis*-IV curves are flat, while those of II and III do show some peaks. The shape of the latter is comparable with that of some *cis*-peaks observed in the lycopene[14] and methylbixin[9] sets.

As demonstrated in Fig. 4 the infrared spectra show a significant influence of the spatial configuration mainly in two regions: (a) in the 7.5–9.0 μ region that had been found by Lunde, *et al.*,[10] to be stereochemically sensitive in diphenylpolyene sets, without the possibility of a clear interpretation; and (b) in the 10.0–10.6 μ region where the presence of a conjugated *cis-trans* diene group[11,12]

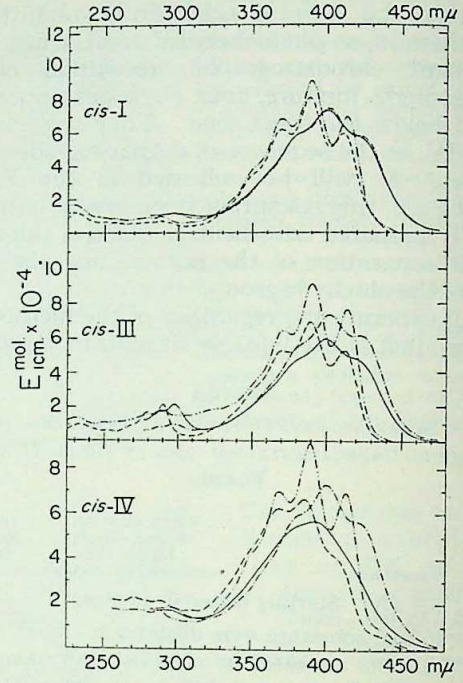

Fig. 3.—Molecular extinction curves of some *cis*-phenylundecapentaenals: fresh solutions: – – – –, in hexane; ———, in benzene; mixture of stereoisomers after iodine catalysis: –·–·–·, in hexane; and –·–·–·, in benzene.

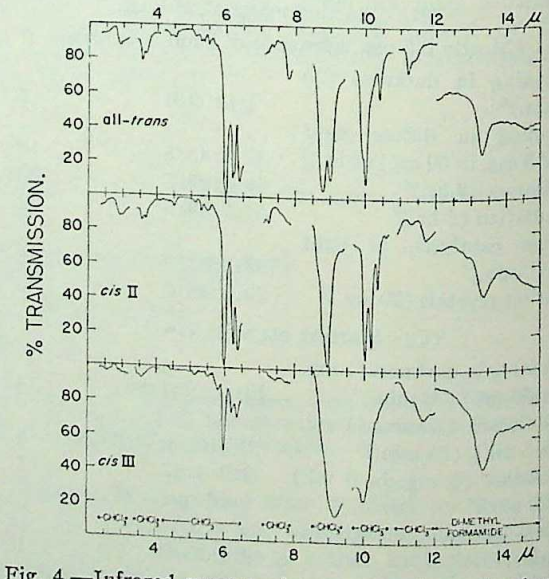

Fig. 4.—Infrared spectra of some stereoisomeric phenylundecapentaenals: from 2.0–12.0 μ in chloroform, and 12.0–15.0 μ in dimethylformamide (1 mm. cells). Concentrations: all-*trans* and *cis*-II, 0.7%; *cis*-III, 0.07% (microcell).

(9) L. Zechmeister and R. B. Escue, This Journal, **66**, 322 (1944).

(10) K. Lunde and L. Zechmeister, *Acta Chem. Scand.*, **8**, 1421 (1954).

(11) J. E. Jackson, R. F. Paschke, W. Talberg, H. M. Boyd and D. H. Wheeler, *J. Am. Oil Soc.*, **29**, 229 (1952).

(12) W. D. Gibbons and A. A. Solomons, This Journal, **75**, 3430 (1953).

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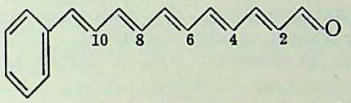
TABLE III

SOME SPECTRAL CHARACTERISTICS OF STEREOISOMERIC PHENYLUNDECAPENTAENALS IN HEXANE SOLUTION

	Main band			
Steric form	Fine structure	Position of λ_{max} (mμ)	Diff. from all-*trans* form at λ_{max} (mμ)	*cis*-Peak
all-*trans*	Very extensive	392	0	none
cis-I	Extensive	389	3	none
cis-II	Extensive	390	2	moderate, peak at 290 mμ
cis-III	Extensive	390	2	moderate, peak at 290 mμ
cis-IV	Very moderate	387	5	none

causes a splitting of the main band (located at 10.02 μ in the case of our all-*trans* compound). This doublet formation became strongly manifest in the curve of *cis*-II-undecapentaenal (new band at 10.19 μ), although only a small shoulder appeared in the *cis*-III curve, at 10.13 μ.



all-*trans*-phenylundecapentaenal

Considering the available experimental data, only tentative configurational assignments can be made at the present time (*cf.* ref. 13 and 14). The condensation product must represent the all-*trans* compound (*cf.* the formula) showing the greatest stability, the deepest color, the highest extinction values and by far the highest melting point. On the basis of observations made in comparable stereoisomeric sets, it is very probable that the *cis*es I-III represent mono*cis* forms.

The *cis*-I isomer, because of its strongest adsorption affinity among the *cis* forms and the absence of a *cis*-peak in its spectral curve, may well possess the 2-*cis* configuration, and hence an essentially straight molecular shape. In the case of *cis*es II and III the 2-*cis* position is excluded because of the presence of marked *cis*-peaks, and the centrally located 6-position is excluded because of the moderate height of these peaks as compared with the maximum values observed in the diphenyloctatetraene and diphenylhexatriene sets. Consequently, we assign the 8-mono*cis* configuration to *cis*-II and the 4-mono*cis* configuration to *cis*-III (or perhaps *vice versa*). The minor isomer IV seems to be a di*cis* compound, although, considering the flatness of its spectral curve in the *cis*-peak region and the small extent of fine structure in the main band, the sterically "hindered" 10-mono*cis* configuration cannot be excluded.[14,1b,c] Either of these assignments would explain the very weak adsorption affinity.

Acknowledgment.—We are indebted to Dr. Eugene F. Magoon for valuable discussions.

Experimental

Materials and Methods.—As adsorbent zinc carbonate (Merck Reagent Gr., precip.) was used. On zinc carbonate Harshaw (Techn. Gr.) and a number of other adsorbents, the stereoisomeric mixtures could not be resolved. The adsorbent was activated by heating, with occasional shaking, in large erlenmeyer flasks, in a drying oven at 120° for 3.5 hr. The powder should remain colorless and appear violet in ultraviolet light; it should be kept in sealed bottles and shaken before use. Overactivation results in too low migration rates on the chromatographic column. All operations should be carried out in quasi-darkness and the chromatographic tubes should be wrapped in black cloth, otherwise the orange colored zones might turn pink on the side facing the window. Benzene (Reagent Gr.) was used as the developer and ethanol as the eluent. Washing of benzene solutions was effected according to LeRosen.[15] Evaporations were carried out *in vacuo*, at near-room temperature. Melting points (cor.) were taken in a Fisher–Johns apparatus. For microanalyses we are indebted to Dr. A. Elek (Los Angeles, Calif.).

All photometric treatments refer to Pyrex volumetric flasks. A Photoflood bulb (Gen. Electric, No. 1) with attached Corning light filter No. 5840 served as the ultraviolet light source; and for irradiations the same bulb was used without the filter. Iodine catalyses (I_2 = 2% of the substance) were carried out in the light of two 120-cm. Mazda lamps (3500°, 40 watt, white and yellowish) at 60 cm. distance. Instruments: Beckman spectrophotometer model DU (quartz cells); Cary recording ultraviolet spectrophotometer model 11 M (quartz cells); and Perkin–Elmer infrared double beam spectrophotometer model 21 (NaCl prism). The extinction coefficients given represent averages of at least two independent experiments. When direct weighing of the substance was impossible, the mol. extinction coefficient of the iodine-equilibrium mixture was used in the calculations as determined by iodine-catalyzing a weighed all-*trans* sample.

All-*trans*-phenylundecapentaenal was prepared by condensing cinnamaldehyde with crotonaldehyde[4] and was freed from its 7-phenylheptatrienal content by extraction with 70% ethanol.[16] After recrystallization from acetone the aldehyde was purified chromatographically (instead of the usual sublimation) as follows. A benzene solution of 17 mg. substance was developed on a 27 × 4.4 cm. column for about 90 min.[17] Above the orange-yellow main zone several other colored zones appeared, evidently containing some higher condensation products (these had been eliminated by Kuhn and Wallenfels[3] by fractional crystallization). The main zone was cut out; its eluate was washed with water, the benzene solution dried with sodium sulfate, evaporated to a few milliliters and crystallized by cautious, dropwise addition, with stirring, of hexane. Brownish-orange prisms with pointed ends, m.p. 185–186°, yield 12 mg. $E^{mol.}_{1\,cm.}$ 9.98 × 10^4 at λ_{max} 392 mμ (in hexane); 7.98 × 10^4 at λ_{max} 403 mμ (in benzene); 8.2 × 10^4 at λ_{max} 406 mμ (in methanol).

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.93; H, 6.83. Found: C, 87.13; H, 7.22.

By chromatographing as described crude all-*trans*-phenylundecapentaenal samples on a much weaker, unactivated adsorbent, such as zinc carbonate Harshaw (Techn. Gr.), the presence of some higher condensation products could be demonstrated in a simple way. (The figures on the left designate thickness of zones, in mm.; the parentheses refer to fluorescence in ultraviolet light; and the spectral data to λ_{max} in benzene):

30 three minor pink zones and interzones
30 pink (dull red): 15-phenylpentadecaheptaenal,[3] 444, 470 mμ
25 empty interzone
40 beige (weak dull red): 13-phenyltridecahexaenal[5] (?), 423 mμ
10 empty interzone
50 orange-yellow (golden-yellow): 11-phenylundecapentaenal, 403 mμ (96% of the recovered pigment)
90 empty section

(13) L. Pauling, *Fortschr. Chem. organ. Naturstoffe*, **3**, 203 (1939).
(14) L. Zechmeister, A. L. LeRosen, W. A. Schroeder, A. Polgár and L. Pauling, THIS JOURNAL, **65**, 1940 (1943).
(15) A. L. LeRosen, *Ind. Eng. Chem., Anal. Ed.*, **14**, 165 (1942).
(16) M. Korach and W. Bergmann, *J. Org. Chem.*, **14**, 1118 (1949).
(17) A chromatographic treatment of relatively more substance on a longer column (*e.g.*, 100 mg.; 40 × 4.4 cm.) should be avoided, because of structural changes causing dark-violet colorations of the zones. Such all-*trans*-zones yielded crimson, rod-like crystals, m.p. 197–200°, λ_{max} at 421 mμ in benzene, *versus* 210–213° and 425 mμ observed for phenyltridecahexaenal). Likewise, some chemical processes (liberation of aldehydes) took place when benzene or hexane solutions of some polyene aldehyde anils, $C_6H_5(CH{=}CH)_nCH{=}N{\cdot}C_6H_5$ (n = 2, 3 or 5) were developed on zinc carbonate, calcium carbonate even sugar. For this reason a planned stereochemical study of the anils was unsuccessful.

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cis-I-Phenylundecapentaenal was obtained from the chromatogram described in the next Section. Since it could not be rechromatographed unchanged, the following data were determined upon iodine catalysis. $E^{mol.}_{1cm.}$ 8.08 × 10^4 at λ_{max} 389 mμ (in hexane); 7.30 × 10^4 at λ_{max} 401 mμ (in benzene).

cis-II-Phenylundecapentaenal.—Seventeen milligrams of pure all-*trans* crystals was dissolved in 15 ml. of benzene on a water-bath and, after cooling to 20°, exposed to intense diffuse daylight on a window sill. After 2 hr. the solution was developed on a 22 × 3.5 cm. column:

20	orange-yellow (golden-yellow): unchanged all-*trans*
5	pale yellow (dull dark brown): *cis*-I
5	empty interzone
23	yellow (golden light yellow): *cis*-II
7	pale yellow (dull brown): *cis*-III
160	empty section

The eluate of the 23-mm. zone was transferred to benzene, dried, concentrated and rechromatographed as described on a 18 × 2 cm. column. The developing process was continued until a narrow but clear interzone appeared between the *cis*-II and *cis*-III zones. The benzene solution obtained from the former was evaporated completely, the crystalline residue dissolved at 25° in the minimum amount of benzene and crystallized by cautious addition of hexane; yield 4 mg. (in all, 20 mg. were prepared). Fine, orange-yellow needles grouped in sheaves or fan-like forms, m.p. 103–105°, or short needles, m.p. 108–110°; $E^{mol.}_{1cm.}$ 7.49 × 10^4 at λ_{max} 390 mμ (in hexane); 6.2 × 10^4 at λ_{max} 401 mμ (in benzene).

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.93; H, 6.83. Found: C, 87.25; H, 7.39.

cis-III-Phenylundecapentaenal.—The 7-mm. zone of the above chromatogram was treated as described for *cis*-II and combined with seven similar zones originating from parallel experiments. After rechromatographing (column, 22 × 3.5 cm.) the benzene solution (50 ml.) was evaporated to 1 ml. at 10° (oil pump, receiver in acetone–Dry Ice). Upon cautious addition of hexane at 20°, this concentrate deposited crystals. Recrystallization in the same manner yielded 3 mg. of small, sturdy, yellow spears. The sample sintered at about 103° and melted at 176–178°, *i.e.*, somewhat below the m.p. of the all-*trans* isomer; evidently, this determination was disturbed by spatial changes in the fused state. The following values were obtained upon iodine catalysis: $E^{mol.}_{1cm.}$ 6.91 × 10^4 at λ_{max} 390 mμ (in hexane); 5.90 × 10^4 at λ_{max} 401 mμ (in benzene).

cis-IV-Phenylundecapentaenal was formed, when a solution of 5 mg. of *cis*-III in 5 ml. of benzene was exposed to sunshine (*cf.* Table IC). In the chromatogram, the thin, pale yellow *cis*-IV zone was located just below *cis*-III. After rechromatographing, the following data were obtained by the iodine catalysis method: $E^{mol.}_{1cm.}$ 6.64 × 10^4 at λ_{max} 387 mμ (in hexane); 5.67 × 10^4 at λ_{max} 394 mμ (in benzene).

PASADENA, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

Structure of Corn Hull Hemicellulose. Part VI. The Synthesis of 5-O-β-D-Galactopyranosyl-L-arabinose[1,2]

BY IRWIN J. GOLDSTEIN, F. SMITH AND H. C. SRIVASTAVA

RECEIVED FEBRUARY 27, 1957

The synthesis of 5-*O*-β-D-galactopyranosyl-L-arabinose is described.

In a previous paper[3] of this series there was discussed the isolation and characterization of 5-*O*-β-D-galactopyranosyl-L-arabinofuranose, a disaccharide formed amongst others when corn hull hemicellulose[4] is subjected to graded hydrolysis with dilute mineral acid.[3]

The formulation of the disaccharide as 5-*O*-β-D-galactopyranosyl-L-arabinose was based upon these observations: Acid hydrolysis showed the presence of galactose and arabinose, while hydrolysis of the phenylosazone of the disaccharide gave galactose, but no arabinose. Hydrolysis of the fully methylated disaccharide furnished 2,3,4,6-tetra-*O*-methyl-D-galactopyranose and 2,3-di-*O*-methyl-L-arabinose. The decision to assign a β-configuration to the galactose residue and a furanose conformation to the arabinose moiety was based upon the rules of isorotation.[3,5]

This communication is concerned with the synthesis of 5-*O*-β-D-galactopyranosyl-L-arabinose in order to confirm the structure assigned to the disaccharide from the corn hull hemicellulose. The synthesis was accomplished as follows: interaction of ethyl 2,3-di-*O*-acetyl-α-L-arabinofuranoside with 2,3,4,6-tetra-*O*-acetyl-α-D-galactosyl bromide in the presence of silver oxide gave a sirup which, when deacetylated and subjected to controlled hydrolysis, afforded 5-*O*-β-D-galactopyranosyl-L-arabinofuranose. This was purified by chromatography on a carbon:Celite column[6] taking care to avoid washing with water to remove monosaccharides, since this leads to imperfect separations.[7] In this manner two isomeric galactose–arabinose disaccharides were obtained. Methylation of the one whose rotation corresponded to that of the galactose–arabinose disaccharide isolated from the corn hull hemicellulose, first with methyl sulfate and 40% potassium hydroxide solution in the absence of air, and then with methyl iodide and silver oxide, gave methyl 5-*O*-(2,3,4,6-tetra-*O*-methyl-β-D-galactopyranosyl)-2,3-di-*O*-methyl-L-arabinofuranoside, a non-reducing sirup which showed $[\alpha]^{24}D$ −45° in methanol. Acid hydrolysis of the latter followed by paper chromatographic analysis afforded two cleavage products, namely, 2,3,4,6-

(1) Paper No. 3730 Scientific Journal Series, Minnesota Agricultural Experiment Station, University of Minnesota.

(2) This research was done under contract with the United States Department of Agriculture and authorized by the Research and Marketing Act of 1946. The contract was supervised by the Northern Utilization Research Branch of the Agricultural Research Service.

(3) H. C. Srivastava and F. Smith, THIS JOURNAL, **79**, 982 (1956).

(4) M. J. Wolf, M. M. MacMasters, J. H. Cannon, E. C. Rosewall and C. E. Rist, *Cereal Chem.*, **30**, 451 (1953).

(5) C. S. Hudson, THIS JOURNAL, **31**, 66 (1909); F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," Circular C440 of the National Bureau of Standards, 1942, p. 514.

(6) R. L. Whistler and D. F. Durso, *ibid.*, **72**, 677 (1950).

(7) F. Smith and H. C. Srivastava, *ibid.*, **78**, 1404 (1956).

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tetra-*O*-methyl-D-galactopyranose and 2,3-di-*O*-methyl-L-arabinose.

Separation of these components was effected by sheet paper chromatography in the usual way using butanone:water azeotrope. The 2,3-di-*O*-methyl-L-arabinose was identified as its crystalline 1,4-di-*p*-nitrobenzoate[3] while the 2,3,4,6-tetra-*O*-methyl-D-galactopyranose afforded the characteristic crystalline aniline derivative.[8]

The characterization[3] of the *O*-D-galactosyl → L-arabinoise disaccharide from the corn hull hemicellulose as 5-*O*-β-D-galactopyranosyl-L-arabinose is therefore correct.

Experimental

The following solvents were used for partition chromatography: A, pyridine:ethyl acetate:water (1:2.5:3.5)[9]; B, 1-butanol:pyridine:water (6:4:3)[10]; C, 1-butanol:acetic acid:water (2:1:1)[11]; and D, butanone–water azeotrope.[12] The sugars were detected on the paper chromatogram by spraying with *p*-anisidine trichloroacetate[13] and/or ammoniacal silver nitrate.[14]

All evaporations were carried out under reduced pressure at 30–40°. R_x represents the rate of movement of sugars with respect to D-xylose.

Ethyl 2,3-Di-*O*-acetyl-5-*O*-trityl-α-L-arabinofuranoside.—Ethyl α-L-arabinofuranoside[15] (1.15 g., m.p. 48–49°) was suspended in dry pyridine (5 ml.) and after the addition of triphenylmethyl chloride (1.8 g.) the mixture was shaken. The reaction mixture which became clear after 10 hr. was kept at room temperature for 20 days. To the reaction mixture, acetic anhydride (5 ml.) was added and the solution kept at room temperature for 20 hr. The mixture was poured with stirring into cold water when a viscous sirup separated. The sirup was extracted with chloroform and the extract washed successively with a dilute aqueous solution of sodium bicarbonate and water. After drying (Na_2SO_4), the chloroform solution was evaporated to give a viscous sirup (3.2 g.) which did not crystallize.

Ethyl 2,3-Di-*O*-acetyl-α-L-araboinfuranoside.—The compound (3.2 g.) obtained in the previous experiment was detritylated by dissolving it in glacial acetic acid (30 ml.) and adding to the cooled solution a saturated solution (2.5 ml.) of hydrogen bromide in acetic acid. The precipitated triphenylmethyl bromide was filtered, the residue washed with acetic acid and the combined filtrates poured into a mixture of cold water and chloroform. The chloroform layer was separated and the aqueous layer extracted twice with chloroform. The combined chloroform extracts were washed with a solution of sodium bicarbonate and then with water. The chloroform solution was dried (Na_2SO_4) and evaporated to give a light colored sirup (1.4 g.) which showed $[\alpha]^{25}D$ −30° in chloroform (*c* 1.7).

2,3,4,6-Tetra-*O*-acetyl-α-D-galactosyl Bromide.—1,2,3,-4,6-Penta-*O*-acetyl-β-D-galactose (7 g.), transformed into the glycosyl bromide in the usual way, was obtained as a liquid (6.5 g.) which showed $[\alpha]^{19}D$ +211° in benzene (*c* 6); lit.[16] $[\alpha]D$ +234°. This product was used directly.

Interaction of Ethyl 2,3-Di-*O*-acetyl-α-L-arabinofuranoside with 2,3,4,6-Tetra-*O*-acetyl-α-D-galactosyl Bromide.—The reagents (chloroform, silver oxide and Drierite) for the condensation reaction were prepared according to the procedure of Reynolds and Evans.[17] The reactants were dried *in vacuo* at 50–60° for 4 hr.

Sirupy ethyl 2,3-di-*O*-acetyl-α-L-arabinofuranoside (1.1 g.) was dissolved in chloroform (7 ml.) and after the addition of Drierite (5 g.) and silver oxide (2.0 g.), the mixture was shaken for 0.5 hr. A solution of iodine (0.2 g.) in chloroform (10 ml.) was added to the mixture and then 2,3,-4,6-tetra-*O*-acetyl-α-D-glactosyl bromide (1.7 g.) in chloroform (7 ml.) was added in small portions during 0.5 hr. The mixture was shaken for 36 hr., filtered and the residue washed with chloroform. The combined filtrate and washings were evaporated to give a sirup (2.2 g.).

The sirup was deacetylated by dissolving it in ethanol (50 ml.), adding 0.1 *N* potassium hydroxide (20 ml.) and heating at 60° for 1 hr. The reaction mixture was evaporated to a sirup which was dissolved in 0.01 *N* sulfuric acid (20 ml.) and the solution heated on a steam-bath for 2 hr. The inorganic ions were removed by passing the solution successively through columns of Duolite A-4[18] and Amberlite IR-100,[19] and the effluent was evaporated to a sirup (1.0 g.). Upon chromatographic analysis using solvent A the sirup was found to contain arabinose (R_x 0.84), galactose (R_x 0.62) and a third component with R_x 0.52. This component was indistinguishable on paper chromatograms using solvents A, B and C from 5-*O*-β-D-galactopyranosyl-L-arabinose[3] isolated by graded hydrolysis of corn hull hemicellulose.

Isolation of 5-*O*-β-D-Galactopyranosyl-L-arabinose.—The sirupy mixture (1.0 g.) containing the galactose–arabinose disaccharide, galactose and arabinose, was dissolved in 2.5% aqueous ethanol and the solution put on a charcoal:Celite column[6] previously washed with 2.5% aqueous ethanol. The column was washed first with 2.5% aqueous ethanol[7] (750 ml.) to displace the monosaccharides and then with 10% aqueous ethanol (900 ml.), collected in six fractions of 150 ml. each, to elute the disaccharide. Fractions 1 and 2 were found to contain negligible amounts of carbohydrate material. Fraction 3, when evaporated, yielded a sirup (181 mg.) which had $[\alpha]^{25}D$ −18° in water (*c* 1). In solvents A, B and C it had the same R_f as that of 5-*O*-galactopyranosyl-L-arabinose obtained from the corn hull hemicellulose. The disaccharide (10 mg.) was hydrolyzed with 0.7 *N* sulfuric acid (3 ml.) for 4 hr. on a steam-bath, neutralized ($BaCO_3$), filtered and evaporated to give a sirup which, upon chromatographic analysis, was found to contain galactose and arabinose.

Fractions 4 and 5 were combined and then evaporated to yield a sirup (217 mg.) which had the same R_f as 5-*O*-β-D-galactopyranosyl-L-arabinose and showed $[\alpha]^{25}D$ −76° in water (*c* 5). Upon acid hydrolysis with 0.7 *N* sulfuric acid it also afforded galactose and arabinose. The structure of this disaccharide will form the subject of a later communication.

Fraction 6, upon evaporation, gave a sirup (6.7 mg.) which was shown to be a mixture of galactosylarabinose and higher oligosaccharides and was not further examined.

Proof of Structure of 5-*O*-β-D-Galactopyranosyl-L-arabinose. Methyl 5-*O*-(2,3,4,6-Tetra-*O*-methyl-D-galactopyranosyl)-2,3-di-*O*-methyl-L-arabinofuranoside.—The galactose–arabinose disaccharide (90 mg., $[\alpha]D$ −18° in H_2O) was methylated in an atmosphere of nitrogen with 40% potassium hydroxide (24 ml.) and methyl sulfate (8 ml.), the reagents being added in eight portions with vigorous stirring at 0° during 1.5 hr.[3] The reaction mixture was stirred for another hour and after it had attained room temperature it was methylated with 40% potassium hydroxide (9 ml.) and methyl sulfate (3 ml.) in the previous manner. The mixture was stirred for 2 hr. and after warming it to 50–60° it was methylated again with methyl sulfate (2 ml.) and 40% potassium hydroxide (6 ml.). The reaction mixture was stirred for 1.5 hr. and then heated at 80–90° for 1.5 hr. The mixture was cooled, stirred with chloroform (50 ml.), filtered and the residue washed with chloroform. The chloroform solution was separated and the remaining aqueous layer extracted twice more with chloroform. The combined chloroform extracts were washed with a saturated solution of sodium sulfate, dried (Na_2SO_4) and evaporated to give a sirup (52.7 mg.). This was dissolved in methyl iodide (10 ml.) and silver oxide (3 g.) added in small portions. The mixture was refluxed for 12 hr. After the reaction, the mixture was filtered, washed with chloro-

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(18) A product of the Chemical Process Co., Redwood City, Calif.
(19) A product of the Rohm and Haas Chemical Co., Philadelphia, Pa.

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form, and the combined filtrates evaporated to give a sirup which was methylated twice more with methyl iodide and silver oxide in the previous manner.

After distilling the methyl iodide, the silver oxide residue was extracted with ether (five 20-ml. portions). Concentration of the ethereal extract gave methyl 5-*O*-(2,3,4,6-tetra-*O*-methyl-D-galactopyranosyl)-2,3-di-*O*-methyl-L-arabinofuranoside as a yellow, non-reducing sirup (48.5 mg.) which showed $[\alpha]^{24}D$ −45° in methanol (*c* 1.6).[3]

Hydrolysis of Methyl 5-*O*-(2,3,4,6-Tetra-*O*-methyl-D-galactopyranosyl)-2,3-di-*O*-methyl-L-arabinofuranoside.—A solution of the methylated disaccharide (48.5 mg.) in 0.3 *N* sulfuric acid (3 ml.) was heated at 100° for 9 hr. The reaction mixture was neutralized ($BaCO_3$) and filtered, the salts being washed thoroughly first with water, then ethanol. Concentration of the filtrate gave a yellow sirup (38 mg.) which showed $[\alpha]^{26}D$ +32° in methanol (*c* 1.3).

Analysis of the sirup by paper chromatography, using solvent D, showed the presence of two components upon spraying either with ammoniacal silver nitrate or with *p*-anisidine, namely, 2,3-di-*O*-methyl-arabinose (R_f 0.43) and 2,3,4,6-tetra-*O*-methylgalactose (R_f 0.68).

Separation of the methylated components was achieved by sheet paper chromatography (Whatman No. 1) using solvent D. In addition to the two components noted, a small amount of the reducing unhydrolyzed methylated disaccharide was obtained, R_f 0.79.

Identification of 2,3,4,6-Tetra-*O*-methyl-D-galactose.—The component corresponding to 2,3,4,6-tetra-*O*-methyl-D-galactose was eluted from the filter paper and concentrated to give a chromatographically pure sirup (13 mg.) which showed $[\alpha]^{25}D$ +58° in ethanol (*c* 0.4). It was converted in the usual manner to N-phenyl-D-galactopyranosylamine 2,3,4,6-tetramethyl ether, m.p. and mixed m.p. 196–197°, $[\alpha]^{27}D$ −78° in acetone (*c* 0.4), after recrystallization from ethanol; lit.[8] m.p. 192°, $[\alpha]D$ −77° (acetone).

Identification of 2,3-Di-*O*-methyl-L-arabinose.—2,3-Di-*O*-methyl-L-arabinose was obtained as a colorless sirup (6.5 mg.) which showed $[\alpha]^{25}D$ +92° in water (*c* 0.3). It was characterized as its 1,4-di-*p*-nitrobenzoate, m.p. and mixed m.p. 149–152°.[3]

Acknowledgment.—The authors thank Professor Eugene Pacsu of Princeton University for a nucleus of ethyl α-L-arabinofuranoside.

ST. PAUL, MINNESOTA

[CONTRIBUTION FROM THE CEREAL CROPS SECTION, NORTHERN UTILIZATION RESEARCH BRANCH[1]]

Starch Formate

BY I. A. WOLFF, D. W. OLDS AND G. E. HILBERT

RECEIVED MARCH 9, 1957

Formylation of starch under the conditions investigated is a reversible reaction; the extent of substitution is dependent upon the ratio of formic acid to starch and on the water content of the system. Appreciation of this fact is required by workers who use formylation of cellulose for accessibility studies and refer to amylaceous materials as standards for comparison, assuming the latter to be 100% accessible. Maximum degree of substitution of starch achieved was 2.3 acyl groups per anhydroglucose unit.

As part of a program at this Laboratory on the preparation of starch esters,[2] formyl derivatives were desired.

Gottlieb, Moe, Nickerson and their co-workers[3–5] esterified starch, using 90% formic acid at room temperature and obtained esters having a degree of substitution approximating, but slightly greater than, one formyl group per anhydroglucose unit. Tarkow and Stamm,[6] using 99% formic acid at 55° also report formation of essentially a monoformate, but in their studies a relatively low ratio of formic acid to carbohydrate was used. All of these authors indicate either exclusive reaction of the formic acid with primary hydroxyl groups or at least preferential, rapid formylation of this grouping. Browning and Sell[7] state that their work "suggests formylation of secondary hydroxyl groups," though more slowly than primary hydroxyl groups. These authors conducted their experiments with 99.3% formic acid at 51° and demonstrated increased formylation of starch at higher formic acid to starch ratios. Their conclusions are based on analytical data alone. Reaction products were not isolated. The use of data on the formylation of cellulose as a measure of its accessibility, with reference to amylaceous materials as standards,[4–6] makes an understanding of the formylation of starch particularly pertinent.

In the studies reported here, starch was esterified at ambient temperature in excess formic acid containing different amounts of water. Formyl esters were isolated by alcohol precipitation at varying time intervals and analyzed for acyl content. Our results indicate that the formylation of starch under the conditions used is best depicted as a reversible reaction

$$\underset{\text{Starch}}{R(OH)_3} + n\text{HCOOH} \rightleftarrows \underset{\text{Starch formate}}{R(OCHO)_n(OH)_{3-n}} + n\text{H}_2\text{O}$$

in which equilibrium is reached in about 8 hr. Fortuitous choice of reaction conditions was apparently responsible for isolation of a monoformate by many earlier workers.

Anhydrous formic acid reacts with starch to give a monoformate in only one-fourth of the time needed with the 90% acid (Fig. 1). The final product obtained with this more concentrated acid approximates a diformate. Use of anhydrous starch, of higher proportions of formic acid relative to the starch or reformylation of an isolated "diformate" all raise the degree of formylation still further. The equilibrium nature of the reaction was demonstrated as follows: Sufficient water was added to the reaction mixture of dry starch with

(1) One of the Branches of the Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

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anhydrous formic acid after maximum reaction was obtained to lower the acid strength to 90%. The product then isolated corresponded to that expected if 90% formic acid had been used initially.

It was not possible to prepare starch triformate by removal of water with anhydrous calcium sulfate or azeotropically with benzene. The highest degree of substitution attained was 2.3 formyls per C_6 unit. However, failure to achieve preparation of the triester may still be simply a question of equilibrium, with the conditions employed being inadequate for removal of the last traces of water from the system. The large effects of small quantities of water in displacing the equilibrium toward the side of deacylation are demonstrated by the work of Hiller[8] on a comparable cellulose–acetic acid system. In studying equilibrium combined acetic acid content of cellulose acetate in homogeneous, uncatalyzed reactions, Hiller found that (at 94.2°) presence of 0.5% water resulted in equilibrium degree of substitution of 2.75 acetyl groups per C_6 unit; 2.8% water in the system gave equilibrium substitution of 1.9.

Our results agree with those of other investigators in indicating preferential reactivity of the 6-hydroxyl group, as deduced from periodate analysis of "mono-" and "di-" formates. Starch monoformate consumed approximately one mole of oxidant per mole of anhydrohexose present. The starch diformate was oxidized by the periodate only to the extent of 0.15 mole of oxidant consumed per anhydroglucose unit. This fact indicates a fair degree of homogeneity for the diformate, although the possibility exists that some monoformate, with compensating amounts of triformate ester, may be present. In other studies we have shown[9] that under conditions employed in the periodate oxidation analysis a minor, but definite and measurable, hydrolysis of formate esters can occur.

The free hydroxyl groups in starch formates can be esterified to give completely substituted mixed esters.

The solid starch esters developed a strong odor of formic acid within several days when left exposed to the laboratory atmosphere.

Experimental

Materials.—High grade commercial corn starch served as the carbohydrate raw material. Eastman Kodak Co. anhydrous formic acid (98–100%) and Merck and Co., Inc., reagent (approximately 90%) formic acid were used in the esterifications.

Analytical Procedures.—Formyl analysis on the starch esters was carried out by saponification at room temperature for 48 hr. with 0.25 *N* potassium hydroxide in aldehyde-free absolute ethanol. An excess of 0.25 *N* hydrochloric acid was added at the end of the saponification period and after several hours the samples were titrated to a phenolphthalein end-point with 0.1 *N* aqueous sodium hydroxide.

Esterification Methods.—Esterifications of the starch were carried out by adding the required amount of starch to formic acid which was being rapidly stirred mechanically at room temperature. Mechanical stirring was continued throughout the reaction period. Gelatinization always occurred in a short time. In about 2 hr. the mixture was practically homogeneous and free from gelled particles. From then on the mixture gradually became clearer and less viscous. At the end of the reaction period the esters were precipitated in absolute ethanol (Waring Blendor), washed three times in the Blendor with this solvent and finally dried *in vacuo* at 25 and 70°. The esters were all white powders.

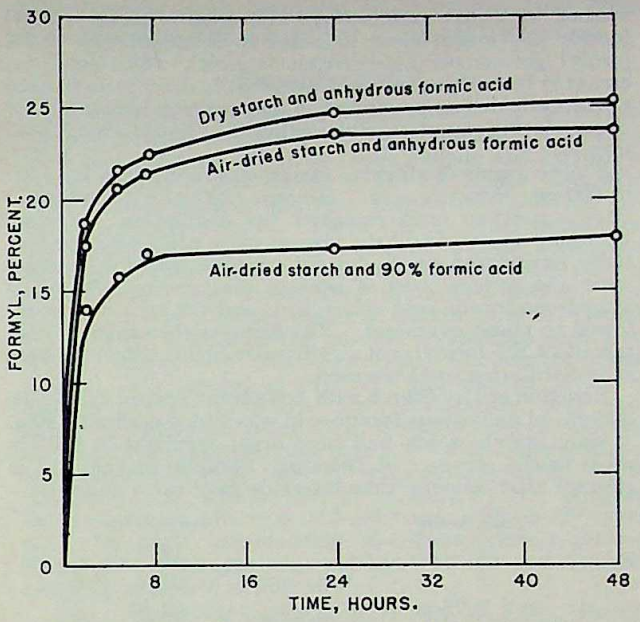

Fig. 1.—Esterification of starch with formic acid.

Reaction of Air-dried Starch with 90% Formic Acid.—Thirty grams of air-dried starch was treated with 300 ml. of 90% formic acid. Samples were withdrawn at various time intervals, precipitated and analyzed:

Reaction time, hours	Formyl, %[a]
2	14.0
5	15.7
7.5	17.0
24	17.3
48	17.9

[a] Calcd. for starch monoformate, $C_7H_{10}O_6$: 15.3% formyl.

Reaction of Air-dried Starch with Anhydrous Formic Acid.—Reaction of 30 g. of air-dried starch with 300 ml. of anhydrous formic acid and withdrawal of samples, as above, gave materials with the following analysis:

Reaction time, hours	Formyl, %[a]
2	17.75
5	20.6
7.5	21.4
24	23.65
72	24.2

[a] Calcd. for starch diformate, $C_8H_{10}O_7$: formyl, 26.6.

If Drierite is added initially to a reaction mixture such as the above, the product after 5 hr. has 20.7% formyl and 1.05% ash.

Twenty-five grams of vacuum oven-dried starch formate (18.8% formyl) prepared by 3 hr. reaction of air-dried starch with anhydrous formic acid was reformylated for 4.5 hr. with 300 ml. of anhydrous formic acid. The formyl content of the product was 24.4%.

To test the effect of concentration 30 g. of air-dried starch was formylated in 600 ml. of anhydrous formic acid. The course of the reaction was as shown:

Reaction time, hours	Formyl, %
2	20.1
5	23.2
7	24.3
24	27.3
48	28.0

The 24-hr. sample above (3.3 g. vac. oven dry wt.) was reformylated for 7.5 hr. with 80 ml. of anhydrous formic acid. The material was precipitated in diethyl Cellosolve,

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washed with that same solvent and dried *in vacuo;* formyl found: 29.5 (equivalent to a degree of substitution of 2.3 formyl groups per anhydroglucose unit). This small increase in formyl content indicates that in other formylations ethanolysis during precipitation and washing is not a factor in preventing complete substitution of hydroxyl groups with formyl.

Thirty grams of air-dried starch was formylated for 4 hr. in 300 ml. of formic acid. Benzene (200 ml.) was added in 50-ml. portions and removed by distillation *in vacuo*. Bumping occurred and the viscous paste containing the partially formylated starch did not mix well with the benzene. After the surface layer of benzene disappeared, 150 ml. of anhydrous formic acid was added, and the mixture was allowed to stand overnight. The formate then isolated contained 24.8% formyl, not significantly higher than if no benzene distillation had been used.

Reaction of Dry Starch with Anhydrous Formic Acid.—To 300 ml. of anhydrous formic acid was added gradually 30 g. f corn starch which had been dried overnight at 110° *in vacuo* in the presence of Drierite. Samples precipitated in ethanol after varying time intervals gave these analyses:

Time, hours	Formyl, %
2	18.7
5	21.7
7.75	22.6
24	24.8
48	25.4

Thirty grams of corn starch was formylated as above. One hundred milliliters of the mixture was precipitated after 24 hr. To the remainder 25 ml. of water was added and reaction was continued for 27 hr. longer. The remainder was then precipitated. The analysis of these products was: 24-hr. product, 26.1% formyl; 51-hr. product, 18.9% formyl.

The starch formates are soluble in pyridine and in formic acid but not in the other common organic solvents tested.

Optical Rotation of Starch Formates.—The rotation of a formyl ester with 1.3 formyl groups per C_6 (19.0% formyl) was $[\alpha]^{25}D$ +180.6° (pyridine, c = 1). A formate containing 2.1 formyl per C_6 (27.7% formyl) had $[\alpha]^{25}D$ +166.5° (pyridine, c 1).

Oxidation of Starch Formate with Periodate.—Samples of starch formate were treated with an excess of sodium periodate. After 24 hr., analysis for excess periodate was carried out.[10] Data are summarized below.

		Starch formate	
Formyl/C_6 unit	Wt. sample, g.	Periodate consumed (millimole)	Millimoles periodate per millimole repeating unit
2.10	0.3050	0.21	0.15
1.16	.1449	.80	1.08

Carbanilation of Starch Formate.—To 19.0 g. of oven-dried starch formate (18.8% formyl, 1.28 formyl per C_6) in 125 ml. of dry pyridine was added 35 g. of phenyl isocyanate, and the mixture was heated for 6 hr. at 100°. The ester, isolated by precipitation with ethanol, had 5.99% N; calcd. 5.94% N. Similar preparation of other mixed esters from starch formates indicates that formyl esters are produced and that the formic acid is not held merely by sorption or solvation onto the carbohydrate.

Acknowledgment.—The authors are indebted to T. A. McGuire and C. H. Van Etten for assistance with the formyl analyses. The use of trade names in this paper does not necessarily constitute endorsement of these products or of the manufacturers thereof.

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Peoria, Illinois

[Contribution from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health Public Health Service]

1,2 :3,5-Di-*O*-benzylidene-α-D-glucose

By Harry B. Wood, Jr., Harry W. Diehl and Hewitt G. Fletcher, Jr.

Received January 31, 1957

Condensation of D-glucose with benzaldehyde in the presence of zinc chloride–acetic acid gives a di-*O*-benzylidene-D-glucose identical with a substance which earlier authors obtained through successive benzylidenation and debenzoylation of 6-*O*-benzoyl-D-glucose diethyl dithioacetal. Evidence is presented showing the acetal to be 1,2:3,5-di-*O*-benzylidene-α-D-glucose.

In 1937, Papadakis[1] published a study of the behavior of 6-*O*-benzoyl-D-glucose diethyl dithioacetal with benzaldehyde in the presence of zinc chloride. Under the conditions which this author employed, the thioethyl groups were lost and a non-reducing *O*-benzoyl-di-*O*-benzylidene-D-glucose was obtained as the sole reaction product. Deacylation of the latter compound afforded a di-*O*-benzylidene-D-glucose, m.p. 163°, which was oxidized to a di-*O*-benzylidene-D-glucuronic acid, thus demonstrating that the di-*O*-benzylidene-D-glucose was unsubstituted at C_6 and that the benzoyl group in the starting material had not wandered in the process of cyclic acetal formation.[2]

In the same year Wolfrom and Tanghe[3] reported a more extensive study of the benzylidenation of 6-*O*-benzoyl-D-glucose diethyl dithioacetal. These authors were able to isolate a 6-*O*-benzoyl-di-*O*-benzylidene-D-glucose diethyl dithioacetal as an intermediate which, on further treatment with benzaldehyde and zinc chloride, afforded a non-reducing *O*-benzoyl-di-*O*-benzylidene-D-glucose melting at 160–160.5°. Debenzoylation gave a di-*O*-benzylidene-D-glucose melting at 163–165°. That Wolfrom and Tanghe's di-*O*-benzylidene-D-glucose and its benzoate were identical with the corresponding compounds prepared by Papadakis seems quite certain although the latter author unfortunately failed to report the rotations of his substances.

Recent investigations in this Laboratory have demonstrated, through experiments in the D-ribose

(1) P. Papadakis, This Journal, **59**, 841 (1937).

(2) Normally, O → O acyl migrations progress toward, rather than away from primary positions although migrations in the opposite direction under acidic and somewhat violent conditions have been observed: R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield and R. M. Goepp, Jr., This Journal, **68**, 927 (1946); R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield, R. M. Goepp, Jr., and S. Soltzberg, *ibid.*, **68**, 930 (1946).

(3) M. L. Wolfrom and L. J. Tanghe, *ibid.*, **59**, 1597 (1937).

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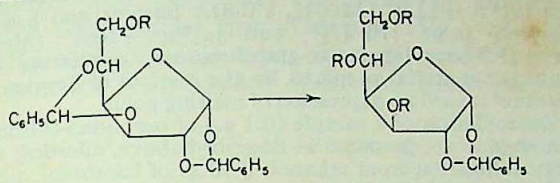
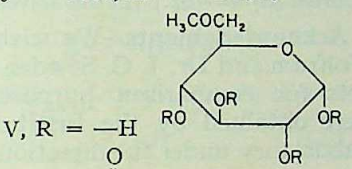
series,[4,5] that condensations of sugars with benzaldehyde in the presence of zinc chloride–acetic acid may give somewhat different results from those obtained when zinc chloride alone is the condensing



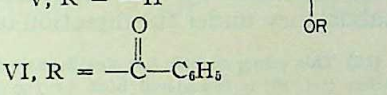
I, R = —H VII, R = —H

II, R = —CCH_3 VIII, R = —CC_6H_5

III, R = —CC_6H_5
IV, R = —CH_3



V, R = —H



VI, R = —$C—C_6H_5$

agent.[6] In the D-glucose series we have shown[7] that benzylidenation with zinc chloride alone affords, in addition to the previously known substances 4,6-*O*-benzylidene-D-glucose[8] and 1,2-*O*-benzylidene-α-D-glucofuranose,[9] 1,2:4,6-di-*O*-benzylidene-α-D-glucose. It was of interest, therefore, to examine the behavior of D-glucose with benzaldehyde in the presence of zinc chloride–acetic acid. Under the conditions employed only two crystalline products, the known 1,2-*O*-benzylidene-α-D-glucofuranose and a di-*O*-benzylidene-D-glucose, were obtained—both in relatively low yield. Comparison of our di-*O*-benzylidene-D-glucose and its benzoate with the corresponding substances kindly provided by Professor Wolfrom showed identity in both cases.

The structure of the di-*O*-benzylidene-D-glucose has now been elucidated in the following simple manner. Methylation afforded a crystalline methyl ether (IV); hydrogenolysis of the latter furnished 6-*O*-methyl-D-glucose (V) which was further characterized as its tetrabenzoate VI. Carbon six in the starting material is, therefore, unsubstituted. Partial hydrogenolysis, facilitated by use of a solvent in which a mono-*O*-benzylidenehexose is sparingly soluble,[7] led to the isolation of the known[9] 1,2-*O*-benzylidene-α-D-glucofuranose (VII). It is apparent, then, that the diacetal is 1,2:3,5-di-*O*-benzylidene-α-D-glucose (I), a furanose derivative in contrast to the isomeric di-*O*-benzylidene-D-glucopyranose reported earlier.[7]

In passing, we would like to observe that the apparent marked variability in catalytic activity of zinc chloride in benzylidenations[3] may actually be due to variations in the benzoic acid content of benzaldehyde since one would expect a zinc chloride–benzoic acid complex to resemble zinc chloride–acetic acid as a catalyst in acetal formation.

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(7) H. B. Wood, Jr., H. W. Diehl and H. G. Fletcher, Jr., This Journal, **78**, 4715 (1956).
(8) L. Zervas, *Ber.*, **64**, 2289 (1931).
(9) J. C. Sowden and D. J. Kuenne, This Journal, **74**, 686 (1952); see also B. Helferich and A. Porck, *Ann.*, **582**, 233 (1953).

Experimental[10]

1,2:3,5-Di-*O*-benzylidene-α-D-glucose (I).—A mixture of 10 g. of powdered, anhydrous D-glucose, 20 g. of freshly fused zinc chloride, 60 ml. of benzaldehyde and 7.7 ml. of glacial acetic acid was shaken at 26° for 17 hr. The light straw-colored solution was then poured with stirring into 200 ml. of ice and water. Three 100-ml. ether extractions of the resulting mixture were combined, washed with water and sodium bicarbonate solution, dried over sodium sulfate, treated with 1 g. of decolorizing carbon and filtered. The filtrate was concentrated, finally at 0.5 mm. and 60° (bath). From 20 ml. of ethanol the product crystallized and, after several days at −5°, was filtered off. The minute prisms (3.1 g., 16%) melted at 141–147° and showed $[\alpha]^{20}D$ + 34.0 in pyridine (*c* 0.85). Recrystallization, first from 25 ml. of hot ethanol using 0.5 g. of decolorizing carbon, and then from ethyl acetate, gave pure 1,2:3,5-di-*O*-benzylidene-α-D-glucose melting at 160–161° and rotating $[\alpha]^{20}D$ +34.8° (pyridine, *c* 1.07) and $[\alpha]^{20}D$ +40° ($CHCl_3$, *c* 1.0). Wolfrom and Tanghe[3] recorded m.p. 163–165° and $[\alpha]^{24}D$ + 35° (pyridine) for their non-reducing di-*O*-benzylidene-D-glucose. Mixed with a sample prepared by Wolfrom and Tanghe, our product melted at 161–164°.

Anal. Calcd. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.13; H, 5.71.

From the original mother liquor there was obtained, in addition to a small quantity of 1,2:3,5-di-*O*-benzylidene-α-D-glucose, 0.51 g. of **1,2-*O*-benzylidene-α-D-glucofuranose**, m.p. 174–175°, $[\alpha]^{20}D$ +11.5° (*c* 1, MeOH) and $[\alpha]^{20}D$ +27.9° (*c* 1.05, pyridine).

6-*O*-Acetyl-1,2:3,5-di-*O*-benzylidene-α-D-glucose (II).—One-half gram of 1,2:3,5-di-*O*-benzylidene-α-D-glucose was acetylated with acetic anhydride in pyridine in the usual fashion to yield, from ethanol, needles (0.4 g., 72%) melting at 144–145° and rotating $[\alpha]^{20}D$ +28.6° ($CHCl_3$, *c* 0.86).

Anal. Calcd. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.23; H, 5.85.

6-*O*-Benzoyl-1,2:3,5-di-*O*-benzylidene-α-D-glucose (III).—One-half gram of 1,2:3,5-di-*O*-benzylidene-α-D-glucose was benzoylated in normal fashion using benzoyl chloride in pyridine to give a crude crystalline product which, recrystallized from 35 ml. of hot absolute ethanol, weighed 0.47 g. (73%), melted at 157–158° and rotated $[\alpha]^{20}D$ +12.9° ($CHCl_3$, *c* 1.1).

Anal. Calcd. for $C_{27}H_{24}O_7$: C, 70.42; H, 5.25. Found: C, 70.60; H, 5.33.

Papadakis[1] reported m.p. 156° while Wolfrom and Tanghe[3] reported m.p. 160–160.5° and $[\alpha]^{-6}D$ +15° ($CHCl_3$) for this substance. Mixed with a sample of the product of these latter authors, our material melted at 158–161°.

1,2:3,5-Di-*O*-benzylidene-6-*O*-methyl-α-D-glucose (IV).—Two grams of 1,2:3,5-di-*O*-benzylidene-α-D-glucose was dissolved in a mixture of 20 ml. of methyl iodide and 10 ml. of dioxane. To the boiling, well-stirred solution 1-g. portions of silver oxide were added at half-hour intervals until 6 g. had been used. After a further hour of stirring and boiling, the solution was cooled, filtered and then concentrated *in vacuo*, the temperature of the material not exceeding 40° at any time. Crystallization was spontaneous: 2.06 g. The product was dissolved in ethanol, decolorized with carbon and crystallized by the addition of pentane. A second recrystallization from cold ether afforded pure material (1.2 g., 58%) melting at 98–100° and rotating $[\alpha]^{20}D$ +25.2° in chloroform (*c* 1).

Anal. Calcd. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 67.81; H, 5.93.

6-*O*-Methyl-α-D-glucose (V).—One gram of 1,2:3,5-di-*O*-benzylidene-6-*O*-methyl-α-D-glucose (IV) was hydrogenolyzed in the customary fashion using 0.5 g. of palladium black suspended in 25 ml. of absolute ethanol. After removal of the catalyst and the solvent the product crystallized: 0.45 g. (86%), m.p. 137–144°. Two recrystallizations from hot absolute ethanol gave pure material (0.22 g.) which was chromatographically homogeneous: m.p. 142–143°, $[\alpha]^{20}D$ +99° (2 min.) → +56° (19 hr., equil.)

(10) Melting points are corrected.

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(c 0.94, water). For 6-*O*-methyl-α-D-glucose Bell[11] reported m.p. 145° and $[\alpha]^{16}D$ +110° → 55° (H_2O). Addition of 90 mg. of this material to a mixture of benzoyl chloride and pyridine which previously had been cooled to 0° led, after the usual manipulations, to the isolation, from ethanol–pentane, of 220 mg. of crystalline material. Recrystallization from hot pentane afforded, with little loss, a product melting at 157–159° and rotating $[\alpha]^{20}D$ +126.5° (c 1.1, $CHCl_3$).

Anal. Calcd. for $C_{35}H_{30}O_{10}$: C, 68.84; H, 4.95. Found: C, 68.81; H, 4.81.

Ohle and Tessmar[12] recorded m.p. 154° and $[\alpha]D$ +120.6° ($CHCl_3$) for 1,2,3,4-tetra-*O*-benzoyl-6-*O*-methyl-α-D-glucose (VI).

1,2-*O*-Benzylidene-α-D-glucofuranose (VII) from 1,2:3,5-Di-*O*-benzylidene-α-D-glucose (I).—A sample (0.5 g.) of palladium black catalyst was suspended in 50 ml. of ethyl acetate and saturated with hydrogen at room temperature and a pressure very slightly in excess of atmospheric. The ethyl acetate was then decanted and a solution of 2.0 g. of 1,2:3,5-di-*O*-benzylidene-α-D-glucose in 30 ml. of warm ethyl acetate added. The reduction was carried out in normal fashion and halted after 17 hr. when approximately two molar equivalents of hydrogen had been consumed. The product, which had precipitated in the course of the reaction, was removed with the catalyst and then extracted from the latter with 10 ml. of hot dioxane. Concentration of the dioxane solution gave a crystalline mass which was washed with a little water (to remove D-glucose) and dried: 0.65 g. (43%), m.p. 172–174°. Recrystallized successively from methyl ethyl ketone and from hot ethyl acetate (carbon treatment) the cyclic acetal (0.3 g.) was obtained as needles, m.p. 176–177°, $[\alpha]^{20}D$ +27.9° ($CHCl_3$, c 1) and $[\alpha]^{20}D$ +11.9° (MeOH, c 0.8). Sowden and Kuenne[9] reported m.p. 176–177° and $[\alpha]^{20}D$ +10.5° (MeOH) for 1,2-*O*-benzylidene-α-D-glucofuranose; admixture with authentic material prepared by the method of Sowden and Kuenne[9] caused no depression of melting point.

Benzoylation of a sample (0.1 g.) of our mono-*O*-benzylidene-D-glucose, prepared as described above, afforded, after recrystallization from ethanol, 0.13 g. of handsome needles melting at 112–114° either alone or in admixture with a sample of 3,5,6-tri-*O*-benzoyl-1,2-*O*-benzylidene-α-D-glucose (VIII) kindly provided by Dr. Sowden.[13] In chloroform (c 1) we found a rotation of −62.7°; the earlier authors reported $[\alpha]^{25}D$ −62.7° in this solvent.

Acknowledgments.—We wish to thank Dr. M. L. Wolfrom and Dr. J. C. Sowden for samples of products for comparison purposes. Analytical data were obtained by the Institutes' Microanalytical Laboratory under the direction of Dr. W. C. Alford.

(11) D. J. Bell, *J. Chem. Soc.*, 859 (1936).

(12) H. Ohle and K. Tessmar, *Ber.*, **71**, 1843 (1929).

(13) This value, slightly but significantly higher than that reported earlier (ref. 9), is considered both by the present authors and Dr. Sowden as the preferred figure for the melting point of 3,5,6-tri-*O*-benzoyl-1,2-*O*-benzylidene-α-D-glucofuranose.

BETHESDA 14, MD.

[CONTRIBUTION FROM NATIONAL BUREAU OF STANDARDS, DIVISION OF CHEMISTRY]

Structure of 5-Aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose[1]

BY ROBERT SCHAFFER AND HORACE S. ISBELL

RECEIVED MARCH 6, 1957

Crystalline dimeric 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose was shown to be bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-cyclic acetal. The following crystalline derivatives were prepared: 5′-*O*-acetyl-[bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-cyclic acetal], 3,5′-di-*O*-acetyl-[bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-cyclic acetal] and 5′-*O*-acetyl-3-*O*-mesyl-[bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-cyclic acetal]. The parent compound and the derivatives have an acetal structure at carbon 5 and a hemiacetal structure at carbon 5′. Both carbon 5 and carbon 5′ are asymmetric and four modifications of each substance are possible. The diacetate differs from the somewhat analogous diacetyl derivatives of Späth and co-workers in that it does not undergo hydrogenolysis with elimination of the hemiacetal acetate group. The two acetyl groups, however, differ in stability, in agreement with the two types of acetyl groups shown in the assigned structure.

Crystalline 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose was prepared in this Laboratory as a raw material for the synthesis of D-glucose-6-C^{14}.[2] The substance was crystallized in the form of a hydrate from water and in the anhydrous form from benzene. The anhydrous product appears to be the same as a crystalline substance reported by Brocca and Dansi,[3] who concluded that the substance was a monomer. Molecular weight determinations reported by the present authors showed that both the hydrate and the anhydrous compound are dimers.[2] The importance of the 5-aldo-derivative for synthetic purposes and the existence of unusual chemical properties to be reported later led us to undertake a more detailed study of its structure.

By acetylation with acetic anhydride and pyridine at low temperature, Brocca and Dansi obtained from their product an amorphous material that was assumed to be 3-*O*-acetyl-5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose. In the present study a crystalline acetate was obtained by the same method. The molecular weight and analysis of this product show that it is a dimer having two acetyl groups.

The monomeric form of 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose (I) would have a free aldehyde group. The infrared spectrum[4] of the crystalline substance, however, showed no absorption corresponding to a free aldehyde group. Hence the aldehyde group must be masked, presumably by formation of a dimer. Structures IIa and IIIa fulfill the requirements that the aldehyde groups be masked and that two hydroxyls be available for acetylation.

The 8-membered ring structure IIa is like one

(1) This work was conducted as part of a project on the development of methods for the synthesis of radioactive carbohydrates, sponsored by the Division of Research of the Atomic Energy Commission.

(2) R. Schaffer and H. S. Isbell, *J. Research Natl. Bur. Standards*, **56**, 191 (1956).

(3) V. Brocca and A. Dansi, *Ann. chim.* (*Rome*), **44**, 120 (1954).

(4) H. S. Isbell, R. Schaffer and J. Stewart, unpublished work.

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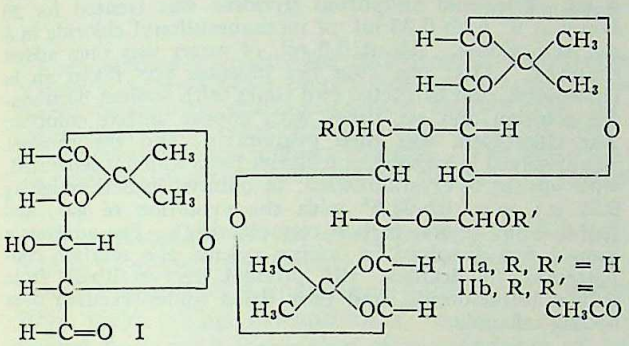
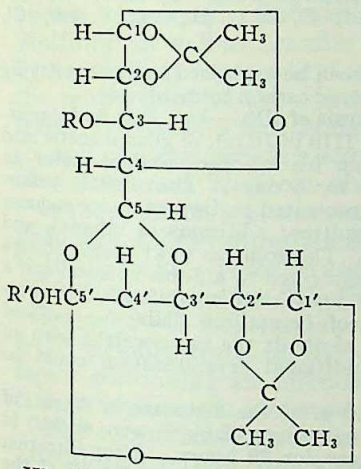
proposed by Bergmann and co-workers[5,6] for certain dimers of β-hydroxy-aldehydes. Subsequent work by Späth and co-workers,[7-9] however, established that β-hydroxy-aldehydes in general have the 6-membered ring structure IVa. Structure IIIa is of the same type, but is more restricted on account of the presence of several fused rings.

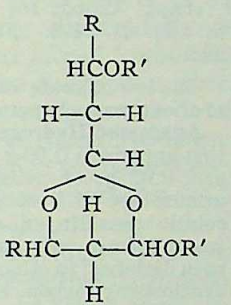


I

IIa, R, R′ = H
IIb, R, R′ = CH_3CO



IIIa, R,R′ = H
IIIb, R,R′ = CH_3CO
IIIc, R = H; R′ = CH_3CO
IIId, R = Ms; R′ = CH_3CO



IVa, R = alkyl; R′ = H
IVb, R = alkyl; R′ = CH_3CO

Späth and co-workers established structure IVa for the dimeric β-hydroxy-aldehydes by showing that the diacetyl derivatives IVb undergo hydrogenolysis with elimination of the hemiacetal acetate group to give the corresponding 1,3-dioxane derivatives in which hydrogen has been substituted for OR′ at carbon 4 of the ring.

Application of the hydrogenolysis procedure in the present case was not successful with either palladium black catalyst[10] in acetic acid or "S-palladium black."[11] It seems possible that the furanose ring fused to the 1,3-dioxane ring in IIIb, a structural feature not present in the acetylated 4-hydroxy-1,3-dioxane derivatives that undergo hydrogenolysis, constitutes a sufficient structural alteration to preclude hydrogenolysis under the conditions used.

(5) M. Bergmann, M. Miekeley and E. von Lippmann, *Ber.*, **62**, 1467 (1929).
(6) M. Bergmann and M. Miekeley, *ibid.*, **62**, 2297 (1929).
(7) E. Späth and H. Schmid, *ibid.*, **74**, 859 (1941).
(8) E. Späth, R. Lorenz and E. Freund, *ibid.*, **76**, 57, 1196 (1943); **77**, 354 (1944).
(9) E. Späth and I. v. Szilágyi, *ibid.*, **76**, 949 (1943).
(10) J. Tausz and N. von Putnoky, *ibid.*, **52**, 1573 (1919).
(11) V. K. Kindler, E. Schärfe and P. Henrich, *Ann.*, **565**, 51 (1949).

Since the structure could not be determined by hydrogenolysis, attention was directed to other methods. Substance IIa has two hemiacetal hydroxyls and no alcoholic hydroxyl, but IIIa has one hemiacetal hydroxyl and one alcoholic hydroxyl. Aside from differences that might arise from the conformation of the 8-membered ring, the two hemiacetal hydroxyls of IIa are alike, and one would not expect the two groups to react at widely different rates, or the corresponding acetyl groups to have widely different properties.

To ascertain whether there was a difference in the reaction rates for the two hydroxyls, a sample of dimeric 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose was acetylated for a short reaction time, and a crystalline product was isolated. The analysis and molecular weight showed that the compound is a dimer substituted with one acetyl group. Its infrared spectrum showed no aldehydic carbonyl absorption[4] and it did not react with phenylhydrazine. Hence all aldehyde groups must be blocked. With methanesulfonyl chloride the monoacetate gave a crystalline mesyl derivative. The analysis showed that the material corresponds to a dimer with one mesyl and one acetyl group. Its infrared spectrum showed no carbonyl absorption.[4] The method of preparation and the stability of the mesyl group in aqueous and alcoholic solution lead to the assignment of the mesyl group to a carbon in the alcoholic state of oxidation rather than in the hemiacetal state. This requires that the substance be IIId and the parent monoacetate be IIIc. The diacetate would then be IIIb.

To confirm the structure of the diacetate, the rate of hydrolysis of the acetyl groups was studied. The results given in the semi-log plot of Fig. 1

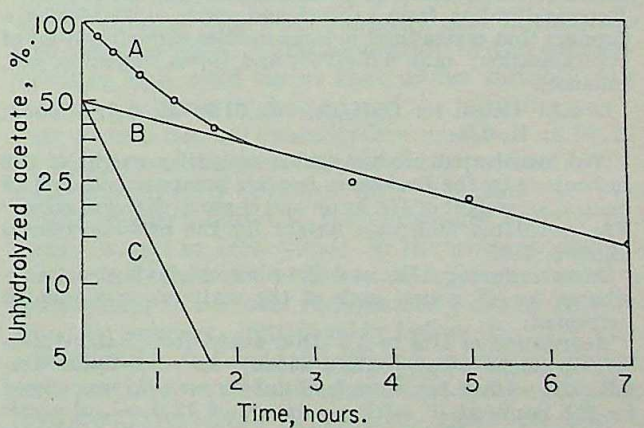


Fig. 1.—Hydrolysis of IIIb in 0.05 *N* hydrochloric acid at 80°: A, experimental curve; B, extrapolated curve for less reactive acetyl group; C, calculated curve for more reactive acetyl group.

clearly show the presence of two types of acetyl groups. The graphical analysis of the data shows that the half-time for the hydrolysis of one acetyl group is 7 or 8 times that for the other. This difference in stability is consistent with structure IIIb but is not in accord with structure IIb. Thus IIa is clearly eliminated as a possibility, and IIIa can be considered the structure of the anhydrous dimer.

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Official nomenclature rules[12] are inadequate for naming the compounds but for the present the following names are suggested: IIIa is bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-cyclic acetal, IIIb is 3,5′-di-*O*-acetyl-[bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-cyclic acetal], IIIc is 5′-*O*-acetyl-[bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-cyclic acetal] and IIId is 5′-*O*-acetyl-3-*O*-mesyl-[bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-cyclic acetal].

Different configurations for carbons 5 and 5′ would give rise to four isomers. Consideration of the configuration of the present compound and the conformation of the cyclic acetal ring will be deferred for inclusion in a study of the infrared spectra now in progress.[4]

Experimental

Bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-Cyclic Acetal (IIIa).—This substance, previously called 1,2-*O*-isopropylidene-D-*xylo*-dialdo-pentofuranose, was obtained by oxidation of 1,2-*O*-isopropylidene-D-glucofuranose with sodium metaperiodate, and crystallization of the product by the method described previously.[2] The hydrate (crystallized first) was converted to the anhydrous form by crystallization from benzene.

Acetylation of IIIa to 5′-*O*-Acetyl-[bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-Cyclic Acetal] (IIIc).—One gram of finely powdered anhydrous IIIa was stirred vigorously at 0° with a mixture consisting of 5 ml. of acetic anhydride and 7 ml. of pyridine. After 8 to 10 minutes the reaction mixture was poured into 200 ml. of cracked ice. The product was extracted with chloroform. Then the chloroform solution was extracted twice with aqueous sodium bicarbonate and six times with copper sulfate solution. Finally the chloroform was evaporated, and subsequently the product was crystallized from carbon tetrachloride. The crystals, fine elongated prisms, weighed 0.54 g. and contained approximately 1.5 moles of carbon tetrachloride per mole of the product. They melted at 96–98°, solidified at 102°, and melted again at 175–176°. Recrystallization from ethanol and water (1:2) yielded a product that crystallized in large needles without solvent of crystallization; m.p. 175–176°, and $[\alpha]^{25}D$ +37.8° (*c* 0.7, ethanol).

Anal. Calcd. for $C_{18}H_{26}O_{11}$: C, 51.7; H, 6.3. Found: C, 51.3; H, 6.5.

The unsolvated product had a molecular weight of 393 in benzene by the Beckmann freezing point method, and an equivalent weight of 418 by an acetyl-group determination.[13] The calculated molecular weight for the mono-acetylated dimer is 418.

After refluxing IIIc and 2,4-dinitrophenylhydrazine in ethanol for 17 hours, each of the materials was isolated unreacted.

Acetylation of IIIa to 3,5′-Di-*O*-acetyl-[bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-Cyclic Acetal] (IIIb).—A 2.5-g. sample of anhydrous IIIa was stirred for 2.5 hours at 0° with a mixture of 12.5 ml. of acetic anhydride and 17 ml. of pyridine. The reaction mixture was poured into ice-water and extracted as described above. The chloroform was evaporated, and the residue was crystallized from ethanol. The crystals weighed 3 g. They contained 0.5 mole of ethanol per mole of dimer, and melted at 113.5–115° with the evolution of gas; $[\alpha]^{20}D$ +44.2° (*c* 2, ethanol).

Anal. Calcd. for $C_{26}H_{38}O_{12}\cdot{}^1/_2C_2H_5OH$: C, 52.1; H, 6.4. Found: C, 51.7; H, 6.4.

The molecular weight in benzene by the Beckmann freezing point method was 321. For the diacetylated dimer with one-half mole of ethanol of solvation the calculated value is 322. The equivalent weight by acetyl analysis was 251, and the calculated value is 242.

The product crystallized from carbon tetrachloride with approximately 0.5 mole of solvent per mole of dimer; m.p. 122–125°.

The unreacted diacetate was recovered unchanged after refluxing 18 hours with phenylhydrazine and with 2,4-dinitrophenylhydrazine.

Mesylation of IIIc to 5′-*O*-Acetyl-3-*O*-mesyl-[bis-(5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose) 5,5′:3′,5-Cyclic Acetal] (IIId).—A solution of 0.209 g. of IIIc and 5 ml. of ice-cold anhydrous pyridine was treated for 20 hours at 0° with 0.35 ml. of methanesulfonyl chloride in 5 ml. of pyridine. About 0.5 ml. of water was then added dropwise. After one hour the mixture was taken up in chloroform, and extracted two times with sodium bicarbonate solution and six times with copper sulfate solution. The chloroform was then evaporated, and the product was dissolved in carbon tetrachloride from which it separated, with solvent of crystallization, in pointed leaflets weighing 0.27 g.; m.p. 92–93.5° with the evolution of gas, and $[\alpha]^{20}D$ +35° (*c* 0.4, carbon tetrachloride). For analysis a sample was dissolved in boiling xylene, the solution concentrated to dryness, the product recrystallized from carbon tetrachloride, and then dried under vacuum over boiling ethanol.

Anal. Calcd. for $C_{19}H_{28}O_{13}S\cdot CCl_4$: C, 36.9; H, 4.3; S, 4.9; Cl, 21.8. Found: C, 37.1; H, 4.4; S, 4.9; Cl, 20.2.

The low chloride value can be explained by loss on drying of about ten mole per cent. of carbon tetrachloride.

Attempted Hydrogenolysis of IIIb.—In a Parr hydrogenation apparatus 0.59 g. of IIIb in 10 ml. of glacial acetic acid and 0.62 g. of palladium black[10] were shaken under an atmosphere of hydrogen for 5 days. The slightly yellow solution was filtered, concentrated to dryness under vacuum several times with intermittent additions of ethanol, and then dissolved in ethanol. This solution was filtered through decolorizing carbon, concentrated to a 2-ml. volume, and a few drops of water and some seed crystals of IIIb were added. About 0.27 g. of crystalline IIIb was isolated leaving a sirupy residue of about the same weight with an $[\alpha]^{20}D$ of +30°. No additional crystallization could be induced.

In another attempt 1.0 g. of the diacetate in 60 ml. of ethanol, and 1 g. of "S-palladium black"[11] were shaken in an atmosphere of hydrogen for 20 hours. After filtration and concentration of the solution, substantially all of the diacetate was recovered unchanged. Glacial acetic acid also was employed as solvent with the "S-palladium black" catalyst, but with the same result.

Acid Hydrolysis of the Diacetate IIIb.—Aliquots of 2 ml. of a stock solution of 0.497 g. of IIIb in 25 ml. of peroxide-free distilled dioxane were transferred to each of several test-tubes. The tubes were placed in a bath at 80 ± 1°, and 2-ml. portions of aqueous 0.1 *N* hydrochloric acid (previously heated to 80°) were added. The tubes were then fitted with reflux condensers. A series of blank samples were set up similarly using 2-ml. aliquots of a solution of 0.388 g. of IIIa in 25 ml. of dioxane and of the aqueous hydrochloric acid. Periodically a sample, or a blank, was removed, cooled in ice-water, and titrated to the phenolphthalein end-point with standard sodium hydroxide. In the blank runs acid formation in excess of the hydrochloric acid initially introduced increased uniformly with time, and amounted after three hours to about the equivalent of one-twentieth of the total hydrolyzable acetate, and to about one-tenth after seven hours. This correction served to reduce the net titers for the liberated acetyl groups at those times by only 3 and 6%, respectively. The results of the experiment are given in Fig. 1, where the curve representing the unsaponified acetate plotted against time was graphically analyzed into two linear curves showing the rates of hydrolysis for the two acetyl groups. The half-time for the rapidly split acetyl group is approximately 0.5 hour and for the slower approximate 3.5 to 4 hours.

The authors express their appreciation to R. A. Paulson and L. Tregoning of the Bureau for the microanalyses.

WASHINGTON 25, D. C.

(12) *Chem. Eng. News*, **31**, 1776 (1953).

(13) D. H. Brauns, THIS JOURNAL, **47**, 1294 (1925).

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[CONTRIBUTION FROM NATIONAL BUREAU OF STANDARDS, DIVISION OF CHEMISTRY]

Reaction of Dimeric 5-Aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose with Cyanide and the Preparation of Calcium 1,2-*O*-Isopropylidene-L-idofururonate-6-C^{14} Dihydrate[1]

BY ROBERT SCHAFFER AND HORACE S. ISBELL

RECEIVED MARCH 6, 1957

A new method is reported for the separation of 1,2-*O*-isopropylidene-L-idofururonic-6-C^{14} acid from the reaction product of dimeric 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose and C^{14}-labeled cyanide. After separation of barium 1,2-*O*-isopropylidene-D-glucofururonate-6-C^{14} hydrate from the reaction mixture, crystalline calcium 1,2-*O*-isopropylidene-L-idofururonate-6-C^{14} dihydrate was obtained in 27% yield. The combined radiochemical yield of the L-iduronic-6-C^{14} and D-glucuronic-6-C^{14} acid epimers was 85%. The high yield shows that under the conditions used the dimeric 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose is cleaved, and the resulting monomer gives a normal cyanohydrin reaction.

By application of the cyanohydrin synthesis to 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose, Sowden[2] obtained D-glucuronic-6-C^{14} acid in about 20% yield. The cyanohydrin reaction mixture turned dark with formation of by-products of unknown character. Subsequently Shafizadeh and Wolfrom[3] as well as Schaffer and Isbell[4] found that by controlling the acidity of the reaction mixture the proportions of the epimeric acids could be altered.[5] By use of a bicarbonate–carbon dioxide buffer and chromatographic separation of the lactones, Shafizadeh and Wolfrom obtained crystalline 1,2-*O*-isopropylidene-D-glucurono-γ-lactone in 15.5% yield and 1,2-*O*-isopropylidene-L-idurono-γ-lactone in 16.1% yield. From an acetate-buffered cyanohydrin reaction mixture Schaffer and Isbell separated barium 1,2-*O*-isopropylidene-D-glucufururonate-6-C^{14} monohydrate in 54% yield and a mother liquor containing an unknown amount of the 1,2-*O*-isopropylidene-L-idofururonic-6-C^{14} epimer.

The continued interest in this synthesis in this Laboratory derives from a program for the development of methods for the preparation of position-labeled radioactive carbohydrates,[6] and from interest in the structure and properties of the crystalline dimer of 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose.

In the present study a crystalline salt of 1,2-*O*-isopropylidene-L-idofururonic acid was sought because this would provide not only a simple means for purifying this acid-sensitive material but would also provide a means for its quantitative determination by use of the isotope dilution technique.

It was shown previously,[4] by isotope dilution analysis, that the D-glucuronate epimer was produced in 58% yield by the cyanohydrin reaction with an acetate buffer and in 38% yield with a bisulfite buffer. In view of these results it seemed probable that with the bisulfite buffer a larger proportion of the product went to the L-iduronate epimer. For this reason a reaction product obtained from a cyanohydrin reaction buffered with sodium bisulfite was used in a search for a crystalline salt of the 1,2-*O*-isopropylidene-L-idofururonic acid. After removal of barium 1,2-*O*-isopropylidene-D-glucofururonate from the reaction mixture, crystalline calcium 1,2-*O*-isopropylidene-L-idofururonate dihydrate was prepared. The new salt crystallizes readily and provides a convenient means for separation of the iduronate epimer in a pure state. In order to utilize the salt for separation of the radioactive L-iduronate from the mother liquor of the preparation of barium 1,2-*O*-isopropylidene-D-glucofururonate-6-C^{14} hydrate it was necessary first to remove the barium acetate (by decationizing and freeze-drying), and the residual barium 1,2-*O*-isopropylidene-D-glucofururonate-6-C^{14} hydrate (by crystallization). Barium in the purified mother liquor was replaced by calcium, and calcium 1,2-*O*-isopropylidene-L-idofururonate-6-C^{14} dihydrate was separated in a radiochemical yield of 27%.[7] The combined yield of the D-glucuronate and L-iduronate epimers was 85%. The separation of the epimeric acids in high yield shows that under suitable conditions the dimer is cleaved and the resulting monomer gives a normal cyanohydrin reaction.

By isotope dilution analysis of the product from a bisulfite-buffered cyanohydrin reaction it was found earlier[4] that the D-glucuronate epimer had been formed in 38% yield; in the present study it was found that the L-iduronate epimer formed in 34% yield. The total radioactive yield of 72% for the two epimers, considerably below the 85% yield obtained in the acetate-buffered reaction, shows a substantial loss of labeled cyanide in the bisulfite-buffered reaction. A greater yield of the L-iduronate epimer (at the expense of the D-glucuronate) can be expected for more alkaline buffered systems, but the limit of alkalinity for an optimum yield of L-iduronate is restricted by the alkali-sensitivity of the 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose. The behavior of this substance in alkaline solution is being studied and will be treated in a future publication.

Experimental Procedure

Calcium 1,2-*O*-Isopropylidene-L-idofururonate Dihydrate.—An aqueous solution of 12.54 g. of 5-aldo-1,2-*O*-isopropyli-

(1) This work was conducted as part of a project sponsored by the Division of Research of the Atomic Energy Commission.

(2) J. C. Sowden, THIS JOURNAL, **74**, 4377 (1952).

(3) F. Shafizadeh and M. L. Wolfrom, *ibid.*, **77**, 2568 (1955).

(4) R. Schaffer and H. S. Isbell, *J. Research Natl. Bur. Standards*, **56**, 191 (1956).

(5) H. S. Isbell, U. S. Patent 2,606,918 (1952).

(6) H. S. Isbell, J. V. Karabinos, H. L. Frush, N. B. Holt, A. Schwebel and T. T. Galkowski, *J. Research Natl. Bur. Standards*, **48**, 163 (1952); H. S. Isbell and J. V. Karabinos, *ibid.*, **48**, 438 (1952); H. L. Frush and H. S. Isbell, *ibid.*, **50**, 133 (1953); **51**, 167 (1953); **51**, 307 (1953); H. S. Isbell, H. L. Frush and N. B. Holt, *ibid.*, **53**, 217 (1954); **53**, 325 (1954); H. S. Isbell, H. L. Frush and R. Schaffer, *ibid.*, **54**, 201 (1955); H. S. Isbell, N. B. Holt and H. L. Frush, *ibid.*, **57**, 95 (1956); H. S. Isbell and R. Schaffer, THIS JOURNAL, **78**, 2858 (1956).

(7) Since the preparation of the labeled epimeric cyanohydrins was made two years prior to the isolation of the L-iduronate-6-C^{14}, a yield greater than 27% may have been produced originally.

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dene-D-*xylo*-pentofuranose, 12.65 g. of sodium pyrosulfite and 3.4 g. of sodium cyanide was prepared at 0°, and allowed to warm to room temperature. After three days the solution was heated at 90° for one hour, then treated with 7 g. of sodium carbonate, and refluxed for three hours. The solution was cooled in an ice-bath, and passed through a column containing 350 ml. of cation exchange resin[8] at ice temperature. The effluent, including washings, was delivered into a flask immersed in an ice-bath, containing 41.6 g. of barium hydroxide octahydrate. After removal of excess barium hydroxide by carbonation and filtration, one-tenth of the filtrate was set aside for analysis by an isotope dilution technique. The remainder of the solution was concentrated under vacuum to a sirup that yielded 7.77 g. of crude crystalline barium 1,2-*O*-isopropylidene-D-glucofururonate monohydrate. After removal of the barium salt, the mother liquor was passed through a column containing 75 ml. of cation exchange resin[8] at ice temperature. The effluent, including washings, was delivered into a flask containing 5 g. of calcium carbonate. The mixture was filtered, and the filtrate concentrated under vacuum. Calcium 1,2-*O*-isopropylidene-L-idofururonate-6-C^{14} dihydrate separated. The product, 4.2 g., was recrystallized from water with the addition of methanol.

Anal. Calcd. for Ca $C_{18}H_{26}O_{14}\cdot 2H_2O$: C, 39.8; H, 5.6; Ca, 7.4. Found: C, 39.8; H, 5.8; Ca, 7.2; $[\alpha]_D^{29}$ −11.8° (*c* 3, water).

Preparation of Calcium 1,2-*O*-Isopropylidene-L-idofururonate-6-C^{14} Dihydrate.—The original synthesis began with 0.005 mole of sodium cyanide-C^{14} (12.5 millicuries) and 1.11 g. of 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose buffered with 0.005 mole of sodium hydroxide and 0.02 mole of acetic acid. The mother liquor that remained after separation of 6.75 millicuries of barium 1,2-*O*-isopropylidene-D-glucofururonate-6-C^{14} monohydrate from the cyanohydrin synthesis previously reported had been set aside for approximately two years before the work reported here was resumed.

The mother liquor was dissolved in 100 ml. of water, treated with 700 ml. of ethanol, and passed through a carbon-coated filter. Under vacuum the filtrate was concentrated to a 50-ml. volume. The concentrate was passed, ice-cold, into a column containing 30 ml. of cation exchange resin,[8] washed through with ice-water, and collected in a flask containing 0.3 g. of barium carbonate. The partially neutralized effluent was freeze-dried to remove the acetic acid present. Addition of methanol to an aqueous solution of the residue yielded 0.18 g. of crude barium 1,2-*O*-isopropylidene-D-glucuronate-6-C^{14} monohydrate.

The purified mother liquor was diluted with ice-water and passed through a column of 12 ml. of ice-cold cation exchange resin[8] into a flask containing 0.13 g. of calcium carbonate. Concentration of the solution under vacuum yielded calcium 1,2-*O*-isopropylidene-L-idofururonate-6-C^{14} dihydrate, which was separated and washed with a mixture of ethanol and water (6:1). Recrystallization from water and ethanol yielded 2.81 millicuries of the salt. By use of non-radioactive carrier, an additional 0.53 millicurie of this product was obtained. The radiochemical yield based on the 12.5 millicuries of cyanide-C^{14} originally used was 27%.

Yield of the L-Iduronate Epimer in a Bisulfite-buffered Cyanohydrin Reaction.—The portion of the solution from the preparation of non-radioactive calcium 1,2-*O*-isopropylidene-L-idofururonate dihydrate kept for the isotope dilution analysis was diluted with a tracer consisting of 95.2 microcuries of calcium 1,2-*O*-isopropylidene-L-idofururonate-6-C^{14} dihydrate (10.68 mg.). After separation of the D-glucuronate epimer as the barium salt, the solution was passed through 15 ml. of cation exchange resin[8] into a flask containing 0.75 g. of calcium carbonate. The excess calcium carbonate was removed, and the calcium salt was crystallized as already described. After two recrystallizations, the air-dried salt had a specific radioactivity of 0.151 μc./mg. This activity corresponds to dilution of the tracer by 620 mg. of calcium 1,2-*O*-isopropylidene-L-idofururonate dihydrate or a 34.3% yield of this substance from the cyanohydrin reaction.

Radioactivity Measurements.—Determinations of C^{14} were made by direct count of the materials in formamide or aqueous formamide solutions.[9] Samples were counted to a probable error of 1%, and the results converted to microcuries by a factor based on the C^{14}-standard issued by the National Bureau of Standards.

The authors express their appreciation to R. A. Paulson and L. Tregoning for the microanalyses.

(8) Amberlite IR-120 H, Resinous Products Division of Rohm and Haas Co., Philadelphia, Pa.

(9) A. Schwebel, H. S. Isbell and J. D. Moyer, *J. Research Natl. Bur. Standards*, **53**, 221 (1954).

WASHINGTON 25, D. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Acyl Migration in the D-Galactose Structure

BY M. L. WOLFROM, A. THOMPSON[1] AND M. INATOME[1]

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When 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-galactose is treated successively with titanium tetrachloride and mercuric acetate, there are obtained two crystalline tetraacetates of D-galactose. The one (isomer A) is convertible to the other (isomer B) by traces of alkali. Both are convertible to β-D-galactopyranose pentaacetate on mild acetylation. Isomers A and B are resistant toward triphenylmethylation. Isomer A yields a *p*-toluenesulfonate which in turn forms a methyl tri-*O*-acetyl-*O*-*p*-toluenesulfonyl-β-D-galactopyranoside, both of which derivatives are different from known isomers believed to have the *p*-toluenesulfonyl group in the sixth position. Both isomers A and B yield tetra-*O*-acetyl-3-*O*-methyl-β-D-galactopyranose on methylation. Positions 2, 3 or 4 are assignable for the open hydroxyl group in each of the two D-galactopyranose tetraacetates, but the present evidence disallows definite allocations.

No tetraacetate of D-galactose is known in which the terminal primary hydroxyl group is unsubstituted. An attempt to prepare such a derivative by a procedure suitable for the synthesis of the analogous D-glucose structure, led to a crystalline D-galactose tetraacetate, m.p. 138–138.5°, $[\alpha]_D$ +37° (chloroform), herein designated isomer A.[2] This substance was considered to have its position six substituted by an acetate group since it was recovered unchanged on treatment with triphenylmethyl chloride and pyridine.[2] Isomer A had been prepared[2] by the successive action of titanium tetrachloride and mercuric acetate on 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-galactopyranose. A second isomer has now been isolated, by chromatographic techniques, from the same reaction mixture. The substance, m.p. 140–141.5°, $[\alpha]_D$ +25.5° (chloroform), designated isomer B, possesses essentially the same melting point as isomer A but the mixed

(1) Research Associate (A. T.) and Fellow (M. I.) of the Corn Industries Research Foundation.

(2) A. Thompson, M. L. Wolfrom and M. Inatome, THIS JOURNAL, **77**, 3160 (1955).

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melting point exhibits a marked depression; rotations and crystal X-ray powder diffraction data are different.

Isomer A is convertible to isomer B by traces of alkali, statements to the contrary[2] being in error. Mild acetylation of both isomers yielded β-D-galactopyranose pentaacetate. Methylation of either resulted in a crystalline monomethyl ether without acetyl loss, and this on deacetylation afforded 3-*O*-methyl-α-D-galactose[3] of established structure. Esterification of isomer B with *p*-toluenesulfonic acid failed to yield a crystalline product but like treatment of isomer A did. This tetra-*O*-acetyl-*O*-*p*-toluenesulfonyl-β-D-galactopyranose was converted to methyl tri-*O*-acetyl-*O*-*p*-toluenesulfonyl-β-D-galactopyranoside through its glycosyl bromide derivative.

While the complete structures of the isomeric D-galactose tetraacetates A and B cannot be established on the basis of the present evidence, some data may be advanced as to their partial structures. Their rotatory powers, method of synthesis and ease of conversion to β-D-galactopyranose pentaacetate would indicate that both contain the pyranose ring and possess an acetate group on carbon one in the β-D-anomeric form. Acyl migrations are catalyzed by both acids and bases and the direction of acyl movement is considered to favor a shift from a secondary to a primary hydroxyl group.[4,5]

Both isomers were resistant to etherification with triphenylmethyl chloride. It is accordingly probable that carbon six is acetylated in both tetraacetates. This conclusion is supported by the nature of the *p*-toluenesulfonate derivative of isomer A. This substance did not react with sodium iodide in acetonylacetone as a primary *p*-toluenesulfonate should, and it was not identical with either of the two known forms of tetra-*O*-acetyl-6-*O*-*p*-toluenesulfonyl-β-D-galactose recorded by Ohle and Thiel[6] (Table I). These workers acetylated the two anomeric forms of D-galactopyranose 6-*p*-toluenesulfonate, prepared in turn from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. There is no established case of *p*-toluenesulfonyl migration, and it is believed that this group, possessing no function quite analogous to a carbonyl, does not migrate. In the case of the β-D-anomer, Ohle and Thiel obtained two products which they considered to be ring isomers. If the *p*-toluenesulfonate group in our isomer A was on position 6, it should have been identical with one of the two ring forms of the β-D-derivatives of Ohle and Thiel. Since this is not the case, position 6 must be occupied by an acetyl group in the *p*-toluenesulfonate ester of isomer A. This conclusion is supported by the fact that the methyl β-D-glycoside of the *p*-toluenesulfonate is not identical with the recorded anomeric forms of methyl tri-*O*-acetyl-6-*O*-*p*-toluenesulfonyl-D-galactopyranoside (Table II).

TABLE I

ISOMERIC FORMS OF TETRA-*O*-ACETYL-*O*-*p*-TOLUENESULFONYL-D-GALACTOSE

Tetra-*O*-acetyl-	M.p., °C.	$[\alpha]^{20\pm5}D$, $CHCl_3$, $c < 5$	Reference
O-*p*-Toluenesulfonyl-β-D-galactopyranose (from isomer A)	154–155	+43°	This work
6-*O*-*p*-Toluenesulfonyl-α-D-galactose	117	+89	6
6-*O*-*p*-Toluenesulfonyl-β-D-galactose, ring isomer 1	126–127	+ 9.3	6
6-*O*-*p*-Toluenesulfonyl-β-D-galactose, ring isomer 2	147	+16	6

TABLE II

ISOMERIC FORMS OF METHYL TRI-*O*-ACETYL-*O*-*p*-TOLUENESULFONYL-D-GALACTOPYRANOSIDE

Methyl tri-*O*-acetyl-	M.p., °C.	$[\alpha]^{20\pm5}D$, $CHCl_3$, $c < 5$	Reference
O-*p*-Toluenesulfonyl-β-D-galactopyranoside (from isomer A)	129–130	+25°	This work
6-*O*-*p*-Toluenesulfonyl-β-D-galactopyranoside	Sirup	*ca.* +2.5	7
	Sirup	−3	8
6-*O*-*p*-Toluenesulfonyl-α-D-galactopyranoside	128	+102	6

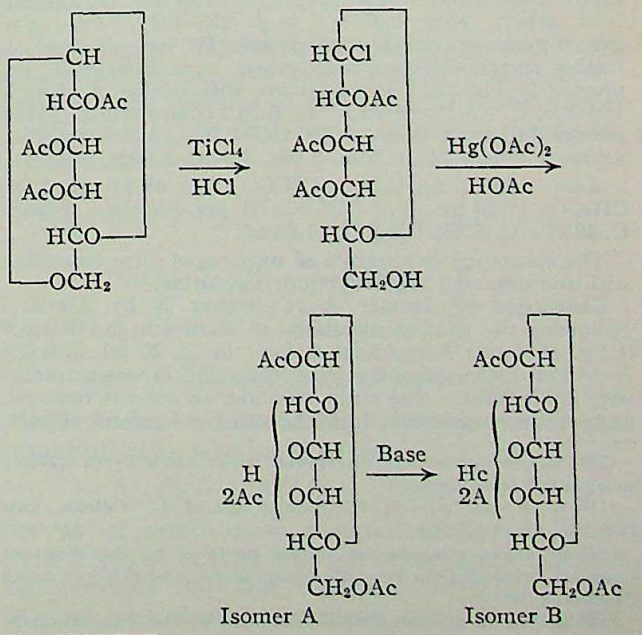
The *p*-toluenesulfonate ester of isomer B failed to crystallize but was obviously different from the corresponding derivative of isomer A. On the other hand, 3-*O*-methyl-α-D-galactose was obtained from both isomers on methylation and deacetylation.

The following reaction is established.

$$A \xrightarrow{\text{Base}} B$$

Thus, isomer B is the more stable form.

2,3,4-Tri-*O*-acetyl-α-D-galactopyranosyl chloride has been prepared in crystalline form by Zemplén, Gerecs and Flesch[9] and was utilized by them



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(4) J. M. Sugihara, *Advances in Carbohydrate Chem.*, **8**, 4 (1953).
(5) J. S. D. Bacon, D. J. Bell and H. W. Kosterlitz, *J. Chem. Soc.*, 1248 (1939).
(6) H. Ohle and H. Thiel, *Ber.*, **66**, 525 (1933).
(7) W. N. Haworth, J. Jackson and F. Smith, *J. Chem. Soc.*, 620 (1940).
(8) J. A. Forbes and E. G. V. Percival, *ibid.*, 1844 (1939).
(9) G. Zemplén, A. Gerecs and Hedwig Flesch, *Ber.*, **71**, 774 (1938).

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in their synthesis of robinobiose, 6-*O*-β-L-rhamnopyranosyl-D-galactose. Thus, the *O*-acylglycosyl chloride must have its terminal primary hydroxyl group unsubstituted. Isomer A was obtained by us on reaction of this halide with mercuric acetate in acetic acid solution. It is then probable that an acetyl shift occurred in this replacement reaction.

The collective evidence then would appear to establish the presence of acetate groups on positions 1 and 6 of the β-D-galactopyranose ring structure, but an assignment of the remaining two acetate groups on positions 2, 3 and 4 in the two isomeric tetraacetates cannot be made on the basis of the present evidence.

Experimental[10]

Isomer A from 2,3,4-Tri-*O*-acetyl-α-D-galactopyranosyl Chloride.—An amount of 1.7 g. of 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl chloride[9] (m.p. 134°) was dissolved in 25 ml. of acetic acid containing 4 g. of mercuric acetate and allowed to stand for 1 hr. Isomer A was isolated from the reaction mixture by the procedure described previously[2]; yield 1.2 g., m.p. 133–135°. Pure material was obtained on crystallization from chloroform–ether; m.p. 140–140.5° undepressed on admixture with an authentic specimen of isomer A.

β-D-Galactopyranose Tetraacetate (Isomer B).—The sirup from the concentration of the mother liquors obtained in the preparation[2] of isomer A, from 7.8 g. of tri-*O*-acetyl-1,6-anhydro-β-D-galactopyranose, was chromatographed, following the general directions of McNeely, Binkley and Wolfrom.[11] The sirup (4.7 g.) was dissolved in a small amount of benzene and placed on a Magnesol[12]–Celite[13] (5:1 by wt.) column (250 × 75 mm., diam.) using 3500 ml. of benzene–*t*-butyl alcohol (100:1 by vol.) as the developer. After the column was extruded and streaked with indicator (1% potassium permanganate in 10% sodium hydroxide), two zones appeared. They were numbered from the bottom to the top of the column.

Zone I, located 125–155 mm. from the top, was eluted with acetone, evaporated to a sirup under reduced pressure and the residue was crystallized from an ether–petroleum ether (b.p. 30–60°) solution; yield 640 mg., m.p. 70–73°, unchanged on admixture with 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-galactopyranose.

Zone II, located 24–75 mm. from the top, was eluted with acetone, the eluate evaporated to a sirup and crystallized from ether; yield 0.37 g., m.p. 138–141°. Pure β-D-galactopyranose tetraacetate (isomer B) was obtained on further recrystallization from ether; m.p. 140–141.5° depressed to 116–122° on admixture with isomer A of m.p. 138–138.5°, $[\alpha]^{32}D$ +25.5° (*c* 2.94, chloroform); X-ray powder diffraction data: 9.77[14] vs,[15] 7.76m, 5.55vw, 4.99vs, 4.60w, 4.36m, 4.21s, 3.82m, 3.69s, 3.56m, 3.40m, 3.27m.

Anal. Calcd. for $C_6H_8O_6(CH_3CO)_4$: C, 48.27; H, 5.79; CH_3CO, 11.48 ml. of 0.1 *N* NaOH per 100 mg. Found: C, 48.40; H, 5.76; CH_3CO, 11.65 ml.

The substance was recovered unchanged after treatment with pyridine and triphenylmethyl chloride.

Conversion of Isomer A to Isomer B by Alkali.—Following the general directions of Helferich and Klein,[16] 0.2 g. of isomer A was shaken for 1 hr. in 20 ml. of 0.001 *N* sodium hydroxide whereupon the solution was extracted with chloroform. The sirup obtained on solvent removal, under reduced pressure, from the dried chloroform extract, was dissolved in ether and crystallization ensued on seeding with isomer B; yield 10 mg., m.p. 138–141° unchanged on admixture with isomer B and depressed to 115–120° on admixture with isomer A, X-ray powder diffraction lines identical with those of isomer B.

The isomer B was obtained in better yield when 0.1 g. of isomer A was shaken for 3.5 hr. with 10 ml. of water and 0.2 g. of Amberlite IR-4B.[17] The resin was removed by filtration and the aqueous solution was extracted with chloroform. The sirup obtained on solvent removal, under reduced pressure, from the dried extract, was crystallized from ether; yield 70 mg., m.p. 140–141.5° unchanged on admixture with isomer B and depressed to 114–125° on admixture with isomer A.

Conversion of Isomers A and B to β-D-Galactopyranose Pentaacetate.—An amount of 100 mg. of isomer A was treated for 18 hr. at 0° with acetic anhydride (1 ml.) and pyridine (2 ml.). The reaction was completed on being maintained at room temperature for 12 hr. The crystalline product that formed on pouring the reaction mixture into ice and water was removed by filtration and recrystallized from ethanol; yield 100 mg., m.p. 137–139° unchanged on admixture with authentic β-D-galactopyranose pentaacetate; X-ray powder diffraction data[14,15] (identical with that of authentic material): 12.93vw, 8.10m, 6.93s, 6.18s, 5.62w, 5.06m, 4.28m, 4.00vs, 3.83s, 3.66vw, 3.42vw, 3.29vw, 3.17vw, 3.08w, 3.03w, 2.94vw, 2.87w, 2.81vw, 2.72vw.

β-D-Galactopyranose pentaacetate was likewise identified on the acetylation of isomer B effected in the same manner.

1,2,4,6-Tetra-*O*-acetyl-3-*O*-methyl-β-D-galactose.—The general procedure of Haworth, Hirst and Teece[18] was followed. An amount of 1.0 g. of isomer A, 50 ml. of methyl iodide and 7 g. of silver oxide was maintained at 50–60° under reflux for 5 hr. Ether was then added and the mixture was filtered. The filtrate was concentrated under reduced pressure and the resultant sirup was crystallized from ether; yield 400 mg., m.p. 118–120°. Recrystallization from ethanol gave pure 1,2,4,6-tetra-*O*-acetyl-3-*O*-methyl-β-D-galactose, m.p. 119–120°, mixed m.p. with isomer A 105–111°, $[\alpha]^{25}D$ +41° (*c* 3, chloroform); X-ray powder diffraction data[14,15]: 10.72s, 8.93m, 7.53m, 6.99m, 6.60vw, 6.23m, 5.53m, 5.13w, 4.93w, 4.44s, 3.97m, 3.90m, 3.69m, 3.46m.

Anal. Calcd. for $C_6H_7O_5(CH_3CO)_4(OCH_3)$: C, 49.71; H, 6.12; OCH_3, 8.57; CH_3CO, 11.00 ml. of 0.1 *N* NaOH per 100 mg. Found: C, 49.70; H, 6.01; OCH_3, 8.61; CH_3CO, 11.01 ml.

Methylation of Isomer B.—The general procedure of Richtmyer and Hudson[19] was followed. An amount of 400 mg. of isomer B, 5 g. of silver oxide and 25 ml. of methyl iodide were shaken in a closed flask for 3 hr. at room temperature. The product was processed in a manner similar to that described for the methylation of isomer A. Crystals were obtained from an ethanolic solution; yield 70 mg., m.p. 119–120° unchanged on admixture with 1,2,4,6-tetra-*O*-acetyl-3-*O*-methyl-β-D-galactoside, the methylation product of isomer A. The X-ray powder diffraction patterns of crystals from the two sources were identical.

3-*O*-Methyl-α-D-galactose.—The 1,2,4,6-tetra-*O*-acetyl-3-*O*-methyl-β-D-galactose was deacetylated by an adaptation of the method of Zemplén and Pacsu.[20] An amount of 500 mg. of the substance was dissolved, under exclusion of moisture, in 10 ml. of dry methanol, and 1.5 ml. of a sodium methoxide solution, prepared by treating 500 mg. of sodium with 100 ml. of methanol, was added. After 30 min., 50 ml. of water was added and the solution was passed successively over Amberlite IR-120[17] and Duolite A-4.[21] The neutral, aqueous solution was concentrated under reduced pressure, and the resultant sirup was crystallized from methanol by seeding with 3-*O*-methyl-α-D-galactose[22]; yield 100 mg., m.p. 146–148° (recorded[3] 144–147°) unchanged on admixture with an authentic specimen of 3-*O*-

(10) All melting points herein reported were taken in Pyrex capillary tubes and are uncorrected.

(11) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, THIS JOURNAL, **67**, 527 (1945).

(12) A synthetic magnesium silicate produced by the Westvaco Chemical Division of the Food Machinery and Chemical Corp., South Charleston, W. Va.

(13) No. 535, a siliceous filter-aid produced by the Johns-Manville Co., New York, N. Y.

(14) Interplanar spacing, CuK_α radiation.

(15) Relative intensity, estimated visually; vs, very strong; s, strong; m, medium; w, weak; vw, very weak.

(16) B. Helferich and W. Klein, *Ann.*, **450**, 219 (1926).

(17) A product of the Rohm and Haas Co., Resinous Products Division, Philadelphia, Pa.

(18) W. N. Haworth, E. L. Hirst and E. G. Teece, *J. Chem. Soc.*, 1405 (1930).

(19) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **63**, 1727 (1941).

(20) G. Zemplén and E. Pacsu, *Ber.*, **62**, 1613 (1929).

(21) A product of the Chemical Process Co., Redwood City, Calif.

(22) Nucleic acid hydrolysate furnished by Prof. T. Reichstein of the University of Basel.

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methyl-α-D-galactose; X-ray powder diffraction data[14,15] (identical with those of authentic 3-*O*-methyl-α-D-galactose): 8.85m, 6.93s, 5.74s, 4.98w, 4.56vs, 3.90vw, 3.76s, 3.62vw, 3.49m, 3.39s, 3.31m, 2.88w, 2.83w, 2.66m, 2.41w, 2.32w, 2.26w.

Tetra-*O*-acetyl-*O*-*p*-toluenesulfonyl-β-D-galactopyranose from Isomer A.—The general experimental procedure followed was that of Helferich and Klein.[16] An amount of 500 mg. of isomer A was treated with 200 mg. of *p*-toluenesulfonyl chloride in 3 ml. of dry pyridine. After 24 hr., the mixture was poured into ice and water. The precipitate that formed was filtered and dissolved in ethanol. Crystals appeared upon concentration of the solution; yield 500 mg., m.p. 153–155°. The product was recrystallized from an acetone–ether–petroleum ether (b.p. 30–60°) mixture; m.p. 154–155°, $[\alpha]^{25}D$ +43° (*c* 3, chloroform); X-ray powder diffraction data[14,15]: 10.52s, 8.44vw, 5.72m, 5.31w, 4.76w, 4.48m, 4.19vw, 4.00vw, 3.53w, 3.45m, 3.14w.

Anal. Calcd. for $C_{21}H_{26}O_{12}S$: C, 50.19; H, 5.21; S, 6.38. Found: C, 50.10; H, 5.30; S, 6.33.

Similar treatment of isomer B with *p*-toluenesulfonyl chloride and pyridine failed to yield a crystalline product.

The *p*-toluenesulfonate (150 mg.) from isomer A yielded a negligible precipitate (5 mg.) of sodium *p*-toluenesulfonate on heating at 100° with 70 mg. (1.5 molar ratio) of sodium iodide in 3 ml. of acetonylacetone for 48 hr. A like experiment utilizing 400 mg. of tetra-*O*-acetyl-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranose, 180 mg. of sodium iodide and 8 ml. of acetonylacetone yielded 141.2 mg. (88%) of sodium *p*-toluenesulfonate.

Methyl Tri-*O*-acetyl-*O*-*p*-toluenesulfonyl-β-D-galactopyranoside from Isomer A.—The general procedure of Haworth, Jackson and Smith[7] was followed. An amount of 500 mg. of tetra-*O*-acetyl-*O*-*p*-toluenesulfonyl-β-D-galactopyranose (from isomer A) was treated for 1 hr. with 5 ml. of a solution containing 30% hydrogen bromide in anhydrous acetic acid:acetic anhydride (1:1 by vol.). Chloroform was then added to the solution and the extract was washed four times with water and dried over sodium sulfate. The dried solution was concentrated under reduced pressure, and the resulting sirup was dissolved in 25 ml. of dry methanol, and 10 g. of freshly prepared silver carbonate was added. The mixture was shaken for 5.5 hr. whereupon it was filtered, and the filtrate was concentrated under reduced pressure. Crystals of the methyl tri-*O*-acetyl-*O*-*p*-toluenesulfonyl-β-D-galactopyranoside appeared during the concentration; yield 240 mg., m.p. 129–130°, $[\alpha]^{25}D$ +24° (*c* 3, chloroform); X-ray powder diffraction data[14,15]: 9.77vs, 6.20w, 5.84m, 5.24s, 4.88m, 4.46w, 4.23w, 4.01s, 3.79vw, 3.65m, 3.51m, 3.37m.

Anal. Calcd. for $C_{20}H_{26}O_{11}S$: C, 50.62; H, 5.52; S, 6.77. Found: C, 50.42; H, 5.71; S, 6.67.

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Deuterium-isotope Effects in the Autoxidation of Aralkyl Hydrocarbons. Mechanism of the Interaction of Peroxy Radicals[1]

BY GLEN A. RUSSELL

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α-Phenethylperoxy radicals interact to form non-radical products 1.9 times as readily as their α-deutero derivatives. This is taken as evidence that the termination reaction is $2C_6H_5CH(D)CH_3COO\cdot \rightarrow C_6H_5COCH_3 + C_6H_5CH(D)OH(D)-CH_3 + O_2$. Yields of hydroperoxide and acetophenone produced in the autoxidation of ethylbenzene at various kinetic chain lengths are consistent with the indicated termination reaction. Evidence is presented that this reaction involves a cyclic transition state and excluding an alternate process proceeding by the formation and disproportionation of alkoxy radicals. The deuterium-isotope effect in the reaction of a peroxy radical with cumene and α-*d*-cumene is $k_H/k_D = 5.5$. The magnitudes of deuterium-isotope effects in the reactions of atoms and radicals with carbon–hydrogen and carbon–deuterium bonds are considered. Reactivities of the attacking atoms or radicals and polar effects in the reaction are discussed.

Despite the fact that the autoxidation of hydrocarbons has been studied intensively,[2] evidence is lacking as to the mechanism and products of the reaction wherein two peroxy radicals are converted to non-radical products. We have, therefore, investigated the products of this termination reaction in the oxidation of ethylbenzene and have demonstrated its detailed mechanism by a study of deuterium-isotope effects. The deuterium-isotope effect in the reaction of a peroxy radical with α-*d*-cumene has been measured, and its magnitude confirms our earlier conclusions in regard to the extent of bond-breaking in the transition state for this reaction.

Results

Autoxidations of cumene, ethylbenzene and various deuterated derivatives were performed at 60° in the liquid phase in the presence of α,α′-azodiisobutyronitrile (AIBN). The rates of oxidation were independent of the oxygen pressure over the range 200–760 mm. indicating that only peroxy radicals were involved in the termination reaction.[2] The kinetics of the reaction under these conditions indicate that the following sequence of events is involved.

$$\text{AIBN} \xrightarrow{k_d} (CH_3)_2\dot{C}CN \xrightarrow{O_2} \text{ROO}\cdot \ (\text{Rate} = R_i)$$

$$\text{ROO}\cdot + \text{RH} \xrightarrow{k_3} \text{ROOH} + \text{R}\cdot$$

$$\text{R}\cdot + O_2 \xrightarrow{\text{fast}} \text{ROO}\cdot$$

$$2\text{ROO}\cdot \xrightarrow{k_6} \text{non-radical products} + O_2$$

Under steady-state conditions the rate of oxygen consumption is calculated to be

$$-d[O_2]/dt = k_3[RH](R_i)^{1/2}/(2k_6)^{1/2} + R_i/2 \quad (1)$$

The rate of initiation, R_i, is equal to $2k_d e[AIBN]^{1/2}$ where *e* represents the fraction of catalyst molecules that produce two free radicals. In Table I the rates of oxidation of cumene and ethylbenzene are presented as a function of hydrocarbon concentration, AIBN concentration and oxygen pressure. The data of column 6 indicate that (1) is obeyed and the rate of oxidation is independent of

(1) Directive Effects in Aliphatic Substitutions. IX. Presented before the Division of Organic Chemistry at the Atlantic City meeting of the American Chemical Society, September, 1956.

(2) J. L. Bolland, *Quart. Revs.*, **3**, 1 (1949); L. Bateman, *ibid.*, **8**, 147 (1954).

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TABLE I

OXIDATION OF CUMENE AND ETHYLBENZENE AT 60.0°

Hydrocarbon	[RH], mole l.$^{-1}$	[AIBN], mole l.$^{-1}$	O_2 pressure, mm.	Rate of oxygen absorption,[a] mole l.$^{-1}$ sec.$^{-1}$ $\times 10^5$	(Rate—$R_i/2$)/[RH][AIBN]$^{1/2}$ $\times 10^5$
Cumene	6.90	0.100	750	2.58	1.16
Cumene	6.90	.100	500	2.58	1.16
Cumene	6.90	.100	200	2.60	1.17
Cumene	6.90	.200	750	3.66	1.14
Cumene	6.90	.050	750	1.75	1.13
Cumene	4.00[b]	.100	750	1.53	1.15
Ethylbenzene	7.82	.100	750	0.58	0.207
Ethylbenzene	7.82	.100	500	.56	.199
Ethylbenzene	7.82	.100	200	.60	.214
Ethylbenzene	7.82	.150	750	.74	.211
Ethylbenzene	7.82	.200	750	.85	.203

[a] Corrected for nitrogen evolved in decomposition of AIBN. [b] Chlorobenzene used as an inert diluent.

the oxygen pressure and proportional to $k(R_i)^{1/2} + R_i/2$. The value of R_i used in the above calculations for 0.1 M AIBN has been taken as 1.38×10^{-6} mole l.$^{-1}$ sec.$^{-1}$ based on a value of 1.15×10^{-5} sec.$^{-1}$ for k_d at 60° and 0.60 for e. The value of k_d in an aromatic solvent was selected from a compilation of various literature references[3,4] while the value of e appears established from the work of Hammond, Sen and Boozer.[5]

Having thus established the course of the reaction, the deuterium-isotope effect in the slow propagation step (k_3) was investigated. α-Deuterocumene was prepared by the reaction of deuterium chloride with α,α-dimethylbenzylpotassium. Analysis by high resolution nuclear magnetic resonance spectroscopy indicated that 58.4% of the tertiary hydrogen atoms of cumene had been replaced by deuterium atoms. Aromatic deuterium atoms were present (0.24 atom/molecule) in the form of d_1-, d_2- and d_3-cumenes, but analysis by high resolution infrared absorption indicated that less than 3% of the molecules contained a β-deuterium atom.

This sample of α-d-cumene oxidized considerably less rapidly than cumene, even though 41.6% of the molecules had an α-hydrogen atom. Since, in the presence of 0.1 M AIBN, cumene was oxidized at a rate of 2.58×10^{-5} mole l.$^{-1}$ sec.$^{-1}$ and α-d-cumene (58.4% pure) at a rate of 1.38×10^{-5} mole l.$^{-1}$ sec.$^{-1}$, it can be calculated that in the slow propagation reaction the deuterium-isotope effect is $k_H/k_D = 5.5$. Based on possible errors in analysis, the isotope effect might be as low as 4.5 and as high as 7.2.

$$ROO\cdot + RH \xrightarrow{k_H} ROOH + R\cdot$$

$$ROO\cdot + RD \xrightarrow{k_D} ROOD + R\cdot$$

$$k_H/k_D = 5.5$$

There can be no deuterium-isotope effect in the termination reaction in the oxidation of α-d-cumene since both cumene and α-d-cumene yield the same α,α-dimethylbenzylperoxy radical.

The data of Table II demonstrate that the yields of hydroperoxide in the autoxidations of cumene and α-d-cumene were essentially quantitative irrespective of kinetic chain length (molecules oxidized per initiating fragment). This supports the conclusion of Boozer[6] that the interaction of cumylperoxy radicals should be formulated

$$2C_6H_5C(CH_3)_2OO\cdot \longrightarrow C_6H_5C(CH_3)_2OOH + C_6H_5CCH_3{=}CH_2 + O_2$$

The yield of hydroperoxide in the oxidation of ethylbenzene was neither quantitative nor independent of kinetic chain lengths (see Table II). The yield of hydroperoxide decreased with decreasing kinetic chain length suggesting that oxygen-containing non-peroxidic products were formed in the termination reaction. In the oxidation of ethylbenzene, under the conditions specified in Table II, an average of 4.2 molecules of oxygen were absorbed per initiating radical. If the termination reaction between two α-phenethylperoxy radical yields one molecule of oxygen and one molecule of oxygen combined in non-peroxidic products, the theoretical yield of hydroperoxide, based on oxygen absorbed, is 88%. The observed yield was 85%. In the oxidation of d_4-ethylbenzene (prepared by the addition of deuterium to phenylacetylene) the kinetic chain length was only 2.0 and the yield of hydroperoxide was 65%. The theoretical yield calculated on the basis of a termination reaction yielding a molecule of oxygen and a molecule of oxygen combined in non-peroxidic products is 75%.

A possible termination reaction, consistent with the above observations, is

$$2C_6H_5CHCH_3OO\cdot \longrightarrow C_6H_5COCH_3 + C_6H_5CHOHCH_3 + O_2$$

Hydroxylic and ketonic products are generally formed in small amounts in low-temperature autoxidations, but these products may represent only the decomposition of some of the initially formed hydroperoxide. However, the formation of exactly one mole of acetophenone per two kinetic chains would give considerable support to the above termination reaction. The oxidates of α-d_1-ethyl-

(3) The following data were used: F. M. Lewis and M. S. Matheson, THIS JOURNAL, **71**, 747 (1949); 80°, xylene, 1.53×10^{-4} sec.$^{-1}$; 70°, xylene, 4.16×10^{-5} (unpublished); 90°, xylene, 5.0×10^{-4} (unpublished); L. M. Arnett, *ibid.*, **74**, 2027 (1952), 77°, xylene, 9.5×10^{-5}; 82°, xylene, 1.45×10^{-4}; M. Talat-Erben and S. Bywater, *ibid.*, **77**, 3712 (1955), 70°, toluene, 4.0×10^{-5}; 80.4°, toluene, 1.55×10^{-4}; 90°, toluene, 4.86×10^{-4}; 100°, toluene, 1.6×10^{-3}; G. S. Hammond, J. N. Sen and C. E. Boozer, ref. 5, 62.5°, benzene, 1.42×10^{-5}; 62.5°, chlorobenzene, 1.54×10^{-5}; C. G. Overberger, M. T. O'Shaughnessy and H. Shalit, *ibid.*, **71**, 2661 (1949), 69.8°, toluene, 3.8×10^{-5}; 80.2°, toluene, 1.66×10^{-4}; G. A. Russell, *ibid.*, **78**, 1044 (1956), 80°, cumene, 1.67×10^{-4}; J. C. Roy, J. R. Nash, R. R. Williams, Jr., and W. H. Hamill, *ibid.*, **78**, 519 (1956), 80°, chlorobenzene, 1.50×10^{-4}; J. W. Breitenbach and A. Schindler, *Monatsh. Chem.*, **83**, 724 (1952), 50°, styrene, 2.97×10^{-5}; 70°, styrene, 4.72×10^{-5}. These data yield the expression $k_d = 1.78 \times 10^{15} \exp(-31,300/RT)$ with serious deviation for the 82° point of Arnett only. Interestingly, the decomposition rates of C. E. H. Bawn and S. H. Mellish [*Trans. Faraday Soc.*, **47**, 1216 (1951)], obtained by use of diphenylpicrylhydrazyl, which supposedly is a measure of $k_d e$,[4,5] are in excellent agreement with this rate expression over the range 40–70°. Decomposition rate constants in nitrobenzene solution are consistently higher. The data of Hammond, ref. 5, 1.79×10^{-5} sec.$^{-1}$ at 62.5°, and of K. Ziegler, W. Deparade and W. Meye [*Ann.*, **567**, 141 (1950)], 2.0×10^{-4} at 80°, 2.25×10^{-3} at 100°, give the expression $k_d = 4.9 \times 10^{15} \exp(-31,200/RT)$.

(4) C. Walling, *J. Polymer Sci.*, **14**, 214 (1954); J. C. Bevington, *Nature*, **175**, 477 (1955), *J. Chem. Soc.*, 1127 (1956).

(5) G. S. Hammond, J. N. Sen and C. E. Boozer, THIS JOURNAL, **77**, 3244 (1955).

(6) C. E. Boozer, B. W. Brauer, J. C. Trisler and C. E. Wrightman, *ibid.*, **78**, 1506 (1956).

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TABLE II
OXIDATION OF ARALKYL HYDROCARBONS AT 60°, 0.1 *M* AIBN

Hydrocarbon (mole)	[RH], mole l.$^{-1}$	Rate[a] mole l.$^{-1}$ sec.$^{-1}$ × 10^5	Kinetic chain length[b]	Oxygen absorbed[a] mole × 10^3	Hydroperoxide found Iodimetric[c]	Hydroperoxide found Stannous chloride[d]	% Oxygen found as hydroperoxide[e]
Cumene (0.1380)	6.90	2.58	19	1.86	1.87	1.80	97
Cumene (0.1380)	6.90	1.75[f]	25	1.12	1.10	1.10	98
"α-d_1-Cumene" (0.0690)	6.90	1.38	10.0	0.90	0.88	0.86	96
Ethylbenzene (0.1562)	7.82	0.58	4.2	2.00	1.80	1.70	85
α-d_1-Ethylbenzene (0.0783)	7.83	0.47	3.4	0.915	0.75	0.72	79
d_4-Ethylbenzene (0.0785)	7.85	0.27	2.0	0.64	0.53	0.42	64

[a] Corrected for nitrogen evalued in decomposition of AIBN. [b] Based on oxygen consumed. [c] Reference 41. [d] Reference 42. [e] Calculated from hydroperoxide found by stannous chloride. [f] 0.05 *M* AIBN.

benzene and d_4-ethylbenzene were therefore analyzed for carbonyl content by infrared absorption. In the oxidation of d_4-ethylbenzene the kinetic chain length was only 2. Therefore, three molecules of hydroperoxide and one molecule each of acetophenone and α-phenethanol were expected per pair of initiating radicals formed. Of the total oxygen absorption of 0.64×10^{-3} mole, $^1/_8$ should be present as acetophenone if the suggested termination reaction occurs. By analysis 0.13×10^{-3} mole of acetophenone was found which is in fair agreement with the theoretical value of 0.16 $(2 \times 0.64/8) \times 10^{-3}$ mole. Based on a kinetic chain length of 3.4, 0.135×10^{-3} mole of acetophenone was expected in the oxidation of α-d_1-ethylbenzene wherein 0.915×10^{-3} mole of oxygen was consumed. The observation that 0.13×10^{-3} mole of acetophenone was formed lends strong support to the suggested termination reaction.

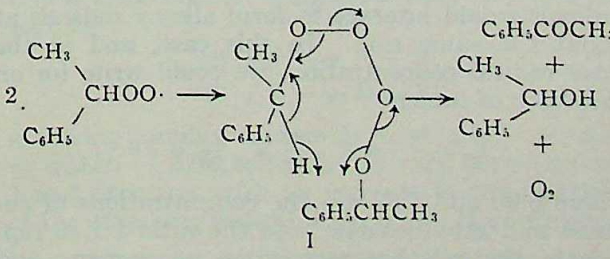
The mechanism of this termination reaction was investigated further by a study of deuterium-isotope effects in the oxidation of ethylbenzene. If there were no deuterium-isotope effect in the termination reaction of α-deutero-α-phenethylperoxy radicals, the ratio of $k_3/k_6^{1/2}$ for the oxidations of ethylbenzene and α-d_1-ethylbenzene[7] should be 1:0.60 provided that the deuterium-isotope effect in the propagation reaction is $k_H/k_D = 5.5$. The observed ratio was 1:0.78. This ratio would be consistent with a termination reaction involving no isotope effect only if the deuterium-isotope effect in the propagation reaction (k_3) was $k_H/k_D = 1.8$. This isotope effect is so inconsistent with the isotope effect of 5.5 determined in the oxidation of cumene that there must be a deuterium-isotope effect in the termination reaction of α-deutero-α-phenethylperoxy radicals.[8] Using an isotope effect in the propagation reaction of $k_H/k_D = 5.5$, it follows that α-phenethylperoxy radicals terminate 1.7 times as readily as the peroxy radicals formed in the oxidation of α-d_1-ethylbenzene. The peroxy radicals formed in the oxidation of α-d_1-ethylbenzene[7] should be 78.8% α-deutero-α-phenethylperoxy and 20.2% α-phenethylperoxy based on the magnitude of the isotope effect in the propagation reaction. If the crossed termination reaction (k_{HD}) is assumed to occur with a rate constant that is the geometric mean of the rate constants for the other two reactions,[9] $k_{HD} = (k_H k_D)^{1/2}$, it can be calculated that the deuterium-isotope effect in the termination reaction is $k_H/k_D = 1.9$. The magnitude of this deuterium-isotope effect, which occurs when a deuterium atom is substituted for an α-hydrogen

$$\left.\begin{array}{l} 2C_6H_5CHCH_3OO\cdot \xrightarrow{k_H} \\ C_6H_5CHCH_3OO\cdot + C_6H_5CDCH_3OO\cdot \xrightarrow{k_{HD}} \\ 2C_6H_5CDCH_3OO\cdot \xrightarrow{k_D} \end{array}\right\} \text{non-radical products}$$

atom in the α-phenethylperoxy radical, suggests that an α-carbon–hydrogen bond of the α-phenethylperoxy radical is broken in the rate-determining step of the termination reaction. This, of course, is in agreement with the termination reaction suggested wherein two α-phenethylperoxy radicals interact to form oxygen, acetophenone and α-phenethanol.

Discussion

Mechanism of Chain Termination.—The observation that α-phenethylperoxy radicals terminate more readily than their α-deutero derivatives allows the assignment of a detailed mechanism to this reaction. A reaction involving a cyclic transition state seems most likely.



I may actually be an intermediate that is formed rapidly and reversibly and which decomposes slowly in an irreversible manner. The reaction path illustrated is consistent with the yield of hydroperoxide and acetophenone observed in the oxidation of ethylbenzene and in view of the exothermicity of the reaction,[10,11] is consistent with a low

(7) Containing 1.1% ethylbenzene.

(8) Since a hydrogen atom of ethylbenzene is less reactive than a hydrogen atom of cumene toward a peroxy radical [G. A. Russell, THIS JOURNAL, **78**, 1047 (1956)], it is expected that if there is a difference in the deuterium-isotope effect in the propagation reaction, then the largest deuterium-isotope effect will occur in the attack of a peroxy radical on ethylbenzene.

(9) See for example, G. M. Burnett, "Mechanism of Polymer Reactions," Interscience Pub., Inc., New York, N. Y., 1954, p. 290.

(10) Using the bond dissociation energies of T. L. Cottrell ["The Strengths of Chemical Bonds," Academic Press, New York, N. Y., 1954] $D_{(-O-O-)}$, 35 kcal. mole^{-1}; $D_{(\equiv C-H,\ benzyl)}$, 78; $D_{(O_2)}$, 117; $E_{(-C=O,\ ketone)} - E_{(\equiv C-O-)}$, 87; $D_{(RO-H)}$, 100 [P. Gray, *Trans. Faraday Soc.*, **52**, 344 (1956)], it is calculated that 157 kcal. is liberated in the interaction of two moles of peroxy radicals. This estimate is high if the oxygen–oxygen bond dissociation energy of a peroxy [illegible] 35 kcal. mole^{-1}. Since estimates of $D_{(RO-O\cdot)}$

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deuterium-isotope effect (k_H/k_D = 1.9) when a deuterium atom is substituted for an α-hydrogen atom.[12]

Vaughan and co-workers have suggested that prim. and sec.-alkylperoxy radicals terminate by the formation and disproportionation of alkoxy radicals.[13]

$$2R_2CHOO\cdot \xrightarrow{k_f} O_2 + 2R_2CHO\cdot \xrightarrow{k_t} R_2CO + R_2CHOH$$

This suggestion lacks experimental verification, particularly in regard to the actual participation of alkoxy radicals in the reaction. However, in the liquid phase oxidation of ethylbenzene a termination reaction involving the formation and disproportionation of alkoxy radicals can be excluded. A deuterium-isotope effect of the magnitude observed would not be expected if alkoxy radicals were formed slowly and disproportionated rapidly ($k_f < k_t$). On the other hand, although a deuterium-isotope effect would be expected if $k_f > k_t$, this process can be eliminated on the basis of stoichiometry of the oxidation reaction, since, if alkoxy radicals were formed rapidly but disproportionated slowly, a majority of the alkoxy radicals would have to enter into chain propagation reactions, *e. g.*

$$C_6H_5CHCH_3O\cdot + RH \longrightarrow C_6H_5CHCH_3OH + R\cdot$$

The observation that only one molecule of oxygen was present in non-peroxidic products per two kinetic chains in the oxidation of ethylbenzene excludes this possibility.

The improbability of $k_f > k_t$ can be demonstrated by a somewhat less direct approach. We can write the following expressions for the oxidation of ethylbenzene performed in the presence of 0.1 *M* AIBN.[14]

$$k_p/k_t = \frac{\text{rate of chain propagation}}{\text{rate of chain termination}} = \frac{k_3[RH][ROO\cdot]}{2k_6[ROO\cdot]^2} = 7.4$$

Therefore, if $k_f > k_t$, $k_p/k_f < 7.4$. It would seem likely that cumylperoxy and α-phenethylperoxy radicals would interact to form alkoxy radicals at about the same rate. In this case, and at the *same* radical concentration, we could write for an oxidation of cumene

$$k_p/k_f < 7.4 \times \frac{6.90}{7.82} \times \frac{1}{1.20} = 5.6$$

where 6.90 and 7.82 are the concentrations of cumene and ethylbenzene, and the ratio 1:1.20 represents the relative reactivities of cumene and ethylbenzene towards a peroxy radical.[8] We have previously shown that α-phenethylperoxy radicals terminate more readily than cumylperoxy radicals.[8,15] Because of this, under conditions of constant rate of initiation, the concentration of peroxy radicals is greater in an oxidation of cumene than in an oxidation of ethylbenzene. It follows, from Table I, that the concentration of peroxy radicals in the oxidation of cumene (0.1 *M* AIBN, 6.90 *M* cumene) is 6.8 times the concentration of α-phenethylperoxy radicals in the oxidation of ethylbenzene (0.1 *M* AIBN, 7.82 *M* ethylbenzene). Therefore, for a 0.1 *M* AIBN-catalyzed oxidation of cumene, $k_p/k_f < 5.6/6.8 = 0.8$. This indicates that if $k_f > k_t$ and if k_f is the same for cumylperoxy and α-phenethylperoxy radicals, that cumylperoxy radicals formed in a 0.1 *M* AIBN-catalyzed oxidation would interact to yield alkoxy radicals more rapidly than they would react with cumene. Such a situation is unlikely in view of the essentially quantitative yield of hydroperoxide obtained in the oxidation of cumene (Table II).

Another possible termination reaction[16] can be

$$2ROO\cdot + R'C_6H_5 \longrightarrow ROOH + R'C_6H_4OOR$$

excluded on the basis of the observed deuterium-isotope effect in the termination reaction and also on the basis of the argument that this reaction should occur as readily for cumylperoxy radicals as for α-phenethylperoxy radicals. In this case the kinetic chain length observed in the oxidation of cumene (0.1 *M* AIBN) should be $^1/_{10}$ (6.90/7.82 × 1/1.20 × 1/6.8) that observed in the oxidation of ethylbenzene (0.1 *M* AIBN) whereas the kinetic chain length is actually much greater in the oxidation of cumene (Table II).

Finally, we would like to point out that the termination mechanism suggested for α-phenethylperoxy radicals is possibly general for prim. and sec.-alkylperoxy radicals. Previously we have demonstrated that most prim.- and sec.-peroxy radical terminate much more readily than sec.-alkylperoxy radicals.[8,15] This suggests that many prim.- and sec.-alkylperoxy radicals terminate in the same manner and that a different termination reaction is involved for ter.-alkylperoxy radicals. Such a circumstance is readily appreciated if prim.- and sec.-alkylperoxy radicals terminate by the cyclic interaction pictured wherein an α-carbon–hydrogen bond is ruptured. Ter.-alkylperoxy radicals, lacking an α-carbon–hydrogen bond, cannot undergo this termination reaction.[6]

Bolland and Cooper have suggested that in the photo-sensitized oxidation of ethanol acetic acid is formed in a termination reaction involving peroxy radicals.[17] In the absence of any data to the contrary, and in view of the present findings, we would prefer to formulate the reactions as shown.

Deuterium-isotope Effects in Aliphatic Substitutions.—The observation that the deuterium-isotope effect observed in the attack of a peroxy radical upon an α-hydrogen atom of an aralkyl hydrocarbon has the magnitude k_H/k_D = 5.5 is in

in the range 45–55 are not unreasonable (see footnote 22), ΔH, may be as low as 59 kcal. per mole of peroxy radical.

(11) C. H. Bamford and M. J. S. Dewar [*Proc. Roy. Soc.* (*London*), **198A**, 252 (1949)] have assigned an energy of activation of about 1, kcal. mole^{-1} to the termination reaction between two α-tetralylperoxy radicals.

(12) K. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

(13) E. R. Bell, J. H. Raley, F. F. Rust, F. H. Seubold, Jr., and W. E. Vaughan, *Disc. Faraday Soc.*, **10**, 242 (1951); F. H. Seubold, Jr., F. F. Rust and W. E. Vaughan, THIS JOURNAL, **73**, 18 (1951).

(14) In the oxidation of ethylbenzene 4.2 molecules of oxygen was consumed per initiating radical. One molecule of oxygen was consumed in the initiating step and one molecule of oxygen was liberated in the termination of two kinetic chains. Therefore, on the average, an α-phenethylperoxy radical abstracted a hydrogen atom 3.7 times before it entered into a termination reaction.

(15) G. A. Russell, THIS JOURNAL, **77**, 4583 (1955).

(16) This reaction is similar to the termination reaction that occurs in peroxidations inhibited by phenols or substituted-anilines [C. E. Boozer and G. S. Hammond, *ibid.*, **76**, 3861 (1954), **77**, 3233, 3238 (1955)].

(17) J. L. Bolland and H. R. Cooper, *Proc. Roy. Soc.* (*London*), **225A**, 405 (1954); **A172**, 413 (1953).

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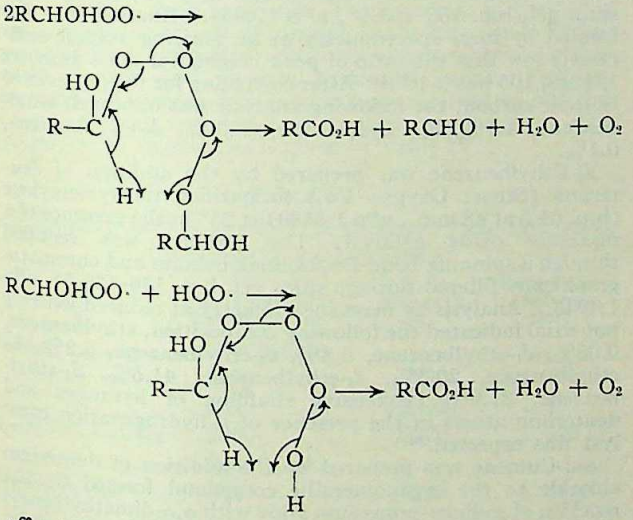
TABLE III

DEUTERIUM-ISOTOPE EFFECT, ENERGY OF ACTIVATION, EXOTHERMICITY AND SELECTIVITY OF ATOMS AND RADICALS IN THE REACTION $X\cdot + RH \rightarrow XH + R\cdot$

X	RH	Exothermicity[a]	Energy of activation	k_H/k_D	Relative reactivity of toluene (prim.-hydrogen) to cumene (ter.-hydrogen)
Cl·	$C_6H_5CH_3$	24.7	2–3[b]	2.0 (80°)[c]	1:4 (80°)[d]
$(CH_3)_3CO\cdot$	$C_6H_5CH_2CH_3$	25.0[e]	..	3.7 (107–116°)[f]	1:5 (135)[g]
Br·	$C_6H_5CH_3$	9.0	7.2[h]	4.8 (77°)[i]	.....
ROO·	$C_6H_5C(CH_3)_2H$	16–26	6.7[j]	5.5 (60°)	1:13 (90°)[k]
$CH_3\cdot$	$C_6H_5CH_3$	23.5	8.3[l]	5.5 (125°)[m]	1:12.5 (91.5°)[m]

[a] Based on bond dissociation energies listed by Cottrell (ref. 10). [b] H. O. Prichard, J. B. Pyke and A. F. Trotman-Dickenson, THIS JOURNAL, 77, 2629 (1955). [c] H. C. Brown and G. A. Russell, *ibid.*, 74, 3995 (1952). [d] Ref. 24. [e] $D_{(RO-H)}$ taken as 100 kcal. mole^{-1}, P. Gray, ref. 10. [f] E. L. Eliel, F. T. Fang and S. H. Wilen, *Preprints of General Papers, Div. Pet. Chem.*, 1, 195 (1956). [g] A. L. Williams, G. A. Oberright and J. W. Brooks, THIS JOURNAL, 78, 1190 (1956). [h] H. R. Anderson, Jr., H. A. Scheraga and E. R. VanArtsdalen, *J. Chem. Phys.*, 21, 1258 (1953). [i] Ref. 12. [j] H. W. Melville and S. Richards, *J. Chem. Soc.*, 944 (1956). [k] Ref. 8. [l] A. F. Trotman-Dickenson and E. R. Steacie, *J. Chem. Phys.*, 19, 329 (1951), this energy of activation may be largely a measure of the reactivity of aromatic hydrogen atoms, see reference cited in footnote [f]. [m] Toward the trichloromethyl radical, E. C. Kooyman, *Disc. Faraday Soc.*, 10, 163 (1951).

excellent agreement with an isotope effect of about 5 reported by Max and Deatherage for the relative rates of autoxidation of *cis*-9-octadecene and its 8,8,11,11-tetradeutero derivative.[18] The isotope



effect reported here has more significance, however, because in the case of the octadecenes isotope effects in both propagation and termination reactions may have been present as well as uncertainties in regard to the rates of initiation.

Wiberg has discussed the correlation between the magnitude of the deuterium-isotope effect in free radical substitution reactions and the reactivity of the attacking radical or atom.[12] In Table III are listed a compilation of data concerning the isotope effect and the reactivity of chlorine atoms, alkoxy radicals, bromine atoms, peroxy radicals and methyl radicals. The exothermicities listed in Table III were calculated assuming a bond dissociation energy for an α-carbon–hydrogen bond of toluene of 77.5 kcal. mole^{-1}.[19] This may be as much as 10 kcal. too low.[20] The exothermicity of the reaction between a peroxy radical and cumene listed in Table III has been calculated assuming $D_{(ROO-H)}$ to be 90–100 kcal. mole^{-1}. This estimate is based on the comments of Vaughan[21] and the recently determined value of $D_{(RO-H)}$ as 100 kcal. mole^{-1}.[10,22]

From Table III it is apparent that the deuterium-isotope effect increases with the energy of activation of the reaction and with the selectivity of the attacking atom or radical. We believe that in reactions involving a low energy of activation and a low deuterium-isotope effect, the carbon–hydrogen (or deuterium) bond is only slightly broken in the transition state. As the atom or radical becomes more selective, the energy of activation increases, the deuterium-isotope effect increases and the transition state for the reaction involves a greater amount of bond breaking. The argument that the transition state in these hydrogen-abstraction reactions varies between one resembling the reactants and one involving a carbon–hydrogen (or deuterium) bond that has been extensively ruptured can be placed on a more quantitative basis. Evans and Polanyi suggested that for processes such as

$$AB + C \longrightarrow A + BC \quad (1)$$
$$DB + C \longrightarrow D + BC \quad (2)$$

involving similar A and D that $\Delta E_1^{\ddagger} - \Delta E_2^{\ddagger} = \alpha(\Delta H_1 - \Delta H_2)$ where α can vary between 0 and 1 and decreases with an increase in the reactivity of the attacking radical or atom.[23] It now appears

(18) R. A. Max and F. E. Deatherage, *J. Am. Oil Chem. Soc.*, 28, 110 (1951).

(19) From the pyrolysis of toluene, M. Szwarc [*J. Chem. Phys.*, 16, 128 (1948)]. From electron-impact measurements a value of 77 ± 3 has been obtained [D. O. Schissler and D. P. Stevenson, *ibid.*, 22, 151 (1954)].

(20) The following bond dissociation energies for a benzyl hydrogen atom have been recently reported: electron-impact, 95 kcal. mole^{-1}, [J. B. Farmer, I. H. S. Henderson, C. A. McDowell and L. P. Lossing, *ibid.*, 22, 1948 (1954), J. B. Farmer, F. P. Lossing, D. H. Marsden and C. A. McDowell, *ibid.*, 24, 52 (1956)]: bromination of toluene, 88 kcal. mole^{-1} [H. R. Anderson, Jr., H. A. Scheraga and E. R. Van Artsdalen, *ibid.*, 21, 1258 (1953)]: pyrolysis of toluene, 90 kcal. mole^{-1} [H. Blades, A. T. Blades and E. W. R. Steacie, *Can. J. Chem.*, 32, 298 (1954)].

(21) W. E. Vaughan, *Disc. Faraday Soc.*, 10, 314 (1951).

(22) Recently published heats of hydroperoxidation of a number of hydrocarbons [W. Pritzkow and K. A. Miller, *Ber.*, 89, 2318 (1956)] are not in disagreement with a bond dissociation energy of 90–100 kcal. if the reaction $R\cdot + O_2 \rightarrow ROO\cdot$ is exothermic by 20–30 kcal. mole^{-1}. For example, the reaction $C_6H_{12} + O_2 \rightarrow C_6H_{11}OOH$ is exothermic by 28 kcal. mole^{-1} while the bond dissociation energy of a cyclohexane carbon–hydrogen bond is about 92 kcal. mole^{-1} [J. L. Franklin, *J. Chem. Phys.*, 21, 2029 (1953)]. If $D_{(ROO-H)}$ is 90–100 kcal., it follows that $D_{(RO-O)}$.) is in the range 45–55 kcal. since $D_{(R-O\cdot)}$ is 92 kcal. [P. Gray, ref. 10].

(23) M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, 34, 11 (1938); E. C. Baughan and M. G. Polanyi, *Nature*, 146, 685 (1940); E. T. Butler and M. Polanyi, *Trans. Faraday Soc.*, 39, 19 (1943); M. G. Evans, *ibid.*, 42, 271 (1947).

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that the value of α can be used not only as a measure of the reactivity of the atom but also as a measure of the extent of bond breaking in the transition state. We have shown previously that in photochlorination α is 0.1 and suggested that this should be interpreted as meaning that the carbon–hydrogen bond is only about 10% broken in the transition state for the attack of a chlorine atom on a branched-chain hydrocarbon.[24] On the other hand, α is 0.5 for the attack of a methyl radical on an aliphatic hydrocarbon indicating that in this case the original carbon–hydrogen bond is half broken in the transition state.[25] For peroxidation a value of α of 0.39 has been found.[26,27] Values of the deuterium-isotope effect (Table III) are in agreement with these conclusions. The deuterium-isotope effect is small for the reactive chlorine atom and large for the less reactive peroxy or methyl radicals. The deuterium-isotope effect, which occurs because of the freezing out of certain vibrational frequencies in the transition state, should be 1.4 at $\alpha = 0$ and, although temperature dependent, can be calculated at $\alpha = 0.5$ (*e.g.*, $k_H/k_D = 4.7$ at 100°).[12,28] Attempts have been made to calculate α from the values of k_H/k_D by assuming a linear relationship between these quantities over the range $\alpha = 0$ to $\alpha = 0.5$ (reactions of the type under discussion with $\alpha > 0.5$ proceed with great difficulty). From the data of Table III the following values of α were calculated, Cl· (80°), $\alpha = 0.08$; $(CH_3)_3CO\cdot$, (120°), $\alpha = 0.43$; Br· (77°), $\alpha = 0.44$; ROO· (60°), $\alpha = 0.50$; $CH_3\cdot$ (125°), $\alpha = 0.50$. These values of α are in surprisingly good agreement with the experimental values.

Polar Effects in Aliphatic Substitutions.—Table III demonstrates that there is not a direct relationship between the reactivity of an atom or radical and the exothermicity of its reaction with a carbon–hydrogen bond. The value of α is a far better measure of the reactivity of an atom or radical than is the heat of the reaction. Chlorine atoms and methyl radicals react with a hydrocarbon with nearly equal exothermicity, but chlorine atoms ($\alpha = 0.1$) are far more reactive than methyl radicals ($\alpha = 0.5$), as judged from the energy of activation or deuterium-isotope effect, and less selective.[29] This is due undoubtedly to stabilization of transition states by polar resonance forms.[8,24,30] For example, transition state resonance forms such as

$$R\cdot{}^{+}H\bar{:}X \qquad R\cdot{}^{+}H\bar{:}OR \qquad R\cdot{}^{+}H\bar{:}OOR$$

should be important in the attack of atoms or radicals having a high electron affinity on a carbon–hydrogen bond. Of course, the exothermicity of the reaction cannot be completely ignored. For example, when the polar effect is held constant, such as in alkoxy and peroxy radicals, the more exothermic reaction (attack by alkoxy radical) proceeds more readily and with a lower selectivity.

Experimental

Materials.—Cumene and ethylbenzene (Phillips 99 mole % minimum) were rectified in a large Podbielniak column (>50 plates) and middle fractions having constant refractive index and boiling point selected. These fractions were combined, chromatographically filtered through activated silica gel (Davidson, 80–100 mesh) and stored under nitrogen at 0°. Cumene, b.p. 69–69.5 at 42 mm., $n^{20}D$ 1.4912; ethylbenzene, b.p. 138.5–139°, $n^{20}D$ 1.4959.[31]

α-d_1-Ethylbenzene was prepared by the reaction of lithium aluminum deuteride (Metal Hydrides Corp.) with α-phenethyl chloride.[32] The α-d_1-ethylbenzene was purified by rectification through a spinning-band Podbielniak column (*ca.* 50 plates) and chromatographically filtered through silica gel, b.p. 133–133.5°, $n^{20}D$ 1.4954. Analysis was performed by mass spectrometry at an ionizing voltage sufficiently low that the ratio of peak heights for mass numbers 106 and 105 was $>10^4$.[33] After correcting for the presence of isotopic carbon, the following analysis was obtained, ethylbenzene, 1.1%, d_1-ethylbenzene, 98.8%, d_2-ethylbenzene, 0.1%.

d_4-Ethylbenzene was prepared by the addition of deuterium (Stuart Oxygen Co.) to purified phenylacetylene (b.p. 64.5 at 48 mm., $n^{20}D$ 1.5489) at 25° in the presence of a platinum oxide catalyst. The product was rectified through a spinning-band Podbielniak column and chromatographically filtered through silica gel, b.p. 136–136.5°, $n^{20}D$ 1.4943. Analysis by mass spectrometry at reduced ionizing potential indicated the following composition, ethylbenzene, 0.05%, d_1-ethylbenzene, 0.8%, d_2-ethylbenzene, 5.2%, d_3-ethylbenzene, 20.5%, d_4-ethylbenzene, 41.5%, d_5-ethylbenzene, 31.9%. Extensive shuffling of hydrogen and deuterium atoms in the presence of a hydrogenation catalyst was expected.[34]

α-d-Cumene was prepared by the addition of deuterium chloride to the organometallic compound formed by the reaction of sodium–potassium alloy with α,α-dimethylbenzyl methyl ether.[35,36] The α,α-dimethylbenzyl methyl ether was prepared by the addition of hydrogen chloride to purified α-methylstyrene (b.p. 81.5–82° at 40 mm., $n^{20}D$ 1.5382) followed by methanolysis in the presence of potassium hydroxide. The ether was rectified through a small packed column (*ca.* 10 plates), b.p. 84.5–85°, $n^{20}D$ 1.4958, d^{20}_4, 0.946. α,α-Dimethylbenzyl methyl ether (100 g.) was added to 1.77 equivalents of potassium in the form of the sodium–potassium alloy (Na:K = 1:5, 54.5 g.) in 5 l. of ether. The deep red solution of the organometallic compound was stirred for 24 hr. under a dry nitrogen atmosphere before neutralization with 1.9 equivalents of deuterium chloride (prepared from benzoyl chloride and 11.3 g. of 99.5+% deuterium oxide).[37] The deep red color of the

(24) G. A. Russell and H. C. Brown, THIS JOURNAL, **77**, 4031, 4578 (1955).

(25) A. F. Trotman-Dickenson, *Quart. Revs.*, **7**, 198 (1953).

(26) J. L. Bolland, *Trans. Faraday Soc.*, **46**, 358 (1950).

(27) α, of course, is not necessarily a constant for a given atom or radical but may increase with a decrease in the reactivity of the carbon–hydrogen bond involved. For this discussion we will consider α to be nearly independent of the reactivity of the hydrocarbon.

(28) This calculation assumes that at $\alpha = 0.5$ all zero point energy differences in the transition states have been lost. This is thus a maximum deuterium-isotope effect.

(29) The energy of activation for attack of a chlorine atom and a methyl radical on methane are 3.8 and 14.3 kcal. mole^{-1}, respectively [H. O. Prichard, J. B. Pyke and A. F. Trotman-Dickenson, THIS JOURNAL, **77**, 2629 (1955); J. R. McNesby and A. S. Gordon, *ibid.*, **76**, 4196 (1954).

(30) Other independent evidence for polar effects in radical–hydrocarbon reactions has been presented [E. C. Kooyman, R. Van Helden and A. F. Bickel, *Koninkl. Ned. Akad. Wetenschap., Proc.*, **B56**, 75 (1953); R. Van Helden and E. C. Kooyman, *Rec. trav. chim.*, **73**, 269 (1954); C. Walling and E. McElhill, THIS JOURNAL, **73**, 1927 (1951); C. Walling and B. Miller, *ibid.*, in press.

(31) All boiling points were determined with uncalibrated iron–constantan thermocouples.

(32) E. L. Eliel, THIS JOURNAL, **71**, 3970 (1949); J. E. Johnson, R. H. Blizzard and H. C. Carhart, *ibid.*, **70**, 3664 (1948).

(33) D. P. Stevenson and C. D. Wagner, *ibid.*, **72**, 5612 (1950); R. E. Honig, *Anal. Chem.*, **22**, 1474 (1950); F. H. Field and S. H. Heatings, *ibid.*, **28**, in press (1956). All mass spectra were obtained at the General Engineering Laboratory of the General Electric Company by Mr. G. Schachter.

(34) R. L. Burwell, Jr., and A. B. Littlewood, *ibid.*, **78**, 4170 (1956).

(35) W. G. Brown, C. J. Mighton and M. Senkus, *J. Org. Chem.*, **3**, 62 (1938).

(36) K. Ziegler and B. Schnell, *Ann.*, **437**, 222 (1934).

(37) H. C. Brown and [illegible], THIS JOURNAL, **64**, 2223 (1942).

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organometallic compound was discharged completely by the first equivalent of deuterium chloride. The solution of α-*d*-cumene in ether was filtered and rectified in the spinning-band Podbielniak column, b.p. 70–70.5° at 47 mm., $n^{20}D$ 1.4908. The product was analyzed after chromatographic filtration by high resolution nuclear magnetic resonance spectroscopy, high resolution infrared spectroscopy and by mass spectrometry.

The high resolution NMR analysis was performed and interpreted by Dr. J. N. Shoolery of Varian Associates. Three different peaks in the spectra of cumene and α-*d*-cumene, each a measure of the concentration of tertiary hydrogen atoms, were compared. The relative heights of all three peaks in the spectra of α-*d*-cumene and cumene (run under comparable conditions) was 1:2.4 ± 0.1. Thus, 41.6% of the cumene molecules contained an α-hydrogen atom and 58.4% of the cumene molecules contained an α-deuterium atom in the sample of α-*d*-cumene. A possible error of ±3% seems possible in this analysis.

Analysis by mass spectrometry at low ionizing voltages (ratio of mass numbers 120 to 119 > 10^4) indicated that 0.85 deuterium atoms were present per molecule of cumene and that the distribution of deuterium was as follows, cumene, 32.8%, d_1-cumene, 52.0%, d_2-cumene, 14.0%, d_3-cumene, 1.2%.

The high resolution infrared absorption spectra were obtained and interpreted by Dr. R. S. McDonald of this Laboratory using a Perkin–Elmer Model 13U spectrometer with a lithium fluoride prism. The spectrum in the 3–4 μ region was resolved into absorption bands for carbon–hydrogen stretching vibrations which are characteristic for aromatic, methyl and tertiary hydrogen atoms. Carbon–deuterium stretching frequencies were resolved in the 4–5 μ region without resort to high resolution techniques. The assignment of frequencies is given in Table IV.

TABLE IV

ASSIGNMENT OF C–H AND C–D STRETCHING FREQUENCIES IN CUMENE AND "α-*d*-CUMENE"

R	R–H stretching frequency, cm.$^{-1}$	R–D frequency, cm.$^{-1}$	Deuterium-isotope shift
C_6H_5–	3100(weak)	..	..
	3080	2280	1.35
	3040	2250	1.35
$C_6H_5CHCH_3CH_2$–	2960	2220	1.345
	2920(weak)	..	..
$C_6H_5C(CH_3)_2$–	2880	2145	1.34

Assuming that $C_6H_5CHCH_3CH_2$–D and $C_6H_5C(CH_3)_2$–D have similar extinction coefficients, it is calculated that not more than 3% of the cumene molecules contained a β-deuterium atom.

From these observations we conclude that 0.24 (0.85 − 0.58 − 0.03) deuterium atoms were present as aromatic deuterium atoms per cumene molecule in the sample of α-*d*-cumene. This is in agreement with the observation that in the NMR spectra the area of the aromatic-hydrogen peak was slightly reduced for the sample of α-*d*-cumene. The neutralization of α,α-dimethylbenzylpotassium is being investigated further in an attempt to prepare pure α-*d*-cumene and to elucidate the mechanism of the formation of ring-deuterated cumenes.

AIBN was recrystallized twice from acetone, m.p. 104–105°. The AIBN was used as a 0.01 *M* solution in benzene which was stored at 0°. The oxygen was 99.3–99.5% pure, the principal impurities being nitrogen and hydrogen.

Procedure.—Oxidations were performed in the general manner described previously.[38] The desired amount of 0.1 *M* AIBN solution was first pipetted into the oxidation flask and the benzene removed under reduced pressure at 0°. The desired amount of hydrocarbon was then weighed into the flask (±0.001 g.) and the oxidation flask attached to a gas buret. The flask, which was a modified 50-ml. erlenmeyer flask, was evacuated at Dry Ice temperature and filled with oxygen five times. After warming to room temperature in the presence of an atmosphere of oxygen, the flask was placed in a shaking rack in a thermostated oil-bath and vigorously shaken while the absorption of oxygen was followed by manual control of the mercury level in a gas buret.

The densities of the deuterated hydrocarbons at 60° were calculated from the densities of cumene, d^{60}_4 0.830,[39] and ethylbenzene, d^{60}_4 0.831,[39] by the equation of McLean and Adams.[40]

Analytical.—The analyses of the deuterated hydrocarbons have been discussed already. The oxidates were analyzed for peroxidic oxygen by the iodimetric procedure of Kokatnur and Jelling[41] and the stannous chloride procedure of Hargrave and Morris.[42] The iodimetric procedure involved the addition of 1 ml. of oxidate to 25 ml. of 99% isopropyl alcohol containing 1 ml. of glacial acetic acid and 1 ml. of saturated potassium iodide solution. This solution was refluxed for 5 minutes under an atmosphere of carbon dioxide, diluted with 25 ml. of water and titrated with 0.1 *N* sodium thiosulfate. There was no blank correction. The stannous chloride procedure used consisted of the reaction of 1 ml. of the oxidate with a mixture of 10 ml. of glacial acetic acid and 10.0 ml. of 0.05 *M* stannous chloride. After 1 hr. at room temperature under a nitrogen atmosphere, the solution was titrated with 0.1 *N* potassium triiodide solution. In this analysis a blank was always run and the concentration of hydroperoxide in the oxidate was proportional to the difference between the blank titer and the titer of the reaction containing the oxidate. The agreement between the two methods (Table II) is somewhat better than expected from the data of Hargrave and Morris.[42]

Analyses for acetophenone in oxidized ethylbenzene were performed by infrared absorption. An appropriate series of standards were prepared and the absorption at 5.9 μ measured by a Perkin-Elmer model 21 spectrometer and plotted as a function of concentration. Attempts to analyze for α-phenethanol by a similar procedure were not successful because of the lack of strong and unique absorption in α-phenethanol.

SCHENECTADY, NEW YORK

(38) G. A. Russell, THIS JOURNAL, **78**, 1041 (1956).

(39) G. Egloff, "Physical Constants of Hydrocarbons," Vol. III, Reinhold Pub. Corp., New York, N. Y., 1946.

(40) A. McLean and R. Adams, THIS JOURNAL, **58**, 804 (1936).

(41) V. R. Kokatnur and M. Jelling, *ibid.*, **63**, 1432 (1941).

(42) K. R. Hargrave and A. L. Morris, *Trans. Faraday Soc.*, **52**, 89 (1956).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

A New Synthesis and the Stereochemistry of Some 2,3-Disubstituted Dioxanes

BY R. K. SUMMERBELL AND GREGORY J. LESTINA

RECEIVED FEBRUARY 11, 1957

A new synthesis of dioxanes involving the condensation of a diene, a mercuric salt and a glycol has been developed. The product from butadiene, mercuric nitrate and ethylene glycol, after precipitation as the halide and replacement of the halomercuri group with iodine, yielded a mixture of *cis*- and *trans*-2,3-bis-(iodomethyl)-*p*-dioxanes. Nitric acid oxidation of the *trans*-bis-(iodomethyl) compound produced the *trans*-dicarboxylic acid in good yields and without isomerization. The anhydride of the *trans*-acid was converted to the *cis*-anhydride by extended refluxing in acetic anhydride, and hydrolysis of the *cis*-anhydride yielded the *cis*-diacid. The facts that *trans*-diacid could be partially resolved, but that *cis*-diacid could not, were used for definite assignment of configuration. Oxidation of the *cis*-2,3-bis-(iodomethyl)-*p*-dioxane failed to produce a diacid but did produce *cis*-3-hydroxymethyl-2-*p*-dioxanecarboxylic lactone. When *cis*-2,3-bis-(*p*-toluenesulfonatomethyl)-*p*-dioxane, which had been formed from the glycol obtained by the reduction of dimethyl *cis*-2,3-*p*-dioxanedicarboxylate, was treated with sodium iodide, the *cis*-bis-(iodomethyl)-*p*-dioxane was obtained, thus relating the latter to the *cis*-diacid. In the original synthesis, equilibration conditions produced predominantly the *trans* compound, indicating it to be more stable than the *cis* isomer.

Introduction

For several years a great deal of study has been devoted to the structures, configuration, properties and theoretical treatment of cyclohexane derivatives. It would seem desirable to have considerable similar information for comparison purposes concerning six-membered ring compounds containing hetero atoms such as dioxanes.

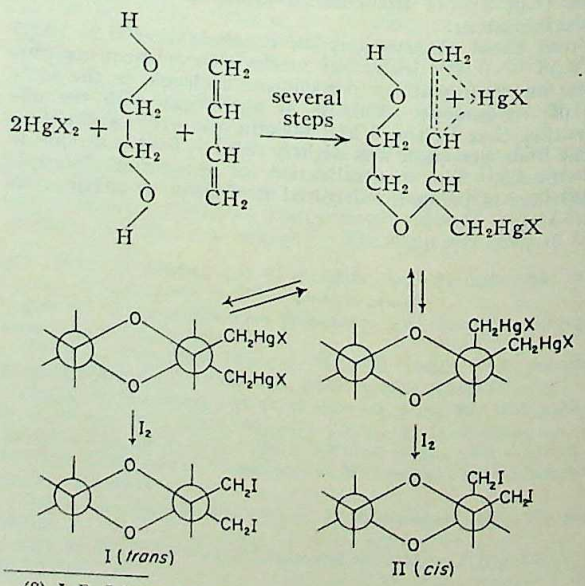
The structures and configuration of several 2,5- and 2,6-disubstituted dioxanes have been definitely established.[1,2] Although a number of 2,3-disubstituted dioxanes have been reported, and a very few speculative assignments of configuration have been made[3–5] on the basis of the meager available evidence, the configuration of no 2,3-disubstituted dioxane is known with certainty. Most of the 2,3-disubstituted dioxanes that have been prepared were not suitable for such studies, either because both members of a pair of isomers were not available, or because the isomers contained no convenient reactive functional group. We therefore decided to attempt the synthesis of appropriate pairs of isomeric, 2,3-disubstituted dioxanes and the determination of their configuration by conclusive chemical means.

We have recently proposed a mechanism[6] to account for the products and isomer ratios when aqueous mercuric salt solutions are used to cyclize allyl alcohol and allyl ether. The same mechanism may be used to explain the recent similar synthesis of dioxanes from allyl ethers of polyols by Werner and Scholz.[7] On the basis of this mechanism it seemed that a new synthesis of dioxanes involving the mercuric salt condensation of dienes with glycols might prove feasible. Furthermore, these seemed to be a good chance of obtaining the desired pairs of *cis* and *trans* isomers, as both the meso and racemic isomers had been formed in good yields when butadiene was condensed[8] with methanolic solutions of mercuric salts.

Discussion

Mercuric nitrate dissolved in aqueous ethylene glycol was observed to condense readily with 1,3-butadiene to form 2,3-disubstituted dioxanes which, after the appropriate sequence of reactions, yielded a mixture of *cis*- and *trans*-2,3-bis-(iodomethyl)-*p*-dioxanes. When the condensation reaction was conducted in the presence of added strong acid, the proportion of *trans* isomer was increased as was the total yield of dioxane compound.

The *trans* isomer I was isolated easily by simple recrystallization, since it was formed in the larger proportion from the acid synthesis and since it was slightly less soluble than the *cis* compound. The *cis* isomer II was isolated by slowly growing crystals from a methanolic solution of both isomers. Rhombic crystals of I and rod-shaped crystals of II formed and were separated by hand picking. The crystals of II were collected and again subjected to the same procedure. The rod-shaped crystals melted at 83.5–84° in a capillary tube, but on a Fisher–Johns block the compound melted at 77–84°.



(1) R. K. Summerbell and James R. Stephens, THIS JOURNAL, **76**, 731, 6401 (1954); **77**, 6080 (1955).
(2) E. Augdahl, *Acta Chem. Scand.*, **9**, 1237 (1955).
(3) N. Stumpf, *Z. Elektrochem.*, **57**, 690 (1953).
(4) R. K. Summerbell and B. Nelson, THIS JOURNAL, **77**, 544 (1955).
(5) J. Boeseken, F. Tellegen and P. C. Henriquez, *Rec. trav. chim.*, **54**, 733 (1935).
(6) R. K. Summerbell, Gregory J. Lestina and Hal Waite, THIS JOURNAL, **79**, in press (1957).
(7) L. H. Werner and C. R. Scholz, *ibid.*, **76**, 2701 (1954).
(8) J. R. Johnson, W. H. Jobling and G. W. Bodamer, *ibid.*, **63**, 131 (1941).

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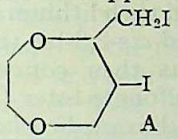
Early experimental results were difficult to interpret until it was realized that we were dealing with two crystalline modifications, IIa and IIb, which were readily interconvertible.

Infrared spectrograms in carbon disulfide solution indicated that I and II were different compounds and that samples of each contained little if any of the other. However, IIa and IIb gave identical infrared spectrograms in carbon disulfide solution, but in potassium bromide pellets a small difference was observed in the region of 10.94 μ where IIa possessed a medium strong absorption which IIb did not have.

It seemed probable that I and II were dioxanes from the method of synthesis, since six-membered rings form more readily than seven-membered ones[9] and 1,4-additions of mercuric salts to butadiene have not been observed, even though carefully sought in a similar situation by McNeely and Wright.[10] If such an addition had occurred here, the product would be a dioxacycloheptane such as A. Chemical evidence supporting the *p*-dioxane



A

structure of I was furnished by the hot concentrated nitric acid oxidation of the iodide I in good yield to a single dicarboxylic acid IV of appropriate empirical formula. Such a compound could hardly be formed by the oxidation of A. Later the smooth conversion of IV back to I afforded additional evidence that Compound I possessed a dioxane rather than a dioxacycloheptane structure.

The presence of a dioxane nucleus in the lower melting iodide II was indicated by the conversion of the *cis*-dicarboxylic acid IX to the *cis*-diiodide II, thus eliminating A as a possible structure for II.

In a somewhat analogous case Johnson[8] and coworkers showed that the two forms of 1,4-diiodo-2,3-dimethoxybutane were diastereoisomers and not structural isomers, since both could be converted to 2,3-dimethoxy-1,3-butadiene by means of a base elimination of hydrogen iodide.

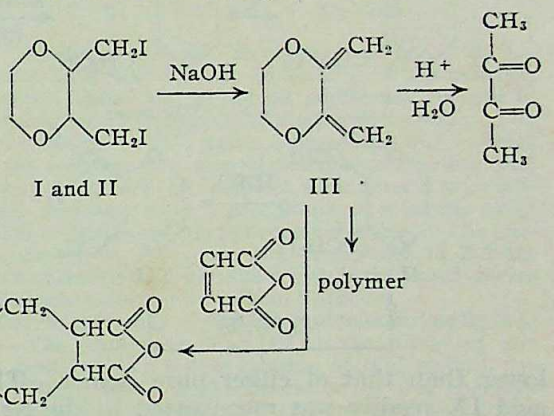
The application of this elimination reaction to 2,3-bis-(iodomethyl)-*p*-dioxane resulted in the formation of an easily polymerized diene which was characterized as 2,3-bis-(exomethylene)-*p*-dioxane (III). This diene readily underwent a Diels–Alder reaction with maleic anhydride to form a compound believed to be 5,8-dioxaoctalin-*cis*-2,3-dicarboxylic anhydride. Substance III was hydrolyzed in dilute hydrochloric acid and, upon treatment of the hydrolysate with phenylhydrazine, a compound was obtained which was identified as the phenylosazone of biacetyl.

The *trans*-iodide I was oxidized to *trans*-2,3-*p*-dioxanedicarboxylic acid (IV) in 73% yield by the action of hot, concentrated nitric acid.[1] The acid which was isolated was believed to be a pure compound and not a mixture of acids by virtue of its unique infrared spectrogram, neutral equivalent, combustion data and sharp melting point.

(9) V. Prelog, *J. Chem. Soc.*, 420 (1950).

(10) K. H. McNeely and G. F. Wright, THIS JOURNAL, **77**, 2553 (1955).

The *trans*-acid IV was converted to *trans*-2,3-*p*-dioxanedicarboxylic anhydride (V) by the action of refluxing acetic anhydride. The empirical formula was indicated by the combustion and neutral equivalent data. The monomeric nature of the anhydride was indicated by the molecular weight of a freshly prepared sample, but when the anhydride was allowed to stand at room temperature for a month, its molecular weight rose from the expected 158 units to 200 units. Upon hydrolysis of the anhydride V the acid IV was regenerated.



I and II III

At one stage in our work, we became suspicious that epimerization might accompany nitric acid oxidation. To test this possibility, we applied our oxidation procedure to a much more sensitive case, the *meso* and racemic diiodo-2,3-dimethoxybutanes and obtained the appropriate corresponding dimethoxysuccinic acids without evidence of isomerization. Such chain compounds would probably be more easily isomerized than our ring compounds. This particular reaction had additional incidental interest in that it supplied chemical evidence to support the supposed configurations of the 1,4-diiodo-2,3-dimethoxybutanes which had been assigned previously on the basis of physical evidence only,[8] when attempted chemical proof by oxidation failed to yield significant products.

As a second test, the acid IV was converted to the iodide I from which it originally was derived by the following reactions which have been shown to proceed without isomerization[1,11] in similar cases. The *trans*-acid IV was esterified with diazomethane to yield dimethyl *trans*-2,3-*p*-dioxanedicarboxylate (VI) which was subsequently reduced with lithium aluminum hydride to an oil assumed to be *trans*-2,3-bis-(hydroxymethyl)-*p*-dioxane. This glycol was converted to *trans*-2,3-bis-(*p*-toluenesulfonatomethyl)-*p*-dioxane (VII) which was then treated with sodium iodide in acetone to yield the *trans*-iodide I.

By extended refluxing in acetic anhydride the *trans*-anhydride V was converted into a new compound which, because of its combustion and neutral equivalent data as well as its melting point, was assumed to be *cis*-2,3-*p*-dioxanedicarboxylic anhydride (VIII). The *cis*-anhydride was hydrolyzed in dilute hydrochloric acid to yield *cis*-2,3-*p*-dioxanedicarboxylic acid (IX). When a mixture of the *cis*-acid IX and the *trans*-acid IV was melted, the melting point of the mixture was considerably

(11) G. A. Harris and L. N. Owen, *J. Chem. Soc.*, 389 (1953).

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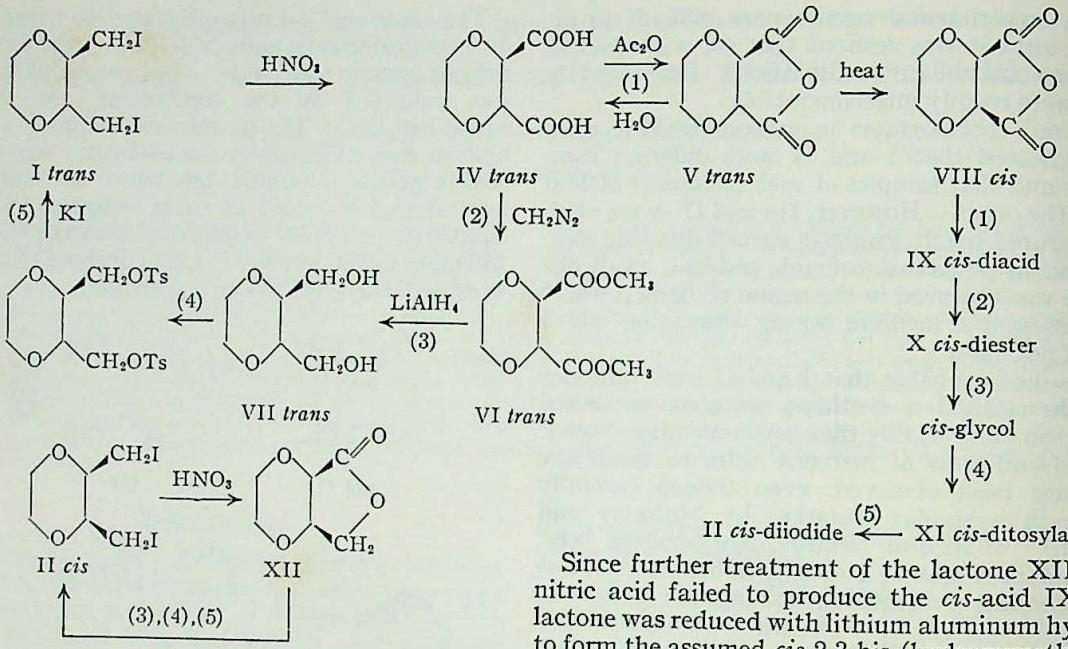


lower than that of either pure isomer. The *cis*-acid IX readily was reconverted to the *cis*-anhydride VIII by the action of refluxing acetic anhydride.

The geometrical nature of the isomerism was indicated by the thermal conversion of the *trans*-anhydride V to the isomeric *cis* compound VIII. The conversion of the *cis*-acid IX to a mixture composed of 58 ± 10% *cis* and 42 ± 10% *trans* by means of aqueous potassium hydroxide, as well as the conversion of the *trans*-acid to a mixture composed of 27 ± 10% *cis* and 73 ± 10% *trans* by the same means, further substantiates the belief that *cis–trans* isomerism rather than skeletal rearrangement is involved.

The relationship between the *cis*-acid IX and the *cis*-iodide II was shown by the following series of reactions, all of which are known to proceed with lack of isomerization.[1,11] The *cis*-acid was esterified with diazomethane to yield dimethyl *cis*-2,3-*p*-dioxanedicarboxylate (X) which was subsequently reduced with lithium aluminum hydride to an oil assumed to be the *cis*-2,3-bis-(hydroxymethyl)-*p*-dioxane. This glycol was converted to *cis*-2,3-bis-(*p*-toluenesulfonatomethyl)-*p*-dioxane (XI) which was treated with sodium iodide in acetone to form the *cis*-iodide II.

When the *cis*-iodide II was treated with concentrated nitric acid in an attempt to form the *cis*-acid IX, a solid was obtained which, when purified, dissolved in water to give a solution neutral to litmus, although its infrared spectrogram indicated the presence of a carbonyl group (strong absorption at 5.6–5.7 μ) and which gave a melting point and combustion analysis different from any of the acids or anhydrides in the dioxane series. The possibility of having formed *cis*-3-hydroxymethyl-2-*p*-dioxanecarboxylic lactone (XII) seemed credible since five-membered rings fused in a *cis* manner to six-membered rings form quite readily.[12]

(12) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, pp. 621 622.

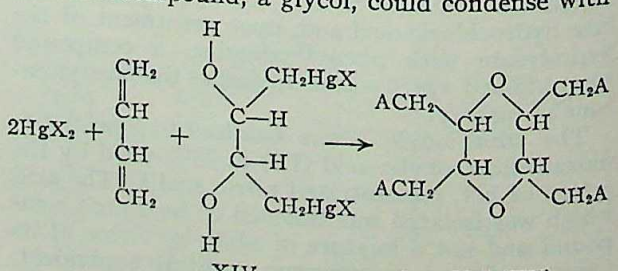
Since further treatment of the lactone XII with nitric acid failed to produce the *cis*-acid IX, the lactone was reduced with lithium aluminum hydride to form the assumed *cis*-2,3-bis-(hydroxymethyl)-*p*-dioxane which was then converted to the now known *p*-toluenesulfonate ester (XI).

The *trans*-2,3-*p*-dioxanedicarboxylic acid is the racemic modification and hence should be resolvable into its optical antipodes, whereas the *cis*-acid is the *meso* form and hence would be non-resolvable.

It was found experimentally that the acid IV could be resolved partially, whereas no resolution could be effected with the acid IX. Hence IV was assigned the *trans* configuration and IX was designated the *cis* isomer.

Chemical evidence already mentioned is consistent with this assignment; for example, thermal conversion of the *trans*-anhydride V to the *cis*-anhydride VIII, since one would expect the *trans*-anhydride to be the less stable compound.[13] The behavior of the two methiodides toward nitric acid, where one (I) produces a dibasic acid and the other (II) a lactone, is also pertinent, since the *cis*-lactone would be quite stable in contrast to a *trans*-lactone which, even if formed,[12] would probably be easily hydrolyzed and oxidized further to the *trans*-diacid.

If butadiene is allowed to react with an aqueous mercuric nitrate solution in the absence of an alcohol, 1,4-dinitratomercuri-2,3-dihydroxybutane (XIV) would be the expected product.[14] Our ideas of the mechanism of this reaction[6] suggested that this compound, a glycol, could condense with



(13) A. Baeyer, *Ann.*, **258**, 213 (1890).

(14) A. N. Nesmeyanov and I. F. Lutsenko, *Bull. acad. sci. U.S.S.R classe sci. chim.*, 386 (1944).

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more butadiene and mercuric salt to form a tetrasubstituted dioxane (XV), which would probably react with iodine to form 2,3,5,6-tetra-(iodomethyl)-*p*-dioxane (XVI). Furthermore, our mechanism implies that if XIV were treated with strong acid, part of it should be decomposed, regenerating the requisite butadiene and mercuric salt to react with the portion that was not decomposed. When this series of reactions was attempted, a small amount of a compound of the correct analysis and molecular weight for 2,3,5,6-tetra-(iodomethyl)-*p*-dioxane was obtained.

We have previously reported the properties of a number of 2,5- and 2,6-disubstituted dioxanes and explained them in terms of a chair conformation and the equatorial–axial concept of Becket, Pitzer and Spitzer.[15] Assuming a chair conformation, the equatorial–axial isomer, the *cis*-2,5- and the *trans*-2,6-, was found to have a lower melting point and to be less stable than its corresponding more symmetrical isomer. In the present series of 2,3-disubstituted dioxanes, the *cis* compounds would be expected to have the lower melting points and the lesser stabilities. Some of the melting points conform to this prediction and some do not, but this is not particularly serious, since as yet only a few compounds have been made, and since in the related cyclohexane compounds, occasional anomalies in melting points have been observed.[11,16] That the *trans* isomer is the more stable one is indicated quite definitely by our original synthesis, since the yield and proportion of that isomer were increased by equilibration conditions of high acidity and long reaction time. In previous work,[6] the same conditions were found to favor the *trans*-2,5- and the *cis*-2,6-isomers.

The assumption of a chair form for most dioxanes would seem to follow current trends. For instance, Brown, Brewster and Schechter[17] have brought together a large amount of evidence indicating that " . . . an oxygen atom in a ring system can result in the same type of conformational effects as a methylene group." They cite several examples involving two oxygens in the ring.

On the other hand, Kumler and Huitric[18] point out: "When heteroatoms . . . replace CH_2 groups in the cyclohexane ring, the energies of the flexible forms are going to be less, due to fewer intereactions between consecutive CH_2 groups and to more favorable angles in the rings." In our studies thus far, the behavior of dioxane derivatives has paralleled that of cyclohexanes very closely.

Acknowledgments.—We wish to express our gratitude to the Abbott Foundation of Northwestern University for a grant of financial aid and to the Allied Chemical and Dye Corporation for a Fellowship held by G.J.L.

Experimental

A. The Formation of 2,3-Bis-(iodomethyl)-*p*-dioxane. 1. The Preparation of 2,3-Bis-(nitratomercurimethyl)-*p*-dioxane.—To 243.0 g. (1.12 moles) of mercuric oxide was added a solution of 300 ml. of concd. (sp. gr. 1.42, 4.7 moles) nitric acid and 150 ml. of water. When solution was complete, there was put in an additional 100 ml. of water and 500 ml. of freshly distilled ethylene glycol. The mixture was cooled to 20°, and 1,3-butadiene was bubbled through the solution at a rate of 2 bubbles/second. The reaction was assumed to be complete when after 3 hr. a 0.5-ml. aliquot no longer gave a precipitate of mercuric oxide when added to a 10% sodium hydroxide solution. The mixture was cooled to −5°, and the precipitate of 2,3-bis-(nitratomercurimethyl)-*p*-dioxane which had formed during the reaction was collected by suction filtration.

Table I

Melting Points of Dioxane Derivatives

	2,3-*cis*	2,3-*trans*	2,5-*cis*	2,5-*trans*	2,6-*cis*	2,6-*trans*
Diacid	183.5	176	178	275	178	162
Dimethylester of diacid	63.5	59	92	143	103	89
Diacid anhydride	116.5	201.5	75	..	106	..
Bis-iodomethyl	77.5 + 84	90	97	158	92	70
Bis-*p*-toluenesulfonatomethyl	97	105	88	205		

2. The Preparation of 2,3-Bis-(iodomercurimethyl)-*p*-dioxane.—The precipitate described in the preceding section was dissolved in a 2-liter solution of 10% sodium hydroxide. There was a slight liberation of free mercury accompanying this solution. To this mixture was added a solution of 133 g. (0.801 mole) of potassium iodide dissolved in 500 ml. of water. A precipitate of 2,3-bis-(iodomercurimethyl)-*p*-dioxane formed. After the solution had been tested for completeness of precipitation, the precipitate was collected by suction filtration. After drying for 24 hr. at 45°, there was obtained 276 g. (0.359 mole), m.p. 196–198°.[19]

3. The Preparation of 2,3-Bis-(iodomethyl)-*p*-dioxane. a. The Isolation of *trans*-2,3-Bis-(iodomethyl)-*p*-dioxane (I).—To a mixture of 800 ml. of chloroform and 200 ml. of water containing 183 g. (0.718 mole) of iodine there was added the substance described in the previous section. The mixture was vigorously stirred and refluxed for 12 hr. When the contents of the flask had cooled, the excess iodine was removed by washing the mixture with a 10% solution of sodium thiosulfate. The mercuric iodide was removed by solution in aqueous potassium iodide. The chloroform layer was separated and evaporated under reduced pressure and the residue dissolved in boiling methanol and filtered. When the solution was cooled slowly, there was obtained 77.0 g. (0.209 mole) of I, m.p. 89–90°, which upon further recrystallization from methanol, deposited rhombic crystals, m.p. 89.5–90°.

Anal. Calcd. for $C_6H_{10}O_2I_2$: C, 19.58; H, 2.71; mol. wt., 368. Found: C, 19.69; H, 2.71; mol. wt., Rast method, 369.

Evaporation of the methanolic mother liquor deposited 42.0 g. (0.114 mole) of crystals, m.p. 57–70°, which, by virtue of the absorbancies in its infrared spectrogram, was adjudged to be a mixture of *cis*- and *trans*-2,3-bis-(iodomethyl)-*p*-dioxane.

Anal. Calcd. for $C_6H_{10}O_2I_2$: C, 19.58; H, 2.71. Found: C, 19.52; H, 2.53.

Thus there was obtained a total of 119 g. (0.323 mole) of 2,3-product for a yield of 56% based on the number of moles of mercuric salt used in the initial reaction. In a similar sequence of reactions, 32 g. (0.1 mole) of mercuric acetate without the addition of any strong acid was treated with excess 1,4-butadiene. There was obtained, after the appropriate sequence of reactions, 7.5 g. (0.02 mole) of 2,3-product, m.p. 64–72°, for a yield of 40%.

b. The Isolation of *cis*-2,3-Bis-(iodomethyl)-*p*-dioxane (II).—The lower melting crops, when dissolved in methanol and allowed to stand in beakers, slowly deposited crystals of the *cis* and *trans* isomers. The *cis* isomer appeared as rod-shaped crystals which could be separated from the rhombic crystalline *trans* isomer by hand picking. The

(15) C. W. Becket, K. S. Pitzer and R. Spitzer, This Journal, **69**, 2488 (1947); see also S. Siegel, *ibid.*, **75**, 1317 (1953).
(16) L. N. Owen and Robis, *J. Chem. Soc.*, 320 (1949).
(17) H. C. Brown, J. H. Brewshter and H. Schecter, This Journal, **76**, 467 (1954).
(18) W. D. Kumler and A. C. Huitric, *ibid.*, **78**, 3369 (1956).
(19) All melting points were taken on a Fisher–Johns block unless otherwise indicated.

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crystals of the *cis* isomer so obtained were recrystallized from methanol and from hexane. Although its melting point was not sharp, it was assumed to be free of the *trans* isomer because of the lack of the strong *trans* absorption at 10.6 μ in its infrared spectrogram.

When this substance was dissolved in boiling hexane and slowly cooled, needle-shaped crystals (IIa) appeared, m.p. 77–77.5°. The compound was dried at 30° and 0.1 mm. for 12 hr. and the melting point remained unchanged.

Anal. Calcd. for $C_6H_{10}O_2I_2$: C, 19.58; H, 2.71; mol. wt., 368. Found: C, 19.72; H, 2.58; mol. wt., Rast method, 368.

When IIa was melted in a capillary or when melted on a steam-bath and suddenly cooled, the melting point rose to 83.5–84° (IIb). A mixed melting point with the 77.5° isomer melted at 83–84°.

Anal. Calcd. for $C_6H_{10}O_2I_2$: C, 19.58; H, 2.71. Found: C, 19.48; H, 2.64.

Both forms depress the *trans* isomer in a mixed melting point determination.

TABLE II

MIXED MELTING POINTS OF THE 2,3-DIIODIDES

Components	M.p., °C.
I and IIa	60–70
I and IIb	63–73
IIa and IIb	83–84

When IIb was dissolved in hot hexane and the solution allowed to cool slowly, there were obtained fine needles, m.p. 77–77.5°. When IIa was melted at 80° on the Fisher–Johns block and the liquid seeded with a crystal of IIb, the liquid slowly solidified and melted at 83.5–84°.

In carbon disulfide solution, forms IIa and IIb gave identical infrared spectrograms. In a 2% mixture of the iodides in potassium bromide, form IIb had a medium strong absorption at 10.94 which form IIa did not possess. The pellets weighed *ca.* 60 mg. and were formed under 6000 p.s.i.

B. **The Synthesis of 2,3-Bis-(exomethylene)-*p*-dioxane (III). 1. The Preparation of III.**—In a 1-liter claisen flask fitted with an addition funnel and a condenser there was placed 100 ml. of carbitol and 44 g. (1.1 moles) of sodium hydroxide dissolved in 50 ml. of water. The temperature of the heating bath was kept between 200–210° so that a slow distillation occurred. By means of the addition funnel 110 g. (0.3 mole) of 2,3-bis-(iodomethyl)-*p*-dioxane suspended in 200 ml. of an equivolume water–carbitol mixture was added in small portions. Each addition was followed by the sudden ebullition of vapor which condensed to give a milky liquid composed of water and III which was collected in a receiver immersed in an ice–salt-bath and under an atmosphere of nitrogen. When the addition of the iodide was completed, 50 ml. of a water–carbitol mixture was added and the heating continued until the distillate became clear. The distillate separated into two layers, the upper layer of water and the lower layer of III. Substance III was removed and dried by means of anhydrous sodium carbonate and stored at −78° under a nitrogen atmosphere. Compound III was considerably soluble in water, hence there was obtained only 14 g. (0.12 mole) of diolefin for a 40% yield, $n^{20}D$ 1.4922.

2. The Polymerization of III.—Substance III, when allowed to stand at 25°, polymerizes noticeably within 5 minutes. At the end of 24 hr. a white, glass-like polymer was obtained which did not melt at 240°.

3. The Hydrolysis of III.—To 40 ml. of water containing two drops of 12 *N* hydrochloric acid 1.0 g. (0.009 mole) of III was added. The mixture was warmed gently for 15 minutes and then allowed to stand overnight. Upon standing, the solution assumed a canary-yellow color. The phenylosazone of biacetyl was prepared according to the method listed by Shriner and Fuson.[20,21] There was obtained 0.75 g. (0.0028 mole) of substance which was assumed to be the phenylosazone of biacetyl, m.p. 243–244° (lit. m.p. 242–243°).[21] There was no depression in the melting point when this osazone was mixed with an authentic sample of the phenylosazone of biacetyl.

Anal. Calcd. for $C_{16}H_{18}N_4$: N, 21.04. Found: N, 21.22.

4. The Reaction of III with Maleic Anhydride.—To 30 ml. of benzene containing 2.0 g. (0.020 mole) of maleic anhydride and 0.5 g. of hydroquinone under a nitrogen atmosphere there was added 2.0 g. (0.018 mole) of III. The ensuing reaction was exothermic so that cooling became necessary. After the mixture was allowed to stand overnight, the benzene was removed under reduced pressure. The residue was extracted twice with 10 ml. of ethyl ether to remove the hydroquinone. The resulting solid was recrystallized from a hexane–benzene mixture to yield 2.22 g. (0.0105 mole) of 5,8-dioxaoctalin-*cis*-2,3-dicarboxylic anhydride, m.p. 81.5–82°, for a 58.3% yield.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.79; neut. equiv., 105. Found: C, 57.36; H, 4.67; neut. equiv., 108.

5. The Reaction of III with Mercuric Acetate in Ethylene Glycol.—To a solution of 200 ml. of ethylene glycol and 10 ml. of acetic acid containing 64 g. (0.036 mole) of mercuric acetate there was added 4.0 g. (0.036 mole) of III. After 4 hr., a yellow gelatinous precipitate formed which was removed by filtration. This precipitate did not dissolve in aqueous sodium hydroxide but did take up iodine in the replacement reaction. There was obtained 0.15 g. of substance, m.p. 118–118.5°, which smelled similar to iodoform and which did not depress authentic iodoform in a mixed m.p. determination.

Aqueous potassium iodide was added to the filtrate of the reaction mixture and a precipitate formed. This precipitate was treated with excess iodine in chloroform for 2 hr. Upon evaporation of the chloroform under reduced pressure there was obtained 0.56 g. (0.0013 mole) of compound which, after crystallization from methanol, melted at 136° and was assumed to be 4a,8a-bis-(iodomethyl)-1,4,5,8-tetroxadecalin.

Anal. Calcd. for $C_8H_{12}O_4I_2$: C, 22.55; H, 2.83. Found: C, 22.66; H, 2.87.

C. **The Oxidation of *trans*-2,3-Bis-(iodomethyl)-*p*-dioxane (I). 1. The Formation of *trans*-2,3-*p*-Dioxanedicarboxylic Acid (IV).**—To 2 liters of concd. (sp. gr. 1.42) nitric acid there was added 161 g. (0.44 mole) of I. The mixture was heated on a steam-bath until only a solid remained. There was obtained 56.5 g. (0.32 mole) of impure IV for a 73% yield. The acid was recrystallized by dissolving it in boiling acetone, adding hexane until a slight cloudiness developed and then allowing the mixture to cool slowly to room temperature. Crystals of IV were thus obtained melting at 175–176°.

Anal. Calcd. for $C_6H_8O_6$: C, 40.91; H, 4.57; neut. equiv., 88.1. Found: C, 40.95; H, 4.50; neut. equiv., 88.9.

2. *trans*-2,3-*p*-Dioxanedicarboxylic Anhydride (V).—A sample, 17.6 g. (0.10 mole), of IV was refluxed in 100 ml. of acetic anhydride for 1 hr. After one-half of the solvent was distilled under reduced pressure, the mixture was allowed to cool to room temperature. Crystals formed which, after collection by filtration, weighed 10.8 g. (0.068 mole) for a 68% yield of impure V. Further crystallization from acetic anhydride produced the solid, m.p. 201–201.5°.

Anal. Calcd. for $C_6H_6O_4$: C, 45.57; H, 3.83; neut. equiv., 79; mol. wt., 158. Found: C, 45.72; H, 3.75; neut. equiv., 79.6; mol. wt., Rast method, 165; mol. wt., Rast method after one month, 200.

3. The Hydrolysis of V.—To 10 ml. of water containing 2 drops of 12 *N* hydrochloric acid there was added 1.0 g. (0.0063 mole) of V, and the mixture was heated for 1 hr. on a steam-bath. When the excess solvent was removed under reduced pressure, there was obtained 0.82 g. (0.0047 mole), yield 74%, of IV which, after recrystallization from acetone–hexane, melted at 175–176° and did not depress the melting point of authentic IV in a mixed m.p. determination.

D. **The Conversion of *trans*-2,3-*p*-Dioxanedicarboxylic Acid (IV) to *trans*-2,3-Bis-(iodomethyl)-*p*-dioxane (I). 1. The Formation of Dimethyl *trans*-2,3-*p*-Dioxanedicarboxylate (VI).**—To 100 ml. of ethyl ether containing a suspension of 3.0 g. (0.017 mole) of IV there was added an ethereal solution of diazomethane[22] until the yellow color of the diazomethane persisted. The ether solution was allowed to

(20) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 117.

(21) R. W. Balcom, THIS JOURNAL, **39**, 315 (1917).

(22) [illegible], Chemistry, **15**, 4 (1935).

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stand for 24 hr. and was then filtered. The filtrate was evaporated to dryness by heating and a colorless oil remained which solidified on standing. After recrystallization from ethyl ether there was obtained 2.5 g. (0.012 mole) of VI, m.p. 59°, for a 71% yield.

Anal. Calcd. for $C_8H_{12}O_6$: C, 47.05; H, 5.92. Found: C, 47.34; H, 5.60.

2. **The Reduction of VI with Lithium Aluminum Hydride.**—To 150 ml. of anhydrous ethyl ether containing a suspension of 2.0 g. (0.052 mole) of lithium aluminum hydride there was added slowly 2.34 g. (0.0115 mole) of VI dissolved in 50 ml. of ethyl ether. The reaction was mildly exothermic. The mixture was refluxed for 4 hr., and then 2 ml. of methyl alcohol was added to destroy the excess anhydride reagent. To this mixture was added 9 ml. of water and the reaction was allowed to stand overnight. The hydroxides were precipitated in the form of pellets which could be removed easily by filtration. This hydroxide precipitate was extracted in a Soxhlet apparatus for three days. Upon evaporation of the combined ether solvents there was obtained *ca.* 1.4 g. of a colorless oil which was assumed to be the *trans*-2,3-bis-(hydroxymethyl)-*p*-dioxane.

3. **The Preparation of *trans*-2,3-Bis-(*p*-toluenesulfonatomethyl)-*p*-dioxane (VII).**—The *p*-toluenesulfonate derivative was made from the oil from the previous experiment according to the method of Tipson.[23] There was obtained 1.26 g. (0.0025 mole) of VII which, after repeated recrystallization from acetone–hexane, melted at 105° for an overall yield of 24% from the dimethyl ester.

Anal. Calcd. for $C_{20}H_{24}O_8S_2$: C, 52.61; H, 5.29. Found: C, 52.53; H, 5.05.

4. **The Conversion of VII to I.**—To 30 ml. of anhydrous acetone[24] containing 2.0 g. (0.013 mole) of anhydrous sodium iodide there was added 0.46 g. (0.001 mole) of VII. The solution was refluxed for 6 hr. during which time a precipitate formed. The acetone was evaporated by means of an air jet, and water was added to the residual solid. The insoluble material (I) was collected by filtration. There was obtained 0.36 g. (0.0098 mole) of compound for a 98% yield. The substance was recrystallized from methanol to yield crystals, m.p. 89.5–90°, which gave no depression with authentic I in a mixed m.p. determination. The infrared spectrogram of this compound was identical to that of authentic I.

E. **The Formation of *cis*-2,3-*p*-Dioxanedicarboxylic Anhydride (VIII).** 1. **The Isomerization of V.**—A mixture of 70 ml. of acetic anhydride and 10.0 g. (0.068 mole) of the *trans*-anhydride V was refluxed for 9 hr. During this time the reaction mixture turned dark brown. The solvent was distilled at reduced pressure until 60 ml. had been collected. The reaction mixture was cooled in an ice–salt-bath and crystals slowly formed. There was collected 1.18 g. (0.0075 mole) of VIII which upon further recrystallization from acetic anhydride melted at 116–116.5° for an 11.8% yield.

Anal. Calcd. for $C_6H_6O_4$: C, 45.57; H, 3.83; neut. equiv., 79.4; mol. wt., 158. Found: C, 45.88; H, 3.86; neut. equiv., 79.4; mol. wt., Rast method, 164.

2. **From IX.**—A mixture of 15 ml. of acetic anhydride and 1.15 g. (0.0065 mole) of *cis*-diacid IX was refluxed for 1 hr. The solvent was then distilled under reduced pressure, and there was obtained on cooling 0.72 g. (0.0046 mole) of substance which upon recrystallization from acetic anhydride melted at 116–116.5° and which did not depress the melting point of VIII in a mixed m.p. determination.

F. **The Formation of *cis*-2,3-*p*-Dioxanedicarboxylic Acid (IX).**—To 25 ml. of water containing 2 drops of concd. hydrochloric acid there was added 1.0 g. (0.0063 mole) of VII. The mixture was heated for 2 hr. on a steam-bath and then the solvent was evaporated at 25° and reduced pressure. There was obtained 0.94 g. (0.0053 mole) of IX, m.p. 177–180°, for an 84% yield. The substance was recrystallized from an acetone–hexane mixture as described in section C to yield crystals, m.p. 182.5–183.5°, which in a mixed m.p. determination with IV melted at 150–163°.

Anal. Calcd. for $C_6H_8O_6$: C, 40.91; H, 4.57; neut. equiv., 88.1. Found: C, 41.15; H, 4.54; neut. equiv., 88.6.

G. **The Conversion of *cis*-2,3-*p*-Dioxanedicarboxylic Acid (IX) to *cis*-2,3-Bis-(iodomethyl)-*p*-dioxane (II).** 1. **The Preparation of Dimethyl *cis*-2,3-*p*-Dioxanedicarboxylate (X).**—The conversion of IX to II was performed in exactly the same manner as that of V to I. The diester was prepared in 83% yield and after recrystallization from ethyl ether melted at 63–63.5°. A mixed melting point with the *trans*-diester melted at 45–55°.

Anal. Calcd. for $C_8H_{12}O_6$: C, 47.05; H, 5.92. Found: C, 47.31; H, 5.69.

2. **The Reduction of X with Lithium Aluminum Hydride.**—After the reduction procedure there was obtained *ca.* 0.7 g. of a clear viscous liquid assumed to be the *cis*-2,3-bis-(hydroxymethyl)-*p*-dioxane.

3. **The Formation of *cis*-2,3-Bis-(*p*-toluenesulfonatomethyl)-*p*-dioxane (XI).**—The *p*-toluenesulfonate derivative was made from the oil obtained in the previous experiment according to the method of Tipson.[23] Substance XI was obtained in 38% yield from the diester and after recrystallization from acetone–hexane melted at 97°.

Anal. Calcd. for $C_{20}H_{24}O_8S_2$: C, 52.61; H, 5.29. Found: C, 52.35; H, 5.03.

4. **The Formation of II from XI.**—After the appropriate reaction there was obtained a compound in 83% yield which after recrystallization from methanol melted at 82–83.5° and which did not depress authentic II in a mixed melting point determination. The infrared spectrogram in carbon disulfide solution was identical to that of authentic II.

H. **The Interconversions of the 2,3-*p*-Dioxanedicarboxylic Acids.** 1. **IV to IX.**—To 50 ml. of water containing 12 g. of potassium hydroxide there was added 1.0 g. of IV. The mixture was heated for 12 hr. on a steam-bath, cooled to 0°, acidified with 6 *N* hydrochloric acid to *p*H 2 and evaporated to dryness by heating on a steam-bath. The residue was pulverized and extracted three times with 30-ml. portions of acetone. The acetone was evaporated to dryness by heating and there was obtained 0.92 g., m.p. 130–138°, for a 92% recovery. The recovered substance had a neutral equivalent of 90 compared to the theoretical value of 88 for the diacids. The mixture contained 73 ± 10% *trans*-acid and 27 ± 10% *cis*-acid as determined by infrared analysis.

2. **IX to IV.**—A solution of 50 ml. of water containing 6.0 g. of potassium hydroxide and 0.5 g. of IX was heated for 12 hr. on a steam-bath. The product was isolated as described in the previous section. There was obtained upon evaporation of the acetone extract 0.33 g., m.p. 140–145°, for a 66% recovery. The recovered substance had a neutral equivalent of 91 as compared to a theoretical value of 88 for the diacids. The mixture contained 58 ± 10% *cis*-acid and 42 ± 10% *trans*-acid as determined by infrared analysis.

3. **Infrared Analysis.**—The analyses were performed by preparing a 2% mixture of the acids in potassium bromide. Pellets of the order of 65 mg. were analyzed on the Baird infrared recording spectrophotometer. The *cis*-acid absorbed at 11.1 and at 11.4 μ, whereas the *trans* isomer absorbed at 11.4 μ. The concentrations were determined by comparing the relative absorptions at 11.1 and 11.4 μ with known mixtures.

The known mixtures were prepared by weighing the appropriate amounts of pure acids, dissolving them in acetone and boiling the acetone to dryness. The resulting solid was pulverized with an agate mortar and pestle and its spectrogram determined in the same manner as the unknown acid mixtures.

I. **The Partial Resolution of *trans*-2,3-*p*-Dioxanedicarboxylic Acid (IV).**—To 2 liters of acetone containing 2.37 g. (0.0060 mole) of brucine there was added 1.0 g. (0.0057 mole) of IV dissolved in 50 ml. of acetone. The solution was

TABLE III

FRACTIONAL CRYSTALLIZATION OF *trans*-ACID BRUCINATE

Fraction	Yield, g.	M.p., °C.	$\alpha^{25}D$[a]
1	1.8	242–243	+0.37°[b]
2	0.34	230–232	−1.0
3	.24	225–230	−0.65
4	.20	232–234	− .60
5	.20	218–223	− .63

[a] Defined as the optical rotation after the removal of brucine. [b] Defined as the rotation observed from the acid obtained from 0.30 g. of brucinate.

(23) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(24) K. Shipsey and E. A. Werner, *J. Chem. Soc.*, **103**, 1855 (1913).

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boiled for 15 minutes and allowed to cool. Overnight some crystals were formed which were removed by filtration. The remainder of the solution was allowed to stand in a 3-liter beaker at room temperature. From time to time crystals of the brucinate salt were deposited and collected.

To each set of crystals was added 1 ml. of concd. ammonium hydroxide. To the mixture containing precipitated brucine there was added 2 ml. of chloroform with vigorous shaking. The resulting two-liquid layers were separated and the ammoniacal layer was extracted twice with chloroform, filtered and put in a one-decimeter polarimeter tube. The magnitude of its optical rotation was measured with an Aminco photomultiplier microphotometer whose accuracy was estimated at ±0.03.

J. The Attempted Resolution of *cis*-2,3-*p*-Dioxanedicarboxylic Acid (IX).—To 1.5 liters of acetone containing 0.48 g. (0.0012 mole) of brucine there was added 0.200 g. (0.0011 mole) of IX in 50 ml. of acetone. The solution was boiled for 15 minutes and allowed to stand. Over the period of a month crystals were deposited and collected.

TABLE IV

FRACTIONAL CRYSTALLIZATION OF *cis* ACID BRUCINATE

Fraction	Yield, g.	M.p., °C.	$\alpha^{25}D$[a]
1	0.19	214–215	+0.03°
2	.13	214–215	0°
3	.23	213–215	0°
4	.10	210–214	+0.03°

[a] Defined as optical rotation after the removal of brucine.

The acids were liberated from the brucine and the optical rotations measured in the same manner as described in the previous section.

K. The Oxidation of *cis*-2,3-Bis-(iodomethyl)-*p*-dioxane (II). 1. The Formation of *cis*-3-Hydroxymethyl-2-*p*-dioxanecarboxylic Lactone (XII).—To 15 ml. of concd. (sp. gr. 1.42) nitric acid there was added 2.0 g. (0.0054 mole) of II. The mixture was heated on a steam-bath for 10 hr. A clear oil was obtained which solidified on standing. The resulting solid, after drying on a clay plate, weighed 0.55 g. (0.0038 mole) for a 70% yield of XII. When it was recrystallized from carbon tetrachloride the substance melted at 86–86.5°.

Anal. Calcd. for $C_6H_8O_4$: C, 50.00; H, 5.59. Found: C, 49.99; H, 5.39.

An infrared spectrogram of this compound was obtained from a 2% mixture in potassium bromide. The compound possessed a strong absorption at 5.62 μ which was attributed to the carbonyl group.

A neutral equivalent was attempted by titrating the sodium salt of the acid with 0.1 *N* hydrochloric acid. When the reaction was followed potentiometrically, no break was observed in the titration curve.

2. The Conversion of XII to XI. a. The Reduction of XII with Lithium Aluminum Hydride.—To 100 ml. of anhydrous ethyl ether containing 0.60 g. (0.015 mole) of lithium aluminum hydride there was added 0.80 g. (0.0056 mole) of XII. The mixture was refluxed for 6 hr. and then hydrolyzed by the addition of 1 ml. of methanol followed by the addition of 3 ml. of water. The mixture was allowed to stand overnight. The hydroxide precipitate was collected by filtration and extracted in a Soxhlet apparatus for 4 days. Upon evaporation of the ether there was obtained *ca.* 0.70 g. of an oil which was assumed to be *cis*-2,3-bis-(hydroxymethyl)-*p*-dioxane.

b. The Formation of XI.—The *p*-toluenesulfonate derivative was made from the oil isolated in the previous experiment according to the method of Tipson.[21] There was obtained 0.70 g. (0.0015 mole) of XI which, after recrystallization from methanol, melted at 96–97° for a 27% yield from the lactone. A mixed m.p. with authentic XI gave no depression (m.p. 96–97°).

L. The Oxidation of 2,3-Dimethoxy-1,4-diiodobutane. 1. The Formation of *meso*-α,α'-Dimethoxysuccinic Acid (XIII).—To 60 ml. of concd. (sp. gr. 1.42) nitric acid there was added 5.35 g. (0.0144 mole) of *meso*-2,3-dimethoxy-1,4-diiodobutane.[8]

The mixture was heated on a steam-bath until a heavy oil remained. There was obtained 1.80 g. (0.0101 mole) of XIII which, after recrystallization from an acetone–hexane mixture, melted at 160–161.5° (lit.[25] m.p. 161°) for a 65.8% yield.

2. The Formation of *rac.*-α,α'-Dimethoxysuccinic Acid (XIV).—To a 20 ml. of concd. (sp. gr. 1.42) nitric acid there was added 1.5 g. (0.0041 mole) of *rac.*-2,3-dimethoxy-1,4-diiodobutane.[8] The mixture was allowed to react and was worked up as described in the previous section. There was obtained 0.22 g. (0.0012 mole) of XIV which, after recrystallization from acetone–hexane, melted at 168–169° (lit.[26] m.p. 168–171°) for a 29% yield. In a mixed m.p. determination with XIII the mixture melted at 140–150°.

M. The Formation of 2,3,5,6-Tetra-(iodomethyl)-*p*-dioxane (XVI).—A solution of 114 g. (0.35 mole) of mercuric nitrate dissolved in 200 ml. of water containing 30 ml. of concd. nitric acid was prepared and 1,4-butadiene was bubbled through at a rate of 2 bubbles/second. The reaction was assumed complete when a 0.5-ml. portion no longer gave a mercuric oxide precipitate when added to a 10% sodium hydroxide solution. During the course of the reaction a precipitate was formed which was removed by filtration and suspended in 50 ml. of 6 *N* nitric acid for 24 hr. The mixture was then added to a liter of 1 *N* sodium hydroxide. A slight liberation of free mercury accompanied this solution. A solution of 40 g. (0.24 mole) of potassium iodide dissolved in 200 ml. of water was added with vigorous stirring. A precipitate formed which was collected and then treated with 25 g. (0.1 mole) of iodine in a water–chloroform mixture. Upon evaporation of the chloroform by an air jet, a solid remained which was recrystallized from methanol to yield 2.0 g. (0.0031 mole) of compound assumed to be XVI, m.p. 206–206.5°.

Anal. Calcd. for $C_8H_{12}O_2I_4$: C, 14.83; H, 1.87; mol. wt., 648. Found: C, 14.87; H, 1.78; mol. wt., Rast method, 654.

EVANSTON, ILLINOIS

(25) T. S. Patterson and D. S. Patterson, *J. Chem. Soc.*, **107**, 155 (1915).

(26) H. Wren and K. Hughes, *ibid.*, **125**, 1742 (1924).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Proximity Effects. IV. Reaction of Cycloöctene Dibromide with Silver Acetate[1]

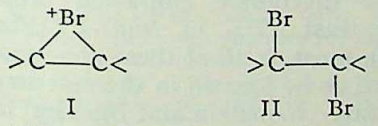
BY ARTHUR C. COPE AND GEOFFREY W. WOOD

RECEIVED MARCH 8, 1957

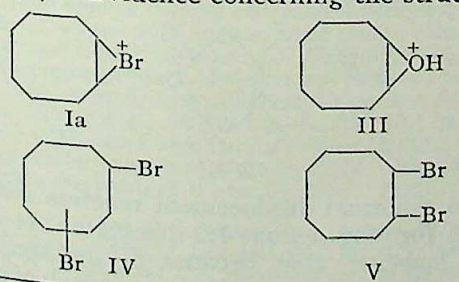
The reaction of cycloöctene dibromide with silver acetate in dry acetic acid has been shown to yield 3-cycloöcten-1-yl acetate, 4-cycloöcten-1-yl acetate, *cis*-1,4-cycloöctanediol diacetate, *trans*-1,4-cycloöctanediol diacetate and only a small amount of the expected *trans*-1,2-cycloöctanediol diacetate. The structures of the cycloöctenyl acetates have been elucidated by ozonolysis of the corresponding phenylurethans and reduction of the ozonides with sodium borohydride, followed by treatment with phenyl isocyanate to form the corresponding octanetriol tris-phenylurethans. Authentic specimens of 1,3,8- and 1,4,8-octanetriol tris-phenylurethans have been prepared for comparison. The course of the reactions leading to the abnormal products listed above is interpreted as resulting from the spatial proximity of opposite sides of the eight-membered ring.

The existence of a "transannular effect" (which we also term a "proximity effect") that influences the course of the reaction between cyclic olefins with medium-sized rings and performic acid has been reported recently.[2-4] In the case of *cis*-cycloöctene this influence results in the formation of a 1,4-cycloöctanediol as well as the expected *trans*-1,2-cycloöctanediol,[2] whereas with both *cis*- and *trans*-cyclononenes and cyclodecenes only the formation of abnormal products has been reported.[3,4] This paper describes the reaction between cycloöctene dibromide and silver acetate in dry acetic acid, which also has been found to be influenced by a "proximity effect."

Addition of bromine to *cis*-cycloöctene has been reported to give *trans*-1,2-dibromocycloöctane (V).[5-7] The addition of bromine to simple olefins is known to proceed *via* an intermediate bromonium ion (I), which then reacts with bromide ion to yield a *trans*-1,2-dibromide (II) (or the *threo* isomer from acyclic olefins).



In the addition of bromine to *cis*-cycloöctene the similarity between the structure of the intermediate bromonium ion Ia and that of protonated *cis*-cycloöctene oxide (III) suggested that the reaction of Ia with bromide ion might give a 1,x-dibromocycloöctane (IV) as well as *trans*-1,2-dibromocycloöctane (V). Evidence concerning the structure of the dibromide was obtained by considering the products formed by treating the dibromide with dimethylamine. This reaction has been found[5,8] to yield 1-bromocycloöctene in 70–77% yield. These observations indicate that the crude dibromide obtained by the addition of bromine to *cis*-cycloöctene probably contains at least 77% of V, although the possibility exists that other dibromides (IV) could be dehydrobrominated abnormally forming 1-bromocycloöctene.



The cycloöctene dibromide described above was treated with silver acetate in dry acetic acid[9] to yield a mixture of acetates, which could be separated by distillation into two fractions. The lower boiling fraction (56–58%) on redistillation afforded material which proved to be a mixture of isomers with the molecular formula $C_{10}H_{16}O_2$. The infrared absorption spectrum of this material contained bands indicative of an isolated ethylenic linkage (3000 and 1620 cm.$^{-1}$) and of an acetoxyl group (1725 and 1200 cm.$^{-1}$) and showed that it was different from the isomeric 2-cycloöcten-1-yl acetate[10] and 1-cycloöcten-1-yl acetate. A specimen of the latter compound was prepared from cycloöctanone and isopropenyl acetate.[11] Saponification of the mixture of acetates gave the corresponding unsaturated alcohols ($C_8H_{14}O$), which on hydrogenation over a platinum catalyst absorbed one mole of hydrogen and formed cycloöctanol, characterized as the phenylurethan. These results established the fact that the unsaturated alcohol fraction was 3-cycloöcten-1-ol (VI) or 4-cycloöcten-1-ol (VII) or a mixture of VI and VII.

The unsaturated alcohol fraction gave a mixture of phenylurethans, which was partially separated by chromatography over alumina into 3-cycloöcten-1-yl phenylurethan (IX), m.p. 101.5–102.5°, and a phenylurethan with m.p. 73–74° that is shown in the following paper to be a mixture of the isomers IX and X. The structures of the phenylurethans IX and XI and the presence of X in the mixture with m.p. 73–74° were proved by ozonolysis, followed by reduction of the ozonides to give (after treatment with phenyl isocyanate) the corresponding *n*-octanetriol tris-phenylurethans XII, XIII and XIV. Some trial ozonizations with XI

(1) Supported by a research grant (NSF-G990) of the National Science Foundation. Presented at the Fourteenth National Organic Chemistry Symposium. Lafayette, Ind., June 14, 1955.

(2) A. C. Cope, S. W. Fenton and C. F. Spencer, THIS JOURNAL, **74**, 5884 (1952).

(3) V. Prelog and K. Schenker, *Helv. Chim. Acta*, **35**, 2044 (1952).

(4) V. Prelog, K. Schenker and W. Kung, *ibid.*, **36**, 471 (1953).

(5) E. P. Kohler, M. Tishler, H. Potter and H. T. Thompson, THIS JOURNAL, **61**, 1057 (1939).

(6) M. W. Lister, *ibid.*, **63**, 143 (1941).

(7) R. Willstätter and E. Waser, *Ber.*, **43**, 1176 (1910).

(8) A. C. Cope and M. Brown, unpublished observation.

(9) Conditions employed in a similar case by S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2780 (1942).

(10) A. C. Cope, M. R. Kinter and R. T. Keller, *ibid.*, **76**, 2757 (1954).

(11) Conditions employed in a similar case by H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

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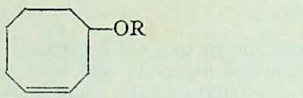
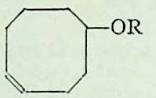
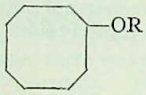
indicated that the ozonide was very unstable, decomposing before it could be reduced to the corresponding triol monophenylurethan by a catalytic hydrogenation procedure. It was found that when a solution of ozone in ethyl acetate at −70°[12]



VI, R = H
IX, R = $OCNHC_6H_5$



VII, R = H
X, R = $OCNHC_6H_5$



VIII, R = H
XI, R = $OCNHC_6H_5$

$RO(CH_2)_5CH(OR)(CH_2)_2OR$
XII, R = $OCNHC_6H_5$

$RO(CH_2)_4CH(OR)(CH_2)_3OR$
XIII, R = $OCNHC_6H_5$

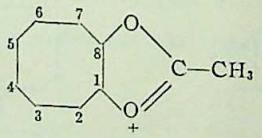
$RO(CH_2)_6CH(OR)CH_2OR$
XIV, R = $OCNHC_6H_5$

was added to a solution of XI in ethyl acetate at −70° until a faint blue color persisted, followed by the immediate addition of an excess of sodium borohydride dissolved in methanol, that XIV could be isolated after treatment with phenyl isocyanate in 90% yield.

In a similar manner IX and the mixture melting at 73–74° that contained X were ozonized, reduced and treated with phenyl isocyanate to give XII and XIII, respectively. It was found that the higher melting phenylurethan corresponded to IX and that it was identical with the phenylurethan prepared from the mixture of cycloöctenols formed in the solvolysis of *cis*-cycloöctene oxide.[13] The identities of XII and XIII were established by a comparison of their melting points and infrared absorption spectra with those of authentic specimens described below.

The physical properties and infrared absorption spectrum of the high boiling fraction (23%) from the reaction of cycloöctene dibromide with silver acetate indicated that it was a mixture of cyclooctanediol diacetates. Hydrolysis of this fraction gave a mixture of the corresponding diols. It was possible to separate all of the 1,2-cycloöctanediol from the diol mixture as the isopropylidene ketal, formed by treating the mixture with acetone and anhydrous cupric sulfate.[14] Chromatography of the resultant mixture separated the less polar isopropylidene ketal from the more polar, and hence more strongly absorbed, cycloöctanediols. This chromatographic procedure for the separation of isopropylidene ketals from glycols has been found to be more convenient than the previous method which involved distillation[2] and has been used throughout this work. The isopropylidene ketal obtained in this way was shown to be derived from *trans*-1,2-cycloöctanediol by comparison of boiling point, index of refraction and infrared absorption spectrum with data for an authentic specimen. Solvolysis of the isopropylidene ketal with formic acid, followed by hydrolysis of the monoformate which was formed, gave *trans*-1,2-cycloöctanediol in 10% yield from the crude diol mixture (2.3% from cycloöctene dibromide). This compound was further characterized by conversion to the bis-*p*-nitrobenzoate. After removal of all of the *trans*-1,2-cycloöctanediol from the crude diol mixture, the residue was chromatographed over alumina and thereby separated into four main fractions. The first fraction (36%, or 8.3% from cycloöctene dibromide) on crystallization from ethyl acetate yielded a material with m.p. 90–91°, which depressed the melting point of the known *cis*-1,4-cycloöctanediol. Elemental analysis and conversion to a bis-phenylurethan indicated that this material was a cycloöctanediol. The diol was identified as *trans*-1,4-cycloöctanediol by preparation of the bis-*p*-nitrobenzoate.[15] Continued development of the chromatogram yielded an intermediate fraction (20%, 4.6% based on cycloöctene dibromide) followed by pure *cis*-1,4-cycloöctanediol (10%, 2.3% based on cycloöctene dibromide), which was further characterized as the bis-*p*-nitrobenzoate. Further development of the chromatogram gave a more polar fraction (17%, 3.9% based on cycloöctene dibromide), which could not be induced to crystallize and has not been identified.

It is of interest that only a 2.3% yield of the "normal" product of reaction of cycloöctene dibromide and silver acetate (*trans*-1,2-cycloöctanediol diacetate) could be isolated while larger amounts of the "abnormal" products, acetates of VI and VII and diacetates of *cis*- and *trans*-1,4-cycloöctanediols, were isolated. Since as previously noted the cycloöctene dibromide employed probably contained at least 77% of *trans*-1,2-dibromocyclooctane (V), most or all of these abnormal products are believed to be formed in the reaction of V with silver acetate. Winstein and Buckles[9] have shown that *trans*- or *threo*-1,2-dibromo compounds react with silver acetate *via* a cyclic acetoxonium ion. In this case the intermediate may be represented by XVII. This intermediate has a structure somewhat similar to the protonated epoxide III, which is an intermediate in the "abnormal" hydroxylation of *cis*-cycloöctene. XVII would be expected to



XVII

undergo a normal displacement reaction with acetate ion forming a *trans*-1,2-diacetate. It is suggested, however, that because of the steric hindrance at C_1, which retards the approach of acetate ion, a transannular hydride shift from C_3 or C_5 to C_1 occurs with concomitant attack by an acetate ion at the relatively unhindered C_3- or C_5-position, forming both stereoisomeric 1,4-cycloöctanediol diacetates. As in the case of *cis*-cycloöctene oxide,[2] it is thought that a 1,3(or 1,5)-hydride shift will be particularly facile because of the close spatial

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proximity of the transannular hydrogen atoms. The loss of a proton from C_2, C_4 or C_6 instead of attack by acetate ion at C_3 or C_5 would give rise to the 3- and 4-cycloöcten-1-yl acetates.

Authentic specimens of the *n*-octanetriol *tris*-phenylurethans obtained from the ozonolysis of IX and X were prepared by the following methods.

Lithium aluminum hydride reduction of dimethyl 4-ketosuberate[16] gave 1,4,8-octanetriol, which on treatment with phenyl isocyanate gave XIII identical with the product obtained from X.

Condensation of the magnesium derivative of diethyl malonate with δ-carbethoxyvaleryl chloride gave after hydrolysis the substituted malonic ester XV. This compound when heated with a catalytic amount of 2-naphthalenesulfonic acid[17] at 200–220° for 7 hr. decomposed to give diethyl 3-ketosuberate (XVI).

$$EtOOC(CH_2)_4COCH(COOEt)_2 \qquad XV$$

$$EtOOC(CH_2)_4COCH_2COOEt \qquad XVI$$

Since the reduction of β-ketoesters with lithium aluminum hydride sometimes gives anomalous results,[18] the carbonyl group in XVI was first reduced with sodium borohydride. The resulting hydroxyester on reduction with lithium aluminum hydride gave 1,3,8-octanetriol, which on treatment with phenyl isocyanate gave XII identical with the product obtained from IX.

Experimental[19,20]

Cycloöctene Dibromide.—A solution of bromine (32 g., 10.9 ml.) in carbon tetrachloride (100 ml.) was added dropwise, with stirring, to a solution of *cis*-cycloöctene (22 g.) in carbon tetrachloride (50 ml.). The internal temperature was maintained between 0–5° during the course of the addition with an external ice–salt cooling bath. The reaction mixture was kept at room temperature for either 1 hr. or overnight, after which the solvent was removed under reduced pressure below 30°. The residue on distillation afforded cycloöctene dibromide (43.5 g., 80%), b.p. 70° (0.15 mm.), $n^{25}D$ 1.5526.

Reaction of Cycloöctene Dibromide with Silver Acetate.—A suspension of silver acetate (44 g.) in glacial acetic acid (100 ml.) and acetic anhydride (5 ml.) was heated at 110° in an oil-bath, with stirring and exclusion of atmospheric moisture for 90 minutes. Cycloöctene dibromide (27 g.) was added dropwise to the foregoing suspension, and the stirring and heating were continued for 14 hr. The reaction mixture was then cooled, diluted with ether and filtered. The organic extract was washed with seven 150-ml. portions of water, with sodium bicarbonate solution until acid free and finally with water. After drying over anhydrous magnesium sulfate, the ether was removed on a steam-bath. The residue on distillation afforded a low boiling fraction (A) (9.8 g., 58%), b.p. 62–65° (0.1 mm.), $n^{25}D$ 1.4694–1.4720, and a high boiling residue (B) (5.2 g., 23%). In three similar experiments the yields of A were 56, 56 and 58%, while the yields of B were 24, 23 and 24%.

Fraction A.—Fractional distillation of A through a semi-micro column[21] yielded a mixture of isomeric cycloöctenyl acetates, b.p. 50° (0.14 mm.), $n^{25}D$ 1.4691.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.71.

Hydrolysis of Fraction A.—Fraction A (15.8 g.) in methanol (220 ml.) was heated under gentle reflux for 1 hour with a solution of sodium hydroxide (20 g.) in water (25 ml.). After removal of the bulk of the methanol under reduced pressure, the residue was diluted with water (150 ml.) and extracted with six 75-ml. portions of ether. After drying the extract with magnesium sulfate, the ether was removed on a steam-bath. The residue (10.96 g., 87%) was distilled through a column with a spinning band (30 × 0.8-cm.) to give five fractions, b.p. 69–69.2° (3.00 mm.), $n^{27.5}D$ 1.4958–1.4965. Fraction 3 ($n^{25}D$ 1.4960) was submitted for analysis.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.36; H, 11.26.

Hydrogenation of a sample of the unsaturated alcohol (252 mg.) in acetic acid (17 ml.) in the presence of 200 mg. of prereduced platinum oxide was complete after the absorption of 102% of one molar equivalent of hydrogen in 1 hr. The reduction product was identified as cycloöctanol by conversion to the phenylurethan, m.p. 56–58°, which was undepressed on admixture with an authentic specimen.

Phenylurethans of the Alcohols Obtained from Fraction A.—The mixture of alcohols (500 mg.) was warmed on a steam-bath with phenyl isocyanate (650 mg.) in a sealed flask for 5–10 minutes. After keeping at room temperature overnight the excess phenyl isocyanate was removed under reduced pressure (50° at 0.01 mm.) to give the phenylurethans as a white solid (1.0 g.). The foregoing solid was dissolved in benzene and passed onto a column of alumina (120 g. of Grade "H"). Elution with benzene:ether (9:1) and benzene:ether (3:1) mixtures afforded a series of crystalline fractions. The early fractions were combined and crystallized from aqueous methanol to give 140 mg. of a mixture (see following paper), m.p. 73–74°, containing the phenylurethans IX and X.

Anal. Calcd. for $C_{15}H_{19}O_2N$: C, 73.43; H, 7.81. Found: C, 73.21; H, 7.76.

The last fractions from the chromatograms were combined and recrystallized from aqueous methanol to give 3-cycloocten-1-yl phenylurethan (IX) (140 mg.), m.p. 101.5–102.5°.

Anal. Calcd. for $C_{15}H_{19}O_2N$: C, 73.43; H, 7.81. Found: C, 73.17; H, 7.68.

Ozonolysis of 2-Cycloöcten-1-yl Phenylurethan.—A saturated solution of ozone in ethyl acetate at −70° was added dropwise with swirling to a solution of the phenylurethan (200 mg.) in ethyl acetate (15 ml.) at −70° until a faint blue color persisted. A solution of sodium borohydride (0.5 g.) in methanol (15 ml.) was then added in one portion and the solution was allowed to warm to room temperature. After 2 hr. it was poured into dilute hydrochloric acid and extracted with ether. Removal of the ether gave a gum (220 mg.), which on treatment with phenyl isocyanate gave 1,2,8-octanetriol tris-phenylurethan (390 mg., 92%), m.p. 122–124°. An analytical sample that was crystallized from aqueous methanol had m.p. 134.5–135.5°.

Anal. Calcd. for $C_{29}H_{33}O_6N_3$: C, 67.02; H, 6.40. Found: C, 67.10; H, 6.14.

Treatment of 3-cycloöcten-1-yl phenylurethan in a similar manner gave 1,3,8-octanetriol tris-phenylurethan, m.p. 143.5–145° (from aqueous methanol).

Anal. Calcd. for $C_{29}H_{33}O_6N_3$: C, 67.02; H, 6.40. Found: C, 67.06; H, 6.55.

Treatment of the mixture of phenylurethans, m.p. 73–74° (see the following paper), in a similar manner gave 1,4,8-octanetriol tris-phenylurethan, m.p. 127–128° (from aqueous methanol), proving that it contained X. Neither of the above tris-phenylurethans depressed the melting points of the corresponding authentic specimens (see below). The mixed melting points of mixtures of *n*-octanetriol tris-phenylurethans are: 1,2,8 and 1,3,8, mixed m.p. 118–122°; 1,2,8 and 1,4,8, mixed m.p. 115–118°; 1,3,8 and 1,4,8, mixed m.p. 113–117°.

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(17) B. Riegel and W. M. Lilienfeld, *ibid.*, **67**, 1273 (1945).
(18) A. S. Dreiding and J. A. Hartman, *ibid.*, **75**, 939 (1953).
(19) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses.
(20) Unless stated otheriwse, the alumina used for chromatography was supplied by Merck and Co., Inc. It was first neutralized and deactivated by treating with ethyl acetate and methanol and then reactivated by heating under reduced pressure before use. The "Grades" used in defining the activity of the alumina are those given by H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941). Grade "H" alumina was supplied by Peter Spence and Sons (Widnes, England) and was used directly. It had activity Grade I–II on the above scale.
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1,4,8-Octanetriol Tris-phenylurethan.—An excess of diazomethane in ether was added with gentle swirling to a suspension of 4-ketosuberic acid[16] (850 mg.) in ether. After the vigorous reaction had subsided, the solvent was removed under reduced pressure to give the corresponding dimethyl ester as an oil (980 mg.). The foregoing ester was dissolved in anhydrous ether (50 ml.) and added to a solution of lithium aluminum hydride (600 mg.) in dry ether (100 ml.). The solution was heated under gentle reflux for 2 hr., after which the excess lithium aluminum hydride was decomposed with ethyl acetate. Dilute sulfuric acid was added to dissolve the inorganic salts, and the reaction mixture was then extracted continuously with chloroform for 5 days to give 1,4,8-octanetriol as a viscous gum. The foregoing triol (330 mg.) was treated with phenyl isocyanate as described before to give a gum (950 mg.), which crystallized with difficulty from aqueous methanol to give 1,4,8-octanetriol tris-phenylurethan, m.p. 127.5–128.5°.

Anal. Calcd. for $C_{29}H_{33}O_6N_3$: C, 67.02; H, 6.40. Found: C, 66.71; H, 6.44.

Diethyl 3-Ketosuberate.—Diethyl malonate (16.2 g.), absolute ethanol (10.5 ml.), dry ether (30 ml.), carbon tetrachloride (0.1 ml.) and clean magnesium turnings (2.5 g.) were heated under gentle reflux with stirring for 3 hr. The reaction mixture was protected from atmospheric moisture with calcium chloride tubes. To the above mixture was added a solution of δ-carbethoxyvaleryl chloride (21 g.) in dry ether (50 ml.) at such a rate that the ether boiled gently. The mixture was then stirred and heated under gentle reflux for 1 hr. Sulfuric acid (40 ml. of 10% by volume) was added slowly with stirring after which the mixture was extracted with ether. Removal of the ether, after drying over magnesium sulfate, gave a residue (34 g.), which was heated with 2-naphthalenesulfonic acid (1.5 g.) in an oil-bath at 190–200° for 4 hr. and at 220° for 3.5 hr., by which time the evolution of carbon dioxide had ceased. The reaction mixture was cooled, diluted with ether and washed with saturated sodium bicarbonate solution. Removal of the ether gave a dark residue, which was flash distilled to give 20.2 g. of a colorless distillate, b.p. 45–140° (0.5 mm.). Fractionation gave substantially pure diethyl 3-ketosuberate (11.1 g., 45%). A sample redistilled for analysis had b.p. 118° (0.55 mm.), $n^{25}D$ 1.4480.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 58.99; H, 8.25. Found: C, 59.31; H, 8.26.

1,3,8-Octanetriol Tris-phenylurethan.—Diethyl 3-ketosuberate (1.25 g.) was dissolved in methanol (10 ml.) and added dropwise to a stirred solution of sodium borohydride (0.5 g.) in methanol (35 ml.) containing one drop of 3 *N* sodium hydroxide solution. The mixture was stirred at room temperature for 45 minutes and then acidified with dilute hydrochloric acid and extracted with ether. The dried ether extract was concentrated under reduced pressure at room temperature and then dissolved in anhydrous ether and added to a solution of lithium aluminum hydride (1.0 g.) in dry ether (50 ml.). The mixture was stirred and heated under gentle reflux for 1 hr. After the excess reagent had been decomposed with ethyl acetate, the reaction mixture was acidified with hydrochloric acid, the ether removed under reduced pressure and the residue extracted continuously with chloroform for 36 hr. to give 1,3,8-octanetriol as a viscous gum (1.1 g.). Treatment of the foregoing triol (300 mg.) with phenyl isocyanate afforded (after crystallizing from aqueous methanol) 1,3,8-octanetriol tris-phenylurethan, m.p. 142.5–144.5°.

Hydrolysis of Fraction B.—Fraction B (7.75 g.) in methanol (200 ml.) was heated under gentle reflux for 1 hr. with a solution of sodium hydroxide (20 g.) in water (25 ml.). After removal of the bulk of the methanol under reduced pressure, the residue was diluted with water (75 ml.) and then extracted continuously with chloroform overnight to give a mixture of diols (4.8 g.). The foregoing diols were dissolved in acetone (150 ml.) and stirred overnight in a stoppered flask with anhydrous cupric sulfate (12 g.). After removal of the cupric sulfate and the acetone the residue was dissolved in benzene and passed onto a column of alumina (100 g., Grade III). Elution with benzene afforded *trans*-1,2-cycloöctanediol isopropylidene ketal (700 mg.), b.p. 109° (22 mm.), $n^{25}D$ 1.4585. Elution with ether:methanol (3:1) afforded a mixture of cycloöctanediols (4.12 g.). The foregoing *trans*-1,2-cycloöctanediol isopropylidene ketal (700 mg.) was dissolved in 88% formic acid (20 ml.) and heated on a steam-bath for 2 hr. After removal of the bulk of the formic acid under reduced pressure, the residue was dissolved in methanol (50 ml.) and heated under gentle reflux with a solution of sodium hydroxide (8 g.) in water (15 ml.) for 30 minutes. After removal of the methanol under reduced pressure, the residue was diluted with water (30 ml.) and then extracted continuously with chloroform for 18 hr. Removal of the chloroform gave *trans*-1,2-cycloöctanediol (480 mg.) as a sirup. The bis-*p*-nitrobenzoate formed short needles from ethyl acetate:methanol with m.p. 105–106°, which was undepressed on admixture with an authentic specimen.

The mixture of cycloöctanediols (4.14 g.) after removal of all of the *trans*-1,2-cycloöctanediol as the isopropylidene ketal was dissolved in the minimum amount of chloroform and passed onto a column of alumina (350 g., Grade III). Elution with ether:methanol (1600 ml., 99:1) gave *trans*-1,4-cycloöctanediol (1.6 g.), which after crystallizing from ethyl acetate had m.p. 90–91°.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.62; H, 11.18. Found: C, 66.45; H, 10.94.

The foregoing diol gave a bis-*p*-nitrobenzoate, which after crystallizing from ethyl acetate:methanol formed needles, m.p. 156–156.6°, undepressed on admixture with an authentic specimen.[15] Treatment of the diol with phenyl isocyanate in the manner described for the alcohols obtained from fraction A afforded (after crystallizing from ethyl acetate) *trans*-1,4-cycloöctanediol bis-phenylurethan, m.p. 180.2–181.7°.

Anal. Calcd. for $C_{22}H_{26}O_4N_2$: C, 69.09; H, 6.85. Found: C, 69.16; H, 6.95.

Continued elution with the same solvent mixture gave an intermediate fraction (960 mg.), m.p. 70–78°. Elution with ether:methanol (98:2) gave *cis*-1,4-cycloöctanediol (450 mg.), m.p. 82–83°, which was undepressed on admixture with an authentic specimen. Elution with ether:methanol (3:1) afforded a more polar material (820 mg.) which has not been identified.

1-Cycloöcten-1-yl Acetate.—Cycloöctanone (2.52 g.), isopropenyl acetate (4.0 g.) and *p*-toluenesulfonic acid (50 mg.) were heated together at a bath temperature of 95° for 3 hr. Acetone (0.7 ml.) was removed through a semimicro column. The reaction mixture was poured into water and extracted with ether. After removal of the ether, the residue was fractionated under reduced pressure to yield the enol acetate, b.p. 50° (0.15 mm.), $n^{25}D$ 1.4697.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.52; H, 9.60.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Proximity Effects. V. Reaction of Cycloöctene Dibromide with Tetraethylammonium Acetate

BY ARTHUR C. COPE AND HERBERT E. JOHNSON[1]

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The reaction of cycloöctene dibromide with tetraethylammonium acetate in acetone, unlike the reaction with silver acetate in acetic acid, has been found to yield only normal elimination and displacement products, rather than compounds formed by "transannular reactions." The compounds isolated were 1-bromocycloöctene (9%), 2-cycloöcten-1-yl acetate (45%), *cis*-2-bromocycloöctyl acetate (9%) and *trans*-1,2-cycloöctanediol diacetate (5%). *trans*-2-Bromocycloöctyl acetate has been prepared from *cis*-cycloöctene oxide and hydrogen bromide and shown to react with tetraethylammonium acetate to form 2-cycloöcten-1-yl acetate (45%) and *cis*-1,2-cycloöctanediol diacetate (17%). The reaction of cycloöctene dibromide with silver acetate in dry acetic acid at 60° has been found to give the same products in approximately the same yields that were obtained at 110–120°.

The results described in the preceding paper[2] show that the reaction of cycloöctene dibromide with silver acetate in dry acetic acid yields only a small amount (2.3%) of *trans*-1,2-cycloöctanediol diacetate, the remaining products being formed by "transannular reactions." Indirect evidence showed that the liquid cycloöctene dibromide probably contained a minimum of 77% of *trans*-1,2-dibromocycloöctane, indicating that most or all of the "transannular products" are formed during the reaction of cycloöctene dibromide with silver acetate, rather than in the addition of bromine to cycloöctene. Since the reaction of silver acetate with halides proceeds by an ionization (SN1) mechanism,[3] it was of interest to investigate the reaction of cycloöctene dibromide with a reagent known to react by a bimolecular (SN2) mechanism. This paper describes the reaction with such a reagent, tetraethylammonium acetate.[4]

Reaction of cycloöctene dibromide with tetraethylammonium acetate in refluxing acetone for 17 hr. resulted in incomplete reaction, and 20% of the dibromide was recovered. Extension of the reaction time to 72 hr. produced essentially complete reaction, and only 1% of the dibromide was recovered. Distillation of the products gave two low boiling fractions: (1) 9% of 1-bromocycloöctene and (2) 45% of 2-cycloöcten-1-yl acetate (yields based on cycloöctene dibromide). The identity of fraction 1 was established by comparison of the physical properties and infrared spectrum with data for an authentic sample of 1-bromocycloöctene. Hydrolysis of fraction 2 followed by the reaction of the resulting alcohol with phenyl isocyanate formed 2-cycloöcten-1-yl phenylurethan, identical by comparison of melting point, mixed melting point and infrared spectra with an authentic sample.[5] The absence of isomeric phenylurethans was established by chromatography of the derivative.

Chromatography of the higher boiling material (fraction 3) on alumina yielded: (a) 1% of cycloöctene dibromide, (b) 9% of *cis*-2-bromocycloöctyl acetate and (c) 5% of *trans*-1,2-cycloöctanediol diacetate.

Hydrolysis of (b) with dilute sulfuric acid formed a 2-bromocycloöctanol which was converted into a 3,5-dinitrobenzoate, m.p. 116.5–117.5°. This derivative was found to be identical with an authentic sample of *cis*-2-bromocycloöctyl 3,5-dinitrobenzoate, which was prepared by the following method. Bromination of cycloöctanone with N-bromosuccinimide formed 2-bromocycloöctanone, which was reduced with sodium borohydride to a mixture of *cis*- and *trans*-2-bromocycloöctanol. The mixture yielded two 3,5-dinitrobenzoates, m.p. 117.0–117.5° and 94–95°, which were separated by crystallization from hexane. The lower melting derivative was identified as the *trans* isomer by comparison with an authentic sample, obtained as follows. The reaction of *cis*-cycloöctene oxide with anhydrous hydrogen bromide in carbon tetrachloride formed *trans*-2-bromocycloöctanol. This alcohol formed a 3,5-dinitrobenzoate, m.p. 95.0–95.6°, that was identical (mixed m.p. and comparison of infrared spectra) with the derivative melting at 94–95° obtained from the mixture of 2-bromocycloöctanols formed by reduction of 2-bromocycloöctanone. The higher melting 3,5-dinitrobenzoate isolated from the mixture, m.p. 117.0–117.5°, accordingly is the *cis* isomer.

Fraction c was saponified and the neutral product was treated with acetone and anhydrous copper sulfate. Subsequent purification by chromatography yielded the isopropylidene ketal of *trans*-1,2-cycloöctanediol, identified by comparison of the infrared spectrum with the spectrum of an authentic sample and showed that no other glycols were present.

The formation of unsaturated compounds from cycloöctene dibromide and tetraethylammonium acetate probably occurs by an elimination process (E2) in which acetate ion serves as the base. Two products could be formed initially by such a process, 1-bromocycloöctene and 3-bromocycloöctene. The first of these compounds was one of the products isolated, while the second would react with tetraethylammonium acetate under the conditions employed to form 2-cycloöcten-1-yl acetate, which also was isolated. Another possible route to 2-cycloöcten-1-yl acetate would involve initial formation of a 2-bromocycloöctyl acetate (probably the *cis* isomer, which has been shown to be one of

(1) National Institutes of Health Postdoctoral Fellow, 1955–1956.
(2) A. C. Cope and G. W. Wood, THIS JOURNAL, **79**, 3885 (1957).
(3) S. Winstein and R. E. Buckles, *ibid.*, **64**, 2780 (1942).
(4) (a) L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4035 (1952); (b) J. D. Roberts, W. G. Young and S. Winstein, THIS JOURNAL, **64**, 2157 (1942); (c) J. Steigman and L. P. Hammett, *ibid.*, **59**, 2536 (1937).
(5) A. C. Cope, M. R. Kinter and R. T. Keller, *ibid.*, **76**, 2757 (1954).

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the products), followed by elimination of hydrogen bromide, with acetate ion serving as the base.

trans-1,2-Cycloöctanediol diacetate, the only glycol derivative isolated from the reaction mixture, could be formed either through a succession of neighboring group participations,[3] or more probably by two Walden inversions, with *cis*-2-bromocycloöctyl acetate as an intermediate. Insufficient *cis*-2-bromocycloöctyl acetate was available to determine whether it would react with tetraethylammonium acetate with inversion. However, the reaction of the more accessible *trans*-2-bromocycloöctyl acetate with tetraethylammonium acetate in refluxing acetone for 72 hr. gave 45% of 2-cycloöcten-1-yl acetate and 17% of *cis*-1,2-cycloöctanediol diacetate (formed by inversion) as the only isolable products. With the shorter reaction time of 24 hr., 43% of the original *trans*-2-bromocycloöctyl acetate was recovered. The observation that *trans*-2-bromocycloöctyl acetate and tetraethylammonium acetate form *cis*-1,2-cycloöctanediol diacetate leads to the conclusion that the intermediate in the reaction in which *trans*-1,2-cycloöctanediol diacetate is formed from cycloöctene dibromide is *cis*-2-bromocycloöctyl acetate.

It is of interest that all of the products isolated from the reaction of cycloöctene dibromide and tetraethylammonium acetate can be formed by normal displacement or elimination reactions from *trans*-1,2-dibromocycloöctane. This result provides good evidence that cycloöctene dibromide is essentially homogeneous and is the *trans*-1,2-dibromide. If appreciable amounts of a dibromide other than the 1,2-isomer had been present, the diacetate formed from it by a normal displacement reaction should have been isolated as a glycol after saponification. As noted above, only the *trans*-1,2-glycol was isolated (as the isopropylidene ketal, by chromatography), under conditions capable of revealing the presence of a fraction of 1% of an isomer.

The results of the bimolecular displacement reaction of cycloöctene dibromide with tetraethylammonium acetate leading solely to normal products are in contrast to the reaction of the dibromide with silver acetate in dry acetic acid, in which abnormal "transannular" products are formed predominantly.[2] A conclusion that receives strong support from these data is that the transannular hydride shift characterizing the "transannular reactions" is favored by the transitory formation of a carbonium ion, as in the removal of bromide ion from cycloöctene dibromide by silver ion (S_N1 or ionization mechanism), and does not occur in the bimolecular nucleophilic displacement (S_N2, reaction with tetraethylammonium acetate. Other "transannular reactions" observed to date have involved the reaction of cyclic olefins with medium-sized rings with performic acid,[6,7] acid hydrolysis or solvolysis of the epoxides of such cyclic olefins[6,8] and the reaction of cyclodecylamine with nitrous acid.[9] All of these reactions were conducted in polar media and proceed through intermediates with at least partially charged (ionic) character. In contrast, reactions involving cyclic compounds with ring sizes favoring "transannular reactions" that have been observed to give only normal products in non-polar media include, in addition to the reaction of cycloöctene dibromide with tetraethylammonium acetate in acetone, the addition of bromine to *cis*-cycloöctene in carbon tetrachloride forming *trans*-1,2-dibromocycloöctane and the reaction of hydrogen bromide with *cis*-cycloöctene oxide in carbon tetrachloride forming *trans*-2-bromocycloöctanol.

In order to make certain that the strikingly different course of the reaction of cycloöctene dibromide with silver acetate[2] and tetraethylammonium acetate was not due in part to a temperature effect, the reaction with silver acetate (previously conducted at 110–120°) was repeated at 60°. The high-boiling diacetate fraction was saponified and gave the same yields of *cis*- and *trans*-1,4-cycloöctanediol and *trans*-1,2-cycloöctanediol that were formed at 110–120°.[2] No 1-bromocycloöctene appeared to be present in the low-boiling fraction. The cycloöctenyl acetate fraction was saponified and the mixture of cycloöctenols was converted to a mixture of phenylurethans, which was chromatographed as before.[2] The first fractions eluted yielded a small amount of 4-cycloöcten-1-yl phenylurethan, m.p. 92–94°, identical with a slightly purer sample, m.p. 93–94°, obtained by the cleavage of 1,4-epoxycycloöctane with acetic anhydride and boron trifluoride.[10] The identity of this derivative was established by ozonization, reduction of the ozonide with sodium borohydride and treatment with phenyl isocyanate, which formed the known 1,4,8-octanetriol tris-phenylurethan.[2] Proof that the previously isolated[2] phenylurethan of m.p. 73–74° was a mixture was obtained by cocrystallization of equal quantities of 3-cycloöcten-1-yl phenylurethan and 4-cycloöcten-1-yl phenylurethan. The material that crystallized had an infrared spectrum identical to the spectrum of the phenylurethan of m.p. 73–74°. As before, the majority of the fractions from the chromatogram were mixtures of 3- and 4-cycloöcten-1-yl phenylurethan, while the final fractions yielded 3-cycloöcten-1-yl phenylurethan, m.p. 102–103°.

Experimental[11]

Reaction of *trans*-1,2-Dibromocycloöctane with Tetraethylammonium Acetate.—A solution of 22.3 g. (0.0825 mole) of cycloöctene dibromide and 62.2 g. (0.30 mole) of tetraethylammonium acetate monohydrate[4c] in 300 ml. of dry acetone was refluxed for 72 hr. At this time the acetone was removed by warming under reduced pressure and the pasty residue was taken up in water and ether. The ether layer was separated and the aqueous phase further extracted with ether. Combination of the ether extracts, drying over anhydrous magnesium sulfate and distillation of the ether left a light yellow residue. Fractional distillation of this

(6) A. C. Cope, S. W. Fenton and C. F. Spencer, THIS JOURNAL, **74**, 5884 (1952).

(7) V. Prelog and K. Schenker, *Helv. Chim. Acta*, **35**, 2044 (1952); V. Prelog, K. Schenker and W. Kung, *ibid.*, **36**, 471 (1953); V. Prelog and V. Boarland, *ibid.*, **38**, 1776 (1955).

(8) A. C. Cope, A. Fournier, Jr., and H. E. Simmons, Jr., THIS JOURNAL, **79**, 3905 (1957).

(9) V. Prelog, H. J. Urech, A. A. Bothner-By and J. Würsch, *Helv. Chim. Acta*, **38**, 1095 (1955).

(10) A. C. Cope and B. C. Anderson, THIS JOURNAL, **79**, 3892 (1957).

(11) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses. Alumina used for chromatography was supplied by Merck and Co., Inc., and prepared as described in footnote 20 of the preceding paper.

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material gave three fractions: (1) 1.44 g. (9%), b.p. 35–40° (0.2 mm.), $n^{25}D$ 1.5003; (2) 6.26 g. (45%), b.p. 49–51° (0.2 mm.), $n^{25}D$ 1.4688; (3) 3.98 g., b.p. 75–79° (0.2 mm.), $n^{25}D$ 1.4830.

Fraction 1 was dissolved in petroleum ether and passed onto a column of 10-mm. diameter containing 65 g. of grade I alumina. Elution with 160 ml. of petroleum ether gave 0.94 g. of a volatile liquid. Distillation of this material afforded 1-bromocycloöctene, b.p. 108° (30 mm.), $n^{25}D$ 1.5150, with an infrared spectrum identical with the spectrum of an authentic sample.[12]

A portion of **fraction 2** was saponified and converted to its phenylurethan by a procedure previously described.[2] Chromatography of 2.54 g. of this material over 200 g. of grade I alumina in a 24-mm. diameter column and elution with benzene–ether (9:1) gave 2-cycloöcten-1-yl phenylurethan as a colorless solid, m.p. 92.5–93.5°, in 80% yield. The mixed melting point of this derivative with an authentic sample[5] showed no depression, and comparison of the infrared spectra showed them to be identical. Although the last fractions (5% of the phenylurethan isolated) eluted from the column were somewhat impure as indicated by the range in melting point, no derivative could be isolated from them other than 2-cycloöcten-1-yl phenylurethan.

Fraction 3 was dissolved in petroleum ether and passed onto a column of 24-mm. diameter containing 200 g. of grade I alumina. Elution with 600 ml. of petroleum ether gave (a) 0.25 g. (1%) of cycloöctene dibromide, $n^{25}D$ 1.5510, identified by comparison of its infrared spectrum with that of an authentic sample. Elution with 800 ml. of 10% ether in petroleum ether gave (b) 1.87 g. (9%) of *cis*-2-bromocycloöctyl acetate. Distillation resulted in isolation of this compound as a colorless, pleasant-smelling liquid, b.p. 72° (0.25 mm.), $n^{25}D$ 1.4960.

Anal. Calcd. for $C_{10}H_{17}BrO_2$: C, 48.20; H, 6.88. Found: C, 48.47; H, 6.86.

A solution of 62 mg. of *cis*-2-bromocycloöctyl acetate in 8 ml. of methanol containing 1 ml. of concentrated sulfuric acid and 3 ml. of water was allowed to stand at room temperature for 16 hr. Most of the volatile material was removed below room temperature by evaporation under reduced pressure. The remaining residue was poured into water and the mixture was extracted with ether. After drying the extracts over anhydrous sodium sulfate, the ether was evaporated, leaving 52 mg. of a nearly colorless liquid. This material was treated with 99 mg. of *p*-toluenesulfonyl chloride and 55 mg. of 3,5-dinitrobenzoic acid in 10 ml. of dry pyridine[13] to give 68 mg. of a nearly white solid, m.p. 107–113°. One crystallization from hexane gave shiny, colorless plates, m.p. 116.5–117.5°. A mixed melting point with an authentic sample of *cis*-2-bromocycloöctyl 3,5-dinitrobenzoate (see below) showed no depression and the infrared spectra of the two compounds were identical in every respect.

Further elution of the column with 1700 ml. of 50% ether in petroleum ether gave (c) 0.97 g. (5%) of *trans*-1,2-cycloöctanediol diacetate. This material was saponified and converted to its isopropylidene ketal with acetone in the presence of anhydrous copper sulfate. Chromatography of the product according to the procedure previously described[2] revealed no isomeric cycloöctanediols, the ketal being the only material that was eluted from the column. The infrared spectrum of the eluted ketal was identical with that of an authentic sample of the isopropylidene ketal of *trans*-1,2-cycloöctanediol.

2-Bromocycloöctanone.—N-Bromosuccinimide (8.40 g., 0.047 mole) was added to a solution of 5.92 g. (0.047 mole) of cycloöctanone in 30 ml. of carbon tetrachloride, and the mixture was refluxed for 2 hr. During this time the reaction proceeded to completion as evidenced by the disappearance of the N-bromosuccinimide. After filtration of the succinimide the solvent was removed by heating under reduced pressure, leaving a dark residue. Distillation afforded 7.50 g. (78%) of 2-bromocycloöctanone as a colorless liquid, b.p. 65–73° (0.2–0.5 mm.), $n^{25}D$ 1.5126; a redistilled analytical sample had b.p. 79–81° (1 mm.), $n^{25}D$ 1.5161, d^{25}_4 1.382.[14]

Anal.[14] Calcd. for $C_8H_{13}BrO$: C, 46.85; H, 6.39; Br, 38.97. Found: C, 47.13; H, 6.41; Br, 38.94.

***cis*- and *trans*-2-Bromocycloöctanol.**—A solution of 2.0 g. (0.054 mole) of sodium borohydride in 50 ml. of absolute methanol was added over a period of 30 minutes to a solution of 2.74 g. (0.0134 mole) of 2-bromocycloöctanone in 20 ml. of absolute methanol. The temperature of the mixture was kept below 25° throughout the addition. After the mixture stood for an additional period of 2 hr. at room temperature, most of the methanol was removed by evaporation under reduced pressure. Fifty milliliters of water was added and the mixture was acidified with dilute hydrochloric acid. The mixture was extracted with ether, and the extracts were dried over anhydrous sodium sulfate and evaporated, leaving a nearly colorless liquid. Distillation gave 1.91 g. (69%) of a colorless liquid mixture of *cis*- and *trans*-2-bromocycloöctanol, b.p. 85–90° (0.7 mm.), $n^{25}D$ 1.5140. Redistillation afforded material of b.p. 72–75° (0.3 mm.), $n^{25}D$ 1.5172. The mixture was not analytically pure, presumably because of some hydrolysis or loss of hydrogen bromide.

***cis*- and *trans*-2-Bromocycloöctyl 3,5-Dinitrobenzoates.**—A 442-mg. sample of the bromohydrin mixture from the reduction of 2-bromocycloöctanone was converted in the usual manner with 460 mg. of 3,5-dinitrobenzoic acid, 820 mg. of *p*-toluenesulfonyl chloride and 15 ml. of pyridine to 766 mg. (94%) of a mixture of dinitrobenzoates, m.p. 82–94°. Three crystallizations from hexane gave pure *cis*-2-bromocycloöctyl 3,5-dinitrobenzoate as colorless, glistening plates, m.p. 117.0–117.5°.

Anal. Calcd. for $C_{15}H_{17}BrN_2O_6$: C, 44.90; H, 4.27; Br, 19.87. Found: C, 44.98; H, 4.39; Br, 19.72.

Evaporation of the mother liquors gave an oil that slowly solidified, m.p. 58–70°. Four crystallizations from hexane gave *trans*-2-bromocycloöctyl 3,5-dinitrobenzoate as colorless needles, m.p. 94–95°. A mixed melting point with an authentic sample (see below) was undepressed and the infrared spectra of the two compounds were identical.

Anal. Calcd. for $C_{15}H_{17}BrN_2O_6$: C, 44.90; H, 4.27; Br, 19.87. Found: C, 45.29; H, 4.52; Br, 20.20.

***trans*-2-Bromocycloöctanol.**—A slow stream of anhydrous hydrogen bromide was passed into a solution of 5.38 g. (0.043 mole) of *cis*-cycloöctene oxide in 50 ml. of carbon tetrachloride for a period of 2 hr. The temperature of the mixture was kept at approximately 20° by a cold water-bath. Evaporation of the solvent left a dark residue which was distilled, yielding 6.46 g. (74%) of *trans*-2-bromocycloöctanol as a colorless liquid, b.p. 80–88° (0.2 mm.), $n^{25}D$ 1.5246. Redistillation afforded material of b.p. 74–75° (0.1 mm.), $n^{25}D$ 1.5246.

Anal. Calcd. for $C_8H_{15}BrO$: C, 46.39; H, 7.30; Br, 38.59. Found: C, 46.13; H, 7.26; Br, 38.37.

A 393-mg. sample of the bromohydrin was treated with 410 mg. of 3,5-dinitrobenzoic acid and 744 mg. of *p*-toluenesulfonyl chloride in 15 ml. of pyridine to give 726 mg. (96%) of derivative, m.p. 90–92°. Three crystallizations from hexane gave pure *trans*-2-bromocycloöctyl 3,5-dinitrobenzoate as clusters of colorless needles, m.p. 95.0–95.6°.

***trans*-2-Bromocycloöctyl Acetate.**—A mixture of 5.95 g. (0.029 mole) of the *trans*-bromohydrin and 3.54 g. (0.035 mole) of acetic anhydride was cooled in an ice-bath. Several drops of concentrated sulfuric acid were added with swirling. After the initial reaction subsided, the mixture was kept at room temperature for 2 hr. and then diluted with 50 ml. of ether. Calcium carbonate was added, and after 30 minutes the mixture was filtered. The ether was evaporated and the residue distilled to give 6.87 g. (96%) of *trans*-2-bromocycloöctyl acetate as a colorless liquid, b.p. 84–85° (0.5 mm.), $n^{25}D$ 1.4962.

Anal. Calcd. for $C_{10}H_{17}BrO_2$: C, 48.20; H, 6.88; Br, 32.08. Found: C, 48.31; H, 6.94; Br, 32.34.

Reaction of *trans*-2-Bromocycloöctyl Acetate with Tetraethylammonium Acetate.—A solution of 3.28 g. (0.013 mole) of *trans*-2-bromocycloöctyl acetate and 6.0 g. (0.029 mole) of tetraethylammonium acetate monohydrate in 70 ml. of dry acetone was refluxed for 72 hr. At the end of this time the acetone was removed by warming under reduced

(12) Prepared by Morton Brown by the procedure of E. P. Kohler, M. Tishler, H. Potter and H. T. Thompson, THIS JOURNAL, **61**, 1057 (1939).

(13) A method of preparing carboxylic esters described by J. H. Brewster and C. J. Ciotti, Jr., *ibid.*, **77**, 6214 (1955).

(14) D. S. Smith, Ph.D. Thesis, Massachusetts Institute of Technology, 1952.

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pressure and the product isolated as described above for the products of the reaction of cycloöctene dibromide with tetraethylammonium acetate to give 2.17 g. of a colorless liquid, b.p. 50–87° (0.4 mm.), $n^{25}D$ 1.4675. Redistillation of this material through a semimicro column gave: (a) 0.95 g. (45%), b.p. 41° (0.2 mm.), $n^{25}D$ 1.4675, identified as 2-cyclooctenyl-1-yl acetate by hydrolysis and conversion to the phenylurethan; (b) 0.40 g. of intermediate fractions, b.p. 41–82° (0.2 mm.), $n^{25}D$ 1.4675–1.4680; and (c) 0.51 g. (17%) of *cis*-1,2-cycloöctanediol diacetate, b.p. 82° (0.2 mm.), $n^{25}D$ 1.4645. A solution of 464 mg. of (c) in 10 ml. of methanol containing 5 ml. of water and 2 g. of sodium hydroxide was refluxed for 2 hr. After cooling, most of the methanol was removed by warming the mixture under reduced pressure. The residue was diluted with water and extracted continuously for 20 hr. with chloroform to give 235 mg. (80%) of a white solid, m.p. 69–75°. One crystallization from hexane gave 190 mg. of colorless glistening plates of *cis*-1,2-cycloöctanediol, m.p. and mixed m.p. with an authentic sample 78.0–78.5°.

Reaction of *trans*-1,2-Dibromocycloöctane with Silver Acetate at 60°.—To a stirred suspension of 42.5 g. (0.25 mole) of silver acetate in 200 ml. of glacial acetic acid and 20 ml. of acetic anhydride at room temperature was added 25.3 g. (0.095 mole) of cycloöctene dibromide. After 2 hr. at room temperature essentially no reaction had taken place. The mixture was then heated to 60° and held at that temperature for 24 hr. After that period the solids were collected on a filter, washed well with glacial acetic acid, slurried with 20% aqueous nitric acid, again separated by filtration, washed with water and dried, giving 33.7 g. (96%) of silver bromide. The acetic acid filtrates were returned to the reaction flask along with 10 g. of silver acetate and stirred for an additional period of 17 hr. at 60°. No more silver bromide precipitated. About 80% of the acetic acid was removed by warming under reduced pressure, and the remaining residue was poured into water. After thorough extraction of the mixture with ether, the extracts were washed with saturated sodium bicarbonate solution until free from acid. The extracts were dried over anhydrous potassium carbonate and evaporated, leaving a nearly colorless residue. Distillation of the residue gave 8.84 g. (57%) of an unsaturated acetate fraction, b.p. 110–112° (20 mm.), $n^{25}D$ 1.4680–1.4693, and 5.34 g. (26%) of a diacetate fraction, b.p. 95–102° (0.25 mm.), $n^{25}D$ 1.4650.

A sample of the unsaturated acetate fraction was saponified and converted to a mixture of phenylurethans. This mixture (4.53 g.) was chromatographed on 400 g. of grade I alumina in a 30-mm. diameter column, eluting with 4:1 petroleum ether:ether followed by 2:1 petroleum ether:ether. Thirty-two crystalline fractions were obtained. From the first three fractions material of m.p. 92–94° was obtained by repeated crystallization from hexane. A mixed melting point with 4-cycloöcten-1-yl phenylurethan of m.p. 93–94° obtained from another source[10] was undepressed, and the infrared spectra of the two compounds were identical with the exception of a small band at 10.2 μ and minor intensity differences indicating the presence of a small amount of an impurity in the derivative with m.p. 92–94°. Crystallization of the intermediate fractions from either hexane or methanol–water failed to narrow the melting range. From the last fractions, material of m.p. 102–103° was obtained as colorless needles from hexane. No depression in melting point was observed upon admixture of this derivative with an authentic sample of 3-cycloöcten-1-yl phenylurethan, and the infrared spectra of the two samples were found to be identical in detail.

A mixture of 21 mg. of the phenylurethan of m.p. 92–94° and 20 mg. of 3-cycloöcten-1-yl phenylurethan was crystallized from methanol–water to give 31 mg. of colorless needles, m.p. 76–78°. The infrared spectrum of this material was found to be identical in every respect to that of the mixture of phenylurethans, m.p. 73–74°, described in the preceding paper.[2]

Saponification of the diacetate fraction gave the same yields of *trans*-1,2-, 1,4- and *cis*-1,4-cycloöctanediol as reported in the preceding paper.[2]

Ozonolysis of 4-Cycloöcten-1-yl Phenylurethan.[15]—An ethyl acetate solution of 35 mg. of 4-cycloöcten-1-yl phenylurethan,[10] m.p. 93–94°, was ozonized, reduced and treated with phenyl isocyanate as previously described[2] to give 78 mg. (98%) of an octanetriol tris-phenylurethan. Several crystallizations from hexane gave 55 mg. of colorless crystals, m.p. 126.5–128.0°. One further crystallization from methanol–water afforded 38 mg. of 1,4,8-octanetriol tris-phenylurethan, m.p. and mixed m.p. with an authentic sample,[2] 127–128°. The infrared spectra of the two compounds were identical in every respect.

(15) Conducted in part by Dr. G. W. Wood.

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Proximity Effects. VI. Stereospecific Syntheses of *cis*- and *trans*-1,4-Cycloöctanediols

BY ARTHUR C. COPE AND BURTON C. ANDERSON

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1,4-Epoxycycloöctane (I) has been prepared by a sequence of reactions beginning with 3,6-epoxycycloheptanecarbonitrile (II and III, *cis* and *trans* isomers). Each of the nitriles was hydrogenated to a single primary amine, but in the synthesis a mixture of amines formed by hydrogenation of a mixture of II and III was employed. The mixture of amines (IV and V) was treated with nitrous acid, and the mixture of alcohols formed was oxidized with N-bromosuccinimide to the ketone IX. Wolff–Kishner reduction of IX yielded I. The 1,4-oxide I was cleaved with acetic anhydride and boron trifluoride to a diacetate, which upon saponification formed *trans*-1,4-cycloöctanediol. The 1,4-oxide I also was cleaved with acetyl bromide, forming *trans*-4-bromocycloöctyl acetate, which was converted into a diacetate by treatment with tetraethylammonium acetate. Saponification of the diacetate yielded *cis*-1,4-cycloöctanediol. The *cis*- and *trans*-1,4-cycloöctanediols obtained by these syntheses proved to be identical with compounds previously prepared by "transannular reactions" from *cis*- and *trans*-cycloöctene, respectively, thereby confirming the structures and stereochemical assignments previously suggested for these compounds.

It has been shown that the solvolysis of *cis*-cycloöctene oxide with formic acid followed by saponification, or hydrolysis of the oxide with dilute hydrochloric acid, forms a 1,4-cycloöctanediol as well as *trans*-1,2-cycloöctanediol.[1] The 1,4-cyclooctanediol formed in this manner tentatively was assigned the *cis* configuration on the basis of a reaction mechanism that was proposed to explain its formation. Later, similar reasoning was used to assign tentatively the *trans* configuration to a 1,4-cycloöctanediol obtained by solvolysis of *trans*-cycloöctene oxide with formic acid followed by saponification.[2] The assignments of configuration to these diols have been confirmed in the

(1) A. C. Cope, S. W. Fenton and C. F. Spencer, THIS JOURNAL, 74, 5882 (1952).

(2) A. C. Cope, A. Fournier, Jr., and H. E. Simmons, Jr., *ibid.*, 79, 3905 (1957).

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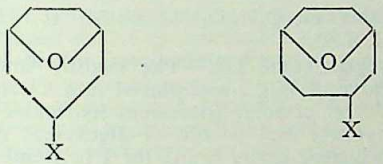
present work by stereospecific syntheses of *cis*- and *trans*-1,4-cycloöctanediols from *cis*-1,4-epoxycyclooctane (I).

A sample of each of the isomeric 3,6-epoxycycloheptanecarbonitriles[3] (II and III) was hydrogenated to the 3,6-epoxycycloheptanemethylamine (IV and V) of similar configuration (*cis* or *trans*) and the amines were identified as crystalline picrates. Since it appeared that the oxide I could be obtained from either of the isomeric amines, the synthesis described below was carried out using a mixture of amines prepared by hydrogenation of a mixture of the nitriles II and III. The nitriles were obtained by decarboxylating a mixture of the isomeric 1-cyano-3,6-epoxycycloheptanecarboxylic acids in quinoline.[3] In this way a mixture of the amines IV and V was obtained from *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate in 44% yield.



II and III, X = C≡N
IV and V, X = CH_2NH_2
VII, X = CH_2OH
VIII, X = CO_2H

I, X = H
VI, X = OH
IX, X = =O

Treatment of the mixture of amines with nitrous acid afforded a mixture of olefins (see below) and 3,6-epoxycycloöctanol (VI), probably contaminated with 3,6-epoxycycloheptanemethanol (VII) and 1-methyl-3,6-epoxycycloheptan-1-ol, if this Demjanov rearrangement is analogous to other well-studied cases.[4] The mixture of alcohols was oxidized with N-bromosuccinimide in aqueous acetone. These conditions should cause no change in the tertiary alcohol, 1-methyl-3,6-epoxycycloheptan-1-ol, while the primary alcohol VII would form 3,6-epoxycycloheptanecarboxylic acid (VIII) by further oxidation of the intermediate aldehyde, if it is attacked at all, and the secondary alcohol VI would be oxidized to 3,6-epoxycycloöctanone (IX). The ketone obtained by this oxidation procedure was contaminated with small amounts of hydroxylic compounds as shown by the infrared spectrum of the product.

The impure ketone IX was reduced to the 1,4-oxide I by the Wolff–Kishner method in 57% yield. The oxide I separated from the reaction mixture by steam distillation as it was formed and was purified by heating with molten sodium and redistillation. The distillate crystallized on cooling and melted at 30.8–32.2°. The infrared spectrum of the 1,4-oxide I showed strong absorption at 9.45 μ (absent from the spectrum of *trans*-cyclooctene oxide) and 12.25 μ (absent from the spectrum of *cis*-cycloöctene oxide).[2] These data ensure that the 1,4-oxide I is not present in preparations of these cycloöctene oxides which have been shown to form 1,4-cycloöctanediols on solvolysis.[1,2]

The olefins from the diazotization, a mixture of some or all of the olefins 3,6-epoxycycloöct-1-ene, 4,7-epoxycycloöct-1-ene, 1-methylene-3,6-epoxycycloheptane and 1-methyl-3,6-epoxycyclohept-1-ene, which showed two olefin bands in its infrared spectrum, was hydrogenated to a mixture of I and 1-methyl-3,6-epoxycycloheptane. The infrared spectrum of this mixture showed all the absorption peaks of I as well as several other strong bands. Chromatography of the mixture on silica gel, with elution by benzene–ether mixtures, afforded a partial separation as shown by the infrared spectra of succeeding fractions.

The oxide I was treated with acetic anhydride and boron trifluoride, which should cleave the ether with Walden inversion[5] forming *trans*-1,4-cycloöctanediol diacetate. The cycloöctenyl acetate which also was formed was distilled from the product and the viscous residue was saponified without purification. The glycol formed was chromatographed on alumina and yielded *trans*-1,4-cycloöctanediol (6% from 1,4-epoxycycloöctane), m.p. 89.5–91°, identical with the diol obtained from *trans*-cycloöctene oxide, and tentatively assigned the *trans* structure,[2] as shown by mixed-melting point and a comparison of the infrared spectra, which were identical.

The low-boiling product of this reaction was saponified and converted in good yield to a crystalline phenylurethan, m.p. 93–94°. It was not identical with 2-cycloöcten-1-yl phenylurethan, m.p. 92.5–93.5°, but absorbed 98% of one mole of hydrogen to form cycloöctyl phenylurethan, identical with an authentic sample. The phenylurethan melting at 93–94° has been shown to be 4-cycloöcten-1-yl phenylurethan by ozonization.[6] It is of interest that there was no indication of the presence of the isomeric 3-cycloöcten-1-yl phenylurethan,[7] which also could be formed from the 1,4-oxide I, in this derivative.

The oxide I was cleaved with acetyl bromide and formed 4-bromocycloöctyl acetate, presumably the *trans* isomer,[5] in 40% yield. This product was converted to *cis*-1,4-cycloöctanediol diacetate by treatment with tetraethylammonium acetate in acetone.[8] Saponification of the crude ester followed by chromatography of the product afforded 30% of *cis*-1,4-cycloöctanediol, which was converted in 81% yield to a bis-*p*-nitrobenzoate. Both the glycol and the bis-*p*-nitrobenzoate were identical with the same compounds prepared from *cis*-cycloöctene oxide as shown by melting points, mixed melting points and infrared spectra.

These syntheses of *cis*- and *trans*-1,4-cycloöctanediols confirm the configurations previously suggested for these compounds.

Experimental[9]

Hydrogenation of 3,6-Epoxycycloheptanecarbonitrile (II or III), M.p. 87–88°.—In a 335-ml. stainless steel autoclave

(3) A. C. Cope and B. C. Anderson, THIS JOURNAL, **78**, 149 (1956).
(4) P. A. S. Smith and D. R. Baer, "The Demjanov and Tiffeneau–Demjanov Ring Expansions," *Org. Reactions*, Vol. IX, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 157.
(5) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," edited by R. C. Elderfield, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 29.
(6) A. C. Cope and H. E. Johnson, THIS JOURNAL, **79**, 3889 (1957).
(7) A. C. Cope and G. W. Wood, *ibid.*, **79**, 3885 (1957).
(8) For a similar displacement with Walden inversion see L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4935 (1952).
(9) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses. Infrared spectra were determined with a Baird double beam recording spectrophotometer, with a sodium chloride prism.

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were placed 0.533 g. of 3,6-epoxycycloheptanecarbonitrile,[2] m.p. 87–88°, 30 ml. of methanol and about 1 g. of commercial Raney nickel (washed with methanol). The mixture was cooled in a Dry Ice–acetone-bath and 30 ml. of liquid ammonia was added. The vessel was sealed, pressured to 1650 p.s.i. with hydrogen and rocked and heated at 140° for 1 hr. After cooling, the autoclave was opened, the catalyst was removed by filtration and the solvents were distilled. The residue was diluted with 20 ml. of 10% aqueous potassium hydroxide and extracted with four 25-ml. portions of ether. The ether solution was dried with potassium hydroxide and the ether was distilled. The residue, 0.254 g., was dissolved in 10 ml. of dry ether and a saturated solution of picric acid in ether was added until no further precipitate formed. There was obtained 0.490 g. (34%) of 3,6-epoxycycloheptanemethylamine (IV or V) picrate, which after four crystallizations from ethyl acetate had m.p. 212.3–214.0° dec.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.70; H, 5.20; N, 14.97.

Hydrogenation of 3,6-Epoxycycloheptanecarbonitrile (II or III), M.p. 102.8–103.6°.—Reduction of 0.625 g. of 3,6-epoxycycloheptanecarbonitrile,[3] m.p. 102.8–103.6°, under conditions similar to those described above afforded 0.290 g. of 3,6-epoxycycloheptanemethylamine (IV or V), which was converted to 0.712 g. (42%) of the amine picrate. A sample of this picrate that was recrystallized from ethyl acetate had m.p. 189.2–190.8° dec.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.54; H, 4.79; N, 14.95.

Ethyl 1-cyano-3,6-epoxycycloheptanecarboxylate was prepared as previously described[3]; 200 g. of *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate yielded 65.4 g. (69%) of a mixture of the isomeric ethyl 1-cyano-3,6-epoxycycloheptanecarboxylates, b.p. 95–111° (0.25 mm.), which partially crystallized.

1-Cyano-3,6-epoxycycloheptanecarboxylic acid was prepared by saponification[3] of the esters described above and afforded 55.5 g. (98%) of a crystalline mixture of the acids which was not further purified.

3,6-Epoxycycloheptanecarbonitriles (II and III).—The mixture of acids (55.5 g.) described above was decarboxylated in quinoline[3] and yielded 34.1 g. (81%) of a waxy semi-solid mixture of the nitriles II and III which was not further purified.

3,6-Epoxycycloheptanemethylamine.—The crude nitrile (34.1 g.) obtained from the decarboxylation was hydrogenated by a procedure similar to the one described above for the reduction of 3,6-epoxycycloheptanecarbonitrile, m.p. 87–88°, and afforded 28.3 g. [44% from *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate] of 3,6-epoxycycloheptanemethylamine, b.p. 104–111.5° (10 mm.), $n^{25}D$ 1.4951–1.5010. A middle fraction showed no absorption characteristic of hydroxylic or carbonyl compounds or nitriles in its infrared spectrum.

A sample of a similar mixture, purified by redistillation, had b.p. 53–54° (0.30 mm.) and $n^{25}D$ 1.4953.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.27; H, 10.58; N, 10.14.

Diazotization of 3,6-Epoxycycloheptanemethylamine (IV and V).—3,6-Epoxycycloheptanemethylamine, 27.0 g., was dissolved in a solution of 17.3 g. of 85% phosphoric acid in 125 ml. of ice-water. The slightly cloudy solution was extracted with ether to remove any neutral impurities, a solution of 13.2 g. of sodium nitrite in 30 ml. of water was added and the solution was allowed to stand for 16 hr. The greenish organic layer which had formed was extracted with ether. The solution was heated at 100° for 1 hr., cooled and extracted with two 100-ml. portions of ether, and the processes of heating and extraction were repeated twice in the same way. Phosphoric acid (1.7 g.) was added, then 1.6 g. of sodium nitrite, and the solution was heated at 100° for 1 hr., cooled and extracted with two 100-ml. portions of ether. The heating and extraction were repeated, the extract was dried with potassium carbonate and distilled. When it was found that the high-boiling residue from this operation was less than 1 g., all of the ether extracts were combined and dried with potassium carbonate and the ether was distilled. The residue was fractionated through a semi-micro column, affording an olefin fraction, b.p. 54–59.5° (11 mm.), and an alcohol fraction, b.p. 60–83° (0.30 mm.). The olefins amounted to 4.95 g. or 22% of the theoretical amount; the alcohols amounted to 11.6 g. or 43%.

N-Bromosuccinimide Oxidation of the Alcohol Mixture.—The alcohol fraction from the nitrous acid reaction, 11.6 g., was dissolved in 400 ml. of reagent acetone and 40 ml. of water. N-Bromosuccinimide (36 g.) was added, and the solution was allowed to stand for 19.5 hr. During the course of the reaction the mixture turned gradually from colorless to orange and back to colorless again. The reaction mixture was neutralized with saturated sodium bicarbonate solution, and the excess N-bromosuccinimide was destroyed with sodium thiosulfate solution. The acetone was distilled, and the solution was cooled and extracted with nine 50-ml. portions of chloroform. The combined extracts were dried with potassium carbonate and the chloroform was distilled. Fractionation through a semi-micro column afforded 9.23 g. or 81% of the theoretical amount of a product, b.p. 58° (1.40 mm.) to 64° (0.18 mm.), $n^{25}D$ 1.4872–1.4933. All fractions gave precipitates with 2,4-dinitrophenylhydrazine reagent. Refractionation of this product through a 30 × 0.8-cm. semi-micro column with a spinning band afforded 6.64 g. (58%) of a product, b.p. 56–61° (0.7 mm.), $n^{25}D$ 1.4893–1.4906. The infrared spectrum of this product showed a small hydroxyl band.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.11; H, 8.80.

1,4-Epoxycycloöctane (I).—The slightly impure ketone described above, 5.65 g., was placed in a Claisen distilling flask with 7.0 g. of solid potassium hydroxide, 5.0 ml. of hydrazine hydrate and 50 ml. of diethylene glycol. The mixture was heated under reflux for 1 hr., and then a mixture of water and the 1,4-oxide I was distilled slowly for 1.5 hr., after which 5.0 ml. of water was added and distilled over the course of 1 hr. Another addition of water followed by distillation gave a clear distillate, indicating that the reaction was complete. The distillates were combined, the water solution was made strongly acidic with hydrochloric acid and the product was extracted with three 20-ml. portions of petroleum ether. The combined extracts were dried with sodium hydride, filtered and the solvent was distilled. Sodium (about 0.5 g.) was added, and the mixture was heated in a flask attached to a semi-micro column until the sodium had melted and this temperature was maintained for 15 minutes. Distillation yielded 2.82 g. (57%) of 1,4-epoxycycloöctane, b.p. 89–95° (53 mm.). The later fractions crystallized when cooled. A middle fraction had b.p. 94° (53 mm.), $n^{25}D$ 1.4720, m.p. 30.8–32.2°.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.44; H, 11.29.

The infrared spectrum of this compound was free of hydroxyl and carbonyl bands (Fig. 1).

***trans*-1,4-Cycloöctanediol.**—1,4-Epoxycycloöctane, 0.95 g., 1.5 g. of acetic anhydride and 0.1 ml. of boron trifluoride etherate were heated on a steam-bath for 90 minutes, cooled and diluted to a volume of 50 ml. with ether. The ether solution was washed with two 20-ml. portions of water, dried overnight with anhydrous magnesium sulfate and the ether was distilled. The residue was placed in a flask attached to a semi-micro column, and 0.47 g. (37%) of material boiling in the range of the cycloöctenyl acetates was distilled. (Characterization of this material is described below.) The residue in the distilling flask was saponified by heating in methanol (15 ml.) with sodium hydroxide (1.0 g.) for 90 minutes. The methanol was distilled, the residue was taken up in water and the water solution was extracted continuously with chloroform overnight. Distillation of the extract afforded 0.16 g. of high-boiling residue which was chromatographed on Brockmann Grade III alumina.

Fractions 1–3 were eluted with benzene and amounted to 0.025 g.; fractions 4–15 were eluted with benzene–ether mixtures (0.002 g.); fractions 16–28 were eluted with 0.5% methanol–99.5% ether (0.009 g.); fractions 29–45 were eluted with 1% methanol–99% ether (0.066 g.); fractions 46–56 were eluted with 2% methanol–98% ether (0.002 g.); and fractions 57 and 58 were eluted with 50% methanol–50% ether (0.002 g.).

Fractions 29–45 contained 0.066 g. or 6% of the theoretical amount of crystalline *trans*-1,4-cycloöctanediol. A sample recrystallized twice from ethyl acetate had m.p. 89.5–91° (hot-stage) and did not depress the melting point (90.5–91.5°) of *trans*-1,4-cycloöctanediol that was identical with a sample prepared from *trans*-cycloöctene.[2] The in-

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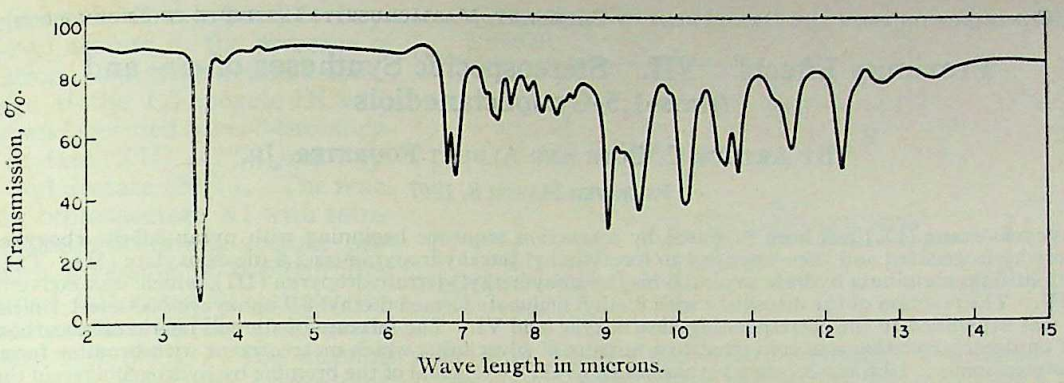

Fig. 1.—Infrared absorption spectrum of 1,4-epoxycycloöctane as a solution (100 mg./ml.) in carbon tetrachloride in the region 2–8μ and in carbon disulfide in the region 8–16μ.

frared spectra of these compounds determined at 1% concentration in a potassium bromide pellet were superimposable.

The other fractions, which did not crystallize, were discarded. There was no indication that they contained the easily crystallized *cis*-1,4-cycloöctanediol.

Treatment of the Low-boiling Fraction.—A mixture of 0.47 g. of the cycloöctenyl acetate fraction, 5.0 ml. of methanol and 2.0 g. of potassium hydroxide was heated under reflux for 40 minutes, and the mixture was then diluted with water. Extraction of the product with ether and fractionation of the dried extracts afforded 0.28 g. (79%) of an unsaturated alcohol. This material was treated with 0.4 g. of phenyl isocyanate, and when the mixture had solidified, the excess phenyl isocyanate was distilled under reduced pressure. Chromatography of the product on alumina afforded 0.472 g. (87%) of a product which was homogeneous. A sample purified by recrystallization from methanol–water had m.p. 93–94°.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.81; N, 5.71. Found: C, 73.55; H, 7.89; N, 5.57.

Hydrogenation of the Phenylurethan, M.p. 93–94°.—In a micro hydrogenation apparatus were placed 15 ml. of 95% ethanol and 0.40 g. of 10% palladium-on-carbon hydrogenation catalyst. After the catalyst and solvent had equilibrated with the hydrogen atmosphere, a sample (0.0307 g.) of the phenylurethan described above was added. When the reduction was complete, after absorption of 98% of one molar equivalent of hydrogen, the solution was filtered and the ethanol was distilled. There was obtained 0.031 g. of a product, m.p. 53–56.5°. Recrystallization from aqueous methanol afforded cycloöctyl phenylurethan, m.p. 55.6–56.6°, alone or admixed with an authentic sample. The infrared spectra of the hydrogenation product and the authentic sample were identical. As noted earlier, the phenylurethan with m.p. 93–94° now has been identified as 4-cycloöcten-1-yl phenylurethan by ozonization.[6]

***cis*-1,4-Cycloöctanediol.**—1,4-Epoxycycloöctane (1.01 g.) and 1.5 g. of acetyl bromide were heated on a steam-bath for 1 hr. The brown mixture was cooled and poured into water. The product was extracted with ether, and the ethereal extract was washed with water, saturated sodium bicarbonate solution and again with water. The extract was dried and fractionated. There was obtained 0.79 g. or 40% of *trans*-4-bromocycloöctyl acetate, b.p. 90–95° (0.17 mm.), $n^{25}D$ 1.4980–1.4994. This product was dissolved in a solution of 0.90 g. of tetraethylammonium acetate monohydrate in 25 ml. of reagent acetone and the solution was heated under reflux for 4 hr. The acetone was distilled, water was added and the product was extracted with three 25-ml. portions of ether. The extracts were combined and dried with magnesium sulfate. The solvent was distilled, and the residue obtained was saponified by heating in methanol (25 ml.) with potassium hydroxide (2.0 g.) for 30 minutes. The methanol was distilled, 20 ml. of water was added and the mixture was extracted continuously with chloroform for 24 hr. Distillation of the solvent afforded 0.30 g. of viscous residue which was chromatographed on activity III alumina.

Fractions 1–14 were eluted with benzene–ether mixtures and amounted to 0.010 g.; fractions 15–18 were eluted with ether (0.005 g.); fractions 18–27 were eluted with 1% methanol–99% ether (no material); fractions 28–47 were eluted with 2% methanol–98% ether (0.137 g.); fractions 48–52 were eluted with 10% methanol–90% ether (0.007 g.); fractions 53–56 were eluted with 30% methanol–70% ether (no material).

Fractions 28–52 crystallized on evaporation of the solvent, and contained only one compound as shown by melting points and mixed melting points. A middle fraction after two recrystallizations from ethyl acetate melted at 83.0–84.5° alone or admixed with *cis*-1,4-cycloöctanediol prepared from *cis*-cycloöctene.[1] The yield of 0.144 g. was 31% from *trans*-4-bromocycloöctyl acetate.

Fractions 1–18 did not crystallize and were discarded.

***cis*-1,4-Cycloöctanediol Bis-*p*-nitrobenzoate.**—A portion (0.0549 g.) of the above glycol was treated with *p*-nitrobenzoyl chloride in pyridine under conditions previously described,[10] and the product was purified by chromatography on alumina. The yield of *cis*-1,4-cycloöctanediol bis-*p*-nitrobenzoate was 0.136 g. (81%), and after two recrystallizations from ethyl acetate the compound melted at 161.5–162.7° alone or admixed with the corresponding ester prepared from *cis*-1,4-cycloöctanediol obtained from *cis*-cycloöctene.[1]

The infrared spectra of the *cis*-1,4-glycol and its bis-*p*-nitrobenzoate were identical with the spectra of the same compounds prepared from *cis*-cycloöctene.

CAMBRIDGE, MASSACHUSETTS

(10) A. C. Cope, A. H. Keough, P. E. Peterson, H. E. Simmons, Jr., and G. W. Wood, THIS JOURNAL, **79**, 3900 (1957).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Proximity Effects. VII. Stereospecific Syntheses of *cis*- and *trans*-1,5-Cyclooctanediols

BY ARTHUR C. COPE AND ALBERT FOURNIER, JR.

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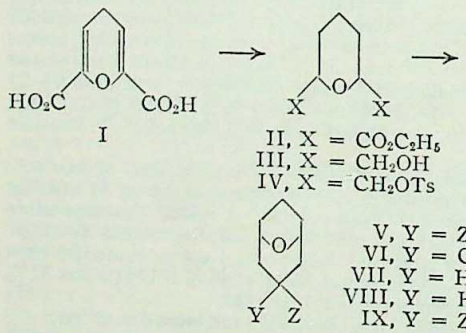
1,5-Epoxycyclooctane (IX) has been prepared by a reaction sequence beginning with pyran-2,6-dicarboxylic acid (I). This acid was hydrogenated and then esterified to form diethyl tetrahydropyran-*cis*-2,6-dicarboxylate (II). The ester was reduced with lithium aluminum hydride to *cis*-2,6-bis-(hydroxymethyl)-tetrahydropyran (III), which was converted to the ditosylate IV. The reaction of the ditosylate with diethyl malonate formed diethyl 3,7-epoxycyclooctane-1,1-dicarboxylate (V), which was saponified to the corresponding dicarboxylic acid VI. The mixture of stereoisomeric monocarboxylic acids VII formed on decarboxylation was converted to a mixture of silver salts, which on treatment with bromine formed a mixture of the stereoisomeric 1-bromo-3,7-epoxycyclooctanes (VIII). Removal of the bromine by hydrogenolysis in the presence of Raney nickel in triethylamine yielded the 1,5-epoxide IX. Cleavage of 1,5-epoxycyclooctane with a mixture of trifluoroacetic acid and acetic anhydride formed *trans*-1,5-cyclooctanediol (X), 4-cycloocten-1-ol (XI) and a very small amount of *trans*-1,4-cyclooctanediol. The reaction of the 1,5-epoxide with acetyl bromide formed *trans*-5-bromocyclooctyl acetate (XII) and 4-cycloocten-1-ol. Treatment of the bromoacetate XII with tetraethylammonium acetate followed by saponification yielded *cis*-1,5-cyclooctanediol (XIII) and 4-cycloocten-1-ol.

This paper reports stereospecific syntheses of *cis*- and *trans*-1,5-cyclooctanediol. The synthesis employed was similar to the one used for preparation of the *cis*- and *trans*-1,4-cyclooctanediols described in the preceding paper.[1] The key intermediate in these syntheses was 1,5-epoxycyclooctane, which was prepared by the reaction sequence outlined below.



Pyran-2,6-dicarboxylic acid (I)[2] was reduced catalytically in the presence of palladium-on-Norit forming *cis*-tetrahydropyran-2,6-dicarboxylic acid, which was esterified without isolation, forming diethyl *cis*-tetrahydropyran-2,6-dicarboxylate (II). Reduction of the ester with lithium aluminum hydride formed the crystalline *cis*-glycol III, which was converted to the crystalline ditosylate IV. The alkylation of diethyl malonate with this ditosylate formed the cyclic ester V in 72% yield. It is of interest that only this product of dialkylation was isolated, even though its formation requires the intramolecular alkylation of an intermediate in which two bulky substituents in a six-membered ring occupy the sterically unfavorable axial positions. Saponification of the dicarboxylic ester V formed the corresponding acid VI (83%), and decarboxylation yielded a mixture of the stereoisomeric monocarboxylic acids VII in 98% yield. Both of these isomers were isolated in pure form. The less soluble and higher melting form with m.p. 137.2–137.8° was purified by crystallization from carbon tetrachloride, while the lower melting isomer, which was present in much smaller amount, was isolated from the mother liquors by partition chromatography by the method of Ramsey and Paterson.[3] The evidence available at present is insufficient to determine which acid contains the carboxyl group *cis* and which *trans* to the oxide bridge.

The method chosen for removal of the carboxyl group in VII was treatment of the corresponding silver salt with bromine. For this purpose, the mixture of the stereoisomers VII was converted to a mixture of the corresponding silver salts. Subsequent treatment with bromine in carbon tetrachloride formed a mixture of the stereoisomeric bromides VIII in 54% yield (allowing for 22% recovery of the higher melting acid VII). Attempts to remove the bromine atom in VIII by hydrogenolysis in the presence of palladium-on-Norit or platinum-in-glacial acetic acid containing sodium acetate were unsuccessful, because the catalysts became poisoned rapidly. However, the hydrogenolysis was successful in the presence of Raney nickel in triethylamine as a solvent and afforded 1,5-epoxycyclooctane (IX) (82%), a very volatile solid, m.p. 52.5–53.9°, with a camphoraceous odor.

Cleavage of the 1,5-oxide IX by treatment with a mixture of zinc chloride and acetic anhydride gave almost exclusively 4-cycloocten-1-ol and very little glycol. The amount of elimination was decreased by using a mixture of acetic anhydride and trifluoroacetic acid for the cleavage. With this mixture, the products isolated after saponification were 4-cycloocten-1-ol (40%), identified as the phenylurethan, and a mixture of glycols (28%) that was separated by chromatography on alumina. This mixture contained *trans*-1,5-cyclooctanediol (X) and *trans*-1,4-cyclooctanediol in a ratio of approximately 4:1. The *trans*-1,5-glycol was obtained as a very viscous oil that has failed to crystallize during a period of months. It formed a crystalline bis-*p*-nitrobenzoate, m.p. 182.3–183.3°, which is different from any of the other seven isomeric cyclooctanediol bis-*p*-nitrobenzoates (mixed melting points are depressed, and the infrared spectra of the isomers differ). The formation of a small amount of *trans*-1,4-cyclooctanediol in this reaction may be explained by addition of

(1) A. C. Cope and B. C. Anderson, THIS JOURNAL, **79**, 3892 (1957).

(2) E. E. Blaise and H. Gault, *Bull. soc. chim. France*, [4] **1**, 129 (1907).

(3) L. L. Ramsey and W. I. Paterson, *J. Assoc. Offic. Agr. Chemists*, **31**, 139 (1948).

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acetic acid to the double bond in 4-cycloöcten-1-yl acetate in the presence of the very strong acid, trifluoroacetic acid.

Cleavage of the 1,5-epoxide IX with acetyl bromide formed *trans*-5-bromocycloöctyl acetate (XII) (47%) and 4-cycloöcten-1-yl acetate (20%). The reaction of the bromoacetate XI with tetraethylammonium acetate in acetone proceeded with inversion of configuration and afforded (after saponification) *cis*-1,5-cycloöctanediol (XIII) (14%) and 4-cycloöcten-1-ol (26%). The alcohols were separated by chromatography on alumina. The *cis*-1,5-glycol was obtained as a crystalline solid, m.p. 73.8–74.5°, which formed a bis-*p*-nitrobenzoate, m.p. 181.4–182.8°, that was different from the corresponding derivative of the *trans* isomer (mixed melting point and comparison of infrared spectra).

Evidence pointing to the steric proximity of groups attached to the 1- and 5-positions of the cycloöctane ring was obtained by observation of the behavior of *trans*-5-bromocycloöctyl acetate on saponification. This reaction resulted in the formation of the 1,5-epoxide IX.

Experimental[4]

Diethyl Tetrahydropyran-*cis*-2,6-dicarboxylate (II).—Diethyl oxaloacetate was regenerated from the commercial sodium enolate by treatment with dilute sulfuric acid and ether and isolated by extraction with ether and distillation; b.p. 92.5° (2.4 mm.), $n^{25}D$ 1.4482–1.4491. To the freshly distilled ester (179 g.) at 0° was added 40 g. of formalin (37% formaldehyde), sufficient 95% ethanol to give a homogeneous solution and 0.85 ml. of glacial acetic acid. Piperidine (3 ml.) was added with stirring while the temperature was maintained at 5–10°, and the solution was then placed in a refrigerator at 5°. After 7 hr. a solution of 1.5 ml. of piperidine and 0.41 ml. of glacial acetic acid in a small volume of ethanol was added to the yellow mixture with stirring, and it was allowed to stand at 5° for an additional period of 36 hr. The nearly solid mass was filtered, and the solid was washed with ice-cold methanol until the yellow color was removed. After drying at 1 mm. and room temperature overnight, there was obtained 136.4 g. (74%) of methylene bis-(diethyl oxaloacetate) as fine white crystals, m.p. 74.7–76.2° (lit.[5] m.p. 81°).

The above ester (228 g.) was stirred and heated under reflux with 230 ml. of concentrated hydrochloric acid and 230 ml. of water until the oily drops of the ester disappeared (about 2 hr.). The solution was concentrated under reduced pressure, and the residue was dried at 1 mm. for 4 hr. and recrystallized from a mixture of acetone and benzene to give 64.4 g. (71%) of α,α'-diketopimelic acid, m.p. 127.8–129.6° (lit.[6] m.p. 127°). Pyran-2,6-dicarboxylic acid[2] was prepared by dissolving 64.4 g. of finely powdered α,α'-diketopimelic acid in 325 ml. of concentrated sulfuric acid with stirring at 10–20° and allowing the solution to stand at 0° for 2.5 hr. The solution was poured into 3 l. of ice and water and the solid was collected on a filter and washed with 3 l. of water and 300 ml. of methanol. After drying at 0.5 mm. and room temperature, the yield of pyran-2,6-dicarboxylic acid was 54 g. (93%) (no definite m.p. below 300°).

A suspension of 54 g. of crude pyran-2,6-dicarboxylic acid in 600 ml. of absolute ethanol was hydrogenated at room temperature and 26–21 p.s.i. in the presence of 5 g. of 10% palladium-on-Norit. After 3.5 hr. the reduction was complete and the very slightly soluble acid had dissolved. The catalyst was removed by filtration and washed with two 150-ml. portions of hot absolute ethanol. Benzene (1.2 l.) and 2 ml. of concentrated sulfuric acid were added and the solution was refluxed overnight. The solution was slowly concentrated at atmospheric pressure during a period of 4 hr. and finally under reduced pressure. The residue was dissolved in ether and the solution was washed with saturated sodium bicarbonate solution, water, saturated sodium chloride solution and dried over Drierite. Distillation of the product gave 64.8 g. (91%) of diethyl *cis*-tetrahydropyran-2,6-dicarboxylate, b.p. 95° (0.07 mm.), $n^{25}D$ 1.4527, d^{25}_4 1.118.

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.35; H, 7.94.

A sample of the ester was refluxed overnight with potassium hydroxide in ethanol. The solution was concentrated, diluted with water, acidified and extracted with chloroform in a continuous extractor. The extract was dried over magnesium sulfate and concentrated to dryness. The residue of tetrahydropyran-*cis*-2,6-dicarboxylic acid had m.p. 191–192.2° (lit.[7] m.p. 193°).

***cis*-2,6-Bis-(hydroxymethyl)-tetrahydropyran (III).**—A solution of diethyl tetrahydropyran-*cis*-2,6-dicarboxylate (64.2 g.) in 550 ml. of dry ether was added with stirring to a slurry of lithium aluminum hydride (13.6 g.) in 400 ml. of dry ether with stirring in a 3-l., three-necked flask which was protected against moisture. The rate of addition was such that a gentle reflux was maintained. After refluxing for an additional 1.5 hr., the excess lithium aluminum hydride was destroyed by the cautious addition of water. The complex was decomposed with approximately 275 ml. of 20% sulfuric acid. The ether layer was separated and dried over magnesium sulfate. The aqueous layer was extracted with chloroform in a continuous extractor for 26 hr. and the chloroform extract dried over magnesium sulfate. The extracts were combined and the product distilled to give 37.6 g. (92%) of *cis*-2,6-bis-(hydroxymethyl)-tetrahydropyran. The product solidified on standing overnight in a refrigerator and had m.p. 41–44.4°. After several recrystallizations from ether–petroleum ether (30–60°) it had m.p. 45.7–46.4°.

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.44; H, 9.65. Found: C, 57.33; H, 9.69.

***cis*-2,6-Bis-(hydroxymethyl)-tetrahydropyran Ditosylate (IV).**—To a solution of *cis*-2,6-bis-(hydroxymethyl)-tetrahydropyran (37.6 g.) in 130 ml. of dry pyridine was added at 0° in one portion *p*-toluenesulfonyl chloride (108 g.) in 400 ml. of dry pyridine. The solution was stirred at 0° for approximately 20 hr. and poured with stirring into about 2 l. of ice and water. The product separated as an oil but soon solidified. It was collected on a filter, washed with large amounts of water and recrystallized from methanol to give 103 g. (95%) of *cis*-2,6-bis-(hydroxymethyl)-tetrahydropyran ditosylate, m.p. 93–94°. An analytical sample that was recrystallized from methanol had m.p. 93.8–94.8°.

Anal. Calcd. for $C_{19}H_{22}O_7S_2$: C, 55.49; H, 5.76. Found: C, 55.42; H, 5.61.

Diethyl 3,7-Epoxycycloöctane-1,1-dicarboxylate (V).—A 3-l. stainless steel autoclave was charged with a solution of diethyl malonate (13.6 g.) in 100 ml. of dry tetrahydrofuran. Sodium hydride (4.1 g.) was added over the course of 2 hr., followed by *cis*-2,6-bis-(hydroxymethyl)-tetrahydropyran ditosylate (35 g.) and 1400 ml. of dry tetrahydrofuran. The autoclave was sealed and rocked and heated at 110–120° for 27 hr. The mixture was rinsed from the bomb with dry ether and concentrated under reduced pressure. To the

(4) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses.

(5) This preparation is a modification of a procedure described by H. Gault, *Bull. soc. chim. France*, [4] **1**, 24 (1907).

(6) E. E. Blaise and H. Gault, *ibid.*, [4] **1**, 78 (1907).

(7) W. Czornodola, *Roczniki Chem.*, **16**, 459 (1936); *C. A.*, **31**, 1807 (1937).

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concentrate was added about 350 ml. of 10% hydrochloric acid, and the product was extracted with three 170-ml. portions of ether. The extracts were combined, washed with saturated sodium chloride solution and dried over magnesium sulfate. Two additional preparations were made under similar conditions from 35 and 33 g. of the ditosylate, respectively. The ether extracts of the three preparations were combined, concentrated and the product was distilled, yielding 43.6 g. (72%) of diethyl 3,7-epoxycycloöctane-1,1-dicarboxylate, b.p. 104° (0.15 mm.), $n^{25}D$ 1.4639. An analytical sample had b.p. 104° (0.15 mm.), $n^{25}D$ 1.4650, d^{25}_4 1.133.

Anal. Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.21. Found: C, 62.40; H, 8.17.

The residue from the distillation was dissolved in methanol and treated with Norit; it yielded 4.25 g. of the recovered crystalline ditosylate.

3,7-Epoxycycloöctane-1,1-dicarboxylic Acid (VI).—Diethyl 3,7-epoxycycloöctane-1,1-dicarboxylate (43.6 g.) was heated under reflux with potassium hydroxide (27 g.) in 130 ml. of 95% ethanol and 20 ml. of water for 21 hr. The solution was concentrated under reduced pressure, 130 ml. of water was added to the residue and the aqueous solution was acidified. The precipitated dicarboxylic acid was removed by filtration and the mother liquor was extracted continuously overnight with chloroform. A total of 28.8 g. (83%) of crude 3,7-epoxycycloöctane-1,1-dicarboxylic acid was obtained, m.p. 167° dec. (the fraction separated by filtration) and 182° dec. (from the chloroform extracts). An analytical sample was obtained by recrystallization from ethyl acetate and had m.p. 186.5–187° dec.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59; neut. equiv., 107. Found: C, 56.18; H, 6.71; neut. equiv., 108.

Decarboxylation of 3,7-Epoxycycloöctane-1,1-dicarboxylic Acid.—3,7-Epoxycycloöctane-1,1-dicarboxylic acid (28.8 g.) was heated at 200° until the evolution of gas ceased. The product, a mixture of the stereoisomeric 3,7-epoxycycloöctane-1-carboxylic acids, weighed 22.8 g. (98%), m.p. 122.5–134°.

Separation of the Isomeric 3,7-Epoxycycloöctane-1-carboxylic Acids (VII).—A 1.509-g. sample of the mixture of isomers was recrystallized once from carbon tetrachloride and gave 1.05 g. of material with m.p. 133–137°, a recovery of 70%. This proved to be one of the isomeric 3,7-epoxycycloöctane-1-carboxylic acids. After two additional recrystallizations, it had m.p. 137.2–137.8°.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.54; H, 8.29; neut. equiv., 170. Found: C, 63.58; H, 8.21; neut. equiv., 168.

The other isomeric 3,7-epoxycycloöctane-1-carboxylic acid was isolated by partition chromatography[3] of the mother liquors from recrystallization of the mixture. The mixture (100 mg.) was chromatographed on 40 g. of 100-mesh silicic acid and during the elution with isoöctane two bands appeared on the column. They were fractionally eluted with 4 fractions being collected. Fraction 1 (41 mg., main portion of the first band) had m.p. 137–137.6°; fraction 2 (9 mg., remainder of the first band) had m.p. 134–135.6°; fraction 3 (19 mg., front portion of the second band) had m.p. 87.2–89.7°; and fraction 4 (18 mg., main portion of the second band) had m.p. 89.6–90.4°.

Fractions 3 and 4 were combined and recrystallized from hexane and furnished the second isomeric 3,7-epoxycycloöctane-1-carboxylic acid, m.p. 90–90.6°. The infrared absorption spectrum of this acid was different from the spectrum of the higher melting isomer.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.54; H, 8.29; neut. equiv., 170. Found: C, 63.85; H, 8.51; neut. equiv., 163.

1-Bromo-3,7-epoxycycloöctane (VIII).—A mixture of the isomeric 3,7-epoxycycloöctane-1-carboxylic acids (11.6 g.) and 50 ml. of water was heated to boiling and neutralized to the phenolphthalein end-point with 30% potassium hydroxide. The solution of the potassium salts was again heated to boiling and treated with a solution of silver nitrate (11.6 g.) in 10 ml. of water with constant agitation. The mixture was allowed to cool and filtered. The solid was washed with 100 ml. of methanol and dried at 1 mm. to give 15.3 g. (81%) of silver 3,7-epoxycycloöctane-1-carboxylate.

The silver salt (14.89 g.) was dried at 0.05 mm. and 90–100° for 34 hr. in a 500-ml. round-bottomed three-necked flask. The flask was then equipped with a Hershberg stirrer and an addition funnel. Carbon tetrachloride which had been dried over phosphorus pentoxide was added and about 50 ml. of the solvent distilled from the flask. A solution of bromine (8.8 g.) in 40 ml. of carbon tetrachloride (the solution was dried over phosphorus pentoxide) was then added dropwise over a period of 17 min. while the temperature was maintained at 0–5°. The mixture was stirred for an additional period of 15 min. at 0–5° and then allowed to warm with stirring to room temperature; during this time some carbon dioxide was evolved. Upon heating under reflux carbon dioxide was evolved vigorously and ceased after 1.3 hr. After cooling, the silver bromide was removed by filtration and washed with a total of 100 ml. of hot carbon tetrachloride. The combined extracts were washed with 20 ml. of 10% sodium carbonate solution and dried over magnesium sulfate. The solution was concentrated under reduced pressure, and the residue was fractionally distilled through a semi-micro column to give 3.76 g. of the crude bromide. Decomposition was noted during the distillation of the last fraction and the distillation was stopped. The residue on short-path distillation yielded an additional 0.964 g. of a waxy solid, making a total of 4.73 g. (43%) of 1-bromo-3,7-epoxycycloöctane. All of the fractions eventually solidified. A center cut had these properties: b.p. 78.5° (1.5 mm.), m.p. 34.7–40°, $n^{25}D$ 1.5298.

Anal. Calcd. for $C_8H_{13}BrO$: C, 46.84; H, 6.39; Br, 38.97. Found: C, 46.75; H, 6.38; Br, 38.72.

The sodium carbonate extract was acidified and 1.97 g. of the higher melting isomer of 3,7-epoxycycloöctane-1-carboxylic acid was separated, m.p. 136.2–137.8° and m.p. 137–137.8° after recrystallization from carbon tetrachloride.

1,5-Epoxycycloöctane (IX).—1-Bromo-3,7-epoxycycloöctane (8.99 g.) in 50 ml. of dry triethylamine was shaken with hydrogen overnight in the presence of approximately 2 g. of Raney nickel at 1500 p.s.i. and 90–100° in a 200-ml. glass-lined autoclave. After cooling, ether was added to the mixture and the solid was removed by filtration and washed several times with ether. The ether solution was washed with iced dilute hydrochloric acid, and the aqueous solution was extracted with two 15-ml. portions of ether. The combined extracts were washed with saturated sodium bicarbonate solution, saturated sodium chloride solution and dried over Drierite. The ether was distilled through a fractionating column and the residue was fractionated through a semi-micro column. The fractions solidified, and a center fraction had the following properties: b.p. 81° (30 mm.), m.p. 52.5–53.9° (after sublimation).

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.90; H, 10.88.

Cleavage of 1,5-Epoxycycloöctane with Acetic Anhydride and Trifluoroacetic Acid.—To 1,5-epoxycycloöctane (1.033 g.) was added a cold mixture of acetic anhydride (2.52 g.) and trifluoroacetic acid (7 g.). The solution was allowed to warm to room temperature, and after 40 min. it was heated at 80–85° for 1 hr. The solution was concentrated at 30 mm. by distillation through a semi-micro column with a final bath temperature of 105°. The dark residue was heated under reflux overnight with potassium hydroxide (4.6 g.) in 14 ml. of ethanol and 7 ml. of water. The solution was concentrated under reduced pressure, water was added to the residue and concentrated hydrochloric acid was added with cooling until a *p*H of 8–9 was reached. The aqueous mixture was extracted continuously with chloroform for 48 hr. and the chloroform removed under reduced pressure, leaving 860 mg. of a dark viscous oil. This product was taken up in 14 ml. of 1:1 ether–benzene and chromatographed on 30 g. of Activity III alumina, in a column 20 mm. in diameter, collecting 30-ml. fractions. Fractions 1, 4–9, 13–14, 30–31, 55–63 and 64–75 were discarded.

4-Cycloöcten-1-ol (XI).—The combined fractions 2 and 3 were distilled in a short-path still under reduced pressure to give a colorless liquid, $n^{25}D$ 1.4952. A 114-mg. sample was treated with 274 mg. of phenyl isocyanate, and the mixture was heated on a steam-bath for a few minutes and allowed to stand at room temperature overnight. Removal of the excess reagent at 1 mm. left 209 mg. of a phenylurethan with m.p. 86.8–93°. After several recrystallizations from hexane it had m.p. 94.5–95.4° and was identified as 4-cycloöcten-1-ol phenylurethan by comparison of the infrared spectrum with the spectrum of an authentic sample.[1]

***trans*-1,5-Cycloöctanediol Bis-*p*-nitrobenzoate.**—Fractions 15–20 (62 mg.) were treated with *p*-nitrobenzoyl

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Fraction	Eluent	Weight, mg.
1	Benzene–ether (1:1)	5
2–3	Benzene–ether (1:1)	364
4–9	Benzene–ether (1:1)	32
13–14	Ether	9
15–20	Ether	63
21–29	Ether	30
30–31	0.5% methanol–ether	3
32–37	0.5% methanol–ether	115
38–46	0.5% methanol–ether	75
47–54	0.5% methanol–ether	27
55–63	1.5% methanol–ether	11
64–75	10% methanol–ether	12

chloride (192 mg.) in a few milliliters of dry pyridine, and the solution was allowed to stand overnight. The solution was poured into water and the solid collected on a filter and washed with water. The product was dissolved in benzene and chromatographed on 5 g. of Activity II alumina to give 133 mg. (72%) of *trans*-1,5-cycloöctanediol bis-*p*-nitrobenzoate, which after recrystallization from ethanol had m.p. 182.3–183.3°.

Anal. Calcd. for $C_{22}H_{22}O_8N_2$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.91; H, 5.19; N, 6.32.

The infrared absorption spectrum of the *trans*-1,5-cyclooctanediol bis-*p*-nitrobenzoate was quite different from the spectra of the bis-*p*-nitrobenzoates of the other seven cyclooctanediols.

Treatment of fractions 21–29 (30 mg.) with *p*-nitrobenzoyl chloride (140 mg.) in the manner described above gave 76 mg. (86%) of *trans*-1,5-cycloöctanediol bis-*p*-nitrobenzoate, m.p. 182–182.8° after recrystallization from ethanol.

trans-1,5-Cycloöctanediol bis-*p*-nitrobenzoate (25 mg.) was heated under reflux with 0.2 g. of potassium hydroxide in 5 ml. of ethanol for 2 hr. The ethanol was removed under reduced pressure, water added and the aqueous solution extracted continuously with chloroform for 2 hr. After drying over magnesium sulfate and removal of solvent, there was left 5 mg. (63%) of *trans*-1,5-cycloöctanediol as an oil which has not crystallized in a period of several months.

Identification of *trans*-1,4-Cycloöctanediol.—Fractions 47–54 (27 mg.) were treated with *p*-nitrobenzoyl chloride (105 mg.) in dry pyridine, and the product was isolated by the procedure described above. The crude bis-*p*-nitrobenzoate amounted to 89 mg. and after six recrystallizations was identified as *trans*-1,4-cycloöctanediol bis-*p*-nitrobenzoate, m.p. 154.9–156.3°, not depressed on mixture with an authentic sample.[8]

Cleavage of 1,5-Epoxycycloöctane with Acetyl Bromide.—To 1,5-epoxycycloöctane (1.01 g.) was added acetyl bromide (2.25 g.), and the mixture was heated under reflux for 75 min. The mixture was cooled, poured into water and the product was extracted with three 15-ml. portions of ether. The combined extracts were washed with saturated sodium bicarbonate solution, water, saturated sodium chloride solution and dried over magnesium sulfate. After removal of the ether the product was distilled through a semi-micro column. A low boiling fraction (1) 228 mg., b.p. 40° (0.2 mm.), $n^{25}D$ 1.4702, was separated from three fractions totaling 948 mg., b.p. 82–83° (0.2 mm.), $n^{25}D$ 1.4955–1.4984. Fraction 1 was identified as 4-cycloöcten-1-yl acetate (20% yield) by saponification to the alcohol (75 mg., $n^{25}D$ 1.4969), which was converted to the phenylurethan, m.p. and mixed m.p. with an authentic sample[1] (after recrystallization from hexane) 93–94.5°. The higher boiling fractions correspond to a 47% yield of *trans*-5-bromocycloöctyl acetate (XII).

1,5-Epoxycycloöctane from *trans*-5-Bromocycloöctyl Acetate.—*trans*-5-Bromocycloöctyl acetate (599 mg.) was heated under reflux with potassium hydroxide (522 mg.) in 5 ml. of absolute ethanol. The mixture was poured into 30 ml. of water and the product was extracted with four 10-ml. portions of ether. The combined extracts were washed with water and saturated sodium chloride solution and dried over magnesium sulfate. The solvent was removed at atmospheric pressure and the product sublimed at 90 mm. and 50°. There was obtained in two fractions 107 mg. (42%) of 1,5-epoxycycloöctane, m.p. 48.2–52.4°.

***cis*-1,5-Cycloöctanediol (XIII).**—Crude *trans*-5-bromocycloöctyl acetate (0.99 g.) and tetraethylammonium acetate monohydrate (1.7 g.) were heated under reflux in 20 ml. of reagent grade acetone for 16 hr. Most of the acetone was removed by distillation and water was added. The product was extracted with ether and the extract washed with water and saturated sodium chloride solution and dried over magnesium sulfate. The ether was removed under diminished pressure and the product heated under reflux with 2 g. of potassium hydroxide in 15 ml. of 95% ethanol. The ethanol was removed under reduced pressure, water was added and the aqueous solution was extracted with ether. The aqueous solution also was extracted continuously with chloroform for several hours, and the total amount of glycol from the two extracts (300 mg.) was chromatographed on 10 g. of grade II alumina in a column 10 mm. in diameter, collecting 15-ml. fractions.

Fraction	Eluent	Weight, mg.
1	Benzene–ether	5
2–10	Benzene–ether	123
11–16	Ether	0
17–23	1% methanol–ether	78

Fractions 2–10 were distilled in a short-path still under reduced pressure and yielded 4-cycloöcten-1-ol, $n^{25}D$ 1.4951, identified as the phenylurethan (m.p. and mixed m.p. of 92.4–93.4°, and by its infrared spectrum, which was identical to the spectrum of an authentic sample[1]).

Fraction 18 solidified on removal of the eluent and had m.p. 72.5–73.5°. After 2 recrystallizations from ether–petroleum ether (30–60°) there was obtained crystalline *cis*-1,5-cycloöctanediol, m.p. 73.8–74.8°.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.62; H, 11.19. Found: C, 66.72; H, 11.13.

The infrared absorption spectrum of the *cis*-1,5-glycol was different from the spectra of the other seven cycloöctanediols.

The combined fractions 19–23 had m.p. 68.7–71.9° and yielded the pure *cis*-1,5-glycol upon recrystallization.

***cis*-1,5-Cycloöctanediol Bis-*p*-nitrobenzoate.**—A sample of the above diol (20 mg.) was treated with *p*-nitrobenzoyl chloride (75 mg.) in a few milliliters of dry pyridine. The yield of *cis*-1,5-cycloöctanediol bis-*p*-nitrobenzoate was 51 mg. (83%). After two recrystallizations from ethanol, the derivative had m.p. 181.4–182.6°. A mixture with *trans*-1,5-cycloöctanediol bis-*p*-nitrobenzoate had m.p. 159–168°. An analytical sample had m.p. 181.4–182.8°.

Anal. Calcd. for $C_{22}H_{22}O_8N_2$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.99; H, 5.13; N, 6.33.

CAMBRIDGE, MASSACHUSETTS

(8) A. C. Cope, A. H. Keough, P. E. Peterson, H. E. Simmons, Jr., and G. W. Wood, THIS JOURNAL, **79**, 3900 (1957).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Proximity Effects. VIII. Solvolysis of *cis*-Cycloöctene Oxide; Synthesis of Alcohols in the Cycloöctane Series[1]

BY ARTHUR C. COPE, ALLEN H. KEOUGH, PAUL E. PETERSON,[2] HOWARD E. SIMMONS, JR.,[3] AND GEOFFREY W. WOOD

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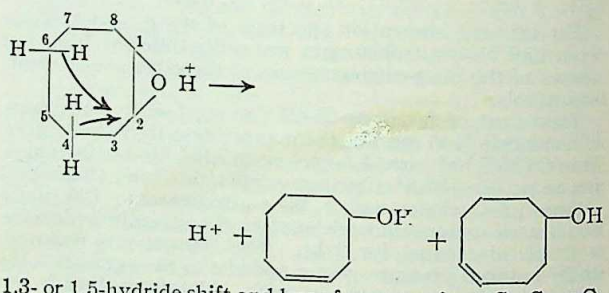
The solvolysis of *cis*-cycloöctene oxide in formic acid has been shown to yield, in addition to the *cis*-1,4- and *trans*-1,2-cycloöctanediols already reported, a lower boiling fraction containing 3-cycloöcten-1-ol and 4-cyloöcten-1-ol (15% total), a saturated alcohol that appears to be a bicycloöctanol (at least 0.1%), cycloöctanone (trace), 1,4- and 1,5-epoxycycloöctane (about 0.1% total) and an unidentified alcohol (about 1%). Three non-stereospecific syntheses of 1,4-cycloöctanediols are reported. *cis*- and *trans*-1,4-cycloöctanediol have been shown to be epimers by oxidation to the same diketone, which on reduction formed a mixture of the two glycols. The *cis* isomer has been converted to the *trans* through the monotosylate (not isolated). *trans*-1,3-Cycloöctanediol has been prepared, and its stereochemistry has been determined by establishing the configuration of the intermediate compound, *trans*-2,3-epoxycycloöctan-1-ol. *trans*-1,3-Cycloöctanediol has been converted to the *cis* isomer through the monotosylate (not isolated). Derivatives of various alcohols in the cycloöctane series have been prepared.

Solvolysis of *cis*-Cycloöctene Oxide.—Previous papers in this series have described reactions of cycloöctane derivatives that are influenced by what has been called a "proximity effect." The original example of such a reaction, *i.e.*, the solvolysis of *cis*-cycloöctene oxide in formic acid,[4] has now been reinvestigated. Additional products have been found, some of which appear to arise through the influence of proximity effects.

Repetitions of the solvolysis of *cis*-cycloöctene oxide resulted in isolation of the previously reported diols, *trans*-1,2-cycloöctanediol (5.6–19%) and *cis*-1,4-cycloöctanediol (23–30%). The structure and *cis* configuration of the latter diol have since been confirmed by synthesis.[5]

In addition, distillation of the alcohol mixture obtained in the solvolysis of the oxide gave a low-boiling fraction amounting to 16–17% of the weight of the oxide. This fraction yielded a phenylurethan which, after several recrystallizations, melted at 102.4–103.6°. This phenylurethan has been shown to be 3-cycloöcten-1-yl phenylurethan.[6] Infrared analysis, based upon the available spectra of 2-cycloöcten-1-ol, 3-cycloöcten-1-ol and 4-cycloöcten-1-ol and upon the spectra of the corresponding phenylurethans, indicated that the low boiling material contained considerable 4-cycloöcten-1-ol in addition to 3-cycloöcten-1-ol. The presence of 4-cycloöcten-1-ol in the alcohol mixture was confirmed by preparation of a *p*-nitrobenzoate. The product, which was isolated in 13% yield, proved to be the *p*-nitrobenzoate of 4-cycloöcten-1-ol, m.p. 83–85°. The failure of 3-cycloöcten-1-yl *p*-nitrobenzoate to crystallize from the mixture was explained when an authentic sample was prepared and found to have a melting point of 32–33°. It is of interest that no appreciable amount of 2-cycloöcten-1-ol, which might be considered a "normal" product of the *cis*-cycloöctene oxide solvolysis, appeared to be present in the alcohol mixture. The unsaturated alcohols therefore represent additional products formed by a transannular reaction. They could originate directly from the oxide by a concerted elimination reaction or could result from dehydration of the initially formed *cis*-1,4-cycloöctanediol.



1,3- or 1,5-hydride shift and loss of a proton from C_3, C_5 or C_7

Hydrogenation of the alcohol mixture resulted in uptake of 92–100% of one mole of hydrogen giving cycloöctanol, which was isolated as its phenylurethan in 85% yield. These results would be expected for an alcohol mixture consisting mostly of 3-cycloöcten-1-ol and 4-cycloöcten-1-ol.

In order to isolate any bicyclic alcohol that might be present in the low-boiling material, a sample was subjected to a separation procedure involving silver nitrate extraction, conversion of alcohols to the phenylurethans, ozonolysis (to remove the phenylurethans of unsaturated alcohols) and chromatography. From the chromatogram the phenylurethan of a saturated alcohol was obtained with an analysis in agreement with a bicycloöctyl phenylurethan structure. The yield was 0.1% based on *cis*-cycloöctene oxide. The presence of a bicyclic alcohol among the solvolysis products could be due to a transannular reaction in which the double bond of one of the cycloöctenols forms a bond bridging the cycloöctane ring subsequent to or concomitant with removal of the protonated hydroxyl group. The absence of either isomer of bicyclo[3.3.0]octan-2-ol[7] in the original alcohol mixture was shown by vapor phase chromatography. Comparison of melting points showed that the saturated phenylurethan of unknown structure is not derived from either of these bicycloöctanols. The structure of the unknown phenylurethan is being investigated.

When the low boiling distillate from *cis*-cycloöctene oxide solvolysis was collected in several

(1) Supported by a research grant (NSF-G990) of the National Science Foundation.

(2) National Institutes of Health Postdoctoral Fellow, 1956–1957.

(3) National Science Foundation Fellow, 1953–1954.

(4) A. C. Cope, S. W. Fenton and C. F. Spencer, THIS JOURNAL, **74**, 5884 (1952).

(5) A. C. Cope and B. C. Anderson, *ibid.*, **79**, 3892 (1957).

(6) A. C. Cope and G. W. Wood, *ibid.*, **79**, 3885 (1957).

(7) A. C. Cope, H. Haldwar and H. E. Petree, to be published.

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fractions, the first fractions contained a carbonyl compound that was shown to be cycloöctanone by comparison of the 2,4-dinitrophenylhydrazone with authentic cycloöctanone 2,4-dinitrophenylhydrazone.

Vapor phase chromatography of the first distillation fractions from the *cis*-cycloöctene oxide solvolysis revealed the presence of two major peaks which could not be attributed to any of the compounds previously identified. Comparison with known samples on the vapor phase column showed that the compounds were not cycloöctadienes or *cis*-cycloöctene oxide. Samples of the unknown materials were collected by condensation from the effluent gas from the vapor-phase apparatus. The infrared spectrum of one of the fractions indicated that it was a mixture of 1,4- and 1,5-epoxycyclooctane.[5,8] These ethers could be formed from the 3- and 4-cycloöcten-1-ol produced in the *cis*-cycloöctene oxide solvolysis.

The infrared spectrum of the second fraction indicated that it was an unsaturated alcohol. Further characterization of this compound will be reported in connection with another problem.

Synthesis of Cycloöctanediols.—Although stereospecific syntheses of 1,4- and 1,5-cycloöctanediols now have been accomplished[5,8] other methods of preparation are of interest as more practical sources of the glycols. Since *cis*-1,4-cycloöctanediol was available from solvolysis of *cis*-cycloöctene oxide, it was made the starting material for synthesis of *trans*-1,4-cycloöctanediol. Oxidation of *cis*-1,4-cycloöctanediol with N-bromosuccinimide in aqueous acetone gave 1,4-cycloöctanedione, characterized by preparation of the dioxime and bis-2,4-dinitrophenylhydrazone, in 63% yield. Hydrogenation of the diketone over Raney nickel gave a mixture of glycols which was separated by chromatography on alumina into approximately equal amounts of *cis*-1,4-cycloöctanediol and *trans*-1,4-cycloöctanediol. The latter glycol formed a bis-*p*-nitrobenzoate identical with a sample derived from the *trans*-1,4-glycol obtained by solvolysis of *trans*-cycloöctene oxide.[9]

Alternatively, the *cis*-1,4-cycloöctanediol was epimerized to the *trans* isomer *via* the crude mono-*p*-toluenesulfonate obtained by reaction of one molar equivalent of *p*-toluenesulfonyl chloride with *cis*-1,4-cycloöctanediol. Treatment of the product with tetraethylammonium acetate followed by hydrolysis and chromatography gave *trans*-1,4-cycloöctanediol (21%) and some recovered *cis*-1,4-cycloöctanediol (5%).

The bromination of 2-cycloöcten-1-yl acetate with N-bromosuccinimide also was studied as a possible route leading eventually to 1,4-cycloöctanediols. A bromoacetate was obtained in 43% yield which is formulated as 4-bromo-2-cycloöcten-1-yl acetate, but presumably exists as a mixture with its allylic isomer, 2-bromo-3-cycloöcten-1-yl acetate. Treatment with tetraethylammonium acetate in acetone followed by hydrogenation and saponification gave a glycol mixture in 47% yield, from which *trans*-1,4-cycloöctanediol was isolated in 19% yield (based on the glycol mixture) by crystallization from ethyl acetate. Chromatography of the mother liquors gave an additional 4% of *trans*-1,4-cycloöctanediol. When silver acetate in acetic acid was allowed to react with the allylic bromoacetate, a 53% yield of unsaturated diacetate was obtained which was converted to a saturated glycol mixture from which *trans*-1,4-cycloöctanediol was isolated in 37% yield (based on unsaturated diacetate).

Another sequence for the synthesis of 1,4-cycloöctanediols was based on the reported ease with which cyclopentadiene and 1,3-cyclohexadiene can be autoxidized.[10] *cis-cis*-1,3-Cycloöctadiene absorbed 40–43% of one mole of oxygen on stirring at room temperature with ultraviolet illumination for 28 hr. The crude reaction mixture was reduced directly with lithium aluminum hydride by modification of a procedure used for reduction of the polymeric peroxide of styrene to phenylethylene glycol,[11] and the resulting mixture of unsaturated glycols was hydrogenated. A mixture of cycloöctanediols was isolated in 8% yield. Treatment of the glycol mixture with acetone and copper sulfate afforded *trans*-1,2-cycloöctanediol isopropylidene ketal in 15% yield. Chromatographic analysis of the glycol residue (66% based on the glycol mixture) showed that it was composed of essentially pure *trans*-1,4-cycloöctanediol.

Previous papers in this series have described the preparation of all the possible cycloöctanediols by methods leading to products of known stereochemistry with the exception of the two epimeric 1,3-cycloöctanediols. Accordingly, the preparation of these diols, needed for comparison with diols obtained in the solvolysis of *trans*-cycloöctene oxide, was undertaken, beginning with 2-cycloöcten-1-ol. Epoxidation of the 2-cycloöcten-1-ol gave 2,3-epoxycycloöctan-1-ol as an oil which was hydrogenated over Raney nickel to give a mixture of 1,2- and 1,3-cycloöctanediols. Reaction of the glycol mixture with acetone in the presence of cupric sulfate gave *trans*-1,2-cycloöctanediol isopropylidene ketal in 75% yield. Crystallization of the glycol residue from the acetone–cupric sulfate reaction gave *trans*-1,3-cycloöctanediol in 12% yield. Assignment of configuration to the latter compound is based in part upon the above results, which show that the oxide group in 2,3-epoxycycloöctan-1-ol is *trans* to the hydroxyl group to the extent of at least 75% and also upon the result of lithum aluminum hydride reduction. When the latter reaction was carried out by addition of lithium aluminum hydride to 2,3-epoxycycloöctan-1-ol, a 1,3-cycloöctanediol identical with the 1,3-glycol obtained by hydrogenation with Raney nickel was isolated in 50% yield. It can thus have been formed only from *trans*-2,3-epoxycycloöctan-1-ol and must therefore be the *trans*-1,3-glycol. The lithium aluminum hydride reduction also gave *trans*-1,2-cycloöctanediol, isolated in 35% yield as the

(8) A. C. Cope and A. Fournier, Jr., THIS JOURNAL, **79**, 3896 (1957).

(9) A. C. Cope, A. Fournier, Jr., and H. E. Simmons, Jr., *ibid.*, **79**, 3905 (1957).

(10) (a) N. D. Zelinsky and A. N. Titowa, *Ber.*, **64**, 1399 (1931); (b) K. Bodendorf, *Arch. Pharm.*, **271**, 1 (1933); (c) H. Hock and F. Depke, *Chem. Ber.*, **84**, 349 (1951).

(11) A. V. Tobolsky and R. B. Mesrobian, "Organic Peroxides," Interscience Publishers, Inc., New York, N. Y., 1954.

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TABLE I

CYCLOÖCTANEDIOLS AND DERIVATIVES

Cycloöctanediol	M.p., °C.	M.p. of bis-phenylurethan, °C.	M.p. of bis-*p*-nitrobenzoate, °C.	M.p. of di-*p*-toluenesulfonate, °C.
cis-1,2-	77.5–79[a]	175.5–176.8[a]	166.2–166.9[b]	94.5–95.5[c]
trans-1,2-	31.0–32.5[m]	176.2–177.4[a]	111.6–112.6[d]	124.6–125.2[e]
cis-1,3-	57.0–58.0		129.4–130.1[f]	
trans-1,3-	106.5–108.0		163.0–165.0[g]	
cis-1,4-	85.0–86.5[a]	186.0–187.5[a]	161.5–162.7[h]	96.5–98.5[a]
trans-1,4-	90.0–91.0[i]	180.2–181.7[j]	156.2–156.7[k]	
cis-1,5-	73.8–74.8[l]		181.4–182.8[l]	
trans-1,5-	Liquid[l]		182.3–183.3[l]	

[a] Reported in ref. 4. [b] Calcd. for $C_{22}H_{22}O_8N_2$: C, 59.72; H, 5.01. Found: C, 59.38; H, 5.23. [c] Calcd. for $C_{22}H_{28}O_6S_2$: C, 58.38; H, 6.24. Found: C, 58.57; H, 6.25. [d] Calcd. for $C_{22}H_{22}O_8N_2$: C, 59.72; H, 5.01. Found: C, 59.95; H, 5.23. [e] Calcd. for $C_{22}H_{28}O_6S_2$: C, 58.38; H, 6.24. Found: C, 58.24; H, 6.13. [f] Calcd. for $C_{22}H_{22}O_8N_2$: C, 59.72; H, 5.01. Found: C, 59.64; H, 5.08. [g] Calcd. for $C_{22}H_{22}O_8N_2$: C, 59.72; H, 5.01. Found: C, 59.52; H, 4.92. [h] Reported in ref. 5. [i] Reported in ref. 6. [j] Calcd. for $C_{22}H_{26}O_4N_2$: C, 69.09; H, 6.85. Found: C, 69.16; H, 6.95. [k] Calcd. for $C_{22}H_{22}O_8N_2$: C, 59.72; H, 5.01. Found: C, 59.70; H, 5.13. [l] Reported in ref. 8. [m] Reported in ref. 4 as a liquid. This glycol crystallized approximately 7 years after it was first obtained as a viscous liquid, purified by distillation. It was purified by recrystallization from ether–pentane.

isopropylidene ketal. These results indicate that the epoxidation of 2-cycloöcten-1-ol results almost exclusively in addition of oxygen *trans* to the hydroxyl group, in contrast to the epoxidation of 2-cyclohexen-1-ol, which forms *cis*-2,3-epoxycyclohexan-1-ol.[12]

2-Cycloöcten-1-one also was investigated as an intermediate which could lead to 1,3-cycloöctanediols. Preparation of this known[13] ketone was accomplished in improved yield by oxidation of 2-cycloöcten-1-ol with active manganese dioxide in pentane. Epoxidation with sodium hydroperoxide in methanol gave 2,3-epoxycycloöctan-1-one. This epoxide was not investigated further, since the corresponding alcohol was obtained more readily.

trans-1,3-Cycloöctanediol was epimerized to the *cis* isomer *via* the crude mono-*p*-toluenesulfonate in a manner similar to that employed in the epimerization of *cis*-1,4-cycloöctanediol. *cis*-1,3-Cycloöctanediol was isolated in 20% over-all yield. *trans*-1,3-Cycloöctanediol was further characterized by oxidation with chromic anhydride–pyridine complex to give 1,3-cycloöctanedione, isolated as the bis-2,4-dinitrophenylhydrazone. The same method was employed to convert both *cis*- and *trans*-1,4-cycloöctanediol to 1,4-cycloöctanedione bis-2,4-dinitrophenylhydrazone. The bis-2,4-dinitrophenylhydrazone of 1,2-cycloöctanedione also was prepared for comparison.

The melting points of all the cycloöctanediols and of the derivatives which have been prepared from them are collected in Table I. Melting points of derivatives of the cycloöctenols are listed in Table II.

Experimental[14]

Solvolysis of *cis*-Cycloöctene Oxide.—Several repetitions of the solvolysis of *cis*-cycloöctene oxide on a large scale have given results of which the following are typical. *cis*-Cycloöctene oxide (80.5 g.) was added in portions over a period of 1 hr. to 1 l. of 90% formic acid heated on a steam-bath. After 2 additional hr. of heating, the formic acid was removed by distillation at 100 mm. The resulting mixture of formates was saponified by stirring with 300 ml. of 40% sodium hydroxide at the reflux temperature for 1 hr. The resulting two-phase mixture was extracted with 300 ml. of chloroform. Short-path distillation of the chloroform extract gave 60.0 g. of material which was distilled through a spinning-band column. A low-boiling material (13.2 g.) was collected in five fractions, b.p. 55–70° (1 mm.), and was shown by the methods described below to consist principally of 3- and 4-cycloöcten-1-ol. This fraction was followed by the glycol fraction, b.p. 115–130° (1 mm.), containing *trans*-1,2-cycloöctanediol and *cis*-1,4-cycloöctanediol.

TABLE II

CYCLOÖCTENOLS AND DERIVATIVES

Cycloöctenol	M.p. of phenylurethan, °C.	M.p. of *p*-nitrobenzoate, °C.
2-Cycloöcten-1-ol	92.5–93.0[a]	104.5–105.0[b]
3-Cycloöcten-1-ol	101.5–102.5[c]	32.0–33.0[d]
4-Cycloöcten-1-ol	93.0–94.0[e]	83.0–85.0[f]

[a] Reported in ref. 13. [b] Calcd. for $C_{15}H_{17}O_4N$: C, 65.44; H, 6.23. Found: C, 65.57; H, 6.41. [c] Reported in ref. 6. [d] Calcd. for $C_{15}H_{17}O_4N$: C, 65.44; H, 6.23. Found: C, 65.31; H, 6.07. [e] Reported in ref. 5. [f] Calcd. for $C_{15}H_{17}O_4N$: C, 65.44; H, 6.23. Found: C, 65.55; H, 6.26.

Identification of 3-Cycloöcten-1-ol and 4-Cycloöcten-1-ol.—Earlier experiments indicated that the low-boiling material consisted mostly of 3-cycloöcten-1-ol or a mixture of cycloöctenols. This was shown by hydrogenation of a sample to cycloöctanol, identified as its phenylurethan, which was isolated in 85% yield, and by preparation of a phenylurethan from the low boiling material. Recrystallization of the unsaturated phenylurethan yielded 3-cycloöcten-1-yl phenylurethan, m.p. 102.4–103.6°, whose structure was known from ozonization.[6]

The presence of 4-cycloöcten-1-ol in the low boiling material was indicated by the infrared spectrum of the crude unsaturated phenylurethan, which contained bands characteristic of 4-cycloöcten-1-yl phenylurethan at 697 and 724 $cm.^{-1}$ as well as those of 3-cycloöcten-1-yl phenylurethan at 685, 705, 768 and 780 $cm.^{-1}$. The absence of any appreciable amount of 2-cycloöcten-1-yl phenylurethan was demonstrated by the fact that there was no band at 950 $cm.^{-1}$ where 2-cycloöcten-1-yl phenylurethan has an absorption band of medium intensity. Further evidence for the composition of the unsaturated alcohol fraction was obtained by comparison of its infrared spectrum with the spectra of authentic samples of 3-cycloöcten-1-ol (described below, strong band at 705 $cm.^{-1}$) and 4-cycloöcten-1-ol (strong band at 725 $cm.^{-1}$). The infrared spectrum of the low-boiling material from the *cis*-cycloöctene oxide solvolysis could be accounted for by assuming it to be a mixture of the two alcohols. Finally, the presence of 4-cycloöcten-1-ol in the low-boiling material was confirmed by isolation of a *p*-nitrobenzoate prepared from the alcohol mixture, which was shown by mixed m.p. and infrared spectrum to be identical with the *p*-nitrobenzoate prepared from authentic 4-cycloöcten-1-ol.

(12) H. B. Henbest and R. A. L. Wilson, *Chemistry & Industry*, 659 (1956).

(13) A. C. Cope, M. R. Kinter and R. T. Keller, THIS JOURNAL, **76**, 2757 (1954).

(14) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses.

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Bicyclic Alcohol.—The presence in the low-boiling material of a small amount of a saturated alcohol isomeric with the cycloöctenols was demonstrated by isolation of the phenylurethan of the alcohol as follows. Distillation fractions 4 and 5 of the low-boiling material (5.94 g.) were treated with 35 ml. of 20% silver nitrate to remove unsaturated compounds. The insoluble saturated compounds were then extracted with ether (35 ml.), and the ether layer was washed twice with 5-ml. portions of 20% silver nitrate. Vapor phase chromatography (described below) of the ether layer showed the presence of at least three components in addition to a band that may have been due to cycloöctenols not removed by the silver nitrate. Evaporation of the ether gave 0.16 g. of a product that was warmed with 0.19 g. of phenyl isocyanate on a steam-bath. Removal of the excess phenyl isocyanate under reduced pressure and ozonolysis followed by reduction with sodium borohydride gave a product that was chromatographed on alumina (Merck, acid-washed). This is the procedure used previously,[6] except that treatment of the reduction product with phenyl isocyanate was omitted. The saturated phenylurethan which was eluted with 20% ether in petroleum ether (0.14 g.) was recrystallized from methanol and water, m.p. 118–119.5°.

Anal. Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.36; H, 7.62; N, 5.75.

Cycloöctanone.—Distillation fractions 1 and 2 of the low boiling material from *cis*-cycloöctene oxide solvolysis gave several peaks upon vapor phase chromatography, in contrast to fractions 4 and 5, which gave a single major peak. The infrared spectrum of fraction 1 showed a carbonyl peak at 1688 cm.$^{-1}$. This unusually low frequency for carbonyl absorption suggested the presence of cycloöctanone (reported[15] carbonyl absorption at 1692 cm.$^{-1}$). The presence of cycloöctanone was confirmed by the preparation of a 2,4-dinitrophenylhydrazone, m.p. 171.0–173.2°, undepressed in mixed m.p. with authentic cycloöctanone 2,4-dinitrophenylhydrazone, m.p. 174.8–175.1°.

1,4- and 1,5-Epoxycycloöctanes and the Unidentified Component.—At this point the two remaining major components of fractions 1 and 2 which gave peaks upon vapor phase chromatography were isolated from the effluent gas stream of the vapor phase apparatus by attaching small collecting vessels as the fractions were eluted from the column. The column employed for this separation was a 12-mm. Pyrex tube with a 180-cm. length of packing consisting of 30% Dow-Corning Silicone oil no. 550 on a ground firebrick support (38–80 mesh). The column was heated to 180° and employed helium introduced under a pressure of about 60 cm. as the gas phase. Detection involved use of thermistors to measure changes in the thermal conductivity of the effluent gases. In preparative use, amounts up to 0.7 ml. were separated on the above column. The purity of the components collected in this manner was then checked by analysis on a column similar to the one described above, except that it was constructed of 8-mm. tubing.

One of the components separated in this manner was present in appreciable quantity only in distillation fraction 1, indicating that it had a relatively low boiling point. The infrared spectrum of this component showed that it was a mixture of 1,4- and 1,5-epoxycycloöctane.[5,8] The yield, estimated by vapor phase chromatography, was 0.1%. The other component appeared in fractions 1 and 2, indicating a somewhat higher boiling point, and no information concerning its structure has been obtained except the infrared spectrum, which indicates that it is an unsaturated alcohol. The estimated yield was 1%.

Cycloöctanediols.—The glycol fraction obtained when the *cis*-cycloöctene oxide solvolysis products were distilled yielded *trans*-1,2-cycloöctanediol as the isopropylidine ketal (5.6%) and *cis*-1,4-cycloöctanediol (23.6%), separated by methods that have been described.[4] In the present case a residue of 9.7% (calculated as diols) did not crystallize. However, the residue consisted mostly of *cis*-1,4-cycloöctanediol as shown by the fact that short-path distillation followed by crystallization yielded additional *cis*-1,4-cycloöctanediol (corresponding to 4.5%) plus non-crystalline material that was chromatographed to give still more crystalline *cis*-1,4-cycloöctanediol. The chromatogram yielded, in addition, several non-crystalline components that were not investigated further. It is estimated that none of the non-crystalline materials was present in over-all yield of as much as 1%.

3-Cycloöcten-1-ol.—Authentic 3-cycloöcten-1-ol, used in the identification of the alcohols formed in the solvolysis of *cis*-cycloöctene oxide, was obtained from the phenylurethan of m.p. 101.5–102.5°, isolated from the low-boiling *cis*-cycloöctene oxide solvolysis products, known to be 3-cycloöcten-1-yl phenylurethan by ozonolysis.[6] The phenylurethan (2.3 g.) was added to 50 ml. of tetrahydrofuran containing 0.4 g. of lithium aluminum hydride. The mixture was heated under reflux for 24 hr. during which time two additional 0.4-g. quantities of lithium aluminum hydride were added. The cooled reaction mixture was diluted with 100 ml. of ether to facilitate the subsequent filtration, and 3 ml. of water was added. Filtration, followed by drying and distillation of the solvent, gave a residual liquid that was distilled through a semi-micro column, yielding 0.45 g. (38%) of 3-cycloöcten-1-ol, b.p. 68° (1.5 mm.).

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.29; H, 11.04.

The infrared spectrum of the alcohol and of the crude phenylurethan prepared from it showed that little if any 4-cycloöcten-1-ol was present in the product. The crude phenylurethan melted at 100–102° and was shown by mixed melting point and infrared spectrum to be 3-cycloöcten-1-yl phenylurethan.

1,4-Cycloöctanedione from *cis*-1,4-Cycloöctanediol.—The oxidation of *cis*-1,4-cycloöctanediol to the corresponding diketone by benzoquinone in an Oppenauer-type oxidation is reported to give 15% yield.[4] The following procedure using N-bromosuccinimide[16] as the oxidizing agent gave 63% of the diketone. To *cis*-1,4-cycloöctanediol (10.5 g.) in 1500 ml. of acetone and 150 ml. of water was added 62.5 g. of N-bromosuccinimide followed by 5 ml. of glacial acetic acid. The mixture was cooled with a water-bath and allowed to stand for 2 hr. The solution was poured into 500 ml. of saturated sodium bicarbonate solution, and 200 ml. of 10% sodium thiosulfate was added. The mixture was filtered, and the filtrate was concentrated below 50° under reduced pressure and extracted with chloroform. The crude product was submitted first to short-path distillation at 1 mm. and then to fractionation through a semi-micro column, giving 6.41 g. (63%) of 1,4-cycloöctanedione, b.p. 73–76° (1 mm.). The diketone was a low-melting solid that had m.p. 46.8° after redistillation.

1,4-Cycloöctanedione Bis-2,4-dinitrophenylhydrazone.—The preparation of 1,4-cycloöctanedione was repeated on a small scale, except that the product from chloroform extraction was treated with 2,4-dinitrophenylhydrazine reagent. From 103 mg. of *cis*-1,4-cycloöctanediol, 361 mg. (101%) of 1,4-cycloöctanedione bis-2,4-dinitrophenylhydrazone was isolated. The product was recrystallized from nitrobenzene–ethanol to a constant melting point of 212° (introduced at 205°) and from mixed melting point and the infrared spectrum was identical with the derivative prepared from the pure diketone, although the melting point of the derivative by the latter route was higher (217.4°). Analytical data for a sample of 1,4-cycloöctanedione bis-2,4-dinitrophenylhydrazone prepared *via* oxidation of *cis*-1,4-cycloöctanediol with chromic anhydride–pyridine complex is reported elsewhere in this paper.

1,4-Cycloöctanedione Dioxime.—1,4-Cycloöctanedione (83 mg.) was heated under reflux with 0.5 ml. of absolute ethanol, 0.5 ml. of pyridine and 100 mg. of hydroxylamine hydrochloride for 2 hr. Evaporation of the solvent, followed by addition of water, gave 42 mg. (65%) of the dioxime, which after recrystallization from 95% ethanol melted at 169.5–170.2°.

Anal. Calcd. for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29. Found: C, 56.73; H, 8.30.

Hydrogenation of 1,4-Cycloöctanedione.—1,4-Cycloöctanedione (1.33 g.) in 4.3 ml. of 95% ethanol was hydrogenated over Raney nickel at 100° and 100 atmospheres. The crude product (1.03 g.) was chromatographed on 75 g. of neutral alumina of activity III, giving 229 mg. of *trans*-1,4-cycloöctanediol (eluted with 0.5% methanol in ether) and 231 mg. of *cis*-1,4-cycloöctanediol (eluted with 2% methanol

(15) V. Prelog, *J. Chem. Soc.*, 420 (1950).

(16) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **72**, 5530 (1950).

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in ether), along with some intermediate fractions that contained both glycols.

4-Bromo-2-cycloöcten-1-yl Acetate.—In a typical preparation a mixture of 2-cycloöcten-1-yl acetate (8.02 g.), N-bromosuccinimide (8.50 g.), carbon tetrachloride (150 ml.) and benzoyl peroxide (0.04 g.) was heated under reflux for 20 min. After cooling, succinimide was separated by filtration, and the filtrate was washed with sodium bicarbonate solution. The solvent was removed without external heating and the residue was subjected to short-path distillation under reduced pressure followed by fractionation through a semi-micro column, giving 4-bromo-2-cycloöcten-1-yl acetate (5.08 g., 43%), b.p. 81.5° (0.27 mm.), $n^{25}D$ 1.5122.

Anal. Calcd. for $C_{10}H_{15}BrO_2$: C, 48.60; H, 6.12; Br, 32.35. Found: C, 48.39; H, 6.03; Br, 32.69.

Cycloöctenediol Diacetate. A. From Tetraethylammonium Acetate.—A solution of 4-bromo-2-cycloöcten-1-yl acetate (5.73 g.) in 75 ml. of dry acetone was heated under reflux for 20 hr. with 10 g. of tetraethylammonium acetate monohydrate. After filtration and removal of acetone under reduced pressure, water was added and the product was extracted with ether. The extract yielded 3.95 g. (75%) of cycloöctenediol diacetate upon distillation through a semi-micro column. An analytical sample had b.p. 90° (0.38 mm.), $n^{26}D$ 1.4700.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.68; H, 8.02. Found: C, 63.44; H, 8.15.

Selenious acid oxidation of *cis*-cycloöctene is reported to give 27% of cycloöctenediol diacetate of unknown stereochemistry.[17]

Cycloöctanediols from Method A.—Cycloöctenediol diacetate (6.32 g.) was hydrogenated over 0.21 g. of Adams platinum catalyst (which had been pre-reduced in 50 ml. of methanol) with absorption of 133% of one molar equivalent of hydrogen, indicating some hydrogenolysis of the allylic acetate. After saponification with 5 g. of sodium hydroxide and 10 ml. of water, the concentrated reaction mixture was extracted with chloroform. The dried chloroform extract yielded a glycol mixture (2.47 g., 62%, based on the unsaturated diacetate) which was crystallized from ethyl acetate. After seeding the ethyl acetate solution, 0.470 g. of *trans*-1,4-cycloöctanediol separated (19% based on the glycol mixture), m.p. 90.7–92°. Chromatography of the mother liquor resulted in isolation of cycloöctanol (10% by weight based on the glycol mixture) and additional *trans*-1,4-cycloöctanediol (4%).

Cycloöctanediol Diacetate. B. From Silver Acetate.—4-Bromo-2-cycloöcten-1-yl acetate (5.12 g.) was stirred overnight with 4 g. of silver acetate in 25 ml. of 100% acetic acid (prepared by adding acetic anhydride to glacial acetic acid). After separation of silver bromide, fractionation gave 2.44 g. (52.6%) of cycloöctenediol diacetate. This mixture was converted to saturated glycols as in method A. In order to separate any 1,2-cycloöctanediol that might be present, the glycol mixture was shaken with acetone and cupric sulfate.[4] Chromatography of the product on alumina resulted in isolation of *trans*-1,2-cycloöctanediol isopropylidene ketal, identified by its infrared spectrum, in a yield of 5%. A later series of chromatographic fractions consisted of *cis*- and *trans*-1,4-cycloöctanediols. The total amount of *trans*-1,4-cycloöctanediol was 0.565 g. (37% based on unsaturated diacetate), and as in the case of the 1,4-cycloöctanedione hydrogenation product, the separation of the epimeric glycols by chromatography was not complete.

Epimerization of *cis*-1,4-Cycloöctanediol.—*p*-Toluenesulfonyl chloride (3.8 g.) was added to a solution of *cis*-1,4-cycloöctanediol (2.88 g.) in pyridine (20 ml.). The crude monotosylate was isolated after the mixture stood overnight by pouring it into water, extracting with benzene and washing the extract with dilute hydrochloric acid and water. The crude monotosylate (5.3 g.) was allowed to react with tetraethylammonium acetate (4.5 g.) in acetone (150 ml.), first at room temperature (24 hr.) and then under reflux (24 hr.). The crude monoacetate was isolated and hydrolyzed with sodium hydroxide, giving 1.66 g. of a product that was chromatographed on alumina, separating an unsaturated alcohol fraction (270 mg.), *trans* 1,4-cycloöctanediol (605 mg., 21%) which was identified by its infrared spectrum, and *cis*-1,4-cycloöctanediol (145 mg., 5%).

Autoxidation of 1,3-Cycloöctadiene.—*cis-cis*-1,3-Cycloöctadiene[18] (22.3 g.) was placed in a flask connected to a gas buret and illuminated with a 275-watt sun lamp under a positive pressure of oxygen for 28 hr., with stirring. During this time 2.13 liters (40% of 1 molar equivalent) of oxygen was taken up, giving a viscous product that was reduced directly. A solution of the reaction mixture in 130 ml. of ether was added dropwise to a slurry of 7.82 g. of lithium aluminum hydride in 200 ml. of anhydrous ether, maintained below 20°. The excess lithium aluminum hydride was destroyed by addition of 40 ml. of ethyl acetate, followed by 60 ml. of saturated ammonium chloride solution. Filtration, followed by short-path distillation (0.3–0.7 mm., 90–180° bath temperature) gave 14.99 g. of low-boiling liquid and 7.79 g. of higher boiling material. The latter yielded 2.32 g. of crude glycols after redistillation and hydrogenation in the presence of pre-reduced platinum oxide. From the crude glycols there was obtained *trans*-1,2-cycloöctanediol isopropylidene ketal (0.43 g., 15%) by the method described previously under "Method B." Chromatography of the glycol residue yielded fractions amounting to 0.95 g. from which *trans*-1,4-cycloöctanediol bis-*p*-nitrobenzoate was prepared.

***trans*-2,3-Epoxycycloöctan-1-ol.**—Commercial 40% peracetic acid (12.0 ml.) to which sodium acetate trihydrate (2.4 g.) had been added to neutralize the sulfuric acid present was added to 2-cycloöcten-1-ol[13] (5.00 g.) maintained at 10–15°. The reaction mixture was made basic with excess sodium hydroxide and extracted with ether. Distillation through a semi-micro column gave 4.70 g. (84%) of *trans*-2,3-epoxycycloöctan-1-ol, b.p. 99–100° (1.8 mm.), $n^{25}D$ 1.4930.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.65; H, 10.27.

Hydrogenation of *trans*-2,3-Epoxycycloöctan-1-ol.—Hydrogenation of a solution of 5.00 g. of *trans*-2,3-epoxycycloöctan-1-ol in ethanol in the presence of W-6 Raney nickel at 125° and 1300 p.s.i. gave 5.00 g. (99%) of a glycol mixture after short-path distillation of the product under reduced pressure. The 1,2-cycloöctanediol in the mixture was converted to the isopropylidene ketal,[4] and the latter compound (2.38 g., 75%) was isolated by distillation. The product, after chromatography on alumina, had an infrared spectrum identical with the spectrum of authentic *trans*-1,2-cycloöctanediol isopropylidene ketal and showed no bands attributable to *cis*-1,2-cycloöctanediol isopropylidene ketal. The ketal was further characterized by hydrolysis to the glycol[4] followed by conversion to the bis-*p*-nitrobenzoate.

***trans*-1,3-Cycloöctanediol.**—The glycol residue remaining after distilling the isopropylidene ketal from hydrogenation of *trans*-2,3-epoxycycloöctan-1-ol was recrystallized from benzene, giving 0.30 g. (12%) of *trans*-1,3-cycloöctanediol, m.p. 103–105°. An analytical sample that was recrystallized from benzene had m.p. 106.5–108°.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.62; H, 11.18. Found: C, 66.76; H, 11.11.

Lithium Aluminum Hydride Reduction of *trans*-2,3-Epoxycycloöctan-1-ol.—A slurry of lithium aluminum hydride (1.60 g.) in 30 ml. of ether was added to a solution of 1.5 g. of *trans*-2,3-epoxycycloöctan-1-ol in 25 ml. of ether. After 4 hr. the excess lithium aluminum hydride was destroyed by the addition of 5 ml. of ethanol, followed by concentrated sodium hydroxide. The ether layer was separated, and the aqueous layer was extracted with chloroform. Upon short-path distillation (100–130° at 1 mm.), 1.45 g. (96%) of a glycol mixture was obtained from the ether and chloroform extracts. The glycol mixture was separated in the manner described above for the hydrogenation products obtained from *trans*-2,3-epoxycycloöctan-1-ol, giving 0.65 g. (35%, based on glycols isolated) of *trans*-1,2-cycloöctanediol isopropylidene ketal, identified by its infrared spectrum, and 0.75 g. (50%) of *trans*-1,3-cycloöctanediol, m.p. 106.5–108°, undepressed on admixture with the glycol obtained by catalytic hydrogenation.

When the normal order of addition of reagents was employed, *i.e.*, when the epoxyalcohol was added to the lithium

(17) V. D. Azatyan and R. S. Gyuli-Kevkhyan, *Doklady Akad. Nauk Armyan. S. S. R.*, **21**, 209 (1955); C. A. **50**, 11257 (1956).

(18) A. C. Cope and J. J. Estes, Jr., THIS JOURNAL, **72**, 1128

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aluminum hydride slurry, there was obtained 44% of *trans*-1,2-cycloöctanediol isopropylidene ketal and 31% of *trans*-1,3-cycloöctanediol, based on the weight of crude glycols, isolated in 82% yield.

2-Cycloöcten-1-one.—2-Cycloöcten-1-ol (5.00 g.) was dissolved in pure pentane (80 ml.) and active manganese dioxide[19] (23.5 g.) was added. After 6 hr. the slurry was filtered. The filtrate yielded 4.02 g. (82%) of a mixture of 2-cycloöcten-1-one and 2-cycloöcten-1-ol which was found to contain 59% of the ketone by comparison of the ultraviolet spectrum with the spectrum of the pure ketone.[13] Repetition of the oxidation gave 3.02 g. (62% over-all) of 2-cycloöcten-1-one of 98% purity as indicated by the ultraviolet spectrum.

2,3-Epoxycycloöctan-1-one.—In a modification of the method of Weitz,[20] sodium hydroxide (10 ml. of a 6 *N* solution) was added to a cooled mixture of 10 ml. of 30% hydrogen peroxide in 75 ml. of methanol. While maintaining a temperature of 0–5°, 2-cycloöcten-1-one (2.00 g.) in methanol (10 ml.) was added. After an hour the mixture was poured into 80 ml. of ice-water, and the solution was extracted with ether. The ether extract yielded 0.095 g. (5%) of recovered 2-cycloöcten-1-one, b.p. 83–84° (11 mm.), and 0.809 g. (36%) of 2,3-epoxycycloöctan-1-one, b.p. 115–116° (5 mm.). The latter compound was a solid which after sublimation had m.p. 92.0–93.0°.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.46; H, 8.40.

Oxidation of *cis*- and *trans*-1,4-Cycloöctanediol with Chromic Anhydride–Pyridine Complex.—*cis*-1,4-Cycloöctanediol (0.100 g.) in dry pyridine (2 ml.) was added to the preformed complex[21] prepared from 0.555 g. of chromic anhydride and 6 ml. of pyridine. After stirring the mixture 30 minutes, it was allowed to stand overnight. The mixture was poured into 25 ml. of ice-water and extracted with four 40-ml. portions of chloroform. The extract was washed with dilute hydrochloric acid and dilute sodium bicarbonate and dried. Evaporation of the chloroform and treatment of the residue with 2,4-dinitrophenylhydrazine (0.270 g.) in ethanol (15 ml.) containing concentrated hydrochloric acid (5 drops) gave 1,4-cycloöctanedione bis-2,4-dinitrophenylhydrazone (0.250 g., 68%), m.p. 211.0–212.0° dec. after boiling the crude derivative with a large volume of ethanol. Recrystallization from nitrobenzene–ethanol gave an analytical sample, m.p. 211.8–212.0° (inserted at 205°).

Anal. Calcd. for $C_{20}H_{20}O_8N_8$: C, 48.00; H, 4.03. Found: C, 48.20; H, 4.15.

Oxidation of *trans*-1,4-cycloöctanediol (0.101 g.) by the same procedure gave 0.147 g. (42%) of 1,4-cycloöctanedione bis-2,4-dinitrophenylhydrazone, m.p. 211.3–211.5° after recrystallization from nitrobenzene–ethanol (1:1). No depression of melting point on admixture with an authentic sample was noted.

1,3-Cycloöctanedione Bis-2,4-dinitrophenylhydrazone.—Oxidation of *trans*-1,3-cycloöctanediol (0.100 g.) with chromic anhydride–pyridine complex followed by treatment with 2,4-dinitrophenylhydrazine as described for *cis*-1,4-cycloöctanediol gave 1,3-cycloöctanedione bis-2,4-dinitrophenylhydrazone (0.090 g., 26%), which had m.p. 233–234° (inserted at 225°) after recrystallization from nitrobenzene–ethanol.

Anal. Calcd. for $C_{20}H_{20}O_8N_8$: C, 48.00; H, 4.03. Found: C, 47.90; H, 4.16.

1,2-Cycloöctanedione Bis-2,4-dinitrophenylhydrazone.—Suberoin[4] (2.97 g.) was oxidized with cupric acetate monohydrate (8.36 g.) in methanol (2 ml.) and 50% aqueous acetic acid (20 ml.).[22] Distillation gave 1.76 g. (60%) of 1,2-cycloöctanedione, b.p. 58–60° (1 mm.), $n^{25}D$ 1.4699. Part of the diketone (0.276 g.) was treated with 2,4-dinitrophenylhydrazine reagent, giving 0.970 g. (99%) of 1,2-cycloöctanedione bis-2,4-dinitrophenylhydrazone. Recrystallization from nitrobenzene gave a sample with m.p. 216.0–216.5° (dec., inserted at 210°).

Anal. Calcd. for $C_{20}H_{20}O_8N_8$: C, 48.00; H, 4.03. Found: C, 48.32; H, 3.96.

***p*-Nitrobenzoates.**—The *p*-nitrobenzoates of the various cycloöctenols and cycloöctanediols prepared during this study were obtained by treating the alcohols with *p*-nitrobenzoyl chloride in pyridine at room temperature for 0.5 to 3.0 hr. followed by isolation in the usual manner,[23] except that in some cases *p*-nitrobenzoic acid and other impurities were removed by passing a solution of the crude *p*-nitrobenzoate through a column of neutral alumina. The melting points and analyses of the new derivatives appear in Tables I and II.

Di-*p*-toluenesulfonates.—The preparations of the new di-*p*-toluenesulfonates (Table II) were similar to the one reported for *cis*-1,4-cycloöctanediol di-*p*-toluenesulfonate.[4]

(19) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(20) E. Weitz and A. Scheffer, *Ber.*, **54B**, 2327 (1921).

(21) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(22) H. S. Corey, Jr., Ph.D. Thesis, M.I.T., 1954.

(23) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 164.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Proximity Effects. IX. Solvolysis of *trans*-Cycloöctene Oxide

BY ARTHUR C. COPE, ALBERT FOURNIER, JR., AND HOWARD E. SIMMONS, JR.[1]

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trans-Cycloöctene oxide has been prepared from *trans*-cycloöctene and peracetic acid. This oxide reacts exothermically with formic acid, forming a mixture of products that was isolated in 55% yield. Components of this mixture that have been isolated and the mole percentage of each include the following: first, products formed by a transannular hydride shift of the kind observed in previous work in this series: *trans*-1,4-cycloöctanediol, 33%; *trans*-1,3-cycloöctanediol, 1%; 4-cycloöcten-1-ol, 12%. In addition, three compounds formed by ring contraction were isolated. These were hexahydro-*o*-tolualdehyde (isolated as the acid), 25%; a liquid glycol $C_8H_{16}O_2$ (A) containing a C-methyl group, 16%; a second liquid glycol $C_8H_{16}O_2$ (B), also containing a C-methyl group, 13%.

trans-Cycloöctene oxide has been described by Ziegler and Wilms,[2] who prepared it from a sample of cycloöctene that is now known to be a mixture of *trans*- and *cis*-cycloöctene in a ratio of approximately 3:2.[3] In this work, *trans*-cycloöctene oxide was prepared from the pure *trans*-olefin and peracetic acid in 93% yield. Unlike *cis*-cycloöctene oxide, which is a crystalline solid, the *trans*-oxide is a liquid; differences in its infrared spectrum from the spectrum of the *cis*-oxide show that it is not contaminated by the *cis* isomer, and vapor phase chromatography indicated that the oxide prepared in this way is homogeneous.

(1) National Science Foundation Fellow, 1953–1954.

(2) K. Ziegler and H. Wilms, *Ann.*, **567**, 1 (1950).

(3) A. C. Cope, R. A. Pike and C. F. Spencer, THIS JOURNAL, **75**, 3212 (1953).

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Ziegler and Wilms heated *trans*-cycloöctene oxide with water at 120° and dilute aqueous sulfuric acid at 170–180°. No change in volume of the water-insoluble layer was noted in the absence of acid, while in the presence of acid a water-insoluble fraction was separated from the aqueous solution, but no products were isolated from either phase. We have found that *trans*-cycloöctene oxide reacts exothermically with formic acid to form a complex mixture. The products that were formed were separated into two fractions by distillation. A low-boiling fraction, b.p. 66–105° (22 mm.), was removed by distillation and contained 40% of the total product. The infrared spectrum of this mixture contained bands at 3000 and 1640 cm.$^{-1}$ (olefinic), 2700 cm.$^{-1}$ (aldehyde C–H), 1723 cm.$^{-1}$ (carbonyl) and 1180 cm.$^{-1}$ (formate ester). This mixture was treated with silver oxide and excess aqueous sodium hydroxide, in order to oxidize the aldehyde to an acid and at the same time to saponify the formate. Acidification of the alkaline solution formed a mixture of acids, $C_8H_{14}O_2$, which was saturated to permanganate and accordingly was composed of alicyclic acids. The infrared spectrum of the mixture contained an absorption band at 1375 cm.$^{-1}$, indicating the probable presence of a C-methyl group, and a Kuhn–Roth C-methyl determination (54% of one C-methyl group) indicated that one such group was present. The alicyclic carboxylic acids containing one C-methyl group that could be derived from *trans*-cycloöctene oxide with minimal ring contraction are *cis*- and *trans*-hexahydrotoluic acids. An amide prepared from the mixture of acids had m.p. 172.8–178.8°, a value consistent with the possibility that the mixture was composed of *cis*- and *trans*-hexahydro-*o*-toluic acids, whose amides melt at 151–153° and 181°, respectively.[4] *cis*-Hexahydro-*o*-toluic acid was prepared by the catalytic reduction of *o*-toluic acid[5] and converted to the *trans* isomer by heating with β-naphthalenesulfonic acid. The *p*-bromophenacyl ester of the *trans*-acid, m.p. 104–106°, proved to be identical with the corresponding derivative of the major component of the mixture of acids derived from the product obtained by rearrangement of *trans*-cycloöctene oxide. The mixture derived from the rearrangement product also contained some of the *cis*-acid, and an impure solid isolated from the mother liquors from recrystallization of the *p*-bromophenacyl ester prepared from the mixture contained characteristic bands at 1730, 1375, 890 and 758 cm.$^{-1}$ that are present in the spectrum of the *p*-bromophenacyl ester of *cis*-hexahydro-*o*-toluic acid, in addition to the bands present in the spectrum of the derivative of the *trans* isomer. Accordingly, the aldehyde formed from *trans*-cycloöctene oxide is hexahydro-*o*-tolualdehyde. It is uncertain from these results whether the aldehyde formed initially is the *cis* or *trans* isomer, for the *cis* isomer might be isomerized to the more stable *trans* form either in the formic acid solvolysis medium or in the presence of base during oxidation with silver oxide. Quite drastic conditions were required to isomerize the *cis*- to the *trans*-acid with β-naphthalenesulfonic acid, and vigorous acid treatment also has been used by others[6,7] to effect the isomerization. It was also shown that the *cis*-acid was affected relatively little if any by heating with aqueous sodium hydroxide at 180° for 8 hr. However, conversion of the *cis*- to the *trans*-aldehyde *via* an enol form would be expected to occur much more easily.

The alcohol formed by hydrolysis of the formate ester during treatment of the low-boiling fraction with alkaline silver oxide was shown to be composed principally of 4-cycloöcten-1-ol by preparation of the phenylurethan, which was compared with an authentic sample.[8] The alcohol was not examined in a manner that would detect the presence of 3-cycloöcten-1-ol unless it was the major component; both of these alcohols now are known to be formed in the solvolysis of *cis*-cycloöctene oxide.[9]

The high-boiling residue (60% by weight of the product) was saponified, and the alcohols that were formed were separated by chromatography on alumina. The first fraction contained 4-cycloöcten-1-ol, identified as the phenylurethan. The next fraction was a liquid glycol $C_8H_{16}O_2$ (A) that formed a bis-*p*-nitrobenzoate, m.p. 154–155°. Another liquid glycol $C_8H_{16}O_2$ (B) that formed a bis-*p*-nitrobenzoate, m.p. 175.5–180.4°, was eluted next. Both of these glycols were shown to be different from the eight isomeric cycloöctanediols by comparison of the infrared spectra of the bis-*p*-nitrobenzoates. Both glycols A and B gave negative periodate tests, indicating that they were not 1,2-glycols, and each contained one C-methyl group according to the Kuhn–Roth C-methyl determinations. From the broad melting range of the bis-*p*-nitrobenzoate, this derivative of glycol B may be a mixture of isomers, possibly stereoisomers. Further work is required to determine the structures of glycols A and B.

2-Hydroxy-2-methylcyclohexanemethanol was prepared from 2-hydroxymethylcyclohexanone and methylmagnesium iodide and shown not to be identical with either glycol A or B by conversion to the bis-*p*-nitrobenzoate, m.p. 214–215°. However, this synthesis apparently yielded predominantly one stereoisomer, and the structure of either glycol A or B may correspond to the other stereoisomer, or both may be position isomers of this formula or indeed may not have six-membered alicyclic rings.

The glycol eluted next from the chromatogram was *trans*-1,4-cycloöctanediol, identified as its bis-*p*-nitrobenzoate, m.p. 155.4–156.6°, which was identical with an authentic specimen. Finally, a small amount of crystalline *trans*-1,3-cycloöctanediol was eluted and identified by comparison with an authentic sample,[9] m.p. 109–111°.

The formation of *trans*-1,4- and *trans*-1,3-cycloöctanediol can be accounted for by hydride shifts across the eight-membered ring with concurrent attack by formic acid on the carbon atom from which the hydride shifts, as postulated for the con-

(4) K. v. Auwers and F. Dersch, *J. prakt. Chem.*, [2] **124**, 233 (1930).

(5) H. H. Hauber and R. Schonfelder, [illegible]

(6) A. Skita, *ibid.*, **431**, 23 (1923).

(7) W. Goodwin and W. H. Perkin, *J. Chem. Soc.*, **67**, 127 (1895).

(8) A. C. Cope and B. C. Anderson, THIS JOURNAL, **79**, 3892 (1957).

(9) A. C. Cope, A. H. Keough, P. E. Peterson, H. E. Simmons, Jr., [illegible] **79**, 3900 (1957).

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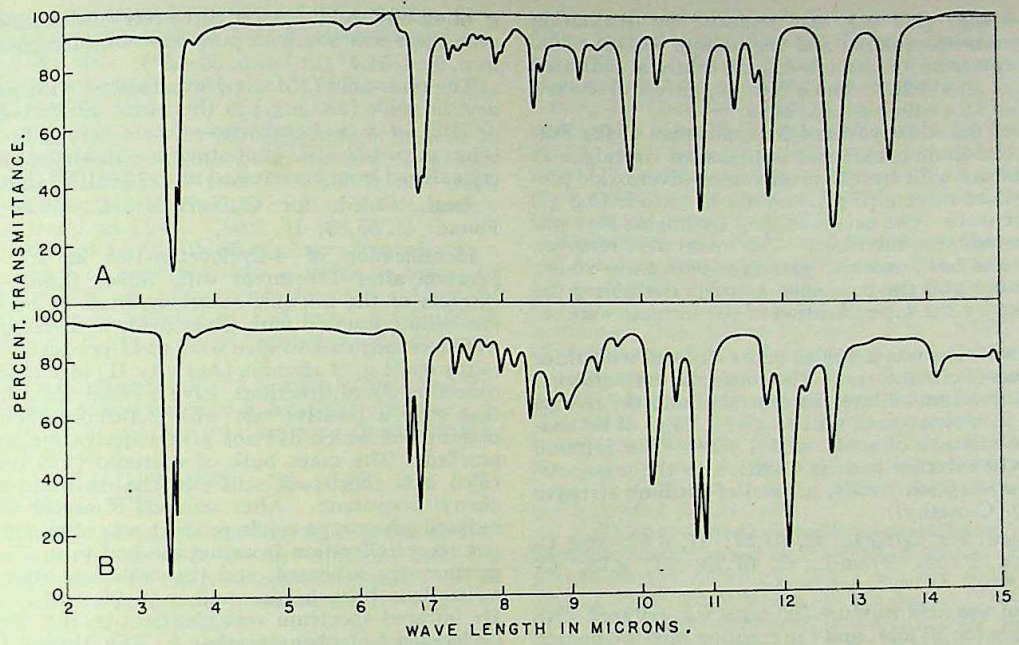
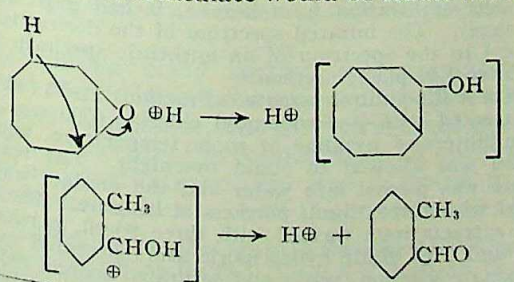


Fig. 1.—Infrared absorption spectra, determined with a Baird double beam infrared recording spectrometer, model B, fitted with a sodium chloride prism: curve A, *cis*-cycloöctene oxide; curve B, *trans*-cycloöctene oxide, both as solutions (100 mg./ml.) in carbon tetrachloride in the region 2–8μ and in carbon disulfide in the region 8–16μ, in a 0.1-mm. cell.

version of *cis*-cycloöctene oxide to *cis*-1,4-cycloöctanediol.[10] 4-Cycloöcten-1-ol may be formed in a similar manner, with loss of a proton accompanying the hydride shift,[9] or could be formed by the dehydration of *trans*-1,4-cycloöctanediol.

The formation of hexahydro-*o*-tolualdehyde in the solvolysis of *trans*-cycloöctene oxide is unusual in that ring contraction by two carbon atoms has occurred. Ring contraction of the oxides of cyclic olefins by one carbon atom has been described previously. For example, 1,4-dihydronaphthalene oxide on treatment with magnesium bromide yields 2-indanaldehyde in addition to β-tetralone.[11] 1-Methylcyclohexene oxide passed over kieselguhr at 220–230° forms 1-methylcyclopentanecarboxaldehyde as well as 2-methylcyclohexanone.[12] It seems likely that the spatial proximity of opposite sides of the eight-membered ring as well as the high degree of strain undoubtedly present in the *trans*-cycloöctene oxide are responsible for the unusual ring contraction that occurs in conversion of the oxide to hexahydro-*o*-tolualdehyde and glycols A and B. One reaction path by which the aldehyde could be formed is formulated below. It is quite possible that the bicyclo[4.2.0]cycloöctan-7-ol that is represented as an intermediate would be stable in formic acid under conditions used for the rearrangement. However, if such an intermediate is formed, cleavage of the four-membered ring could occur as formulated before the energy derived from cleavage of the strained *trans*-oxide was dissipated.



Work is in progress to determine the structures of glycols A and B.

Experimental[13]

trans-Cycloöctene Oxide.—*trans*-Cycloöctene (24.0 g.), purified by the aqueous silver nitrate extraction procedure,[3] was added dropwise during a period of 1 hr. with stirring to 65 ml. of commercial 40% peracetic acid[14] to which 13 g. of sodium acetate trihydrate had been added to neutralize the sulfuric acid present, with cooling to maintain a temperature of 0°. The mixture was stirred for 3 hr. at room temperature and then stored overnight at 5°. It was then placed in a separatory funnel containing crushed ice and neutralized to litmus by adding 30% sodium hydroxide solution. The aqueous solution was extracted with three 125-ml. portions of ether, and the combined extracts were washed with water and dried over magnesium sulfate. The solution was concentrated and the residue fractionated through a semi-micro column. The yield of *trans*-cycloöctene oxide, b.p. 85–86° (22 mm.), n^{25}D 1.4741, was 25.4 g. (93%). An analytical sample had b.p. 85.5° (22 mm.), n^{25}D 1.4740. Its infrared spectrum is shown in Fig. 1, together with the spectrum of *cis*-cycloöctene oxide.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.95; H, 10.98.

Solvolysis of *trans*-Cycloöctene Oxide with Formic Acid.—A 100-ml. three-necked flask equipped with a dropping funnel, thermometer and stirrer was charged with 24 ml. of 88% formic acid heated to 48°. *trans*-Cycloöctene oxide (6.7 g.) was added dropwise with stirring in a nitrogen atmosphere, while the temperature was maintained at 48–51° by cooling with an ice-bath. The reaction mixture was heated at 90–95° for 1 hr., cooled and poured into 95 ml. of water. The product was extracted with four 80-ml. portions of ether, and the combined extracts were washed with saturated sodium bicarbonate solution, water and dried over Drierite. Material with b.p. 66–105° (22 mm.),

(10) A. C. Cope, S. W. Fenton and C. F. Spencer, THIS JOURNAL, **74**, 5884 (1952).
(11) B. Tchoubar, *Compt. rend.*, **214**, 117 (1942).
(12) M. Tiffeneau, THIS JOURNAL, **195**, 1280 (1932).
(13) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses. Infrared spectra were determined with a Baird double beam recording spectrometer, model B, fitted with a sodium chloride prism.
(14) Obtained from Buffalo Peroxo Sales Corp., Buffalo, N. Y.

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$n^{25}D$ 1.4487–1.4657 (2.7 g.), was removed by distillation through a semi-micro column and the residue was set aside. An infrared spectrum of the low-boiling material indicated the presence of an aldehyde and a formate ester and showed the presence of an olefinic double bond.

Oxidation of the Aldehyde and Saponification of the Formate.—The low-boiling material was shaken overnight at room temperature with freshly precipitated silver oxide prepared from silver nitrate (9 g.), sodium hydroxide (5.3 g.) and 40 ml. of water (the excess sodium hydroxide also was present in the reaction mixture). The solids were removed by filtration, the basic solution extracted with three 20-ml. portions of ether and the combined extracts containing the alcohol formed by the saponification of the formate were set aside.

The basic solution was acidified and extracted with three 20-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate, concentrated and the residue was distilled in a short-path still to give 1.03 g. of an analytically pure mixture of acids, $n^{25}D$ 1.4580. The infrared spectrum of the mixture had, in addition to the usual carboxylic acid absorption bands, a band of medium strength at 1375 $cm.^{-1}$ (C-methyl).

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92; one C-methyl group, 10.55. Found: C, 67.79; H, 9.73; C-methyl, 5.78.[15]

A portion of the acid mixture (90 mg.) was refluxed with thionyl chloride for 30 min. and the reaction mixture poured into iced concentrated ammonium hydroxide. The product was filtered and a very poor yield of a mixture of amides was obtained. After two recrystallizations from water, it had m.p. 172.8–178.8°.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.70. Found: C, 68.19; H, 10.80.

Identification of *cis*- and *trans*-Hexahydro-*o*-toluic Acid.—The acid mixture (208 mg.) was treated with *p*-bromophenacyl bromide (408 mg.) according to the method of Shriner and Fuson.[16] A crude derivative was obtained (343 mg., 70%) with m.p. 80–96°. After four recrystallizations from hexane an analytical sample was obtained with m.p. 104–106° (hot-stage).

Anal. Calcd. for $C_{16}H_{19}BrO_3$: C, 56.66; H, 5.62. Found: C, 56.91; H, 5.62.

A mixture of this derivative with authentic *trans*-hexahydro-*o*-toluic acid *p*-bromophenacyl ester showed no depression and the infrared spectra of the two derivatives were identical.

The mother liquors from the recrystallization of the *p*-bromophenacyl ester of the acid mixture were concentrated to give a residue which after recrystallization from hexane had m.p. 52–90° (hot-stage). The infrared spectrum of this mixture indicated it to be mostly *cis*-hexahydro-*o*-toluic acid *p*-bromophenacyl ester, contaminated with the *trans* isomer.

***cis*-Hexahydro-*o*-toluic Acid *p*-Bromophenacyl Ester.**—A solution of *o*-toluic acid (15 g.) in glacial acetic acid (50 ml.) containing concentrated hydrochloric acid (0.5 ml.) was hydrogenated at room temperature in the presence of 3.3 g. of Adams platinum catalyst at 38–30 p.s.i. The reduction was complete in 2.5 hr. After filtration, the solvent was removed under reduced pressure and the product distilled to give 12.9 g. (81%) of *cis*-hexahydro-*o*-toluic acid, b.p. 83–85° (1 mm.), $n^{25}D$ 1.4620.

A portion of the acid was converted to the amide, which after two recrystallizations from water had m.p. 154.5–156° (lit.[4] m.p. 151–153°).

cis-Hexahydro-*o*-toluic acid (302 mg.) was converted to the *p*-bromophenacyl ester in 82% yield in the usual way.[16] After three recrystallizations from hexane, it had m.p. 83.0–84.2°.

Anal. Calcd. for $C_{16}H_{19}BrO_3$: C, 56.66; H, 5.62. Found: C, 56.54; H, 5.69.

***trans*-Hexahydro-*o*-toluic Acid *p*-Bromophenacyl Ester.**—*cis*-Hexahydro-*o*-toluic acid (4 g.) was refluxed for 30 min. with 200 mg. of β-naphthalenesulfonic acid. The residue was distilled in a short-path still at 120° (5 mm.) to give 3.8 g. of an oily solid. After three recrystallizations from benzene there was obtained pure *trans*-hexahydro-*o*-toluic acid, m.p. 52.4–54.4° (lit.[7] m.p. 50–52°).

The *trans*-acid (151 mg.) was treated with *p*-bromophenacyl bromide (280 mg.) in the usual way[16] to give 288 mg. or 80% of *trans*-hexahydro-*o*-toluic acid *p*-bromophenacyl ester, m.p. 102–103° (hot-stage). An analytical sample recrystallized from hexane had m.p. 104–106° (hot-stage).

Anal. Calcd. for $C_{16}H_{19}BrO_3$: C, 56.66; H, 5.62. Found: C, 56.88; H, 5.93.

Identification of 4-Cycloöcten-1-ol in the Low-boiling Fraction after Treatment with Silver Oxide.—The ether extracts of the alkaline solution obtained by treating the low-boiling fraction with silver oxide and sodium hydroxide were concentrated to give 0.67 g. of product. Chromatography on 21 g. of alumina (Activity II) in a 15-mm. column, collecting 20-ml. fractions, gave a small amount of material that gave a positive test with 2,4-dinitrophenylhydrazine reagent but which did not give a derivative that could be purified. The main bulk of material (115 mg.) was distilled in a short-path still and the distillate treated with phenyl isocyanate. After removal of excess reagent under reduced pressure, a crude product was obtained which after one recrystallization from hexane had m.p. 73–135°. The product was sublimed, and the sublimate after two recrystallizations from hexane had m.p. 92.0–94.5° (hot-stage). Its infrared spectrum was identical to the spectrum of 4-cycloöcten-1-ol phenylurethan.[8] The alcohol fraction was not examined in a way that would have detected the presence of 3-cycloöcten-1-ol as a minor component.

Saponification of the Residue of Diformates.—The residue (4.1 g.) from the distillation of the low-boiling product obtained by treating *trans*-cycloöctene oxide with formic acid was refluxed overnight with alcoholic potassium hydroxide (5.5 g.). The ethanol was removed under reduced pressure and replaced by 50 ml. of water. The product was extracted with three 40-ml. portions of chloroform, and the combined extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure to give 3.2 g. of product which was chromatographed on 105 g. of Merck acid-washed alumina (Activity II) in a 22-mm. column, collecting 100-ml. fractions. Fractions 1, 8–10, 60, 61–62 and 68–70 were discarded.

Fraction	Eluent	Weight, mg.
2–7	Benzene	331
11–13	Benzene–ether (9:1)	94
14–15	Benzene–ether (9:1)	156
16–19	Benzene–ether (9:1)	432
20–30	Benzene–ether (3:2)	483
31–36	Benzene–ether (1:1)	51
37–42	Ether	34
43–48	Ether–methanol (66:1)	725
50–59	Ether–methanol (97:3)	633
65–67	Ether–methanol (17:3)	38

4-Cycloöcten-1-ol.—Fractions 2–7 were distilled in a short-path still to give 170 mg. of distillate with an infrared spectrum that was identical to the spectrum of authentic 4-cycloöcten-1-ol. It was treated with phenyl isocyanate overnight to give, after removal of excess reagent under reduced pressure, a crude phenylurethan with m.p. 81–94°. After recrystallization from hexane, it had m.p. 94–96° (hot-stage). The infrared spectrum of the derivative was identical to the spectrum of an authentic specimen of 4-cycloöcten-1-yl phenylurethan.[8]

Glycol A Bis-*p*-nitrobenzoate.—Fractions 11–13 (96 mg.) were treated with *p*-nitrobenzoyl chloride (500 mg.) in a few milliliters of pyridine at room temperature, and the solution was allowed to stand overnight. The reaction mixture was poured into water and the product was extracted with three 10-ml. portions of benzene. The combined extracts were washed with three 80-ml. portions of water and with dilute hydrochloric acid, saturated sodium bicarbonate solution, water and saturated sodium chloride solution. The benzene solution was dried by concentrating to about 5 ml. at atmospheric pressure and passed over 5 g. of Activity II alumina. There was obtained after elution with benzene 201 mg. (68%) of a bis-*p*-nitrobenzoate with An analytical sample had m.p. 154–155°

(15) By the Microchemical Specialties Co., Berkeley, Calif.

(16) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 157.

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after four recrystallizations from ethanol. A mixture with authentic *trans*-1,4-cyclooctanediol bis-*p*-nitrobenzoate[9] was depressed to 133–148°.

Anal. Calcd. for $C_{22}H_{22}N_2O_8$: C, 59.72; H, 5.01. Found: C, 60.08; H, 5.15.

A portion of fractions 14–15 (69 mg.) was converted in 83% yield to the corresponding bis-*p*-nitrobenzoate as above. After three recrystallizations from ethanol it had m.p. 154.0–155.2° and did not depress the m.p. of the derivative prepared from fractions 11–13.

An aliquot of fractions 16–19 (86 mg.) was treated with a 100% molar excess of *p*-nitrobenzoyl chloride as before to give 233 mg. or 87% of a bis-*p*-nitrobenzoate. After six recrystallizations from ethanol it had m.p. 154.0–155.2° and did not depress the m.p. of the derivative obtained from fractions 11–13.

Glycol B Bis-*p*-nitrobenzoate.—A portion of fractions 20–30 (137 mg.) was converted into a bis-*p*-nitrobenzoate in 78% yield. After seven recrystallizations from ethanol, it had m.p. 175.5–180.4°.

Anal. Calcd. for $C_{22}H_{22}N_2O_8$: C, 59.72; H, 5.01. Found: C, 59.89; H, 5.22.

A comparison of infrared spectra showed that the derivative prepared from fractions 20–30 was different from the bis-*p*-nitrobenzoates of the isomeric cyclooctanediols and of glycol A. A mixture of the bis-*p*-nitrobenzoates of glycol A and glycol B had m.p. 140–170°.

Fractions 31–36 (51 mg.) were treated with 280 mg. of *p*-nitrobenzoyl chloride in pyridine to give a derivative in 71% yield. After five recrystallizations from ethanol, it had m.p. 172–180°. A mixture with the derivative prepared from fractions 20–30 had m.p. 171.0–179.5°.

Periodate Tests and C-Methyl Determinations on Glycols A and B.—Both glycols A and B gave negative reactions with periodic acid (see ref. 16, p. 115). C-methyl determinations[15] gave the following values: glycol A, 9.57; glycol B, 8.98; calcd. for one C-methyl group, 10.55.

***trans*-1,4-Cyclooctanediol Bis-*p*-nitrobenzoate.**—A portion of fractions 43–49 (116 mg.) was treated overnight with a 100% excess of *p*-nitrobenzoyl chloride in a few milliliters of pyridine. There was obtained 284 mg. or 83% of crude *trans*-1,4-cyclooctanediol bis-*p*-nitrobenzoate, which after four recrystallizations from ethanol had m.p. 155.4–156.6°. A mixture with an authentic specimen[9] had m.p. 155.5–157.0°.

An aliquot of fractions 50–59 (169 mg.) was converted in 79% yield into a bis-*p*-nitrobenzoate in the same manner. After four recrystallizations from ethanol, it had m.p. 155.5–157.0°. A mixed m.p. with the derivative prepared from fractions 43–49 showed no depression.

***trans*-1,3-Cyclooctanediol.**—Fractions 65–67 (38 mg.) were sublimed at 70° (1 mm.) to give (after two recrystallizations from ethyl acetate) *trans*-1,3-cyclooctanediol, m.p. 109–111° (hot-stage). A mixture with an authentic specimen[9] showed no depression, and the infrared spectra of the two samples were identical.

Derivatives of 2-Hydroxy-2-methylcyclohexanemethanol.—A solution of methylmagnesium iodide was prepared from 6.9 g. of methyl iodide and 1.2 g. of magnesium in 30 ml. of ether. A solution of 2.4 g. of 2-hydroxymethylcyclohexanone[17] (b.p. 82° at 2.6 mm., $n^{25}D$ 1.4767) in 30 ml. of ether was added dropwise over a period of 20 min., and the mixture was refluxed for 1 hr. Water was added to the cooled mixture, followed by iced dilute hydrochloric acid. The ether layer and chloroform extracts of the aqueous layer were dried over magnesium sulfate and distilled, yielding 1.7 g. of 2-hydroxy-2-methylcyclohexanemethanol, b.p. 79° (0.15 mm.), $n^{25}D$ 1.4814, which was converted to the following derivatives.

2-Hydroxy-2-methylcyclohexanemethanol bis-*p*-nitrobenzoate was prepared by treating the glycol (402 mg.) with *p*-nitrobenzoyl chloride (1.6 g.) in a few milliliters of pyridine at room temperature for 1.5 days. The product was isolated in the usual manner and yielded 467 mg. (36%) of a derivative (calculated as the bis-*p*-nitrobenzoate). An analytical sample obtained after four recrystallizations from ethyl acetate had m.p. 214–215°.

Anal. Calcd. for $C_{22}H_{22}N_2O_8$: C, 59.72; H, 5.01. Found: C, 59.69; H, 5.08.

2-Hydroxy-2-methylcyclohexanemethanol mono-*p*-nitrobenzoate was prepared by treating 204 mg. of the glycol with 1.05 molar equivalent of *p*-nitrobenzoyl chloride in pyridine at 5° overnight. The product amounted to 382 mg. (92%) of a derivative (calculated as the mono-*p*-nitrobenzoate). After four recrystallizations from cyclohexane, it had m.p. 91.5–92.5°.

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.52. Found: C, 61.09; H, 6.72.

(17) Prepared from cyclohexanone and formaldehyde by the method of C. Mannich and W. Brose, *Ber.*, **56**, 841 (1923).

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Structures of the Adducts of Cyclopentadiene and Methacrylic Acid and Some of its Derivatives[1]

BY JOHN S. MEEK AND WALTER B. TRAPP[2]

RECEIVED JUNE 4, 1956

The condensation of methacrylic acid and some of its derivatives with cyclopentadiene was studied in an effort to ascertain whether the methyl group or the negative group such as the carboxyl would be in the *endo* position in the major adduct. It was found that the carboxyl and the amide group showed a preference for the *exo* position. The aldehyde group showed an increasing tendency to prefer the *endo* position with longer reaction times and higher temperatures.

Methacrylic acid,[3] methyl methacrylate[3] and methacrolein[4,5] have been reported to give adducts with cyclopentadiene, but their structures were not proven. Recently the condensation of cyclopentadiene and methacrylic acid was reported to give both isomeric adducts I and II and the major product was tentatively assigned structure I[6] in accordance with Alder and Stein's orientation rule of diene syntheses.[7] However, we have found that the major adduct of cyclopentadiene and methacrylic acid is II.

Beckmann, Schaber and Bamberger attempted to prove structures of I and II by treatment with 50 volume per cent. sulfuric acid for 16 hours to see which acid would give a lactone. They re-

(1) This work was supported in part by the Office of Naval Research.

(2) Taken in part from the Ph.D. Thesis of W. B. Trapp, University of Colorado, 1952.

(3) A. A. Petrov and N. P. Sopov, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*), **18**, 1781 (1948).

(4) R. Morris, U. S. Patent 2,450,765.

(5) H. Joy and J. Rust, U. S. Patent 2,873,568.

(6) S. Beckmann, R. Schaber and R. Bamberger, *Chem. Ber.*, **87**, 997 (1954).

(7) K. Alder and G. Stein, *Ann.*, **514**, 1, 197 (1934).

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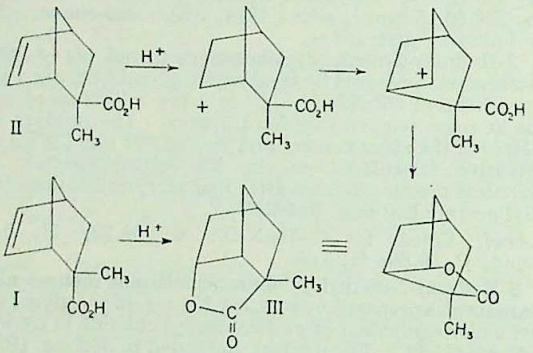
ported the major isomer gave a 9% yield of a lactone melting at 122–123° plus a 66% yield of an hydroxy acid. Their minor isomer gave a different lactone and hydroxy acid in unspecified yield. Prior to the appearance of their work we had tried to lactonize our isomers with 75% sulfuric acid at 25° and found that the major isomer gave a 43% yield of a compound melting at 124–125°. The infrared spectrum showed this compound to have a five-membered lactone ring and structure III was assigned to it. Our minor isomer also gave this same lactone in a yield of only 10% although this isomer appeared to react more rapidly when treated with sulfuric acid. A Wagner–Meerwein rearrangement of the *exo*-acid should give the same lactone as the *endo*-acid as

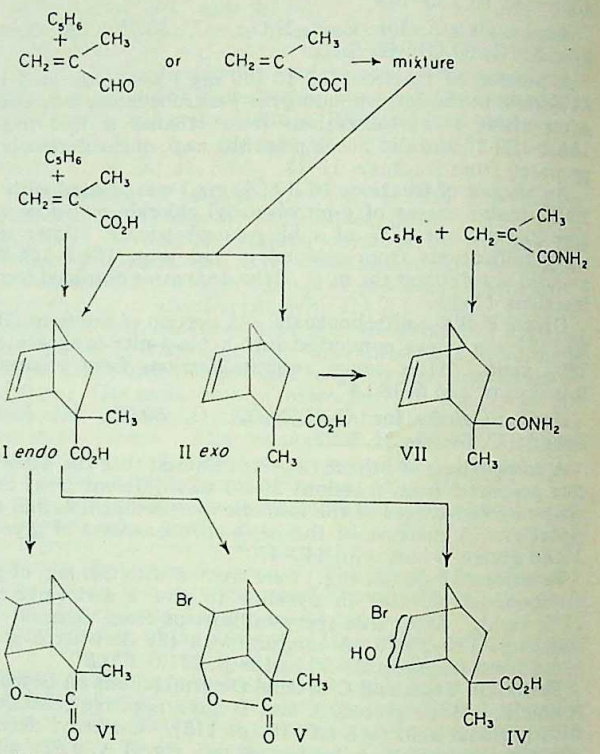


Hence, a structure proof by this method is not satisfactory.

Our assignment is based on the observations that the major isomer formed a bromohydrin IV under the same conditions that led to a bromolactone V from the minor isomer. The major isomer was unreactive toward iodine stock solution[8] while the minor isomer gave an iodolactone VI.

The melting point of our major isomer was 79–80° and that of the minor isomer was 94–95°. Beckmann, Schaber and Bamberger reported melting points of 83 and 109°. Bicyclic compounds frequently have large melting point depressions and our lower melting point for the minor isomer may be explained by this and by the fact that material melting at 92–95° was found by iodine titration to be approximately 94% pure.

Methacrylic acid and cyclopentadiene when heated for 10 minutes at 93° in acetic acid gave a 24% yield of the *endo* isomer I and a 46% yield of isomer II (*exo*). Longer heating at the same temperature or at 150° increased the yield of the *endo* isomer only slightly. When the *exo*-acid was heated at 115° for two hours in a sealed tube no odor of methacrylic acid or cyclopentadiene was noted upon opening the tube. The melting point of the acid was not lowered significantly and recrystallization led only to the recovery of starting material. Therefore, the predominance of II is not due to an equilibrium between the isomers. The *exo*/*endo* ratio was approximately two to one which is not in accordance with Alder's rule of the maximum accumulation of double bonds.[9]



Methacrylamide and cyclopentadiene at 120° gave a 16% yield of crude product which on recrystallization gave only one adduct (VII). This compound was shown to be the *exo* isomer since it could also be prepared from the *exo*-acid II.[6]

Methacrylyl chloride and cyclopentadiene condensed readily at room temperature to give an oil. This was hydrolyzed to a mixture of I and II in which the *endo*-acid predominated.

The cyclopentadiene adduct of methyl methacrylate upon saponification is reported to give almost entirely the *exo*-acid.[6] It is to be noted that there is no α-hydrogen atom in the ester and thus ready epimerization is excluded.

Methacrolein and cyclopentadiene gave evidence of forming increasing amounts of the *endo* isomer with increasing severity of conditions. Beckmann, Schaber and Bamberger found that heating for two to three hours on a water-bath at reflux temperature gave an oil which after several distillations melted at 56–58° and upon purification through the semicarbazone melted at 67–68°. Oxidation by silver oxide gave only the *exo*-acid.[6] Reaction temperatures of 150° for 11 hours gave us material which after distillation was separated into a fraction, m.p. 55–60°, an intermediate fraction and a third fraction, m.p. −5 to +13°. The first fraction on oxidation with silver oxide gave the *exo*-acid. The third and largest fraction gave the *endo*-acid.

Heating the aldehyde adduct at 195° gave cyclopentadiene and methacrolein. It seems likely that at low temperatures the product composition is largely *exo* due to kinetic control while at higher

(8) This reagent was used after C. S. Rondestvedt, Jr., and C. D. Ver Nooy (THIS JOURNAL, **77**, 4878 (1955)) showed that quantitative yields of iodolactones were obtained with adducts of cyclopentadiene and various *trans*-cinnamic acids where the carboxyl group was *endo* while the isomers with *exo*-carboxyl groups were inert.

(9) For a statement of the Alder rules and a discussion of them, see M. C. Kloetzel, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 10.

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temperatures the reaction is reversible and the product composition is under thermodynamic control. Generally *exo* isomers predominate under severe conditions and are thermodynamically more stable.[10] In these cases the isomers differ in the positions of a carbon-containing moiety and a hydrogen atom. In the present case the isomers differ in the location of a methyl and a formyl group which are comparable sterically.

Experimental

2-Methylbicyclo[2.2.1]-5-heptene-2-carboxylic Acid (I and II).—Glacial methacrylic acid (17.2 g., 0.2 mole) and freshly distilled cyclopentadiene (13.2 g., 0.2 mole), 0.1 g. of *p-t*-butylcatechol and 25 ml. of toluene were heated in a sealed glass tube for 2 hours at 150–157°. Distillation gave 3 g. of methacrylic acid and 20.8 g. (68%) of product, b.p. 113° (4.5 mm.), m.p. 41–57°. Upon recrystallization from 50% acetic acid, 80% of the material was separated manually into needles of I, m.p. 94–95°, and granules of II, m.p. 79–81.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found for isomer I: C, 70.94; H, 7.94. Isomer II: C, 70.97; H, 8.16.

Lactonization of I and II.—Equal quantities (0.89 g.) of I and II were placed in glass-stoppered flasks along with 10 ml. of 75% sulfuric acid and shaken at 25°. After ten minutes all of I had dissolved, but 40 minutes was required for II. At that time both samples were diluted with 500 vol. per cent. of water. Unchanged II (0.02 g.) precipitated and the remaining solution was ether extracted to obtain the product. With sample I no unchanged acid appeared. The ether extracts were shaken with sodium bicarbonate and the product from I after removal of the ether and recrystallization from ethanol gave 90 mg. (10%) of III, m.p. 121–122°. The product from II after sublimation weighed 0.37 g. (42%) and melted at 124–125° and its melting point was not depressed when mixed with the product from I. The analytical sample melting point was not depressed when mixed with the product from I. The analytical sample melted at 125–126° after recrystallization from aqueous ethanol; reported[6] 122–123°.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95; sapn. equiv., 152. Found: C, 71.30; H, 7.92; sapn. equiv., 152.

Bromolactone V.—To a solution of 0.400 g. (2.62 mmoles) of I in 10 ml. of 5% sodium carbonate was added bromine water containing a trace of potassium bromide. The temperature was maintained below 10° and the addition was stopped when the color persisted. On standing, 0.40 g. (66.5%) of V precipitated, m.p. 74–75°. The material was insoluble in 10% sodium bicarbonate, and had a peak at 5.58 μ in its infrared spectrum which indicated a five-membered lactone ring.

Anal. Calcd. for $C_9H_{11}BrO_2$: C, 46.77; H, 4.80. Found: C, 46.64; H, 4.84.

Bromohydrin of II.—Compound II when treated similarly gave no precipitate on standing. However, acidification resulted in a 73% yield of IV, m.p. 141–147°; recrystallization from acetone–petroleum ether, raised the melting point to 150–151.5°.

Anal. Calcd. for $C_9H_{13}BrO_3$: C, 43.43; H, 5.22. Found: C, 43.32; H, 5.42.

Dibromide of II.—Five grams (0.033 mole) of II was dissolved in 70 ml. of 5% sodium bicarbonate and agitated at 5–10°. Bromine dissolved in petroleum ether (30–60°) was added dropwise until color persisted. A white dibromide precipitated, weighing 1.58 g. (21%), m.p. 198–199°. The dibromide was soluble in 5% sodium bicarbonate and the infrared spectrum showed a carboxylic carbonyl peak at 5.87 μ.

Anal. Calcd. for $C_9H_{12}Br_2O_2$: C, 34.64; H, 3.88. Found: C, 34.52; H, 4.00.

Iodolactone VI.—One gram of I gave 1.30 g. of iodolactone, m.p. 83–86°, when treated with iodine in basic solution.[8]

Anal. Calcd. for $C_9H_{11}IO_2$: C, 38.87; H, 3.99. Found: C, 39.13; H, 3.83.

(10) R. B. Woodward and H. Baer, THIS JOURNAL, 66, 645 (1944).

A 0.2263-g. sample of I, m.p. 92–95° absorbed 94% of the calculated amount of iodine stock solution. When II was similarly treated with a small amount of iodine no discharge of color occurred and acidification precipitated 88% of unchanged II.

Formation of I under Various Conditions.—A series of samples of 43 g. gross weight containing 0.2 mole each of methacrylic acid and cyclopentadiene in acetic acid (12 ml.) with *p-t*-butylcatechol were exposed to varying conditions of time and temperature. Aliquots were then assayed for I with iodine stock solution.

Time	Temp., °C.	Mole % endo
0 min.	25	0
10 min.	93	24
45 min.	93	27
8 hr.	93	27
2.5 hr.	150	29

Hydrolysis of V and VI.—One-half gram (2.16 mmoles) of V was added to a solution of 1.0 g. of potassium hydroxide in 15 ml. of water and 15 ml. of 95% ethanol and the mixture was heated on a steam-bath for 30 minutes. The solution was cooled, filtered and extracted with ether. Acidification of the aqueous solution followed by a fourfold ether extraction, drying over sodium sulfate and evaporation of the solvent gave 260 mg. (71.7%) of hydroxy lactone, m.p. 124–128°. Recrystallization from water raised the melting point to 129–130°.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.21; H, 7.07.

The compound gave a positive periodate test, indicating a vicinal diol was formed by hydrolysis in the reagent. The infrared spectrum showed the following in hexachlorobutadiene and Nujol mulls: carbonyl at 5.78 μ, hydroxyl at 3.02 μ (sharp, indicates either intramolecular bonding or intermolecular bonding where the bonding plays a prominent part in the crystal structure), carboxyl type stretch absent; in CCl_4 solution: 2.79 μ free OH, 2.94 μ bonded OH, 5.60 μ unbonded lactone carbonyl, 5.70 μ bonded lactone carbonyl. Upon dilution the ratio of the intensities of the unbonded peaks to the bonded peaks increased, showing intermolecular bonding. From chemical and spectral evidence the assignment of **2-methylbicyclo[2.2.1.]-5,6-di-endohydroxyheptane-2-endocarboxylic acid 2,6-lactone** was made.

A 396-mg. sample of VI was similarly treated with base, and 175 mg. (73%) of product was obtained, m.p. 124–129°. There was no melting point depression when mixed with the hydroxy lactone prepared from V.

2-Methylbicyclo[2.2.1.]-5-heptene-2-carboxamide (VII).—One-tenth of a mole (8.5 g.) of methacrylamide, 13.2 g. (0.2 mole) of cyclopentadiene, 0.1 g. of *p-t*-butylcatechol and 12 ml. of methanol were heated together at 120° for 4.5 hours in a sealed glass tube. The methanol was evaporated and the residue was extracted with water to remove methacrylamide. Extraction with ethanol left 5 g. of polymeric material which was removed by filtration. Upon standing three weeks the alcoholic solution afforded 2.5 g. (16.5%) of crystals, m.p. 110–120°. Sublimation at 92° gave 1.9 g. (12.6%) of VII, m.p. 154–155°; reported[3] 152–153°.

A 4.6-g. sample of II was treated with thionyl chloride in ether and gave 4.5 g. (76%) of acid chloride, b.p. 57° (4.5 mm.), $n^{20}D$ 1.4950, $n^{25}D$ 1.4929, d^{25}_4 1.1266.

Anal. Calcd. for $C_9H_{11}ClO$: C, 63.34; H, 6.50; *MR*, 43.78. Found: C, 63.05; H, 6.76, *MR*, 43.85.

Ten ml. of cold concentrated ammonium hydroxide was added dropwise to 150 mg. of the acid chloride of II. The mixture was diluted with 20 ml. of water and filtered, yielding 120 mg. (93%) of solid amide, m.p. 157–157.5°. Purification by sublimation raised the m.p. to 157.5–158°. When this material was mixed with VII it melted at 154–155°.

A 460-mg. sample of I gave 80 mg. of acid chloride, $n^{20}D$ 1.4910.

Anal. Calcd. for $C_9H_{11}ClO$: C, 63.34; H, 6.50. Found: C, 63.23; H, 6.53.

Since the acid chlorides from I and II differed significantly in their refractive index, attempts to thermally isomerize the acid chloride of II were made. However, no change in the refractive index was noted after 51 days at room temperature in the dark, 60 hours at 80°, 2 hours at 150° or one hour at

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175° although slight discoloration occurred in the latter two cases.

Condensation of Methacrylyl Chloride and Cyclopentadiene.—A mixture of 5.0 g. (0.048 mole) of methacrylyl chloride, prepared from glacial methacrylic acid and thionyl chloride, 6.6 g. (0.1 mole) of cyclopentadiene and 0.1 g. *p-t*-butylcatechol was kept in a sealed glass tube for a week at room temperature. Distillation of the black oil gave a 61% yield of heart fraction, b.p. 126° (95 mm.), $n^{22}D$ 1.4930, d^{29}_4 1.1227; lit.[3] for the chloride prepared from mixed acid adducts $n^{20}D$ 1.4950.

A mixture of 10 ml. of 10% aqueous potassium hydroxide and 1.12 g. (6.6 mmoles) of the acid chloride adduct was heated at 55–60° for 10 minutes. A small amount of tar was removed by filtration, and acidification gave 1.07 g. of acid, m.p. 60–63°. Recrystallization gave 0.85 g. of mixed crystals which were separated manually; 60% (0.51 g.) melted at 93–94° and this melting point was not depressed with samples of I previously obtained. The remaining 40% (0.34 g.) melted at 78–79° and showed no melting point depression when mixed with II.

2-Methylbicyclo[2.2.1]-5-heptene-2-carboxaldehyde.—A mixture of 285 g. (4.06 moles) of methacrolein, 225 g. (3.4 moles) of cyclopentadiene and 1 g. of *p-t*-butylcatechol was heated in a 2-l. steel bomb at 150–155° for 11 hours. An exothermic reaction occurred at about 95° when the reactants were heated. Distillation through an 18″ Vigreux column gave 388.8 g. (84%) of adduct, b.p. 80–85° (31 mm.). Cooling and decantation gave three fractions: 22%, m.p. 55–60°; 28%, m.p. 20–45°, and 50%, m.p. −5 to +13°.

Anal. Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88. Found for the first fraction: C, 79.42; H, 8.80. For the last fraction: C, 79.41; H, 8.66.

Other preparations conducted at slightly higher temperatures gave products containing less of the higher melting (*exo*) isomer while runs conducted under less severe conditions gave increased amounts of this isomer.

When the crude product was heated at atmospheric pressure to a temperature of 180–195°, a distillate consisting of both methacrolein and cyclopentadiene came over at a head temperature of 58°.

A 2.72-g. (0.02 mole) sample of the third fraction above was oxidized with silver oxide, and 1.95 g. (65%) of crude I was obtained, m.p. 88–91°. Recrystallization from 50% acetic acid gave 1.4 g. (46%), m.p. 95–96°, which gave no melting point depression with I obtained previously.

Oxidation of the first fraction gave 2.3 g. of crude II, m.p. 70–76°. Recrystallization raised the melting point to 79–80°, yield 1.8 g. (60%). A mixed melting point with II was not depressed.

When 21 g. of methacrolein, 24 g. of cyclopentadiene and a tenth gram of inhibitor were heated in a sealed tube at 170° for 10 hours, more than the usual amount of methacrolein was recovered and a relatively small amount of adduct was obtained. In addition 3 g. of product was obtained, b.p. 170–178° (50 mm.), $n^{20}D$ 1.5242, d^{20}_4 1.0718. This was believed to be **2-methyl-1,2,3,4,5,8,9,10-octahydro-1,4,5,8-dimethanonaphthalene-2-carboxaldehyde.**

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97; *MR*, 57.62. Found: C, 83.93; H, 8.71, *MR*, 57.75.

A 2,4-dinitrophenylhydrazone formed in 86% yield, m.p. 208–210°. After two recrystallizations from ethanol the m.p. was raised to 218–219°, yield 75%.

Anal. Calcd. for $C_{20}H_{22}N_4O_4$; N, 14.65. Found: N, 14.49.

Acknowledgment.—The analyses were performed by Galbraith Laboratories. The methacrylamide and methracylic acid were gifts of the Rohm and Haas Co. The authors wish to thank Dr. W. J. Potts of the Dow Chemical Co. for running and interpreting the spectrum of the hydroxy lactone.

BOULDER, COLORADO

[CONTRIBUTION FROM ABBOTT LABORATORIES]

Reactions of α,α-Diphenyl-β-propiolactone with Amines and Thiols

BY H. E. ZAUGG, H. J. GLENN, R. J. MICHAELS, R. U. SCHOCK AND L. R. SWETT

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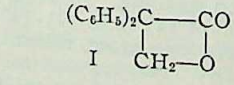
The reactions of α,α-diphenyl-β-propiolactone with four heterocyclic secondary amines, two primary amines, with the sodium salts of ethyl mercaptan and of thiophenol and with thiourea are described and compared with analogous reactions of β-propiolactone itself. The conversion of products of these reactions to compounds of potential pharmacological interest is reported.

The seemingly capricious nature of the aminolysis reaction of β-propiolactone has been demonstrated by Gresham and co-workers.[1] Three principal factors, namely, solvent, mode of combination of the reactants and nature of the amine used, were found to be operative in determining whether hydroxy amides (carbonyl–oxygen bond fission) or β-amino acids (alkyl–oxygen bond fission) are formed. Hurd and Hayao[2] later showed that aromatic amines tend to react with β-propiolactone to give almost exclusively the corresponding amino acids. In contrast, a more recent study[3] with β-(*p*-nitrophenyl)-β-propiolactone showed that this β-hindered lactone reacts with most amines, regardless of conditions, to give β-hydroxy amides. Only benzylamine and cyclohexylamine give appreciable yields of the corresponding amino acids, and then only under carefully controlled conditions.

The present work extends the study of these reactions to the α-hindered lactone, α,α-diphenyl-β-propiolactone (I).[4] Reaction of I with excess N-(γ-aminopropyl)-morpholine at room temperature without solvent gave the amino acid IIa in 60% yield and the hydroxy amide IIIa in 12% yield. From the reaction with *n*-butylamine, only the hydroxy amide IIIb could be isolated albeit in only 45% yield. The four heterocyclic amines piperidine, morpholine, pyrrolidine and N-methylpiperazine gave the corresponding amino acids, IIb, c, d and e, as the only isolable products, the first three in high yields (80–90%) but the last in only 46% yield. Employment of acetonitrile as solvent seemed to have little influence on the course of these amine reactions. However, non-polar media such



I

(1) T. Gresham, J. Jansen, F. Shaver, R. Bankert and F. Fiedorek, THIS JOURNAL, 73, 3168 (1951).

(2) C. Hurd and S. Hayao, *ibid.*, 74, 5889 (1952).

(3) A. Dornow and E. Schumacher, *Arch. Pharm.*, 286, 205 (1953).

(4) H. E. Zaugg, THIS JOURNAL, 72, 2998 (1950).

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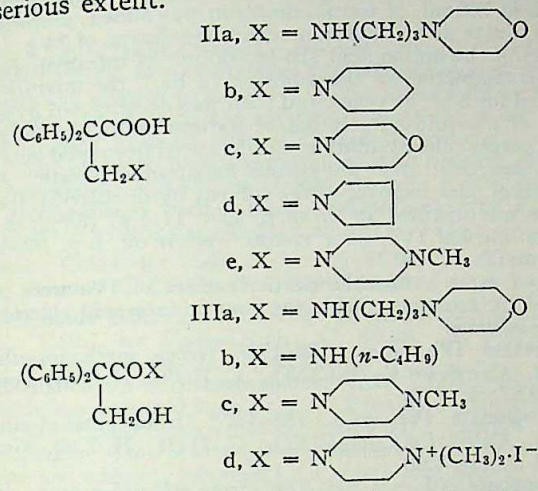
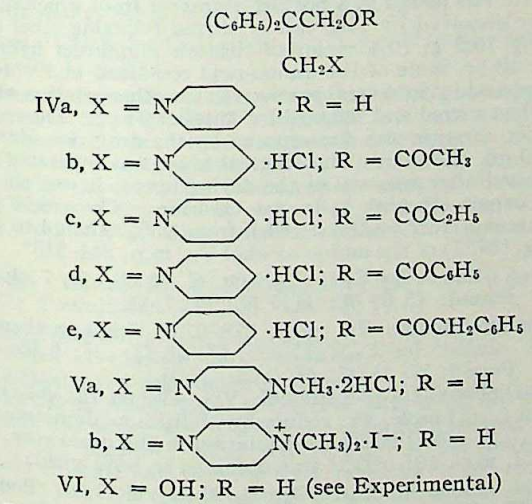
as ether or even boiling benzene, retarded them to a serious extent.

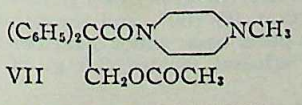


For the purpose of pharmacological evaluation, the two amino acids IIb and IIe were reduced with lithium aluminum hydride to the amino carbinols IVa and Va, respectively. The four O-acyl derivative IVb, c, d, and e were then prepared from IVa, and the methiodide Vb was made from Va.



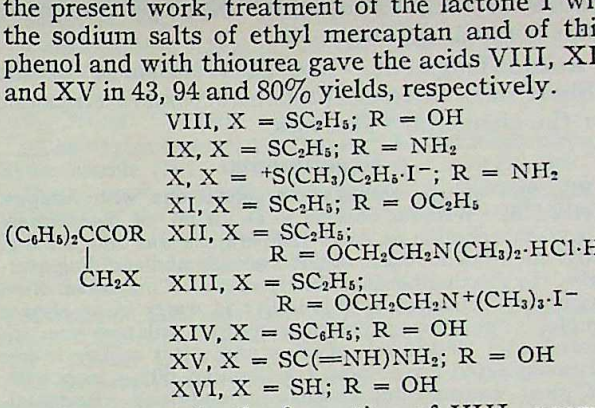
VI, X = OH; R = H (see Experimental)

The hydroxy amide IIIc and its monomethiodide IIId were prepared from α-phenyltropic acid[5] by acetylation of the hydroxyl group followed by conversion to the acid chloride and reaction with N-methylpiperazine to give the acetoxy amide VII which readily hydrolyzed to IIIc. All attempts to prepare the acid chloride of O-acetyl-α-phenyltropic acid directly from the β-lactone I by treatment with acetyl chloride failed. Mild conditions gave only recovered lactone; and heating the reactants at 100° in an autoclave in the presence of a few drops of concentrated sulfuric acid as catalyst seemed to result in some reaction, but treatment of the crude product with N-methylpiperazine gave none of either amide VII or IIIc. In contrast, β-propiolactone itself reacts with acetyl chloride at only slightly elevated temperatures to give β-acetoxypropionyl chloride in 67% yield.[6]



VII

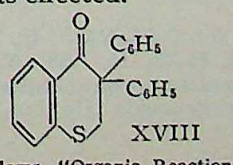
All reactions between β-propiolactone and organic sulfur compounds which have been reported thus far[7] involve alkyl–oxygen bond fission to give derivatives of β-thiolpropionic acid. Likewise, in the present work, treatment of the lactone I with the sodium salts of ethyl mercaptan and of thiophenol and with thiourea gave the acids VIII, XIV and XV in 43, 94 and 80% yields, respectively.



As by-product in the formation of VIII, appreciable quantities of ethyl diphenylacetate, $(C_6H_5)_2CHCOOC_2H_5$, were formed. It might seem that this ester was produced primarily by reaction of the lactone I with the ethanol solvent to give ethyl α-phenyltropate, which readily would undergo aldol-reversal in alkaline medium to give the above cleavage product.[5] However, another possible route for this degradation reaction could involve initial carbonyl–oxygen bond fission of the lactone I to give the ethylthiol ester of α-phenyltropic acid, isomeric with VIII. This thiol ester would be expected to undergo aldol-reversal even more readily than the corresponding oxygen ester because its anionic fission product $[(C_6H_5)_2CCOSC_2H_5]^{\ominus}$, is a weaker base than is the anion $[(C_6H_5)_2CCOOC_2H_5]^{\ominus}$, formed initially by cleavage of ethyl α-phenyltropate. Once formed, the thiol ester would readily undergo ester interchange in the basic ethanolic medium to give the corresponding oxygen ester. The latter route for this cleavage reaction is given some credence by the fact that when water was substituted for ethanol as the solvent in the reaction of I with sodium ethyl mercaptide, a 42% yield of ethyl diphenylthiolacetate, $(C_6H_5)_2CHCOSC_2H_5$ (XVII), actually was isolated. At any rate, formation of XVII shows that a β-lactone can react with an organic sulfur compound by carbonyl–oxygen bond fission.

The thioacid VIII readily formed an acid chloride which gave the amide IX and the two esters XI and XII on treatment with the appropriate reactants. Reaction of the amide IX with methyl iodide gave, with difficulty, the sulfonium salt X. Treatment of the ester XII with methyl iodide likewise gave a methiodide, which is presumed to be the ammonium salt XIII rather than the sulfonium salt because of its relatively facile formation.

By the action of concentrated sulfuric acid on the thioacid XIV, ring-closure to the thiachromanone XVIII readily was effected.



XVIII

(5) H. Zaugg, THIS JOURNAL, 72, 3001 (1950).
(6) T. Gresham, J. Jansen and F. Shaver, ibid., 72, 50 (1950).
(7) H. Zaugg in Adams, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 345.

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Finally alkaline hydrolysis of the acid XV formed the thiolpropionic acid XVI.

Many of the products reported above were submitted for testing as potential analgesics, antispasmodics or local anesthetics. None showed more than minimal activity.

Acknowledgment.—Mr. E. F. Shelberg of the Abbott microanalytical laboratory was responsible for the elementary analyses.

Experimental

Reaction of α,α-Diphenyl-β-propiolactone with Amines. Method A. Without Solvent.—To 10 ml. of N-(γ-aminopropyl)-morpholine at room temperature was added 2.5 g. (0.011 mole) of I. After slight warming and standing overnight, the mixture became homogeneous. Completion of reaction was indicated by miscibility in water of an aliquot sample. The viscous colorless reaction mixture was triturated with 50–100 ml. of ether and, after cooling in ice, the precipitated amino acid IIa (2.45 g., 60%), m.p. 186–187° dec., was collected by filtration and dried. Recrystallization from methanol did not change the melting point.

Anal. Calcd. for $C_{22}H_{28}N_2O_3$ (IIa): C, 71.71; H, 7.66; N, 7.60. Found: C, 72.03; H, 7.68; N, 7.74.

The ether filtrate was washed with water and then extracted with dilute hydrochloric acid. The aqueous extract was made alkaline with sodium hydroxide, and the precipitated oil was taken up in ether, dried and concentrated. The hydroxy amide IIIa (0.50 g., 12%), m.p. 133–134°, slowly crystallized from the concentrated ether solution. Recrystallization from methanol did not raise the melting point.

Anal. Calcd. for $C_{22}H_{28}N_2O_3$ (IIIa): C, 71.71; H, 7.66. Found: C, 71.83; H, 7.34.

In like manner reaction of I with *n*-butylamine gave only the hydroxy amide IIIb, m.p. 70–72° (from hexane), in 45% yield.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80. Found: C, 76.79; H, 7.84.

Reaction of I with piperidine gave only the amino acid IIb in 87% yield, m.p. 137–139° (from acetone). When mixed with an authentic specimen of IIb,[8] m.p. 137–138°, it produced no melting point depression.

Reaction of I with morpholine gave a 95% yield of the morpholinium salt of the amino acid IIc, m.p. 173° dec.

Anal. Calcd. for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.53; H, 7.45; N, 7.23.

When this salt was heated for 5 hr. at 110° under reduced pressure (20 mm.), the free amino acid IIc, m.p. 163–164°, was obtained.

Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.19; H, 7.03; N, 4.63.

Method B. In Acetonitrile.—The reaction of I with piperidine did not take place in ether solution at room temperature nor even in refluxing benzene to give IIb. A more polar solvent seemed necessary.

To a stirred solution of 2.65 g. (0.0307 mole) of piperidine in 10 ml. of acetonitrile was added 4.6 g. (0.0205 mole) of the lactone I. In about an hour at room temperature, the reaction mixture set to a solid mass. After standing overnight, the solid was collected and washed with pentane. There was obtained 5.5 g. (87%) of the amino acid IIb, m.p. 138–139° dec.

In like manner, the reaction of I with pyrrolidine gave the amino acid IId in 83% yield, m.p. 133°.

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.08; H, 7.34; N, 4.81.

Similarly, N-methylpiperazine with I in acetonitrile gave the amino acid IIe in 46% yield, m.p. 175–176° (from 95% ethanol).

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.28; H, 7.58; N, 8.56.

A crude by-product also was obtained from this reaction, possibly the hydroxy amide IIIc, but it could not be purified.

2,2-Diphenyl-3-piperidinopropanol (IVa).—To a stirred suspension of 9.4 g. (0.25 mole) of lithium aluminum hydride in 700 ml. of tetrahydrofuran was added, dropwise at such a rate as to maintain reflux, a solution of 34 g. (0.11 mole) of the amino acid IIb in 500 ml. of tetrahydrofuran. After completion of the addition (1 hr.), the mixture was stirred for 2 hr. at reflux and then was decomposed by addition of a saturated solution of sodium potassium tartrate. The purple colored solution was decanted from solid salts and was then dried over anhydrous magnesium sulfate. After filtration, and removal of the solvent by distillation, the residue was distilled *in vacuo* to give 11.4 g. (35%) of the amino alcohol IVa, as a viscous yellow oil, b.p. 165–166° (0.7 mm.).

Four ester hydrochloride derivatives of IVa were prepared by treatment with the appropriate acid chloride in ether solution:

Acetate IVb, m.p. 173–175° (from methanol–ether). *Anal.* Calcd. for $C_{22}H_{28}ClNO_2$: C, 70.66; H, 7.55. Found: C, 70.87; H, 7.40.

Propionate IVc, m.p. 155–157° (from ethanol–ether). *Anal.* Calcd. for $C_{23}H_{30}ClNO_2$: C, 71.21; H, 7.80. Found: C, 71.25; H, 7.68.

Benzoate IVd, m.p. 218–219° (from ethanol–ether). *Anal.* Calcd. for $C_{27}H_{30}ClNO_2$: C, 74.38; H, 6.94. Found: C, 74.32; H, 6.66.

Phenylacetate IVe, m.p. 174–176° (from ethanol–ether). *Anal.* Calcd. for $C_{28}H_{33}ClNO_2$: C, 74.73; H, 7.17. Found: C, 74.47; H, 7.13.

2,2-Diphenyl-3-(N-methylpiperazino)-propanol (Va).—Twenty-two and four-tenths grams (0.1 mole) of the amino acid IIe was placed in a Soxhlet extractor from which it was slowly dissolved by 1500 ml. of stirred refluxing ether containing 15.2 g. (0.4 mole) of lithium aluminum hydride. After 48 hr. some of the amino acid remained undissolved, so it was added in several portions to the ether solution which was then stirred and refluxed for another 24 hr. The cooled reaction mixture was decomposed by the dropwise addition of 200 ml. of water. The ethereal layer was separated and dried and after removal of the drying agent, it was treated with excess ethereal hydrogen chloride. The crude precipitate was recrystallized twice from 95% ethanol to give 21.7 g. (57%) of the amino alcohol Va, m.p. 244–246°.

Anal. Calcd. for $C_{20}H_{28}Cl_2N_2O$: C, 62.66; H, 7.36; N, 7.31. Found: C, 62.63; H, 7.55; N, 7.43.

Monomethiodide Vb, m.p. 278–279° (from methanol). *Anal.* Calcd. for $C_{21}H_{29}IN_2O$: C, 55.75; H, 6.46; N, 6.19. Found: C, 55.97; H, 6.58; N, 6.19.

2,2-Diphenyl-1,3-propanediol (VI).—When the β-lactone I (22.5 g., 0.1 mole) was reduced with lithium aluminum hydride (0.25 mole) in ethereal solution in the usual way, the diol VI, m.p. 101–103°,[9] was obtained in 84% yield.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.77; H, 7.15.

N-Methylpiperazides of Acetyl-α-phenyltropic Acid (VII) and of α-Phenyltropic Acid (IIIc).—A mixture of 6.9 g. (0.03 mole) of α-phenyltropic acid[6] and 5.5 g. (0.07 mole) of acetyl chloride was refluxed on the steam-bath for 3 hr., and the excess acetyl chloride was removed by distillation. Then 7.1 g. (0.06 mole) of thionyl chloride was added, and the mixture was refluxed for 4 hr. The excess thionyl chloride was also removed by distillation and the residual oil (acetoxy acid chloride) was taken up in 50 ml. of dry ether. This solution, previously chilled in ice, was then added slowly to an ice-cold solution of 7.0 g. (0.07 mole) of N-methylpiperazine in 50 ml. of dry ether. After standing at room temperature overnight, the reaction mixture was extracted with excess dilute hydrochloric acid. The separated aqueous extract was made alkaline with cold 40% sodium hydroxide solution, and the precipitated oil was taken up in chloroform. Removal of the chloroform gave an oily free base which could not be crystallized. This material was dissolved in ether and the hydrochloride was fractionally precipitated by the slow addition of a solution of hydrogen chloride in isopropyl alcohol. Two fractions of the hydrochlorides were obtained. The first (hygroscopic) gave a crude crystalline base (3.5 g.), m.p. 95–100°, and the second hydrochloride fraction gave a purer base, which after two recrystallizations from aqueous ethanol yielded 2.3 g. of VII, m.p. 111–112°.

(8) H. Zaugg, B. Horrom and M. Vernsten, THIS JOURNAL, **75**, 288 (1953).

(9) J. Burr, Jr., *ibid.*, **73**, 5770 (1951), reports m.p. 102–103° for obtained VI.

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Anal. Calcd. for $C_{22}H_{26}N_2O_3$: C, 72.10; H, 7.15; N, 7.65; O, 13.10. Found: C, 71.93; H, 6.88; N, 7.80; O, 13.80.

The 3.5 g. of crude base (m.p. 95–100°) was dissolved in a solution of 25 ml. of concentrated hydrochloric acid in 25 ml. of water and allowed to stand for 60 hr. After heating for 1 hr. on the steam-bath, the mixture was cooled in ice and made strongly alkaline with 40% sodium hydroxide solution. The liberated base was extracted with benzene, which was removed by distillation to leave a solid residue which was recrystallized from aqueous ethanol to give 2.5 g. (80%) of the hydroxy amide IIIc, m.p. 141–142°.

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.35; H, 7.63; N, 8.82.

Methiodide IIId, m.p. 234–235° (from methanol–ether). *Anal.* Calcd. for $C_{21}H_{27}IN_2O_2$: C, 54.08; H, 5.84; N, 6.01. Found: C, 54.37; H, 5.78; N, 6.07.

2,2-Diphenyl-3-ethylthiopropionic Acid (VIII).—Sodium ethoxide was prepared from 4.6 g. (0.2 mole) of sodium in 40 ml. of dry ethanol. A solution of 12.4 g. (0.2 mole) of ethyl mercaptan in 10 ml. of ethanol was then added dropwise with cooling and stirring, followed by a solution of 33.6 g. (0.15 mole) of α,α-diphenyl-β-propiolactone in 100 ml. of ethanol. After standing at room temperature for 48 hr., the mixture was refluxed for 20 hr., cooled and poured into 200 ml. of water. Non-acidic material was eliminated by an ether extraction, and the aqueous layer was acidified with hydrochloric acid. The liberated acid was taken up in ether and dried. Removal of the ether by distillation gave the crude product, which after one recrystallization from dilute ethanol yielded 18.5 g. (43%) of VIII, m.p. 146–147°.

Anal. Calcd. for $C_{17}H_{18}O_2S$: C, 71.30; H, 6.33. Found: C, 71.07; H, 6.30.

From the neutral fraction was obtained 2.4 g. of ethyl diphenylacetate, m.p. 55–57°, identified by analysis and by mixed melting point with an authentic specimen.

When the β-lactone was treated with sodium ethylmercaptide in aqueous rather than alcoholic solution, the desired acid VIII was obtained in very poor yield together with a 42% yield of ethyl diphenylthiolacetate (XVII), m.p. 48–49°.

Anal. Calcd. for $C_{16}H_{16}OS$: C, 74.97; H, 6.29; S, 12.51. Found: C, 75.11; H, 6.33; S, 12.51.

Mixed with an authentic specimen, m.p. 49°,[10] there was no depression of melting point.

2,2-Diphenyl-3-ethylthiopropionamide (IX).—To a solution of 6.3 g. (0.031 mole) of the acid VIII in 40 ml. of dry benzene was added 4.8 g. of thionyl chloride dissolved in 10 ml. of dry benzene. After refluxing for 3 hr., the excess thionyl chloride and benzene were removed under reduced pressure. To the cooled residue of acid chloride was added 30 ml. of concentrated ammonium hydroxide. The oil which resulted was taken up in ether. Removal of the ether by distillation left a solid which after two recrystallizations from 75% ethanol gave 3.4 g. (54%) of the amide IX, m.p. 84–85°. (In another experiment a second dimorph, m.p. 95–96° was obtained.)

Anal. Calcd. for $C_{17}H_{19}NOS$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.53; H, 6.46; N, 5.04.

Methiodide X, m.p. 158–160° (from ethanol), was obtained by the reaction of methyl iodide with IX in refluxing acetone.

Anal. Calcd. for $C_{18}H_{22}INOS$: C, 50.59; H, 5.19; N, 3.28. Found: C, 51.10; H, 5.22; N, 3.41.

(10) H. Staudinger, G. Rathsam and F. Kjelsberg, *Helv. Chim. Acta*, **3**, 853 (1920).

Ethyl 2,2-Diphenyl-3-ethylthiopropionate (XI).—By substituting ethanol for the ammonium hydroxide in the above procedure, the ester XI, b.p. 202° (2.5 mm.), $n^{26}D$ 1.5685, was obtained in 52% yield.

Anal. Calcd. for $C_{19}H_{22}O_2S$: C, 72.59; H, 7.05. Found: C, 72.40; H, 6.92.

A methiodide of XI, m.p. 125–126°, was obtained, but it could not be purified completely.

Anal. Calcd. for $C_{20}H_{25}IO_2S$: C, 52.63; H, 5.52; S, 7.02. Found: C, 54.07; H, 5.70; S, 6.68.

β-Dimethylaminoethyl 2,2-Diphenyl-3-ethylthiopropionate Hydrochloride (XII).—Treatment of the acid chloride of VIII with excess β-dimethylaminoethanol in benzene gave a 46% yield of the ester XII in the form of the monohydrate, m.p. 117–119° (from acetone–ether).

Anal. Calcd. for $C_{21}H_{30}ClNO_3S$: C, 61.22; H, 7.34; N, 3.40. Found: C, 61.39; H, 7.57; N, 3.45.

Methiodide XIII, m.p. 151–152° (from isopropyl alcohol). *Anal.* Calcd. for $C_{22}H_{30}INO_2S$: C, 52.90; H, 6.05; N, 2.81. Found: C, 52.83; H, 6.19; N, 2.95.

2,2-Diphenyl-3-phenylthiopropionic Acid (XIV).—To a solution of 2.20 g. (0.02 mole) of thiophenol in 50 ml. of dry methanol containing sodium methoxide (prepared from 0.46 g. of sodium) was added 4.48 g. (0.02 mole) of the lactone I. After standing at room temperature for two weeks (a shorter time probably would suffice), the methanol was removed under reduced pressure and the residue was taken up in 75 ml. of water. After extraction with two 50-ml. portions of ether, the aqueous solution was acidified with concentrated hydrochloric acid. The precipitated oil crystallized slowly, was removed by filtration and washed with water to give 6.33 g. (94%) of the acid XIV, m.p. 95–100°. Two recrystallizations from hexane (Skellysolve B) raised the melting point to 103–104°.

Anal. Calcd. for $C_{21}H_{18}O_2S$: C, 75.42; H, 5.42. Found: C, 75.57; H, 5.54.

3,3-Diphenylthiachromanone (XVIII).—To 5 ml. of concentrated sulfuric acid at room temperature was added 0.97 g. of 2,2-diphenyl-3-phenylmercaptopropionic acid. After constant swirling for 10 minutes, the deep red solution was poured onto ice, the resulting solid was collected at the filter and washed with water. The crude dry product (0.9 g.) was recrystallized twice by dissolving in acetone and adding hexane (Skellysolve B) to the warm solution. The pure thiachromanone XVIII melted at 163–164°.

Anal. Calcd. for $C_{21}H_{16}OS$: C, 79.72; H, 5.10. Found: C, 79.94; H, 5.36.

Reaction of the β-Lactone I with Thiourea. Preparation of XV.—To a boiling solution of 0.40 g. (0.0053 mole) of thiourea in 10 ml. of dry ethanol was added 1.12 g. (0.005 mole) of the lactone I. Refluxing for 3 hr. resulted in the precipitation of a colorless, crystalline solid, which after refrigeration overnight was collected at the filter and dried. There was obtained 1.20 g. (80%) of XV, m.p. 159.5–162°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.97; H, 5.37; N, 9.33; S, 10.67. Found: C, 63.96; H, 5.57; N, 8.51; S, 10.37.

2,2-Diphenyl-3-thiolpropionic Acid (XVI).—Approximately 13.3 g. of crude XV was warmed with a 10% sodium hydroxide solution until most of it dissolved. After filtering and allowing to stand several hours, the alkaline solution was acidified and the precipitated product (7.3 g., m.p. 180–190°) was dried. Two recrystallizations from methanol gave colorless prisms of XVI, m.p. 200–202.5°.

Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.39. Found: C, 69.91; H, 6.02; S, 12.68.

NORTH CHICAGO, ILLINOIS

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[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

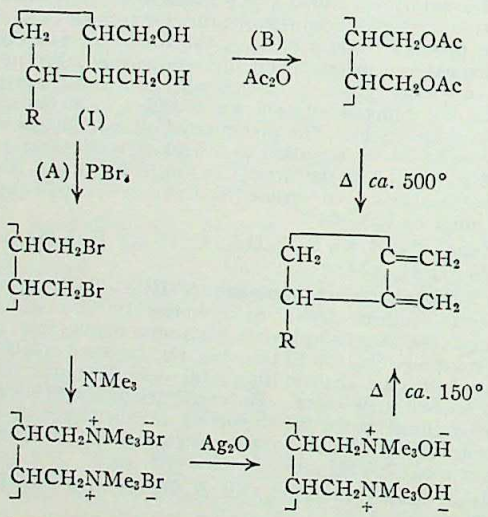
1,2-Dimethylenecyclohexane. Synthesis and Polymerization[1]

BY A. T. BLOMQUIST AND D. T. LONGONE

RECEIVED FEBRUARY 6, 1957

1,2-Dimethylenecyclohexane has been obtained by the thermal decomposition of 1,2-bis-(dimethylaminomethyl)-cyclohexane dimethohydroxide. The syntheses of the precursors for the diene involved standard classical transformations starting with diethyl phthalate. The over-all yield was 27%. A number of polymerizations utilizing several systems and for various reaction times showed that the monomer was much less reactive than its smaller ring homologs, 1,2-dimethylenecyclobutane and 1,2-dimethylenecyclopentane. Polymers obtained were either oils or highly crystalline non-rubbery solids. On the basis of infrared spectra the polymers appeared to be comprised of all *cis*-1,4-units. The polymerization characteristics of this diene appear to be due, at least in part, to its six-membered ring structure.

Previous investigations carried out in this Laboratory concerning the study of conjugated exocyclic dienes have utilized two quite different preparative methods. Both methods may be viewed as starting with the same appropriate glycol I and proceeding as



Path A involves the Hofmann degradation of the appropriate bis-quaternary ammonium hydroxide and path B the pyrolytic decomposition of the requisite diacetate.

On comparing the two methods of preparation it has been found that the Hofmann elimination affords a product of greater purity and in higher yield. It also gives a single product, whereas with acetate pyrolysis a large forerun must be carefully removed in the purification of the diene.

The high pyrolytic temperatures (*ca.* 500°) required in the latter method may lead to ring cleavage in more sterically strained cyclic systems. Thus it has been shown that pyrolysis of 1,2-bis-(acetoxymethyl)-cyclobutane at 485° gives only 2-vinyl-1,3-butadiene while the desired product, 1,2-dimethylenecyclobutane, may be obtained *via* the Hofmann method in 28% yield.[2]

More recently[3] a direct comparison of both methods was made in the synthesis of 1,2-dimethylenecyclopentane and its 3-methyl homolog. Yields and product purity were superior using the Hofmann method.

Because of the encouraging results obtained in these earlier studies it seemed desirable to restudy the synthesis of 1,2-dimethylenecyclohexane (II). This diene has been prepared previously in this Laboratory *via* the acetate pyrolysis at 525° in 29% yield.[4] Emulsion polymerization of the diene, using potassium persulfate as initiator, was carried out at 53° and gave a 53% conversion to a highly crystalline polymer with no rubber characteristics whatsoever. The synthesis and polymerization of II also has been reported by two other groups of investigators. Wicklatz and Short[5] first prepared this diene by dehydrohalogenation of 1,2-bis-(iodomethyl)-cyclohexane and by diacetate pyrolysis at 300–500°; while Bailey and Golden[6] repeated the diacetate pyrolysis at 520°.

Wicklatz and Short[7] obtained a homopolymer of II and described the product as a brittle resin. They also report the ionic polymerization of II using aluminum trichloride at −70° to produce "oily polymers." Bailey and Golden[6] obtained a white crystalline homopolymer melting at 165° using a peroxide-catalyzed emulsion system, an identical polymer from ionic polymerization using boron trifluoride etherate, and a viscous oil using boron trifluoride gas.

The physical properties of the homopolymers of II obtained in the work summarized above are in marked contrast to those of the homopolymers of the smaller ring homologs prepared in this Laboratory. 1,2-Dimethylenecyclobutane[2] and 1,2-dimethylenecyclopentane[3] readily gave elastomeric homopolymers using a persulfate emulsion system. Both monomeric dienes were prepared *via* the Hofmann method. Of further interest is the fact that Bailey obtained only a highly crystalline, non-rubber homopolymer of 1,2-dimethylenecyclopentane using monomer prepared *via* the acetate pyrolysis.[8]

These anomalies led us to suspect that traces of impurities might be present in the monomeric dienes prepared *via* the more drastic acetate py-

(1) The work reported here was done as part of a general research program in organic chemistry at Cornell University sponsored by the B. F. Goodrich Co.

(2) A. T. Blomquist and J. A. Verdol, THIS JOURNAL, **77**, 1806 (1955).

(3) A. T. Blomquist, J. Wolinsky, Y. C. Meinwald and D. T. Longone, *ibid.*, **78**, 6057 (1956).

(4) J. A. Verdol, Ph.D. Thesis, Cornell University, Ithaca, N. Y., 1955.

(5) J. E. Wicklatz and J. N. Short, U. S. Patent 2,601,075; *C.A.*, **47**, 4366 (1953).

(6) W. J. Bailey and H. R. Golden, THIS JOURNAL, **75**, 4780 (1953).

(7) J. E. Wicklatz and J. N. Short, U. S. Patent, 2,600,454 (1952); *C. A.*, **46**, 11769 (1952).

(8) W. J. Bailey, "Conference on Elastomer Research and Development," National Academy of Sciences and National Research Council Publication 370, January 12–13, 1954, p. 115.

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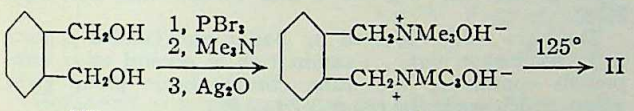
rolysis. Olefinic impurities, inherent in the latter method of preparation, would be expected to affect the polymerization of the dienes in a number of possible ways—retarder or inhibitor action, etc.

Since, 1,2-dimethylenecyclohexane (II) had not been prepared by the Hofmann method and information was available concerning its preparation *via* acetate pyrolysis and subsequent polymerization, this investigation was initiated.

The immediate goal was to determine whether the highly crystalline, non-rubber characteristics of the homopolymer II were due to impurities in the monomer prepared *via* the acetate pyrolysis or were unique to this particular six-membered ring system.

1,2-Dimethylenecyclohexane (II).—The synthesis of II was achieved as indicated below.



III IV

The glycol 1,2-bis-(hydroxymethyl)-cyclohexane (III) was made by lithium aluminum hydride reduction of diethyl 1,2-cyclohexanedicarboxylate obtained from the catalytic reduction of diethyl phthalate. The over-all yield of III from diethyl phthalate was 84%. Treatment of III with phosphorustribromide gave 1,2-bis-(bromomethyl)-cyclohexane in 90% yield. Conversion of the dibromide to the bis-quaternary ammonium hydroxide IV was effected by treatment with methanolic trimethylamine followed by reaction with freshly prepared moist silver oxide.

Thermal decomposition of IV at 120–125° gave II (40%). After one distillation under nitrogen and reduced pressure the pure diene showed b.p. 73–74° (139 mm.), n^{25}D 1.4717, and an ultraviolet spectrum maximum (in isoöctane) at 220 mμ with log ε 3.82.

Polymerization of II.—Freshly prepared and purified diene was subjected to a number of free radical initiated polymerizations using conventional emulsion and oxidation–reduction recipes and one typical Ziegler recipe. The rate of polymerization in all cases was very slow and homopolymer products were either oils or brittle, powdery solids depending upon extent of polymerization time.

The solid homopolymers were highly crystalline as evidenced by their complete insolubility in all common organic solvents and high melting points. The comparatively narrow melting point ranges indicate absence of extensive crosslinking. The polymerization results are summarized in Table I.

Infrared spectra of the solids (KBr) show the absence of terminal methylene groups and indicate all *cis*-1,4-units in the polymers. Molecular weight estimations either by the Signer—Barger ebullioscopic method, applicable to molecular weights of about 5000, or by intrinsic viscosity measurements could not be made because of solvent difficulties.

The homopolymers reported here are thus very similar to the oils and brittle resins of Wolinsky[9] and Short and the high-melting crystalline solids of Bailey and Golden.

TABLE I

HOMOPOLYMERS OF 1,2-DIMETHYLENECYCLOHEXANE

System	Temp., °C.	Time	Conversion, %	M.p., °C.
Emulsion	50	20 hr.	Oil	.....
Emulsion	50	50 hr.	Oil	.....
Emulsion	50	60 hr.	100	148–152
Emulsion	50	80 hr.	100	148–152
Emulsion	50	135 hr.	100	148–152
Emulsion	50	144 hr.	100	148–152
Oxidation–reduction	50	117 hr.	100	135–144
Oxidation–reduction	5	5 wk.	Oil	.....
Mass (benzoyl peroxide)	50	2 wk.	29	132–135
Ziegler	50	24 hr.	0	.....

Since the diene II was prepared and purified by the same methods used for 1,2-dimethylenecyclopentane and 3-methyl-1,2-dimethylenecyclopentane, its extremely slow rate of polymerization appears to be peculiar to the six-membered ring system. In addition to the increased steric effect present in going from the five-carbon to the six-carbon cyclic monomer a more significant structural difference is the spatial relationship of the exocyclic double bonds. In 1,2-dimethylenecyclobutane and the 1,2-dimethylenecyclopentanes, which polymerize rapidly, the exocyclic double bonds are forced to be coplanar by the steric requirements of the cyclobutane and cyclopentane rings. In 1,2-dimethylenecyclohexane, however, there is a large deviation from coplanarity of the double bond system when the cyclohexane ring is in the chair conformation. The angle between the planes of the double bonds approaches 60° in this conformation. Cyclohexane is known to exist predominantly in the chair form at moderate temperatures and only at elevated temperatures is the boat form important. The ultraviolet absorption maxima of the dienes are a measure of the relative coplanarity of the double bond system. 1,2-Dimethylenecyclohexane has a maximum absorption about 30 mμ lower than the corresponding four- and five-membered ring dienes.

This non-coplanarity of the conjugated system would be expected to decrease the reactivity of the monomer toward 1,4-addition. Free radical addition to one of the exocyclic methylene groups and resultant formation of the endocyclic double bond (1,4-addition) requires twisting the ring system so that the originally non-planar methylene carbon atoms become coplanar. In the smaller ring analogs no such ring contortions are required in the formation of the internal double bond.

Whether this factor is significant enough to account entirely for the marked decrease in the reactivity of the monomer cannot be ascertained at the present time. It is pertinent, however, to mention the extreme difficulty Laughlin[9] encountered in attempting to polymerize 4-neopentyl-1,2-dimethylenecyclohexane in a wide variety of systems; and the low conversions (29–75%) Wolinsky[10] obtained on polymerization of 1,2-dimethylene-4-methylcyclohexane.

(9) R. G. Laughlin, Ph.D. Thesis, Cornell University, 1955.
(10) J. Wolinsky, Ph.D. Thesis, Cornell University, 1956.

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Experimental Part

Diethyl 1,2-Cyclohexanedicarboxylate (V).—In a stainless steel hydrogenation bomb diethyl phthalate, 236 g. (1.06 moles), was reduced over Raney nickel at 170° to give crude V. The crude was fractionated through a 60-cm. Vigreux column to give pure diester (94%), b.p. 124–125° (5.4 mm.), $n^{25}D$ 1.4503 (Bailey and Golden[6] reported b.p. 150–152° (23 mm.), $n^{25}D$ 1.4505).

1,2-Bis-(hydroxymethyl)-cyclohexane (III).—Lithium aluminum hydride reduction of 122 g. (0.53 mole) of V carried out in the usual way gave 67 g. (89%) of III, b.p. 142–143° (3.8 mm.), $n^{25}D$ 1.4905 (Haggis and Owen[11] reported b.p. 110–130° (0.3 mm.), $n^{20}D$ 1.4914; Bailey and Golden[6] found b.p. 134–136° (3 mm.), and Wicklatz and Short[5] reported b.p. 145–146° (5 mm.), $n^{25}D$ 1.4880).

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.73; H, 11.13.

1,2-Bis-(bromomethyl)-cyclohexane (VI).—Using the procedure described for the preparation of 1,2-bis-(bromomethyl)-cyclopentane,[3] from 76 g. (0.53 mole) of III there was obtained pure dibromide (90%), b.p. 112–113° (2.5 mm.), $n^{25}D$ 1.5413, d^{25}_4 1.6276; MD calcd. for $C_8H_{14}Br_2$ 52.5, found 52.2 (no correction for exaltation due to the six-membered ring).

Anal. Calcd. for $C_8H_{14}Br_2$: C, 35.58; H, 5.23; Br, 59.19. Found: C, 35.63; H, 5.32; Br, 59.33.

1,2-Bis-(dimethylaminomethyl)-cyclohexane Dimethobromide (VII).—A mixture of 59 g. (1.00 mole) of trimethylamine, 44 g. (0.16 mole) of VI and 10 ml. of methanol was kept in a sealed Pyrex bomb at room temperature until separation of solid precipitate was complete. Evaporation of the reaction mixture to dryness *in vacuo* gave the bis-quaternary ammonium bromide (88%). Attempted recrystallization of the crude salt was unsuccessful. A portion of it was converted to the quaternary ammonium picrate which was recrystallized from 95% ethanol. Two picrates were obtained: A, difficultly soluble in hot ethanol and B, very soluble in hot ethanol. Picrate A had m.p. 192–194° and B a m.p. of 166–167°.

Anal. Calcd. for $C_{26}H_{36}O_{14}N_8$: C, 45.61; H, 5.30; N, 16.37. Found: A: C, 45.28; H, 5.11; N, 16.41; B: C, 45.35; H, 5.13; N, 16.18.

1,2-Dimethylenecyclohexane (II).—The crude quaternary ammonium bromide VII (38.2 g., 0.098 mole) was dissolved in a minimum amount of water. Freshly prepared silver oxide was added to the aqueous solution in small portions with stirring. The reaction vessel was cooled with an ice-bath. An immediate exothermic reaction occurred with the formation of yellow silver bromide. The addition of silver oxide was continued until the formation of silver bromide ceased, as was evidenced by the persistence of the dark brown color due to excess oxide. The solid mixture of silver bromide and silver oxide was filtered off and the filtrate, an aqueous solution of 1,2-bis-(dimethylaminomethyl)-cyclohexane dimethohydroxide, was transferred directly into a 200-ml. round-bottomed flask for pyrolysis. The flask was equipped with a Vigreux head and condenser take-off which led to a receiver immersed in an ice-bath. The cold receiver had an outlet leading to a trap immersed in Dry Ice. Hydroquinone was added to the pyrolysis flask and the receiver and the entire system purged with nitrogen. The flask was heated slowly with an oil-bath and under reduced pressure (142–146 mm.). At bath temperature from 90 to 115° mostly water came over at a vapor temperature 66–68°. In the range 115 to 125° oil and water co-distilled at *ca.* 68°. The oil-bath was kept at 125° until the decomposition was complete. The ice-bath receiver contained all the crude diene (upper layer) and it was separated from the water layer and washed with 10% hydrochloric acid to convert the trimethylamine, formed during pyrolysis, to its ammonium salt. After washing with water, until neutral to litmus, and drying over magnesium sulfate the crude diene was distilled from a 25-ml. pear-shaped flask. Distillation was carried out in an atmosphere of nitrogen and in the presence of hydroquinone. Pure diene (5.0 g., 40%) showed b.p. 73–74° (136 mm.), $n^{25}D$ 1.4717 (Wicklatz and Short[5] reported b.p. 48.8–49.4° (55 mm.), $n^{25}D$ 1.4710; Bailey and Golden[6] found b.p. 60–61° (90 mm.), 124° (740 mm.), $n^{25}D$ 1.4718; Verdol[4] gave b.p. 80–81° (130 mm.), $n^{20}D$ 1.4741).

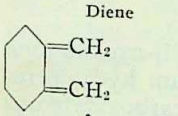
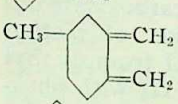
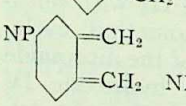
Anal. Calcd. for C_8H_{12}: C, 88.82; H, 11.18. Found: C, 88.85; H, 11.30.

Reaction of II with Maleic Anhydride.—Maleic anhydride (1.42 g., 0.0145 mole) and 25 ml. of ether were placed in a 50-ml. round-bottomed flask equipped with a reflux condenser. After the addition of 1.57 g. (0.0145 mole) of pure diene II the mixture was allowed to stand overnight during which time a white crystalline solid separated. The ether was evaporated, using a water aspirator, and the crude product recrystallized from ether to give pure $\Delta^{9,10}$-octahydronaphthalene-2,3-dicarboxylic acid anhydride, m.p. 139.5–140.0° (Bailey and Golden[6] reported m.p. 139–140° and Verdol[4] gave m.p. 142–143°).

Absorption Spectra of II.—The infrared spectrum of II was similar to those reported for the smaller ring analogs.[3] Strong absorption is present at 3.26 and 6.08 μ indicative of unsaturation and at 11.35 μ characteristic of the terminal methylene group.

The ultraviolet spectrum of II shows only one peak, λ_{max} (isoöctane) 220 mμ, log ϵ 3.82 (Bailey and Golden[6] reported λ_{max} 220, log ϵ 4.00 and Verdol[4] λ_{max} 220, log ϵ 3.74).

The log ϵ value reported by Bailey and Golden appears to be somewhat high. Examination of several other compounds containing the same chromophoric group gives values which are in the range 3.7 to 3.8.

Diene	λ_{max}, mμ	log ϵ	Reference
	220	3·82	This work
	220	4·00	6
	220	3·74	4
	218 (Ethanol)	3·80	10
	217 (Isoöctane)	3·77	10
	221	3·69	9

NP = neopentyl

Homopolymerization of II.—All polymerizations were carried out on about one-gram samples of freshly prepared and purified diene in sealed glass tubes. All polymerizations but one were at 50° in a rotating constant-temperature water-bath. The oxidation–reduction charge at 5° was kept in a refrigerator and frequently hand-agitated. In all cases before sealing, the glass tubes were purged with purified nitrogen to remove oxygen.

The recipes used were

(a) Emulsion

Monomer, 1.0 g.
Ivory soap, 0.1 g.
Initiator solution, 0.1 ml. (3% potassium persulfate soln.)
Water, 2.5 ml.

(b) Oxidation–reduction emulsion

Monomer	1.0 g.
Water	3.3 ml.
Ivory soap	0.03 g.
Catalyst ($K_2S_2O_8$)	.33 ml. (3% soln.)
Activator (Na_2SO_3)	.00., g.

(c) Mass

Monomer	1.0 g.
Benzoyl peroxide	0.01 g.

(d) Ziegler[12]

Benzene	21.5 ml.
Triisobutylaluminum	0.063 ml. (added as 10% soln. in benzene)
Titanium tetrachloride	0.027 ml. (5% soln. in benzene)
Diene	2.0 ml.

In the Ziegler system no visible change occurred after 24

(11) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 389 (1953).

(12) We are indebted to C. E. Brockway of the B. F. Goodrich Research Laboratory who carried out this polymerization.

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hours at 50°. Addition of 50 ml. of methanol did not precipitate polymer; only a trace of flocculent white solid separated. On standing overnight in an open heater, the solvent evaporated off, leaving a clear yellow sticky wax, evidently very low molecular weight polymer or air oxidation product of monomer.

All other reactions were quenched by chilling the tubes before opening and pouring the contents into a 2% sol. of PBNA in absolute ethanol. Where solid polymers were obtained, they precipitated as gummy particles which on stirring balled up into one mass. After drying at room temperature *in vacuo* the solids were hard, brittle white resins. They were found to be completely insoluble and generally unswollen in all common organic solvents.

Where oils were obtained, unreacted monomer could be recovered as its maleic anhydride adduct from an ether extract of the coagulating solution. The presence of monomer rather than dimer, even after heating at 50° for 50 hours (see Table I), indicates further the decreased activity of this diene. 1,2-Dimethylenecyclopentane, in comparison, dimerizes very readily above 90° or on contact with silica gel to form a self Diels–Alder adduct.[3]

The homopolymers obtained as oils were not further investigated.

Anal. of polymer (solid). Calcd. for $(C_8H_{12})_x$: C, 88.82; H, 11.18. Found: C, 89.09; H, 10.98.

ITHACA, NEW YORK

[CONTRIBUTION FROM THE PROCTER & GAMBLE CO., MIAMI VALLEY LABORATORIES]

Preparation and Properties of Some Hexadecyl Hydrogen Esters of Dibasic Acids

BY W. FREDERICK HUBER AND E. S. LUTTON

RECEIVED MARCH 4, 1957

Hexadecyl hydrogen esters of the dibasic acids succinic, glutaric, pimelic, maleic and itaconic were prepared and their crystallization behavior studied by means of X-ray diffraction. The compounds melt in the range of 59–77° and show only one crystal form whether from solvent or melt. Each appears to crystallize in double chain-length structure; each shows rather individualistic diffraction behavior except the similar homologous pair, the glutarate and the pimelate.

Introduction

Little is known of the preparation and properties of the longer monoalkyl hydrogen esters of dibasic acids. The preparation of hexadecyl hydrogen succinate by the reaction of succinic anhydride with hexadecanol has been reported.[1] Herein are reported the preparation and X-ray diffraction patterns of the hexadecyl hydrogen esters of succinic, glutaric, pimelic, maleic and itaconic acid.

Experimental

M.p.'s and analyses of the products appear in Table I.

TABLE I

M.P.'S AND ANALYSES OF HEXADECYL HYDROGEN ESTERS

n-Hexadecyl hydrogen ester	M.p., °C.	Analyses, % Neut. equiv. Calcd.	Neut. equiv. Found	Sapn. equiv. Calcd.	Sapn. equiv. Found
Succinate	63.5–64.5	342.5	340.0	171.3	172.2
Maleate	70–71.5	340.5	338.8	170.3	172.1
Itaconate	76–76.5	354.5	356.0	177.3	175.8
Glutarate	68.5–69.5	356.5	356.7	178.3	177.7
Pimelate	58–59	384.6	382.5	192.3	191.4

The succinate, maleate and itaconate were prepared by heating molar equivalents of the requisite acid anhydride with hexadecyl alcohol at 130–140° for 10 minutes. Hexadecyl hydrogen glutarate and pimelate were obtained by refluxing hexadecanol with excess dibasic acid for about 10 hr. in benzene with *p*-toluenesulfonic acid as a catalyst. The products were purified by recrystallization from hexane. In the case of the pimelate it was necessary to wash the hexane solution with warm water to remove pimelic acid. The structure of the products is unequivocal with the exception of hexadecyl hydrogen itaconate. In this case, esterification can open the anhydride to form either hexadecyl hydrogen α-methylenesuccinate or hexadecyl β-methylenesuccinate. The chemical structure of the itaconate was not explored.

Thermal and X-Ray Diffraction Technique.—Rapid complete m.p.'s and regular complete m.p.'s[2] were determined, the latter on both melted-chilled and solvent-crystallized samples. The single melting-level has been reported under sample preparation. "Rod pellets" of both solvent-crystallized and melted-chilled samples were X-rayed and found to have substantially identical patterns. Flat-film patterns were obtained with a General Electric XRD-1 unit employing nickel-filtered CuKα radiation and a 0.025-in. pinhole system. Sample-to-film distance was normally 10 cm.

X-Ray diffraction data are listed in the following order: compound; long spacing, L.S. (in Å.); short spacings, S.S. (in Å.). Relative intensities of diffraction lines are indicated by (V.S.) = very strong, (S) = strong, (M) = medium, (W) = weak.

Hexadecyl H succinate: L.S. 42.8; S.S. 4.54(S+), 3.98(S), 3.77(W), 3.63(S+)
Hexadecyl H glutarate: L.S. 45.2; S.S. 4.63(W), 4.4(W), 4.11(V.S.), 3.76(S)
Hexadecyl H pimelate: L.S. 50.8; S.S. 4.60(W), 4.14(V.S.), 3.79 (S)
Hexadecyl H maleate: L.S. 29.4; S.S. 5.28(W), 4.64(S), 3.78(V.S.)
Hexadecyl H itaconate: L.S. 40.7; S.S. 4.68(M), 4.44(W), 4.16(V.S.), 3.74(S)

Discussion

While the dibasic acids from which these hexadecyl monoesters were made show a range of m.p.'s covering 90°, the esters show a spread of only 18° with little correlation between relative melting level in the acid and ester series. Each ester shows the same single solid phase whether from solvent or from melt. The several compounds are quite individualistic in X-ray diffraction behavior except for the glutarate and pimelate which are adjacent odd homologs; they show a beta prime-type of pattern rather similar to those exhibited by palmitic and stearic acids. It is a little surprising that the higher homolog melts 10° lower, especially when the acid m.p.'s are in the reverse order.

The chain lengths of these hexadecyl esters should be of the order 28–30 Å. The long spacings which mostly run from 40–50 Å. bespeak tilted [illegible] structures. The maleate long

(1) J. T. Davies and E. K. Rideal, *Proc. Roy. Soc.* (*London*), **A194**, 417 (1948).

(2) E. S. Lutton, F. L. Jackson and O. T. Quimby, THIS JOURNAL, **70**, 2441 (1948).

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spacing is remarkably short at 29 Å. and may signify a single-chain-length structure, but the fact that the intensities of various orders of long spacing follow a sequence similar to those of the succinate suggests a double-chain-length structure.

CINCINNATI 31, OHIO

COMMUNICATIONS TO THE EDITOR

THE STRUCTURE OF RUSCOGENIN[1]

Sir:

Ruscogenin, isolated by Lapin and Sannié[2] in 1955 from *Ruscus aculeatus L.*, was identified as 19-hydroxydiosgenin.[3] However, we wish to report recent evidence which invalidates the structure proposed by the French workers. For purpose of clarity we shall assume that this new sapogenin is x-hydroxydiosgenin and later in this communication arrive at the most probable structure.

Recrystallized ruscogenin[4] diacetate (m.p. 191–194°, $[\alpha]^{25}D$ −80.5°, 1.03% in $CHCl_3$; diol,[5] m.p. 205–211°, $[\alpha]^{25}D$ −118°, 1% in $CHCl_3$) was degraded[6] by methods well established in the sapogenin field[3,7] to the oily diacetate of 5,16-pregnadiene-x,3-diol-20-one I in 70% yield. Beckmann rearrangement[8] of the oxime (m.p. 188–197° dec.; C, 69.82; H, 8.02), followed by mild acid treatment yielded x-acetoxydehydroepiandrosterone acetate II (m.p. 97–99°) and 147–149°; C, 71.44; H, 8.31), which on vigorous alkaline hydrolysis afforded x-hydroxydehydroepiandrosterone III (m.p. 195–197°; C, 74.71; H, 8.99). Diol III was stable to acid and reverted to II on acetylation. Controlled acid-catalyzed methanolysis of the diacetate II led, after chromatography, to x-acetoxydehydroepiandrosterone IV (m.p. 136.5–138°; C, 72.91; H, 8.97) in about 65% yield.

When the diol III was treated with aluminum isopropoxide and cyclohexanone in refluxing toluene, 1,4-androstadiene-3,17-dione[9] (m.p. 139.5–140.5°; λ_{max}^{MeOH} 243 mμ, ε 16,000) was obtained in approximately 30% yield, as shown by comparison (infrared and mixed m.p.), with an authentic sample prepared according to Djerassi and Scholz.[9b] The monoacetate IV was carefully oxidized with chromic acid in acetone[10] to an oily ketone V, which on treatment with potassium acetate in refluxing ethanol or aqueous potassium hydroxide in methanol at room temperature, again afforded 1,4-androstadiene-3,17-dione (m.p. 139–140.5°) in approximately 40% and 50% yield respectively. These results could best be rationalized by assuming the additional hydroxyl to be situated on carbon 1 of the steroid nucleus.

In order to obtain additional information as to the position and configuration of the functional groups, the diol III was reduced with sodium borohydride in methanol to 5-androstene-1,3β,17β-diol VIa (m.p. 275–280° dec.; C, 74.24; H, 9.97; triacetate VIb, m.p. 145–147°; C, 69.24; H, 8.57), which on catalytic hydrogenation in presence of Adams catalyst in ethanol containing a trace of hydrochloric acid, afforded in 93% yield androstane-1,3β,17β-triol VII (m.p. 217–219°; C, 74.01; H, 10.47). Triol VII was found to be different (infrared and mixed m.p.) from authentic androstane-1α,3β,17β-triol (m.p. 236–238°; C, 73.71; H, 10.54), obtained from 1-androstene-3,17-dione by α-epoxidation with alkaline hydrogen peroxide, followed by stepwise reduction with sodium borohydride and lithium aluminum hydride.[11]

Conclusive proof of structure was finally obtained when the triol VIa and its triacetate VIb were compared with authentic samples[12] of 5-androstene-1β,3β,17β-triol, m.p. 270–278° dec. and its triacetate m.p. 147.5–148.5°. They were respectively found to be identical in all respects (infrared and mixed m.p.).

The positions of the two hydroxyl groups and of the double bond in ruscogenin are thus firmly established. In light of our results and the conversion of ruscogenin to diosgenin by Lapin and Sannié,[2] we conclude that this new sapogenin is very likely 1β-hydroxydiosgenin.

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RECEIVED MAY 25, 1957

(1) After this work was completed a recent communication—D. Burn, B. Ellis and V. Petrow, *Proc. Chem. Soc.*, 119 (1957)—dealing with this subject, came to our attention.

(2) H. Lapin and C. Sannié, *Bull. Soc. Chim.*, 1552 (1955).

(3) C. Sannié and H. Lapin, *ibid.*, 1556 (1955).

(4) We wish to thank Mr. J. Monnet of Société des Usines Chimiques Rhône-Poulenc, for a generous supply of a mixture—as shown by paper chromatography and infrared analysis—of ruscogenin and its ring-F isomer.

(5) This sample of ruscogenin, derived from the diacetate, belonged to the "iso" series as shown by its infrared absorption spectrum.

(6) We are indebted to Dr. G. P. Mueller of this laboratory for his advice and help in this degradation.

(7) G. P. Mueller, R. E. Stobaugh and R. S. Winniford, THIS JOURNAL, **75**, 4888 (1953); M. E. Wall, H. E. Kenney and E. S. Rothman, *ibid.*, **77**, 5665 (1955); A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones and A. G. Long, *J. Chem. Soc.*, 2807 (1955).

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(9) (a) H. H. Inhoffen, G. Zühlsdorff and Huang-Minlon, *Ber.*, **73B**, 451 (1940); (b) C. Djerassi and C. R. Scholz, *J. Org. Chem.*, **13**, 697 (1948).

(10) C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(11) *Cf.* the extensive work of Tamm and co-workers—F. Salmann and C. Tamm, *Helv. Chim. Acta*, **39**, 1340 (1956), and earlier references on analogous systems, where it was shown that a similar sequence of reactions always led to the 1α,3β-diol as the major product.

(12) R. M. Dodson, A. H. Goldkamp, R. D. Muir, THIS JOURNAL, **79**, 3920 (1957).

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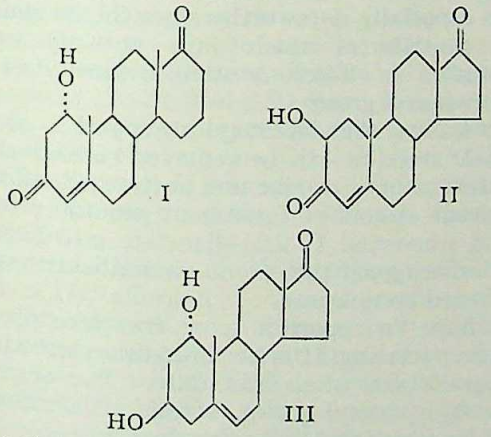
MICROBIOLOGICAL HYDROXYLATION OF C_{19}-STEROIDS AT POSITIONS C-1 AND C-2

Sir:

Extensive studies[1] have shown that steroids can be hydroxylated by microörganisms at positions 6β, 7α, 7β, 8- and/or 9-, 10, 11α, 11β, 14α, 15α, 15β, 16α, 17α and 21. We now wish to report the preparation of 1α-hydroxy-4-androstene-3,17-dione (I); m.p. 218–221°; $[\alpha]D$ +184° ($CHCl_3$); $\lambda_{max}^{methanol}$ 240 mμ (15,000); (found: C, 75.32; H, 8.46); and 2β-hydroxy-4-androstene-3,17-dione (II); m.p. 143–145°; $[\alpha]D$ −36.8° ($CHCl_3$); $\lambda_{max}^{methanol}$ 242 mμ (14,200); (found: C, 75.80; H, 8.71); by the microbiological action of a species of *Penicillium*, isolated from local soil, on 4-androstene-3,17-dione. By subjecting dehydroepiandrosterone to the same oxidative fermentation, we obtained, besides I, 1α-hydroxydehydroepiandrosterone (III); m.p. 275–277.5°; $[\alpha]D$ +10.6° ($CHCl_3$); (found: C, 74.92; H, 9.21). The hydroxylated steroids were prepared by the fermentation and extraction techniques previously described,[2] and, in the case of the hydroxylated androstenediones, were purified by chromatography on silica gel. 1α-Hydroxydehydroepiandrosterone (III) was readily obtained by direct crystallization on concentration of the methylene chloride extract.



The structure of II was indicated by the contribution of the new hydroxyl to the molecular rotation of the compound (ΔM_D −658),[3a] by a positive "blue tetrazolium" test, and by the characteristic change of ultraviolet spectra with time in 0.1 *N* methanolic potassium hydroxide.[4] The structure was established by converting II to its acetate, m.p. 157–158°; $[\alpha]D$ −5.9° ($CHCl_3$); $\lambda_{max}^{methanol}$ 243 mμ (15,300); (found: C, 73.47, H; 8.04); and epimerizing II acetate, by heating with anhydrous potassium acetate in glacial acetic acid,[5] to the known 2α-acetoxy-4-androstene-3,17-dione,[3b] m.p. 209–211°; $[\alpha]D$ +146.8° ($CHCl_3$); $\lambda_{max}^{methanol}$ 239.5 mμ (15,500).

The structure of I was established by the conversion of I acetate, m.p. 112.5–113.5°; $[\alpha]D$ +191.7° ($CHCl_3$); $\lambda_{max}^{methanol}$ 239.5 mμ (16,500); (found: C, 72.71; H, 8.07); by means of dilute methanolic sodium hydroxide to 1,4-androstadiene-3,17-dione,[6] m.p. and mixed m.p. 139–140°. Comparison of the infrared spectrum with that of an authentic sample confirmed identity. Oppenauer oxidation of III to 1,4-androstadiene-3,17-dione[6] established the structure of III.

The configuration of the 1-hydroxyl group in both I and III was initially assigned on the basis of molecular rotatory contributions.[7] The structure of III was definitively confirmed by its catalytic reduction to 1α,3β-dihydroxyandrostan-17-one (IV), m.p. 202–203.5°; $[\alpha]D$ +88.2° ($CHCl_3$); (found: C, 74.32; H, 9.74); followed by reduction of IV with sodium borohydride to 1α,3β,17β-androstanetriol (V), m.p. 238–239°; $[\alpha]D$ +20.2° ($CHCl_3$); (found: C, 73.99; H, 10.47). This compound (V) was identical in all respects with that prepared by Benn, Colton, and Pappo[8] by the reduction of 1α,2α-oxidoandrostane-3,17-dione.

Reduction of III with sodium borohydride or lithium aluminum hydride gave 5-androstene-1α,3β,17β-triol (VI), m.p. 212–213°; $[\alpha]D$ −54.8° ($CHCl_3$); (found: C, 74.41; H, 10.22); triacetate, m.p. 179–181°; (found: C, 69.11; H, 8.24). Cautious acetylation of III produced 1α-hydroxy-3β-acetoxy-5-androsten-17-one (VII), m.p. 243–244°; $[\alpha]D$ −6.7° ($CHCl_3$); (found: C, 72.58; H, 8.83); which was oxidized with chromium trioxide in pyridine to 3β-acetoxy-5-androstene-1,17-dione (VIII), m.p. 156–157.5°; $[\alpha]D$ +40.7° ($CHCl_3$); (found: C, 73.27; H, 8.27). The reduction of VIII with sodium borohydride yielded VI and 5-androstene-1β,3β,17β-triol (IX), m.p. 270–278°; triacetate, m.p. 147.5–148.5°; $[\alpha]D$ −32.4° ($CHCl_3$); (found: C, 69.11; H, 8.54). Compound IX and its triacetate were identical in all respects (m.p., mixed m.p., and infrared) with the corresponding triol and triacetate obtained from Ruscogenin by Benn, Colton, and Pappo.[8]

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RECEIVED MAY 25, 1957

MICROBIOLOGICAL TRANSFORMATION OF STEROIDS. 2β-HYDROXYLATION

Sir:

It has become increasingly evident that enzymatic hydroxylations of steroid occurring in the mammalian tissues will inevitably find their counterparts in microbially-induced transformations of the same or similar substrates. Of the hydroxylation processes occurring in mammals the

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reactions at 2α[1], 2β[2], 6α[3], 18-[4] and 19-[4] have not as yet been duplicated by incubations with microorganisms.[4a]

We wish to report that microbiological 2β-hydroxylation of 4-pregnene-17α,21-diol-3,20-dione (I, Reichstein's Compound S) has now been achieved with the aid of several unidentified *Streptomyces* species isolated from soil (Schering collection numbers FC7-206, FC6-53S, DS 81-B). Incubation of Compound S (600 mg.) in a peptone–soybean meal–yeast extract–cerelose medium with a 72-hour growth culture of *Streptomyces* sp. DS-81-B with rotary shaking at 28° for 48 hours afforded, after chloroform extraction and chromatography, 35 mg. of 4-pregnene-2β,17α,21-triol-3,20-dione (II), m.p. 215–220° dec. Further recrystallization from acetone–hexane raised the m.p. to 225.5–228° dec. and gave II with the following constants: $[\alpha]^{25}D$ −58° (dioxane), λ_{max}^{MeOH} 243 mμ (ϵ = 14,500), λ_{max}^{Nujol} 3.01 μ (OH), 5.81 μ (20-carbonyl), 5.94 μ (3-carbonyl) and 6.18 μ (Δ^4); three hydroxyl groups by integration of the OH band. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.81; H, 8.76. A polymorphic modification of II exists which possesses an altered infrared spectrum, λ_{max}^{Nujol} 2.87 μ (OH), 5.82 μ (20-carbonyl), 5.89 μ and 6.02 μ (3-carbonyl) and 6.20 μ (Δ^4). The latter polymorph is converted to the former by recrystallization from acetone–hexane and seeding with the former. The infrared spectra of the two forms differed in considerable detail from the 6β, 11α, 11β, 15α and 15β-hydroxy derivatives of I. The 2,21-diacetate of II, prepared with acetic anhydride and pyridine melts at 218–219°, $[\alpha]^{25}D$ +9° (dioxane), λ_{max}^{MeOH} 244 mμ (ϵ = 16,200), λ_{max}^{Nujol} 2.73, 2.83, 2.97 μ (OH), 5.71 μ (acetate carbonyl), 5.78 μ (20 carbonyl), 5.95 μ (3-carbonyl), 6.16 μ (Δ^4), 8.06 μ and 8.25 μ (C–O–C of acetate). Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 66.99; H, 7.74. The 21-monoacetate of II, prepared with one equivalent of acetic anhydride in pyridine solution, melted at 234–235°, $[\alpha]^{25}D$ −24° (dioxane), λ_{max}^{MeOH} 243 mμ (ϵ = 14,300), $\lambda_{max}^{CHBr_3}$ 2.86 μ (OH), 5.71 μ (acetate carbonyl), 5.76 μ (20-carbonyl), 5.95 μ (3-carbonyl), 6.17 μ (Δ^4) and 8.12 μ (C–O–C of acetate). Calcd. for $C_{23}H_{30}O_6$; C, 68.29; H, 7.97. Found: C, 68.00; H, 7.63.

The structure of II has been assigned on the basis of the following arguments and experiments. Appearance of the conjugated carbonyl band at 5.94 μ is interpreted as indicating a hydrogen bond interaction between the carbonyl at 3- and an hydroxyl group on an adjacent carbon atom. This is further substantiated by the observed interaction of the neighboring acetate with the 3-carbonyl) in the 2,21-diacetate of II as well. The observed ultraviolet maximum of II excludes 4- as a site for neighboring hydroxyl since enols of α,β-diketones absorb in the region of 280 mμ. Measurement of the ultraviolet absorption in alkaline solution, according to Meyer,[5] after heating at 60° for 4 hours, afforded a curve which corresponded exactly in location of maxima with the highly characteristic curve from 2α-hydroxy-4-androstene-3,17-dione.[5] The rotation of the 2,21-diacetate of II differs markedly from that reported for 4-pregnene-2α,17α,21-triol-3,20-dione 2,21-diacetate[6] ($[\alpha]^{25}D$ +122° (chloroform), m.p. 200–202°, 215–217° (polymorphs)). In like fashion II contrasts with the 4-pregnene-2α,17α,21-triol-3,20-dione, $[\alpha]^{25}D$ +130° (chloroform), m.p. 219–221°. Since 2β-hydroxyl reaches equilibrium with 2α-hydroxyl in mildly alkaline solution,[7] it is obvious that the same alkaline ultraviolet spectrum must result for both configurations in a given pair of 2-hydroxy-3-keto-Δ^4-steroids.[5] Hence, II must contain a 2β-hydroxyl group.

The assignment is corroborated by the fact that the predicted shift in molecular rotation (ΔM-581)[7] based on the only 2β-hydroxy-3-keto-Δ^4-steroid known previously, 2β-hydroxytestosterone 2,17-diacetate[7] (2β-hydroxytestosterone itself[2] is characterized incompletely), is in reasonable agreement with the observed values of the shift for 21-acetate of I *vs.* 2,21-diacetate of II (ΔM-500). This is especially noteworthy since the 2β-hydroxyl group contributes much more strongly to the levorotation of 3-keto-Δ^4-steroids than does any other hydroxyl group.

It is known that hydroxyl groups at 2- or 6- in 3-keto-Δ^4-steroids can be removed reductively by mild treatment with zinc and acetic acid, affording the parent steroid.[7] Treatment according to this method converted II 2,21-diacetate into I 21-acetate, indistinguishable from an authentic sample by infrared comparison.

We hope to report a more complete proof of structure, relating II with 2β-hydroxytestosterone by degradation, at a later date. The chemistry of the 2β-hydroxyl group, heretofore a rather inaccessible function, is being studied.

We wish to acknowledge the helpful advice of Dr. André Meyer in the interpretation of the alkaline ultraviolet spectra.

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RECEIVED JUNE 3, 1957

TRANSFORMATION OF STEROIDS BY FUNGI. INTRODUCTION OF 1ξ AND 2β-HYDROXYL GROUPS INTO REICHSTEIN'S COMPOUND S.

Sir:

Heretofore, no unambiguous microbiologically induced hydroxylation of steroid substrates has

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been observed.[1] In the preceding communication[2] we have described the first 2β-hydroxylation of Compound S with *Streptomyces* sp. We wish now to report the microbiological hydroxylation of 4-pregnene-17α,21-diol-3,20-dione (I, Reichstein's Compound S) in the 1ξ and 2β positions by *Rhizoctonia ferrugena* (CBS, Holland). The fermentation of I (3.0 g.) by *R. ferrugena* was carried out in a medium containing corn steep liquor, ammonium dihydrogen phosphate, yeast extract, dextrose, soybean oil and calcium carbonate. In the fermentation stage a forty-eight hour culture was incubated with the steroid substrate (introduced in ethanolic solution) on a rotary shaker for five days at 23°. The culture filtrate was extracted with chloroform and chloroform–methanol (4:1), and the extracts were concentrated to dryness in vacuo below room temperature. The residue was redissolved in dry, acid and alcohol-free chloroform and the solution was chromatographed on a silicic acid adsorption column. A methanol–chloroform gradient elution[3] was utilized to separate the two steroidal transformation products and residual substrate. The steroid substrate, I, was collected in the first fractions, the 2β-hydroxylated product, II, in the middle fractions and the 1-hydroxylated product, III, in the last fractions. Homogeneity was indicated by paper chromatography.

Crystallization of the middle fractions from chloroform–ether mixture afforded 101 mg. of 4-pregnene-2β,17α,21-triol-3,20-dione (II), m.p. 214–220° dec. Further recrystallization from acetone–hexane raised the m.p. to 220–222° dec. The infrared spectrum of II was identical with that of an authentic sample,[2] and the mixed m.p. showed no depression.

The crystallization of the last group of fractions (Product III) afforded 163 mg. of crystalline solid, m.p. 180–200° dec. Cautious recrystallization from acetone–hexane without application of heat, raised the m.p. to 193–207° dec. (with a transition of about 170°), $[\alpha]^{25}D$ +89 (dioxane) (corrected for acetone of solvation), λ_{max}^{MeOH} 241 mμ (ϵ = 16,500 —corrected for acetone of solvation), λ_{max}^{Nujol} 2.83 μ (OH), 5.81 μ (20-carbonyl), 6.04 μ (3-carbonyl), 6.18 μ (Δ^4) (one additional polymorphic variety has been observed.) Calcd. for $C_{21}H_{30}O_5 \cdot C_3H_6O$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.66.

The identity of III was established in the following manner. Integration of the hydroxyl bands of the infrared spectrum confirmed the presence of three hydroxyl groups. Measurement of the ultraviolet spectrum of III in alkaline solution[4] showed a shift in the maximum to 245 mμ but no peak in the 380 mμ region after two hours at 60°. This is consistent with the conversion of a 1-hydroxy-3-keto-Δ^4-steroid into a $\Delta^{1,4}$-diene-3-keto-steroid, which transformation would be expected to occur under these conditions. Also the ultraviolet spectrum of III was strikingly different from that of a 2-hydroxy-3-keto-Δ^4-steroid in alkaline solution.[2,4] The presence of the dienone among the products from the alkaline treatment of III was further substantiated by the measurement of the polarographic reduction potential of the solution.[5] A shift in the half-wave potential from 1.46 volts (III) to 1.31 volts (after alkaline treatment) corresponds well to the shifts observed for cortisone *vs.* prednisone (0.16 volt) and cortisol *vs.* prednisolone (0.17 volt). Furthermore, pyrolysis of a sample of III at the melting point for ten minutes afforded a mixture of products whose infrared spectrum contained the characteristic $\Delta^{1,4}$-diene-3-one bands.

Finally, a solution of III in glacial acetic acid was refluxed for one hour. Upon concentration of the solution *in vacuo*, chromatography of the residue on Florisil and recrystallization from acetone–hexane there was obtained 1,4-pregnadiene-17α,21-diol-3,20-dione, m.p. 237–240°, whose infrared spectrum was identical with that of an authentic sample.[6] From this evidence we conclude that the structure of III is clearly 4-pregnene-1ξ,17α,21-diol-3,20-dione. The configuration of the 1-hydroxyl group remains to be fixed.

With cortisol, cortisone, corticosterone, desoxycorticosterone, progesterone and testosterone transformations occur upon incubation in the presence of *R. ferrugena* as determined by paper chromatographic examination of the product. The structure of the transformation products in these instances remains to be elucidated.

Other species of *Rhizoctonia* have effected the transformation of I into cortisol, cortisone and 11-epicortisol; a more detailed account of these findings will be published subsequently. Additional conversion products obtained with organisms of this genus are now under investigation.

We wish to make the following acknowledgments. From the Schering Corporation we acknowledge the helpful advice of Drs. André Meyer and Alexander Nussbaum, the assistance of Dr. P. Kabasakalian and Mr. J. McGlotten who carried out the polarographic reductions, of Dr. J. Y. Chen who interpreted the infrared spectra, and of Mrs. M. J. Gentles. From the Institute of Microbiology we acknowledge the technical assistance of Mr. A. Chernov. We also wish to thank Dr. C. M. Haenseler for his helpful advice and for various cultures of *Rhizoctonia*.

(1) S. Kushinsky (Abstracts of Papers, 131st Meeting of the Am. Chem. Soc., Miami, Florida, April 7–12, 1957, p. 36-O) mentions the isolation of a 1- or 2-hydroxy intermediate from conversion of 19-nortestosterone 17-acetate to estradiol 17-acetate by the action of *Corynebacterium simplex*.

(2) H. L. Herzog, M. J. Gentles, F. Carvajal, D. Sutter, W. Charney, E. B. Hershberg and C. P. Schaffner, THIS JOURNAL, **79**, 3921 (1957).

(3) T. K. Lakshmanan and S. Lieberman, *Arch. Biochem. Biophys.*, **53**, 258 (1954).

(4) A. S. Meyer, *J. Org. Chem.*, **20**, 1240 (1955).

(5) P. Kabasakalian, S. DeLorenzo and J. McGlotten, *Anal. Chem.*, **28**, 1669 (1956).

(6) A. Nobile, W. Charney, P. L. Perlman, H. L. Herzog, C. C. Payne, M. E. Tully, M. A. Jevnik and E. B. Hershberg, THIS JOURNAL, **77**, 4184 (1955).

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RECEIVED JUNE 3, 1957

CYCLOPENTENE-3,5-DIONE

Sir:

The synthesis of many substituted and unsubstituted cyclopentenone derivatives of theoretical

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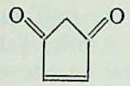
and practical importance is hindered by the lack of readily available intermediates. With few exceptions, substituted cyclopentadienes are too unstable to be isolated, and these exceptions have not proved useful for further synthetic work.[1,2] We wish to report the synthesis of cyclopentene-3,5-dione (I),



I

a yellow, stable, crystalline, highly reactive molecule which promises to provide an entry into many new synthetic fields.

Cyclopentene-3,5-dione can be prepared easily from cyclopentadiene by bromination,[3] and treatment of the resultant 3,5-dibromocyclopentene with tetraethylammonium acetate in dry acetone.[4] Hydrolysis affords cyclopentene-3,5-diol which can be oxidized to I in 50% yield with chromic acid in acetic acid. After crystallization from ether–pentane and two sublimations it showed m.p. 36–37°. *Anal.* Calcd.: mol. wt., 96. Found: C, 62.3; H, 4.0; mol. wt., 96; ultraviolet: λ_{max} 222 (4.16), 322 (1.30), 367 (1.30); infrared: 5.73, 5.83.

We shall report on the details of several of its reactions later, but the following will indicate their scope. (1) It is readily reduced to 1,3-cyclopentanedione (m.p. 150–151°, reported[5] 151–152°) and this sequence may provide the best synthesis of this useful compound. (2) The enedione is highly reactive in the Diels–Alder reaction, and readily gives adducts with cyclopentadiene, anthracene and other dienes. (However, it is *less* reactive than maleic anhydride. We consider this difference significant, and will discuss it in due course.) (3) Cyclopentene-3,5-dione condenses rapidly with aldehydes and ketones in the presence of weak bases. These and other reactions are being explored.

The dione is an acid (*p*H of a 0.1 *N* aqueous solution, 4.5) which is rapidly destroyed by base. Despite its acidity, the molecule appears to be completely ketonic. It does not give a ferric chloride test. In its enolic form it would be a derivative of cyclopentadienone and as such perhaps partake of the unfavorable electronics which have been suggested to explain the lack of existence of that molecule. In addition to its interest for its own sake, we believe that this unique molecule, containing as it does three different types of functional groups and with each of its carbon atoms potentially reactive, will be a useful intermediate in the synthesis of many hitherto unavailable molecules.

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(1) C. H. DePuy and W. von E. Doering, THIS JOURNAL, **75**, 5955 (1953).

(2) F. Ramirez and S. Levy, *ibid.*, **79**, 67 (1957).

(3) W. G. Young, H. K. Hall, Jr., and S. Winstein, *ibid.*, **78**, 4338 (1956).

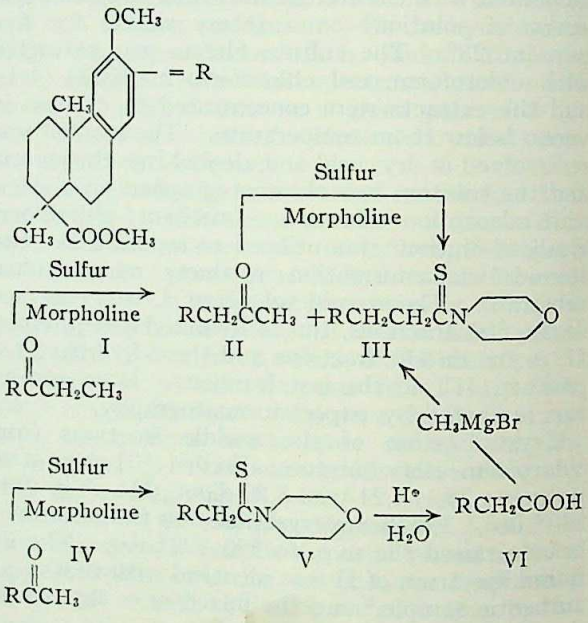
(4) L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4043 (1952).

(5) J. H. Booth, R. G. Wilkinson, S. Kusbner and J. H. Williams, THIS JOURNAL, **75**, 1732 (1953).

A NEW TYPE OF PRODUCT FROM THE WILLGERODT REACTION

Sir:

We wish to report the migration of a keto group to an adjacent carbon atom during a Willgerodt reaction. Methyl O-methyl-7-propionylpodocarpage (I) under Willgerodt conditions is converted (10% yield) to methyl O-methyl-7-acetonylpodocarpate (II). Since this new ketone is also converted to the thiomorpholide (III) under Willgerodt conditions, it is probable that at least part of the material goes through II as an intermediate.



The reaction of methyl O-methylpodocarpate[1] and propionyl chloride in the presence of aluminum chloride gave methyl O-methyl-7-propionylpodocarpate [I, m.p. 103.5–105°, λ max 255 mμ (ε = 10,500)[2] and 315 mμ (ε = 4,090), 5.82 and 5.98 μ μ(CHCl₃); $[\alpha]^{25}D$ +134° (ethanol); calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 74.04; H, 8.54]. Chromatography of I on silica under conditions which were shown to separate I and II failed to reveal the presence of any II.

A mixture of methyl O-methyl-7-propionylpodocarpate (107.5 g.), sulfur (14.4 g.), and morpholine (39.2 g.) was heated at reflux for 10 hr. The reaction mixture was dissolved in benzene, filtered, and the solvent was removed. The expected thiomorpholide, (III, 85.6 g., m.p. 172–177°) crystallized when an ether solution was concentrated. Further recrystallization from a mixture of chloroform and methanol gave the pure thiomorpholide [m.p. 177–178.5, λ max 281 μ (ε = 18,000), $[\alpha]^{25}D$ +110° (chloroform); calcd. for $C_{26}H_{37}NO_4S$: N, 3.05; S, 6.98; OCH_3, 13.50. Found: N, 3.08; S, 6.94; OCH_3 13.02]. The material in the mother liquors from this reaction was chromatographed over silica (1700 g.). Among the compounds eluted with 2% ethyl acetate in benzene was methyl O-methyl-7-acetonylpodocarpate (II) which crystallized from aqueous methanol as

(1) I. R. Sherwood and W. F. Short, *J. Chem. Soc.*, 1006 (1938).

(2) The analytical determinations were made by the Analytical Laboratory under the direction of Dr. Robert T. Dillon.

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colorless platelets [11.1 g., m.p. 105.5–107.5°, λ_{max} 281 mμ (ε = 3,160) and 287 mμ (ε = 3,140), 5.82, 6.18, 6.37, and 7.37 μ (chloroform): $[\alpha]^{25}D$ +122°; calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; OCH_3, 17.32. Found: C, 73.93; H, 8.43; OCH_3, 17.05]. Compound II formed a bright yellow 2,4-dinitrophenylhydrazone [m.p. 203.5–207.5°, λ_{max} 3.04, 5.83, 6.23, 6.33, and 7.61 μ; calcd. for $C_{28}H_{34}N_4O_7$: C, 62.44; H, 6.36. Found: C, 62.64; H, 6.46].

To confirm the structure assigned to II, methyl O-methyl-7-acetonylpodocarpate was synthesized in the following manner: methyl O-methyl-7-acetylpodocarpate[3] (IV) was converted by a Willgerodt reaction to the corresponding thiomorpholide [V, m.p. 177–180.5°, λ_{max} 281 mμ (ε = 17,600), 5.81, 6.20, 6.37 and 6.71 μ (chloroform); $[\alpha]^{25}D$ +101° (ethanol); calcd. for $C_{25}H_{35}NO_4S$: S, 7.20; N, 3.14. Found: S, 7.20; N, 3.17]. Hydrolysis of V with sulfuric acid in acetic acid gave the corresponding monobasic acid [VI, m.p. 144.5–147°, presoftened, λ max 281 mμ (ε = 2,690) and 287 mμ (ε = 2,630), 5.82, 6.18, 6.35, and 6.66 μ (KBr); calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83; OCH_3, 17.22; COOH, 12.49. Found: C, 70.23; H, 8.03; OCH_3, 16.87; COOH, 12.33]. Addition of an ether solution of VI to an excess of methylmagnesium bromide gave II which was identical [melting point, no depression on mixing: ultraviolet and infrared spectra] with the compound derived from the Willgerodt reaction on methyl O-methyl-7-propionylpodocarpate.

When heated with sulfur and morpholine, methyl O-methyl-7-acetonylpodocarpate (II) was converted to III (41% yield).

(3) W. P. Campbell and D. Todd, THIS JOURNAL, **62**, 1287 (1940).

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RECEIVED JUNE 3, 1957

THE PREPARATION OF BERYLLIUM AMALGAM[1]

Sir:

The preparation of a beryllium amalgam by electrolysis of concentrated solutions of $BeCl_2$ into a mercury cathode has been claimed by Prytz[2] but this method is not confirmed elsewhere. A new and novel method, involving electrolysis of beryllium from a NaCl–$BeCl_2$ fused salt mixture into a mercury cathode has been developed in this laboratory and applied to the preparation of beryllium metal.[3]

Procedure.—Equimolar quantities of NaCl and $BeCl_2$ are melted together (224°)[4] to form an electrolyte. Beryllium chloride can be prepared by hydrochlorination of beryllium metal at 500°.

The electrolysis cell consists of a 4-liter resin reaction flask with a cylindrical inner sleeve to facilitate removal of the electrolyte at the conclusion of the electrolysis. Heat is supplied by an electric heating mantle.

Mercury (5000 g.) is placed in the cell and chunks of electrolyte are added quickly. The cell is closed and the electrolyte is melted down in an atmosphere of argon. A carbon anode is then inserted and the electrolysis commenced at about 5 volts and 6 amperes at temperatures of 300–350°.

Amalgam tends to climb through the salt to the anode. Therefore it is desirable to stir the cathode during electrolysis to avoid premature termination of the experiment. At the conclusion of the electrolysis (50–100 amp.-hr.) the cell is opened and the inner sleeve removed with the electrolyte within it. The amalgam, which varies in viscosity from a free flowing liquid to a semi-solid paste, depending on beryllium concentration, is found floating on the mercury at the bottom of the cell. The current efficiency of the electrolysis is approximately 65%.

The formation of amalgam evidently is sensitive to small traces of oxygen. Rigorous purification of the argon cover is required and it is essential that the cell be leak tight if amalgam is to be formed.

It is evident from this description that it also might be possible to prepare a beryllium amalgam by a displacement reaction with sodium amalgam and the fused-salt mixture used in electrolysis.

Properties of the Amalgam.—The amalgam is unstable in air, decomposing spontaneously with the formation of a black powder which is approximately 75% Be by weight. Dilute amalgams can be concentrated to about 2% beryllium by pinholing. The 2% amalgam is a thick pasty material from which additional mercury can be removed by such methods as pressing in a die or heating *in vacuo*.

Surprisingly, the room temperature X-ray diffraction pattern of the amalgam is the same as solid (−78°) mercury. The exact nature of the amalgam is not known. By analogy with the Mg–Hg system the compound $BeHg_2$ (2.2% Be) is suspected. It is hoped this information will assist in further investigation of the Be–Hg system.

(5) Stanford Research Institute, Menlo Park, California.

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RECEIVED JUNE 10, 1957

TOTAL SYNTHESIS OF PENTACYCLOSQUALENE[1]

Sir:

Despite the probable genesis of the pentacyclic hydropicene triterpenes[2] from squalene by cation-olefin cyclization with subsequent rearrangement of carbon and hydrogen,[3,4,5] the pentacyclic substance I which would be formed from squalene by

(1) Presented at Miami meeting of American Chemical Society April 7–12, 1957. Research supported by the Atomic Energy Commission.

(2) M. Prytz, *Z. anorg. allgem. Chem.*, **193**, 113 (1930).

(3) M. C. Kells, R. B. Holden, C. I. Whitman, AEC report SEP-207 (1956).

(4) J. M. Schmidt, *Bull. soc. chim.*, **39**, 1686–1703 (1926).

(1) This investigation was supported by a fellowship (AF-6570) from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

(2) α-Amyrin, β-amyrin, taraxerol, taraxasterol, friedelin, alnusenol and their oxygenated derivatives.

(3) A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

(4) E. J. Corey and J. J. Ursprung, THIS JOURNAL, **78**, 183 (1956).

(5) T. T. Tchen and K. Bloch, *ibid.*, **78**, 1516 (1956).

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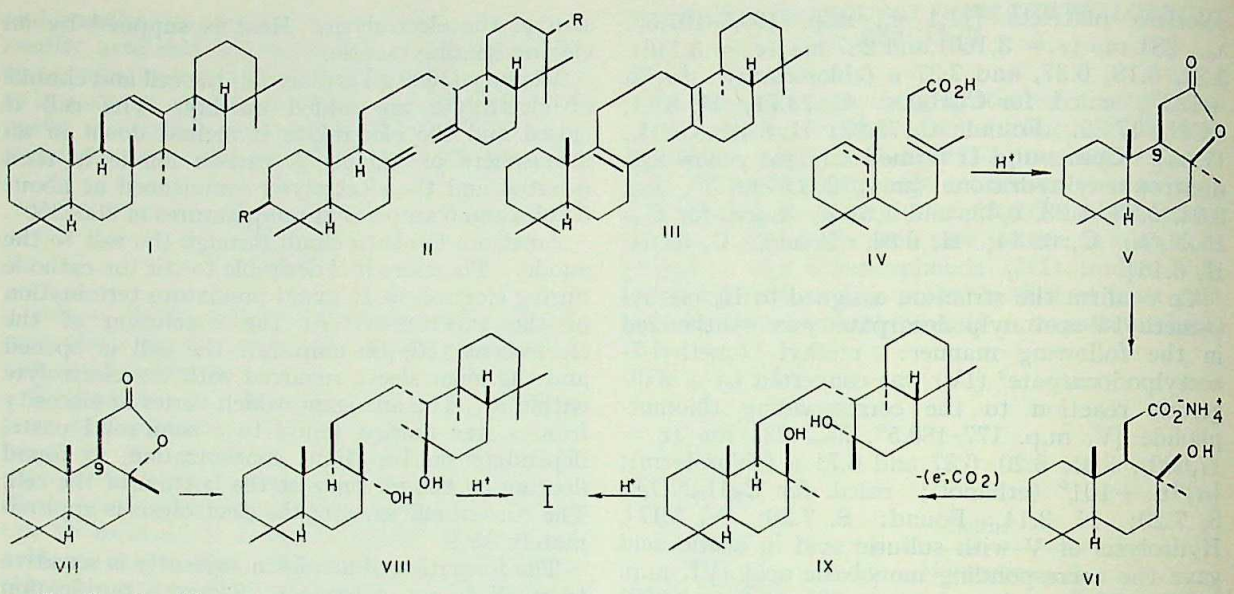

cyclization,[6] *without rearrangement*, has not yet been detected in nature. In addition, numerous attempts to effect the synthesis of pentacyclosqualene by acid-catalyzed cyclization of squalene have failed.[7]

We outline here a total synthesis of this substance, heretofore obtained only by partial synthesis from α-onoceradienediol[8] (II, R = OH), and, incidentally, the synthesis of both α-onoceradiene (II, R = H)[8] and β-onoceradiene (III).[8,9]

Acid-catalyzed cyclization of either α- or β-monocyclohomofarnesic acid (IV) leads to a mixture of lactones from which the (±)-lactone V has been isolated.[10,11] Hydrolysis of the (−)-lactone in methanolic potassium hydroxide followed by careful acidification and ammonolysis gave the ammonium salt VI in high yield. Oxidative electrolytic coupling of VI in refluxing methanol at a smooth platinum anode[12] gave after chromatography the diol IX (m.p. 185–186.5°, $[\alpha]_D$ +420; found: C, 80.58; H, 12.29). Cyclization of IX with perchloric acid in benzene-acetic acid yielded (+)-pentacyclosqualene, I (m.p. 275–276.5° (sealed capillary), $[\alpha]_D$ +86°) identical in all respects with "γ-onocerene" prepared from α-onoceradienediol (II, R = OH).[8] Dehydration of the diol IX with phosphorus oxychloride–pyridine gave β-onoceradiene (m.p. 159–161°, $[\alpha]_D$ +140°) identical with an authentic sample.

Similarly, the (+)-lactone VII led to the diol VIII (m.p. 270-271°, $[\alpha]_D$ +13°; found: C, 80.41; H, 12.34) which on cyclization also gave (+)-pentacyclosqualene (I). α-Onoceradiene (II, R = H; m.p. 199.5–201°, $[\alpha]_D$ +25°) was obtained from VIII by $POCl_3$ dehydration.[13]

It is a pleasure to thank Drs. D. H. R. Barton, G. Lucius and M. Stoll for gifts of materials and Dr. Sherlock Swann, Jr., and Mr. W. Garrison for valuable aid with the electrolytic experiments.

(6) Following the same stereocourse which leads to the triterpenes cited in ref. 2.

(7) See L. Ruzicka, *Experientia*, **9**, 359 (1953).

(8) D. H. R. Barton and K. Overton, *J. Chem. Soc.*, 2639 (1955).

(9) J. D. Cocker and T. G. Halsall, *ibid.*, 4262 (1956); K. Schaffner, R. Viterbo, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **39**, 174 (1956).

(10) G. Lucius, *Angew. Chemie*, **68**, 257 (1956); G. Lucius, private communication.

(11) Mild acid treatment of the (+)-*trans*-lactone VII obtained from sclareol served as a convenient source of the epimeric *cis*-lactone V; *cf.* L. Ruzicka and M. Janot, *Helv. Chim. Acta*, **14**, 645 (1931), and M. Stoll and M. Hinder, *Helv. Chim. Acta*, **36**, 1995 (1953). The lactone of L. Ruzicka, C. F. Seidel and L. L. Engel, *Helv. Chim. Acta*, **25**, 621 (1942), was shown by its characteristic infrared spectrum to correspond to the third lactone of Lucius[10] and is probably the C_9 epimer of VII since it can be prepared from *either* V or VII by acid-catalyzed isomerization. Further data on the sterochemistry and interconversions of these lactones will be reported later.

(12) The best yields of coupled material were obtained with high current density, refluxing methanol, and high salt concentrations. Ammonia was added periodically to inhibit lactonization.

(13) The dehydration products of the two epimeric diols IX and VII confirm, respectively, the diaxial and diequatorial orientations of the hydroxyl groups; *cf.* D. H. R. Barton, A. Campos-Neves and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

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RECEIVED JUNE 17, 1957

MACROLIDE ANTIBIOTICS. VI. A STANDARD OF ABSOLUTE CONFIGURATION AMONG MACROLIDE ANTIBIOTICS

Sir:

As pointed out in a recent review,[1] the macrolide group of antibiotics represents a therapeutically and biogenetically important class of natural products. Knowledge concerning the absolute configuration of these substances is limited to a single center (C-10) of magnamycin[1] and this is of no direct applicability to the other antibiotics of this class since magnamycin follows the "acetate" rather than "propionate" pattern so common among macrolide antibiotics. Attempts to use rotation rules such as Hudson's lactone rule for the determination of the absolute configuration in the erythromycin series[2] have led to ambiguous results. We should now like to report certain reactions with neomethymycin (Ia)[3] which establish the absolute

(1) R. B. Woodward "Festschrift Arthur Stoll," Birkhäuser, Basel, 1957, pp. 524–544; *Angew. Chem.*, **69**, 50 (1957).

(2) K. Gerzon, E. H. Flynn, M. V. Sigal, P. F. Wiley, R. Monahan and U. C. Quarck, THIS JOURNAL, **78**, 6396 (1956), footnote 21.

(3) Y. Sato, C. Djerassi and O. Halpern, *ibid.*, **79**, 2022 (1957).

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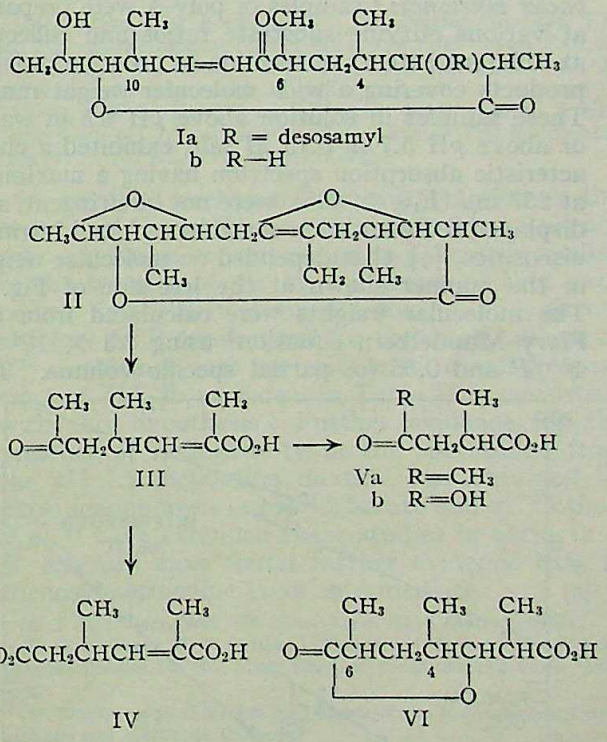
configurations of C-4 and C-6 of neomethymycin (Ia) as well as of methymycin,[4] pikromycin[5,6] and narbomycin[7] (see ref. 15).

When neomethymycin (Ia)[3,8] was boiled for 10 min. with 5 *N* sulfuric acid, extracted with ether and the *unwashed* ether extracts dried and distilled at 200° and 40 mm., there was isolated in over 70% yield the cyclic enol ether II[9] (m.p. 168–170° (from dilute methanol), $[\alpha]_D$ +124.5° (dioxane),[10] no high u.v. maximum, $\lambda_{max}^{CHCl_3}$ 5.75 μ (lactone) and 5.88 μ (enol ether) but no hydroxyl absorption, negative iodoform test; found for $C_{17}H_{26}O_4$: C, 69.15; H, 9.03; O, 22.22, OCH_3, 0.0; (5)C-CH_3, 23.84).[11] Ozonolysis of II at −80° in methylene chloride solution, decomposition of the ozonide with boiling water, saponification with 5% sodium hydroxide solution and purification of the acid fraction by silica gel chromatography and distillation yielded 6-oxo-2,4-dimethyl-2-heptenoic acid (III) (b.p. 100° at 0.001 mm., $[\alpha]_D$ +46° (chloroform), 11 $\lambda_{max}^{CHCl_3}$ 5.80, 5.88 and 6.02 (m) μ and broad "acid absorption" in 3.4 μ region, positive iodoform test; found for $C_9H_{14}O_3$: C, 62.96; H, 8.37) which formed a bright yellow 2,4-dinitrophenylhydrazone (m.p. 142–144°; found for $C_{15}H_{18}N_4O_6$: C, 51.46; H, 5.57; N, 16.05; neut. equiv., 340). Brief warming of the keto acid III with sodium hypoiodite solution in aqueous dioxane gave iodoform and crystalline 1,3-dimethyl 1-butene-1,4-dioic acid (IV), which may be a mixture of *cis–trans* isomers since it could not be obtained sharp melting after distillation at 120° and 0.001 mm. and recrystallization from ether–hexane (m.p. 130–155°, $[\alpha]_D$ +41° (chloroform), λ_{max}^{EtOH} 215 mμ, log ϵ 4.05; found for $C_8H_{12}O_4$: C, 55.60; H, 7.09; neut. equiv., 88). Ozonolysis of the unsaturated keto acid III followed by permanganate oxidation produced α-methyllevulinic acid (Va), $[\alpha]_D$ −5.6° (chloroform), which was characterized as the yellow 2,4-dinitrophenylhydrazone (m.p. 194–196° with sublimation from 165°; found for $C_{12}H_{14}N_4O_6$: C, 46.69; H, 4.64; N, 17.94; neut. equiv., 306). Hypoiodite oxidation of α-methyllevulinic acid (Va) furnished iodoform and (−)-methylsuccinic acid (Vb) (m.p. 111.5–113°, $[\alpha]_D$ −17.5° (*c* 0.97 in ethanol), $[\alpha]_D$ −9° (*c*, 1.0 in H_2O) found for $C_5H_8O_4$; C, 45.32; H, 6.03; neut. equiv., 65) identified by infrared comparison with an authentic sample kindly provided by Dr. E. J. Eisenbraun.[12] By proceeding without isolation of intermediates, a 20% over-all yield of (−)-methylsuccinic acid (Vb) could be realized from the enol ether II.

Since (−)-methylsuccinic acid has been related with L-glyceraldehyde,[12,13] the absolute configuration of C-4 in neomethymycin (Ia) has been established. In view of the fact that neomethymycin[3] as well as methymycin,[4] pikromycin,[14] and narbomycin[14] have been transformed into the identical lactonic acid VI, which still retains C-4 and C-6 of the parent compounds, and since the acid VI has been converted[14] into meso-α,α'-dimethylglutaric acid, the absolute configuration of C-4 and C-6[15] in all four antibiotics has been related experimentally to L-glyceraldehyde.



We are indebted to the Squibb Institute for Medical Research and the National Heart Institute (grant No. H-2574) of the National Institutes of Health, U. S. Public Health Service for financial assistance. The microanalyses were performed by

(4) Papers III and IV, C. Djerassi and J. A. Zderic, THIS JOURNAL, **78**, 2907, 6390 (1956).
(5) R. Anliker and K. Gubler, *Helv. Chim. Acta*, **40**, 119 (1957).
(6) H. Brockmann and R. Oster, *Ber.*, **90**, 605 (1957).
(7) R. Corbaz, L. Ettlinger, E. Gäumann, W. Keller, F. Kradolfer, E. Kyburz, L. Neipp, V. Prelog, R. Reusser and H. Zähner, *Helv. Chim. Acta*, **38**, 935 (1955).
(8) In our earlier communication (ref. 3) bearing on the structure proof of neomethymycin, we neglected to state that the methyl group was placed at C-10 rather than the equally plausible C-11 position because successive treatment of dihydroneomethynolide (Ib with double bond reduced) with lithium aluminum hydride, periodate oxidation, steam distillation of acetaldehyde and finally treatment of the residue with sodium hypoiodite did *not* yield any iodoform.
(9) The same product was obtained when neomethynolide (Ib) or cycloneomethynolide (VIa in ref. 3) was shaken with acidified ether and then distilled at 40 mm.
(10) The substance showed a positive plain dispersion curve (*cf.* C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957))—in contrast to the three starting materials—thus demonstrating the disappearance of the ketone function.
(11) Single positive Cotton-effect curve in methanol solution (peak $[\alpha]_{315}$ + 560°).
(12) E. J. Eisenbraun and S. M. McElvain, THIS JOURNAL, **77**, 3383 (1955); see also E. Berner and R. Leonardson, *Ann.*, **538**, 1 (1939).
(13) For a summary of Fredga's work see J. A. Mills and W. Klyne in W. Klyne's "Progress in Stereochemistry," Academic Press, Inc., New York, N. Y., 1954, Vol. I, p. 203.
(14) R. Anliker, D. Dvornik, K. Gubler, H. Heusser and V. Prelog, *Helv. Chim. Acta*, **39**, 1785 (1956).
(15) Provided pikromycin and narbomycin possess a hydroxyl group at C-3. If the hydroxyl group is located at C-5—as has been suggested as a preferred structural alternative for pikromycin (ref. 5, 6)—then it should be noted that C-4 and C-6 as marked in formula VI correspond to C-2 and C-4 of pikromycin and since the sterochemical convention is then changed, the absolute configuration of these two centers in pikromycin would correspond to the D-series. This point will obviously not be settled until the constitution of pikromycin (and narbomycin) has been established unambiguously at which time it will be known which carbon atoms of the antibiotics correspond to those of the lactone acid VI. In any event, the latter represents the standard of absolute configuration for this portion of these macrolide antibiotics.

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Mr. Joseph F. Alicino (Squibb Institute for Medical Research, New Brunswick, New Jersey).

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RECEIVED JUNE 3, 1957

POLYNUCLEOTIDES. I. MOLECULAR PROPERTIES AND CONFIGURATIONS OF POLYRIBOADENYLIC ACID IN SOLUTION[1]

Sir:

We wish to report the discovery of two configurations of polyriboadenylic acid (poly-A): one a flexible, randomly coiled, molecularly dispersed form and the other a rigid, presumably helical form composed of variable numbers of poly-A molecules.

Using polynucleotide phosphorylase from *Azotobacter vinelandii*,[2] samples of poly-A were prepared at various enzyme–substrate ratios and collected at different extents of reaction in order to provide products covering a wide molecular weight range. These samples in solution above *p*H 6.5 in water or above *p*H 5.7 in 0.15 *M* salt, exhibited a characteristic absorption spectrum having a maximum at 257 mμ ($E_{1\%} \cong 295$), were not birefringent, and displayed sedimentation constants, s^0, and intrinsic viscosities, $[\eta]$, that depended on molecular weight in the manner shown at the left side of Fig. 1. The molecular weights were calculated from the Flory–Mandelkern equation[3] using 2.3×10^6 for $\Phi^{1/3}/P$ and 0.55 for partial specific volume. The

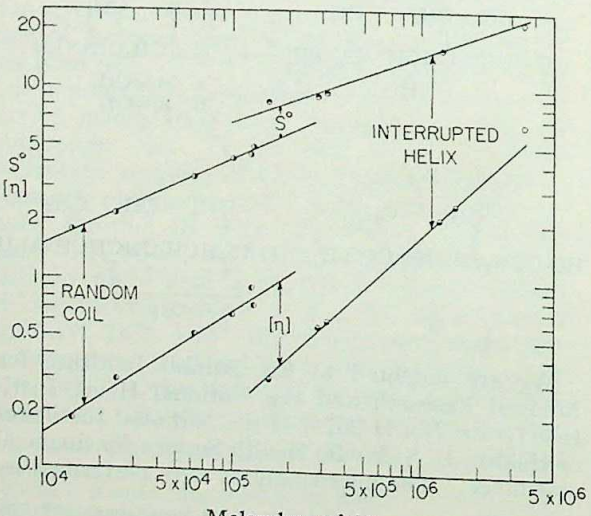

Fig. 1.—Molecular weight dependence of sedimentation constant, S^0_{20} in svedbergs and intrinsic viscosity $[\eta]_{25}$, in dl./g., of the two configurations of poly-A. For the curves on the left, the solvent was 0.15 *M* NaCl, 0.015 *M* citrate, *p*H 7.1; for those on the right it was 0.15 *M* acetate, *p*H 4.9. The open circle (○) represents measurements at *p*H 3.7 with no added salt present.

slopes, 0.45 and 0.65, respectively, are typical of randomly coiled chains: we conclude that this is the configuration under these conditions.

However, below *p*H 5 in 0.15 *M* salt and below *p*H 6.5 in water the poly-A samples displayed a different spectrum having a maximum at 252 mμ ($E_{1\%} \cong 255$) and had values of s^0 and $[\eta]$ that depended on the concentration and the temperature at which the transition had been brought about by lowering the *p*H.

By varying the concentration of poly-A (0.2 to 1.5 g./100 cc. for the sample having a molecular weight of 126,000) prior to lowering the *p*H to 4.9 (acetate buffer of ionic strength 0.15) the solutions were found to exhibit systematic variations in s^0 and $[\eta]$ that were clearly indicative of the formation of stable aggregates. The weights of these aggregates increased with the concentration of poly-A at which the transition was induced. Calculating the molecular weights (or particle weights) as before, it was found that the s^0 and $[\eta]$ varied with weight as shown in the right side of Fig. 2. The linear relations that result and the values of the slopes, 0.36 and 0.92, respectively, indicate that the species are homologous in structure and that the differences in weight are the result of different extents of linear growth. Unlike the randomly coiled configuration, this form does not show a marked increase in specific viscosity upon removal of salt. This and the behavior in flow birefringence lead to the conclusion that the structure is relatively rigid and rod-like, but not quite to the extent found for deoxyribonucleic acid (DNA). The stability of this structure appears to result from the lowering of the electrostatic energy brought about by titrating about half of the adenine groups. The failure to find spectra intermediate in character between the two described further suggests that the transition is abrupt and complete and that practically all the chromophoric groups (adenine) undergo the same change in environment. Moreover, at *p*H 4.9 in 0.15 *M* acetate, the transition to the randomly coiled form occurs in a very narrow temperature range near 75°, only a few degrees below the transition temperature observed for DNA. This coöperative behavior indicates a highly ordered arrangement of secondary bonds for the acid-stable form.

These observations are compatible with a structure in which poly-A molecules are associated through hydrogen-bonded base-pairing in a double stranded helix,[4] each strand of which has gaps where one poly-A molecule ends and another begins. This would resemble the interrupted helical model once proposed for DNA,[5] but the gaps in our case may be larger. The increased rotational freedom at the gaps would account for the smaller space filling properties exhibited by this configuration

(1) This investigation was supported by a research grant (C-2170) from the National Cancer Institute, Public Health Service.

(2) M. Grunberg-Manago and S. Ochoa, THIS JOURNAL, **77**, 3165 (1955); M. Grunberg-Manago, P. J. Ortiz and S. Ochoa, *Biochim. Biophys. Acta*, **20**, 169 (1956). We are very grateful to Professor Ochoa for making available to us unpublished information on the purification of the enzyme.

(3) P. J. Flory and L. Mandelkern, *J. Chem. Phys.*, **29**, 212 (1958).

(4) A two-stranded structure of this type has been proposed by F. H. C. Crick, D. Davies, A. Rich and J. D. Watson and is discussed by J. D. Watson in "The Chemical Basis of Heredity," W. D. McElroy and B. Glass, editors, the Johns Hopkins Press, Baltimore, 1957 and by A. Rich in the *Proc. Acad. Sci., New York*, in press. It is not necessary that the detailed atomic arrangements of the helical configuration in solution be the same as that which may ultimately be established in the solid state.

(5) C. A. Dekker and H. Schachman, *Proc. Natl. Acad. Sci.*, **40**, 894

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relative to DNA. If this structural proposal is the correct one, it may be possible for ribonucleic acid, also, to assume a double-stranded configuration in solution through pairing of only the adenine nucleotides.[6]

(6) We are very much indebted to Mrs. Elizabeth Klemperer who was reponsible for many of the measurements in this investigation.

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RECEIVED MAY 23, 1957

INCORPORATION OF THE CARBON CHAIN OF METHIONINE INTO SPERMIDINE[1,2]

Sir:

The cumulative work of several laboratories has indicated the metabolic importance of the polyamines putrescine, spermidine and spermine in diverse biological systems. Tabor, *et al.*,[3] have shown that putrescine is the source of the four-carbon chain of spermidine and spermine. Recent results obtained by the author show that the side chain of methionine is an efficient precursor of the three carbon chain of spermidine in *Neurospora crassa*.

Neurospora crassa strains 74A-3b (wild type) and 38706 (blocked in the conversion of homocysteine to methionine) were grown at room temperature on Fries minimal medium supplemented with 50 μg./ml. of DL-methionine-2C^{14}. The spermidine was isolated by grinding the mold with sand and 5% TCA[4] and chromatography of the extract on 0.6 × 20 cm. columns of Dowex 50-X2 using an HCl gradient. The spermidine containing fractions were combined and dried; spermidine trihydrochloride was crystallized from methanolic hydrogen chloride and ethyl acetate. The specific activities of the added methionine and the isolated spermidine are compared in Table I. Amine concentrations were determined as described by Rosenthal and Tabor.[5] Radiopurity of the isolated spermidines was checked by paper ionophoresis in *p*H 8.2 borate buffer and by descending paper chromatography (3 parts 1-propanol:1 part 0.2*M* sodium acetate buffer). In all cases the radioactivity moved in one spot and was in the same position as added authentic spermidine trihydrochloride.

TABLE I

Strain	Specific Activities: Methionine (initial) c.p.m./μmole	Spermidine (isolated) c.p.m./μmole	Ratio Spermidine/ Methionine
74A-3b	6.36×10^4	3.38×10^4	0.53
38706	11.4×10^4	6.34×10^4	0.56

Spermidine was degraded by oxidation with alkaline permanganate. The small yield of succinate, from the four carbon chain, was isolated by chromatography on Dowex 1[6] and on paper using aqueous phenol.[7] The succinate isolated from the oxidation product of synthetic spermidine,[8] labeled in the four carbon chain, contained about 33% of the radioactivity put on the Dowex 1 column, while less than 0.5% of the radioactivity was found in the succinate from the oxidation products of isolated spermidine and synthetic spermidine[8] labeled in the three carbon chain. The low level of activity in the succinate shows that the isolated spermidine is not labeled in the four carbon chain and is consistent with labeling in the three carbon chain.

TABLE II

*p*H	Total radioactivity in spermidine fractions, c.p.m. + ATP	− ATP
7.2	2.1×10^4	520
8.2	2.5×10^3	795

Incubation, four hours at 37°; incubation mixture, 100 μg. 2C^{14}-DL-methionine (3.8×10^5 c.p.m.) per vessel, 0.01 *M* putrescine, 0.008 *M* glutathione, 0.003 *M* $MgCl_2$, 0.00001 *M* pyridoxal phosphate, 0.1 *M* buffer, 2.5 ml. 1:1 extract of 74A-3b, 0.02 *M* K_4ATP as indicated, total volume 5 ml.; buffers are *p*H 7.2, potassium phosphate + Tris hydrochloride (1:1), *p*H 8.2, Tris hydrochloride.

A possible mechanism for this reaction is the transfer of the methionine side chain from S-adenosyl methionine to putrescine in a manner similar to the transfer of the methyl group of this compound first observed by Cantoni.[9] The almost absolute ATP requirement for the incorporation of C^{14} methionine into spermidine by a cell free extract of 74A-3b as shown in Table II is consistent with this hypothesis. Further evidence for the presence of radioactivity in the spermidine from the *p*H 7.2 incubation mixture was obtained by paper ionophoresis in *p*H 8.2 borate buffer. Tabor, *et al.*,[10] have extended these studies in extracts of *E. coli* and have found further evidence that S-adenosylmethionine is an intermediate.

(1) A preliminary report of this work was presented before the American Society of Biological Chemists; *Federation Proc.*, **16**, 189 (1957).

(2) This work was supported in part by Research Grant C-3436(A) from the National Cancer Institute, National Institutes of Health, Bethesda 14, Md.

(3) H. Tabor, S. M. Rosenthal and C. W. Tabor, *Federation Proc.*, **15**, 367 (1956).

(4) Abbreviations used are: TCA, trichloroacetic acid; ATP, adenosine triphosphate; Tris, tris-hydroxymethylaminomethane.

(5) S. M. Rosenthal and C. W. Tabor, *J. Pharmacol. and Exptl. Ther.*, **116**, 131 (1956).

(6) J. K. Palmer, Bull. 589 Conn. Agric. Expt. Station (1955).

(7) H. K. Berry, H. E. Sutton, L. Cain and J. S. Berry, Biochemical Institute Studies IV, No. 5109, Univ. of Texas, Austin, Texas, 1951, p. 22.

(8) Kindly supplied by Dr. E. Jackson of the National Institute of Arthritis and Metabolic Diseases.

(9) G. L. Cantoni, "Phosphorus Metabolism," Vol. II, Johns Hopkins Press, Baltimore, Md., 1952, p. 129.

(10) H. Tabor, S. M. Rosenthal and C. W. Tabor, personal communication.

RADIOISOTOPE SERVICE, VETERANS ADMINISTRATION HOSPITAL, AND DEPARTMENT OF BIOCHEMISTRY, DUKE UNIVERSITY, SCHOOL OF MEDICINE, DURHAM, NORTH CAROLINA, AND NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, BETHESDA 14, MARYLAND RONALD C. GREENE

RECEIVED MAY 9, 1957

THE HETEROGENEITY OF POLYSACCHARIDES AS REVEALED BY ELECTROPHORESIS ON GLASS-FIBER PAPER

Sir:

Glass-fiber paper[1] has been used in conjunction with a borate buffer *p*H 9–10 for the electrophoretic separation[2] of a wide variety of organic substances

(1) M. J. O'Leary, R. B. Hobbs, J. K. Missimer and J. J. Erving, *Tappi*, **37**, 446 (1954).

(2) D. R. Briggs, E. F. Garner, R. Montgomery and F. Smith, *Anal. Chem.*, **28**, 1383 (1956).

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including polysaccharides[3] and it has been reported that the method can be used for differentiating certain specimens of glycogen from various sources[4]; dextrans and other bacterial polyglucosans also may be distinguished.[4] The advantage of using the glass-fiber paper rather than cellulose paper is that complexes between the polysaccharide and the fiber are avoided[5] and the location of polysaccharides of all types is no longer a problem.[3,4] While it is possible to separate certain polysaccharides such as fructans, glucans and pentosans which have entirely different structures, using a borate buffer,[6] the inhomogeneity of a single polysaccharide cannot be ascertained in the same way, probably because of molecular association. We have found, however, that by replacing the borate buffer with 2*N* sodium hydroxide considerable information can be obtained. By this technique it has been shown that many polysaccharides hitherto assumed to be essentially homogeneous can be separated into two or more components.

All glycogen specimens from a wide variety of sources[7] thus far encountered have been found to be composed of two fractions, the major one moving at about ten times the rate of the other. In all cases the slow-moving component moved at the same rate but some of the glycogen specimens can be differentiated by the rate of movement of the faster moving component. Thus a specimen of liver glycogen obtained from a pregnant rabbit[8] can be distinguished by the fact that the faster moving component moves more slowly than the corresponding component of normal rabbit liver glycogen.

Amylopectins from a wide variety of starches have not only been found to be heterogeneous but also to differ from one another; three components have been detected in corn amylopectin, one of which corresponds to one of the components of corn amylose which is likewise heterogeneous. Repeated precipitation fails to separate all the amylose component(s) from amylopectin and both corn and potato amylose display heterogeneity even after repeated crystallization. The reason for this is not yet clear, but it is of interest to note that amylitol, obtained from corn amylose by sodium borohydride reduction,[9] moves on the glass paper largely as a single component and shows a mobility quite distinct from that of amylose.

Gums from *Acacia arabicum, A. pychnantha, A. senegal, A. seyal, Anogeissus latifolia* (gum ghatti) and gum tragacanth (*Astragalus sp.*) were all found to be heterogeneous whereas Black Wattle gum from *A. decurrens* and mesquite gum from *Prosopis juliflora* appeared to be homogeneous. Immunological examination has recently indicated the heterogeneity of gum arabic.[10]

The gums from the seeds of guar (*Cyamopsis tetragonaloba*), locust bean (*Ceratonia siliqua L.*), Kentucky coffee bean (*Gymnocladus dioica*), ivory nut (*Phytelephas macrocarpa*), tara (*Caesalpinia spinosa*), and those from flat (*Linum usitatissimum*) and *Plantago lanceolata*, all proved to be heterogeneous, two components being detected in each case.

The hemicelluloses separated from corn hulls, wheat straw, flax straw and ramie grass, and the so-called hemicelluloses from aspen wood, slash pine, loblolly pine and Western Hemlock all proved to be heterogeneous in nature. On the other hand the crystalline xylans[11] prepared from birch wood and barley straw by partial hydrolysis and also a specimen of the galactoaraban of sugar beet pulp proved to be homogeneous. These two crystalline xylans had almost identical mobilities on glass-fiber paper while the galactoaraban moved most rapidly, probably because of the more readily ionizable character of the primary alcoholic groups. Potassium hydroxide has been found to be a better electrolyte than sodium hydroxide for the separation of certain hemicelluloses; this observation may be related to the long-established fact[12] that it is better to use potassium hydroxide than sodium hydroxide for methylating hemicelluloses by the methyl sulfate method.

The fructans from rye flour (graminin), dahlia and perennial rye grass which have relatively low molecular weights were found to be homogeneous while the fructans from the ti (*Cordyline terminalis*) root, and from cocksfoot (*Dactylis glomerata*) contained small amounts of a second slow moving component.

Carraggenin already recognized as being heterogeneous[13] was found to consist of several components; one of the components corresponded to the K-fraction precipitated with potassium chloride, which was found to be homogeneous. Similarly agar has been found to be a mixture, a result in agreement with the recent report[14] that it consists of a neutral (agarose) and an acidic (agaropectin) component. Floridean starch also exhibits heterogeneity as also does laminarin from both *Laminaria digitata* and *L. cloustoni*. The reduced ($NaBH_4$) laminarin from *L. cloustoni* displays homogeneity.

Glass-fiber paper electrophoresis has also shown that yeast mannan and the glucomannans from Konjak mannan and Iles mannan are heterogeneous while the three mucopolysaccharides, heparin, hyaluronic acid, and chondroitin sulfate which individually behave as homogeneous polymers can be separated from each other with relative ease.

The movement of carbohydrate polymers on the glass paper appears to depend on the ionization of the alcoholic groups under the influence of the alkaline electrolyte. This is supported by the

(3) D. R. Briggs, E. F. Garner and F. Smith, *Nature*, **178**, 154 (1956).

(4) J. A. Cifonelli, B. A. Lewis, R. Montgomery and F. Smith, p. 30, of Abstracts 129th A.C.S. meeting, Dallas, Texas, 1956.

(5) *Cf.* E. J. Bourne, A. B. Foster and P. M. Grant, *J. Chem. Soc.*, 4311 (1956).

(6) *Cf.* K. W. Fuller and D. H. Northcote, *Biochem. J.*, **64**, 657 (1956).

(7) M. Abdel-Akher and F. Smith, THIS JOURNAL, **73**, 994 (1951).

(8) S. Peat, P. J. P. Roberts and W. J. Whelan, *Biochem. J.*, **51**, XVII (1952).

(9) M. Abdel-Akher, J. K. Hamilton and F. Smith, THIS JOURNAL, **73**, 4691 (1951).

(10) *Cf.* M. Heidelberger, J. Adams and Z. Dische, *ibid.*, **78**, 2853 (1956).

(11) A. P. Yundt, *ibid.*, **71**, 757 (1949).

(12) H. A. Hampton, W. N. Haworth and E. L. Hirst, *J. Chem. Soc.*, 1739 (1929).

(13) D. B. Smith and W. H. Cook, *Arch. Biochem. Biophys.*, **45**, 232 (1953).

(14) C. Araki, *et al.*, *Chem. Soc. Japan*, **29**, 543 (1956).

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fact that the non-reducing neutral oligosaccharides, sucrose, raffinose, stachyose, and the α- and β-Schardinger dextrins display considerable mobility, and like the free sugars, glucose and maltose, show no evidence of heterogeneity.

Electrophoretic separations were carried out on strips of glass-fiber paper (7 × 40 cm.) at 120 volts and 110 milliamperes for 10 hours:[15] The mobilities of the polysaccharide components are expressed conveniently as the ratio of the distance of migration of the component from the origin to the distance moved by the faster and major component of calf liver glycogen whose mobility is taken as 100. In a typical experiment the two components of glycogen moved 4.0 and 0.4 cm., thus having mobilities of 100 and 10, respectively. Likewise the three components of the seaweed polysaccharide from *Laminaria cloustoni* had mobility values of 10, 105 and 130 whereas the apparently homogeneous polysaccharides, birch wood xylan, sugar beet galactoaraban, Dahlia inulin and levosine (from rye flour) have mobility values of 110, 160, 130 and 140, respectively.

The components of a number of the above polysaccharides are now being separated on a larger scale with the object of ascertaining the structural significance of the phenomenon of heterogeneity as revealed by glass paper electrophoresis. It seems evident even at this early stage of the work that heterogeneity in polysaccharides especially those of fairly high molecular weight may be the rule rather than the exception. It is also conceivable that this phenomenon is analogous to the heterogeneity already recognized in proteins[16] and it may have some bearing on the specificity of the chemical components of the various species of plants and animals.

(15) The glass fiber sheets were obtained through the courtesy of Dr. R. B. Hobbs of the Bureau of Standards, Washington, D. C., to whom the authors express their thanks.

(16) J. R. Colvin, D. B. Smith and W. H. Cook, *Chem. Rev.*, **54**, 687 (1954).

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Received February 7, 1957

THE ACID DENATURATION OF FERRIHEMOGLOBIN[1]

Sir:

A series of important studies by Steinhardt and Zaiser[2] has demonstrated that hemoglobin undergoes a drastic configurational change below *p*H 4. The reaction is slow enough to permit spectroscopic and titrimetric observation of both the native and the altered form near *p*H 3.5. It is characterized by a change in absorption spectrum, and by the binding of about 36 protons per molecule (mol. wt., 67,000); *i.e.*, near *p*H 3.5 the "denatured" form contains about 36 more bound protons than the native form.

This communication reports the viscosity change accompanying the reaction. Figure 1 shows the

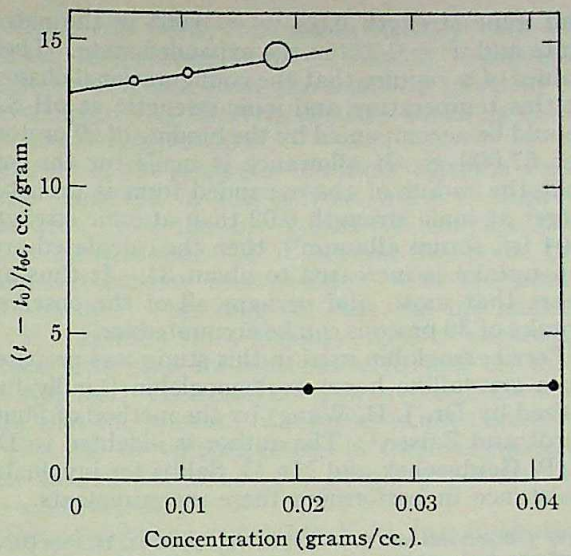

Fig. 1.—Viscosity data for native ferrihemoglobin (●) and for the same protein exposed to *p*H 3.5 for about 10 to 15 minutes (O). t represents flow time for the solution of concentration c, and t_0 flow time for solvent. All measurements were performed at ionic strength 0.04 at 25°.

data obtained from flow times in an Ubbelohde viscometer. To obtain intrinsic viscosities ($[\eta]$) from these data one must add 0.5 to the limiting value of the ordinate at zero concentration, so as to correct for the density difference between solution and solvent[3] and for the kinetic energy of the effluent solution. One obtains $[\eta]$ = 3.5 cc./gram for the native protein in neutral solution, in good agreement with a determination by Cohn and Prentiss.[4] At *p*H 3.5, after the configurational change has occurred, $[\eta]$ = 13.5 cc./gram. The configurational change thus clearly involves a marked expansion of the protein molecule, much like that observed for serum albumin.[5] Hemoglobin dissociates into half-molecules, at a *p*H much higher than that at which the configurational change occurs.[6] If this dissociation is assumed to occur without appreciable change in $[\eta]$, then, by Einstein's equation, the radius of an equivalent sphere (for half-molecules) is 26.5 Å. in the native state and 41.5 Å. in the expanded state.

The finding here reported is of special interest because it suggests a simple explanation for the uptake of protons observed by Steinhardt and Zaiser.[2] For expansion implies penetration of solvent into the molecular domain, which profoundly affects the titration curve by reducing all electrostatic interactions.[7] Specifically, the factor w, which occurs in the usual equation for the titration curve,[5,7] becomes much smaller and the titration curve itself becomes steeper. Equations derived earlier[7] enable this effect to be calculated if a spherical model is assumed. For spherical half-molecules with the radii given above we get, at 25°

(1) This work was supported by research grant RG-2350 from the National Institutes of Health, Public Health Service.

(2) Summarized by J. Steinhardt and E. M. Zaiser, *Advances in Protein Chem.*, **10**, 186 *et seq.* (1955).

(3) C. Tanford, *J. Phys. Chem.*, **59**, 798 (1955).

(4) E. J. Cohn and A. M. Prentiss, *J. Gen. Physiol.*, **8**, 619 (1927).

(5) J. T. Yang and J. F. Foster, This Journal, **76**, 1588 (1954); C. Tanford, J. G. Buzzell, D. G. Rands and S. A. Swanson, *ibid.*, **77**, 6421 (1955).

(6) E. O. Field and J. R. P. O'Brien, *Biochem. J.*, **60**, 656 (1955).

(7) C. Tanford, *J. Phys. Chem.*, **59**, 788 (1955).

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and ionic strength 0.02, $w = 0.065$ in the native state and $w = 0.023$ in the expanded state. These values of w require that the configurational change, at this temperature and ionic strength, at pH 3.5, should be accompanied by the binding of 29 protons per 67,000 g. If allowance is made for the fact that the radius of the expanded form is probably larger at ionic strength 0.02 than at ionic strength 0.04 (*cf.* serum albumin[5]), then the calculated proton uptake is increased to about 34. It thus appears that most, and perhaps all of the observed uptake of 36 protons can be accounted for.

Ferrihemoglobin used in this study was prepared from crystalline horse oxyhemoglobin (kindly furnished by Dr. J. H. Wang) by the method of Steinhardt and Zaiser.[8] The author is indebted to Dr. E. P. Geiduschek and Mr. G. Saliba for invaluable assistance in performing these measurements.

(8) J. Steinhardt and E. M. Zaiser, THIS JOURNAL, **75**, 1599 (1953).

(9) Department of Chemistry, State University of Iowa, Iowa City, Iowa. John Simon Guggenheim Memorial Fellow, 1956–57.

STERLING CHEMISTRY LABORATORY
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CHARLES TANFORD[9]

RECEIVED JUNE 3, 1957

S-(DICHLOROVINYL)-L-CYSTEINE: AN AGENT CAUSING FATAL APLASTIC ANEMIA IN CALVES[1]

Sir:

We are reporting the synthesis of the compound S-(dichlorovinyl)-L-cysteine which upon oral administration produces a fatal aplastic anemia in young calves similar to that which we have observed with toxic trichloroethylene-extracted soybean oil meal (TESOM).

S-(Dichlorovinyl)-L-cysteine was synthesized by treating equimolar quantities of trichloroethylene (TCE) with the disodium salt of L-cysteine in liquid ammonia by a modification of the method of du Vigneaud.[2] The product precipitated on adjusting the pH to 5.0 with acetic acid and was crystallized from water–ethanol, 60–70% yield; m.p. 155–156° (decomp.). *Anal.* Calcd. for $C_5H_7O_2NSCl_2$: C, 27.29; H, 3.27; N, 6.48; S, 14.84; Cl, 32.82. Found: C, 27.83; H, 3.29; N, 6.47; S, 14.9; Cl, 32.8. *Ultraviolet absorption* in water: λ max. 210 mμ, $\epsilon = 8600$; λ max. 258 mμ, $\epsilon = 3200$. *Titration.* Neut. equiv., calcd. 216; found, 216; pI′, 5.4. *Paper chromatography.* 70:30 1-propanol–H_2O on Whatman No. 1, R_f 0.72; positive ninhydrin, 4-(p-nitrobenzyl)-pyridine (4-NBP),[3] ultraviolet and iodoplatinate tests.

Preliminary data indicate that the compound is S-(1,2-*trans*-dichlorovinyl)-L-cysteine.

The biological response of young calves to oral administration of S-(dichlorovinyl)-L-cysteine was studied by the methods established for the toxicity assay of TESOM.[4] The assay results are shown in Table I. The 500 and 200 mg./100 lb./day dosage levels were not tolerated by the assay calves and had to be discontinued after 5 and 7 days, respectively; however, all dosage levels tested produced the complete clinical, hematologic and postmortem picture of severe aplastic anemia of the bovine.[4]

TABLE I

BIOLOGICAL RESPONSE OF CALVES TO ORAL ADMINISTRATION OF S-(DICHLOROVINYL)-L-CYSTEINE

Dosage mg./ 100 lb./ day	Days to develop						
	Thrombocytopenia[a]	Leucopenia[b]	Lymphocytosis[c]	Elev. temp.	Fecal blood	Visible hemor.	Death[d]
500	10	9	13	13	13	11	14
200	12	10	10	11	11	13	14
50	14	19	21	21	17	19	23
20	18	22	22	25	25	22	27
10	20	27	31	51	27	26	60

[a] Platelet count below 200,000. [b] Leucocytes below 5000. [c] Over 85% lymphocytes. [d] Necropsied when moribund. Typical severe lesions of aplastic anemia.

We recently reported[5] on fractionation studies of toxic TESOM which indicated that the aplastic anemia causing entity is associated with the protein component of the meal. Analyses indicated that toxic TESOM contained 0.5 mole less sulfhydryl groups per 10^6 g. and about 25 p.p.m. more chlorine than did hexane-extracted meal from the same beans. In addition evidence that TCE would react with cysteine was obtained from sealed tube experiments. Of fourteen amino acids tested, only cysteine gave more than one ninhydrin spot by paper chromatography and one of these absorbed ultraviolet light and gave a positive 4-NBP test. Likewise reduced glutathione liberated chloride equivalent to its sulfhydryl content in sealed tube reactions and gave strong spots of R_f 0.50 and 0.70 which absorbed ultraviolet light and were 4-NBP positive. These facts and the knowledge that heat is required for the apparent interaction of TCE with soybean flakes to form toxic TESOM suggested the attempt to interact TCE with cysteine on a larger scale suitable for characterization and assay of the product.

Oral administration of S-(dichlorovinyl)-L-cysteine at the 20 and 10 mg./100 lb./day levels produces the typical syndrome of aplastic anemia in calves consuming levels of toxic TESOM'S ranging from $^3/_4$ to $^1/_5$ lb./100 lb./day and to samples of our isolated toxic protein at levels ranging from $^3/_8$ to $^1/_{10}$ lb./100 lb./day.

Paper chromatograms of fractions from a proved toxic pancreatic digest of TESOM's protein show ultraviolet absorbing 4-NBP and S positive spots with an R_f 0.45 and 0.70 with 70–30 1-propanol–H_2O on Whatman no. 1 paper. Similarities of the chemical and physical characteristics of these spots with those of S-(dichlorovinyl)-L-cysteine and its derivatives (TCE + glutathione) plus the observation that S-(dichlorovinyl)-L-cysteine pro-

(1) A report of work done, in part, under contract with the U. S. Department of Agriculture and authorized by the Research and Marketing Act. Contract supervised by Northern Utilization Research and Development Division, Agricultural Research Service.

(2) V. du Vigneaud and W. F. Patterson, *J. Biol. Chem.*, **114**, 533 (1936).

(3) (a) T. A. Geissman, H. Hochman and R. T. Fukuto, THIS JOURNAL, **74**, 3313 (1952); (b) J. Epstein, R. W. Rosenthal and R. J. Ess, *Anal. Chem.*, **27**, 1435 (1955).

(4) V. Perman, C. E. Rehfeld, J. H. Sautter and M. O. Schultze, *J. Agr. Food Chem.*, **4**, 959 (1956).

(5) L. L. McKinney, F. B. Weakley, R. E. Campbell, A. C. Eldridge, J. C. Cowan, J. C. Picken, Jr. and N. L. Jacobson, *J. Am. Oil Chemists' Soc.*, in press.

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duces in calves the typical TESOM toxicity syndrome, suggest that S-(dichlorovinyl)-L-cysteine may be related in structure to a part of, or may possibly be, the toxic principle of TESOM. Attempts to isolate sufficient toxic material from TESOM for chemical characterization are under way at the present time.

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RECEIVED JUNE 10, 1957

THE MAGNETIC SUSCEPTIBILITY OF MOLTEN NICKEL(II) COMPLEXES

Sir:

The paramagnetism exhibited by the bis-N-methylsalicylaldiminenickel(II) complex, diamagnetic in the solid state, when dissolved in "non-coördinating" solvents such as benzene and chloroform, has been interpreted as being due to the conversion of a proportion of the molecules of the complex from a planar to a tetrahedral configuration.[1] A similar behavior is observed for complexes of the series from bis-N-ethyl- to bis-N-amylsalicylaldiminenickel(II).[2]

The electric dipole moment measurements made on such complexes dissolved in dioxane and benzene have afforded evidence against such a view.[2] On the other hand, the hypothesis that paramagnetic octahedral disolvated complexes are formed, although improbable in the light of the investigations by Basolo and Matoush[3] on the coördinating tendencies of the methylbenzenes, cannot be ruled out.[4] In fact the existence of a silver perchlorate–benzene complex[5] shows that benzene and metal atoms may bind together.

In order to determine whether or not benzene molecules do coördinate with these nickel(II) complexes to yield paramagnetic solutions, magnetic measurements have been made on bis-N-alkylsalicylaldiminenickel(II) complexes, from bis-N-ethyl- to bis-N-decyl-, in the molten state. The magnetic susceptibilities of the molten compounds were measured between 80 and 200° by the Gouy method. In order to have samples of a lower melting point, mixtures of two complexes in the molecular ratio of 1:1 also were used.

Complexes which are diamagnetic in the solid state are paramagnetic with moments ranging from 0.8 to 1.15 B.M. in the molten state. Graphs of the magnetic moment *vs.* temperature for all of the complexes examined have very similar shapes and sometimes coincide. In the case of complexes or mixture of complexes melting below 100°, the curves have a minimum near 120°. Since the paramagnetism of bis-N-methylsalicylaldiminenickel(II) in benzene and chloroform, as measured by Clark and Odell,[1b] decreases steadily with increasing temperature from −16 to 43°, magnetic measurements have been also made on solutions of the complexes in dibutylphthalate which permits measurements up to 200°.

Curves of the magnetic moments of these complexes dissolved in this solvent likewise show a minimum. For the bis-N-methyl- complex this minimum falls near 120°. Beyond this point the magnetic moment rises steadily with increasing temperature. This suggests that the mechanism of the transition from diamagnetism to paramagnetism is the same for solutions as it is for the molten systems. The results of this investigation also show that the presence of solvents is not necessary to give rise to paramagnetism in these complexes, their diamagnetism being a property peculiar to the solid state only.

The equilibrium constants K = [paramagnetic form]/[diamagnetic form] have been calculated from values of magnetic susceptibility. The plots of log K against $1/T$ give a minimum which demonstrates an inversion of sign in the enthalpy of values of the equilibrium.

The possibility that the paramagnetism of the molten compounds can result from dissociation of the complexes into free Ni^{++} ions and chelate molecules has been excluded by measurements of electrical conductivity made on these complexes in the molten state.

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PALERMO, ITALY

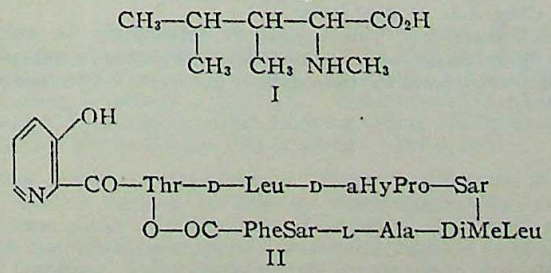
LUIGI SACCONI
RENATO CINI
FRANCESCO MAGGIO

RECEIVED MAY 31, 1957

THE STRUCTURE OF ETAMYCIN

Sir:

This communication reports the complete structure of the antibiotic Etamycin[1] (Viridogrisein[2]), the isolation of which recently was described independently and simultaneously by two groups.[1,2] The antibiotic possesses interesting activity against Gram-positive organisms, and in addition causes a reversible leucopenia in dogs. Etamycin is a surprisingly lipophilic peptide (soluble in benzene and carbon tetrachloride) with a molecular weight in the range 800–900. The presence of 3-hydroxypicolinic acid, L-alanine, *allo*-hydroxy-D-proline, D-leucine and threonine was reported.[1,2] We have now shown Etamycin to be a macrocyclic lactone (22-membered ring) which contains in addition to the above-mentioned components sarcosine, α-



(1) (a) J. B. Willis and D. P. Mellor, THIS JOURNAL, **69**, 1237 (1947); (b) H. C. Clark and A. L. Odell, *J. Chem. Soc.*, 3431 (1955).
(2) L. Sacconi, P. Paoletti and G. Del Re, THIS JOURNAL, in the press.
(3) F. Basolo and W. R. Matoush, *ibid.*, **75**, 5663 (1953).
(4) *Cf.* H. C. Clark and A. L. Odell, *J. Chem. Soc.*, 520 (1956).
(5) R. R. Rundle and J. H. Goring, THIS JOURNAL, **72**, 5337 (1950).

(1) B. Heinemann, *et al.*, *Antibiotics Annual*, **2**, 728 (1954–1955).
(2) Q. R. Bartz, *et al.*, *ibid.*, **2**, 777, 784 (1954–1955); the identity of Viridogrisein with Etamycin was established in the laboratories of the

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phenylsarcosine (PheSar) and β,N-dimethylleucine (DiMeLeu, I), the latter two of which have not been encountered previously in a natural product.

The presence of N-methylamino acids was indicated by color tests[3] on hydrolysates, and confirmed by an N-methyl determination, which demonstrated the presence of three N-methyl groups per molecule of Etamycin. For the isolation of the three N-methylamino acids, an Etamycin total hydrolysate was deaminated to destroy threonine, alanine and leucine and subjected to preparative paper chromatography.

One of the amino acids was identified as sarcosine by conversion to the dinitrophenyl derivative, m.p. 185–186°, undepressed upon admixture with an authentic sample.

The second amino acid, $C_9H_{11}NO_2$, m.p. 245–246° (sublimes) (Found: C, 65.30; H, 6.66; N, 8.57) had infrared and ultraviolet spectra indicating the presence of a benzene ring. It was proved to be identical with synthetic D,L-α-phenylsarcosine, m.p. 246–247° (sublimes), by infrared and ultraviolet spectra and chromatographic behavior. The optical inactivity is expected since optically active α-phenylglycine is known[4] to racemize rapidly with hot 10% hydrochloric acid.

The third amino acid, $C_8H_{17}NO_2$, m.p. 315–316° dec., (Found: C, 60.12; H, 10.47; N, 8.77) was optically active, $[\alpha]^{28}D$ +36.2° (*c*, 2.4 in 5*N* HCl). Hypochlorite degradation[5] gave methylamine, identified as the dinitrophenyl derivative, and the isopropylmethylacetaldehyde, isolated as the 2,4-dinitrophenylhydrazone, m.p. 125.2–126.0°, $[\alpha]^{28}D$ −38.7° (*c*, 1.5 in $CHCl_3$), which was identical (m.p., mixed m.p., infrared spectra) with a sample of the DNPH of (−)-isopropylmethylacetaldehyde obtained by ozonolysis[6] of ergosterol.[7] Thus, the third amino acid is β,N-dimethylleucine (I). It may be significant that the new amino acid and ergosterol have a common structural unit.

Etamycin contains only one each of the eight components according to quantitative paper chromatography and analyses of Etamycin, $C_{44}H_{62}N_8O_{10}$ (Found: C, 59.95; H, 7.40; N, 13.07; dried at 135° (0.01 mm.) and Etamycin hydrate, $C_{44}H_{62}N_8O_{10}\cdot H_2O$ (Found: C, 58.96; H, 7.17; N, 12.54; N-CH_3, 4.63; eq. wt., 890; dried at 110° (0.01 mm.).

Evidence that Etamycin contains a lactone structure was obtained as follows. On treatment with 0.1 *N* sodium hydroxide at room temperature it is converted into an antibiotically inactive acid, which contains the hydroxypicolinic acid and all amino acids. In Etamycin the threonine resists oxidation with chromic acid, whereas under the same conditions, in Etamycin acid the threonine is destroyed to the extent of 80%. Consequently the lactone link must involve the C-terminal carboxyl group and the hydroxyl group of threonine.

The absence of a terminal free amino group and the presence of unusual amino acids presented difficulties in the application of the conventional chemical and enzymatic methods of peptide sequence determination. However, catalytic hydrogenation of the obviously N-terminal hydroxypicolinic acid provided a secondary amino function, and alkali treatment gave a terminal carboxyl group, thus making possible the application of the Edman method.[8] Seven successive degradations revealed the sequence as hydroxypicolinic acid—Thr–D-Leu–D–aHyPro–Sar–DiMeLeu–L–Ala(?)–(PheSar). The course of the degradation was followed by paper chromatography of the phenylthiohydantoins,[9] dinitrophenylation and hydrolysis of each successive peptide, followed by paper chromatography of the resulting DNP-amino acids,[10] and by quantitative estimation of the amino acid content of each successive peptide after total hydrolysis and two dimensional paper chromatography. The sequence was completed by degradation from the carboxyl end with hydrazine,[11] which established phenylsarcosine as C-terminal. The structure of Etamycin is represented by II.

NOTE ADDED IN PROOF.—Comparison of the rotation of the DiMeLeu in neutral and acid solution has shown it to be in the L-series. Another isolation after mild hydrolysis gave PheSar having $[\alpha]^{31}D$ + 118° (*c*, 4.8 in *N* HCl), from which it can be deduced that it probably is in the L-series.

We are indebted to Bristol Laboratories of Syracuse, N. Y., for our supply of Etamycin, for microbiological assays and for some financial aid.

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CAMBRIDGE 39, MASS.

JOHN C. SHEEHAN
HANS GEORG ZACHAU[12a]
WILLIAM B. LAWSON[12b]

RECEIVED JUNE 19, 1957

(3) Paper chromatograms showed three weakly ninhydrin-positive spots, two of which gave red color tests with *p*-nitrobenzoyl chloride–pyridine according to P. A. Plattner and U. Nager, *Helv. Chim. Acta*, **31**, 220 (1948).

(4) F. Ehrlich, *Biochem. Z.*, **8**, 446 (1908).

(5) K. Langheld, *Ber.*, **42**, 2360 (1909); P. A. Plattner and U. Nager, *Helv. Chim. Acta*, **31**, 2192 (1948).

(6) G. Slomp, *et al.*, THIS JOURNAL, **77**, 1216 (1955).

(7) W. Bergmann and H. A. Stansbury, *J. Org. Chem.*, **9**, 281 (1944); the DNPH prepared by these authors had $[\alpha]^{28}D$ −37.7 and m.p. 124–124.5°.

(8) P. Edman, *Acta Chem. Scand.*, **4**, 283 (1950).

(9) J. Sjöquist, *ibid.*, **7**, 447 (1953).

(10) S. Blackburn and A. G. Lowther, *Biochem. J.*, **48**, 126 (1951).

(11) S. Akabori, K. Ohno and K. Narita, *Bull. Soc. Chem. Jap.*, **25**, 214 (1952).

(12) (a) Supported by a grant from the National Institutes of Health; (b) National Institutes of Health Postdoctoral Fellow, 1956–1957.

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BOOK REVIEWS

Modern Instruments in Chemical Analysis. First Edition. By FRANK M. BIFFEN, B.Sc., F.R.I.C., Research Specialist, Johns–Manville Corporation, and WILLIAM SEAMAN, M.S., Ph.D., Research Fellow, American Cyanamid Company. McGraw–Hill Book Company, Inc., 330 West 42nd St., New York 36, N. Y. 1956. ix + 333 pp. 16 × 23.5 cm. Price, $7.50.

The announced objective of the authors is to provide information for the general analytical chemist, and for others, regarding many of the leading physical principles and the instruments that are very frequently employed in chemical analysis. In spite of the somewhat different purposes and orientation, this book compares very favorably, as to scope and manner of treatment, with the three leading books of similar character that are more specifically aimed toward instruction in university courses.

The authors have concentrated their attention primarily upon photometric methods, electrical techniques and radioactive measurements.

After a brief consideration of the electromagnetic spectrum, chapter 1, the succeeding seven chapters deal, respectively, with: 2. Emission spectrographic methods. 3. Flame photometry. 4. Visible and ultraviolet absorptiometric methods. 5. Infrared spectroscopy. 6. Raman spectroscopy. 7. Mass spectrometry. 8. X-Ray diffraction. Five of the remaining chapters deal with electrical methods: 9. Survey of electroanalysis. 10. Polarography and amperometric titrations. 11. Potentiometric analysis. 12. Conductometric analysis, including the high-frequency method. 13. Coulometric analysis. The concluding chapter is: 14. Radioactivity.

Some topics that might have been expected have been omitted, as for example, fluorimetry as applied to solutions and solids, thermal methods such as enthalpy (thermometric) titrations and thermal conductance measurements. The latter topic has become of great importance in connection with vapor-phase chromatography.

In general, each chapter and each major topic is treated briefly and clearly, with generous use of line drawings and photographs of major features of the instruments. A good selection of reference books and selected journal articles is included in a rather extensive bibliography at the end of each chapter. This feature will enable the technical man to go fully into the more detailed aspects of any of the subjects that are treated.

The book is very readable, and the general composition is very good and quite free from misprints and other defects of manufacture.

FRICK CHEMICAL LABORATORY
PRINCETON UNIVERSITY
PRINCETON, N. J. N. H. FURMAN

Ion Exchange and Its Applications. Papers read at the Conference in the William Beveridge Hall, London University, 5th–7th April, 1954, with the discussions that followed. Society of Chemical Industry. The Macmillan Company, 60 Fifth Avenue, New York 11, N. Y. 1956. 173 pp. 22 × 28 cm. Price, $7.50.

This book is a set of some twenty review papers, each on somewhat different aspects of the field and written by different authors, with apparently no or little editing. Inevitably then, one encounters a considerable amount of duplication; the space allotted to each topic is often not commensurate with its extent or importance, and the contributions are of rather uneven quality.

The first section on *theoretical aspects* begins with a paper on the synthesis and general properties of resins; this is the best, short discussion of the topic this reviewer has seen. The paper on ion-exchange equilibria appears to skim over the more fundamental concepts, concentrating too much on the more formal but less informative contributions. Little information is given for the reader interested primarily in practical applications. Ion-exchange kinetics are discussed briefly and in general terms. The chromatographic column operations is essentially a review of the elegant contributions of its author, but does not mention the more simple treatments of other authors which lead to equally good values for calculated theoretical plate heights. The practical aspects of rate phenomena are, unfortunately, ignored.

The section on *industrial applications* includes two papers on water treatment and demineralization, both of which are so vague and general as to be of little practical value. The following two papers on the recovery of copper and on metallurgical applications contain interesting information, but are too brief and too general in nature.

The section on *inorganic and analytical applications* contains an introductory paper on analytical aspects, one which is entirely vague and often misleading. An article on the recovery of gold from cyanide solution is excellent. It shows how to attack the problem of the separation of a complex system, going from the laboratory through the pilot plant to plant operation. An article on the use of resins for concentrating traces of dissolved metals for analytical purposes is interesting, but its subject matter is so limited that it does not merit the accorded space. This section continues with an excellent review of continuous ion-exchange processes, presented in an authoritative and well documented manner. The subsequent article on the use of resins in the study of complex ions, where the resin is used either as a sorbent for an ion or for one of its complexes, is similarly authoritative. A much too brief summary of the use of membranes for desalting purposes concludes the section.

The section on *organic and biochemical applications* starts with a contribution dealing with amino acids, peptides and proteins, one which summarizes the older work well but devotes only a short section to the recent and most successful methods. Two brief and excellent reviews of applications to the wine industry and to medical practice follow. The summary of cation-exchange processes in soils does not attempt to relate these phenomena with other, related topics in the book.

This section is concluded with three papers: the first an excellent review on the separation of nucleic acid degradation products; the second a short description of dye purification processes making use of the "sieve" effect; the third a résumé of ion-exchange methods for the separation of alkaloids.

Each paper is followed by its discussion. It is here that the lack of editing is particularly felt, because so much of the discussion centered on questions to which there was no answer.

These papers understandably stress British contributions in this field, but space limitations mean that this is often done at the expense of equally valuable work by others. Further, most of the contributors devote entirely too much space to historical introductions and to material covered by other papers, with the result that about one-third of the available space is wasted. This being the case, the price of this book seems too high.

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Tables of Chemical Kinetics, Homogeneous Reactions. National Bureau of Standards Circular 510, Supplement 1. National Bureau of Standards, Office of Technical Information, Washington 25, D. C. Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C. xiv + 472 pp. 23 × 29 cm. Price, $3.25.

This present supplement to "Tables of Chemical Kinetics" covers work up to 1953 on Rearrangements, Isomerizations, Condensations and Solvolyses, including much work published prior to 1951 but not presented in the original volume. Exhaustive search of American and British journals only is claimed, but since articles cited in these are also included, the coverage is actually much wider. To each table is appended a section of comments which amplify and explain the data given in the table. These com-

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ments are usually very much to the point and make it clear that this is not an uncritical compilation of published data.

The problem of devising a suitably flexible and rational system of classification for a work such as this is a formidable one. The task is made doubly difficult by the frequent failure of authors to ascertain the products of the reactions they study kinetically. On the whole, the present system is a reasonable one although it occasionally results in unusual juxtapositions and, conversely, sometimes separates reactions that belong together. One finds, for example, that "Ester Solvolysis" includes displacements effected by added reagents or by the conjugate base of the solvent. In contrast to this, the ethanolysis and acetolysis of sulfonate esters are tabulated separately under "Ester Solvolysis" and "Ester Exchange," respectively. The classification of alkyl halides as "esters" is somewhat distressing to an organic chemist. Indeed, the section on "Ester Solvolysis" could stand a considerable overhaul in organization, since in its present form it covers a very large and rapidly expanding field.

The above comments are intended mainly to warn the reader that he may not always find what he seeks where he expects to find it. Obviously, no conceivable system of classification would please everyone. Many possible objections could be met by an alphabetical index expanded to include extensive cross listings according to type of reaction, of reactant(s) and of product(s). One hesitates to suggest additional work to the authors, who are to be congratulated for their willingness to undertake the arduous task of compiling this work, but such an index should add greatly to the usefulness of the "Tables."

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Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology. By ROBERT E. WOODSON, JR., Ph.D., Professor of Botany, Washington University, Senior Taxonomist, Missouri Botanical Garden, HEBER W. YOUNGKEN, Ph.D., Sc.D., Phm.D., Research Professor of Pharmacognosy and Botany, Massachusetts College of Pharmacy, EMIL SCHLITTLER, Ph.D., Director of Research, CIBA Pharmaceutical Products Inc., Summit, New Jersey, and JURG A. SCHNEIDER, M.D., Director of Physiology Research, CIBA Pharmaceutical Products Inc., Summit, New Jersey. Little, Brown and Company, 34 Beacon Street, Boston 6, Massachusetts. 1957. xii + 149 pp. 16 × 24 cm. Price, $5.50.

In the fourth edition (1949) of Henry's "The Plant Alkaloids" 5 pages and 49 references sufficed for presenting the chemistry and pharmacology of the seven rauwolfia alkaloids known at that time. Except for rauwolscine, which had been identified as a yohimbine isomer, their structure chemistry was as yet uncharted territory. Their pharmacology was on the whole unexciting and held little promise of therapeutic utility. While extracts of *Rauwolfia serpentina* were known to exert hypotensive and sedative effects, it was not clear whether these were due to an alkaloidal constituent. In the intervening 8 years, and particularly since the discovery of reserpine by Mueller, Schlittler and Bein (1952), this picture has changed radically. More than 40 alkaloids isolated from Rauwolfia species are now on record, and the structures of a great majority of these have been elucidated. Only last year we have seen these achievements culminate in Woodward's brilliantly conceived and executed synthesis of reserpine. There was a commensurate expansion of pharmacological research, most of it concerned with analyzing the unique combination of properties exhibited by reserpine, as well as revival of interest in the botany and pharmacognosy of the genus.

Obviously the time was ripe for reviewing the various aspects of the field anew in the light of these recent advances. The authors of "Rauwolfia," each of whom has in his area of competence made important contributions to the present state of knowledge, have succeeded admirably in imparting the new look on the topic. The four chapters of the little book are written in the manner of brief review articles. There is no attempt to bring in technical detail, except in the chapters on the botany (R. E. Woodson) and on the pharmacognosy (H. W. Youngken), where much of the space is naturally given over to the description and visualization of morphological subject matter. While the chemist interested in the Rauwolfia alkaloids will rarely have need for this kind of information, he will be well advised to read the initial sections in the botanical chapter which deal with the taxonomy, synonomy, geographical distribution of the species, and their culture and propagation. For instance, it may be new to him that *R. tetraphylla*, *canescens*, *heterophylla* and *hirsuta* are not, as he may have been led to believe by the chemical literature, different species. and that according to the nomenclature rules *tetraphylla* deserves preference. Likewise, he may be unaware of the fact that *R. canescens* is not indigenous in India, but was transplanted there a century ago from the West Indies.

The chemical chapter, by E. Schlittler, opens with a very useful set of tables listing the alkaloids so far isolated from the various species, together with their melting points, rotations and references to the papers reporting their discovery. In the following exposition of their structure chemistry some order is brought into the chaos of names by grouping the compounds according to certain structural criteria (anhydronium bases, indoline types, tertiary bases with heterocyclic, or alicyclic, ring E). The numerous more "conventional" representatives (yohimbine types) of the last-named group are treated somewhat cursorily, to allow fuller discussion in the following section of its most important members, reserpine and its two congeners, deserpidine and rescinnamine. That the proof of structure and the elucidation of the stereochemistry of these compounds should have received authoritative and lucid treatment by the originator of this whole line of research was only to be expected. In the stereochemical argument one could perhaps disagree with the author on one or two points in his evaluation of the evidence. Thus, this reviewer was a little surprised to find one of the early proofs for the *cis*-fusion of rings D and E, the formation of a quaternary N-4 tosylate from methyl reserpate 18-tosylate on treatment with collidine, discussed not in this context, but in connection with the configuration of C-17, on which this observation bears only indirectly. The chapter ends with a brief review of the synthetic studies so far on record, including the Woodward synthesis of reserpine, which is conveniently outlined in a flow sheet.

The present status of pharmacological knowledge is ably summarized by J. A. Schneider in the last chapter. It opens with an introductory section dealing with the historical aspects and the effects of crude extracts from various species. The pharmacodynamic properties of the individual alkaloids, grouped for this purpose as in the chemical chapter, are then reviewed. It is, of course, the subsection on reserpine which gives real substance to the chapter. Here the author could draw on a comparative wealth of recently published material which lent itself to classification according to pharmacological criteria and more detailed discussion in terms of specific effects.

In brief, the booklet provides all the essential information on Rauwolfia in highly condensed, yet readable form. It will be equally useful to the expert as a source of references and to the newcomer who needs orientation in one or the other aspect of the field.

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PHYSICAL AND INORGANIC CHEMISTRY

[CONTRIBUTION FROM THE GIBBS LABORATORY, DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

The Thermal Denaturation of Desoxyribose Nucleic Acid

BY STUART A. RICE AND PAUL DOTY

RECEIVED SEPTEMBER 19, 1956

Several samples of thymus desoxyribose nucleic acid in saline solutions have been studied by light scattering, viscosity and sedimentation methods after exposure to a series of elevated temperatures. For exposure times of one hour, changes are noticed at temperatures above 89° for two of the samples and above somewhat lower temperatures for the others. From this characteristic temperature up to 100° the viscosity falls about 12-fold (as Zamenhof first noted), the mean end-to-end length decreases by about 15-fold and the molecular weight remains unchanged according to light scattering studies. Sedimentation measurements reveal a broadening of the distribution of sedimentation constants but no significant change in the average value. Typical denaturing agents lower the temperature range in which these changes occur by 10–20° but have no effect at room temperature. It appears that the changes at the elevated temperatures are due to the melting out of regions of hydrogen-bonded structure within DNA molecules and this coöperative breakdown of the highly organized, native structure is termed denaturation. At a given elevated temperature the viscosity quickly reaches an equilibrium value but it cannot be decided whether this indicates existence of a true equilibrium between native and denatured regions of the DNA molecules or a distribution of denaturation temperatures for different regions. It is shown that the completely denatured state can be achieved without chain degradation and it is surmised that in this state the polynucleotide strands are held together by remaining or reformed hydrogen bonds.

During the last three years it has become increasingly clear that desoxypentose nucleic acids (DNA) possess a uniquely ordered structure which is maintained in aqueous salt solutions but which can be irreversibly disordered by exposure to acid, alkali, heat and other agents. This breakdown of a specific structure is accompanied by a drastic fall in viscosity, a substantial rise in optical density in the ultraviolet and a shift to a different titration curve. Since the advent of the Watson–Crick structure for DNA it has been suggested frequently that this configurational change be identified with the breakdown of hydrogen bonding between the base pairs of the two polynucleotide chains.

When dissolved in 0.2 *M* NaCl, DNA can be exposed to *p*H values as low as 2.6 for several hours without significant chemical degradation. A study of the physical changes[1] showed that when brought to this *p*H the DNA molecules contracted without change in molecular weight. In this acid condition, the optical density at 258 mμ is raised about 32%.[2] A recent analysis of the titration curves of such acid–treated DNA shows that essentially all the original hydrogen bonds are broken if the temperature is 25° but that only about half are broken at low temperatures (0.4°).[3] It also has been shown that prolonged exposure to *p*H 2.6 at 25° leads to detectable chemical degradation: purines are liberated in substantial numbers, the polynucleotide chains undergo slow scission and the remaining hydrogen bonded areas disappear.[4]

The study reported here began in 1953 as a parallel investigation of the changes brought about in DNA by heat. Since the occurrence of a sharp fall in viscosity in a critical temperature range was readily apparent,[5] our first concern was to establish whether this was purely a configurational change as in the case of acid treatment or whether a molecular weight change was involved. In addition, we were concerned with characterizing the heat-treated DNA and elucidating the mechanism of the thermally induced transition. Further, these considerations led to an exploration of the problem of the separation of the two polynucleotide strands in DNA. Some results have been given in a preliminary note.[6]

(1) M. E. Reichmann, B. H. Bunce and P. Doty, *J. Polymer Sci.*, **10**, 109 (1953).

(2) R. Thomas, *Biochem. Biophys. Acta*, **14**, 231 (1954).

(3) R. A. Cox and A. R. Peacocke, *J. Polymer Sci.*, **23**, 765 (1957).

(4) C. A. Thomas and P. Doty, THIS JOURNAL, **78**, 1854 (1956).

(5) S. Zamenhof, H. E. Alexander and G. Leidy, *J. Exp. Med.*, **98**, 373 (1953).

(6) P. Doty and S. A. Rice, *Biochim Biophys. Acta*, **16**, 446 (1955).

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Experimental

Samples.—Four preparations of calf thymus DNA were employed. Two of these have been described before in an earlier publication.[7] The sample listed there as Simmons B is designated here as SB-1 and the one listed as Varin is designated here as V-1. The third sample was prepared by Dr. Norman Simmons (University of California, Los Angeles) and is designated as SC-1. The fourth sample, on which most work was done, was prepared according to Simmons Method B and is designated SB-11. Briefly, this preparative procedure involves multiple extractions of minced thymus in saline–citrate (0.015 *M* sodium citrate and 0.15 *M* NaCl) by blending and centrifuging to obtain a sediment containing the nucleoprotein. 30% sodium *p*-xylene sulfonate is used to deproteinize the nucleoprotein. The protein is then precipitated upon dilution and filtered off. The DNA in solution is precipitated with isopropyl alcohol, redissolved and precipitated several times.

The molecular weight and radii of gyration as determined by light scattering are listed in Table I together with the intrinsic viscosity at zero gradient. The higher values for sample SB-11 are thought to be due to instantaneous transfer of the thymus gland from the freshly killed animal to Dry Ice and its remaining at this low temperature until blended in cold saline–citrate.

TABLE I

SUMMARY OF MOLECULAR PROPERTIES OF DNA SAMPLES

Sample	Mol. wt.	Radius of gyration, Å.	Intrinsic viscosity, 100 cc./g.
V-1	6,850,000	2050	48
SB-1	5,850,000	2000	53
SC-1	6,600,000	2700	62
SB-11	8,200,000	3000	72

Analytical Constants and Experimental Techniques.—The values of the extinction coefficient, refractive index increment, etc., are the same as those previously employed[7] and the techniques of light scattering and viscosity measurement are the same as described before.[7] In particular any viscosity measurement quoted implies that if gradient dependence were present, measurements in the range of 30 to 100 sec.$^{-1}$ were extrapolated to zero gradient to yield the value listed. Gradient dependence was found to disappear at intrinsic viscosities of about 10. Sedimentation measurements were made in a Spinco Model E ultracentrifuge using 30 mm. cells. Bar angles as low as 5° were used for the most dilute solutions. The saline–citrate solvent mentioned above (0.015 *M* sodium citrate and 0.15 *M* NaCl) was used throughout.

Experimental Results

Viscosity.—Preliminary measurements on all of the DNA samples confirmed Zamenhof's[5,8] observation that the viscosity of DNA solutions in physiological saline falls rapidly in the vicinity of 80°. A systematic study was carried out as follows. DNA solutions were made by dissolving the sample in water in the cold room to yield a concentration of about 40 mg./dl. This was adjusted to the standard saline–citrate solvent and a concentration of 4 to 7 mg./dl. Aliquots of this stock solution were heated at various temperatures by immersion in thermostats for one hour. The aliquots were then placed in ice and the viscosities measured within a day at 25°.

Results for samples V-1 and SB-11 are shown in Fig. 1. It is seen that the intrinsic viscosity of V-1 begins to fall at about 70° and reaches half its original value at 89°. Sample SB-1 showed a similar behavior. However, for sample SB-11 (and SC-1, not shown) the viscosity did not begin to fall until 85° and it reached half its value only at 94°. All samples reached about the same value of intrinsic viscosity at 100°, that is, 4.5 ± 1.5. The uncertainty is large here because of the high dilution employed in these particular measurements.

The relative sharpness of the viscosity fall in all four samples is indicative of a configurational change having the characteristics of a melting or denaturation of a periodic intramolecular structure. At first thought it appears that the process may involve only the passage of the individual DNA molecules from the original state of high viscosity to the final state of low viscosity. If it is assumed that the transition consists of a single first-order process, the data in Fig. 1 may be used to derive the temperature dependence of the first-order rate constant. When this is done, an activation energy of 35–40 kcal./mole is found for samples V-1 and SB-1 and a value of 93 kcal./mole for samples SB-11 and SC-1. Corresponding entropies of activation are calculated to be in the range of 63–75 entropy units for the first two samples and 220 e.u. for the SB-11 and SC-1 samples. These values are comparable with those found in protein denaturation studies and indicate that a highly ordered structure is being irreversibly broken down. Insofar as the term *denaturation* denotes the disappearance of a periodic structure by a rate process grossly characterized by a high entropy and high energy of activation, the transition described here can be termed denaturation.

The nature of the denaturation process was examined in more detail by observing the change in viscosity as a function of the time of exposure to elevated temperatures. Several results are shown in Fig. 2. The striking feature of these results is that they show that the viscosity falls rapidly and levels out at a plateau which is lower the higher the temperature. While it was not to be expected that the viscosity would measure precisely the extent of denaturation, except in the event of all-or-none reactions within individual DNA molecules, it clearly should give a qualitative indication of the progress of the reaction. Hence the leveling off of these curves demonstrates that the denaturation essentially comes to a stop short of completion by an amount dependent on the temperature. The implications which this observation carries are discussed later. However, at this point it is clearly evident that this observation invalidates the interpretation offered in the preceding paragraph.

The temperature range in which thermal denaturation occurs rapidly would be expected to be lowered by substances which are effective in denaturing proteins, as a consequence, measurements of the viscosity at 25° of a series of DNA solutions which had been heated at various temperatures for 1 hour were carried out in the presence of typical denaturing agents. The results for 8 *M* urea, 3.2 *M* guanidine hydrochloride and 0.8 *M* sodium salicylate are shown in Fig. 3 for sample SB-11. It is seen that the viscosity plots are approximately shifted to lower temperatures by these agents. The temperature at which the viscosity has fallen

(7) M. E. Reichmann, S. A. Rice, C. A. Thomas and P. Doty, THIS JOURNAL, 76, 3047 (1954).

(8) S. Zamenhof, G. Griboff and N. Marullo, *Biochim. Biophys. Acta*, 13, 459 (1954).

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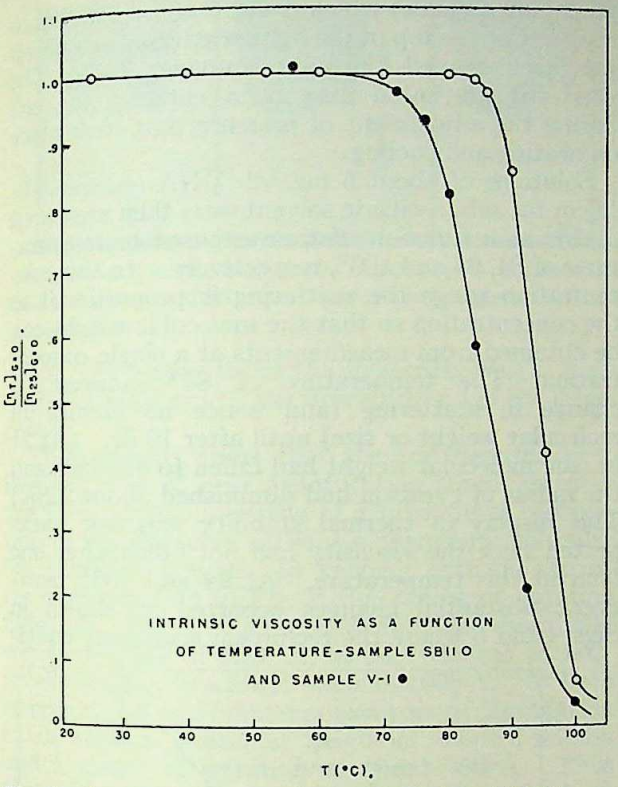

Fig 1.—Intrinsic viscosity of samples V-1 and SB-11 as a function of the temperature of one hour heating.

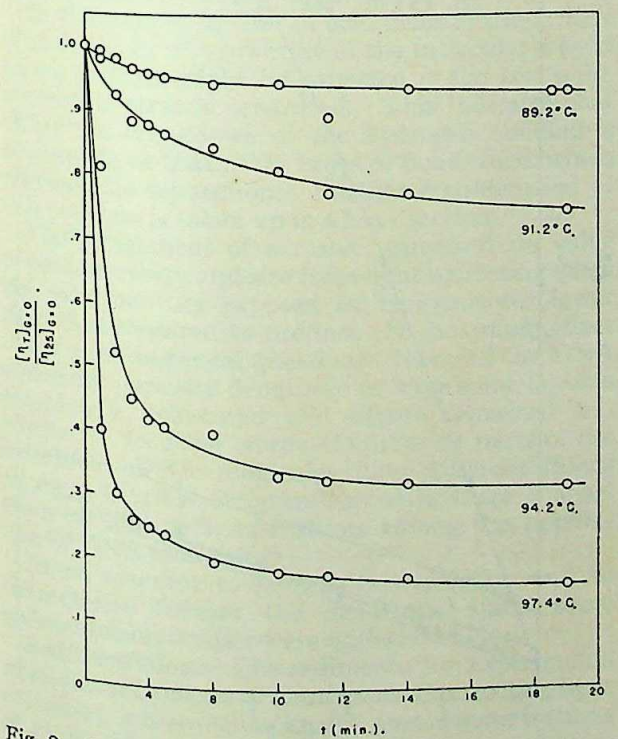

Fig. 2.—Intrinsic viscosity of sample SC-1 as a function of time at several temperatures.

by half is lowered 19, 14 and 8°, respectively, for the urea, guanidine hydrochloride and sodium salicylate. However, because of the difference in concentrations the molar efficiency of these agents is in the reverse order, similar to that usually found for proteins. It is also apparent that the viscosity of the denatured material is different in these various

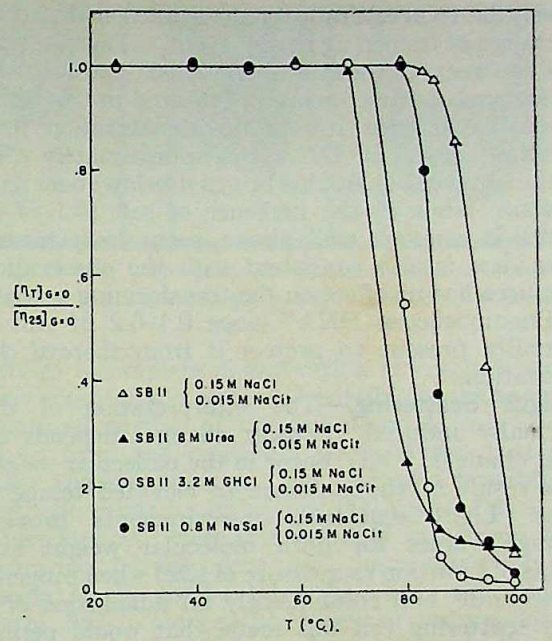

Fig. 3.—Intrinsic viscosity of sample SB-11 in the presence of hydrogen bond breaking agents as a function of the temperature of one hour heating.

solvents. It is lowest in the guanidine hydrochloride; this is probably due at least in part to the suppression of the electrostatic repulsions among the phosphate groups by the guanidinium ion. Separate experiments have also established that the molecular weight of DNA after exposure to 3.2 *M* guanidine hydrochloride at 100° for one hour is lowered to 940,000, which, as we shall subsequently see, is markedly lower than after comparable treatment in the absence of any denaturing agent. It is important to note that the DNA solutions employed here always contained 0.15 *M* NaCl and 0.015 *M* sodium citrate before the denaturing agent was added. The addition of any of these denaturing agents did not significantly change the intrinsic viscosity, 72. Hence the only observed effect of these agents, provided that they are added to saline solutions of DNA, is to lower by as much as 20° the denaturation temperature range of DNA. They have no effect at room temperature.

These conclusions stand in apparent conflict with the investigations of Conway[9] for he has found that 6 *M* urea raises the intrinsic viscosity (at zero shear) of aqueous solutions of DNA and lowers it substantially in the presence of 0.1 *M* NaCl. Since these observations appear reliable and the intrinsic viscosity of the DNA sample, 45, is high enough to ensure that it is not seriously denatured, it appears that the fall in viscosity in the presence of 0.1 *M* NaCl could only have come about if the urea was added before the salt. From the work of Thomas[2] and that of M. Litt[10] in this Laboratory it is clear that the denaturation temperature range is lowered markedly as the ionic strength is reduced so that in the absence of added salt and at rather high dilution denaturation takes place in the vicinity of room temperature. The effect of adding urea and other denaturing agents under this condition will

(9) B. E. Conway, *J. Polymer Sci.*, **20**, 299 (1956).

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clearly be to accelerate the denaturation that is on the verge of occurring in any event. Thus the conflict between Conway's observations and our own is removed if our conclusion is stated in this form; concentrated urea lowers the denaturation temperature range of DNA by approximately 20°. In the absence of salt this brings it below room temperature while in the presence of salt (0.1 *M* or more) it remains well above room temperature. This view is also consistent with the observation that urea has no effect on the transforming activity of Pneumococcus DNA[11] since 0.1–0.2 *M* salt is generally present to protect it from thermal denaturation.

Light Scattering.—The interpretation of the thermally induced viscosity changes depends on what changes, if any, occur in the molecular weight as a result of the exposure to elevated temperatures. Light scattering measurements provide average values for both molecular weight and radius of gyration (a measure of size) when properly carried out[7] and consequently an adaptation of a light scattering cell was made that would permit angular intensity measurements to be made on the same DNA solution before and after heating without removal from the cell. This was done by sealing a sintered glass frit (ultra-fine) to a tapered glass joint (female) which could then be fitted onto the joint at the top of the light scattering cell which was itself shaped like an erlenmeyer flask. The glass frit prevented dust from entering the cell during the adjustment of pressure that took place on heating and cooling.

Solutions of about 6 mg./dl. DNA (sample SB-11) in the saline–citrate solvent were then measured at 25° as a function of time exposed to temperatures of 84, 94 and 100°, respectively. In this concentration range the scattering is proportional to the concentration so that the molecular weight can be obtained from measurements at a single concentration. The temperature of 84° induced no change in scattering (and hence no change in molecular weight or size) until after 10 hr. (At 21 hr. the molecular weight had fallen to one-half and the radius of gyration had diminished about 25%.) This display of thermal stability was not unexpected since the viscosity had not fallen after one hour at this temperature. At 94 and 100°, however, substantial changes occurred as shown in Figs. 4 and 5 where the reciprocal scattering envelopes (Kc/R_θ) are plotted as a function of $\sin^2(\theta/2)$ (θ is the scattering angle and R_θ the reduced intensity of light scattered at θ). In both cases the slope of the plot falls abruptly while maintaining essentially the same intercept showing thereby that the molecular size is greatly diminished while the molecular weight remains approximately con-

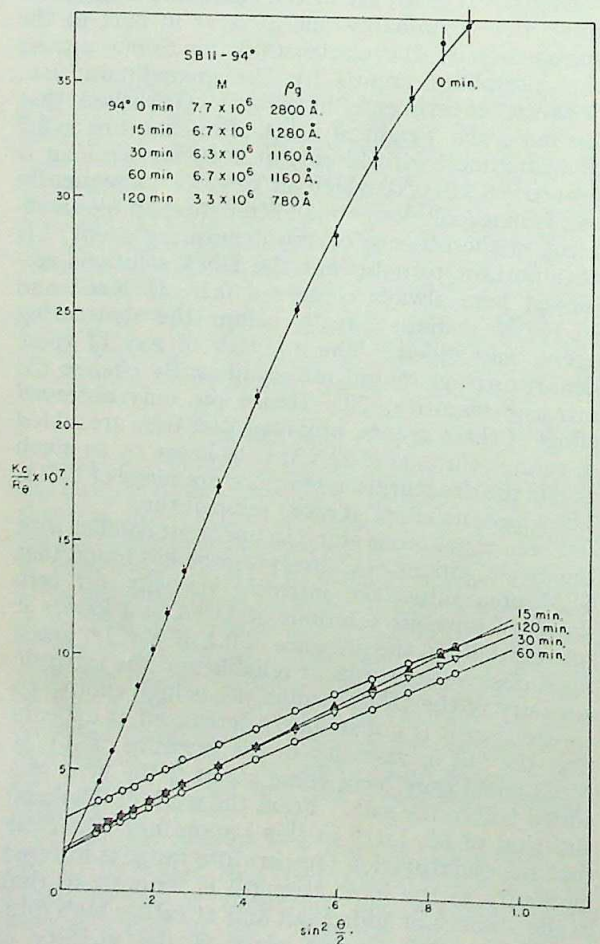

Fig. 4.—Angular distribution of scattered light for sample SB-11 heated at 94°.

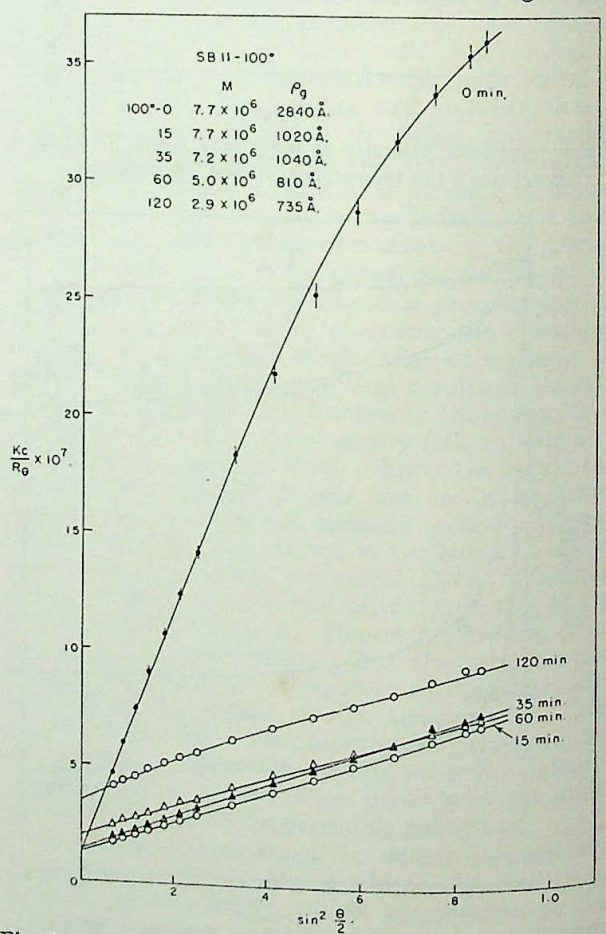

Fig. 5.—Angular distribution of scattered light for sample SB-11 heated at 100°.

(11) H. Ephrussi-Taylor, "McCollum–Pratt Symposium on the Chemical Basis of Heredity," Johns Hopkins Press, 1957, p. 230.

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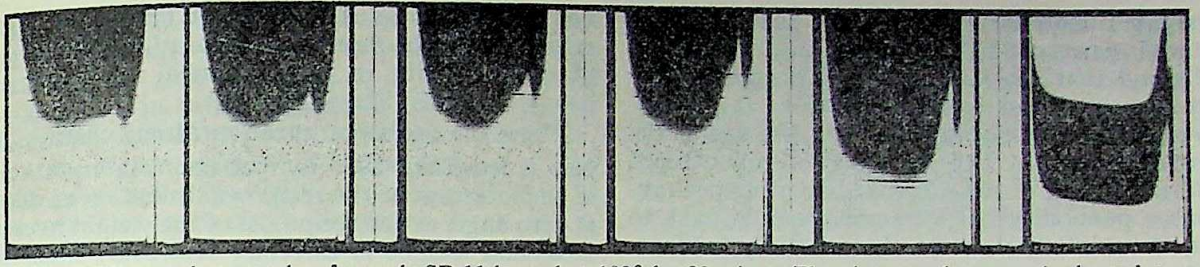

Fig. 6.—Schlieren photographs of sample SB-11 heated at 100° for 20 min. The photographs are at 4 minute intervals, the rotor speed is 37020 r.p.m. and the bar angle is 15, 7.5, 5, 5, 5 and 5° reading from right to left. The DNA concentration is 0.0429%.

stant. At longer times the molecular weight does decrease as shown by the upward trend of the intercepts.

These results show that thermal denaturation, like the case of acid denaturation summarized in the Introduction, consists of a substantial contraction of the molecule without a change in molecular (or particle) weight. In keeping with the viscosity results shown in Fig. 2 the radius of gyration falls from 2800 Å. to an intermediate and essentially constant value of 1250 Å. at 94° whereas at 100° it falls quickly to a lower value of 1000 Å. At both temperatures two hour exposures cause degradation to an average molecular weight of about 3 million and a radius of gyration of about 750 Å. Thus thermal denaturation appears to reach its final extent at a given temperature rather quickly and is then followed by a slow degradation.

In this case as in that of acid denaturation, there is no evidence of a lowering of the molecular weight to one-half as might be expected if the two polynucleotide strands separated. This indicates that either the breakdown of the hydrogen bonding is incomplete or that other types of bonds form which prevent the separation. Further consideration of this problem is taken up in a later section.

The attainment of a stable, intermediate value of both viscosity and size from light scattering when the solutions are exposed to temperatures lower than that required to produce the maximum effect raises a fundamental question. Have all the DNA molecules partially denatured or have some become completely denatured and others remained unaffected? In other words, do different parts of the individual DNA molecules have different resistances to thermal denaturation or is there a spectrum of melting temperatures among the population of DNA molecules?

In an attempt to answer this question and to characterize further the denatured state, some sedimentation studies were undertaken.

Sedimentation.—The sedimentation experiments were carried out in a manner similar to the light scattering experiments except that concentrations of 35 mg./dl. rather than 10 mg./dl. were employed. After heating at various times up to six hours at 84° no change in the sedimentation pattern or rate was observed over that of the unheated material. Heating at 94° for one hour brought about a slight broadening in the sedimentation pattern but it still remained hypersharp. The observed sedimentation constants (11.8 S. at 35 mg./dl. and 8.5 at 70 mg./dl.) are not much different than for the unheated material. In view of the previous evidence that a state of incomplete denaturation is reached under these conditions it appeared possible that the more denatured portion of the sample could not be resolved from the relatively undenatured material under these conditions. To test this possibility, synthetic mixtures of native DNA and DNA denatured at 100° were mixed and it was found that separation did not occur until the relative concentration of the native DNA had been reduced to nearly 10%. Hence the observed sedimentation diagrams of the 94° material could not discriminate between the two possibilities mentioned at the end of the preceding section.

When DNA solutions exposed to 100° for 15 or 20 minutes were examined it was found that half of the material appeared as a rather sharp, but not hypersharp, peak and that the remainder sedimented faster as a very diffuse shoulder that eventually separated (see Fig. 6). The pattern did not differ significantly over the concentration range of 35 to 53 mg./dl. In each case the sedimentation rate of the sharper peak was about 21 ± 2 and the diffuse peak extended from about 25 to 40 S.

The appearance of two differently sedimenting species in solutions in which it was thought that denaturation had gone essentially to completion posed a difficult problem. We had originally interpreted it as incomplete denaturation and associated the diffuse peak with the completely denatured material. This was the basis of the assignment of 30 as the sedimentation constant of the denatured DNA in the preliminary note.[6] However, quite recently, Dr. K. V. Shooter and Professor J. A. V. Butler have examined our sample SB-11 by ultraviolet optics in the ultracentrifuge[12,13] and found that the distribution of sedimentation coefficients broadened but remained single-peaked at 21 S. when heated at 100° for 15 min. at a concentration of 10 mg./dl.

Now it is well known that when DNA is thermally denatured at higher concentrations (>100 mg./dl.) the initial fall in viscosity is gradually restored and even surpassed. This presumably is due to the formation of intermolecular hydrogen bonds making use of the large number of sites opened up in the denaturation process. When this is taken together with the absence of the double peak at 10 mg./dl. it appears possible that our observation at intermediate concentrations was made on partially

(12) K. V. Shooter and J. A. V. Butler, *Trans. Faraday Soc.*, **52**, 734 (1956).

(13) K. V. Shooter, R. H. Pain and J. A. V. Butler, *Biochim. Bio-*

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aggregated material; that is, the faster, diffuse material corresponded to aggregated denatured DNA and that the sharper peak was still molecularly dispersed and corresponds to what was observed at lower concentration with the aid of the ultraviolet optics. The possibility of undenatured material staying in the slower sedimenting peak remains a possibility but its amount would have to be quite small because of the relatively low viscosity.

The Denatured State

Molecular Weight.—From the results presented in Figs. 4 and 5 it appears that the exposure of DNA in saline solution to temperatures of 94 and 100° produces denaturation (as seen in the lowering of the slopes) followed by the gradual onset of chemical degradation (as seen in the eventual rise in intercepts). At 94° the slope, and hence the radius of gyration, is not lowered as much as at 100° in keeping with the viscosity results (Fig. 2) which shows that denaturation proceeds only to an intermediate point at 94°. The fact that there is a delay in the onset of the fall in molecular weight after completion of the denaturation is seen in Fig. 7 where the light scattering molecular weight results for samples SB-11 and V-1 are plotted as a function of time. The denaturation, judged either in terms of viscosity or light scattering, is essentially complete at 15 min. but the initial fall in molecular weight is not evident until about 45 min. The fall in molecular weight continues as long as the sample is held at the elevated temperature, and it exhibits no leveling off at any particular value.

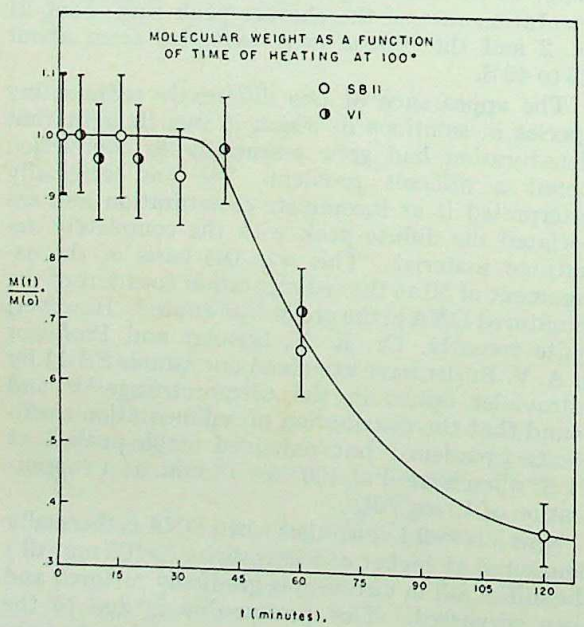

Fig. 7.—Molecular weight (from light scattering) as a function of time of heating at 100°.

In the case of thermal denaturation studied here as well as in the case of acid denaturation[1] the denatured material, prior to its eventual degradation, exhibits the same intercept in the light scattering plots as the original sample. Although we do interpret this as showing that denaturation occurs without change in molecular weight, the conclusion is not as obvious as it appears at first sight. The reason lies in the recent demonstration[14] of the role of polydispersity in the reciprocal scattering envelopes of chain-like molecules.

When the radius of gyration of the chain molecule is less than 1000 Å., the usual interpretation of the intercept of the reciprocal radiation envelope at zero angle as the reciprocal of the weight average molecular weight is correct. However, when the radius of gyration exceeds 1000 Å., the reciprocal scattering envelope that is experimentally accessible will not yield the weight average molecular weight unless the molecular weight distribution happens to be the most probable (*i.e.*, one in which the various molecular weight averages stand in the ratios $M_z:M_w:M_n = 3:2:1$). When the molecular weight distribution is not of this form, the interpretation of the experimental data must be modified. For these other cases, the reciprocal radiation envelope will either approach or coincide with an asymptote whose intercept on the ordinate provides the reciprocal of two times the number average molecular weight, M_n. The implications of this possibility of ambiguity in assigning the type of average that is being determined by light scattering measurements on DNA is discussed elsewhere.[15] It is sufficient to say here that several lines of evidence indicate that the distribution of molecular weights in DNA does correspond roughly to that of the most probable distribution. If we call the molecular weight obtained from the scattering measurements in the usual angular range the "light scattering" molecular weight, we may conclude that in the present case the weight average molecular weight of denatured DNA is within probable experimental error equal to the light scattering average molecular weight for undenatured DNA.

Sedimentation Constant and Intrinsic Viscosity of Denatured DNA.—The intrinsic viscosity of thermally denatured DNA has been found in this study to be 4.5 ± 1.5. This is in need of more accurate and precise determination, but it is sufficiently reliable for the present purpose which is to explore the interpretation of this quantity in combination with the sedimentation constant. The work of Professors Butler[13] and Schachman[16] and their colleagues indicates that there is a rather broad distribution of sedimentation constants in DNA and that this broadens further upon thermal denaturation. On sample SB-11 the value determined at 10 mg./dl. (20.0 S) upon correction for concentration dependence becomes 21 S. Taken at face value, these measurements are in apparent contradiction with the viscosity and light scattering results found in this research. The constant value of the sedimentation constant would imply that two molecules with the same mass but which differ by a factor of three in radius of gyration (a factor of 27 in molecular volume) sediment at the same

(14) H. Benoit, A. M. Holtzer and P. Doty, *J. Phys. Chem.*, **58**, 635 (1954).

(15) P. Doty, The Physical Chemistry of DNA, Oak Ridge Symposium on Physical Chemistry of Biocolloids, April, 1956 (to be published).

(16) V. N. Schumaker and H. Schachman, *Biochim. Biophys. Acta*, **23**, 628 (1957).

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rate. Since the chemical composition remains unchanged, the interactions of the individual monomers with the solvent should be of the same order of magnitude in both cases, and if we allow the denatured molecule to have a frictional coefficient more in accord with that characteristic of the single polynucleotide chain, the net resistance to flow per monomer must decrease. Even if the frictional coefficient per monomer were to remain the same, the large decrease in molecular volume at constant molecular weight would of necessity be accompanied by an increase in sedimentation rate. We can invent no mechanism which would enable a constant sedimentation constant to be coupled with a constant molecular weight and a greatly diminished molecular volume. The use of the sedimentation data of Professors Butler and Schachman with our molecular weights and viscosities also stand in contradiction with the empirically well established Flory–Mandelkern relation[17]

$$s_0 = 2.6 \times 10^6 \frac{M^{2/3}}{[\eta]^{1/3}} \frac{(1 - \bar{v}\rho)}{\eta_0 N}$$

In order to be compatible with the observed molecular weight of 8.2×10^6, the observed value of the sedimentation constant would have to be increased by a factor of 2.3.[18]

The problem posed by this large discrepancy is a serious one. The result obtained from sedimentation and viscosity is subject to several criticisms. First, so little is known about the molecular form of the denatured state that the application of the foregoing equations based upon simple models may not be justified. Secondly, the distribution of sedimentation constants, particularly in the denatured material, appears to be so broad that the weight average sedimentation constant, which is the one required in the above relations, may not have been properly determined. Thirdly, as we have pointed out previously,[6] the free draining coil model does permit a contraction of a chain-like molecule with only a small change in sedimentation constant but large decrease in viscosity. The relationship between s, $\overline{r^2}$, and $[\eta]$ is, in this model

$$s_0 = \frac{(1 - \bar{V}\rho)\overline{r^2}}{3600\eta_0[\eta]}$$

which predicts a value for s_0 of 20, in substantial agreement with experiment. However, this model does not fit the sedimentation data for native DNA as well, and the native molecule would be expected to be even more "free draining." Moreover, its applicability to non-homologous molecules may not be justified. Admittedly, the applicability of this model has been very limited but it may possibly be relevant in this case. On the other hand, the light scattering results are not dependent upon a model for their interpretation. With regard to the light scattering experiments it appears that aside from gross experimental errors the only complication that could account for the difference indicated here would be the existence of some aggregates having the same spacial distribution and radius of gyration as the individual denatured DNA molecules. These aggregates would have to have such large sedimentation constants, however, that they would for the most part be removed by the usual centrifuging employed in clarifying light scattering solutions. Such effects were not observed.

In our opinion, then, the light scattering results should be accepted but this dilemma cannot be considered satisfactorily settled until the sedimentation and viscosity data are rigorously interpreted.

Other Characteristics of the Denatured State.—In Fig. 8 the titration curves of undenatured and denatured (15 min. at 100°) DNA with dilute HCl (0.00494 N) are shown. The change produced upon thermal denaturation is similar to that found for exposure to acid[19] and in thermal denaturation studies being currently reported by Cox and Peacocke.[3] This agreement supports the view that essentially the entire hydrogen-bonded structure is destroyed by the thermal denaturation at 100°.

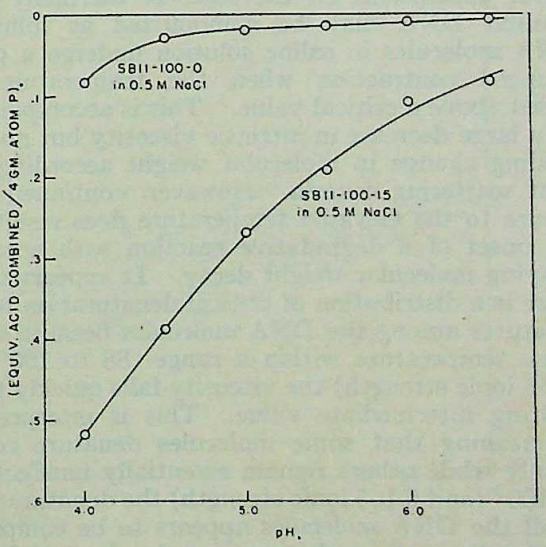

Fig. 8.—Potentiometric titration curve of samples SB-11 in 0.5 M NaCl before and after heating at 100° for 15 min.

If the hydrogen-bonded structure is essentially eliminated by the denaturation, it would be expected that the resulting molecule would be quite flexible in contrast to undenatured DNA. It is well known that typical polyelectrolyte molecules expand when the ionic strength is reduced and that this results in an increase in the reduced specific viscosity. That denatured DNA behaves in this manner while undenatured DNA does not is shown in Fig. 9 where the reduced specific viscosity is shown for solutions of each. In this experiment a portion of a DNA solution in saline–citrate (ionic strength = 0.165) was thermally denatured and then each solution was diluted stepwise with water producing thereby a continuous diminution in ionic strength. The rise in reduced specific viscosity in the case of the denatured DNA shows that its flexibility is comparable to that of ordinary flexible polyelectrolytes. The constancy shown

(17) L. Mandelkern and P. J. Flory, *J. Chem. Phys.*, **20**, 212 (1952).

(18) The use of a value of 2.6×10^6 in the foregoing equation has been shown to imply a very narrow molecular weight distribution [M. L. Hunt, S. Newman, H. A. Scheraga and P. J. Flory, *J. Phys. Chem.*, **60**, 1278 (1956)]. However, if the distribution were as broad as the most probable distribution ($M_z:M_w:M_n$::3:2:1) the calculated value of s_0 would still be 2.1 times that observed.

(19) G. R. Cox and A. R. Peacocke, *J. Chem. Soc.*, 2499 (1956).

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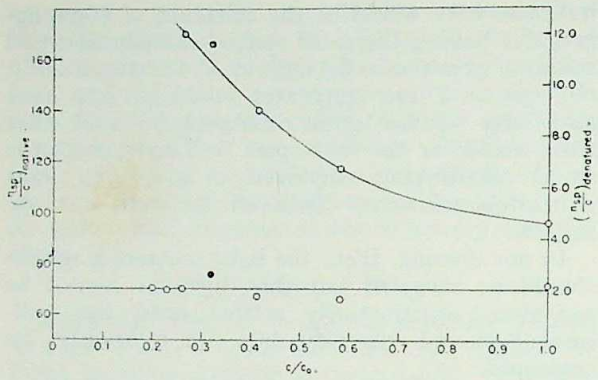

Fig. 9.—The expansion of denatured (15 minutes at 100°) DNA as a function of decreasing ionic strength as shown by η_{sp}/c.

by undenatured DNA reflects its rigidity. The experiment was conducted in the region of salt concentrations where intermolecular interactions are suppressed. At still lower ionic strengths these intermolecular interactions dominate and would mask any polyelectrolyte expansion.

Our conclusions on the state of thermally denatured DNA may be summarized as follows. DNA molecules in saline solution undergo a pronounced contraction when the temperature is raised above a critical value. This is accompanied by a large decrease in intrinsic viscosity but no attending change in molecular weight according to light scattering criteria. However, continued exposure to the elevated temperature does result in the onset of a degradative reaction with accompanying molecular weight decay. It appears that there is a distribution of critical denaturation temperatures among the DNA molecules because at a given temperature within a range (88 to 100° at 0.165 ionic strength) the viscosity falls quickly to a limiting intermediate value. This is interpreted as meaning that some molecules denature completely while others remain essentially unaffected. At 100° (and 0.165 ionic strength) the denaturation of all the DNA molecules appears to be complete in 15 min. and no change in molecular weight is evident. This condition is referred to as the completely denatured state. The extinction coefficient at the 259 mμ peak is 15% greater than before denaturation. The intrinsic viscosity is reduced by a factor of about 15 and the radius of gyration by a factor of 3. The sedimentation constant is apparently not greatly changed although this point in particular deserves further study. When the denaturation is carried out at higher concentrations than those employed here, reaggregation is apparent. This indicates a potential associating tendency of the denatured molecules that may only be operative intramolecularly at the higher dilution used in this work.

The Denaturation Process.—The course of the transition from the native to the denatured state has been followed principally by viscosity studies as illustrated in Figs. 1 and 2. If it is assumed that the intrinsic viscosity is a direct measure of the extent of the denaturation reaction and that the measurements made upon cooling to room temperature do represent the state of affairs existing at the temperature prior to cooling, two deductions are possible.

One of these recognizes that the viscosity has fallen to an equilibrium value within the time of one hour heating and that an apparent equilibrium constant can then be evaluated by interpreting the fractional lowering of the intrinsic viscosity in terms of fractional conversion of the native to the denatured state. (This interpretation of the data of Fig. 1 in terms of an equilibrium constant replaces the kinetic treatment mentioned previously.) When this is done for sample SB-11 a plot of the logarithm of the apparent equilibrium constant against the reciprocal of absolute temperature is found to be linear with the exception of the 100° point where it is known that substantial degradation has occurred. From the slope of this plot a heat of reaction of 110 kcal. and an entropy of reaction of 300 e.u. is derived. The data obtained in the presence of denaturing agents (Fig. 3) is fitted with the same heat of reaction and slightly higher entropy values (308 to 319 e.u.). Similar results are found for sample SC-1; for samples SB-1 and V-1 the values obtained are only one-third of those for the other two samples. These values emphasize that the denaturation reaction involves very large heat and entropy changes without chemical bond scission and in addition these two quantities offer a means of formally characterizing the course of the denaturation when it is carried through a series of temperatures with equilibration permitted at each temperature.

The other possible deduction relates to the kinetics rather than the equilibrium aspect of the reaction. If again the viscosity is assumed to represent quantitatively the progress of the reaction, the initial slope of the viscosity–time plots such as those in Fig. 2 can be subjected to the orthodox treatment of rate constants. When this is done for sample SC-1, the results are found to be linear in an Arrhenius plot (log of rate constant against reciprocal of absolute temperature) and from this an energy of activation of 145 kcal. and an entropy of activation of 325 e.u. is found.

Even if the assumptions on which these numerical results have been obtained are accepted their interpretation remains unclear because it is not known whether they refer to a mole of DNA molecules or to a mole of "segments" or intramolecular regions of DNA molecules. In other words the unit step by which the denaturation process proceeds is not known. The failure of sedimentation studies to settle this point is indeed unfortunate. However, by comparison with other hydrogen bonded systems it appears that the energy of activation and the heat of reaction per base pair should fall within the range of 1 to 10 kcal. Since there are of the order of 10,000 base pairs in a DNA molecule this would imply that values of 10,000 to 100,000 kcal. would be expected if the entire molecule passed from the native state through the transition state into the completely denatured state in one coördinate step. Hence it appears that the unit process cannot involve the entire molecule but only a segment of it composed of 10 to 100 base pairs.

The arguments that can be raised against this

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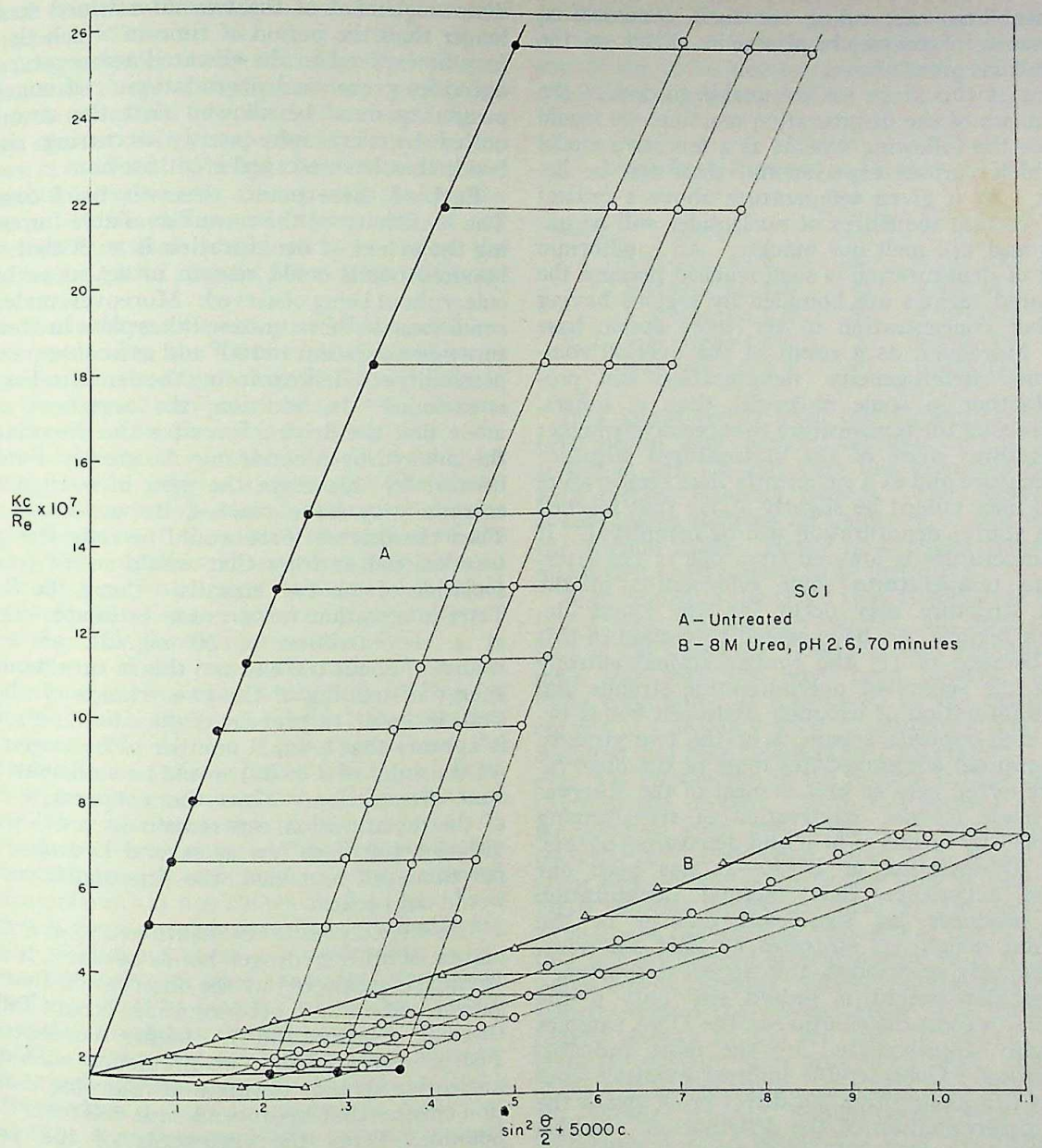

Fig. 10.—Angular distribution of scattered light of sample SC-1 before and after treatment with 8 *M* urea at *p*H 2.6.

interpretation are, however, very serious indeed. Two illustrations will suffice. If the denaturation proceeds by the melting out of one sequence of base pairs after another, the viscosity would be expected to fall sharply when the first few sequences melt out and then respond more gradually. Thus it would not represent a quantitative measure of the extent of the denaturation reaction as assumed in the above calculations. In addition, the previously mentioned difficulties in interpreting the intrinsic viscosity of the denatured state must also extend to the partially denatured state.[20] A more serious difficulty lies in the assumption that equilibrium is achieved at a given temperature and that the distribution so produced is preserved upon cooling. Obviously, much work will have to be done at the temperature of interest in order to assay directly the extent of denaturation and to prove or disprove this assumption.

Thus far no mention has been made of the possible effect of chemical heterogeneity, and indeed the present observations do not require its consideration. Since there are two types of base pairs and since these probably have a difference in stability, the compositional variations revealed by recent fractionation studies[21] would imply variations in the stability of different molecules and it may be expected that this variation would be exhibited among the sequences of segments which may be the unit of the denaturation process. If different regions of the DNA molecules had different ther-

(20) Another indication of the difficulty in interpreting the partially denatured state is shown by comparing the intrinsic viscosity and radius of gyration of material denatured at 94° (Figs. 1 and 4). In this case the radius of gyration has fallen to within 25% of the value for completely denatured DNA while the viscosity has only decreased half-way. Since the radius of gyration depends upon a higher average than the intrinsic viscosity this behavior is obviously incompatible with any simple model of the denaturation process based upon analogies with ordinary polymer molecules.

(21) See, for example, E. Chargaff and J. N. Davidson, "The Nucleic Acids," Vol. I, Academic Press, New York, N. Y., 1955, p. 358.

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mal stabilities depending on their composition, this would, of course, have serious effects on the calculations given above.

Since at this stage we are unable to deduce the mechanism of the denaturation reaction, we would propose the following scheme as a tentative model for which various experimental tests can be designed. At a given temperature above a critical value, certain sequences of nucleotides will be unstable and will melt out quickly. An equilibrium extent of denaturation is soon reached because the denatured regions are bounded by regions having a higher concentration of the more stable base pair. Moreover, as a result of the over-all compositional heterogeneity, denaturation will proceed further in some molecules than in others. Upon raising the temperature to successively higher temperatures more of the undenatured sequence will denature and at a sufficiently high temperature (which may indeed be slightly above that reached in this study) denaturation will be completed. If the temperature is lowered from one of the intermediate temperatures some reformation of the native structure may occur but the longer denatured regions can be expected to remain in this state because of (1) the configurational entropy gain of the separated polynucleotide strands and (2) the formation of irregular hydrogen bonds between non-opposite segments of the two strands. This proposal accommodates most of the observations reported here as well as most of the observations made on the inactivation of transforming principle[22] by means of heat and denaturing agents.

The Dissociation of DNA.—It has been our uniform experience that thermal denaturation alone produces no significant change in the molecular weight *as measured by light scattering*. As previously mentioned, this apparent constancy in molecular weight is indeed real only if the molecular weight distribution in the DNA samples is roughly approximated by the most probable distribution. Considerable indirect evidence does support this assumption but direct proof awaits the actual determination of the distribution. In this discussion this assumption is made.

At the ionic strength employed in this work an exposure of about 15 min. at 100° represents the most severe thermal treatment possible without inducing a gradual and continuous decay in molecular weight. In terms of light scattering, viscosity, titratability of basic groups[3] and the change in optical density at 259 mμ[2] the denaturation reaction has reached completion during this treatment. If this conclusion is strictly true, it would be expected that the two polynucleotide strands making up the DNA molecule according to the Watson–Crick structure would separate and the molecular weight would be reduced by half. Upon finding that this does not occur, we are led to conclude (1) that indeed not every hydrogen bond has been dissociated by this condition, (2) that the potential hydrogen bonding capacity of the polynucleotide chains is such that some hydrogen bonds form again between the two previously mated chains or (3) that the time required for the disentanglement of the two intertwined strands is longer than the period of time in which the DNA may be exposed to the elevated temperature without risking chemical degradation. Of course, the possibility must be allowed that the strands are united by very infrequently occurring chemical bonds that have escaped identification.

Each of these points deserves brief comment. The sensitivity of the means available for estimating the extent of denaturation is such that several hundred bonds could remain intact in each molecule without being observed. Moreover, under these conditions the denaturation takes place in a temperature range adjacent to 100° and as a consequence the possibility of safely exceeding the denaturation range is excluded. In addition, the argument can be made that the driving force for the dissociation of the last hydrogen bonds may be greatly diminished because by this stage the gain in configurational entropy may have reached its maximum value. Then the driving force would be only the gain in translational entropy that would result from dissociation of the two strands. Using the Sackur–Tetrode equation for a crude estimate, one finds at a concentration of 50 mg./dl. an entropy change of about 100 e.u. and this in turn requires an energy of binding of the two strands of about 30 kcal. in order to prevent dissociation. From this it appears that a small number of hydrogen bonds (of the order of 3 to 30) would be sufficient to prevent dissociation. Thus the coöperative nature of the denaturation can remain as previously envisioned, but if as few as several hydrogen bonds per thousand remained, the dissociation of DNA would not occur.

The second possibility mentioned above, the formation of other hydrogen bonds between denatured strands, is supported by the observation that aggregation and indeed gel-formation occurs following thermal denaturation at higher concentrations. The proximity of the two previously mated polynucleotide strands during and following denaturation ensures that hydrogen bonds will form if this is possible. From the arguments of the previous paragraph, only a few would be needed to keep the two strands together. At this point, it is relevant to emphasize that fairly extensive hydrogen bonding between the previously mated chains could develop when the temperature is lowered without contradicting any of the previously mentioned evidence. That is, if the newly formed bonds did not unite the previously matched base pairs but rather only led to a disorganized and incomplete pairing, the titratability of the groups involved would remain normal. Moreover, the observed 15% rise in optical density (measured at room temperature following thermal denaturation) is far short of the maximum possible, that is, the 55% attained in complete hydrolysis.[2] Consequently, the possibility of substantial hydrogen bonding of a disorganized type in the denatured material at room temperature appears possible. A structure of this kind would resemble a highly swollen gel particle and may offer a means of explaining the curious hydrodynamic behavior exhibited by denatured DNA.

The final possibility, the requirement of a long

(22) See, for example, S. Zamenhof in "Progress in Biophysics and Biophysical Chemistry," Vol. 6, Pergamon Press, London, 1956, p. 85.

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period of time for disentanglement, has a picturesque appeal. However, the time scale in which equally long polymer chains of rubber-like material explore a wide range of configurations, as exhibited in the fast retraction of stretched rubber, argues strongly against this view. Again, however, the existence of transient hydrogen bonds, forming and dissociating in such a way as to greatly prolong the time required for diffusional movements of the polynucleotide strands, could perhaps extend the time scale enough to account for a delay of the order of minutes.

With these three different possibilities, each capable of explaining the absence of dissociation in DNA under the conditions described, the failure to observe the dissociation is not unexpected. Nevertheless, it would be desirable to bring about the complete dissociation if possible. It would, for example, provide polydesoxyribonucleotide material for experimentation, permit through molecular weight measurement the direct assessment of the number of interruptions, if any, that may occur in the individual polynucleotide strands and it would add belatedly additional evidence for the existence of the Watson–Crick model in solution.

With this in mind, we have made several attempts to bring about the dissociation of DNA by carrying out both acid and thermal denaturation in the presence of 8 *M* urea. In a typical case, the DNA solution in saline–citrate which had been made 8 *M* in urea was brought to *p*H 2.6 for about 1 hour. Then the urea was removed by dialysis against saline–citrate solvent. The light scattering results on this sample compared with the untreated DNA (sample SC-1) are shown in Fig. 10. It is clear that there is no change in the light scattering molecular weight but there is a contraction to the much smaller molecular size; the radius of gyration changes from 2600 to 950 Å.; the value characteristic of the completely denatured state.

Repetition of this and some related experiments, some of which are summarized in Table II, have failed to produce a drop to one-half in molecular weight unless degrading conditions were maintained for the right length of time (see *p*H 2.4 entry in table). However, there are so many possibilities to explore that eventual success in obtaining dissociation without degradation is by no means unlikely. However, it appears appropriate to note here our doubts concerning the claim of Alexander and Stacey[23,24] to have achieved this dissociation. They have reported that a fall to one-half of the original molecular weight could be brought about by (1) exposure to *p*H 2.2 followed by neutralization and (2) exposure to 4 *M* urea at room temperature. In the latter case, a previous treatment of the DNA with ethylenediamine tetraacetate was found to be necessary for thymus DNA but not for herring sperm DNA.

(23) P. Alexander and K. A. Stacey, *Biochem. J.*, **60**, 194 (1955).
(24) P. Alexander and K. A. Stacey, *Nature*, **176**, 162 (1955).

TABLE II

SUMMARY OF ATTEMPTS TO DISSOCIATE DNA

Sample	Condition	Time of exposure, min.	After removal of urea M_w	ρg, Å.
V-1	8 *M* urea, *p*H 2.7	150	8,100,000	1200
	8 *M* urea, *p*H 2.6	45	8,400,000	1120
	8 *M* urea, *p*H 2.4	30	4,100,000	1060
SC-1	8 *M* urea, *p*H 2.6	70	6,700,000	950
	8 *M* urea, *p*H 2.6	70	6,700,000	950

In a recent report from this Laboratory[4] it has been shown that chemical degradation can be detected at *p*H 2.6 and that this increases rapidly with further lowering thereof. The degradation is continuous showing no tendency to stop at half the original value. Hence we consider the above-mentioned observations to be fortuitous.

With regard to the claim that dissociation occurs in 4 *M* urea we can only suggest that during some part of the operation of adding and removing the urea, salt may not have been present. Under these conditions, as mentioned in the earlier discussion of Conway's work, denaturation may have occurred and been followed by dissociation. However, the implication in the reports is that salt was continuously present. With salt present at room temperature even denaturation, a necessary prerequisite to dissociation, does not occur. This point was checked in particular with herring sperm DNA samples kindly provided by Dr. Alexander. In this case, the intrinsic viscosity of the DNA solution was unchanged after exposure to 4 *M* urea in saline–citrate solvent. Moreover, the urea treated sample showed the characteristic 15% increase in optical density at 259 mμ and the 12-fold fall in intrinsic viscosity after heating to 100°. This also showed that the native structure was intact after the exposure to urea. Similar results were obtained with thymus DNA before and after treatment with ethylenediamine tetraacetate. It is on this basis that the present evidence for the dissociation of DNA seems unconvincing.

Acknowledgments.—This work was supported by Public Health Service Grant (C2170(C5)). One of us (S.A.R.) is pleased to acknowledge the award of a Union Carbide and Carbon Fellowship (1953–54) and a Charles A. Coffin Fellowship (1954–55). We are indebted to Dr. N. S. Simmons for two of the DNA samples used in this work and for many helpful discussions.

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[CONTRIBUTION FROM THE LABORATORY OF THE CHILDREN'S CANCER RESEARCH FOUNDATION]

Polypeptides. XV.[1] Infrared Spectroscopy and the Kinetics of the Synthesis of Polypeptides: Primary Amine Initiated Reactions

BY M. IDELSON AND E. R. BLOUT[2]

RECEIVED MARCH 21, 1957

An infrared spectroscopic method for determining the kinetics of polymerizing systems has been developed. This method has been applied to the determination of the kinetics of the primary amine initiated polymerization of γ-benzyl-L-glutamate-N-carboxyanhydride. Through the infrared kinetic studies it has been shown that the two successive polymerization rate constants k_{2a}(slower) and k_{2b}(faster), are correlated with the formation of low molecular weight (β_L)-polypeptide and high molecular weight (α) polypeptide, respectively. When the polymerization is carried out in dioxane solution the β_L-polypeptide has a degree of polymerization between 3 and 6. Through the use of deuterium labeled hexylamine it has been shown that the β_L-polypeptide is the precursor of the α-polypeptide. This fact and the DP data on the β_L-fractions indicate that the α-helical configuration manifests itself at DP's not much above 6. Measurements on pure α-fractions of primary amine initiated poly-γ-benzyl-L-glutamate show that the DP_w/DP_n is approximately 2 which is indicative of the moderate polydispersity expected for the most probable molecular weight distribution. The infrared kinetic method has the advantage of directly measuring simultaneously both the disappearance of reactant (monomer) and the appearance of product (polypeptide). When different products with different infrared spectra are formed, either simultaneously or consecutively (β_L- and α-polypeptides), their production may be correlated with the reaction rate.

Introduction

Amine initiation has been used for the polymerization of various α-amino acid N-carboxyanhydrides (NCAs) to polypeptides,[3] and the kinetics of the reaction has been treated theoretically[4] as well as investigated experimentally by gasometric methods,[5,6] through which Doty and Lundberg have found that the polymerization exhibits two successive propagation rates. In this paper we describe an infrared spectroscopic technique used to measure the rates of polymerization and present the results of an investigation of amine initiated polymerizations of such anhydrides.[7] Through this infrared method it is shown (1) that there are at least three products of the polymerization reaction, and (2) that the two main products are low molecular weight (β_L) polypeptides which are formed at a slow rate, and higher molecular weight (α) polypeptides, which are formed at a many times faster rate. Finally it is shown that the β_L-polypeptides are precursors of, and are converted into α polypeptides.

We henceforth designate low molecular weight "β" polypeptides as β_L-polymers to differentiate from extended configurations of high molecular weight polypeptides which have also been called β-polypeptides. These latter materials can assume helical configurations under certain conditions and therefore they should be differentiated from the β_L-polymers which cannot assume a helical configuration. We designate the β-forms of high molecular weight polypeptides as β_h-polymers. It is recognized that there may be a molecular weight range of polypeptides having properties overlapping those shown by pure β_L- and β_h-polypeptides.

The method used for determining the kinetics of the polymerization reaction by means of infrared spectroscopy involves determining the consumption of NCA in a polymerizing system. The decrease in the absorbance of the characteristic NCA C=O stretching vibrations at 1860 and 1790 cm.$^{-1}$ is measured as a function of time. Typical spectral data from which such measurements are made are shown in Fig. 1. The solid line (curve A) shows the spectrum of the NCA at the start of the reaction. In addition to the two carbonyl bands due to the NCA moiety, there is an additional C=O absorption frequency at 1735 cm.$^{-1}$ due to the benzyl ester carbonyl group. This band remains unchanged during the reaction and serves as a convenient "internal standard" for the reaction. The dotted line shows the spectrum obtained when approximately 50% of the NCA has been consumed. Of course no change is found in the intensity of the 1735 cm.$^{-1}$ band, but the 1860 cm.$^{-1}$ band has decreased to about 50% of its initial value. In addition, two new bands have appeared, one at 1655 cm.$^{-1}$ and one at 1550 cm.$^{-1}$, which are due to the secondary amide (peptide) groups formed during polymerization. These polymer absorption bands are due, respectively, to C=O stretch (amide I) and NH deformation coupled with C=N stretch (amide II).[8] At the end of the reaction there is no absorption due to the carbonyl bands of the NCA; a typical spectrum for this case is shown by curve C, the dashed line in Fig. 1.

Experimental

Equipment.—All infrared measurements were performed on a Perkin–Elmer Model 21 Double-Beam Spectrometer using a sodium chloride prism. The sample and reference cells were matched pairs with rock salt windows; most experiments were carried out in 0.2 mm. cells at an initial anhydride concentration of 4%. A few experiments were performed in 1 mm. cells with an initial anhydride concentration of 1%. Measurements were made in an air-conditioned room whose temperature was held to ±1°.

The temperature of the polymerizing solution was experimentally determined by means of a thermocouple placed in the cell during a polymerization reaction. The tempera-

(1) For the last papers in this series see XIV, P. Doty and R. D. Lundberg, *Proc. Natl. Acad. Sci.*, **43**, 213 (1957). XIII, E. R. Blout and H. Lenormant, *Nature*, **179**, 960 (1957).

(2) Chemical Research Laboratory, Polaroid Corporation, Cambridge 39, Massachusetts.

(3) For references up to 1950 see E. Katchalski, in *Advances in Protein Chem., VI*, 123 (1951). For more recent references see C. H. Bamford, A. Elliott and W. E. Hanby "Synthetic Polypeptides," Academic Press, New York, N.Y., 1956.

(4) E. Katchalski, Y. Shalitin and M. Gehatia, THIS JOURNAL, **77**, 1925 (1955).

(5) (a) S. G. Waley and J. Watson, *Proc. Roy. Soc. (London)*, **A199**, 499 (1948); (b) D. G. H. Ballard and C. H. Bamford, *ibid*, **223**, 495 (1954).

(6) (a) P. Doty and R. D. Lundberg, THIS JOURNAL, **78**, 4810 (1956); (b) R. D. Lundberg and P. Doty, *ibid.*, **79**, 3961 (1957).

(7) We use NCA henceforth to mean α-amino acid N-carboxyanhydrides.

(8) R. D. B. Fraser and W. C. Price, *Nature*, **170**, 490 (1952).

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ture was 34 ± 1°. The ambient temperature around the absorption cells was maintained at 31 ± 1°.

Because of the effects of small amounts of impurities, especially hydroxide,[9] all glassware was cleaned in chromic acid cleaning solution and rinsed in distilled water until the water was neutral to brom cresol purple indicator.

For the gasometric method the apparatus used for measuring the evolution of carbon dioxide was essentially that described by Doty and Lundberg.[6] The method uses the change in conductivity of a 0.01 *M* barium hydroxide solution as the carbon dioxide is absorbed with the formation of barium carbonate.

Methods.—The Infrared Kinetic Method.—The γ-benzyl-L-glutamate-N-carboxyanhydride,[9] which is stored at −30°, was weighed at −30° into an erlenmeyer flask which was placed in a desiccator and allowed to warm to room temperature. The NCA was then dissolved in a portion of dioxane (or other solvent) and the initiator was thoroughly mixed in a separate flask with the remainder of the dioxane. The anhydride solution was poured into the initiator solution with vigorous swirling. A portion of this solution was transferred to the infrared absorption cell and measurements were begun. Spectra of the polymerizing solution were taken at convenient time intervals through the wave length range 1500 to 1900 cm.$^{-1}$ until the reaction was complete. Pure dioxane was used in the reference cell. The plot of log of absorbancy (or optical density) at 1860 and/or 1790 cm.$^{-1}$ gave the rate curve directly (*cf.*, Fig. 2).

The rate constants derived from anhydride consumption k_{2a} and k_{2b}, were calculated from eq. 1–5.

$$A + I \longrightarrow P + CO_2 \quad (1)$$

$$P + nA \longrightarrow P_{n+1} + nCO_2 \quad (2)$$

$$[P] + \Sigma[P_{n+1}] = [I] \quad (3)$$

$$-\frac{d[A]}{dt} = k[A][I] \quad (4)$$

Equation 1 represents the initiation step which is much faster than the subsequent polymerization reactions indicated by eq. 2. If it is assumed that, during a polymerization which requires a few hours for completion, termination reactions are negligible, eq. 3 is valid; that is the concentration of all the growing chains is constant and the same as the original initiator concentration, [I]. Under these circumstances the rate eq. 4 expresses the change in concentration of NCA, [A], at any time, *t*. The integrated form of this rate equation gives 5, the equation for a pseudo-first-order reaction, where OD represents the optical density of the anhydride absorption bands at 1860 or 1790 cm.$^{-1}$ and is directly proportional to [A]

$$k = \frac{\ln (OD_1/OD_2)}{(t_2 - t_1)[I]} \quad (5)$$

For a comparison of this idealized reaction scheme see the Discussion section and footnote 13.

While polymerization was going on in the sample cell used for the rate measurements it was proceeding also in the remaining large portion of the solution at room temperature. The polymer in this portion of the reaction mixture was isolated the following morning by precipitation into diisopropyl ether. To separate the "α"- and "β"-polymer fractions the following procedure was used. The "β"-polypeptide fraction is the lower molecular weight, more soluble portion of the product. It is soluble in hot ethanol and was separated from the total precipitate by extraction. After removal of the solvent from the ethanol-soluble fraction and drying, its infrared spectrum was determined and found to be that of essentially pure "β_L" material; the ethanol insoluble fraction gave an infrared spectrum characteristic of higher molecular weight "α" polymer.[10,11] The viscosity of the ethanol-insoluble α fraction in dichloroacetic acid was used to determine its molecular weight.[9]

Carbon Dioxide Evolution Kinetic Method.—The anhydride sample was weighed into a reaction vessel at −30° and warmed to room temperature in a desiccator. The dioxane and initiator were added, the vessel was attached

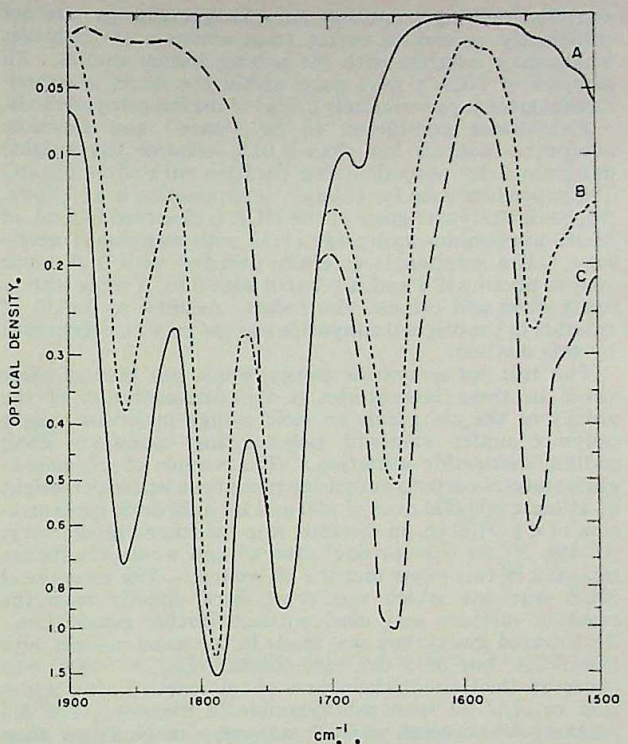

Fig. 1.—Infrared spectra of 4% (by weight) solutions of γ-benzyl-L-glutamate-N-carboxyanhydride in dioxane measured during the polymerization; A/I = 20; initiator, *n*-hexylamine: A———, spectrum at start of reaction; B - - - - -, spectrum at time 50% of NCA consumed; C — — —, spectrum at end of reaction.

to the rest of the apparatus in a thermostated water-bath at 25 ± 0.02° and a stream of purified dry nitrogen saturated at 25° with dioxane was bubbled through the polymerization mixture. The evolved carbon dioxide was carried into and absorbed by a 0.0100 *M* $Ba(OH)_2$ solution in the conductivity cell. The addition of a few drops of *n*-butanol to the $Ba(OH)_2$ solution was essential to disperse the gas for efficient absorption of the carbon dioxide.

The extent of the reaction was calculated from eq. 6 and 7

$$\alpha = WM\left(\frac{R - R_0}{R}\right) \quad (6)$$

$$A = A_0 - \alpha \quad (7)$$

where α was the number of moles of CO_2 evolved; *W* was the weight in grams of $Ba(OH)_2$ solution of molality *M*; R_0 was the initial resistance of the $Ba(OH)_2$ solution and *R* the resistance at time *t*; A_0 was the initial quantity of anhydride in moles and *A* the quantity of anhydride remaining at time *t*. The plot of log A_0/A *vs.* *t* gave the rate curve, and eq. 8 gives the rate constant.

$$k = \frac{\ln \frac{A_0}{A_2} - \ln \frac{A_0}{A_1}}{(t_2 - t_1)[I]} \quad (8)$$

The polymer was isolated as described under the infrared method.

Materials. Anhydrides.—Although most of the work reported in this paper was performed using a single preparation of γ-benzyl-L-glutamate-N-carboxyanhydride (No. MI-I-62C), a number of other anhydride samples, prepared by the same method,[9] also were investigated. At A/I's of 20 and below all anhydrides gave the same values for k_{2a} and k_{2b}. Above A/I 20, however, the polymerization rate k_{2b} was not identical for all preparations, although the k_{2a} was essentially constant from preparation to preparation. Some of the values are shown in Table I. Our experience has been that it is very difficult to prepare two samples of anhydride which behave identically in *all* respects. The usual tests for purity of organic materials, *e.g.*, elementary

(9) E. R. Blout and R. H. Karlson, THIS JOURNAL, **78**, 941 (1956).
(10) J. C. Mitchell, A. E. Woodward and P. Doty, *ibid.*, **79**, 3955 (1957).
(11) E. R. Blout and A. Asadourian, *ibid.*, **78**, 955 (1956).

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analysis, melting point and infrared spectroscopy, are not sufficiently precise to detect trace amounts of impurities which may interfere with the polymerization studies. All samples of NCA's were pure within the limits of experimental error (approximately 0.3%) of the foregoing methods.

Anhydrides considered to be "pure" and therefore acceptable contain less than 0.01% chloride (by weight) determined by potentiometric titration with silver nitrate. The procedure used for chloride determination is as follows. Approximately one gram of the NCA is dissolved in 5 ml. of dilute ammonium hydroxide (1:1) with warming if necessary. The solution is carefully acidified with 6 *N* nitric acid to about *p*H 4 and is titrated with 0.01 *N* silver nitrate using silver and calomel electrodes. As little as 0.01% of chloride in the original anhydride sample may be determined by this method.

The test for anhydride purity which has been of some value in these laboratories is the demonstration of the ability of the anhydride to yield a high molecular weight polymer under standard polymerizing conditions using sodium methoxide initiation.[9] If a sample of γ-benzyl-L-glutamate-N-carboxyanhydride produces a molecular weight of at least 360,000 at *A*/*I* 200 and an anhydride concentration of 4 g./100 cc. in dioxane, it is considered satisfactory. All the NCAs (except one) studied and whose results are reported in this paper met the above test. The exceptional NCA was one which was crystallized directly from the reaction mixture and used without further purification. An infrared kinetic run was made in the usual manner with this NCA, but only one rate constant (k_{2a} = 0.006) was observed throughout the course of the reaction after initiation to *A*/*I* 20 with *n*-hexylamine in dioxane. The β_L-portion of the total product was very much larger than usually observed at this *A*/*I*.[11] With this impure anhydride the β_L-fraction was about 45% of the total product whereas usually it is less than 20% of the product. It was determined subsequently that the NCA used in this experiment had 0.13% by weight (1 mole %) of chloride ion, which was far greater than the amount found (less than 0.01%) in acceptable NCAs.[9]

Initiators.—The *n*-hexylamine was fractionally distilled from calcium hydride; b.p. 131°. It was diluted 1:9 with dioxane and dispensed by means of a Gilmont ultramicroburet (Emil Greiner Co.).

Solvents.—The solvents were purified as previously described.[9] Half of the freshly distilled dioxane froze over a range of 0.25°.

Preparation of Polypeptides from Deuterium Labeled Amine. (a) ***n*-Hexylamine-1d_2.**—5.76 g. of *n*-capronitrile (0.0595 mole) in 10 ml. of anhydrous ether was added dropwise to a solution of 2.50 g. of lithium aluminum deuteride (0.0595 mole) in 50 ml. of ether in a 250-ml. 3-necked flask equipped with a Hershberg stirrer, a dropping funnel with pressure equalizer, and a condenser protected by a soda lime tube. The addition required about ½ hr. and the mixture was stirred for an additional ten minutes. It was then hydrolyzed very carefully with the minimum amount of water to destroy excess deuteride and the complex; a few grams of anhydrous magnesium sulfate was added to dry the mixture which was filtered with suction; the solids were thoroughly washed several times with anhydrous ether. The combined ether solutions were carefully distilled through a 10-cm. Vigreux column; the *n*-hexylamine-1-d_2 fraction boiling at 130–131° was collected and weighed 3.36 g. (55%); $n^{25}D$ 1.4210; for 100% 1-d_2 % D calcd., 13.3; % D found, 11.8.

(b) **Deuterium Labeled Polypeptides.**—10.2 g. of γ-benzyl-L-glutamate-N-carboxyanhydride was dissolved in 250 ml. of dioxane and 1.0 g. of *n*-hexylamine-1-d_2 (*A*/*I* = 4) was added. When the polymerization was complete, the dioxane was removed by freeze drying. Extraction of the product in a Soxhlet with ethyl ether gave β_L-polymer which was not soluble in cold ethyl ether and "γ"-polymer which remained in solution at 0°. The β_L-polymer was filtered and washed with ethyl ether, redissolved in dioxane, and freeze dried (1.0 g.). The infrared spectrum of this material (product A) showed it to be pure β_L-polymer.

The fraction of the original polymer which was insoluble in ethyl ether was dried at room temperature and then extracted with ethanol. The cooled ethanol solution yielded an additional β_L-fraction which was contaminated with some α-polymer, while the ethanol insoluble portion was shown to be pure α-polymer (product B).

End group (free amino) titration of the γ-polymer and ether extracted β_L-polymer (product A) indicated a degree of polymerization (DP) of 4 and 5.9, respectively. These values are equal to or higher than the actual DP, since any cyclization to substituted α-pyrrolidone[12] would increase the DP measured by titration as compared to the actual DP. The molecular weights of these materials were measured by the Archibald method[10,13]; γ-fraction, mol. wt. = 400, DP (subtracting 1 molecule hexylamine) = 1.4; β_L-fraction, mol.wt. = 800, DP_w = 3.2 (product A).

(c) **Initiation with D-Labeled β_L-Polymer.**—0.265 g. of above β_L-polymer (A) was dissolved in 25 ml. of dioxane and 1.00 g. of anhydride was added (*A*/*I* = 20, or theoretical DP = 26). After completion of the reaction the dioxane was lyophilized, and the product was extracted with ethanol. The ethanol extract contained 0.261 g. of β_L-polymer (product C) while the residue was α polymer contaminated with some β_L-polymer. The remaining β_L-polymer in the α-polymer was removed by formic acid extraction[11] and weighed 0.149 g. (product C′). This polymer (product C′) is insoluble in hot ethanol and is higher molecular weight than product C; it therefore contains less deuterium than product C. The formic acid insoluble portion was pure α polymer and weighed 0.688 g. (product D). The results of these experiments are given in Table III.

Determination of Free Amino Groups in Polymers.—The terminal amino groups were titrated with perchloric acid in glacial acetic acid using crystal violet as indicator. 0.0583 g. of product A (β_L-polymer) was dissolved in 5 ml. of glacial acetic acid containing a drop of crystal violet indicator solution (0.1% in glacial acetic acid). Using a Gilmont ultramicroburet, this titration required 0.5055 ml. of 0.081 *N* perchloric acid to reach the green end-point of the indicator. The indicator blank was negligible. Found free amino groups in polymer product *A* = 7.16 $\times 10^{-4}$ meq./mg.

Molecular Weight Determinations.—The reduced specific viscosities of poly-γ-benzyl-L-glutamates in dichloroacetic acid solution were used to obtain the molecular weights in a manner previously described.[9,16] This method of obtaining molecular weights is sufficiently accurate (±10%) for molecular weights above 20,000, *i.e.*, degree of polymerization (DP) >90. It was therefore used for the total reaction products or for the α-polypeptide fraction. The α-polypeptide fractions of *n*-hexylamine initiated polymerizations of γ-benzyl-L-glutamate-N-carboxyanhydride at *A*/*I*'s of 10, 20, 40 and 80 were separated from the β_L-fraction as described above. In each case the α fraction had a weight average DP between 100 and 300 which appeared to be essentially independent of *A*/*I* over the range *A*/*I* 10 to 80. However, as the *A*/*I* was increased, the amount of α fraction increased (*cf.*, ref. 9).

Results

It has been shown previously[10,11] that initiation of γ-benzyl-L-glutamate anhydride with primary amine yields two products, the first a low molecular weight peptide, which is soluble in formic acid and designated β_L-polymer; the second a higher molecular weight polypeptide which is insoluble in formic acid and has been designated α-polymer. The α-material shows a strong C=O amide I absorption at 1655 cm.$^{-1}$, both in solution and in the solid state, whereas the β_L-material shows an amide I frequency at 1630 cm.$^{-1}$ in the solid state and around 1675 cm.$^{-1}$ in dilute dioxane solution. It is this background information that is used in the interpretation of the following results.

Infrared Data.—In the present investigation *n*-hexylamine initiated polymerizations of γ-benzyl-L-glutamate anhydride were performed in dioxane solution of *A*/*I*'s of 4, 10, 20 and 40. Plots

(12) W. C. Hanby, S. G. Waley and J. Watson, *J. Chem. Soc.*, 3239 (1950).

(13) W. J. Archibald, *J. Phys. Colloid Chem.*, **51**, 1204 (1947); S. M. Klainer and G. Kegeles, *ibid.*, **59**, 952 (1955); *Arch. Biochem. Biophys.*, **68**, [illegible]

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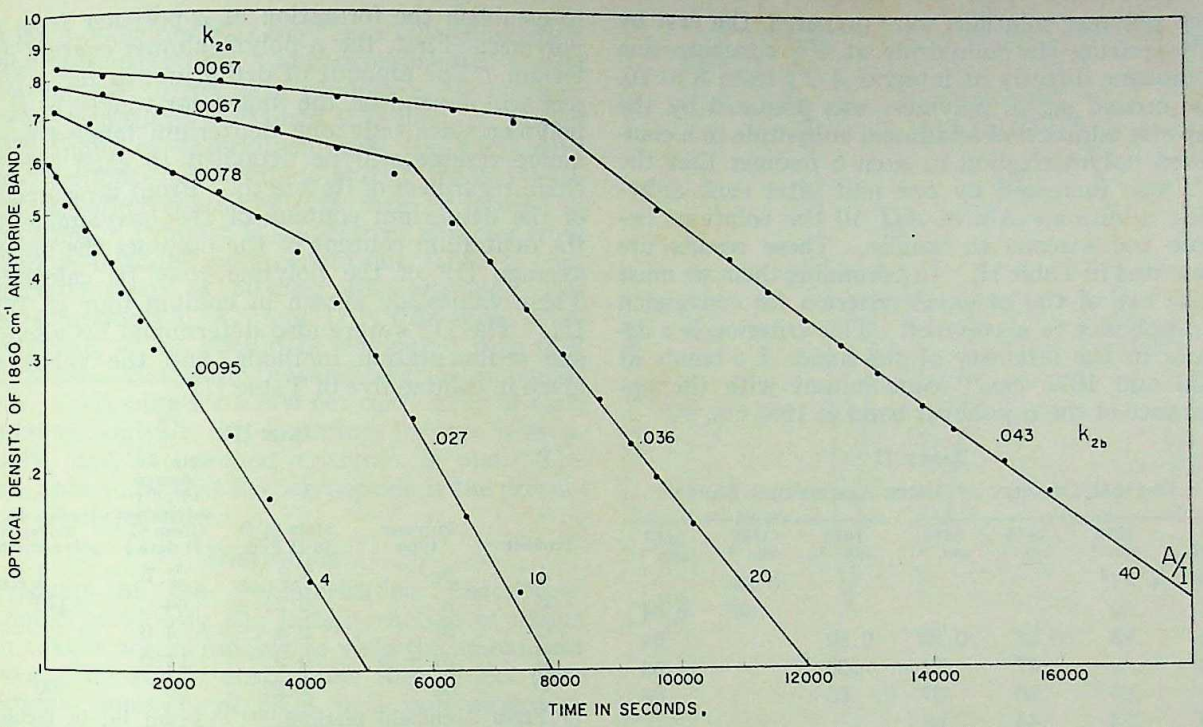

Fig. 2.—Plots of optical density of 1860 cm.$^{-1}$ NCA C=O band measured as a function of time during *n*-hexylamine initiated polymerizations of γ-benzyl-L-glutamate-N-carboxyanhydride at A/I 4, 10, 20 and 40. The initial rate constants, k_{2a}, are shown below the symbol. The final rates, k_{2b}, are shown in a horizontal line with the symbol.

of the rate of disappearance of anhydride as a function of time for these A/I's are shown in Fig. 2.

The reaction rate may be determined by following either the monomer (NCA) concentration or the peptide (polymer) concentration. If the rate is calculated from the appearance of polymer, the optical density must be measured at the end of the reaction, and this value appears in the calculation of every point on the rate curve. This measurement, therefore, requires the greatest accuracy in precisely the region where optical density measurements are least accurate—the region of high densities. However, by following the monomer (NCA) concentration, there is no single measurement upon which all the calculations depend. Further, the measurement of OD_∞ (the zero line) is not necessary for the monomer band method because its value disappears in the calculation of the rate equation. From these data rate constants have been calculated[15] as shown in Table I.

Table I

Rate Constants from Infrared and Carbon Dioxide Evolution Methods

A/I	k_{2a} (l. mole^{-1} sec.$^{-1}$ × 10^3) Infrared[a]	k_{2a} CO_2[b]	k_{2b} (l. mole^{-1} sec.$^{-1}$ × 10^3) Infrared[a]	k_{2b} CO_2[b]	No. of experiments Infrared	No. of experiments CO_2
4	9.5				1	
10	7.3 ± 0.3	5.1 ± 0.2	25 ± 2	23 ± 1	3	3
20	8.0 ± 1.2	4.7 ± .2	31 ± 6	34 ± 2	7	2
40	7.0 ± 0.7	4.9 ± .6	44 ± 10	47 ± 3	4	3
80	6.9 ± .6		52 ± 3		3	

[a] Measurements using infrared method were at 34 ± 1°. [b] Measurements using CO_2 method were at 25 ± 0.02°.

Katchalski, *et al.*,[4] have discussed theoretically the successive stages in the polymerization of NCA's—initiation (k_1), polymerization (k_2), and termination (k_3 and k_4). The *n*-hexylamine first reacts very rapidly with the anhydride at a rate designated k_1. This reaction was not measured, but it is about one order of magnitude faster than the polymerization reactions. For this reason we may assume that the reaction of anhydride with hexylamine is instantaneous and therefore denote the k_{2a} reaction as the first reaction. At A/I 4 the anhydride disappears at a constant rate, whereas at A/I's of 10 and above the rate of disappearance of anhydride is slow at the beginning (k_{2a}) but later increases several-fold (k_{2b}). Thus successive reactions proceeding at two different rates occur during the course of this polymerization as first demonstrated by Doty and Lundberg by using a gasometric method.[6] If, however, one examines the spectral data from which the plots in Fig. 2 were obtained, it is observed that when the anhydride is being consumed at a low rate (at A/I 4, or k_{2a} in A/I's 10, 20 and 40), the polymer that is formed shows amide I absorption at 1675 cm.$^{-1}$. The 1630 cm.$^{-1}$ band is not seen at A/I's of 10 and above since the concentration of β_L-polymer in the solution is too low.[11] On the other hand, when the reaction proceeds at the faster rate, k_{2b}, α-polymer is formed, as shown by the appearance and increasing intensity of the 1655 cm.$^{-1}$ (amide I) and 1550 cm.$^{-1}$ (amide II) absorption bands. It is now logical to inquire whether the low molecular weight β_L-material is the precursor of the high molecular weight α-polymer.

An attempt was made to answer this question by noting whether, in a series of polymerizations at A/I's from 3 to 10, the total amount of β_L-polymer, as indicated by infrared spectra of the solutions, decreased with increasing A/I. Two sets of

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such polymer solutions were prepared, the first by polymerizing the anhydride at 4% concentration in dioxane directly at integral A/I's from 3 to 10. The second set of polymers was prepared by the stepwise addition of additional anhydride to a completed polymerization in such a manner that the A/I was increased by one unit after each anhydride addition. Above A/I 10 the solutions became too viscous to handle. These results are presented in Table II. In examining them we must make use of the assumed criterion for conversion of β-polymer to α-polymer. This criterion is a *decrease* in the intensity of the amide I β-bands at 1630 and 1675 cm.$^{-1}$ concomitant with the appearance of the α-polymer band at 1655 cm.$^{-1}$.

TABLE II

OPTICAL DENSITY OF AMIDE ABSORPTION BANDS

	Solution			Solid		
A/I	1675 cm.$^{-1}$	1655 cm.$^{-1}$	1630 cm.$^{-1}$	1655 cm.$^{-1}$	1640 cm.$^{-1}$	1630 cm.$^{-1}$
3[a]	0.47[d]				0.59	
4	.39				.55[c]	0.64
5	.33	0.36	0.23	0.50		.64
6	.29	.37	.31	.56		.63
7	.25	.40	.37	.53		.66
9	.23	.44	.37			
10	.21	.54	.36			
4[b]	.39					
5	.33	.31	.31	.50[c]		.71
6	.27	.37	.43	.55		.70
7	.25	.38	.43	.58		.65
8	.25	.40	.39	.63		.66
9	.21	.48	.43			

[a] A/I by successive integral additions of NCA. [b] A/I by direct initiation of NCA. [c] Shoulder. [d] All optical density values are adjusted to a constant benzyl ester band at 1735 cm.$^{-1}$ of 0.60 optical density.

The data in Table II show that the absorption of the 1630 cm.$^{-1}$ band reaches a maximum at A/I 7 and does not thereafter decrease within experimental error. The 1675 cm.$^{-1}$ band, however, shows a uniform decrease in its intensity as the A/I is increased. It has been shown previously that dilute solutions of β_L-polypeptides absorb at 1675 cm.$^{-1}$, while concentrated solutions or solid films absorb at 1630 cm.$^{-1}$.[11] From results reported here it may be seen that at A/I 3 the amide I band is located at 1675 cm.$^{-1}$ and is very intense (Fig. 3). At A/I 4 this absorption is weaker (Table III) and continues to decrease in intensity as the A/I increases. The 1630 cm.$^{-1}$ appears for the first time in solution at A/I 5 and increases to a constant maximum value at A/I 6–7. The 1655 cm.$^{-1}$ (α-amide I band) also appears at A/I 5 and continues to increase with increasing A/I. Because there is no significant decrease in the amount of β_L-polymer, these data, unfortunately, neither demonstrate nor exclude the conversion of β_L-polymer to α-polymer.

Deuterium Labeled Polypeptides.—To establish β_L-polypeptide is the precursor of the α-polymer, β_L-polymer labeled with deuterium in the *n*-hexylamine initiator was prepared (see Experimental section). The pure deuterium labeled β_L-polymer was used to initiate additional anhydride at A/I 20. Two criteria have to be satisfied to establish the formation of α-polymer from β_L-polymer. First, the α-polymer must contain deuterium. The amount of deuterium in the α-polymer will depend on the molecular weight of the α polymer since only one deuterium labeled hexylamine residue will be attached to each polymer chain regardless of its length. From measurement of the deuterium content of the hexylamine and the deuterium content of the polymer the number average DP of the polymer may be calculated. These values are shown in column four of Table III. The DP's were also determined by viscosity and sedimentation methods, and the values are given in column five of Table III.

TABLE III

Product	Polymer type	Mole % D in H Fed.	No. av. degree of polymerization (from % D detn.)	Wt. av. degree of polymerization
A	β_L	3.8	2.7	3.2[a]
B	α	0.21	64	140[b]
C	β_L	2.4	4.6	
C′	$\beta_L + \alpha$	0.9	14.0	
D	α	0.22	60	100[b]

[a] From Archibald method.[13,14] [b] From $[\eta]$ in dichloroacetic acid.[15,16]

The weight average DPs are seen to be consistently higher than the number average DPs and the ratio DP_w/DP_n, indicative of the polydispersity of the polymer, is approximately 2 for the pure α-fractions. This is the value expected for the most probable distribution of molecular weights and is the minimum value that could be expected in this situation. It may therefore be concluded that the DP_n, derived from deuterium determination, is not in disagreement with DP_w derived from viscosity measurements; hence the first criterion for the growth of β_L-polymer into α-polymer is established.

The second criterion for the growth of β_L to α-polymers is that there must be a deuterium balance in the experiments. More exactly, the deuterium content of the deuterium labeled β_L-polymer used for the initiator should equal the sum of the deuterium contents in the newly formed α-polymer

(14) We are indebted to Dr. P. Doty and Mr. J. C. Mitchell for these measurements.

(15) The equation for the calculation of k_{2b} is not strictly correct. At least three reactions must be proceeding simultaneously during this portion of the reaction. Since it has been shown the β_L-polypeptide is the precursor of α polymer (*vide infra*), and since the β_L-concentration appears to reach a constant maximum, an equilibrium must exist between production of new (or longer) β_L-polymer and the loss of β_L-polymer in forming α polymer chains.

Further, the rate of conversion of β_L-chains to rapidly polymerizing α-chains must be in equilibrium with some chain termination process (or processes).[4] During the faster portion of the reaction there are occurring simultaneously (a) slow production of β_L-polymers, (b) rapid growth of α-polymer, and (c) termination processes. β_L-polymerization and termination are neglected, both of which consume NCA; it is not the initiator (*n*-hexylamine) concentration, but rather the *growing* α-chain concentration which must appear in the calculation of k_2b (eq. 1 and 4). Although the final concentration of α-chains may be determined from molecular weight measurement after the reaction is completed, this does not reveal what the actual concentration of growing chains is at any instant during the polymerization. The values of k_{2b} in Table I are, therefore, less than the minimum possible value of the actual rate constant.

(16) P. Doty, J. H. Bradbury and A. M. Holtzer, THIS JOURNAL, 78, 947 (1956).

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and the β_L-polymer that remains at the completion of the polymerization. The experimental results are as follows: 0.265 g. of product A (β_L-polymer used for initiation) contained 0.38 meq. of labeled *n*-hexylamine as determined from the 3.8% deuterium content. Products C and C′ totaled 0.410 g. and together contained 0.29 meq. of labeled *n*-hexylamine. Product D (α-polymer obtained from labeled β_L-initiated polymerization), 0.688 g. contains 0.05 meq. of labeled *n*-hexylamine. The sum of products C, C′ and D is 0.34 meq. of *n*-hexylamine, which should be compared with 0.38 meq. of *n*-hexylamine in the initiating polymer product A. Allowing for a few per cent. error in each deuterium analysis, the deuterium balance is satisfactory, and the second criterion is met. The above data show that β_L-polypeptide is the precursor of α-polypeptide.

Discussion

Products of the Polymerization Reaction.—As noted previously the initial reaction of amine with a NCA occurs quickly to yield the amino acid amide. The amino acid amide then reacts with additional amounts of NCA in a polymerization reaction, and it is the products and rates of this reaction that have been investigated.

γ-Peptides.—This material has not been isolated as a pure compound but from molecular weight, spectroscopic, solubility and kinetic data, and from the method of its preparation it is apparent that γ-peptide has the properties of a DP 1 to 3 polymer. The titrations have been described in the Experimental section. The Archibald method for the determination of the molecular weight gave a value of approximately 400 for γ-peptide from *n*-hexylamine and γ-benzyl-L-glutamate NCA. The spectroscopic evidence includes: (a) only 1675 cm.$^{-1}$ amide I absorption is observed in solution; (b) the amide I absorption in the solid phase lies at a different frequency (1640 cm.$^{-1}$) from that observed with β-peptide (1630 cm.$^{-1}$); (c) the 1675 cm.$^{-1}$ band decreases with increasing A/I indicating conversion of the γ-peptide to another product. When isolated γ-peptide is used to initiate further polymerization, both the β-rate (k_{2a}) and the α rate (k_{2b}) are observed. Finally, γ-polymer is over 90% of the product of A/I 3 polymerizations. All these observations lead to the conclusion that the γ-peptide is a precursor of the α- and β-peptides, and is thus consistent with the γ-peptide being a DP 1 to 3 polymer.

β_L-Peptides.—β_L-Polypeptides have a DP between 3 and 6. The evidence for this is as follows: (1) The infrared spectroscopic properties of β_L-peptides of poly-γ-benzyl-L-glutamate have been described,[11] and are consistent with a low molecular weight non-intramolecularly hydrogen bonded amide. From the present work there is no spectroscopic evidence of β_L-polymer being formed at A/I's less than 3. The product from the A/I 3 reaction shows no 1630 cm.$^{-1}$ (β-amide I) band in solid state measurements. However, from A/I's 4 through 20 β_L-polypeptide is formed as indicated by the presence of the 1630 cm.$^{-1}$ band in solid state measurements. (2) The end group titrations of isolated β_L-polypeptide fractions, from which

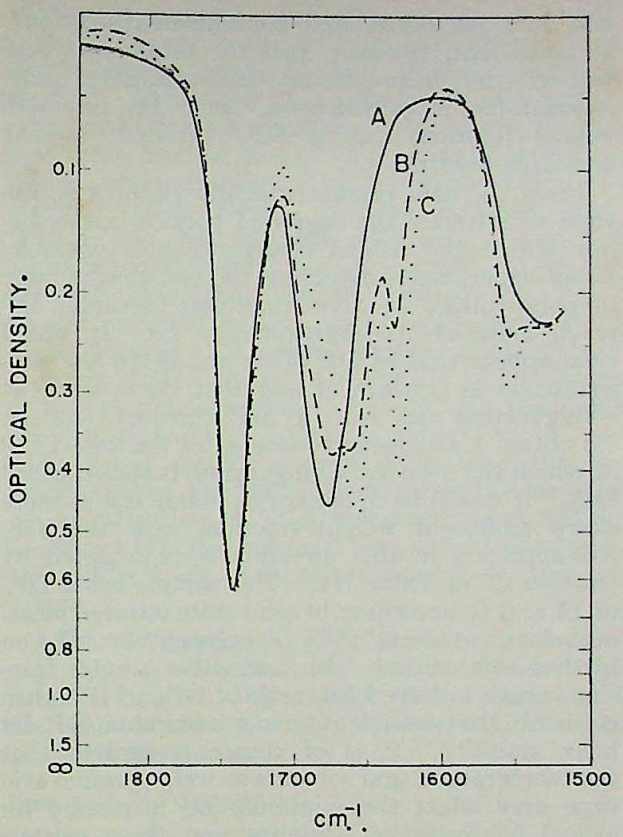

Fig. 3.—Infrared spectra of dioxane solutions at the end of polymerizations of 4% (by weight) of γ-benzyl-L-glutamate-N-carboxyanhydride initiated by *n*-hexylamine: A ———, A/I 3; B — — —, A/I 5 (obtained by addition of NCA to A/I 3 solution); C - - - -, A/I 8 (obtained by addition of NCA to A/I 5 solution). (Note: 1675 cm.$^{-1}$ (γ- and β_L-solution) band in curves A and B. The concentrated solution β_L band at 1630 cm.$^{-1}$ is seen in curves B and C as well as the α band at 1655 cm.$^{-1}$.)

both γ- and α-polymers have been removed, indicated that the DP is not higher than 6. (3) The deuterium experiments indicate the isolated β_L-product has a DP between 3 and 5. (4) Elementary analyses of the isolated β_L product indicate that its DP lies in the range 4 to 6. (5) A measurement of the molecular weight of β_L-polymer by the Archibald method[13] gave a value of 800 or a DP between 3 and 4.[14] (6) Finally, β_L-polymer shows lower solubility in organic solvents than does γ-polymer but greater solubility than α-polymer. When the above facts are considered, it is clear that there is strong evidence for β_L polymer having a DP between 3 and 6.

α-Peptides.—This material is the high molecular weight, least soluble fraction of primary amine initiated polymerizations at A/I's > 4. It is also the exclusive product of strong base initiated polymerizations[9] and has been shown to exist as the α-helix of Pauling and Corey[17] in both the solid state and in most solvents. All samples of unfractionated α-polypeptide isolated from amine initiated polymerizations in dioxane had weight average DP's between 100 and 300 and have the characteristic α-amide I band in the solid state

(17) L. Pauling, R. B. Corey and H. R. Branson, *Proc. Natl. Acad. Sci.*, **37**, 205 (1951).

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and in both dilute and concentrated solution.[11] It is evident, however, that the total α-polypeptide fraction from primary amine initiated polymerizations is polydisperse, since (as discussed below) fractions having DP_n's around 15 have been isolated from it.

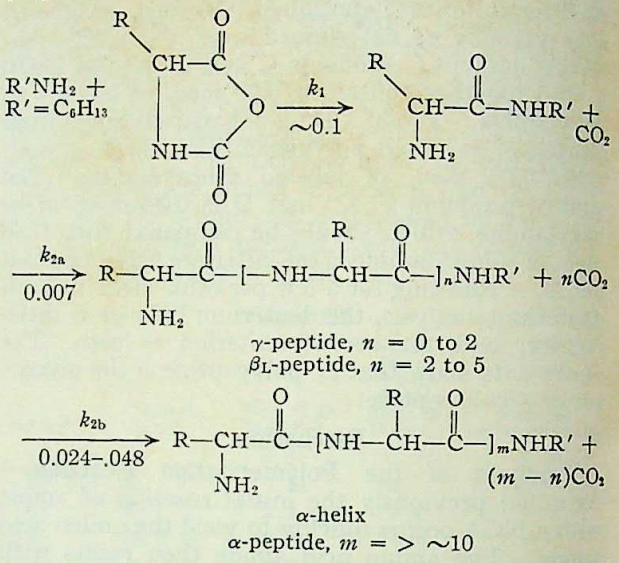
From the data presented in this paper it is possible to estimate the degree of polymerization below which the helical configuration is unstable. From experiments involving the isolation of pure β_L-polypeptides we have found that maximum DP of β_L-materials is approximately six. It would thus appear that at DP of six and below the configuration is non-helical and that the helical (α) configuration may exist at DP's greater than six. To obtain a satisfactory measure of the lowest DP at which the α-helical configuration is stable, called DP_c,[10] it would be necessary to isolate one or more sharp molecular weight fractions near this DP. An approach in this direction is represented by fraction C′ in Table III. This sample has a DP_n of 14 and is, according to solid state infrared measurements, at least 90% α-polypeptide. If, on further examination, this and other similar fractions prove to have a low ratio of DP_w to DP_n then it should be possible to fix a minimum DP for helix stability. It is of course recognized that the temperature, and solvents as well as amino acid type may affect the minimum *DP* necessary for helical configuration stability and these matters are being investigated. At present, however, it is clear that a DP of more than 6 is necessary to produce a helical configuration in poly-γ-benzyl-L-glutamate.

Polymerization Rates and the Reaction Sequence.—It has been shown previously[6] and in this study that the primary amine initiated polymerization of NCA's in dioxane solution show two successive rates of polymerization, the second rate, k_{2b}, being at least several times the primary polymerization rate, k_{2a}. Through the infrared kinetic studies reported here, it has been shown that k_{2a} is associated with production of low DP polymer (γ and β_L), and the k_{2b} rate occurs when higher DP polymer, (α) is being formed. Since γ-polymer yields both β- and α-polymer, it is apparent that γ-polymer is the precursor of β- and α-polymer.

As may be seen from Table I, the results obtained from the two kinetic methods are essentially in complete agreement. The difference observed in k_{2a} is due to the temperature at which the two series of experiments were performed, 25° for the carbon dioxide evolution experiments and 34° for the infrared experiments.

Although there is apparent agreement between the values of k_{2b} determined at different temperatures by both methods, this agreement may be fortuitous; the rates of the initiation, propagation and termination reactions may vary with temperature in such a manner that the observed over-all rate of reaction is coincidentally the same at both 25 and 34°, or the activation energy may be small.

The question whether β-polypeptide is the precursor of α-polypeptide, and is thus converted to α-polypeptide, was answered affirmatively by the experiments using deuterium labeled amine (*vide supra*). Thus it is clear that the reaction sequence from the *n*-hexylamine initiated polymerization of NCA's may be formulated as



The infrared kinetic studies show that α-polypeptide is formed at a rate (k_{2b}) several times that observed for β_L-peptide formation. This fact permits two conclusions: Either (1) the rate of addition of anhydride to a growing α-helix is greater because the growing chain end is relatively accessible to additional anhydride as compared with the β_L (non-helical) form or (2) the α-helix configuration is more sterically favorable for further anhydride addition. In any case, the rate of anhydride addition and polymer growth is very much greater when the growing chain has a helical configuration as compared to a non-helical configuration. Although other factors may influence the absolute rate of anhydride addition, there can be no doubt of the effect of the configuration of the growing chain.

Advantages and Limitations of the Infrared Method.—The infrared technique for determining the rates of polymerization reactions as described above has proved valuable but has certain restrictions which may limit its general applicability. First, the monomer should have at least one strong absorption band in a region free of solvent and product absorption. Secondly, the solvent must dissolve both monomer and polymer in reasonable concentration—*i.e.*, approximately 1% or greater. This latter condition is true for most kinetic work, but is especially important in the infrared method because low solubility entails long solvent path lengths with resultant decrease in the precision of measurement of absorption. Thirdly, a practical consideration is that the polymeric reaction products are often difficult to remove completely from the thin infrared cells. This necessitates repolishing the inner faces of the cell at frequent intervals. If the cell is not thoroughly clean, any residual polymer may influence the rate of a reaction performed in the cell. Finally, for accurate kinetic work, better temperature control, possibly by thermostated cells,[18] should be used. It is re-

(18) N. R. Trenner, R. Arison and R. W. Walker, *Applied Spect.*, **7**, 166 (1953).

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markable, considering the temperature was only controlled to ±1° in the present work, that the results are satisfactorily reproducible.

Despite its limitations, the infrared technique gives information which is not available from any other kinetic method. The first advantage of the infrared method is that it allows the simultaneous determination of the monomer and polymer concentrations throughout the reaction, and thus the determination of *both* the rate of disappearance of monomer and the rate of appearance of polymer. By following the disappearance of monomer, it is not necessary to carry the reaction to completion in order to determine the rate as is necessary in the polymer determination of rate. In the particular type of polymerization discussed in this paper, involving N-carboxyanhydrides, the monomers have two carbonyl absorption bands of different intensities. At the monomer concentrations and cell thicknesses used, the disappearance of the less intense band at 1860 cm.$^{-1}$ was followed for the first 80% of the reaction, while the more intense band at 1790 cm.$^{-1}$ was followed for the last 20% of the reaction. This fortunate circumstance allows the accurate determination of the rate of monomer disappearance up to at least 90% anhydride consumption.

The most important advantage of the infrared method is that during the polymerization it is possible to distinguish qualitatively, quantitatively and simultaneously two or more reaction products (if the various products have different infrared spectra). This allows the correlation of reaction rates with reaction products. For example, the gasometric method showed that primary amine initiated polymerizations of NCA's involved two different reaction rates; previous infrared work showed that two different polymers (α and β_L) could be isolated from such reactions. Using the presently described infrared method for determining reaction rates, correlations have been made between the initial slower reaction rate (k_{2a}) and the formation of the low DP (β_L) polymer as well as the later faster reaction rate (k_{2b}) and the formation of high DP (α) polymer.

Finally, it should be noted that, since this infrared method has been applied advantageously to the investigation of NCA polymerizations, within the above specified scope, it also should have general utility in the study of the kinetics of other reactions.

Acknowledgment.—We are pleased to acknowledge the support of this work by the Office of the Surgeon General, Department of the Army, and the valuable assistance of Miss Evelyn DesRoches in the kinetic studies.

BOSTON 15, MASSACHUSETTS

[CONTRIBUTION FROM THE GIBBS LABORATORY, DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

Polypeptides. XVI. The Polydispersity and Configuration of Low Molecular Weight Poly-γ-benzyl-L-glutamates[1]

BY J. C. MITCHELL, A. E. WOODWARD AND PAUL DOTY

RECEIVED MARCH 21, 1957

Titrations of amine and carboxyl groups in samples of poly-γ-benzyl-L-glutamate prepared by primary amine initiation show that (1) amine groups are nearly preserved throughout the polymerization but are easily lost during polymer isolation and storage, presumably by end group cyclization with the elimination of benzyl alcohol and (2) carboxyl groups are present to the extent of about one per three hundred residues regardless of the molecular weight of the sample. From this value it can be concluded that the Sela and Berger termination step will have a negligible broadening effect on the molecular weight distributions of these low molecular weight polypeptides. In order to estimate the molecular weight distributions the weight average molecular weights of a number of samples in the range of 1000 to 20,000 molecular weight were determined in the ultracentrifuge by means of the Archibald approach-to-equilibrium method. The results show pronounced deviations from the intrinsic viscosity–molecular weight relation established for higher molecular weight samples. The ratios of the weight to number average degrees of polymerization are found to be extraordinarily large[3-11] and suggest striking anomalies in polymerization. It is not surprising, therefore, to find that the samples can be separated into two fractions of widely different molecular weights and having different configurations (α and β) by a variety of means: solvent extraction, paper chromatography and dialysis. The minimum degree of polymerization required for stability of the α-helical configuration in dioxane and dimethylformamide solution is found to be approximately 10.

Early in 1955 end group determinations and intrinsic viscosity measurements on numerous low molecular weight samples of poly-γ-benzyl-L-glutamates clearly suggested that the molecular weight distributions in samples prepared by hexylamine initiation were extremely broad in contrast to the very narrow Poisson distribution generally expected. A rigorous and quantitative proof of this result required, however, the correlation of intrinsic viscosity measurements with weight average molecular weights in the region below 20,000. Since this correlation has only now been achieved, by use of the Archibald approach-to-equilibrium technique in ultracentrifugation, the publication of these results has been delayed. In the interim, however, knowledge of these results and corresponding infrared investigations[2] have motivated kinetic studies of the polymerization in a search for the origin of the observed polydispersity. A preliminary report of the findings has been made[3] and the full reports[4] are being published concurrently with this one.

Another reason for pursuing the absolute es-

(1) For the last papers in this series see XV, M. Idelson and E. R. Blout, THIS JOURNAL **79**, 3948 (1957), and XIV, P. Doty and R. D. Lundberg, *Proc. Natl. Acad. Sci.*, **43**, 213 (1957).

(2) E. R. Blout and A. Asadourian, THIS JOURNAL, **78**, 955 (1956).

(3) P. Doty and R. D. Lundberg, *ibid.*, **78**, 4810 (1956).

(4) (a) R. D. Lundberg and P. Doty, *ibid.*, **79**, 3961 (1957); (b) M. Idelson and E. R. Blout, *ibid.*, **79**, 3948 (1957).

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tablishment of molecular weights in this relatively low molecular weight region lies in the desire to determine the critical length of the polypeptide chain required for the α-helical configuration to become the stable configuration. Of course this critical degree of polymerization will depend on the nature of the polypeptide residues and on the solvent. The results presented here identify fairly well this critical chain length in two solvents and, in conjunction with infrared spectra,[2,4b] in the solid state as well.

Following a presentation of experimental details this report takes up the titration of amine and carboxyl groups of poly-γ-benzyl-L-glutamates and the relation these bear to number average molecular weights. The calibration of intrinsic viscosity in dichloroacetic acid solutions against weight average molecular weight is considered next. This then permits an assessment of the magnitude of the polydispersity in the samples. In the final section the problem of helix stability and molecular weight is examined.

Experimental Details

Reagents.—Dimethylformamide and dichloroacetic acid were purified as described elsewhere.[4a] Phenol (Analytical Reagent Grade) was purified according to the method of Waltz and Taylor.[5] Phenol solutions were prepared by dissolving 83 g. of purified phenol in 17 g. of absolute ethanol and stored in the dark.

Sodium methoxide solution was prepared by dissolving 1.0 g. in 1800 ml. of methanol (Reagent Grade) and also stored in the dark. Standardization was made against potassium acid phthalate.

Perchloric acid solutions were made by mixing 2 ml. of 70% perchloric acid (Analytical Reagent Grade) with two liters of methanol. Standardization was carried out conductometrically, as described below, against standard sodium methoxide solution in a mixture of 45 ml. of phenol, 8 ml. of absolute ethanol and 8 ml. of distilled water.

Polypeptides.—Titration studies were made on a number of poly-γ-benzyl-L-glutamate samples prepared by Blout and Karlson[1,6] but only three of these are reported on in detail here. These three samples (no. 862, 834 and 863) were made in dioxane solution by hexylamine initiation using anhydride–initiator mole ratios ([A]/[I]) of 4.0, 8.0 and 20.0, respectively. After the polymerization was 99% complete the product was precipitated by pouring into 20 volumes of diisopropyl ether and dried at 50° *in vacuo*. More recently, three other polypeptides made in dioxane solution in this [A]/[I] range became available for viscosity and molecular weight measurements. Two of these (no. 428 L of [A]/[I] = 4.0 and RL-V202 of [A]/[I] = 20.0) were prepared by R. D. Lundberg and the other (no. 384-10 at [A]/[I] = 10) by M. Idelson and E. R. Blout.[4b]

The samples used in the viscosity–molecular weight study had to be of relatively narrow molecular weight distribution. Consequently fractions and samples prepared in dimethylformamide solution were employed. Details concerning these will be given later.

Titration.—In order to estimate all the groups present, both acid and base titrations were performed. The sample weight was chosen so as to require from 1 to 5 ml. of titrant: this was delivered from 5-ml. micro-burets.

Titrations with 0.01 *N* perchloric acid were carried out conductometrically in the solvent system phenol–ethanol–water[5] with sodium chloride being added, when necessary, to increase the starting conductivity to a measurable value. A dipping type conductivity cell with a constant, *K*, of 1.00 was used. Two conductivity bridges (Industrial Instruments) were employed; one was a Model RC with a maximum reading of 2.5×10^5 ohms, the other a Model RC 16 B with a maximum of 2.5×10^6 ohms.

The polymer samples were dissolved in a given amount of phenol solution in ethanol and then equivalent volumes of ethanol and water were added. The amount of each solvent used depended on how much ethanol and water the polymer would tolerate prior to precipitation while the total volume was kept within about 70 ml.

To check the method, known amounts of *n*-hexylamine and glycylglycine were titrated in 35 ml. of phenol solution, 15 ml. of ethanol and 15 ml. of water. The agreement was found to lie within ±4%. Duplicate titrations of poly-γ-benzyl-L-glutamates were found to agree within ±3% for a polymer of $\overline{DP}_n$ equal to 19 and ± 8% for one with a $\overline{DP}_n$ of 226.

Titrations with 0.01 *N* sodium methoxide were carried out in 25 ml. of chloroform and 10 ml. of absolute ethanol with 0.1% phenolphthalein in ethanol as indicator: the titer of the solvent alone was subtracted from the sample titer. To compare the method with an aqueous titration, an acetic acid solution was titrated in both the chloroform–ethanol system and distilled water; the values obtained agree within 1%. As a further check a low molecular weight polypeptide was titrated in (1) chloroform–ethanol, (2) potentiometrically in 20% water–80% dioxane (volume/volume), (3) in dioxane–water–formaldehyde solution and (4) in benzyl alcohol with phenolphthalein as indicator. The average value of these titrations varied from ±2% for a low molecular weight polymer to ±5% for one of $\overline{DP}_n = 550$.

Viscosity Measurements.—All viscosity measurements were made at 25° with a modified Ubbelohde type capillary viscometer using dichloroacetic acid as the solvent. The solutions were clarified by passing them through a medium sintered glass filter.

Ultracentrifuge Measurements.—Weight average molecular weights were determined by the Archibald[7] approach-to-sedimentation-equilibrium method following the procedure given by Klainer and Kegeles.[8,9] The essential feature of this method is that the vanishing of the flux of solute across the two cell boundaries, meniscus and bottom, allows the application at these planes of the equation for sedimentation equilibrium

$$(\bar{M}_w)_{app} = \frac{RT}{(1 - \bar{v}\rho)\omega^2}\left[\frac{dc/dx}{xc}\right]_m$$

in which $(\bar{M}_w)_{app}$. is the apparent weight average molecular weight (differing from the true weight average molecular weight by a correction for the non-ideality of the solution), R the gas constant, T the absolute temperature, $\bar{v}$ the partial specific volume of the solute, ρ the density of the solution, ω the angular velocity, c the solute concentration and x the radial distance from the center of rotation. The subscript "m" on the square bracket indicates that the enclosed ratio is evaluated at the air-liquid meniscus.

The measurements were made with a Spinco model E ultracentrifuge equipped with a phase-contrast schlieren diaphragm. A 2-degree centerpiece modified to form synthetic boundaries between solvent and solution according to the suggestion of Kegeles[10] was used in the determination of the concentration at the meniscus.

The angle of the schlieren diaphragm was maintained at 80° in all measurements. Photographs of the schlieren patterns were made on Kodak type II-O and III-O spectroscopic plates through a Wratten #34 A filter and were read using a modified toolmaker's microscope equipped with a projection head[11] as a two-dimensional microcomparator.

The vertical comparator readings were corrected for solvent gradient in the following manner. It was observed that at several speeds the solvent gave only a horizontal schlieren line except for a slight downward curvature, possibly due to diffraction effects, within 0.03 mm. of the meniscus. Thus the average comparator reading of the horizontal (plateau) region in a solution photograph was subtracted from the readings in the curved region, with an appropriate correction for the solvent curvature in the immediate vicinity of the meniscus.

The partial specific volume of poly-γ-benzyl-L-glutamate in dimethylformamide was found to be 0.791 ± 0.006.

(5) J. E. Waltz and G. B. Taylor, *Anal. Chem.*, **19**, 448 (1947).

(6) E. R. Blout and R. H. Karlson, This Journal, **78**, 941 (1956).

(7) W. J. Archibald, *J. Phys. Colloid Chem.*, **51**, 1204 (1947).

(8) S. M. Klainer and G. Kegeles, *ibid.*, **59**, 952 (1955).

(9) S. M. Klainer and G. Kegeles, *Arch. Biochem. Biophys.*, **63**, 247 (1956).

(10) G. Kegeles, This Journal, **74**, 5532 (1952).

(11) Available from the Gaertner Scientific Corp., 1201 Wrightwood Ave., Chicago, Ill.

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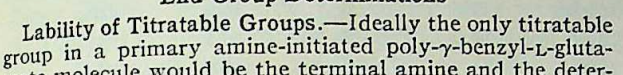
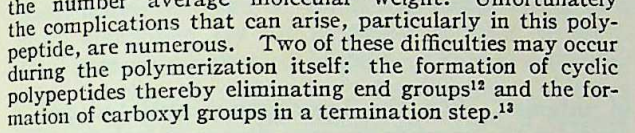
The measurement was made at 25° in a special pycnometer consisting of a volumetric flask with its neck replaced by part of a 0.1-ml. capillary-bore volumetric pipet.

End Group Determinations

Lability of Titratable Groups.—Ideally the only titratable group in a primary amine-initiated poly-γ-benzyl-L-glutamate molecule would be the terminal amine and the determination of amine groups would therefore lead directly to the number average molecular weight. Unfortunately the complications that can arise, particularly in this polypeptide, are numerous. Two of these difficulties may occur during the polymerization itself: the formation of cyclic polypeptides thereby eliminating end groups[12] and the formation of carboxyl groups in a termination step.[13]



After the polypeptide has been formed, two other reactions may occur that would alter the number of titratable groups. These are (1) the loss of amine groups by end group cyclization to form substituted pyrrolidone rings[14] as shown



and (2) the production of carboxyl groups by debenzylation.

Titration of amine groups in reaction mixtures showed at once that the number present was essentially equal to the number added as initiator: consequently significant amounts of cyclic polypeptide formation (and condensation) could be ruled out under the polymerization conditions (25°). However, it soon became apparent that the ordinary procedures of isolation, drying and storage at room temperature as either solid or solution were accompanied by a continuous loss of amine groups. The isolation procedure used for the three samples of the 800 series involving drying at 50° leads to losses of 50 to 70% of the amine groups present in the reaction mixture (Table I). Moreover, 80% loss of amine groups was produced by exposure to a steam-bath for 5 hours. Thus lyophilization of the reaction product (dioxane solution) appeared to be the best way of preserving most of the amine groups. When this was carried out on an [A]/[I] = 4 sample (no. 428 L) over a period of 48 hours the amine content was 85% of that added as initiator. No significant loss of amine groups occurs during storage at −30° over a period of several months. It is of interest to note that no change in intrinsic viscosity was observed during these alterations of amine group concentrations. As a consequence condensation was ruled out here as well and the end group cyclization reaction was accepted as the explanation of the depletion of amine groups.

The carboxyl group concentration of numerous samples was found to be in the same range as for the three polymers listed in Table I. The number of carboxyl groups was essentially unaltered by ordinary isolation procedures and as a consequence it seemed likely that those initially present might arise from the termination reaction of Sela and Berger.[13] However, the carboxyl group concentration could be increased by more drastic treatment. For example it would double upon five hours exposure to 100° presumably due to hydrolysis of the benzyl ester groups.

Discussion

The conservation of amine groups during the polymerization is indicative of the absence of the formation of cyclic polypeptides and condensation reactions, and it clearly indicates that the number average DP of the product is essentially that given by the anhydride–initiator ratio. This conclusion makes use of the observation from kinetic studies[2-4] that all the hexylamine initiator reacts rapidly to produce polymer.

The lability of the amine group due to end group cyclization prevents its assay from being useful as an accurate measure of number average molecular weight. However, it is clear that by lyophilization and cold storage the amine groups can be largely conserved. The loss of amine groups through this reaction is not serious in polymerizations lasting a few hours at room temperature. But polymerization carried out at higher temperatures or for longer times would be expected to show a decay in rate due to this reaction.

The constant carboxyl group concentration found here can be interpreted as arising from a termination reaction. The amount found, about 15 $\times 10^{-6}$ equivalent per gram, upon multiplication by the residue molecular weight gives 0.0033 which, in view of the unknown extent of the debenzylation reaction, would be interpreted as an upper limit for the probability of chain termination occurring each time a monomer adds to the polypeptide chain. More recent work of Lundberg and Doty,[4a] however indicates that this value is considerably too high and that the situation is complicated by the end group cyclization reaction acting as an additional termination step. Nevertheless it can be concluded from these findings that termination steps play a small role in these polymerizations and cannot be held responsible for the unusually wide molecular weight distributions mentioned above.[15]

The Molecular Weight Dependence of Intrinsic Viscosity for Short Polypeptide Chains

In an earlier study[16] of this polypeptide the intrinsic viscosity was related to weight average molecular weights determined by light scattering for degrees of polymerization ranging from 100 to 2000 in two solvent systems, one in which the chain configuration was randomly coiled (dichloroacetic acid) and one in which it was helical (chloroform saturated with formamide). For the purposes of this paper it was necessary to extend this intrinsic viscosity–molecular weight relation down to degrees of polymerization in the neighborhood of 5. The Archibald approach to equilibrium method was used for this purpose. The measurements were made on dimethylformamide solutions of a number of samples prepared either by fractionating the products of polymerizations in dioxane[1,6] or by polymerization in dimethylformamide, a polymerization medium in which it has been discovered that the molecular weight distribution produced is very narrow.[3,4a]

The weight average molecular weights were determined as described briefly in the Experimental Section. In each case the concentration depend-

(12) D. G. H. Ballard and C. H. Bamford, Chemical Society, Special Publication No. 2, 25 (1955).
(13) M. Sela and A. Berger, This Journal, 77, 1893 (1955).
(14) W. E. Hanby, S. G. Waley and J. Watson, *J. Chem. Soc.*, 3239 (1950).
(15) The molecular weight distribution arising in the case of the Sela and Berger termination has been calculated: E. Katchalsky, Y. Shalitin and M. Gehatia, This Journal, 77, 1925 (1955).
(16) P. Doty, J. H. Bradbury and A. M. Holtzer, *ibid.*, 78, 947 (1956).

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TABLE I

CHARACTERISTICS OF LOW MOLECULAR WEIGHT POLY-γ-BENZYL-L-GLUTAMATES PREPARED IN DIOXANE

Sample No.	[A]/[I]	Titrations NaOCH₃	(meq./g.) HClO₄	[A]/[COOH]	[A]/[NH₂]	[η]	DP_w	$\frac{DP_w}{DP_n}$
862	4	0.018	0.359	250	12	0.08	13	3.3
834	8	.012	.205	380	21	.15	68	8.5
863	20	.014	.088	280	45	.21	128	6.4
428L	4				5	.12	40	10.0
384-10	10					.20	115	11.5
RL V-202	20					.265	170	8.5

ence of the apparent molecular weight as expressed in the second virial coefficient was employed to obtain the actual molecular weight at infinite dilution. The virial coefficient was found to increase substantially with decreasing molecular weight. The magnitude of this effect is surprising and is being investigated further.

The molecular weights thus determined are plotted against the intrinsic viscosity in dichloroacetic acid on a double logarithmic scale in Fig. 1 as open circles. The earlier results for the higher molecular weight range are shown as filled circles. It is seen that deviations from the linearity of the higher molecular region set in at a DP of about 100 and become quite marked below a DP of 50. In this connection it is of interest to note that in the case of polystyrene a somewhat similar study[17] has shown that the deviations set in at a molecular weight of about 5000. Such a molecule of polystyrene has a chain length equivalent to poly-γ-benzyl-L-glutamate of DP 86. Hence the onset of deviation from the Mark–Houwink behavior occurs at roughly the same chain length in these two cases.

Polydispersity and Fractionation of Polypeptides Prepared in Dioxane

The results of the two foregoing sections now permit a quantitative assessment of the polydispersity of the poly-γ-benzyl-L-glutamate samples of interest. For the hexylamine initiated polypeptides the number average degree of polymerization, DP_n, can be taken as equal to the anhydride–initiator ratio. The weight average value, DP_w, can be assessed from the intrinsic viscosity determinations with the use of Fig. 1. The ratio, DP_w/DP_n, is a direct measure of the polydispersity. For the Poisson distribution it should approach 1 (that is, it should equal $1 + 1/DP_n$) and for the most probable distribution, expected for many polycondensations, it should be equal to 2.

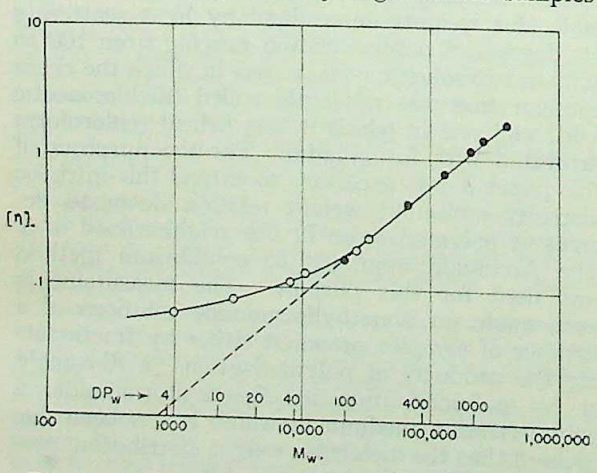

Fig. 1.—Double logarithmic plot of intrinsic viscosity measured in dichloroacetic acid against weight average molecular weight of poly-γ-benzyl-L-glutamate: ●, molecular weights determined by light scattering measurements; O, molecular weights determined by the Archibald ultracentrifugal method.

The results on six polypeptides produced in dioxane are assembled in Table I. The polydispersity is seen to be very great indeed. Actually it is so large that the values of DP_w obtained from Fig. 1 are probably somewhat too low because the intrinsic viscosity corresponds to an average slightly lower than the weight average. Measurements on samples with [A]/[I] values greater than 20 show a continual decrease of the polydispersity with molecular weight.[3,6] These results are of course incompatible with the growth of polypeptide chains by the addition of monomer units through a single rate process following rapid initiation. The origin of this broadening of the molecular weight distribution has been found[3] and is described in detail in the accompanying papers.[4]

Fractionation.—With this evidence of very wide molecular weight distributions it was expected that a sample could be fractionated easily into two parts having quite different molecular weights. This has been done in three different ways. The first was fractional extraction with formic acid[2] or hot ethanol.[4b] These liquids appear to dissolve almost exclusively those polypeptide chains that are too short to form stable helical configurations. Consequently, polypeptides such as those listed in Table I were divided in a single step into two parts having intrinsic viscosities in dichloroacetic acid of the order of 0.06 and 0.20. Even if only the earlier viscosity–molecular weight relation were employed this would indicate a difference in molecular weight of a factor of about 5. With the use of Fig. 1 it is seen that this indeed corresponds to differences of about 25-fold in molecular weight.

As a particular example, the two fractions of sample 384–10 prepared by ethanol extraction by Idelson and Blout were examined by both the Archibald method and intrinsic viscosity. The lower fraction (entirely of the β-configuration in the solid state according to the infrared spectrum) had a DP_w of 4 while the higher fraction (entirely of the α-configuration) was of a DP_w of 150. For the unfractionated material the DP_w by the Archibald method was 104. Thus the very great polydispersity is confirmed.

(17) M. Marzolph and G. V. Schulz, *Makromolekulare Chem.*, 13, 120 (1954).

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A similarly striking separation into two parts was found in paper chromatograms. Chloroform solutions were applied to strips of Whatman No. 4 filter paper. When dry, the strips were developed in a closed chamber by the descending method using the *n*-butanol–acetic acid–water system. After drying and spraying with ninhydrin two purple spots developed, one at the origin and another at a point described by an R_f value of 0.92 ± 0.02. The chromatograms of fractions showed only one spot: at the origin ($R_f = 0$) for the high fractions and $R_f = 0.92$ for low fractions. Thus it is clear that the short chains not in the helical configuration move in this system while those in the helical configuration remain at the point of application.

The third method of fractionation employed was simple dialysis. A bag made of cellophane tubing and conditioned stepwise to a dioxane–water mixture (25:1) was filled with a 3.4 g./dl. solution in dioxane of a polypeptide with a DP_w of 37. Within a week (two changes of solvent of volume twice that of the bag) the loss from the bag had stopped. The material that had remained inside had a DP_w of 120 and that collected on the outside had DP_w of 4. The two fractions showed only single spots on paper chromatograms. Thus this type of separation has produced results very similar to the other two.

Molecular Weight Dependence of Helix Stability

The onset of helix stability with increasing chain length will be expected to occur rather abruptly[18] and the critical chain length, DP_c, at which it occurs will depend on a number of factors: the composition of the polypeptide, the environment of the polypeptide chain (solid state or solvent) and the temperature. The determination of DP_c for a given set of these factors would be simple if samples of uniform chain length were available. When the actual samples have a distribution of molecular weights the assignment of the value of DP_c is subject to an error proportional to the breadth of the distribution. Thus the accuracy with which DP_c can be specified increases as the molecular weight distribution is narrowed.

For example, sample number 834 was found to be half in the β-configuration (β_L form in Blout's terminology[4b]) and half in the α-configuration as a result of infrared studies on the solid material.[2] Yet it would be misleading indeed to conclude that DP_c was equal to the DP_w of this polypeptide. Since fractionation of this sample[2] produced two parts, one nearly pure β_L and one pure α having DP_w values of 2 and 100, respectively, it is clear that the proportion of α and β configuration shown in the original polypeptide was only a reflection of the amounts of material present having chain lengths below and above DP_c. Thus the value of DP_c must be located within the range of chain lengths present in the sample but it cannot be more definitely fixed.

The fractions produced by formic acid extraction by Blout and Asadourian[2] have somewhat narrower molecular weight distributions and a comparison of their configuration as deduced from infrared spectra with the DP_w values that can now be assigned to them by the use of Fig. 1 permits an approximate estimation of DP_c in the solid state. Their results and our own may be summarized by the statement that peptides containing at least 90% β_L configuration have not been observed with $[\eta]$ greater than 0.075. This intrinsic viscosity corresponds to DP_w to 10. However, the uncertainty in the intrinsic viscosity measurements (± 0.005) and in the possible lack of detection of small amounts of material in the samples place an uncertainty of ± 3 on this estimate. Moreover, since the DP_n of these fractions was not well known the polydispersity of the samples can only be estimated. It is for this reason that the value assigned to DP_c is only an estimate.

In order to obtain a more accurate value of DP_c, particularly in solutions, use was made of the observation that poly-γ-benzyl-L-glutamate samples prepared in dimethylformamide solution were of much narrower molecular weight distribution than those made in dioxane.[4a,19] Two such samples prepared at [A]/[I] of 4 and 10 have been used for the present study. These samples were found to have DP_w values of 5 and 14, respectively. Taking DP_n as equal to [A]/[I] it is seen that the chain length distributions in these samples are very narrow.

The fraction of residues in the helical configuration for dioxane and dimethylformamide solutions of these polypeptides was determined by rotatory dispersion measurements.[20] The results, along with those for a high molecular weight, completely helical sample, are plotted in accordance with Moffitt's equation in Fig. 2. The helical content is deduced from the value of b_0 (obtained from the slopes of the plots). Since the high molecular weight sample was found to have $b_0 = -682°$ in dioxane and −620 in dimethylformamide, the per cent. helical configuration in solution is taken as $100b_0/-682$ and $100b_0/-620$, respectively.

The results are summarized in Table II where it is seen that the [A]/[I] = 4 sample shows no helical content, whereas the [A]/[I] = 10 sample is nearly half helical.[21]

These results permit the assessment of an upper and lower limit to the critical chain length for helix stability, DP_c, in these solvents. If the [A]/[I] = 10 sample were of uniform chain length of 14 and exhibited 50% helical content DP_c would equal 14. However, since some spread in molecular weight distribution exists this can only be taken as an upper limit. It is likely to be several units lower. The lower limit can be found by taking into account the molecular weight distribution

(18) J. A. Schellman, *Compt. rend. trav. lab. Carlsberg, Serie chim.*, **29**, No. 15 (1955).

(19) Current work by J.C.M. is demonstrating that samples prepared in this manner do indeed approach the expected Poisson distribution.

(20) J. T. Yang and P. Doty, THIS JOURNAL, **79**, 761 (1957).

(21) The coefficient of the normal dispersive term, a_0, was found to be quite concentration dependent as the two values in Table II illustrate. This is similar to the behavior already witnessed in chloroform solution[20] and appears to be due to an intermolecularly hydrogen bonded form that breaks up upon dilution to give the solvated β_L chains as first observed by Blout and Asadourian.[3] The use of the high molecular weight value of b_0 to calibrate the scale of helical content may possibly involve some uncertainty in this application since the effect per residue may be somewhat different due to end effects in short chains.

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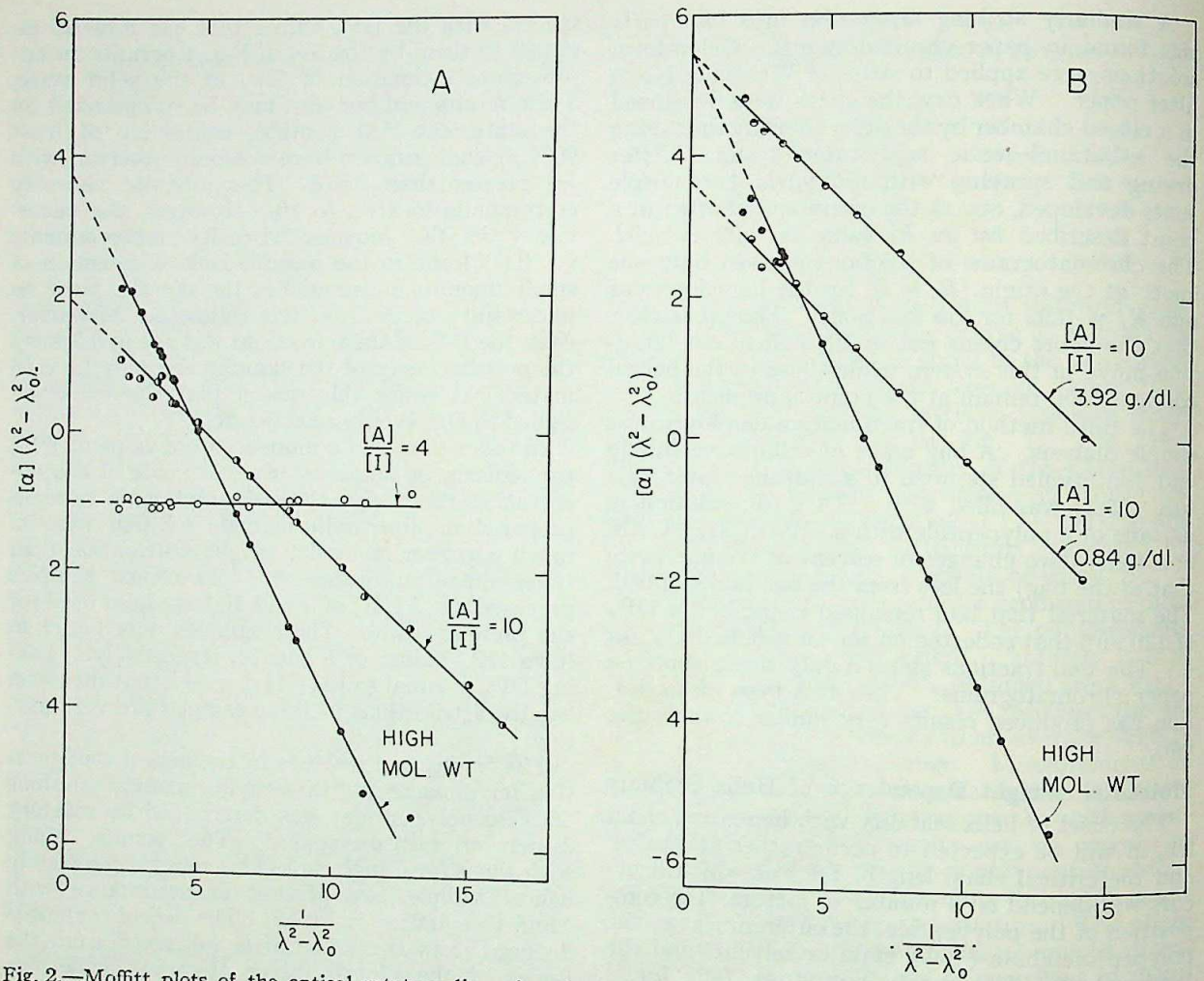

Fig. 2.—Moffitt plots of the optical rotatory dispersion of poly-γ-benzyl-L-glutamate in (A) dimethylformamide and (B) dioxane: λ is in microns; λ_0 is taken as 0.212 μ.

of the [A]/[I] = 4 sample. Since the DP_w is equal to that expected for a Poisson distribution, this distribution can be assumed. In this distribution about 10% of the sample by weight has a DP in excess of 7. If this were helical it could clearly be detected by the rotatory dispersion method. Consequently this forms the lower limit of DP_c. Thus these preliminary studies locate DP_c for these polypeptide–solvent systems between 7 and 14. The average of this range, that is DP of 10, appears as a reasonable estimate of DP_c but further investigation of fractionated samples of polypeptides produced in dimethylformamide will be required to reach the most accurate and precise value of this constant.

TABLE II

THE ROTATORY DISPERSION CONSTANTS[a] AND HELICAL CONTENT OF LOW MOLECULAR WEIGHT POLY-γ-BENZYL-L-GLUTAMATES

Sample No.	[A]/[I]	DP_w	Solvent	a_0	b_0	% Helix
RS-8	4	5	Dimethylformamide	−40	0	0
RL-III 156	10	14	Dimethylformamide	69	−298	44
RK-421	High	High	Dimethylformamide	135	−620	100
RL-III 156	10	14	3.42 g./dl. dioxane	196	−304	44
RL-III 156	10	14	0.84 g./dl. dioxane	132	−318	47
RK-421	High	High	Dioxane	198	−682	100

[a] Uncorrected for the dispersion of the refractive index.

Acknowledgment.—We wish to acknowledge the helpful discussions and occasional assistance provided by Drs. E. R. Blout, R. D. Lundberg, M. Idelson and J. T. Yang throughout the course of this work. We are especially indebted to Professor Gerson Kegeles for informative discussions and for his assistance in obtaining our synthetic boundary cell and to Dr. Blout and Miss Ann Asadourian for the infrared spectral studies. Financial support was provided by the Office of Naval Research (N5Ori-07654) and the American Cancer Society (Institutional Grant).

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[CONTRIBUTION FROM THE GIBBS LABORATORY, HARVARD UNIVERSITY]

Polypeptides. XVII. A Study of the Kinetics of the Primary Amine-initiated Polymerization of N-Carboxy-anhydrides with Special Reference to Configurational and Stereochemical Effects

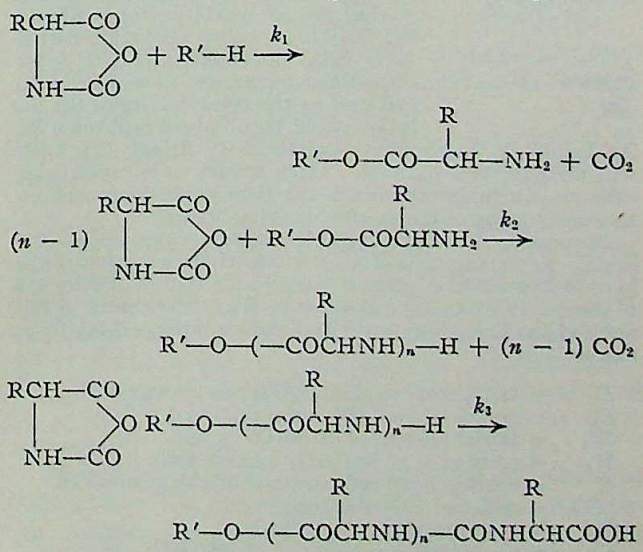
BY R. D. LUNDBERG[1] AND PAUL DOTY

RECEIVED MARCH 26, 1957

The primary amine-initiated polymerization of N-carboxy-anhydride of γ-benzyl-L-glutamate in a number of solvents is shown to proceed at two successive rates following a relatively rapid initiation. The rate constant for the second propagation step is at least five times larger than that for the first and as a consequence those growing chains that first achieve the condition for the faster propagation then grow rapidly and, by lowering the anhydride concentration, reduce the rate of growth of the chains that have not attained the condition for fast growth. This is the origin of the very broad molecular weight distributions previously observed. In dioxane the transition from the slow to the fast propagation rate occurs when the average chain length has reached approximately 8 residues. Since this chain length lies in the range (7 to 13) which has been assigned to the critical length for stabilization of the α-helical configuration in this solvent it appears that the cause of the change in propagation constants is the configurational transition. It is shown that very minor HCl contamination of the N-carboxy-anhydride can substantially lower the second propagation constant and in the limit prevent its appearance altogether. Two alternative termination steps are identified and their combined effect limits the average degree of polymerization to about 500. In dimethylformamide only a single rate constant is observed and the molecular weight distribution of the resulting polypeptides is greatly reduced over that of the dioxane case. Thus the preparation of low molecular weight polypeptides having the narrow Poisson distribution of molecular weights appears possible. Investigation of the rate of polymerization of racemic and D,L-mixtures of N-carboxy-anhydride shows a pronounced lowering of the propagation rate relative to that of the pure L-anhydride. While the growing chain is non-helical the lowering is less than a factor of two and is thereby accounted for in terms of a preference of the chain to add the isomer corresponding to its terminal residue. Later, when the growing chain has reached the helical configuration, the lowering of the rate is greater than a factor of two and this indicates a preference exerted by residues lying behind the terminal one. When optical rotation as well as CO_2 evolution is used to follow polymerizations of L-, DL- and D-N-carboxy-anhydrides with preformed L-polypeptide (helical configuration) it is found that the screw sense of the initiating helix tends to be continued. In the D-anhydride case, the reversal of the helix sense occurs after about four residues have added; in the DL-anhydride case, reversal occurs later presumably as a result of the occasional addition of four D-residues in sequence.

The polymerization of N-carboxy-α-amino acid anhydrides has been generally thought to proceed by a repetitive, stepwise addition of the peptide units with the simultaneous expulsion of carbon dioxide.[2-7] If initiation is not slow relative to propagation and side reactions do not occur, chain growth should proceed at a nearly uniform rate producing a Poisson distribution of molecular weights. Recently a termination step has been suggested[8a] and the broadening of the molecular weight distribution which this would bring about has been analyzed.[8b] Thus the polymerization is presumed to occur by the mechanism shown.

The purpose of this investigation has been to determine to what extent the formation of poly-γ-benzyl-L-glutamate from its N-carboxy-anhydride follows this kinetic scheme. This particular amino acid residue was chosen because it is one of the few precursors of naturally occurring amino acids whose anhydride and polypeptide are both soluble in liquids suitable for polymerization. Earlier investigations in this series[9,10] had raised questions concerning the adequacy of the foregoing scheme even when primary amines were used as initiators. The most obvious difficulty arose from finding that the molecular weight distribution of the resulting polymer was extraordinarily broad, that is, far broader than that which could be accounted for by any adjustment of the above mechanism. Consequently, we wished to search for the kinetic origin of this abnormally broad molecular weight distribution and eliminate it if possible. Finally, there



was obvious interest in seeing if optical isomers had an effect in the kinetics and if particular preference was exhibited in the polymerization. This last point gained interest as evidence accumulated that the helical configuration had only one screw sense (probably right handed)[11,12] and when it was

(1) United States Public Health Service Predoctorate Fellow, 1955-1957.

(2) F. Wessely and F. Sigmund, *Z. physiol. Chem.*, **159**, 102 (1926).

(3) R. B. Woodward and C. H. Schramm, THIS JOURNAL, **69**, 1551 (1947).

(4) W. G. Waley and J. Watson, *Proc. Roy. Soc.* (*London*), **A199**, 499 (1949).

(5) E. Katchalski, *Advances in Protein Chem.*, **6**, 123 (1951).

(6) J. W. Breitenbach and K. Allinger, *Monatsh. Chem.*, **84**, 1103 (1953).

(7) C. H. Bamford, A. Elliott and W. E. Hanby, "Synthetic Polypeptides," Academic Press, New York, N. Y., 1956; D. G. H. Ballard and C. H. Bamford, Special Pub. No. 2, Chem. Soc. (London), p. 25.

(8) (a) M. Sela and A. Berger, THIS JOURNAL, **77**, 1893 (1955); (b) E. Katchalski, Y. Shalitin and M. Gehatia, *ibid.*, **77**, 1925 (1955).

(9) E. R. Blout and R. H. Karlson, *ibid.*, **78**, 941 (1956).

(10) J. C. Mitchell, A. E. Woodward and P. Doty, *ibid.*, **79**, 3955 (1957).

(11) J. T. Yang and P. Doty, *ibid.*, **78**, 498 (1956).

(12) W. Moffitt and J. T. Yang, *Proc. Natl. Acad. Sci.*, **42**, 596 (1956).

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found that the helical configuration was substantially less stable when the polypeptide contained both D- and L-residues.[13] It is these questions as well as those which arise in a conventional kinetic study that must be answered before this type of polymerization can be employed in making polypeptides that approach the specifications which are required of protein analogs.

Experimental Details

Measurement of CO_2 Evolution.—The rate of carbon dioxide evolution provides a convenient method for measuring the progress of this reaction. Since previous investigators[14] have shown that the manometric techniques may lead to difficulties when the carbon dioxide pressure increases, a method similar to that of Breitenbach and Allinger[6] was used. The gas was swept out by a stream of prepurified nitrogen and absorbed in a previously standardized solution of barium hydroxide. Although any strong base may be employed, barium hydroxide was used here because of the relatively large change in resistance resulting from precipitation. By measuring the decrease of conductivity of this solution with time, the amount of carbon dioxide evolved is measured and from this the amount of anhydride consumed is determined.

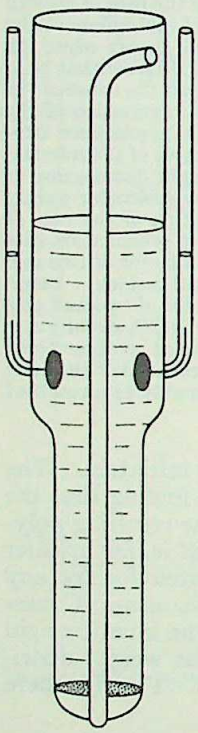

Fig. 1.—Carbon dioxide absorption cell.

For convenience the $Ba(OH)_2$ solution was prepared in 20 liter volumes. Several solutions of different strength (0.005 *M*, 0.01 *M*, 0.02 *M*) were made up and used according to the amount of carbon dioxide to be measured. It was necessary to add 0.5% of *n*-butanol in order to obtain complete absorption of the gas. The solutions were standardized with known amounts of carbon dioxide evolved from the permanganate–oxalic acid reaction.

An absorption cell was constructed so that the gas would be dispersed into the $Ba(OH)_2$ solution through a fritted glass disk. As shown in Fig. 1, a set of platinum electrodes were sealed into this cell so the conductivity of the solution could be obtained continuously. An Industrial Instruments Conductivity Bridge (RC 16B) was used for this purpose. With a number of absorption cells an equivalent number of reactions could be run simultaneously using only one conductivity bridge.

In practice the amounts of gas measured were about 10^{-3} mole. In the interests of greater sensitivity a volume of the barium hydroxide solution was used such that W_t at the end of the reaction would be about $5 \times W_0$. The theory of this method has been described[15] and can be expressed briefly as follows. If

C_0 = initial concn. of $Ba(OH)_2$ soln. in equiv./l.
C_t = concn. of $Ba(OH)_2$ soln. at time t
W_0 = initial resistance of $Ba(OH)_2$ soln.
W_t = resistance of $Ba(OH)_2$ soln. at time t
K = conductivity cell constant of absorption cell
$[CO_2]$ = moles of CO_2 absorbed.
V = vol. of $Ba(OH)_2$ soln. in l.
Λ = equivalent conductance of $Ba(OH)_2$

Then

$$2[CO_2] = V(C_0 - C_t) = V\left[\frac{1000K}{\Lambda W_0} - \frac{1000K}{\Lambda W_t}\right]$$

$$[CO_2] = \frac{1000VK}{2\Lambda}\left[\frac{1}{W_0} - \frac{1}{W_t}\right]$$

$$= \frac{VC_0}{2}\left[1 - \frac{W_0}{W_t}\right]$$

$$C_0 = \frac{1000K}{W_0}$$

$$C_t = \frac{1000K}{W_t}$$

The presence of precipitated $BaCO_3$ had almost no effect on C_0 in this range.

Anhydride Preparation.—All the anhydrides used in this work were prepared by Drs. E. R. Blout, M. Idelson and G. Fasman and R. H. Karlson according to the procedure they have described.[9] It is important to note that all possible steps in the preparation and purification of these anhydrides were done at −30° to preclude the reaction of water with anhydride. These anhydrides were recrystallized until the chloride content was less than 0.01 weight %. However, it was shown eventually that HCl even at this low level had a detectable effect on the reaction.

These anhydrides were then stored at either −30° or at Dry Ice temperatures. Under these conditions reproducible runs were obtained even after months of storage.

The technique for handling the anhydride was as follows. The anhydride was transferred to small tared capped vials at −30°. These were stored at −30° or Dry Ice temperatures until used. A vial was then brought to room temperature in a desiccator and weighed. After the desired amount of initiator was added to the solvent by means of a Burroughs–Wellcome micrometer syringe, the vial containing the anhydride was uncapped and added to initiate the polymerization. Solution of the anhydride was complete in about 1–2 minutes. As a precaution against the presence of water, solvents were fractionally distilled immediately before using. All transfers of anhydride were conducted at −30° with the exception of the final one which took only about two seconds.

The carbon dioxide was driven out of the reaction vessel by a flow of prepurified nitrogen which was saturated with the reaction solvent. This was then absorbed in the $Ba(OH)_2$ solution. Resistance measurements were made at intervals until the reaction was 90% complete. However, as a check, the reaction was allowed to proceed until 98–100% of the theoretical amount of CO_2 was evolved.

Polymer Isolation.—After the reactions were at least 99% complete the polymers were isolated by lyophilization or precipitation into reagent grade isopropyl ether. The former technique was necessary for the low A/I material.

Solvents.—Dioxane was purified according to Fieser's method and then fractionally distilled from sodium before using. Alternatively, dioxane was purified by refluxing with sodium for 24 hours, fractionally distilling, storing over sodium and redistilling immediately before use. The dioxane prepared by these methods was identical in its behavior. The latter method was more generally used.

Nitrobenzene was treated with anhydrous P_2O_5, decanted and then fractionally distilled before use. Ethylene dichloride was fractionally distilled. Dimethylformamide was treated with $NaHCO_3$, decanted and fractionally distilled from phthalic acid at reduced pressure (40 mm., T = 75°).

Dichloroacetic acid was fractionally distilled at reduced pressure.

Molecular Weight Determinations.—Intrinsic viscosities were measured in dichloroacetic acid using a modified Ubbelohde viscometer. Weight average molecular weights were obtained from these results by means of previously established relations.[10]

Titrations.—The method used in analyzing for amine groups was a conductimetric one.[10] The polymer was dissolved in a phenol–ethanol medium and the change in conductivity was followed as 0.0100 *M* $HClO_4$ was added. The intersection of two straight lines gives the end-point.

The titration of N-carboxy-anhydride with sodium methoxide has been described.[16] The titrations were conducted in dioxane solvent after bubbling prepurified nitrogen through the solution to drive out CO_2. The base (0.100 *M*)

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(14) D. G. H. Ballard and C. H. Bamford, *Proc. Roy. Soc.* (*London*), **A223**, 495 (1954).

(15) S. Ivekovic and S. Asperger, *Arkiv. Kemi*, **22**, 238 (1950).

(16) A. Berger, M. Sela and E. Katchalski, *Anal. Chem.*, **25**, 1554 (1953).

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was added rapidly to prevent polymerization of the anhydride.[9] The reproducibility of the method was ±2%.

Polymerizations in Dioxane

Initiation and Propagation.—According to the reaction scheme given in the Introduction the consumption of anhydride can be represented as follows using [A], [I] and [P] for the molar concentrations of anhydride, initiator and polymer, respectively.

$$-\frac{d[A]}{dt} = k_1[A][I] + k_2[A][P] + k_3[A][P]$$

However, if $k_1 \geqslant k_2 \gg k_3$ and $[P] = [I] < [A]$ this can be represented adequately by a pseudo first-order rate equation

$$-\frac{d[A]}{dt} = k_2[A][P] = k'[A]$$

Consequently the conventional first-order plot of log ($[A_0]/[A]$) against time can be expected to be applicable. Our data are presented in this manner but the rate constants given are always bimolecular in units of liter mole^{-1} sec.$^{-1}$.

Some typical results are shown in Fig. 2. These correspond to four polymerizations at different anhydride–initiator mole ratios: 4, 10, 20 and 40. The intercepts of the plots, extended back to zero time, are equivalent to the reaction of equimolar amounts of anhydride and initiator. This shows that the initiation by hexylamine is fast relative to the propagation step. From a study of the early part of the reaction the initiation rate constant can be estimated as 0.2 ± 0.1 liter mole^{-1} sec.$^{-1}$

For the case where [A]/[I] is 4 the reaction is seen to proceed in a completely linear fashion throughout. However, for the other three cases two successive linear regions are found. At first encounter this behavior may be thought to be simple autocatalysis. But the repeated and never failing display of two linear regions for all the purified anhydrides available prevents the acceptance of this interpretation. Consequently, we conclude that two successive propagation reactions do occur and that two propagation constants, k_{2a} and k_{2b}, can be used to describe the kinetics of the reaction. Values of these constants derived from the slopes of the two linear regions are listed in Table I for a number of

TABLE I

PROPAGATION CONSTANTS FOR AMINE-INITIATED POLYMERIZATIONS IN DIOXANE

Anhydride no.	$k_{2a} \times 10^3$ 4	20	40	80	$k_{2b} \times 10^3$ 20	40	80
442	5.2	4.6	4.4		28	32	
489	7.4	5.6	5.3		32	31	
		4.6			32		
		5.4			34		
498	8.1	9.3	6.6	9.4	28	31	30[a]
531			4.6			32	
548	7.1	8.1			34		
	8.5	6.3	8.2		35	45	
550		5.9			37		
		6.9	4.6	5.5	33	30	27
			4.9			29	
			5.0			30	
			5.3			31	
GF 31A		4.8			28		
I 62C			4.9			41	
			5.8			42	

[a] A/I = 100

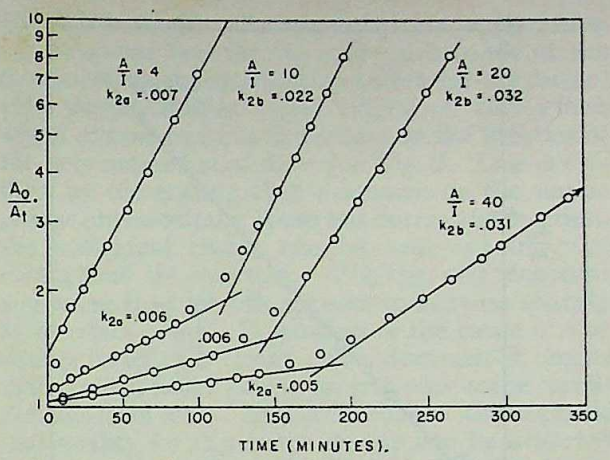

Fig. 2.—Log of ratio of original anhydride concentration to that at time *t versus* time for four different anhydride–initiator ratios; $[A_0] = 0.152$.

experiments. It is seen that k_{2a} is about 0.006 and k_{2b} is about 0.033 liter mole^{-1} sec.$^{-1}$. The somewhat higher values k_{2b} are associated with anhydrides of exceptional purity. In general the reproducibility of k_{2a} for a given anhydride was within ±20%; that for k_{2b} was within ±5%.

The other conclusion worth drawing from Fig. 2 concerns the location of the transition between the two linear regions of the kinetic plot. It is seen that in terms of fraction of anhydride consumption it occurs earlier in the reaction as the ratio [A]/[I] increases. The other polymerizations listed in Table I showed similar behavior. An eventual explanation of the two successive propagation steps must therefore also elucidate dependence of the transition on the [A]/[I] ratio and its absence at very low values of this ratio.

Initiation by Preformed Polymer.—It is of interest to determine whether the second propagation rate is continued in the presence of more anhydride. Therefore a preformed polymer was prepared in dioxane by initiating to [A]/[I] of 20 and followed kinetically to 98% completion (k_{2a} = 0.0063, k_{2b} = 0.035). Sufficient anhydride was added to give an additional [A]/[I] = 12, and more solvent added to maintain a concentration of 4%. The rate curve obtained (Fig. 3) is linear except for the very early stages of the reaction. In this region one must allow for complete solution of the anhydride in the viscous medium. However, some of the curvature may be real, caused by generation of more of the faster reacting species. The rate constant obtained for the linear portion of the curve is k_2 = 0.038 liter mole^{-1} sec.$^{-1}$, which is in good agreement with k_{2b}.

Molecular Weights of Polypeptides Prepared in Dioxane.—The number and weight average molecular weights of poly-γ-benzyl-L-glutamate samples prepared in dioxane by hexylamine initiation have been investigated by Mitchell, Woodward and Doty.[10] Their relevant results together with supporting observations of our own are summarized here.

The number average degree of polymerization, according to the proposed reaction scheme, should be equal to the [A]/[I] ratio. The proof that this is the case could be obtained by showing that the

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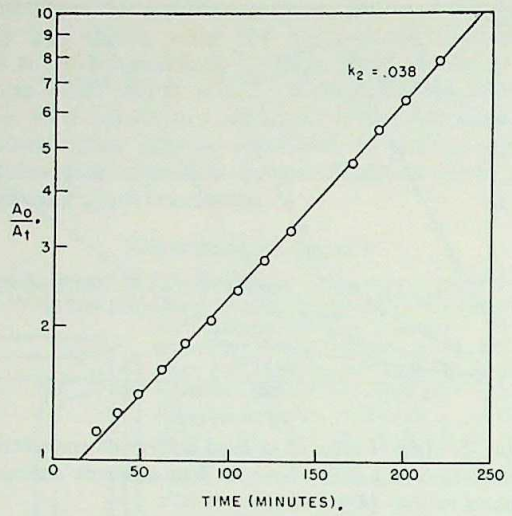

Fig. 3.—Kinetic curve for polymerization initiated by preformed polymer: $[A_0] = 0.063$, $[I] = 0.0046$.

moles of amine groups in the product is the same as the moles of initiator added. The following experiment offers a test of this point. A polymerization at [A]/[I] = 20 was allowed to proceed for 10 hours whereupon it would be expected to have reached 99.8% of completion. It was then lyophilized to remove the dioxane over a period of another 10 hours. When this product was dissolved and titrated it was found to contain 85% of the amine groups added as initiator. This indicates that the number has not substantially altered during this long polymerization. Since the reaction of the initiator was found to be very rapid and since any that might have remained would have been lost during lyophilization, it appears that amine groups are conserved during the ordinary polymerization. Therefore each initiator appears to have given rise to one polypeptide chain and the number average degree of polymerization, DP_n, can be taken as equal to the ratio, [A]/[I].

The weight average degree of polymerization, DP_w, is derivable from intrinsic viscosity measurements in dichloroacetic acid as a result of recent studies.[10] (The average value actually falls slightly below the weight average for samples having a broad molecular weight distribution but this need not concern us here.) Consequently the ratio DP_w/DP_n can be evaluated and used as an indication of the breadth of the molecular weight distribution. Some typical results are shown in Table II where they are compared with the result expected for a Poisson distribution, that is, the distribution expected for the mechanism described earlier provided that the termination reaction is negligible. If the termination reaction is not negligible the value of the ratio, DP_w/DP_n, will be increased toward a limiting value of 2. The observation is, however, that the ratio is much greater than this. Its magnitude exceeds that generally encountered in any kind of polymerization and consequently its explanation should require a very substantial alteration in the mechanism proposed.

It is relevant to note that if trace amounts of water or other possible initiator had interfered in these polymerizations they would have increased the

Table II

The Polydispersity of Typical Polymers Prepared in Dioxane

[A]/[I]	[η]	DPw	DPw/DPn Poisson	DPw/DPn Found
4	0.08	13	1.25	3.3
20	.27	170	1.05	8.5
40	.34	225	1.03	5.5

number of chains produced and hence have lowered the molecular weight over that expected. Consequently an explanation cannot be expected from this source.

Termination Steps.—Evidence for a termination step of the kind indicated in the Introduction was provided by titration data[10] which showed that carboxyl groups were present. Since the concentration of these groups (about one for each 300 residues) was independent of the [A]/[I] ratio and hence of the time required for the polymerization, and since the production of carboxyl groups by debenzylation was not detectable under polymerization conditions, these results were interpreted as favoring the termination step mentioned. If this were the only termination step involved, a check could be made on this suggestion by carrying out a polymerization at a [A]/[I] ratio that exceeded 300. If the proposed termination step were valid the rate of polymerization should gradually slow and come to a stop before all of the anhydride was consumed.

A polymerization of this kind was carried out and the kinetic plot is shown in Fig. 4. The anhydride concentration was determined in this case directly by titrating with sodium methoxide.[16] The solid circles correspond to a control experiment under identical conditions with no added initiator. The qualitative behavior of the polymerization is clearly of the type anticipated above. A quantitative consideration of this experiment, however, leads to an inquiry into other aspects of the polymerization.

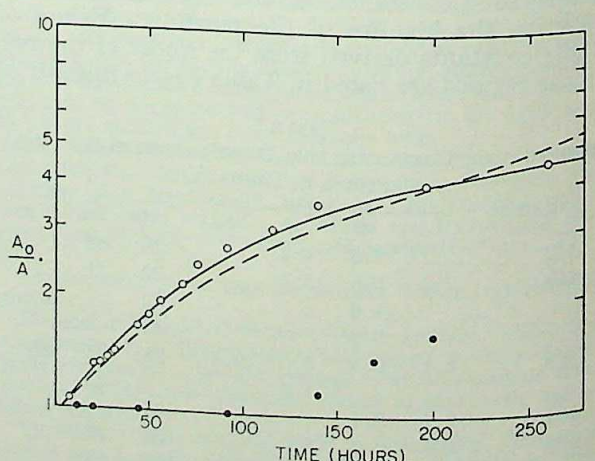

Fig. 4.—Kinetic curve for polymerization initiated by *n*-hexylamine at very high [A]/[I]. The dashed line is the calculated curve for Sela–Berger termination reaction. Solid line is calculated assuming termination through cyclization. The solid points are those for a control with no initiator added.

The calculated curve for $k_{2b} = 0.032$ and $k_3 =$ $k_2/300$ shows very poor agreement with the experi-

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mental data. Indeed the value of k_{2b} calculated from the initial slope of the data in Fig. 4 is only 0.015. On the basis of a subsequent discussion on the effect of residual HCl in the anhydride it is evident that the most likely explanation of the low apparent value of k_{2b} is that some of the initiator was inactivated by reaction with HCl. The amount of HCl required to remove half of the initiator and therefore restore the value of k_{2b} to that usually found is 1.3×10^{-4} g. per gram of anhydride. Since the residual chloride content is at just this level (0.01%)[9] this explanation seems tenable. If this is accepted, the [A]/[I] in this case was actually about 1000. If the anhydride consumption is recomputed on this basis a fairly satisfactory fit of data can be obtained if $k_3 \sim k_{2b}/1000$ (dashed line in Fig. 4). This result indicates that only one-third as many chains are terminated with carboxyl groups as titration results had indicated.[10] Thus the majority of the carboxyl groups found by titration may have been the result of debenzylation.

Having gone into this matter in so much detail it becomes necessary to pursue the possible effects of another termination step that is peculiar to this particular polypeptide, that is, the loss of amine end groups through a cyclization reaction with the elimination of benzyl alcohol.[9,17] The experiment described in the last section shows this reaction proceeds at a detectable rate (about 0.5–1.0% amine loss per hour).[6] Over the period of time taken for polymerization of [A]/[I] of 40, for example, it produces termination of about 5% of the chains. But during the much longer reaction time of the polymerization for [A]/[I] of 510 (or 1000) this cyclization reaction would have very pronounced effects. Indeed the assumption of 1% loss per hour of amine groups by a unimolecular mechanism can account for nearly all of the decay in rate observed (solid line in Fig. 4 calculated on this basis). It is clear however, that the role of this termination will be negligible in the other polymerization discussed in this paper because they were completed in much shorter times.

The result of these considerations is to show that a termination is readily demonstrated at very high anhydride–initiator ratios, and therefore a ceiling does exist for the molecular weight. The present evidence does not enable us to delineate the relative importance of the two termination steps. However, the effect of these termination reactions is not large enough to be revealed kinetically for [A]/[I] of 40 and less. For example, in a polymerization of [A]/[I] = 20 carried to 95% completion (5 hours) one would estimate that less than 7% of the chains would be terminated.

Helix Formation as the Cause of the Change in the Propagation Constant and the Consequent Broadening of the Molecular Weight Distribution.—The termination steps discussed in the previous section are obviously of minor importance in the kinetics of the polymerization in the anhydride–initiator ratios dealt with in this investigation [A]/[I] 4 to 40. Consequently, no explanation can be found here for the extreme breadth of the molecular weight distribution shown by the molecular weight studies. The origin of this effect would appear to lie in the nature of the kinetics of the polymerization as shown in Fig. 2. This is evident by recognizing that inasmuch as the amine groups are essentially preserved during the reaction, the individual chains can be expected to grow throughout the reaction. Yet the rate constant governing their growth appears to increase sharply at a certain point. Regardless of the cause of this change its effect is clearly the endowment of chains with a much faster rate of growth once some condition has been met. As a consequence, those chains that qualify for this faster growth can be expected to undergo a rapid increase in chain length. Those chains that may, for statistical reasons, be somewhat delayed in attaining the conditions for vast growth will be further delayed by the rapid consumption of anhydride by the fast growing ones. Therefore, many of the chains may never actually reach the condition for rapid growth and as a consequence a very broad molecular weight distribution would result. Thus the extreme broadening of the molecular weight distribution is seen to be the direct result of the phenomenon of two successive propagation constants for chain growth.

The cause of the shift from a slow propagation constant to a fast one is of obvious interest. The mid-point of the transition from one rate to another is seen (Fig. 2) to occur at a point where the anhydride molecules consumed per initiator is in the region of 7 to 12 for an [A]/[I] 20. That is, the transition occurs when a certain chain length is reached and is not obviously related to the anhydride–initiator ratio. Since previous studies[10] have shown that the minimum chain length required for formation of the α-helical configuration is about 10, it appears that this configurational change is the cause of the dramatic shift in propagation rates. Convincing evidence for this conclusion and proof of the transfer of chains from this β to the α configurations through growth has been provided by an infrared spectral study of the reaction by Idelson and Blout.[18] They have shown that the βL-polypeptide (non-helical) is produced in the region corresponding to the lower rate, and simultaneously with the incidence of the higher rate the formation of the α-polypeptide (helical) is observed. Through the use of deuterium labeled initiator, these investigators have shown that the βL-form is indeed the precursor of the α-polypeptide. Since the energy of activation for both rate constants is found to be low (<10 kcal.) the change in rate accompanying the configurational change is apparently due to a lowering of the entropy of activation resulting from an increased accommodation provided for the anhydride molecule at the end of a helix.

We may express the above interpretation through the equations

$$A + I \xrightarrow{k_1} P_1 + CO_2$$

(17) The rate of disappearance of amine groups in the lyophilized solid sample is about 0.5% per hour at 25°. Consequently titrations must be carried out promptly or the material must be stored at −30° or lower. Other experiments[10] also support this conclusion.

(18) M. Idelson and E. R. Blout, THIS JOURNAL, 79, 3948 (1957).

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$$A + P_1 \xrightarrow{k_{2a}} P_2 + CO_2$$
$$\vdots \qquad \vdots$$
$$A + P_9 \xrightarrow{k_{2a}} P_{10} + CO_2$$
$$A + P_{10} \xrightarrow{k_{2b}} P_{11} + CO_2 \ldots$$

$$-\frac{d[A]}{dt} = k_{2a}[A]\left(\sum_{i=1}^{10}[P_i]\right) + k_{2b}[A]\left(\sum_{10}^{\infty}[P_j]\right)$$

where $[P_i]$ represents the concentration of the polymer chain containing i peptide units.

Thus in the early stages of the polymerization, the anhydride consumption should be first order. This is the situation that is observed at an [A]/[I] of 4, and in the early regions at higher [A]/[I]. However, if additional anhydride is available to increase the chain length sufficiently to form an α-helix, this configuration may react at a new and higher rate (k_{2b}). The flux of polymer chains through the region of critical chain length will result in an autocatalytic reaction since

$$\frac{d\sum_{j=10}^{\infty}[P_j]}{dt} = k_{2a}[A][P_{10}]$$

This conversion is dependent on the concentration of chains just below the critical size and the anhydride concentration. When both have been lowered sufficiently the reaction will again be pseudo first order. This is the effect observed in Fig. 2. Consequently, a relatively large number of the more slowly propagating chains will remain as such because insufficient anhydride is available for them to reach the critical size. Because of this, the rate constant obtained for the second propagation rate will be an underestimate of its true value, perhaps by as much by a factor of 2—see also footnote 13 in reference 18. Ostensibly, at sufficiently high [A]/[I] all of the chains should be able to pass through this critical size region before the anhydride is consumed. A trend of higher rate constants for k_{2b} should therefore be observed with increasing [A]/[I]. This is the observed behavior in Fig. 2 at [A]/[I] of 10 and 20 but not beyond. A subsequent discussion on the role of impurities in this polymerization demonstrates that a small amount of HCl is sufficient to suppress this trend at higher [A]/[I]. However, Idelson and Blout do observe an increase in k_{2b} with [A]/[I] with a highly purified anhydride sample.[18] Thus the kinetic behavior and the molecular weight distribution of the products are compatible with the concept that a configuration change under the conditions of this polymerization has effected a change in reaction rate.

Effect of Impurities.—It has been observed that some samples of γ-benzyl-L-glutamate anhydride gave a rate constant for k_{2b} which differed from each other more than could be explained by probable experimental error. To investigate the origin of these occasional variations, a sample of the N-carboxy anhydride was polymerized directly after its first crystallization. At an [A]/[I] of 20, a linear pseudo first-order behavior was observed throughout the polymerization (case A, Fig. 5) in marked contrast to the two successive growth stages previously observed. However, after one recrystallization of this anhydride from methylene dichloride, two successive propagation rates became clearly evident (B in Fig. 5). In both cases the initial propagation rates of the polymerization, k_{2a}, were about equal.

In addition to the difference in kinetic behavior, there was a striking difference in the reaction mixtures when the polymerizations neared completion. The solution of impure anhydride was a quite rigid gel, whereas the product of the recrystallized anhydride was a viscous solution. The α-helical content estimated from infrared spectra was about 40% in case A and about 75% for case B. Such marked differences in kinetic behavior and reaction products must therefore be the result of different growth mechanisms.

One of the impurities to be removed by recrystallization of the anhydride is HCl. Analysis of the unpurified anhydride showed the HCl content to be 1.0 mole %. Since this could react with the initiator, *n*-hexylamine, to produce a salt which in turn may affect the course of the polymerization, a series of reactions were carried out on a highly purified anhydride at an A/I of 20 (case C, Fig. 6) to which 5.0, 0.67, and 0.23 mole % of *n*-hexylamine hydrochloride had been added (D, E and F, respectively, in Fig. 6). The results show that this adduct completely eliminates the second propagation rate in cases D and E.

Further evidence that the propagation mechanism has been altered drastically is offered by the molecular weights of the products. The weight average DP was determined in the ultracentrifuge by the Archibald approach-to-equilibrium method for case C and E, and found to be 170 and 46, respectively. The DP_w expected in absence of any complicating factors would be 21. In concordance with the evidence introduced earlier it is seen that the absence of the second propagation step has reduced the weight average DP and therefore narrowed the molecular weight distribution. (It can be argued that since alkali halides[6] do initiate the polymerization, then the presence of this added amine salt could lower the molecular weight. Actually, the amount added corresponds to only 13% of the initiator present on a molar basis. Also, the initial propagation rate is not affected significantly; this indicates that the salt is no more active as an initiator than the amine itself.)

The kinetic behavior in the presence of only 0.23 mole % of amine salt (case F of Fig. 6) deserves further comment. Under these conditions the second propagation rate is just beginning to appear. Taken by itself this behavior might be falsely interpreted as an autocatalytic reaction. However, the behavior observed with the more highly purified anhydride (case C) clearly indicates that this is just the emergence of the second propagation rate. The explanation for the variation in k_{2b} for different anhydride samples is now evident. Since the lower limit of chloride detectability is about 0.08 mole %, it is apparent that amounts of HCl beyond detection can have a large effect on the rate. The difficulty in obtaining exactly reproducible results from one anhydride preparation to another can be ascribed to variations in HCl content all of which

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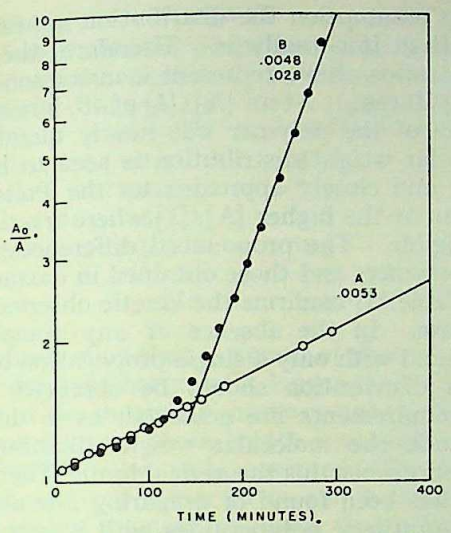

Fig. 5.—Initiation with *n*-hexylamine to [A]/[I] = 20 in dioxane. Case A corresponds to impure anhydride and Case B to the same anhydride after one recrystallization; $[A]_0$ = 0.152.

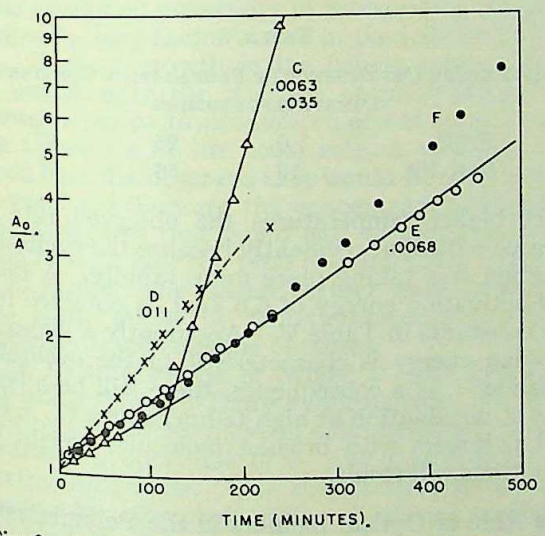

Fig. 6.—Polymerizations under same conditions as Fig. 5. Case C is a highly purified anhydride (HCl < 0.1 mole %). Case D, E and F correspond to the addition of *n*-hexylamine hydrochloride to the extent of 5.0, 0.67 and 0.23 mole %, respectively.

are below the limits of detection. This emphasizes the importance of sufficient recrystallizations to eliminate this impurity. We are indebted to Dr. E. R. Blout for suggesting the examination of the anhydride after its first crystallization and of the role of hexylamine hydrochloride.

The Occurrence and Elimination of the Two-stage Propagation in Other N-Carboxy-anhydride–Solvent Systems

L-Leucine N-Carboxy-anhydride.—The kinetic behavior of γ-benzyl-L-glutamate anhydride has been correlated with the molecular weight distribution of the products, and the origin of the behavior traced to the coil-helix transition during chain growth. However, since this anhydride cannot be purified through sublimation, the possibility remains that some impurity not removable through recrystallizations is responsible for the observed behavior. Therefore, a study of the polymerization of the anhydride of L-leucine purified in the same way was carried out. These polymerizations were conducted in nitrobenzene solution at an [A]/[I] of 20 and are shown in Fig. 7. The polymer formed does

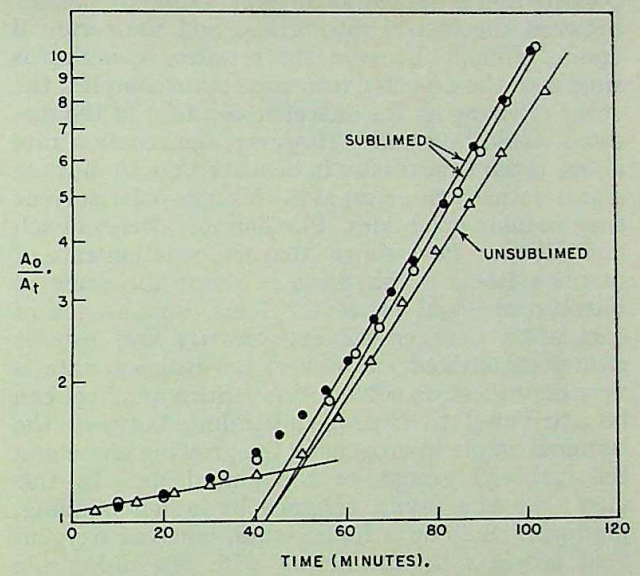

Fig. 7.—Polymerization of L-leucine N-carboxy-anhydride with initiation by *n*-hexylamine; $[A_0]$ = 0.134, [I] = 0.0066; (k_{2a} = 0.013, k_{2b} = 0.090 l. mole^{-1} sec.$^{-1}$).

precipitate under these conditions after the reaction is about 25% complete. As a result the quantitative significance of the rate constant obtained is questionable, but the demonstration of a large increase in rate similar to the γ-benzyl-L-glutamate case is apparent. (Precipitation of the polymer would be expected to decrease the rate so that this does not affect the argument.) When this anhydride was sublimed its polymerization was found to be essentially the same as for the unsublimed case. These observations therefore support the argument that the analogous behavior exhibited by γ-benzyl-L-glutamate is not due to the method of anhydride purification and indicate that two-stage propagation may be a general feature in the formation of polypeptides by this reaction. Similar behavior has also been found with L-phenylalanine anhydride.

Polymerization of γ-Benzyl-L-glutamate Anhydride in Other Solvents.—The phenomenon of two apparent rate constants in the polymerization of γ-benzyl-L-glutamate in dioxane has been observed in a number of solvents. The rate constants obtained are listed in Table III.

TABLE III
PROPAGATION RATE CONSTANTS IN VARIOUS SOLVENTS
T = 25°, [A]/[I] = 20

Solvent	Dielectric constant	k_{2a}	k_{2b}
Nitrobenzene	36	0.021	0.11
Ethylene chloride	10.3	.015	.14
Chloroform	5.1	.045	.30
Benzene	2.3	.062	.31
Dioxane	2.3	.006	.032

There is seen to be a surprising lack of correlation of rate with dielectric constant of the solvent.

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Bamford,[7] *et al.*, have noted that the propagation rate of the polymerization of several racemic anhydrides is very dependent on solvent polarity. They have observed that the polymerization of γ-benzyl-L-glutamate is less sensitive to the solvent polarity and proposed as an explanation a complex between the benzyl ester group and the terminal amine group.[7] Because the resulting complex is similar to the expected transition state complex, the effect of changing the dielectric constant of the medium would be small. However, the reaction rate above is ten times faster in benzene than in dioxane and is actually more rapid in this non-polar solvent than in more polar ones. Furthermore, Breitenbach and Allinger[6] have shown that the reaction rate of DL-phenylalanine anhydride is about the same in nitrobenzene and benzene. Thus, an absence of correlation between solvent *polarity* and rate is clearly manifested; however, the reaction rate is very dependent on solvent type. Such an effect can be attributed to hydrogen bonding between the terminal amine hydrogens in the growing chain and the carbonyl groups of the anhydride. In this view, benzene would enhance hydrogen bonding, producing thereby a higher rate, whereas oxygenated solvents by competing with the anhydride molecules for the growing chain would suppress the rate. Thus the solvation of the end of the growing chain would be greatly dependent on the solvent type.

The Absence of Two-stage Propagation in Dimethylformamide.—To elucidate further the effect of solvent upon the course of the polymerization, a medium was desired which was strongly solvating and yet inert in its behavior toward the anhydride. Dimethylformamide has been shown to prevent intermolecular association of polypeptides and would appear to satisfy these requirements.

When polymerizations were conducted in this medium it was found that the kinetic behavior contrasted strikingly with dioxane and other solvents. Only linear rate curves for the disappearance of anhydride were obtained at [A]/[I] of 20, 40 and 80 ($k_2 = 0.057 \pm 0.004$). The viscosities of the polymers were much less than those obtained from polymerizations conducted at the same [A]/[I] in dioxane. This indicated a considerably lower DP_w and assuming [A]/[I] = DP_n, a narrower distribution.[10] Because of the insensitivity of intrinsic viscosities in this low DP region, the weight average molecular weights were measured directly on several polymers; the results on two are given in Table IV.

TABLE IV

THE POLYDISPERSITY OF TYPICAL POLYMERS PREPARED IN DIMETHYLFORMAMIDE

[A]/[I]	[η]	DP_w	DP_w/DP_n Poisson	DP_w/DP_n expt.
10	0.081	14	1.1	1.4
40	.13	48	1.03	1.2

Since lyophilization of dimethylformamide is not practical those products had to be isolated through precipitation, and therefore fractionation was a serious problem for the lower [A]/[I] samples. Consequently, the [A]/[I] ratio is not strictly equal to DP_n for [A]/[I] of 10, and by making this assumption the distribution appears more broad than it actually is. Therefore, the experimental ratios above represent a maximum for the [A]/[I] 10 case. At an [A]/[I] of 40, however, the isolation of the polymer was nearly quantitative. The molar weight distribution is seen to be quite narrow and closely approximates the Poisson distribution at the higher [A]/[I] where fractionation is negligible. The pronounced difference between these polymers and those obtained in dioxane solution (Table II) confirms the kinetic observations in each case. In the absence of any complicating factors and with only a single propagation rate, the Poisson distribution should be observed. When those requirements are achieved, as in dimethylformamide the molecular weight distribution at least approaches this theoretical limit. Therefore, a means has been found of preparing low molecular weight synthetic polypeptides with a very narrow molecular weight distribution.

Reactions were conducted at several temperatures in dimethylformamide and the rate constants obtained are given in Table V.

TABLE V

TEMPERATURE DEPENDENCE OF PROPAGATION CONSTANTS IN DIMETHYLFORMAMIDE

T, °C.	0	25	40
$k_2 \times 10^3$	19	56	87

At higher temperatures the observed rate decreased with time, evidently because the cyclization reaction was taking place more rapidly. A rather low activation energy of 6.6 kcal. is obtained from the constants in Table V. Apparently a higher activation energy is characteristic of the cyclization reaction. As a consequence, there will be a larger rate of termination at high temperatures ($T > 50°$) and polymers with broader molecular weight distributions will result.

The Role of Optical Isomers in the Polymerization

The Polymerization of Racemic N-Carboxy-anhydride in Dioxane.—N-Carboxyanhydrides of γ-benzyl-DL-glutamate were prepared in the same way as the L-isomer. Upon initiation with *n*-hexylamine at [A]/[I] equal to 20 the kinetic data were found to exhibit the same general features as the L-isomer, but quantitatively there were two differences. The propagation constants were substantially lower, $k_{2a} = 0.004$ and $k_{2b} = 0.013$ liter mole^{-1} sec.$^{-1}$, and more anhydride was consumed before the transition in rates took place.

In order to ensure that these differences were not due to residual impurities in the racemic anhydride, further experiments were carried out with N-carboxy-anhydrides of the pure L- and pure D-isomers and then with the equimolar (racemic) mixture of the two (D + L). The results in dioxane at the usual concentration (4 g. anhydride/100 cc.) and for two [A]/[I] values are summarized in Table VI.

The lower rate of propagation for the racemic mixture is clearly evident: k_{2a} is reduced to about two-third and k_{2b} to about one-half of the values for the pure isomeric forms.

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TABLE VI

PROPAGATION CONSTANTS OF ISOMERIC AND RACEMIC N-CARBOXY-ANHYDRIDES OF γ-BENZYL-GLUTAMATE

Isomer or mixture	[A]/[I] = 4 $k_{2a} \times 10^3$	[A]/[I] = 20 $k_{2a} \times 10^3$	[A]/[I] = 20 $k_{2b} \times 10^3$
L	7.4	5.6	32
D	7.1	7.4	34
DL	5.1	4.5	13
D + L	5.5	4.5	15
		4.2	17
		4.4	16

The observation that the onset of the faster propagation constant occurs at a longer chain length in the case of the racemic N-carboxy-anhydrides indicates that a longer chain length is required for the helical configuration to be assumed. This is to be expected, if a copolymer of L- and D-residues has formed, due to the demonstration that helix stability does decrease upon the introduction of increasing amounts of the opposite optical isomer into the polypeptide chain.[13]

Standing in contrast to this correlation, however, is the intriguing possibility of interpreting the lowering of k_{2b} by a factor of two in the following manner. If chain growth in the helical form at least did permit only the addition of pure isomers to themselves so as to produce chains of pure D- and pure L-residues at the usual rate, it would be expected that the observed rate would be only half of the usual one because the concentration of anhydride molecules that could add to any one chain would be only half the total concentration. In order to explore this matter further some investigations were made in dimethylformamide where greater accuracy could be obtained.

The Polymerization of Mixed D- and L-N-Carboxy-anhydrides in Dimethylformamide.—Kinetic measurements were made on polymerizing mixtures of various proportions of D- and L-anhydrides in dimethylformamide. The results were first order in each case; the propagation constants are listed in Table VII.

TABLE VII

DEPENDENCE OF PROPAGATION CONSTANTS ON ANHYDRIDE COMPOSITION IN DIMETHYLFORMAMIDE

% L-isomer	100	92.5	85.5	74.7	50	0
$k_2 \times 10^3$	56	46	39	30	22	58
					22	
					21	

The effect of the opposite optical isomer on the rate of the polymerization is seen to be quite large and about the same as exhibited for k_{2b} in dioxane. Such an effect can be explained only if the propagation step is quite selective with respect to the optical isomers. This can be demonstrated more clearly by analyzing the reaction on the assumption that selectivity is determined only by the terminal residue with which the anhydride reacts. Thus in dimethylformamide solution we have

$$\text{Rate} = -\frac{d[A]}{dt} = k_2[A][I]$$

Since we wish to consider the effect on the rate of varying amounts of L- and D-anhydride ($[A_L]$ and $[A_D]$) but keeping their sum constant, we shall use mole fractions, denoted by primes. Thus

$$[A_L'] = [I_L']$$
$$[A_D'] = [I_D']$$
$$[A_D'] + [A_L'] = 1$$
$$[I_D'] + [I_L'] = 1$$
$$\text{Rate} = k'([I_D']^2 + [I_L']^2) + 2k''([I_D'][I_L'])$$

Where

$[I_D']$ = Mole fraction of polymer ending in D-residues
k' = Propagation constant for reaction between D-anhydride and polymer molecule ending in D-residue
k'' = Propagation constant for reaction between D-anhydride and polymer ending in L-residue

The dependence of the rate (and therefore the observed rate constant) on the composition of optical isomer is quadratic. Introduction of a new variable z such that $[I_L'] = z + 0.5$ leads to the simpler form

$$\text{Rate} = z^2(2k' - 2k'') + 0.5(k' + k'')$$

This expression is shown in Fig. 8 as the solid line for $k'' = 0$ (or the case where no cross-reaction exists). The values in Table VII are also plotted. It is rather surprising to find that the experimental points fall consistently below the line, whereas for any positive value of k'' they should fall above this calculated line.

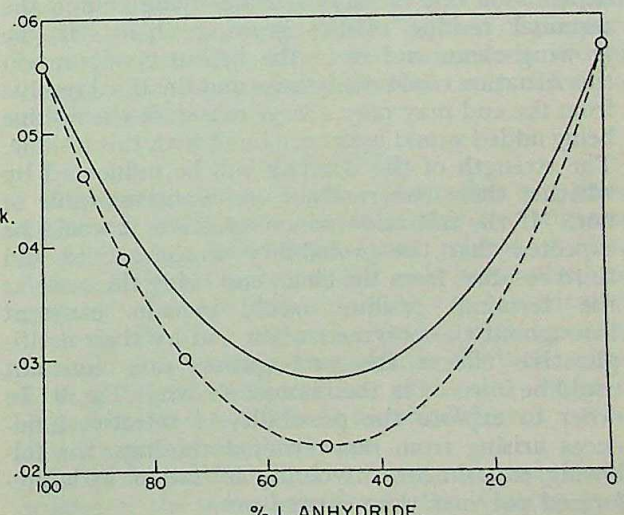

Fig. 8.—Propagation constants obtained in dimethylformamide at [A]/[I] = 20 as a function of varying D- and L-anhydride compositions. The solid line is calculated assuming L-anhydride does not react with polymer ending in D-residues (absolute preference).

The data may be treated more quantitatively by taking the log of the above expression together with the experimental points as shown in Fig. 9. The experimental points are seen to fall on a straight line within probable experimental error and this line is below the theoretical one for complete selectivity.

It is apparent therefore, that the rate constants obtained do agree with the interpretation that this polymerization is preferential with respect to the optical isomers. A complication is presented, however, in that the rate constants are lower than the

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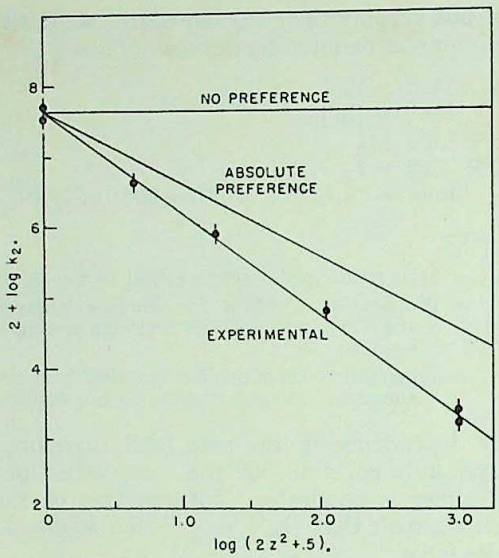

Fig. 9.—Quantitative treatment of data in Table VII according to equations in text.

minimum possible for a preferential reaction of the type assumed. Consequently, the assumption that the selectivity of this reaction is due only to interaction between the anhydride and the last residue in the chain is seen to be an invalid one. The most reasonable alternative seems to be that selectivity depends on one or more residues lying behind the terminal residue of the growing chain. If the growing chain end is in the helical configuration this situation could easily arise and the third residue from the end may play a large role since the residue being added would hydrogen bond with this residue. The strength of the bonding will be influenced by whether these two residues are enantiomorphic or not. If the initiation is non-selective, it would be expected that the probability of the second and third residues from the chain end being the same as the terminal residue would remain constant throughout the polymerization and by their multiplicative effects the propagation rate constant could be lowered in the manner shown in Fig. 9. In order to explore the possibility of selective influences arising from non-terminal residues, the following experiments involving initiation with preformed polymer were carried out.

The Polymerization of Racemic and Enantiomorphic N-Carboxy-anhydride by Preformed Polypeptide.—The polypeptide used for initiation was that made in dimethylformamide at [A]/[I] equal to 20 from L-anhydride. Consequently, it had a narrow molecular weight distribution and was predominantly in the helical configuration[10] when employed as initiator in dimethylformamide solution. Equal aliquots of this initiating polymer were added to solutions of L-, D- and DL-anhydride in such proportion that an average of 12 residues would be expected to add to each initiating chain. The results are shown in Fig. 10. It is seen that the L-anhydride continues to react at about the same rate as the initiating L-polymer. In the DL-anhydride case the reaction initially has a rate somewhat slower than in the L-anhydride case and then the rate decreases before half of the anhydride has been consumed. This is the behavior which would be anticipated from the earlier observations on the amine initiated case. That is, initially the L-anhydride present would be consumed more rapidly than the D-anhydride and as it is depleted, the rate, calcu-

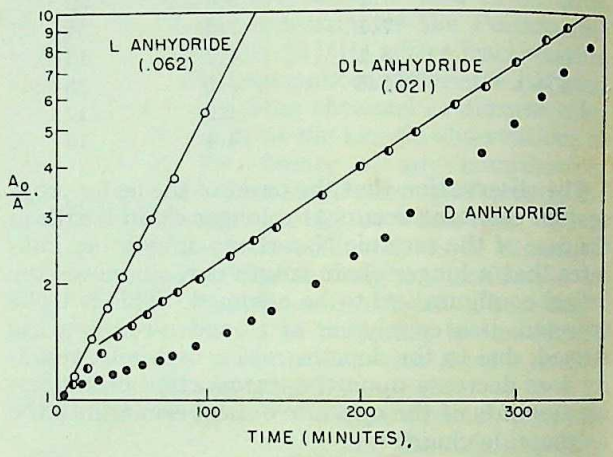

Fig. 10.—Initiation by aliquots of preformed polymer (DP = 20 of polybenzyl-L-glutamate on L (○), DL (◐), and D (●), carboxy-anhydrides of γ-benzyl-glutamate in dimethylformamide; $[A_0] = 0.058$; $[I] = 0.0048$.

lated on the basis of total anhydride concentrations, would be expected to fall. Meanwhile, one would expect the D-anhydride to be gradually added to the growing chains. The result would be an autocatalytic one according to the equation

$$-\frac{d[A_D]}{dt} = k''[A_D][I_L] + k'[A_D][I_D]$$

Since $k'' < k'$, the rate should increase as the more reactive species I_D is produced. The observed behavior is qualitatively similar to this expectation. However, the initial portion of the curve is nearly linear and has a rate constant of *ca.* 0.011 or about $^1/_5$ of that for the reaction of the pure isomer. The apparent linearity over this region is interpreted as meaning that several D-residues must add to the L-polymer before the period of autocatalysis begins.

A possible explanation for this behavior can be obtained from following the same polymerization by optical rotation. Such a study conducted in dioxane solution is shown in Fig. 11. Here equal amounts of L-, DL- and D-anhydride have been initiated by L-polymer.

The addition of L-anhydride ($[\alpha]^{25}D$ −16°) to L-polymer ($[\alpha]^{25}D$ +10) causes the optical rotation to increase continuously throughout the reaction.

The addition of DL-anhydride produces a large increase in the optical rotation because the DL-helix thus formed has a preferred screw sense in the same direction as the initiating polymer and this contributes a large positive rotation.[13]

In the case of the addition of D-anhydride, the first residues to add do so in the same helix sense as that of the initiating L-polymer. Measurement of the number of moles of CO_2 given off at the time of the maximum in the curve indicate that an average of about 4 peptide units have added to each L-polymer chain at this point. The optical rotation of a racemic helix directed in one screw sense at this wave length has been measured and found to be large and

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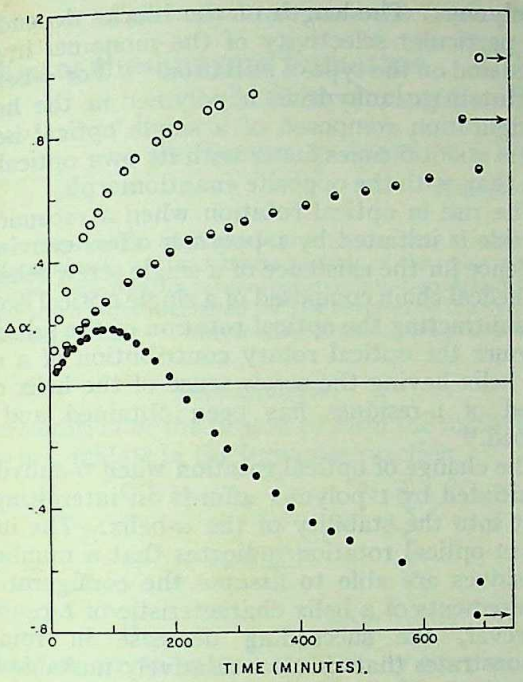

Fig. 11.—The change in optical rotation of L(○), DL (◐), and D (●), carboxy-anhydride of γ-benzyl-glutamate during polymerization initiated by aliquots of an L-polymer; $[A_0] = 0.076$; $[I] = 0.0034$; polarimeter tube length 20 cm.

positive.[13,19] The intrinsic residue rotation of D-peptide units is also large and positive.[19] The additive nature of these two effects is evidently what makes it possible to observe the increase in rotation at all. The fall in rotation after the maximum has been reached indicates that after sufficient D units have added the helix sense is inverted and the helix characteristic of D-peptides is formed, the mirror image of the L-peptide helix. This same behavior has been observed in dimethylformamide solution.

These results are consistent with the hypothesis that D-anhydride reacts more rapidly with a polymer chain characteristic of D-peptide residues. It is apparent that a number of these must exist in a sequence (at least 4) before this configuration can be realized, and the rate of the pure isomer obtained.

To summarize, the effect of the opposite enantiomorph on the reaction rate is seen to be greater than can be expected if it is assumed that only the last residue of a growing chain exerts selectivity. The most probable explanation is based on the steric influences of residues further removed, and these would be relatively large if the polymer configuration were helical.[13] The existence of this configuration under the reaction conditions has been amply demonstrated above, and elsewhere.[10,18]

In dimethylformamide a single propagation rate is observed for the L-isomer of γ-benzyl-glutamate anhydride (Fig. 12). On the basis of the above hypothesis there should be a perceptible difference in rate for the racemic anhydride corresponding to whether the growing chain is helical or not. Because of the additional interference of peptide residues further removed from the last one in a growing chain, it would be predicted that the rate should be less in the region where the helix exists as the stable configuration. Therefore at an [A]/[I] of 20 two rates should be perceptible for the racemic anhydride. Such an effect is detectable in Fig. 12, where a rate corresponding to $^3/_5$ that of the pure isomer obtains for the first 25–30% of the reaction, and then a lower rate prevails ($^2/_5$) that of the pure isomer). However, the small magnitude of the change between the rates precludes any definitive test of the hypothesis.

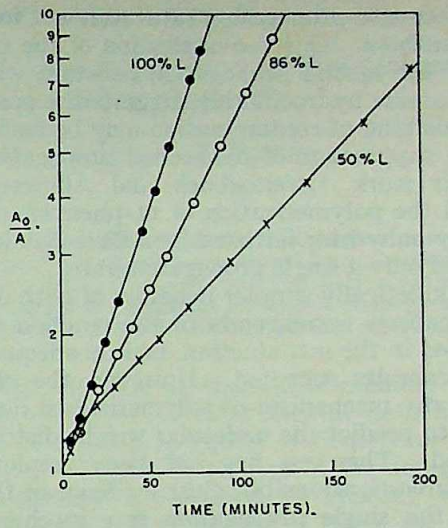

Fig. 12.—Initiation by *n*-hexylamine in dimethylformamide on N-carboxyanhydrides of γ-benzyl-glutamate with various percentages of D- and L-isomers present: 100% L (●), 86% L (○), 50% L (X); $[A_0] = 0.152\ M$; $[I] = 0.0076$.

Discussion

Relation to Other Work.—The rather surprising nature of the kinetic results of this investigation invites comparison with other related studies. Actually there appear to be only two other examinations of the kinetics of this polymerization that are relevant: others have dealt with sarcosine N-carboxy-anhydride, the polymer of which cannot form a helical configuration, and other types of initiation which give rise to a quite different mechanism than that explored here.

Ballard and Bamford[7,14] have reported kinetic studies of the polymerization of the N-carboxy-anhydride of γ-benzyl-L-glutamate in dioxane ($k_2 = 0.022$) and in nitrobenzene ($k_2 = 0.070$) and of DL-leucine in nitrobenzene ($k_2 = 0.042$). In all these cases they have found a behavior that is essentially that of a single propagation constant with occasional mild increases in rate toward the end of the reaction which they attribute to autocatalysis. The rate constants they find are intermediate between the k_{2a} and k_{2b} values we have reported above. These authors place great emphasis on the need of eliminating moisture but it seems unlikely that this can play any role in our results because of the absence of polymerization in blank experiments and the finding of a higher DP than expected, not a lower one that would result from introducing more initiating centers. Thus we find agreement in the magnitude of our rate constants with those of Ballard and Bamford but sharp difference in that

(19) P. Doty and R. D. Lundberg, *Proc. Natl. Acad. Sci.*, **43**, 213 (1957).

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two successive propagation rates were not found by these authors. Our demonstration of the elimination of the second propagation constant with sufficient amine hydrochloride suggests the possibility that this kind of contamination may be responsible for the suppression of the second propagation rate in their work. Breitenbach and Allinger[5] have studied the polymerization of DL-phenylalanine N-carboxy-anhydride initiated by a diethylamide, and reported only a single propagation rate.

The kinetically simpler behavior of both of these investigations corresponds to the reaction scheme described in the introduction, and its adequacy has been generally accepted. However, the ultimate test of any mechanism of polymerization lies in its ability to predict the molecular weight distribution obtained. This test has not been employed in earlier investigations but clear evidence of the failure of the single propagation rate mechanism is contained in the work of Blout and Karlson[9] who found that the DP_w did not vary in the predicted manner with the anhydride–initiator ratio. The demonstration of the existence of a broad molecular weight distribution[10] then became the basis of the starting point of this investigation.

Whether the contrast between the experimental findings of this work and that of other investigators is a function of the particular amino acid used, its non-racemic nature, the purity of the anhydride, or other undetermined factors, is not clear. *However, the consistent reproduction of the results reported herein, the abnormally broad molecular weight distribution, the suppression of this anomaly by careful selection of solvent, or by deliberate addition of an impurity, and the infrared spectral studies on both the rate and products*[18] *provide clear and consistent support for the contention that two successive propagation rates do exist for this polymerization.*

The dependence of these propagation rates on the anhydride–initiator ratio leads to the presumption that the two propagation rates are a development of the configurational change occurring in solution. Independent infrared spectral evidence has been presented[18] to support this postulate.

Role of Optical Isomers in the Polymerization.—The effect of the enantiomorph on the rate of the polymerization has been investigated very little. The evidence presented above demonstrates the presence of a rather large selectivity in the reaction. Therefore the product of the polymerization of racemic N-carboxy-anhydrides is not a polymer composed of randomly mixed D- and L-peptide residues, but approaches very closely that of a block copolymer. The length of the blocks depends on the particular selectivity of the monomer investigated and on the type of initiation.[20] For γ-benzyl-DL-glutamate anhydride a polymer in the helical configuration composed of a single optical isomer reacts about 5 times faster with its own optical isomer than with the opposite enantiomorph.

The rise in optical rotation when a racemic anhydride is initiated by L-polymer offers convincing evidence for the existence of a single screw sense for the helical chain composed of a single optical isomer. By subtracting the optical rotation of the initiating polymer the optical rotary contribution of a racemic helix having the screw sense of the helix composed of L-residues has been obtained and described.[19]

The change of optical rotation when D-anhydride is initiated by L-polymer affords an interesting insight into the stability of the α-helix. The initial rise in optical rotation indicates that a number of D-residues are able to assume the configurational requirements of a helix characteristic of L-residues. However, the succeeding decrease in rotation demonstrates that this is a relatively unstable configuration. If the eventual breakup of the helical configuration is assumed to be due to side chain steric repulsion, it can be shown that maximum repulsion is attained when the L-peptide residues are in a right-handed helical sense. In this structure the side chains are directed along the chain such that L- and D-groups would interfere when a block polymer of L and D-residues is prepared. The existence of a left-handed helix for L-residues would result in the side chains being directed in opposite directions for the two residues with a consequent loss of interference. Therefore the helical breakup affords additional indirect evidence that L-peptide residues exist in a helix of right-handed screw sense as first suggested by Perutz.[21]

Acknowledgment.—We are pleased to acknowledge as a gift the N-carboxy-anhydrides used herein from Dr. E. R. Blout and Mr. Roy Karlson. We also would like to acknowledge the help and advice of Dr. J. T. Yang and Mr. J. C. Mitchell, one of whom (J.C.M.) was responsible for many of the molecular weight measurements reported. Financial support was provided by the Office on Naval Research (N5ori-07654).

(20) A more extreme selectivity has been noted in polymerizations initiated by methoxide ion by E. R. Blout and M. Idelson, THIS JOURNAL, **78**, 3857 (1956).

(21) M. F. Perutz, *Ann. Repts. on Prog. Chem.* (*Chem. Soc. London*), **48**, 361 (1951).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

Studies of the Enzyme Fumarase. VI.[1] Study of the Incorporation of Deuterium into L-Malate during the Reaction in Deuterium Oxide[2,3]

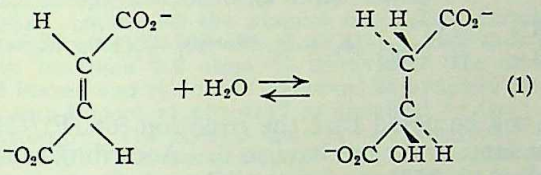
BY ROBERT A. ALBERTY, WILMER G. MILLER AND HARVEY F. FISHER

RECEIVED JANUARY 28, 1957

The incorporation of deuterium into L-malate during the dehydration to fumarate by fumarase in deuterium oxide has been determined. After various periods of time the reaction was stopped and the L-malate analyzed for non-exchangeable deuterium. Deuterium is incorporated into L-malate more slowly than fumarate is produced, and the rate is in quantitative agreement with that expected for the reversal of the over-all reaction. In order to explain the absence of exchange and of a deuterium rate effect it is necessary to introduce a further intermediate into the mechanism of the fumarase reaction.

Introduction

The addition of the proton to form the methylene group in L-malate in the fumarase reaction



(1)

has been shown to be stereospecific by carrying out the reaction in deuterium oxide.[4] The L-malate which is formed by the action of pig heart fumarase contains one atom of deuterium in the methylene group. Since the hydroxyl deuterium exchanges rapidly with an aqueous medium, and is always exchanged out before analysis for deuterium, the product will be referred to as monodeutero-L-malate. By use of nuclear magnetic resonance experiments at low temperatures it has been possible to show that the two protons in the monodeutero-L-malate are in the gauche position in solid L-malic acid.[5] When the monodeutero-L-malate was dehydrated enzymatically in ordinary water it was found that both the maximum initial velocity and the Michaelis constant are the same as for ordinary L-malate. If the breaking of the methylene carbon–hydrogen bond were rate determining, substitution of deuterium for the hydrogen would be expected to produce a decrease in rate of approximately two to sevenfold.[6,7] The absence of deuterium rate effect in the dehydration of monodeutero-L-malate suggests that there might be an exchange of this specific hydrogen atom with hydrogen atoms of the medium proceeding at a rate considerably faster than that of the dehydration reaction. Usually an exchange reaction is studied in the absence of an over-all reaction so that there is only a "virtual" reaction.[8] If in the present case we started with an equilibrium mixture of fumarate and L-malate in D_2O it would be difficult to detect a slow direct exchange of a methylene hydrogen of L-malate with the medium because the amount of exchange would be obtained from the experimental data by subtraction of the incorporation of deuterium due to reaction 1. Greater sensitivity in the detection of direct exchange is obtained by starting with L-malate in D_2O. A correction is made for the incorporation of deuterium into L-malate in the hydration of the fumarate produced by the use of equations recently derived for first-order reactions.[9]

Theory

A considerable simplification in the calculation of the deuterium incorporation into L-malate by the reverse reaction is made possible by carrying out the reaction under conditions where the approach to equilibrium is first order.

$$\mathrm{M} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{F}\ (+\mathrm{H_2O}) \qquad (2)$$

If only L-malate is initially present

$$\ln \frac{(\mathrm{M})_0 - (\mathrm{M})_{eq}}{(\mathrm{M}) - (\mathrm{M})_{eq}} = \ln \frac{(\mathrm{F})_{eq}}{(\mathrm{F})_{eq} - (\mathrm{F})} = (k_1 + k_2)t = 0.693t/t_{1/2} \qquad (3)$$

where $(\mathrm{M})_0$ is the initial concentration of L-malate, $(\mathrm{M})_{eq}$ is the equilibrium concentration and (M) is the concentration at time t. The concentrations used throughout are total molar concentrations without regard to the extent to which the weak acids exist in various ionized forms. The second form of the logarithmic term comes from the fact that $(\mathrm{M})_0 = (\mathrm{M}) + (\mathrm{F}) = (\mathrm{M})_{eq} + (\mathrm{F})_{eq}$. The first-order rate constants k_1 and k_2, which for the enzymatic reaction are directly proportional to the enzyme concentration, may be calculated from a plot of $\log [(\mathrm{F})_{eq} - (\mathrm{F})]$ *versus* t, and the apparent equilibrium constant for reaction 2.

$$K_{app} = \frac{(\mathrm{F})_{eq}}{(\mathrm{M})_{eq}} = \frac{(\mathrm{F})_{eq}}{(\mathrm{M})_0 - (\mathrm{F})_{eq}} = \frac{k_1}{k_2} \qquad (4)$$

It is shown[10] readily that for mechanisms of the type

$$\mathrm{M} + \mathrm{E} \rightleftharpoons \mathrm{X_1} \rightleftharpoons \mathrm{X_2} \rightleftharpoons \cdots \rightleftharpoons \mathrm{F} + \mathrm{E} \qquad (5)$$

where E represents the enzymatic site and X_1, X_2, . . . are intermediates, the over-all reaction will be pseudo first order under conditions where the Michaelis constants for the forward and reverse re-

(1) The preceding article in this series is R. A. Alberty and W. H. Peirce, THIS JOURNAL, **79**, 1526 (1957).

(2) Presented at the 129th meeting of the American Chemical Society in Dallas, April 10, 1956.

(3) This research was supported by grants by the National Science Foundation and by the Research Committee of the Graduate School of the University of Wisconsin from funds supplied by the Rockefeller Foundation and by the Wisconsin Alumni Research Foundation.

(4) H. F. Fisher, C. Frieden, J. S. McKinley McKee and R. A. Alberty, THIS JOURNAL, **77**, 4436 (1955).

(5) T. C. Farrar, H. S. Gutowsky, *et al.*, *ibid.*, **79**, 3978 (1957).

(6) F. H. Westheimer and N. Nicolaides *ibid.*, **71**, 25 (1949).

(7) K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

(8) H. A. C. McKay, *Nature*, **142**, 997 (1938).

(9) R. A. Alberty and W. G. Miller, *J. Chem. Phys.*, **26**, 1231 (1957).

(10) R. A. Alberty and B. E. Meyers, THIS JOURNAL, **79**, in press (1957).

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actions are equal.[11] This statement applies under conditions where $(E)_0 << (M)_0$ and the time required to reach the steady state is negligible. Fortunately, conditions under which the Michaelis constants for the two substrates are equal can be achieved experimentally.[12,13] Carrying out the reaction under first-order conditions does not lead, of course, to any actual simplification of the mechanism but just to a simpler calculation of the fraction of L-malate present at any time that has been formed by the reverse reaction. The integrated rate equation[14] for mechanism 5 shows that the pseudo first-order rate constants k_1 and k_2 in equation 3 are proportional to enzyme concentration and are functions of the initial concentration of L-malate.

When the over-all reaction is carried out under pseudo first-order conditions in D_2O, the incorporation of deuterium through the reversal of the forward reaction may be represented by

$$\mathrm{M} \underset{k_2(\mathrm{T})}{\overset{k_1}{\rightleftharpoons}} \mathrm{F} \underset{k_1}{\overset{k_2(\mathrm{T}^*)}{\rightleftharpoons}} \mathrm{M}^* \qquad (6)$$

where M* is L-malate with deuterium in the specific methylene position, and (T) and (T*) are the mole fractions of the two isotopically different forms of the solvent. Thus (T) + (T*) = 1. The use of k_1 for the specific rate constant for the dehydration of both M and M* is justified by the absence of any isotope rate effect.[4] Since (T*) >> (T) in the experiments to be considered, the fact that F may react with H_2O and D_2O at somewhat different rates in the same solution would not introduce an appreciable error in these calculations.

The integrated rate equations for reaction 6 for the boundary condition (M) = $(M)_0$, (F) = 0, and (M*) = 0[15] at $t = 0$ are[9]

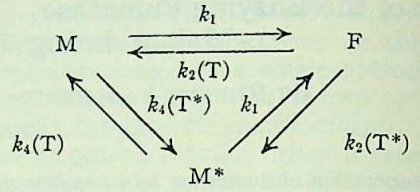
$$\frac{(M)}{(M)_0} = \frac{(T)}{(k_1 + k_2)} [k_2 + k_1 e^{-(k_1+k_2)t}] + (T^*)e^{-k_1 t} \qquad (7)$$

$$\frac{(F)}{(M)_0} = \frac{k_1}{(k_1 + k_2)} [1 - e^{-(k_1+k_2)t}] \qquad (8)$$

$$\frac{(M^*)}{(M)_0} = \frac{(T^*)}{(k_1 + k_2)} [k_2 + k_1 e^{-(k_1+k_2)t}] - (T^*)e^{-k_1 t} \qquad (9)$$

Once the values of k_1 and k_2 have been obtained from studies of the over-all reaction, the concentration of deutero-L-malate, M*, expected from mechanism 6 may be calculated for any time. There is an induction period in the formation of M* which arises initially as a function of t^2.

If deuterium is incorporated into the specific methylene position of L-malate by an additional process, for example by a rapid exchange of an intermediate with the medium, the first-order rate constant of this additional process is represented by the value of k_4 in



(10)

The integrated rate equations for this mechanism are[9]

$$\frac{(M)}{(M)_0} = \frac{(T)}{(k_1 + k_2)} [k_2 + k_1 e^{-(k_1+k_2)t}] + (T^*)e^{-(k_1+k_4)t} \qquad (11)$$

$$\frac{(F)}{(M)_0} = \frac{k_1}{(k_1 + k_2)} [1 - e^{-(k_1+k_2)t}] \qquad (12)$$

$$\frac{(M^*)}{(M)_0} = \frac{(T^*)}{(k_1 + k_2)} [k_2 + k_1 e^{-(k_1+k_2)t}] - (T^*)e^{-(k_1+k_4)t} \qquad (13)$$

It will be noted that the equation for $(F)/(M)_0$ is the same as for mechanism 6. According to mechanism 10, M* appears initially as a linear function of time.

Procedure

The reactions were carried out in deuterium oxide[16] solutions containing potassium succinate which acted as a buffer and provided a convenient dilution of the D_2O obtained by burning the dry sample. The potassium succinate, prepared from Merck succinic acid (m.p. 185–187°), contained less than 0.01 mole % fumarate as determined spectrophotometrically by treatment with fumarase. Succinate acts as a competitive inhibitor of fumarase and so it does combine with the enzymatic site, but investigation showed that fumarase does not catalyze the exchange of the hydrogen atoms of succinate with the medium under the conditions of the present experiments. The L-malic acid was obtained from the Pfanstiehl Chemical Company and was recrystallized from ethyl acetate.[17] Absorbancy measurements at 250 mμ showed that the L-malate preparation contained less than 0.03 mole % fumarate. If malic acid absorbs at all at this wave length, the percentage of fumarate impurity is less than 0.03%.

In view of the importance of the observation[4] that deutero-L-malate is dehydrated enzymatically at the same rate as ordinary L-malate when a rather large effect might be expected,[6,7] this rate experiment was repeated. Monodeutero-L-malate prepared enzymatically was purified by partition chromatography,[18] using a 35% butanol–65% chloroform mixture as the flowing phase and 0.5 *N* sulfuric acid supported on Hyflo Super-Cel as the stationary phase. The Michaelis constants in ordinary water obtained using 0.05 *M* phosphate buffer of *p*H 7.3 were 2.2 m*M* for ordinary L-malate and 2.7 m*M* for the deutero-L-malate. The ratio of the maximum initial velocities in H_2O for the normal to the deutero compound was 0.94, which is equal to unity within the experimental error in conformance with the earlier result.[4]

The solutions for the exchange experiments were prepared by dissolving L-malic acid and potassium succinate in D_2O, titrating to the desired *p*H with potassium hydroxide dissolved in D_2O, and finally diluting to the desired concentration. The *p*H values of the D_2O solutions determined with a Beckman Model G *p*H meter cannot be given to simple interpretation, but it was noted that they are very nearly equal to the *p*H values obtained after reconstituting the dried reaction mixtures in ordinary water at 25°.

(11) W. E. Lands and C. Niemann, This Journal, **77**, 6508 (1955), have shown that an enzymatic reaction which goes to completion is pseudo first order if the competitive inhibition constant for the product is equal to the Michaelis constant for the substrate.

(12) R. A. Alberty, V. Massey, C. Frieden and A. R. Fuhlbrigge, *ibid.*, **76**, 2485 (1954).

(13) C. Frieden and R. A. Alberty, *J. Biol. Chem.*, **212**, 859 (1955).

(14) R. A. Alberty, *Advances in Enzymology*, **17**, 1 (1956).

(15) By dealing with atom per cent. excess it is possible to avoid the necessity of a small correction for the normal isotopic abundance of deuterium in the methylene position of malate.

(16) The D_2O(99.5%) was supplied by the Stuart Oxygen Company, Berkeley, Calif., and obtained on allocation from the Isotopes Division, U. S. Atomic Energy Commission.

(17) C. Frieden, R. G. Wolfe and R. A. Alberty, This Journal, **79**, 1523 (1957).

(18) W. W. Cleland and M. L. Johnson, *J. Biol. Chem.*, **220**, 595 (1956).

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Fumarase crystallized from pig heart muscle extract by the method of Frieden, Bock and Alberty[19] was used in these experiments. The reaction was started by the addition of enzyme which had been diluted to the desired concentration in 99.5% D_2O. The reaction mixture was placed in cuvettes in a Beckman DU spectrophotometer, and the absorbancy was recorded at one minute intervals at 300 mμ. The spectrophotometer was equipped with thermospacers held at 25 ± 0.3° by water circulated from a thermostat.

In order to stop the reaction at appropriate times 3-ml. aliquots of the reaction mixture were pipetted into 3 ml. of boiling ethyl alcohol. The samples were evaporated to dryness on a steam-bath and the ionizable deuterium was exchanged out by redissolving the samples three times in 3 ml. of water and each time evaporating to dryness. Finally the samples were dried at 35° in a vacuum oven. Blanks were run to determine the rate of non-enzymatic incorporation of deuterium into L-malate and succinate during the reaction period and during the evaporation on the steam-bath. These blanks were found to contain the normal isotopic abundance of deuterium.

Before combustion the samples containing appreciable deuterium were diluted with malic acid so that they contained less than 0.8 atom % deuterium. The samples were burned and the water converted to hydrogen by use of a zinc furnace at 410–414° as described by Graff and Rittenberg.[20] The H_2–HD samples were analyzed with a Consolidated mass spectrometer.[21] The normal abundance of deuterium in the L-malate used was found to be 0.012 atom per cent.

The fumarase concentration was determined at various times during the reaction by diluting 0.1 ml. of the reaction mixture to 4.1 ml. in ordinary water containing 0.05 M L-malate and 0.05 M phosphate buffer of pH 7.3. The turnover number for the enzyme under these conditions[17] is 10^5 min.$^{-1}$. The initial steady-state rate was determined using a DUR spectrophotometer.[12]

Experimental Data

A plot of the apparent first-order rate constant according to equation 3 is given in Fig. 1 for experiment B over a period of eight half-lives. The fact that the plot has a slope of 5×10^{-4} min.$^{-2}$ M rather than a zero slope, as would be expected for a first-order reaction, indicates that under these conditions the Michaelis constants for the forward and reverse reactions are not quite equal. The deviation from first-order behavior is small enough to be negligible. The rate constants calculated from equations 3 and 4 are $k_1 = 0.107$ min.$^{-1}$ M and $k_2 = 0.024$ min.$^{-1}$ M for this enzyme concentration which is 3.3×10^{-7} M. Therefore, the first-order constants for one molar enzyme are

$$k_1' = (0.024 \text{ min.}^{-1} M)/(3.3 \times 10^{-7} M)(60) = 1.2 \times 10^3 \text{ sec.}^{-1}$$

$$k_2' = (0.107 \text{ min.}^{-1} M)/(3.3 \times 10^{-7} M)(60) = 5.3 \times 10^3 \text{ sec.}^{-1}$$

Under conditions where the Michaelis constants for the forward and reverse reactions are equal, the integral equation[14] for mechanism 5 reduces to

$$\ln \frac{(F)_{eq}}{(F)_{eq} - (F)} = \frac{V_M + V_F}{K_M + (M)_0} t \qquad (14)$$

where V_M and V_F are maximum initial velocities for L-malate and fumarate as substrate and K_M is the Michaelis constant for L-malate. Since in the present experiments $(M)_0 >> K_M$, k_1' above would be interpreted as $V_M/(M)_0$ and k_2' as $V_F/(M)_0$. The experimental values of k_1' and k_2' are slightly smaller than would be expected from the values of V_F and V_M for phosphate and tris-(hydroxymethyl)-aminomethane buffers.

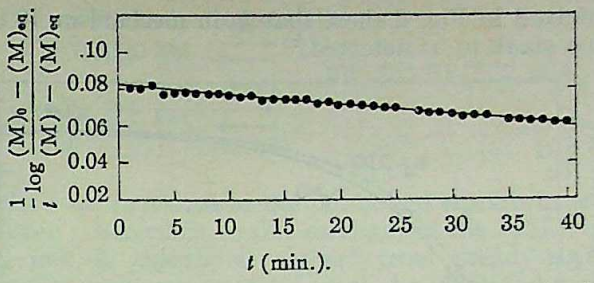

Fig. 1.—Plot of kinetic data for the fumarase reaction in D_2O at 25°. The reaction mixture contained 0.952 M potassium L-malate, 0.952 M potassium succinate and had a pH of 5.8 when reconstituted in H_2O.

The fractions of total substrate deuterated at various times are given for two experiments in Table I. For experiment A the pH of the reaction mixture reconstituted in ordinary water was 6.6 at 25° and for experiment B was 5.8. In experiment A the initial concentrations of potassium L-malate and potassium succinate were each 0.1 M. The enzyme concentration was such that the half time ($t_{1/2}$) for the over-all reaction was 21.8 min., and samples were taken for analysis after 3.7 and 40 min. In experiment B the initial concentrations of potassium L-malate and potassium succinate were each 0.0952 M. The half-time for the over-all reaction was 5.25 min., and the reaction was stopped in samples for analysis 2, 10, 25, 75, 226 and 291 minutes after addition of fumarase. The calculated values of the fractions of the substrate which are expected to be deutero-L-malate were obtained using mechanism 6 and equation 9, letting $k_1 = 1$, $k_2 = 4.55$, (T) = 0.03, and (T*) = 0.97. The time variable in equation 9 is a generalized time τ and is determined by correlation with the half-time of the fumarate to L-malate reaction. The error in measuring the equilibrium constant causes most of the uncertainty in the calculated values, since the values for k_1, k_2 and the relationship between the generalized time τ and the experimental half-times are dependent upon the equilibrium constant. The experimental data

TABLE I

INCORPORATION OF DEUTERIUM INTO L-MALATE DURING THE FUMARASE REACTION

$t/t_{1/2}$	τ	Molecules of deutero-malate / Total molecules of substrate: Exptl.	Eq. 9
		Expt. A	
0.18	0.022	0.002 ± 0.001	0.003 ± 0.002
1.5	0.186	0.046 ± 0.005	0.055 ± 0.007
		Expt. B	
0.38	0.047	0.0067 ± 0.0005	0.004 ± 0.002
1.91	0.236	.071 ± .004	.075 ± .005
4.76	0.590	.26 ± .01	.263 ± .008
14.3	1.77	.59 ± .01	.631 ± .007
43.0	5.34	.77 ± .02	.791 ± .005
55.5	6.88	.75 ± .02	.794 ± .005

(19) C. Frieden, R. M. Bock and R. A. Alberty, THIS JOURNAL, **76**, 2482 (1954).

(20) J. Graff and D. Rittenberg, *Anal. Chem.*, **24**, 878 (1952).

(21) The deuterium analyses were made in the Biochemistry Department by courtesy of Professor Robert H. Burris and in the Department of Chemistry by courtesy of Professor Irving Shain.

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plotted in Fig. 2 show that k_4 in mechanism 10 is too small to be detected.[22]

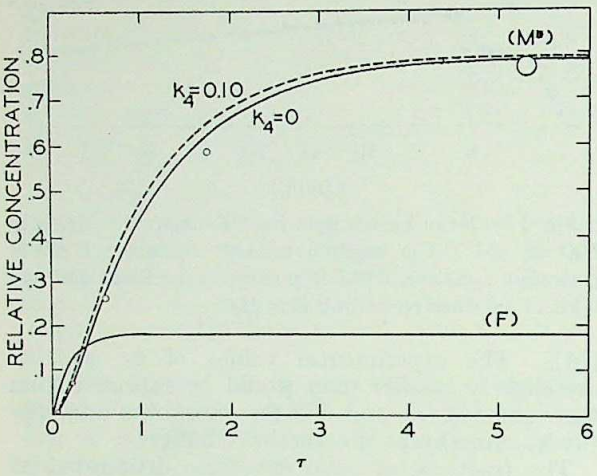

Fig. 2.—Relative concentrations of fumarate and monodeutero-L-malate as a function of generalized time. The lines are calculated using equations 8 and 9 letting $k_1 = 1$, $k_2 = 4.55$, (T) = 0.03 and (T*) = 0.97. The dashed line shows the relative concentration of monodeutero-L-malate expected if k_4 in mechanism 10 is 0.10 (calculated with equation 13).

The concentration of active enzyme is given in Table II as a function of time for experiment B.

TABLE II

CONCENTRATION OF ACTIVE ENZYME AS A FUNCTION OF TIME

Time (min.)	Molar concn. of active enzyme × 10^7	Time (min.)	Molar concn. of active enzyme × 10^7
18	3.7	131	3.3
48	2.9	279	3.3
81	3.3		

Av. = 3.3×10^{-7} M

The concentration of active enzyme as determined by the standard assay remained constant within the experimental accuracy during the entire reaction period.

The apparent equilibrium constant for the fumarase reaction defined by equation 4 has been determined earlier[23] as a function of ionic strength, pH and temperature. Since the values in heavy water are required in this research they have been determined at 99.5% D_2O. At 25°, pH values from 5.8 to 7.5 and ionic strengths up to 0.4, the equilibrium constant is approximately 5% lower than the corresponding values for ordinary water. In this connection it is interesting to note that the equilibrium constant for the hydrolysis of ethyl acetate is the same in D_2O and H_2O.[24]

Table III gives the molar absorbancy indices of dipotassium fumarate in D_2O at 25° and also the ratios of the absorbancy indices determined for D_2O and H_2O solutions.

(22) This conclusion is in contradiction with that reached in preliminary experiments[4] in which only very small extents of reaction were used.

(23) R. M. Bock and R. A. Alberty, THIS JOURNAL, **75**, 1921 (1953).

(24) Nachod, *Z. Elektrochem.*, **44**, 72 (1938); Kailan and Ebeneder, *Z. physik. Chem.*, **A180**, 157 (1937).

TABLE III

ABSORBANCY INDICES OF DIPOTASSIUM FUMARATE IN D_2O AT 25°

Wave length (mμ)	a, M^{-1} cm.$^{-1}$	a_{D_2O}/a_{H_2O}	Wave length (mμ)	a, M^{-1} cm.$^{-1}$	a_{D_2O}/a_{H_2O}
300	34	0.90	250	1325	0.95
290	101	.93	240	2210	.89
280	250	.96	230	3950	.89
270	475	.95	220	8350	.91
260	805	.95			

Discussion

The observed concentration of monodeutero-L-malate is in good agreement with that calculated for mechanism 6. Actually all that can be done experimentally is to set a maximum value for k_4 in mechanism 10. The dashed line in Fig. 2 for $k_4 = 0.10$ shows that if exchange accompanies the over-all reaction, the value of k_4 must be less than a tenth the value of k_1. Since no exchange has been detected the carbon–hydrogen bond must be formed in a step preceding the rate-determining step, or in the rate-determining step, in the hydration of fumarate. Since there is no isotope rate effect, the carbon–hydrogen bond must be formed in a step preceding the rate-determining step. Earlier kinetic calculations[1] had shown that the dissociation of fumarate from the enzyme is not the rate-determining step in the dehydration of L-malate. If this were not true it would be expected that an appreciable value of k_4 would have been obtained in the present experiments. Englard and Colowick[25] have obtained results showing that deuterium is incorporated into citrate under the action of aconitase *via* the process: citrate → aconitate ⇄ labeled citrate.

The significance of the absence of both a deuterium rate effect and exchange in the fumarase reaction may be discussed with reference to the possibilities indicated in Table IV.[26] These are the general types of simple mechanisms which might be followed by the fumarase reaction. The abbreviations HCCOH, C=C and $^-$CCOH represent the enzyme–substrate complexes and intermediates in the reaction from which the indicated ions, H^+ or OH^-, have been removed. The HCCOH intermediate dissociates to produce free enzyme and L-malate, while the C=C intermediate dissociates to produce free enzyme and fumarate. The fact that no deuterium rate effect and no exchange are observed would appear to eliminate a concerted mechanism[27] and indicates that the reaction follows a mechanism of the first type. Thus in order to account for these observations it has been necessary to introduce a further intermediate into the mechanism for the fumarase reaction. Thus the earlier representation[28] of the intermediates which were required to account for the effect of pH on the forward and reverse reactions may be extended as shown in Fig. 3. According to this mechanism the acid dissociation constants for EM obtained as described in the preceding article in this series would

(25) S. Englard and S. P. Colowick, *J. Biol. Chem.*, in press.

(26) The authors are indebted to Dr. John F. Brown for helpful discussion of these possibilities.

(27) C. G. Swain and J. F. Brown, THIS JOURNAL, **74**, 2538 (1952).

(28) R. A. Alberty, *J. Cellular and Comp. Physiol.*, **47**, 245 (1956).

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TABLE IV

EXPECTED DEUTERIUM RATE EFFECTS AND EXCHANGE FOR VARIOUS FUMARASE MECHANISMS

			Isotope rate effect	Exchange
Hydroxyl removed first				
$HCCOH \rightleftharpoons OH^- + HCC^+ \rightleftharpoons H^+ + C{=}C$				
(1)	slow	fast	No	No
(2)	fast	slow	Yes	No
Hydrogen removed first				
$HCCOH \rightleftharpoons H^+ + {}^-CCOH \rightleftharpoons OH^- + C{=}C$				
(3)	slow	fast	Yes	No
(4)	fast	slow	No[a]	Yes
Concerted mechanism				
(5)	$HCOOH \rightleftharpoons H^+ + C{=}C + OH^-$		Yes[b]	No

[a] Isotope effects on equilibria would be expected to be too small to show up in measured rates. [b] A smaller isotope rate effect than the "normal" might be expected.

be those for the enzyme-L-malate complex, but those for EF would be a weighted average of the acid dissociation constants for the two intermediates shown on the left. The movement of the positive charge on RH^+ to the dicarboxylic acid in the new intermediate may be the cause of the acid strengthening of K_{aEF} over K_{aE} which is found experimentally and which stands in contrast with the acid weakening caused by the binding of L-malate.

The data of Table I are further evidence for the absence of even a small effect of the substitution of deuterium for hydrogen on the rate of dehydration of L-malate. If ordinary L-malate were dehydrated faster than the monodeutero-L-malate formed, the concentration of fumarate would go through a maximum which easily could be observed. If the ratio of first-order rate constants for the dehydration of ordinary malate and monodeutero-L-malate was 1.36, a maximum fumarate concentration 10% greater than the equilibrium fumarate concentration would be reached after six half lives for the over-all reaction.

The treatment of the data in terms of mechanisms 6 and 10 is required by the complicated nature of the actual mechanism and the fact that kinetic data can be obtained only in the steady state. The actual mechanism is of the type

$$\left.\begin{array}{l} M + E \underset{}{\overset{}{\rightleftharpoons}} EM \overset{\text{slow}}{\rightleftharpoons} \\ M + E \underset{}{\overset{}{\rightleftharpoons}} EM^* \overset{\text{slow}}{\rightleftharpoons} \end{array}\right\} EX \rightleftharpoons EF \rightleftharpoons E + F \qquad (15)$$

where the reactions in the unmarked equilibria are faster. According to this mechanism the values of k_3 and k_4 calculated earlier[1] from steady-state studies over a range of pH would be identified with the rate constants for EM $\rightleftarrows$ EX rather than EX $\rightleftarrows$ EF. It is necessary to postulate an intermediate EX in order to explain the absence of an isotope rate effect and of exchange. The branch in the mechanism is placed at EX because if EM could exchange with D_2O to give M*, there would be no induction period in the formation of M*. If the branch was placed at EF it would be necessary to introduce a further intermediate to keep the mechanism symmetrical with respect to M and M*. Speyer and Dickman[29] believe that the aconitase reaction follows mechanism 14 and have suggested that EX contains a "bound" carbonium ion.

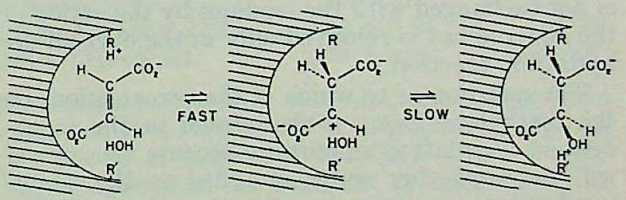

Fig. 3.—Structures of intermediates in the fumarase reaction suggested by the study of the effect of pH on the kinetics and the absence of a deuterium isotope rate effect or exchange.

On the basis of the mechanisms in Table IV it is predicted that L-malate containing O^{18} in the hydroxyl group would not show exchange during dehydration but that there should be an isotope rate effect. This prediction is being tested.

Acknowledgment.—The authors are indebted to Professor E. L. King for helpful discussions and to Drs. Raymond G. Wolfe, Jr., and Nehemia Shavit for preparations of crystalline fumarase.

MADISON, WISCONSIN

(29) J. F. Speyer and S. R. Dickman, *J. Biol. Chem.*, **220**, 193 (1956).

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

The Mechanism of the Stereospecific Enzymatic Hydration of Fumarate to L-Malate[1]

BY T. C. FARRAR, H. S. GUTOWSKY, R. A. ALBERTY AND W. G. MILLER

RECEIVED FEBRUARY 7, 1957

It is found that the addition of water to the double bond of fumarate occurs in a *cis* manner when catalyzed by the enzyme fumarase from pig heart muscle. This is shown by the configuration of the monodeutero-L-malate formed when the hydration is carried out with deuterium oxide. The configuration of the monodeutero-L-malate was established by observing the dipolar broadening of the proton magnetic resonance absorption in solid DOOCCH(D)C(OD)HCOOD.

Introduction

When the hydration of fumarate to L-malate is catalyzed in deuterium oxide by the fumarase from pig heart muscle, the L-malate which is formed contains one deuterium atom per molecule which is not readily exchangeable with the medium.[2] Since only monodeutero-L-malate is formed in the over-all reaction and the fumarate does not incorporate deuterium, the addition of the deuterium is stereospecific, as is the addition of the OH or OD group. This observation has been confirmed.[3] Further work has shown that the deuterium atom is not exchanged with the medium by the action of the enzyme but is removed only in the over-all dehydration reaction.[4]

The question as to which of the two positions on the methylene group is deuterated in the monodeutero-L-malate is important because the answer will show whether water is added to the double bond of fumarate in a *cis* or *trans* manner. Whereas it frequently is assumed that substrates are bound on the surface of an enzyme, a *cis* addition by fumarase would prove that the entering groups came from the same side, and presumably from that of the protein since their addition is under stereochemical control. The ability of the enzyme to distinguish unerringly between the two hydrogen positions on the methylene group of L-malate may find practical application in the determination of the structure of partially deuterated compounds which may be transformed to malic acid.

The stereospecificity of the diphosphopyridine dehydrogenases already has been investigated.[5] It has been found that the hydrogen transfer catalyzed by the β-hydroxysteroid dehydrogenase[6] and glucose dehydrogenase[7] occurs at the opposite side of the nicotamide ring from that used by the alcohol, lactic and malic dehydrogenases. Therefore, it is not to be assumed that fumarase from other sources would necessarily cause deuterium to be added in the same position as pig heart fumarase.

The question of whether the fumarase catalyzed hydration occurs in a *cis* or *trans* manner can be answered by establishing the steric relation of the fumarate protons on carbons 2 and 3 in the monodeutero-L-malic acid. This is shown schematically in the right-hand portion of Fig. 1. If the hydration occurs in the *cis* manner as depicted in the figure, the protons are gauche to one another. On the other hand, if the hydration is *trans*, then the protons are *trans*. These particular relations hold only if the carboxyl groups are *trans* in L-malic acid, as shown; if the carboxyl groups are gauche, then the proton–proton relations are the reverse of those just given.

X-Ray diffraction studies of succinic and tartaric acids[8] have shown that in the crystalline solids the carboxyl groups are *trans*, and undoubtedly they are also *trans* in crystalline malic acid. Therefore, the only structural feature to be established is whether the protons are gauche or *trans* in the monodeutero-L-malic acid. This type of structural problem is suitable for proton magnetic resonance solid-state methods. The hydroxyl and acidic protons exchange readily with D_2O to give DOOCH(D)C(OD)HCOOD, in which the protons in question are the most important magnetic nuclei. The dipolar broadening of the proton magnetic resonance in the solid depends very largely on the intramolecular proton–proton distance. The broadening is very sensitive to the interproton distance so it is relatively easy to determine unequivocally whether the configuration is *trans* or gauche, as has been done for solid *sym*-tetrachloro- and tetrabromoethane.[9]

Experimental

Preparation of Deutero-L-malic Acid.—Crystalline fumarase obtained from pig heart extract[10] was added to a solution containing 0.2 *M* potassium fumarate and 0.0083 *M* dipotassium phosphate and 0.0017 *M* monopotassium phosphate in 99.5% D_2O[11] and the reaction was allowed to proceed to equilibrium, as determined spectrophotometrically. The reaction was stopped by heating to 90° for 3 minutes and the solution was then lyophilized.

The deutero-L-malate was separated from the 0.18 mole fraction fumarate present at equilibrium by partition chro-

(1) The nuclear magnetic resonance experiments were supported by the U. S. Office of Naval Research and by a grant-in-aid from the Upjohn Co. The enzymatic experiments were supported by grants from the National Science Foundation and from the Research Committee of the Graduate School of the University of Wisconsin from funds supplied by the Wisconsin Alumni Research Foundation.

(2) H. Fischer, C. Frieden, J. S. McKinley McKee and R. A. Alberty, THIS JOURNAL, **77**, 4436 (1955).

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(4) R. A. Alberty, W. G. Miller and H. Fisher, THIS JOURNAL, **79**, 3973 (1957).

(5) B. Vennesland and F. Westheimer, in W. D. McElroy and B. Glass, "The Mechanism of Enzyme Action," Johns Hopkins Press, Baltimore, Md., 1954.

(6) P. Talalay, F. A. Loewus and B. Vennesland, *J. Biol. Chem.*, **212**, 801 (1955).

(7) H. R. Levy, F. A. Loewus and B. Vennesland, *ibid.*, **222**, 685 (1956).

(8) R. W. G. Wyckoff, "Crystal Structures," Interscience Publishers, Inc., New York, N. Y., 1955, Vol. II, Chap. XIIIC.

(9) M. Takeda and H. S. Gutowsky, *J. Chem. Phys.*, **26**, 577 (1957).

(10) C. Frieden, R. M. Bock and R. A. Alberty, THIS JOURNAL, **76**, 2482 (1954).

(11) The D_2O was supplied by the Stuart Oxygen Company, Berkeley, California, and obtained on allocation from the Isotopes Division, U. S. Atomic Energy Commission.

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matography as described by Cleland and Johnson[12] with 0.5 *N* HCl replacing 0.5 *N* H_2SO_4 as the stationary phase. Treatment with $AgNO_3$ showed the deuteromalic acid recovered from the eluent to be free of chloride. Aqueous extractions of fractions collected midway between the fumaric acid and deuteromalic acid peaks showed no evidence of either substrate upon addition of concentrated solutions of fumarase, thus indicating that the separation was quantitative. The deuteromalic acid was redissolved three times in 1.5 ml. of 99.5% D_2O and each time lyophilized to dryness to replace exchangeable hydrogen with deuterium.

The resulting compound, DOOCCH(D)C(OD)HCOOD, had a melting point of 97–99° as compared with 103–104° for normal L-malic acid. The change in melting point upon deuteration is in the direction predicted by Schäfer[13] and compares favorably with the lowering of the melting point of succinic acid upon deuteration.[14] The deuteromalic acid contained 0.97 atom of deuterium per molecule in the specific methylene position and about 2.85 atoms of deuterium per molecule in the carboxyl and hydroxyl positions, as determined by mass spectrometric analysis.

Nuclear Magnetic Resonance Apparatus.—The broad line magnetic resonance spectrometer has been described elsewhere.[15] It consists of a self-detecting oscillator, a 30 c.p.s. phase sensitive amplifier and a strip chart recorder. The magnetic field is modulated at 30 c.p.s. with an amplitude a small fraction of the line width. The magnetic field is also swept linearly in time at an adjustable rate of about 3 gauss/min., while the frequency of the oscillator is constant. The system thus records the derivative of the magnetic resonance absorption as a function of applied magnetic field. A permanent magnet with a field strength of 6300 gauss was used in these experiments. The sample was 0.3 g. and was contained in a small, sealed test-tube. Measurements were made at liquid nitrogen temperature with a special cryostat, to improve signal to noise and also to ensure that motional narrowing[16] was unimportant.

Experimental Results and Discussion

The broadening of the magnetic resonance absorption is expressed quantitatively most conveniently by the second moment of the absorption line, *i.e.*, by the mean square deviation of the absorption intensity from the line center. For a crystal powder in which nuclear motions are unimportant, the second moment, ΔH_2^2, is given theoretically[17] by the equation

$$\Delta H_2^2 = \frac{6}{5}\frac{I(I+1)}{N} g^2\beta^2 \sum_{i>k} r_{ik}^{-6} + \frac{4}{15}\frac{\beta^2}{N}\sum_{i,f} I_f(I_f+1)\, g_f^2 r_{if}^{-6}$$

In this equation g is the g-value of the nuclear species observed, in this case the proton, and g_f is the value for other "foreign" magnetic species in the sample. I and I_f are the nuclear spins; r, the internuclear distances; and N is the number of protons considered in the calculation.

Because of the r^{-6} dependence of the broadening, the most important contributions arise from the dipolar interactions within the CHD–CH group. These intramolecular terms can be calculated quite accurately from the molecular structure.

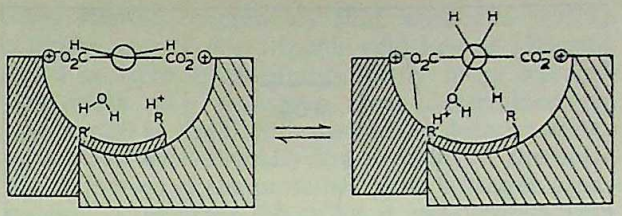

Fig. 1.—Schematic representations of the enzyme–fumarate and enzyme-L-malate complexes for the case of *cis* hydration (*cf.* Fig. 4 of the preceding article[4]).

The results for the *trans* and gauche configurations are summarized in Table I. In the calculations,

TABLE I

VALUES FOR THE SECOND MOMENT OF THE PROTON MAGNETIC RESONANCE CALCULATED FOR THE *trans* AND GAUCHE CONFIGURATIONS OF THE PROTONS IN DOOCCH(D)C(OD)HCOOD

	trans	gauche
CHD–CH: H–H	0.46 gauss^2	1.63 gauss^2
D–H	0.18	0.16
CH_2–CH: H–H	8.90	8.90
Intramolecular	1.02	2.14
Intermolecular	1.4 ± 0.4	1.8 ± 0.5
Effect of CO_2H and OH	−0.16 ± 0.03	−0.3 ± 0.05
Net ΔH_2^2 predicted	2.25 ± 0.5	3.65 ± 0.6

tetrahedral bond angles were assumed and the bond distances used were C–C,[8] 1.50 Å. and C–H, 1.09 Å. The D–H distance in the CHD group is sufficiently short that the resultant broadening of the proton resonance is significant, even though the magnetic moment of deuterium is small. For the same reason, the contribution to the proton second moment from the CH_2 group interactions cannot be neglected even though only 3 mole % of the molecules are CH_2–CH. In calculating this correction, it must be remembered that the relative contributions to ΔH_2^2 of protons in different molecular species depend upon the proton fraction rather than the mole fraction. Thus the contribution of the 3 mole % CH_2–CH is 0.045 × 8.9 gauss.^{2}

An accurate calculation of the other contributions to the broadening requires a knowledge of the crystal structure of malic acid, which does not appear to have been determined. However, an estimate sufficiently good for our purpose can be made by referring to the calculations made[9] for *trans* and gauche $CHCl_2CHCl_2$. The main additional contributions are from the proton–proton interactions between neighboring molecules. Consideration of the crystal structures of succinic and tartaric acids suggests that, as in the *sym*-tetrachloroethane, the intermolecular broadening will be greater for the gauche configuration than for the *trans*, but not by as large a factor. The molar volume of the *sym*-tetrachloroethane is 1.25 that of malic acid, so if all intermolecular distances were reduced proportionally, the intermolecular contribution to the second moment in malic acid would be $(1.25)^2 = 1.5$ times that in the tetrachloroethane. In the latter, the *trans* and gauche intermolecular contributions were calculated to be 0.7 ± 0.2 and 1.4 ± 0.3 gauss.^{2} Using the arguments just outlined, the values for the monodeutero-L-malic acid are estimated to be 1.4 ± 0.4 and 1.8 ± 0.5 gauss.^{2}

(12) W. W. Cleland and M. J. Johnson, *J. Biol. Chem.*, **220**, 595 (1956).
(13) K. Schäfer, *Z. Elektrochem.*, **52**, 245 (1948).
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(15) H. S. Gutowsky, L. H. Meyer and R. E. McClure, *Rev. Sci. Instr.*, **24**, 644 (1953).
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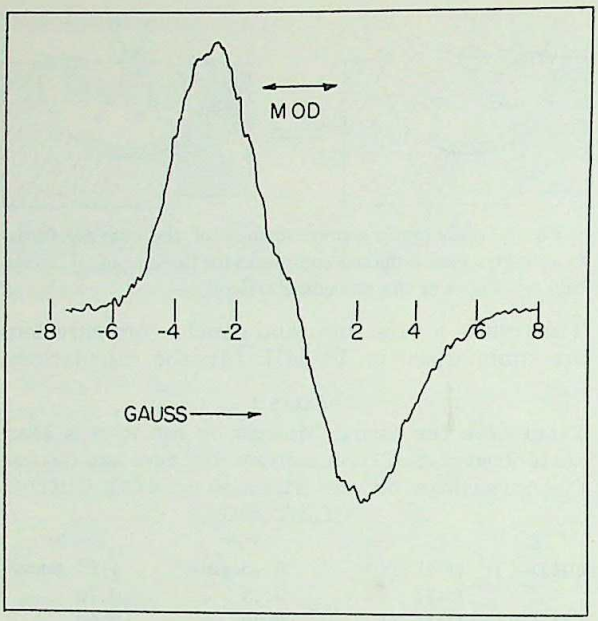

Fig. 2.—The first derivative of the proton magnetic resonance absorption in DOOCCH(D)C(OD)HCOOD at −196°, plotted as a function of applied magnetic field at a fixed frequency of 25.27 Mc. The arrow indicates the amplitude of the 30 c.p.s. modulation of the magnetic field.

The final correction is for the incomplete exchange of protons in the CO_2H and OH groups. These protons have no near magnetic neighbors and thus they have a much smaller second moment than protons in the CHD–CH group. A value of 0.3 ± 0.1 gauss^2 is estimated. About 5% of the protons in the CO_2H and OH groups were not exchanged. This reduces the net second moment by 7.5% of the difference between 0.3 ± 0.1 gauss^2 and the value computed assuming complete exchange. The various terms are summarized in Table I. The net values predicted for ΔH_2^2 are 2.25 ± 0.5 gauss^2 for the *trans* and 3.65 ± 0.6 gauss^2 for the gauche configuration.

A typical recording of the first derivative of the proton absorption in the monodeutero-L-malic acid sample at −196° is reproduced in Fig. 2. Numerical integration of this curve gave a value of 3.43 gauss^2 for one side and 3.63 gauss^2 for the other. A second curve gave values of 3.28 and 3.71 gauss.^{2} The resulting best experimental ΔH_2^2 is 3.5 ± 0.2 gauss.^{2} Line shapes plotted at room temperature had the same widths as those at low temperature so motional narrowing does not appear to be important. Comparison of the experimental value for the second moment with the calculated values shows conclusively that the protons are in the gauche configuration.

In addition, line shapes were plotted at −196° for a sample of $DOOCH_2CH(OD)COOD$. The second moment for this sample was 11.2 ± 0.6 gauss.^{2} A detailed comparison of this value with the intramolecular value of 8.9 gauss^2 computed for CH_2–CH confirms the estimates of the intermolecular contributions to the broadening. The experimental second moments were corrected for the modulation broadening[18] produced by the relatively large modulation used.

In the preceding article,[4] the deuterium labelling experiments and the effect of *p*H on the kinetics of the enzymatic hydration of fumarate indicated that the reaction occurs in the *cis* manner represented by the structures of the enzyme–fumarate and enzyme–L-malate complexes given in Fig. 1. The finding here that the protons in crystalline DOOCCH(D)C(OD)HCOOD are in the gauche configuration proves that the addition is *cis*. In view of this mechanism it is perhaps not surprising that *meso*-tartrate is a much more powerful competitive inhibitor of pig heart fumarase than *d*- or *l*-tartrate.[19]

(18) E. R. Andrew, *Phys. Rev.*, **91**, 425 (1953).
(19) C. Frieden, Doctoral Thesis, University of Wisconsin, 1955.

URBANA, ILLINOIS
MADISON, WISCONSIN

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

Heats of Adsorption of Water Vapor on Bovine Serum Albumin[1]

BY C. H. AMBERG[2]

RECEIVED FEBRUARY 21, 1957

Heats of adsorption of water vapor on bovine serum albumin were measured calorimetrically at 20° and are presented together with the isotherms. The heat curves are discussed and critically compared with calculated values from the literature. Possible mechanisms for the adsorption process are considered, with special regard to the high initial heats and the appearance of a maximum in the heat-coverage curve near the B.E.T. value for a complete monolayer.

Introduction

The interaction of proteins and water is a subject of considerable interest to the biochemist and biologist. An extensive amount of data has been accumulated over the past two or three decades, the bulk of the systems studied having been aqueous solutions of various proteins. While this has yielded important information regarding the extent of hydration as well as the size and shape of the hydrated molecules,[3] solution techniques tend to be insensitive to non-uniformity in properties over various regions of the interacting polymer molecule. For this reason, a number of workers

(1) Supported by the Office of Naval Research under contract N8-onr-66902. This paper was presented before the Colloid Division of the 128th National Meeting of the American Chemical Society in Minneapolis, Minn., September, 1955.

(2) Division of Applied Chemistry, National Research Council, Ottawa 2, Canada.

(3) J. T. Edsall in "The Proteins," Vol. I, part B, Academic Press, New York, N. Y., 1953, p. 549.

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have studied the hydration of quasi-anhydrous proteins from the vapor phase. (A comprehensive review of this work was published by McLaren and Rowen.[4]) From the point of view of those interested in biological systems this method of attack has a disadvantage in that proteins such as the serum albumin discussed in this report occur naturally in solution or in an advanced state of hydration. Moreover, the adsorption of vapors is most conveniently studied in vacuum systems on the purest possible adsorbents whereas, of course, natural systems exist in the presence of both interacting and non-interacting gases and solutes. Nevertheless, there can be no doubt that, from the physicochemical point of view, the simplest systems are desirable provided they can be prepared without introducing permanently irreversible changes in the protein molecule.

Adsorption isotherms of water vapor on a variety of purified proteins were measured by Bull[5] at 25° and at 40°, in the presence of air. His data were discussed by Pauling[6] and an analysis of heat, free energy and entropy changes was undertaken by Dole and McLaren[7] and Davis and McLaren.[8] Although Bull did not measure desorption isotherms for all the systems studied by him, it is evident from his and also later work that many of these systems show marked hysteresis. In view of this the computation of thermodynamic equilibrium functions from either the adsorption or desorption branch of the hysteresis loop is of questionable significance and may actually result in grossly misleading values. This is demonstrated by the work done in this Laboratory which will be discussed later.

Pauling[6] concluded that in most cases the initial water uptake proceeded in such a manner that one water molecule would attach itself to a polar side chain. His view that internal hydrogen bonding of the peptide carbonyl and imido groups would largely preclude adsorption of water molecules by these groups was not substantiated by Mellon, Korn and Hoover.[9] These authors examined a series of polyglycine polymers with from two to six units per molecule and found definite correlation between the increase of water adsorption and increasing number of peptide links. By benzoylating successively higher numbers of free amino groups in casein these authors[10] demonstrated that amino groups are responsible for approximately one quarter of the total water uptake.

As part of their series of investigations on The Surface Areas of Proteins, Benson and his coworkers have given a detailed account of the adsorption of water vapor on a variety of proteins.[11–13] They showed conclusively that while the B.E.T. nitrogen area of egg albumin and bovine albumin could be increased substantially by spray freezing techniques, the analogous areas determined by application of the B.E.T. method to data on water adsorption were virtually independent of the state of subdivision of the protein. With nitrogen areas roughly in the range 1–5 m.²/g. it was obvious from these data that water molecules would have to penetrate into the interstices of the protein structure much more extensively than nitrogen. It was held likely that water adsorption in contrast to nitrogen adsorption is a specific molecular property of the protein.

In view of the uncertainties connected with the calculation of heats of adsorption from isotherms exhibiting hysteresis it was felt that the calorimetric measurement of heats of adsorption of water vapor on a suitable protein would be of value. It seemed particularly interesting to check by direct measurement the anomalous negative "net" heats obtained by Seehof, *et al.*,[11] for the system H_2O–bovine serum albumin between 20 and 25°, which were also discussed by Benson and Richardson[13] in the light of more recent experiments. As a reliable calorimetric method had been developed in this Laboratory in connection with other adsorption problems[14–16] such measurements were carried out using bovine serum albumin, fraction V.

Experimental

Material.—The adsorbent used was a sample of bovine serum albumin, fraction V, milled powder, lot No. N-12302, kindly provided by Dr. J. L. Oncley. Its nitrogen surface area was found to be 1.4 m.²/g. 2.774 g. of the undried material was loaded into the calorimeter. Crystalline egg albumin (Armour, lot No. E-90115) was used for two preliminary runs, but it was abandoned in favor of the bovine albumin which has somewhat greater resistance to heat denaturation and is free from additives. It is not denatured at temperatures up to 70°.[17] The egg albumin had been spray frozen from an approximately 1% aqueous solution and had a nitrogen surface area of 26.4 m.²/g. Poor reproducibility was experienced in the calorimetry with this adsorbent which may have been due to the necessarily low out-gassing temperature (two days at room temperature) or to inherent structural features of the crystallized material. Surface active agents frequeutly used in the crystallization process may also have influenced the behavior of the adsorbent.

Distilled water was used as the adsorbate; it was outgassed by boiling under reduced pressure and by further pumping down while the reservoir was kept in a Dry Ice–acetone bath. This procedure was repeated several times.

Apparatus and Procedure.—The apparatus used was described in detail by Beebe and Amberg.[18] Its essential features are the calorimeter, mercury U-tube manometer and water reservoir, all joined to a vacuum manifold and immersed in a constant temperature bath.

The calorimeter was the same in principle as the one used for previous work in this Laboratory.[14] A glass jacket surrounded the platinum cylinder (7 cm. long, 2 cm. diameter), the spacing between the two being about 1 cm. A copper–constantan thermocouple junction was soldered to the outside of the platinum cylinder and the leads joined to the external measuring system through Kovar-Pyrex seals de-

(4) A. D. McLaren and J. W. Rowen, *J. Polymer Sci.*, **7**, 289 (1951).
(5) H. B. Bull, THIS JOURNAL, **66**, 1499 (1944).
(6) L. Pauling, *ibid.*, **67**, 555 (1945).
(7) M. Dole and A. D. McLaren, *ibid.*, **69**, 651 (1947).
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(9) E. F. Mellon, A. H. Korn and S. R. Hoover, THIS JOURNAL, **70**, 3040 (1948).
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(11) J. M. Seehof, B. Keilin and S. W. Benson, *ibid.*, **75**, 2427 (1953).
(12) S. W. Benson, D. A. Ellis and R. W. Zwanzig, *ibid.*, **72**, 2102 (1950).
(13) S. W. Benson and R. L. Richardson, *ibid.*, **77**, 2038 (1955).
(14) R. A. Beebe, B. Millard and J. Cynarski, *ibid.*, **75**, 839 (1953); R. A. Beebe and D. M. Young, *J. Phys. Chem.*, **58**, 93 (1954).
(15) C. H. Amberg, W. B. Spencer and R. A. Beebe, *Can. J. Chem.*, **33**, 305 (1955).
(16) R. A. Beebe and R. M. Dell, Office of Naval Research Contract N8-onr-66902, Technical Report No. 4.
(17) J. L. Oncley, private communication.
(18) R. A. Beebe and C. H. Amberg, Office of Naval Research Contract N8-onr-66902, Technical Report No. 7.

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scribed in a previous publication.[15] The platinum cylinder contained a removable platinum bucket with a set of close-fitted iron fins and a threaded brass cap. Both the fins and cap had been successively nickel and chrome plated and the cap provided with two small holes for vapor admission. A 140 ohm heater wound from enamel covered Advance wire and wrapped in aluminum foil was housed axially in a 3 mm. well in the center of the fins.

Water vapor pressures were read on the mercury manometer by means of a Gaertner travelling microscope. The water reservoir, 30 ml. in volume, was about half filled with water. It was connected to the rest of the system through a two-way stopcock and ground glass joint and could be removed for weighing.

All runs were carried out at 20°. The constant temperature bath was controlled to ±0.01° but effective fluctuations in the calorimeter with the outer jacket evacuated were only ±0.003°.

The methods employed for the measurement of electrical energy input during calibrations and for amplification and recording of the thermal e.m.f. have been described in previous publications from this Laboratory. A Perkin–Elmer d.c. breaker-amplifier was used in conjunction with an Esterline–Angus automatic recorder. The procedure outlined by Beebe and Dell[16] was followed.

Before runs 1–3 the adsorbent was outgassed at room temperature for about 36 hr. and then the temperature was slowly raised to 50° where it remained for about 6 hr. A Dry Ice–acetone trap was used to collect the water removed. Before runs 4 and 5 the temperature was maintained at 100° for two hours each in order to test the possible effects of denaturing the adsorbent.

Helium dead-space calibrations were carried out using a conventional gas buret system. The variation in dead-space in the U-tube manometer with increasing pressure was negligible.

Before each run, a small quantity of helium (of the order of 0.3 mm. pressure) was admitted to the system to facilitate heat conduction inside the calorimeter. It had been found during the initial runs with egg albumin that in the absence of helium heat evolution became too slow to calculate heats of adsorption with any degree of confidence, particularly for the first vapor increment where the calculated heat was as much as 6 kcal./mole below that obtained in the presence of helium. With helium, the "adiabatic" method[16] resulted in constant reconstructed heat values 5–8 min. after vapor admission (±0.2% deviation from total heat of adsorption per increment) showing that if any further heat was evolved after that period, it was evolved too slowly to be detected by that method. The estimated maximum heat quantity that might thus have remained undetected would fall well within the expected precision stated below. Helium was admitted to the outer calorimeter jacket 30 minutes after vapor admission to speed up final temperature equilibration. After a further period of 30 min. no significant changes in vapor pressure were detected so that equilibrium was taken to have been reached one hour after vapor admission.

In order to calculate water vapor pressures, the partial pressure of helium in the system had to be subtracted from the total observed pressure. Table I shows a selection of pressure values from run 3 together with an estimate of the accuracy achieved in the final partial pressures of water vapor. Column 1 shows the total equilibrium pressures read on the manometer, column 2 the calculated partial pressures of helium, column 3 the partial pressures of water vapor, *i.e.*, the difference between columns 1 and 2, and column 4 the estimated per cent. accuracy of the values of column 3.

TABLE I

CALCULATION OF WATER VAPOR PRESSURES

(1) Obsd. pressure, mm.	(2) Partial pressure of helium, mm.	(3) Partial pressure of water vapor, mm.	(4) % Accuracy
0.699	0.319	0.380	1.3
2.097	.267	1.83	0.7
6.026	.205	5.82	.3
10.617	.145	10.47	.2

Except for the somewhat smaller increments in the first half of run 1, the amount of water vapor admitted to the system ranged between 20 and 30 mg. per increment. The estimated precision is between 1 and 2% in the weighing of each increment, and no worse than 5% in the measurement of the heat evolved per increment.

Results and Discussion

The results of runs 2 to 5 are shown in Figs. 1 and 2 (isotherms), and Figs. 3 and 4 (calorimetric heats of adsorption). Those for run 1 show too much scatter to be entirely reliable and have, therefore, been omitted.

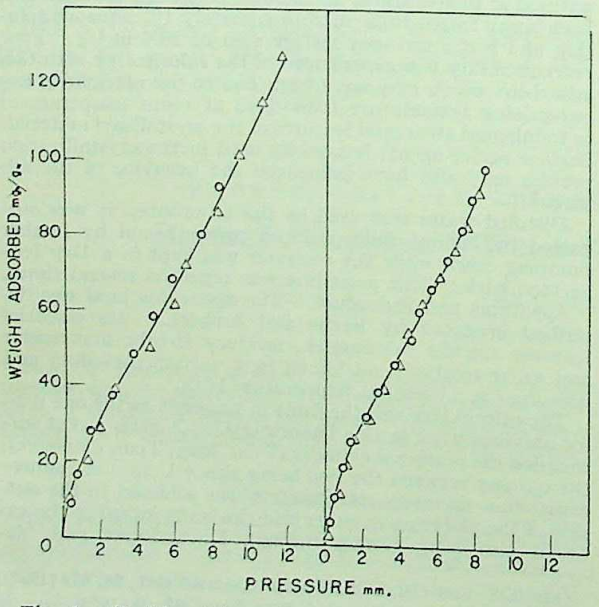

Fig. 1. (Left).—Adsorption of water vapor on bovine serum albumin, fraction V, at 20.0°: run 2, O; run 3, △; outgassed at 50°.

Fig. 2. (Right).—Adsorption of water vapor on bovine serum albumin, fraction V, at 20.0°: run 4, O; run 5, △; outgassed at 100°.

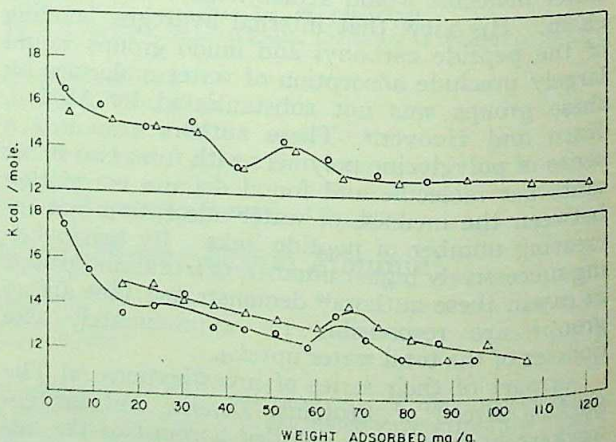

Fig. 3. (Top).—Heats of adsorption of water vapor on bovine serum albumin, fraction V, at 20.0°: run 2, O; run 3, △; outgassed at 50°.

Fig. 4. (Bottom).—Heats of adsorption of water vapor on bovine serum albumin, fraction V, at 20.0°: run 4, O; run 5, △; outgassed at 100°.

The two preliminary runs with crystalline egg albumin are not recorded because of very low reproducibility in both the isotherms and heat curves. It may, however, be stated that the heats of adsorption were of about the same magnitude as those for the bovine albumin.

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The isotherms shown in Figs. 1 and 2 are of the S-shaped (Type II) variety. Amounts adsorbed are given on the basis of the initial protein weight. By duplicating as closely as possible the actual drying conditions, it was found in a separate experiment that at 50° the albumin was dehydrated to the extent of 5.07% of the initial weight. Nevertheless, as this was done in a separate adsorption system with the albumin in a simple adsorption bulb rather than the calorimeter, it was felt that the efficiency of dehydration may have differed somewhat in the two cases. Because of this uncertainty the initial weight of protein was not corrected to "dry weight." Low and Richards[19] have shown in the case of human serum mercaptalbumin mercury dimer that the extent of dehydration is relatively insensitive to the temperature of outgassing. While a total of 10% of water was removed by pumping to constant weight over P_2O_5 at temperatures up to 100°, all but about 1% of this was removed at 25°. The slight shift toward higher adsorption at a given vapor pressure when the present system was outgassed at 100° is very likely due to a similar small increase in the extent of dehydration. It was unfortunately not possible to determine whether the expected simultaneous degradative changes in the protein at 100° also affected the adsorption of water vapor. Both isotherms agree reasonably well with that of Seehof, Keilin and Benson[11]; their values were only slightly lower.

B.E.T. surface areas calculated from the isotherms shown in Figs. 1 and 2 were 204 m.²/g. on the average, differences being within experimental error. This corresponds to an amount of 58.2 mg./g. of water vapor adsorbed at the B.E.T. monolayer. (Accepting the above correction to "dry weight" of protein, 61.2 mg./g. would be the resulting corrected value.) Here again it should be pointed out that the meaning of such figures is obscure. If calculated from the adsorption branch of an isotherm showing hysteresis they will represent a minimum area significant, at best, on a comparative basis. In view of the uncertainties involved in applying the B.E.T. equation, it is most surprising that the c-value computed by the B.E.T. method from Fig. 2 resulted in a heat of adsorption term only some 500–600 cal./mole below that measured calorimetrically at the "monolayer."[11] This may well be regarded as fortuitous; McLaren and Rowen[4] have examined in some detail the applicability of equations of the B.E.T. form to water sorption by proteins and compared B.E.T. heats with Clausius–Clapeyron heats. In general they found poor agreement between the two, as is to be expected from the simplifying assumptions involved in the B.E.T. function.

The heats of adsorption plotted against amount adsorbed are shown in Figs. 3 and 4. Initially they are in the region of 16 to 18 kcal./mole as measured. It was not possible by the method employed to determine heats down to very low coverages; the heats for such initial increments might well be higher. After a fairly rapid decrease the curves flatten out in the neighborhood of 15 kcal./mole. For runs 2 and 3 there occurs a minimum at 43 mg./g. of vapor sorbed, rising from about 13 kcal./mole by 1 kcal. to a maximum at 53 mg./g. and then decreasing fairly rapidly to flatten out again at 13 kcal./mole and 68 mg./g., and then decreasing very gradually. Run 4 follows the same pattern, except that the whole curve is shifted by some 15 mg./g. toward higher amounts adsorbed. A further small shift is indicated by run 5. These shifts may again be explained on the basis of improved dehydration, their order of magnitude being consistent with the data of Low and Richards[19] and with the percentage dehydration determined in this Laboratory; this was discussed above.

The molar heat of vaporization of liquid water at 20° is 10.54 kcal. All heats measured calorimetrically were larger than this, which clearly confirms the view of Benson and co-workers,[11,13] that their calculated negative "net" heats of adsorption were anomalous. On the other hand, the curves computed by Davis and McLaren[8] from Bull's data[5] do not show any evidence of negative "net" heats. They are, moreover, qualitatively similar to the curves obtained in this Laboratory, in that they have initially high heats and also a maximum in the B.E.T. monolayer region, notably in the case of egg albumin and lyophilized lactoglobulin. Their absolute heat values are somewhat lower, but in view of the fact that they were obtained on proteins other than bovine serum albumin, and in view of the irreversible nature of these systems, this has probably little significance.

Frey and Moore[20] have measured the adsorption of water vapor on the amino acids glycine and leucine and on the cyclic anhydride of glycine, diketopiperazine, at 15, 25 and 40°. They obtained reversible isotherms and calculated isosteric heats that agreed well with the values for bovine serum albumin at half the B.E.T. monolayer coverage, but then decreased slightly more rapidly. They estimated that at the monolayer there would be one molecule of H_2O sorbed per polar group (NH_3^+ and COO^-) for glycine and leucine and one molecule of H_2O per carbonyl group in the diketopiperazine.

Following Pauling[6] several workers have correlated the number of polar side chains in the protein with the number of H_2O molecules adsorbed at the B.E.T. monolayer and have found an approximate one-to-one correspondence. Such data were collected and critically reviewed by McLaren and Rowen.[4] They report a water sorption value of 3.74 mmoles per gram of serum albumin and a polar group content of 4.24 mmoles per gram. The first figure was obtained by Bull[5] (using horse rather than bovine albumin[6]), the second was calculated from the amino acid analysis of Brand, Kassell and Saidell.[21] A summation of hydroxy and carboxyl side chains together with cationic nitrogens carried out by Klotz and Urquhart[22] on the basis of analytical data by Brand[23]

(19) B. W. Low and F. M. Richards, THIS JOURNAL, 76, 2511 (1954).

(20) H. J. Frey and W. J. Moore, *ibid.*, 70, 3644 (1948).

(21) E. Brand, B. Kassell and L. J. Saidell, *J. Clin. Invest.*, 23, 437 (1944).

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results in the slightly lower value of 4.06 mmoles/g. If one takes our monolayer value to be 61.2 mg./g. of dry protein, *i.e.*, 3.40 mmoles/g., a molar ratio of 0.84 is obtained for water adsorbed per polar group in the adsorbent. It is not surprising that this ratio differs somewhat from unity, even if one accepted the B.E.T. monolayer value as an exact measure of the coverage of all high energy sites. (Being probably a minimum value when determined from the *adsorption* branch of a hysteresis loop, one might expect a corrected ratio to be closer to unity.) It is very likely that not all polar groups are available for the binding of H_2O molecules, either because of intramolecular and intermolecular hydrogen bonding or because of spatial restrictions. Furthermore it may be assumed from the evidence with other proteins[4] that the peptide linkage will take part in the adsorption of water before the monolayer is complete. One must therefore regard the above ratio as including a partial compensation of these two phenomena by each other.

Hydrogen bonding of the O–H . . . O and N–H . . . O type is often assumed to be largely responsible for the binding of water molecules to polar sites in the protein. It is difficult to assign energies to such bonds in a structure as complex as is that of a protein molecule. Undoubtedly the interaction energy of any polar group will be influenced by neighboring groups. Nevertheless the initial high differential heats of adsorption (up to 17 kcal./mole) are not likely to be due to the formation of only one hydrogen bond per molecule of water for which the highest values quoted[24] do not appear to be in excess of one-half of the above value. One is, therefore, faced with two possible explanations, not necessarily mutually exclusive: (1) Two hydrogen bonds may be formed per molecule of water. This may take place between suitably spaced native polar centers or between a polar group and a water molecule already present. One must not lose sight of the fact that even dried proteins contain a residual quantity of firmly held water. An acceptance of this type of mechanism would even further invalidate the 1:1 correlation of water molecules to polar groups mentioned above. (2) The second explanation would be the existence of bonds in which the hydrogen does not take part; these would be of the ion–dipole type, *i.e.*, they would constitute a hydration of ions. The heats would be of a plausible order of magnitude for such bonds, and again the existence of the residual fraction of water in the "dehydrated" protein is also compatible with this concept.

The minimum for the heats of adsorption and rise by 1 kcal./mole to a maximum observed near the monolayer is in qualitative agreement with the curves calculated by Davis and McLaren.[8] It is clear that previously bound water molecules must be involved in causing the heats to increase with further adsorption, otherwise these more stable bonds would have been formed at much lower coverage. One way in which this could take place is through adsorption on two polar side chains which protrude from one protein helix (or adjacent helices) with spacing appropriate for a third water molecule to wedge between two adsorbed molecules, thus forming two hydrogen bonds. As is indicated by Figs. 3 and 4 about one-sixth of the quantity of water needed to complete the "monolayer" would be bound in this manner. It is interesting to note that this quantity corresponds almost exactly to that needed to account for the 0.84:1 ratio of water molecules to polar groups estimated above. Whether this is significant is again subject to the qualifications expressed in connection with that estimate.

An involvement in some way of the peptide linkage at this stage of the adsorption process cannot be entirely discounted. Marshall and Moore[25] examined the adsorption of ammonia on silk fibroin, which contains only 2 mole % of polar side chains. Nevertheless, a maximum similar to ours in the heat curve was obtained in the region of monolayer coverage. It should be noted, however, that both the isosteric heats as well as the surface area were calculated from a system showing marked hysteresis and, as pointed out by the authors, are therefore only apparent values. Yet it is quite likely that such apparent values are at least a qualitative representation of reality.

Several of the isosteric heat curves calculated by Davis and McLaren[8] show a second maximum in the region of about one mole of water adsorbed per 100 g. of protein, notably so for egg albumin, β-lactoglobulin, gelatin and wool. Unfortunately, calorimetric measurements in this Laboratory were not carried out at that coverage because the rate of adsorption became too low. It is conceivable that a process similar to that postulated above occurs for a second time. Interestingly enough, Buchanan, Haggis, Hasted and Robinson[26] estimated that in an aqueous solution of bovine serum albumin the same amount of water, *i.e.*, one mole per 100 g. of protein, is irrotationally bound; this was on the basis of dielectric measurements in the 1–10 cm. region.

Acknowledgments.—The author wishes to express his gratitude to Dr. R. A. Beebe, in whose laboratory this work was carried out, for his continued interest and valuable advice, to Dr. J. L. Oncley for the gift of a sample of bovine serum albumin and to him and to Dr. B. W. Low for discussions. He is indebted to Dr. R. M. Dell for design of part of the apparatus and to Mr. W. B. Spencer for carrying out one of the runs.

AMHERST, MASS.

(24) F. W. Putnam in ref. 3, p. 885.

(25) P. A. Marshall and W. J. Moore, THIS JOURNAL, **74**, 4779 (1952).

(26) T. J. Buchanan, G. H. Haggis, J. B. Hasted and B. G. Robinson, *Proc. Roy. Soc.* (*London*), **A213**, 379 (1952).

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[CONTRIBUTION FROM INSULATING MATERIALS SECTION, CHEMICAL AND METALLURGY, DIVISION OF GENERAL ELECTRIC CO.]

Infrared Spectra of α,β-Unsaturated Esters

BY W. L. WALTON AND R. B. HUGHES

RECEIVED AUGUST 13, 1956

A number of ester families have been shown to have characteristic absorptions in the 10–15 μ region. These absorptions are quite constant in wave length for all members of the ester family (*i.e.*, esters derived from the same acid). The esters which show such absorptions are those that have unsaturation α,β- to the ester group. It is postulated that the vibration responsible for the most prominent of the absorptions is an out-of-plane deformation at the ester carbon atom. However, the interaction of this vibration with other out-of-plane vibrations is probable and, therefore, more or less of such other vibration is also presumed to be involved. Some evidence suggests that the vibration type may be general for 4-atom systems with a given "Y" structure even including some saturated types. However, the vibration is not necessarily so prominent in the saturated types and the more limited generalization that the absorption is prominent in coplanar unsaturated types is thus of greater value for prediction purposes.

Introduction

The recognition of esters by their infrared spectra generally is based on the observation of strong absorption bands resulting from the C=O and the two C–O–C stretching modes. The bands due to the latter two modes may overlap, however, and appear as one. Therefore, with two, or at most three, bands to utilize, recognition of esters in mixtures frequently is quite unsatisfactory and further characteristic bands are needed. If in addition to locating such bands the vibrational modes giving rise to them can be elucidated, then their applicability can be defined more readily and their utility enhanced.

Recent work[1] on the spectra of maleates and fumarates showed that the fumarates have a fixed absorption at 12.9 ± 0.05 μ which is insensitive to the alcohol of the ester. The maleates, on the other hand, showed no constant absorption bands in the 10 to 15 μ range. This feature was puzzling and merited further investigation. The present paper presents a possible assignment of the 12.9 μ fumarate absorption band which not only explains the difference between maleates and fumarates but also leads to a generalization concerning this type of vibration in α,β-unsaturated esters.

Thompson and Torkington, in a paper[2] treating extensively the C–O stretching vibrations of esters, also noted some peaks in the region beyond 10 μ. There were two peaks of relatively constant frequency for acetate and propionate esters near 16 μ, one of which they associated with the whole ester group skeleton and one with a part of the ester group skeleton. All other constant peaks beyond 10 μ seemed relatable to the hydrocarbon part of the acid moiety—or else these workers simply found no basis for any assignment more specific than to the ester family. The present work attempts to supplement this knowledge of ester spectra by providing more correlations and an assignment in the 10–15 μ region.

Generalization

A step toward the development of the generalization was the theoretical consideration of an effect which was first proposed by Price,[3] that the ester groups are both coplanar with the ethylene in fumarate esters whereas this is not the case in the maleates. (This structual feature was then used by Price to explain the fact that fumarates copolymerize better than maleates. This he explained was due to *absence* of steric hindrance to the approach of a growing free radical to the ethylene linkage in fumarates.) On exploring several types of esters, it was found in the present work that only one ester group conjugated with an unsaturated group was needed to give absorption like the 12.9 μ peak of a fumarate. As detailed below, there is evidence that the liquid maleates have no ester group coplanar with the ethylene structure.

The generalization may be stated as follows: wherever an ester group is conjugated with an unsaturated linkage and the ester group is free to assume one of its normal positions coplanar to that linkage a prominent absorption occurs which is constant for (and therefore *characterizes*) the ester family. By means of polarized infrared coupled with examination of oriented crystal films, this absorption has been shown to be due to an out-of-plane vibration. Further it is postulated that the specific vibration is the out-of-plane deformation at the ester carbon atom.

The following ester families fulfill the requirements of the generalization: fumarates, acetylenedicarboxylates, acrylates, methacrylates and *trans*-crotonates. They all have been found to show strong characterizing absorptions, all in the range 11.8–13.5 μ. Maleates constitute the one well explored negative case (*i.e.*, a case in which a conjugated system is present and the ester groups are constrained from coplanarity by steric and electrostatic forces). Halogenated esters have not been examined and, in general, the question of size or electrical charge of a group in the α-position or β-*cis* position necessary to interfere with coplanarity has not been studied.

The generalization has been investigated briefly for possible application to types other than esters, and it appears that several other types may fit. The types which appear to match the "family" absorptions are the corresponding acids, amides, alkyl amides, acid halides and nitro compounds. Further, the several types have their characterizing peak at approximately the same wave length as the esters. This weakens the analytical value of such a peak as a guide to the recognition of an ester—but it extends the range of its value as a means to the recognition of the grouping which directs the absorption to the region.

(1) W. L. Walton and R. B. Hughes, *Anal. Chem.*, **28**, 1388 (1956).
(2) H. W. Thompson and P. Torkington, *J. Chem. Soc.*, 640 (1945).
(3) C. C. Price, *J. Polymer Sci.*, **1**, 86 (1946).

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TABLE I

ASSIGNED VIBRATIONS COMPARED WITH ACETATE ESTER ABSORPTIONS

Compound	λ, μ	Assignment	λ, μ	Assignment	Reference
Sodium acetate	16.26	⊥ rocking of CO_2	15.50	In-plane deformation of CO_2	5
Acetate esters	16.34	"Part of the ester group skeleton"	15.61	"Ester group skeleton"	2
Nitromethane	16.68	⊥ rocking of NO_2	15.46	In-plane deformation	6

Discussion of Assignment of "Family Absorption"

Since the simplest α,β-unsaturated ester is a many-atomed molecule of low symmetry, it is not surprising that no vibrational analysis of any example of the type has been reported. Thus no wholly trustworthy model is available in the literature for comparison with the compounds treated here. On the other hand, in the case of the particular fundamental which we are proposing, there are a number of parallels worthy of consideration.

If the type be defined broadly as the planar structure illustrated by Fig. 1 in which, first, all atoms are heavier than hydrogen[4] and second, the BC and BD bonds are highly polar, whereas the AB bond is of a low order of polarity, then the models to consider are nitromethane and sodium acetate. Table I shows the assignments compared with the acetate esters.

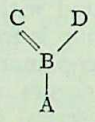

Fig. 1.

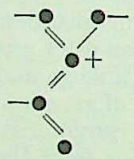
Fig. 2.

An analysis of the equal and opposite actions in the whole molecule permits a mode which is reasonably well described as out-of-plane deformation at the central atom in the Y structure, and this clearly is that which is termed perpendicular "rocking" (Table I), in the cases of sodium acetate and nitromethane.

Now since, in α,β-unsaturated esters, a degree of double bond character is present at the bond between the central atom and the α-atom, added restraint against bending is present and the frequency of the vibration will be greater.[7]

The absorption in the 15.5 μ region of the spectra of nitromethane and sodium acetate was assigned to a vibration which consists of in-plane-bending of the two oxygen atoms. The motion alternately increases and decreases the angle at the central atom with a relatively smaller motion of the central atom itself. Therefore, this second vibration is less subject to influence by the bond strength of the bond between the central and the α-atom.

The fact that *two* peaks are insensitive to the alcohol group in the acetate esters[2] suggests strongly that they are due to the acetate moiety only. That all the frequencies of the table should be so much "of a pattern" would also seem to be more than chance.

If the restriction that the A–B bond in Fig. 1 must be non-polar be discounted, then a number of even better known parallels are available for comparison. The nitrate and carbonate salts are completely symmetrical Y, planar structures. Their fundamental vibrations have all been assigned and besides highly similar absorption patterns are observed for the two types as theory predicts. In the calcium salts containing these ions, the out-of-plane deformation is at 11.54 μ for $CO_3^=$ and at 12.11 μ for NO_3^-, whereas the second vibration noted above is at 14.00 and 14.20 μ, respectively.[8] The out-of-plane vibration is thus found in much the same region as the absorptions we have observed in α,β-unsaturated esters.

Still another similar structure is that of the organic nitrates which were compared with nitric acid and in which the out-of-plane vibration has been assigned[9] to the peak at 13.29 μ.

In summary it seems reasonable to state that the evidence from the literature of similar type compounds indicates that the vibration illustrated in Fig. 2 for α,β-unsaturated esters should be in the region 10–15 μ.

Experimental

Spectra.—The spectra were run on a Perkin–Elmer, model 21, double beam spectrophotometer. Capillary films of pure liquid between optical rock salt plates were used except where otherwise noted. Scanning times (2.0–15.5 μ) were 14–25 minutes with suppression setting of two units. Slit schedule 3 and sodium chloride prism were used.

Films were prepared for the polarized spectra by the steps of: 1, heating the compound in question between square rock-salt plates to slightly above its melting point; 2, differentially cooling the "sandwich"; and 3, seeding the melt at the coldest corner.

The preparation was then checked by microscopic examination between crossed nicols to ascertain that uniform, and nearly parallel, crystal structure was available for study.

The data for Tables II and III were taken mainly from spectra which were accumulated over a period of about two years. Wave length values quoted are believed to be accurate to ±0.5 μ except where otherwise noted.

Compounds.—In the preparation of methyl acetylenedicarboxylate a 15 molar portion of anhydrous methanol was refluxed 15 hr. with 1 mole of acetylenedicarboxylic acid and 0.01 mole of toluenesulfonic acid. The mixture was then cooled, diluted with water and extracted with benzene. The benzene solution was washed with 5% sodium bicar-

(4) Should one of the atoms be hydrogen, mechanical effects would cause the bond to the hydrogen to become the primary site of the vibration and the frequency of vibration would then be substantially increased.

(5) L. H. Jones and E. McLaren, *J. Chem. Phys.*, **22**, 1796 (1954).

(6) D. C. Smith, C. Y. Pan and J. R. Nielsen, *ibid.*, **18**, 706 (1950).

(7) It has been pointed out by a referee that the out-of-plane bending vibration of the methyl group should interact strongly with the out-of-plane Y-deformation, one result of which would be that the vibrations would move farther apart in frequency. Further, according to the assignments of this methyl frequency,[5,6] the effects would be to *lower* the out-of-plane Y-deformation and increase the out-of-plane methyl bending frequency from what would otherwise have been their normal values. If equally strong interaction is not present in the α,β-unsaturated esters, then the effect will be in the same direction as that argued above. Thus, a second reason for predicting the out-of-plane deformation absorption of α,β-unsaturated esters at a wave length shorter than the 16 μ region of the models above is encountered.

(8) T. Y. Wu, "Vibrational Spectra and Structure of Polyatomic Molecules," Second Ed., Edwards Brothers, Ann Arbor, Mich., 1946, p. 207.

(9) J. D. Brown, THIS JOURNAL, **77**, 6348 (1955).

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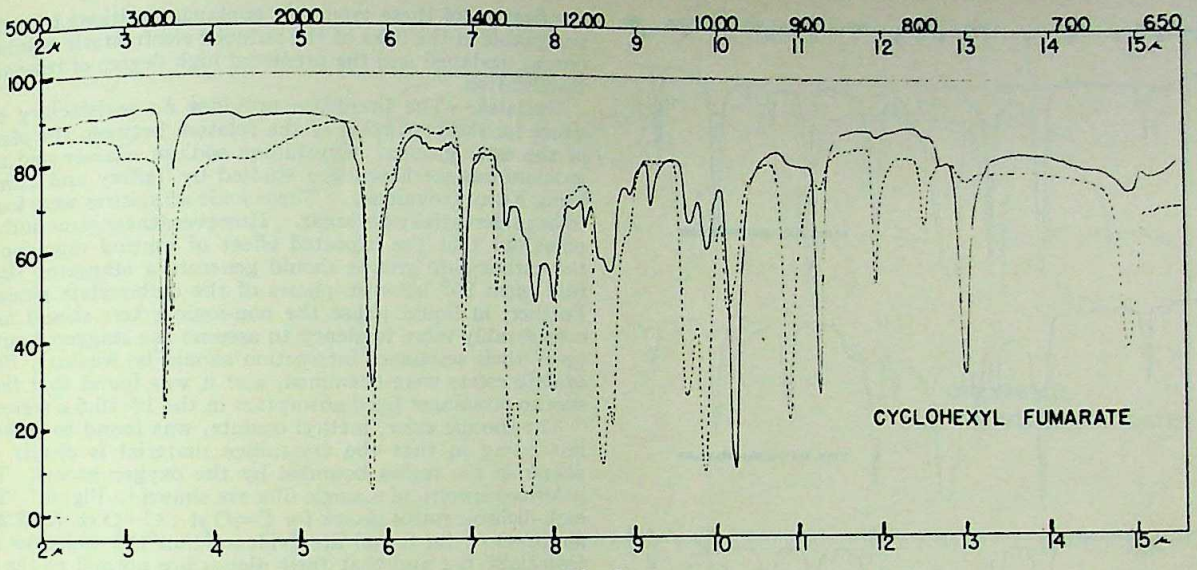


Fig. 3.

bonate solution and then with water and concentrated by distillation, using benzene to dry the ester azeotropically.

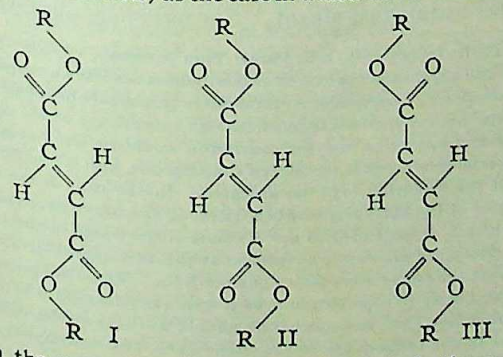
It was found that methyl acetylenedicarboxylate prepared by this method contained a considerable amount of an impurity which was higher boiling. On consulting the literature it was found that this side reaction had been explained.[10] The spectral data are in complete accord with Mommaerts interpretation that methanol added to this triple bond yielding an α-methoxy maleate which was partially removed by distillation with rejection of the higher boiling materials. The spectrum of the methyl acetylenedicarboxylate shown in Fig. 4 shows an absorption at 6.05 μ due to remaining impurity of this methoxy maleate ester.

Other esters of acetylenedicarboxylic acid were prepared by the method of Jeffery and Vogel.[11]

Spectra of Ester Families. Fumarates and Coplanarity.—Coplanarity of the ethylene and carbonyl in conjugated esters is generally accepted in the literature from which it would follow that the ester groups in a diester, such as a fumarate, would also be coplanar. Moreover, in the case of the fumarates some direct evidence of coplanarity can be deduced from the infrared spectra.

The carbonyl stretching absorption is at longer wave length by approximately 0.02 μ than the corresponding maleates. This indicates a greater degree of resonance stabilization.

Further, a peak at about 6.06 μ in maleates and fumarates is assigned to stretching of the C=C bond. With maleates, the 6.06 μ peak is regularly more intense and broader than the corresponding peak of fumarates. This constitutes one point of evidence since, in coplanar fumarate structures, two of the three pseudo-isomers would be centrosymmetric throughout the fumarate part of the structure. Defining *s-cis* (single-bond *cis*) as the case in which the C=C and C=O



lie on the same side of the single bond, it is the *s-cis*, *s-trans* structure II which is non-centrosymmetric. Thus, barring substantial contribution to dissymmetry from the alcohol portion of the fumarates, one would anticipate weaker infrared activity in this band (since only one isomer in three is infrared active) than in the maleates which are incapable of assuming a centrosymmetric configuration.

The third line of evidence that the fumarates are coplanar is based on observations of oriented crystal films with polarized infrared light.

Figure 3 shows the spectra of an oriented crystalline film of cyclohexyl fumarate. The solid curve was run with the polarizer setting such that the electric vector of the polarized beam was parallel to the direction of crystal growth of the sample. The dotted curve was run with the sample in the same position but with the polarizer rotated 90° from the first position. The carbonyl stretching absorption is intense in this preparation, but shows a greater absorption at the polarizer setting 90° from the direction of crystal growth. As both C–O peaks (7.4–8.0 μ and 8.6–8.7 μ) are intense with this same setting of the polarizer, it follows that both ester groups are essentially planar and normal to the direction of crystal growth. This most fortunate circumstance permits an easy analysis of the data, which might otherwise have been very complex. The C–O stretching vibrations are necessarily non-parallel because of the oxygen valence angle and would have yielded low dichroic ratios or considerably different angles of maximum absorption by any other orientation. Thus, this most fortunate orientation is clearly the actual one.

The out-of-plane ethylene hydrogen bending which is that consistently noted at 10.2 μ in fumarate esters is of moderate dichroism and is oriented as expected. The 12.9 μ appears slightly displaced (13.0 μ) but clearly identifiable as the strongest absorption is this region and of approximately the same intensity relative to say 10.2 μ as in liquid spectra. (Its intensity in relation to oppositely oriented peaks is normal as shown by mull spectra or this same crystal preparation without use of a polarizer.)

The spectrum of crystalline cyclohexyl fumarate is not appreciably different from that of the liquid as regards any of the absorptions noted above. It is different in that the C=C absorption at about 6.1 μ is very weak. Thus, evidently structure II above is eliminated in the crystallization process.

Our preparations of crystalline methyl fumarate have not provided high dichroic ratios, but the low ratios which were obtained were qualitatively in the same direction for each of the above-mentioned absorptions.

Acetylenedicarboxylates.—The spectra of six acetylenedicarboxylic esters are shown in Fig. 4. These spectra show peaks at 13.4 and 14.9 μ which are remarkably constant. Further, as in the case of the fumarates,[1] the lower frequency absorption is the less intense.

The first significant theoretical point learned from the acetylenedicarboxylates is that the fixed peaks are clearly not generated by hydrogen atom vibrations. And, since they are quite similar in frequency and intensity to the 12.9

(10) Henri Mommaerts, *Bul. soc. chim. Belg.*, **52**, 79 (1943).
(11) Geo. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 658 (1948).

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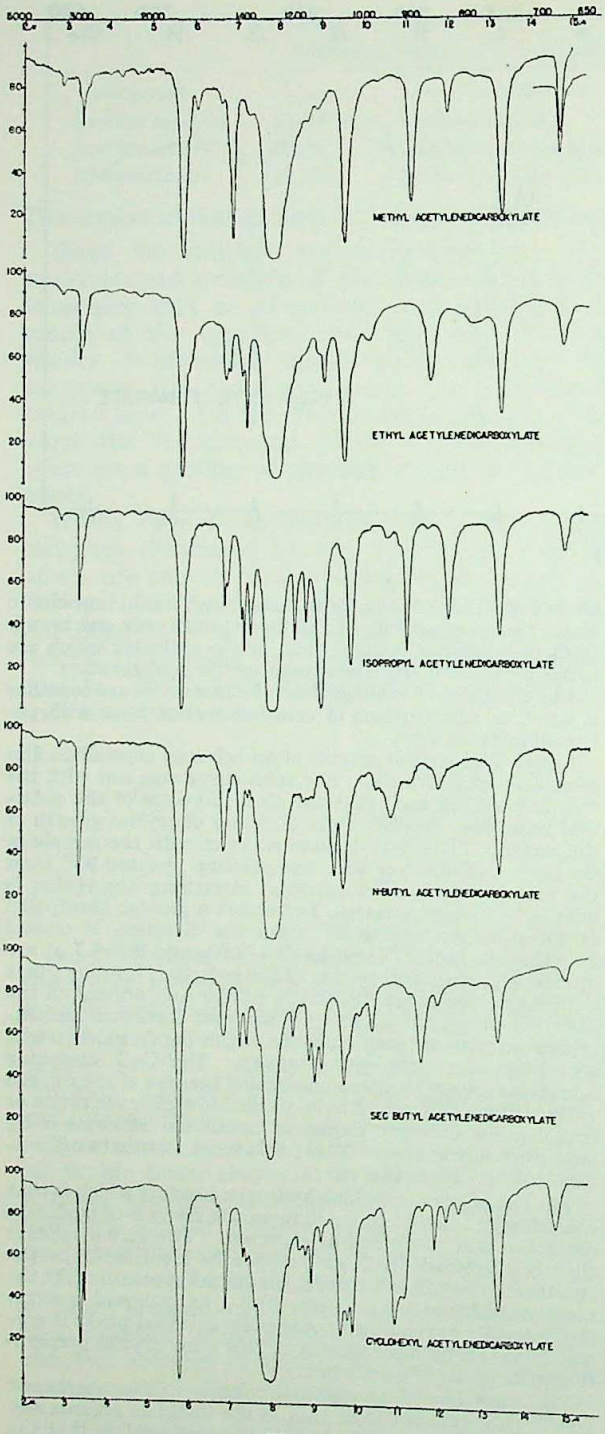

Fig. 4.

and 15.0 μ peaks of fumarates, it was at once apparent that the fumarate peaks were probably not due to hydrogen vibrations.

Figure 5 shows the spectra of cyclohexyl acetylenedicarboxylate run with polarized light. The solid curve is that in which the electric vector of the plane of polarization was parallel to the direction of crystal growth. The dotted curve had the plane of polarization 90° from the first position. Polarizations of the carbonyl stretching and of the complex C–O stretching absorptions are seen to be parallel to each other and at right angles to the 13.4 μ band.

As there obviously can be no steric restraint to free rotation of the ester groups about the linear axis of the four carbons in this compound, it is somewhat surprising to find any evidence of coplanarity of these ester groups. However, the fixation of these groups in coplanar positions is readily acceptable in the light of the reduced electrostatic repulsion (*versus* oxalates) and the predicted high degree of resonance stabilization.

Oxalates.—The literature provides no satisfactory evidence for the prediction of the relation between the planes of the ester groups. Crystalline sodium oxalate and ammonium oxalate have been studied by Jeffrey and Parry[12] using X-ray techniques. These ionic structures were found to be preferentially coplanar. However, these same authors point out that the expected effect of mutual repulsion of the carboxylate groups should generate a staggered structure (near 90° between planes of the carboxylate groups). Further, in liquid phase the non-ionic esters should have considerably more tendency to assume the staggered structure: their resonance interaction should be weaker. Four oxalate esters were examined, and it was found that there was no prominent fixed absorption in the 10–15.5 μ region.[13]

The specific ester, methyl oxalate, was found to be very interesting in that the crystalline material is clearly coplanar in the region bounded by the oxygen atoms. The polarized spectra of a single film are shown in Fig. 6. The high dichroic ratios shown for C=O st., C—O st. (at 8.2 μ) and C–O st. (at 8.6 μ) are evidence that the molecules are essentially flat and that their planes are normal to the direction of crystal growth in the film. The possibility that one carbonyl might be normal to the film plane and the other oriented to give absorption intensity as observed in the polarized spectrum can be disproved, since mull spectra show the same ratio of intensity for C=O st. and C–O st. as in the oriented films. Further, the high dichroic ratios for all three carbon-to-oxygen bond stretching vibrations, coupled with the knowledge of the near 120° angles involved in the ester groups, give additional proof.

Two strong sharp absorptions are observed at 10.81 and 12.81 μ. The former is believed to be out-of-plane deformation of the methyl group (it is not observed in sodium or calcium oxalate whereas the 12.8 μ peak is). The latter is probably a "double, out-of-plane Y-deformation" or essentially a motion of the two central carbon atoms simultaneously above and then below the plane of the oxygen atoms. This should be the only strongly infrared active vibration perpendicular to the plane and common to salts and methyl oxalate.

The methyl groups themselves are nearly in the plane of the molecules. This is clearly indicated by the very definite polarization of the 7.25 μ symmetrical deformation of the methyl groups.

Acrylates and Methacrylates.—In Fig. 7 are shown the spectra of several esters of each of the two series, the acrylates and the methacrylates. It is noteworthy that in both series only the methyl ester shows separation of the second C–O st. absorption into two bands paralleling the slight abnormality noted for the frequencies of the family peaks of these esters in Table II.

As can be seen from the data of Table II and the curves in Fig. 7, certain obvious features of the spectra are available for differentiation of the two families: with acrylates a doublet is resolvable in the 6.1 μ region and fairly constant peaks are noted at 9.4, 10.15 and 10.5 μ, whereas with methacrylates a peak at about 10.65 μ is characteristic and the other features are absent. The foregoing, together with

(12) G. A. Jeffrey and G. S. Parry, This Journal, **76**, 5283 (1954).

(13) The conclusion that an ester family does not have a characterizing absorption in a particular spectral range can be safe based on rather few esters; indeed, it could happen that no coincidence would occur in the first two examined and the conclusion would be valid even then. The reverse, proving that a peak is a constant one, also is readily established if the following logic be accepted. In the case of the 13.4 μ absorption of the acetylenedicarboxylates, all the esters have this peak falling within a range of 0.10 μ. A count of the peaks in the 10–15.5 range, which are one-tenth as intense as the 13.4 μ peak or stronger, shows that the peaks occur about one per 1.1 μ. Thus, the probability of a peak falling in a particular 0.10 μ wide range is only 0.1/1.1, and the probability that six such esters should all have peaks falling by accident in the same range is less than $^1/_{10}{}^6$. Two assumptions have been made: that each increment along the wave length scale is equally likely to find an absorption falling in it and that the absorption to be counted should have a certain minimum intensity. The first of these is probably fallacious but no doubt an arbitrary choice with order of magnitude accuracy when limited to the 10–15 μ range. The second is arbitrary and undoubtedly conservative as to its effect on the answer.

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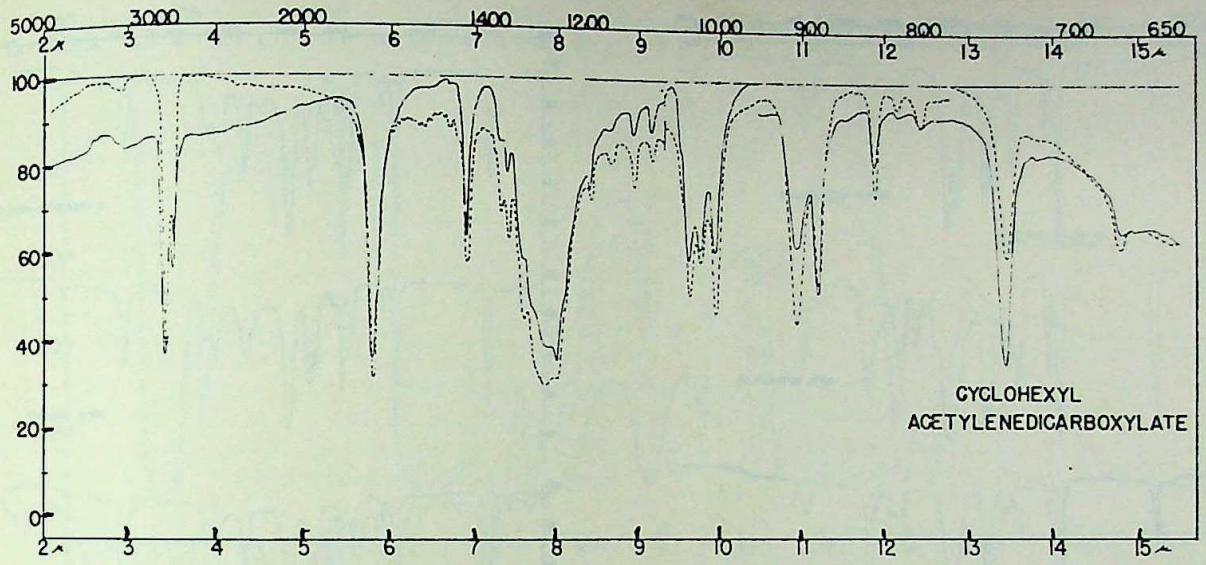

Fig. 5.

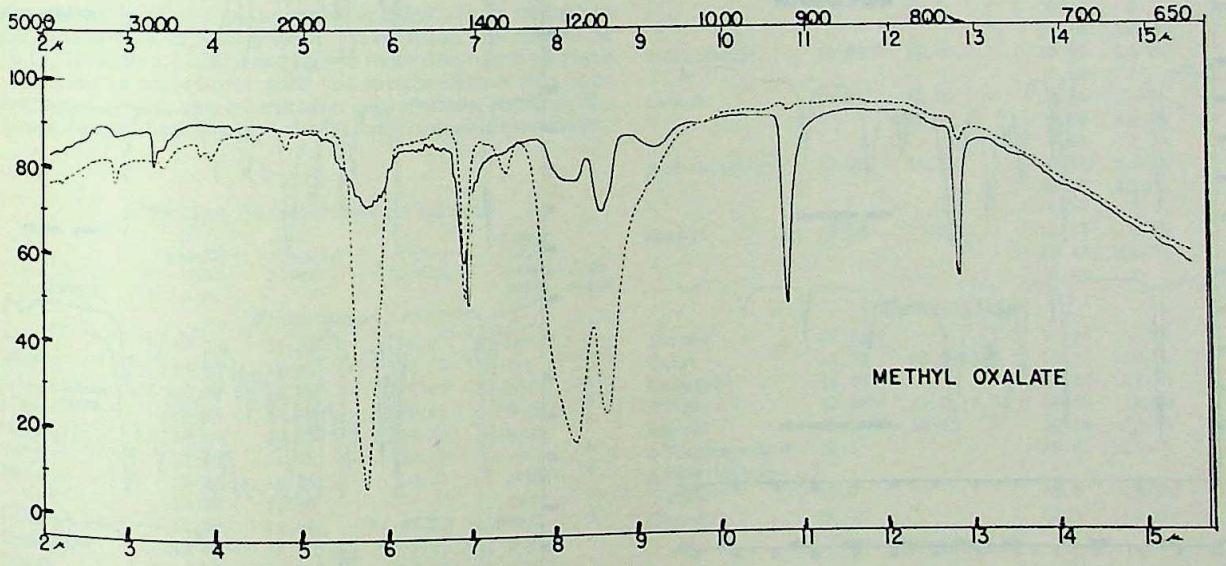

Fig. 6.

the information from an accurate measurement of the 12.3 μ absorption, can serve to distinguish the families rather conclusively. The moderately fixed absorption at around 15 μ is sometimes noted in the table and sometimes not. In general, this peak has offered less of analytical value—being somewhat weaker, less constant in a family and therefore not readily identified. It is probable that in some cases, not listed in the table, it will be found only if sufficiently thick samples are employed in searching for it.

The identification of the hydrogen vibrations has proved difficult. However, an interpretation which is marred by only one inconsistency has been developed: first, it is assumed that (1) vibrational coupling occurs between the hydrogen out-of-plane bending and the ester out-of-plane deformation, (2) coupling results in greater wavelength shifts when the mass of two hydrogen atoms instead of one is vibrating and (3) the theoretical positions of the bands (without coupling effects) would have been only slightly different from the positions in the hydrocarbons. Now, since methacrylates have a structure RR'C=CH_2 for which in hydrocarbons a peak at 11.22 μ is assigned, it is proposed that this peak is shifted to 10.65 μ. A "pattern" has been assigned to α-alkyl acrylates,[14] namely, peaks at 10.6 and 12.2 μ. Thus, the present interpretation for methacrylates is probably applicable to the broader class on which empirical correlation is not new. The acrylates are compounds of the structure R—HC=CH_2 for which in hydrocarbons an absorption at 10.95 μ is assigned to the H_2 bending and an absorption at 10.05 μ is assigned to the H. (These are, of course, not presumed to be free of coupling in the hydrocarbon but rather must be spread to some extent already by the coupling effect.) The H_2 bending is then shifted to 10.5 μ and the H bending to 10.15 μ. The latter is in line with the small shifts observed as the result of both chemical-shift (variation between ester type and hydrocarbon) and coupling-shift in *trans*-crotonates, *trans*-cinnamates and fumarates. With the acrylates, however, it must be assumed that the chemical effect and coupling effect are in opposite directions and that the chemical effect is the greater.

The one seriously discordant observation is that acrylic acid in liquid form shows three broad peaks at 10.2, 10.8 and 12.3 μ. Possibly the identity of the peaks is in the same order except that for some reason their frequencies are not as true.

There is a basis for believing that the vibrations in question are all directed normal to the plane in the planar molecules, namely, that their structures are essentially similar to that of acrylamide.

Acrylamide.—Figure 8 shows the spectra of acrylamide (in oriented crystals) run on the same film but with two settings of the polarizer. The CH stretching vibrations and the carbonyl stretching vibration show their strong absorption at the same position of the plane of polarization. Thus these absorptions, and therefore most of the atoms of

(14) C. J. Albisetti, D. C. England, M. J. Hogsed and R. M. Joyce, This Journal, 78, 472 (1956) (acknowledgment to J. R. Dowing).

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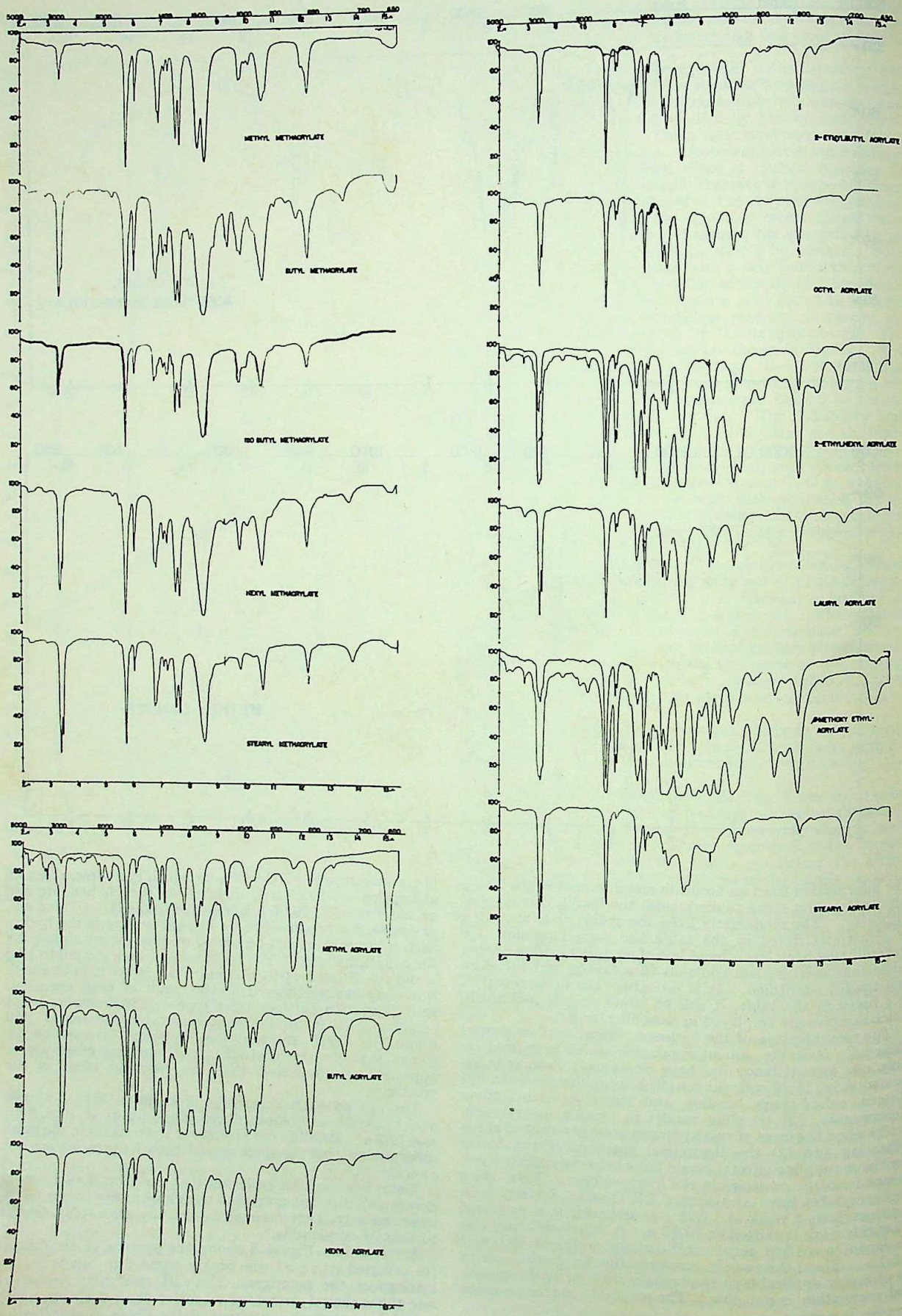

Fig. 7.

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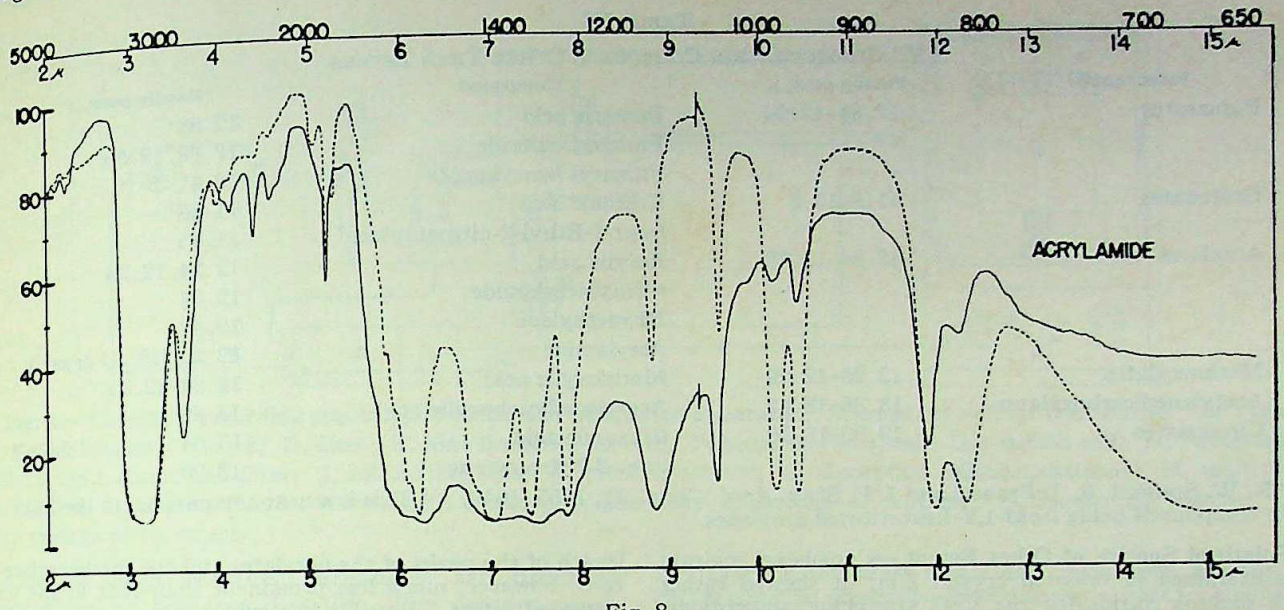

Fig. 8.

the molecule, lie in a plane which incidentally is normal to the direction of crystal growth. The three absorptions at 10.17, 10.42 and 12.30 μ are shown to be due to out-of-plane vibrations in accordance with the interpretation that they are, respectively, the α-hydrogen out-of-plane bending, the β-out-of-plane bending and the Y out-of-plane deformation.

TABLE II

INFRARED ABSORPTIONS OF ESTERS

Esters	Family[e] peak, μ	Second peak, μ	Other peaks, μ	Other peak assignment	Technique
Fumarates					
Methyl	12.94	14.98		⊥Bending of hydrogen on ethylene	c
Ethyl	12.92	15.03	10.22		b
Propyl	12.90	14.99	10.21		b
Isopropyl	12.90	14.96	10.21		b
Butyl	12.84	14.96	10.20		b
Isobutyl	12.88	14.92	10.23		b
	12.92	14.98	10.21		a
sec-Butyl	12.89	15.00			b
Cyclohexyl	12.90	14.98	10.20	⊥Bending of hydrogen on ethylene	a
Nonyl	12.89	14.90[b]	10.21		a
Lauryl	12.90	14.91[b]	10.23		a
Tetrahydrofurfuryl	12.93	14.94	10.20		a
	12.94	15.02	10.20		a
β-Methoxyethyl	12.93	14.91	10.24		b
Polydipropylene[i]	12.94	14.98	10.19		a
Allyl	12.94	...	...		
Acetylenedicarboxylates					
Methyl	13.37	14.77			a
Ethyl	13.38	14.87			a
Isopropyl	13.36	14.91			a
Butyl	13.38	14.83			a
sec-Butyl	13.37	15.00			a
Cyclohexyl	13.37	14.76	round ±0.05		a
	13.36				a?
Acrylates					
Methyl	12.301[f]	15.14	10.12	⊥α-H	
			10.34	⊥β-H₂	
Butyl			9.36	?	
	12.34[b]	15.5[b]	10.19	⊥α-H	a
	12.37[a]		10.40	⊥β-H₂	
Hexyl			9.43	?	
	12.326[f]	15.08	10.16	⊥α-H	a
			10.39	⊥β-H₂	
2-Ethylbutyl			9.43	?	
	12.329[f]		10.15	⊥α-H	a
			10.40	⊥β-H₂	
Octyl			9.44	?	
	12.326[f]		10.16	⊥α-H	a
			10.40	⊥β-H₂	
			9.45	?	
			10.16	⊥α-H	
2-Ethylhexyl	12.326[f]	15.05	10.39	⊥β-H₂	b
			9.42	?	
Lauryl	12.34	15.07	10.15	⊥α-H	a
			10.40	⊥β-H₂	
			9.44	?	
β-Methoxyethyl	12.35	14.88	10.14	⊥α-H	a
			10.40	⊥β-H₂	
			9.37	?	
Stearyl	12.38	15.00	10.17	⊥α-H	a
			10.42	⊥β-H₂	
			9.41	?	
Methacrylates					
Methyl	12.247[f]		10.65	⊥β-H₂	a
Butyl	12.28	15.2–15.4	10.66	⊥β-H₂	a
Isobutyl	12.29		10.65	⊥β-H₂	a
Hexyl	12.262[f]	15.2–15.35	10.69	⊥β-H₂	a
Stearyl	12.269[f]	15.45	10.68	⊥β-H₂	a
β-Vinyloxyethyl[g]	12.3		10.6	⊥β-H₂	
β-Polyvinyloxyethyl[g]	12.3		10.6	⊥β-H₂	
Glycidil[h]	12.3		10.6	⊥β-H₂	
Crotonates[h]					
Ethyl	11.90	14.40	10.30	*trans*-Hydrogen ⊥ bending	
Vinyl	12.00	14.80	10.18		
Butyl	11.88	14.60	10.30		
Glycidil	12.00	14.60	10.30		
***trans*-Cinnamates**					
Methyl	13.03	14.05	10.17	*trans*-Hydrogen ⊥ bending	d
		14.64			
		14.10			
Butyl	13.02	14.65	10.20		a
Propionates					
Methyl	12.40				c,i
Ethyl	12.46	weak			c
	12.41				b
Butyl	12.39	weak			a,k
Cyclohexyl	12.40	weak			a

[a] Sandwich cell, pure liquid. [b] Std. cell, pure liquid. [c] Std. cell, solution in CS_2. [d] Crystal film. [e] Ester out-of-plane deformation. [f] These measurements were carried out with maximum precision in comparison with ammonia vapor peaks at 12.381 and 12.684 μ. Wave lengths are probably more accurate than ±0.005 μ. It is noted that wave lengths ranges are specific for the ester family except that the methyl esters are both about 0.02 μ lower wave length than the rest of the family (as far as explored). [g] H. C. Haas and M. S. Simon, *J. Polymer Sci.*, 17, 422 (1955). [h] W. A. Patterson, *Anal. Chem.*, 26, 830 (1954). [i] Polyester based on commercial dipropylene glycol and fumaric acid. [j] In benzene. [k] Benzene present.

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TABLE III

"Y" CONFIGURATION COMPOUNDS OTHER THAN ESTERS

Ester family	Family peak, μ	Compound	Family peak, μ
Fumarates	12.84–12.94	Fumaric acid	12.88
		Fumaryl chloride	12.62, 12.59
		Fumaryl benzylamide	12.4[a]
Crotonates	11.9–12.0	Crotonic acid	11.88
		trans-1-Ethyl-2-nitroethylene[b]	11.85
Acrylates	12.34–12.38	Acrylic acid	12.24, 12.29
		t-Butylacrylamide	12.34
		Nitroethylene	12.48
		Acrylamide	12.22 (12.30 cryst.)
Methacrylates	12.26–12.29	Methacrylic acid	12.24–12.39
Acetylenedicarboxylates	13.36–13.42	Acetylenedicarboxylic acid	13.42
Cinnamates	13.00–13.10	Cinnamic acid	13.04
		trans-β-Nitrostyrene	13.00

[a] R. W. Stafford, R. J. Francel and J. F. Shay, *Anal. Chem.*, 21, 1455 (1949). [b] This is a near comparison, in the light of both compounds being *trans*-1,2-disubstituted ethylenes.

Polarized Spectra of Other Esters.—Cyclohexyl maleate was examined in oriented crystal film; it showed rather high dichroic ratios for the C–O stretching absorptions. Further, those absorptions were strong at the same setting of polarizer that gave strong absorption by the C=C stretching vibration. Thus, a high degree of coplanarity for the ester group and the ethylene exists. Significantly, the absorption at 8.2 μ which was shown to be characteristic of maleates[1] was absent. Thus, this molecule is preferentially oriented in crystallization and could be substantially unlike *normal* maleates. Another point of abnormality recorded in the earlier paper is that the melting point of the maleate is in this case higher than the fumarate: 86° *vs.* 35–36°.

Methyl cinnamate was studied; it yielded only moderate dichroic ratios in any assigned peaks. However, such ratios as were noted were again qualitatively in accord with expectations based on our generalization.

Tabulated Spectral Data.—Table II shows the wave lengths of the family-constant peak for the various ester families. Other peaks of interest also are shown.

Several ester families were examined to see if constant peaks were present in the 10–15 μ region and none were found. These included succinates, acetates and oxalates. However, the propionates have a peak that is remarkably constant at 12.4 μ as had been noted by Tompson and Torkington in 1945.[2] This absorption is very near the wave length of the peaks of the acrylates and the methacrylates. It is, however, much less prominent than that in the unsaturated esters. Possibly the explanation of this absorption could be that a low degree of double bond character exists at the C–C bond between the carbonyl and α-carbons and that some portion of the molecules at a given instant assume the conformation that most nearly matches that of the acrylates.

Types Other Than Esters.—It was noted early in this investigation that the corresponding acids have peaks which match the family-constant ester peak. As the study progressed more compounds of related types were examined and confidence increased in the greater breadth of the generalization. Table III lists other types in comparison with the esters.

Acknowledgments.—The authors are grateful to Drs. R. S. McDonald, J. F. Brown, Jr., and A. Pozefsky for helpful comments on the theoretical aspects of this work. They are also grateful to Dr. J. Rosenberg for valuable help in obtaining many of the compounds used in this study and to Dr. J. F. Brown, Jr., for the data on the nitroethylene spectra.

SCHENECTADY, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Light Induced Spectral Shift of the Thiazine Dyes in the Bound State[1]

BY NEIL WOTHERSPOON AND GERALD OSTER

RECEIVED MARCH 8, 1957

We have found that thiazine dyes in the presence of polymethacrylic acid or polyacrylic acid undergo a spectral shift when irradiated with visible light. A combined recording spectrophotometer and irradiation apparatus was used to follow the reaction either at a fixed wave length or by scanning the spectrum repetitively. Two photo products are formed, one in the absence of oxygen and the second by the photoöxidation of the first. The rate of formation of the second product is retarded by small amounts of paraphenylenediamine or by potassium iodide suggesting that long-lived excited states are involved. The final photoproduct is the same for all the thiazine dyes studied and is identical to thionine. The reaction requires a polyacrylic acid but does not take place in the presence of other high polymeric acids or of dibasic acids.

Introduction

During the course of our studies on the photochemical properties of methylene blue, we observed that a purple species having a bright red fluorescence was formed when a solution of the dye containing polymethacrylic acid was illuminated. It is the purpose of the present study to investigate the nature of this photochemical reaction. In particular, we are concerned with determining which dye and high polymer combinations exhibit this phenomenon.

The photochemical properties of many dyes

(1) (a) This paper represents a part of the dissertation to be submitted by Neil Wotherspoon to the faculty of the Graduate School of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under Contract No. AF 18(600)1182.

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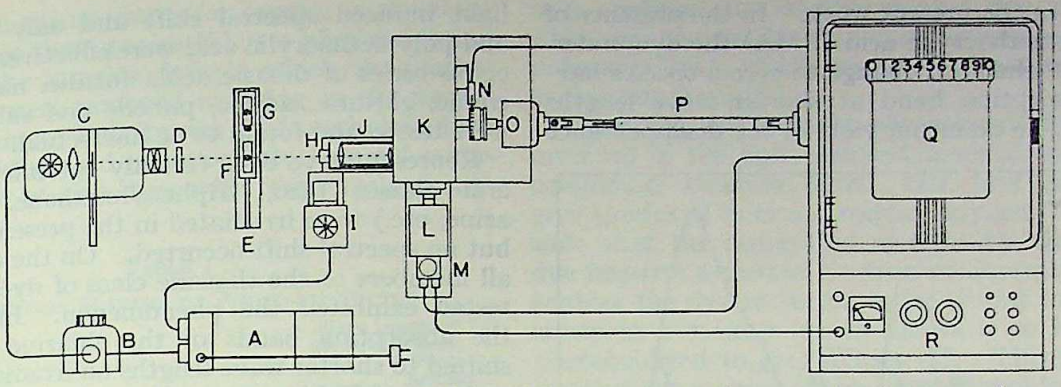

Fig. 1.—Combined recording spectrophotometer and irradiation apparatus: A, constant voltage transformer; B, Variac; C, Kodak Master projector; D, filter; E, slide transport for cells; F, blank (solvent) cell; G, reaction cell; H, fluorescence cell; I, light source and filter; J, collimating lens; K, monochromator; L, absorption cell compartment; M, multiplier phototube; N, microswitch for wave length marker; O, gear box; P, mechanical coupling; Q, Speedomax recorder; R, high voltage power supply.

bound to high polymer substrates are different from those of the free dyes.[2,3] The present work differs from previous studies of the photochemistry of bound dyes, however, in that only one class of dyes, namely, the thiazines, exhibits the light induced spectral shift. Furthermore, the high polymeric substrate for the reaction is highly specific and is apparently confined only to polyacrylic acid and polymethacrylic acid.

Experimental

Materials.—Methylene blue, Merck, zinc free, was used without further purification. All other thiazine dyes were histological grade from National Aniline Division of Allied Chemical and Dye Corp.

Polymethacrylic acid (PMA) was prepared by polymerizing 10 g. of distilled methacrylic acid in 200 ml. of water containing 0.2 g. of potassium persulfate at 90° for 30 minutes. The mixture was previously degassed by bubbling with nitrogen. The polymer solution was dialyzed against distilled water for three days, and then freeze-dried.

Apparatus.—The equipment was conveniently arranged for both irradiating the dye solutions and simultaneously recording the absorption spectrum (Fig. 1).

The light source for the photochemical reactions was a 1000 watt Kodak Master slide projector. A Variac was used to reduce the input voltage to 65 volts in order to provide a convenient light intensity and to prolong the life of the lamp. Constancy of illumination was assured by a 500 VA Sola constant voltage transformer. Filters could be inserted in the projector slide carrier. The optical cells were made by cementing Pyrex plate glass disks (2.25 inch diam.) to a half inch section of 2.25 in. heavy wall Pyrex tubing in which two capillary tubes were sealed to permit bubbling with helium. Araldite epoxy resin was used as cement. The reaction cell and a blank cell filled with water were mounted on a transverse sliding block which allowed either cell to be irradiated.

The measurement of monochromatic radiant flux incident upon the cell was carried out with a calibrated Eppley thermopile whose output was read on a Leeds and Northrup Microvolt Amplifier No. 9835-A. This is a chopper stabilized amplifier inherently capable of high precision and freedom from zero drift.

The spectrophotometer consisted of a Bausch and Lomb 250 mm. grating monochromator in conjunction with a Leeds and Northrup Speedomax recorder. The recorder was modified by the inclusion of a special high impedance amplifier for use with an RCA 1P22 multiplier phototube. The recorder was adapted to permit direct mechanical coupling *via* gears and a pair of universal joints to the monochromator grating screws. In this way a linear relationship between the chart paper movement and wave length was obtained. A microswitch provided marker pulses to operate a marker pen at the right-hand side of the chart at intervals of 100 mμ. By reversing the chart motor and rescanning, a series of curves could be superimposed on the same chart for comparison. The recorder contained controls for dark current suppression and for sensitivity which could be made as high as 10^{-10} amp. per mm. A Scientific Specialties Corp. Regulated High Voltage Power Supply, Model PS-22M, was used to provide from 500 to 1000 volts for the phototube. The stability was such that phototube sensitivity drift was negligible over a period of an hour.

For kinetic studies the monochromator was set at the wave length of an absorption band of either a reactant or a product and the transmission of the solution recorded as a function of time of irradiation. Spectra of photosensitive systems were obtained by placing the solutions in the cell compartment between the monochromator and the phototube where the light intensity is very low.

Fluorescence spectra were recorded by rearranging the light source and optical cell. Either the mercury arc or the ribbon filament lamps supplied with the Bausch and Lomb Monochromator were used to illuminate a square optical cell which was placed near the entrance slit collimating lens. This lens formed an image of the fluorescence cell on the slit and thus excluded almost all of the scattered light. Only the front edge of the cell was imaged on the slit in order to avoid self absorption effects. The chart record of the fluorescence intensity *vs.* wave length had to be corrected for the unequal phototube sensitivity at each wave length. This was done by determining the phototube response to a ribbon filament lamp whose color temperature was measured by the National Bureau of Standards. From the Planck energy distribution equation and the phototube response, the absolute phototube sensitivity was calculated. This method eliminated the effect of anomalies in the transmission of the grafting monochromator.

Procedure.—The kinetic transmission curves were recorded at a given wave length by setting the blank transmission at or near the full scale of the recorder after adjusting the dark current to zero. The initial rate of disappearance of dye was used to calculate the quantum yield. In some experiments atmospheric oxygen was permitted to participate in the reaction. In order to prevent air oxidation helium (Airco) was used to degas the solution.

In order to determine the quantum yield for the conversion of methylene blue, a solution of the dye and PMA was irradiated by the light from the 500 watt projector lamp filtered by a Baird Associates interference filter with a peak transmission of 63% at 665 mμ and a half band width of 10 mμ. The rate of disappearance of the methylene blue absorption band at 665 mμ was obtained from the initial slope of the transmission *vs.* time curve as plotted by the recorder. The slope was converted into a rate by the use of the absorbancy index of the dye and of the initial transmittance. From the measured radiant flux (659 μw./cm.²) obtained by the use of the thermopile and the rate of dye conversion, the quantum yield was obtained.

Results

Methylene blue at concentrations of the order of 10^{-5} *M* is stable to visible light of intensities

(2) G. Oster, *Trans. Faraday Soc.*, **47**, 660 (1951).
(3) G. Oster and J. S. Bellin, THIS JOURNAL, **79**, 294 (1947).

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considered in the present work. In the presence of excess polymethacrylic acid (PMA) the dye undergoes a photochemical change to give a species having an absorption band at shorter wave lengths (Fig. 2). The quantum yield of the disappearance

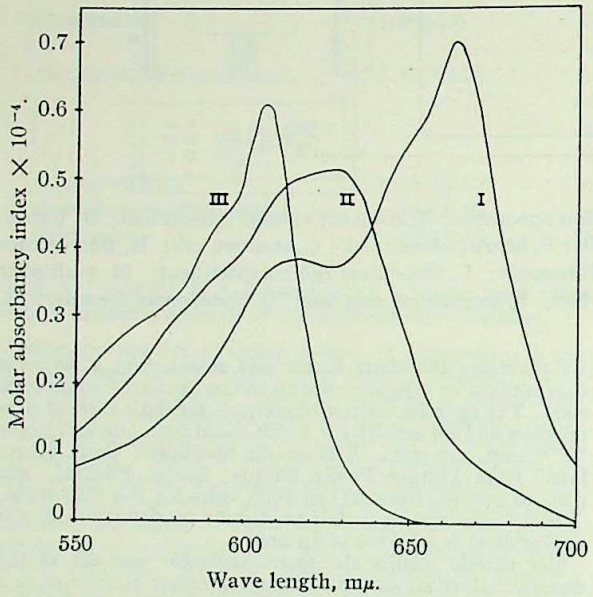

Fig. 2.—Light induced spectral shifts in methylene blue; dye concentration 10^{-5} *M*, PMA concentration 5×10^{-4} *M* (monomer basis), *p*H 7: I, unirradiated; II, irradiated in the absence of oxygen; III, irradiated in the presence of oxygen.

of methylene blue is 0.0035. If the irradiation is carried out with oxygen present, the dye (curve I) is converted to a purple species (curve III). Whereas methylene blue free or bound is only feebly fluorescent (quantum yield less than 1%), the light produced species exhibits a strong red fluorescence with a quantum yield greater than 10%. An intermediate species is produced because the initial rate of disappearance of species I is greater than the appearance of species III. This is more clearly seen by carrying out the reaction in the complete absence of oxygen. Under this condition, a substance with an absorption band (curve II) intermediate between the other two is produced and no purple species is formed. If now a solution containing species II is irradiated in the presence of oxygen the purple species (curve III) is produced. It appears, therefore, that methylene blue undergoes an anaerobic photochemical transformation to species II which, in turn, undergoes a photoöxidation to species III.

The rate of production of species III was reduced to about one-half its normal value in the presence of either 10^{-5} *M* of KI or of *p*-phenyldiamine. The rate of production of species II, on the other hand, was not influenced by the addition of these substances up to a concentration of 10^{-2} *M*.

A number of high polymeric acids including desoxyribose nucleic acid (molecular weight about 5×10^6), alginic acid, hyaluronic acid, polyglutamic acid, hydrolyzed maleic anhydride–vinyl methyl ether copolymer, and agar were tested with methylene blue. None of these substances produced the light induced spectral shift and only polyacrylic and polymethacrylic acid were effective. A homologous series of dibasic acids (oxalic, malonic, succinnic, glutaric, adipic, pimelic and suberic acids) were tested and found to be ineffectual.

Representative dyes (mainly cationic) from several classes (azo, triphenylmethane, xanthene, azine, etc.) were irradiated in the presence of PMA but no spectral shift occurred. On the other hand, all members of the thiazine class of dyes which we tested exhibited the phenomenon. In all cases, the absorption bands of the thiazine dyes were shifted to shorter wave lengths on irradiation in the presence of PMA and oxygen resulting in a strongly red fluorescent species (Table I). The absorption spectra of the photo-product is for all these cases identical with that of thionine. Similarly, the fluorescence spectrum of the photo-product is identical with that of thionine (Fig. 3). The photo-

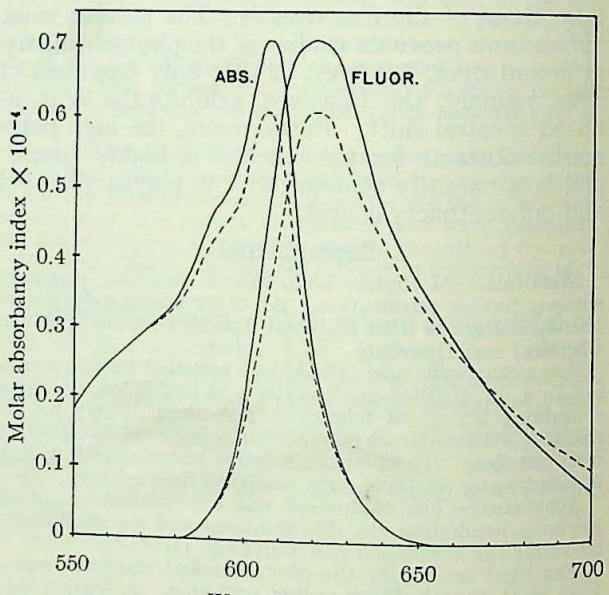

Fig. 3.—Absorption and fluorescence spectra of thionine and of the photoöxidation product: solid curves, thionine; dotted curves, photoöxidation products of methylene blue. Fluorescence curves are drawn to arbitrary ordinates.

product (species III) is an acid–base indicator and changes reversibly from purple to red in basic solutions. Thionine behaves similarly but methylene blue does not show this reversible color change at high *p*H values.

Discussion

The phenomenon of light induced spectral shift in dye–polymer mixtures has not heretofore been observed as far as we have been able to ascertain. It differs from light induced *cis–trans* conversions in that a specific polymer must be present and furthermore the reaction is irreversible.[4]

It is clear that in all cases the photo-product is identical with thionine. This is shown from the close resemblance between species III and thionine as regards their absorption spectra, fluorescence spectra and behavior as a *p*H indicator. This fact,

(4) Compare, for example, G. M. Wyman, *Chem. Revs.*, **55**, 625 (1955).

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together with the necessity for oxygen in the reaction, indicates that species III is a photooxidation product of the thiazine dyes in which the methyl substituents were removed resulting in the formation of thionine. It is known that methylene blue may be demethylated by non-photochemical oxidation in alkali to give dyes with fewer methyl substituents.[5]

TABLE I

ABSORPTION MAXIMA OF PHOTO-PRODUCTS

Dye	Wave length of absorption max. Free dye	Photo-product with PMA
Thionine	599	607
Azure C (monomethylthionine)	616	607
Azure A (u-dimethylthionine)	620	608
Azure B (trimethylthionine)	652	605
Methylene blue (tetramethylthionine)	665	606

The highly specific nature of the polymer required for the reaction implies that the polyacrylic acids serve as substrates for a very special type of dye binding. In the dye–polymer complex the transition from the ground to the first electronic excited state does not differ from that of the free dye since the absorption spectra are virtually identical. Transitions from the first electronically excited state to other states must, however, be profoundly affected by the complexation with the specific polymers. It appears that the spatial arrangement of the carboxyl groups on the polyacrylic acids is particularly suited to complex with the thiazines *via* their amino groups to distort the electron configuration of the excited dye molecules. This arrangement does not exist for any of the other polymeric acids which were tested nor for the dibasic acids studied.

There are two distinct photochemical processes involved in the light induced spectral shift of the complexed thiazine dyes. The first process to give species II does not require oxygen. It is possible that the absorption of light by the original dye imparts a certain electron configuration which enables the dye molecule to be bound to the substrate in a manner which allows it to be readily photooxidized to give species III. This first process does not require oxygen and probably does not involve long-lived states. On the other hand, the second process involves long-lived states because very small amounts of KI or *p*-phenylenediamine retard the reaction. From the observed retardation we estimate, using the Stern–Vollmer expression and the calculated diffusion controlled encounter frequency in solution,[6] that the lifetime of the excited species which reacts with oxygen to be about 10^{-5} sec. By analogy with other dyes whose rate of photochemical conversion is influenced by O_2, KI and *p*-phenylenediamine, we propose that this long-lived excited state is a triplet state. It has been shown with triphenylmethane dyes[3] that binding can encourage triplet formation. Here, however, it appears that a specific substrate is required and that the binding takes place only after the dye is excited. The low quantum yield observed is probably accounted for in terms of internal conversion to the ground state which are competitive to transitions to the long-lived state.

(5) H. J. Conn, "Biological Stains," 5th Ed., Biotech Publications, Geneva, N. Y., 1946.

(6) G. Oster and A. H. Adelman, THIS JOURNAL, **78**, 913 (1956).

BROOKLYN 1, N. Y.

[CONTRIBUTION FROM THE MELLON INSTITUTE AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Diketene: Infrared Spectrum and Structure. II[1]

BY FOIL A. MILLER AND GERALD L. CARLSON

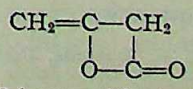
RECEIVED MARCH 16, 1957

Earlier temperature-dependence measurements on the infrared spectrum of diketene vapor by Miller and Koch have been repeated, and have been found to be incorrect. There is no evidence from the vapor spectrum for an equilibrium between two forms. Furthermore the spectrum of the solid, the liquid and the vapor are essentially the same. It follows that diketene in all its states exists predominantly or entirely in a single form, which other X-ray and nuclear magnetic resonance spectra studies have shown to be the 3-buteno-β-lactone structure. It appears that the five strong bands in the double bond stretching region, long a stumbling block to understanding the structure, are due to two fundamentals and three combination tones.

Introduction

Some time ago Miller and Koch[2] studied the infrared spectrum of diketene vapor as a function of temperature between 30 and 180°. They found reversible changes which were attributed to the existence of two forms of diketene in equilibrium. This conclusion helped explain the presence of five strong bands in the region 1650–1950 cm.$^{-1}$, and was attractive for understanding the welter of other conflicting evidence concerning the structure of diketene.

Since then an X-ray diffraction study by Katz and Lipscomb[3] has shown that crystalline diketene has the 3-buteno-β-lactone structure



3-buteno-β-lactone

This was confirmed by a nuclear magnetic resonance spectra study of crystalline diketene by Ford and

(1) (a) From a thesis submitted by G. L. Carlson in partial fulfillment of the requirements for the degree of Master of Science at the University of Pittsburgh. (b) This work was supported in part by a grant from the National Science Foundation.

(2) F. A. Miller and S. D. Koch, Jr., THIS JOURNAL, **70**, 1890 (1948).

(3) L. Katz and W. N. Lipscomb, *Acta Cryst.*, **5**, 313 (1952).

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Richards,[4] which demonstrated that the protons occur only in CH_2 groups. More recently Bader, Gutowsky, Williams and Yankwich,[5] also using nuclear magnetic resonance, concluded that this same form is the only significant one existing in the liquid between 25 and 120°.

Because these results for solid and liquid directly contradict the earlier conclusions drawn for the vapor, it was deemed desirable to repeat the earlier work to see whether it was in error or whether the vapor really does have a different composition from the liquid and solid. This has been done, and the finding is that the earlier infrared work was in error. There is no temperature dependence to indicate an equilibrium between two forms.

Experimental

Commercial diketene (obtained from the Carbide and Carbon Chemicals Company through the courtesy of R. C. Miller of Mellon Institute) was distilled at reduced pressure (b.p. 43.5° at 48 mm.). It was then further purified by fractional crystallization. Because this appears to have been an especially effective method, the procedure will be described. Diketene melts at −7°. A cold-bath was prepared from a 1:1 solution of sodium thiosulfate in water, and cooled with Dry Ice until slushy. The sample was immersed in this slush, and stored in a Dewar flask in a cold room at −5°. In about 24 hr. large crystals of diketene had formed. Cooling was allowed to proceed until about half of the sample had crystallized. The remaining liquid was decanted, and the pure sample was stored at −5° under nitrogen until used; $n^{20}D$ 1.4376.

A Perkin–Elmer model 112 infrared spectrometer (single beam, double pass) was used with a NaCl prism, and with a slit servo accessory to approximately level out the 100% line. The instrument was completely flushed with dry, CO_2-free air, and the range 700–4000 cm.$^{-1}$ was covered.

The spectrum of the solid was obtained in a low temperature cell, similar to one described by Lord, McDonald and Miller,[6] which had a conventional vapor-tight liquid cell about 0.05 mm. thick attached to the Housekeeper seal. The liquid sample was slowly solidified in this cell by adding Dry Ice slush to the coolant reservoir. After the spectrum of the solid had been obtained, the sample was melted and the liquid spectrum was measured in the same cell.

The system for handling and heating the vapor was similar to that used by Miller and Koch,[2] but a considerable improvement was made in the manner of sealing the windows onto the cell. The ends of the 5-cm. long Pyrex cell body were flanged and ground flat. Rocksalt windows were clamped against the flanges with metal rings and tie rods. A very satisfactory grease was compounded of 10% extremely fine silica (Monsanto's Santocel 54) and 90% Dow-Corning No. 200 silicone oil. This grease, used on both the flanged surfaces and the stopcocks, gave a vacuum-tight system at temperatures up to at least 250°. Because the windows are not attached to the glass with a rigid seal, but are merely pressed against the flanges, there is no problem with differential expansion.

In this work the temperature of the vapor was varied between 40 and 180°. A sample pressure of 19 mm., measured at 40°, was used. There was no evidence of any decomposition of the sample after hours of heating. Another grease, compounded from lithium stearate (10 g.) and No. 60 lubricating oil (40 g.),[7] caused sample decomposition at temperatures as low as 100°. Carbon dioxide was a product, but there was no ketene, allene nor methylacetylene.

Results and Discussion

The infrared frequencies agree well with the earlier results of Whiffen and Thompson[8] and Miller and Koch[2] and references cited by them. Whiffen and Thompson's spectrum shows the 1130 band to be considerably more intense than 1106, whereas our finding is that it is only slightly more so. This is certainly due to an impurity in their sample, for the spectrum of our crude material matched theirs in this region, whereas purification diminished the 1130 cm.$^{-1}$ band.

Our spectra for the liquid and for the solid were essentially the same, as shown in Table I. The cell (0.05 mm.) was far too thick for some of the bands, which makes it impossible to locate their maxima accurately. This also is the reason why only two bands are reported in the double bond region; the four strong bands have merged into two very broad ones. The significant finding is that the liquid and solid spectra are essentially the same. This reinforces the conclusion of Bader, Gutowsky, Williams and Yankwich[4] that diketene has the same single structure in the liquid as in the solid.

The spectrum of the vapor at room temperature already has been shown to be essentially identical with that of the liquid.[2] It must therefore be concluded that it too consists of a single form of diketene.

Table I

Infrared Frequencies (in Cm.$^{-1}$) of Solid and Liquid Diketene

(solid, *ca.* −40°; liquid, *ca.* 25°)

Solid	Liquid	I^a	Solid	Liquid	I^a
812	810	vs	1520	1517	w
862–884[b]	832–884[b,c]	vs	..	1538	w
959	960	s	1555	1555	w
1024	984–1017[b,d]	vs	1572	..	m
1060	1050	m	1704[b]	1704[b,e]	vs
1115	1100	m	1847 } [b]	1875[b,e]	vs
1143	1130	w	1886 }		
1173	..	w	1946	1957	sh
1196	1193	m	2030	2010	m
1247	1237	vs	2079	2073	m
1365	1374 }		2222	2213	w
1396	1391 }	s	2348	2337	m
1416	1408 }		3020	.. }	
1458 }	1463	m	3065	3075 }	m
1474 }			3181	3163 }	

[a] w, weak; m, medium; s, strong; v, very; sh, shoulder. [b] Too intense to measure accurately in 0.05 mm. cell. [c] Thinner sample gives band at 870 with shoulder at 840. [d] Thinner sample gives band at 1011. [e] See Table II.

The earlier evidence for an equilibrium between several forms—the change of the vapor spectrum with temperature—could not be repeated. A careful comparison of the spectrum at 40° with that at 180° over the range 700–4000 cm.$^{-1}$ showed no significant differences, but only the expected flattening and broadening of the bands at higher temperature. An especially careful study was made of the regions where Miller and Koch had noted marked changes, and no such changes were observed. There was no band at 1797, at 1133 nor at 1185 cm.$^{-1}$. It has already been mentioned that much of the 1133 cm.$^{-1}$ intensity could have been due to an impurity. None of the other effects were duplicated. It is con-

(4) P. T. Ford and R. E. Richards, *Disc. Faraday Soc.*, **19**, 193 (1955).

(5) A. R. Bader, H. S. Gutowsky, G. A. Williams and P. E. Yankwich, This Journal, **78**, 2385 (1956).

(6) R. C. Lord, R. S. McDonald and F. A. Miller, *J. Opt. Soc. Am.*, **42**, 149 (1952).

(7) I. E. Puddington, This Journal, **65**, 990 (1943).

(8) D. H. Whiffen and H. W. Thompson, *J. Chem. Soc.*, 1005 (1946).

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TABLE II

EXPLANATION OF THE INTENSE BANDS IN THE DOUBLE BOND REGION

Vapor			CCl₄ soln.[b]			Liquid[b]	
Cm.⁻¹		Assignment	Cm.⁻¹	I	Assignment	Cm.⁻¹	
1676	s	2 × 838 = 1676 803 + 887 = 1690 670(R) + 1007 = 1677	1675	s	2 × 840 = 1680 804 + 875 = 1679 670(R) + 1006 = 1676	1689	vs, broad
1720	vs	C=C stretch	1708	vs	C=C stretch		
1776	m	2 × 887 = 1774	1752	s	2 × 875 = 1750	1744	m
1875	s	887 + 1007 = 1894[a]	1867	s	875 + 1006 = 1881[a]	1864	vs
1922	vs	C=O stretch	1900	vs	C=O stretch	1897	vs

R = Raman frequency. [a] Fermi resonance with C=O stretch. [b] Frequencies measured with CaF_2 prism.

cluded that the earlier work was incorrect, and that diketene exists in the 3-buteno-β-lactone form only.

An attempt was made to explain the temperature-induced changes observed by Miller and Koch. Their raw curves were re-examined, and there is no doubt that changes were clearly indicated. One possibility is that some component of the glyptal seal distilled into the cell at high temperature and condensed out at low temperature, even though a blank run was made to test this possibility. Since it is known that phthalic anhydride can be distilled out of glyptal, its vapor spectrum was determined. A glyptal resin (General Electric Company's No. 1202) also was examined by placing a sample at the bottom of the evacuated gas cell and heating to 200°. Neither material accounted for the earlier observations, and we are at a loss to explain them.

There is still the problem of accounting for the five strong bands in the 1650–1950 cm.⁻¹ region on the basis of the single 3-buteno-β-lactone structure. This structure would be expected to have only two fundamentals there. One is the carbonyl stretching frequency, which will be abnormally high because of being external to a 4-membered lactone, and which we can guess will be about 1830 cm.⁻¹.[9] The other is the olefinic stretching frequency, which also will be abnormally high because of being exocyclic to a four-membered ring.[9] We would predict it to be about 1720 cm.⁻¹. Actually the C=O frequency must be the band at 1900 in solution (1922 in the vapor) while the C=C stretch must be 1708 in solution (1720 in the vapor) (see Table II.) The intensity of the latter is remarkably high for an olefinic stretch.

The remaining three strong bands are then presumably to be explained as combination tones, in spite of their considerable intensity. Table II shows that this can be done as far as the frequencies are concerned, although it is still hard to understand their high intensity. It will be noted that in the pure liquid there are only four bands. The double bond frequency appears to be lower than its value of 1708 in the solution, and it apparently merges with the 1675 band to give a single very broad band at 1689.

(9) R. C. Lord and F. A. Miller, *App. Spectros.*, **10**, 115 (1956).

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE SHELL DEVELOPMENT COMPANY]

Hydrogen Peroxide–Olefin Reactions in the Vapor Phase

BY E. R. BELL, W. E. VAUGHAN AND FREDERICK F. RUST

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Hydrogen peroxide has been decomposed in the presence of ethylene, propylene and isobutylene at temperatures between 435 and 630°. The products are traceable to an initial attack by hydroxy radical involving either addition to the double bond or abstraction of a hydrogen atom from the olefin. As a consequence of the latter process diallyl and dimethallyl are major products from propylene and isobutylene, respectively. Many other compounds must originate from radical association reactions. Much fragmentation of the olefins seems to have had its genesis in the initial addition of a hydroxy radical to the olefin double bond. In cases where the carbon skeleton has been retained, hydrogenation and dehydrogenation processes can be significant. Reaction steps which logically interpret the data have been proposed.

Introduction

Hydrogen peroxide has a thermal stability much greater than that of the organic peroxides and for this reason its significance to combustion phenomena in temperature regions beyond the cool flame zone is substantially greater. Moreover, this stability suggests that hydrogen peroxide may have useful properties as a high temperature reactant.

Its thermal decomposition is apparently a complex of both heterogeneous and homogeneous processes. McLane[1] has reported that the decomposition in nitrogen begins to be essentially homogeneous only above 470° in reactors whose walls have been treated with boric acid. Although the reaction showed first-order kinetics in the temperature range 470–540°, the activation energy increased from 40 kcal. in a reactor whose surface to volume ratio was 7 cm.⁻¹ to 50 kcal. in one with a ratio of 3 cm.⁻¹. (A boric acid-coated reactor of surface–volume ratio 0.4 cm.⁻¹ has been chosen for these studies.)

The near coincidence of this high activation energy with the O–O bond strength in hydrogen perox-

(1) C. K. McLane, *J. Chem. Phys.*, **17**, 379 (1949).

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ide (53 kcal.[2,3]) suggests that this decomposition should be an effective source of hydroxy radicals.

Since it is known that hydrogen peroxide can be a significant product of hydrocarbon oxidation at temperatures in the region of 475°[4,5] a study of the high temperature peroxide–hydrocarbon reactions which must be proceeding concomitantly with the oxidation processes leading to hydrogen peroxide formation would seem to be desirable. One of the principal objectives of this investigation was to gain some insight into the behavior of certain of the simpler olefins when exposed to the radicals from decomposing hydrogen peroxide.

Experimental

A flow system was used in these experiments. The flow of hydrogen peroxide (30% aqueous solution) through a capillary was calibrated against the air pressure above the peroxide. The peroxide was then fed onto a vertically descending spiral glass rod (about 2 mm. o.d.) fused onto the inner wall of a 44 mm. glass tube. The outer wall of this tube was heated by a flexible tape heater. Its temperature was measured by a thermocouple between the heater and tube in the lower third of its length. For low peroxide flows, (0.3–0.5 g./min.) the wall was heated to 100°; for high (*ca.* 2.0 g./min.) the wall was heated to 180°. Tests of this vaporizer showed that negligibly small amounts of peroxide were decomposed. The hydrocarbon was metered as vapor and flowed through the vaporizer into the reactor.

The latter was a glass tube 48 mm. o.d. by 75 cm. long sealed directly to the vaporizer and heated by a "Hevi-Duty" furnace. This reactor was periodically soaked overnight with a saturated boric acid solution and then drained. For the experiment at 630° and high flow rates a "Vycor" reactor 18 mm. o.d. by 20 cm. long was used. It was found necessary to provide a baffle near the inlet to cause turbulence which accelerated the attainment of reaction temperature by the vapors.

The product collection system consisted of a water condenser followed by a trap at 0° and then a series of traps at −78°. The non-condensable gas was collected over brine. When the non-condensable gas was excessive, as with ethylene, an aliquot of the gas was collected by means of an interval timer and a solenoid valve arrangement while the remainder was vented through a wet test meter.

Product work-up consisted of the following steps: (1) the contents of the Dry Ice traps were distilled through a 3 ft. Vigreux column until the C_4 hydrocarbons had been taken overhead; (2) the bottoms from this distillation were combined with the contents of the 0° trap; (3) the aqueous and oil phases were separated and the oil phase washed several times with ice-water; (4) the oil phase, after it had been dried with anhydrous potassium carbonate, was distilled through a Piros–Glover micro-spinning band column or through a 20 theoretical plate helices-packed column; (5) the combined aqueous phase and washings were titrated iodometrically for residual peroxide; (6) the residual peroxide was decomposed by gentle warming of the aqueous phase over platinum oxide; (7) the aqueous phase was then analyzed by standard methods for acid, ester, α-glycol, formaldehyde, total carbonyl, saturated carbonyl, total hydroxyl and saturated hydroxyl; on occasion the aqueous phase was flashed to an overhead temperature of 100°, and the distillate redistilled through the 20-plate column to provide material for identification; (8) all gas samples and low temperature distillation cuts were analyzed by both mass spectrometric and Orsat methods; (9) the analysis of the C_5 fraction was obtained by Podbielniak distillation coupled with appropriate chemical and spectroscopic analyses of the fractions; (10) the other hydrocarbon fractions were characterized by boiling point, refractive index and infrared spectroscopy.

The products of reaction of hydrogen peroxide with ethylene, propylene and isobutylene are summarized in Tables I, II and III. The oxygenated compounds have been identified by derivative preparation and quantitatively estimated by functional group analyses of the appropriate fractions. The gaseous products—C_1 to C_4—were analyzed by mass spectrometry. Fractionation of the higher boiling hydrocarbon components and infrared analysis of the fractions are the bases for the identification and estimation of the higher hydrocarbons.

TABLE I

PRODUCT BALANCE FOR REACTION OF HYDROGEN PEROXIDE WITH ETHYLENE

	Temp., 435°; contact time, ~26 sec.; feed ratio: C_2H_4, 17.1; H_2O, 4.4; H_2O_2, 1; peroxide decomposed, 98.5%; ethylene reacted, 2.8 moles/moles H_2O_2		Temp., 525°; contact time, ~10 sec.; feed ratio: C_2H_4, 20; H_2O, 4.4; H_2O_2, 1; peroxide decomposed, 100%; ethylene reacted, 1.4 moles/mole H_2O_2	
Product	Moles[a]/ 100 moles H_2O_2 reacted	Moles[a]/ 100 moles C_2H_4 reacted	Moles[a]/ 100 moles H_2O_2 reacted	Moles[a]/ 100 moles C_2H_4 reacted
H_2	..	..	11.8	8.3
CO	61.5	21.8	37.2	26.6
CO_2	4.9	1.8	2.0	1.4
CH_4	11.5	4.1	5.9	4.2
C_2H_6	21.5	7.5	6.0	4.3
C_2H_2	..	..	19.6	14.0
C_3H_8	7.2	2.5	..	..
C_3H_6	68.2	24.2	30.4	21.7
C_3H_4	0.2	0.1	..	..
C_4H_{10}[b]	3.0	1.1	..	..
C_4H_8[b]	5.7	2.0	1.8	1.3
C_4H_6	0.4	..	3.9	2.8
C_5 and higher[c]	19.0	6.7	10.0	7.0
Acid	5.5	1.9	0.2	0.1
Alcohol	11.3	4.0	.3	.2
α-Glycol	4.4	1.6	.3	.2
Acetaldehyde	14.0	5.0	..	..
Formaldehyde	6.3	2.2	5.8	4.1

[a] Calculated loss-free basis. [b] Almost entirely straight chain [c] Calculated as C_6.

Discussion and Mechanism

A major problem in the study of the reaction of hydrocarbons with hydrogen peroxide is the known proclivity of hydrogen peroxide to decompose to water and oxygen by way of the chain reaction steps 1–4.[6]

$$H_2O_2 \longrightarrow 2HO \qquad \text{Initiation} \qquad (1)$$

$$HO + H_2O_2 \longrightarrow H_2O + HO_2 \qquad \text{Propagation} \qquad (2)$$

$$HO_2 + H_2O_2 \longrightarrow H_2O + O_2 + HO \qquad (3)$$

$$HO + HO_2 \longrightarrow H_2O + O_2 \qquad \text{Termination} \qquad (4)$$

When a hydrocarbon is present, its reaction with the most reactive species, hydroxy, becomes an important characteristic of the new system.

$$HO + RH \longrightarrow H_2O + R \qquad (5)$$

In principle, since the reaction of hydroxy with hydrocarbons is the subject of interest, step 5 and related reactions are promoted at the expense of 2–4 by operation with high hydrocarbon concentrations and the lowest practical peroxide concentrations. In practice it is not easy to conclude that this has been accomplished successfully since many products of the reaction of hydrocarbons with hydrogen per-

(2) P. A. Giguere, *Can. J. Research*, **25B**, 135 (1947).
(3) K. H. Geib, *Ergeb. exakt. Natur.*, **15**, 44 (1936).
(4) P. J. Kooyman, *Rec. trav. chim.*, **66**, 5, 491 (1947).
(5) B. M. Sturgis, *S.A.E. Trans.*, **63**, 253 (1947).

(6) W. C. Schumb, C. N. Satterfield and R. H. Wentworth, "Hydrogen Peroxide," Reinhold Publishing Corp., New York, N. Y., 1955, p. 457.

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oxide are identical with those of the high temperature reaction with oxygen which might have come from peroxide decomposition.

TABLE II

PRODUCT BALANCE FOR REACTION OF HYDROGEN PEROXIDE WITH PROPYLENE

	Temp., 530°; contact time, 1.0 sec.; feed ratio: C_3H_6, 20.4; H_2O_2, 1; H_2O, 4.4; H_2O_2 reacted, 71.0%; C_3H_6 reacted, 1.8 moles/mole H_2O_2		Temp., 630°; contact time, 0.1 sec.; feed ratio: C_3H_6, 20.5; H_2O_2, 1; H_2O_2, 4.4; H_2O_2 reacted, 84.0%; C_3H_6 reacted, 1.7 moles/mole H_2O_2	
Product	Moles/100 moles[a] H_2O_2 reacted	Moles/100 moles[a] C_3H_6 reacted	Moles/100 moles[a] H_2O_2 reacted	Moles/100 moles[a] C_3H_6 reacted
H_2	1.1	0.6	2.5	1.4
CO	12.6	7.0	13.5	8.0
CO_2	2.9	1.6	2.5	1.5
CH_4	16.2	9.0	21.0	12.5
C_2H_6	4.0	2.2	2.8	1.7
C_2H_4	23.3	13.1	8.5	5.0
C_2H_2	2.9	1.6	5.4	3.2
C_3H_8	9.4	5.2	..	..
C_3H_4	2.2	1.2	16.3	9.7
C_4H_{10}	0.7	0.4	0.4	0.3
C_4H_8	5.3	3.0	10.7	6.4
C_4H_6	1.4	0.8	0.2	0.1
C_5 HC's[d]	6.1	3.4	4.8	2.8
C_6 HC's other than diallyl[c]	5.6	3.1	2.5	1.5
Diallyl[b]	27.6	16.0	31.2	18.5
C_9's[e]	8.4	4.7	6.0	3.6
Sat. ROH	3.2	1.8	1.9	1.1
Allyl alcohol	4.7	2.6	4.4	2.6
α-Glycol	4.7	2.6	3.3	2.0
Acrolein	3.1	1.7	3.3	2.0
Sat. C_2 + C_3 carbonyl	5.8	3.2	6.5	3.8
H_2CO	1.3	0.7	0.9	0.6
Acid + ester	7.5	4.1	7.6	4.7

[a] Calculated on a loss-free basis. [b] Cut from 57–62, $n^{20}D$ 1.4030; lit. diallyl 59.4°, $n^{20}D$ 1.4040. [c] Cut from 62–90°. [d] Cut from 15–57°. [e] Hydrocarbon material boiling above 90°.

A further complication in interpretation arises because the high temperature oxidation of hydrocarbons is presumed to propagate to a significant extent by means of hydroxy radicals. Thus the distinction between the two systems is one of degree; oxidation involves a low concentration of hydroxy radicals in the presence of a high concentration of oxygen while the present system is designed for the study of a high concentration of hydroxy radicals in the presence of little or no oxygen.

The success in achieving this end must be judged in terms of those products which are peculiar to the hydrogen peroxide–hydrocarbon system and the trends of the product distribution with hydrocarbon to hydrogen peroxide ratio. It is felt that the results presented indicated a satisfactory suppression of hydrocarbon–oxygen reactions.

Two alternatives are open to hydroxy, *viz.*, hydrogen abstraction or addition to the olefinic double bond. Most of the products are ultimately traceable to one of these two initial modes of reaction.

TABLE III

PRODUCT BALANCE FOR REACTION OF HYDROGEN PEROXIDE WITH ISOBUTYLENE

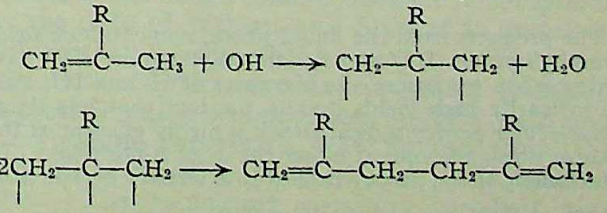
Temp., 530°; contact time, 9 sec.; feed composition, *i*-C_4H_8, 19; H_2O, 4.4; H_2O_2, 1; peroxide decomposed, 100%; isobutylene reacted, 1.76 moles/mole H_2O_2 converted

Product	Moles/100 moles[a] H_2O_2 reacted	Moles/100 moles[a] *i*-C_4H_8 reacted
H_2	2.7	1.5
CO	6.8	3.8
CO_2	1.0	0.5
CH_4	15.1	8.6
C_2H_4	6.9	3.9
C_2H_6	0.5	0.3
C_3H_4	2.2	1.2
C_3H_6	4.3	2.5
C_3H_8	0.8	0.4
C_4H_{10}	7.0	4.0
C_5's[b]	2.8	1.5
C_6's[c]	7.1	4.0
C_7's[d]	6.8	3.8
C_8's other than dimethallyl[f]	6.0	3.4
C_{10}'s[g]	5.3	3.0
Dimethallyl[e]	36.6	20.8
Sat. alcohol	3.2	1.9
Sat. carbonyl	4.7	2.7
Ester	6.5	3.7
Unsat. alcohol	7.5	4.3
Methacrolein	4.1	2.4
α-Glycol	5.1	2.9
H_2CO	2.4	1.3

[a] Calculated on a loss-free basis. [b] Distilled +15–37°. [c] Distilled +38–90°. [d] Distilled +90–111°. [e] Distilled 111–118°; $n^{20}D$ 1.4300–1.4310; lit. dimethallyl 114.3°; $n^{20}D$ 1.4293. [f] Distilled 118–164°. [g] Bottoms.

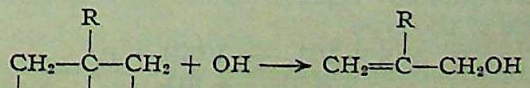
Depending upon the olefin and the point of attack, the resultant radical R will be either an allylic or vinylic radical—in the case of ethylene entirely vinylic, and for propylene and isobutylene largely allylic, although it should be borne in mind that the selectivity of attack customary at lower temperatures will be less obvious at 500°.

The high yields of diallyl from propylene, and dimethallyl from isobutylene are probably the most notable characteristics of the high temperature reactions with hydrogen peroxide. They present probably the most convincing evidence that molecular oxygen from decomposing peroxide is an insignificant factor in these studies because these diolefins have never been reported to be formed in the presence of oxygen. There can be little doubt that formation of these diolefins takes place as



where R is H or CH_3.

Allyl (or methallyl) alcohol is then a logical consequence of



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and the olefins, which are formed in substantial quantity, of

$$\cdot CH_2-\underset{R}{\overset{|}{C}}-CH_2 + R \longrightarrow CH_2=\underset{R}{\overset{|}{C}}-CH_2R$$

1-butene from propylene by way of allyl and methyl is an example of the foregoing.

At a temperature of 630° the hydrogen peroxide–propylene reaction is noticeably productive of C_3H_4 (allene). Inasmuch as radical–radical association reactions are important paths to some end products, it is not unreasonable to ascribe other compounds, *e.g.*, allene, to radical–radical disproportionations.

$$CH_2-CH-CH_2 + R \longrightarrow CH_2=C=CH_2 + RH$$

The importance of allyl radical reactions in the case of propylene is demonstrated by the fact that 55 and 70% of the reacted propylene at 530 and 630°, respectively, yields products traceable to allyl radical precursors. Products which stem from initial abstraction of vinylic hydrogen atoms are evident, particularly in the case of ethylene and in the higher temperature region.

$$CH_2=CH_2 + OH \longrightarrow CH_2=CH- + H_2O$$
$$2CH_2=CH- \longrightarrow CH_2=CH-CH=CH_2$$
$$CH_2=CH- \longrightarrow CH\equiv CH + H$$

Although vinyl radicals can be postulated as intermediates in other reactions, butadiene and acetylene seem to be devoid of reasonable alternate antecedents. A significant yield of acetylene (5.4%) from propylene seems likewise to be a result of vinyl hydrogen removal.

$$CH_3CH=CH_2 + OH \longrightarrow CH_3CH=CH- + H_2O$$
$$CH_3CH=CH- \longrightarrow CH_3 + CH\equiv CH$$

Addition of a hydroxy radical to the double bond must be the single most important reaction with ethylene even at 525° and must be progressively less important with propylene and isobutylene. The resultant hydroxyalkyl radicals can be stabilized as alcohols by hydrogen capture, but evidently the more usual evolution of hydroxyalkyl leads to eventual fragmentation of the molecule. Methane, carbon monoxide and formaldehyde are important products of the hydrogen peroxide–ethylene experiments and in the propylene studies these plus, in particular, ethylene must be accounted for. The initial hydroxyethyl radical which seems to be a step in the breakdown of ethylene, shows little evidence of instability and, in fact, rather limited reaction opportunities. The complete absence of hydrogen at 435° precludes a β-scission of a carbon–hydrogen bond so that it can only be concluded that hydroxyethyl is a hydrogen donor. That some donor of considerable efficiency is present can be deduced from the important yields of ethane. The reaction steps suggested then become

$$-CH_2CH_2OH + X \longrightarrow CH_2=CHOH + XH$$
X = olefin or radical
$$CH_2=CHOH \longrightarrow CH_3CHO$$
$$CH_3CHO + R \longrightarrow CH_3\dot{C}O + RH$$
$$CH_3\dot{C}O \longrightarrow CH_3 + CO$$

At 435° acetaldehyde is a significant product and its decomposition to methyl and carbon monoxide frequently has been demonstrated.[7] Thus, this course of fragmentation for ethylene—and for propylene—seems reasonable.

The production of hydrocarbons of higher carbon number is surely a consequence of radical addition to olefin double bonds. Indicative of the number of processes yet to be explored is the analysis of a broad product fraction boiling from 15 to 57°—identified among the products as C_5's. The C_5 hydrocarbons in the fraction were identified as pentanes 2.9%, amylenes 32.2%, pentadienes 32.8%, cyclopentane 2.5%, cyclopentene 13.2% and cyclopentadiene 2.1%.

(7) E. W. R. Steacie, "Atomic and Free Radical Reactions," Vol. I, 2nd Ed., Reinhold Publishing Co., New York, N. Y., 1954, p. 206.

EMERYVILLE, CALIF.

[CONTRIBUTION FROM THE SHELL DEVELOPMENT COMPANY]

Intramolecular Oxidation. The Autoxidation of Some Dimethylalkanes

BY FREDERICK F. RUST

RECEIVED MARCH 2, 1957

The products from the liquid phase, non-catalytic oxidations of 2,3-dimethylpentane (I), 2,4-dimethylpentane (II), 2,5-dimethylhexane (III) and 2,6-dimethylheptane (IV) have been identified and related to one facet of the mechanism of hydrocarbon oxidation. In the cases of II and III, the 2,4- and 2,5-dihydroperoxides, respectively, were made in extraordinarily high yields despite the fact that less than 10% of the hydrocarbons reacted. The results show that intramolecular peroxy radical attack is highly efficient at the β-position, somewhat less so at the γ-position and apparently of little or no significance at either the α- or Δ-positions. The efficiency of intramolecular oxidation appears to be favored by attachment of the peroxy radical to a tertiary carbon atom.

Introduction

Although the oxidation of aliphatic hydrocarbons is conventionally represented as an intermolecular process of the type

$$RO_2 + RH \longrightarrow RO_2H + R$$
$$R + O_2 \longrightarrow RO_2$$

increasing evidence indicates that an oxidation chain does not necessarily propagate from molecule to molecule, but, depending on conditions, can propagate from one point to another within the molecule. The formation of β-dicarbonyl compounds and oxirane rings in the gas phase oxidation

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of pentane,[1] hexane[2] and 2,2,4-trimethylpentane[3] and the production of a 2,5-dihydroperoxide from the cobalt catalyzed liquid phase oxidation of 2,5-dimethylhexane[4] have been interpreted on this basis.

The present study covers the liquid phase non-catalytic oxidation of hydrocarbons of the general structure C–C–(C)$_x$–C–C, where x was varied from 0 to 3. From the reaction products of this series of hydrocarbons can be deduced some of the characteristics of intramolecular oxidation.

Materials

The 2,3- and 2,4-dimethylpentanes were obtained from Phillips Chemical Company. The first was the technical grade, 95+%, which was further fractionated. A center cut was collected at 89.0–89.5°; n^{20}D 1.3917. The 2,4-dimethylpentane was research grade and used without further treatment (b.p. 80.6°, n^{20}D 1.3811). The 2,5-dimethylhexane was prepared by a Grignard coupling reaction with methallyl chloride followed by separation and hydrogenation of the dimethallyl. The product used distilled at 108.6–109.6°; n^{20}D 1.3928. 2,6-Dimethylheptane was obtained by dehydrating diisobutylcarbinol over alumina at 390° and then hydrogenating the resulting olefin. A fraction, 133.5–135.2°, n^{20}D 1.4013, was oxidized.

Experimental

The hydrocarbons were oxidized in a closed system comprised of a Pyrex reactor, an all-glass pump, a hydraulically pressured steel oxygen reservoir fitted with a sight gage, and Dry Ice-cooled traps in the system immediately following the reactor and the reservoir. Oxygen at 35 p.s.i.g. was circulated through the hydrocarbon at 115–120°. The oxygen consumption was measured at constant pressure by following the rising water level in the calibrated reservoir.

The peroxide in the product was determined iodimetrically by reduction with acidified (acetic acid) potassium iodide in isopropyl alcohol solution under reflux for five minutes.

The hydrocarbon charge was usually 400 cc. of which from 5–8% was oxidized and in general the product was concentrated to *ca.* 70 cc. by flashing off the unreacted hydrocarbon. If necessary, pressure was reduced during concentration to keep the kettle temperature below 60° in order to minimize peroxide breakdown. The concentrate was diluted to *ca.* 300 cc. with isopropyl alcohol and reduced with hydrogen and platinum oxide catalyst. The products were then separated by fractional distillation. Where small amounts of product were to be analyzed, separation was effected on a Piros–Glover spinning band micro-still. Significant departures from this procedure are discussed under the individual hydrocarbons.

In most cases the oxidation product had two phases, but after topping off the traces of water and a substantial fraction of the unreacted hydrocarbon under reduced pressure, a single phase usually was obtained. In the case of 2,5-dimethylhexane the dihydroperoxide is a crystalline solid which readily can be separated by filtration.

Results

2,3-Dimethylpentane.—The autoxidation of this hydrocarbon resulted in a 52.5% yield of peroxide based upon consumed oxygen—the lowest for the four hydrocarbons investigated. Following the removal of the hydrocarbon, water and the low boiling scission products, an analysis of the residue for total oxygen and peroxide oxygen showed 0.340 g. atom of combined oxygen of which 0.214 was in peroxide groups. The remainder, 0.126 g. atom, is essentially carbonyl and hydroxyl and, as such, is assumed to have its genesis in a radical–oxygen association. This remainder, therefore, requires 0.126 g. mole of oxygen for its formation or 0.252 g. atom. This, with the peroxide oxygen, gives a total of 0.466 g. atom of oxygen required to form the high boiling products. The difference between this value and the 0.27 mole of oxygen reacted (0.54 g. atom) is 0.08 g. atom. This last figure indicates the magnitude of the scission reactions and other losses. Small amounts of acetone and methyl ethyl ketone are produced.

A peroxide concentrate was obtained in sufficient quantity for distillation in a falling-film molecular still by combining the products of two runs. Four fractions totalling 40.2 g. were collected.

Fraction no.	Grams	% C	% H	% O (diff.)	Empirical formula	% Peroxide (ROOH)
I	4.0	65.1	12.2	22.7	$C_7H_{15.8}O_{1.83}$	63.7[a]
II	32.5	63.4	11.8	24.8	$C_7H_{15.7}O_{2.02}$	73.4[a]
III	2.0	58.7	10.4	30.9	$C_7H_{14.9}O_{2.76}$	55.0[b]
IV	1.7	57.4	10.0	32.6	$C_7H_{14.7}O_{3.0}$	55.7[b]

[a] Calculated as $C_7H_{16}O_2$. [b] Calculated as $C_7H_{14}O_3$.

2,3-Dimethyl-2-(and-3)-hydroperoxypentane, which is a principal component, has 63.6% carbon, 12.1% hydrogen. Fraction II which accounts for more than 80% of the total, shows an average of two oxygen atoms per molecule although only 73.4% of all molecules contain a peroxide group. Infrared inspection shows a significant amount of carbonyl. When the peroxide groups are hydrogenated to hydroxyls, a carbonyl analysis indicates that at least 16% of this product has two oxygen atoms per molecule and evidently is largely 4-hydroxy-3,4-dimethyl-2-pentanone because as indicated by a very low periodate value the ketone and hydroxyl groups are for the most part non-adjacent.

2,4-Dimethylpentane.—The oxidation of 2,4-dimethylpentane is the least complicated of any in this series. Under comparable conditions this hydrocarbon takes up oxygen to give an 89% peroxide yield. Hydrogenation of the peroxide concentrate gives 2,4-dimethyl-2,4-pentanediol in 95% yield based on the input oxygen. The remainder is accounted for by 2,4-dimethyl-2-pentanol; 2,4-dihydroperoxy-2,4-dimethylpentane crystallized from the sirupy product after standing for about a week.

2,5-Dimethylhexane.—The cobalt stearate catalyzed oxidation of 2,5-dimethylhexane is computed from the data of Wibaut and Strang[4] to give 2,5-dihydroperoxy-2,5-dimethylhexane in 15% yield. In the non-catalytic autoxidation system discussed here total peroxide was produced in 83% yield and the crystalline diperoxide was filtered from the hydrocarbon in 50% yield—based on consumed oxygen. The remaining peroxidic product was concentrated by distilling off unoxidized hydrocarbon under reduced pressure and then hydrogenated in 2-propanol solution at not above 50° with platinum oxide catalyst. The 2,5-dimethyl-2-hexanol was isolated by distillation. The high boiling residue amounting to 20% mole of the product had an empirical formula, based on carbon and hydrogen

(1) M. R. Barusch, J. T. Neu, J. Q. Payne and J. R. Thomas, *Ind. Eng. Chem.*, **43**, 2766 (1951).
(2) H. C. Bailey and R. G. W. Norrish, *Proc. Roy. Soc.* (*London*), **212**, 311 (1952).
(3) D. O. Collamer and F. F. Rust, THIS JOURNAL, **76**, 1055 (1954).
(4) J. P. Wibaut and S. Strang, *Koninkl. Ned. Akad. Wetenschap. Proc. B*, **54**, 231 (1951).

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analyses, of $C_8H_{16.8}O_{2.9}$. A small amount of crystalline material was separated from this residue which showed a strong test for ketone and gave a carbon–hydrogen analysis in agreement with a 40–60 molar mixture of 2,5-dimethyl-2,5-hexanediol and 2,5-dimethyl-3-keto-2,5-hexanediol.

When about 30% of the hydrocarbon charge was oxidized and the volatile components removed at 70° under vacuum pump pressure a clear peroxidic residue was obtained. This was run through a falling film molecular still at 56°. The distillate was treated with 30% sodium hydroxide, the solid precipitate filtered off, dissolved in a minimum of water and the pure peroxide released by bubbling carbon dioxide into the solution. This peroxide layer was extracted with an isopentane–ether mixture and the mixed solvent then removed under vacuum. Upon standing for a week the somewhat viscous peroxide crystallized. Carbon and hydrogen analyses (59.0% C and 11.0% H) and mol. weight of 159, computed from peroxide determination, showed it to be 2,5-dimethyl-5-hydroperoxy-2-hexanol (theory 59.3% C; 11.1% H; mol. wt. 162). Reduction in 2-propanol with hydrogen and platinum oxide catalyst gave 2,5-dimethyl-2,5-hexanediol (m.p. and mixed m.p. 87.5°). The diperoxide obtained at low levels of hydrocarbon conversion is apparently partially reduced or becomes difficult to recover as the oxidation proceeds.

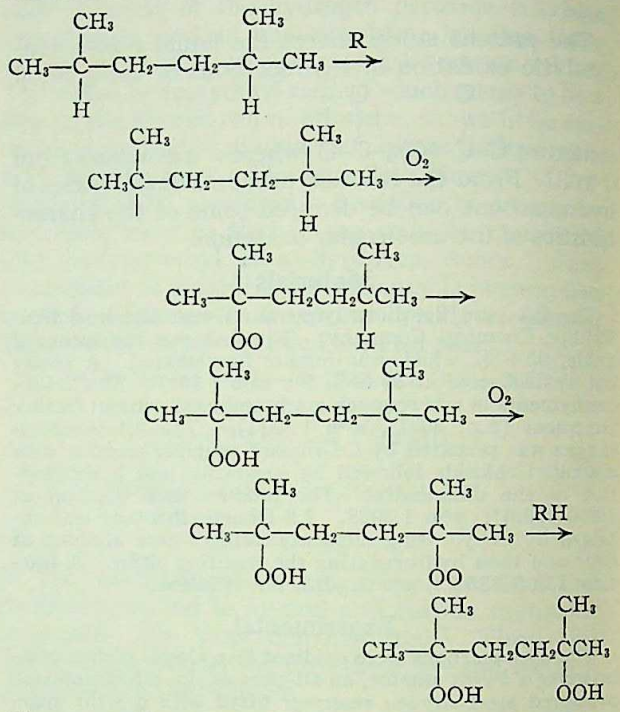
2,6-Dimethylheptane.—In contrast to the oxidations of 2,4-dimethylpentane and 2,5-dimethylhexane, the oxidation of 2,6-dimethylheptane is far less clear cut. The evidence is strong, however, that intramolecular oxidation is an important determinant. Under conditions where not more than 8% of the 2.25 mole input hydrocarbon was oxidized, there was isolated from the hydrogenated product 0.038 mole of 2,6-dimethyl 2-heptanol and 0.087 mole of higher boiling products with an empirical formula $C_9H_{19.1}O_{2.4}$. Of the total combined oxygen in this mixture only 10% was associated with ester and acid groups which would be a consequence of carbon skeleton cleavage reactions. Calculating on the basis that one oxygen molecule was required to place one atom of oxygen in the final reduced product an approximate oxygen balance can be struck.

From 2,6-dimethyl, 2-heptanol	0.038 mole O_2
From $C_9H_{19.1}O_{2.4}$ (0.087 × 2.4)	0.209 mole O_2
	0.247 mole O_2
Total oxygen consumed	0.273 mole

Efforts were made to isolate 2,6-dimethyl-2,6-heptanediol and although fractions were isolated which showed the correct carbon and hydrogen analyses, these results were inadequate because the product was a thick clear liquid rather than crystals of the 2,6-diol (m.p. 76°). In one experiment crystals were collected from an unhydrogenated concentrate which had both peroxide and carbonyl groups and an empirical formula of $C_9H_{18}O_4$ (% carbon 57.2; % hydrogen 9.5; theory 56.8% and 9.5%). The structure $(CH_3)_2COOHCH_2COCH_2COH(CH_3)_2$ is proposed.

Discussion

As pointed out by Wibaut and Strang the liquid phase oxidation of 2,5-dimethylhexane can best be interpreted by an intramolecular attack of the initially formed tertiary peroxy radical upon the remaining tertiary hydrogen atom followed by formation of a second peroxy group.



The crystalline diperoxide was the same as that first prepared by Tannenberger[5] from the glycol and hydrogen peroxide.

This study has sought to arrive at some assessment of the importance of intramolecular oxidation to liquid hydrocarbon systems and accordingly has concerned itself with autoxidation rather than the cobalt-catalyzed reactions which are less favorable to peroxide preservation.

By selecting a series of hydrocarbons in which the reactive tertiary hydrogen atoms are separated by interposing up to three methylene groups, it has been possible to estimate the preferred positions of intramolecular oxidative attack. By far the most favored pattern of reaction involves attack of the peroxy radical in the β-position. This is exemplified by the oxidation of 2,4-dimethylpentane which resulted in about 90% of the product being substituted by oxygen in both the 2- and 4-positions. This preparation of a β-diperoxide by autoxidation is believed to be novel, although this compound has been prepared recently from hydrogen peroxide and the glycol by Criegee and Paulig.[6]

The oxidation of 2,5-dimethylhexane, which gives high yields of the 2,5-diperoxide demonstrates that intramolecular attack in the γ-position by the peroxy radical is the next most favored possibility.

In the case of 2,6-dimethylheptane such a preponderant fraction of the oxygen consumed was involved in the production of polyoxygenated products that it seems improbable that these products could have been formed by other than an intramolecular mechanism similar to that discussed for the other dimethylalkanes. However, the case for Δ-attack by a peroxy radical was not conclusively re-

(5) R. Tannenberger, Doctoral Dissertation, Karlsruhe, 1945.
(6) R. Criegee and G. Paulig, *Chem. Ber.*, **88**, 72 (1955).

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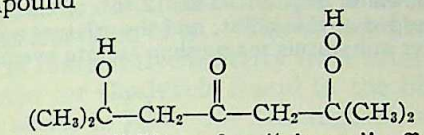
solved. Thus, despite the apparent inability of a peroxy radical in the 2-position to remove a hydrogen atom in the 6-position—at least with any facility—there is considerable indication that removal of hydrogen from the 4- and 5-positions is occurring with considerable regularity. In this connection the tentative identification of a crystalline compound



suggests the possibility of a "zipper" effect in the oxidation of certain linear hydrocarbons. The amount of this compound was, however, too small to suggest that such an effect would be important in any but special situations.

When 2,3-dimethylpentane is oxidized and the peroxides reduced, 2,3-dimethyl-2-(and 3)-pentanol are the principal and almost equally important products. It is significant that 3,4-dimethyl-2-pentanone-4-ol, which is the only reduction product which would be expected by a β-oxidation mechanism, is the most important of the remaining products retaining the original carbon skeleton. α-Attack by a peroxy radical seems to be of no significance.

In view of the foregoing results it seems reasonable to relate much of the formation of keto-acids, lactones, etc., in conventional paraffin oxidation to intramolecular chain propagation. However, no such extensive intramolecular reaction has been observed in the oxidation of the normal paraffins as was found for these branch chain hydrocarbons. Therefore, it is concluded that the well recognized effect of a gem-dimethyl grouping[7] in favoring ring closures is important here in intramolecular attack by peroxy groups.

Acknowledgment.—The author wishes to acknowledge particularly helpful discussions with Drs. H. E. De La Mare and D. E. Winkler.

(7) P. D. Bartlett, *J. Chem. Ed.*, **30**, 27 (1953).

EMERYVILLE, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Free Radicals from the Heterogeneous Decomposition of Butane[1]

BY SYDNEY W. FLEMING AND K. A. KRIEGER

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A method which provides information about the nature of certain adsorbed intermediates is described. Essentially the method consists in observing the decomposition of a hydrocarbon (butane) into free radicals on a heated wire acting as a catalyst. The reaction is carried out at pressures of 1–2 μ in a vessel whose walls are coated with radioactive iodine. The alkyl iodides formed are separated and their activities measured. Catalyst temperatures ranged from 305 to 1490°. Both aluminum (oxide) and tungsten catalysts produce free radicals ranging in complexity from methyl to *sec*-butyl. The radicals formed depend upon the catalyst used and on the temperature. Platinum produces no free radicals under these conditions.

Introduction

A major problem in catalysis is that of discovering the nature of the intermediates whose formation is critical in determining the course of the reaction. In the case of heterogeneous catalysis the methods of studying the intermediates are especially limited, owing to the necessary presence of a catalyst, most often a solid, on whose surface the critical intermediate is formed, and which greatly interferes with the usual methods of observation. In seeking a solution to this difficulty some success has been attained by the use of infrared spectroscopy, which, in suitable circumstances, is able to detect alterations in chemical bonds attendant on adsorption.

The present paper is an attempt, along quite different lines, to approach the observation of adsorbed intermediates. Unfortunately, the method is not quite direct, as the description will show, but it does apparently succeed at least in detecting certain immediate products of desorption, before their nature has been changed by subsequent reaction.

The results reported here are limited to a single reactant and three catalysts, and it is difficult with these limited data to make with certainty any very broad generalizations. The collection of future data, with more varied reactants and catalysts, is expected to remedy this defect. Additional work utilizing this method is in progress in this Laboratory, but this report is made now in the hope that others may find the technique useful.

(1) Based on a thesis submitted to the University of Pennsylvania, 1954 in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Experimental

Briefly, the method involves production of free radicals by decomposition of butane on catalysts in the form of metal wires and trapping of the free radicals released by the catalyst into the vapor phase by means of a radioactive iodine mirror, followed by fractional distillation and determination of the activities of individual fractions. These activities give the relative quantities of the alkyl iodides formed from the original free radicals trapped by the mirror.

Apparatus.—The experimental apparatus, shown in Fig. 1, consisted of a reaction chamber, L, with a wire catalyst suspended in the center and equipped with electrical connections for heating the wire. Associated apparatus was provided for metering butane into the reaction chamber at the very low rates required. The mirror was formed on the walls of the reaction vessel, and in order for free radicals formed on the wire to reach the wall without suffering collision with butane molecules, the butane pressure was kept between 1 and 2 μ, giving a mean free path on the order of the tube diameter of 5 cm.

During each run the vessel containing the iodine mirror was maintained at Dry Ice temperature. At the end of each run the reaction vessel was warmed to room temperature to allow the product along with the excess free iodine to dis-

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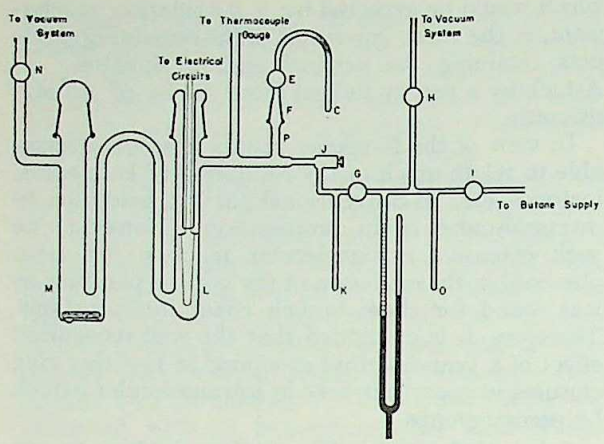

Fig. 1.

til over into M, held at liquid air temperature, after which the carrier alkyl iodides were added to the mixture. The unreacted free iodine was removed by extraction with aqueous sodium sulfite and the alkyl iodides removed, dried and distilled. Following distillation, the activities of the individual fractions were determined in a counting device designed to accommodate the tube in which the fractions were collected. This device consisted of six Nuclear Instrument and Chemical Corp. Type D76 Geiger–Mueller tubes held vertically and arranged in a circle nearly touching each other. A space of just over one-half inch in the center of these tubes was available to accommodate the fraction tube, which was supported so that the sample itself was nearly centered in the active counting space. With this arrangement, counting efficiency was approximately independent of exact sample shape and placement so that all of the many sample tubes used were effectively identical.

Reagents.—The radioactive iodine was obtained from The Atomic Energy Commission, Oak Ridge, Tennessee. The solution as received was diluted so that each ml. contained about 1 millicurie of activity, and appropriate amounts of this solution were withdrawn for each run.

The butane was research grade *n*-butane obtained from Phillips Petroleum Company. This butane was $99.78 \pm 0.08\%$ pure and was used directly from the cylinder as received.

The alkyl iodides came from Eastman Kodak Company, Mathieson and Bell, and Paragon Laboratories. In each case, the iodides were distilled once through a glass packed column about one meter long before being used. In the case of ethyl iodide, where special purity was required, the material was distilled twice and further purified by shaking it with red phosphorus and by passing it through a column of activated silica gel. Blank runs were made on each batch of ethyl iodide to make sure that the blank activity was suitably low in each case.

The No. 30 platinum wire used for filaments was obtained from Bishop Platinum Company. The No. 24 soft-drawn aluminum wire of approximately 98% purity was obtained from Arthur H. Thomas Company, and was treated by immersion in dilute KOH solution before initial use.

The tungsten filaments were cut intact with their attached leads from 150 watt electric light bulbs made by the Westinghouse Electric Corporation, and were used without treatment.

Procedure.—Approximately 2 mg. of iodine having an activity of about 0.5 millicurie was distilled into finger C at liquid air temperature, after which the finger was assembled into the main apparatus as shown in Fig. 1. The entire apparatus then was evacuated thoroughly, after which C was allowed to warm slowly as a vessel of liquid air was being raised around reaction vessel L. In this way a fairly uniform mirror of iodine was deposited on the walls of L; the liquid air was replaced by a Dry Ice–acetone mixture before proceeding with the run.

Butane was admitted during each run from finger K, held at the melting point of methylcyclohexane, by means of needle valve J at such a rate as to maintain a pressure of 1 μ in vessel L as recorded by a thermocouple vacuum gage. Throughout the run vessel M was held at liquid air temperature to trap any materials, including unreacted butane, that might escape from L.

At the conclusion of a run, stopcock N was closed and vessel L warmed to allow all reaction products to condense on the bottom of vessel M. The cap to M was then removed and 12 ml. of ethyl iodide carrier[2] and an aqueous sodium sulfite solution containing small quantities of potassium iodide and sodium bicarbonate was added. After stirring and removing this aqueous layer, followed by several washings, 12 ml. each of propyl and butyl iodides were added, and the organic layer removed by means of the pipet shown in Fig. 2. The 12 ml. of carrier methyl iodide was added at this point, and the mixture was allowed to stand over anhydrous magnesium sulfate overnight.

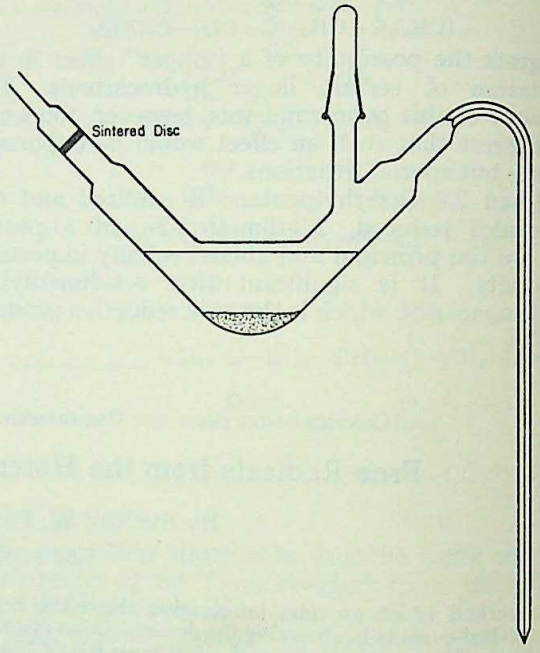

Fig. 2.

The liquid was charged into the still pot for distillation by tilting the pipet so that the liquid ran out through the sintered glass disc which retained the drying agent; the process was hastened by applying gentle air pressure over the liquid.

Distillations were made in a conventional glass-packed column of approximately 12 mm. inside diameter and 1 meter length. Take-off was controlled by a timer-operated solenoid valve. Two-ml. samples were collected in calibrated tubes made from 12-mm. Pyrex tubing.

In each run 12 ml. each of methyl, ethyl, *n*-propyl and *n*-butyl iodides were used as carriers, so that with normal losses, five samples of 2 ml. each could be obtained for each carrier after distillation. In each distillation the methyl and ethyl fractions were taken off at atmospheric pressure, after which 20 ml. of *n*-amyl iodide was added to serve as a chaser, and the pressure reduced to approximately 210 mm. before continuing the distillation. At this pressure the maximum temperature reached was about 112° for the amyl fraction, so that decomposition was minimized. The activity of each fraction was determined immediately after removal from the column; counting was usually complete before the subsequent fraction was ready to be counted. When necessary, suitable correction was made for radioactive decay.

Results and Discussion

The results of several of the runs reported are presented in the form of graphs on which are plotted the activities of the fractions collected and the corresponding boiling point curves. The various fractions are identified across the bottom of each graph, and the boiling point curves serve to define

(2) When a mixture containing all alkyl iodides was added at this point, high spurious activities were found in the methyl iodide fraction. Addition of ethyl iodide only at this time, followed by the others later, resulted in lower blanks than any other method tried.

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the transitions between them. The boiling points are shown in °C. along the right-hand ordinate, with the jagged line indicating the point at which the distillation pressure was reduced from atmospheric to approximately 210 mm. Relative activities are plotted along the left-hand ordinates, the highest activity found in a given run being taken as unity and all others in that run being plotted as fractions of it. The values used for calculation of this relative activity were total activities uncorrected for the levels found in the blank runs, and the absolute value for the highest activity is shown in counts per minute (c.p.m.) in each graph. The activity labeled R in the graphs was that of a 2-ml. sample of the pot residue at the end of the distillation.

Blank Runs.—Blank tests of various kinds were made as follows.

Pure lead tetraethyl vapor was passed at a low pressure through the reaction chamber, a short section of which was heated to 200°. A platinum filament heated to approximately 400° was employed to make decomposition more nearly complete. An iodine-131 mirror of the usual type was entirely consumed in about an hour, and the activity appearing in the ethyl fraction was extremely high, demonstrating that when free radicals are present they can be detected. Results are shown in run 35, Fig. 3.

The appearance of radicals which were not in fact formed from butane by the action of the catalyst might have been simulated by: (a) exchange between free radioactive iodine and the alkyl iodides used as carriers; (b) exchange between labeled alkyl iodides and carrier iodides; (c) reaction between primary free radicals and the reactant (butane) or a second primary radical to form new (secondary) free radicals; (d) radiolysis of butane or carrier iodides before extraction of excess radioactive iodine.

That (a) did not occur to a significant extent (provided ethyl iodide only was added as carrier before the excess radioactive iodine was removed) was shown by blank runs, 29 and 44, Fig. 3.

These are the blanks which showed the highest and lowest activities, respectively, of all blanks run. It was at first thought that the activities observed in the blanks were caused by exchange, but this could not account for the butyl peak when only ethyl iodide had been in contact with radioactive iodine or significant concentrations of radioactive iodide ion. The other possibility was that the ethyl iodide underwent radiolysis by the high-energy β- and γ-rays emitted by iodine-131 itself. The work of a number of authors supports this conclusion.[3,4] A number of different materials were tried as the extracting medium, but carefully purified ethyl iodide was found to result in the lowest blanks.

As noted, the possibility of radiolysis of alkyl iodides cannot be entirely eliminated, but it is clearly at worst a minor source of radicals, insufficient to interfere with the observation of appreciable quantities of authentic free radicals.

(3) R. H. Schuler and W. H. Hamill, THIS JOURNAL, 74, 6171 (1952).
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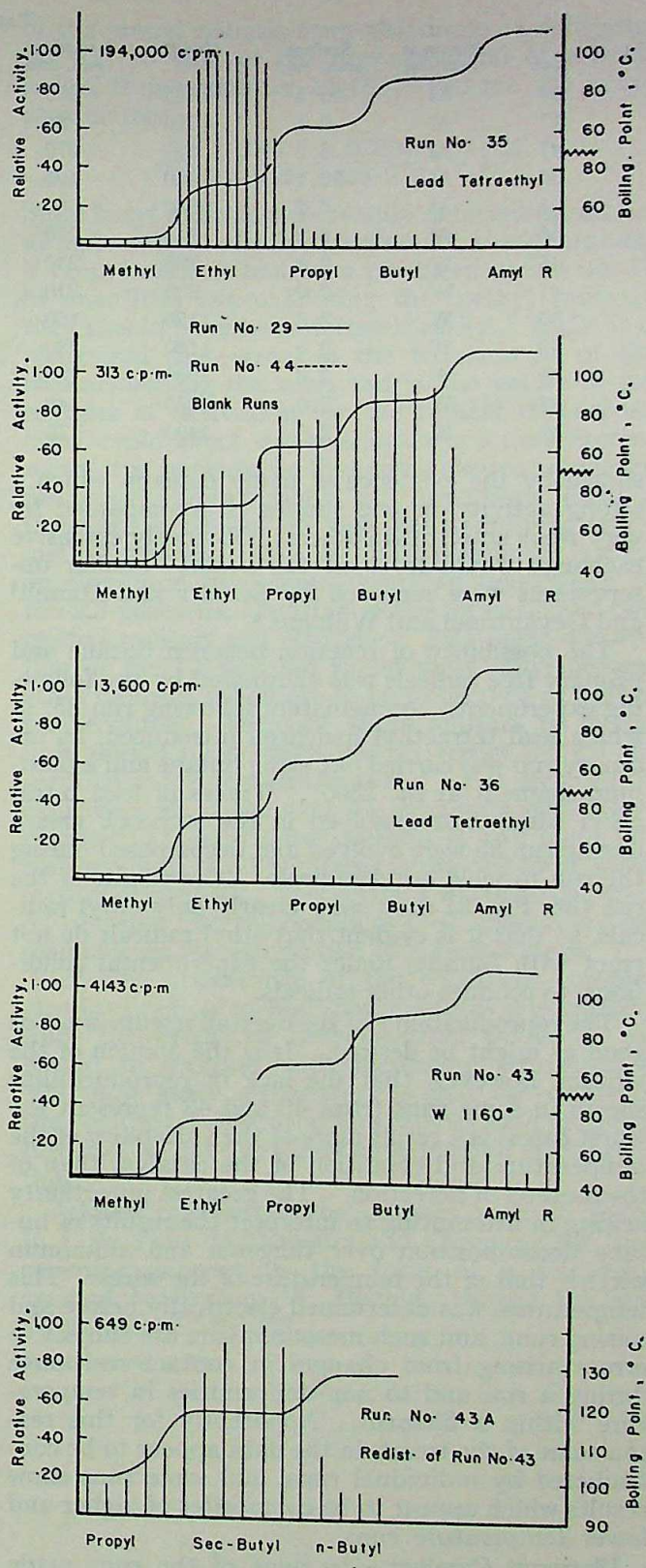

Fig. 3.

To make certain that no radiolysis of butane was occurring either during a run or after a run when all materials were distilled into the extraction vessel, run No. 44 was performed exactly as a normal run, except that the wire was left cold. After distillation the activities of all fractions were found to be considerably below the level of run no. 29, the standard reference blank.

Exchange between labeled and carrier alkyl iodides cannot occur to any considerable extent, as is

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TABLE I

Run	Filament material	Surface area, cm.²	Temp., °C.	Length of run, min.	Moles of butane × 10⁵	Apparent collision efficiency × 10⁷ Methyl	Ethyl	*sec*-Butyl	*n*-Butyl
49	Al	40.1	305	250	14.5	0.8			
17	Al	9.1	360	80	3.7	39			
47	Al	6.2	430	270	16.7				7
50	Al	40.1	440	195	11.2	0.8		0.9	1
31	Al	6.2	540	60	3.1	4	8	7	
46	Al	6.2	540	210	12.2			8	
45	W	2.0	780	210	12(est.)		9		
41	W	2.0	820	210	12.9		10		
39	W	2.0	1125	160	10(est.)	25	54	37	
43	W	2.0	1160	230	13.2	10	16	37	
40	W	2.0	1200	190	12.1	38	85	20	
38	W	2.0	1335	140	3.6	16	13	6	
42	W	2.0	1490	70	2.3		35	26	16

shown by the existence of many cases in which a strong activity in one species is accompanied by very weak activities in others. Obviously extensive exchange would level off the peaks. Similar observations were recorded by Schuler and Hamill[3] and Gevantman and Williams.[4]

The possibility of reaction between butane and primary free radicals was eliminated by the following experiment. Immediately following run 35, in which lead tetraethyl had been introduced, an ordinary run was carried out using butane and a platinum filament at *ca.* 1300°. Traces of lead tetraethyl which had dissolved in the stopcock grease during run 35 were evolved and decomposed during the run to yield ethyl radicals. The results of the run (36, Fig. 3) show very clearly only ethyl radicals, so that it is evident that ethyl radicals do not react with butane, under the experimental conditions, to produce other radicals.

The reproducibility of the over-all results is not as good as might be desired. It is the opinion of the writers, however, that the lack of reproducibility shown in some runs (runs 40 and 43 represent the worst cases) is a result more of the variability of the temperature and condition of the catalyst than of the method of detection. The greatest uncertainty arising in attempting to interpret the results of butane decomposition over tungsten and aluminum wires is that of the temperature of the wires. This temperature was determined electrically before and during runs, and such measurements are subject to errors arising from changes in contact resistance during a run and to non-uniformities in temperature within a filament. Apparently for this reason some of the trends in the data appear to be contradicted by individual runs, and some runs show results which appear to be composites of higher and lower temperature runs.

Platinum Catalyst.—In none of the runs made with platinum wires were significant quantities of free radicals detected, and so these runs are not individually reported. The temperatures used ranged from 400 to 1200°, and platinized platinum wires as well as smooth wires were tried. The negative results obtained indicate that if decomposition occurred, it proceeded through a mechanism not involving free radicals, or by a mechanism in which free radicals did not leave the surface of the wire. It would seem reasonable to assume that the principal products of any decomposition that might have occurred were unsaturated compounds rather than free radicals.

Tungsten Catalyst.—The results of all runs performed with tungsten and aluminum catalysts are presented in Table I. The apparent collision efficiency shown in this table is the ratio of the number of radicals found to the number of butane molecules colliding with the catalyst, and is therefore a measure of the relative tendency of the catalysts to form radicals of the kind shown.

Examination of Table I will show that the tungsten filaments produced ethyl radicals at all temperatures, and that at the higher temperatures secondary butyl radicals were produced in significant amounts. In none of the runs was secondary butyl iodide added as a carrier; this radical showed up between the propyl and *n*-butyl fractions as a sharp peak rather than a broad plateau. Figure 3 (run 43) shows the boiling point and activity curve obtained, and a subsequent redistillation (run 43A) of a small cut of the secondary butyl peak with the addition of carrier secondary butyl iodide. This redistillation supports the identification of the peak as due to secondary butyl radicals, although isobutyl radicals remain an unlikely possibility.

Aluminum (Oxide) Catalyst.—The results of the aluminum runs may be summarized by saying that at temperatures around 300° only methyl radicals were detected in significant amounts, while at somewhat higher temperatures (430–440°) only normal butyl radicals (and some indication of secondary butyl) were detected, and at the highest temperatures (approximately 540°) principally secondary butyl radicals were detected.

Conclusions

In spite of some irregularities in individual runs, some generalizations emerge from the data as a whole.

(a) The character of the products *in general terms* is a function of the temperature. Thus, both Al and W produce chiefly products of C–C bond scission at lower, and of C–H bond scission at higher, temperatures. This result is to be expected on purely energetic grounds, and it is noted that the catalytic effect of these metals is not sufficient to produce deviations from the expected result. However, the failure of products of C–C bond scission to appear in the case of Pt may mean that C–H bond scission occurs to such an extent, even at low

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temperatures, that unsaturates (which would not be detected in this procedure), rather than free radicals, are formed. Unfortunately we can produce no direct evidence for this process.

(b) The character of the products *in detail* is affected by the catalyst used, and hence it is clear that the effect being observed is not purely thermal. Individual differences have been pointed out in the preceding section. An explanation for the apparent tendency of W to produce ethyl radicals and for Al to produce methyl radicals, at the lowest temperatures, for example, is not readily forthcoming, however.

(c) The favoring of those radicals which have been generally regarded as most stable is noted. Thus *sec*-butyl radicals in preference to *n*-butyl are observed at the highest temperatures. Whether the disappearance of *n*-butyl and the appearance of *sec*-butyl reflects a changing activity of the catalysts with temperature, or whether it is a result of isomerization of the *n*-butyl radicals originally formed is not entirely certain, but it should be noted that *n*-butyl radicals were observed in some runs and there is therefore some reason to suppose that the shift to *sec*-butyl is a property of the catalyst and not merely a result of isomerization.

The failure to detect propyl radicals of any kind in significant amounts is a striking result, especially in the face of quite high methyl activities, which suggest a 1,2 C–C bond scission. There appear to be at least three possible explanations for their nonappearance: (1) propyl radicals may be formed, along with methyl, but may remain adsorbed. Since the energy required to desorb a propyl radical would be expected to be little different from that for methyl, this assumption does not appear tenable; (2) propyl radicals may be formed but undergo decomposition into ethylene plus methyl radicals. A comparison of the energies of activation[5] for the reactions

$$C_3H_7\cdot \longrightarrow C_2H_4 + CH_3\cdot \qquad E = 20 \text{ kcal.}$$
$$n\text{-}C_4H_9\cdot \longrightarrow C_2H_4 + C_2H_5\cdot \qquad E = 23 \text{ kcal.}$$
$$n\text{-}C_4H_9\cdot \longrightarrow C_3H_6 + CH_3\cdot \qquad E = 23 \text{ kcal.}$$

leads to the conclusion (assuming equal frequency factors) that the ratio of the rate of decomposition of the propyl radicals from aluminum at 360° (run no. 17) to that of the decomposition of *n*-butyl radical from aluminum at 430° (run no. 47) is approximately

$$\exp\left(\frac{23{,}000}{703 \times 2} - \frac{20{,}000}{633 \times 2}\right) = 1.75$$

Since butyl radicals were readily detected in run no. 47 and methyl radicals in run no. 17, it appears that if propyl radicals had been produced in run no. 17 in quantities approximating the methyl radicals, they should have been detected easily. While it is recognized that errors in the temperature of the radicals leaving the wire, and in the values of the energies of activation for the radical decompositions, could affect this conclusion in a quantitative sense, it is improbable that some clearcut evidence for propyl radicals would not have been found if they are produced in quantities approximating methyl radicals. (3) The third possibility is that on aluminum two point adsorption takes place at the 2,3-positions, resulting in the formation of two methyl radicals and ethylene. Two point adsorption in the 1,2-position would yield ethylene and ethyl radicals, which are in fact observed at higher temperatures. Although there appears to be no firm ground upon which the preference for 2,3-adsorption at low temperatures and 1,2 at high can be explained, all of the data on aluminum which correspond to C–C scission conform to two point adsorption, and this hypothesis is the one most satisfactory at present. It is perhaps worth noting that on tungsten also the results of C–C scission are explainable on the assumption of 2,3-adsorption.

(d) The appearance of the relatively complex *sec*-butyl radical at high temperatures is surprising since the extent of decomposition would be expected to increase with increasing temperature. The most likely explanation is that the residence time on the catalyst decreases rapidly with temperature, but we have no direct experimental evidence of this.

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PHILADELPHIA, PA.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENTS, ST. PETER'S COLLEGE AND BROOKHAVEN NATIONAL LABORATORY]

Radical Production in the Radiolysis of Liquid Butane[1]

BY CHARLES E. McCAULEY AND ROBERT H. SCHULER[2]

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The distribution of radical species produced during the radiolysis of liquid butane has been studied by the radioiodine scavenging method. While the radiation yield for formation of total alkyl iodide product increases from a value of 5.6 molecules per 100 electron volts at an iodine concentration of 2×10^{-3} M to a value of 9 at 2×10^{-2} M, the yield for each of the monoiodide products is constant. These yields are, respectively, 0.4, 0.9, 0.1, 0.0, 1.0 and 2.1 for methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and *sec*-butyl iodides. The increase in yield of total organic iodides at the greater iodine concentrations is due to a large increase in the yield of higher boiling material which most probably represents diiodide products. The constancy of the yields for the less complex products appears to be an additional indication of the validity of the iodine scavenging method since hydrogen abstraction reactions of the radicals are not affected by changes in the scavenger concentration in the region studied.

Radical production in the radiolysis of liquid hydrocarbons has previously been studied by employing iodine at low concentrations to scavenge the radicals formed.[3-6] It has been shown that the radiation yield for uptake of iodine is independent of concentration below 5×10^{-3} M and is presumably a good measure of the yield of radicals produced. The present investigation was undertaken in order to obtain information on the fragmentation pattern in the radiation decomposition of a typical liquid aliphatic hydrocarbon. Liquid butane was chosen since previous experience had shown it possible to obtain adequate separation of the expected alkyl iodides with boiling points up to that of *n*-butyl iodide[7,8] while at the same time the butane molecule is complex enough to allow for the possibility of several different modes in the resulting decomposition. In this work, radioiodine has been used as the detector and the yields of individual products have been determined by carrier isolation methods similar to those originally employed by Gevantman and Williams in studies of the radical distribution in the radiolysis of hydrocarbon vapors.[9]

Experimental

Materials.—Matheson C.P. *n*-butane, stated to be 99.0% pure, was used without further purification. Partition chromatograms of this material showed two barely detectable impurities below the butane peak and none above it, the indicated impurity being of the order of several tenths of a per cent. The alkyl iodides used as carriers were purified by washing with aqueous thiosulfate, drying over anhydrous magnesium sulfate and distilling at reduced pressures through a six foot packed column.

Sample Preparation and Irradiation.—A weighed quantity of radioiodine (5–45 mg.) was placed in the irradiation cell which was then cooled in liquid nitrogen and evacuated. Butane was condensed into a reservoir on the vacuum line and the desired quantity (7–9 cc.) distilled into the irradiation cell. The sample was frozen in liquid nitrogen, evacuated and sealed and the exact weight determined upon opening the cell after irradiation. The irradiation cells consisted of 8.5 mm. i.d. heavy-walled tubing 150 mm. long. Irradiations were carried out at 25° inside a cylindrical Co^{60} source of 30,000 roentgens per hour intensity.[10]

Product Analysis.—The extent of reaction of iodine was determined, as in previous work,[6] by measuring the fraction of iodine found to be organically combined after thiosulfate extraction. The radiation yield was calculated from this information combined with knowledge of the initial iodine concentration and energy absorbed by the sample. Together with the ratios of the activity of the individual components to that of the total sample this served to give the yields for each of the products.

After irradiation, the sample was cooled to about −40°, opened and added to a total of about 250 cc. of precooled mixed carriers. In general, transfer of the sample to the carriers appeared to proceed with little difficulty. The carrier mixture was allowed to come to room temperature and a portion taken for measurement of the ratio of *organic* activity to *total* activity. The bulk of the mixed carriers was then extracted with thiosulfate solution and a portion of this extracted mixture reserved for measurement of the specific activity. The remainder was separated into the individual components by fractional distillation at reduced pressure in a manner similar to that employed in earlier work.[7,8] The relative activities of the various fractions were measured in an annular jacketed geiger counter after a tenfold dilution with carbon tetrachloride. Because of this dilution, differences in the density of the various solutions were slight and resulted in correspondingly small variations in the counting efficiency. Appropriate corrections were, however, applied where necessary. The total activity of a particular component was determined from its specific activity and the volume of carrier initially added. The carriers consisted of 25–50 ml. of each of the suspected components together with about 5 g. of inactive iodine which was added to the mixture for the purpose of diluting any possible reaction between the active iodine present and the carriers. Of the butyl iodides, only *n*-butyl and *sec*-butyl iodide were added as carriers. Since the formation of isobutyl and *t*-butyl iodide involve somewhat complicated rearrangements, these iodides are not expected in any appreciable yield. However, any isobutyl iodide formed would have been carried in the *sec*-butyl iodide fraction while *t*-butyl iodide would have exchanged with the large amount of inactive iodine added[7] and hence would not appear as organic activity. In addition to the activity found in the added carriers, it was observed that the residue remaining in the stillpot after take off of a representative methylene iodide fraction had a higher specific activity than the methylene iodide itself. The activity in excess of the methylene iodide component is here referred to as the residue and presumably consists largely of high boiling diiodides. The total activity in this fraction was determined from the volume of material remaining in the stillpot and the specific activity of this residue.

Results

Radiation Yield for Uptake of Iodine.—Results of the radiochemical measurement of the fractional

(1) Research performed in part under the auspices of the U. S. Atomic Energy Commission.

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TABLE I

DISTRIBUTION OF ALKYL IODIDES PRODUCED IN THE RADIOLYSIS OF IODINE SOLUTIONS IN LIQUID BUTANE

Iodine concn., M	Irradiation period, min.[a]	Reaction, %	Specific rate,[b] moles/g./min. $\times 10^9$	Product distribution, %[c] CH_3I	C_2H_5I	i-C_3H_7I	n-C_3H_7I	s-C_4H_9I	n-C_4H_9I	CH_2I_2	Residue	Material balance[d]
0.0024	702	25.84	1.56	8.2	16.4	0.7	1.6	37.5	18.2	11.2	6.2	1.052
.0046	780	14.85	1.53	11.0	16.5	0.3	1.9	34.5	18.0	11.3	6.5	0.990
.0093	1500	16.9	1.85	6.4	..	..	..	..	..	..	..	...
.0113	1157	11.57	1.94	20.5	14.5	0.3	2.0	29.5	16.0	9.9	7.3	0.971
.0189	2340	17.0	2.42	7.4	..	..	..	..	..	..	..	...
.0214	3460	20.76	2.23	4.4	11.2	0.3	1.3	29.0	12.6	17.2	24.0	1.002
.0230	1578	9.56	2.47	10.1	9.3	0.5	1.3	23.0	10.8	16.4	28.6	1.006

[a] Corrected for decay of source; dose rate in butane is 3.30×10^{16} e.v./g./min. [b] Ferrous oxidation rate in Fricke dosimeter is 8.25 μM/min. [c] Per cent. of the sum of the individual activities. [d] Ratio of the sum of the individual activities to that of the total sample.

TABLE II

RADIATION YIELDS[a]

Iodine concn., M	Total organic iodide	CH_3I	C_2H_5I	i-C_3H_7I	n-C_3H_7I	s-C_4H_9I	n-C_4H_9I	CH_2I_2	Residue
0.0024	5.71	0.47	0.94	0.04	0.09	2.14	1.04	0.64	0.35
.0046	5.59	.62	.92	.02	.10	1.93	1.01	.63	.36
.0093	6.7	.43	..	..	..	..	..	..	..
.0112	7.09	1.44	1.02	.02	.14	2.07	1.12	0.69	0.52
.0189	8.9	0.65	..	..	..	..	..	..	..
.0214	8.15	.36	0.91	.03	.11	2.36	0.99	1.40	1.96
.0230	9.05	.91	.84	.05	.12	2.08	.98	1.48	2.56

[a] Molecules of product per 100 e.v. of absorbed energy.

reaction of iodine are given in Table I along with the corresponding specific rates observed in each of the experiments. These rates are expressed in units of moles of total alkyl iodide product per gram of sample per minute of exposure in the 30,000 roentgens/hr. source. Absolute radiation yields were determined by comparison with the specific rate of ferrous iron oxidation in the Fricke dosimeter. Correction has been made for decay of the Co^{60} source to November 1, 1955, at which time the rate of ferric ion formation was 8.25 μM/min. The corrected irradiation periods are given in Table I. Assuming that $G(Fe^{+++})$ is 15.5 and that energy absorption is proportional to the electron density of the irradiated material, a value of 3.30×10^{16} e.v./g./min. is obtained for the rate of energy dissipation in the butane. The absolute radiation yields calculated from this figure are given in Table II.

Possible Importance of Self-radiolysis.—Since the addition of carrier materials results in a 50-fold dilution of the activity and since only a small fraction of the total activity appears in any particular component, it is necessary to use high specific activity radioiodine, at least in the case of experiments carried out in more dilute solutions. The possibility therefore arises that appreciable reaction will result from self-radiolysis of the sample due to the radiations from I^{131}. With this in mind, contact between the radioiodine and the liquid butane was kept to a minimum and, in general, the standing periods were not more than a few days. However, some estimate of the extent of this self-radiolysis is in order. In these experiments the activity level was approximately 0.1 millicurie per gram of sample. Taking the average absorbed energy per disintegration as 0.2 Mev., it is estimated that the I^{131} dissipates energy in the butane at the rate of 6.4×10^{16} e.v./g./day. This compares with a total energy deposition in the sample of the order of 3.3×10^{19} e.v./g. from the Co^{60} field. It is seen, therefore, that the effects of self-radiolysis are negligible here (~1%) but that they must be taken into account if one were to use an appreciably higher specific activity material.

Product Distribution.—The distribution of activity among the various products is given in Table I along with the material balance obtained by comparing the sum of the total activities found for each component to that of the mixed carrier sample. Essentially all of the activity is accounted for. The radiation yield for each individual component is given in Table II.

Effect of Iodine Concentration.—The radiation yields for ethyl, *n*-propyl, isopropyl, *sec*-butyl and *n*-butyl iodides are essentially independent of iodine concentration over the region studied. The observed yield of activity in the methyl iodide shows a considerably greater scatter than appears in any other of the iodides. This scatter makes determination of the functional dependence of the radiation yield upon iodine concentration somewhat elusive although it is believed that here too the yield is substantially independent of iodine concentration and has a value of about 0.4.

The cause for the scatter in the case of methyl iodide is unknown but apparently does not originate in the fractionation procedure since quite adequate fractionations have been obtained in other investigations.[7,8,11,12] Although the higher iodides exhibit a negligibly small rate of thermal exchange

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with radioiodine, methyl iodide, especially if impure, reacts at a considerably higher rate. Because of the low fractional reactions in these radiolysis studies, several tenths of a per cent. pickup of the activity by the methyl iodide carrier would amount to an appreciable increase in the apparent yield. It is probable, therefore, that the high yields of methyl iodide in the experiments at 0.0112 and 0.0230 *M* are due to some defect in the experimental procedure, possibly to reaction of radioiodine with an impurity present in the batches of carrier used in these particular experiments. Two experiments in which only methyl iodide was determined were carried out as specific checks on the methyl iodide yield and are also reported in Table I. Here the activity was separated as quickly as possible after addition of the sample to the carrier mixture to minimize any possible exchange.

Discussion

Although the amounts of the simpler alkyl iodide products are independent of concentration, it is seen that the radiation yield of total combined iodine increases in the concentration region studied from 5.6 to about 9. This observed increase is due to the formation of methylene iodide and more importantly to the formation of other high boiling products and is about twice as large as that found in similar studies with cyclohexane.[6] The constancy in the yields of monoiodide products is a somewhat surprising fact in view of the drop in the hydrogen yield resulting from these scavenger concentrations in the case of cyclohexane.[13] The radical products are unaffected by changes in the physical and chemical processes which cause the drop in hydrogen and increase in diiodide yields and, therefore, appear to be formed in the early stages of the radiation decomposition. Of particular importance is the indication from the constancy of the *n*-butyl and *sec*-butyl yields at high iodine concentrations that production of butyl radicals by abstraction reactions such as

$$H\cdot + C_4H_{10} \longrightarrow H_2 + C_4H_9\cdot \qquad (1)$$

is unimportant. It seems likely therefore, as has also been indicated in other studies, that the observed hydrogen gas is produced by an ultimate molecule reaction rather than by an abstraction reaction similar to 1.

The increase in diiodide products interestingly occurs in the concentration region of 10^{-2} *M* where it has been shown[13] that the molecular hydrogen yield drops. Williams and Hamill[14] have called attention to the importance of electron traps in this region of solute concentration and have suggested that iodine can act as an electron scavenger. This change in the primary species might permit the production of stable diiodide products by a direct radiation-induced reaction between the iodine and the hydrocarbon.

Relative Importance of Various Modes of Fragmentation.—The interaction of radiation with matter produces as primary fragments both radical and ionic species, the chemical importance of each being as yet undetermined. Although there has been a theoretical indication that charge neutralization takes place in the case of liquids before chemical reactions come into play,[15,16] recent work with the mass spectrometer has shown that the cross-sections for ion–molecule reactions are very large[17] and has indicated that these reactions may be important intermediary processes in the radiation chemistry of liquids.[18] The present study includes at least one indication that ionic mechanisms play an important role. If the radiation decomposition involves radicals but not ions, equivalent amounts of methyl and *n*-propyl radicals would be expected to result from the radiolysis of butane. It is seen here that the yield of *n*-propyl iodide is only one fourth that of methyl iodide. This low value can scarcely result from the thermal dissociation of propyl radicals since if such were an important process, the measured propyl iodide yield should be dependent on the concentration of iodine. It thus seems necessary to include in the mechanism some step other than simple homolytic dissociation of butane molecules into radicals.

Although comparison of results obtained from the mass spectrometer and from the irradiation of liquid systems cannot be simple, it is worth noting that the most abundant ion in the mass spectrum of butane is $C_3H_7^+$ and that the ratio $C_3H_7^+/CH_3^+$ is about 17. The ratio of the complementary radicals will thus be presumably considerably larger than unity in qualitative agreement with data of Table II. Gevantman and Williams[9] have pointed out that such a complementarity is observed between the relative abundance of radicals detected by radioiodine and of ions formed in the mass spectrometer in the case of propane, *n*-pentane, and neopentane vapors. Present data on liquid butane are quite analogous to the results of Gevantman and Williams on pentane vapor but show no correlation with their results for butane vapor.

It is seen that the ratio for formation of *sec*-butyl and *n*-butyl radicals is about two to one, although the ratio of primary to secondary hydrogen atoms is about three to two. A similar preferential rupture for particular bonds has, of course, already been shown in the case of alkyl iodides, alcohols and carboxylic acids. This appears to be in accord with semi-quantitative theories for mass spectra of polyatomic molecules,[19] where it is postulated that decomposition occurs only after the positive ions have undergone a number of vibrations which effectively distribute the energy throughout the whole molecule.

The carrier distillation method employed here is quite tedious and of limited scope due to the difficulties of separating the iodides. However, the introduction of simpler vapor chromatographic proce-

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dures now available should make the radioiodine detection method more generally useful. Since it has been shown recently that carrier-free mixtures of the organic bromides can be separated on partition columns,[20] use of this technique may avoid difficulties due to failure to add proper carrier components. It is hoped that extension of these studies may reveal much more in the way of the fine structure of the radical spectrum produced by radiation.

Acknowledgment.—We wish to express our thanks to Mr. Paul R. Geissler for assistance in making some of the measurements reported here.

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(20) J. B. Evans and J. E. Willard, THIS JOURNAL, **78**, 2908 (1956).

[CONTRIBUTION FROM THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

The Evaluation of Inductive and Resonance Effects in Reactivity. II. Thermodynamic Properties of Hydrogenation of Non-conjugated Olefins, Aldehydes and Ketones[1]

BY ROBERT W. TAFT, JR., AND M. M. KREEVOY

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The effect of unconjugated (α,β-saturated) substituents on the enthalpies of hydrogenation of mono- and *trans*-disubstituted ethylenes, $\Delta\Delta H°$, and on the free energies of hydrogenation of carbonyl compounds, $R_1R_2C{=}O$, $\Delta\Delta F°$, are found to follow with acceptable precision eq. 2: $\Delta\Delta H°$ (or $\Delta\Delta F°$) $= (\Sigma\sigma^*)\rho^* + (\Delta n)h$. This empirical relationship is suggested by and is correlated with the hypothesis that polar and hyperconjugative effects of the substituents contribute approximately additively to give the observed effect on the thermodynamic property. This hypothesis unifies diverse observed effects of substituents with theory. An important polar contribution to the thermodynamic properties for these reactions is expected in view of the change from the sp^2 to the sp^3 valence state of carbon which accompanies the hydrogenation. Evidence is obtained that hyperconjugation stabilization is much less susceptible to electron demand at the reaction center than is stabilization by inductive electron-release. The hyperconjugation stabilization per α-hydrogen atom in an open chain olefin or carbonyl compound is found to be about 0.5 kcal./mole.

The effect of alkyl substituents on the enthalpies of hydrogenation of olefins has been commonly attributed to hyperconjugation of the group with the C–C double bond.[2,3] If the entire effect of the substituent on the enthalpy of hydrogenation is attributed to hyperconjugation or conjugation in the olefin, the resulting hyperconjugation energies obtained for alkyl groups appear to be unreasonably large compared to the conjugation energies obtained for α,β-unsaturated substituents.[4]

Adkins and students have determined the free energies of hydrogenation of numerous aldehydes and ketones in dilute toluene solutions at 60°.[5] Hyperconjugation of alkyl substituents with the carbonyl group is reasonably expected to make at least as important contribution to these hydrogenation equilibria as those for olefin hydrogenation. However, the effects of alkyl groups on the free energies of hydrogenation of aldehyde and ketones do not show a distinct hyperconjugation order. In fact, conjugation effects of unsaturated groups on the free energies of hydrogenation are frequently not (or only slightly) discernible.

The hydrogenation of double bonded compounds is accompanied by a marked decrease in the intrinsic electronegativity of the atoms at the double bond.[6] This results from the fact that the sp^2 valence state of a given atom is appreciably more electronegative than the sp^3 state. Rates and equilibria for reactions which involve a substantial change in the electron demand at the reaction center show large susceptibilities to the electron attracting and releasing powers of substituent groups. That is, polar effects of substituents are large for reactions of this kind.

Important inductive, as well as hyperconjugation, effects are therefore expected to contribute to the observed effects of substituents on the enthalpies and free energies of hydrogenation of olefins, aldehydes and ketones.

In paper I it was shown that the very large effects of substituents on the rates of hydrolysis of diethyl acetals and ketals (of non-conjugated aldehydes and ketones) are correlated in an approximately quantitative manner by an equation which attributes the total effect of the substituent on the free energy of activation to the sum of independent inductive and hyperconjugation effects.[7] The acid-catalyzed rate constants in this reaction series follow with acceptable precision the equation

$$\log (k/k_0) = (\Sigma\sigma^*)\rho^* + (\Delta n)h \qquad (1)$$

where $\Sigma\sigma^*$ is the sum of the polar substituent constants, σ^*, for the substituents, R_1 and R_2, of the acetal or ketal of the general formula $R_1R_2C(OC_2H_5)_2$. These polar substituent constants were ob-

(1) The work herein reported was carried out on Project NR055-328 between the Office of Naval Research and The Pennsylvania State University. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) (a) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 149; (b) R. S. Mulliken, C. A. Rieke and W. G. Brown, THIS JOURNAL, **63**, 41 (1941).

(3) J. W. Baker, "Hyperconjugation," Oxford at the Clarendon Press, 1952, p. 40, has pointed out that while the enthalpy data are consistent with hyperconjugation theory, it cannot be regarded as evidence for the validity of the concept.

(4) K. S. Pitzer, "Quantum Chemistry," Prentice–Hall, Inc., New York, N. Y., 1953, p. 184.

(5) H. Adkins, R. M. Elofson, A. G. Rossow and C. C. Robinson, THIS JOURNAL, **71**, 3622 (1949).

(6) (a) R. S. Mulliken, *J. Chem. Phys.*, **2**, 782 (1934); **3**, 573 (1935); *cf.* also comments on the importance of the electronegativity of the valence state in reactivity considerations, R. W. Taft, Jr., *J. Chem. Phys.*, **26**, 93 (1957).

(7) M. M. Kreevoy and R. W. Taft, Jr., THIS JOURNAL, **77**, 5590 (1955).

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tained by Taft from data on the acid-catalyzed hydrolysis and the alkaline saponification of esters, $RCO_2C_2H_5$.[8] n is the total number of hydrogen atoms in R_1 and R_2 of the general compound (for which k is the rate constant). Δn is the difference between n and n_0, where n_0 pertains to the standard of comparison (for which k_0 is the rate constant). The standard was chosen so that $R_1 = R_2 = CH_3$ ($\Delta n = n - 6$, $\Sigma\sigma^* = 0.000$). The empirical reaction constant, ρ^*, measures the susceptibility of the hydrolysis reaction to polar effects. The empirical constant h is interpreted as a measure of the hyperconjugative stabilization of the reaction transition state by a single α-hydrogen atom.

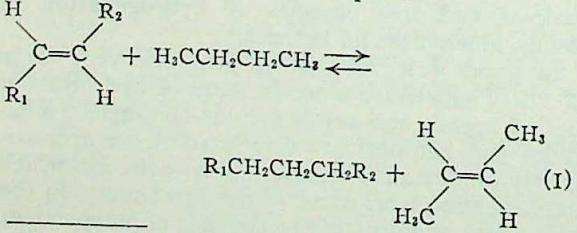
In this paper we report the correlation of the effect of substituents on the enthalpies of hydrogenation of *trans*-substituted, unconjugated olefins, $\Delta\Delta H°$, and of free energies of hydrogenation of unconjugated aldehydes and ketones, $\Delta\Delta F°$, by the equation

$$\Delta\Delta H° \text{ (or } \Delta\Delta F°) = (\Sigma\sigma^*)\rho^* + (\Delta n)h \qquad (2)$$

The empirical correlation eqs. 1 and 2 provide a simple, self-consistent theory of the effects of substituents on these rates and equilibria. In paper III it is shown that the evaluation of hyperconjugation and inductive effects by eqs. 1 and 2 can be used to obtain approximately quantitative values of the conjugation effects of α,β-unsaturated substituents.[9] The relative magnitudes of the hyperconjugation and conjugation effects obtained in this manner are quite reasonable.

Enthalpies of Hydrogenation of Gaseous Olefins.—Kistiakowsky and co-workers[10] have determined calorimetrically the vapor phase enthalpies of hydrogenation for a number of olefins. In addition a number of enthalpies of hydrogenation can be derived from accurate data on heats of formation.[11-13] The largest body of reliable data is available at 355°K.

The effect of structure on the enthalpy of hydrogenation of mono- and *trans*-disubstituted ethylenes is given by the enthalpy change, $\Delta\Delta H°_{355}$, of the following reaction, using *trans*-2-butene ($\Delta n = n - 6$) as the standard of comparison



$$R_1CH_2CH_2CH_2R_2 + \text{(trans-2-butene)} \qquad (I)$$

(8) R. W. Taft, Jr., This Journal, **74**, 3120 (1952); **75**, 4231 (1953). For a recent compilation of σ^* values, *cf.* M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 619.

(9) M. M. Kreevoy and R. W. Taft, Jr., *ibid.*, **79**, 4016 (1957).

(10) (a) J. B. Conant and G. B. Kistiakowsky, *Chem. Revs.*, **20**, 182 (1937); (b) M. A. Dolliver, J. L. Gresham, G. B. Kistiakowsky, E. A. Smith and W. E. Vaughan, This Journal, **60**, 440 (1938); (c) earlier references given in (a) and (b).

(11) E. Schjanberg, *Z. physik. Chem.*, **179A**, 39 (1937).

(12) F. D. Rossini, K. S. Pitzer, R. L. Arnett, R. M. Braun and G. C. Pimental, "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," Carnegie Press, Pittsburgh, Pennslyvania, 1953, pp. 704-746.

(13) The fact that heats of hydrogenation derived from several types of measurements are all correlated by eq. 2 lends additional support to the validity of the treatment.

where R_1 or R_2 is any substituent which is not conjugated with the functional group (hereafter referred to as an α,β-saturated substituent). The 21 available enthalpies of hydrogenation, $\Delta\Delta H°_{355}$, of this class cover a range of 5.2 kcal./mole, and are correlated by eq. 2 with a mean difference between calculated and observed values of 0.1 kcal. The latter figure is approximately the same as the estimated experimental uncertainty.[10-12]

The values of ρ^* and h which give the best fit of the data to equation 2 are: $\rho^* = -2.409 \pm 0.151$ and $h = 0.437 \pm 0.51$ (with a residual of $+0.1$ kcal./mole). Table I also lists the corresponding enthalpies at absolute zero, $\Delta\Delta H°_0$. It is important to note that corresponding values of $\Delta\Delta H°_{355}$ and $\Delta\Delta H°_0$ are nearly the same, and that eq. 2 therefore holds for the enthalpies at absolute zero.

The enthalpies of hydrogenation of *cis*- and vicinally disubstituted ethylenes and cyclic olefins are not generally fitted with precision by eq. 2. Deviations from eq. 2 for a number of typical olefins of this kind are given in Table II.

For the *cis*- and vicinally disubstituted olefins the deviations are reasonably attributed to steric effects which result from the shorter bond lengths and greater rigidity of the olefins as compared with the saturated hydrocarbons. For the cyclic olefins the deviations can be attributed to changes in the number of eclipsed carbon–hydrogen bonds on going from the unsaturated to the saturated compound.[14]

The enthalpies of hydrogenation of conjugated olefins also do not follow eq. 2. In this case the positive differences between the calculated and the observed enthalpies are thought to be close measures of the increase in resonance stabilization resulting from conjugation (*cf.* paper III).[9]

Free Energies of Hydrogenation of Aldehydes and Ketones.—Adkins and co-workers[5] made an extensive study of the equilibrium constants (which we shall denote by K/K_0) for the general reaction

$$R_1R_2C{=}O + (CH_3)_2CHOH \rightleftharpoons R_1R_2CHOH + (CH_3)_2CO \qquad (II)$$

The reactions were carried out in dilute toluene solution, and were catalyzed by aluminum *t*-butoxide. Most of the data were obtained at 60° but a few data at other temperatures are included since the position of equilibrium does not appear to be appreciably temperature dependent. Seventeen available free energies, $\Delta\Delta F^0 = -2.303RT \log (K/K_0)$, for unconjugated aldehydes and ketones have a total spread of nearly 6 kcal./mole. These free energies are correlated by eq. 2 with an average deviation between observed and calculated values of 0.4 kcal., a figure of the same magnitude as the experimental uncertainty.[2,3] The standard of comparison is acetone ($\Delta n = n - 6$; $\Sigma\sigma^* = 0.000$) and the values of ρ^* and h which give the best fit of the data to eq. 2 are: $\rho^* = -6.39 \pm 0.26$, and $h = 0.54 \pm 0.06$ (with a residual of $+0.6$ kcal./mole).

Table III illustrates the fit of these free energies to eq. 2. The values given by Adkins, *et al.*, for dimethoxyacetone, formaldehyde and chloral have

(14) H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

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TABLE I

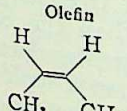
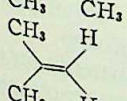
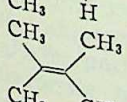
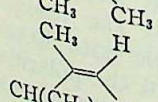
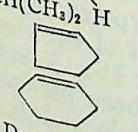
CORRELATION OF ENTHALPIES OF HYDROGENATION OF GASEOUS MONO- AND *trans*-DISUBSTITUTED ETHYLENES BY EQ. 2

Substituents R_1	R_2	$\Sigma\sigma^*$	n	$\Delta\Delta H°_{355}$, kcal./mole Calcd. eq. 2	$\Delta\Delta H°_{355}$, kcal./mole Exp l.	$\Delta\Delta H°_{355}$ exptl. kcal./mole	$\Delta\Delta F°_{355}$,[b] kcal./mole Exptl.	$\Delta\Delta F°_{355}$,[b] kcal./mole "Cor.[f]"
CH_2OH	H	1.045	2	−4.3	−3.9[a]	...	...	...
H	H	0.980	0	−4.9	−5.2[a]	−5.1	−5.0	−4.9
$RO_2C(CH_2)_2$[e]	H	.750	2	−3.5	−3.5[c]	...	...	...
$H_2C{-}CH{-}CH_2$	H	.620[d]	2	−3.1	−3.0[a]	−2.6	−2.3	−1.8
$H_2C{-}CH{-}(CH_2)_2$	H	.535	2	−2.9	−2.7[a]	...	...	...
CH_3	H	.490	3	−2.4	−2.5[a]	−2.1	−1.4	−1.9
C_2H_5	H	.390	2	−2.6	−2.7[a]	−2.7	−2.0	−2.5
n-C_3H_7	H	.375	2	−2.6	−2.6[a]	−2.5	−1.8	−2.3
n-C_4H_9	H	.360	2	−2.5	−2.6[b]	−2.5	−1.9	−2.4
n-C_5H_{11}	H	.360	2	−2.5	−2.5[a]	−2.5	−1.8	−2.3
i-C_4H_9	H	.365	2	−2.5	−2.5[b]	−2.7	−2.7	−2.7
neo-C_5H_{11}	H	.325	2	−2.4	−1.9[a]	...	...	...
i-C_3H_7	H	.300	1	−2.8	−2.7[a]	−2.2	−2.1	−2.1
s-C_4H_9	H	.280	1	−2.8	−2.8[b]	−2.6	−1.8	−1.8
t-C_4H_9	H	.190	0	−3.0	−2.7[a]	−2.9	−2.7	−2.7
RO_2CCH_2[e]	CH_3	.710	5	−2.1	−2.0[c]	...	...	...
CH_3	CH_3	.000	6	+0.1	(0.0)[a]	(0.0)	(0.0)	(0.0)
C_2H_5	CH_3	− .100	5	−0.1	0.0[b]	−0.1	+1.3	+0.8
n-C_3H_7	CH_3	− .115	5	−0.1	0.0[b]	+0.1	+0.4	+0.4
i-C_3H_7	CH_3	− .190	4	−0.3	−0.2[b]	+0.5	0.0	0.0
C_2H_5	C_2H_5	− .200	4	−0.3	0.0[b]	−0.1	−0.1	−0.1

[a] Ref. 1; $\Delta H°_{365}$ for *trans*-butene-2 is −27.6 kcal. [b] Ref. 12. [c] Ref. 11. [d] The σ^* value for $CH_3CH{=}CHCH_2$ was used. [e] Average value for seven different esters; mean deviation ±0.8 kcal./mole. [f] The values of $\Delta\Delta H°_{355}$ and $\Delta\Delta F°_{355}$ differ by terms involving partition functions for translational, rotational and vibrational motions. (*Cf.* ref. 18, pp. 563–564): $\Delta\Delta H° - \Delta\Delta F° = RT^2\,[\mathrm{d}(\ln \pi Q)/\mathrm{d}t] + RT \ln (\pi Q)$; $(\pi Q) = \frac{q_P q_{R_0Y}}{q_{P_0} q_{RY}}$, where q's are partition functions for the substances involved in reactions I and II and generalized by the notation: $RY + P_0 \rightleftarrows R_0Y + P$. The similarity of products and reactants in reaction I or II suggests that the partition functions will be nearly the same for products and reactants, *i.e.* $(\pi Q) \cong 1$, except that in a number of cases the "symmetry numbers" which enter into rotational partition functions (*cf.* ref. 23, p. 296) will be different. These "symmetry numbers" have no effect on $\Delta\Delta H°$ but they may alter $\Delta\Delta F°$ appreciably. The effect is calculated readily and can be subtracted from the observed values of $\Delta\Delta F°$. For olefin hydrogenation the resulting "corrected" values of $\Delta\Delta F°_{355}$ are generally more nearly equal to corresponding $\Delta\Delta H°$ values than the uncorrected $\Delta\Delta F°_{355}$ values.

TABLE II

DEVIATIONS FROM EQ. 2 FOR *cis*- AND VICINALLY SUBSTITUTED ETHYLENES AND CYCLIC OLEFINS

Olefin	$\Delta\Delta H°_{355}$,[a] kcal./mole	$\Delta\Delta H°_{355}$ calcd. eq. 2 kcal./mole
	−1.0	+0.1
	−0.8	+0.1
	+1.0	+5.2
	−0.4	−0.3
	+0.7	−0.1[b]
	−1.0	−0.3[c]

[a] Data of ref. 10. [b] Calculated value is based on σ^* for methylethylethylene. [c] Calculated value is based on $\sigma°$ for diethylethylene.

been omitted from the correlation. The data for these compounds appear to be unreliable. The original authors report doubt as to whether equilibrium was established in these cases. It was also suspected that side reactions, *e.g.*, polymerization and acetal formation, may have been involved.[15]

TABLE III

CORRELATION OF FREE ENERGIES OF HYDROGENATION OF ALDEHYDES AND KETONES ($R_1R_2C{-}O$) BY EQ. 2[a]

Substituents R_1	R_2	$\Sigma\sigma^*$	n	$\Delta\Delta F°_{333}$, kcal./mole Calcd. eq. 2	Exptl.
CH_3	H	+0.490	3	−4.2	−4.4
i-C_4H_9	H	+ .365	2	−3.9	−4.2
t-C_4H_9	H	+ .190	0	−3.9	−3.8
CH_3OCH_2	CH_3	+ .520	5	−3.3	−2.8
$(C_6H_5)_2CH$	CH_3	+ .405	4	−3.2	−2.4
$C_6H_5CH_2$	CH_3	+ .205	5	−1.3	−0.5
CH_3	CH_3	.000	6	+0.6	(0.0)
C_2H_5	CH_3	− .100	5	+0.7	+0.3
Cyclo-C_6H_{11}	CH_3	− .150	4	+0.5	+0.6
i-C_3H_7	CH_3	− .190	4	+0.7	+0.3
t-C_4H_9	CH_3	− .300	3	+0.9	+0.4
$C_6H_5CH_2$	$C_6H_5CH_2$	+ .430	4	−3.2	−4.0
C_2H_5	C_2H_5	− .200	4	+0.8	+0.9
n-C_3H_7	n-C_3H_7	− .230	4	+1.0	+1.4
n-C_4H_9	n-C_4H_9	− .260	4	+1.2	+1.4
i-C_4H_9	i-C_4H_9	− .250	4	+1.1	+1.3
i-C_3H_7	i-C_3H_7	− .380	2	+0.9	+1.4

[a] "Symmetry numbers" corrections of $\Delta\Delta F°_{333}$ (*e.g.*, those given in Table I) are small (on the order of experimental uncertainty), and therefore "corrected" $\Delta\Delta F_{333}$ values are not included in Table III.

(15) R. M. Elofson, Ph.D. Thesis, University of Wisconsin, 1944.

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α,β-Unsaturated substituents are not included in the correlation because of expected conjugation effects. The difference between the free energies calculated by eq. 2 and the observed values for such system are taken as measures of the energies of conjugation stabilization in the aldehyde or ketone (*cf.* paper III[9]).

Discussion and Conclusions

In accord with expectations based upon the greater electron demand made by the sp^2 than the sp^3 valence state, the correlation of the enthalpies and free energies of hydrogenation by eq. 2 provides evidence of an appreciable polar contribution to these thermodynamic properties.

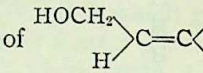
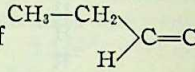
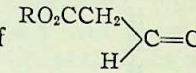
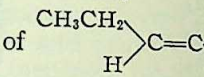
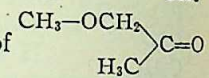
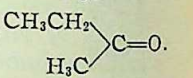
The hydrogenation of aldehydes and ketones is much more favored by electron-withdrawing substituents ($\rho^* = -6.39$) than is the hydrogenation of olefins ($\rho^* = -2.41$). This result is reasonably attributed to a significant contribution from the form $>C^+—O^-$ which makes a carbonyl carbon atom more electron deficient than those of the olefin C–C double bond. The magnitude of the ρ^* values as well as that of the difference between them is perhaps larger than expected but since a quantitative theory for prediction of ρ^* values has not been developed further comment is unwarranted.

In contrast to the marked difference in susceptibilities (ρ^*) of the thermodynamic properties of hydrogenation to inductive electron-releasing power of substituent groups, the hyperconjugation parameter, h, is the same within the combined uncertainties for olefins ($h = 0.44 \pm 0.05$) as for aldehydes and ketones ($h = 0.54 \pm 0.06$). This result is in line with other evidence (*cf.* paper III) which indicates that the resonance stabilization in these systems is much less susceptible to electron demand at the reaction center than is stabilization by inductive electron-release.[9] The availability of an open orbital for conjugation or hyperconjugation appears to be the important variable contributing to resonance stabilization.

The empirical parameter, h, measures the hyperconjugation stabilization due to a single α-H atom in an olefin, aldehyde or ketone in kcal./mole since the effect on the hydrogenation equilibrium is assumed to be associated entirely with the unsaturated state.

Kreevoy and Eyring have recently adopted a model for theoretical consideration of hyperconjugation. Their results are in approximate accord with the values of the h parameter and the linear dependence of hyperconjugation energy on the number of α-hydrogen atoms.[16]

While the correlations of eq. 1 and 2 provide no apparent evidence of C–C hyperconjugation, it is quite probable that such interactions exist. Evaluation of the effects due to such interaction requires more critical data than are presently available.

Dewar and Pettit have recently suggested that enthalpies of hydrogenation of olefins (and several similar reactions) can be explained without involving the concept of hyperconjugation.[17] From certain simplified theoretical considerations, these authors conclude that all olefins having the general formula $H_2C=CH(CR_1R_2R_3)$ should have a characteristic enthalpy of hydrogenation, as should olefins of the given general formula $(R_1R_2R_3C)CH=CH(CR_4R_5R_6)$, etc. However, this conclusion is not in accord with available data, unless the R groups are confined to alkyl groups. Thus, the hydrogenation of  is 1.2 kcal. more exothermic than that of  , and the hydrogenation of  is 2.0 kcal. more exothermic than that of  . The free energy of hydrogenation of  is 3.1 kcal. more negative than that of  .

According to eq. 2 these differences are due to polar contributions to the thermodynamic properties.

The near constancy of the enthalpies of hydrogenation for a given structural type with substitution of only *alkyl groups* is typical of a number of similar observations. In terms of eq. 1 and 2, which consistently describe the behavior of other types of substituents, this constancy results from an approximate cancellation of opposed polar and hyperconjugation effects of the *alkyl groups*.

An interesting feature of the correlation of the free energies of hydrogenation of the carbonyl compounds by eq. 2 is that the classical distinction between aldehydes and ketones is not required. In terms of eq. 2, the more positive free energy of reduction displayed by a ketone than the corresponding aldehyde results from the greater electron-releasing power of alkyl groups (than a hydrogen atom) through both inductive and hyperconjugative interactions with the carbonyl group.

The effects of α,β-saturated substituents on rates and equilibria for a number of other reactions are correlated by eqs. 1 and 2. These reactions are of such character that hyperconjugation effects are expected and it is reasonable that steric effects should be nearly constant within the reaction series. Unfortunately, the available data do not cover either a wide enough range in the polarities of the substituent groups or in hyperconjugation effects to provide a convincing test of eq. 1 or 2. Examples are summarized in Table IV. Reaction series 1 and 2 of Table IV have been previously correlated (less precisely) with σ^* values alone.[18,19]

It was noted earlier that the effects of substituents on the enthalpies of hydrogenation of olefins at 0°K are also correlated satisfactorily by eq. 2. Evidence is thus provided that the thermodynamic

(16) M. M. Kreevoy and H. Eyring, THIS JOURNAL, **79**, in press (1957).

(17) M. J. S. Dewar and R. Pettit, *J. Chem. Soc.*, 1625 (1954).

(18) R. W. Taft, Jr., in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 607, reaction 3 of Table IX.

(19) A. Streitwieser, Jr., THIS JOURNAL, **78**, 4935 (1956).

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TABLE IV

REACTION SERIES CORRELATED BY EQ. 1 OR 2

Reaction	Equation	Ref.
1. Ionization of carboxylic acids, RCO_2H, H_2O, 25°	$\log (K/K_0) = (1.72)\sigma^* + (n - 3)(-0.08)$[a]; K_0, ionization constant for acetic acid	*Cf.* ref. 18
2. Rate of solvolysis of *t*-carbinyl chlorides $R(CH_3)_2CCl$, aq. ethanol, 25°	$\log (k/k_0) = (-3.40)\sigma^* + (n - 3)(0.25)$[b]; k_0, rate constant for *t*-butyl chloride	*Cf.* ref. 19
3. Rate of solvolysis of 3-substituted 1,1-dimethylprop-2-ynyl chlorides, $RC{\equiv}C(CH_3)_2CCl$, aq. ethanol, 25°	$\log (k/k_0) = (-3.79)\sigma^* + (n - 3)(0.45)$[c]; k_0, rate constant for $CH_3C{\equiv}C(CH_3)_2CCl$	20
4. Vapor phase hydrogenation of substituted acetylenes, $R_1C{\equiv}CR_2$, 355°K.	$\Delta\Delta H°_{335} = (-5.53)(\sigma^*) + (n - 6)(0.59)$[d]; $\Delta H°_0$, enthalpy of hydrogenation of dimethylacetylene	12, 21

[a] Mean deviation of calcd and observed values ± 0.05 log units for 18 acids covering a range of 3.75 log units. [b] Mean deviation of calcd. and observed values ± 0.18 log units for 12 compounds covering a range of 3.8 log units. [c] Mean deviation between calcd. and observed values ± 0.05 log units for 5 compounds covering a range of 3.3 log units. [d] Mean deviation been calculated and observed values ± 0.2 kcal./mole for 8 compounds covering a range of 9.5 kcal./mole.

properties are good estimators of potential energy terms.[22]

For hydrogenation of aldehydes and ketones, $\Delta\Delta H°$ values are not generally available. However, $\Delta\Delta F°_{333}$ values for acetaldehyde and methyl ethyl ketone, −4.4 and +0.3 kcal./mole, respectively, may be compared with corresponding $\Delta\Delta H°_{355}$ values determined directly in the vapor phase,[10] −3.4 and +0.2 kcal./mole, respectively. The nature of the agreement lends support to the conclusion that the $\Delta\Delta F°_{333}$ values are significant measures of potential energies.

Equations 1 and 2 provide evidence that polar and hyperconjugation effects contribute independently (at least approximately) to the free energies. This conclusion bears an analogy to first order perturbation theory, which gives the following relationship.[23]

$$E = E_0 + \lambda_n \int \psi_0^* H_n \psi_0 d\tau$$

In this equation E_0 is the energy of the unperturbed system, λ_n is a parameter characteristic of the perturbation n, ψ_0 is the eigenfunction of the unperturbed system, and H_n is an operator characteristic of perturbation n. E is the energy of the slightly perturbed system. If more than one kind of perturbation is made, E is obtained from the sum of independent small perturbation energies. Since the effects with which eq. 1 and 2 deal are in the order of 0–10 kcal./mole, while bond energies are of the order of 50–100 kcal./mole, the assumption of the independent character of polar and hyperconjugation terms is apparently equivalent to the use of first order perturbation theory.

Calculation of Parameters Giving Best Fit of Data to Eq. 2.—The values of ρ^* and h giving best fit of the experimental data to eq. 2 have been obtained from the generalized equations of Anderson and Bancroft.[24] Pavelich has set these equation into a form convenient for determining best fit of data to an equation (*e.g.*, eq. 2) in two variables.[25]

Acknowledgment.—The comments and criticisms of Profs. J. W. Baker and Andrew Streitwieser, Jr., in the preparation of this manuscript are gratefully acknowledged.

(20) A. Burawoy and E. Spinner, *J. Chem. Soc.*, 3752 (1954).
(21) J. B. Conn, G. B. Kistiakowsky and E. A. Smith, THIS JOURNAL, 61, 1868 (1939).
(22) *Cf.* ref. 18, p. 660, 665.
(23) H. Eyring, J. Walter and G. E. Kimball, "Quantum Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 95.
(24) R. L. Anderson and T. A. Bancroft, "Basic Statistical Theory and Analysis of Experimental Models by Least Squares," McGraw-Hill Book Co., Inc., Chap. 14, New York, N. Y., 1952.
(25) W. A. Pavelich, Ph.D. Thesis, The Pennsylvania State University, June, 1955; W. A .Pavelich and R. W. Taft, Jr., THIS JOURNAL, in press.

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[CONTRIBUTION FROM THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

The Evaluation of Inductive and Resonance Effects in Reactivity. III. Extra Resonance Energies of Conjugation[1]

BY MAURICE M. KREEVOY AND ROBERT W. TAFT, JR.

RECEIVED JANUARY 25, 1957

The extra resonance energies of conjugation of α,β-unsaturated substituents in aldehydes, ketones and mono- or *trans*-disubstituted ethylenes have been evaluated by correcting the observed free energies and enthalpies of hydrogenation for polar and hyperconjugation effects. The results show the following systematic relationships to structure: (1) substitution of an α,β-unsaturated substituent at a C–C or C–O double bond leads to about 6 kcal. of extra resonance energy. This figure has been found to hold for a wide variety of α,β-unsaturated substituents within which resonance varies markedly, *e.g.*, $CH_3CH{=}CH-$, $C_6H_5CH{=}C-$, C_6H_5-, $-\overset{H}{\overset{|}{C}}{=}O$, $-\overset{O}{\overset{\|}{C}}-OC_2H_5$. (2) Substitution of two α,β-unsaturated substituents at the $>C{=}O$ bond, or *trans* in the $-C{=}C-$ system, leads to about 11 kcal. of extra resonance energy. (3) The extra resonance energy of mono-conjugation of an α,β-unsaturated substituent is approximately ten times greater than that of hyperconjugation by an α-hydrogen atom. All of these structural relationships are correlated by theoretical calculations based upon the LCAO–MO method. The extra resonance energies of conjugation for the transition states for the acid-catalyzed hydrolysis of diethylacetals and ketals are evaluated and discussed. Some applications to rates of addition of carbonyl compounds are discussed.

In papers I and II, the effects of unconjugated (α,β-saturated) substituents, R, on (1) the acid-catalyzed rates of hydrolysis of diethyl acetals and ketals, $R_1R_2C(OC_2H_5)_2$; (2) the enthalpies of hydrogenation of gaseous *trans*-substituted ethylenes, $\begin{matrix} R_1 \\ H \end{matrix}\!\!>\!C{=}C\!<\!\!\begin{matrix} H \\ R_2 \end{matrix}$, and (3) the free energies of hydrogenation of aldehydes and ketones $R_1R_2C{=}O$, were shown to follow the equation[2]

$$\Delta\Delta F^\circ \text{ (or } \Delta\Delta H^\circ, \text{ or } \Delta\Delta F^\ddagger) = (\Sigma\sigma^*)\rho^* + (\Delta n)h \quad (1)$$

The effects of α,β-unsaturated substituents on the thermodynamic properties deviate from eq. 1 in the direction expected for extra resonance stabilization in the conjugated system.[2] In the present paper these deviations are considered in detail.

We define a thermodynamic property conjugation effect parameter ($\Delta\Delta F_\psi$, for example) by the relationship

$$\Delta\Delta F_\psi = \Delta\Delta F^\circ - (\Sigma\sigma^*)\rho^* - (\Delta n)h \quad (2)$$

The utility of this definition depends upon the degree of approximation attending the following assumptions: (1) the substituent effect on the thermodynamic property ($\Delta\Delta F^\circ$, for example) is equal to the sum of independent polar, hyperconjugation and conjugation ($\Delta\Delta F_\psi^\circ$) effects[3]; (2) the polar and hyperconjugation effects are evaluated by the terms $(\Sigma\sigma^*)\rho^*$ and $(\Delta n)h$, respectively; and (3) the steric effects of substituents are constant within the reaction series.

The polar effect susceptibility parameter, ρ^*, and the hyperconjugation parameter, h, are determined for each reaction series by the substituents which do not have α,β-unsaturation (*cf.* papers I and II). The fact that the effects of α,β-saturated substituents of markedly varying steric requirements are successfully correlated by eq. 1—without the inclusion of a steric effect term—strongly suggests that steric effects specific to α,β-unsaturated substituents are small.

Polar effects are implied to make important contributions to the thermodynamic properties for α,β-unsaturated substituents since σ^* values are appreciably more positive (electron-withdrawing) for this type of substituent than for the methyl group (for example, $\sigma^* = 0.600$ for C_6H_5 and 0.360 for $CH_3CH{=}CH-$), and ρ^* values of large magnitude have been established.[2]

The quantity $[(\Sigma\sigma^*)\rho^* + (\Delta n)h]$ may be regarded by the present treatment as the effect on the thermodynamic property expected for the hypothetical α,β-unsaturated substituent without conjugation stabilization. It is apparent from eq. 2 that the conjugation effect parameter is obtained as the difference between the observed and this hypothetical value of the substituent effect on the thermodynamic property.

Each of the reaction series treated in papers I and II (and in this paper) involves a state for which the reaction center is saturated. In accord with the usual convention that conjugation and hyperconjugation interactions are considered to be negligible at saturated centers,[4] the conjugation effect parameter obtained from eq. 2 may be taken as a measure of the extra resonance energy of conjugation between substituent and unsaturated center involved in each reaction.

Although the conjugation energies derived by eq. 2 are rough because of the approximations listed above, the results (given in Tables I, II and III) are obtained from a reasonable extension suggested by earlier correlations and interpretations of reactivity. It will be shown in this paper that the results are uniquely more systematic and self-consistent than earlier estimates. The results are also reasonably correlated by calculations from simple molecular orbital theory.

(1) The work herein reported was carried out on Project NR055-328 between the Office of Naval Research and The Pennsylvania State University. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) (a) M. M. Kreevoy and R. W. Taft, Jr., THIS JOURNAL, **77**, 5570 (1955); (b) R. W. Taft, Jr., and M. M. Kreevoy, *ibid.*, **79**, 4011 (1957).

(3) This same model has been employed earlier by P. B. D. De la Mare (*J. Chem. Soc.*, 1602 (1952)) and also L. Bateman and J. I. Cunneen (*ibid.*, 2283 (1951)), in procedures for empirically calculating enthalpies of hydrogenation. However, these authors were unable to deal adequately with polar effects and, as a result, their resonance parameters are unrelated to those reported in this paper.

(4) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N.Y., 1955, p. 152.

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TABLE I

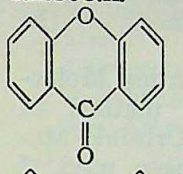
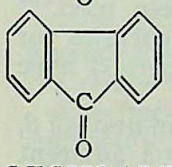
EXTRA RESONANCE ENERGY OF CONJUGATION FROM ENTHALPIES OF HYDROGENATION OF GASEOUS OLEFINS[1]

Compound	$\Delta\Delta H°_{355}$,[g] kcal./mole	$(\Sigma\sigma^*)\rho^* + (\Delta n)h$	$\Delta\Delta H_\psi$, kcal.	ΔE_ψ, kcal.
Monoconjugated				
$CH_3CH{=}CHCHO$[h]	+2.4	−4.9[a]	7.3	6.6 (0.49 β)
$C_6H_5CH{=}CH_2$[h]	−1.0[b]	−5.3	4.3	5.8 (.43 β)
$CH_2{=}CHCH{=}CH_2$[h]	+0.8[c]	−4.3[d]	5.1	6.3 (.47 β)
$CH_3CH{=}CHCH{=}CH_2$[h]	+3.7[e]	−1.8	5.5	6.3 (.47 β)
$CH_3CH{=}CHCO_2R$[i]	−0.4	−6.1[f]	5.7	6.6 (.49 β)
$C_2H_5CH{=}CHCO_2R$[i]	+0.1	−6.3[f]	6.4	6.6 (.49 β)
Diconjugated				
$C_6H_5CH{=}CHCO_2CH_3$[f]	+2.9	−8.9	11.8	12.8 (.95 β)
$C_6H_5CH{=}CHC_6H_5$[j]	+7.0	−5.5	12.5	12.6 (.93 β)
$C_2H_5O_2CCH{=}CHCO_2C_2H_5$[j]	−2.2	−12.3[f]	10.1	13.4 (.99 β)
Other				
$C_6H_5CH{=}CHCH{=}CHC_6H_5$[j,k]	+10.8	−8.3	19.1	19.4 (1.40 β)

[a] σ^* value of +1.65 used for −CH=O group. [b] $\Delta\Delta H°_{355}$ value obtained by subtracting value for hydrogenation of ethylbenzene from that for complete hydrogenation of styrene. [c] $\Delta\Delta H°_{355}$ value obtained by subtracting the value for hydrogenation of 1-butene from that for complete hydrogenation of 1,3-butadiene. [d] σ^* value of +0.360 used for $HC{\equiv}C-$ group. [e] $\Delta\Delta H°_{355}$ value obtained by subtracting the value for hydrogenation of 1-pentene from that for complete hydrogenation of 1,3-pentadiene. [f] σ^* value of +2.000 used for $-CO_2C_2H_5$ group. [g] $\Delta H°_{355} = -27.6$ kcal./mole for standard of comparison, *trans*-butene-2. [h] M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky, E. A. Smith and W. E. Vaughan, THIS JOURNAL, 59, 831 (1937); 60, 440 (1938); J. B. Conant and G. B. Kistiakowsky, *Chem. Revs.*, 20, 181 (1937). [i] E. Schjånberg, *Z. physik. Chem.*, 179A, 39 (1937). The values quoted are average values for six esters of the general formula $CH_3CH{=}CHCO_2R$ and for seven esters of the general formula $C_2H_5CH{=}CHCO_2R$. The mean deviations from the average value are ±0.6 and ±0.7 kcal./mole, respectively. [j] Data of R. B. Williams, THIS JOURNAL, 64, 1395 (1942), corrected to 355°K. and the vapor phase by G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 80. [k] The tabulated values pertain to the sum of successive hydrogenations of the two non-benzenoid double bonds. Effectively this compound provides a triconjugated system. [l] The conjugation effect parameters, $\Delta\Delta H_\psi$, are obtained from the equation, $\Delta\Delta H°_{355} - [(\Sigma\sigma^*)\rho^* - (\Delta n)h]$, using values of $\rho^* = -2.41$ and $h = 0.44$ given in paper II,[2b] and the available data[h-j] on the gas phase enthalpies of hydrogenation of conjugated *trans*-substituted ethylenes. The enthalpies of hydrogenation of α,β-saturated cyclic and *cis*-substituted ethylenes do not follow eq. 1.[2b] Therefore, no *cis* or cyclic conjugated olefins have been included in Table I since eq. 2 is of questionable applicability.

TABLE II

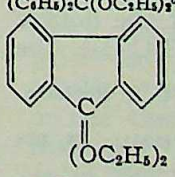
EXTRA RESONANCE ENERGY OF CONJUGATION FROM FREE ENERGIES OF HYDROGENATION OF ALDEHYDES AND KETONES[g]

Compound	$\Delta\Delta F°_{338}$,[a] kcal./mole	$(\Sigma\sigma^*)\rho^* + h(\Delta n)$, kcal./mole	$\Delta\Delta F_\psi$, kcal./mole	ΔE_ψ, kcal./mole
Monoconjugated				
$CH_3CH{=}CHCHO$	−3.0	−8.1	5.1	6.6 (0.49 β)
$C_6H_5CH{=}CHCHO$	−2.6	−8.4	5.8	7.0 (.52 β)
$C_6H_5COCH_3$	−3.1	−10.2	7.1	5.9 (.44 β)
$C_6H_5COC_2H_5$	+0.6	−5.4	6.0	5.9 (.44 β)
$C_6H_5CO\text{-}n\text{-}C_3H_7$	+0.6	−5.3	5.9	5.9 (.44 β)
$C_6H_5CO\text{-}i\text{-}C_3H_7$	+0.8	−5.2	6.0	5.9 (.44 β)
$C_6H_5CO\text{-}n\text{-}C_4H_9$	+0.2	−5.3	5.5	5.9 (.44 β)
$C_6H_5CO(CH_2)_3C_6H_5$	+0.6	−5.1	5.7	5.9 (.44 β)
$C_6H_5CO(CH_2)_2C_6H_5$	+0.7	−6.1	6.8	5.9 (.44 β)
$C_6H_5COCH_2C_6H_5$	+0.4	−6.5	6.9	5.9 (.44 β)
$C_6H_5COCH_2OCH_3$	−0.3	−7.3	7.0	5.9 (.44 β)
$(CH_3)_3CCOCHO$	−3.8	−9.3	5.5	5.9 (.44 β)
$CH_3COCO_2C_2H_5$	−5.3	−11.3[b,c]	6.0	5.9 (.44 β)
$CH_3COCO_2i\text{-}C_3H_7$	−7.8	−14.4[d]	6.6	5.9 (.44 β)
$C_6H_5COC(CH_3)_3$	−7.8	−14.4[d]	6.6	5.9 (.44 β)
$C_6H_5COCH(OCH_3)C_6H_5$	−1.8	−5.1	3.3	5.9 (.44 β)
$C_6H_5COCH(OCH_3)_2$	−3.2	−11.2	8.0	5.9 (. 44 β)
	−3.8	−12.9[e]	9.1	5.9 (.44 β)
Diconjugated				
$C_6H_5COC_6H_5$	+0.1	−10.9	11.0	11.2 (.83 β)
	+0.3	−10.9[f]	11.2	12.6 (.93 β)
	+0.6	−10.9[f]	11.5	11.1 (.82 β)
$C_6H_5COCO_2\text{-}i\text{-}C_3H_7$	−7.0	−19.8[d]	12.8	11.2 (.83 β)

[a] From ref. 5; standard of comparison is $(CH_3)_2C{=}O$. [b] Calculated on the basis of reduction of the faster reacting ketone carbonyl group. [c] Value of $\sigma^* = +1.35$ used for the −C=O group. [d] Value of $\sigma^* = +2.00$ used for $CO_2C_2H_5$ and $CO_2\text{-}i\text{-}C_3H_7$ groups. [e] Value of $\sigma^* = 1.00$ used for $CH(OCH_3)_2$ group. [f] Value of $\Sigma\sigma^* = +1.200$ used, as for two phenyl substituents. [g] The conjugation effect parameters, $\Delta\Delta F_\psi$, are obtained from the equation, $\Delta\Delta F_\psi = \Delta\Delta F°_{333} - [(\Sigma\sigma^*)\rho^* + (\Delta n)h]$, using the values of $\rho^* = -6.39$ and $h = 0.54$ in paper II,[2b] and the available data on the substituent effects on free energy taken from the work of Adkins, *et al.*[5] (which was carried out in dilute toluene solutions at 60°). Cyclic α,β-unsaturated substituents have not been treated (for the reason given in the previous section), except in the cases of fluorenone and xanthone. The latter compounds do not appear to involve much bond deformation, and the systems are planar for both the ketone and the alcohol.

TABLE III

EXTRA RESONANCE ENERGY OF CONJUGATION IN THE TRANSITION STATES FOR THE ACID-CATALYZED HYDROLYSIS OF DIETHYL ACETALS AND KETALS[a]

Compound	$k_1^{25°}$, l. mole sec.$^{-1}$	$\Delta\Delta F^{\ddagger}_{298}$, kcal./mole	$(\Sigma\sigma^*)$ $(+4.91) + (\Delta n) (-0.73)$	$-\Delta\Delta F^{\ddagger}_\psi$, kcal./mole
Monoconjugated				
$CH_2CH{=}CHCH(OC_2H_5)_2$[a]	2.98×10^2	0.55	7.85	7.3
$C_6H_5CH{=}CHCH(OC_2H_5)_2$[a]	1.52×10^2	0.95	8.10	7.1
$C_6H_5CH(OC_2H_5)_2$[a]	7.07	2.77	9.77	7.0
$p\text{-}NO_2C_6H_4CH(OC_2H_5)_2$[b]	1.12×10^{-1}	6.59	13.60[c]	7.0
$C_6H_5C(C_2H_5)(OC_2H_5)_2$[b]	7.40×10	1.38	5.40	4.0
Diconjugated				
$(C_6H_5)_2C(OC_2H_5)_2$[b]	3.27×10^{-1}	4.58	10.31	5.7
	4.38	3.06	10.31[d]	7.3

[a] Data of paper I, ref. 2a. The standard of comparison is acetonal, $k_2 = 7.52 \times 10^2$. [b] New data, *cf.* Experimental. [c] The value of σ^* for the $p\text{-}NO_2C_6H_4$ is taken as the sum of the σ^* for C_6H_5 plus the Hammett σ value for $p\text{-}NO_2$, *i.e.*, $\sigma^* = +1.38$. [d] The value of $\Sigma\sigma^*$ taken as +1.200, that for two phenyl groups. [e] The conjugation effect parameters, $-\Delta\Delta F_\psi^{\ddagger}$, are obtained from the equation, $-\Delta\Delta F_\psi^{\ddagger} = \Delta\Delta F^{\ddagger}_{298} - [(\Sigma\sigma^*)(+4.91) - (\Delta n)(-0.73)]$, in accord with the results of paper I. The free energies of activation pertain to the second-order rate constants for the acid-catalyzed hydrolysis of diethyl acetals and ketals at 25.0° in 50% dioxane–water.

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The essential difference in the conjugation energies derived from eq. 2 and those estimated by earlier methods (the difference in some instances is very substantial—*Cf.* Discussion) is that an explicit basis is proposed for evaluating expected polar and hyperconjugation contributions to the thermodynamic properties. In effect, the present method is more objective than earlier ones in providing an appropriate standard of comparison on which to base the extra resonance energy of the conjugated system.

Conjugation Energies Estimated from Molecular Orbital Theory.—The Hückel method of "Linear Combination of Atomic Orbitals–Molecular Orbital" (LCAO-MO) has been used.[6-8] Several of the values of resonance energies for conjugated olefins obtained by this method have been reported previously.[9]

The resonance energies are obtained in units of β, the resonance integral for p-orbitals on adjacent carbon atoms, *i.e.*, $\int \psi_1 H \psi_2 \, d\tau = \beta$. For compounds having oxygen as part of the conjugated system, the difference between the coulomb integral for a p-orbital on carbon, $E_0^\circ = \int \psi_c \psi_c \, dT$, and on oxygen, $E_0^\circ = \int \psi_c \psi_c \, dT$, must be evaluated, as well as the resonance integral for the carbon–oxygen π bond.

Although there is considerable disagreement as to the appropriate values of these coulomb integrals,[10] the present calculations are not very sensitive to the values chosen.[11] A value of 0.5 β has been used for $E_0^\circ - E_0^c$, a value similar to that used by Jaffé (0.51 β).[12] For the resonance integral for the carbon–oxygen π bond the same value (β) as for the carbon–carbon π bond has been used. For the resonance integral for p-orbitals on carbon and on a *saturated* oxygen atom, a value of 0.5 β has been used (Jaffé has used the value 0.56 β[12]).

Using these values it was found that the calculated resonance energy arising from the conjugation of a double bond with a carbonyl group (0.49 β) is essentially unchanged if a saturated oxygen atom is attached to the carbonyl carbon (the new value is 0.47 β). Accordingly, the calculations for all ester groups were simplified by treating the group as the corresponding aldehyde.

Resonance energies were calculated in the usual manner.[13] The extra resonance energy of the conjugated system was obtained from the difference between the resonance energy of this system and that of the appropriately saturated system. That is, if the product of hydrogenation of the double bond contains unsaturation (*e.g.*, $C_2H_5C_6H_5$), the extra resonance energy of the conjugated system ($C_6H_5CH{=}CH_2$) is obtained as the difference of the resonance energies for the two systems.

Tables I and II list in parentheses values of extra resonance energies in units of β which have been calculated in this manner. Also listed, as ΔE_ψ values, are figures obtained by arbitrarily assigning to β the value 13.5 kcal./mole.

Discussion

A number of striking regularities are apparent from the empirical conjugation energies given in Tables I and II. These regularities are well illustrated by "mean" values of the extra resonance energies of conjugation for systems which we shall refer to as mono- or diconjugated (*cf.* Table IV). The conjugation number is defined as the number of α,β-unsaturated substituents substituted at the unsaturated carbon reaction center ($-\overset{\diagdown}{\underset{\diagup}{C}}{=}\overset{\diagdown}{\underset{\diagup}{C}}-$, for olefins: $>C{=}O$, for aldehyde or ketone: $>C\begin{smallmatrix}\diagup OC_2H_5^+\\ H\\ \diagdown OC_2H_5\end{smallmatrix}$, for the hydrolysis transition state).

The use of "mean" values should not be taken as an implication that individual values should necessarily conform to the mean. Instead the mean values provide a "norm" from which individual values generally do not deviate by more than 1 kcal. (*cf.* average deviations from the mean listed in Table IV). Deviations of individual values from the mean which appear to be significant are discussed below.

TABLE IV

"MEAN" VALUES OF EXTRA RESONANCE ENERGIES FOR MONO- AND DICONJUGATED OLEFINS, ALDEHYDES AND KETONES

	Olefin $\Delta\Delta H^\circ_\psi$, kcal.	Aldehyde, ketone $\Delta\Delta F_\psi$, kcal.
Monoconjugated	5.7 ± 0.8	6.2 ± 0.5
Diconjugated	11.5 ± 0.9	11.6 ± 0.6

Monoconjugation of an aliphatic carbon–carbon double bond, a phenyl group, a cinnamyl group, an aldehyde carbonyl group, or ester carbonyl group with a carbonyl carbon all give rise to nearly the same value of $\Delta\Delta F_\psi$ (*cf.* Tables II and IV). In turn mono-conjugation of these same groups with a carbon–carbon double bond gives rise to nearly the same value of $\Delta\Delta H_\psi$ (*cf.* Tables I and IV). The mean value for the extra resonance energy resulting from monoconjugation with the C=C group is essentially the same (perhaps only slightly less) than that for the C=O group (in spite of the very large difference in the susceptibility to polar effects of the hydrogenation of olefins, $\rho^* = -2.41$ and of carbonyl compounds $\rho^* = -6.39$). *We may thus draw the important generalization that the extra resonance energy of conjugation of the two double bonds in these systems is approximately independent of the nature of these double bonds.*

Secondly, the extra resonance energy resulting from diconjugation is nearly the sum of the monoconjugation energies produced by the groups individually. For example, fluorenone, xanthone and benzophenone give essentially the same value for $\Delta\Delta F_\psi$,

(5) H. Adkins, R. M. Elofson, A. G. Rossow and C. C. Robinson, THIS JOURNAL, **71**, 3622 (1949).

(6) E. Hückel, *Z. Physik*, **70**, 204 (1931); **72**, 310 (1931); **76**, 628 (1932).

(7) H. Eyring, J. Walter and G. E. Kimball, "Quantum Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 254.

(8) C. A. Coulson, "Valence," Oxford at the Clarendon Press, 1953, p. 238.

(9) *Cf.* ref. 8, p. 235.

(10) *Cf.* ref. 8, p. 244, and ref. 12.

(11) The insensitivity of resonance energy calculations to the values of the various coulomb integrals has been noted previously by N. Muller, L. W. Rickett and R. S. Mulliken, THIS JOURNAL, **76**, 4770 (1954), and H. H. Jaffé, ref. 12.

(12) H. H. Jaffé, *J. Chem. Phys.*, **20**, 279 (1952).

(13) *Cf.* ref. 8, p. 239.

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and this is only slightly less than twice the mean $\Delta\Delta F_\psi$ value for monoconjugation (*cf.* Tables II and IV).

A third striking regularity is revealed by a comparison of the extra resonance energies of monoconjugation with the corresponding monohyperconjugation parameters, h, obtained in papers I and II.[3] The ratio of these two parameters, as may be seen in Table V, is essentially constant (approximately 10 to 1) for each reaction series. Thus the polar correction of observed substituent effects, which is the essence of the treatment in the papers of this series, has removed the objection noted earlier that hyperconjugation energies based upon observed substituent effects are unreasonably large compared to the conjugation energies.[14] We conclude from the above figures that hyperconjugation is truly second order compared to conjugation.

TABLE V

COMPARISON OF MEAN ENERGIES OF MONOHYPERCONJUGATION AND MONOCONJUGATION

	Hydrolysis transition state	Olefin	Aldehyde, ketone
Hyperconjugation parameter, h, kcal./mole	0.73 ± 0.08	0.44 ± 0.05	0.54 ± 0.06
Monoconjugation parameter, kcal./mole	7.0 ± 0.1	5.5 ± 0.9	6.6 ± 0.6

The constancy of the ratio of conjugation to hyperconjugation parameters constitutes a limited linear resonance energy relationship. The assumption used in papers I and II that the total hyperconjugation effect is obtained approximately as the product of the number of α-hydrogen atoms times a fixed hyperconjugation parameter, h, for a single α-H atom finds support in the present results, namely, in the fact that the much larger extra resonance energies for monoconjugation also contribute approximately additively to give the extra resonance energy of diconjugation.

The values of the extra resonance energy of conjugation given in Tables I, II and III in general support the basis of eq. 2, *i. e.*, that these resonance energies are independent (within approximately 1 kcal.) of the polarity and the number of α-hydrogen atoms in the substituent groups. The few apparent exceptions are discussed individually in later sections of the discussion. For the acetal hydrolysis transition states, the $-\Delta\Delta F_\psi^{\ddagger}$ values are essentially the same (7.1 kcal.) for benzacetal, cinnamacetal, crotonacetal and *p*-nitrobenzacetal, in spite of the fact that the σ^* values for the substituent groups involved vary from +0.850 to +1.870, and reaction rates vary by more than four powers of ten.

The importance of the polar and hyperconjugation contributions to the enthalpies of hydrogenation of olefins is illustrated by comparing some typical values of the extra resonance energy of conjugation obtained from eq. 2 with corresponding values obtained by Wheland by earlier methods[15] (Table VI).

(14) K. S. Pitzer, "Quantum Chemistry," Prentice–Hall, Inc., New York, N. Y., 1953, p. 184.
(15) Ref. 4, p. 80, 85.

ADDED IN PROOF.—Compare, however, with "obsd. conjugation Energies" calculated by A. Lofthus, THIS JOURNAL, 79, 24 (1957), based upon the method of R. S. Mulliken and R. G. Patt, *J. Chem. Phys.*, 19, 1271 (1951).

TABLE VI

COMPARISON OF EXTRA RESONANCE ENERGIES OF CONJUGATION (KCAL./MOLE) OBTAINED BY THE PRESENT AND EARLIER METHODS

Substance	From eq. 2	From Wheland
1,3-Butadiene	5.1	3.5
Styrene	4.3	0.9
Crotonaldehyde	7.3	2.4
trans-Methylcinnamate	11.8	2.9
trans-Ethyl fumarate	10.1	−2.2

It is apparent from Table VI that none of the generalizations given above may be derived from the earlier values of conjugation energies.

The importance of polar and hyperconjugation contributions to the effects of α,β-unsaturated substituents on the free energies of hydrogenation of aldehydes and ketones is even more dramatic (*cf.* Table II). Thus, for example, the free energy of hydrogenation of benzophenone is within 0.1 kcal. of that of acetone, and the value for benzaldehyde is actually 3.1 kcal. more negative than that of acetone. In themselves, these values provide no evidence of resonance stabilization (a positive value is required) in the conjugated system. Yet the values of $\Delta\Delta F_\psi$ derived from eq. 2 using these values of $\Delta\Delta F^\circ$ are in accord with the generalizations concerning the relationship of extra resonance energies of conjugation to structure.

The simple molecular orbital calculations predict each of the three generalizations established from the empirical values of the extra resonance energy of conjugation obtained from eq. 2. Arbitrarily assigning β the value of 13.5 kcal./mole (a figure somewhat lower than that used to correlate resonance energies of aromatic hydrocarbons) the extra resonance energies of 28 conjugated olefins, aldehydes and ketones, with values varying from 4 to 19 kcal./mole, are obtained with an average difference of less than 1 kcal. between the theoretical and the empirical values. The agreement is considered satisfactory in light of the simplicity of both the theoretical model and of eq. 2.

The accord between the empirical and theoretical values of resonance energies of conjugation establishes a consistency between resonance theory and a theory of structural effects on reactivity which unifies diverse effects of structure on reactivity (compare corresponding values of $\Delta\Delta H^\circ$, $\Delta\Delta F^\circ$ and $\Delta\Delta F_\psi^{\ddagger}$ of Tables I, II and III). These results provide further evidence that steric effects in the thermodynamic properties of olefin, aldehyde and ketone hydrogenations are small, as well as in the formation of the hydrolysis transition state from the acetal or ketal.[2]

Although direct steric effects appear to be absent or small, an indirect one, steric inhibition to resonance in the conjugated systems, apparently is definitely present. "Compression energies," of course, always reduce "observed" values of resonance energies.[16] The value of $\Delta\Delta F_\psi$ for pivalo-

(16) *Cf.* ref. 8, p. 236.

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phenone (3.3 kcal.) is significantly less than the mean value for monoconjugated aldehydes or ketones (6.2 kcal.) indicating (in accord with molecular models) an appreciable steric inhibition of phenylcarbonyl conjugation by the adjacent *t*-butyl group. Judging from the generalizations reached above steric inhibition appears to be small or at least roughly constant in other olefins and carbonyl compounds of Tables I and II.

Steric inhibition of resonance in the transition state also apparently accounts for the lower value of $-\Delta\Delta F_\psi^\ddagger$ for the diethyl ketal of propiophenone (4.0 kcal.) than the mean value (7.1 kcal.) for monoconjugated acetal transition states. The values of $\Delta\Delta F_\psi^\ddagger$ for fluorenone and benzophenone diethyl ketals (7.2 and 5.7 kcal., respectively) are markedly less than that estimated by the additivity rule (14 kcal.). The additivity rule appears applicable since the L.C.A.O.–M.O. calculated extra resonance energy for the $(C_6H_5)_2CH^+$ ion is, for example, nearly twice that for the $C_6H_5CH_2^+$ ion. Two explanations may be invoked to account for the exceptional behavior. First, steric inhibition of resonance in the transition state may reduce the value. Second, there is a probable breakdown in the implied parallelism between corresponding free energies of the hydrolysis transition state and that of the intermediate oxocarbonium ion.[2a] With increased resonance stabilization of the carbonium ion, the transition state is reasonably expected to resemble the carbonium ion less and become more like the conjugated acid of the ketal, which is insensitive to resonance stabilization by conjugation.

The $\Delta\Delta F_\psi$ values obtained from eq. 2 for the hydrogenation of three carbonyl compounds (in addition to pivalophenone) do not fit the general picture: (the values for these compounds were not used in obtaining the "mean" values given in Table IV) dimethoxyacetophenone, phenylmethoxyacetophenone and diethyloxomalonate. The value obtained for the latter (23 kcal.) is appreciably greater than for comparable compounds (and is not listed in Table II). Elofson has noted that these compounds are very slow to equilibrate, and has suggested that the equilibrium value reported for the oxomalonic acid ester may be in error for this reason or because of an interfering side reaction.[17] The marked deviation of these compounds from normal behavior suggests that the reported $\Delta\Delta F°$ values may be in considerable error.

Applications.—The figure of five to seven kcal./mole for the extra resonance energy of monoconjugation has useful application to the effect of structure on reactivity in a number of carbonyl addition reactions. The polar and steric effects of a phenyl group or a hydrogen atom substituted at the carbonyl carbon atom have been found to be very similar in the rates of esterification or hydrolysis of esters.[18] It may be proposed that this close similarity in polar and steric effects holds for other carbonyl addition reactions. Further, it is reasonable that the transition states for most such reactions are nearly saturated at the carbonyl reaction center. It is expected then that the free energy of activation for the conjugated reactant will be increased by an amount nearly equal to its extra resonance energy of conjugation.[18]

Making these assumptions, the difference in the free energy of activation for the corresponding phenyl and hydrogen substituted carbonyl compound, $\Delta F_{C_6H_5}^\ddagger - \Delta F_H^\ddagger$ ($= -2.303RT \log (k_{C_6H_5}/k_H)$), should be approximately 6 kcal./mole. Values of the relative rates $k_{C_6H_5}/k_H$ predicted in this manner and corresponding observed values are listed in Table VII for several reactions. The agreement is considered to support satisfactorily the assumptions made.

Apparently, the extra resonance energy of conjugation of ethyl benzoate (or benzoic acid) is perhaps only slightly less than that of acetophenone (or benzaldehyde, etc.) in spite of the substantial resonance within the ester group itself. This is a result in accord with the M.O. calculation cited earlier, which indicates that the extra resonance energy of conjugation of an α,β-unsaturated carboxylic acid or ester is 0.02 β (0.3 kcal./mole) lower than that of the corresponding unsaturated aldehyde.

In this connection it is also of interest that the extra resonance energy of conjugation of an α,β-unsaturated carboxylate ion is calculated by the M.O. method to be 0.06 β (0.8 kcal./mole) lower than that of the α,β-unsaturated acid. Branch and Calvin,[19] and Taft,[20] by methods which parallel those described in this paper, have estimated from relative ionization constants in water at 25° that the extra resonance energy of conjugation is about one kcal. less in the carboxylate ion than in the acid. The fact that the reduction is small indicates that the energies of the various resonances are roughly independent of one another (only a small saturation effect is shown), in accord with the approximate additivity generalization given earlier. Further, the linear resonance energy relationship, namely, that the hyperconjugation effect of a single α-hydrogen atom is about one-tenth that of the conjugation effect of an α,β-unsaturated substituent is followed, for in paper II the hyperconjugation effect on the free energy of ionization is given as 0.1 kcal. per α-hydrogen atom.[2b]

Applying to a carboxylic ester the linear resonance energy relationship, the hyperconjugation parameter, h, for the free energy of activation for the hydrolysis of the ester may be estimated to be about 0.5 kcal. On this basis, and the model applied above to conjugation effects on rate, the rate of hydrolysis of an acetate ester ($n = 3$) at 25° is expected to be retarded by about 1.1 powers of ten compared to the corresponding formate ($n = 0$). This figure is very close to the factor usually observed for the relative rates of acid-catalyzed hydrolysis or esterification (of the corresponding acids).[21] Taft has ascribed this factor to a steric effect and included it within the steric

(17) R. M. Elofson, Ph.D. Thesis, University of Wisconsin, 1944.

(18) R. W. Taft, Jr., in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 670.

(19) G. E. K. Branch and M. Calvin, "Theory of Organic Chemistry," Prentice–Hall Book Co., Inc., New York, N. Y., 1941, p. 243.

(20) *Cf.* ref. 18, p. 656.

(21) *Cf.* R. W. Taft, Jr., This Journal, 74, 2729 (1952).

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TABLE VII

PREDICTED AND OBSERVED RELATIVE RATES

Reaction	Conditions	Ref.	$k_{C_6H_5}/k_H$ Obsd.	Predicted
$RCO_2C_2H_5 + H_2O \rightarrow RCO_2H + C_2H_5OH$	Acid-cat. hydrolysis, 60% (vol.) aq. acetone, 25°	[a]	8.3×10^3	2.5×10^4
$RCO_2C_{10}H_{19} + CH_3OH \rightarrow RCO_2CH_3 + C_{10}H_{19}OH$	Methoxide ion catalysis CH_3OH, 30°	[b,c]	7.6×10^3	2.0×10^4
$R(CH_3)C{=}O + H_2NNHCONH_2 \rightarrow R(CH_3)C{=}NNHCONH_2 + H_2O$	Phosphate buffer *p*H 7, 25°	[d,e]	1.5×10^4	2.5×10^4

[a] W. B. S. Newling and C. N. Hinshelwood, *J. Chem. Soc.*, 1357 (1936). [b] R. W. Taft, Jr., M. S. Newman and F. H. Verhoek, THIS JOURNAL, 72, 4511 (1950). [c] W. A. Pavelich and R. W. Taft, Jr., unpublished results. [d] J. B. Conant and P. D. Bartlett, THIS JOURNAL, 54, 2881 (1932). [e] F. P. Price, Jr., and L. P. Hammett, *ibid.*, 63, 2387 (1941).

substituent constant, E_s.[22] The present results suggest, therefore, that the steric substituent constants include small but significant contributions from hyperconjugation effects. However, in accord with the basic arguments of the method,[23] these effects are not expected to alter Taft's polar substituent constants, σ^*.

Experimental

The technique for measuring acetal and ketal hydrolysis rates and the preparation of the 50% dioxane–water mixture have been previously described.[24] Propiophenone diethyl ketal,[25] b.p. 104° (14 mm.), benzophenane diethyl ketal,[26] m.p. 49–50.5°, and fluorenone diethyl ketal,[27] m.p. 78–80°, are all previously known compounds.[28] The diethyl acetal of *p*-nitrobenzaldehyde, a slightly yellow liquid with b.p. 162–163° (14 mm.), is not a previously reported compound.

Anal. Calcd. for $C_{11}H_{15}O_4N$: C, 58.67; H, 6.67; N, 6.22. Found[29]: C, 58.31; H, 6.56; N, 6.47.

(22) R. W. Taft, Jr., THIS JOURNAL, 74, 3120 (1952).
(23) *Cf.*, ref. 18, p. 588.
(24) M. M. Kreevoy and R. W. Taft, Jr., THIS JOURNAL, 77, 3146 (1955).
(25) E. L. Beals and F. A. Gilfillan, *J. Am. Pharm. Assoc.*, 25, 426 (1936).
(26) Mack, *J. Chem. Soc.*, 69, 990 (1887).
(27) Smedley, *ibid.*, 87, 4252 (1905).
(28) All boiling points are uncorrected, melting points are corrected.
(29) Microanalysis was performed by Clark Microanalytical Laboratory, Urbana, Illinois.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTH CAROLINA]

The Temperature Dependence of Ion Pair Dissociation Constants. I. *o*-Dichlorobenzene[1]

BY H. L. CURRY AND W. R. GILKERSON

RECEIVED MARCH 18, 1957

The conductances of tetraethylammonium, tetra-*n*-propylammonium and tetra-*n*-butylammonium picrates in *o*-dichlorobenzene have been determined as a function of concentration at 25, 35, 45, 55 and 65°. The ion pair dissociation constants and limiting equivalent conductances have been calculated at each temperature. The variation of the dissociation constant with temperature is discussed with reference to Bjerrum's theory and also a recent one proposed by one of the authors.

As has been pointed out in a recent critical review of the ion pair concept,[2] Bjerrum's[3] theory of ion pair dissociation qualitatively but not quantitatively describes experimental results that have been obtained. His theory gives

$$K^{-1} = \frac{4\pi N}{1000}(\epsilon^2/DkT)^3\, Q(b) \qquad (1)$$

where $b = \epsilon^2/aDkt$. Here, N is Avogadro's number, ϵ is the unit of charge and a is the distance of closest approach, being an empirical parameter. While a, as determined experimentally, is generally larger than the charge separation as determined from dipole moment measurements, it may also be much smaller.

The dependence of K upon the dielectric constant at constant temperature has been investigated in solvent mixtures and while the agreement is quite good for the water–dioxane system,[4] a discrepancy has been observed[5] in nitrobenzene–carbon tetrachloride mixtures. Further, specific solvent effects have been shown when results in ethylene chloride ($D = 10.23$), ethylidene chloride ($D = 9.90$) and *o*-dichlorobenzene ($D = 9.93$) are compared at 25°.[6] The ratio of the dissociation constant of Et_4NPi in ethylene chloride to that in *o*-dichlorobenzene is 13.9, far too large to be accounted for on the basis of the difference in dielectric constant alone. There are very few data available concerning K as a function of temperature. An early study in anisole,[7] while in qualitative agreement with Bjerrum's equation, is of doubtful validity due to approximations that were necessary to evaluate the K values. Studies in ethylene chloride, ethylidene chloride and propylene chloride have been reported.[8] It seemed, in view of the scarcity of information, of interest to extend such studies to other solvents, using salts which have been the subject of previous examina-

(1) Presented at the Southwide Chemical Conference, Memphis, December 6, 1956.
(2) C. A. Kraus, *J. Phys. Chem.*, 60, 129 (1956).
(3) N. Bjerrum, *Kgl. Danske Videnskab. Selskab.*, 7, No. 9 (1926).
(4) R. M. Fuoss and C. A. Kraus, THIS JOURNAL, 55, 1019 (1933).
(5) H. Sadek and R. M. Fuoss, *ibid.*, 76, 5905 (1954).
(6) F. Accascina, E. L. Swarts, P. L. Mercier and C. A. Kraus, *Proc. Natl. Acad. Sci.*, 39, 917 (1953).
(7) G. S. Bien, R. M. Fuoss and C. A. Kraus, THIS JOURNAL, 56, 1860 (1934).
(8) (a) K. H. Stern and A. E. Martell, *ibid.*, 77, 1983 (1955); (b) J. R. Donoghue and J. B. Kinsey, *ibid.*, 77, 2615 (1955).

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tion. The choice of solvent, *o*-dichlorobenzene, was made on the basis of its dielectric constant and the previously noted abnormally low K values found at 25°. The salts chosen were tetraethylammonium, tetra-*n*-propylammonium and tetra-*n*-butylammonium picrate.

Experimental Solvent.—*o*-Dichlorobenzene (Eastman red label) was run through a column packed with silica gel and then fractionally distilled on a three-foot column packed with glass helices. Only the middle fraction was retained. This was received in a two-liter flask protected from moisture by a calcium chloride tube. The purified solvent was stored in a dry-box under an atmosphere of nitrogen. The specific conductivity of the solvent was 3×10^{-10}/ohm cm. at 25°.

Salts.—The hydroxide corresponding to each salt was prepared from the available halide (Eastman) by metathesis with freshly prepared silver oxide in alcoholic suspension. The alcoholic hydroxide was then neutralized with picric acid. The resulting picrates were recrystallized from ethanol three times and dried *in vacuo*. The melting points were: Et_4NPi, 259–261°; Pr_4NPi, 117.0–117.4°; Bu_4NPi, 89.8°.

Conductance Measurements.—The bridge used was similar to that of Eisenberg and Fuoss.[9] Several cells were used, all similar to those of Kraus and co-workers. Cell constants were determined by intercomparison, using a 0.01 D KCl solution[10] as standard. The solutions were made up by weight in an atmosphere of nitrogen, and dilutions of stock solutions were made similarly. The solutions in the cells were stirred continuously, using a Teflon-covered magnet as agitator. The oil-filled thermostat was maintained at the stated temperature within 0.005°. Temperatures were determined with a resistance thermometer calibrated by the National Bureau of Standards. Two series of conductance measurements were run for each salt at each temperature. These agreed within 0.2%.

Physical Constants.—The solvent density and viscosity were determined at each temperature. The latter was measured in a Cannon–Fenske viscometer. The values obtained are listed in Table I.

TABLE I

PHYSICAL CONSTANTS OF *o*-DICHLOROBENZENE

t, °C.	d, g./cc.	$\eta \times 10^2$	D
25.00	1.3007	1.2778	9.939
35.00	1.2885	1.1036	9.571
45.00	1.2784	0.9701	9.202
55.00	1.2674	.8669	8.836
65.00	1.2558	.7720	8.515

The dielectric constant, D, of the solvent was measured, using a General Radio type 716-C capacitance bridge, with a type 716-P4 guard circuit. All measurements were made at 100 kc. The dielectric cell was similar in design to that of Sadek and Fuoss.[5]

Results

The equivalent conductances found for each concentration are given for Et_4NPi at 35° in Table II.

TABLE II

EQUIVALENT CONDUCTANCE OF Et_4NPi AT 35° IN *o*-DICHLOROBENZENE

$C \times 10^4$, M	Λ	$C \times 10^4$, M	Λ
2.419	12.30	0.4998	22.22
2.030	13.22	.4490	22.95
1.453	15.07	.3251	25.37
0.9683	17.50	.2605	27.30
.8246	18.58	.1873	29.69

(9) H. Eisenberg and R. M. Fuoss, THIS JOURNAL, **75**, 2914 (1953).
(10) G. Jones and B. C. Bradshaw, *ibid.*, **55**, 1780 (1933).

The conductance–concentration data were treated by the method of Shedlovsky[11] both graphically, to determine any inconsistencies, and by least squares to get the best values of Λ_0 and K. The latter are shown in Table III. The values at 25° agree well

TABLE III

VALUES OF Λ_0 AND K IN *o*-DICHLOROBENZENE

Salt	Λ_0 25°	35°	45°	55°	65°
Et_4NPi	47.8	51.56	55.91	65.40	71.38
Pr_4NPi	40.3		50.31	58.33	66.14
Bu_4NPi	36.8	41.45	46.26	53.88	60.53
	$K \times 10^5$ 25°	35°	45°	55°	65°
Et_4NPi	1.23	1.389	1.511	1.343	1.362
Pr_4NPi	1.64		1.710	1.568	1.467
Bu_4NPi	1.92	1.983	2.021	1.820	1.715

with those determined elsewhere.[6] However, the K values found in this work are somewhat higher. A close comparison of the data shows that our Λ are slightly larger than those of Accascina. This may be due to some discrepancy in cell constants. Of more intrinsic interest is the variation of K with temperature. In the cases cited previously[8] for ethylene chloride and ethylidene chloride, the K values decreased with rising temperature. Here, however, they are seen to increase to a maximum at 45° and then decrease.

Values of Bjerrum's parameter, a, have been calculated from eq. 1 and appear in Table IV. It may be seen that these show a definite increase with temperature, except for the last two temperatures, where they remain constant. In ethylene chloride (ref. 8a), a for Bu_4NPi may be calculated at 5.69, 25 and 35° to be 5.83, 5.77 and 5.85 Å., respectively.

TABLE IV

VALUES OF BJERRUM'S PARAMETER, $a \times 10^8$ CM., IN *o*-DICHLOROBENZENE

t, °C.	Et_4NPi	Pr_4NPi	Bu_4NPi
25	3.92	4.03	4.10
35	4.01		4.18
45	4.05	4.11	4.19
55	4.05	4.12	4.20
65	4.09	4.13	4.19

If one is to allow a to vary with temperature, then it would be expected to increase as the temperature increases. However, there seems to be a closer correlation between a and the product DT. In *o*-dichlorobenzene, DT decreases with T; in ethylene chloride, DT increases; in ethylidene chloride, DT again decreases. The a values vary in an inverse manner. A recent study of Et_4NPi in a series of phthlate esters as solvents[12] shows the same trend. Kraus has shown[13] that a values calculated from Bjerrum's are much larger than the separation of charge as determined from the dipole moments of salts in benzene.

An expression for K which takes into account specific ion–solvent interaction has been derived

(11) T. Shedlovsky, *J. Franklin Inst.*, **225**, 739 (1938).
(12) C. M. French and N. Singer, *J. Chem. Soc.*, 1424 (1956).
(13) J. A. Geddes and C. A. Kraus, *Trans. Faraday Soc.*, **32**, 585 (1936); C. S. Hooper and C. A. Kraus, THIS JOURNAL, **56**, 2265 (1934).

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recently[14] on the basis of Kirkwood's free-volume theory of solutions. This theory gives

$$K = \left(\frac{2\pi\mu kT}{h^2}\right)^{3/2} (gv\sigma) \exp\left(-\frac{E_s}{RT} - \frac{N\epsilon^2}{aRDT}\right) \quad (2)$$

where $\mu = m_+m_-/(m_- + m_+)$, m_i being the mass of the ith ion, $E_s = E_- + E_+ - E_\pm$, E_i being the interaction energy between the ith ion and surrounding solvent, $E_\pm$ being the energy of interaction between solvent and the ion pair, the factor $(gv\sigma) = (g_+g_-v_+v_- \sigma_+\sigma_-)/(g_\pm v_\pm \sigma_\pm)$, g_i being the rotational and vibrational contribution to the partition function of the ith particle, v_i being the free volume available to the ith particle and σ being a factor varying between unity for solids and e for gases. If values of K as a function of T are available, the parameters $(gv\sigma)$ and E_s, characteristic of the solvent and salt, can be chosen so as to give a value of a, the distance of closest approach, which is independent of the temperature and solvent. Using the data obtained in this study, such calculations have been made. The results are shown in Fig. 1, where values of $F = \log K - 3/2 \log T + E_s/T$ are plotted *vs.* $1/DT$. The values of a, E_s and $(gv\sigma)$ for each salt are given in Table V. At this point, no generalizations can be made concerning the variations in E_s and $(gv\sigma)$, due to their complex nature and the lack of more extensive data. It may be said that the free-volume theory accounts for the observed facts as well as Bjerrum's theory. Certainly a constant value of a is more satisfying than one which varies in an unpredictable manner. It may be noted that the a value for Bu_4NPi in this solvent is the same as that found[14] in the solvents ethylene chloride, ethylidene chloride, propylene chloride and anisole. This work is being extended to other solvent systems in an effort to accumulate data which may lead to some correlation for the values of E_s and $(gv\sigma)$ thus obtained.

TABLE V

SALT PARAMETERS IN *o*-DICHLOROBENZENE

Salt	$a \times 10^8$, cm.	E_s, cal./mole	$(gv\sigma)$, cm.^{3}
Et_4NPi	1.59	4800	1.2×10^{-13}
Pt_4NPi	1.88	2880	2.4×10^{-17}
Bu_4NPi	2.51	1903	2.2×10^{-19}

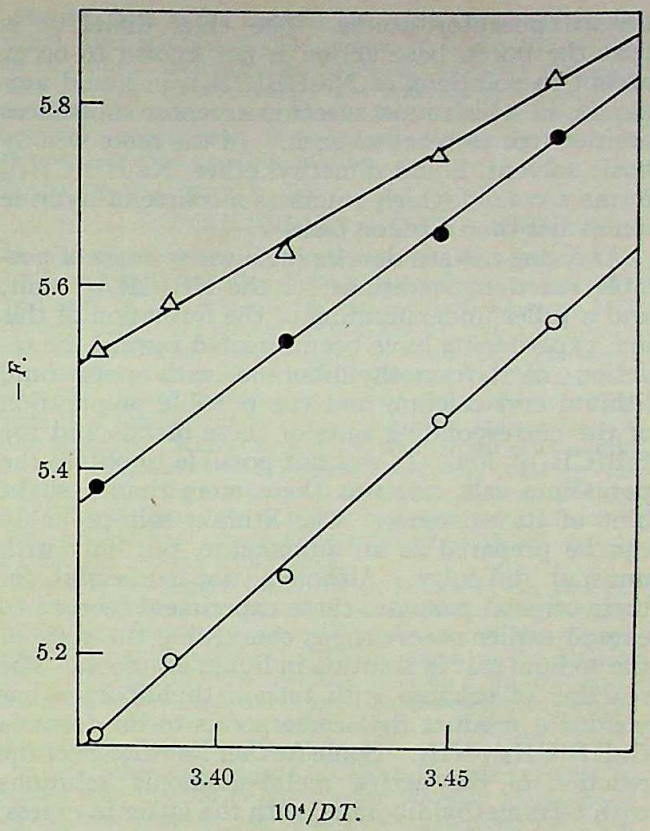

Fig. 1.—Values of the function F are plotted *vs.* $1/DT$ for the salts Et_4NPi (open circle), Pr_4NPi (closed circle, $F + 1.00$) and Bu_4NPi (triangle, $F + 1.500$) in *o*-dichlorobenzene.

Acknowledgment.—We wish to acknowledge the support of this work by contract with the United States Army, Office of Ordnance Research.

COLUMBIA, S. C.

(14) W. R. Gilkerson, *J. Chem. Phys.*, **25**, 1199 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF HOUSTON]

Further Studies of the Boron Bases: $CaHB(CH_3)_2$[1]

BY GEORGE W. CAMPBELL, JR.[2]

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The reaction of tetramethyldiborane with calcium in liquid ammonia has produced the new compound $CaHB(CH_3)_2 \cdot NH_3$. The Lewis base activity of this salt is lower than that of the comparable sodium salt, as indicated by its inactivity toward $B(CH_3)_3$ in liquid ammonia. $CaHB(CH_3)_2 \cdot NH_3$ reacted with tetramethyldiborane, to produce NH_3-soluble $Ca[H_2B(CH_3)_2]_2 \cdot XNH_3$ and a second product, formulated in speculation as "$Ca[B(CH_3)_2]_2$." In methyl ether solution, $CaHB(CH_3)_2 \cdot NH_3$ reacted with SiH_3Cl to product SiH_4 in equal molal quantity. Cryoscopic and tensiometric measurements of $CaHB(CH_3)_2$ in NH_3 indicate the monomer state of the salt in solution. The identity of $CaHB(CH_3)_2 \cdot NH_3$ as a salt of the $HB(CH_3)_2^-$ anion is argued on the basis of chemical evidence. Attempts to prepare the lithium and potassium salts of the $HB(CH_3)_2^-$ have suggested that the lithium salt can be prepared, but only hinted that the potassium salt can exist. Neither salt was obtained in a state approaching purity. However, these studies have provided a possible explanation for the contamination of the sodium salt with $B(CH_3)_3$, and the formation of $B(CH_3)_3$ in the reactions of tetramethyldiborane with potassium and with sodium in liquid ammonia.

The discovery of the boron base $Na_2HB(CH_3)_2$ and its ability to establish a firm B–B bond by reacting with trimethylboron in liquid ammonia[3] implies the possibility of forming previously unknown bonds by an electron-donor action of boron

(1) Presented in part at the 129th National Meeting of the American Chemical Society, Dallas, Texas, April 12, 1956.

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(3) A. B. Burg and G. W. Campbell, Jr., THIS JOURNAL, **74**, 3744 (1952).

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toward acceptor atoms. The chief difficulty is that the boron base action is not known to occur except in solutions of $Na_2HB(CH_3)_2$ in liquid ammonia, in which most electron-acceptor substances are not free to react as such. In the more weakly basic solvent, liquid dimethyl ether, $Na_2HB(CH_3)_2$ forms a colloid which reacts as a source of hydride ion rather than a boron base.

As a step toward developing a wider range of possible reaction conditions for the $HB(CH_3)_2^-$ unit, and a fuller understanding of the formation of this ion, experiments have been directed toward the reaction of tetramethyldiborane with potassium, lithium and calcium and the possible preparation of the corresponding salts of these metals and the $HB(CH_3)_2^-$ ion. It was not possible to obtain the potassium salt, nor was there more than a slight hint of its existence. The lithium salt probably can be prepared as an ammoniate, but only with unusual difficulty. Although not successful for their original purpose, these experiments served to extend earlier observations concerning the state of the sodium salt in solution in liquid ammonia. The reaction of calcium with tetramethyldiborane has yielded a product that corresponds to the formula $CaHB(CH_3)_2 \cdot NH_3$. Some further knowledge of the reaction of the active metal–ammonia solutions with tetramethyldiborane, with the latter in excess, also was obtained.

Experimental

Materials.—The $(CH_3)_4B_2H_2$ used in these studies was prepared by the reaction of B_2H_6 with $B(CH_3)_3$.[4] It was purified by fractional condensation at −80° until the vapor tension at 0° was 48.0 mm. (literature value 48.0 mm.) prior to each use. Hydrolysis of 0.232 mmole produced 0.452 mmole of H_2 (calculated 0.464) and 0.464 mmole of $(CH_3)_2BOH$ (calculated 0.464).

Anhydrous 99.9% NH_3, purchased from the Matheson Company, was stored *in vacuo* with dissolved Na. The NH_3 was distilled from this solution for use in these experiments.

The dimethyl ether, reported to be 99.9% pure by the manufacturer, contained considerable CO_2, and required NaOH-washing before use. The purified ether had a vapor pressure of 34.0 mm. at −78.6° (literature value 34 mm.).

The SiH_3Cl was prepared by the Al_2Cl_6 catalyzed reaction of SiH_4 with HCl.[5] It was purified by distillation in the high vacuum apparatus.

The Reaction of $(CH_3)_4B_2H_2$ with Calcium in Liquid NH_3.—The addition of approximately one-half mmole of $(CH_3)_4B_2H_2$ to a liquid ammonia solution of calcium (>20 mg.), and the subsequent steps for the isolation of the product were carried out in the same manner as described for the preparation of $Na_2HB(CH_3)_2$,[3] except that the repeated treatments with trimethylamine were found to be ineffective and of no value. Also, it was found that this preparation was far less sensitive to temperature, and the reaction occurred readily and cleanly below −65°. It was further observed that a large excess of calcium was not necessary, but that the mixture required adequate mixing to prevent a local excess of $(CH_3)_4B_2H_2$, which would react with the calcium salt first formed.

After removal of the solvent NH_3, and all volatile (at 50°) components, the non-volatile product of this process, if formulated by analogy to the sodium salt, was $CaHB(CH_3)_2 \cdot NH_3$, and all attempts to remove the remaining ammonia were unsuccessful.

The hydrolysis of the product, in acid solution, produced H_2, $(CH_3)_2BOH$ and NH_3, according to the equation

$$CaHB(CH_3)_2 \cdot NH_3 + 3H_2O \longrightarrow Ca(OH)_2 + (CH_3)_2BOH + NH_3 + 2H_2 \quad (1)$$

On fourteen samples, the ratio H_2 to $(CH_3)_2BOH$ was 1.99 (calculated 2.00), and, on nine samples, the ratio of $(CH_3)_2BOH$ to Ca (determined gravimetrically) was 1.04 (calculated 1.00). The ammonia content was not constant, but always was slightly more than corresponds to the 1-ammoniate, and averaged 1.22 ± 0.26 for six samples. The average of the analyses of two weighed samples, after correcting for ammonia content, gave 41.6% Ca (calculated 48.9); 47.1% $(CH_3)_2B$ (calculated 49.9); ratio of H_2 to $(CH_3)_2B$ was 1.94 (calculated 2.00). These analyses were made on samples of 0.28 and 0.51 mmole, representing sample weights of 23 and 43 mg., respectively. It has not been possible so far to prepare larger samples of relatively pure product apparently because of the high reactivity of $CaHB(CH_3)_2 \cdot NH_3$ toward $(CH_3)_4B_2H_2$. It should be noted, however, that in two experiments, where $(CH_3)_4B_2H_2$ was carefully added in equal molal quantity to approximately 0.5 mmole of calcium, the blue color faded out after approximately 15 minutes at −75°. After removing the volatile components at temperatures up to 50°, the NH_3-soluble residue was found to be $CaHB(CH_3)_2 \cdot NH_3$ by analysis. Due to the extreme sensitivity of the product toward air or moisture, a methyl ether solution of the sample was filtered into a tube and the tube separated from the filter apparatus[3] *in vacuo*. The methyl ether was then distilled away from the sample, and the tube evacuated, removed from the vacuum line and weighed. The tube was then returned to the vacuum line for analysis of the sample, after which the clean evacuated tube was reweighed to determine the sample weight. Since the sample weight never exceeded 50 mg., and the accuracy of measurement of gas volumes was approximately 5%, the estimated accuracy of the analyses was not better than 5%.

Attempts to Prepare the Potassium Salt.—The addition of $(CH_3)_4B_2H_2$ to a liquid ammonia solution of potassium and the subsequent steps for the isolation of the salt product were carried out in the same manner as for the sodium salt,[3] with the difference that the removal of the solvent was far less difficult in this case. However, in the product most nearly approaching the expected formula "$K_2HB(CH_3)_2$," hydrolysis yielded 15% more than the calculated amount of $(CH_3)_2BOH$, 12% too much hydrogen and $B(CH_3)_3$ amounting to 0.23 mole per K_2X unit. Thus it would appear 35% of the expected $HB(CH_3)^-$ units were bonded by the electron acceptors $B(CH_3)_3$ or $HB(CH_3)_2$. In the most deviant experiment the attached $B(CH_3)_3$ amounted to 0.58 mole per K_2X unit, while $(CH_3)_2BOH$ ran 14% low and H_2 24% high—as though some $CH_3BH_2^-$ ions were taking the place of $HB(CH_3)_2^-$ ions.

Attempts to Prepare $Li_2HB(CH_3)_2$.—For the preparation of "$Li_2HB(CH_3)_2$" it was considered necessary to choose an alkali metal solvent which would not solvate the Li^+ ion so strongly as to make it impossible to isolate the desired product. For this purpose methylamine proved to be almost suitable, and certainly far better than ammonia. In the best experiment the supposed "$Li_2HB(CH_3)_2$" was hydrolyzed to give only 56% of the expected $(CH_3)_2BOH$ (based upon a lithium-analysis which might have been somewhat high), while H_2 ran only 8% high. However, no $B(CH_3)_3$ could be found in the products. Thus the disproportionation of the $(CH_3)_2BH$ evidently was important, but it differed sharply from the reactions involving sodium and potassium where the disproportionation was accompanied by methyl group migration. In this respect it is comparable to the reaction of $(CH_3)_4B_2H_2$ with calcium, for in that reaction no $B(CH_3)_3$ was ever formed either.

The Use of Methylamine to Extract the Sodium Salt.—Some advantage was found in the use of methylamine instead of dimethyl ether as a solvent for extracting $Na_2HB(CH_3)_2$ from excess sodium after the removal of the ammonia from the original reaction mixture.[3] The yields varied from 74 to 84% (based upon half the tetramethyldiborane) and the conformity to the ideal formula $Na_2HB(CH_3)_2$ was good. However, it was not possible to remove the methylamine effectively except in very small scale experiments (0.6 mmole or less), and even then a mono-amine solvate was obtained. Hence the product could be used only for chemical studies in solution, as in liquid ammonia.

Hydridic Behavior of $Na_2HB_2(CH_3)_5$.—The salt $Na_2HB_2(CH_3)_5$ reacted with SiH_3Cl in dimethyl ether to form SiH_4 as readily as the original $Na_2HB(CH_3)_2$ had done,[3] indicating that the addition of $B(CH_3)_3$ to the $HB(CH_3)_2^-$ unit had not seriously impaired the hydridic reactivity of the B–H bond.

(4) H. I. Schlesinger and A. O. Walker, THIS JOURNAL, 57, 621 (1935)
(5) Stock and Somieski, *Ber.*, 52, 695 (1919)

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The experiment was done with a sample of $Na_2HB_2(CH_3)_5$ which had been formed directly from $(CH_3)_4B_2H_2$ and sodium in liquid ammonia containing $B(CH_3)_3$. The time allowed for completion of the B–B bond was 150 minutes (at −78°); then the last of the ammonia was displaced by trimethylamine and the salt was extracted with methylamine. The sample was suspended in 2 ml. of dimethyl ether and treated with excess SiH_3Cl during 14 hours at −78°. The reaction yielded 0.59 mmole of SiH_4, while the sodium analysis indicated 0.47 mmole of the original salt, $Na_2HB_2(CH_3)_5$. A low sodium analysis and some extra B–H bonds were possible sources of the discrepancy. The recovered $B(CH_3)_3$ (0.26 mmole with the SiH_4 and 0.05 mmole more by hydrolysis of the residue) and $(CH_3)BOH$ were low, for salt residue of such reactions contains boron and methyl groups in a situation which is not yet understood.

In passing, it is worthy of note that the action of C_2H_5Cl upon $Na_2HB(CH_3)_2$ in dimethyl ether (6 days at −78°) was virtually negligible. However, there was an indication of ethane: a 3% yield (0.013 mmole) of a gas having the right volatility. At least the reaction was far slower than the conversion of SiH_3Cl to SiH_4.

Tensiometric Determination of the Molecular Weight of $CaHB(CH_3)_2$ in Solution.—Samples of the calcium salt "$CaHB(CH_3)_2 \cdot NH_3$" were prepared in a suitable bulb which could be attached to a differential manometer for the comparison of the vapor tension of the pure solvent with that of the solution. The two bulbs, one containing the solution and the other the pure solvent, were then immersed in melting chlorobenzene, thus establishing a constant uniform temperature of approximately −46°. In two experiments in liquid ammonia, the results indicated a molecular weight of 87 and 89, respectively, ±10% (formula weight 81.8) at an average molality of 0.27.[6] Although the formula weight and empirical molecular weight agree within the limits of accuracy, the results suggest the possibility of a small amount of association of solute molecules.

When liquid methyl ether was the solvent, an apparent molecular weight of 213 ± 10% was found, corresponding to an average association of 2.6 "$CaHB(CH_3)_2$" units. The clear colorless solution contained 0.50 mmole of "$CaHB(CH_3)_2$" in 1.0 g. of dimethyl ether.

Cryoscopic Determination of the Molecular Weight of the Calcium Salt in NH_3.—The apparatus used in the cryoscopic determination was described in an earlier paper.[3] By comparison with pure ammonia, it was observed that 0.0286 g. of "$CaHB(CH_3)_2$"[6] in 2.73 g. of ammonia lowered the freezing point 0.129 ± 0.006°, indicating a molecular weight value of 79 ± 4 (calculated value 81.8).

The Conductance of the Calcium Salt in NH_3.—The conductance of $CaHB(CH_3)_2$ in liquid ammonia at −70 to −75° was measured by conventional methods. The detailed results are given in Table I.

TABLE I

THE ELECTROLYTIC CONDUCTANCE OF $CaHB(CH_3)_2$ IN LIQUID AMMONIA

Sample	1	2	3
Temp., °C.	−75	−75	−70
Molarity	0.0185	0.0218	0.0272
Specific conductance (ohms^{-1})	8.1×10^{-4}	8.7×10^{-4}	1.03×10^{-3}
Molar conductance (ohms^{-1})	43.0	39.9	37.9

Samples 1 and 2 were prepared by the reaction of $(CH_3)_4B_2H_2$ with calcium (present in excess), followed by a methyl ether extraction of the sample. Sample 3 was prepared by the addition of equal molal quantities of $(CH_3)_4B_2H_2$ and Ca, in liquid ammonia.

These results would compare with an estimated 10% ionization for a uni-univalent salt in this medium, since electrolytes in liquid ammonia at −33° have molar conductances around 300 at infinite dilution. However, an accurate basis for comparison is not available since most di-divalent salts do not dissolve or ionize in liquid ammonia.

(6) In these experiments the sample weight was calculated as "$CaHB(CH_3)_2$" on the basis of the analysis of the sample, since the NH_3 content of this compound is variable, and the solvent tetrahydrofuran

The Reaction of the Calcium Salt with Chlorosilane.—A methyl ether solution of 0.45 mmole of $CaHB(CH_3)_2 \cdot NH_3$ was treated with more than an equivalent quantity of chlorosilane at −78° for 48 hours. The reaction produced 0.47 mmole of silane, and the excess chlorosilane was recovered apparently unchanged. It is suggested that the reaction proceeded according to the equation

$$2CaHB(CH_3)_2 + 2SiH_3Cl \longrightarrow \text{"}Ca[B(CH_3)_2]_2\text{"} + CaCl_2 + 2SiH_4 \quad (2)$$

The non-volatile residue from this reaction was found to be 33.6% calcium (calculated 34.3 according to eq. 10). Treatment of this non-volatile residue with aqueous HCl produced only 0.076 mmole of $(CH_3)_2BOH$, but 0.38 mmole of H_2 was produced, corresponding to a ratio of 1.6 moles of H_2 per calculated mole of "$Ca[B(CH_3)_2]_2$." The production of H_2 started rapidly, but slowed down such as to indicate that equilibrium was approached but apparently not quite attained. When the non-volatile portion of this mixture was evaporated to dryness with H_2SO_4, charring was observed indicating the presence of organic carbon, and the typical green flame-test of boron was observed. Hence it seems evident that the residue retained (CH_3)–B groups in a manner not yet understood.

Attempts to Prepare $CaHB(CH_3)_2 \cdot B(CH_3)_3$.—In two experiments $B(CH_3)_3$ was added to solutions of $CaHB(CH_3)_2 \cdot NH_3$ in liquid ammonia at −75°. In one of the experiments the results indicated $B(CH_3)_3$ added to the $CaHB(CH_3)_2 \cdot NH_3$ in the mole ratio of 0.39 to 1 in two days. This could not be repeated in the second experiment, where five days were allowed for reaction, yet no $B(CH_3)_3$ was retained by the "$CaHB(CH_3)_2 \cdot NH_3$."

In two other experiments, $(CH_3)_4B_2H_2$ was brought to reaction with calcium in liquid ammonia with an excess of $B(CH_3)_3$ also present. In these two experiments only $CaHB(CH_3)_2 \cdot NH_3$ was obtained and all of the $B(CH_3)_3$ was recovered as the sublimable $B(CH_3)_3 \cdot NH_3$. Hence it appears that the apparent addition of $B(CH_3)_3$ to $CaHB(CH_3)_2 \cdot NH_3$ was due to incomplete sublimation of the $B(CH_3)_3 \cdot NH_3$, and that no addition reaction occurred with the boron base.

The Reaction of $CaHB(CH_3)_2 \cdot NH_3$ with $(CH_3)_4B_2H_2$.—The reaction of $(CH_3)_4B_2H_2$ with $CaHB(CH_2)_2 \cdot NH_3$ in liquid ammonia produced a clear solution at −75°, but a solid precipitate was formed after 14 hours. The solid residue obtained, after removal of the solvent and all components volatile at 25°, was 28.4% Ca, and released 3.26 moles of H_2 per mole of Ca by hydrolysis (calculated for $Ca(CH_3)_4B_2H_2$; Ca 32.4%; ratio $H_2/Ca = 3.0$). Hydrolysis also produced 1.6 moles of $(CH_3)_2BOH$, but some organic carbon was retained by the non-volatile residue, since evaporation with H_2SO_4 caused charring. The analysis and properties of the non-volatile product obtained in this reaction corresponds in every respect to that produced by the reaction of Ca (in NH_3) with $(CH_3)_4B_2H_2$ when the latter was in excess, as described below.

The Reaction of Calcium with $(CH_3)_4B_2H_2$, the Latter Present in Excess.—When $(CH_3)_4B_2H_2$ was added to a Ca–NH_3 solution (mole ratio = 1.5 to 2.0) at −75°, the blue color of the metal solution faded and a milky suspension was formed which finally dissolved to produce a colorless, clear solution. After standing for several hours, a permanent precipitate was formed from the solution. In one experiment, where the mole ratio of $(CH_3)_4B_2H_2$ to Ca was 2.0, after reaction all volatile components of the mixture were removed at 25°, leaving a solid residue that was 29.6% Ca (calcd. for $Ca(CH_3)_4B_2H_2$, 32.4%) correcting for NH_3 content (mole ratio $NH_3/Ca = 0.24$). Hydrolysis of this residue produced 3.35 moles of H_2 and 1.60 moles of $(CH_3)_2BOH$ per mole of calcium. A wet combustion of this non-volatile portion of the hydrolysis mixture produced CO_2 corresponding to an additional 0.273 mole of $(CH_3)_2B$-groups, to give a total ratio of $(CH_3)_2B/Ca$ of 1.87. Hence it appears that the non-volatile solid obtained from the reaction of $(CH_3)_4B_2H_2$ with Ca corresponds approximately to the speculative formula $Ca(CH_3)_4B_2H_2$.

In three other similar experiments $(CH_3)_4B_2H_2$ and calcium (mole ratio ≧ 1.5) were brought to reaction and the solvent and all volatile products were removed at 25°, but liquid ammonia was then added to the non-volatile residue and the mixture was filtered. The NH_3-soluble product had the empirical formula $Ca[(CH_3)_2BH_2]_2 \cdot XNH_3$ (X = 1.4 to 2.4). The combustion, hydrolysis analyses, corrected for NH_3

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are as follows: Ca, 32.1% (31.8 calcd.); ratio H_2/Ca = 3.99 (4.00 calcd.); ratio R_2B/Ca = 2.04 (2.00 calcd.).

In the further experiments, where the mole ratio of $(CH_3)_4B_2H_2$ to calcium was equal to or greater than 2.5, the reaction resulted in a product that was permanently soluble in NH_3. After removal of all volatile products at 25°, the residue was readily and completely soluble in NH_3. Analysis of the product corresponded to the formula $Ca[(CH_3)_2BH_2]_2 \cdot XNH_3$.

However, when the ratio of $(CH_3)_4B_2H_2$ to calcium was 1.5, almost exactly half of the calcium was converted to $Ca[(CH_3)_2BH_2]_2$, the other half apparently forming the hypothetical $Ca[(CH_3)_2B]_2$. Thus, in one experiment, 0.622 mmole of $(CH_3)_4B_2H_2$ was added to 0.427 mmole of calcium in liquid ammonia, at −75°. The solution turned milky white, then clear within 30 minutes. After 14 hours, however, a precipitate had formed. When all volatile components were removed at 65°, it was possible to extract 0.206 mmole of $Ca[H_2B(CH_3)_2]_2$ from the residue by means of liquid NH_3. The insoluble portion produced less than 0.1 mmole of H_2 and no detectable amount of $(CH_3)_2BOH$ when treated with H_2O-HCl. Examination of the volatile components of the reaction mixture, which were removed by distillation showed that 0.26 mmole of $(CH_3)_2BNH_2$ was present. Since the total mmoles of $(CH_3)_2B$-groups added was 1.24, and 0.41 were found as Ca $[(CH_3)_2BH_2]_2$, and 0.26 as $(CH_3)_2BNH_2$, there remains 0.57 mmole to be accounted for. Due to the low volatility of polymeric $(CH_3)_2BNH_2$, especially in the presence of NH_3, it is conceivable that as much as 0.15 mmole, as an upper limit, could be lost in this analysis. Hence, it would appear that the 0.22 mmole of calcium which was not removed as $Ca[(CH_3)_2BH_2]_2$ was present as NH_3-insoluble "$Ca[(CH_3)_2B]_2$."

Discussion

The Reaction of Tetramethyldiborane with Calcium in Ammonia.—The preparation of the compound which appears to be $CaHB(CH_3)_2 \cdot NH_3$ was accomplished by condensing tetramethyldiborane on a previously prepared and frozen solution of calcium in ammonia, followed by rapid warming to −70 to −75° with thorough mixing. A second product, apparently $(CH_3)_2BHNH_3$, was decomposed thermally, *in vacuo* at 25 to 50°, and the $(CH_3)_2BNH_2$ and H_2 were removed as gases and identified. Hence, it would appear that this reaction parallels that of sodium with tetramethyldiborane,[3] and therefore it would be described by the equation

$$Ca + (CH_3)_4B_2H_2 + NH_3 \xrightarrow[NH_3(l)]{-70^\circ} CaHB(CH_3)_2 \cdot XNH_3 + (CH_3)_2BHNH_3 \quad (3)$$

This system was not as temperature sensitive as that where sodium was the active metal, nor was it necessary that there be a large excess of the active metal to avoid secondary reactions. However, the product does react with tetramethyldiborane, so the mixing of the reactants was quite critical. Based upon this equation, the calcium salt was readily obtained in 80% yield, or higher.

This new calcium salt was soluble in ammonia, dimethyl ether and diethylene-glycol dimethyl ether (diglyme). In most of the experiments dimethyl ether was used to extract this product from the excess calcium in the preparation.

Cryoscopic and tensiometric measurements on the liquid ammonia solutions of $CaHB(CH_3)_2$ clearly indicate the monomeric salt, while conductance measurements suggest some ionization, but considerably less than that indicated for the sodium salt.

In liquid methyl ether the salt formed an aggregate of approximately 2.6 "$CaHB(CH_3)_2$" units according to the vapor tension of the solution, thus apparently differing from the colloidal state of $Na_2HB(CH_3)_2$ in this medium only in the degree of aggregation.

The Chemical Properties of the Calcium Salt.—In sharp contrast to $Na_2HB(CH_3)_2$, the calcium salt did not react as a Lewis-base toward trimethylboron in liquid ammonia solution. A further attempt to cause such an addition, by bringing tetramethyldiborane to reaction with calcium in the presence of trimethylboron, in liquid ammonia, apparently produced $CaHB(CH_3)_2 \cdot NH_3$ as the only non-volatile product, yet this method did give excellent samples of $Na_2HB(CH_3)_2 \cdot B(CH_3)_3$ when sodium was the active metal.[3]

In liquid dimethyl ether chlorosilane reacted with "$CaHB(CH_3)_2$" to produce an equal molal quantity of silane.

The reaction of $CaHB(CH_3)_2$ with tetramethyldiborane (mole ratio 1:1) in liquid ammonia, produced a water clear solution which did not change visibly for 3 hours at −75°, but after 14 hours at −78° an insoluble product had formed. The analysis of the non-volatile (at 50° *in vacuo*) residue from this reaction corresponded approximately to the formula $Ca(CH_3)_4B_2H_2$, and retained a slight and probably insignificant amount of ammonia. However, a substance empirically formulated as $Ca[H_2B(CH_3)_2]_2$, could be extracted from this solid by liquid ammonia. These results suggest that the mixture consisted of nearly equal molal parts of the substance $Ca[H_2B(CH_3)_2]_2$ and the speculative, probably polymeric, salt "$Ca[B(CH_3)_2]_2$" which would compare with the substance tentatively formulated as "$NaB(CH_3)_2$" in a previous publication.[3] It should be noted further that the products of this reaction of $CaHB(CH_3)_2 \cdot NH_3$ with tetramethyldiborane appear to be identical to those obtained by the reaction of tetramethyldiborane (present in excess) with calcium in liquid ammonia.

The Nature of the Calcium Salt.—On the basis of the analyses alone, the calcium salt can reasonably be formulated as $CaHB(CH_3)_2 \cdot NH_3$ or as the amido salt $H_2NCaH_2B(CH_3)_2$. In accord with the latter postulate, the reaction of tetramethyldiborane with calcium in liquid ammonia might be written as

$$Ca + (CH_3)_4B_2H_2 + NH_3 \longrightarrow H_2NCaH_2B(CH_3)_2 + (CH_3)_2BHNH_3 \quad (4)$$

It appears also that this postulate would be in good agreement with some of the observed chemical and physical properties of this calcium salt. Hence, the failure of this compound to add trimethylboron would be expected if the $H_2B(CH_3)_2^-$ ion were present instead of the boron base, providing also that the amido ion were not available enough from the calcium salt to compete with the ammonia. Also, the moderate electrolytic conductance of the calcium salt would conform well to this interpretation.

On the other hand, the reactions of the calcium salt with tetramethyldiborane and with chlorosilane appear to favor the boron base formulation.

It should be noted that when the calcium salt was brought to reaction with an equal molal quantity of $(CH_3)_4B_2H_2$, the products of the reaction appeared to be identical to those resulting from the reaction of

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calcium metal with $(CH_3)_4B_2H_2$, when the mole ratio was 1:2, respectively. In both cases a solid mixture was produced with nearly identical composition, and approximately corresponding to the empirical formula $Ca(CH_3)_4B_2H_2$, but from which $Ca[H_2B(CH_3)_2]_2$ could be extracted. Also, if the ratio of $(CH_3)_4B_2H_2$ to calcium metal was reduced to 1.5:1, exactly half of the calcium was converted to NH_3-soluble $Ca[H_2B(CH_3)_2]_2$, the rest of the calcium apparently forming the NH_3 insoluble, apparently polymeric, substance empirically formulated to be $Ca[(CH_3)_2B]_2$. If it is assumed that the reaction of $(CH_3)_4B_2H_2$ with calcium produces the amido-salt $H_2NCaH_2B(CH_3)_2$, according to eq. 4, the formation of $Ca[H_2B(CH_3)_2]_2$ would reasonably be written as

$$(CH_3)_4B_2H_2 + 2NH_3 \longrightarrow (CH_3)_2BNH_2 + NH_4^+H_2B(CH_3)_2^- \quad (5)^7$$

$$NH_4^+H_2B(CH_3)_2^- + NH_2CaH_2B(CH_3)_2 \longrightarrow 2NH_3 + Ca[H_2B(CH_3)_2]_2 \quad (6)$$

This interpretation, however, cannot account for the fact that this reaction produced a mixture of $Ca[H_2B(CH_3)_2]_2$ and a second calcium compound "$Ca[B(CH_3)_2]_2$." In fact any reaction of $(CH_3)_4B_2H_2$ with $NH_2CaH_2B(CH_3)_2$ to form $Ca[H_2B(CH_3)_2]_2$ and $Ca[B(CH_3)_2]_2$ would require a transfer of B–H hydrogen to N–H hydrogen, which appears quite unlikely in view of the failure of ND_3 to undergo H–D exchange with diborane.[8]

On the other hand, if it is assumed that the formula $CaHB(CH_3)_2 \cdot NH_3$ represents the correct structure for this salt, the suggested reaction sequence is as

$$2CaHB(CH_3)_2 + (CH_3)_4B_2H_2 \longleftarrow 2"CaHB(CH_3)_2 \cdot HB(CH_3)_2" \quad (7)$$

$$2"CaHB(CH_3)_2 \cdot HB(CH_3)_2" \longrightarrow Ca[H_2B(CH_3)_2]_2 + "Ca[B(CH_3)_2]_2" \quad (8)$$

In this postulate, the formation of the hypothetical "$CaHB(CH_3)_2 \cdot HB(CH_3)_2$" would represent base activity of the $CaHB(CH_3)_2$, and it would further explain the ability of $(CH_3)_4B_2H_2$ to increase the solubility of $CaHB(CH_3)_2$ in NH_3. The disproportionation of this salt according to eq. 8, and probably the polymerization of the $(CH_3)_2B^-$ anion would explain the slow formation of a precipitate in the NH_3 solution. Also, since both of the products of eq. 8 would be non-volatile, the mixture would correspond, in composition, to the formula $Ca(CH_3)_4B_2H_2$.

It was also observed that additional $(CH_3)_4B_2H_2$, beyond that required by eq. 7, produced a higher percentage of the calcium as $Ca[H_2B(CH_3)_2]_2$, with a nearly quantitative conversion of calcium to the borohydride derivative when 2.5 moles of $(CH_3)_4B_2H_2$ is added to one mole of the metal. In explanation of this, it is postulated that the disproportionation of "$CaHB(CH_3)_2 \cdot HB(CH_3)_2$" in the presence of NH_4^+ and $H_2B(CH_3)_2^-$ ions[7] would reasonably occur as

$$"CaHB(CH_3)_2 \cdot HB(CH_3)_2" + NH_4^+H_2B(CH_3)_2^- \longrightarrow Ca[H_2B(CH_3)_2]_2 + NH_3HB(CH_3)_2 \quad (9)$$

The reaction of the calcium salt with chlorosilane gives further support to the boron base interpretation, since the non-volatile product of this reaction was apparently $Ca[B(CH_3)_2]_2$. Had the calcium salt been $H_2NCaH_2B(CH_3)_2$, one mole of SiH_4 would have been produced, leaving a dimethylborine group, which would not have reacted further with the chlorosilane,[9] unless it were bonded to the NH_2^- group. However, no $(CH_3)_2B^-$ polymer could have been formed without transfer of B–H hydrogen to the NH_2-group and the presence of $(CH_3)_2BH$-groups or $(CH_3)_4B_2H_2$ in the reaction products would not have escaped detection.

On the basis of these arguments, it seems likely that the new calcium salt is best interpreted as another boron base, and an analog of $Na_2HB(CH_3)_2$. However, the chemical properties of $CaHB(CH_3)_2 \cdot NH_3$ suggest a reduced, yet definite base activity, whereas the availability of the hydride ion from this salt is comparable to that of the sodium salt.

The Preparation of Salts of the $HB(CH_3)_2^-$ Ion.—It has been reported[3] that the preparation of relatively pure $Na_2HB(CH_3)_2$, by the reaction of Na–NH_3 with $(CH_3)_4B_2H_2$, required an excess of sodium. When this requirement was not met, or when an excess of $(CH_3)_4B_2H_2$ was present, a reaction occurred which always produced some $B(CH_3)_3$. Apparently the same reaction occurred also when $(CH_3)_4B_2H_2$ was added to a solution of $Na_2HB(CH_3)_2$ in liquid NH_3. In all of the attempts to prepare $K_2HB(CH_3)_2$, even with very large excesses of potassium, it was impossible to prevent this further reaction, and considerable $B(CH_3)_3$ was produced in each experiment. In contrast to the sodium and potassium reactions, in the attempts to prepare $Li_2HB(CH_3)_2$, no $B(CH_3)_3$ was produced, although $Li_2HB(CH_3)_2$ was not obtained in a state approaching purity.

The preparation of $CaHB(CH_3)_2$ is particularly noteworthy, for it has been prepared with consistently less contamination than any of the other salts of the $HB(CH_3)_2^-$ ion, and $B(CH_3)_3$ has never been found in the reaction products. Also, a nearly pure sample of $CaHB(CH_3)_2$ was prepared when neither reactant was in excess.

It appears likely that the reaction of active metals with $(CH_3)_4B_2H_2$, in liquid ammonia, first forms salts of the $HB(CH_3)_2^-$ ion plus $(CH_3)_2BH \cdot NH_3$, as indicated in eq. 3. Further reaction of the $HB(CH_3)_2^-$ ion with $(CH_3)_4B_2H_2$ can then occur under one or more of the following conditions: if the $(CH_3)_4B_2H_2$ is present in excess; if the stirring is inadequate, leading to local excesses of $(CH_3)_4B_2H_2$; if the rate of reaction of the $HB(CH_3)_2^-$ with $(CH_3)_4B_2H_2$ is rapid relative to the reaction whereby the $HB(CH_3)_2^-$ is formed. Since the results suggest that this additional reaction cannot be prevented using potassium, but is progressively easier to prevent when the reactive metals are sodium, (lithium) and calcium, respectively, it appears that the rate of reaction of the salts of $HB(CH_3)_2^-$ with $(CH_3)_4B_2H_2$ is quite dependent upon the nature of the metal ion, and particularly upon the charge density of the cation.

If it is assumed that the potassium salt of the

(7) This represents the ammoniation of tetramethyldiborane, corresponding to the ammoniation of diborane as suggested by G. W. Schaeffer, M. D. Adams and J. J. Koenig, THIS JOURNAL, **78**, 725 (1956).

(8) A. B. Burg, *ibid.*, **69**, 747 (1947).

(9) It has been shown in this Laboratory that $Ca[H_2B(CH_3)_2]_2$ reacts with chlorosilane in methyl ether solution according to the equation

$$Ca[H_2B(CH_3)_2]_2 + 4SiH_3Cl \longrightarrow CaCl_2 + 2SiH_4 + (CH_3)_4B_2H_2.$$

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boron base has some existence, then the great difficulty of avoiding contamination of the potassium salt by donor-acceptor bonding of the $HB(CH_3)_2^-$ ion to methylated borine units may be less surprising than the relative ease of making nearly pure $Na_2HB(CH_3)_2$ and $CaHB(CH_3)_2$ in the presence of the complex $(CH_3)_2BH\cdot NH_3$, for a base much stronger than ammonia as the $HB(CH_3)_2^-$ ion must be, should quickly capture methylated borine units from their ammonia complexes. Also requiring explanation is the failure of the $HB(CH_3)_2^-$ ion to react rapidly with ammonia at low temperatures removing a proton to form amide ion, as various carbon-bases do. Furthermore, it will be recalled,[3] that a relatively clean preparation of $Na_2HB(CH_3)_2$ is possible only when sodium is in large excess, as though it served in some way to block the addition of methylated borine units or ammonia to the $HB(CH_3)_2^-$ ion. Finally, it appears that the blocking of such an addition is even more effective if the metal is calcium or lithium instead of sodium.

In explanation of all these facts, it may be suggested that ammonia in the solvation sphere of a metal ion is partly replaced by the stronger boron base ion, so that one may consider the equilibrium

$$(NH_3)_xM^{+m} + HB(CH_3)_2^- \rightleftharpoons (NH_3)_yM{:}\overset{H}{B}(CH_3)_2^{(m-2)} \quad (\text{where } x > y) \quad (10)$$

to lie farthest to the right for ions of highest charge density, and at their highest concentration. Thus, the availability of the free $HB(CH_3)_2^-$ ion may be very low in the presence of much sodium ion, but considerably higher if potassium is the positive ion, or if there is no excess of sodium—conditions under which the capture of borine units by the $HB(CH_3)_2^-$ ions is hard to prevent. And with calcium or lithium as the positive ion, the electron-donor action of the $HB(CH_3)_2^-$ ion would be blocked still more effectively.

Also, it appears likely that $(CH_3)_4B_2H_2$ and possibly the partially ammoniated $(CH_3)_4B_2H_2$ are capable of providing methylated borine units for reaction with the $HB(CH_3)_2^-$ ion but that $(CH_3)_2BH\cdot NH_3$ is not able to do so, for reaction mixtures containing the boron base and $(CH_3)_2BH\cdot NH_3$ have been kept in contact as long as 36 hours at −78° without detectable reaction. This failure to react might well be attributed to the absence of a convenient mechanism, and suggests that the di-ammoniate of tetramethyldiborane is not readily converted to $(CH_3)_2BH\cdot NH_3$ and that this is not a component of the tetramethyldiborane–ammonia system.[7] This is further supported by the fact that dimethylborine ammine does not measurably react with sodium in liquid ammonia, in sharp contrast to the behavior of the diammoniate of tetramethyldiborane.

In considering the new compound, $CaHB(CH_3)_2\cdot NH_3$, it appears that the attachment of the calcium ion is quite strong, both on the basis of the chemical properties of this compound and the physical properties in solution, as indicated by the tensiometric and cryoscopic studies. It should also be noted, in this connection, that the liquid ammonia solution of $Na_2HB(CH_3)_2$ and apparently that of "$K_2HB(CH_3)_2$," (assuming by analogy that it is the product of the reaction of tetramethyldiborane with potassium in liquid ammonia) are strongly yellow and show high base activity of the $HB(CH_3)_2^-$ ion. In comparison $CaHB(CH_3)_2$ solutions are colorless and it appears that if $Li_2HB(CH_3)_2$ has existence, it is only faintly yellow in liquid ammonia, and both of the latter cases appear to have reduced base activity.

The moderate electrolytic conductance of $CaHB(CH_3)_2$ in liquid ammonia solution, however, would not appear to support the interpretation that the calcium ion is strongly bonded to the boron base. It is possible that this conductance was due to small quantities of highly conducting impurities such as calcium metal or the dimethylborohydride salt. On the other hand, it should be recognized that the solubilities of ionic di-divalent salts in liquid ammonia are generally very low, suggesting that any ionization of $CaHB(CH_3)_2$ would reasonably involve extensive solvation or association. Also, the results of the tensiometric studies suggested that some association was likely since the apparent molecular weight in solution was higher than the formula weight, although within the estimated margin of accuracy. Hence it is suggested, in speculation, that the production of ions necessary for electrolytic conductance might well have proceeded according to the equation

$$2CaHB(CH_3)_2 + xNH_3 \rightleftharpoons (CH_3)_2BHCaHB(CH_3)_2^- + Ca^{++}\cdot NH_3 \quad (11)$$

It should be noted that the $HB(CH_3)_2^-$ ion is not free on either side of this equation, thus meeting the requirement that the base activity be low. Also, this equilibrium should not affect appreciably the properties of the solution that are based upon the vapor pressure of the solvent.

The Reactions of Active Metals with Tetramethyldiborane, when the Latter Is in Excess.—In previous studies the liquid ammonia reaction of sodium with tetramethyldiborane, when the mole ratio of reactants was less than 2:1, respectively, gave results that were not readily understandable.[3] However, the similar system involving calcium instead of sodium appears to be more easily interpreted in terms of equations 3, 7, 8 and 9 above, and these results suggest a reasonable interpretation for the reactions of all of the active metals with tetramethyldiborane in liquid ammonia.

In considering the reactions observed with sodium and potassium, it is significant that the only observed difference from those involving calcium was that trimethylboron always appeared among the reaction products. In this connection it is also of interest that the reaction of lithium aluminum hydride with trimethylboron according to Wartik and Schlesinger produced dimethylaluminum hydride and lithium monomethylborohydride, but apparently none of the dimethylborohydride.[10] Therefore it appears likely that the dimethylborohydride disproportionates quite easily, and it may well be that the sodium and potassium salts of this anion are incapable of stable existence. In con-

(10) T. Wartik and H. I. Schlesinger, THIS JOURNAL, 75, 835 (1953).

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trast, lithium appears to behave more like calcium in that no trimethylboron has been found among the reaction products, and the dimethylborohydrides of both of these metals have been isolated.

The explanation of the differences in the apparent stabilities of these salts is not obvious, although the lattice energies of the calcium and lithium salts would certainly be greater than those of the sodium and potassium salts, and the lattice energy may well serve to stabilize the dimethylborohydride ion in the solid state. In solution it could be postulated that ion aggregation, also dependent upon change density, would serve to stabilize the calcium and lithium salts.

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[CONTRIBUTION FROM THE CHEMISTRY DIVISION, ARGONNE NATIONAL LABORATORY]

Kinetics of Reactions Involving Neptunium(IV), Neptunium(V) and Neptunium(VI) Ions in Sulfate Media[1]

BY J. C. SULLIVAN, DONALD COHEN AND J. C. HINDMAN

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The rates of the forward and reverse reactions involved in the equilibrium Np(IV) + Np(VI) $\rightleftarrows$ 2Np(V) have been measured in sulfate solution. Both forward and reverse reactions involve multiple parallel reaction paths. The rate of the forward reaction can be expressed in the form $R = k_0'[Np^{+4}][NpO_2^{++}][H^+]^{-2} + \{k_1[NpSO_4^{++}][NpO_2^{++}] + k_2[NpSO_4^{++}][NpO_2SO_4]\}\{k_3[H^+]^{-2} + k_4[H^+]^{-3}\}$. At 25° and $\mu = 2.2$, $k_0' = 2.69$ mole l.$^{-1}$ min.$^{-1}$, $k_1 = 4.27$ mole^{-1} l. min.$^{-1}$, $k_2 = 7.12$ mole^{-1} l. min.$^{-1}$, $k_3 = 3.6$ mole^2 l.$^{-2}$ and $k_4 = 1.7$ mole^3 l.$^{-3}$. The rate of the disproportionation reaction may be represented by $R = \{k_5[NpO_2^+]^2[HSO_4^-] + k_6[NpO_2^+]^2[HSO_4^-]^2\}\{k_7 + k_8[H^+]\}$. At 25° and $\mu = 2.2$, $k_5 = 0.30$ mole^{-2} l.^{2} min.$^{-1}$, $k_6 = 0.090$ mole^{-3} l.^{3} min.$^{-1}$, $k_7 = 0.74$, and $k_8 = 0.14$ mole l.$^{-1}$. Apparent activation energies are given. Probable restrictions on the geometrical configurations for the transition state complexes and the mechanism of the electron transfer processes are considered. Relationships of the reactions in sulfate solution to similar reactions occurring in perchlorate media are discussed.

Three prior investigations of the kinetics of the neptunium(IV)–neptunium(VI) reaction have been reported.[2-4] In perchloric acid solution the mechanism of the reaction appears to involve hydrolysis products of neptunium(IV).[2] In mixed ethylene glycol–water media the mechanism is altered, ethylene glycol apparently being present in the activated complex.[3] In sulfate solution the only measurements made were in one molar sulfuric acid.[4] The present research has been carried out to see if alternate paths involving complex ion species are available. The sulfate system has been selected for further investigation for two reasons. First, data on the complexity constants of neptunium(IV) and sulfate are now available.[5] Second, measurement of the reverse reaction, the disproportionation of neptunium(V), is possible in this medium. Interest in the latter reaction is due to the apparent difference in reaction mechanism deduced from kinetic and equilibrium data in perchlorate solution[2] and the reaction which would be expected if the behavior of neptunium(V) paralleled that of uranium(V).

Experimental

The stock solutions of the neptunium ions in perchloric acid were prepared according to previously described methods. The sulfuric acid was reagent grade standardized by titration with sodium hydroxide.

The experimental technique also has been previously described.[2] The only major modification of that technique used in this investigation was the preparation of calibration curves necessary to determine the concentration of Np(IV) in the sulfuric acid–perchloric acid mixtures. The interaction between Np(IV) and bisulfate is reflected in the lowering and slight shift in wave length of the band at 724 mμ which is most useful for analytical purposes.

Results

I. The Np(IV) + Np(VI) ⟶ 2Np(V) Reaction

Effect of Metal Ion.—The stoichiometry of the reaction with respect to each of the metal ions was determined by experiments in which the concentration of Np(IV) and Np(VI) were varied in the reaction mixture. Data were obtained at total sulfuric acid concentrations of 0.0865 and 1.00 molar. At zero bisulfate the reaction is bimolecular.[2] In the bisulfate solutions the data were also found to be consistent for a bimolecular process. The rate constants, k_{obsd}, were computed from the experimental data both by graphical evaluation of the initial rate[6] and by means of the integrated equation for a bimolecular reaction

$$k_{obsd} = \frac{2.303}{([Np(IV)]^0 + [Np(VI)]^0)t} \log \frac{[Np(VI)]^0}{[Np(IV)]^0}\left(\frac{[Np(VI)]^0 - x}{[Np(IV)]^0 - x}\right) \quad (1)$$

(1) Based on work performed under the auspices of the U. S. Atomic Energy Commission.

(2) J. C. Hindman, J. C. Sullivan and D. Cohen, THIS JOURNAL, 76, 3278 (1954).

(3) D. Cohen, E. S. Amis, J. C. Sullivan and J. C. Hindman, *J. Phys. Chem.*, 60, 701 (1956).

(4) L. B. Magnusson, J. C. Hindman and T. J. LaChapelle, "The Transuranium Elements," edited by G. T. Seaborg, J. J. Katz and W. M. Manning (McGraw-Hill Book Co., New York, N. Y., 1949), National Nuclear Energy Series, Plutonium Project Record, Div. IV, Vol. 14B, paper 15.11, p. 1134.

(5) J. C. Sullivan and J. C. Hindman, THIS JOURNAL, 76, 5931 (1954).

(6) *Cf.* R. Livingston, "Technique of Organic Chemistry," Vol. VIII, Interscience Publishers, Inc., New York, N. Y., 1953, p. 182.

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where $[Np(IV)]^0$ and $[Np(VI)]^0$ represent the initial total concentrations of reactants, and x the concentration of Np(IV) at time t. In the calculations involving equation 1 only the data for the first 10% of the reaction were used in order to minimize the correction for the back reaction. The data are summarized in Table I.

TABLE I

DETERMINATION OF METAL ION DEPENDENCE FOR THE REACTION Np(IV) + Np(VI) → 2Np(V)

$t = 25°$, $\mu = 2.2$

Initial $[H_2SO_4]$, mole l.$^{-1}$	Initial $[H^+]$, mole l.$^{-1}$	$10^3 \times [Np(IV)]^0$, mole l.$^{-1}$	$10^3 \times [Np(VI)]^0$, mole l.$^{-1}$	Apparent rate k_{obsd}, l. mole^{-1} min.$^{-1}$
0.0865	1.96	2.64	18.78	3.87
.0865	1.95	5.26	15.65	4.01
.0865	1.92	13.36	6.26	3.55
.0865	1.94	10.70	9.08	3.70
1.00	1.04	9.82	9.27	2.20
1.00	1.04	12.60	6.26	2.39
1.00	1.04	5.27	15.65	2.28

Effect of $[HSO_4^-]$.—Table II summarizes the data on the effect of bisulfate on the apparent rate of the reaction. Examination of the data in this table shows that the rate increases to a maximum and then decreases as the bisulfate concentration is further increased. The maximum in the rate occurs when $\bar{n}_{IV}$ is close to one, that is, where the average number of sulfate groups attached to a neptunium(IV) ion is unity[5] (see Fig. 1). It would therefore appear that the rate is increased by the addition of a single sulfate ion to the Np(IV). At the point where the maximum in the rate is observed the Np(VI) is presumably largely NpO_2^{++}. Thus far successful measurements of the complex constants for the Np(VI) sulfate system have not been made.[7] The degree of complex formation was therefore estimated using the constants for the U(VI) system.[8] Calculations of the solution composition have been made using the above complexing data and a value of 0.080 for the dissociation constant of $[HSO_4^-]$ at $\mu = 2.2$.[9] These calculations have been made as

TABLE II

EFFECT OF $[HSO_4^-]$ ON THE RATE OF THE REACTION Np(IV) + Np(VI) ⇄ 2Np(V)

$t = 25.1°$, $\mu = 2.2$, $[H^+]_i = 2.20$ *M*

Initial $[HSO_4^-]$, mole l.$^{-1}$	Total [Np(IV)], mole l.$^{-1}$ × 10^3	Total [Np(VI)], mole l.$^{-1}$ × 10^3	Apparent rate k_{obsd}, l. mole^{-1} min.$^{-1}$
0.00	6.86	7.30	0.59[b]
0.00	...	...	0.61
1.02×10^{-3}	6.86	7.30	0.776
3.07×10^{-3}	6.86	7.30	1.26
3.22×10^{-3}	10.52	9.21	1.64
3.11×10^{-3}	6.86	7.42	1.13
6.14×10^{-3}	6.86	7.30	1.61
1.02×10^{-2}	6.86	7.30	2.12
1.64×10^{-2}	6.86	7.30	2.58
2.02×10^{-2}	10.50	9.21	2.21
3.07×10^{-2}	6.86	7.30	3.11
5.12×10^{-2}	6.86	7.30	3.38
9.21×10^{-2}	6.86	7.30	3.36
0.1228	6.86	7.30	3.20
.168	10.98	10.70	2.51
.2075	6.86	7.42	2.65
.311	6.86	7.42	2.17
.498	6.86	7.42	1.57
.504	10.88	10.70	1.36
.942	10.70	10.70	0.716
.942	9.64	9.27	0.760
1.93[a]	10.84	10.70	0.320

[a] $H^+ = 2.11$. [b] Reference 2.

$$[\Sigma HSO_4^-]_i = [HSO_4^-]_{free} + [SO_4^{--}]_{free} + [\Sigma \bar{n}_i Cm_i] \quad (2)$$

where

$$\bar{n} = \frac{\beta_1[HSO_4^-] + 2\beta_2[HSO_4^-]^2}{1 + \beta_1[HSO_4^-] + \beta_2[HSO_4^-]^2} \quad (3)$$

and

$$Cm_i = [\Sigma Np(IV)] \text{ or } [\Sigma Np(VI)] \quad (4)$$

combining with

$$0.080 = \frac{[H^+][SO_4^{--}]}{[HSO_4^-]} \quad (5)$$

and

$$[H^+] = [H^+]_i + [SO_4^{--}]_f + [\Sigma n_i Cm_i] \quad (6)$$

where

$$[H^+]_i = \text{initial hydrogen ion concn.} \quad (7)$$

and solving for $[HSO_4^-]_f$, we get

$$[HSO_4^-]_f^2 - [HSO_4^-]_f(2[\Sigma HSO_4^-]_i + [H^+]_i + 0.080 - [\Sigma \bar{n}_i Cm_i]) + ([H^+]_i[\Sigma HSO_4^-]_i + [\Sigma HSO_4^-]_i^2 - [H^+]_i[\bar{n}_i Cm_i] - [\Sigma HSO_4^-]_i[\bar{n}_i Cm_i]) = 0 \quad (8)$$

The quadratic is solved for $[HSO_4^-]_f$. To obtain a final value for the bisulfate concentration it is necessary to make successive approximations. This is done as follows. The $\bar{n}_i Cm_i$ terms are obtained using $\bar{n}$ values taken from a plot of $\bar{n}$ *versus* free bisulfate or by solution of equation 3. The plot is obtained using $\beta_1 = 270/[H^+]$ and $\beta_2 = 2970/[H^+]^2$ for the constants of the Np(IV) system at a given acidity and $\beta_1 = 6.25/[H^+]$ and $\beta_2 = 7.6/[H^+]^2$ for approximating the constants of the Np(VI) sulfate system. In the first approximation the free $[HSO_4^-]$ is set equal to the total sulfuric acid concentration and the $\bar{n}$ values read from the plot. $[HSO_4^-]_f$ values are then calculated from equation 8 and the process repeated.

The degree of formation of the individual complex is computed from the relation

$$a_i = \frac{[MA_i]}{Cm} = \frac{\beta_i[A_i]^i}{1 + \sum_{i=1}^{J} \beta_i[A]^i} \quad (9)$$

whence concentrations of the individual complex species are calculated readily.

The decrease in k_{obsd} (Table II) at high bisulfate concentration is coincident with the formation of the complexes $Np(SO_4)_2$ and $NpO_2(SO_4)_2^{--}$, suggesting that these complexes do not contribute appreciably to the reaction. The general rate equation that would take into account the complex de-

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pendence of the rate on the bisulfate concentration can be written as

$$R = [Np(IV)][Np(VI)]k_{obsd} = k_0'[Np^{+4}][NpO_2^{++}] + k_1[NpSO_4^{++}][NpO_2^{++}] + k_2[NpSO_4^{++}][NpO_2SO_4] + k_3[Np(SO_4)_2][NpO_2^{++}] + k_4[Np^{+4}][NpO_2SO_4] + \ldots \quad (10)$$

Analysis of the data shows that the rate may be reproduced within the experimental uncertainties by a rate equation involving only the first three terms on the right-hand side of equation 10. Using a value of $k_0 = 0.59$ for the 2.2 molar acid solution, the least square value for $k_1 = 4.27$ mole^{-1} l. min.$^{-1}$ and for $k_2 = 7.12$ mole^{-1} l. min.$^{-1}$. The agreement between the calculated and experimental data is shown in Fig. 1. The calculated values of the rate constant were obtained using the equation

$$k_{obsd} = k_0\left[1 - \sum_{i=1}^{J} a_i\right]_{Np(IV)}\left[1 - \sum_{i=1}^{J} a_i\right]_{Np(VI)} + k_1[a_{NpSO_4^{++}}] \times \left[1 - \sum_{i=1}^{J} a_i\right]_{Np(VI)} + k_2[a_{NpSO_4^{++}}][a_{NpO_2SO_4}] \quad (11)$$

valid for a given condition of acidity. In equation 11 and subsequent equations, the terminology

$$\left[1 - \sum_{i=1}^{J} a_i\right] = \frac{[Np^{+4}]}{[Np(IV)]}, \quad [a_{NpSO_4^{++}}] = \frac{[NpSO_4^{++}]}{[Np(IV)]}, \text{ etc.}$$

is used for simplicity.

The Effect of Hydrogen Ion Concentration.—The effect of varying the hydrogen ion concentration at constant bisulfate concentration is summarized in Table III. Two initial bisulfate concentrations were used. One corresponds approximately to the concentration at which the rate of reaction is at a maximum. The second, higher concentration is for the region in which the rate has again decreased to a relatively low value. Examination of the data shows that k_{obsd} for both regions is inversely proportional to a value between the second and third power of the hydrogen ion concentration.

TABLE III

EFFECT OF HYDROGEN ION CONCENTRATION ON THE RATE OF THE Np(IV)-Np(VI) REACTION IN SULFATE SOLUTION

$\mu = 2.2$, $t = 25°$

Original [H$^+$], mole l.$^{-1}$	Original [HSO$_4^-$], mole l.$^{-1}$	[Np(IV)] × 10^3, mole l.$^{-1}$	[Np(VI)] × 10^3, mole l.$^{-1}$	k_{obsd}, l. mole^{-1} min.$^{-1}$	k_{calcd} l. mole^{-1} min.$^{-1}$
1.96	0.0865	2.64	18.78	3.87	3.71
1.95	.0865	5.26	15.65	4.01	3.77
1.94	.0865	10.70	9.08	3.70	3.84
1.92	.0865	13.36	6.26	3.55	3.87
1.09	.0865	10.00	9.08	11.1	12.0
0.680	.0865	10.00	9.08	34.0	29.8
0.288	.0865	10.00	9.08	138	146
2.20	.943	9.64	9.27	0.67	0.80
1.55	1.00	10.35	9.08	1.30	1.18
1.04	1.00	10.27	9.08	1.76	1.79
0.651	1.00	10.18	9.08	2.84	2.60
0.285	1.00	10.26	9.08	4.77	4.95

The variation of the reaction rate with variation in hydrogen ion concentration can be represented as a combination of five hydrogen ion dependent paths as represented by the equation

$$k_{obsd} = k_0\frac{[a_{Np^{+4}}][a_{NpO_2^{++}}]}{[H^+]^2} + \{k_1[a_{NpSO_4^{++}}][a_{NpO_2^{++}}] + k_2[a_{NpSO_4^{++}}][a_{NpO_2SO_4}]\}\left\{\frac{k_3}{[H^+]^2} + \frac{k_4}{[H^+]^3}\right\} \quad (12)$$

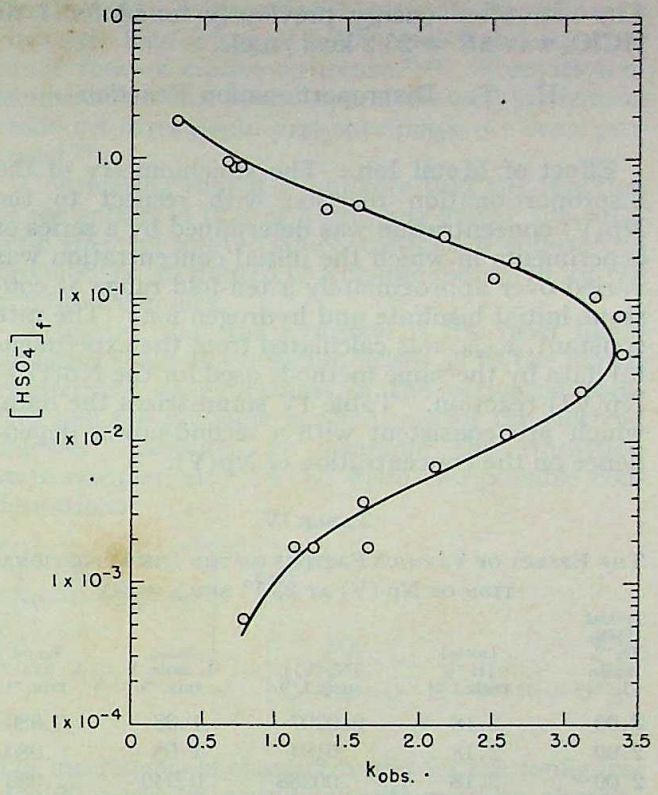

Fig. 1.—Variation of k_{obsd} with free bisulfate at constant hydrogen ion; $[H^+] = 2.2\ M$; $\mu = 2.2$; $t = 25.0°$. Solid line calculated from equation 11.

It is not possible to reproduce the data by a simpler equation involving only two sulfate dependent paths with different hydrogen ion dependencies. The four sulfate containing activated complexes implied by equation 12 are formally the same as the principal activated complexes found in sulfate solution for the disproportionation reaction of Np(V) (see later Discussion).

The least squares values of the constants are $k_3 = 3.6$ mole^2 l.$^{-2}$ and $k_4 = 1.7$ mole^3 l.$^{-3}$ for the low bisulfate region and $k_3 = 3.8$ mole^2 l.$^{-2}$ and $k_4 = 2.8$ mole^3 l.$^{-3}$ for the high bisulfate region. At the 95% confidence level the uncertainties in the precision of the constants are approximately 20%. Within the experimental uncertainties the k_3 values are the same for both sets of data. It is by no means certain that the apparent differences in k_4 values are significant. The variation in solution composition is so great that appreciable deviations in the activity coefficients of the various species would not be unexpected.

Temperature Effect.—The variation of the reaction rate with temperature was determined for solutions initially 0.084 and 0.943 M in HSO_4^-. The temperatures were 15.1, 25.0 and 35.2°. The apparent activation energies were $\Delta E = 23.1 \pm 3.3$ kcal./mole and $\Delta E = 23.3 \pm 3.2$ kcal./mole for the 0.084 and 0.943 M bisulfate solutions, respectively.

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The activation energy previously found for 1 M $HClO_4$ was $\Delta E = 25.2$ kcal./mole.

II. The Disproportionation Reaction

$$2\ Np(V) \rightarrow Np(IV) + Np(VI)$$

Effect of Metal Ion.—The stoichiometry of the disproportionation reaction with respect to the Np(V) concentration was determined by a series of experiments in which the initial concentration was varied over approximately a ten-fold range at constant initial bisulfate and hydrogen ion. The rate constant, k_{obsd}, was calculated from the experimental data by the same methods used for the Np(IV)–Np(VI) reaction. Table IV summarizes the data, which are consistent with a second-power dependence on the concentration of Np(V).

TABLE IV

THE EFFECT OF VARIOUS FACTORS ON THE DISPROPORTIONATION OF Np (V) AT 25.1° AND $\mu = 2.2$

Initial $[HSO_4^-]$, mole l.$^{-1}$	Initial $[H^+]$, mole l.$^{-1}$	[Np(V)], mole l.$^{-1}$	k_{obsd}, l. mole^{-1} min.$^{-1}$	k_{calcd} l. mole^{-1} min.$^{-1}$
2.00	2.18	0.0207	1.08	0.980
2.00	2.18	.0104	1.08	.980
2.00	2.18	.00288	0.940	.980
2.00	2.18	.00196	.890	.980
1.00	2.18	.0214	.380	.385
0.466	2.18	.0214	.154	.164
.938	1.18	.0218	.342	.327
.895	0.583	.0218	.287	.284
.823	0.184	.0218	.232	.241

The Effect of Bisulfate and Hydrogen Ion.—The rate of the disproportionation reaction is a monotonic increasing function of the bisulfate concentration. Analysis of the data in Table IV by standard methods results in a non-integral bisulfate dependence of 1.3 over the range of concentration $2.00 \leq [HSO^4{}^-] \leq 0.466$ M.

Empirical analysis of the data in Table IV also reveals that the rate of the reaction is dependent on the 0.1 power of the hydrogen ion concentration over the acid range $2.18 \leq [H^+] \leq 0.184$ M. The empirical form of the rate equation is then

$$R = [Np(V)]^2 k_{obsd} = k[Np(V)]^2[HSO_4^-]^{1.32\pm0.02} \times [H^+]^{0.092\pm0.002} \quad (13)$$

The value of $k = 0.364 \pm 0.022$ at the 95% confidence level.

As in the case of the Np(IV)–Np(VI) reaction, the non-integral bisulfate and hydrogen ion dependencies indicate that the Np(V) disproportionation reaction is complex. It is possible to express the results in the equation

$$k_{obsd} = \{k_5[HSO_4^-] + k_6[HSO_4^-]^2\}\{k_7 + k_8[H^+]\} \quad (14)$$

The least squares values for the specific constants are $k_5 = 0.300$ mole^{-2} l.^{2} min.$^{-1}$, $k_6 = 0.0877$ mole^{-3} l.^{3} min.$^{-1}$, $k_7 = 0.739$ and $k_8 = 0.135$ mole^{-1} l. Calculated values of k_{obsd} using this equation are given in Table IV, column 5. It is possible to reproduce the results if the hydrogen ion dependent terms are neglected; however, the fit to the data is not quite as good. This might be justified on the basis that the environmental conditions are altered sufficiently to give an effect of this magnitude. The resulting equation then would be

$$k_{obsd} = k_5'[HSO_4^-] + k_6'[HSO_4^-]^2 \quad (15)$$

with $k_5' = 0.26$ mole^{-2} l.^{2} min.$^{-1}$ and $k_6' = 0.14$ mole^{-3} l.^{3} min.$^{-1}$.

It should be pointed out that the four paths indicated by equation 14 yield stoichiometric formulas for the activated complexes identical with three of those obtained for the four bisulfate dependent paths of the Np(IV)–Np(VI) reaction. The principle of detailed balancing requires that all possible paths exist for the disproportionation reaction. The applicability of the simpler equation is therefore indicative of the relative rates of reaction for the several paths and the limited precision of the data.

The Effect of Temperature.—The temperature coefficient of the reaction rate was measured for solutions initially 2.18 M in $[H^+]$ and 2.00 M in $[HSO_4^-]$. Temperatures were 15.15, 25.1 and 35.15°. The apparent activation energy was $\Delta E = 14.3 \pm 3.1$ kcal./mole. The activation energy previously measured for 1 M $HClO_4$ solutions was 17.1 ± 1.6 kcal./mole.

Discussion

The stoichiometric formulas for the activated complexes derived from the rate data can be written

$$A = |NpO_2NpOOHSO_4^{+1}|^{\pm}$$
$$B = |NpO_2Np(OH)_2(SO_4)_2|^{\pm}$$
$$C = |NpO_2Np(OH)_2SO_4^{+2}|^{\pm}$$
$$D = |NpOOHNp(OH)_2(SO_4)_2^{+1}|^{\pm}$$
$$E = |NpO_2Np(OH)_3(SO_4)_2^{-1}|^{\pm}$$

Representation of the stoichiometry as above does not necessarily imply the existence of the given entities in the actual configurations of the activated complexes. Alternate representations can be given. The transition states A and B represent those for the predominant reaction paths for the Np(V) disproportionation. C and D also represent activated complexes for the disproportionation reaction. The states A, B and C are common to both the disproportionation reaction and the Np(IV)–Np(VI) reaction. Since it is a requirement of the principle of microscopic reversibility that the transition state be the same for both the forward and reverse reaction, the fact that the state D is derived only from the rate equation for the disproportionation and the state E only from the rate equation for the Np(IV)–Np(VI) reaction is therefore only indicative of the relative rates of reaction for the several paths of these two reactions.

Examination of the stoichiometric formulas for the activated complexes suggests certain conclusions as to the probable geometrical configurations of the transition states and probable restrictions on the mechanism for the electron transfer process. First, the data suggest that the neptunium ions must attain a configuration close to that of a O–Np–O$^+$ ion before the electron transfer can occur. As a corollary, it would further appear that it is unlikely that the mechanism can involve the rupture of a Np–O bond of the linear complex in the rate-determining step. That these conditions should be met is not surprising. The O–M–O structure for the ions of the penta- and hexapositive

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oxidation states of the actinide elements is very stable, persisting both in solution and in the solid state as an entity.[10-13]

The principal experimental observation supporting the idea that the neptunium ions attain a configuration that readily yields NpO_2^+ before electron transfer occurs is the hydrogen ion dependencies observed for those reactions involving oxidation of Np(IV). For the Np(IV)–Np(VI) reaction in perchlorate solution the dominant reaction path yields a stoichiometry for the activated complex that may be represented as $[NpO_2Np(OH)_2^{+4}]^{\ddagger}$.[2] Similarly, the oxidation of Np(IV) to Np(V) by Fe(III) involves a hydrogen ion dependence that yields the stoichiometric formula, $[Fe(OH)Np(OH)_2^{+4}]^{\ddagger}$.[14] Analogous results have been found for the disproportionation reaction of Pu(IV), where similar species are involved.[15-17] In this case the transition state for the slow step[16] may be represented as $[Pu(OH)_2PuOH^{+5}]^{\ddagger}$. For the reactions in the present research, the importance of the hydrogen ion dependence is emphasized by the participation of sulfate in the reaction. That is, the equivalent of the reaction occurs despite the fact that this equilibrium

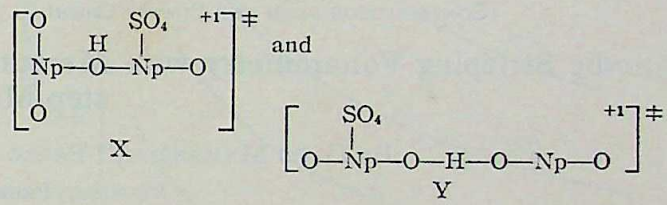
$$Np^{+4}(aq.) + 2H_2O \rightleftharpoons Np(OH)_2^{++} + 2H^+ \quad (16)$$

which lies far to the left in perchlorate solutions of equivalent acidity, will be further shifted in this direction by the presence of sulfate attached to the Np(IV). The same general argument would apply whether the hydrogen ion is split off in a preequilibrium similar to reaction 16 or in the process of formation of the activated complex. The fact that Np(IV) sulfate complexes containing more than one sulfate group do not participate in the reaction to an appreciable extent undoubtedly is partially explicable on the basis that the more sulfate groups attached, the less favorable are conditions for removal of hydrogen ions.

A second factor that may affect the number of sulfate groups involves the question of whether or not the sulfate acts as a bridging ligand in the activated complex. Considering the available data on the relative effectiveness of different bridging groups,[18,19] it appears likely that if there is a choice between bridging through sulfate or hydroxyl, the hydroxyl would be highly favored. In this connection it might be mentioned that in the solid compounds $Th(OH)_2SO_4$ and $Th(OH)_2CrO_4 \cdot H_2O$, the structure appears to consist of chains of thorium ions linked by hydroxide bridges with the sulfate or chromate ions acting to hold these chains together in the form of a layer structure.[20,21] Formation of similar structures in the hydrolysis–polymerization reactions of uranium and thorium have been proposed.[22]

Considering that it is unlikely that the function of the sulfate is that of a bridging group, the catalytic effect of limited concentrations of sulfate can probably be attributed to a charge reduction for the activated complex.

Assuming that the hydroxyl is the most likely bridging anion the question arises as to the actual geometrical configurations in the activated complex and the probable mechanisms for the electron transfer. Consider for example the transition state complex, A. We can write two possible configurations



X Y

The mechanism of charge transfer for the configuration X could be considered either as an electron transfer through a hydroxyl bridge or as a hydroxy atom transfer. If we accept our argument that the tendency is to form and maintain the O–M–O structure, then we can rule out the hydroxyl atom transfer mechanism. There is no *a priori* way of deciding whether an electron transfer or a hydrogen atom transfer mechanism, corresponding to the configuration Y, is the correct one. It might be pointed out, however, that formation of complexes corresponding to the general configuration Y involves no rearrangement of the hydration spheres of the reacting ions in the formation of the bridge. The transition state is also more symmetrical for those complexes with the Y configuration.

If we assume that the bridging is by way of either hydroxyl or hydrogen, then the fundamental mechanism for the electron transfer process is probably the same in the presence or absence of sulfate. We can then advance a reasonable explanation for the apparent anomalies previously discussed for experiments in perchlorate media.[2,23] For example, it was found that the Np(IV)–Np(VI) reaction in perchlorate solution could be adequately represented by

$$-\frac{d[Np^{+4}]}{dt} = k_0'[Np^{+4}][NpO_2^{++}][H^+]^{-2} \quad (17)$$

Combining this with the equation for the over-all equilibrium involving Np(IV), Np(V) and Np(VI), it was deduced that the Np(V) disproportionation reaction could be written as a mechanism which

$$-\frac{d[NpO_2^+]}{dt} = k_1'[NpO_2^+]^2[H^+]^2 \quad (18)$$

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differed in stoichiometry with respect to hydrogen ion from the analogous U(V) reaction.[24] On the other hand, one of the paths for the Np(IV)–Np(V) exchange reaction had the stoichiometry of the U(V) disproportionation.

$$-\frac{d[NpO_2^+]}{dt} = k_1''[NpO_2^+]^2[H^+] \qquad (19)$$

It was found further that the energetics for the overall equilibrium was not in accord with the energetics for the two reactions, (19) and (17). It appears likely from the present observations that the explanation for the disparities is that multiple reaction paths are involved. With this possibility in mind the data for the Np(IV)–Np(VI) reaction were re-examined. Least squares analysis showed that the hydrogen ion dependence was $[H^+]^{-2.08 \pm 0.06}$ (95% confidence level). From this it is possible to write a kinetic expression involving two hydrogen ion dependent paths as

$$k_{obsd} = k_1[H^+]^{-2} + k_2[H^+]^{-3} \qquad (20)$$

with $k_1 = 2.59$ and $k_2 = 0.074$. Although it is clear that the predominant reaction involves only two hydrogen ions these computations lend some support to the hypothesis that more than a single reaction path is involved in perchlorate solution.

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LEMONT, ILLINOIS

[CONTRIBUTION FROM THE COATES CHEMICAL LABORATORY, LOUISIANA STATE UNIVERSITY]

Anodic Stripping Voltammetry with Mercury Electrodes—Potential-step and Current-step Methods

BY GLEB MAMANTOV,[1a] PAOLO PAPOFF[1b] AND PAUL DELAHAY

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An amalgam forming metal is deposited on a stationary mercury electrode and then is anodically oxidized. Anodic stripping is carried out either by sudden switching of potential (potential-step method) or by passing a constant current through the cell (current-step method). A theoretical analysis is developed for both methods for conditions of semi-infinite linear diffusion. The following derivations are given: equations for current–time, current–potential and potential–time curves; diffusion current and transition time for the stripping process; sensitivity gain. Detailed experimental results are discussed for the anodic stripping of cadmium from a hanging mercury drop, and theory and experiment are compared. Sensitivity gains with respect to voltammetry with stirred solution can be larger than 100. Application to concentrations as low as 10^{-7}–10^{-9} molar appears feasible. The two methods are compared with anodic stripping at continuously varying potential (Nikelly and Cooke).

Anodic stripping methods which have been known for years[2] recently have been applied again to the analysis of traces of metals.[3–5] The metal to be determined in a solution is first deposited on a solid[3,5] or amalgamated[4] electrode, and then is stripped from this electrode by anodic oxidation. The amount of metal ion in solution is determined from the quantity of electricity consumed in the stripping process. Nikelly and Cooke[6] recently modified the method and used a mercury pool electrode for deposition of the metal to be analyzed. They reoxidized the metal at continuously varying potential and obtained current–potential curves not unlike those of oscillographic polarography. These curves exhibit a peak from the height of which the concentration of metal is deduced directly. The method of Nikelly and Cooke is a voltammetric procedure whereas previous methods belong to coulometry. These authors coined the expression "anodic stripping polarography" for their method, but we prefer to call it "anodic stripping voltammetry," thus reserving the term "polarography" for methods involving the use of the dropping mercury electrode.[7]

In addition to the method of Nikelly and Cooke, two other simple methods can be conceived: (a) the "potential-step" method in which the metal is oxidized by sudden variation of potential to a more anodic value; and (b) the "current-step" method in which the stripping process is carried out at constant current. These methods are discussed and compared in this paper for the case of stationary mercury electrodes.

Potential-step Method

Diffusion Stripping Current.—A metal M is deposited at constant potential on a stationary mercury electrode in stirred solution. The conditions are such that the electrolysis current is constant; *i.e.*, the volume of solution is so large and the plating time so short that depletion of ions M^{+n} in solution can be neglected. Electrolysis is carried out at a potential corresponding to the limiting current range. Mercury is not stirred, and M is supposed to diffuse in the bulk of mercury under conditions of semi-infinite linear diffusion. After τ seconds, the potential is changed abruptly to a sufficiently anodic value at which metal M is oxidized at a rate that is solely diffusion controlled. The resulting *diffusion stripping current* will now be derived. This current is obtained by deriving the flux of metal M at the electrode surface, *e.g.*, by solving

(1) (a) Predoctoral fellow, 1955–1957; (b) on leave from the Physical Chemistry Department, University of Modena, Italy.

(2) C. Zbinden, *Bull. soc. chim. biol.*, **13**, 35 (1931).

(3) S. S. Lord, Jr., R. C. O'Neill and L. B. Rogers, *Anal. Chem.*, **24**, 209 (1952).

(4) K. W. Gardiner and L. B. Rogers, *ibid.*, **25**, 1393 (1953).

(5) M. M. Nicholson, THIS JOURNAL, **79**, 7 (1957).

(6) J. G. Nikelly and W. D. Cooke, paper presented at the International Congress of Pure and Applied Chemistry, Lisbon, September 9–16, 1956.

(7) See P. Delahay, "New Instrumental Methods in Electrochemistry," Interscience Publishers, Inc., New York, N. Y., 1954, p. 11.

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Fick's equation for the following initial and boundary conditions.

The initial condition expresses the concentration of M in mercury at time τ, *i.e.*, at the instant of switching of potential. This concentration is[8]

$$C_M(x,0) = \frac{i_p}{nFAD_M}\left[2\left(\frac{D_M\tau}{\pi}\right)^{1/2}\exp\left(-\frac{x^2}{4D_M\tau}\right) - x\ \mathrm{erfc}\left(\frac{x}{2D_M^{1/2}\tau^{1/2}}\right)\right] \quad (1)$$

There, x is the distance from the electrode surface in the mercury, i_p the plating current during deposition of M on mercury, D_M the diffusion coefficient of M in mercury, n the number of electrons for the discharge of M^{+n}, F the faraday, A the electrode area, and "erfc" represents the error function complement. We write $C_M(x,0)$ to indicate that the origin of time in the following derivation is taken at the beginning of the stripping process.

As boundary condition we prescribe that M is immediately oxidized to M^{+n} as it reaches the electrode surface. Hence, $C_M(0,t) = 0$ for $t > 0$. Finally, $C_M(x,t) \to 0$ for $x \to \infty$ and for $t \geqslant 0$.

This boundary value problem is quite similar to the one previously studied in this Laboratory for two consecutive electrode reactions in voltammetry at constant current.[9] The result is[10]

$$-\frac{i_{s,d}}{i_p} = \frac{2}{\pi}\left(\frac{\tau}{t}\right)^{1/2} - \frac{1}{2} - \frac{1}{\pi}\sin^{-1}\frac{\tau - t}{\tau + t} \quad (2)$$

where $i_{s,d}$ is the diffusion stripping current. According to polarographic practice, the anodic current $i_{s,d}$ is negative and the cathodic current i_p is positive in (2).

Variations of $-i_{s,d}/i_p$ with t/τ are shown in Fig. 1 (solid curves). It is seen from this diagram that the ratio $-i_{s,d}/i_p$ is much larger than unity provided that t/τ is sufficiently small. One has[11] $i_{s,d}/i_p \to \infty$ for $t/\tau \to 0$, and $-i_{s,d}/i_p \to 0$ for $t/\tau \to \infty$.

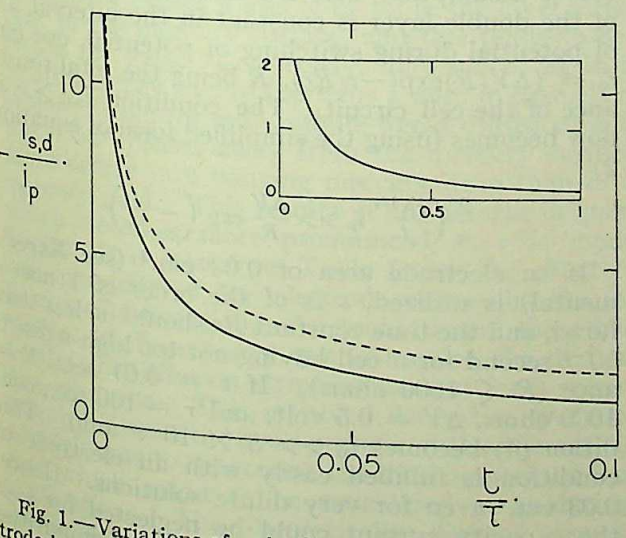

Fig. 1.—Variations of $-i_{s,d}/i_p$ with t/τ for the plane electrode in the potential-step method. Solid curve represents exact solution in equation 2; dashed curve corresponds to the approximate solution $-i_{s,d}/i_p = (2/\pi)(\tau/t)^{1/2}$.

(8) (a) Z. Karaoglanoff, *Z. Elektrochem.*, **12**, 5 (1906); (b) see ref. 7, p. 180.

(9) T. Berzins and P. Delahay, THIS JOURNAL, **75**, 4205 (1953).

(10) The detailed and rather involved derivation is given in Mamantov's Ph.D. dissertation, June, 1957.

(11) Note that $\sin^{-1}(-1) = -\pi/2$.

Tracings of experimental curves $i_{s,d}$ against t are shown in Fig. 2 for the anodic stripping of cadmium for different pre-electrolysis times. For reasons discussed in the Experimental part, these curves were recorded with a hanging mercury drop and not with a mercury pool. Furthermore, the mechanical stirrer was stopped at the end of pre-electrolysis and 4 seconds were allowed to elapse before the recording of the current–time stripping curves. Deformation of the drop during stripping was avoided in this fashion, and results were more reliable. These conditions do not correspond to the foregoing theoretical analysis, which should be regarded primarily as a guide for a judicious choice of experimental conditions. Note that the experimental curves have the same general shape as the theoretical curve of Fig. 1 (see also below).

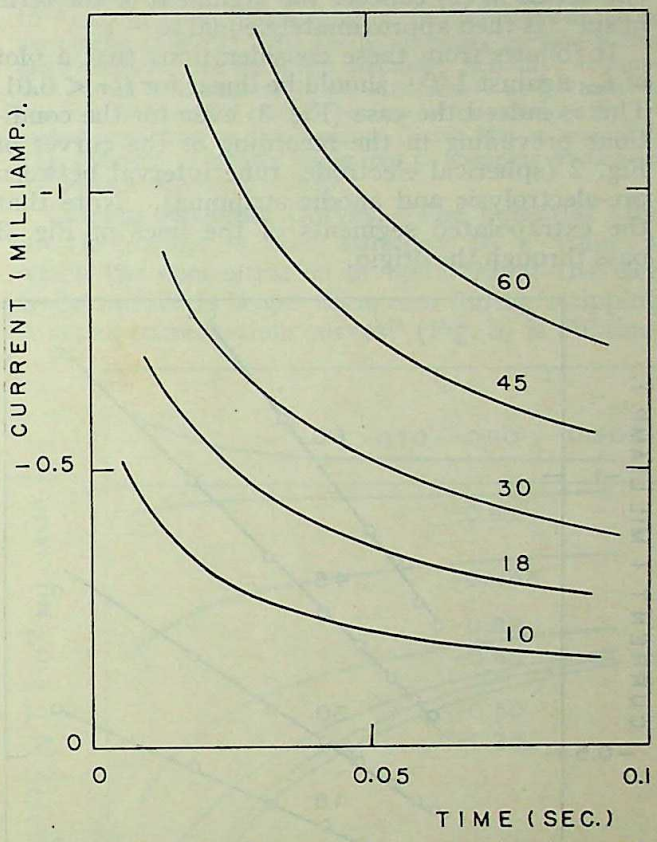

Fig. 2.—Tracings of current–time curves for the anodic stripping of cadmium in 1 *M* potassium chloride at −0.25 volt (*versus* S.C.E.). Numbers on curves are pre-electrolysis times in seconds. Time interval between pre-electrolysis and stripping, 4 seconds.

The term $(2/\pi)(\tau/t)^{1/2}$ in equation 2, which is determinative for short and very long times (dashed curve in Fig. 1), is the ratio $-i_{s,d}/i_p$ one would calculate by assuming that the concentration $C_M(x,0)$ at the instant of switching of potential is independent of x and equal to the concentration at $x = 0$. Thus, one deduces from (1) for $t = 0$ (*i.e.*, after τ seconds of pre-electrolysis)

$$C_M(0,0) = 2\left(\frac{D_M\tau}{\pi}\right)^{1/2}\frac{i_p}{nFAD_M} \quad (3)$$

By introducing this concentration in the Ilkovic equation, as written for the plane electrode, there follows the approximate relationship $-i_{s,d}/i_p = (2/\pi)(\tau/t)^{1/2}$. The resulting approximation is

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quite satisfactory for short times, *i.e.*, for $t/\tau < 0.01$. For larger values of t/τ, the effect of the non-uniform initial concentration distribution is very pronounced (Fig. 1) at least until t/τ is much larger than unity. The term $(2/\pi)(\tau/t)^{1/2}$ is again determinative for $t/\tau >> 1$ because the last two terms in (2) cancel: the argument of the term in $\sin^{-1}$ is then approximately equal to -1.

It follows from these considerations that a plot of $i_{s,d}$ against $1/t^{1/2}$ should be linear for $t/\tau < 0.01$. This is indeed the case (Fig. 3) even for the conditions prevailing in the recording of the curves of Fig. 2 (spherical electrode, time interval between pre-electrolysis and anodic stripping). Note that the extrapolated segments of the lines of Fig. 3 pass through the origin.

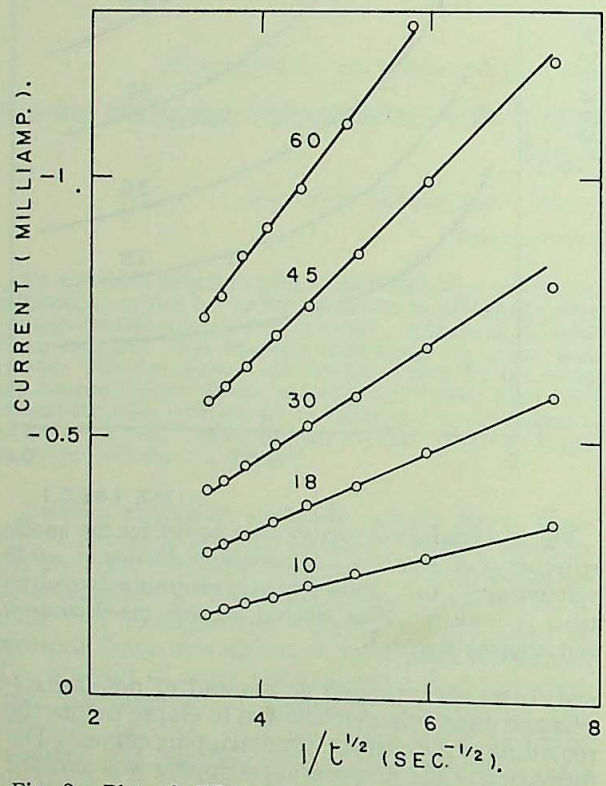

Fig. 3.—Plot of diffusion stripping against $1/t^{1/2}$. Data are from Fig. 2.

It is of interest to calculate the recovery of metal M during stripping. The recovery, which is defined as the ratio $[-\int_0^t i_{s,d}\,dt]/i_p\,\tau$, is obtained by integrating $i_{s,d}$ from 0 to t. Integration is performed by expanding $\sin^{-1}[(\tau - t)/(\tau + t)]$ in series[12] and by retaining only the first term. The resulting approximation is fairly good since the argument is practically equal to unity for $t/\tau << 1$ and the term in $\sin^{-1}$ is quite unimportant. Variations of the recovery with t/τ are shown in Fig. 4. It is seen from this diagram that the recovery is small ($< 10\%$) for $t/\tau < 0.01$. For long times, the recovery is surprisingly good; it approaches unity for $t/\tau \to \infty$.

Sensitivity Gain.—The gain in sensitivity can be expressed in two ways: (a) as the ratio $-i_{s,d}/i_p$

(12) $\sin^{-1} y = y + \frac{y^3}{6} + \frac{1 \times 3}{2 \times 4} \times \frac{y^5}{5} \ldots\ldots$

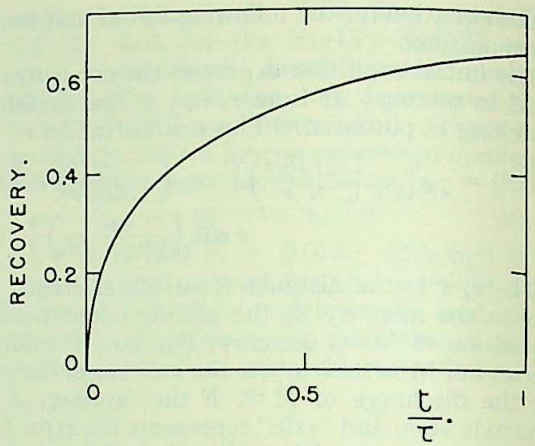

Fig. 4.—Recovery as a function of t/τ in the potential-step method.

of equation 2; or (b) as the gain $-i_{s,d}/i_d$ where i_d is the diffusion current measured directly with the analyzed solution (*e.g.*, without pre-electrolysis) and for the same time t as $i_{s,d}$. Both methods will be discussed.

The gain in sensitivity, as expressed by equation 2, corresponds to the comparison between the stripping method and voltammetry with a stationary electrode in stirred solution. It follows from the discussion of equation 2 that the gain for $t/\tau << 1$ is approximately $(2/\pi)(\tau/t)^{1/2}$. The ratio $(\tau/t)^{1/2}$ should be as large as possible, but there are two limitations: (a) convection interferes with diffusion when τ is too long thus causing unreliability; and (b) the charging (or discharging) of the double layer interferes with the stripping current when t is too short. Obviously, one should have $i_{s,d} >> i_c$ where i_c is the charging current of the double layer. If one makes the rather coarse assumption that the differential capacity c of the double layer is constant in the interval ΔV of potential during switching of potential, one has $i_c = (\Delta V/R)\exp(-t/Rc)$, R being the total resistance of the cell circuit. The condition $i_{s,d} >> i_c$ now becomes (using the simplified form of equation 2)

$$\frac{2}{\pi}\left(\frac{\tau}{t}\right)^{1/2} i_p >> \frac{\Delta V}{R} \exp\left(-\frac{t}{Rc}\right) \qquad (4)$$

If an electrode area of 0.03 cm.^{2} (see Experimental) is utilized, c is of the order of 1 microfarad, and the time constant Rc should be less than 10^{-3} second for a cell having not too high a resistance ($R \leqslant 1000$ ohms). If $t = 0.01$ sec., $R = 1000$ ohms, $\Delta V = 0.5$ volt, and $\tau = 100$ sec., condition (4) becomes $i_p >> 5 \times 10^{-10}$ amp. This condition is fulfilled easily with an electrode of 0.03 cm.^{2} even for very dilute solutions. Hence, the capacity current could be neglected for $t \geqslant 0.01$ sec. Actually, there are traces of impurities adsorbed on the electrode, and the switching of potential generally causes a variation in the surface concentration of these impurities. Variations of surface concentrations are quite slow,[13] and the capacity current may not die out for times appreciably longer that $t = 0.01$ sec. Removal of traces of adsorbable organic substances, possibly

(13) P. Delahay and T. Berzins, *J. Am. Chem. Soc.*, **75**, 555 (1953); H. Matsuda and H. Fischer, *Z. Elektrochem.*, **57**, 494 (1953); H. Matsuda and H. Reichtenberg, THIS JOURNAL, in press.

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by chromatography,[14] is recommended. At any rate, experimental gains of the order of 100 are possible. Since voltammetry with stirred solution is applicable to concentrations as low as 10^{-6} to 10^{-7} molar,[15,16] application of the potential-step stripping method to solutions even as dilute as 10^{-8} molar appears feasible.

Experimental gains are given in Table I for conditions similar to those of Fig. 2 (hanging mercury drop, 4 second interval between pre-electrolysis and anodic stripping). Gains of the order of 100 were obtained for the longest plating time (180 sec.). Experimental and theoretical gains which are in fairly good agreement for short pre-electrolysis times (τ = 10 sec.), are quite different for the larger values of τ. There are two main reasons for this discrepancy. Firstly, convection of metal M in mercury causes a loss of metal in the layer adjacent to the mercury surface, and this tends to decrease the gain. Conversely, diffusion of M in a small mercury sphere (perhaps 1 mm. in diameter) is slower than for semi-infinite linear diffusion, and metal M diffuses away from the mercury surface more slowly in a hanging mercury drop than in a mercury pool. This results in an increase in gain, which becomes more pronounced as τ is made larger. It is seen from Table I that the effect of the sphericity of the electrode outweighs the influence of convection. An evaluation of these two sources of discrepancy would require the derivation of the diffusion stripping current for a spherical electrode. This involved derivation was not attempted since the main purpose of this theoretical analysis was to determine the most important factors which ought to be considered in analytical applications. The theoretically derived general conclusions are confirmed by experiment.

TABLE I

EXPERIMENTAL GAIN FOR HANGING MERCURY DROP *versus* CALCULATED GAIN FOR PLANE ELECTRODE—ANODIC STRIPPING OF CADMIUM

τ, sec.	$t \times 10^{-2}$, sec.	$i_{s,d}$,[a] ma.	$-i_{s,d}/i_p$ Exptl.	Calcd.
180	3	4.62	136	48.4
180	6	3.18	93.5	34
180	9	2.49	73	27.5
60	3	1.29	50	27.5
60	6	0.90	35	19.1
60	9	.73	28	15.5
30	2.8	.68	26	19.8
30	5.8	.49	18.8	13.3
30	8.8	.40	15.4	10.8
10	2.8	.274	10.5	11.0
10	5.8	.196	7.54	7.40
10	8.8	.160	6.16	5.80

[a] The pre-electrolysis current was 26 microamp. except for τ = 180 sec. for which it was 34 microamp.

The second method of expressing the sensitivity gain is to compare $i_{s,d}$ with the diffusion current i_d measured at time t in direct voltammetry without pre-electrolysis. The current i_d is given by the Ilkovic equation written for the plane electrode. The gain calculated by the simplified form of equation 2 and by replacing i_p by its value, $i_p = nFADD_{M^{+n}}C^0/\delta$ (C^0 bulk concentration of M^{+n}, δ diffusion layer thickness), is $(2/\pi^{1/2})(D^{1/2}\tau^{1/2}/\delta)$.

One has $i_{s,d}/i_d \backsimeq 40$ for data of the following orders of magnitude: $D = 10^{-5}$ cm.^{2} sec.$^{-1}$, τ = 100 sec., and $\delta = 10^{-3}$ cm. (an approximate value of the conditions in the experimental study[17]). The anodic stripping method is thus more sensitive than the direct method. Actually, we found that direct voltammetry is not satisfactory at low concentrations (below 10^{-5} molar) because of interference by adsorbed impurities on the electrode (oxide film on mercury). This difficulty is greatly minimized in stripping voltammetry because of pre-electrolysis.

Current–Potential Curves.—The potential after pre-electrolysis is now switched to a value at which the concentration of metal M at the electrode surface is larger than zero during stripping. A set of current–time curves[18] (Fig. 5) is obtained for different stripping potentials. By measuring the current on each of these curves at a given time, one can construct a current–potential curve for that particular stripping time. These curves will now be discussed on the assumption that the Nernst equation is applicable. It first will be assumed that the solution is stirred during stripping and that there is no time interval between pre-electrolysis and stripping.

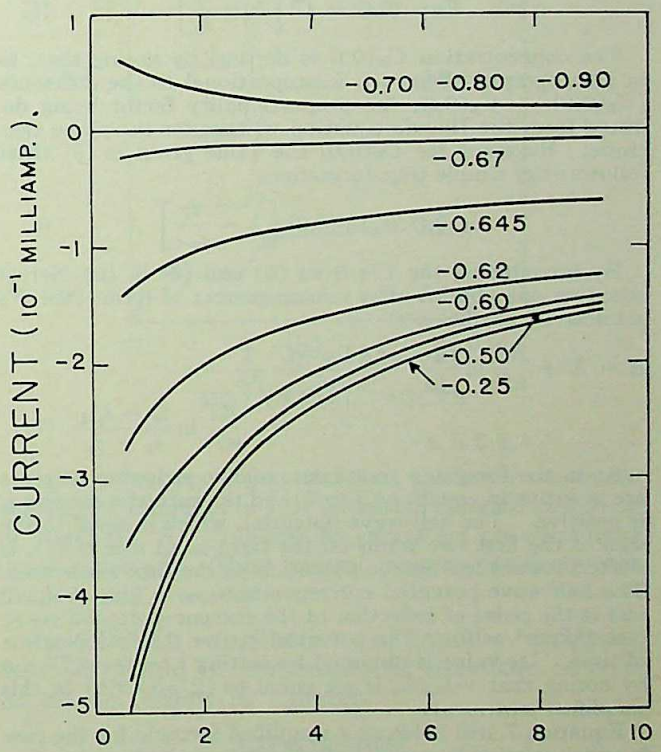

Fig. 5.—Tracings of current–time curves for the anodic stripping potentials (in volts *versus* S.C.E.). Pre-electrolysis time, 10 seconds; time interval between pre-electrolysis and stripping, 4 seconds.

(14) As far as we know, chromatography was first used in the purification of electrolytes in electrochemical studies by P. J. Hillson, *Trans. Faraday Soc.*, **50**, 385 (1954).

(15) T. S. Lee, THIS JOURNAL, **74**, 5001 (1952).

(16) J. G. Nikelly and W. D. Cooke, *Anal. Chem.*, **28**, 243 (1956).

(17) Data were: $i_p \backsimeq 3 \times 10^{-5}$ amp., n = 2, $A \backsimeq 3 \times 10^{-2}$ cm.^{2}, $D = 10^{-5}$ cm.^{2} sec.$^{-1}$, $C^0 = 5 \times 10^{-7}$ mole cm.$^{-3}$.

(18) Note that the curves for −0.90, −0.80 and −0.70 volt in Fig. 5 correspond to the limiting current range for pre-electrolysis. The current decreases progressively because of concentration polarization. Thus, the electrolysis circuit was open after pre-electrolysis and closed again after the interval of 4 seconds, the solution being not stirred after pre-electrolysis.

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To derive the equation of the i_s *versus* t curves for any potential we could use again the initial condition (1) for M and prescribe that the ratio $C_{M^{+n}}/C_M$ at $x = 0$ is equal to a constant readily given by the Nernst equation. Another boundary condition would be obtained by prescribing that the sum of the fluxes of M and M^{+n} at $x = 0$ is equal to zero. The approach is the same as in the rigorous derivation of reversible polarographic waves,[19] but the algebra is far more involved—in fact, too involved for the result to be achieved. It is much easier to assume that C_M is independent of x at $t = 0$ and has the value given by equation 3. This approximation is very good for $t/\tau \leqslant 0.01$ (see above) but is poor for $t/\tau > 0.1$. The concentrations $C_{M^{+n}}(0,t)$ and $C_M(0,t)$ are calculated as follows.

The concentration $C_{M^{+n}}(0,t)$ during stripping is deduced from the condition that the sum of the fluxes of M and M^{+n} at $x = 0$ is equal to zero. On the basis of the Nernst diffusion layer treatment, the flux of M^{+n} during stripping which is equal to i_s/nFA is $D_{M^{+n}}[C_{M^{+n}}(0,t) - C^0]/\delta$, δ being the diffusion layer thickness, and C^0 the bulk concentration of M^{+n}. The thickness δ can be evaluated from $i_p = nFA \cdot D_{M^{+n}}C^0/\delta$. Hence

$$C_{M^{+n}}(0,t) = C^0\left[1 - \frac{i_s}{i_p}\right] \qquad (5)$$

The concentration $C_M(0,t)$ is derived by noting that, as in polarography theory, i_s is proportional to the difference $[C_M(0,0) - C_M(0,t)]$, the proportionality factor being deduced from the Ilkovic equation written for the plane electrode. By using for $C_M(0,0)$ the value given in (3) there follows after simple transformations

$$C_M(0,t) = C_M(0,0)\left[1 - \frac{i_s}{i_{s,d}}\right] \qquad (6)$$

By introducing the C's from (5) and (6) in the Nernst equation one obtains after rearrangement of terms (the F's are activity coefficients)

$$E = E + \frac{RT}{nF}\ln\frac{f_{M^{+n}}}{f_M}\frac{nFAD_M^{1/2}C^0}{\pi^{1/2}i_p}\frac{1}{t^{1/2}} - \frac{RT}{nF}\ln\frac{i_s - i_{s,d}}{i_p - i_s} \qquad (7)$$

As in the foregoing treatment, anodic stripping currents are negative in equations 5 to 7, and the cathodic current i_p is positive. The half-wave potential, which is equal to the sum of the first two terms on the right-hand side of (7), is shifted toward less anodic potentials as the time t increases. The half-wave potential corresponds to $i_s = (i_{s,d} + i_p)/2$ and is the point of inflection of the current–potential curve (set $d^2E/di^2 = 0$). The potential at $i = 0$ is independent of time. Its value is obtained by setting $i_s = 0$ in (7) and by noting that $-i_{s,d}/i_p$ is set equal to $(2/\pi)(\tau/t)^{1/2}$ in this simplified treatment.

Equation 7 still holds as a simplified formula for the case in which stirring is stopped after pre-electrolysis and a time interval elapses before anodic stripping, but the half-wave potential has now the value $E^0 + (RT/nF)\ln(f_{M^{+n}}/f_M)(D_M/D_{M^{+n}})^{1/2}$ and is independent of time. This is the value derived in the theory of reversible polarographic waves.

Current–potential curves deduced from the data of Fig. 5 are plotted in Fig. 6 for different values of t. The half-wave potential is independent of time and has the same value (−0.64 volt *versus* S.C.E.) as the polarographic half-wave potential. The foregoing approximate analysis is thus quite satisfactory for the stripping times involved here.

Current-step Method

Transition Time and Sensitivity Gain.—The conditions are the same as in the potential-step method except that anodic stripping is carried out at constant current. The potential of the amalgam electrode is followed during anodic stripping, and a potential–time curve is recorded. This curve exhibits a rapid variation of potential at the transition time τ_s, *i.e.*, at the time at which $C_M(0, \tau_s) = 0$ (Fig. 7). The ratio τ_s/τ, of the transition time τ_s to the pre-electrolysis time τ, was calculated in a previous paper[9]

$$\frac{\tau_s}{\tau} = \frac{1}{\left(1 - \frac{i_s}{i_p}\right)^2 - 1} \qquad (8)$$

with i_p positive and i_s negative. Experimental and calculated values of τ_s/τ are compared in Table II for the anodic stripping of cadmium from a hanging amalgam drop. The agreement is relatively good in view of the two sources of discrepancy, sphericity of the electrode and loss of metal in mercury by convection. The effect of sphericity becomes more pronounced as the electrolysis is prolonged (compare data for $\tau = 10$ sec. and $\tau = 75$ sec.).

TABLE II

EXPERIMENTAL RATIO τ_s/τ FOR HANGING MERCURY DROP *versus* CALCULATED GAIN FOR A PLANE ELECTRODE—ANODIC STRIPPING OF CADMIUM

i_s,[a] μa.	τ, sec.	τ_s, sec.	τ_s/τ Exptl.	Calcd.
9.9	10	17.5	1.75	2.18
19.6	10	8.5	0.85	1.02
49.4	10	2.4	.24	0.32
49.4	25	7.8	.31	.32
49.4	50	16.0	.32	.32
49.4	75	27.2	.36	.32

[a] Pre-electrolysis current, 48 microamperes; electrode area, 3.16×10^{-2} cm.^{2}.

The sensitivity gain can be expressed by comparing τ_s with the transition time τ_d that would be observed in direct electrolysis at current i_s without pre-electrolysis. Since $\tau_d^{1/2}$ is proportional to the bulk concentration of reducible substance, the ratio $(\tau_s/\tau_d)^{1/2}$, and not τ_s/τ_d, should be considered to express the gain in sensitivity. The gain is $(\tau/\tau_d)^{1/2}[(1 - i_s/i_p)^2 - 1]^{-1/2}$. For the data of Table II ($\tau = 10$ sec., $\tau_s = 17.5$ sec.), one evaluates a gain, $(\tau_s/\tau_d)^{1/2}$, of approximately 6 over the direct method.[20] Actually, the direct method is not applied easily at low concentrations (adsorbed impurities, capacity effect), and the stripping method is more advantageous than this simple calculation of the gain would indicate.

Potential–Time Curves.—As in the potential-step method, we consider only the case in which the Nernst equation is applicable. By introducing the value of the concentration previously derived[9]

$$C_M(0,t) = \frac{2[i_p(\tau + t)^{1/2} - (i_p - i_s)t^{1/2}]}{\pi^{1/2}nFAD_M^{1/2}} \qquad (9)$$

and $C_{M+N}(0,t)$ from equation 5 in the Nernst equation there follows after simple transformations (no time interval between pre-electrolysis and stripping)

$$E = E^0 + \frac{RT}{nF}\ln\frac{f_{M^{+n}}}{f_M}\frac{\pi^{1/2}nFAD_M^{1/2}C^0}{2i_p} - \frac{RT}{nF}\ln\left[(\tau + t)^{1/2}\frac{i_p}{i_p - i_s} - t^{1/2}\right] \qquad (10)$$

Potential–time curves do not have a point of inflection, and the potential becomes progressively more anodic as the electrolysis proceeds (Fig. 7). The potential at $t = 0$ is readily deduced from (10); it depends on pre-electrolysis time and current. It follows from (10) that a plot of log $[(\tau + t)^{1/2}[i_p/(i_p - i_s)] - t^{1/2}]$ against E should have the reciprocal slope of $0.059/n$ at 25°.

(19) See ref. 7, pp. 52–57. Note that this derivation is different from the one usually given in the polarographic literature.

(20) On the basis of the evaluated value $\tau_d \approx 0.5$ sec.

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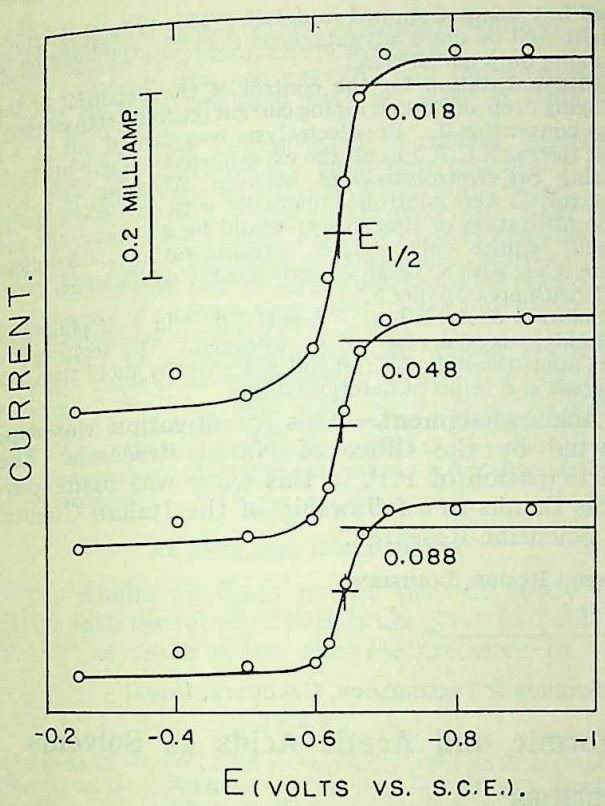

Fig. 6.—Current–potential curves from the data of Fig. 5. Numbers on curves are the times in seconds at which current was measured.

Potential–time curves for the case in which stirring is stopped after pre-electrolysis can be analyzed readily in an approximate fashion on the basis of previous results for voltammetry at constant current (g).

Application to Analysis

The two methods studied in this paper and the method of Nikelly and Cooke[6] (anodic stripping with continuously varying potential) are of interest in the analysis of traces of amalgam forming metals in the concentration range in which direct voltammetry and polarography fail. Hence, anodic stripping methods have a practical value for concentrations below 10^{-6} molar.[21] The sensitivity gain that is achieved results from concentration of the metal to be analyzed in a thin layer at the surface of the mercury electrode. Rather high gains are possible because the metal is deposited in stirred solution at a much higher rate than it diffuses into the bulk of mercury. In this respect, anodic stripping methods can be compared to extraction.[22] It should be emphasized that the gain does not result so much from an increase in current to be measured *per se* (very low currents are quite easy to measure) but rather from an enhancement of current under conditions in which the capacity current is not particularly increased.

(21) For a review of voltammetric and polarographic methods for trace analysis see P. Delahay in "Symposium on Trace Analysis," J. H. Yoe and H. J. Koch, Eds., John Wiley and Sons, New York, N. Y., in preparation, 1955.

(22) Comparison also should be made with the method of N. H. Furman, C. E. Bricker and B. McDuffie, *J. Wash. Acad. Sci.*, **38**, 159 (1948), in which the metal to be analyzed is plated on mercury and is subsequently dissolved in acid after removal of mercury by distillation. See also A. Hickling, J. Maxwell and J. V. Shennan, *Anal. Chim. Acta*, **14**, 287 (1956).

A comparison of the gains obtained by the three anodic stripping methods would require actual application to trace analysis, and only the tentative conclusion that the potential-step method is the most sensitive will be made here.[23]

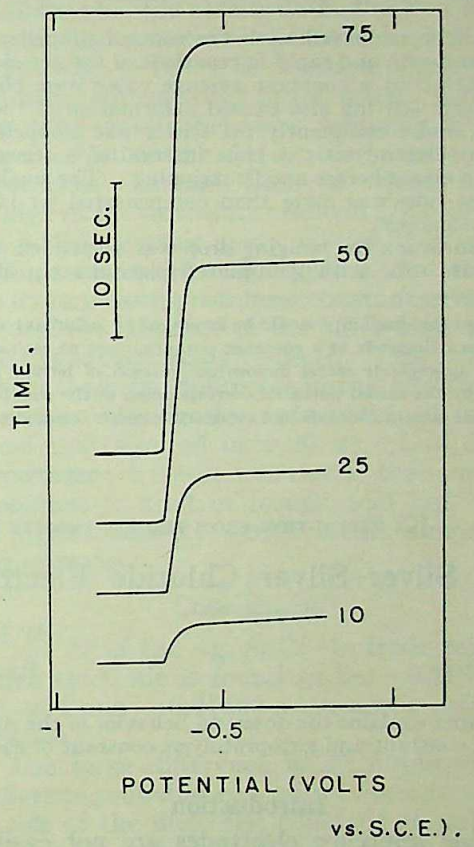

Fig. 7.—Tracings of potential–time curves for the anodic stripping of cadmium in 1 *M* potassium chloride at 1.56×10^{-3} amp.cm.$^{-2}$. Numbers on curves are pre-electrolysis times in seconds. Time interval between pre-electrolysis and stripping, 4 seconds.

An obvious application of anodic stripping methods would be amperometric titrations at concentrations below 10^{-6} molar.

Experimental

A cell with hanging mercury drop[24] of the type previously used in this Laboratory[25] was utilized. A mercury drop falling from a conventional dropping mercury electrode was caught in a small glass spoon and then hung (by rotation of the spoon) on a small gold-plated platinum wire (perhaps 0.1 mm. long) sealed in a glass tube with fine tip. The cell also was provided with a constant speed stirrer of the propeller type. The blades of the propeller were below the tip of the dropping mercury electrode and the hanging drop to avoid the projection of mercury drops on the hanging drop. The stopper was made of plastic and was carefully machined to fit the ground glass collar of the cell. Accuracy in the spacing of the electrodes and spoon was far more easily achieved with a plastic stopper than with a ground glass stopper. A saturated calomel electrode was prepared in the other arm of the cell, and the cell had the usual nitrogen inlet.

It was found that the solution could be rather vigorously

(23) The sensitivity gain of the method of Nikelly and Cooke can be evaluated by noting that the Randles–Sevcik treatment of oscillographic polarography is applicable as a first approximation when the stirrer is stopped before anodic stripping.

(24) First used, as far as we know, by H. Gerischer, *Z. physik. Chem.*, **202**, 302 (1953).

(25) (a) T. Berzins and P. Delahay, THIS JOURNAL, **77**, 6448 (1955); (b) W. Vielstich and P. Delahay, *ibid.*, in press.

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stirred without the dislodging of the hanging drop, and pre-electrolysis limiting currents were relatively large (diffusion layer thickness of the order of 10^{-3} cm.). Because of vigorous stirring, the pre-electrolysis current dropped within 1–2 seconds to an average constant value upon switching on. The area of the hanging drop was reproducible with an error smaller than 1% (a conservative estimate) in a given medium.[26]

The stirring achieved with the rotated propeller stirrer was not uniform, and rapid fluctuations of the pre-electrolysis current about a constant average value were observed. Non-uniform stirring also caused deformation of the hanging drop, and consequently the stirrer was stopped at the end of pre-electrolysis. A time interval of 4 seconds was allowed to elapse before anodic stripping. The small loss in sensitivity gain was more than compensated by improvement in accuracy.

A cell in which the hanging drop was suspended on a rotating glass tube with gold-plated platinum tip also was used but was not studied in detail. This type of electrode might well be more advantageous than the combination of hanging drop and stirrer.

Instrumentation for the control of the potential of the hanging drop and the stripping current (current-step method) was conventional. Pre-electrolysis was carried out at −1 volt (*versus* S.C.E.) in all the experiments. Time intervals during pre-electrolysis and between stripping and pre-electrolysis were controlled manually with an electric timer. The utilization of time relays would be advantageous and would require only simple instrumentation. Recordings were made with a Tektronix cathode-ray oscilloscope, model 531, with preamplifier 53D.

Solution composition: 0.5 mM Cd^{++} in 1 M potassium chloride; oxygen removal by nitrogen. The temperature was approximately 25°; it did not vary by more than 1–2 degrees in a series of determinations.

Acknowledgment.—This investigation was supported by the Office of Naval Research. The participation of P.P. in this work was made possible thanks to a fellowship of the Italian Council of Scientific Research.

Baton Rouge, Louisiana

(26) The reproducibility would be improved by polarizing the dropping mercury electrode at a constant potential (not so cathodic as to cause any appreciable metal deposition) instead of letting the electrode acquire the mixed potential corresponding to the condition that the algebraic sum of faradaic and capacity currents is equal to zero.

[Contribution from the University College of Science & Technology, Calcutta, India]

The Silver–Silver Chloride Electrode in Formic and Acetic Acids as Solvents

By L. M. Mukherjee[1]

Received April 1, 1957

This paper explains the observed behavior of the Ag/AgCl electrode in formic and acetic acids, as solvents, in terms of the dielectric constant and autoprotolysis constant of each medium.

Introduction

Suitable reference electrodes are not easily obtainable for use in formic and acetic acid solutions. Cells employed in previous studies[2,3] of acids and bases in acetic acid, for instance, seem to consist essentially of an aqueous calomel reference electrode in conjunction with chloranil or glass electrode, both with and without salt bridge. To eliminate the difficulties encountered with the use of the calomel electrode, Fritz[4] and Glenn[5] recommended the Ag/AgCl electrode as a reference standard in acetic acid. Accordingly, the purpose of the present investigation is to determine the standard potential of the Ag/AgCl electrode (relative to hydrogen electrode as zero) in both formic and acetic acids with a view to test its performance as a reference electrode and also to explain the observed E^0 values in terms of the properties of the solvents themselves.

Experimental

Cells of the following type were studied in both the solvents

$$\mathrm{Pt,\ H_2;\ HCl_{non\text{-}aq};\ AgCl/Ag}$$

$$E_{obs} = E^0 - \frac{2RT}{F} \ln a^0{\pm}\mathrm{HCl}$$

The observed e.m.f.'s were extrapolated to obtain the standard potential $E°$ of the silver–silver chloride electrode by the procedure outlined by Harned,[6] taking into account the Gronwall–LaMer–Sandved extended terms. Due to incomplete ionization of HCl in formic acid and acetic acid, the extrapolation formula has been modified in each case by replacing the concentration C by α. $C\ (= \sqrt{KC})$ where α and K represent, respectively, the degree of dissociation, and the dissociation constant of HCl as obtained from the previous conductance data in the particular medium. The values of the dissociation constant of HCl in formic and acetic acids used in the present case refer, respectively, to the work of Schlesinger and Martin[7] and of Kolthoff and Willman.[8]

Of the solvents employed in the present study, acetic acid was purified as: 99–100% glacial acetic acid (E. Merck) was refluxed with a little solid $K_2Cr_2O_7$ for about 5 hours on a sand-bath and then distilled in an all-glass Pyrex apparatus provided with $CaCl_2$ guard tube directly into a clean, dry Jena bottle. The distillate so obtained was then frozen out, the liquid portion was discarded and the crystals (m.p. 16.6°) were collected and stored in Jena bottles which were kept in a closed chamber containing some dehydrated silica gel. The sample so obtained was finally characterized by ultraviolet spectrophotometry.

One hundred per cent. A.R. quality formic acid (E. Merck) was used as such without any initial treatment; the acid and the prepared solutions as well were preserved in a closed chamber kept in a refrigerator.

Solutions of HCl were obtained by absorbing in the respective solvents, in almost complete absence of air, HCl gas prepared from concd. H_2SO_4 and NaCl (E. Merck, G.R., oven-dried at 105–110°) and dried by passing through concd. H_2SO_4. Due to very low solubility of HCl in acetic acid, solutions of concentrations higher than 0.00533 N could not be studied in this solvent. Aliquots of the HCl solutions so prepared were taken in water and then estimated either by weighing as AgCl or by back titration of $AgNO_3$ added in

(1) Chemistry Department, The Florida State University, Tallahassee, Florida.

(2) N. F. Hall and J. B. Conant, This Journal, **49**, 3047 (1927).

(3) (a) P. C. Markunas and J. A. Riddick, *Anal. Chem.*, **23**, 337 (1951); (b) R. T. Moore, *et al.*, *ibid.*, **23**, 1639 (1951); (c) C. N. Pifer and E. G. Wollish, *ibid.*, **24**, 300 (1952); (d) W. Seaman and E. Allen, *ibid.*, **23**, 592 (1951).

(4) J. S. Fritz, *ibid.*, **22**, 1028 (1950).

(5) R. A. Glenn, *ibid.*, **25**, 1916 (1953).

(6) H. S. Harned, This Journal, **60**, 336 (1938).

(7) H. I. Schlesinger and A. W. Martin, *ibid.*, **36**, 1589 (1914).

(8) I. M. Kolthoff and J. F. Willman, *ibid.*, **56**, 1007 (1934).

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excess against standard KCNS in aqueous solution. The concentrations were calculated in molarity.

The hydrogen electrode assembly and the silver–silver chloride electrode employed were the same as those described before.[9]

After preparation the silver–silver chloride electrodes were kept short-circuited for some time and finally preserved in dilute aqueous solution of KCl in the dark. The electrodes were usually washed thoroughly with water and then with the desired solvent prior to use in non-aqueous solutions. Before and after the experiments, the electrodes (*viz.*, the hydrogen and the silver–silver chloride electrodes) were checked in aqueous solutions of known activities of hydrogen or halide ions as the case may be.

The e.m.f.'s were recorded at intervals of about 30 minutes for 3 to 4 hours at 35 ± 0.25° with the help of a Leeds and Northrup Type K2 potentiometer and a Hartmann Braun galvanometer till the values were constant within ±0.0001 volt. An additional thermionic amplifier was used to aid the measurements in acetic acid solutions because of their high resistance.

Results and Discussions

The results obtained in the present study together with the relevant details are given in Table I. The E^0 of silver–silver chloride (relative to hydrogen electrode as zero) is found to be −0.11995 and −0.61800 volt, respectively, in formic and acetic acids.

TABLE I

E^0 Ag/AgCl = −0.11995 v. (molar); −0.13022 v. (molal) (formic acid) = −0.61800 v. (molar); −0.62084 v. (molal) (acetic acid). $AgCl + {}^1/_2H_2 \rightleftharpoons Ag + H^+ + Cl^-$; temp. = 35°

Formic acid pK_{HCl} = 1.398, D = 58.5 (16°), a^0 = 6 Å.		Acetic acid pK_{HCl} = 9.292, D = 6.15 (20°), a^0 = 5 Å.	
Concn. of HCl, M	E.m.f. obsd. (v.) cor. to 1 atm. H_2 press.	Concn. of HCl, M	E.m.f. obsd. (v.) cor. to 1 atm. H_2 press.
0.00033	0.17695	0.00090	0.14000
.00120	.15100	.00098	.13770
.00146	.14690	.00125	.13165
.00187	.14065	.00139	.12900
.00273	.13140	.00144	.12515
.00362	.11570	.00226	.10100
.00468	.10730	.00311	.08130
.00563	.09910	.00533	.04970
.00655	.09410		
.00844	.08155		
.01690	.05500		

(9) L. M. Mukherjee, *J. Phys. Chem.*, **58**, 1042 (1954).

It follows from a consideration of the actual values of the standard reduction potentials for the silver–silver chloride electrode in the two solvents, *viz.*, formic and acetic acids, that the reaction $AgX + {}^1/_2H_2 \rightarrow Ag + H^+ + X^-$ is more likely to occur in the former solvent than in the latter. The reason for this difference in behavior probably lies in the combined effect of the dielectric constant and the autoprotolysis constant both of which are relatively high in the case of formic acid (D = 58.50 and pK_s = 6.20 for formic acid; D = 6.15 and pK_s = 14.45 for acetic acid). It appears that the effect due to its large autoprotolysis constant acts in such a way that the influence of the fairly high dielectric constant is substantially reduced. This is also evident from the large difference in the E^0 value of the silver–silver chloride electrode obtained in formic acid and that secured in a 20 wt. % of dioxane–water mixture—a medium of nearly the same dielectric constant as that of formic acid but of much lower proton activity which seems almost equal to that of water.

Conclusions

1. The E^0 of the Ag/AgCl electrode relative to hydrogen electrode is found to be −0.11995 v. in formic acid and −0.61800 v. in acetic acid in the molar scale.

2. The large difference in E^0 obtained in the two solvents probably can be ascribed to the combined role of the dielectric constant as well as the autoprotolysis constant of the solvents concerned and not simply to the influence of any one of these two factors.

Acknowledgments.—My grateful thanks are due to Dr. S. K. Mukherjee, Reader, Department of Applied Chemistry, University of Calcutta, and to Dr. A. K. Ganguly, Senior Research Officer, Department of Atomic Energy, Govt. of India, for helpful suggestions and valuable criticism of the work.

CALCUTTA 9, INDIA

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, MINNESOTA MINING AND MANUFACTURING COMPANY]

The Hydrogen Fluoride Solvent System. IV. Metallic Complexes in Liquid HF[1]

BY A. F. CLIFFORD[2] AND J. SARGENT

RECEIVED MARCH 28, 1957

Evidence is presented for the existence in liquid HF of complexes of Co(II), Co(III), Ni(II), Cu(II), Zn(II), Hg(II) and Pb(II). In particular the system Ni(II)–CH_3CN is discussed and evidence presented for the existence of the ions $NiCH_3CN^{+2}$ and $Ni(CH_3CN)_{1+x}^{+2}$. The instability constant for the former was found to be 1.4×10^{-3}.

Introduction

The existence of metallic complexes in a solvent so extremely acidic as liquid hydrogen fluoride, in which the complexing agents themselves must exist largely in cationic form, is of practical and theoretical interest.[3]

As one of the commonest types of complex ion in water is the ammono complex, such as $Cu(NH_3)_4^{+2}$, so in the search for complexes in liquid HF, one

(1) Presented before the Division of Physical and Inorganic Chemistry, 119th National A.C.S. Meeting, Cleveland, Ohio, April 10, 1951.

(2) Department of Chemistry, Purdue University, West Lafayette, Indiana.

(3) The acid–base relationships in liquid HF have been treated by A. F. Clifford, *et al.*, in Parts I, II and III of this Series, *J. Inorg. Nucl. Chem.*, in press.

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may first think of aquo complexes, such as $Cu(H_2O)_x^{+2}$. Indeed, evidence for these does exist. Thus, it is found[4] that several metallic fluorides, whose solubility in water solution is decreased by increasing the concentration of potassium fluoride, on the other hand become more soluble as the concentration of hydrofluoric acid is increased. After a maximum is reached, however, the solubility decreases as anhydrous hydrogen fluoride is approached (*i.e.*, as the concentration of water is decreased). Thus the compounds CoF_2, NiF_2, CuF_2, ZnF_2 and MnF_2 are found to decrease in solubility in aqueous solutions of KF and NH_4F, obviating the formation of complex ions such as CuF_3^-, and yet their solubility increases in aqueous HF solutions. The solid phases in equilibrium with the HF solutions of high water concentration are found generally to be hydrated, and often contain a ratio of water molecules per metal ion that might be expected for a complex aquo ion. Examples of these are $CoF_2 \cdot 4H_2O$, $NiF_2 \cdot 4H_2O$, $CuF_2 \cdot 2H_2O$ and $ZnF_2 \cdot 4H_2O$. It is to be noted that none of these contain "HF of crystallization" in contrast to the substances which form anionic fluoro complexes. An example of the latter case is AlF_3[4] which forms $AlF_3 \cdot 3H_2O \cdot 3HF$ and $AlF_3 \cdot 6H_2O \cdot 3HF$, which are presumably $[H_3O^+]_3[AlF_6^{-3}]$ and $(H_3O^+)_3[AlF_6^{-6}] \cdot 3H_2O$.

An exact parallel is found in the case of ammono complexes. Thus, the oxides and hydroxides of most metals are quite insoluble in anhydrous ammonia.[5] With the transition metal hydroxides, however, as the concentration of water increases, the solubility increases to a maximum (*i.e.*, a solution of the "ammono complex" is produced), finally decreasing again to a minimum as pure water is approached. The available data do not permit actual calculation of constants of the aquo complexes in HF.

It might be expected, however, that more strongly complexing groups than the aquo group could form complexes of reasonable stability in liquid HF. This paper is a report on some of those which were found.

Discussion of Results

A wide variety of complexes was investigated. In most cases the complexes were not sufficiently stable to withstand isolation of solid phases, so that most of the work was confined to the observation of what complexes were capable of formation in solution. In general this was accomplished by observing simply whether a metallic fluoride could be taken into solution by addition of the complexing agent.

In Table I are listed the results of the reactions between various metal–agent pairs. As nearly as possible the metals and the agents are listed in order of increasing ability to form *covalent* or *inner* complexes.

It can be seen from this table that many complexes which form in aqueous solution apparently do not do so in HF. Moreover, those which do survive in HF are the most "covalent" in nature—*i.e.*, those of Ni, Cu, Zn, Pb, which also involve nitrogen and sulfur.

The colors of the complexes were generally close to those of their aqueous counterparts and are listed in Table II. The colors of lead complexes with thiosalicylic acid and diphenylthiocarbazone (dithizone) could not be observed because of the intensity of the red-brown solutions of the reagents themselves.

The complexes of iron were for the most part weak and ill-defined. It was found that diglycolic acid precipitated from its solution in HF on

TABLE I

METALLIC COMPLEXES IN LIQUID HF[a]

↓ Decreasing electronegativity of ligand — Agent	Increasing electronegativity of metal → Th^{+4}	Mg^{+2}	Mn^{+2}	Zn^{+2}	Pb^{+2}	Fe^{+2}	Co^{+2}	Ni^{+2}	Fe^{+3}	Hg^{+2}	Co^{+3}	Cu^{+2}
KNO_3	O	O										
CF_3CO_2H	O	O			X							
CH_3CO_2H	O	O			X							
Anth.		O	O					?				
Citric		O							?			
EtAcAc		O							O			X
Tart.		O										X
$O(CH_2CO_2H)_2$		O				X			X			
Ophen.	O	O				?		?	?			X
Dmg.		O									X	
NH_4F		O										X
8-OH		O		X		X	X	X		X	X	X
CH_3CN		O						X				X
$(CH_2CN)_2$		O					X^b				X	
α-NO		O			X							
Dithizone		O			X							X
Thiosal.		O				X		O				
CO		O										

[a] X = complex formed; O = no evidence of complex formation; Anth. = anthranilic acid; Citric = citric acid; EtAcAc = ethyl acetoacetate; Tart. = tartaric acid; Ophen = orthophenanthroline; Dmg = dimethylglyoxime; 8-OH = 8-hydroxyquinoline; α-NO = α-nitroso-β-naphthol; Thiosal. = thiosalicylic acid. [b] Gives Co(III) complex.

(4) A. Seidell, "Solubilities of Inorganic and Metal Organic Compounds," 3rd Ed., Vol. 1, D. Van Nostrand Co., Inc., New York, N. Y., 1940.

(5) E. C. Franklin, "The Nitrogen System of Compounds," Reinhold Pub. Corp., New York, N. Y., 1935, p. 31.

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TABLE II

COLORS AND SOLUBILITIES OF COMPLEXES[a]

Complex	Solubility	Color	Complex	Solubility	Color
Fe–CO			Cu(II)–ophen	s	Blue-green
Less stable	s	Emerald	Cu(II)–tart	s	Blue-green
More stable	s	Yellow	Cu(II)–EtAcAc	s	Deep-blue
$Fe–O(CH_2COH)_2$					
From Fe	i	Colorless	$Cu(II)–CH_3CN$	s	Cobalt
From FeF_3	i	Tan	$Cu(II)–(CH_2CN)_2$	s	Green
$Fe(II)–CH_3CN$	s	Colorless	Cu(II)–8–OH	i	Yellowish-green
$Co(II)–CH_3CN$	s	Red	Cu(II)–thiosal	i	Dark brown
$Co(III)–CH_3CN$	s	Cherry	$Zn–CH_3CN$	s	Colorless
$Co(III)–NH_4F$	i	Red-orange	$Hg–CH_3CN$	s	Colorless
Co(III)–α-NO	i	Deep red	$Pb(II)–CH_3COOH$	s	Colorless
$Ni–CH_3CN$	s	Steel blue	$Pb(II)–CF_3COOH$	s	Colorless
$Ni–(CH_2CN)_2$	s	Dark blue	Pb(II)–dithizone	i	Obscured
			Pb(II)–thiosal	s	Obscured

[a] See footnote *a* of Table I.

addition of FeF_3, although no iron could be detected in the solution. The composition of the solid phase was variable and corresponded to no definite ratio of acid to iron. A typical analysis was Fe 32%, F 25% corresponding to an atom ratio of F to Fe of 2.3 (theoretical for FeF_3, Fe 49%). Apparently reaction took place on the surface of the ferric fluoride or iron metal to form an insoluble complex.

When iron pentacarbonyl was mixed with liquid HF a two phase system resulted, at the interface of which gas was evolved in a somewhat more rapid reaction than was observed with nickel tetracarbonyl. If the solution were at least as cold as 0°, and not acidified (*e.g.*, with BF_3), a clear emerald green solution resulted. If the solution were warmed to 20°, acidified with BF_3 or allowed to stand at 0°, or if the initial reaction were carried out under these conditions, a bright yellow solution resulted. Neither of these colors was extractable into CCl_4. This solution partially decomposed in a matter of hours, precipitating FeF_2 and FeF_3 (the latter probably resulting from oxidation by atmospheric oxygen). Complete decomposition to these products resulted when either solution was evaporated. Both of these solutions when treated with solid KI became deep purple. When the purple solution was shaken with CCl_4, the color was extracted into the CCl_4, giving a deep red solution which was found to contain iron tetracarbonyl iodide. This was identified by means of its pyridine complex. The fact that both of these solutions yielded $Fe(CO)_4I_2$ shows that both the green and yellow complexes must contain at least four carbonyl groups. Since both solutions were found to be electrolytic, the complexes must have been ionized.

Nickel tetracarbonyl differed from $Fe(CO)_5$ in decomposing at the liquid–liquid interface directly to NiF_2 with no evidence for the formation of an intermediate complex. For this reason it was used in some experiments as a source of pure, fresh NiF_2.

As in water, the α-nitroso-β-naphthol complex of Co(III) was insoluble. It is interesting that this could be prepared from Co(II) just as in aqueous solution, as well as directly from Co(III). The reaction also proceeded with Co(II) in 48% aqueous HF. Because of the heterogeneous nature of these reactions, however, the products were of variable composition.

Certain of the complexes were strong enough that the free metals would dissolve in solutions of the complexing agents with liberation of hydrogen. Thus in acetonitrile solution zinc dissolved vigorously; nickel, readily; and cobalt and iron, slowly, the last with subsequent precipitation of white iron(II) fluoride. This probably indicates decreasing stability of the complexes of Ni(II), Co(II) and Fe(II) in this order. The greater vigor of dissolution of zinc, on the other hand, may be related to its more electropositive character. Acetonitrile dissolved CoF_3, giving a cherry red solution which on evaporation gave a red solid which oxidized hydrochloric acid and was 46.1% Co (theoretical for CoF_3, 50%; for $CoF_3.CH_3CN$, 37.5%). The solid resulting from evaporation of the Cu(II)–acetonitrile solutions contained a white phase analyzing 0% Cu, 31% F (theoretical for CH_3CNHF, 33.7% F) and a blue phase analyzing 44.2% Cu (theoretical for $CuF_2 \cdot CH_3CN$, 45% Cu).

The gummy solid residue from the Cu(II)–ethyl acetoacetate complex analyzed Cu 10%, F 27%. (A mixture of one part CuF_2 to 3.1 parts $[C_6H_{10}O_3 \cdot H_2]F_2$ would analyze Cu 10%, F 28%.)

In the case of the acetate and trifluoroacetate complexes of lead, the fact that the residue from evaporation of solutions of the former approximated $Pb(C_2H_3O_2)F$, (75% Pb, theoretical 73% Pb) and of the latter, PbF_2 (83% Pb, theoretical 84.5%), may indicate greater stability of the former. This would accord with expectation based on the relative strengths of the free acids. That these were not oxonium fluoroplumbates was shown by the non-reaction of PbF_2 with HF solutions of water, ethanol and KF.

Since none of the metals involved is amphoteric in HF, as shown by the inability of NaF solutions to dissolve the metal fluorides, reaction can in no case be attributed to that cause. That none of the reagents acted as an acid is attested by the complete lack of reaction with the magnesium vessel.

Chromium.—In addition to the complexes already discussed, it was attempted to form an ethyl acetoacetate complex of chromium(III). It was

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found that CrF_3 dissolved in ethyl acetoacetate solution in HF to give a deep green solution identical in appearance with that of CrF_3 in KF solutions in HF. The solid obtained on evaporation of the solution corresponded in analysis to no simple cationic complex, Cr 23%, F 29%.

Quantitative Studies.—The nickel–acetonitrile complex was made the subject of a quantitative study by observing the concentration of nickel taken into solution when introduced as metal powder into HF solutions of known acetonitrile concentration. A plot of the curve obtained is shown in Fig. 1. The numerical data are given in Table III.

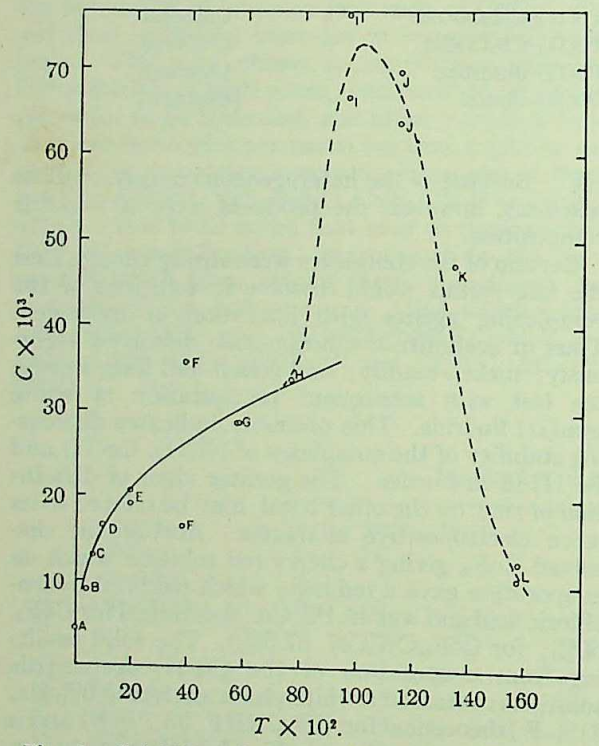

Fig. 1.—Solubility of Ni in HF *vs.* concentration of CH_3CN at −10°. Solid curve: $(T - C)/C^3 = 2.0 \times 10^4$; C = molar concentration of Ni(total); $T = [CH_3CN]_{total}$.

The reaction times quoted show that equilibrium was attained in at least one hour.

If the ionization of acetonitrile as a base ($CH_3CN + HF \rightleftarrows CH_3CNH^+ + F^-$) is ignored, the equations involved in this system are

(1) $F = 2C$ where $F = [F^-]$, C = [complex]

(2) $T = nC + A$ where $T = [CH_3CN]_{total}$, $A = [CH_3CN]$

(3) $MF^2 = s$ where $M = [Ni^{+2}]$, $s = K_{sp}(NiF_2) = 2.81 \times 10^{-7}$ at −10° (calcd. from ref. 6)

(4) $MA^n = jC$ where j = instability constant of complex, n = coördination no.

from which $(T - nC)^n/C^3 = 4j/s$ = const.

It can be seen from Table III that up to point H the value of $(T - nC)^n/C^3$ is very nearly constant for $n = 1$. Consequently, for concentrations of CH_3CN up to 0.60 M, the predominant complex in solution must be $[Ni(CH_3CN)]^{+2}$.

Eliminating point B, and points above H, an average value is found for $4j/s$ of $2.0 \pm 0.2 \times 10^4$.

(6) A. W. Jache, Ph.D. Thesis, University of Washington, 1952.

TABLE III

SOLUBILITY OF NICKEL *versus* CONCENTRATION OF CH_3CN AT −10°[a]

Point	$T \times 10^2$, M	Stirring time, hr.		$C \times 10^3$, M	$\frac{(T-C)}{C^3} \times 10^{-4}$	$\frac{(T-2C)^2}{C^3} \times 10^{-3}$
A	0			4.1 (ref. 6)		
B	3.8	3.00		9.2	3.8	0.52
C	5.7	2.00		12.9	2.1	0.45
D	9.5	2.00		16.5	1.7	0.86
E	19.1	0.75	19.1	19.7	2.3	3.0
		2.00	20.4			
F	38.1	2.00	35.5	26.4	1.9	5.9
		2.00	16.3			
G	57.2	1.00	28.4	28.5	2.3	11.0
		3.00	28.5			
H	76.2	3.00		33.5	1.9	13.0
I	95.4	0.75	66.4	71.2	0.24	1.8
		3.00	76.0			
J	114.3	3.00	69.5	66.5	0.37	3.5
		3.00	63.5			
K	133.3	3.00		47.0	1.3	15.0
L	157.5	2.00	12.7	11.4	12.0	1700
		3.00	10.6			

[a] T = total concentration of CH_3CN; C = total concentration of nickel.

From this the instability constant is found to be $j = 1.4 \times 10^{-3}$.

(If the alternative simplification is made, that the basic ionization of CH_3CN is large, the concentration of fluoride ion therefore being primarily the result of this ionization and also the concentration of free nitrile as a result being negligible in comparison to the nitrile in other forms, then the following calculations result

(5) $F = H$ where $H = [CH_3CNH^+]$

(6) $T = H + nC$

(7) $HF = bA$ where b = ionization constant of CH_3CN, which in conjunction with (3) and (4) give

$$\frac{(T - nC)^{2n-2}}{C} = \frac{b^n j}{s} = \text{const.}$$

This is constant for no integral value of n.)

The portion of the curve from H to I corresponds to the formation of a higher complex. However, the data are not sufficient to determine the nature of the complex. Since in this region the concentration of $[Ni(CH_3CN)]^{+2}$ cannot be considered negligible, the mathematical equation for the curve—even with the same simplification as before—is necessarily complicated. It takes the form

$$(8)\quad k = \frac{js(4jC^2)^{n-1}(T - nC)^{n-2}}{[4jC^3 - s(T - C)][4jC^2 - s(n - 1)]^{n-1}}$$

where k is the instability constant of the new complex. The values of this expression calculated from points H and I are not consistent for any value of n.

The portion of the curve from I to L appears to correspond to the formation of an insoluble phase, presumably $Ni(CH_3CN)_nF_2$. Since with the available data the value of n cannot be determined, however, it is not possible to treat this quantitatively.

Experimental

Apparatus.—The cell employed for these experiments was a magnesium cylinder, 6 cm. in internal diameter and 5 cm.

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deep, closed at top and bottom with Teflon-gasketed Kel-F plates for visibility. The top window was removable. Connections to a reflux condenser of coiled polyethylene tubing, to drainage and to an inlet for liquid HF were provided through magnesium fittings in the walls. These were protected from atmospheric moisture with anhydrous $CaSO_4$ and could be closed by means of magnesium bodied stopcocks with Teflon plugs held in place by spring tension. The drainage outlet was used for obtaining samples of supernate. The HF (General Chemical Company, sulfur-free) was led through a copper coil condenser to a cooled calibrated magnesium reservoir with a Kel-F window from which measured quantities of HF could be delivered to the cell. The cell itself was provided with a cooling coil which maintained the temperature close to −10°.

Thorough mixing of the solutions was ensured by use of a magnetic stirrer. The internal magnet was sealed in a polyethylene capsule for protection.

The Nickel–Acetonitrile Complex.—A portion of pure nickel powder weighed with the magnet, and known volume of acetonitrile, measured by pipet, were placed in the dry cell through the top window, which was then closed tightly. One hundred ml. of HF was now delivered to the cell and stirring begun. In most cases the evolution of hydrogen, brisk at first, was no longer observable after 30 minutes. Stirring was maintained for a longer period (Table III) to ensure attainment of equilibrium. When equilibrium was deemed to have been reached, the cell was drained and washed out with HF until the washes were colorless. The magnet with the unreacted nickel clinging to it was then removed quickly to an anhydrous potassium fluoride desiccator and subsequently weighed. From the loss in weight of the nickel the concentration of nickel in solution was calculated. In two blank runs in the absence of acetonitrile and with different weights of nickel, it was found that complete transfer of the nickel could be accomplished by this method. Because of the formation of a fluoride coating on the metal, the weight increased each time exactly 3.62%, agreeing within the accuracy of the analytical balance. All weights of nickel found during the course of the investigation were corrected by this amount before calculation of the concentration of nickel in solution. The data so obtained are those appearing in Fig. 1 and Table III.

Reagents.—The complexing agents used were of reagent grade in all cases except that of the diglycolic acid, which was of technical grade.

The metal powders were of reagent grade. The metal fluorides were commercial materials obtained from Penn Salt. The $Ni(CO)_4$ was obtained from the International Nickel Company, and the $Fe(CO)_5$ from Chemical Commerce.

Analytical.—All analyses were done by the analytical laboratories of the Central Research Department of Minnesota Mining and Manufacturing Company.

In all cases where analyses were carried out on solutions, the solution of complexing agent was treated with an excess of the solid metallic fluoride.

St. Paul, Minn.

[Contribution from Cobb Chemical Laboratory, University of Virginia]

Heats of Formation of Potassium Chromate, Potassium Dichromate, Chromate and Dichromate Aqueous Ions. Entropy of Dichromate Ion

By C. N. Muldrow, Jr., and L. G. Hepler

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We have determined the heats of solution of K_2CrO_4(c), $K_2Cr_2O_7$(c) and $(NH_4)_2Cr_2O_7$(c) and the heats of reaction of $K_2Cr_2O_7$(c) and CrO_3(c) with aqueous alkali and of K_2CrO_4(c) with aqueous acid. From the results of these determinations we have calculated the heats of formation of K_2CrO_4(c), $K_2Cr_2O_7$(c), $(NH_4)_2Cr_2O_7$(c), $CrO_4^=$(aq) and $Cr_2O_7^=$(aq) to be, respectively, −331.9, −486.4, −425.0, −207.6 and −345.2 kcal./mole. From our heats of formation and reaction, equilibrium constants and entropy data from the literature, we have calculated the entropies of $Cr_2O_7^=$(aq) and $HCrO_4^-$(aq) to be 70.5 and 47.8 cal./deg. mole, respectively. The standard free energies of $CrO_4^=$(aq), $Cr_2O_7^=$(aq) and $HCrO_4^-$(aq) have also been calculated to be −170.1, −303.4 and −179.0 kcal./mole, respectively.

Investigation of the experimental data on which the thermodynamic properties of $CrO_4^=$(aq) and $Cr_2O_7^=$(aq) as given by the Bureau of Standards,[1] Bichowsky and Rossini[2] and Latimer[3] are based showed that these values were not reliably known. Especially, it became apparent that the heats of formation of these ions and of various chromates and dichromates (*e.g.*, K_2CrO_4, $K_2Cr_2O_7$, etc.) were based on questionable heats of reaction of CrO_3 and heats of solution of chromates and dichromates. Calculation of standard heats of formation at 298°K. from the results of many of the pertinent earlier investigations is difficult because most of that work was carried out under such conditions that heats of dilution and heat changes in correcting observed heats of reaction to 298°K. are both large and uncertain. Therefore we have undertaken an investigation of the thermochemistry of $K_2Cr_2O_7$(c), $Cr_2O_7^=$(aq), K_2CrO_4(c) and $CrO_4^=$(aq) by means of solution calorimetry. This work also has involved the study of CrO_3(c) and $(NH_4)_2Cr_2O_7$(c).

(1) "Selected Values of Chemical Thermodynamic Properties," Circular 500, National Bureau of Standards, 1952.
(2) F. R. Bichowsky and F. D. Rossini, "The Thermochemistry of Chemical Substances," Reinhold Publ. Corp., New York, N. Y., 1936.
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Experimental

Our high-precision solution calorimeter used in previous investigations[4,5] has been improved by several changes. The rate of stirring has been increased and more efficient stirrers have been used. This improved stirring has markedly lessened the time required to attain thermal and reaction equilibrium in the calorimeter, without significantly changing the calorimetric drifts, and has therefore reduced extrapolation uncertainties. A second improvement has been more accurate timing of the heating periods. The calibrated stopwatch has been replaced by a Standard electrical timer read to 0.01 second. The timer is wired through a triple pole-double throw switch that is used to switch the electrical power from the dummy heater to the calorimeter heater. We estimate that the total uncertainty in elapsed time for the heating periods due to variation in the frequency of the local 60 cycle a.c. current, etc., is no more than 0.05 second.

All of the reactions investigated have been rapid. In every experiment the reaction was completed and steady after-period drifts were obtained less than five minutes after breaking the sample bulbs. The heating periods varied from 55–200 seconds.

All of the heats have been determined at 25.0 ± 0.3°.

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Materials.—The potassium dichromate ($K_2Cr_2O_7$) used was Mallinckrodt primary standard analytical reagent and the potassium chromate (K_2CrO_4) was Mallinckrodt A.C.S. Reagent. The ammonium dichromate [$(NH_4)_2Cr_2O_7$] was Mallinckrodt analytical reagent. All of these reagents were thoroughly dried before use.

Two brands of CrO_3 were used: Coleman and Bell C.P. and Baker and Adamson Reagent. Samples of both were analyzed by reaction of CrO_3 with standardized ferrous ammonium sulfate solution and titration of the excess ferrous ions with standardized potassium dichromate solution. The titrations were carried out in sulfuric acid–phosphoric acid solution with sodium diphenylaminesulfonate indicator. The two samples of CrO_3 were found to be 99.7 and 99.6% pure, respectively. By making use of a dry box, we were able to load CrO_3 into a weighed calorimeter bulb, weigh the bulb plus CrO_3 and fasten the bulb to the calorimeter stirrer without exposing the CrO_3 to the atmosphere.

The perchloric acid and potassium hydroxide solutions used in the calorimetric runs were prepared by dilution of previously standardized stock acid and alkali solutions.

Results

The difference in the heats of formation of $Cr_2O_7^=$(aq) and $CrO_4^=$(aq) was determined in two different ways, each of which involved the calorimetric determination of two different heats of reaction. We have expressed the difference in these heats of formation in terms of the standard heat of reaction 1 at infinite dilution. This has been done for two purposes: (a) for the calculation of several heats of formation, (b) for the calculation of ΔS_1° from ΔH_1° and ΔF_1°. Because the entropy of every species in (1) except $Cr_2O_7^=$(aq) is known, a value for ΔS_1° makes possible the calculation of the partial molal entropy of $Cr_2O_7^=$(aq).

$$2CrO_4^=(aq) + 2H^+(aq) = Cr_2O_7^=(aq) + H_2O \quad \Delta H_1^\circ \quad (1)$$

The first method for the experimental investigation of the heat of reaction 1 involved determination of the heat of solution of potassium chromate to give potassium and chromate ions and determination of the heat of reaction of potassium chromate with aqueous perchloric acid to give potassium and dichromate ions. The calorimetric reactions are given by eq. 2 and 3, respectively. In the case of reaction 3, the solutions were in every experiment so dilute that no potassium perchlorate was precipitated.

$$K_2CrO_4(c) = 2K^+(aq) + CrO_4^=(aq) \quad \Delta H_2 \quad (2)$$

$$K_2CrO_4(c) + H^+(aq) = 2K^+(aq) + {}^1/_2Cr_2O_7^=(aq) + {}^1/_2H_2O \quad \Delta H_3 \quad (3)$$

The results of these experiments are given in Table I. The starred heats for reaction 2 indicate solution in 7.5×10^{-4} M potassium hydroxide and the others refer to solution in pure water.

Table I

Heat of Solution (2)				Heat of Reaction (3)		
Moles K_2CrO_4/950 ml. soln.	ΔH_2 (kcal./mole)	Moles K_2CrO_4/950 ml. soln.	ΔH_2 (kcal./mole)	Moles K_2CrO_4 × 10^3/950 ml. soln.	Moles $HClO_4$ × 10^3/950 ml. soln.	ΔH_3 (kcal./mole K_2CrO_4)
0.01084	4.32	0.02571	4.32	4.724	5.256	4.37
.01506	4.30	.02714	4.35*	8.432	9.557	4.03
.02064	4.33*			10.427	14.34	3.97
				11.463	14.34	3.89
				14.481	19.11	3.76
				15.604	19.11	3.77

We have extrapolated the heats of (2) and (3) to infinite dilution in order to obtain ΔH_2° and ΔH_3°, which are, respectively, 4.2 and 4.6 kcal./mole K_2CrO_4. We have also calculated $\Delta H_1^\circ = 2\,\Delta H_3^\circ - 2\,\Delta H_2^\circ = +0.8$ kcal. The estimated uncertainty in the measured heats ΔH_2 and ΔH_3 is 0.05 kcal./mole and the uncertainties in the extrapolated values for ΔH_2° and ΔH_3° are 0.1 and 0.2 kcal., respectively.

The second method for the experimental investigation of the heat of reaction 1 involved the heat of solution of potassium dichromate to give potassium and dichromate ions and determination of the heat of reaction of potassium dichromate with aqueous potassium hydroxide to give potassium and chromate ions. The calorimetric reactions are given by eq. 4 and 5, respectively.

$$K_2Cr_2O_7(c) = 2K^+(aq) + Cr_2O_7^=(aq) \quad \Delta H_4 \quad (4)$$

$$K_2Cr_2O_7(c) + 2OH^-(aq) = 2K^+(aq) + 2CrO_4^=(aq) + H_2O \quad \Delta H_5 \quad (5)$$

The results of these experiments are given in Table II. All of the heats of solution of potassium dichromate to give $Cr_2O_7^=$(aq), except one, were carried out in very dilute perchloric acid (10^{-3} to 10^{-4} M). The starred run indicates solution in pure water. No potassium perchlorate was precipitated in any of these runs.

Table II

Heat of Solution (4)				Heat of Reaction (5)		
Moles $K_2Cr_2O_7$/ × 10^3/950 ml. soln.	ΔH_4 (kcal./mole)	Moles K_2CrO_7 × 10^3/950 ml. soln.	ΔH_4 (kcal./mole)	Moles $K_2Cr_2O_7$ × 10^3/950 ml. soln.	Moles KOH × 10^3/950 ml. soln.	ΔH_5 (kcal./mole $K_2Cr_2O_7$)
1.139	19.87	5.330	18.72	7.221	17.04	−7.29
2.005	19.77	5.342	18.80	7.234	17.04	−7.29
2.610	19.86	5.806	18.60*	8.747	24.34	−7.39
3.445	19.18	5.829	18.76	10.100	48.72	−7.36
5.199	18.80	6.870	18.59	15.320	48.72	−7.45
				19.999	48.72	−7.40

We have extrapolated the heats of reactions 4 and 5 to infinite dilution in order to obtain ΔH_4° and ΔH_5°, which are, respectively, 20.0 and −7.3 kcal./mole $K_2Cr_2O_7$. We estimate the uncertainties in the measured heats ΔH_4 and ΔH_5 to be 0.1 and 0.05 kcal./mole. The estimated uncertainties in the extrapolated values for ΔH_4° and ΔH_5° are 0.2 and 0.1 kcal. In order to calculate ΔH_1° from our values for ΔH_4° and ΔH_5° we need to know the standard heat of reaction 6 and have therefore

$$H^+(aq) + OH^-(aq) = H_2O(l) \quad \Delta H_6^\circ \quad (6)$$

calculated $\Delta H_6^\circ = -13.36$ kcal. from Bureau of Standards[1] heats of formation. From the relation $\Delta H_1^\circ = \Delta H_4^\circ + 2\,\Delta H_6^\circ - \Delta H_5^\circ$ we have calculated $\Delta H_1^\circ = 0.6$ kcal. This heat is in satisfactory accord with the value obtained by our first method and we take as a best value $\Delta H_1^\circ = +0.7$ kcal. It is difficult to estimate the uncertainty in this heat because so much of the uncertainty arises from the various extrapolations to infinite dilution rather than from calorimetric or reaction difficulties. However, we believe that the uncertainty in the average ΔH_1° given above is less than 0.3 kcal.

A large number of workers have investigated the various equilibria between $CrO_4^=$(aq), $Cr_2O_7^=$(aq) and intermediate species. In particular,

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Neuss and Rieman,[6] Tong and King,[7] and Davies and Prue[8] have investigated the equilibrium constant for reaction 7 and have obtained values in

$$Cr_2O_7^=(aq) + H_2O = 2HCrO_4^-(aq) \quad K_7 \quad (7)$$

satisfactory agreement. On the basis of these investigations we take $K_7 = 0.029$ and $\Delta F_8^\circ = +2.10$ kcal. Neuss and Rieman[6] also have investigated the acid dissociation of hydrogen chromate ion ($HCrO_4^-$) as in eq. 8. They report K_8

$$HCrO_4^-(aq) = CrO_4^=(aq) + H^+(aq) \quad K_8 \quad (8)$$

$= 3.2 \times 10^{-7}$ and we calculate $\Delta F_8^\circ = +8.86$ kcal.

We have used these equilibrium constants and free energies to calculate $K_1 = 3.37 \times 10^{14}$ and $\Delta F_1^\circ = -19.82$ kcal. We further calculate $\Delta S_1^\circ = (\Delta H_1^\circ - \Delta F_1^\circ)/T = 68.8$ cal./deg.mole. We take entropies of H_2O, H^+ and $CrO_4^=$ from the Bureau of Standards and calculate from ΔS_1° that the partial molal entropy of $Cr_2O_7^=(aq)$ is 70.5 cal./deg. mole.

The heats of solution and reaction reported above are sufficient to determine the heat of hydrolysis of $Cr_2O_7^=(aq)$ to $CrO_4^=(aq)$ and thence the entropy of $Cr_2O_7^=(aq)$. However, in order to obtain heats of formation of $CrO_4^=(aq)$, $Cr_2O_7^=(aq)$ and the potassium salts, it is necessary to carry out at least one additional calorimetric investigation. Accordingly, we have measured the heat of reaction of CrO_3 with aqueous potassium hydroxide to give chromate ions. This heat of reaction, with the heat of formation of CrO_3 and the Bureau of Standards heats of formation of the other substances involved, suffices to give us the heat of formation of $CrO_4^=(aq)$. The calorimetric reaction is given by eq. 9 and the results are given in Table

$$CrO_3(c) + 2OH^-(aq) = CrO_4^=(aq) + H_2O \quad \Delta H_9 \quad (9)$$

III. We have extrapolated these heats to infinite dilution and take $\Delta H_9^\circ = -28.0$ kcal./mole CrO_3. The estimated uncertainty in ΔH due to extrapolation to infinite dilution and the small amount of impurity in the CrO_3 is 0.2 kcal.

TABLE III

REACTION OF $CrO_3(c)$ WITH $OH^-(aq)$

Moles $CrO_3(c) \times 10^3$/ 950 ml. soln.	Moles $OH^- \times 10^3$/ 950 ml. soln.	ΔH_9 kcal./ mole CrO_3
4.881	12.11	−28.01
5.692	14.60	−28.09
7.447	17.04	−28.10

The largest error involved in this procedure comes from the uncertainty in the heat of formation of CrO_3. This heat of formation depends upon the heat of oxidation of Cr_2O_5 to CrO_3 as determined by Roth and Becker[9] and on the heat of formation of Cr_2O_3. The heat of formation of Cr_2O_3 has been investigated recently by Mah[10] (combustion calorimetry) and by Ramsey and co-workers[11] (temperature coefficient of dissociation pressure), who have discussed the earlier work on Cr_2O_3. On the basis of the results of these investigations we have chosen −270.0 kcal./mole as the standard heat of formation of $Cr_2O_3(c)$.

This is identical with the heat of formation chosen earlier by Brewer[12] and close to that adopted by the Bureau of Standards[1] (−269.7). We calculate from this heat of formation and Roth and Becker's heat of oxidation that the heat of formation of $CrO_3(c)$ is −138.0 kcal./mole.

We have used the above values of ΔH_9° and the heat of formation of CrO_3 with the Bureau of Standards[1] heats of formation of H_2O and $OH^-(aq)$ to calculate the standard heat of formation of $CrO_4^=(aq)$ to be −207.6 kcal./mole. By combining this heat of formation with heats of formation of $K^+(aq)$, H_2O and $OH^-(aq)$ as given by the Bureau of Standards[1] and our ΔH_1°, ΔH_2°, ΔH_3°, ΔH_4° and ΔH_5° we have calculated the heats of formation of $Cr_2O_7^=(aq)$, $K_2CrO_4(c)$ and $K_2Cr_2O_7(c)$ to be, respectively, −346.2, −331.9 and −486.4 kcal./mole.

We have also determined the heat of solution of $(NH_4)_2Cr_2O_7$ in very dilute perchloric acid (10^{-3} to 10^{-4} M). The calorimetric reaction is given by eq. 10 and the results are given in Table IV.

$$(NH_4)_2Cr_2O_7(c) = 2NH_4^+(aq) + Cr_2O_7^=(aq) \quad \Delta H_{10} \quad (10)$$

We have extrapolated the observed heats to infinite dilution to obtain $\Delta H_{10}^\circ = 15.3 \pm 0.2$ kcal./mole. This heat was used with our heat of formation of $Cr_2O_7^=(aq)$ and the Bureau of Standards[1] value for $NH_4^+(aq)$ to calculate the heat of formation of $(NH_4)_2Cr_2O_7(c)$ to be −425.0 kcal./mole. Kapustinskii and Shidlovskii[13] investigated the heat of combustion of $(NH_4)_2Cr_2O_7$ to give N_2, H_2O and Cr_2O_3 and reported the heat of formation of $(NH_4)_2Cr_2O_7$ to be −430 ± 6 kcal./mole. This is seen to be in satisfactory agreement with our heat of formation. In so far as our work is concerned, the only likely large source of error is the appreciable uncertainty in the heat of formation of CrO_3. The combustion work avoids this difficulty and therefore it would be desirable to have a better heat of combustion of $(NH_4)_2Cr_2O_7$.

TABLE IV

HEAT OF SOLUTION OF $(NH_4)_2Cr_2O_7(c)$

Moles $(NH_4)_2Cr_2O_7(c) \times 10^3$/ 950 ml. soln.	ΔH_{10} (kcal./mole $(NH_4)_2Cr_2O_7$)
4.256	15.21
4.976	15.02
8.426	14.59
9.610	14.55

We have calculated the standard free energies of formation of $CrO_4^=(aq)$ and $Cr_2O_7^=(aq)$ from our heats of formation and entropies to be, respectively, −170.1 and −303.4 kcal./mole. It would also be desirable to calculate the standard oxidation potential of the $Cr^{+++}/Cr_2O_7^=$ couple. There are several possible ways to carry out this calculation. The heat of formation of $Cr^{+++}(aq)$ can be used with an estimated entropy to calculate the

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free energy of formation of Cr^{+++}(aq) which can then be combined with our free energy of formation of $Cr_2O_7^{=}$(aq) to give $\Delta F°$ and $E°$ for the Cr^{+++}/$Cr_2O_7^{=}$ couple. Or the heat of reduction of $Cr_2O_7^{=}$(aq) to Cr^{+++}(aq) can be combined with an estimated entropy of Cr^{+++}(aq), and our entropy of $Cr_2O_7^{=}$(aq) to give $\Delta F°$ and $E°$ for the Cr^{+++}/$Cr_2O_7^{=}$ couple. Data from the literature for the pertinent heats[3,14] are so unreliable as to make these calculations virtually meaningless.

From the results of the investigation by Davies and Prue[8] of the temperature dependence of the equilibrium constant for reaction 7 we calculate $\Delta S_7° = 8.5$ cal./deg. mole $Cr_2O_7^{=}$ and $\Delta H_7° = 4.64$ kcal./mole $Cr_2O_7^{=}$. These data have been combined with our heat of formation and entropy of $Cr_2O_7^{=}$(aq) and the National Bureau of Standards values for water to give the heat of formation of $HCrO_4^{-}$(aq) as -205.0 kcal./mole and the entropy as 47.8 cal. deg./mole. We also have calculated the standard free energy of formation of $HCrO_4^{-}$ to be -179.0 kcal./mole.

Discussion

Latimer[3] and the National Bureau of Standards[1] have taken the entropy of $HCrO_4^{-}$(aq) to be 16.5 cal./deg.mole. Our value (47.8) is much more nearly in accord with what one should expect from comparison with MnO_4^{-} (45.4),[3] ReO_4^{-} (48.3),[15] and ClO_4^{-} (43.2).[3] We also see that the entropy of ionization of $HCrO_4^{-}$ (-38.6) as calculated from our entropy is in accord with the entropies of ionization of HSO_4^{-} (-26.2), HSO_3^{-} (-33), $H_2PO_4^{-}$ (-29.9), HCO_3^{-} (-35.4) as taken from Latimer.[3]

Our heat of solution of K_2CrO_4(c) ($\Delta H_2°$) is in good agreement with the results obtained by earlier workers.[1] Our heat of solution of $K_2Cr_2O_7$(c) ($\Delta H_4°$) is about 3 kcal./mole more positive than heats reported by earlier investigators.[1] It is impossible to compare our heats of reaction of K_2CrO_4(c) with H^{+}(aq) ($\Delta H_3°$) and of $K_2Cr_2O_7$(c) with OH^{-}(aq) ($\Delta H_5°$) with the older heats[1,2] because the older work was carried out in relatively concentrated solutions and at temperatures lower than 25°. Our heat of reaction of CrO_3(c) with OH^{-}(aq) ($\Delta H_9°$) is several kcal./mole more exothermic than earlier heats. We attribute this to the fact that the older work was carried out in more concentrated solutions at temperatures lower than 25° and possibly with less pure CrO_3.

Acknowledgments.—We are pleased to express our gratitude to Mr. Robert L. Graham for help with some of the calorimetric work and to the Research Corporation for financial assistance.

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CHARLOTTESVILLE, VA.

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

A Copper Analog of the Alkali Tungsten Bronzes

BY LAWRENCE E. CONROY AND M. J. SIENKO[1]

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Non-stoichiometric solids of the form Cu_xWO_3 have been prepared by electrolytic reduction at 800° of molten mixtures of $CuWO_4$ and WO_3. Copper content has been varied from $x = 0.26$ to $x = 0.77$. Two kinds of crystals have been found—orthorhombic with $a = 3.88$ Å., $b = 3.73$ Å., and $c = 7.74$ Å., taken from the preparation for which $x = 0.26$, and triclinic with $a = 5.85$ Å., $b = 6.65$ Å., $c = 4.88$ Å., $\alpha = 134°45'$, $\beta = 91°40'$, and $\gamma = 93°37'$, taken from the preparation for which $x = 0.77$. The molar magnetic susceptibility at 26° of the powder for which $x = 0.26$ was observed to be $+34 \pm 1 \times 10^{-6}$. Conductivity measurements from $-160°$ to $+80°$ made on single triclinic crystals taken from the preparation for which $x = 0.77$ showed typical semi-conductor behavior. At 26° the specific resistance was 12.6 ohm-cm. perpendicular to the c-axis and 17.2 ohm-cm. parallel to the c-axis. Energies of activation for the conduction process were found to be 0.147 and 0.149 electron volt, respectively. Attempts to measure the Hall voltage of a single crystal indicated 13 cc. per coulomb as an upper limit for the Hall constant, from which it is deduced that the minimum concentration of current carriers is 5×10^{17} particles per cc. It is proposed that these materials are analogous to the tungsten bronzes.

The alkali tungsten bronzes are non-stoichiometric solids of composition M_xWO_3, where M is an alkali metal and x can vary from 0 to 1. Although known since their discovery by Wöhler[2] in 1824, it is only recently that these bronzes have been well characterized.[3] The sodium tungsten bronzes, for which the data are most extensive, have been shown to have a cubic perovskite structure[4] if x is greater than about 0.35, a high electronic[5] conductivity which passes through a maximum[6] at $x = 0.75$, and a feeble paramagnetism[7,8] which is independent of temperature.[8] The Hall coefficient is negative, and its magnitude indicates that there is approximately one free electron per sodium atom.[5] Chemically, all the alkali tungsten bronzes are quite inert, being attacked only by strong alkalies.

As discussed in a previous paper,[9] the tungsten

(1) On leave of absence at the Laboratorie de Chimie Minérale, University of Toulouse, Toulouse, France.

(2) F. Wöhler, *Pogg. Ann.*, **2**, 350 (1824).

(3) G. Hägg, *Z. physik. Chem.*, **B29**, 192 (1935); G. Hägg, *Nature*, **135**, 874 (1935); M. F. Straumanis and S. S. Hsu, THIS JOURNAL, **72**, 4027 (1950); A. Magneli, *Arkiv. Kemi*, **1**, 213 (1949); A. Magneli and B. Blomberg, *Acta Chem. Scand.*, **5**, 377 (1951).

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(5) E. J. Huibregtse, D. B. Barker and G. C. Danielson, *Phys. Rev.*, **84**, 142 (1951).

(6) B. W. Brown and E. Banks, *ibid.*, **84**, 609 (1951).

(7) F. Kupka and M. J. Sienko, *J. Chem. Phys.*, **18**, 1296 (1950).

(8) P. M. Stubbin and D. P. Mellor, *Proc. Roy. Soc. N. S. Wales*, **82**, 225 (1948).

(9) L. E. Conroy and M. J. Sienko, THIS JOURNAL, **74**, 3520 (1952).

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bronzes can best be considered as solutions of M in WO_3, in which each M atom is dissociated into M^+ and an electron. The cubic bronzes can then be visualized as consisting of a simple cubic arrangement of tungsten atoms with shared oxygen atoms on the cube edges and with vacancies in the cube centers more or less occupied by alkali metal cations. Each alkali metal atom has thus effectively contributed one free electron to the electron gas which permeates the whole lattice. Since Cu(I) has approximately the same ionic radius as the sodium ion, it might be possible to substitute copper cations for sodium cations in the above structure and thereby obtain a Cu_xWO_3 analogous to Na_xWO_3. In the following, the preparation and properties of Cu_xWO_3 are described.

Experimental Procedure and Results

Preparation.—Cu_xWO_3 was prepared by electrolytic reduction of fused mixtures of $CuWO_4$ and WO_3. The $CuWO_4$ was made by mixing tungstic acid, H_2WO_4, and basic copper carbonate, $CuCO_3 \cdot Cu(OH)_2$, in a 2:1 molar ratio and adding enough water to make a thin slurry. The mixture was heated at about 70° for 3 to 4 hr. and the remaining water was then evaporated off at 130° in a drying oven. The product was a green-brown powder melting at about 680°. The WO_3 was made as previously described.[9]

To produce Cu_xWO_3, mixtures of various proportions of $CuWO_4$ and WO_3 were electrolyzed at 800° using platinum electrodes. The applied potential was six volts at the electrodes with a cathode current density of 0.06 to 0.08 amp. per cm.^{2}. Electrolysis was continued for four hours. The cooled melt, on being heated with 5% NaOH solution at 80° overnight, disintegrated into a mixture of black crystals and red Cu_2O. After the Cu_2O was removed with concentrated HCl, the remaining crystals were further leached with 5% NaOH for one hour, washed alternately with aqueous HF and NH_4OH, and finally rinsed with water. Chemically, the Cu_xWO_3 was found to be as inert as the alkali tungsten bronzes.

Three different preparations of Cu_xWO_3 were produced, having values of x of 0.26, 0.34 and 0.77. These materials were prepared from melts containing one, two and six moles of $CuWO_4$, respectively, per one mole of WO_3.

Chemical Analysis.—The products were brought into solution by fusion with a mixture consisting of three parts of $NaNO_3$ to one part of Na_2CO_3 by weight. The cooled melt was then dissolved in water. Tungsten was determined as the trioxide by the nitric acid–cinchonine precipitation.[10] Copper was determined (1) electrolytically[11] in ammoniacal solution and (2) polarographically using a dropping mercury electrode. For the latter method, the copper diffusion current of the analysis solution was compared with the copper diffusion current of a standard copper solution containing all other ions in the same concentrations as in the analysis solution. The two methods agreed within 4% of the copper content. Oxygen content, calculated by difference, amounted to 2.9 ± 0.3 gram-atoms per gram-atom of tungsten.

X-Ray Studies.—Powder X-ray patterns of the three products prepared were very similar. The lines in all cases were quite diffuse in the high angle region and could not be measured more accurately than 0.1 mm. Indexing the powder pattern lines proved to be a formidable task, so single crystal photographs were taken of two crystals. Crystal I was taken from the preparation having the composition $Cu_{0.26}WO_3$ and crystal II, $Cu_{0.77}WO_3$.

Crystal I was a needle about 0.7 mm. long and 0.08 mm. in diameter. It was mounted for oscillation about the direction of elongation. Fifteen-degree oscillation photographs and zero and first layer Weissenberg photographs were taken using copper Kα radiation. The zero layer Weissenberg photograph showed the axes to be orthogonal within 0.2°. This photograph also showed the systematic absence of any spots with indices l odd. The lattice parameters were calculated to be: $a = 3.88$ Å., $b = 3.73$ Å., and $c = 7.74$ Å. The zero and first layer Weissenberg photographs about the b-axis showed no other special extinctions. Since photographs were not taken about the other axes, the crystal symmetry could be classified only as far as orthorhombic.

Crystal II was a needle about 0.9 mm. in length and 0.07 mm. in diameter. This crystal was mounted for oscillation about the elongation direction, and 15° oscillation photographs were taken. The layer line spacings indicated an interplanar spacing of 4.90 Å. Zero layer and first layer equi-inclination Weissenberg photographs were taken about the same axis. It was found that two series of spots could be indexed on these photographs, indicating that the crystal was twinned. The apparent presence of a symmetry plane led us at first to the erroneous assumption that the symmetry was monoclinic. Further studies[12] on other crystals of this preparation, however, have shown that the symmetry is actually triclinic. The lattice parameters of the "best" primitive cell have been taken as: $a = 5.85$ Å., $b = 6.65$ Å., and $c = 4.88$ Å. with $\alpha = 134°45'$, $\beta = 91°40'$, and $\gamma = 93°37'$. The needle axis is always in the direction of c, and the crystals are twinned about a. (The proximity of β to 90° was responsible for our original assumption of monoclinic symmetry.) The space group is either P1 or $P\bar{1}$.

Magnetic Susceptibility.—The molar magnetic susceptibility of a powder sample having the composition $Cu_{0.26}WO_3$ was determined by the Gouy method using the apparatus and the procedure previously described.[9] The observed susceptibility at 26° for a mole of $Cu_{0.26}WO_3$ was found to be $+34 \pm 1 \times 10^{-6}$ c.g.s. units. Furthermore, using 3 cm. radiation, there was no detectable paramagnetic resonance absorption in magnetic fields ranging from zero to 9000 oersted, either at 26° or at liquid nitrogen temperature.

Electrical Conductivity.—The electrical conductivity of some apparently single crystals of $Cu_{0.77}WO_3$ was measured as a function of temperature over the range 110 to 350°K. The crystals used were of the triclinic form and were 2 to 3 mm. long and 0.5 to 1 mm. in diameter. They were cleaved approximately perpendicular to the long axis and were mounted in a brass crystal holder between indium-faced pressure contacts by means of a micromanipulator. The potential drop across the crystal was measured with a Leeds and Northrup type K-2 potentiometer. The current flowing through the crystal was measured by noting the potential drop across a standard resistor in series with the crystal. The crystal holder itself was mounted on a Plexiglas rod support and enclosed in a silvered Dewar flask by a Plexiglas cover sealed with a rubber O-ring. The gas pressure in the Dewar jacket could be varied through a side-arm and stopcock. The temperature of the crystal was measured by a copper–constantan thermocouple mounted on the brass crystal holder with the junction in contact with one of the pressure contacts which held the crystal.

Before each set of conductivity measurements, the Dewar containing the crystal was flushed for 30 min. with dried argon or oil-pumped nitrogen. For the low temperature measurements, dry air was let into the Dewar jacket and the Dewar and contents immersed in liquid nitrogen. The Dewar jacket was then pumped out and the liquid nitrogen-bath removed. Readings were then taken as the crystal slowly warmed to room temperature. For temperatures above room temperature the Dewar was immersed in a heated water-bath.

A typical crystal had a resistance of 2 to 3 thousand ohms, so that the current through the crystal from a 6-volt dry cell source was a few milliamperes. Using this apparatus, the conductivity curve for a given crystal could be reproduced to within the precision of the thermocouple reading (*ca.* 0.5%). Reversal of the polarity of the imposed potential produced no detectable change in the conductivity. For specific resistivity values the crystal dimensions were measured with a microscope, using a micrometer eyepiece. The data obtained for several crystals are represented in Fig. 1 as a plot of the logarithm of the specific resistivity against the reciprocal of the absolute temperature. At 26° a typical crystal showed a specific resistivity of 12.6 ohm-cm. perpendicular to the crystal elongation axis (c-axis) and 17.2 ohm-cm. parallel to the same axis. Assuming an exponential form of the dependence of resistivity on the reciprocal of the absolute temperature, we obtain for

(10) F. P. Treadwell and W. T. Hall, "Analytical Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1937, p. 226.

(11) Ref. 10, p. 68.

(12) R. E. Hughes and H. Katz, private communication. Detailed structure studies are now in progress.

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the energy of activation of the process 0.147 electron volt for conductance perpendicular to the c-axis and 0.149 e.v. for conductance parallel to the c-axis. Measurements using sputtered contacts in place of the pressure plates give essentially the same values.

Measurement of the Hall Coefficient.—A three-probe method was used. One probe was mounted on one side of the crystal; the other two were connected through a 100,000 ohm helipot and were in contact with the opposite side of the crystal. With the center tap of the helipot connected to the voltage-measuring apparatus, the IR drop between the probes in the direction of the current in the crystal could be balanced out by obtaining a minimum voltage reading with current flowing in the crystal in the absence of a magnetic field. Any change in the voltage when the magnetic field was applied must then be due solely to the magnetic field. The probes were 10 mil diameter tungsten wires, sharpened by dipping repeatedly in molten potassium nitrite. The magnetic field was supplied by a small magnetron magnet with half-inch diameter pole faces rated at 7500 gauss.

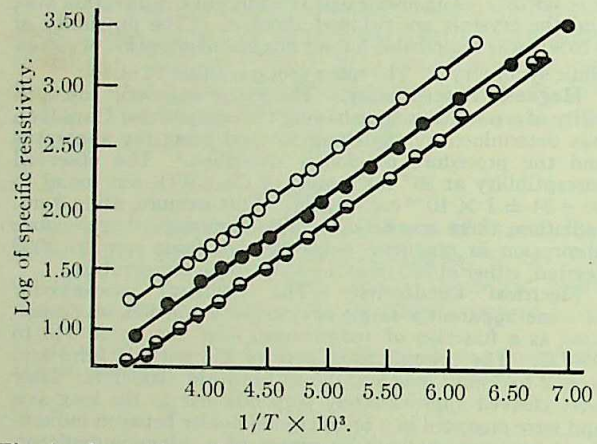

Fig. 1.—Logarithm of the specific resistivity *vs.* reciprocal temperature of three different crystals of $Cu_{0.77}WO_3$.

Attempts to measure the Hall voltage using direct current through the crystal did not give reproducible results. An alternating current method, using a 50-cycle square wave of 10 milliamperes through the crystal and a narrow-band amplifier tuned to 50 cycles at the output of the Hall probes, indicated that there was no Hall voltage measurable above the noise level of the equipment. Thus, it was possible to set only an upper limit on the Hall voltage of 0.25 millivolt, which was the limit of sensitivity of the apparatus.

Discussion

Compared to the sodium tungsten bronzes, in which the magnetic susceptibility and conductivity behavior are typically metallic, the substances Cu_xWO_3 offer a contradiction in these properties. Their low magnetic susceptibility can be interpreted in terms of an electron gas, but such an electron gas structure would suggest fairly high conductivity. In fact, the conductivity of Cu_xWO_3 is low and increases with temperature, a behavior more representative of a typical semi-conductor. It is true that many semi-conductors show also a low magnetic susceptibility but this in general is due to the low concentration of impurity centers. In Cu_xWO_3, which may be considered as solutions of impurity copper in WO_3, the concentration of impurity centers is large enough to be expected to produce an easily detected paramagnetism.

If we assume that the copper atoms in Cu_xWO_3 are dissociated into Cu^+ ions and free electrons, then we would have in $Cu_{0.26}WO_3$ 0.26 mole of free electrons. Using the free electron model described in a previous paper,[9] we would calculate -12×10^{-6} for the molar susceptibility of $Cu_{0.26}WO_3$. If the electrons are not free but are bound singly, as for example to tungsten atoms so that formally some of the W(VI) of WO_3 is converted to W(V), then we would calculate a value of $+218 \times 10^{-6}$ for one mole of $Cu_{0.26}WO_3$. These values are to be compared with the experimentally observed susceptibility of $+34 \times 10^{-6}$. Evidently, the experimental value is closer to the electron gas model than to the W(V) model. The discrepancy between -12×10^{-6} and $+34 \times 10^{-6}$ could be accounted for qualitatively by assuming that the electrons are not absolutely free as in an ideal electron gas but are feebly bound to some centers in the lattice. Even feeble binding would tend to make the spin paramagnetism of the electrons start to appear.

However, feeble binding of the electrons implies that the electrons are rather free to move through the lattice, a prediction contradicted by the observed low conductivity. Therefore, in spite of the support offered by the low magnetic susceptibility, the free electron gas model does not seem applicable to Cu_xWO_3 as it is to the sodium tungsten bronzes.

What is the alternative? To account simultaneously for the low conductivity and the low susceptibility, it is necessary to assume that the odd electron of each copper atom is bound in the lattice not singly but is paired with another electron. There are several mechanisms by which this pairing could occur. An electron could be physically transferred from one copper atom to another, so that the material might consist of a solution of Cu^+ and Cu^- ions in a WO_3 lattice. Alternatively, the odd electron could be localized on a copper atom but coupled by an exchange interaction with an electron on a neighboring copper atom. There might even be coupling by superexchange through the intermediacy of an intervening oxygen atom. A third possibility would be for the electron of each copper atom to be transferred to the WO_3 network with subsequent coupling of neighboring W(V) states by superexchange through intervening oxygen atoms. In any case, the spin paramagnetism of the odd electron of the copper would have to be cancelled to agree with experimental observations. Localization of the electrons would have to be assumed, to agree with the low conductance observed.

Although the measurement of the Hall effect described above is inconclusive, there are some inferences which can be drawn from it. If we set the upper limit of the Hall voltage at 0.25 millivolt, then by using the relation

$$R_H = \frac{10^8 V_H t}{IH}$$

where V_H is the Hall voltage in volts, t is the thickness of the crystal in cm., I is the current in amperes, and H is the magnetic field in gauss, we calculate 13 cc. per coulomb as an upper limit for the Hall constant, R_H. According to theory,[13] if conduction is by electrons, the Hall constant is in-

(13) See, for example, W. Shockley, "Electrons and Holes in Semiconductors," D. Van Nostrand Co., Inc., New York, N. Y., 1950, p. 211.

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versely proportional to the density of conducting electrons. Using

$$R_H = -\frac{1}{ne}$$

where n is the number of conduction electrons per cc. and e is the electronic charge in coulombs, we find 5×10^{17} as a lower limit for the number of free electrons per cc. This figure is in substantial agreement with the number 10^{18} absorbing centers per cc. deduced from very crude measurements of the intensity of infrared absorption by powdered Cu_xWO_3.

In view of the crudity of our Hall voltage measurement, only qualitative significance can be given to the numerical comparison offered above. We are now in the process of refining our measurements to make the comparison more meaningful. In addition, we are extending our investigations to newly prepared $Pb_{0.4}WO_3$, which seems to be typically metallic, and to $Ag_{0.4}WO_3$, which is apparently semi-conducting.

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Free Energy Change and the Electron Electrode in Liquid Ammonia

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The standard free energy change for the reaction $Na_{(s)} \rightarrow Na^+_{(NH_3)} + e^-_{(NH_3)}$ has been determined experimentally by combining measurements on two types of galvanic cells: Na|NaI in liquid ethylamine|Na amalgam, for which the standard e.m.f. was found to be 0.828 ± 0.000 and 0.835 ± 0.001 volt at -50 and $-70°$, respectively, and Na amalgam|NaI in liquid ammonia‖Na in liquid ammonia|inert metal, for which the standard e.m.f. was found to be -0.933 ± 0.020 volt at $-50°$ and -0.947 ± 0.020 volt at $-70°$. These results have been used to obtain directly an experimental value for the solvation free energy of sodium ion in ammonia. Measurements are also reported for the distribution of sodium between mercury and liquid ammonia.

The existence of ion-like electrons in sodium–liquid ammonia solutions[2] suggests the possibility of constructing a galvanic cell which would give directly the free energy change for the reaction

$$Na_{(s)} \longrightarrow Na^+_{(NH_3)} + e^-_{(NH_3)}$$

The most obvious design—solid sodium as one electrode and an inert metal as the other, both immersed in the same solution of sodium in liquid ammonia—gives no useful information because the over-all cell reaction shown above comes to equilibrium as a dissolution equilibrium at the solid sodium–liquid ammonia interface. To bypass this difficulty, we have constructed two cells—in one of which the dissolution equilibrium was completely suppressed by amalgamation of the sodium and in the other of which the effect of such amalgamation on the voltage was determined. The two types of cells and their designations in this paper are

Cell I $\quad Na_{(s)}|NaI \text{ in } EtNH_2|Na_{(Hg)}$

Cell II $\quad Na_{(Hg)}|NaI \text{ in } NH_3‖Na \text{ in } NH_3|\text{inert metal}$

Before describing the structure and operation of these cells, we note two problems that arose in the course of this research. In order to choose an amalgam concentration that would be sufficient to repress the sodium dissolution equilibrium, it was necessary that we investigate the distribution of sodium between mercury and liquid ammonia. The second problem dealt with the choice of metal to use as an inert "electron electrode" in liquid ammonia. Kraus[3] in his work on transference numbers and Laitinen and Nyman[4] in their polarographic work with the "electron electrode" used platinum as the inert conductor. For ease in constructing the complicated closed systems of glass required to keep the sodium–ammonia solutions away from air, we used tungsten. However, since tungsten does not give reproducible results when used as an electrode in aqueous solutions, it was necessary that we show for ammonia solutions that platinum and tungsten electrodes give substantially equivalent results.

Experimental Procedure

Preparation of Materials.—All procedures were carried out in a high vacuum chain capable of producing pressures less than 1×10^{-6} mm. Degassing and baking out were carried out where needed. Ammonia, obtained from Matheson as anhydrous 99.9% pure, was triply distilled from its solutions with sodium before use. Sodium, obtained from Mallinckrodt, was purified by the method of Watt and Sowards.[5] Ethylamine, obtained from Eastman Kodak as a 33% solution in water, was first concentrated by distilling it off from a slurry of calcium oxide and then purified by redistilling it from its solution of lithium metal. Sodium iodide, Baker and Adamson reagent grade, was used directly without further purification except for drying. Mercury for the amalgams was scrubbed in a mercury oxifier, washed with nitric acid and triply distilled before use.

Distribution Experiments.—The distribution of sodium between mercury and liquid ammonia was determined in an all-glass system with a built-in pipet which served both to introduce gas for stirring the liquid ammonia solutions and to take samples of the solutions for analysis. In operation, a sodium–ammonia solution was formed in an outer jacket and a weighed amount of mercury dropped in through a ball-and-socket valve manipulated from the outside. Prepurified hydrogen bubbled through the pipet tip served to mix the solution. A pair of tungsten electrodes sealed through the outer jacket wall enabled concentration changes in the solution to be followed from measurements of the a.c. electrical resistance. After distribution equilibrium had been established, hydrogen pressure could be applied to force a sample of the ammonia solution into the pipet. Distribution experiments were also performed in which

(1) On leave of absence at the Laboratoire de Chimie Minérale, University of Toulouse, Toulouse, France.

(2) See, for example, W. N. Lipscomb, *J. Chem. Phys.*, **21**, 52 (1953).

(3) C. A. Kraus, THIS JOURNAL, **36**, 864 (1914).

(4) H. Laitinen and C. Nyman, *ibid.*, **70**, 3002 (1948).

(5) G. W. Watt and D. M. Sowards, *ibid.*, **76**, 4742 (1954).

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equilibrium was approached from the other side—that is, ammonia was added to a sodium amalgam.

After a sample of the ammonia phase had been taken, the apparatus was quenched in liquid nitrogen, the outside tube was detached, and the ammonia in the outside jacket and in the pipet separately evaporated off into measured volumes of standard sulfuric acid. Sodium in the pipet was determined by washing it out with ethanol and water and titrating the wash solution with standard acid. Total sodium in the jacket was determined similarly after washing out the sodium and the sodium amalgam, boiling with water until all reaction between amalgam and water had ceased, and titrating.

Cell I.—The "sodium–sodium amalgam" cell consisted essentially of an inverted "Y" tube with a tungsten electrode sealed into each arm of the "Y." The sodium electrode was formed by melting sodium around the tungsten in one arm; the sodium amalgam electrode, by breaking a sodium-containing ampule into a mercury pool in the other arm. Ethylamine could then be condensed into the cell on sodium iodide which had been added previously. For reproducible voltages, it was found necessary that the leads from the tungsten wires to the outside of the thermostat bath be insulated from the bath by lengths of glass tubing sealed to the cell. Furthermore, it was found that the observed cell voltage could vary as much as 10 to 20 millivolts from one run to the next unless the amalgam electrodes were annealed for at least an hour just below their eutectic temperature of −47°.

Cell II.—The "sodium amalgam–electron electrode" cell consisted essentially of an "H," with a tungsten electrode sealed in each leg of the "H" and a fritted glass disk in the cross-bar. The disk was originally of medium porosity but for our purposes it had been almost completely fused closed by careful heating around the edge. By trial and error it was possible to produce a disk which effectively prevented liquid transfer between the two compartments but still gave a reasonably low electrical resistance. For filling cell II, a weighed quantity of mercury, a weighed ampule of sodium, and a weighed quantity of sodium iodide were placed in one compartment and a weighed ampule of sodium in the other. Ammonia could then be distilled into the cell after evacuation and degassing of the fritted disk. Usually the voltage settled down in a matter of minutes but data were not considered reliable unless the voltage remained constant within two millivolts for at least an hour. In contrast to cells of type I, which essentially lasted indefinitely, the lifetime of cells of type II was only four or five hours, after which time the e.m.f. became somewhat erratic. This onset of erratic behavior was attributed to autocatalytic decomposition of the sodium–ammonia solution at the fritted disk. For analysis, ammonia was boiled off into measured volumes of standard sulfuric acid. With the pressures involved, only a negligible amount of ammonia could have been forced through the fritted disk.

Temperature Control and Measurement.—The distribution apparatus was thermostated by immersion in a large test-tube of boiling liquid ammonia, the temperature of which was −33.2 ± 0.2°. Cells I and II, which were run at both −50 and −70°, were immersed in a large Dewar flask filled with cold acetone. The bath was stirred mechanically, and the temperature was regulated manually by the addition of small pieces of Dry Ice. The temperature could be kept constant to ±0.2° by this method. More precise control was not necessary because it was observed that the thermal coefficients of the cells were low. Temperatures were measured by means of a copper–constantan thermocouple and a Leeds and Northrup Portable Precision Potentiometer. The junctions were immersed in tubes of paraffin oil with the reference junction kept at the ice point. The thermocouple was calibrated at the ice point, the freezing point of mercury and the CO_2 point.[6]

Test for Reversibility.—The thermodynamic reversibility of a galvanic cell can be determined by applying an external voltage to the cell just sufficient to balance its e.m.f. and then changing the external voltage infinitesimally so as to pass current in opposite directions through the cell.[7] If the electrode reactions are reversible, there should be no discontinuity in the voltage–current proportionality at the null point. In this research, we measured the voltages in the external circuit which were required to produce small galvanometer deflections on either side of the null point. Since the galvanometer was in series with the cell under investigation, its deflection was a measure of the current through the cell. For each of the cells studied, such a plot of external voltage *vs.* current produced a straight line.

Platinum–Tungsten Equivalence Test.—To test platinum and tungsten as equivalent electron electrodes, cell I was modified by the insertion of a piece of copper wire on the end of which was soldered a strip of platinum wire. With sodium–ammonia solution in the cell the voltage between the platinum and each of the tungsten electrodes was observed to be 0.00006 ± 0.00001 volt; it did not change from one tungsten electrode to the other. It may be that even this voltage was due not to any real difference between tungsten and platinum but rather to a small temperature gradient at the copper-to-platinum junction, which was only a few cm. below the level of the surrounding external thermostat bath.

Results

Distribution Experiments.—The distribution experiments were performed (1) by adding mercury to a solution of sodium in liquid ammonia and (2) by adding ammonia to a concentrated sodium amalgam. In every experiment of the first set, all of the sodium was extracted from the ammonia by the mercury. This by itself is not significant since geometrical considerations limited us to quantities of reagents such as to preclude formation of a sodium amalgam richer than 6.0 atomic % sodium. In the second set of experiments, four quite concentrated amalgams were equilibrated with liquid ammonia. The distribution results are shown in Table I. It is evident that the most dilute of these concentrated amalgams, even though it already contains 36.4 atomic % sodium, is still too dilute to allow any detectable sodium in the ammonia phase. Since in the following cells we did not exceed 2.5 atomic % sodium for the composition of the amalgam electrode, we can be reasonably sure that the dissolution equilibrium of sodium in ammonia has been completely repressed.

Table I

Distribution of Sodium between Mercury and Liquid Ammonia at −33.2°

Amalgam	Equilibrium mole fraction of sodium: Ammonia phase	Mercury phase
1	Not measurable	0.364
2	2.10×10^{-4}	.503
3	6.15×10^{-3}	.582
4	1.12×10^{-2}	.603

Cell I.—Of the two "sodium–sodium amalgam" cells that were prepared, the first showed 0.8277 ± 0.0005 volt at −50° and 0.8331 ± 0.0003 volt at −70° and the second, 0.8284 ± 0.0002 volt at −50° and 0.8364 ± 0.0009 volt at −70°. As an average, we have taken the values

at −50° $E = 0.828 \pm 0.000$ v.

at −70° $E = 0.835 \pm 0.001$ v.

Cell II.—For the "sodium amalgam–electron electrode" cells, the observed voltages at −50° and at −70° are shown in Table II. The column headed "Sodium, m" indicates the concentration of sodium in the liquid ammonia adjacent to the "electron electrode" and the column headed

(6) American Institute of Physics, "Temperature, Its Measurement and Control in Science and Industry," Reinhold Publ. Corp., New York, N. Y., 1941, p. 212.

(7) S. Glasstone, "Introduction to Electrochemistry," Van Nostrand Co., New York, N. Y., 1942, p. 184.

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"NaI, m" indicates the concentration of sodium iodide in the liquid ammonia adjacent to the "sodium amalgam" electrode. The error limits quoted for E are the observed voltage fluctuations at a given temperature. In addition, there may be an uncertainty of 0.020 volt in each value of E because of possible strains in the sodium amalgam electrode—strains which could not in practice be annealed because of the limited lifetime of the cells.

TABLE II

OBSERVED E.M.F. OF "SODIUM AMALGAM–ELECTRON ELECTRODE" CELLS

Cell	Sodium, m	NaI, m	$-E$ at $-50°$	$-E$ at $-70°$
1	0.209	0.0445	0.6961 ± 0.0004	0.7250 ± 0.0005
2	.210	.172	.7210 ± .0003	.7608 ± .0008
3	.344	.0961	.7165 ± .0002	.7528 ± .0014
4	.377	.0902	.7132 ± .0005	.7411 ± .0012
5	.752	.0763	.6889 ± .0018	.7132 ± .0005

Discussion

For a cell of the type II, the over-all cell reaction can be written

$$Na_{(Hg)} \longrightarrow Na^{+}_{(NH_3)} + e^{-}_{(NH_3)}$$

Because the cell contains a liquid junction, the observed voltage, E, includes a liquid junction potential, E_L. Using the Nernst relation, we may write

$$E = E^\circ - \frac{RT}{F} \ln \frac{a_{Na^+(NH_3)}\, a_{e^-(NH_3)}}{a_{Na(Hg)}} + E_L \qquad (1)$$

where E° is the standard voltage, $a_{Na^+(NH_3)}$ and $a_{e^-(NH_3)}$ are the activities of sodium ion and of the electron in liquid ammonia, and $a_{Na(Hg)}$ is the activity of the sodium in the amalgam. Actually, this last quantity is a constant. The sodium–mercury system[8] shows at 2.5 atomic % sodium an eutectic between pure mercury and the compound $NaHg_4$ and an eutectic temperature of about $-47°$. Thus, any sodium amalgam having less than 2.5 atomic % sodium, as in our work, when cooled either to -50 or $-70°$, separates into pure mercury and an eutectic mixture of mercury and $NaHg_4$. Since all the sodium is present only as the compound $NaHg_4$, we can consider $a_{Na(Hg)}$ as a constant in eq. 1. If this constant is absorbed into E°, eq. 1 becomes

$$E = E^{\circ\prime} - \frac{RT}{F} \ln a_{Na^+} a_{e^-} + E_L \qquad (2)$$

where $E^{\circ\prime}$ indicates the standard e.m.f. referred to the new standard state and the NH_3 subscripts have been omitted for simplicity. Assuming that the activity of the sodium ion and of the electron in ammonia can be represented by the product of a molality m and an activity coefficient γ, we write

$$E = E^{\circ\prime} - \frac{RT}{F} \ln m_{Na^+} m_{e^-} - \frac{RT}{F} \ln \gamma_{Na^+}\gamma_{e^-} + E_L \qquad (3)$$

The first and third terms of the equation are known from these experiments; the fourth and fifth need to be estimated in order to find $E^{\circ\prime}$.

For the fourth term, because of the scarcity of data on activity coefficients in liquid ammonia, we have had to assume that the single ionic activity coefficients needed are approximately the same (at corresponding concentrations) as those found by Sedlet and DeVries[9] for the mean ionic activity coefficients of sodium chloride in ammonia. Table III shows the numerical values assumed in the different cells and the magnitude of the activity coefficient term that would then appear in eq. 3. The error limits quoted correspond approximately to a 100% error in choice of activity coefficient.

TABLE III

ACTIVITY COEFFICIENTS ASSUMED FOR e^- AND Na^+

Cell	γ_{e^-}	γ_{Na^+}	$-(RT/F) \ln \gamma_{Na^+}\gamma_{e^-}$ At $-50°$	At $-70°$
1	0.1	0.3	0.067 ± 0.02	0.061 ± 0.02
2	.1	.1	.089 ± .02	.081 ± .02
3	.07	.2	.082 ± .02	.075 ± .02
4	.06	.2	.085 ± .02	.077 ± .02
5	.04	.2	.093 ± .02	.085 ± .02

The liquid junction potential has been estimated by using the Henderson equation.[10] For a boundary between two solutions of uni-univalent electrolytes, this equation takes the form

$$E_L = \frac{RT}{F} \frac{(U_1 - V_1) - (U_2 - V_2)}{(U_1 + V_1) - (U_2 + V_2)} \ln \frac{U_1 + V_1}{U_2 + V_2}$$

where U_1 is the product of the molality and the ionic mobility of the cation on one side of the boundary and U_2 is the product of the molality and ionic mobility of the cation on the other side of the boundary. V_1 and V_2 are the corresponding quantities for anions. According to Kraus and Bray[11] the ionic mobilities of sodium ions and iodide ions are 1.35×10^{-3} and 1.77×10^{-3} cm. per second, respectively, over a wide range of concentration. The ionic mobilities of electrons in liquid ammonia, as calculated from the transport numbers obtained by Kraus for sodium in liquid ammonia solutions, vary between 4.12×10^{-2} and 8.31×10^{-2} cm. per second over the range of concentrations we used. Columns two and three of Table IV give the results we have calculated for the liquid junction potentials of the various cells. The error limits indicated are those obtained by applying the Henderson equation to aqueous solutions.

The last two columns of Table IV give the results finally calculated from eq. 3 for $E^{0\prime}$ of each cell. As most probable values for the "sodium amalgam–electron electrode" cell,

TABLE IV

ESTIMATED LIQUID JUNCTION POTENTIALS AND CALCULATED STANDARD E.M.F.'s

Cell	E_L ± 0.005 at $-50°$	E_L ± 0.005 at $-70°$	$-E^{0\prime}$ ± 0.05 at $-50°$	$-E^{0\prime}$ ± 0.05 at $-70°$
1	0.0771	0.0704	0.930	0.938
2	.0544	.0497	.928	.950
3	.0751	.0686	.939	.956
4	.0785	.0716	.942	.949
5	.1033	.0948	.940	.943

we take the following

at $-50°$ $E^{0\prime} = -0.933 \pm 0.02$ v.

at $-70°$ $E^{0\prime} = -0.947 \pm 0.02$ v.

(8) H. E. Bent and A. F. Forziatti, THIS JOURNAL, 68, 2220 (1946).

(9) J. Sedlet and T. DeVries, *ibid.*, 73, 5808 (1951).

(10) S. Glasstone, ref. 7, p. 212.

(11) C. A. Kraus and W. C. Bray, THIS JOURNAL, 35, 1315 (1913).

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For cells of type I, the net reaction is

$$Na_{(s)} \longrightarrow Na_{(Hg)}$$

and the observed e.m.f. is given by

$$E = E^0 - \frac{RT}{F} \ln a_{Na(Hg)}$$

Again, since the concentration of sodium in the amalgam is kept below 2.5 atomic %, the sodium is in the electrode only as $NaHg_4$ and its activity is a constant. The observed voltage is invariant except with temperature, a prediction that agrees with our experiments, and, if the constant activity term is again absorbed into $E°$, the observed voltage is just the $E°'$ of the cell.

Combining the $E°'$ of the two cells, I and II, gives an $E°$ for the reaction

$$Na_{(s)} \longrightarrow Na^+_{(NH_3)} + e^-_{(NH_3)}$$

(In so doing it might be noted that a true $E°$ referred to pure sodium as standard state is obtained and not an $E°'$. The term depending on the activity of sodium in the amalgam cancels out because it comes in negatively in the $E°'$ of cell I and positively in the $E°'$ of cell II.) The results are

at $-50°$ $E° = -0.10 \pm 0.02$ v. $\Delta F° = 2.4$ kcal./mole

at $-70°$ $E° = -0.11 \pm 0.02$ v. $\Delta F° = 2.6$ kcal./mole

Corresponding to these values of the standard free energy change is a standard entropy change of approximately 10 cal. per degree per mole.

These results are in remarkable agreement with those expected on the basis of the thermodynamic functions in liquid ammonia suggested by Jolly.[12] For 25° Jolly suggests

$$Na_{(s)} \longrightarrow Na^+_{(NH_3)} + e^-_{(ext)} \qquad E° = 1.89 \text{ v.}$$

$$e^-_{(NH_3)} \longrightarrow e^-_{(ext)} \qquad E° = 1.93 \text{ v.}$$

Using standard heats of formation (−38.1 kcal./mole for sodium ion and 40.5 kcal./mole for the electron) to change these values from 25 to −50° and −70° we would have predicted the following

$$Na_{(s)} \longrightarrow Na^+_{(NH_3)} + e^-_{(ext)} \qquad E°_{-50} = 1.82 \text{ v.}; \quad E°_{-70} = 1.80 \text{ v.}$$

$$e^-_{(NH_3)} \longrightarrow e^-_{(ext)} \qquad E°_{-50} = 1.88 \text{ v.}; \quad E°_{-70} = 1.87 \text{ v.}$$

$$Na_{(s)} \longrightarrow Na^+_{(NH_3)} + e^-_{(NH_3)} \qquad E°_{-50} = -0.06 \text{ v.}; \quad E°_{-70} = -0.07 \text{ v.}$$

An experimentally determined value for the standard free energy change of

$$Na_{(s)} \longrightarrow Na^+_{(NH_3)} + e^-_{(NH_3)}$$

makes possible an experimental evaluation of single ion solvation free energies. The over-all process above can be represented by the following cycle: (1) sublimation of solid sodium, (2) ionization of sodium gas, (3) ammoniation of sodium ions, (4) ammoniation of electrons. The free energy change of step (1) is well known and is equal to 18.7 kcal./mole at 25°. The free energy change of step (2) can be estimated from the first ionization potential of sodium as equal to 118.9 kcal./mole. For step 4 the free energy change can be rather reasonably estimated to be −11.9 kcal./mole. This value we have obtained by considering the reverse process, the desolvation of electrons from liquid ammonia. Its free energy change is 18.4 kcal., the energy required to expel electrons from liquid ammonia, less 6.5 kcal., the energy released when the cavities left behind collapse. The number 18.4 kcal. comes from 0.8 electron volt, the observed photoelectric work function of sodium–ammonia solutions reported by Ogg.[13] The number 6.5 kcal. is the calculated surface energy of a mole of cavities in liquid ammonia. For the surface tension, we have used 35.4 ergs per cm.^{2} from the work of Stairs and Sienko.[14] For the radius of the cavity, we have used 3.2 Å. as suggested by Lipscomb[2] on the basis of the density measurements of Kraus, Carney and Johnson.[15]

Using 2.5 kcal. for the free energy change of the over-all reaction, we calculate the free energy change of step 3 by difference to be −123.2 kcal./mole. There is probably a large uncertainty in this figure, perhaps as much as 10 kcal., because in several of the steps we have had to use data at different temperatures and to assume, in the absence of information on the entropy changes, that the free energy change is the same as the energy change. However, the result is of more than qualitative interest because it indicates that, at least in principle, it is possible experimentally to get a single ion solvation free energy, one which does not depend on any arbitrary apportionment of solvation effects between cations and anions.

ITHACA, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Mechanism of Substitution Reactions of Complex Ions. XII.[1] Reactions of Some Platinum(II) Complexes with Various Reactants[2]

BY DEBABRATA BANERJEA, FRED BASOLO AND RALPH G. PEARSON

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Kinetic studies are reported for the reactions of some platinum(II) complexes in aqueous solution with a variety of nucleophilic reagents. The reactions studied fall into two categories: (1) those that are first order in complex but zero order in reactant and all of nearly the same rate; (2) those that are first order in both the complex and the reactant and faster than those of the first category. In general the reactants of category (1) are low in the *trans*-effect series whereas reactants of category (2) have a high *trans*-effect. The significance of the role played by the reactant in reactions of platinum(II) complexes is not involved in the current *trans*-effect theories of Chatt and Orgel. However these theories can be extended to explain the marked correlation between the reactivity of different reactants and their *trans*-directing properties. A "dissociation" mechanism is proposed for substitution reactions of "square" complexes.

The *trans*-effect in platinum(II) complexes, first recognized by Werner[3] and so designated somewhat later by Chernyaev,[4] has received considerable attention in recent years. In a review Quagliano and Schubert[5] have described the qualitative aspects of the *trans*-effect and its practical utility in the preparation of the geometrical isomers of platinum(II) complexes, as well as in some structural investigations. Several theories have been advanced by different authors, *e.g.*, Grinberg,[6] Syrkin,[7] Cardwell,[8] Chatt[9] and Orgel,[10] to account for the *trans*-effect. The theories of Chatt and of Orgel are very similar and are based on quantum mechanical (π-bonding) considerations which can satisfactorily account for the high *trans*-labilizing influence of unsaturated molecules such as C_2H_4, CO, NO, etc.

Quantitative rate data on the subject are lacking in the literature except for a recent publication by Zvyagintsev and Karandasheva[11] who have investigated the kinetics of substitution by pyridine of a halide group in some platinum(II) complexes of the type $Pt(NH_3)XYZ$, where Y and Z are negative groups (Cl^-, Br^- or NO_2^-) and X is the halide group displaced under the *trans*-influence of Z. The reactions were found to be second order as expected for an S_N2 mechanism as postulated by Cardwell,[8] Chatt[9] and Orgel.[10] Furthermore the rates decreased in the order $NO_2^- > Br^- > Cl^-$ for the ligand Z in agreement with decreasing *trans*-effects for these groups. The Russian workers also observed that $Pt(C_2H_4)Cl_3^-$ reacts with pyridine too fast to be measurable. This is expected because of the strong *trans*-effect of the olefin.[12] Grantham, Elleman and Martin[13] have studied the rate of acid hydrolysis of $PtCl_4^{2-}$ and its rate of exchange with radioactive chloride ion and found that exchange proceeded by way of the acid hydrolysis step and its reverse.

Except for some further exchange studies on symmetrical complexes which will be referred to later, nothing appears to have been done by way of studying the effect on the rate of the nature of the entering group. This present work furnishes the results of a fairly wide sampling of the kinetics of a variety of nucleophilic reagents and several platinum(II) complexes.

The compounds studied were *cis*- and *trans*-dichlorodiammineplatinum(II), dichloroethylenediamineplatinum(II), chlorotriammineplatinum(II) chloride and potassium tetrachloroplatinate(II). The rates of substitution of chlorine in one or more of these complexes by pyridine, ammonia, glycine, aniline, thiourea, allyl alcohol, water hydroxide ion, nitrite ion, oxalate ion and chloride ion itself have been investigated. In case of the chloride ion the rate of exchange has been followed kinetically by the radio-isotopic tracer method using chloride ion tagged with $^{36}Cl^-$. In the case of the other substituting groups, the progress of the reaction was estimated at intervals by physico-chemical methods such as the change in electrical conductance or change in optical density at a suitable wave length of the reacting solution in question, or by titrating the released chloride ion potentiometrically with standard silver nitrate solution using a glass–Ag/AgCl electrode assembly in acidified acetone–water medium (*cf.* Brown and Ingold[14]).

Experimental

A. Preparation of Materials.—*cis*-Dichlorodiammineplatinum(II) was prepared, from K_2PtCl_4 and ammonia in aqueous solution, following the method of Ramberg.[15] The product was purified by recrystallization from hot water acidified with hydrochloric acid.

trans-Dichlorodiammineplatinum(II) was prepared from tetrammineplatinum(II) chloride by heating the solid salt to 250° for about ½ hr., extracting with hot water acidified with hydrochloric acid and cooling. The product which separated was purified by recrystallization from acidified hot water.[16]

Dichloroethylenediamineplatinum(II) was prepared in a pure state from aqueous solution of K_2PtCl_4 and ethylene-

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(2) This investigation was supported by a grant from the U. S. Atomic Energy Commission under contract AT(11-1)-89-project No. 2.

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diamine following the method of Drew[16] as modified by Basolo, Bailar and Tarr.[17]

Chlorotriammineplatinum(II) chloride was prepared from *cis*-dichlorodiammineplatinum(II) according to the procedure described by Tschugaev.[18] The purity of the sample was checked by analysis.

Anal. Calcd. for $[Pt(NH_3)_3Cl_2]Cl$: Pt, 61.51; N, 13.24; H, 2.84. Found: Pt, 60.98; N, 13.50; H, 2.90.

B. Determination of the Rate of Exchange of Radiochloride Ion.—This has been determined in case of both *trans*-dichlorodiammineplatinum(II) and the chlorotriammineplatinum(II) cation in aqueous solutions 0.2 *M* in potassium nitrate. To an aqueous solution of the desired complex were added the requisite amounts of solid potassium nitrate and hydrochloric acid containing $^{36}Cl^-$ of known concentration; the solutions were then diluted to the requisite volume and thermostated at 25°. Aliquots of 0.50 cc. were removed at known intervals and to the aliquots were added a constant amount of a solution of potassium chloride (to form a sufficient precipitate of AgCl). The free chloride ion was then precipitated by adding 10% excess of the requisite quantity of silver nitrate solution. The mixture was centrifuged for 10 min. and then an aliquot of the clear supernatant liquid was withdrawn and evaporated on a disc of filter paper in an aluminum tray under strong infrared light. The activity of all these samples were then counted in a Scaling Unit, Model 162, Nuclear Instruments and Chemical Corporation, Inc. Since in $Pt(NH_3)_2Cl_2$ there are two equivalent chlorine atoms, it can be shown that the rate constant, k, for the constant rate of exchange of chlorine in the complex with the chloride ions in solution will be given by

$$k = \frac{2[Cl^-] \times 2.303}{\{2[Pt(NH_3)_2Cl_2] + [Cl^-]\}t} \log \frac{(C_\infty - C_0)}{(C_\infty - C_t)} \quad (1)$$

where C_0, C_t and C_∞ represent the counts per minute of the evaporated samples corresponding to the aliquots of reacting solution treated at zero time, t minutes and ∞, respectively. The latter has been calculated assuming complete exchange of both the chlorine atoms in the complex so that the radioactive isotope is distributed equally between the covalent and ionic chlorine in the system. This value was checked experimentally on one sample which was allowed to stand for several days before being treated. From the slopes of the curves obtained by plotting $\log (C_\infty - C_0)/(C_\infty - C_t)$ *vs.* t, k was calculated using eq. 1. The results are given in Table I.

The experimental procedure in the case of $Pt(NH_3)_3Cl^+$ was identical. Since, however, there is only one chlorine in the complex, k was evaluated graphically from eq. (2)

$$k = \frac{2.303}{t} \log \frac{(C_\infty - C_0)}{(C_\infty - C_t)} \quad (2)$$

by plotting $\log (C_\infty - C_0)/(C_\infty - C_t)$ *vs.* t at two different concentrations of chloride ion. The results are recorded in Table I.

C. Determination of the Rates of Release of Chloride Ion from the Chloro Complexes of Platinum(II) under the Influence of Water, Ammonia, Aniline, Pyridine, Glycine, Thiourea, Allyl Alcohol, Hydroxide Ion, Nitrite Ion and Oxalate Ion.—These reactions have been followed by one or more of the several physico-chemical methods described below.

(1) Change in Conductance.—The reactions of non-ionic and cationic complexes with neutral molecules like aniline, pyridine, glycine, thiourea and allyl alcohol (freshly prepared solutions were used) were followed by measuring the change in conductance of the solution under investigation, thermostated at 25°, using a Conductivity Bridge (Model RC 16, Industrial Instruments, Inc.). Relatively large excess of the reagent was used to follow the reaction as one of pseudo first-order type, in case it is not truly first order. Rate constants have been evaluated graphically from the equation

$$k = \frac{2.303}{t} \log \left(\frac{R_0 - R_\infty}{R_0}\right)\left(\frac{R_t}{R_t - R_\infty}\right) \quad (3)$$

where R's stand for resistances in ohms of the reacting solution measured at different times in the same cell. In the case of $Pt(NH_3)_3Cl^+$ the experimental value of R_∞ which agreed closely with the value expected for a compound of the type $[PtA_4]X_2$, was used in the calculations. This is also true for the reaction of *trans*-$Pt(NH_3)_2Cl_2$ with allyl alcohol, where only one chloride ion is released giving $[PtA_3Cl]Cl$, even after a week. But in the reaction of *trans*-$Pt(NH_3)_2Cl_2$ with pyridine, aniline and glycine both chloride ions are ionized successively. Hence, in this case the value of R_∞ used in the calculations was taken as double the observed value of the resistance after three weeks. Determination of the chloride ion at this stage by potentiometric titration (*vide infra*) indicated that both the chlorines were displaced. Results of these determinations are given in Table I. Interestingly enough $Pt(NH_3)_3Cl^+$ did not react at all with allyl alcohol, even at 50°. The reaction of *trans*-$Pt(NH_3)_2Cl_2$ with thiourea was so fast that the conductivity of the solution reached a value expected for an ionic compound of the type $[PtA_4]X_2$ within a few minutes of mixing of the constituents, and hence the rate of the reaction could not be measured.

A conductivity method was utilized in studying the reaction of hydroxide ion with $PtCl_4^{2-}$. Equimolecular amounts of the reactants were mixed and the change in conductance, due to replacement of OH^- in solution by Cl^- was followed

$$PtCl_4^{2-} + OH^- \longrightarrow Pt(OH)Cl_3^{2-} + Cl^- \quad (4)$$

The value of R_∞ could not be determined experimentally, as the solution on standing overnight became turbid due to separation of a bluish-black precipitate. R_∞ was calculated assuming that $PtCl_4^{2-}$ and $Pt(OH)Cl_3^{2-}$ have the same value of the equivalent conductance and using the known values of the equivalent conductance of $PtCl_4^{2-}$, OH^- and Cl^- ions. Since a first-order plot was obtained for this equimolecular mixture it was concluded that the reaction is independent of the OH^- ion concentration. The value of the rate constant was also checked by following the reaction by titrating the unreacted OH^- ion at different stages potentiometrically as described below.

To check the influence of ionic strength of the medium on the rate constants some of these determinations were repeated in 0.2 *M* potassium nitrate solution using the potentiometric titration technique (*vide infra*) to follow the rate of release of the chlorine ligand from the complex as chloride ion into the solution. These data are also recorded in Table I.

(2) Potentiometric Titration.—The rates of displacement of coördinated chloride ion from chloroammineplatinum(II) complexes by ammonia in ammonium nitrate buffer medium (to suppress the basic dissociation of ammonia), water, hydroxide ion, oxalate ion and nitrite ion have been investigated by potentiometric titration of the released chloride ion. Aliquots of 25 cc. of the reacting solution under investigation, thermostated at the desired temperature, were removed at intervals and immediately run into 150 cc. of acidified acetone (25 cc. of concd. nitric acid per 1 kg. of acetone) cooled in ice. The glass–Ag/AgCl electrode assembly was dipped into the solution which was kept cooled in ice and well stirred by a mechanical stirrer during the titration. Titration was carried out by gradually adding from a microburet (5 cc./0.01) a standard solution of silver nitrate (strength 10 times the molar concentration of the total chlorine in the reacting solution) and following the change in potential with a *p*H millivoltmeter (Beckman, model G). The end-point was marked by a very sharp change (decrease) in potential per 0.01 cc. of the titrant. The rate constant was calculated graphically from the usual first-order equation. The value of V_∞ used was calculated from the known concentration of the complex in solution. This calculated value always was checked experimentally and good agreement found in most cases. The results are recorded in Table I.

It is interesting to note that the reaction of the *trans*-dichloro compound with nitrite ion was so fast at 25° that it could not be conveniently followed experimentally. But from the data presented below it appears that the rate is also dependent on the concentration of nitrite ion, as in the case of the corresponding *cis*-compound, or the chlorotriammineplatinum(II) complex cation:

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trans-$Pt(NH_3)_2Cl_2$, 0.0005 *M*, and NO_2^- (KNO_2), 0.02 *M*; 25°

Time, min.	0 (immediately after mixing)	12	Total Cl equiv. to 2.5 cc. of 0.01 *M* $AgNO_3$
Titer/25 cc. (cc. $AgNO_3$, 0.01 *M*)	1.92	2.44	

trans-$Pt(NH_3)_2Cl_2$, 0.0005 *M*, and NO_2^-, 0.001 *M*; 25°

Time, min.	0	15	Total Cl equiv. to 2.5 cc. of 0.01 *M* $AgNO_3$
Titer/25 cc. (cc. $AgNO_3$, 0.01 *M*)	0.76	1.90	

The reaction of OH^- ion with $PtCl_4^{2-}$ has been followed by titration of the free alkali at different stages of progress of the reaction in a solution 0.002 *M* in both K_2PtCl_4 and KOH. An alkali-glass electrode (Beckman E) with a saturated calomel reference electrode was used in conjunction with a Beckman *p*H meter (Model G) to follow the change in *p*H during the course of the titration with 0.01 *M* $HClO_4$. Titration was carried out to a *p*H of 8.0 ± 0.05 to determine the amount of free OH^-. V_∞ was taken as zero, as is expected for the equimolecular mixture. A first-order plot was obtained and the rate constant thus calculated was identical to that obtained by the conductance method.

(3) **Spectrophotometric Method.**—This was applied in studying the reaction of $Pt(NH_3)_3Cl^+$ with nitrite ion. The rate of reaction was followed spectrophotometrically at 260 mμ, where the chloro and nitro compounds have different absorbancy, the latter absorbing more strongly. The selection of wave length was made by first plotting the spectra using a Cary recording spectrophotometer, Model 11, in the region 400–220 mμ. Final measurements at the selected region were made in a Beckman DU quartz spectrophotometer, with thermostated cell compartment. The absorbancy of the nitro compound was obtained by mixing a solution of the chloro compound with excess of potassium nitrite, keeping it overnight and measuring the absorption against a blank of potassium nitrite solution of the same concentration as in the solution under investigation. This was checked daily until a reasonably constant value was obtained. It can be shown that the rate constant, *k*, is given by

$$k = \frac{2.303}{t} \log \frac{(O.D.)_\infty - (O.D.)_0}{(O.D.)_\infty - (O.D.)_t} \qquad (5)$$

where all the optical densities are measured against a blank of potassium nitrite solution of the same concentration as in the reacting solution. The value for $(O.D.)_\infty$ was obtained as described above. The same procedure has been employed in studying the reaction of $PtCl_4^{2-}$ with allyl alcohol. Measurements were carried out at the selected wave length of 300 mμ where the allyl alcohol has practically no absorption while the product of the reaction, presumably $[Pt(CH_2H_6O)Cl_3]^-$, absorbs much more than $PtCl_4^=$. The results of some determinations are also presented in Table I.

D. **Temperature Dependence.**—The effect of temperature on some of these reactions has been studied and the activation energy, E_a has been calculated from the usual Arrhenius equation. These are presented in Table II.

Discussion

The reactions studied fall into two categories. (1) Those that are first order in the complex and zero order in the attacking reagent and (2) those that are first order in both the complex and the reagent. Furthermore, those reactions which are totally first order for a given complex have very nearly identical rates for several reagents. Thus some step other than the reaction with the reagent is rate determining in these cases. This may be a slow SN2 reaction of the complex with water to form the aqua complex

$$PtA_3Cl + H_2O \xrightarrow{\text{slow}} PtA_3H_2O^+ + Cl^- \qquad (6)$$

followed by a rapid reaction of the aqua complex with the reagent Y

$$PtA_3H_2O^+ + Y \xrightarrow{\text{fast}} PtA_3Y^+ + H_2O \qquad (7)$$

Or it may be an SN1 dissociation of the complex followed by rapid reaction of a three-coördinated intermediate with Y and/or water.

$$PtA_3Cl \xrightarrow{\text{slow}} PtA_3^+ + Cl^- \qquad (8)$$

$$PtA_3^+ + Y \xrightarrow{\text{fast}} PtA_3Y^+ \qquad (9)$$

It is possible in a favorable case to distinguish between these two paths by studying the rate of reaction of the aqua complex with Y to see if it is rapid enough to be consistent. In the present studies some experiments were done to check the reactivity of the aqua complexes. If the chloro complexes are dissolved in water and allowed to stand for some time it is found that *cis*-$Pt(NH_3)_2Cl_2$ comes to an equilibrium within a few days in which 45% of the original coördinated chlorine is ionic. The product is assumed to be 90% *cis*-$[Pt(NH_3)_2(H_2O)Cl]Cl$ and 10% unreacted dichloro, since $Pt(NH_3)_3Cl^+$ was found not to release any ionic chloride after several days standing. If alkali is added to a solution of *cis*-$Pt(NH_3)_2Cl_2$, both chlorines are replaced. Upon acidifying with perchloric acid, a little over one-half of the chlorine very rapidly re-enters the complex, giving the same equilibrium mixture as before.

The *trans*-isomer of $Pt(NH_3)_2Cl_2$, on standing in solution for several weeks does not form any ionic chloride as judged by titration of the chloride ion and by conductivity. This is in disagreement with the conductivity data reported by others[19] who claimed that the *trans*-complex over a period of several hours attained an appreciable conductivity. However, our results were checked several times on different preparations of the complex obtained by heating $[Pt(NH_3)_4]Cl_2$ to 250°. An attempt to make *trans*-$Pt(NH_3)_2Cl_2$ by the method used by Drew gave a material with quite different properties from that obtained by thermal decomposition. Furthermore the analysis of this material did not agree with a dichlorodiammine of platinum(II). If the *trans* complex is treated with alkali, all of the chlorine is replaced. Upon acidifying, 75% of the chlorine rapidly returns to the coördinated form. That this is not due to a mixture of *cis*-$[Pt(NH_3)_2(H_2O)Cl]Cl$ and *trans*-$Pt(NH_3)_2Cl_2$ being formed has been proven by measuring the optical density of the solution at three different wave lengths (220, 230 and 240 mμ) where the *cis*- with *trans*-compounds absorb differently, the *trans* isomer having the greater optical density. It has been found that the solution under investigation had an optical density even higher than that expected for the pure *trans*-compound. This indicates the existence of a different species, presumably a polynuclear one, in solution, which is formed from the aqua complexes reacting with Cl^- ion. The nature of this polynuclear species is not known but it cannot be the dimer, $[Pt(NH_3)(NH_2)Cl]_2$, said to be isolated from the reactions of *cis* and of *trans*-$Pt(NH_3)_2Cl_2$ individually with sodium hydroxide followed by hydro-

(19) H. D. K. Drew, F. W. Pinkard, W. Wardlaw and E. G. Cox, *J. Chem. Soc.*, 988 (1932); I. I. Chernyaev and M. M. Yakshin, *Ann Inst. platine (U.S.S.R.)*, **17**, 29, 42 (1940).

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TABLE I

RATES OF REACTIONS OF SOME PLATINUM(II) COMPLEXES

Reactant, Y	Concn. of Y in soln. M	Added substance	Rate const., k, min.$^{-1}$[c]
trans-$Pt(NH_3)_2Cl_2$, 0.0005 M; 25°; $Pt(NH_3)_2Cl_2 + Y \rightarrow Pt(NH_3)_2YCl + Cl^-$			
$^{36}Cl^-$(HCl)	0.005	0.2 M KNO_3	2.1×10^{-3}
	.01	.2 M KNO_3	2.1×10^{-3}
OH^- (KOH)	.00096	.....	6.1×10^{-3}
	.0064	.....	6.1×10^{-3}
	.016	.....	6.1×10^{-3}
NH_2CH_2COOH	.01	.....	4.6×10^{-3}
	.02	.....	4.6×10^{-3}
$C_6H_5NH_2$[a]	.01	.....	5.7×10^{-3}
	.02	.....	5.7×10^{-3}
C_5H_5N[a]	.005	0.2 M KNO_3	6.5×10^{-3}
	.01	.2 M KNO_3	6.5×10^{-3}
	.01	.....	5.0×10^{-3}
NH_3	.009	0.1 M NH_4NO_3	1.1×10^{-2}
	.018	.1 M NH_4NO_3	2.1×10^{-2}
$CH_2{=}CHCH_2OH$	.005	.....	3.8×10^{-3}
	.01	.....	7.5×10^{-3}
	.015	.....	10.8×10^{-3}
$C_2O_4^{2-}$ ($Na_2C_2O_4$)	.01	.....	4.8×10^{-3}
	.02	.....	9.0×10^{-3}
NO_2^- (KNO_2)			Extremely rapid
$SC(NH_2)_2$			Extremely rapid
trans-$Pt(NH_3)_2(OH)Cl$, 0.0005 M; 40°; $Pt(NH_3)_2(OH)Cl + OH^- \rightarrow Pt(NH_3)_2(OH)_2 + Cl^-$			
OH^- (KOH)	0.008	.....	2.3×10^{-3}
	.016	.....	2.3×10^{-3}
cis-$Pt(NH_3)_2Cl_2$, 0.0005 M; 25°; $Pt(NH_3)_2Cl_2 + Y \rightarrow Pt(NH_3)_2YCl + Cl^-$			
H_2O	Aq. soln.	0.01 M HNO_3	2.3×10^{-3}
OH^-	0.008	.....	2.3×10^{-3}
	.016	.....	2.3×10^{-3}
cis-$Pt(NH_3)_2(OH)Cl$, 0.0005 M; 25°; $Pt(NH_3)_2(OH)Cl + OH^- \rightarrow Pt(NH_3)_2(OH)_2 + Cl^-$			
OH^- (KOH)	0.016	.....	1.3×10^{-3}
	.032	.....	1.3×10^{-3}
cis-$[Pt(NH_3)_2(H_2O)Cl]^+$, 0.0005 M; 25°; $Pt(NH_3)_2(H_2O)Cl^+ + Y \xrightarrow{fast} Pt(NH_3)_2YCl + H_2O$; $Pt(NH_3)_2YCl + Y \rightarrow Pt(NH_3)_2Y_2 + Cl^-$			
1. C_5H_5N	0.01	.....	1.5×10^{-3}
	.02	.....	1.5×10^{-3}
2. NO_2^- (KNO_2)	.0032	.....	3.9×10^{-3}
	.005	.....	5.8×10^{-3}
$Pt(en)Cl_2$, 0.0005 M; 25°; $Pt(en)Cl_2 + Y \rightarrow Pt(en)YCl + Cl^-$			
1. H_2O	Aq. soln.	0.01 M HNO_3	
2. OH^- (KOH)	0.008	.....	3.2×10^{-3}
	.016	.....	3.2×10^{-3}
$Pt(en)(OH)Cl$, 0.0005 M; 25°; $Pt(en)(OH)Cl + OH^- \rightarrow Pt(en)(OH)_2 + Cl^-$			3.2×10^{-3}
OH^-	0.008	.....	1.5×10^{-3}
	.016	.....	1.5×10^{-3}
$[Pt(NH_3)_3Cl]^+Cl^-$, 0.0005 M; 25°; $Pt(NH_3)_3Cl^+ + Y \rightarrow Pt(NH_3)_3Y + Cl^-$			
1. $^{36}Cl^-$ (HCl)	0.0045	0.2 M KNO_3	0.9×10^{-3}
	.0105	.2 M KNO_3	$.9 \times 10^{-3}$
2. C_5H_5N	.01	.....	1.3×10^{-3}
	.01	0.2 M KNO_3	1.0×10^{-3}
	.02	.....	1.3×10^{-3}
3. NH_3	.009	0.2 M NH_4NO_3	1.9×10^{-3}
	.009	.1 M KNO_3, 0.1 M NH_4NO_3	1.7×10^{-3}
	.009	.15 M KNO_3, 0.05 M NH_4NO_3	1.5×10^{-3}
	.036	.1 M KNO_3, 0.1 M NH_4NO_3	2.1×10^{-3}
	.036	.1 M NH_4NO_3	2.7×10^{-3}
4. NO_2^- (KNO_2)	.005	.....	3.2×10^{-3}
	.01	.....	5.8×10^{-3}

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TABLE I—(*continued*)

Reactant, Y	Concn. of Y, in soln. *M*	Added substance	Rate const., *k*, min.$^{-1c}$
5. $SC(NH_2)_2$	.005	.....	2.5×10^{-2}
	.01	.....	4.7×10^{-2}
	.015	.....	8.4×10^{-2}
6. $CH_2{=}CHCH_2OH$			No reaction
	K_2PtCl_4, 0.002 *M*; 25°; $PtCl_4^- + Y^- \rightarrow PtYCl_3 + Cl^-$		
OH^- (KOH)	0.002	.....	1.9×10^{-3} min.$^{-1}$
$CH_2{=}CHCH_2OH$	.06	.....	1.6×10^{-3}
	.12	.....	3.0×10^{-3}
	.30	.....	8.5×10^{-3}
$^{36}Cl^-$	..	.....	2.3×10^{-3}[b]

[a] The value of *k* given is 1/2 the observed *k*. See Discussion. [b] This is the result of Grantham, Elleman and Martin, ref. 13. [c] First order or pseudo-first order.

chloric acid.[20] Thus these experiments, while incomplete, indicate that the aqua complexes are very reactive, at least to chloride ion. This means that it is not possible to distinguish between the SN2 and SN1 mechanisms in these cases.

TABLE II

VARIATION OF THE RATE CONSTANTS FOR $[Pt(NH_3)_3Cl]^+$ WITH TEMPERATURE, $[Pt(NH_3)_3Cl]Cl$, 0.0005 *M*

	Rate constant × 10^3, min.$^{-1}$			*Ea*, kcal./mole
Temp., °C.	18	25	35	
C_5H_5N (0.01 *M*)	0.5	1.3	3.9	20.6
$SC(NH_2)_2$ (0.005 *M*)	11.5	25.3	51.0	14.7

The reagents which give second-order rates follow the reactivity sequence $SC(NH_2)_2 > NO_2^- > NH_3 > CH_2{=}CHCH_2OH > C_2O_4^{2-}$. Ammonia is second order with *trans*-$Pt(NH_3)_2Cl_2$ but not with $Pt(NH_3)_3Cl^+$. Also $Pt(NH_3)_3Cl^+$ does not appear to react at all with allyl alcohol. This is not surprising since the product would be of a cationic type that is known not to be stable, $Pt(NH_3)_3olefin^+$. Thus, it may be an unfavorable equilibrium constant and not an unfavorable rate which is responsible. The following approximate sequence of ligands in order of decreasing *trans* effect has been given[12]: $CN^- \sim C_2H_4 \sim CO \sim NO > SC(NH_2)_2 \sim R_2S \sim R_3P \sim NO_2^- \sim I^- \sim CNS^- > Br^- Cl^- >$ pyridine $> NH_3 > OH^- > H_2O$. It is striking that it is just the ligands which have a large activating influence when in a *trans* position to a replaceable group, which react rapidly and bimolecularly when taking the role of external reagents. Furthermore, the poor reagents, H_2O, OH^-, pyridine and Cl^- are down near the bottom in *trans* activating influence. It is indeed remarkable that OH^-, which is such a powerful reagent for organic halides and for the complexes of cobalt(III) and chromium(III), is so *ineffective* as a reagent for the planar complexes of platinum(II). On the other hand, the relatively great reactivity of allyl alcohol (reacting as an olefin) is unusual since the nucleophilic and basic properties of the double bond are very small. It is also known from the work of Jensen[20] and of Chatt and Wilkins[21] that trialkyl phosphines, arsines and stibines react very rapidly with the corresponding dichloroplatinum(II) complexes.

(20) K. A. Jensen, *Z. anorg. allgem. Chem.*, **229**, 252 (1936).
(21) J. Chatt and R. G. Wilkins, "Symposium on Coördination Compounds," Danish Chemical Society, Copenhagen, 1955, pp. 57–60.

The picture given by Chatt[9] and by Orgel[10] for the mode of reaction of systems containing *trans* activating groups can be extended to accommodate these new observations on the effect of the nature of the reagent. It has been postulated by them that π-bonding occurs in which electrons from a filled d orbital of platinum are donated in part to a π-orbital in unsaturated ligands such as C_2H_4, CO, NO_2^-, etc., or to a ligand with empty d orbitals such as R_2S and R_3P. This is shown schematically in Fig. 1 in which the four groups attached to platinum lie in the *xy*-plane and the filled d_{xz} orbital forms a π-bond to the ligand. The resulting decrease in electron density allows a nucleophilic reagent to approach the opposite side from above or below the plane. The transition state will then approximate a trigonal bipyramid with the entering group, the departing group and the group *trans* to it all in the trigonal plane. Also in the trigonal plane will be two d orbitals belonging to platinum and filled with two electrons each. These will be the d_{xz} and $d_{x^2-z^2}$ as shown in Fig. 2 where the three groups and the two orbitals lie in the *xz*-plane. It is clear that π-bonds can be formed from either of the two d orbitals with any of the three groups in the plane. If the entering group can form a π-bond, this will be a factor stabilizing the transition state and hence causing an increase in the rate of reaction as observed. As in the theories of Chatt[9] and Orgel,[10] a group in the *trans* position to the leaving group stabilizes the transition state by removing electrons from the regions in which the entering and departing groups are placed. It also may be argued that π-bonding by the group being

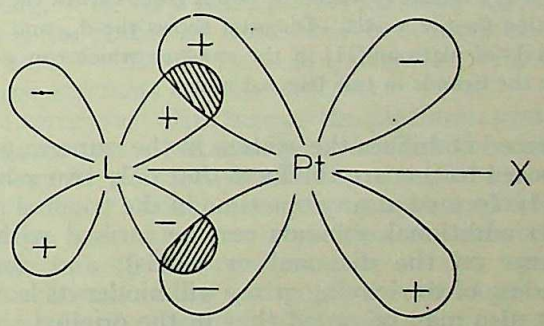

Fig. 1.—d-d-π-Bonding in platinum(II) complexes. If ligands L and X lie in the *xy*-plane than the d orbitals shown are either d_{xz} or d_{yz}.

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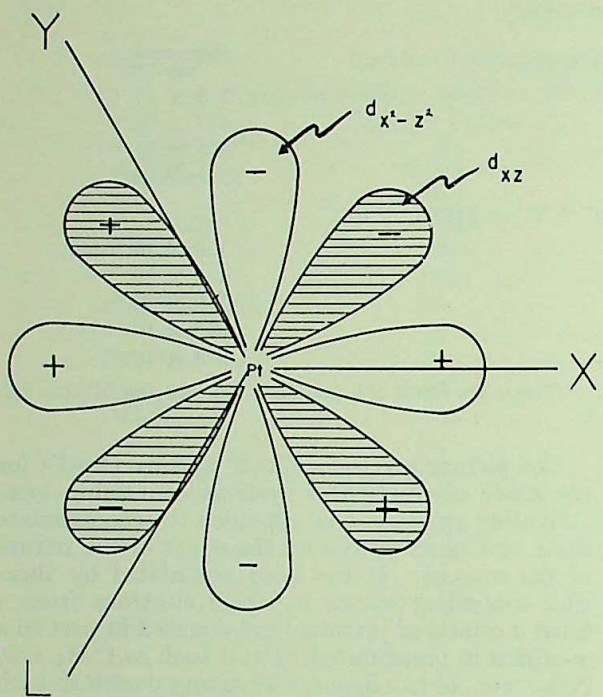

Fig. 2.—Trigonal xz-plane of trigonal bipyramid intermediate, PtA_2LXY, where the two A groups are at the apical position on the y-axis. Diagram shows the d_{xz} and $d_{x^2-z^2}$ orbitals of platinum(II) in the xz-plane which can π-bond with the ligands in this trigonal plane.

replaced stabilizes the system in the same way, but opposed to this are the facts that only two π-bonds can be formed at any one time in the trigonal plane (two additional π-bonds can be formed with the groups on the diagonal or y-axis), and double-bonding of the leaving group will hinder its leaving.

It also may be noted that in the original square planar form only three π-bonds involving metal d orbitals[22] can be formed, with d_{xz}, d_{yz} and d_{xy}. Hence if platinum is coördinated to four potential π-bonding groups, there will be an extra driving force to add a fifth group and become a trigonal bipyramid, since now four π-bonds can be formed. This explains the puzzling phenomenon observed by Grinberg and Nikolśkaya.[23]

These workers, in studying the rate of exchange of PtX_4^{2-} with labeled X^-, found the rates to increase in the order $Cl^- < Br^- < I^- < CN^-$. Since this is the order of increasing stability of the complexes as well, it implies that the most stable complex is also the most labile. The order given is also that of increasing *trans*-effect, which explains the rates. Thus in spite of the strength of the Pt–CN bond, the transition state is sufficiently stabilized by four cyano groups which can form π-bonds.

Another factor which should be considered in evaluating the stability of various transition states for platinum(II) is the change in crystal field stabilization energy in going from the original square planar configuration. The crystal field stabilization energy (CFSE) is a property of a complex ion resulting from the preferential occupation by d electrons of the central atom of the orbitals which point away from the ligands.[24]

The energies of the various d orbitals for square planar and trigonal bipyramid complexes have been calculated by Ballhausen and Klixbüll Jørgensen.[25] There are some approximations that must be made in applying these calculations to any real system but a result good enough for the present purposes can be obtained. Thus for a symmetrical, square planar complex containing eight d electrons, the CFSE is about 25 Dq, less the energy required to couple two electrons in one orbit. The parameter Dq can be obtained from spectral data and is about Dq = 4.5 kcal. in order of magnitude for a divalent, third transition series element.[26] For a symmetrical trigonal bipyramid structure, the corresponding stabilization energy is only 14 Dq and if the complex remains diamagnetic the electron coupling energy remains constant. Hence there is a loss of about 11 Dq or 50 kcal. in CFSE in a reaction going by the SN2 mechanism postulated above. Although a calculation cannot be made easily, it is certain that π-bonding by any of the groups in the trigonal plane will appreciably reduce the loss in CFSE by the process already discussed.

As opposed to this path, an SN1 mechanism in which one group leaves and the remaining three groups maintain their original positions, leads to only a small decrease in CFSE, of the order of 2 Dq. Such a reaction path might be favored by a reagent which cannot form π-bonds, *e.g.*, H_2O, NH_3 and oxalate ion. In such a case, however, it is difficult to account for the second-order kinetics observed with the last two reagents and *trans*-$Pt(NH_3)_2Cl_2$. Also an inspection of Table I shows that the reactions which are independent of the concentration of entering reagent are remarkably insensitive to the net charge on the platinum complex. Thus the ions *cis* and *trans*-$Pt(NH_3)_2Cl_2$, $PtenCl_2$, $Pt(NH_3)_3Cl^+$, *cis*-$Ptpy(NH_3)_2Cl^+$ and $PtCl_4^{2-}$ all react at the same rate within a factor of about three. By comparison $Co(NH_3)_5Cl^{2+}$ reacts slower than *trans*-$Co(NH_3)_4Cl_2^+$ by a factor of about 1000.

Such an insensitivity to coulombic effects is quite incompatible with an SN1 mechanism which goes predominantly by bond breaking. It is instead what one would expect if both bond making and bond breaking were of comparable importance. Furthermore both mechanisms described above for a square planar complex ignore a fact which has become quite apparent from recent experimental work and from elementary energetic considerations. This fact is that a square planar complex invariably will have two further groups coördinated above and below the plane at a greater distance than the four primary ligands.[27] These groups may be solvent, or solute, molecules in solution, and anions, solvent of crystallization or even

(22) G. E. Kimball, *J. Chem. Phys.*, **8**, 188 (1940).

(23) A. A. Grinberg and L. E. Nikolśkaya, *Zhur. Priklad. Khim.*, **22**, 542 (1949); **24**, 893 (1951).

(24) See L. E. Orgel, *J. Chem. Soc.*, 4756 (1956); *J. Chem. Phys.*, **23**, 1819 (1955).

(25) C. J. Ballhausen and C. Klixbüll Jørgensen, *Kgl. Danske Videnskab Selskab*, **29**, No. 14 (1955).

(26) C. Klixbüll Jørgensen, *Acta Chem. Scand.*, **10**, 517 (1956).

(27) L. Tschugaeff, *Compt. rend.*, **161**, 563 (1915); A. K. Sundaram and E. B. Sandell, THIS JOURNAL, **77**, 855 (1955); L. Malatesta and L. Vallarino, *J. Chem. Soc.*, 1867 (1956); C. M. Harris and R. S. Nyholm, *ibid.*, 4375 (1956).

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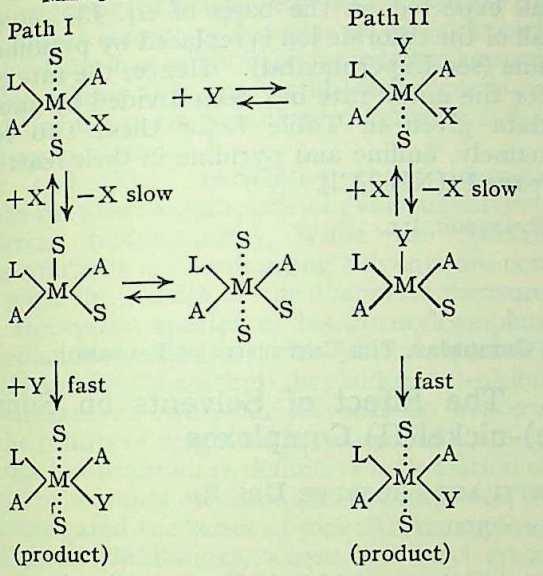
metal atoms from another complex in the solid state.

Accordingly the following mechanism is proposed for reactions of "square planar" complexes in solution

$$MLA_2X + Y \longrightarrow MLA_2Y + X \qquad (10)$$



Thus the reaction goes by a dissociation mechanism of a tetragonal complex in which two groups above and below the plane move in to help displace the group X. The five-coördinated intermediate will probably rearrange to a trigonal bipyramid, particularly if L or Y is a π-bonding group. In path II, Y can directly enter the square plane. Otherwise the aqua (or corresponding) complex will be an intermediate in a further sequence of dissociations until Y is picked up.

Such a reaction scheme accounts for (1) the over-all stereospecificity of such reactions (2) the activating influence of a π-bonding group on the ligand *trans* to it, (3) the reactivity and second-order kinetics of π-bonding reagents, (4) the small influence of electrostatic factors on the rates and (5) the second-order kinetics observed for some non π-bonding reagents such as NH_3 and oxalate ion. Furthermore it is in agreement with the almost certainly tetragonal structure of the complexes.

The mechanism also can be correlated with those postulated for the reactions of cobalt(III) complexes. These are SN1 dissociations for acid hydrolyses with usually a square pyramid structure for the five-coördinated intermediate, and SN1CB dissociations for base hydrolyses with rearrangement to a trigonal bipyramid intermediate.[28] There are two differences between the platinum(II) and cobalt(III) systems and each leads to important differences in the observed kinetics of their reactions. One difference is that platinum(II) is a d^8-system whereas cobalt(III) is a d^6-system. The extra pair of electrons in the case of platinum (originally in the d_{z^2} orbital) would lie in the trigonal plane, if a trigonal, pyramid is formed, occupying the $d_{x^2-z^2}$ orbital. In the case of cobalt(III), this orbital would be empty. This means that only ligands that are unsaturated, or have empty d or p orbitals, can stabilize the trigonal form in the case of platinum, whereas only ligands with unshared pairs of electrons (OH^- and NH^-) can stabilize the cobalt system. This is in agreement with the observed rates of reaction of these systems. Thus in platinum(II) the electron donation in π-bonding is from metal to ligand and in cobalt(III) it is from ligand to metal. Because of the original position of the extra pair of electrons on platinum, only the *trans* ligand can enter the trigonal plane and stabilize it. A *cis* ligand, even if a potential π-bonder such as $P(C_2H_5)_3$, would form a higher energy system if it became part of an *xy* trigonal plane because the extra pair of electrons would no longer be in this plane. This restriction does not hold for cobalt and in fact *cis* electron donors are more effective than *trans*.

The second difference is that all six groups in the case of cobalt are firmly held, their identity is fixed and the remaining bond distances remain nearly constant during the dissociation of one of the groups. In platinum, two of the groups are labile and can be replaced by other ligands in the solution. Further these two labile groups are believed to move in closer to platinum during the dissociation of the leaving group. This means that an external reagent, Y, can easily influence the rate of reaction of platinum complexes but not of cobalt complexes. Also cobalt complexes will react primarily by bond breaking, with very little help from bond making, whereas in platinum there will be contributions from both.[29] All of this is in agreement with the experimental facts on these systems.

The tetragonal structure of the platinum system also guarantees stereospecificity in that the entering group Y will always take up the position vacated by X. This is because the two groups labeled A always maintain a *trans* position to each other and hence hold the configuration in the square plane. A *trans* configuration for the two A groups does not fix the stereochemistry in an octahedral complex. Hence rearrangement is possible for cobalt(III) reactions.[28]

The rates of reaction for platinum complexes studied in this work are about as expected for varying *trans* ligands. Table I shows that for complexes of the same electrical charge the rates run $Cl^- > NH_3 > OH^-$, the same order as in the *trans* effect series listed above.

The reactions of *trans*-$Pt(NH_3)_2Cl_2$ with aniline and pyridine require special considerations. The experimentally observed rate of release of Cl^- was found to be approximately twice that of the hydroxide ion or glycine reactions. This can be accounted for on the basis of the mechanism

$$Pt(NH_3)Cl_2 + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Pt(NH_3)_2(H_2O)Cl^+ + Cl^- \qquad (11)$$

$$Pt(NH_3)_2(H_2O)Cl^+ + Y \xrightarrow{k_3} Pt(NH_3)_2YCl^+ + H_2O \qquad (12)$$

$$Pt(NH_3)_2YCl^+ + H_2O \underset{k_5}{\overset{k_4}{\rightleftharpoons}} Pt(NH_3)_2Y(H_2O)^{++} + Cl^- \qquad (13)$$

(28) R. G. Pearson and F. Basolo, THIS JOURNAL, 78, 4878 (1956).

(29) It is also possible that, in some cases, reaction of square planar complexes may be completely determined by bond making. That is, addition of Y to the platinum atom even in a weakly held position may be sufficient to ensure that the reaction will go to completion.

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$$Pt(NH_3)_2Y(H_2O)^{++} + Y \xrightarrow{k_6} Pt(NH_3)_2Y_2^{++} + H_2O \quad (14)$$

By using the steady-state assumption for the concentration of the intermediates $Pt(NH_3)_2(H_2O)Cl^-$, $Pt(NH_3)_2YCl^+$ and $Pt(NH_3)_2Y(H_2O)^{++}$, the rate equation reduces to

$$\frac{d[Cl^-]}{dt} = 2k_1\left(1 - \frac{k_2[Cl^-]}{k_2[Cl^-] + k_3[Y]}\right)[Pt(NH_3)_2Cl_2] \quad (15)$$

It actually has been observed that the initial, rather rapid, rate of liberation of Cl^- drops to a much lower value even before half of the total chlorine has been liberated, and that the smaller the concentration of the incoming group, Y, in the solution, the earlier this drop off occurs. Furthermore, if chloride ion is added to the solution to begin with, then for the same concentration of Y, the slowing down takes place earlier. Addition of more Y at this stage again speeds up the reaction. These are all expected on the basis of eq. 15. Eventually all of the chloride ion is replaced by pyridine or aniline (see Experimental). Hence, the rate constant for the initial rate has been divided by two for the data given in Table I for these two reagents, namely, aniline and pyridine in their reaction with *trans*-$Pt(NH_3)_2Cl_2$.

EVANSTON, ILL.

[CONTRIBUTION FROM THE INSTITUTE OF GENERAL CHEMISTRY, THE UNIVERSITY OF PALERMO]

Studies in Coördination Chemistry. I. The Effect of Solvents on Some Bis-(N-alkylsalicylaldimine)-nickel(II) Complexes

BY LUIGI SACCONI, PIERO PAOLETTI AND GIUSEPPE DEL RE

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A series of bis-(N-alkylsalicylaldimine)-nickel(II) complexes in the solid state and in solution of organic solvents was submitted to magnetic, spectrophotometric and electric moment measurements. The results of dipole moment determination afford evidence against the hypothesis of a tetrahedral structure of such complexes when dissolved in "non-coördinating" solvents. The paramagnetism developed in such solutions and some characteristic features of the absorption spectra can be understood with the hypothesis of an equilibrium involving an "outer orbital" $4s4p^24d$ planar configuration. The magnetic behavior and the absorption spectral data of these complexes in the solid state are discussed in terms of this concept. Observations on the influence of the length of the *n*-alkyl chains attached to the nitrogen atoms on these properties are reported. The zigzag shape of the curves of magnetic moments, atomic polarizations and melting points for this series of complexes are correlated with changes of base strength and coördination power of the parent amines. The smaller the coördination power of the amine, the greater the polarity and thus the "outer orbital" character of the coördinate bonds of the complex. This is also accompanied by a greater ease of bending vibrations of the chelate rings and a greater tendency for interactions between the polarizable molecules in the crystals.

The magnetic behavior of nickel complexes has proved of considerable value in obtaining useful information concerning the bond type and the stereochemistry of such compounds.

Generally magnetic measurements have been carried out on metal complexes in the solid state. However, some measurements also have been made on complexes dissolved in organic solvents. French, Magee and Sheffield,[1] postulate that the weak paramagnetism (1.9 B.M.) exhibited by a methanol solution of diamagnetic bis-(formylcamphor)-ethylenediaminenickel(II) is caused by a partial conversion of the planar complex to a tetrahedral form. Subsequently Willis and Mellor[2] found that a number of tetracovalent nickel(II) complexes, diamagnetic in the solid state, exhibit paramagnetism in various solvents such as pyridine, alcohols, dioxane, chloroform and benzene. The paramagnetism observed in pyridine solutions, corresponding to two unpaired electrons, was attributed to an expansion of the coördination number to six. This solvation reaction was confirmed by Basolo and Matoush[3] through the isolation of the corresponding paramagnetic complexes containing two molecules of pyridine.

Some complexes such as bis-(formylcamphor)-ethylenediaminenickel(II), bis-(salicylaldoxime)-nickel(II) and bis-(N-methylsalicylaldimine)-nickel-(II), diamagnetic in the solid state, exhibit paramagnetism even in "non-coördinating" solvents such as benzene and chloroform.[2] In such cases, where the magnetic moment is intermediate between 0 and 3.2 B.M., it was suggested that a proportion of the molecules of the complex is converted from a planar to a tetrahedral configuration.[2]

In this connection Basolo and Matoush[3] found that no direct correlation exists between the magnetic moment of bis-(formylcamphor)-ethylenediaminenickel(II) in methylbenzenes and the base strength of these solvents. They concluded that the paramagnetism must therefore not be due to solvation but rather to formation of tetrahedral nickel(II) compounds.

Nyholm[4] recently suggested that the intermolecular crystalline forces in solids may sometimes favor the square configuration, whereas in solution, the tetrahedral arrangement of lowest potential energy may be adopted by the isolated molecule.

The magnetic measurements by Fujii and Sumitani[5] and by Clark and Odell[6] on solutions of such complexes in non-coördinating solvents over a

(1) H. S. French, M. Z. Magee and E. Sheffield, THIS JOURNAL, **64**, 1924 (1942).

(2) J. B. Willis and D. P. Mellor, *ibid.*, **69**, 1237 (1947).

(3) F. Basolo and W. R. Matoush, *ibid.*, **75**, 5603 (1953).

(4) R. S. Nyholm, *Chem. Revs.*, **53**, 263 (1953).

(5) S. Fujii and M. Sumitani, *Sci. Repts. Tôhoku Imp. Univ., First Series*, **37**, 49 (1953).

(6) H. C. Clark and A. L. Odell, *J. Chem. Soc.*, 3431 (1955).

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temperature range of 100°, confirmed the occurrence of temperature-dependent equilibria between dia- and paramagnetic forms. Calculation of the thermodynamic quantities associated with the equilibria were retained as supporting Nyholm's suggestion that for certain complexes in solution the paramagnetic, probably tetrahedral, form is the state of lowest energy. However no direct experimental evidence has as yet been reported in support of the hypothesis that the tetrahedral form is responsible for the paramagnetism in benzene and in chloroform solutions.

Clark and Odell[7] correlated their magnetic data with the absorption spectra in various solvents at different temperatures. While the spectral data for solutions in coördinating solvents are consistent with the results of the magnetic measurements, absorption spectra of bis-(formylcamphorethylenediamine)-nickel(II), bis-(salicylaldoxime)-nickel(II) and bis-(N-methylsalicylaldimine)-nickel-(II) complexes in non-polar solvents do not correlate the results of magnetic measurements.

In order to obtain more definitive information on the effect of solvents on these nickel complexes, we have investigated the series of nickel(II) complexes of N-alkylsalicylaldimines, where the alkyl group increase from methyl through *n*-amyl. Chloroform, benzene and dioxane solutions of these complexes were submitted to dipole moment, magnetic and spectrophotometric measurements. Magnetic and spectrophotometric measurements also were made on the solid compounds. Relatively few spectral investigations of complexes in the crystalline state are reported in the literature.[8]

Experimental

Preparation of Compounds.—The following general method was used: bis-salicylaldehydenickel(II) dihydrate was suspended in excess of an aqueous alcoholic solution of *n*-alkylamine and heated on the water-bath under reflux for several minutes. The crystalline products obtained were then recrystallized from alcohol or from chloroform and petroleum ether. The olive-green complexes are soluble in alcohol, ether, benzene and chloroform. The solubility in non-polar solvents increases with increasing *n*-alkyl chain length.

Bis-(N-methylsalicylaldimine)-nickel(II) was prepared according to Klemm and Raddatz.[9] This compound melts between 192 and 202°.

Bis-(N-ethylsalicylaldimine)-nickel(II): m.p. 173–174°. *Anal.* Calcd. for $C_{18}H_{20}O_2N_2Ni$: N, 7.89; Ni, 16.53. Found: N, 8.05; Ni, 16.31.

Bis-(N-propylsalicylaldimine)-nickel(II): m.p. 160–161°. *Anal.* Calcd. for $C_{20}H_{24}O_2N_2Ni$: N, 7.32; Ni, 15.33. Found: N, 7.55; Ni, 15.22.

Bis-(N-butylsalicylaldimine)-nickel(II): m.p. 140–141°. *Anal.* Calcd. for $C_{22}H_{28}O_2N_2Ni$: N, 6.82; Ni, 14.27. Found: N, 6.97; Ni, 14.05.

Bis-(N-amylsalicylaldimine)-nickel(II): m.p. 142–143°. *Anal.* Calcd. for $C_{24}H_{32}O_2N_2Ni$: N, 6.38; Ni, 13.36. Found: N, 6.37; Ni, 13.24.

Magnetic Susceptibility Measurements.—Susceptibility measurements on the solids were made with the modified Bhatnagar balance described previously.[10] Magnetic measurements on the complexes dissolved in the different solvents were executed using a Gouy-type magnetic balance. The susceptibilities of the complexes were determined according to the formula

$$\chi_{g(complex)} = [\chi_{g(solution)} - \chi_{g(solvent)}(1-x)]/x$$

where x = fraction by weight of complex in solution. After calculation of the molar susceptibilities, diamagnetic corrections for the organic ligands were computed from Pascal's constants.[11] The solutions employed were of equivalent concentration. The only exception to this was the chloroform solution of the first complex, which is very sparingly soluble in this solvent.

Spectrophotometric Measurements.—Absorption spectra were obtained with a Beckman DU spectrophotometer. The silica absorption cells had a 1-cm. light path. The concentrations of the complexes in solutions were between 1.7×10^{-4} and 2.07×10^{-2} mole per liter depending upon the degree of absorption. Measurements in the solid state were made by the potassium bromide method.[12] Extinction coefficients for the ultraviolet spectra by the disk method were calculated from the familiar equation $E = 1/cd \log_{10}(I_0/I)$ in which c is reported in moles per liter of potassium bromide, and d is the length of the light path (0.080–0.085 cm.).

Dipole Moment Measurements.[13]—The dielectric constants of the solutions relative to those of the solvents were determined with a heterodyne oscillator and a cell as previously described.[14] The solvents (benzene and dioxane) were purified by the standard procedures. In each case 4 or 5 solutions were measured. The refractive indices were determined with a Pulfrich refractometer. Densities were measured with a pycnometer. The main source of error in the determinations was the low solubility of the compounds investigated, especially for the benzene solution of the first member of the series.

The molar polarizations of the solutes at infinite dilution ($P_{2\infty}$) were determined by the method of Halverstadt and Kumler.[15] The plots of dielectric constants ϵ_{12} and densities d_{12} *vs.* molar fractions were found to be straight lines with slopes α and β, respectively. The extrapolated values (ϵ_1 and d_1) for $f_2 = 0$ were always close to the experimental values for the pure solvents. The P_E values were determined experimentally, and varied according to the additivity rule of molar refractions.

Results and Discussion

The diamagnetism exhibited by these complexes in the solid state (*cf.* Table I) is indicative of a covalent dsp^2 planar configuration. Table I and Fig. 1 report the values of magnetic moments of the complexes dissolved in dioxane, benzene and chloroform.

The values of the magnetic moments found for bis-(N-methylsalicylaldimine)-nickel, ranging from 1.9 to 2.3 B.M. depending on the solvent used, are in good agreement with the results of Willis and Mellor[2] and with those of Clark and Odell.[6,7] The susceptibilities of the successive members of the series are much lower. In benzene and dioxane solutions they vary between 0.3 and 0.8 B.M. In chloroform the values are higher, ranging from 0.9 to 1.2 B.M. It may be remarked that the plot of $\mu_{eff.}$ *vs.* the number of carbon atoms in the *n*-alkyl chain has the shape of a zigzag. In this plot the lower points correspond to alkyl chains with an even number, the upper points to alkyl chains with an odd number of carbon atoms.

The values of magnetic moments, which vary between zero and that required for two unpaired

(7) H. C. Clark and A. L. Odell, *J. Chem. Soc.*, 520 (1956).

(8) *Cf.* J. P. Faust and J. V. Quagliano, THIS JOURNAL, **76**, 5346 (1954).

(9) W. Klemm and K. H. Raddatz, *Z. anorg. allgem. Chem.*, **250**, 207 (1942).

(10) L. Sacconi, THIS JOURNAL, **76**, 3402 (1954).

(11) P. W. Selwood, "Magnetochemistry," Interscience Publishers, Inc., New York, N. Y., 1943, pp. 51–55.

(12) M. M. Stimson and M. J. O'Donnell, THIS JOURNAL, **74**, 1805 (1952).

(13) These measurements were made at the Istituto di Chimica Organica dell'Università, Napoli.

(14) G. Speroni, G. Del Re and C. Caselli, *Ricerca Sci.*, **26**, 3115 (1956).

(15) I. Halverstadt and W. Kumler, THIS JOURNAL, **64**, 2988 (1942).

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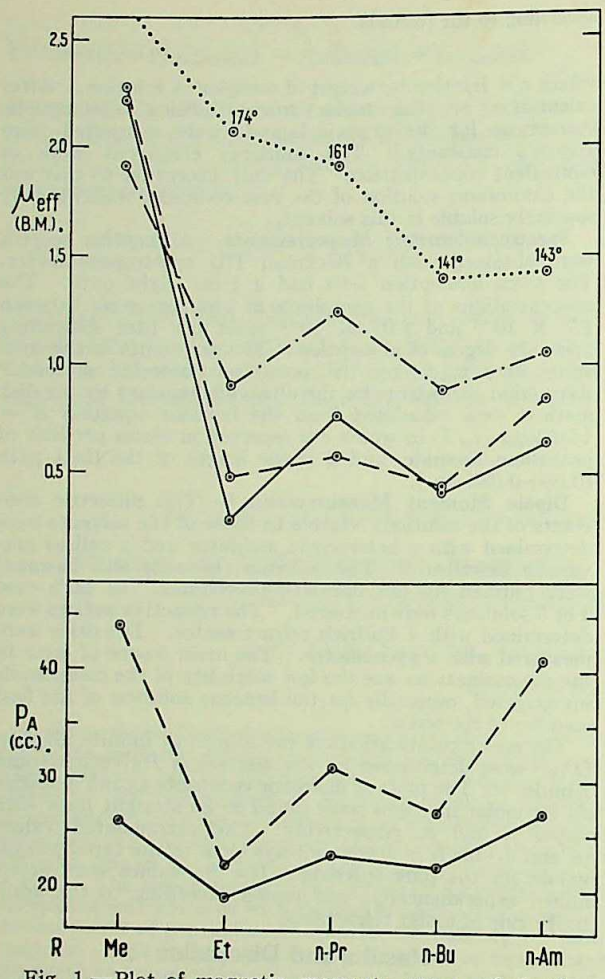

Fig. 1.—Plot of magnetic moments, atom polarizations and melting points of the bis-N-alkylsalic.-Ni complexes *vs.* R = *n*-alkyl chain. Solvents: benzene (———); dioxane (– – – –); chloroform (–·–·–·). In the curve (.....) only the upper values of melting points are reported.

TABLE I

MAGNETIC SUSCEPTIBILITY DATA FOR BIS-(N-ALKYLSALICYLALDIMINE)-NICKEL(II) COMPLEXES AT 20°

Bis-N-alkyl-Ni-complex	$-\chi \times 10^6$ (solid)	Solvent	Concn. g./g.	Concn. mM/g.	$\chi_A \times 10^6$	$\mu_{eff.}$ (B.M.)
N-Methyl-	0.329	Chl	2.12	6.5	1586	1.92
		Bz	1.70	5.2	2106	2.22
		Diox	1.50	4.6	2246	2.28
		Pyr	2.10	6.42	4296	3.16
N-Ethyl-	.435	Chl	2.86	8.06	357	0.91
		Bz	1.85	5.2	36	.29
		Diox	1.63	4.6	103	.49
		Pyr	2.28	6.42	4174	3.12
N-Propyl-	.519	Chl	3.09	8.06	665	1.25
		Bz	1.99	5.2	271	0.78
		Diox	1.76	4.6	148	.59
		Pyr	2.46	6.42	4294	3.16
N-Butyl-	.437	Chl	3.32	8.06	337	0.89
		Bz	2.14	5.2	78	.42
		Diox	1.89	4.6	85	.45
		Pyr	2.64	6.42	4247	3.14
N-Amyl-	.521	Chl	3.54	8.06	478	1.06
		Bz	2.28	5.2	184	0.65
		Diox	2.02	4.6	304	.84
		Pyr	2.82	6.42	4121	3.11

range from 0.63 to 0.88 *D* for the benzene solutions and from 0.83 to 1.29 *D* for the dioxane solutions. These data were obtained by assuming $P_A = 10\% P_E$, *i.e.*, by using P_A values ranging from 10 to 14 cc., both for benzene and dioxane solutions. In this connection it may be remembered that Sutton and co-workers[16] showed that the P_A values for several metal acetylacetonates greatly exceed the 10% P_E, being *ca.* 30 cc. For a series of copper(II) and nickel(II) chelates of analogs of bis-(acetylacetone)-ethylenediimine, where the metal is joined to two oxygen and two nitrogen atoms at the center of three ortho condensed chelate rings, McCarty and Martell[17] made the allowance for P_A of 36–41 cc. = 35–50% P_E. Besides MacQueen and J. W. Smith[18] computed P_A values ranging from 21 to 31 cc. for a number of *trans*-planar complexes of copper(II) and nickel(II) in benzene and

TABLE II

DIELECTRIC POLARIZATION DATA FOR BIS-(N-ALKYLSALICYLALDIMINE)-NICKEL(II) AND COPPER(II) COMPLEXES AT 25°

Bis-N-alkylsalic. complex	Solvent	ϵ_1	α	d_1	β	R_D (cc.)	$P_{2\infty}$ (cc.)	$P_{2\infty} - R_D$ (cc.)	$\mu_{app.}$ (D) 10%	$\mu_{app.}$ (D) 20%
N-Methyl-Ni	Bzn	2.2714	3.52	0.8724	1.43	99	125	26	0.88	0.54
	Diox	2.2077	5.30	1.0280	1.02	99	143	44	1.29	1.08
N-Ethyl-Ni	Bzn	2.2787	3.13	0.8726	1.46	109	128	19	0.63	..
	Diox	2.2189	3.74	1.0277	0.82	108	130	22	.73	..
N-Propyl-Ni	Bzn	2.2739	2.89	0.8736	1.24	117	140	23	.73	..
	Diox	2.2251	4.25	1.0265	0.88	117	148	31	.96	0.63
N-Butyl-Ni	Bzn	2.2758	2.92	0.8732	1.29	127	149	22	.66	..
	Diox	2.2221	4.06	1.0258	0.82	127	154	27	.83	0.31
N-Amyl-Ni	Bzn	2.2714	3.18	0.8726	1.18	138	165	27	.79	..
	Diox	2.2189	3.70	1.0268	0.66	138	179	41	1.17	0.80
N-Methyl-Cu	Diox	2.2194	5.40	1.0276	1.01	94	146	52	1.45	1.21
N-Ethyl-Cu	Diox	2.2222	6.66	1.0272	0.95	107	174	67	1.66	1.50

electrons, suggest the occurrence of an equilibrium between diamagnetic and paramagnetic forms of such complexes. This is more evident for the odd members of the series.

Table II contains the dielectric polarization data obtained for the five nickel(II) complexes and for two analogous copper(II) chelates. The values of the "apparent" moment for the nickel complexes

(16) A. Finn, G. Hamps and L. Sutton, *J. Chem. Soc.*, 1254 (1938); I. Coop and L. Sutton, *ibid.*, 1269 (1938).

(17) J. McCarty and A. E. Martell, THIS JOURNAL, **78**, 2106 (1956).

(18) J. MacQueen and J. W. Smith, *J. Chem. Soc.*, 1821 (1956); J. W. Smith, "Electric Dipole Moments," Butterworths Scientific Publications, London, 1955, pp. 276–279.

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dioxane solutions. In our measurements if allowance is made for P_A = 17–26% P_E in benzene and 21–44% P_E in dioxane, the values of μ (D) become equal to zero. If, according to the treatment of MacQueen and Smith,[18] we interpret the difference between P_2 and R_D as atom polarizations, values of P_A ranging from 19 to 27 cc. for benzene solutions are found. This fact leads to the conclusion that the dipole moments are practically zero when correct allowance for the atom polarization is made. On the basis of these data both the *cis*-planar and the tetrahedral structure are to be rejected and therefore a *trans*-planar configuration can be ascribed to all the nickel chelates in Table II. This conclusion is corroborated by the results of dipole moment measurements on some analogous copper(II) chelates. For bis-(N-methylsalicylaldimine)-copper(II), where a *trans*-planar configuration is generally accepted, if allowance is made[19] for P_A = 20% P_E, then the same value of $\mu_{app.}$ = 1.21 D (solvent dioxane) is found. Besides the value of P_A of *ca.* 50 cc., computed from the difference between $P_{2\infty}$ and R_D agrees with the value of 54 cc. calculated by MacQueen and Smith from the data of Charles and Freiser[19] for this copper chelate. The complex bis-(N-ethylsalicylaldimine)-copper(II) in dioxane exhibits a still higher moment of 1.50 D (P_A = 20% P_E)(*cf.* Table II).

The spectra of the complexes in chloroform solutions (see Table III and Figs. 2 and 3) show three bands in the 326, 414–418 and 610–620 mμ regions. The absorption curves of the chelate groups in dioxane and benzene solutions are quite similar, excepting a shift of 2–20 and 3–25 mμ toward the red in dioxane and benzene solutions, respectively.

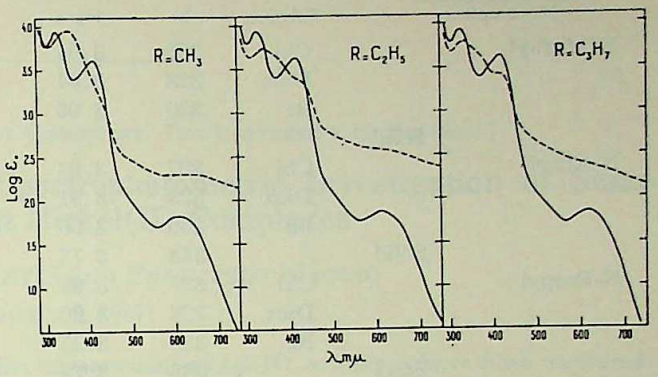

Fig. 2.—Absorption curves of bis-N-alkylsalic.-Ni complexes in chloroform (———) and in the solid state (– – – –). The spectra of bis-N-butyl and bis-N-amyl complexes are very similar to that of the bis-N-propyl complex and therefore are not shown.

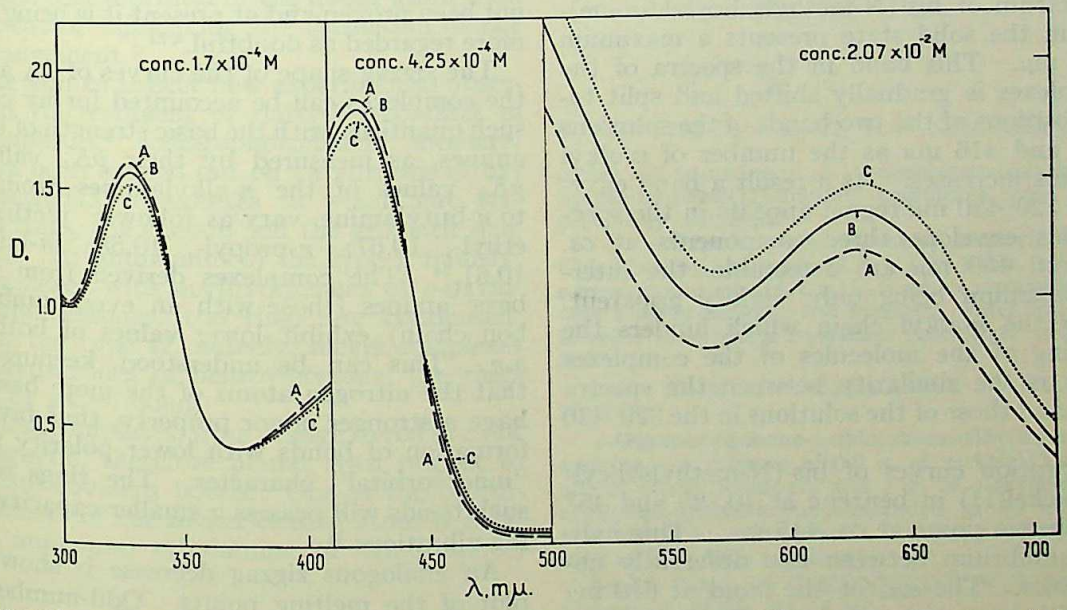

Fig. 3.—Absorption curves of bis-N-methylsalic.-Ni(II) complex in benzene at different temperatures: A (- - - -), 10°; B (———), 25°; C (. . . . .), 45°. At *ca.* 445 mμ the isosbestic point.

Furthermore it is remarkable that the values of $P_{2\infty}$ and $P_{2\infty} - R_D$ found for all the complexes investigated in solution of dioxane are slightly higher than those in benzene, in accordance with the results of both Sutton and MacQueen and Smith. In accordance with the conclusions of these authors, the high P_A values found for the square complexes of the series of N-alkyl-salicylaldimine can be explained as principally due to bending vibrations of the rings as units relative to the remainder of the molecule. These vibrations of the six-membered rings would involve a folding or twisting of the molecule as a whole.

This shift increases gradually with increasing λ_{max} of the bands. The very strong absorption band at *ca.* 420 mμ (log $\epsilon > 3.5$) may be identified as the band characteristic of covalent nickel chelates.[20] The weak band at 610–640 mμ can be considered as due to the central metallic cation.[21] The intensity of this band (log $\epsilon < 2$) is that typical of a forbidden transition, probably 3d-3d.[22] This fact leads to the assumption of the existence of unoccupied 3d levels in these complexes when dis-

(19) R. G. Charles and H. Freiser, THIS JOURNAL, 73, 5223 (1951).

(20) J. E. Mills and D. P. Mellor, *ibid.*, 64, 181 (1942); 69, 1237 (1947); H. A. McKenzie, D. P. Mellor, J. E. Mills and L. N. Short, *J. Proc. Soc., N. S. Wales*, 78, 70 (1944).

(21) *Cf.* K. Sone, THIS JOURNAL, 75, 5204 (1953).

(22) R. J. P. Williams, *J. Chem. Soc.*, 137 (1955).

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TABLE III

SPECTROPHOTOMETRIC ABSORPTION DATA FOR BIS-(N-ALKYLSALICYLALDIMINE)-NICKEL(II) COMPLEXES[a]

Bis-N-alkylsalic.-Ni-complexes	Solvent	λ_1	log ϵ_1	λ_2	log ϵ_2	λ_3	log ϵ_3	λ_4	log ϵ_4
N-Methyl-	Chl	326	3.94			414	3.61	610	1.82
	Diox	328	3.94			418	3.62	625	1.75
	Bz	330	3.96			422	3.64	628	1.82
	Solid			354	3.95				
N-Ethyl-	Chl	327	3.93			416	3.62	615	1.85
	Diox	328	3.91			420	3.62	625	1.85
	Bz	330	3.96			426	3.64	640	1.85
	Solid	343	3.73	(~360)	3.68	(~430)	3.35		
N-Propyl-	Chl	327	3.93			418	3.63	620	1.84
	Diox	328	3.90			422	3.58	630	1.84
	Bz	330	3.95			424	3.64	640	1.86
	Solid	338	3.79	(~360)	3.70	(~420)	3.4		
N-Butyl-	Chl	327	3.93			417	3.64	615	1.84
	Diox	328	3.90			422	3.61	635	1.83
	Bz	330	3.96			426	3.66	640	1.86
	Solid	338	3.67	(~360)	3.59	(~420)	3.3		
N-Amyl-	Chl	327	3.93			418	3.63	615	1.85
	Diox	328	3.86			422	3.59	630	1.80
	Bz	330	3.95			424	3.67	635	1.86
	Solid	345	3.61	(~360)	3.55	(~420)	3.20		

[a] The values of the wave lengths of the inflections are enclosed in parentheses.

solved in the above solvents, in accordance with the results of magnetic measurements.

The spectrum of bis-(N-methylsalicylaldimine)-nickel(II) in the solid state presents a maximum at *ca.* 354 mμ. This band in the spectra of the other complexes is gradually shifted and split toward the positions of the two bands of the solutions at *ca.* 326 and 416 mμ as the number of *n*-alkyl carbon atoms increases. As a result a band envelope in the 320–430 mμ region appears in the spectra. In this envelope three components at *ca.* 340, 360 and 430 mμ are detectable, the intermediate maximum being only slightly apparent. The longer the *n*-alkyl chain which hinders the close packing of the molecules of the complexes the greater is the similarity between the spectra of the solid and those of the solutions in the 320–430 mμ region.

The absorption curves of bis-(N-methylsalicylaldimine)-nickel(II) in benzene at 10, 25 and 45° have a isosbestic point at *ca.* 445 mμ. This indicates an equilibrium between two differently absorbing species. The ϵ_{max} of the band at 610 mμ increases with increasing temperature, an increase which takes place also by dilution at constant temperature. The two forms in equilibrium correspond, evidently, to the diamagnetic and the paramagnetic one revealed by the magnetic measurements of Clark and Odell.[6]

Our observation that the paramagnetic form possesses a non-polar, planar structure can be explained by assuming that the four bonds from the nickel atom in this form are of the "outer orbital" $4s4p^24d$ type. This signifies that the equilibrium existing in such solutions is not between a planar and a tetrahedral form but probably between an "inner" and an "outer orbital" one. In the solid, only the "inner orbital" $3d4s4p^2$ form probably exists, owing to the influence of the crystalline field which forces a complete spin coupling.

In this connection it should be remembered that the existence of tetrahedral Ni(II) complexes has not been proven and at present it is being more and more regarded as doubtful.[4,23]

The zigzag shape of the curves of P_A and $\mu_{eff.}$ of the complexes can be accounted for by correlating such quantities with the basic strength of the parent amines, as measured by their pK_a values. The pK_a values of the *n*-alkylamines from methyl- to *n*-butylamine, vary as follows: methyl-, 10.64; ethyl-, 10.67; *n*-propyl-, 10.58; *n*-butylamine, 10.61.[24] The complexes derived from the more basic amines (those with an even-numbered carbon chain) exhibit lower values of both P_A and $\mu_{eff.}$. This can be understood, keeping in mind that the nitrogen atoms of the more basic amines have a stronger donor property, thus favoring the formation of bonds with lower polarity and more "inner orbital" character. The rings containing such bonds will possess a smaller capacity of bending vibrations.[18]

An analogous zigzag decrease is shown by the plot of the melting points. Odd-numbered complexes which have more polar bonds, exhibit relatively higher melting points, presumably as a consequence of a stronger interaction between the molecules. It is probable, however, that steric factors of the type which are operative in melting of normal alkanes,[25] expressed in terms of different orientation of the carbon chain within the unit

(23) J. Bjerrum and C. K. Joergensen, *Rec. trav. chim.*, **75**, 661 (1956); C. J. Ballhausen, *ibid.*, 665, 669; R. S. Nyholm, "Complex Compounds of Transition Metals," Proceedings of Tenth Solvay Conference, Brussels, May, 1956.

(24) *Cf.* E. A. Braude and F. C. Nachod, "Determination of Organic Structure by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, p. 573. See also J. Bjerrum, *Chem. Revs.*, **46**, 381 (1950).

(25) *Cf.* E. A. Braude and F. C. Nachod, ref. 24, pp. 3–12; J. A. A. Ketelaar, "Chemical Constitution," Elsevier Publishing Co., Amsterdam, 1953, pp. 350–368.

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cell, may play some role also in the phenomenon considered here.

Acknowledgment.—We are indebted to the Italian "Consiglio Nazionale delle Ricerche" (C.N.R.) for the financial support of this work.

PALERMO, ITALY

[CONTRIBUTION FROM THE INSTITUTE OF GENERAL CHEMISTRY, THE UNIVERSITY OF PALERMO]

Studies in Coördination Chemistry. II. Spectrophotometric Investigation of Some Hydrazidic Tetracovalent Nickel(II) Complexes

BY LUIGI SACCONI, PIERO PAOLETTI AND FRANCESCO MAGGIO

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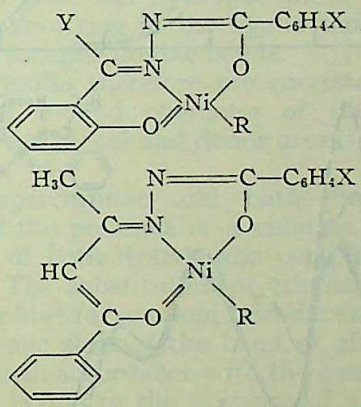
The ultraviolet absorption spectra of a number of hydrazidic tetracovalent nickel(II) complexes have been measured. The effect of certain atomic grouping adjacent to the chelate ring has been studied and discussed in terms of the hypothesis of dative π-bond in metal complexes.

The concept of double bond formation between metals and donor atoms is now regarded as of great importance in many complexes.[1]

Pauling was the first to explain the unusual strength and shortening of some metal–ligand bonds in certain coördination compounds by the hypothesis of double bonding.[2] In the case of nickel complexes it was suggested that the formation of double bond using d_π electron pairs of the metal and a vacant p or d orbital of the donor atom is an important factor influencing the formation of the square arrangement.[3]

With the aim to collect new experimental observations on the problem of dative π-bonding in metal complexes,[4] spectrophotometric measurements have been carried out on two groups of hydrazidic nickel(II) complexes in which two six-membered rings, the chelate and the aromatic one, are present. In compounds of the type I, namely, nickel complexes with acylhydrazones of *o*-oxyaldehydes and ketones, the rings are condensed; in those of the type II, namely, nickel complexes with acylhydrazones of benzoylacetone, the rings are joined by a C–C bond.

All of these complexes, from orange to red in color are diamagnetic, therefore planar with respect to the four dsp^2 covalent bonds. One of the coördinative valences of the nickel central atom is saturated by ammonia, ethylamine or triethylphosphine.



I

II

Y = H, CH_3; X = H, Cl; R = NH_3, $NH_2C_2H_5$, $P(C_2H_5)_3$

Experimental

Preparation of Compounds.—Salicylidenebenzoylhydrazonenickel(II)-ammine, salicylidene-*p*-chlorobenzoylhydrazonenickel(II)-ammine, *o*-oxyacetophenonebenzoylhydrazonenickel(II)-ammine, benzoylacetonebenzoylhydrazonenickel (II)-ammine and benzoylacetone-*p*-chlorobenzoylhydrazonenickel(II)-ammine complexes were prepared as previously described.[5]

***o*-Oxyacetophenone-*p*-chlorobenzoylhydrazone.**—*p*-Chlorobenzoylhydrazide (1.3 g.) in 8 ml. of alcohol and *o*-oxyacetophenone (1.1 g.) in 3 ml. of alcohol were refluxed over a water-bath for few minutes; water was then added in order to obtain a crystalline precipitate melting at 223–225°.

Anal. Calcd. for $C_{15}H_{13}O_2N_2Cl$: N, 9.70. Found: N, 9.68.

***o*-Oxyacetophenone-*p*-chlorobenzoylhydrazonenickel(II)-ammine.**—A mixture of 0.9 g. of nickel(II) acetate in 10 ml. of concd. ammonia and 1 g. of *o*-oxyacetophenone-*p*-chlorobenzoylhydrazone suspended in 15 ml. of alcohol was heated on a water-bath. Orange needles which do not melt at 270° were obtained.

Anal. Calcd. for $C_{15}H_{14}O_2N_3ClNi$: N, 11.59; Ni, 16.19. Found: N, 11.63; Ni, 16.10.

Salicylidenebenzoylhydrazonenickel(II)-ethylamine.—A mixture of 1 g. of nickel(II) acetate in 16 ml. of 50% alcohol and 8 ml. of 33% ethylamine and 0.66 g. of salicylidenebenzoylhydrazone in 30 ml. of alcohol was warmed on a water-bath to obtain red needles of m.p. 132° dec.

Anal. Calcd. for $C_{16}H_{17}O_2N_3Ni$: N, 12.28; Ni, 17.16. Found: N, 12.19; Ni, 17.17.

Salicylidenebenzoylhydrazonenickel(II)-triethylphosphine.—Nickel(II) acetate (1 g.) in 16 ml. of 50% alcohol and 1 g. of triethylphosphine was mixed with 0.66 g. of salicylidenebenzoylhydrazone in 30 ml. of alcohol. The mixture was warmed on a water-bath under reflux. Orange tablets of m.p. 105–106° dec. were obtained.

Anal. Calcd. for $C_{20}H_{25}O_2N_2PNi$: N, 6.75; P, 7.47; Ni, 14.14. Found: N, 6.97; P, 8.05; Ni, 14.40.

***o*-Oxyacetophenonebenzoylhydrazonenickel(II)-ethyl-**

(1) R. S. Nyholm, *Rev. Pure Appl. Chem.* (*Australia*), **4**, 15 (1954); A. E. Martell and M. Calvin, "Chemistry of the Metal Chelate Compounds," Prentice–Hall, Inc., New York, N. Y., 1952, p. 160; Y. K. Syrkin and M. E. Dyatkina, "Structure of Molecules," Butterworths Sci. Publ., London, 1950, p. 361.

(2) L. Pauling, "The Nature of the Chemical Bond," 2nd Ed., Cornell University Press, Ithaca, N. Y., 1948, p. 250.

(3) R. S. Nyholm, *Chem. Revs.*, **53**, 276 (1953).

(4) *Cf.* G. E. Coates, *J. Chem. Soc.*, 2003 (1951); J. Chatt and A. A. Williams, *ibid.*, 3061 (1951); J. Chatt and R. G. Wilkins, *ibid.*, 273, 4300 (1952); R. S. Nyholm and F. H. Burstall, *ibid.*, 3570, 3579 (1952); J. Chatt, L. A. Duncanson and L. M. Venanzi, *ibid.*, 4461 (1955); R. K. Murmann and F. Basolo, THIS JOURNAL, **77**, 3484 (1955).

(5) L. Sacconi, *Gazz. chim. ital.*, **83**, 884 (1953); *Z. anorg. allgem. Chem.*, **275**, 249 (1954); THIS JOURNAL, **75**, 5434 (1953).

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amine.—Nickel(II) acetate (1 g.) in 20 ml. of alcohol and 10 ml. of 33% ethylamine was mixed with 1 g. of *o*-oxyacetophenonebenzoylhydrazone in 30 ml. of alcohol. The mixture was heated on a water-bath for few minutes to yield red prisms of m.p. 141–142° dec.

Anal. Calcd. for $C_{17}H_{19}O_2N_3Ni$: N, 11.80; Ni, 14.49. *Found:* N, 11.84; Ni, 14.43.

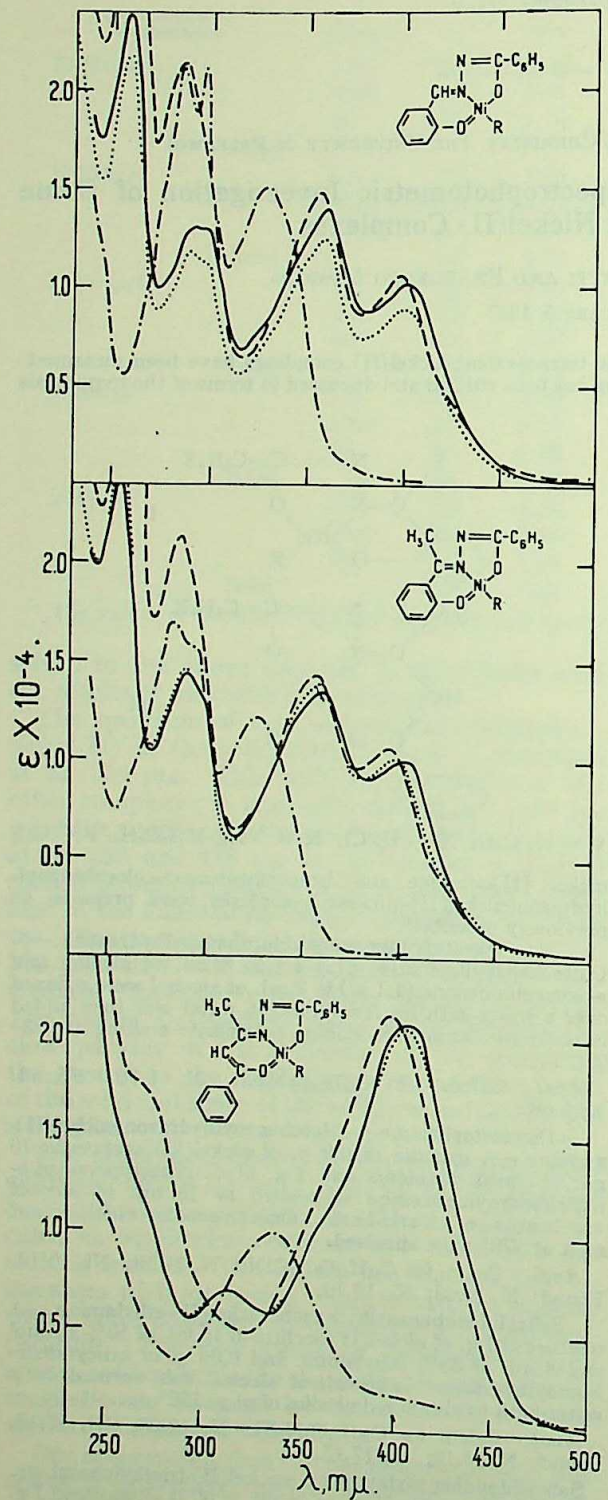

Fig. 1.—Absorption spectra of the ligands with X = H (-·-·-·-) and related complexes with R = NH_3 (———), R = $NH_2C_2H_5$ (.....) and R = $P(C_2H_5)_3$ (--------).

o-Oxyacetophenonebenzoylhydrazonenickel(II)-triethylphosphine.—A solution of 1 g. of nickel(II) acetate in 6 ml. of water, 12 ml. of alcohol and 1 g. of triethylphosphine was mixed with 1 g. of *o*-oxyacetophenonebenzoylhydrazone suspended in 30 ml. of alcohol. The mixture was warmed on a water-bath under reflux for a few minutes. Orange-red prisms were obtained which melt, with decomposition, at 98–99°.

Anal. Calcd. for $C_{21}H_{27}O_2N_2PNi$: N, 6.55; P, 7.22; Ni, 13.68. Found: N, 6.71; P, 7.65; Ni, 13.63.

Benzoylacetonebenzoylhydrazonenickel(II)-ethylamine.—A mixture of 1 g. of nickel(II) acetate in 20 ml. of water and 10 ml. of 33% ethylamine and 1.1 g. of benzoylacetonebenzoylhydrazone in 20 ml. of alcohol was warmed on a water-bath under reflux for few minutes. Addition of water facilitates the formation of red-orange needles of m.p. 130–131° dec.

Anal. Calcd. for $C_{19}H_{21}O_2N_3Ni$: N, 11.00; Ni, 15.36. Found: N, 11.40; Ni, 15.43.

Benzoylacetonebenzoylhydrazonenickel(II)-triethylphosphine.—A mixture of 1 g. of nickel(II) acetate in 20 ml. of alcohol and 1 g. of triethylphosphine and 1.1 g. of benzoylacetonebenzoylhydrazone in 40 ml. of alcohol was warmed on a water-bath under reflux for few minutes. On standing at 0–5° red crystals separated which melt with decomposition at 101–102°.

Anal. Calcd. for $C_{23}H_{29}O_2N_2PNi$: N, 6.15; P, 6.81; Ni, 12.89. Found: N, 6.37; P, 6.79; Ni, 12.85.

All the complexes are soluble in alcohol, ether, benzene, chloroform. Those with triethylphosphine are also soluble in petroleum ether.

Spectra of Ligands and Complexes.—Spectrophotometric measurements were made with a Beckman DU spectrophotometer using silica cells 1 cm. long, on alcohol solutions of chelating agents and nickel complexes of 8.5×10^{-5} *M* concentration.

Results

Spectral data for acylhydrazones and complexes are recorded in Table I, where ϵ signifies molecular extinction coefficient.

TABLE I

ABSORPTION CHARACTERISTIC OF LIGANDS AND COMPLEXES

	λ_{max} (mμ)	$\epsilon_{max} \times 10^{-4}$
Type I		
o-Oxyacetophenonebenzoylhydrazone	326	1.23
o-Oxyacetophenone-*p*-chlorobenzoylhydrazone	328	1.36
Salicylidenebenzoylhydrazone	328	1.51
Salicylidene-*p*-chlorobenzoylhydrazone	330	1.66
Type II		
Benzoylacetonebenzoylhydrazone	335	1.01
Benzoylacetone-*p*-chlorobenzoylhydrazone	336	1.25
Type I		
o-Oxyacetophenone-benzoylhydrazone-Ni-NH_3	400	0.97
o-Oxyacetophenone-*p*-chlorobenzoylhydrazone-Ni-NH_3	402	1.12
o-Oxyacetophenonebenzoylhydrazone-Ni-$NH_2C_2H_5$	398	1.01
o-Oxyacetophenonebenzoylhydrazone-Ni-$P(C_2H_5)_3$	394	1.07
Salicylidenebenzoylhydrazone-Ni-NH_3	402	1.02
Salicylidene-*p*-chlorobenzoylhydrazone-Ni-NH_3	404	1.16
Salicylidenebenzoylhydrazone-Ni-$NH_2C_2H_5$	400	0.90
Salicylidenebenzoylhydrazone-Ni-$P(C_2H_5)_3$	396	2.11
Type II		
Benzoylacetonebenzoylhydrazone-Ni-NH_3	405	2.10
Benzoylacetone-*p*-chlorobenzoylhydrazone-Ni-NH_3	409	2.39
Benzoylacetonebenzoylhydrazone-Ni-$NH_2C_2H_5$	404	2.03
Benzoylacetonebenzoylhydrazone-Ni-$P(C_2H_5)_3$	396	2.11

Experimental absorption curves for compounds with X = H are shown in Fig. 1. Compounds with X = Cl exhibit analogous features.

Discussion

The spectra obtained for the ligands of the type I show two bands in the 280–290 and 326–336 mμ

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regions. The latter maximum could be considered as the 325 mμ band of the salicylaldehyde[6] shifted toward longer wave lengths owing to the formation of the benzoylhydrazone. This band can be ascribed to the existence of a chelate enol ring stabilized through hydrogen-bond formation and enol resonance.[7]

Beside showing a very strong absorption band in the ultraviolet region below 250 mμ, the spectra of the ligand molecules of type II show a maximum at 336 mμ. This band presumably can be related to the band at 310 mμ ascribed to the enol form of benzoylacetone.[6]

The spectra of the complexes of type I show four absorption bands at *ca.* 260, *ca.* 280, *ca.* 360 and 400–410 mμ. The band at *ca.* 410 mμ may be identified as the characteristic band of covalent nickel chelates, which is due to the presence of a chelate ring of which the metal is a member.[8] The intensity of this band (of $\epsilon \simeq 10^4$) is that of an allowed transition.[9]

The main features of the absorption spectra of type II complexes consist of two absorption bands in the 340 and 400–410 mμ regions. The former, of smaller intensity, is lacking in the complex with triethylphosphine. The band at 406–410 mμ can be recognized as that of the Ni chelates with dsp^2 covalent structure.

Table I shows that the molecular extinction coefficient of the nickel band maximum at 400–410 mμ increases from the values 9,000–11,600 for the complexes of the type I, to values 21,100–23,900 for the complexes of the type II. Hence the position of the aromatic nucleus, adjacent to the chelate ring in the complexes of type I, attached by a C–C bond in the complexes of type II, influences the chromophoric grouping responsible for this band, *i.e.*, the chelate ring containing the nickel atom. This fact can be related to the existence in the chelate ring of the complexes of a completely conjugated resonance which interferes with the resonance of the aromatic nucleus when the two rings are condensed. Thus a "crossed resonance" of the type already studied for some copper chelates[10] is produced. This "cross conjugation"[11] implies the participation of a nickel atom in the π-bond system of the coördinate ring.

The absence of an hyperchromic effect in the maxima at 326–336 mμ of the spectra of ligands of type II can be explained keeping in mind that the chromophore possibly responsible for such maxima is not a completely conjugated system. In fact it is obvious that the hydrogen atom which completes the enol ring in the ligand molecules is incapable of forming double bonds.

These results therefore are consistent with the concept of π-bond character of the coördinate links between nickel and donor atoms in the above complexes.

The hyperchromic and bathochromic effects caused by the presence of a chlorine atom in the molecules of both ligands and complexes must be noticed. The substitution of ethylamine and triethylphosphine for ammonia produces only a little hypsochromic shift of the band at about 400 mμ. This fact is in accordance with the assumption that this band is due to the presence of a chelate ring including the nickel atom.

Acknowledgment.—We are indebted to the Italian "Consiglio Nazionale delle Ricerche" (C.N.R.) for the financial support of this work.

(6) A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold Publishers, Ltd., London, 1954, pp. 128, 223.
(7) L. N. Ferguson, "Electron Structures of Organic Molecules," Prentice–Hall, Inc., New York, N. Y., 1952, p. 216.
(8) *Cf.* H. A. McKenzie, D. P. Mellor, J. E. Mills and L. N. Short, *J. Proc. Roy. Soc. N.S. Wales*, **78**, 70 (1944); A. E. Martell and M. Calvin, ref. 1; K. Sone, THIS JOURNAL, **75**, 5207 (1953).
(9) *Cf.* R. J. P. Williams, *J. Chem. Soc.*, 137 (1955).
(10) M. Calvin and R. H. Bailes, THIS JOURNAL, **68**, 949 (1946); *cf.* A. E. Martell and M. Calvin, ref. 1, p. 164.
(11) L. N. Ferguson, ref. 7, p. 43.

PALERMO, ITALY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Gluconate Complexes. IV. The Cadmium–Gluconate System

BY ROBERT L. PECSOK AND JIRI SANDERA

RECEIVED MARCH 1, 1957

Cadmium in varying concentrations of gluconate has been investigated polarographically from *p*H 2 to 14. A number of complexes are formed. Those which were identified and studied have a ratio of cadmium to gluconate of 1:2 (*p*H 5 to 8), 2:3 (*p*H 13 to 14), and 2:1 (*p*H 13 to 14). Half-wave potentials and dissociation constants are given.

Although it is known that gluconic acid forms complexes with many metal ions, no previous description of the cadmium–gluconate system is available. The complexes do not give spectra suitable for study, therefore this investigation is entirely polarographic. As in most supporting electrolytes, cadmium in gluconate solutions gives well-defined, reversible polarograms which are subject to thermodynamic interpretation.

Experimental

The polarographic equipment and methods used have been described previously.[1] The purification and preparation of solutions of gluconic acid and sodium gluconate also have been described.[1] A stock solution of cadmium perchlorate was prepared by dissolving cadmium hydroxide in perchloric acid and standardized electrolytically. Conductivity water was used throughout. The ionic strength was adjusted to

(1) R. L. Pecsok and R. S. Juvet, Jr., THIS JOURNAL, **77**, 202 (1955).

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1.0 with sodium perchlorate or potassium nitrate except where otherwise indicated. Sufficient time was allowed for equilibrium to become established (3–4 hr. at pH 10–11). In alkaline solutions, it is necessary to add the sodium gluconate before the sodium hydroxide in order to prevent precipitation. The temperature was maintained at 25.0 ± 0.1° by a water thermostat.

The half-wave potential of cadmium in nitrate or perchlorate media of ionic strength 1.0 was found to be −0.583 v. *vs.* the saturated calomel electrode (used throughout this study). The half-wave potentials were determined graphically on the recorded polarograms, and were reproducible to ±2 mv. The reversibility was tested by measuring the difference, $E_{3/4}$–$E_{1/4}$, which was no more than 2 mv. from the theoretical value of 28 mv. for a 2 electron reduction.[2]

Results and Discussion

The general reaction for the reduction of the cadmium–gluconate complexes at the dropping mercury electrode is assumed to be

$$\text{complex} + x\text{H}^+ + \text{Hg} + 2e^- = \text{Cd(Hg)} + p\text{GH}_4^- \quad (1)$$

or the equivalent in basic solution

$$\text{complex} + \text{Hg} + 2e^- = \text{Cd(Hg)} + p\text{GH}_4^- + x\text{OH}^- \quad (2)$$

from which it follows[3] that

$$(E_{1/2})_c - (E_{1/2})_s = 0.0296 \log K(k_s/k_c) - 0.0296(p) \log (\text{GH}_4^-) - 0.0296(x) \log (\text{OH}^-) \quad (3)$$

where K is the dissociation constant of the pertinent complex. The symbols follow those previously described.[1] (GH_4^-) represents the free gluconate ion concentration

$$(\text{GH}_4^-) = (\text{GH}_4^-)_{\text{total}}/[1 + (\text{H}^+)/K_A]$$

where the subscript "total" indicates the free ion plus the acid and lactones, and K_A is the dissociation constant of gluconic acid, 2.75×10^{-4}.

Several series of solutions were prepared, all containing 2.14×10^{-4} M cadmium, at either constant pH or constant concentration of gluconate, the other being varied. The discussion of the results can be divided conveniently into regions of pH units in which the several species are predominant and the polarographic behavior is similar. Below pH 2 no complexing is detectable, and the addition of gluconic acid does not affect the half-wave potential.

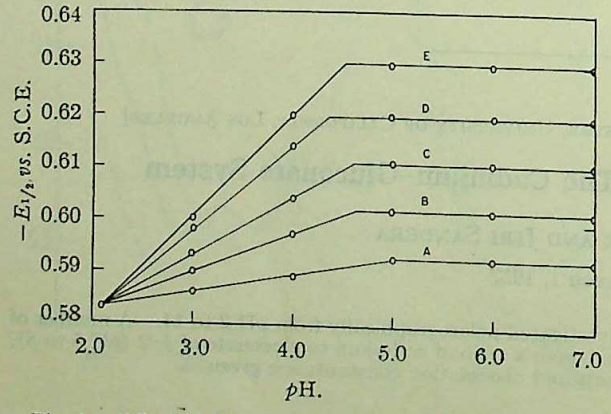

Fig. 1.—Effect of pH on the polarographic $E_{1/2}$ potential obtained with solutions 2.14×10^{-4} M Cd(II) and various sodium gluconate concentrations at ionic strength 1.0: A, 0.080 M; B, 0.200 M; C, 0.300 M; D, 0.500 M; E, 0.700 M sodium gluconate.

(2) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishing Co., New York, N. Y., 1952.

(3) R. L. Pecsok and R. S. Juvet, Jr., THIS JOURNAL, 78, 3967 (1956).

*p*H 2 to 5.—The half-wave potentials are plotted *vs.* pH (constant concentration of gluconate) in Fig. 1. As the pH or gluconate concentration is decreased, the degree of complexing becomes vanishingly small and the half-wave potentials approach that of the aquo-cadmium ion. Furthermore equation 3, in which it is assumed that a large excess of ligand is present, is no longer valid. The calculated values of the dissociation constant for the 1:2 complex (*vide infra*), included in Table I, likewise show deviations from the average value obtained at higher pH. There is probably a mixture of a 1:1 and a 1:2 complex present in this pH region. However, the change in half-wave potential is too small to warrant exact interpretation.

*p*H 5 to 8.—Above pH 5 the conditions of equation 3 are fulfilled, and it can be seen from Fig. 1 that a definite complex predominates. Since the half-wave potential is independent of pH in this region, the reduction does not involve hydrogen ion. For solutions containing more than 0.2 M gluconate, the half-wave potential changes by 59 mv. per tenfold change in gluconate concentration and the number of gluconates per cadmium in the complex is 1.8 ± 0.14. Therefore $p = 2$ and $x = 0$ in this region, and the formula of the complex is $\text{Cd(GH}_4)_2$. In Table I are computed values for $pK_{1:2}$ as defined by

$$pK_{1:2} = \frac{(E_{1/2})_c - (E_{1/2})_s}{-0.0296} + \log \frac{(i_d)_s}{(i_d)_c} - 2 \log \frac{(\text{GH}_4^-)_{\text{total}}}{1 + (\text{H}^+)/K_A} \quad (4)$$

TABLE I

HALF-WAVE POTENTIALS OF THE CADMIUM–GLUCONATE SYSTEM BELOW *p*H 8

pH	$(\text{GH}_4^-)_{\text{total}}$, M	$(\text{GH}_4^-)_{\text{free}}$, M	$-E_{1/2}$, v. *vs.* S.C.E.	$pK_{1:2}$
2.90	0.200	0.036	0.585	2.91
2.90	.500	.090	.596	2.69
2.90	.700	.126	.593	2.33
3.00	.200	.043	.589	2.92
3.00	.300	.064	.593	2.83
3.00	.500	.108	.598	2.49
3.00	.700	.152	.600	2.39
3.40	.200	.082	.592	2.51
4.00	.200	.147	.597	2.25
4.00	.300	.221	.604	2.10
4.00	.500	.368	.614	2.09
4.00	.700	.515	.620	2.04
5.00	.200	.194	.599	2.08
5.00	.300	.290	.610	2.07
5.00	.500	.483	.621	2.12
5.00	.700	.677	.630	2.12
6.00	.200	.200	.599	2.05
6.00	.300	.300	.610	2.06
6.00	.500	.500	.621	2.09
6.00	.700	.700	.630	2.08.
6.31	.050	.050	.590	
6.50	.080	.080	.593	
6.83	.100	.100	.597	
7.10	.300	.300	.610	2.06
7.04	.500	.500	.621	2.09
7.00	.700	.700	.530	2.11

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The average value of $pK_{1:2}$ is 2.10 with a mean error of ± 0.05.

pH 8 to 12.—The half-wave potentials are plotted *vs.* pH (constant gluconate concentration) in Fig. 2, and *vs.* concentration of gluconate (constant pH) in Fig. 3. From the latter, it is seen that the ratio of Cd:G remains constant at 1:2; but from the former, it is apparent that in this region the complex is becoming hydroxylated (or the gluconate bound in the complex is losing hydrogen ions from the secondary hydroxyl groups). Furthermore, solutions in this region required several hours to reach equilibrium, and the data were not exactly reproducible as in the other regions. For these reasons, the nature of the complexes and their constants were not determined.

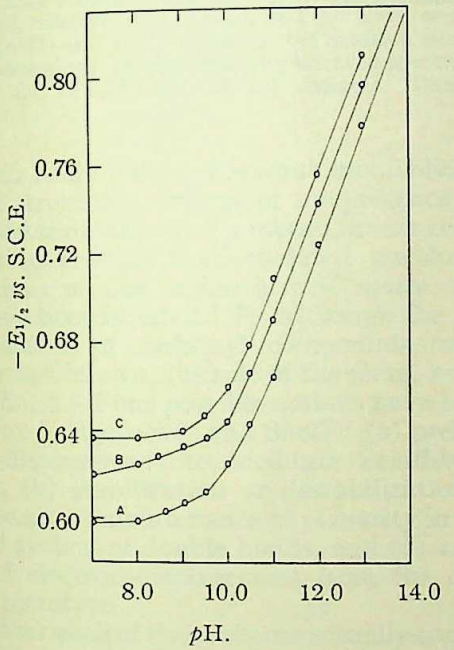

Fig. 2.—Effect of pH (above 8.00) on polarographic $E_{1/2}$ potential obtained with solutions 2.14×10^{-4} M Cd(II) and various sodium gluconate concentrations and constant ionic strength 1.0: A, 0.200 M; B, 0.500 M; C, 0.900 M sodium gluconate.

pH 13 to 14.—Solutions of cadmium, sodium gluconate and sodium hydroxide were polarographed. The data indicate that two complexes exist, one in solutions having less than 0.05 M gluconate, and another in solutions having greater than 0.05 M gluconate. Above 0.05 M gluconate, the ratio of Cd:G is 2:3 and the ratio of Cd:OH is 2:5. For calculation of the dissociation constant of this complex, equation 3 becomes

$$pK_{2:3} = \frac{(E_{1/2})_c - (E_{1/2})_s}{0.0296} - \log \frac{(i_d)_s}{(i_d)_c} - 1.5 \log (GH_4^-) - 2.5 \log (OH^-) \quad (5)$$

Values of $pK_{2:3}$ are shown in Table II, the average value being 10.25 ± 0.64. This value applies to solutions with an ionic strength of 1.0. A number of solutions were used in which the ionic strength was not adjusted to 1.0, but estimated on the basis of the concentration of the various species present. The maximum deviation in $pK_{2s:3}$ was 0.05 log unit at ionic strength 0.1.

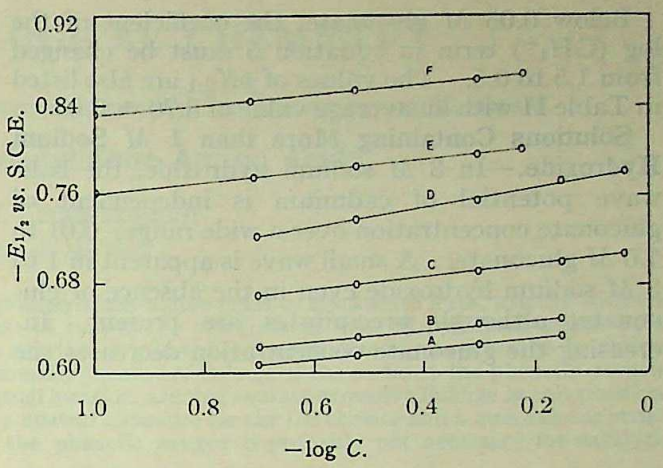

Fig. 3.—Effect of total sodium gluconate concentration on polarographic $E_{1/2}$ potential obtained with solutions 2.14×10^{-4} M Cd(II) and various pH at constant ionic strength 1.0: A, pH 9.00; B, pH 10.00; C, pH 11.00; D, pH 12.00: E, pH 13.00; F, 0.90 M sodium hydroxide.

TABLE II

HALF-WAVE POTENTIALS OF THE CADMIUM–GLUCONATE SYSTEM ABOVE pH 8

$(NaGH_4)$, M	$(NaGH_4)$, M	(NaOH), S.C.E.	$-E_{1/2}$, v. *vs.* $pK_{2:1}$	$pK_{1:3}$
0.010	0.500	0.786	8.70	
.010	0.700	.797	8.70	
.010	1.00	.807	8.67	
.020	0.500	.790	8.72	
.020	0.700	.800	8.67	
.020	1.00	.814	8.75	
.030	0.500	.794	8.80	
.030	0.700	.802	8.64	
.030	1.00	.814	8.66	
.050	1.00	.818	8.70	
.050	0.100	.748		10.48
.050	.200	.772		10.43
.050	.300	.784		10.27
.050	.500	.798		10.16
.050	.700	.808		10.07
.100	.100	.763		10.29
.100	.200	.784		10.37
.100	.300	.799		10.29
.100	.500	.812		10.24
.100	1.00	.830		
.200	0.100	.777		10.19
.200	.200	.800		10.27
.200	.300	.812		10.23
.200	.500	.827		10.17
.200	.700	.836		10.15
.400	.100	.792		10.20
.400	.200	.813		10.17
.400	.300	.826		10.25
.400	0.500	.841		10.20
.400	1.00	.859		10.22
.800	0.010	.733		10.209
.900	0.100	.815		10.40
	1.00	No red.		
	2.00	0.85		
	3.00	.86		
.10	1.00	.84		
.10	2.00	.85		
.10	3.00	.86		

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Below 0.05 M gluconate, the coefficient of the log (GH_4^-) term in equation 5 must be changed from 1.5 to 0.5. The values of $pK_{2:1}$ are also listed in Table II with an average value of 8.70 ± 0.05.

Solutions Containing More than 1 M Sodium Hydroxide.—In 3 M sodium hydroxide, the half-wave potential of cadmium is independent of gluconate concentration over a wide range: 0.01 to 1.0 M gluconate. A small wave is apparent in 1 to 3 M sodium hydroxide even in the absence of gluconate, although precipitates are present. Increasing the gluconate concentration decreases the amount of precipitate and increases the height of the wave, but does not change the half-wave potential, which becomes constant at a value of −0.86 v. in 3 M sodium hydroxide. These results indicate that cadmium forms a slightly soluble hydroxy complex (cadmiate) in high concentrations of hydroxide ion. No definite species can be identified in this region.

Acknowledgment.—We wish to thank the Research Corporation for a grant-in-aid in partial support of this work.

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ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, THE UNIVERSITY OF MICHIGAN]

Metal Chelates of Pyridoxylidene Amino Acids

BY HALVOR N. CHRISTENSEN[1]

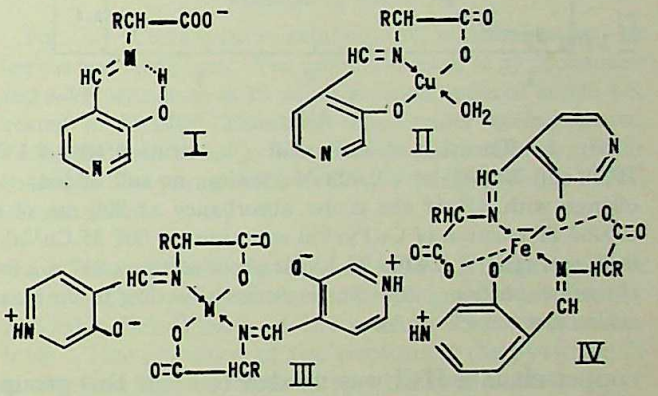
RECEIVED MARCH 15, 1957

The writer has prepared numerous metal chelates of the pyridoxylidene amino acids in crystalline form, usually with the composition M (pyridoxal·amino acid)$_2$, although in the case of copper the composition was M·pyridoxal·amino acid. For the more strongly catalytic Fe(III) and Cu chelates the titration attributed to the pyridine N was found to be shifted downward, relative to pyridoxal, by 3 *p*H units or more, presumably because of linkage of the metal to the phenolic oxygen. In the Mn(II) and Ni(II) chelates this titration was near its usual location, arguing against extensive linkage in this position. These conclusions are supported by infrared spectra showing a neutral structure for the Cu chelate and a zwitterionic structure for the Mn(II) and Ni(II) chelates. Chelation to the phenolic oxygen is probably not necessary for catalytic activity.

Amino acids undergo several metabolically important structural changes in the presence of pyridoxal and transition-group metals, under conditions permitting formation of chelated pyridoxylidene derivatives of the amino acid,[2,3] many of which now have been isolated.[4-6] Although the destabilizing action of carbonyl compounds on amino acids is well known, the role of the metal here is not well defined. Four possible actions have been suggested by Longenecker and Snell[7]: (a) preliminary proton-displacement to facilitate Schiff-base formation, (b) stabilization or destabilization of the Schiff base, (c) maintenance of planarity in the conjugated system of double bonds, and (d) reinforcement of electron-displacement from the α-carbon by the metal ion.

Whether each of these effects actually contributes to a given degradation will depend upon the structure of the catalytic intermediate and the extent of its formation. In particular, atoms of the amino acid will not be held in the plane of the aromatic ring unless the chelation joins them to this ring in a planar structure. Snell and his associates have generally written a 1:1:1 chelate (*e.g.*, formula II), which for copper probably yields 3 coplanar rings. On the other hand several metals with strong catalytic activity may or may not tend to maintain coplanarity; these may not even be chelated to the aromatic ring.

Eichhorn and Dawes[3] postulated the 3-point attachment to the Schiff-base for the Ni(II) as well as the Cu chelate on the basis of spectral changes upon adding pyridoxal to nickel plus alanine solutions. Evidence will be presented here that Mn(II), Zn(II), Fe(II) and Ni(II), in chelates crystallizing from ternary mixtures, instead are largely unbonded to the phenolic oxygen, in contrast to Fe(III) and Cu(II).



Chelate structures: I, Schiff base anion, proposed by Metzler; II to IV, proposed here for metal chelates. The 6-methyl and 5-hydroxy methyl groups have been omitted.

The procedures used have permitted the crystallization of chelates of a large variety of amino acids; of these the chelates of L-valine were selected for this comparison; these were uniformly crystalline. The investigation actually began as an attempt to explain the paradox that an electrically neutral chelate crystallized out when either Mn(II) or Fe(II) combined with two pyridoxylidenevaline anions (formula I) or when Cu(II) combined with only one pyridoxylidenevaline. If one Mn(II) suffices to neutralize the charge of two pyridoxylidenevaline anions, then one Fe(III) should yield a positively charged product, and one Cu(II) combining with a single Schiff-base anion should also form a cation.

These difficulties appear to be avoided if we may freely place protons on the pyridine nitrogens or not as is required for electroneutrality. The isoelectric form of the chelate may be much less soluble than the anionic or cationic forms, so that it crystallizes out, enriching the solution with or depriving it of a hydrogen ion as the case may be. If so the Fe(III) chelate should require for optimal precipitation a more alkaline solution than the Mn(II), Fe(II) or Ni(II) chelate. This is by no means the case. Indeed one can separate the Fe(II) from the Fe(III) chelate by raising the *p*H to 6.0, whereby the Fe(III) chelate, crystallizing at *p*H 4.5 to 5, is redissolved. In order to explain this paradox the *pK* of at least one dissociating group must have very different values in some of these chelates than in others.

(1) Supported in part by a Grant (C-2645) from National Cancer Institute, U. S. Public Health Service. The scintillation-counting equipment was obtained through the Faculty Research-Research Equipment Fund of the Horace H. Rackham School of Graduate Studies, University of Michigan.

(2) D. E. Metzler, M. Ikawa and E. E. Snell, THIS JOURNAL, **76**, 648 (1954).

(3) G. L. Eichhorn and J. W. Dawes, *ibid.*, **76**, 5663 (1954).

(4) J. Baddiley, *Nature*, **170**, 711 (1952).

(5) H. N. Christensen and S. Collins, *J. Biol. Chem.*, **220**, 279 (1956).

(6) H. N. Christensen, *Biochem. Preparations*, **6**, in press (1957).

(7) J. B. Longenecker and E. E. Snell, THIS JOURNAL, **79**, 142 (1957).

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Evidence for the Structure of the Chelates from Titrations.—The titration of each of the chelates showed a sigmoid area with a slope approximately appropriate to the dissociation of a free group, taken to be the pyridine N (Figs. 1, 2). In the copper chelate HCl was needed to show this group, titrating with a mid-point at *p*H 5.6 (Fig. 1). One equivalent of OH^- per mole of the Fe(III) chelate showed for it a similarly situated dissociation, centered at *p*H 5.4 and having the theoretical slope. The other pyridine N known to be present in this chelate presumably associated a proton below *p*H 4.5, but the titration could not readily be followed because of the intense destabilization of the chelate in this region.

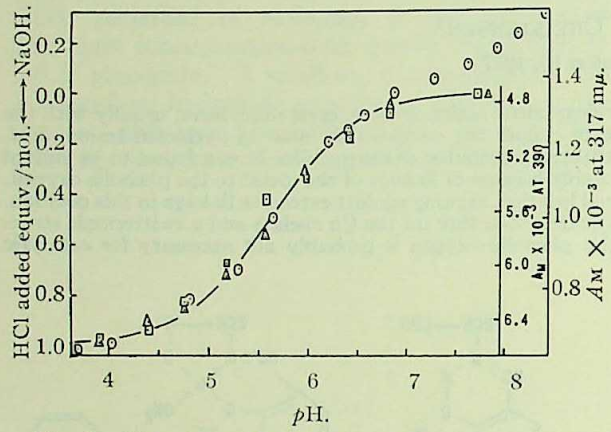

Fig. 1.—Titration of CuPyrVal: ⊙, titration with 0.1 *N* HCl (and NaOH) of a 0.023 *M* solution, no salt added; △, change with *p*H of the molar absorbancy at 390 mμ of a 0.0005 *M* solution of CuPyrVal containing 0.007 *M* $CuVal_2$; ionic strength = 0.016; ⊡, molar absorbancy at 317 mμ for the same solution. The line is drawn according to the mass action law for $pK = 5.6$.

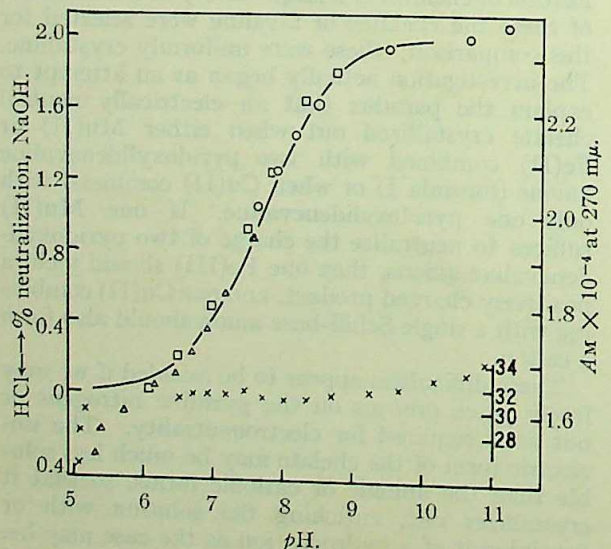

Fig. 2.—Titration of $Ni(PyrVal)_2$: circles, % neutralization *versus* *p*H for 0.05 *M* $Ni(PyrVal)_2$ prepared by dissolving the chelate in 0.45 equivalent NaOH; scale at left. Triangles, titration curve continued into region of lower solubility using 0.005 *M* $Ni(PyrVal)_2$. Squares, the molar absorbancy index for $Ni(PyrVal)_2$ 0.0001 *M* in 0.01 *M* $Ni(Val)_2$, scale at right. Crosses, the molar absorbancy index at 940 mμ *versus* *p*H, 0.005 *M* $Ni(PyrVal)_2$, scale at lower right. Ionic strengths 0.05. The solid line is drawn according to the mass action law for $pK_1 = 7.3$, $pK_2 = 8.1$.

These two titrations were bounded above and in the case of Cu also below by regions of much weaker buffering so that their positions were not equivocal. The Fe(III) chelate consumed little OH^- from *p*H 7 to 9, and the spectral transmittance between 270 and 600 mμ was scarcely altered. Above *p*H 10 it became highly unstable to OH^-. CuPyrVal[8] consumed OH^- all the way from *p*H 7 to 11. This behavior could be differentiated from the group titration under study not only by its low slope, but also by two other observations: (a) changes in the absorbancies at 317 and 390 mμ which occurred symmetrically about the pK' of about 5.6 were terminated at about *p*H 7; (b) the absorbancy at the peak at 670 mμ was nearly constant from *p*H 4 to 7, but was decreased steadily by the further addition of alkali. This titration was attributed to displacement of other ligands from the Cu by OH^-.

The writer has not determined why the absorbancy changes at 317 and 390 mμ occurred when a proton was associated at *p*H 5.6. Possibly a part of the uncharged chelate takes the form of a chelated aminoacetal[9] absorbing at 317 mμ and is converted to the aldimine chelate absorbing at 390 mμ upon proton-addition. Titration of the 0.5 m*M* CuPyrVal in the presence of 20 m*M* $Cu(Val)_2$ (Fig. 1) led to essentially the same results, except that the very rapid destabilization which otherwise occurred just below *p*H 4.0 was prevented. Accordingly the titration behavior was attributed to CuPyrVal and not to its dissociation products, pyridoxal or PyrVal. Clearly CuPyrVal hydrolyzes only slightly even in dilute solution.

The pK's of the dissociating group of the Ni(II) and Mn(II) chelates were not as readily fixed. The Ni chelate gave a dissociation curve centered at about *p*H 7.5; the upper limits of the titrations were quite distinct (Fig. 2), especially when shown in fairly concentrated solutions. The lower limit was also distinguishable, although rapid breakdown took place below *p*H 5.3. H^+ consumption by the group-titration and by the cleavage of the chelate were differentiated as follows. The absorption at 940 mμ, characteristic of the Ni-chelated aldimine structure,[3] remained constant from *p*H 6 to 10; it increased moderately above *p*H 10 (exaggerated in Fig. 3 by the use of a dilute solution) and decreased rapidly below *p*H 6.3, in association with the extra OH^- and H^+ requirements. The titration of the free chemical group in the Ni(II) chelate also was described by an increase in absorbancy at 270 mμ (Fig. 3). The shape of the dissociation curve for $Ni(PyrVal)_2$ suggested that the two dissociating groups had pK's of approximately 7.3 and 8.1 (Fig. 3).

The much less stable Mn(II) and Zn(II) chelates split enough in saturated watery solution to raise the *p*H to 7.8 and 7.4, respectively, and after adjustment to a *p*H below 7.2 and 7.0, respectively,

(8) Abbreviations: Pyr = pyridoxylidene; Val = valine; Orn = ornithine; Pro = proline; Aib = α-aminoisobutyrate.

(9) D. E. Metzler, this Journal, 79, 485 (1957).

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H^+ consumption continued for many minutes. Accordingly the limit and position of the lower part of the pyridine N dissociation was not obtained accurately; $MnVal_2$ and $ZnVal_2$ were themselves not sufficiently stable to serve as stabilizers above *p*H 8. By dissolving in slightly more than an equivalent of NaOH per mole, the concentration of the chelate could be brought to 0.05 *M*, thereby improving the stability; the part of the titration obtained by adding more alkali to this solution supported a mid-point of about 8.2 for the entire titration attributed to the two pyridine N's in each chelate. In addition the titration above *p*H 7.3 was marked by much less change in stability (as indicated by change in absorbancy at 390–412 mμ) than below *p*H 7.3. These results, together with the infrared spectral demonstration that these two chelates are zwitterionic, indicate that they resemble the Ni(II) chelate.

Interpretation.—The foregoing titration behaviors are the ones required by the isoelectric formulations shown above for the crystalline chelates: the Cu chelate without a proton on the pyridine N; the Fe(III) chelate with a proton on only one pyridine N, and the Ni(II), Mn(II) and Zn(II) chelates with protons on both pyridine N's. Accordingly, the Ni(II), Mn(II) and Zn(II) chelates lose H^+ from their pyridine N's at much higher *p*H values than the Cu and Fe(III) chelates. What is the significance of this difference?

In CuPyrVal and Fe(III)$(PyrVal)_2$ the shift in the position of the pK_a' of the pyridine N from its normal position at about *p*H 8.6 in pyridoxal to about *p*H 5 is a predictable consequence of linkage to the phenolic oxygen. For comparison, O-methylation of pyridoxal lowers this *pK* to 4.75.[10] Similarly, Metzler[9] has concluded recently that this *pK* is lowered to 5.9 in pyridoxylidenevaline by bonding of a proton to the phenolic O, the proton being stabilized in this position by H-bonding to the imine N.[9] Displacement of this proton by a metal ion should reproduce this effect, unless the metal remains unbonded to the phenolic O.

Three explanations may be considered for the absence of the expected downward shift in the *pK* of the pyridine N in the Ni(II), Mn(II) and Zn(II) chelates:

1. Bonding between the metal and the phenolic oxygen may be totally absent.
2. The bonding may be so unstable that the *pK* shift is small.
3. The bonding may have less influence on the acidity of the pyridinium ion whenever it makes the metal electronegative.

According to the last alternative the Fe(III) chelate also ought to have a high *pK* for at least one pyridinium group. The second explanation, which is considered the most likely, means that the linkage of metal to the phenolic oxygen is broken most of the time in solution.[11]

According to this interpretation the most abundant form of the chelates of Mn(II), Ni(II) and zinc at isoelectric *p*H values is zwitterionic, and simply a double Schiff-base of the amino acid–metal chelate. The presence of the proton on the pyridine N is attested by the infrared spectra (see below).

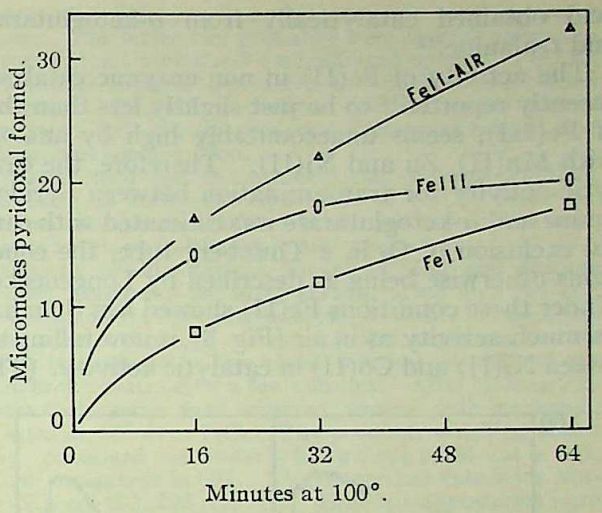

Fig. 3.—Comparative catalysis of transamination by ferrous and ferric ions. Ten millimoles each of pyridoxamine and α-ketoglutarate in 10 ml. of solution buffered at *p*H 4.8, heated in N_2-filled Thunberg tubes under boiling water. Fe, 0.000125 *M* added as ferrous ammonium sulfate or ferric chloride. The triangles show values we obtained with Fe(II) in open tubes.

The Fe(II) chelate was not readily prepared free of Fe(III); its titration was difficult because of intense instability to O_2 and OH^-; presumably it resembled the Mn(II), and Ni(II) chelates in structure. The much greater stability of the Ni than the Mn and Zn chelates discourages one from attributing the structural difference merely to low chelate stability.

The somewhat lower catalytic activity in transaminations and similar reactions of the Mn(II). Zn(II) and Ni(II) chelates suggests a rather limited role for linkage to the phenolic O in this function. These results do not permit us to conclude whether bonding to the phenolic O facilitates catalysis by producing planarity or by stabilizing the aldimine link or not at all. Incidentally, a low pK_a for the pyridine N, other factors being equal, might appear to handicap the catalytic activity of the chelate at higher *p*H values, if the proton carried on this group must receive an electron in the electromeric shift believed to underly the catalysis.[2]

The illustrated bonding of both carboxyl groups to Fe(III) has not been proved, but is proposed for the following reason: If an amino acid–metal chelate reacts with pyridoxal, bonding of the metal to the phenolate ion requires at above *p*H 6, as shown here, the displacement of a proton from the pyridinium group. Accordingly, the link to the carboxylate group probably is more stable than that to the phenolic O. The chelate does not contain a pyridine N titrating in the *p*H range 7–9; accordingly, Fe(III) is taken to be bonded to both phenolic oxygens; hence both carboxyl groups also may well be bonded. Incidentally, the bonding of a second Schiff-base to the metal shown here has been proposed to explain the excess of L-glutamic

(10) D. E. Metzler and E. E. Snell, THIS JOURNAL, 77, 2431 (1955).

(11) The finding that the zinc chelate has the composition $Zn(PyrVal)_2$ provides additional support for assigning structure III to this group of chelates. With a coördination number of 4 it is unlikely that the zinc ion is joined to each of the two Schiff base residues at three points.

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acid obtained catalytically from α-ketoglutarate and L-alanine.[12]

The activity of Fe(II) in non-enzymic catalysis, recently reported[13] to be just slightly less than that of Fe(III), seems unaccountably high by analogy with Mn(II), Zn and Ni(II). Therefore, the catalytic activity for transamination between pyridoxamine and α-ketoglutarate was estimated with careful exclusion of O_2 in a Thunberg tube, the conditions otherwise being as described by Longenecker. Under these conditions Fe(II) showed less than half as much activity as in air (Fig. 3), it now falling between Ni(II) and Co(II) in catalytic activity. (This experiment was kindly made by Mr. Walter B. Dempsey of this Laboratory.)

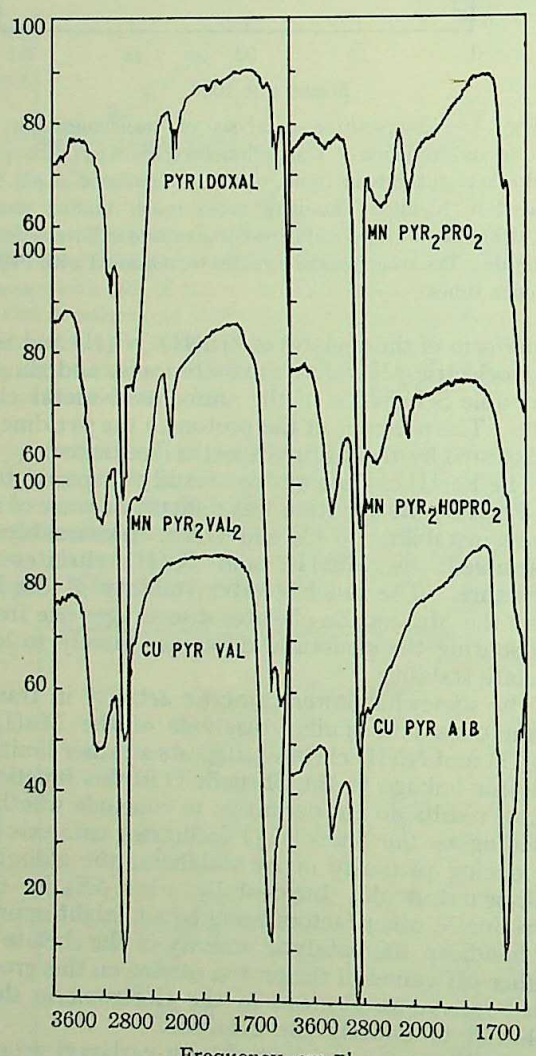

Fig. 4.—Portions of infrared spectra of chelates compared with that of pyridoxal. One frequency scale interval is 400 cm.$^{-1}$ from 4000 to 2000 cm.$^{-1}$ and 100 cm.$^{-1}$ below 2000 cm.$^{-1}$. Attention is directed to: (a) increased aliphatic hydroxyl absorption (*ca.* 3200 cm.$^{-1}$) and appearance of the aldimine absorption (*ca.* 1600 cm.$^{-1}$) upon formation of the amino acid but not the imino acid derivatives; and (b) the ionic properties (1900 to 2600 cm.$^{-1}$) of Mn but not of Cu chelates. Ni(II) and Zn(II) chelates gave curves resembling those of Mn(II) chelates.

(12) J. B. Longenecker and E. E. Snell, *Proc. Nat. Acad. Sci.*, **42**, 221 (1956).

(13) J. B. Longenecker and E. E. Snell, THIS JOURNAL, **79**, 142 (1957).

Infrared Absorption.—The infrared spectrum of CuPyrVal on one hand is very different from the spectra of the corresponding Mn(II), Zn(II), Ni(II) chelates, on the other. The latter two resemble pyridoxal in having prominent peaks at about 2100 and 2700 cm.$^{-1}$ (Fig. 4), thus supporting their zwitterionic structure. The isoelectric copper chelate in contrast, shows essentially no absorption in this region, revealing it to be uncharged. This result confirms the presence of protons on the pyridine N atoms in crystals of the Mn and Ni chelates precipitating at neutral *p*H, and the absence of such a proton on CuPyrVal precipitated at similar *p*H values. The spectrum of the Fe(III) chelate in the indicated region has an appearance intermediate between the non-ionic Cu and the strongly ionic Mn chelate. Figure 4 also shows portions of the infrared spectra of chelated pyroxylidene derivatives of proline and α-aminoisobutyric acid, showing also the non-ionic nature of the copper chelates and the decreased absorption attributable to the hydroxymethyl group and to an aldimine group, undoubtedly arising from their being largely in aminoacetal forms.

Isotopic Study of Metal Exchange.—The usual procedure is to mix the chelate under investigation with a labeled complex of the same metal (the latter complex being known to exchange rapidly) and then to reseparate the two complexes. Instead, in the cases of Fe(III) and Mn(II) use was made of the soluble monopyridoxylideneornithine chelates (which appear to have below *p*H 7.5 the usual structure involving only one amino group). A large portion of the less-soluble pyridoxylidenevaline chelate readily was reisolated for radioactive counting. (More could have been recovered but with an undesirable delay.) The method yields information on the exchange rate between the two chelates without telling which exchange is rate-limiting. For the copper chelate, exchange between $Cu^{64}Val_2$ and CuPyrVal was studied, the latter being reisolated upon concentration of the solution.

The Fe of Fe(III)$(PyrVal)_2$ recrystallized from a solution also containing half the molar quantity of $Fe^{59}(PyrOrn)_2$ by lowering the *p*H from 7.3 to 4.7, and collected in a minimal operating time of 5 min., had only 11% of the specific activity shown by the 46% of the Fe remaining in solution. When the solution was first incubated 30 min. at 0°, the exchange was 43% complete; in 15 min. at 25°, 58% complete.

$Mn(PyrVal)_2$ in contrast exchanged completely with the corresponding labeled ornithine chelate in the minimal 20 min. (mostly at 0°) required for mixing, concentrating to reprecipitate it, and collecting the precipitate. The proportions taken and reisolated were similar to those used with Fe. The copper of CuPyrVal likewise exchanged very rapidly with Cu^{64} of $CuVal_2$ (representing 1/5 of the total Cu), being completely exchanged in the 15 minutes at 0–15° required to reisolate the CuPyrVal.

These results appeared to limit to the Fe(III)

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the possibility of testing for biological acceleration of exchange. Another method, however, gave a lower rate of exchange for CuPyrVal. When a 0.0005 *M* solution was brought to 0.1 *M* in valine at *p*H 7, the decrease in absorbancy at 380 mμ due to the reaction CuPyrVal + Val → Cu⁺Val + Pyr⁻Val, continued for more than an hour at 25°, with a half-time of over 5 min.

Acknowledgments.—The writer is grateful to Miss Jane LeFever for assistance with some of the experiments, to Miss Lois Walker for copper and amino acid analyses, and to Mr. Walter B. Dempsey for performing the experiments of Fig. 3. He has benefited from discussing the infrared spectra with Dr. J. L. Johnson of the research laboratories of the Upjohn Company.

Experimental

Apparatus and Materials.—A Beckman model G *p*H meter and model DU spectrophotometer were used. To permit reading solutions as concentrated as possible (to diminish dissociation) 0.5 cm. photometer cells usually were used. Highly active Fe^{59} and Cu^{64} were obtained from Carbon and Carbide Co., Oak Ridge, and Mn^{54} from Nuclear Science and Engineering Corporation, Pittsburgh; all were used as the chlorides. Disintegrations were counted in a Nuclear-Chicago well-type scintillation counter, at 20 to 200 times background rates. Infrared spectra were obtained in a Nujol mull using a Perkin–Elmer instrument.

Pyridoxal hydrochloride (Merck and Co.) was converted to the free base by adjusting a strong aqueous solution to *p*H 6.5 with potassium hydroxide; the crystals were washed, and dried over P_2O_5 at room temperature. The inorganic salts were of analytical reagent grade. The amino acids, when optically active, were the L-forms, and were obtained from Nutritional Biochemicals, Inc., or in a few cases from the H. M. Chemical Company. Reagent grade methanol and ethanol were used without purification.

General Procedure for Preparation of Chelates.—The amino acid was dissolved in an equivalent quantity of methanolic or aqueous sodium hydroxide, and a mole of pyridoxal dissolved in this solution to form the sodium salt of the Schiff base, which remained in solution. The metal salt was then added in aqueous or methanol solution, using the metal acetate in the latter case. If crystallization did not follow from methanolic solutions, ethanol (for small-molecular amino acids) or water (for large-molecular amino acids) was added, often by way of the vapor phase. Acetate added either as the metal salt, or separately as an acetate buffer, in several cases served to accept hydrogen ion from the chelate to facilitate crystallization in the isoelectric form.

Composition of the chelates could be determined by analyzing colorimetrically a solution in 0.1 *N* sulfuric acid for pyridoxal,[14] for amino acids[15] and for the metal, Cu being determined as the diphenyldithiocarbamate derivative,[16] manganese after oxidation to permanganate,[17] iron as the complex ferric thiocyanate ion,[18] and nickel as the dimethylglyoxime chelate.[19]

Procedure for Cu Chelates, Illustrated by CuPyrVal.—One hundred and fifty micromoles of the Schiff-base in 0.5 ml. of methanol was treated with 0.36 *M* (approximately saturated) aqueous cupric acetate, followed by 2 ml. of ethanol. In a few minutes the solution filled with long green needles. After cooling at 5° overnight, the crystals were removed and washed with ethanol, and dried at 56° over P_2O_5. The product, weighing 35 to 40 mg., contained one valine in 343 g., one pyridoxal in 338 g. and one copper in 329 g.; the theoretical 1:1:1 composition $C_{13}H_{16}O_4N_2Cu$ corresponds to a molecular weight of 328. The chelate dissolved in water to about 0.025 *M* at 25°. Similarly, 1:1:1 compositions were shown by the isoleucine, methionine, β-alanine, phenylalanine, α-aminoisobutyric and sarcosine chelates. The latter two probably were largely aminoacetals rather than aldimines[9] (see infrared spectra, Fig. 5); the α-aminoisobutyric derivative was dark brown rather than green. Crystalline chelates obtained with several other amino acids showed moderate excesses of copper over the theoretical composition.

Chelates could also be obtained from aqueous solution, often using an additional equivalent of NaOH to render them less soluble; the chelates of alanine and proline were obtained in this way although in amorphous form.

Procedure for Manganous, Nickelous, Zinc and Ferrous Chelates, Illustrated for Mn(PyrVal)₂.—One hundred and fifty micromoles of the Schiff base in 0.5 ml. of methanol was treated with 0.15 ml. of a fresh 0.5 *M* manganous acetate solution in methanol. The brown solution crystallized out square brown plates after a few minutes. After chilling 2 or 3 hours the crystals were removed, washed with methanol, and dried at 56° over P_2O_5. The product, weighing about 25 mg., contained one valine in 310 g., one pyridoxal in 305, and one manganese in 603. The theoretical values for Mn(PyrVal)₂ are 292, 292 and 583. Similar compositions were obtained for chelates from alanine, serine, threonine, isoleucine, proline and hydroxyproline. The latter two probably were aminoacetals, the Schiff bases and the chelates being light yellow in color. For Mn, glycine is the only amino acid so far obtained in a 1:1:1 chelate, and that from a non-aqueous solution.[5]

Manganous pyridoxylidenevaline and zinc pyridoxylidenevaline also were obtained readily by dissolving 200 micromoles each of L-valine and pyridoxal in 0.2 ml. of *N* NaOH, and then adding 0.1 ml. of *M* aqueous manganous acetate or zinc chloride. The square plates were washed with water, in which the solubility was, for Mn(II), about 5.6 m*M* at 0°, 8.5 m*M* at 25°, and 12 m*M* at 37°; for Zn, about 4 m*M* at 25°.

Ni(PyrVal)₂ was obtained readily by the latter procedure (clear yellow rectangular blocks), as was Fe(II)(PyrVal)₂ (clear blue square and octagonal plates) at 0° although oxygen had to be excluded strictly in the latter case to prevent autoöxidation to the red Fe(III) chelate.

Fe(III)(PyrVal)₂.—0.2 ml. of a molar aqueous solution of the sodium salt of the Schiff base, formed as usual, was treated with 0.1 ml. of a molar aqueous solution of ferric chloride. A deep red color resulted, and crystallization began at once. 0.1 ml. of an acetate buffer (1.5 molar each in acetic acid and sodium acetate) was then added. After standing overnight in the refrigerator the crystals were separated and washed with cold water to yield 45 mg. of chelate. This was recrystallized by dissolving carefully in 0.3 *N* NaOH, keeping the *p*H below 8 and centrifuging to clarify the deep red solution. Upon adding 0.1 ml. of the acetate buffer the chelate recrystallized in beautiful red complexly truncated right-triangular prisms (orthorhombic hemimorphic). The crystals upon redissolving in water produced a *p*H below 4.5 which rose rapidly because of the low stability at this *p*H, until the dissociation products reached levels which stabilized the chelate.

The crystalline product contained one pyridoxal in 290, one valine in 287, one Fe in 579 mg. (theoretical m.w. = 583).

Titrations were made at 25–26° at the ionic strengths indicated in the figures, disregarding the ionic strength arising from any dipolar ion.

Isotopic Exchange.—0.5 ml. of an aqueous solution, *p*H 7.3, containing 80 micromoles of previously crystallized Fe(III)(PyrVal)₂ chilled to 0° was mixed with 0.25 ml. of a similarly cold solution of 40 micromoles of Fe^{59}(III)(PyrOrn)₂ (prepared in solution by mixing the components) also at *p*H 7.3. Instantly 0.15 ml. of 3 *M* acetate buffer *p*H 4.7 was mixed with the solution. Within 40 sec. of the original mixing centrifuging was begun and continued 4 min. at high speed. The crystalline precipitate was washed three times with water at 0°. In other experiments an interval at 0 or 25° was allowed before addition of the acetate buffer.

Four ml. of a saturated Mn(PyrVal)₂ solution (50 micromoles) was concentrated to 1.5 ml., and chilled in ice; then 25 micromoles of Mn^{54}(PyrOrn)₂ was added in 0.3 ml. of water (both solutions at *p*H 7.0). Concentration *in vacuo* 4 min. (10–15°) started crystallization; this was continued 10 min. at 0°. After 5 min. of centrifuging the liquor was removed and the precipitate washed 3 times. Forty per

(14) D. E. Metzler and E. E. Snell, THIS JOURNAL, **74**, 979 (1952).
(15) S. Moore and W. H. Stein, *J. Biol. Chem.*, **176**, 367 (1948).
(16) A. J. Woiwod, *Biochem. J.*, **45**, 412 (1949).
(17) J. R. Boyd, *Anal. Chem.*, **24**, 205 (1952).
(18) S. Y. Wong, *J. Biol. Chem.*, **77**, 409 (1928).
(19) A. M. Mitchell and M. G. Mellon, *Anal. Chem.*, **17**, 380 (1945).

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cent. each of the Mn and of the radioactivity was precipitated; the precipitate contained the appropriate amounts of pyridoxal and amino acid.

To 4 ml. of ice-cold 0.020 *M* CuPyrVal, previously crystallized, was added 0.33 ml. of 0.060 *M* $Cu^{64}Val_2$, both solutions at *p*H 7.2 and the solution concentrated quickly in the cold to about 0.5 ml. After holding 5 min. at 0°, the suspension was centrifuged 4 min. at high speed, and the crystals washed twice with water. In a representative test, 32.2% of the copper and 33.1% of the radioactivity had been precipitated.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Hydrogen Ion Equilibria of a Single Group Attached to Serum Albumin: Some Implications as to the Surface Characteristics of Protein Molecules

BY IRVING M. KLOTZ AND JANET AYERS

RECEIVED MARCH 18, 1957

The ionization equilibria of the dimethylamino group of $(CH_3)_2N$—⟨⟩—N=N—⟨⟩—Hg— attached to bovine serum albumin have been studied in various aqueous solvents. In water the pK_a of this dye when attached to cysteine is 3.3; when linked to protein, 1.8. In 8 *M* urea, the pK_a is approximately 3.3 for the dye on the protein or amino acid, near 5 in 0.03 *M* dodecyl sulfate in both cases. These results and the more detailed behavior of the ionization equilibria are not in concordance with electrostatic expectations. It is suggested that the pK_a's reflect the structure of the water envelope of the protein. A variety of observations can be described in terms of changes in the order in this aqueous framework.

Introduction

Proton equilibria of acid–base groups on proteins have been the subject of numerous investigations for over 50 years. The early literature has been summarized by Cohn and Edsall[1] and more recent work has been reviewed by Steinhardt.[2] In general, the maximum uptake or release of protons corresponds well with the number of acidic and basic groups presumed to be on the protein from analyses of its content of specific amino acids. The course of the *p*H-titration curve, however, usually differs markedly from what one might calculate for the corresponding number of comparable proton-dissociating groups in an ordinary aqueous environment.

The modified acidity of groups on a protein molecule has been ascribed in part to electrostatic interactions between successively dissociating sites.[3–6] These interactions account reasonably well for the titration curves of some proteins[4,7] but more often there are large deviations, in both directions, from electrostatic predictions. Such discrepancies have been attributed to changes in molecular weight or shape,[8–10] to binding of small ions[6] and to the influence of hydrogen bonding between polar groups on the *pK*'s of proton-dissociating groups.[7,11]

The interpretation of acid–base ionizations of protein molecules is complicated in part by the fact that the measurements reflect the composite behavior of a large number of groups. Even in limited regions of *p*H, for example, 3–5, where only one type of equilibrium is involved, —COOH ⇌ —COO^-, the number of participating carboxyl groups is very large. There are usually fewer imidazole or tyrosine groups in a protein, but even these are commonly present in appreciable number and their proton equilibria overlap those of amino groups, so that a sharp separation cannot be made by electrometric methods.

The proton-donor group usually present in smallest number in proteins is the sulfhydryl. A direct study of its dissociation by electrometric methods is not feasible, however, since the equilibria of amino and tyrosine groups would obscure the contribution of –SH. In principle, it might be possible to adapt the optical method used by Benesch and Benesch[12] for the determination of pK_{SH} of cysteine, a method which takes advantage of the appearance of an absorption peak at 240 mμ when –SH is converted to $-S^-$. In most proteins, however, absorption of light at this wave length is very strong even in dilute solution and even when the mercaptan group is not ionized. It would be difficult, therefore, to measure the small differences in absorption accompanying ionization of the –SH, against the strong background absorption of the relatively concentrated protein solution which would be needed to supply an appreciable concentration of mercaptan groups.

An alternative approach which could still take advantage of the small number of –SH groups on a protein would be to introduce a molecule which reacts specifically with the mercaptan side-chain, and which contains a substituent whose proton uptake, or release, is accompanied by a marked change in visible absorption spectrum. A class of such molecules are the azomercurials, (I), in which

X—⟨⟩—N=N—⟨⟩—Hg—Ac

I

(1) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Chap. 20, Reinhold Publ. Corp., New York, N. Y., 1943.
(2) J. Steinhardt, *Advances in Protein Chem.*, **10**, 151 (1955).
(3) K. Linderstrøm-Lang, *Compt. rend. trav. lab. Carlsberg*, **15**, No. 7 (1924).
(4) R. K. Cannan, A. C. Kibrick and A. H. Palmer, *Ann. N. Y. Acad. Sci.*, **41**, 243 (1941).
(5) G. Scatchard, *ibid.*, **51**, 660 (1949).
(6) C. Tanford, THIS JOURNAL, **72**, 441 (1950).
(7) C. Tanford and J. D. Hauenstein, *ibid.*, **78**, 5287 (1956).
(8) G. Scatchard, *Am. Scientist*, **40**, 61 (1952).
(9) C. Tanford and J. Epstein, THIS JOURNAL, **76**, 2163 (1954).
(10) C. Tanford, S. A. Swanson and W. S. Shore, *ibid.*, **77**, 6414 (1955).
(11) M. Laskowski, Jr., and H. A. Scheraga, *ibid.*, **76**, 6305 (1954).
(12) (a) R. Benesch and R. E. Benesch, *ibid.*, **77**, 5877 (1955).

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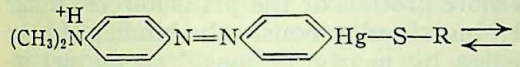
X is the substituent with acidic or basic properties (*e.g.*, $(CH_3)_2N-$ or $-OH$). These substances combine specifically with the mercaptan groups of proteins[13] and undergo marked alterations in absorption over a characteristic *p*H range, depending on the nature of the substituent. From changes in the spectra one can follow the ionic state of these substituents in the protein environment without obscurant effects from other groups of the protein which are simultaneously involved in acid–base equilibria.

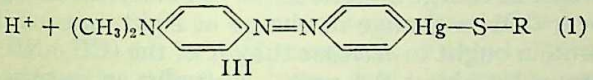
The complex between one such mercurial, 4-(*p*-dimethylaminobenzeneazo)-phenylmercuric acetate [(I) with X = $(CH_3)_2N-$], and a protein with one –SH group, bovine serum albumin, has been previously prepared.[13] Its proton equilibria, described in this paper, provide a basis for examining the surface characteristics of this protein.

Experimental

The acidity constant for the ionization



II



III

(1)

was computed from changes in the visible absorption spectrum with *p*H. The acidic species II has an absorption peak near 520 mμ, the conjugate base at about 460 mμ. The fraction of the azomercurial in the acid form, α, was calculated by means of the equation

$$\alpha = \frac{\text{optical density soln. } \alpha - \text{optical density basic soln.}}{\text{optical density very acid soln.} - \text{optical density basic soln.}} \quad (2)$$

the optical densities all being measured at the same wave length, usually 520 mμ. A graph was then made of α *vs.* *p*H. For most comparisons the value of the *p*H at which α = 0.50 was taken as the *pK*, since for reaction 1

$$pK = p\text{H} - \log \frac{(\text{III})}{(\text{II})} = p\text{H}_{\alpha=0.5} \quad (3)$$

Where α = 0.5, (II) = (III). For some purposes, *pK*'s were calculated at several *p*H's by substitution of the appropriate values for II and III in eq. 3.

In eq. 1, R represents either the protein, bovine serum albumin, or a small-molecule mercaptan, such as cysteine. When the protein was studied, a 0.2% solution (3×10^{-5} *M*) was prepared in the desired solvent and to this was added a few crystals of azomercurial. The solution was stirred gently for several hours, until an appreciable amount of dye had dissolved, as judged by the intensity of the color. The protein-linked dye was in the range $(0.8–1.5) \times 10^{-5} M$. A similar procedure was used with cysteine, except that cysteine hydrochloride was at a concentration of 1×10^{-4} *M*; the cysteine–azomercurial complex, nevertheless, was maintained at about 1×10^{-5} *M*.

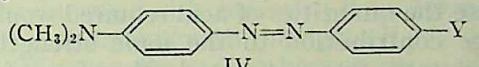
To the solution of bound azomercurial was added a small portion of hydrochloric acid (0.05–0.5 *M*) or sodium hydroxide (0.01 *M*) and the optical density was measured. A second portion of acid or base was then added and the absorption measured again. This was repeated[14] until some 20 points were available for graphing. Suitable corrections were made for dilution of the solution by added acid or base. In most cases a full absorption spectrum was taken over the region 350–600 mμ. From a graph of optical density *versus* *p*H, α was computed, and then it was plotted as a function of *p*H, so that the *pK*'s could be determined readily.

Crystallized bovine serum albumin was purchased from Armour and Company. Previous experiments[13] with the same samples have shown 0.66 mole SH per mole protein. Cysteine hydrochloride was obtained from Nutritional Biochemical Corp., and cysteine ethyl ester and glutathione from Schwarz Laboratories. Thioglycolic acid was given to us by the Toni Research Laboratories and thiomalic acid by Evans Chemetics. The sodium dodecyl sulfate was a specially purified sample supplied by the Fine Chemicals Division of E. I. du Pont de Nemours and Company. The urea and inorganic salts were reagent grade. Sorbitol monohydrate was purchased from Mann Research Laboratories.

The absorption of light was measured with the Beckman spectrophotometer, model DU, at about 25°; *p*H was obtained with a Beckman model G *p*H meter.

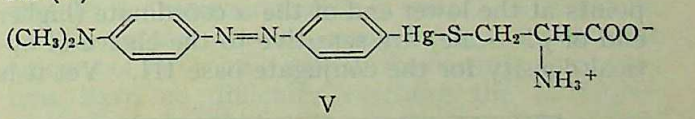
Results

Choice of Reference Compound.—The pK_a of dimethylaminoazobenzene (IV, Y = H)



IV

in aqueous solution is 3.5 and is not very sensitive to the nature of the opposite substituent Y.[15] For example, with Y = OH or Y = SO_3^-, the *pK* is 3.4. Nevertheless, if we wish to examine the effect of protein environment on the acidity of the $(CH_3)_2N-$ group, it seemed desirable to have information on the behavior of the azomercurial attached to a small-molecule mercaptan, so that any effect of the –Hg–S– linkages could be accounted for. Among the small molecules examined were thioglycolic acid, thiomalic acid, glutathione, cysteinyl ethyl ester and cysteine. The last proved most convenient experimentally, for it combined with the azomercurial rapidly and the complex obtained was stable over long periods of time. S-(*p*-Dimethylaminobenzeneazophenylmercuric) - cysteine (V)



V

was used, therefore, as a reference compound to ascertain the behavior of the $(CH_3)_2N-$ group in a non-protein environment.

Effect of Salts on pK_a.—Titrations with the cysteine–azomercurial (V) were carried out in water and in 0.1 *M* NaCl. The optical titration curves (Fig. 1) were normal, that is, similar to those

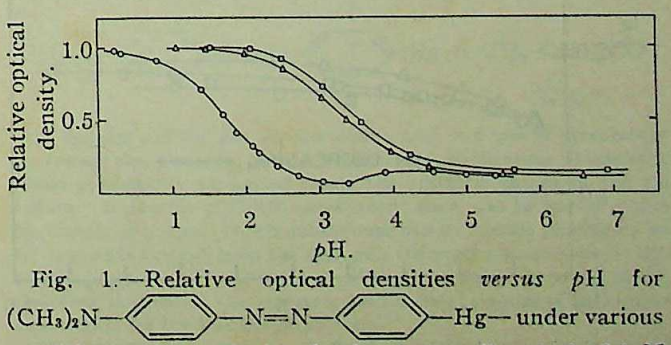


Fig. 1.—Relative optical densities *versus* *p*H for $(CH_3)_2N-C_6H_4-N=N-C_6H_4-Hg-$ under various conditions: O attached to bovine serum albumin in 0.1 *M* NaCl; △, attached to cysteine, in aqueous solution, with no salt; □, attached to cysteine, in 0.1 *M* NaCl.

(13) M. G. Horowitz and I. M. Klotz, *Arch. Biochem. Biophys.*, **63**, 77 (1956).

(14) In some cases a separate fresh portion of solution was used for each *p*H measurement. This procedure was followed whenever there was an indication of fading in acid solutions.

(15) I. M. Klotz, H. A. Fiess, J. Y. Chen Ho and M. Mellody, THIS JOURNAL, **76**, 5136 (1954).

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for related substituted azobenzenes in aqueous solution, and the pK in solutions of constant ionic strength (3.39) was not appreciably different from that in water (3.26). For an ionization of the type represented by eq. 1, one would not expect much sensitivity to ionic strength.

When the azomercurial is attached to the protein, the titration curve of the $(CH_3)_2N-$ group is markedly different than in the cysteine complex. The course of a typical titration is shown in Fig. 1. Proceeding from pH 6 down, we find first a plateau, followed by a region between pH's 5 to 3.5 with a small hill and then a very steep rise in absorption between pH 3 to about 1, with every indication of a plateau below pH 1. It was not feasible to determine the height of the acid plateau by adding further quantities of strong acid both because of the instability of the protein in such solutions and because the quantities of acid required would make a large contribution to the ionic strength. The acid plateau was estimated, therefore, from an extrapolation of the optical density readings *versus* $1/(H^+)$. Having obtained the absorption of the fully acid form and taking the lowest readings of the optical density, near pH 3, as the absorption of the basic form of the dye, we can read off the pK readily as the pH at which the absorption is midway between the two extremes. For the azomercurial attached to bovine serum albumin in water the pK is 1.9 (Table I), in 0.1 M NaCl, 1.72.

One can also compute pK's from *each* of the optical density readings not too close to the completely acid or basic forms. Such a calculation has been made for the experiments in 0.1 M and in 0.5 M NaCl, and the results have been assembled in Fig. 2. There is some indication of an increase in pK with decreasing pH. We are not certain, however, that this trend is significant, for the points at the lower end of the α coördinate (higher end of pH scale) are sensitive to the choice of optical density for the conjugate base III. Yet it is in this range (pH 3) that the protein undergoes some modification leading to changes in the spectrum of III, as is apparent from the small hill in Fig. 1.

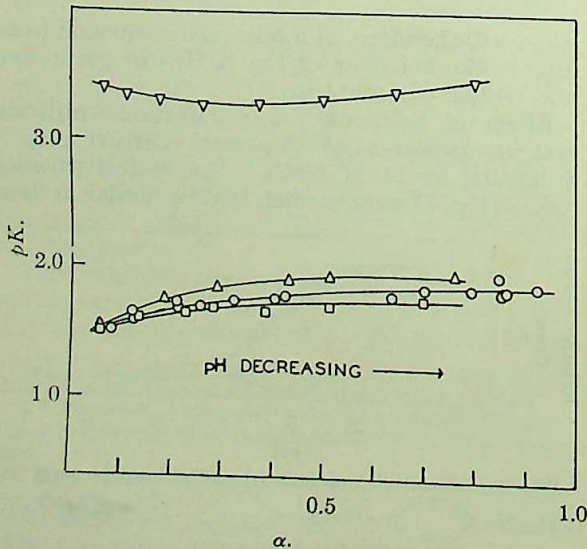

Fig. 2.—Variation of pK with extent of formation (α) of $(CH_3)_2\overset{+}{N}H$-form of the azomercurial attached to protein: △, in water; ⊡, in 0.1 M NaCl; ⊙, in 0.5 M NaCl; ▽, in 8 M urea.

In any event, whether the trend in Fig. 2 is real or negligible, it is apparent that the pK does *not decrease* with decrease in pH as one might expect from a consideration of electrostatic factors. As the pH is lowered, one would expect the protein to acquire an increasingly positive charge which ought to lower the pK of the $(CH_3)_2NH^+-$ group. In solutions of moderate ionic strength, bovine albumin becomes almost saturated with hydrogen ions when the pH drops to near[10,16] 2; thus that portion of the ionization of the azomercurial on the protein which takes place below pH 2 occurs at essentially constant protein charge and the pK's in this region should not change appreciably with pH. In the range from pH 2 to 3, however, the protein does change its charge appreciably. In the absence of salt, for example, bovine albumin acquires 25 more protons as the pH is lowered from[16] 2.8 to 2.1; but simultaneously the binding of chloride increases by nearly 17 ions,[16] so the net increase in charge is eight units. For an ionic strength near 0.01, a change in charge of eight units on the protein ought to *decrease* the pK of the $(CH_3)_2NH^+-$ group by about 0.4 unit. Actually an *increase* is observed (Fig. 2) over the pH range 3 to 2. It would seem, therefore, that the ionization of the $(CH_3)_2NH^+-$ group is unaffected by changes in charge on the protein, at least within the pH region open to examination.

TABLE I

ACIDITY CONSTANTS OF

$(CH_3)_2\overset{+}{N}H-C_6H_4-N=N-C_6H_4-Hg-S-R$ AT 25°

R	Solution	pK_a
$-CH_2-\underset{\displaystyle NH_3^+}{\underset{\vert}{CH}}-COO^-$	Water	3.26
	0.1 M NaCl	3.39
	8 M urea	3.42
	0.03% sodium dodecyl sulfate	(~3)
	1.0% sodium dodecyl sulfate	5.18
Bovine serum albumin[a]	Water	1.9
	0.1 M NaCl	1.72
	0.5 M NaCl	1.80
	1 M urea	2.38
	6 M urea	3.25
	8 M urea	3.32
	0.03% sodium dodecyl sulfate	<1.3
	1% sodium dodecyl sulfate	4.7
	40% sorbitol	1.4
	60% sorbitol	1.3

[a] It should be emphasized that in the presence of protein, the pK_a listed refers only to the midpoint of the titration curve, for titrations of the azomercurial linked to serum albumin cannot be fitted to the simple form of equation (3).

(16) G. Scatchard, J. S. Coleman and A. L. Shen, THIS JOURNAL, 79, 12 (1957).

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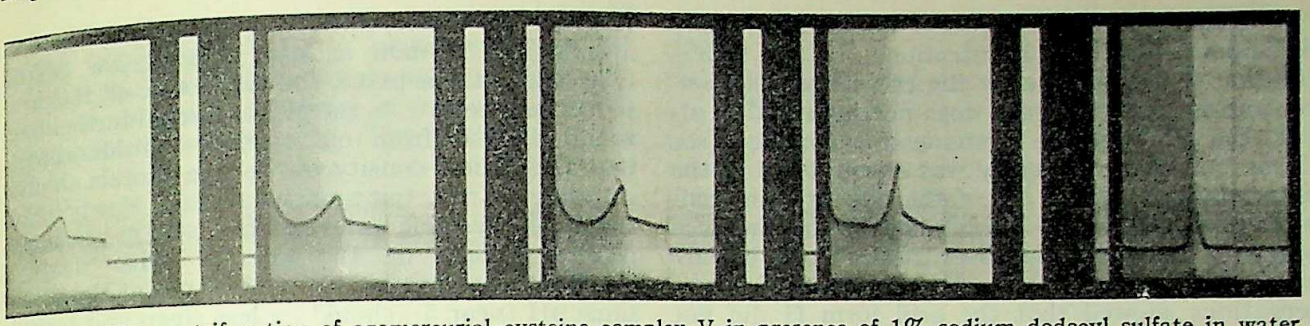


Fig. 3.—Ultracentrifugation of azomercurial–cysteine complex V in presence of 1% sodium dodecyl sulfate in water. The boundary of the dye, shown by the edge of the yellow color (dark area), coincides with the boundary of the dodecyl sulfate micelles, given by the peak in the schlieren pattern. Spinco ultracentrifuge model E was used with synthetic boundary cell rotating at 59,780 r.p.m. Purple filter inserted to increase color contrast. Times (in minutes) after formation of boundary (reading from right to left): 0, 11, 27, 43, 59. In absence of dodecyl sulfate, the color of a corresponding dye (methyl orange) diffused throughout the entire field in about 20 minutes.

A similar conclusion would be reached from the small effect of 0.5 *M* NaCl, as compared to water, on the *p*K of this group (Table I).

Effect of Urea.—The significance of *p*H, as measured with a glass electrode standardized in aqueous buffer, may be somewhat ambiguous in concentrated urea solutions. This ambiguity was minimized by obtaining first the *p*K of the $(CH_3)_2NH^+-$ group of the azomercurial complex of cysteine. This *p*K in 8 *M* urea, 3.42 (Table I), is not significantly different from that in water, and hence the mercurial attached to the small molecule provides a stable reference point.

Turning to the protein complex, we find a marked change in *p*K in 8 *M* urea, 3.32 as compared to 1.9 in water. It is particularly interesting that in aqueous urea the dye attached to protein behaves in its ionization just like the dye in water free from the protein. The urea thus acts like an "unmasking" reagent just as it does in connection with other groups, such as mercaptan, on proteins. An important distinction must be made in the present instance, however, in that naturally masked groups (such as –SH) were built into the protein during its biosynthesis, whereas the $(CH_3)_2N-$ group was attached thereafter.

A 6 *M* concentration of urea has about the same influence as the 8 *M* solution (Table I). Substantially lower concentrations, such as 1 *M*, have much smaller effects, but nevertheless in the same direction, *i.e.*, an increase in *p*K in the presence of urea. Our observations with $(CH_3)_2NH^+-$ thus parallel those of Foster and Sterman[17] in their electrometric titrations of the carboxyl groups of serum albumin in the presence of urea.

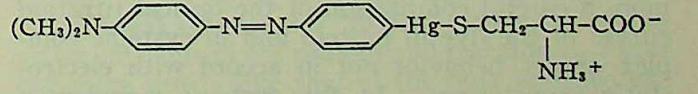
Effect of Sodium Dodecyl Sulfate.—This reagent, in a class with urea as a denaturant, has markedly different effects on the ionization of the $(CH_3)_2NH^+-$ group than does urea. In a 1% solution (0.03 *M*), sodium dodecyl sulfate forms micelles[18] which carry a large negative charge. In this solution the cysteine complex of the azomercurial has a *p*K of 5.18 (Table I), very substantially higher than in water alone. This elevation of the *p*K might be due to the preferential absorption of the cationic acid form of the dye by the anionic micelles, or to the existence of a higher concentration of protons within the micelles. The former explanation may be ruled out, however, from ultracentrifugation experiments with the dye and 1% dodecyl sulfate (Fig. 3); the yellow basic form of the dye travels with the anionic micelle. Thus it seems clear that a mixed micelle is formed by the azomercurial and dodecyl sulfate and that the equilibrium of eq. 1 is shifted to the left because of the higher H^+ concentration within the anionic micelle.[19] If the *p*H of the solution external to the micelle is used to compute pK_a within the micelle, the resultant pK_a comes out higher than that in the aqueous phase.

The behavior of the azomercurial attached to the protein in the presence of 1% dodecyl sulfate is similar to the cysteine complex, the *p*K, 4.7, being almost three *p*H units above that in water alone. It seems fair to conclude, therefore, that this detergent forms micelles on the protein surface, since the dye attached to the protein shows acid–base properties very similar to those of the cysteine–dye complex in the mixed micelle in water. The micelle on the protein surface must have a substantial amount of water built into its framework, since protons have no difficulty reaching the $(CH_3)_2N-$ group buried within. The strong negative charge of the sulfate groups at the ends of the aliphatic chains produces an increase in the local concentration of hydrogen ions, so that the concentration of $(CH_3)_2\overset{H^+}{N}-$ is greatly increased.[20]

(17) J. F. Foster and M. D. Sterman, THIS JOURNAL, **78**, 3656 (1956).

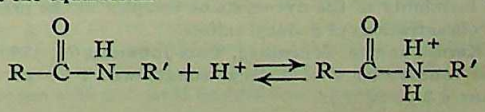
(18) M. L. Corrin and W. D. Harkins, *ibid.*, **69**, 683 (1947).

(19) It is of interest to note in passing that these results give some insight into the constitution of detergent micelles. In a mixed micelle of



with dodecyl sulfate, the dipolar amino acid end would presumably be facing the aqueous phase, whereas the azobenzene framework would presumably be buried inside the aliphatic chains of the C_{12} sulfate. Hence the $(CH_3)_2N-$ substituent must also be buried within the lipophilic phase. If this substituent has no trouble picking up an H^+ ion, as is evident from the high *p*K, the proton must have no difficulty penetrating the cluster of aliphatic chains. It seems likely, therefore, that within this cluster is a substantial amount of H_2O acting as a vehicle for the transfer of protons.

(20) Micelle formation on the surface of protein molecules would also shift the equilibrium



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The effect of sodium dodecyl sulfate is critically dependent on its concentration. In an 0.03% solution (0.001 *M*), below the critical micelle concentration, the detergent does not appreciably affect the pK[21] of the cysteine–dye complex (see Table I). Some difficulty was encountered in the determination of the pK of the dye–protein compound because of its insolubility in the presence of 0.03% dodecyl sulfate over the *p*H range 5.4–2.7 and below *p*H 0.8. Nevertheless the optical observations showed that the acid form II did not even begin to form until the *p*H dropped to about 2, and that the pK for the ionization of eq. 1 must be below 1.3. It is immediately evident, therefore, that at 0.001 *M* concentration the detergent does not form micelles on the surface of the protein; otherwise the pK ought to be much above 1.8–1.9. There can be little doubt, nevertheless, that the detergent ions are bound to the protein since even at higher *p*H's where the protein carries a negative charge essentially all of the anionic detergent in solution is bound to the protein.[22] In our solutions, acid to the isoelectric point, binding would be further strengthened by the positive charge of the protein.

Despite the binding of some 30 anions by each albumin molecule[23] and the consequent acquisition of some 30 negative charges by the protein, the pK_{H^+} of the $(CH_3)_2N-$ group was not elevated, as one would expect from simple electrostatic considerations. Quite the contrary, its acidity was increased by at least 0.6 *p*H unit over that in water in the absence of detergent (see Table I). It is of interest in this connection that very concentrated sorbitol solutions have a similar effect on the pK of the protein-linked dye (Table I) as does sodium dodecyl sulfate, the pK being lowered to approximately 1.3.

Discussion

The fact that the pK of the $(CH_3)_2NH^+-$ group is 1.8–1.9 when it is attached to the protein and 3.3 when it is in a small molecule in water shows that the protein environment has a very profound effect on the ionizing abilities of this group. It seems unlikely that electrostatic effects are directly responsible. As has been mentioned above, appreciable changes in the charge of the protein, either by change in *p*H in the region of 2.7 to 2 or by addition of some 30 dodecyl sulfate anions, do not shift the pK_a in the expected direction. Furthermore a careful comparison of the optical titration curves of the dye in protein and in cysteine complex shows behavior not in accord with electrostatic expectations. In the cysteine complex, a rise in absorption becomes detectable with increasing acidity as soon as one passes below *p*H 5 (Fig. 1). The same initial rise is shown by the dye attached to protein as one drops below *p*H 5 (Fig. 1). At this point, the net charge on the protein is near zero. As the *p*H is lowered further one would expect, from electrostatic considerations, that the optical density of the dye–protein should continue to rise, but somewhat more slowly than that of the cysteine complex, due to the increasingly positive charge on the protein. The titration curve in the protein should start to rise at about the same *p*H (near 5), should be less steep and spread out more over a wider *p*H range, but should be of the same general form as the cysteine complex.

Actually the optical density of the azomercurial on the protein reaches a small maximum at about *p*H 4.2 and then drops rapidly to a minimum at about *p*H 3.3. Clearly some profound change has occurred in the environment of the dye as the *p*H drops below about 4.2. This effect is shown even more strikingly if one examines the full spectra (Fig. 4). A marked shift in spectrum occurs at about *p*H 3, with the maximum of the dye (on the protein) shifting from about 455 to 420 mμ. (Only at much lower *p*H's does the characteristic spectrum of the acid form of the dye appear with a peak at 520 mμ.)

It is of course well known[24] now from a variety of experiments that serum albumin undergoes marked changes in physical characteristics at *p*H's below 4, and these have usually been interpreted in terms of swelling of the protein molecule.[8,10,24] Such an expansion is not in itself adequate to explain our observations, however, for the net result should be merely a decrease in the electrostatic broadening effect on the titration curve of the $(CH_3)_2NH^+-$ group.

The actual appearance of the optical titration curve of the dye–protein in the region below *p*H 3, where the absorption rises smoothly with decreasing *p*H (Fig. 1), is similar to that of the dye–cysteine complex except that the whole curve is displaced by about 1.5 *p*H units. The steepness of rise, once it starts, is if anything greater with protein than with cysteine. From electrostatic influences plus molecular expansion, one would expect the titration curve of dye–protein not to be displaced but to start upwards at about the same *p*H as does the cysteine complex, to rise less steeply at first and to increase in steepness, without exceeding that of the cysteine complex, as the *p*H is lowered further. The observed displacement of the titration curve of the dye–protein suggests that the protein effect is rather one of "masking" or hindering access to the $(CH_3)_2N-$ group similar to the masking of other, but naturally occurring, functional groups in protein molecules.

It seems inappropriate in the present case to attribute such masking to hydrogen-bonding between $(CH_3)_2\ddot{N}-$ and a donor group (see formula VI) because of our background of spectroscopic information. The dye–cysteine complex has a peak at 458 mμ. In the protein the absorption peak of the dye is much flatter, but the maximum is near 455 mμ at *p*H 5 and drops to 420 mμ below *p*H 4. If hy-

toward the right. Perhaps this effect is responsible for the catalysis of amide and peptide hydrolysis in the presence of dodecylsulfonate described by J. Steinhardt and C. H. Fugitt, *J. Research Natl. Bur. Standards*, **29**, 315 (1942). The explanation offered by these authors is slightly different; they attributed the catalysis to the binding of anion directly to the amide or peptide group.

(21) The pK could not be determined precisely in these solutions because of instability of the dye–cysteine complex in the presence of these low concentrations of dodecyl sulfate.

(22) F. Karush and M. Sonenberg, THIS JOURNAL, **71**, 1369 (1949).

(23) The concentration of dodecyl sulfate was 1×10^{-3} *M*, of serum albumin 3×10^{-5} *M*.

(24) For rather complete references see M. D. Sterman and J. F. Foster, THIS JOURNAL, **78**, 3652 (1956).

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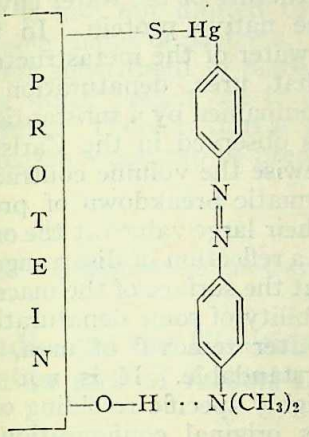
drogen bonding occurred in the protein one would expect the peak to shift to higher wave lengths ($\sim$ 500 mμ) instead of lower, and to higher extinctions, as seems to occur in related dimethylaminobenzeneazo dyes.[25,26] The observed shifts



VI

with the azomercurial albumin to lower wave lengths and reduced extinctions argue against a hydrogen bond from protein to $(CH_3)_2N-$ substituent.

In essence the phenomena observed show that the azo dye attached to serum albumin does not behave as it would in a normal aqueous environment, that attachment to the protein hinders access from the water to the $(CH_3)_2N-$ group. One is led to ask, therefore, whether the water in the vicinity of the protein is not different in structure from that in the bulk of the solution.

The importance of "icebergs" around polar (and non-polar) species in an aqueous environment was perhaps first emphasized by Frank and Evans,[27] who also mentioned that these structures might be of significance biologically. We have previously obtained good indications that "frozen" water molecules play a role in determining the enthalpy and entropy changes accompanying the formation of protein complexes.[28] Likewise Jacobson[29] has shown that dielectric behavior of aqueous protein solutions may be interpreted in terms of oriented water molecules. From a variety of very striking fluorescence experiments in ordinary ice, Szent-Györgyi[30] has suggested that muscular contraction and relaxation (as well as other biological phenomena) may be a response to a rearrangement in structure of the water envelope of proteins.

In the context of the present experiments we would view the drop in pK_a of the dimethylamino group in the environment of the protein as a consequence of the rigid iceberg structure in the neighborhood of the macromolecule. With serum albumin this freezing seems to become extensive as the pH drops below about 4.2. In the neighborhood of pH 5 to 4.2, the dye gives indications of normal ionization behavior and hence, at least in

(25) I. M. Klotz, R. K. Burkhard and J. M. Urquhart, THIS JOURNAL, **74**, 202 (1952).
(26) W. L. Peticolas and I. M. Klotz, *ibid.*, **78**, 5257 (1956).
(27) H. S. Frank and M. W. Evans, *J. Chem. Phys.*, **13**, 507 (1945).
(28) I. M. Klotz and J. M. Urquhart, THIS JOURNAL, **71**, 847 (1949).
(29) B. Jacobson, *ibid.*, **77**, 2919 (1955).
(30) A. Szent-Györgyi, *Science*, **124**, 873 (1956).

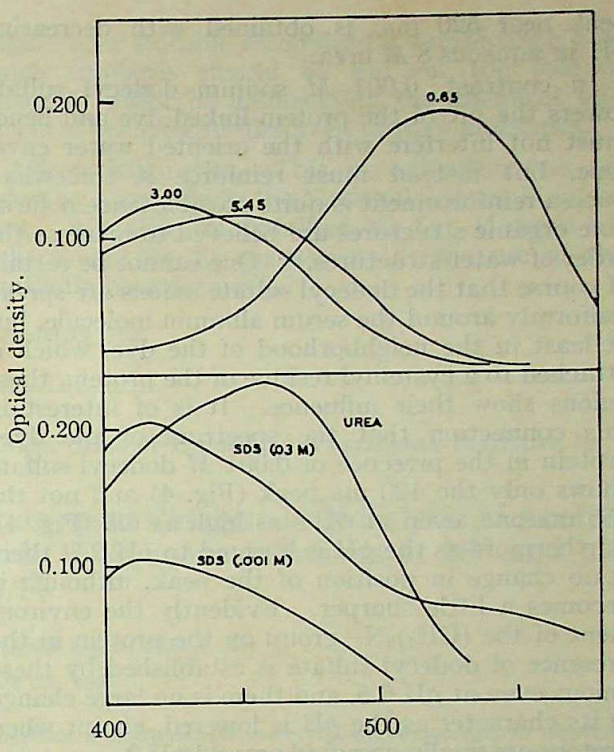


Fig. 4.—Spectra of $(CH_3)_2N-C_6H_4-N=N-C_6H_4-Hg-$ attached to bovine serum albumin: top, in water at pH's 5.45, 3.00 and 0.65; bottom: in 8 M urea at pH 7.22; in 0.001 M sodium dodecyl sulfate at pH 6.50; in 0.03 M sodium dodecyl sulfate at pH 5.45.

the vicinity of the $(CH_3)_2N-$ group of the dye attached to the cysteinyl residue of the protein, there is no indication of "frozen" water. Below pH 4.2, the accumulation of substantial net positive charge may increase strongly the extent and rigidity of the hydration envelope of the protein so as to produce effects on ionization properties as well as perhaps to contribute to the marked changes in hydrodynamic properties and other optical characteristics described in the literature.[24]

In line with this viewpoint, the effect of urea, bringing the pK_a back up to 3.3, is easy to understand. In essence in the presence of urea, the dye attached to protein behaves in its ionization just like the dye in water, free from the protein. An appropriate inference might be, therefore, that urea, because of its strong hydrogen-bonding characteristics, breaks down the "frozen" structure of the water envelope of the protein and transforms it into one more nearly like that of the bulk aqueous environment.[30a] It is of interest in this connection that the absorption spectrum of the protein-linked dye in the presence of 8 M urea shows a peak only at about 455 mμ (Fig. 4) and fails to develop the absorption peak at 420 mμ, characteristic of the masked $(CH_3)_2N-$ group, as the pH is lowered. Only the usual acid spectrum of azo dye, with a

(30a) In terms of the picture of masking as a steric effect, it is difficult to see (1) how the protein can provide side chains to block the $(CH_3)_2N-$ group at the extreme end of the azomercurial substituent attached to the surface of the protein; (2) why urea, a hydrogen-bond breaker, should be able to abolish completely any such lipophilic type of interaction even if it could be established *de novo*.

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peak near 520 mμ, is obtained with decreasing *p*H in aqueous 8 *M* urea.

In contrast, 0.001 *M* sodium dodecyl sulfate lowers the *pK* of the protein-linked dye and hence must not interfere with the oriented water envelope, but instead must reinforce it somewhat. Such a reinforcement is quite possible since polarizable organic structures are believed to increase the order of water structures.[27] One cannot be certain of course that the dodecyl sulfate anions are spread uniformly around the serum albumin molecule, but at least in the neighborhood of the dye, which is attached to a cysteinyl residue of the protein, these anions show their influence. It is of interest in this connection that the spectrum of the dye–protein in the presence of 0.001 *M* dodecyl sulfate shows only the 420 mμ peak (Fig. 4) and not the 455 mμ one, even at *p*H's as high as 6.5 (Fig. 4). Furthermore as the *p*H is lowered to *p*H 2.7, there is no change in position of the peak, although it becomes a little sharper. Evidently the environment of the $(CH_3)_2N-$ group on the protein in the presence of dodecyl sulfate is established by these anions even at *p*H 6.5, and there is no large change in its character as the *p*H is lowered, except when protons are finally accepted around *p*H 2.

At a higher concentration of dodecyl sulfate, 0.03 *M*, the nature of the water envelope is dominated by the surface micelles. It is clear that these micelles must have water within their framework since protons have no difficulty reaching the $(CH_3)_2N-$ group attached to the protein. At the surface of the protein, the micellar water seems to be highly ordered, nevertheless, for the spectrum of the protein-linked dye shows a peak at 420 mμ even at *p*H 7.5. As with more dilute detergent, this peak remains unchanged as the *p*H is lowered. With 0.03 *M* dodecyl sulfate, however, the micellar charge more than compensates for the rigidity of the water and protons are bound by the $(CH_3)_2N-$ groups at a much higher *p*H.

It is perhaps worthwhile to extend the scope of concepts of protein structure to include the organization which the macromolecule imposes upon its aqueous envelope. One might speak perhaps of the *meta*-structure of the protein, the framework which it imposes upon its environment beyond its own boundaries. The ordering of water molecules so produced may be limited to local regions of the surface or may be general around the whole protein molecule, and would probably depend on the distribution of polar groups within the protein. In the present studies with serum albumin and, as far as ionization of the specific dye of the class I is used as a probe (over the limited *p*H range of about 5 and below), the freezing of the water seems to be general. For the region of "masking" of the $(CH_3)_2N-$ group parallels that in which hydrodynamic properties indicate an increase in effective volume.

"Masking" of other, *naturally occurring*, functional groups of proteins might also be due to a "freezing" of the water structure in the neighborhood of the group. Lack of reactivity of such hindered groups (*e.g.*, mercaptan) is usually only relative and dependent on the reagent. The effectiveness of a reagent in combining with a masked group might very well be related to its ability to "dissolve" in the iceberg covering the group. Similarly, the effects of denaturing agents, such as urea, in "unmasking" blocked functional groups may be due to the rearrangements which they produce in the structure of the water envelope characteristic of the native protein. In terms of the "melting" of water of the metastructure it is quite reasonable that urea denaturation of proteins should be accompanied by a substantial contraction in volume, as observed in the Carlsberg Laboratory.[30b] Likewise the volume contractions accompanying enzymatic breakdown of proteins,[30b] and particularly their large values at the onset of proteolysis, may be a reflection of disarrangements in the water lattice at the surface of the macromolecule.

The reversibility of some denaturation processes, for example after removal of urea, is also more readily understandable. It is not necessary to postulate a highly specific refolding of the peptide chain into its original configuration but merely the refreezing of water when the disturbing, melting influence has been removed. Other denaturing factors, such as strong acid or alkali, or increased temperature can also be interpreted in terms of their influence on the structure of bound water. For example, the marked decrease in rate of exchange of deuterium in ribonuclease[30c] as the temperature is lowered would seem most plausible since the extent of the rigid iceberg structure should surely increase as the solution is cooled.

Likewise coöperative effects, such as the increased reactivity of the successively reacting sites after the first one on a protein has combined with a substrate,[31] may be transmitted through the water envelope. The original protein would have a *meta*-structure determined in part by its prosthetic groups and in part by its specific amino acid residues. When a molecule, *e.g.*, O_2, combines with the prosthetic group or specific site, the structure of water at that point could be changed significantly. Since the structure at this point is part of a more extensive water framework, it is evident that the effects due to combination at a specific site could be transmitted some distance and result in a disordering of the water structure some distance away. In consequence, a prosthetic group or specific site at a distance from the initially reactive one could have its water mask loosened and hence access to the second site could be significantly eased. Similarly specific ions bound at one site or region of a protein molecule could modify the framework for some distance by changing the water structure at that point and hence produce effects on a reactive site not in its immediate vicinity.

As has been mentioned, the present experiments have been limited in range of *p*H and in protein used. However, it is readily evident that corresponding experiments can be carried out with the present class of dye (I) and other proteins with mercaptan groups.[13] In addition analogous investigations can be made over other *p*H ranges by sub-

(30b) K. Linderstrom-Lang, *Cold Spring Harbor Symposia on Quantitative Biology*, **14**, 117 (1950).

(30c) A. Hvidt, *Biochim. et Biophys. Acta*, **18**, 306 (1955).

(31) The increased affinity of hemoglobin for the second oxygen molecule is a prime example of this phenomenon.

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stituting groups in place of the $(CH_3)_2N-$ substituent on the azobenzene nucleus of I. A corresponding dye with a *para* O–H group, for example, would allow one to study ionization behavior in the region near *p*H 7–8, an *ortho* O–H group, higher *p*H ranges. One is also not limited to attachments at mercaptan side chains of proteins. The use of a sulfonyl chloride substituent in place of –HgAc in I, for example, would permit one to make adducts to lysine residues. There is thus a wide range of covalent complexes which can be prepared. These should offer suitable examples for establishing how much emphasis should be put on the role of "frozen" water in determining the chemical and physical behavior of dissolved protein molecules.

Acknowledgments.—This investigation was assisted by a grant from the National Science Foundation. We also are indebted to Dr. Howard K. Schachman for his suggestions in the use of the synthetic boundary cell.

EVANSTON, ILL.

[CONTRIBUTION NO. 2170 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Further Studies on the Kinetics of the α-Chymotrypsin Catalyzed Hydrolysis of Acetyl-L-tyrosinamide and of Acetyl-L-tryptophanamide in Aqueous Solutions at 25° and *p*H 7.9 ± 0.1[1]

BY RICHARD A. BERNHARD AND CARL NIEMANN[2]

RECEIVED JANUARY 25, 1957

It has been found that the values of K_S, k_3 and K_P for the system α-chymotrypsin-acetyl-L-tyrosinamide, in aqueous solutions at 25° and *p*H 7.9 ± 0.1, obtained by observing the rate of formation of either one of the two reaction products, are identical within the limits of experimental error, that the values of K_S and K_P are independent of the nature and concentration of the buffer components of the four buffer systems investigated and that the values of k_3 are dependent upon the concentration of the buffer components and indirectly upon the nature of the buffer species. More limited observations with the system α-chymotrypsin–acetyl-L-tryptophanamide suggest that the behavior of this system is identical with that observed for the system α-chymotrypsin–acetyl-L-tyrosinamide. An experimental criterion for the recognition of bi- and trifunctionality in anionic competitive inhibitors of the type $RCH_2CO_2^-$ and $R'CONHCHRCO_2^-$ has been noted.

In a previous study Thomas, MacAllister and Niemann[3] examined the kinetics of the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tyrosinamide in aqueous solutions at 25° and *p*H 7.9 ± 0.1 and 0.02 *M* in the THAM[4] component of a THAM–HCl buffer, or 0.02 *M* in the EDA[5] component of an EDA–HCl buffer, by determining the rate of formation of acetyl-L-tyrosinate ion. The results obtained by these investigators were re-evaluated by Foster and Niemann[6] and by Foster, Shine and Niemann[7] and it was concluded that the above reaction systems could be represented throughout their course by equations 1 and 2, where P_{1f} is acetyl-L-tyrosinate ion and P_{2f} either ammonia or ammonium ion, and that their rates could be described, within the limits of experimental error, by eq. 3, where $K_S = (k_2 + k_3)/k_1 = 32 \pm 4 \times 10^{-3}$ *M*[6], $K_P = k_5/k_4 = 110 \pm 30 \times 10^{-3}$ *M*[7] and $k_3 = 2.4 \pm 0.3 \times 10^{-3}$ *M*/min./mg. protein nitrogen per ml.[6].

$$E_f + S_1 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E_f + P_{1f} + P_{2f} \quad (1)$$

$$E_f + P_{1f} \underset{k_5}{\overset{k_4}{\rightleftharpoons}} EP_1 \quad (2)$$

$$k_3[E]_t = K_S\,(1 + [S]_0/K_P)\ln([S]_0/[S]_t) + (1 - K_S/K_P)([S]_0 - [S]_t) \quad (3)$$

When the above values of K_S and k_3 are compared with those reported earlier,[8–11] and which were obtained by determining the rate of formation of ammonia and ammonium ion in aqueous solutions at 25° and *p*H 7.8 and 0.1 *M* in an unspecified phosphate buffer containing sufficient lithium chloride to bring the initial ionic strength to 0.292, it is seen, *cf.* Table I, that such a comparison leaves unanswered a number of questions whose answers are required for a more complete understanding of the reaction under consideration. It is the purpose of

TABLE I

KINETIC CONSTANTS FOR THE α-CHYMOTRYPSIN CATALYZED HYDROLYSIS OF ACETYL-L-TYROSINAMIDE IN AQUEOUS SOLUTIONS AT 25° AND *p*H 7.9 ± 0.1

Ref.	K_S[a]	k_3[b]	K_P[a]
3, 6, 7	32 ± 4[c,d]	2.44 ± 0.3[c,d]	110 ± 30[c,d]
8	23[e,f]	2.7[e,f]	.....
9	32.6[e,f]	2.7[e,f]	.....
10	27[e,f,g]	3.0[e,f,g]	.....
11	29[e,f]	3.1[e,f]	.....

[a] In units of 10^{-3} *M*. [b] In units of 10^{-3} *M*/min./mg. protein-nitrogen per ml. [c] Reaction system 0.02 *M* in the THAM component of a THAM–HCl buffer or 0.02 *M* in the EDA component of an EDA–HCl buffer. [d] Based upon the determination of the rate of formation of acetyl-L-tyrosinate ion. [e] Reaction system 0.1 *M* in an unspecified phosphate buffer containing sufficient lithium chloride to bring the initial ionic strength to 0.292. [f] Based upon the determination of the rate of formation of ammonia and ammonium ion. [g] Said to be preferred to the two sets of values immediately above.

(1) Supported in part by a grant from the National Institutes of Health, Public Health Service.
(2) To whom inquiries regarding this article should be sent.
(3) D. W. Thomas, R. V. MacAllister and C. Niemann, THIS JOURNAL, 73, 1548 (1951).
(4) Tris-(hydroxymethyl)-aminomethane.
(5) Ethylenediamine.
(6) R. J. Foster and C. Niemann, THIS JOURNAL, 77, 1886 (1955).
(7) R. J. Foster, H. J. Shine and C. Niemann, *ibid.*, 77, 1878 (1955).
(8) S. Kaufman and H. Neurath, *Arch. Biochem.*, 21, 245 (1949).
(9) S. Kaufman and H. Neurath, *J. Biol. Chem.*, 180, 181 (1949).
(10) G. W. Schwert and S. Kaufman, *ibid.*, 180, 517 (1949).
(11) S. Kaufman and H. Neurath, *ibid.*, 181, 623 (1949).

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this communication to provide answers to several of these questions, *i.e.*, are the same values of K_S, k_3 and K_P obtained when the reaction is examined by observing the rate of formation of both P_{1f} and P_{2f}, are the values of K_S, k_3 and K_P derived from studies of the reaction in THAM–HCl and EDA–HCl buffers identical with those observed for systems containing sodium or potassium phosphate buffers and is there any dependence of the values of K_S, k_3 and K_P upon the concentration of the buffer components?

A colorimetric procedure for the determination of ammonia, based upon the earlier work of Moore and Stein,[12] was developed with due consideration being given to its applicability in systems containing α-chymotrypsin, acetyl-L-tyrosinamide, acetyl-L-tyrosine and THAM hydrochloride as well as ammonium chloride. This procedure was capable of determining quantities of ammonia, present as ammonium chloride, of from 0 to 0.6×10^{-3} *M*.

With the above analytical procedure it became possible to examine the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tyrosinamide in aqueous solutions at 25° and *p*H 7.9 ± 0.1 and 0.02 *M* in the THAM component of a THAM–HCl buffer with respect to the rate of formation of ammonia and ammonium ion. Thirty-two experiments were conducted, *cf.* Table II, and it was found that with 18 the extent of reaction was sufficient to permit the use of the graphical procedure of Foster and Niemann[13–15] for the evaluation of the experimental data. The above graphical procedure could not be used for the evaluation of the remaining fourteen experiments because of a more limited extent of reaction. Therefore, in these latter cases the corrected initial velocities were evaluated by the procedure of Jennings and Niemann[16–18] and these values of v_0 were then used in an Eadie plot[15] to obtain values of K_S and k_3 but not of K_P.

Two separate evaluations were performed. In the first the experimental data obtained from the ten experiments conducted at [E] = 0.200 mg. protein-nitrogen per ml., *cf.* Table II, were presented in a $([S]_0 - [S]_t)/t$ *vs.* $(\ln ([S]_0/[S]_t))/t$ plot[13–15] and from this plot the following values were obtained: $K_S = 34 \pm 2 \times 10^{-3}$ *M*, $k_3 = 2.5 \pm 0.1 \times 10^{-3}$ *M*/min./mg. protein-nitrogen per ml. and $K_P = 80 \pm 20 \times 10^{-3}$ *M*. As the preceding values were derived from experimental data obtained under conditions where $[E] = 5.7 \times 10^{-5}$ *M*,[19] E's = $[E]/K_S = 0.2 \times 10^{-2}$ and S's = $[S]/K_S = 0.15$ to 1.28 it follows that all assumptions inherent in the evaluation procedure have been satisfied.[6,7]

In the second evaluation, based upon the results obtained in all 32 experiments, *cf.* Table II, the initial velocities, obtained from either a $([S]_0 - [S]_t)/t$ *vs.* $(\ln ([S]_0/[S]_t))/t$ plot or by the procedure of Jennings and Niemann,[16–18] were normalized to an enzyme concentration of 0.200 mg. protein-nitrogen per ml. assuming that the initial velocities were directly proportional to the enzyme concentrations. A line was then fitted to the 32 values of v_0 and of $v_0/[S]_0$ and from the slope and intercepts of this line and the slopes of the 18 lines of slope $-K_S(K_P + [S]_0)/(K_P - K_S)$ the following values were obtained; $K_S = 34 \pm 4 \times 10^{-3}$ *M*, $k_3 = 2.5 \pm 0.3 \times 10^{-3}$ *M*/min./mg. protein-nitrogen per ml. and $K_P = 80 \pm 20 \times 10^{-3}$ *M*. With [E] between the limits of 0.76 to 6.3×10^{-5} *M*,[19] E's between 0.02 and 0.2×10^{-2} and S's between 0.09 and 1.28 it is clear that the conditions required for a proper evaluation of K_S, k_3 and K_P were satisfied.[6,7]

A comparison of the values of K_S, k_3 and K_P for the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tyrosinamide in aqueous solutions at 25° and *p*H

TABLE II

α-CHYMOTRYPSIN CATALYZED HYDROLYSIS OF ACETYL-L-TYROSINAMIDE IN AQUEOUS SOLUTIONS AT 25° AND *p*H 7.9 ± 0.1 AND 0.02 *M* IN THE THAM COMPONENT OF A THAM–HCl BUFFER

[E][a]	$[S]_0$[b]	t_{max}[c]	% Hydrol.[f]
0.222[d]	10	110	72.0
	10	110	72.0
.200[d]	5	122	86.4
	5	110	71.6
	10	110	70.2
	15	150	84.2
	20	150	78.6
	25	150	79.7
	30	165	77.5
	35	150	69.6
	40	180	76.8
	45	150	65.4
.179[e]	5	110	72.4
	5	110	67.2
	10	110	66.9
	10	110	62.5
	30	150	67.5
	40	150	65.1
.133[e]	3	60	40.0
	3	60	40.7
	3	60	39.7
	5	60	38.0
	5	60	39.0
	5	60	44.0
	10	60	37.2
	10	60	38.2
	10	60	36.9
	10	60	37.6
	10	60	36.0
.0266[e]	5	60	8.3
	10	60	7.2
	10	60	7.6

[a] In units of mg. protein-nitrogen per ml. [b] In units of 10^{-3} *M*. [c] Maximum time of observation in minutes with a total of seven observations taken within the time indicated. [d] Armour preparation no. 00592. [e] Armour preparation no. 10705. [f] The first 18 experiments were evaluated by the procedure of Foster and Niemann,[13–15] the remainder by the procedure of Jennings and Niemann.[16–18]

(12) S. Moore and W. H. Stein, *J. Biol. Chem.*, **176**, 367 (1948).
(13) R. J. Foster and C. Niemann, *Proc. Natl. Acad. Sci.*, **39**, 999 (1953).
(14) T. H. Applewhite and C. Niemann, THIS JOURNAL, **77**, 4923 (1955).
(15) R. R. Jennings and C. Niemann, *ibid.*, **77**, 5432 (1955).
(16) R. R. Jennings and C. Niemann, *ibid.*, **75**, 4687 (1953).
(17) W. E. M. Lands and C. Niemann, *ibid.*, **77**, 6508 (1955).
(18) Based upon a value of $K_S = 32 \times 10^{-3}$ *M*.
(19) Value of [E] is based upon an assumed molecular weight of monomeric α-chymotrypsin of 22,000 and a nitrogen content of 16.0%.[6,7]

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7.9 ± 0.1 and 0.02 M in the THAM component of a THAM–HCl buffer with respect to the rate of formation of acetyl-L-tyrosinate ion, *i.e.*, $K_S = 32 \pm 4 \times 10^{-3}$ M, $k_3 = 2.4 \pm 0.3 \times 10^{-3}$ M/min./mg. protein-nitrogen per ml. and $K_P = 110 \pm 30 \times 10^{-3}$ M,[3,6,7] and with respect to the rate of formation of ammonia and ammonium ion, *i.e.*, $K_S = 34 \pm 2 \times 10^{-3}$ M, $k_3 = 2.5 \pm 0.1 \times 10^{-3}$ M/min./mg. protein-nitrogen per ml. and $K_P = 80 \pm 20 \times 10^{-3}$ M[20] shows that within the limits of experimental error the same values of K_S, k_3 and K_P are obtained irrespective of whether the reaction is studied by determining the rate of formation of P_{1f} or P_{2f}.

From a series of experiments based upon the determination of the amount of ammonia and ammonium ion liberated in aqueous solutions at 25° with [E] = 0.200 mg. protein-nitrogen per ml., $[S]_0 = 5 \times 10^{-3}$ M and $t = 110$ minutes it was found that the *p*H optimum for the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tyrosinamide in a system 0.02 M in the phosphate component of a sodium phosphate buffer is *ca.* 7.9.

With the knowledge that the *p*H optimum for the above reaction system is identical, within the limits of experimental error, with the *p*H optima for the comparable systems 0.02 M in the THAM or EDA component of a THAM– or EDA–HCl buffer[3] it was decided to evaluate K_S, k_3 and K_P for the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tyrosinamide in aqueous solutions at 25° and *p*H 7.9 ± 0.1 and 0.1 M in the phosphate component of a sodium or potassium phosphate buffer[21] by determining the rate of formation of ammonia and ammonium ion. The experimental conditions employed in this study are summarized in Table III.

TABLE III

α-CHYMOTRYPSIN CATALYZED HYDROLYSIS OF ACETYL-L-TYROSINAMIDE IN AQUEOUS SOLUTIONS AT 25° AND *p*H 7.9 ± 0.1 AND 0.1 M IN THE PHOSPHATE COMPONENT OF A SODIUM OR POTASSIUM PHOSPHATE BUFFER[a]

$[S]_0$[b]	t_{max}[c]	% Hydrol.	$[S]_0$[b]	t_{max}[c]	% Hydrol.
Sodium phosphate buffer			Potassium phosphate buffer		
5	110	88.0	5	110	87.0
10	110	81.6	10	110	81.2
30	150	85.8	20	150	88.7
40	150	80.3	30	150	83.7
			35	120	74.1
			40	150	80.0

[a] With [E] = 0.200 mg. protein-nitrogen per ml. of Armour preparation no. 00592. [b] In units of 10^{-3} M. [c] Maximum time of observation in minutes with a total of seven observations taken within the time indicated.

Since data were available for the extended reaction each set was evaluated by the procedure of Foster and Niemann.[13–15] From the two $([S]_0 - [S]_t)/t$ *vs.* $(\ln ([S]_0/[S]_t))/t$ plots the following values were obtained. For the 0.1 M sodium phosphate buffer; $K_S = 32 \pm 2 \times 10^{-3}$ M, $k_3 = 3.3 \pm 0.2 \times 10^{-3}$ M/min./mg. protein-nitrogen per ml., $K_P = 70 \pm 20 \times 10^{-3}$ M, [E] = 5.7×10^{-5} M,[19] E's = 0.2×10^{-2} and S's = 0.16 to 1.25. For the 0.1 M potassium phosphate buffer; $K_S = 33 \pm 2 \times 10^{-3}$ M, $k_3 = 3.25 \pm 0.15 \times 10^{-3}$ M/min./mg. protein-nitrogen per ml., $K_P = 80 \pm 20 \times 10^{-3}$ M, [E] = 5.7×10^{-5} M,[19] E's = 0.2×10^{-2} and S's = 0.15 to 1.21.

The identity, within the limits of experimental error, of the above two sets of values of K_S, k_3 and K_P demonstrates that in the α-chymotrypsin-catalyzed hydrolysis of acetyl-L-tyrosinamide in aqueous solutions at 25° and *p*H 7.9 ± 0.1 there is no detectable difference in the behavior of systems containing either 0.1 M sodium or potassium phosphate buffers. However, it will be noted that whereas the values of K_S and K_P evaluated in these latter systems, *i.e.*, 32 ± 2 and 33 ± 2 × 10^{-3} M and 70 ± 20 and 80 ± 20 × 10^{-3} M, are identical, within the limits of experimental error, with the values of K_S and K_P obtained in comparable systems 0.02 M in the THAM component of a THAM–HCl buffer, *i.e.*, 32 ± 4[3,6,7] and 34 ± 2 + 10^{-3} M and 110 ± 30[3,6,7] and 80 ± 20 × 10^{-3} M, the corresponding values of k_3 in systems 0.1 M in a sodium or potassium phosphate buffer, *i.e.*, 3.3 ± 0.2 and 3.25 ± 0.15 × 10^{-3} M/min./mg. protein-nitrogen per ml., are significantly greater than those observed in systems 0.02 M in the THAM component of a THAM–HCl buffer, *i.e.*, 2.4 ± 0.3[3,6,7] and 2.5 ± 0.1 × 10^{-3} M/min./mg. protein-nitrogen per ml.

Since the situation noted immediately above could be due to a difference in the nature of the buffer component and/or their concentrations it was decided to examine the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tyrosinamide in aqueous solutions at 25° and *p*H 7.9 ± 0.1 and 0.2 M and 0.4 M in the phosphate component of a sodium phosphate buffer. As before data were obtained with respect to the rate of formation of ammonia and ammonium ion for the extended reaction, *cf.* Table IV, and K_S, k_3 and K_P were evaluated from $([S]_0 - [S]_t)/t$ *vs.* $(\ln ([S]_0/[S]_t)/t$ plots.[13–15] For the system 0.2 M in phosphate $K_S = 30 \pm 2 \times 10^{-3}$ M, $k_3 = 3.85 \pm 0.3 \times 10^{-3}$ M/min./mg. protein-nitrogen per ml., $K_P = 80 \pm 20 \times 10^{-3}$ M,

TABLE IV

α-CHYMOTRYPSIN CATALYZED HYDROLYSIS OF ACETYL-L-TYROSINAMIDE IN AQUEOUS SOLUTIONS AT 25° AND *p*H 7.9 ± 0.1 AND 0.2 M AND 0.4 M IN THE PHOSPHATE COMPONENT OF A SODIUM PHOSPHATE BUFFER[a]

$[S]_0$[b]	t_{max}[c]	% Hydrol.	$[S]_0$[b]	t_{max}[c]	% Hydrol.
0.2 M sodium phosphate buffer			0.4 M sodium phosphate buffer		
5	110	87.2	5	90	96.8
5	110	93.2	10	90	92.4
10	110	90.0	30	90	82.2
10	110	88.8	40	90	73.3
30	150	90.0			
40	150	87.1			

[a] With [E] = 0.200 mg. protein-nitrogen per ml. of Armour preparation no. 00592. [b] In units of 10^{-3} M. [c] Maximum time of observation with a total of seven observations taken within the time indicated.

(20) Of the two sets of values given earlier the one presented here is preferred because it was obtained by a more certain evaluation procedure.

(21) While it would have been desirable to study systems which were 0.02 M in the phosphate component such systems could not be poised at *p*H 7.9 for extended reactions at relatively high specific substrate concentrations. The minimum practical concentration is 0.1 M.

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$[E] = 5.7 \times 10^{-5}\ M$,[19] $E'_S = 0.2 \times 10^{-2}$ and $S'_S = 0.17$ to 1.33. For the system 0.4 M in phosphate, $K_S = 31 \pm 3 \times 10^{-3}\ M$, $k_3 = 5.0 \pm 0.3 \times 10^{-3}\ M$/min./mg. protein-nitrogen per ml., $K_P = 75 \pm 20 \times 10^{-3}\ M$, $[E] = 5.7 \times 10^{-5}\ M$,[19] $E'_S = 0.2 \times 10^{-2}$ and $S'_S = 0.16$ to 1.29.

The information that is now available with respect to the dependence or independence of values of K_S, k_3 and K_P for the system α-chymotrypsin–acetyl-L-tyrosinamide in aqueous solutions at 25° and pH 7.9 ± 0.1 upon components of the reaction system that are not represented in eq. 1 and 2 is summarized in Table V. Having established for the case at hand that the same values of K_S, k_3 and K_P are obtained irrespective of whether the reaction is followed by determining the rate of formation of P_{1f} or P_{2f}, *vide ante*, it is seen from the information given in Table V that the values of K_S and K_P are independent, within the limits of experimental error, of the nature or concentration of any of the components of the reaction system which may have been added to maintain the system at a constant pH but that the values of k_3 are clearly dependent upon either the nature and/or concentration of such components.

TABLE V

SUMMARY OF KINETIC CONSTANTS FOR THE α-CHYMOTRYPSIN CATALYZED HYDROLYSIS OF ACETYL-L-TYROSINAMIDE IN AQUEOUS SOLUTIONS AT 25° AND pH 7.9 ± 0.1

Buffer system	K_S[a]	k_3[b]	K_P[a]	Ref.
0.02 M THAM or EDA[c]	32 ± 4	2.4 ± 0.3	110 ± 30	3,6,7
.02 M THAM[d]	34 ± 2	2.5 ± 0.1	80 ± 20	..
.1 M PO_4[e]	32 ± 2	3.3 ± 0.2	70 ± 20	..
.1 M PO_4[f]	33 ± 2	3.25 ± 0.15	80 ± 20	..
.1 M PO_4[g]	27	3.0	.....	10
.1 M PO_4[g]	29	3.1	.....	11
.2 M PO_4[h]	30 ± 2	3.85 ± 0.3	80 ± 20	..
.4 M PO_4[i]	31 ± 3	5.0 ± 0.3	75 ± 20	..
Any of above	32 ± 2[j]	.....	80 ± 20[j]	..

[a] In units of 10^{-3} M. [b] In units of 10^{-3} M/min./mg. protein-nitrogen per ml. [c] System 0.02 M in the THAM component of a THAM–HCl buffer or 0.02 M in the EDA component of an EDA–HCl buffer and followed by determining the rate of formation of acetyl-L-tyrosinate ion. [d] System 0.02 M in the THAM component of a THAM–HCl buffer and followed by determining the rate of formation of ammonia and ammonium ion. [e] System 0.1 M in the phosphate component of a sodium phosphate buffer and followed by determining the rate of formation of ammonia and ammonium ion. [f] Same as *e* except system 0.1 M in the phosphate component of a potassium phosphate buffer. [g] System 0.1 M in an unspecified phosphate buffer containing sufficient lithium chloride to bring the ionic strength to 0.292 and followed by determing the rate of formation of ammonia and ammonium ion. [h] Same as *e* except system 0.2 M in the phosphate component. [i] Same as *e* except system 0.4 M in the phosphate component. [j] Preferred values.

The observation that the value of K_S for the system α-chymotrypsin–acetyl-L-tyrosinamide in aqueous solutions at 25° and pH 7.9 ± 0.1 appears to be independent of added THAM and its hydrochloride, EDA and its hydrochloride or sodium or potassium phosphate recalls the experience of Shine and Niemann[22,23] who found that the value of K_S for the system α-chymotrypsin–chloroacetyl-L-tyrosinamide in aqueous solutions at 25° and pH 7.75 and 0.02 M in the THAM component of a THAM–HCl buffer is essentially independent of added sodium or potassium chloride[22] or of added sucrose.[23] In view of the relatively high concentrations of sodium and potassium phosphate employed in the present studies we can now regard these two salts along with sodium and potassium chloride as members of that class of electrolytes which appear to have no demonstrable effect upon the K_S value of an amide type trifunctional specific substrate.

It is known that the K_I values, *i.e.*, the enzyme-inhibitor dissociation constants, of certain bifunctional anionic competitive inhibitors of α-chymotrypsin, when evaluated in aqueous solutions at 25° and pH 7.9 ± 0.1, are strikingly dependent upon whether the value was obtained by examination of a reaction system 0.02 M in the THAM component of a THAM–HCl buffer or one 0.1 M in an unspecified phosphate buffer.[24–26] Since it was noted previously[26] that no information was available with respect to the behavior of a single trifunctional anionic competitive inhibitor of the type $R'CONHCHRCO_2^-$ in 0.02 M THAM–HCl and 0.1 M phosphate buffers it was of particular interest to find that the K_P value, *i.e.*, the K_I value, of acetyl-L-tyrosinate ion determined in this study was essentially independent of the nature of the buffer systems which included not only 0.02 M THAM–HCl but also 0.1, 0.2 and 0.4 M sodium phosphate, *cf.* Table V. With the knowledge that under certain conditions the K_I values of a trifunctional anionic competitive inhibitor of α-chymotrypsin is independent of the presence of added phosphate and the K_I value of a comparable bifunctional anionic competitive inhibitor of this enzyme appears to be dependent upon the presence of added phosphate it is clear that we now possess an experimental basis for recognizing bi- and trifunctionality in anionic competitive inhibitors of the type $RCH_2CO_2^-$ and $R'CONHCHRCO_2^-$.

In contrast to the essential independence of values of K_S and K_P upon the concentration of the sodium phosphate buffer it is seen from the information summarized in Table V that the value of k_3 for the system α-chymotrypsin–acetyl-L-tyrosinamide in aqueous solutions at 25° and pH 7.9 ± 0.1 increases with increasing concentration of the sodium phosphate buffer. It was noted previously[22] that with added sodium or potassium chloride the value of k_3 for the α-chymotrypsin catalyzed hydrolysis of chloroacetyl-L-tyrosinamide in aqueous solutions at 25° and pH 7.75 and 0.02 M in the THAM component of a THAM–HCl buffer increased linearly in accordance with the relation $\log (k_3/k_3^0) = 0.30 \pm 0.01\sqrt{M}$ where k_3^0 is the value observed in the absence of added sodium or potassium chloride and M the molality of the added salt. When the limited data summarized in Table V were examined with respect to possible relationships between values of k_3 and sodium phosphate concentration, or some function thereof, it was noted that with plots of k_3 *vs.* M, log k_3 *vs.* M, log

(22) H. J. Shine and C. Niemann, THIS JOURNAL, 77, 4275 (1955).
(23) H. J. Shine and C. Niemann, *ibid.*, 78, 1872 (1956).
(24) H. Neurath and J. A. Gladner, *J. Biol. Chem.*, 188, 407 (1951).
(25) H. T. Huang and C. Niemann, THIS JOURNAL, 74, 5963 (1952).
(26) R. J. Foster and C. Niemann, *ibid.*, 77, 3365 (1955).

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k_3 *vs.* $\sqrt{M}$ and log k_3 *vs.* $\sqrt{\mu}$[27] only the first and third gave reasonably linear plots although all could have been considered to be linear within the limits of experimental error. The log k_3 *vs.* $\sqrt{M}$ plot was selected as the most suitable for an empirical extrapolation and from the relation log $(k_3/k_3^0) = 0.575\sqrt{M}$ the following values of k_3^0, *i.e.*, the value of k_3 in the absence of sodium phosphate, were computed: 2.2, 2.1 and 2.2 $\times 10^{-3}$ M/min./mg. protein-nitrogen per ml. With log $k_3^0 = 0.333 \times 10^{-3}$ M/min./mg. protein-nitrogen per ml. the above relation gave an expected value of $k_3 = 2.6 \times 10^{-3}$ M/min./mg. protein-nitrogen per ml. for a system 0.02 M in the phosphate component of a sodium phosphate buffer of *p*H 7.9 ± 0.1. The agreement of this value of k_3 with that obtained for the comparable system 0.02 M in the THAM component of a THAM–HCl buffer, *i.e.*, $2.5 \pm 0.1 \times 10^{-3}$ M/min./mg. protein-nitrogen per ml. suggests that values of k_3 are basically independent of the nature of the buffers considered in this study but that the dependency of the value of k_3 for a particular specific substrate upon the concentration of the buffer components may vary with the nature of the buffer.

It has been shown[6,7,28] that for the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tryptophanamide in aqueous solutions at 25° and *p*H 7.9 ± 0.1 and 0.02 M in the THAM component of a THAM–HCl buffer $K_S = 5.0 \pm 0.5 \times 10^{-3}$ M, $k_3 = 0.55 \pm 0.1 \times 10^{-3}$ M/min./mg. protein-nitrogen per ml. and $K_P = 10 \pm 2 \times 10^{-3}$ M when the reaction is followed by determining the rate of formation of acetyl-L-tryptophanate ion. In order to determine whether several of the results noted previously could be observed with a second specific substrate the above system was re-examined under conditions where the 0.02 M THAM–HCl buffer was replaced by a potassium phosphate buffer which was 0.1 M in the phosphate component and where the reaction was followed by determining the rate of formation of ammonia and ammonium ion. The reaction conditions employed in this latter study are summarized in Table VI and when the primary data were evaluated through the use of a $([S]_0 - [S]_t)/t$ *vs.* $(\ln ([S]_0/[S])_t)/t$ plot[13-15] the following values were obtained: $K_S = 5.7 \pm 0.3 \times 10^{-3}$ M, $k_3 = 0.68 \pm 0.02 \times 10^{-3}$ M/min./mg. protein-nitrogen per ml., $K_P = 7.3 \pm 0.6 \times 10^{-3}$ M, $[E] = 6.3 \times 10^{-5}$ M,[19] E's = 0.1×10^{-2} and S's = 1.75 to 7.05.

A comparison of the above values of K_S, *i.e.*, 5.0 ± 0.5 and 5.7 ± 0.3 $\times 10^{-3}$ M, k_3, *i.e.*, 0.55 ± 0.1 and 0.68 ± 0.02 $\times 10^{-3}$ M/min./mg. protein-nitrogen per ml. and $K_P = 10 \pm 2$ and 7.3 ± 0.6 $\times 10^{-3}$ M reveals a common pattern in the behavior of acetyl-L-tyrosinamide and acetyl-L-tryptophanamide. As with the former specific substrate the value of K_S for the latter appears to be independent of the nature and/or concentration of the buffer components and whether the reaction is followed by determining the rate of formation of P_{1f} or P_{2f}. In contrast, the value of k_3 again appears to be dependent upon the concentration of the buffer components and it is noteworthy that the percentage increase in the value of k_3 in passing from a 0.02 M THAM–HCl buffer to a 0.1 M potassium phosphate buffer is *ca.* 30% for acetyl-L-tyrosinamide and *ca.* 20% for acetyl-L-tryptophanamide. Finally, it may be noted that the value of K_P for the system α-chymotrypsin–acetyl-L-tryptophanate ion in aqueous solutions at 25° and *p*H 7.9 ± 0.1 also appears to be independent of the nature and/or concentration of the buffer components. In this connection it is of interest to recall that Cunningham and Brown[29] have reported that the K_I value of acetyl-L-tryptophanate ion in aqueous solutions at 25° and *p*H 8 and 0.0033 M in the THAM component of a THAM–HCl buffer and 0.1 M in calcium chloride is $8.7 \pm 2 \times 10^{-3}$ M, a value which may be compared with the values of 10 ± 2 and 7.3 ± 0.6 $\times 10^{-3}$ M given above.

Table VI

α-Chymotrypsin Catalyzed Hydrolysis of Acetyl-L-tryptophanamide in Aqueous Solutions at 25° and *p*H 7.9 ± 0.1 and 0.1 M in the Phosphate Component of a Potassium Phosphate Buffer[a]

$[S]_0$[b]	t_{max}[c]	% Hydrol.
10	150	80.5
15	150	70.5
15	150	70.5
20	150	61.3
20	150	59.4
25	150	55.1
30	150	49.8
40	150	41.9

[a] With [E] = 0.222 mg. protein-nitrogen per ml. of Armour preparation no. 00592. [b] In units of 10^{-3} M. [c] Maximum time of observation in minutes with a total of seven observations taken within the time indicated.

Experimental[30]

Analytical Procedure.—The procedure used in this study was based upon one described by Moore and Stein.[12] Because of the necessity, in some cases, of determining small amounts of ammonia in the presence of substantial amounts of THAM many precautions had to be taken beyond those required for a more conventional application of the original procedure. The procedure to be described was the result of a large number of experiments designed to establish optimum conditions for the determination of ammonia in the presence of THAM and phosphate buffers. While these experiments[31] will not be described here it should be realized that the directions given below are based upon a large number of observations and are in no sense arbitrary. Strict adherence to the described procedure is required if satisfactory results are to be obtained.

A. Reagents.—Commercial ninhydrin was recrystallized from hot water, after decolorization with Norite A, the product dried *in vacuo* and stored in a sealed amber colored container. Anhydrous stannous chloride, prepared from the crystalline dihydrate by reaction with acetic anhydride,[32] was dried *in vacuo* and stored in a sealed container. Reagent grade citric acid monohydrate was further purified by recrystallization from hot water. Peroxide-free Methyl Cellosolve was prepared by refluxing the commercial product with anhydrous stannous chloride until a negative test for peroxides was obtained. The reaction mixture was then

(27) Based upon the following dissociation constants for phosphoric acid: $k_1 = 1.1 \times 10^{-2}$, $k_2 = 7.5 \times 10^{-8}$ and $k_3 = 4.8 \times 10^{-13}$.

(28) H. T. Huang and C. Niemann, This Journal, 73, 1541 (1951).

(29) L. N. Cunningham and C. S. Brown, *J. Biol. Chem.*, **221**, 287 (1956).

(30) All melting points are corrected.

(31) R. A. Bernhard, Ph.D. Thesis, Calif. Inst. Tech., Pasadena, Calif., 1955.

(32) H. Stephen, *J. Chem. Soc.*, 2786 (1930).

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fractionally distilled and the fraction b.p. 123–125° stored in a sealed amber colored container. Peroxide-free isopropyl alcohol is also required.

B. Reagent Solutions.—A 0.2 *M* sodium citrate buffer of *p*H 4.8 ± 0.1 was prepared from 42 g. of recrystallized citric acid monohydrate and 16 g. of reagent grade sodium hydroxide pellets in 1000 ml. of distilled water. A few crystals of thymol were added and the solution stored at 4° prior to use. This solution was prepared weekly. The ninhydrin reagent was prepared by first dissolving 0.0240 g. of C.P. stannous chloride dihydrate in 15.0 ml. of the citrate buffer and passing dry nitrogen through the solution for three minutes. A solution of 0.600 g. of recrystallized ninhydrin in 15.0 ml. of peroxide-free Methyl Cellosolve was then prepared and dry nitrogen passed through the solution for three minutes. The first solution now was added to the second and the resulting ninhydrin reagent stored in a polyethylene container under an atmosphere of nitrogen. This reagent was prepared immediately prior to use. A diluent solution was prepared daily from equal volumes of distilled water and peroxide-free isopropyl alcohol.

C. Procedure.—Prior to the starting of a given kinetic experiment a series of G. S. volumetric flasks were assembled, the capacities being determined by the amount of ammonia expected in a 1.0-ml. aliquot of the reaction mixture, *i.e.*, for 0.0–3.0 × 10^{-3} *M* a 5-ml. flask, for 3.0–7.0 × 10^{-3} *M* a 10-ml. flask, for 7.0–17.5 × 10^{-3} *M* a 25-ml. flask and for 17.5–35.0 × 10^{-3} *M* a 50-ml. flask. To each of the 10-ml. flasks was added *ca.* 8.5 ml. of the 0.2 *M* citrate buffer and when 5-, 25- and 50-ml. flasks were employed the amount of buffer added was *ca.* 3.5, 23.5 and 47.5 ml., respectively. At selected time intervals 1.0-ml. aliquots were withdrawn from the reaction mixture and added to the contents of the above flasks and the solutions made up to volume with the citrate buffer. After the completion of the experiment 1.0-ml. aliquots of each of the above solutions were added to 1.0-ml. aliquots of the ninhydrin reagent contained in a series of 13 cm. rimless Pyrex test-tubes, the tubes capped with close fitting cylindrical aluminum caps and heated in a water-bath maintained at 99–100° for exactly 20 minutes. The tubes were then withdrawn from the bath, allowed to cool for five minutes and a 50-ml. aliquot of the diluent solution added to each of the tubes. The optical density of the resulting solutions, for a 1 cm. path in a Corex cell at 565 mμ, was then promptly determined in a model B Beckman spectrophotometer. A sample of the diluent solution was used as a control.

D. Calibration Curves and Blanks.—The examination of solutions of the 0.2 *M* citrate buffer of *p*H 4.8 ± 0.1 containing aliquots of simulated reaction mixtures composed of varying amounts of acetyl-L-tyrosinamide, acetyl-L-tyrosine and ammonium chloride and fixed amounts of α-chymotrypsin and the buffer system employed in the original reaction mixture revealed that for concentrations of ammonia up to 0.04 *M* in the original reaction mixture the optical density was proportional to the ammonia concentration within the limits of experimental error. However, the proportionality constant was found to depend upon the particular ninhydrin reagent employed and upon the concentration of the THAM-HCl buffer when this buffer system was used in the original reaction mixture. Therefore, for each particular reaction system a standard calibration curve was prepared and coincidently with each series of determinations two solutions, one containing all of the components of the original reaction mixture except the specific substrate and the other containing all components present in the first and in addition a known amount of a standard ammonium chloride solution, were prepared and analyzed along with the other solutions of the series.

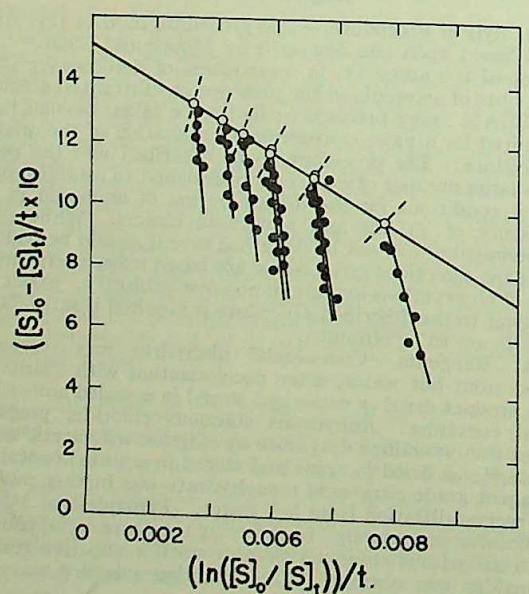

Fig. 1.—Foster–Niemann plot of data obtained for the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tryptophanamide in aqueous solutions at 25° and *p*H 7.9 ± 0.1 and 0.1 *M* in the phosphate component of a potassium phosphate buffer.

Specific Substrates.—Acetyl-L-tyrosinamide, m.p. 226–228°, $[\alpha]^{24}D$ +52 ± 1° (*c* 0.8% in water) was prepared as directed by Thomas, MacAllister and Niemann.[3] Acetyl-L-tryptophanamide, m.p. 192–193°, $[\alpha]^{25}D$ +20 ± 1° (*c* 2% in methanol) was prepared as described by Huang and Niemann.[28]

Buffer Systems.—A stock solution 0.20 *M* in the thrice recrystallized THAM component of a THAM–HCl buffer of *p*H 8.0 at 25° was prepared. A 1:10 dilution of this stock solution in the reaction mixture gave a solution of *p*H 7.90 ± 0.05 at 25°. Sodium phosphate stock solutions 1.0, 2.0 and 4.0 *M* in the phosphate component were prepared by the addition of sufficient 5 *N* aqueous sodium hydroxide to aqueous solutions of reagent grade sodium dihydrogen phosphate to give solutions of *p*H 8.05 at 25° after the solutions were made up to volume. One to ten dilutions of these stock solutions in the reaction mixture gave solutions of *p*H 7.9 ± 0.05 at 25°. A 1.0 *M* potassium phosphate stock solution was prepared similarly from potassium dihydrogen phosphate and 5 *N* aqueous potassium hydroxide.

Enzyme Solutions.—Crystalline bovine α-chymotrypsin containing magnesium sulfate (Armour lot no. 10705) and crystalline bovine α-chymotrypsin salt-free (Armour lot no. 00592) were employed in these studies. Stock solutions of these preparations were prepared daily.

TABLE VII

α-CHYMOTRYPSIN CATALYZED HYDROLYSIS OF ACETYL-L-TRYPTOPHANAMIDE[a]

t (min.)	O.D.[b]	$([S]_0 - [S]_t)$[c]	$([S]_0 - [S]_t)/t$	$(\ln([S]_0/[S]_t))/t$
20	0.462	2.175	0.109	0.00784
25	.504	2.550	.102	.00746
50	.748	4.775	.096	.00767
75	.930	6.450	.086	.00749
100	1.105	8.050	.081	.00768
125	1.237	9.225	.074	.00763
150	1.383	10.575	.071	.00814

[a] In aqueous solutions at 25° and *p*H 7.9 ± 0.1 and 0.1 *M* in the phosphate component of a potassium phosphate buffer with [E] = 0.222 mg. protein-nitrogen per ml. of Armour preparation no. 00592 and $[S]_0$ = 15 × 10^{-3} *M*. [b] Optical density based upon a 1:25 dilution of a 1-ml. aliquot of the reaction mixture and a blank value of 0.227. [c] Based upon a value of O.D. = 1.976 for 16 × 10^{-3} *M* ammonium chloride.

Enzyme Experiments.—The substrate was dissolved in 3 to 7 ml. of distilled water contained in a 10-ml. G. S. volumetric flask, 1.0 ml. of the appropriate buffer stock solution added and the solution placed in a 25.0 ± 0.05° bath for 20 to 25 minutes. At minus 20 seconds from time zero the volumetric flask was withdrawn from the bath and at time zero 1.0 ml. of the enzyme stock solution was added and the solution made up to volume with distilled water. The contents of the flask were mixed by gently inverting the flask 12 times and the flask then returned to the bath. 1.0-

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ml. aliquots were withdrawn at convenient time intervals, delivered into a series of volumetric flasks containing the 0.2 *M* citrate buffer of *p*H 4.8 ± 0.1, the solution immediately made up to volume with the citrate buffer and then analyzed as directed above.

Analysis of Data.—Data representative of a single kinetic experiment are given in Table VII. Sets of these data were graphically evaluated by the method of Foster and Niemann[13-15] as illustrated in Fig. 1.

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[CONTRIBUTION NO. 2172 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

The Dependence of the Enzyme-Inhibitor Dissociation Constants of Several Bifunctional Anionic Competitive Inhibitors of α-Chymotrypsin upon Added Potassium Phosphate[1]

BY RICHARD A. BERNHARD AND CARL NIEMANN[2]

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It has been observed that the enzyme-inhibitor dissociation constants of two representative bifunctional anionic competitive inhibitors of α-chymotrypsin, *i.e.*, β-(β-indole)-propionate and phenyl acetate, when evaluated in aqueous solutions at 25° and *p*H 7.9 ± 0.1 may be decreased by increasing the concentration of the uni-univalent buffer system, or by the addition of sodium chloride or potassium phosphate. A detailed analysis has indicated that the effect produced by added potassium phosphate is to be associated with a general increase in ionic strength and a specific ion effect.

It has been recognized that the enzyme-inhibitor dissociation constants of a number of bifunctional anionic competitive inhibitors of α-chymotrypsin, when evaluated in aqueous solutions at 25° and *p*H 7.9 and 0.02 *M* in the THAM[3] component of a THAM–HCl buffer,[4-6] are substantially greater than the constants obtained for the same inhibitors in aqueous solutions at 25° and *p*H 7.8 and 0.1 *M* in an unspecified phosphate buffer.[7,8] However, the lack of a suitable analytical procedure has prevented, until recently, a more direct comparison of the behavior of certain bifunctional anionic competitive inhibitors of α-chymotrypsin in the presence of THAM–HCl and phosphate containing buffers. With the development of a procedure which was suitable for following the rate of the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tyrosinamide in aqueous solutions at 25° and *p*H 7.9 ± 0.1 in the presence of THAM–HCl or sodium or potassium phosphate buffers[9] it was thought desirable to re-examine several of the experiments reported earlier[4-8] and if possible to clarify and explain the behavior noted above.

In the first series of experiments the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tyrosinamide in aqueous solutions at 25° and *p*H 7.0 ± 0.1 and 0.02 *M* in the THAM component of a THAM–HCl buffer was examined in the presence of added potassium β-(β-indole)-propionate, β-(β-indole)-propionamide, potassium phenylacetate, phenylacetamide or tryptamine hydrochloride. As before[9] the reaction was followed by determining the rate of formation of ammonia and ammonium ion and the primary data so obtained were graphically evaluated by the method of Foster and Niemann.[10-12] The experimental conditions employed in this study are summarized in the footnotes to Table I. It will be seen from these data that the extent of reaction was sufficient to justify the use of the above evaluation procedure.[13] From the evaluated data given in Table I it is evident that all values of K_I were obtained under conditions that were compatible with the assumptions inherent in the procedures used for their evaluation.[6,10-12,14,15]

TABLE I

K_I VALUES OF FIVE COMPETITIVE INHIBITORS OF α-CHYMOTRYPSIN EVALUATED IN AQUEOUS SOLUTIONS AT 25° AND *p*H 7.9 ± 0.1 AND 0.02 *M* IN THE THAM COMPONENT OF A THAM–HCl BUFFER[a]

Competitive inhibitor	K_I[b]	E_I'[c]	I_I
Potassium β-(β-indole)-propionate	11 ± 1.5[e]	0.52	3.6
β-(β-Indole)-propionamide	1.7 ± 0.3[f]	3.4	0.88
Potassium phenylacetate	170 ± 15[g]	0.03	0.88
Phenylacetamide	10 ± 1[h]	0.57	1.0
Tryptamine hydrochloride	1.5 ± 0.3[i]	3.8	6.7

[a] Evaluated against acetyl-L-tyrosinamide with $K_S = 32 \times 10^{-3}$ *M*, [E] = 5.7×10^{-5} *M*, [d] $E_S' = 0.17 \times 10^{-2}$ and $S_S' = 0.625$ to 1.25. [b] In units of 10^{-3} *M*. [c] In units of 10^{-2}. [d] Based upon an assumed molecular weight of monomeric α-chymotrypsin of 22,000 and a nitrogen content of 16.0%. [e] Based upon 4 sets of experiments with $[S]_0 = 20, 25, 30$ and 40×10^{-3} *M*, [I] = 40×10^{-3} *M*, *t* = 150 minutes with a total of 7 observations of extent of reaction within this time interval, with a total extent of reaction of 36.5, 35.4, 32.2 and 30.0%, respectively, and with [E] = 0.200 mg. protein-nitrogen per ml. of Armour preparation no. 00592. [f] Same as *e* but with [I] = 1.5×10^{-3} *M* and total extent of reaction of 66.3, 64.0, 61.8 and 58.0% respectively. [g] Same as *e* but with [I] = 150×10^{-3} *M* and total extent of reaction of 61.3, 59.0, 56.8 and 52.8%, respectively. [h] Same as *e* but with [I] = 10×10^{-3} *M* and total extent of reaction of 58.5, 57.3, 55.2 and 53.4%, respectively. [i] Same as *h* but with total extent of reaction of 24.3, 23.8, 22.7 and 22.4%, respectively.

(1) Supported in part by a grant from the National Institutes of Health, Public Health Service.
(2) To whom inquiries regarding this article should be sent.
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In a second series of experiments, *cf.* Table II, the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tyrosinamide in aqueous solutions at 25° and *p*H 7.9 ± 0.1 and 0.1 *M* in the phosphate component of a potassium phosphate buffer was examined in the presence of the above five competitive inhibitors using the same procedures as before.

TABLE II

K_I VALUES OF FIVE COMPETITIVE INHIBITORS OF α-CHYMOTRYPSIN EVALUATED IN AQUEOUS SOLUTIONS AT 25° AND *p*H 7.9 ± 0.1 AND 0.1 *M* IN THE PHOSPHATE COMPONENT OF A POTASSIUM PHOSPHATE BUFFER[a]

Competitive inhibitor	K_I[b]	E_I'[c]	I_I'
Potassium β-(β-indole)-propionate	4.0 ± 0.4[e]	1.4	2.5
β-(β-Indole)-propionamide	1.8 ± 0.2[f]	3.2	0.83
Potassium phenylacetate	60 ± 5[g]	0.10	0.83
Phenylacetamide	11 ± 1[h]	0.52	0.90
Tryptamine hydrochloride	1.4 ± 0.3[i]	4.5	3.6

[a] Evaluated against acetyl-L-tyrosinamide with K_S = 32 × 10^{-3} *M*, [E] = 5.7 × 10^{-5} *M*[d], E_S' = 0.17 × 10^{-2} and S_S' = 0.156 to 1.25. [b] In units of 10^{-3} *M*. [c] In units of 10^{-2}. [d] Based upon an assumed molecular weight of monomeric α-chymotrypsin of 22,000 and a nitrogen content of 16.0%. [e] Based upon 4 sets of experiments with $[S]_0$ = 5, 10, 30 and 40 × 10^{-3} *M*, [I] = 10 × 10^{-3} *M*, *t* = 110 minutes for values of $[S]_0$ = 5 and 10 × 10^{-3} *M* and 150 minutes for values of $[S]_0$ = 30 and 40 × 10^{-3} *M* with a total of 7 observations of extent of reaction within these time intervals, with a total extent of reaction of 44.8, 43.7, 51.3 and 46.9%, respectively, and with [E] = 0.200 mg. protein-nitrogen per ml. of Armour preparation no. 00592. [f] Based upon 4 sets of experiments with $[S]_0$ = 20, 25, 30 and 40 × 10^{-3} *M*, [I] = 1.5 × 10^{-3} *M*, *t* = 150 minutes with a total of 7 observations of extent of reaction within this time interval, with a total extent of reaction 74.4, 72.8, 70.7 and 68.3%, respectively, and with [E] = 0.200 mg. of protein-nitrogen per ml. of Armour preparation no. 00592. [g] Same as *f* but with [I] = 50 × 10^{-3} *M* and total extent of reaction of 74.4, 72.8, 70.7 and 68.3%, respectively. [h] Same as *e* but with extent of reaction of 64.6, 61.3, 66.7 and 63.4%, respectively. [i] Same as *e* but with [I] = 5 × 10^{-3} *M* and extent of reaction of 40.4, 37.8, 47.3 and 44.6%, respectively.

The enzyme-inhibitor dissociation constants obtained from the two series of experiments are given in Table III where they are compared with the previously determined values.[4-6,8] It will be seen that in general the values of K_I obtained in this study are in reasonable agreement with those reported earlier. Where significant differences exist the more recent values are to be preferred.

TABLE III

SUMMARY OF ENZYME-INHIBITOR DISSOCIATION CONSTANTS

Competitive inhibitor	K_I × 10^3, *M* In 0.02 *M* THAM H + N[a]	In 0.02 *M* THAM This study	In 0.1 *M* phosphate N + G[b]	
β-(β-Indole)-propionate[c]	15 ± 3	11 ± 1.5	4.0 ± 0.4	2.5
β-(β-Indole)-propionamide	2.3 ± 0.4	1.7 ± 0.3	1.8 ± 0.2	..
Phenylacetate[c]	200 ± 50	170 ± 15	60 ± 5	42
Phenylacetamide	15 ± 3	10 ± 1	11 ± 1	..
Tryptamine[d]	2.3 ± 0.4	1.5 ± 0.3	1.4 ± 0.3	..
Acetyl-L-tryptophanate[e]	8.0 ± 1.0[f]	.....	7.3 ± 0.3[f]	..
Acetyl-L-tyrosinate[e]	110 ± 30[f]	80 ± 20[f]	80 ± 20[f]	..

[a] Value of Huang and Niemann.[4-6] [b] Value of Neurath and Gladner[8]. [c] Present as the potassium salt. [d] Present as the hydrochloride. [e] Formed from the amide in the reaction mixture. [f] Actually K_P values, see ref. 9.

From the constants given in Table III we may conclude as before[4-6] that the K_I values of the two bifunctional uncharged competitive inhibitors, *i.e.*, β-(β-indole)-propionamide and phenylacetamide, and the single bifunctional cationic competitive inhibitor, *i.e.*, tryptammonium ion, for aqueous systems at 25° and *p*H 7.9 ± 0.1 and 0.02 *M* in the THAM component of a THAM–HCl buffer or 0.1 *M* in the phosphate component of a potassium phosphate buffer, are identical within the limits of experimental error. In contrast to the above situation it is again seen[4-6] that the K_I values of the two bifunctional anionic competitive inhibitors, *i.e.*, β-(β-indole)-propionate and phenylacetate, in aqueous solutions at 25° and *p*H 7.9 ± 0.1 and 0.02 *M* in the THAM component of a THAM–HCl buffer are substantially greater than those observed in comparable systems 0.1 *M* in the phosphate component of a potassium phosphate buffer. While the K_I values observed in this study, *i.e.*, 11 ± 1.5 and 4.0 ± 0.4 × 10^{-3} *M* and 170 ± 15 and 60 ± 5 × 10^{-3} *M*, lead to differences which are but *ca.* 3-fold in both cases and are thus but *ca.* one-half of the 5–6 fold differences inferred from the earlier values of K_I[4-6,8] there can be no doubt that the observed differences are real and that they suggest a basic difference in the behavior of this class of competitive inhibitors in THAM–HCl and potassium phosphate buffers of *p*H 7.9 ± 0.1. Furthermore, with the above difference in the behavior of two representative bifunctional anionic competitive inhibitors of α-chymotrypsin in 0.02 *M* THAM–HCl and 0.1 *M* potassium phosphate buffers of *p*H 7.9 ± 0.1, which has now been verified by a new set of observations, we can reaffirm our earlier conclusion[9] that the different behavior of bi- and trifunctional anionic competitive inhibitors of this enzyme, with respect to the dependence or lack of dependence of the values of K_I upon the nature of the buffer components in two specified buffers, *cf.* Table III, provides an experimental basis for recognizing bi- and trifunctionality in anionic competitive inhibitors of the type $RCH_2CO_2^-$ and $R'CONHCHRCO_2^-$.

From the observations noted above it is not clear whether the different behavior of β-(β-indole)-propionate and of phenylacetate in 0.02 *M* THAM–HCl and 0.1 *M* potassium phosphate buffers of *p*H 7.9 ± 0.1 is due to a general ionic strength and/or a specific ion effect. To answer this question the inhibition of the α-chymotrypsin catalyzed hydrolysis of acetyl-L-tyrosinamide in aqueous solutions at 25° and *p*H 7.9 ± 0.1 by potassium β-(β-indole)-propionate and by potassium phenylacetate was examined in systems containing varying amounts of the THAM–HCl and/or potassium phosphate buffer components and in one case added sodium chloride, *cf.* Table IV.

A summary of all available information relative to the dependence of values of K_I for β-(β-indole)-propionate and for phenylacetate upon the composition of the reaction system is presented in Table V. Examination of these data and of the plot presented in Fig. 1 indicates that there are at least two factors that appear to have an influence on values of K_I for the bifunctional anionic competi-

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TABLE IV

K_I VALUES OF POTASSIUM β-(β-INDOLE)-PROPIONATE AND OF POTASSIUM PHENYLACETATE IN AQUEOUS SOLUTIONS AT 25° AND pH 7.9 ± 0.1 AS A FUNCTION OF THE NATURE AND CONCENTRATION OF SEVERAL BUFFER COMPONENTS[a]

Competitive inhibitor[c]	K_I[d]	E_I'[e]	I_I'
β-(β-Indole)-propionate[f]	7.6 ± 0.4	0.75	1.32
β-(β-Indole)-propionate[g]	4.7 ± 0.4	1.2	2.1
β-(β-Indole)-propionate[h]	7.5 ± 0.5	0.76	1.33
β-(β-Indole)-propionate[i]	8.0 ± 0.3	0.71	1.25
β-(β-Indole)-propionate[j]	7.6 ± 0.4	0.75	1.32
β-(β-Indole)-propionate[k]	6.6 ± 0.4	0.86	1.52
β-(β-Indole)-propionate[l]	5.1 ± 0.3	1.12	1.96
β-(β-Indole)-propionate[m]	3.2 ± 0.5	1.97	3.1
β-(β-Indole)-propionate[n]	2.5 ± 0.3	2.28	4.0
Phenylacetate[o]	110 ± 10	0.052	1.36

[a] Evaluated against acetyl-L-tyrosinamide with K_S = 32×10^{-3} M, [E] = 5.7×10^{-5} M[b], $E_S' = 0.17 \times 10^{-2}$ and $S_S' = 0.625$ to 1.25 unless otherwise noted. [b] Based upon an assumed molecular weight of monomeric α-chymotrypsin of 22,000 and a nitrogen content of 16.0%. [c] Evaluated with $[S]_0$ = 20, 25, 30 and 40 $\times 10^{-3}$ M, [I] = 10×10^{-3} M, t = 150 minutes with a total of 7 observations of extent of reaction within this time interval and with [E] = 0.200 mg. of protein-nitrogen per ml. of Armour preparation no. 00592 unless otherwise noted. [d] In units of 10^{-3} M. [e] In units of 10^{-2}. [f] System 0.4 M in the THAM component of a THAM–HCl buffer with total extent of reaction of 60.0, 57.5, 56.3 and 52.1%, respectively. [g] System 0.4 M in the THAM component of a THAM–HCl buffer, 0.4 M in added sodium chloride with total extent of reaction of 65.6, 62.7, 61.3 and 58.9%, respectively. [h] System 0.4 M in the THAM component of a THAM–HCl buffer, 0.0001 M in the phosphate component of a potassium phosphate buffer with total extent of reaction of 60.3, 57.9, 55.0 and 53.1%, respectively. [i] System 0.4 M in the THAM component of a THAM–HCl buffer, 0.001 M in the phosphate component of a potassium phosphate buffer with total extent of reaction of 62.1, 59.5, 57.5 and 54.4%, respectively. [j] System 0.27 M in the THAM component of a THAM–HCl buffer, 0.01 M in the phosphate component of a potassium phosphate buffer with total extent of reaction of 59.3, 57.2, 56.0 and 52.9%, respectively. [k] System 0.2 M in the THAM component of a THAM–HCl buffer, 0.04 M in the phosphate component of a potassium phosphate buffer with total extent of reaction of 58.0, 55.8, 52.2 and 51.8%, respectively. [l] System 0.0725 M in the phosphate component of a potassium phosphate buffer with total extent of reaction of 53.8, 52.1, 50.8 and 47.8%, respectively. [m] System 0.2 M in the phosphate component of a potassium phosphate buffer with total extent of reaction of 50.0, 47.6, 57.7 and 54.4%, respectively, and with $[S]_0$ = 5, 10, 30 and 40 $\times 10^{-3}$ M, [E] = 0.222 mg. protein-nitrogen per ml., *i.e.*, [E] = 6.3×10^{-5} M[b], $E_S' = 0.2 \times 10^{-2}$, $S_S' = 0.16$ to 1.25, t = 110 minutes for values of $[S]_0$ = 5 and 10×10^{-3} M and 150 minutes for values of $[S]_0$ = 30 and 40×10^{-3} M. [n] System 0.4 M in the phosphate component of a potassium phosphate with total extent of reaction of 58.1, 56.2, 57.7 and 53.0% buffer, respectively. [o] System 0.3 M in the THAM component of a THAM–HCl buffer with total extent of reaction of 66.0, 65.3, 61.8 and 58%, respectively, and with [I] = 150×10^{-3} M.

tive inhibitors considered in this study. That one factor may be ionic strength and the other the nature of the ion species is seen from the observation that while an increase in ionic strength associated with an increasing concentration of the THAM–HCl buffer components causes a measurable decrease in the enzyme-inhibitor dissociation constants of this class of competitive inhibitors, the presence of significant amounts of potassium phosphate either alone or in the above buffer system produces a still greater decrease in the value

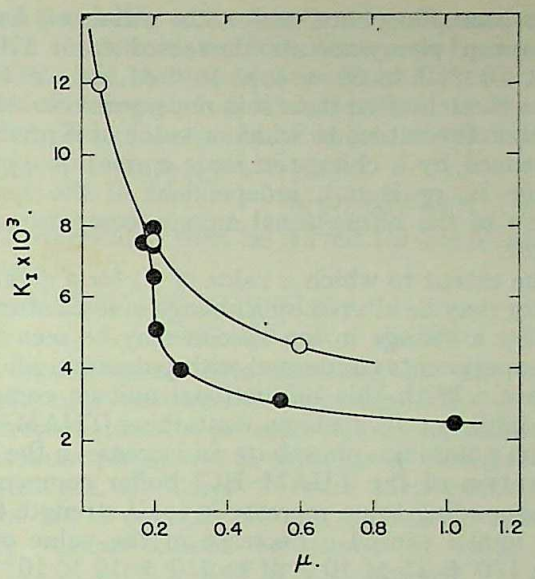

Fig. 1.—Effect of ionic environment upon the enzyme-inhibitor dissociation constants of β-(β-indole)-propionate; open circles THAM–HCl or THAM–HCl and sodium chloride, filled circles potassium phosphate with or without THAM–HCl.

of K_I when the comparisons are made for systems of comparable ionic strength.

TABLE V

EFFECT OF IONIC ENVIRONMENT UPON THE ENZYME-INHIBITOR DISSOCIATION CONSTANTS OF TWO BIFUNCTIONAL ANIONIC COMPETITIVE INHIBITORS

Competitive inhibitor	THAM concn.[a]	Phos. concn.[b]	μ[c]	K_I[d]
β-(β-Indole-propionate[e]	0.02	0.00	0.05	11 ± 1.5
	.40	.00	.20	7.6 ± 0.4
	.40	.00	.60[f]	4.7 ± .4
	.40	.0001	.20	7.5 ± .5
	.40	.001	.20	8.0 ± .3
	.27	.01	.17	7.6 ± .4
	.20	.04	.20	6.6 ± .4
	.00	.0725	.20	5.1 ± .3
	.00	.10	.28	4.0 ± .4
	.00	.20	.55	3.2 ± .5
	.00	.40	1.09	2.5 ± .3
Phenylacetate[e]	.02	.00	0.16	170 ± 15
	.30	.00	.30[g]	110 ± 10
	.00	.10	.30[g]	60 ± 5

[a] Molar concentration of the THAM component of a THAM-HCl buffer of pH 7.9 ± 0.1 at 25°. [b] Molar concentration of the phosphate component of a potassium phosphate buffer at pH 7.9 ± 0.1 at 25°. [c] Ionic strength. [d] In units of 10^{-3} M for aqueous solutions at 25° and pH 7.9 ± 0.1. [e] Present as the potassium salt. [f] 0.4 M sodium chloride also present. [g] 0.15 M in potassium phenylacetate.

In passing from a system in which the ionic strength was 0.05 in the presence of a 0.02 M THAM–HCl buffer to one in which the ionic strength was 0.28 in the presence of a 0.1 M potassium phosphate buffer the value of K_I for potassium β-(β-indole)-propionate decreased from 11 ± 1.5 $\times 10^{-3}$ M to 4.0 ± 0.4 $\times 10^{-3}$ M, *i.e.*, *ca.* 64%. Similarly, in passing from a system in which the ionic strength was 0.16 in the presence of a 0.02 M THAM–HCl buffer to one in which the ionic strength was 0.8 in the presence of a 0.1 M

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potassium phosphate buffer the value of K_I for potassium phenylacetate decreased from 170 ± 15 × 10^{-3} M to 60 ± 5 × 10^{-3} M, *i.e.*, *ca.* 65%. From these limited data it is not possible to decide whether the extent to which a value of K_I may be influenced by a change in ionic species or concentration is, or is not, independent of the specific nature of the bifunctional anionic competitive inhibitor.

The extent to which a value of K_I for a given inhibitor may be altered by a change in ionic strength and by a change in ion species may be seen from the experiments conducted with potassium phenylacetate. With this bifunctional anionic competitive inhibitor in systems containing THAM–HCl but no potassium phosphate an increase in the concentration of the THAM–HCl buffer components corresponding to an increase in ionic strength from 0.16 to 0.3 caused a decrease in the value of K_I from 170 ± 15 × 10^{-3} M to 110 ± 10 × 10^{-3} M, *i.e.*, *ca.* 35%, corresponding to a decrease in $-\Delta F^0$ of *ca.* 320 cal. per mole. However, in passing from a system containing the THAM–HCl buffer components in an amount corresponding to an ionic strength of 0.16 to one containing the potassium phosphate buffer components in an amount corresponding to an ionic strength of 0.3 the value of K_I was observed to decrease from 170 ± 15 × 10^{-3} M to 60 ± 5 × 10^{-3} M, *i.e.*, *ca.* 65%, corresponding to a decrease in $-\Delta F^0$ of *ca.* 670 cal. per mole. Thus, the presence of the 0.1 M potassium phosphate buffer components caused a decrease in $-\Delta F^0$, in addition to that associated with an increase in ionic strength caused by an increase in the concentration of the THAM–HCl buffer components, of *ca.* 350 cal. per mole.

Since there is reason to believe that there are one or more negatively charged groups at or near the catalytically active site of α-chymotrypsin, when this enzyme is present in aqueous solutions at 25° and pH 7.9 ± 0.1,[4-8,16,17] an increase in the ionic strength of the reaction medium would be expected to facilitate the approach of a negatively charged anionic competitive inhibitor to the negatively charged region of the catalytically active site of the enzyme. Thus, since combination would be enhanced the value of K_I would be reduced. While this effect has been observed with the two bifunctional anionic competitive inhibitors considered in this study the fact that the enzyme-inhibitor dissociation constants of the two trifunctional anionic competitive inhibitors that have been examined to date[9] appear to be uninfluenced by the presence of substantial amounts of added potassium phosphate[9] or of calcium chloride[17] suggests that even with what may be regarded, as a first approximation, as an ionic strength effect associated with an increased dielectric constant of the reaction medium there is a striking difference in the nature of the interaction of α-chymotrypsin with bifunctional and trifunctional anionic competitive inhibitors. It is not obvious at the present time as to why the K_I values of trifunctional anionic competitive inhibitors of α-chymotrypsin should be independent of the ionic strength of the reaction system particularly since it is known that the apparent protonation of one or more of the negatively charged groups which are present in the region of the catalytically active site of α-chymotrypsin does result in an expected decrease in the values of K_I for both bi- and trifunctional anionic competitive inhibitors of this enzyme.[5,17,18]

With regard to the possible nature of the specific ion effect noted earlier it may be assumed that the interaction of α-chymotrypsin with a bifunctional anionic competitive inhibitor, in aqueous solutions at 25° and pH 7.9 ± 0.1 in the absence of potassium phosphate, proceeds, in large part, *via* a R_2–ρ_2 interaction[19] with the R_3–ρ_3 interaction[19] being either small or of a negative character particularly in systems of low ionic strength. Thus, the principal attractive forces leading to combination of the enzyme with a bifunctional anionic competitive inhibitor of the type $R_2CH_2R_3$, where R_3 is a carboxylate group, would arise from a one center, *i.e.*, a R_2–ρ_2, interaction. However, if it is also assumed that there is a region of the active site of the enzyme, adjacent to the ρ_3 center, that is receptive to interaction with phosphate[20] then in the presence of phosphate and upon the approach of a bifunctional anionic competitive inhibitor a R_2–ρ_2 interaction would occur and the R_3 group, *i.e.*, the carboxylate group, would attempt to make its usual R_3–ρ_3 approach. However, the presence of combined phosphate near the ρ_3 center of the active site would provide an additional negative charge which would repel the negatively charged carboxylate group more effectively than would the negatively charged group or groups which are normally present at the catalytically active site and the inhibitor would be forced from its normal modes of combination into alternate modes of combination wherein the R_3 group could contribute more effectively to the total binding energy either in a positive or in a less negative sense. Thus phosphate combined with the site would supply the energy required to consummate alternative and more effective modes of combination which are denied to bifunctional anionic competitive inhibitors in the absence of phosphate. Presumably these alternative modes of combination would be unavailable to the trifunctional anionic competitive inhibitors because of steric reasons and thus this class of competitive inhibitors would be unaffected by the presence of phosphate in the reaction system.

For the case of immediate interest the interaction of enzyme, specific substrate and bifunctional anionic competitive inhibitor in the presence of phosphate may, in the first instance, be represented by equations 1 to 7 inclusive where B is taken to be the combining phosphate species. It is not necessary to consider equations such as $E_f + B_f \rightleftarrows EB$ since this implies competitive inhibition by B and it

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(17) L. W. Cunningham and C. S. Brown, *J. Biol. Chem.*, **221**, 287 (1956).

(18) R. R. Jennings, Ph.D. Thesis, California Institute of Technology, Pasadena, California, 1954.

(19) H. T. Huang and C. Niemann, THIS JOURNAL, **73**, 3223 (1951).

(20) The term "phosphate" is used here in its broadest sense. While it is possible that $HPO_4^=$ may be the active species this point cannot be established because of restrictions arising from the necessity of using reaction systems at a definite pH, *i.e.*, 7.9 ± 0.1.

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is known[9] that this situation does not obtain. It is also appropriate to recall[9] that the constant $K_S = (k_2 + k_3)/k_1$ is essentially independent of the ionic strength and of the concentration of B.

$$E_f + S_f \rightleftarrows ES \xrightarrow{k_3} E + P_{1f} + P_{2f} \quad (1)$$

$$E_f + I_f \rightleftarrows EI \quad (2)$$

$$B_f + E_f \rightleftarrows BE \quad (3)$$

$$B_f + ES \rightleftarrows BES \xrightarrow{k_3'} BE + P_{1f} + P_{2f} \quad (4)$$

$$BE + S_f \rightleftarrows BES \xrightarrow{k_3'} BE + P_{1f} + P_{2f} \quad (5)$$

$$BE + I_f \rightleftarrows BEI \quad (6)$$

$$B + EI \rightleftarrows BEI \quad (7)$$

If it is assumed that all equilibria are attained rapidly relative to the rate of appearance of the reaction products and that [S] >> [E], [B] > [E], $[S_f] \doteq [S]$; $[I_f] \doteq [I]$, $[B_f] \doteq [B]$, $d[ES]/dt \doteq 0$ and $d[BES]/dt \doteq 0$ then with $K_S = [E][S]/[ES]$, K_I^0[21] $= [E][I]/[EI]$, $K_{BE} = [B][E]/[BE]$, $K_{BES} = [B][ES]/[BES]$, $K_{BES'} = [BE][S]/[BES]$, $K_{BEI} = [BE][I]/[BEI]$ and $K_{BEI'} = [B][EI]/[BEI]$ it can be shown that $K_S K_{BES} = K_{BE} K_{BES'}$, $K_I^0 K_{BEI'} = K_{BE} K_{BEI}$ and $K_{BE} = K_S K_{BES}/K_{BES'} = K_I^0 K_{BEI'}/K_{BEI}$. From the relations $[E_f] = [ES]\,K_S/[S] = ([E] - [ES] - [EI] - [BE] - [BES] - [BEI])$ and $v_0 = -d[S]/dt = (k_3[ES] + k_{3'}[BES]) = (k_3 + k_{3'}[B]/K_{BES})[ES]$ we may derive equations 8, 9 and 10.

$$v_0 = \{(k_3 + k_3'[B]/K_{BES})[E]\}/\{1 + (K_S/[S])[1 + [I]/K_I^0 + [B]/K_{BE} + [B][I]/K_{BEI'}K_I^0] + [B]/K_{BES}\} \quad (8)$$

$$K_{BE} = [B]/\{[([E]/v)(k_3 + k_3'[B]/K_{BES}) - 1 - [B]/K_{BES}][[S]/K_S] - 1 - [I]/K_I^0 - [B][I]/K_{BEI'}K_I^0\} \quad (9)$$

$$K_{BEI'} = [B][I]/\{K_I^0\{[([E]/v)(k_3 + k_3'[B]/K_{BES}) - 1 - [B]/K_{BES}][[S]/K_S] - 1 - [I]/K_I^0 - [B]/K_{BE}\}\} \quad (10)$$

Since values of K_S are unaffected by the presence of B in the reaction system one is led to two conclusions, *i.e.*, either K_{BE} and K_{BES} are infinitely large relative to K_S and K_I^0 and hence there is little or no BE and BES formed, or K_S is equal to $K_{BES'}$ and there effectively is no difference between the path by way of ES to products and by way of BES to products. If one examines the latter case and assumes that K_S is equal to $K_{BES'}$ and that k_3 is equal to $k_{3'}$[22] then from the relation $K_{BE} = K_S K_{BES}/K_{BES'}$, K_{BE} may be considered as being equal to K_{BES}. Substituting K_{BE} for K_{BES} in equation 9 and solving for K_{BE} leads to equation 11. An approximate evaluation of equation 11, insofar as the experimental data permitted, indicated that values of K_{BE} will be extremely large relative to values of K_S and K_I^0. Thus, it may be assumed as a reasonable approximation that values of K_{BE}, K_{BES} and K_{BEI} will be so large that they may be ignored for the case at hand. If the validity of this assumption is granted we may regard equations 3, 5 and 6 as being of no practical significance and represent the situation under discussion by equations 1, 2, 4 and 7 where equations 1 and 4 are to be regarded as being equivalent, *vide ante*. It is now possible to simplify equation 8 and to obtain equation 12 which may then be solved for $K_{BEI'}$ as in equation 13.

$$K_{BE} = \{[B][k_3 - (v/[E])[(K_S/[S]) + 1]]\}/\{-k_3 + (v/[E])[1 + (K_S/[S])(1 + [I]/K_I^0 + [B][I]/K_{BEI'}K_I^0)]\} \quad (11)$$

$$v_0 = k_3[E]/\{1 + (K_S/[S])(1 + [I]/K_I^0 + [I][B]/K_I^0 K_{BEI'}\} \quad (12)$$

$$K_{BEI'} = [B]/\{(K_I^0/[I])\{(k_3[E][S]/v) - [S](1/K_S) - 1 - [I]/K_I^0\}\} \quad (13)$$

The experimental data obtained for the system α-chymotrypsin–acetyl-L-tyrosinamide–β-(β-indole)-propionate in the presence of varying amounts of potassium phosphate in systems of comparable ionic strength, *cf.* Table V, were then evaluated with the aid of equation 13 and the known values for the various kinetic constants. A value of $K_{BEI'} = 150 \pm 50 \times 10^{-3}\ M$ was obtained.

It should be noted that meaningful values of $K_{BEI'}$ cannot be obtained for low values of B because the anticipated small differences in values of v_0 would be well within the limits of error associated with the evaluation of K_I^0. It will also be noted that the value of $K_{BEI'}$ is large relative to values by K_I^0. Consequently, contributions of BEI will be quite small for low values of B. This is in agreement with the experimental observations given in Table V.

It is now possible to relate changes in the values of K_I to changes in the concentration of B. In the absence of inhibition by the hydrolysis products, *i.e.*, for initial rates, the velocity expression is given by equation 14. From equation 12 we may obtain equation 15. By equating equations 14 and 15 and solving for K_I we may obtain equation 16.

$$v_0 = k_3[E][S]_0/\{K_S(1 + [I]/K_I) + [S]_0\} \quad (14)$$

$$v_0 = k_3[E][S]/\{K_S(1 + [I]/K_I^0 + [I][B]/K_I^0 K_{BEI'} + [S]\} \quad (15)$$

$$K_I = K_I^0 + [B]/K_{BEI'} \quad (16)$$

Equation 16 yields values of K_I which are in reasonable agreement with the experimentally determined values of K_I, *cf.* Table VI. Thus it may be seen that for the case at hand the argument given above provides a satisfactory description of the inhibition of the α-chymotrypsin catalyzed hydroly-

TABLE VI

ENZYME-INHIBITOR DISSOCIATION CONSTANTS FOR AQUEOUS SOLUTIONS AT 25° AND *p*H 7.9 ± 0.1

Inhibitor	[B][a]	K_I[b] Expt.	K_I[b] Calcd.[c]
β-(β-Indole)-propionate	0.00	7.6 ± 0.4	7.6
	.0001	7.5 ± .5	7.6
	.001	8.0 ± .3	7.6
	.01	7.6 ± .4	7.1
	.04	6.6 ± .4	6.0
	.0725	5.1 ± .3	5.1
	.10	4.0 ± .4	4.5
	.20	3.2 ± .5	3.3
	.40	2.5 ± .3	2.1
Phenylacetate	.1	60 ± 5	65

[a] [B] = total concentration of phosphate in *M*. [b] In units of 10^{-3} *M*. [c] From equation 16 and $K_I^0 = 7.6 \times 10^{-3}$ *M*.

(21) K_I^0 is herein defined as the value of K_I observed in the absence of B but in systems in which the ionic strength is maintained at a level equivalent to those in which K_I is evaluated in the presence of varying amounts of B.

(22) There is at present no information available as to the effect of varying amounts of B upon k_3 at constant ionic strength.

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sis of acetyl-L-tyrosinamide by two representative bifunctional anionic competitive inhibitors in aqueous solutions at 25° and *p*H 7.9 ± 0.1 in the presence of varying amounts of potassium phosphate.

The authors wish to express their indebtedness to Drs. Robert Bock, Ralph Lutwack and Myron Arcand for many helpful suggestions and criticisms offered during the course of this investigation.

Experimental[23]

Specific Substrate and Competitive Inhibitors.—Acetyl-L-tyrosinamide, colorless needles, m.p. 226–228°, $[\alpha]^{24}D$ + 51.8° (*c* 0.8%, in water) was prepared as described previously.[9] β-(β-Indole)-propionic acid, colorless needles, m.p. 133–134°, was recrystallized twice from a mixture of water and methanol. β-(β-Indole)-propionamide, fine, stunted colorless needles, m.p. 205–207°, was prepared as described previously.[4] Phenylacetic acid, shiny platelets, m.p. 77–78°, was recrystallized three times from a mixture of ethanol and water. Phenylacetamide, short, colorless needles, m.p. 157–158°, was prepared as described previously.[4] Tryptamine hydrochloride, short dense colorless prisms, m.p. 250–251°, was recrystallized twice from aqueous 5 *N* hydrochloric acid.

Enzyme Experiments.—The analytical procedure described previously[9] was employed without modification. The anionic competitive inhibitors were introduced into the reaction mixtures in the form of their potassium salts. The buffer compounds were prepared as before.[9] Crystalline bovine α-chymotrypsin Armour lot no. 00592 was employed in all experiments. The primary data were evaluated as before.[9]

PASADENA, CALIFORNIA

(23) All melting points reported are corrected.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOPHYSICS, WEIZMANN INSTITUTE OF SCIENCE, AND THE UNIVERSITY LABORATORY OF PHYSICAL CHEMISTRY RELATED TO MEDICINE AND PUBLIC HEALTH, HARVARD UNIVERSITY]

The Availability of the Disulfide Bonds of Human and Bovine Serum Albumin and of Bovine γ-Globulin to Reduction by Thioglycolic Acid

BY EPHRAIM KATCHALSKI, GEORGE S. BENJAMIN AND VIOLET GROSS

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The extent of reduction of the disulfide bonds of human and bovine serum albumin and of bovine γ-globulin by thioglycolic acid at different *p*H values was investigated. Upon reduction human and bovine serum albumin acquired a maximum of one thiol group per molecule in the *p*H range 5.0 to 7.0. Beyond this range an increasing number of disulfide bonds became susceptible to reduction. In the case of bovine γ-globulin a maximum of one thiol group per molecule appeared upon reduction in the range of *p*H 3.5 to 5.0. With an increase in *p*H an increasing number of disulfide bonds could be reduced. The effect of *p*H on the number of disulfide bonds available for reduction was found to be reversible for bovine serum albumin and for bovine γ-globulin in the *p*H ranges of 1.2 to 10.2 and 5.0 to 10.2, respectively. In the three proteins investigated reduction of most of the disulfide bonds could be effected at *p*H values above 10 in the presence of guanidine. The conversion of unreactive disulfide bonds into reactive ones is explained as being due to changes in the configuration of the protein molecule, which may be either reversible or irreversible ones.

In contrast to the extensive literature dealing with the chemical reactivity of the thiol groups of native and denatured proteins,[1] only a few investigations on the reactivity of the disulfide groups of proteins have been published. Most of the work on the chemical reactivity of protein disulfide groups is concerned with their reduction which can be performed under mild experimental conditions. Reductions of the disulfide bonds of insulin,[2] keratin[3] and lactogenic hormone[4] have been reported. In the case of egg and serum albumin[5] and insulin[6] it was demonstrated that complete reduction of the disulfide bonds by thioglycolic acid can only occur after denaturation. The number of detectable –SH and S–S groups were found by Mirsky and Anson[7] to be closely linked with the extent of denaturation. On reversal of denaturation the number of detectable S–S groups decreased.

In the present article the reduction of the disulfide bonds of human and bovine serum albumin and of bovine γ-globulin by thioglycolic acid at different *p*H values will be described. The results obtained suggest that reversible as well as irreversible changes in the configuration of these proteins may occur.

Experimental

Materials.—Human serum albumin was prepared according to Cohn, *et al.*,[8] and crystallized three times in the presence of decanol. Its thiol content, determined by titration with methyl mercury nitrate (see below), was about 0.3 mole –SH per mole of albumin, assuming 65,000 as the molecular weight of the protein.[9] For the discussion below the value of 17 cystine residues per serum albumin molecule reported by Hughes[9] will be accepted.

Mercaptalbumin.—Mercury–mercaptalbumin dimer was prepared according to Hughes[10,11] and recrystallized five times before use. A pure aqueous solution of mercaptalbumin monomer was obtained from the mercury dimer according to the procedure of Dintzis.[12,13] Titration of the resulting concentrated mercaptalbumin solution with

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methyl mercury nitrate (see below) indicated that the mercaptalbumin regenerated contained 0.95 to 1.00 sulfhydryl groups per protein molecule assuming a molecular weight of 65,000.

Bovine serum albumin was obtained from Armour Laboratories, Lot No. 66706, and found to contain 0.25 to 0.35 sulfhydryl group per molecule assuming a molecular weight of 65,000.[9] Also in this case the presence of 17 cystine residues per molecule will be assumed.[9]

Bovine γ-globulin was obtained from Armour Laboratories, Lot B. P. 201–204. No sulfhydryl groups could be detected in this protein on titration with methyl mercury nitrate. The analytical data of Smith and Greene[14] show that the protein contains 18 cystine residues per molecule assuming a molecular weight of 150,000.[9]

Thioglycolic acid was obtained from Eastman Kodak Co. and distilled *in vacuo* before use.

Guanidine Reagent.—Concentrated hydrobromic acid (48%) was added to solid guanidine carbonate until the *p*H was neutral to Hydrion paper. The mixture was filtered and brought to *p*H 10 to 11 with anhydrous sodium carbonate. Solid ethylenediaminetetraacetic acid (Sequestrene, Alrose Chemical Co.) was added to make the solution 0.01 molar in this substance. The ethylenediaminetetraacetic acid was included to bind any traces of heavy metal ions which interfere with the nitroprusside reaction.[11] The final concentration of the guanidine hydrobromide was approximately 5 *M*.

Methyl Mercury Nitrate Solution.—Methyl mercury iodide was crystallized three times from ethanol and a weighed amount of the purified material dissolved in a minimal amount of 95% ethanol. The solution was mixed with an equivalent amount of silver nitrate which had been dissolved in a small volume of water. The precipitated silver iodide was filtered and washed thoroughly with water. The filtrate and washings were combined and diluted with water to give a 10^{-3} *M* methyl mercury nitrate solution. The 10^{-3} *M* methyl mercury nitrate solution could be stored without change for several months in a brown bottle at 0°.

Methods. Reduction of Protein Disulfide Bonds.—Protein solutions of approximately 8% were prepared. Water was used as solvent for human and bovine serum albumin and 2% aqueous sodium chloride for bovine γ-globulin. The desired *p*H was obtained by the addition of 0.1 *N* hydrochloric acid for values below the isoelectric point, of 4% aqueous sodium carbonate for values between the isoelectric point and *p*H 10, or of 1 *N* sodium hydroxide for *p*H values above 10. Protein concentration was then determined by Kjeldahl nitrogen analysis.

The protein solution (5 ml.) was mixed in a Thunberg tube with 0.2 *M* aqueous thioglycolate (5 ml.), previously adjusted to the *p*H of the protein solution, and with water (10 ml.). The resultant *p*H did not differ significantly from that of the component solutions. The reaction mixture was frozen in an ice–salt-bath and the tubes were evacuated and filled with oxygen-free nitrogen. This procedure was repeated three times to ensure complete removal of oxygen. The reduction was finally allowed to proceed at 0°. When the reduction was carried out in the presence of guanidine, a 5 *M* guanidine hydrobromide solution (10 ml.), previously adjusted to the required *p*H, was added to the protein–thioglycolate mixture instead of water.

The final reduction mixtures contained approximately 10 to 20 molecules of reducing agent per protein disulfide bond. The data of Bersin and Steudel[15] for the reduction of cystine seem to indicate that the excess of reducing agent used is adequate for the complete reduction of all available protein disulfide links in the *p*H range investigated.

Titration of Protein –SH Groups.—Sufficient protein to contain approximately 0.5 micromole –SH (*e.g.*, 50 mg. of albumin) was dissolved in 2 ml. of cold guanidine hydrobromide reagent. (Some proteins including serum albumin coagulate as a gel when treated in the dry state with concentrated guanidine salt solution. In such cases, it was advantageous to dissolve the protein first in a small amount, 0.5 ml. or less, of water or diluted guanidine reagent.) A drop of 10% $Na_2Fe(CN)_5NO$ was added and the solution was then titrated with 10^{-3} *M* methyl mercury nitrate to the disappearance of the purple color. The titration was carried out in the cold near 0°. If the solution was not properly cooled or if the titration was unnecessarily prolonged, the end-point was confused by a persistent orange or yellow color. The titration values obtained for a given sample did not deviate by more than 5% from their average.

The protein present in the reduction mixture was prepared for SH– analysis as follows: To an aliquot (2 ml.) of the reduction mixture, 3% trichloroacetic acid (10 ml.) was added and the precipitated protein was centrifuged. The supernatant containing excess thioglycolic acid was discarded and the precipitate resuspended in 3% trichloroacetic acid (10 ml.). The protein was again centrifuged and the procedure repeated five times. The final supernatant contained no thiol groups and the sulfhydryl content of the protein precipitated remained unaltered on further washing with 3% trichloroacetic acid.

Results

Reduction of Human Serum Albumin.—The course of reduction of human serum albumin at different *p*H values in the range of *p*H 3.0 to 10.0 is given in Fig. 1. The figure shows that at each

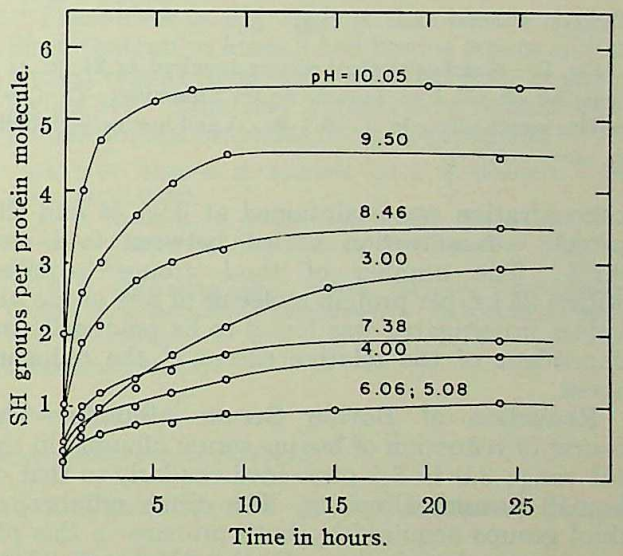

Fig. 1.—Course of reduction of human serum albumin at different *p*H values.

of the *p*H values investigated the number of thiol groups acquired per albumin molecule approached a final value within 24 hr. This value as a function of *p*H is given in Fig. 2, curve 1. The protein reduced in the *p*H range 5.0 to 7.0 was found to contain only one thiol group per molecule. Decreasing or increasing the *p*H of reduction beyond this range resulted in an increase in the number of thiol groups per molecule, the increase being greater in the alkaline range.

When mercaptalbumin was treated with thioglycolic acid in the *p*H range 5.0 to 7.0, no thiol groups in addition to the one originally present per molecule appeared. Furthermore a plot of the data obtained for mercaptalbumin over the whole *p*H range 3.0 to 10.0 gave a curve identical with that obtained with human serum albumin (Fig. 2, curve 1).

Reduction of human serum albumin in the presence of guanidine at *p*H 10.3 caused the appearance of 30 to 31 thiol groups per molecule as compared to the appearance of only 6 thiol groups per molecule at *p*H 10.0 in the absence of guanidine.

In order to ascertain whether the excess of thioglycolate used was sufficient to reduce all the susceptible disulfide bonds, reductions were carried out at *p*H 4.2, 6.0 and 8.45, where the thioglycolate

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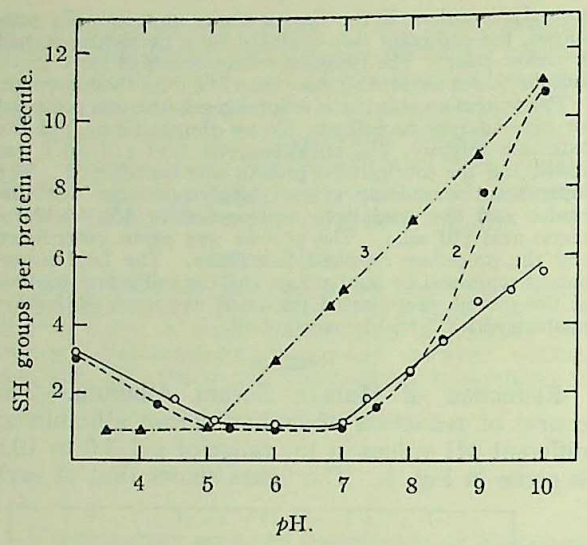

Fig. 2.—Number of thiol groups acquired in 24 hr. as a function of *p*H by: human serum albumin (—○—○—), bovine serum albumin (- - -●- - -●- - -) and bovine γ-globulin (·—▲·—·—▲·—).

concentration was maintained at 0.05 *M* and the protein concentration varied between 0.46 and 3.7%. The number of thiol groups acquired within 24 hr. per protein molecule at any of the *p*H values investigated was found to be practically independent of the relative excess of the reducing agent.

Reduction of Bovine Serum Albumin.—The course of reduction of bovine serum albumin in the *p*H range 3.0 to 8.5 proceeded similarly to that of human serum albumin. The final number of thiol groups acquired by both proteins in this *p*H range was also similar. In the *p*H range 8.5 to 10.0, however, bovine serum albumin acquired a considerably larger number of thiol groups than human serum albumin (see Fig. 2, curve 2). In the presence of guanidine approximately 26 thiol groups were acquired by bovine serum albumin upon reduction at *p*H 11.0. Denaturation of the protein leads therefore, as in the case of human serum albumin, to the exposure of most of the protein disulfide bonds to reduction.

To study whether the effect of *p*H on the availability of disulfide bonds to reduction is reversible, the following experiments were performed. Solutions of bovine serum albumin of various hydrogen ion concentrations were allowed to stand at 0° for different periods of time. The *p*H was then adjusted to 6.0 and the protein reduced with thioglycolate as already described. It was found (Table I) that samples of bovine serum albumin kept at *p*H ranges 1.2 to 3.5 and 8.1 to 10.2 acquired on reduction approximately one thiol group per albumin molecule. As the same number of thiol groups was obtained upon the reduction of freshly prepared protein solutions at *p*H 6.0, it can be concluded that the changes in the albumin molecule in the above acidic and basic ranges are reversible. Samples which were kept at *p*H 13.0 for as little as 1.5 hr. acquired on reduction at *p*H 6.0 four SH-groups per albumin molecule. This indicates that at *p*H 13.0 an irreversible change occurred. A similar irreversible change, but to a somewhat lesser extent, occurred at *p*H 11.0 and 11.9.

TABLE I

THE EXTENT OF REDUCTION OF BOVINE SERUM ALBUMIN AT *p*H 6.0 AFTER PRIOR EXPOSURE TO DIFFERENT *p*H VALUES

*p*H Prior to reduction[a]	Time of exposure, hours	SH/protein molecule after reduction[b]
1.2	24	0.85
1.7	24	.90
2.35	24	.94
3.5	24	.98
8.1	24	.95
9.0	24	.99
9.6	2.5	.95
10.2	24	1.00
11.0	2	0.97
11.0	6.5	1.00
11.0	24	1.35
11.9	3	1.10
11.9	24	1.80
13.0	1.5	4.03
13.0	6.0	4.80

[a] Concentration of albumin 6.5 to 7.0% (w./v.). [b] The reduction mixture contained approximately 2% albumin and thioglycolic acid at a 0.05 *M* concentration. The values given were obtained after reduction at *p*H 6.0 for 24 hr.

Reduction of Bovine γ-Globulin.—The rate of reduction of bovine γ-globulin was as a rule somewhat faster than that of human or bovine serum albumin. The maximum number of thiol groups acquired on reduction with thioglycolic acid at different *p*H values is recorded in Fig. 2, curve 3. In the *p*H range 5.0 to 10.0 the number of protein –SH groups increased almost linearly with *p*H. In the *p*H range 3.5 to 5.0 only one thiol group per protein molecule was found. At *p*H 10.0 in the presence of guanidine hydrobromide 20 to 22 sulfhydryl groups per γ-globulin molecule appeared.

Experiments to study the reversibility of the exposure of disulfide bonds of bovine γ-globulin to reduction analogous to those carried out with bovine serum albumin were performed. The protein was kept in solution at 0° for 24 hr. at *p*H values in the range of *p*H 5.0 to 12.0. The *p*H of the aqueous solutions was then adjusted to *p*H 5.0 and the reduction with thioglycolate carried out as usual. The samples thus treated in the *p*H range 5.5 to 10.2 acquired on reduction at *p*H 5.0 approximately one thiol group per globulin molecule. The exposure of disulfide bonds of γ-globulin in the above *p*H range is therefore reversible. Bovine γ-globulin samples exposed to *p*H 12.0 for only 2 hr. acquired on reduction at *p*H 5.0, 3.5 SH–groups per molecule, indicating that an irreversible change occurred.

Discussion

The results reported above show that each of the three proteins investigated is characterized by a *p*H range at which no significant reduction of disulfide bonds by thioglycolic acid takes place. Beyond this region the number of disulfide bonds susceptible to reduction increases. The change in reactivity of the protein disulfide groups toward thioglycolic acid may be explained by assuming a change in the shape and configuration of the protein mole-

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cule transforming chemically unreactive groups to chemically active ones.

Extensive unfolding of the peptide chains of native proteins caused by the breaking up of intramolecular hydrogen bonds is known to take place in the presence of denaturing agents such as urea and guanidine.[1] Such a far reaching change in the configuration of the protein molecule would explain the result obtained where in the presence of guanidine at *p*H 10 most of the disulfide bonds of each of the three proteins investigated were reduced.

The respective *p*H ranges at which human and bovine serum albumin and bovine γ-globulin were found to have a minimal number of disulfide bonds available for reduction correspond to those *p*H ranges where these proteins are known to have a relatively small net electrical charge. Increasing the acidity or alkalinity beyond this *p*H range led to an increase in the number of disulfide bonds reduced. This suggests that increasing the net electrical charge leads to some unfolding of the protein molecule due to electrostatic repulsion thereby exposing a few disulfide bonds to reduction. The observed reversal of the number of disulfide bonds available for reduction implies that the change in configuration of bovine serum albumin in the *p*H range 1.2 to 10.2 (see Table I) and of bovine γ-globulin in the *p*H range 5.0 to 10.2 are reversible.

Similarly, other investigators have concluded that bovine serum albumin can undergo reversible configurational changes within limited *p*H ranges. Klotz, *et al.*,[16] observed that the binding of anionic dyes by this protein is reversible and increases from *p*H 6.8 to 9.2. This was explained as being due to a reversible change in the intramolecular bonding of the protein leading to the exposure of new side chains capable of interaction within the specific dye molecules. Tanford[17] found that the electrostatic interaction factor w decreases for bovine serum albumin from *p*H 5.0 to 2.5. The decrease in w was interpreted to be the result of a corresponding increase in the radius of the molecule. Champagne and Sadron[18] measured the viscosity and diffusion of bovine serum albumin over the *p*H range 3.5 to 10.0. From the data obtained they concluded that the shape of the molecule undergoes a reversible change from a sphere at its isoelectric point, *p*H 5.3, to an elongated ellipsoid of revolution in the *p*H ranges 5.3 to 3.45 and 5.3 to 7.4.

The curves in Fig. 2 show that bovine γ-globulin in contrast to human and bovine serum albumin already exists in a partially unfolded state at physiological *p*H. This may somehow be related to the immunological functions of the γ-globulins.

(16) I. M. Klotz, R. K. Burkhard and J. M. Urquhart, *J. Phys. Chem.*, **56**, 77 (1952).

(17) C. Tanford: T. Shedlovsky, Editor, "Electrochemistry in Biology and Medicine," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 248.

(18) M. Champagne and C. Sadron, "Simposio Internazionale di Chimica Macromoleculare," Supplemento a "La Ricerca Scientifica," Anno 25°, 1955, p. 3.

REHOVOTH, ISRAEL

[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

The Carbonyl Absorption of Carbamates and 2-Oxazolidones in the Infrared Region

BY S. PINCHAS AND D. BEN-ISHAI

RECEIVED JANUARY 28, 1957

The data for the C=O frequency in 21 carbamates show that each type of a carbamic group has its own characteristic absorption region. Primary carbamates, both in the solid phase and in solution in chloroform, absorb at 1725 ± 3 cm.$^{-1}$. Secondary carbamates absorb at 1705–1722 and tertiary at 1687 ± 4 cm.$^{-1}$. The C=O frequency of the carbamic group in linear carbamates with a cyclic nitrogen atom depends upon the electronic effects of the ring and its substituents. Fourteen 2-oxazolidones showed their cyclic carbamic C=O frequency at 1746–1810 cm.$^{-1}$. An appreciable absorption band at 1029–1059 cm.$^{-1}$ is characteristic for the 2-oxazolidone ring.

Although the carbonyl absorption band of the carbamates, $R_1R_2N\text{-}\overset{\overset{O}{\|}}{C}\text{-}OR_3$, has already been reported to appear in the 1690–1736 cm.$^{-1}$ region,[1] only two exact values for this frequency in the case of simple carbamates could be found in the literature[2] these being 1661 cm.$^{-1}$ for an oil paste of ethyl carbamate (urethan) and 1706 cm.$^{-1}$ for a liquid layer of ethyl N-methylcarbamate (methylurethan). Recently the carbonyl frequency of various esters of phenylcarbamic acid (phenylurethans) was measured[3] and was also found to be in this region being about 40 cm.$^{-1}$ higher than in anilides.

Since simple amides can usually be recognized as primary, secondary or tertiary amides from the frequency of their C=O stretching vibration in dilute non-polar solutions, this frequency appearing at about 1690, 1680 and 1650 cm.$^{-1}$, respectively,[4] it was interesting to see whether a parallel regularity could also be found for the similar carbamates. In view of the already mentioned lack of data for the carbonyl frequency in individual simple carbamates, their measurement seemed worth while and, since a series of such compounds was at our disposal, this measurement was undertaken.

Table I summarizes the results obtained for the carbamic carbonyl group frequency in 21 various carbamates.

(1) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen & Co., London, 1954, p. 191; (b) H. Thompson, D. Nicholson and L. Short, *Discussions Faraday Soc.*, **9**, 229 (1950).

(2) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, pp. 157–159.

(3) (a) N. F. Hayes, R. H. Thomson and M. St. C. Flett, *Experientia*, **11**, 61 (1955); (b) D. A. Barr and R. N. Haszeldine, *J. Chem. Soc.*, 3428 (1956).

(4) R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1248 (1947).

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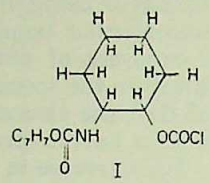
TABLE I

THE INFRARED FREQUENCY OF THE CARBAMIC CARBONYL GROUP STRETCHING VIBRATION IN VARIOUS CARBAMATES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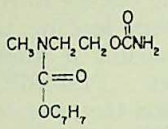
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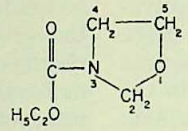
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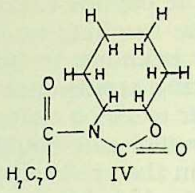
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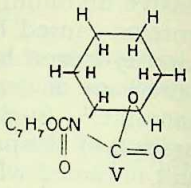
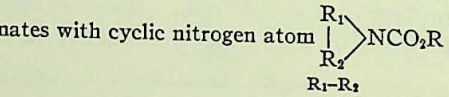
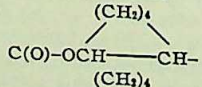
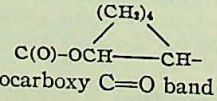

V

No.	Material	R	R_1	R_2	Concn., g. + ml.		Frequency, $cm.^{-1}$
	Primary carbamates: NH_2COOR						
1	Ethyl carbamate	C_2H_5	.....	.....	0.21	1 $CHCl_3$	1725
					Oil paste		1728
2	Benzyl carbamate	C_7H_7	.....	.....	.04	1 $CHCl_3$	1724
3	2-Aminoethyl carbamate hydrobromide	$CH_2CH_2NH_2HBr$	.....	.....	Oil paste		1726
4	2-Carbobenzyloxyaminoethyl carbamate	$CH_2CH_2NHCOOC_7H_7$	.....	.....	Low and unknown; in $CHCl_3$		1718
	Secondary carbamates: NHR_1COOR						
5	N-Carboxyglycine dibenzyl ester	C_7H_7	$CH_2COOC_7H_7$	.....	0.12	1 $CHCl_3$	1714
					Oil paste		1715
6	Ethyl N-(2-hydroxyethyl)-carbamate	C_2H_5	CH_2CH_2OH	.....	0.043	1 CCl_4	1705
7	N_1-Carbobenzyloxyglycine-N_2-(2-chloroethyl)-amide	C_7H_7	$CH_2CONHCH_2CH_2Cl$	.....	In $CHCl_3$		1715[a]
8	2-Carbobenzyloxyaminocyclohexyl-chlorocarbonate (I)	C_7H_7	$C_6H_{10}OCOCl$	.....	0.11	1 $CHCl_3$	1722[b]
	Tertiary carbamates: NR_1R_2COOR						
9	Ethyl dimethylcarbamate	C_2H_5	CH_3	CH_3	0.054	1 $CHCl_3$	1684
10	Benzyl methyl-2-chloroethylcarbamate	C_7H_7	CH_3	CH_2CH_2Cl	.11	1 $CHCl_3$	1691
11	N-Carbobenzyloxy-N-methyl-2-aminoethyl carbamate (II)	C_7H_7	CH_3	$CH_2CH_2OCONH_2$	.046	1 $CHCl_3$	1687, 1722
	Linear carbamates with cyclic nitrogen atom 			R_1–R_2			
12	N-Carboethoxy-1,3-oxazolidine (III)	C_2H_5		CH_2–OCH_2CH_2–	0.05	1 CCl_4	1706
13	N-Carboethoxy-2-pentamethyleno-1,3-oxazolidine	C_2H_5		C_6H_{10}–OCH_2CH_2–	.068	1 $CHCl_3$	1678
14	N-Carbopropoxy-2-pentamethyleno-1,3-oxazolidine	C_3H_7		C_6H_{10}–OCH_2CH_2–	.10	1 $CHCl_3$	1678
15	N-Carboethoxy-2-oxazolidone	C_2H_5		C(O)–OCH_2CH_2–	.05	1 $CHCl_3$	1722
16	N-Carbopropoxy-2-oxazolidone	C_3H_7		C(O)–OCH_2CH_2–	.042	1 $CHCl_3$	1718
17	N-Carboallyloxy-2-oxazolidone	C_3H_5		C(O)–OCH_2CH_2–	.050	1 $CHCl_3$	1718
18	N-Carbobenzyloxy-2-oxazolidone	C_7H_7		C(O)–OCH_2CH_2–	.073	1 $CHCl_3$	1726
19	N-Carbo-*p*-nitrobenzyloxy-2-oxazolidone	$C_7H_6NO_2$		C(O)–OCH_2CH_2–	.036	1 $CHCl_3$	1731
20	N-Carbobenzyloxy-*cis*-4,5-tetramethyleno-2-oxazolidone (IV)	C_7H_7			.095	1 $CHCl_3$	1720
21	N-Carbobenzyloxy-*trans*-4,5-tetramethyleno-2-oxazolidone (V)	C_7H_7			.070	1 $CHCl_3$	1726

[a] Shows the amide C=O band at 1675 $cm.^{-1}$. [b] Shows the chlorocarboxy C=O band at 1768 $cm.^{-1}$.

Discussion

It can be seen from Table I that, as in the case of amides, the different classes of simple carbamates, primary, secondary and tertiary, may in fact be identified by their characteristic carbonyl frequency. Thus, a frequency of 1725 ± 3 $cm.^{-1}$ is common to all the primary carbamates reported here, a frequency of 1714 ± 9 $cm.^{-1}$ (1722–1705 $cm.^{-1}$) is typical for all the secondary carbamates and a value of 1687 ± 4 $cm.^{-1}$ represents the frequency of all the tertiary carbamates. The somewhat wide limits of the secondary carbamate frequency region are caused by having them include two secondary carbamates in which two special effects are operating to respectively increase and decrease the normal carbonyl frequency. If these cases are ignored, the limits can be set as 1714 ± 3 $cm.^{-1}$ but then only on the basis of two examples. In the case of the primary–secondary carbamate (no. 4) there appears only one carbonyl band as can be expected from the nearness of the characteristic ranges for the primary and secondary carbamic groups, which probably causes the merging together of the two carbonyl absorptions. The united carbonyl band would be expected to occur about half way between 1714 and 1725 $cm.^{-1}$, in good agreement with the observed value of 1718 $cm.^{-1}$. In the case of the primary–tertiary carbamate (no. 11) the interval between the corresponding regions is bigger, and the two absorptions appear therefore as two separate bands at 1687 and 1722 $cm.^{-1}$.

The value of 1728 $cm.^{-1}$ found here for the carbonyl group absorption of an oil paste of ethyl carbamate is in line with that obtained for an oil paste of the similar compound no. 3 (1726 $cm.^{-1}$) and agrees with the value of 1725 $cm.^{-1}$ obtained for it in solution as well as with the value of 1724 $cm.^{-1}$

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of benzyl carbamate in solution. This value contradicts, however, the value of 1661 cm.$^{-1}$ given by Randall, *et al.*,[2] for the C=O frequency of an oil paste of ethyl carbamate (urethan), although their spectrum also shows a shoulder at 1730 cm.$^{-1}$, which after subtracting the atmospheric water vapor absorption in this region may turn out to be a strong band. It is true that an oil paste (but not a chloroform solution) of ethyl carbamate shows also strong and diffuse bands at about 1662 and 1614 cm.$^{-1}$, but none of these can be ascribed to the C=O frequency as can be judged from the values cited above for this frequency in similar compounds. Another argument against such an assignment is that in analogy to amides[4] one must assume the primary carbamate C=O group to absorb at a higher frequency than the C=O group of secondary and tertiary carbamates because of a stronger contribution from the resonating structure VI to the actual structure of the carbamates in the

$$R_1R_2N^+=C-OR_3$$
$$\qquad\quad |$$
$$\text{VI}\qquad O^-$$

latter case. It can be seen from Table I that this is the case if we assign, as was done above, the 1725 cm.$^{-1}$ band to the C=O stretching vibration of primary carbamates. If, however, the 1662 cm.$^{-1}$ band is assigned to this stretching vibration, then the primary carbamate C=O absorption is not higher than the secondary and tertiary carbamate C=O absorption at 1714 and 1687 cm.$^{-1}$, respectively, but lower. This 1662 cm.$^{-1}$ band also cannot be due to a strongly hydrogen bonded C=O frequency of the solid state since the C=O oil paste frequency of N-carboxyglycine dibenzyl ester (no. 5; see also no. 3) appearing at 1715 cm.$^{-1}$ is not materially different from the solution frequency while it is still mainly due to the carbamic group as can be judged from the fact that there is no other remarkable band down to 1530 cm.$^{-1}$. This means that in contradistinction to the amidic groups[4] the carbamic groups are not much affected by hydrogen bonding. This might be due to the lower polarization of its C=O double bond because of the electronegative effect of the neighboring OR group and has its analogy in ketones, the C=O frequency of which is also only slightly affected by ordinary hydrogen bonds.[5] The 1662 and 1614 cm.$^{-1}$ bands (Randall, *et al.*,[2] give 1661 and 1618 cm.$^{-1}$) seem therefore to stem from a splitting of the carbamic N–H group bending frequency because of the presence of two such hydrogen atoms here, the corresponding frequency in the case of solid primary amides[4] being shown at 1620–1650 cm.$^{-1}$. Such a splitting of a vibration because of a doubling of the vibrating unit on the same atom is very common.[6] In a chloroform solution these bands move to lower frequencies and unite in a broad band centered at about 1590 cm.$^{-1}$. This fact supports the above assignment, for the primary amide N–H band also behaves similarly by moving to about 1600 cm.$^{-1}$ in solution.[4] The Raman band observed for this substance in the melted form[7] at about 1692 cm.$^{-1}$ (besides a band at 1606 cm.$^{-1}$) may be a joint band made up of the bands at about 1728 and 1662 cm.$^{-1}$.

The value of 1714 ± 9 cm.$^{-1}$ found here for the C=O frequency in secondary carbamates agrees with the value of 1706 cm.$^{-1}$ given by Randall, *et al.*,[2] for ethyl N-methylcarbamate and with the value of 1704 cm.$^{-1}$ found by Baker and Joseph[3] in the case of an oil paste of a complex secondary carbamate which contains a hydroxy group in a γ-position to the carbonyl group. The somewhat lower carbonyl frequency in this case, relative to the usual frequency of about 1714 cm.$^{-1}$, as also in the case of compound 6, is probably the result of an internal hydrogen bond between the γ-hydroxy group and the carbonyl group (chelation). The small increase in the C=O frequency of I (no. 8) —1722 cm.$^{-1}$—seems to be due to the strong negative inductive effect of the chlorocarboxy group on the carbamic C=O group polarization. The even higher frequencies of this group observed by Randall, *et al.*,[2] in various substituted carbamates (*e.g.*, ethyl methoxycarbamate (methoxyurethan), 1727 cm.$^{-1}$; ethyl N-α-toluylcarbamate (phenacetylurethan), 1748 cm.$^{-1}$) must also be explained similarly, the effect of the substituents being here stronger because of their direct bond to the nitrogen atom. The frequencies of 1727 and 1745 cm.$^{-1}$ observed[3b] for the C=O group (in the undiluted phase) of ethyl N-trifluoromethylcarbamate and ethyl N-heptafluoropropylcarbamate, respectively, are probably fully analogous.

Thus it is clear that the C=O frequency of simple secondary carbamates appears at about 1715 cm.$^{-1}$ both in solution in chloroform and in the solid phase. This value contradicts the figures of 1735 and 7000 (probably a misprint for 1700) cm.$^{-1}$ reported by Thompson, *et al.*,[1b] for the C=O band in secondary urethans in chloroform solution and the liquid or solid phase, respectively (without giving any actual value). The values given by Thompson, *et al.*,[1b] for the C=O absorption of primary and tertiary urethans in chloroform solution are, however, in good agreement (1728 and 1690 cm.$^{-1}$, respectively) with the results reported above. Their value of 1690 cm.$^{-1}$ for undiluted primary urethans seems again to be due to non-resolution of the broad bands at about 1725 and 1660 cm.$^{-1}$.

The NH bending frequency appeared at 1530 cm.$^{-1}$ in an oil paste of compound 5 (Thompson, *et al.*,[1b] give 1540 cm.$^{-1}$ for a N–H bending in the solid or liquid phase of secondary urethans; see also ref. 3a) and at 1512 cm.$^{-1}$ in chloroform solution (Thompson, *et al.*, 1530). Compound 6 showed this band in carbon tetrachloride solution at 1516 cm.$^{-1}$, compound 7 showed a broad N–H bending absorption at 1514 cm.$^{-1}$ in $CHCl_3$ (both an amidic and a carbamic band) and compound 8 showed it (in $CHCl_3$) at 1509 cm.$^{-1}$. The corresponding amidic band appears[9] in solution at 1550–1510 cm.$^{-1}$ and in the solid phase at 1570–1515 cm.$^{-1}$.

(5) R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, THIS JOURNAL, 71, 1068 (1949).
(6) See, *e.g.*, E. D. Bergmann and S. Pinchas, *Rec. trav. chim.*, 71, 161 (1952).
(7) J. Wagner, *Z. physik. Chem.*, B43, 333 (1939).
(8) B. R. Baker and J. P. Joseph, THIS JOURNAL, 77, 15 (1955).
(9) Reference 1, p. 170.

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The value of 1687 ± 4 cm.$^{-1}$ for the frequency of the tertiary carbamates means that while the first alkyl group introduced into the primary carbamate molecule decreases its frequency by about 10 cm.$^{-1}$ only, the second alkyl group decreases it by about 25 cm.$^{-1}$. The same phenomenon is also shown by amides in dilute solution as can be judged from the values of 1690 (primary), 1680 (secondary) and 1650 cm.$^{-1}$ (tertiary).[4] The reason for this behavior is difficult to see but may be connected with the direction of the positive inductive effect of the alkyl groups (which increases the contribution of the polar form VI to the actual structure of the carbamate molecule). Thus, because of the pyramidal form of the trivalent nitrogen atom[10] (with the lone pair of electrons above it), this effect is directed, in monoalkyl carbamates, not toward the N–CO bond but at an angle to it, while in dialkylcarbamates the resultant of the effects of the two alkyl groups is (taking in account its projection on the basal plane) in this direction and is therefore much more efficient in increasing the contribution of the resonating structure VI to the structure of the tertiary carbamates.

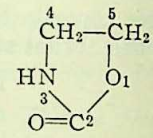
If the results for the linear carbamates which contain a cyclic nitrogen atom are examined, it can be seen that their C=O frequency reflects clearly the electronic effects of their substituents, especially those in the 2-position of the oxazolidine ring. Thus, N-carboethoxy-1,3-oxazolidine, which bears no substituent in this position, absorbs at 1706 cm.$^{-1}$ while its 2-pentamethylene derivative (as also the similar compound 14) absorbs at 1678 cm.$^{-1}$. This decrease in frequency is probably the result of the positive inductive effect of the 5 methylene groups, attached in the latter case to the 2-carbon atom, which strengthens the polarization of the carbonyl group. The reason for the value of 1706 cm.$^{-1}$ for N-carboethoxy-oxazolidine itself which is higher than that of ordinary tertiary carbamates (1687) seems to be its $-CH_2O-$ group, attached to the nitrogen atom, which probably does not possess a positive inductive effect. This compound should therefore be looked at, in this respect, as a secondary, rather than tertiary, carbamate which absorbs in this region.

In the case of the N-carboalkoxy-2-oxazolidones, the substituent in the 2-position (the oxygen atom) has a strong negative inductive effect, and therefore an increase of their carbamate carbonyl frequency must be expected. Indeed, all the oxazolidonic carbamates measured (no. 15–21) show this band in the higher frequency range of 1718–1731 cm.$^{-1}$. This value may be compared with the value of 1736 cm.$^{-1}$ obtained by Randall, *et al.*,[2] for the carbamic C=O frequency of the somewhat similar ethyl methylbenzoylcarbamate. It is interesting to note that the highest frequency is observed with the *p*-nitrobenzyl ester where there exists an appreciable electron attraction away from the carbamic C=O group. This attraction would of course tend to increase the bond strength of this carbonyl group.

The 2-Oxazolidone C=O Absorption.—If the carbamic ester grouping is part of a five-membered ring, *e.g.* in 2-oxazolidones, then an additional factor must be taken into account when its C=O frequency is considered. This factor is the strain of such a five-membered ring which as a rule increases its exocyclic stretching frequencies.[11] This strain is apparent in the C=O frequency of γ-lactones which rises to about 1770 cm.$^{-1}$ as compared with the value of about 1740 cm.$^{-1}$ in the case of esters and six-membered lactones.[12] The C=O frequency of oxazolones is also very high,[13] at about 1820 cm.$^{-1}$, partly because of this strain. Thus the C=O frequency of simple 2-oxazolidones would already be expected to be quite high, while in N-acetylated oxazolidones this frequency would be expected to rise even more. Table II shows that this is really the case.

TABLE II

THE FREQUENCY OF THE 2-OXAZOLIDONE C=O STRETCHING VIBRATION



Material	Concn. g. + 1 ml. $CHCl_3$[a]	Frequency, cm.$^{-1}$	Bands in 1100–1000 cm.$^{-1}$ region
2-Oxazolidone	0.056	1760(broad)	1085, 1029
4-Dimethyl-	.034	1748	1043
N-Methyl-	.05	1746	1049
N-Phenyl-	.031	1753	1053
N-Acetyl-	.056	1785[b]	1057, 1038
N-Benzoyl-	.050	1793[c]	1100, 1041
N-Carboethoxy-	.050	1798	1079, 1043
N-Carbopropoxy-	.042	1795	Not measured
N-Carboallyloxy-	.050	1805	Not measured
N-Carbobenzyloxy-	.073	1810	1085, 1039
N-Carbo-*p*-nitro benzyloxy-	.036	1798	Not measured
4,5-Tetramethyleno-2-oxazolidones			
N-Benzoyl-	0.048[e]	1791[d]	1099, 1059
N-Carbobenzyloxy-*cis*- (IV)	.095	1807	1073, 1033
N-Carbobenzyloxy-*trans*- (V)	.070	1807	1090, 1037

[a] Unless otherwise stated. [b] The amidic CO group absorbs at 1695 cm.$^{-1}$. [c] The amidic CO group absorbs at 1679 cm.$^{-1}$. [d] The amidic CO group absorbs at 1677 cm.$^{-1}$. [e] 1 ml. CCl_4.

It is interesting to note that N-methyloxazolidone absorbs at a lower frequency than oxazolidone (1746 as compared with 1760 cm.$^{-1}$) as can be expected from the inductive effect of the N-methyl group. The high polarization of N-methyloxazolidone, as evidenced by its high electric moment,[14] would also suggest that its CO frequency is not relatively high. This decrease in frequency is especially remarkable because of the stable hydrogen bonded dimer form of 2-oxazolidone (VII) which persists even in dilute solution,[14] since such a structure would probably diminish considerably the

(10) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," new ed., Oxford University Press, Oxford, 1942, p. 30.

(11) P. Bladon, J. M. Fabian, H. B. Henbest, H. B. Koch and G. W. Wood, *J. Chem. Soc.*, 2410 (1951).

(12) J. F. Grove and H. A. Willis, *ibid.*, 877 (1951).

(13) H. W. Thompson, R. R. Brattain, H. M. Randall and R. S. Rasmussen, "The Chemistry of Penicillin," Princeton Univ. Press, Princeton, N. J., 1940, p. 400.

(14) E. Fischer, *J. Chem. Soc.*, 4525 (1952).

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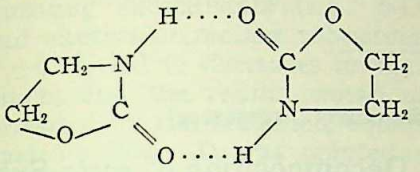
C=O frequency of oxazolidone from its "free" value. It must be added that when methyl oxazolidone was measured in a carbon tetrachloride solution and not in chloroform (which is known to



VII

decrease the C=O frequency of the materials dissolved in it[15]), it showed this band at about 1760 cm.$^{-1}$.

The value of 1724 cm.$^{-1}$ is reported in the literature[16] for the CO frequency of 2-oxazolidone in the solid phase.

The case of 4-dimethyloxazolidone seems to be similar and here also a stable dimer must be expected with an accompanying decrease in the C=O frequency. The further decrease of this frequency in this case (1748 as compared with 1760 cm.$^{-1}$ for oxazolidone) probably is due to the positive inductive effect of the two neighboring methyl groups on the nitrogen atom, in analogy to the effect of the pentamethylene group in the case of carbamates 13 and 14 (see above).

The relatively low C=O frequency of N-phenyloxazolidone (1753 cm.$^{-1}$) is also remarkable, especially since in anilides the phenyl ring has an opposite effect.[1a] In N-phenyl carbamates, however, the C=O frequency observed in the solid phase was also relatively low (1690–1720 cm.$^{-1}$).[3a]

In comparison with the oxazolidonic C=O frequency, that of 2-pyrrolidone and N-methyl-2-pyrrolidone was also measured. Pyrrolidone showed the CO band in carbon tetrachloride solution (0.046 g. + 1 ml.) at 1678 cm.$^{-1}$ and N-methylpyrrolidone, in chloroform, at 1688 cm.$^{-1}$. 2-Pyrrolidone is known to form hydrogen bonded dimers even in dilute solutions[17] and its lower frequency is therefore understandable. Mecke and Mecke[16] give the value of 1690 cm.$^{-1}$ for this frequency in the liquid phase and 1706 cm.$^{-1}$ for a 0.05–0.1 mole per liter solution in CCl_4. The last value seems to be due to the "free" molecule which is probably present in this dilution. The much lower frequency of N-methylpyrrolidone, relative to that of N-methyloxazolidone (1746 cm.$^{-1}$), seems to suggest a much larger ionic character in the former case as is the case in amides in general. This assumption, however, is at variance with the present view[14,18] based on electric moment measurements. It must also be pointed out that in going over from an open structure to a five-membered ring the tertiary carbamates suffer the biggest increase in the CO frequency. Thus the increase in this case is about 60 cm.$^{-1}$ as compared with about 45 cm.$^{-1}$ for secondary carbamates, 40 cm.$^{-1}$ for tertiary amides and 30 cm.$^{-1}$ for saturated esters.

(15) See, *e.g.*, K. Dobriner, E. R. Katzenellenbogen and R. N. Jones, "Infrared Absorption Spectra of Steroids," Interscience Publishers, Inc., New York, N. Y., 1953, p. ix.
(16) R. Mecke and R. Mecke, *Ber.*, **89**, 343 (1956).
(17) E. Fischer, *J. Chem. Soc.*, 1382 (1955).
(18) E. Fischer, *ibid.*, 2836 (1953).

The acyl groups can again be observed, in Table II, to increase appreciably the C=O frequency, this effect being highest in the case of the aromatic acyl derivatives (*e.g.*, N-benzoyl-oxazolidone, 33 cm.$^{-1}$), maybe because of the higher polarization of the acylic C=O group in this case. The still higher oxazolidonic C=O range (1795–1810 cm.$^{-1}$) of the N-carboalkoxy-oxazolidones is to be expected in the light of the increased electron attraction power of the carboalkoxy group.

Apart from the oxazolidone C=O frequency another band seems to be characteristic for the oxazolidonic ring. This medium-strong band appears at 1029–1059 cm.$^{-1}$ in all the measured compounds containing such a ring, as can be seen from Table II. Sometimes this band is split into two branches. These bands seem to be due to the C–OC(O) ring stretching vibrations in analogy to the antisymmetrical ring stretching band of tetrahydrofuran[19] at about 1080 cm.$^{-1}$ and to the N–C–O stretching bands at about 1160, 1130 and 1100 cm.$^{-1}$ of oxazolidines.[20] The Raman band found in solid primary carbamates[7] at about 1120 cm.$^{-1}$ may be the counterpart of this band in the case of the open NC(O)O–C group. The decrease in the stretching frequency of the C–OR bond when this is part of a strained ring is then the usual behavior of such (endocyclic) bonds.[11]

Experimental

The infrared absorption measurements were carried out with a Perkin–Elmer, model 12C, infrared spectrometer equipped with a sodium chloride prism. The synthesis of most of the materials used in this investigation has already been described by Ben-Ishai.[21] The rest of them were either of commercial origin or synthesized according to the literature.

Ethyl carbamate, showed (in solution) also bands at: 3370, 1589, 1468, 1403, 1373, 1324, 1237, 1170, 1061, 985, 956, 889 and 849 cm.

2-Aminoethyl carbamate hydrobromide showed (in an oil paste) the NH_3^+ bands at 1970 and 1920 cm.$^{-1}$ (besides a band at about 3200 cm.$^{-1}$.

2-(Carboethoxyamino)-ethanol showed (in CCl_4 solution) also bands at 3360, 2930, 1516, 1379, 1330, 1248, 1081 and 1036 cm.$^{-1}$.

Carbobenzyloxyglycine-(2-chloroethyl)-amide showed also bands (in $CHCl_3$) at 1514, 1452, 1355, 1261, 1049 and 981 cm.$^{-1}$.

N-Carboethoxy-2-pentamethyleno-1,3-oxazolidine showed (in $CHCl_3$) also bands at 1425, 1379, 1349, 1330, 1277, 1175, 1139, 1073, 1037, 973, 946, 910 and 844 cm.$^{-1}$.

N-Carbopropoxy-2-pentamethyleno-1,3-oxazolidine showed (in $CHCl_3$) also bands at 1452, 1419, 1363, 1341, 1324, 1280, 1237, 1132, 1072, 1024, 978, 942, 910 and 843 cm.$^{-1}$.

N-Carboethoxy-2-oxazolidone showed (in $CHCl_3$) also bands at 1477, 1385, 1307, 1184, 1079 and 1043 cm.$^{-1}$.

N-Carbobenzyloxy-2-oxazolidone showed (in $CHCl_3$) also bands at 3475, 2925, 1590, 1462, 1386, 1315, 1085, 1039, 981 and 908 cm.$^{-1}$.

2-Oxazolidone showed (in $CHCl_3$) bands also at 3440, 3290, 3160, 2925, 1484, 1399, 1332, 1320, 1246, 1085, 1029, 960 and 924 cm.$^{-1}$.

4-Dimethyl-2-oxazolidone showed (in $CHCl_3$) bands also at 3440, 3240, 1466, 1377, 1294, 1235, 1043, 986 and 937 cm.$^{-1}$.

N-Phenyloxazolidone showed (in $CHCl_3$) bands also at 2930, 1599, 1487, 1406, 1309, 1130, 1053, 991, 955 and 899 cm.$^{-1}$.

N-Acetyloxazolidone showed also (in $CHCl_3$) bands at 3465, 3160, 2925, 1482, 1383, 1315, 1240, 1146, 1057, 1038 and 956 cm.$^{-1}$.

(19) G. M. Barrow and S. Searles, THIS JOURNAL, **75**, 1175 (1953).
(20) E. D. Bergmann, E. Zimkin and S. Pinchas, *Rec. trav. chim.*, **71**, 168 (1952).
(21) D. Ben-Ishai, THIS JOURNAL, **78**, 4962 (1956).

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N-Benzoyloxazolidone showed also (in $CHCl_3$) bands at 3160, 2925, 1602, 1481, 1450, 1379, 1328, 1186, 1100, 1041, 987, 912 and 882 cm.$^{-1}$.

N-Benzoyl-4,5-tetramethyleno-2-oxazolidone showed also (in CCl_4) bands at 2925, 1596, 1454, 1355, 1330, 1309, 1253, 1205, 1177, 1126, 1099, 1059, 999, 969, 942, 907 and 896 cm.$^{-1}$.

2-Pyrrolidone and **N-methyl-2-pyrrolidone** were commercial products purified by vacuum distillation.

REHOVOTH, ISRAEL

[CONTRIBUTION OF THE SCHOOL OF SCIENCE, BRANDEIS UNIVERSITY]

Polar Factors in Radical Dissociations. Kinetics of Decomposition of *meta*-Substituted Phenylazotriphenylmethanes[1a]

BY STANLEY SOLOMON, CHI HUA WANG AND SAUL G. COHEN[1b]

RECEIVED JANUARY 9, 1957

meta-Substituted phenylazotriphenylmethanes, m-X—C_6H_4N=NC$(C_6H_5)_3$, X = CH_3, Br, NO_2, (H), have been prepared and decomposed in toluene at two temperatures. The decompositions showed first-order kinetics with activation energies in the range 26–30 kcal. mole^{-1}. The substituent CH_3 led to increased rates, the substituents Br and NO_2 to decreased rates of decomposition, the effects being quite similar to those of p-substituents studied previously. The results for m-substituents were correlated by the Hammett equation, ρ −0.85, and indicated that phenyl radicals may be rendered less stable by electron withdrawal. Factors affecting homolytic dissociation processes are discussed. Decomposition of phenylazotriphenylmethane in acetic acid led to benzene (>40% yield), to biphenyl (10% yield) and to no succinic acid. The origin of the products is discussed.

As part of our study of the effects of structure on the homolytic dissociation of organic compounds, which lead to the formation of free radicals, we have been examining the effects of substituents in the phenyl group of phenylazotriphenylmethanes on the kinetics of their decomposition. The ease with which homolytic dissociation occurs, or the strength of the bond or bonds concerned may be considered in terms of steric effects, polar factors, and the difference in the resonance stabilization of the ground states and transition states.

The decomposition of substituted ethanes[2] R_3–C–C–R_3 shows marked increase in rates and decrease in activation energies as the alkyl groups R are made more complex or are changed to aryl groups, the variations resulting from steric factors, which affect the central carbon–carbon bond, and resonance stabilization of the radicals. Azo-bis-alkanes and azo-bis-arylalkanes R_3C—N=N—CR_3 are related materials, in which the azo linkage facilitates decomposition while reducing steric effects. Substitution of α-alkyl and aryl groups for hydrogen in the parent compound azomethane, R = H, leads to successive and approximately additive increase in rate and decrease in activation energy, which have been interpreted in terms of resonance stabilization of the radicals,[3] and hence of the transition states. Steric effects have also been observed in the decomposition of certain azo compounds, largely due to β-substituents.[4]

Substituents in the nuclei of hexaarylethanes, whether electron attracting or electron donating, increase the extent of their dissociation, the large effects of o-substituents commonly being attributed to steric and resonance factors, and the effects of p-substituents, to resonance.[5] The effect of m-substituents, often attributed to steric factors, may result largely from the charge (+ or −) which they impose upon the aromatic rings to which they are attached, leading, in symmetrically substituted ethanes, to electrostatic repulsions between the two halves and weakening of the central bond. That the effect of m-substituents is comparable to and frequently greater than that of p-substituents indicates that this polar factor may be of importance in the latter case also.

In the decomposition of substituted benzoyl peroxides,[6] electron-donating substituents were found to increase the rates, electron-attracting substituents, (except nitro) to decrease them, and the data fitted the Hammett equation fairly well, ρ −0.38. This was interpreted[6a] in terms of the effects of the substituents on the size of the negative ends of the dipoles, postulated to exist at the central oxygen–oxygen bond and thus on repulsive forces operating between the two halves of the molecules. Similar effects of substituents were observed in the decomposition of t-butyl perbenzoates.[7] Also, in the dissociation of five symmetrically substituted 1,1,4,4-tetraphenyl-2,3-dibenzoyltetrazanes,[8] in which the phenyl substituents were CH_3, H and Br, the equilibrium constants were correlated with the Hammett equation, ρ −1.52. This was interpreted as resulting from stabilization by electron-donating substituents of the positive charge on the α-nitrogen in one of the resonance forms of the hydrazyl radicals. Further study of the dissociation of these tetrazanes indicated that the Hammett equation success-

(1) (a) Taken in part from a dissertation submitted by Stanley Solomon in partial fulfillment of the requirements for the M.A. degree in Chemistry, Brandeis University. (b) To whom inquiries should be addressed.

(2) K. Ziegler and W. Deparade, *Ann.*, **567**, 123 (1950).

(3) S. G. Cohen and C. H. Wang, THIS JOURNAL, **77**, 2457, 3628 (1955).

(4) C. G. Overberger, W. F. Hale, M. B. Berenbaum and S. B. Firestone, *ibid.*, **76** 6185 (1954).

(5) For discussion with references, see G. W. Wheland, "Advanced Organic Chemistry," 2nd edition, John Wiley & Sons, Inc., New York, N. Y., 1949, pp. 694–697, and J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp. 377–383.

(6) (a) C. G. Swain, W. H. Stockmayer and J. T. Clarke, THIS JOURNAL, **72**, 5426 (1950); (b) A. T. Blomquist and A. S. Buselli, *ibid.*, **73**, 3883 (1951).

(7) A. T. Blomquist and J. A. Berstein, *ibid.*, **73**, 5546 (1951).

(8) W. [illegible] and N. Schwartz, *ibid.*, **77**, 4543 (1955).

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fully correlated the rates of both the dissociation and the recombination.[9]

In the decompositions of *p*-substituted phenylazotriphenylmethanes[10] we observed that both electron-donating substituents (*e.g.*, *p*-CH_3O, σ −0.27) and electron-attracting substituents (*e.g.*, *p*-NO_2, σ +0.78) led to decreases in the rates of decomposition, and the results would of course not be correlated by the Hammett equation with conventional σ-values. It was pointed out that both types of substituents could increase the resonance stabilization of the ground state by increasing conjugation of the phenyl and azo groups and strengthen the phenyl–nitrogen bond. It was suggested that this effect might be modified by the effects of the substituents on the stability of the phenyl radical and thus on the stabilization of the transition states, with electron-donating substituents stabilizing the radicals and partly counteracting the stabilization of the ground states. Alternatively the observed order could be interpreted in terms merely of the inductive effect, −I substituents decreasing the stability of phenyl radicals. In order to minimize the effect of the substituent on the conjugation of the azo linkage with the phenyl group and to isolate the effect of the substituent on the phenyl radical, it seemed desirable to study some *m*-substituted phenylazotriphenylmethanes. The compounds *m*-X—C_6H_4-N=NC(C_6H_5)$_3$, X = CH_3, Br, NO_2 and (H) were each synthesized by (1) preparation of the substituted phenylhydrazine hydrochloride, (2) condensation of the hydrazine salts with triphenylmethyl chloride to form the hydrazo compounds, *m*-X-C_6H_4-NH-NH-C(C_6H_5)$_3$, and oxidation of the latter to the azo compounds. The unsubstituted hydrazo compound autoxidized during purification leading directly to the azo compound. The *m*-nitro compound was resistant to oxidation, treatment with amyl nitrite finally proving effective. This reagent was used to oxidize the *m*-bromo and *m*-methyl compounds, the reaction in the latter case being quite vigorous. We were unfortunately unable to prepare *m*-methoxyphenylhydrazine and *m*-acetaminophenylhydrazine.

The rates of decomposition of the azo compounds in *ca.* 0.01 *M* solution in toluene were determined under oxygen-free nitrogen at two temperatures by measurement of the volume of evolved nitrogen (V_t) as a function of time, essentially as described previously.[10] Several runs were made at each temperature. Small induction periods (*ca.* 5 minutes) were observed, and zero time readings were obtained by linear extrapolation of a zero-order plot for the first 10% of the reaction back to zero time. These values were used in calculation of V_∞. Linear plots of ln $V_\infty/(V_\infty - V_t)$ *vs.* time were obtained, indicating that the decompositions were first order. Typical plots are given in Fig. 1. One compound, X = *m*-Br, was decomposed at 0.02 mole/l. and at 0.007 mole/l. concentration with no change in rate constant. Rate constants were determined from the slopes, activation energies from the Arrhenius equation and entropies of

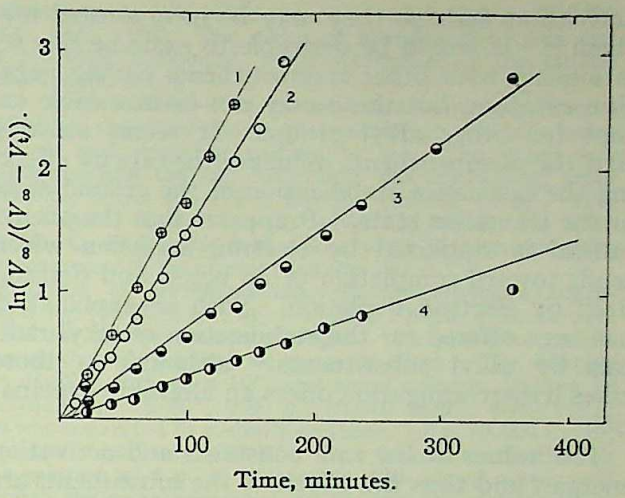

Fig. 1.—Decomposition of *m*-XC_6H_4—N=NC(C_6H_5)$_3$ in toluene, 53.80°: curve 1, X = CH_3; curve 2, X = H; curve 3, X = Br; curve 4, X = NO_2.

activation according to the transition state theory. The data are summarized in Table I.

TABLE I

DECOMPOSITION OF SUBSTITUTED PHENYLAZOTRIPHENYLMETHANES, *m*-X—C_6H_4N=NC(C_6H_5)$_3$

m-X	*T*, °C. ±0.05	No. of runs	$k_1 \times 10^4$ sec.$^{-1}$	E, kcal., mole^{-1}	$\Delta S^\pm$, cal. mole^{-1} deg.$^{-1}$
CH_3	53.80	7	2.77 ± 0.10	27.2 ± 1.5	6 ± 4
CH_3	43.80	3	0.74 ± 0.02		
H	53.80	8	2.40	27.6	7
H	43.80	3	0.63		
Br	53.80	4	1.14	29.9	13
Br	64.00	2	4.58		
NO_2	53.80	4	0.58	26.5	1
NO_2	64.00	3	1.99		

The CH_3 substituent increased the rate of decomposition slightly while the groups Br and NO_2 led to decreased rates. The results are correlated satisfactorily by the Hammett equation (Fig. 2),

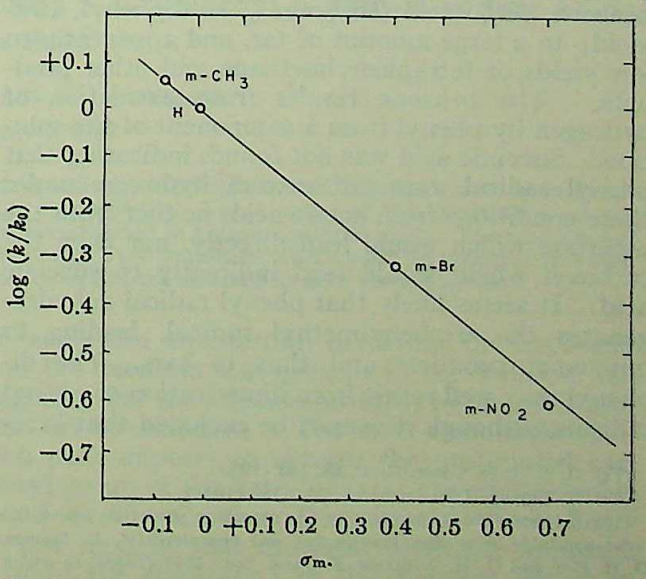

Fig. 2.—ρ–σ plot for decomposition rate constants, *m*-X—C_6H_4N=NC(C_6H_5)$_3$, in toluene at 53.80°.

ρ −0.85; σ CH_3, Br, NO_2: −0.07, +0.39, +0.71, respectively. The entropies of activation are not constant, but since they change with the energies of

(9) W. K. Wilmarth and N. Schwartz, THIS JOURNAL, **77**, 4551 (1955).

(10) S. G. Cohen and C. H. Wang, *ibid.*, **77**, 6504 (1955).

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activation perhaps they may be incorporated into them.[11] It would be desirable to examine this relationship with other *m*-substituents having negative σ-values, but these may not be accessible except for other alkyl groups. It seems unlikely that the *m*-substituents influence the rate by affecting the resonance stabilization of the ground state or the transition state. It appears that the phenyl radical is stabilized by electron accession which tends toward completion of an octet, and destabilized by electron depletion. Such an explanation has been offered for the stabilization of alkyl radicals by alkyl substituents,[12] although in those cases hyperconjugation offers an alternate explanation.

The values of the rate constants and activation energies and thus the effects of the substituents are quite similar for the *m*-substituted and for the *p*-substituted compounds in the cases in which we can make comparisons. (It may be noted that *m*- and *p*-substituents show similar effects in the dissociation of hexaarylethanes.) Indeed, if log k/k_0 for the *p*-substituted phenylazotriphenylmethanes[10] (CH_3, CH_3O, HO, Br, NO_2) is plotted against *meta* σ-values, the points, with the exception of *p*-methoxyl, lie fairly close to the line drawn through the *m*-values. Whether this is fortuitous, the *p*-effects being the resultant of the several factors discussed above, or whether the effect of *p*-substituents arises in similar fashion to the *m*-effects, possibly from electrostatic effects on the phenyl radicals, is not clear.[13]

Products of Decomposition.—Previous studies of the products of decomposition of phenylazotriphenylmethane have indicated that benzene[14a] was formed in low yield, but that diphenyl was not found except when the decomposition was carried out in benzene,[14b] the solvent contributing one phenyl group to this product, which was formed in low yield. In our work, decomposition of phenylazotriphenylmethane in acetic acid led to benzene, 40% yield (58% cor.); to diphenyl, 10% yield; to a large amount of tar, and apparently to low yields of tetraphenylmethane and other products. The benzene results from extraction of hydrogen by phenyl from a component of the solution. Succinic acid was not found, indicating that phenyl radical does not extract hydrogen under these conditions from acetic acid, neither from the α-carbon which would lead directly, nor from the carboxyl which would lead indirectly to succinic acid. It seems likely that phenyl radical dehydrogenates the triphenylmethyl radical, leading to quinonoid products and thus to tars. The diphenyl may well result from dimerization of phenyl radicals, although it cannot be excluded that it results from substitution by phenyl radical into the benzene which is formed in low concentration during the course of the reaction.

(11) H. H. Jaffe, *Chem. Revs.*, **53**, 193 (1953).

(12) H. Eyring, THIS JOURNAL, **75**, 5183 (1953).

(13) A referee kindly brought to our attention an article which became available after this manuscript was complete (G. L. Davies, D. H. Hey and G. H. Williams, *J. Chem. Soc.*, 4397 (1956)) in which our earlier work (ref. 10) and related studies are interpreted in terms of desolvation in the transition state. It is regrettable that an unequivocal interpretation cannot be given.

(14) (a) H. Wieland, E. Popper and H. Seefried, *Ber.*, **55**, 1816 (1922); (b) D. H. Hey, *J. Chem. Soc.*, 1966 (1934); W. A. Waters, "The Chemistry of Free Radicals," 2nd Edition, Oxford, 1948, pp. 147–148.

Experimental[15]

m-**Nitrophenylhydrazine Hydrochloride.**[16]—A solution of 10 g. (0.145 mole) of sodium nitrite in 70 ml. of water was added dropwise to a solution of 20 g. (0.145 mole) of *m*-nitroaniline (Fisher) in 200 ml. of concentrated hydrochloric acid at 0–5°. The solution was stirred at room temperature for one hour and recooled, and to it was added slowly a solution of 65 g. (0.29 mole) of $SnCl_2 \cdot 2H_2O$ in 65 g. of concentrated hydrochloric acid. A tan precipitate was collected and crystallized from absolute ethanol, m.p. 208–210°, 16.8 g., 61% yield. *Anal.* Calcd. for $C_6H_8N_3O_2Cl$: C, 38.02; H, 4.24. Found: C, 38.50; H, 4.54.

m-**Bromophenylhydrazine Hydrochloride.**[17]—A solution of 20 g. (0.116 mole) of *m*-bromoaniline (Eastman Kodak Co.) in 200 ml. of hydrochloric acid was treated at 0–5° first with a solution of 8.0 g. (0.116 mole) of sodium nitrite in 16 ml. of water for 0.5 hour, and then with a solution of 52 g. (0.23 mole) of $SnCl_2\ 2H_2O$ in 52.5 g. of hydrochloric acid. A white precipitate was collected, dissolved in 250 ml. of boiling water, neutralized with 3 *N* sodium hydroxide, cooled and extracted with ether. The extract was dried over calcium chloride and treated with dry hydrogen chloride leading to a precipitate which was crystallized from 2-propanol, m.p. 225°, 8.4 g., 32% yield. *Anal.* Calcd. for $C_6H_8N_2BrCl$: C, 32.24; H, 3.60. Found: C, 32.04; H, 3.96.

m-**Tolylhydrazine Hydrochloride.**[18]—A solution of 20 g. (0.19 mole) of *m*-toluidine (Eastman Kodak Co.) in 200 ml. of hydrochloric acid was treated at 0.5° with a solution of 13 g. (0.19 mole) of sodium nitrite in 50 ml. of water, stirred at room temperature for 0.5 hour, recooled and treated with 84 g. (0.37 mole) of $SnCl_2\ 2H_2O$ in 84 ml. of hydrochloric acid. The product was collected, dissolved in hot water, saturated with hydrogen sulfide, filtered, made slightly alkaline with 3 *N* sodium hydroxide, cooled and extracted with ether. The extract was dried, treated with dry hydrogen chloride until precipitation was complete. Excess hydrogen chloride led to decomposition. The product was crystallized from 2-propanol, m.p. 168–170°, 8.6 g., 32% yield. *Anal.* Calcd. for $C_7H_{11}N_2Cl$: C, 52.99; H, 6.99. Found: C, 52.34; H, 6.99.

Toward a-*m*-**Methoxyphenylhydrazine and** *m*-**Acetaminophenylhydrazine.**—A. *m*-Aminophenol, 1.0 mole, was converted to *m*-hydroxyacetanilide, 0.87 mole, m.p. 149°, reported[19] 148°. This product, 0.73 mole, treated with methyl sulfate. led to *m*-methoxyacetanilide, 0.30 mole, m.p. 79–80°, reported[19] 80–81°. This was hydrolyzed with dilute hydrochloric acid, leading to *m*-anisidine, b.p. 249°, reported 251°.[20] Attempts to diazotize the amine and reduce the diazonium compound led to a product which decomposed at room temperature.

b. An unsuccessful attempt was made to prepare *m*-acetaminophenylhydrazine by treatment of a solution of 5 g. (0.27 mole) of *m*-aminoacetanilide hydrochloride in 200 ml. of hydrochloric acid with 1.85 g. (0.027 mole) of sodium nitrite in 15 ml. of water, followed by treatment with 12 g. (0.053 mole) of $SnCl_2$ in 12 g. of hydrochloric acid. No precipitate formed and treatment with alkali, extraction with ether and treatment with dry hydrogen chloride led to a dark oil.

m-**X-Phenylazotriphenylmethanes.**—Equimolar quantities of the substituted phenylhydrazine hydrochloride and triphenylmethyl chloride were allowed to react in dried pyridine at 20° with stirring for three hours. Quantities of materials used are summarized in Table II.

Pyridine hydrochloride was filtered off and washed with cold pyridine and the filtrates were diluted with water. The precipitates were collected and worked up along with ether extracts of the diluted filtrates.

(15) Melting points are uncorrected; elementary microanalyses are by Dr. S. M. Nagy, Massachusetts Institute of Technology.

(16) A. Bischler and S. Brodsky, *Ber.*, **22**, 2809 (1889).

(17) M. Gomberg and A. Campbell, THIS JOURNAL, **20**, 786 (1898).

(18) K. Buchka and F. Schachtebeck, *Ber.*, **22**, 841 (1889).

(19) F. Neverdin and A. de Luc, *ibid.*, **47**, 7537 (1914).

(20) P. Friedländer, *Monatsh.*, **4**, 611 (1883).

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a. X = H.—The hydrazo compound was partially oxidized during evaporation of the ether, leading to a yellow solid. This was dissolved in 600 ml. of absolute ethanol and concentrated in vacuum below room temperature leading to 14.7 g. (0.0425 mole), 77% yield, of crude azo compound, m.p. 107–108° dec., reported 111°.[21] Decomposition of a sample at 100° in decalin led to 67% of the theoretical yield of nitrogen. The nitrogen was swept with carbon dioxide and collected over 50% potassium hydroxide. Four additional crystallizations from absolute ethanol led to a product melting at 110–112° which, when decomposed, led to 96% yield of nitrogen.

TABLE II

REACTION OF TRIPHENYLMETHYL CHLORIDE WITH PHENYLHYDRAZINE

X	m-X-$C_6H_4NHNH_2HCl$, g.	$(C_6H_5)_3CCl$, g.	C_5H_5N, ml.
H	8.0	16.0	120
NO_2	9.7	14.1	130
Br	5.0	6.2	80
CH_3	4.1	8.0	80

b. X = m-NO_2.—The crude hydrazo product melted at 140–150° and was somewhat difficult to oxidize. It was not affected by treatment in ether solution at room temperature with 35% hydrogen peroxide in the presence and absence of sodium bicarbonate. It was oxidized slowly by hydrogen peroxide in acetone. It was apparently oxidized by nitrogen dioxide in acetic acid, but the results were not consistent. Amyl nitrite led to satisfactory results and was used in subsequent syntheses. The hydrazo compound, 2.32 g., was suspended in anhydrous ether and treated with two molar equivalents of amyl nitrite and a few drops of acetyl chloride, a clear yellow solution resulting. The solution was filtered and evaporated in vacuum and the azo compound was crystallized from methanol, m.p. 111–112°, reported[17] 111–112°.

c. X = m-Br.—The crude hydrazo product was suspended in ether and oxidized as described above. The ether was evaporated and the product was washed with methanol, m.p. 108–109°, reported[17] 110°, 3.9 g. (0.0091 mole), 41% yield. The yields of nitrogen from this and the preceding compound, when determined in the kinetic runs were 100 ± 3%.

d. X = m-CH_3.—The crude hydrazo compound was oxidized as described above, the reaction in this case being vigorous and requiring cooling in ice. The ether was evaporated and the azo compound was crystallized from methanol, m.p. 108–109°, 6.0 g., (0.0165 mole), 64% yield. *Anal.* Calcd. for $C_{26}H_{22}N_2$: C, 86.15; H, 6.12. Found: C, 84.88; H, 6.16. The yield of nitrogen from this compound in the kinetic runs was 100 ± 2%.

Products of Decomposition.—Phenylazotriphenylmethane, 8.6 g. (0.025 mole), was heated in 100 ml. of acetic acid at 63° for 24 hours under nitrogen. Air was then passed through the solution with no apparent effect. The solution was distilled through a 10″ glass spiral column, leading to benzene, b.p. 78–80°, 0.80 g., (0.010 mole), 40% yield; this was converted to m-dinitrobenzene. 1.5 g. (0.009 mole), m.p. and mixed m.p. 88–89°. In a blank run distillation of a solution of 1 g. of benzene in 100 ml. of acetic acid through the same apparatus led to recovery of benzene in 70% yield. The remainder of the acetic acid was distilled off and the residue was extracted with 40 ml. of hot water. Concentration of the aqueous extract to dryness led to no succinic acid.

The residue was further extracted with 80 ml. of hot ethanol, leading to an insoluble tar; a suspended solid, 0.025 g., m.p. 270°, apparently tetraphenylmethane, 0.3% yield, reported[21] m.p. 267°; and the alcoholic extract. The latter was cooled, leading to a tar; a solid, 0.5 g., m.p. 120–140°, from which, after recrystallization from alcohol there was obtained a product, 0.030 g., m.p. 146°, possibly hexaphenylethane 0.5% yield, reported[22] m.p. 145–147°; and the alcohol solution. The latter was steam distilled, leading to biphenyl, 0.2 g. (0.0013 mole), 10% yield, m.p. and mixed m.p. 68–69°. Extraction of the tars with hot benzene led to an impure solid, 0.42 g., m.p. 80–92, which was not worked up further.

Acknowledgment.—We are pleased to acknowledge generous support of this work by the National Science Foundation.

(21) M. Gomberg, *Ber.*, **30**, 2044 (1897).

(22) M. Gomberg and L. H. Cone, *ibid.*, **37**, 2037 (1904).

WALTHAM, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SIR JOHN CASS COLLEGE]

The Kinetics of Ring Closure of Alkyl-substituted 3,3-Dimethyl-5-keto-hexanoic Acids by Sulfuric Acid

BY W. E. SILBERMANN AND T. HENSHALL[1]

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Acid-catalyzed ring-closures of 3,3-dimethyl-5-keto-hexanoic acid and of 6-alkyl-substituted homologs have been found to give dimedone and 3,3-dimethyl-6-alkyl-cyclohexanediones-1,5, respectively. The kinetics of the cyclizations of the hexanoic acid and of four alkyl-substituted derivatives have been investigated in aqueous sulfuric acid. The reaction has also been followed in acetic acid–sulfuric acid solution. The kinetic results are consistent with a reaction sequence in which the rate-controlling stage is electrophilic attack by C_1^+ on the double bond of the enolized form of the keto-acid.

The results of preliminary experiments on the cyclization of 3,3-dimethyl-5-keto-hexanoic acid (III, R = H) to dimedone by aqueous sulfuric acid already have been reported.[2] In further work on this reaction, the range of acid concentrations has been extended, and it has been observed that the activation energy for the process is markedly dependent on the acidity of the solvent, decreasing as the concentration of sulfuric acid increases (Table II). This effect is interpreted in terms of an acid–base equilibrium involving the keto-acid and the oxonium ions present in the solution and suggests that the reaction proceeds by way of a protonated intermediate. The most reasonable reaction path appears to involve the protonated carboxyl group of the keto-acid and the enolic double bond at C_5=C_6 (see Discussion). Accordingly it was thought that the most profitable approach toward the elucidation of this reaction lay in an investigation of the effects of substituent groups with definite electronic properties on the π-electrons of the enol form. The choice of suitable substituents, is, however, strictly limited both by the ease of preparation by synthesis and by the stability

(1) Material taken from part of a thesis presented by W.E.S. in support of candidature for the Ph.D. degree of London University.

(2) T. Henshall, W. E. Silbermann and J. G. Webster, THIS JOURNAL, 77, 6656 (1955).

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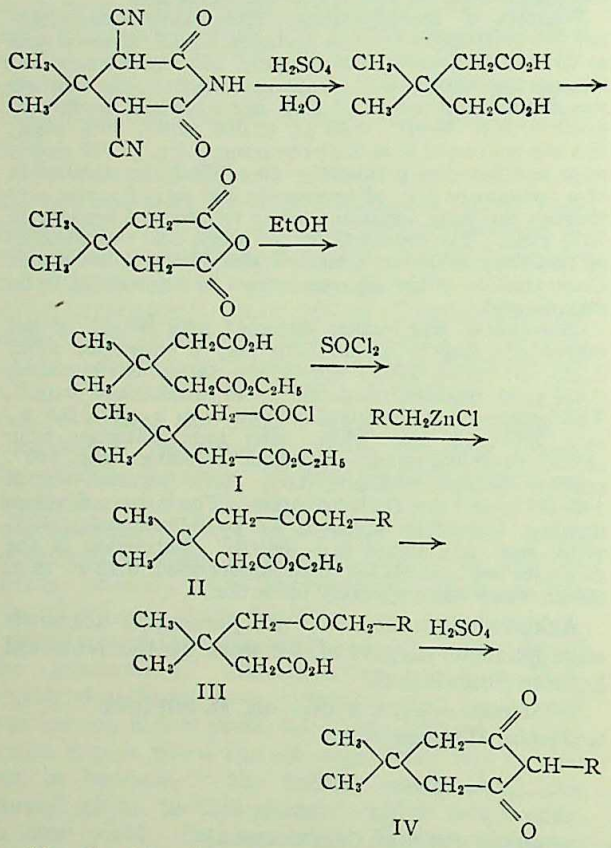
of such groups to the reaction medium. A start has been made with those keto-acids substituted on C_6[3] by methyl, ethyl, *n*-propyl and isopropyl groups. These were prepared by the route outlined below, in which α,α'dicyano-β,β-dimethylglutarimide, obtained from acetone and cyanoacetic ester by Guareschi's method, is converted successively into β,β-dimethylglutaric acid, anhydride, half-ester, ester chloride, keto-ester and keto-



acid. In kinetic measurements on these acids, only the trimethyloctanoic acid (III, R = isopropyl) showed any departure from simple kinetic order, an effect which may arise from the bulky nature of the isopropyl group. The activation energies for ring closure of the substituted acids were found to be significantly lower than for the parent compound, and the same dependence of activation energy on sulfuric acid concentration of the medium was observed also for the heptanoic, octanoic and nonanoic acids. The curves of E_a against "% H_2SO_4" are roughly parallel (see figure) corresponding to a differential heat, ΔH, of the order of 2 kcal. mole^{-1} over the range of investigation.

Additional evidence in support of the proposed mechanism has been obtained from kinetic measurements in acetic acid–sulfuric acid mixtures; in the presence of high concentrations of sulfuric acid the kinetics in this medium are much more complicated than those in aqueous solution, but good first-order rate constants are obtained from measurements in acetic acid containing small proportions of sulfuric acid. Rates similar to those obtained in aqueous solutions were induced by these relatively smaller amounts of the mineral acid, indicating the probability of easier proton transfer from the acetoxonium ion to the basic centers of the keto-acid molecule. The activation energies in acetic acid solution were also much lower than in water. Traces of water added to the acetic acid–sulfuric acid solvent had only slight effects on the total rate but raised the energy of activation and correspondingly reduced the entropy of activation. Small quantities of acetic anhydride apparently inhibited the reaction rate in acetic acid–sulfuric acid solution, and in the presence of sufficient anhydride (up to 5%) the reaction was completely suppressed. Also there was no measurable reaction in pure acetic acid or in "moist" acetic acid free of mineral acid.

A correlation of reaction rate of the substituted acids with the Hammett acidity function H_0 and with stoichiometric acid concentration $C_{H_2SO_4}$ has been attempted. The results are similar to those for the hexanoic acid, *i.e.*, plots of log k_{100}[4] against H_0 were slightly curved (except for the heptanoic acid) and the average slopes lie between 0.42 and 0.47, while the linear plots of log k_{100} against log $C_{H_2SO_4}$ show gradients of 4.0, 4.8 and 5.0 for the heptanoic, octanoic and nonanoic acids, respectively. There is apparently no simplification of these relationships in aqueous perchloric acid solution; for preliminary experiments with the heptanoic acid gave

$$\delta(\log k)/\delta(\log C_{HClO_4}) \doteqdot 5 \text{ and } -\delta(\log k)/\delta(H_0) \doteqdot 0.5$$

and the investigations in these solutions were not pursued further.

It is proposed to extend the study of the cyclization reactions and especially to determine the influence of substituents on C_2 and of different groups on C_3 of the keto-acids; the results of such experiments will be communicated.

Experimental

Preparation and Purification of Materials. 3,3-Dimethyl-5-keto-hexanoic acid was prepared and purified as described previously.[2] δ-Keto-acids of

general formula $(CH_3)_2C(CH_2COCH_2R)(CH_2CO_2H)$ (III, R = alkyl)

Ethyl hydrogen β,β-dimethylglutarate was obtained by heating β,β-dimethylglutaric anhydride[5] (0.84 mole) on the steam-bath for 29 hr. with 300 ml. of absolute ethanol. The excess of alcohol was removed and the residue fractionally distilled, the main fraction (b.p. 148–150° (2.5 mm.)) being collected very slowly. The distillate failed to crystallize at −12°; it was freed of about 9 g. of the acid anhydride. The colorless oily half-ester was obtained in 82% yield (equivalent weight found 186.2, calcd. for $C_9H_{16}O_4$, 188.2).

Acid Chloride I, Keto-esters II and Keto-acids III.—The acid chloride I was prepared as required by treating 20- to 30-g. portions of the half-ester with twice the theoretical quantity of thionyl chloride (b.p. 76–78°) for 1.5 to 1.8 hr. at room temperature and then for 0.5 hr. at 40°. The excess of thionyl chloride was removed and the residual liquid immediately distilled. The acid chloride was col-

(3) The 3,3-dimethyl-5-keto-acids are numbered conventionally; abbreviated names: hexanoic acid, heptanoic acid, octanoic acid, trimethyloctanoic acid and nonanoic acid occasionally used in the subsequent text all refer to keto-acids of type III (R = H, CH_3, C_2H_5, iso-C_3H_7, *n*-C_3H_7, respectively.) In order that each carbon atom shall retain the same number, the cyclic products IV will be named as 3,3-dimethyl-6-alkyl-cyclohexane-1,5-diones.

(4) k_{100} is the first-order rate constant at 100.0° on the scale of the Anschütz standard thermometer.

(5) A. Lapworth, *J. Chem. Soc.*, 1761 (1934).

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lected (70–85% yield) between 115° (13 mm.) and 121° (16 mm.).[6]

Ethyl esters II of the required keto-acids were prepared by reaction of the ester acid chloride I with alkyl zinc chlorides, RCH_2ZnCl. The latter reagents were prepared in the usual way[7] from the Grignard reagent, RCH_2MgBr, and freshly fused and ground anhydrous zinc chloride in dry ether. Most of the ether was replaced by dry benzene before the acid chloride, dissolved in dry benzene, was gradually added to the alkyl zinc chloride reagent. The well-stirred reaction mixture was heated under gentle reflux (temp. in liquid, 62°) for about 3 hr. after all the acid chloride had been added, then cooled in ice-water and decomposed by cold water containing some hydrochloric acid. The organic liquid layer was separated, combined with a benzene washing of the aqueous layer, dried ($MgSO_4$) and the solvent removed. The residual liquid was fractionally distilled. Yields of the colorless oily keto-esters were between 67 and 85% based on the acid chloride.

Ethyl ester	B.p., °C.	Mm.
3,3-Dimethyl-5-keto-heptanoate	95	2
3,3-Dimethyl-5-keto-octanoate	104–105	3
3,3-Dimethyl-5-keto-nonanoate	129.5–131	1
3,3,7-Trimethyl-5-keto-octanoate	123–125	3.5

Hydrolysis of the esters with concentrated aqueous alcoholic potassium hydroxide gave the corresponding δ-keto-acids III, which were collected by means of ether and purified by distillation. (It is noteworthy that hydrolysis of ethyl 3,3-dimethyl-5-keto-heptanoate by aqueous alcoholic potash gave also about 15% of the cyclized product, 3,3,6-trimethylcyclohexanedione-1,5.) The colorless or faintly yellow oily acids did not crystallize at −12°; they were freed of any traces of solid and stored in the desiccator.

The δ-keto-acids III had the following properties:

R = CH_3: b.p. 129.5° (0.7 mm.); equiv. wt. found 176.3, calcd. for $C_9H_{16}O_3$ 172.2; $n^{18}D$ 1.4490[8a]; ultraviolet spectrum of Na salt: λ_{max} 294 mμ, ε 560; semicarbazone, m.p. 137.5–138°.[8b]

R = C_2H_5[8c]: b.p. 146–147° (2 mm.); equiv. wt. found 189.3, calcd. for $C_{10}H_{18}O_3$ 186.3; $n^{22}D$ 1.4463; ultraviolet spectrum of Na salt: λ_{max} 294 mμ, ε 163; semicarbazone, m.p. 132° dec. Found: C, 54.4, 54.75; H, 8.6, 8.7; N, 17.4. Calcd. for $C_{11}H_{21}O_3N_3$: C, 54.3; H, 8.7; N, 17.3.

R = iso-C_3H_7: b.p. 142.5–143° (1.3 mm.); equiv. wt. found 199.0 and 198.5, $C_{11}H_{20}O_3$ requires 200.3; $n^{22}D$ 1.4444; ultraviolet spectrum of Na salt: λ_{max} 288 mμ, ε 54; semicarbazone, m.p. 156.5–157.5° dec. Found: C, 55.9, 55.9; H, 9.2, 9.0; N, 16.5. $C_{12}H_{23}O_3N_3$ requires: C, 56.0; H, 9.0; N, 16.3.

R = n-C_3H_7: b.p. 170–171° (0.9 mm.). The distilled acid was dissolved in 150 ml. of 5 N (pure) sodium hydroxide solution, and after 50 hr. at room temperature the solution was cooled in ice-water and carefully acidified to congo red by hydrochloric acid. The oily keto-acid was collected by means of pure ether, and the ether was completely removed under low pressure (with agitation of the liquid by dry air), any last traces of solvent being removed by heating *in vacuo* for 10 min. at 100°; equiv. wt. 193.2, $n^{22}D$ 1.4476; ultraviolet spectrum of Na salt; λ_{max} 294 mμ, ε 173; semicarbazone, m.p. 132° dec. Found: C, 56.2; H, 8.9; N, 16.8.

Sulfuric acid solutions for the kinetic runs were prepared by weighing colorless, concentrated sulfuric acid (May & Baker, 99%), and the acid content was checked by alkali titration.

Acetic acid for use as solvent in the kinetic runs was purified by distilling AnalaR glacial acetic acid through a 50 × 1.5 cm. Fenske column. The purified acid melted at 16.52–16.55° (three-quarters melted)—16.60° (last crystals); this indicated a purity of 99.9$_5$%.[9]

Cyclization of the δ-Keto-acids to 3,3-Dimethyl-6-alkylcyclohexanediones-1,5.—A sample of each of the keto-acids was heated in aqueous sulfuric acid solution (10 ml.), and the reaction mixture was cooled and poured into water. After cooling in ice-water the solid product was filtered off and dried *in vacuo* over concentrated sulfuric acid.

The 3,3-dimethyl-5-keto-heptanoic acid (0.9 g.) (72% H_2SO_4, 132°, 1 hr.) gave 0.8 g. of crude white 3,3,6-trimethylcyclohexanedione-1,5 (m. range 152–162°); the dione was recrystallized from aqueous alcohol and dried *in vacuo* and finally had m.p. 163–165.5°[10] (flat white needles),[11a] equiv. wt. found 153.5, calcd. for $C_9H_{14}O_2$ 154.1.

The 3,3-dimethyl-5-keto-octanoic acid (0.9 g.) (72% H_2SO_4, 130°, 1.3 hr.) gave 0.7 g. of crude 3,3-dimethyl-6-ethylcyclohexanedione-1,5, (m. range 154–158°); the recrystallized product had m.p. 156–157.5° (colorless crystals)[11b]; equiv. wt. found 167.5, calcd. for $C_{10}H_{16}O_2$ 168.1.

The 3,3,7-trimethyl-5-keto-octanoic acid (1.1 g.) (79% H_2SO_4, 100°, 3.3 hr.) gave 0.55 g. of 3,3-dimethyl-6-isopropylcyclohexanedione-1,5; m.p. of recrystallized dione, 167° (softening from 155°).[11c] Found: C, 72.9; H, 10.05; equiv. wt., 178, 180.5. Calcd. for $C_{11}H_{18}O_2$: C, 72.5; H, 9.96; equiv. wt., 182.2.

The 3,3-dimethyl-5-keto-nonanoic acid (0.75 g.) (63% H_2SO_4, 130°, 1.5 hr.) gave 0.62 g. of 3,3-dimethyl-6-n-propylcyclohexanedione-1,5, m.p. (recrystallized) 161.5–163° (colorless lustrous plates and needles).[11d] Found: C, 72.3; H, 9.7; equiv. wt., 180.5.

Kinetic Studies. (a) The Analytical Method.—The cyclic reaction products were estimated by means of the ultraviolet absorption spectra of their sodium enolates, as previously indicated for dimedone. Samples of the hot reaction mixtures were taken with a calibrated 1-ml. pipet, and each sample was mixed with 500 ml. of 0.1 N NaOH solution. The optical density of each alkaline solution was measured, at the wave length for maximum absorption, by comparison with a standard blank solution containing identical amounts of NaOH and sulfuric acid.

Ultraviolet spectra of the diones were recorded on freshly prepared and purified samples in 0.1 N aqueous NaOH. Measurements on two series of standard alkaline solutions of each dione showed that Beer's law was accurately obeyed in every case. Measurements were made in 10.0 mm. quartz cells, using a Unicam SP500 spectrophotometer.

	$\lambda_{max}^{(enol\ ion)}$ mμ	ε
3,3,6-Trimethylcyclohexanedione-1,5[12]	294.5	24300
3,3-Dimethyl-6-ethylcyclohexanedione-1,5	295	24050
3,3-Dimethyl-6-isopropylcyclohexanedione-1,5	295	23450
3,3-Dimethyl-6-n-propylcyclohexanedione-1,5	295.5	23250

(b) Rate Measurements.—A vapor-bath thermostat, with pure liquids boiling under atmospheric pressure, was again used; temperature constancy to within ±0.1–0.15° generally was obtained without difficulty. All runs were started by adding a weighed sample of the keto-acid in a small glass thimble to the solvent after the temperature had become quite steady and then shaking rapidly.

(c) The Reaction in Aqueous Solution. (i) Order of Reaction with Respect to the Keto-acids.—Ring-closures of the heptanoic, octanoic and nonanoic acids followed simple first-order kinetics over all ranges of reaction; very satisfactory reproducibility of the rate constants was observed. The cyclization of the trimethyloctanoic acid did not quite conform to the simple first-order law, the value of $2.303 \log (C_0/C_t) \div t$ declining by about 10–15% from time $t = 0$ to later stages of the reaction, but no evidence was found for any marked reversibility of this ring closure. Rate

(6) A. J. Birch and R. Robinson, *J. Chem. Soc.*, 488 (1942), give 110° (10 mm.).

(7) R. Adams, Ed., "Organic Reactions," Vol. VIII, John Wiley & Sons, Inc., New York, 1954, Ch. 2.

(8) R. D. Desai, *J. Chem. Soc.*, 1079 (1932), gives: (a) 1.4492; (b) 138°; (c) describes preparation of this acid ambiguously and gives $n^{22}D$ 1.4491, semicarbazone m.p. 137°.

(9) G. L. Foster, *ibid.*, 2788 (1954).

(10) The m.p.'s of the diones appear to depend somewhat on the conditions of heating; values recorded here are for samples immersed in a Thiele tube at about 20° below the m.p. and then heated at a normally slow rate.

(11) R. D. Desai, ref. 8, gives m.p.'s: (a) 163°, (b) 153°, (c) 156°, (d) 162°.

(12) E. G. Meek, J. H. Turnbull and W. Wilson, *J. Chem Soc.*, 2891 (1952), report ε 24000 at 295 mμ in 94200 in aqueous ethanolic NaOH.

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constants for the latter acid were derived from careful estimates of the initial rate.

(ii) Activation Energy.—First-order rate constants were measured at three or more temperatures in each of a number of sulfuric acid solutions. Activation energies were obtained from the linear plots of $5 + \log k$ against $1/T$. Reaction temperatures were indicated by a sensitive mercury thermometer kept liquid-immersed next to the reaction tube. When two thermometers were both used in the measurement of an activation energy, these were compared directly and appropriate correction was made to the reading of one.

TABLE I

RATE CONSTANTS, k, IN SEC.$^{-1}$

Percentages H_2SO_4 are by weight; temperature, T, in °C. abs.

R = H, 61.% H_2SO_4

T[a]	390.4	390.2	383.4	372.8
10^5k	11.53	11.18	6.32	2.56

R = CH_3

44.8% H_2SO_4		50.7% H_2SO_4		61.0% H_2SO_4	
T[a]	10^5k	T[a]	10^5k	T[b]	10^5k
383.1	37.8	383.0	66.50	372.7	105.2
378.6	25.55	373.3	31.45	372.3	101.0
373.7	18.64	361.1	11.95	360.1	38.2
361.0	6.30			359.6	35.9
				353.7	24.8
				351.7	20.62

R = C_2H_5

42.8% H_2SO_4		50.7% H_2SO_4		61.0% H_2SO_4	
T[a]	10^5k	T[a]	10^5k	T[b]	10^5k
382.5	8.31	389.8	37.0	372.9	39.0
372.8	3.88	383.2	22.75	359.9	13.82
360.6	1.33	373.7	10.98	353.2	8.34
		360.4	3.60		

65.4% H_2SO_4		72.5% H_2SO_4		79.5% H_2SO_4	
T[b]	10^5k	T[b]	10^5k	T[b]	10^5k
372.5	67.15	372.0	142.3	359.0	86.40
359.2	24.60	359.5	56.0	353.1	56.20
353.9	14.90	353.7	35.0	337.1	13.98
352.4	13.47				

R = n-C_3H_7

50.7% H_2SO_4		65.4% H_2SO_4		72.1% H_2SO_4	
T[c]	10^5k	T	10^5k	T	10^5k
382.5	26.50	373.1	80.90	370.0	143.0
372.7	12.68	360.1	30.77	359.6	67.7
359.6	4.43	353.3	18.10	352.8	38.2

R = iso-C_3H_7, 61.0% H_2SO_4

T	390.3	382.9	373.2
10^5k	7.5	5.05	2.7

[a] Anschütz standard thermometer. [b] E-MIL standard thermometer with total immersion scale. [c] Gallenkamp standard thermometer (10-mm. immersion scale) for all temperatures in this and the following sections.

Table II summarizes the experimental activation energies for ring closure of the keto-acids III in aqueous sulfuric acid.

TABLE II

R = H		R = CH_3		R = C_2H_5	
H_2SO_4, %	E_a, cal. mole^{-1}	H_2SO_4, %	E_a, cal. mole^{-1}	H_2SO_4, %	E_a, cal. mole^{-1}
72.3	23400	61.0	20050	79.5	20150
61.0	24600	50.7	21650	72.5	19900
50.6[a]	25400	44.8	22200	65.4	20900
				61.0	20700
				50.7	22050
R = n-C_3H_7		R = iso-C_3H_7		42.8	22800
H_2SO_4, %	E_a, cal. mole^{-1}	H_2SO_4, %	E_a, cal. mole^{-1}		
72.1	19800	61.0	17300		
65.4	19800				
50.7	21400				

[a] This corrects a computation error in the earlier communication.[2]

(ii) The ring-closures were found to be of simple first order with respect to the keto-acid in acetic acid solutions containing not too large amounts of sulfuric acid. The solvent mixtures were prepared by direct weighing of the pure acetic acid and of 100% sulfuric acid, prepared by mixing 99% H_2SO_4 and oleum (20% SO_3) (repeated gravimetric and volumetric analyses gave results all between 100.0 and 100.7% H_2SO_4), and were kept for at least 12 hr. before being used for kinetic experiments. The kinetic and analytical procedures were essentially as for the experiments in aqueous solutions. First-order rate constants for the ring-closures in acetic acid solution are given in Table III.

TABLE III

R = H

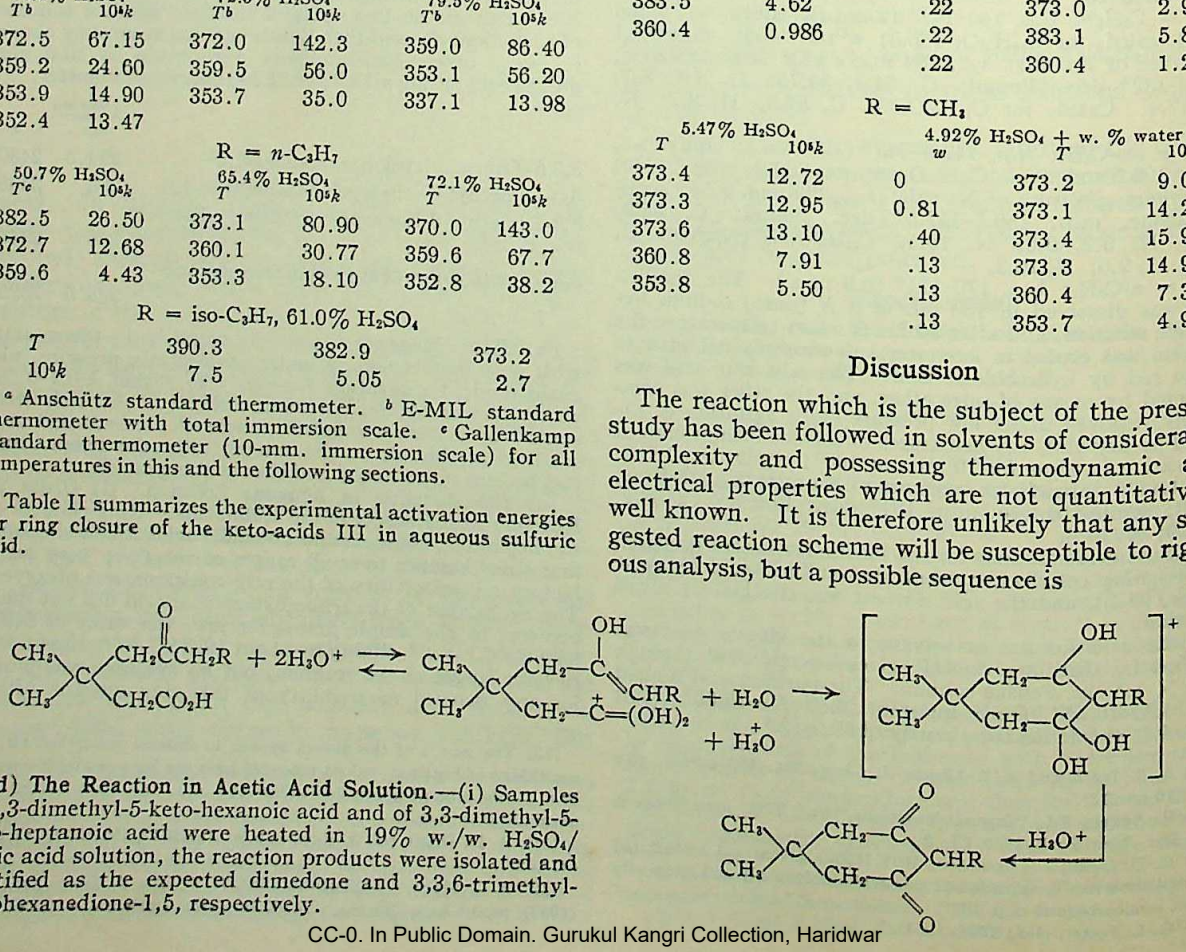
8.94% H_2SO_4		10.05% H_2SO_4 + w. % water		
T	10^5k	w	T	10^5k
373.3	2.303	0	372.8	2.47
373.3	2.338	0.72	373.1	2.71
383.5	4.62	.22	373.0	2.96
360.4	0.986	.22	383.1	5.82
		.22	360.4	1.22

R = CH_3

5.47% H_2SO_4		4.92% H_2SO_4 + w. % water		
T	10^5k	w	T	10^5k
373.4	12.72	0	373.2	9.0
373.3	12.95	0.81	373.1	14.20
373.6	13.10	.40	373.4	15.90
360.8	7.91	.13	373.3	14.95
353.8	5.50	.13	360.4	7.33
		.13	353.7	4.96

Discussion

The reaction which is the subject of the present study has been followed in solvents of considerable complexity and possessing thermodynamic and electrical properties which are not quantitatively well known. It is therefore unlikely that any suggested reaction scheme will be susceptible to rigorous analysis, but a possible sequence is



(d) The Reaction in Acetic Acid Solution.—(i) Samples of 3,3-dimethyl-5-keto-hexanoic acid and of 3,3-dimethyl-5-keto-heptanoic acid were heated in 19% w./w. H_2SO_4/acetic acid solution, the reaction products were isolated and identified as the expected dimedone and 3,3,6-trimethylcyclohexanedione-1,5, respectively.

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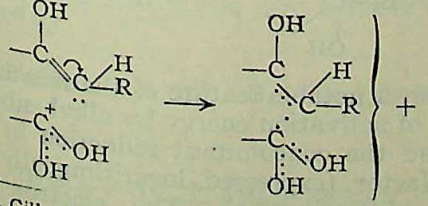
Enolization of keto-methylene groups in acid solutions is well known, and there is good evidence for the protonation of carboxylic acid groups in the presence of sulfuric acid.[13,14] For each keto-acid there is approximately the same change of activation energy corresponding to a given variation of solvent composition (see Fig. 1); this suggests that at least two terms contribute to the experimental activation energy, one a true activation energy for the rate-determining stage involving the transition state and the other a heat change depending on the solvent. In nearly anhydrous solvents proton transfers may be rate-controlling,[15] but in aqueous solution proton transfer to a basic oxygen atom is invariably rapid and leads to an equilibrium concentration of the conjugate acid. Ionization of a molecule of the keto-acid may then be represented by

$$A + 2H_3O^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} AH_2^{++} + 2H_2O \qquad (1)$$

If the trend of the curves of $E_a \sim \%\ H_2SO_4$ is continued to very high sulfuric acid concentrations (at which accurate kinetic measurements cannot be made), a lower limiting value of the activation energy tends to be approached (see especially results for the octanoic acid); this should be the true activation energy for the rate-determining stage. Under those conditions the equilibrium 1 is presumably displaced much more completely to the right, and so the energy change involved ceases to contribute significantly to the measured activation energy. Heat changes occurring on proton transfer to basic oxygen atoms under the conditions of these experiments have not been independently determined, but increments of E_a from the lower limiting values to values measured in the less acid solvents are consistent with rapid attainment of the pre-equilibrium 1.

Both ketones and carboxylic acids are completely protonated in anhydrous sulfuric acid, but in the aqueous acid solution the base strength of ketones apparently is greater than that of structurally similar carboxylic acids.[14] Since rather high concentrations of sulfuric acid are required for measurable rates of cyclization and since enolization of keto-methylene groups is known to be a reasonably facile process in much less strongly acid solution, the addition of another proton to the carboxylic acid group would appear to be a necessary prerequisite for ring-closure. The carbon atom of the $-CO_2H$ group can approach close to the terminal methylene group, and when the former bears a partial positive charge while C_6 is attached by an enolic double bond, the situation is favorable to cyclization



(13) R. J. Gillespie and J. A. Leisten, *Quart. Revs.*, **8**, 40 (1954).
(14) L. A. Flexser, L. P. Hammett and A. Dingwall, THIS JOURNAL, **57**, 2103 (1935).
(15) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 284.

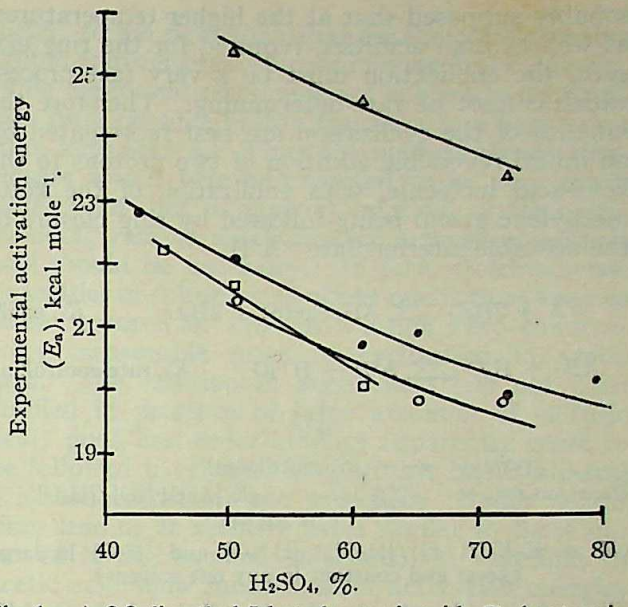


Fig. 1.—△, 3,3-dimethyl-5-keto-hexanoic acid; □, -heptanoic acid, ●, -octanoic acid; ○, -nonanoic acid.

The rapid and reversible proton transfers may be simultaneous with each other and with any other fast stages preceding the rate-controlling process. The reaction rate may then be determined by rate of conversion to enol or, more probably, by the rate of (unimolecular) ring-closure of the enolized intermediate $^+A'H$; in each case the rate equation would be of first order in keto-acid.

If the rate of enolization were rate-determining, the over-all reaction rate would be that for the process[16]

$$^+AH + H_2O \longrightarrow A'\text{ (enol)} + H_3O^+$$

Data recorded for aliphatic ketones show that an alkyl substituent on the α-carbon tends to accelerate acid-catalyzed enolization because of hyperconjugative electron release,[17] but this effect appears to be very much smaller than the increase in the rate of ring closure which has been found to result from substitution on C_6 of the 5-keto-acid by alkyl groups.

TABLE IV

C_6-Substituent	H	CH_3	C_2H_5	n-C_3H_7	iso-C_3H_7
Relative rate[a]	1.00 (ref.)	38	14.5	18.7	1

[a] From rate constants at 100.0° in 61% H_2SO_4. The probable reason for the slow reaction of the iso-C_3H_7 compound will be discussed.

Further, from the large amount of kinetic data available, especially that of Zucker and Hammett,[18] it is clear that rates of enolization of (aromatic) ketones become very great in highly acid solutions, and rates for the aliphatic ketones appear generally to be even greater.[19] Also, activation energies for acid-catalyzed enolization of (aromatic) ketones have normally large values,[20] and so it may be rea-

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(18) L. Zucker and L. P. Hammett, THIS JOURNAL, **61**, 2791 (1939).
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sonably supposed that at the higher temperatures, as well as high acidities, required for the ring closure, the enolization must be a very fast process which cannot be rate-determining. Therefore the kinetics of the cyclization are best represented by an initial reversible addition of two protons to the keto-acid molecule, with enolization of the keto-methylene group being followed by ring closure of the unstable intermediate $^{+}A'H$.

$$A + 2H_3O^{+} \rightleftharpoons {}^{++}AH_2 \text{ (keto)} + 2H_2O \qquad K_1\text{, equil.}$$

$${}^{++}AH_2 + H_2O \rightleftharpoons {}^{+}A'H + H^{+}{}_3O \qquad K_2\text{, rate-controlling}$$

$$\downarrow (k)$$

$$\text{product} \longleftarrow \text{(intermediates)}$$

$$\text{Reaction rate } v = k[{}^{+}A'H] = kK_2K_1[A][H^{+}{}_3O]/[H_2O]$$
$$= kK[A]$$

($K = K_1K_2[H^{+}{}_3O]/[H_2O]$; $[H^{+}{}_3O]$ and $[H_2O]$ in large excess and constant in any one solvent)

The observed rate constant will be $k_{obs} = kK$, where k is the specific rate of the slow stage and the value of K varies with the solvent composition. It follows that $E_a = E_{a(true)} + \Delta H$; $E_{a(true)}$ is the true activation energy for the rate-determining stage and ΔH is a heat change term depending on the value of K, *i.e.*, on the nature of the solvent. This conforms to the suggestion already made to account for the change of E_a with acidity. Some part of the variation of rate with acidity might possibly be due to changes in the dielectric constant of the medium, but this possibility cannot be tested at present.

For this reaction sequence the rate equation is (f_T = the activity coefficient of the transition

$$v = k[{}^{+}A'H]f_{{}^{+}A'H}/f_T$$

state) and on insertion of the equilibrium constants in terms of activities thus gives

$$\text{specific rate } k_0 = kK_2K_1[H^{+}{}_3O] \times \frac{1}{a_{H_2O}} \times \frac{f_A f_{H^{+}{}_3O}}{f_T} \quad (2)$$

This expression would reduce to the form

$$\text{specific rate} = \text{(constant)}\,[H^{+}{}_3O] \times \frac{1}{a_{H_2O}} \times \frac{f_A f_{H^{+}{}_3O}}{f_T} = ca_{H^{+}}\frac{f_A}{f_T}$$

only provided that K_2 and K_1 are constant.

It may be justifiable to assume the ratio of activity coefficients constant in equation 2 because of the constitutional similarity of the transition state and the intermediate $^{+}A'H$, which is a keto-acid molecule plus a proton; but the value of K_1 probably increases with the acidity of the solvent. For aqueous sulfuric acid at 25° between 50 and 79% w./w. H_2SO_4, the data[21] show that $(a_{H_2O})^{-1}$ is not a simple function of $[H_3O^{+}]$, but on applying the simple relationship $(a_{H_2O})^{-1} = \alpha[H_3O^{+}]^n$ to the upper and lower ends of the range, values of n between 2.5 and 13 are indicated. If $[H_3O^{+}]$ is measured by the stoichiometric acid concentration, $C_{H_2SO_4}$, it appears from equation 2 that the dependence of rate of ring closure on acidity should be of much higher order than the first. Linear plots of log k_{100} against log $C_{H_2SO_4}$ show that in fact: specific rate = const. $(C_{H_2SO_4})^m$, the values of m being 4.6, 4.0, 4.8 and 5.0 for the hexanoic, heptanoic, octanoic and nonanoic acid, respectively.

The effect of varying acidity on rates of ring-closure is almost wholly through its influence on the activation energy. Results summarized in Table V show that entropies of activation vary little and in no significantly regular manner with the sulfuric acid content of the solution. Therefore the effect on rate of the mineral acid strength apparently is connected principally with the variable pre-equilibrium.

TABLE V

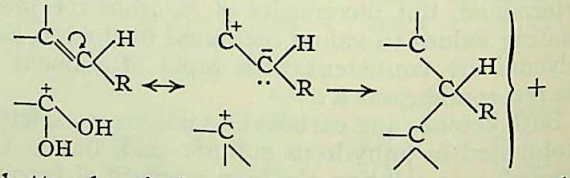
STANDARD ENTROPIES OF ACTIVATION, $\Delta S°$, AT 100.0°[22]

Keto-acid (III) R =	H_2SO_4, % 42.8	44.8	50.7	61.0	72.3–72.5
H			−15.5	−16.6	−15.7
CH_3		−18.6	−19.4	−20.6	
C_2H_5	−19.8		−20.3	−20.6	−20.5
n-C_3H_7			−21.5	−21.7	−20.9
i-C_3H_7				−35.5	

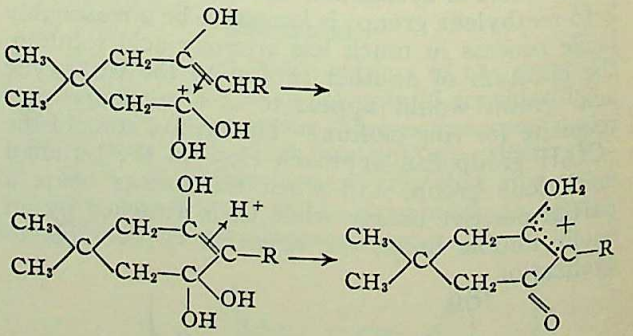
($\Delta S° = 2.303 \times 1.987$ (log PZ − log kT/h) − 1.987; log PZ = log $k + E_a/2.303RT$, where E_a is the "smoothed" value of E_a read from the graph. An error of 0.3 kcal. in E_a would change $\Delta S°$ by 0.8 e.u.)

The largely negative values of $\Delta S°$ are consistent with the rate-determining process being the formation of a cyclic transition state from a non-cyclic intermediate (*cf.* later discussion of solvent effects.)

Formation of the transition state in the ring-closure may be classically represented as electrophilic attack by C_1^{+} on the enolic double bond



A better description of this step would seem to be the creation of a molecular bond[23] by donation of the π-electrons of the double bond to the vacant bonding orbital of C_1^{+}, according to the scheme



Further, a notable feature of the reaction is the lowering of activation energy by alkyl substituents on C_6 and the concomitant reduction in the frequency factor (expressed logarithmically by the entropy of activation). The electron-releasing

(21) N. C. Deno and R. W. Taft, Jr., THIS JOURNAL, 76, 244 (1954); S. Shankman and A. R. Gordon, *ibid.*, 61, 2370 (1939).

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(23) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Clarendon Press, Oxford, 1949, p. 17.

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alkyl groups must tend to reduce the electron affinity of the double bond which they flank, *i.e.*, they lower the ionization potential of the π-electrons. Consequently the energy needed to make these electrons available for donation to the vacant orbital of the acceptor atom C_1^+ is diminished. This is consistent with the activation energy for electrophilic attack by C_1^+ on the double bond of the enol form, as the postulated rate-determining stage, being reduced by alkyl substitution on C_6 of the keto-acid. The effect would be expected to increase with higher tendency for electron release by the substituent, *i.e.*, primary alkyl < $-CH(CH_3)_2$ if inductive electron release only is considered. Some contribution by first-order hyperconjugation may account for the methyl group being a little more effective than the ethyl.

Inspection of models indicates that whereas in the keto-acid molecule there is likely to be little restriction on the positions of any of the alkyl substituents, in a cyclic transition state the isopropyl substituent at C_6 can be accommodated only in a narrowly defined range of configurations, whilst the positions of the ethyl and *n*-propyl groups appear to be less severely limited and that of the methyl group hardly at all. Thus the relative restriction in numbers of favorable configurations as between transition state and keto-acid molecule would be predicted to increase in the order shown, and entropies of activation are found to fall in this order.

$$H < CH_3 < C_2H_5 \sim n\text{-}C_3H_5 \ll -CH(CH_3)_2$$

ΔS° decreases →

slightly.....sharply

(The change of ΔS° on substitution with methyl, ethyl and *n*-propyl might perhaps be explicable on general statistical grounds,[24] the primary effect of structural modification being on the activation energy. The bulky isopropyl group, however, exerts a direct spatial effect.)

The *gem*-dimethyl groups on C_3 of the keto-acid must greatly facilitate ring-closure by constraining the molecule to adopt a configuration in which the potential reaction centers are fairly close together; in the absence of these groups or of one of them it seems likely that the molecule would exist preferentially in an extended form. It has in fact been observed that 3-phenyl-5-keto-hexanoic acid and 5-keto-hexanoic acid do not cyclize measurably under conditions like those used for the 3,3-dimethyl compounds. This point is being investigated.

The Ring-closure in Non-aqueous Solution.—Proton transfer to a keto-acid molecule in anhydrous sulfuric acid–acetic acid solvent must be represented by

$$2CH_3\overset{+}{C}O_2H_2 + A \rightleftharpoons \overset{++}{A}H_2 + 2CH_3CO_2H$$

or

$$2H_2SO_4 + A \rightleftharpoons \overset{++}{A}H_2 + 2HSO_4^-$$

Since acetic acid is a much weaker base than water, the first equilibrium should lie much more completely to the right than that for the corresponding proton transfer between oxonium ion and keto-acid, while the second reaction is not subject to competition from possible proton transfers to a base other than keto-acid A. Thus the acid-catalyzed ring-closure would here be expected to be very much faster than that in aqueous solution, or for corresponding rates a much smaller amount of sulfuric acid should be necessary. In fact, stoichiometric quantities of sulfuric acid about one-fifth as large as those required in aqueous solution gave conveniently measurable rates of cyclization in acetic acid. The reaction in acetic acid has not been studied in presence of large amounts of sulfuric acid; good first-order kinetics apparently cease to be followed if certain though fairly small mineral acid concentrations are exceeded. Under conditions leading to reaction rates similar to those observed in the aqueous solutions, the reactions in acetic acid show much smaller activation energies and also lower entropies of activation.

TABLE VI

Acid	Catalyst	E_a, cal. mole^{-1}	ΔS°	ΔG°, cal. mole^{-1}[a]
3,3-Dimethyl-5-keto-hexanoic	8.94% w./w. H_2SO_4 (anhydrous)	18300	−33.1	29900
	10.05% w./w. H_2SO_4 + 0.2% water	18900	−30.9	29750
3,3-Dimethyl-5-keto-heptanoic	5.47% w./w. H_2SO_4 (anhydrous)	11450	−48.0	28600
	4.92% w./w. H_2SO_4 + 0.13% water	14900	−38.5	28450

[a] ΔG° = free energy of activation.

Because of the very low dielectric constant of acetic acid,[25] electrostatic orientation effects are probably very much less important in this solvent than in aqueous solution. Formation of the cyclic transition state from the intermediate $^+A'H$ involves a decrease in polarity, and it might thus be expected that solvation of the reactant is more effective (relative to that of the transition complex) in the solvent of high dielectric constant (water). Since greater solvation of the reactant may lead to increased activation energies due to the inclusion of a "heat of solvation" term,[26] the observed lowering of activation energy when acetic acid is substituted for water as reaction solvent is consistent with the assumptions made about the polar nature of the reactant species and of the transition complex. Also, if solvent orientation tends to diminish when the transition state is formed, the entropy of activation should be least in the solvent of lowest dielectric constant. Thus, if the fundamental entropy change is $-X$ in a solvent of low dielectric constant in which the solvation change associated with formation of the transition state is perhaps negligible, then in another solvent with higher dielectric constant the release of molecules from solvation

(24) R. A. Fairclough and C. N. Hinshelwood, *J. Chem. Soc.*, 538, 1573 (1937).

(25) C. P. Smyth and H. E. Rogers, THIS JOURNAL, **52**, 1824 (1930).

(26) Reference 21, p. 410.

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may contribute a degree of "disordering," *i.e.*, an entropy term $+Y$. The entropy of activation in the latter solvent then becomes $-X + Y$, which is less negative than $-X$. ($\Delta S°$ for the hexanoic acid: in water, $\doteqdot -16$, in acetic acid, $\doteqdot -33$, and similarly for the heptanoic acid.)

When small amounts of water are added, the solvent system obviously becomes very complicated; the water may promote ionization of the sulfuric acid, which is otherwise very incomplete[27]

$$CH_3CO_2H + H_2SO_4 \rightleftharpoons CH_3\overset{+}{C}(OH)_2 + HSO_4^-$$

Also, owing to the low polarity of the acetic acid, water molecules or oxonium ions may become partially segregated in the neighborhood of the keto-acid molecules; in that case the environment of the reactant will be unlike that in anhydrous acetic acid and may tend toward conditions prevailing in aqueous solutions. This would account for the reaction parameters in "wet" acetic acid having values between those observed in the anhydrous solvent and those in aqueous solution. Inhibition of the ring-closure by acetic anhydride is believed to be due to the presence of acetylium ion, $CH_3\overset{+}{C}O$;[28] the latter must function as a strong acid and electrophilic reagent and may attack the basic centers of the keto-acid or the enolic double bond.

Acknowledgments.—The authors wish to thank Imperial Chemical Industries, Ltd., for a grant toward the cost of materials and Mr. P. R. Wood for some of the elementary analyses.

(27) H. A. E. Mackenzie and E. R. S. Winter, *Trans. Faraday Soc.*, **44**, 159 (1948).

(28) H. Burton and P. F. G. Praill, *Quart. Revs.*, **6**, 314 (1952).

LONDON E.C. 3, ENGLAND

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, YALE UNIVERSITY]

Reactions of Nitrous Acid with *p*-Hydroxycinnamic Acid and its Derivatives[1]

BY CHRISTINE ZIOUDROU,[2] WILLIAM L. MEYER AND JOSEPH S. FRUTON

RECEIVED MARCH 21, 1957

p-Hydroxycinnamic acid reacts with HNO_2 in dilute aqueous solution to form *p*-hydroxymandelaldehyde. With derivatives of *p*-hydroxycinnamic acid in which the carboxyl group is substituted (*e.g.*, the methyl ester), the predominant reaction is a nitration *ortho* to the phenolic hydroxyl. Because of the production of nitrite by the nitrate reductase of plants, the possibility exists that reactions of HNO_2 with *p*-hydroxycinnamic acid and its derivatives may occur in plant tissues.

Previous studies in this Laboratory[3,4] have led to the finding that N-acetyldehydrotyrosine (N-acetamino-*p*-hydroxycinnamic acid) is readily converted by dilute HNO_2 to N-acetyl-*p*-hydroxymandelic acid amide. This conversion was first observed[3] upon acidification of suspensions of *Escherichia coli* grown in a culture medium supplemented with acetyldehydrotyrosine. Subsequent studies[4] showed that the role of the bacteria is to reduce nitrate (a component of the basal medium[5]) to nitrite, presumably by the action of nitrate reductase[6]; upon acidification of the culture filtrate to *p*H 4 or less, a rapid non-enzymic reaction between HNO_2 and acetyldehydrotyrosine ensues. Because of the widespread occurrence, among plants, of nitrate reductase and of *p*-hydroxycinnamic acid (*p*-coumaric acid) and its derivatives (*e.g.*, caffeic acid, coniferyl alcohol), the new reaction merited further study in relation to several problems of plant metabolism.

Reaction of *p*-Hydroxycinnamic Acid with HNO_2.—In analogy with the action of HNO_2 on acetyldehydrotyrosine, the expected product of the reaction with *p*-hydroxycinnamic acid is *p*-hydroxymandelaldehyde, which does not appear to have been described previously; the isomeric 1,4′-dihydroxyacetophenone was prepared by Robinson.[7] Upon treatment of *p*-hydroxycinnamic acid with 2 equivalents of HNO_2 at *p*H 2, CO_2 is evolved with the formation of a product whose strong reducing properties, absorption spectrum, elementary analysis, and derivatives (2,4-dinitrophenylhydrazone, semicarbazone, phenylosazone) support its identification as *p*-hydroxymandelaldehyde. On treatment with 2.5 moles of $NaIO_4$ per mole of product, the expected amount of formic acid was released, and *p*-hydroxybenzaldehyde (identified as its phenylhydrazone) was formed. However, with a 1:1 molar ratio of periodate to product, 50% of the expected formic acid was released more rapidly than the rest, suggesting that the *p*-hydroxymandelaldehyde is present in aqueous solution as a dimer that is slowly cleaved during the reaction with periodate. This possibility is supported by the fact that the semicarbazone isolated from aqueous solution gave an elementary analysis in agreement with the values calculated for a derivative of a dimer.

The rate of the reaction of *p*-hydroxycinnamic acid with nitrite is markedly dependent on *p*H. At 30°, in the presence of 0.11 *M* citric acid–sodium citrate buffer containing 4×10^{-3} *M* nitrite (introduced as sodium nitrite) the apparent first-order rate constants (in min.$^{-1}$) for the disappearance of *p*-hydroxycinnamic acid (initial concentration, 4×10^{-4} *M*) were found to be: *p*H 5.1, 0.0010; *p*H 4.1, 0.0068; *p*H 2.9, 0.092. At lower *p*H

(1) This work was supported by grants from the Rockefeller Foundation and from the National Science Foundation.

(2) Postdoctoral Fellow of the Greek Fellowship Foundation.

(3) J. S. Fruton, S. Simmonds and V. A. Smith, *J. Biol. Chem.*, **169**, 267 (1947).

(4) G. Taborsky, P. S. Cammarata and J. S. Fruton, *ibid.*, **226**, 103 (1957).

(5) C. H. Gray and E. L. Tatum, *Proc. Natl. Acad. Sci.*, **30**, 404 (1944).

(6) A. Nason, in W. D. McElroy and B. Glass, "Inorganic Nitrogen Metabolism," Johns Hopkins Press, Baltimore, Md., 1956, p. 109.

(7) R. Robinson, *J. Chem. Soc.*, 1464 (1928).

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values, the rate was too rapid to be measured accurately with the available equipment. These rate constants were determined by observation of the decrease in the absorbance at the wave length corresponding to the maximum absorption of *p*-hydroxycinnamic acid; these maxima were (molar absorbance values being given in parentheses): *p*H 5.1, 286 mμ (19,600); *p*H 4.1, 305 mμ (19,200), *p*H 2.9, 308 mμ (21,600). The absorption spectrum of *p*-hydroxymandelaldehyde at acidic *p*H values has a maximum at 273 mμ (molar absorbance, 2620); near 300 mμ, the molar absorbance is about 950 (*cf.* Fig. 1). Beer's law was assumed to hold under the conditions of these experiments.

The effect of *p*H on the rate of the disappearance of *p*-hydroxycinnamic acid indicates that the reactive species is HNO_2 (pK' *ca.* 3.4) or a substance derived from it in acid solution. Although insufficient kinetic data are available for their use in the formulation of a mechanism of the reaction, the results are consistent with the hypothesis advanced previously[4] that the reaction involves an attack by the nitrosonium ion (NO^+), which may arise from nitrous acid by the reaction $HNO_2 + H^+ \rightarrow NO^+ + H_2O$.[8]

Reaction of Caffeic Acid with HNO_2.—When caffeic acid (3,4-dihydroxycinnamic acid) was treated with 2 equivalents of nitrous acid at *p*H 2, CO_2 was evolved, and an orange-colored solution resulted, from which no well-defined product could be isolated. The conversion of the initial product (possibly 3,4-dihydroxymandelaldehyde) to other substances is indicated by spectrophotometric observations. In acid solution, caffeic acid exhibits maximal absorption at 315 mμ (molar absorbance, 21,500). Two minutes after treatment with HNO_2 at room temperature, the absorption spectrum of the reaction mixture had changed to one exhibiting maximal absorption at 347 mμ, with a lesser peak at 284 mμ. During the succeeding 2 hours, the peak at 315 mμ gradually diminished, but the other peak was retained. From the reaction mixture (after 2 hours), there was obtained a brown amorphous material that is soluble in water, acetone and alcohol; it is insoluble in hydrochloric acid but dissolves in NaOH to give a dark red solution.

Nitration of *p*-Hydroxycinnamic Acid Derivatives by HNO_2.—It has long been known that phenols can be nitrated by means of nitrous acid (*e.g.*, salicylic acid is converted to 5-nitrosalicylic acid). Presumably, the initial attack by NO^+ at the position *ortho* to the phenolic hydroxyl gives rise to the nitroso compound, which is oxidized to the nitro derivative.[9] It is of interest therefore that, in the reaction of *p*-hydroxycinnamic acid or of its α-acetamido derivative with HNO_2 under the conditions described above, no evidence was obtained of nitration. This suggests that the α-carbon of *p*-hydroxycinnamic acid is more reactive toward an electrophilic reagent such as NO^+ than is the carbon *ortho* to the phenolic hydroxyl group. However, when the methyl ester of *p*-hydroxycinnamic acid was treated with one equivalent of HNO_2 in dioxane–water (*p*H *ca.* 2), the principal product was 3-nitro-4-hydroxycinnamic acid methyl ester, indicating a preferential attack of the ring by the nitrosonium ion. In this case, decarboxylation cannot occur, as with *p*-hydroxycinnamic acid, thus removing from the over-all process a strongly exergonic reaction that may be expected to favor nitrosation of the α-carbon. A similar situation appears to apply in the action of HNO_2 on derivatives of benzalacetophenone such as 4,4′-dihydroxychalcone; from the reaction mixture in dioxane–water a product was obtained which, on alkaline degradation, gave 3-nitro-4-hydroxybenzoic acid. Studies on the action of nitrous acid on hydroxychalcones will be reported in a subsequent communication from this Laboratory.

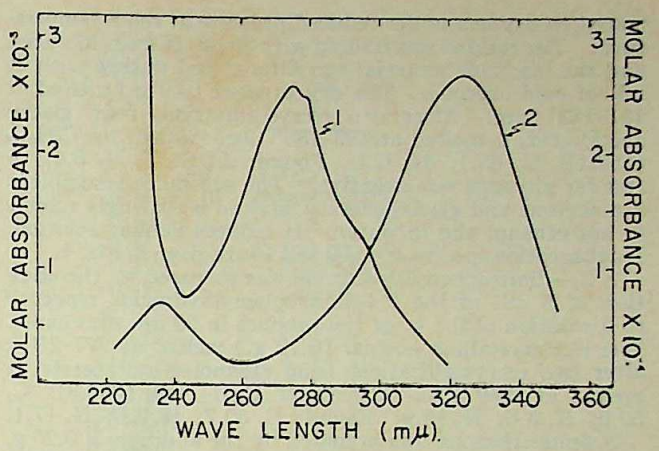

Fig. 1.—Absorption spectra of *p*-hydroxymandelaldehyde at *p*H 2 (curve 1, ordinate at left) and at *p*H 10 (curve 2, ordinate at right).

Discussion.—The extensive studies of Freudenberg[10] and others have drawn renewed attention to the possibility that the biosynthesis of lignin involves the oxidation and polymerization of phenylpropane derivatives. This view is supported by isotope experiments indicating the utilization of *p*-hydroxyphenylpyruvic acid for lignin formation.[11] Although speculation about the role of nitrite in lignin formation would be premature at present, the reactions described in the present communication, when considered in relation to the widespread occurrence of nitrate reductase in plants, suggest that consideration be given to the possibility that *p*-hydroxycinnamic acid derivatives may be oxidized in plant tissues, not only in the H_2O_2-dependent reactions already examined,[12] but also in reactions that involve HNO_2 as the oxidant.

Experimental

Formation of *p*-Hydroxymandelaldehyde.—To a solution of *p*-hydroxycinnamic acid (3 g., 0.0182 mole) in 50 ml. of freshly distilled dioxane was added a solution of sodium nitrite (2.45 g., 0.036 mole) in 50 ml. of water; the mixture was adjusted to *p*H 2 by the addition of about 4 ml. of 5 *N* hydrochloric acid. The resulting yellow solution was shaken for 1.5 hours at room temperature, and then was concentrated to dryness under reduced pressure at 40°. The residue was extracted 8 times with 50-ml. portions of hot acetone, and the combined acetone extracts were concen-

(8) F. Seel and R. S. Schwachel, *Z. anorg. allgem. Chem.*, **274**, 169 (1954).

(9) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 285.

(10) K. Freudenberg, *Angew. Chem.*, **68**, 84, 508 (1956).

(11) W. J. Schubert, S. N. Acerbi and F. F. Nord, THIS JOURNAL, **79**, 251 (1957).

(12) S. M. Siegel, *Quart. Rev. Biol.*, **31**, 1 (1956).

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trated to dryness under reduced pressure at room temperature. The residue was treated with 80 ml. of ice-cold water, and the insoluble material was filtered and washed with 20 ml. of cold acetone. The dry product (0.9 g.) melted at 181–183° dec. After two recrystallizations from glacial acetic acid, it melted at 183–185° dec. Calcd. for $C_8H_8O_3$ (152.1): C, 63.1; H, 5.3. Found: C, 62.5; H, 5.4. A test for nitrogen was negative. The substance is soluble in hot acetone and glacial acetic acid, and is sparingly soluble in hot ethanol and in water. It reduces Fehling solution. Its absorption spectra at *p*H 2 and 10 are given in Fig. 1.

A 2,4-dinitrophenylhydrazone was prepared by the addition of 5 ml. of the 2,4-dinitrophenylhydrazine reagent[13] to a solution of 0.1 g. of the product in 20 ml. of ethanol. The red crystalline powder (0.12 g.) melted at 277–280°; after two recrystallizations from ethanol–ethyl acetate, it melted at 280° dec. Calcd. for $C_{14}H_{12}N_4O_6$ (332.3): C, 50.6; H, 3.6; N, 16.9. Found: C, 50.7; H, 3.8; N, 17.1.

A semicarbazone was prepared by the addition of 0.25 g. of semicarbazide hydrochloride to a hot solution of 0.2 g. of the product in 10 ml. of water containing 0.6 g. of sodium acetate. The mixture was heated for 5 minutes on the steam-bath and chilled; the resulting crystalline product (0.2 g.) melted at 165° dec. After 3 recrystallizations from water it melted at 168° dec. Calcd. for a semicarbazone of a dimer, $C_{17}H_{19}N_3O_6$ (361.35): C, 56.5; H, 5.2; N, 11.6. Found: C, 56.4; H, 5.4; N, 11.6.

An osazone was prepared by the addition of 0.6 g. of phenylhydrazine hydrochloride and of 0.5 ml. of saturated sodium bisulfite solution (to prevent the formation of tarry products) to a hot solution of 0.2 g. of the product in 10 ml. of water containing 1.1 g. of sodium acetate. The mixture was heated for about 20 minutes on the steam-bath and chilled; the resulting yellow product (0.25 g.) melted at 190°. After 5 recrystallizations from ethanol–water it melted at 198–199°. Calcd. for $C_{20}H_{18}N_4O$ (330.3): C, 72.7; H, 5.45; N, 16.9. Found: C, 72.3; H, 5.6; N, 16.7.

For the oxidation of the product with periodate, 600 mg. (2.6 millimoles) of $NaIO_4$ was added to a solution of 200 mg. (1.3 millimoles) of *p*-hydroxymandelaldehyde in 300 ml. of water. The mixture was allowed to stand overnight at room temperature, extracted 10 times with 50-ml. portions of ether, and the combined ether extracts were concentrated to dryness. The residue was dissolved in 5 ml. of ethanol; 2 ml. of glacial acetic acid and 0.5 ml. of phenylhydrazine were added. The resulting phenylhydrazone melted at 176°. A mixed melting point with an authentic sample of the phenylhydrazone of *p*-hydroxybenzaldehyde showed no depression.

The quantitative determination of the formic acid produced on oxidation with periodate was performed in the manner described by Potter and Hassid.[14] When 100 mg. (0.65 millimole) of *p*-hydroxymandelaldehyde in 150 ml. of water was treated with 140 mg. (0.65 millimole) of $NaIO_4$, only 14.3 mg. (0.31 millimole) of formic acid was released. However, upon treatment of same amount of the aldehyde with 350 mg. of $NaIO_4$, the expected amount (30.3 mg., 0.66 millimole) of formic acid was released.

Reaction of *p*-Hydroxycinnamic Acid Methyl Ester with HNO_2.—To a solution of the ester (1 g., 0.0056 mole) in 15 ml. of dioxane was added a solution of $NaNO_2$ (0.4 g., 0.0056 mole) in 15 ml. of water; the mixture was acidified with 5 *N* hydrochloric acid to *p*H 2. Upon standing at room temperature for 4 hours, a yellow precipitate (0.65 g., yield 58%) separated. After recrystallization from ethanol, the product melted at 148°. Calcd. for $C_{10}H_9O_5N$ (223.2): C, 53.8; H, 4.1; N, 6.3. Found: C, 53.6; H, 3.8; N, 6.4. The same product was obtained when 0.2 g. of the ester was treated with 0.1 g. of $NaNO_2$ in 300 ml. of dilute aqueous hydrochloric acid (*p*H 2). Saponification of the product with 2 *N* alcoholic KOH gave an acid which melted at 223–225° after recrystallization from ethanol. Calcd. for $C_9H_7O_5N$ (209.1): N, 6.7. Found: N, 6.7. Johnson and Kohmann[15] prepared 3-nitro-4-hydroxycinnamic acid and reported a melting point of 223° for the compound; they also reported a melting point of 142–144° for the methyl ester.

(13) G. D. Johnson, THIS JOURNAL, **73**, 5888 (1951).

(14) A. L. Potter and W. Z. Hassid, *ibid.*, **70**, 3488 (1948).

(15) T. B. Johnson and E. F. Kohmann, *ibid.*, **37**, 166, 1876 (1915).

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

Heats of Hydrogenation. I. Apparatus and the Heats of Hydrogenation of Bicyclo[2,2,1]heptene, Bicyclo[2,2,1]heptadiene, Bicyclo[2,2,2]octene and Bicyclo[2,2,2]octadiene

BY RICHARD B. TURNER, W. R. MEADOR AND R. E. WINKLER

RECEIVED FEBRUARY 25, 1957

A calorimeter for the measurement of heats of catalytic hydrogenation in solution is described together with the results obtained for hydrogenations of bicyclo[2,2,1]heptene (−33.1 kcal./mole), bicyclo[2,2,1]heptadiene (−68.1 kcal./mole), bicyclo[2,2,2]octene (−28.3 kcal./mole) and bicyclo[2,2,2]octadiene (−56.2 kcal./mole) in acetic acid at 25°.

Some years ago Kistiakowsky[1] and his associates measured the heats of catalytic hydrogenation of a variety of unsaturated organic substances in the gas phase at 82°. The results obtained for the fifty-one compounds that were included in this investigation, have had important theoretical consequences of continuing interest. Since the gas phase technique is applicable only to substances possessing appreciable volatility, extension of the method to the liquid phase (29°) was undertaken in the Harvard laboratories by Williams,[2] and the heats of hydrogenation of nine additional compounds were determined by the latter procedure in 1942. Since that time no further experiments involving direct measurements of heats of hydrogenation have been reported, and in view of the considerable potential of the method, a continuation of this study appeared to be most desirable. The present paper constitutes the first report of work carried out in this Laboratory with the object of examining heat changes involved in reactions of the type

$$X(\text{dissolved}) + H_2(\text{gas}) \longrightarrow Y(\text{dissolved})$$

conducted in acetic acid solution at 25°.

(1) (a) G. B. Kistiakowsky, H. Romeyn, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, THIS JOURNAL, **57**, 65 (1935); (b) G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *ibid.*, **57**, 876 (1935); (c) **58**, 137 (1936); (d) **58**, 146 (1936); (e) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky and W. E. Vaughan, *ibid.*, **59**, 831 (1937); (f) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky, E. A. Smith and W. E. Vaughan, *ibid.*, **60**, 440 (1938); (g) J. B. Conn, G. B. Kistiakowsky and E. A. Smith, *ibid.*, **61**, 1868 (1939). See also J. B. Conant and G. B. Kistiakowsky, *Chem. Revs.*, **20**, 181 (1937).

(2) R. B. Williams, THIS JOURNAL, **64**, 1395 (1942).

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Method.—Determination of the heats of hydrogenation of compounds included in the present series was carried out by measuring the change in temperature of the calorimeter and its contents due to simultaneous hydrogenation of the compound in question and of the platinum oxide catalyst. At the end of each hydrogenation run the calorimeter was cooled and was calibrated electrically over the temperature range and time interval recorded in the hydrogenation experiment. Correction of observed temperature changes, expressed in ohms, for the heating effects of stirring and for heat exchange between the calorimeter and its surroundings was made by application of an improved form of the Regnault-Pfaundler equation.[3] The results were further corrected for heat dissipation in the heater leads during electric calibration and for small heat changes within the calorimeter accompanying condensation of acetic acid from the vapor phase during hydrogenation. The heat of hydrogenation was calculated finally as the difference between the total heat evolved and that associated with reduction of the catalyst, the latter quantity being determined separately.

Apparatus.—The calorimeter (Fig. 1), which is based on the Williams design,[2] consists of a silvered Dewar flask of approximately 450 ml. capacity with a recessed 34/45 ground glass joint at the top, through which the calorimeter head is introduced. Two 19/38 recessed joints also pass through the top of the calorimeter and carry vacuum-jacketed glass tubes—of which one (A) is shown—for the support of ampoules (B) of catalyst and of the test substance. One of these tubes extends a few millimeters below the solvent surface and terminates at its upper end in a 14/20 ground glass joint equipped with a stopcock (C) through which hydrogen can be admitted in order to displace air from the calorimeter and solvent prior to a run (see Procedure).[4] The second tube (not shown) is cut off just below the recessed joint and is closed at the upper end by a ground glass stopper.

The calorimeter head is constructed of a 34/45 ground glass joint, closed at each end and evacuated, through which pass the stirrer shaft housing and connecting tubes to the thermometer and heater wells (D and E, respectively). The stirrer shaft housing is joined to the hydrogen inlet tube (F) which makes connection through a 10/30 ground glass joint and manifold to an open end manometer, a jacketed, mercury-filled measuring buret that serves as the hydrogen reservoir and a pump for evacuating the system.

Stirring is accomplished by means of a glass propeller and shaft (G) which passes through loose-fitting Teflon guides (H) to one member of a magnetic coupling[5] enclosed in a vacuum tight glass housing, of which the cover (J) provides the bearing surface for the stirrer. The stirring assembly is driven by a variable speed, thyratron-controlled, d.c. motor[6] coupled to the driving magnet through a right angle gear box and universal joints to permit flexibility of alignment. Tests of the motor and control system established that the variation in speed at any given setting is less than 1%.

The thermometer is a Western Electric 14-B thermistor, temperature coefficient of resistance at 25°, −3.9% per degree C., nominal resistance at 25°, 2000 ohms. This unit was stabilized by heating to 105° for two months prior to use[7] and has proved to be entirely reliable. The thermistor has been compared periodically against a Beckmann thermometer and no significant variations in the temperature response of the element have been observed.

Resistance changes are measured with a conventional Wheatstone bridge circuit employing a Shallcross No. 817-B decade box (total resistance 1111.1 ohms) and a Leeds and Northrup No. 2430 d.c. galvanometer. Variation of the voltage across the bridge provides a sensitivity adjustment, which is normally set so that a temperature change of 0.001°, corresponding to a resistance change of about 0.1 ohm, produces a galvanometer deflection of 2–3 mm.

(3) W. P. White, "The Modern Calorimeter," Chemical Catalog Co. (Reinhold Publ. Corp.), New York, N. Y., 1928, p. 41.

(4) This arrangement permits thorough clearance of dissolved air from the solvent and was found to be essential for obtaining reproducible results.

(5) "Lew" Magnetic Stirrer, Scientific Glass Apparatus Co., Bloomfield, N. J.

(6) Model 6701, Servospeed, Paterson, N. J.

(7) Cf. M. J. Rand and L. P. Hammett, THIS JOURNAL, 72, 287 (1950).

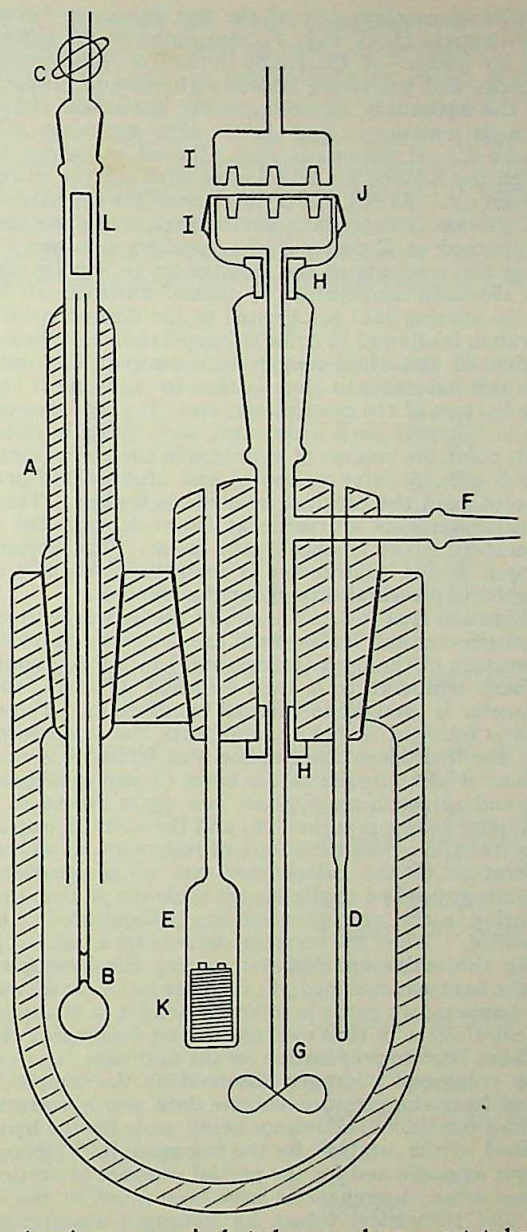

Fig. 1.—A, vacuum-jacketed ampoule support tube; B, evacuated ampoule; C, stopcock to hydrogen cylinder; D, thermometer well; E, heater well; F, connection to buret system and manometer; G, stirrer; H, Teflon guides; I, magnetic coupling; J, stirrer bearing surface; K, heater; L, magnet. Shaded portions are evacuated.

The electric heater (K) consists of 8.4 ft. of enameled manganin wire (B. and S. 36, total resistance 96 ohms) wound on a Teflon form and immersed in mineral oil in the well E. Leads from the heater and from the resistance thermometer pass out through the connecting tubes to terminals mounted on the calorimeter head. Power dissipation in the heating element is determined in the usual way[8] by means of a potential divider, a standard resistance (10 ohms) and a potentiometer.

During operation the calorimeter is immersed to a point just above the hydrogen inlet tube F in a thermostat bath held constant at 24.6 ± 0.004°. The parts of the assembly that project above the surface of the bath are surrounded by a copper can, to which a coil of copper tubing is soldered. Thermostat water is circulated through the coil and through the jacket of the gas-measuring buret.

Procedure.—Hydrogenation Run.—The calorimeter containing 225 ml. of acetic acid is assembled with evacuated

(8) J. M. Sturtevant, Chapter X in A. Weissberger, "Physical Methods of Organic Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1945.

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ampoules of catalyst and of the test substance,[9] wired to small magnets (L of Fig. 1), suspended in the supporting tubes by means of externally mounted Alnico magnets. Stopcocks and joints are sealed with apiezon grease, and, after the apparatus has been tested for leaks, the entire system is evacuated and filled with hydrogen through stopcock C. Hydrogen is then allowed to bubble slowly through the solvent for 10 minutes with stirring to remove dissolved air. At the end of this period the evacuation and filling process is repeated several times, and the system is finally closed at C under 3 mm. positive pressure. After heating the contents of the calorimeter to a point slightly above the bath temperature by means of the electric heater (K), the stirring rate is adjusted to the desired speed, and the system is allowed to come to equilibrium as indicated by linearity of the time–temperature curve. The ampoule of the test substance is then broken by allowing it to drop to the bottom of the calorimeter, and the time–temperature curve is followed until a constant slope is again obtained. At this point the volume of hydrogen in the buret (measured under 3 mm. positive pressure) and atmospheric pressure are noted, and the catalyst ampoule is broken. Temperature measurements are made at intervals until the time–temperature curve is once again linear. The pressure of hydrogen in the calorimeter is maintained slightly above atmospheric pressure throughout the reaction.

Calibration Run.[10]—At the end of the hydrogenation run, the calorimeter and its contents are cooled by allowing the temperature of the bath (refrigerated) to fall to about 18°. The bath temperature is then returned to 24.6°, and the calorimeter is brought to thermal equilibrium. The rating period is followed as before, and when the temperature at which the hydrogenation reaction was initiated is reached, the volume of hydrogen in the buret (3 mm. positive pressure) and atmospheric pressure are again recorded. The calorimeter heater is turned on, and the voltage drop across the heater and across the standard resistance, as well as the temperature of the calorimeter, are noted at intervals. The voltage applied to the heater is chosen so that the rate of heating in the hydrogenation run is duplicated as nearly as possible. When the temperature reaches a point approximating the maximum achieved during the hydrogenation run, the heater is switched off, the time being noted, and the time–temperature curve is followed until it is finally linear. The calorimeter is then dismantled and thoroughly cleaned with aqua regia in preparation for the next run.

The volume of hydrogen absorbed by the sample is calculated from the pressure–volume data and is corrected to standard conditions, allowance being made for the hydrogen absorbed by the catalyst, for the free space in the evacuated catalyst ampoule and for the partial pressure of acetic acid. In cases where discrepancies have been noted in the calculated and theoretical values for hydrogen absorption, the heats of hydrogenation reported are based upon hydrogen uptake. This procedure avoids possible complications resulting from losses of trace amounts of sample through retention in the ampoule stem or through evaporation and provides partial compensation for the presence of small amounts of impurities. In the few runs where discrepancies in hydrogen uptake of more than 1% have been observed (for example, see Paper IV), a special effort has been made to ascertain the nature of the impurities.

Tests of the Calorimeter.—Several preliminary tests were carried out for the purpose of assessing the precision and accuracy of results given by the calorimeter. It was first determined that the energy equivalent of the calorimeter, expressed in cal./ohm,[11] is independent of the rate of heat input over a given temperature interval. The results of a typical test run, in which the rate of stirring was the same as that employed in the hydrogenation experiments, are recorded in Table I. Since the resistance–temperature response of the thermistor may not be treated as linear over resistance intervals greater than 10 ohms (approximately 0.112°), the energy equivalent as a function of resistance is dependent to some degree upon the total resistance change. The difference in this value for successive hydrogenation and calibration runs can, however, easily be held to less than 2 ohms, and hence no significant error is introduced by extrapolation of the calibration data to the resistance interval of the hydrogenation run.

(9) *Approximately 100 mg. of platinum oxide is used in each run. Organic samples of a size sufficient to absorb 1 to 5 mmoles of hydrogen are employed.*

(10) *Each hydrogenation run is calibrated individually.*

(11) *The calorie employed throughout this investigation is defined as 4.1833 International Joules.*

TABLE I

ELECTRIC CALIBRATION OF THE CALORIMETER CONTAINING 225 ML. OF ACETIC ACID

(Total resistance change, 50 ohms)

	Energy input, cal./min.	Energy equivalent, cal./ohm
1	2.624	1.708
2	5.823	1.716
3	9.813	1.707
	Average	1.710 ± 0.004[a]

[a] Standard deviation.

No attempt has been made in the present investigation to obtain resistance readings with a precision exceeding 0.05) ohm (~0.0005°). The major part of the deviation (0.23%) recorded in Table I can thus be attributed to this source. Somewhat less precise results are expected for the hydrogenation runs (Tables II, III and IV), but in only a few cases has the experimental variation been appreciably greater than ±0.5%, and in many instances it has been significantly less.

Of the compounds that have been examined in this Laboratory thus far, five were included in the earlier investigations. An estimate of the accuracy of the present data can therefore be made by comparison of our results with those obtained previously (Table II). The experimental value reported by

TABLE II

HEATS OF HYDROGENATION OF FIVE REFERENCE COMPOUNDS

	ΔH, kcal./mole	
	This investigation	Previous results
Diethyl fumarate	−28.94 ± 0.05	−29.08 ± 0.15[a]
Cyclohexene	−27.10 ± .08	−28.59 ± .01[b]
Cycloheptene	−25.85 ± .09	−26.52 ± .02[c]
cis-Cycloöctene	−22.98 ± .10[d]	−23.53 ± .04[e]
Cycloheptatriene	−70.49 ± .39	−72.85 ± .01[a]

[a] Data of R. B. Williams (ref. 2) corrected for the heat of solution of diethyl fumarate. [b] Gas phase data (82°) of Kistiakowsky (ref. 2c). [c] Gas phase data (82°) of Kistiakowsky (ref. 2g). [d] R. B. Turner and W. R. Meador, THIS JOURNAL, 79, 4133 (1957).

Williams[2] for the heat of the reaction

diethyl fumarate(liq.) + H_2(gas) ⟶ diethyl succinate (dissolved)

is −28.98 ± 0.15 kcal./mole. When this figure is corrected for the heat of solution of diethyl fumarate in acetic acid (~100 cal./mole) a value of −29.08 ± 0.15 kcal./mole is obtained, which agrees with our result within experimental error. Since Williams' instrument was compared with the Kistiakowsky gas phase calorimeter by measurement of the heat of hydrogenation of heptene-1 and appropriate correction of the liquid phase results to the gas phase at 82°, it may be concluded that all three calorimeters give concordant values, although the actual measurements apply to different conditions of state. A direct comparison of our results for the heats of hydrogenation of cyclohexene, cycloheptene and *cis*-cycloöctene with the Kistiakowsky values is unfortunately not possible in the absence of the requisite thermodynamic data. It will be observed, however, that the solution measurements on these monoölefins run about 0.5 to 1.5 kcal./mole lower than the corresponding gas phase values, as compared with a difference of about 0.5 kcal. between liquid phase and gas phase results for heptene-1 noted by Williams.[2] A somewhat larger correction term would be expected for cycloheptatriene with three double bonds,[12] and in this case a rough comparison of the solution and gas phase data can be made in the following manner. Calculation of the "resonance energy" of cycloheptatriene from the heat of hydrogenation of this substance and three

(12) See the discussion commencing on p. 1399 of reference 2.

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times the heat of hydrogenation of cycloheptene gives, for the gas phase, a value of 6.7 kcal./mole. A corresponding calculation employing the solution data furnishes a value of 7.1 kcal./mole. The agreement is closer than might have been expected in view of complications that may arise in solution work from solvent–solute interactions. It would appear, however, that such effects are small in the case of relatively non-polar molecules, and it seems unlikely that the over-all error in our results is greater than about 1%. With regard to precision and accuracy, the present calorimeter is therefore comparable to that described by Williams, who used somewhat larger quantities of material than were employed in this work.

Materials.—The platinum oxide catalyst was obtained in a single batch from Baker and Co., Newark, N. J., and was thoroughly mixed and equilibrated with air at constant humidity prior to weighing. X-Ray examination of this material, carried out through the courtesy of Dr. J. Waser, revealed the presence of small amounts of free platinum mixed with the platinum oxide.

Acetic acid employed as the solvent was J. T. Baker Chemical Co. reagent grade, which was stirred with platinum in a hydrogen atmosphere and distilled before use. The solvent was prepared in large batches to ensure uniformity in any given series of experiments. Periodic calibration of the catalyst in various solvent samples, however, showed no significant variation in heat evolved.

Electrolytic hydrogen was supplied from a cylinder through a Deoxo purifier (Baker and Co., Newark, N. J.).

Diethyl fumarate, Eastman Kodak Co. product, was twice distilled at atmospheric pressure, b.p. 213–214°, n^{20}D 1.4412. **The cyclohexene** employed in this investigation was obtained from the American Petroleum Institute, sample No. 522-5S, impurity, 0.023 ± 0.02%. **Cycloheptene**, b.p. 113°, n^{25}D 1.4562, was made available through the courtesy of Dr. W. von E. Doering. The sample was prepared by acid-catalyzed dehydration of cycloheptanol and was purified by distillation through a 4-ft., 50-plate column packed with glass helices. **Cycloheptatriene** (tropilidene), n^{20}D 1.5239, was prepared by F. L. Detert, Hickrill Chemical Research Foundation, from benzene and diazomethane according to the procedure of Doering and Knox.[13a] The material used for hydrogenation was part of the same sample employed in the thermodynamic studies of Waddington and his associates,[13b] who report a m.p. of −75.24° and a purity of 99.986 mole % for this substance. This specimen is therefore purer than the sample, m.p. −79.5°, used by Kistiakowsky.[2g] **Bicyclo[2,2,1]heptene**, purified by passage through a Perkin–Elmer vapor fractometer, was also provided by Dr. Doering. We are further indebted to Drs. S. J. Cristol and J. Hine for samples of **bicyclo[2,2,1]heptadiene**, b.p. 82.1–82.3°, n^{20}D 1.4700, and of **bicyclo[2,2,2]octene**, m.p. 114–115°. **Bicyclo[2,2,2]octadiene**, m.p. 57°, was prepared especially for the hydrogenation work through the courtesy of Dr. C. A. Grob.[14] At Dr. Grob's suggestion the material was subjected to vapor phase chromatography and was found to be entirely homogeneous.

Results and Discussion

The values obtained for the heats of hydrogenation of the platinum oxide catalyst and of the various olefins are given in Tables III and IV, respectively. The heat evolved in reduction of the catalyst is expressed as cal./100.0 mg. and that for the olefins as kcal./mole. The averages of individual determinations on the various compounds are listed together with the corresponding standard deviations. Since the heats of hydrogenation of the olefins were uniformly determined as the difference between the total heat evolved and that associated with reduction of the catalyst, the uncertainty in the latter value is included as an appropriate term in the deviations reported for the unsaturated compounds.

(13) (a) W. von E. Doering and L. H. Knox, THIS JOURNAL, **72**, 2305 (1950); (b) H. L. Finke, D. W. Scott, M. E. Gross, J. F. Messerly and G. Waddington, *ibid.*, **78**, 5469 (1956).

(14) *Cf.* C. A. Grob, H. Kny and A. Gagneux, *Helv. Chim. Acta*, **40**, 130 (1957).

The progress of hydrogenation was followed volumetrically as well as calorimetrically. The reactions are initially fast owing to rapid reduction of the platinum oxide, which is complete in less than two minutes. The subsequent rates of reduction exhibit considerable variation from compound to compound and are generally higher for those substances showing a high heat of hydrogenation per double bond than for those for which the heat of hydrogenation per double bond is low.

TABLE III

HEAT OF HYDROGENATION OF THE CATALYST (ACETIC ACID)

PtO_2, mg.	$-\Delta H$, 25°, cal./100.0 mg.
99.67	30.86
100.08	30.90
101.00	31.13
100.80	30.99
100.61	31.75
99.85	30.75
Average	30.95 ± 0.13

TABLE IV

HEATS OF HYDROGENATION OF VARIOUS OLEFINS (ACETIC ACID SOLUTION)

Compound	Mmoles	PtO_2, mg.	$-\Delta H$, 25°, kcal./mole
Diethyl fumarate	2.592	99.71	28.99
	2.980	101.60	28.88
	Average		28.94 ± 0.05
Cyclohexene	3.695	100.31	27.03
	3.796	99.98	27.16
	Average		27.10 ± 0.08
Cycloheptene	2.717	100.40	25.92
	2.837	99.70	25.78
	Average		25.85 ± 0.09
Cycloheptatriene	1.144	99.50	70.86
	1.061	99.80	70.12
	Average		70.49 ± 0.39
Bicyclo[2,2,1]heptene	2.974	99.95	33.34
	2.491	99.90	32.93
	Average		33.13 ± 0.21
Bicyclo[2,2,1]heptadiene	1.855	99.23	68.14
	1.754	99.52	68.62
	1.637	99.20	67.58
	Average		68.11 ± 0.41
Bicyclo[2,2,2]octene	3.115	100.10	27.90
	3.086	99.62	28.45
	3.079	99.43	28.40
	Average		28.25 ± 0.20
Bicyclo[2,2,2]octadiene	1.741	100.48	56.30
	2.006	100.26	56.20
	1.455	100.04	56.13
	Average		56.21 ± 0.10

With reference to recent discussions of the phenomenon of "homoallylic resonance,"[15] the question of the existence or absence of homoallylic stabilization (*cf.* structure IV) in bicyclo[2,2,1]-heptadiene (I) is one of considerable interest. This substance has been shown by Winstein[16] to

(15) (a) M. Simonetta and S. Winstein, THIS JOURNAL, **76**, 18 (1954); (b) E. E. van Tamelen, *ibid.*, **77**, 1704 (1955); (c) J. Hine, J. A. Brown, L. H. Zalkow, W. E. Gardner and M. Hine, *ibid.*, **77**, 594 (1955).

(16) S. Winstein and M. Shatavsky, *Chemistry & Industry*, 59 (1956); Gurukul Kangri Collection, Haridwar

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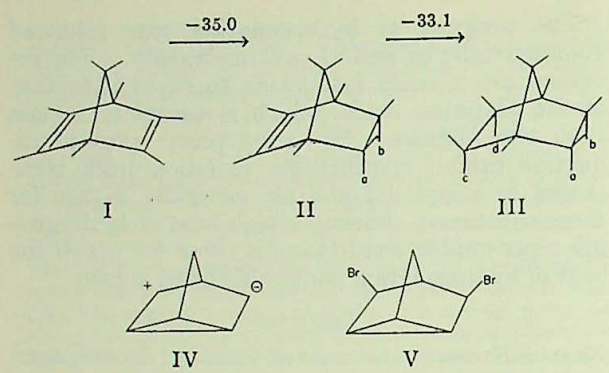
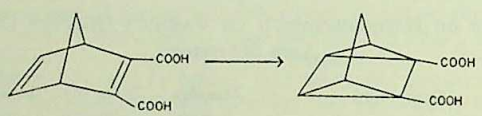


undergo bromination with double bond participation to give, among other products, *cis*-3,5-dibromomonortricyclene (V).[17] Bridging in the bicycloheptadiene system also has been observed by Cristol and Snell,[18] who showed that bicyclo[2,2,1]-heptadiene-2,3-dicarboxylic acid (VI) is readily converted into tetracyclo[2,2,1,$0^{2,6}0^{3,5}$]heptane-2,-3-dicarboxylic acid (VII) on irradiation with ultra-



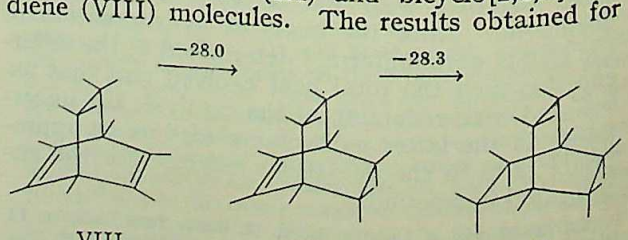
violet light. The formation of bridged products in these reactions, however, does not demonstrate the existence of homoallylic resonance in the resting bicycloheptadiene and bicycloheptadienedicarboxylic acid molecules, since bridging in these cases may be conditioned by attack of an electrophilic reagent or by radiation induced excitation. In this connection it should be noted that the shifts observed in the spectra of 2,5-dihydroacetophenone[19] and of various bicycloheptadiene and bicyclooctadiene derivatives[20] are subject to similar restrictions of interpretation. In any event it is clear that homoallylic resonance, if present in these systems, must be small since the orientation of the π-orbitals involved is not favorable for efficient overlap.[21]

A quantitative investigation of this problem by the hydrogenation method has now been undertaken. Although interpretation of the data is unfortunately complicated by uncertainties in the magnitudes of certain steric interactions and strain effects, the results indicate that structures of type IV make no important contribution to the energy of the bicycloheptadiene molecule.

The heats of hydrogenation of bicyclo[2,2,1]-heptene (II) and of bicyclo[2,2,1]heptadiene (I) are −33.13 ± 0.21 and −68.11 ± 0.41 kcal./mole, respectively. As a basis for estimating "homoallylic resonance energy" in the diene system, twice the bicycloheptene value, or −66.26 ±0.42 kcal./mole, has been taken as a point of reference. If, in accordance with the procedure adopted by Kistiakowsky,[16] "resonance energy" in the diene is defined as the difference between the heat of hydrogenation observed for this substance and that calculated for the "non-resonating" reference model, the "resonance energy" estimated for bicycloheptadiene is *negative* and equal to −1.9 kcal./mole. An alternate, but entirely equivalent, approach involves comparison of the heat change calculated for hydrogenation of the diene to olefin (−35.0 kcal./mole) with that observed for reduction of the olefin to the corresponding paraffin (−33.1 kcal./mole). Now hydrogenation of the first double bond of bicycloheptadiene results in the introduction of two hydrogen atoms (a and b of II) that do not encounter the steric repulsions a → c and b → d (*cf.* III) introduced on hydrogenation of bicycloheptene. Since an increase in steric compression in the reduction product will be reflected in a relative decrease in the heat of hydrogenation, the heat change calculated for reduction of "non-resonating" bicycloheptadiene from twice the figure for bicycloheptene will be too low. The apparent value for "resonance energy" must therefore be revised upwards to correct for this effect. The magnitude of the correction term is difficult to assess, but in view of the value assigned to the rotational barrier in ethane (2.8 kcal./mole),[22] it seems unlikely that the interactions in question can involve more than about one kcal. To the extent that this approximation is valid, and within the limits of experimental error, it would appear that bicycloheptadiene is devoid of homoallylic stabilization.

A further obvious complication in the treatment of the bicycloheptene–bicycloheptadiene system arises from the high degree of strain associated with these molecules. The heat of hydrogenation of bicycloheptene is one of the highest yet recorded, being 6 kcal. higher than that of cyclohexene, and the heat developed in the conversion of bicycloheptadiene into bicycloheptene is surpassed only by the heat of hydrogenation of *cis*-di-*t*-butylethylene.[23] Clearly, if the strain energy in bicycloheptadiene is more than twice that of the corresponding monoölefin, calculations of the type indicated above can lead to an apparent negative resonance energy.

In an effort to limit the uncertainties attending the strain problem, we have investigated the heats of hydrogenation of the relatively unstrained bicyclo[2,2,2]octene (IX) and bicyclo[2,2,2]octadiene (VIII) molecules. The results obtained for



(17) Similar attempts on the part of van Tamelen (reference 15b) to demonstrate participation in reactions of 1,4-cyclohexadiene were unsuccessful.

(18) S. J. Cristol and R. L. Snell, THIS JOURNAL, **76**, 5000 (1954).

(19) K. Bowden and E. R. H. Jones, *J. Chem. Soc.*, 52 (1946); see also E. A. Braude, E. R. H. Jones, F. Sondheimer and J. B. Toogood, *ibid.*, 607 (1949), and D. J. Cram and H. Steinberg, THIS JOURNAL, **73**, 5691 (1951).

(20) E. R. H. Jones, G. H. Mansfield and M. C. Whiting, *J. Chem. Soc.*, 4073 (1956).

(21) C. A. Coulson, "Valence," Oxford University Press, London, 1952, p. 71.

(22) K. S. Pitzer, *Chem. Revs.*, **27**, 39 (1940).

(23) Paper VI of this series (forthcoming).

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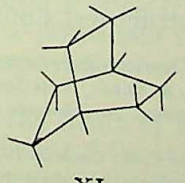
these substances are -28.25 ± 0.02 and -56.21 ± 0.10 kcal./mole, respectively. Since the heat change calculated for the process VIII → IX (−28.0 kcal./mole) is, within experimental error, essentially identical with that observed for the transformation IX → X, the "resonance energy" of bicycloöctadiene must be equated to the correction terms that are applied. As in the case of bicycloheptadiene, account must be taken of the discrepancy introduced by the appearance of two additional 1:3 hydrogen–hydrogen repulsions in the second step of the hydrogenation sequence VIII → XI → X. Assuming for these interactions the arbitrary figure taken in the bicycloheptadiene treatment, the stabilization energy in bicycloöctadiene is estimated to have a maximum value of the order of one kcal. However, in the light of arguments presented in the following paragraphs, there is reason to believe that the steric repulsion correction for bicycloöctadiene should be less than that for bicycloheptadiene. Thus, although a definitive statement regarding homoallylic resonance in bicycloöctadiene cannot be made, the present results suggest that stabilization of this sort is minimal.

The heat of hydrogenation of bicycloöctene to bicycloöctane (−28.3 kcal./mole) is surprisingly high in view of the number of 1:2- and 1:3- eclipsed interactions that appear in the latter product. Cyclohexene, which affords a reduction product possessing a staggered conformation, has a heat of hydrogenation of −27.1 kcal./mole. One would therefore anticipate that the heat of hydrogenation of bicycloöctene would lie somewhat below this value. A consistent argument based upon conformational properties can be advanced in explanation of this apparent anomaly. The conformation of bicycloöctane shown in structure X is totally eclipsed and possesses six 1:2- and six 1:3- opposed hydrogen–hydrogen interactions, as well as three pairs of opposed carbon–carbon bond repulsions. This arrangement represents an energy maximum for non-bonded interactions, which can be relieved considerably by twisting about the central axis to give a partially eclipsed conformation XI. Examination of molecular models indicates that



XI

twisting amounting to about 10° can be accommodated without distortion of bond angles. Similar twisting in bicycloheptane is restricted by the presence of one-carbon bridging. Since a small reduction in each of the interactions noted above can account for a relatively large total energy change, the high heat of hydrogenation of bicycloöctene can be attributed to heat evolution accompanying the conformational transition X → XI. As an alternative to this suggestion it will be noted that if twisting in bicycloöctene is also permitted, the accompanying increase in torsional strain of the double bond will be reflected in a corresponding increase in the heat of hydrogenation of this substance.

Although a final decision between these alternatives cannot be made at the present time, we prefer the second explanation for the following reasons. The heat change accompanying hydrogenation of bicycloöctadiene to bicycloöctene, a process that results in the introduction of two 1:2- and two 1:3- opposed hydrogen–hydrogen interactions,[24] is also abnormally high (−28.0 kcal./mole) when compared with the cyclohexene value. This result is difficult to explain in terms of a totally eclipsed conformation for bicycloöctene but can be rationalized if bicycloöctene possesses a twisted structure.

Comparison of the heats of hydrogenation of cyclopentene and cyclohexene with those of bicycloheptene and bicycloöctene provides an interesting illustration of the relative importance of angle strain and non-bonded repulsions in these systems. The heat evolved in the hydrogenation of cyclopentene[26] is 1.7 kcal. *less* than that produced in the hydrogenation of cyclohexene, despite the fact that bond angles in the former substance must deviate from the normal values. Since in five-membered carbocycles departures from planarity are relatively small,[25] the hydrogen atoms of cyclopentane are all eclipsed, or nearly so, whereas the hydrogen atoms of cyclohexane ("chair" form) adopt a staggered arrangement. In this case it is clear that steric repulsion effects predominate.

The situation with respect to bicycloheptene and bicycloöctene differs from that found in the monocyclic compounds and can best be deduced from inspection of models. It is observed that, apart from certain minor differences, the same numbers of interactions—*e.g.*, two 1,2- and four 1,3-hydrogen–hydrogen repulsions—are introduced in the hydrogenation of both olefins. Whereas bicycloöctane, and probably also bicycloöctene, can twist off from the position of maximum eclipsing, a similar adjustment in the bicycloheptane–bicycloheptene system is not possible, and steric factors would hence be expected to raise the heat of hydrogenation of bicycloöctene relative to that of bicycloheptene. The fact that the heat of hydrogenation of bicycloöctene is almost 5 kcal. lower than that of bicycloheptene must therefore be attributed to angle strain in bicycloheptene, which is more severe than in the case of cyclopentene owing to geometric requirements of the bridged system.

Acknowledgment.—We are indebted to the Eli Lilly Co., Indianapolis, for generous support of this work and to Professor G. B. Kistiakowsky for his invaluable advice and encouragement. It is a pleasure to acknowledge also the assistance that has been rendered us by Professor W. O. Milligan in connection with a variety of problems arising in the course of this investigation.

HOUSTON, TEXAS

(24) In this connection it should be pointed out that eclipsing of the bridge-head hydrogen atoms by two ethylenic hydrogens is relieved on hydrogenation.

(25) J. E. Kilpatrick, K. S. Pitzer and R. Spitzer, THIS JOURNAL, 69, 2483 (1947); C. G. Le Fèvre and R. S. W. Le Fèvre, *J. Chem. Soc.*, 3549 (1956).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

Heats of Hydrogenation. II. Heats of Hydrogenation and the Acid-catalyzed Isomerization of Some Unsaturated Steroids[1]

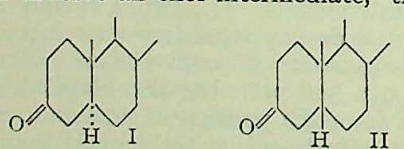
BY RICHARD B. TURNER, W. R. MEADOR AND R. E. WINKLER

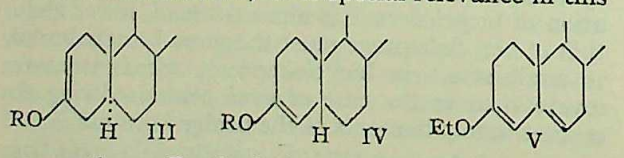
RECEIVED FEBRUARY 25, 1957

The heats of hydrogenation of cholest-1-ene, cholest-2-ene, cholest-3-ene, cholest-5-ene, cholest-6-ene and of 3α-hydroxy-Δ^{11}-cholenic acid have been determined and correlated with conformational properties of these molecules. The observed stability order—$\Delta^2 \simeq \Delta^5 > \Delta^1 \simeq \Delta^6 > \Delta^3 > \Delta^{11}$—is consistent with various observations made in connection with a study of acid-catalyzed double bond migration in these systems.

In connection with a general program dealing with measurements of heats of catalytic hydrogenation in solution, the heats of hydrogenation of several steroid olefins have been determined. The results provide a quantitative measure of stability relationships among olefins possessing double bonds at various positions in a fused ring system. The experimental procedure employed in this investigation has been described in the first paper of this series[2] and requires no further discussion. As a supplement to the hydrogenation experiments, a study of the isomerization of steroid olefins under conditions of acid catalysis also was undertaken. The results of these two lines of investigation are reported in the present communication.

It has been known for many years that monobromination of cholestan-3-one (I) furnishes mainly 2-bromocholestan-3-one, whereas monobromination of coprostan-3-one (II) yields 4-bromocoprostan-3-one as the only isolable product.[3] Similar directional specificity is encountered in sulfonation of the two ketones[4] and in various other allied reactions. Since the bromination reaction has been shown to involve an enol intermediate,[5] the demonstration that cholestan-3-one furnishes enol derivatives (ethers and esters) of structure III, whereas coprostan-3-one yields analogous derivatives of structure IV,[6] is of special relevance in this connection. Particularly noteworthy is the fact that partial catalytic hydrogenation of cholestenone enol ether (V) yields III (R = C_2H_5) with double bond migration rather than the expected Δ^3-isomer.[6b] It may therefore be concluded that a double bond at the 2,3-position of the cholestane nucleus is energetically favored over a double bond at the 3,4-position and that the converse is true for the corresponding olefins of the coprostane series.





Examination of molecular models of coprost-2-ene and of coprost-3-ene reveals a severe steric compression of the 4α- and 7α-hydrogen atoms in coprost-2-ene, which has no counterpart in the Δ^3-isomer and which may be expected to contribute to the thermodynamic instability of the Δ^2-olefin. Other conformational aspects of the coprostene problem have been discussed by Taylor[7] in terms of properties of the *cis*-octalins. The origins of the apparent energy difference between cholest-2-ene and cholest-3-ene recently have been dealt with by Corey and Sneen[8] and are considered further from a slightly different point of view in a later section of this paper.

Directional specificity of the type noted above also has been observed in various derivatives of *cis*- and *trans*-decalin. Thus, dehydration of *trans*-2-decalol over potassium bisulfate yields almost pure *trans*-2-octalin, whereas similar treatment of *cis*-2-decalol affords a mixture in which *cis*-1-octalin represents the major component.[9] Substitution reactions of *trans*-2-decalone occur mainly at the 3-position, but the situation with respect to *cis*-2-decalone is less well defined. Chlorination of this substance gives, in low yield, a product that has been formulated as a 3-chloro derivative.[10] Great caution must therefore be exercised in extrapolating stability relationships from one series of compounds to another, in spite of the existence of close structural similarities.[11,12]

(1) The work described in this paper was supported by funds made available by the Eli Lilly Co. and by the Research Corporation.

(2) R. B. Turner, W. R. Meador and R. E. Winkler, THIS JOURNAL, 79, 4116 (1957).

(3) A. Butenandt and A. Wolff, *Ber.*, 68, 2091 (1935).

(4) A. Windaus and E. Kuhn, *Ann.*, 532, 52 (1937); A. Windaus, and K. H. Mielke, *ibid.*, 536, 116 (1938).

(5) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 231.

(6) (a) H. H. Inhoffen, G. Stoeck, G. Kölling and V. Stoeck, *Ann.*, 568, 52 (1950); (b) H. H. Inhoffen, W. Becker and G. Kölling, *ibid.*, 568, 181 (1950); (c) W. G. Dauben, R. A. Micheli and J. F. Eastham, THIS JOURNAL, 74, 3852 (1952).

(7) D. A. H. Taylor, *Chemistry & Industry*, 250 (1954).

(8) E. J. Corey and R. A. Sneen, THIS JOURNAL, 77, 2505 (1955).

(9) W. Hückel, R. Danneel, A. Schwartz and A. Gerke, *Ann.*, 474, 121 (1929).

(10) The observation of J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 817 (1937), that condensation of *cis*-2-decalone with ethyl oxalate occurs at the 3-position can be explained in terms of product equilibrium and is hence not relevant to the present discussion; *cf.* G. Stork and R. K. Hill, THIS JOURNAL, 79, 495 (1957).

(11) *Cf.* G. Stork and A. W. Burgstahler, THIS JOURNAL, 77, 5068 (1955).

(12) With reference to the structural analogy drawn between coprostan-3-one and *cis*-2-decalone, it will be noted that whereas the steroid ring system is relatively rigid, owing to constraints imposed by the *trans* fusion between rings B and C, the conformational mobility of *cis*-2-decalone is not thus restricted. The entropy contribution to free energy will thus assume greater importance in the *cis*-decalin than in the coprostane series, while this differentiation between *trans*-decalin derivatives and cholestane derivatives should be less marked. Arguments based solely on steric interactions that have been advanced in connection with the coprostanone problem will not necessarily hold with equal force for *cis*-2-decalone, particularly since relief of steric strains could be attained more easily in the more flexible molecule.

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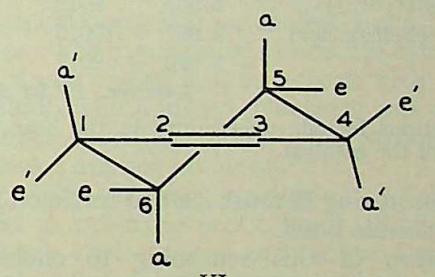
Hydrogenation Data.—The values for the heats of hydrogenation (acetic acid solution, 25°) of six steroid olefins are given in Table I. The precision of the results obtained in this series was limited by the amounts of material that could be employed in view of the relatively low solubility of these substances and of the reduction product, cholestane, in acetic acid. Cholest-4-ene was not included in this investigation, since catalytic hydrogenation of this derivative yields a mixture of stereoisomers.

All of the substances in question possess an olefinic double bond in a six-membered ring, and, with the exception of cholest-5-ene, all are of the *cis*-disubstituted type. The relatively large differences in heat content observed in this series—3 kcal. in the case of compounds 2 and 6—are therefore of considerable interest. In this connection it should be noted that the resonance energy calculated for butadiene from hydrogenation data is 3.5 kcal./mole[13] and that resonance coupling of the benzene ring and vinyl group in styrene results in additional stabilization of only 1.6 kcal./mole.[14] It is evident that steric effects of a rather subtle nature may often overshadow the resonance effect.

The lowest heats of hydrogenation, and hence maximum thermodynamic stabilities, are encountered in the Δ^2- and Δ^5-cholestenes, the values obtained for these substances being indistinguishable within the limits of experimental error. Catalytic hydrogenation of 5:6-unsaturated steroids is known to yield mainly A/B *trans*-fused products, but small amounts (2–4%) of the corresponding A/B *cis* derivatives have been obtained in isolated instances.[15] However, since the energy difference between cholestane (A/B *trans*) and coprostane (A/B *cis*) is small (~ 0.8 kcal./mole),[16] the formation of a few per cent. of coprostane in the reduction of cholest-5-ene should not compromise comparison of the heat of hydrogenation of this substance with that of cholest-2-ene, which yields only cholestane. On the basis of the substitution effect, cholest-5-ene (trisubstituted) should be more stable than cholest-2-ene (disubstituted) by about 1.5 kcal./mole.[17] The 5:6-double bond is, however, exocyclic to ring A, and it is clear from the hydrogenation data that a positional effect of approximately the same magnitude must operate in favor of cholest-2-ene.

The difference in the heats of hydrogenation of cholest-2-ene and cholest-3-ene is 2.1 kcal./mole. The direction of the energy difference establishes the fact that cholest-2-ene is the more stable isomer, and the magnitude of the effect provides an adequate basis for interpretation of the directional specificity observed in the various enol reactions noted previously. The discrepancy between the result obtained for cholest-2-ene (−25.9 kcal./mole) and the heat of hydrogenation of cyclohexene (−27.1 kcal./mole)[2] is presumably attributable in large part to interactions of the axial C.10 methyl group of cholestane with axial hydrogen atoms, which interactions are replaced by hydrogen–hydrogen repulsions in the case of cyclohexane.[18]

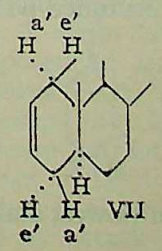
The stability difference between cholest-2-ene and cholest-3-ene has been ascribed by Corey and Sneen[8] to a reduction of the distance separating the C.10 methyl group and the C.6 β-hydrogen atom in the latter compound. An equivalent, but less detailed, treatment of the problem can be given as follows. The preferred conformation adopted by cyclohexene is now generally regarded as the "half-chair" conformation VI, in which carbon atoms 1, 2, 3 and 4 lie in a single plane.[19] The substituent groups attached to carbon atoms 5 and 6 are staggered with respect to each other and are hence considered to have the axial and equatorial properties associated with similarly situated substituents in cyclohexane.



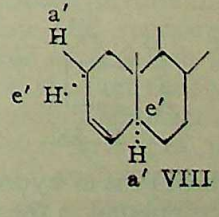
VI

On the other hand, distortion of the molecule necessitated by the planar arrangement of carbon atoms 1–4 forces the substituents on carbon atoms 1 and 4 into partial eclipse with those on carbons 6 and 5, respectively. Atoms or groups attached to carbon atoms adjacent to a double bond are hence neither truly axial nor truly equatorial and are termed quasi-axial (a′) and quasi-equatorial (e′) as the case may be.

With reference to cholest-2-ene (VII), the a′,e′ bonds are all attached to hydrogen, and as a consequence the conformation of ring B is essentially unaffected. On the other hand, in cholest-3-ene (VIII) the 5:6-bond must be quasi-equatorial with respect to ring A if the double bond is planar, and ring B is therefore forced into a deformed "chair" conformation with resultant increase in strain.



VII



a′ VIII

Conversely, restoration of the most favored con-

(13) G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, THIS JOURNAL, **58**, 146 (1936).
(14) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky and W. E. Vaughan, *ibid.*, **59**, 831 (1937).
(15) T. Reichstein and A. Lardon, *Helv. Chim. Acta*, **24**, 955 (1941); E. B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle and L. Kuhlen, THIS JOURNAL, **73**, 1144 (1951).
(16) R. B. Turner, *ibid.*, **74**, 2118 (1952).
(17) J. B. Conant and G. B. Kistiakowsky, *Chem. Revs.*, **20**, 181 (1937).
(18) It is of interest to note that the energy difference between axial and equatorial methyl groups in the 6-membered ring has been estimated as 1.8 kcal./mole by S. Winstein and N. J. Holness, THIS JOURNAL, **77**, 5562 (1955).
(19) C. W. Beckett, N. K. Freeman and K. S. Pitzer, *ibid.*, **70**, 4227 (1948); D. H. R. Barton, R. C. Cookson, W. Klyne and C. W. Shoppee, *Chemistry & Industry*, 21 (1954).

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TABLE I

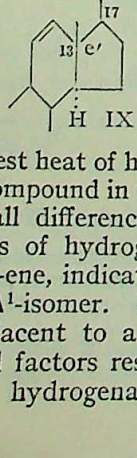
HEATS OF HYDROGENATION OF VARIOUS STEROID OLEFINS (ACETIC ACID, 25°)

No.	Compound	Mmoles	PtO_2, mg.	$-\Delta H$, kcal./mole
1	Cholest-1-ene	1.375	99.7	27.08
		1.354	99.8	27.52
		Average		27.30 ± 0.24[a]
2	Cholest-2-ene	1.078	99.9	25.81
		1.379	100.0	26.01
		0.921	99.8	25.73
		Average		25.85 ± 0.17
3	Cholest-3-ene	1.370	99.0	28.04
		1.290	99.0	27.74
		1.046	99.6	28.08
		Average		27.97 ± 0.14
4	Cholest-5-ene	1.352	99.6	25.77
		1.323	100.0	25.92
		Average		25.85 ± 0.13
5	Cholest-6-ene	1.304	100.0	27.43
		1.337	99.7	27.28
		Average		27.36 ± 0.10
6	3α-Hydroxy-Δ^{11}-cholenic acid	2.065	99.8	29.10
		2.087	100.3	28.85
		2.098	99.7	28.84
		Average		28.93 ± 0.15

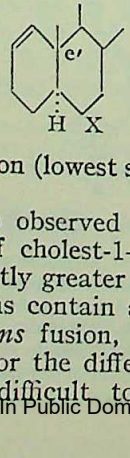
[a] Deviations include uncertainty in the heat of hydrogenation of the catalyst.

formation in ring B must lead to torsional strain in the 3:4-double bond.

Extension of this reasoning to cholest-6-ene, which possesses a double bond adjacent to two *trans* fusions, would suggest that this substance should be thermodynamically less stable than cholest-3-ene, in which only one *trans* fusion is directly involved. Comparison of the heats of hydrogenation of these compounds, however, indicates that cholest-6-ene is more stable than cholest-3-ene by a small, but experimentally significant, amount. A rationalization of this apparent anomaly can be derived from examination of the cholest-6-ene model. In this substance the deformation of ring C, brought about by the presence of a planar olefinic linkage at the 6:7-position, is such that the transoid character of the C/D fusion is somewhat reduced. In the case of 3α-hydroxy-Δ^{11}-cholenic acid (IX), however, introduction of a quasi-equatorial bond at the 13:17-position increases the transoid character of the C/D fusion with resultant increase in strain, and this substance possesses



IX



X

the highest heat of hydrogenation (lowest stability) of any compound in the series.

A small difference was also observed between the heats of hydrogenation of cholest-1-ene and cholest-3-ene, indicating a slightly greater stability for the Δ^1-isomer. Both olefins contain a double bond adjacent to a single *trans* fusion, and the structural factors responsible for the difference in heats of hydrogenation are difficult to assess. It may be noted, however, that in cholest-1-ene the bulky C.10 methyl group possesses an a′-orientation and that in this molecule, but not in cholest-3-ene, conformational effects associated with ring A are directly transmitted to ring C through a quasi-equatorial bond (*cf.* X).

No mention has thus far been made of the part that hyperconjugation may play in determining stability relationships in this series. Since the relative abilities of a′ and e′ hydrogen atoms to participate in hyperconjugation have not been established,[20] any consideration of the hyperconjugative phenomenon is subject to considerable uncertainty. Although it is clear from the data of Table II that more hydrogens are available for possible hyperconjugation in the most stable, than in the least stable, olefins, we do not feel that any useful generalization of this information can be made at the present time.

TABLE II

STABILITY ORDER AND α-HYDROGEN BOND TYPE

Stability order	$\Delta^2 \simeq \Delta^5$	>	$\Delta^1 \simeq \Delta^6$	>	Δ^3	>	Δ^{11}
No. of a′ hydrogens	2	2	1	2	2	1	
No. of e′ hydrogens	2	2	1	0	1	0	

In 1954, Henbest, Meakins and Wood[21] reported a stability order ($\Delta^2 > \Delta^3 \simeq \Delta^1 > \Delta^6 > \Delta^{11}$) for the cholestenes based upon examination of the infrared spectra of these compounds in the olefinic stretching and C–H out-of-plane bending regions. The principal difference between the order proposed by the British investigators and that derived from the hydrogenation data (Table II) lies in the position assigned to cholest-3-ene. Now the strain introduced in these molecules by the presence of unsaturation will be distributed over torsional strain in the olefinic linkages, angle strain in tetrahedral and trigonal bonds and steric strain associated with non-bonded repulsive interactions in such a way that the total energies of the molecules will be minimized. It is not surprising, therefore, that heat of hydrogenation differences, which as a first approximation reflect total energy differences, should give a stability order at variance with the infrared measurements, which are concerned mainly with strain in the double bonds.

Acid-catalyzed Isomerizations.—In addition to the hydrogenation experiments discussed in preceding paragraphs, the behavior of various cholestenes in the presence of acid has been investigated. This work was originally undertaken in the hope that equilibria could be established, which would furnish quantitative data on free energy relationships in this series. However, owing to the intervention of skeletal rearrangement, this hope was realized only for the cholest-4-ene–cholest-5-ene system, and the information that has been obtained is therefore of qualitative rather than of quantitative interest.

When cholest-5-ene is treated with *p*-toluenesulfonic acid in a refluxing mixture of acetic acid

(20) *Cf.* A. Streitwieser, R. H. Jagow and S. Suzuki, THIS JOURNAL, **77**, 6713 (1955); S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955); V. J. Shiner, *ibid.*, **78**, 2653 (1956).

(21) H. B. Henbest, G. D. Meakins and G. W. Wood, *J. Chem. Soc.*, 800 (1954).

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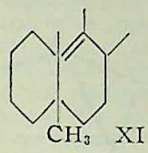
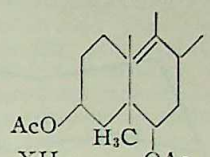
and cyclohexane (85°), it is rapidly converted into an oily mixture containing both cholest-5-ene and cholest-4-ene as indicated by infrared analysis. No other components, for example acetate esters or other double bond isomers, are spectrophotometrically detectable, and the specific rotation of the product (−17.5°) suggests the presence in the mixture of approximately 55% of cholest-4-ene and 45% of cholest-5-ene, corresponding to a free energy difference of only 0.1 kcal./mole. The infrared spectrum of a synthetic mixture of this composition is indistinguishable from that of the isomerization product. Similar treatment of cholest-4-ene affords identical material, and since no further change is effected by prolonged heating with acid under the conditions specified above, the isomerization product is regarded as an equilibrium mixture.

Treatment of the equilibrium mixture, or of either pure olefin, with *p*-toluenesulfonic acid in refluxing acetic acid for 2.5 hr., results in the formation of a colorless oil, which has resisted all attempts at crystallization. Although this product appears to be chromatographically homogeneous, it is not unlikely that the material represents a mixture of two or more substances. Unsaturation was demonstrated by the tetranitromethane test, and examination of the ultraviolet spectrum of the tetranitromethane treated material indicated the presence of a tetrasubstituted double bond.[22] Support for this conclusion is derived from the failure of the product to undergo catalytic hydrogenation under normal conditions. Hydrogenation can, however, be accomplished under forcing conditions,[23] and the oily product obtained in this way proved to be saturated in the tetranitromethane test.

In intact cholestane or coprostane structures only three positions, 8:9, 8:14 and 17:20, can accommodate a tetrasubstituted double bond. The 17:20-position is unlikely in view of the general difficulty encountered in the introduction of a tetrasubstituted double bond in this position[24] and would further appear to be excluded by the observation that both cholest-7-ene and cholest-8:14-ene furnish a different isomerization product. Examination of the infrared spectrum of the reduced material revealed no detectable amounts of cholestane or coprostane. Since forced hydrogenation of 8:9- and of 8:14-cholestene and coprostene derivatives leads to the formation of the corresponding cholestanes and coprostanes, respectively,[23,25] it follows that the tetrasubstituted olefin described above must be formed by skeletal rearrangement. The most reasonable suggestion that can be made regarding the structure of this material is that it represents the product of Wagner–Meerwein rearrangement (XI) involving intermediate formation of a C.5 carbonium ion followed by migration of the C.10-methyl group. The resulting 9:10-olefin can, of course, equilibrate the corresponding 8:9- and 8:14-unsaturated derivatives. An analogy for such a rearrangement is available in the observation that cholestane-3β,5α,6β-triol 3,6-diacetate



XI



XII

undergoes rearrangement on acid-catalyzed dehydration to yield a substance for which structure XII has been established with reasonable certainty.[26]

Cholest-1-ene, cholest-2-ene, cholest-3-ene and cholest-6-ene, on treatment with *p*-toluenesulfonic acid in acetic acid-cyclohexane at 85°, are unaffected apart from the appearance of small amounts of acetate esters formed by addition of acetic acid to the double bonds. These observations are consistent with the fact that secondary carbonium ions, obtained by proton addition to the four olefins noted above, are less stable than the tertiary carbonium ion derived from cholest-4-ene and cholest-5-ene. The appearance of acetate ester in the absence of isomerization is in accord with the suggestion that olefin addition reactions can occur by a mechanism in which conventional carbonium ion intermediates are not involved.[27]

Under more vigorous conditions (*p*-toluenesulfonic acid in refluxing acetic acid), cholest-1-ene, cholest-2-ene, cholest-3-ene and cholest-6-ene are all slowly transformed into material which, after removal of acetate esters, shows infrared absorption characteristics identical with those of product XI. Interruption of the cholest-1-ene and cholest-3-ene isomerizations at an intermediate stage gives, after removal of esters, material consisting very largely of cholest-2-ene, as indicated by infrared analysis. The predominance of cholest-2-ene in these cases is consistent with the results of the hydrogenation experiments, which establish that this olefin is more stable than the Δ^1- and Δ^3-isomers by 1.5 and 2.1 kcal./mole, respectively. It is of interest to note that cholest-3-ene is converted into XI with prior isomerization into cholest-2-ene, rather than directly through cholest-4-ene.

The rearrangement of cholest-6-ene into product XI is regarded as proceeding through cholest-5-ene as an intermediate. The particular point of interest that arises in this connection is the preference of the Δ^6-olefin for isomerization in this direction as opposed to isomerization and rearrangement *via* cholest-7-ene. A possible explanation for this observation may be found in the fact that the C.7 carbonium ion, formed by proton addition at C.6, possesses a 1,3-diaxial methyl–hydrogen interaction that is absent in the C.6 carbonium ion, obtained by attack at C.7. As a corollary to this argument, it will be observed that proton addition (a) in the axial sense at C.6 (see XIII) is sterically

(22) E. Heilbronner, *Helv. Chim. Acta*, **36**, 1121 (1953).
(23) A. Windaus and G. Zühlsdorff, *Ann.*, **536**, 204 (1938).
(24) B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944); O. Dalmer, F. v. Werder, H. Honigmann and K. Heyns, *Ber.*, **68**, 1814 (1935).
(25) J. C. Eck and E. W. Hollingsworth, THIS JOURNAL, **63**, 2986 (1941); R. B. Turner and E. C. Kendall, unpublished results.
(26) V. A. Petrow, O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 677 (1938); V. A. Petrow, *ibid.*, 998 (1939); P. Bladon, H. B. Henbest and G. W. Wood, *ibid.*, 2737 (1952).
(27) G. S. Hammond and T. D. Nevitt, THIS JOURNAL, **76**, 4121, 4124 (1954); D. H. R. Barton and E. Miller, *ibid.*, **72**, 370, 1066 (1950).

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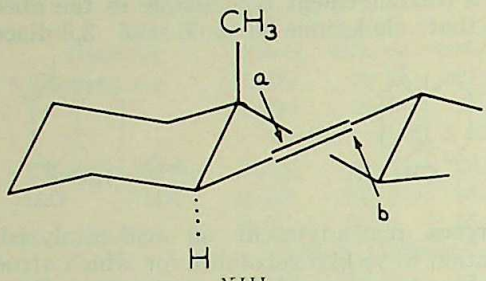
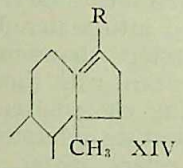
hindered by the C.10 methyl group, whereas approach of a proton as in (b) is unencumbered.[28]



XIII

Treatment of cholest-7-ene with *p*-toluenesulfonic acid in acetic acid–cyclohexane at 85° results in rapid conversion of this compound into a noncrystalline mixture in which cholest-8:14-ene predominates. Prolonged treatment of the mixture, or of pure cholest-8:14-ene, under these conditions furnishes an unsaturated oil with infrared absorption characteristics differing from those of the starting materials and of product XI. As in the case of XI, the material possesses a tetrasubstituted double bond,[22] and on forced hydrogenation it furnishes a saturated, amorphous substance in which the presence of traces of cholestane can be detected by infrared measurements. However, since cholestane is a minor constituent of the reduction product, it seems reasonable to assume that the tetrasubstituted olefin consists mainly of rearrangement products of type XIV.



XIV

Double bond isomerizations in the steroid series, particularly those involving the 7:8-, 8:9-, 8:14 and 14:15-positions are well known and are conventionally brought about by saturated solutions of hydrogen chloride in chloroform.[29] In no previous case, however, has the problem of skeletal rearrangement received attention, and the observations that have been made in connection with this investigation may be taken as a warning that such rearrangements occur under relatively mild conditions. It seems probable that the poor yields encountered in hydrogen chloride–chloroform isomerizations that are not conducted at low temperature may be attributed to this phenomenon.

Experimental[30]

Materials.—**Cholest-1-ene**, m.p. 68–69°, $[\alpha]_D$ +12° (*c* 1.5, chloroform) was prepared from cholest-1-en-3-one by a procedure developed by Henbest.[31] The conjugated ketone was reduced with lithium aluminum hydride, and the resulting unsaturated alcohol was converted into the corresponding 3-chloro derivative by treatment with thionyl chloride. Reductive removal of chlorine with lithium aluminum hydride furnished a crude sample of the desired olefin. Final purification was accomplished by recrystallization of the dibromide, m.p. 134–136°, from which pure cholest-1-ene was obtained by the action of zinc dust in acetic acid.

Cholest-2-ene was prepared by the method of Fieser and Dominguez.[32] The crude olefin was purified through the dibromide, m.p. 124–125°, from which cholest-2-ene, m.p. 74–75°, $[\alpha]_D$ +69.7° (*c* 0.9, chloroform), was regenerated by treatment with zinc and ethanol.

Preparation of **cholest-3-ene** was carried out according to the procedure of Lardelli and Jeger.[33] The product obtained in this way, after purification through the dibromide, m.p. 123–124°, melted at 73.5–74.5°, $[\alpha]_D$ +58.2° (*c* 0.9, chloroform): literature values, 72–73°, $[\alpha]_D$ +65° (chloroform)[33]; 72–72.5°, $[\alpha]_D$ +57° (chloroform).[34]

Cholest-4-ene, m.p. 80–83°, $[\alpha]_D$ +66° (*c* 1.0, chloroform) was synthesized as described by Barton and Rosenfelder.[34]

Cholest-5-ene was obtained by sodium–alcohol reduction of cholesteryl chloride as described by Mauthner and Suida.[35] Crystallization of the crude product from ether–methanol afforded material melting at 92–94°, $[\alpha]_D$ −55.0° (*c* 1.5, chloroform).

The preparation of **cholest-6-ene** was accomplished by a modification of the procedure reported by Cremlyn and Shoppee.[36] A solution of 80.0 g. of 7-ketocholesteryl acetate in 2 l. of benzene containing 80.0 g. of *p*-toluenesulfonic acid was heated under reflux in a nitrogen atmosphere for 7 hr. The solution was then cooled, diluted with ether and washed successively with water, dilute sodium carbonate solution, water and a saturated solution of sodium chloride. After drying over magnesium sulfate and removing the solvents, the residual material was crystallized, first from ethanol and then from acetone. Fifty grams of cholesta-3,5-dien-7-one, m.p. 112–114°, was obtained in this way.

A solution of 20.0 g. of dienone in 200 ml. of ether and 250 ml. of acetic acid was stirred with 2.0 g. of platinum oxide catalyst in an atmosphere of hydrogen for 14 hr., at the end of which time the absorption of hydrogen had ceased. The catalyst was removed by filtration, and the filtrate was diluted with ether and washed with water and dilute sodium hydroxide solution. After drying, the solvent was removed under reduced pressure, and the residual material was chromatographed on alumina. Cholestan-7α-ol (4.4 g.), m.p. 90–94°, was obtained from the petroleum ether–benzene eluates.[37] Two recrystallizations from acetone afforded 3.4 g. of pure material melting at 95–97°. Benzoylation furnished 2.9 g. of the corresponding benzoate as long needles, m.p. 158–160°. A further 940 mg., m.p. 155–158°, was obtained as a second crop.

Pyrolysis of the benzoate (2.47 g.) was carried out under reduced pressure at a bath temperature of 400°. The total crude product, after removal of the benzoic acid, was chromatographed on alumina, whereupon 1.43 g. of pure cholest-6-ene, m.p. 84–85°, $[\alpha]_D$ −84.3° (*c* 1.56, chloroform) was obtained.

Cholest-7-ene has been prepared by Cremlyn and Shoppee[36] by chromatography of the *p*-toluenesulfonyl derivative of cholestan-7β-ol on neutral or alkaline alumina. Four grams of cholestan-7β-ol, m.p. 110–113.5°, obtained in the preceding experiment, was converted into the corresponding tosylate and passed through a column of neutral alumina. The hydrocarbon fraction was reserved for subsequent purification, and the cholestan-7α-ol formed simultaneously was removed from the column and recycled, either by oxidation to cholestan-7-one followed by sodium–alcohol reduction or by epimerization with sodium butylate.[36]

(28) Mechanisms for double bond migration other than the one pictured here can also be formulated, *e.g.*, isomerization through bridged ion intermediates and concerted isomerization–rearrangement processes. The carbonium ion mechanism is employed for illustrative purposes for reasons of simplicity.

(29) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 248.

(30) All melting points are corrected. Infrared spectra were measured in carbon disulfide solution on a Perkin–Elmer model 12C infrared spectrometer.

(31) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).

(32) L. F. Fieser and X. A. Dominguez, THIS JOURNAL, **75**, 1704 (1953).

(33) G. Lardelli and O. Jeger, *Helv. Chim. Acta*, **32**, 1817 (1949).

(34) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

(35) J. Mauthner and W. Suida, *Monatsh.*, **15**, 85 (1894).

(36) R. J. W. Cremlyn and C. W. Shoppee, *J. Chem. Soc.*, 3515 (1954).

(37) Later fractions contained cholestan-7β-ol, which was utilized for the preparation of cholest-7-ene.

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The total olefin obtained in this way, after recrystallization from acetone and from ether–methanol, melted at 85.8–87°, $[\alpha]_D$ +6°. The infrared spectrum indicated contamination by small amounts of cholest-6-ene, which could not be removed by repeated crystallization.[33] The product was finally rechromatographed on alkaline alumina and, after several passes, a sample, m.p. 86–87°, $[\alpha]_D$ +11.7°, free of cholest-6-ene was obtained.

Cholest-8:14-ene, m.p. 53.5–55°, $[\alpha]_D$ +20° (*c* 1.0, chloroform) was prepared from cholest-7-ene by isomerization over palladium (hydrogenation conditions) as described by Eck and Hollingsworth.[25]

The 3α-hydroxy-Δ^{11}-cholenic acid employed in this investigation was a purified sample, m.p. 165–166°, of material prepared some years ago at the laboratories of Merck and Co., Rahway, N. J.

Acid Isomerization at 85°.—A solution of the olefin and an equal weight of *p*-toluenesulfonic acid in a mixture of acetic acid and cyclohexane (4:1, 6 ml. of solvent for 30 mg. of olefin) was heated to reflux temperature in an electrically heated oil-bath in a flask fitted with a thermometer extending below the surface of the solution. At the end of the selected heating period, the solution was poured into dilute sodium hydroxide, and the aqueous layer was extracted three times with petroleum ether. The combined organic fractions were then washed with dilute alkali, water, saturated sodium chloride and filtered through anhydrous magnesium sulfate. After evaporation of the solvent, the product was twice dissolved in carbon disulfide and taken to dryness in order to ensure removal of the last traces of hydrocarbon solvent prior to infrared analysis.

(38) Cremlyn and Shoppee obtained pure cholest-7-ene directly from the alumina column.

Acid Isomerization at 120°.—The procedure employed for isomerizations at the higher temperature resembled that described above, except that after the reflux temperature had been reached, about 30% of the solvent was distilled off. The cyclohexane and water passed over as an azeotrope, and the temperature of the solution rose to about 120°. When reactions were carried out in acetic acid alone, without removal of small amounts of water that are present under these conditions, the results obtained were erratic. At the end of the reaction period, the products were isolated as before, and the acetate esters were removed by chromatography on alumina before infrared analysis of the hydrocarbon fractions.

Hydrogenation of Product XI.—A sample of product XI was dissolved in 40 ml. of acetic acid–cyclohexane (4:1) and stirred in a hydrogen atmosphere with pre-reduced platinum oxide catalyst. No hydrogen was absorbed, and the recovered material proved to be unsaturated in the tetranitromethane test. The experiment was then repeated with 200 mg. of XI in 35 ml. of acetic acid–cyclohexane (4:1), to which 4 drops of 12 *N* hydrochloric acid was added. After 42 hr. at 60°, 110% of the calculated amount of hydrogen had been absorbed, and the product gave no reaction with tetranitromethane. The infrared absorption spectra of the reduced material showed no detectable amounts of cholestane or of coprostane.

Hydrogenation of Product XIV.—Hydrogenation was carried out at 60° with added hydrochloric acid as described in the preceding experiment. The reaction product showed a negative tetranitromethane test for unsaturation, and the infrared spectrum gave evidence of the presence of small amounts of cholestane.

HOUSTON, TEXAS

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE RICE INSTITUTE AND OF YALE UNIVERSITY AND FROM THE HICKRILL CHEMICAL RESEARCH FOUNDATION]

Heats of Hydrogenation. III. Hydrogenation of Cycloöctatetraene and of Some Seven-membered Non-benzenoid Aromatic Compounds[1]

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The heats of hydrogenation of several potentially aromatic substances have been measured in solution, and resonance energies have been estimated by comparison of the heats of hydrogenation of these compounds with heats calculated for reasonable models. The compounds that have been examined together with the ΔH values and calculated resonance energies are as follows: cycloöctatetraene ($-\Delta H$ 97.96 ± 0.05 kcal./mole, R.E. 2.4 kcal./mole), 1,3,5-cycloöctatriene ($-\Delta H$ 72.36 ± 0.26 kcal./mole, R.E. 0.9 kcal./mole), azulene ($-\Delta H$ 98.98 ± 0.13 kcal./mole, R.E. 28 kcal./mole), heptafulvene ($-\Delta H$ 92.63 ± 0.41 kcal./mole, R.E. 13 kcal./mole), heptafulvalene ($-\Delta H$ 130.77 ± 0.31 kcal./mole for six molar equivalents of hydrogen, R.E. 28 kcal./mole), dihydroheptafulvalene ($-\Delta H$ 138.81 ± 0.20 kcal./mole) and tropone ($-\Delta H$ 67.58 ± 0.30 kcal./mole to cycloheptanone).

Since the heats of hydrogenation of benzene, and of various related substances including styrene, hydrindene and furan, were measured by Kistiakowsky and his associates[2] some twenty years ago, no further studies of heats of hydrogenation in the aromatic series have been reported. In the meantime several potentially aromatic compounds of considerable theoretical interest have been prepared in sufficiently pure condition for hydrogenation studies. Of these substances cycloöctatetraene, azulene, methylenecycloheptatriene (heptafulvene), cycloheptatrienylidenecycloheptatriene (heptafulvalene), 7-(7′-cycloheptatrienyl)-cycloheptatriene (dihydroheptafulvalene) and cycloheptatrienylium oxide (tropone) have now been examined in the hydrogenation calorimeter.

Experimental

The technique for measurement of heats of hydrogenation in solution described in Paper I[3] was employed in the present investigation with the following modifications. In the cases of heptafulvene and heptafulvalene, Diethylcarbitol was used as the solvent, since these substances are subject to rapid polymerization in acetic acid. Despite extensive purification of the Diethylcarbitol, reduction of the platinum oxide catalyst gave higher heat values in this solvent (−32.94 ± 0.21 cal./100.0 mg.) than in acetic acid (−30.95 ± 0.13 cal./100.0 mg.) and consumed one cc. more hydrogen (*e.g.*, 16.25 cc./100.0 mg. in 275 cc. of Diethylcarbitol *vs.* 15.12 cc./100.0 mg. in 225 cc. of acetic acid). The results were nevertheless consistent, and no discrepancies traceable to the solvent have been noted. All reductions in

(1) This work was supported by the Eli Lilly Co., Indianapolis, and by the Office of Ordnance Research, Contract DA-19-059-ORD-1562 with Yale University.

(2) (a) G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, THIS JOURNAL, **58**, 146 (1936); (b) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky and W. E. Vaughan, *ibid.*, **59**, 831 (1937); (c) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky, E. A. Smith and W. E. Vaughan, *ibid.*, **60**, 440 (1938).

(3) R. B. Turner, W. R. Meador and R. E. Winkler, *ibid.*, **79**, 4116 (1957).

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Diethylcarbitol were carried out in volumes of 275 ml.; hydrogenations in acetic acid were conducted in 225 ml. of solvent.

The hydrogenation of tropone over platinum-in-acetic acid proceeded with the absorption of 92% of the theoretical amount of hydrogen, calculated on the basis of 4 molar equivalents. However, the clean absorption of 3 molar equivalents of hydrogen was observed over palladium supported on barium sulfate, and the results reported for tropone were obtained in acetic acid with this catalyst. All runs in which palladium was used were carried out in the following manner. The calorimeter containing the solvent, catalyst and an evacuated ampoule containing tropone was flushed with hydrogen according to the previously described procedure.[3] After absorption of hydrogen by the catalyst was complete and thermal equilibrium had been established, the hydrogenation reaction was initiated by breaking the ampoule of tropone. The final results were corrected for the heat of solution of tropone (-0.14 ± 0.01 kcal./mole), which was determined separately, and thus are referable to the dissolved state.

Materials.—A sample of **cycloöctatetraene** obtained from the General Aniline and Film Corp. was purified by conversion into the silver nitrate complex, m.p. 173° dec., as described by Cope and Hochstein.[4] Regeneration and fractionation afforded a sample boiling at 141–141.5° (19 mm.), $n^{25}D$ 1.5350. Examination of the infrared spectrum of this material for the styrene band at 11.08 μ gave no evidence for contamination by the latter substance.

1,3,5-Cycloöctatriene was prepared by the procedure of Cope and Hochstein[4]; $n^{24}D$ 1.5248.

Azulene was synthesized as described by Doering, Mayer and DePuy.[5] The sample employed for hydrogenation, m.p. 99–100°, was purified by chromatography on alumina.

Solutions of **heptafulvene** in Diethylcarbitol were freshly prepared for each run by the method of Wiley.[6] The heptafulvene was collected in a trap containing small amounts of Diethylcarbitol cooled to −40°. The resulting solutions were then made up to 275 ml. and were hydrogenated at once. The stability of heptafulvene in Diethylcarbitol was established by the negligible decrease of the extinction coefficient of the absorption band at 405 mμ over a period of 24 hr. at room temperature.

Heptafulvalene, m.p. 121–122°, was prepared by the method of Mayer.[7]

Dihydroheptafulvalene, m.p. 61°, was obtained by the procedure of Doering and Knox.[8]

Tropone was synthesized as described by Doering and Detert[9] and was purified by recrystallization and evaporative distillation; $n^{25}D$ 1.6155, m.p. −5°.

For reductions in Diethylcarbitol (diethylene glycol diethyl ether) the solvent was purified by (a) distillation at 10 mm. (b.p. 85–86°), (b) treatment with lithium aluminum hydride at 50° for 4 days and distillation at 2–3 mm. (b.p. 65–66°) and (c) distillation through a 24-inch helix-packed column under nitrogen at 37 mm. (b.p. 100°). The product was collected in 350-ml. fractions which were sealed at once under nitrogen in Pyrex flasks, m.p. −46 to −45°.

Results and Discussion

The results obtained in the present investigation are given in Table I. For the evaluation of resonance energies[10] from heats of hydrogenation, the measurements should ideally be carried out in the gas phase. The fact that the values reported here were obtained in solution therefore constitutes an obvious disadvantage, since corrections for solvent–solute interactions involving both the unsaturated derivatives and the hydrogenation products require thermodynamic data that are not generally available. The uncertainties that are introduced by the solvation problem, however, would appear to be small in view of evidence that has been cited previously.[3] Thus calculation of the resonance energy of cycloheptatriene from the gas phase data of Kistiakowsky[11] gives a value of 6.7 kcal./mole, based on a reference standard equal to three times the heat of hydrogenation of cycloheptene. The same method of calculation applied to the measurements made in acetic acid furnishes a comparison value of 7.1 kcal./mole. In any event, ambiguities that arise from uncertainties in the formulation of appropriate "non-resonating" models undoubtedly constitute a more important source of difficulty than do solvent–solute interactions, at least in the case of relatively non-polar molecules.

TABLE I

HEATS OF HYDROGENATION IN SOLUTION[a]

Compound	Mmoles	Catalyst, mg.	$-\Delta H(25°)$, kcal./mole
Cycloöctatetraene	1.259	100.2	97.96
	1.307	100.0	97.96
		Average	97.96 ± 0.05[b]
1,3,5-Cycloöctatriene	1.553	100.2	72.63
	1.315	98.8	72.06
	1.648	98.8	72.39
		Average	72.36 ± 0.26
Azulene	0.8103	99.8	98.75
	0.8007	99.7	99.20
		Average	98.98 ± 0.13
Heptafulvene[c]	1.614	100.2	93.24
	1.560	100.5	92.08
	1.555	100.5	92.56
		Average	92.63 ± 0.41
Heptafulvalene[c]	4.176[d]	110.0	130.86[e]
	4.189[d]	100.5	130.68[e]
		Average	130.77 ± 0.13[e]
Dihydroheptafulvalene	0.7347	99.0	138.90
	0.7593	99.3	138.72
		Average	138.81 ± 0.20
Tropone[f]	0.9813	Pd–$BaSO_4$	67.75
	0.8417	Pd–$BaSO_4$	67.89
	1.938	Pd–$BaSO_4$	67.09
		Average	67.58 ± 0.30

[a] Except in the cases indicated, all hydrogenations were carried out in acetic acid with a platinum oxide catalyst. [b] Deviations include uncertainty in the heat of hydrogenation of the platinum oxide. [c] Hydrogenations of heptafulvene and of heptafulvalene were carried out with Diethylcarbitol as the solvent. [d] Millimoles of *hydrogen* absorbed. [e] These values are based upon the absorption of 6 molar equivalents of hydrogen (see Discussion). [f] Tropone was reduced over 1.0-g. samples of a 5% palladium-on-barium sulfate catalyst. In these experiments the catalyst was equilibrated with hydrogen, and the hydrogenation reaction was initiated by solution of the tropone. The results are corrected for the heat of solution of tropone in acetic acid.

Cycloöctatetraene.—Cycloöctatetraene is one of the earliest molecules to derive its importance from a potential bearing on the theory of aromatic

(4) A. C. Cope and F. A. Hochstein, THIS JOURNAL, **72**, 2515 (1950).

(5) W. von E. Doering, J. R. Mayer and C. H. DePuy, *ibid.*, **75**, 2386 (1953).

(6) D. W. Wiley, Ph.D. Dissertation, Yale University, Sept., 1954.

(7) J. R. Mayer, Ph.D. Dissertation, Yale University, May, 1955.

(8) W. von E. Doering and L. H. Knox, THIS JOURNAL, **79**, 352 (1957).

(9) W. von E. Doering and F. L. Detert, *ibid.*, **73**, 876 (1951).

(10) As used throughout this paper, "resonance energy" is defined as the difference between the measured heat of hydrogenation (reaction) of a given compound and that estimated for one or more reasonable models. It should be emphasized that resonance energy is not an intrinsic property of a molecule but that it depends on, and varies with, the choice of the model.

(11) J. B. Conn, G. B. Kistiakowsky and E. A. Smith, THIS JOURNAL, **61**, 1868 (1939).

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character.[12] The conformation and resonance energy of this substance have been subjects of considerable controversy in recent years. Although a large body of evidence has been variously interpreted in favor of the "tub" structure on the one hand and the "crown" structure on the other,[13] it is now generally agreed that cyclooctatetraene exists in the "tub" form.[14] This structure allows each olefinic linkage to assume a strainless, planar configuration with C=C—C angles approximating 120° but with angles between adjacent double bonds of nearly 90° owing to rotation about the intervening C–C single bonds. Conjugative stabilization in such a non-planar molecule should be largely suppressed, and the resonance energy would therefore be expected to be small.[15] Support for this conclusion is provided by the X-ray analyses of Kaufman, Fankuchen and Mark[16] which show that in the crystal the carbon–carbon bond lengths are alternately 1.54 and 1.34 Å. as in paraffinic and olefinic substances, respectively. This result contrasts with the single value of 1.39 Å. reported for the carbon–carbon distances in benzene.[17]

Following publication of data on the heat of formation of cyclooctatetraene[18] shortly after World War II, Pink and Ubbelohde[19] calculated a resonance energy of 25.3 kcal./mole for this substance. This result is inconsistent with the chemical properties of cyclooctatetraene, in particular with its ready conversion into derivatives of bicyclo-[4,2,0]octadiene,[20] and a considerably lower value was subsequently suggested by Person, Pimentel and Pitzer[14a] on the basis of conventional calculations employing the 1950 combustion data of Prosen, Johnson and Rossini[21] and bond energies (4 C=C, 4 C—C and 8 C—H bonds) given by Pitzer.[22] An alternative method of treatment of the Rossini data, however, furnishes a still lower and, we believe, more reliable result.

The heat of isomerization of cyclooctatetraene into styrene (gas phase) derived from Rossini's results is −36.3 kcal./mole.[21,23] Taking 36.9 kcal./mole as the resonance energy of styrene[24] and 72.5 kcal./mole as the heat of formation of "non-resonating" styrene, calculated by Franklin's method of group equivalents (Table II),[25] the heat of formation of styrene can be expressed as 35.6 kcal./mole.

TABLE II

CALCULATION OF HEATS OF FORMATION (NON-RESONATING STRUCTURES)[25]

Styrene	ΔH_f	Cyclooctatetraene	ΔH_f
2 C=C (*cis*)	37.8	4 C=C (*cis*)	75.5
		Total	75.5
1 C=C	20.2		
1 C=C	15.0	Naphthalene	
		4 C=C (*cis*)	75.5
1 C_6-ring corrn.	−0.5	1 C=C	24.6
		2 C_6-ring corrn.	−1.0
Total	72.5	Total	99.1
Azulene			
3 C=C (*cis*)	56.6		
2 C=C	40.4		
1 C_5-ring corrn.	5.7		
Total	102.7		

From this result and from the isomerization data it follows that the heat of formation of cyclooctatetraene is 71.9 kcal./mole. Calculation of the heat of formation of "non-resonating" cyclooctatetraene by the Franklin method[25] gives a value of 75.5 kcal./mole (Table II), and resonance stabilization of this molecule is hence estimated to be of the order of 3.6 kcal./mole. The result obtained by this procedure is in good agreement with the value of 4.8 kcal./mole recently derived by Springall, White and Cass[26] from heat of combustion data and selected average bond energies.

Since all of the values thus far reported for resonance energy in the cyclooctatetraene system are based upon combustion experiments, determination of this quantity by an independent method seemed most desirable. The heat of hydrogenation of cyclooctatetraene was accordingly measured in acetic acid solution at 25° and was found to be −97.96 ± 0.05 kcal./mole (Table I).

Assuming the superficially reasonable reference standard of four times the heat of hydrogenation

(12) R. Willstätter and E. Waser, *Ber.*, **44**, 3423 (1911); R. Willstätter and M. Heidelberger, *ibid.*, **46**, 517 (1913).

(13) *Cf.* O. Bastiansen, O. Hassel and A. Langseth, *Nature*, **160**, 128 (1947); E. R. Lippincott, R. C. Lord and R. S. McDonald, THIS JOURNAL, **73**, 3370 (1951).

(14) (a) W. B. Person, G. C. Pimentel and K. S. Pitzer, *ibid.*, **74**, 3437 (1952); (b) I. L. Karle, *J. Chem. Phys.*, **20**, 65 (1952).

(15) An approximate valence-bond treatment of *planar* cyclooctatetraene (G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, New York, N. Y., 1955, p. 142) gives a resonance energy of 39 kcal./mole.

(16) H. S. Kaufman, I. Fankuchen and H. Mark, *J. Chem. Phys.*, **15**, 414 (1947); *Nature*, **161**, 165 (1948).

(17) L. Pauling and L. O. Brockway, *J. Chem. Phys.*, **2**, 867 (1934).

(18) W. Reppe, B.I.O.S. Final Report, No. 137, Item No. 28, H. M. Stationery Office, London, 1945, p. 3.

(19) R. C. Pink and A. R. Ubbelohde, *Trans. Faraday Soc.*, **44**, 708 (1948).

(20) W. Reppe, O. Schlichting, K. Klager and T. Toepel, *Ann.*, **560**, 1 (1948).

(21) E. J. Prosen, W. H. Johnson and F. D. Rossini, THIS JOURNAL, **72**, 626 (1950). The heat of formation of cyclooctatetraene (liq., 25°) is given as +60.82 ± 0.32 kcal./mole. A value of 40 kcal./mole was employed by Pink and Ubbelohde (reference 19).

(22) K. S. Pitzer, *ibid.*, **70**, 2140 (1948).

(23) The liquid phase value is −36.1 kcal./mole. Correction of this quantity to the vapor phase has been made for the sake of consistency only, from the data of D. W. Scott, M. E. Gross, G. D. Oliver and H. M. Huffmann, *ibid.*, **71**, 1634 (1949), and K. S. Pitzer, L. Guttman and E. F. Westrum, *ibid.*, **68**, 2209 (1946).

(24) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, New York, N. Y., 1955, p. 80. The value cited by Wheland is obtained from Kistiakowsky's hydrogenation data.

(25) J. L. Franklin, *Ind. Eng. Chem.*, **41**, 1070 (1949); THIS JOURNAL, **72**, 4278 (1950).

(26) H. D. Springall, T. R. White and R. C. Cass, *Trans. Faraday Soc.*, **50**, 816 (1954).

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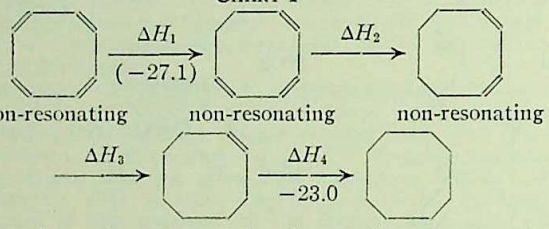
of *cis*-cycloöctene (−22.98 ± 0.10 kcal./mole),[27] the resonance energy calculated for cycloöctatetraene is *negative* and equal to −6.0 kcal./mole. It will be noted, however, that owing to severe repulsions between non-bonded atoms in cycloöctane,[11,27] the heat of hydrogenation of *cis*-cyclooctene is considerably lower than that of cyclohexene (−27.10 kcal./mole),[3] which furnishes a reduction product in which non-bonded interactions are minimized.[28] Since the repulsions that are introduced in the last of the four hypothetical steps in the hydrogenation of "non-resonating" cyclooctatetraene (Chart I) are undoubtedly greater

CHART I



than those introduced in the earlier stages, the use of ΔH_4 to represent the heat of all four steps is a poor choice, which leads to an unreasonably low prediction. In order to correct for this effect, the cyclohexene value (−27.1 kcal./mole) has been assigned to ΔH_1 on the grounds that the heat of hydrogenation of the first double bond of the model should closely approximate that of a representative, *cis*-disubstituted olefin. An average of this figure and that obtained experimentally for ΔH_4 (−23.0 kcal./mole) gives an average heat of hydrogenation for all four double bonds of −25.1 kcal./mole. The resonance energy calculated for cycloöctatetraene on the basis of these assumptions is 2.4 kcal./mole, a result that agrees reasonably well with the lower values derived from combustion data.

As a further check on the magnitude of the cyclooctatetraene resonance, the heat of hydrogenation of cycloöctatetraene has been compared with that of 1,3,5-cycloöctatriene in analogy with the procedure followed by Kistiakowsky and his associates[2a] in their treatment of the resonance energy of benzene. By subtracting the heat of hydrogenation of 1,3-cyclohexadiene to cyclohexane from that of benzene to the same product, the heat of the reaction benzene + H_2 → 1,3-cyclohexadiene can be calculated. This change is *endothermic* to the extent of 5.6 kcal./mole, as compared with the hydrogenation of an unconjugated, *cis*-disubstituted double bond, *exothermic*, −28.6 kcal./mole (gas phase). The reduction in heat evolution of 34.2 kcal./mole observed in this case represents the increase in stabilization resulting from introduction of a third double bond into the 1,3-cyclohexadiene molecule and is defined[10] as the resonance energy of benzene relative to the cyclohexene—1,3-cyclohexadiene model.[29]

Returning now to the question of cycloöctatetraene, it follows that a quantitative measure of the aromatic character of this substance can be gained from the extent to which the heat change for the process cycloöctatetraene + H_2 → 1,3,5-cycloöctatriene deviates from the standard value of −27.1 kcal./mole (solution). The quantity calculated for this transformation from the heats of hydrogenation of cycloöctatetraene and of 1,3,5-cycloöctatriene to cycloöctane is −25.6 kcal./mole. The discrepancy in this case is hence only 1.5 kcal./mole, a value that is comparable in magnitude to the resonance energy of simple conjugated dienes.

With reference to the triene problem it is interesting to note that the heat of hydrogenation of 1,3,5-cycloöctatriene (−72.4 kcal./mole) is *higher* than that of 1,3,5-cycloheptatriene (tropilidene) (−70.5 kcal./mole) despite the fact that the heat of hydrogenation of *cis*-cycloöctene is *lower* than that of cycloheptene by almost 3 kcal.[3,27] The resonance energy of 1,3,5-cycloöctatriene (0.9 kcal./mole) is obtained directly as the difference between the resonance energy of cycloöctatetraene (2.4 kcal./mole) and the contribution of the fourth double bond (1.5 kcal./mole). The stabilization of tropilidene is 9.8 kcal./mole based on Kistiakowsky's data[11] or 9.0 kcal./mole based on the solution data,[3] both figures being referable to a "non-resonating" model in which cyclohexene is used for the first double bond, cycloheptene for the third and an average of the two for the second.

The negligible resonance energy of 1,3,5-cyclooctatriene probably is due to its non-planar structure. By analogy one can assume that a non-planar cycloheptatriene structure for tropilidene would also lead to little or no resonance energy. The fact that tropilidene has a relatively high degree of stabilization is in better accord with a planar conformation.[30] It should be mentioned that such an arrangement involves considerable angular strain, of which no account is taken in formulation of the comparison standard. This inadequacy of the model serves to lower the calculated resonance energy.[31]

Azulene.—In view of widespread interest in the properties of non-benzenoid aromatic compounds, we have measured the heat of hydrogenation of azulene. This substance undergoes rapid reduction in acetic acid with clean absorption of five molar equivalents of hydrogen and furnishes a ΔH value of −98.98 ± 0.13 kcal./mole. Simple calculations based on

(27) R. B. Turner and W. R. Meador, THIS JOURNAL, **79**, 4133 (1957).

(28) In this connection cyclohexene is regarded as a typical unstrained, *cis*-disubstituted olefin, the hydrogenation of which is uncomplicated by the steric repulsion problem. It will be recalled that the gas phase values obtained for cyclohexene and for *cis*-butene (−28.6 kcal./mole) by G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *ibid.*, **57**, 876 (1935) and **58**, 137 (1936), are identical.

(29) The value of 36.0 kcal./mole for the resonance energy of benzene is based on a model consisting of three molecules of cyclohexene and differs from the figure given above by the resonance energy of 1,3-cyclohexadiene (1.8 kcal./mole).

(30) For additional discussion of this problem see W. von E. Doering, G. Laber, R. Vonderwahl, N. F. Chamberlain and R. B. Williams, THIS JOURNAL, **78**, 5448 (1956). The resonance energy obtained in the present investigation compares favorably with that calculated by Wheland (reference 24, p. 132) for planar cycloheptatriene. The recent suggestion of M. V. Evans and R. C. Lord, "Abstracts of Papers," 130th Meeting, American Chemical Society, Atlantic City, N. J., Sept. 16, 1956, p. 41R, that tropilidene is bicyclo[3,2,0]heptadiene-1,5 is at variance with results of E. Vogel (private communication) which indicate that a synthetic product of this structure is not identical with tropilidene.

(31) A similar problem is encountered in the case of benzene, since the actual molecule possesses compressional energy not found in the cyclohexene model.

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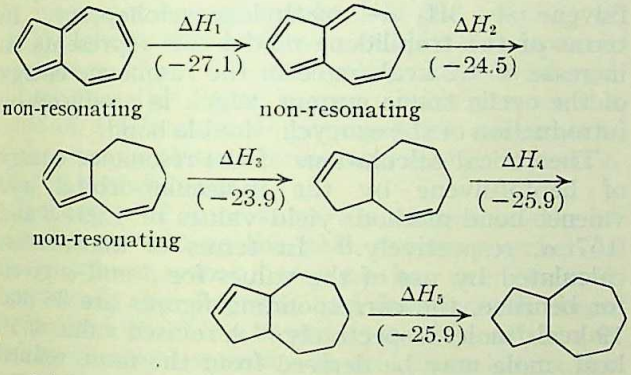
twice the heat of hydrogenation of cyclopentene (−25.9 kcal./mole)[32] and three times the heat of hydrogenation of cycloheptene (−25.9 kcal./mole)[3] give a resonance energy of 30.5 kcal./mole for this substance. Correction for steric repulsion effects is more difficult in this instance than in the cyclooctatetraene case, and the situation is further complicated by the presence in azulene of two trisubstituted double bonds at bridge head positions. The treatment that follows must, therefore, be regarded as a very crude approximation at best.

The heat of hydrogenation of the non-resonating model is again obtained as the summation of heats evolved in a hypothetical reduction process (Chart II). The cyclohexene value (−27.1 kcal./

CHART II



mole) is assumed for ΔH_1, and the cycloheptene and cyclopentene[32] figures have been taken for ΔH_4 and ΔH_5, respectively.[33] The heats of hydrogenation ΔH_2 and ΔH_3 present a special problem, and the values that have been chosen, −24.5 kcal./mole for ΔH_2 and −23.9 kcal./mole for ΔH_3, are based upon averages of the heats of hydrogenation of 1-methylcycloheptene and ethylidenecyclopentane and of 1-methylcyclopentene and methylenecycloheptane,[34] respectively, after correction of the methylenecycloheptane value for the substitution effect.[35] The heat of hydrogenation of the non-resonating model is then −127.3 kcal./mole, and the estimated resonance energy of azulene is 28.3 kcal./mole.[36] Since azulene possesses a dipole moment of approximately 1.0 *D*,[37] solvation energy should be larger in this case than in the case of non-polar molecules. "Resonance energy" calculated from solution data thus includes a factor for solvation.

In 1947, Heilbronner and Wieland[38] reported a value of 46 kcal./mole for the resonance energy of azulene, derived from consideration of: (a) the difference in heats of combustion of the isomer guaiazulene and cadalene (−29.6 ± 2.1 kcal./mole),[39] taken also as the difference in heats of formation of the isomeric pair azulene and naphthalene; (b) the heat of formation of naphthalene (solid state); (c) the heat of sublimation of carbon; (d) the heat of sublimation of azulene and (e) various bond energies given by Pauling.[40]

An equivalent, but more direct, evaluation of the azulene resonance can be made on the basis of the following relationships, in which all quantities refer to the vapor phase.

(1) ΔH_f (non-resonating naphthalene) − R.E. (naphthalene) = ΔH_f (naphthalene)

(2) ΔH_f (naphthalene) + $\Delta H_{isom.}$ (azulene → naphthalene) = ΔH_f (azulene)

(3) ΔH_f (non-resonating azulene) − ΔH_f (azulene) = R.E. (azulene)

(4) R.E. (azulene) = R.E. (naphthalene) + ΔH_f (non-resonating azulene) − ΔH_f (non-resonating naphthalene) − $\Delta H_{isom.}$ (azulene → naphthalene)

The heats of formation (ΔH_f) of non-resonating molecules of azulene and of naphthalene determined by Franklin's method of group equivalents[25] (Table II) are 102.7 and 99.1 kcal./mole, respectively. The heat of isomerization of azulene into naphthalene, corrected for the difference in heats of vaporization of these two substances,[38] is 33.2 kcal./mole, and it follows that R.E. (azulene) = R.E. (naphthalene) −29.6 kcal. Assuming Pauling's value of 75 kcal./mole for the resonance energy of naphthalene,[41] the resonance energy calculated for azulene by this method is 45.6 kcal./mole. However, evidence that has accumulated during the past few years suggests that the Pauling resonance energies are high. Franklin[25] has given a value of 62 kcal./mole for the resonance energy of naphthalene, and values of 60, 61 and 52.6 kcal./mole have resulted from revised calculations by the valence-bond and molecular-orbital methods.[42] A new experimental value recently has been obtained by Linstead and Jackman,[43] who have investigated the heats of *dehydrogenation* of various hydroaromatic systems by tetrachloro-*o*-benzoquinone. By comparison of the heat changes accompanying the conversions of 1,4-cyclohexadiene into benzene and of 1,4-dihydronaphthalene into naphthalene and assumption of Kistiakowsky's value of 36.0 kcal./mole for the benzene resonance, a tentative value of 67.6 ± 2 kcal. has been obtained for the resonance energy of naphthalene.

(32) This solution value for cyclopentene is approximate and was obtained by subtracting 1.0 kcal., an average value for the discrepancy between our solution results and Kistiakowsky's gas phase data (see Table II, reference 3), from the gas phase value for cyclopentene (reference 2b.

(33) The order in which the various double bonds are considered is immaterial to the present argument.

(34) R. B. Turner and R. H. Garner, in press.

(35) *Cf.* J. B. Conant and G. B. Kistiakowsky, *Chem. Revs.*, **20**, 181 (1937).

(36) G. Berthier and A. Pullman, *Compt. rend.*, **229**, 561 (1949), give a calculated value of 3.082 β (*cf.* benzene, 2.0 β).

(37) G. W. Wheland and D. E. Mann, *J. Chem. Phys.*, **17**, 264 (1949).

(38) E. Heilbronner and K. Wieland, *Helv. Chim. Acta*, **30**, 947 (1947).

(39) E. Perottet, W. Taub and E. Briner, *ibid.*, **23**, 1260 (1940).

(40) The cadalene employed in the combustion experiments of Perottet, Taub and Briner (ref. 39) is described as an oil, b.p. 155–157° (12 mm.), d^{20}_4 0.9737, $n^{20}D$ 1.5572. The physical state of the guaiazulene was not specified, but it is reasonable to suppose that the data for this compound are also referable to the liquid phase. The heat of formation of azulene (solid state), calculated by Heilbronner and Wieland as the sum of the heats of formation of naphthalene (solid) and the heat of isomerization of guaiazulene into cadalene was not corrected for this discrepancy, and inclusion of an approximate correction term derived from the heats of fusion of azulene and of naphthalene (ref. 38) gives a revised resonance energy value of 44 kcal./mole.

(41) L. Pauling, "Nature of the Chemical Bond," 2nd Ed., Cornell University Press, Ithaca, N. Y., 1944, p. 136.

(42) See ref. 24, p. 132.

(43) R. P. Linstead and L. Jackman, private communication.

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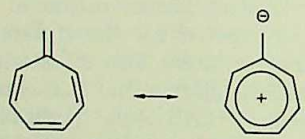
Recalculation of the resonance energy of azulene employing Franklin's result of 62 kcal./mole for stabilization in the naphthalene system gives a value of 32.4 kcal./mole in reasonable agreement with the results obtained in the present investigation. Conversely, the resonance energy derived for azulene from the hydrogenation data provides independent experimental support for a low value (58 to 60 kcal.) for the resonance energy of naphthalene.

In 1955, the heat of combustion of azulene was measured for the first time by Kováts, Günthard and Plattner, from whose results a value of −34.9 kcal./mole can be calculated for the gas phase heat of isomerization of azulene into naphthalene.[44] The use of this figure and the Franklin value of 62 kcal./mole for the naphthalene resonance in equation 4 leads to a resonance energy of 30.7 kcal./mole for azulene. Direct calculation of the azulene resonance from the heat of combustion data by the Franklin-Wheland method[44a] gives a value of 35.8 kcal./mole.

Heptafulvene.—Heptafulvene (I) contains a cyclic system of conjugated double bonds, for which the theoretical treatment of Pullman and Pullman[45] has predicted aromatic properties. Although the

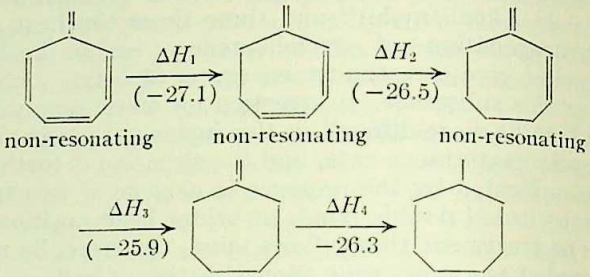


Ia Ib

substance has never been obtained in pure form, owing to its extreme reactivity, solutions of moderate stability have been prepared.[6] The sensitivity of heptafulvene to acids precluded the use of acetic acid as a solvent for the hydrogenation experiments, which were carried out on freshly prepared samples dissolved in Diethylcarbitol. The amount of material present was determined by the amount of hydrogen absorbed.

The heat of hydrogenation of heptafulvene is −92.63 ± 0.41 kcal./mole. An approximate evaluation of the heat of hydrogenation of the non-resonating system can be made on the basis of the following assumptions. The standard value of −27.1 kcal./mole is assigned to ΔH_1 of the accompanying reduction sequence (Chart III), and the cycloheptene value (−25.9 kcal./mole) is taken as a reasonable approximation of ΔH_3. An average of these figures gives −26.5 kcal./mole for ΔH_2. ΔH_4 has been determined experimentally and is found to be −26.3 kcal./mole.[34] Summation gives an over-all value of 105.8 kcal./mole and an estimated resonance energy of 13.2 kcal./mole as compared with 36.9 kcal./mole and 2.4 kcal./mole,

CHART III

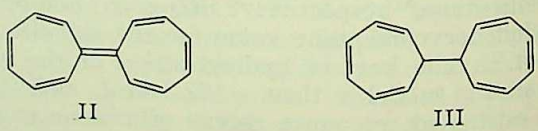


respectively, for the isomeric compounds styrene and cyclooctatetraene.

By comparing the heat of hydrogenation of heptafulvene (−92.6 kcal./mole) with that of methylenecycloheptane (−26.3 kcal./mole), a heat change of 66.3 kcal./mole is derived for the reaction, heptafulvene + $3H_2$ → methylenecycloheptane. In terms of the tropilidene model this represents an increase of 4.2 kcal./mole in the resonance energy of the cyclic triene system, which is produced by introduction of the exocyclic double bond.

Theoretical calculations of the resonance energy of heptafulvene by the molecular-orbital and valence-bond methods yield values of 1.994 β and 0.57 α, respectively.[45] In terms of kilocalories, calculated by use of the values for β and α given for benzene, the corresponding figures are 36 and 19 kcal./mole, respectively. A revised value of 16 kcal./mole may be derived from the more refined calculations of Bergmann, *et al.*[46]

Heptafulvalene and Dihydroheptafulvalene.—The resonance energy of heptafulvalene (II), which possesses two conjugated cycloheptatriene rings, has been calculated as 1.496 γ by the molecular-orbital method.[47] A corresponding calculation for the isomeric substance, stilbene, gives a value of 2.446 γ. On the basis of Wheland's value of 77 kcal./mole[42] for stilbene, the resonance energy of



II III

heptafulvalene can be expressed as 47 kcal./mole. A considerably lower figure is obtained from the hydrogenation data.

In view of the instability of heptafulvalene in the presence of acids, the hydrogenation of this substance was carried out in diethylcarbitol as in the case of heptafulvene. Unfortunately reduction proceeded with the absorption of only 95% of the theoretical amount of hydrogen for *six double bonds*. The heat of hydrogenation of this substance (−130.77 ± 0.31 kcal./mole) was thus calculated as six times the heat developed per mole of hydrogen absorbed.[48] The heat of hydrogenation of the non-resonating system was obtained by doubling

(44) E. Kováts, Hs. H. Günthard and Pl. A. Plattner, *Helv. Chim. Acta*, **38**, 1912 (1955). The values for the heats of combustion (vapor phase, 25°) of azulene and of naphthalene given in line 4 of Table 4 (−1680.7 kcal./mole and −1239.5 kcal./mole) are typographical errors and should read −1280.7 kcal./mole and −1245.8 kcal./mole, respectively. The naphthalene value cited by these authors was obtained from unpublished results of F. D. Rossini.

(44a) Reference 24, p. 94.

(45) B. Pullman and A. Pullman, "Les Théories Électronique de la Chimie Organique," Masson et Cie., Paris, 1952, p. 227.

(46) E. D. Bergmann, E. Fischer, D. Ginsburg, Y. Hirshberg, D. Lavie, M. Mayot, A. Pullman and B. Pullman, *Bull. soc. chim.*, **18**, 684 (1951).

(47) E. D. Bergmann, D. Ginsburg, Y. Hirshberg, M. Mayot, A. Pullman and B. Pullman, *ibid.*, **18**, 697 (1951).

(48) Although the product was not isolated, it is assumed to be cycloheptylidenecycloheptane in view of the known difficulty encountered in reductions of tetrasubstituted olefins under the conditions of these experiments.

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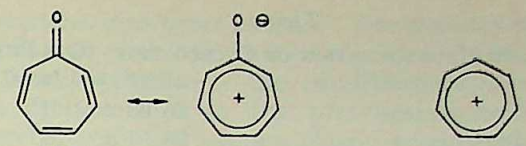
the sum of the values assumed for ΔH_1, ΔH_2 and ΔH_3 in the heptafulvene treatment (−159.0 kcal./mole). The difference between these two figures gives an approximate value of 28 kcal./mole for the resonance energy of heptafulvalene.

Hydrogenation of dihydroheptafulvalene (III) proceeded smoothly in acetic acid solution with absorption of six molar equivalents of hydrogen and a heat evolution of 138.81 ± 0.20 kcal./mole or 69.4 kcal. per cycloheptatriene ring. The latter value is in good agreement with the cycloheptatriene result (−70.5 kcal./mole)[3] if account is taken of non-bonded interactions in the reduction product involving one ring and hydrogen atoms of the other. Comparison of the results obtained for dihydroheptafulvalene and for heptafulvalene (hydrogen uptake, 6 molar equivalents) indicates that the resonance energy involved in the coupling of two cycloheptatriene rings in the latter compound amounts to about 8.0 kcal./mole. It is of interest to note that this figure is approximately twice the value of 4.2 kcal./mole obtained for conjugation of the cycloheptatriene ring and exocyclic double bond in heptafulvene.

Tropone.—Of interest as the oxygen analog of heptafulvene and as the next simpler member of the tropolone system, tropone has been treated theoretically by Brown[49] and has recently been synthesized.[9,50] The basicity of this substance and its chemical stability in acid have led to the formulation of the conjugate acid as a hydroxycycloheptatrienylium ion and to the formulation of tropone itself as cycloheptatrienylium oxide (IV). The considerable stability of the cycloheptatrienylium ion (V), which is regarded as the symmetrical parent of the seven-membered aromatic system, has been clearly demonstrated by Doering and Knox.[51]



IVa IVb V

The heat of hydrogenation of tropone to cycloheptanone over palladium-on-barium sulfate in acetic acid solution is −67.58 ± 0.30 kcal./mole. Assuming a planar structure for this molecule and using tropilidene (heat of hydrogenation, −70.49 ± 0.39 kcal./mole)[3] as the model for a tropone in which there is no interaction of the carbonyl group with the ring, the extra resonance energy in tropone resulting from this interaction is calculated as 2.9 kcal./mole. Although this stabilization can be rationalized in terms of contributing structures of type IVb, a larger value might have been expected in view of the large resonance energy (3.00 β) calculated for V. It is clear, however, that the stabilization achieved in IVb is accomplished at the expense of considerable electrostatic work of charge separation, which has the effect of reducing the measurable resonance energy.

It should be noted, finally, that the resonance energy associated with coupling of the tropilidene system with a carbonyl group (2.9 kcal./mole) is somewhat less than that derived from coupling with an olefinic linkage (4.2 kcal./mole in heptafulvene). This result finds a parallel in the benzene series where it has been shown that styrene possesses a higher resonance energy (38.2 kcal./mole)[52] than benzaldehyde (35 kcal./mole).[52] A further analogy is provided by the observation that the heat of hydrogenation of pentadiene-1,3 to pentene-1 is 1.1 kcal. lower than that of crotonaldehyde to butyraldehyde.[2c]

(49) R. D. Brown, *J. Chem. Soc.*, 2670 (1951).
(50) H. J. Dauben and H. J. Ringold, THIS JOURNAL, **73**, 876 (1951).
(51) W. von E. Doering and L. H. Knox, *ibid.*, **76**, 3203 (1954).
(52) The styrene and benzaldehyde values given here are calculated by comparable methods from combustion data (see ref. 24, pp. 98, 99).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

Heats of Hydrogenation. IV. Hydrogenation of Some *cis*- and *trans*-Cycloölefins[1]

BY RICHARD B. TURNER AND W. R. MEADOR

RECEIVED FEBRUARY 25, 1957

The heats of hydrogenation of the *cis*- and *trans*-cycloöctenes, cyclononenes and cyclodecenes have been measured in acetic acid solution at 25°. The values (kcal./mole) obtained for these olefins are as follows: *cis*-cycloöctene, −22.98 ± 0.10, *trans*-cycloöctene, −32.24 ± 0.21; *cis*-cyclononene, −23.62 ± 0.07, *trans*-cyclononene, −26.49 ± 0.14; *cis*-cyclodecene, −20.67 ± 0.08, *trans*-cyclodecene, −24.01 ± 0.09.

The heats of hydrogenation of cyclopentene, cyclohexene, cycloheptene and of *cis*-cycloöctene were measured several years ago in the gas phase by Kistiakowsky and his associates. The results of this work (Table I) were correlated by Conn, Kistiakowsky and Smith,[2] who advanced a consistent interpretation of the data based upon consideration of non-bonded repulsions appearing in the products of the various hydrogenation processes. An important outcome of the investigation was the demonstration that the heat of hydrogenation of cyclopentene is 1.7 kcal./mole *lower* than that of cyclohexene, despite the fact that strain of the cyclopentene double bond is clearly *greater* than that of the olefinic linkage in cyclohexene. Al-

(1) The work reported in this paper was supported by the Eli Lilly Co., Indianapolis.
(2) J. B. Conn, G. B. Kistiakowsky and E. A. Smith, THIS JOURNAL, **61**, 1868 (1939).

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TABLE I

HEATS OF HYDROGENATION OF CYCLOÖLEFINS (GAS PHASE)

Compound	$-\Delta H$(82°, kcal./mole)
Cyclopentene	26.92 ± 0.01[a]
Cyclohexene	28.59 ± .01[b]
Cycloheptene	26.52 ± .02[c]
cis-Cycloöctene[d]	23.53 ± .04[c]

[a] M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky and W. E. Vaughan, THIS JOURNAL, 59, 831 (1937). [b] G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *ibid.*, 58, 137 (1936); [c] Data from reference 2. [d] The cycloöctene was prepared by E. P. Kohler, M. Tishler, H. Potter and H. T. Thompson, *ibid.*, 61, 1057 (1939), by dehydration of cycloöctanol with β-naphthalenesulfonic acid. Material obtained by this route is substantially pure *cis*-cycloöctene.

though the hydrogenation data do not conform with predictions based on strain effects in these molecules, an entirely satisfactory explanation of the results was provided by the observation that the C–H bonds in cyclopentane are extensively eclipsed, whereas those in cyclohexane are staggered.[3] It was thus concluded that the enthalpy difference associated with repulsive interactions arising in the reduction products, cyclopentane and cyclohexane, is sufficiently large to obscure the difference in enthalpy resulting from variations of strain in the corresponding olefins. Calculations of "total strain energy" in the cyclohexane, cyclopentane, cyclohexene and cyclopentene molecules carried out by Pitzer[4] are consistent with this interpretation. The hydrogenation results have been further verified by combustion experiments, which show that the difference between the heats of formation ($\Delta H°_f$, 25°, gas phase) of cyclohexane and cyclopentane (−10.97 kcal./mole)[5] is greater than the difference between the heats of formation of cyclohexene and cyclopentene (−9.57 kcal./mole)[6] by a factor of 1.4 kcal./mole.

In their summarizing paper, Conn, Kistiakowsky and Smith[2] also directed attention to the fact that the heats of hydrogenation of cycloölefins decrease progressively in the series cyclohexene, cycloheptene, *cis*-cycloöctene in a manner suggestive of increased internal crowding in the larger cycloparaffins. The crowding hypothesis is now supported by evidence from a variety of sources which indicates that congestion in the "medium-sized" (8- to 12-membered) rings is severe. Maximum hindrance probably is attained in the cyclodecane system, although this point has not been established with certainty. An excellent summary of work in this field up to 1950 has been given by Prelog.[7] Considerable additional information bearing on the problem of internal hindrance in cyclic systems has appeared more recently. Evidence establishing the close proximity of hydrogen atoms and ring carbon atoms in medium-sized cycles is provided by the remarkable transannular hydride shifts that occur in reactions of cycloöctene,[8] cyclononene,[9] cyclodecene[10] and of cycloundecene[11] with performic acid.[12] Studies of the rates of solvolysis of various cycloalkyl *p*-toluenesulfonates have revealed a marked acceleration of rate in the 7- to 11-membered derivatives, which is attributed to relief of steric strain in the transition states in these instances.[13] Maximum acceleration of solvolysis is observed in the case of cyclodecyl *p*-toluenesulfonate.

Mention should be made finally of the precision combustion measurements of Kaarsemaker and Coops (Table II),[14] which demonstrate that in the

TABLE II

HEATS OF COMBUSTION OF CYCLOPARAFFINS (GAS PHASE, 25°)

Compound	$-\Delta H$, kcal./methylene group
Cyclopentane	158.7
Cyclohexane	157.4
Cycloheptane	158.3
Cycloöctane	158.7
Cyclononane	158.9
Cyclodecane	*158.6*[a]

[a] Older data of (W. Hückel, A. Gercke and A. Gross, *Ber.*, 66, 563 (1933).

cycloparaffin series heats of combustion per methylene group increase in order from the C_6- to the C_9-compounds. Although the numerical differences observed in this series are small, the variations nevertheless fall outside the limits of experimental error.

In view of continued interest in the properties of cycloölefins possessing medium-sized rings, and especially in the behavior of the highly strained *trans* isomers,[15] we have measured the heats of hydrogenation of the *cis*- and *trans*-cycloöctenes, cyclononenes and cyclodecenes in acetic acid solution at 25°. The results of this investigation are listed in Table III. For purposes of comparison, the

(3) This view, which was apparently first expressed in the present connection by V. Schomaker, has since been amply confirmed. *Cf.* W. G. Dauben and K. S. Pitzer, Chapter 1 in "Steric Effects in Organic Chemistry," M. S. Newman, Editor, John Wiley and Sons, Inc., New York, N. Y., 1956, and references cited therein.

(4) K. S. Pitzer, *Science*, 101, 672 (1945).

(5) "Selected Values of Properties of Hydrocarbons," Circular C461 of the National Bureau of Standards (1952).

(6) M. B. Epstein, K. S. Pitzer and F. D. Rossini, *J. Research Natl. Bur. Standards*, 42, 379 (1949).

(7) V. Prelog, *J. Chem. Soc.*, 420 (1950).

(8) A. C. Cope, S. W. Fenton and C. F. Spencer, THIS JOURNAL, 74, 5884 (1952).

(9) V. Prelog, K. Schenker and W. Kung, *Helv. Chim. Acta*, 36, 471 (1953).

(10) V. Prelog and K. Schenker, *ibid.*, 35, 2044 (1952); see also V. Prelog, H. J. Urech, A. A. Bothner-By and J. Würsch, *ibid.*, 38, 1095 (1955).

(11) V. Prelog and V. Boarland, *ibid.*, 38, 1776 (1955).

(12) Considerable interest is attached to the fact that *cis*-1,4-cycloheptanediol has been obtained as a minor product in the solvolysis of cycloheptene oxide [A. C. Cope, T. A. Liss and G. W. Wood, *Chemistry & Industry*, 823 (1956)] and that *trans*-1,4-cyclohexanediol has been identified among the products of the reaction of cyclohexene with performic acid [A. C. Cope, H. E. Johnson and J. S. Stephenson, THIS JOURNAL, 78, 5599 (1956)]. The yields of these substances are, however, exceedingly small. The reaction of cyclododecene with performic acid appears to proceed normally [V. Prelog and M. Speck, *Helv. Chim. Acta*, 38, 1786 (1955)].

(13) R. Heck and V. Prelog, *Helv. Chim. Acta*, 38, 1541 (1955); H. C. Brown and G. Ham, THIS JOURNAL, 78, 2735 (1956).

(14) Sj. Kaarsemaker and J. Coops, *Rec. trav. chim.*, 71, 261 (1952).

(15) The preparation and chemistry of the *trans*-cycloölefins has been discussed by: (a) K. Ziegler and H. Wilms, *Ann.*, 567, 1 (1950); K. Ziegler, H. Sauer, L. Bruns, H. Froitzheim-Kühlhorn and J. Schneider, *ibid.*, 589, 122 (1951); (b) A. T. Blomquist, R. E. Burge and A. C. Sucsy, THIS JOURNAL, 74, 3636 (1952); A. T. Blomquist, L. H. Liu and J. C. Bohrer, *ibid.*, 74, 3643 (1952); (c) A. C. Cope, R. A. Pike and C. F. Spencer, *ibid.*, 75, 3212 (1953); A. C. Cope, D. C. McLean and N. A. Nelson, *ibid.*, 77, 1628 (1955); (d) V. Prelog, K. Schenker and H. H. Günthard, *Helv. Chim. Acta*, 35, 1598 (1952), and reference 9.

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solution values for cyclohexene and for cycloheptene[16] are included also.

TABLE III

HEATS OF HYDROGENATION OF CYCLOÖLEFINS (ACETIC ACID SOLUTION)

Compound	Mmoles	PtO_2, mg.	$-\Delta H$(25°, kcal./mole)
cis-Cycloöctene	4.598	100.6	22.88
	4.526	100.5	23.08
	Average		22.98 ± 0.10[a]
trans-Cycloöctene	2.487	99.7	32.44
	2.436	99.6	32.04
	Average		32.24 ± 0.21
cis-Cyclononene	3.517	100.8	23.67
	2.516	99.7	23.56
	Average		23.62 ± 0.07
trans-Cyclononene	3.484	100.7	26.62
	3.609	99.3	26.36
	Average		26.49 ± 0.14
cis-Cyclodecene	3.553	99.3	20.63
	3.937	99.2	20.60
	3.960	100.0	20.77
	Average		20.67 ± 0.08
trans-Cyclodecene	3.744	99.8	23.92
	3.751	99.3	24.07
	3.773	100.7	24.05
	Average		24.01 ± 0.09
Cyclohexene	Average		27.10 ± 0.08[b]
Cycloheptene	Average		25.85 ± 0.09[b]

[a] Deviations include uncertainty in the heat of hydrogenation of the catalyst. [b] Data from reference 16.

Although the data are largely self-explanatory, the following points may be singled out for special comment. It will be noted first that the values obtained for the *cis*-olefins show a decrease of 6.4 kcal. in passing from cyclohexene (−27.1 kcal./mole) to *cis*-cyclodecene (−20.7 kcal./mole). The general trend established for the series cyclohexene to *cis*-cycloöctene (Table I) is thus projected at least as far as the 10-membered ring derivative. While it would appear that increased steric compression in the higher cycloparaffins plays a dominant role in lowering the heats of hydrogenation of the larger cycloölefins, it is clear that differences in angular and repulsive strains in the unsaturated compounds cannot be disregarded. The fact that the heat of hydrogenation of *cis*-cyclononene is higher than that of *cis*-cycloöctene, whereas the inverse relation might have been expected in view of the combustion data of Table II, can best be explained on the basis of such considerations.

In each *cis–trans* isomer pair for which data are given, the *trans* modification possesses the higher heat of hydrogenation and hence the lower stability. The heats of isomerization (*trans* → *cis*) calculated for the 8-, 9- and 10-membered olefins from the hydrogenation results are −9.2, −2.9 and −3.3 kcal./mole, respectively, as compared with the value of −1.0 kcal./mole reported by Kistiakowsky[17] for the heat of isomerization of *cis*-butene into *trans*-butene. Conclusions regarding isomer stability that have been drawn from qualitative studies of the equilibrium behavior of the cyclic olefins in the presence of acid[15] are thereby confirmed and are placed on a quantitative basis. The difference of 9 kcal. observed in the heats of hydrogenation of *cis*- and of *trans*-cycloöctene is the largest yet obtained for any pair of *cis–trans* isomers and reflects the severe strain that accompanies incorporation of a *trans* double bond in the eight-membered ring. The question of the point in the cyclic series at which the *trans* isomer may become more stable than the *cis*, as in open-chain olefins, presents an interesting problem for future investigation.[18]

With reference to the data for *cis*-cyclodecene, mention should finally be made of the fact that the heat of hydrogenation of this substance is the lowest yet recorded for a compound possessing an isolated double bond.[19] The highest such value thus far encountered is that obtained for *cis*-di-*t*-butylethylene (−35.5 kcal./mole).[20] The spread of almost 15 kcal. in the heats of hydrogenation of these two *cis*-disubstituted olefins provides a striking demonstration of the extent to which environmental factors may be implicated in chemical transformations.

Experimental

The calorimetric procedure followed in this investigation was that described in Paper I.[16] Acetic acid was employed as the solvent in all cases, and platinum oxide was used as the catalyst throughout.

Samples of *cis*-cycloöctene, $n^{25}D$ 1.4690, b.p. 74–75° (84 mm.), and of *trans*-cycloöctene, $n^{25}D$ 1.4742, b.p. 75° (78 mm.), were kindly supplied by Prof. A. C. Cope. In view of the instability of *trans*-cycloöctene, the specimen of this substance was shipped to us in Dry Ice by air express. Upon receipt, the material was sealed in evacuated ampoules, which were stored at −15°. Measurements were carried out on the two days following arrival of the sample, and at the end of the experiment a spare ampoule was broken and the contents examined in the infrared. The absorption spectrum proved to be identical with that of pure *trans*-cycloöctene showing that no polymerization or isomerization to the *cis* isomer had occurred. Professor Cope has informed us that *trans*-cycloöctene is completely stable in acetic acid solution at room temperature for periods up to 2 hr. Careful examination of the calorimetric time–temperature curves before and after dissolution of the sample, but prior to initiation of the hydrogenation reaction, has confirmed this view.

The cyclononene and cyclodecene samples, which were generously provided by Prof. V. Prelog, possessed the following constants: *cis*-cyclononene, $n^{20}D$ 1.4791; *trans*-cyclononene, $n^{19}D$ 1.4789; *cis*-cyclodecene, $n^{21}D$ 1.4849, b.p. 90.3° (33 mm.); *trans*-cyclodecene, $n^{20}D$ 1.4799, b.p. 198–199° (760 mm.). The specimens of *cis*-cyclononene and of *cis*-cyclodecene absorbed only 95.3 and 98.0%, respectively, of the theoretical amount of hydrogen. Since both compounds were prepared by partial hydrogenation of the corresponding cycloalkynes, the most likely contaminant would appear to be cycloparaffin. Although impurities of this type would have no effect on heats of hydrogenation

(16) R. B. Turner, W. R. Meador and R. E. Winkler, THIS JOURNAL, **79**, 4116 (1957).

(17) G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *ibid.*, **57**, 876 (1935).

(18) The conclusion of N. L. Allinger, *Experientia*, **10**, 328 (1954), derived from correlations of boiling points, densities and refractive indices, that *trans*-cyclodecene should be more stable than the corresponding *cis* isomer has been revised in the light of other considerations (N. L. Allinger, private communication).

(19) In systems possessing a high degree of resonance stabilization low heats of hydrogenation are, of course, expected. Thus benzene, with a resonance energy of 36 kcal./mole, has a heat of hydrogenation (gas phase) of 16.6 kcal. per "double bond" [G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *ibid.*, **58**, 146 (1936)].

(20) R. B. Turner, W. R. Meador, R. E. Winkler and A. D. Mitchell, *ibid.*, **79**, 4133 (1957).

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calculated on the basis of hydrogen uptake, the presence of any appreciable amounts of unreduced acetylenes (which would, however, lead to high hydrogen uptake values) would be more serious. Careful scanning of the infrared absorption spectra of the two compounds, however, revealed no trace of acetylenic absorption.

It is a pleasure to acknowledge the considerable contribution made to this work by Professors Prelog and Cope, whose coöperation in supplying samples has been of the greatest assistance.

HOUSTON 1, TEXAS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Reaction of Cyanogen Halides with the Silver Salts of Carboxylic Acids

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The reaction of cyanogen halides with the silver salts of carboxylic acids was studied. The major products were found to be the corresponding nitrile, acid and anhydride. The yields of these three compounds varied with the solvent employed, the yield of nitrile being highest (32%) in acetonitrile, the yield of acid being highest (82%) in nitromethane and the yield of anhydride (88%) in trichloroethylene. It is postulated that an intermediate acyl cyanate is formed and this material reacts further to give rise to nitrile and anhydride.

The silver salt–bromine degradation of Hunsdiecker has been widely used to prepare alkyl halides.[1] Recently, this reaction has been employed in the preparation of complex C^{14}-carboxyl labeled acids according to the following sequence (eq. 1).[2] Considering the relative ease by

$$RCOOH \xrightarrow[2,\ Br_2]{1,\ Ag^{\oplus}} RBr \xrightarrow{C^*N^{\ominus}} RC^*N \xrightarrow{H_2O} RC^*OOH \quad (1)$$

which C^{14}-labeled cyanogen halides can be prepared from labeled alkali metal or silver cyanides[3] and the similarity of such compounds with a halogen molecule, a modification and extension of the Hunsdiecker reaction using cyanogen halides instead of bromine was studied. Other than the usual chemical interest in the reaction of pseudohalogens, it also was of interest to see if replacement of an unlabeled carboxyl group by a labeled cyanide group could be achieved in one step (eq. 2).

$$R{-}COOAg + C^*NX \longrightarrow R{-}C^*N + AgX + CO_2 \quad (2)$$

In 1947,[4] Zappi and Bouso described a similar reaction, and in their work solid alkali metal salts of carboxylic acids were pyrolyzed in the presence of cyanogen halides at temperatures between 200–300° and nitriles were isolated in variable yields. When this reaction was performed with C^{14}-carboxyl labeled benzoic acid, Douglas, Eccles and Almond[5] observed that no displacement occurred, the evolved carbon dioxide was not labeled and the generated benzonitrile was labeled. On the other hand, when a carboxyl labeled aliphatic acid was used in the pyrolysis reaction, the carbon dioxide was labeled and the nitrile was not radioactive.[5] Evaluation of these conflicting results must await further work.

It was obvious that the drastic conditions used in this alkali metal salt and cyanogen halide reaction would limit the usefulness of the reaction to acids of simple structure if, indeed, displacement did occur. If, however, the reaction could be run with the silver salts of carboxylic acids under the conditions of the silver salt–bromine degradation of Hunsdiecker, the reaction might become a valuable method for the introduction of C^{14} into organic compounds. In line with this concept are the findings of Haszeldine and Jander[6] who report that when the silver salt of an aliphatic trifluorocarboxylic acid is allowed to react with nitrosyl chloride under the conditions of the Hunsdiecker reaction, an alkylnitroso compound and carbon dioxide are obtained.

Although the mechanism of the Hunsdiecker reaction is not clearly understood,[1] the most likely route would involve the reaction of a bromine cation, $Br^{\oplus}$, with the silver salt to form an acylhypohalite which, in turn, would decompose to alkyl halide and carbon dioxide. From what is known of the chemistry of the cyanogen halides,[7] it is clear that under certain conditions these compounds do generate $CN^{\oplus}$, and it appears that cyanogen chloride would be more likely to do this than cyanogen bromide and the bromide more likely than the iodide.[8] In the present work, cyanogen bromide was utilized since it is easier to handle than the gaseous cyanogen chloride and the easily subliming cyanogen iodide. Furthermore, since the main aim of the study was to obtain a good yield of nitrile, most experiments were not performed under identical conditions. The acid chosen for the most investigations was γ-phenylbutyric acid since this acid shows the features of both an aromatic ring and an aliphatic acid.

(1) R. G. Johnson and R. K. Ingham, *Chem. Revs.*, **56**, 219 (1956); C. H. F. Allen and C. V. Wilson, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 578.

(2) S. Bergström, K. Pääbo and M. Rottenberg, *Acta Chem. Scand.*, **6**, 1127 (1952); S. Bergström, M. Rottenberg and J. Voltz, *ibid.*, **7**, 481 (1953); S. Bergström, K. Pääbo and M. Rottenberg, *ibid.*, **7**, 1001 (1953); D. R. Howton, R. H. Davis and J. C. Nevenzel, THIS JOURNAL, **76**, 4970 (1954).

(3) S. Graf, M. Engelman, H. B. Gillespie and A. M. Graf, *Cancer Research*, **11**, 388 (1951); F. Weygand and H. Simon in Houben-Weyl, "Methoden der Organischen Chemie," Vol. IV, part 2, Georg Thieme Verlag, Stuttgart, 1955, p. 558.

(4) E. V. Zappi and O. Bouso, *Ann. asoc. quim. Argentina*, **35**, 137 (1947).

(5) D. E. Douglas, J. Eccles and A. E. Almond, *Can. J. Chem.*, **31**, 1127 (1953).

(6) R. N. Haszeldine and J. Jander, *J. Chem. Soc.*, 4172 (1953).

(7) V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publishing Corp., New York, N. Y., 1947, p. 97; D. T. Mowry, *Chem. Revs.*, **42**, 189 (1948).

(8) G. Lord and A. A. Woolf, *J. Chem. Soc.*, 2546 (1954); T. Kikindai, *Bull. Chem. Soc. Japan*, **18**, 799 (1951).

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It was found that when the silver salt of γ-phenylbutyric acid was allowed to react with cyanogen bromide in carbon tetrachloride, the reaction was sluggish compared to the Hunsdiecker reaction. No carbon dioxide could be observed in the cold or at room temperature. Only after heating on a steam-bath was carbon dioxide evolved. The main product of the reaction was not the expected nitrile but the anhydride of the acid. The yield of nitrile was 9% and of anhydride was 75%. The silver salt mixture isolated from the reaction mixture was shown to contain silver cyanate. In several cases, approximately equimolecular amounts of anhydride and cyanate were found.

The formation of an anhydride in the reaction of silver salts is well known. For example, the anhydrides of mono- and dicarboxylic acids are obtained when their silver salts are allowed to react with iodine. Thus, silver phthalate gives phthalic anhydride and silver hypoiodite which, in turn, disproportionates into silver iodate and silver iodide.[9] Also, silver trifluoroacetate and iodine in benzene form trifluoroacetic anhydride.[10] By analogy, a reasonable explanation for the formation of anhydride and cyanate in the cyanogen halide reaction can be represented as shown below (eq. 3, 4, 5) and involves the formation of an intermediate acyl

$$RCOOAg + CNBr \longrightarrow RCOOCN + AgBr \quad (3)$$

$$RCOOCN + RCOOAg \longrightarrow RCOOCOR + AgOCN \quad (4)$$

$$RCOOCN \longrightarrow RCN + CO_2 \quad (5)$$

cyanate which can react with silver salt to form an anhydride or can decompose to give rise to a nitrile and carbon dioxide. Since such a postulate indicates a bimolecular displacement reaction for the formation of the anhydride, the influence of different solvents has been investigated. The solvents used and the results obtained are summarized in Table I.

TABLE I

REACTION OF SILVER SALTS OF CARBOXYLIC ACIDS WITH CYANOGEN BROMIDE IN VARIOUS SOLVENTS

	Solvent, %					
Nitrile	Carbon tetrachloride	Nitromethane	Acetonitrile	N,N-Dimethylformamide	Nitrobenzene	Trichloroethylene
Anhydride	9	5	32	17	21	5
Acid	75	15	28	8	64	88
	1	82	36	40	5	5

It is seen that the best yields of nitrile are obtained when a solvent of high dielectric constant is employed, the dielectric constants for acetonitrile, nitrobenzene and N,N-dimethylformamide being 37.5, 35.7 and 37.6, respectively.[11] However, when the solvent was nitromethane, a compound also possessing a dielectric constant of 37.5,[11] the yield of nitrile was very low. Simultaneously, the yield of acid was high and this reaction must be attributed to the acidic nature of the solvent. The yield of acid was also high in acetonitrile, an acidic solvent, and N,N-dimethylformamide. In this last solvent, the N,N-dimethylamide of γ-phenylbutyric acid also was formed, and this reaction may account for the liberation of free starting acid. Although no definite decision can be given as to the role of solvent in the formation of anhydride, since the various reactions were not run under the same conditions, it does seem apparent that a solvent of low dielectric constant favors the formation of this species. Such a conclusion clearly shows the oversimplification of the above postulated mechanistic pathway for the formation of the anhydride. The assumption of an intermediate acyl cyanate, nevertheless, offers a reasonable explanation for the concomitant formation of the anhydride and the silver cyanate and also accounts for the formation of the nitrile and carbon dioxide.

An alternate pathway for the formation of nitrile also must be considered. It is known that when the anhydride of a carboxylic acid is heated with potassium cyanate in benzene, imides are formed[12] and that imides on mild heating decompose to a nitrile and an acid.[13] Accordingly, silver cyanate and the anhydride, products of the silver salt–cyanogen bromide reaction, could react similarly to yield an imide which could decompose to a nitrile and an acid. It was found that under the same or similar conditions to those used in the silver salt–cyanogen bromide reaction, no imide, nitrile or acid was formed when pure silver cyanate and an anhydride were allowed to react.

Two exploratory experiments were performed with silver γ-phenylbutyrate and the other cyanogen halides. With cyanogen iodide in carbon tetrachloride, the products were 1.5% nitrile, 68% anhydride and 18% acid while with cyanogen chloride the yields were 7% nitrile, 73% anhydride and 8% acid. In addition, in this latter case, 3-phenylpropyl chloride was isolated in 2% yield. This is the only case among all the experiments where a halide was isolated and, indeed, this is surprising since cyanogen chloride should be the halide least likely to yield an $X^{\oplus}$ ion. The non-occurrence of halide in the cyanogen halide reactions explains the fact that in no instance could Simonini ester formation be demonstrated.[1]

To extend the scope of this reaction, a brief study was made with a typical aromatic acid, benzoic acid, and a typical aliphatic acid, decanoic acid. In both cases cyanogen bromide was employed and it was found that the results did not differ from those obtained with γ-phenylbutyric acid. It is of interest to note that no aromatic ring substitution was found with either acid containing an aromatic nucleus. Such substitutions have been observed in the Hunsdiecker reaction with aromatic acids containing activating groups on the ring.[14]

Finally, it can be stated that the difference between the alkali metal salt–cyanogen bromide reaction with benzoic acid run under pyrolytic conditions and the reaction performed with silver

(9) K. Birnbaum and H. Reinherz, *Ber.*, **15**, 456 (1882); H. Wieland and F. G. Fischer, *Ann.*, **446**, 49 (1925).

(10) F. Swarts, *Anales soc. espan. fis. y quim.*, **27**, 683 (1929); *Chem. Zentr.*, 1763 (1930).

(11) A. A. Maryott and E. R. Smith, Table of Dielectric Constants of Pure Liquids, Natl. Bur. Standards Circ. 514 (1951); G. R. Leader and J. F. Gormley, THIS JOURNAL, **73**, 5731 (1951). All values are at 20°.

(12) K. Brunner, *Ber.*, **47**, 2671 (1914).

(13) F. Krafft, *ibid.*, **23**, 2389 (1890).

(14) W. G. Dauben and H. Tilles, THIS JOURNAL, **72**, 3185 (1950); K. A. Ingles and J. J. Hlavka, *ibid.*, **72**, 3188 (1950).

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benzoate in an organic solvent are that, in the former case, besides benzonitrile, also benzamide and cyaphenin, the trimer of benzonitrile, are isolated[4,5] but no anhydride, whereas in the latter case mainly anhydride, nitrile and acid are the products, but no amide or cyaphenin is formed. The yield of nitrile is better when the reaction is run under the pyrolytic conditions.

Experimental[15]

All solvents were purified and carefully dried. The silver salts of the carboxylic acids were prepared in the usual manner[16] and they were either dried in a vacuum oven at 60° or in a vacuum desiccator over phosphorus pentoxide at room temperature for at least 24 hr. Their purity was checked by combustion analysis.

The cyanogen halides cyanogen chloride,[17] cyanogen bromide[18] and cyanogen iodide[19] were prepared by metathesis of the halogens with alkali metal cyanides. The cyanogen bromide, before being added to the silver salts, was dried in carbon tetrachloride over phosphorus pentoxide.

All liquid reaction products were distilled through a 20″ wire-screen filled column of 12-plate efficiency if not otherwise mentioned.

Determination of Cyanate Ion. (a) Quantitative Test.[20]—A sample of the silver salt mixture obtained from the reaction of the silver salt of a carboxylic acid with the cyanogen halide was mixed in a mortar with cobaltous acetate and potassium chloride. Addition of a few drops of acetic acid followed by mixing produced a blue color when cyanate-ion was present.

(b) Quantitative Test.[20] **Cyanate Carbon.**—A sample of silver salt from the reaction mixture was treated with excess 1 *N* hydrochloric acid and the evolved carbon dioxide absorbed in standardized sodium hydroxide solution. If stronger acid concentrations were used, the cyanide was also hydrolyzed to formate and the carbon values were too high.

Cyanate Nitrogen.—The residual acidified mixture above was made alkaline with 1 *N* potassium hydroxide solution and the liberated ammonia absorbed in standardized sulfuric acid solution. Stronger potassium hydroxide solution hydrolyzed also the cyanide.

Silver cyanate was prepared from potassium cyanate and silver nitrate[21] and dried in a desiccator over phosphorus pentoxide. Following the above procedure a freshly prepared and dried sample of silver cyanate was analyzed.

Anal. Calcd. for AgOCN (149.90): C, 8.01; N, 9.34. Found: C, 7.84; N, 9.22.

In the same manner a well dried sample of silver cyanide was analyzed.

Anal. Calcd. for AgCN (133.90): C, 8.97; N, 10.46. Found: C, 0.0; N, 0.0.

An equimolecular mixture of the silver salts of decanoic, cyanic, hydrocyanic and hydrobromic acids was prepared and dried in a desiccator over phosphorus pentoxide. A sample was analyzed as above.

Anal. Calcd. for AgOCN in mixture [AgOOC-$(CH_2)_8$-CH_3 (279.26); AgOCN (149.90); AgCN (133.90); AgBr (187.80)]: C, 1.60; N, 1.87. Found: C, 1.44; N, 1.81.

Experiments with Silver γ-Phenylbutyrate and Cyanogen Bromide.—(a) In Carbon Tetrachloride as the Solvent; Addition of the Cyanogen Bromide to the Silver Salt.—A suspension of 108.4 g. (0.4 mole) of silver salt in 800 ml. of carbon tetrachloride was distilled until 100 ml. of distillate had been collected and then cooled in an ice-bath. A solution of 47 g. (0.45 mole) of cyanogen bromide in 315 ml. of carbon tetrachloride was added dropwise with stirring over a period of 1 hr. No carbon dioxide evolution could be detected. Upon heating on a steam-bath to reflux temperature, a slow evolution of carbon dioxide began. Heating and stirring were continued for 5 hr. At the end of the heating period the carbon dioxide evolution had stopped. The silver salts were filtered and washed several times with carbon tetrachloride. The carbon tetrachloride solution was extracted three times with 2 *N* sodium carbonate solution.

The alkaline aqueous extracts were combined and were acidified with 6 *N* sulfuric acid. The acidic aqueous solution was extracted with ether in an apparatus for continuous extraction. After removal of the ether the residue was distilled under reduced pressure to a cold finger and 422 mg. (0.6%) of γ-phenylbutyric acid, m.p. 47–48°, was obtained.

Subsequent extraction of the carbon tetrachloride layer with 4 *N* sodium hydroxide solution did not yield any extractable material. The carbon tetrachloride solution, washed with water until neutral, was dried with Drierite. The solvent was removed and the residue was fractionally distilled. The forerun (0.5 g., b.p. 120–126° (10 mm.)) was shown not to contain 3-phenylpropyl bromide (b.p. 120.5–121.5° (20 mm.)). The next fraction was a colorless oil, b.p. 126–127° (10 mm.), and was γ-phenylbutyronitrile, (lit.[22] b.p. 129–131° (10 mm.)), yield 5 g. (8%).

A sample of the nitrile was hydrolyzed with 25% ethanolic potassium hydroxide and gave in 80% yield γ-phenylbutyric acid.

The distillation residue crystallized at room temperature to a waxy substance which was insoluble in 2 *N* sodium hydroxide solution and which had a m.p. 25–28°. Recrystallization of a sample from ether–petroleum ether at −30° yielded γ-phenylbutyranhydride, m.p. 28–29°. The infrared spectrum was identical with that of an authentic sample.

Anal. Calcd. for $C_{20}H_{22}O_3$ (310.38): C, 77.39: H, 7.14. Found: C, 77.39; H, 7.41.

A sample of the distillation residue (13 g.) was refluxed overnight with 350 ml. of 10% aqueous sodium hydroxide solution. The alkaline solution was saturated with potassium carbonate and was continuously extracted with ether for 24 hr. No alcoholic material could be detected in this ether extract. The aqueous phase of this extraction was acidified with 6 *N* sulfuric acid (acid to congo red). This acidic mixture was continuously extracted with ether for 24 hr. The ether extract was dried with magnesium sulfate and yielded γ-phenylbutyric acid (95%), m.p. 45–47°. Hence, the non-distillable fraction consisted of 46.9 g. (75%) of the anhydride of γ-phenylbutyric acid.

The silver salts from the reaction were treated with 500 ml. of 6 *N* hydrochloric acid using a vibrating mixer. A violent evolution of hydrocyanic acid occurred and the mixture warmed up. The mixture was filtered through a mat of filter aid. The filter cake was shaken several times with portions of diisopropyl ether, and the filtrate was extracted several times with the same solvent. The combined ether extracts yielded 4 g. (6%) of γ-phenylbutyric acid, m.p. 45–47°.

γ-Phenylbutyranhydride was prepared by refluxing a mixture of 32.8 g. (0.2 mole) of acid with 200 ml. of acetic anhydride and 200 ml. of pyridine for 3 hr. After removal of the excess reagents under reduced pressure the residue was fractionally distilled, yield 21 g. (68%). This compound can only be distilled with losses due to decomposition, b.p. 200–205° (3 mm.), m.p. 28–29°. The compound shows strong absorption peaks in the infrared at 5.5, 5.83 and 9.7 μ.

Anal. Calcd. for $C_{20}H_{22}O_3$ (310.88): C, 77.39; H, 7.14. Found: C, 77.48; H, 7.35.

(b) In Carbon Tetrachloride as the Solvent; Addition of the Silver Salt to the Cyanogen Bromide.—A solution of 47 g. (0.45 mole) of cyanogen bromide in 1200 ml. of carbon tetrachloride was cooled to 0°, and a 10-g. portion of silver salt was added. After 10 minutes, the mixture was brought to reflux on a steam-bath, whereupon carbon dioxide evolution commenced. Over the period of 1 hr. 108.4 g. (0.4 mole) of silver salt was added and the heating and stirring

(15) Quantitative analyses by the Microanalytical Laboratory of the Department of Chemistry, University of California, Berkeley.

(16) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1950, p. 271.

(17) G. H. Coleman, R. W. Leeper and C. C. Schulze, in "Inorganic Syntheses," Vol. II, McGraw-Hill Book Co., New York, N. Y., 1946, p. 90.

(18) G. Brauer, "Handbuch der präparativen anorganischen Chemie," F. Enke Verlag, Stuttgart, 1954, p. 505.

(19) B. Bak and A. Hillebert, *Org. Syntheses*, **32**, 29 (1952).

(20) H. E. Williams, "Cyanogen Compounds," 2nd Ed., Edward Arnold and Co., London, 1948, p. 400.

(21) H. Hecht, "Präparative anorganische Chemie," Springer-Verlag, Berlin, 1951, p. 112.

(22) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Vol. IV, rev. ed., Oxford University Press, New York, N. Y., 1953, p. 110.

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was continued for 10 hr. Processing in the usual way (see above) gave 500 mg. (1%) of γ-phenylbutyric acid from the sodium carbonate extract, 7.3 g. (12%) of nitrile and 44 g. (71%) of anhydride.

(c) **In Nitromethane as the Solvent.**—The silver salt (108.4 g., 0.4 mole) was suspended in 400 ml. of carbon tetrachloride, and 400 ml. of the solvent was distilled. Nitromethane (700 ml.) was then added, and over the period of 1.5 hr. 50 g. (0.47 mole) of cyanogen bromide in 350 ml. of nitromethane was added, with stirring, to the reaction mixture. During the first 0.5 hr. of the addition the reaction mixture was at room temperature and no carbon dioxide evolution occurred. The reaction mixture was then heated to slow reflux and the addition of cyanogen bromide continued. At this elevated temperature carbon dioxide evolution occurred and the heating was continued for 8.5 hr. The silver salts were filtered and washed well with carbon tetrachloride. The filtrate was processed in the usual way. The neutral fraction gave 3 g. (5%) of pure nitrile and 9.3 g. (15% assuming pure γ-phenylbutyranhydride) of crude anhydride. This crude anhydride gave a weakly positive Beilstein test for halogen. The acidified alkaline extract yielded 54 g. (82% assuming pure γ-phenylbutyric acid) of crude acidic material. This material had a m.p. of 42–45° and it gave a positive Beilstein test. When this material was distilled, approximately 4 g. of higher boiling material was obtained as a tarry distillation residue which gave a strongly positive Beilstein test.

(d) **In Acetonitrile as the Solvent.**—To a suspension of 80 g. of silver salt in 1200 ml. of purified acetonitrile containing 2 g. of cuprous cyanide, 36 g. of cyanogen bromide dissolved in 350 ml. of acetonitrile was added during the course of 2.5 hr. Upon initial heating a blue color developed which later discharged. During the entire reaction carbon dioxide was evolved. After an additional hour of heating the reaction mixture was allowed to stay at room temperature overnight.

The usual working-up procedure was modified due to the water solubility of acetonitrile. The acetonitrile layer was diluted with a large volume of carbon tetrachloride, the aqueous layer was saturated with sodium chloride, and the reaction mixture was processed in the normal manner. A yield of 32% nitrile, 28% anhydride and 36% acid was obtained.

(e) **In N,N-Dimethylformamide as the Solvent.**—A mixture of 108.4 g. (0.4 mole) of silver salt with 1500 ml. of N,N-dimethylformamide was prepared. The mixture was stirred and heated on a steam-bath and a solution of 45 g. (0.43 mole) of cyanogen bromide in 450 ml. of carbon tetrachloride was added during 1.5 hr. The carbon dioxide evolution was rather slow. The mixture was heated on the steam-bath overnight. After 8 hr. of heating there was still some carbon dioxide evolution. To the cooled mixture was added carbon tetrachloride in order to precipitate more of the silver salts. These were filtered and washed with the same solvent. Shaking the filtrate with 2 *N* sodium carbonate solution precipitated more silver salts which were filtered. The sodium carbonate extracts were continuously extracted with ether for three days in order to extract the water-soluble N,N-dimethylformamide. The acidified aqueous phase yielded 26 g. (40%) of pure γ-phenylbutyric acid. The combined carbon tetrachloride layers were dried with magnesium sulfate. After removal of the solvent a brown oil was obtained which was fractionated with a column; 6 g. (10%) of pure γ-phenylbutyronitrile was obtained, b.p. 126–127° (10 mm.). On further heating the distillation residue began to decompose. The distillation was interrupted. This residue was a liquid in which crystallization could not be induced by seeding with γ-phenylbutyranhydride. The residue was subjected to a fast distillation in a Claisen flask. This operation separated a fraction which boiled mainly between 150 and 180° at a pressure of 1 mm. from a distillation residue which solidified. This solidified material eventually yielded 5.3 g. (8%) of γ-phenylbutyranhydride. In a third distillation, using again a column, the fraction with b.p. 150–180° (1 mm.) was split into 4 g. (7%) of γ-phenylbutyronitrile and a distillation residue (20 g., dark brown) which did not solidify and which contained nitrogen. This water-insoluble oil was refluxed with 500 ml. of 10% aqueous sodium hydroxide solution until the water-insoluble layer had disappeared and until the evolution of dimethylamine ceased. The mixture from the hydrolysis yielded after acidification and after purification 16 g. (24%) of γ-phenylbutyric acid. Hence the dark oil contained N,N-dimethyl-γ-phenylbutyramide, b.p. 151–152° (1.5 mm.) (see below).

N,N-Dimethyl-γ-phenylbutyramide.—A solution of 68 g. (0.37 mole) of distilled γ-phenylbutyryl chloride[23] dissolved in 300 ml. of hexane was added with shaking to 860 ml. of an ice-cold commercial 25% aqueous solution of dimethylamine. The amide separated as an oil which did not solidify and was separated and dissolved in methylene chloride. The methylene chloride solution was washed with 2 *N* sodium carbonate solution and with water and dried with magnesium sulfate. After removal of the solvent the amide was distilled, 60 g. (84%) of a yellow oil. It distilled with decomposition at 151–152° (1.5 mm.). Upon cooling the distillate to Dry Ice temperature, large glassy crystals are formed, which melt around 20°. The amide can be recrystallized from methylene chloride–hexane, but care must be exerted since the compound is highly hygroscopic. The analytical sample was dried in a high vacuum for 24 hr. at 60° and sealed under vacuum.

Anal. Calcd. for $C_{12}H_{17}ON$ (191.26): C, 75.35; H, 8.96; N, 7.32. Found: C, 75.41; H, 8.87; N, 7.24.

(f) **In Nitrobenzene as the Solvent.**—A mixture of the silver salt (108.4 g., 0.4 mole) and 1500 ml. of purified nitrobenzene was heated on a steam-bath. During the course of 0.5 hr. 45 g. (0.43 mole) of cyanogen bromide dissolved in 450 ml. of carbon tetrachloride was added dropwise. The carbon dioxide evolution was slow and heating was continued overnight. The bulk of the solvents was distilled under reduced pressure. Carbon tetrachloride was added in order to precipitate the silver salts which were filtered. Extraction with 2 *N* sodium carbonate solution and subsequent acidification yielded 3 g. (5%) of γ-phenylbutyric acid. The carbon tetrachloride extracts, after fractional distillation, gave 12 g. (21%) of nitrile and 39.6 g. (64%) of anhydride.

(g) **In Trichloroethylene as the Solvent.**—The reaction was carried out in the usual manner using 108.4 g. (0.4 mole) of silver salt and 1500 ml. of purified trichloroethylene. The mixture was heated on a steam-bath in an atmosphere of dry nitrogen, and 45 g. (0.43 mole) of cyanogen bromide dissolved in 450 ml. of carbon tetrachloride were added during 1 hr. The carbon dioxide evolution was slow, and heating and stirring was continued for 9 more hours. The silver salts were filtered, washed with carbon tetrachloride and dried for 24 hr. in a desiccator at room temperature *in vacuo* over phosphorus pentoxide. Their weight was 68.5 g. Using the usual working-up procedure the following yields and products were obtained: 3.5 g. (5%) of γ-phenylbutyric acid from the sodium bicarbonate extract, 2.9 g. (5%) of nitrile and 55 g. (88%) of anhydride. Assay of a sample of the silver salt mixture: cyanate-C, 2.85%; cyanate-N, 3.28%. This is equimolecular to 52.3 g. of anhydride. Found: 55 g. of anhydride.

Silver Benzoate and Cyanogen Bromide.—From a mixture of 91.6 g. (0.4 mole) of silver salt and 2000 ml. of carbon tetrachloride, 500 ml. of solvent was distilled. Then 45 g. (0.43 mole) of cyanogen bromide dissolved in 450 ml. of carbon tetrachloride was added to the heated solution during the course of 1 hr. The carbon dioxide evolution was rather slow. The stirring and the refluxing were continued for 14 more hours. The weight of the dried silver salts was 70 g. Using the usual working-up procedure the following yields and products were obtained: From the sodium bicarbonate extract 5 g. (10%) of benzoic acid, which was purified by sublimation, m.p. 121–122°; 2 g. (5%) of benzonitrile, b.p. 80–81° (8 mm.) (lit.[24] 69° (10 mm.)); and 31.5 g. (70%) of benzoic anhydride, b.p. 210–220° (20 mm.), m.p. 41–43° (lit.[25] same b.p., m.p. 43°). The silver salts were treated with dilute (1:1) hydrochloric acid. This mixture was exhaustively extracted with ether, and after removal of the solvent 4 g. (8%) of benzoic acid was obtained. The assay of a sample of the silver salt mixture gave: cyanate-C, 2.16%; cyanate-N, 2.64%. This is equimolecular to 29.2 g. of benzoic anhydride. Found: 31.5 g. of anhydride.

Separation of a Mixture of Benzonitrile, Benzimide[26] and

(23) H. Rupe, *Ann.*, **395**, 118 (1913).

(24) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Vol. I, rev. ed., Oxford University Press, New York, N. Y., 1953, p. 256.

(25) H. T. Clarke and E. J. Rahrs, in "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 91.

(26) A. Pinner, *Ber.*, **23**, 2869 (1890).

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Benzoic Acid.—If equimolecular amounts of the above listed compounds were dissolved in carbon tetrachloride, a quantitative separation could be performed by extraction of the acid with saturated sodium bicarbonate solution, the imide with 2 *N* sodium hydroxide solution, leaving the benzonitrile in the carbon tetrachloride.

Experiments with Silver Decanoate and Cyanogen Bromide.—From a mixture of 111.6 g. (0.4 mole) of silver salt and 700 ml. of carbon tetrachloride, 100 ml. of solvent was distilled. Afterwards 47 g. (0.45 mole) of cyanogen bromide dissolved in 450 ml. of carbon tetrachloride was added at room temperature over the period of 45 minutes. No carbon dioxide evolution could be observed. The mixture was refluxed on a steam-bath for 12 hr. The carbon dioxide evolution was slow. Using the usual working-up procedure the following yields and products were obtained: 49 g. (75%) of anhydride[27] and 10.7 g. (17%) of nitrile, b.p. 109–110° (10 mm.) (lit.[28] 243.7°). Only traces of acid were recovered in this experiment.

In a second experiment, where the cyanogen bromide was added to the heated mixture over a period of 1.5 hr., the carbon dioxide evolution was complete after a total heating time of 3 hr. The yield of nitrile was 4.5 g. (7%).

Experiment with Silver γ-Phenylbutyrate and Cyanogen Iodide.—Cyanogen iodide (39 g., 0.25 mole) dissolved in 400 ml. of carbon tetrachloride was added in the usual manner in portions to 62.4 g. (0.23 mole) of the silver salt in 600 ml. of carbon tetrachloride heated on a steam-bath over a period of 1 hr. The carbon dioxide evolution ceased about 0.5 hr. after the last addition of cyanogen iodide. The reaction mixture was refluxed with stirring overnight. After the usual working-up procedure 0.5 g. (1.5%) of nitrile, 24.2 g. (68%) of anhydride and 6.8 g. (18%) of acid were obtained.

Silver γ-Phenylbutyrate and Cyanogen Chloride.—Approximately 60 ml. (excess) of cyanogen chloride (b.p. 13°) was distilled over the period of 1.5 hr. directly into a slurry of 112 g. (0.41 mole) of the silver salt and 1100 ml. of carbon tetrachloride at room temperature. The reaction flask was equipped with a cold finger condenser filled with Dry Ice and *n*-butyl Carbitol. The content of the cold finger was then replaced with a Dry Ice and methanol mixture and the temperature in the cold finger kept at −20 to −10°. The reaction mixture was heated to about 60–70° and stirring was continued. There was a great initial carbon dioxide evolution, but the evolution came to an end after about 1 hr., albeit cyanogen chloride was still escaping. The mixture was stirred and refluxed for 7 more hours. Using the usual working-up procedure 4.0 g. (7%) of nitrile, 45.1 g. (73%) of anhydride, 5.4 g. (8%) of acid and 1.2 g. (2%) of 3-phenylpropyl chloride[29] were obtained.

(27) J. M. Wallace and J. E. Copenhaver, THIS JOURNAL, **63**, 699 (1941).

(28) Reference 24, p. 421.

(29) J. B. Conant and W. R. Kirner, THIS JOURNAL, **46**, 232 (1924).

BERKELEY 4, CALIFORNIA

[CONTRIBUTION FROM THE ROHM & HAAS CO.]

Chemistry of the 1,4-Diamino-1,3-butadienes. I. Preparation[1]

BY MARIAN F. FEGLEY, NEWMAN M. BORTNICK AND CHARLES H. MCKEEVER

RECEIVED NOVEMBER 3, 1956

1,4-Bis-(dimethylamino)-2-butyne (I), on heating with sodium, was rearranged to 1,4-bis-(dimethylamino)-1,3-butadiene (II). The preparation and rearrangement of several homologs of I are described. On standing at room temperature, II is isomerized to a geometric isomer. Infrared evidence is adduced to assign the initial form the *cis,trans* and the new isomer, the *trans,trans* structure. In the presence of potassium bases, dimerization of I rather than intramolecular rearrangement occurred. This mixture of isomeric dimers was itself subject to rearrangement. The structures of the dimeric products were not definitely ascertained. The mechanism for these transformations of I is discussed.

We have found that 1,4-bis-(dimethylamino)-2-butyne (I) may be rearranged to 1,4-bis-(dimethylamino)-1,3-butadiene (II) by means of finely divided metallic sodium.

$$\underset{\text{I}}{(CH_3)_2NCH_2C{\equiv}CCH_2N(CH_3)_2} \xrightarrow{Na} \underset{\text{II}}{(CH_3)_2NCH{=}CHCH{=}CHN(CH_3)_2}$$

II had first been prepared in these laboratories by McKeever and Nemec[2] by passage of I over chromium oxide-containing catalysts at 300–450° in the vapor phase. Our present discovery has permitted the facile preparation of II on a large laboratory scale.

In order to control this exothermic rearrangement, dried, redistilled I was added dropwise to a stirred boiling mixture of hexane and metallic sodium dispersed in xylene.[3] From 50 g. to 300 g. of I, depending on its purity, could be converted to II per gram of sodium. The product was isolated in yields of 80 to 90% of the theoretical by distillation without prior removal or destruction of the catalyst. Alfin catalyst[4] (55% yield), metallic lithium (81% yield), metallic potassium (9% yield) and sodamide (12% yield) were catalysts of limited utility, while sodium acetylide and metallic calcium were inactive.

This rearrangement was extended to the 1,4-diamino-2-butyne derivatives shown in Table I. These were prepared by means of the cuprous chloride-catalyzed Mannich reaction[5,6] applied to acetylene and to the intermediate 3-dialkylamino-1-propynes. Properties of the corresponding 1,4-diamino-1,3-butadienes are shown in Table II. Dispersed sodium alone was not a satisfactory catalyst for the isomerization of many of the higher

(1) Given in part at the 123rd Meeting of the American Chemical Society, Los Angeles, Calif., March 16, 1953.

(2) C. H. McKeever and J. W. Nemec (Rohm & Haas Co.), U. S. Patent 2,617,827 (Nov. 11, 1952); *C. A.*, **48**, 1429 (1954). Their product was probably the *trans,trans*-modification. The similar rearrangement of 3-amino-1-butynes to the corresponding 1,3-butadienes over activated alumina at 250–300° has been described recently by W. Reppe, *Ann.*, **596**, 12 (1955).

(3) V. L. Hansley, *Ind. Eng. Chem.*, **43**, 1759 (1951); U. S. Patent 2,394,608 (E. I. du Pont de Nemours & Co.) Feb. 12, 1946; *C. A.*, **40**, 2598 (1946). We wish to thank the U. S. Industrial Alcohol Division of National Distillers, Inc., for samples of these dispersions.

(4) A. A. Morton, *Ind. Eng. Chem.*, **42**, 1488 (1950); A. A. Morton, E. E. Magat and R. L. Letsinger, THIS JOURNAL, **69**, 950 (1947).

(5) (a) C. Mannich and F. T. Chang, *Ber.*, **66**, 418 (1933). (b) W. Reppe, E. Keyssner and O. Hecht, U. S. Patent 2,273,141 (General Aniline & Film Corp.) Feb. 17, 1942; *C. A.*, **36**, 3807 (1942). (c) W. Reppe, *Ann.*, **596**, 12 (1955).

(6) The processes which have permitted the satisfactory preparation of these materials at low pressures of acetylene were worked out in collaboration with Dr. J. O. Van Hook, Dr. L. R. Freimiller and Dr. J. S. Killeffer and are described in the Experimental section.

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TABLE I

1,4-DIAMINO-2-BUTYNES $R_1R_2NCCH_2C{\equiv}CCH_2NR_5R_6$ (with R_3 and R_4 on the two methylene carbons)

R_1	R_2	R_3	R_4	R_5	R_6	Method[a]	B.p. °C.	Mm.	$n^{20}D$	Nitrogen, % Calcd.	Found
CH_3	CH_3	H	H	CH_3	CH_3	A	181–183[b]		1.4550	20.0	19.9
C_2H_5	C_2H_5	H	H	C_2H_5	C_2H_5	A	95	7	1.4587	14.3	14.6
n-C_4H_9	n-C_4H_9	H	H	n-C_4H_9	n-C_4H_9	A	136	0.7	1.4600	9.1	9.1
$O(CH_2CH_2)_2$		H	H	$O(CH_2CH_2)_2$		A or B	M.p. 88–90		....	12.5	12.7
$(CH_2)_4$		H	H	$(CH_2)_4$		B	97	2.0	1.5008	14.6	14.4
$O(CH_2CH_2)_2$		CH_3	H	CH_3	CH_3	E D	112–114	1.0	1.4828	14.3	14.0
CH_3	CH_3	C_8H_{17}[c]	C_8H_{17}[c]	CH_3	CH_3	C D	140–143	1.1	1.4617	7.7	7.4

[a] Refers to description in the Experimental. [b] Reference 5b lists b.p. 180°. [c] C_8H_{17} = $(CH_3)_3CCH_2CH(CH_3)CH_2$–.

TABLE II

1,4-DIAMINO-1,3-BUTADIENES $R_1R_2NC(R_3){=}CHCH{=}C(R_4)NR_5R_6$

R_1	R_2	R_3	R_4	R_5	R_6	Method[a]	B.p. °C.	Mm.	$n^{20}D$	Nitrogen, % Calcd.	Found	U.v. absorption spectrum (in 2,2,4-trimethylpentane) ϵ_{max}	Wave length, mμ
CH_3	CH_3	H	H	CH_3	CH_3	F	108	15	1.5500	..	..	19,600	291
C_2H_5	C_2H_5	H	H	C_2H_5	C_2H_5	F	64	0.25	1.5155	14.3	14.4	19,400	292.5
n-C_4H_9	n-C_4H_9	H	H	n-C_4H_9	n-C_4H_9	G	142	0.35	1.5020	9.1	9.1	20,400	300
$O(CH_2CH_2)_2$		H	H	$O(CH_2CH_2)_2$		F, G	M.p. 139–140		....	12.5	12.2	28,000	285
$(CH_2)_4$		H	H	$(CH_2)_4$		F	125–132	0.3[b]	1.601	14.6	14.5	19,300	306
$O(CH_2CH_2)_2$		CH_3	H	CH_3	CH_3	F	110–115	0.3	1.5625	14.2	13.9	20,800	287.5
CH_3	CH_3	C_8H_{17}[c]	C_8H_{17}[c]	CH_3	CH_3	G	187–192	3.8	1.4982	7.7	7.5	21,900	295

[a] Refers to description in the Experimental. [b] Isomerization occurred rapidly on standing. The solid *trans,trans* derivative isolated from one run had m.p. 94–97°, ϵ_{max} 22,600 at 300 mμ. [c] C_8H_{17} = $(CH_3)_3CCH_2CH(CH_3)CH_2$–.

homologs of I. However, a previously prepared mixture of dispersed sodium and a small amount of I served well.

Although the products were not obtained in analytical purity, the large index of refraction change which was observed when 1,4-bis-(dimethylamino)-1,4-diphenyl-2-butyne was heated with the "sodium-I" catalyst indicated that rearrangement had occurred. A corresponding change was noted when 1,4-bis-(dimethylamino)-1,4-diisopropyl-2-butyne was treated in the same fashion. No pure product was isolated from the attempted rearrangement of 1,4-bis-(methylphenylamino)-2-butyne.

Our attempts to rearrange 1-dimethylamino-2-butyne and 1-dimethylamino-2-heptyne to the corresponding 1,3-butadienes failed. Inconclusive results were obtained with 1,4-dihydroxy-2-butyne, its diacetate or its dimethyl ether.

The ultraviolet absorption spectra of the butyne–butadiene pairs provided a means of estimating semi-quantitatively whether rearrangement had occurred. Since the molar extinction coefficients of most of the butadienes were 20,000–25,000 at their maxima (which fell at 280–310 mμ), while the butynes were transparent, an estimate of conversion and purity could be made on the very first experiment. The refractive indices proved more convenient for purity estimation once the best values were established for the two pure materials.

As initially formed, II is a liquid which melts below −100°. It can be stored in full containers at 5° or in carefully dried, sealed vials at room temperature for many months without change. It may be stabilized by simply not distilling the rearrangement reaction mixture. On prolonged storage at room temperature II isomerized to a form which had m.p. −1 to −3°. This isomerization occurred more rapidly when II was heated or was exposed to moisture, carbon dioxide or acids. Figures 1, 2 and 3 show the infrared absorption spectra of the two forms of II and the initial form after standing. The second form shows the relatively weak single C=C stretching absorption (Fig. 1) and strong sharply peaked hydrogen wagging absorption (Fig. 2) characteristic of *trans*-olefins and accordingly has the *trans,trans* (*t–t*) structure.

The direct rearrangement product contains a *trans*-type olefin group (Fig. 2) by its hydrogen wagging absorption; *cis* geometry is indicated by strong, doubly peaked absorption in the C=C stretching region (Fig. 1) and by broad hydrogen-wagging absorption at long wave lengths (Fig. 3). These results are consistent with the assignment of the *cis,trans* (*c–t*) structure to the isomer formed directly by rearrangement of I. This conversion of *c–t* to *t–t* II probably occurs by way of an intermediate such as $(CH_3)_2N{=}CHCH_2CH{=}\overset{+}{C}HN(CH_3)_2$.

When compound I was heated with solid potassium hydroxide, an exothermic reaction occurred at 150–180°. No II was obtained. The product was almost exclusively dimeric. The exothermic reaction was controlled by gradual addition of I to a solution of potassium *n*-octoxide in boiling xylene. At 120–140°, conversions of 70–85% to similar dimeric products were conveniently realized. These products were mixtures which rearranged on further heating in the presence of sodium dispersion with

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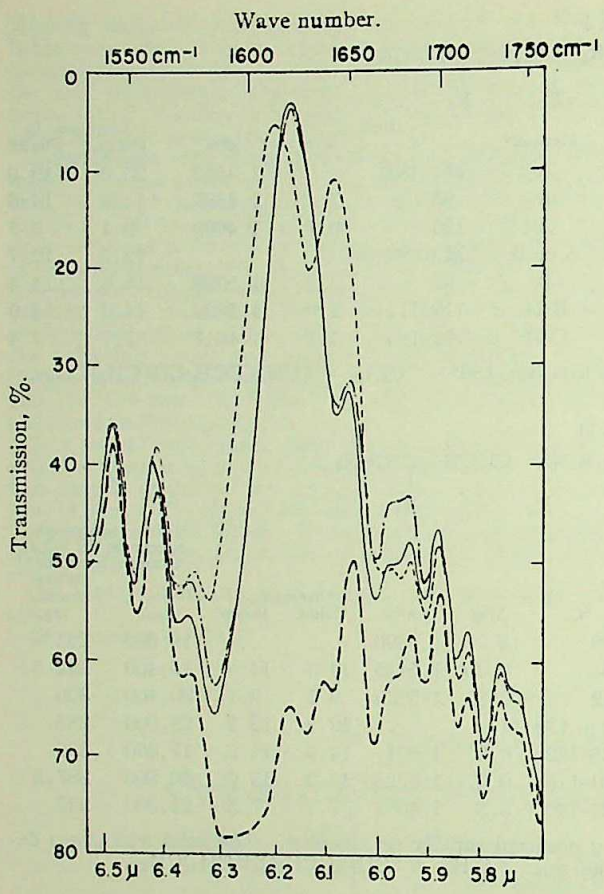

Fig. 1.—Infrared spectra of 1,4-bis-(dimethylamino)-1,3-butadienes, double bond stretching region: ———, *t,t*-II; – – – –, *c,t*-II; — · —, *c,t*-II on standing; – – – –, $CHCl_3$.

changes in refractive index and ultraviolet absorption spectra but without noticed changes in boiling range and empirical formula, $C_{16}H_{32}N_4$.

Hydrogenation in ethanol solution in the presence of Raney nickel catalyst led to the absorption of 2.8 ± 0.5 moles of hydrogen. A liquid, $C_{14}H_{31}N_3$, and a small amount of a solid, $C_{16}H_{36}N_4$,[7] were isolated, together with dimethylamine.

The dimeric product mixture decomposed slowly with evolution of dimethylamine when heated at 200°. Presence of solid potassium hydroxide stabilized the system so that heating to 240° was required to observe this decomposition. The presence of a trace of hydrogen chloride lowered the decomposition temperature to 140°, two moles of dimethylamine were eliminated per mole of dimer and a brittle black resin remained.

Attempts to extend the dimerization reaction to higher homologs were largely unsuccessful. 1,4-Bis-(diethylamino)-2-butyne gave dimeric material in very poor yield while neither the 1,4-bis-(dibutylamino) nor the 1,4-dimorpholino derivative could be converted by means of potassium *n*-octoxide in boiling xylene.

(7) The similarity between the ultraviolet absorption spectra of 1,4-bis-(dimethylamino)-2-butene and of the solid suggested the possibility that the grouping N—C—C=C—C—N may be present in the latter. If the remaining double bond is sufficiently hindered, hydrogenolysis of the allylic bond might be expected to occur in preference to double bond saturation to give $C_{16}H_{31}NC=C(CH_3)NR_2$.

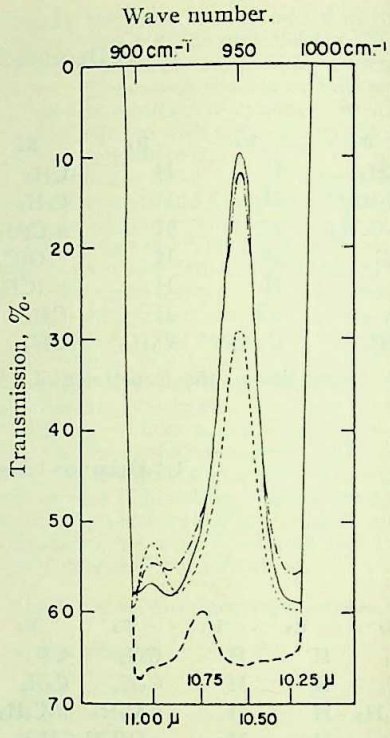

Fig. 2.—Infrared spectra of 1,4-bis-(dimethylamino)-1,3-butadienes, *trans*-olefin hydrogen wagging region: ———, *t,t*-II; – – – –, *c,t*-II; — · —, *c,t*-II on standing; – – – –, $CHCl_3$.

Dimerization was effected concurrent with rearrangement to II when metallic potassium or sodamide was employed. Although other sodium derivatives (the hydroxide, methoxide and *n*-octoxide) were ineffective in short time, small scale experiments, prolonged heating of I with sodium ethyleneglycoxide gave some dimeric material.

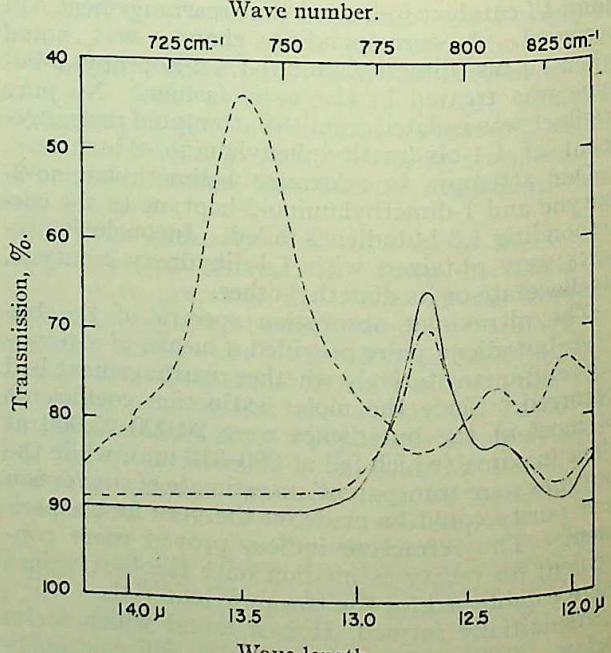

Fig. 3.—Infrared spectra of 1,4-bis-(dimethylamino)-1,3-butadienes, *cis*-olefin hydrogen wagging region: ———, *c,c*-II; – – – –, *c,t*-II; — · —, *c,t*-II on standing.

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Complete recovery of II in experiments in which it was heated with potassium hydroxide, in the presence or absence of I, showed that II was not an intermediate in the dimerization process.

We propose a mechanism for these base-catalyzed transformations of I similar to that recently described by Jones, Whitham and Whiting[8] for the case of prototropic rearrangements of acetylenic acids.

$$\underset{\text{I}}{XCH_2C{\equiv}CCH_2X} + B^- \longrightarrow \underset{A_1}{X\bar{C}HC{\equiv}CCH_2X} + BH$$

$$\underset{A_1}{X\bar{C}HC{\equiv}CCH_2X} \longleftrightarrow \underset{A}{XCH{=}C{=}\bar{C}CH_2X} \longleftrightarrow \underset{A_2}{XCH{=}C{=}\bar{C}CH_2X}$$

$$\underset{A_2}{XCH{=}C{=}\bar{C}CH_2X} + I \rightleftharpoons \underset{B}{XCH{=}C{=}CHCH_2X} + A_1$$

$$\underset{B}{XCH{=}C{=}CCH_2X} + A \rightleftharpoons$$

$$\underset{C_1}{XCH{=}C{=}CH\bar{C}HX} + I \text{ or } B$$

$$\underset{C_1}{XCH{=}C{=}CH\bar{C}HX} \longleftrightarrow \underset{C}{XCH{=}\bar{C}{-}CH{=}CHX} \longleftrightarrow \underset{C_2}{XCH{=}\bar{C}{-}CH{=}CHX}$$

$$\underset{C_2}{XCH{=}\bar{C}{-}CH{=}CHX} + I \text{ or } B \longrightarrow$$

$$\underset{II}{XCH{=}CH{-}CH{=}CHX} + A \text{ or } C$$

The geometrical configuration is not set until the very last step in this series. Ion C must assume the conformation which makes carbon atom 2 most amenable to approach by I or B. Inspection of molecular models suggests that the $\Delta^{1,2}$-double bond must have the *cis* and the $\Delta^{3,4}$-double bond should have the *trans* orientation for this situation to obtain.

In the presence of potassium bases or if higher temperatures are used with sodium bases, ions A and C may add to I or B to give intermediates which abstract protons from I to give dimeric products. These in turn could isomerize to more highly conjugated structures.[9]

Acknowledgments.—We wish to thank Dr. James D. Stroupe and Mrs. Florence Farnum of these laboratories for their determination and interpretation of the ultraviolet and infrared absorption spectra reported herein.

Experimental[10]

1,4-Bis-(dimethylamino)-2-butyne (I). Method A.—Bis-(dimethylamino)-methane (5.0 moles, 543 g. of 94% purity) was treated with aqueous formaldehyde solution (5.75 moles, 539 g. of 36.2% concentration) with stirring and cooling to keep the temperature below 50°. Cuprous chloride (20 g., 0.2 mole) was added. The flask was then fitted with a gas inlet tube which extended below the surface of the liquid and a gas outlet tube which was connected to a manometer. All stoppers and connections were wired in place. A stream of acetylene, which had been washed with water and with concentrated sulfuric acid, then dried over soda lime, was admitted at about 1.33 atm. The absorption of acetylene was very rapid; in 50 minutes, 136 g. (5.23 moles) was absorbed. The temperature was maintained at about 50° by intermittent cooling. The mixture was maintained at 50° for an additional 3 hr., then cooled and filtered with the aid of Celite. The mixture was dried over flaked sodium hydroxide then distilled at atmospheric pressure. 3-Dimethylamino-1-propyne (78 g., 9%), b.p. 82°, and I (491 g., 73%), b.p. 181–183°, were obtained.

Method B.—Method A was modified by preparing the intermediate, R_2NCH_2OH, by adding R_2NH (1.0 mole) to 36% aqueous formaldehyde solution (1.02–1.05 moles) with cooling. The lower concentration of R_2NCH_2OH thus employed led to higher ratios of mono- to disubstituted acetylene derivatives than did method A.

Method C.—Method A was modified by preparing the intermediate, $R_2NHCH(R^1)OH$, by adding R_2NH (1.0 mole) to the aldehyde (1.0 mole) in the absence of solvent, while maintaining the temperature below 35°. When R^1 was not H, the monosubstituted acetylene derivative was the major product of the reaction.

2,2,4,11,13,13-Hexamethyl-6,9-bis-(dimethylamino)-7-tetradecyne. Method D.—3,5,5-Trimethylhexanal (1066 g., 7.5 moles) was treated with dimethylamine (339 g., 7.5 moles) through a gas inlet while the mixture was stirred and maintained below 50° by external cooling. An aqueous phase separated and was discarded. The organic layer, after drying over anhydrous sodium sulfate (1141 g., 6.1 moles of crude alkylolamine), 3-dimethylamino-5,7,7-trimethyl-1-octyne (1171 g., 6.0 moles) and cuprous chloride (2 g.) were combined and heated at 170–190° for 6 hr. The reaction mixture was cooled and filtered. The filtrate was distilled under reduced pressure to give the product (1541 g., 4.24 moles, 71%), b.p. 128–133° (1 mm.), $n^{20}D$ 1.4617.

1,4-Bis-(methylphenylamino)-2-butyne.—This compound was prepared from 1,4-dichloro-2-butyne and N-methylaniline according to the procedure of W. Reppe (reference 5c, p. 79).

Anal. Calcd. for $C_{18}H_{20}N_2$: N, 9.1. Found: N, 9.1.

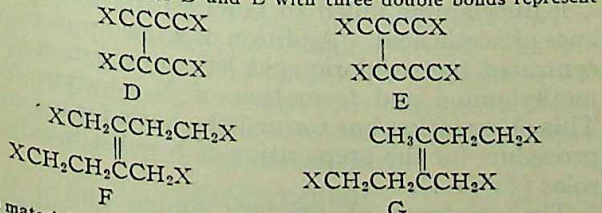
3-Morpholino-1-butyne.[11,5c] **Method E.**—A solution of cuprous chloride (13.5 g.) in concentrated hydrochloric acid (84 g.) was added to morpholine (200 g., 2.3 moles) with stirring and cooling. Acetylene (89 g., 3.4 moles) was introduced through a gas inlet tube and was absorbed at about 1.33 atm. during 20 hours while the temperature was maintained at 105–115°. The mixture was diluted with ethanol (1 volume) and filtered. The ethanol was removed by distillation under reduced pressure, and the residue was washed with 13% sodium hydroxide solution (230 ml.). The organic layer was separated, the aqueous layer was washed with diethyl ether (two 100-ml. portions), and the combined organic layers were dried over anhydrous potassium carbonate. Distillation gave 3-morpholino-1-butyne (108 g., 0.77 mole), b.p. 55–62° (0.1 mm.), $n^{20}D$ 1.4715, in 34% yield based on morpholine and 45% yield based on the acetylene absorbed.

***cis,trans*-1,4-Bis-(dimethylamino)-1,3-butadiene (II). Method F.**—Sodium (16 g., of 50% dispersion[3] in xylene, 0.35 mole) was treated with xylene (90 ml.) and hexane (500 ml.), and the mixture was heated to reflux (72°). The heat source was removed and freshly distilled 1,4-bis-(dimethylamino)-2-butyne (I, 1500 g., 10.7 moles) was added in a fine stream during 3.5 hr. A log was kept of the refractive index *vs.* I added to ensure that unreacted I did not accumulate. The product was distilled under reduced pressure to remove first the hexane then the xylene. The product (1275 g., 85% yield) had b.p. 75–80° (7 mm.), $n^{20}D$ 1.549.

***trans,trans*-1,4-Bis-(dimethylamino)-1,3-butadiene.**—On standing in a stoppered bottle at room temperature for two

(8) E. R. H. Jones, G. H. Whitham and M. C. Whiting, *J. Chem. Soc.*, 3201 (1954).

(9) Partial structures D and E with three double bonds represent such materials. One possible structure for the tetrahydrodimer $C_{16}H_{36}N_4$ is F, and G would be the corresponding $C_{14}H_{31}N_3$ hydrogenolysis product.



(10) Elemental analyses were carried out by the analytical laboratories of the Rohm & Haas Co. All melting and boiling points are uncorrected.

(11) C. Gardner, V. Kerrigan, J. D. Rose and B. C. L. Weedon, *J. Chem. Soc.*, 780 (1949), described the preparation of this compound at acetylene partial pressures of 100–200 p.s.i.g.

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months *cis,trans*-II had darkened somewhat and had rearranged to a form which had m.p. −4°. Redistillation gave the pure *trans,trans*-II, b.p. 80° (2 mm.), $n^{20}D$ 1.555, m.p. −3 to −1°.

Anal. Calcd. for $C_8H_{16}N_2$: N, 19.97. Found: N, 19.91, 19.95.

This rearrangement could be carried out much more rapidly by adding traces of acids or water. In 24 hr. at room temperature or 3 hr. at 65–70° in the presence of 1 drop of water or acetic acid, the melting point of II (10 g.) rose from <−70° to −4°. Prolonged room temperature storage of *trans,trans*-II led to resinification.

2,2,4,11,13,13-Hexamethyl-6,9-bis-(dimethylamino)-6,8-tetradecadiene. Method G.—Hexane (50 g.) and 50% sodium dispersion[3] in xylene (4 g.) were heated to reflux, the source of heat was removed and compound I (14 g., 0.10 mole) was added dropwise. Thereafter, 2,2,4,11,13,13-hexamethyl-6,9-bis-(dimethylamino)-7-tetradecyne (136 g., 0.37 mole) was added during 39 minutes. The reaction mixture was stirred and heated for an additional 2.5 hr. Distillation under reduced pressure gave (a), 10 g., b.p. 68–187° (4 mm.), $n^{20}D$ 1.5420; and (b), 131 g., b.p. 187–192° (4 mm.), $n^{20}D$ 1.4986. Cut a was chiefly II while cut b represented a 94.5% yield of the desired product in high purity as judged by its ultraviolet spectrum (ϵ_{max} 21,900 at 295 mμ).

Dimerization of 1,4-Bis-(dimethylamino)-1,3-butadiene.—A mixture at I (150 g., 1.07 mole), xylene (150 ml.) and potassium metal (0.75 g., 0.02 mole) dissolved in 1-octanol (4.25 g.) was stirred and heated under reflux for 5 hr. Distillation under reduced pressure gave the product (126 g., 84%), b.p. 72–132° (0.2 mm.). Redistillation (powdered potassium hydroxide in the pot) of a combination of products from several such runs gave a series of fractions at 1.0 mm. whose physical properties indicated that a mixture of dimeric materials was present.

Hydrogenation of 1,4-Bis-(dimethylamino)-2-butyne Dimer.—The once-distilled dimer, b.p. 115–118° (0.15 mm.), $n^{19}D$ 1.5220–1.5250, prepared as above (133 g., 0.475 mole), ethanol (30 ml.) and Raney nickel (10 g. of catalyst rinsed with ethanol) were hydrogenated at 170 atm. and 110–116° during 8.5 hr. Dimethylamine (0.227 mole) was recovered in the processing. Distillation and redistillation of selected cuts gave 8.5 g. of liquid, b.p. 81–90° at 0.20 mm., $n^{20}D$ 1.4693. (*Anal.* Calcd. for $C_{14}H_{31}N_3$: N, 17.41; mol. wt., 241. Found: N, 17.46; mol. wt., 253) along with some solid material m.p. after recrystallization from heptane 104–105.5°.

Anal. Calcd. for $C_{16}H_{36}N_4$: C, 67.60; H, 12.68; N, 19.72; mol. wt., 284. Found: C, 67.76; H, 12.57; N, 19.04; mol. wt., 277.[12]

The same solid was obtained in low yields by hydrogenation in ethanol solution at 3 atmospheres in the presence of platinum oxide catalyst.

(12) By a modified Menzies–Wright ebulliometric procedure; W. E. Barr and V. J. Anhorn, "Scientific and Industrial Glass Blowing and Laboratory Techniques," Instrument Publishing Co., Pittsburgh, Pa., 1949, p. 284.

PHILADELPHIA, PENNA.

[CONTRIBUTION FROM THE ROHM & HAAS CO.]

Chemistry of 1,4-Diamino-1,3-butadienes. II. A New Synthesis of N-Substituted Pyrroles[1]

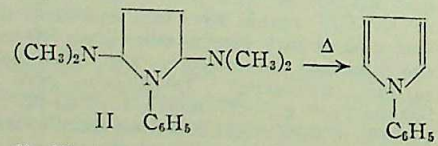
BY MARIAN F. FEGLEY, NEWMAN M. BORTNICK AND CHARLES H. MCKEEVER

RECEIVED NOVEMBER 3, 1956

N-Substituted pyrroles have been prepared by interaction of 1,4-bis-(dimethylamino)-1,3-butadiene and primary amines in the presence of an acidic catalyst.

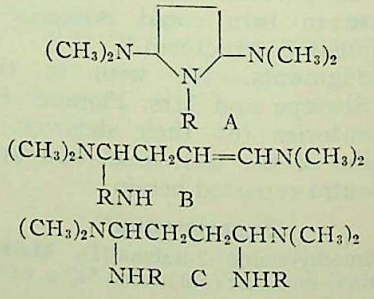
Primary amines have been found to react with 1,4-bis-(dimethylamino)-1,3-butadiene (I)[2] in the presence of catalytic amounts of acids. The unstable cyclic addition product II was formed with evolution of heat when I and aniline were mixed in the presence of a trace of acetic acid.

$$C_6H_5NH_2 + \underset{\text{I}}{(CH_3)_2NCH{=}CHCH{=}CHN(CH_3)_2} \longrightarrow$$



When II was distilled at atmospheric pressure, a low yield of N-phenylpyrrole was isolated together with dimethylamine, aniline, I and polymeric products.

The reaction of benzylamine with I required the addition of more acetic acid for its initiation than was the case with aniline and I. Ultraviolet spectroscopic assay[2] of an equimolar mixture showed that 85% of I had disappeared. Thus, a 1:1 addition product must have constituted a major portion of the mixture. It seems likely that products having the structures A–C were all in equilibrium with the starting materials.



Distillation of the reaction mixture gave a 40% yield of N-benzylpyrrole.

n-Butylamine failed to react with I in the presence of acetic acid. Addition of a few drops of concentrated hydrochloric acid led to evolution of dimethylamine and formation of N-*n*-butylpyrrole. This observation has formed the basis for a general procedure for the preparation of N-substituted pyrroles (Table I).

The mixtures of primary amine and I were treated with acid while a stream of inert gas was used to sweep out the dimethylamine as it was liberated. The reaction mixtures were treated with solid potassium carbonate and then distilled to isolate the pyrroles. In some experiments, removal

(1) Given in part at the 124th Meeting of the American Chemical Society, Chicago, Ill., September 9, 1953.

(2) M. F. Fegley, N. M. Bortnick and C. H. McKeever, THIS JOURNAL in press.

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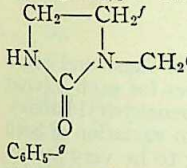
TABLE I

PYRROLES PREPARED BY TRANSAMINATION

N-Substituted pyrrole	Boiling point °C.	Mm.	$n^{20}D$	Reactants, moles I	Amine	Reaction conditions Time, hours	Temp., °C.	$(CH_3)_2$-NH liberated, moles	Yield, %	Nitrogen, % Found	Calcd.
CH_3–[a]	114		1.4855[k]	0.57	3.2	5.5	27–44	..	46	16.7	17.3
n-C_4H_9–[b]	170–171		1.4730	.33	1.04	4	47–90	0.70	64	11.2	11.4
$(CH_3)_3C$–	74–79	42	1.4722	.5	1.0	9.5	30–45	1.1	16	10.9	11.4
$(CH_3)_2CCH_2C(CH_3)_2$–	58–59	1.5	1.4790	.1	.23	2 / 0.5	50–70 / 90 [j]	.20	66	8.0	7.8
$(CH_3)_3CCH_2CH(CH_3)CH_2CH_2$–	93–94	4.3	1.4686	.1	.22	3 / 1	50–70 / 80–90 [j]	.17	67	7.4	7.2
n-$C_{18}H_{37}$–	172–174	1	Solid	.11	.20	3	55–80	.21	47	4.5	4.4
CH_2=CH–CH_2–[c]	63	36	1.4933[l]	.25	.53	5	27–60	.5	67	12.9	13.1
$(CH_2)_5CH$–[d]	62–63	1	1.5111	.53	.76	4.75	30–75	.73	70.5	9.4	9.4
–CH_2–CH_2–[i]	M.p. 107.5–108[i]		....	.5	.5	5.5	60	.97	24 / 30 } 54	17.4 / 24.8	17.5 / 25.4
NH_2–CH_2–CH_2–[e,i]	50	1[i]	1.5188								
NH_2–$(CH_2)_6$–	91–120		1.4920	.35	.40	2 / 1.75	30 / 80 [j]	.6	17	16.8	16.9
HO–CH_2–CH_2–	210–215		1.5162	.3	.51	6.5	30–65	.3+	38	12.7	12.6
CH_2=CH–O–CH_2–CH_2–	100	20.5	1.5000	.25	.57	4.5	55–65	.46	57	10.4	10.2
HO–CH_2–CH_2–NH–CH_2–CH_2–	109–113	65	1.5218	.60	.88	14	50	.94	48	18.4	18.2
$O(CH_2CH_2)_2N$–$CH_2CH_2CH_2$–	162.5–163	19.5	1.5092	.25	.46	7	53	.47	75	14.4	14.4
	198 M.p. 114–115.5	4	Solid	.14	.23	0.5	68	.28	50	23.5	23.5
C_6H_5–[g]	220–225		Solid	.21	.51	9	30–55	.2	5	..	..
C_6H_5–CH_2–[h]	67–68	0.35	1.5655[m]	.6[n]	1.0	6+	70	1.1	42.5	..	..

[a] N. D. Zelinsky and J. K. Jurjew, *Ber.*, **62**, 2589 (1929), gave $n^{21}D$ 1.4858; G. Ciamician and M. Dennstedt, *Ber.*, **17**, 2951 (1884), gave b.p. 114–115° (747.5 mm). [b] T. Reichstein, *Helv. Chim. Acta*, **10**, 389 (1927), gave b.p. 53–54 (11 mm.); L. C. Craig and R. M. Hixon, THIS JOURNAL, **53**, 187 (1931), gave b.p. 165–180° (atm.); N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, **6**, 867 (1952), gave $n^{25}D$ 1.4700, b.p. 52–53° (9 mm.). [c] G. Ciamician and M. Dennstedt, *Ber.*, **15**, 2581 (1882), gave b.p. 105° (48 mm.). [d] H. Adkins and L. G. Lundsted, THIS JOURNAL, **71**, 2964 (1949), reported b.p. 114° (19 mm)., $n^{25}D$ 1.5140. [e] O. Klamerth and W. Kutscher, *Chem. Ber.*, **85**, 444 (1952), gave b.p. 75–78° (12 mm.). [f] Recryst. from petroleum ether (30–60°). [g] N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, **6**, 867 (1952), gave b.p. 131–133° (30 mm.) and m.p. 57–59°; A. Pictet and P. Crepieux, *Ber.*, **28**, 1905 (1895), gave b.p. 234°; M. Kottnitz, *J. prakt. Chem.*, [2] **6**, 148 (1872), gave m.p. 62°. [h] Yu. K. Yur'ev, V. A. Tronova, N. A. L'vova and Z. Ya. Bukshpan, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 1128 (1941), *C. A.*, **37**, 4071 (1943), gave $n^{20}D$ 1.5839, b.p. 132–133° (13 mm.). [i] Both products were isolated from a single run. [j] The reaction was started at the lower temperature and completed at the higher temperature. [k] At 23.5°. [l] At 23°. [m] At 24°. [n] $[O(CH_2CH_2)_2NCH{=}CH]_2$.

of excesses of the amine reactant was accomplished by washing an ether solution of the reaction mixture with cold dilute hydrochloric acid solution, with water and then with dilute sodium hydroxide solution. Drying and distillation gave pure samples.

The method worked well for primary amines of proper basicity ($K_b \geq 10^{-7}$). Neither the presence of –OH, $-NH_2$, CH_2=$CHCH_2$–, CH_2=CHO–, cyclic urea groups nor branching at the carbon atom bearing the amino group interfered with pyrrole formation.

The reaction failed when aminoacetonitrile, α-aminoisobutyronitrile or 2-aminopyridine was employed. The low yield obtained when aniline was employed was not improved with subsequent study. Only polymeric material resulted when the reaction of ammonia with I was investigated.

Experimental[3]

Reaction of Aniline with 1,4-Bis-(dimethylamino)-1,3-butadiene (I).—A mixture of aniline (9.3 g., 0.10 mole) and I (14.0 g., 0.10 mole) was treated with glacial acetic acid (6 drops) whereupon an exothermic reaction ensued. The temperature was kept below 60° with cooling until the entire reaction mixture solidified. The temperature rose to 65–70°. The crude addition product was crystallized from diethyl ether or petroleum ether (30–60°) by cooling to −70°, m.p. 71–73°. The infrared absorption spectrum showed no absorption bands corresponding to the stretching of C=C, C=N or N–H bonds. The normal monosubstituted aromatic bands at 3100, 3060, 3030, 1603 and 1508 cm.$^{-1}$ were in evidence. The product decomposed on standing at room temperature; this fact accounts for the poor analysis shown below.

Anal. Calcd. for $C_{14}H_{23}N_3$: N, 18.0. Found: N, 16.8.

A batch of material prepared as above and then treated with potassium carbonate (1 g.) was distilled at atmospheric pressure. Dimethylamine was evolved, considerable tar remained in the pot and from the distillate was obtained aniline (5 g.) and a fraction, b.p. 225–250° (1 + g.). Redistillation of the latter gave 0.5 g., b.p. 80–90° (1 mm.), which froze in the receiver. Two recrystallizations from 30–60° petroleum ether gave N-phenylpyrrole, m.p. 60–61°.

Reaction of Benzylamine with I.—Benzylamine (5.35 g., 0.05 mole) and I (7.00 g., 0.05 mole) were treated with glacial acetic acid (3 drops). A mildly exothermic reaction ensued; the temperature rose to 53° before falling slowly to room temperature. From the ultraviolet absorption spectrum of the mixture, 85% of I had disappeared. All efforts to isolate a pure sample of the addition product failed. The reaction mixture was distilled at atmospheric pressure. The cut (3 g., 40% yield), b.p. 225–260°, m.p. 128°, was redistilled to give the analytical sample, 1.5 g.,

(3) All temperatures are uncorrected. Elemental analyses were carried out by the analytical laboratories of the Public Domain. CC-0. Gurukul Kangri Collection, Haridwar

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b.p. 80-100° (1 mm.), 246° (760 mm.), m.p. 15°, $n^{20}D$ 1.569.

Anal. Calcd. for $C_{11}H_{11}N$: N, 8.9. Found: N, 8.9.

N-Methylpyrrole.—A mixture of 40% aqueous methylamine (219 g., 3.2 moles), I (80 g., 0.57 mole), glacial acetic acid (15 drops) and concentrated hydrochloric acid (9 drops) was heated slowly with stirring to 44°, then the heat source was removed. After 30 minutes at that temperature, the mixture became homogeneous. The mixture was maintained at 44° for another hour then allowed to stand at room temperature overnight. The reaction mixture was cooled in an ice-bath and acidified by the careful addition of 18% hydrochloric acid. The mixture was thrice extracted with ether and the combined organic layers were dried over anhydrous potassium carbonate, filtered and distilled to give the product, 21 g. (46% yield), b.p. 114°, $n^{23.5}D$ 1.4855.

N-Cyclohexylpyrrole.—Cyclohexylamine (75 g., 0.75 mole) and I (75 g., 0.53 mole) were treated with acetic acid (9 drops) and concentrated hydrochloric acid (5 drops) while nitrogen was swept slowly through the stirred mixture. The vent gas from the condenser was passed through a scrubber which contained 350 ml. of 2.8 *N* hydrochloric acid solution. After the mixture was heated at 70 ± 5° for 4 hr., 1.0 mole of dimethylamine had been liberated. Potassium carbonate (1 g.) was added and distillation of the reaction mixture gave (a) b.p. 53–60° (17 mm.), 17 g., $n^{20}D$ 1.4589 (recovered amine); (b) b.p. 60° (17 mm.) to 62° (1 mm.), 8.5 g., $n^{20}D$ 1.5060 (intermediate cut, contained product contaminated with 10% recovered amine); (c) b.p. 62–63° (1 mm.), 48 g., $n^{20}D$ 1.5111; (d) residue, 18 g., polymeric.

Anal. (Cut c) Calcd. for $C_{10}H_{15}N$: N, 9.4. Found: N, 9.4.

PHILADELPHIA, PENNA.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES, AND FLORIDA STATE UNIVERSITY]

Correlation of Solvolysis Rates. VIII. Benzhydryl Chloride and Bromide. Comparison of *m*Y and Swain's Correlations[1]

BY S. WINSTEIN, ARNOLD H. FAINBERG AND E. GRUNWALD

RECEIVED JANUARY 17, 1957

In this paper are reported rates of solvolysis of benzhydryl chloride and bromide and the correlation of these and other data in the literature by means of the *m*Y relation. The dispersion of log *k vs.* Y plots into separate lines for each solvent pair, observed previously with *t*-butyl, α-phenylethyl and neophyl halides, is even more marked with the benzhydryl halides. The contributing causes of such dispersion include structural limitations of the *m*Y relation with respect to variation of both the R and X parts of RX. The leaving group specificity is especially marked with F, fluorides tending to be very fast in carboxylic acid solvents. Ion pair return, which depresses the observed solvolysis rate below the ionization rate by variable amounts depending on the nature of the solvent, contributes to the observed dispersion in some cases. Swain and Mosely's conclusion that the solvolysis of *t*-butyl chloride is not limiting and that gradation of mechanism continues far past *t*-butyl as structure is varied so as to make solvolysis more nearly limiting is based to a large extent on the solvolytic behavior in the series *n*-BuBr, *t*-BuCl, $(C_6H_5)_3CF$. In the view of Swain and Mosely, the unusually high rate of solvolysis of trityl fluoride in acetic acid is caused by the change in structure of the R part of RX from *t*-Bu to $(C_6H_5)_3C$. In our view, it is caused instead by the change of X in RX from Cl to F. Examination of $(k_{ROH}/k_{AcOH})_Y$ values for a whole group of substances supports the designation of *t*-butyl chloride solvolysis in the common solvents as limiting. The relations between Grunwald and Winstein's two-parameter, Swain, Dittmer and Kaiser's three-parameter and Swain, Mosely and Bown's four-parameter correlations of solvolysis rates are discussed and the numerical fits obtained are compared.

The three preceding papers of this series[2-4] were concerned with the correlation of the rates of solvolysis of *t*-butyl, α-phenylethyl and neophyl halides by the linear free energy relationship[5] 1.

$$\log k = \log k_0 + mY \qquad (1)$$

A marked dispersion of the data into separate lines, one for each solvent pair, was noted. In this paper we examine new data for benzhydryl chloride and bromide and related data from the literature which show this dispersion to an even greater degree.

The point of view adopted in this paper is somewhat different from that of 1948.[5a] In the original *m*Y treatment,[5a] the intent was to separate the total effect of solvent change into a variable Y, characteristic of the solvent, and a variable *m*, characteristic solely of RX. With the limited data then available, this approach succeeded for aliphatic compounds. However, the data for α-phenylethyl and benzhydryl chloride could not be fitted to the Y values for the aliphatic compounds in all of the solvent pairs with a single value of *m*. This was, of course, a manifestation of dispersion[2-4,5d] of lines and was recognized as a limitation of the *m*Y relationship. It was handled by introducing a second set of Y values with which it was possible to correlate the data for both compounds and which was recommended for general use with α-aryl derivatives. The parameter *m* was still considered constant for any one RX.

As more data became available,[2-4,5d,6] the limitations of the original *m*Y treatment became more and more apparent, and the pattern of dispersed lines evolved. To fit the data in the next higher approximation, *m* is a function of both RX *and* of the solvent pair.[2-4,5d] Since the burden of accounting for the structural limitations of the original *m*Y treatment[5a] has thus been shifted on to *m*, there is no advantage in retaining more than one set of Y values. The set based on *t*-butyl chloride[5c] has therefore been used in this paper.

On the basis of the new findings, the use of sol-

(1) Research sponsored by the Office of Ordnance Research, U. S. Army.

(2) A. H. Fainberg and S. Winstein, THIS JOURNAL, **79**, 1597 (1957).

(3) A. H. Fainberg and S. Winstein, *ibid.*, **79**, 1602 (1957).

(4) A. H. Fainberg and S. Winstein, *ibid.*, **79**, 1608 (1957).

(5) (a) E. Grunwald and S. Winstein, *ibid.*, **70**, 846 (1948); (b) S. Winstein, E. Grunwald and H. W. Jones, *ibid.*, **73**, 2700 (1951); (c) A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 (1956); (d) S. Winstein, Discussion at 13th National Organic Chemistry Symposium of the American Chemical Society, Ann Arbor, Mich., June 17, 1953.

(6) L. Wilputte-Steinert and P. J. C. Fierens, *Bull. soc. chim. Belges*, **64**, 277, 287, 299, 308 (1955).

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volysis rates to detect limiting solvolysis[5a,b,7] has been re-examined, and the mY correlation of solvolysis rates has been compared with other correlations recently proposed by Swain and coworkers.[8,9]

Results

Table I lists all of the first-order rate constants now available for the solvolysis of benzhydryl chloride and bromide in mixtures of water with ethanol, methanol, acetic acid, dioxane and acetone, and in mixtures of acetic and formic acids. About two-thirds of the data are new; the others duplicate previous values or are taken directly from literature sources.

TABLE I

SPECIFIC RATES OF SOLVOLYSIS[a] OF BENZHYDRYL CHLORIDE AND BROMIDE

Solvent, vol. %[b]	$10^5 k$, sec.$^{-1}$[c] 25.0°	50.0°	$\Delta H^{\ddagger}$, kcal./mole (25°)	$\Delta S^{\ddagger}$ e.u. (25°)
	Benzhydryl chloride[d]			
EtOH–H_2O				
100	5.41[e]	89.0	20.84[e]	−7.9[e]
95	19.2[10]			
90	48.7[f]			
80	172[10]			
MeOH–H_2O				
100	83.3	25.2[g]	19.8	−6
96.7	145[9a]			
90	374			
AcOH–HCOOH				
100[h]	0.526[i]			
100[m]	0.611	12.41	22.45	−6.9
95[h]	2.18[k]			
90[h]	7.6[k]			
85.3[h]	23.5[k]			
75[j]	300[k]			
AcOH–H_2O[v]				
0.50 M H_2O	1.434	25.4	21.41	−8.9
2.00 M H_2O	9.43	137	19.89	−10.2
4.00 M H_2O	52[k]			
Dioxane–H_2O[n]				
90				
80	0.168[p]	2.40	19.76	−18.7
70	2.67	41.2	20.35	−11.2
60	20.4	315[q]	20.4	−7
	128			
Me_2CO–H_2O				
90				
80	0.460[11]	5.80[11]	18.8	−20
70	7.27[r]	113[s]	20.4	−9
50	32.0[11]			
	1650[13]			
i-PrOH	0.57[12]			
AcOH[m,u]	Benzhydryl bromide[d]			
	1.67	31.9	22.00	−6.6
AcOH–H_2O[v]				
0.50 M H_2O	4.2	72.8	21.2	−7
2.00 M H_2O	32.6			
Dioxane–H_2O				
90	4.35			
80	56			
70	377			
Me_2CO–H_2O				
90	18[13]	201[11b]	17.8	−16
80	153[14]			
70	1200[13]			
Dioxane–EtOH[w]				
60	4.60	0.263[t]	17.93	−18.2
40	18.6	.93[t]	18.83	−12.4
20	52.5	2.24[t]	19.82	−7.0
EtOH	124	4.66[t]	20.63	−2.6

[a] Unless otherwise noted, halide analysis was employed. [b] x vol. % A − B means x volumes of A plus 100 − x volumes of B, each at 25° before mixing. [c] The over-all average deviation of the rates which were constant was ±1.0% of k. [d] Unless otherwise noted, initial concentration 0.02–0.03 M. [e] Recalculation of data previously reported gives at 25.0°, $10^5 k$ = 5.63,[15] 5.30,[17] 5.72,[16] 5.75,[10] 4.85[18]; $\Delta H^{\ddagger}$ 21.99,[15] 19.16,[10] 20.69[18]; $\Delta S^{\ddagger}$ −4.2,[15] −13.6,[10] −8.9.[18] [f] Previously reported[10] 49.3. [g] At 15.0°, reported by Benfey, Hughes and Ingold.[14] [h] Contained 0.032 M lithium acetate and/or formate, plus 0.01 M Ac_2O. [i] Calculated for 0.032 M lithium acetate from data[19] at other salt concentrations. [j] Contained 0.065 M lithium acetate and/or formate plus 0.01 M Ac_2O. [k] Initial rate constants; these rates drifted down during the runs; see Experimental section. [m] Contained 0.068 M lithium acetate plus 0.01 M Ac_2O. [n] Böhme and Schürhoff[20] report data at several temperatures in eight solvent compositions covering the range 60–95 wt. % dioxane–H_2O. [p] Initial rate constant; the rate drifted up in the course of the run; see Experimental section. [q] Average deviation ±3%, followed over the range 50–90% reaction. [r] This value is the average of data previously reported.[11,21,22] [s] Calculated from data previously reported[11,21,22] at 0.0°. [t] At 0.0°. [u] $10^5 k$ at 40.0° = 10.60. [v] Contained 0.068 M lithium acetate. [w] Acidimetric analysis employed; initial concentration of benzhydryl bromide 0.010–0.012 M.

Table I also lists the values of the thermodynamic quantities of activation, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. The solvent range covered by these data is narrower than in the case of the t-butyl,[3,23] α-phenylethyl[2,3] and neophyl halides,[4] because of the difficulty of determining solvolysis rates in the highly aqueous solvents. The region in which the varia-

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(8) C. G. Swain and D. C. Dittmer, *ibid.*, **75**, 4627 (1953).

(9) (a) C. G. Swain, R. B. Mosely and D. E. Bown, *ibid.*, **77**, 3731 (1955); (b) C. G. Swain, D. C. Dittmer and L. E. Kaiser, *ibid.*, **77**, 3737 (1955).

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(11) (a) M. G. Church, E. D. Hughes and C. K. Ingold, *ibid.*, 966 (1940); (b) L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold and N. A. Taher, *ibid.*, 979 (1940).

(12) S. Altscher, R. Baltzly and S. W. Blackman, THIS JOURNAL, **74**, 3649 (1952).

(13) C. G. Swain, C. B. Scott and K. H. Lohman, *ibid.*, **75**, 136 (1953).

(14) O. T. Benfey, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 2488, 2494 (1952).

(15) N. A. Taher, H. R. Zaidi and R. R. Srivastave, *J. Osmania Univ.*, **13**, 65 (1947–8); *C. A.*, **44**, 4762i (1950).

(16) N. T. Farinacci and L. P. Hammett, THIS JOURNAL, **59**, 2542 (1937).

(17) N. A. Taher, *J. Osmania Univ.*, **6**, 28 (1938); *C. A.*, **34**, 3972[9] (1940).

(18) J. F. Norris and A. A. Morton, THIS JOURNAL, **50**, 1795 (1928).

(19) A. H. Fainberg and S. Winstein, unpublished work.

(20) H. Böhme and W. Schürhoff, *Chem. Ber.*, **84**, 28 (1951).

(21) R. T. Arnold, K. Murai and R. M. Dodson, THIS JOURNAL, **72**, 4193 (1950).

(22) E. D. Hughes, C. K. Ingold and N. A. Taher, *J. Chem. Soc.*, 949 (1940).

(23) A. H. Fainberg and S. Winstein, THIS JOURNAL, **79**, in press.

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tion of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ with solvent composition had previously been found to be the most complex for other compounds[2,3,23] had, unfortunately, to be omitted.

The general level of $\Delta S^{\ddagger}$ for benzhydryl chloride in ethanol, methanol and the acetic and aqueous acetic acid solvents is -8 ± 1 e.u.; this value compares with -4 and -9 for *t*-butyl and α-phenylethyl chlorides, respectively, in the same solvents.

For benzhydryl chloride, in acetic acid–water mixtures, the increase in rate in going from anhydrous acetic acid to acetic acid 2 *M* in water involves principally a decrease in $\Delta H^{\ddagger}$, this being opposed by a much smaller decrease in the entropy term. Employing the **ABC** classification scheme set up in an earlier paper[23] to describe the relative contributions of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ to change in rate due to solvent variation, this behavior can be described as **C**. In the aqueous dioxanes and acetones, the increase in rate arising from increase in water content is principally the result of a large increase in $\Delta S^{\ddagger}$, opposed by a much smaller increase in the $\Delta H^{\ddagger}$ term; this behavior is **A**. The trends observed with benzhydryl chloride are quite analogous to those previously found for *t*-butyl,[23] α-phenylethyl[2] and neophyl[4] chlorides over the same ranges of solvent composition.

For the four solvents for which comparison can be made, the increase in rate arising from change of leaving group from chloride to bromide is made up of an average decrease in $\Delta H^{\ddagger}$ of 0.5 ± 0.3 kcal./mole plus an average increase in $\Delta S^{\ddagger}$ of 3 ± 2 e.u. Again, these results are similar to those previously noted for the *t*-butyl,[3] α-phenylethyl[3] and neophyl[4] systems.

For benzhydryl bromide in 0–60% dioxane–ethanol, *ca.* two-thirds of the increase in rate with increasing ethanol content is contributed by increase in $\Delta S^{\ddagger}$, the remainder being furnished by decrease in $\Delta H^{\ddagger}$. For these data, which fall into the **B** class, $\Delta S^{\ddagger}$ is quite accurately linear in $\Delta H^{\ddagger}$. Salomaa[24] has previously reported linear relations between $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ for solvolysis of several α-haloethers in dioxane–ethanol mixtures; however, in contrast with our results, his data describe an **A** behavior.

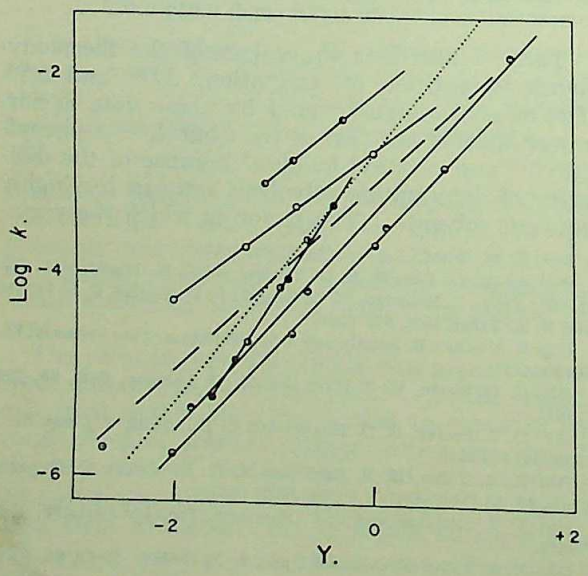

Fig. 1.—Plot of log *k vs.* Y for solvolysis of benzhydryl chloride at 25.0° in: EtOH–H_2O, ○; MeOH–H_2O, ◐; *i*-PrOH, ⊙; dioxane–H_2O, ◒; Me_2CO–H_2O, ◓; AcOH–H_2O, ●; AcOH–HCOOH, ◑. The dashed line is the least squares line for all of the data; the dotted line is given by equation 5, based on Swain, Mosely and Bown's compound parameters.

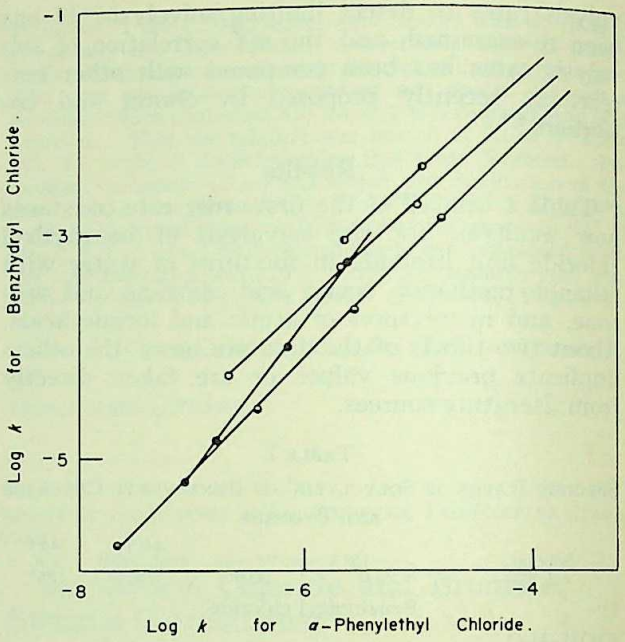

Fig. 2.—Plot of log *k* for solvolysis of benzhydryl chloride at 25.0° *vs.* log *k* for solvolysis of α-phenylethyl chloride at 25.0° in: EtOH–H_2O, ○; MeOH–H_2O, ◐; dioxane–H_2O, ◒; AcOH–H_2O, ●.

*m***Y Plots.**—When the data for benzhydryl chloride at 25.0°, in 24 solvent compositions, are fitted to equation 1 by the method of least squares, values of $m = 0.927$ and $\log k_0 = -3.062$ are obtained. However, the probable error of the fit,[25] *r*, equal to 0.408, is very large for this whole group of solvents. The plot in Fig. 1 of log *k* for benzhydryl chloride *vs.* **Y** shows clearly that each solvent pair should be considered separately. Thus, the four points for dioxane–water in the 60–90 vol.% range form an excellent straight line lying below those for ethanol–water and methanol–water mixtures, while the lines for the carboxylic acid-containing mixtures start low and cut across the others with very much higher slopes. The parameters *m* and log k_0 of equation 1, together with the probable error of the fit,[25] *r*, for the separate lines for each solvent pair are listed in Table II for benzhydryl chloride. With this modification of the original[5a] *m***Y** relation, the average *r* is now 0.02, quite satisfactory for correlative and interpolative purposes. However, for extrapolation these relations should be applied with caution if high accuracy is desired. While curvature of the lines is almost imperceptible in the ranges covered, it is obvious that at least some

(24) P. Salomaa, *Ann. Univ. Turkuensis*, **A14**, (1953).

(25) (a) A. H. Margenau and G. M. Murphy, "Mathematics of Physics and Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1943, p. 502; (b) W. J. Youden, "Statistical Methods for Chemists," John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 12, 15.

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TABLE II

CORRELATION OF SOLVOLYSIS RATES WITH Y

Compound	n	Solvent range	Temp., °C.	m	log k_0[a]	r
$(C_6H_5)_2$ CHCl	24	All solvents	25	0.927	−3.062	0.408
	4	80–100% EtOH–H_2O	25	.740	−2.763	.002
	3	90–100% MeOH–H_2O	25	.820	−2.181	.005
	4	85–100% AcOH–HCOOH[b]	25	1.713	−2.477	.009
	4	0–4 M H_2O in AcOH[c]	25	1.561	−2.660	.016
	3	0–2 M H_2O in AcOH[c]	50	1.351	−1.697	.007
	3	50–90% Me_2CO–H_2O[f]	25	1.106	−3.332	.053
	2	80–90% Me_2CO–H_2O	50	1.09	−2.21	...
	4	60–90% Dioxane–H_2O[d]	25	1.049	−3.668	.024
	3	70–90% Dioxane–H_2O	50	1.037	−2.517	.004
$(C_6H_5)_2$CHBr	4	0–4 M H_2O in AcOH[c]	25	1.687	−2.017	.008
	3	0–2 M H_2O in AcOH[c]	50	1.448	−1.118	.006
	3	70–90% Me_2CO–H_2O	25	0.913	2.099	.085
	3	70–90% Dioxane–H_2O	25	.954	−2.442	.008
$(C_6H_5)_2$CHF[9a]	2	50–80% EtOH–H_2O	25	.98	−6.56	...
$(C_6H_5)_3CF$[9a,26,27]	2	69.5–96.7% MeOH–H_2O	25	.77	−2.84	...
	3	40–100% EtOH–H_2O	25	.890	−3.530	.044
	4	40–70% Me_2CO–H_2O[e]	25	1.58	−5.02	.13
$(C_6H_5)_3COC_6H_4NO_2$[9a]	2	40–80% EtOH–H_2O	25	0.57	−3.35	...
$(C_6H_5)_3COOCC_6H_5$[13]	2	50–60% Me_2CO–H_2O	25	.79	−4.02	...
$(C_6H_5)_3COOCCH_3$[9a]	2	69.5–96.7% MeOH–H_2O	25	.48	−2.86	...
$(C_6H_5)_3COOCCH_3$[9a]	2	60–80% EtOH–H_2O	25	.50	−3.28	...
	2	50–80% Me_2CO–H_2O	25	.83	−4.28	...
$(C_6H_5)_3CSCN$[9a]	2	69.5–96.7% MeOH–H_2O	25	.39	−2.96	...
	3	50–80% Me_2CO–H_2O	25	.261	−3.076	.010
$(C_6H_5)_3SiF$[27]	5	50–83.4% Me_2CO–H_2O	45	.468	−5.587	.038

[a] k in sec.$^{-1}$. [b] Containing 0.038 M lithium acetate and/or formate. [c] Containing 0.068 M lithium acetate. [d] This equation reproduces the data of Böhme and Schürhoff,[20] reported for a mole ratio of [RCl]/[H_2O] of 1/500 in 60–90 wt. % dioxane–H_2O, with a probable error r = 0.037. [e] Data in 80 and 85% Me_2CO–H_2O lie considerably above this line. [f] The point for 70% Me_2CO–H_2O is far out of line and was omitted in this calculation.

of the lines for the aqueous solvents must curve very considerably in the higher water region, since they must all intersect at pure water.

Although the data listed in Table I for benzhydryl bromide cover a more limited solvent range than for the chloride, they suffice to show that the plot of log k for the bromide *vs.* Y involves even greater dispersion than was found for the chloride. This is in line with the previous observation[3] comparing the α-phenylethyl halides. Again, treating the data for each solvent pair separately, the fits are satisfactory, as is shown in Table II.

Also listed in Table II are the values of m and log k_0 for a number of related compounds, including benzhydryl and triphenylsilyl fluorides and five trityl derivatives, for which suitable data are available from the literature. The data are not sufficient in most cases to test adequately the validity of equation 1 for each of the solvent pairs.[28] Nevertheless, on fitting the data to equation 1, the phenomenon of dispersion is again observed. The dispersion of the lines from each other, and of individual points for other solvent pairs from these lines is large, for trityl acetate rivaling and for trityl fluoride exceeding that shown by benzhydryl chloride in Fig. 1.

(26) C. G. Swain and C. B. Scott, THIS JOURNAL, **75**, 246 (1953).

(27) C. G. Swain, R. M. Esteve, Jr., and R. H. Jones, *ibid.*, **71**, 965 (1949).

(28) The lines for trityl thiocyanate in 50–80% Me_2CO–H_2O and for trityl fluoride in 40–100% EtOH–H_2O are quite good; that for trityl fluoride in aqueous acetone shows considerable positive curvature, particularly in the low water region (Table II, footnote *e*).

Dispersion of mY Plots.—It is clear from this and preceding papers in this series that dispersion of the plots of log k *vs.* Y into separate lines for each binary solvent pair is a general phenomenon. There are definite structural limitations to the linear free energy relationship 1. For one thing, the structure of the R part of RX cannot be varied indiscriminately without introducing marked dispersion. Thus, it already has been noted[4] that the plot of log k for α-phenylethyl chloride *vs.* log k for *t*-butyl chloride (*i.e.*, *vs.* Y) shows much more dispersion and curvature of lines than a plot of log k for α-phenylethyl chloride *vs.* log k for neophyl chloride. In the former comparison, only one of the compounds possesses a phenyl group to delocalize charge in the transition state, while in the latter case, both compounds have a phenyl group. Thus it can be anticipated that a plot of log k for benzhydryl chloride *vs.* log k for α-phenylethyl chloride will show much less dispersion than the plot *vs.* Y; this is shown in Fig. 2. The parameters for the equations for the lines in this plot are presented in Table III.

The lines for the ethanol–, methanol– and dioxane–water mixtures can be extrapolated to yield an average value of log k = 0.7 ± 0.2 for benzhydryl chloride in pure water at 25°. The probable reason for the high initial slope for the acetic acid–water line is discussed below; from Fig. 2 it would appear that this line must curve strongly downward to meet the other lines at the point for pure water.

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TABLE III

CORRELATION OF SOLVOLYSIS RATES AT 25.0° *via* THE EQUATION LOG k_{RX} = a LOG $k_{R'Y}$ + b

RX	RY	Solvent range	No. of points	a	b	r
$(C_6H_5)_2CHCl$	$C_6H_5CHClCH_3$	80–100% EtOH–H_2O	3	0.910	1.814	0.031
$(C_6H_5)_2CHCl$	$C_6H_5CHClCH_3$	90–100% MeOH–H_2O	2	.955	2.313	...
$(C_6H_5)_2CHCl$	$C_6H_5CHClCH_3$	60–90% dioxane–H_2O	4	.973	1.737	.045
$(C_6H_5)_2CHCl$	$C_6H_5CHClCH_3$	0–4 M H_2O in AcOH	4	1.335	4.203	.014
$(C_6H_5)_2CHBr$	$(C_6H_5)_2CHCl$	EtOH, 80% Me_2CO–H_2O,[a] 70–90% dioxane–H_2O	5	0.938	1.058	.019
		0–2 M H_2O in AcOH	3	1.085	0.880	.000

[a] The points for 70 and 90% Me_2CO–H_2O appear to be out of line and were omitted from this calculation.

Another structural limitation to the mY relation is a leaving group specificity, the blend of solvent influences for correlation of, *e.g.*, a chloride being not quite appropriate for, *e.g.*, a bromide. This was illustrated most clearly with the neophyl halides in the preceding paper.[4] As before,[3,4] the effect of variation of leaving group can be isolated by plotting log k for benzhydryl bromide *vs.* log k for the chloride as in Fig. 3. From this plot, it is seen that the dispersion of lines for the mixtures of water with ethanol, dioxane and acetone is minor; it is the acetic acid-containing solvents that show large dispersion, bromide appearing to be too slow in rate with respect to chloride by as much as one power of ten. The parameters for the equations of these lines are listed in Table III.

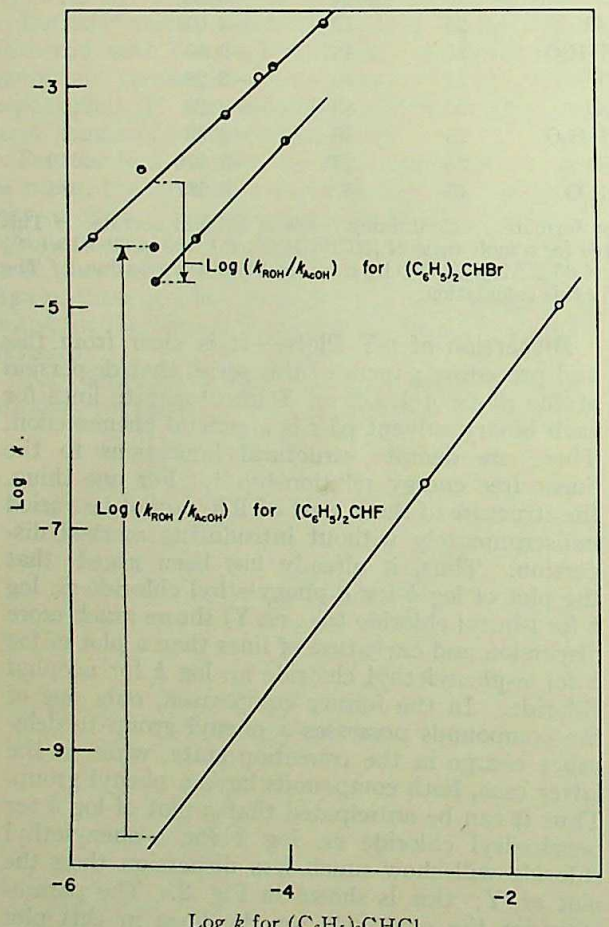

Fig. 3.—Plot of log k for benzhydryl bromide and fluoride *vs.* log k for benzhydryl chloride at 25.0° in: EtOH–H_2O, O; dioxane–H_2O, ◒; Me_2CO–H_2O, ◓; AcOH, ●; AcOH–H_2O, ◑.

As in the case of the neophyl halides,[4] a useful measure of the effect of the leaving group specificity is the quantity log k_{ROH} − log k_{AcOH}, the vertical gap between the aqueous alcohol line and the acetic acid point in a plot of log k for bromide *vs.* log k for chloride. This is given in Table IV along with the analogous information for the t-butyl, α-phenylethyl and neophyl halides. For the neophyl system, data on the toluenesulfonate are available[19] and, as shown in Table IV, the sign for log k_{ROH} − log k_{AcOH} is negative instead of positive as in the case of the bromide. In other words, using chloride as standard, neophyl p-toluenesulfonate tends to be relatively fast in acetic acid while the bromide tends to be slow.

TABLE IV

VERTICAL GAPS, LOG k_{ROH} − LOG k_{AcOH}, IN PLOTS OF LOG k_{RX} *vs.* LOG k_{RCl}

RX	Temp., °C.	log k_{ROH} − log k_{AcOH}
Neophyl OTs[19]	50	−0.30
Neophyl Br	50	+ .45
t-Butyl Br	25	.52
α-Phenylethyl Br	25	.80
Benzhydryl F	25	−5
Benzhydryl Br	25	+0.93

The importance of the leaving group specificity is most strikingly demonstrated by the plot of log k for benzhydryl fluoride *vs.* benzhydryl chloride in Fig. 3. Benzhydryl fluoride is relatively very fast in acetic acid, log k_{ROH} − log k_{AcOH} being estimated as −5.

Previously[4] it seemed reasonable to discuss the leaving group specificity in terms of the importance of hydrogen bonding to the leaving group in the solvolysis transition state. On this basis, the data in Table IV suggest that the importance of hydrogen bonding falls off in the order F >> OTs > Cl > Br. This order is a reasonable one, the position of F in this series being in line with the well-known tendency for fluorine to hydrogen bond. Another indication of the tendency for strong interaction between fluorine and a proton donor in solvolysis is the acid catalysis observed with fluorides.[29,30]

In this connection, it is instructive to note that a large fluoride specificity is *not* evident with the p-

(29) W. T. Miller, Jr., and J. Bernstein, THIS JOURNAL, 70, 3600 (1948).

(30) N. B. Chapman and J. L. Levy, *J. Chem. Soc.*, 1677 (1952).

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nitrobenzoyl system, the ratio $(k_{ROH}/k_{AcOH})_Y$ for the fluoride being closely similar to that for the chloride. This is shown in Table V, which also contains other data required in subsequent sections. The data appear to indicate that carbon–halogen bond breaking is not involved in the rate-determining step, the solvolysis presumably involving an addition mechanism.[43]

such return exists, the "titrimetric" solvolysis rate constant, k_t, is only a fraction, F, of the true ionization rate constant, k_1. In the solvolysis of *exo*-norbornyl bromide, for instance, the ionization rate, measured polarimetrically,[46] exceeds the titrimetric rate by a factor of 24 in acetic acid but only 5 in 80% ethanol. With *threo*-3-phenyl-2-butyl *p*-toluenesulfonate, the ionization rate exceeds the titrimetric one by a factor of 4.6 in acetolysis but only 1.2 in formolysis.[47]

TABLE V

SUMMARY OF COMPOUND PARAMETERS IN CORRELATION OF SOLVOLYSIS OF VARIOUS SUBSTANCES

Compound	Temp., °C.	c_1	c_2	m: EtOH–H_2O	m: AcOH–HCOOH	$(k_{ROH}/k_{AcOH})_Y$
p-$O_2NC_6H_4COF$[9a]	25	1.67	0.49	0.53[a]	0.57	10,000
p-$O_2NC_6H_4COCl$[9a]	25	1.09	.21	.33	.35	13,000
$MeBr$[5b,33,34,35]	50	0.80	.27	.26	..	300[b]
$EtOTs$[5b,31,32]	50	.65	.24	.25	.42	70
$EtBr$[5b,33,36,37]	55	.80	.36	.34	..	80[b]
n-$BuBr$[33,38]	75	.77	.34	.33	..	....
$C_6H_5CH_2OTs$[5b]	25	.69	.39	.39	..	30
i-$PrOBs$[5a,31,40]	70	.63	.48	.40	.55	6
i-$PrBr$[5b,33,39,41]	50	.90	.58	.52	.56[c]	40
t-BuCl	25	(1.00)	(1.00)	(1.00)	(1.00)	(1)
t-BuBr	25	[d]	[d]	0.94	0.95	3
$(CH_3)_3CCH(OBs)CH_3$[5a,31,40]	70	0.76	0.87	.64	.72[c]	0.4
2-Br–$C_6H_{10}OBs$[5b]	50	.80	.87	.70	.83	1.0
Neophyl OTs[19]	50	..	..	.50	.63	0.4
Neophyl Cl[4]	50	..	..	.83	.84	0.5
Neophyl Br[4]	50	..	..	.81	.82	1.0
1-Bromobicyclo[2.2.2]octane[f]	100	.96	.99	.88	.92	0.7
$C_6H_5CHClCH_3$[2]	25	..	..	.97	1.19	5
$C_6H_5CHBrCH_3$[3]	25	..	..	.82	..	30
$(C_6H_5)_2CHF$[9a]	25	.32	1.17	.98	..	0.0002
$(C_6H_5)_2CHCl$	25	1.24	1.25	.74	1.71	20
$(C_6H_5)_2CHBr$	25	..	..	..	..	90
$(C_6H_5)_3CF$[7b]	25	0.37	1.12	0.89	..	0.0008

[a] Using the data for 40 and 100% EtOH–H_2O only; the point for 80% EtOH–H_2O appears to be far out of line. [b] $(k_{ROH}/k_{HCOOH})_Y$. [c] At 100°. [d] Swain, Mosely and Bown[9a] omitted the data for *t*-butyl bromide from their calculations, stating "they appeared to interfere with convergence of the successive approximation procedure employed." [e] Rate in formic acid at 70.0° estimated from rate reported[31] at 25.13° by assuming $\Delta S^{\ddagger} = +1.5$ e.u.; the value found[40] for acetic acid. [f] Given by Streitwieser,[42] who calculated it from unpublished data of W. E. Doering and M. Finkelstein.

Superimposed on the dispersion arising from variations in structure discussed above is the disturbance arising from ion pair return.[44] This phenomenon, first demonstrated in the acetolysis and rearrangement of α,α-dimethylallyl chloride,[45] involves return to the covalent condition of a varying fraction of the ion pair intermediates. Where

Since Y is a measure of solvent ionizing power, equation 1 is designed to correlate rates of ionization to the first intermediate in solvolysis rather than composite titrimetric rate constants, k_t. When ion pair return is involved, k_t falls below the true ionization rate to a degree which bears no necessary relation to the ionizing power of the solvent. For example, ion pair return is serious in solvolysis of α,α-dimethylallyl chloride[45] in acetic acid, but it is absent in ethanol, a solvent with a closely similar Y value.

With the benzhydryl halides, there is evidence that ion pair return strongly influences the titrimetric rate. Unpublished exploratory work employing thiocyanate ion as a carbonium ion-trap in the acetolysis of benzhydryl chloride and bromide suggests that the true ionization rate of these compounds in acetic acid is at least 10 times the titrimetric solvolysis rate for the chloride and 15–20 times that for the bromide. For α-phenylethyl chloride and bromide, the corresponding factors are

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3 and 7. Thus, ion pair return would appear to account for part of the apparent slowness of these bromides in acetic acid when compared with the corresponding chloride. It also accounts for a part of the over-all slowness of these compounds in acetic acid relative to other solvents in which ion pair return plays a lesser role. It is significant in this connection that similar experiments with *t*-butyl chloride indicate that its titrimetric acetolysis rate is very close to, if not identical with, its rate of ionization.

The pattern of the plots of log k for benzhydryl chloride *vs.* Y and *vs.* log k for α-phenylethyl chloride in Figs. 1 and 2 is consistent with some disturbance from ion pair return. For example, the very high slopes observed for the acetic acid–water lines, as compared with those for the non-acid containing solvent mixtures, would arise from decreasing[46] ion pair return as the water content of the mixtures is increased. Furthermore, the relatively complete elimination of return at an intermediate solvent composition would be expected to give rise to the downward curvature in the acetic acid–water line that appears to be required in Fig. 2, in order for this line to intersect those for the other aqueous solvents at the point for pure water.

Limiting Solvolysis.—In the view of Swain and Mosely,[7] solvolysis of *t*-butyl chloride is not limiting, the gradation of mechanism continuing far past *t*-butyl as structure is varied to favor such solvolysis. Their conclusion is based to a large extent on the gradation in solvolytic behavior in the structural series *n*-BuBr, *t*-BuCl, $(C_6H_5)_3CF$. Trityl fluoride[7b] fails to yield a single line in an mY plot and the rate in acetic acid is anomalously fast, being *ca.* 10^3 times as fast in this solvent as in aqueous alcohol with a corresponding Y value (Table V). This relatively high rate in acetic acid was in line with Swain's expectations based on the trend in the $(k_{ROH}/k_{AcOH})_Y$ ratio from *n*-BuBr to *t*-BuCl (Table V) and appeared to confirm his views.

In our view, the very low value of $(k_{ROH}/k_{AcOH})_Y$ for trityl fluoride compared to *t*-butyl chloride is caused primarily by the change in departing group from Cl to F rather than by the change in R from *t*-butyl to trityl. The theory that solvolysis rates of fluorides in acetic acid are relatively very fast due to specific hydrogen bonding[4] has already been explored and is consistent with the data for the benzhydryl system (Table IV). It is significant that trityl fluoride is relatively fast in acetic acid by a factor similar to that for benzhydryl fluoride (Table V). In fact, in a plot of log k for trityl fluoride *vs.* log k for benzhydryl fluoride, the point for acetic acid lies within 0.2 log unit of the ethanol–water line. On the other hand, in contrast with the fluoride, benzhydryl chloride is not relatively fast, but in fact relatively slow, in acetic acid (Table V).

In previous work, which was restricted to OTs, Cl and Br leaving groups,[5b] the approach to limiting character of solvolysis was judged from the $(k_{ROH}/k_{AcOH})_Y$ ratios, which were used as measures of $(\partial \log k/\partial N)_Y$. While the dispersion in mY plots makes this ratio not as quantitative a criterion as it was formerly believed, it is still useful in a semi-quantitative fashion if one omits the fluorides. As is brought out in Table V, $(k_{ROH}/k_{AcOH})_Y$ drops from *ca.* 10^4 to 1 as structure is varied in the direction of more limiting solvolysis from *p*-nitrobenzoyl chloride through methyl bromide, ethyl bromide, benzyl *p*-toluenesulfonate and isopropyl bromide to *t*-butyl chloride. The ratio is also *ca.* unity (within a very small factor) for pinacolyl, *trans*-2-bromocyclohexyl and neophyl arylsulfonates, neophyl chloride and bromide, and 1-bromobicyclo-[2.2.2]octane. Since *t*-butyl chloride is no more sensitive to nucleophilic character of solvent than these compounds, with their unique structural features favoring limiting solvolysis, the indications are strong that *t*-butyl chloride solvolysis is also limiting in the usual solvents.

As brought out earlier in this paper, $(k_{ROH}/k_{AcOH})_Y$ ratios increase again as structure is varied through the α-phenylethyl and benzhydryl chlorides and especially the bromides. This apparent increased sensitivity to nucleophilic character is logically ascribed, not to the ionization step in the solvolysis of these materials, but rather to ion pair return.

Swain, Mosely and Bown's Four-parameter Equation.—In principle, one could hope to correlate all solvolysis rates with one equation, including those in which there is nucleophilic participation by solvent. Such an equation[48] is 3, which is an integrated form of equation 2 employed by Winstein, Grunwald and Jones[5b] in their discussion of the contributions of nucleophilic character, N, and ionizing power, Y, to solvolysis rate. Thus, if the partial derivatives in equation 2 are constant at l and m, respectively, equation 2 leads to the integrated form 3.

$$d \log k = \left(\frac{\partial \log k}{\partial N}\right)_Y dN + \left(\frac{\partial \log k}{\partial Y}\right)_N dY \quad (2)$$

$$\log (k/k_0) = lN + mY \quad (3)$$

$$\log (k/k_0) = c_1d_1 + c_2d_2 \quad (4)$$

While Winstein, Grunwald and Jones[5b] were interested in relative values of $(\partial \log k/\partial N)_Y$, or l, for different substances, they employed the integrated form of equation 2 only where lN was regarded as either negligible (Lim.) or as relatively constant. An example of the latter is the solvolysis of *n*-butyl bromide in a series of aqueous alcohols. As a measure of $(\partial \log k/\partial N)_Y$, there was employed the ratio $(k_{ROH}/k_{RCOOH})_Y$.

Swain and co-workers[9a] have attempted recently a general correlation of solvolysis rates with the aid of the four-parameter equation 4. Formally, this is simply equation 3 with different notation for the compound and solvent parameters. However, there do exist some differences of viewpoint.

Swain stresses specific solvation of the leaving group and the reacting carbon atom, each by an individual solvent molecule in an electrophilic or nucleophilic role, respectively. The parameters d_1 and d_2 are measures of solvent nucleophilic and electrophilic character, respectively, and c_1 and c_2

(48) In view of the structural limitations discussed above and in the previous paper,[4] it would seem that really successful fits would require more than two terms on the right-hand side of equation 3. For example, dissection[4] of the mY term into two contributing terms already makes three terms necessary.

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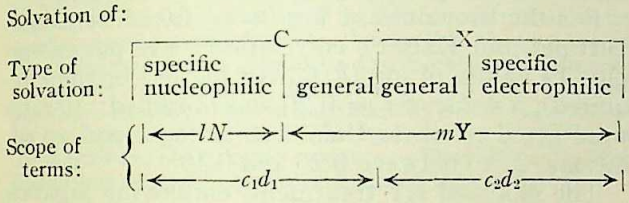
are measures of substrate sensitivity to these solvent characteristics. There apparently exists a difference in the kind of solvation meant to be accommodated by the lN and mY terms, on the one hand, and the c_1d_1 and c_2d_2 terms, on the other. It is helpful to first divide solvation[49] into solvation of carbon and solvation of X and also to classify solvent functions[50] into (i) general and (ii) specific short range nucleophilic or electrophilic ones. Then the difference in intended meaning of the lN and mY or the c_1d_1 and c_2d_2 terms may be depicted by the scheme.



Swain's use of the term nucleophilic character, measured by d_1, is broader than ours. We restrict the term nucleophilic to covalent solvation, according to the original more conventional usage, while Swain uses it for electrostatic as well as covalent solvation.[51]

A substantial body of solvolysis data has been processed on the basis of equation 4 by Swain, Mosely and Bown.[9a] The data covered a wide range of nucleophilic participation, either by solvent or by a neighboring group, and covered various departing groups, including F, OTs, Cl and Br. The conditions imposed were $d_1 = d_2 = 0.00$ for 80% ethanol, $c_1 = c_2 = 1.00$ for t-butyl chloride, $c_1/c_2 = 3.00$ for methyl bromide and $c_1/c_2 = 0.333$ for trityl fluoride. There are a number of fundamental difficulties associated with this treatment. (1) The *a priori* choice of c_1/c_2 values for methyl bromide and trityl fluoride is, in effect, an arbitrary assumption regarding the reaction mechanism for these compounds. (2) The treatment makes no allowance for ion pair return; the rate constants used in the treatment are titrimetric rate constants, k_t, whereas the rate constants which one might hope to be able to correlate are $k_1 = k_t/F$. Although F may vary from unity to small values, no provision is made for such a variation. (3) No allowance is made for leaving group specificity.[4]

Although Swain, Mosely and Bown's measures of fit of the four-parameter equation were generally satisfactory,[9a] this indication of the success of their treatment is to some extent illusory. For most of the solvents they treated, d_1 values are within the narrow range of -0.2 ± 0.2. For these solvents, the contribution of the c_1d_1 term in equation 4 tends to be negligible for many substances. In Table VI are listed some compounds for which this is true. Omitting the acetic acid or formic acid solvent, the rate constants may be fitted with the c_2d_2 term alone with a mean deviation of ± 0.25 in the log k for the 9 compounds, in contrast with ± 0.20 using both the c_2d_2 and c_1d_1 terms. The c_2d_2 term alone does essentially as well as both terms for the nucleophilic solvents for this group of compounds, which includes benzoyl chloride, t-butyl chloride, benzhydryl chloride and trityl fluoride. Thus, c_2d_2 is essentially equal to mY in the treatment employing equation 1. In fact, the c_2 values tend to be equal to the m values of the mY correlation in aqueous alcohol mixtures. Table V shows this near identity of c_2 and m values for MeBr, EtOTs, EtBr, n-BuBr, $C_6H_5CH_2OTs$ and i-PrBr. The only commonly employed solvents with significantly lower nucleophilic character are acetic and formic acids, with d_1 values of -4.6 ± 0.2. More often than not, the rate constant in only one of these solvents was available. Therefore, this one solvent often constituted the only one where the c_1d_1 term was really significant. In such cases, the d_1 value used for this solvent was essentially responsible for setting the c_1 value. Without additional solvents to cover a more substantial range of d_1 values, a good test of the four-parameter equation is not obtained.

TABLE VI

COMPARISON OF THE FITS OF SWAIN'S FOUR-PARAMETER EQUATION WITH THOSE OBTAINED EMPLOYING ONLY THE c_2d_2 TERM

Compound	No. of solvents[a]	No. of solvents omitted	Average deviation: 4-parameter equation 4	Average deviation: $\log(k/k_0) = c_2d_2$
C_6H_5COCl	11	1	±0.23	±0.23
p-$CH_3C_6H_4COCl$	3	1	±0.28	±0.27
2-$CH_3OC_6H_{10}OBs$	3	1	± .09	± .18
2-$BrC_6H_{10}OBs$	3	1	± .11	± .22
$(C_6H_5)_2CHCl$	7	2	± .16	± .29
$(C_6H_5)_3CSCN$	6	0	± .09	± .10
$(C_6H_5)_3COC_6H_4NO_2$	3	1	± .09	± .09
$(C_6H_5)_3CF$	6	1	± .28	± .34
t-BuCl	11	4	± .25	± .34
	Weighted average		± .20	± .25

[a] Includes all solvents except those containing carboxylic acid, for which the d_1 term is large and cannot be neglected.

Because of the fundamental difficulties associated with the treatment, the derived c_1 parameters must be regarded as completely empirical and as having no mechanistic significance as measures of substrate sensitivity to nucleophilic character of the solvent.[5d] This fact also has been pointed out by Swain, Mosely and Bown,[9a] but we wish to emphasize it by means of further examples. Thus, according to the c_1 substrate parameter, sensitivity to nucleophilic character increases in the order: MeBr = EtBr < i-PrBr < t-BuCl. Also, it increases as structure is changed from isopropyl to pinacolyl p-bromobenzenesulfonate. Furthermore, according to c_1 values, solvolysis of *trans*-2-bromocyclohexyl p-bromobenzenesulfonate, with neighboring bromine playing the close-range nucleophilic role, is just as sensitive to nucleophilic character of solvent as is the solvolysis of methyl bromide. Just as striking a discrepancy is supplied by the case of the bridgehead bromide, 1-bromobicyclo[2.2.2]octane, studied by Doering and Finkelstein.[52] Thus, according to the c_1 values, solvolysis of this substance is more sensitive to nu-

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(50) E. Gelles, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 2918 (1954).
(51) See comment of V. J. Shiner, Jr., THIS JOURNAL, **75**, 2925 (1953), footnote 17.
(52) W. E. Doering and M. Finkelstein, unpublished work cited by Streitwieser.[1c]

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cleophilic character of solvent than is the solvolysis of methyl bromide.

The four-parameter equation offers little assistance with the problem of dispersion of lines which has been treated in this and preceding papers.[2-4] For the sake of illustration, the case of benzhydryl chloride will be examined more closely. For this substance, c_1 and c_2 are essentially equal,[9a] being 1.24 and 1.25, respectively (Table V). For *t*-butyl chloride, $c_1 = c_2 = 1.00$, by definition. The plot of log *k* for benzhydryl chloride *vs.* Y is therefore predicted by equation 4 to have the form 5, using an average value $c_1 = c_2 = 1.245$. Thus, one single straight line should encompass all solvent mixtures. This line is shown in Fig. 1 by a dotted line. Obviously, the observed dispersion is not anticipated.

$$\log k = \log k_0 + 1.245\mathrm{Y} \qquad (5)$$

Comparison of Numerical Fits.—In this section we compare the fit of the modified *m*Y treatment with that of the four-parameter equation and also with the "special two-parameter equation" 6 of Swain, Dittmer and Kaiser.[9b] Equation 6 was

$$\log (k/k_0)_{\mathrm{RX}} = \log (k/k_0)_{\mathrm{MeBr}} + ab \qquad (6)$$

proposed as an alternative to equation 4; *a* is a compound parameter and *b* is a solvent parameter.[53]

Swain and co-workers[9] have tested the "goodness of fit" of their equations by means of a variable, Φ, which evaluates the deviations from the equations in relation to the variation of the data. By this criterion their correlations were satisfactory for both of their equations. When the same criterion is used to evaluate the modified *m*Y treatment, the correlation is nearly perfect, Φ being close to 100%.

An alternative measure of fit is the probable error, *r*, which evaluates the deviations regardless of the variation of the data and discounts the adjustable parameters.[54] While Φ is more useful when one wishes to find out whether or not a given equation will correlate a set of data, the probable error is more useful, after the correlation has been demonstrated, in testing whether or not the data are being fitted within their experimental error. For the rate constants reported in this and preceding papers in this series, the probable error in log *k* is about 0.01. However, since data from other sources are also used, we estimate that a perfect correlation might yield a somewhat larger *r*, probably not exceeding 0.02.

In the initial correlation[5a,b] of solvolysis rates with the two-parameter equation 1, in which all rate constants for a given compound were fitted to a single line, 74 values of log (k/k_0) were fitted with 38 constants with a probable error of 0.06; the two worst fits were off by 0.27 and 0.13 unit in log *k*.

(53) It should be noted that equation 6 contains one more parameter than equation 1. This becomes evident when equation 1 is written in the form

$$\log (k/k_0)_{\mathrm{RX}} = m \log (k/k_0)_{\mathrm{BuCl}}$$

Inasmuch as we regard equation 1 as a two-parameter equation, we regard equation 6 as a three-parameter equation.

(54) $r = 0.6745\sqrt{\Sigma d^2/(n-f)}$, where d_i is the absolute value of the difference between the *i*th calculated and experimental value, *n* is the number of pieces of data being fitted, and *f* is the number of adjustable parameters employed.

Using the same basis for comparison, Swain, Mosely and Bown[9a] correlated a much wider range of compounds and solvents with the 4-parameter equation. They fitted 146 values of log (k/k_0) with 86 constants with a probable error of 0.20; of these, 11 values were fitted to worse than 0.40 and an additional 23 to between 0.20 and 0.40 in log *k*. The 15 rate constants for *t*-butyl chloride were fitted with a probable error of 0.30. Ten rate constants for benzhydryl chloride were fitted with a probable error of 0.30, not much improved over the 0.40 obtained by the single *m*Y line treatment of the 24 pieces of data listed in Table I.

For the 91 values of log (k/k_0) fitted by Swain, Dittmer and Kaiser's correlation[9b] (34 parameters plus 19 values of log (k/k_0) for methyl bromide required), a value of $r = 0.20$ was obtained; 10 rates were fitted to worse than 0.40 in log *k* and an additional 21 to between 0.20 and 0.40.

The modified *m*Y treatment, employing separate lines for each solvent pair, applied to all of the data reported and summarized in this and preceding[2-4,5c,23] papers fits 760 values of log *k* with 372 constants[55] with a probable error of *ca.* 0.025 in log *k*. This modification of the original *m*Y relation permits inclusion of many cases of non-limiting solvolysis, even in solvent mixtures of varying nucleophilic character such as acetic acid–water. For comparison, application of Swain, Mosely and Bown's four-parameter correlation[9a] to this same set of data would have required 434 constants.

In our opinion, equations 4 and 6 may be useful for obtaining fairly rough estimates of rate constants over a rather wide range of compounds and solvents. The modified *m*Y treatment comes close to fitting data within their experimental error and is most suitable for accurate fitting over a more narrow range of compounds and solvents.

Experimental Part

Benzhydryl Chloride.—The method of Farinacci and Hammett[16] was used to prepare the benzhydryl chloride, b.p. 137° (5.0 mm.), f.p. 17.8°, f.p. depression to half frozen 0.4°, $n^{20}\mathrm{D}$ 1.5959, $n^{25}\mathrm{D}$ 1.5937; reported b.p. 146.5–147.6° (6 mm.),[16] f.p. 17.6°,[56] $n^{19.5}\mathrm{D}$ 1.5959.[57] An average of 49 solvolysis infinities gave a purity of 98.7 ± 0.4%. The material was quite stable when stored *in vacuo* in the solid state at 5°.

Benzhydryl Bromide.—Treatment of a pentane solution of benzhydrol, m.p. 65.5–66.5°, with anhydrous hydrogen bromide, as described by Courtot[58] gave benzhydryl bromide, b.p. 151–153° (5 mm.), m.p. 38.2°. Alternatively, diphenylmethane, b.p. 114° (5 mm.), f.p. 24.6–24.8°, was brominated[59] to give benzhydryl bromide, b.p. 153–156° (5 mm.), m.p. 36.2–37.4°. Recrystallization from pentane followed by distillation at 107° (0.7 mm.) raised the f.p. to 38.7°, f.p. depression to half frozen 0.4°. Other authors[58-63] have reported f.p.'s ranging from 42 to 46°.

(55) These include 130 values of Y, all of which can be calculated from the 40 parameters required for the power series for Y in terms of mole fraction of fast component (Table II of ref. 5c).

(56) A. Weissberger and R. Sängewald, *Z. physik. Chem.*, **B20**, 149 (1933).

(57) V. Grignard and K. Ono, *Bull. soc. chim.*, [4] **39**, 1594 (1926).

(58) C. Courtot, *Ann. chim.*, [9] **5**, 80 (1916).

(59) C. Friedel and M. Balsohn, *Bull. soc. chim.*, [2] **33**, 339 (1880).

(60) W. M. Budde and S. J. Potempa, THIS JOURNAL, **74**, 258 (1952).

(61) J. U. Nef, *Ann.*, **298**, 232 (1897).

(62) N. P. Buu-Hoï, *ibid.*, **556**, 8 (1944).

(63) O. O. Orazi and J. Meseri, *Annales assoc. quim. Argentina*, **37**, 263 (1949); C. A. **44**, 6320b (1950).

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An average of 39 solvolysis infinities gave a purity of 99.3 ± 0.3% for the sample employed.

Solvents.—Preparation of solvents was described in detail in an earlier paper in this series[5c]; in general, the solvents employed for the rate runs herein reported were from the same batches as those employed[5c] to determine Y.

Kinetic Measurements.—The techniques employed for the kinetic runs and halide analysis have been described previously.[5c] Some hydrolysis was found to occur in the case of the benzhydryl halides during the extraction procedure (*e.g.*, 2% hydrolysis in forty shakes of a 5-ml. aliquot of 0.032 *M* benzhydryl chloride in AcOH in 25 ml. of pentane with 10 ml. of H_2O; *ca.* 3% hydrolysis for the bromide under the same conditions). However, it was shown, for benzhydryl chloride, that if rigorous standardization[64] of the extraction procedure[5c] is adhered to, the amount of hydrolysis during extraction is proportional to the concentration of unreacted organic halide present. Under this circumstance, it can be shown that, as long as, in the calculation of the integrated rate constant, all points, and particularly the zero point, are based on the concentration of halide ion obtained *via* the extraction procedure, this hydrolysis has no effect on the magnitude of the rate constants. Thus, if f is the fraction of unreacted RX hydrolyzed during the extraction

$$(a - fa)/[(a - x) - f(a - x)] = a(1 - f)/[(a - x)(1 - f)] = a/(a - x)$$

and, therefore, the integrated rate constant $k = (2.303/t) \log [a/(a - x)]$ is unaffected by such hydrolysis.

Experimental Results.—The new data reported in Table I were based on an average of 7 points per run followed past 50 to 80% of completion. The average deviation for all of the rates which were first order within experimental error was ±0.9% for benzhydryl chloride and ±1.0% for the bromide. For the rate runs which drifted, the entries in Table I, suitably footnoted, are the estimated initial rates. These estimates were made empirically by linear extrapolation to zero reaction of a plot of integrated rate constant *versus* percentage reaction. The magnitudes of these drifts, expressed empirically as percentage change in k per 0.01 *M* reaction calculated from the true zero of reaction time, are listed in Table VII. The drifts are manifestations of opposing salt effects, and they will be considered more fully in a later paper.

(64) The extent of hydrolysis was shown to depend on the number of shakes employed in the first aqueous extraction.

TABLE VII

DRIFTS IN RATE CONSTANTS DURING SOLVOLYSIS OF BENZHYDRYL CHLORIDE AT 25°

Solvent	Change in k per 0.01 *M* reacn., %
90% Dioxane–H_2O	+3
100% AcOH[a]	0
95% AcOH–HCOOH[b]	−5
90% AcOH–HCOOH[b]	−8
85% AcOH–HCOOH[b]	−11
75% AcOH–HCOOH[a]	−16
4 *M* H_2O in AcOH[a]	−5

[a] Contained 0.068 *M* lithium acetate and/or formate. [b] Contained 0.038 *M* lithium acetate and/or formate.

LOS ANGELES 24, CALIF.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SPRAGUE ELECTRIC CO.]

The Solvolyses of Some Tertiary Halides in Dimethylformamide and N-Methylpropionamide

BY SIDNEY D. ROSS AND MORTIMER M. LABES

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The solvolyses of *t*-butyl bromide and dimethylneopentylcarbinyl chloride have been studied in both N-methylpropionamide and dimethylformamide, and *t*-butyl chloride has been studied in the latter solvent. The results obtained are discussed in terms of current mechanisms for solvolytic reactions.

There has been considerable interest recently in dimethylformamide as a medium for organic reactions.[1] The attractive properties of dimethylformamide are its exceptional solvent power for both organic and inorganic compounds and its high polarity, as indicated by its dielectric constant of 36.71 at 25°.[2] In this latter respect, N-methylpropionamide, which has received very little attention, perhaps because it is not available commercially, is of even greater interest, since its dielectric constant at 30° is 164.3,[2] a value more than twice that of the dielectric constant of water.

Because of these highly polar characteristics, dimethylformamide and N-methylpropionamide might be expected to be particularly effective solvents for S_N1 solvolyses.[3] To explore this possibility, we have studied the rates of solvolysis of three tertiary, aliphatic halides, *t*-butyl chloride, *t*-butyl bromide and dimethylneopentylcarbinyl chloride, in these two solvents. Since the inception of this work, some results on the reaction of *t*-butyl bromide in dimethylformamide have appeared in the literature.[1d]

Experimental

Materials.—Eastman Kodak Co. White Label *t*-butyl bromide and *t*-butyl chloride were distilled from phosphorus pentoxide prior to use, b.p.'s 72–73° and 50–51°, respectively. Dimethylneopentylcarbinyl chloride was prepared by the procedure described in the literature[4]; b.p. 51.5–53° at 28 mm., $n^{20}D$ 1.4308. Eimer and Amend, C.P. sodium bromide was dried in a vacuum oven over phosphorus pentoxide for two days prior to use. Eastman Kodak Co. White Label tetraethylammonium bromide was crystallized from isopropyl alcohol and dried *in vacuo*. Tetraethylammonium nitrate was prepared by adding equivalent nitric acid to a 10% aqueous solution of tetraethylammonium hydroxide (Eastman Kodak Co.). The solution was concentrated by distillation at a water-pump vacuum, and the salt which crystallized was recrystallized two times from isopropyl alcohol and dried *in vacuo;* m.p. 280° dec.[5]

N,N-Dimethylformamide (du Pont technical grade) was

(1) (a) E. Rochow and K. Gingold, THIS JOURNAL, **76**, 4852 (1954). (b) N. Kornblum, H. O. Larsen, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto and G. E. Graham, *ibid.*, **78**, 1497 (1956). (c) H. K. Hall, Jr., *ibid.*, **78**, 2717 (1956). (d) N. Kornblum and R. K. Blackwood, *ibid.*, **78**, 4037 (1956).

(2) G. R. Leader and J. F. Gormley, *ibid.*, **73**, 5731 (1951).

(3) E. D. Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).

(4) (a) F. C. Whitmore and H. A. Southgate, THIS JOURNAL, **60**, 2572 (1938); F. C. Whitmore, C. D. Wilson, J. V. Capinjola, C. O. Tongberg, G. H. Fleming, R. V. McGrew and J. N. Cosby, *ibid.*, **63**, 2035 (1941). (b) H. C. Brown and H. L. Berneis, *ibid.*, **75**, 10 (1953).

(5) J. N. Tucker and C. A. Kraus, *ibid.*, **69**, 454 (1947).

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distilled from calcium oxide; b.p. 45–46° at 12–13 mm., $n^{25}D$ 1.4299, specific resistance 1.7×10^6 ohm-cm. N-Methylpropionamide was prepared according to D'Alelio and Reid[6] and distilled from calcium oxide before use; b.p. 103° at 12–13 mm., $n^{25}D$ 1.4340, specific resistance 8.3×10^5 ohm-cm. The latter solvent contained 0.002–0.008% water by volume, the former 0.09–0.13% water, as determined by Karl Fischer titration in both cases.

Rate Measurements.—All of the reacting solutions were kept in thermostats which maintained the temperatures given in Tables I and II to ±0.1°. The reactions were run either in glass-stoppered flasks from which aliquots were taken at appropriate time intervals or individual aliquots were sealed in glass ampoules, which were then placed in the thermostats. Aliquots were quenched by adding them to benzene, and the benzene solution was extracted first with dilute nitric acid and then two times with distilled water. Except as otherwise indicated in Tables I and II, the aqueous extracts were analyzed for halide ion by the Volhard method for runs in which the initial concentrations of organic halide were greater than 0.02 *M*, and by potentiometric titration using a silver–silver halide electrode and a Leeds–Northrup type K-2 potentiometer where the initial concentrations of organic halide were below 0.02 *M*.

Results

The results of all the rate studies in dimethylformamide are compiled in Table I, and the rates in N-methylpropionamide are given in Table II. In the case of *t*-butyl bromide, the product results almost entirely from an elimination reaction, as indicated by the final olefin titers and the fact that, in the one case where the rate was followed by titrating for the olefin formed, the rate constant does not differ appreciably from the rate constant obtained by halide titration.[7] It is also probable that small amounts of *t*-butyl alcohol are formed in these reactions as a result of the traces of moisture present in the two solvents.

Some typical data for the reaction of *t*-butyl bromide in dimethylformamide are given in Tables III and IV and in Table V for the same halide in N-methylpropionamide. At low halide concentrations in dimethylformamide (Table III) and at all halide concentrations in N-methylpropionamide, the instantaneous rate constants show no trend with time. At higher initial halide concentrations in dimethylformamide (Table IV), the instantaneous rate constants increase with time. This is due to the operation of a positive salt effect as shown in Fig. 1. The ionic strengths shown in this plot are the concentrations of the added salts plus one-half the initial *t*-butyl bromide concentrations, *i.e.*, the ionic strength at 50% reaction.

It is particularly noteworthy that the two bromides accelerate the rate more strongly than does tetraethylammonium nitrate. Spieth and Olson[8] have reported similar results for *t*-butyl bromide in aqueous acetone with added lithium perchlorate, lithium bromide and lithium chloride. All three salts accelerated the rate, with the perchlorate having the largest effect and the chloride the least effect. In connection with our data, we consider it

TABLE I

REACTION RATES IN DIMETHYLFORMAMIDE

Compound	Initial concn., mole l.$^{-1}$	T, °C.	Added salt, mole l.$^{-1}$	$k \times 10^5$, sec.$^{-1}$	Final % olefin[c]
t-BuCl	0.0875	50.7		0.0095 ± 0.0011	
t-BuCl	.0648	80.0		.244 ± 0.003	
DNCCl[d]	.0137	24.8		.012 ± 0.001	
DNCCl	.0725	24.8		.014 ± 0.002	
DNCCl	.0760[b]	24.8		.014 ± 0.002	
t-BuBr	.0835[b]	24.8		.26 ± 0.01	
t-BuBr	.1710[b]	40.3		1.6 ± 0.1	
t-BuBr	.1580[a]	40.3		1.40 ± 0.1	84
t-BuBr	.00917	50.7		4.27 ± 0.02	
t-BuBr	.0855	50.7		5.2 ± 0.2	94
t-BuBr	.0835	50.7	0.0083 Et_4N^+, NO_3^-	5.2 ± 0.2	85
t-BuBr	.0837	50.7	.0417 Et_4N^+, NO_3^-	5.7 ± 0.2	90
t-BuBr	.0828	50.7	.0970 Et_4N^+, NO_3^-	7.0 ± 0.2	101
t-BuBr	.0852	50.7	.1668 Et_4N^+, NO_3^-	8.0 ± 0.2	89
t-BuBr	.0830	50.7	.1035 NaBr	8.7 ± 0.2	85
t-BuBr	.0858	50.7	.0760 Et_4N^+, Br^-	7.7 ± 0.1	

[a] The rate was measured by determining olefin as a function of time. [b] Run conducted in glass-stoppered flask. All other runs were in sealed tubes. [c] Measured after at least ten half-lives. [d] Abbreviation for dimethylneopentylcarbinyl chloride.

TABLE II

REACTION RATES IN N-METHYLPROPIONAMIDE

Compound	Initial concn., mole l.$^{-1}$	T, °C.	Added salt, mole l.$^{-1}$	$k \times 10^5$, sec.$^{-1}$
DNCCl[c]	0.0126	24.8		0.044 ± 0.002
DNCCl	.0880[b]	24.8		.045 ± 0.002
t-BuBr	.0137[b]	24.8		.23 ± 0.03
t-BuBr	.0955[a]	39.2		.12 ± 0.01
t-BuBr	.197	39.2		.13 ± 0.01
t-BuBr	.0785	50.7		5.0 ± 0.2
t-BuBr	.0810	50.7	0.1002 Et_4N^+, NO_3^-	5.4 ± 0.1
t-BuBr	.0788	50.7	0.0922 Et_4N^+, Br^-	4.9 ± 0.2

[a] Final olefin titer = 97%. [b] Run conducted in glass-stoppered flask. All other runs were in sealed tubes. [c] Abbreviation for dimethylneopentylcarbinyl chloride.

In the one run where the olefin formed was determined as a function of time, the ampoules, containing a 5-ml. aliquot, were broken under 100 ml. of carbon tetrachloride containing 10 ml. of a freshly standardized solution of bromine in carbon tetrachloride. This solution was allowed to stand 30 minutes, 10 ml. of 10% aqueous potassium iodide was added and the liberated iodine was titrated with standard thiosulfate solution. This same procedure was used in determining infinity olefin titers.

(6) G. F. D'Alelio and E. E. Reid, THIS JOURNAL, **59**, 109 (1937).

(7) This result does not necessarily contradict Kornblum and Blackwood's[1d] isolation of only a 46% yield of isobutylene from the reaction of *t*-butyl bromide in dimethylformamide, since the losses on isolation may be substantial.

(8) F. Spieth and H. D. Olson, THIS JOURNAL, **77**, 1412 (1955).

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TABLE III

SOLVOLYSIS OF 0.00917 *M* *t*-BUTYL BROMIDE IN DIMETHYLFORMAMIDE AT 50.7 ± 0.1°

Time, hr.	Reaction, %	$k \times 10^5$, sec.$^{-1}$
1.0	14.2	4.25
2.0	26.0	4.28
3.0	36.9	4.26
4.1	46.5	4.27
5.0	54.0	4.31
7.0	66.0	4.28

TABLE IV

SOLVOLYSIS OF 0.0855 *M* *t*-BUTYL BROMIDE IN DIMETHYLFORMAMIDE AT 50.7 ± 0.1°

Time, hr.	Reaction, %	$k \times 10^5$, sec.$^{-1}$
1.0	15.8	4.78
2.0	29.8	4.91
3.5	47.4	5.10
5.0	60.8	5.20
7.5	77.8	5.57

TABLE V

SOLVOLYSIS OF 0.0785 *M* *t*-BUTYL BROMIDE IN N-METHYLPROPIONAMIDE AT 50.7 ± 0.1°

Time, hr.	Reaction, %	$k \times 10^5$, sec.$^{-1}$
1.00	17.2	5.25
1.75	26.7	4.93
2.75	38.9	4.93
4.00	50.3	4.85
5.50	63.2	5.05
7.00	72.0	5.05

pertinent that conductivity measurements on potassium nitrate and potassium bromide in dimethylformamide at 25°[9] indicate that the bromide is much less associated than is the nitrate in this solvent, since the bromide shows only a small deviation from the calculated, limiting Onsager slope, whereas the nitrate shows a very sizable deviation. This suggests that the differences that we observe between bromides and nitrates may be due, in part at least, to differences in the extent of ion-pairing. At any rate, there is no evidence for any retardation of the rate by bromide ion. In dimethylformamide there is a clear acceleration of the rate with added bromide ion. In N-methylpropionamide, the instantaneous rate constants are constant with time, and a run with added tetraethylammonium bromide shows no significant slowing of the rate.

Discussion

The usual description of the mechanism of solvolysis reactions is in terms of the SN1–SN2 (and/or E_1–E_2) classification of the Hughes–Ingold school.[3,10] The SN1 and E_1 reactions involve a rate-determining ionization to a cationic intermediate. The solvent functions, largely in an electrophilic manner, to heterolyze the C–X bond and solvate the anion, and no covalent interaction between the cation and the solvent is required. The SN2 and E_2 mechanisms, on the other hand, involve a concerted process, in which the solvent functions both

(9) D. P. Ames and P. G. Sears, *J. Phys. Chem.*, **59**, 16 (1955).

(10) E. D. Hughes and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941).

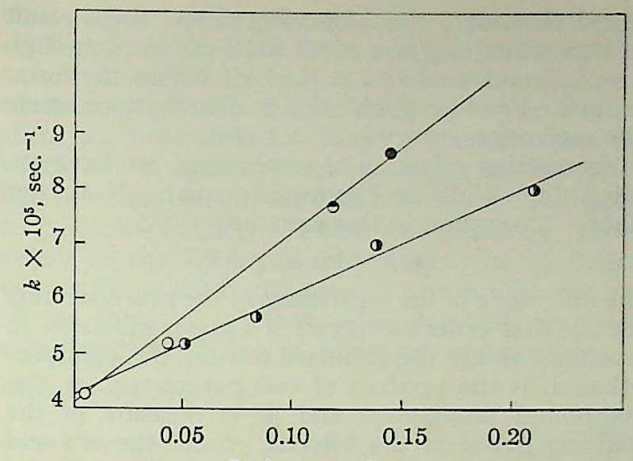

Fig. 1.—Salt effect in the solvolysis of *t*-butyl bromide in dimethylformamide at 50.7 ± 0.1°: ○, nothing added; ◑, tetraethylammonium nitrate added; ◓, tetraethylammonium bromide added; ●, sodium bromide added.

by virtue of its ionizing power and its nucleophilic character.

It is now generally recognized that these reaction categories are limiting mechanistic extremes of a gradation of mechanisms, reflecting a continuous spectrum of transition states. The existence of borderline or intermediate cases has been recognized by the Hughes–Ingold school.[10,11] Winstein, Grunwald, *et al.*, classify all cases in which there is evidence both for an intermediate and covalent interaction of the cation with the solvent as borderline cases and have discussed these in terms of the canonical structures, I, II and III, contributing to the transition state.[12] Swain and his coworkers[13] have emphasized the importance of ion–dipole solvation bonds to the cation as well as co-

Z: R–X	Z–R: X	Z: R^+: X
I	II	III

valent solvation bonds to the cation and have argued that, in almost all solvolytic reactions, the solvent is involved in both a nucleophilic and an electrophilic capacity.

A striking feature of the solvolysis reactions in dimethylformamide and N-methylpropionamide is that they are unexpectedly slow, even if one allows that these solvents do not rival hydroxylic solvents in their capacity for electrostatic solvation.[14] More striking, the rates in the two solvents are very similar in spite of the fivefold difference in dielectric constant. Nevertheless, the activation energies in these solvents are the ones usually obtained for these halides.[12] We have rate data at three temperatures in both solvents for *t*-butyl bromide and at two temperatures in dimethylformamide for *t*-

(11) E. D. Hughes, C. K. Ingold and U. G. Shapiro, *J. Chem. Soc.*, 225 (1936); M. L. Dhar, E. D. Hughes and C. K. Ingold, *ibid.*, 2058 (1948).

(12) E. Grunwald and S. Winstein, THIS JOURNAL, **70**, 846 (1948); S. Winstein, E. Grunwald and H. W. Jones, *ibid.*, **73**, 2700 (1951); A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 (1956).

(13) (a) C. G. Swain, *ibid.*, **70**, 1119, 2989 (1938). (b) C. G. Swain and R. B. Mosely, *ibid.*, **77**, 3727 (1955); C. G. Swain, R. B. Mosely and D. E. Bown, *ibid.*, **77**, 3731 (1955); C. G. Swain, D. C. Dittmer and L. E. Kaiser, *ibid.*, **77**, 3737 (1955).

(14) E. Gelles, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 2918 (1954).

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butyl chloride. For *t*-butyl bromide, these result in activation energies of 23 ± 1 kcal. in N-methylpropionamide and 22.1 ± 0.5 kcal. in dimethylformamide. For *t*-butyl chloride in dimethylformamide the activation energy is 25 ±1 kcal.

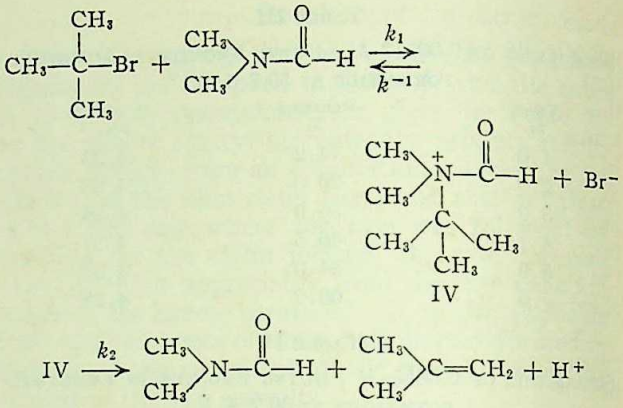
As another criterion of mechanism, we have applied the Winstein–Grunwald equation[12] to our data. According to this equation

$$\log k = \log k_0 + mY$$

the difference in the logarithms of the rate constants for the first order solvolysis of a given substance in a solvent and in the standard solvent, 80% aqueous ethanol, is the product of two parameters, m, the compound parameter, and Y, a measure of the ionizing power of the solvent. Since the m's and log k_0's are known[4b,12] for all three halides, we can calculate Y-values for both solvents. For dimethylformamide, we can obtain three Y-values, one for each halide on which we have rate data. The resulting values for Y are −3.47 from *t*-butyl chloride, −2.46 from *t*-butyl bromide and −3.72 from dimethylneopentylcarbinyl chloride. Similarly, for N-methylpropionamide, we can obtain two Y-values, −2.60 from our rate data with *t*-butyl bromide and −3.14 from our rate data with dimethylneopentylcarbinyl chloride. Clearly, our rate results are not correlated satisfactorily by the Winstein–Grunwald equation. However, in spite of the impressive success achieved by the Winstein–Grunwald equation in correlating the rates of solvolysis of organic halides with solvent change and the usefulness of this equation in diagnosing solvolytic mechanisms, it does not follow that an absence of correlation, in a particular instance, necessitates a basic difference in mechanism.

This point has been emphasized in a searching and cogent analysis of the Winstein–Grunwald relation by Wilputte-Steinert and Fierens.[15] As these authors have indicated, for a given halide m cannot be expected to be constant in all solvents, since the delocalization of charge must produce variable perturbations which depend on the nature, and composition of the solvent.[16] Also, the ionizing power, Y, is not an intrinsic property of the solvent. The solvation process is not limited to the carbon–chlorine bond. It must involve the entire circumference of the halide structure and, as the halide structures are varied, there must result differences in the degree of solvation of the initial states and transition states.

The reactions of halides in dimethylformamide have been discussed in terms of an intermediate or product involving covalent bonding of the cation to the solvent.[1c,d] For the solvolysis of *t*-butyl bromide in dimethylformamide, one might write[17]

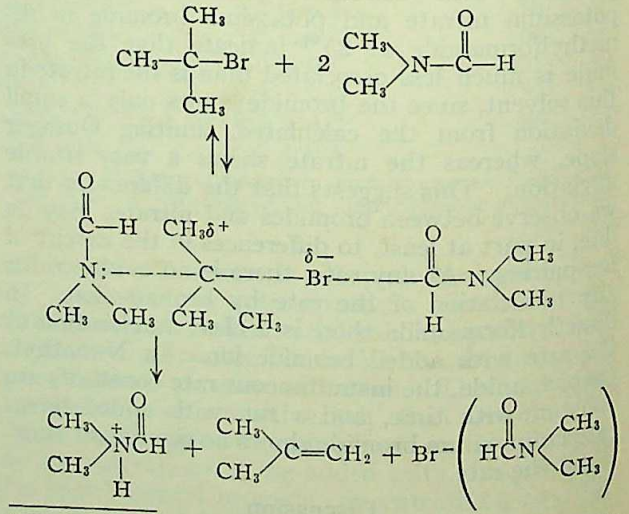


As written, this mechanism suggests a backside attack by the solvent on the C–Br bond. However, it is possible that IV results from a frontside attack as the C–Br bond is being broken. If we assume a steady state with respect to IV, the rate expression is

$$\text{rate} = \frac{k_1 k_2(\text{bromide})}{k_{-1}(\text{Br}^-)} + k_2$$

Since, in this case, there is no slowing of the rate by added bromide ion and since the rate of bromide ion liberation is equal to the rate of olefin formation, $k_2 >> k^{-1}(\text{Br}^-)$, and the rate $\cong k_1$(bromide).[18]

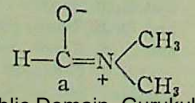
In addition, there is the possibility of a concerted elimination reaction involving two or more solvent molecules. This type of mechanism was first suggested by Holysz,[19] who studied the dehydrohalogenation of 4-halo-3-ketosteroids in dimethylformamide. This mechanism might be represented as



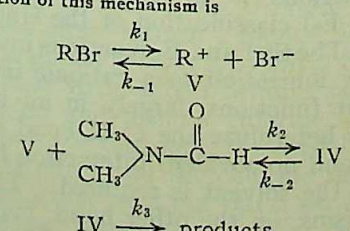
(15) L. Wilputte-Steinert and P. J. C. Fierens, *Bull. soc. chim. Belg.*, **64**, 308 (1955).

(16) In this connection, it is pertinent to point out that the substituent constants in the Hammett equation vary markedly with solvent changes; H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(17) In structure IV we have followed the previous practice[1c,d] of making the nitrogen atom the nucleophilic center of the dimethylformamide molecule. As was pointed out by a referee, it is also probable that, in dimethylformamide, the nitrogen acts electrophilically and the oxygen nucleophilically. Dimethylformamide shows restricted rotation about its carbon–nitrogen bond (W. D. Phillips, *J. Chem. Phys.*, **23**, 1363 (1955); H. S. Gutowsky and C. H. Holm, *ibid.*, **25**, 1228 (1956)) suggesting a large contribution from structure a.



(18) A variation of this mechanism is



If we assume a steady state with respect to both IV and V and, further, that terms involving (k_{-1}(Br$^-$)) are negligible with respect to the other terms present, we again find that rate $\cong k_1$(bromide).

(19) C. Holysz, THIS JOURNAL, **75**, 4432 (1953).

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Although this mechanism has been depicted as involving only two solvent molecules, it is possible that more than two are involved or, alternatively, that a single solvent molecule is involved in a cyclic transition state as suggested by Kornblum and Blackwood.[1d] In this case, too, the roles of the oxygen and nitrogen atoms of dimethylformamide may be reversed.[17] Also, the ion–dipole solvation bond to carbon may be from the front rather than the rear. In any case, the kinetics would be those observed.

Our results do not permit us to make a choice between these possibilities. It is clear that there may be solvolytic reactions in which the solvent functions in a purely electrophilic manner. It is equally probable that there are solvolytic mechanisms in which the action of the solvent is entirely nucleophilic. Between these two extremes there must be a broad range of mechanisms in which two or more solvent molecules are involved and in which the solvent acts both electrophilically and nucleophilically. These mechanisms, thus, reflect an equally broad and continuous spectrum of transition states differing in the configurations of the solvating solvent molecules and are best considered as differing in degree but not in kind.

North Adams, Mass.

[Contribution from the Baker Laboratory of Chemistry, Cornell University]

Perfluoroalkylzinc Compounds. I. The Preparation and Properties of Perfluoroalkylzinc Halides[1,2]

By William T. Miller, Jr., Elliot Bergman[3] and Arnold H. Fainberg

Received January 30, 1957

Convenient methods for the preparation of perfluoroalkylzinc compounds of the type R_FCF_2ZnI (solvated) are described together with the results of related work on the reactions of fluoroperhaloalkyl bromides and iodides with metallic zinc. The perfluoroalkylzinc iodides as exemplified by perfluoro-*n*-propylzinc iodide are shown to be thermally stable in solution and inert to carbon dioxide and to oxygen. They are strong Lewis acids, in contrast to the alkylzinc iodides. They are readily hydrolyzed, cleaved by halogen and converted into olefins by pyrolysis. They are unreactive with organic electrophiles, but under vigorous conditions in the presence of such compounds containing active hydrogen they tend to yield R_FCF_2H rather than addition products.

Introduction

Evidence for the existence of perhaloalkylzinc compounds was first obtained in attempting to dehalogenate fluoroperhalo compounds which do not contain halogens other than fluorine in the 1,2-relation to produce olefins. Reduced products were isolated by hydrolysis of reaction mixtures under conditions which suggested the intermediate formation of perhalo zinc compounds.[4] Efforts were then made to prepare perfluoroalkylzinc compounds, and it was found that perfluoro-*n*-propylzinc iodide could be obtained readily in dioxane solution.[5] The present paper presents work on the preparation and properties of solvated perfluoroalkylzinc compounds of the type R_FCF_2ZnX and on related reactions of fluoroperhaloalkyl iodides and bromides with metallic zinc.

The preparation of solutions of zinc and cadmium perfluoroalkyls from trifluoromethyl iodide and heptafluoro-*n*-propyl iodide has been reported independently by Haszeldine[6] with experimental work on heptafluoro-*n*-propylzinc iodide appearing more recently.[7] Earlier attempts by Emeléus and Haszeldine to prepare organozinc compounds from trifluoroiodomethane and pentafluoroiodoethane yielded only fluoroform and pentafluoroethane as organic products.[8]

Discussion and Results

In the present work all of the fluoroperhaloalkyl iodides and bromides tested were found to react with zinc dust in donor-type solvents such as aliphatic ethers and pyridine at or below reflux temperatures. Depending upon the structure of the perhaloalkyl halide and the choice of solvent and reaction conditions, one or more products of the type shown below were isolated. Organozinc compounds have been obtained only when Y is fluorine. When Y is chlorine intramolecular dehalogenation ordinarily occurs readily and always with great ease when Y is bromine or iodine.

$$R_FCFYCF_2X + Zn \xrightarrow{\text{solvent}} R_FCF{=}CF_2 \quad (I)$$

X = Br or I: R_FCFYCF_2ZnX (II)

Y = F or other halogen: $R_FCFYCHF_2$ (III)

$[R_FCFYCF_2-]_2$ (IV)

Perfluoro-*n*-propyl iodide was found to react readily with zinc in dioxane to yield more than 75% perfluoro-*n*-propylzinc iodide (II) plus small amounts of heptafluoropropane (III). Perfluoro-*n*-propyl bromide reacted in 1,2-dimethoxyethane after a long induction period to yield 60% of the corresponding zinc compound (II). Perfluoro-*n*-pentyl iodide reacted sluggishly with zinc in dioxane to yield a mixture of perfluoro-*n*-pentylzinc iodide (II), undecafluoro-*n*-pentane (III) and perfluoro-*n*-decane (IV). The perhalomethanes failed to

(1) Taken, in part, from a thesis submitted by Elliot Bergman to the Graduate School, Cornell University, Ithaca, N. Y., June, 1955.

(2) This research was supported in part by the Office of Naval Research.

(3) Procter and Gamble Fellow, 1953–1954.

(4) A. H. Fainberg and W. T. Miller, Jr., Abstracts of Papers, 120th Meeting, American Chemical Society, New York, N. Y., Sept., 1951, p. 7K; W. T. Miller, Jr., and J. M. Howald, unpublished work.

(5) W. T. Miller, Jr., A. H. Fainberg and E. Bergman, Abstracts of Papers, 122nd Meeting, American Chemical Society, Atlantic City, N. J., Sept., 1952, p. 14-K.

(6) R. N. Haszeldine, *Nature*, **168**, 1028 (1951).

(7) R. N. Haszeldine and E. G. Walaschewski, *J. Chem. Soc.*, 3606 (1953).

(8) H. J. Emeléus and R. N. Haszeldine, *ibid.*, 2948, 2953 (1949).

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give detectable quantities of organozinc compounds under any of the conditions utilized. Trifluoroiodomethane was converted into fluoroform (III), dichlorofluoroiodomethane yielded dichlorofluoromethane (III) plus the dimer product (IV) and bromodichlorofluoromethane yielded condensed material in addition to undergoing general decomposition to form inorganic products. 1,2-Dichloro-1,2,2-trifluoroiodoethane yielded only its dehalogenation product, chlorotrifluoroethylene (I), under the experimental conditions utilized.[9]

The reactions between zinc and fluoroperhaloalkyl iodides and bromides were greatly facilitated by the presence of a donor-type solvent. In the absence of solvent or in the presence of non-donor type solvents such as benzene, methylene chloride and ethyl heptafluoro-*n*-butyrate, no reaction was observed with *n*-propyl iodide at temperatures up to 100°. Haszeldine and Walaschewski obtained somewhat similar results at moderate temperatures and have reported that perfluoro-*n*-propyl iodide and zinc react at 310° to yield perfluoro-*n*-hexane.[7] The behavior of perfluoroalkyl iodides with zinc differs from that of alkyl iodides, which yield dialkylzinc compounds at elevated temperatures in the absence of solvent.[10]

Perfluoro-*n*-propylzinc Iodide.—It was found that perfluoro-*n*-propylzinc iodide could be conveniently prepared in high yield by reaction of zinc with perfluoro-*n*-propyl iodide in dioxane or 1,2-dimethoxyethane solution at temperatures up to about 100°. Other donor-type solvents such as pyridine also could be utilized. Small amounts of heptafluoropropane always were formed during reaction of the perfluoroiodide with zinc, but once formed the zinc compound was stable in solution at reflux temperatures for prolonged periods and on storage at room temperature for more than a year. This thermal stability in solution, which is in striking contrast to the instability at relatively low temperatures exhibited by the corresponding magnesium[11,12] and lithium[13] compounds, suggests that the formation of monohydroperfluoroalkanes during the preparation of perfluoroalkylzinc compounds proceeds by free radical abstraction of a hydrogen atom from solvent rather than by removal of a proton by a perfluorocarbanion as previously suggested.[7] The low order of reactivity found with carbonyl compounds described below also argues against the availability of a reactive carbanion.[14]

Attempts to prepare perfluoro-*n*-propylzinc iodide in ethyl ether solution led to the rapid evolution of heptafluoropropane with the production of little, if any, zinc compound. This anomalous result in diethyl ether is attributed to small amounts of peroxide which were found to be present. Since typical free radical type inhibitors such as hydroquinone (quinone) were found to quench the reaction, these observations can be accounted for by an organic peroxide–zinc induced free radical chain reaction between the iodide and ether. Similarly, Emeléus and Haszeldine isolated only pentafluoroethane from the reaction of pentafluoroiodoethane with zinc–copper couple in ethyl ether.[8] However, Haszeldine and Walaschewski[7] subsequently reported no difficulty with this solvent. Pierce, McBee and Judd,[13] following up our preliminary report,[4] obtained only heptafluoropropane by reaction of perfluoro-*n*-propyl iodide with zinc in commercial dioxane, a solvent which readily forms peroxide on exposure to air. The choice and purity of solvent utilized for the preparation of perfluoroalkylzinc compounds is thus shown to be of primary importance. Peroxide-free dioxane and 1,2-dimethoxyethane were found to be effective and convenient solvents; 1,2-dimethoxyethane was especially advantageous in some instances because of greater solubility of its addition compounds.[15] The purity of the zinc metal utilized for reaction was not indicated as critical. All dry unoxidized samples of commercial zinc dust tested worked well. Similarly the reaction temperature did not exert a major effect upon the yield of perfluoro-*n*-propylzinc iodide over the range investigated (*ca.* 25–100°).

The concentration of heptafluoropropyl iodide in solution was found to be the most important variable in determining the relative yields of organozinc compound II and of dimer product IV. With dropwise addition of the iodide to zinc dust suspended in dioxane no perfluoro-*n*-hexane could be isolated. On the other hand, when a concentrated solution of iodide was employed in a sealed tube, a vigorous exothermic reaction occurred to form perfluorohexane as the major product. These observations suggest that the dimerization reaction proceeds by a bimolecular homolytic type reaction of the iodide on the zinc surface rather than by secondary reaction with perfluoropropylzinc iodide. This conclusion was supported by the observed failure of a filtered solution of perfluoropropylzinc iodide in dioxane to react with additional added iodide. Haszeldine and Walaschewski[7] obtained perfluoro-*n*-hexane in up to 45% yield by a sealed-tube reaction of perfluoro-*n*-propyl iodide with zinc in dioxane. Henne obtained 77% perfluoro-*n*-hexane by the same type reaction in refluxing acetic anhydride–methylene chloride.[16,17]

The chemical reactivity of the perfluoroalkylzinc compounds was found to lie between that of the stable relatively unreactive perfluoroalkylmercury compounds[8] and the unstable highly reactive perfluoroalkylmagnesium compounds.[5,11,12] The fol-

(9) Some coupled product probably was formed also; see R. N. Haszeldine, *J. Chem. Soc.*, 4423 (1952); A. L. Henne, THIS JOURNAL, **77**, 2334 (1955).

(10) E. Frankland, *Ann.*, **71**, 171 (1849). Zinc–copper couple: C. R. Noller, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 184–187.

(11) R. N. Haszeldine, *J. Chem. Soc.*, 3423 (1952); 1748 (1953); 1273 (1954).

(12) A. L. Henne and W. C. Francis, THIS JOURNAL, **73**, 3518 (1951); **75**, 992 (1953).

(13) O. R. Pierce, E. T. McBee and G. F. Judd, *ibid.*, **76**, 474 (1954).

(14) The highly reactive heptafluoropropyllithium also does not yield heptafluoropropane in the absence of acidic hydrogen.[13]

(15) This solvent has been found especially suitable for the preparation of other organo-metallic compounds; H. L. Cohen and G. F. Wright, *J. Org. Chem.*, **18**, 432 (1953).

(16) A. L. Henne, THIS JOURNAL, **75**, 5750 (1953).

(17) Higher temperatures (100°) were found by Haszeldine and Walaschewski to favor the formation of coupled product (IV) under their reaction conditions.[7] Henne found a controlled low temperature essential (40–45°).[16]

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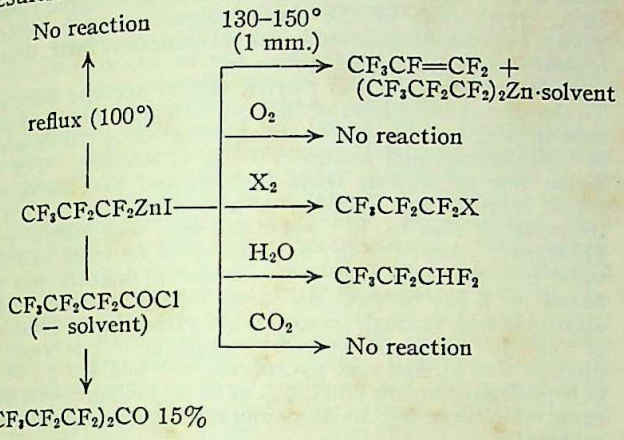
lowing chart summarizes illustrative experimental results.



No reaction was observed with oxygen over long periods. Hydrolysis proceeded slowly with the addition of water at room temperature. The addition of aqueous acid or base increased the rate of hydrolysis markedly. Chlorinolysis and brominolysis occurred exothermally, but heating to 80–100° was required for rapid reaction with iodine. This behavior is in strong contrast to that of the lower alkyl zinc compounds which react vigorously with water at room temperature and ignite with the halogens and with oxygen.[18] The hydrolysis and halogenolysis reactions demonstrate the presence of the carbon–zinc bond.

An outstanding property of the perhaloalkylzinc halides is their strength as Lewis acids. Perfluoropropylzinc iodide exhibits a low order of reactivity with organic electrophilic systems. Attempts to carry out typical organo-metallic synthetic reactions in dioxane solution were unsuccessful. At low temperatures little reaction occurred. Perfluoropropylzinc iodide could be prepared in acetone solution. Carbon dioxide was without effect at 100°. Aldehydes, ketones, anhydrides and acid halides containing enolizable hydrogen were unreactive but yielded heptafluoropropane and condensation and solvent cleavage products on long refluxing. Less complete consumption of the zinc compound took place with reactants containing no α-hydrogen, but none of the desired addition products could be isolated.[19] By largely removing the dioxane solvent from perfluoro-*n*-propylzinc iodide at low pressure and treating the solid residue with perfluoro acid chlorides the corresponding perfluoro ketones were obtained in low yields. However, even under these conditions acetyl chloride and acetic anhydride, which contain enolizable hydrogen, yielded only heptafluoropropane.

The increase in acid strength of the perhaloalkylzinc halides over that of the alkylzinc compounds may be accounted for by the strong electron-attracting property of the perfluoropropyl group, which results in a more polar carbon–zinc bond and higher solvation energies. The high energies of solvation contribute to the ease of formation of the zinc compounds in donor-type solvents and to their stability once formed. Efforts to remove solvent completely without decomposition were unsuccessful.[21] As indicated above, removal of solvent *in vacuo* left a crystalline residue of solid perfluoropropylzinc iodide solvent complex. Sublimation of the solid dioxane complex yielded perfluoropropene and a very small amount of perfluoropropylzinc dioxanate. Pyrolysis of the corresponding 1,2-dimethoxyethane addition compound gave a higher yield (50%) of perfluorodi-*n*-propyl zinc as the etherate in addition to perfluoropropene.[22]

(18) E. Frankland, *Ann.*, **85**, 346 (1853); **95**, 28 (1855).

(19) Partial condensation of aldehydes and ketones by perfluoropropyllithium[12] and of acetone by heptafluoropropylmagnesium iodide[12] with formation of heptafluoropropane has been reported. Pawlow similarly obtained ethane and mesityl oxide by reaction of acetone with diethylzinc.[20]

(20) D. Pawlow, *Ann.*, **188**, 104 (1877)

Experimental[23–25]

Starting Materials.—Perfluoroacids were purchased from the Minnesota Mining and Manufacturing Co. Silver salts of perfluoroacids were prepared by previously described procedures.[26] Pure, peroxide-free dioxane was prepared by the method of Fieser.[27] Other ethers were purified by refluxing with and distilling from sodium wire under dry nitrogen. They were stored in the dark over sodium under nitrogen. Baker and Adamson 90% zinc dust was used in all experiments.

Perfluoroalkyl Iodides.—Heptafluoro-*n*-propyl iodide was prepared in 92% yield by a procedure similar to that described by Hauptschein and Grosse.[26] Found: b.p. 39.3° (736 mm.), f.p. −95.3, f.p. dep. 0.1°, $n^{20}D$ 1.3281, d^{20}_4 2.0566, mol. wt. 295 and 299 (vapor density), $MR^{20}D$ 29.22; reported[26]: b.p. 41.2°, $n^{20}D$ 1.3272, d^{20}_4 2.0626; calculated for C_3F_7I: mol. wt. 296, $MR^{20}D$ 29.64.[28]

Perfluoro-*n*-amyl iodide was prepared in 65% yield by heating an intimate mixture of 108 g., 0.257 mole of dry silver perfluoro-*n*-hexanoate and 85 g., 0.334 mole, of iodine in a distilling flask with a free flame. Found: b.p. 94° (755 mm.), $n^{17}D$ 1.3310; reported[29]: b.p. 94°, $n^{31.5}D$ 1.3243.

Trifluoroiodomethane was prepared in 80% yield by the method of Henne.[30] It was washed with aqueous alkali, dried by passage through concentrated sulfuric acid or phosphorus pentoxide and used without further purification.

Bromodichlorofluoromethane was prepared by the vapor phase bromination of dichlorofluoromethane at 475° by the procedure of Miller and Howald.[31] Found: b.p. 50.4° at 727 mm., $n^{20}D$ 1.4308; reported[31]: b.p. 50.2° (734 mm.), $n^{20}D$ 1.4304.

Dichlorofluoroiodomethane was prepared in 44% yield by treating bromodichlorofluoromethane with sodium iodide in acetone for 3 hr. at 120°.[31] Found: b.p. 87–90° (735 mm.), reported[31] b.p. 90°.

Perfluoroacid Chlorides.—Perfluoroacid chlorides were prepared by the reaction of the corresponding acids with phosphorus pentachloride (10–20 mole per cent. excess) followed by distillation of the crude product from a small

(21) The isolation of small amounts of $CF_3CF_2CF_2ZnI$ by fractional vacuum sublimation has been reported by Haszeldine and Walaschewski.[7]

(22) W. T. Miller, Jr., and E. Bergman, Abstracts of Papers, 126th Meeting, American Chemical Society, New York, N. Y., Sept., 1954, p. 35M. In contrast, alkylzinc compounds are readily separated from ether solvents. See, for example: L. F. Hatch, G. Sutherland and W. J. Ross, *J. Org. Chem.*, **14**, 1130 (1949).

(23) Melting and boiling points are uncorrected unless otherwise indicated.

(24) Infrared spectra were measured on a Perkin–Elmer model 21, double-beam recording spectrophotometer.

(25) Freezing points were determined by a procedure similar to that described by A. R. Glasgow, Jr., A. J. Streiff and F. D. Rossini, *J. Research Natl. Bur. Standards*, **35**, 355 (1945).

(26) M. Hauptschein and A. V. Grosse, THIS JOURNAL, **73**, 2461 (1951).

(27) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 368.

(28) A. H. Fainberg and W. T. Miller, Jr., unpublished work.

(29) M. Hauptschein, A. V. Grosse and R. L. Kinsman, THIS JOURNAL, **74**, 849 (1952).

(30) A. L. Henne and W. C. Finnegan, *ibid.*, **72**, 3806 (1950).

(31) R. J. Koshar, Ph.D. Thesis, Cornell University, 1953.

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amount of dimethylaniline. In this way trifluoroacetyl chloride, b.p. −20 to −19° (740 mm.), and perfluoro-*n*-butyryl chloride, b.p. 38–39° (740 mm.), were obtained in 76 and 89% yields, respectively.

Perfluoro-*n*-propylzinc Iodide.—The following preparative procedure gave consistently reproducible results. A 1-l. three-necked flask was fitted with a sealed stirrer, a dropping funnel and a reflux condenser in series with a Dry Ice trap and charged with 39.2 g., 0.60 gram-atom, of zinc dust. The apparatus was flushed with warm dry nitrogen and 120 ml. of dioxane added; 20 ml. of a solution of 88.8 g., 0.300 mole, of perfluoro-*n*-propyl iodide in 60 ml. of dioxane was added and the stirred solution warmed to 100°. The reaction started at about 60°.[32] The remainder of the solution was added without external heating at such a rate that gentle reflux was maintained. Shortly after this period of about 2 hr. reaction was complete, as evidenced by a drop in temperature. The Dry Ice trap contained 5.2 g., 10%, of 1,1,2,2,3,3,3-heptafluoropropane; 25 g. of water was added to the reaction flask, and the mixture refluxed for 4 hr. during which time 39 g., 77%, of heptafluoropropane was collected. Found: b.p. −17° (735 mm.), f.p. −148.5° without depression, mol. wt. 168 and 168, narrow carbon–hydrogen infrared absorption band at 3.36 μ; reported[33]: b.p. −18 to −17°; calculated for C_3HF_7, mol. wt., 170.

In order to demonstrate positively that the heptafluoropropane produced during the reaction could not be accounted for by hydrolysis of the zinc compound,[34] the reaction was run under rigorously anhydrous conditions in an all-glass apparatus. The zinc dust was introduced into the apparatus and dried with a stream of nitrogen while warming the flask. Dry dioxane, 158 g., was introduced under a blanket of nitrogen. The zinc was maintained in suspension by a magnetic stirrer and the dioxane refluxed. After 15 minutes a 15-ml. sample of dioxane was removed and a Karl Fischer titration[35] for water was found to be indistinguishable from a blank determination. Perfluoro-*n*-propyl iodide, 93.0 g., 0.314 mole, was added dropwise to the stirred zinc suspension at such a rate that the mixture remained at approximately 75°. A total of 6.8 g. (13%) of heptafluoropropane, free of perfluoropropene, and 6.2 g. (7%) of starting iodide were collected in the trap.[36] The reaction mixture was filtered free of zinc through a sintered glass filter and the residual zinc washed with 43 g. of dioxane. The combined filtrates were refluxed with 50 ml. of water to yield 36.3 g., 68%, of heptafluoropropane. One to two grams of an oil, b.p. >100°, remained in the hydrolyzate.

The above procedure was repeated using 1,2-dimethoxyethane as solvent. The reaction could be started at room temperature. A 0.240-mole run afforded 2.5 g., 6%, of perfluoropropane and 2 g., 3%, of starting iodide. Hydrolysis of the filtered solution yielded 33.5 g. which on redistillation gave 30.5 g., b.p. −19° (739 mm.), of heptafluoropropane corresponding to a 75% yield of zinc compound based on starting iodide.

Using 84 g. of pyridine and 42 g. of benzene as solvent and maintaining the reaction temperature at 60° by the rate of iodide addition, 71 g. of heptafluoro-*n*-propyl iodide yielded 5% heptafluoropropane, 10% recovered iodide and 42% zinc compound. The reaction mixture unlike those obtained with the above ether solvents was dark colored, tarry and difficult to filter.

The all-glass apparatus also was used as described above with ethyl ether as solvent. Upon addition of each portion of a total of 62 g. of iodide to 39 g. of zinc in 92 g. of ether, a deep red color appeared which gradually faded. A total of 37 g. of material was condensed in the cold trap. Distillation gave 15 g. of heptafluoropropane, b.p. −17° (734 mm.), and 22 g. of ether-soluble residue which contained iodine (sodium fusion). The residue reacted with zinc in ether to give a gas and was assumed to be unchanged iodide, 36%. Hydrolysis of the dark ethereal reaction mixture gave <1 g. of heptafluoropropane showing that little, if any, organozinc compound was present.

A similar reaction was carried out in acetone solution. To the stirred suspension of 10.4 g., 0.16 gram-atom, of zinc dust in 44 g. of dry acetone was added 39 g., 0.13 mole, of heptafluoropropyl iodide in 11 g. of acetone. The reaction was so mild at room temperature that all of the iodide solution was added over a 2-minute period. The temperature rose to 50° when the zinc was stirred very vigorously. After 0.5 hr. only 0.5 g. of material had distilled into the cold trap. The reaction mixture was refluxed for 8 hr. to yield 8.4 g. of volatile product which after bubbling through concentrated sulfuric acid consisted of 5.3 g., 24%, of heptafluoropropane. The reaction mixture was filtered and hydrolyzed to yield 7.0 g., 31%, of heptafluoropropane and 3.3 g. of an oil boiling over a wide range which appeared to be mainly condensation products of acetone.

Perfluoro-*n*-propylzinc Bromide.—A glass ampoule was charged with 5.0 g., 0.020 mole, of perfluoro-*n*-propyl bromide, 1.6 g., 0.025 gram-atom, of zinc dust and 10 ml. of 1,2-dimethoxyethane and rocked mechanically while heated up stepwise to 90° over a 73-hr. period. The zinc did not appear to react. The ampoule was set aside, and it was observed after 1.5 months that the zinc was etched and crystalline material had formed. No heptafluoropropane or starting material was found. Hydrolysis yielded 2.0 g. of heptafluoropropane corresponding to a 60% yield of heptafluoro-*n*-propyl zinc bromide.

Perfluoro-*n*-amylzinc Iodide.—A solution of 49.0 g., 0.124 mole, of perfluoro-*n*-amyl iodide in 50 ml. of dioxane was added dropwise to a stirred suspension of 9.2 g., 0.14 gram-atom, of zinc in 100 ml. of dioxane maintained at 65° by an oil-bath. The reaction was not exothermic. The second half of the iodide solution was added over a 0.5-hr. period with the temperature held at 85°. After stirring for an additional 5 hr. at 80–82° and standing overnight, 7.0 g. of undecafluoropentane was isolated which was identified by its infrared spectrum and its b.p. of 45° (755 mm.). Traces of unsaturated material were present as indicated by decolorization of acetone permanganate solution. A lower liquid layer separated out of the dioxane. This material, 8.0 g., b.p. 146–148° at 755 mm., $n^{20}D$ <1.3 and m.p. 32°, contained fluorine but no iodine; reported[37] for perfluoro-*n*-decane: b.p. 144°, m.p. 36°.

Hydrolysis of the reaction mixture yielded 9.5 g., 28% of undecafluoropentane, b.p. 45° and $n^{20}D$ <1.3. Calcd. for C_5HF_{11}: C, 22.23; mol. wt., 270. Found: C, 22.4; mol. wt., 271, 271.

Attempted Reaction of Perfluoro-*n*-propylzinc Iodide with Heptafluoro-*n*-propyl Iodide.—A filtered solution of 0.22 mole of heptafluoro-*n*-propylzinc iodide in 105 ml. of 1,2-dimethoxyethane was refluxed with 64.5 g., 0.218 mole of heptafluoro-*n*-propyl iodide for 24 hr. No insoluble material separated. Distillation yielded 51.5 g., b.p. 39–42°, $n^{20}D$ 1.3283, an 80% recovery of the propyl iodide. Similar reactions with dioxane solutions of perfluoropropylzinc iodide and *t*-butyl chloride, perfluoroallyl iodide and 1,2-dichlorotrifluoroiodoethane also failed to give coupled products.

Dimerization of Heptafluoro-*n*-propyl Iodide. Perfluoro-*n*-hexane.—The exact procedure of Henne[16] was repeated and found to yield 62% perfluoro-*n*-hexane and 13% heptafluoropropane. In a second run the acetic anhydride was replaced by 1,2-dimethoxyethane. Forty-eight grams, 0.162 mole, of heptafluoro-*n*-propyl iodide, 19.6 g. (0.298 gram-atom) of zinc dust, 16 ml. of 1,2-dimethoxyethane and 42 ml. of methylene chloride were sealed in a Pyrex ampoule at Dry Ice temperature. On warming to room temperature an exothermic reaction took place. After rocking one day at room temperature, it was observed that a new liquid layer had appeared. After eight days the ampoule was vented to yield 3 g., 11%, of heptafluoropropane. The residue was distilled *in vacuo* to yield a two-phase system. The lower layer, 19.8 g., after separation, yielded 17 g., b.p. 57.0°, 62%, of perfluoro-*n*-hexane; found: $n^{20}D$ <1.3, d. 1.71 (gravitometer), mol. wt. 336,

(32) Induction periods of a few minutes were observed in only two out of more than fifty preparations.

(33) A. F. Benning and J. D. Park (1950), U. S. Patent 2,490,764.

(34) Since heptafluoropropane was evolved throughout the reaction period, it was considered unlikely that simple hydrolysis could explain its formation.

(35) J. Mitchell and D. M. Smith, "Aquametry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 120.

(36) Unless otherwise indicated trap materials were worked up as follows. The trap was immersed in an ice-bath and the material b.p. <0° was distilled into another trap. The crude fractions were identified by spectroscopic examination and chemical tests, *e.g.*, the unsaturation test with potassium permanganate.

(37) C. Marsh, Haridas and F. Smith, *J. Chem. Soc.*, 3617 (1950).

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and 344, immiscible with benzene or ether; reported[16]: n_D^{20} <1.3, d^{20}_4 1.6995, b.p. 57°., calcd. for C_6F_{14}: mol. wt. 338. The residual salts in the ampoule were hydrolyzed to yield 5.5 g., 20%, of heptafluoropropane.

The above procedure was repeated using only 1,2-dimethoxyethane as solvent. Heptafluoropropane, perfluoro-*n*-hexane and heptafluoro-*n*-propylzinc iodide were obtained in 15, 47 and 29% yields, respectively.

Attempted Preparation of Other Zinc Compounds.—Reactions between powdered zinc metal and the following compounds were carried out under conditions found favorable for the preparation of heptafluoro-*n*-propylzinc iodide.

Trifluoroiodomethane.—A 500-ml. three-necked flask which was fitted with a mechanical stirrer, a thermometer and a Dry Ice reflux condenser and connected in series with Dry Ice and liquid nitrogen traps was charged with 19.6 g., 0.30 gram-atom, of zinc and dried as described above; 14 g. of 1,2-dimethoxyethane and 21 g. of trifluoroiodomethane were added to the flask. Reaction started on warming with the palm of the hand but was quenched by adding 124 g. of additional solvent; 20 g. of additional iodide was added slowly to the flask through the Dry Ice condenser but reaction failed to start. On warming a sudden reaction caused the loss of some material, but now the remaining 35 g. of the total of 76 g., 0.39 mole, of iodide was added at such a rate that the reaction mixture remained at 60–65°. During the reaction 10 g., 39%, of fluoroform (infrared spectrum) was collected in the liquid nitrogen trap. Found: mol. wt., 70.8, 70.9. Calcd. for CHF_3: mol. wt., 70.0. Hydrolysis of the reaction mixture gave no fluoroform indicating that a stable zinc compound was not formed. Considerable fluoride ion was present in the reaction mixture.

Bromodichlorofluoromethane.—This reaction was carried out as described above for the preparation of heptafluoro-*n*-propylzinc iodide in dioxane in the all-glass apparatus; 36.4 g., 0.20 mole, of bromide was added to the stirred suspension of 16 g., 0.23 gram-atom, of zinc in 80 ml. of dioxane maintained at 50°. The mixture became dark in color and after stirring overnight at 55–60° was black. No material was collected in the cold trap on hydrolysis. The filtered solution yielded no low boiling material. Steam distillation yielded 2.1 g., n_D^{20} 1.4198, and a liquid residue of 11 g. The hydrolysis mixture gave strong tests for fluoride, chloride and bromide ions.

Dichlorofluoroiodomethane.—As described above, 92 g., 0.402 mole, of iodide and 41 g. of 1,2-dimethoxyethane were added to 57.6 g., 0.88 gram-atom, of zinc suspended in 199 g. of solvent at such a rate that the temperature was maintained at 30°. The reaction mixture was distilled to yield 21 g., b.p. up to 25°, and 18 g., 44%, of dichlorofluoromethane, b.p. 10–13°, identified by its infrared spectrum; reported[38] b.p. 8.9°. This material contained formaldehyde and methyl iodide in small amounts. A dinitrophenylhydrazone, m.p. 162–165°, was prepared; its infrared spectra was superimposable with that of authentic formaldehyde dinitrophenylhydrazone. Steam distillation of the reaction mixture gave no dichlorofluoromethane, showing that no zinc compound was present, but gave 10 g. of a liquid product. Redistillation yielded 5.7 g., b.p. 86–101°, n_D^{26} 1.4041 to 1.4118. This material contained fluorine and chlorine, and its infrared spectrum corresponded to that of *sym*-difluorotetrachloroethane n_D^{26} 1.4122, b.p. 91°. It corresponded to 14% of the starting material.

1,2-Dichlorotrifluoroiodoethane.—A solution of 21.1 g., 0.076 mole, of iodide in 34 ml. of dioxane was added to 6.5 g., 0.10 gram-atom of zinc, suspended in 24 ml. of dioxane during a 2-hr. period while maintaining the temperature at 15–20°. A total of 5.5 g., b.p. <0°, identified as chlorotrifluoroethylene (63%) by its infrared spectrum, was isolated. Hydrolysis of the reaction mixture yielded no hydrogen compounds.

Pyrolysis of Perfluoro-*n*-propylzinc Iodide.—An apparatus consisting of a 500-ml. round flask, with a 1-in. diameter neck 13 in. long was connected in series with two traps and charged with 78 ml. of dioxane solution containing 0.244 mole[39] of perfluoro-*n*-propylzinc iodide. The dioxane was removed *in vacuo* to the second trap by gradually warming the flask to 60° and lowering the pressure to 1 mm. With the pressure at 1 mm. the flask and first trap were isolated from the rest of the system by a stopcock, and the first trap was cooled in liquid nitrogen. The flask was immersed in a deep oil-bath, 3.5 in. of the neck of the flask was covered with oil and the temperature raised to 150–160°. Distillate was collected in the trap and small amounts of a white crystalline sublimate condensed on the cooler portion of the neck of the flask. After 15 hr. the reaction was stopped and the volatile material in the trap bubbled through concentrated sulfuric acid to remove dioxane. In this way 29 g., 79%, of perfluoropropene (infrared spectrum), b.p. less than 0°, was collected. Photochemical bromination of 8.1 g. (0.054 mole) of the propene distillate from a similar pyrolysis with 6.5 g. (0.041 mole) of bromine in a Pyrex ampoule yielded on simple distillation 11.7 g. of 1,2-dibromohexafluoropropane. Found: b.p. 70.0–72.0° (734 mm.), $n^{20}D$ 1.3588, d^{20}_4 2.163, MR_D 31.53, reported[40]: b.p. 72–73° at 740 mm., $n^{20}D$ 1.3588, d^{20}_4 2.1693; calcd. for $C_3Br_2F_6$: $MR^{20}D$ 31.50.[28]

The white hygroscopic sublimate (*ca.* 0.5 g.) contained traces of iodide which could be removed by resublimation. It reacted with water to give a gas, decomposed on heating to give perfluoropropene (infrared spectrum), reacted vigorously with bromine, gave a Tollens test and burned only when held in a flame. The reactions of this sublimate suggested that it was perfluorodi-*n*-propylzinc dioxanate.

Reactions of Perfluoro-*n*-propylzinc Iodide.—The following reactions were carried out with perfluoropropylzinc iodide prepared as described above. Solid dioxane solvate containing from one to two moles of dioxane per mole of perfluoro-*n*-propylzinc iodide was prepared by removing excess solvent under reduced pressure.

Iodine.—When 0.17 mole of zinc compound was treated with 50.8 g., 0.200 mole, of iodine in 90 ml. of diozane, no apparent reaction occurred until the mixture was warmed. The mixture was refluxed and perfluoro-*n*-propyl iodide distilled out. A total of 38.7 g., 77%, of product was thus obtained. Found: b.p. 39 to 41°, $n^{20}D$ 1.3281, mol. wt. 292 and 293.

Bromine.—Similarly to the reaction with iodine, 64 g., 0.40 mole, of bromine was added dropwise to 0.18 mole of zinc compound in 100 ml. of dioxane. The mixture turned iodine colored and the temperature rose to 80°. After approximately one-half of the bromine was added, refluxing occurred at the distillation head which was cooled by ice-water. The low boiling material, 33 g., was collected in a Dry Ice trap. Distillation yielded: (1) 26.8 g., b.p. 11.0–13.8° (740 mm.), mol. wt. 231 and 232; (2) 8 g., b.p. 25–45°, 2 g. of which b.p. 35–45°, $n^{20}D$ 1.3281. Fraction 1 was estimated by infrared spectrum and molecular weight, to be a mixture of heptafluoropropane and heptafluoropropyl bromide corresponding to yields of 23 and 44%. Redistillation of (1) yielded an end fraction, mol. wt. 246 and 247, f.p. −145.5 to −146.5°; found for perfluoro-*n*-propyl bromide prepared from silver perfluoro-*n*-butyrate and bromine: b.p. 12°, f.p. −144.0°; calcd. for C_3BrF_7: mol. wt. 249. Fraction 2 was principally perfluoro-*n*-propyl iodide, presumably formed by reaction of iodine with the zinc compound.

Chlorine.—Twenty-eight ml. of dioxane solution containing 0.029 mole of perfluoro-*n*-propylzinc iodide was placed in a two-necked flask fitted with a thermocouple extending into the solution and a Dry Ice reflux condenser in series with a trap. Chlorine, 19 g., 0.27 mole, was condensed into the flask; the temperature rose to 75° and the mixture turned iodine colored. The mixture was allowed to reflux for several hours and the volatile product then passed through a strongly basic sulfite solution to yield 5.5 g. of material identified as a mixture of heptafluoropropane, 46 mole per cent., and perfluoro-*n*-propyl chloride, 54 mole per cent., by infrared and molecular weight analysis; found: mol. wt. 189; calcd. for C_3ClF_7: mol. wt. 205. Ampoule-to-ampoule distillation yielded an end fraction, 0.5 g., with an infrared spectrum essentially identical with that of perfluoro-*n*-propyl chloride; found: mol. wt. 205, 207.

Hydrolysis of the reaction mixture gave no heptafluoropropane nor did any perfluoro-*n*-propyl iodide separate from

(38) A. F. Benning and R. C. McHarness, *Ind. Eng. Chem.*, **31**, 912 (1939).

(39) For convenience the titers of the zinc compound solutions given are calculated from the moles of perfluoro-*n*-propyl iodide used to prepare the zinc compound minus the moles of heptafluoropropane and of unchanged iodide isolated during the preparation.

(40) W. T. Miller, Jr., Chap. 32, *Nat. Nuclear Energy Ser.*, Div. VII, I, "Prepn., Properties and Technol. of Fluorine and Org. Fluorine Compds.," McGraw-Hill Book Co., Inc., New York, N. Y., 1951.

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the aqueous solution. The production of heptafluoropropane during the bromination and chlorination of perfluoro-*n*-propylzinc iodide presumably was due to reaction with hydrogen halide produced by the halogenation of dioxane at the reaction temperatures employed.[41]

Oxygen.—A solution of 0.114 mole of zinc compound in 90 ml. of dioxane failed to gain weight or show any positive signs of reaction when dry oxygen was bubbled into it at a rate of 0.5 mole per hour at room temperature. Likewise, at 90° after two days no evidence of reaction was observed. One gram, 5%, of heptafluoropropane was evolved during this period. Hydrolysis yielded 15 g. or a total of 16 g., 82%, of heptafluoropropane and the hydrolyzate was free of fluoride ion.[42]

In a parallel experiment with oxygen, 0.144 mole of zinc compound in dioxane was illuminated with eight G.E. 15 watt B.L. fluorescent bulbs placed concentrically around and one inch from the Pyrex reaction flask. No positive evidence of reaction was observed during 48 hr. with the solution at 35° and an oxygen flow of 0.5 mole per hour. The temperature was raised to 90–100° and the oxygen flow continued for five days during which time 18 g. of condensate collected in the Dry Ice trap. The system lost 9 g. in weight, presumably by oxygen entrainment. Separation of the trap material yielded 1.5 g., 6%, of heptafluoropropane, and 11 g., b.p. 40°, $n^{20}D$ 1.3290, identified as perfluoro-*n*-propyl iodide, 26%. Hydrolysis of the reaction mixture, which gave a faint test for fluoride, yielded 3 g., 12%, of heptafluoropropane. Distillation of the hydrolysate from excess silver sulfate yielded only 1.4 meq. of acid.

Carbon Dioxide.—A solution of 0.261 mole of zinc compound was placed in a dry lecture cylinder and 70 g., 1.6 moles, of carbon dioxide was added with the cylinder cooled in Dry Ice. The cylinder was closed with a steel valve and heated in a reciprocating shaker at 106° for 110 hr. Carbon dioxide was vented through a sintered glass disk into 500 ml. of 14*N* caustic to yield 4 g. of heptafluoropropane, 9%, which was free of perfluoropropene as tested by infrared spectrum and acetone permanganate. Water, 50 ml., was added to the bomb which was then heated at 100° for 2 hr. to yield 30 g. of material, b.p. <0°, which on redistillation gave 25 g., 56%, of heptafluoropropane, b.p. −13.0 to −12.5° (740 mm.). No perfluorobutyric acid was obtained by distillation of the hydrolyzate from excess silver sulfate.

Carbonyl Compounds.—The essential technique in the reactions summarized below was to heat the reactants together under the conditions specified. The volatile products were isolated by distillation and the residual salts hydrolyzed in order to estimate the quantity of unchanged zinc compound. The percentage yields listed are regarded as approximate values. Water-insoluble products remaining in the hydrolyzate were partially investigated. Only in the case of perfluoro acid chlorides were detectable quantities of the desired products, ketones, produced. The reaction mixtures in which most of the zinc compound was consumed during the heating period were characteristically dark and tarry. The reaction mixtures in which most of the zinc compound was unchanged, despite the relatively high temperatures employed, remained fairly clean. Varying amounts of ester by-products were shown to be formed by cleavage of dioxane in the reactions with acid halides and anhydrides.

Illustrative results are summarized below. In each case following the name of the organic reagent is given: the number of moles organic reagent per mole of zinc compound, the reaction time and temperature, the percentage heptafluoropropane (I) evolved during the reaction period and the percentage unchanged zinc compound II and/or other products isolated. Percentages are based on the initial concentration of zinc compound.[39]

Perfluoro-*n*-propylzinc Iodide in Dioxane Solution.—*Paraformaldehyde:* 3.3, 5.5 days at 130°, 46% I (containing some formaldehyde), 42% II. *Benzophenone:* 0.82, 18 hr. at 80° plus 7 days at 115°, 8% I, 62% II. *Ethyl perfluoro-n-butyrate:* 1.1, 24 hr. at 80° plus 4 hr. at 105°, I and II were not determined quantitatively, but 75% ethyl perfluoro-*n*-butyrate was recovered. *Benzoyl chloride:* 0.84, 18 hr. at 90°, 14% I, 49% II (β-chloroethyl benzoate, ethylene glycol dibenzoate and possibly β-iodoethyl benzoate were shown to be present). *Perfluoro-n-butyryl chloride:* 1.5, 2 hr. at 60°, 8% I, 76% II. 1.4, 16 hr. at 110°, 63% I (containing some acid chloride), 31% II.

Perfluoro-*n*-propylzinc Iodide Solid Dioxane Solvate.—One to two moles of dioxane plus approximately 0.25 mole of zinc iodide were present per mole of organozinc compound. Complete conversion of the zinc compound took place in each case. *Acetic anhydride:* 5.6, 12 hr. at 110°, 56% I. *Acetyl chloride:* 4.4, 12 hr. at 90°, 78% I. *Benzoyl chloride:* 1.8, 12 hr. at 130–140°, 59% I, 17% heptafluoro-*n*-propyl iodide. *Trifluoroacetyl chloride:* 2.4 (plus chlorobenzene diluent), 15 hr. at 120°, compound I was mixed with trifluoroacetyl chloride and was not determined quantitatively, 6% perfluoro-2-pentanone. *Perfluoro-n-butyryl chloride:* 1.9, 65 hr. at 120°, compound I was mixed with perfluoro-*n*-butyryl chloride; 15% perfluoro-4-heptanone, b.p. 72–74° (738 mm.), yielded a solid ammonia adduct, m.p. 57.5–58.5°, phenylhydrazone, m.p. 35–37°, and formed a liquid hydrate; reported[43] for perfluoro-*n*-heptanone b.p. 75° (740 mm.).

(41) C. L. Butler and L. H. Cretcher, THIS JOURNAL, **54**, 2987 (1932).

(42) The postulated product, $CF_3CF_2CF_2OZnI$, would be expected to break down to give perfluoropropionic acid and hydrogen fluoride.

(43) A. L. Henne and W. C. Francis, THIS JOURNAL, **75**, 991 (1953).

ITHACA, NEW YORK

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

Preferential Replacement Reactions of Highly Fluorinated Alkyl Halides. I. Preparation of Certain Fluorinated Allyl Iodides[1,2]

BY WILLIAM T. MILLER, JR., AND ARNOLD H. FAINBERG

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Certain fluorinated allyl chlorides, including 3-chloropentafluoropropene and 2,3-dichlorotetrafluoropropene, have been found to react readily with sodium iodide in anhydrous acetone to yield 3-iodopentafluoropropene and 2-chloro-3-iodotetrafluoropropene, respectively. Other compounds such as 1,1,2,3-tetrachlorodifluoropropene and 1,3-dichlorotetrafluoropropene were completely inert under more rigorous conditions. The resistance of the latter two compounds to substitution suggests that the ready reaction of the first two does not involve direct reaction at the α-carbon atom, but rather anionic attack by iodide ion on the γ-carbon atom, with allylic shift and elimination of chloride ion, an S_N2' mechanism.

As part of a general investigation of the reactivity of X in highly halogenated compounds of the type RCF_2X, $RCFXR'$ and $RR'R''CX$, where X = Cl, Br or I, a number of compounds containing the group $CClF_2$ in the allylic and benzylic positions have been prepared. Physical properties for these compounds, and for their precursors and derivatives, are listed in Table I. For the

(1) Presented at the 119th Meeting of the American Chemical Society, Boston, Mass., April, 1951, Abstracts of Papers, p. 24-M. Based in part on the thesis submitted by Arnold H. Fainberg to the Graduate School of Cornell University in partial fulfillment of the requirements for the Ph.D. degree, June, 1950.

(2) This work has been supported in part by the Office of Naval Research.

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TABLE I

PHYSICAL PROPERTIES OF COMPOUNDS

No.	Compound	B.p.[a] (760 mm.), °C.	B. range,[b] °C.	F.p., °C.	F.p. dep.,[c] °C.	$n^{20}D$	d^{20}_4	$MR^{20}D$ Found[d]	$MR^{20}D$ Calcd.[e]
Ia	$CClF_2CClFCClF_2$	73.9	0.1	{"α," −141.3; "β," −135.0}	<0.1	1.3501	1.6541[g]	30.89	30.97
Ib	$CClF_2CClFCClF_2$	73.7	.1	−142.7[f]		1.3502	1.6545	30.89	
Ic[h]	$CClF_2CClFCClF_2$	73.7	1.0	Glass at −150		1.3504	1.6563	30.87	
	$CClF_2CClFCClF_2$[4]	74.0	..	−72 ± 3		1.3512	1.6631	30.81	
IIa	$CF_2=CFCClF_2$	7.3	< .1	−139.8	<0.1	....	1.5152[i]		
IIb	$CF_2=CFCClF_2$	7.4	< .1	−143.	..	....	1.5162[i]		
	$CF_2=CFCClF_2$[4]	7.5	..	Glass		1.3050[j]	1.5116[j]	20.96[k]	21.09
III	$CBrF_2CBrFCClF_2$	113.1	< .1	−118.0	0.2	1.4028	2.2016	36.15	36.19
	$CBrF_2CBrFCClF_2$[8]	56 (105)	2	−123.1	0.6	1.4029	2.205		
IV	$CClF=CFCF_3$	8.0	<0.1	−150.1	Large[l]	....	1.5158[i]		
	$CClF=CFCF_3$[5a]	7.9[m]	..	−158.	5[l]	....	....		
	$CClF=CFCF_3$[4]	8.4	..	−156.8	2.8[l]	....	....		
Va	$CCl_2FCClFCF_3$	73.4	< .1	−55.1	0.4	1.3530	1.6634	30.95	30.97
Vb	$CCl_2FCClFCF_3$	73.4	.4	−68	Large	1.3532	1.6612	31.00	
	$CCl_2FCClFCF_3$[5a]	73.5[m]	..	Glass	..	1.3529	1.6643	30.92	
VI	$CF_2=CFCF_3$	−29.7	1	−155.5	0.1	....	....	...	
	$CF_2=CFCF_3$[9]	−29.8	..	−156.2	..				
VII	$C_6H_5CF_3$	102.2	<0.1	−28.9	< .1	1.4148	1.1887	30.77	[n]
	$C_6H_5CF_3$[10]	102.0	.01	−29.14	.02				
VIII	$C_6H_5CClF_2$	140.6	0.1	−49.8	<0.1	1.4648	1.2509	35.92	35.81[o]
	$C_6H_5CClF_2$[11]	142.2		..		1.4697[p]	1.2544[p]	36.17[k]	
IX	$C_6H_5CCl_2F$	94.8 (50)	.1	−26.8	<0.1	1.5126	1.3116	41.00	40.85[o]
	$C_6H_5CCl_2F$[12]	178–180		..		....	....		
X	$C_6H_5CCl_3$	146.9 (100)	< .2	−4.5	<0.1	1.5580	1.3734	45.89	[n]
	$C_6H_5CCl_3$[13]	89 (10)	.5	−4.4	..	1.5579	1.3741	45.86	
XI	$CCl_2=CClCCl_3$	141.4 (100)	< .2	−72.9	Large	1.5491	1.7621	44.91	45.1
	$CCl_2=CClCCl_3$[14]	211.6[m]				1.5491	1.766	44.82	
XII	$CCl_2=CClCCl_2F$	170.3	< .2	−95.5	<0.4	1.5053	1.7075	40.37	40.3
	$CCl_2=CClCCl_2F$[5b]	170.2[m]	..	Glass	..	1.5050	1.7041	40.44	
XIII	$CCl_2=CClCClF_2$	128.1	< .1	−102.8	0.2	1.4572	1.6562	35.51	35.4
	$CCl_2=CClCClF_2$[5b]	128.0[m]		−103.0		1.4573	1.6598	35.44	
XIV	$CCl_2=CClCF_3$	88.4	< .1	−114.9	<0.1	1.4094	1.6165	30.52	30.54
	$CCl_2=CClCF_3$[5b]	88.3[m]		−114.7		1.4095	1.6188	30.49	
XVa	$CClF_2CCl_2CClF_2$	112.3	< .1	−45.9	1.7	1.3960	1.7184	35.50	35.50
XVb	$CClF_2CCl_2CClF_2$	112.4	< .1	−44.7	1.5	1.3954	1.7181	35.46	
XVI	$CClF_2CCl_2CClF_2$[15]	112.0[m]		−42.9	1.	1.3958	1.7199	35.45	
	$CF_2=CClCClF_2$	44.8	< .1	−120.7	0.1	1.3484	1.5399	25.46	25.48
XVII	$CF_2=CClCClF_2$[5b]	44.7[m]		−121.2		1.3484	1.5406	25.45	
XVIII	$CBrF_2CBrClCClF_2$	86.7 (100)	< .1	−44	[q]	1.4471	2.2480	40.75	40.71
XIX	$CF_2=CFCF_2I$	54.7	.1	{"α," −143.3; "β," −131.6}	0.9	1.3886	2.1093	28.90	29.1
	$CF_2=CClCF_2I$	92.4	< .1	−106.6	0.5	1.4409	2.1567	33.59	33.5

[a] Computed from the observed b.p. t_0 at pressure p_0 with the equation $t_{760} = t_0 + 0.043(760 - p_0)$.[6] [b] Boiling range of the center cut on which all other physical properties were taken. [c] F.p. depression with the material half frozen. [d] $MR^{20}D$ found $= (n^2 - 1)M/(n^2 + 2)d$. [e] Calculated from the group and atomic refractions proposed elsewhere.[7] These refractions are based in part on the data of Table I. [f] "β" phase not obtained. [g] d^{30}_4 1.6310. [h] These properties are substantially identical with those previously reported[8] for a material of the same origin. [i] At 0.0°. [j] At 1.4°. [k] Corrected to 20.0°, assuming the temperature dependence of MR to be +0.015% per °C.[7] [l] Presumably a mixture of *cis–trans* isomers, and therefore not necessarily an indication of the presence of other impurity. [m] Pressure not specified. [n] On the basis that $MR^{20}D$ for $C_6H_5CH_3$ = 31.095[16] and $AR^{20}D$ H = 1.029,[16] these data yield $AR^{20}D$ Cl = 5.96 and $AR^{20}D$ F = 0.92 in $C_6H_5CX_3$. [o] Based on the data calcd. for $C_6H_5CCl_3$ and $C_6H_5CF_3$.[n] [p] At 13°. [q] See exptl. section.

most part, the present data supplement or substantially revise data previously reported.

(3) W. T. Miller, Jr., J. M. Phelan and A. H. Fainberg, Abstracts of Papers, 119th Meeting of the American Chemical Society, Boston, Mass., April, 1950, p. 23-M.

(4) A. L. Henne and T. H. Newby, THIS JOURNAL, **70**, 130 (1948).

(5) (a) A. L. Henne and T. P. Waalkes, *ibid.*, **68**, 496 (1946); (b) A. L. Henne, A. M. Whaley and J. K. Stevenson, *ibid.*, **63**, 3478 (1941); (c) A. H. Fainberg and W. T. Miller, Jr., unpublished work.

(6) N. A. Lange, "Handbook of Chemistry," 3rd Ed., Handbook Publishers, Inc., Sandusky, Ohio, 1939, p. 667.

(7) A. H. Fainberg and W. T. Miller, Jr., forthcoming publication.

3-Chloropentafluoropropene.—This compound was prepared by dechlorination of 1,2,3-trichloropentafluoropropane, and its identity therefore depended on the identity of the latter compound.

(8) W. T. Miller, Jr., Nat. Nuclear Energy Ser., Div. VII, I, "Prepn., Properties, and Technol. of Fluorine and Org. Fluorine Compds.," McGraw-Hill Book Co., Inc., New York, N. Y., 1951, chap. 32, pp. 567–685.

(9) E. G. Young and W. S. Murray, THIS JOURNAL, **70**, 2814 (1948).

(10) J. C. Potter and J. H. Saylor, *ibid.*, **73**, 90 (1951).

(11) F. Swarts, *Bull. classe sci., acad. roy. Belg.*, [3] **35**, 375 (1898).

(12) F. Swarts, *ibid.*, 414 (1900).

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The bulk of the trichloride was prepared by the photochemical addition of chlorine to the chloropentafluoropropene fraction obtained from the high-temperature thermal reaction of chlorotrifluoroethylene.[3,8] The physical properties of this trichloride (compound Ic in Table I) were found to differ markedly from those previously reported in the literature for 1,2,3-trichloropentafluoropropane by Henne and Newby.[4] For this reason, pure samples of the trichloride were synthesized from several compounds of known identity. The purity of these samples (Ia, Table I) was established by cooling curves; in both cases freezing point depressions were less than 0.1°. Repetition of the synthesis of Henne and Newby gave a trichloride Ib with virtually the same properties as Ia. These properties differ markedly from those of the other isomeric trichlorides which can be formed by the addition of chlorine to the isomeric chloropentafluoropropenes, namely, 1,1,2-trichloropentafluoropropane (V) and 1,2,2-trichloropentafluoropropane.[5a-c] On the basis of the physical properties of the pure compounds, it was concluded that Ic was at least 75%, and probably > 90% 1,2,3-trichloride, the impurity being the 1,1,2- and/or the 1,2,2-trichlorides.

The chloropentafluoropropene IIb obtained by dechlorination of Ic was therefore at least 75% 3-chloropentafluoropropene, the impurity being the 1- and/or 2-chloroölefins.

In view of the similarity of the physical properties, particularly f.p. and density, of the 1,1,2-trichloride (Va) to those reported by Henne and Newby[4] for their 1,2,3-trichloride, it was considered advisable to check their report that 3-chloropentafluoropropene undergoes rearrangement on treatment with antimony trifluorodichloride to form 1-chloropentafluoropropene. Their result was fully confirmed by the present work.

Reactions with Iodide Ion.—α-Chloro-α,α-difluorotoluene, 1,3-dichlorotetrafluoropropene, and 1,1,2,3-tetrachlorodifluoropropene were found to be completely inert to the action of sodium iodide in anhydrous acetone, even at elevated temperatures for prolonged periods of time. In sharp contrast, 3-chloropentafluoropropene and 2,3-dichlorotetrafluoropropene reacted readily at room temperature with the iodide reagent to yield, respectively, 3-iodopentafluoropropene and 2-chloro-3-iodotetrafluoropropene. These reactions have been shown to involve reversible equilibria, in which the allyl chlorides are highly favored over the iodides.[17] That the iodides can be isolated at all is attributed only to the enormously greater solubility of sodium iodide than that of sodium chloride in anhydrous acetone,[18] with consequent displacement of the equilibria toward the iodides.

The resistance of the allylic chlorine in $CClF{=}CFCClF_2$ and $CCl_2{=}CClCClF_2$ to attack by iodide ion suggested that the ready reaction of $CF_2{=}CFCClF_2$ and $CF_2{=}CClCClF_2$ does not involve direct reaction at the α-carbon atom. This is in line with the observation that the chlorine in compounds of the type RCF_2Cl, where R is phenyl or saturated perhaloalkyl, is not capable of substitution by iodine under the same reaction conditions.

On the other hand, an S_N2' mechanism[20,21,22] involving initial attack by the iodide ion on the far γ-carbon atom with allylic shift and elimination of chloride ion, as shown below, is consistent with the observed differences of reactivity of the allyl chlorides

$$I^- + CF_2{=}\underset{|}{C}{-}CF_2Cl \rightleftharpoons$$

$$[I\cdots CF_2\cdots\underset{|}{C}\cdots CF_2\cdots Cl]^- \rightleftharpoons ICF_2{-}\underset{|}{C}{=}CF_2 + Cl^-$$

Implicit in this formulation is the structural requirement: attack by iodide ion productive of allyl iodide occurs on $CF_2{=}$, but not on $CFCl{=}$ or $CCl_2{=}$. It is considered of direct significance that the identical structural requirement has been found for base-catalyzed additions to fluoroölefins leading to saturated products. Thus, in every case reported to date in which olefins of the type $CF_2{=}CX^1X^2$ (X = H, Br, Cl and/or F) have been treated under basic conditions with BH (B = OAlk,[23 to 31] OAr,[32] NR_2,[25,33] SR[34]), saturated addition products have been reported.[35] Furthermore, these products invariably have the structure

(13) A. L. Henne and M. S. Newman, THIS JOURNAL, **60**, 1697 (1938).

(14) M. Prober, *ibid.*, **76**, 4189 (1954).

(15) A. L. Henne and M. W. Renoll, *ibid.*, **61**, 2489 (1939).

(16) "Selected Values of Properties of Hydrocarbons and Related Compounds," American Petroleum Institute Research Project 44, Table 21b, April 30, 1954.

(17) A. H. Fainberg and W. T. Miller, Jr., Abstracts of Papers, 120th Meeting of the American Chemical Society, New York, N. Y., Sept., 1950, p. 7-K.

(18) The following solubility data have been reported for sodium iodide and sodium chloride in anhydrous acetone at 18°: NaI, 1.29 mole/l.; NaCl, 5.5×10^{-6} mole/l.[19]

(19) A. Lannung, *Z. physik. Chem.*, **A162**, 262 (1932).

(20) E. D. Hughes, *Trans. Faraday Soc.*, **34**, 185 (1938).

(21) R. E. Kepner, S. Winstein and W. G. Young, THIS JOURNAL, **71**, 115 (1949).

(22) W. G. Young, I. D. Webb and H. L. Goering, *ibid.*, **73**, 1076 (1951).

(23) W. E. Hanford and G. W. Rigby, U. S. Patent 2,409,274, Oct. 15, 1946; *C. A.*, **41**, P982b (1947). Hanford and Rigby were the first to imply the structural requirement.

(24) W. T. Miller, Jr., E. W. Fager and P. H. Griswold, THIS JOURNAL, **70**, 431 (1948).

(25) M. D. Hurwitz and W. T. Miller, Jr., Abstracts of Papers, 114th Meeting, American Chemical Society, Washington, D. C., Aug., 1948, p. 4-L.

(26) J. D. Park, *et al.*, THIS JOURNAL, **70**, 1550 (1948).

(27) J. T. Barr, *et al.*, *ibid.*, **72**, 4480 (1950).

(28) J. D. Park, *et al.*, *ibid.*, **73**, 861 (1951).

(29) J. D. Park, *et al.*, *ibid.*, **73**, 1329 (1951).

(30) P. Tarrant and H. C. Brown, *ibid.*, **73**, 1781 (1951).

(31) J. A. Young and P. Tarrant, Abstracts of Papers, 120th Meeting, American Chemical Society, New York, N. Y., Sept., 1951, p. 4-K.

(32) P. Tarrant and H. C. Brown, THIS JOURNAL, **73**, 5831 (1951).

(33) R. L. Pruett, *et al.*, *ibid.*, **72**, 3646 (1950).

(34) K. E. Rapp, *et al.*, *ibid.*, **72**, 3642 (1950).

(35) There are two apparent exceptions; Tarrant and Brown[30] reported the isolation of only unsaturated ethers from the reaction of $CF_2{=}CCl_2$ and $CF_2{=}CClF$ with sodium *t*-butoxide in *t*-butyl alcohol, and Pruett, *et al.*,[33] obtained $CHClFCF{=}NC_4H_9$ from the action of $C_4H_9NH_2$ with $CF_2{=}CClF$. However, in both cases the authors believe that the saturated addition product was actually formed first, and that it subsequently split out HF. This view is partly substantiated by the report of Barr, *et al.*,[27] of the isolation of a saturated ether from the reaction of $CF_2{=}CClF$ with *t*-butyl alcohol in the presence of base; this ether was found to be highly unstable both thermally and in

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$CF_2BCX^1X^2H$,[36] in which the anionic fragment B is attached to the carbon atom bearing the two fluorine atoms.

In sharp contrast to the behavior of the fluoroolefins containing the $CF_2=$ group described above, those containing $CClF=$ or $CCl_2=$ such as $CClF=CClF$,[25] $CCl_2=CClF$[25] and $CCl_2=CClCF_3$[37] are relatively unreactive and do not appear to undergo base-catalyzed addition leading to saturated products. Under conditions resulting in reaction, they tend to give vinyl ethers instead.

A two-stage mechanism which accounts for the phenomenon of base-catalyzed addition and elimination of vinyl and allyl halogen, as well as for the highly preferred orientation of addition, has been proposed by Miller, *et al.*[24,25] In it, the first, rate-controlling step involves nucleophilic attack on $CF_2=$. Similarly, the S_N2' mechanism here proposed for the iodide–chloride interchange requires rate-controlling attack at the $CF_2=$ group by such relatively mild nucleophiles as iodide and chloride ion.

It is obvious that the allyl chlorides which have been found reactive to the iodide reagent are of such a structure as to yield the same organic iodide by allylic rearrangement as by direct substitution at the allylic carbon atom. For these compounds, it would appear that a definitive proof of mechanism can only be obtained by the use of labeled carbon. However, product analyses and kinetic results are consistent with the proposed S_N2' mechanism for the reactions with halide ions of structures of the type $CF_2=CXCCl_2F$, X = F or H.[38]

Properties of the Fluorinated Allyl Iodides.—The fluorinated allyl iodides were obtained as clear, colorless liquids by distillation in the dark under an inert atmosphere (for $CF_2=CClCF_2I$ vacuum distillation was necessary, since some thermal decomposition was encountered at the boiling point at atmospheric pressure). In the air and on exposure to light they rapidly turned purple due to liberated iodine, $CF_2=CClCF_2I$ being less stable than $CF_2=CFCF_2I$. The allyl iodides were found to be strongly lachrymatory, as were also $CF_2=CClCClF_2$ and the olefin dibromides.

Some reactions of these iodides have been investigated, and will be reported in a subsequent paper in this series.

Experimental Methods

Dehalogenation.—Dechlorinations were carried out by adding, through an addition funnel, the compound being dechlorinated to a well-stirred refluxing mixture of zinc dust in absolute methyl or ethyl alcohol. Induction periods could be substantially eliminated by the initial addition of a small amount of zinc chloride to the reaction mixture.[39] To take care of the very considerable heat of reaction, water-cooling of the reaction flask was employed. The product was continuously distilled out of the reaction mixture as formed. With these techniques, the rate of reaction for virtually all the dechlorinations run in this Laboratory to date employing zinc dust and methyl or ethyl alcohol as the solvent was found to be very rapid. This is in contrast to several reports in the literature of very sluggish reaction.[40,41]

Products and recovered starting materials were always obtained as minimum boiling azeotropes with the alcohol used as the solvent. Physical properties and compositions of some of the azeotropes encountered are given in Table II.

TABLE II

AZEOTROPES

Component A	Component B	B.p., °C. Pure A[a]	B.p., °C. Azeotrope[b]	Bar. press., mm.	$n^{20}D$ Pure A	$n^{20}D$ Azeotrope	Wt. % B in azeotrope
$CF_2=CFCClF_2$	CH_3OH	6.5	5.5	741	....	....	2
$CF_2=CFCClF_2$	C_2H_5OH	6.4	6.0	740			<1
$CClF_2CClFCClF_2$	CH_3OH	73.0	51.9	739	1.3501	1.3432	10
$CClF_2CClFCClF_2$	C_2H_5OH	73.7	61.6	756	1.3501	1.3514	20
$CF_2=CClCClF_2$	C_2H_5OH	43.9	41.3	739	1.3484	1.3492	6
$CClFCClFCF_2CF_2$	CH_3OH	59.2	45.4	745	1.3342	1.3320	
$CClFCClFCF_2CF_2$	C_2H_5OH	59.0	51.5	739	1.3342	....	6
$CBrFCBrFCF_2CF_2$	C_2H_5OH	132.6	73.0	745	1.3884	....	
$CF=CFCF_2CF_2$	C_2H_5OH	0.2	0.1	739	....	....	<1
$CBrF_2CBrF_2$	CH_3OH	46.3	39.8	735	1.3702	1.3662	

[a] B.p. t_c adjusted to barometric pressure p_0 at which azeotrope b.p. was taken by use of equation $t_c = t_0 + 0.043(p_0 - p_0)$ where t_0 is observed b.p. of pure compound at pressure p_0.[6] [b] Observed value.

It would appear that azeotrope formation between halogenated compounds and alcohols is a general phenomenon. It has proved to be very useful in the recovery of high-boiling products, since it eliminates having to work up the residue.

For compounds boiling below room temperature, the alcohol was removed by treatment with P_2O_3 and fractional distillation therefrom. Compounds boiling above room temperature were extracted with ice-water, treated with P_2O_5, filtered and fractionally distilled. Distillation from P_2O_5 is not recommended for compounds boiling higher than about 70°, because of decomposition of the products of the P_2O_5–alcohol reaction.

Allylic Fluorination.—Swarts[42] prepared $C_6H_5CCl_2F$ and $C_6H_5CClF_2$ by treating benzotrichloride with SbF_3 for

(36) Hanford and Rigby[23] in a patent claimed that ethers with the reverse orientation were also formed. However, they cited no experimental evidence for this. They did report that $CF_2=CClF$ and $CF_2=CHCl$ gave $CHClFCF_2OEt$ and CH_2ClCF_2OEt, respectively, and gave chemical evidence for the structure of the latter. Tarrant and Brown[30] cite the formation of both difluoro- and chlorofluoro- acetamides from $CF_2=CClF$ and amines "under certain conditions." These results appear to be in contrast to those of other workers (see above).

(37) J. D. Park, *et al.*, THIS JOURNAL, **74**, 4104 (1952).

(38) W. T. Miller, Jr., J. Fried and M. Gazi, *ibid.*, **79**, 4300 (1957).

(39) This effect also has been observed by T. Alfrey, Jr., H. B. Hass and C. W. Lewis, THIS JOURNAL, **73**, 2851 (1951).

(40) A. L. Henne and T. P. Waalkes, *ibid.*, **68**, 496 (1946).

(41) A. L. Henne and W. J. Zimmerschied, *ibid.*, **69**, 281 (1947).

(42) F. Swarts, *Bull. classe sci., Acad. roy. Belg.*, [3] **38**, I 414 (1900).

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periods of two weeks or more at room temperature. The method proved unsatisfactory for large-scale preparation, particularly of the monofluoride. In line with previous observation,[43] heating the mixture at atmospheric pressure gave only benzotrifluoride and the reaction was accompanied by much decomposition. However, it was found that rapid reaction between the SbF_3 and benzotrichloride sets in at 100–110°. This is too low a temperature to permit distillation at atmospheric pressure out of the reaction mixture of the intermediate fluorination products ($C_6H_5CClF_2$ boils at 140°, $C_6H_5CCl_2F$ at 180°). By lowering the pressure to 25–50 mm. so as to bring the boiling points of the intermediate fluorination products below the temperature at which reaction sets in, it was found possible to isolate either of the intermediates as the predominant product.

This technique was found to be equally effective in the isolation of the intermediate fluorination products of hexachloropropylene, and will very likely prove applicable to allylic fluorinations in general.

The fluorination products invariably carried over volatile antimony salts with them. These salts were difficult to remove quantitatively by the usual technique of washing with aqueous HCl, nor could they be separated by fractional distillation. It was found that they could be removed quantitatively by treatment of the material with a high-boiling organic base, such as quinoline. An insoluble complex was formed, which could be filtered off; the excess quinoline was then separated by fractional distillation.

Quantitative removal of the volatile antimony salts prior to distillation was found essential in the isolation of the intermediate fluorination products of benzotrichloride, for they were found to cause disproportionation[44,45] of these products to the trifluoride and trichloride. This reaction was also encountered with the intermediate fluorination products of hexachloropropylene.[47]

The formation of a cloudy solution or precipitate on the addition of one drop of quinoline to several ml. of a compound was found to constitute a sensitive test for the presence of antimony halides. Application of this test to other compounds prepared by fluorination with antimony salts revealed that all compounds so prepared boiling higher than 75–100° contained trace amounts of antimony salts. Such compounds were therefore given the quinoline treatment prior to distillation. It is suggested that the rather wide discrepancies between the densities of a number of compounds reported in this paper and those previously reported may be due to the presence of small amounts of antimony salts in the earlier preparations (densities previously reported are consistently higher).

Physical Properties and Analytical Data.—Physical properties were determined as described previously.[7,44] Densities of liquids boiling below room temperature were taken in sealed 10- or 25-ml. pycnometers.

Samples were decomposed for halide analysis by peroxide fusion in a Parr bomb.[48]

Experimental Results

Fluorination of $CCl_3CClFCCl_2F$ and $CCl_2FCClFCClF_2$.—These fluorinations were carried out by the method of Henne and Flanagan.[49] A steel lecture cylinder (Matheson Co.) was charged with 122 g. of HF, 173 g. of HgO (1.60 eq.) and 96 g. of $CCl_3CClFCClF_2$[50] (0.33 mole). The cylinder was sealed with a steel valve and heated to 175° for 40 hours with shaking. The reaction product was steam distilled from the cylinder into an aqueous solution of KOH, separated as the lower layer, dried over P_2O_5, and fractionally distilled to give 54 g. of $CClF_2CClFCClF_2$, b.p. 72–74° (0.23 mole, 70% yield), center cut Ia, b.p. 72.9° (738 mm.).

In a similar manner, 35 g. of $CCl_2FCClFCClF_2$[51] (0.14 mole), 93 g. of HF and 32 g. of HgO (0.30 eq.), held at 175° for 24 hours with shaking, gave 22 g. of $CClF_2CClFCClF_2$, b.p. 72.8–73.3° (0.093 mole, 65% yield); the center cut had physical properties virtually identical with those found for Ia.

In neither of the above runs was anything obtained boiling lower than 72°, thus further demonstrating the resistance of terminal $-CClF_2$ and internal $-CClF-$ groups in saturated perhalo compounds to further fluorination under the reaction conditions employed.[52]

Fluorination of $CCl_3CClFCCl_3$.—The fluorination of $CCl_3CClFCCl_3$ was carried out with SbF_3Cl_2, following the directions of Henne and Newby[4] as closely as possible. The fluorinating agent was prepared by condensing 44 g. of Cl_2 (0.62 mole) in a lecture cylinder containing 216 g. of SbF_3 (1.20 moles), sealing it, and warming to room temperature for 3 hours. By reaction of 160 g. of $CCl_3CClFCCl_3$[54] (0.53 mole) with this fluorinating agent there was obtained 109 g. of material, $n^{20}D$ 1.3489, the bulk of which distilled (from quinoline) at 70–73°. Physical properties of the purest cut, Ib, b.p. 72.7° (737 mm.), are listed in Table I.

Dechlorination of $CClF_2CClFCClF_2$.—In a typical run, 1188 g. of $CClF_2CClFCClF_2$ (5.0 moles, Ic)[55] was dechlorinated with 500 g. of 90% zinc dust in 1400 ml. of absolute ethanol to which 20 g. of $ZnCl_2$ had been added, to give 770 g. of an ethyl alcohol azeotrope (<1% EtOH) of $CF_2{=}CFCClF_2$, b.p. 5.6–6.3°, plateau at 6.3° (743 mm.) (91% conversion, 95% yield), plus 60 g. of material, b.p. 61.6° (756 mm.), shown to be the ethyl alcohol azeotrope of $CClF_2$-$CClFCClF_2$ (*ca.* 20% EtOH). Thus, drowning the latter in water, and treating with P_2O_5, followed by fractional distillation gave $CClF_2CClFCClF_2$, b.p. 73.1° (743 mm.), d^{20}_4 1.653, $n^{20}D$ 1.3505. Fractional distillation of the ethyl alcohol–$CF_2{=}CFCClF_2$ azeotrope from P_2O_5 gave IIb, b.p. 6.2° (732 mm.); mol. wt. calcd. 166.5, found 165.

The purest sample of $CF_2{=}CFCClF_2$ obtained, IIa, b.p. 6.5° (741 mm.), was prepared by dechlorination of Ia. It added bromine readily to give $CBrF_2CBrFCClF_2$ (III), b.p. 112.4° (744 mm.).

Reaction of $CF_2{=}CFCClF_2$ with SbF_3Cl_2.—The procedure of Henne and Newby[4] was followed as closely as possible. To a fluorinating agent prepared as described above from 82 g. of SbF_3 (0.61 mole) and 13 g. of Cl_2 (0.18 mole) in a lecture cylinder was added 102 g. of $CF_2{=}CFCClF_2$ (IIb, 0.61 mole). The cylinder was warmed, with shaking, to 95–105° for 21 hours, then 125–130° for 12 hours more. From the cylinder was distilled 98 g. of material, which gave, on fractional distillation, 6 g. of $CF_2{=}CFCF_3$ (VI), b.p. −30.7 to −29.6° (741 mm.) (0.04 mole, 7% yield), plus 64 g. of a C_3ClF_5, b.p. 5.5–7.7° (0.38 mole, 63% yield), center cut b.p. 7.4° (745 mm.), shown to be almost pure $CClF{=}CFCF_3$ (IV) by photochemical chlorination to CCl_2-$FCClFCF_3$ (Va), b.p. 71.1° (737 mm.). Physical properties of a somewhat less pure sample (judging by the respective cooling curves) of $CCl_2FCClFCF_3$ (Vb), b.p. 72.5–.9° (744 mm.), prepared[56] by the addition of F_2 to $CCl_2{=}CClCF_3$, are also listed in Table I for comparison.

Fluorination of $C_6H_5CCl_3$.—In a typical run in which the monofluoride was the desired product, 293 g. of $C_6H_5CCl_3$ (1.5 moles), held at 115–120°, was treated in several portions with 90 g. of SbF_3 (1.5 equiv.) at a pressure of 50 mm., the product being distilled out as formed. It was treated with 10 ml. of quinoline, filtered through charcoal, and fractionally distilled to give 1 g. of $C_6H_5CF_3$, b.p. 46.5–47.5° (100 mm.) (1% yield); 37 g. of $C_6H_5CClF_2$, b.p. 79–81° (100 mm.) (0.23 mole, 19% yield); 101 g. of $C_6H_5CCl_2F$, b.p. 108–113° (100 mm.) (0.56 mole, 46% yield); and 54 g. of $C_6H_5CCl_3$ (0.28 mole, 18% recovered).

The yield of difluoride was improved by using twice the above proportion of SbF_3 and operating at 25 mm.

(43) A. L. Henne, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 52.

(44) A. H. Fainberg, Ph.D. Thesis, Cornell University, 1950.

(45) This reaction was independently reported by Prober.[46]

(46) M. Prober, THIS JOURNAL, **76**, 4189 (1954).

(47) A similar reaction has been reported for $CCl{=}CClCF_2CCl_2CF_3$ by A. L. Henne and W. J. Zimmerschied, *ibid.*, **67**, 1235 (1945).

(48) Analyses were carried out by J. M. Howald.

(49) A. L. Henne and J. V. Flanagan, THIS JOURNAL, **65**, 2362 (1943).

(50) This compound was furnished by G. Gavlin, who prepared it by the addition of F_2 to $CCl_2{=}CClCCl_3$. Physical properties for this sample are listed elsewhere.[7]

(51) This compound was furnished by M. D. Hurwitz, who prepared it by addition of F_2 to $CCl_2{=}CClCCl_2F$.

(52) Similar results have also been obtained with perhalobutanes.[53]

(53) E. Rutner and W. T. Miller, Jr., unpublished work.

(54) The sample of $CCl_3CClFCCl_3$ used was prepared[7] by chlorination of $CH_3CClFCH_2Cl$.[7]

(55) From the addition of Cl_2 to the C_3ClF_5 fraction from the pyrolysis of $CClF{=}CF_2$.[2,3]

(56) M. Phelan and W. T. Miller, Jr., unpublished work.

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Refractionation of the above compounds gave center cuts $C_6H_5CF_3$ (VII), b.p. 100.9° (731 mm.); $C_6H_5CClF_2$ (VIII), b.p. 139.7° (739 mm.); $C_6H_5CCl_2F$ (IX), b.p. 94.5° (50 mm.); and $C_6H_5CCl_3$ (X), b.p. 146.9° (100 mm.).

Fluorination of CCl_2=$CClCCl_3$.—Fluorination of CCl_2=$CClCCl_3$ at atmospheric pressure has been reported.[5b] To increase the yields of the intermediate fluorination products, the reduced pressure technique was employed. In a 1-liter 3-neck flask fitted with stirrer, addition funnel, and wide bore take-off tube leading to an ice-cooled receiver was placed 720 g. of SbF_3 (4.0 moles). The reaction flask was immersed in an oil-bath at 200–230°, the pressure lowered to 150 mm., and 1245 g. (5.0 moles) of CCl_2=$CClCCl_3$, (XI), b.p. 141.4° (100 mm.) added over a half-hour period. The stirrer was started up as soon as possible, and a mixture of products distilled out at 100–130 mm. The crude mixture was extracted several times with 1:2 aq. HCl, treated with 20 ml. of quinoline, filtered through charcoal, and given a rapid preliminary fractional distillation at 30 mm. Under these conditions, the following yields were obtained. The variations in yield were determined by the rate of take-off, slower take-off favoring the more highly fluorinated products.

Run	Recovered CCl_2=$CClCCl_3$, %	Yield, % CCl_2=$CClCCl_2F$	Yield, % CCl_2=$CClCClF_2$	Yield, % CCl_2=$CClCF_3$
1	6	15	62	7
2	6	39	51	5
3	18	62	29	3
4	34	79	15	1

Refractionation gave the following center cuts: CCl_2=$CClCCl_2F$ (XII), b.p. 169.2° (735 mm.); CCl_2=CCl-$CClF_2$ (XIII), b.p. 127.1° (738 mm.); and CCl_2=$CClCF_3$ (XIV), b.p. 87.4° (730 mm.).

Preparation of CF_2=$CClCClF_2$.—Dechlorination[5b] of $ClF_2CCl_2CClF_2$ (XVa)[7] with zinc dust in ethanol gave CF_2=$CClCClF_2$ (XVI), b.p. 43.8° (747 mm.), in 90% yield. The cooling curve for the olefin had a freezing point depression of <0.1°, in contrast to the much larger depression of 1.7° found for its precursor XVa, which had been prepared by fluorination of $CCl_3CCl_2CClF_2$.[7] However, photochemical addition of Cl_2 to XVI gave a ClF_2CCl_2-$CClF_2$ (XVb), b.p. 111.7° (747 mm.), which had a f.p. depression of 1.5°. Apparently XVa contained a small amount of a dechlorinatable impurity capable of depressing its freezing point, but which, on dechlorination, gave an olefinic impurity in the CF_2=$CClCClF_2$ which formed a solid solution with the latter.

Photochemical addition of Br_2 to XVI gave $CBrF_2$-$CBrClCClF_2$ (XVII) for which a satisfactory cooling curve could not be obtained.

Action of Sodium Iodide in Acetone on CF_2=$CFCClF_2$.—In a typical reaction, 1250 g. of CF_2=$CFCClF_2$ (IIb, 7.5 moles) was treated with 1366 g. of NaI (9.1 moles) in 3500 ml. of anhydrous acetone (prepared by refluxing reagent grade acetone over Drierite, and fractionally distilling therefrom). Reaction occurred at room temperature as evidenced by the precipitation of NaCl (of greater than 98% purity in the early stage of reaction). After ten days at room temperature, the remaining low-boiling material was rapidly distilled off, and the product was worked up by drowning the reaction mixture, in five times its volume of water, washing with several portions of iced dilute aqueous $NaHSO_3$ to remove iodine and acetone, drying over P_2O_5, filtering and fractionally distilling. In this way was obtained 324 g. of recovered C_3ClF_5, b.p. 5.3–6.3° (737 mm.); 1150 g. of CF_2=$CFCF_2I$, b.p. 53.0–53.6° (738 mm.) (4.5 moles, 60% conversion); and 30 g. of higher boiling material, discussed further below. Refractionation of the CF_2=$CFCF_2I$ gave a center cut XVIII, b.p. 53.6° (734 mm.).

Anal. Calcd. for C_3F_5I: I, 49.2; mol. wt., 258. Found: I, 49.2; mol. wt., 264.

Boiling point, molecular weight, iodine analysis, unsaturation to $KMnO_4$ in acetone, and molar refraction support the molecular formula C_3F_5I. The structural formula proposed is consistent with substitution of chlorine in CF_2=$CFCClF_2$ by iodine with or without allylic rearrangement; any other structure would involve rearrangement of carbon–fluorine bonds, which is considered highly unlikely under the conditions of the reaction. In further support of the allylic structure is the fact that a number of reactions[17] of the iodide regenerate, directly or indirectly, the known CF_2=$CFCClF_2$ and $ClF_2CClFCClF_2$.

In another run, using the same quantity of reagents, the reaction was carried out by holding the mixture at reflux. The temperature of the reaction mixture rose asymptotically from 20 to 47° in five days, and remained at 47° for the next five days. In this way, 1250 g. of CF_2=$CFCClF_2$ (7.5 moles, b.p. 6.8° (755 mm.), b. range 0.1°, f.p. −144.2°, f.p. dep. 2°, obtained from dechlorination of Ic) gave 120 g. of C_3ClF_5, b.p. 6.6–7.1° (center cut b.p. 6.6° (743 mm.), b. range <0.1°, f.p. −151°, f.p. dep. very large), plus 980 g. (3.8 moles, 51% conversion) of CF_2=$CFCF_2I$, b.p. 52–54° (center cut b.p. 53.8° (739 mm.), f.p. −130.6°, f.p. dep. 0.2°), plus smaller amounts of several higher boiling by-products which appear to have been formed by substitution of fluorine by iodine. Among these were 55 g. of a compound, b.p. 93–98°, center cut, b.p. 97.5° (744 mm.), b. range 0.1°, d^{20}_4 2.1270, $n^{20}D$ 1.4010; and 200 g. of another compound, b.p. 70.6° (50 mm.), b. range 0.1°, f.p. −43.6°, f.p. dep. 0.1°, d^{20}_4 2.1691, $n^{20}D$ 1.4811. In addition, a small amount of a compound b.p. −30° was obtained. Further work on these by-products is in progress.

A portion of the recovered C_3ClF_5 fraction was treated with NaI in acetone, and found to react further, thus demonstrating the presence of CF_2=$CFCClF_2$. However, evidence that at least one other C_3ClF_5 isomer also was present was furnished not only by the physical properties of the material itself, but also by addition of chlorine to another portion of the material to give a $C_3Cl_3F_5$, b.p. 71.5–72.0° (739 mm.), d^{20}_4 1.6606–1.6609, $n^{20}D$ 1.3512–1.3517. It is believed that the impurity resulted from a concentration of impurity originally present in the starting material, rather than rearrangement of the allyl chloride.

Action of Sodium Iodide in Acetone on CF_2=$CClCClF_2$.—To a solution of 825 g. of NaI (5.50 moles) in 2000 ml. of anhydrous acetone at 22° was added 905 g. of CF_2=CCl-$CClF_2$ (XVI, 4.94 moles). Reaction occurred at a considerably faster rate than for CF_2=$CFCClF_2$; in half an hour the temperature rose to 32°, then started falling. After 45 hours at room temperature, the reaction product was drowned in water and worked up as described above for CF_2=$CFCF_2I$ to give 160 g. (0.87 mole, 18%) of recovered CF_2=$CClCClF_2$, b.p. 35–45°, center cut b.p. 43.6° (740 mm.), b. range <0.1°, f.p. −120.8°, f.p. dep. 0.1°, d^{20}_4 1.5398, $n^{20}D$ 1.3483; and 950 g. of CF_2=$CClCF_2I$, b.p. 37–38° (100 mm.), center cut XIX, b.p. 37.5° (100 mm.), 91.4° (737 mm.) (3.5 moles, 70% conversion, 85% yield.)

Anal. Calcd. for C_3ClF_4I: Cl, 12.9; I, 46.3; mol. wt., 274.5. Found: Cl, 12.8; I, 46.4; mol. wt., 274.

Compounds Unreactive to Sodium Iodide in Acetone.—Each of the following compounds was treated with an equivalent amount of sodium iodide in anhydrous acetone at reflux temperature for periods of 24 to 150 hours: Cl_2=$CClCClF_2$, $CClF$=$CFCClF_2$,[57] $C_6H_5CClF_2$ and $CClF_2$-$CClFCClF_2$. No precipitate formation was observed for any of these compounds, a very sensitive sign of reaction, and they were recovered unchanged in substantially quantitative amounts.

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(57) Isolated from the thermal reaction of $CClF$=CF_2.[3,8]

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[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

Preferential Replacement Reactions of Highly Fluorinated Alkyl Halides. II.[1] Some Reactions of Fluorinated Allyl Iodides[2,3]

BY ARNOLD H. FAINBERG AND WILLIAM T. MILLER, JR.

RECEIVED MARCH 12, 1957

The preferential replacement of iodine in 3-iodopentafluoropropene and in 2-chloro-3-iodotetrafluoropropene by reaction with chlorine and bromine and with chloride and bromide ions is described. Ionic and free radical type reaction mechanisms which involve initial reagent attack at the double bond rather than at the allylic carbon atom are proposed for these reactions. The reactions with halide ion are shown to be reversible. Treatment of the above compounds with metallic zinc results in the replacement of iodine by hydrogen or in the formation of dimeric products with elimination of iodine. The dimerization reaction furnishes a method for the preparation of perfluoro and other highly halogenated 1,5-hexadienes. Perfluoro-1,5-hexadiene on heating undergoes an unusual isomerization to form a saturated compound which is formulated as perfluorobicyclo[2,2,0]hexane.

Introduction

The fluorinated allyl iodides are highly reactive materials which have been found to be versatile intermediates for the preparation of a variety of fluorinated compounds. Illustrative reactions of 3-iodopentafluoropropene and 2-chloro-3-iodotetrafluoropropene are described below. The clean-cut character of the reactions of these compounds, which do not contain hydrogen, is particularly noteworthy. In most cases products of high purity are isolated readily in high yields, without formation of tars and intractable residues. Table I lists

TABLE I

PHYSICAL PROPERTIES OF COMPOUNDS[a]

No.	Compound	B.p., 760 mm.,[b] °C.	B. range,[c] °C.	F.p., °C.	F.p. dep.,[d] °C.	$n^{20}D$	d^{20}_4	$MR^{20}D$ Found[e]	$MR^{20}D$ Calcd.[f]
Ia	$CF_2=CFCBrF_2$	26.5	<0.1	Glass at −165	..	1.3322	1.812	23.89	23.9
Ib	$CF_2=CFCBrF_2$	26.5	< .05	Glass at −160	..	1.3320	1.8139	23.86	
II	$CF_2=CClCBrF_2$	64.5	< .1	105.0	0.3	1.3829	1.8735	28.31	28.3
III	$CBrF_2CBrClCBrF_2$	87.0 (50)	.2	−54.5	< .1	1.4719	2.4955	43.44	43.43
IV	$CBrF_2CBrFCBrF_2$	133.6	< .2	−99.9	< .2	1.4284	2.4570	38.86	38.91
Va	$CClF_2CClFCClF_2$[g]	73.8	< .1	{"α" −141.5; "β" −134.7}	< .1	1.3502	1.6540	30.90	30.97
Vb	$CClF_2CClFCClF_2$	73.7	.1	{"α" −141.4; "β" −134.8}	< .2	1.3501	1.6546	30.88	
VI	$CClF_2CClFCBrF_2$	93.2	< .1	−134.8	.2	1.3768	1.9294	33.59	33.69
VII	$CBrF_2CClFCBrF_2$	113.1	< .1	−106.2	.2	1.4026	2.1903	36.32	36.41
VIII	$CF_2=CFCHF_2$	1.8	< .1	−101.2	< .1	....	1.4607[h]		
IX	$CBrF_2CBrFCHF_2$	95.9	.2	−98.2	.8	1.3898	2.2004	31.43	31.3[l]
X	$CClF_2CClFCHF_2$[i]	56.3	< .1	−91.1	.2	1.3295	1.5886	26.03	26.1[l]
XI	$C_2H_5OCOCH_2COOC_2H_5$[j]	134.4 (100)	< .2	−52.3	.4	1.4139	1.0534	37.99	
XII	$CF_2=CFCF_2CH_2CF=CF_2$	59.6	< .1	−70.0	< .1	1.296	1.6090	30.08	30.1
XIII	$CClF_2CClFCH_2CF_2CClFCClF_2$	89 (50)	1	.....	..	1.3683	1.8132	50.18	50.21
XIVa	$(C_2H_5OCOCF_2-)_2$[k]	96 (20)	.4	−48.4	.2	1.3670	1.2794	43.20	42.9[m]
XIVb	$(C_2H_5OCOCF_2-)_2$[k]	95 (20)	< .2	−47.9	< .1	1.3670	1.2773	43.27	42.9[m]
XV	$CF_2-CF_2-CF_2$ / $CF_2-CF_2-CF_2$	43.8		41					
XVI	$CF_2=CClCF_2CF_2CCl=CF_2$	113.9	< .2	−34.1	.3	1.3613	1.6789	38.9	38.90

[a] Compounds V, X, XI and XIV have been reported previously. [b] Computed from the observed boiling point t_0 at pressure p_0 (given in the Experimental section) with the equation $t_{760} = t_0 + 0.043(760 - p_0)$.[4,6] [c] The boiling range of the center cut on which all other physical properties were taken. [d] The freezing point depression with the material half frozen.[5,6] [e] MR found $= (n^2 - 1)M/(n^2 + 2)d$. [f] Calculated from the atomic and group increments proposed elsewhere.[6] These increments were based in part on the data of Table I. [g] Previously reported[1] b.p. 73.9° (760 mm.), f.p. "α" −141.3°, "β" −135.0°, f.p. dep. <0.1°, $n^{20}D$ 1.3501, d^{20}_4 1.6541. [h] At 0.0°. [i] Previously reported b.p. 56.0°, $n^{20}D$ 1.3288, "may contain $CHClFCClFCF_3$."[7] [j] Reported b.p. 198.9° (760 mm.),[8] f.p. −49.9°,[8] $n^{20}D$ 1.4142,[9] d^{20}_4 1.0554,[9] $MR^{20}D$ 37.94. [k] Reported[10] b.p. 89° (15 mm.), $n^{20}D$ 1.3690, $n^{23.2}D$ 1.3642,[11] d^{20}_4 1.2640, $MR^{20}D$ 43.94. [l] Using a tentative value for $AR^{20}D$ H of 1.0. [m] Calculated for $MR^{20}D$ 42.39 for diethyl succinate,[12] by subtracting 4H and adding 4F (H = 1.029, F = 1.165).[6]

(1) Preceding paper in this series, W. T. Miller, Jr., and Arnold H. Fainberg, THIS JOURNAL, 79, 4164 (1957).

(2) Presented at the 120th Meeting of the American Chemical Society, New York, N. Y., Sept., 1951, Abstracts of Papers, p. 7-K.

(3) This work has been supported by the Office of Naval Research and by a grant-in-aid made by E. I. du Pont de Nemours and Co. to the Department of Chemistry, Cornell University.

(4) N. A. Lange, "Handbook of Chemistry," 3rd ed., Handbook Publishers, Inc., Sandusky, Ohio, 1939.

(5) Essentially as described by A. R. Glasgow, A. J. Streiff and F. D. Rossini, *J. Research Nat. Bur. Standards*, **35**, 355 (1945); A. H. Fainberg, Ph.D. Thesis, Cornell University, 1950.

(6) A. H. Fainberg and W. T. Miller, Jr., forthcoming publication.

(7) M. Hauptschein and L. A. Bigelow, THIS JOURNAL, **73**, 1428 (1951).

(8) J. Timmermans, *Bull. soc. chim. Belg.*, **25**, 300 (1911).

(9) C. Contzen-Crowet, *ibid.*, **35**, 165 (1926).

(10) A. L. Henne and W. J. Zimmerschied, THIS JOURNAL, **69**, 281 (1947).

(11) M. Hauptschein, C. S. Stokes and A. V. Grosse, *ibid.*, **74**, 1976 (1952).

(12) K. Auwers and W. S. Walls, *ibid.*, **53**, 527 (1931).

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the physical properties of the compounds involved, most of which are new.

Reactions with Halide Ions.—In the preceding paper in this series was described the preparation of the allylic iodides 3-iodopentafluoropropene and 2-chloro-3-iodotetrafluoropropene by treatment of the corresponding fluorinated allyl chlorides with sodium iodide in acetone. The consistent recovery of unreacted allyl chloride in the earlier work suggested that an equilibrium reaction is involved, equation 1, which is displaced toward the formation

$$NaI + CF_2{=}CXCClF_2 \xrightarrow[\text{acetone}]{\text{anhydrous}} ICF_2CX{=}CF_2 + NaCl\downarrow \quad (1)$$

of allyl iodide by virtue of the extremely low solubility of the sodium chloride in the anhydrous acetone.

This equilibrium has been confirmed in the present work. Thus, treatment of perfluoroallyl iodide with sodium chloride in anhydrous acetone gave perfluoroallyl chloride under conditions in which the more volatile chloride was progressively distilled out of the reaction mixture. Furthermore, the rate of formation of the allyl chloride was increased markedly by the addition of water to the acetone; the water increases the solubility of the sodium chloride in the solvent.

In addition, it was shown that the allyl chloride is thermodynamically favored over the bromide. The allyl bromide reacted under equilibrium conditions with lithium chloride in anhydrous acetone, equation 2, to give perfluoroallyl chloride in high yield. Substantially complete reaction occurred

$$Cl^- + CF_2{=}CFCBrF_2 \rightleftharpoons CClF_2CF{=}CF_2 + Br^- \quad (2)$$

in less than five minutes at 0°. Likewise, treatment of the allyl iodide with lithium bromide in acetone, equation 3, gave a 90% yield of 3-bromopentafluoropropene of high purity.

$$Br^- + CF_2{=}CFCF_2I \rightleftarrows CBrF_2CF{=}CF_2\uparrow + I^- \quad (3)$$

All of the above reactions are postulated to proceed *via* an S$_N$2′ mechanism,[1] equation 4. This

$$Y^- + CF_2{=}CFCF_2X \rightleftharpoons [Y\cdots CF_2\cdots CF\cdots CF_2\cdots X]^- \rightleftharpoons YCF_2CF{=}CF_2 + X^- \quad (4)$$

mechanism involves rate-controlling attack by halide ion Y^- on the terminal vinyl carbon atom, with allylic shift and elimination of halide ion X^-. It is striking that such usually mild nucleophiles as chloride and bromide ion are so effective in these reactions with fluoroallyl halides.

Reactions with Elemental Bromine and Chlorine.—3-Iodopentafluoropropene and 2-chloro-3-iodotetrafluoropropene reacted rapidly with bromine in the dark at room temperature to yield the corresponding allyl bromides almost quantitatively. Similarly, perfluoroallyl iodide reacted with chlorine in diffuse light to give the allyl chloride in high yield. In none of the above reactions was any trace of saturated compounds produced.

Heptafluoropropyl iodide does not react with bromine under the same conditions.[13] This result supports the view that the allyl iodides are attacked by the halogen, not at the allylic carbon atom, but at the terminal vinyl carbon atom, a reaction path analogous to that proposed for the reactions with halide ions (4). Inasmuch as some free iodine was always present at the start of these reactions, due to the instability of the allyl iodides, it is considered likely that reaction proceeds largely *via* the inter-halogen compounds, by an S$_N$2′ type of mechanism as shown in equations 5 and 6. A cyclic transition state may be involved which

$$X_2 + I_2 \longrightarrow 2IX \quad (5)$$

$$I^{\delta+}{-}X^{\delta-} + CF_2{=}CX'CF_2I \longrightarrow CF_2XCX'{=}CF_2 + I_2 \quad (6)$$

yields an iodine molecule directly.[14]

Perfluoroallyl bromide did not appear to undergo a dark reaction with chlorine corresponding to that obtained with the allyl iodide. However, photochemical chlorination gave appreciable amounts of at least three other perhalopropanes, in addition to the expected chlorine adduct; see Table II.

TABLE II

PRODUCTS OF THE PHOTOCHEMICAL CHLORINATION OF $CF_2{=}CFCBrF_2$

Compound	Yield, %
$CClF_2CClFCClF_2$	22
$CBrF_2CClFCClF_2$	52
$CBrF_2CBrFCClF_2$	7
$CBrF_2CClFCBrF_2$	14
($CBrF_2CBrFCBrF_2$)	*ca.* 1
Total	96

These products clearly establish that a large amount of carbon–bromine bond cleavage took place, with the formation of bromine atoms. The reaction may well represent the free radical counterpart of the dark reaction of chlorine with perfluoroallyl iodide, as shown in equations 7, 8 and 9.

$$Cl_2 + h\nu \longrightarrow 2Cl\cdot \quad (7)$$

$$Cl\cdot + CF_2{=}CFCBrF_2 \longrightarrow CClF_2\dot{C}FCBrF_2 \quad (8)$$

$$CClF_2\dot{C}FCBrF_2 \longrightarrow CClF_2CF{=}CF_2 + Br\cdot, \text{ etc.} \quad (9)$$

Reactions with Zinc.—Perfluoroallyl iodide, on treatment with zinc dust in methanol, reaction 10, gave the reduction product

$$CF_2{=}CFCF_2I + Zn + MeOH \longrightarrow CF_2{=}CFCHF_2 + Zn(OMe)_2 \quad (10)$$

1,1,2,3,3-pentafluoropropene in high yield. This latter compound added chlorine and bromine readily at low temperatures in the presence of light with no evidence of hydrogen substitution. It was necessary to raise the temperature *ca.* 40° in order to further chlorinate the $CClF_2CClFCHF_2$ to the known trichloride. This sequence of reactions thus constitutes a proof of structure for the initial reduction product and its halogen adducts.

In anhydrous dioxane, the perfluoroallyl iodide reacted with zinc dust to give a good yield of the coupled product, decafluoro-1,5-hexadiene. This diene added two moles of chlorine to give a saturated tetrachloride. The 1,5-positions of the double bonds was proved by oxidation of the diene

(13) A. H. Fainberg and W. T. Miller, Jr., unpublished work.

(14) The relationship of entering and departing groups has been shown to be *cis* for S$_N$2′ reactions of some cyclohexene derivatives; G. Stork and W. N. White, THIS JOURNAL, **75**, 4119 (1953); **78**, 4699 (1956).

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to tetrafluorosuccinic acid, isolated as the diethyl ester; see Table I.

Thermal reaction of the diene resulted in the formation of a remarkable isomeric compound, m.p. 41°, boiling only 3° higher, for which the structure decafluorobicyclo[2.2.0]hexane, CF_2–CF–CF_2 / CF_2–CF–CF_2, is proposed. The application of this new ring closure reaction to longer chain terminally unsaturated dienes is under investigation.

Experimental Results

Physical Properties.—Physical properties were determined as previously described.[1,6] Structure assignments were tested in all cases by correlation of physical properties and MR_D in addition to the other evidence cited.

Apparatus.—Unless otherwise indicated, all reactions were carried out in a three-neck round-bottom flask fitted with an all-glass stirrer, thermometer, addition funnel, and a 25 cm. × 1.5 cm. i.d. glass helix packed column surmounted by a water-cooled variable take-off head connected to a receiver and traps cooled in ice and in Dry Ice.

CF_2=$CFCF_2I$ + NaCl in Acetone.—Redistilled CF_2=$CFCF_2I$,[1] 129 g., was added to a suspension of 58 g. of NaCl in 500 ml. of anhydrous acetone and the mixture heated to reflux with stirring for ten days. Slow but continuous evolution of CF_2=$CFCF_2Cl$ occurred to yield a total of 23 g., b.p. 5–9°, center cut b.p. 6.2° (738 mm.), f.p. −141°; previously reported[1] b.p. 7.3° (760 mm.), f.p. −139.8°. In another run, the addition of 1% by wt. H_2O, which increases the solubility of NaCl in acetone by a factor of 10, speeded up the rate of formation of the CF_2=$CFCClF_2$ by a factor of more than 3.

CF_2=$CFCF_2I$ + LiBr in Acetone.—To a well-stirred solution of 104 g. of LiBr (1.2 moles) in 800 ml. of anhydrous acetone at 20° was added, over a ten-minute period, 258 g. of CF_2=$CFCF_2I$ (1.0 mole), which had been cooled to 0°. The temperature rose to 27° during mixing. The reaction mixture was heated to reflux and 204 g. of material, b.p. 27–28°, distilled out during seven hours (180 g. during three hours). Redistillation of the volatile product from 7 g. of P_2O_5 yielded 190 g., 90%, of CF_2=$CFCBrF_2$, b.p. 25.5–25.7°, center cut Ia, b.p. 25.5° (738 mm.).

CF_2=$CFCBrF_2$.—Compound Ia contained bromine, was unsaturated to $KMnO_4$ in acetone, and added one mole of bromine to give a saturated tribromide. The same compound was obtained from the action of bromine on the perfluoroallyl iodide, see below. Molecular weight, molar refraction and boiling point support the molecular formula C_3BrF_5. The allylic position of the bromine was demonstrated by the ready interconvertibility of the compound with the known allyl chloride and iodide.

CF_2=$CFCBrF_2$ + LiCl in Acetone.—To 400 ml. of anhydrous acetone in a 500-ml. Pyrex bottle was added 25.4 g. of LiCl (0.60 mole, a 20% excess). The mixture was equilibrated at 0°, thus giving a saturated solution in which *ca.* 20 g. of LiCl was present as a solid phase.[15] To this mixture was added 105.5 g. of CF_2=$CFCBrF_2$ (0.50 mole), also at 0°. The bottle was tightly stoppered and shaken vigorously. Within five minutes, almost all of the solid phase had gone into solution, about 1 g. of LiCl remaining undissolved. There was no further change during the next three hours. The solution was poured on cracked ice in a separatory funnel with some loss of volatile product. The lower layer was fractionally distilled to give 65 g., 80%, of CF_2=$CFCClF_2$, b.p. 6.3° (739 mm.), f.p. −141°. No trace of unreacted starting material, b.p. 25°, was found.

CF_2=$CFCBrF_2$ and CF_2=$CClCBrF_2$ + NaI in Acetone.—In a qualitative test, CF_2=$CFCBrF_2$ was found to react readily with 10% NaI in anhydrous acetone, a heavy precipitate of NaBr forming in one minute at room temperature. Under the same conditions, CF_2=$CClCBrF_2$ gave a precipitate instantaneously.

CF_2=$CFCF_2I$ + Br_2.—To 985 g. of CF_2=$CFCF_2I$ (3.8 moles) in a one-liter reaction flask at room temperature in the dark was added, with stirring, 400 g. of bromine (2.5 moles) during one hour. Characteristic sharp cracking sounds were produced during the reaction and sufficient heat of reaction was developed to distil about a quarter of the product, b.p. 25 to 30°, out of the reaction flask. The flask then was warmed gently to drive over the rest of the product, leaving free iodine behind. The volatile product was washed with iced aqueous KOH and fractionally distilled to give 730 g., 90% conversion, 95% yield, of CF_2=$CFCBrF_2$, b.p. 25.8–25.9°, center cut Ib, b.p. 25.9° (745 mm.); mol. wt. calcd. 211, found 214. Fifty grams, 5%, of unreacted CF_2=$CFCF_2I$, b.p. 55°, was recovered. No material boiling higher than 55° was found.

CF_2=$CClCF_2I$ + Br_2.—To 147 g. of CF_2=$CClF_2I$[1] (0.53 mole) in a 200-ml. flask in the dark was slowly added 50 g. of Br_2 (0.30 mole). As with the CF_2=$CFCF_2I$, sharp cracking sounds were produced during the addition. The evolution of a large amount of heat necessitated cooling in an ice-bath; most of the reaction was carried out at 30–35°. The reaction mixture, almost solid at this point, was treated with dilute aqueous KOH. The lower layer was separated and fractionally distilled to give 5% of recovered starting material and 100 g., 82% conversion, 87% yield, of CF_2=$CClCBrF_2$, b.p. 63.0–63.5°, center cut II, b.p. 63.5° (736 mm.); mol. wt. calcd. 227.5, found 231.5.

The CF_2=$CClCBrF_2$ added one mole of bromine slowly at room temperature, with illumination furnished by a 100 w. lamp, to give $CBrF_2CBrClCBrF_2$ (III), b.p. 86.9–87.1° (50 mm.).

CF_2=$CClCBrF_2$ and $CBrF_2CBrClCBrF_2$.—The olefin II contained fluorine, chlorine and bromine, but no iodine. Its molecular formula C_3BrClF_4 is supported by its molecular weight, molar refractivity and boiling point as well as by the molar refractivity of its bromine adduct III. Any structures other than CF_2=$CClCBrF_2$ for II and $CBrF_2CBrClCBrF_2$ for III would necessitate postulating rearrangements for which no analogous cases exist.

CF_2=$CFCF_2I$ + Cl_2.—A solution of 108 g. of CF_2=$CFCF_2I$ (0.42 mole) in 200 g. of CCl_2FCClF_2 was placed in a 500-ml. three-neck flask fitted with gas inlet tube, thermometer and Dry Ice-cooled reflux condenser connected to an ice-cooled and a Dry Ice-cooled trap. Chlorine was passed into the solution rapidly in diffuse room light (no light directly on flask). After about four minutes during which the initial purple iodine color was bleached, the liquid became opaque black and evolved sufficient heat to raise the temperature from 30 to 45°. A low-boiling liquid (CF_2=$CFCClF_2$, b.p. +7°) started refluxing back into the flask. The temperature of the reaction mixture fell slowly with the continued rapid addition of chlorine, as the low boiling product built up, and a large amount of free iodine crystallized out of solution. Finally, the solid iodine liquefied rather suddenly (ICl formed), and the chlorine input was stopped. The reaction flask was warmed on a water-bath to distil out material boiling up to the boiling point of the solvent CCl_2FCClF_2 (47°). The product, a clear, light amber colored liquid was shaken with a small amount of mercury to remove traces of free halogen and fractionally distilled to give 58 g. of CF_2=$CFCClF_2$, b.p. 6–8° (85% yield), center cut b.p. 6.3° (739 mm.), f.p. −141°.

CF_2=$CFCBrF_2$ + Br_2.—The CF_2=$CFCBrF_2$ (Ib) added bromine initially rather slowly at its reflux temperature with illumination furnished by a 100-w. incandescent lamp, the bromine being only sparingly soluble in the olefin. The rate of reaction increased rapidly as the product built up, and the reflux temperature rose. The product, obtained in substantially quantitative yield, was the expected tribromide $CBrF_2CBrFCBrF_2$ (IV), b.p. 132.4° (733 mm.); mol. wt. calcd. 371, found 365; Br calcd. 64.7, found 65.0, 64.9.[17]

CF_2=$CFCBrF_2$ + Cl_2.—The CF_2=$CFCBrF_2$ did not appear to react with chlorine at room temperature in diffuse light. It did, however, react rapidly with chlorine when illuminated with 2–15 w. G.E. 360 BL ultraviolet fluorescent lamps. The chlorination product from 422 g. of CF_2=$CFCBrF_2$ (Ib, 2.00 moles) was let stand overnight with dissolved chlorine and illumination. After washing to remove excess chlorine, distillation yielded: 54 g., 13%, of recovered CF_2=$CFCBrF_2$, b.p. 19–25°,

(15) The solubility of LiCl in acetone at 0° is 1.73 g./100 g. of acetone.[16]

(16) W. R. G. Bell, *J. Chem. Soc.*, 1927 (1930).

(17) Analyses for halogen were carried out by J. M. Howald.

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b.p. plateau 25.5° (734 mm.); 91 g., 22% yield, of $CClF_2$-$CClFCClF_2$, b.p. 72–74°, center cut Va, b.p. 73.1° (743 mm.); 257 g., 52% yield, of $CBrF_2CClFCClF_2$, see below, b.p. 91–93°, center cut VI, b.p. 92.7° (749 mm.); 120 g., 21% yield, of $C_3Br_2ClF_5$'s, b.p. 111–112°, see below, center cut, b.p. 111.9° (732 mm.); and about 1% higher b.p. material, possibly $CBrF_2CBrFCBrF_2$.

$CBrF_2CClFCClF_2$.—Fraction VI above was shown to have the molecular formula $C_3BrCl_2F_5$. Its cooling curve indicated a single substance. These observations supported the conclusion that it was the expected chlorine adduct $CClF_2CClFCBrF_2$. In addition, VI was found not to react with sodium iodide in acetone. Other work[13] has shown that bromine in terminal $-CBrF_2$ groups is inert toward iodide ion in acetone while internal $-CBrF-$ is readily attacked.

$CBrF_2CBrFCClF_2$ and $CBrF_2CClFCBrF_2$.—The fraction of b.p. 112° formed by chlorination of $CF_2=CFCBrF_2$ was saturated to permanganate in acetone and contained bromine, chlorine and fluorine. It had the following physical properties: b.p. 113.1° (760 mm.), b. range <0.1°, f.p. −115.8°, f.p. depression very large, $n^{20}D$ 1.4026, d^{20}_4 2.1935. The large freezing range showed that the fraction was a mixture of isomers. Its boiling point supports the molecular formula $C_3Br_2ClF_5$. Excluding rearrangement of carbon–fluorine bonds the components of the mixture could be only $CBrF_2CBrFCClF_2$ and $CBrF_2$-$CClFCBrF_2$. It was predicted, on the basis of observations made with other structures,[13] that while the 1,2-dibromide would react with NaI in acetone to give $CF_2=CFCF_2Cl$ plus free iodine the 1,3-dibromide would not react at all under the same conditions. Verification of this prediction, see below, led to the isolation of 1,3-dibromide (VII) in pure form.

The composition of the $C_3Br_2ClF_5$ fraction was thus shown to be about one-third $CBrF_2CBrFCClF_2$ and two-thirds $CBrF_2CClFCBrF_2$.

$CBrF_2CClFCBrF_2$. **Debromination of $CBrF_2CBrFCClF_2$ with NaI in Acetone.**—To a solution of 120 g. of NaI (0.80 mole) in 500 ml. of anhydrous acetone was added 116.5 g. (0.36 mole) of the $C_3Br_2ClF_5$ fraction, b.p. 112°, see above. The solution, initially clear, became cloudy within a minute and a white precipitate settled out on standing. After six days at room temperature, during which time a small amount of low boiling material appeared in the Dry Ice trap, the solution was drowned in ice-water. Titration of the solution with standard aqueous $Na_2S_2O_3$ showed 0.125 mole of free I_2 present. The organic layer was washed with iced aq. $NaHSO_3$ and fractionally distilled to give: 11 g. of material b.p. below room temperature, assumed to be $CF_2=CFCClF_2$, 18% yield; 9 g., 10%, $CF_2=CFCF_2I$, b.p. 51–53°, plateau 53.1° (732 mm.); 68 g., 59%, $CBrF_2CClFCBrF_2$, b.p. 110–112°, center cut VII, b.p. 112.0° (735 mm.), mol. wt. calcd. 326, found 319. The physical properties of $CBrF_2CBrFCClF_2$ differentiate it from $CBrF_2CClFCBrF_2$; previously reported for $CBrF_2$-$CBrFCClF_2$[1] b.p. 113.1° (760 mm.), f.p. −118.0°, $n^{20}D$ 1.4028, d^{20}_4 2.2016.

$CF_2=CFCF_2I$ + Zn in CH_3OH. $CF_2=CFCHF_2$.—To a well-stirred suspension of 120 g. of Zn dust in 700 ml. of anhydrous methyl alcohol in a one-liter flask at reflux was added slowly 194 g. of $CF_2=CFCF_2I$ (0.75 mole). Reaction started immediately, as evidenced by heat evolution, and material boiling from below room temperature up to the boiling point of the methyl alcohol was collected. Distillation of the product gave three fractions: A, b.p. 1.3° (749 mm.); B, b.p. 35.0° (749 mm.); C, b.p. 45° (746 mm.).

Fraction B was tentatively identified as the methyl alcohol azeotrope of $CF_2=CFCF_2OCH_3$, obtained in 0 to 16% conversion. It appeared to undergo decomposition with the evolution of acid fumes when distilled from P_2O_5, and was not treated further. Fraction C appeared to be the methyl alcohol azeotrope of unreacted $CF_2=CFCF_2I$; about 3% was so recovered.

Redistillation of fraction A from P_2O_5 gave $CF_2=CF$-CHF_2, center cut VIII, b.p. 1.2° (746 mm.); mol. wt. calcd. 132, found 133 (74% to 90% conversion).

The $CF_2=CFCHF_2$ added bromine rapidly with illumination at its boiling point to give $CBrF_2CBrFCHF_2$ (IX), b.p. 95.0–95.2° (741 mm.); mol. wt. calcd. 292, found 292; Br calcd. 54.8, found 55.0, 55.0.

Addition of 35 g. of Cl_2 (0.49 mole) to 73 g. of $CF_2=CFCHF_2$ (0.55 mole) with illumination at 0 to 10°, resulted in rapid reaction without evolution of HCl. Fractionation of the product gave 7 g., 10%, of recovered $CF_2=CFCHF_2$, b.p. below room temperature; and 96 g., 92% yield, of $CClF_2CClFCHF_2$, b.p. 52–55°, center cut X, b.p. 55.2° (735 mm.), mol. wt. calcd. 203, found 203. There was no sign of higher boiling material.

Chlorination of $CClF_2CClFCHF_2$ occurred slowly at 45 to 55°, to give in substantially quantitative yield $CClF_2$-$CClFCClF_2$ (Vb), b.p. 72.7° (736 mm.). The formation of this well characterized compound substantiated the structures of compounds VIII and X.

$CF_2=CClCF_2I$ + Zn in C_2H_5OH.—To a well-stirred suspension of 120 g. of zinc dust in 500 ml. of absolute ethyl alcohol at reflux was added, over a half-hour period, 274.5 g. of $CF_2=CClCF_2I$ (1.00 mole). Reaction occurred with sufficient heat evolution to require external cooling during the addition. A low-boiling fraction A, 41 g., slowly accumulated in the Dry Ice trap during the addition and for three hours thereafter. A second fraction B boiling from 40 to 77° was then distilled out of the reaction flask leaving a residue, fraction C, a thick slurry.

Fraction A was fractionally distilled from P_2O_5, with which it appeared to react, for only a trace of material boiling below room temperature was obtained, b.p. <17°. The bulk of the material, 32 g., 25% yield, as yet unidentified, b.p. 32.9–33.6° (745 mm.), center cut b.p. 33.4° (738 mm.), b. range <0.1°, f.p. −105°, f.p. dep. <1.3°, d^{20}_4 1.1980, $n^{20}D$ 1.3342, mol. wt. found 125, MR^{20}_D found 21.5, contained fluorine and chlorine, was unsaturated to $KMnO_4$ in acetone and burned with a smoky flame.

Fraction B, 40 g., was found to be an azeotropic mixture of ethyl alcohol and higher boiling products, all unsaturated to $KMnO_4$ in acetone. It was not treated further.

Fraction C, the residue, was dissolved in water, acidified with HCl, and extracted with benzene using a continuous liquid–liquid extractor. Fractional distillation of the benzene extract gave 60 g., 37% yield, of diethyl malonate, b.p. of center cut XI, 134.4° (100 mm.). The diethyl malonate, in which all that is left of the original perhaloolefin is the three carbon skeleton, may have arisen from hydrolysis of a diether $C_2H_5OCF_2CH_2CF_2OC_2H_5$. The latter would have been produced by a series of basic displacements and base-catalyzed additions accompanying reduction. These interesting reactions are under further investigation.

$CF_2=CFCF_2I$ + Zn **in Anhydrous Dioxane.** $CF_2=CFCF_2CF_2CF=CF_2$.—To a well-stirred suspension of 200 g. of Zn dust in 1500 ml. of anhydrous dioxane (refluxed with and fractionally distilled from Na) at reflux was slowly added 1032 g. of $CF_2=CFCF_2I$ (4.00 moles). Rather sudden heat evolution was observed after about one-third of the iodide was added. From this point on,[18] reaction proceeded smoothly. The reaction mixture was held slightly below reflux for several hours, after which material boiling from 52 to 100° was distilled out. The residue contained no water-insoluble material. Redistillation of the volatile product gave 4% of unreacted starting material and an 83% yield of $CF_2=CFCF_2CF_2CF=CF_2$, b.p. 57–59°, center cut XII, b.p. 58.4° (733 mm.), iodine-free; mol. wt. calcd. 262, found 264.

The 1,5-position of the two double bonds in XII was demonstrated by its oxidation, described below, to the known tetrafluorosuccinic acid.

Photochemical addition of chlorine to XII yielded $CClF_2$-$CClFCF_2CF_2CClFCClF_2$ (XIII), b.p. 89° (50 mm.); mol. wt. calcd. 404, found 405; Cl calcd. 35.1, found 34.8, 35.0.

Oxidation of $CF_2=CFCF_2CF_2CF=CF_2$.—To a well-stirred mixture of 274 g. of $KMnO_4$ (1.7 moles) and 358 g. of $NaHCO_3$[19] (4.3 moles) in 800 ml. of water cooled to 10°, in a 3-l. 3-neck r.b. flask fitted with a Dry Ice-cooled reflux condenser, was added 200 ml. of reagent grade acetone.[20]

(18) The induction period probably can be eliminated by the initial addition of some $ZnCl_2$ to the reaction mixture.

(19) The use of $NaHCO_3$ instead of NaOH or KOH with $KMnO_4$ for oxidation of perhaloölefins has been found generally advantageous in that degradation of the oxidation products is reduced, R. T. Carroll and W. L. Miller, Jr., unpublished work.

(20) On one occasion uncontrolled oxidation of the acetone occurred when the temperature was allowed to rise on mixing. However, no difficulty was encountered when the reaction mixture was kept below 20° after the acetone was added.

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To this mixture was added 141.5 g. of $CF_2=CFCF_2CF_2-CF=CF_2$ (0.5 mole) during about one hour with the temperature kept below 20°.[20] Stirring was continued for an additional three hours until the evolution of carbon dioxide ceased. The oxidation mixture was worked up by reducing with SO_2 until there was no further lightening in color, filtering the slurry, acidifying the filtrate with 120 ml. of concd. H_2SO_4, and distilling out material up to the boiling point of water, mostly CO_2, SO_2 and acetone. The residue was extracted with diethyl ether in a continuous liquid–liquid extractor. The ether was then removed and the residue treated with 300 ml. of absolute ethyl alcohol. The excess alcohol was distilled off at atmospheric pressure, and the product fractionally distilled to give 75 g., 60% yield, of $C_2H_5OCOCF_2CF_2COOC_2H_5$ (XIVa), b.p. 96° (20 mm.). The physical properties of this material differed substantially from those reported by Henne and Zimmerschied[10]; see Table I, footnote *k*. For this reason, another sample of $C_2H_5OCOCF_2CF_2COOC_2H_5$ was prepared from $\underbrace{CF=CFCF_2CF_2}$.[10]

Oxidation of $\overbrace{CF=CFCF_2CF_2}$.—The oxidation of this compound, b.p. 0.2° (740 mm.), was carried out at atmospheric pressure, and the diethyl ester of perfluorosuccinic acid isolated by the technique described above for the oxidation of XII. The olefin, 81 g. (0.50 mole), was distilled into the reaction flask containing 137 g. of $KMnO_4$, 179 g. of $NaHCO_3$, 200 ml. of acetone and 800 ml. of water. No external cooling was required, since the refluxing olefin kept the mixture below 12°. Most of the olefin had reacted in 9 hours. From the resulting mixture was obtained 85 g., 70% yield, of $C_2H_5OCOCF_2CF_2COOC_2H_5$ (X), center cut (XIVb) b.p. 95° (20 mm.). The physical properties of XIVb were substantially identical with those of XIVa; see Table I.

$CF_2—CF—CF_2$
| | |
$CF_2—CF—CF_2$

Thermal Reaction of $CF_2=CFCF_2CF_2-CF=CF_2$.—The diene XII was metered from a constant head dropping funnel into a copper coil vaporizer immersed in an oil-bath held at 100° and the vapor passed into a 45 cm. × 3.8 cm. i.d. electrically heated nickel reactor tube. A thermocouple well extended into the center of the reactor tube. The mixture of product and unreacted starting material was condensed by a water-cooled copper condenser with receiver connected to Dry Ice and liquid air-cooled traps. Before and after each run the system was swept out with dry nitrogen. The product, boiling 17° lower than the starting material, was separated readily by fractional distillation. In the first run, 0.84 mole of XII was passed through the tube at 350° with a contact time of two minutes to give less than 1% conversion to product; 97% of the starting material was recovered. In the second run, the temperature was raised to 450°; 0.62 mole of XII gave a 60% conversion to product and 37% of the starting material was recovered. In the third run, with the temperature at 450°, the contact time was increased to 6 minutes; 0.46 mole of XII gave a 70% conversion to product, and 27% of the starting material was recovered.

The product, compound XV, a solid melting at 41°, b.p. 42.6° (732 mm.), mol. wt. calcd. 262, found 262, was saturated to chlorine plus light and to $KMnO_4$ in acetone. It formed an azeotrope with CCl_4, b.p. 41.6° (737 mm.).

The structure proposed for this compound, perfluorobicyclo[2.2.0]hexane, is based on the following considerations. The formation of a single product from the diene XII with the same molecular weight and with more than 97% total weight recovery indicated that XV was formed from XII by thermal isomerization, a process which requires only an electronic rearrangement. The loss of two double bonds necessitates a bicyclo structure for XV. The relatively high freezing point and very small liquid range (about 3° at atmospheric pressure) suggest a high degree of symmetry. The marked ease of formation of four-membered rings by thermal reaction of a variety of olefins containing the terminal $CF_2=$ structure is well known. In addition, a compound analogous to XV, which contains three fused four membered rings, perfluorotricyclo[4.2.0.$0^{2,5}$]-octane, is known to be formed by thermal reaction of perfluoro-1,3-butadiene.[21]

An X-ray investigation of XV[22] failed to shed much light on the structure, because the material was found to show rotational disorder.

$CF_2=CClCF_2I$ + Zn in Anhydrous Dioxane: $CF_2=CCl-CF_2CF_2CCl=CF_2$.—To a well-stirred suspension of 100 g. of Zn dust in 400 ml. of anhydrous dioxane at reflux was added 169 g. of $CF_2=CClCF_2I$ (0.62 mole) over a half-hour period. There was no noticeable heat effect at any time; the mixture was held near reflux for 6 hours, and material was distilled out to the boiling point of dioxane, 100.7° (747 mm.). The distillate contained nothing boiling below room temperature. It contained a small amount of unidentified material boiling at 45°, having a very pungent odor, but was principally a dioxane azeotrope, b.p. 98.5° (747 mm.), n_D^{20} 1.3989, *ca.* 54% dioxane by wt., which gave on drowning in water a 32% yield of $CF_2=CClCF_2CF_2CCl=CF_2$ (XVI), b.p. 112.8° (735 mm.). The structure proposed for this material is based on analogy with that demonstrated for XII.

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Methyl-fluorinated Methyldiarylcarbinols and Related Compounds

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Nine methyl-fluorinated derivatives of diphenylmethylcarbinol have been prepared by the Grignard reaction from suitable substitution products of ethyl fluoroacetate or acetophenone. The ultraviolet and infrared spectra of these carbinols are discussed. Some of the above acetophenones also have been reduced and the corresponding secondary alcohols condensed with chlorobenzene in the presence of fuming sulfuric acid. The chemical reactions of the new substances have been studied. Ethyl fluoroacetate is α-chlorinated by sulfuryl chloride in the presence of benzoyl peroxide.

The interesting biological properties[1–3] of the diaryl-(trifluoromethyl)-carbinols[4,5] made a study of

(1) A. S. Tahori, *J. Econom. Entomol.*, **48**, 638 (1955).

(2) S. Reuter, S. Cohen, R. Mechoulam, A. Kaluszyner and A. S. Tahori, *Rivista di Parassitol.*, **17**, 125 (1956).

(3) K. R. S. Ascher, *Science*, **125**, in press (1957).

(4) E. D. Bergmann, A. S. Tahori, A. Kaluszyner and S. Reuter, *Nature*, **176**, 266 (1955).

(5) A. Kaluszyner, S. Reuter and E. D. Bergmann, THIS JOURNAL, **77**, 4164 (1955).

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analogous methyl-fluorinated methyldiarylcarbinols appear worthwhile.

The purification of the products (I) from the Grignard reactions of arylmagnesium bromides (phenyl, *p*-chlorophenyl, *p*-bromophenyl and *p*-methoxyphenyl) with ethyl *difluoroacetate* was made difficult by the presence of the biphenyl derivatives formed as by-products. Combination of distillation under reduced pressure and chromatography gave the pure carbinols, which were oils and showed ultraviolet and infrared spectra similar to those of the corresponding diaryl-(trifluoromethyl)-carbinols. In the infrared spectrum, the OH valency stretching frequency was observed at 3600 cm.$^{-1}$.

$(p\text{-}XC_6H_4)_2(COH)CHF_2$ I $(p\text{-}CH_3OC_6H_4)_2C{=}CF_2$ II

$(p\text{-}ClC_6H_4)_2C(OH)CHFCl$ III $(p\text{-}XC_6H_4)_2C(OH)CF_2Cl$ IV

$(p\text{-}XC_6H_4)_2C(OH)CFCl_2$ V

The *p*-methoxyphenyl compound lost water spontaneously, even under mild conditions, and gave 1,1-di-(*p*-methoxyphenyl)-2,2-difluoroethylene (II), which has practically the same ultraviolet spectrum (λ 241 mμ, log ϵ 4.42) as 1,1-di-(*p*-chlorophenyl)-ethylene.[6] In the infrared, the hydroxyl frequency was absent; instead a band appeared at 1700 cm.$^{-1}$ which may be assigned to the C=CF_2 bond, conjugated with the *p*-methoxyphenyl groups.

The Grignard reaction between ethyl *chlorofluoroacetate* and *p*-chlorophenylmagnesium iodide gave the expected carbinol III, an oily liquid. In this connection it may be worthy of note that ethyl chlorofluoroacetate[7] can be prepared more easily (in 30% yield) by chlorination of ethyl fluoroacetate with sulfuryl chloride in the presence of benzoyl peroxide as catalyst than by the previously reported method.

The esters of *difluorochloro-* and *dichlorofluoro*-acetic acid reacted smoothly with phenylmagnesium bromide, giving the carbinols IV and V (X = H). Surprisingly, the reaction with *p*-chlorophenylmagnesium bromide was extremely sluggish, even under stringent conditions. The main reaction product was 4,4′-dichlorobiphenyl. These two esters, therefore, behave similarly to ethyl trichloroacetate.[8] A detour had to be employed for the preparation of the di-*p*-chloro-derivatives (X = Cl) of IV and V. The corresponding ketones VI and VII were prepared from difluorochloro- and dichlorofluoroacetic acid and an excess of *p*-chlorophenylmagnesium bromide according to the method of Sykes, Tatlow and Thomas.[9] These ketones gave the desired carbinols when treated for a considerable length of time with a twofold excess of *p*-chlorophenylmagnesium bromide.

$p\text{-}ClC_6H_4COCF_2Cl$ VI $p\text{-}ClC_6H_4COCFCl_2$ VII

$(p\text{-}ClC_6H_4)_2C(OH)CH_2F$ VIII $p\text{-}ClC_6H_4COCH_2C_6H_4Cl\text{-}p$ IX

Finally, ethyl *fluoroacetate* was converted, by reaction with *p*-chlorophenylmagnesium bromide, into 1,1-di-(*p*-chlorophenyl)-2-fluoroethanol (VIII). As a by-product, 4,4′-dichlorodesoxybenzoin (IX) was obtained, in analogy with the observations of Bergmann and Kalmus.[10] Dehydration of the carbinol VIII gave 1,1-di-(*p*-chlorophenyl)-2-fluoroethylene (X), whilst the chlorine-free parent compound of VIII gives a hydrindene derivative under these conditions.[10] The structure of X follows from the identity of its absorption spectrum (λ 240 mμ, log ϵ 4.22) with those of 1,1-di-(*p*-chlorophenyl)-ethylene[6] and II, and from its oxidation to *p*,*p*′-dichlorobenzophenone. Upon reduction with iodine and red phosphorus, the carbinol VIII was converted into 1,1-di-(*p*-chlorophenyl)-ethane.

When the ketones VI and VII and *p*-chloro-ω-fluoroacetophenone[11] were reduced with lithium aluminum hydride, the corresponding secondary alcohols were obtained, without loss of the aliphatic halogen atoms. Condensation of the three alcohols with chlorobenzene in the presence of fuming sulfuric acid gave 1,1-di-(*p*-chlorophenyl)-2,2-difluoro-2-chloroethane (XI), -2,2-dichloro-2-fluoroethane (XII) and -2-fluoroethane (XIII).

$(p\text{-}ClC_6H_4)_2C{=}CHF$ X $(p\text{-}ClC_6H_4)_2CHCF_2Cl$ XI

$(p\text{-}ClC_6H_4)_2CHCFCl_2$ XII $(p\text{-}ClC_6H_4)_2CHCH_2F$ XIII

$(p\text{-}ClC_6H_4)_2C{=}CF_2$ XIV $(p\text{-}ClC_6H_4)_2C{=}CClF$ XV

Compound XI melted at 54–55° and was obviously not identical with the product of m.p. 90° which has been obtained by Pouterman and Giraudet[12] by the treatment of DDT with antimony trifluoride and to which they assigned formula XI.

It appeared interesting to compare the behavior of the compounds XI and XII against alkali with that of the corresponding trifluoro compound. Whilst in the latter the CF_3 group is converted into a carboxyl or carbalkoxy group,[13] the former lose hydrogen chloride and give 1,1-di-(*p*-chlorophenyl)-2,2-difluoro- and -2-fluoro-2-chloroethylene (XIV, XV). Both olefins proved to be highly unstable; especially in contact with air they are converted quickly into brown polymers. The same behavior has been noted by Dittman and Wrightson[14] for the analogous 1,1-diphenyl-2,2-difluoroethylene. The fact that II is stable is undoubtedly due to the effect of the *p*-methoxy groups. This may be the same effect which makes 1,1-di-(*p*-methoxyphenyl)-ethylene stable to dimerization reactions.[15]

The **ultraviolet spectra** of the new carbinols show the longest wave length maximum at about

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250–270 mμ; it is sometimes split into a doublet. Halogen in the *p*-positions has a distinct, though weak bathochromic affect, an observation which has also been made in the case of the diaryltrifluoromethylcarbinols.[5]

Also the infrared spectra of the tertiary carbinols described are fairly similar. The tertiary hydroxyl group absorbs at 3600 cm.$^{-1}$. In the acetyl derivatives, the carbonyl frequency at 1760 cm.$^{-1}$ is somewhat unusual; its shift from the expected frequency of about 1735 cm.$^{-1}$ may be due to the accumulation of negative substituents in the vicinity, in the same way as malonic esters absorb at 1761 cm.$^{-1}$ and ethyl trichloroacetate absorbs at 1768 cm.$^{-1}$.[16] As in the case of the diaryl-(trifluoromethyl)-carbinols,[5] there is no indication of internal hydrogen bonding. The biological properties of the substances described here will be reported elsewhere; the compounds have not shown any significant insecticidal properties.

Experimental

Difluoromethyl-diarylcarbinols (I).—To the Grignard solution, prepared from 0.1 mole of the aryl bromide in 50 ml. of ether, a solution of ethyl difluoroacetate (0.05 mole) in ether (25 ml.) was added at 0° and with vigorous agitation. The reaction mixture was cooled in an ice–salt mixture and decomposed by the slow addition of a saturated aqueous solution of ammonium chloride. The clear supernatant layer was decanted from a little sludge and the latter treated with a small amount of dilute hydrochloric acid, which was then extracted with ether. The combined ethereal layers were washed with sodium bicarbonate solution and water and dried with sodium sulfate. After removal of the solvent, the product was fractionated under reduced pressure. The crude carbinol fraction was dissolved in light petroleum ether and chromatographed on activated alumina, an ether–petroleum ether mixture (1:4) serving as the eluent. The fraction containing the carbinol was redistilled under reduced pressure. The carbinols gave a strong red-violet color with concentrated sulfuric acid. Their properties are summarized in Table I.

TABLE I

(DIFLUOROMETHYL)-DIARYLCARBINOLS, $(p\text{-}XC_6H_4)_2C(OH)CHF_2$

X	B.p. °C.	Mm.	$n^{25}D$	Yield, %	Analysis Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	U.v. spectrum, mμ (log ε) (in alcohol)
H	120	0.16	1.5620	48	71.8	71.6	5.1	5.1	210 (4.10) 254 (2.70) 258 (2.74)
Cl[a]	140	0.03	1.5783	27	55.5	55.6	3.3	3.5	225 (4.45) 260 (2.94) 265 (2.94)
Br[b]	150	0.01	1.6030	25					230 (4.45) 250–260 (3.38)

[a] Calcd.: Cl, 23.4. Found: Cl, 23.2. [b] Calcd.: F, 9.7. Found: F, 9.6.

1,1-Di-(*p*-methoxyphenyl)-2,2-difluoroethylene (II).—The reaction with *p*-methoxyphenylmagnesium bromide, carried out as above, gave—after distillation under reduced pressure (123–125° (0.001 mm.))—a solid product of m.p. 54.5–55.5°.

Anal. Calcd. for $C_{16}H_{14}F_2O_2$: C, 69.6; H, 5.1. Found: C, 69.5; H, 5.1.

Ethyl chlorofluoroacetate was obtained by the method of Young and Tarrant[7] or—in 30% yield—by the chlorination of ethyl fluoroacetate with sulfuryl chloride in the presence of benzoyl peroxide.

The mixture of 31.8 g. of ethyl fluoroacetate, 53.6 g. of sulfuryl chloride, 150 ml. of carbon tetrachloride and 0.1 g. of benzoyl peroxide was refluxed until the expected weight loss (30 g.) had taken place. The solution was distilled without further treatment and gave 13 g. (30%) of ethyl chlorofluoroacetate, b.p. 128–130°, $n^{20}D$ 1.3913.

Fluorochloromethyl-di-(*p*-chlorophenyl)-carbinol (III).—To the Grignard solution prepared from 2.4 g. of magnesium and 24 g. of *p*-chloroiodobenzene, an ethereal solution of 5.65 g. of ethyl chlorofluoroacetate was added at 0° within 2 hr. The mixture was kept at room temperature for 2 hr. and decomposed by addition of 10 g. of ammonium chloride in ice-water. The aqueous layer was extracted with ether, and the combined ethereal solutions were washed with sodium thiosulfate solution and water and dried. The carbinol boiled at 140–144° (0.15 mm.); it was a yellowish oil of $n^{21}D$ 1.4763; ultraviolet spectrum in alcohol (log ε): 226 mμ (4.27), 256–266 mμ (3.17).

Anal. Calcd. for $C_{14}H_{10}Cl_3FO$: Cl, 33.0; F, 5.9. Found: Cl, 33.3; F, 5.8.

Ethyl Difluorochloroacetate.[17]—A mixture of difluorochloroacetic acid (General Chemical Division, Allied Chemical and Dye Corp., Morristown, N. J.) (56 g.), absolute ethanol (46 ml.) and concd. sulfuric acid (25 ml.) was heated on the water-bath for 2 hr. The layers were separated and the organic layer was washed twice with water. The acid layer then was added to the aqueous washings, whereupon a further quantity of ester separated. The combined portions of the crude ester were dried over phosphorus pentoxide and distilled in a Vigreux column; b.p. 96–97.5°, yield 62 g. (78.5%), $n^{30}D$ 1.3525, d^{30}_{30} 1.2471; *MR* calcd. 27.43, found 27.45.

Ethyl dichlorofluoroacetate[17a] was prepared by the same procedure from dichlorofluoroacetic acid (General Chemical Division, Allied Chemical and Dye Corp., Morristown, N. J.) (74 g.); b.p. 130–132°, yield 76 g. (86%), $n^{30}D$ 1.4002, d^{30}_{30} 1.307; *MR* calcd. 32.02, found 32.46.

Difluorochloromethyldiphenylcarbinol (IV, X = H).—To a boiling Grignard solution, prepared from magnesium (6 g.) and bromobenzene (39.2 g.) in ether (200 ml.), a solution of ethyl difluorochloroacetate (15.9 g.) in ether (60 ml.) was added, dropwise and with stirring, within 20 minutes. The heating was continued for another 10 minutes and the solution decomposed with ice and hydrochloric acid. The carbinol (IV) distilled at 130–160° (8 mm.), solidified and was recrystallized from petroleum ether; yield 15 g. (56%), m.p. 78–79°. Ultraviolet spectrum in alcohol: (log ε): 259 mμ (2.58), 263 mμ (2.52).

Anal. Calcd. for $C_{14}H_{11}F_2ClO$: C, 62.7; H, 4.1. Found: C, 62.3; H, 4.2.

The acetate was prepared by heating the carbinol (1 g.) with acetic anhydride (5 ml.) and sulfuric acid (2 drops) for 4 hr. at 100°. After hydrolysis of the excess of acetic anhydride with water, extraction with ether, evaporation of the solvent and recrystallization from methanol, the acetate was obtained as colorless prisms, m.p. 82–83°, yield 0.7 g. (61%); ultraviolet spectrum 264 mμ (log ε 2.64).

Anal. Calcd. for $C_{16}H_{13}ClF_2O_2$: C, 61.9; H, 4.2. Found: C, 61.7; H, 4.5.

Dichlorofluoromethyldiphenylcarbinol (V, X = H).—The carbinol V was obtained analogously from ethyl dichlorofluoroacetate (17.5 g.), magnesium (6 g.) and bromobenzene (39.2 g.). It distilled as a heavy yellowish oil at

(16) E. J. Hartwell, R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1436 (1948).

(17) *Cf.* F. Swarts, *Chem. Centr.*, **67**, I, 1237 (1906); **68**, II, 581 (1907).

(17a) F. Swarts, *Bull. Soc. chim. France*, [3], **13**, 992 (1898).

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140–145° (2 mm.) and could not be induced to crystallize; yield 15 g. (52%), $n^{30}D$ 1.5821, d^{30}_{30} 1.342; *MR* calcd. 71.06, found 70.78; ultraviolet spectrum in alcohol (log ε): 254 mμ (3.12).

Anal. Calcd. for $C_{14}H_{11}Cl_2FO$: Cl, 25.0. Found: Cl, 24.6.

The acetate was obtained as described above, m.p. 78–79°, yield 65%; ultraviolet spectrum 257 mμ (log ε 2.53).

Anal. Calcd. for $C_{16}H_{13}Cl_2FO_2$: C, 58.7; H, 4.0. Found: C, 58.2; H, 4.1.

Reaction of *p*-Chlorophenylmagnesium Bromide and Ethyl Difluorochloroacetate.—To the solution prepared from magnesium (5.3 g.) and *p*-chlorobromobenzene (42.2 g.) in ether (200 ml.), toluene (100 ml.) was added and the ether distilled off at 90–100°. The ester (15.85 g.) in toluene (60 ml.) was then added to the hot mixture, dropwise and with stirring, within 15 minutes, and the heating continued for another 15 minutes. After decomposition of the mixture with ice and hydrochloric acid, removal of the solvents and distillation *in vacuo*, the main product proved to be 4,4′-dichlorobiphenyl; the desired carbinol could not be separated in pure form, though the crude reaction product gave the typical color reaction with concentrated sulfuric acid.

ω,ω-Difluoro-ω,*p*-dichloroacetophenone (VI).—A solution of difluorochloroacetic acid (32.6 g.) in ether (70 ml.) was added at 10–15° to a Grignard solution, prepared from *p*-chlorobromobenzene (144 g.) and magnesium (18 g.) in ether (300 ml.), during 90 minutes. After decomposition with ice and hydrochloric acid and removal of the solvent, the reaction product was fractionally distilled *in vacuo;* the ketone VI distilled at 110–125° (25 mm.) and upon redistillation at 211–213° (760 mm.); yield 35 g. (63%), $n^{30}D$ 1.5241, d^{30}_{30} 1.445; *MR* calcd. 45.37, found 47.60; ultraviolet spectrum in ethanol (log ε): 222 mμ (4.00) 1263 mμ (3.03); infrared spectrum: $\nu_{C=O}$ 1710 cm.$^{-1}$.

Anal. Calcd. for $C_8H_4Cl_2F_2O$: C, 42.7; H, 1.8. Found: C, 42.5; H, 2.0.

It is well known[18] that the halogen in α-halogenoketones raises the frequency of the carbonyl group (for liquid acetophenone, $\nu_{C=O}$ is 1682 cm.$^{-1}$). Neither in this case nor in those of VII or of *p*-chloro-ω-fluoroacetophenone have we observed doublets (at about 1700 and 1682 cm.$^{-1}$) as reported, *e.g.*, for ω-chloro- and ω,ω-dichloroacetophenone by Bellamy, Thomas and Williams[19] and ascribed to rotational isomers of the compounds. On the other hand, the observation[19,20] has been confirmed that in such α-halogenations only the first halogen has a major effect on the location of the carbonyl frequency.

ω-Fluoro-ω,ω,*p*-trichloroacetophenone (VII).—The ketone VII was prepared from dichlorofluoroacetic acid (37 g.), *p*-chlorobromobenzene (144 g.) and magnesium (18 g.). It distilled at 110–130° (9 mm.) and upon redistillation, at 245–250° (760 mm.); yield 24 g. (38%), $n^{30}D$ 1.5522, d^{30}_{30} 1.450; *MR* calcd. 50.21, found 52.96; ultraviolet spectrum (log ε): 221 mμ (4.04), 257 mμ (2.32); infrared spectrum: $\nu_{C=O}$ 1700 cm.$^{-1}$.

Anal. Calcd. for $C_8H_4Cl_3FO$: Cl, 44.0; Found: Cl, 43.8.

Difluorochloromethyl-di-(*p*-chlorophenyl)-carbinol (IV, X = Cl).—A solution of VI (16 g.) in ether (50 ml.) was added, dropwise and with stirring, to a boiling Grignard solution prepared from *p*-chlorobromobenzene (15.5 g.) and magnesium (1.9 g.) in ether (100 ml.), over a period of 15 minutes. The heating was continued for 10 minutes and the mixture decomposed with ice and hydrochloric acid. Part of the ketone (2.5 g.) was recovered unchanged; the desired carbinol (IV, X = Cl) distilled at 175–178° (2 mm.) as a colorless oil, yield 7.5 g. (24%), $n^{22}D$ 1.5750; d^{22}_{22} 1.548; *MR* calcd. 76.41, found 76.53; ultraviolet spectrum in alcohol (log ε): 226 mμ (4.20); 266 mμ (2.88).

Anal. Calcd. for $C_{14}H_9Cl_3F_2O$: C, 49.8; H, 2.7. Found: C, 50.3; H, 3.1.

The acetate, prepared as described above, had m.p. 78–79°, yield 72%; ultraviolet spectrum: 227 mμ (4.23), 264 mμ (2.66).

Anal. Calcd. for $C_{16}H_{11}Cl_3F_2O_2$: C, 50.6; H, 2.9. Found: C, 50.7; H, 3.1.

Dichlorofluoromethyl-di-(*p*-chlorophenyl)-carbinol (V, X = Cl) was prepared from a solution of VII (10 g.) in ether (50 ml.) and a Grignard solution, prepared from *p*-chlorobromobenzene (15.5 g.) and magnesium (1.9 g.) in ether (150 ml.). It distilled at 190–195° (2 mm.) and solidified spontaneously. By recrystallization from petroleum ether, waxy prisms of m.p. 79–80° were obtained, yield 9.5 g. (60%); ultraviolet spectrum in alcohol (log ε): 230 mμ (4.14), 260 mμ (2.84), 265 mμ (2.86).

Anal. Calcd. for $C_{14}H_9Cl_4FO$: C, 47.5; H, 2.6. Found: C, 47.7; H, 2.7.

The acetate melted at 100.5–101.5°, yield 72%. *Anal.* Calcd. for $C_{16}H_{11}Cl_4FO_2$: C, 48.5; H, 2.8. Found: C, 48.6; H, 3.0.

1,1-Di-(*p*-chlorophenyl)-2-fluoroethanol (VIII).—To an ice-cold Grignard solution, prepared from magnesium (6.9 g.) and *p*-chlorobromobenzene (57.5 g.) in ether (150 ml.), a solution of ethyl fluoroacetate (17. g.) in ether (150 ml.) was added within 20 minutes. This was followed immediately by a cold saturated solution of ammonium chloride in water. The organic layer was separated, washed and filtered with the help of filter-aid and evaporated. The solid residue was recrystallized from methanol. Thus 4,4′-dichlorodesoxybenzoin (IX) (4 g.), m.p. 113–114°, was obtained; it was identified by its mixed m.p. with an authentic sample. The methanolic mother liquor was evaporated and the residue distilled *in vacuo*. 1,1-Di-(*p*-chlorophenyl)-2-fluoroethanol (VIII) boiled at 173–176° (2 mm.). It solidified and was recrystallized from petroleum ether; m.p. 75–76°, yield 24.6 g. (58%); ultraviolet spectrum in alcohol (log ε): 226 mμ (4.24), 266 mμ (2.60), 275 mμ (2.44).

Anal. Calcd. for $C_{14}H_{11}Cl_2FO$: C, 59.0; H, 3.9. Found: C, 59.5; H, 4.0.

1,1-Di-(*p*-chlorophenyl)-2-fluoroethylene (X).—The mixture of VIII (1 g.) and concentrated sulfuric acid (20 g.) was kept for 12 hr. at room temperature. By addition of ice, extraction with ether, evaporation of the solvent and recrystallization of the solid residue from methanol, 0.5 g. (53%) of X was obtained, m.p. 79–80°; ultraviolet spectrum: 240 mμ (log ε 4.22); infrared spectrum (KBr pellet): 3500, 3000, 1640, 1500, 1400, 1178, 1088, 1070, 1015, 925, 840, 830, 822, 765, 705 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_9Cl_2F$: C, 63.0; H, 3.4; Cl, 26.6. Found: C, 63.4; H, 3.2; Cl, 26.0.

When the carbinol VIII (2 g.) was refluxed with acetic anhydride (10 ml.) and concentrated sulfuric acid (2 drops) for 3 hr., the ethylene X was obtained in 80% yield.

Oxidation.—The ethylene X (1 g.) was refluxed with chromic acid (2 g.) in glacial acetic acid (10 ml.) for 30 minutes. By addition of water, extraction with ether, evaporation of the solvent and recrystallization of the residue from ethanol, 4,4′-dichlorobenzophenone (0.5 g.) was obtained. It was identified by its melting point and by a mixed melting point with an authentic sample.

1,1′-Di(*p*-chlorophenyl)-ethane.—The carbinol VIII (1.5 g.) was refluxed in glacial acetic acid (10 ml.) with red phosphorus (0.6 g.) and iodine (0.25 g.) for 30 minutes. Water (0.1 ml.) was added and the heating continued for 48 hr. The product was diluted with water, extracted with ether and the extract washed with a solution of sodium thiosulfate and water. Evaporation of the solvent and recrystallization of the residue from methanol gave 1,1-di-(*p*-chlorophenyl)-ethane (0.7 g., 54%), identified by its melting point (54–55°) and by the mixed melting point with an authentic sample.

***p*-Chloro-ω-fluoroacetophenone.**—Finely divided aluminum chloride (250 g.) and subsequently a solution of fluoroacetyl chloride (80 g.) in ethylene dichloride (300 ml.) was added to 1 l. of ethylene dichloride with vigorous agitation which was continued for 30 minutes. The dark solution was decanted into a three-necked flask, cooled at 0° and a mixture of chlorobenzene (90 g.) and ethylene dichloride (75 ml.) added dropwise, with stirring, within 20 minutes; stirring was continued for 15 minutes and the mixture poured onto ice and hydrochloric acid. The

(18) R. N. Jones and C. Sandorfy in "Chemical Applications of Spectroscopy," Interscience Publishers, Inc., New York, N. Y., 1916, p. 474.

(19) L. J. Bellamy, L. C. Thomas and R. L. Williams, *J. Chem. Soc.*, 3704 (1956).

(20) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).

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organic layer was separated, washed with water and sodium bicarbonate solution and dried. *p*-Chloro-ω-fluoroacetophenone distilled at 115–119° (8 mm.) and crystallized immediately as plates, m.p. 54–55° (from aqueous ethanol), yield 72 g. (52%). This ketone also has been described by Bergmann, Kalmus and Breuer,[11] who also have carried out the reduction with lithium aluminum hydride, described below; ultraviolet spectrum: 255 mμ (log ε 4.25); infrared spectrum (KBr pellet): $\nu_{C=O}$ 1700 cm.$^{-1}$.

Anal. Calcd. for C_8H_6ClFO: C, 55.8; H, 3.5. Found: C, 55.7; H, 4.5.

1-(*p*-Chlorophenyl)-2-fluoroethanol.—To an ice-cold solution of lithium aluminum hydride (1.5 g.) in anhydrous ether (80 ml.), a solution of *p*-chloro-ω-fluoroacetophenone (12 g.) in ether (50 ml.) was added during 90 minutes. After 10 minutes, the mixture was decomposed with a solution of sulfuric acid (1 ml.) in 30 ml. of ice-water, and the ethereal layer separated, washed and dried. 1-(*p*-Chlorophenyl)-2-fluoroethanol distilled at 124–134° (8 mm.) as a colorless oil; yield 11 g. (90%), $n^{29}D$ 1.5398; infrared spectrum: 3400, 1500, 1100, 1010, 900, 830 and 750 cm.$^{-1}$.

Anal. Calcd. for C_8H_8OClF: C, 55.2; H, 4.6. Found: C, 55.5; H, 4.7.

1,1-Di-(*p*-chlorophenyl)-2-fluoroethane (XIII).—To an ice-cold mixture of 1-(*p*-chlorophenyl)-2-fluoroethanol (2 g.) and chlorobenzene (5 g.), a mixture of concentrated sulfuric acid (20 ml.) and fuming sulfuric acid (4 ml.) was added dropwise. The reaction mixture was shaken mechanically for 2 hr., then poured onto ice and extracted with ether. The ethereal solution was washed, dried, evaporated and the product distilled *in vacuo*. It boiled at 155–165° (2 mm.) and solidified spontaneously; from methanol, m.p. 54–55°, yield 1 g. (32%).

Anal. Calcd. for $C_{14}H_{11}Cl_2F$: Cl, 26.3. Found: Cl, 26.0.

Reaction with Alkali.—The compound XIII (0.3 g.) was refluxed with 1 *N* methanolic potassium hydroxide solution (5 ml.) for 1 hr., hydrochloric acid (2 ml.) and water (30 ml.) added and the product extracted with ether. The ether residue was recrystallized from methanol (0.2 g.) and melted at 84–85°. It was identified as **1,1-di-(*p*-chlorophenyl)-ethylene** by comparison with an authentic sample; infrared spectrum: 3400, 1600, 1500, 1420, 1190, 1120, 1085, 1018, 970, 855, 825, 790, 725 cm.$^{-1}$.

Difluorochloromethyl-*p*-chlorophenylcarbinol.—A solution of the ketone VI (11.3 g.) in ether (30 ml.) was added, dropwise, to a well-stirred ice-cold suspension of lithium aluminum hydride (1.5 g.) in ether (50 ml.). An ice-cold mixture of sulfuric acid (10 ml.) and water (50 ml.) was added cautiously, the ethereal layer separated, washed with water and concentrated and the residue distilled *in vacuo*; b.p. 115–120° (10 mm.), colorless liquid, $n^{28}D$ 1.5144, yield 9 g. (80%).

Anal. Calcd. for $C_8H_6Cl_2F_2O$: C, 42.3; H, 2.7. Found: C, 42.4; H, 2.8.

Dichlorofluoromethyl-*p*-chlorophenylcarbinol.—The ketone VII (4 g.) in ether (15 ml.) was reduced with lithium aluminum hydride (0.5 g.) in ether (20 ml.). The product distilled at 120–125° (2 mm.) as a colorless liquid, $n^{30}D$ 1.543, yield 3.5 g. (87%); infrared spectrum: 3500, 1600, 1400, 1200, 1085, 1010, 950, 870–880, 820, 795, 771, 715 cm.$^{-1}$.

Anal. Calcd. for $C_8H_6Cl_3FO$: Cl, 43.7. Found: Cl, 43.4.

1,1-Di-(*p*-chlorophenyl)-2,2-difluoro-2-chloroethane (XI).—To a well-stirred mixture of chlorobenzene (4.5 g.), concentrated sulfuric acid (10 ml.) and 20% fuming sulfuric acid (3 ml.), was added, slowly and with cooling, *p*-chlorophenyldifluorochloromethylcarbinol (5 g.). The mixture was then shaken for 5 hr., added to crushed ice and extracted with ether. After removal of the ether and excess chlorobenzene by distillation, the ethane XI distilled at 160–165° (2 mm.), yield 6 g. (85%). The product solidified; after recrystallization from methanol, it melted at 54–55°; ultraviolet spectrum: 228 mμ (4.20); 260 mμ (2.60); 267 mμ (2.62); infrared spectrum (KBr pellet): 1500, 1400, 1210, 1170, 1090, 1015, 962, 765 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_9Cl_3F_2$: C, 52.3; H, 2.8. Found: C, 52.1; H, 2.9.

Reaction with Alkali.—The compound XI (1 g.) was refluxed for 1 hr. with 1 *N* methanolic potassium hydroxide (20 ml.). Water was added and the mixture extracted with ether. After removal of the solvent, **1,1-di-(*p*-chlorophenyl)-2,2-difluoroethylene (XIV)** distilled at 165–169° (2 mm.), yield 0.7 g. (79%), $n^{30}D$ 1.5732. The substance was so unstable that only approximate analyses could be obtained. However, the spectrum indicated (see above) that the compound had structure XIV; ultraviolet spectrum (isoöctane): 228 mμ (4.46); 255 mμ (4.06).

1,1-Di-(*p*-chlorophenyl)-2,2-dichloro-2-fluoroethane (XII).—Condensation of *p*-chlorophenyldichlorofluoromethylcarbinol (2.5 g.) and chlorobenzene (2 g.) in the presence of concentrated sulfuric acid (5 ml.) and 20% fuming sulfuric acid (1.5 ml.) gave XII (2 g., 57%); b.p. 180–185° (2 mm.), m.p. after recrystallization from methanol 78–79°; ultraviolet spectrum (log ε): 232 mμ (4.26), 260 mμ (2.74), 267 mμ (2.76); infrared spectrum (KBr pellet): 1500, 1400, 1120, 1090, 1015, 940, 810, 780 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_9Cl_4F$: C, 49.8; H, 2.7. Found: C, 50.4; H, 2.8.

Reaction with Alkali.—Upon alkaline hydrolysis of the ethane XII (0.75 g.) as described above, **1,1-di-(*p*-chlorophenyl)-2-chloro-2-fluoroethylene (XV)** (0.55 g., 85%) was very probably obtained. It distilled at 165–166° (3 mm.) as a colorless but unstable oil, of $n^{28}D$ 1.6059.

TEL-AVIV, ISRAEL

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY OF THE HEBREW UNIVERSITY-HADASSAH MEDICAL SCHOOL]

ω-Fluoroacetophenone. III. Reaction of Fluoroacetyl Chloride with Halobenzenes. On the Mechanism of Side-chain Chlorination by Sulfuryl Chloride

BY FELIX BERGMANN, ABRAHAM KALMUS AND ELI BREUER[1]

RECEIVED FEBRUARY 8, 1957

The synthesis of ω-fluoroacetophenone has been extended to halobenzenes. The mechanism of side-chain chlorination of these ketones by sulfuryl chloride has been studied and a reaction scheme proposed.

The synthesis of ω-fluoroacetophenone (I), which was described previously,[2] was based on the observation that prolonged contact of I with aluminum chloride is responsible for halogen exchange, producing ω-chloroacetophenone (II). Short reaction periods are required to secure sizable yields of I. It remained undecided, however, whether the same type of exchange proceeds with fluoroacetyl chloride, prior to condensation. This possibility was tested by treating the latter with the Friedel-Crafts catalyst in methylene chloride at room tem-

(1) Part of a M.Sc. thesis, submitted to the Faculty of Science, The Hebrew University, Jerusalem, 1957.

(2) F. Bergmann and A. Kalmus, THIS JOURNAL, 76, 4137 (1954).

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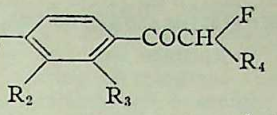
TABLE I

PROPERTIES AND ANALYSES OF KETONES 

R_1	R_2	R_3	R_4	M.p. or b.p. (mm.), °C.	Recrystallized from	Analyses, % Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Cl	H	H	H	53–54	Petr. eth.	55.8	55.6	3.5	3.6
F	H	H	H	50–51	Petr. eth.	61.5	61.4	3.8	3.9
F	H	F	H	62–63	Ligroin	55.2	55.6	2.9	3.1
H	NO_2	H	H	95–96	Ethanol	52.5	52.7	3.3[a]	3.3
F	H	H	Cl	33, 84–88 (10)	.....	50.5	50.6	2.6	2.9
F	H	H	Br	120–130 (14)	.....	40.9	42.5	2.1	2.8
F	H	H	I	42–45	.....	Unstable			

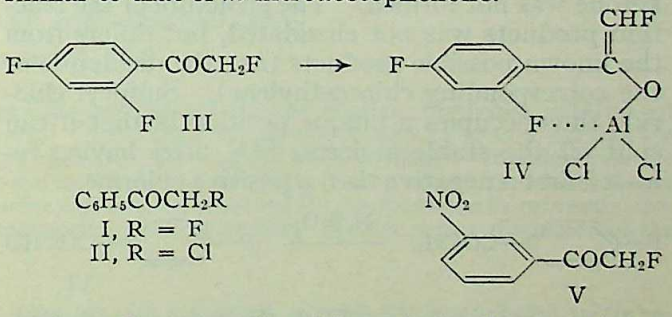
[a] Calcd.: N, 7.7. Found: N, 7.8.

perature for six hours, then cooling the solution to 0°, adding benzene and carrying out the reaction exactly as described previously. The product (50% yield), consisted of about equal parts of I and its chloro analog II. The pretreatment thus decreased the yield of I considerably. However, halogen exchange with fluoroacetyl chloride proceeds at a much lower rate than with the ketone I. The latter, when incubated under similar conditions, is converted almost quantitatively into chloroacetophenone.

When substituted benzenes were submitted to the same reaction, only the halogeno derivatives gave positive results, albeit yields were much inferior to benzene itself (see Table I). Chlorobenzene produced, in addition to 24% of the ω-fluoroketone, also about 3% of *p*,ω-dichloroacetophenone.[3] With fluorobenzene, the yield of ketones was nil when standard conditions were applied. A highly viscous oil was isolated instead, indicating the occurrence of secondary condensation reactions. However, when the reaction was carried out at 0° and interrupted after 10 minutes, a 55% yield of *p*,ω-difluoroacetophenone was obtained. The structure of this compound was established in the way described below. Bromobenzene did not react with fluoroacetyl chloride at 0°. At room temperature, some debromination took place also, in addition to condensation, and no defined product was isolated from the mixture. Anisole gave, even after very short reaction times, a resinous product, which decomposed at about 180° when vacuum distillation was attempted.

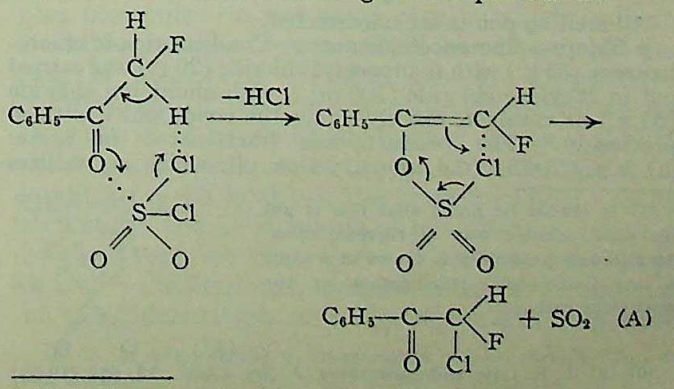
In contrast to fluorobenzene, *m*-difluorobenzene had to be exposed to much more drastic conditions in order to promote condensation with fluoroacetyl chloride (30 minutes at 0° and 30 minutes at room temperature). The reaction product is assumed to be III. Although in this case the yield was only 10%, no trace of the ω-chloro derivative accompanied III. The ketone III proved to be rather stable toward halogen exchange, presumably because of competition of the *o*-fluorine with the ω-halogen in complexing the metal atom (as *e.g.* in IV). On this basis it was expected that during a Grignard reaction the intermediate would similarly be protected against rearrangement to a desoxybenzoin[2] by complexing of the metal atom with *o*-fluorine. Therefore, a mixture of phenylmagnesium bromide and 2,4,ω-trifluoroacetophenone (III) in ether was refluxed for four hours. The product, however, was identified as a desoxybenzoin and no trace of its precursor, the tertiary carbinol, was detected.

Nitration of I in acetic acid gave the *m*-nitro derivative V, the point of substitution being proved by oxidation to *m*-nitrobenzoic acid. Likewise, the ultraviolet absorption spectrum of V is quite similar to that of *m*-nitroacetophenone.



$C_6H_5COCH_2R$
I, R = F
II, R = Cl

The *p*-fluoro- and *p*-chloro derivatives of I can be halogenated by the methods available for ω-fluoroacetophenone itself.[4] The chlorination with sulfuryl chloride was studied in more detail. Acetophenone reacts instantaneously at room temperature, and chlorination is completed within 2 hours, giving a practically quantitative yield of II. With ω-fluoroacetophenone—as described previously—reaction starts at room temperature with a marked delay (about 0.5 hour) and requires 16 hours for its completion. With *p*,ω-difluoroacetophenone and *p*-chloro-ω-fluoroacetophenone substitution can be effected only with refluxing sulfuryl chloride. The ketones III and V were not attacked even under these conditions. No trial was made at still higher temperatures.



(3) D. Woodcock, *J. Chem. Soc.*, 203 (1949); Gautier, *Ann. chim.*, 14, 395 (1888).

(4) F. Bergmann, A. Kalmus and S. Vromen, THIS JOURNAL, 77, 2494 (1955).

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TABLE II

2,4-DINITROPHENYLHYDRAZONES OF THE KETONES OF TABLE I, $R_1C_6H_3(CH_2F)C{=}NNHC_6H_3(NO_2)_2$

R_1	R_2	M.p., °C.	Recrystd. from	Analyses, % Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Fluorine, % Calcd.	Fluorine, % Found
Cl	H	218–219	Butyl acetate	47.7	47.7	2.8	3.1	..	..	5.4	5.3
F	H	210–211	Acetic anhyd.	50.0	50.0	3.0	3.2	16.7	16.9	..	..
F	F	182–183	*n*-Butyl alc.	47.3	47.8	2.5	2.7	15.8	15.3	..	..

The outstanding capacity of sulfuryl chloride to chlorinate methyl as well as fluoromethyl, in α-position to the carbonyl, may be interpreted by way of a cyclic mechanism, indicated in scheme A. Here, the reagent is assumed first to polarize the carbonyl group strongly, forming an enol ester and eliminating HCl. In the second phase of the reaction, the electronic cycle swings back and introduces positive chlorine into the α-position.[5]

In order to test this hypothesis, other acid chlorides, capable of forming similar enol esters and carrying out the corresponding electronic cycles, were tried. Oxalyl chloride was found unreactive. Phosphorus pentachloride attacked the carbonyl group, but the expected ω-chloro-ω-fluoro ketone was not formed. The structure of the reaction products was not elucidated, but differs from the known possible products (*i.e.*, the dichloride or the corresponding chloroethylene). Sulfuryl chloride thus occupies a unique position in that it can split off the stable molecule SO_2, after having released first a negative then a positive chlorine.

$$F{-}C_6H_4{-}COCH_3 \xrightarrow{H_2SeO_3} F{-}C_6H_4{-}COCHO$$

VI

In an attempt to establish the point of substitution in the ketone, obtained by fluoroacetylation of fluorobenzene, the usual methods of oxidation of the side chain did not give the expected aromatic acids, suitable for identification. Therefore, the following method was adopted: *p*-Fluoroacetophenone[6a,b] was converted by selenious acid into the glyoxal VI. The bis-dinitrophenylhydrazone of VI decomposes at about 296°. In order to identify unequivocally this compound with the corresponding derivative, obtained from *p*,ω-fluoro-ω-chloroacetophenone (Table II), the X-ray powder diagrams were compared. They were found to be identical, as did also the infrared spectra of the hydrazones from the two sources.

Experimental

All melting points are uncorrected.

p-Chloro-ω-fluoroacetophenone.—Condensation of chlorobenzene (35 g.) with fluoroacetyl chloride (29 g.) was carried out in ethylene chloride (100 ml.), with aluminum chloride (65 g.) as catalyst, exactly under the conditions described previously.[2] The product was fractionated *in vacuo*: (a) b.p. 73–75° (0.4 mm.), yellow oil, which crystallizes spontaneously. From petroleum ether needles of m.p. 53–54°; 13 g. (24%) yield of *p*-chloro-ω-fluoroacetophenone; (b) b.p. 90° (0.4 mm.), yield, 2 g. (3%) of *p*,ω-dichloroacetophenone; from ethanol needles of m.p. 100–101°[3]; oxime m.p. 101°.[7]

p-Chloro-ω-fluoroacetophenone (1 g.) was dissolved in sulfuryl chloride (5 ml.). No evolution of gas occurred at room temperature (26°) during 12 hours, and the starting material could be recovered. Upon refluxing the solution, hydrogen chloride and sulfur dioxide escaped slowly. After 5 hours' heating, the reaction mixture was decomposed with ice and extracted with ether. The ether residue was strongly lachrymatory and tended to decompose during vacuum distillation. It was, therefore, converted directly into a bis-2,4-dinitrophenylhydrazone, which decomposed at about 280° but was so difficultly soluble that no suitable medium for recrystallization could be found.

p,ω-Difluoroacetophenone.—Aluminum chloride (80 g.) was stirred with ethylene dichloride (300 ml.) for 20 minutes and the solution decanted and cooled to 0°. Fluoroacetyl chloride (18 g.) in ethylene dichloride (60 ml.) was added and immediately thereafter fluorobenzene (25 g.) in the same solvent (60 ml.) during 10 minutes. Stirring at 0° was continued for another 10 minutes, and the mixture poured at once into concentrated hydrochloric acid and ice. The ketone was isolated in the usual way and purified by distillation, b.p. 85–90° (4 mm.). The substance crystallized immediately, and after recrystallization from petroleum ether formed sharp-edged plates of m.p. 50–51°. Its 2,4-dinitrophenylhydrazone crystallized from acetic anhydride in deep-red columns.

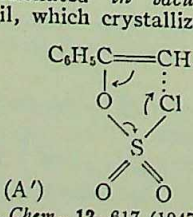
p,ω-Difluoroacetophone (15 g.) was dissolved in sulfuryl chloride (35 ml.). No reaction occurred at room temperature, but evolution of hydrogen chloride was observed when refluxing the solution. After 5 hours, the mixture was decomposed with ice and extracted with ether. The ether residue distilled smoothly *in vacuo*, b.p. 84–88° (10 mm.). The yellow oil solidified when kept in a refrigerator. The lachrymatory product, *p*,ω-difluoro-ω-chloroacetophenone, melted at 33°, yield, 12.5 g. (68%). The ketone formed a bis-2,4-dinitrophenylhydrazone which crystallized from pyridine–*n*-butyl acetate in red needles of m.p. 295–296°. *Anal.* Calcd. for $C_{20}H_{13}O_8N_8F$: C, 46.8; H, 2.5. Found: C, 46.7; H, 2.4.

Bromination was effected at room temperature by the method described for ω-fluoroacetophenone.[2] *p*,ω-Difluoro-ω-bromoacetophenone was purified by distillation *in vacuo*, b.p. 120–130° (14 mm.), but did not crystallize; yield 65%. The substance is a strongly irritating tear gas. When the ω-bromo ketone was dissolved in ethanol containing an equivalent of sodium iodide, reaction proceeded at room temperature within half an hour. *p*,ω-Difluoro-ω-iodoacetophenone could not be purified, since it is unstable even at room temperature and easily soluble even in petroleum ether. It is a very powerful lachrymator.

2,4-ω-Trifluoroacetophenone (III).—*m*-Difluorobenzene[8] was added to a mixture of fluoroacetyl chloride and aluminum chloride in methylene chloride at 0°. The mixture was stirred for 30 minutes at 0° and an additional half-hour at room temperature. The product was isolated as usual and crystallized immediately after evaporation of the solvent. From ligroin, plates of m.p. 62–63° were obtained. The 2,4-dinitrophenylhydrazone crystallized from *n*-butyl alcohol in rods of m.p. 182–183°.

m-Nitro-ω-fluoroacetophenone (V).—ω-Fluoroacetophenone (10 g.) in concentrated sulfuric acid (22 ml.) was cooled

(5) It should be noted that this is not the only possible way of representation. An alternate possibility is shown in scheme A′ as nucleophilic substitution at the methylene carbon.



(A′)

(6) (a) R. E. Lutz and co-workers, *J. Org. Chem.*, **12**, 617 (1947); (b) Ng. Ph. Buu-Hoï, Ng. Hoán and Pierre Jacquignon, *Rec. trav. chim.*, **68**, 781 (1949).

(7) A. Collet, *Bull. soc. chim.*, [3] **27**, 539 (1902).

(8) The authors wish to thank Dr. G. C. Finger of the State Geological Survey Division, Urbana, Illinois, for the generous supply of this product.

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to −15°. A mixture of nitric acid (d. 1.42) (10 ml.) and sulfuric acid (10 ml.) was added dropwise, the temperature being kept below −5°. Stirring was continued for 30 minutes and the mixture poured on ice. The solid material was filtered, washed with water and twice with ethanol and recrystallized from methanol or ethanol; yellow rods of m.p. 95–96°, yield 8.8 g. (66%).

p-Fluorophenylglyoxal (VI).—To a solution of selenious acid (43 g.) in dioxane (200 ml.), warmed to 60°, *p*-fluoroacetophenone[6a,b] (46 g.) was added slowly. After 5 minutes, a red precipitate formed. The solution was refluxed for 4 hours and left overnight. It was then decanted from the red precipitate and fractionated. At 105–115° (30–35 mm.) a thick, yellow oil went over which showed no tendency to crystallize; yield 35 g. (78%). The oil was dissolved in benzene and a few drops of water added. This resulted in the formation of a white powder. Recrystallization from water gave the hydrate of VI as glistening, white leaflets, m.p. 80°.

Anal. Calcd. for $C_8H_5O_2F\cdot H_2O$: C, 56.5; H, 4.1. Found: C, 56.9; H, 4.3.

The bis-2,4-dinitrophenylhydrazone crystallized from pyridine–*n*-butyl acetate, decomposition point 296°.

Grignard Reaction with 2,4,ω-Trifluoroacetophenone (III).—To a Grignard solution, prepared from bromobenzene (4.7 g.) and magnesium (0.7 g.) in ether, was added slowly an ethereal solution of 2,4,ω-trifluoroacetophenone (4.5 g.) during 15 minutes. The mixture was refluxed for 2 hours and then left overnight. It was decomposed with ammonium chloride and worked up in the usual way. Fractional distillation gave 5.2 g. of a yellow oil of b.p. 135–138° (4 mm.).

Anal. Calcd. for $C_{14}H_{10}OF_2$: C, 72.4; H, 4.3. Found: C, 72.0; H, 4.7.

The 2,4-dinitrophenylhydrazone crystallized from isopropyl alcohol in pointed plates of m.p. 165–167°.

Anal. Calcd. for $C_{20}H_{14}O_4N_4F_2$: N, 13.6. Found: N, 13.4.

The authors wish to thank Prof. E. Alexander, Department of Physics, for the X-ray spectra and Mrs. Hanna Feilchenfeld, Department of Organic Chemistry, for the infrared measurements used for identification of *p*,ω-difluoroacetophenone.

JERUSALEM, ISRAEL

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Relative Reactivities of Substituted Toluenes toward Chlorine Atoms[1]

BY CHEVES WALLING AND BERNARD MILLER[2]

RECEIVED JANUARY 23, 1957

Competitive halogenations of a series of substituted toluenes have been carried out and relative reactivities determined by the precise deuterium tracer technique of Russell and Brown.[7] For photochlorination the results yield a ρ value for attack of chlorine atoms of −0.76, appreciably smaller than the value of −1.5 reported by Kooyman.[15] Identical relative reactivities and k_H/k_D ratios are observed in photochlorination and in reaction with SO_2Cl_2, giving no evidence for different chain carriers in this system. However, some variation in relative reactivity is observed for reactions run in primarily aromatic media and in carbon tetrachloride. Data on photobromination are also presented, together with a discussion of the importance of polar effects in free radical halogenation.

The reaction of chlorine with aliphatic hydrocarbons and the side-chains of alkyl-aromatics is well established[3] as a radical chain process involving the chain carrying steps.

$$Cl\cdot + RH \longrightarrow HCl + R\cdot \qquad (1)$$

$$R\cdot + Cl_2 \longrightarrow RCl + Cl\cdot \qquad (2)$$

With hydrocarbons containing more than one type of C–H bond (or in mixtures of hydrocarbons) the products formed evidently will depend upon the relative rates of reactions of type (1) of chlorine atoms with the different sorts of C–H bond available. The work of Hass, McBee and Weber[4] has shown clearly that, with aliphatic hydrocarbons, the case of hydrogen displacement lies in the order primary < secondary < tertiary, the selectivity being somewhat greater in the vapor than in the liquid phase and decreasing with increasing temperature. Recently Pritchard, Pyke and Trotman-Dickenson[5] have studied the competitive chlorination of a number of simple hydrocarbons with results leading to similar conclusions, and have actually determined rate constants for hydrogen abstraction by carrying out competitions with the process

$$Cl\cdot + H_2 \longrightarrow HCl + Cl\cdot \qquad (3)$$

for which the rate constant is known over a wide temperature range.[6] Since C–H bond dissociation energies lie in the order primary > secondary > tertiary, decreasing approximately 4 kcal. with each substitution, this weakening, presumably due to resonance stabilization of the resulting radicals, has commonly been given as the explanation of the observed order of chlorine atom substitution.

Unfortunately for this simple picture, more complex molecules do not yield results which indicate a simple parallel between C–H bond strength and ease of attack by chlorine atoms. Competitive chlorination of toluene and *t*-butylbenzene shows[7] that the C–H bonds of the former are only slightly more reactive in spite of the great resonance stabilization (∼ 25 kcal.) of the benzyl radical. More strikingly, the C–H bonds of cyclohexane prove to be *more* reactive than those of toluene by a factor of 2.7.[7,8] Still more anomalous results are observed in the chlorination of molecules containing other

(1) Taken from a portion of a dissertation submitted by Bernard Miller in 1955 to the Graduate Faculties of Columbia University in partial fulfillment of the requirements for the degree of Doctor of Philosophy; a preliminary report of this work was made at the 126th meeting of the American Chemical Society, New York, September, 1954.

(2) University Fellow, Columbia University, 1954–1955.

(3) Extensive experimental evidence is reviewed by E. W. R. Steacie, "Atomic and Free Radical Reactions," 2nd Ed., Reinhold Publ. Corp., New York, N. Y., 1954, Chapter X.

(4) H. B. Hass, E. T. McBee and P. Weber, *Ind. Eng. Chem.*, **28**, 333 (1930).

(5) H. O. Pritchard, J. B. Pyke and A. F. Trotman-Dickenson, THIS JOURNAL, **77**, 2629 (1955).

(6) P. G. Ashmore and J. Chanmugam, *Trans. Faraday Soc.*, **49**, 254 (1953).

(7) G. A. Russell and H. C. Brown, THIS JOURNAL, **77**, 4578 (1955).

(8) H. C. Brown and G. A. Russell, *ibid.*, **74**, 3995 (1952).

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substituent atoms. Brown and Ash[9] have recently summarized data on the chlorination of 1-chlorobutanes and related compounds which show plainly that the presence of a chlorine atom decreases the ease of further chlorine substitution at the same and adjacent carbons, in spite of the fact that the C–H bonds are weakened.[10] In a number of cases the chlorinating agent was actually SO_2-Cl_2; see below. Similarly, radical chlorination of aliphatic acids and their derivatives (acid chlorides, esters and nitriles)[9,11] gives predominantly substitution along the chain with little α-attack in spite of the expected resonance stabilization of the resulting $-\dot{C}H-CO-$ radical, and the known fact that alkyl radicals preferentially attack acid derivatives in the α-position.[12]

In 1950 Mayo and Walling[13] suggested that the anomalous results in the chlorination of alkyl halides and aliphatic acid derivatives might be explained on the basis of the importance of polar contributions to the transition state of the radical displacement, an idea which may be restated by saying that structures such as

$$Cl\cdot \; H\text{—}R \longleftrightarrow Cl^{-}\overset{+}{H}\;\dot{R} \qquad (4)$$

can aid in lowering the activation energy in the attack of chlorine atoms on hydrocarbons but would be relatively unimportant in the presence of strongly electron-withdrawing groups. Brown and Ash[9] have interpreted the situation similarly but less specifically in terms of the inductive effect of –Cl and –COR groups in decreasing electron availability at the adjacent C–H bonds.

One of the most effective techniques for separating such polar effects from others arising from steric and related factors is by studying the effect of *m*- and *p*-substituents on the side-chain reactions of benzene, and treating the results in terms of the Hammett equation

$$\log k/k_0 = \rho\sigma \qquad (5)$$

in which k and k_0 are rate (or equilibrium) constants for reaction of substituted and unsubstituted benzenes, respectively, and ρ and σ are parameters determined, respectively, by the particular reaction under investigation and the substituent involved.[14] Accordingly, we have undertaken a study of the effects of *m*- and *p*-substituents on the liquid-phase, side-chain photochlorination of toluenes, employing a competitive technique, since, as noted above, this method gives directly the relative rates of hydrogen abstraction from different molecules by chlorine atoms, without involving the complicated over-all kinetics of the long-chain processes involved.

Shortly after this work was initiated, Kooyman published a similar study of the side-chain bromination of toluene,[15a] and has subsequently extended his work to the sulfuryl chloride chlorination,[15b] finding that, in both cases, substitution is facilitated by electron supplying and retarded by electron withdrawing groups. Qualitatively, the results of the study reported here are in agreement with Kooyman's sulfuryl chloride data. However, we have employed a more extensive series of derivatives and a more precise analytical method, and have arrived at a somewhat different interpretation which we believe makes a detailed report desirable.

Experimental

Materials

Substituted toluenes—except as indicated—were commercial materials, fractionally distilled (and dried if necessary) before use. ***p*-*t*-Butyltoluene** was prepared by the alkylation of toluene with isobutyl alcohol in the presence of H_2SO_4.[16] ***m*-Phenyltoluene** was prepared by treating *m*-tolylmagnesium bromide with cyclohexanone, dehydrating the resulting alcohol by heating with $KHSO_4$, and dehydrogenating the 1-(*m*-tolyl)-cyclohexene over 10% Pd on charcoal at 280–300° in an over-all yield of 56.5%, b.p. 148–152° (20 mm.), $n^{20}D$ 1.6002. *Anal.* Calcd. for $C_{13}H_{12}$: C, 92.86; H, 7.14. Found: C, 92.87; H, 7.12. ***p*-Phenyltoluene** was prepared similarly from *p*-bromotoluene and recrystallized from petroleum ether, m.p. 46–47°; lit.[17] 47–48°, over-all yield, 44%. **Toluene-α-d_1** was prepared in 76% yield from benzylmagnesium bromide and DCl by the method of Russell and Brown.[7] The reaction product was twice distilled from sodium through a 10-plate helix packed column, b.p. 110–110.5°, $n^{20}D$ 1.4947. The toluene-α-d_1 was combined with its volume of pure toluene for use, and, after completion of a series of runs, combined reaction mixtures were fractionated and combined with fresh toluene-α-d_1 and toluene. All these mixtures are referred to below as *deuterotoluene*.

Solvents.—Carbon tetrachloride was washed three times with a 50% aqueous ethanol solution of KOH, with water, and dried over $CaSO_4$. It was then treated for 15 hours with chlorine and light, dried over $MgSO_4$ and fractionated through a 10-plate column, b.p. 76°. Thiophene-free **benzene** was washed with sulfuric acid and water, dried, distilled from sodium, and fractionally crystallized, m.p. 5.2°, $n^{25}D$ 1.4494. ***o*-Dichlorobenzene** was dried over P_2O_5 and fractionally distilled through a 10-plate column, b.p. 179–180°, $n^{25}D$ 1.5501.

Halogenating Agents.—Chlorine was commercial material, distilled through sulfuric acid before use. **Bromine** was distilled from P_2O_5, and **sulfuryl chloride** was a colorless middle cut obtained by fractionating commercial material. It was stored in an aluminum foil covered flask until used.

Halogenations

Our technique in general involved the halogenation of mixtures of toluene-α-d_1 and substituted toluenes and determining relative reactivities by analysis of the DCl–HCl mixture evolved. This method, which was used by Brown and Russell,[7,8] is capable of high precision, but was checked in several cases by fractional distillation of our reaction mixtures.

Photochlorinations were carried out in the apparatus shown in Fig. 1. With stopcock A open and C closed, chlorine was condensed in B by chilling with a Dry Ice-bath. Trap B was graduated to permit measurement of the volume of chlorine condensed (1.5–2.5 ml.) at its boiling point. With the stirrer, F, running, a gentle stream of prepurified nitrogen was next passed through C, the mixing bulb D, and the rest of the apparatus to remove traces of

(9) H. C. Brown and A. B. Ash, THIS JOURNAL, **77**, 4019 (1955); *cf.* also A. B. Ash and H. C. Brown, *Rec. of Chem. Progr.*, **9**, 81 (1948).

(10) The value of $D(CCl_3\text{–}H)$ is 89 kcal. compared with $D(CH_4\text{–}H)$ of 102 kcal., T. L. Cottrell, "The Strength of Chemical Bonds," Academic Press, Inc., New York, N. Y., 1954.

(11) A. Bruylants, M. Tits and R. Danby, *Bull. soc. chim. Belg.*, **58**, 310 (1949); A. Bruylants, M. Tits, C. Dieu and R. Gautier, *ibid.*, **61**, 366 (1952).

(12) M. S. Kharasch and M. Gladstone, THIS JOURNAL, **65**, 15 (1943); C. C. Price and H. Morita, *ibid.*, **75**, 3686 (1953).

(13) F. R. Mayo and C. Walling, *Chem. Revs.*, **46**, 191 (1950).

(14) L. P. Hammett, THIS JOURNAL, **59**, 96 (1937); L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 184–207. A recent review of the validity of this equation is given by H. H. Jaffe, *Chem. Revs.*, **53**, 191 (1953).

(15) (a) E. C. Kooyman, R. van Helden and A. F. Bickel, *Koninkl. Ned. Akad. Wetenschap. Proc.*, **B56**, 75 (1953); (b) R. van Helden and E. C. Kooyman, *Rec. trav. chim.*, **73**, 269 (1954).

(16) H. Meyer and K. Bernbaum, *Monatsh.*, **53**, 730 (1926).

(17) A. Gattermann, *Ann.*, **347**, 381 (1906).

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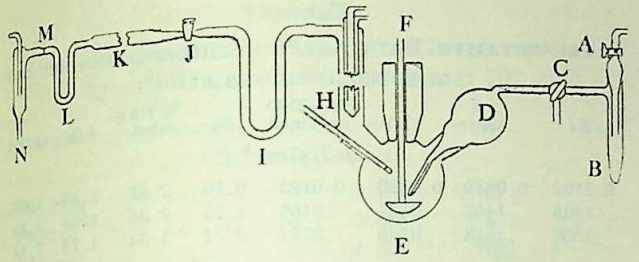

Fig. 1.—Apparatus for competitive liquid-phase halogenation of toluenes.

air. With A closed, and C turned so that all three tubes were connected, the bath around B was lowered and chlorine swept by the nitrogen stream into the reaction flask E which was illuminated by a 200-watt incandescent bulb at the distance of one inch. Both reaction flask and bulb are submerged in a thermostat kept at 69.5 ± 0.5°.

The gases generated passed through an efficient condenser H and Dry Ice trap I where any organic vapors are condensed. They next reached the tube K, packed at both ends with glass wool, and containing a 2-mole excess of tightly packed silver oxide, where the DCl–HCl was converted to D_2O–H_2O. Since this reaction is strongly exothermic, K was cooled and kept from light by a wet towel. Prior to reaction, the entire system beyond J was carefully dried by pumping on a vacuum pump for a half-hour. After all the chlorine had been introduced the stream of nitrogen was continued for 15 minutes to sweep out residual DCl–HCl. The stopcock J was then closed, and the water drawn by a vacuum pump connected to the end of the system into the U-tube L, containing more silver oxide, and cooled by Dry Ice. Next the pump was stopped, the bath lowered, and the water, after melting, shaken with silver oxide. It was then distilled under vacuum through the sintered plate M into the final Dry-Ice trap N where it was weighed and a drop withdrawn and tested for halide with silver nitrate. The water was finally pipetted into a centrifuge tube, centrifuged to remove air bubbles, and the deuterium content measured.

In typical experiments, 0.25–0.35 mole of mixed toluenes was treated with 0.035–0.045 mole of chlorine and E had a volume of 100 ml. In runs using solvents, 100 cc. of solvent and a larger 250-ml. reaction flask were employed, and an additional trap, immersed in an ice-salt bath, was interposed between H and I.

Photobrominations.—A similar apparatus was employed and bromine was pipetted into B, which was maintained at 50° by a water-bath during the reaction.

Sulfuryl Chloride Reactions.—Here the apparatus for halogen introduction was replaced by a pressure equalized dropping funnel, and benzoyl peroxide, rather than light, was used as an initiator. Three ml. of sulfuryl chloride was placed in the funnel, and the system flushed with nitrogen. Next, 0.5 ml. of sulfuryl chloride was dropped into E, and after vigorous reaction began (5–15 min.) the balance introduced over two hours. In operation it was found that the SO_2 and most of the HCl produced condensed in the Dry Ice trap I, so it was necessary to close off the system between H and I by an additional stopcock, and distil the HCl–DCl into K under reduced pressure. The rest of the procedure was similar to that used in photochlorination.

Vapor Phase Reactions.—A mixture of toluene and toluene-α-d_1 was photochlorinated in the vapor phase in order to determine the magnitude of the isotope effect under these conditions. The apparatus used is shown in Fig. 2. In operation, deuterotoluene was placed in B, and chlorine condensed in A by means of a Dry Ice trap. The receiver E was cooled with Dry Ice, while B and the reaction coil D were maintained at 69.5° by a thermostat. During reaction, the pressure in the system was maintained at 85 mm. by a vacuum pump at the end of the usual absorption and conversion train attached at F, and the toluene mixture continually distilled from B through coil D, which was illuminated by a 200-watt incandescent lamp at a distance of one inch, passed into E, and was recycled. Chlorine slowly was introduced by lowering the cooling bath around A, the whole reaction taking 2–3 hours, and the toluene recycling about once every 20 minutes. The absorption of the DCl–HCl mixture and conversion to D_2O–H_2O was accomplished in the same manner as in the liquid-phase experiments.

In addition, we also investigated the competitive chlorination of toluene and cyclohexane in the vapor phase. Here, because of the difference in volatility of the two components, it was not possible to use a recycling system. Accordingly, in place of the flask B, an apparatus was attached consisting of a vaporizer maintained at 100–120° and a coil immersed in the thermostat and intended to bring the vaporized hydrocarbon mixture to thermal equilibrium with the system. The toluene–cyclohexane mixture was dripped slowly into the vaporizer from a pressure-equalized dropping funnel. Considerable difficulty was encountered with this set-up, and only two satisfactory runs were achieved. Accordingly, we have some reservations about the accuracy of our results.

Analytical Methods

Deuterium Determinations.—Measurement of the deuterium content of water was done by the falling drop method[18] in which water density is effectively measured from the time required for uniform droplets to sink a predetermined distance in a carefully thermostated column of *o*-fluorotoluene. A standard curve for sinking time was constructed using known mixtures of D_2O–H_2O, and frequently rechecked. Three or more drops were timed for each sample, the reproducibility being ±0.01% D_2O.

Deuterium analysis in our deuterotoluene was done by burning samples in a conventional apparatus for C–H determination, and collecting the water in a Dry Ice trap protected by a soda-lime tube. On completion of the combustion, the water was distilled into a second trap, and redistillation from a crystal of $KMnO_4$ showed no measurable change in deuterium content.

Total Halogen.—A 2-ml. sample of reaction mixture was refluxed 2–3 hours with xylene and sodium according to the method of Landis and Wichmann.[19] The xylene was distilled from sodium before use and butyl alcohol was used to activate the reaction since commercial amyl alcohol was found to contain significant halogen. The resulting chloride ion was determined by Mohr titration.

Benzyl Halogen.—A 2-ml. sample of reaction mixture was refluxed 2 hr. with 10 ml. of 0.487 *N* NaOH and 30 ml. of ethanol. After neutralization with dilute nitric acid, chloride ion was determined by Mohr titration.

The difference between the two analyses presumably represents non-side-chain substitution, and amounted to 1–4% of the total halogen. Our deuterium concentrations were corrected accordingly, and with chloro- and cyanotoluenes where the method was inapplicable, a correction of 1.5% was used.

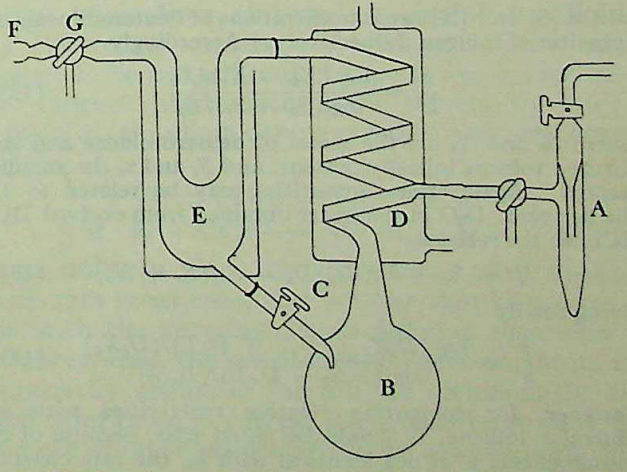

Fig. 2.—Apparatus for vapor-phase halogenation.

Treatment of Data

Isotope Effects.—In a "deuterotoluene" (toluene-α-d_1–toluene mixture) the rate of reaction of halogen with

(18) A. S. Keston, D. Rittenberg and R. Schoenheimer, *J. Biol. Chem.*, **122**, 227 (1937); A. P. Wolf, Ph.D. Thesis, Columbia University, 1952, p. 90.

(19) Q. Landis and H. T. Wichmann, *Ind. Eng. Chem., Anal. Ed.*, **2**, 314 (1930).

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replaceable hydrogen and deuterium is given by

$$d[HCl]/dt = -d[H]/dt = k_H [Cl\cdot][H] \quad (6a)$$

$$d[DCl]/dt = -d[D]/dt = k_D [Cl\cdot][D] \quad (6b)$$

where [Cl·] represents the concentration of halogen atoms and [H] and [D] of replaceable hydrogen and deuterium, respectively. Division of (6*a*) by (6*b*) gives

$$d[H]/d[D] = (k_H/k_D)[H]/[D] \quad (7)$$

Equation 7 is integrated readily, and, since (6*a*) and (6*b*) are of the same kinetic order, concentrations may be expressed as total moles of material present

$$\frac{k_H}{k_D} = \frac{\log (H_0 - H_r)/H_0}{\log (D_0 - D_r)/D_0} \quad (8)$$

where H_0 and D_0, respectively, represent moles of replaceable hydrogen and deuterium originally present, and H_r and D_r moles reacted. The foregoing derivation assumes that only one hydrogen is substituted in each toluene molecule reacted, a circumstance assured by using an approximately ten-fold excess of deuterotoluene.

The quantities in (8) are related to the analytically determined deuterium concentrations by the relations

$$H_0 = 3S_0 - D_0 \qquad H_r = T(100 - D_s)$$
$$D_0 = 8D_s S_0/100 \qquad D_r = TD_s/100 \quad (9)$$

where S_0 and T represent initial moles of deuterotoluene and halogen employed and D_0 and D_s, respectively, the per cent. D_2O in the water obtained on combustion of the particular sample of deuterotoluene and on conversion of the DCl–HCl evolved to D_2O–H_2O.

Table I lists three runs which illustrate the reproducibility of our data treated in this way.

TABLE I

ISOTOPE EFFECT IN THE PHOTOCHLORINATION OF TOLUENE

D_0 (4 DETERMINATIONS) 2.30, 2.30, 2.31, 2.31, AV. 2.305

T	S_0	D_s	k_H/k_D
0.041	0.271	3.45	2.05
.037	.316	3.40	2.11
.039	.312	3.39	2.08

Determination of Relative Reactivities.—In a similar manner to that above, the rates of halogenation of deuterated toluene and a substituted toluene are given by

$$-d[S]/dt = k' [S][Cl\cdot] \quad (10)$$
$$-d[X]/dt = k [X][Cl\cdot] \quad (11)$$

where [S] and [X] are concentrations of deuterotoluene and substituted toluene, respectively. Accordingly

$$\frac{k}{k'} = \frac{\log (X_0 - X_r)/X_0}{\log (S_0 - S_r)/S_0} \quad (12)$$

where S_0 and X_0 are the moles of deuterotoluene and substituted toluene initially present, and S_r and x_r the amounts reacted. Again, these quantities may be related to D_x, the per cent. D_2O in the water obtained from evolved DCl–HCl, *via* the relations

$$T = S_r + X_r, \; D_x/D_s = S_r/(S_r + X_r) \quad (13)$$

giving finally

$$\frac{k}{k'} = \frac{\log (D_sX_0 - D_sT + D_xT)/(D_sX_0)}{\log (D_sS_0 - D_xT)/(D_sS_0)} \quad (14)$$

However, for comparing relative reactivities with *undeuterated* toluene, it should be noted that, because of the isotope effect, k' is not identical with k_0, the rate constant for reaction of halogen atoms with undeuterated toluene. The ratio k'/k_0, however, may be obtained by applying an equation similar to (14) to mixtures of a deuterotoluene and undeuterated toluene, or calculated from the k_H/k_D ratio *via* the relation

$$\frac{k'}{k_0} = 1 - \frac{F}{3}\left(1 - \frac{k_D}{k_H}\right) \quad (15)$$

where F represents the mole fraction of toluene-α-d_1 in the deuterotoluene, determined by combustion. Table II presents typical data for *p*-xylene and *p*-chlorotoluene.

TABLE II

REPRESENTATIVE DATA ON PHOTOCHLORINATION OF SUBSTITUTED TOLUENES AT 70°

X_0	S_0	T	H_2O–D_2O obtained	D_x	% ring subst.	k/k'	k/k_0[b]
			p-Xylene[a]				
0.2102	0.0839	0.0390	0.0192	0.70	2.87	1.85	1.69
.1535	.1455	.0335	.0169	1.55	2.06	1.66	1.54
.1058	.1648	.0369	.0174	2.11	1.94	1.78	1.64
			p-Chlorotoluene				
.1139	.1213	.0330	.0169	3.76	..	0 79	0.725
.0846	.1790	.0350	.0176	4.71	..	80	.73
.1810	.0679	.0337	.0170	2.13	..	75	.69

[a] k ratios corrected by a statistical factor of 2. [b] k'/k_0 = 0.92 for this sample of deuteroluene.

Our technique of determining relative reactivities was also checked for the toluene–*p*-chlorotoluene system by carrying out several larger scale runs using ordinary toluene, and determining the unreacted toluenes by fractional distillation. Data from one experiment appear in Table III, the composition of intermediate fractions being estimated by index of refraction. Three similar experiments, the last two carried out in benzene solution, gave k/k_0 = 0.63, 0.72 and 0.73, average 0.69, which appears within experimental error of the more precise deuterium technique.

TABLE III

FRACTIONATION OF PRODUCT FROM PHOTOCHLORINATION OF 0.386 MOLE TOLUENE, AND 0.3575 MOLE *p*-CHLOROTOLUENE WITH 0.212 MOLE CHLORINE

B.p., °C.	Wt., g.	$n^{25}D$	Moles C_7H_8	Moles C_7H_7Cl
109–112	20.0	1.4943	0.217	....
113–158.5	6.1	1.5049	.031	0.0257
159–163	25.9	1.5191	...	.206
164–177.5	8.6	1.5271	...	.032
			.248	.263

(Moles not recovered) − (Chlorine used) = 0.021

k/k_0 = 0.69

Results and Discussion

Our data on relative reactivities of substituted toluenes are summarized in Table IV, and in Fig. 3 our values of log k/k_0 are plotted against Hammett ρ values of substituents, taken from Jaffe's review.[18] A straight line, drawn by the method of least squares through all points with the exception of the phenyl substituents (which are discussed further below) fits the equation log $k/k_0 = -0.76 + 0.03$, whence $\rho = -0.76$. Our results are thus in qualitative agreement with those of Kooyman (who reports $\rho = -1.5$) in that electron supplying groups facilitate, and electron withdrawing groups retard, the attack of chlorine atoms on toluene. This observation we also consider to be a polar effect perhaps best interpreted in terms of resonance structures of the sort indicated in eq. 4. However, before discussing this matter further we should consider the quantitative differences between the two sets of results.

Kooyman's study[15] differs from ours in that he employed sulfuryl chloride as his chlorinating agent, operated in a solvent (benzene), used a different analytical method (competitions were run against *t*-butylbenzene and products analyzed by separation or by differential rates of alkaline hydrolysis) and a somewhat different method of treating his data. Consideration of each of these

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TABLE IV

RELATIVE REACTIVITIES OF SUBSTITUTED TOLUENES TOWARD RADICAL HALOGENATING AGENTS AT 70°

Substituent	Solvent	No. expts.	k/k_0	Av. dev.[b]	Lit.
		Photochlorination			
p-Methyl	.....	3	1.62[a]	0.05	
p-Phenyl	.....	3	1.59	.03	
m-Methyl	.....	3	1.33[a]	.022	
m-Phenyl	.....	3	1.12	.05	
None	.....	3	1.0	.02	
p-Chloro	.....	3	0.72	.017	
p-Chloro	Benzene	2	.69	.01	
p-Chloro	CCl_4	2	.465	.015	
m-Chloro	.....	3	.54	.017	
p-Cyano	.....	3	.38	.015	
m-Cyano	.....	3	.36	.015	
Cyclohexane[c]	Vapor	2	2.12	.03	
		Photobromination			
p-*t*-Butyl	.....	1	1.6	...	1.5[14]
m-Bromo	.....	1	0.37	...	0.37[15]
p-Cyano	.....	1	0.28	...	0.22[15]
		SO_2Cl_2			
p-Chloro	.....	2	0.69	.01	0.35[15]
m-Cyano	.....	2	0.33	.01	0.16[15]

[a] A statistical factor of two was used in calculating k/k_0. [b] Average deviation from the mean of individual experiments. [c] This experiment was a competitive vapor-phase chlorination of toluene and cyclohexane, and a statistical factor of 4 was used in computing k/k_0.

points in turn provides a convenient basis for presenting some of the conclusions of this work.

Since discovery of the reaction by Kharasch and Brown in 1939,[20] the radical initiated chlorination of hydrocarbons by sulfuryl chloride has generally been considered as a chain process involving chlorine atoms as the chain carriers, and hence it should be identical in selectivity to photochlorination. However, Russell and Brown[21] have recently reported a significantly higher selectivity for tertiary *vs.* primary C–H bonds in the sulfuryl chloride reaction. They have suggested that, at least under some conditions, the $\cdot SO_2Cl$ radical may be the attacking species,[22] and have used the discrepancy between the preliminary report of our work[11] and that of Kooyman to support this interpretation. However, as shown in Table IV, competitive experiments with *p*-chloro- and *m*-cyanotoluene, in our hands, yield results indistinguishable from our photochlorinations. Chlorine and sulfuryl chloride also give indistinguishable k_H/k_D ratios, so we conclude that our substituted toluene experiments give no evidence for different carrier species in the two reactions.

On the other hand, Russell and Brown[7] have reported a k/k_0 value in the competitive chlorination of toluene and cyclohexane of 3.5 at 80°, compared with 2.8 for photochlorination. We have carried out the photochlorination in the vapor phase, obtaining $k/k_0 = 2.12$, which may be within experimental error of the liquid phase reaction, but certainly differs significantly from the SO_2Cl_2 result, particularly since, as observed by Hass,[3] chlorine atom selectivity is generally greater in the vapor than in the liquid phase.

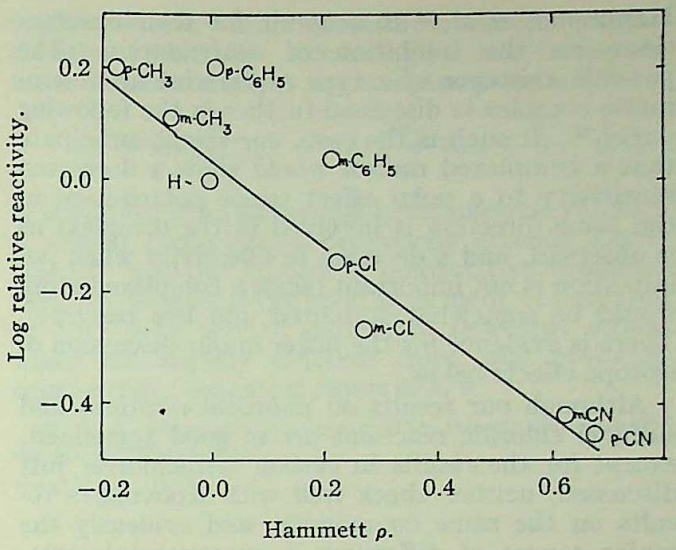

Fig. 3.—Relative reactivities of substituted toluenes toward chlorine atoms *vs.* Hammett ρ values for substituents.

To see if change of solvent plays any role in our systems, we have determined the relative reactivity of *p*-chlorotoluene in benzene and carbon tetrachloride, the systems being approximately 3 *M* in mixed toluenes. In benzene (the solvent used by Kooyman) no significant change occurs, but in carbon tetrachloride selectivity is increased about 50%, a result which has been checked by fractionation of larger runs (two experiments give $k/k_0 = 0.49, 0.43$, in excellent agreement with the isotope method). This then appears to be one of the very few examples of a significant variation in the relative rates of two radical reactions with change of medium and we are unable to afford any convincing explanation, although there also appears to be a significant change in k_H/k_D, see below. Direct interference of the solvent by interaction with the chain carrying radicals by processes such as

$$Cl\cdot + CCl_4 \longrightarrow Cl_2 + \cdot CCl_3 \qquad (16)$$

$$\text{or} \quad R\cdot + CCl_4 \longrightarrow RCl + \cdot CCl_3 \qquad (17)$$

seems unlikely since the reverse of (16) should occur with great ease, and neither should compete well with the very fast chain carrying reactions.[23]

Conceivably, the properties of a chlorine atom in a primarily aromatic solvent are significantly altered from those in carbon tetrachloride, so that, in the bulk of our measurements, we are studying the properties of a complexed radical. Such a suggestion has been made by Russell and Brown,[21] and the possibility of such complexes of peroxy radicals (with more strongly electron donating aromatic systems) has been advanced by Boozer,

(20) M. S. Kharasch and H. C. Brown, THIS JOURNAL, **61**, 2142 (1939).

(21) G. A. Russell and H. C. Brown, *ibid.*, **77**, 4031 (1955).

(22) M. S. Kharasch and A. F. Zavist, *ibid.*, **73**, 964 (1951), have also suggested the participation of $\cdot SO_2Cl$ radicals in SO_2Cl_2–olefin reactions to account for the formation of β-chlorosulfones when terminal olefins are employed.

(23) Reaction 16 would compete with hydrogen abstraction which has a rate constant of $>10^{10.6}$ while the rate constant for (17) may be estimated as <1 from values of chain-transfer with CCl_4 and chain propagation in styrene polymerization where a similar radical is involved.

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Hammond, *et al.*,[24] to account for their observations on the inhibition of autoxidation. The possible existence of a type of chlorine atom–aromatic complex is discussed further in the following paper.[25] If such is the case, one might anticipate that a complexed radical would show a decreased sensitivity to a polar effect (since polarization in the same direction is involved in the complex) as is observed, and a decrease in selectivity when polarization is not important (since a complexed atom would be somewhat stabilized and less reactive). There is evidence for the latter in our discussion of isotope effects below.

Although our results on photochlorinations and sulfuryl chloride reactions are in good agreement, except for the results in carbon tetrachloride just discussed, neither check well with Kooyman's results on the same compounds, and evidently the major source of difference is experimental error. Although Kooyman has used a plausible experimental technique, with the exception of *p*-chlorotoluene (run in duplicate with an experimental error given as 14%) his data represent single experiments. Accordingly, in view of our excellent reproducibility and the good check given by fractionation of reaction mixtures, we believe our results give, at present, the best measure of relative reactivity of substituted toluenes toward chlorine atoms. Actually, it should be pointed out that part of the difference lies in the manner of treatment of data. Kooyman has determined ρ by a "best line" passing through the origin (toluene point), and the resulting slope is heavily influenced by the point for *p*-nitrotoluene for which the "usual" value of 0.778 was employed. In some other radical reactions, better Hammett plots have been obtained by using 1.27, the value for polar reactions involving anilines and phenols.[26] If the larger value is used (or if the *p*-nitrotoluene point is disregarded) and the toluene point is not given special weight, a value of $\rho \cong -1.0$ is obtained.

The negative sign of ρ in our series again points to the importance of polar effects in halogen atom reactions, particularly since any contribution to the transition state due to radical stabilization should produce an effect in the opposite direction.[12] However, our value now indicates a lower selectivity and smaller effect of polar contributions to the transition-state in chlorination than in bromination. For photobromination, Kooyman has reported $\rho = -1.05$, and, from Table IV, our results on three substituted toluenes are in good agreement with his. Actually, there is some uncertainty as to the significance of bromination data due to the reversibility of hydrogen abstraction, but deferring this point for the moment, the difference appears in a reasonable direction. Hydrogen abstraction from toluene by chlorine atoms occurs at a rate comparable to attack on ordinary secondary aliphatic C–H bonds,[8] and, from Pritchard, Pyke and Trotman-Dickenson's work,[5] the latter reaction (in the gas phase, at least) has an activation energy of ~ 1 kcal. In contrast, the bromine atom reaction has a reported[27] activation energy of 7 kcal. One would anticipate that, other things being equal, a low-activation energy process would show less sensitivity to a polar, or any other sort of, effect due to structural variation of the reactants.

Kooyman[15a] has suggested a simple correlation between ρ in radical reactions involving the toluene side-chain and the electronegativity[28] of the attacking atom, based on data involving chlorine and bromine atoms and $\cdot CCl_3$ and succinimide radicals. Our results with photochlorination indicate that the correlation was fortuitous, and it seems implausible to use an electronegativity value for a simple atom for highly substituted species such as the $\cdot CCl_3$ and succinimide radicals, particularly since copolymerization results[13] and recent data on aromatic substitution[29] show plainly that polar effects in the selectivity of carbon radicals vary markedly with the radical structure. Rather, it appears to us that the magnitude of polar effects depends upon an "effective electronegativity" of a radical, markedly influenced by substituents, and the size of the energy barrier to the reaction involved.

As is evident from Fig. 3, our data on phenyl-substituted toluenes indicate anomalously high reactivities. Berliner[30] has reviewed evidence for the value of the *p*-phenyl group, and suggests that at least two different sigma values should be assigned since ". . . effects are much greater where strong resonance interaction of the substituent group is possible, or where it can be enhanced in the transition state." Apparently participation of the *p*-phenyl group in resonance structures of type (4) here represents such a case. The value for *m*-phenyl was given originally on the basis of a single reaction,[14] and has been recalculated by Lichtin and Leftin,[31] from the ionization of *m*-phenylbenzoic acid, as 0.06 ± 0.03, a result which is in better agreement with our data. Thus nei-

TABLE V

ISOTOPE EFFECTS IN THE RADICAL HALOGENATION OF TOLUENE

Reagent	Solvent	No. expts.	k_H/k_D	Av. dev.[a]
Cl_2, light	.....	3	2.08	0.03
Cl_2, light	Benzene	3	2.09	.01
Cl_2, light	*o*-Dichlorobenzene	3	2.09	.03
Cl_2, light	CCl_4	4	1.99	.02
Cl_2, light	Vapor phase	3	2.08	.03
SO_2Cl_2	.....	4	2.105	.012
Br_2, light	.....	3	(3.08)	(.02)

[a] Average deviation from the mean of individual experiments.

(24) C. E. Boozer, G. S. Hammond, C. E. Hamilton and J. N. Sen, THIS JOURNAL, **77**, 3238 (1955).

(25) B. Miller and C. Walling, *ibid.*, **79**, 4187 (1957).

(26) C. Walling, E. R. Briggs, K. B. Wolfstirn and F. R. Mayo, *ibid.*, **70**, 1537 (1948). *Cf.* also ref. 13 which discusses further the justification for this choice.

(27) H. R. Anderson, H. A. Scheraga and E. R. Van Artsdalen, *J. Chem. Phys.*, **21**, 1258 (1953); there are, however, some unexplained peculiarities in this study, since it yields a value of $D(C_6H_5CH_2\text{–}H)$ significantly higher than the generally accepted value.

(28) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1946, pp. 58–88.

(29) R. L. Dannley and E. C. Gregg, Jr., THIS JOURNAL, **76**, 2997 (1954); J. I. G. Cadogan, D. H. Hey and G. H. Williams, *J. Chem. Soc.*, 1425 (1955).

(30) E. Berliner and L. L. Liu, THIS JOURNAL, **75**, 2417 (1953).

(31) N. N. Lichtin and P. Leftin, *ibid.*, **74**, 4207 (1952).

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ther of our phenyl results appear particularly inconsistent with our picture.

Finally, a series of k_H/k_D ratios for halogen atom attack on toluene are collected in Table V. Results for photochlorination in no solvent, vapor, benzene and *o*-dichlorobenzene are experimentally indistinguishable from each other and from the sulfuryl chloride reaction, in accord with our other data on relative reactivities, but the value in CCl_4 is significantly lower, further evidence for some difference in this solvent.

Our value of 3.08 for photobromination is larger than for chlorination, as might be anticipated for a process of higher activation energy,[32] but is actually too low,[33] since photobromination is significantly reversible. Accordingly, the measurement actually involves the complex process

$$RH + Br\cdot \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\cdot + HBr \xrightarrow[k_2]{Br_2} RBr + \cdot Br \quad (18)$$

in which k_2 and k_{-1} have roughly comparable values.[27] A similar complication necessarily attends Kooyman's[15a] and our studies of competitive brominations, so, in spite of the good agreement, it may well be that both sets of data here represent values which are slightly different from, and probably smaller than, the actual ratios of k_2's.

(32) An admirable review of the relation between reaction properties and isotope effects is given by K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955); *cf.* also G. S. Hammond, THIS JOURNAL, **77**, 334 (1955).

(33) K. B. Wiberg, private communication, the actual value (in the absence of HBr) is 4.6–4.9.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Displacement of Aromatic Substituents by Halogen Atoms[1]

BY BERNARD MILLER[2] AND CHEVES WALLING

RECEIVED JANUARY 23, 1957

The reaction of chlorine with bromobenzene to give chlorobenzene and bromine is apparently a radical chain process on the basis of the following evidence: (1) the reaction is light catalyzed; (2) the analogous reaction using sulfuryl chloride is accelerated by benzoyl peroxide; (3) the reaction is inhibited by nitro-, azo- and azoxybenzene; (4) reactions run in competition with the side-chain chlorination of toluene yield comparable ratios of products in light and dark. Similar reactions of substituted bromobenzenes have been studied and competitive experiments show that the displacement is retarded by electron withdrawing groups. Benzenesulfonyl chloride and diphenylsulfone also undergo ready photochemical reaction with chlorine to give chlorobenzene and SO_2, and the photochemical exchange of bromobenzene and Br_2[82] has been demonstrated. Radical chain sequences are proposed, and the critical step, $Cl\cdot + C_6H_5Br \rightarrow C_6H_5Cl + Br\cdot$, is suggested as possibly involving the rearrangement of an intermediate radical–substrate "pi complex."

The difficulty with which aromatic halogen is replaced by polar reagents is well known[3] and chlorination of bromobenzene in the presence of ferric or aluminum chloride proceeds smoothly to give chiefly *o*- and *p*-chlorobromobenzene.[4] However, in 1903 Eibner[5] reported that bromobenzene, on standing with chlorine at room temperature in the absence of catalysts, gave 50% chlorobenzene, together with polyhalogenated products. Molecular bromine was produced, and the reaction was stated to be favored by moisture and direct light.

Similar displacements have been reported in attempts to chlorinate bromotoluenes. Although the successful preparation of *ortho*-,[6] *meta*-[7] and *para*-bromobenzyl chlorides[8] by this route have all been claimed, in 1890 Srpek[9] reported that room temperature chlorination of *p*-bromotoluene gives an inseparable mixture of products with chlorine and bromine in both ring and side-chain. These reactions have been reinvestigated by Asinger,[10] who found that extensive nuclear substitution of chlorine for bromine occurred in all cases.

More recently, Goerner and Nametz reported similar nuclear displacement of bromine during the reaction of bromotoluenes with sulfuryl chloride and benzoyl peroxide at 93°.[11]

While our work was in progress, Voegtli, Muhr and Langer[12] have also described similar displacements on substituted bromobenzenes during photochlorination in refluxing carbon tetrachloride, the three isomeric chlorobromobenzenes giving 82–90% of the corresponding dichlorobenzenes. *p*-Fluorobromobenzene gave *p*-fluorochlorobenzene in similar yield, but under these conditions bromobenzene yielded only 68% chlorobenzene together with a dark residue.

Interestingly, iodine apparently is not replaced as is bromine, chlorination of iodobenzene producing only iodobenzene dichloride,[13] and similar dichlorides are reported from *p*-bromoiodobenzene and *sym*-tribromoiodobenzene.

(1) Taken from a portion of a dissertation submitted by Bernard Miller in 1955 to the Graduate Faculties of Columbia University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) University Fellow, Columbia University, 1954–1955.

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter XV; thus nucleophilic displacements occur with ease only in the presence of strongly electron withdrawing substituents as in 2,4-dinitrochlorobenzene.

(4) M. A. F. Holleman and T. Van der Linden, *Rec. trav. chim.*, **30**, 253 (1911).

(5) A. Eibner, *Ber.*, **36**, 1229 (1903).

(6) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **20**, 665 (1915).

(7) H. Berger, *J. prakt. Chem.*, **2**, 241, 346 (1932).

(8) M. J. Boeseken, *Rec. trav. chim.* **23**, 99(1904).

(9) O. Srpek, *Monatsh.*, **11**, 431 (1890).

(10) F. Asinger, *ibid.*, **64**, 153 (1934).

(11) G. L. Goerner and R. C. Nametz, THIS JOURNAL, **73**, 2940 (1951). A similar observation was made by C. W. in 1946 in an attempt to prepare *m*-bromobenzal chloride.

(12) W. Voegtli, H. Muhr and P. Langer, *Helv. Chim. Acta*, **37**, 1627 (1954)

(13) K. Willgerodt, *J. prakt. Chem.*, **2**, 33, 154 (1886).

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The reported effect of light, and the efficacy of the sulfuryl chloride–peroxide, a well-recognized radical halogenating system,[14] in these displacements, made it appear very likely that they are radical processes, and this paper reports work intended to settle this point, and characterize this sort of reaction more fully.

Results and Discussion

Bromobenzene.—Preliminary experiments confirmed literature reports of the ease of the exchange. When chlorine was bubbled slowly through a slight excess of bromobenzene at 90° under strong illumination, bromine was liberated and chlorobenzene produced in 81% yield based on the equation

$$2C_6H_5Br + Cl_2 \longrightarrow 2C_6H_5Cl + Br_2 \qquad (1)$$

In the dark under similar conditions, but using excess chlorine, the yield was only 39%. The photo-induced reaction also occurs at room temperature, but is accompanied by the formation of a small amount of halogen addition to give mixed polychlorobromocyclohexanes. The presence of bromine at the start of a reaction leads to no reduction in yield, but the photochemical reaction was found to be inhibited completely in the presence of nitrobenzene, azobenzene or azoxybenzene. With sulfuryl chloride, yields of chlorobenzene were low (12–20%) at room temperature or reflux, either in the presence or absence of benzoyl peroxide, but peroxide was observed to eliminate a marked induction period before the appearance of the bromine color.

All of these observations, notably the increase in yield in the presence of light, the accelerating effect of peroxide on the sulfuryl chloride reaction, and the inhibition of the reaction by nitrobenzene, azobenzene and azoxybenzene are consistent with a radical chain process involving halogen atoms. However, in order to obtain more conclusive evidence, and also get an idea of the rate of the displacement step, the competitive reaction of bromobenzene and toluene with chlorine was investigated. Fractionation of the products, and treatment of the data as arising from competitive processes first order in halogen atom and substrate, essentially as described in the preceding paper,[15] yielded a value of k_1/k_2 in the equation

$$\frac{\mathrm{d} \ln [C_7H_8]}{\mathrm{d} \ln [C_6H_5Br]} = \frac{k_1}{k_2} \qquad (2)$$

of 4.0 for a reaction run at 90° in the dark and 5.6 for one run under strong illumination. The difference is probably within experimental error, and, since the chlorination of toluene under these conditions yields almost entirely benzyl chloride by a strongly photocatalyzed radical chain process, in which chlorine atoms are the chain carriers,[15,16] we consider this a crucial experiment establishing that chlorine atoms are involved in the displacement on bromobenzene as well.

(14) M. S. Kharasch and H. C. Brown, THIS JOURNAL, 61, 2142 (1939).

(15) C. Walling and B. Miller, *ibid.*, 79, 4181 (1957).

(16) M. S. Kharasch and M. G. Berkman, *J. Org. Chem.*, 6, 810 (1941).

Substituted Bromobenzenes.—We have also investigated bromine displacement in the presence of chlorine and light in a number of substituted bromobenzenes, both alone and in competitition with bromobenzene. In the latter case, a deficiency of chlorine was used and relative reactivities (again calculated as arising from competitive first-order processes) calculated from product analyses. Results are summarized in Table I, and indicate that, while displacement still occurs in the presence of electron withdrawing groups, reactivity is reduced and the reaction fails with *p*-nitrobromobenzene.

TABLE I

REACTIONS OF BROMOBENZENES WITH CHLORINE AND LIGHT (IN CCl_4 OR $CHCl_3$ AT 65–70° UNDER ILLUMINATION)

Substituent	Yield, %[a]	k/k_0[c]
None	81	1.0
p-Cl	98	0.91
o-COOH	~100	.23
m-COOH	...	.26
p-SO_2Cl	97[b]	< .12
p-NO_2	0	....

[a] Of corresponding chlorobenzene. [b] Of *p*-dichlorobenzene (see below). [c] Relative reactivities compared with bromobenzene from competitive experiments.

Other Displacements.—In our investigation of the photochemical reaction of chlorine with *p*-bromobenzenesulfonyl chloride (Table I) we observed that both bromine and sulfonyl chloride groups were displaced to give a 97% yield of *p*-dichlorobenzene. A similar displacement of the sulfonyl chloride group occurs with benzenesulfonyl chloride to give chlorobenzene (97%). Since chlorine is regenerated in the over-all reaction

$$C_6H_5SO_2Cl + Cl_2 \xrightarrow{h\nu} C_6H_5Cl + SO_2 + Cl_2 \qquad (3)$$

less than stoichiometric quantities are required and slow passage of only 25 mole % of chlorine into benzenesulfonyl chloride at 70° in carbon tetrachloride under illumination gave chlorobenzene in 92% yield. This facile displacement was surprising since the only analogous cases in the literature involve reactions of *o*-toluenesulfonyl chloride and fluoride to give *o*-chlorobenzyl and benzal chlorides at higher temperatures, and have been attributed to the *ortho* orientation of the two reaction sites.[17]

Our results with sulfonyl chlorides led us to investigate the chlorine atom displacement of other groups, and we find that diphenylsulfone reacts smoothly with excess chlorine on illumination in carbon tetrachloride to give chlorobenzene[18]

$$C_6H_5SO_2C_6H_6 + Cl_2 \longrightarrow 2C_6H_5Cl + SO_2 \qquad (4)$$

However, phenyl and methyl benzenesulfonates showed no displacement, even at temperatures of

(17) W. Davies and J. H. Dick, *J. Chem. Soc.*, 2042 (1932). The usual technique for conversion of a $-SO_2Cl$ group $-Cl$ involves the use of PCl_5 at 200–220°; C. M. Suter "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y. 1944, p. 500.

(18) The reaction at 120–130° to give chlorobenzene and benzenesulfonyl chloride has been described by R. Otto, *Ann.*, 141, 93 (1867), who also noted the reaction of 1,2-dichlorosulfonylethane with chlorine at 180° to give 1,2-dichloroethane, chlorobenzene, benzenesulfonyl chloride and other products, R. Otto *J. prakt. Chem.*, [2] 30, 179 (1884).

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150–170°. Displacements also were attempted with N-phenylphthalimide, azobenzene and azoxybenzene. The first was chosen since displacement should yield a presumably rather stable phthalimide radical, and the latter two since the reaction might gain driving force by the elimination of nitrogen. However, in no case were we able to detect any trace of chlorobenzene in the products.

Using Br^{82} as a tracer, we have also been able to show that bromine atoms displace bromine from bromobenzene. At room temperature under strong illumination, exchange between molecular bromine and bromobenzene is approximately 30% complete in 17 hours, while in the dark the reaction is negligible. The ease of this sort of halogen exchange evidently decreases as one ascends the periodic table, iodine showing very little photochemical exchange at room temperature, although a thermal exchange occurs at elevated temperatures.[19]

Reaction Mechanism.—The properties of the reactions we have observed are certainly consistent with a radical chain process which, for the photochemical chlorine–bromobenzene reaction, we may write as

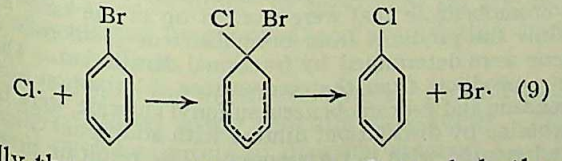
$$Cl_2 \overset{h\nu}{\rightleftharpoons} 2Cl\cdot \quad (5)$$

$$Cl\cdot + C_6H_5Br \longrightarrow BrCl + Cl\cdot \quad (6)$$

$$Br\cdot + Cl_2 \longrightarrow BrCl + Cl\cdot \quad (7)$$

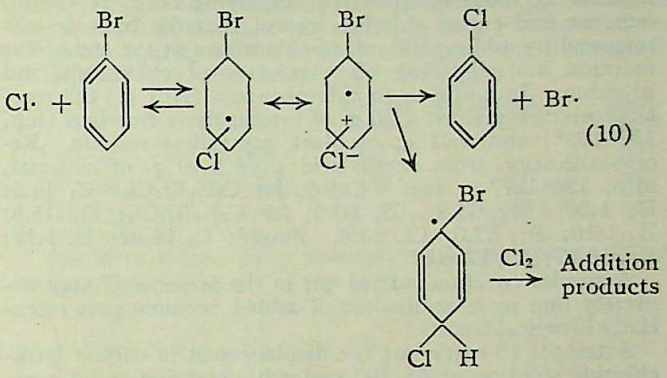
$$2BrCl \rightleftharpoons Br_2 + Cl_2 \quad (8)$$

with additional or alternative steps possible to account for the regeneration of chlorine atoms and the formation of molecular bromine. The interesting and critical step in the sequence is the displacement (6), which at first glance might be pictured either as addition to the aromatic ring followed by bromine atom loss, or as a direct displacement, analogous to the S_N2 displacements observed with negatively substituted halobenzenes.[3] However, either formulation presents difficulties.[20] Addition appears well established as the usual path of attachment of halogen atoms or alkyl or aryl radicals on aromatic systems.[21] However, here, addition would have to occur to the already substituted carbon



(9)

actually the most unlikely point of attack, both on grounds of steric hindrance and resonance stabilization of the resulting radical. Conceivably, of course, addition could be essentially at random, but highly reversible (as actually appears to be the case in the first step of chlorine addition to benzene) with the result that only that fraction of addition which occurs as indicated in (9) leads to displacement. The alternative of direct displacement cannot be ruled out, but would represent one of the very few examples of a direct radical displacement on carbon, and is accordingly somewhat suspect. A third alternative also exists, namely, that both displacements of the sort described here and the more familiar halogen additions to aromatics arise through rearrangement of an initial loose "pi-complex," *i.e.* analogous to the complexes of aromatics with electrophilic reagents discussed by Brown.[22]



(10)

In the case of our sulfonyl chloride and sulfone displacements analogous chains are plausible

$$C_6H_5SO_2Cl + Cl\cdot \longrightarrow C_6H_5Cl + \cdot SO_2Cl \quad (11a)$$

$$\cdot SO_2Cl \longrightarrow SO_2 + Cl\cdot \quad (11b)$$

$$C_6H_5SO_2C_6H_5 + Cl\cdot \longrightarrow C_6H_5Cl + C_6H_5SO_2\cdot \quad (12a)$$

$$C_6H_5SO_2\cdot + Cl_2 \longrightarrow C_6H_5SO_2Cl + Cl\cdot \quad (12b)$$

or

$$C_6H_5SO_2\cdot \longrightarrow C_6H_5\cdot + SO_2 \quad (12c)$$

$$C_6H_5\cdot + Cl_2 \longrightarrow C_6H_5Cl + Cl\cdot \quad (12d)$$

but we have no convincing explanation for the relative stability of benzene sulfonate esters.

Finally, two properties of these displacements need to be pointed out which must be accounted for in any complete reaction scheme. The first is the retarding effect of electron withdrawing groups (Table I) which is certainly consistent with a "pi-complex" scheme, but is actually a general characteristic of all chlorine atom processes.[15] The second is the extremely high *rate* of the displacement step, established by competition with the side-chain chlorination of toluene. Our results indicate that reaction 6 has approximately the same rate constant as that for the attack of a chlorine atom on a single benzyl C–H bond, a process which, as discussed further in our preceding paper,[15] probably has a rate constant of 10^{10}, and an activation energy of < 2 kcal. These displacements are thus extremely facile processes, with rates considerably higher than most radical–substrate reactions, and this, to us, makes them of particular interest.

Experimental

Reaction of Bromobenzene with Chlorine.—Fifty-nine grams (0.376 mole) of bromobenzene was placed in a 3-necked flask fitted with gas inlet tube, stirrer, reflux condenser and thermometer. The flask was illuminated by a 200 watt light bulb at a distance of three inches and maintained at 90°. Chlorine (0.156 mole, obtained by evapor-

(19) S. Levine, Thesis, Columbia University, 1955.

(20) An alternative scheme involving displacement on halogen

$$C_6H_5Br + Cl\cdot \longrightarrow C_6H_5\cdot + ClBr \quad (6a)$$

would be endothermic by ~10 kcal. and is accordingly ruled out by the high rate of the displacement step discussed below.

(21) For a discussion of this point, *cf.* J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1956, Ch. 22.

(22) H. C. Brown and J. D. Brady, THIS JOURNAL, 74, 3570 (1952). The second step in the normal halogen addition process, in their terminology would correspond to the rearrangement of a π to a σ complex.

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ating 3.5 ml. of liquid chlorine) was bubbled through the system during one hour. Within five minutes the reaction mixture turned orange and then red, and soon bromine refluxed in the condenser. The cooled reaction mixture was stirred with sodium bisulfite solution, extracted with ether, dried over NaOH pellets and fractionated through a 10-plate Fenske column. The yield of chlorobenzene was 31.5 g. (0.254 mole, 81% based on chlorine). A similar reaction carried out in the dark (with the system wrapped in aluminum foil) gave a yield of only 39%.

The photochemical reaction was carried out in a similar manner at room temperature employing 30 g. of chlorobenzene and excess chlorine, except that the bromine was removed by adding 100 ml. of chloroform at the end of the reaction and distilling off a mixture of chloroform and bromine. In addition to chlorobenzene (20.1 g.) the reaction mixture yielded 2.26 g. of intermediate fractions (b.p. 136–160°) and 4.41 g. of black crystalline residue. Recrystallization from acetic acid gave 2.00 g. of material, m.p. 126–127°. *Anal.* Calcd. for $C_6H_5Br_4Cl_3$: C, 14.3; H, 1.00; Br, 63.8; Cl, 20.9; for $C_6H_5Br_3Cl_4$: C, 15.8; H, 1.10; Br, 52.0; Cl, 30.8. Found: C, 14.62; H, 1.19; Br, 59.87; Cl, 22.90

A similar reaction carried out in the presence of approximately one mole equivalent of added bromine gave essentially identical results.

Attempts to carry out the displacement in carbon tetrachloride solution at 65–70° under illumination in the presence of nitrobenzene, azobenzene or azoxybenzene gave no material boiling between 125 and 135° or indication of the liberation of bromine.

Reaction of Bromobenzene with Sulfuryl Chloride.—Bromobenzene (35.1 g.) and freshly distilled sulfuryl chloride (20 ml.) were mixed and allowed to stand at room temperature. After two hours the initially light yellow solution turned light orange, and, 15 minutes later, dark red. After standing overnight the reaction mixture was poured into aqueous sodium bisulfite solution, extracted with ether, and the ether layer dried over calcium chloride and distilled to give a 12% yield of chlorobenzene and 85% recovered bromobenzene. A similar experiment carried out in the presence of 0.207 g. of benzoyl peroxide turned deep red within 11 minutes, but the yield of chlorobenzene was still only 15%. When the same quantities of bromobenzene and sulfuryl chloride were refluxed together the deep bromine color developed in 35 minutes, and, after 6 hours, the mixture yielded 12% chlorobenzene. Addition of benzoyl peroxide gave the bromine color within three minutes and 16% chlorobenzene after six hours.

Reaction of Substituted Bromobenzenes with Chlorine.—*p*-Chlorobromobenzene (31.0 g.) was dissolved in 200 ml. of carbon tetrachloride and heated to 70° under a reflux condenser. A rapid stream of chlorine was passed through the solution while it was illuminated by a 200 watt light bulb at a distance of three inches. The solution soon turned red, and after 90 minutes the solvent was evaporated to give 23.7 g. (98%) of *p*-chlorobenzene, m.p. 46–49°. Two recrystallizations from ethanol gave 20.0 g., m.p. 51–53°: other displacements on substituted bromobenzenes were carried out similarly using either chloroform or carbon tetrachloride as solvent with results listed in Table I. With *o*- and *p*-nitrobromobenzene, no bromine color developed, and starting materials were recovered unchanged.

Competitive Reaction of Toluene and Bromobenzene.—A mixture of 0.645 mole of toluene and 0.694 mole of bromobenzene was placed in a stirred reaction-flask and heated to 90° while illuminated by a 200 watt incandescent light. Chlorine (0.376 mole) was introduced over 90 minutes, and the mixture first turned yellow, but then became colorless. The product was fractionally distilled through a 12-plate glass helix packed column, using dicyclohexyl as a chaser, and the composition of intermediate fractions determined by index of refraction. In a parallel experiment in the dark, chlorine was introduced over two hours, and the product compositions shown in the following table were determined. Relative reactivities were calculated from the relation

$$\frac{k}{k_0} = \frac{\log [C_7H_8]_{initial}/([C_7H_8]_{initial} - [C_7H_7Cl])}{\log [C_6H_5Br]_{initial}/([C_6H_5Br]_{initial} - [C_6H_5Cl])} \quad (13)$$

Since material balances were not quantitative, the values of k/k_0 are subject to considerable uncertainty but it seemed

	Light (moles)	Dark (moles)
Cl_2 (initial)	0.376	0.400
C_6H_5Br (initial)	.649	.720
C_7H_8 (initial)	.645	.747
C_6H_5Br (recovered)	.549	.572
C_7H_8 (recovered)	.264	.373
C_6H_5Cl	.069	.074
C_7H_7Cl	.297	.263
C_6H_5Br unaccounted for	.031	.074
C_7H_8 unaccounted for	.034	.054
k/k_0	5.6	4.0

that the best way of determining the amount of unreacted toluene and bromobenzene (the denominators in the fractions of eq. 13) was by subtracting the amount of isolated products from the accurately known initial quantities of reactants. Accordingly the values for k/k_0 reported are probably a little high. The alternate method of using values for recovered toluene and bromobenzene (corrected for the small amount of benzyl bromide formed), since it involves larger numerical quantities presumably subject to the same percentage error as those for chlorobenzene and benzyl chloride, appears less accurate and gives k/k_0's of 3.1 and 2.4 for the light and dark reactions, results which must be considerably too low.

Competitive reactions of bromobenzenes were carried out under illumination in chloroform solution at approximately 65° with over-all results summarized in Table I. In a typical experiment 0.175 mole of *m*-bromobenzoic acid and 0.185 mole of bromobenzene in 300 ml. of chloroform were treated with 0.095 mole of chlorine during two hours. The solution was cooled, the solid acids filtered off, and washed free of bromine with fresh chloroform. The filtrate and washings were stirred with aqueous sodium sulfite–sodium hydroxide, washed with water, and the aqueous extracts acidified. The resulting precipitate was combined with the acids originally isolated, and recrystallized from chloroform to give 33 g. of mixed acids containing 35.9% Br and 2.28% Cl by analysis. Bromobenzene and chlorobenzene were determined by fractionation of the chloroform layer, and the following material balance obtained

	Mole
C_6H_5Br (initial)	0.185
$C_6H_4BrCOOH$ (initial)	.175
C_6H_5Br (recovered)	.092
$C_6H_4BrCOOH$ (recovered)	.148
C_6H_5Cl	.074
$C_6H_4ClCOOH$	.021
C_6H_5Br unaccounted for	.019
$C_6H_4BrCOOH$ unaccounted for	.004

Relative reactivities were calculated in the same manner as for the toluene–bromobenzene experiment. The products from the competitive chlorination of bromobenzene and *o*-bromobenzoic acid were worked up in the same manner, while the products from bromobenzene–*p*-chlorobromobenzene were determined by fractional distillation. The reaction products from the competitive chlorination of bromobenzene and *p*-bromobenzenesulfonyl chloride were freed of bromine by distillation, diluted with additional chloroform, and treated with dry ammonia. The resulting precipitate was recrystallized from benzene and found to be chlorine-free *p*-bromobenzenesulfonamide, m.p. 165–166°. The difference between the amount obtained and the amount of *p*-bromobenzenesulfonyl chloride initially present was taken as the quantity of the former which underwent bromine displacement. Since some of the material was necessarily consumed by displacement of the sulfonyl chloride group, the resulting calculated reactivity for displacement of bromine represents merely an upper limit, and is so indicated in Table I.

Reaction of Chlorine with Benzenesulfonyl Derivatives.—*p*-Bromobenzenesulfonyl chloride (32.4 g.) was dissolved in 250 ml. of carbon tetrachloride and kept at 70° in an illuminated flask while a rapid stream of chlorine was passed through the solution for two hours. Evaporation of the solvent and bromine gave 18.1 g. (97%) of *p*-dichlorobenzene, m.p. 47–50°. A similar experiment using benzenesulfonyl chloride gave 97% chlorobenzene. When a limited

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amount of chlorine (0.078 mole for 0.308 mole of benzenesulfonyl chloride) was employed, the mixture at the end of the reaction showed no peak in the infrared spectrum at 8-9 μ, characteristic of sulfonyl chlorides, and gave 92% chlorobenzene on distillation.

Under the same conditions diphenylsulfone also gave chlorobenzene in essentially quantitative yield, but phenyl benzenesulfonate and methyl benzenesulfonate gave no chlorobenzene and good yields of starting material when treated with chlorine and light, either at 70° in carbon tetrachloride or at 150–170° in absence of solvent.

Other Attempted Displacements.—Treatment of azobenzene, azoxybenzene and N-phenylphthalimide with chlorine and light at 70° in carbon tetrachloride solution gave only starting material and no trace of chlorobenzene. Similarly no displacement was observed when iodobenzene was refluxed with sulfuryl chloride in the presence of benzoyl peroxide, or when benzenesulfonyl chloride or diphenylsulfone was illuminated in the presence of bromine.

Exchange of Br^{82}_2 with Bromobenzene.—Twenty-five ml. of bromine containing Br^{82}, 50 ml. of bromobenzene and 75 ml. of carbon tetrachloride were mixed and then divided into three equal portions placed in stoppered flasks. One flask was kept for 18 hours at room temperature while being illuminated at a distance of 8 inches by a 200 watt incandescent light, the others were stored in the dark. The contents of the illuminated flask and one other were washed with sodium bisulfite solution and then three portions of water, and the radioactivity of the organic layer determined, using a Geiger counter of the type described by Sibbett.[23] The contents of the third flask were used to determine total radioactivity. In a second experiment a similar mixture was irradiated for four hours at 50° and overnight at room temperature. The bromine was then washed out, and the radioactivity of the organic layer determined. In order to establish that the radioactivity was confined to bromobenzene, the organic layer was next carefully fractionated and the radioactivity of the bromobenzene fraction determined. Results of both experiments are shown below.

Run	Total	Activity (counts/min.) Organic	C_6H_5Br	Background
1 (light)	12,344	2272	...	50
1 (dark)	12,344	90	...	50
2 (light)	21,317	4211	4110	62

(23) D. L. Sibbett, Thesis, Columbia University, 1951, pp. 11–12.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA, UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

Structure and Properties of Cyclic Compounds. IX.[1] Hemiketal Formation of Cyclic Ketones

BY OWEN H. WHEELER

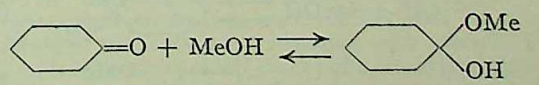
RECEIVED SEPTEMBER 20, 1956

Cyclohexanone has been found to undergo acid-catalyzed hemiketal formation with methanol in dioxane solution. The extent of hemiketal formation of a number of cyclic ketones in pure methanol is in agreement with I-strain prediction and is reduced by steric effects. Less reaction takes place with ethanol and no reaction is observed with isopropyl alcohol or water.

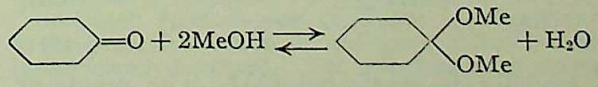
During the course of routine spectroscopic measurements,[2] it was observed that the intensity of absorption of cyclic ketones in methanol depended on the sample of methanol used as solvent. Addition of a drop of concentrated hydrochloric acid greatly reduced the intensity. The decreased absorption of aldehydes in polar solvents has been noted by many workers[3] and has been attributed to hemiacetal formation. This suggests that the above results may be due to a similar reaction. A decrease in the refractive index of solutions of acetone and cyclohexanone in methanol on the addition of acids has been noted[4] and is probably caused by the same effect.

The reaction between cyclohexanone and methanol was studied using dioxane as solvent. Solutions of cyclohexanone in dioxane showed λ_{max} 290 mμ (ϵ 15.8 ± 0.1, mean of five readings). In the presence of 0.05 *M* hydrogen chloride the absorption was unchanged. Similarly the absorption intensity of cyclohexanone in dioxane containing 0.07, 0.12 and 0.26 *M* methanol was ϵ 15.85, 15.75, 15.8, respectively, with the maxima at the same wave length. These solutions showed no change in absorption on standing. Thus the decrease in intensity in methanolic hydrogen chloride solution cannot be due to reaction between the ketone and the acid or to a non-acid-catalyzed reaction between the ketone and methanol.

The most probable reactions of cyclohexanone and methanol catalyzed by acids are those of hemiketal (1) and ketal (2) formation. Both reactions are first order in ketone but reaction 1 is first order



(1)



(2)

and reaction 2 second order in alcohol. The reaction was studied in dioxane containing 0.05 *M* hydrogen chloride using varying concentrations of ketone and alcohol (Table I). The concentration of unreacted ketone was calculated from the extinction coefficient of the solution and the known extinction of cyclohexanone in dioxane in the absence of acid. The concentration of the addition compound is then the difference between this and the initial ketone concentration. In the first case the final methanol concentration is the difference between the initial concentration and the concentration of addition compound and in the second the difference with twice the addition compound concentration. The dissociation constants K^1_D and

(1) Part VIII, *Chemistry & Industry*, 1388 (1956).
(2) *Cf.* O. H. Wheeler and J. L. Mateos, *Anal. Chem.*, **29**, 538 (1957).
(3) (a) W. Harold and K. L. Wolf, *Z. physik. Chem.*, **21**, 165 (1931); (b) A. M. Buswell, E. C. Dunlop, W. H. Rodebush and J. B. Swartz, THIS JOURNAL, **62**, 325 (1940); (c) I. L. Gaudity, *Z. physik. Chem.*, **48**, 228 (1941); (d) N. Melchior, THIS JOURNAL, **71**, 3647 (1949); (e) P. Rampf and C. Bloch, *Compt. rend.*, **223**, 1364 (1951); (f) C. D. Hurd and W. H. Saunders, THIS JOURNAL, **74**, 5324 (1952).
(4) T. Tomonari, *Angew. Chem.*, **46**, 269 (1933); *J. Soc. Chem. Ind. Japan*, **36**, 485 (1933)

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TABLE I

REACTION OF CYCLOHEXANONE AND METHANOL IN DIOXANE[a]

$[MeOH]_I$, M	$[\bigcirc\!\!=\!O]_I$, M	ϵ^b	K^1_D	K^2_D
0.492	0.0169	13.2	2.46	0.957
.492	.0325	13.3	2.62	1.25
.492	.0519	13.4	2.70	1.29
1.220	.0311	11.0	2.75	3.28
1.220	.0494	10.9	2.69	3.16
2.490	.0251	7.37	2.16	5.30
2.490	.0519	7.71	2.34	5.64
2.490	.0698	7.95	2.48	5.93
		Mean	2.53 ± 0.15	

[a] In the presence of 0.05 M hydrogen chloride at 25.0 ± 0.2°. [b] ϵ at 290 mμ.

K^2_D for the first and second reactions were calculated, and it can be seen that while K^1_D is sensibly constant, K^2_D varies considerably and thus the reaction must be first order in both ketone and alcohol and is the hemiketal equilibrium (1).[5] That the only function of the hydrogen chloride is to act as an acid catalyst is shown by the fact that the dissociation constants of the hemiketals of cyclopentanone and cyclohexanone are independent of acid concentration over a range of 50-fold (Table II).

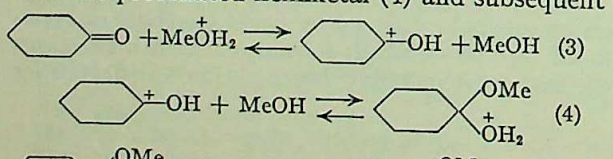
TABLE II

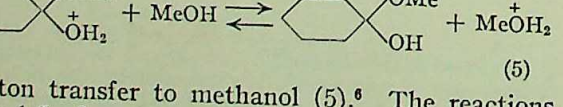
EFFECT OF ACID CONCENTRATION[a]

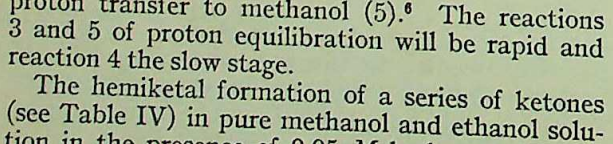
	0.002 M HCl		0.01 M HCl		0.05 M HCl		0.1 M HCl	
	ϵ	K^1_D	ϵ	K^1_D	ϵ	K^1_D	ϵ	K^1_D
Cyclopentanone	5.63	15.4	5.59	15.3	5.55	15.1	5.68	15.4
Cyclohexanone	1.01	2.35	0.93	2.13	0.98	2.16	0.99	2.30

[a] In methanol at 25.0 ± 0.2°.

Equation 1 only represents the stoichiometry of the reaction. The mechanism probably will involve initial formation of the protonated ketone (3), followed by nucleophilic attack of methanol to form the protonated hemiketal (4) and subsequent







proton transfer to methanol (5).[6] The reactions 3 and 5 of proton equilibration will be rapid and reaction 4 the slow stage.

The hemiketal formation of a series of ketones (see Table IV) in pure methanol and ethanol solution in the presence of 0.05 M hydrogen chloride has been measured. The concentration of unreacted ketone [Ket.$_f$] is proportional to the extinction coefficient (ϵ_a) of the acid solution, and the concentration of hemiketal [Hemiket.] is proportional to the difference between the extinction coefficients of the neutral (ϵ_0) and acidified solutions.

The concentration of methanol and ethanol was taken as the molarity of the pure solvent.[7]

$$K_D = [\text{Ket.}_f][\text{ROH}]/[\text{Hemiket.}] = 32 \text{ (or } 46)\epsilon_a/\epsilon_0 - \epsilon_a$$

The results with cyclopentanone and cyclohexanone are in agreement with the I-strain concept of Brown.[8] Cyclohexanone is reactive since addition to the double bond relieves angle strain in the ring and the small interference of the α-hydrogen atoms with the keto group, while addition to the carbonyl grouping of cyclopentanone gives a product in which there is considerable interaction with the ring hydrogen atoms and these additions are not favored. In the case of cyclobutanone this ketone is highly strained[8c] and addition reactions will be facilitated. However, the hemiketal will be a crowded molecule, and ring hydrogen interactions will tend to decrease its stability. Thus though cyclobutanone methyl hemiketal is more stable than cyclohexanone methyl hemiketal, the reverse is true for the ethyl hemiketal where repulsion of the bulky ethoxy group decreases the stability of the cyclobutanone addition compound. Addition to the ketone groupings of cycloheptanone and cycloöctanone will also not be favored because of the hindered nature of the hemiketals, and no reaction was observed between these ketones and ethanol.

The presence of methyl groups in cyclic ketones at positions not adjacent to the ketone grouping has been found[1,9] to decrease the reactivity toward cyanohydrin formation due to steric repulsion across the ring between the methyl and cyano groups. Similarly in methyl hemiketal formation 3-methylcyclopentanone is less reactive than cyclopentanone itself, and 3,3,5,5-tetramethylcyclohexanone is very unreactive, and neither compound reacts with ethanol. Bridge ring ketones are also unreactive toward addition reactions,[10] and the methyl hemiketal of camphor is very unstable, and no reaction occurs with ethanol. Di-*n*-propyl ketone has the same number of carbon atoms as cycloheptanone, but the chains are staggered in space and not confined in a ring, and accordingly steric hindrance to addition is greater. In the case of diisopropyl ketone, the two bulky isopropyl groups prevent any reaction from taking place.

The methyl hemiketal formation of di-*n*-propyl ketone, cyclobutanone, cyclopentanone and cyclohexanone was also measured at 1.5° and the heat of formation of the hemiketals (ΔH) calculated (see Table III). Since it was difficult to measure the small amounts of unreacted ketone in the case of cyclobutanone and cyclohexanone, the results are only approximate, but addition to the ketone grouping of cyclohexanone involves less energy change than in di-*n*-propyl ketone, whereas additions to

(5) The initial rapid formation of hemiketal may be followed by slow formation of a ketal, but this could not be detected since on long standing the absorption intensity increased and the maximum was shifted to shorter wave length, the ketones probably undergoing self-condensation.

(6) Cf. C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.*, **20**, 1695 (1955).

(7) No appreciable error is involved in this assumption since the ketone concentration was never greater than 0.1 M.

(8) (a) H. C. Brown, R. S. Fletcher and R. B. Johannesen, THIS JOURNAL, **73**, 212 (1951); (b) H. C. Brown, J. H. Brewster and H. Schechter, *ibid.*, **76**, 467 (1954); (c) H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

(9) Unpublished work with O. Chao.

(10) O. H. Wheeler, R. Cetina and J. Z. Zabicky, *J. Org. Chem.*, in press.

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TABLE III

HEMIKETAL FORMATION WITH METHANOL AND ETHANOL

	25°		1.5°		25°		K_D^{MeOH}		25°	
	MeOH[a]	MeOH/HCl[b]	MeOH	MeOH/HCl	EtOH	EtOH/HCl	25°	1.5°	K_D^{EtOH}	ΔH[c]
Di-*n*-propyl ketone	282:24.6	18.1	23.9	12.3	23.4	23.7	89.0	34.0		6.7
Diisopropyl ketone	284:19.5	19.5			19.6	19.4	∞			
Cyclobutanone	278:16.95	0.57	16.55	0[d]	15.0	13.15	1.11	0[e]	327	..[f]
Cyclopentanone	288:17.3	5.55	16.7	2.17	17.65	16.7	15.1	4.79	810	8.0
Cyclohexanone	282:14.9	0.98	14.1	0.49	16.6	13.9	2.16	1.15	237	4.3
Cycloheptanone	284:19.5	12.2			18.55	18.65	53.5		∞	
Cyclooctanone	282:19.2	17.15			21.8	21.9	268		∞	
3-Methylcyclopentanone	288:19.45	11.30			21.7	21.7	23.3		∞	
3,3,5,5-Tetramethylcyclohexanone	288:50.2	39.5			46.8	46.5	118		∞	
Camphor	290:30.8	29.9			30.5	31.5	1060		∞	

[a] All measurements at 25.0 ± 0.2° unless otherwise stated. 0.05 *M* hydrogen chloride in all cases. [c] ΔH, kcal. in MeOH at 25°. [d] ϵ 0.05. [e] $K < 0.2$. [f] ΔH *ca.* 11.9 kcal.

cyclobutanone and cyclopentanone are more difficult due to the steric repulsions produced in the hemiketals.

The spectra of di-*n*-propyl ketone, cyclopentanone and cyclohexanone were measured in water and 2-propanol containing 0.05 *M* hydrogen chloride (Table IV). In neither case was there

TABLE IV

SPECTRA IN WATER AND ISOPROPYL ALCOHOL

	Water		Isopropyl alcohol	
	−	+ 0.05 *M* HCl	−	+ 0.05 *M* HCl
Di-*n*-propyl ketone	275:28.2	28.4	283:24.0	23.8
Cyclobutanone	273:19.7	19.6	.....	..
Cyclopentanone	280:20.4	20.2	298:18.8	19.2
Cyclohexanone	278:18.6	18.8	284:16.8	17.2

any decrease in absorption intensity as compared with the spectra in neutral solution.[11] This difference in the behavior of methanol and ethanol, on the one hand, and water and 2-propanol on the other, cannot be due to the differing nucleophilic properties of the solvents since water is a stronger nucleophile than methanol. The unreactivity of water probably is due to its high self-solvation and the high free energy necessary for its "desolvation," before solvation of a ketone can take place. In the case of 2-propanol, steric hindrance to the formation of a bulky isopropoxide derivative probably prevents reaction. The non-reactivity of cyclobutanone is interesting in that cyclopropanone is known only as its hydrate,[12] but in the latter case I-strain in the ketone is so great that hydrate formation is favored.

The closest analogous addition reaction to that of hemiketal formation is the cyanohydrin reaction, and it is interesting to compare the results for the two series (Table V). Comparing di-*n*- and diisopropyl ketone and cycloheptanone and cyclooctanone in the two reactions, the hemiketal appears to have larger steric requirements, and this is to be expected since the methoxy group with the lone pair of electrons on the oxygen atom and the hydrogen atoms of the methyl group will be larger than the linear cyano group. The cyclization of open chain hydroxyaldehydes to form intramolecular cyclic hemiketals has been investigated.[13] In this case the stabilities will depend on both the ease of ring closure and the resulting I-strain in the ring,

TABLE V

COMPARISON WITH OTHER DATA

	K_D^{MeOH}[a]	$K_D^{HCN} \times 10^2$	K^{ketals}[d]
Di-*n*-propyl ketone	89.0	13.4[b]	...
Diisopropyl ketone	∞	19.3[b]	...
Ring size, $n = 4$	1.11		
$n = 5$	12.1	2.1[c]	0.13
$n = 6$	2.1	0.1[c]	0.065
$n = 7$	53.5	13[c]	5.7
$n = 8$	268	86[c]	...

[a] Present work. [b] In 96% ethanol at 35°; C.P. Evans and J. R. Young, *J. Chem. Soc.*, 1310 (1954). [c] In 96% ethanol at 22–23°. V. Prelog and M. Kobelt, *Helv. Chim. Acta*, **32**, 1187 (1949). [d] Dissociation constants of cyclic ketals, in 75% dioxane at 25°. Calculated from the results of C. D. Hurd and W. H. Saunders, ref. 13.

and the large dissociation constant of the seven-membered cyclic hemiketal probably is due to an unfavorable combination of these effects.

Experimental

The ketones used were specimens which had been fractionally distilled or purified through their semicarbazones.

Methanol and ethanol were dried by refluxing with and distilling from their magnesium alkoxides[14] and isopropyl alcohol by distilling with sodium. Dioxane was refluxed with potassium hydroxide and fractionated from a fresh quantity and this treatment repeated with metallic sodium. The first fraction contained traces of aromatic hydrocarbons which made it unsuitable for spectroscopic work.[15]

Hydrogen chloride was generated by dropping A. R. hydrochloric acid into A. R. sulfuric acid and was absorbed in the required solvent. The solutions were standardized with carbonate-free sodium hydroxide and used immediately after preparation.

The spectroscopic measurements were made using a Beckman DU spectrophotometer fitted with thermospacers, through which water was circulated at 25.0 ± 0.2° from a constant temperature bath or at 1.5 ± 0.2° from an ice–water-bath.

The solvents were kept in the constant temperature baths until needed; 1-cm. quartz cells were used and the comparison cell contained solvent of the same composition. Readings were taken after 10 min. and again after 0.5 hr., but no differences were noted. However, after about 1 hr. the readings began to increase. The determinations were carried out in duplicate or triplicate using different solu-

(11) The hydration of acetone has been shown to be less than 1% in aqueous solution; R. P. Bell and J. C. Clunie, *Trans. Faraday Soc.*, **48**, 439 (1952).

(12) P. Lipp, J. Buchkremer and H. Seeles, *Ann.*, **499**, 1 (1932).

(13) C. D. Hurd and W. H. Saunders, THIS JOURNAL, **74**, 5324 (1952).

(14) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).

(15) *Cf.* C. A. Kraus and R. A. Vingee, THIS JOURNAL, **56**, 511 (1934).

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tions, and the mean of the values is reported in the tables. No departures from Beer's law were observed except in the cases of cyclobutanone and cyclohexanone in methanolic hydrogen chloride solution, when only inflections or very broad maxima were observed.

Acknowledgment.—This work was made possible by generous grants from the Rockefeller Foundation, New York.

MÉXICO 20, D.F.

[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE]

3α-(2-Diethylaminoethyl)-aminotropane and Related Compounds[1,2]

BY S. ARCHER, T. R. LEWIS AND M. J. UNSER

RECEIVED, FEBRUARY 20, 1957

Tropinone was reductively aminated in the presence of diethylaminoethylamine and the resulting triamine was quaternized to furnish a bismethiodide in which the secondary amine function was still present. The compound is a tropane and not a pseudotropane as was shown by converting 3α-benzylaminotropane to the known 3α-aminotropane. The corresponding triamine derived from pseudopelletierine was prepared by catalytic reduction of the Schiff base. Evidence is presented which lends additional support to the view that in the reductive amination process it is the Schiff base and not the carbinolamine which is hydrogenated. The triamines in the pseudo series were prepared by sodium–alcohol reduction of the Schiff bases from diethylaminoethylamine and tropinone or pseudopelletierine.

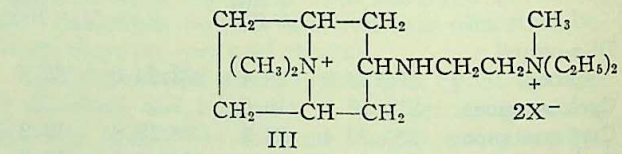
The proven clinical utility of "hexamethonium" in the control of malignant hypertension has stimulated further investigation of many bis 'onium types of peripheral ganglionic blocking agents.[3] More recently it has been shown by Cavallito and his coworkers[4] that by appropriate manipulation of the length of the chain separating the 'onium centers and the groups attached to the quaternary nitrogen atoms, it was possible to prepare hypotensive agents whose action was predominantly central rather than peripheral.

As a part of a chemical–pharmacological program, we have prepared a series of compounds of which the prototypes are the quaternary salts III and IV. Since the pharmacological aspects of this work already have been published,[5] we will confine our discussion to the more interesting chemical features of the joint endeavor.

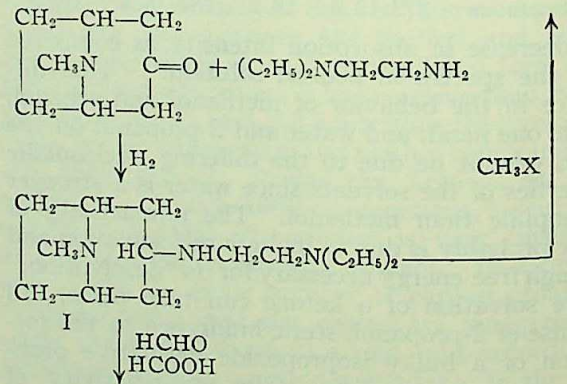
The general method of synthesis is shown in the equation chart.

Since isomerism is possible at C-3 in the triamine I, it became necessary to establish which stereoisomer was formed in the reductive amination. Willstätter[6] prepared 3β-aminotropane by sodium–alcohol reduction of tropinone oxime. The same oxime furnished 3α-aminotropane upon reduction with sodium amalgam. We were able to obtain 3α-aminotropane by catalytic reduction of tropinone oxime. After our work was completed, a similar preparation was reported by Stoll.[7]

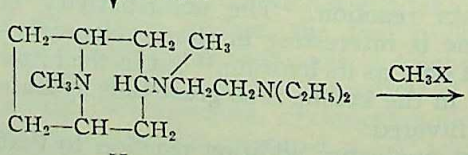
Hydrogenation of tropinone affords tropine[8] which has been isomerized to pseudotropine under alkaline conditions.[9] Similarly, 3α-aminotropane was isomerized to 3β-aminotropane with the aid of



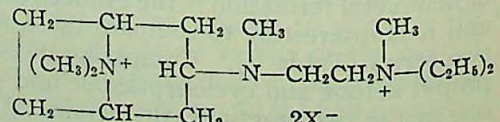
III



I



II



IV

sodium amoxide.[6] The configuration of the tropines has been established,[10] and in view of the marked similarities in preparation and isomerization of the two aminotropanes, it seems clear that

(1) A portion of this paper was presented at the XIV Congress for Pure and Applied Chemistry, Zurich, July, 1955.

(2) The configurations of the tropanes are designated according to the convention proposed by Fodor (ref. 10).

(3) *Inter alios, cf.* A. Marxer and K. Miescher, *Helv. Chim. Acta*, **34**, 924 (1951); J. Fakstorp, J. Christiansen and J. G. A. Pedersen, *Acta Chim. Scand.*, **7**, 184 (1953); F. Bergel, *Chimia*, **6**, 190 (1952); D. D. Libman, D. L. Pain and R. Stack, *J. Chem. Soc.*, 2305 (1952).

(4) C. J. Cavallito, A. P. Gray, T. B. O'Dell, *Arch. Internat. Pharmacodyn.* **101**, 38 (1955); T. B. O'Dell, C. Luna and M. D. Napoli, *J. Exp. Pharm. and Therapeutics*, **114**, 306, 317 (1955).

(5) H. E. Lape, D. J. Fort and J. O. Hoppe, *ibid.*, **116**, 462 (1956).

(6) R. Willstätter and W. Moller, *Ber.*, **31**, 1202 (1898).

(7) A. Stoll, E. Jucker and A. Ebnöther, *Helv. Chim. Acta*, **38**, 559 (1955).

(8) L. R. Keagle and W. H. Hartung, THIS JOURNAL, **68**, 1608 (1946).

(9) R. Willstätter, *Ber.*, **29**, 930 (1896).

(10) G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953).

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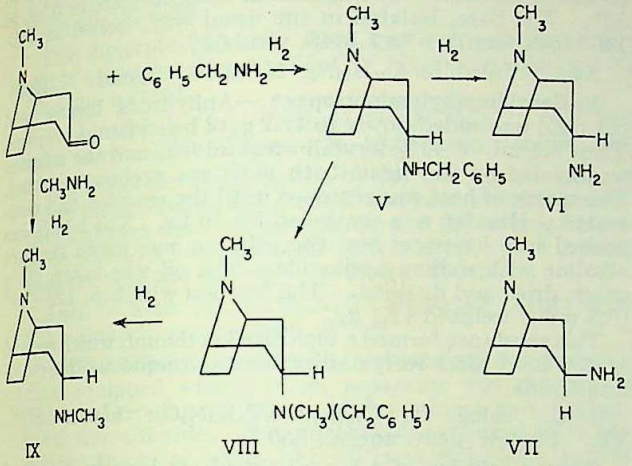
3α-tropylamine is best represented as shown in VI and 3β-aminotropane is VII.

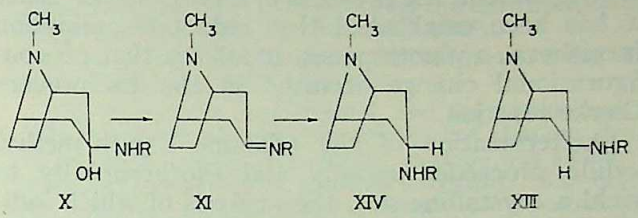


The reductive amination of tropinone in the presence of benzylamine led to 3α-benzylaminotropane (V) which was catalytically hydrogenolyzed to give 3α-aminotropane (VI). Thus the amine V is a member of the tropane group and by analogy the triamine I is also a member of the tropane and not the pseudotropane family.

The question whether it is the intermediate carbinolamine or the Schiff base which is hydrogenated in the reductive amination of ketones with primary amines, has never been completely answered. The consensus seems to be that it is the Schiff base that is hydrogenated.[11] Cope[12] found that in the reductive amination of carbonyl compounds with ethanolamine it was best to pre-reduce the platinum oxide catalyst in order to avoid induction periods. In our study of the preparation of the triamine I we were able to confirm this observation, but further investigation revealed that this induction period could be eliminated by premixing the ketone and amine and that it was not necessary to pre-reduce the Adams catalyst. Furthermore if the platinum oxide were reduced and the reagents were added separately to the hydrogenation vessel containing the catalyst, the induction period re-appeared.

Since the conditions necessary to effect reductive amination would serve also to reduce tropinone to tropine, the above results are in harmony with the suggestion that the carbinolamine forms rapidly and protects the ketone from attack by hydrogen. This is followed by a slower dehydration to the Schiff base and, as soon as a sufficient quantity of this species is formed, hydrogenation begins.

Further support for this suggestion can be found in a consideration of the stereochemistry of the reduction process. Alder[13] has pointed out that addition to the carbonyl group of tropinone or pseudopelletierine takes place in the "exo" sense. On conformational grounds it would be expected that the larger group would occupy the less hindered equatorial positions.[14] For these reasons the carbinolamine would be expected to have the structure X. Bonner[15] showed that hydrogenolysis of a carbon–oxygen bond proceeded with retention of configuration. Thus the amine which would be formed as the result of cleavage of the carbinolamine by hydrogen would be a 3β-aminotropane XIII.



This is contrary to the observed fact (see above) On the other hand, if it is the Schiff base XI which is reduced, one can predict the correct stereochemistry, XIV, by the invocation of Alder's principle[13] of "exo" addition of hydrogen.

We were unable to reductively aminate pseudopelletierine under conditions that were more strenuous than required for the tropinone series. It was found necessary to prepare and isolate the Schiff base[16] prior to catalytic hydrogenation in order to prepare the required 3-(2-dialkylaminoalkylamino)-9-methylgranatolines. The slow rate of formation of Schiff bases in the pseudopelletierine series is a reflection of the higher degree of hindrance that results from the interpolation of an additional methylene group in the bridge. Obviously, in this series it is not the carbinolamine which is being hydrogenated. The evidence adduced in this work lends further support to the belief that it is the Schiff bases and not the carbinolamines which are attacked by hydrogen in the reductive amination reaction.

In order to prepare the corresponding members in the pseudo series the ketimines derived from both tropinone and pseudopelletierine were reduced with the aid of sodium and either hexanol or ethanol. The mixture of triamines (I and its epimer at C-3) in the tropine series was separated as the phenylthioureides. The β-form predominated in the ratio of 25:1. In the pseudopelletierine series metal–alcohol reduction afforded a mixture in which a very substantial amount of the normal (axial) isomer was present. This is in accord with the presumed greater hindrance at C-3 in the granatoline.[17]

The conversion of the triamine I to the methylated amine II was accomplished by the formaldehyde–formic acid methylation. Although Parham[18] showed that inversion at carbon does not accompany methylation in the Eschweiler–Clarke reaction, we thought it advisable to confirm this

(11) W. S. Emerson, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 174.
(12) A. C. Cope and E. M. Hancock, THIS JOURNAL, **64**, 1503 (1942).
(13) K. Alder and A. A. Dortmann, *Ber.*, **86**, 1544 (1953).
(14) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).
(15) W. A. Bonner, J. A. Zderic and G. A. Casaletto, THIS JOURNAL, **74**, 5086 (1952).
(16) During the course of our work D. H. Norton, *et al.*, *J. Org. Chem.*, **19**, 1054 (1954), described a method for the isolation and reduction of aliphatic ketimines that was similar to ours.
(17) Reduction of hindered ketones in the carbocyclic series by metal–alcohols frequently furnishes axial carbinols (Barton, ref. 9). Alder (ref. 8) reported that reduction of pseudopelletierine afforded the equatorial isomer, but from inspection of the experimental details it is apparent that appreciable quantities of another substance were present in the crude reduction mixtures.
(18) W. E. Parham, W. T. Hunter, R. Hanson and T. Lahr THIS JOURNAL, **74**, 5048 (1952).

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point since we were working in the thermodynamically less stable series. Accordingly, 3α-benzylaminotropane (V) was converted to the methylated amine VIII. The latter was catalytically debenzylated to 3α-methylaminotropane (IX). This same amine was prepared by reductive amination of tropinone in the presence of methylamine. Since it has been established that reductive amination furnishes α-aminotropanes, it follows that no configurational change occurred in the Eschweiler–Clarke reaction.

Quaternization of the triamine I with methyl iodide proceeded rapidly and exothermically to yield a crystalline salt, the analysis of which indicated the formation of a bis-methiodide. That this substance was best represented by formula III follows from the analogous results obtained by Marxer and Miescher,[3] the fact that the infrared spectrum displayed a strong NH band and no significant absorption in the 4.0 μ region characteristic of ammonium salts.[19] Similarly the fully alkylated amine II furnished a bis-methobromide (IV, X = Br) when treated with methyl bromide.

Higher homologs of the triamine III were prepared by acylation of the secondary amine I with the appropriate anhydride and reduction of the corresponding amides with lithium aluminum hydride. Quaternization of these homologs proceeded at a noticeably slower rate in acetonitrile.

Experimental[20]

3α-Aminotropane.—A solution of 23 g. of tropinone oxime[5] in 150 ml. of methanol was reduced in the presence of 0.5 g. of Adams platinum oxide catalyst. After seven hours at 50° the reduction was stopped and the catalyst was filtered. After the solvent was removed, the residue furnished 5.5 g. of 3-aminotropane, b.p. 98–102° (20 mm.), $n^{25}D$ 1.5018. A large high-boiling residue (ditropylamine?) was not investigated.

The above amine (0.5 g.) in 3 ml. of methanol was treated with 1.0 ml. of phenyl isothiocyanate. A crystalline solid separated almost immediately. The thioureide melted at 160–161°[21] after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{15}H_{21}N_3S$: N, 15.26. Found: N, 15.20.

The 3β-aminotropane prepared by sodium–amyl alcohol[6] reduction of tropinone oxime boiled at 104–106° (22 mm.), $n^{25}D$ 1.4995, and furnished a thioureide, m.p. 173–175°.[22]

3α-Methylaminotropane.—A solution of 45 g. of tropinone in 100 ml. of methanol was mixed with a solution of 40 ml. of 7.9 *N* methylamine in methanol. Adams catalyst was added and the mixture was heated to 50° to initiate the hydrogenation which then proceeded to completion in 90 minutes. The catalyst and solvent were removed and the residue was distilled to give a fraction, b.p. 59–60° (0.5 mm.), wt. 43.5 g.

Anal. Calcd. for $C_9H_{17}N_2$: N, 18.3. Found: N, 17.6.

When a sample of the above amine was treated with excess alcoholic picric acid, a dipicrate separated which melted at 255° dec., after recrystallization from ethanol.

Anal. Calcd. for $C_9H_{18}N_2 \cdot 2C_6H_3N_3O_7$: neut. equiv., 306.2. Found: neut. equiv., 305.

The phenyl thioureide was prepared in methanol solution with the aid of phenyl isothiocyanate; m.p. 160–161° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{16}H_{22}N_3S$: N, 14.9. Found: N, 14.5.

3α-Benzylaminotropane.—A solution of 45 g. of tropinone and 32 g. of benzylamine in 80 ml. of ethanol was added to 1.5 g. of pre-reduced Adams platinum oxide suspended in 30 ml. of ethanol. Hydrogenation was complete in 3 hr. at 50°. The base, isolated in the usual way, boiled at 143–146° (0.05 mm.), $n^{25}D$ 1.5445, yield 63%.

Anal. Calcd. for $C_{15}H_{22}N_2$: N, 12.16. Found: N, 12.14.

3α-Benzylmethylaminotropane.—Anhydrous formic acid (21.6 g.) was added slowly to 19.2 g. of benzylaminotropane. Then 8.4 ml. of 40% formalin was added, and the solution was heated on the steam-bath until gas evolution started. The source of heat was removed until the reaction had moderated. Heating was continued for 16 hr. The whole was poured into ice-water and the solution was made strongly alkaline with sodium hydroxide. The oil was taken up in ether, dried and distilled. The fraction with b.p. 126–129° (0.3 mm.) weighed 11.1 g.

This substance formed a **dipicrate** in ethanol, which melted at 230–232° after recrystallization from aqueous dimethylformamide.

Anal. Calcd. for $C_{16}H_{24}N_2 \cdot 2C_6H_3N_3O_7$: neut. equiv., 351. Found: neut. equiv., 350.[23]

When a solution of 4.3 g. of the above base in 30 ml. of dry ethanol was treated with 3.5 ml. of methyl iodide, crystals of the **monomethiodide** started to separate within 15 minutes. The whole was left overnight and filtered. The salt was crystallized from methanol, wt. 3.9 g., m.p. 233–237° dec.

Anal. Calcd. for $C_{17}H_{27}IN_2$: I, 32.84; N, 7.25. Found: I, 32.55; N, 7.26.

Catalytic Debenzylation of 3α-Benzylmethylaminotropane. Ten grams of 3-benzylmethylaminotropane in 100 ml. of ethanol was hydrogenolyzed in the presence of 10% palladium-on-charcoal. Distillation of the oil that remained after removal of the catalyst and ethanol furnished an oil, b.p. 116–118° (18 mm.). When this base was treated with phenyl isothiocyanate in methanol, a phenyl thioureide separated which melted at 160–161°, after crystallization from ethyl acetate. When admixed with an authentic sample there was no depression in melting point.

Catalytic Debenzylation of 3α-Benzylmethylaminotropane.—In a similar fashion 22.8 g. of 3α-benzylaminotropane was hydrogenated in the presence of 10% palladium-on-charcoal. The tropylamine that was formed boiled at 118–120° (43 mm.), $n^{25}D$ 1.5014. The phenyl thioureide, m.p. 158–160°, did not depress the melting point of an authentic sample.

3α-(2-Diethylaminoethyl)-aminotropane.—A solution of 30 g. of tropinone and 24 g. of diethylaminoethylamine in 100 ml. of dry ethanol was allowed to stand for 2 hr. During this time 1.2 g. of platinum oxide catalyst was reduced in 50 ml. of ethanol. The solution of the bases was added to the catalyst and the reduction which proceeded without delay was 80% complete in 1 hr. The mixture was heated to 50° to finish the reaction. After the usual work-up there was obtained 33.2 g. (66%) of the desired triamine, b.p. 111–115° (0.5 mm.).

In another experiment the catalyst was pre-reduced, and the tropinone and diethylaminoethylamine were added separately without mixing. In this case no reduction occurred at room temperature. The contents of the hydrogenation vessel were heated to 50° whereupon the required amount of hydrogen was consumed within the next few hours. There was obtained, in 70% yield, the desired base, b.p. 115–118° (0.5 mm.).

In our preferred procedure, 204 g. of tropinone and 174 g. of diethylaminoethylamine in 1 liter of methanol was allowed to stand overnight. The solution was added to 2.0 g. of Adams catalyst (*under nitrogen*), and the reduction was allowed to proceed at room temperature and 1000 p.s.i. Over 75% of the required amount of hydrogen was absorbed within the first hour at room temperature. The remainder was consumed at 60°. The triamine was collected at 99–101° (0.2 mm.), wt. 273 g., $n^{25}D$ 1.4842.

The phenyl thioureide was prepared by dissolving 3.8 g. of the above base in 30 ml. of methanol and treating the solution with 2.2 g. of phenyl isothiocyanate. After 1 hr. 5.0 g. of crystals was collected. Recrystallization from

(19) B. Witkop, THIS JOURNAL, **76**, 5597 (1954).

(20) Analyses were carried out under the supervision of Mr. K. D. Fleischer. The infrared spectra were determined under the supervision of Dr. F. C. Nachod. Melting points are corrected.

(21) Willstätter (ref. 5) reported the m.p. as 142–143° (typographical error?). Stoll (ref. 6) reported the m.p. was 153–154°.

(22) Willstätter (ref. 5) reported the m.p. to be 171–172°.

(23) The neutral equivalent was determined by titrating the picric acid with sodium methoxide in anhydrous methanol. The value for the unmethylated base is 344.

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ethanol and ethyl acetate furnished the pure compound, m.p. 168–170°, wt. 3.7 g.

Anal. Calcd. for $C_{21}H_{34}N_4S$: N, 14.95; S, 8.56. Found: N, 14.96; S, 8.29.

The dipicrate prepared from two equivalents of picric acid in ethanol melted at 168–170° after crystallization from the same solvent.

Anal. Calcd. for $C_{14}H_{29}N_3 \cdot 2(C_6H_3N_3O_7)$: N, 18.00; neut. equiv., 350. Found: N, 18.06; neut. equiv., 350.[23]

The tripicrate was prepared by (a) treating the base with excess picric acid in hot ethanol and recrystallizing the salt from aqueous dimethylformamide and (b) adding alcoholic picric acid to a hot alcoholic solution of the above dipicrate. In either case the derivative melted at 230–232°.

Anal. Calcd. for $C_{14}H_{29}N_3 \cdot 3(C_6H_3N_3O_7)$: neut. equiv., 310. Found: neut. equiv., 307.[23]

3-(N-2-Diethylaminoethyl)-tropinoneimine.—A one-liter flask equipped with a water separator was charged with 69.5 g. of tropinone, 500 ml. of dry toluene and 500 mg. of fused zinc chloride. The mixture was refluxed for 1 hr. to remove traces of water (0.2 ml. was collected), and then 63.8 g. of diethylaminoethylamine was added. Reflux was resumed and in 12 minutes 50% of the theoretical amount of water was collected, and in 4 hr. the reaction was complete. On cooling, the mixture deposited a few crystals which were filtered off. The clear filtrate was distilled to yield 92.2 g. (78%) of the Schiff base, b.p. 117–131° (0.6 mm.), mainly at 128–131° (0.6 mm.).

A tripicrate, prepared in ethanol, melted at 184–185° after recrystallization from the same solvent.

Anal. Calcd. for $C_{14}H_{27}N_3 \cdot 3(C_6H_3N_3O_7)$: neut. equiv., 308. Found: neut. equiv., 312.[23]

Hydrogenation of the Schiff base in the presence of Raney nickel catalyst occurred at 60° and 1,000 p.s.i. The oil that resulted after removal of the nickel and the ethanol was converted directly to the phenyl thioureide. The crude derivative melted at 167–169° and did not depress the m.p. of the sample prepared as above. No appreciable quantity of the isomeric base was present.

Similarly, reduction of 24.6 g. of the Schiff base in the presence of Adams catalyst (0.6 g.) occurred in 75 minutes at room temperature. Distillation afforded 21.5 g. (85%) of 3α-(2-diethylaminoethyl)-aminotropane, b.p. 100–105° (0.2 mm.), $n^{25}D$ 1.4832.

When 11.8 g. of the Schiff base in 100 ml. of dry ether was reduced with the aid of 2.0 g. of lithium aluminum hydride, there was obtained 7.8 g. of a colorless oil. This was converted to a crude phenyl thioureide, m.p. 166–169°, which did not depress the m.p. of the previously prepared sample.

3β-(2-Diethylaminoethyl)-aminotropane.—To a hot solution of 47.4 g. (0.2 mole) of the Schiff base in 375 ml. of absolute ethanol, 22.0 g. of freshly cut sodium was added in small pieces in a 2-hr. period. After all the metal had been added, the suspension was refluxed for 1 hr. The clear solution was cooled, and just enough concentrated hydrochloric acid was added slowly to neutralize the sodium ethoxide. The salt was removed by filtration, and the clear filtrate was concentrated to leave an oil which was dissolved in a small quantity of water. The desired amine was thrown out of the aqueous solution with solid potassium carbonate. It was collected with ether, dried and distilled to give a yellow base, b.p. 108–112° (0.3 mm.), wt. 26.5 g.

A solution of 11.1 g. of the above crude amine was dissolved in 75 ml. of methanol and treated with 6.75 g. of phenyl isothiocyanate in 25 ml. of methanol. The solution warmed slightly, but no crystals separated. The reaction mixture was left in the refrigerator overnight. The crystalline solid that deposited was collected on a filter, m.p. 165–168°, wt. 0.8 g. This compound did not depress the m.p. of the phenyl thioureide of 3α-(2-diethylaminoethyl)-aminotropane.

The filtrate was concentrated to leave a yellow gum (wt. 17.4 g.) which was dissolved in 100 ml. of ethyl acetate. The solution was concentrated to 60 ml. and cooled. The crystals were filtered; wt. 12.7 g., m.p. 136–138°. After one recrystallization from ethyl acetate, the phenyl thioureide of 3β-(α-diethylaminoethyl)-aminotropane melted at 138–139.5°.

Anal. Calcd. for $C_{21}H_{34}N_4S$: N, 14.95; S, 8.56. Found: N, 15.06; S, 8.38.

Addition of pentane to the filtrate caused the separation of an additional 2.6 g. of crystals, m.p. 110–115°. This was not further investigated.

A solution of 11.7 g. of the above phenyl thioureide, m.p. 136–138°, in 50 ml. of ethanol was mixed with 25 ml. of 8 *N* alcoholic hydrogen chloride and allowed to stand at room temperature for 2 hr. The solid that separated was filtered and a small portion was recrystallized from methanol. The compound, which proved to be the dihydrochloride of the phenyl thioureide, melted at 219–221°.

Anal. Calcd. for $C_{21}H_{34}N_5S \cdot 2HCl \cdot H_2O$: S, 6.88; H_2O, 3.87. Found: S, 6.80; H_2O, 4.11.

The filtrate was concentrated, and the residue together with the above salt were dissolved in hot absolute alcohol; 25 ml. of 8 *N* alcoholic hydrogen chloride was added, and the solution was allowed to stand overnight. The crystals were filtered and the above process was repeated. The first and second crop of crystals were united (wt. 8.0 g.) and recrystallized from a large volume of ethanol to give the pure trihydrochloride, m.p. 268° dec.

Anal. Calcd. for $C_{14}H_{29}N_3 \cdot 3HCl$: C, 48.3; H, 9.22; Cl, 30.5. Found: C, 48.0; H, 9.33; Cl, 30.1.

3β-(2-Diethylaminoethyl)-aminotropane Bis-methiodide.—An aqueous solution of the above trihydrochloride was treated with potassium carbonate, and the liberated base was removed with the aid of ether and dried. Distillation furnished the free base, b.p. 117–119° (1.5 mm.), $n^{25}D$ 1.4839.

One hundredth mole of the base (2.4 g.) was dissolved in 50 ml. of absolute ethanol; 2 ml. of methyl iodide was added, and the solution was allowed to stand at room temperature for 5 hr. The crystals (3.0 g.) were filtered and recrystallized from methanol, m.p. 270.5–271.5°.

Anal. Calcd. for $C_{16}H_{35}N_3I_2$: N, 8.03; I, 48.5. Found: N, 8.09; I, 48.4.

3α-(α-Diethylaminoethyl)-aminotropane Bis-methiodide.—Six grams of the triamine I dissolved in 30 ml. of dry ethanol was chilled to 0°, and 3.5 ml. of methyl iodide was added. The solution was left at room temperature overnight. The solid which separated (wt. 10.4 g.) was crystallized from aqueous ethanol to give 7.5 g. of the bis-methiodide, m.p. 265–266°. The infrared spectrum (KBr pellet) showed a strong NH band.

Anal. Calcd. for $C_{16}H_{35}I_2N_3$: I, 48.5. Found: I, 48.2.

N,N-Diethyl-N′-(3-[9-methylgranatanyl])-ethylenediamine Phenyl Thioureide.—A solution of 15.7 g. of pseudopelletierine hemihydrate[24] in 100 ml. of dry toluene was refluxed under a water separator. The dried solution was treated with 12.0 g. of diethylaminoethylamine and 100 mg. of zinc chloride. After 4 hr. only 50% of the theoretical amount of water was collected and after 12 hr. only 83% (*cf.* the same reaction with tropinone). The mixture was distilled to give a small fore-run (b.p. 90–120°, 1.0 mm.) which contained pseudopelletierine and the main fraction, b.p. 130–135° (0.5 mm.), wt. 13.7 g. (57%). On redistillation the Schiff base boiled at 131–139° (0.7 mm.), $n^{25}D$ 1.5050.

Reduction of 10.5 g. of the redistilled Schiff base in ethanol with 0.5 g. of Adams catalyst took 5 hr. at 60°. The triamine, isolated in the usual way, boiled at 116–122° (0.2 mm.) and weighed 9.0 g. (85%). On redistillation the base boiled at 128–130° (0.6 mm.), $n^{25}D$ 1.4920.

When 600 mg. of the base was treated with 320 mg. of phenyl isothiocyanate, the corresponding phenyl thioureide separated, which melted at 188–190° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{22}H_{36}N_4S$: N, 14.42; S, 8.25. Found: N, 14.49; S, 8.22.

N,N-Diethyl-N′-(3-pseudo-[9-methylgranatanyl])-ethylenediamine Phenyl Thioureide.—To a suspension of 7.5 g. of sodium sand in 175 ml. of refluxing toluene there was added over a 5.5-hr. period a solution of 20.5 g. of the Schiff base derived from pseudopelletierine and diethylaminoethylamine in 32.8 g. of 4-methyl-2-pentanol. After all had been added, the mixture was stirred for an additional half hour. The cooled reaction mixture was treated cautiously with 30 ml. of 10% sodium carbonate. The organic layer was separated, and the water layer was satu-

(24) A. C. Cope, *et al.*, This Journal, **73**, 3416 (1951).

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rated with potassium carbonate. The aqueous phase was extracted with benzene and the united organic portions were dried and distilled *in vacuo* to leave 22.8 g. of a residue. This was combined with 7.0 g. of a similar preparation, and the resulting 29.8 g. of mixed bases was dissolved in 100 ml. of ethanol and treated with 17.5 g. of phenyl isothiocyanate. After 1 hr. the mixture was chilled in ice and filtered. This was called fraction A. The filtrate was evaporated to leave a red oil which was called fraction B.

Fraction A was crystallized from a large volume of ethyl acetate. There deposited 20.3 g. of a phenyl thioureide, m.p. 189–191°, undepressed when mixed with the same derivative obtained from the triamine prepared by catalytic reduction of the Schiff base. The filtrate was concentrated to 300 ml. and cooled. The crop that separated weighed 2.0 g., m.p. 185–187°. The combined yield of the normal isomer was 22.3 g.

The above filtrate was further concentrated to 25 ml. On cooling 1.8 g. of the phenyl thioureide of the pseudo isomer, m.p. 133–135°, separated. Fraction B was dissolved in 50 ml. of ethyl acetate. On cooling 12.0 g. of the same isomer separated, m.p. 131–133°. The combined yield of the pseudo isomer was 13.8 g. Further crystallization from ethyl acetate raised the m.p. to 135–136°.

Anal. Calcd. for $C_{22}H_{36}N_4S$: N, 14.42; S, 8.25. Found: N, 14.70; S, 7.96.

N,N-Diethyl-N′-(3-pseudo-[9-methylgranatanyl])-ethylenediamine Trihydrochloride.—A suspension of 10.2 g. of the phenyl thioureide described directly above (m.p. 135–136°) in 100 ml. of absolute alcohol was mixed with 15 ml. of 8 *N* alcoholic hydrogen chloride and left overnight at room temperature. A small amount of insoluble material was removed by filtration and the filtrate was carefully treated with 150 ml. of dry ether to precipitate the crude trihydrochloride, wt. 9.1 g. After recrystallization from equal parts of methanol and ethanol, the salt melted at 264–267° dec.

Anal. Calcd. for $C_{15}H_{31}N_3 \cdot 3HCl$: C, 49.7; H, 9.45; Cl, 29.3. Found: C, 49.9; H, 9.54; Cl, 29.2.

The bis-methiodide was prepared from 2.6 g. of the trihydrochloride. The base was liberated from an aqueous solution of the salt with potassium carbonate and dissolved in ether. The dried ether solution was evaporated to an oil which was dissolved in 10 ml. of methanol. The solution was treated with 1.2 ml. of methyl iodide, left overnight and then filtered. The bis-quaternary salt was purified by crystallization from methanol; m.p. 270–272° dec.

Anal. Calcd. for $C_{17}H_{37}I_2N_3$: I, 47.2; N, 7.82. Found: I, 47.3; N, 7.88.

3α-(N-Diethylaminoethyl)-methylaminotropane.—Sixty-nine grams of 3α-(2-diethylaminoethyl)-aminotropane was cooled, and 76 ml. of 98% formic acid was added slowly. The solution was allowed to warm to room temperature before 29 ml. of 37% formalin was added. The solution was heated on the steam-bath for 17 hr., cooled, poured into ice-water and made strongly basic with 35% sodium hydroxide. The oil was removed and the aqueous layer was washed twice with methylene chloride. The united oil layers were dried over Drierite and distilled to give a fraction, b.p. 120–124° (0.9 mm.), $n^{25}D$ 1.4873, which was taken as the methylated base, wt. 59.7 g.

Twenty grams of this base was dissolved in 250 ml. of absolute alcohol, and to it was added a freshly prepared solution of alcoholic hydrogen bromide to *p*H 3. The mixture was allowed to stand 18 hr. and was filtered. The trihydrobromide which weighed 34 g. was recrystallized from methanol. It was quite hygroscopic and melted unsharply in the range 135–145°.

Anal. Calcd. for $C_{15}H_{31}N_3 \cdot 3HBr$: C, 36.3; H, 6.91; Br, 48.3. Found: C, 35.9; H, 7.09; Br, 47.9.

The bis-methobromide was prepared by adding gaseous methyl bromide to 5.0 g. of the base in 50 ml. of acetonitrile for 4 minutes. The temperature rose from 23 to 30°, and the product started to separate during this time. After 3 hr. at room temperature the mixture was filtered and the salt was crystallized from isopropyl alcohol; wt. 4.4 g., m.p. 230–232° dec.

Anal. Calcd. for $C_{17}H_{37}Br_2N_3$: Br, 36.1. Found: Br, 35.7.

3α-(N-2-Diethylaminoethyl)-acetylaminotropane.—A solution of 24 g. of N,N-diethyl-N′-(3-tropanyl)-ethylenediamine in 20 ml. of acetic anhydride was heated on the steam-bath for 2 hr. The mixture was allowed to stand overnight and then it was poured into ice-water. The solution was rendered strongly alkaline. The oil was taken up in benzene, dried by azeotropic distillation and then distilled to give 20.1 g. (73%) of a viscous oil, b.p. 143–150° (0.05–0.15 mm.). Upon redistillation it boiled at 142–144° (0.09 mm.), $n^{25}D$ 1.4980.

A portion was converted to the dipicrate which melted at 194–195° after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{31}N_3O \cdot 2(C_6H_3N_3O_7)$: N, 3.70. Found: N, 3.74.[25]

3α-(N-2-Diethylaminoethyl)-ethylaminotropane Bis-methiodide.—The above amide (10.3 g.) was reduced in 100 ml. of dry ether with 4.0 g. of lithium aluminum hydride. The mixture was refluxed for 2 hr. after all the amide had been added. Excess reducing agent was destroyed with ethyl acetate followed by 10 ml. of water. The inorganic matter was filtered off and washed thoroughly with ether. The combined ethereal fractions were dried and distilled. The product boiled at 142° (2.0 mm.) and weighed 10.0 g., $n^{25}D$ 1.4845.

A solution of the base (470 mg.) in 10 ml. of acetonitrile was treated with 0.5 ml. of methyl iodide. No temperature rise was noted, but in two minutes crystals of the bis-methiodide started to separate. After 2.5 hr. the solid was collected and dried, wt. 630 mg., m.p. 217.5–219.5° dec.

Anal. Calcd. for $C_{18}H_{39}I_2N_3$: I, 46.0; N, 7.63. Found: I, 45.4; N, 7.74.

3α-(N-2-Diethylaminoethyl)-propionylaminotropane.—3α-(2-Diethylaminoethyl)-aminotropane (48 g.) was cooled under the tap as 50 ml. of propionic anhydride was added. The temperature rose to 70°. The mixture was allowed to stand for 2.5 hr. and then worked up as in the case of the lower homolog. The viscous propionyl derivative boiled at 160° (0.5 mm.), $n^{25}D$ 1.4945, wt. 45.8 g.

The dipicrate prepared in ethanol melted at 173–176° after recrystallization from aqueous dimethylformamide.

Anal. Calcd. for $C_{17}H_{33}N_3O \cdot 2(C_6H_3N_3O_7)$: neut. equiv., 377. Found: neut. equiv., 373.[23]

3α-(N-2-Diethylaminoethyl)-propylaminotropane Bis-methiodide.—One-tenth mole of the propionamide (29.5 g.) was reduced with 4.0 g. of lithium aluminum hydride in 100 ml. of ether. The mixture was worked up as in the previous case to furnish an oil, b.p. 119–126° (0.1 mm.), $n^{25}D$ 1.4835, wt. 23.6.

Two grams of the above base in 30 ml. of acetonitrile was treated with 2.0 ml. of methyl iodide. The solution warmed noticeably, but crystals did not appear until about 10 minutes after the halide was added. The mixture was allowed to stand overnight, cooled to 5° and filtered. The salt was washed successively with acetonitrile, absolute alcohol and pentane; m.p. 193–195° dec.

Anal. Calcd. for $C_{19}H_{41}I_2N_3$: I, 44.9; N, 7.44. Found: I, 44.5; N, 7.56.

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(25) Acetic–perchloric acid titration of basic nitrogen.

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[CONTRIBUTION FROM THE BOTANICAL INSTITUTE, FACULTY OF SCIENCE, UNIVERSITY OF TOKYO]

Interconversion of Chalcones and Flavanones of a Phloroglucinol-type Structure

BY MASAMI SHIMOKORIYAMA

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Naturally occurring flavanone glycosides with a phloroglucinol-type structure were converted to the corresponding chalcone glycosides. The method of preparation and the properties of the latter compounds are described. Some preliminary evidence was obtained for the existence of an enzyme, "flavanone synthease," which converts phloroglucinol-type chalcone glycosides to flavanone glycosides. It is postulated that a chalcone glycoside may in certain cases serve as an intermediate in the biogenesis of a flavanone glycoside.

In a previous paper[1] it was shown that the flavonoid pigments of *Coreopsis tinctoria* consist of a chalcone, a flavanone and a benzalcoumaranone derivative of corresponding structure. It was found that the chalcone, marein, is oxidized easily to the corresponding aurone, maritimein, but at the same time it has a great tendency to isomerize into the related flavanone, flavanomarein. The unusual behavior shown by marein suggests that there may be a close relationship among the three types of flavonoid pigments. This finding, in addition to a number of reports in the literature which are summarized below, prompted us to investigate the interconversion of chalcones and flavanones; flavanone glycosides with a phloroglucinol type of structure, *viz.*, naringin, poncirin, hesperidin and isosakuranin, were used for this purpose.

A majority of the naturally occurring flavanones have a phloroglucinol structure. However, no chalcone possessing a phloroglucinol or a 2′,6′-dihydroxy structure with free hydroxyl groups in the 2′- and 6′-positions is known in nature. Salipurposide found in *Salix purpurea*[2] is fairly stable in the chalcone form (isosalipurposide); it has a glucosidoxy residue in place of one of the *o*-hydroxyl groups. Other examples of the co-existence of a flavanone with a corresponding chalcone have been reported by Seshadri.[3]

Narasimhachari and Seshadri,[4] in their study of a number of substituted flavanones, found that naringenin, isosakuranetin, naringenin 4′,7-dimethyl ether, etc., dissolve readily in cold 10% sodium hydroxide and are precipitated unchanged by acidification, whereas 5-methoxy- and 5,7-dimethoxyflavanone dissolve in this reagent only on warming and give only the corresponding 2′-hydroxy chalcones on acidification. From these experiments they pointed out that when the 5-hydroxyl group is present in the flavanone, the equilibrium in the chalcone–flavanone isomerization is shifted in favor of the flavanone because of hydrogen-bonding stabilization between the 5-hydroxyl group and the carbonyl.[4]

Of particular interest are optically active flavanones, a few of which have been found in nature.[5]

In 1942, Zemplén and co-workers[6] synthesized an isosakuranetin glucoside (m.p. 214°, $[\alpha]_D$ −73.4° in pyridine) through its chalcone form and ascribed to it the structure of a 7-glucoside. Natural isosakuranetin-7-glucoside (m.p. 190°, $[\alpha]^{13}_D$ −41.4° in 60% acetone) was isolated from the wood of *Prunus donarium* var. *spontanea* by Hasegawa and Shirato[7] who attributed the discrepancy in the two preparations to the difference in the optical activity of the aglycon.

Wawra and Webb[8] reported the preparation of hesperidin chalcone by dissolving hesperidin in cold alkali; upon neutralization the chalcone crystallized. Their preparation melted at 251–252° and showed ultraviolet absorption maxima at 332 and 308 mμ. Almost the same procedure was repeated by the author, giving pale yellow crystals, which did not show any of the absorption characteristics of chalcones. It will be shown below that, under the comparatively mild conditions used by Wawra and Webb, the equilibrium, flavanone ⇄ chalcone, is not shifted to the right.

The existence in nature of optically active flavanones suggests that an enzyme may be involved in the chalcone–flavanone isomerism; various sources were tested for the presence of such an enzyme.

Experimental[9]

Isosakuranin from Poncirin.—Poncirin isolated from *Poncirus trifoliata*[5e] was partially hydrolyzed by refluxing a solution of 2 g. in 25 ml. of 50% ethanol and 0.5 ml. of 20% hydrochloric acid for 3 hr. Paper chromatography revealed that the poncirin had almost disappeared, while the isosakuranetin spot was still weak and a spot of intermediate R_f was most prominent. In agreement with this finding, a marked spot of rhamnose was detected, whereas glucose showed a weak spot. When the hydrolyzate was allowed to stand overnight, colorless needles of isosakuranin separated almost completely; yield 0.4 g. The isosakuranin was repeatedly recrystallized from 50% ethanol; m.p. 172–178°, $[\alpha]^{20}_D$ −48.4° (*c* 0.25, 90% ethanol).

Anal. Calcd. for $C_{22}H_{24}O_{10}\cdot 1.5H_2O$: C, 55.57; H, 5.72; H_2O, 5.69. Found: C, 55.76; H, 5.43; H_2O, 5.60.

Chalcones.—The following procedure exemplifies the preparation of the chalcones from the corresponding flavanones:

(A) **Isosakuranin.**—Isosakuranin (1 g.) was heated with 2 g. of potassium hydroxide and 4 ml. of water on a boiling water-bath for 2 minutes. On cooling, the mixture was acidified with 20% hydrochloric acid. The resulting orange-yellow crystalline precipitate was recrystallized from 40 ml. of 30% ethanol as yellow needles, m.p. 172–175°, yield 0.55 g.

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(6) G. Zemplén, R. Bognár and L. Mester, *Ber.*, **75**, 1432 (1942).
(7) M. Hasegawa and T. Shirato, THIS JOURNAL, **77**, 3557 (1955).
(8) C. Z. Wawra and J. L. Webb, *Science*, **96**, 302 (1942); *C. A.*, **36**, 7090[8] (1942).
(9) All melting points are not corrected.

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Anal. Calcd. for $C_{22}H_{24}O_{10}\cdot 1.5H_2O$: C, 55.57; H, 5.72; H_2O, 5.69. Found: C, 55.80, 55.52; H, 5.93, 6.01; H_2O, 5.80.

(B) Poncirin.—The reaction mixture, obtained by similar treatment of 1 g. of poncirin, was acidified to *p*H 2. Treatment of the oily precipitate with ethyl acetate gave crystals which, upon three recrystallizations from 50% ethanol, yielded yellow needles, m.p. 195–205°, yield 0.45 g.

Anal. Calcd. for $C_{28}H_{34}O_{14}\cdot H_2O$: C, 54.90; H, 5.92; H_2O, 2.94. Found: C, 55.02; H, 5.64; H_2O, 3.00.

(C) Naringin.—Naringin (1.3 g.) isolated from the peel of *Citrus natsudaidai*[10] was treated as described for poncirin. The chalcone was obtained as yellow needles, m.p. 185–200°, yield 0.7 g.

Anal. Calcd. for $C_{27}H_{32}O_{14}\cdot H_2O$: C, 54.18; H, 5.73; H_2O, 3.01. Found: C, 54.15; H, 5.51; H_2O, 3.20.

(D) Hesperidin.—Yellow needles of the chalcone were obtained from hesperidin isolated from *Citrus nobilis* peel. The hesperidin chalcone melted at 180° and the melted mass, gradually losing color, solidified as colorless crystals which melted at 250°, the melting point of hesperidin.

Anal. Calcd. for $C_{28}H_{34}O_{15}\cdot 2.5H_2O$: C, 51.30; H, 6.00; H_2O, 6.87. Found: C, 51.19; H, 5.49; H_2O, 7.12.

These chalcones dissolved instantly in cold, dilute aqueous alkali giving an orange color; their ethanolic solutions gave a brown color with ferric chloride.

Preparation of Racemic Flavanones from Chalcones. (A) Isosakuranin.—Isosakuranin chalcone (1.0 g.) was heated on a water-bath with 0.3 g. of sodium acetate and 3 ml. of water according to the method of Zemplén.[6] The separation of colorless crystals of the flavanone, which occurred after a few minutes, was almost complete in 15 minutes. The product was recrystallized from 50% ethanol; m.p. 210–214°, $[\alpha]^{20}D$ −39.2° (*c* 0.25, 90% ethanol).

Anal. Calcd. for $C_{22}H_{24}O_{10}\cdot 1.5H_2O$: C, 55.57; H, 5.72; H_2O, 5.69. Found: C, 55.94; H, 5.82; H_2O, 5.42.

(B) Poncirin.—A mixture of 0.1 g. of the chalcone, 1 ml. of 50% ethanol and 0.1 ml. of McIlvaine buffer solution of *p*H 7 was heated on a water-bath for 3 minutes. The reaction mixture was extracted with ethyl acetate, the extract evaporated *in vacuo* and the residue crystallized from absolute ethanol; yield 40 mg. The crystals softened at 160° and melted at 170–175°, $[\alpha]^{20}D$ −82.5°; natural poncirin, $[\alpha]^{20}D$ −93.8° (*c* 0.8, 90% ethanol).

(C) Naringin.—The chalcone (0.1 g.) was heated with 1 ml. of 50% ethanol and 0.1 ml. of McIlvaine buffer solution (*p*H 6). The mixture was added to an equal volume of water and allowed to stand overnight. The crystals which separated were recrystallized from 20% ethanol as colorless needles, m.p. 80–83°, yield 80 mg., $[\alpha]^{20}D$ −72.1°; natural naringin, $[\alpha]^{20}D$ −82.0° (*c* 1, 90% ethanol).

(D) Hesperidin.—Racemic hesperidin, prepared by the procedure described for racemic naringin, was recrystallized from pyridine as colorless needles, m.p. 250°.

Enzymatic Hydrolysis of Isosakuranin with Emulsin.—Isosakuranin (0.1 g.) suspended in 6 ml. of water was added to 6 ml. of a solution containing 60 mg. of emulsin, prepared from Japanese apricot. The mixture was covered with toluene and incubated at 30°. The hydrolysis was almost complete in three days. The aglycon was filtered and recrystallized from dilute ethanol; m.p. 170°, reported[7] m.p. 170°; $[\alpha]^{20}D$ −13.8° (*c* 1, 90% ethanol).

Anal. Calcd. for $C_{16}H_{14}O_5\cdot{}^1/_2H_2O$: C, 65.08; H, 5.12. Found: C, 65.35; H, 5.36.

The filtrate, separated from the aglycon, was evaporated to about 1 ml. and chromatographed with 1-butanol–acetic acid–water (4:1:1) as the solvent and a benzidine solution as the developer. The concentrate gave a single spot, which corresponded to glucose (R_f 0.17).

When racemized isosakuranin was hydrolyzed by emulsin, an optically inactive isosakuranetin (m.p. 190°) was obtained.

Stability of Chalcones at Various *p*H Values.—The behavior of chalcones in dilute ethanolic solution was studied at various *p*H's. The times required for the complete decolorization of the buffered solutions, *i.e.*, for the complete conversion of the chalcone to flavanone, are given in Table I.

TABLE I

DECOLORIZATION TIME IN MINUTES OF CHALCONES AT VARIOUS *p*H VALUES

To 0.2 ml. of ethanolic solution of chalcones (0.01 *M*) were added 0.5 ml. of water and 0.3 ml. of McIlvaine buffer solution (22°) ppt and PPT indicate the presence of crystals of chalcone and flavanone, respectively.

Chalcone	*p*H 3	4	5	6	7	8
Isosakuranin	ppt ∝	ppt ∝	ppt ∝	70	PPT 22	PPT 15
Poncirin	ppt ∝	ppt ∝	ppt ∝	65	22	16
Naringin	ppt ∝	∝	PPT 400	PPT 70	PPT 20	PPT 15
Hesperidin	∝	∝	PPT 420	PPT 80	PPT 21	PPT 15

This isomerization reaction also was followed by measuring the changes in the absorption of buffered chalcone solutions at 370 mμ with a spectrophotometer against an appropriate buffer blank; the data are recorded in Fig. 1. This isomerization is a monomolecular reaction. The rate constant *k* was calculated from the formula

$$k = \frac{2.303}{t} \log \frac{E_0}{E_t}$$

where E_0 and E_t represent the optical densities of the solution at 370 mμ at zero time and at *t* minutes, respectively. The following values were obtained for *k*: 0.150 at *p*H 7, 0.055 at *p*H 6, 0.018 at *p*H 5, 0.001 at *p*H 4 and 0.000 at *p*H 3.

Preparation of an Enzyme Solution from the Peel of *Citrus aurantium*.—One hundred grams of the peel was macerated twice with 300 ml. of cold ethanol, and the almost colorless powder obtained was then extracted with 300 ml. of water. The aqueous solution was mixed with one-tenth volume of a saturated ammonium sulfate solution and then centrifuged. The supernatant was saturated with ammonium sulfate and the resulting precipitat was filtered, redissolved and reprecipitated by the same procedure as above. The precipitate was then dissolved in 20 ml. of water, dialyzed and filtered. In order to test the activity of the "flavanone synthease," 10 mg. of the chalcone glycoside suspended in 0.5 ml. of water (in some cases buffered with McIlvaine solution) was added to 0.5 ml. of the above enzyme solution. The mixture was covered with toluene and incubated at 30°. A blank test was always run on the same quantity of the chalcone suspended in 1 ml. of water. The conversion of the chalcone to flavanone was readily detected by disappearance of the chalcone or by appearance of the resulting flavanone in crystals.

TABLE II

THE ACTIVITY OF "FLAVANONE SYNTHEASE" FROM VARIOUS SOURCES

Species	Tissue	Relative activity[a]
Citrus aurantium	Peel	+ + +
	Leaf	−
C. natsudaidai	Peel	+ +
	Leaf	−
C. junos	Peel	±
C. nobilis	Peel	±
C. pseudoparadisi	Peel	±
Poncirus trifoliata	Peel	+
	Leaf	−
Cosmos sulphureus	Ray	−
	Leaf	−
Coreopsis lanceolata	Ray	−
	Leaf	−
C. tinctoria	Ray	−
	Leaf	−
Dahlia variabilis	Ray	−
(a white variety)	Leaf	−

[a] + + + denotes almost complete conversion of the chalcone glycoside (10 mg. in 0.5 ml. of water plus 0.5 ml. of enzyme solution) in 3 days, + + in 5 days, + signifies partial conversion, ± slight activity and − no activity.

(10) M. Tsujimura, *Bull. Inst. Phys. Chem. Res. (Tokyo)*, **6**, 1111 (1927).

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Some other plant materials were tested for enzymatic activity in the same way; the results are summarized in Table II.

No isomerization reaction was observed if the enzyme solution had been boiled for about 10 minutes. The activity also was inhibited completely by mercuric chloride (0.002*M*) but not affected by potassium cyanide (0.002*M*). The cyclization did not occur at *p*H 3–4. The spontaneous reaction, however, occurs so readily at *p*H 5 and so rapidly at *p*H 6–7 that it was impossible to find the optimum *p*H for the enzyme. If an unbuffered aqueous suspension was used, the chalcone was almost perfectly stable during a week's incubation, owing to its insolubility in water. When these chalcones were subjected to the oxidizing action of the chalconase[11] in *Cosmos* or *Coreopsis*, the conversion into the corresponding aurones was not, however, observed. As chromatographic analysis showed, the marein from *Coreopsis tinctoria*[1] and the coreopsin from *Cosmos sulphureus*[12] were not isomerized by the "flavanone synthease"; flavanomarein[1] and flavanocoreopsin, obtained as described below, served as controls.

Enzymatic Resynthesis of Flavanones. (A) **Naringin.**—A mixture of the chalcone (0.5 g.), suspended in 25 ml. of water, and 25 ml. of the enzyme solution prepared from the peel of *Citrus aurantium* was covered with toluene and incubated at 30°. The reaction was complete in 3–4 days; by that time no yellow crystals of chalcone remained and colorless needles of naringin had appeared. The mixture was cooled in a refrigerator overnight, and the flavanone was filtered and recrystallized from 20% ethanol; m.p. 80–83°, $[\alpha]^{20}D$ −74.3° (*c* 1, 90% ethanol).

(B) **Isosakuranin.**—Isosakuranin prepared from the chalcone in the same way melted at 175–190°, $[\alpha]^{20}D$ −43.0° (*c* 0.25, 90% ethanol).

(C) **Poncirin.**—Poncirin chalcone, which had been incubated with the enzyme, gave an almost clear, pale brown solution which was extracted with ethyl acetate. The extract was evaporated *in vacuo* and the residue crystallized twice from absolute ethanol to yield colorless crystals of the flavanone, m.p. 160–170°, $[\alpha]^{17}D$ −84.2° (*c* 0.8, 90% ethanol).

Flavanocoreopsin.—Coreopsin (1.2 g.) was heated on a water-bath with 3.6 g. of sodium acetate and 18 ml. of water for about 2 hr. Then the solution was slightly acidified with a few drops of 20% acetic acid and extracted with ethyl acetate. The acetate solution was evaporated and the residue was dissolved in 10 ml. of ethanol. The pale yellow needles which separated were recrystallized repeatedly from ethanol to yield almost colorless needles which melted at 166–168° and gave a green color with ferric chloride. The flavanocoreopsin gave an R_f value of 0.62 (1-butanol–acetic acid–water, 4:1:2; Whatman No. 1; 20°); that of coreopsin was 0.54.

Anal. Calcd. for $C_{21}H_{22}O_{10}\cdot H_2O$: C, 55.75; H, 5.35; H_2O, 3.98. Found: C, 55.81; H, 5.84; H_2O, 4.04.

The conversion did not, however, occur under the conditions used for the cyclization of phloroglucinol-type chalcones. Flavanocoreopsin could not be detected even in trace amounts in the fresh extract of the ray flowers of *Cosmos sulphureus*.

Discussion

All of the chalcones obtained from phloroglucinol-type flavanone 7-glycosides as described above are fairly stable even when dissolved in ethanol, either concentrated or dilute. They are readily soluble in strong ethanol and recrystallizable from dilute ethanol. That these substances have a chalcone structure is indicated by the following experiments and considerations: They are bright yellow, while the original as well as the reconverted flavanones are colorless. They dissolve instantly in cold, dilute aqueous alkali giving an orange color. They gave a brown color with ferric chloride, whereas the flavanones studied in the present work gave a purple color. The chalcones gave well-sepa-

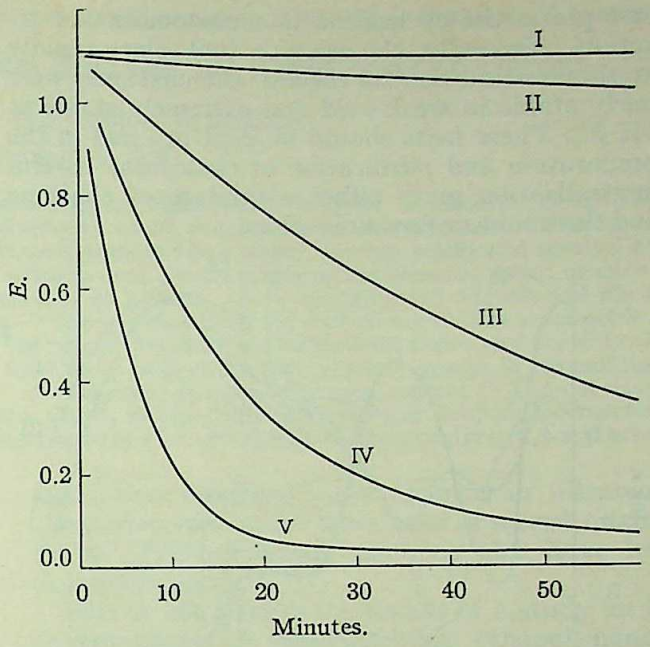

Fig. 1.—Isomerization of naringin chalcone to the flavanone at various *p*H values (22°). To 1.0 ml. ethanolic solution of the chalcone (0.003 *M*) were added 1.0 ml. of McIlvaine buffer solution and 8.0 ml. of water. I, II, III, IV and V indicate the reaction curves measured at *p*H 3, 4, 5, 6 and 7, respectively.

rated yellow spots on a paper chromatogram, not accompanied by even a faint spot of corresponding flavanones; while the mother liquor of recrystallization, after being allowed to stand a few days, gave both spots. The R_f values are shown in Table III. Their ultraviolet absorption spectra, two examples of which are shown in Fig. 2 with one typical flavanone curve, confirm the chalcone structure assigned to these compounds. An imperfect chalconization or careless treatment gave a pale yellow preparation which had an absorption curve between that of the chalcone and the flavanone.

TABLE III

R_f VALUES AND COLORS OF CHROMATOGRAPHED CHALCONES AND FLAVANONES (BuOH–HOAc–H_2O, 4:1:2; 13°; WHATMAN NO. 1)

		Untreated[a]		NH_3	
	R_f	V	UV	V	UV
Isosakuranin chalcone	0.79	Y	B	OY	Bk
Isosakuranin	.76	C	pY	C	Y
Poncirin chalcone	.68	Y	B	OY	Bk
Poncirin	.61	C	pY	C	Y
Naringin chalcone	.64	Y	B	OY	Bk
Naringin	.54	C	pY	C	Y
Hesperidin chalcone	.38	Y	B	OY	Bk
Hesperidin	.36	C	pY	C	Y

[a] B brown, Bk black, C colorless (not visible), O orange, p pale, UV ultraviolet light, V visible light, Y yellow.

The stability of the chalcones at various *p*H values exceeded our expectation. An equilibrium may exist in the interchange, chalcone ⇄ flavanone, and this equilibrium is shifted to the left in an alkaline medium and to the right in an acid medium. Our study of the behavior of chalcones in a dilute ethanolic solution of various *p*H values (Table I and Fig. 1) is noteworthy in two respects. In the

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first place, the cyclization is a monomolecular reaction. Secondly, the reaction took place rapidly in alkaline and neutral media; the chalcones were fairly stable in weak acid and extremely stable at *p*H 3. These facts should be kept in mind in the preparation and purification of chalcones; careful neutralization gives either a mixture of chalcone and flavanone or flavanone alone.

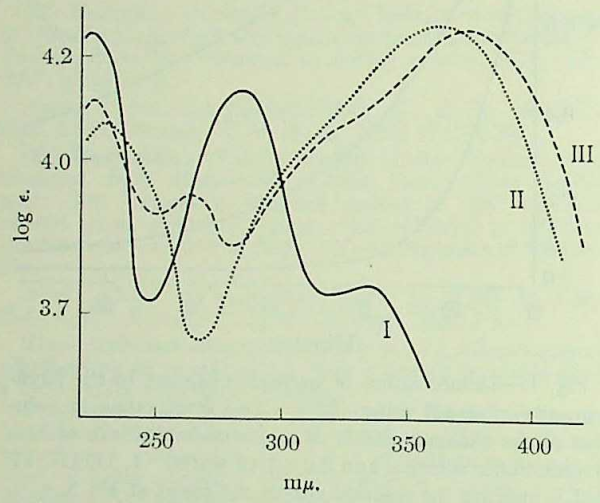

Fig. 2.—Ultraviolet absorption spectra: I, pocirin and isosakuranin; II, poncirin chalcone and isosakuranin chalcone; III, hesperidin chalcone (in 98% ethanol).

The existence of optically active flavanones in nature suggested that if a chalcone was produced as a precursor in the biosynthesis of a flavanone, an enzyme may be involved in the chalcone–flavanone isomerism. The fact that the phloroglucinol-type chalcone glycosides are unstable in the *p*H range prevailing in living cells and form optically inactive flavanones supports this hypothesis. Some evidence for the existence of such an enzyme, "Flavanone synthease," was obtained. The aqueous, cell-free extract of the peel of *C. aurantium* proved to be the most active preparation. The enzyme in the peel of *Citrus* fruits acted in almost the same way on all the phloroglucinol-type chalcones tested, but it did not seem to exert any effect on the coreopsin from *Cosmos sulphureus* and the marein from *Coreopsis tinctoria*. No activity was detected in the ray and the leaves of *Cosmos*, *Coreopsis* and *Dahlia*.

Few optically active forms of flavanone glycosides have been found in nature. By the usual procedure for the hydrolysis of a glycoside, however, some racemization always takes place. Consequently, enzymatic hydrolysis is the best method for obtaining an optically active aglycon from a flavanone glycoside. Isosakuranin prepared from poncirin was hydrolyzed readily by an emulsin from Japanese apricot to give optically active isosakuranetin; Hasegawa and Shirato[7] obtained the same results with isosakuranin from *Prunus*. When isosakuranin chalcone was recyclized, it gave isosakuranin (m.p. 210–214°) which is regarded as identical with the isosakuranin described by Zemplén and co-workers.[6] A mixture of racemic isosakuranin and the original preparation gave on recrystallization a preparation which melted between 180 and 200°. Enzymatically resynthesized isosakuranin melted in the same temperature range, a finding which suggests that it contains some optically active isosakuranetin. The specific rotation values of these preparations are in good accord with these facts: $[\alpha]^{20}D$ for isosakuranin prepared from poncirin was −48.4°, that of the completely racemized glucoside was −39.2°, and that of the enzymatically recyclized preparation −43.0°. Although the isosakuranin from poncirin is, of course, partially racemized during hydrolysis and purification, the isosakuranin enzymatically resynthesized from the chalcone is fairly rich in optically active isosakuranetin.

In the case of poncirin and naringin, there was almost no difference between the melting points of the completely racemized compounds obtained *via* the chalcone and those of the original flavanones. However, the specific rotation powers of the recyclized flavanones were about 10° less than those of the original compounds, a difference which indicates that the aglycon occurs in the plant in an optically active form; it would necessarily be partly racemized during extraction and purification. The specific rotation values of the enzymatically resynthesized glycosides indicate that the products contain optically active aglycon to some extent.

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[Contribution from the Chemistry Department, State University College of Forestry at Syracuse University]

Lignin Structure. XI. A Quantitative Study of the Alcoholysis of Lignin[1]

By Kyosti Sarkanen and Conrad Schuerch

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The following changes occur on re-ethanolysis of ethanol–spruce lignins, isolated in 57% yield: a maximum of 42 to 57% of the guaiacylpropane units become ethoxylated by a rapid reaction which seems to be independent of the liberation of phenolic groups. New phenolic hydroxyl and α-carbonyl groups are generated by a slower cleavage reaction in nearly 1-to- 1 molar ratio. The concurrent decrease in molecular weight indicates that the liberation of the phenolic group usually results in fission of the molecule but that some cyclic structures may be present. Both unconjugated phenols and phenols with a carbonyl in the α-position are formed by the cleavage. The α-carbonyl groups formed are mainly responsible for the change in the ultraviolet spectrum during ethanolysis. The rate of the phenolic liberation decreases more rapidly than would be expected if only a single structure were reacting. Only about 60% of the para-phenoxy groups in ethanol lignin are converted to free phenols by acid-catalyzed ethanolysis. An extensive decrease in oxygen content (0.3 to 0.6 oxygen atom per guaiacyl propane unit) takes place and is apparently due to independent intramolecular dehydration reactions. Most of these observations correspond closely to similar changes occurring on ethanolysis of guaiacylglycerol β-aryl ethers.

Alcoholysis is one of the important degradative reactions which can be used to dissolve lignin from the tissues of woody plants. Although the reaction can be considered formally analogous to the alcoholysis or hydrolysis of proteins or polysaccharides, there are marked differences between the degradation of lignin by this reaction and the degradation of other polymers. For example, the final products even from a softwood lignin, which apparently is derived almost exclusively from a single monomeric skeleton, are always a complex mixture of oligomers. Furthermore, that small fraction of lignin which has been degraded to propylguaiacyl monomers has had the functional groups on the aliphatic side chains extensively rearranged.

Four monomeric ethanolysis products from spruce lignin have been isolated and identified by Hibbert.[2] These are probably degradation and rearrangement products derived from a single structure, such as a derivative of α-oxyconiferyl alcohol[3] or guaiacylglycerol,[4–8] which exists as a part of the lignin macromolecule in wood. The reactions occurring in that part of lignin which resists degradation to the monomeric state are, however, less clear. The introduction of ethoxyl groups,[9] the formation of phenolic hydroxyl[10] and C-methyl groups,[11] the increase in structures capable of yielding benzene tetra- and pentacarboxylic acids by direct oxidation[12] or *m*-hemipinic acid by oxidation of the methylated product,[13] depolymerization reactions[14] and changes in ultraviolet absorption spectrum[15] have been observed qualitatively. Polymerization reactions also have been claimed to occur.[14]

This article reports the results of a study on the re-ethanolysis of ether-insoluble ethanol lignins, isolated under mild conditions[16,17] from spruce wood. The formation of monomeric products by re-ethanolysis from analogous preparations has been shown to be almost negligible (less than 3%).[14] Therefore, these results describe reactions which occur on that portion of lignin which remains almost exclusively as a complex mixture of low polymers.

It is quite possible that several independent reactions occur on re-ethanolysis of ethanol lignin. The interpretation of analytical data is therefore not as obvious as in the case of simple homogeneous materials. For example, if two functional groups are formed or destroyed in a simple molar ratio (1:1 or 2:1) after some period of time, it is not justified to conclude that the changes are caused by a single reaction. However, there is little likelihood that two independent reactions would have exactly the same rate and therefore if such a ratio is constant throughout the reaction it is very probable that the two molecular changes are caused by the same reaction. Therefore by following changes in analysis over a period of time, it is possible to distinguish which changes are independent and which are probably interrelated. As will be shown in detail, changes in light absorption and in number-average molecular weight may similarly be interrelated with changes in functional group content. For correlations of this type, it is obviously necessary to recover quantitatively and analyze carefully a number of samples allowed to react for varying periods of time. The method used in this investigation seems suitable for application to the reactions of many substrates, the homogeneity of which is doubtful.

It seemed advantageous to isolate fractions of the whole substrate as soon after solution as practicable in order to follow the ethanolysis through as large a fraction of the whole reaction as possible. Therefore samples SI, SII and SIII were isolated

(1) The authors gratefully acknowledge support of this research by a grant from the Research Corporation. This article is abstracted from a portion of a thesis submitted by Kyosti Sarkanen in partial fulfillment of the requirements of the degree of Doctor of Philosophy, State University College of Forestry at Syracuse University. The subject matter was presented before the Division of Cellulose Chemistry at the 130th Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956.

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as ether-insoluble fractions of ethanol lignins in that order from a single batch of spruce wood meal by successive, mild ethanolyses. In all essential aspects, the characteristics of SII were intermediate between SI and SIII. The study on this sample was therefore less comprehensive than that of the other two fractions. Sample NI is a part of SI, separated from it by countercurrent distribution in 10% yield. It differs from the rest of sample SI by the fact that its phenolate is extracted from aqueous alkali by chloroform–ethanol. It is called NI to indicate its apparently "neutral" character. The "neutral" parts of SII and SIII were negligibly small and were not investigated separately.

Experimental

Preparation of Ethanol–Spruce Lignins.—The ethanol lignins used in this study were those prepared as described previously[17] by a three-step ethanolysis of Norway spruce woodmeal in anhydrous chloroform–ethanol (volume ratio 4/1) using 0.2 *N* hydrogen chloride as catalyst. The ether-insoluble powders SI, SII and SIII were extracted in that order and amounted to 28, 14 and 15% of the original Klason lignin. An ether-insoluble fraction poor in phenolic groups, NI, was separated in about 10% yield from SI, or 2.8% of the original Klason lignin, by countercurrent distribution between chloroform–alcohol and alkali as previously.[16]

Re-ethanolysis Experiments.—Lignin samples (1 g.) were dissolved in 100 ml. of ethanolysis solution (0.38 *N* hydrogen chloride in chloroform–ethanol 4:1) and heated in sealed round-bottomed flasks for different periods of time in a constant-temperature bath adjusted to 65 ± 0.02°. The reaction was stopped by cooling the flask in crushed ice. The flask was opened and the contents shaken with a saturated sodium bicarbonate solution to neutral reaction and finally with distilled water. If some cloudiness appeared during the extraction, ethanol was added until the solution became clear. The solution was dried with sodium sulfate and evaporated in water-pump vacuum under nitrogen atmosphere. Ten ml. of dioxane (freshly distilled over sodium) was added to the residue and evaporated again. The residue was dissolved in 8 ml. of dioxane and transferred for freeze drying into a test-tube (diam. 6/8″, length 3.5″) with a small indentation in the middle. The contents were thoroughly frozen in an acetone–Dry Ice-bath, placed inside the evaporation flask of a freeze-drying apparatus and the solvent sublimed for 21 hr. under oil-pump vacuum. The final drying was done *in vacuo* over phosphorus pentoxide at 40° for three days.

Because of the tendency of hydrogen chloride to evaporate from chloroform–ethanol, the ethanolysis stock solution was frequently rechecked by titration and the acid concentration corrected by adding a proper amount of a more concentrated ethanolysis solution.

Analysis of Samples.—The methods used for the determination of methoxyl, ethoxyl, phenolic hydroxyl content and ultraviolet absorption spectra have been given previously.[17] Carbon and hydrogen analyses were carried out by Dr. K. Ritter, Basel, Switzerland. The number average molecular weight determinations were made by Dr. Sonja K. Gross in this Laboratory using a cryoscopic determination in ethylene carbonate.[18] A standard Beckmann freezing point apparatus was used. Lignin concentrations were 2%, and molecular weights were found to be nearly concentration independent.

The analytical data are given in Table I. It may be noted that dissolving sample SI in cold ethanolysis solution and recovering it immediately caused a slight change in composition. Samples SII and SIII, on similar treatment, remained unchanged. It seems probable that, in the preparation of SI, the removal of carbohydrates was incomplete and therefore the data on SI_0 were used in subsequent calculations.

Table I

Analytical Data on Ethanol Lignin Samples

Sample	Time of re-ethanolysis, hr.	Carbon, %	Hydrogen, %	Methoxyl, %	Ethoxyl, %	Phenolic hydroxyl, %	Cryoscopic mol. wt.	Absorptivity,[a] l.(mole MeO^{-1}) cm.$^{-1}$ At 305 mμ	At 255 mμ	Formulas
SI	0	62.86	6.45	13.80	10.80	2.75	..	..	..	$C_9H_{8.2}O_{2.57}(OMe)_{0.93}(OEt)_{0.50}$
SI_0[b]	0	62.81	6.73	14.70	10.20	2.75	908	2560	3180	$C_9H_{8.7}O_{2.52}(OMe)_{0.99}(OEt)_{0.48}$
SI_1	4.1	...	..	14.55	11.75	3.38	800	3240	3490	
SI_2	11.2	...	..	14.45	11.70	4.06	743	3720	3760	
SI_3	17.6	64.99	6.80	14.75	12.30	4.31	787	4000	3930	$C_9H_{8.2}O_{2.07}(OMe)_{0.93}(OEt)_{0.56}$
SI_4	42.0	...	..	14.80	11.70	4.79	654	4620	4440	
SI_5	59.8	...	..	14.50	11.80	4.99	585	4910	4780	
SI_6	83.9	...	..	14.50	11.30	4.91	626	4900	4870	
SI_7	115.7	66.60	6.34	14.60	11.05	5.05	..	5340	5590	$C_9H_{7.3}O_{1.91}(OMe)_{0.93}(OEt)_{0.48}$
NI_0	0	64.0	6.66	14.46	10.4	1.03	955	..	..	$C_9H_{8.4}O_{2.31}(OMe)_{0.95}(OEt)_{0.47}$
NI_1	19.0	...	..	14.82	12.0	3.54	..	..	..	
NI_2	25.3	...	..	14.82	11.9	3.90	..	..	..	
NI_3	50.0	...	..	14.90	11.7	4.57	..	..	..	
NI_4	115.5	...	..	14.90	11.7	4.57	..	..	..	
SII	0	63.40	6.46	14.55	10.2	3.02	..	..	..	
SII_1	7.2	...	..	14.62	11.0	3.94	858	..	..	
SII_2	13.0	...	..	14.60	10.4	4.51	571	..	..	
SIII	0	62.57	6.23	14.55	8.69	3.11	1320	2980	3990	$C_9H_{8.0}O_{2.66}(OMe)_{0.97}(OEt)_{0.40}$
$SIII_1$	7.2	...	..	14.95	9.05	3.56	1127	3520	4470	
$SIII_2$	13.0	...	..	14.55	10.30	3.53	959	..	..	
$SIII_3$	46.7	64.58	6.30	15.20	8.85	4.28	828	4110	4850	$C_9H_{7.7}O_{2.24}(OMe)_{0.97}(OEt)_{0.39}$
$SIII_4$	91.7	...	..	14.68	8.95	..	734	4560	5440	
$SIII_5$	141.0	64.15	5.88	14.60	8.30	4.41	705	4610	5730	$C_9H_{7.1}O_{2.41}(OMe)_{0.94}(OEt)_{0.36}$

[a] Solvent: SI and SII series, 95% ethanol, containing 2% of dioxane; SIII series, dioxane. [b] Sample SI_0 is SI dissolved in cold re-ethanolysis solution and immediately recovered similarly to the reacted samples. SI_1, SI_2, etc., are samples of SI recovered after various periods of re-ethanolysis.

Results

Changes in Ethoxyl Content.—The changes in

(18) S. K. Gross and C. Schuerch, *Anal. Chem.*, **28**, 277 (1956); S. K. Gross, K. Sarkanen and C. Schuerch, manuscript in preparation.

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ethoxyl and phenolic hydroxyl content of samples NI, SI and SIII occurring during re-ethanolysis are shown in Fig. 1. First, it is obvious that the ethoxylation reaction has been completed in sample SIII before it is isolated from the woodmeal and is nearly complete in the fractions SI and NI isolated earlier. A rapid rate previously has been reported for the ethoxylation of black spruce "native lignin."[19]

The ethoxyl content reaches a maximum value of about 0.55 ethoxyl group per monomer unit in lignin SI after a few hours of re-ethanolysis and thereafter decreases slightly. The ethoxyl content of fraction SIII may also decrease very slowly on re-ethanolysis from an initial value of 0.41 unit per monomer.

While the ethoxyl content is thus remaining almost unchanged, the phenolic hydroxyl content is increasing substantially. It is clear, therefore, that these changes are not connected and the cleavage reaction at this stage of the process should properly not be called ethanolysis at all. The assumption that phenolic liberation and ethoxyl introduction are related during[20] the original isolation from wood therefore appears unlikely.

Liberation of Phenolic Groups.—Just as the ethoxyl content reaches a nearly constant value which is much less than one ethoxyl group per propylguaiacyl unit, the phenolic content also reaches a constant value of 0.55 to 0.65 phenolic group per monomer (Fig. 1). Since every propylguaiacyl unit contains either a phenoxy derivative such as a phenolic ether or a free phenolic hydroxyl group, there are present in the completely reacted samples 0.35–0.45 "unreactive" phenolic ether group per monomer unit that cannot be cleaved by the ethanolysis reaction.

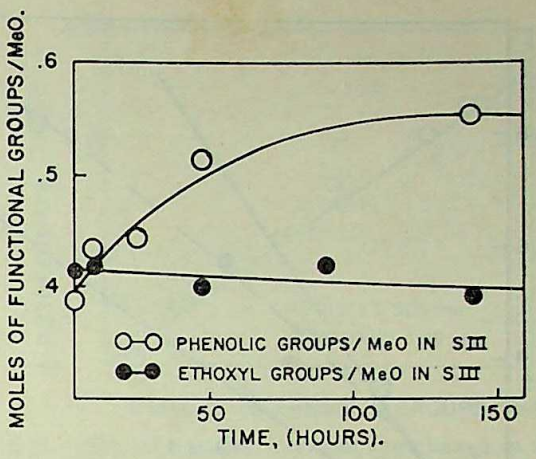
Some information regarding the structure of the "reactive" phenoxy derivatives in ethanol lignin can be obtained by a study of the rate of their ethanolysis. In most acid-catalyzed reactions the rate is known to be first order with respect to the substrate.[21] The rate constant k can therefore be computed using the equation

$$\ln (A_0/A) = kt$$

where A_0 and A are the amounts of the reactant at the start of the reaction and after time t, respectively. For the liberation of phenolic groups, A can be defined as the moles of "reactive" phenolic ether groups per mole methoxyl. These are not directly determinable. However, if no side-reactions occur, the number of "reactive" phenolic ether groups at the beginning of the reaction equals the total number of phenolic hydroxyl groups liberated after infinite time of reaction. The latter quantity can be estimated from the experimental data with a reasonable accuracy and the above equation thus assumes the form

$$\ln \frac{(\Delta C_6H_5OH)_\infty}{(\Delta C_6H_5OH)_\infty - (\Delta C_6H_5OH)_t} = kt$$

where ΔC_6H_5OH denotes the amount of phenolic



Change in phenolic hydroxyl and ethoxyl contents in the re-ethanolysis of sample SIII.

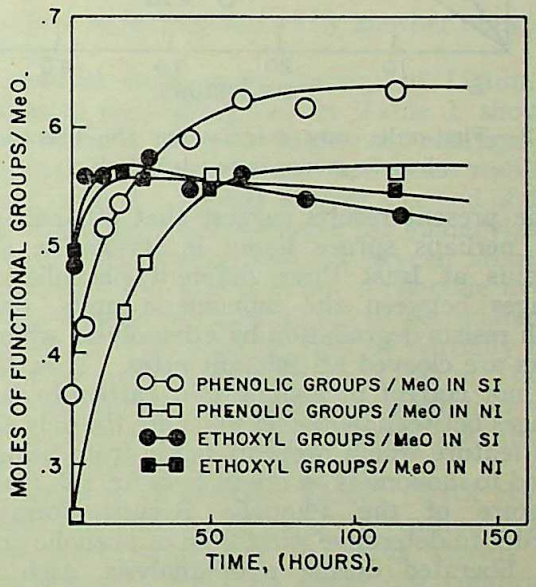


Fig. 1.—Change in phenolic hydroxyl and ethoxyl contents in the re-ethanolysis of samples SI and NI.

groups liberated in moles per mole methoxyl, t is time in hours and subscripts ∞ and t refer to infinite time and time t, respectively.

If the formation of phenolic groups in ethanolysis were due to the cleavage of one single reactive phenolic ether structure, the logarithmic plot of the data against time in Fig. 2 should form a single straight line, regardless of the ethanolic lignin preparation. This condition is obviously not fulfilled. The rate of liberation of phenolic groups in sample SIII is clearly less than the initial rate in sample SI or NI and the data on sample SI suggest that its first-order rate constant becomes less as the reaction proceeds.

The observed kinetic behavior would be expected if phenolic hydroxyl groups were liberated from two (or more) "reactive" phenolic ether structures. As the reaction proceeded the constant decrease in the ratio of rapidly reacting phenolic ether groups to those reacting slowly would result in a decrease in the over-all rate, as was observed in case of sample SI. Since sample SIII, when isolated, had been subjected to ethanolysis for a longer period of time than SI, it would be expected to contain proportionately less of the rapidly reacting groups and would have a lower rate as is observed.

(19) E. Adler and J. Gierer, *Acta Chem. Scand.*, **9**, 84 (1955).
(20) C. Schuerch, THIS JOURNAL, **73**, 2385 (1951).
(21) K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1950, p. 282.

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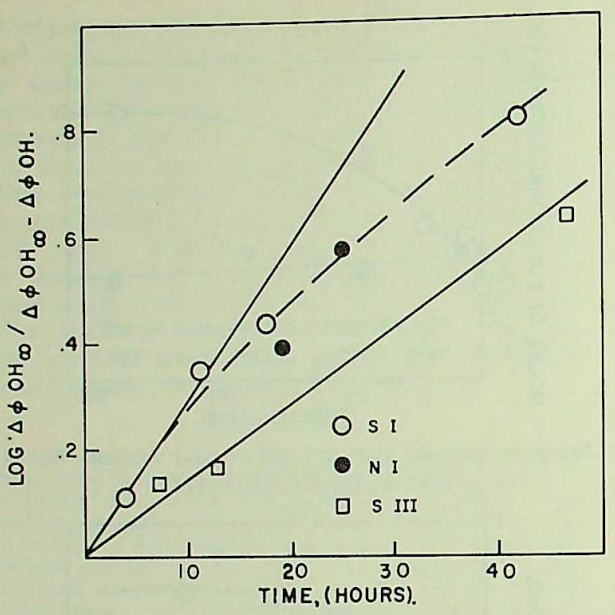


Fig. 2.—First-order rate diagram for the liberation of phenolic groups in re-ethanolysis.

The present results suggest that ethanol lignin (and perhaps spruce lignin in its native state) contains at least three different phenolic ether linkages between the monomeric units, one of which resists degradation by ethanolysis, while the others are cleaved at different rates. It is, therefore, not correct to assume that carbon-to-carbon linkages between monomer units are the only structural feature which prevents lignin from being degraded to monomers on ethanolysis (*cf.* ref. 14).

Nature of the Phenolic Groups Formed.—In order to determine what kind of phenolic groups were liberated during re-ethanolysis, each individual product from re-ethanolysis of SI was dissolved in neutral and alkaline solution, and the difference in the spectra of the two solutions was determined by the method of Goldschmid.[22] The height of the two maxima of the difference spectra of these products at various stages of reaction are given in Table II. The increase in the peak at

Table II

Maxima in the Difference Spectra between Neutral and Alkaline Solutions of Reacted SI Samples

Time of reacn., hr.	Absorptivity, l. g.$^{-1}$ cm.$^{-1}$[a] At 300 mμ	At 350 mμ
0	0.45	1.80
4.1	1.27	4.01
13.0	0.96	6.49
17.5	..	7.55
59.8	0.40	11.60

[a] Because of the low solubility of samples 30% of ethanol was used in *p*H 12 and 6 buffer solutions.

350 mμ during re-ethanolysis can be interpreted[23] to mean that phenols with a carbonyl group in the α-position of the side chain are formed throughout the re-ethanolysis. The increase in the 300 mμ peak during the first 5-hour period of the same reaction indicates the formation of unconjugated phenols early in the reaction. The disappearance of the peak later may be due either to the formation of more α-carbonyl groups, from a previously unconjugated side chain, or may simply be due to the formation of more conjugated phenols, since the values of their difference spectra are generally negative in the 300 mμ region.[23]

Changes in the Ultraviolet Spectra.—Ultraviolet spectral changes occurring during ethanolysis were determined by subtracting the spectra of neutral solutions of the original lignin samples SI or SIII from the neutral solutions of the same products after re-ethanolysis for various periods of time. In both series the spectral change was greatest at 255 and at 305 mμ (Fig. 3a). Since there is little difference between the molar absorptivity of a phenol and its simple derivatives at these wave lengths, the change in spectrum must indicate the formation of another functional group than the phenolic hydroxyl. It must be unsaturated and conjugated with the aromatic ring because guaiacylpropane derivatives show absorption at wave lengths higher than 305 mμ only when such groups are present. In order to establish the nature of this group, comparison was made to similar spectral changes in known model compounds.

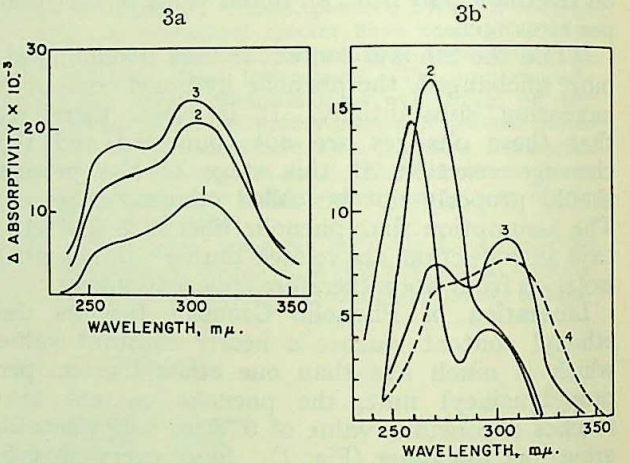
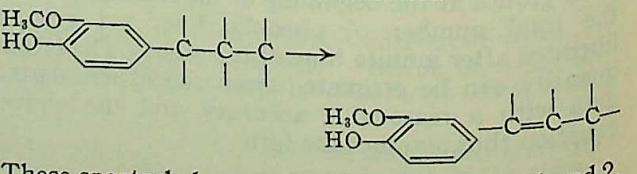


Fig. 3a.—Change in ultraviolet spectrum in the re-ethanolysis of sample SI; time of reaction: curve 1, 11.2 hr.; curve 2, 43.0 hr.; curve 3, 85.9 hr.

Fig. 3b.—Spectral changes caused by the introduction of a conjugated ethylenic bond (curves 1 and 2) or a conjugated carbonyl group (curves 3 and 4) to guaiacyl derivatives.

By subtracting the reported absorption spectrum of *p*-propylguaiacol from that of isoeugenol and of dihydro-dehydrodiisoeugenol from that of dehydrodiisoeugenol,[24] typical spectral changes were obtained for the transformation



These spectral changes are shown as curves 1 and 2, respectively, in Fig. 3b. Similarly, by subtracting the reported spectrum of guaiacylglycerol-β-guaiacyl ether from that of ketone I[25] and of dihydroeugenol from that of II (on a methoxy basis), spec-

(22) O. Goldschmid, *Anal. Chem.*, **26**, 1421 (1954).
(23) G. Aulin-Erdtman, *Svensk Papperstidn.*, **56**, 287 (1953).
(24) G. Aulin-Erdtman, *ibid.*, **55**, 745 (1952).
(25) L. Kaila, B. O. Lindgren and U. Saeden, *ibid.*, **55**, 245 (1952).

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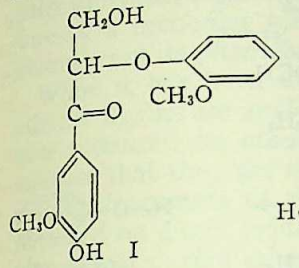
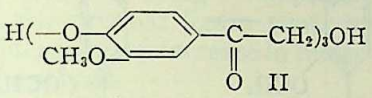
tral changes were obtained for the following trans-

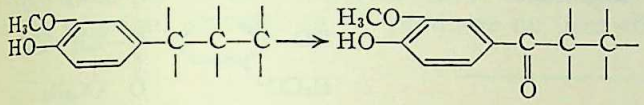


I



II

formation (curves 4 and 3, respectively, in Fig. 3b).



The spectral change for the formation of a conjugated ethylenic bond in this series is characterized by a strong main peak at 260–270 mμ and a shoulder or low maximum at 300 mμ. The spectral change corresponding to the formation of an α-carbonyl, however, contains a main peak at 305 mμ and a somewhat lower maximum in the 270 mμ region (Fig. 3b) and is thus very similar to that produced during ethanolysis (Fig. 3). The absorptivity change at 305 mμ is therefore almost certainly due to the formation of an α-carbonyl group during ethanolysis.

Furthermore, when the change in absorptivity at 305 mμ (ΔA_{305}) is plotted as a function of change in phenolic content, a single linear correlation between the two changes is found for the products from both SI and SIII (Fig. 4). This appears to be strong evidence that a phenolic hydroxyl and an α-carbonyl group are produced in the same reaction.

It can be shown by the following reasoning that these two functional groups must also be produced in nearly equivalent amounts rather than in some non-stoichiometric ratio. The maxima of curves 3 and 4 (Fig. 3b) at 305 mμ are 8.7×10^3 and 7.8×10^3 l. mole^{-1}cm.$^{-1}$, respectively. The average of these two values, 8.3×10^3, gives the approximate change in absorptivity at 305 mμ, caused by the introduction of one mole of α-carbonyl in a guaiacylpropane derivative. On the other hand, the liberation of one mole of phenolic group in the ethanolysis of lignin corresponds to a change in absorptivity of 9.17×10^3 l. (mole CH_3O)$^{-1}$cm.$^{-1}$ (Fig. 4). By comparing this figure with the average value given above, it can be concluded that for every liberated phenolic hydroxyl group approximately 1.1 α-carbonyl groups are formed. The 10% variation between these numbers is well within the range of uncertainty introduced by ignoring those functional groups in the model substances which contribute less to ultraviolet absorption.

The formation of an α-carbonyl very largely explains the ultraviolet spectral changes during re-ethanolysis, but the rate of formation of the 255 mμ peak differs somewhat from that at 305 mμ. Furthermore, the 255 mμ peak continues to grow as long as ethanolysis continues while the change at 305 mμ is very slight in those later periods of ethanolysis during which there is little or no phenolic liberation. The 255 mμ peak must therefore be formed in part by another unexplained reaction.

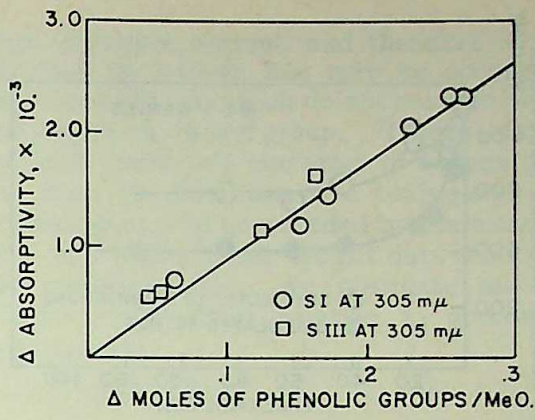


Fig. 4.—The relationship between the change in absorptivity at 305 mμ and the change in phenolic hydroxyl content in the re-ethanolysis of samples SI and SIII.

Decrease in Oxygen Content of Lignin.—The molecular formulas given in Table I show that quantitatively the most important reaction occurring during re-ethanolysis is one which results in a loss of oxygen. Sample SI over a period of 116 hr. loses about 0.6 atom of oxygen per guaiacylpropane unit and SIII loses about 0.3 oxygen atom. For comparison the total number of phenolic hydroxyl groups formed are 0.28 and 0.16 per guaiacylpropane unit. This reaction may be partially related to the increase in absorptivity at 255 mμ, but it is not possible to make any linear correlation such as was possible with phenolic hydroxyl liberation and change in absorptivity at 305 mμ.

Change in Molecular Weight (With Sonja K. Gross).—In the past, repolymerization reactions have been postulated to occur during lignin ethanolysis.[14] However, under our conditions of high dilution in a good solvent system, the number average molecular weight at first decreased and then, like the phenolic hydroxyl content, remained constant (Fig. 5). It seemed possible, therefore, that the fission of phenolic ether linkages might be the only reaction altering the lignin molecular weight.

Now in linear or branched polymers, it is obvious that a cleavage reaction will be accompanied by a decrease in number average molecular weight corresponding to the formation of two molecules from one. This relationship can be expressed by the equation

$$M_n = \frac{G_o \bar{M}_{no}}{G(1 + \Delta F_s \bar{M}_{no})} \qquad \text{(III)}$$

where G represents the content of some stable functional group (in the case of lignin, methoxyl expressed as per cent.), and ΔF_s is the *increase* in the number of moles of *product* functional group per gram (in the case of lignin ethanolysis, phenolic hydroxyls).

If during a cleavage reaction the molecular weight decreases less than this equation predicts, the molecular structure cannot be linear but must contain cycles of some size which are opened by the reaction, or side reactions must be occurring.

Theoretical number average molecular weights

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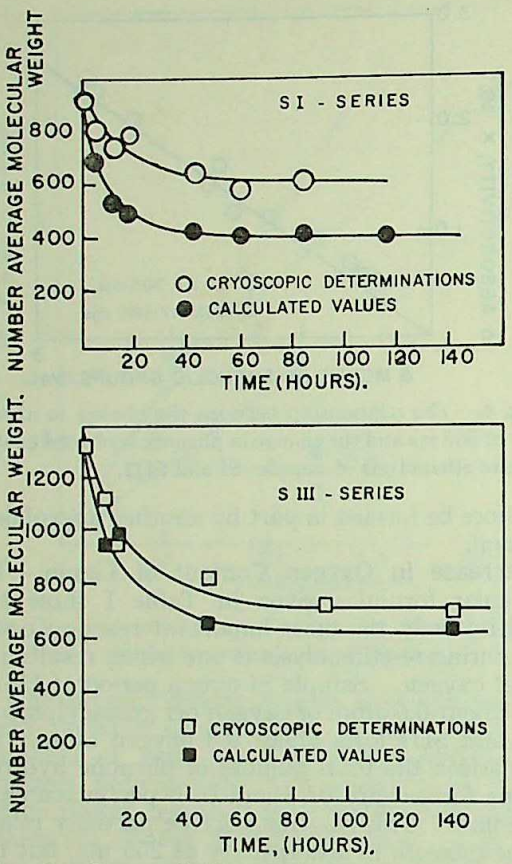


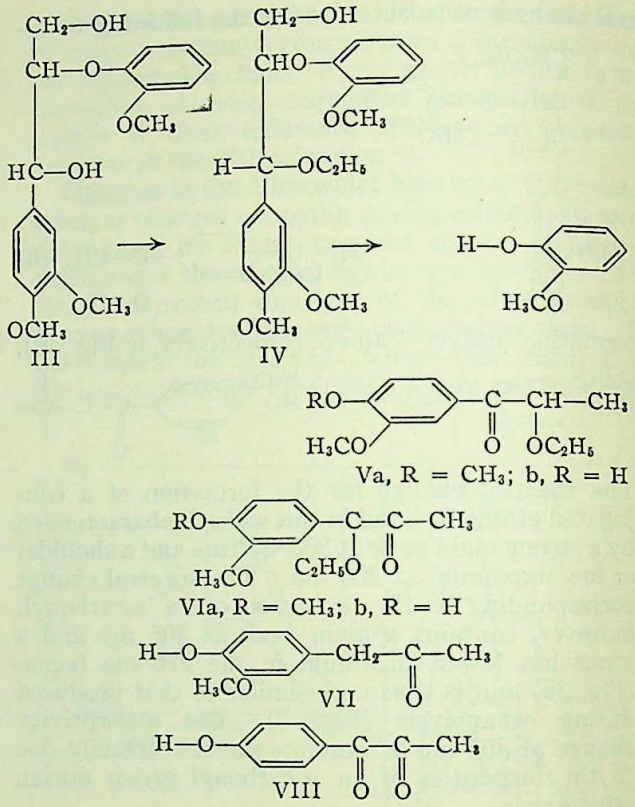
Fig. 5.—Cryoscopically determined number-average molecular weights compared with a hypothetical curve calculated from the change in phenolic group content.

experimental molecular weights of the starting materials SI and SIII and from the corresponding increase in phenolic content using the above equation and thus assuming that each liberation of a phenolic group resulted in the formation of two molecules from one. The calculated values were consistently lower than the experimental values (Fig. 5) although the changes followed each other closely. There may therefore be some cyclic structures initially present or new bonds formed during degradation. In any case, this method of gaining evidence of cyclic structures in lignin should be applied further as our knowledge of lignin reactions develops and molecular weight determinations of lignin are improved.

Discussion

The behavior of ethanol–spruce lignins on re-ethanolysis is rather closely analogous to that of guaiacylglycerol-β-aryl ethers. Compounds of this general structure have been proposed as the structural elements of lignin responsible for the formation of the ethanolysis monomers,[5-8] and they now appear to be satisfactory models for at least two of the reactions occurring on the amorphous portion of lignin.

Veratrylglycerol-β-guaiacyl ether (III) reacts with ethanolic hydrogen chloride first to form an ethyl ether, presumably IV, and later to form small amounts of guaiacol and the two phenylpropane derivatives V_a and VI_a and an amorphous product containing carbonyl groups.[6]



Veratrylglycerol reacts similarly.[8] From the ethanolysis products of guaiacylglycerol (Vb, R = H), VII and VIII have been isolated and probably VIb also is formed.[8] The careful work of Gardner[26] shows that ethanolysis of oxyconiferyl alcohol, a compound which may well exist as a reaction intermediate from guaiacylglycerol, produces all four lignin ethanolysis monomers V_b, VI_b, VII and VIII. Furthermore, the two compounds (Vb and VIII) with α-carbonyl groups amount to 83% of the monomeric products of ethanolysis.

This research shows that lignin re-ethanolysis gives results similar in many respects to the above. The ethoxyl content of lignin rises sharply during the initial phase of the ethanolysis (compare references 22 and 23). The ethoxylation of lignin is accompanied by a slower reaction in which a phenolic hydroxyl and an α-carbonyl group are formed in nearly equimolar proportions. The ethoxyl content of the lignin decreases slightly during re-ethanolysis as might be expected if a conversion like that giving rise to VII and VIII were occurring.

It is reasonable to assume that the same reactions here shown to be occurring on about one-fifth of the units in SI, SII and SIII on re-ethanolysis must have occurred throughout the extraction process as well, that a very substantial fraction of the phenolic groups liberated must have been liberated by the same reaction and that the liberation of monomers by ethanolysis followed a similar course. The best present model for these reactions of ethoxylation and cleavage seems to be the guaiacylglycerol-β-aryl ether system.

The fact that the liberation of phenolic groups was not kinetically homogeneous does not necessarily mean that the reacting structures were origi-

(26) T. F. Gardner, *Can. J. Chem.*, **32**, 532 (1954).

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nally different, for a change in the side chain structure of a monomer unit could affect the rate of liberation of its phenolic group.

While it has been implied that the amorphous ethanol lignins are analogous to the reversion products produced on ethanolysis of III,[6] our results indicate that they are nearer to being incompletely reacted fragments of the original lignin since we obtained no direct evidence of an increase in molecular weight during ethanolysis.

There is, however, an unexplained loss of oxygen (0.6 atom per C_9 unit in SI) in the re-ethanolysis. The proposed cleavage of IV produces no over-all change in oxygen content, and therefore it seems likely that the oxygen loss may be occurring in those monomer units which do not react to produce a free phenolic hydroxyl group. If this is the case, these units lose nearly one atom of oxygen per C_9 unit. Since the formation of a conjugated ethylenic bond appears to be excluded by the ultraviolet spectra and the molecular weight data seem to exclude repolymerization, we postulate an intramolecular condensation reaction to account for this oxygen loss.

SYRACUSE, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

The Constitution of Corn Starch Dextrin[1]

BY J. D. GEERDES, BERTHA A. LEWIS AND F. SMITH

RECEIVED JANUARY 16, 1957

Commercial corn starch dextrins have been fractionated and subjected to periodate oxidation studies and one of them has been examined by methylation. Periodate oxidation shows that the amount of glucose stable to oxidation is higher (5%) in the dextrin than in the parent starch. The hydrolyzate of the methylated dextrin has been shown to contain: 2,3,4,6-tetra-*O*- (16.5%); 2,3,6-tri-*O*- (57.3%), 2,3,4-tri-*O*- (2.6%), 2,4,6-tri-*O*- (1.2%), 2,3-di-*O*- (6.3%), 2,6-di-*O*-(10.0%), 3,6-di-*O*- (3.2%), 2-*O*- (1.5%), 3-*O*- (0.8%) and 6-*O*-methyl-D-glucose (0.5%). From the periodate and methylation data it is deduced that dextrinization is accompanied by considerable transglycosidation and the development of a highly branched structure.

In spite of the industrial importance of starch dextrins, prepared from native starches by roasting usually in the presence of acidic reagents, little is known about the detailed structural changes that the starch undergoes during the dextrinization process. In the early work[2,3] it was suggested that dextrins are formed by cleavage of the starch chains with concomitant anhydro-ring formation to give smaller molecules terminated by non-reducing units of the levo-glucosan type. Dextrinization of amylose and amylopectin also has been investigated by adsorption chromatography[4] whereby it was shown that amylopectin undergoes dextrinization more readily than amylose.[4,5] Methylation studies[5] enabled the deduction to be made that the dextrinization process caused breakdown of the starch molecules to smaller fragments which were much more highly branched than the original starch. This was recognized from the increased percentage of 2,3,4,6-tetra-*O*-methyl-D-glucose obtained from the methylated dextrin as compared with the yield from the methylated derivative of the parent starch.

This paper deals with periodate oxidation studies on a number of acid converted corn starch dextrins and methylation studies on one of them.

Four commercial corn starch dextrins were fractionated from aqueous solution with ethanol and the various fractions (see Table II) were examined by a procedure[6] involving periodate oxidation, reduction and hydrolysis. This procedure not only provides the usual information on the periodate consumption and formic acid production, but it also determines the percentage of glucose residues in the dextrin that are immune to periodate cleavage. Since the native starches contain less than 1% of glucose residues that are immune to periodate oxidation, it was tentatively concluded that the relatively high percentage of glucose residues in the dextrin that survived periodate oxidation was an indication of the structural rearrangements that occur during the dextrinization process.

On the basis of these periodate oxidation studies (see Tables I and II), the dextrin fraction chosen for further investigation by the methylation technique was one which was found[6] to contain the largest percentage of glucose units that were immune to periodate oxidation.

TABLE I

PERIODATE OXIDATION OF DEXTRIN

Reacn. time, hr.	Moles anhydro-hexose per mole formic acid produced	Moles of periodate consumed per mole of anhydro-hexose	Reacn. time, hr.	Moles anhydro-hexose per mole formic acid produced	Moles of periodate consumed per mole of anhydro-hexose
0	22.6	0.19	144	4.7	0.99
17	10.7	.45	241	4.7	0.99
45	5.5	.49	480	4.5	1.00
91	4.8	.87	700	4.3	1.00

The dextrin fraction, purified through its acetate, was exhaustively methylated with methyl sulfate and alkali in the usual way after which it was hydrolyzed. The composition of the mixture of methylated sugars so formed, as revealed by column[7] partition chromatography using buta-

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TABLE II

PERIODATE OXIDATION OF STARCH DEXTRIN FRACTIONS

Dextrin fraction Commercial No.	Water: ethanol ratio used to ppt. dextrin	Oxidn. time, hr.	No. anhydro-hexose units per mole of formic acid produced	Moles periodate consumed per anhydro-hexose unit	Glucose not oxidized (by chromato-graphic analysis), %
724[a]	1:1	284	4.96	1.05	1.56
724[a]	1:2	278	4.35	1.06	1.87
800[a]	1:1	277	10.77	1.00	
		650	10.37	1.02	1.40
800[a]	1:2	276	8.73	1.05	
		650	7.94	1.03	2.33
9533-R[b]	1:1	276	5.35	1.07	
		650	5.03	1.09	4.11
9533-R[b]	1:2	275	4.84	1.08	
		650	4.47	1.14	4.92
B-2[c]	1:1	275	10.85	0.98	
		650	10.68	1.00	2.38

[a] Supplied by Clinton Foods, Inc., Clinton, Iowa. [b] Supplied by Stein Hall Co., New York, N. Y. [c] Supplied by American Maize Products Co., Roby, Indiana.

none:water azeotrope as the solvent,[8] is given in Table III (see later). The identity of these components was established by preparing suitable crystalline derivatives.

Since the commercial dextrin was produced from native starch, which contains amylopectin and amylose, a detailed structural discussion is not warranted. However, it is possible to make certain deductions concerning the structural changes that occur during the dextrinization process by an inspection of the nature and amounts of the components of the hydrolyzate of the methylated dextrin (see Table III).

Of the ten components in Table III only 1, 2 and 5 are obtained in quantity from methylated amylopectin and only components 1 and 2 from methylated amylose. The characterization of the other seven components, 3, 4 and 6–10, derived from the methylated dextrin coupled with the isolation of a relatively high percentage of component 1 (2,3,4,6-tetra-*O*-methyl-D-glucose), indicates that the dextrin has a much more complicated structure than either the amylose or the amylopectin of the parent corn starch.

The highly branched character of the dextrin molecule is shown by the complexity of the mixture of the di-*O*- and mono-*O*-methyl derivatives of glucose (Table III) and also by the fact that one out of every 6 glucose units occupies a terminal non-reducing position as revealed by the yield of 2,3,4,-6-tetra-*O*-methyl-D-glucose. This last finding is in agreement with that derived from a previous methylation study of a dextrin.[5] Support for this highly branched structure for the dextrin as revealed by the methylation studies is also provided by the results of the periodate oxidation studies which showed that 1.14 moles of periodate were consumed per anhydroglucose unit with the concomitant formation of 1 mole of formic acid for every 4.5 moles of anhydroglucose.

The identification of the 2,4,6-tri-*O*-, 2,6- and 3,6-di-*O*- and the 2-, 3- and 6-*O*-methyl-D-glucose also agrees with the observation that the dextrin contains a considerable number of glucose units that are stable to periodate oxidation.

While it is conceivable that certain of the partially methylated glucose derivatives obtained in small yield may have arisen as a result of incomplete methylation or demethylation during hydrolysis, it is not believed that this is the explanation for the isolation of the relatively large amount (10%) of 2,6-di-*O*-methyl-D-glucose. On the contrary, it is believed that the identification of the latter proves that the dextrinization process not only involves a shortening of the chains as shown by periodate oxidation and methylation studies and a decrease in molecular weight as revealed by viscosity studies, but also by a considerable amount of transglycosidation. This phenomenon which is probably one of the chief characteristics of the dextrinization process is most likely responsible for the formation of new glycosidic linkages and development of the highly branched structure as revealed by the identification of components 6–10 as well as components 3 and 4. This deduction is supported by the observation that starch dextrins are stable to β-amylase.[5] Although the possibility of anhydro-ring formation has been suggested,[2,3] a careful search of all the components of the hydrolyzate of the methylated dextrin failed to produce any supporting evidence for this hypothesis; no methyl derivatives of 3,6-anhydro-D-glucose were isolated and moreover there was no evidence for sugars other than D-glucose that might arise from ethylene oxide type sugar units.

Since transglycosidation is the characteristic reaction of "high conversion" dextrins, it would appear that the progress and control of dextrinization could be ascertained by determining the increase in the number of glucose residues in the dextrin that are resistant to periodate oxidation. It is also apparent that, inasmuch as dextrinization is accompanied by transglycosidation, it should be possible to bring about the synthesis of new carbohydrate polymers by a process of co-dextrinization (co-polymerization) with other substances such as sugars, oligosaccharides, polyhydric alcohols and also with other polysaccharides.

Experimental

Isolation of Dextrin Fractions.—The various "acid converted dextrins" (hereinafter called dextrins) were each extracted with 4 parts of water at room temperature and the solution centrifuged. To the supernatant liquid an equal volume of ethanol was added slowly with stirring to give one fraction, and after this had been removed (centrifuge) another volume of ethanol equal to the first was added to give a second fraction. Each fraction was redissolved in water and precipitated by pouring with stirring into about 4 volumes of ethanol. The white amorphous precipitates so obtained were washed successively with ethanol, ether, light petroleum ether and dried *in vacuo*. The two dextrin fractions so obtained were slightly reducing to Fehling solution while the product remaining dissolved in the aqueous ethanolic mother liquor from the initial precipitation was strongly reducing, doubtless due to the presence of glucose and oligosaccharides.

Acetylation and Fractionation of Dextrin.—The fraction (35 g.) of Dextrin #724, precipitated with two volumes of ethanol, was dissolved in formamide (250 ml.) with stirring at room temperature and acetylated by adding pyridine (250 ml.) followed by acetic anhydride (200 ml.), the latter

(8) L. Boggs, L. S. Cuendet, I. Ehrenthal, R. Koch and F. Smith, *Nature*, **166**, 520 (1950).

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being added over a 1-hr. period.[9] After standing at room temperature for 3 hr., the solution was poured into water (3 l.) with stirring. The precipitated acetate was filtered and washed with water. Further purification of the acetate was effected by dissolving it in chloroform, drying this solution with anhydrous magnesium sulfate, and reprecipitating the product by pouring the chloroform solution into light petroleum ether. The dry purified dextrin acetate was dissolved in chloroform (175 ml.) and fractionally precipitated in the usual way by adding increasing amounts of diethyl ether. Each fraction was separated, washed with petroleum ether and dried *in vacuo*. Examination of the 8 fractions so obtained showed that fractions 1–5 amounting to 7.1, 14.0, 11.3, 6.0 and 3.6 g., respectively, showed $[\alpha]^{25}D$ +140° (approx.) in chloroform (*c* 1), while fractions 6–8, amounting to 3.1, 1.3 and 1.9 g., respectively, showed $[\alpha]^{25}D$ +132° (approx.) in chloroform (*c* 1). Reacetylation of the second fraction caused no change in rotation (Found: OAc, 43.5).

Periodate Oxidation of Dextrin.—A portion (12.0 g.) of the dextrin acetate (composite of fractions 1–5) was deacetylated by treatment with a mixture of acetone (100 ml.) and *N* sodium hydroxide (150 ml.) for 1 hr. at 50°. The acetone was then removed under reduced pressure leaving an aqueous alkaline solution of the dextrin. The solution was neutralized with acetic acid and the dextrin precipitated by pouring the solution slowly with stirring into ethanol (4 volumes). The polysaccharide was dried as described above to give a fine white amorphous powder.

The dextrin (0.5000 g.) was dissolved in 0.1 *N* sodium periodate (500 ml.) and the oxidation allowed to proceed at 5° in the dark; at suitable intervals an aliquot (5 ml.) of the reaction mixture was withdrawn and added to 0.1 *N* As_2O_3 (5 ml.), sodium bicarbonate (2 g. approx.) and a crystal of potassium iodide. After standing for 0.5 hr. the excess arsenite was titrated with standard iodine solution in the usual way.[10] The periodate consumption was determined after correcting for a blank carried out under identical conditions.

An additional aliquot (20 ml.) was withdrawn and added to a solution containing 50% ethylene glycol (2 ml.) to destroy the excess of the periodate present and the formic acid was titrated with 0.01 *N* sodium hydroxide using methyl red as the indicator. A blank was carried out at the same time. The results are recorded in Table I.

Similar oxidations were carried out on other dextrin fractions with results given in Table II, the procedure being the same except that a 3-g. sample was oxidized in 2 liters of 0.05 *N* sodium periodate.

Determination of Anhydroglucose Units Not Oxidized by Periodate.—Following the periodate oxidation of the dextrin fractions, the number of anhydroglucose units not oxidized was determined by quantitative paper chromatography as previously described.[11] The results are recorded in Table II.

Methylation of Starch Dextrin.—The fraction of the "acid converted dextrin" No. 9533, precipitated from aqueous solution with 2 volumes of ethanol, was chosen for the methylation study since the periodate oxidation procedure showed that this was most highly branched and contained more periodate-stable glucose residues than the other dextrins examined (see Table II).

The dextrin (20 g.) was acetylated[9] as described above and freed from impurity by dissolution in acetone and precipitation with water (yield 26 g.). The acetate (20 g.) was dissolved in acetone and methylated with methyl sulfate (100 ml.) and 30% (w./w.) aqueous sodium hydroxide during 2 hr. in the usual way. The temperature was kept below 25° until the reaction mixture no longer reduced Fehling solution after which it was raised to 55°. The methylated product readily separated upon completion of the reaction. Seven further methylations were applied in the same manner at 55°, acetone being used as the solvent medium. The product from the final methylation was dissolved in chloroform and washed with water to remove inorganic impurities. After drying ($CaCl_2$) the chloroform solution was freed from solvent and the residual methylated dextrin further purified by extraction with diethyl ether followed by precipitation from ethereal solution with petroleum ether (b.p. 30–60°). Filtration and drying yielded the methylated dextrin as a white powder (yield 12 g. (approx.)). The material, which left no ash upon ignition, showed $[\alpha]^{25}D$ +173° (*c* 1.3) in chloroform, OMe, 43.0%; a sample examined after seven methylations had the same properties.

Fractional Precipitation of the Methylated Dextrin.—The methylated dextrin obtained above was dissolved in ether and subjected to fractional precipitation with light petroleum ether in the usual way. Examination of the 6 fractions so produced showed that the methylated dextrin was essentially homogeneous, the rotation ranging from $[\alpha]^{25}D$ +173 to +166° in chloroform (*c* 1) and the OMe from 43.2 to 42.8%.

Hydrolysis of the Methylated Starch Dextrin.—A composite sample (5.0 g., $[\alpha]^{25}D$ +173° in chloroform (*c* 1), OMe, 43.0) of the first 5 fractions of the methylated dextrin was dissolved in methanol (150 ml.) containing 2% hydrogen chloride and the solution refluxed until the rotation was constant, $[\alpha]^{26}D$ +169° (initial), +72° (7 hr.), +72° (12.5 hr.) (constant value). The solution was neutralized with ethereal diazomethane and evaporated *in vacuo* to a sirupy mixture of methyl glycosides (5.8 g.).

A solution of the mixture of glycosides in *N* sulfuric acid (110 ml.) was heated on a boiling water-bath until the rotation was constant, $[\alpha]D$ +74° (initial), +88° (constant value after 9 hr.). The solution was neutralized ($BaCO_3$), filtered and evaporated to a sirup. The sirup was dissolved in water and the solution, after treatment with a little charcoal, filtered and passed successively through a cation (Amberlite IR 120) and an anion (Duolite A4) exchange resin. Concentration of the effluent *in vacuo* gave a clear colorless sirup (yield 5.26 g.).

Separation of Component Sugars by Column Chromatography.—A portion (1.77 g.) of the sugar mixture from the hydrolysis above was separated into its component sugars by column chromatography using cellulose–hydrocellulose[7] and butanone:water azeotrope as the solvent.[8,12] The eluate from the column was collected in tubes automatically changed every 10 minutes for the faster moving components (1 to 4) and every 30 minutes for the rest. The location of sugars in the various tubes was determined by spotting a small amount of eluate from each tube on filter paper and spraying with *p*-anisidine–trichloroacetic acid reagent.[13] The eluates from any tubes which appeared to be free of sugars by this color test were first evaporated to dryness before discarding to check for possible non-reducing sugars. Fractions that showed overlapping were resolved by paper chromatography. The yields of the various methylated sugars obtained by this separation are recorded in Table III.

TABLE III

COLUMN CHROMATOGRAPHY OF THE HYDROLYZATE OF METHYLATED DEXTRIN

Component	Methyl derivative of D-glucose	Yield		
		Wt., g.	%	Mole ratio
1	2,3,4,6-Tetra-*O*-	0.299	16.5	35
2	2,3,6-Tri-*O*-	.979	57.3	123
3	2,3,4-Tri-*O*-	.045	2.6	6
4	2,4,6-Tri-*O*-	.020	1.2	3
5	2,3-Di-*O*-	.101	6.3	14
6	2,6-Di-*O*-	.160	10.0	21
7	3,6-Di-*O*-	.052	3.2	7
8	2-*O*-	.022	1.5	3
9	3-*O*-	.012	0.8	1.7
10	6-*O*-	.007	0.5	1
	Wt. recovd.	1.697 g. (or 96%)		

Identification of the Components of the Hydrolyzate of the Methylated Dextrin. (a) **2,3,4,6-Tetra-*O*-methyl-D-glucose.**—Component 1 (Table III), crystallized completely and after recrystallization from petroleum ether gave 2,3,4,6-tetra-*O*-methyl-α-D-glucose, m.p. and mixed m.p. 97°, $[\alpha]^{24}D$ +113° → +84.4° in water (*c* 0.8); lit.[14,15] m.p. 96°

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and $[\alpha]_D$ +92° → +84° in water. *Anal.* Calcd. for $C_{10}H_{20}O_6$: OMe, 52.5. Found: OMe, 52.7.

(b) 2,3,6-Tri-*O*-methyl-D-glucose.—The sirupy component 2 (Table III, 0.979 g.) crystallized when nucleated with 2,3,6-tri-*O*-methyl-D-glucose and had m.p. 117–118° undepressed when mixed with an authentic specimen after recrystallization from ethyl ether, $[\alpha]^{24}D$ +92° → +68.7° in water (*c* 1.1); lit.[16–18] m.p. 122–123° and $[\alpha]_D$ +90.2° → +70.5° in water.

(c) 2,3,4-Tri-*O*-methyl-D-glucose.—The sirupy component 3 (Table III, 0.045 g.) had $[\alpha]^{24}D$ +61° in methanol (*c* 0.7) and was chromatographically identical with 2,3,4-tri-*O*-methyl-D-glucose when developed either with butanone:water azeotrope or with benzene:ethanol:water:ammonium hydroxide (200:47:14:1). Treatment of component 3 with aniline in ethanol yielded the crystalline anilide of 2,3,4-tri-*O*-methyl-D-glucose, $[\alpha]^{23}D$ −103° in ethanol (*c* 0.4), and m.p. 150°, undepressed by admixture with an authentic specimen; lit.[19] m.p. 145–146°.

(d) 2,4,6-Tri-*O*-methyl-D-glucose.—The sirupy product (0.065 g.) recovered from the mother liquors of the 2,3,6-tri-*O*-methyl-D-glucose was allowed to react with 0.5% methanolic hydrogen chloride (10 ml.) at room temperature for 20 hr. until the rotation became constant (final value, $[\alpha]^{23}D$ +20°). Neutralization (Ag_2CO_3), filtration and concentration gave a sirupy product which was resolved by paper chromatography using butanone:water azeotrope into two components. The faster moving component consisted of methyl 2,3,6-tri-*O*-methyl-D-glucofuranoside while the slower component (0.020 g.) proved to be 2,4,6-tri-*O*-methyl-D-glucose, $[\alpha]^{24}D$ +64° in methanol (*c* 0.3). Treatment of this slower moving tri-*O*-methyl-D-glucose with ethanolic aniline in the usual way afforded N-phenyl-D-glucopyranosylamine 2,4,6-tri-*O*-methyl ether, m.p. and mixed m.p. 156–158°, lit.[20] m.p. 162–166°.

(e) 2,3-Di-*O*-methyl-D-glucose.—Component 5 (Table III, 0.101 g.) yielded crystalline 2,3-di-*O*-methyl-D-glucose when nucleated with an authentic specimen. After recrystallization from ethyl acetate it had m.p. and mixed m.p. 117–119°, $[\alpha]^{26}D$ +51.3° in acetone (*c* 0.8); lit.[21] m.p. 110°, $[\alpha]_D$ +50.9° in acetone. Treatment of the 2,3-di-*O*-methyl-D-glucose with aniline in ethanol yielded the crystalline anilide of 2,3-di-*O*-methyl-D-glucose, m.p. 133–135°; lit.[22] m.p. 134°.

(f) 2,6-Di-*O*-methyl-D-glucose.—The sirupy component 6 (Table III, 0.160 g.) which had $[\alpha]^{23}D$ +65.5° in water (*c* 1.2)[23] was chromatographically identical with 2,6-di-*O*-methyl-D-glucose; lit.[22] $[\alpha]_D$ +63.3° in water. Treatment of the sirup with *p*-phenylazobenzoyl chloride in pyridine gave 2,6-di-*O*-methyl-D-glucose 1,3,4-tri-azobenzoate, m.p. 206–208°, $[\alpha]^{25}D$ −341° (*c* 0.4 in chloroform), after recrystallization from ethyl acetate–light petroleum ether. The mixed melting point with an authentic specimen (m.p. 200°, $[\alpha]^{25}D$ −329° in chloroform) was 205°; lit.[24] m.p. 205–207°.

(g) 3,6-Di-*O*-methyl-D-glucose.—Component 7 (Table III, 0.052 g.) was chromatographically identical with 3,6-di-*O*-methyl-D-glucose. When a portion (0.017 g.) of it was treated with methanolic hydrogen chloride (0.5%) at 20°, the rotation changed from $[\alpha]_D$ +75° to +22° in 2 hr. indicating furanoside formation and hence the presence of a free hydroxyl group at C_4 in the di-*O*-methyl-D-glucose. Component 7 crystallized completely when nucleated with an authentic specimen[25] of 3,6-di-*O*-methyl-D-glucose. After recrystallization from ethyl acetate, 3,6-di-*O*-methyl-α-D-glucose was obtained, m.p. 118–119°, $[\alpha]^{24}D$ +60° in water (*c* 0.6). Admixture with an authentic specimen (m.p. 111–112°)[25] gave m.p. 111–112°; lit.[26] m.p. 114–115°, $[\alpha]^{18}D$ +61.5° in water.

(h) 2-*O*-Methyl-D-glucose.—Component 8 (Table III, 0.022 g.) which crystallized spontaneously was chromatographically identical with 2-*O*-methyl-D-glucose. After recrystallization from ethanol the 2-*O*-methyl-β-D-glucose had m.p. and mixed m.p. 156–158°, $[\alpha]^{23}D$ +63° (equilibrium value) in water (*c* 0.8); lit.[27] m.p. 157–159° and $[\alpha]_D$ +66° (equilibrium value) in water.

(i) 3-*O*-Methyl-D-glucose.—Component 9 (Table III, 0.012 g.) which was chromatographically identical with 3-*O*-methyl-D-glucose, crystallized spontaneously as the β-anomer, m.p. and mixed m.p. 135°, $[\alpha]^{24}D$ +58° (equilibrium value) in water (*c* 0.4); lit.[28,29] m.p. 133.5–135° and $[\alpha]_D$ +55° (equilibrium value) in water.

(j) 6-*O*-Methyl-D-glucose.—Component 10 (Table III, 0.007 g.), which showed the same R_f and color on paper chromatograms when sprayed with *p*-anisidine–trichloroacetic acid as 6-*O*-methyl-D-glucose, crystallized when nucleated with the authentic specimen. The crystalline 6-*O*-methyl-α-D-glucose had m.p. and mixed m.p. 143–144° and $[\alpha]^{26}D$ +54° (equilibrium value) in ethanol (*c* 1.2); lit.[30,31] m.p. 143–145° and $[\alpha]_D$ +60° (equilibrium value) in water. The osazone prepared in the usual way had m.p. and mixed m.p. 175–180°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Degradation of Glycogen to Isomaltotriose[1] and Nigerose

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Isomaltotriose and nigerose were found among the oligosaccharides in the acid hydrolyzate of beef liver glycogen, indicating that some of the α-D-(1 → 6) linkages in this molecule lie in adjacent positions and that a small amount of α-D-(1 → 3) linkages are present. Crystalline panose is shown to be dimorphous.

There are five predictable trisaccharides bound by α-D-glucopyranosyl-(1 → 4) or (1 → 6) linkages or combinations thereof. Three of these entities, *O*-α-D-glucopyranosyl-(1 → 6)-*O*-α-D-glucopyranosyl-(1 → 4)-D-glucopyranose (panose),[3–5] *O*-α-

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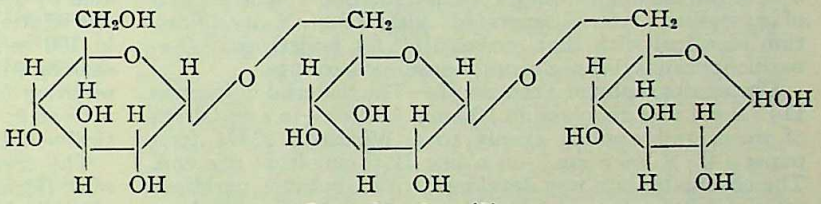
D-glucopyranosyl-(1 → 4)-*O*-α-D-glucopyranosyl-(1 → 4)-D-glucopyranose (maltotriose)[6-8] and *O*-α-D-glucopyranosyl-(1 → 6)-*O*-α-D-glucopyranosyl-(1 → 6)-D-glucopyranose (isomaltotriose, I)[9,10] have been isolated from natural sources and characterized on a crystalline basis. The remaining two trisaccharides, *O*-α-D-glucopyranosyl-(1 → 4)-*O*-α-D-glucopyranosyl-(1 → 6)-D-glucopyranose and *O*-α-D-glucopyranosyl-(1 → 4)-*O*-[α-D-glucopyranosyl-(1 → 6)]-D-glucose have not been described. All of these substances are of value as reference materials in the identification of polysaccharide linkages by fragmentation analytical methods. Maltose, isomaltose,[11] maltotriose[11] and panose[12] have been described as hydrolytic products of glycogens. We report herein that isomaltotriose and nigerose (3-*O*-α-D-glucopyranosyl-D-glucose) are likewise constituents of the glycogen molecule. Nigerose has been established as a constituent of amylopectin (waxy maize starch)[13] where it is encountered in larger amount than in glycogen. The hydrolytic conditions employed in our work were designed to reduce the formation of the isolated materials by reversion[14] to a negligible amount.

The sugars were isolated from the hydrolyzate of beef liver glycogen by a combination of carbon column chromatography, essentially as described by Whistler and Durso,[15] paper and silicate[16] column chromatography, and paper electrophoresis.[17,18]

The material (amorphous), which was identified as isomaltotriose, was chromatographically homogeneous, moving on paper at a rate slightly slower than panose but on paper electrophoresis moving at a rate much greater. A similar fast moving spot had been noted[12] in a yeast glycogen hydrolyzate but was not further investigated. The isomaltotriose displayed $[\alpha]_D$ +141°, which is in agreement with the reported value of +145°. The substance was further identified by molecular weight determination (on the dodecaacetate of its alditol) and by fragmentation analysis of the free sugar and its alditol. Paper chromatography and paper electrophoresis of a partial acid hydrolyzate of the alditol indicated the presence of only D-glucose, isomaltose, and unchanged material. Silicate chromatography of an acetylated partial hydrolyzate of the alditol (reduced trisaccharide) produced β-D-glucopyranose pentaacetate, D-glucitol (sorbitol) hexaacetate, β-isomaltose octaacetate and isomaltitol nonaacetate. These substances, which were fully identified by melting point and X-ray powder diffraction patterns, characterize the parent trisaccharide as isomaltotriose (I). The presence of this trisaccharide in a hydrolyzate of glycogen indicates that some of the α-D-(1 → 6) linkages occur in adjacent positions in the glycogen molecule.

In the course of this work, maltose, isomaltose, maltotriose and panose were again encountered and crystalline panose was shown to be dimorphous.



Isomaltotriose (I)

Experimental

Hydrolysis of Glycogen.—The glycogen used in this work was beef liver glycogen, $[\alpha]_D$ +198° (*c* 4, water). This material (92 g., dry basis) was hydrolyzed, in three portions, at a concentration of 0.4% in 0.1 *N* hydrochloric acid, by heating in a boiling water-bath. The hydrolysis was followed quantitatively by copper reduction and was stopped after 5.8 hr. at approximately 69% of completion. The hydrochloric acid was removed from the combined hydrolyzate by passage through a column of Duolite A4.[19]

Fractionation of the Glycogen Hydrolyzate on Carbon.—The sugars in the hydrolyzates were subjected to a preliminary separation on a carbon (Nuchar C unground[20]; no filter-aid added) column (800 × 65 mm., diam.) essentially according to the procedure of Whistler and Durso.[15] To prevent the accumulation of a large amount of D-glucose on the carbon, the neutralized hydrolyzate was placed on the same column in three portions, washing with water, after each addition, until the effluent exhibited a negative Benedict test. The water effluent, normally containing only D-glucose, was discarded. The developing solvent for the column was then changed to 5% ethanol and the addition continued (about 20 liters) until the effluent again showed a negative reaction toward Benedict solution. This effluent was evaporated to a sirup under reduced pressure; yield 15 g. (fraction I). The developer was changed to 10% ethanol and the washing continued until the effluent exhibited a negative reaction toward Benedict solution. Solvent was removed under reduced pressure; yield 7.2 g. of a sirup (fraction II).

Chromatography of Fraction I; Maltose, Isomaltose and Nigerose.—The sirupy fraction I (15 g.) was acetylated by heating to the boiling point with 100 ml. of acetic anhydride and 7 g. of anhydrous sodium acetate. The solution was then cooled and poured onto 300 ml. of ice and water. After the excess acetic anhydride was hydrolyzed, the solution was extracted with chloroform and the water-washed and dried extract was evaporated under reduced pressure; yield 25 g. of a sirup. The product was dissolved in ethanol and allowed to crystallize; yield 5.2 g.; after recrystallization from ethanol, m.p. 155–157° unchanged on admixture with known β-maltose octaacetate, $[\alpha]^{20}_D$ +62.7° (*c* 4, chloroform). The mother liquor was concentrated to a sirup; yield approx. 20 g.

The above sirup was dissolved in 200 ml. of benzene and chromatographed in four portions on Magnesol[16]–Celite[16] (5:1) columns (270 × 75 mm., diam.) using 4000 ml. of

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(7) J. M. Sugihara and M. L. Wolfrom, *ibid.*, **71**, 3357 (1949).
(8) A. Thompson and M. L. Wolfrom, *ibid.*, **74**, 3612 (1952).
(9) Allene Jeanes, C. A. Wilham, R. W. Jones, H. M. Tsuchiya and C. E. Rist, *ibid.*, **75**, 5911 (1953).
(10) R. W. Jones, Allene Jeanes, C. S. Stringer and H. M. Tsuchiya, *ibid.*, **78**, 2499 (1956).
(11) M. L. Wolfrom, E. N. Lassettre and A. N. O'Neill, *ibid.*, **73**, 595 (1951).
(12) S. Peat, W. J. Whelan and T. E. Edwards, *J. Chem. Soc.*, 355 (1955).
(13) M. L. Wolfrom and A. Thompson, This Journal, **78**, 4116 (1956).
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(15) R. L. Whistler and D. F. Durso, *ibid.*, **72**, 677 (1950).
(16) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, *ibid.*, **67**, 527 (1945).
(17) A. B. Foster, *Chemistry & Industry*, 1050 (1952).
(18) A. B. Foster, *J. Chem. Soc.*, 982 (1953).
(19) A product of The Chemical Process Co., Redwood City, Calif.
(20) A product of the West Virginia Pulp and Paper Co., Chicago, Ill.

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benzene–*t*-butyl alcohol (100:1 by vol.) as developer. The column was extruded and streaked with indicator (1% potassium permanganate in 10% aqueous sodium hydroxide). A zone appearing 145 to 215 mm. from the column top was excised and eluted with acetone. Upon evaporation of the combined acetone solutions from the four columns, a sirup was obtained which was crystallized from ethanol; yield 4.6 g., m.p. 145–146° unchanged upon admixture with an authentic sample of β-isomaltose octaacetate, $[\alpha]^{20}D$ +96° (*c* 4, chloroform). These constants are in agreement with those of β-isomaltose octaacetate.[21]

The material in a zone appearing at 90 to 125 mm. from the column top was eluted with acetone. After evaporation, the resulting sirup (2.95 g.) was rechromatographed, in the same manner, on a Magnesol[16]–Celite[16] (5:1) column (270 × 75 mm., diam.) with 4000 ml. of benzene–*t*-butyl alcohol (100:1 by vol.) as developer. The material obtained on solvent removal from the acetone eluate of a zone appearing 90 to 125 mm. from the column top yielded a small amount of a gel from ethanol. The gel was isolated by decantation and from its ethanol solution a small amount of crystalline material separated; yield 2 mg., X-ray diffraction identical with that recorded[13,14] for β-nigerose (3-*O*-α-D-glucopyranosyl-β-D-glucopyranose) octaacetate.

Chromatography of Fraction II.—The material in fraction II (7.2 g.) was dissolved in 100-mg. portions, in a few drops of water and applied evenly to a Whatman 3MM filter paper (47 × 56.5 cm.) on a line 12.5 cm. from one end. The chromatogram was developed with 1-butanol–pyridine–water (3:2:1.5 by vol.) for 40 hr. A pilot strip, cut from the edge of the paper, was sprayed with aniline phthalate (1.66 g. of phthalic acid, 0.93 g. of aniline in 100 ml. of 1-butanol saturated with water) and heated for a few minutes in an oven at 105° to indicate the positions of the zones on the paper. Two main zones, A and B, appeared with several smaller zones. These two main zones, which moved at rates approximating those of maltotriose and panose as determined by comparison with the known sugars, were cut out of the papers. A total of 72 papers were prepared in this manner and the respective zones were combined. The sugars were recovered by pulping the paper in water, filtering and washing with water. The combined filtrates and washings were evaporated under reduced pressure to sirups; yield 2.95 g. from zone A and 1.58 g. from zone B.

Panose and its Dimorphism.—The slower moving zone A material above (2.95 g.) crystallized from methanol on being maintained at 60° overnight; yield 1.2 g. Pure material (form 2) was obtained on recrystallization from methanol; yield 1.05 g., m.p. 220–221° dec., unchanged on admixture with an authentic specimen of panose (form 1) received from Dr. S. C. Pan (m.p. 220°), $[\alpha]^{25}D$ +160.4 → 150.6° (140 min., *c* 3.8, water); X-ray powder diffraction data of our isolated crystals (form 2): 6.88[22] vw,[23] 5.96w 5.38m, 5.11w, 4.84vs, 4.25m, 4.03vw, 3.90vw, 3.81w, 3.58w, 3.29w, 3.19w, 3.01m, 2.76vw, 2.71vw, 2.60 vw. These data are identical with those obtained on a sample of panose isolated from potato starch and submitted to us by Dr W. J. Whelan.

Anal. Calcd. for $C_{18}H_{32}O_{16}$: C, 42.85; H, 6.39. Found: C, 42.76; H, 6.44; sample dried before analysis 2 hr. at 78° and 1 mm. pressure over phosphoric anhydride, 0.55% loss, no loss on further heating for 4 hr. at 110°, X-ray powder diffraction pattern unchanged.

The above data on crystalline form 2 are in agreement with those for the sample of panose prepared by Dr. Pan with the exception of the X-ray powder diffraction data[22,23] which, for this modification (form 1) are: 9.51vw, 8.29vw, 6.09vw, 5.81vw, 5.48m, 5.18w, 4.87vs, 4.69w, 4.43vw, 4.27vw, 4.16vs, 4.01vw, 3.76w, 3.64vw, 3.49vw, 3.23m, 3.05w, 2.89vw, 2.73w. A sample of form 1 was heated over phosphoric anhydride for 2 hr. at 78° and 1 mm. and lost 0.26% with no further loss after 2 hr. at 110°.

Our infrared absorption spectrum for form 1 (Nujol mull) agrees with that published by Whiffen[24] in the range of 700 to 900 cm.$^{-1}$, but is slightly different from the spectrum (Nujol mull) of the new modification (form 2) in this range as well as in the range 1100 to 1400 cm.$^{-1}$.

Sirupy panitol (50 mg.), which had been prepared by reducing form 2 of panose with Raney nickel catalyst and 2000 p.s.i. of hydrogen at 80°, was acetylated with 5 ml. of acetic anhydride and 50 mg. of sodium acetate at the boiling point and the product was isolated as described above and crystallized from ethanol; yield 70 mg., m.p. 145–147° with no depression on admixture with a sample of known panitol dodecaacetate prepared from form 1; X-ray powder diffraction data[22,23]: 12.11vs, 10.43vw, 9.36vw, 8.63vs, 7.80w, 7.03w, 6.41vw, 6.07vw, 5.72vw, 5.29vw, 4.96vw, 4.62s, 4.44s, 4.14vw, 4.03vw, 3.89vw, 3.76w, 3.62w, 3.50w, 3.39m, identical with those of a sample of panitol dodecaacetate[4,25] prepared from a sample of panose (form 1) submitted to us by Dr. Pan.

An amount of 50 mg. of panose (form 1) was acetylated with hot acetic anhydride and sodium acetate in the manner described above for the disaccharide portion of the hydrolyzate. There resulted a sirupy acetate which was deacetylated by dissolving in 0.5 ml. of methanol and adding a drop of a solution of sodium methoxide (0.5 g. of sodium dissolved in 100 ml. of methanol). The sodium was removed by shaking with a small amount of Amberlite 120.[26] The sirup resulting on solvent removal was crystallized from boiling methanol; yield 25 mg., X-ray powder diffraction data identical with those of form 2.

The crystalline modification of panose isolated in this work (form 2) was recrystallized five times by dissolving in a small amount of water, filtering with carbon, removing the water by evaporation under reduced pressure and refluxing with methanol. The resulting material then gave an X-ray powder diffraction pattern identical with that of form 1.

These data indicate that the two crystalline forms are dimorphous and have indistinguishable melting points (decomposition points).

Isomaltotriose.—The mother liquors from the crystallization of panose were combined and evaporated under reduced pressure to an amorphous product; yield 1.79 g. This material was separated by means of paper zone electrophoresis with an apparatus similar to that described by Foster.[17] Whatman 3MM paper (14 × 57 cm.) was used and the material was applied in 75-mg. portions uniformly on lines 70 mm. and 225 mm. from the ground end of the plates. Three such papers were wet with borate buffer (*p*H 10) and clamped, one above the other, between the glass plates. In this way a total of 150 mg. of material could be separated in each run. A current of 400 volts and 45 milliamp. was applied for 4 hr. After the papers were removed from the apparatus, a pilot strip was removed from one edge and the zones were located therein by means of aniline phthalate indicator[17] and excised from the paper. Only two zones appeared. The faster moving zone had a M_G[17] value of 0.71 as compared with those of isomaltose 0.67,[17,27] maltose 0.37,[17,27] panose 0.33 and maltotriose 0.33. After 1.79 g. of amorphous material had all been subjected to this treatment, the papers holding the fast moving zone were pulped by stirring in water and the resultant suspension was filtered and washed with water. The filtrate and washings were combined and the sodium ion was removed by stirring the solution with Amberlite 120[26] until neutral. The solution was then evaporated to dryness under reduced pressure. The boric acid residue was removed as the volatile methyl ester by repeated distillation with methanol. The residue was dissolved in methanol, filtered with carbon and evaporated under reduced pressure to dryness; yield 0.67 g., $[\alpha]^{20}D$ +141°, a value comparable with that (+145°) found by Jeanes and associates[9] for isomaltotriose. A sample (50 mg.) of this material was dissolved in 2.5 ml. of 0.05 *N* hydrochloric acid and heated on a boiling water-bath for 5 hr. The acid was removed by shaking with a small amount of Duolite A4[19] ion exchange resin and the solution evaporated to dryness under reduced pressure. Paper chromatography, using 1-butanol, pyridine, water (3:2:1.5 by vol.) as developer, and electrophoresis, using a

(21) M. L. Wolfrom, L. W. Georges and I. L. Miller, This Journal, **71**, 125 (1949).

(22) Interplanar spacing, Å., CuKα radiation.

(23) Intensity of lines, estimated visually: vs, very strong; s, strong; m, medium; w, weak; vw, very weak.

(24) D. H. Whiffen, *Chemistry & Industry*, 129 (1957).

(25) A. Thompson and M. L. Wolfrom, This Journal, **73**, 5849 (1951).

(26) A product of the Rohm and Haas Co., Philadelphia, Pa.

(27) K. Aso and S. Hamada, *Tôhoku J. Agr. Research*, **5**, 317 (1955); *J. Fermentation Technol. (Japan)*, **33**, 45 (1955); *C. A.*, **49**, 16480 (1955).

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borate buffer (*p*H 10), indicated the presence of only D-glucose, isomaltose and unhydrolyzed material.

The amorphous unhydrolyzed product (250 mg.) was dissolved in 30 ml. of water and reduced with hydrogen at 2000 p.s.i. and 80° with Raney nickel catalyst. The solution was filtered and evaporated to a sirup under reduced pressure; yield 200 mg., $[\alpha]^{20}D$ +114° (*c* 2.5, water). A 50-mg. sample of this material was acetylated with 3 ml. of hot acetic anhydride and 25 mg. of sodium acetate as described above; yield 60 mg. of sirup.

Anal. Calcd. for $C_{18}H_{22}O_6(CH_3CO)_{12}$: mol. wt., 1010.9. Found: mol. wt., 1018 (Rast).

Fragmentation Analysis of the Reduced Trisaccharide (Isomaltotriitol).—An amount of 134 mg. of the reduced and unacetylated product described above was dissolved in 10 ml. of 0.05 *N* sulfuric acid and heated on a boiling water bath for 7 hr. The excess acid was removed by shaking with a slight excess of Duolite A4[19] and filtering. The solution was evaporated under reduced pressure to a sirup which was acetylated with hot acetic anhydride (5 ml.) and sodium acetate (75 mg.) as described above. The resulting sirup was chromatographed on a column (235 × 35 mm., diam.) of Magnesol–Celite (5:1 by wt.) using 1000 ml. of benzene–*t*-butyl alcohol (100:1 by vol.) as developer. Three zones were located on the extruded column by streaking with the alkaline permanganate indicator. These were excised and eluted with acetone. The sirups obtained on solvent removal from the acetone eluates and from the column effluent were crystallized from ethanol. That from a zone located 25–40 mm. from the column top was identified as isomaltitol nonaacetate[28]; yield 3.8 mg. The material was crystallized from ethanol; m.p. 111–113°; X-ray powder diffraction pattern,[22,23] identical with that of authentic material: 10.98vs, 9.31s, 8.35w, 7.22vw, 6.86m, 6.39vw, 5.75vw, 5.14m, 4.72m, 4.43vw, 4.09s, 3.81w, 3.60vw. The product obtained from the zone 55–85 mm. from the column top was identified as β-isomaltose octaacetate[21]; yield 0.5 mg., m.p. 142–144°, X-ray powder diffraction data[14] identical with that of the authentic substance. The crystalline material found in the third zone located 240–290 mm. from the column top was identified as D-glucitol (sorbitol) hexaacetate; yield 0.8 mg., m.p. 95–96°; X-ray powder diffraction pattern,[22,23] identical with that of an authentic sample: 10.34w,, 8.43w, 7.58w, 7.02s, 6.56vw, 6.35vw, 5.96vw, 5.62vw, 5.05vs, 4.69w, 4.37w, 4.20vw, 4.01w, 3.89vw, 3.74m, 3.43s, 3.27vw, 3.18vw, 2.95m, 2.80vw, 2.72vw, 2.65w. The crystalline material from the column effluent was identified as β-D-glucopyranose pentaacetate; yield 25 mg., m.p. (on recrystallization from ethanol) 126–128° unchanged on admixture with an authentic specimen.

β-Maltotriose Hendecaacetate.—The material (1.58 g.) of the faster moving zone B from the paper chromatography of fraction II was placed upon paper and separated by electrophoresis, using a sodium borate buffer at *p*H 10, by the procedure described above for the separation of isomaltotriose. There resulted two zones, the slower of which had an M_G value of approximately 0.33 or that of maltotriose. The material in this zone was isolated; yield 950 mg. Acetylation of this product with hot acetic anhydride and sodium acetate was effected as described above for the acetylation of fraction I. This material failed to crystallize from ethanol and was chromatographed on a column (210 × 42, diam.) of Magnesol–Celite (5:1 by wt.) by development with 1000 ml. of benzene–*t*-butyl alcohol (100:1 by vol.). Two zones were located on the extruded column by streaking with the alkaline permanganate indicator. The amorphous material (180 mg.), obtained from the acetone eluate of a zone located 25–50 mm. from the column top, was not further investigated. The material obtained on solvent removal from the acetone eluate of a zone located 25–50 mm. from the column top, was crystallized from ethanol; yield 120 mg., m.p. 134–136° unchanged on admixture with authentic β-maltotriose hendecaacetate.[6,7]

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(28) M. L. Wolfrom, A. Thompson, A. N. O'Neill and T. T. Galkowski, THIS JOURNAL, **74**, 1062 (1952).

[CONTRIBUTION FROM THE ROBERT W. LOVETT MEMORIAL LABORATORIES FOR THE STUDY OF CRIPPLING DISEASES, MASSACHUSETTS GENERAL HOSPITAL, AND THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

The Synthesis of D-Gulosamine Hydrochloride[1a,b]

BY ZOFIA TARASIEJSKA AND ROGER W. JEANLOZ

RECEIVED MARCH 5, 1957

D-Gulosamine hydrochloride has been prepared in crystalline form from methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside and has been characterized through the following crystalline derivatives: *N*-(2′-hydroxynaphthylidene), methyl *N*-acetyl-α-D-glycoside and methyl *N*-acetyl-3,4,6-tri-*O*-acetyl-α-D-glycoside.

The isolation of a new aminosugar from streptothricin and streptolin B has been reported recently, and the structure of a 2-amino hexose, D-gulosamine (VII), has been proposed for it.[2] This appears to be the first isolation of a 2-amino hexose from natural sources since D-galactosamine was extracted from cartilage 40 years ago and the well known D-glucosamine from chitin nearly a century ago. It seems also to be the first isolation of a natural sugar with the D-gulose configuration.

Confirmation of the structure proposed by van Tamelen, *et al.*, by an unequivocal synthetic procedure seemed of interest. The preparation of D-allosamine from D-glucosamine has been accomplished in our laboratory.[3] In the present study a similar reaction sequence was applied to D-galactosamine and methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (I)[4] was transformed into the 3-*O*-methylsulfonyl derivative II. Reaction with sodium acetate in methyl cellosolve[5] failed, however, to proceed in a similar way as described for the glucosamine derivative[3] and the starting material was recovered unchanged. This failure was unexpected, as the benzylidene derivative of galactosamine II possesses the general conformation of a *cis*-decalin, much more flexible than the *trans*-decalin confor-

(1) (a) Studies on hyaluronic acid and related substances XVII. This is publication No. 211 of the Robert W. Lovett Memorial Laboratories for the Study of Crippling Diseases, Department of Medicine, Harvard Medical School, Boston, and the Massachusetts General Hospital. This investigation has been supported by a research grant from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service (Grant A-148-C3). Presented before the Division of Carbohydrate Chemistry at the 131st Meeting of the American Chemical Society, Miami, Florida, April, 1957. (b) A preliminary note has been published, THIS JOURNAL, **79**, 2660 (1957).

(2) E. E. van Tamelen, J. R. Dyer, H. E. Carter, J. V. Pierce and E. E. Daniels, THIS JOURNAL, **78**, 4817 (1956).

(3) R. W. Jeanloz, *ibid.*, **79**, 2591 (1957).

(4) P. J. Stoffyn and R. W. Jeanloz, *ibid.*, **76**, 561 (1954).

(5) B. R. Baker, R. E. Schaub, J. P. Joseph and J. H. Williams, *ibid.*, **76**, 1441 (1954).

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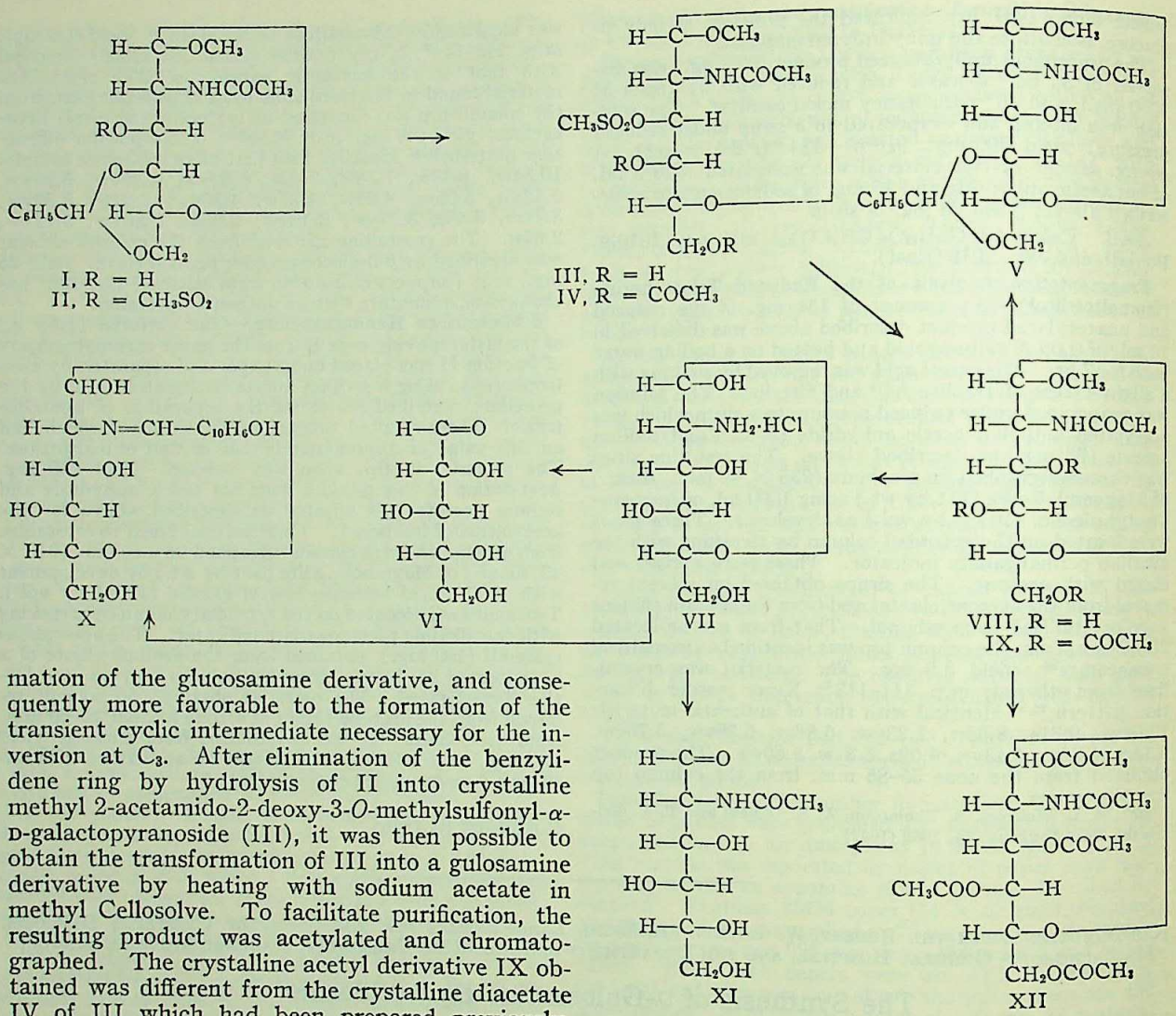

mation of the glucosamine derivative, and consequently more favorable to the formation of the transient cyclic intermediate necessary for the inversion at C_3. After elimination of the benzylidene ring by hydrolysis of II into crystalline methyl 2-acetamido-2-deoxy-3-*O*-methylsulfonyl-α-D-galactopyranoside (III), it was then possible to obtain the transformation of III into a gulosamine derivative by heating with sodium acetate in methyl Cellosolve. To facilitate purification, the resulting product was acetylated and chromatographed. The crystalline acetyl derivative IX obtained was different from the crystalline diacetate IV of III which had been prepared previously. Alkaline hydrolysis of IX afforded a crystalline methyl 2-acetamido-2-deoxy-α-D-glycopyranoside (VIII), different from methyl 2-acetamido-2-deoxy-α-D-galactopyranoside, and consequently belonging to the D-gulosamine series. Acid hydrolysis of VIII gave in a 66% yield the crystalline α-form of 2-amino-2-deoxy-D-gulose hydrochloride (D-gulosamine hydrochloride) (VII). In view of the report of the formation of the 1,6-anhydro derivative of D-gulosamine hydrochloride by acid treatment of VII[2] the mother liquors of the preparation of VII were thoroughly studied. However, no trace of the anhydro compound could be detected by paper chromatography, using as standard of comparison D-galactosamine and 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose hydrochloride.[6] The synthetic D-gulosamine exhibited a decomposition range of temperature, a starting and a final mutarotation identical to those of the natural product. It was definitely distinct from D-glucosamine, D-galactosamine and D-allosamine by direct paper chromatography. Degradation with ninhydrin in the presence of pyridine[7] gave rise to D-xylose (VI), identified by paper chromatography. As the free hydrochloride decomposes over a large range of temperature and the comparison of the mutarotation is an unsatisfactory method of identification, the preparation of crystalline derivatives was attempted in addition to the two crystalline glycosides described above. Starting from the hydrochloride VII, preparation of the *N*-acetyl derivative XI gave only a sirupy product. A sirup was also obtained when the *N*-acetyl derivative XI was obtained from the tri-*O*-acetylglycoside IX transformed by acetolysis to the sirupy pentaacetate XII, followed by alkaline *O*-deacetylation. However, the *N*-(2′-hydroxynaphthylidene) derivative X was crystalline. Another crystalline derivative was obtained by condensation of the glycoside VIII with benzaldehyde, to which the structure of a methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-gulopyranoside (V) was ascribed by analogy; however, the possibility of a 3,4-*O*-benzylidene structure cannot be completely discarded.

After this work had been completed, a short note appeared in the literature describing a synthesis of D-gulosamine starting from D-xylose.[8] The structure of the final product is not unequivocally established by this work since two aminosugars,

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(7) P. J. Stoffyn and R. W. Jeanloz, *Arch. Biochem. Biophys.*, **52**, 373 (1954).

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D-gulosamine and D-idosamine, are formed. In addition, the value of the starting mutarotation of the aminosugar obtained differed significantly from the values of both the natural product and the synthetic product described above. Furthermore, no crystalline derivatives with definite melting point were reported.

Experimental[9]

Methyl 2-Acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside.—This compound was obtained for identification purposes by conventional acetylation of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (I)[4] with pyridine and acetic anhydride. Crystallization from a mixture of acetone, ether and pentane gave elongated prisms, m.p. 219–220°, $[\alpha]^{23}D$ +186 ± 1° (in chloroform, *c* 0.74). *Anal.* Calcd. for $C_{18}H_{23}O_7N$: C, 59.17; H, 6.34. Found: C, 59.07; H, 6.39.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-α-D-galactopyranoside (II).—To a solution of 2.0 g. of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (I)[4] in 25 ml. of anhydrous pyridine previously chilled at −20° was added 1.0 ml. of methanesulfonyl chloride. After standing 3 days at 0°, ice was added, and the solution was extracted with chloroform. This extract was washed thrice each time with ice-cold 2 *N* sulfuric acid, saturated sodium bicarbonate and water and dried over sodium sulfate. After evaporation *in vacuo* the residue was dissolved in methanol, filtered through a layer of Darco G-60, and concentrated. Crystallization from mixtures of acetone and ether or acetone and pentane gave 2.14 g. (86%) of elongated prisms, melting at 205–207° dec., when started at room temperature, or at 219–220°, when started at 210°, $[\alpha]^{24}D$ +169 ± 1° (in chloroform, *c* 1.12). *Anal.* Calcd. for $C_{17}H_{23}O_8NS$: C, 50.86; H, 5.77; S, 7.99. Found: C, 50.93; H, 5.86; S, 7.90.

After heating in methyl Cellosolve solution in the presence of sodium acetate and extracting as previously described,[3] a recovery of approximately 90% of starting material was obtained.

Methyl 2-Acetamido-2-deoxy-3-*O*-methylsulfonyl-α-D-galactopyranoside (III).—A solution of 2.75 g. of II in 65 ml. of 60% acetic acid was heated a half-hour on a water-bath. The benzaldehyde and the solvents were removed by distillation *in vacuo*, followed by co-distillation with water then with absolute toluene. The residue was crystallized from a mixture of methanol and ether to give an almost quantitative yield of needles, m.p. 179–180° dec., $[\alpha]^{22}D$ +132 ± 1° (in methanol, *c* 0.88). *Anal.* Calcd. for $C_{10}H_{19}O_8NS$: C, 38.33; H, 6.11. Found: C, 38.48; H, 6.22.

Acetylation of 51 mg. of III with acetic anhydride and pyridine in the usual way gave the 4,6-di-*O*-acetyl derivative IV. Crystallization from a mixture of methanol and ether gave 59 mg. (91%) of short prisms, m.p. 163–164°, $[\alpha]^{24}D$ +96 ± 2° (in chloroform, *c* 0.83). *Anal.* Calcd. for $C_{14}H_{23}O_{10}NS$: C, 42.31; H, 5.83. Found: C, 42.22; H, 5.79.

Methyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-gulopyranoside (IX).—A solution of 1.0 g. of III and 0.9 g. of sodium acetate trihydrate in 25 ml. of 95% methyl Cellosolve was heated under reflux for 40 hours. After concentration to dryness *in vacuo*, the residue was acetylated with 10 ml. of anhydrous pyridine and 7 ml. of acetic anhydride overnight at room temperature. The mixture was filtered, the solution concentrated to dryness *in vacuo*, and the residue dissolved in chloroform and chromatographed on 50 g. of silicic acid. Pure ethyl acetate eluted crystalline fractions. Crystallization from a mixture of methanol and ether gave 0.65 g. of triangular prisms, m.p. 123–124°, $[\alpha]^{21}D$ +76 ± 1° (in chloroform, *c* 0.91). *Anal.* Calcd. for $C_{15}H_{23}O_9N$: C, 49.86; H, 6.42. Found: C, 49.71; H, 6.45. The yield based on the starting material III was 56%.

Methyl 2-Acetamido-2-deoxy-α-D-gulopyranoside (VIII).—To a cold solution of 300 mg. of IX in 2 ml. of methanol was added 0.3 ml. of 1.5 *N* barium methylate. After standing overnight at 0°, the solution was neutralized with carbon dioxide and diluted with water at the same time. After filtration through a double layer of Celite and Darco G-60, the last traces of barium were removed by filtering through a short column of Dowex 50 and the solution evaporated *in vacuo*. The residue was crystallized from a mixture of acetone and ether to give 142 mg. (72%) of short prisms, m.p. 79–82°, $[\alpha]^{25}D$ +72 ± 1° (in methanol, *c* 0.74). *Anal.* Calcd. for $C_9H_{17}O_6N$: C, 45.95; H, 7.29. Found: C, 45.80; H, 7.22.

VIII (49 mg.) was shaken overnight with 80 mg. of zinc chloride and 0.3 ml. of benzaldehyde. After addition of 2 ml. of water, the solution was extracted with hexane to remove the benzaldehyde in excess. The water solution was then extracted exhaustively with chloroform. This extract was dried over sodium sulfate, concentrated and chromatographed on 2 g. of silicic acid. After elution of benzoic acid with ether, a crystalline product was eluted with methanol. Crystallization from a mixture of methanol and acetone gave 38 mg. (57%) of prisms, m.p. 111–114°, $[\alpha]^{25}D$ +71 ± 2° (in methanol, *c* 0.90). *Anal.* Calcd. for $C_{16}H_{21}O_6N$: C, 59.43; H, 6.55. Found: C, 59.08; H, 7.07. The structure of **methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-gulopyranoside** (V) was attributed to this compound.

2-Amino-2-deoxy-α-D-gulose Hydrochloride (α-D-Gulosamine Hydrochloride) (VII).—A solution of 227 mg. of VIII in 2.2 ml. of 2 *N* hydrochloric acid was heated on the water-bath for two hours. After evaporation *in vacuo*, the last traces of hydrochloric acid, water and acetic acid were removed by codistillation *in vacuo* with absolute ethanol. The residue was dissolved in aqueous methanol, filtered through a double layer of Celite and Darco G-60 and the solution concentrated. Crystallization from aqueous ethanol gave 138 mg. (66%) of prisms decomposing between 150 and 170°; the largest prisms started to decompose only at 162°. The product showed a complex mutarotation: $[\alpha]^{22}D$ +6.0° (10 minutes), −11° (30 minutes), −21° (one hour); −26° (2 hours), −26° (4 hours), −18 ± 1° (at equilibrium, after 36 hours, in water, *c* 0.90).[10] *Anal.* Calcd. for $C_6H_{14}O_5NCl$: C, 33.26; H, 6.48; N, 6.50; Cl, 16.44. Found: C, 33.47; H, 6.56; N, 6.32; Cl, 16.52. The reaction with ninhydrin was positive. In a descending paper chromatography on Whatman #54 paper in the mixture of *n*-propyl alcohol–water–ammonia 21:9:0.1, VII migrated 1.18, compared to D-glucosamine 1.00, D-galactosamine 0.91, and D-allosamine[3] 1.03. A small amount degraded with ninhydrin and pyridine as previously described[7] gave a spot migrating in paper chromatography with a R_f identical to the one of D-xylose (VI).

The rotation of the mother liquors of VII was $[\alpha]^{24}D$ +5°, showing that a maximum amount of 30% of 1,6-anhydro derivative could be present in it. However, any amount of untransformed starting material could be responsible for this figure. Before crystallization of VII, the crude mixture had an $[\alpha]^{24}D$ −10°, showing the presence of at least 90% of VII. Chromatographed in the mixture *n*-propyl alcohol–ammonia no spot faster than VII could be detected. A small amount of recrystallized VII was heated in 2 *N* hydrochloric acid solution at 100° for 7 hours in a sealed tube. After drying in a desiccator in presence of soda lime, the residue was chromatographed on paper in the mixture *n*-propyl alcohol–ammonia. No spot faster than VII could be detected. By comparison, 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose hydrochloride[6] migrated 1.45.

2-Acetamido-2-deoxy-D-gulose (XI) (from IX).—To a mixture of 2.7 ml. of acetic anhydride and 0.05 ml. of concentrated sulfuric acid was added 273 mg. of IX. After standing one hour at room temperature, ice was added. The solution was neutralized with solid sodium bicarbonate, and extracted with chloroform. This solution was dried over sodium sulfate, concentrated and chromatographed on 10 g. of silicic acid. Elution with a mixture of ethyl acetate and acetone 4:1 gave 235 mg. of the sirupy **2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-gulopyranose (XII)**, which has thus far failed to crystallize; $[\alpha]^{24}D$ +51 ± 1° (in chloroform, *c* 1.08). *Anal.* Calcd. for $C_{16}H_{23}O_{10}N$: C, 49.35; H, 5.95. Found: C, 49.66; H, 5.74.

To a cold solution of 215 mg. of XII in 2.5 ml. of methanol was added 0.2 ml. of 1.5 *N* barium methylate. After 48 hours at 0°, it was diluted with water, neutralized with carbon dioxide, filtered and the solution passed through a short column of Dowex 50. After concentration, a quantitative yield of XI was obtained as a colorless sirup, $[\alpha]^{23}D$

(9) R. W. Jeanloz, THIS JOURNAL, 76, 555 (1954); R. W. Jeanloz and D. A. Jeanloz, *ibid.*, 79, 2579 (1957).

(10) E. E. van Tamelen, *et al.*,[2] reported m.p. 152–162° dec. and $[\alpha]^{21}D$ +50° (5 min.) → −18° (24 hr. and final) (in water, *c* 2.9).

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$-47 \pm 2°$ (in methanol, *c* 1.32). *Anal.* Calcd. for $C_8H_{15}O_6N$: C, 43.44; H, 6.83. Found: C, 43.26; H, 6.99.

From VII.—To a solution of 19.5 mg. of VII in 1.5 ml. of methanol were added 30 mg. of silver acetate and 0.022 ml. of acetic anhydride. After standing at room temperature overnight, the solution was filtered. One drop of dilute hydrochloric acid was added and after two hours the solution was filtered through a double layer of Celite and Darco G-60. After concentration, a quantitative yield of sirup was obtained; $[\alpha]^{27}D$ $-50 \pm 1°$ (in methanol, *c* 1.82).

2-Deoxy-2-(2′-hydroxynaphthylidenamino)-D-gulose (X).—A solution of 48 mg. of VII and 32 mg. of sodium acetate trihydrate in 1 ml. of water was treated as previously described[11] with 100 mg. of 2-hydroxynaphthaldehyde in 10 ml. of methanol. Purification was carried out by chromatography on 5 g. of silicic acid. The substance was eluted by a mixture of acetone and methanol 9:1. Crystallization from a mixture of methyl Cellosolve and acetone gave 36 mg. (49%) of small yellow crystals, m.p. 186–188° dec., $[\alpha]^{22}_{5461}$ $-150 \pm 5°$ (at equilibrium, in methyl Cellosolve, *c* 0.60). *Anal.* Calcd. for $C_{17}H_{19}O_6N$: C, 61.26; H, 5.75. Found: C, 61.16; H, 5.86.

(11) R. W. Jeanloz, THIS JOURNAL, **74**, 4597 (1952).

Acknowledgments.—The authors are indebted to Hoffmann-La Roche, Basel, for a generous gift of D-galactosamine. Z. T. wishes to thank the Belgian Federation of University Women for a travel fellowship.

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[CONTRIBUTION FROM BIOCHEMICAL LABORATORY, COLLEGE OF AGRICULTURE, KYOTO UNIVERSITY]

An Acyl Migration in Acetohalogenoglucosamines[1]

BY YOSHIYUKI INOUYE, KONOSHIN ONODERA, SHOZABURO KITAOKA AND HIDEO OCHIAI

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The acetobromoglucosamine (2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-D-glucosyl bromide) described in the literature was proved to be 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrobromide, in support of the finding of Micheel, *et al.* However, methyl β-D-glucosaminide and 1-*p*-tolyl-2-amino-2-deoxy-β-D-glucosylamine tetraacetates could be prepared by the Koenigs–Knorr reaction using the freshly prepared chloroform solution obtained from the reaction mixture of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine with hydrogen bromide in acetic acid. A new disaccharide acetate of the trehalose type which consisted of two molecules of D-glucosamine tetraacetate also was prepared from this chloroform solution with silver oxide as the condensing agent. These results indicate that acetobromoglucosamine is actually formed by the usual method of preparation and then rapidly undergoes an acetyl migration. Additional evidence was obtained as well in the case of a crystalline analog, acetochloroglucosamine, which was converted into 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrochloride, partially upon refluxing in moist chloroform and completely upon refluxing in acid-containing moist chloroform.

Micheel, van de Kamp and Wulff[2] recently have reported that the acetobromoglucosamine (2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-D-glucosyl bromide) (IIa) prepared by the method of Moggridge and Neuberger,[3] (in which N-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) is treated with hydrogen bromide in acetic acid and the reaction mixture is dissolved in chloroform, washed with sodium bicarbonate solution, and the product is crystallized by concentrating the dried chloroform solution *in vacuo*), is actually 1,3,4,6-tetra-*O*-acetyl-α D-glucosamine hydrobromide (IVa). We had been engaged in some synthetic work starting from acetobromoglucosamine and had independently reached the same conclusion. The so-called acetobromoglucosamine obtained by the methods of Moggridge and Neuberger[3] and Baker, Joseph, Schaub and Williams,[4] the latter of which is a modification of the former, was 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrobromide (IVa), which was identified by conversion into N-acetyl-tetra-*O*-acetyl-α-D-glucosamine (Ib), 2-*N*-(*o*-carboxybenzoyl)-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (V) and 2-*N*-anisilydene-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (VI). IVa was also converted into 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (VII). Our attempts to synthesize the D-glucosaminides and disaccharides containing D-glucosamine as a component starting from IVa had resulted in failure. Similar failures have been described by the above authors.[2–4] However, Kuhn and Kirschenlohr[5] successfully prepared a series of alkyl-β-D-glucosaminide tetraacetates[5a] and 6-*O*-(2-amino-2-deoxy-β-D-glucosyl)-D-glucose and 6-*O*-(2-amino-2-deoxy-β-D-glucosyl)-D-galactose octaacetates[5b] from their acetobromoglucosamine preparation by the use of mercury cyanide as the condensing agent, and Bertho and Koziollek[6] obtained arylamine-*N*-β-D-glucosaminide tetraacetates from their acetobromo compound. However, these authors have given no detailed description of their acetobromoglucosamine preparations.

In our investigations, some of these D-glucosaminides were obtained by employing a slightly modified reaction procedure: *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) was treated with hydrogen bromide in acetic acid in the usual manner. The reaction mixture was added to chloroform, washed quickly with an aqueous sodium bicarbonate solution and then with water and dried over anhydrous sodium sulfate. *This fresh chloroform solution* could be used to prepare D-glucosaminides. The reaction of this solution with methanol in the presence of silver oxide gave rise to methyl-β-D-glucosaminide tetraacetate (IIIa),[5a] and the reaction with *p*-toluidine yielded *p*-toluidine-*N*-β-D-glucosaminide tetraacetate (IIIb).[6,7]

(1) Presented in part at the Annual Meeting of the Agricultural Chemical Society of Japan, Tokyo, on March 30, 1956. A preliminary communication: *Bull. Agr. Chem. Soc. Japan*, **20**, 157 (1956).

(2) F. Micheel, F. P. van de Kamp and H. Wulff, *Chem. Ber.*, **88**, 2011 (1955).

(3) R. C. G. Moggridge and A. Neuberger, *J. Chem. Soc.*, 745 (1936).

(4) B. R. Baker, J. P. Joseph, R. E. Schaub and J. H. Williams, *Org. Chem.*, **19**, 1786 (1954).

(5) (a) R. Kuhn and W. Kirschenlohr, *Chem. Ber.*, **86**, 1331 (1953); (b) **87**, 384 (1954).

(6) A. Bertho and D. Koziollek, *ibid.*, **87**, 934 (1954).

(7) Y. Inouye, K. Onodera and S. Kitaoka, *J. Agr. Chem. Soc. Japan*, **29**, 908 (1955); *Bull. Insi. Chem. Research, Kyoto Univ.*, **33**, 215 (1955).

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Attempts to prepare 1-*O*-(2-amino-2-deoxy-β-D-glucosyl)-D-glucoside octaacetate by shaking the above chloroform solution of acetobromoglucosamine with 2,3,4,6-tetra-*O*-acetyl-D-glucose, silver oxide, iodine and anhydrous sodium sulfate resulted in the isolation of a small yield of a disaccharide containing two molecules of D-glucosamine acetate in the trehalose type linkage. This new disaccharide, presumably 1-*O*-(2-amino-2-deoxy-β-D-glucosyl)-2-amino-2-deoxy-β-D-glucoside octaacetate or 2,2′-diamino-2,2′-dideoxy-isotrehalose octaacetate, also was prepared by shaking the acetobromoglucosamine solution with silver oxide and drying agents. It did not reduce Fehling solution until after heating in 3 *N* hydrochloric acid for 5 hr. The corresponding glucose–glucose disaccharide, isotrehalose octaacetate, was obtained from acetobromoglucose in moist ethereal silver carbonate in 1% yield as the by-product of 2,3,4,6-tetra-*O*-acetyl-D-glucose.[8] Sharp and Stacey[9] prepared α-D-glucopyranosyl-β-D-glucopyranoside octaacetate from β-acetofluoroglucose.

It is noted that in the above *O*-glucosaminide synthesis silver oxide, one of the usual condensing agents in the Koenigs–Knorr reaction, is able to catalyze the reaction. Kuhn and Kirschenlohr[5a] reported that the synthesis was first achieved by the use of mercury cyanide. They cited the results of Moggridge and Neuberger[3] who reported that silver oxide, silver carbonate and pyridine were ineffective. This latter result is understandable since it is supposed that the synthetic work was started from tetra-*O*-acetyl-D-glucosamine hydrobromide (IVa). Lloyd and Stacey[10] found that silver carbonate catalyzed the synthesis of alkyl 2-(2,4-dinitrophenyl)-amino-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucosides from 2-(2,4-dinitrophenyl)-amino-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucosyl bromide.

The above success in our laboratory in the D-glucosaminide synthesis indicates that acetobromoglucosamine (IIa) is formed by the reaction of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) with hydrogen bromide in acetic acid and, in fact, exists in the fresh chloroform solution. It appears to be very unstable[11] and rapidly undergoes an acetyl migration to form IVa. Attempts to crystallize acetobromoglucosamine have hitherto resulted in failure. This rearrangement was also observed for the much stabler analog, acetochloroglucosamine (2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucosyl chloride) (IIb),[4] from which Baker, Joseph, Schaub and Williams[4] prepared a puromycin analog in which 3-amino-3-deoxy-D-ribose is replaced by *N*-acetyl-D-glucosamine. The crystalline acetochloroglucosamine was converted into 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrochloride (IVb), partially upon refluxing for 1 hr. in moist chloroform and completely upon refluxing in acid-containing moist chloroform. IVb was converted to 2-*N*-(*o*-carboxybenzoyl)-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (V) and 2-*N*-anisilydene-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (VI) for identification. It is noteworthy that refluxing IIb in absolute chloroform for the same period did not induce the acetyl migration.

Sugihara[12] has reviewed the literature on acyl group migration in the carbohydrate field. The migration is understood to proceed *via* an ortho acid ester as an intermediate. The intramolecular N→O and O→N acyl migrations in a variety of partially acylated amino alcohols have been reported,[13] and the reaction mechanism has been extensively studied. It has been established that the N→O and O→N acyl migrations are reversible, depending upon the presence of hydrogen and hydroxyl ions, respectively, and that they also proceed *via* an ortho acid ester intermediate (A). In some cases, oxazolines were isolated, but Phillips and Baltzly[14] preferred the ortho acid ester (A) to the oxazoline intermediate (B) in the conversion of various ethanolamides into the corresponding aminoethyl ester hydrochlorides.

van Tamelen[15] suggested that the ortho acid ester is also the intermediate to the formation of the oxazoline structure. Stereochemical studies have been made of the acyl migrations in inosamine[13b,16] and ephedrine and other amino alcohols.[17] It might be noted that White[18] was the first to observe an acyl migration in D-glucosamine in which 1,3,4,6-tetra-*O*-acetyl-D-glucosamine hydrochloride was converted into *N*-acetyl-D-glucosamine by the action of methanolic ammonia. Foster and Stacey[19] interpreted that this migration proceeded *via* an orthoacetate. Our present acetyl migration from II to IV should also proceed through the orthoacetate structure.

The results herein reported do not agree with the proposal made by Micheel, van de Kamp and Wulff[2] that the reaction of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) with hydrogen bromide–acetic acid produces primarily tetra-*O*-acetyl-D-glucosamine hydrobromide (IVa), which they showed is converted into 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-D-glucosyl bromide hydrobromide by further reaction with hydrogen bromide–acetic acid. These German researchers also stated that in the hydroxyl group-containing solvents 1,3,4,6-tetra-*O*-acetyl-D-glucosamine formed an oxazoline ring. This kind of conversion could occur under certain conditions, and further investigations are highly desirable.

Experimental[20]

1,3,4,6-Tetra-*O*-acetyl-α-D-glucosamine Hydrobromide (IVa).[3]—Thirty grams of acetic acid was saturated with dry

(8) E. Fischer and K. Delbrück, *Ber.*, **42**, 2776 (1909).
(9) V. E. Sharp and M. Stacey, *J. Chem. Soc.*, 285 (1951).
(10) P. E. Lloyd and M. Stacey, *Chemistry & Industry*, 917 (1955).
(11) M. Stacey, *J. Chem. Soc.*, 272 (1944), found very labile bromine in acetobromogalactosamine which readily yielded tetraacetyl galactosamine monohydrate.
(12) J. M. Sugihara, *Advances in Carbohydrate Chem.*, **8**, 1 (1953).
(13) Literature is well cited in (a) H. S. Isbell and H. L. Frush, THIS JOURNAL, **71**, 1579 (1949); (b) G. E. McCasland, *ibid.*, **73**, 2295 (1951); (c) G. Fodor and L. Ötovös, *Chem. Ber.*, **89**, 701 (1956).
(14) A. P. Phillips and R. Baltzly, THIS JOURNAL, **69**, 200 (1947).
(15) E. E. van Tamelen, *ibid.*, **73**, 5773 (1951).
(16) L. Anderson and H. A. Lardy, *ibid.*, **72**, 3141 (1950); G. I. Drummond and L. Anderson, *ibid.*, **78**, 1750 (1956).
(17) See references in 13c.
(18) T. White, *J. Chem. Soc.*, 1498 (1938).
(19) A. B. Foster and M. Stacey, *Advances in Carbohydrate Chem.* **7**, 247 (1952).
(20) All melting points are uncorrected. The petroleum ether used throughout the experiments has b.p. 30–70°. Microanalyses were performed by Mr. Masuo Kurokawa, Microanalytical Laboratory, Kyoto University.

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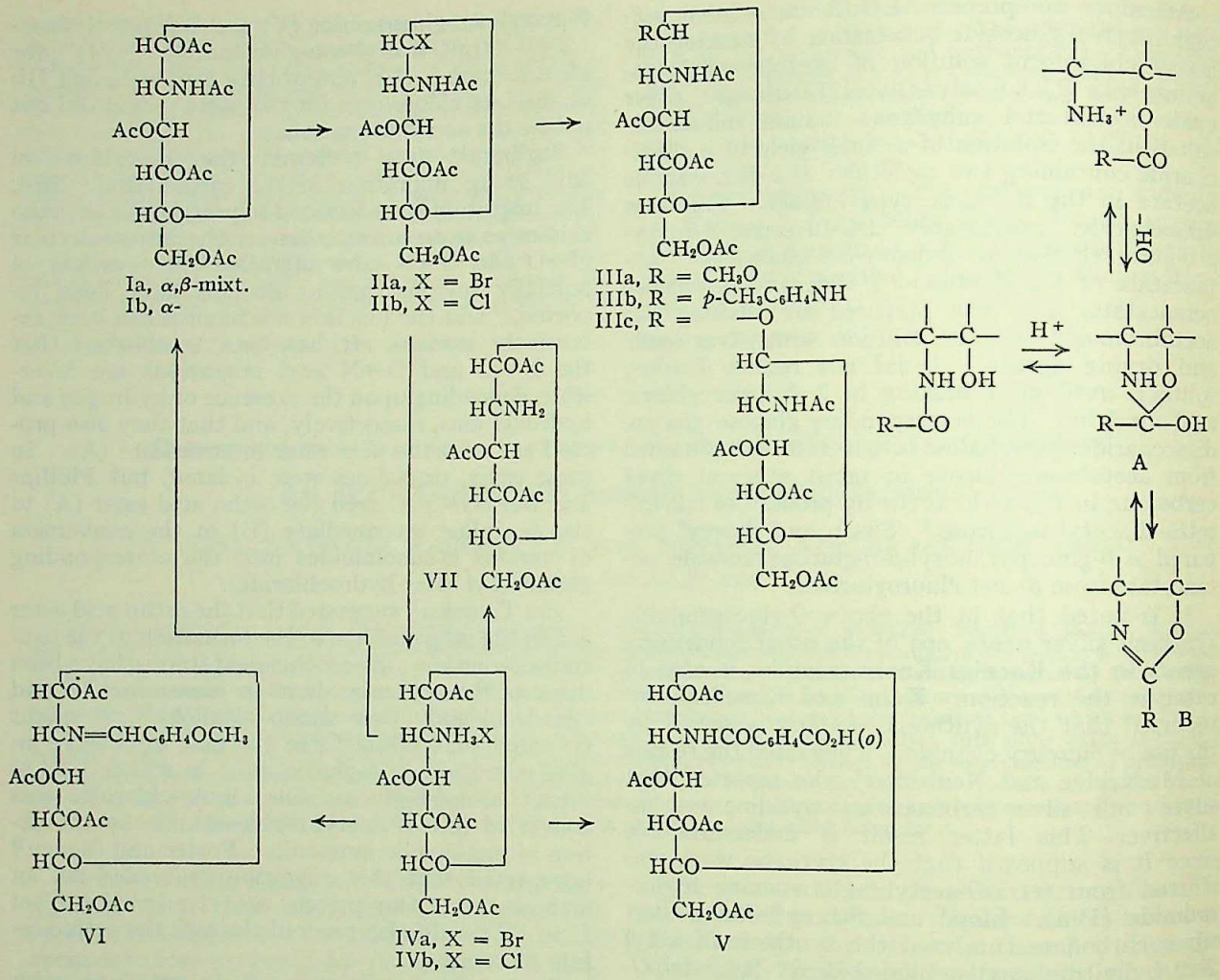

hydrogen bromide at 0°, and to this was added 10 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia).[21] The mixture was allowed to stand overnight at room temperature; 80 ml. of chloroform was added with ice-cooling. The mixture was shaken, poured into ice-water, the aqueous layer was extracted with 20 ml. of chloroform and the extract was combined to the main chloroform layer. The chloroform solution was washed with three 20–30-ml. portions of ice-cold, saturated aqueous sodium bicarbonate, then with two portions of ice-cold water and dried over anhydrous sodium sulfate. The dried chloroform solution was concentrated under reduced pressure to a pale-yellow sirup, which on addition of a small volume of ethyl acetate and then of ether gave 5.5 g. (50%) of IVa. Repeated recrystallization from methanol by adding ether yielded colorless needles which charred gradually between 210 and 230°, $[\alpha]^{13}D$ +129° (*c* 1, water).

Anal. Calcd. for $C_{14}H_{22}NO_9Br$: C, 39.26; H, 5.18; N, 3.27. Found: C, 39.44; H, 5.41; N, 3.21.

IVa was soluble in water and methanol but not in chloroform. Concentration of the aqueous layer of the reaction mixture under reduced pressure to approximately one-tenth volume, followed by addition of methanol and keeping at ice-box temperatures, gave crystalline D-glucosamine hydrobromide.

N-Acetyl-tetra-*O*-acetyl-α-D-glucosamine (Ib).[22]—Two grams of IVa, dissolved in 10 ml. of water, was treated with 0.8 g. of anhydrous sodium acetate and 20 ml. of chloroform, and the mixture was well shaken. Acetic anhydride (1 g.) was added and the mixture was stirred for 30 minutes. The chloroform layer was separated, washed with a small volume of water and dried over anhydrous sodium sulfate. Crystallization occurred upon concentration under reduced pressure followed by treatment with ether. Recrystallization from an acetone–ether–petroleum ether mixture gave 1.3 g. (71%) of needles, whose m.p. and mixed m.p. with authentic Ib[23] were 137°, $[\alpha]^{22}D$ +92° (*c* 1, chloroform).

Anal. Calcd. for $C_{16}H_{23}NO_{10}$: C, 49.35; H, 5.95. Found: C, 49.47; H, 5.65.

2-*N*-(*o*-Carboxybenzoyl)-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (V).—IVa (2 g.) was dissolved in 10 ml. of water, and to this was added 0.8 g. of anhydrous sodium acetate. This solution was extracted with three portions (8 ml. each) of chloroform. The extract was washed with a small volume of water and dried over anhydrous sodium sulfate. After filtration the dried chloroform extract was added to 0.7 g. of phthalic anhydride, and the mixture was refluxed for 1 hr. on a water-bath. The reaction solution was cooled to room temperature and extracted with three 10-ml. portions of saturated aqueous solution of sodium bicarbonate. The combined extract was passed through a Celite layer and acidified with *N* hydrochloric acid to give 1.5 g. (65%) of V, m.p. 176° after thorough washing with cold water and drying.

Anal. Calcd. for $C_{22}H_{25}NO_{12}$: C, 53.33; H, 5.09; N, 2.83. Found: C, 53.05; H, 5.09; N, 2.88.

The β-isomer was described by Baker, Joseph, Schaub and Williams.[4]

2-*N*-Anisilydene-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (VI).[2]—To two grams of IVa in 10 ml. of water was added 0.8 g. of anhydrous sodium acetate, and the mixture was extracted with three 8-ml. portions of chloroform. The combined extract was washed with cold water, dried over anhydrous sodium sulfate and filtered. The filtrate was treated with 1.5 g. of anisaldehyde with stirring and was allowed to stand overnight. An excess of ether and petro-

(21) C. A. Lobry de Bruyn and W. A. van Ekenstein, *Rec. trav. chim.*, **18**, 83 (1899).

(22) O. Westphal and H. Holzmann, *Ber.*, **75**, 1274 (1942).

(23) Y. Inouye, K. Onodera, S. Kitaoka and S. Hirano, THIS JOURNAL, **78**, 1122 (1956).

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leum ether was then added and the mixture was kept at ice-box temperatures for crystallization. Colorless needles were collected by filtration and washed with ether; yield 0.7 g. (32%) (after recrystallization from acetone–ether–petroleum ether), m.p. 174°, $[\alpha]^{24}D$ +123° (*c* 0.4, chloroform).

Anal. Calcd. for $C_{22}H_{27}NO_{10}$: C, 56.77; H, 5.85; N, 3.01. Found: C, 56.91; H, 6.03; N, 3.20.

The β-isomer was described by Bergmann and Zervas.[24]

1,3,4,6-Tetra-*O*-acetyl-α-D-glucosamine (VII).[2,24]—1,3,4,6-Tetra-*O*-acetyl-α-D-glucosamine hydrobromide (IVa) (1 g.) was dissolved in water which contained 0.38 g. of sodium acetate. The solution was extracted three times with 10-ml. portions of chloroform. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated to 1 ml. The addition of ether gave crystals which were recrystallized twice from acetone–ether–petroleum ether, needles, yield 350 mg. (43%), m.p. 132°, $[\alpha]^{11}D$ +157° (*c* 0.5, chloroform). The substance easily was soluble in acetone, chloroform and methanol and was soluble in water. It was insoluble in ether and petroleum ether. The reported constants[2] are m.p. 118–119° and $[\alpha]D$ +145.5° (*c* 1, chloroform).

Anal. Calcd. for $C_{14}H_{21}NO_9$: C, 48.41; H, 6.09; N, 4.03. Found: C, 48.34; H, 6.39; N, 4.00.

The β-isomer of this compound was reported by Bergmann and Zervas.[24]

Acetochloroglucosamine (IIb).[4]—To 10 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) dissolved in 150 ml. of anhydrous chloroform was added with stirring 6.2 g. of titanium tetrachloride dissolved in a small volume of anhydrous chloroform. After thorough shaking, the mixture was refluxed with exclusion of moisture for 3.5 hr., cooled, washed three times with ice-water and dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by treatment of the resulting sirup with ether and then with petroleum ether produced 2.1 g. (22%) of IIb, which was recrystallized from a small volume of chloroform by adding ether and petroleum ether; m.p. 127° (dec.), $[\alpha]^{24}D$ +117.5° (*c* 1, chloroform).

Anal. Calcd. for $C_{14}H_{20}NO_8Cl$: C, 45.97; H, 5.51; N, 3.83. Found: C, 45.97; H, 5.47; N, 3.81.

1,3,4,6-Tetra-*O*-acetyl-α-D-glucosamine Hydrochloride (IVb).—IIb (0.1 g.) in 10 ml. of anhydrous chloroform was refluxed for 1 hr. with the addition of one drop of 0.1 *N* hydrochloric acid. After cooling, the solution was concentrated under reduced pressure, and to the resulting sirup was added a small volume of methanol and then ether to give 0.1 g. (95%) of IVb as colorless needles, soluble in water and methanol and insoluble in ether, decomposition point 185° after gradual charring, $[\alpha]^{11}D$ +140° (*c* 1, water).

Anal. Calcd. for $C_{14}H_{22}NO_9Cl$: C, 43.81; H, 5.79; N, 3.65. Found: C, 44.05; H, 5.77; N, 3.41.

The β-isomer is known.[24]

Refluxing IIb in anhydrous chloroform with addition of one drop of water yielded 30–40% of IVb, and unreacted IIb was recovered from the filtrate. When IIb was refluxed in anhydrous chloroform for the same period, no IVb was obtained, but the original amount of IIb was recovered.

IVb was converted into V and VI in the same manner as described above for the conversions from IVa.

In one experiment, IIb (6 g.) was dissolved in acetone (25 ml.), and to this was added freshly prepared silver carbonate (7 g.). The mixture was shaken for 10 min. and after dilution with 1 ml. of water was refluxed for one hour. Freshly prepared silver oxide (5.7 g.) was added and the reaction mixture was refluxed for another hour. The procedure was repeated. The reaction mixture which had a negative chlorine test was filtered, and the filtrate was treated with active carbon, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The sirup was extracted with an excess amount of ether, and the extract was concentrated under reduced pressure to dryness; yield 4 g. (70%), m.p. 55–70°. It was recrystallized from ether; m.p. 70–80°, $[\alpha]^{11}D$ + 63° (final) (*c* 1, chloroform). The substance had a negative chlorine test and reduced the Fehling solution. It was soluble in water, methanol, chloroform and acetone.

(24) M. Bergmann and L. Zervas, *Ber.*, **64**, 975 (1931); **65**, 1201 (1932).

Anal. Calcd. for $C_{14}H_{21}NO_9$: C, 48.41; H, 6.09; N, 4.03. Found: C, 48.27; H, 6.22; N, 4.15.

It is noted that this compound has the same composition as that for VII.

The substance was dissolved in a small volume of methanol, and hydrogen chloride was added to the solution. The reaction mixture was allowed to stand at room temperature for 20 min. Upon addition of ether it yielded crystals, m.p. 185° (dec.). The yield was almost quantitative. The melting point of a mixture with a sample of 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrochloride (IVb) obtained above was not depressed.

Methyl *N*-Acetyl-3,4,6-tri-*O*-acetyl-β-D-glucosaminide (IIIa).[5a]—Twenty grams of acetic acid was saturated at 0° with dry hydrogen bromide, and to this was added in the cold 5 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia).[21] The mixture was allowed to stand for 24 hr. in the dark at room temperature. Chloroform (50 ml.) was added to the reaction mixture in the cold and quickly washed with 50 ml. of ice-water. The combined washing was extracted with 10 ml. of cold chloroform and the extract was combined to the main extract. The extract was then washed, as quickly as possible, with three 15-ml. portions of ice-cold saturated aqueous solution of sodium bicarbonate and then with 30 ml. of ice-water. The chloroform extract was immediately dried with anhydrous sodium sulfate with shaking. After filtration it was immediately used for the glycosidation. When kept for a time in the cold or when ether was added, crystallization of IVa occurred.

To the above chloroform extract of acetobromoglucosamine were immediately added 15 g. of anhydrous sodium sulfate, 5 g. of anhydrous methanol, 10 g. of silver oxide and 0.2 g. of iodine. The mixture was shaken for 48 hr. at room temperature in the dark. The reaction mixture was filtered to remove solid matter, which was washed with chloroform and the washings were combined to the filtrate. The chloroform solution was washed repeatedly with water until it no longer gave turbidity with silver nitrate solution, and then dried over anhydrous sodium sulfate. Upon concentration, a sirup that contained amorphous matter was obtained. Treatment with petroleum ether gave a colorless powder which was recrystallized repeatedly from methanol with ether and petroleum ether; m.p. 160°, $[\alpha]^{18}D$ −24° (*c* 1, chloroform). The yield was 2.1 g. (45% based on *N*-acetyl-tetra-*O*-acetyl-D-glucosamine); it was dependent on the conditions under which the chloroform extract of IIa was prepared.

Anal. Calcd. for $C_{15}H_{23}NO_9$: C, 49.86; H, 6.42; N, 3.88. Found: C, 49.86; H, 6.41; N, 3.89.

***p*-Toluidine *N*-(*N*-Acetyl-3,4,6-tri-*O*-acetyl)-β-D-glucosaminide (IIIb).**[6,7]—To a fresh chloroform solution of acetobromoglucosamine (IIa), prepared from 5 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) in the same way as above, was added 10 g. of *p*-toluidine. A precipitate appeared immediately. The mixture was shaken and allowed to stand at room temperature for 24 hr. The precipitate was filtered, washed with a small volume of chloroform, and the washings were combined to the filtrate. The combined filtrate was then concentrated under reduced pressure to a small volume to precipitate unreacted *p*-toluidine, which was dissolved in a large excess of ether, and the insoluble *p*-toluidine hydrobromide was removed by filtration. Upon standing the filtrate at ice-box temperatures for a while, the solution yielded 3.4 g. (61% based on *N*-acetyl-tetra-*O*-acetyl-D-glucosamine) of IIIb, colorless leaves, m.p. 183° (from methanol), $[\alpha]^{18}D$ −2° (*c* 1, methanol).

Anal. Calcd. for $C_{21}H_{28}N_2O_8$: C, 57.79; H, 6.47; N, 6.42. Found: C, 57.45; H, 6.45; N, 6.38.

2,2′-Diamino-2,2′-dideoxy-isotrehalose Octaacetate (IIIc).—Dried fresh chloroform solution of acetobromoglucosamine (IIa), prepared from 10 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia), was immediately shaken in the dark with 10 g. of silver oxide, 0.5 g. of iodine and 20 g. of anhydrous sodium sulfate for 48 hr. The mixture was filtered and the solid matter was washed twice with hot chloroform. The washings were combined with the filtrate which then was washed repeatedly with cold water until no reaction with silver nitrate was observed in the washings. The chloroform solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to a thick pale-yellow sirup. Warm ether was added to

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this sirup to dissolve it and then to yield a fine amorphous precipitate. This was collected by filtration, thoroughly washed with ether, dried in a vacuum desiccator and crystallized from hot methanol to give 0.2 g. (2.3% based on *N*-acetyl-tetra-*O*-acetyl-D-glucosamine) as colorless needles; decomposing point 324–326° (after gradual charring), $[\alpha]^{20}D$ +2.5° (*c* 0.2, chloroform).

Anal. Calcd. for $C_{23}H_{40}N_2O_{17}$: C, 49.70; H, 5.96; N, 4.14. Found: C, 49.58; H, 6.03; N, 4.23.

IIIc is soluble in hot water, hot methanol, chloroform and acetone and insoluble in ether and petroleum ether. It did not reduce Fehling solution under ordinary conditions, but after heating in 3 *N* hydrochloric acid for 5 hr., it reduced Fehling solution.

Attempted experiments to prepare 1-(D-glucosaminido)-D-glucose acetate (1-*O*-(2-acetamido-2-deoxy-β-D-glucosyl)-D-glucoside heptaacetate) by shaking the chloroform solution of acetobromoglucosamine from 10 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine with 10 g. of silver oxide, 0.5 g. of iodine, 5 g. of 2,3,4,6-tetra-*O*-acetyl-D-glucose[25] and 20 g. of anhydrous sodium sulfate resulted in the isolation of IIIc.

Acknowledgment.—The authors gratefully acknowledge the generous supply of D-glucosamine hydrochloride by Kaken-Yaku Kako Co., Ltd., Yamashina, Kyoto.

(25) C. M. McCloskey and G. H. Coleman, *Org. Syntheses*, **25**, 53 (1944)

KITASHIRAKAWA, KYOTO, JAPAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Heterocyclic Compounds. IV. The Structures of 2-Phenylpyrroline and 2,4-Diphenylpyrroline

BY MILTON C. KLOETZEL, JACK L. PINKUS AND ROBERT M. WASHBURN[1]

RECEIVED MARCH 2, 1957

Chemical and spectral evidence is presented for ascribing the Δ^1-structure to the 2,4-diphenylpyrroline obtained by reductive cyclization of 1,3-diphenyl-4-nitro-1-butanone and to the 2-phenylpyrroline obtained from the reaction of phenylmagnesium bromide with γ-chlorobutyronitrile.

The exact assignment of the position of unsaturation in pyrrolines has been the subject of repeated misinterpretation and contradiction. Much of the difficulty stems from the arbitrary assignment of a Δ^2-pyrroline structure (such as II) to the examples of these compounds reported in the earlier literature.[2–5] In at least one instance[6] such a structure was assigned to a compound which proved later not to be a pyrroline at all.[7]

It is conceivable that some of these earlier investigators silently entertained the opinion to which Sonn[8] eventually gave expression; that is, that Δ^1- and Δ^2-pyrrolines are chemically indistinguishable.

However, the application of both physical and chemical methods recently has provided evidence that many pyrrolines, such as myosmine[9] and those obtained from reactions of Grignard reagents with γ-chlorobutyronitrile[10–12] or from reduction of certain pyrroles,[12] are best represented by Δ^1-structures. Indeed, Witkop[9] has come to the conclusion that "there are probably no authentic secondary Δ^2-pyrrolines."

Evidence now is presented for ascribing the Δ^1-structure to the 2,4-diphenylpyrroline obtained by reductive cyclization of 1,3-diphenyl-4-nitro-1-butanone (I), and to the 2-phenylpyrroline prepared for parallel study by the reaction of phenylmagnesium bromide with γ-chlorobutyronitrile.

Kohler and Drake[13] reported that hydrogenation of 1,3-diphenyl-4-nitro-1-butanone (I) over platinum black gave disappointing results which depended on factors that could not be controlled. Reduction was not confined to a single step and gave only oily products. 2,4-Diphenylpyrroline was not reported to be among the reduction products.[14] However, by reducing the nitro ketone with acetic acid and zinc or iron, Sonn[8] was able to obtain a 42% yield of 2,4-diphenylpyrroline.

We now have found that low pressure hydrogenation of 1,3-diphenyl-4-nitro-1-butanone (I) over ordinary Raney nickel at 25° affords a 79% yield of 2,4-diphenylpyrroline. With freshly prepared Raney nickel the reaction proceeds further to give a 77% yield of 2,4-diphenylpyrrolidine. One may reasonably assume that stepwise reduction occurs,

(1) Partially abstracted from a portion of the Ph.D. dissertation of Jack L. Pinkus. Previous papers in this series include M. C. Kloetzel, J. E. Little and D. M. Frisch, *J. Org. Chem.*, **18**, 1511 (1953), and I. J. Pachter and M. C. Kloetzel, THIS JOURNAL, **74**, 971 (1952).

(2) R. Hielscher, *Ber.*, **31**, 277 (1898).

(3) S. Gabriel and J. Colman, *ibid.*, **41**, 513 (1908).

(4) S. Gabriel, *ibid.*, **42**, 1238 (1909).

(5) H. Rupe and F. Gisiger, *Helv. Chim. Acta*, **8**, 338 (1925).

(6) A. Wohl, *Ber.*, **34**, 1914 (1901).

(7) F. E. King, J. R. Marshall and P. Smith, *J. Chem. Soc.*, 239 (1951).

(8) A. Sonn, *Ber.*, **68**, 148 (1935).

(9) B. Witkop, THIS JOURNAL, **76**, 5597 (1954).

(10) J. B. Cloke, *ibid.*, **51**, 1174 (1929); P. Lipp and H. Seeles, *Ber.*, **62**, *2456 (1929)*; J. B. Cloke, L. H. Baer, J. M. Robbins and G. E. Smith, *ibid.*, **67**, 2155 (1945).

(11) P. M. Maginnity with J. B. Cloke, *ibid.*, **73**, 49 (1951).

(12) G. G. Evans, *ibid.*, **73**, 5230 (1951).

(13) E. P. Kohler and N. L. Drake, *ibid.*, **45**, 2144 (1923).

(14) Kohler and Drake obtained a solid, m.p. 179–180°, by treatment of their mixture of reduction products with benzoyl chloride. They ascribed to this derivative the composition $C_{23}H_{19}NO_2$ and cited its formation as evidence that the reduction mixture contained an hydroxylated diphenylpyrroline. However, it is not unlikely that this benzoyl derivative is identical with 4-benzoylamino-1,3-diphenyl-1-butanone (VIII), $C_{23}H_{21}NO_2$, m.p. 180–181°, obtained by Sonn[8] from the reaction of benzoyl chloride with "2,4-diphenyl-Δ^2-pyrroline" (II), and by us (with m.p. 182–183°) similarly from 2,4-diphenyl-Δ^1-pyrroline (IV). Thus, the benzoyl derivative obtained by Kohler and Drake may have resulted from the presence of 2,4-diphenylpyrroline, rather than an hydroxylated pyrroline, in their mixture of reduction products.

It is likely, moreover, that the benzoyl derivative, m.p. 180°, obtained by Rupe and Gisiger[5] from "2,4-diphenyl-Δ^2-pyrroline" also is the aforementioned amido ketone. On the basis of an analysis for nitrogen, these authors ascribed to their derivative the structure 1-benzoyl-2,4-diphenylpyrroline. However, this analysis is an inadequate criterion since the cyclic and acyclic amides in question do not differ sufficiently in nitrogen content.

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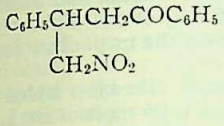
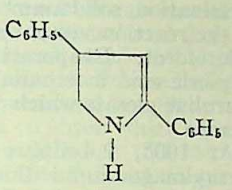
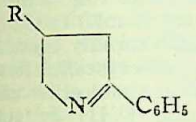
for the pure pyrroline also is hydrogenated smoothly to the pyrrolidine in the presence of fresh catalyst. None of the pyrrolidine results from disproportionation of the pyrroline[15] for the latter is not affected even by extended treatment at 42° with fresh Raney nickel in ethanol.[16]



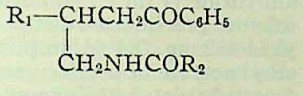
I



II



III, R = H
IV, R = C_6H_5



V, R_1 = H; R_2 = CH_3
VI, R_1 = H; R_2 = C_6H_5
VII, R_1 = C_6H_5; R_2 = CH_3
VIII, R_1 = R_2 = C_6H_5

The same 2,4-diphenylpyrroline is obtained, in yields up to 43 and 39%, respectively, when the nitro ketone I is reduced by hydrazine in the presence of Raney nickel or by zinc dust and aqueous ammonium chloride. In the latter instance, part of the product is isolated as a complex with zinc chloride unless all ionic zinc is first precipitated as the sulfide. The catalyzed hydrazine reduction of aromatic nitro compounds has been reported previously,[18,19] but the method does not appear to have been applied to aliphatic nitro compounds heretofore.[20]

The 2,4-diphenylpyrroline obtained from these reductions was characterized by formation of several solid salts and evidently is identical with that obtained by Rupe and Gisiger[5] and by Sonn.[8] There is no band in the NH region in its infrared absorption spectrum, although the general level of absorption at 2.5–3.5 μ is relatively high (Nujol mull). Moreover, changes in the infrared spectrum accompanying protonation of the basic nitrogen parallel those described by Witkop for the spectra of myosmine (2-β-pyridyl-Δ^1-pyrroline)[9] and other Schiff bases.[22] For example, the spectrum of 2,4-diphenylpyrroline hydrochloride shows a broad ammonium band at 3.80–4.08 μ with a maximum at 3.91 μ (compare 3.94 μ for myosmine monohydrochloride); immonium absorption occurs at 5.34 μ (at 5.30 μ for myosmine monohydrochloride); and the hypsochromic shift of the conjugated C=N band from 6.19 μ in the spectrum of the free base to 6.05 μ in the spectrum of the hydrochloride also is observed. These spectral characteristics are in harmony with the Δ^1-structure (IV) for this 2,4-diphenylpyrroline.

Zerewitinoff determinations at 25° and at 100° provided confirmatory evidence for the structure of 2,4-diphenyl-Δ^1-pyrroline (IV). Neither significant active hydrogen nor addition of methylmagnesium iodide was detected and the base was recovered in greater than 90% yield. Inertness of the azomethine group toward addition of Grignard reagent is to be expected, since the unsaturated carbon bears no hydrogen, but the compound might be expected to react through its enamine form.[23] The fact that no reaction occurs may be taken as evidence that 2,4-diphenyl-Δ^1-pyrroline is not readily tautomerized.

Acetylation and benzoylation of 2,4-diphenyl-Δ^1-pyrroline (IV) occur with concurrent rupture of the heterocyclic ring to yield acyclic amido ketones VII and VIII, respectively. As in the case of the benzoylation product,[14] amido ketone VII was erroneously assigned a cyclic structure (1-acetyl-2,4-diphenyl-Δ^2-pyrroline) by Rupe and Gisiger[5] on the basis of inadequate evidence. Their analysis for nitrogen failed to disclose the presence of the second oxygen atom in this compound, whose structure we have ascertained by means of analytical and infrared absorption data.

Dehydrogenation of 2,4-diphenyl-Δ^1-pyrroline (IV) was effected readily with sulfur or selenium, to produce 2,4-diphenylpyrrole in yields of 69 or 49%, respectively. Rogers[17] has obtained a 55% yield with selenium under similar conditions but reported that the use of sulfur gave inferior yields.

2-Phenylpyrroline, prepared by the method of Craig, Bulbrook and Hixon,[24] displayed spectral and chemical properties similar to those of 2,4-diphenyl-Δ^1-pyrroline. No unequivocal conclusion could be drawn from an examination of the 3 μ region in the infrared absorption spectrum of the free base.[25] However, conversion to the hydrochloride resulted in the appearance of broad ammonium absorption with a maximum at 3.88 μ, immonium absorption at 5.33 μ, and the hypsochromic shift of conjugated C=N band from 6.18 μ (in the base) to 6.06 μ in the infrared spectrum.

Consistent with a Δ^1-structure (III) for this pyrroline was the fact that a Zerewitinoff determination in anisole detected neither the presence of active hydrogen nor addition of methylmagnesium iodide.[26]

(15) Compare J. P. Wibaut and J. Th. Hackmann, *Rec. trav. chim.*, 51, 1157 (1932).

(16) Rogers[17] has reported that prolonged heating of 2,4-diphenylpyrroline at 350° produced only a trace of the corresponding pyrrole.

(17) M. A. T. Rogers, *J. Chem. Soc.*, 590 (1943).

(18) L. P. Kuhn, THIS JOURNAL, **73**, 1510 (1951).

(19) D. Balcom and A. Furst, *ibid.*, **75**, 4334 (1953).

(20) Chubb[21] first employed this method for reduction of γ-nitro ketones in this Laboratory in 1952.

(21) F. L. Chubb, Doctoral Dissertation, University of Southern California, 1952.

(22) B. Witkop, *Experientia*, **10**, 420 (1954).

(23) M. S. Kharash and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice–Hall, Inc., New York, N. Y., 1954, p. 1208.

(24) L. C. Craig, H. Bulbrook and R. M. Hixon, THIS JOURNAL, **53**, 1831 (1931).

(25) In our experience, the NH region in the infrared absorption spectra of pyrrolidines and pyrrolines is difficult to interpret. Intensity of absorption in this region varies considerably, depending both upon the nature of substituents in the vicinity of the nitrogen atom and upon the medium in which the spectrum is determined.

(26) Maginnity and Cloke[11] reported that 2-phenylpyrroline caused no gas evolution upon contact with methylmagnesium iodide for 30 hours but "consumed" 1 mole of Grignard reagent. These authors referred to the product of this reaction as an "addition complex" and stated that "analysis of the reaction mixture demonstrated that a considerable portion of the original compound was recovered unchanged." Evidently the complex was decomposed by water and no addition of Grignard reagent to azomethine linkage had occurred. Under these circumstances it is difficult to understand how the complex could resist hydrolysis, during decomposition of excess Grignard reagent with water in the customary Zerewitinoff procedure, and so lead to the conclusion that Grignard reagent had been "consumed."

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2-Phenyl-Δ^1-pyrroline (III) was characterized through its solid hydrochloride, picrate and methiodide. As in the case of its 2,4-diphenyl analog, acetylation and benzoylation of this base occur with simultaneous ring cleavage. The structures of the resulting amides (V and VI, respectively) have been confirmed spectroscopically.

Acknowledgment.—The authors are indebted to Parke, Davis and Co., Detroit, Mich., for generous financial aid which made this study possible, and to R. Bruce Scott, Research Department, Parke, Davis and Co., for his help in determining and interpreting infrared spectra during the initial stages of this investigation.

Experimental[27]

2,4-Diphenyl-Δ^1-pyrroline.—Catalytic hydrogenation of 1,3-diphenyl-4-nitro-1-butanone (I) was effected at room temperature by shaking a slurry of the ketone[28] (20 g.) and Raney nickel[29] (4 g.) in ethanol (200 ml.) for 28.5 hours under hydrogen at a pressure of 38–48 p.s.i. Distillation of the filtered solution yielded 13 g. (79%) of **2,4-diphenyl-Δ^1-pyrroline** (IV), b.p. 154–155° at 2 mm., which solidified in the receiver; m.p. 50–52°. Crystallization from ether furnished colorless needles, m.p. 52°; Sonn[8] reported a m.p. of 48–49°. Rupe and Gisiger[5] evidently obtained the same compound, m.p. 50°, by reduction of 2,4-diphenyl-4-oxobutanonitrile but designated it 2,4-diphenyl-Δ^2-pyrroline (II).

Anal. Calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33; mol. wt., 221. Found: C, 86.83; H, 6.82; N, 6.29; mol. wt., 225 (Rast method, in exaltone).

The infrared absorption spectrum determined on a Nujol mull of this base showed principal maxima at 6.19, 6.36, 6.71, 7.45, 9.26, 9.52, 9.80, 13.12 (broad) and 14.27 μ (broad).

The base decolorized a 3% solution of bromine in carbon tetrachloride but not a 1% solution of potassium permanganate in acetone

2,4-Diphenyl-Δ^1-pyrroline in anhydrous ether reacted with anhydrous hydrogen chloride to produce the insoluble **hydrochloride**, which subsequently crystallized from benzene in colorless, hygroscopic needles, m.p. 165–166.5° with slight decomposition (sealed tube).

Anal. Calcd. for $C_{16}H_{16}ClN$: C, 74.55; H, 6.25; N, 5.43. Found: C, 74.56; H, 6.36; N, 5.60.

The infrared absorption spectrum of the hydrochloride, determined on a Nujol mull, showed principal maxima at 3.91 (broad), 5.34, 6.05, 6.16, 6.25, 6.33, 6.68, 7.47, 7.76, 8.38, 9.75, 10.84 (broad) and 13.32 μ (broad).

2,4-Diphenyl-Δ^1-pyrroline perchlorate, prepared in a mixture of isopropyl alcohol and ether and crystallized twice from a similar mixture containing some ethyl acetate, melted at 110.5–111.5°

Anal. Calcd. for $C_{16}H_{16}ClNO_4$: Cl, 11.02. Found: Cl, 10.73.

The picrate formed readily in ethanol and separated from a mixture of chloroform and ether in green-yellow needles, m.p. 160–161° with sintering beginning at 157°. Rupe and Gisiger[5] and Sonn[8] reported 156° and 155–156°, respectively, for their picrates.

Anal. Calcd. for $C_{22}H_{18}N_4O_7$: C, 58.66; H, 4.03; N, 12.44. Found: C, 58.38; H, 4.32; N, 12.66.

The oxalate was prepared by adding a saturated acetone solution of anhydrous oxalic acid to an acetone solution of 2,4-diphenyl-Δ^1-pyrroline until no further precipitation occurred. After three crystallizations from ethyl acetate the colorless crystals sintered at 160° and melted at 168° with gas evolution. Rupe and Gisiger[5] reported 157–158°.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.19; H, 5.31; N, 4.40.

Zerewitinoff determinations on 2,4-diphenyl-Δ^1-pyrroline were conducted in anisole in the usual manner[11,30] and unused methylmagnesium iodide was back titrated by addition of water. At 25° the base evolved no methane and added no Grignard reagent. After completion of the determination, solid ammonium chloride and water were added to the reaction vessel and the contents were extracted with chloroform. Evaporation of the dried extract and addition of picric acid in ethanol yielded 90.4% of 2,4-diphenyl-Δ^1-pyrroline picrate which did not depress the m.p. of authentic picrate.

At 100°, 2,4-diphenyl-Δ^1-pyrroline likewise added no methylmagnesium iodide and evolved 0.09 mole of methane.

Acetylation of 2,4-diphenyl-Δ^1-pyrroline (822 mg.) was accomplished by heating for 2.5 hours at 100° with acetic anhydride (1 ml.). Addition of water (5 ml.) to the cooled mixture precipitated the product which rapidly crystallized; yield 882 mg. (84%), m.p. 91–101°. Recrystallization from ethyl acetate or a mixture of chloroform and ether afforded 4-acetylamino-1,3-diphenyl-1-butanone (VII) in colorless platelets (624 mg.), m.p. 100–104°. A final crystallization raised the m.p. to 105°, the m.p. of Rupe and Gisiger's product.[5]

The infrared absorption spectrum determined on a Nujol mull of VII showed principal maxima at 3.06 μ (N—H), 5.95 μ (ketone C=O), 6.08 μ (amido C=O) and 6.47–6.50 μ (amide).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.55; H, 7.11; N, 4.69.

Benzoylation of 2,4-diphenyl-Δ^1-pyrroline (616 mg.) was accomplished by shaking with benzoyl chloride (1 ml.) and 10% aqueous sodium hydroxide (10 ml.) until excess benzoyl chloride was hydrolyzed. Crystallization of the crude product from ethyl acetate yielded 673 mg. (70%) of 4-benzoylamino-1,3-diphenyl-1-butanone (VIII) in colorless needles, m.p. 180–182°. The m.p. was raised to 182–183° by further crystallization.

A Nujol mull of VIII displayed infrared absorption maxima at 3.06 μ (N—H), 5.97 μ (ketone C=O), 6.12 μ (amido C=O) and 6.58 μ (amide).

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.42; H, 6.14; N, 4.11.

Dehydrogenation of 2,4-diphenyl-Δ^1-pyrroline (IV) was accomplished by heating 2.0 g. of the base with 2.2 g. of selenium at 250° for 3 hours in a slow stream of nitrogen. From a benzene extract of the cooled product 980 mg. (49%) of 2,4-diphenylpyrrole was obtained, m.p. 175–178°. Recrystallization from ethanol yielded colorless microcrystals, m.p. 178–179°, the m.p. reported by Rogers.[17]

When a mixture of 440 mg. of IV and 64 mg. of sulfur was heated, evolution of hydrogen sulfide began at 180°. The temperature was then raised to 260° over a period of 7 minutes. A decolorized toluene solution of the reaction product yielded 2,4-diphenylpyrrole in colorless needles, m.p. 176–178°, yield 300 mg. (69%).

Hydrogenation of 2,4-diphenyl-Δ^1-pyrroline (2.21 g.) in ethanol (20 ml.) was effected in 5 hours at 25° and 45 p.s.i. in the presence of 1 g. of freshly prepared Raney nickel. The oily product (1.92 g.) distilled at 150–155° at 1 mm. pressure and was treated with 1.8 ml. of phenyl isothiocyanate in the usual manner. The resulting phenylthiourea (2.06 g.) formed colorless plates, m.p. 188–189°, which did not depress the m.p. of the phenylthiourea prepared from authentic 2,4-diphenylpyrrolidine.[28]

When 15 g. of 1,3-diphenyl-4-nitro-1-butanone (I) in 150 ml. of anhydrous ethyl acetate was hydrogenated for 26 hours under similar conditions in the presence of 5 g. of freshly prepared Raney nickel, 2,4-diphenylpyrrolidine was again the product; yield 9.5 g. (77%), b.p. 155° at 1 mm. pressure. A liquid film of this base showed an infrared absorption maximum at 2.96 μ; in chloroform solution, at 2.98 μ. The phenylthiourea melted at 189–190° and did not depress the m.p. of a sample prepared from authentic 2,4-diphenylpyrrolidine.

A solution of 2,4-diphenyl-Δ^1-pyrroline (368 mg.) in absolute ethanol (10 ml.) was stirred with Raney nickel (1 g.) for 17.5 hours at 42°. Unchanged pyrroline (81%) was

(27) Microanalyses are by William Schenck and Joseph Pirie, both formerly of the University of Southern California, and by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, Calif. Infrared spectra were obtained with a Perkin–Elmer model 13 double beam spectrophotometer with sodium chloride prism and cells. Melting points are uncorrected.

(28) M. C. Kloetzel, THIS JOURNAL, 69, 2271 (1947).

(29) R. Mozingo, *Org. Syntheses*, 21, 15 (1941).

(30) S. Siggia, "Quantitative Organic Analysis, *Via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 44.

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recovered as the picrate, m.p. 159–160°, and the residual oily material, after being washed with aqueous sodium hydroxide to remove excess picric acid, gave no phenylthiourea when treated with phenyl isothiocyanate.

Reduction of 1,3-Diphenyl-4-nitro-1-butanone (I) with Hydrazine and Raney Nickel.—During a period of 3 hours, a solution of 8 ml. of 85% hydrazine hydrate in 12 ml. of methanol was added to a mechanically stirred mixture of 10 g. of the nitro ketone I, 100 ml. of methanol and 2 g. of Raney nickel (4 months old) maintained at 35–40°. Stirring was continued for 3 hours after all nitro ketone had dissolved and the catalyst was then removed by filtration. Evaporation of the filtrate yielded an oil (from which a small amount of solid was filtered) which distilled at 150–158° at 12–13 mm. to give 3.53 g. (43%) of 2,4-diphenyl-Δ^1-pyrroline (IV), m.p. 47–50°. Recrystallized material did not depress the m.p. of the pyrroline obtained from the aforedescribed hydrogenation of nitro ketone I.

Reduction of 1,3-Diphenyl-4-nitro-1-butanone (I) with Zinc and Aqueous Ammonium Chloride.—To a mechanically-stirred mixture of 20 g. of nitro ketone I, 24 g. of ammonium chloride, 80 ml. of water and 330 ml. of methanol, maintained at a temperature of 10–15°, were added 4-g. portions of 90% zinc dust every 15 minutes until a total of 96 g. had been added. Stirring and cooling were prolonged for an additional period of 2 hours and the solids were then removed by filtration and washed with methanol. The combined filtrates were concentrated to a volume of 75 ml. under reduced pressure and the aqueous layer was decanted.

The residual oil partially solidified and was extracted with 50 ml. of ethyl acetate. The colorless insoluble solid (5.88 g.) melted at 202–212°; recrystallization from ethanol gave small needles, m.p. 227°.

Anal. Calcd. for $(C_{16}H_{15}N)_2ZnCl_2$: C, 66.39; H, 5.22; N, 4.84. Found: C, 66.30; H, 5.31; N, 4.35.

Distillation of the ethyl acetate solution yielded 5.25 g. (32%) of 2,4-diphenyl-Δ^1-pyrroline (IV), b.p. 162–165° at 3 mm., m.p. 45–47°. Recrystallized material did not depress the m.p. of the pyrroline obtained from hydrogenation of nitro ketone I.

In another instance, all zinc was removed from the filtered aqueous methanol reduction solution by precipitation with hydrogen sulfide. The filtered solution was then concentrated and extracted with ether continuously for at least 36 hours. Benzene was added to the ether extract to redissolve some oil which had separated. Distillation of the dried solution under reduced pressure then yielded 6.5 g. (39%) of 2,4-diphenyl-Δ^1-pyrroline.

2-Phenyl-Δ^1-pyrroline.—A sample of the base prepared by the method of Craig, Bulbrook and Hixon[24] distilled at 88–89° at 3 mm. and then separated from petroleum ether (b.p. 30–35°) in large colorless plates, m.p. 41–42°. Gabriel and Colman[3] reported 44–45°.

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.71; H, 7.64; N, 9.65. Found: C, 82.53; H, 7.59; N, 9.61.

The infrared absorption spectrum determined on a liquid film of the base showed principal maxima at 3.22, 3.36, 6.18, 6.34, 6.68, 6.90, 7.47, 9.54, 9.72, 10.10, 10.34, 10.85, 13.10 (broad) and 14.37 μ (broad).

The base decolorized bromine in carbon tetrachloride solution but not 2% potassium permanganate in acetone.

The hydrochloride was crystallized from a mixture of ethyl acetate and ether; m.p. 210.5–212.5° with sintering from 205°. Gabriel and Colman[3] reported 210–212° with sintering from 200°.

Anal. Calcd. for $C_{10}H_{12}ClN$: C, 66.12; H, 6.66; N, 7.71. Found: C, 65.57; H, 6.53; N, 8.14.

The hydrochloride showed infrared absorption maxima (Nujol mull) at 3.88 (broad), 5.33, 6.06, 6.25, 7.51, 7.60, 8.41, 8.67, 9.46, 10.16, 10.69 (broad) and 13.19 μ (broad).

The picrate of 2-phenyl-Δ^1-pyrroline separated from ethanol in glistening plates, m.p. 196.5–198.5° dec. Gabriel and Colman reported 198° and Sonn[3] 198° dec.

2-Phenyl-Δ^1-pyrroline Methiodide.—A mixture of 0.58 g. of the base, 5 ml. of 12% sodium hydroxide in aqueous methanol (2.5:1) and 1.0 g. of dimethyl sulfate was stirred at 62° for 1.5 hours and then allowed to stand at 25° for 12 hours. After being twice extracted with ether, the aqueous phase of the reaction mixture was made slightly acidic with hydrochloric acid. Dropwise addition of concentrated aqueous sodium iodide afforded colorless platelets of the methiodide in 44% yield, m.p. 221–224°. Recrystallization from ethanol raised the m.p. to 237–238°.

Anal. Calcd. for $C_{11}H_{14}IN$: C, 46.01; H, 4.91; N, 4.88; I, 44.20. Found: C, 45.71; H, 5.02; N, 4.59; I, 44.05.

Behavior of 2-Phenyl-Δ^1-pyrroline toward Methylmagnesium Iodide.—A Zerewitinoff determination in anisole at 29° showed 0.02 mole of active hydrogen and 0.01 mole of Grignard reagent addition. Unchanged pyrroline was recovered in 93.4% yield in the manner previously described for the 2,4-diphenyl analog.

An attempt was made to force a reaction between 2-phenyl-Δ^1-pyrroline and Grignard reagent in the following manner. Over a period of 45 minutes, a solution of 2.0 g. of the base in 25 ml. of anisole was added to the Grignard reagent prepared from 3.1 ml. of methyl iodide, 1.16 g. of magnesium and 25 ml. of anisole. The mixture was heated on a steam-bath during addition of the base and then for an additional period of 2.5 hours. Stirring was continued at 25° for 2.2 hours and then the mixture was decomposed with aqueous ammonium chloride. After removal of anisole the residual oil yielded 4.408 g. (85.4%) of the picrate of 2-phenyl-Δ^1-pyrroline which did not depress the m.p. of an authentic sample.

A slurry of the picrate in ether was shaken with 10% aqueous lithium hydroxide. The ether layer yielded 75.5% of 2-phenyl-Δ^1-pyrroline which did not depress the m.p. of an authentic sample and whose infrared absorption spectrum was identical with that of an authentic sample.

Acetylation of 2-phenyl-Δ^1-pyrroline, as described for the 2,4-diphenyl analog, produced 4-acetylamino-1-phenyl-1-butanone (V) in 73% yield, m.p. 89–93.5°. Recrystallization from aqueous ethanol or from ethyl acetate furnished colorless platelets, m.p. 94–95°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.36; N, 6.82. Found: C, 70.04; H, 7.27; N, 6.54.

The infrared absorption spectrum determined on a Nujol mull of V showed principal maxima at 3.00 μ (N—H), 5.97 μ (ketone C=O), 6.07 μ and 6.12 μ (amido C=O), 6.26 μ (phenyl) and 6.41–6.46 μ (amide).

Benzoylation of 2-phenyl-Δ^1-pyrroline, as described for the 2,4-diphenyl analog, yielded 64% of crude product, m.p. 120–123°. Recrystallization from acetone or ethanol gave pure 4-benzoylamino-1-phenyl-1-butanone (VI) in colorless platelets, m.p. 124.5–125.5°. Gabriel and Colman[3] and Sonn[3] obtained benzoyl derivatives melting at 125–126 and 126°, respectively.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.51; H, 6.23; N, 5.04.

A Nujol mull of VI displayed infrared absorption maxima at 3.05 μ (N—H), 5.97 μ (ketone C=O), 6.13 μ (amido C=O), 6.27 μ, 6.37 μ, and 6.45, 6.48 and 6.52 μ (amide triplet) and 6.73 μ; in chloroform solution at 2.93–2.99 μ (N—H), 5.95 μ (ketone C=O), 6.02 μ (amido C=O), 6.27 μ, 6.34 μ and 6.74 μ.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Heterocyclic Compounds. V. β-Pyridyl β-Styryl Ketone[1]

BY MILTON C. KLOETZEL AND FRANCIS L. CHUBB

RECEIVED MARCH 18, 1957

The base-catalyzed condensation of benzaldehyde with 3-acetylpyridine can be made to yield β-pyridyl β-styryl ketone (I) or 1,3,5-trinicotinoyl-2,4-diphenylpentane (VI). Michael type condensations of I with nitroalkanes, alkyl malonates, fluorene and 9-carboethoxyfluorene have been effected. The reaction with fluorene produced mixtures of the expected adduct XII and a trimolecular product. However the diethylamine-catalyzed condensation of I with 9-carboethoxyfluorene afforded a quantitative yield of the normal adduct XIII.

Reduction of γ-nitro ketones II–V by methods which have been explored in our laboratory[2,3] might be expected to yield a series of pyrrolidines and pyrrolines related to nicotine. Anticipating such studies, we have prepared the requisite β-pyridyl β-styryl ketone (I) and have investigated some of its reactions, including its conversion to the nitro ketones II–V.

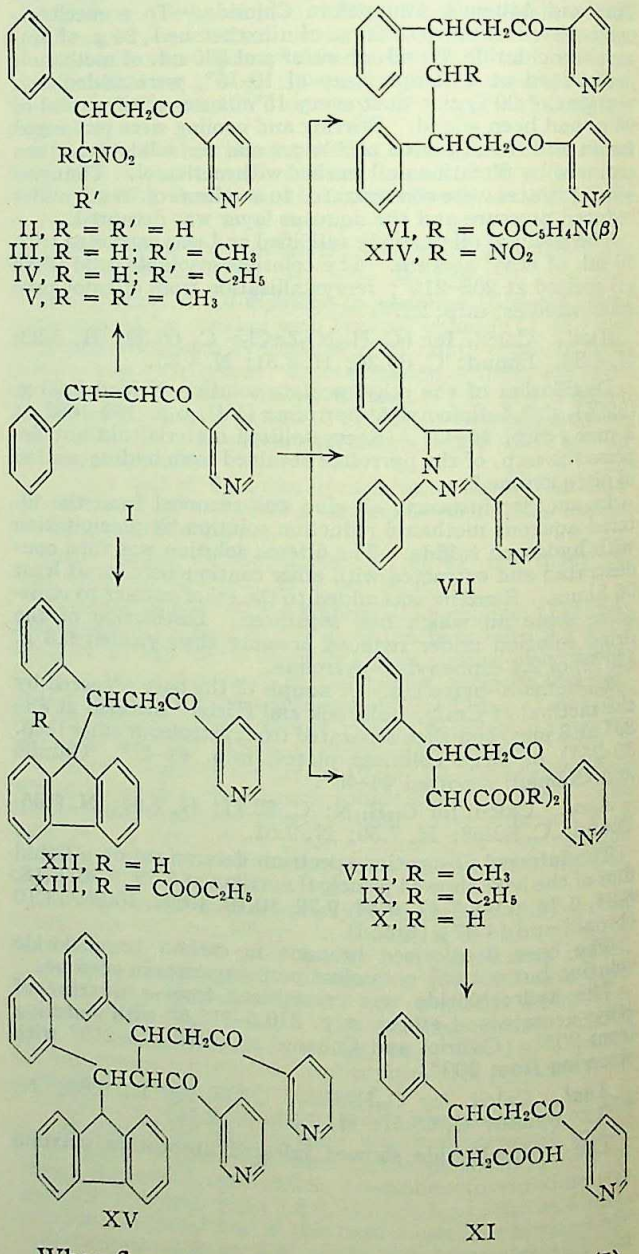
Ketone I was obtained in 92% yield when aqueous sodium hydroxide solution was added slowly to an equimolar mixture of benzaldehyde and 3-acetylpyridine in a large volume of water. Under more strongly basic conditions the condensation was more complex and yielded 1,3,5-trinicotinoyl-2,4-diphenylpentane (VI).[4] Effected in ethanol solution in the presence of benzyltrimethylammonium hydroxide, the reaction afforded two diastereoisomers of VI.

β-Pyridyl β-styryl ketone (I) reacted with phenylhydrazine in boiling acetic acid or in ethanol at room temperature under the catalytic influence of benzyltrimethylammonium hydroxide to yield the same product. Since hot acetic acid is known[5,6] to rearrange phenylhydrazones of α,β-unsaturated ketones, this substance has been designated 1,5-diphenyl-3-(3-pyridyl)-pyrazoline (VII). In dilute ethanolic acetic acid at room temperature, ketone I reacted with two molecules of phenylhydrazine, presumably producing the phenylhydrazone of 2-phenylhydrazino-2-phenylethyl 3-pyridyl ketone.

Diethylamine effectively catalyzed the Michael addition of nitro alkanes to β-pyridyl β-styryl ketone (I), affording nitro ketones II–V in 73–95% yields. Both nitroethane and 1-nitropropane yielded mixtures of diastereoisomeric nitro ketones.

The use of a 10:1 molar ratio of nitromethane to β-pyridyl β-styryl ketone effectively suppressed diketone formation and permitted the isolation of II in 75% yield. However, two diastereoisomers of 1,5-dinicotinoyl-3-nitro-2,4-diphenylpentane (XIV) resulted when the unsaturated ketone was employed in excess.

Diethylamine likewise promoted the reaction of β-pyridyl β-styryl ketone (I) with methyl and ethyl malonate to form adducts VIII and IX, respectively. These were hydrolyzed to the corresponding malonic acid X, which subsequently was decarboxylated at 180° to produce 5-oxo-3-phenyl-5-(3-pyridyl)-pentanoic acid (XI).



When fluorene and β-pyridyl β-styryl ketone (I), in molar ratio of 2 to 1, were allowed to react in aqueous pyridine containing sodium hydroxide (conditions which afforded[7] a quantitative yield of adduct in the case of benzalacetophenone), there was obtained 39% of the expected adduct XII, to-

(1) Abstracted from a portion of the Ph.D. dissertation of Francis L. Chubb.

(2) M. C. Kloetzel, THIS JOURNAL, 69, 2271 (1947).

(3) M. C. Kloetzel, J. L. Pinkus and E. M. Washburn, *ibid.*, 79, 4222 (1957).

(4) Compare (a) St. v. Kostanecki and G. Rossbach, *Ber.*, 29, 1488 (1896); (b) C. Engler and A. Engler, *ibid.*, 35, 4061 (1902); (c) D. B. Andrews and R. Connor, THIS JOURNAL, 57, 895 (1935).

(5) K. Auwers and H. Voss, *Ber.*, 42, 4411 (1909).

(6) L. C. Raiford and H. L. Davis, THIS JOURNAL, 50, 156 (1928).

(7) G. A. Reker and G. E. Hilbert, *ibid.*, 68, 2014 (1946).

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gether with 55% of a trimolecular condensation product. The yield of XII was increased to 62% when the molar ratio of fluorene to I was 10 to 1 but still 11% of the trimolecular product was formed.

Neither 9-ethylfluorene nor 9-benzylfluorene will add to the highly reactive acceptor, acrylonitrile, in the presence of a strongly basic catalyst.[8] Therefore it is not likely that our trimolecular condensation product results from addition of a second molecule of I at the 9-position of the fluorene nucleus in XII. Accordingly, XV is proposed as the more probable structure of the trimolecular product.

To circumvent the formation of trimolecular products in the Michael condensation, we examined the reaction of I with the more reactive addendum, 9-carboethoxyfluorene. 9-Carboalkoxyfluorenes have been reported to add to unsaturated nitriles[9,10] or ketones[11] but always in the presence of potassium hydroxide. We now have found that the condensation of 9-carboethoxyfluorene with β-pyridyl β-styryl ketone (I) is efficiently catalyzed by diethylamine and affords a quantitative yield of adduct XIII.

Experimental[12]

Ethyl nicotinate was obtained consistently in yields of 67%[13] by the following procedure. A mixture of nicotinic acid (200 g.), absolute ethanol (400 ml.) and sulfuric acid (120 ml.) was heated to reflux for 3 hours and then concentrated by distillation of 200 ml. of ethanol. The cooled solution was added slowly, with stirring, to 2000 g. of 20% aqueous sodium carbonate and the ester was extracted with ether. Distillation of the dried extract yielded 166 g. of ester, b.p. 132–133° at 14 mm.

3-Acetylpyridine.—Rapid evolution of hydrogen began soon after ethyl nicotinate (50 g.), ethyl acetate (44 g.) and sodium hydride (12 g.) were mixed by stirring under a nitrogen atmosphere. After the initial violence of the reaction had subsided the mixture was warmed on a steam-bath for 3 hours and excess sodium hydride was then decomposed by the cautious addition of 10 ml. of ethanol and 200 ml. of water. Concentrated hydrochloric acid (100 ml.) was added to the cooled solution and the mixture was then heated to reflux for 2 hours. After removal of excess ethyl acetate by distillation, the cooled solution was made alkaline by addition of 50% aqueous sodium hydroxide and the precipitated oil was extracted with ether. Distillation of the dried extract under reduced pressure yielded 33.6 g. (84%) of colorless 3-acetylpyridine, b.p. 80° at 2–3 mm.

A similar condensation was effected when a mixture of ethyl nicotinate (198 g.), ethyl acetate (176 g.) and commercial sodium methoxide (102 g.) was heated on a steam-bath for 3 hours with continuous stirring. To the cooled mixture was added 800 ml. of water and 400 ml. of concentrated acid and the afore-described procedure was followed; yield 130 g. (82%) of 3-acetylpyridine.

The use of sodium ethoxide to effect this condensation afforded 81–85% yields of 3-acetylpyridine.[13,14]

β-Pyridyl β-styryl ketone (I) was obtained in 92% yield from the reaction of 3-acetylpyridine with benzaldehyde, following a procedure described by Engler and Engler[4b] for the preparation of the α-pyridyl isomer. The product, after distillation under reduced pressure, separated from ethanol or heptane in green-yellow needles, m.p. 84–85°.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30. Found: C, 80.49; H, 5.27.

A picrate was formed in quantitative yield when equimolar ethanol solutions of ketone I and picric acid were mixed, and separated from ethanol in yellow needles, m.p. 199–200°.

Anal. Calcd. for $C_{20}H_{14}N_4O_8$: C, 54.79; H, 3.22. Found: C, 54.74; H, 3.56.

1,3,5-Trinicotinoyl-2,4-diphenylpentane (VI).—A solution of 3-acetylpyridine (6.0 g.) and benzaldehyde (5.4 g.) in ethanol (25 ml.), to which had been added 0.5 ml. of 40% benzyltrimethylammonium hydroxide solution, was allowed to stand at room temperature for 2 weeks. The solid precipitate was separated into two fractions by recrystallization from ethanol. The higher melting stereoisomer of VI (3.1 g.) formed colorless needles, m.p. 240–241°.

Anal. Calcd. for $C_{35}H_{29}N_3O_3$: N, 7.79. Found: N, 7.84.

A second isomer of VI (0.7 g.) also formed colorless needles but melted at 203–205°.

Anal. Calcd. for $C_{35}H_{29}N_3O_3$: N, 7.79. Found: N, 7.61.

When 10.8 g. of benzaldehyde and 12.1 g. of 3-acetylpyridine were allowed to react under the conditions employed by Kohler and Chadwell[15] for the preparation of benzalacetophenone, a yellow gum was obtained. Recrystallization from benzene afforded 8.1 g. of the stereoisomer of VI melting at 203–205°.

Reaction of β-Pyridyl β-Styryl Ketone with Phenylhydrazine.—Mild evolution of heat occurred when 0.1 ml. of 40% benzyltrimethylammonium hydroxide solution was added to a solution of ketone I (5.2 g.) and phenylhydrazine (2.7 g.) in ethanol (10 ml.). The solid which separated when the solution was allowed to stand for 12 hours at room temperature was crystallized from ethanol and afforded 5.4 g. (73%) of **1,5-diphenyl-3-(3-pyridyl)-pyrazoline (VII)** in green-yellow needles, m.p. 126–128°.

Anal. Calcd. for $C_{20}H_{17}N_3$: C, 80.23; H, 5.72. Found: C, 80.18; H, 5.79.

The same compound was formed when a mixture of β-pyridyl β-styryl ketone (5.2 g.), phenylhydrazine (2.7 g.) and acetic acid (25 ml.) was heated to reflux for 2 hours. The solvent was evaporated under reduced pressure and 6 ml. of concentrated hydrochloric acid was added. Crystallization of the residue from aqueous ethanol yielded the pyrazoline hydrochloride (3.9 g.) in yellow plates, m.p. 224–240° dec., from which VII was obtained by neutralization in ethanol with dilute aqueous sodium hydroxide.

When equimolar quantities of VII and picric acid were combined in hot ethanol, the **picrate of 1,5-diphenyl-3-(3-pyridyl)-pyrazoline** was obtained in quantitative yield. This substance sometimes separated from ethanol in orange-red leaflets, m.p. 195–196°, but from a mixture of ethanol and acetone in red crystals, m.p. 193–194°.

Anal. Calcd. for $C_{26}H_{20}N_6O_7$: C, 59.09; H, 3.83. Found: C, 58.96; H, 4.18.

Upon standing at room temperature for 3 hours, a solution of ketone I (1 g.), phenylhydrazine (600 mg.) and acetic acid (0.15 ml.) in 95% ethanol (10 ml.) deposited 600 mg. of crystalline solid, m.p. 145–148°. Several crystallizations from ethanol raised the m.p. of the presumed phenylhydrazone of 2-phenylhydrazino-2-phenylethyl 3-pyridyl ketone to 153–155°.

Anal. Calcd. for $C_{26}H_{25}N_5$: C, 76.62; H, 6.18. Found: C, 76.42; H, 6.35.

Reaction of β-Pyridyl β-Styryl Ketone with Nitro Alkanes. (a) With Nitromethane.—When a mixture of ketone I (10.4 g.), nitromethane (61 g.), methanol (30 ml.) and diethylamine (7.3 g.) was allowed to stand at room temperature for 12 hours and the solvents were then removed under reduced pressure, there remained a solid residue which crystallized from a mixture of ethanol and petroleum ether (b.p. 63–69°) to give 10.1 g. (75%) of **4-nitro-3-phenyl-1-(3-pyridyl)-1-butanone (II)** in colorless needles, m.p. 93–95°. Further crystallization raised the m.p. to 97–99°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22. Found: C, 66.33; H, 5.04.

(8) N. Campbell and A. E. S. Fairfull, *J. Chem. Soc.*, 1239 (1949).
(9) S. H. Tucker, *ibid.*, 2182 (1949).
(10) A. Campbell and S. H. Tucker, *ibid.*, 2623 (1949).
(11) H. W. D. Stubbs and S. H. Tucker, *ibid.*, 3288 (1950).
(12) Microanalyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, and by Mr. Joseph Pirie, formerly of the University of Southern California. Melting points are uncorrected.
(13) Compare H. O. Burrus and G. Powell, THIS JOURNAL, **67**, 1468 (1945).
(14) H. G. Kolloff and J. H. Hunter, *ibid.*, **63**, 490 (1941).
(15) E. P. Kohler and H. M. Chadwell, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y. 1941, p. 78.

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The oxime of II[16] formed colorless needles, m.p. 113–114°.

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.23; H, 5.52; N, 14.52.

A solution of ketone I (5.2 g.), nitromethane (0.76 g.) and diethylamine (0.27 g.) in 95% ethanol (50 ml.) was allowed to stand at room temperature. After 4 days, the precipitate (2.1 g., m.p. 200–206°) was filtered and recrystallized from dioxane. 1,5-Dinicotinoyl-3-nitro-2,4-diphenylpentane (XIV) formed colorless needles, m.p. 215–216° dec., containing one molecule of dioxane of crystallization.

Anal. Calcd. for $C_{33}H_{33}N_3O_6$: C, 69.82; H, 5.86. Found: C, 69.74; H, 5.80.

A sample dried at 75° in vacuum for 2 hours still contained one-half molecule of dioxane of crystallization.

Anal. Calcd. for $C_{31}H_{29}N_3O_5$: C, 71.11; H, 5.58. Found: C, 71.06; H, 5.20.

Dioxane of crystallization was removed completely by heating the crystals to constant weight at 95° in vacuum. The substance then melted at 220–222° dec.

Anal. Calcd. for $C_{29}H_{25}N_3O_4$: C, 72.63; H, 5.25. Found: C, 72.57; H, 5.31.

The original reaction mixture from which XIV had been filtered was evaporated under reduced pressure. Crystallization of the residue from chloroform and then from a mixture of acetone and benzene afforded 1.4 g. of a second diastereoisomer of XIV in colorless needles, m.p. 198–199°, containing one molecule of acetone of crystallization.

Anal. Calcd. for $C_{32}H_{31}N_3O_6$: N, 7.82. Found: N, 7.48.

Solvent of crystallization was removed by heating to constant weight at 95° in vacuum.

Anal. Calcd. for $C_{29}H_{25}N_3O_4$: C, 72.63; H, 5.25; N, 8.76. Found: C, 72.70; H, 5.26; N, 8.63.

(b) With Nitroethane.—After standing for 12 hours at room temperature, a mixture of ketone I (5.2 g.), nitroethane (5.6 g.), diethylamine (0.55 g.) and methanol (10 ml.) was evaporated under reduced pressure and the residual liquid mixture of nitro ketones was dissolved in a mixture of ethanol (20 ml.) and concentrated hydrochloric acid (3 ml.). The solution gradually deposited 2.8 g. of **4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone hydrochloride** in colorless needles, m.p. 165–170°. Several crystallizations from absolute ethanol raised the m.p. to 178–179°. The hydrochloride was decomposed by addition of dilute aqueous sodium hydroxide in the presence of ether. Evaporation of the ether afforded **4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone** (III) which separated from a mixture of ethanol and petroleum ether in colorless needles, m.p. 91–92°.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67. Found: C, 67.67; H, 5.03.

With an equivalent quantity of picric acid in 95% ethanol, this nitro ketone formed a **picrate** which separated from ethanol in yellow needles, m.p. 134–135°.

Anal. Calcd. for $C_{22}H_{19}N_5O_{10}$: C, 51.46; H, 3.73. Found: C, 51.69; H, 3.74.

The **oxime** of this isomer of III formed colorless needles, m.p. 152–154°.

Anal. Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.33; H, 6.14; N, 13.98.

The original reaction mixture, from which the aforementioned hydrochloride had been filtered, was evaporated and the residue was shaken with aqueous sodium hydroxide and ether. Evaporation of the ethereal extract left a residue which, together with 3.7 g. of picric acid, was dissolved in the minimum volume of boiling 95% ethanol. Upon cooling, the solution deposited 4.9 g. of the picrate of a diastereoisomeric nitro ketone III which formed yellow needles when recrystallized from 95% ethanol, m.p. 155–156°.

Anal. Calcd. for $C_{22}H_{19}N_5O_{10}$: C, 51.46; H, 3.73. Found: C, 51.74; H, 3.68.

The diastereoisomeric **4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone** (III), formed by decomposition of this picrate with 3% aqueous ethanolamine in the presence of ether, separated from a mixture of ethanol and petroleum ether in colorless needles, m.p. 82–84°.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67. Found: C, 67.97; H, 5.93.

(c) With 1-Nitropropane.—A solution of ketone I (10.4 g.), 1-nitropropane (13.4 g.) and diethylamine (1.1 g.) in methanol (20 ml.) deposited 12.7 g. (86%) of **4-nitro-3-phenyl-1-(3-pyridyl)-1-hexanone** (IV), melting above 142°, upon standing at room temperature. The ketone separated from methanol in colorless needles, m.p. 145–146°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.08. Found: C, 68.56; H, 6.22.

The **oxime** of IV formed colorless needles, m.p. 143–144°.

Anal. Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11. Found: C, 64.95; H, 6.20.

The original Michael condensation mixture, from which IV had been filtered, was evaporated under reduced pressure to yield a residue which was recrystallized from a mixture of absolute ethanol and petroleum ether. The resulting diastereoisomeric **4-nitro-3-phenyl-1-(3-pyridyl)-1-hexanone** (1.5 g., 10%) formed colorless needles, m.p. 84–85°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.08. Found: C, 68.52; H, 5.95.

The **picrate** of this isomer formed yellow needles, m.p. 138–139°.

Anal. Calcd. for $C_{23}H_{21}N_5O_{10}$: C, 52.37; H, 4.01. Found: C, 52.66; H, 4.17.

The **oxime** separated from aqueous ethanol in colorless needles, m.p. 152–153° dec.

Anal. Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.13; H, 6.20; N, 13.63.

(d) With 2-Nitropropane.—Pure **4-methyl-4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone** (V), m.p. 141–142°, separated in colorless needles when a solution of ketone I (10.4 g.), 2-nitropropane (6.7 g.) and diethylamine (0.55 g.) in methanol (20 ml.) was allowed to stand at room temperature for 3 days; yield 14.0 g. (95%).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.08. Found: C, 68.41; H, 6.52.

The **picrate** formed yellow leaflets, m.p. 189–190°.

Anal. Calcd. for $C_{23}H_{21}N_5O_{10}$: C, 52.37; H, 4.01. Found: C, 52.60; H, 4.33.

When 1 g. of V was warmed with 0.5 ml. of phenylhydrazine, 10 ml. of 95% ethanol and 2 drops of acetic acid, there were obtained two isomeric **phenylhydrazones**. One crystallized directly in yellow leaflets, m.p. 173–175°, when the reaction mixture was cooled; yield 600 mg. (46%).

Anal. Calcd. for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23. Found: C, 71.31; H, 6.38.

Concentration of the reaction yielded 300 mg. (23%) of an isomeric phenylhydrazone in colorless needles, m.p. 128–130°.

Anal. Calcd. for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23. Found: C, 71.42; H, 6.19.

Reaction of β-Pyridyl β-Styryl Ketone with Malonic Acid Esters.—After standing for 2 days at room temperature, a solution of ketone I (5.2 g.), dimethyl malonate (3.3 g.) and diethylamine (0.55 g.) in methanol (10 ml.) had deposited 7.8 g. of colorless needles. Concentration of the solution brought the total yield of **dimethyl 1-phenyl-3-(3-pyridyl)-3-oxopropylmalonate** (VIII) to 8.3 g. (98%), colorless needles, m.p. 95–96°.

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61. Found: C, 66.79; H, 5.46.

Ketone I reacted similarly with diethyl malonate in ethanol to give **diethyl 1-phenyl-3-(3-pyridyl)-3-oxopropylmalonate** (IX), m.p. 76–77°, in 68% yield.

Ester VIII (5 g.) was hydrolyzed readily when it was heated at 60–70° for 5 minutes with 20% aqueous potassium hydroxide (50 ml.). The resulting cooled solution was diluted with water to 100 ml. and any unhydrolyzed ester was separated. After acidification of the solution with concentrated sulfuric acid, aqueous sodium hydroxide was added as long as **1-phenyl-3-(3-pyridyl)-3-oxopropylmalonic acid** (X) precipitated; yield 3.6 g. (78%), m.p. 147–147.5°. The acid separated from aqueous ethanol in colorless needles, m.p. 149–150°.

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82. Found: C, 65.17; H, 4.83.

(16) R. L. Shriner and R. C. Fuson, "Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 202, procedure B.

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The same acid was obtained when ester IX was hydrolyzed.

When 5 g. of acid X was heated to 180° until evolution of carbon dioxide ceased, there remained 4 g. (93%) of 5-oxo-3-phenyl-5-(3-pyridyl)-pentanoic acid which separated from 95% ethanol in colorless needles, m.p. 147–148°.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61. Found: C, 71.24; H, 5.68.

Reaction of β-Pyridyl β-Styryl Ketone with Fluorene Derivatives.—Ketone I (5.2 g.) was allowed to react with fluorene (8.4 g.) and 50% aqueous sodium hydroxide (5 ml.) in pyridine (50 ml.) for 12 hours at room temperature and the solvents were then removed under reduced pressure. Crystallization of the residue from benzene yielded 4.0 g. (55%) of 5-(9-fluoryl)-4-nicotinoyl-3,5-diphenyl-1-(3-pyridyl)-1-pentanone (XV), m.p. 258–260°.

Anal. Calcd. for $C_{41}H_{32}N_2O_2$: C, 84.22; H, 5.52. Found: C, 84.07; H, 5.72.

The mother liquor from crystallization of XV was evaporated and the residue was dissolved in hot 95% ethanol. Excess fluorene separated from the cooled solution. Addition of 3.0 g. of picric acid to the filtered ethanol solution produced 5.8 g. (representing 39% of XII) of the picrate of 9-(2-nicotinoyl-1-phenylethyl)-fluorene in yellow needles, m.p. 180–182°.

Anal. Calcd. for $C_{33}H_{24}N_4O_8$: C, 65.55; H, 4.00; N, 9.26. Found: C, 65.68; H, 3.87; N, 9.18.

When 2 g. of the picrate was shaken with 100 ml. of 3% aqueous ethanolamine there was obtained 1.0 g. of ketone XII, which melted at 105–106° after crystallization from ethanol.

Anal. Calcd. for $C_{27}H_{21}NO$: C, 86.37; H, 5.64. Found: C, 86.48; H, 5.74.

The yields of XV and XII were 11 and 62%, respectively, when this condensation was repeated with a 10-to-1 molar ratio of fluorene to ketone I.

A mixture of ketone I (5.2 g.), 9-carboethoxyfluorene (5.9 g.) and 95% ethanol (20 ml.) was warmed until all solids had dissolved and diethylamine (0.5 g.) was then added. After 2 days at room temperature the crystalline adduct was filtered. Concentration of the mother liquor afforded additional material making the yield of 9-carboethoxy-9-(2-nicotinoyl-1-phenylethyl)-fluorene (XIII) essentially quantitative; m.p. 87–91°. Recrystallization from ethanol raised the m.p. to 91–92°.

Anal. Calcd. for $C_{30}H_{25}NO_3$: C, 80.51; H, 5.63. Found: C, 80.48; H, 5.82.

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, THE ARMOUR LABORATORIES]

The Preparation of Methyl-substituted DL-Phenylalanines

BY ROSS R. HERR, TAKASHI ENKOJI AND JOSEPH P. DAILEY

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A number of methyl-substituted phenylalanines and the corresponding diethyl acetamidomalonate intermediates have been prepared. The amino acids were evaluated as phenylalanine antagonists in the *E. coli* assay. The substituted malonates were prepared by the reaction between sodium diethyl acetamidomalonate and the appropriate benzyl bromide, benzyl chloride or benzyltrimethylammonium iodide. A modified procedure for the condensation of a quaternary iodide with sodium diethyl acetamidomalonate was devised. Hydrolysis and decarboxylation of these condensation products resulted in 2-methyl-, 3-methyl-, 4-methyl-, 2,3-dimethyl-, 2,4-dimethyl-, 2,5-dimethyl-, 2,6-dimethyl, 3,4-dimethyl-, 3,5-dimethyl- and 2,4,6-trimethylphenylalanines. Of these, only 3-methylphenylalanine will inhibit completely the growth of *E. coli*. Each of the compounds will reverse the growth-inhibiting effect of β-2-thienylalanine.

In view of the potential usefulness of compounds which are competitively antagonistic to specific amino acids, we have prepared a series of compounds which are chemically similar to phenylalanine. Each compound possesses the basic structure of phenylalanine with one or more methyl groups in different positions on the aromatic ring.

Previous investigators have shown that some *dl*-phenylalanines substituted in the phenyl ring act as competitive antagonists in the utilization of phenylalanine by microörganisms. Some of these compounds also are capable of replacing phenylalanine in reversing the inhibitory action of other competitive antagonists such as β-2-thienylalanine.[1–3]

The effect of methyl substituents in these phenylalanines would be expected to be more steric than polar. Information pertaining to the relationship between steric and polar effects and that between utilization and competitive antagonism could possibly be obtained by means of these methyl-substituted phenylalanines. Alkyl substitution in any position on the phenyl ring would hinder the hydroxylation of that position, and this, in turn, would block some of the possible pathways through which this amino acid could be metabolized.

Dakin[4] has prepared 4-methylphenylalanine and found it to cause a 35% inhibition of DOPA decarboxylase in dogs. In later studies,[3] it was found to reverse the inhibitory action of β-2-thienylalanine in *E. coli*. Burckhalter and Stephens[1] prepared 3-methylphenylalanine, and Harper, Furst and Morris[5] found that this compound did not inhibit the growth of *Leuconostoc mesenteroides* P-60, a lactobacillus, in concentrations up to 100 γ per cc. of medium.

The compounds listed in Table I were synthesized by condensing benzyl halides or benzyltrimethylammonium iodides with sodium diethyl acetamidomalonate, and the resulting substituted malonic esters were hydrolyzed and decarboxylated by refluxing with a halogen acid.[6]

Three methods were used for the preparation of the substituted malonic esters, and the data pertaining to these products are summarized in Table II. Method A consists of condensing diethyl acetamidomalonate with the methyl-substituted ben-

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TABLE I

PHYSICAL AND MICROBIOLOGICAL PROPERTIES OF METHYL-SUBSTITUTED PHENYLALANINES

Phenylalanine	Empirical formula	M.p., °C. dec.	Recryst. solvent	Amount required to reverse effect of 5 γ of β-2-thienylalanine on *E. coli* γ/6 cc.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Methyl (I)	$C_{10}H_{13}NO_2$	260–262	Water	10	67.0	7.31	7.82	66.8	7.39	7.64
3-Methyl (II)	$C_{10}H_{13}NO_2$	242–246	Ethanol–water	10[a]	67.0	7.31	7.82	66.8	7.53	7.82
4-Methyl (III)	$C_{10}H_{13}NO_2$	276–279	Water	2.5	67.0	7.31	7.82	67.0	7.33	7.68
2,3-Dimethyl (IV)	$C_{11}H_{15}NO_2$	244–245	Water	5	68.4	7.83	7.25	68.3	7.84	7.06
2,4-Dimethyl (V)	$C_{11}H_{15}NO_2$	244–246	Water	25	68.4	7.83	7.25	68.3	7.81	7.28
2,5-Dimethyl (VI)	$C_{11}H_{15}NO_2.H_2O$	243–245	Water	10	62.5	8.11	6.63	62.7	8.07	6.69
2,6-Dimethyl (VII)	$C_{11}H_{15}NO_2$	236–237	Acetic acid	500	68.4	7.83	7.25	68.4	7.76	7.23
3,4-Dimethyl (VIII)	$C_{11}H_{15}NO_2$	249–251	Water	2.5	68.4	7.83	7.25	68.4	7.81	7.10
3,5-Dimethyl (IX)	$C_{11}H_{15}NO_2$	245–249	Water	25	68.4	7.83	7.25	68.4	7.73	7.34
2,4,6-Trimethyl (X)	$C_{12}H_{17}NO_2$	242–244	Acetic acid	250	69.5	8.27	6.76	69.6	8.28	7.00

[a] 2000 γ/6 ml. media causes complete inhibition of growth of *E. coli*. The other methyl-substituted phenylalanines do not inhibit the growth of *E. coli* at 10,000 γ/6 ml. media.

TABLE II

PREPARATION AND PROPERTIES OF METHYL-SUBSTITUTED DIETHYL BENZYLACETAMIDOMALONATES

Diethyl benzylacetamidomalonate	Empirical formula	M.p., °C.	React. time, hr.	Yield, %	Hydrolyzing agent	Recryst. solvent	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found N	Found H
2-Methyl (Ia)	$C_{17}H_{23}NO_5$	88–89	4	70[a]	20% HBr[d,i]	Hexane	63.5	7.21	4.36	63.4	7.12	4.32
3-Methyl (IIa)	$C_{17}H_{23}NO_5$	108–109	3	47[a]	20% HBr[d,i]	Cyclohexane–hexane or 95% ethanol	63.5	7.21	4.36	63.4	7.53	4.34
4-Methyl (IIIa)	$C_{17}H_{23}NO_5$	111–113	8	73[a]	25% HCl[e,i]	Benzene–hexane	63.5	7.21	4.36	63.6	7.22	4.43
2,3-Dimethyl (IVa)	$C_{18}H_{25}NO_5$	92.5–93.5	20	63[c]	Concd. HCl[d,j]	Hexane	64.5	7.51	4.18	64.5	7.64	4.24
2,4-Dimethyl (Va)	$C_{18}H_{25}NO_5$	118–119	3	54[a]	20% HBr[d,i,j] or 25% HCl	Cyclohexane or hexane	64.5	7.51	4.18	64.7	7.54	4.27
2,5-Dimethyl (VIa)	$C_{18}H_{25}NO_5$	76–77	4	74[a]	25% HCl[f,i]	Hexane	64.5	7.51	4.18	64.8	7.62	4.51
2,6-Dimethyl (VIIa)	$C_{18}H_{25}NO_5$	99–100	20	88[c]	Concd. HCl[g,j]	Ethanol	64.5	7.51	4.18	64.4	7.73	4.28
3,4-Dimethyl (VIIIa)	$C_{18}H_{25}NO_5$	109–110	3	53[b]	Concd. HCl[d,j]	Hexane	64.5	7.51	4.18	64.7	7.49	4.47
3,5-Dimethyl (IXa)	$C_{18}H_{25}NO_5$	149–150	7	67[a]	25% HCl[h,j]	95% Ethanol	64.5	7.51	4.18	64.5	7.51	4.16
2,4,6-Trimethyl (Xa)	$C_{19}H_{27}NO_5$	81–82	11	59[a]	25% HCl[f,i]	Hexane	65.3	7.79	4.01	65.4	7.68	4.14

[a] Method A. [b] Method B. [c] Method C. [d] Hydrolysis time 6 hr. [e] Hydrolysis time 3.5 hr. [f] Hydrolysis time 4 hr. [g] Hydrolysis time 5 hr. [h] Hydrolysis time 8 hr. [i] Neutralizing agent IR-4B. [j] Neutralizing agent, concd. NH_4OH.

zyl halide, using sodium hydride as the condensing agent and toluene as the solvent.[6] The three xylyl bromides were obtained commercially. Side-chain bromination of mesitylene with N-bromosuccinimide resulted in 3,5-dimethylbenzyl bromide. Chloromethylation of *p*-xylene, *m*-xylene and mesitylene yielded 2,4-dimethyl-, 2,5-dimethyl- and 2,4,6-trimethylbenzyl chlorides, respectively.[7,8]

In Method B, a methyl-substituted benzyl chloride was condensed with diethyl acetamidomalonate in the presence of an equivalent amount of sodium ethoxide in ethanol. The starting 3,4-dimethylhexyl chloride was prepared by the chlorination of 3,4-dimethylbenzyl alcohol with thionyl chloride. The alcohol, in turn, was prepared by the reaction of the Grignard reagent from 4-bromo-*o*-xylene[9] with formaldehyde.[10]

A convenient method for the preparation of the 2,3-dimethyl- and the 2,6-dimethylbenzyl halides was not found, and the corresponding benzyl trimethylammonium iodides of these compounds were prepared. In Method C, these quaternary iodides were condensed with sodium diethyl acetamidomalonate in xylene by a procedure adapted from that used by Snyder and Smith.[11] The successive treatment of benzyltrimethylammonium iodide with sodium amide in liquid ammonia was used to prepare 2,3-dimethylbenzyltrimethylammonium iodide.[12] A Sandmeyer reaction of 2,6-dimethylaniline, using a mixture of sodium, potassium and cuprous cyanides yielded 2-cyano-*m*-xylene, which was reduced to 2,6-dimethylbenzylamine with lithium aluminum hydride. Methylation and quaternization of this amine with methyl iodide resulted in 2,6-dimethylbenzyltrimethylammonium iodide.

The methyl-substituted phenylalanines, which were prepared from the hydrolysis and decarboxylation of these condensation products, were evaluated as amino acid antagonists in the *E. coli* assay as described by Dittmer.[13] The concentrations of amino acids needed to reverse the effect of 5 γ of β-2-thienylalanine per 6 cc. of medium were also determined. These data are summarized in Table I.

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Experimental

Side-chain Bromination of Mesitylene with N-Bromosuccinimide.—A mixture of 63.0 g. (0.53 mole) of mesitylene, 89.0 g. (0.50 mole) of N-bromosuccinimide, 0.5 g. of benzoyl peroxide and 200 ml. of dry carbon tetrachloride was refluxed

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for 1 hr. under anhydrous conditions. After filtration, the solvent was removed under reduced pressure, and the residue was distilled at 10 mm. pressure. The material boiling up to 140° was redistilled at 8–10 mm., yielding 53.0 g. (53%) of 3,5-dimethylbenzyl bromide, b.p. 100–105°.

Chloromethylation of Mesitylene.—A stream of hydrogen chloride gas was bubbled through a stirred mixture of 120 g. (1.0 mole) of mesitylene, 100 g. (1.3 moles) of 38% aqueous formaldehyde and 450 ml. of concentrated hydrochloric acid for 1 hr. with the temperature maintained at 60–70°. The two layers were separated at room temperature, and after extracting the aqueous layer with ether, the organic layer and ether extracts were combined, washed with water and dried over anhydrous magnesium sulfate. After distillation of the ether, a crystalline material separated from the cooled residue. It was removed by filtration and recrystallized from *n*-hexane to give 40.0 g. (19%) of α^2,α^4-dichloropentamethylbenzene, m.p. 103–106°. The filtrate was fractionated at 16–18 mm. pressure and the material which distilled at 60–145° was redistilled at 15–16 mm. to give 46.0 g. (27%) of 2,4,6-trimethylbenzyl chloride, b.p. 125–126°.

Chlorination of 3,4-Dimethylbenzyl Alcohol.—A solution of 18.2 g. (0.15 mole) of thionyl chloride in 80 ml. of anhydrous ether was added dropwise with stirring to 9.8 g. (0.072 mole) of 3,4-dimethylbenzyl alcohol and 0.8 ml. of pyridine in 160 ml. of anhydrous ether. After 30 min., the mixture was washed with water, dried over anhydrous magnesium sulfate and distilled to remove the ether. The residue was distilled at 10 mm., and 3.8 g. (34%) of 3,4-dimethylbenzyl chloride was collected at 95–96°.[14]

2-Cyano-*m*-xylene.—A stirred mixture of 82.3 g. (0.68 mole) of 2,6-dimethylaniline in 400 ml. of 6 *N* hydrochloric acid was cooled to −5°, and a cold solution of 50.0 g. (0.73 mole) of sodium nitrite in 340 ml. of water was added dropwise. After 30 minutes, the mixture was neutralized with solid sodium bicarbonate and slowly added to a cold solution of 39.2 g. (0.80 mole) of sodium cyanide, 104.0 g. (1.6 moles) of potassium cyanide and 80.0 g. (0.89 mole) of cuprous cyanide in 500 ml. of water. After 30 minutes, the temperature was permitted to rise to 25° and maintained until the evolution of nitrogen had ceased. The mixture was steam distilled until 2 liters of distillate was collected in a well-cooled series of traps. The distillate was extracted with ether and washed with 2 *N* sodium hydroxide and water. After drying over anhydrous magnesium sulfate, the ether was removed by distillation and the residue crystallized upon cooling. The solid was recrystallized from *n*-hexane; yield 64.6 g. (66%), m.p. 89–91°.

Lithium Aluminum Hydride Reduction of 2-Cyano-*m*-xylene.—To a stirred suspension of 11.4 g. (0.3 mole) of lithium aluminum hydride in 30 ml. of anhydrous ether was added dropwise a solution of 26.2 g. (0.2 mole) of 2-cyano-*m*-xylene in 350 ml. of anhydrous ether. After 25 ml. of the nitrite solution was added, the reaction was heated until it was self-sustaining, and the addition was completed with occasional heating when necessary. The mixture was refluxed 30 minutes and, after cooling in an ice-bath, the excess lithium aluminum hydride was decomposed by the dropwise addition of 50 ml. of water. This was followed by 500 ml. of 20% sodium potassium tartrate solution and the aqueous emulsion was separated from the ether solution and re-extracted with ether. The ether layers were combined, washed with water, dried over anhydrous magnesium sulfate and the ether removed by distillation. The residue was distilled twice to yield 22.7 g. (84%) of 2,6-dimethylbenzylamine, b.p. 96–98°.

2,6-Dimethylbenzyltrimethylammonium Iodide.—To a stirred mixture of 72.6 g. (0.51 mole) of methyl iodide and 200 ml. of water was added 12.0 g. (0.3 mole) of sodium hydroxide pellets. A solution of 19.0 g. (0.14 mole) of 2,6-dimethylbenzylamine in 20 ml. of ethanol was added at a rate to maintain the temperature at approximately 50°. After stirring 2 hr., the mixture was cooled in ice and the precipitated solid was collected by filtration and dried. The dried solid was dissolved in 20 ml. of boiling methanol and the crystalline product which separated after addition of an equal volume of absolute ether was collected by filtration; yield 32.2 g. (75%), m.p. 197–201°. A sample for analysis was recrystallized from absolute methanol and the product partially decomposed at 194°, finally melting at 199–204.

Anal. Calcd. for $C_{12}H_{20}NI$: C, 47.2; H, 6.61; N, 4.59; I, 46.6. Found: C, 47.1; H, 6.27; N, 4.66; I, 42.4.

Preparation of Methyl-substituted Diethyl Benzylacetamidomalonates. Diethyl 4-Methylbenzylacetamidomalonate (IIIa) (Method A).—To a stirred solution of 65.0 g. (0.35 mole) of *p*-xylyl bromide in 50 ml. of dry redistilled toluene was added 8.4 g. (0.35 mole) of sodium hydride, followed by 72.0 g. (0.33 mole) of diethyl acetamidomalonate. The suspension was stirred and refluxed under anhydrous conditions for 8 hr., at which time the evolution of hydrogen, as indicated by a bubble counter, had almost ceased. The unreacted sodium hydride was decomposed by the addition of a few ml. of absolute ethanol, followed by a few ml. of 50% aqueous ethanol and then sufficient water to bring the volume of the aqueous layer to approximately 200 ml. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer and ether extracts were washed thoroughly with water, dried over anhydrous sodium sulfate and filtered. Concentration of the filtrate to approximately 100 ml. and cooling in an ice-bath caused a crystalline product to separate. Two crops yielded 78.0 g. (74%), m.p. 108–110°.

Diethyl 3,4-Dimethylbenzylacetamidomalonate (VIIIa) (Method B).—To a solution of 1.3 g. (0.057 g. atom) of sodium in 70 ml. of dry absolute ethanol[15] was added 12.4 g. (0.057 mole) of diethyl acetamidomalonate, followed by 7.9 g. (0.051 mole) of crude 3,4-dimethylbenzyl chloride. The mixture was refluxed for 3 hr. under anhydrous conditions and filtered. The addition of 200 ml. of water caused the separation of an oil which crystallized upon cooling. The product was collected by filtration; yield 9.0 g. (53%), m.p. 106–109°.

Diethyl 2,6-Dimethylbenzylacetamidomalonate (VIIa) (Method C).—To a solution of 1.04 g. (0.045 g. atom) of sodium in 150 ml. of dry absolute ethanol was added 10.9 g. (0.050 mole) of diethyl acetamidomalonate, followed by 375 ml. of dry xylene. The mixture was distilled with stirring until the temperature reached 135° and approximately 200 ml. of distillate was collected. Crystalline sodium diethyl acetamidomalonate separated at this point.[16] The condenser was arranged for reflux and 13.6 g. (0.045 mole) of 2,6-dimethylbenzyltrimethylammonium iodide was added. The suspension was stirred and refluxed for 20 hr. and filtered. The xylene from the filtrate was removed under vacuum on the steam-bath. The last traces of the solvent were removed by adding 20 ml. of water and distilling to dryness. The residue was dissolved in 200 ml. of 95% ethanol, treated with charcoal and Celite and filtered. An equal volume of water was added to the filtrate, and cooling and scratching produced a crystalline solid which was collected by filtration; yield 13.2 g. (88%), m.p. 98–99°.

Hydrolysis and Decarboxylation of Methyl-substituted Diethyl Benzylacetamidomalonates. 3,5-Dimethylphenylalanine (IX).—A suspension of 33.5 g. (0.1 mole) of IXa in 400 ml. of 25% hydrochloric acid was refluxed for 8 hr., and the solid which separated was collected by filtration and extracted with 125 ml. of boiling water. The insoluble material from the extraction was separated by filtration to give 6.5 g. of unhydrolyzed starting material. The filtrate was concentrated to 100 ml., cooled in an ice-bath and the crystals collected; yield 18.5 g. (99%) based on recovery of 6.5 g. starting material. A solution of 5.0 g. (0.022 mole) of this amino acid hydrochloride in 200 ml. of hot water was neutralized to *p*H 7.0 with concentrated ammonium hydroxide, and the precipitate which formed upon cooling in an ice-bath was collected by filtration; yield 3.9 g. (92%), m.p. 229–231° dec.

2,3-Dimethylphenylalanine (IV).—A suspension of 4.0 g. (0.012 mole) of IVa in 40 ml. of concentrated hydrochloric acid was refluxed for 6 hr. and filtered. The filtrate was cooled in an ice-bath and the crystals were collected by filtration; yield 2.2 g. (80%), m.p. 234–235° dec. A solution of 1.0 g. (0.0043 mole) of the amino acid hydrochloride

(14) The bulk of the material appeared to decompose and polymerize during the distillation to give a fluorescent, viscous oil. In subsequent preparations, the crude 3,4-dimethylbenzyl chloride was used without distillation in the condensation with diethylacetamidomalonate with satisfactory results.

(15) H. Lund and J. Bjerrum, *Ber.*, **64**, 761 (1946).

(16) If the diethyl acetamidomalonate is not pure or if anhydrous conditions are not used, a brown viscous oil sometimes separates and this results in a poor yield. When this situation is encountered, we have found it advantageous to recrystallize the diethyl acetamidomalonate from toluene.

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in 50 ml. of hot water was neutralized to *p*H 7 with concentrated ammonium hydroxide. The solution was concentrated under vacuum on the steam-bath until a precipitate began to form. The mixture was cooled in an ice-bath and the precipitate collected. Two crops yielded 0.84 g. (100%), m.p. 237–242° dec.

2-Methylphenylalanine (II).—A suspension of 33.5 g. (0.11 mole) of IIa in 400 ml. of 20% hydrobromic acid was refluxed for 6 hr., and the solution was concentrated under vacuum on the steam-bath until a solid began to form. The mixture was cooled in an ice-bath and the crystals collected by filtration; yield 21.0 g. (78%). A solution of 18.0 g. (0.069 mole) of the amino acid hydrobromide in 200 ml. of water was added to an aqueous slurry of 70.0 g. of Amberlite IR-4B ion-exchange resin (basic form). The mixture was stirred and filtered and the resin washed with an additional 100 ml. of water. The combined filtrates were concentrated under vacuum until a precipitate formed. The solid which separated upon cooling in an ice-bath was collected. Two crops yielded 10.5 g. (85%), m.p. 240–243° dec.

KANKAKEE, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, THE ARMOUR LABORATORIES]

Analogs of Phenylalanine Containing Sulfur

BY ROBERT L. COLESCOTT, ROSS R. HERR AND JOSEPH P. DAILEY

RECEIVED DECEMBER 26, 1956

Analogs of phenylalanine containing a sulfur group in the *para* position have been synthesized and tested as growth inhibitors of *Escherichia coli*. The mercapto, symmetrical disulfide, methylmercapto, ethylmercapto, methylsulfinyl, methyl sulfonyl and sulfamyl analogs were prepared by hydrolysis and decarboxylation of the corresponding diethyl acylamidomalonates.

The substitution of various groups on the benzene ring of phenylalanine has often resulted in compounds that are competitive antagonists of phenylalanine or tyrosine, the *para* substituted compounds being the most active. Some of these *para* substituted analogs of phenylalanine that have been previously reported include the nitro,[1] amino,[1] fluoro,[2] chloro,[1] methyl,[3] dimethylamino,[4] mercapto,[5,6] sulfamyl[7,8] and the symmetrical disulfide.[5,6] Because of the potential usefulness of amino acid antagonists in chemotherapy, we have prepared a group of compounds related to phenylalanine wherein a sulfur containing group is substituted in the *para* position of this amino acid. In these compounds, variations in the oxidation state of the sulfur results in groups having a range of electronic effects, from the electron-donating mercapto group to the electron-withdrawing sulfonamide. In this way we hoped to obtain information about the relationship between electronic character of the substituent and antagonism or utilization of the amino acid. We have prepared the mercapto, disulfide, methylmercapto, ethylmercapto, methylsulfinyl, methylsulfonyl and sulfamyl substituted phenylalanines.

The general method of preparation of these amino acids was by way of the corresponding diethyl acetamidomalonate (Table I).

The amino acid was then prepared by hydrolysis and decarboxylation (Table II).

The preparation of *p*-mercaptophenylalanine was first reported by Johnson and Brautlecht[5] and later by Elliott and Harington.[6] A more direct route and one which resulted in higher yield was found in the reaction of potassium ethyl xanthate with diethyl *p*-diazobenzylacetamidomalonate. The diazo-compound was prepared readily from the corresponding amine and this, in turn, was obtained by hydrogenation of diethyl *p*-nitrobenzylacetamidomalonate.[1] The hydrolysis of the xanthate, the hydrolysis of the amide and ester groups, as well as the decarboxylation, were accomplished in one step to give the amino acid hydrochloride in 86% yield. Oxidation of the *p*-mercaptophenylalanine to the corresponding disulfide was carried out according to the procedure of Elliott and Harington using iodine in potassium iodide solution.

Chloromethylation of thioanisole or thioanethole with chloromethyl ether yielded the *para* substituted benzyl chloride. The thioanethole was prepared by the reaction of diethyl sulfate with thiophenol. Condensation of these benzyl halides with diethyl acetamidomalonate resulted in the production of the substituted acetamidomalonates which were then hydrolyzed and decarboxylated to yield *p*-methylmercaptophenylalanine and *p*-ethylmercaptophenylalanine.

Controlled oxidation of the diethyl *p*-methylmercaptobenzylacetamidomalonate with hydrogen peroxide resulted in the sulfinyl substituted malonate and hydrolysis of this yielded *p*-methylsulfinylphenylalanine. Oxidation with an excess of hydrogen peroxide gave the sulfone which was hydrolyzed to yield the corresponding sulfonyl amino acid.

Two methods were employed successfully in the preparation of *p*-sulfamylphenylalanine.[7] Chlorosulfonation of diethyl benzylacetamidomalonate followed by reaction with ethereal ammonia and hydrolysis and decarboxylation resulted in the sulfonamide in 16% yield. The alternate procedure utilized side chain bromination of *p*-toluene-

(1) J. B. Burckhalter and V. C. Stephens, THIS JOURNAL, **73**, 56 (1951).

(2) E. L. Bennett and C. Niemann, *ibid.*, **72**, 1800 (1950).

(3) J. G. Martin, R. Brendel and J. M. Beiler, *Exp. Med. & Surg.*, **8**, 5 (1950).

(4) D. F. Elliott, A. T. Fuller and C. R. Harington, *J. Chem. Soc.*, 85 (1948).

(5) T. B. Johnson and C. A. Brautlecht, *J. Biol. Chem.*, **12**, 175 (1912).

(6) D. F. Elliott and C. Harington, *J. Chem. Soc.*, 1374 (1949).

(7) J. C. Nevenzel, W. E. Shelberg and C. Niemann, THIS JOURNAL, **71**, 3024 (1949).

(8) This compound exhibited chemotherapeutic activity when evaluated in *Streptococcus hemolyticus* infected rabbits. C. Schaffer, *Proc. Soc. Exp. Biol. & Med.*, **37**, 648 (1937).

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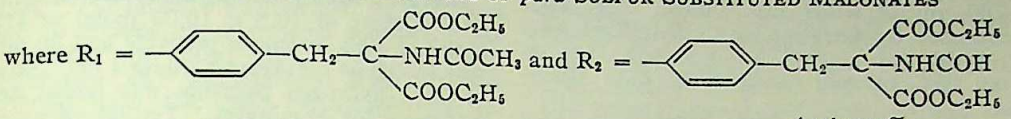
TABLE I

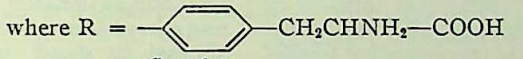
PHYSICAL PROPERTIES AND ANALYSES OF *para*-SULFUR SUBSTITUTED MALONATES



Malonate	Empirical formula	Recrystallization solvent	M.p., °C.	Analyses, % Calcd. C	H	N	S	Cl	Found C	H	N	S	Cl
$C_2H_5OC(=S)-S-R_1$ (Ia)	$C_{10}H_{25}NO_6S_2$	70% Ethanol	103–105	53.40	5.85	3.28	15.00	..	53.48	5.83	3.19	14.96	..
CH_3S-R_1 (IIIa)	$C_{17}H_{21}NO_6S$	95% Ethanol	108.5–109.5	57.49	6.53	3.97	9.00	..	57.67	6.42	3.98	8.84	..
$C_2H_5S-R_1$ (IVc)	$C_{18}H_{25}NO_6S$	95% Ethanol	96–97	58.85	6.81	3.81	8.72	..	59.03	6.97	3.92	8.90	..
$CH_3C(=O)-R_1$ (Va)	$C_{17}H_{23}NO_6S$	Water	142–143	55.28	6.23	3.79	8.67	..	55.15	6.16	3.77	8.55	..
$CH_3S(=O)-R_1$ (VIa)	$C_{17}H_{23}NO_7S$	95% Ethanol	174–176	52.99	5.97	3.64	8.31	..	53.30	5.61	3.63	8 15	..
$ClSO_2-R_1$ (VIIa)	$C_{16}H_{20}ClNO_7S$	Chloroform–hexane	123–124	47.35	4.93	3.45	7.89	8.75	47.38	4.91	3.86	7.89	8.37
$NH_2SO_2-R_1$ (VIIb)	$C_{16}H_{22}N_2O_7S$	60% Methanol	240–241	49.69	5.70	7.25	8.28	..	49.76	5.61	7.14	8.09	..
$NH_2SO_2-R_1$ (VIIe)	$C_{16}H_{20}N_2O_7S$	Dioxane–hexane	239–240	48.40	5.37	7.80	8.61	..	48.43	5.57	7.36	8.78	..

TABLE II

PHYSICAL AND MICROBIOLOGICAL PROPERTIES OF *para*-SULFUR SUBSTITUTED PHENYLALANINES



Amino acid	Empirical formula	M.p., °C. (dec.)	Complete inhibition of growth of *E. coli* γ/6 ml. media	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
HS-R·HCl (I)	$C_9H_{11}NO_2S\cdot HCl$	248–249[f]	> 1,000[a,e]	...	..	...	...	...	..	...	...
R-S-S-R (II)	$C_{18}H_{20}N_2O_4S_2$	276–278[g]	>250[a,e]	...	..	...	...	...	..	...	...
CH_3S-R (III)	$C_{10}H_{13}NO_2S$	245–247[g]	10,000[b,d]	56.87	6.16	6.63	15.16	57.06	6.13	6.62	15.16
C_2H_5S-R (IV)	$C_{11}H_{15}NO_2S$	224–226[g]	3,000[c,d]	58.67	6.67	6.22	14.22	58.47	6.53	6.38	13.97
$CH_3S(=O)-R$ (V)	$C_{10}H_{13}NO_3S$	250–251[h]	>10,000[e]	52.86	5.73	6.17	14.10	52.57	5.81	6.12	13.85
$CH_3S(=O)_2-R$ (VI)	$C_{10}H_{13}NO_4S$	266–267[g]	>10,000[e]	49.39	5.36	5.64	12.90	48.92	5.84	5.52	12.86
NH_2SO_2-R (VII)	$C_9H_{12}N_2O_4S$	251–252[i]	>10,000[e]	44.30	4.93	11.47	13.11	44.06	4.84	11.31	13.21

[a] Insoluble at higher concentrations. [b] Inhibition was reversed by 50 γ of tyrosine, not by phenylalanine up to 1000 γ. [c] Inhibition was reversed by 100 γ of tyrosine, not by phenylalanine up to 1000 γ. [d] 500 γ reversed the inhibition of B-2-thienylalanine. [e] No effect on β-2-thienylalanine inhibition. [f] Recrystallized from 20% HCl. [g] Recrystallized from water. [h] Recrystallized from water–ethanol mixture. [i] Recrystallized from water–acetone mixture.

sulfonyl chloride with N-bromosuccinimide followed by selective reaction of the sulfonyl chloride group with ammonia. The resulting sulfamylbenzyl bromide was condensed with diethyl formamidomalonate and subsequently hydrolyzed and decarboxylated. This method gave a 27% yield of product based on the amount of *p*-toluenesulfonyl chloride consumed.

The compounds were assayed in the *E. coli* microbiological system described by Dittmer, *et al.*,[9] and the results are shown in Table II.

Acknowledgments.—The authors wish to express their appreciation to Mrs. G. M. Robinson who conducted the microbiological assays and to Dr. T. J. Bardos for helpful discussions and suggestions.

Experimental

Diethyl *p*-Xanthylbenzylacetamidomalonate (Ia).—To a stirred suspension of 16.15 g. (0.045 mole) of diethyl *p*-aminobenzylacetamidomalonate·HCl[2] in 30 ml. of 6 *N* HCl at 0° was added slowly 4.1 g. (0.06 mole) of sodium nitrite in 8 ml. of water. After the addition was completed, the solution was adjusted to *p*H 7 by the addition of solid sodium carbonate. The temperature was maintained at 0°, and a solution of 9.3 g. (0.058 mole) of potassium ethyl xanthate was added slowly. The solution was allowed to reach room temperature and then stirred at 60° for 1 hr. The product was extracted from the aqueous layer with three 100-ml. portions of ether. The ether solution was dried over magnesium sulfate and the ether distilled, leaving a viscous oil. The product was obtained by crystallization from 70% ethanol; yield 8.5 g. (47%), m.p. 103–105°.

***p*-Mercaptophenylalanine Hydrochloride (Thiotyrosine) (I).**—A mixture of 1.0 g. (0.0028 mole) of Ia and 10 ml. of concentrated hydrochloric acid was refluxed for 5 hr. This solution was evaporated to 5 ml. under reduced pressure and chilled overnight. The product was collected and dried under vacuum over solid sodium hydroxide; yield 0.52 g. (86%), m.p. 243–246° dec. Recrystallization from 20% hydrochloric acid raised the melting point to 248–249° dec.[6]

***p,p'*-Phenylalanine Disulfide (II).**—A solution of 0.3 g. (0.0015 mole) of I in 10 ml. of water was treated with a slight excess of 2 *N* iodine in 5% potassium iodide. This solution was heated on the steam-bath and adjusted to *p*H 5 with ammonium hydroxide. The white solid that precipitated upon cooling was collected and dried under vacuum; yield 0.16 g. (66%), m.p. 276–278° dec.[5]

Diethyl *p*-Methylmercaptobenzylacetamidomalonate (IIIa).—To a solution containing 7.4 g. (0.32 gram atom) of sodium dissolved in 700 ml. of absolute ethanol was added 69.9 g. (0.32 mole) of diethyl acetamidomalonate. Fifty-five grams (0.32 mole) of *p*-methylmercaptobenzyl

(9) K. Dittmer, G. Ellis, H. McKennis and V. du Vigneaud, *J. Biol. Chem.*, **164**, 761 (1946).

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chloride[10] was added and the mixture refluxed for 2.5 hr. Approximately 80% of the alcohol was removed by distillation and 750 ml. of water was added. The crude product was collected by filtration and crystallized from 95% ethanol; yield 113 g. (84%). A sample was recrystallized from 95% ethanol for analysis, m.p. 108.5–109.5°.

p-**Methylmercaptophenylalanine** (III).—The amino acid was obtained by refluxing 5.0 g. (0.0136 mole) of IIIa with 50 ml. of concentrated hydrochloric acid for 4 hr. Upon cooling, the hydrochloride salt separated and was removed by filtration. It was dissolved in 100 ml. of hot water and neutralized to *p*H 7 with concentrated ammonium hydroxide. The amino acid which crystallized upon cooling was collected by filtration, washed with acetone and dried; yield 2.87 g. (95%), m.p. 245–247° dec.

Thioanethole (IVa).—To 120 ml. of cold 20% sodium hydroxide was added 50 g. (0.455 mole) of thiophenol. The mixture was stirred and 71 g. (0.46 mole) of diethyl sulfate was added dropwise over a period of 30 minutes. Stirring was continued for 4 hr. at room temperature and then the solution was extracted with ether. The ether extract was dried over magnesium sulfate and the ether removed by distillation. The residue was distilled under reduced pressure and the thioanethole collected at 89° (15 mm.); yield 52.6 g. (83%).

p-**Ethylmercaptobenzyl Chloride** (IVb).—A mixture of 45 g. (0.32 mole) of IVa, 26 g. (0.32 mole) of chloromethyl ether and 260 ml. of glacial acetic acid was heated at 65–70° for 40 hr. The solution was cooled, poured into 500 ml. of ice-water and extracted with chloroform. The chloroform extract was dried over magnesium sulfate and the chloroform removed by distillation. The residue was distilled under reduced pressure and the *p*-ethylmercaptobenzyl chloride collected at 149° (15 mm.), yield 20.3 g. (34%).

Anal. Calcd. for $C_9H_{11}ClS$: C, 57.92; H, 5.90; S, 17.17; Cl, 19.04. Found: C, 57.82; H, 5.82; S, 17.02; Cl, 19.13.

Diethyl *p*-**Ethylmercaptobenzylacetamidomalonate** (IVc).—To a solution containing 1.93 g. (0.084 gram atom) of sodium dissolved in 210 ml. of absolute ethanol was added 18.2 g. (0.084) of diethyl acetamidomalonate. To this solution was added 15.6 g. (0.084 mole) of IVb and the mixture refluxed for 2 hr. Approximately 80% of the ethanol was removed by distillation and 400 ml. of water was added. The mixture was cooled and the crude product removed by filtration. Recrystallization from methanol–water yielded 19.7 g. (64%). A sample was recrystallized from 95% ethanol for analysis, m.p. 96–97°.

p-**Ethylmercaptophenylalanine** (IV).—The amino acid was obtained by refluxing 19 g. (0.0517 mole) of IVc with 190 ml. of concentrated hydrochloric acid for 4 hr. The hydrochloride salt crystallized on cooling and was collected by filtration. The salt was dissolved in 100 ml. of boiling water and adjusted to *p*H 7 by the addition of concentrated ammonium hydroxide. The amino acid crystallized on cooling and was collected by filtration; yield 7 g. (60%), m.p. 224–226° dec.

Diethyl *p*-**Methylsulfinylbenzylacetamidomalonate** (Va).—To a solution of 11 g. (0.03 mole) of IIIa in 20 ml. of acetic acid was added 3.1 ml. (0.03 mole) of 30% hydrogen peroxide. The solution was cooled under tap water for a few minutes, stirred at room temperature for 15 minutes and then at 90° for 15 minutes. After cooling, the solution was poured into 150 ml. of water and cooled in the refrigerator. The crude product was collected by filtration and dried *in vacuo;* yield 8.2 g. (90%), m.p. 141–143°. A sample was recrystallized from water for analysis, m.p. 142–143°.

p-**Methylsulfinylphenylalanine** (V).—The amino acid was obtained by refluxing 22 g. (0.06 mole) of Va with 220 ml. of concentrated hydrochloric acid for 4 hr. The solution was evaporated to dryness under reduced pressure and the solid dissolved in 100 ml. of water. The free amino acid was obtained by passing the solution of hydrochloride salt through a column of Duolite A-2 ion-exchange resin. The resulting solution was evaporated to 50 ml. under reduced pressure, diluted with 50 ml. of ethanol and then chilled in an ice–salt bath. The product was collected by filtration and dried *in vacuo;* yield 7.5 g. (55%), m.p. 246–250° dec. A sample was recrystallized from water–ethanol for analysis, m.p. 250–251° dec.

Diethyl *p*-**Methylsulfonylbenzylacetamidomalonate** (VIa).—A mixture of 10.6 g. (0.03 mole) of IIIa, 9 ml. (0.08 mole) of 30% hydrogen peroxide and 30 ml. of acetic acid was heated on the steam-bath for 1 hr. An additional 3 ml. of 30% hydrogen peroxide was added and the heating continued for 30 minutes. Ten ml. of water was added to the hot solution and then it was cooled in the refrigerator. The crude product was collected by filtration and recrystallized from 95% ethanol; yield 8.2 g. (71%), m.p. 174–176°.

p-**Methylsulfonylphenylalanine** (VI).—The amino acid was obtained by refluxing 8.0 g. (0.021 mole) of VIa with 80 ml. of concentrated hydrochloric acid for 4 hr. The solution was evaporated to dryness under reduced pressure and the remaining solid was dissolved in 200 ml. of water. The solution was heated to boiling and adjusted to *p*H 7 by the addition of concentrated ammonium hydroxide. After cooling, the product crystallized and was collected by filtration; yield 4.3 g. (85%), m.p. 264–267° dec. A sample was recrystallized from water for analysis, m.p. 266–267° dec.

p-**Sulfamylphenylalanine** (VII). **Method A. Diethyl** *p*-**Chlorosulfonylbenzylacetamidomalonate** (VIIa).—A 150-ml. portion of chlorosulfonic acid was stirred at 15° and to it was added slowly 103 g. (0.335 mole) of diethyl benzylacetamidomalonate[11] over a period of 1 hr. The mixture was stirred 1 hr. at room temperature, 1 hr. at 65° and then allowed to stand overnight at room temperature. The mixture was added slowly to 750 g. of crushed ice. The crude product precipitated as a viscous oil. It was washed twice with cold water and finally with cold water containing 2% ether. The product was placed in a desiccator over calcium chloride and dried *in vacuo*. It was recrystallized from anhydrous chloroform–hexane to yield 65 g. (54%), m.p. 123–124°.

Anal. Calcd. for $C_{16}H_{20}ClNO_7$: C, 47.35; H, 4.93; N, 3.45; S, 7.89; Cl, 8.75. Found: C, 47.38; H, 4.91; N, 3.86; S, 7.89; Cl, 8.37.

Diethyl *p*-**Sulfamylbenzylacetamidomalonate** (VIIb).—A large excess of anhydrous ammonia was passed into a solution of 28 g. (0.069 mole) of VIIa in 200 ml. of anhydrous ether. The solid which was formed was collected by filtration, washed with ether and recrystallized from methanol–water to yield 14.2 g. (53%), m.p. 240–241°.

p-**Sulfamylphenylalanine** (VII).—The amino acid hydrobromide was obtained by refluxing 3 g. (0.008 mole) of VIIb with 20 ml. of 20% hydrobromic acid for 4 hr. The free amino acid was obtained by passing the solution of hydrobromide salt through a column of Duolite A-2 ion-exchange resin. The resulting solution was evaporated to 10 ml. under reduced pressure, and 10 ml. of acetone was added. The crude product was collected by filtration and recrystallized from water–acetone, m.p. 251–252° dec., yield 1.2 g. (63%).

p-**Sulfamylphenylalanine** (VII). **Method B.** α-**Bromo-***p*-**toluenesulfonyl Chloride** (VIIc).—A mixture of 49 g. (0.252 mole) of N-bromosuccinimide, 48 g. (0.252 mole) of *p*-toluenesulfonyl chloride and 2.42 g. (0.01 mole) of benzoyl peroxide in 250 ml. of carbon tetrachloride was refluxed for 2 hr. The mixture was cooled to room temperature and the succinimide removed by filtration. The carbon tetrachloride was removed from the filtrate by distillation under reduced pressure, and the oil that remained was extracted with three 150-ml. portions of boiling heptane. Fifty-five grams of crude product was obtained from the cooled extract. It was recrystallized from heptane to yield 51.3 g. (76%), m.p. 74–76°.

α-**Bromo-***p*-**toluenesulfonamide** (VIId).—A large excess of anhydrous ammonia was passed into a solution of 10 g. (0.037 mole) of VIIc in 350 ml. of anhydrous ether. The resulting precipitate was removed by filtration, washed with ether and crystallized from acetone, yield 7 g. (73%). A sample recrystallized from methanol–water for analysis, m.p. 191–192°.

Anal. Calcd. for $C_7H_8BrNO_2S$: C, 33.60; H, 3.24; N, 5.60; S, 12.80; Br, 32.00. Found: C, 33.58; H, 3.75; N, 5.69; S, 12.61; Br, 31.60.

Diethyl *p*-**Sulfamylbenzylformamidomalonate** (VIIe).—To a solution containing 0.45 g. (0.0195 gram atom) of

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(11) W. L. Albertson and S. Archer, THIS JOURNAL, 67, 308 (1945).

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sodium dissolved in 10 ml. of absolute ethanol was added 3.98 g. (0.0195 mole) of diethyl formamidomalonate. To this solution was added 4.92 g. (0.0195 mole) of VIId in 15 ml. of ethanol. The mixture was refluxed for 5 hr. and then evaporated to dryness under reduced pressure. One hundred ml. of water was added with stirring, the solid removed by filtration and recrystallized from ethanol; yield 4.6 g. (63%), m.p. 236–240°. A sample was recrystallized from dioxane–heptane for analysis, m.p. 239–240°.

p-Sulfamylphenylalanine (VII).—The amino acid hydrochloride was obtained by refluxing 21 g. (0.056 mole) of VIIe with 200 ml. of concentrated hydrochloric acid for 5 hr. The solution was evaporated to dryness under reduced pressure. The hydrochloride salt was dissolved in 100 ml. of water and the solution passed through a column of Duolite A-2 ion-exchange resin to obtain the free amino acid. The resulting solution was evaporated to 125 ml. under reduced pressure and 100 ml. of acetone added. The solution was cooled overnight and the crude product was collected; yield 10.5 g. (76%), m.p. 248–249° dec. A sample was recrystallized from water–acetone for analysis, m.p. 251–252° dec.

KANKAKEE, ILLINOIS

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Organic Sulfur Derivatives. II.[2] Sulfides, Sulfoxides and Sulfones from Thiols and 10-Undecenoic Acid

BY N. H. KOENIG AND DANIEL SWERN

RECEIVED FEBRUARY 22, 1957

Sulfides are formed by the addition of thiols (RSH) to 10-undecenoic acid (equation 1). The reactions proceed moderately rapidly at temperatures below 100° under free-radical conditions, often with the assistance of ultraviolet light. The acids [$RS(CH_2)_{10}CO_2H$] have a terminal substituent R, which is alkyl (propyl, butyl, hexyl, heptyl, octyl, undecyl or dodecyl), hydroxyethyl, carboxymethyl, acetyl, benzyl, phenyl or 2-naphthyl. Some of the sulfides have been oxidized to sulfoxides by bromate–bromide solution; many have been oxidized to sulfones by peracetic acid. However, an attempt to prepare the sulfone of 11-(acetylthio)-undecanoic acid yielded 11-sulfoundecanoic acid. Other compounds prepared include diesters of 11-(carboxymethylthio)-undecanoic acid and a sulfonium salt, methyl-*n*-octyl-10-carboxydecylsulfonium iodide.

This investigation continues our systematic study of the preparation of long-chain sulfur compounds of known structure. In our first paper[2] it was shown that a high yield of 11-(carboxymethylthio)-undecanoic acid readily is obtained by the addition of an equimolar amount of mercaptoacetic acid to 10-undecenoic acid. We have now shown that this reaction is general. It has been extended to include many other thiols; the resulting (alkylthio)- and (arylthio)-undecanoic acids have been converted in many instances to sulfoxides, sulfones, esters and other derivatives. Aside from 11-(carboxymethylthio)-undecanoic acid,[3] 11-(*n*-dodecylthio)-undecanoic acid[3] and 11-sulfoundecanoic acid,[4] all of the compounds described in this paper are new. Some similar alkylthio, alkylsulfinyl and alkylsulfonyl acids, prepared in different ways, have been reported.[5,6]

Alkanethiols add moderately rapidly to 10-undecenoic acid as shown in equation 1. Previous evidence,[2] as well as infrared and X-ray diffraction studies to be reported separately, indicates that

$$RSH + CH_2{=}CH(CH_2)_3CO_2H \longrightarrow RS(CH_2)_{10}CO_2H \quad (1)$$

R = *n*-propyl, butyl, hexyl, heptyl, octyl, undecyl or dodecyl.

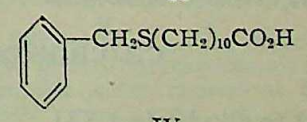
the addition products isolated have an unbranched structure, *i.e.*, the sulfur atom is attached at the 11-(terminal) rather than at the 10-position, and that they are formed *via* free-radical intermediates. The free-radical addition mechanism is also supported by the activating influence of ultraviolet light.

Other types of terminally substituted undecanoic acids, (I-VI) are formed by the addition of mercaptoethanol, mercaptoacetic acid, thiolacetic acid, α-toluenethiol, benzenethiol or 2-naphthalenethiol, respectively.

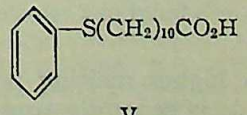
$HO(CH_2)_2S(CH_2)_{10}CO_2H$ I

$HO_2C(CH_2)S(CH_2)_{10}CO_2H$ II

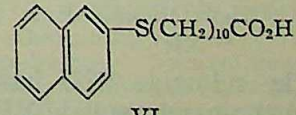
$CH_3CS(CH_2)_{10}CO_2H$ III



IV



V



VI

The pure acids, $RS(CH_2)_{10}CO_2H$, are odorless, white, crystalline solids. They are insoluble in water, sparingly soluble in petroleum ether at room temperature or 0° and moderately soluble in more polar solvents such as acetone and ethanol. Other characteristics of these compounds are given in Table I.

The chemical behavior of these sulfides is illustrated by some reactions of 11-(*n*-octylthio)-undecanoic acid, $CH_3(CH_2)_7S(CH_2)_{10}CO_2H$ (VII). Controlled oxidation with bromate–bromide solution gives the sulfoxide VIII, while excess peracetic acid forms the sulfone IX. Methyl iodide adds to

$CH_3(CH_2)_7SO_x(CH_2)_{10}CO_2H$ VIII, $x = 1$ IX, $x = 2$

VII to give the sulfonium salt, methyl-*n*-octyl-10 carboxydecylsulfonium iodide (X). The carboxyl

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TABLE I

(ALKYLTHIO)- AND (ARYLTHIO)-UNDECANOIC ACIDS, $RS(CH_2)_{10}CO_2H$

R	Formula	M.p.,[a] °C.	Neut. equiv. Calcd.	Neut. equiv. Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
n-Propyl	$C_{14}H_{28}O_2S$	44	260	259	64.6	64.6	10.8	10.9	12.4	12.2
n-Butyl	$C_{15}H_{30}O_2S$	55	274	275	65.6	65.3	11.0	10.8	11.7	11.9
n-Hexyl	$C_{17}H_{34}O_2S$	53	303	302	67.5	67.5	11.3	11.4	10.6	10.8
n-Heptyl	$C_{18}H_{36}O_2S$	54	317	317	68.3	68.5	11.5	11.5	10.1	10.2
n-Octyl	$C_{19}H_{38}O_2S$	60	331	332	69.0	69.0	11.6	11.8	9.70	9.30
n-Undecyl	$C_{22}H_{44}O_2S$	68	373	372	70.9	70.7	11.9	11.9	8.60	8.82
n-Dodecyl	$C_{23}H_{46}O_2S$	68	387	388	71.4	71.5	12.0	11.8	8.29	8.09
2-Hydroxyethyl	$C_{13}H_{26}O_3S$	70	262	266	59.5	59.1	10.0	10.1	12.2	12.0
Carboxymethyl	$C_{13}H_{24}O_4S$	99	138	140	56.5	56.4	8.75	8.72	11.6	11.7
Acetyl	$C_{13}H_{24}O_3S$	59	260	264	60.0	59.8	9.29	9.27	12.3	12.6
Benzyl	$C_{18}H_{28}O_2S$	55	308	308	70.1	69.9	9.15	9.14	10.4	10.4
Phenyl	$C_{17}H_{26}O_2S$	84	294	294	69.3	69.5	8.90	9.26	10.9	11.2
2-Naphthyl	$C_{21}H_{28}O_2S$	99	345	344	73.2	73.1	8.19	8.12	9.31	9.24

[a] Determined with a micro hot-stage.

TABLE II

SULFOXIDES, $RSO(CH_2)_{10}CO_2H$, AND SULFONES, $RSO_2(CH_2)_{10}CO_2H$, FROM (ALKYLTHIO)- AND (ARYLTHIO)-UNDECANOIC ACIDS

RSO or RSO_2	Formula	M.p.,[a] °C.	Neut. equiv. Calcd.	Neut. equiv. Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
n-Heptylsulfonyl	$C_{18}H_{36}O_4S$	112	349	348	62.0	62.2	10.4	10.2	9.20	9.19
n-Octylsulfinyl	$C_{19}H_{38}O_4S$	88	347	345	65.8	65.5	11.1	10.8	9.25	9.32
n-Octylsulfonyl	$C_{19}H_{38}O_4S$	114	363	364	63.0	62.5	10.6	10.3	8.84	8.90
2-Hydroxyethylsulfonyl[b]	$C_{13}H_{26}O_5S$	94–96	294	290–294[c]	53.0	52.8	8.90	9.39	10.9	11.0
Carboxymethylsulfinyl	$C_{13}H_{24}O_5S$	92	146	147	53.4	53.5	8.27	8.35	11.0	10.4
Carboxymethylsulfonyl	$C_{13}H_{24}O_6S$	141	154	154	50.6	50.6	7.84	8.02	10.4	10.2
Benzylsulfonyl	$C_{18}H_{28}O_4S$	127	340	341	63.5	63.8	8.29	8.43	9.42	9.41
Phenylsulfinyl	$C_{17}H_{26}O_3S$	61	310	311	65.8	66.0	8.44	8.84	10.3	10.4
Phenylsulfonyl	$C_{17}H_{26}O_4S$	86	326	328	62.6	62.7	8.03	8.04	9.82	9.89
2-Naphthylsulfonyl	$C_{21}H_{28}O_4S$	117	377	374	67.0	66.8	7.50	7.57	8.52	8.81

[a] Determined with a micro hot-stage. [b] Calcd. OH, 5.48. Found: OH, 5.26. [c] Fading end-point.

group reacts normally in conversion of VII to the *p*-bromophenacyl ester XI and

$$[CH_3(CH_2)_7\overset{+}{S}(CH_2)_{10}CO_2H]I^- + X \rightarrow CH_3(CH_2)_7S(CH_2)_{10}CO_2CH_2CO—C_6H_4\text{-}p\text{-}Br$$

XI

of II to alkyl esters XII.

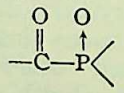
$RO_2C(CH_2)S(CH_2)_{10}CO_2R$ R = *n*-butyl or 2-ethylhexyl

XII

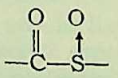
The sulfoxide VIII has a higher melting point than the parent sulfide VII, as is generally true for alkylsulfinyl aliphatic acids.[6] A lowering of melting point takes place, however, in forming the sulfoxide of II, *i.e.*, 11-(carboxymethylsulfinyl)-undecanoic acid, and of V, 11-(phenylsulfinyl)-undecanoic acid.

Sulfones have been prepared by peracetic acid oxidation of sulfides I, II, IV, V, VI, VII and 11-(*n*-heptylthio)-undecanoic acid. Characteristics of the sulfoxides and sulfones are given in Table II.

An attempt to prepare 11-(acetylsulfonyl)-undecanoic acid, the sulfone of III, led instead to the formation of 11-sulfoundecanoic acid ($HO_3S(CH_2)_{10}CO_2H$), a compound previously prepared by other methods. It seems plausible that a sulfoxide, sulfone or other intermediate is formed[7] but is readily cleaved because of the positive charges on neighboring carbon and sulfur atoms. This instability parallels that of acylphosphonates, in which the



group is analogous to the



group.[8] Furthermore, it is significant that the only α-ketosulfones we have found in the literature are probably special cases, since both the carbonyl and the sulfonyl groups are attached to benzene rings.[9]

Experimental

Starting Materials.—10-Undecenoic acid (b.p. 136° at 1.5 mm., $n^{30}D$ 1.4458) was purified by fractional distillation of the best commercial material. *n*-Octanethiol was purified by fractional distillation, taking a central cut, b.p. 77° at 33 mm. Other thiols were used as received. *n*-Dodecanethiol (b.p. 146–148° at 15 mm.) was obtained from Matheson, Coleman and Bell Division, The Matheson Co., Inc.[10] The *n*-undecanethiol was furnished by G. S. Sasin and R. Sasin of Drexel Institute of Technology. Benzenethiol (b.p. 71° at 15 mm.) was from Evans Chemetics, Inc. The remaining thiols were Eastman Kodak Co. White Label organic chemicals except for 2-mercaptoethanol

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(10) Mention of company or trade names in this paper does not constitute recommendation by the U. S. Department of Agriculture over others not mentioned.

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and α-toluenethiol, which were Practical Grade. Peracetic acid (approximately 40%) in acetic acid was used as received.

Sulfides (Table I). 11-(*n*-Heptylthio)-undecanoic Acid (XIII).—The following reaction conditions are typical. 10-Undecenoic acid (45.6 g., 0.25 mole) and *n*-heptanethiol (33.3 g., 0.25 mole) were mixed in a quartz flask. No noticeable change occurred in 16 hr. The solution was then irradiated at a distance of 1 inch by a 140 watt ultraviolet lamp (high pressure quartz mercury arc). Within 3 minutes, a precipitate formed on the walls of the flask (internal temperature, 35°). After 1 hr., during which the temperature rose to 80°, the extent of reaction was checked by cooling the solution to room temperature. Since the mixture was only about one-fifth solid, it was irradiated for 2 more hr. The reaction product, which appeared entirely solid at room temperature, was crystallized three times at 4° from 600-ml. portions of petroleum ether, yielding 49 g. of XIII as transparent crystals, m.p. 53–54° (62% yield). All melting points were obtained with a micro hot-stage.

Ultraviolet irradiation was unnecessary in the addition of mercaptoethanol, which resembles mercaptoacetic acid in being an unusually reactive thiol.[2] Compound I was formed simply by stirring mercaptoethanol and 10-undecenoic acid for 1.5 hr. at 60°. The crude product was recrystallized three times from acetone–petroleum ether and once from acetonitrile (m.p. 69°). An additional recrystallization from carbon tetrachloride yielded the analytical sample, m.p. 70°.

In the preparation of V, 1% of lauroyl peroxide catalyst was substituted for ultraviolet irradiation, and the mixture was heated overnight at 60° (yield 61%). This reaction was the only one conducted under a nitrogen atmosphere.

Methyl-*n*-octyl-10-carboxydecylsulfonium Iodide (X).—A solution of VII (1.0 g., 0.003 mole) in methyl iodide (4.9 g., 0.035 mole) was sealed and left in the dark for 8 days. The resulting precipitate was washed with ether and dissolved in 5 ml. of methanol. Addition of 85 ml. of ether precipitated an oil that changed to a solid when rubbed with a glass rod. Filtration and drying gave 0.55 g. of X as a pale yellow solid, m.p. 68–70°.

Anal. Calcd. for $C_{20}H_{41}IO_2S$: I, 26.9; S, 6.79; neut. equiv., 473. Found: I, 27.1; S, 7.07; neut. equiv., 453.

***p*-Bromophenacyl 11-(*n*-Octylthio)-undecanoate.**—VII was converted to the *p*-bromophenacyl ester by the conventional procedure.[11] Recrystallization of the ester from ethanol gave white platelets, m.p. 73°.

Anal. Calcd. for $C_{27}H_{43}BrO_3S$: Br, 15.2; S, 6.08. Found: Br, 14.9; S, 5.71.

Di-*n*-butyl 11-(Carboxymethylthio)-undecanoate.—II was esterified with *n*-butyl alcohol by a published procedure,[2] giving an 84% yield of product, b.p. 138° at 0.003 mm.

Anal. Calcd. for $C_{21}H_{40}O_4S$: C, 64.9; H, 10.4; S, 8.25. Found: C, 65.0; H, 10.9; S, 8.09.

Di-(2-ethylhexyl) 11-(Carboxymethylthio)-undecanoate.—Esterification of II with 2-ethylhexyl alcohol gave a 58% yield of product, b.p. 168° at 0.0005 mm.

Anal. Calcd. for $C_{29}H_{56}O_4S$: C, 69.5; H, 11.3; S, 6.40. Found: C, 69.6; H, 11.5; S, 6.13.

Sulfoxides.—The (sulfinyl)-undecanoic acids (Table II) were prepared by dissolving or suspending the sulfide in glacial acetic acid acidified with hydrochloric acid and adding 0.5 *N* bromate–bromide solution dropwise.[6]

11-(*n*-Octylsulfinyl)-undecanoic Acid (VIII).—Crude VIII (m.p. 79–86°, neut. equiv. 345, yield 91%) was dissolved in boiling acetone–petroleum ether (4:1) and crystallized at 4° to yield analytically pure VIII as white platelets, m.p. 88°.

11-(Carboxymethylsulfinyl)-undecanoic Acid.—This sulfoxide was fairly soluble in aqueous acetic acid and was recovered in low yield. The best material was a white powder or needles, m.p. 91–92°.

11-(Phenylsulfinyl)-undecanoic Acid.—The crude product was purified by dissolving it in acetone and adding 5 volumes of petroleum ether. The resulting oil, when rubbed with a glass rod, gave a white powder, m.p. 60–61°, in 90% yield.

Sulfones. 11-(*n*-Heptylsulfonyl)-undecanoic Acid (XIV).—Most of the sulfones (Table II) were prepared by slight modifications of the following procedure. XIII (15.8 g., 0.05 mole) was suspended in 100 ml. of acetic acid. Peracetic acid (20 ml. of 40% acid, 0.12 mole) was added, with stirring, over a 15-minute period. The rate of addition was controlled so that the maximum temperature of the resulting solution was 70°. Little or no heat was evolved during the addition of the last 5 ml. of peracetic acid. A positive starch–iodide paper test for excess peracetic acid was obtained a few minutes after its addition was completed. As the solution cooled, a heavy precipitate formed; it was stirred with 400 ml. of water, filtered through a coarse fritted disk, washed with water and vacuum dried. The product, a microcrystalline solid, weighed 17.1 g. (yield 98%), neut. equiv. 346, m.p. 110–111°. One gram of this solid was recrystallized from 80 ml. of acetonitrile, yielding 0.45 g. of white needles of analytically pure XIV, m.p. 111–112°.

11-(2-Hydroxyethylsulfonyl)-undecanoic Acid (XV).—The gel-like original product was dissolved in ethyl acetate, and the solution was dried with sodium sulfate. Addition of petroleum ether precipitated XV as a white powder, m.p. *ca.* 94–96°.

11-(Carboxymethylsulfonyl)-undecanoic Acid.—The solid that precipitated from aqueous acetic acid was gelatinous. It was difficult to filter and dry, and it melted at 122–126°. Three recrystallizations from acetonitrile gave the analytical sample, a granular crystalline solid, m.p. 140–141°.

11-(Benzylsulfonyl)-undecanoic Acid.—Water was not added after the peracetic acid. Instead, the mixture was evaporated to constant weight in a vacuum desiccator containing excess sodium hydroxide and a dehydrating agent. The crude solid (m.p. 104–112°) was recrystallized from acetone–petroleum ether, forming a white powder, m.p. 126–127° (93% yield).

11-Sulfoundecanoic Acid (XVI).—After adding peracetic acid to the acetic acid solution of III, the reaction mixture was dried over sodium hydroxide under vacuum at 25°. The crude product, m.p. 59–62°, neut. equiv. 141, corresponded to 11-sulfodecanoic acid hemihydrate, m.p. *ca.* 65°, neut. equiv. 138.[4] An ether-insoluble fraction was separated and discarded; the ether-soluble acid was purified by recrystallization from ether–benzene. Vacuum desiccation at room temperature gave anhydrous XVI, m.p. *ca.* 94° (reported[4] *ca.* 99° and 95–99° by two other methods of preparation).

Acknowledgment.—The authors thank C. L. Ogg, Ruth B. Kelly and associates for the elementary analyses.

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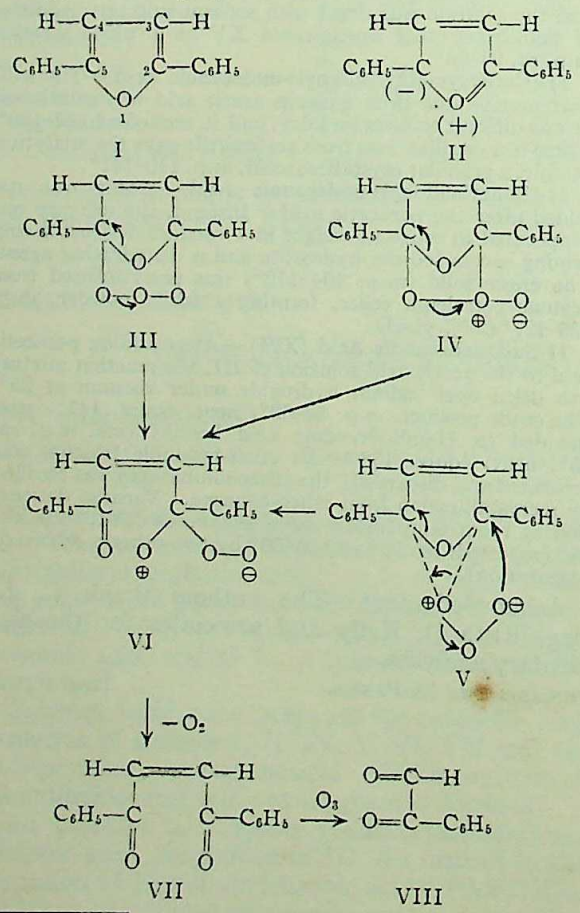
COMMUNICATIONS TO THE EDITOR

1,4-ADDITION OF OZONE TO FURANS AND PYRROLES

Sir:

Wibaut and co-workers[1,2] have obtained products from the ozonolyses of methylated pyrroles and furans which cannot be accounted for by cleavage of the double bonds in the normal structures of these substances. Similarly, we have obtained a 14% yield of phenylglyoxal (VIII) from ozonolysis of 2,5-diphenylfuran (I). The solvent was a methanol–acetone mixture, the temperature was −40°, two mole equivalents of ozone were absorbed, the peroxidic ozonolysis products were reduced with hydrogen over palladium catalyst and the other major product was benzoic acid (81% yield).

Wibaut and co-workers[1,2] have explained "abnormal" results such as these as being reactions of ionic structures such as II. It hardly seems likely, however, that ozone would polarize the molecule to, and attack, such an unstable structure as II, especially since the reactive positions of the furan and pyrrole ring systems are 2 and 5.[3] We have felt that the "abnormal" reactions are the result of the 1,4-addition of ozone. We wish now to report confirmatory evidence for this.



When the ozonolysis just described was stopped after the absorption of one mole equivalent of ozone and the reaction mixture was partially evaporated, a 12% yield of *cis*-1,2-dibenzoylethylene (VII) precipitated (m.p. 130–135°, identification by a mixture melting point with an authentic sample[4]). Similar results were obtained using a mixture of ozone and nitrogen instead of ozone and oxygen, showing definitely that the reaction is one of ozone and not of oxygen.

This material cannot arise from ozonolysis of II. The furan ring has been cleaved but the 3,4 bond is still intact. The *cis* configuration, which is that of the labile isomer,[5] proves that the double bond at the 3 and 4 positions was formed before the ring was cleaved. This can occur only by a 1,4-addition of ozone to the conjugated system of the furan. Any one of structures III, IV or V could have been the intermediate.

We believe a similar mechanism holds true for the reactions of Wibaut and co-workers.[1,2] Further, we believe ozone will attack the ends of other conjugated systems, if the ends are spatially close together. We have found previously that this holds true with anthracene.[6]

We wish to thank the University of Texas Research Institute and the Research Corporation for grants which made this work possible.

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Henry O. Colomb, Jr.

Received June 25, 1957

ISOLATION AND BEHAVIOR OF *spiro*[2,5]OCTA-1,4-DIENE-3-ONE

Sir:

Recently[1] spectroscopic evidence was reported for the formation of *spiro*[2,5]octa-1,4-diene-3-one (III) as a transient intermediate in solvolytic reactions of 2-*p*-hydroxyphenyl-1-ethyl bromide (I). We now report the successful isolation of this interesting reactive molecular species.

Passage of an ethereal solution of 2-*p*-hydroxyphenyl-1-ethyl bromide (I) through a column of a basic alumina[2] gives a *ca.* 10^{-3} *M* solution of *spiro*[2,5]-octa-1,4-diene-3-one (III) free from phenolic species.

If carefully treated glassware is employed, so as to ensure a dry neutral glass surface, ether solutions of this species can be evaporated at reduced pressure to give a crystalline solid, soluble in most

(1) S. Winstein and R. Baird, This Journal, **79**, 756 (1957).

(2) J. Castells and G. A. Fletcher, *J. Chem. Soc.*, 3245 (1956).

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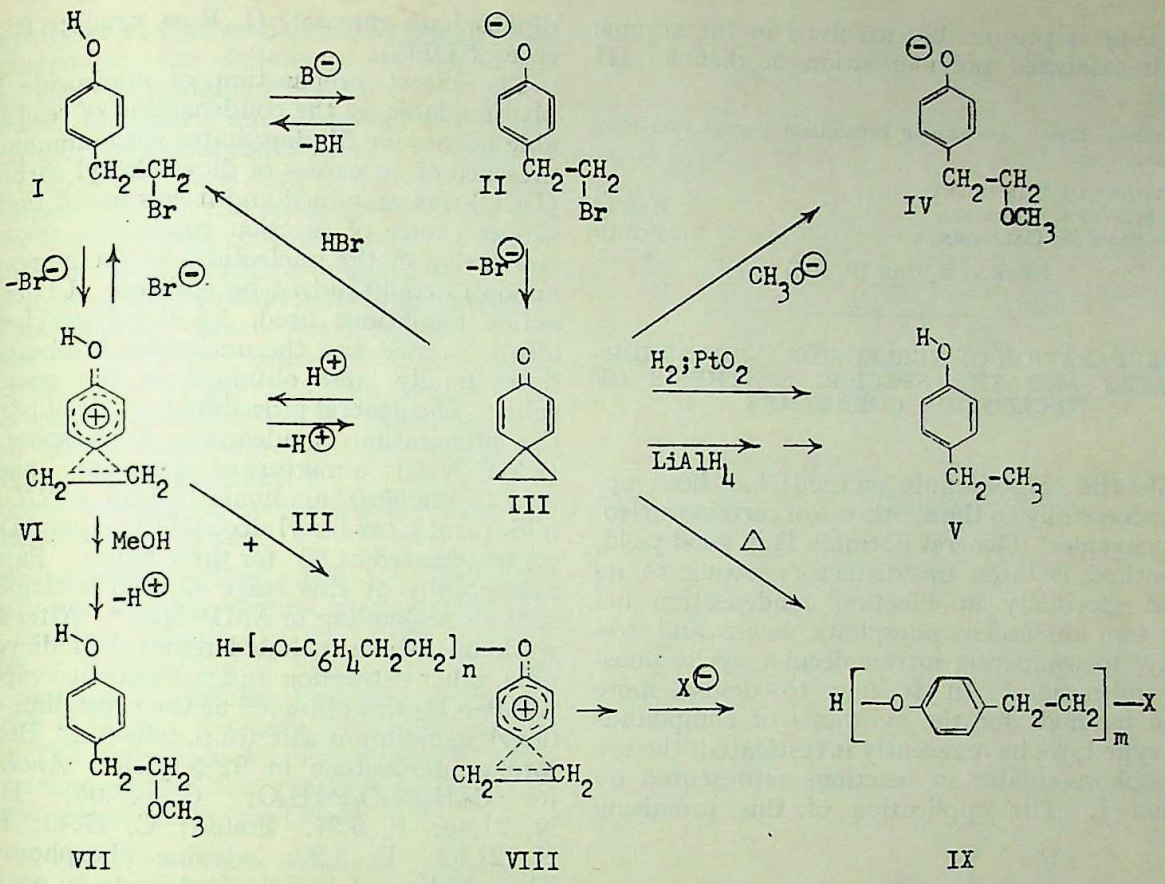

common solvents. Recrystallization from ether–pentane at low temperatures gives crystals, m.p. 43–46°, with the correct carbon–hydrogen analysis for dienone III, and which show strong absorption maxima for a highly conjugated carbonyl in the infrared at 1650 cm.$^{-1}$ in carbon disulfide and at 1640 cm.$^{-1}$ in chloroform. In the ultraviolet strong maxima are observed at 261 mμ in ether, 271 mμ in *t*-butyl alcohol, 274 mμ in methanol and *ca.* 282 mμ in water, the maxima in methanol and *t*-butyl alcohol being identical with those obtained previously.[1]

The dienone III at low concentrations reacts with a variety of reagents to open the 3-ring and restore the phenolic system. Reduction of the dienone III with lithium aluminum hydride or by catalytic hydrogenation gives *p*-ethylphenol (V) in good yield.

Solvolytic opening of the 3-ring occurs under basic, neutral and acidic conditions, a few spectroscopically measured rate constants being summarized in Table I. The rate of disappearance in methanol with added methoxide is within one per-

TABLE I

FIRST ORDER RATE CONSTANTS FOR SOLVOLYTIC CLEAVAGE OF DIENONE III AT 25°

Solvent	Added solute	10^4k (sec.$^{-1}$)
HOH	...	34.2
MeOH	...	3.87
MeOH	0.01 *N* NaOMe	9.14
MeOH	10^{-5} *N* $HClO_4$	>700

cent. of that reported previously[1] for the transient intermediate observed spectroscopically.

The opening of the dienone III is especially sensitive to acid catalysis, the half-life of III at 25° in 10^{-5} *M* methanolic perchloric acid being less than ten seconds. Under these conditions, and at least partly under neutral conditions, the solvolysis presumably involves the bridged-ion VI, also an intermediate in the solvolysis of suitable 2-*p*-hydroxyphenyl-1-ethyl derivatives.

The ion VI is attacked not only by solvent species, but by other nucleophiles such as bromide ion. Thus, treatment of the dienone III with excess ethereal hydrogen bromide gives rise to the parent bromoethylphenol I, m.p. and mixed m.p. with authentic I, 89–91.5°.

Although ether solutions of dienone III as concentrated as 5×10^{-3} *M* can be kept for about a week, the solid seldom is stable for more than 20 to 30 minutes, probably due to the presence of traces of stray catalysts. On standing, or more rapidly on warming above its m.p., dienone III is converted to a material melting in the range 160–200°, which is insoluble in the common solvents. The infrared spectrum (KBr), quite different from that of dienone III, resembles that of 2-*p*-anisylethyl bromide, especially with respect to the aromatic substitution patterns and the strong aromatic ether absorption band at 1235 cm.$^{-1}$. These data, along with carbon–hydrogen analyses, suggest the polymeric ether structure IX.

With respect to ionic mechanisms for polymerization of dienone III, different processes may be visualized which involve either attack of a growing aryloxide ion on dienone III, or attack of dienone III on a growing cation of the type of VIII. The

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latter type is presumably involved in the stannic chloride-catalyzed polymerization of dienone III in ether.

(3) National Science Foundation Predoctoral Fellow, 1953–1955, 1956–1957.

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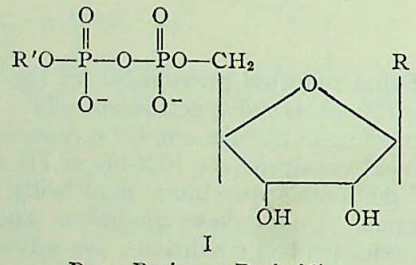
R. BAIRD[3]
S. WINSTEIN

RECEIVED JUNE 19, 1957

THE PREPARATION OF NUCLEOSIDE 5′-PHOSPHORAMIDATES AND THE SPECIFIC SYNTHESIS OF NUCLEOTIDE COENZYMES

Sir:

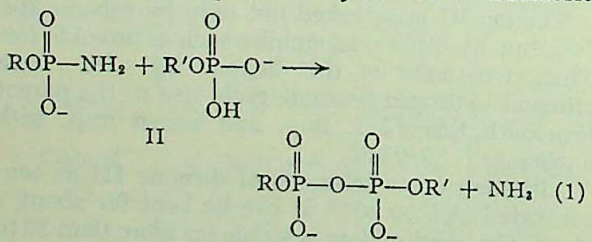
While the carbodiimide method[1] has been applied successfully to the syntheses of certain nucleotide coenzymes[2] (General Formula I) in good yield, the method is often unsatisfactory owing to its lack of specificity in effecting condensation between two dissimilar phosphate esters and frequently, to competing intramolecular cyclic phosphate formation.[3] In seeking to devise more specific methods for the synthesis of compounds of the type I, we have recently investigated[4] the use of phosphoramidates in reactions represented by equation 1. The application of this promising



I

R = Purine or Pyrimidine
R′ = Sugar, etc.

approach to the practical synthesis of nucleoside



R = nucleoside
R′ = H, sugar, etc.

pyrophosphate derivatives (I) was limited, however, by the relative inaccessibility of the key intermediates, nucleoside 5′-phosphoramidates[4] (II) and more direct methods for the preparation of these derivatives were, therefore, sought. In the present communication we outline a convenient one-step preparation of these compounds and record their use in highly improved syntheses of the unsymmetrical pyrophosphates, adenosine 5′-diphosphate (I, R = adenine; R′ = H; ADP) and uridine diphosphate glucose[5,6] (I, R = uracil; R′ = glucose; UDPG).

The direct preparation of nucleoside 5′-phosphoramidates by the condensation of readily available nucleoside 5′-phosphates with ammonia in the presence of an excess of dicyclohexyl carbodiimide (DCC) was examined and it was found that by the proper choice of reaction conditions, quantitative conversion of the nucleotides to the corresponding amidates could indeed be realized. Under the reaction conditions used, 1,3-dicyclohexylguanidine also is formed and the nucleoside 5′-phosphoramidates finally were obtained as the guanidinium salts. The general procedure may be illustrated by the preparation of adenosine 5′-phosphoramidate (AMP–NH_2): a mixture of adenosine 5′-phosphoric acid (3 mmoles), ammonia (7.5 ml. of 2*N*), formamide (5 ml.), *tert*-butyl alcohol (18 ml.) and DCC (3.0 g.) was heated at 80° for three hours. Paper chromatography at this stage showed a single strong spot corresponding to AMP–NH_2.[4] After a simple work up, which included removal of dicyclohexyl urea, ether extraction and subsequent evaporation, AMP–NH_2 was obtained as the crystalline dicyclohexylguanidinium salt (m.p. 240–241°, dec.) from formamide–acetone in 92% yield. *Anal.* Calcd. for $C_{23}H_{40}N_9O_6P\cdot 1H_2O$: C, 47.05; H, 7.21; N, 21.46; P, 5.27. Found: C, 47.46; H, 6.98; N, 21.92; P, 5.20; adenine phosphorus, 1.02. The addition of lithium hydroxide to an aqueous solution of the salt liberated the theoretical amount of free dicyclohexylguanidine (m.p. 181–182°; reported m.p. 182°).[7] Acidification of the above salt with hydrochloric acid liberated dicyclohexyl guanidinium hydrochloride; m.p. 296–297°, dec.

By the same procedure we have prepared the dicyclohexylguanidinium salts of the amidates derived from uridine 5′-phosphoric acid (75%) and monophenylphosphoric acid (68%).

In the previously reported experiments[4] on the synthesis of pyrophosphates from the phosphoramidic acids, formamide solutions of the free acids were used. In the present work, AMP–NH_2 reacted with orthophosphoric acid in *o*-chlorophenol to give 60% yield of ADP, which is easily separated from the other products of the reaction, AMP and orthophosphate, by ion exchange chromatography.[8] This new procedure should lead to more satisfactory syntheses of all the nucleoside 5′-diphosphates.[9] For the synthesis of the nucleoside pyrophosphate esters, it has now been found that pyridine solutions may be employed. In model experiments, dicyclohexylguanidium salts of uridine 5′- and adenosine 5′-phosphoramidates reacted in anhydrous pyridine with monophenylphosphoric acid to give, respectively, 87 and 70% yields of the corresponding pyrophosphates (I, R = uracil or adenine; R′ = phenyl). The application of this technique

(1) H. G. Khorana, THIS JOURNAL, **76**, 3517 (1954).
(2) E. P. Kennedy, *J. Biol. Chem.*, **222**, 185 (1956).
(3) H. G. Khorana, G. M. Tener, R. S. Wright and J. G. Moffatt, THIS JOURNAL, **79**, 430 (1957).
(4) R. W. Chambers and H. G. Khorana, *Chemistry and Industry*, 1022 (1956).
(5) R. Caputto, L. F. Leloir, C. E. Cardini and A. C. Paladini, *J. Biol. Chem.*, **184**, 333 (1950).
(6) For earlier syntheses of this substance see: (a) G. W. Kenner, A. R. Todd and R. F. Webb, *J. Chem. Soc.*, 2843 (1954); (b) A. M. Michelson and A. R. Todd, *ibid.*, 3459 (1956).
(7) U. S. Patent, *Chem. Abs.*, **37**, 540 (1953).
(8) In a recent paper, Clark, *et al.*, describe the use of monobenzylphosphoramidic acid in the synthesis of ADP and ATP: V. M. Clark, G. W. Kirby and A. R. Todd, *J. Chem. Soc.*, 1497 (1957).
(9) Syntheses in the uridine and cytidine series are in progress

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to the synthesis of true nucleotide coenzymes was demonstrated by the following preparation of UDPG. Dicyclohexylguanidiniumuridine 5′-phosphoramidate (1 equiv.) and tri-*n*-octylammonium hydrogen glucose-1-phosphate[6] (4 equiv.) were allowed to react for three days in dry pyridine at room temperature and the products were then separated by ion exchange chromatography. UDPG was the major ultraviolet absorbing product (66%) and was isolated readily as the amorphous dilithium salt. This material, which was homogeneous by paper and ion exchange chromatography, had uridine to phosphorus to glucose ratios of 1:1.95:1.01 and was enzymatically active.[10] Its behavior to acid and alkali paralleled that reported for the naturally occurring substance.[11]

This work is being extended to the synthesis of other nucleotide coenzymes.

Acknowledgments.—The work at New York University was aided by grants from the National Cancer Institute (Grant C-2784) of the National Institutes of Health, United States Public Health Service, and the Rockefeller Foundation; that at the British Columbia Research Council by a grant from the Life Insurance Medical Research Fund. R.W.C. acknowledges the generous support and encouragement of Dr. Severo Ochoa.

(10) H. M. Kalckar, "Methods in Enzymology," Vol. II, p. 676. Academic Press, Inc., New York, N. Y., 1955.
(11) A. C. Paladini and L. F. Leloir, *Biochem. J.*, **51**, 426 (1952).

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Received June 5, 1957

THE STABILITY OF POTASSIUM BOROHYDRIDE IN ALKALINE SOLUTIONS[1]

Sir:

In connection with an undergraduate research program to investigate some properties of KBH_4, it became necessary to determine its stability toward hydrolysis in alkaline solutions. It is generally stated in the literature that aqueous borohydride solutions are stable at a *p*H greater than 9,[2] but quantitative data on this point are meager. Pecsok[3] has presented a study on the hydrolysis of $NaBH_4$ solutions buffered at various *p*H values between 7.7 and 9.5. Jensen[4] has determined the stability of $NaBH_4$ in solutions buffered at *p*H 9.6 and 10.1 and of $NaBH_4$ dissolved in 1.00, 0.25 and 0.10 *N* sodium hydroxide.

Experimental.—0.10 *M* solutions of KBH_4 were prepared by dissolving the commercially available material[5] in a saturated $Ca(OH)_2$ solution[6] and placed in a water-bath thermostated at 25.0 ± 0.1°. At intervals of time, aliquot portions were analyzed for borohydride content by determining the volume of hydrogen liberated upon acidification.

Results and Discussion.[7]—A plot of the logarithm of borohydride content *vs.* time proved to be linear, indicating that the hydrolysis is first order with respect to borohydride at a constant *p*H. Likewise, it can be shown that Jensen's data fit the relation

$$-d(BH_4^-)/dt = k'(BH_4^-) \qquad (1)$$

where k' is a function of *p*H.

The relation between log k' and *p*H is shown in Fig. 1, indicating that the reaction is also first order in hydronium ion. The results shown in Fig. 1 support Pecsok's conclusion that the rate of hydrolysis of borohydride solutions is controlled by the formation of $HBH_4{\cdot}xH_2O$. This intermediate hydrolyzes immediately to an aquated borine radical which also hydrolyzes rapidly. It would appear from Fig. 1 that the rate of hydrolysis of the BH_4^- ion at any given *p*H is independent of the presence of Na^+, K^+, or Ca^{++} cations.

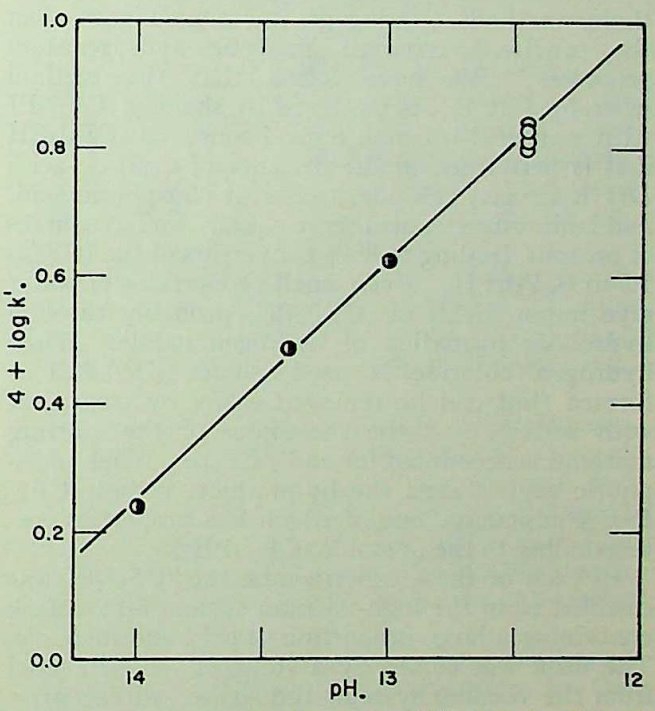

Fig. 1.—Rate constant of equation (1) as a function of *p*H: ○, KBH_4 in $Ca(OH)_2$ solutions at 25°; ◑, $NaBH_4$ in NaOH solutions at 24°.

Extrapolation of the line of Fig. 1 to lower *p*H values does not fit the data of Jensen or of Pecsok for the hydrolytic stability of the borohydride ion in buffered solutions. Nor do Jensen's data with the borate buffer lie on the same line as do Pecsok's

(1) This investigation was supported by a grant from the Denison University Research Foundation.
(2) H. I. Schlesinger, *et al.*, This Journal, **75**, 215 (1953); H. R. Hoekstra, A.E.C.D. 2144 (June 1947).
(3) R. L. Pecsok, This Journal, **75**, 2862 (1953).
(4) E. H. Jensen, "A Study on Sodium Borohydride with Special Reference to its Analytical Application in Organic Chemistry," Nyt Fordisk Forlag, Arnold Busch, Copenhagen, 1954, pp. 38–48.
(5) Metal Hydrides, Inc., Beverly, Mass., Lot No. K-12, Purity 97+%.
(6) Saturated $Ca(OH)_2$ at 25° has a *p*H of 12.45 and has been recommended as a buffer solution for defining the National Bureau of Standards standard *p*H scale; R. G. Bates, V. E. Bower and E. R. Smith, *J. Research Natl. Bur. Standards*, **56**, 305 (1956).
(7) More complete details will soon be published in *J. Sci. Labs.*, *Denison Univ.*

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data for pyrophosphate buffer. This would indicate that the rate of hydrolysis is influenced by the presence of different anions, which is contrary to the conclusion of Hoekstra[2] that, in the *p*H range below 9, the hydrolysis is independent of the type of buffer system used.

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JOHN B. BROWN
MARGUERITE SVENSSON

A NEW SYNTHESIS OF BIS-TRIFLUOROMETHYL-PHOSPHINE, $(CF_3)_2PH$[1]

Sir:

Compounds of the type $(R_F)_2PH$ are important enough to the development of fluorocarbon–phosphorus chemistry to warrant a search for new synthetic methods offering greater convenience than the previously-reported catalytic hydrogenation processes.[2] We have found that the method whereby $P_2(CF_3)_4$ is produced by shaking $(CF_3)_2PI$ with mercury[3] becomes a good source of $(CF_3)_2PH$ if it is performed in the presence of a protic acid. Dry hydrogen chloride, technical phosphoric acid, and trifluoroacetic acid serve equally well as sources of protons, leading to 35% conversion of the $(CF_3)_2PI$ to $(CF_3)_2PH$. Even small proportions of water give minor yields of $(CF_3)_2PH$, probably through hydrolytic formation of hydrogen iodide. When hydrogen chloride is used, some $(CF_3)_2PCl$ is formed (but can be removed easily by treatment with water), and the remainder of the starting material is accounted for as $P_2(CF_3)_4$. When phosphoric acid is used the by-products include CF_3–P–O compounds, one of which has properties corresponding to the unstable $(CF_3)_2PHO$.

In each of these experiments, the $(CF_3)_2PI$ was distilled from the high-vacuum system into a flask containing a large proportion of acid and mercury. The flask was closed by a stopcock, disconnected from the vacuum system, and shaken while warming to room temperature, and for 15 minutes thereafter. The volatile products were brought into the vacuum system and separated by distillation methods. The $(CF_3)_2PH$ was identified by observation of a 760 mm. vapor tension at 2° (literature b.p. 1°) and a molecular-weight value of 170 (calcd., 170.00). The F^{19} nuclear magnetic resonance spectrum (obtained with the aid of Dr. Harden McConnell and Philip Bromberg at the California Institute of Technology) showed spin–spin interactions with one P^{31} and one H^1 nucleus to give a pair of doublets. The proton magnetic spectrum consisted of two groups of seven lines due to spin–spin splitting of one phosphorus nucleus and six equivalent fluorine nuclei. Quantitative data on the splittings and chemical shifts will be published elsewhere.

An insight into the course of the $(CF_3)_2PI$–Hg–acid reaction was obtained from an experiment in which 0.50 mmole of $(CF_3)_2PI$ was first shaken with mercury alone to give a 95% yield of $P_2(CF_3)_4$. Then the non-volatile residue was treated with dry hydrogen chloride, producing an amount of $(CF_3)_2PH$ which would account for the missing 5% of the original $(CF_3)_2P$ groups. Thus it would appear that a phosphorus–mercury bond had been established, possibly as $(CF_3)_2PHg_2I$, from which one could get either $(CF_3)_2PH$ by the action of acid or $P_2(CF_3)_4$ by further action of $(CF_3)_2PI$. It is proposed that a wide variety of new materials containing the $(CF_3)_2P$ group might be made by shaking $(CF_3)_2PI$ with mercury in the presence of halides of polyvalent metals or non-metals.

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RECEIVED JULY 1, 1957

(1) This research was supported by the United States Air Force under Contract AF 33(616)-2743, monitored by the Materials Laboratory, Wright Air Development Center, Wright–Patterson Air Force Base, Ohio.

(2) F. W. Bennett, H. J. Emeléus and R. N. Haszeldine, *J. Chem. Soc.*, 3896 (1954).

(3) F. W. Bennett, H. J. Emeléus and R. N. Haszeldine, *ibid.*, 1565 (1953).

IDENTIFICATION OF RUTHENIUM SPECIES IN AQUEOUS SOLUTION

Sir:

We have used an ion-exchange technique for identifying aqueous ruthenium species. The method promises to be very useful in studies of this element where solutions usually contain a mixture of complex ions and polymers which do not equilibrate rapidly. The method will be applicable to other systems with similar characteristics.

Two experiments are performed: the first measures the ionic charge per ruthenium atom, *a*, while the second gives the net ionic charge of the species, *b*. The ratio *b*/*a* equals the number of ruthenium atoms per species, *i.e.*, the degree of polymerization. Using the oxidation number, the number of negatively charged groups in the complex can be inferred. If only one complexing anion is present, the stoichiometric formula of the species is fixed.

The charge per ruthenium atom is determined from the equivalents of charge with an ion-exchange resin per gram atom of ruthenium. It was convenient to use a column technique[1] because separation and concentration of the ruthenium species could be achieved simultaneously. A dilute solution of ruthenium species, primarily in the +3 oxidation state, was stirred with Dowex 50, 200–400 mesh resin in the hydrogen ion form until most of the ruthenium was taken up by the resin. This resin was added to the top of a tapered column already containing approximately one tenth as much resin in the hydrogen ion form. The column was eluted slowly with a dilute cerous perchlorate–perchloric acid solution. The cerous ion displaced most of the ruthenium species, which formed nearly pure bands as they descended. Several samples of a particular band were collected, analyzed for total ruthenium and hydrogen ion, and the spectra checked as an indication of purity. The value of *a* is equal to the molarity of hydrogen ion plus 3 times that of cerous ion in the elutriant, minus the molarity of hydrogen ion in the eluted

(1) Similar in principle to that of D. A. Everest and J. E. Salmon, *J. Chem. Soc.*, 1442 (1955).

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ruthenium solution, all divided by the gram atoms of ruthenium per liter in the eluted solution.

The charge per species is found from the concentration dependence of the exchange of ruthenium with a known ion—in our case hydrogen ion

$$Ru_{b/a}X^{+b} + bH^{+}_{R} = Ru_{b/a}X^{+b}_{R} + bH^{+}$$

$$Q = \frac{[RU_{b/a}X^{+b}]_R\,[H^+]^b}{[Ru_{b/a}X^{+b}]\,[H^+]^b_R}$$

where X denotes anions in the ruthenium species, R designates the resin phase and concentrations are indicated by brackets. The ratio of ruthenium concentrations is proportional to the ratio of hydrogen ion concentrations to the $-b$ power. From two equilibrations at different hydrogen ion concentrations b may be calculated. Conditions were chosen such that the great majority of the resin was in the hydrogen ion form and most of the ruthenium was present in the resin phase. There is an unpredictable change in activity coefficients in the aqueous phase but the method is believed to be sufficiently accurate in most cases because b must be an integer as well as a multiple of a.

It can be shown that any changes in hydrolysis on exchange do not affect the results.

This method has been used to establish the formulas of the species Ru^{+3} and $RuCl^{+2}$.

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HOWARD H. CADY
ROBERT E. CONNICK

RECEIVED JULY 10, 1957

SEMI-QUANTITATIVE GAS CHROMATOGRAPHY

Sir:

We have found relationship (1) reasonably accurate in relating the fraction by weight of a component in a mixture to the corresponding area in a liquid–vapor chromatogram obtained using helium as the carrier gas and a tungsten wire thermal conductivity gage as detector

$$\left(\frac{m_i}{W}\right) = \frac{A_i\sqrt{M_i}}{\sum_i A_i\sqrt{M_i}} \qquad (1)$$

where (m_i/W) is the fraction by weight of the ith component, A_i the planimeter-determined area under the peak on the chromatogram corresponding to the ith component and M_i the molecular weight of the ith component.

Clearly the equation may be applied only to mixtures which are completely resolved and such that all components appear in the chromatogram.

Component	Known mole %	Known wt. %	Found area %	Calcd. wt. %
Ethanol	43.4	45.4	47.3	44.6
Water	46.6	19.1	31.1	18.3
1,8-Cineole	10.0	35.5	21.5	37.1

The equation has been applied with comparable results to chromatograms of several mixtures: α and β-pinene plus ethanol; α and β-pinene plus benzene; methyl ethyl ketone, n-propyl alcohol and p-xylene.

Although the expression was arrived at empirically, the appearance of the square root function is not unreasonable on the basis of kinetic theory. Further, it is apparent that the expression may be utilized to determine the molecular weight of a component from the chromatogram of a mixture of known weight composition of the material of unknown molecular weight with a known substance. Although the square root function through its leverage places a premium on accurate determination of the areas on the chromatogram, we have had some success in this utilization of the relationship.

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RICHARD H. EASTMAN

RECEIVED JUNE 7, 1957

TETRAACETYL DIBORATE AND SO-CALLED "BORON ACETATE"

Sir:

There has been considerable confusion in the literature over the constitution of the product obtained by the reaction between orthoboric acid and acetic anhydride. Two types of compounds have been reported at various times. One, said to melt around 121°, has been called boron triacetate, $(CH_3CO_2)_3B$,[1,2,3] and the other, m.p. 150–152°, pyroboron acetate, $(CH_3CO_2)_2BOB(O_2CCH_3)$.[4,5,6] Both have been supported by analytical data but, in several cases, the authors used identical procedures only to obtain different products.

We have repeated some of the previous preparations, our results agreeing with those of Gerrard and Wheelans[6]; no evidence was obtained for boron triacetate, although the methods described for its preparation[1,2] were carefully followed. The analytical data for $(CH_3CO_2)_2BOB(O_2CCH_3)_2$ were improved and extended and the name *tetraacetyl diborate* is proposed.

The reaction between orthoboric acid and acetic anhydride was found to occur according to the equation

$$2H_3BO_3 + 5(CH_3CO_2)_2O \longrightarrow (CH_3CO_2)_2BOB(O_2CCH_3)_2 + 6CH_3CO_2H$$

Orthoboric acid (0.534 mole) and acetic anhydride (1.96 mole) were heated together at 50–100° with vigorous stirring in a nitrogen atmosphere until all the solid had dissolved. On cooling, the product crystallized as colorless needles. One sample was purified by recrystallization from a benzene–chloroform mixture, another by precipitation from solution in dry acetic acid by the addition of ether. Both melted at 147–148°.

All filtrations were carried out using a pressure of dry nitrogen and the products were dried in vacuum at room temperature before being transferred to a dry box for subsequent handling.

The acetate content was determined by titration with standard base, the end-point (around pH 6.7)

(1) A. Pictet and A. Geleznoff, *Ber.*, **36**, 2219 (1903).
(2) H. Cook, L. Ilett, B. Saunders and G. Stacey, *J. Chem. Soc.*, 3125 (1950).
(3) T. Ahmad and M. Khundkar, *Chem. and Ind.*, 248 (1954).
(4) O. Dimroth, *Ann.*, **446**, 97 (1925).
(5) H. Meerwein and H. Maier-Hüser, *J. prakt. Chem.*, **134**, 51 (1932).
(6) W. Gerrard and M. Wheelans, *Chem. and Ind.*, 758 (1954).

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being detected with a Beckmann *p*H meter. Boron was estimated, using the same solution, by further titration with base in the presence of excess mannitol to the phenolphthalein end-point. Analysis with the Karl Fischer reagent under anhydrous conditions caused the reaction

$$(CH_3CO_2)_2BOB(O_2CCH_3)_2 + 2MeOH \longrightarrow H_2O + 2(CH_3CO_2)_2BOMe$$

to be driven to the right, the reagent quantitatively removing the water.[7] The "hydroxyl equivalent" was calculated as mg. water/g. of sample. This reaction afforded unequivocal proof of the nature of the product, because boron triacetate could not react at all with the Karl Fischer reagent. The molecular weight measurement was carried out ebullioscopically in dry chloroform, the concentrations of the solutions being given in g. of sample per 1000 g. of solvent in parentheses after each value.

EXPERIMENTAL VALUES

Sample crystallized from	M.p., °C.	% CH_3CO_2	% B	Hydroxyl equiv. mg. H_2O/g.	CH_3CO_2/B ratio
Chloroform–benzene	147–148	85.0	7.86	67.2	1.98
		85.6	7.96	67.9	1.97
Acetic acid–ether	147–148	85.6	7.67	...	1.99

Molecular weight of sample crystallized from chloroform–benzene: 345 (1.30), 302 (3.30), 312 (5.51), 302 (9.40)

CALCULATED VALUES

Compound	Mol. Wt.	% CH_3CO_2	% B	Hydroxyl equiv. mg. H_2O	CH_3CO_2/B ratio
$(CH_3CO_2)_2BOB(O_2CCH_3)_2$	273.6	86.3	7.90	65.9	2
$(CH_3CO_2)_2BOH$	145.9	81.0	7.42	123.4	2
$(CH_3CO_2)_3B$	187.9	94.2	5.76	0	3

These data clearly establish the product of the reaction to be $(CH_3CO_2)_2BOB(O_2CCH_3)_2$, tetraacetyl diborate.

X-Ray powder diffraction patterns were taken with copper K_α radiation (nickel filter).

X-RAY POWDER DIFFRACTION DATA FOR TETRAACETYL DIBORATE

d	*I*	*d*	*I*	*d*	*I*
7.37	M	3.59	W	2.39	W
6.28	MS	3.46	VW	2.28	VW
5.55	MS	3.32	VW	2.19	VW
4.72	VW	3.11	VW	2.12	VW
4.41	W	2.94	VW	1.94	VW
4.11	W	2.74	VW	1.83	W
3.78	VS	2.51	M		

A sample of the tetraacetyl diborate was heated in acetic anhydride in an attempt to cause further acetylation, the product being precipitated by the addition of ether, m.p. 120–140°. Analysis showed that slight decomposition with decrease in acetate content occurred under these conditions, analogously to Dimroth's observation[4] that tetraacetyl diborate lost acetic anhydride on heating. However, an X-ray powder photograph was identical with the one we obtained for tetraacetyl diborate.

A further experiment in which we followed as closely as possible the method of Cook, *et al.*,[2] yielded a crystalline product, m.p. 149–150° (Cook gave m.p. 120°). This checks very well with the melting point of tetraacetyl diborate.

From the above evidence, we reach a conclusion similar to that of Gerrard and Wheelans.[6] Although it may be possible to prepare boron triacetate, our experience confirms the existence of only tetraacetyl diborate.

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RECEIVED JUNE 11, 1957

(7) H. C. Mattraw, C. E. Erickson and A. W. Laubengayer, THIS JOURNAL, 78, 4901 (1956).

REACTIONS OF GASEOUS IONS. III. FORMATION OF PROTONATED METHANE

Sir:

Recent publications[1,2,3,4] have reported the formation of CH_5^+ (or CD_5^+) in a bimolecular reaction between CH_4^+ (or CD_4^+) ions and CH_4 (or CD_4) molecules taking place in the ionization chamber of a mass spectrometer. However, the formation of protonated methane by reactions involving methane ions and molecules other than methane has not been reported.

We have observed the formation of CD_4H^+ in mixtures of CD_4 with other hydrogen-containing substances. The formation of CD_4H^+ is first-order in CD_4^+ and first-order in the hydrogen-containing substance and appearance potential measurements of CD_4H^+ more closely correspond to the ionization potential of CD_4 than to any other possible ionic species in the system. We thus write for the formation of CD_4H^+

$$CD_4^+ + XH \longrightarrow CD_4H^+ + X \qquad (1)$$

We have calculated rate constants relative to the rate constant taking XH = CH_4 for several such reactions by the relationship

$$\frac{k_{XH}}{k_{CH_4}} = \frac{[CH_4]}{[XH]} \frac{\left(\frac{I_{CD_4H^+}}{I_{CD_4^+} + I_{CD_4H^+}}\right)_{XH}}{\left(\frac{I_{CD_4H^+}}{I_{CD_4^+} + I_{CD_4H^+}}\right)_{CH_4}} \qquad (2)$$

where the *I*'s are the observed ion-currents and $[CH_4]$ and [XH] are the ionization chamber gas concentrations. We assumed that the ratio of ionization chamber concentrations was equal to the ratio of gas reservoir partial pressures, an assumption well within experimental error. The values obtained (averages of replicate measurements) are shown in Table I.

Within experimental error the appearance potential of CD_4H^+ coincides with the ionization potential of CD_4. If we assume that (1) cannot be endothermic (any exponential term involving significant activation energy would so decrease the

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Table I

Relative Rates of Formation of CD_4H^+

Reaction	k_{XH}/k_{CH_4}
$CD_4^+ + CH_4 \longrightarrow CD_4H^+ + CH_3$	1.00
$CD_4^+ + C_2H_6 \longrightarrow CD_4H^+ + C_2H_5$	0.11
$CD_4^+ + C_3H_8 \longrightarrow CD_4H^+ + C_3H_7$	.05$_6$
$CD_4^+ + \text{iso-}C_4H_{10} \longrightarrow CD_4H^+ + C_4H_9$	.04$_6$
$CD_4^+ + CH_3Cl \longrightarrow CD_4H^+ + CH_2Cl$	.04$_1$
$CD_4^+ + NH_3 \longrightarrow CD_4H^+ + NH_2$	.08$_3$
$CD_4^+ + H_2S \longrightarrow CD_4H^+ + HS$	.17
$CD_4^+ + HCl \longrightarrow CD_4H^+ + Cl$	.56

probability of a reactive collision that we could not observe the reaction), then the energetics of the reactions that do take place (Table I) lead us to the conclusion that the heat of formation of CD_4H^+ is $\Delta H_f \leq 234$ kcal/mole. On the other hand, we have not been able to find any evidence of CD_4H^+ formation in CD_4–H_2O and CD_4–H_2 mixtures. If these reactions are not observable for energetic reasons, one calculates the heat of formation of CD_4H^+ to be $\Delta H_f \geq 218$ and $\Delta H_f \geq 233$ kcal./mole, respectively. Thus, the implied value for the heat of formation of CD_4H^+ is 233–234 kcal./mole, and if this is correct, then the proton affinity of methane is 113 kcal/mole.

Although we have made no rate measurements, we have observed in the systems studied reactions (3), (4) and (5), which we believe have not been reported as yet

$$H_2S^+ + H_2S \longrightarrow H_3S^+ + HS \quad (3)$$

$$H_2S^+ + CD_4 \longrightarrow H_2DS^+ + CD_3 \quad (4)$$

$$HCl^+ + CD_4 \longrightarrow HDCl^+ + CD_3 \quad (5)$$

Relative rate measurements have indicated that (5) has about the same rate as the reaction between CD_4^+ and HCl shown in Table I.

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THE REACTION OF TRIARYL PHOSPHITES WITH SULFONYL CHLORIDES

Sir:

Gilbert and McGough[1] reported that trialkyl phosphites react with sulfonyl chlorides to yield a mixture of the trialkyl phosphate, O,O-dialkyl-S-substituted thiophosphate and an alkyl chloride

$$3(RO)_3P + R'SO_2Cl \longrightarrow 2(RO)_3PO + (RO)_2P(O)SR' + RCl$$

This reaction has been confirmed recently by Hoffmann and his co-workers.[2] It is most likely that the reaction proceeds in three consecutive stages—the first two involving oxygen transfer

$$(RO)_3P + R'SO_2Cl \longrightarrow (RO)_3PO + R'SOCl \quad (1)$$

$$(RO)_3P + R'SOCl \longrightarrow (RO)_3PO + R'SCl \quad (2)$$

$$(RO)_3P + R'SCl \longrightarrow (RO)_2P(O)SR' + RCl \quad (3)$$

Reaction 3 which is analogous to the Michaelis–Arbuzov reaction can occur only if one of the R groups is labile; in the case of trialkyl phosphites, this has been amply demonstrated by Gilbert and McGough[1] and by Morrison.[3]

With triaryl phosphites, however, O,O,S-trisubstituted thiophosphates are not formed under the same mild conditions. Thus, refluxing a mixture of triphenyl phosphite and benzenesulfonyl chloride (mole ratio 3:1) in dry benzene under a nitrogen atmosphere, then fractionating *in vacuo* gave triphenyl phosphate, diphenyl disulfide, chlorobenzene and possibly diphenyl phosphorochloridite (not definitely identified). The results support the stoichiometric equation

$$6(PhO)_3P + 2PhSO_2Cl \longrightarrow 5(PhO)_3PO + (PhS)_2 + PhCl + (PhO)_2PCl$$

The phosphate and disulfide were obtained almost quantitatively.

Diphenyl sulfide and O,O-diphenyl-S-phenyl thiophosphate were not found, thus indicating that triphenyl phosphite does not react with diphenyl disulfide. This inference was confirmed by demonstrating that triphenyl phosphite and diphenyl disulfide are recovered quantitatively after refluxing a mixture of them in benzene. With triethyl phosphite under the same conditions, however, diphenyl disulfide reacts quantitatively in refluxing benzene solution

$$(PhS)_2 + (EtO)_3P \longrightarrow (EtO)_2P(O)SPh + PhSEt$$

This reaction had been observed previously with dialkyl disulfides by Jensen and his co-workers[4] and it now appears to be generally applicable to trialkyl phosphites and diaryl disulfides.

Our conclusion is that the first two stages (reactions 1 and 2) occur with both triaryl and trialkyl phosphites but the third stage (reaction 3), in contrast to phosphites bearing at least one alkyl group, does not take place with triaryl phosphites. This is demonstrated readily by carrying out a reaction of triphenyl phosphite with benzenesulfenyl chloride when diphenyl disulfide but not O,O,S-triphenyl phosphate is formed

$$(PhO)_3P + 2PhSCl \longrightarrow Ph—S—S—Ph + (PhO)_3PCl_2$$

Unstable quasi-phosphonium intermediates seem likely at each stage of the reaction; however, the nature of these phosphonium complexes, the manner in which oxygen transfer occurs, and the interpretation of disulfide formation requires critical examination to clarify the course of this reaction. Disulfone or disulfoxide intermediates are unlikely—both are expected to react giving other products. However, the mechanistic and experimental details of this novel and convenient reduction of sulfonyl chlorides to disulfides by triaryl phosphites will be presented in a forthcoming publication.

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Received May 22, 1957

(1) (a) E. E. Gilbert and C. J. McGough, U.S. Patent 2,690,450 (1954); (b) 2,690,451 (1954).
(2) F. W. Hoffmann, T. R. Moore and B. Kagan, This Journal, 78, 6413 (1956).
(3) D. C. Morrison, *ibid.*, 77, 181 (1955).
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DEGREE OF IODINATION AND LOCALIZING ACTIVITY OF RABBIT ANTIKIDNEY γ-GLOBULIN

Sir:

The precipitation of chemically modified antibody γ-globulin by homologous antigen has been used by many workers as an index of residual biological activity.[1,2] Data obtained in this manner have been considered by analogy to hold for certain iodinated γ-globulins possessing *in vivo* localizing activity.[3,4,5,6] The danger in making this type of extrapolation is evident when one examines the results of a more direct approach.

Anti-rat kidney γ-globulin obtained from immunized rabbits was radioiodinated essentially as in ref. (6) and then was dialyzed exhaustively against large volumes of *p*H 8 borate buffer. The dialysates were counted as was the content of the bag. This gave the percentage of the original iodine bound to the protein. The amount of original protein was determined gravimetrically and the weight of insoluble residue found after dialysis was subtracted. As long as the starting γ-globulin solution was free from turbidity the insoluble fraction contained the same ratio of I^{131} as the rest of the solution. This fraction was always very minor. The values given for degree of substitution are considered accurate to not less than ±10%. The molecular weight of γ-globulin was taken as 160,000. Iodination and dialysis were performed at 0–5°.

The labeled γ-globulin was then injected into rats and the extent of localization determined three days later according to the method of Pressman.[7] The results are shown in the table and are all for the same preparation of γ-globulin.

Expt.	No. of rats	Atoms I / Molecule	% Injected dose bound to kidney, ±1 std. error
1	7	0.5	1.47 ± 0.07
2	6	0.6	1.68 ± .03
3	6	1.3	1.21 ± .05
4	4	2.7	1.15 ± .10
5	3	3.2	0.87 ± .08
6	4	4.0	0.82 ± .07

It would appear, therefore, that the conclusions of the workers earlier referred to (that antibodies can be substituted with from 2 to 9 atoms of iodine per molecule without apparent modification of activity) are based upon relatively insensitive criteria. In the experiments reported here, the extent of binding started to diminish at about 1 atom I/protein molecule. It was noted also that the cross localization in the liver fell off at a slower rate,[8] indicating a concomitant loss in the specificity of the γ-globulin. Since the specific activity of I^{131} is very high, a small degree of substitution such as is suggested by this work, could still yield a preparation of high radioactivity.

The interest of Dr. D. Pressman in this work is gratefully acknowledged. Supported in part by A.E.C. Contract #AT (30–1)-1771.

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(8) A. E. Powell, paper in preparation.

(9) Department of Surgery, Western Reserve University, School of Medicine, Cleveland 6, Ohio.

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INTERMEDIATES IN THE SYNTHESIS OF DIPHOSPHOPYRIDINE NUCLEOTIDE FROM NICOTINIC ACID[1]

Sir:

A previous communication from this laboratory reported synthesis of DPN[2] by human erythrocytes at low concentrations of nicotinic acid.[3] Nicotinamide, at similar concentrations, did not elevate the pyridine nucleotide level significantly, presumably eliminating free NAm as an intermediate and suggesting that amidation may occur after NA is converted to some presently unknown derivative.

Incubation of 0.72 μmole of NA with glutamine, 0.1 *M* P_i buffer, *p*H 7.4, glucose and 3.5 ml. of defibrinated erythrocytes resulted in synthesis of 0.181 μmole of DPN. After incubation of 0.72 μmole of nicotinic acid-7-C^{14} (4.4×10^5 c.p.m.) under the same conditions and chromatographing aliquots of the deproteinized filtrate on Whatman No. 1 paper with a solvent system of 0.1 *M* PO_4 buffer *p*H 6.8, 600 g. of ammonium sulfate per liter, 2% 2-propanol, 3 radioactive spots could be detected. One corresponded to NA (25% of the total radioactivity). A second traveled between NR and NMN (Compound I-39% of the total radioactivity) and the third traveled with DPN (Compound II, 36% of the total radioactivity). Whereas omission of glutamine reduced DPN synthesis by 70%, glutamine had no effect on the amount of radioactivity in the two nucleotide spots, indicating that at least two NA derivatives other than DPN had been synthesized. Omission of glucose reduced the percentage of the total radioactivity of Compound I from 37 to 18% and Compound II from 63 to 27%.

Extracts of acetone powdered-eythrocytes, which cannot synthesize DPN from NA, do synthesize both Compounds I and II. Synthesis of Compound I requires Mg^{++}, P_i and either R5P or PRPP. NaF (0.02 *M*) inhibits synthesis of Compound I from R5P by 88% and from PRPP by only 25%. PRPP formation from R5P and ATP is known to be inhibited 60 to 70% by 0.02 *M* NaF in erythrocyte acetone powder extract.[4] Hypoxanthine, which is known to condense with PRPP to

(1) These studies were supported in part by contract AT-(40-1)-289 between Duke University and the United States Atomic Energy Commission and by Grant RG-91 from the National Institutes of Health.

(2) These abbreviations are used: NA, nicotinic acid; NAm, nicotinamide; GAm, glutamine; DPN, diphosphopyridine nucleotide; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; R5P, ribose 5-phosphate; ATP, adenosine triphosphate; PRPP, 5-phosphoryl-ribose 1-pyrophosphate; P_i, inorganic phosphate.

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(4) J. Preiss and P. Handler, *J. Biol. Chem.*, **225**, 759 (1957).

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form inosinic acid in these extracts,[4] inhibits Compound I formation by about 50%. These results suggest that Compound I is nicotinic acid mononucleotide and is formed by condensation of PRPP with NA.

To characterize these compounds, a large-scale incubation of erythrocyte acetone powder extracts with nicotinic acid-7-C^{14} was performed. A neutralized perchloric acid filtrate was then passed through a Dowex 1 formate column; 15-ml. aliquots were collected and assayed for radioactivity and absorption at 260 mμ. The various fractions were pooled and components identified by paper chromatography. Radioactive fractions were adsorbed on a Norit A column and, after washing with water, were eluted with 10% aqueous isoamyl alcohol. Ribose and phosphate analyses and absorption spectra suggested that Compounds I and II were the nicotinic acid analogs of NMN (desamido-NMN) and DPN (desamido-DPN), respectively. Compound II was not active with alcohol dehydrogenase and did not form a fluorescent acetone addition product.[5] Further work on the identification of these compounds is in progress.

TABLE I

SYNTHESIS OF DPN FROM DESAMIDO-DPN

Complete incubation system consisted of 1.7 μmoles of desamido DPN, 20 μmoles of glutamine, 2 μmoles of ATP, 5 μmoles of ATP, 40 μmoles of P_i buffer, *p*H 7.4, and 4 cc. of dialyzed yeast autolysate. Total volume 1.0 cc. after incubation of 100 minutes 1 cc. of H_2O was added and the protein denatured at 100° for 1.5 minutes; 1-cc. aliquots were taken for alcohol dehydrogenase assay of DPN formed.

Omission and/or Additions	μmoles DPN synthesized
None	0.116
−Desamido DPN	.028
−ATP	.011
$-Mg^{++}$	.014
−Glutamine	.026
−Glutamine + NH_4Cl 20 μm.	.015
−Glutamine + glutamate 20 μm.	.019
"0 time"	.007

Dialyzed yeast autolysates have been found slowly to synthesize DPN upon addition of glutamine, ATP, PRPP, Mg^{++}, F^- and NA but not NAm. With nicotinic acid-7-C^{14} in the medium, accumulation of compounds I and II was again observed. Compound II prepared with erythrocytes or yeast exhibited an R_f in 70% ethanol, 30% 1 *M* ammonium acetate, *p*H 5.0 identical to that of an authentic sample of the nicotinic acid analog of DPN kindly supplied to us by Dr. N. O. Kaplan. This solvent system adequately separates Compound II from DPN. Synthesis of Compound II from NA by yeast autolysate is dependent on ATP, PRPP and Mg^{++}. R5P is 10% as effective as PRPP. Glutamine, ATP and Mg^{++} are required for synthesis of DPN from desamido-DPN (Table I). NH_4^+ and glutamate are inactive as amide donors. Further investigations of the mechanisms of these enzymatic syntheses, purification of the enzymes, and a study of their distribution in bacterial and mammalian systems are in progress.

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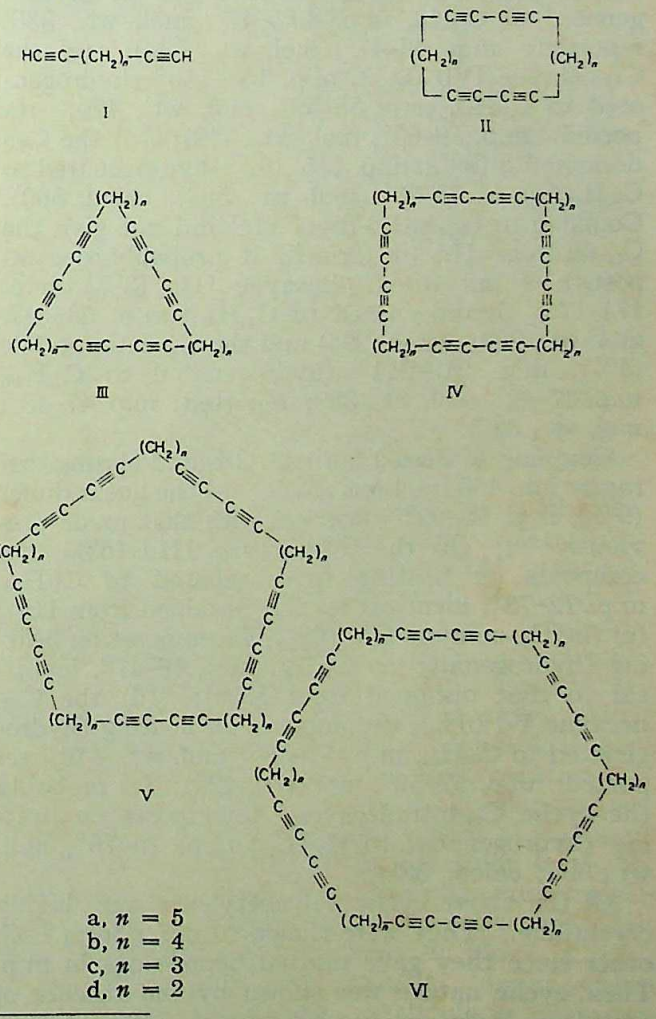
RECEIVED JUNE 14, 1957

(5) N. Levitas, J. Robinson, F. Rosen and W. A. Perlzweig, *J. Biol. Chem.*, **167**, 511 (1947).

UNSATURATED MACROCYCLIC COMPOUNDS. V.[1] LARGE RING POLY-ACETYLENES

Sir:

We have shown recently that the oxidation of terminal diacetylenes of type I with oxygen in the presence of cuprous chloride and ammonium chloride in aqueous ethanol leads to the cyclic dimers II besides linear compounds.[1,2] We have studied this type of coupling of terminal diacetylenes under a variety of conditions, especially in homogeneous media. The surprising discovery has been made that when diacetylenes of type I in pyridine solution are simply heated with neutral cupric acetate,[3] not only the cyclic dimers II are formed, but also the cyclic trimers III, tetramers IV, pentamers V, hexamers VI and higher cyclic



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(2) (a) F. Sondheimer and Y. Amiel, *ibid.*, **78**, 4178 (1956); *ibid.*, in press; (b) Y. Amiel, F. Sondheimer and R. Wolovsky, *Proc. Chem. Soc.*, 22 (1957).

(3) This sort of oxidation has been shown to result in the smooth coupling of simple acetylenes and to give the cyclic monomer, and dimer in the case of I, $n = 10$ (and of a diacetylenic diester) when carried out under conditions of high dilution (G. Eglinton and A. R. Galbraith, *Chem. & Ind.*, 737 (1956)).

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polyacetylenes. Except in the case of Id, only small amounts of the linear coupling products result.

For example 1 part of nona-1,8-diyne (Ia) in 100 parts of pyridine was heated and stirred with 15 parts of neutral cupric acetate at 55° for 3 hours. The product on chromatography on 200 parts of alumina into *ca.* 300 fractions gave successively: (a) the C_{18}-tetrayne IIa (10%), m.p. 210–212° (identical with that made previously[1,2b]); (b) the C_{27}-hexayne IIIa (13%), m.p. 125–126° (hydrogenated to $C_{27}H_{54}$,[4] m.p. 47–48°, mol. wt., 374[5]; calcd. 378); (c) the C_{36}-octayne IVa (11%), m.p. 135–136° (hydrogenated to $C_{36}H_{72}$,[4] m.p. 70–71°, mol. wt., 517; calcd., 504); (d) the C_{45}-decayne Va (4%), m.p. 144–145° (hydrogenated to $C_{45}H_{90}$,[4] m.p. 78.5–79°, mol. wt., 618; calcd., 630); (e) probably the C_{54}-dodecayne VIa (4%), m.p. 144–145° (hydrogenated to $C_{54}H_{108}$,[4] m.p. 90–91°, mol. wt. not determined due to insolubility).

A similar coupling of octa-1,7-diyne (Ib) gave: (a) the C_{16}-tetrayne IIb (9%), m.p. 162–163° (identical with that made previously[2a]); (b) the C_{24}-hexayne IIIb (14%), m.p. 173–174° (hydrogenated to $C_{24}H_{48}$, m.p. 46.5–47°, mol. wt., 330; reported: m.p. 46–47°, mol. wt., 336); (c) the C_{32}-octayne IVb (8%), m.p. 154–155° (hydrogenated to $C_{32}H_{64}$, m.p. 58–59°, mol. wt., 429; reported: m.p. 59–60°, mol. wt., 448); (d) the C_{40}-decayne Vb (9%), m.p. 155–157° (hydrogenated to $C_{40}H_{80}$,[4] m.p., 74–75°, mol. wt., 568; calcd. 560). Coupling of hepta-1,6-diyne (Ic) did not give the C_{14}-tetrayne IIc (if formed, it probably decomposed),[1,2b] but the C_{21}-hexayne IIIc (3%), m.p. 174–175° (hydrogenated to $C_{21}H_{42}$,[4] m.p. 63–64°, mol. wt., 289; calcd. 294) and the C_{28}-octayne IVc (4%), m.p. 213–214° (hydrogenated to $C_{28}H_{56}$, m.p. 47–48°, mol. wt., 389; reported: m.p. 47–48°, mol. wt., 398).

Coupling of hexa-1,5-diyne (Id) and chromatography into 450 fractions gave: (a) the linear dimer (9%), m.p. 98–99° (identical with that made previously[1,2b]); (b) the C_{18}-hexayne IIId (6%), decomposes on heating (hydrogenated to $C_{18}H_{36}$, m.p. 72–73°, identical to that obtained from IIa); (c) the C_{24}-octayne IVd (6%), decomposes on heating (hydrogenated to $C_{24}H_{48}$, m.p. 46–47°, identical to that obtained from IIIb); (d) the C_{30}-decayne Vd (6%), decomposes on heating (hydrogenated to $C_{30}H_{60}$, m.p. 57–58°; mol. wt., 416; reported m.p. 57–58°, mol. wt., 420); (e) probably the cyclic C_{42}-tetradecayne, decomposes on heating (hydrogenated to $C_{42}H_{84}$,[4] m.p. 75–76°, mol. wt., 598; calcd., 588).

All the above cyclic polyacetylenes were highly crystalline. They were shown to differ from each other since they gave mutual depressions in m.p. Their cyclic nature was shown by the absence of acetylenic hydrogen (no band at *ca.* 3300 cm.$^{-1}$ in the infrared, no precipitate with silver nitrate) and by the absence of terminal methyl groups (no band at *ca.* 1380 cm.$^{-1}$) in the corresponding saturated compounds. The latter gave satisfactory analytical results, but most of the polyacetylenes exploded on attempted combustion and gave low carbon values. In all the four series studied, cyclic polyacetylenes of higher mol. wt. than those described were also obtained; their structures are now under investigation.

The present method makes available in one step highly unsaturated large ring alicyclic hydrocarbons (and by hydrogenation the corresponding saturated ones) over a wide range of size, including considerably larger ones than the thirty-four membered cycle which is the biggest alicyclic ring prepared previously.

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(4) This is a previously unknown cycloalkane.

(5) All molecular weights were determined by the Rast method in camphene.

THE CHANGE OF OPTICAL ACTIVITY OF POLY-γ-BENZYL-L-GLUTAMATE IN AN ELECTRIC FIELD

Sir:

The optical activity of a molecule is different along different directions. Therefore we expect the optical activity of a solution of these molecules to change if the molecules are oriented. However, this effect has not been described. We wish to report the change of optical activity of a solution of poly-γ-benzyl-L-glutamate (PBLG) caused by orientation of the molecules in an electric field.

An equation relating the change in optical activity to molecular parameters at infinite dilution has been derived.[1] For a helical molecule the

$$\frac{[\alpha]_E - [\alpha]_0}{E^2} = \frac{2}{45}([\alpha_{33}] - [\alpha_{11}])[p_3^2 + (q_{33} - q_{11})]$$

change in the specific optical activity in an electric field[2] E is proportional to the difference in optical activity for light incident parallel to the helical axis $[\alpha_{33}]$ and perpendicular to the helical axis $[\alpha_{11}]$. The proportionality factor is the electrical orientation term which involves the permanent and induced dipole moments of the molecule. The specific optical activity in the absence of a field $[\alpha]_0$ is just $(2[\alpha_{11}] + [\alpha_{33}])/3$.

In order to measure the change of optical activity in an electric field, the light must be incident parallel to the field. Only along this direction is the refractive index and optical absorption the same for all directions of the plane of polarization.[3]

A one-cm. cell with transparent conducting glass[5] electrodes was used. The optical rotation with the electric field off, then on, was measured from $\lambda = 330$ to 550 mμ in a Rudolph automatic spectropolarimeter[6] for two concentrations of $M_w = 64{,}000$ PBLG[7] in ethylene dichloride. The

(1) I. Tinoco, Jr., and W. G. Hammerle, *J. Phys. Chem.*, **60**, 1619 (1956).

(2) The units of E are e.s.u./cm. (1 e.s.u. = 300 volts).

(3) The change of refractive index in an electric field is electrical birefringence or Kerr effect.[4] The change of optical absorption is electrical dichroism; it has not been reported.

(4) C. G. LeFèvre and R. J. W. LeFèvre, *Revs. Pure Appl. Chem.*, **5**, 261 (1955).

(5) We wish to thank Dr. E. M. Greist of Corning Glass Works for kindly furnishing this glass (E-C #7740).

(6) We wish to thank Professors J. B. Nielands and H. K. Schachman, and Mr. B. Burnham for the use of this instrument.

(7) We wish to thank Dr. E. R. Blout for kindly supplying a sample of PBLG (MS-408) for these measurements.

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rotatory dispersion in the absence of the field was in good agreement with the measurements of Doty and Yang.[8,9] In the presence of the electric field an increase in optical rotation was observed at all wave lengths. The change was found to be proportional to the square of the electric field strength as predicted; an easily measurable change of about 0.1° occurred for a field of about 2,000 volts/cm.

As the electrical orientation term is not known, quantitative values of $[\alpha_{33}]$ and $[\alpha_{11}]$ cannot be obtained. However, an estimate of this term from electrical birefringence studies[10] allows us to make the following conclusions. Both $[\alpha_{33}]$ and $[\alpha_{11}]$ are very large in absolute magnitude, but $[\alpha_{33}]$ is positive and $[\alpha_{11}]$ is negative. Both values increase in absolute magnitude as the wave length decreases; however $[\alpha_{11}]$ increases faster, thus leading to the change in sign of the average optical activity $[\alpha]_0$ at $\lambda = 425$ mμ. These conclusions are in good agreement with Moffitt's prediction.[11]

(8) P. Doty and J. T. Yang, This Journal, **78**, 498 (1956).
(9) J. T. Yang and P. Doty, *ibid.*, **79**, 761 (1957).
(10) I. Tinoco, Jr., *ibid.*, in press.
(11) W. E. Moffitt, *Proc. Natl. Acad. Sci., U. S.*, **42**, 736 (1956).

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VITAMIN B_{12} AND PROTEIN BIOSYNTHESIS. II. EFFECT OF VITAMIN B_{12} ON AMINO ACID INCORPORATION IN MICROSOMAL PREPARATIONS

Sir:

It has been reported from this laboratory that, while vitamin B_{12} has no effect on nucleic acid biosynthesis,[1] there is a decreased incorporation of C^{14}-labeled amino acids into liver protein in vitamin B_{12}-deficient animals,[2,3] indicating that vitamin B_{12} is involved in the incorporation of amino acids into protein.

Following these findings with the whole animal, the incorporation of C^{14}-labeled amino acids into protein has been studied *in vitro* using the microsomal fraction of liver and of spleen from both B_{12}-deficient and normal rats.

The rats were killed by decapitation and the livers removed and microsomes prepared by the procedure of Zamecnik and Keller.[4] This microsome fraction was freed only of mitochondria and nuclei since, as Keller and Zamecnik[5] have reported, the supernatant fraction is essential along with microsomes for the incorporation of amino acids into protein. These preparations containing microsomes and supernatant were then incubated under oxygen (95% O_2, 5% CO_2) with fructose diphosphate, C^{14}-amino acid, ATP[6] and GTP[6] for one hour in the Dubnoff shaker. They were then inactivated by the addition of TCA,[6] and the proteins were isolated and counted at infinite thickness in a GM gas-flow counter. The results are given in Table I.

Table I

Incorporation of C^{14}-Amino Acids into Protein by Microsome Preparations[a] from the Liver and the Spleen of Vitamin B_{12}-Deficient and Normal Rats[b]

	Liver microsome preparation, c.p.m./mg. protein		Spleen microsome preparation, c.p.m./mg. protein	
B_{12} status	$-B_{12}$	$+B_{12}$	$-B_{12}$	$+B_{12}$
$C^{14}H_3$-Methionine	16	76	26	94
2-C^{14}-Alanine	12	57	21	69

[a] Complete system contained 0.1 μM. FDP (6), 0.5 μM. ATP, 0.25 μM. GTP, 0.5 ml. of microsome preparation and labeled amino acid, made to 1 ml. with 0.15 molar KCl. [b] Each figure is the mean for three rats and run in duplicate. Excellent agreement was obtained between replicate animals.

In another series of experiments, the enzyme preparations were supplemented with vitamin B_{12}. The results are given in Table II.

Table II

The Effect of Addition of Vitamin B_{12} to Liver and Spleen Microsome Preparations[a] on the Incorporation of C^{14}-Amino Acids into Protein[b]

B_{12} status of animals	B_{12} added to microsome prep.	Liver microsome preparation, c.p.m./mg. protein		Spleen microsome preparation, c.p.m./mg. protein	
		$-B_{12}$	$+B_{12}$	$-B_{12}$	$+B_{12}$
C^{14}-Methionine	None	19	64	14	81
C^{14}-Methionine	50 mμg	53	73	51	88
2-C^{14}-Alanine	None	12	44	21	67
2-C^{14}-Alanine	50 mμg	40	66	48	90

[a] See Table I. [b] Each figure is the mean for two rats, run in duplicate. Agreement was excellent between animals.

Table I clearly shows that there is much less incorporation of labeled amino acids into protein in the case of microsome preparations prepared from the livers and spleens of vitamin B_{12}-deficient rats than in those from normal animals. These results agree with our previous data on intact animals.[2] In an additional experiment, in which the effect of level of substrate (labeled amino acid) concentration on incorporation was studied, it was found that an increase in the incorporation of amino acids was obtained with microsome preparations (both liver and spleen) from B_{12}-normal animals, upon incubation with increasing levels of amino acid, but that these substrate increments had no effect in preparations from deficient animals. This indicates an enzymatic block in protein synthesis in deficient animals. Again, when the microsome preparations, particularly from the deficient animals, were supplemented with crystalline vitamin B_{12} increased incorporation of the amino acids occurred, bringing the incorporation almost to a normal level (the stepwise increase obtained with graded levels of vitamin B_{12} and also amino acid increment data will be reported in full

(1) S. R. Wagle and B. C. Johnson, *Federation Proc.*, **16**, 401 (1957).
(2) S. R. Wagle and B. C. Johnson, *Arch. Biochem. Biophys.*, in press.
(3) Presented in part before annual meeting, National Vitamin Foundation, March 6, 1957, New York; B. C. Johnson, *Am. J. Clin. Nutrition*, in press.
(4) P. C. Zamecnik and E. B. Keller, *J. Biol. Chem.*, **209**, 337 (1954).
(5) E. B. Keller and P. C. Zamecnik, *ibid.*, **221**, 45 (1956).
(6) ATP = adenosine triphosphate; GTP = guanosine triphosphate; TCA = trichloroacetic acid; FDP = fructose diphosphate.

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later). All these data indicate that vitamin B_{12} is a co-factor for the incorporation of amino acids into protein–protein biosynthesis. A study of the distribution of radioactivity among the liver subcellular fractions following injection of 1 microcurie of Co^{60}-labeled vitamin B_{12} showed a high percentage of radioactivity in the microsomes (46%) and the supernatant fraction (25%) as related to the radioactivity of all the fractions. This high percentage in these fractions most implicated in protein synthesis is in agreement with the hypothesis that vitamin B_{12} is a co-factor for protein synthesis indicated by the amino acid incorporation studies. Work on the isolation of the enzyme containing B_{12} is in progress.

This work was supported in part by a grant-in-aid from the National Vitamin Foundation, New York. We are grateful to Dr. C. Rosenblum of Merck and Co., Inc., for a generous gift of Co^{60}-labeled vitamin B_{12}.

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RECEIVED JUNE 7, 1957

BOOK REVIEWS

Lectures in Immunochemistry. By MICHAEL HEIDELBERGER, Emeritus Professor of Immunochemistry, College of Physicians and Surgeons, Columbia University, New York; Visiting Professor, Institute of Microbiology, Rutgers University, New Brunswick, New Jersey. Academic Press, Inc., Publishers, 111 Fifth Avenue, New York 3, N. Y. 1956. ix + 150 pp. 14.5 × 22 cm. Price, $4.00.

The author of this short volume is a chemist who began his distinguished scientific career at the Rockefeller Institute for Medical Research in 1912. It was he who, together with the great bacteriologist Oswald T. Avery, isolated the capsular polysaccharides of several pneumococcal types and showed that they were endowed with immunological specificity. This was an achievement of no small magnitude, as subsequent events revealed.

Immunology was a lively field of investigation during the two decades prior to this discovery. Although the science was relatively new, chemists were already beginning to make important contributions to an understanding of the processes involved in immune phenomena. The monumental work of Karl Landsteiner concerning the specificity of proteins, and his discovery of the specific blood groups, an achievement for which he later received the Nobel Prize, were but two of the great contributions of this period. The classical studies of Arrhenius and of Madson on the quantitative aspects of the toxin-antitoxin reaction had brought a new interpretation of a phenomenon which, but a few years before, had scarcely been conceived of as a chemical reaction.

The discovery in the early twenties of the specific bacterial polysaccharides and of the role which they played in antipneumococcal immunity added a new, imposing milestone to the progress which both the chemist and the bacteriologist have made to our understanding of immune reactions.

Six of the lectures found in this volume, delivered in 1954 at the University of Tokyo, are a summation of the contributions which the author has made to the modern field of chemical immunology. These lectures deal for the most part with his quantitative studies on the precipitin and agglutination reactions, with the chemical nature of complement, and its role in the hemolytic system, and with the relationship between the chemical constitution and specificity of proteins and of carbohydrates. Three other lectures are included in the volume. Two of these, delivered in Europe, have to do with an evaluation of antipneumococcal immunity in humans following administration of the pneumococcal polysaccharides, while the third, delivered in New Brunswick, New Jersey, presents a study of the serological properties of native and denatured proteins.

For those who wish to obtain a broad background in the field of chemical immunology and a knowledge of the developments which have occurred in this field during the past several decades, or for those who wish to gain a broad scope in this specialized and many faceted field of biochemistry, this is not the book. However, for those who wish to learn something of the individual contributions of a contemporary and distinguished biochemist in a rapidly expanding field the volume is to be recommended warmly, although it is regrettable that many of the statements in the lectures, and in particular those regarding the work of others, are not better documented.

THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH
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WALTHER F. GOEBEL

Enzyme Antigen and Virus. A Study of Macromolecular Pattern in Action. By F. MACFARLANE BURNET, Kt., F.R.S., F.R.C.P. Cambridge University Press, American Branch, 32 East 57th Street, New York 22, N. Y. 1956. viii + 193 pp. 13 × 18.5 cm. Price $3.50.

This monograph is an extension and revision of the author's earlier monograph ("The Production of Antibodies"[1]). It is concerned with the process of biological replication of specific patterns. Burnet is primarily interested in the replication of active proteins and presents evidence for the thesis that protein is synthesized by or on a RNA template. The content of the monograph is best summarized by the titles of the chapters and their contents.

I. Introduction: Enzyme Action and Protein Synthesis. (1) Enzyme specificity; (2) Adaptive enzymes in microorganisms; (3) Chemical aspects of the biosynthesis of protein; (4) The nature of adaptive enzyme synthesis.

II. Antibody Production. (1) The self-marker concept; (2) Antibody production after the elimination of antigen; (3) The site of antibody production; (4) Theoretical approach to antibody production; (5) Weaknesses of the present hypothesis.

III. The Self-marker Hypothesis in Relation to Cellular Proliferation and Control. (1) Immunological aspects of tumour transplantation; (2) The implications of cutaneous sensitization to simple compounds; (3) Application of Weiss's concepts of cell control to the self-marker hypothesis; (4) Summary.

IV. Virus Multiplication. Influenza Virus Multiplication: (1) Nucleic acid in relation to influenza virus; (2) An attempted visualization of the structure of influenza virus particles; (3) Process of infection; (4) Interference; (5) Incompleteness; (6) The dynamics of influenza virus multiplication in the allantoic cavity; (7) Recombination phenomena; (8) Mutation; (9) Summary.

V. The Scope of Biological Generalization. (1) Information theory in biology; (2) The application of pattern concepts to biological problems.

The monograph outlines very effectively much of the current thought on protein synthesis, antibody production and virus multiplication and, as a monograph should, it presents

(1) F. M. Burnet and F. Fenner, "The Production of Antibodies," Macmillan and Co., Melbourne, 1949.

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very strongly the views of the author himself. Burnet attempts to present both sides of arguments. He was not able, unfortunately, to include some very pertinent recent work. For example, in connection with the problem of whether or not antigen persists during the period of antibody production, as required by the template theory, he was not able to include the very important work of Garvey and Campbell[2] which indicated that immunologically active fractions of proteins containing S^{35}-labeled azobenzene sulfonate groups persist in the liver of injected animals for several weeks. This is contrary to the work in the same system quoted by Burnet, namely, that of Ingraham,[3] who was not able to find such active components.

The author presents a great deal of information on the important and currently popular phenomenon of tissue tolerance. Although the recognition unit concept as described by Burnet is an appealing one, it is difficult to see how all the component substances of an organism could have a certain self-marker unit which would be recognized by the cells. It is known that slight chemical alteration of an individual's own proteins will render them antigenic to the same individual, and it does not seem possible that any such slight alteration would always affect the recognition unit.

Burnet concludes with the statement that "the generalizations that are needed for the technical control of biological processes will not come from the elaboration either of structural chemistry or of information theory in its conventional sense. These can only provide a background against which effective working concepts can be oriented and rendered more intellectually appealing. The handling of biological material will always be the business of scientists using their own working concepts based essentially on a not very deeply analyzed concept of specific pattern with which we have been concerned."

Since many chemists require sound basis and deep structural analysis for their effective function and do not consider these factors as mere "intellectual appeal," they may be dismayed at the loose use of the term "Specific Pattern," without concern about the actual nature and configuration of the pattern.

Instead of adopting an open mind to the possible contribution of all fields to the study of living processes, *Burnet openly minimizes the past contributions of chemistry and he is pessimistic about future contributions from chemistry* as shown by the following quotations which are typical: "Without ever being able to state the precise point at which technique must break down, we can yet be quite certain that no conceivable development of organic chemistry will provide us with the detailed structure of trypsin or of the particular nucleic acid that can transfer a new antigenic quality from one pneumococcus to another." "The attempt to press the structural, physical and chemical approach to the understanding of living process seems to have reached the phase of diminishing return for the effort involved. We are approaching an asymptotic barrier and it may be that some modification in the outlook and approach of theoretical biology will soon be needed."

(2) J. S. Garvey and D. H. Campbell, *J. Immunol.*, **76**, 36 (1956).
(3) J. A. Ingraham, *J. Infect. Dis.*, **89**, 117 (1951).

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The Calculation of Atomic Structures. Based on lectures given under the auspices of the William Pyle Philips Fund of Haverford College, 1955. Structure of Matter Series. Maria Goeppert Mayer, Advisory Editor. By Douglas R. Hartree, John Humphrey Plummer, Professor of Mathematical Physics in the University of Cambridge, England, and Philips Visitor at Haverford College. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 1957. xiii + 181 pp. 15.5 × 23.5 cm. Price, $5.00.

Calculation of accurate wave functions for atoms is an important undertaking, but it has proved to be very frustrating because of the tedious numerical work involved. Renewed interest in the problem has been stimulated recently by development of large digital computing machines, and we soon hope for improved functions for the normal and more important excited states of atoms, from which transition probabilities and energies may be derived. Methods developed and tested for atoms are also of obvious importance in the problem of molecular structure calculations.

It is fortunate that we have now, for the first time, a very detailed and complete account of methods used by Professor Hartree and others in the self-consistent field treatments of atomic structure, especially for atoms with many electrons. The present book is based on a series of lectures delivered at Haverford College and repeated later in Princeton University. The emphasis is on technical rather than on descriptive aspects of the problem, but one may obtain a general view of what has been done and see how calculations may be improved without working through the numerous mathematical results. However the book is especially valuable for the specialist who plans similar or improved computations. In this connection, Chapter 10, on "Better Approximations," is particularly important, and might well have been amplified.

The Appendix contains tables of new (and recalculated) results, and it is very convenient to have this material collected in one book. The numerous references appear to be complete and extend into 1956.

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Textbook of Polymer Chemistry. By Fred W. Billmeyer, Jr., University of Delaware and Polychemicals Department, E. I. du Pont de Nemours and Co., Inc. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1957. viii + 518 pp. 16 × 23.5 cm. Price, $10.50.

This book, according to its author, was written as a text in the physical and organic chemistry of high polymers at the senior or graduate student level. It is intended that the text be expanded by lectures and supplementary reading.

The first third of the book deals with the physical chemistry of high polymers, including their physical and chemical structure, thermodynamic properties in solution, a discussion of molecular weight methods, and ends with a section on rheology and viscoelastic properties. The kinetics of polymerization occupies the next fifth of the text and includes such topics as linear condensation polymerization, addition polymerization, copolymerization kinetics and the reactivity of monomers and radicals. A short section on molecular weight distributions, and chapters on emulsion polymerization, ionic polymerization and polymer degradation follow.

The properties of plastics are next dealt with, starting with a section on polymer processing, including injection and compression molding, plasticization and reinforcement. This is followed by a series of chapters on polymers from polystyrene, the acrylates, vinyl polymers, halogen-containing polymers, linear and cross-linked condensates, cellulose and the silicone polymers. This is essentially the organic polymers section of the text, occupying about 20% of its space.

Chapters on the properties of fibers are concerned with the physical and chemical properties of synthetic and natural fibers, fiber fabrication, and after-treatment. The subject of elastomers completes the text with chapters on vulcanization and reinforcement, as well as ones on natural rubber, GRS and other synthetic elastomers. The book concludes with a complete list of symbols giving their dimensions, units, definitions and chapter where used, and an appendix of trade names and manufacturers.

The field of the physics and chemistry of polymers is so extensive in terms of fundamental work as well as applied work that no text of manageable size could possibly cover it completely. Since this text treats almost every aspect of the field, the author has been forced to present only its essentials. In this his achievements have been truly remarkable. Each of the many chapters (57 in all) had to be necessarily short (they average 8 pages), but they are all authoritative and written in an extraordinarily clear manner. This was made particularly difficult because many of the derivations depend upon a sophisticated knowledge of theory, particularly statistical thermodynamics. The bases of the derivations are explained and the important intermediate and final expressions alone presented; this is as it should be.

This text is extremely readable. The material is well organized, making it easy to locate topics. The appendices

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are excellent, particularly the one listing the many symbols used, 179 in all.

It is probable that a specialist in the organic chemistry of polymers would like to see more of his field covered and the same will doubtless be true of the physical chemist and the applied chemist. Each, however, will find the essentials of his subject ably and authoritatively presented.

In the opinion of this reviewer, this book is the outstanding general text in this field. It should also serve as an invaluable reference book for the non-specialist. While more complete books are available on advanced topics and on limited, applied phases of the field, this text will serve as an "initiator" to the field of polymer chemistry.

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Crystal Structures. Volume II. Chapter XI. Miscellaneous Inorganic Compounds. Chapter XII. Structure of the Silicates. By Ralph W. G. Wyckoff, Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1957. 261 pp. 19.5 × 24.5 cm. Price, $7.00.

Previously issued sections of this very valuable loose-leaf reference work have already been reviewed.[1,2]

The present section includes detailed structure data on the silicates and on miscellaneous inorganic compounds: complex and basic halides, thio salts, complex sulfides, complex oxides, and a few other compounds not belonging in these or other categories previously included. Coverage of the results of detailed structure analyses of all classes of chemical substances is not complete, except for some figures and the most recent work, which will presumably be covered in supplements to be issued later.

The world owes Dr. Wyckoff and the publishers a big debt of gratitude for the preparation and publication of this monumental work.

(1) J. Donohue, This Journal, **74**, 5554 (1952).
(2) M. L. Huggins, *ibid.*, **75**, 6089 (1953).

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Encyclopedia of Chemical Reactions. Volume VI. Samarium, Scandium, Selenium, Silicon, Silver, Sodium. Compiled by C. A. Jacobson, Late Professor of Chemistry, West Virginia University. Edited by Clifford A. Hampel, Manager, Chemical Equipment Division, Fansteel Metallurgical Corp., Editor, "Rare Metals Handbook." Reinhold Publishing Corporation, 430 Park Avenue, New York 22, N. Y. 1956. 438 pp. 16 × 23.5 cm. Price, $12.50.

Volume VI of the Encyclopedia covers the reactions of six elements, samarium, scandium, selenium, silicon, silver and sodium. In general this reviewer can simply repeat the same criticisms as were voiced by the reviewers of previous volumes (This Journal, 68, 1678 (1946); 71, 2278 (1949); 75, 5772 (1953)). The main objection is still the incompleteness of the coverage. To be sure, a compilation of a comprehensive encyclopedia is a Gargantuan and unenviable task; however, if such work is to have any usefulness, at least an attempt should be made at reasonable completeness.

In order to illustrate the extent of this work it is sufficient to mention that there is a total of 77 reactions listed for samarium, of which 52 date to 1883 and 1885, and 51 reactions are listed for scandium, 46 of which are taken from pre-World War I literature!

The appendix contains a list of 93 journals from which the abstracts were made. One cannot but wonder why journals such as *Oil and Soap* or *Soap and Sanitary Chemicals* are included, while *Acta Chem. Scand.*, *Canadian J. Chem.*, or *J. Ind. Chem. Soc.* are omitted and the only Russian journal listed is the *J. Russ. Phys. Chem. Soc.* which ceased publication in 1930?

One easily comes to the conclusion that the title "Encyclopedia of Chemical Reactions" is certainly too pretentious. It is rather a limited collection of chemical reactions. As such it may have some usefulness for a research worker. To claim that the work is encyclopedic is certainly unrealistic.

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BOOKS RECEIVED

June 10, 1957–July 10, 1957

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JOURNAL OF THE
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PHYSICAL AND INORGANIC CHEMISTRY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF REED COLLEGE]

The Atomic Weights of Fluorine and Silver

BY ARTHUR F. SCOTT AND WILLIAM R. WARE

RECEIVED JANUARY 30, 1957

This is the first chemical determination of the atomic weight of fluorine by the Harvard method. Perfluorobutyryl chloride was prepared by the reaction between PCl_5 and carefully fractionated perfluorobutyric acid. The chloride was purified by fractional distillation in vacuum systems. Samples of the chloride were hydrolyzed in pyridine solution and the chloride was precipitated with a known amount of silver. The end-point was determined nephelometrically, the final adjustment being made after the precipitate had stood for two years. The atomic weight of fluorine is calculated to be 18.999 as the average result of six analyses. This new value is shown to be in excellent agreement with the best atomic weight values derivable from mass-spectrographic measurements and from nuclear reaction data. The question of unifying the chemical and physical atomic weight scales by assigning the value 19 to the mass of the anisotopic element F is discussed.

The present chemical value 19.00 of the atomic weight of fluorine is based upon a number of determinations[1] by two different methods: the chemical analysis of pure fluorine compounds; and the measurement of the gas density of fluorine compounds of carbon and silicon. In the case of this element the analytical determinations presented special difficulties and are generally regarded as inferior to those by the gas density method. By way of illustration of the status of the analytical determinations it may be noted that of the five determinations of this type the one which is given most weight is Smith and Van Haagen's[2] conversion of sodium fluoride to sodium sulfate, a determination which comprised only three experiments involving samples of sodium fluoride ranging in weight between 0.3 and 1.1 g. Obviously, this determination by Smith and Van Haagen leaves much to be desired in many respects. The atomic weight of fluorine derived from Smith and Van Haagen's measurements is 19.005.

The discovery of isotopes of oxygen by Giauque and Johnston in 1929 led to the acceptance by chemists and physicists of two different scales: chemists have continued to assign the value 16 to oxygen as found in nature, *i.e.*, to the naturally occurring mixture of isotopes; physicists, on the other hand, have consistently assigned the value 16 to the isotope O^{16}. The difference between these two scales is very small and conversions between them are readily made by means of a conversion factor (1.000275). However, following the discovery[3] that the isotopic composition of natural oxygen is not fixed and constant, the chemists are in the position of using an atomic weight scale based on a variable "constant." Although the variations in question are of no consequence with respect to present chemical atomic weight values, it has seemed desirable, for the sake of logic at least, to replace oxygen as the basis of the chemical scale by some anisotopic element.

Fluorine is a promising replacement for oxygen.[4] Its one serious disqualification is the simple fact that no strictly chemical atomic weight determination has been satisfactory, especially no determination relating fluorine to silver which, because of the part the latter plays in the Harvard atomic weight method, has become the "practical" basis of atomic weight values of a majority of the elements. The present investigation is the culmination of a series[5]

(1) For a review of these determinations see A. F. Scott and M. Bettman, *Chem. Revs.*, **50**, 363 (1952).

(2) E. F. Smith and W. K. Van Haagen, Carnegie Inst. Pub. No. 267, 1918.

(3) By M. Dole in 1935. For references and discussion see review article by M. Dole, *Chem. Revs.*, **51**, 263 (1952).

(4) Dole, ref. 3, discusses this question. In 1936 he suggested protium and sodium as suitable replacements for oxygen; in his 1952 article his list includes fluorine as a third possibility.

(5) These studies have been senior projects under the Senior Thesis program of the College. The pioneering students were: Hilary B. Willis (1938); Robert W. Moen (1939); Joseph H. Gill and Arthur H. Livermore (1940); Chester Schink and Louis G. Stang, Jr.* (1941); Joseph F. Bunnett (1942); Edward L. Bennett* (1943); Dale C. Buitner* (1948); Earl S. Scott* (1949). Theses by these students are on file in the College Library. Students who worked on the preparation and analysis of derivatives of trifluoroacetic acid are indicated by

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of studies which has been carried out for the purpose of finding a fluorine compound suitable for the determination of the atomic weight of fluorine by the Harvard method.

The preliminary experiments involved the preparation, purification and analysis of trifluoroacetyl chloride, trifluoroacetyl bromide and silver trifluoroacetate; samples of the last two compounds were painstakingly analyzed. Although these compounds appeared rather promising, a final series of these experiments with them was not undertaken because pure perfluorobutyric (heptafluorobutyric) acid became available commercially, and its acid chloride appeared to have a number of advantages over trifluoroacetyl bromide. For example, the heptafluoro compound has the higher boiling point (39° *vs.* −5°) and the higher percentage of fluorine (57% *vs.* 32%).

A pathfinding preparation and study of perfluorobutyryl chloride and silver heptafluorobutyrate were carried out by Swanson[6] in this Laboratory. These experiments showed that the acid chloride was very promising for atomic weight purposes; these experiments also laid the groundwork for a new preparation and analysis of perfluorobutyryl chloride described in this article.

Preparation and Purification of Materials

After some trial experiments a final sample of perfluorobutyryl chloride was prepared as follows.[7] A two pound sample of perfluorobutyric acid obtained from Minnesota Mining and Manufacturing Co. was twice fractionated using a 20-plate Oldershaw column with an automatic vapor-dividing head. In the first distillation concentrated sulfuric acid was present as a drying agent. In both distillations one-third of the charge in the pot was equally divided between the head and tail fractions which were rejected. The purified acid (1.7 moles) was converted to the acid chloride by slowly adding it to reagent grade phosphorus pentachloride (3.8 moles). The all-glass reaction system consisted of three flasks provided with ball and socket joints, so that they could be joined together, or disconnected and capped as desired. The first or reaction flask carried a separatory funnel; the third flask was essentially a stillpot since it was sealed to a 10-plate Oldershaw column. Considerable pains were taken to remove all moisture from the glass system prior to use and to prevent admission of moist air at any time. The preparation of the acid chloride was carried out in the first flask. During the reaction the flask temperature was kept at 0°; at the end of the reaction the temperature was raised to 80°. The acid chloride condensed in the middle flask kept at −70°. When the reaction was completed the product was distilled into the third flask, and then the connecting tube was sealed off. The acid chloride product which was light yellow at this stage was refluxed for 4 hours, the cold finger in the head being maintained at −50 to −20°. During this refluxing operation a very small amount of distillate was condensed in a receiver at −60°. This distillate was yellow and was discarded; it apparently was the contaminant originally in the main product since the latter became colorless during the first hour of the refluxing operation.

Without changing the apparatus the acid chloride was distilled three times at atmospheric pressure. The first was simply a careful distillation from the preparation apparatus. In the second distillation the large middle fraction from the first step was fractionally distilled through a 20-plate Oldershaw column with a vapor dividing head. The middle fraction (about nine-tenths of the charge) was again distilled, the procedure and apparatus being the same as in the preceding step.

The middle fraction from this (third) distillation was fractionated further in a new apparatus which included a 10-plate Oldershaw column. Although great care had been taken in the previous distillations to remove and exclude moisture there was always the possibility that the acid chloride had come into contact with trace amounts of moisture which would result in the formation of hydrogen chloride. The new apparatus was designed to exclude moisture completely; and the preliminary part of the distillation was carried out so as to eliminate hydrogen chloride if any were present. Following this a small light fraction was removed and the bulk (*ca.* 100 ml.) of the acid chloride was distilled (reflux ratio 1:10 to 1:50) into a flask fitted with a capillary "valve" for subsequent distillation under vacuum. Once the middle fraction was collected the "valve" flask was sealed off from the distillation column, and then evacuated in a manner to cause the vapor of the acid chloride product to sweep out most of the air present. The tube connecting the evacuated "valve" flask to the pump was then sealed.

The acid chloride material was finally distilled a fifth and sixth time in evacuated systems. The general scheme of distillations of this type has been described many times.[8] In the present experiments, however, the apparatus and technique involved two new features. It was found possible without using ground-glass joints or grease, to incorporate a 10-plate Oldershaw column in the vacuum system and so improve the degree of fractionation obtainable. Also, the usual solenoid-hammer device for breaking the capillary "valve" was modified so that the hammer dropped vertically[9] rather than being moved horizontally and was moved by a small magnet.

In the first vacuum distillation small head and tail fractions were taken and the bulk of the material was collected in a capillary valve flask. There was some evidence of a small amount of air in the system.

The second distillation employed the same apparatus as the previous one, except that small sample bulbs (*ca.* 2 cm. in diameter) were included in the system for collecting the entire charge. The apparatus was pumped down to 0.001 mm. for several days and repeatedly flamed. Then the middle fraction from the previous vacuum distillation was transferred to the pot through the capillary valve, refluxed for one-half hour, and distilled. A very minute trace of air was apparently present in the system during the filling of the first three bulbs (#8, 9 and 10), and was successfully trapped in bulb #11. In filling the remaining bulbs (#12–18) the vapor literally rushed into the bulb the instant it was cooled, indicating the complete absence of air. All the acid chloride was collected by the time bulb #18 was filled. Seven of the samples collected in this distillation were subsequently analyzed.

The silver used in these analyses were prepared by Kurt H. Nelson.[10] The purification process[11] involved the electrolytic transport of the silver three times through a saturated silver nitrate solution contained in long quartz trays. The electrolytic crystals were fused into buttons of suitable size in a quartz furnace on a bed of pure lime in an atmosphere of slightly moist hydrogen. The fused buttons were etched several times with nitric acid, washed and dried at 100° in air, then at 400° *in vacuo*. The standard silver solution employed for fine adjustment of the weight of silver in the analyses was made with a small quantity of electrolytic crystals which also had been heated to 400°. Samples of these electrolytic crystals were examined spectrographically[12] and the only impurities detected were Al, Fe, Mg, Si and Cu. The percentage of each of the first four fell in the range 0.0001–0.001; that of Cu was less than 0.0001.

Water, nitric acid and pyridine were purified by distillation. Hydrogen was commercial tank gas which, after passing through a Deoxo unit to remove oxygen, was passed through a set of six all-glass Emmerling towers containing the following solutions in the order given: alkaline plumbite; 20% NaOH; concd. sulfuric acid; concd. sulfuric

(6) John L. Swanson, Senior Thesis, 1951, Reed College.

(7) The details of this preparation appear in the Senior Thesis, 1953, of the junior author.

(8) See, for example: G. P. Baxter and A. F. Scott, *Proc. Am. Acad. Arts and Sci.*, **59**, 19 (1923); A. F. Scott and F. H. Hurley, THIS JOURNAL, **59**, 1905 (1937).

(9) This new arrangement has certain advantages over the older one. A note describing it will be submitted for publication shortly.

(10) Kurt H. Nelson, Senior Thesis, 1948, Reed College.

(11) G. P. Baxter and O. W. Lundstedt, THIS JOURNAL, **62**, 1829 (1940).

(12) For this test we thank the Metallurgical Division, Bureau of Mines, at the Laboratory, Albany, Oregon.

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acid; 20% NaOH; water. To adjust the aqueous vapor pressure in the hydrogen to the desired value[11] the gas was finally passed through two cold towers, the first kept at 0° and the second, at −18°.

Comparison[13] of the perfluorobutyryl chloride with silver followed conventional lines.[14] The scheme of this comparison can be presented briefly. A weighed sample bulb was placed in a thick-walled flask containing 25 ml. of pyridine and 50 ml. of water, and the flask was closed with a tight-fitting, ground glass stopper. After the flask was cooled to about 4° in the cold room the bulb was broken inside the flask by violent shaking and the perfluorobutyryl chloride was allowed to react with the aqueous pyridine. Due to the presence of the pyridine, the chloride samples were completely soluble in this mixture. Although the white fog formed upon breaking the bulb disappeared within one-half hour, the flask was allowed to stand for a day before opening. The solution was filtered through a Munroe platinum crucible using a specially designed filtering apparatus[15]; the filtrate was collected in a liter round-bottom flask and transferred from this to a 4-liter glass stoppered bottle.

After obtaining the weight of perfluorobutyryl chloride, the equivalent weight of silver was calculated. In the early analyses, for the purpose of this calculation, the atomic weight of fluorine was assumed to be slightly greater than 19.00; in the last few analyses it was assumed to be slightly less than 19.00. The silver, after being weighed out, was transferred to a flask fitted with a tower of bulbs, and dissolved in 50–100 ml. of 1:1 nitric acid. The quantity of acid used was such as to make the final analytical solution 0.2–0.3 *M* in nitric acid.

The precipitation of the chloride was carried out in a dark room by adding the dissolved silver to the pyridine solution of perfluorobutyryl chloride in small portions with constant agitation. After the quantitative addition of the silver solution, the amount added was immediately adjusted to the calculated value by the addition of silver nitrate or sodium chloride from carefully prepared solutions of the purified substances. These standard solutions contained approximately 0.1 mg. of silver or its equivalent per milliliter. The final volumes of the analytical solutions were between 2,000 and 3,000 ml. The solutions were shaken vigorously four or five times a day following precipitation and during the preliminary nephelometric tests. Following these tests the solutions were allowed to stand with occasional shaking for a period of two years before they were subjected to the final nephelometric tests and "crossing of the end-point."

Nephelometric tests of the silver and chloride concentrations in the analytical solutions were made with the usual precautions. The nephelometric test suspensions were prepared by the "uniform" precipitation device described by Scott and Hurley.[16] The opalescence of a test suspension was determined by use of a new Coleman Nephelocolorimeter. It may be recalled here that Scott and Hurley,[14] in connection with their analyses of benzoyl chloride, found that the presence of pyridinium nitrate in the analytical solution has no significant effect on the opalescences of nephelometric test suspensions.

Preliminary determinations (summer 1953) of the opalescence ratios for the seven analytical solutions, immediately after precipitating the chloride, were encouragingly close to unity. Nothing further could be established at the time because of other obligations. When it was realized that the determination would have to be put off for a period of time, suitable additions of silver nitrate or sodium chloride, in the form of the very dilute standard solutions, were made to the analytical solutions of analyses #1–#5 to make the amount of silver present in each solution equal to that calculated on the assumption that the atomic weight of fluorine is 19.000. These additions were all small. No additions were made to the analytical solutions of analyses #6 and #7, the silver for which was calculated on the assumption that the atomic weight of fluorine is 18.997. All seven analytical solutions were kept in a light-tight cupboard in a dark room from the summer of 1953 to the summer of 1955 when the analyses were completed. It is believed that this two year period was advantageous for several reasons. It certainly must have reduced the amount of colloidal silver in suspension; it also favored the aging of the precipitate and the establishment of equilibrium between the precipitate and mother liquor.

The final determination of the end-point was performed by Marvin H. Lehr.[17] To begin with the solutions were well shaken and then allowed to stand for several days. Next, on two consecutive days test samples were withdrawn from the analytical solutions, and the opalescence ratios determined by means of the Coleman nephelometer. These two measurements of the opalescence ratios, which were in very satisfactory agreement, all showed a slight excess of silver ion. It was estimated that in no case was this excess of silver greater than 0.15 mg.; and on this assumption chloride ion equivalent to 0.15 mg. of silver was added to each analytical solution in the form of very dilute standard solution. The solutions were then shaken repeatedly, and three measurements of the new opalescence ratios were made in the course of a week. The last two sets of measurements were in satisfactory agreement. These new ratios showed that the end-point had been crossed except in the case of analysis #5 in which case the ratio was 1.07. From the known values of the ratios before and after the addition of the chloride ion (equivalent to 0.15 mg. silver) and assuming that the variation in opalescence ratio with added chloride ion is linear, it is possible to estimate readily the amount of chloride necessary to bring the opalescence ratio to unity. This estimate was used in calculating the amount of silver added or subtracted in solution to give the exact end-point. In passing it is interesting to note that from this final series of nephelometric tests one can derive a new estimate of the sensitivity of the opalescence ratio. On the average it was found that a change of 0.01 in the opalescence ratio is caused by 0.006 mg. of silver ion or its equivalent in chloride ion.

Results of Analyses

The results obtained from the analysis of seven samples of the perfluorobutyryl chloride are given in Table I.[18] These samples formed a consecutive series and no accidents or mishaps occurred. All the weights in the table are corrected to the vacuum basis. The additions of silver tabulated in column 4 are those made *after* the nephelometric tests were begun.

TABLE I

RESULTS C_4F_7OCl:Ag

No. of analysis	Fraction of C_4F_7OCl	Wt. of C_4F_7OCl *in vacuo*, g.	Wt. of Ag added or subtracted in soln., g.	Cor. wt. of Ag *in vacuo*	Ratio C_4F_7OCl: Ag
1	8	6.37666	+0.00093	2.95871	2.15522
2	9	4.70614	− .00085	2.18369	2.15513
3	17	5.31133	+ .00311	2.46453	2.15511
4	18	1.70873	+ .00078	0.79279	2.15534
5	16	3.92030	+ .00812	1.81908	2.15510
6	11	3.86748	− .00099	1.79453	2.15516
7	12	4.24157	+ .00217	1.96816	2.15510
		Mean (A) (all analyses)			2.15517
		Mean (B) (excluding 4)			2.15513
		Mean (C) (excluding 1 and 4)			2.15512

Discussion of Results

With a series of analyses such as that reported above an important question is whether the variations in the results are due to differences in the samples analyzed or arise from the analytical operations. At first glance it is disturbing to find

(13) These operations, up to the final nephelometric tests, were performed by the junior author, as a research associate, in the summer of 1953.

(14) For the important details of the weighing and analytical procedures see account given in article on analysis of benzoyl chloride by A. F. Scott and F. H. Hurley, THIS JOURNAL, **59**, 1905 (1937).

(15) A note describing this arrangement will be submitted for publication shortly.

(16) A. F. Scott and F. H. Hurley, THIS JOURNAL, **56**, 333 (1934).

(17) Reed College, 1954.

(18) The authors are greatly indebted to Marvin H. Lehr for his help in rechecking the calculations from beginning to end.

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that the ratio values for the lightest (no. 8) and the heaviest (no. 18) fractions stand out as greater than the ratio values of the other five samples; for this might be an indication of a variation in the samples due to fractionation. This interpretation, however, appears to be contradicted by two lines of evidence. Most important is the fact that the results of adjacent fractions do not show any gradation in ratio values. Also significant is the fact that the most probable impurities (hydrogen chloride in the light fraction and phosphorus chloride or oxychloride in the heavy fraction) would result in low rather than high ratio values. Although the high ratio value of the lightest fraction (no. 8) presumably does not arise from the fractionation of the acid chloride material, it is conceivable that it is an indication of some impurity in the sample; for, as will be recalled, this fraction was the only one in the series which showed milkiness upon condensation of the sample, due possibly to a trace of air in the system.

If we assume the samples of acid chloride to have been uniform and the variations in the ratio values to have their origin in the analytical operations, we can treat the experimental data as follows. First, on the basis of the Pierce–Chauvenet criterion we find that the ratio value of analysis no. 4 most probably involves some mistake and can therefore be rejected as an aberrant measurement. Omitting no. 4 for the series we get the mean value "B" in Table I. If we also omit the result of analysis no. 1 on the ground that it is suspect because of the possible contamination with a trace of air as mentioned above, we get the mean value "C" of Table I. Information relating to the statistics of the experimental data is summarized in Table II.

TABLE II

INFORMATION PERTAINING TO THE PRECISION OF RATIO VALUES

Mean	No. of analyses in set	Mean value of ratio	Stand. dev.	Range of mean
A	7	2.15517	0.000081	
B	6	2.15514	.000043	±0.00004
C	5	2.15512	.000023	± .00002

The range of the mean represents the 90% confidence limits. As is evident, there is little difference between means B and C. Both values, however, will be carried along in the following discussion. It is of interest to note that the uncertainty of the mean values is 1–2 parts in 10^5.

First, following the traditional treatment we shall use the experimentally determined ratio C_4F_7OCl:Ag to calculate the atomic weight of fluorine. For this purpose we note first the necessary atomic weight values given in the most recent "Report on Atomic Weights"[19]

Oxygen	16
Chlorine	35.457
Silver	107.880
Carbon	12.011

There can be no question regarding the acceptability of the first three of these atomic weight values. They have been used in calculations of atomic weight determinations by the Harvard method for the past 30 years. Also there are no alternative values to consider.

Concerning the atomic weight of carbon the following notes are offered. The present accepted value for the chemical atomic weight of carbon 12.011 was derived from a combination of two physical measurements: mass determinations of C^{12} and C^{13} from observations of energy changes accompanying nuclear reactions; and mass spectrographic determinations of the relative abundance of the two isotopes. As a matter of fact, in the 1954 Report, the chemical atomic weight derivable from these physical measurements was estimated to range from 12.0113 and 12.0116, depending on the source of the carbon; and the value given (12.011) is a rounded-off figure. For our purposes we shall use the mean value 12.0114 as the best estimate of the chemical atomic weight of carbon. Finally, it may be noted that an uncertainty of 0.0002 unit in the atomic weight of carbon introduces an uncertainty of less than 0.0002 in the derived atomic weight of fluorine.

The atomic weight of fluorine calculated from the experimentally determined ratio C_4F_7COCl:Ag and the atomic weights of C, O, Cl and Ag given above are as follows, the last digit being of questionable significance.

Using mean ratio value	Atomic weight fluorine
"B"	18.9990
"C"	18.9987

These values can be compared with the value 18.9992 ± 0.0002 obtained by two physical methods. Nier[20] gives this figure as the best atomic weight value derivable from existing mass-spectrographic data; and exactly the same value is derived from the nuclear reaction data of Li, Whaling, Fowler and Lauritsen.[21] It is noteworthy, as Nier[20] points out, that the uncertainty in the physical values stems from the uncertainty in the conversion factor needed to convert from the physical to the chemical scale rather than from the physical measurements themselves. As is evident, the atomic weight of fluorine derived from our analyses of perfluorobutyryl chloride is in excellent agreement with the physical values. The evidence, therefore, is quite conclusive for revising the chemical atomic weight from the present value 19.00 to 18.999.

Since the chemical atomic weight of fluorine has been so well established by physical methods,[20,21] it is of interest to calculate the atomic weight of silver based on it. If we accept the usual values for Cl and O, and take F ± 18.9992 and C = 12.0114, we obtain from the results of our analyses of perfluorobutyryl chloride the following for the atomic weight of silver

Using mean ratio value	Atomic weight of silver
"B"	107.880
"C"	107.881

(19) E. Wichers, THIS JOURNAL, **76**, 3235 (1956).

(20) A. O. Nier, *Science*, **121**, 737 (1955).

(21) C. W. Li, W. Whaling, W. A. Fowler and C. C. Lauritsen, *Phys. Rev.*, **83**, 512 (1951).

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The derived value is in excellent agreement with the figure 107.880 which has been accepted for many years by chemists. Although this outcome is just another way of showing that the results of our present series of analyses are consistent with the physical values for the atomic weights of fluorine and carbon, it is of particular importance because of the special position of the atomic weight of silver as the practical basis of the chemical atomic weight scale. The significance of this last point will be elaborated further in the section which follows.

The possibility of comparing fluorine and silver by the analysis of perfluorobutyryl chloride opens the way for a consideration of a number of questions. For one thing serious consideration can now be given to the adoption of fluorine as the basis of the chemical atomic weight scale. Some of the arguments in favor of the change may be noted here: The element is anisotopic[22] and hence, unlike oxygen, its chemical atomic weight is constant. Further to go from natural oxygen (16) to an assigned value of 19 for fluorine would mean an increase in the chemical atomic weight values of the other elements by less than 1 part in 20,000, a very minor change which should not present serious practical problems. Finally, since the atomic mass of fluorine can be established quite accurately on the physical scale by physical methods, fluorine could serve as a bridge between the two scales. Naturally, if fluorine were to be accepted as the basis of the chemical scale there would be need of further work to establish as accurately as possible the relationship between fluorine and silver. It would be desirable not only to repeat the analyses of perfluorobutyryl chloride and undertake the analyses of a pure sample of the corresponding bromide, but it would be important to explore the suitability of the acid halides of other perfluoroaliphatic acids for comparing the atomic weights of fluorine and silver.

In the latest "Report on Atomic Weights" Wichers[19] presents a most enlightening discussion of the "Problem of Two Scales" and raises the question of unifying the chemical and physical atomic weight scales. Of the various possibilities Wichers regards a common scale, based on fluorine with an assigned mass of 19, as the most attractive one. The fact that our work gives a comparison between the atomic weights of fluorine and silver (the practical basis of many chemical atomic weight values) lends support to Wicher's conclusion.

Acknowledgments.—This work on atomic weight of fluorine has received partial support from several grants to the senior author. Small grants from the Cyrus M. Warren Fund and the Permanent Science Fund of the American Academy of Arts and Sciences in 1937–38 were of great help; in fact a Troemner No. 10 balance, purchased at that time, was used in the present series of experiments. All the work on derivatives of trifluoroacetic acid carried out immediately following the war was supported by funds from an ONR Contract (onr #71600). A contract with the Division of Research, A.E.C., and a grant from the National Science Foundation, both primarily in support of other atomic weight projects, provided invaluable assistance at critical points in the present set of experiments. The senior author acknowledges gratefully all of this financial assistance.

PORTLAND, OREGON

(22) This term has been proposed by H. E. Duckworth (private communication) as more correct etymologically than the older terms "monoisotopic" and "simple" to describe an element having only one atomic species. For further discussion of term "anisotopic," see footnote 46, ref. 19.

[CONTRIBUTION FROM THE RICHARD BENBRIDGE WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY]

The Preparation and Properties of Rhenium Oxychloride (ReO_3Cl)[1]

BY CLARENCE J. WOLF,[2] A. F. CLIFFORD AND W. H. JOHNSTON

RECEIVED APRIL 15, 1957

Rhenium oxychloride has been prepared in good yields by direct chlorination of rhenium trioxide. The gaseous infrared spectrum, the gas density and the vapor pressure were determined at room temperature. The general handling procedure and some properties of this compound are discussed.

Introduction

Rhenium oxychloride has been prepared by several investigators.[3–7] All of these preparations use essentially one of two procedures, either the reaction between rhenium(VII) oxide and rhenium tetrachloride ($ReCl_4$)[5] in a combustion tube or the oxidation of rhenium trichloride ($ReCl_3$). The present paper describes a direct procedure which gives a superior product which needs only be vacuum distilled to remove dissolved chlorine.

A limited number of physical properties of rhenium oxychloride have been reported. In 1932 Bruke and Ziegler[1] described it as a colorless liquid melting at 4.5°, boiling at 131°, and hydrolyzing immediately in air to perrhenic ($HReO_4$) and hydrochloric acids. In the following year Geilmann and Wrigge[5] reported it to be light sensitive, turning purple in sunlight and becoming colorless in the

(1) This work was supported in part by the United States Atomic Energy Commission under Contract No. At(11-1)-166 with Purdue University

(2) Taken in part from research work done by Clarence J. Wolf for a thesis to be submitted to the Graduate School of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) A. Bruke and K. Zielger, *Ber.*, **65**, 916 (1932).

(4) H. V. A. Brisco, P. L. Robinson and A. J. Rudge, *J. Chem. Soc.*, 2043 (1931).

(5) W. Geilmann and Fr. W. Wrigge, *Z. anorg. allgem. Chem.*, **214**, 248 (1933).

(6) O. W. Kolling, *Trans. Kansas Acad. Sci.*, **56**, 378 (1953).

(7) Rhenium tetrachloride is a mixture of the trichloride and the pentachloride.

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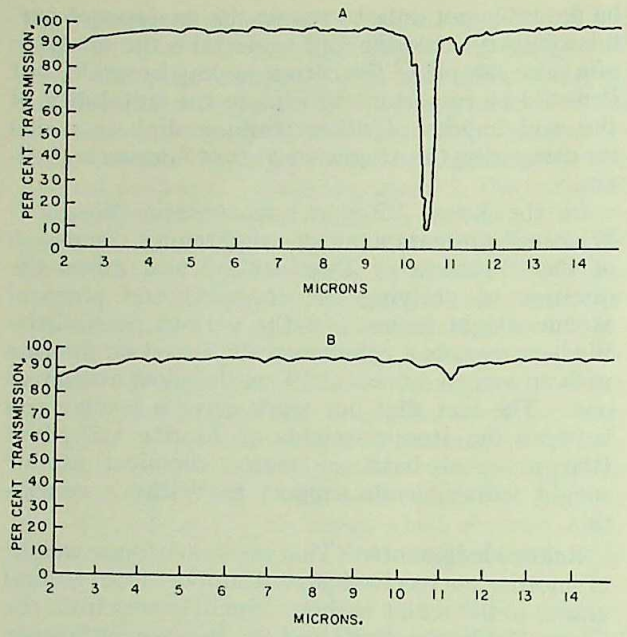

Fig. 1.—Infrared absorption spectrum of ReO_3Cl: upper (A), gaseous ReO_3Cl; lower (B), evacuated gas cell.

dark. In 1952 the microwave spectrum was studied by Amble, *et al.*,[8] who reported the structure as a symmetric top with an Re–Cl distance of 2.230 ± 0.004 Å., and Re–O distance of 1.761 ± 0.003 Å., and the Cl–Re–O angle as 108° 20′ ± 1°. Recently Eichhoff and Weigel[9] studied the Raman spectrum of rhenium oxychloride but encountered difficulty in photodecomposition of the sample. Some additional properties of this compound are reported in the present work.

Experimental

Rhenium(VII) oxide (Re_2O_7) readily is converted to rhenium(VI) oxide (ReO_3) by reduction with dioxane.[10] The reactions are

$$Re_2O_7 + xC_4H_8O_2 \longrightarrow Re_2O_7\cdot(C_4H_8O_2)_x$$

$$Re_2O_7\cdot(C_4H_8O_2)_x \xrightarrow{125\text{–}145^\circ} ReO_3 + \text{decomposition products}$$

The rhenium(VI) oxide is then allowed to react with chlorine in a dry combustion tube between 160 and 190°

$$2ReO_3 + Cl_2 \xrightarrow{160\text{–}190^\circ} 2ReO_3Cl$$

The yield obtained from these reactions is above 70%. The product is quite pure and is colored slightly yellow due to dissolved chlorine; this, however, may be removed readily by vacuum distillation leaving a clear colorless liquid boiling at 128° (uncor.). Analyses for chlorine were 12.74 and 12.71% as compared to the theoretical value of 13.14%. This slightly low value was caused by some hydrolysis in air during weighing.

Some precautions are necessary in the handling of this compound. Rhenium oxychloride reacts immediately with mercury and with ordinary stopcock grease; therefore, it must be trapped before reaching the diffusion pump. Furthermore, a special stopcock grease such as "Halocarbon grease" (Halocarbon Products Corporation) should be used to minimize the decomposition. Even this grease, however, caused some slight decomposition of the oxychloride leaving a purple colored substance, probably rhenium(VI) oxide (ReO_3).

To test the hypothesis that the purple color was due to this oxide, some ReO_3 was dissolved in a small amount of the oxychloride. It is interesting to note that a similar purple solution was formed.

The rhenium oxychloride can be kept without decomposition in a greaseless system of glass, Kovar and Monel. In this manner, we were able to keep the liquid colorless for several weeks.

Rhenium oxychloride is extremely reactive toward mercury, silver and a large number of organic compounds. Carbon tetrachloride, however, was found to be a good solvent, giving a clear, colorless, solution. The oxychloride does not appear to react with brass that has been first chlorinated, or with stainless steel.

The infrared spectrum of gaseous rhenium oxychloride was measured in a ten centimeter gas cell with potassium bromide windows, using a double beam Perkin–Elmer Recording Infrared Spectrometer Model 21. The spectrometer is shown in Fig. 1. Curve A is the absorption spectrum of the vapor in the cell and curve B is the absorption spectrum of the cell after removal of the oxychloride. The vapor pressure as measured with a Bourdon gage is 4.5 ± 0.5 mm. of mercury at room temperature. The vapor density of rhenium oxychloride at room temperature is 6.5×10^{-5} g./ml. (average of two determinations). Assuming the ideal gas law, the experimental molecular weight was 268 g. compared to a theoretical value of 270 g.

LAFAYETTE, INDIANA

(8) E. Amble, S. L. Miller, A. L. Schawlow and C. H. Towner, *J. Chem. Phys.*, **20**, 192 (1952).

(9) H. J. Eichhoff and F. Weigel, *Z. anorg. allgem. Chem.*, **275**, 267 (1954).

(10) L. F. Audrieth, Editor-in-chief; "Inorganic Syntheses," Vol. III, McGraw-Hill Book Co., New York, N. Y., 1950, p. 186.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

The Thermal Decomposition of Uranium Peroxide, $UO_4\cdot 2H_2O$

BY JAMES E. BOGGS AND MUNZIR EL-CHEHABI

RECEIVED APRIL 1, 1957

$UO_4\cdot 2H_2O$ decomposes slowly in the temperature range 90–195° to form a different peroxide, U_2O_7. The rate of this reaction has been followed and the properties of U_2O_7, which has not been isolated previously, have been investigated.

Uranium peroxide, $UO_4\cdot 2H_2O$, has been known since 1876[1] and has been subjected to intensive investigation in recent years. Nevertheless, its constitution is still unknown, some authors considering it to be a true peroxide hydrate, others a peroxy acid, and others an addition compound of uranium oxide, $UO_3\cdot H_2O_2\cdot H_2O$.

The existence of one other peroxide of uranium, U_2O_7, has been suggested. Evidence for a hydrated form of this substance was found by Hüttig and von Schroeder[2] in their experiments on the decomposition of hydrated UO_4. Later, Kraus[3] ob-

(1) T. Fairley, *Chem. News*, **33**, 237 (1876).

(2) G. F. Hüttig and E. von Schroeder, *Z. anorg. allgem. Chem.*, **121**, 243 (1922).

(3) C. A. Kraus, Manhattan District Project Report A-281, Sept. 7, 1942.

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tained a red powder with the composition $UO_{3.14}$ to $UO_{3.38}$ by heating $UO_4 \cdot 2H_2O$ at 139° for 24 hours, then raising the temperature to 300°. Based on our experiments, this was probably a mixture of U_2O_7 and UO_3.

Hüttig and von Schroeder[2] studied the decomposition of $UO_4 \cdot xH_2O$ under 15 mm. water vapor pressure between 20 and 500°. They report that $UO_4 \cdot 4.5H_2O$ is stable up to about 55°, at which temperature water begins to be lost. At about 63°, one-half of the peroxide oxygen is lost, resulting in a composition corresponding to $U_2O_7 \cdot 6H_2O$. Between 63 and 162° the oxygen content remains unchanged while the water content gradually falls to $U_2O_7 \cdot 4H_2O$. At about 162°, water and oxygen are lost together, forming the hydrated oxide $UO_3 \cdot 0.5H_2O$. These results are very difficult to understand in view of the repeated success of many workers in preparing $UO_4 \cdot 2H_2O$ by drying freshly precipitated uranium peroxide at 100° for a short time.

More recently, Duval[4] has studied the decomposition of hydrated uranium peroxide, using a thermogravimetric balance. He concludes that water is smoothly driven off up to a temperature of 90°, at which point the composition corresponds to $UO_4 \cdot 2H_2O$. Between 90 and 180°, one molecule of H_2O_2 is lost, forming $UO_3 \cdot H_2O$. This is followed by the gradual loss of water, leaving anhydrous UO_3. From this he concludes that "uranium peroxide" must really be $UO_3 \cdot H_2O_2 \cdot H_2O$, although, as he points out, it is surprising that a substance containing a combined molecule of hydrogen peroxide is still relatively stable in the 100° region.

We have reinvestigated the decomposition of $UO_4 \cdot 2H_2O$ between 90 and 200° in a controlled atmosphere, making certain that the time of heating was adequate to ensure equilibrium.

Experimental

Materials.—Hydrated uranium peroxide was precipitated from $UO_2(NO_3)_2 \cdot 6H_2O$ (Calcd.: U, 47.4. Found: U, 47.5) purchased from Baker Chemical Co., using the procedure described by Watt, Achorn and Marley.[5] The resulting precipitate was washed with distilled water, dried at 100° for 4 hours, and stored over $CaCl_2$. (Calcd. for $UO_4 \cdot 2H_2O$: U, 70.4; peroxidic oxygen, 9.46. Found: U, 69.9; peroxidic oxygen, 9.25.)

Analytical Methods.—Uranium was determined either by ignition to U_3O_8[6] or by a volumetric method.[7] Peroxidic oxygen was determined by dissolving the compound in dilute sulfuric acid and titrating with potassium permanganate.

Experimental Method.—A tube furnace was constructed, the temperature of which could be regulated and maintained within ±0.5° by means of an automatic controller. A stream of oxygen or air was allowed to bubble through water at a controlled temperature, below the temperature of the room, in order to pick up a controlled quantity of water vapor, then passed over a sample of 2 to 2.5 g. of $UO_4 \cdot 2H_2O$ in a porcelain boat in the furnace. Samples of the decomposed uranium peroxide were removed periodically and analyzed for peroxidic oxygen. These analyses were checked at intervals by analysis for uranium and by determination of the total weight loss.

Results

The first experiments were performed by heating $UO_4 \cdot 2H_2O$ at a constant temperature in an atmosphere of oxygen containing 30 mm. water vapor pressure. Subsequent experiments showed that the same results were obtained using an atmosphere of air instead of oxygen and using water vapor pressures down to 8 mm. All of the experiments at temperatures up to 195° showed the slow decomposition of $UO_4 \cdot 2H_2O$ according to the equation

$$4UO_4 \cdot 2H_2O \longrightarrow 2U_2O_7 + O_2 + 8H_2O \qquad (1)$$

The reaction was followed to completion at temperatures of 130° and above. At lower temperatures, down to 90°, the reaction was still incomplete after a month of heating at constant temperature, but the resulting mixture showed the characteristic properties of U_2O_7.

Pure U_2O_7 (Calcd.: U, 80.96. Found: U, 80.72) was an orange hygroscopic solid which decomposed to UO_3 and oxygen gas in contact with water, and to uranyl salts and oxygen gas in contact with acids. The addition of U_2O_7 to acid permanganate solutions did not decolorize them, although oxygen was liberated. At higher temperatures U_2O_7 slowly loses oxygen to form UO_3. A weighed sample of U_2O_7 was added to dilute sulfuric acid and the oxygen released was collected. The volume obtained was 94% of that predicted from the equation

$$2U_2O_7 + 8H^+ \longrightarrow 4UO_2^{++} + 4H_2O + O_2$$

and the remaining 6% can be accounted for by solubility in the water.

U_2O_7 was pelleted with KBr and the infrared spectrum scanned between 2 and 16 μ on a Baird model 4–55 recording spectrophotometer. In addition to the usual absorption above 10 μ, which can be attributed to the U–O bond, U_2O_7 showed a sharp peak at 7.1–7.2 μ. This peak was not found in UO_3 or $UO_4 \cdot 2H_2O$.

The time required for reaction 1 to reach completion is very long. As an illustration, the data at 130° are presented in Table I. The $KMnO_4$ titration used in the analysis determined the peroxidic oxygen in the undecomposed $UO_4 \cdot 2H_2O$, but not that in the U_2O_7 produced. Even at 90°, reaction 1 occurred very slowly, as evidenced by the evolution of oxygen when $UO_4 \cdot 2H_2O$ which had been heated at this temperature for a long time

TABLE I

RATE OF CONVERSION OF $UO_4 \cdot 2H_2O$ TO U_2O_7 AT 130°

Time, hr.	$\%UO_4 \cdot 2H_2O$ remaining	$k \times 10^2$ (hr.$^{-1}$)
51	51.1	1.32
68	35.4	1.53
92	23.3	1.58
116	18.4	1.46
179	9.60	1.31
228	6.31	1.21
275	3.42	1.37
		Av. 1.40

(4) C. Duval, *Anal. Chem. Acta*, **3**, 337 (1949).
(5) G. W. Watt, S. L. Achorn and J. L. Marley, THIS JOURNAL, **72**, 3341 (1950).
(6) W. W. Scott, "Standard Methods of Chemical Analysis," Vol. 1, 5th ed., D. Van Nostrand Co., New York, N. Y., 1939, p. 1022.
(7) U. S. Atomic Energy Commission Laboratory, New Brunswick, N. J., "Manual of Analytical Methods for the Determination of Uranium and Thorium in their Ores," U. S. Govt. Printing Office, Washington, D. C., 1955, p. 1.

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was added to water. At temperatures of 200° and above, the decomposition of $UO_4 \cdot 2H_2O$ leads to UO_3 without the formation of U_2O_7.

The rate of decomposition of $UO_4 \cdot 2H_2O$ to U_2O_7 was found to give surprisingly good agreement with first-order kinetics, the rate of decomposition being proportional to the quantity of undecomposed peroxide. Table I shows the first-order rate constant calculated at 130°, the agreement being as good as could be expected from the accuracy of the measurements. In a similar manner the rate constant was found to be 4.4×10^{-4} hr.$^{-1}$ at 100°, 4.0×10^{-3} hr.$^{-1}$ at 120°, and 1.3×10^{-1} hr.$^{-1}$ at 150°. An Arrhenius plot of these data gives a very good fit to a straight line, from which the activation energy can be calculated to be 35 kcal./mole. It is questionable whether such good results would have been obtained if preparations of radically different crystal size had been used.

Discussion

The results obtained in this investigation are in striking disagreement with those reported by Duval[4] and in the earlier work by Hüttig and von Schroeder.[2] The explanation may lie in the extremely long time required for reaction 1 to reach completion. In the thermogravimetric method used by Duval, sufficient time for reaction 1 to reach completion could not possibly have been allowed, and Hüttig and von Schroeder do not state the length of time they heated their samples.

It may also be significant that both Hüttig and von Schroeder and Duval started with moist UO_4, containing an amount of water in excess of that required by the formula $UO_4 \cdot 2H_2O$, while in this investigation dried $UO_4 \cdot 2H_2O$ was employed.

On the basis of our experiments it may be concluded that $UO_4 \cdot 2H_2O$ decomposes to U_2O_7 in the temperature range between 90 and 195° and that the decomposition reaction does not give any evidence to support the formulation of uranium peroxide as $UO_3 \cdot H_2O_2 \cdot H_2O$.

AUSTIN 12, TEXAS

[CONTRIBUTION FROM THE LINCOLN LABORATORY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Hydrolysis of $A^{III}B^{V}$ Intermetallic Compounds[1]

BY J. A. KAFALAS, H. C. GATOS AND M. J. BUTTON

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$A^{III}B^{V}$ intermetallic compounds hydrolyze to a varying degree. Phosphides hydrolyze readily in acid media at room temperature with formation of phosphine. Arsenides and antimonides hydrolyze to a lesser extent.

Intermetallic compounds of the type $A^{III}B^{V}$ (InSb, GaAs, etc.) have become of considerable importance in recent years because of their semi-conducting properties.[2] During and after their preparation these compounds are generally brought into contact with aqueous media. They are usually prepared, for example, using an excess of constituent A; A is subsequently leached by an acid which does not appreciably attack the compound itself. Furthermore, for certain applications the crystal surfaces are treated with acid or basic solutions. The purpose of this study was to determine whether the above intermetallic compounds hydrolyze in aqueous media to form highly toxic hydrides of the type $B^{V}H_3$ (*viz.*, PH_3, AsH_3, SbH_3) according to the reaction

$$A^{III}B^{V} + 3H_2O \longrightarrow A^{III}(OH)_3 + B^{V}H_3$$

Preparation of Samples.—The representative intermetallic compounds used were InP, GaAs and GaSb, containing radioactive P, As and Sb, respectively. They were prepared as follows.

InP.—Elementary P, containing P^{32}, and In were placed in a quartz tube which was subsequently evacuated and sealed off. The mixture was then heated for one hour at 1050°.[3] The resulting sample was treated briefly with cold concentrated HNO_3 in order to remove the excess indium. An X-ray powder pattern confirmed the formation of InP. The radioactive P^{32} was obtained from $Ca_3(PO_4)_2$, containing P^{32}, by reduction with charcoal and SiO_2 at 1300°.

GaAs.—Elementary arsenic containing radioactive As^{73-74} together with non-radioactive GaAs was placed in a quartz tube which was then evacuated and sealed off. The end of the tube containing the GaAs was heated for several hours above the melting point (1280°) of GaAs. This treatment ensured homogeneous distribution of radioactive arsenic throughout the GaAs. The radioactive arsenic was obtained from radioactive $AsCl_3$ by reduction with H_3PO_2 and $SnCl_2$.

GaSb.—Radioactive Sb^{125} was homogeneously distributed in GaSb in the manner described for GaAs (m.p. of GaSb 725°). The radioactive antimony was obtained from $SbCl_3$ by reduction with iron and $SnCl_2$ in 16% HCl solution.

Experimental Technique.—The above compounds were crushed to coarse powders and were employed in this form. Measurements of the radioactive content of weighed fractions showed that the radioactive species were distributed homogeneously throughout the samples.

The apparatus employed in this study is shown in Fig. 1. The various coarse powders were placed on a fritted disk F in the reaction chamber S. A solution of known *p*H was added through the funnel P and a moderate stream of nitrogen was bubbled through the solution and through the adsorption traps T_1 and T_2 which contained an oxidizing solution of iodine, KI and $NaHCO_3$. The stream of nitrogen was employed for the purpose of stirring the reaction mixture and for carrying any SbH_3, AsH_3, PH_3 or other volatile hydrides formed into the adsorption traps as rapidly as possible. The reaction chamber S was designed so that no radioactivity was carried into the traps other than that associated with the gaseous products. Several blank tests were performed in which chamber S contained a radioactive solution, but not radioactive gases. In all cases, the nitrogen stream carried no detectable radioactivity into the traps.

Each sample of the intermetallic compounds was exposed to the solution for 16 hours. Upon completion of each run,

(1) The research reported in this document was supported jointly by the Army, Navy and Air Force under contract with Massachusetts Institute of Technology.

(2) L. Pincherle and J. M. Radcliffe, *Advances in Phys.*, **5**, 271 (1956).

(3) Because the vapor pressure of free P is very high at this temperature one end of the quartz tube was kept at a lower temperature. In this way explosions were prevented. Similar precautions were taken in the preparation of arsenides.

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liquid samples were withdrawn from the adsorption traps and counted by means of a cylindrical, well-type scintillation counter. All experiments were performed at room temperature.

Results.—The results obtained are summarized in Table I. It can be seen that InP reacts readily in acid solutions to form volatile hydrides of phosphorus. This result is to be expected in view

TABLE I

FORMATION OF VOLATILE HYDRIDES BY HYDROLYSIS OF $A^{III}B^{V}$ INTERMETALLIC COMPOUNDS IN CONTACT WITH AQUEOUS MEDIA FOR 16 HOURS

Intermetallic compd.	Soln. used	Amt. of hydride recovered, expressed in γ per cm.^{2} of $A^{III}B^{V}$	Hydride
InP	10 *N* NaOH	N.S.[a]	PH_3
	1 *N* NaOH	N.S.	
	0.1 *N* NaOH	N.S.	
	Dist. H_2O	N.S.	
	0.1 *N* HCl	0.35	
	1 *N* HCl	45.0	
	10 *N* HCl	Gross amounts (samples dissolve readily)	
GaAs	1 *N* NaOH	N.S.	AsH_3
	0.1 *N* NaOH	N.S.	
	0.01 *N* NaOH	N.S.	
	Dist. H_2O	N.S.	
	0.1 *N* HCl	0.35	
	1.2 *N* HCl	0.35	
	12.0 *N* HCl	0.35	
GaSb	Dist. H_2O	N.S.	SbH_3
	0.06 *N* HCl	0.01	
	1.8 *N* HCl	0.01	
	6.1 *N* HCl	N.S.	
	12 *N* HCl	N.S.	

[a] Not significant, <0.005 microgram.

of the fact that PH_3 is best prepared from AlP and H_2SO_4.[4] PH_3 prepared in this way usually contains traces of P_2H_4. It is of interest to note that InP reacts with HCl solutions, dilute or hot concentrated HNO_3, but it does not react with concentrated HNO_3 at room temperature. In this respect InP behaves like germanium which exhibits chemical passivity in concentrated HNO_3.[5] Similarities in crystalline structure and physical properties between the $A^{III}B^{V}$ intermetallic compounds and the Group IV_A elements are already known.[2] GaAs reacts to a lesser extent in acid solutions than does InP. AsH_3 is presumably formed in this reaction; it is the only known hydride of arsenic and its preparation from arsenides, such as Zn_3As_2, with H_2SO_4

(4) L. Moser and A. Brukl, *Z. anorg. Chem.*, **121**, 73 (1922).
(5) M. C. Cretella and H. C. Gatos, to be submitted for publication to the *J. Electrochem. Soc.*

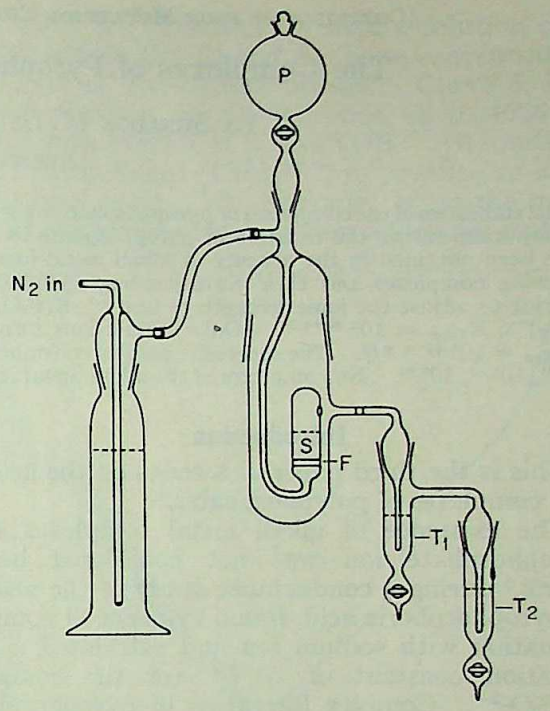

Fig. 1.—Apparatus for studying the hydrolysis of intermetallic compounds.

is well known.[6] GaAs, like InP, becomes passive in concentrated HNO_3 at room temperature. GaSb reacts to an even lesser extent in acid solutions than does GaAs. The formation of SbH_3 is known to take place by the action of H_2SO_4 on Sb–Mg alloys.[7] Apparently, SbH_3 can be prepared in any appreciable amounts in the presence of excessive nascent hydrogen.

From the above it follows that InP and, in general, all $A^{III}P$ compounds should be considered as potential health hazards when in contact with acid solutions. Arsenides and antimonides also represent potential hazards in acid solutions but to a lesser degree than the corresponding phosphides.

It should be pointed out that the amounts of volatile hydrides recovered in the adsorption traps do not represent quantitatively the extent of hydrolysis of the above intermetallic compounds. Since the hydrides are rather unstable, particularly that of antimony, they undoubtedly undergo a certain amount of decomposition in the solution. In this study, however, we were concerned only with that portion of volatile products which persists in the gaseous phase and, thus, constitute a health hazard.

LEXINGTON, MASS.

(6) N. V. Sidgwick, "The Chemical Elements and Their Compounds," Clarendon Press, Oxford, 1950, p. 760.
(7) Ref. 6, p. 761.

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[CONTRIBUTION FROM MCPHERSON CHEMICAL LABORATORY, THE OHIO STATE UNIVERSITY]

The Complexes of Pyrophosphate Ion with Alkali Metal Ions

BY SHELDON M. LAMBERT[1] AND JAMES I. WATTERS[2]

RECEIVED MARCH 18, 1957

The stabilities of the complexes of pyrophosphate ion with sodium, potassium and lithium ions have been calculated from the *p*H lowering during the titration of pyrophosphate ion with hydrogen ion. The acidity constants of pyrophosphoric acid have been obtained in the absence of alkali metal ions and compared with those of ortho- and triphosphoric acid. The following complexes and their corresponding complexity constants were obtained at 25° using tetramethylammonium chloride to adjust the ionic strength to unity. $K(P_2O_7)^{3-}$, $K_{Kpy} = 10^{0.80 \pm 0.06}$; $Na(P_2O_7)^{3-}$, $K_{Napy} = 10^{1.00 \pm 0.06}$; $Li(P_2O_7)^{3-}$, $K_{Lipy} = 10^{2.39 \pm 0.06}$. Only lithium ions formed an acidic complex with the ligand ($HP_2O_7^{3-}$); $Li(HP_2O_7)^{2-}$, $K_{LiHpy} = 10^{1.03 \pm 0.06}$. The successive acidity constants of pyrophosphoric acid at 25° and unity ionic strength were $10^{0.82}$, $10^{1.81}$, $10^{6.13}$, $10^{8.93}$. No complexes of the alkali metal ions with orthophosphate ion were detected.

Introduction

This is the third paper of a series on the acidity and complexes of polyphosphates.[3,4]

The existence of alkali metal complexes with pyrophosphate ion was not considered before Monk,[5] during a conductance study of the acidity of pyrophosphoric acid, found evidence of complex formation with sodium ion and calculated a dissociation constant of $10^{-2.45}$ for the complex, $NaP_2O_7^{3-}$. Complex formation of pyrophosphate with alkali metal ion is of considerable importance since alkali metal ions usually are added to adjust ionic strength or as a source of pyrophosphates.

The classic conductivity measurements of Abbott and Bray[6] yielded reliable values for the acidity constants of pyrophosphoric acid, particularly the first and second constants, while Kolthoff and Bosch[7] obtained excellent values for the third and fourth ionization constants extrapolated to infinite dilution. The tendency of pyrophosphate to form complexes with many metals through chelate ring formation has been the subject of numerous studies.[8-16]

In the present study the acidity constants of pyrophosphoric acid were evaluated at various ionic strengths in the presence of tetramethylammonium chloride with alkali metal ions absent. As in the second paper of this series[4] on triphosphate complexes with alkali metal ions the lowering of the apparent acidity constants of pyrophosphoric acid in the presence of an excess of various alkali metal ions was used as a means of evaluating the extent of complex formation.

(1) Abstracted from the Ph.D. thesis of Sheldon M. Lambert submitted in partial fulfillment of the requirements for the Ph.D. degree, The Ohio State University, 1957.

(2) To whom communications should be directed.

(3) J. I. Watters, E. D. Loughran and S. M. Lambert, THIS JOURNAL, **78**, 4855 (1956).

(4) J. I. Watters, S. M. Lambert and E. D. Loughran, *ibid.*, **79**, 3651 (1957).

(5) C. B. Monk, *J. Chem. Soc.*, 423 (1949).

(6) G. A. Abbott and W. C. Bray, THIS JOURNAL, **31**, 729 (1909).

(7) I. M. Kolthoff and W. Bosch, *Rec. trav. chim.*, **47**, 826 (1928).

(8) I. M. Kolthoff and J. I. Watters, *Ind. Eng. Chem., Anal. Ed.*, **15**, 8 (1943).

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Theoretical

If an acid can be titrated in the presence of a relatively large excess of metal ion without precipitate formation, it is possible to investigate complex formation by the lowering of the *p*H. When the inflections at the various equivalence points persist for the stepwise addition or removal of hydrogen ions, the calculations are greatly simplified. In this case, it is evident that each ligand adds one hydrogen ion in a stepwise manner even though the ligand may also be bound to a metal ion. Under these conditions it is expedient to define a function which is called the apparent acidity constant,[11] K'_{4-n}, for this stepwise addition of hydrogen ion as

$$K'_{4-n} = \frac{[H^+]\Sigma q(M_m(H_nP_2O_7)_q^{(q(4-n)-m)-})}{\Sigma q(M_m(H_{n+1}P_2O_7)_q^{(q(3-n)-m)-})} \quad (1)$$

where m, n and q indicate the number of metal, hydrogen and pyrophosphate ions in any particular species. In this paper parentheses indicate concentrations and brackets indicate activities. The number of bound hydrogen ions, n, has a single value from zero to four if the addition of hydrogen ion is stepwise while m and q may have several values if several complex species, and the uncomplexed ligand, as well, are in equilibrium. The general equation for the stepwise addition of hydrogen ion to pyrophosphate ion and the corresponding acidity constant are

$$H^+ + H_nP_2O_7^{(4-n)-} \rightleftharpoons H_{n+1}P_2O_7^{(3-n)-}$$

$$K_{4-n} = \frac{[H^+](H_nP_2O_7^{(4-n)-})}{(H_{n+1}P_2O_7^{(3-n)-})} \quad (2)$$

The general equation for the formation of any complex ion and the corresponding complexity constant, $\beta_{M_mH_nL_q}$, are

$$mM^+ + qH_nP_2O_7^{q(4-n)-} \rightleftharpoons M_m(H_nP_2O_7)_q^{(q(4-n)-m)-}$$

$$\beta_{M_mH_nL_q} = \frac{(M_m(H_nP_2O_7)_q^{(q(4-n)-m)-})}{(M^+)^m(H_nP_2O_7^{(4-n)-})^q} \quad (3)$$

where the subscript L indicates the ligand $P_2O_7^{4-}$.

The equations used to calculate the complex formation constants were derived by substituting equations having the forms of (2) and (3) into (1) with m and q assumed to be equal to unity.

$$K_3' = \frac{[H^+][(HP_2O_7^{3-}) + (MHP_2O_7^{2-})]}{(H_2P_2O_7^{2-})} = K_3 + K_{MHL}K_3(M^+) \quad (4)$$

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$$K_4' = \frac{[H^+][(P_2O_7^{4-}) + (MP_2O_7^{3-})]}{(HP_2O_7^{3-}) + (MHP_2O_7^{2-})} = \frac{K_4 + K_{ML}K_4(M^+)}{1 + K_{MHL}(M^+)} \quad (5)$$

K_3 and K_4 are the acidity constants of pyrophosphoric acid, while K_{ML} and K_{MHL} are the formation constants for the complexes $M(P_2O_7)^{3-}$ and $M(HP_2O_7)^{2-}$.

From these equations it follows that the apparent acidity constants are constants if the concentration of unbound metal ion is constant, provided precautions are taken to avoid changes in activity coefficients. A high concentration of an essentially non-complexing electrolyte and relatively low concentrations of metal ion and pyrophosphate ion were used for this purpose. For the titration of pyrophosphate ion with hydrogen ion in the absence of metal ions the acidity constants can be calculated by the following form of eq. 1. In the presence of metal ions K'_{4-n} is calculated by the same equation

$$K_{4-n} = \frac{[H^+][(n + 1 - a)C_p - K_w/[H^+]f + H^+/f]}{(a - n)C_p + K_w/[H^+]f - [H^+]/f} \quad (6)$$

where a is the number of moles of hydrogen ion per mole of pyrophosphate ion present in any form. The symbol f indicates the activity coefficient of a univalent ion. If the acid is not too dilute the constants have the same value as the pH at $a = n + 1/2$.

Experimental

The source of pyrophosphate ion for most of the experiments was $Na_4P_2O_7 \cdot 10H_2O$, Mallinckrodt analytical reagent grade. The pyrophosphoric acid was prepared from sodium pyrophosphate by the use of the acid form of the ion-exchange resin Dowex 50-X12, 100–200 mesh, low porosity in a manner exactly analogous to that described for the preparation of triphosphoric acid.[3] Potassium pyrophosphate was prepared by heating anhydrous dipotassium hydrogen phosphate at 500 to 700° for 3 hr.[8] Lithium pyrophosphate was prepared in the same manner as lithium triphosphate in the previous study using the exchange resin Dowex 50-X12 charged with lithium ions. All other reagents and the general experimental procedure are described in the previous paper.[4]

The titrations were performed in an aqueous thermostat adjusted to 25 ± 0.1° using the Beckman model G pH meter equipped with a "general purpose" glass electrode.

The $H_4P_2O_7$ or $((CH_3)_4N)_4P_2O_7$ solutions obtained from the columns were tested for removal of sodium ion.[3] The extent of hydrolysis of $((CH_3)_4N)_4P_2O_7$ was tested by titrations and found to be negligible after periods of one week if the solution was stored in a freezer at −15°. Crowther and his co-workers[17,18] studied the hydrolysis of pyrophosphoric acid and found it to be acid catalyzed but not base catalyzed. In the present study no appreciable hydrolysis was observed if the tetramethylammonium pyrophosphate solution was left at room temperature for one hour.

Results and Discussion

The Acidity of Pyrophosphoric Acid.—Since all previous studies of the acidity of pyrophosphoric acid at large ionic strength were made in the presence of alkali metal ions, the acidity constants were re-evaluated using tetramethylammonium chloride to adjust the ionic strength but with alkali metal ions absent.

Curve 1, Fig. 1, was obtained for the titration of 0.02968 $M((CH_3)_4N)_4P_2O_7$ with a solution containing 0.2805 M HCl and the same concentration of $H_4P_2O_7$ as the solution titrated. Curve 5, Fig. 1, was obtained for the titration of 0.04524 M $H_4P_2O_7$ with 0.08901 M $(CH_3)_4NOH$. All solutions contained sufficient $(CH_3)_4NCl$ to produce an ionic strength of unity. The ordinate "a" is the number of equivalents of acid or base added per mole of

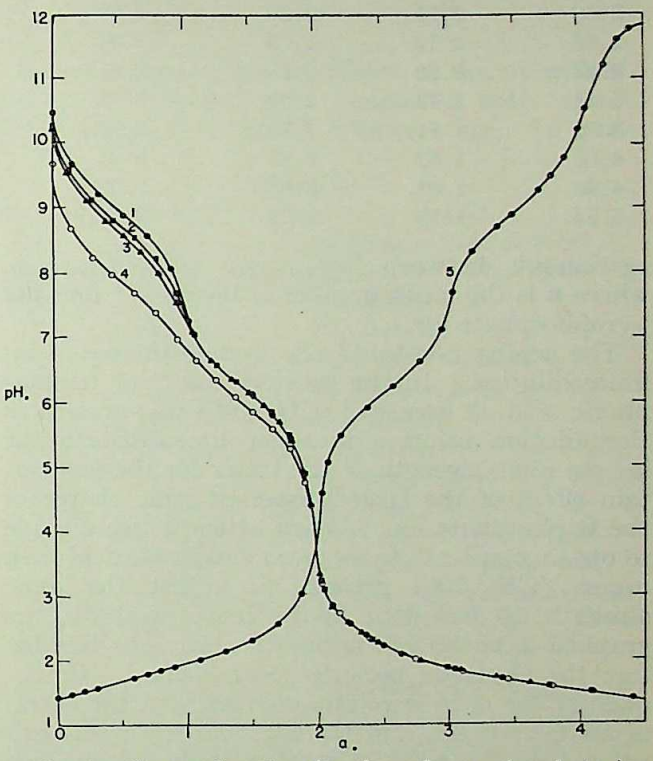

Fig. 1.—Curves for the titration of pyrophosphate ion with hydrochloric acid and the titration of pyrophosphoric acid with tetramethylammonium hydroxide. A comparison of the effects of potassium, sodium and lithium ion on the titration curve of pyrophosphate ion with hydrochloric acid. Curve 1, 0.02968 M $((CH_3)_4N)_4P_2O_7$ titrated with a solution 0.2805 N in HCl and 0.02968 M in $H_4P_2O_7$; curve 2, similar to curve 1, but 0.12 M in K^+; curve 3, 0.12 M in Na^+; curve 4, 0.12 M in Li^{++}; curve 5, 0.04524 M $H_4P_2O_7$ titrated with a solution 0.08901 M $(CH_3)_4NOH$. All solutions adjusted to $\mu = 1$ with $(CH_3)_4NCl$.

pyrophosphate present in any form. The titration curves for pyrophosphoric acid indicate that the first two hydrogen ions are highly dissociated and that the values for their ionization constants are not widely separated. Therefore, Bjerrum's method was used to evaluate these constants in the same manner as for triphosphoric acid.[3] The expression for the stepwise complexity constants is

$$\beta_n = \frac{(H_nP_2O_7^{(4-n)-})}{[H^+]^n(P_2O_7^{4-})}$$

where parentheses indicate concentrations and brackets indicate activities.

Due to the absence of appreciable concentrations of the species $P_2O_7^{4-}$ and $HP_2O_7^{3-}$ at pH values below 3 the simultaneous solution of Bjerrum's formation equation[3] for β_3 and β_4 in groups of two yielded the values of log $\beta_3 = 1.81 \pm 0.05$ and log $\beta_4 = 2.63 \pm 0.05$. Converting to the usual stepwise acidity constants the values are $pK_2 = 1.81 \pm 0.05$ and $pK_1 = 0.82 \pm 0.05$. Table I shows the

(17) J. D. Crowther and A. E. R. Westman, *Can. J. Chem.*, **32**, 42 (1954).

(18) J. D. McGilvery and J. P. Crowther, *ibid.*, **32**, 174 (1954).

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TABLE I

The titration of 20 ml. of a solution of 0.02968 M $((CH_3)_4N)_4P_2O_7$ with a solution 0.2805 M in HCl and 0.02968 M in $H_4P_2O_7$. Both solutions contained sufficient $(CH_3)_4NCl$ to produce an ionic strength of 1.0.

a	pH	$\bar{n}_{theory}$	$\bar{n}_{experiment}$
2.10	2.93	2.07	2.06
2.24	2.61	2.14	2.14
2.37	2.42	2.22	2.22
2.50	2.25	2.29	2.32
2.63	2.13	2.35	2.34
3.03	1.89	2.53	2.51
3.41	1.73	2.64	2.68
3.75	1.61	2.75	2.79
4.08	1.52	2.83	2.88
4.93	1.31	3.00	3.00
5.84	1.15	3.05	3.11

agreement between $\bar{n}_{experimental}$ and $\bar{n}_{theoretical}$, where $\bar{n}$ is the mean number of bound H^+ ions per pyrophosphate ion.

The acidity constants also were evaluated at infinite dilution. In the previous study of triphosphoric acid an excess of $(CH_3)_4NCl$ was present in the dilution solution in order to substitute the known ionic strength of the latter for the less certain effect of the larger dispersed ionic charge of the triphosphate ion. When attempts were made to obtain similar data for pyrophosphoric acid with excess $(CH_3)_4NCl$ present to adjust the ionic strength, as was done in the previous study, the graphed data did not approach a straight line before the electrode became poorly poised. Consequently the data were obtained without the extraneous electrolyte, and the ionic strength was calculated on the basis of total pyrophosphate ionic charge.

The values of K_2, K_3 and K_4 at concentrations approaching infinite dilution were calculated using eq. 6 which contains terms for the degree of hydrolysis and dissociation. The activity coefficients of Harned and Ehlers[19] were used. The p values of K_3 and K_4 at an ionic strength of unity were $pK_3 = 6.13$ and pK_4 8.93. At an ionic strength of 0.1, the value of pK_2, pK_3 and pK_4 were 2.22, 6.36 and 9.11, respectively. The graphic extrapolation to infinite dilution yielded $pK_2 = 2.64$, $pK_3 = 6.76$ and $pK_4 = 9.42$. It is of interest to observe that the last two constants for K_3 and K_4 are quite close to the values $pK_3 = 6.679$ and $pK_4 = 9.391$ obtained by Kolthoff and Bosch using a hydrogen electrode with sodium ion added as the pyrophosphate salt. It is evident from the magnitude of the sodium complexes constant that the latter should not affect their result at infinite dilution.

On the basis of these results the dilution experiments for triphosphoric acid were repeated using the same conditions. These revised constants are included in Table II. The agreement of our data for pyrophosphoric acid using the glass electrode with Kolthoff and Bosch's value using the hydrogen electrode supports these values.

pK_1 was determined by Bates,[20] pK_2 by Bates and Acree[21] and pK_3 by Abbott and Bray.[6] Constants

(19) H. S. Harned and R. W. Ehlers, THIS JOURNAL, **55**, 2179 (1933).

(20) R. G. Bates, *J. Research Natl. Bur. Standards*, **47**, 127 (1951).

(21) R. G. Bates and S. F. Acree, *ibid.*, **30**, 129 (1947).

TABLE II

THERMODYNAMIC IONIZATION CONSTANTS

Acid	H_3PO_4[20,21,6]	$H_4P_2O_7$	$H_5P_3O_{10}$
pK_1	2.15	$-\infty$	$-\infty$
pK_2	7.20	2.64	$-\infty$
pK_3	12.44	6.76	2.30
pK_4	...	9.42	6.50
pK_5	...	..	9.24

having pK values indicated by $-\infty$ were too large to measure.

The Complexes of the Alkali Metals with Pyrophosphate.—Curves 2, 3 and 4, Fig. 1, illustrate the pH lowering effect due to the presence of approximately 0.10 M potassium, sodium and lithium ions in the titration of approximately 0.03 M $((CH_3)_4N)_4P_2O_7$ with a solution containing approximately 0.28 M HCl and the same concentration of $H_4P_2O_7$ as the solution titrated. Since curves 1 to 4 coincide at "a" values beyond 2, it is evident that no complex formation occurs between any of the alkali metal ions and $H_2P_2O_7^{2-}$ or $H_3P_2O_7^{1-}$. Furthermore the reactants are sufficiently dilute so there is no measurable effect on the activity coefficients. Consequently the pH lowering at "a" values below 2 must be due to complex formation.

Comparing curve 2 obtained in the presence of potassium with curve 1, a lowering of the pH occurred only for "a" values less than unity proving the absence of detectable concentrations of potassium hydrogen pyrophosphate complexes, so eq. 5 reduced to the form

$$K_4' = K_4 + K_{KL}K_4(K^+)$$

Using the acidity constants of pyrophosphoric acid taken from the previous section and estimating the concentration of the free potassium ion to be the total concentration less the concentration of pyrophosphate ion one obtains a temporary complexity constant. More accurate values of (K^+) were then obtained on the basis of the temporary constant.

$$K^+ + P_2O_7^{4-} \rightleftharpoons KP_2O_7^{3-}$$

$$K_{KL} = \frac{(KP_2O_7^{3-})}{(K^+)(P_2O_7^{4-})} = 10^{0.80 \pm 0.06}$$

As shown in curve 3 obtained in the presence of sodium ion the pH was lowered only for "a" values less than unity proving the absence of detectable concentrations of acidic sodium complexes. Substituting the values of K_4 and the free sodium ion into eq. 7 as before, one obtains

$$Na^+ + P_2O_7^{4-} \rightleftharpoons NaP_2O_7^{3-}$$

$$K_{NaL} = \frac{(NaP_2O_7^{3-})}{(Na^+)(P_2O_7^{4-})} = 10^{1.00 \pm 0.06}$$

As shown in curve 4, Fig. 1, obtained in the presence of lithium ions, pH lowering occurred for n or "a" values less than 2 proving the presence of complexes of lithium ion with both $P_2O_7^{4-}$ and $HP_2O_7^{3-}$. Substituting the individual values for the apparent constant, K_3, and (Li^+) into eq. 5 yields the values of K_{LiHL} given in Table III for the reaction

$$Li^+ + HP_2O_7^{3-} \rightleftharpoons LiHP_2O_7^{2-}$$

$$K_{LiHL} = \frac{(LiHP_2O_7^{2-})}{(Li^+)(HP_2O_7^{3-})} = 10^{1.03 \pm 0.06}$$

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TABLE III

Metal ion	"a"	pH	$C_L \times 10^{3a}$	$C_M \times 10^{3a}$	log K^b / log K_{KL}
Potassium	0.50	8.71	27.16	109.9	0.78
	.50	8.87	19.87	20.01	.82
	.50	8.72	10.11	100.31	.80
				Av.	.80 ± 0.06
					log K_{NaL}
Sodium	0.50	8.87	2.175	16.20	0.98
	.50	8.84	2.200	28.80	1.02
	.50	8.80	2.180	36.38	0.99
				Av.	1.00 ± 0.06
					log K_{LiL}
Lithium	0.50	8.13	3.667	30.21	2.38
	.50	8.08	3.667	39.80	2.36
	.50	7.98	3.667	50.41	2.43
				Av.	2.39 ± 0.06
					log K_{LiHL}
	1.50	6.00	3.667	30.21	1.02
	1.50	5.97	3.667	39.80	1.00
	1.50	5.91	3.667	50.41	1.06
				Av.	1.03 ± 0.06

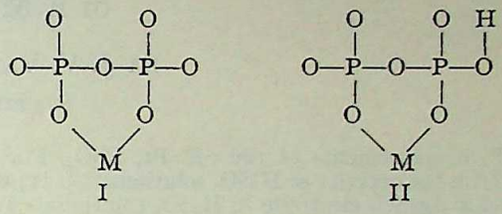
[a] C_L is the total ligand, $P_2O_7^{4-}$, concentration while C_M is the total metal ion concentration. [b] Ionic strength adjusted to unity with $(CH_3)_4NCl$, 25°.

Substituting the values for the apparent acidity constant, K_4', the acidity constant, K_4, the metal concentration, (Li^+), and the above acid complex formation constants into eq. 4 yields the values of the formation constant given in the last column of Table III for the reaction

$$Li^+ + P_2O_7^{4-} \rightleftharpoons LiP_2O_7^{3-}$$

$$K_{LiL} = \frac{(LiP_2O_7^{3-})}{(Li^+)(P_2O_7^{4-})} = 10^{2.39 \pm 0.06}$$

Regarding the structure of the complex, $MP_2O_7^{3-}$, the most pertinent information is the fact that no alkali metal complexes were obtained with orthophosphate ion even though the latter has a greater affinity than pyrophosphate ion for the first associated hydrogen ion. This eliminates the possibility that the metal ion is associated with one or two oxygen atoms of a single phosphorus atom in the pyrophosphate ion. It is possible that the metal ion is a member of a six-membered ring, structure I, which can be formed without strain. However, the bonding with the alkali metal ions is probably essentially electrostatic rather than covalent in nature so the exact position of the metal ion as a part of a chelate ring may be more a function of field strength than of bond direction. If this structure persists for the acidic complex $MHP_2O_7^{2-}$ which forms with lithium ion it seems probable that the hydrogen ion is bonded to one oxygen atom, structure II, possibly with some hydrogen bonding to the other available oxygen atom bonded with the same phosphorus atom, since two six-membered rings involving both phosphorus atoms cannot be formed without some strain. The possibility of strong bonding of a hydrogen ion to one or two oxygen atoms of a single phosphorus atom is evident from the small second and third acidic dissociation constants of orthophosphoric acid.



A comparison of the stabilities of the pyrophosphate and triphosphate complexes with alkali metals shown in Table IV is interesting. In general, the constants of the triphosphate complexes are $10^{0.56 \pm 0.1}$ larger than those of pyrophosphate. As suggested by Martell and Schwarzenbach[11] for the calcium complex this may be due to a tridentate structure involving two six-membered rings containing oxygens bound to all three phosphorus atoms. However, the following factors also may be responsible. The statistical probability of complex formation with triphosphate ion with one metal ion is greater by a factor of 2 if the metal ion enters at a chelating position or by a factor of 8/6 if the metal enters the complex at a single oxygen. Thus the statistical factor may account for $10^{0.3}$ or about half of the difference. Furthermore, the triphosphate ion has a total negative charge of 5 while pyrophosphate has a total negative charge of 4 which may be partially localized in the vicinity of the metal ion. Consequently there is a possibility that the structure of triphosphate complexes with alkali metals may be similar to those of pyrophosphate complexes.

TABLE IV

Metal ion	Ligand	log K^a
K^+	$P_2O_7^{4-}$	log K_{KPy} = 0.80 ± 0.06
K^+	$P_3O_{10}^{1-}$	log K_{KTp} = 1.37 ± 0.06
K^+	$HP_2O_7^{3-}$	Not detected
K^+	$HP_3O_{10}^{4-}$	Not detected
Na^+	$P_2O_7^{4-}$	log K_{NaPy} = 1.00 ± 0.06
Na^+	$P_3O_{10}^{5-}$	log K_{NaTp} = 1.64 ± .06
Na^+	$HP_2O_7^{3-}$	Not detected
Na^+	$HP_3O_{10}^{4-}$	log K_{NaHTp} = 0.77 ± 0.06
Li^+	$P_2O_7^{4-}$	log K_{LiPy} = 2.39 ± 0.06
Li^+	$P_3O_{10}^{5-}$	log K_{LTp} = 2.87 ± .06
Li^+	$HP_2O_7^{3-}$	log K_{LHPy} = 1.03 ± 0.06
Li^+	$HP_3O_{10}^{4-}$	log K_{LHTp} = 1.88 ± .06

[a] Complex formation constants were obtained at an ionic strength adjusted to unity with $(CH_3)_4NCl$, 25°. Pyrophosphate is designated by Py and triphosphate by Tp.

The formation constants of the acidic complexes with either $HP_2O_7^{3-}$ or $HP_3O_{10}^{4-}$ are about $10^{1.2 \pm 0.2}$ smaller than those with hydrogen ion absent. This is consistent with our finding no detectable concentrations of the acid complexes of potassium with either $HP_2O_7^{3-}$ or $HP_3O_{10}^{4-}$ and sodium with $HP_2O_7^{3-}$ since their constants would probably be of the order of unity or smaller.

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[CONTRIBUTION FROM THE OAK RIDGE NATIONAL LABORATORY CHEMISTRY DIVISION]

A Study of the Effect of Dissolved Ag_2SO_4 on the Activity of H_2SO_4 Solutions by Means of E.M.F. Measurements[1]

BY J. V. VAUGHAN AND M. H. LIETZKE

RECEIVED DECEMBER 17, 1956

E.M.F. measurements of the cell Pt, PbO_2, $PbSO_4$, $H_2SO_{4(m)}$, Ag_2SO_4, Ag have been used to demonstrate the effect of Ag_2SO_4 on the activity of H_2SO_4 solutions. It is pointed out that care must be used in the interpretation of data involving the use of a Ag_2SO_4 electrode in H_2SO_4 solutions. It is necessary to refer the thermodynamic functions of the H_2SO_4 to a Ag_2SO_4 solution, the concentration of which may be by no means inappreciable.

Introduction

In a previous paper[2] the solubility of Ag_2SO_4 in H_2SO_4 solutions was described as a function of H_2SO_4 concentration and temperature. It was shown that the solubility increased with H_2SO_4 concentration and that this effect became very pronounced at higher temperatures. Hence when the Ag, Ag_2SO_4 electrode is used in H_2SO_4 solutions account must be taken of the solubility of the Ag_2SO_4 in these solutions. For example, the thermodynamic functions of H_2SO_4 are not those of H_2SO_4 in pure aqueous solution but are referred to a Ag_2SO_4 solution, the concentration of which may be by no means inappreciable. In the present paper it will be shown how e.m.f. measurements of the cell Pt, PbO_2, $PbSO_4$, $H_2SO_{4(m)}$, Ag_2SO_4, Ag can be used to determine the effect of dissolved Ag_2SO_4 on the activity of H_2SO_4 solutions.

Experimental

Two types of Pt, PbO_2, $PbSO_4$ electrodes were used in the present work.

(1) Electrodes were prepared according to the method suggested by Vosburgh and Craig[3] and used by Hamer.[4] Essentially, this type of electrode consisted of a platinum wire covered with a slurry of PbO_2 and $PbSO_4$. The PbO_2 was prepared by electrolysis of a solution of $Pb(NO_3)_2$ in HNO_3. After being treated in hot H_2SO_4 the PbO_2 was mixed with $PbSO_4$ and slurried in H_2SO_4 of the concentration to be studied.

(2) Electrodes were also prepared by plating onto platinum a hard, tightly adhering deposit of PbO_2 from a 35% HNO_3 solution saturated with $Pb(NO_3)_2$. The electrodeposition was carried out at reflux temperature (*ca.* 111°). In the course of the investigation the time of deposition was varied from a few seconds to several hours and the current from 10 milliamperes to one ampere. In all cases the electrode base consisted of a spatula of platinum made by flattening a 25 mm. length of 18 gage wire on one end. The platinum was sealed in a soft glass tube for support so that the average dimensions of the exposed part were 15 × 2 × 0.25 mm. Connection to the platinum was accomplished by soldering stranded insulated copper wire to the end within the glass tube. In the first experiments the electrode was surrounded with $PbSO_4$ slurried in H_2SO_4 of the concentration to be studied. The slurry was held in place with a loose sleeve of Fiberglas or a wad of glass wool. In the later experiments this practice was abandoned and the hot, freshly plated electrode was placed directly in the sulfuric acid cell-medium. Solid $PbSO_4$ was added to the excess Ag_2SO_4 in the cell to maintain a saturated solution with respect to both components.

The Ag, Ag_2SO_4 electrode consisted of a spiral of silver wire spotted to a platinum wire which was sealed into a soft glass tube. Connection with the silver electrode was accomplished in the same fashion as with PbO_2, $PbSO_4$ electrode. The silver spiral was surrounded with crystals of Ag_2SO_4 prepared by the method described by Archibald.[5] A sufficient amount of Ag_2SO_4 was used so that the H_2SO_4 solution was saturated with Ag_2SO_4 at all temperatures. The electrodes and solution were sealed into a Fischer and Porter tube provided with the necessary flanges to hold the Teflon ends in place. This type of apparatus was suitable for use to about 140°.

The electrode assembly was heated in an electric oven provided with a circulating fan. The temperature was controlled to ±1° and was measured by means of an iron–constantan thermocouple.

Electrode and thermocouple e.m.f.'s were measured by means of a Rubicon Portable Precision Potentiometer.

Results and Discussion

In the course of the work an attempt was first made to use the type of Pt, PbO_2, $PbSO_4$ electrode described by Hamer (type 1 above). It was observed, however, that different e.m.f. values were obtained from two different platinum wires immersed in the same PbO_2, $PbSO_4$ slurry when measured against a Ag, Ag_2SO_4 electrode. Although new platinum wires were used which showed no difference in potential between each other in H_2SO_4 solutions, they sometimes showed a difference of at least 100 mv. when immersed in the PbO_2, $PbSO_4$ slurry. The same phenomenon was observed with old platinum wires that had been in contact with lead solutions. No explanation for this behavior is available, although it may be due in some way to adsorption of lead or a lead compound on the platinum.

It was possible to bring two platinum electrodes in PbO_2, $PbSO_4$ slurry to the same e.m.f. *vs.* a Ag, Ag_2SO_4 electrode by connecting them together for a short time. The agreement was temporary, however, and an e.m.f. between them returned on standing. A pair of platinum wires sealed in glass and left for several weeks in a PbO_2, $PbSO_4$ slurry still showed a difference in potential of 1.5 mv. Even annealing the wires in a muffle furnace did not significantly reduce the potential difference. Because of the difficulty of obtaining reproducible results with this type of PbO_2, $PbSO_4$ electrode, attention was directed to a study of the electrode made by plating PbO_2 on platinum (type 2 above).

Hard, mechanically resistant PbO_2 for electrode purposes has been prepared by others.[6] While not all these modifications have been investigated in the present work, the method of preparation described as type 2 seemed to offer the most promise. Merely plating PbO_2 onto platinum by electrolysis of $Pb(NO_3)_2$–HNO_3 solutions without regard to

(1) This document is based on work performed for the Atomic Energy Commission at the Oak Ridge National Laboratory.

(2) M. H. Lietzke and R. W. Stoughton, THIS JOURNAL, **78**, 3023 (1956).

(3) W. C. Vosburgh and D. N. Craig, *ibid.*, **51**, 2009 (1929).

(4) W. J. Hamer, *ibid.*, **57**, 9 (1935).

(5) E. H. Archibald, "The Preparation of Pure Inorganic Substances," John Wiley and Sons, Inc., New York, N. Y., 1932.

(6) K. Sugino, *Bull. Chem. Soc. Japan*, **23**, 115 (1950).

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the concentrations and temperature given did not produce a satisfactory electrode. Besides variability in initial potential from sample to sample the electrodes tended to suffer a decrease in potential with age. This and other possible sources of error in work involving the use of the PbO_2, $PbSO_4$ electrode have been considered by Brown and Zimmer.[7]

Figure 1 shows the e.m.f. values obtained with the cell Pt, PbO_2, $PbSO_4$ (type 2), $H_2SO_{4(m)}$, Ag_2SO_4-(sat.), Ag as a function of temperature and concentration. The various points on the graph were obtained in the course of several different runs at each concentration (6 in the case of 1 m H_2SO_4). A new Pt, PbO_2, $PbSO_4$ electrode was used in each run. The mean values of the e.m.f. (in millivolts) for the system at each concentration of H_2SO_4 as a function of temperature are given by the equations 1a to 1d obtained by the method of least squares.

$$E_{(0.3\ m\ H_2SO_4)} = 838.8 + 0.1041t \quad (1a)$$

$$E_{(0.5\ m\ H_2SO_4)} = 850.8 + 0.2723t \quad (1b)$$

$$E_{(1.0\ m\ H_2SO_4)} = 891.9 + 0.3406t \quad (1c)$$

$$E_{(2.0\ m\ H_2SO_4)} = 928.7 + 0.6126t \quad (1d)$$

Equations 1a to 1d were solved to give mean e.m.f. values at 25° intervals from 0 to 125°.

When the Ag, Ag_2SO_4 electrode is measured against the Pt, PbO_2, $PbSO_4$ electrode in H_2SO_4 the cell reaction is

$$2Ag + PbO_2 + 2H_2SO_4 = Ag_2SO_4 + PbSO_4 + 2H_2O \quad (2)$$

Hence the e.m.f. of the cell can be expressed by the Nernst equation in the form

$$E = E^0 - \frac{RT}{2F} \ln \frac{a_w^2}{a^2 H_2SO_4} \quad (3)$$

Therefore

$$E = E^0 - \frac{RT}{F} \ln a_w + \frac{RT}{F} \ln a_{H_2SO_4} \quad (4)$$

where $a_{H_2SO_4}$ represents the activity of H_2SO_4 in a solution saturated with Ag_2SO_4. In the present work it was not possible to obtain reproducible e.m.f. values over the entire temperature range at H_2SO_4 concentrations much below 0.3 m. If all e.m.f. measurements are referred to the values at 0.3 m and substituted into equation 4, it *follows that*

$$E_m - E_{(0.3)} = \frac{RT}{F} \ln \frac{a_{w(0.3)}}{a_{wm}} + \frac{RT}{F} \ln \frac{a_{H_2SO_4m}}{a_{H_2SO_4(0.3)}} \quad (5)$$

Equation 5 can be rearranged to give

$$\log \frac{a_{H_2SO_4m}}{a_{H_2SO_4(0.3)}} = \frac{F}{2.303RT}(E_m - E_{(0.3)}) - \log \frac{a_{w(0.3)}}{a_{wm}} \quad (6)$$

Values of $a_{H_2SO_4(m)}/a_{H_2SO_4(0.3)}$ were then calculated at 25° intervals from 0 to 125°. For convenience in representing the data and in order to facilitate comparison of $a_{H_2SO_4(m)}/a_{H_2SO_4(0.3)}$ ratios at different molalities values of the ratios were multiplied at each concentration by a constant k_m^{-1}, where $k_m = [a_{H_2SO_4(m)}/a_{H_2SO_4(0.3)}]_0$. This process normalized all the plots to unity at 0°. Values of k_m as a function of concentration both for pure H_2SO_4 solutions and for H_2SO_4 solutions saturated with Ag_2SO_4 are shown in Table I.

The a_w's in equation 6 represent the activity of water in H_2SO_4 solutions saturated with Ag_2SO_4. Since these data were not available a_w's in pure aqueous H_2SO_4 solutions were used in the calculations.[8] Since the terms $\log a_{w(0.3)}/a_{wm}$ are small compared to the $F/2.303$ $(E_m - E_{(0.3)})$ terms this introduces no very large error in the calculations. Values of a_w above 60° were derived by a linear extrapolation of the values measured between 0 and 60°.

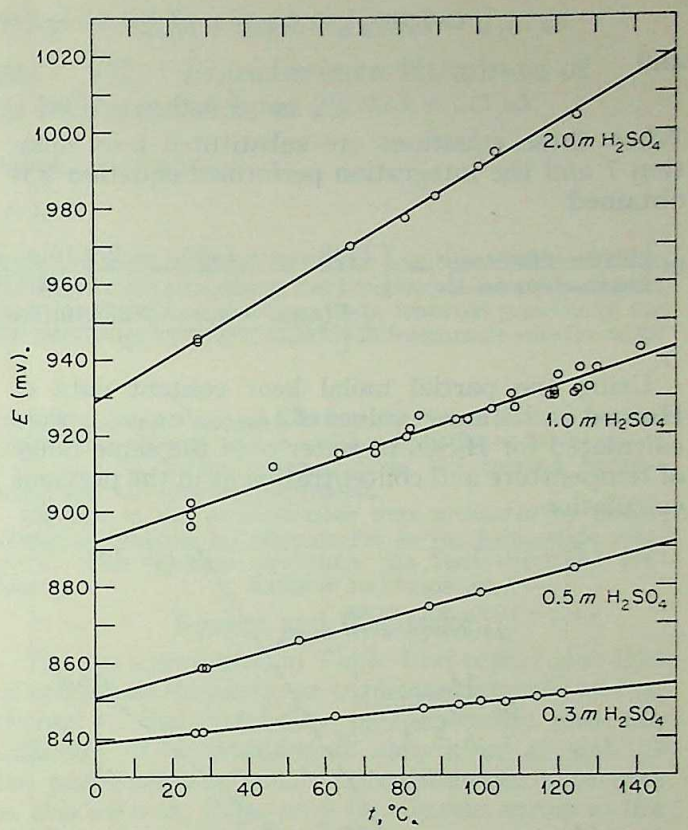

Fig. 1.—E.m.f. of the cell Pt, PbO_2, $PbSO_4$, $H_2SO_4(m)$, Ag_2SO_4, Ag as a function of temperature and H_2SO_4 concentration.

TABLE I

VALUES OF $k_m = [a_{H_2SO_4(m)}/a_{H_2SO_4(0.3)}]_0$ AS A FUNCTION OF CONCENTRATION

$m_{H_2SO_4}$	0.5	1.0	2.0
$k_{H_2SO_4}$	2.8690	14.423	109.48
$k_{H_2SO_4 + Ag_2SO_4}$	1.652	9.270	41.93

In order to compare the values of $a_{H_2SO_4}/a_{H_2SO_4(0.3)}$ measured in H_2SO_4 solutions saturated with Ag_2SO_4 with values of the same ratio measured in H_2SO_4 solutions containing no Ag_2SO_4 equation 7 was integrated over the desired temperature range.

$$\frac{\partial \ln a_m/a_{(0.3)}}{\partial T} = \frac{\bar{L}_2(T)_{(0.3)} - \bar{L}_2(T)_m}{RT^2} \quad (7)$$

In this equation a_m and $a_{(0.3)}$ refer to activities of H_2SO_4 in water and $\bar{L}_2(T)_m$ and $\bar{L}_2(T)_{(0.3)}$ to the corresponding partial molal heat content values of the H_2SO_4 which are functions of the temperature. The $\bar{L}_2(T)$ values have been determined by Hamer and can be expressed as quadratic functions of the temperature as shown in equations 8 and 8a.

(7) D. J. Brown and J. C. Zimmer, THIS JOURNAL, 52, 1 (1930).

(8) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, N. Y., 1950, p. 436.

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$$\bar{L}_2(T)_{(.3)} = \bar{L}_2(0)_{(0.3)} + \alpha_{(0.3)}t + \beta_{(0.3)}t^2 \quad (8)$$

and

$$\bar{L}_2(T)_m = \bar{L}_2(0)_m + \alpha_m t + \beta_m t^2 \quad (8a)$$

When these equations are substituted into equation 7 and the integration performed equation 9 is obtained

$$\ln \frac{[a_{H_2SO_4m}/a_{H_2SO_4(0.3)}]_t}{[a_{H_2SO_4m}/a_{H_2SO_4(0.3)}]_0} = \left[\frac{\bar{L}_2(0)_{(0.3)} - \bar{L}_2(0)_m - 273.16(\alpha_{(0.3)} - \alpha_m) + 273.16^2(\beta_{(0.3)} - \beta_m)}{273.16RT}\right](T - 273.16) + \left[\frac{(\alpha_{(0.3)} - \alpha_m) - 2(273.16)(\beta_{(0.3)} - \beta_m)}{R}\right]\ln T/273.16 + \left[\frac{(\beta_{(0.3)} - \beta_m)(T - 273.16)}{R}\right] \quad (9)$$

Using the partial molal heat content data of Harned and Hamer[9] values of $a_{H_2SO_4m}/a_{H_2SO_4(0.3)}$ were calculated for H_2SO_4 in water over the same range of temperature and concentration as in the previous calculation.

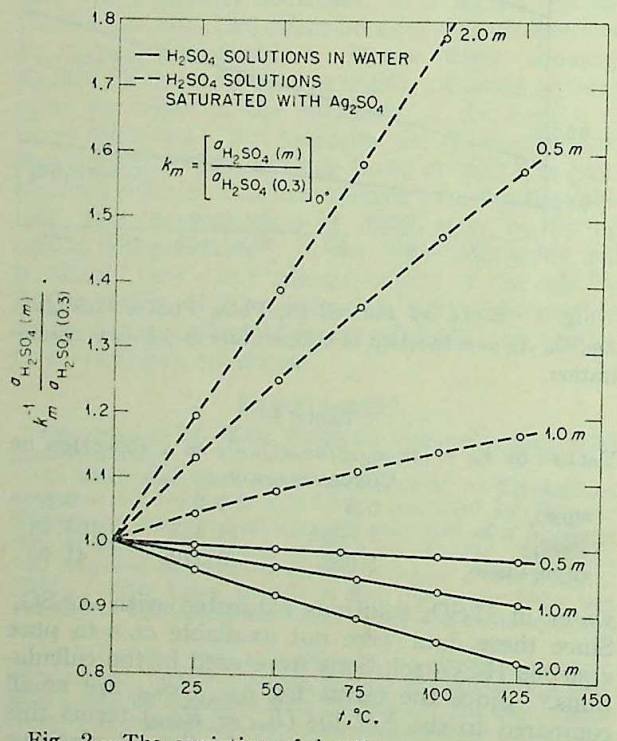

Fig. 2.—The variation of $k_m^{-1}(a_{H_2SO_4(m)}/a_{H_2SO_4(0.3)})$ as a function of temperature and H_2SO_4 concentration both in the presence and absence of Ag_2SO_4.

(9) H. S. Harned and W. J. Hamer, This Journal, **57**, 27 (1935).

Figure 2 shows the variation of k_m^{-1} $(a_{H_2SO_4(m)}/a_{H_2SO_4(0.3)})$ as a function of temperature and H_2SO_4 concentration both in the presence and absence of Ag_2SO_4. It is seen that in the absence of Ag_2SO_4 the values of the normalized ratios decrease as the temperature is raised and that values of the ratios at higher concentrations of H_2SO_4 decrease more than those at lower concentrations. In the presence of Ag_2SO_4 values of the activity ratio function increase with temperature at all the concentrations studied. However, when the H_2SO_4 is saturated with Ag_2SO_4 the plot of the $2.0m/0.3m$ ratios lies above the other two plots, while the $1.0m/0.3m$ plot lies below that for $0.5m/0.3m$. Although the activity ratios vary almost linearly with temperature in the presence of Ag_2SO_4, no simple relationship between activity and molality could be found based only on the assumption that H_2SO_4 acts like a 1–1 electrolyte and that the only important ionic species in solution are H^+, HSO_4^-, $SO_4^=$ and Ag^+. This is not surprising, however, since HSO_4^- is slightly dissociated in the concentration range studied, the dissociation being larger at the lower concentrations of H_2SO_4. Moreover, the enhanced solubility of Ag_2SO_4 in the H_2SO_4 means a further change of species in solution, while the effect of ionic strength on the second dissociation constant of H_2SO_4 provides an additional complication. No completely satisfactory explanation of the inversion in order of the plot of k_m^{-1} $(a_{H_2SO_4(2m)}/a_{H_2SO_4(0.3)})$ in the presence of Ag_2SO_4 could be obtained, although it may be tied in with the fact that the change of solubility of Ag_2SO_4 with H_2SO_4 concentration goes through a maximum in this range.[10]

Acknowledgment.—The authors wish to express their appreciation to Dr. R. W. Stoughton of the ORNL Chemistry Division for helpful discussions on the work and to M. P. Lietzke for help in performing the calculations.

Oak Ridge, Tenn.

(10) G. Åkerlöf and H. C. Thomas, *ibid.*, **56**, 593 (1934).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KENTUCKY]

Solvents Having High Dielectric Constants. VII. Transference Numbers of Potassium and Chloride Ions in Formamide at 25°[1]

BY LYLE R. DAWSON AND CARL BERGER

RECEIVED APRIL 4, 1957

Approximate transference numbers of potassium and chloride ions in formamide at 25° have been determined by the Hittorf method within the concentration range of 0.2 to 0.6 *N*. Extrapolation of a plot of the Longsworth function yielded a limiting cation transference number of 0.406. From the present results and conductance data reported previously the calculated limiting transference number of the solvated proton in a solution of hydrogen chloride in formamide was found to be 0.37 at 25°.

The electrical conductances of solutions of potassium chloride in formamide have been reported in an earlier paper[2] from this Laboratory. It was shown that the slope of the plot of Λ *vs.* $\sqrt{C}$ corresponds closely to the theoretical slope below 0.01 *N* and that potassium chloride is completely dissociated in formamide even at concentrations considerably above 0.1 *N*.

Transference data have been obtained by the moving boundary method in ethanol and in methanol[3] but numerous experimental difficulties prevented using this method for formamide solutions. The present investigation was designed to apply the Hittorf method in an attempt to obtain information concerning the relative solvent–solute interaction in this medium and in other more familiar solvents for which reliable data are available in the literature.

Experimental

Apparatus.—Use was made of the familiar type of Hittorf cell[4] which was constructed from large Pyrex glass tubing. The cell was held in a thermostated water-bath. Care was exercised to avoid exposure of the solution to the atmosphere and to prevent its contamination in any other way.

Silver and silver–silver chloride electrodes were constructed from No. 24 B. and S. gage silver wire. A device employing a 6F6 pentode tube on a power line with relatively small voltage fluctuation maintained a constant current.

A Richards silver coulometer was used in the circuit. Specially constructed weight burets were used for the transfer of larger amounts of solutions.

Salt.—Potassium chloride which had been purified especially for accurate *p*H work was purchased. The salt was dried at 110° for ten hours and used without further treatment.

Solvent.—Commercial grade formamide was distilled three times at reduced pressure over calcium oxide. The middle portion retained from the third distillation was carried through several fractional freezing cycles using the procedure described by the present authors in an earlier paper.[5] Physical properties at 25° of the solvent used were as follows: density = 1.129 g./ml.; viscosity = 0.0331 poise; dielectric constant = 109.5 at 10 mc.; conductivity = $1\text{–}5 \times 10^{-5}$ ohm^{-1} cm.$^{-1}$.

The solvent was used as promptly as possible after final purification and was protected from light while in storage.

Procedure.—Dissolution of the salt required several hours with frequent agitation of the solution. All solutions were prepared out of contact with air and dry nitrogen was bubbled through a solution for one hour before it was transferred to the cell. Lubriseal was used on the stopcocks and the usual precautions were observed to ensure tight seals and the absence of air bubbles in the cell.

After the cell had been in the thermostat long enough to establish temperature equilibrium the circuit was closed and electrolysis allowed to proceed for from 24 to 30 hours at 1–3 ma. At higher concentrations the current became larger and the time was decreased.

Changes in salt concentration were measured by potentiometric titration for chloride ion in the formamide solutions. This titration procedure has been described previously.[5]

Results and Discussion

The data presented in Table I represent averages of consistent duplicate or triplicate determinations. Owing to the instability of formamide and the difficulty of maintaining it anhydrous as well as the problems involved in potentiometric titrations in this solvent, there may be inherent errors in the results amounting to 2 or 3%.

TABLE I

POTASSIUM CHLORIDE IN FORMAMIDE

Concn. × 10^3	I (ma.)	G. of Ag$^+$ deposited	t_+
20.04	1.0	0.1247	0.40
20.80	1.0	.1214	.40
24.37	1.2	.1337	.40
28.98	1.4	.1612	.39
57.28	2.0	.1871	.38
58.91	2.2	.1917	.38

Although experimental difficulties prevented extension of the study to dilute solutions, an attempt was made to obtain an approximate value for the limiting transference number by extrapolating a plot of the Longsworth function.[6]

$$t_+^{0\prime} = (t_+\Lambda^1 + {}^1/_2\beta C^{1/2})/(\Lambda^1 + \beta C^{1/2})$$

In this expression, $\Lambda^1 = \Lambda_t - (\alpha\Lambda_0 + \beta)C^{1/2}$, $\beta = 82.42/(DT)^{1/2}\eta$ and $\alpha = 8.204 \times 10^5/(DT)^{3/2}$. D is the dielectric constant, η is the viscosity and C is the concentration in equivalents per liter. The entries in Table I correspond to the plot in Fig. 1. A value of 0.406 for the limiting transference number of the potassium ion was obtained by extrapolation of the plot; therefore, the limiting transference number of the chloride ion is 0.594. Above 3×10^{-2} *N* the plot deviates sharply from a straight line. Conductance data from another study in progress in this Laboratory, which support the general validity of these values, will be reported in a subsequent paper.

Using data from the work of Dawson, Newell and McCreary[2] with a value of approximately 29.7 ohms^{-1} cm.^{2} equiv.$^{-1}$ for the limiting equivalent conductance of potassium chloride at 25° and our value for t_{K^+}, the limiting equivalent ionic con-

(1) Taken from a Ph.D. dissertation submitted by Carl Berger.
(2) L. R. Dawson, T. M. Newell and W. J. McCreary, THIS JOURNAL, **76**, 6024 (1954).
(3) J. Smisko and L. R. Dawson, *J. Phys. Chem.*, **59**, 84 (1955).
(4) D. A. MacInnes and M. Dole, THIS JOURNAL, **53**, 1357 (1931).
(5) C. Berger and L. R. Dawson, *Anal. Chem.*, **28**, 1011 (1956).
(6) T. Shedlovsky, THIS JOURNAL, **54**, 2741 (1932).

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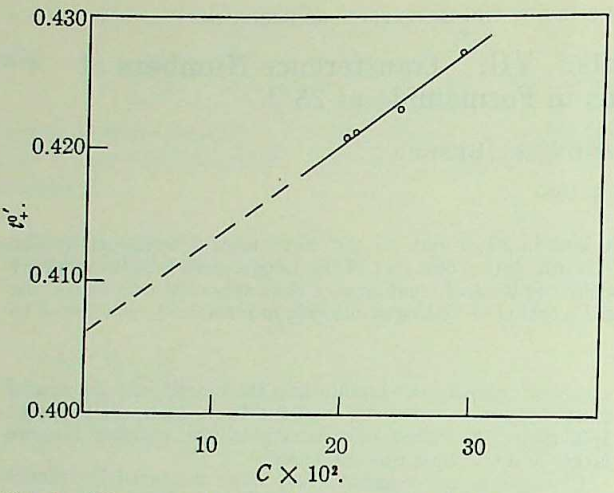

Fig. 1.—The concentration dependence of the Longsworth function for potassium chloride in formamide.

ductances become $\lambda^0_{K^+} = 12.1$, and $\lambda^0_{Cl^-} = 17.6$. Similarly from a value of 27.9 ohms^{-1} cm.$^{-2}$ equiv.$^{-1}$ for the limiting equivalent conductance of hydrogen chloride in formamide at 25°, and $\lambda^0_{Cl^-} = 17.6$, the calculated λ^0 value for the solvated hydrogen ion is 10.3 and its transference number is 0.37.

In passing from water ($t^0_{K^+}$ in KCl = 0.49) to formamide solutions the limiting transference number of the potassium ion in potassium chloride is decreased 17%. The relatively larger solute–solvent interaction with the potassium ion in the latter solvent probably is an ion–dipole effect resulting from the greater dipole moment of the formamide.[7] Evidence that the large dipole moment of formamide produces strong ion–dipole forces appears also in the decrease in transference numbers of the solvated proton from 0.82 in water to 0.37 in formamide. In formamide dissociated protons are held by the solvent molecules with sufficient force to prevent easy transfer from molecule to molecule as occurs in aqueous solutions.

The limiting equivalent ionic conductance–viscosity products for the potassium ion at 25°, in ohm^{-1} cm.^{2} equiv.$^{-1}$ poise, in methanol, ethanol, formamide and water are 0.283, 0.255, 0.400 and 0.656. A complete explanation of the relative magnitudes of these values would involve not only direct ion–solvent interactions but also short-range viscosity effects resulting from the influence of the ions in modifying the normal solvent structure.

(7) W. W. Bates and M. E. Hobbs, THIS JOURNAL, **73**, 2151 (1951).

LEXINGTON, KY.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

The Copper(II)–Pyridine Complexes and their Reaction with Hydroxide Ions

BY D. L. LEUSSING AND R. C. HANSEN[1]

RECEIVED FEBRUARY 21, 1957

The formation constants have been evaluated at an ionic strength of 1.0 and 25.0° for the reactions: $Cu^{++} + py \rightleftarrows Cupy^{++}$, $Cu^{++} + 2py \rightleftarrows Cupy_2^{++}$, . . ., $Cu^{++} + 5py \rightleftarrows Cupy_5^{++}$. The values found are 3.92×10^2, 2.14×10^4, 8.5×10^5, 3.5×10^6 and $1.0_6 \times 10^7$, respectively. Mixtures of these complexes react with hydroxide to form a dimer: $py_2Cu(OH)_2Cupy_2^{++}$. The constant for the reaction $2Cu^{++} + 2OH^- + 4py \rightleftarrows py_2Cu(OH)_2Cupy_2^{++}$ is $5.1 \times 10^{+24}$. The absorption spectra of each of the complexes were determined and the spectral behavior of the solutions was found to be in accordance with the interpretation based upon equilibrium concentration measurements.

Recent publications have described the formation of mixed hydroxy complexes of copper(II) with ethylenediaminetetraacetate,[2] ethylenediamine,[3] 1,10-phenanthroline,[4] α,α'-dipyridyl[5] and ammonia.[6] The hydroxide was shown to occupy a fifth or sixth coördination position on the copper in the case with bis-ethylenediamine and ethylenediaminetetraacetate. However, with 1,10-phenanthroline and α,α'-dipyridyl the coördination of copper is lower (excluding water) as only one molecule of the bidentate ligand per copper was observed in the mixed complexes. The existence of the hydroxy ammonia complex[6] was inferred from spectral evidence and its composition was assumed to be $Cu(NH_3)_3OH^+$. Only in the case of ethylenediaminetetraacetate was the constant for the formation of the mixed complex evaluated. This was found to have a pK of 11.3 for the reaction

$$CuY^- + OH^- \rightleftarrows CuYOH^=$$

The reactions of the copper–pyridine complexes were investigated in order to throw more light on the nature of the reactions of the copper ammines with hydroxide. Pyridine was chosen because it is a monodentate ligand and its activity in aqueous solutions can be determined very easily by measuring the distribution into toluene. The conventional pH method of Bjerrum[7] cannot be used in the present case to determine the nature and stability of the mixed complexes because the pyridinium ion does not exist in appreciable quantities at the pH values optimum for the reaction with hydroxide. In Bjerrum's method the concentration of

(1) The authors wish to express their gratitude for partial support of this work by the Wisconsin Alumni Research Foundation and the du Pont Grant-in-Aid. Preliminary experiments were carried out by W. E. Ohnesorge at the Massachusetts Institute of Technology supported by a research grant of the Atomic Energy Commission.

(2) M. C. Bennett and N. O. Schmidt, *Trans. Faraday Soc.*, **51**, 1412 (1955).

(3) H. B. Jonassen, R. E. Reeves and L. Segal, THIS JOURNAL, **77**, 2748 (1955).

(4) R. T. Pflaum and W. W. Brandt, *ibid.*, **76**, 6215 (1954).

(5) T. Wagner-Jauregg, B. E. Hackley, Jr., T. A. Lies, O. O. Owens and R. Proper, *ibid.*, **77**, 922 (1955).

(6) J. Bjerrum, C. J. Ballhausen and C. K. Jorgensen, *Acta Chem. Scand.*, **8**, 1275 (1954).

(7) J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, Denmark, 1941.

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the pyridinium ions in the solution must be known so that the concentration of free pyridine can be determined using the measured pH.

It is necessary to know the stabilities of the copper–pyridine complexes before their reaction with hydroxide can be assessed. Bruehlman and Verhoek[8] report values of 2.52, 1.86, 1.31 and 0.85 for the logarithms of the successive stepwise formation constant in 0.50 M potassium nitrate, 0.100 M nitric acid and 0.0300 M cupric nitrate at 25°. Bjerrum and Nielsen[9] report corresponding values of 2.41, 1.88, 1.14 and 0.60 in 0.50 M pyridinium nitrate at 25°. However, because of a change in the experimental conditions in the present work it was deemed necessary to redetermine these constants. Distribution and pH measurements both were used to evaluate the formation constants in 0.99 M potassium nitrate, 0.030 M cupric nitrate and 0.0110 M pyridinium nitrate at 25°. The small amount of pyridinium nitrate was used so that the formation of any hydroxy complexes through reactions such as

$$Cupy_n^{++} + H_2O \rightleftharpoons Cupy_mOH^+ + (n - m - 1)py + pyH^+$$

could be detected by a discrepancy in the value of the free pyridine concentration as measured by the pH and distribution methods.

Experimental

Pyridine, Baker Analyzed Reagent was refluxed over barium oxide for 6 hours and then distilled. The fraction boiling over the range 113–114° at 743 mm. was collected. The redistilled pyridine was stored and transferred under a blanket of nitrogen. Solutions of known concentration were prepared by weight from the reagent.

Copper nitrate, 0.1565 M, was prepared from the Mallinckrodt, Reagent Grade, product and standardized electrolytically. The stock solution was made up 0.005 M in nitric acid to prevent hydrolysis. The amount of acid present was checked by the method of Blaedel and Panos.[10]

Perchloric acid, anhydrous, 0.500 M in glacial acetic acid, was prepared and standardized according to the directions of Kolthoff and Bruckenstein.[11]

Potassium nitrate, 3.05 M, was prepared from the Baker and Adamson reagent grade product.

Nitric acid, 0.504 M and sodium hydroxide, 0.1025 M, were prepared and standardized according to the usual procedures.

The pH measurements were made with a Beckman model G pH meter using a 1190-80 glass electrode. The instrument was standardized before and checked after a measurement with Beckman buffer at pH 7.00.

All solutions were prepared with air-free redistilled water and were equilibrated at 25.0 ± 0.1°.

Absorption spectra were determined using a Cary Model 14 and a Beckman DU spectrophotometer. The Beckman instrument was equipped with a cell compartment thermostated at 25.0 ± 0.2 and the Cary was in a room thermostated at 25°.

The distribution measurements were made by shaking an aqueous phase containing an initially known amount of pyridine with 15.0 ml. of toluene. The rate of equilibration was rapid. The equilibrium concentration of pyridine in the toluene phase was determined by titrating an aliquot introduced into acetic acid with the standard solution of perchloric acid. The experiments were designed so that the equilibrium volume of the aqueous phase was 30.0 ml. A preliminary run was made for each experiment to determine approximately the amount of pyridine transferred and in the final run the volume of the aqueous phase was adjusted appropriately. Also, it was necessary to know the final volume of the toluene phase to compute the results. The volume changes of the two phases accompanying pyridine transfer were calculated using values of the apparent molar volume of pyridine which were determined to be 80 ml. per mole in the aqueous phase and 76 ml. per mole in the toluene phase.

The equilibrium distribution of free pyridine between the two phases was determined in experiments in which the copper(II) nitrate was replaced by an equivalent amount of barium nitrate. At a constant ionic strength of 1.0 the distribution of free pyridine was the same within experimental error regardless of whether the solution contained 0.030 M barium nitrate or only pyridinium and potassium nitrates. It was found that the equilibrium concentration of free pyridine in the aqueous phase is given by the equation

$$(py)_w = 0.373\ (py)_{tol} + 0.064\ (py)_{tol}^2$$

The standard deviation in $(py)_w$ was found to be ±0.002 M from the results of 14 experiments throughout the range of $(py)_{tol}$ from 0.028 M to 1.130 M.

The value of pK_a for the pyridinium ion was found to be 5.51 for solutions in which barium ions replaced copper(II). As above this value was found to be independent of the type of the electrolyte as long as the ionic strength remained constant.

The Copper(II)–Pyridine Complexes.—In solutions containing copper(II) the values of $\bar{n}$, the average number of molecules of pyridine combined with a copper(II) ion, were calculated from the results of the pH and distribution measurements using the method outlined by Bjerrum.[7] The conventional pH method was used on 13 solutions in which the free pyridine concentration covered the range 1.5×10^{-4} to 0.0694 M (values of $\bar{n}$ from 0.057 to 2.82) and the distribution measurements were made on 17 solutions covering the range 0.018 to 0.388 M free pyridine ($\bar{n}$ 1.87 to 4.11).[12]

The pH of the aqueous phase was also determined in each of the distribution experiments. To determine whether or not significant hydrolysis of the copper(II) occurred in these solutions the values of pH calculated assuming no hydrolysis were compared with those observed. If significant formation of hydroxy complexes occurred this would result in an increase in the pyridinium ion concentration and the observed pH would be lower than that calculated. The agreement between the calculated and observed values of pH was found to be within 0.02–0.03 unit. Positive and negative deviations were scattered randomly. This shows that in 0.030 M copper(II) solutions the presence of 0.0110 M pyridinium nitrate is sufficient to repress the formation of appreciable amounts of the hydroxy complexes.

The values of $\bar{n}$ could then be calculated directly from the data. These values showed no tendency to level off to a value of $\bar{n}$ equal to four as the pyridine concentration was increased. Plots of the data according to the method of Rossotti and Rossotti[13] indicated the existence of complexes up to $Cupy_5^{++}$. Letting the symbol β_n represent the overall formation constant for the reaction: $Cu^{++} + npy \rightleftarrows Cupy_n^{++}$, values of β_1 and β_2 were evaluated from the plots using the method of least squares to effect the extrapolation. Values of β_3, β_4 and β_5 were obtained by using the method of least squares to obtain three simultaneous equations. The values so calculated are 392, $2.14 \times 10^{+4}$, 8.5×10^5, 3.5×10^6 and $1.0_6 \times 10^7$ for $\beta_1, \ldots \beta_5$, respectively. Values of $\bar{n}$ calculated using these constants agree with those observed with an average deviation of ±2% in the range of $\bar{n}$ from 4.11 to 2.9, ±1.8% in the range 2.6 to 1.0 and ±3% in the range 0.86 to 0.056.

Absorption spectra were determined for solutions of the aquo copper(II) ion and eleven solutions covering values of $\bar{n}$ from 0.34 to 4.1. These spectra were resolved into those

(8) R. J. Bruehlman and F. H. Verhoek, THIS JOURNAL, **70**, 1401 (1948).

(9) J. Bjerrum and E. J. Nielsen, *Acta Chem. Scand.*, **2**, 297 (1948).

(10) W. J. Blaedel and J. J. Panos, *Anal. Chem.*, **22**, 910 (1950).

(11) I. M. Kolthoff and S. Bruckenstein, THIS JOURNAL, **78**, 1 (1956).

(12) At the higher values of $\bar{n}$, the distribution method was found to be more precise. At a value of $\bar{n}$ equal to four, the error of about 1% in the determination of the free pyridine concentration introduces an error of about 3% into the calculated value of $\bar{n}$. At this same value of $\bar{n}$, an error of 0.02 pH unit in determining the pH introduces an error of 13% into $\bar{n}$. On the other hand, at the low values of $\bar{n}$ the pH measurements are better because the titration errors in the distribution experiments assume relatively large importance.

(13) F. J. C. Rossotti and H. S. Rossotti, *Acta Chem. Scand.*, **9**, 1166 (1955).

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of the complexes. To do this a plot was made at each chosen wave length of the absorbance *vs.* $-\log (py)_w$. A smooth curve was drawn through the points and values from this curve together with the equilibrium constants reported above were used to obtain five simultaneous equations which were solved for the extinction coefficients of the complexes. The resolved spectra are shown in Fig. 1. Values of the absorbance of mixtures of the complexes calculated from the equilibrium constants and the values in Fig. 1 agree with those observed within 1–2%.

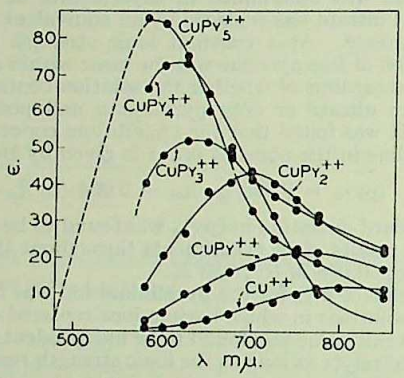

Fig. 1.—The absorption spectra of the copper(II)–pyridine complexes.

The Reaction with Hydroxide.—Most of the solutions for the study of the reaction with hydroxide were prepared in the same manner as those described above except the nitric acid was omitted, varying amounts of standard sodium hydroxide were added and the final solutions were made 1.00 *M* in potassium nitrate. Several additional distribution measurements were made on solutions which were 0.060 *M* in copper nitrate and 0.91 *M* in potassium nitrate.

It was found that the amount of sodium hydroxide taken up by the solution before the appearance of a precipitate (cupric hydroxide or basic nitrates) depends greatly on the concentration of free pyridine in the solution. Only in those solutions in which the concentration of free pyridine was 0.13 *M* or greater was it possible to add sufficient hydroxide without precipitation to obtain interpretable results. The amount of hydroxide that is held in dilute pyridine solutions was found to be less than one mole per mole of copper. However, in 10 *M* pyridine, 0.030 *M* copper nitrate it was found possible to titrate the copper with a solution of sodium hydroxide and obtain no precipitate until the molar ratio of hydroxide to copper reached 1:1.

The details for the experiments carried out in dilute pyridine solutions are given in Table I.

$Cupy_{\bar{m}}OH^+$. The value of $\bar{m}$ can be obtained using the equations

$$(Cupy_{\bar{m}}OH^+) = [OH^-] - [HNO_3] + (pyH^+)$$

$$(Cupy_{\bar{n}}^{++}) = [Cu^{++}] - (Cupy_{\bar{m}}OH^+)$$

$$\bar{m} = \frac{[py]_w - \bar{n}(Cupy_{\bar{n}}^{++}) - (py)_w - (pyH^+)}{(Cupy_{\bar{m}}OH^+)}$$

where the quantities in brackets refer to total concentrations and the quantities in parentheses refer to equilibrium concentrations. The pyridinium ion arises from hydrolysis and its concentration was calculated from pK_a and the measured values of *p*H and concentration of pyridine, $(py)_w$. The nitric acid is from the copper nitrate stock solution. The value of $\bar{n}$ was calculated using the experimental values of $(py)_w$ and the formation constants determined above.

The results of the calculations of $\bar{m}$ are presented in Table I. The deviation is calculated on the basis of an error of ±2% in the value of $\bar{n}$.

In solutions 0.030 *M* in copper(II) the value of $\bar{m}$ comes close to 2 within the experimental error.[14] Also, the values of $\bar{m}$ show no trend with increasing concentration of pyridine. Therefore, only one mixed complex of the general formula $Cupy_2OH^+$ appears to be formed under the present experimental conditions.

Apparent equilibrium constants, K_m and K_d, were calculated assuming monomer and dimer formation for the equilibria

$$Cupy_3^{++} + OH^- \rightleftarrows Cupy_2OH^+ + py$$

and

$$Cupy_3^{++} + OH^- \rightleftarrows {}^1/_2py_2Cu(OH)_2Cupy_2^{++} + py$$

These "constants" are also reported in Table I. Concentration units were used except for the hydroxide ion which is in terms of activity. The values of K_d show less relative deviation than do those of K_m. Also, better agreement is observed with the K_d values when comparing the 0.030 and 0.060 *M* copper(II) solutions. The most convincing evidence favoring the dimer formulation lies in the agreement discussed above between the calculated and observed values of *p*H in the distribution determination of $\bar{n}$. The magnitude of K_m is such that the experimental values of *p*H should have been appreciably lower than those calculated. The value of K_d is of the correct order to agree with the observations. The difference lies in the fact that the dimer concentration varies inversely as the square of the hydrogen ion concentration and, therefore, the change of about one *p*H unit in the experimental conditions exerts considerable effect on the dimer concentration.

Absorption spectra were determined for solutions 5, 6 and 10 of Table I and for a solution containing 0.0313 *M* copper nitrate, 0.496 *M* pyridine and 0.0205 *M* NaOH in 1.0 *M* KNO_3. For each solution the absorbance due to py_2Cu-

Table I

The Reaction of Hydroxide with Copper(II) in Solutions Containing Pyridine

Exp.	$(py)_w$, moles l.$^{-1}$	$[py]_w$, moles l.$^{-1}$	*p*H	(pyH^+), moles l.$^{-1}$ × 10^{+3}	$(Cupy_{\bar{m}}OH^+)x$, moles Cu l.$^{-1}$	$(Cupy_{\bar{n}}^{++})$, moles l.$^{-1}$	$\bar{n}$	α_3	$\bar{m}$	K_m × 10^{-5}	K_d × 10^{-6}
1	0.135	0.228	7.39	1.77	0.0076	0.0224	3.39	0.51	2.0 ± 0.2	3.7	3.0
2	.217	.321	7.68	1.46	.0073	.0227	3.74	.38	2.4 ± .2	3.9	3.2
3	.220	.317	7.71	1.39	.0106$_8$	.0193	3.76	.38	2.2 ± .1	6.2	4.3
4	.223	.314	7.95	0.80	.0135	.0165	3.76	.38	2.1 ± .1	5.4	3.3
5	.310	.407	8.02	0.95	.0102	.0198	4.00	.28	1.7 ± .2	5.4	3.8
6	.311	.406	8.18	0.66	.0134	.0166	4.00	.28	2.1 ± .1	5.9	3.6
7	.400	.506	8.19	0.83	.0101	.0199	4.18	.21	2.2 ± .2	6.3	4.4
8	.341	.577	7.73	1.76	.0101	.0499	4.06	.24	(3.1)	5.3	3.8
9	.345	.573	7.80	1.76	.0135	.0465	4.08	.25	(2.7)	6.4	3.9
10	.348	.569	7.89	1.45	.0166	.0434	4.08	.25	(2.6)	6.9	3.8
									Av.	5.5	3.7

Calculations.—The results of the titration in 10 *M* pyridine show that copper and hydroxide react in the molar ratio of 1:1 to form a soluble complex. This stoichiometry is that most likely to be maintained in the experiments described in Table I as in these solutions there was always an excess of copper over hydroxide. Then analogous to the definition of $\bar{n}$, the average composition of the hydroxy complexes present in a solution can be represented by the formula,

(14) In the solutions containing 0.060 *M* copper(II) the values of $\bar{m}$ are slightly higher. These latter values are not as reliable because only slight changes in the distribution coefficient of pyridine or in the equilibrium constants with the slightly different conditions would bring about appreciable changes in $\bar{m}$. The equilibrium constants calculated from the results in 0.060 *M* solutions reflect these slight changes much less and can be compared directly with those calculated for the 0.030 *M* copper(II) solutions.

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$(OH)_2Cupy_2^{++}$ was obtained by subtracting the calculated absorbance of the aquopyridino complexes from the observed absorbance. On a molar basis the resulting spectra are identical within the experimental error. In the visible, the curve consists of a single broad peak with a maximum at 625 mμ having an extinction coefficient of 57 ± 2 (mole copper)$^{-1}$ l. cm.$^{-1}$ (the extinction coefficient based on the dimer concentration is twice this value). The resolved absorption spectrum agreed very closely with that obtained directly for a 0.014 *M* solution of the dimer in 10 *M* pyridine. This latter spectrum exhibits a maximum at 625 mμ with an extinction coefficient of 61 (mole copper)$^{-1}$ l. cm.$^{-1}$. Considering the fact that in the former experiments all errors are lumped into the calculated extinction coefficients, the agreement is very good and lends support to the interpretation of the equilibrium data.

In addition, the absorption spectrum of the dimer has a very intense maximum at about 320 mμ. This was not investigated in greater detail, however.

Discussion

It is not surprising that the earlier workers[8,9] did not report the existence of $Cupy_5^{++}$ as this is formed in a region where not much reliance would be placed on the results of ordinary *p*H measurements with the glass electrode. The pyridine system is not unique as the ammonia and ethylenediamine–copper(II) systems also take up a fifth nitrogen[6,7,9,15] but with less ease. For example the value of the stepwise constant, K_5, for the formation of the pentammine from the tetrammine is 0.33 with ammonia[15] but is 30 with pyridine.

The spectral changes accompanying the uptake of the fifth ligand are also different with pyridine than with ammonia and ethylenediamine. These latter systems show a progressive shift of the absorption maximum to the blue with the uptake of successive ligand but with the addition of the fifth group a shift back toward the red is noted.[6,9] With pyridine the shift continues toward the blue with the uptake of the fifth group.

Qualitatively, the difference in the values of K_5 can be correlated with the positions of the absorption maxima of the pentammine on the basis of arguments taken from the crystal field theory.[16,17] The position of the absorption maximum reflects the contribution to the stability of the molecule caused by the splitting of the 3d orbitals of the metal ion by the field of the ligands. This energy is seen to be more favorable with pyridine than ammonia, resulting in a larger value of K_5. On this basis the copper–pyridine system is similar to the copper–dipyridyl and 1,10-phenanthroline systems which have been classified by Bjerrum and Jorgensen[17] as normal octahedral systems of coördination number 6. For the reaction

$$2Cu^{++} + 4py + 2OH^- \rightleftharpoons py_2Cu(OH)_2Cupy_2^{++}$$

the concentration constant is calculated to be $5.1 \times 10^{+24}$. This value was calculated using the values of K_d and β_3 reported herein and a value of 0.59 for the square of the hydroxide ion activity coefficient assuming this to be equal to the quantity $\gamma_H\gamma_{OH}/a_{H_2O}$ as reported by Harned and Owen.[18]

The aquo copper(II) ion also hydrolyzes to form a dimer,[19] the value of *pK* being 10.6 for the reaction

$$2Cu^{++} + 2H_2O \rightleftharpoons Cu(OH)_2Cu^{++} + 2H^+$$

The analogous reaction in the copper–pyridine system is

$$2Cupy_2^{++} + 2H_2O \rightleftharpoons py_2Cu(OH)_2Cupy_2^{++} + 2H^+$$

with a value of *pK* equal to 11.5 calculated using 1.7×10^{-14} as the value of the concentration product of water.[18] Thus, as might be expected the acidity of the dipyridinocopper(II) ion is less than that of the aquo ion.

The spectral changes occurring in the visible region with the formation of the hydroxy complex are similar with pyridine to those reported for 1,10-phenanthroline[4] and ethylenediaminetetraacetate.[2] No great change occurs in the position of the absorption maximum but the height of the maximum decreases with the uptake of the hydroxide ion. The position of the absorption maximum is not different in 10 *M* pyridine. This does not necessarily mean that the hydroxy complex does not take up more pyridine but may indicate that the binding is not strong as is the case with $Cu(NH_3)_6^{++}$.[6] The results with ethylenediamine[3] and ethylenediaminetetraacetate[2] lead one to expect higher complexes with higher pyridine concentration.

The very intense absorption maximum at about 320 mμ exhibited by the hydroxypyridine complex is more likely due to charge transfer.[20] The hydroxy ammonia complex exhibits an intense absorption in this same region. Very likely, the composition of this complex is similar to that of the pyridine complex.

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MADISON, WISCONSIN

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[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

Activity Coefficients of Electrolytes of High Charge: Tris-(ethylenediamine)-platinum-(IV) Perchlorate and Tris-(ethylenediamine)-cobalt (III) Chloride

BY C. H. BRUBAKER, JR.

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Activity and osmotic coefficients of aqueous solutions of $Pt(en)_3(ClO_4)_4$ and $Co(en)_3Cl_3$ have been determined at 25° by isopiestic comparison with KCl solutions. Measurements have been made on solutions varying from about 0.05 m to saturation. The solubilities of $Pt(en)_3(ClO_4)_4$ and $Co(en)_3Cl_3$ were found to be 0.2229 and 1.110 m, respectively. The platinum complex appears to be a strong 4-1 electrolyte, but the cobalt compound does not behave as a typical 3-1 salt.

As part of a program of investigation of the properties of solutions of electrolytes of high charge,[1,2] two additional compounds, tris-(ethylenediamine)-platinum(IV) perchlorate and tris-(ethylenediamine)-cobalt(III) chloride, which showed some promise of serving as representative electrolytes of high charge and large size, have been prepared and studied. The first seems to qualify as a 4–1 electrolyte, perhaps stronger than potassium octacyanomolybdate(IV),[2] but the cobalt complex is very different in behavior from other 3–1 chlorides.[3] Osmotic coefficients of these salts were determined by isopiestic comparison with potassium chloride solutions at 25° and activity coefficients have been derived from the osmotic coefficients.[4]

Experimental

The experimental procedure and apparatus were the same as in the previous work,[2] with the exception that the gold plated sample containers have been replaced with platinum ones. The temperature was 24.953 ± 0.005°.

Tris-(ethylenediamine)-platinum(IV) perchlorate was prepared by a quantitative metathesis reaction between $Pt(en)_3Cl_4$[2] and $AgClO_4$ in aqueous solution. An excess of freshly prepared, nitrate free, Ag_2O was treated with 0.1 M $HClO_4$ and the resulting 0.1 M $AgClO_4$ solution was separated from the excess Ag_2O by filtration. From this a 0.0580 M solution was prepared.

2.1127 g. of $Pt(en)_3Cl_4$ in 25 ml. of water was titrated with the $AgClO_4$ solution and care was taken that only a drop or two excess $AgClO_4$ was used. The silver chloride was filtered off after being digested on a steam-bath for one hour and the $Pt(en)_3(ClO_4)_4$ was recovered by evaporation. This product was dried in an oven at 70° and was weighed. 3.1532 g. of $Pt(en)_3(ClO_4)_4$ was obtained; the theoretical yield would be 3.159 g.

The $Pt(en)_3(ClO_4)_4$ was then recrystallized from water three times and was dried at 70° and stored over barium oxide. This salt occurs as a hydrate in equilibrium with water at room temperature, but much water is lost on standing in air and the compound can be completely dehydrated at 70° or by drying over barium oxide. The exact degree of hydration was not determined, but there are probably $2H_2O$ or $2.5H_2O$ (compare $Pt(en)_3(NO_3)_4 \cdot 2H_2O$[5] and $Pt(en)_3Cl_4 \cdot 2.5H_2O$).[6] The anhydrous material does not absorb moisture from the air readily and was the form weighed in these experiments.

$Co(en)_3Cl_3$ was prepared according to the method in "Inorganic Syntheses"[7] and the product was purified by recrystallizing three times from water. The trihydrate is prepared by this process, but the water is removed by drying in an oven at 100° and the anhydrous salt can be weighed conveniently.

Results and Discussion

The notation employed in this section is that used in reference 4. In Table I are given the experimental molalities and osmotic coefficients for $Pt(en)_3(ClO_4)_4$ and $Co(en)_3Cl_3$. The concentrations of the saturated solutions were found to be 0.2229 and 1.110 m, respectively. Of course the hydrated forms of the two salts are in equilibrium with these solutions, although the samples were prepared from the anhydrous compounds.

TABLE I

ISOPIESTIC MOLALITIES, OBSERVED AND CALCULATED OSMOTIC COEFFICIENTS OF $Pt(en)_3(ClO_4)_4$ AND $Co(en)_3Cl_3$

$Pt(en)_3(ClO_4)_4$			$Co(en)_3Cl_3$		
m_{av}	ϕ_{obsd}	ϕ_{calcd}	m_{av}	ϕ_{obsd}	ϕ_{calcd}
0.03390	0.8260	0.8279	0.05351	0.6705	0.6734
.04411	.8178	.8178	.07027	.6524	.6524
.06586	.8070	.8015	.1069	.6219	.6214
.08594	.7860	.7854	.1102	.6141	.6192
.09715	.7751	.7754	.2244	.5654	.5666
.1470	.7338	.7339	.3497	.5318	.5318
.2229[a]	.6792	.6792	.5055	.4995	.4994
			.5086	.5064	
			.7635	.4864	
			.9930	.4685	
			1.110[a]	.4833	

[a] Saturated solutions.

It was found that the osmotic coefficients of both salts, up to about 0.25 m could be calculated (Table I) very well from

$$(1 - \phi)_{calc} = 0.7676 S_m(f) \sigma_m \sqrt{m} + {}^1/_2 Bm - (\Delta\phi)_{smoothed} \quad (1)$$

where

$$\Delta\phi = 0.7676 S_m(f) \sigma_m \sqrt{m} + {}^1/_2 Bm - (1 - \phi)_{obs}$$

The smoothed values are obtained by the method discussed by Scatchard and Prentiss[8] in treating freezing point data. The $\Delta\phi$ are smallest (*ca.* 1% or less) when, for $Pt(en)_3(ClO_4)_4$, $\mathring{a} = 11.5$ and $B = 2.06$ and for $Co(en)_3Cl_3$, $\mathring{a} = 3.42$ and $B = 0.610$. We notice that the sign of the linear term is positive and that the $\mathring{a}$ for $Co(en)_3Cl_3$ is much too small. This only serves to emphasize the empirical nature of equation 1. The chief virtues of this equation are that, besides giving good agreement with observed osmotic coefficients, it approaches the limiting value with the theoretical limiting slope. In the case of $Co(en)_3Cl_3$, above 0.25 m the $\Delta\phi$ become large and so calculated values are not

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given at higher concentrations (it appears that a negative term in m^2 would have to be added to equation 1 to keep $\Delta\phi$ small at the higher concentrations).

We notice that $\mathring{a}$ for the platinum compound (11.5) is somewhat greater than the 8–10 Å. we might expect, if we consider the crystal radii[5] of $Pt(en)_3^{+4}$ and ClO_4^-, but perhaps it is not unreasonably large. Thus, this compound may represent a strong 4–1 electrolyte.

If equation 1 is used in treating the data for $K_4Mo(CN)_8$ instead of the simple form previously employed,[2] $\mathring{a}$ can be increased only from 4.33 to about 4.85 and the activity coefficients are changed by less than 1%. It appears, then, that the much larger $\mathring{a}$ for the platinum salt is not wholly a result of using a different extrapolation than was used for $K_4Mo(CN)_8$.

It is certain that $Co(en)_3Cl_3$ is not strong and perhaps should not even be considered a 3–1 electrolyte. The osmotic coefficients do not resemble those of other 3–1 chlorides at similar concentrations.[3] It is not surprising that this is not a strong electrolyte for conductance measurements[9] also suggest incomplete dissociation.

In view of the manner of calculating the osmotic coefficients and of the smallness of $\Delta\phi$, the activity coefficients of $Pt(en)_3(ClO_4)_4$ and of $Co(en)_3Cl_3$ (up to $m = 0.25$) were calculated by the method Smith[10] employed for sodium chloride solutions at the boiling points.

$$\ln \gamma\pm = -\frac{2.303 S_m(f)\sqrt{m}}{1 + A'_m\sqrt{m}} - Bm + \int_0^m \frac{\Delta\phi}{m}\,dm + \Delta\phi \qquad (2)$$

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Since $\Delta\phi$ becomes large for $Co(en)_3Cl_3$ at concentrations above 0.25 m, the values of ln $\gamma\pm$ from $m = 0.25$ to $m = 1.110$ were determined by graphical integration of

$$\ln \gamma\pm = -(1 - \phi) - 2\int_{0.25}^m \frac{(1 - \phi)}{\sqrt{m}}\,d\sqrt{m} - 1.4862 \qquad (3)$$

where 1.4862 is twice the calculated (from 2) value of the integral from $m = 0$ to $m = 0.25$.

In Table II are given the smoothed values of the osmotic and activity coefficients for solutions of $Pt(en)_3(ClO_4)_4$ and $Co(en)_3Cl_3$. Those for $Pt(en)_3(ClO_4)_4$ differ considerably from those for $K_4Fe(CN)_6$[3] and $K_4Mo(CN)_8$,[2] but that may be due to its being a stronger electrolyte. Not only is $\mathring{a}$ large, but isopiestic molalities of KCl and $Pt(en)_3(ClO_4)_4$ are nearly in a ratio of 5:2 (*i.e.*, at equilibrium, $\nu_1 m_1 \cong \nu_2 m_2$). This is not true in the case of $K_4Mo(CN)_8$.

TABLE II

SMOOTHED ACTIVITY AND OSMOTIC COEFFICIENTS FOR $Co(en)_3Cl_3$ AND $Pt(en)_3(ClO_4)_4$ AT 25°

	$Co(en)_3Cl_3$		$Pt(en)_3(ClO_4)$	
m	$\gamma\pm$	ϕ	$\gamma\pm$	ϕ
0.01	0.508	0.7993	0.502	0.8463
.025	.384	.7326	.426	.8301
.050	.295	.6802	.372	.8147
.075	.264	.6513	.339	.7960
.10	.221	.6266	.308	.7770
.15	.188	.5975	.270	.7395
.2229	.156	.5660	.227[a]	.6785
.2500	.148	.5580		
.50	.101	.5003		
.75	.0805	.4774		
1.00	.0691	.4687		
1.110	.0659[a]	.4833		

[a] Saturated solutions.

LANSING, MICH.

[CONTRIBUTION OF THE RICHARDSON CHEMISTRY LABORATORIES OF TULANE UNIVERSITY]

Inorganic Complex Compounds Containing Polydentate Groups. XIV. The Stability of the Complexes Formed between the Nickel(II) Ion and Tetraethylenepentamine

BY HANS B. JONASSEN AND LOWELL WESTERMAN

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The basicity constants of tetraethylenepentamine and the formation constants of the complex ions formed between nickel (II) and tetraethylenepentamine were measured by the method of Schwarzenbach. The formation constant of the complex was also measured by the method of Bjerrum. The complex ions NiHtetren^{+3} and Nitetren^{+2} were found to be present in aqueous solution having log K values of 12.6 ± 0.1 and 17.6 ± 0.1, respectively, at 25°.

Introduction

The stability of complexes of various metal ions of the transition series with members of the polyethyleneamine series has been the subject of considerable investigation. Bjerrum[1] developed a method for determining the stability constants for the formation of metal amine complexes in aqueous solution which is based upon the stepwise formation of the complex ion. Jonassen, *et al.*,[2–4] extending the equations derived by Bjerrum measured the dissociation constants of diethylenetriamine and triethylenetetramine and also the formation constants of the complexes formed between these ligands and the nickel(II) ion.

Schwarzenbach[5] has pointed out that "hydrogen complexes" (complexes formed by adding one or more protons to the polyamine(s) coördinated to the metal ion) also must be considered in addition to the simple MZ_x type, where Z is the polyamine and x equals 1,2,3,. . .n. Schwarzenbach developed a method for determining these complexes from a study of neutralization curves, and studied the complexes of nickel(II) with all of the members of

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the polyethyleneamine series below tetraethylenepentamine and measured their stabilities.[6-8]

Previous work in these laboratories[9] has indicated the presence of complexes of nickel(II) with tetraethylenepentamine other than the simple MZ_x type. The purpose of this investigation was to utilize the methods of Schwarzenbach and Bjerrum to identify and measure the stabilities of the complexes formed in aqueous solution.

Experimental

A. Reagents and Instruments.—Carbide and Carbon Chemicals Corporation technical grade tetraethylenepentamine (abbreviated tetren) was purified as the pentahydrochloride salt by methods developed in these laboratories.[10]

Freshly boiled distilled water was used in the preparation of all solutions. Solutions 0.00200 M in respect to tetren·5HCl and 0.15 M in respect to $KClO_4$ were prepared from the purified tetren·5HCl and Baker C.P. $KClO_4$.

G. Frederick Smith and Company reagent grade $Ni(ClO_4)_2$ and Baker C.P. potassium hydroxide were used in the preparation of the nickel perchlorate and carbonate-free base solutions. The KOH solutions were standardized by titration against primary standard potassium acid phthalate using phenolphthalein as an indicator. Nickel perchlorate solutions were standardized by quantitatively precipitating nickel as nickel dimethylglyoxime. The tetren·5HCl solutions were standardized potentiometrically by titration with standard KOH solution.

All pH determinations were made with a Beckman, model G pH meter using a glass electrode with a saturated calomel electrode as the reference electrode. The instrument was standardized against Beckman standard buffer solutions pH 4, 7 and 10.

B. "Metal-free" Curve.—The "metal-free" curve was obtained as follows. Fifty milliliters of 0.00200 M tetren·5HCl in 0.15 M $KClO_4$ was measured into a four-necked flask immersed in a constant temperature bath regulated to ±0.1°. This was diluted with 50 ml. of distilled water resulting in a solution which was 0.00100 M with respect to tetren·5HCl and 0.075 M with respect to $KClO_4$. The four-necked flask was equipped with a stirrer, glass and calomel electrodes, and nitrogen bubbler. Nitrogen was passed through the solution for at least 15 min. prior to the titration. The titration was carried out by the addition of 0.100 N KOH solution from a 5-ml. buret.

C. "Excess-metal Ion" Curve.—The "excess-metal ion" curve was obtained in the same fashion as the "metal free" curve by titrating a solution 0.00100 M in respect to tetren·5HCl, 0.075 M in $KClO_4$, and 0.0100 M in respect to nickel(II) perchlorate with 0.100 N KOH.

D. "Equivalent" Curve.—The "equivalent" curve was obtained by measuring 25 ml. of 0.00200 M tetren·5HCl in 0.15 M $KClO_4$ and 25 ml. of 0.00200 M $Ni(ClO_4)_2$ solution into 60-ml. glass-stoppered bottles. To each bottle was added various volumes of 0.0500 N KOH solution, after nitrogen had been passed through the solution for at least 15 min. The bottles were suspended in a constant temperature bath for a period of one week, after which pH measurements were made on each solution.

All the above measurements were made at 15, 25 and 35 ± 0.1°, numerous curves being taken of each type and the best curves picked for calculations. The neutralization curves obtained at 25° are shown in Fig. 1.

E. Bjerrum's Method.—For determination of the stability constant of the nickel(II)–tetren complex by the method of Bjerrum, a titration of a solution 0.000500 M in tetren·5HCl and 0.000500 M in $Ni(ClO_4)_2$ with 0.0125 N KOH was conducted in the same fashion as described above for the "equivalent" curve. This titration was only conducted at 25 ± 0.1°.

Method of Calculation and Results

A. Basicity Constants for Tetraethylenepentamine by the Method of Schwarzenbach.

—Using the general method derived by Schwarzenbach[5] the basicity constants for tetren may be calculated from the neutralization curve obtained from the titration of tetren·5HCl with KOH ("metal-free" curve). The following equilibria and equations apply to the case of tetren (abbreviated T in the following equations)

$$T + H^+ \rightleftharpoons TH^+;\ K^H_{TH} = [TH^+]/[H^+][T]$$

$$TH^+ + H^+ \rightleftharpoons TH_2^{2+};\ K^H_{TH_2} = [TH_2^{2+}]/[H^+][TH^+]$$

$$TH_2^{2+} + H^+ \rightleftharpoons TH_3^{3+};\ K^H_{TH_3} = [TH_3^{3+}]/[H^+][TH_2^{2+}]$$

$$TH_3^{3+} + H^+ \rightleftharpoons TH_4^{4+};\ K^H_{TH_4} = [TH_4^{4+}]/[H^+][TH_3^{3+}]$$

$$TH_4^{4+} + H^+ \rightleftharpoons TH_5^{5+};\ K^H_{TH_5} = [TH_5^{5+}]/[H^+][TH_4^{4+}]$$

total concn. of tetren present in soln. =

$$[T]_t = [T] + [TH^+] + [TH_2^{2+}] + [TH_3^{3+}] + [TH_4^{4+}] + [TH_5^{5+}] \quad (1)$$

If a = apparent degree of neutn. of cation acid, TH_5^{5+} = (ml. base added) (N base)/(concn. of tetren)(ml. soln.) and g = number of protons which appear on the average to be bound to tetren· = true degree of neutn., then

$$[H^+]_t = [T]_t(5 - a) = [H^+] - [OH^-] + [TH^+] + 2[TH_2^{2+}] + 3[TH_3^{3+}] + 4[TH_4^{4+}] + 5[TH_5^{5+}]$$

and

$$[T]_t \times g = [TH^+] + 2[TH_2^{2+}] + 3[TH_3^{3+}] + 4[TH_4^{4+}] + 5[TH_5^{5+}] \quad (2)$$

but

$$g = m - a + ([OH^-] - [H^+])/[T]_t \quad (3)$$

where m = maximum number of protons which may be associated with tetren = 5.

Combining equations 1, 2 and 3 the following equation is obtained

$$g + (g-1)[H^+]K^H_{TH} + (g-2)[H^+]^2\bar{K}^H_{TH_2} + (g-3)[H^+]^3\bar{K}^H_{TH_3} + (g-4)[H^+]^4\bar{K}^H_{TH_4} + (g-5)[H^+]^5\bar{K}^H_{TH_5} = 0 \quad (4)$$

where $\bar{K}^H_{TH_n}$ = product of the constants from K^H_{TH} to $K^H_{TH_n}$. The first two constants may be considered in the first approximation, allowing equation 4 to be reduced to

$$g + (g-1)[H^+]K^H_{TH} + (g-2)[H^+]^2\bar{K}^H_{TH_2} = 0 \quad (5)$$

Dividing equation 5 through by $\bar{K}^H_T$ the following equation results

$$g(1/K^H_{TH}) + (g-1)[H^+] + (g-2)[H^+]^2K^H_{TH} = 0 \quad (6)$$

if we let $x = 1/K^H_{TH}$, and $y = K^H_{TH_2}$ then

$$gx + (g-1)[H^+] + (g-2)[H^+]^2y = 0 \quad (7)$$

solving for y

$$y = -\{gx/(g-2)[H^+]^2\} - \{(g-1)[H^+]/(g-2)[H^+]^2\}$$

If $A = -g/(g-2)\ [H^+]^2$, and $B = -(g-1)\ [H^+]/(g-2)\ [H^+]^2$ then equation 7 becomes

$$y = Ax + B \quad (8)$$

which is the slope intercept form of the linear equation.

A and B may be found for a number of points on the curve where the first two constants are important (a = 3–5) and equation 8 may be solved graphically or algebraically for x and y thus yielding approximate values for K^H_{TH} and $K^H_{TH_2}$.

Using these approximate values it is now possible

(6) G. Schwarzenbach, *Helv. Chim. Acta*, **33**, 963 (1950).
(7) G. Schwarzenbach, *ibid.*, **33**, 974 (1950).
(8) G. Schwarzenbach and J. E. Prue, *ibid.*, **33**, 985 (1950).
(9) H. B. Jonassen and L. Westerman, *J. Phys. Chem.*, **61**, 1006 (1957).
(10) R. I. Stearns, a thesis, Tulane University, 1955.

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to solve for $K^{H}_{TH_3}$ by using equation 4 omitting the last two terms. $K^{H}_{TH_3}$ is thus obtained in the first approximation from

$$K^{H}_{TH_3} = \frac{-g-(g-1)[H^+]K^{H}_{TH}-(g-2)[H^+]^2\bar{K}^{H}_{TH_2}}{(g-3)[H^+]^3\bar{K}^{H}_{TH_2}} \quad (9)$$

Having found $K^{H}_{TH_3}$ to the first approximation the fourth term of equation 4 may be used to redetermine K^{H}_{TH} and $K^{H}_{TH_2}$ in the same manner as described above. By recourse to equation 9, a better value for $K^{H}_{TH_3}$ may be obtained. This process of successive approximations is repeated as many times as necessary to get consistent values for K^{H}_{TH}, $K^{H}_{TH_2}$ and $K^{H}_{TH_3}$.

The best values for these first three constants may then be used to calculate $K^{H}_{TH_4}$ and $K^{H}_{TH_5}$ using equation 4, and solving sets of simultaneous equations in two unknowns from the points on the curve between $a = 0$ and 2.

The results of these calculations are given in Table I.

TABLE I
BASICITY CONSTANTS FOR TETREN

	Temp., °C. 15	25	35
log K^{H}_{TH}	9.90	9.78	9.60
log $K^{H}_{TH_2}$	9.51	9.38	9.23
log $K^{H}_{TH_3}$	8.22	8.14	8.09
log $K^{H}_{TH_4}$	4.94	4.83	4.73
log $K^{H}_{TH_5}$	3.17	3.15	3.12

B. Apparent Basicity Constants for Tetren in the Presence of Excess Nickel(II) Ion and Formation Constants for the Nickel–Tetren Complexes by the Method of Schwarzenbach.—The apparent basicity constants of tetren in the presence of excess nickel(II) ion may be calculated from the neutralization curve obtained by titrating tetren·5HCl in the presence of a tenfold excess of the nickel(II) ion, with KOH. Since only a small fraction of the nickel(II) ion is removed from the solution due to complex formation the concentration $[Ni^{2+}]$ may be considered to be practically constant.

This "excess-metal ion" curve then follows equation 10 where $'K^{H}$ refers to the apparent basicity constants. This equation has the same form as equation 4.

$$g+(g-1)[H^+]\,'K^{H}_{TH}+(g-2)[H^+]^2\,'\bar{K}^{H}_{TH_2}+(g-3)[H^+]^3\,'\bar{K}^{H}_{TH_3}+(g-4)[H^+]^4\,'\bar{K}^{H}_{TH_4}+(g-5)[H^+]^5\,'\bar{K}^{H}_{TH_5}=0 \quad (10)$$

From this equation may be calculated the apparent basicity constants in a manner similar to that described above for the basicity constants. In the case of the nickel(II) ion with tetren, however, a buffer zone ($a = 1$ to $a = 4$) characteristic of a "three-proton in one step" process is indicated as shown in Fig. 1, so that the terms $(g-2)[H^+]^2\,'\bar{K}^{H}_{TH_2}$ and $(g-3)[H^+]^3\,'\bar{K}^{H}_{TH_3}$ are smaller in comparison to the preceding and following terms in equation 10. Equation 10 may then be reduced to

$$g+(g-1)[H^+]\,'K^{H}_{TH}+(g-4)[H^+]^4\,'\bar{K}^{H}_{TH_4}+(g-5)[H^+]^5\,'\bar{K}^{H}_{TH_5}=0 \quad (11)$$

The constants $'K^{H}_{TH}$, $'\bar{K}^{H}_{TH_4}$ and $'\bar{K}^{H}_{TH_5}$ may be obtained by solving sets of simultaneous equations in three unknowns using successive points on the "excess-metal ion" curve. By appropriate division, $'K^{H}_{TH}$, $'K^{H}_{TH_2}$, $'\bar{K}^{H}_{TH_3}$, $'K^{H}_{TH_4}$ and $'K^{H}_{TH_5}$ may be obtained. The results of these calculations are given in Table II.

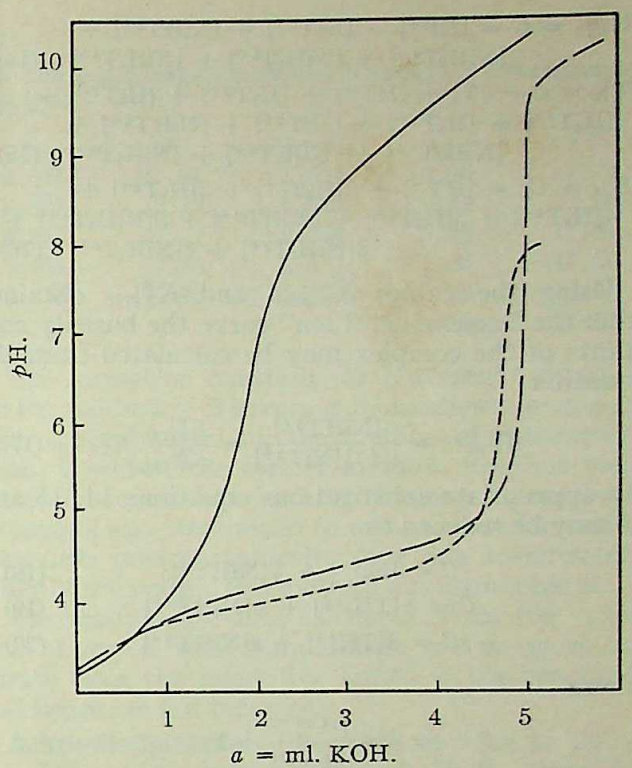

Fig. 1.—Neutralization curves at 25°: ———, "metal free" curve; — — —, "equivalent" curve; – – – – –, "excess metal ion" curve.

TABLE II
APPARENT BASICITY CONSTANTS OF TETREN IN PRESENCE OF TENFOLD EXCESS OF NICKEL(II) ION

	Temp., °C. 15	25	35
log $'K^{H}_{TH}$	5.08	5.11	5.09
log $'K^{H}_{TH_2}$ $'K^{H}_{TH_3}$ $'K^{H}_{TH_4}$	12.87	12.46	12.13
log $'K^{H}_{TH_5}$	3.18	3.15	3.13

From consideration of the equilibria of the nickel(II) ion with tetren the following equations may be derived to determine the formation constants $K^{Ni}_{NiHT^{+3}}$ and $K^{Ni}_{NiT^{+2}}$

$$K^{Ni}_{NiHT^{3+}} = \frac{1}{[Ni^{2+}]}\left[\frac{\bar{K}^{H}_{TH_2}K^{H}_{TH_3}K^{H}_{TH_4}K^{H}_{TH_5}}{'K^{H}_{TH_2}\,'K^{H}_{TH_3}\,'K^{H}_{TH_4}\,'K^{H}_{TH_5}}-1\right] \quad (12)$$

$$K^{Ni}_{NiT^{2+}} = \frac{1}{[Ni^{2+}]}\left[\frac{\bar{K}^{H}_{TH_5}}{'\bar{K}^{H}_{TH_5}}-1\right] \quad (13)$$

These equations are derived on the assumption that no polynuclear complexes are formed. The proof of the absence of polynuclear complexes is obtained if the value of $K^{Ni}_{NiT^{2+}}$ obtained from the "excess-metal ion" curve agrees with that calculated, as follows, from the "equivalent" curve.

The "equivalent" curve is obtained through the neutralization of tetren·5HCl in the presence of an equal molar quantity of the nickel(II) ion. Since the concentration $[Ni^{2+}]$ of the free nickel(II) ion is not constant, equation 10 is not applicable. If the assumption is made that no complexes with more than one T per complex species is formed then the equations may be written

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$$[Ni^{2}]_t = C = [Ni^{2+}] + [NiT^{2+}] + [NiHT^{3+}] + [NiH_2T^{4+}] + [NiH_3T^{5+}] + [NiH_4T^{6+}] \quad (14)$$

$$[T]_t = C = [T] + [HT^{+}] + [H_2T^{2+}] + [H_3T^{3+}] + [H_4T^{4+}] + [H_5T^{5+}] + [NiT^{2+}] + [NiHT^{3+}] + [NiH_2T^{4+}] + [NiH_3T^{5+}] + [NiH_4T^{6+}] \quad (15)$$

$$[H]_t = Cg = [HT^{+}] + 2[H_2T^{2+}] + 3[H_3T^{3+}] + 4[H_4T^{4+}] + 5[H_5T^{5+}] + [NiHT^{3+}] + 2[NiH_2T^{4+}] + 3[NiH_3T^{5+}] + 4[NiH_4T^{6+}] \quad (16)$$

Using the values $K^{Ni}_{NiHT^{3+}}$ and $K^{Ni}_{NiT^{2+}}$ obtained from the "excess metal ion" curve the basicity constants of the complex may be calculated from the equation

$$K^{H}_{NiHT^{3+}} = \frac{[NiHT^{3+}]}{[H^{+}][NiT^{2+}]} = \frac{K^{Ni}_{NiHT^{3+}}}{K^{Ni}_{NiT^{2+}}} K^{H}_{TH} \quad (17)$$

By appropriate substitutions equations 14, 15 and 16 may be reduced to

$$C = [Ni^{2+}] + \gamma[NiHT^{3+}] \quad (18)$$

$$C = \alpha[TH_4^{4+}] + \gamma[NiHT^{3+}] \quad (19)$$

$$gC = \beta[TH_4^{4+}] + \delta[NiHT^{3+}] \quad (20)$$

where

$$\gamma = \frac{[H^{+}]^{-1}}{K^{N}_{HNiHT^{3+}}} + 1$$

$$\alpha = \frac{[H^{+}]^{-4} + [H^{+}]^{-3}\bar{K}^{H}_{TH} + [H^{+}]^{-2}\bar{K}^{H}_{TH_2} + [H^{+}]^{-1}\bar{K}^{H}_{TH_3} + \bar{K}^{H}_{TH_4}}{\bar{K}^{H}_{TH_4}}$$

$$\beta = \frac{[H^{+}]^{-3}\bar{K}^{H}_{TH} + 2[H^{+}]^{-2}\bar{K}^{H}_{TH_2} + 3[H^{+}]^{-1}\bar{K}^{H}_{TH_3} + 4\bar{K}^{H}_{TH_4}}{\bar{K}^{H}_{TH_4}}$$

$$\delta = \frac{K^{H}_{NiHT^{3+}}[H^{+}]}{K^{H}_{NiHT^{3+}}[H^{+}]} = 1$$

For the reaction

$$Ni^{2} + TH_4^{4+} \rightleftharpoons NiHT^{3+} + 3H^{+}; \quad K_I = \frac{[NiHT^{3+}][H^{+}]^3}{[Ni^{2+}][TH_4^{4+}]} \quad (I)$$

The concentrations $[NiHT^{3+}]$, $[H^{+}]$, $[Ni^{2+}]$ and $[TH_4^{4+}]$ thus can be obtained easily and K_I may be calculated.

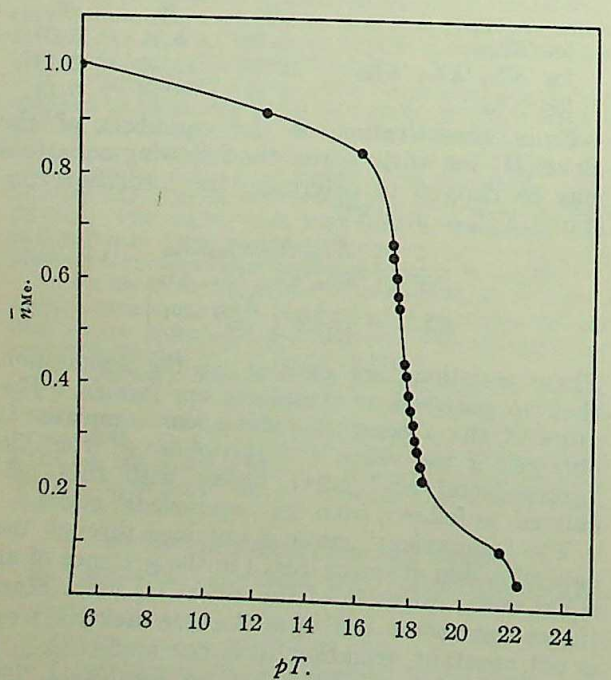

Fig. 2.—Formation curve for the complex species formed between $Ni(ClO_4)_2$ and tetren at 25°.

Having found K_I the formation constants of any of the metal complexes are easily obtained, thus for $K^{Ni}_{NiT^{2+}}$ and $K^{Ni}_{NiHT^{3+}}$ the following equations are used to calculate the constants.

$$K^{Ni}_{NiT^{2+}} = \frac{K_I\bar{K}^{H}_{TH_4}}{K^{H}_{NiHT}} \quad (21)$$

$$K^{Ni}_{NiHT^{3+}} = \frac{K^{H}_{TH_5^{5+}}}{K_I} \quad (22)$$

The results of the calculations for these constants are given in Table III.

TABLE III

FORMATION CONSTANTS FOR NICKEL(II)–TETREN COMPLEXES

	Temp., °C. 15	25	35
	"Excess-metal Ion" curve		
$\log K^{Ni}_{NiT^{2+}}$	18.00	17.78	17.74
	"Equivalent" curve		
$\log K^{Ni}_{NiHT^{3+}}$	13.04	12.66	12.20
$\log K^{Ni}_{NiT^{2+}}$	17.63	17.51	17.39

C. Formation Constants by the Method of Bjerrum.—The calculation of the formation constants for metal ions with amines has been described by Bjerrum[1] and the extension of his equations has been given by Jonassen, *et al.*,[2,3] for the formation constants of metal ions with polyamines. The acid constants used in the calculations were those measured by Jonassen, Frey and Schaafsma.[11] The formation curve obtained is shown in Fig. 2, and the results of the calculations are given in Table IV, where

C_{Me} = total concn. of metal ion
C_{HCl} = total concn. of HCl
C_T = total tetren concn. in the soln.
C_A = concn. of hydrogen ions bound to uncomplexed tetren
$\bar{n}_T$ = av. no. of hydrogen ions bound to tetren = C'_A/C'_T
C'_T = total concn. of tetren not bound to the metal ion

$$\bar{n}_{Me} = \frac{(C_T - C_A)/\bar{n}_T}{C_{Me}}$$

$$\log K = pT + \log \bar{n}_{Me}/(1 - \bar{n}_{Me})$$

Discussion

The basicity constants of tetren given in Table I are slightly higher than those reported by Jonassen, Frey and Schaafsma.[11] This is as would be expected due to the higher ionic strength at which they were determined.

Comparison of the apparent basicity constant $'K^{H}_{TH_5}$ with the basicity constant $K^{H}_{TH_5}$ shows equality of the two constants. This indicates that no complex formation takes place in the region $a = 0$ to $a = 1$, which is in agreement with conclusions drawn previously.[9] Only the product of the apparent basicity constants, $'K^{H}_{TH_2}$ $'K^{H}_{TH_3}$ $'K^{H}_{TH_4}$ could be calculated in the buffered region of the "Excess-metal ion" curve, $a = 1$ to $a = 4$, indicating a "three-proton in one step" neutralization and complex formation process is taking place. This

(11) H. B. Jonassen, F. W. Frey and A. Schaafsma, *J. Phys. Chem.*, 61, 504 (1957).

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TABLE IV

FORMATION CONSTANT CALCULATED BY METHOD OF BJERRUM FOR THE EQUILIBRIUM BETWEEN NICKEL(II) PERCHLORATE AND TETREN AT 25°

pH	$C_{Mo} \times 10^4$	$C_{HCl} \times 10^3$	C_T	C_A	$\bar{n}_T$	pT	$C_T - C'_T$	$\bar{n}_{Mo}$	log K
4.26	4.505	1.014	4.505	0.9590	3.547	17.91	1.801	0.40	17.73
4.29	4.484	0.9524	4.484	.9011	3.527	17.83	1.929	.43	17.70
4.33	4.464	.8929	4.464	.8461	3.502	17.71	2.048	.46	17.69
4.39	4.405	.7154	4.405	.6747	3.464	17.59	2.457	.56	17.69
4.44	4.386	.6579	4.386	.6216	3.433	17.45	2.570	.59	17.60
								Av. log K	17.68

may be illustrated by the equation

$$Ni^{2+} + tetrenH_4^{4+} \rightleftharpoons [Ni\ Htetren]^{3+} + 3H^+$$

The formation constant for the "hydrogen" complex formed in this process was calculated, the results being given in Table III.

The agreement of the formation constants calculated from the "Excess-metal ion" curve and the "Equivalent" curve indicates that no polynuclear complexes are formed. Thus for the over-all neutralization process and complex formation the following equations are descriptive.

$$tetrenH_5^{5+} \xrightarrow[-H^+]{} tetrenH_4^{4+} \xrightarrow[-3H^+]{Ni^{2+}} NiHtetren^{3+} \xrightarrow[-H^+]{} Nitetren^{2+}$$

The formation constant for Nitetren^{2+} obtained by the method of Bjerrum is in excellent agreement with that obtained by the method of Schwarzenbach; however, the former method does not yield formation constants for the "hydrogen complex." Attempts also were made to measure the formation constants polarographically, but due to irreversibility of the system this method was unsuccessful.

Thermodynamic data calculated from the variation of log K with temperature are no more accurate than the reliability limits of the constants and hence are not reported.

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NEW ORLEANS 18, LOUISIANA

[CONTRIBUTION FROM THE RICHARDSON CHEMISTRY LABORATORY AT TULANE UNIVERSITY]

Inorganic Complex Compounds Containing Polydentate Groups. XVI. A Study of the Complex Ions Formed by the Copper(II) Ion with Triethylenetetramine, Tetraethylenepentamine and Pentaethylenehexamine[1]

BY HANS B. JONASSEN, J. AARON BERTRAND, FRANK R. GROVES, JR., AND ROBERT I. STEARNS

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The complexes of the copper(II) ion with triethylenetetramine, tetraethylenepentamine and pentaethylenehexamine have been studied polarographically. It has been shown that the copper(II) ion exhibits an amine coördination number of five with these compounds and that hydrogen complexes are formed.

Introduction

The polarographic study of complex ions is a well established method[2] provided that the complex ion to be investigated is reduced reversibly at the dropping mercury electrode. If a plot of $E_{d.e.}$ *versus* the corresponding values of log $(i_d - i)/i$ from equation I is a straight line with slope 2.303 (RT/nF) the reduction process is reversible.

$$E_{d.e.} = E_{1/2} + 2.303\ RT/nF \log (i_d - i)/i \qquad (I)$$

Where

$E_{d.e.}$ = voltage at the dropping mercury electrode
$E_{1/2}$ = half-wave potential of the complex
i_d = diffusion current
i = current at any $E_{d.e.}$
n = number of electrons transferred

The composition of the complex can be determined from the equation

$$(E_{1/2})_c - (E_{1/2})_a = 2.303\ RT/nF \log K_c - 2.303\ RT/nFp \log C_x \qquad (II)$$

Where

$(E_{1/2})_c$ = half-wave potential of the complex
$(E_{1/2})_a$ = half wave potential of the simple aquo metal ion
K_c = dissociation constant of the complex
p = no. of moles of ligand per mole of metal ion in the complex
C_x = concn. of ligand in moles/l. (C_x must be in considerable excess over the concn. of the metal ion in order that the concn. of the simple aquo metal ion will be negligible.)

A plot of $(E_{1/2})_c$'s of several solutions of varying C_x *versus* log C_x will yield a straight line of slope 2.303 RT/nFp from which p can be calculated.

Using the value of p established in equation II pK_c can be calculated.

The polyamines which become protonated to varying degrees depending upon the pH of the solution become a special case. Their dissociation occurs as shown in the reaction

$$H_z(H_qX)_a^{+(z+q)} \rightleftharpoons zH^+ + pHqX^{+q}$$

(1) Abstracted in part from the Master's Theses submitted to Tulane University, New Orleans, Louisana, by J. Aaron Bertrand, 1956, Frank R. Groves, Jr., 1951, and Robert I. Stearns, 1955.

(2) I. M. Kolthoff, "Polarography," Interscience Publishers, New York, N. Y., 1952.

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Where

z = no. of protons dissociated from the acid amine
q = no. of protons associated with the amine in the complexes formed

The equilibrium constant of this dissociation is

$$K_a = \frac{[H^+]^z[H_qX^{+q}]^p}{[H_z(H_qX)_p]} \quad \text{(III)}$$

According to this notation the ligand is H_qX^{+q} and the term C_x of equation II is given by $[H_qX^{+q}]$. Also

$$[H_z(H_qX)_p] = \Sigma[(HX_p)^+] + [(H_2X)_p^{+2}] + \ldots + [H_{z+q}(X)_p] \quad \text{(IV)}$$

Solving (III) for $p \log [H_qX^{+q}]$

$$p \log [H_qX^{+q}] = zp\mathrm{H} + \log K_a + \log [H_z(H_qX)_p] \quad \text{(V)}$$

Substituting (V) into (II)

$$(E_{1/2})_c - (E_{1/2})_a = 2.303 \frac{RT}{nF} \log K_c - 2.303 \frac{RT}{nF} (zpH - \log K_a + \log [H_z(H_qX)_p] \quad \text{(VI)}$$

The reduction of a complex ion of a protonated polyamine occurs then as

$$M(H_qX)_p^{+(v+q)} + ve^- \longrightarrow M^0 + pH_qX^{+q}$$

M denotes the metal and v its oxidation state.

Combining this with the dissociation of the protonated amine the over-all reaction occurs

$$M(H_qX)^{+(v+q)} + zH^+ + ve^- \longrightarrow M^0 + H_z(H_qX)p^{+(z+q)}$$

A series of solutions may be prepared in which all the factors are constant except the pH and the $(E_{1/2})_c$'s which are measured and plotted *versus* each other. By equation VI such a plot will be a straight line of slope $2.303(RT/nF)z$ from which the value of z may be calculated.

Approximate thermodynamic values can be calculated by the usual equations.[3]

Experimental

The technical grades of triethylenetetramine (trien), tetraethylenepentamine (tetren) and the mixture of amines designated "Polyamine H" were obtained from Carbide and Carbon Chemicals.

I. **Purification of Triethylenetetramine.**—Stock solutions of trien were made by weighing out accurately proper amounts of trien which had been purified previously.[4] More dilute solutions were prepared by diluting aliquot portions of this stock solution.

II. **Purification of Tetraethylenepentamine.**—Tetren pentahydrochloride was obtained in the pure state by adding 100 g. of technical grade tetren to 100 ml. of benzaldehyde slowly and with vigorous stirring so as to avoid overheating. After the addition of the benzaldehyde the mixture was allowed to cool to room temperature with occasional stirring. At this point the mixture became quite viscous. The Schiff base separated when about 15 to 20 times its volume of water was added.

The water layer containing some unreacted tetren and other water-soluble impurities was separated from the oily Schiff base at the bottom of the beaker. About 200 ml. of concentrated HCl was then added slowly to the Schiff base. The mixture was heated after dilution with 100 ml. of water until it dissolved.

After cooling the solution in an ice-bath the tetren pentahydrochloride was precipitated with methanol. This recrystallization was repeated several times until a pure white product was obtained. The product was then washed with acetone and finally with ether, and then dried in the oven at about 80°.

Tetren pentahydronitrate was prepared similarly by using nitric acid.

The products were analyzed for primary amine nitrogen content by the Van Slyke method[5]; calcd. for tetren·5HCl, 7.54%; observed, 7.48%. Calcd. for tetren·5HNO_3, 5.56; observed, 5.65.

III. **Purification of Pentaethylenehexamine.**—About 1.5 l. of "Polyamine H" was distilled under a pressure of 10 to 20 mm. with about 1 l. of distillate being collected. Four hundred ml. of this distillate was redistilled and the fraction boiling at 220–250° (10–20 mm. pressure) was collected.

Forty milliliters of this fraction was dissolved in 250 ml. of methanol and cooled in an ice-bath. Concentrated HCl was added dropwise while stirring and a precipitate formed after the addition of about 50 ml. This was filtered, washed with acetone and ether and dried in a vacuum desiccator.

By the method of Van Slyke[5] the primary amine nitrogen content was determined; calcd. N, 6.21%; observed, 6.26%. By means of a potentiometric determination against NaOH the equivalent weight was determined; calcd., 75.19; observed, 75.13.

Aqueous stock solutions using boiled distilled water of tetren pentahydrochloride, tetren pentahydronitrate and hexen hexahydrochloride were prepared and standardized potentiometrically against NaOH. Other solutions of these amines were prepared by dilution of these stock solutions.

Stock solutions of cupric perchlorate (G. Frederick Smith Chemical Co.) and cupric nitrate were prepared using boiled distilled water and standardized electrolytically.

A carbonate-free solution of NaOH was obtained by first preparing a saturated solution of NaOH and letting it stand about a week. This was then filtered and diluted with distilled water and standardized against potassium acid phthalate.

Concentrated HCl and HNO_3 were diluted with distilled water and the stock solution standardized against NaOH.

The solutions used in the polarographic determinations of the trien and hexen complexes were prepared with the stock acid amine solutions to which a calculated amount of NaOH was added to neutralize the acid. By the addition of HNO_3 the pH for the trien complexes was varied.

The pH determinations were made with a Beckman Model G pH meter, standardized with Beckman buffer solutions (pH's of 4, 7 and 10).

The polarograph was one assembled according to the Leeds and Northrup technical manual 77-12-0-8, using Leeds and Northrup parts.

Results and Discussion

Stability Studies.—Polarograms were determined in the usual way. The $E_{1/2}$ (S.C.E.)'s for the various solutions are listed in Table I.

The polarographic data which showed reversible reduction were then used to determine the constitution of the complexes, the dissociation constants, and other thermodynamic functions. It was also shown that the reduction occurs in one step involving the transfer of two electrons.

A plot of the values of $(E_{1/2})_c$ *versus* the corresponding values of log C_{trien}, C_{tetren} and C_{hexen} resulted in a straight line whose slope indicated a value of 1 for p in the formation equation

$$Cu^{2+} + p\begin{pmatrix}\text{trien,}\\ \text{tetren}\\ \text{or}\\ \text{hexen}\end{pmatrix} \longrightarrow \left[Cu\begin{pmatrix}\text{trien,}\\ \text{tetren}\\ \text{or}\\ \text{hexen}\end{pmatrix}_p\right]^{2+}$$

where $p = 1$

Using equation II and the $E_{1/2}$ values listed in Table I, the dissociation constants of the complex ions $[Cutrien]^{2+}$, $[Cutetren]^{2+}$ and $[Cuhexen]^{2+}$ were calculated. In these calculations the value of $(E_{1/2})$s was taken to be +0.04.[6] The results of these calculations are shown in Table II.

(3) F. Daniels, "Outline of Physical Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1948.

(4) H. B. Jonassen, R. B. LeBlanc, A. W. Meibohm and R. M. Rogan, THIS JOURNAL, **72**, 2430 (1950).

(5) D. D. Van Slyke, *J. Biol. Chem.*, **83**, 425 (1929).

(6) H. H. Willard, L. L. Merritt and J. A. Dean, "Instrumental Methods of Analysis," D. Van Nostrand, Inc., New York, N. Y., 1952.

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TABLE I

MEASUREMENT OF HALF-WAVE POTENTIALS

C_{amine}, $M \times 10^{-2}$	C_{salt}, M	$E_{1/2}$ 25°	30°	35°	45°
		(a)			
trien	$NaNO_3$				
2.0	0.1		−0.542		
5.0	.1		− .538		
7.5	.1		− .553		
8.7	.1		− .555		
		(b)			
tetren	KCl				
0.5	0.1	−0.607		−0.610	−0.609
1.0	.1	− .617		− .620	− .610
1.5	.1	− .622		− .622	− .615
2.0	.1	− .630		− .630	− .621
		(c)			
hexen	NaCl				
0.5	0.1	−0.638		−0.647	−0.647
1.0	.1	− .643		− .660	− .652
1.5	.1	− .648		− .654	− .660
2.0	.1	− .652		− .668	− .660

(a) $[Cu^{2+}] = 5.0 \times 10^{-4}$ M; maximum suppressor was methyl red

(b) $[Cu^{2+}] = 4.0 \times 10^{-4}$ M; maximum suppressor was gelatin

(c) $[Cu^{2+}] = 4.0 \times 10^{-4}$ M; maximum suppressor was gelatin

TABLE II

AVERAGE pK_c VALUES

	25°	30°	35°	45°
$[Cutrien]^{2+}$		20.7		
$[Cutetren]^{2+}$	24.25		23.58	22.64
$[Cuhexen]^{2+}$	25.13		24.74	24.22

The approximate thermodynamic data of these complexes are listed in Table III. The data for the $[Cutrien]^{2+}$ complex are added for comparison.[7]

TABLE III

APPROXIMATE THERMODYNAMIC VALUES IN KCAL./MOLE

	25°	30°	35°	45°
$[Cutrien]^{2+}$				
ΔH^0		22.0		
ΔF^0		28.6		
$[Cutetren]^{2+}$				
ΔH^0	32.69		32.69	32.69
ΔF^0	33.07		33.24	32.95
$[Cuhexen]^{2+}$				
ΔH^0	19.62		19.62	19.62
ΔF^0	34.28		34.86	35.26

It has been shown that for most polyamines the amine coördination number of the copper(II) ion is less than six.[7,8]

Since a relatively large increase of the stability of the $[Cutetren]^{2+}$ ion over that of the $[Cutrien]^{2+}$ ion occurs, it is indicated that the coördination number of the copper(II) ion is greater than four, possibly five.

The pK_c of the $[Cuhexen]^{2+}$ ion is about the same as that of the $[Cutetren]^{2+}$ which seems to indicate that in both cases five copper to nitrogen bonds exist. The ΔH^0 values, however, indicate that the $[Cuhexen]^{2+}$ ion is less thermally stable than the $[Cutetren]^{2+}$ ion since its dissociation is accompanied by endothermic ΔH^0 of 19.62 kcal./mole, whereas the ΔH^0 of $[Cutetren]^{2+}$ is 32.69 kcal./mole. This would be expected since an additional amine group is present which does not seem to be bound to the copper(II) ion.

pH Studies.—Plots of $(E_{1/2})_c$ *versus* pH (Figs. 1, 2, 3) give the value of z of equation VI. For all

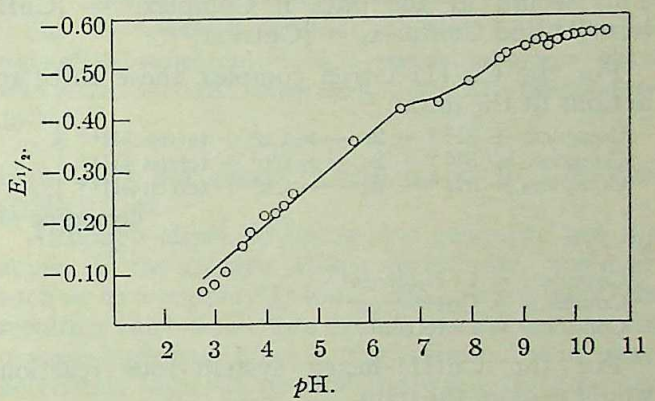

Fig. 1.—Cu(II)–triethylenetetramine system: each solution 4×10^{-4} M $Cu(ClO_4)_2$, 1×10^{-2} M triethylenetetramine, 0.1 M KCl, 0.01% gelatin; slope = 0.086.

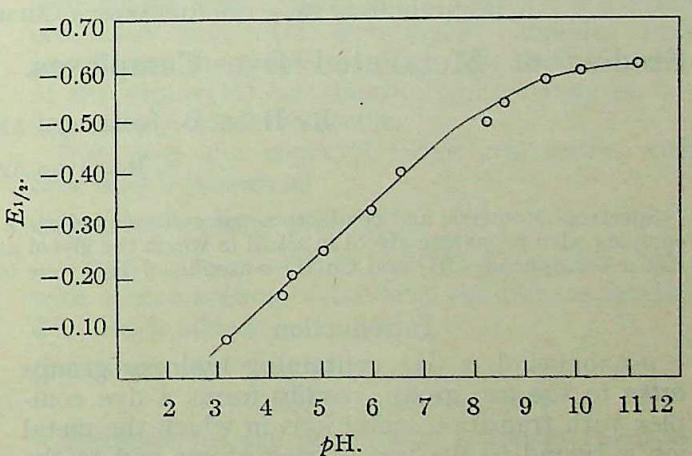

Fig. 2.—Cu(II)–tetraethylenepentamine system: each solution 4×10^{-4} M $Cu(ClO_4)_2$, 1×10^{-2} M tetraethylenepentamine, 0.1 M KCl, 0.01% gelatin; slope = 0.093.

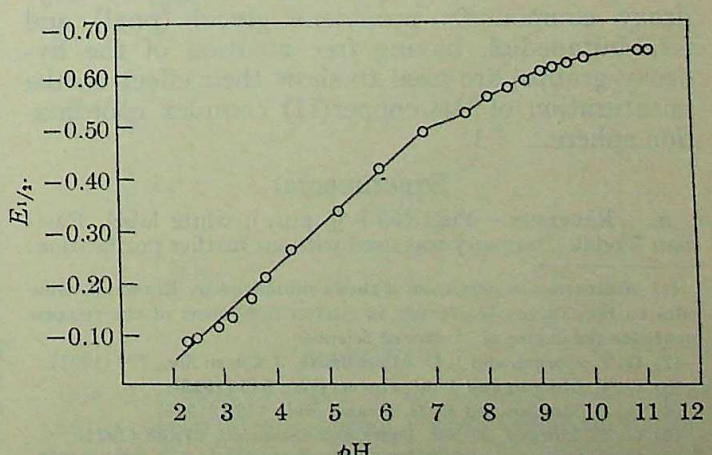

Fig. 3.—Cu(II)–pentaethylenehexamine system: each solution 4×10^{-4} M $Cu(ClO_4)_2$, 1×10^{-2} M pentaethylenehexamine, 0.1 M NaCl, 0.01% gelatin; slope = 0.093. Dashed line for 3 theoretical slope = 0.089.

(7) H. B. Jonassen, G. G. Hurst, R. B. LeBlanc and A. W. Meibohm, *J. Phys. Chem.*, **56**, 16 (1952).

(8) H. B. Jonassen, R. B. LeBlanc and R. M. Rogan, THIS JOURNAL, **72**, 4968 (1950).

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three complexes the maximum slope found in the *p*H regions of about 3 to 6 corresponded to a value of 3 for *z*.

Considering the species of the protonated amines existing in the *p*H regions of the study the following reactions are indicated:

For the Cu(II)–trien complexes with decreasing *p*H two reactions may occur

$$\text{Complex}_1 + 3H^+ + 2e \longrightarrow Cu^0 + \text{trien } 4H^{4+}$$
$$\text{Complex}_2 + 3H^+ + 2e \longrightarrow Cu^0 + \text{trien } 3H^{3+}$$

decreasing *p*H

This would fit the data if $\text{Complex}_1 = [\text{CuH-trien}]^{3+}$ and $\text{Complex}_2 = [\text{Cutrien}]^{2+}$

For the Cu(II)–tetren complex these three reactions fit the data.

$$\text{Complex}_1 + 3H^+ + 2e \longrightarrow Cu^0 + \text{tetren } 5H^{5+}$$
$$\text{Complex}_2 + 3H^+ + 2e \longrightarrow Cu^0 + \text{tetren } 4H^{4+}$$
$$\text{Complex}_3 + 3H^+ + 2e \longrightarrow Cu^0 + \text{tetren } 3H^{3+}$$

decreasing *p*H

if

$\text{Complex}_1 = CuH_2\text{tetren}^{4+}$
$\text{Complex}_2 = \text{CuHtetren}^{3+}$
$\text{Complex}_3 = \text{Cutetren}^{2+}$

For the Cu(II)–hexen system four reactions would explain the data

$$\text{Complex}_1 + 3H^+ + 2e \longrightarrow Cu^0 + \text{hexen } 6H^{6+}$$
$$\text{Complex}_2 + 3H^+ + 2e \longrightarrow Cu^0 + \text{hexen } 5H^{5+}$$
$$\text{Complex}_3 + 3H^+ + 2e \longrightarrow Cu^0 + \text{hexen } 4H^{4+}$$
$$\text{Complex}_4 + 3H^+ + 2e \longrightarrow Cu^0 + \text{hexen } 3H^{3+}$$

decreasing *p*H

If

$\text{Complex}_1 = CuH_3\text{hexen}^{5+}$
$\text{Complex}_2 = CuH_2\text{hexen}^{4+}$
$\text{Complex}_3 = \text{CuHhexen}^{3+}$
$\text{Complex}_4 = \text{Cuhexen}^{2+}$

This also seems to indicate that three of the copper to amine bonds in the copper(II) polyethyleneamine complexes are of about the same order of strength, far greater than the strength of the proton to amine bond. The other copper to amine bonds are of about the same order of strength as the proton to amine bond and an equilibrium is set up between them. At least three of the amine groups are bound to the copper(II) ion, the rest are protonated depending upon the *p*H of the medium.

Acknowledgment.—The financial support of part of this work by the Office of Ordnance Research, U. S. Army, is gratefully acknowledged.

NEW ORLEANS, LA.

[CONTRIBUTION FROM THE RICHARDSON CHEMISTRY LABORATORY AT TULANE UNIVERSITY]

Studies of Metallated Dye Complexes. III. Copper(II)–*o*-Azophenol Complexes

BY HANS B. JONASSEN AND ELWOOD J. GONZALES[1]

RECEIVED APRIL 22, 1957

Spectrophotometric and conductometric evidence indicates that the copper(II)–*o*-azophenol complex forms a copper(II) complex with propylene glycol in alkali in which the glycol and copper(II)–dye react in a 1:1 mole ratio. The complexes K[Cu–*o*-azophenol–OH] and Cu(II)–*o*-azophenol–H_2O were isolated from ethanolic solution.

Introduction

o-Azophenol, a dye containing hydroxy groups *ortho* to the azo group, readily forms a dye complex with transition metal ions in which the metal ion is bound to the two oxygen atoms and to the azo linkage as shown by investigations of Morgan and co-workers,[2–8] Drew and Landquist,[9] Wilson,[10] and Oliver.[11] In the present investigation dihydroxy compounds, propylene glycol (pngl) and *l*-2,3-butanediol, having free rotation of the hydroxy groups, are used to show their effect on the unsaturation of the copper(II) complex coördination sphere.

Experimental

A. Reagents.—Pngl (99+% pure), white label, Eastman Kodak Company was used without further purification.

A sample of dye prepared according to Willstätter and Benz[12] was kindly furnished by Mr. Gayle Strickland. The melting point was found to be 172–173° (lit. value 172°).

l-2,3-Butanediol, kindly furnished by Dr. R. E. Reeves, was used in polarimetric studies, $[\alpha]_D$ −12.8°.

Formamide, C.P. grade, Fisher Scientific Company, was distilled at 8 mm. pressure and the fraction boiling at 89–90° collected. The refractive index at 23° was 1.4468.

Molar solutions of pngl, *l*-2,3-butanediol, and the dye were prepared by direct weighing and dilution to volume with oxygen-free 95% ethanol prepared by bubbling nitrogen deoxygenated by alkaline pyrogallol into ethanol for at least one hour.

Aqueous molar solutions of copper(II) chloride were prepared by weighing directly reagent grade $CuCl_2 \cdot 2H_2O$, dried over partially dehydrated $CuSO_4 \cdot 5H_2O$, and diluting to volume.

A molar solution of copper(II) nitrate was prepared by dissolving reagent grade $Cu(NO_3)_2 \cdot 3H_2O$ in one liter of distilled water. A drop of C.P. concd. nitric acid was added to suppress hydrolysis. The copper(II) ion concentration was determined by electrolysis.

Aqueous molar potassium hydroxide solutions were prepared by weighing the appropriate quantities of potassium hydroxide. Standardization was against potassium acid phthalate using phenolphthalein as indicator.

B. Spectrophotometric Studies.—Absorption measurements in the visible spectral region were made with a Beckman Model B spectrophotometer using 1-cm. matched Corex cells. All solutions were diluted to 100 milliliters with oxygen-free 95% ethanol prepared by bubbling nitrogen deoxygenated by alkaline pyrogallol into ethanol for at least

(1) Abstracted in part from a thesis submitted by Elwood J. Gonzales to the Tulane University in partial fulfillment of the requirements for the degree of Master of Science.
(2) G. T. Morgan and J. D. Main-Smith, *J. Chem. Soc.*, 704 (1921).
(3) G. T. Morgan and J. W. Porter, *ibid.*, 645 (1915).
(4) G. T. Morgan and E. D. Evans, *ibid.*, 1126 (1919).
(5) G. T. Morgan, *J. Soc. Dyers and Colourists*, **37**, 43 (1921).
(6) G. T. Morgan and J. D. Main-Smith, *J. Chem. Soc.*, 2866 (1922).
(7) G. T. Morgan, *ibid.*, 1731 (1924).
(8) G. T. Morgan and J. E. Moss, *J. Soc. Chem. Ind.*, 461T (1923).
(9) H. D. K. Drew and J. K. Landquist, *J. Chem. Soc.*, 292 (1938).
(10) J. S. Wilson, Doctoral Dissertation, Tulane University, 1952.
(11) J. Oliver, THIS JOURNAL, **79**, (1957).
(12) R. Willstätter and M. Benz, *Ber.*, **39**, 3492 (1906).

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one hour. Absorbancy values were determined at the wave lengths noted in the figures at 25–26°.

C. **Conductometric Studies.**—An Heath oscilloscope and a signal generator were used as a null point indicator in connection with a Leeds and Northrup slide wire potentiometer and decade resistance box. The conductance cell used was a vertical dipping type with platinized platinum electrodes. All conductometric work was carried out at 30°, under nitrogen in a constant temperature bath. In all cases the volume of the solution at the start of the titration was 100 ml. and conductances were corrected for dilution effects.

D. **Preparation of Complexes.**—Attempts to isolate the pngl complex of the Cu(II)–dye compound were unsuccessful. Instead the complexes listed below were obtained.

(1) K(Cu–dye–OH).—A compound K(Cu–dye–OH) was prepared by mixing 84 ml. (0.008 mole) of KOH, 0.002 mole of $Cu(OH)_2$, made by Segal,[13] 0.002 mole of pngl and 0.002 mole of dye. The solution turned from blue to deep red on adding the pngl and dye. A dark brown precipitate resulted. This was filtered, washed with distilled water and 150 ml. of ether until the filtrate was colorless. The residue was dried in a 120° oven overnight.

Anal. Calcd. for K(Cu–dye–OH): C, 43.44; H, 2.73; N, 8.44; ash, 38.17 (based on CuO and K_2O). Found: C, 43.39; H, 2.88; N, 8.51; ash, > 36.14 (sample popped slightly on combustion due to the —N=N— linkage).

(2) [Cu(II)–dye–H_2O].—A second compound was isolated by mixing 50 ml. of the pure pngl and 0.6 g. of the dye. The whole was stirred until some of the dye dissolved in the pngl. Then 1 g. of $Cu(NO_3)_2$ in 20 ml. of distilled water and 40 ml. of 95% ethanol was added. The solution immediately turned deep red. The whole was stirred and dissolved on the hot plate for 15 minutes. Filtration and dilution to 300 ml. with distilled water with subsequent slow evaporation to 100 ml. gave a brownish-red solution. Dilution to 200 ml. with distilled water and cooling in an ice–salt bath gave a brownish-black precipitate. The filtered and washed precipitate was dried in a 110° oven for 2 hours.

Anal. Calcd. for [Cu(II)–dye–H_2O]: C, 49.06; H, 3.43; N, 9.54; ash, 27.08 (as CuO). Found: C, 49.18; H, 3.15; N, 9.54; ash, 27.00 (as CuO).

Discussion and Results

A. **Spectrophotometric Studies.**—The spectrophotometric titration in Fig. 1 indicates that no change in absorption occurs until the two hydrogen ions liberated in the copper(II)–*o*-azophenol interaction have been neutralized. No sharp break is noted after two equivalents of KOH have been added such as was observed in the Jonassen, Cook and Wilson investigation.[14] Hence seemingly no Cu(II)–dye–hydroxy complex forms in the presence of pngl.

The change in slope occurring near 2.5 equivalents KOH is similar to a weak acid–strong base type interaction which the pngl–KOH reaction is. The pngl thus seems capable of coördinating with the Cu(II)–dye complex.

Nine equivalents of KOH are necessary to produce maximum absorption without formation of a precipitate. In Wilson's studies,[14] in the absence of pngl, seven equivalents of KOH are needed to give the maximum absorption without precipitation. If the same reaction mechanism is assumed as in Wilson's investigation,[14] *i.e.*, addition of OH^- ions to give the hydroxy complex which then decomposes to $[Cu(OH)_5]^{3-}$, then the additional two hydroxide ions in this investigation must have reacted with the pngl giving first the [copper(II)–dye–pngl]$^{2-}$ complex which then decomposes at high OH^- ion concentration again to the $[Cu(OH)_5]^{3-}$ ion.

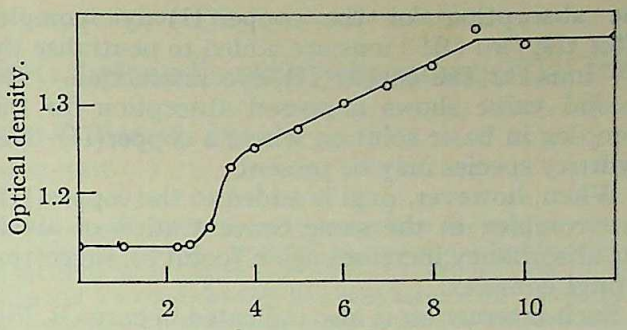

Fig. 1.—Spectrophotometric titration: 0.01 mmole copper(II)–*o*-azophenol + 0.01 mmole propylene glycol with 0.1119 *M* KOH; wave length, 525 mμ; temperature, 25–26°.

Although alcoholic hydrogens generally are not acidic, if the oxygen atoms coördinate, however, such as to a copper(II) ion in the dye complex, the resulting shift in electron density would weaken the oxygen–hydrogen bond giving enhanced acid characteristics such as reaction between tartrate and copper(II) ion in Fehling solution. If the other oxygen of the pngl behaves similarly, then two OH^- ions would be required if the pngl reacted as a bidentate ligand which would indicate a five coordinated [copper(II)–dye–pngl]$^{2-}$ complex proposed from the titration data. The sixth position of the copper(II) coördination sphere may be occupied by a solvent molecule.

The pngl and copper(II)–dye interaction with base may be shown as

$$\text{Cu(II)–dye} + \text{pngl} + 2OH^- \rightleftharpoons [\text{Cu(II)–dye–pngl}]^{2-} + 2H_2O \quad \text{(I)}$$

with decomposition of the pngl complex as further OH^- ion is added

$$[\text{Cu(II)–dye–pngl}]^{2-} + 5OH^- \rightleftharpoons [Cu(OH)_5]^{3-} + \text{dye ion} + \text{pngl ion} \quad \text{(II)}$$

Evidence for the presence of a copper(II)–dye–hydroxy complex in the absence of pngl is indicated by inspection of curve A, Fig. 2. The first value is

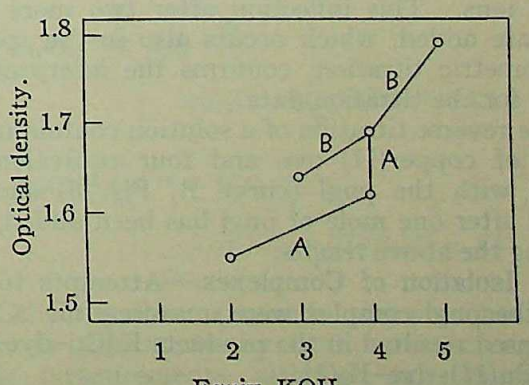

Fig. 2.—Effect of alkali on the copper(II)–*o*-azophenol and the copper(II)–*o*-azophenol + propylene glycol systems; wave length, 510 mμ; temperature, 25–26°. Curve A, points 1 and 2 contain 0.01 mmole copper(II)–*o*-azophenol; curve A, point 3 and curve B, points 1, 2, and 3 contain 0.01 mmole copper(II)–*o*-azophenol plus 0.01 mmole propylene glycol.

(13) L. Segal, Doctoral Dissertation, Tulane University, 1954.
(14) H. B. Jonassen, M. M. Cook and J. S. Wilson, THIS JOURNAL, 73, 4683 (1951).

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the absorption for the copper(II)–dye complex after the two OH^- ions are added to neutralize the H^+ ions for the copper(II)–dye interaction. The second value shows increased absorption for this complex in basic solution where a copper(II)–dye–hydroxy species may be present.

When, however, pngl is added to the copper(II)–dye complex in the same concentration of alkali, the absorbancy increases again (point 3), suggesting a pngl complex.

Such interaction is also indicated in curve B, Fig. 2 where, to equivalent quantities of copper(II)–dye and pngl, additions of the same 4 equivalents of OH^- ion cause increases in absorption to the same value. Addition of 5 equivalents of OH^- ion leads to point 3, curve B.

B. Conductometric Titration Studies.—Titration for a 1:1 molar ratio of the copper(II)–dye and pngl with KOH (curve A, Fig. 3) exhibits two

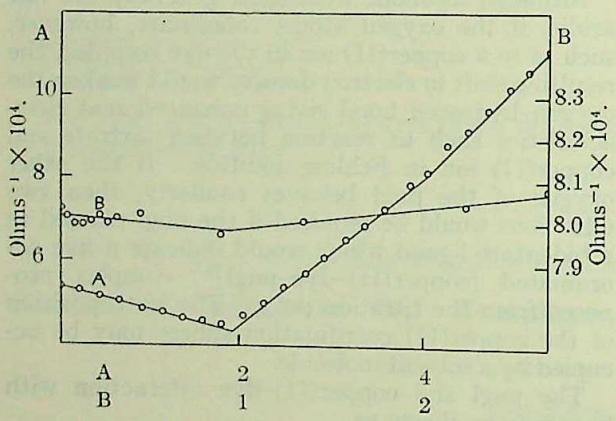

Fig. 3.—Conductometric titrations at 30°: curve A, 0.05 mmole copper(II)–*o*-azophenol in 0.05 mmole propylene glycol with 0.1119 *M* KOH; curve B, 0.05 mmole copper(II)–*o*-azophenol in 0.20 mmole KOH with 0.0236 *M* propylene glycol.

breaks: the first at the neutralization of the two hydrogen ions liberated in the copper(II)–dye reaction. The second break occurs at about four OH^- ions. This inflection after two more OH^- ions are added, which occurs also in the spectrophotometric titration, confirms the interpretation given for the titration data.

The reverse titration of a solution containing one mole of copper(II)–dye and four equivalents of KOH with the pngl (curve B, Fig. 3) shows a break after one mole of pngl has been added, confirming the above results.

C. Isolation of Complexes.—Attempts to prepare the pngl complex were unsuccessful. Conditions used resulted in the products K[Cu–dye–OH] and [Cu(II)–dye–H_2O].

In the preparation of K[Cu–dye–OH] small quantities of distilled water were used. High base concentration in the method results in the anionic complex having a coördinated OH group.

A second compound, [Cu(II)–dye–H_2O], isolated by using large amounts of water resulted in a coördinated H_2O molecule.

Depending on the method employed, the reactions may be

$$Cu(OH)_2 + \text{dye} + KOH \rightleftarrows K[\text{Cu–dye–OH}] + 2H_2O \quad \text{(III)}$$

and

$$Cu(NO_3)_2 + \text{dye} + H_2O \rightleftarrows [\text{Cu(II)–dye–}H_2O] + 2HNO_3 \quad \text{(IV)}$$

These compounds were found to be quite soluble in formamide and pngl. Determination of their absorption values at the wave length noted in Table I indicates the hydroxy complex in formamide has greater absorption than the aquo complex in the same solvent. This agrees with the data of curve A, Fig. 2, in which the dye complex in excess alkali also has greater absorption indicating a hydroxy complex.

TABLE I

System	mμ	Optical density
1×10^{-4} *M* K[Cu–dye–OH][a]	510	1.900
1×10^{-4} *M* [Cu(II)–dye–H_2O][a]	510	1.700
2×10^{-5} *M* K[Cu–dye–OH][a]	510	0.278
2×10^{-5} *M* K[Cu–dye–OH][b]	510	.382
2×10^{-5} *M* [Cu(II)–dye–H_2O][a]	510	.328
2×10^{-5} *M* [Cu(II)–dye–H_2O][b]	510	.337

[a] In formamide. [b] In pngl.

If the isolated compounds of same concentrations are dissolved in formamide and in pngl, the absorption values (Table I) are greater in both instances when pngl is added which might be another confirmation of pngl complexes. Furthermore, since the difference in optical densities in formamide and pngl for the hydroxy complex is at least tenfold over that of the aquo compound, this indicates the OH group is necessary in pngl ion formation.

It was also attempted to follow the complexing reaction polarimetrically by using *l*-2,3-butanediol, an optically active glycol. If the concentration of the glycol is kept constant, then the change in optical activity would be due to the optical activity of the [copper(II)–dye–glycol]$^{2-}$ complex. To facilitate visual observation solutions 1×10^{-5} *M* in copper(II)–dye and 3×10^{-4} *M* in glycol were used but the changes in activity were too small to be measured accurately.

Acknowledgment.—The financial support of the Research Corporation and the American Cyanamid Company for this work is gratefully acknowledged.

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[CONTRIBUTION FROM THE W. A. NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

The Kinetics of Aquation of *cis*-Dichloro-bis-(ethylenediamine)-chromium(III) Ion[1]

BY JOEL SELBIN[2] AND JOHN C. BAILAR, JR.

RECEIVED MARCH 30, 1957

The kinetics of acid hydrolysis of *cis*-$[Cr\ en_2Cl_2]^+$ has been studied at *p*H 1.0 at three temperatures and under various conditions of added electrolytes by a procedure which employs a chloride concentration cell to measure chloride release. The pseudo first-order rate constant for the loss of one chloride is given by $k_1 = 9.65 \times 10^{11} \exp(-21{,}100/RT)$ sec.$^{-1}$, and $\Delta S^{\ddagger} = -5.72$ e.u. A value for the specific rate constant for the loss of a second chloride has been estimated. Results of studies on the change in optical rotation of *l*-*cis*-$[Cr\ en_2Cl_2]^+$ are interpreted in terms of an initial aquation without loss of optical activity followed by racemization of the chloroaquo product. Analogies with the corresponding cobalt complexes suggest that complexes of the two metals follow similar mechanisms during acid hydrolysis. A suggestion is made as to why chromium(III) complexes resemble cobalt(III) complexes so closely.

Introduction

A large amount of kinetic data has accumulated in the literature on simple substitution reactions in octahedral complexes of the types: (I) $[MA_5X]^{+2\ or\ +1}$ and (II) $[MA_4YX]^{+1\ or\ +2}$ where M has been Co(III), Cr(III) or Ir(III) for type (I) and M has been Co(III) and, in a few cases, Cr(III) for type (II). The A represents a non-replaceable ligand and may be monodentate or polydentate, including N- and/or C-substituted polyamines. The X and Y, with X being the replaceable group, may be F^-, Cl^-, Br^-, I^-, NCS^-, NO_2^-, NO_3^-, N_3^-, $CO_3^=$, HCO_3^-, OCH_3^-, $C_2H_3O_2^-$, OH^- or H_2O.

The three types of substitution reactions which have been studied are: (1) aquation, or replacement by water in neutral or acid solution; (2) hydrolysis, or replacement by hydroxide ion in basic media; and (3) anation, or substitution of X by another anion.[3]

Although kinetic studies on complex ions were reported as early as 1911,[4] it has been only recently that the emphasis in the study of the kinetics has been on the elucidation of the mechanism by which substitution reactions occur.

Practically all of the recent work on complexes of types (I) and (II) has been concerned with the complexes of cobalt(III). These have been studied mainly by Basolo, Pearson and co-workers,[5] Taube and co-workers,[6] and by Ingold, Nyholm and Tobe[7] in aqueous solution, and by Brown, Ingold and Nyholm[8] in absolute methyl alcohol.

Relatively few kinetic experiments[9] have ever been carried out on chromium(III) complexes of type (I) and only three have concerned complexes of type (II).[9b,e,g]

Experiments by Adamson and Wilkins[9c] on the rates of aquation and exchange in the $[Cr(NH_3)_5NCS]^{+2}$ and $[Co(NH_3)_5NCS]^{+2}$ ions led them to suggest that different mechanisms for substitution may be operating for the two metals. Furthermore, the difference in electronic configuration existing between cobalt(III) and chromium(III),[10] coupled with the invariably greater rates of aquation found for chromium(III) complexes as compared with the analogous cobalt(III) complexes, might lead one to suspect a difference in mechanism. Therefore, the purpose of the work reported in this paper was to further compare the chemistry of cobalt(III) and chromium(III) complex ions. The compound chosen for study was *cis*-$[Cr\ en_2Cl_2]Cl \cdot H_2O$. The reasons for this choice are: (1) the complex is readily prepared and reasonably stable for long periods of time (months) if kept in a desiccator in the dark; (2) the corresponding cobalt(III) complex has been thoroughly studied[5,11]; (3) the complex undergoes aquation at a rate which can be followed conventionally; and (4) the complex is easily resolved into its optical isomers, allowing studies of racemization.

The aquation reaction, which has been studied, in 0.10 *N* acid solution, takes place in two steps which may be written

$$\underset{A}{cis\text{-}[Cr\ en_2Cl_2]^+} + H_2O \xrightarrow{k_1} \underset{B}{cis\text{-}[Cr\ en_2Cl(H_2O)]^{+2}} + Cl^- \quad (1)$$

$$\underset{B}{cis\text{-}[Cr\ en_2Cl(H_2O)]^{+2}} + H_2O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{C}{cis\text{-}[Cr\ en_2(H_2O)_2]^{+3}} + Cl^- \quad (2)$$

That the aquation proceeds stepwise has been shown in this study by both conductivity and kinetic measurements, although salts containing

(1) This article is based upon part of a dissertation submitted in partial fulfillment of the requirements for the Ph.D. degree at the University of Illinois, 1957.

(2) Socony-Mobil Laboratories Fellow in Chemistry, 1956–1957.

(3) F. Basolo, *Chem. Revs.*, **52**, 459 (1953).

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(5) F. Basolo, J. G. Bergmann and R. G. Pearson, *J. Phys. Chem.*, **56**, 22 (1952); R. G. Pearson, C. R. Boston and F. Basolo, THIS JOURNAL, **75**, 3089 (1953); G. Basolo, B. D. Stone, J. G. Bergman and R. G. Pearson, *ibid.*, **76**, 3079 (1954); R. G. Pearson, C. R. Boston and F. Basolo, *J. Phys. Chem.*, **59**, 304 (1955); R. G. Pearson, R. E. Meeker and F. Basolo, THIS JOURNAL, **78**, 709, 2673 (1956); F. Basolo, W. R. Matoush and R. G. Pearson, *ibid.*, **78**, 4883 (1956); A. W. Adamson and F. Basolo, *Acta Chem. Scand.*, **9**, 1261 (1955).

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(9) H. Freundlich and R. Bartels, *Z. physik. Chem.*, **101**, 177 (1922); H. Freundlich and H. Pape, *ibid.*, **86**, 458 (1914); A. Adamson and R. G. Wilkins, THIS JOURNAL, **76**, 3379 (1954); C. Postmus and E. L. King, *J. Phys. Chem.*, **59**, 1216 (1955); D. M. Grant and R. E. Hamm, THIS JOURNAL, **78**, 3006 (1956); M. Ikuta, H. G. McAdie and W. MacF. Smith, *Can. J. Chem.*, **34**, 1361 (1956); R. E. Hamm, THIS JOURNAL, **75**, 609 (1953).

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ion B never have been isolated. As will be shown, reaction 1 proceeds at a rate approximately 10 times that of reaction 2, so that no serious interference is caused by reaction 2 in the study of reaction 1. The diaquo cation (C) is stable only in strongly acid solution and has been shown to retain the *cis* configuration.[12] It will revert to the *cis*-dichloro cation only on standing for several days in a concentrated hydrochloric acid solution or upon evaporation of a concentrated hydrochloric acid solution.[13] Therefore, under the conditions of the experiments reported here, it is reasonable to assume that equilibrium is not established either in reaction 1 or 2 and that in any case, an equilibrium in reaction 1 would lie far toward the right. Indeed, the experimental data allow an approximation of k_2 to be made.

Experimental

Preparation of Compounds.—*cis*-[Cr en_2Cl_2]Cl·H_2O was prepared according to the method described by Rollinson and Bailar.[14] The recrystallization procedure was modified as follows. The impure salt was dissolved quickly in water (4 ml. for each gram of salt) which had been acidified with several drops of concentrated hydrochloric acid and the solution was heated to about 65°. The solution was filtered rapidly into ice-cold concentrated hydrochloric acid (1.5 ml. for each gram of salt used) and the filtrate was cooled to −5° in an ice–salt mixture. The red-violet needles which came out were collected on a sintered glass funnel, washed well with alcohol and ether, and then dried in a vacuum desiccator. Equivalent conductance at zero time, Λ_{700} = 103, which is in the correct range for a uni-univalent salt containing a complex cation.[15] *Anal.* Calcd. for [Cr en_2Cl_2]Cl·H_2O: C, 16.19; H, 6.12; N, 18.88. Found: C, 16.14; H, 6.03; N, 18.40. The complex salt, *cis*-[Cr en_2Cl_2]Cl·H_2O, was resolved into its optical isomers by a modification of the method of Werner.[16] To a freshly prepared solution of [Cr en_2Cl_2]Cl·H_2O (12.0 g., 0.0404 mole) in 200 ml. water at 19° was added ammonium *d*-α-bromocamphor-π-sulfonate (22.5 g., 0.0687 mole) with vigorous stirring. The solution was kept at 19°. After several minutes the sulfonate salt separated. It was filtered and washed with alcohol and ether (10.0 g., 89.5% diastereoisomer), and was then dissolved in concentrated HCl in the ratio of 4 ml./g. To this solution was added two volumes of alcohol, which precipitated fine, dark-red crystals. These crystals were filtered, washed well with alcohol and ether, and dried in a vacuum desiccator. The yield was 3.85 g. or 71.8%. The observed rotation for a 0.075% solution was +0.235; $[\alpha]^{25}D$ +314. *Anal.* Calcd. for *l-cis*-[Cr en_2Cl_2]Cl·H_2O: C, 16.19; H, 6.12; N, 18.88; Cr, 17.28. Found: C, 16.44; H, 6.12; N, 18.50; Cr, 17.54. All other reagents were commercially available materials of reagent grade, and were used without further purification.

Kinetic Measurements.—Preliminary determinations of the rate of loss of chloride from *cis*-[Cr en_2Cl_2]$^+$ were made by titrating the ionic chloride potentiometrically with silver nitrate after the reaction had been quenched by running the aliquot being analyzed into an ice-cold 1:1 ethanol–water mixture. The results indicated that the reaction is too fast to follow conveniently by a titration technique. Therefore, a more rapid and, at the same time, a more accurate means of following the loss of chloride, was sought.

The method finally adopted was to employ a concentration cell composed of two Ag–AgCl electrodes. The cell design appears in Fig. 1. The Ag–AgCl electrodes were prepared by plating silver from a $KAg(CN)_2$ bath onto platinum plates having an area of 1 cm.^{2}, followed by anodization of the plates in a 1.0 *M* hydrochloric acid-bath at a current of 25 ma. for 10 min. Electrodes prepared in this way were stable for several months and never had an asymmetry potential greater than 0.2 mv. Between runs they were stored in 0.05 *M* hydrochloric acid in the dark. The cell was immersed in a constant temperature bath controlled to within ±0.05°. A Rubicon K-2 potentiometer and Leeds and Northrup galvanometer were employed for the potential measurements. A stock solution of standard chloride ion concentration of 0.0100 *M* was prepared from NaCl and either 0.100 *M* $HClO_4$ or 0.100 *M* HNO_3.

For runs not involving added electrolytes, the procedure was as follows: 50 ml. of standard chloride solution was placed in Vessel A. A weighed amount of complex was dissolved in 50.0 ml. of 0.100 *M* acid (either $HClO_4$ or HNO_3, but the same as was used to prepare the standard solution) which previously had been brought to the proper temperature. This solution of the complex was placed in Vessel B and the solutions from both A and B were allowed to flow into the corresponding cell compartments with the pinch clamps closed over the Tygon tubing (see Fig. 1). The clamps were released after the compartments were filled and junction was thereby made in the center bulb. All of this required just under one minute from the time the solution of the complex was prepared. The rate of chloride production in the compartment containing the complex was then continuously and readily followed by observing the change in cell potential.

The 0.100 *M* acid present in each solution served a twofold purpose. First, it prevented any reaction of hydroxyl ion from interfering with normal aquation of the complex, and second, it eliminated concern over a junction potential in the cell.

To be sure that no chloride ion transfer occurred from one cell compartment to the other during the time of a normal run, standard chloride solutions of differing concentrations were allowed to run into the cell compartments and the potential was measured periodically. No change in potential occurred over a period of time equal to that of a normal kinetic run.

The runs which involved added electrolytes were carried out in the same way except that a weighed amount of the material whose effect upon the rate of aquation was to be determined was added to 50.0 ml. of the standard solution and to 50.0 ml. of the solution of the complex to produce the desired concentration.

The run in "strong light" was made with a 60-watt bulb approximately one foot from the cell.

Racemization Measurements.—Measurements of change in optical rotation of *l-cis*-[Cr en_2Cl_2]Cl·H_2O were made in a 10 cm. jacketed polarimeter tube maintained at 21.9 ± 0.1°. The polarimeter used is a Schmidt and Haensch No. 9143. Measurements were made at the sodium-D line or approximately 5890 Å. Solutions were 0.005 *M* (0.148%) in complex and 0.100 *M* in $HClO_4$ or HNO_3. At this concentration, precision is initially poor due to the high absorbancy of yellow light by the solution. This absorbancy decreases fairly rapidly so that readings after about 20–25 minutes are more precise. The rotatory dispersion curve of this complex[17] indicates that the rotatory power is highest at a wave length of approximately 5490 Å. However, at this wave length practically all light is absorbed by the complex solution, which is red-violet in color. At the red end of the spectrum (about 6000 Å.) very little light is absorbed by the solution, but the rotatory power is small and the eye is not very sensitive to changes in light intensity. Hence, the sodium-D line was a compromise choice.

Results and Discussion

The measured potential of the concentration cell was converted to a chloride concentration by means of the relation

$$E = 2.303 \frac{RT}{nF} \log_{10} \frac{a}{x}$$

where E is the measured potential, a is the fixed standard chloride concentration, and x is the chloride concentration in the solution of the com-

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(13) P. Pfeiffer, *ibid.*, **56**, 261 (1907).

(14) C. L. Rollinson and John C. Bailar, Jr., "Inorganic Syntheses," Vol. II, McGraw-Hill Book Co., Inc., New York, N. Y., 1946, p. 200.

(15) H. J. Emeleus and J. S. Anderson, "Modern Aspects of Inorganic Chemistry," D. Van Nostrand Co., Inc., New York. N. Y., 1955, pp. 106, 108, 111.

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(17) J. P. Mathieu, *Bull. soc. chim.*, **3**, 476 (1936).

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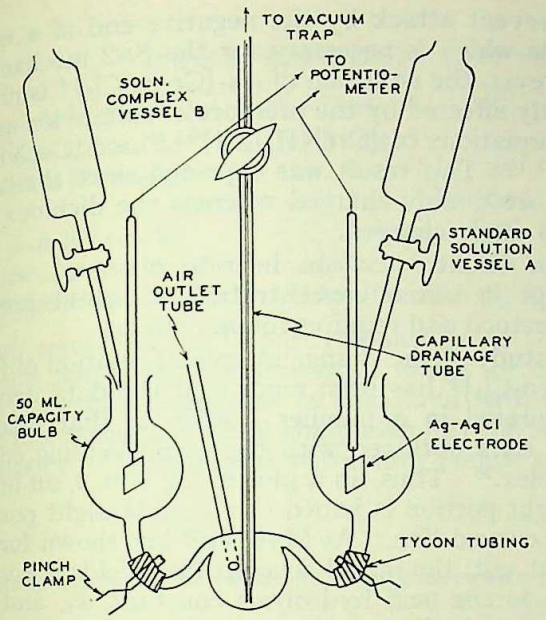

Fig. 1.—Concentration cell for measuring rate of chloride ion production.

plex at any time. The conditions at early reaction times may be represented as

$$\underset{(c - x_1)}{[Cr\ en_2Cl_2]^+} + \underset{c}{Cl_a^-} + H_2O \xrightarrow{k_1} \underset{x_1}{[Cr\ en_2ClH_2O]^{+2}} + \underset{c}{Cl_a^-} + \underset{x_1}{Cl_b^-} \quad (3)$$

At later times reaction (4) also must be considered

$$\underset{(x_1 - x_2)}{[Cr\ en_2ClH_2O]^{+2}} + \underset{c}{Cl_a^-} + \underset{x_1}{Cl_b^-} + H_2O \xrightarrow{k_2} \underset{x_2}{[Cr\ en_2(H_2O)_2]^{+3}} + \underset{c}{Cl_a^-} + \underset{x_1}{Cl_b^-} + \underset{x_2}{Cl_c^-} \quad (4)$$

The quantity measured experimentally is $(c + x_1 + x_2) = (Cl^-)$, but at early times $x_2 \sim 0$ and the value measured is $\sim (c + x_1)$. Hence, the concentration of $[Cr\ en_2Cl_2]^+$ left at any time is given by $(c - x_1)$ or $(2c - [Cl^-])$, where c is the initial concentration. Plots of log $(c - x_1)$ *vs.* time were found to be linear up to a time representing about 60% completion of reaction 3. A sample plot appears in Fig. 2. Thus, it is seen that reaction 3 is pseudo first order. The positive deviations from linearity were assumed to arise from the slower reaction indicated by eq. 4. Thus, at times greater than about 40 minutes x_2 begins to become significant and therefore account must be taken of the fact that what is really plotted is $(c - x_1 - x_2)$. By extrapolating the straight line to longer times and taking the difference between the value for the projected first-order decomposition and the actual value observed, a measure of x_2 is obtained, *i.e.*, $(c - x_1 - x_2) - (c - x_1) = -x_2$. Using the standard equation[18] for the series first-order reactions

$$\underset{(a - x_1)}{A} \xrightarrow{k_1} \underset{(x_1 - x_2)}{B} \quad ; \quad \underset{(x_1 - x_2)}{B} \xrightarrow{k_2} \underset{x_2}{C}$$

which is

$$(x_1 - x_2) = a \frac{k_1}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t})$$

it was possible by the method of successive approximations to obtain a value for k_2 from known or measured values of a, k_1, x_1, x_2 and t.

The specific rate constant, k_1, for reaction 3 is given in Table I for the conditions specified. In most cases duplicate runs agreed within ± 2%, with ± 3% being the maximum discrepancy. The rate constant, k_2, for reaction 4 is also included, but its value should be considered less accurate due to the method by which it was obtained.

TABLE I

RATES OF ACID HYDROLYSIS OF *cis*-$[M\ en_2Cl_2]^+$ IN 0.10 *M* HNO_3

Complex	Temp., °C.	Ionic strength	k_1, sec.$^{-1}$ × 10^4	k_2, sec.$^{-1}$ × 10^5
cis-$[Cr\ en_2Cl_2]^+$	20.0	0.105	1.60	1.0
	20.0	.155[a]	1.57	..
	25.0	.105	3.30	2.8
	30.0	.105	5.88	..
cis-$[Co\ en_2Cl_2]^+$	25	.105	2.5[b]	
	25	.022[d]	1.2[c]	
	30	.022[d]	2.15[c]	
	25.0	.105	1.76[e]	

[a] 0.05 *M* $NaClO_4$. [b] Value obtained by Pearson, *et al.*[5d] [c] Values obtained by Mathieu.[11] [d] 0.012 *M* HNO_3 and 0.01 *M* complex used. [e] See Discussion.

Several rate constant values for the cobalt complex are included and, as is seen, agreement among the several values is poor. Conductivity measurements were used by Mathieu[11] in obtaining the low value; spectrophotometric measurements were used by Pearson, *et al.*,[5d] in obtaining the high value; the intermediate value was obtained in our

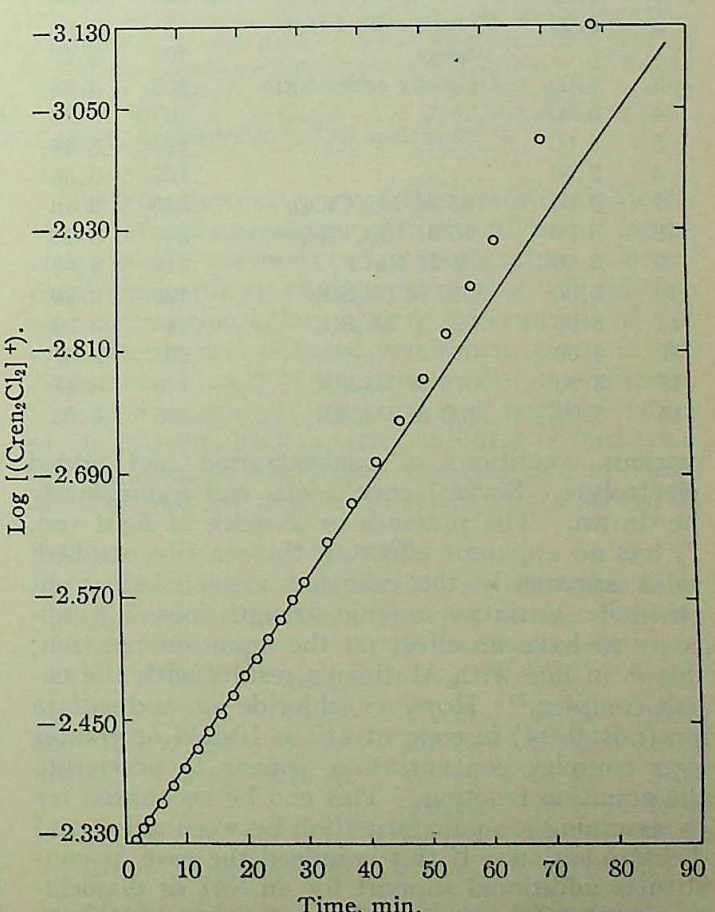

Fig. 2.—First-order rate plot for acid hydrolysis of *cis*-$[Cren_2Cl_2]^+$.

(18) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 153.

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concentration cell. The latter measurements were not as precise as was expected, due to interaction between the cobalt complex and the Ag–AgCl electrode, preventing the rapid establishment of equilibrium conditions between solution and electrode. Thus, meaningful readings could not be taken for at least ten minutes after the solution of the complex was placed in the cell, and experimental scattering was increased. The chromium complex did not affect the electrodes in this manner. No further study of this phenomenon was made. However, as expected, the chromium complex aquates faster than the corresponding cobalt complex.

The thermodynamic data for reaction 3, which were obtained from a linear Arrhenius plot of log k *vs.* $1/T$ are: $\Delta E^{\ddagger} = 21.1$ kcal., $\Delta H^{\ddagger} = 20.5$ kcal., $\Delta F^{\ddagger}_{298^\circ} = 22.2$ kcal., $\Delta S^{\ddagger} = -5.72$ cal./deg. and log $Z = 11.98$. Corresponding values for the acid hydrolysis of the cobalt complex, *cis*-[Co en$_2$Cl$_2$]$^+$, are[11]: $\Delta E^{\ddagger} = 22.25$ kcal., $\Delta H^{\ddagger} = 21.6$ kcal., and log $Z = 14.02$. The energy required to form the activated complex is therefore similar for both metals, but is slightly lower in the case of chromium, as is expected.

Table II records the rate of acid hydrolysis at 25.0° and a pH = 1.0 (obtained with HClO$_4$) under various conditions of concentration and added electrolyte. Several conclusions can immediately be drawn. The presence or absence of light (no. 2) has no apparent effect on the reaction studied, as is apparently the case for some cobalt complexes.[7a] Variation in ionic strength (nos. 7, 8) appears to have no effect on the aquation reaction; this is in line with Mathieu's results with the cobalt complex.[11] However, chloride ion and sulfate ion (nos. 9–14) in concentrations 10-fold or greater over complex concentration appear to accelerate the aquation reaction. This can be accounted for by assuming ion-pair formation between anion and dichloro cation. If this is indeed the case, it constitutes additional support for an Sn1 or dissociation type mechanism. Thus, an ion pair [Cr en$_2$Cl$_2$]$^+$–SO$_4^=$ would induce an easier breaking of the Cr–Cl bond and at the same time would tend to prevent attack by the negative end of a water dipole which is necessary for the Sn2 mechanism. However, the aquation of *cis*-[Cr en$_2$Cl$_2$]$^+$ is not as greatly affected by the presence of sulfate ion as are the aquations of [Cr(NH$_3$)$_5$Cl]$^{+2}$ [9f] and [Co(NH$_3$)$_5$Cl]$^{+2}$.[19] This result was expected since the latter ions are doubly charged whereas the dichloro cation is singly charged.

Table II

Rates of Acid Hydrolysis of *cis*-[Cr en$_2$Cl$_2$]$^+$ under Various Conditions at 25.0° and pH 1.0 (HClO$_4$)

No.	Concn. of complex, $M \times 10^3$	Added electrolyte or other condition	Ionic strength	k_1, sec.$^{-1}$ $\times 10^4$
1	5.00	.....	0.105	3.30
2	5.00	60 watt bulb 1 foot away	.105	3.27
3	5.00	Optically active form	.105	3.38
4	6.00	.....	.106	3.22
5	4.00	.....	.104	3.47
6	2.50	.....	.102	3.58
7	5.00	0.05 M Mg(ClO$_4$)$_2$	.255	3.18
8	5.00	.05 M Ni(ClO$_4$)$_2$	.255	3.20
9	5.00	.05 M NaCl	.115	3.63
10	5.00	.010 M Na$_2$SO$_4$	.135	3.30
11	5.00	.025 M Na$_2$SO$_4$	.180	3.28
12	5.00	.050 M Na$_2$SO$_4$	.255	3.57
13	5.00	.075 M Na$_2$SO$_4$	.330	3.68
14	5.00	.100 M Na$_2$SO$_4$	.405	4.03

The slight variation in rate observed with a change in initial concentration is not at present understood and requires further study.

A study of the change in optical rotation of *l-cis*-[Cr en$_2$Cl$_2$]$^+$ has been made and the data may be interpreted in a manner similar to that used to treat data obtained with the corresponding cobalt complex.[20] Thus, in a plot of log α *vs.* t, an initial straight portion is joined to a final straight portion by a curved line. As Mathieu[20] has shown for the cobalt salt, the initial straight line yields a k value close to the acid hydrolysis constant, k_1, and the final straight line yields a specific rate constant for racemization of the species being formed by the first process, which in this case is *l-cis*-[Cr en$_2$Cl H$_2$O]$^{+2}$. If k_2 (Table I) is compared with k_r (Table III), it is seen that the optically active chloroaquo cation racemizes at a faster rate than it loses chloride. This is similar to what has been observed[20] in the case of the analogous cobalt complex and indicates that a different mechanism is operating to produce racemization than is operating to produce further aquation. A similar treatment has been given for the change in rotation of *d-cis*-[Co en$_2$ F$_2$]$^+$.[5f] Table III records the rates of acid hydrolysis, mutarotation and racemization for the above compounds. It appears that the initial change in rotation is due mainly to the formation of the optically active chloro-aquo compound, which then undergoes racemization.

It would seem from this work that the ions *cis*-[Co en$_2$Cl$_2$]$^+$ and *cis*-[Cr en$_2$Cl$_2$]$^+$ are not very different in their behavior, at least toward acid hydrolysis and optical change. This observation suggests that the two metal complexes follow a similar mechanism during the course of acid hydrolysis. Although the purpose of this work was not to attempt to decide upon a mechanism, the results would seem to favor for the chromium complex the Sn1 mechanism suggested by Basolo, Pearson, *et al.*,[5] for the acid hydrolysis of cobalt complexes.

If the assumption is true that both cobalt(III) and chromium(III) are using 3d^{2}4s4p^3 hybrid orbitals in their complex compounds, then the remaining three 3d orbitals are filled in cobalt and half-filled in chromium. It may well be that the strong similarity found between cobalt(III) and chromium(III) complexes is related to this fact. The similarity in reactivity between elements having the same orbital set either empty, half-filled, or filled has been noted before in both the transition and inner transition elements. Such orbital arrangements seem always to lead to greater stability than would otherwise be predicted. Thus it is suggested here that the filled orbitals in the cobalt complexes and the half-filled orbitals in the chro-

(19) F. J. Garrick, *Trans. Faraday Soc.*, **34**, 7088 (1938).
(20) J. Mathieu, *Bull. soc. chim.*, **4**, 687 (1937).

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TABLE III

RATES OF ACID HYDROLYSIS, MUTAROTATION AND RACEMIZATION GIVEN IN k (SEC.$^{-1}$)

Initial compd.	(Acid)	Temp., °C.	k_1, acid hydrolysis	k_m, mutarotation	k_r, racemization
l-cis-[Co en$_2$Cl$_2$]$^{+a}$	0.012	30	2.15×10^{-4}	5.37×10^{-4}	6.13×10^{-5}
d-cis-[Co en$_2$F$_2$]$^{+b}$	.001	25	6.0×10^{-6}	8.2×10^{-6}	3×10^{-6}
	.1	25	5×10^{-5}	10.3×10^{-5}	6.5×10^{-6}
l-cis-[Cr en$_2$Cl$_2$]$^{+}$	.1	22	2.30×10^{-4}	2.28×10^{-4}	1.48×10^{-4}
	.1	25	3.30×10^{-4}	3.30×10^{-4}	2.0×10^{-4}

[a] Values from Mathieu.[20] [b] Values from Basolo, *et al.*[5f]

mium complexes are in part responsible for (1) the general non-labile characteristics found for cobalt and chromium complexes as compared with other first row transition metal complexes, (2) the strong similarity of cobalt and chromium complexes in ease of substitution-type reactions, and (3) the ease with which Cr(II) goes to Cr(III) in systems which can form d^2sp^3 hybrid-orbital complexes with Cr(III).

URBANA, ILLINOIS

[CONTRIBUTION NO. 62 FROM THE THERMODYNAMICS LABORATORY, PETROLEUM EXPERIMENT STATION, BUREAU OF MINES, U. S. DEPARTMENT OF THE INTERIOR]

Pyridine: Experimental and Calculated Chemical Thermodynamic Properties between 0 and 1500°K.; a Revised Vibrational Assignment[1]

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From studies by low temperature calorimetry, comparative ebulliometry, flow calorimetry and combustion calorimetry, values were obtained for the entropy, heat capacity and heat of formation of pyridine in the ideal gaseous state. The calorimetric values of entropy and heat capacity served as guides in revising the vibrational assignments for pyridine and several deuteropyridines. The revised assignment for pyridine and molecular structure data were used in computing values of the thermodynamic functions at selected temperatures between 0 and 1500°K. Values of the heat, free energy and equilibrium constant of formation were calculated at the same selected temperatures. The experimental investigations provided the following information: values of heat capacity for the solid (13–224°K.), the liquid [$C_{satd} = 33.633 - 9.1446 \times 10^{-2}T + 3.8478 \times 10^{-4}T^2 - 3.3430 \times 10^{-7}T^3$, cal. deg.$^{-1}$ mole^{-1} (240–347°K.)], and the vapor [$C_p^\circ = -8.262 + 10.608 \times 10^{-2}T - 5.4662 \times 10^{-5}T^2$, cal. deg.$^{-1}$ mole^{-1} (374–500°K.)]; the heat of fusion [1978.6 cal. mole^{-1}] at the triple point [231.49°K.]; the entropy of the liquid at 298.16°K. [42.52 cal. deg.$^{-1}$ mole^{-1}]; the vapor pressure [$\log_{10} p$(mm.) = 7.04162 − 1374.103/(t + 215.014), (67–153°)]; the heat of vaporization [$\Delta Hv = 13077 - 10.201\ T - 4.7941 \times 10^{-3}T^2$, cal. mole^{-1} (346–388°K.)]; the second virial coefficient in the equation of state, $PV = RT\ (1 + B/V)$, [$B = -15$–$84.5 \exp(950/T)$, cc. mole^{-1} (346–500°K.)]; and the standard heat of formation of the liquid at 298.16°K. [23.89 kcal. mole^{-1}].

Thermodynamic investigations of organic nitrogen compounds were begun recently in this Laboratory as part of American Petroleum Institute Research Project 52. The objective is to provide comprehensive thermodynamic data for nitrogen compounds that are important in petroleum technology. This paper is the first of a projected series on cyclic nitrogen compounds. Results are reported for pyridine, a compound important in theoretical considerations concerning molecular structure as well as in practical considerations as an industrial chemical. Some thermodynamic data for pyridine have been reported previously,[2] but many of the basic data are not of the accuracy that can be obtained by present-day methods.

The experimental part of this investigation consisted of measurements of thermodynamic properties by the methods of low temperature calorimetry, comparative ebulliometry, flow calorimetry and combustion calorimetry. Descriptions of the experiments and detailed results are given in the Experimental part of the paper. For convenience, the most important experimental results—values of the entropy, heat capacity and heat of formation for the ideal gaseous state—are collected in Table I. The entropy and heat capacity data served as guides in revising the vibrational assignment for pyridine and as checks on thermodynamic properties calculated by the methods of statistical

TABLE I

OBSERVED AND CALCULATED MOLAL THERMODYNAMIC PROPERTIES OF PYRIDINE IN THE IDEAL GASEOUS STATE

	Entropy, $S°$, cal. deg.$^{-1}$			Heat capacity, $Cp°$, cal. deg.$^{-1}$	
T, °K.	Obsd.	Calcd.	T, °K.	Obsd.	Calcd.
346.65	70.65	70.65	374.20	23.79	23.79
366.11	71.86	71.89	397.20	25.23	25.24
388.40	73.27	73.30	420.20	26.65	26.65
			450.20	28.43	28.40
			500.20	31.12	31.21

Heat of formation, $\Delta Hf°_{298.16}$ (obsd.) = 33.50 kcal.

(1) (a) This investigation was performed as part of American Petroleum Institute Research Project 52 on "Nitrogen Constituents of Petroleum," which is conducted at the University of Kansas in Lawrence, Kansas, and at the Bureau of Mines Experiment Stations in Laramie, Wyoming, and Bartlesville, Oklahoma. (b) Presented at 130th American Chemical Society Meeting, Atlantic City, N. J., September, 1956.

(2) (a) C. H. Kline and J. Turkevich, *J. Chem. Phys.*, **12**, 300 (1944); (b) D. P. Biddiscombe, E. A. Coulson, R. Handley and E. F. G. Herington, *J. Chem. Soc.*, 1957 (1954); (c) E. F. G. Herington and J. F. Martin, *Trans. Faraday Soc.*, **49**, 154 (1953) [and references cited there]; (d) G. S. Parks, S. S. Todd and W. A. Moore, THIS JOURNAL, **58**, 398 (1936); (e) J. N. Pearce and H. M. Bakke, *Proc. Iowa Acad. Sci.*, **38B**, 450 (1929).

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mechanics. The experimental value of the heat of formation and the calculated thermodynamic properties were used in computing values of the heat, free energy and equilibrium constant of formation at selected temperatures between 0 and 1500°K. These calculations are discussed in the following section.

Calculation of Thermodynamic Properties

The Vibrational Assignment.—The vibrational spectra of pyridine and several deuteropyridines have been studied by a number of investigators.[3] Corrsin, Fax and Lord (CFL) have given detailed vibrational assignments for pyridine and pyridine-d_5.[3a] Anderson, Bak, Brodersen and Rastrup-Andersen[3b] have given assignments for 4D-pyridine, 3D-pyridine and 2D-pyridine based on the assignments of CFL. When the published vibrational assignment for pyridine was used in calculating thermodynamic properties, the results disagreed with the experimental values of $C_p°$ and $S°$ listed in Table I (the discrepancies were about 2 and 0.3%, respectively). Because the accuracy uncertainty of the observed values of $C_p°$ is 0.2%, a revision of the vibrational assignment for pyridine was required for calculating accurate thermodynamic properties. The revised assignment for pyridine and its deuterated species is given in Table II.

The vibrational assignment of CFL is based on good spectroscopic evidence. It was considered likely that the choice of only one fundamental frequency was seriously in error. To obtain agreement between calculated and observed values of both $C_p°$ and $S°$, it was apparent that a frequency near 700 cm.$^{-1}$ had to be eliminated and replaced by one near 1000 cm.$^{-1}$. Corresponding changes in the assigments for the deuteropyridines had to be made to retain consistency with the product rule for isotopic substitution.

There are only three observed frequencies near 700 cm.$^{-1}$ in the spectrum of pyridine: 675 (infrared, weak); 703 (infrared, very strong; Raman, very weak); 749 (infrared, strong; Raman, very weak) cm.$^{-1}$. These frequencies had been assigned by CFL to ν_4, ν_{11} and ν_{10b},[4] respectively. The assignment of CFL was retained for the infrared band at 675 cm.$^{-1}$, which cannot be assigned as a likely overtone or combination. The other pair of frequencies was replaced by a single fundamental frequency by interpreting the 703–749 cm.$^{-1}$ doublet as the result of Fermi resonance between an a_1 mode near 720 cm.$^{-1}$, taken to be ν_{6a}, and the overtone of ν_{16a}, 2×374 (a_2) = 748-(A_1). This reinterpretation necessitated revised assignments for b_2 modes ν_{10b} and ν_{11}. The frequency previously assigned to ν_{6a}, 605 cm.$^{-1}$, was reassigned to ν_{11}. The assignment of the 605 cm.$^{-1}$ frequency to a b_2 rather than an a_1 mode is consistent with the reported depolarization of the Raman line.[5] The frequency at 981 cm.$^{-1}$, previously assigned to the a_2 mode ν_{17a} in violation of the strict selection rules of C_{2v} symmetry, was chosen for the other b_2 mode. However, this frequency was assigned to ν_5 and CFL's choice for ν_5, 940 cm.$^{-1}$, was assigned instead to ν_{10b}. (The latter change was made to obtain better over-all consistency among the assignments for pyridine, benzene and their deuterated species.[3b,6]

The result of the foregoing changes was to eliminate from the earlier assignment a frequency near 700 cm.$^{-1}$ and leave ν_{17a} available for assignment of a frequency near 1000 cm.$^{-1}$. The a_2 mode ν_{17a} may be unobserved, for it should appear with very low intensity in the Raman spectrum and is forbidden in the infrared. Although the weak Raman line at 1043 cm.$^{-1}$ could be due to ν_{17a}, it was interpreted as the sum-combination, 374 (a_2) + 675 (b_2) = 1049 (B_1). It was assumed that ν_{17a} is obscured in the Raman spectrum by the strong line of ν_{12} at 1030 cm.$^{-1}$, and that frequency was chosen for ν_{17a}. A value of 1030 cm.$^{-1}$ for ν_{17a} results in a slightly more satisfactory product-rule ratio, τ_{obsd}, for the a_2 frequencies of pyridine and pyridine-d_5.

Table II

Revised Vibrational Assignment for Pyridine and Some Deuteropyridines

Freq. No.	Species[a]	Frequency, cm.$^{-1}$ Pyridine	Pyridine-d_5	4D-Pyridine	3D-Pyridine	2D-Pyridine
1		992	962	989	980	989
2		3055[d]	2293[d]	3033	3038	3040
6a		720[b]	690[d]	720[b]	717	748
8a		1583	1530	1575	1570[c]	1576
9a	a_1	1218	887[d]	1212[d]	1195	1149
12		1030[d]	1006	1015	1033	1029
13		3055[d]	2270	2285	3053	3051
18a		1068	823	1068	1050	1059
19a		1483	1340	1476	1468	1461
20a		3035	2254	3019	3022	2258
3		1200	908	1212[d]	1217	1212
6b		653	625	635[c]	650[c]	640[c]
7b		3055[d]	2285	3069	2289	3068
8b		1571	1542	1559	1570[c]	1570
14	b_1	1377	1322	1347	1337	1357
15		1146	887[d]	1121	1108	1112
18b		1085	833	862	848	834
19b		1440	1301	1413	1416	1424
20b		3080	2293[d]	3069	3077	3075
10a		885	713	890[c]	823	814
16a	a_2	374	329	365[c]	350[c]	360[c]
17a		1030[d]	798	1015	965[d]	997
4	b_2	675	582	633[c]	632[c]	638
5		981	690[d]	968	965[d]	970
10b		940	762	834	902	901
11		605	530	597	599	600
16b		405	371	370	404	405

[a] The species designation is for C_{2v} symmetry, that of pyridine, pyridine-d_5 and 4D-pyridine. [b] Fermi resonance assumed between ν_{6a} and $2 \times \nu_{16a}$. [c] Approximate values; see ref. 3b. [d] Frequencies assigned to more than one fundamental.

(3) (a) L. Corrsin, B. S. Fax and R. C. Lord, *J. Chem. Phys.*, **21**, 1170 (1953), and earlier references cited there; (b) F. A. Anderson, B. Bak, S. Brodersen and J. Rastrup-Andersen, *ibid.*, **23**, 1047 (1955); (c) unpublished data from Chemical Research Laboratory, Teddington, Middlesex, England.

(4) The designation of normal modes of vibration is that given in ref. 3a.

(5) K. W. F. Kohlrausch, "Ramanspektren," Akademische Verlagsgesellschaft, Becker and Erler, Leipzig, 1943, p. 353.

(6) (a) C. K. Ingold and co-workers, *J. Chem. Soc.* (*London*), 222 ff. (1946); (b) R. L. Mait and D. F. Hornig, *J. Chem. Phys.*, **17**, 1236 (1949).

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Two additional minor changes have been made in the assignment for pyridine. Infrared bands at 1200 and 1085 cm.$^{-1}$ were observed recently by workers at the Chemical Research Laboratory[3c] and are assigned to ν_3 and ν_{18b}. These fundamentals were previously assigned (by CFL) the same values as ν_{9a} and ν_{18a}, 1218 and 1068 cm.$^{-1}$.

The revision of CFL's vibrational assignment for pyridine made necessary corresponding changes in the previous assignments for the deuterated pyridines.[3a,3b] The revised assignments for the deuterated species, given in Table II, were made concurrently with the revision of the assignment for pyridine.

The vibrational assignments in Table II are as consistent internally as those of refs. 3a and 3b. The comparisons of observed and calculated product rule ratios, τ_{obsd} and τ_{calcd}, in Table III show

Table III

Product-rule Ratios for Pyridine and Pyridine-d_5

Symmetry class	$\tau_{calcd.}$ from ref. 3a	Ref. 3a	$\tau_{obsd.}$ This work
a_1	5.49	5.38	5.45
b_1	5.07	4.89	4.90
a_2	1.84	1.80	1.82
b_2	2.56	2.55	2.54

that good agreement was retained. Also, all observed frequencies in the spectra of these compounds that were not chosen as fundamentals can be assigned readily as allowed overtones or combinations. For the most part, the intercomparison of assignments for pyridine, benzene and their deuterated species is slightly improved, although it is apparent that some of the fundamental frequencies of pyridine and benzene differ more than in the earlier assignment.[3a] Actually, spectroscopic evidence alone is not sufficient to choose between the assignment in Table II and that of CFL. The fact, discussed later, that excellent agreement between calculated and observed values of $C_p°$ and $S°$ was obtained by use of the revised assignment ensures that the set of fundamentals chosen is essentially correct. Uncertainties that may remain in the assigment of observed frequencies to particular modes of vibration can be removed only by additional spectroscopic evidence.

It should be noted that the net effect of these reassignments is merely the replacement of fundamentals at 703 and 749 cm.$^{-1}$ by fundamentals at 720 and 1030 cm.$^{-1}$—that is, the change that was found necessary to obtain agreement between calculated and experimental values of both $C_p°$ and $S°$.

Note added in proof. J. K. Wilmshurst and H. J. Bernstein of the Canadian National Research Council have recently made new spectroscopic studies of pyridine and some deuteropyridines. Dr. Bernstein courteously provided us with a copy of his manuscript, which is soon to be published. The data of Wilmshurst and Bernstein require further revision of the vibrational assignment for pyridine. In their forthcoming paper, Wilmshurst and Bernstein will present a new vibrational assignment that is consistent with the available spectroscopic and calorimetric data. Use of their assignment in calculating thermodynamic properties results in no significant changes in the calculated values listed in Tables I and III of this paper.

The Moments of Inertia and Anharmonicity Contributions.—The moments of inertia of the pyridine molecule have been determined in several recent microwave studies.[7-9] The difference between values of the product of principal moments of inertia calculated from the results of these studies is not significant, but the value actually used in calculation of thermodynamic properties, 5.691×10^{-113} g.^{3} cm.^{6}, was computed from the data of ref. 9. The symmetry number of over-all rotation is 2.

The contributions of anharmonicity to the thermodynamic functions were treated by the empirical

Table IV

The Molal Thermodynamic Properties of Pyridine[a]

T, °K.	$(F° - H°_0)/T$, cal. deg.$^{-1}$	$(H° - H°_0)/T$, cal. deg.$^{-1}$	$H° - H°_0$, kcal.	$S°$, cal. deg.$^{-1}$	$C_p°$, cal. deg.$^{-1}$	$\Delta Hf°$,[b] kcal.	$\Delta Ff°$,[b] kcal.	$\log_{10} Kf$[b]
0	0	0	0	0	0	37.52	37.52	Infinite
273.16	−55.44	10.59	2.893	66.03	16.99	33.82	44.48	−35.59
298.16	−56.40	11.19	3.336	67.59	18.67	33.50	45.47	−33.33
300	−56.47	11.24	3.372	67.71	18.80	33.48	45.54	−33.18
400	−60.07	13.97	5.588	74.04	25.42	32.38	49.74	−27.18
500	−63.49	16.85	8.425	80.34	31.11	31.52	54.18	−23.68
600	−66.81	19.62	11.772	86.43	35.72	30.88	58.77	−21.41
700	−70.03	22.20	15.54	92.23	39.44	30.41	63.47	−19.82
800	−73.15	24.55	19.64	97.70	42.49	30.07	68.21	−18.63
900	−76.17	26.69	24.02	102.86	45.04	29.86	72.99	−17.72
1000	−79.08	28.63	28.63	107.71	47.17	29.76	77.79	−17.00
1100	−81.89	30.40	33.44	112.29	48.99	29.75	82.59	−16.41
1200	−84.62	32.02	38.42	116.64	50.54	29.82	87.37	−15.91
1300	−87.23	33.49	43.54	120.72	51.88	29.92	92.18	−15.50
1400	−89.77	34.85	48.79	124.62	53.04	30.07	96.96	−15.14
1500	−92.22	36.10	54.15	128.32	54.05	30.24	101.73	−14.82

[a] To form an internally consistent set of values and to retain the higher accuracy of increments with temperature of a given property, some of the values in this table are given to one more significant figure than is justified by their absolute accuracy. [b] The standard heat, standard free energy and common logarithm of the equilibrium constant for the formation of pyridine by the reaction: $5C(graphite) + 5/2H_2(g) + 1/2N_2(g) \rightarrow C_5H_5N(g)$.

(7) K. E. McCulloh and G. F. Pollnow, *J. Chem. Phys.*, **22**, 681 (1954).

(8) B. B. DeMore, W. S. Wilcox and J. H. Goldstein, *ibid.*, **22**, 876 (1954).

(9) B. Bak, L. Hansen and J. Rastrup-Andersen, *ibid.*, **22**, 2013 (1954).

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method described in an earlier paper from this Laboratory.[10] The parameters $Z = 0.340$ cal. deg.$^{-1}$ mole^{-1} and $\nu = 750$ cm.$^{-1}$ were selected to give agreement with the calorimetric values of $C_p°$. The contributions of anharmonicity to the thermodynamic properties are small at 400°K., 0.03 and 0.11 cal. deg.$^{-1}$ mole^{-1} in $S°$ and $C_p°$, but increase to 0.62 and 0.92 cal. deg.$^{-1}$ mole^{-1} in $S°$ and $C_p°$ at 1500°K.

The Chemical Thermodynamic Properties.—The vibrational assignment, product of principal moments of inertia and anharmonicity parameters given in preceding paragraphs were used in computing values of the following thermodynamic functions at selected temperatures between 0 and 1500°K.: $(F° - H°_0)/T$, $(H° - H°_0)/T$, $H° - H°_0$, $S°$ and $C_p°$. The results are listed in columns 2–6 of Table IV.[11]

The calculated and observed values of $C_p°$ and $S°$ are compared in Table I. Agreement within 0.1% was obtained over the entire range of temperature of the experimental data. Because the observed values of $S°$ and $C_p°$ are entirely independent, the excellent agreement obtained for $S°$ is another confirmation of the third law of thermodynamics.

The Heat, Free Energy and Equilibrium Constant of Formation.—The calculated values of the thermodynamic functions of pyridine, the experimental value of $\Delta Hf°_{298.16}$ (Table I) and values of the thermodynamic functions of C(graphite),[12] H_2(g)[12] and N_2(g)[12] were used in computing values of $\Delta Hf°$, $\Delta Ff°$ and $\log_{10}Kf$ at selected temperatures between 0 and 1500°K. These results are listed in columns 7–9 of Table IV.

Experimental

Physical Constants.—The 1951 International Atomic Weights[13] and the 1951 values of fundamental physical constants[14] were used. The results are based on a molecular weight of 79.098 for pyridine and the following relations: 0° = 273.16°K.; and 1 cal. = 4.1840 abs. j. = 4.1833 int. j. Measurements of temperature were made with platinum resistance thermometers calibrated in terms of the International Temperature Scale[15] between 90 and 500°K. and the provisional scale[16] of the National Bureau of Standards between 11 and 90°K. Measurements of mass, energy and resistance were made in terms of standard devices calibrated at the National Bureau of Standards.

The Material.—The sample of pyridine used in the low temperature thermal studies, vapor pressure measurements and heat of combustion experiments was part of the Standard Sample of Nitrogen Compound, API-USBM-52-1, prepared and purified by American Petroleum Institute Research Project 52b at the Laramie, Wyoming, Station of the Bureau of Mines. In a calorimetric study of the melting point to be discussed subsequently, the purity of this sample was found to be 99.92 mole %. A second sample of 99.8 mole % purity was used in studies of the heat of vaporization and vapor heat capacity.

The samples of pyridine were received in sealed ampoules and were dried in the liquid phase with CaH_2. Transfers of sample were made by distillation under vacuum.

The Heat Capacity in the Solid and Liquid States.—The low temperature thermal studies were made in an adiabatic calorimeter system similar to that described in previous publications.[17] The sample, 0.66591 mole, was sealed in a platinum calorimeter. About 27 mm. helium pressure, at room temperature, was left in the calorimeter to promote thermal equilibration at low temperatures.

The observed values of heat capacity at saturation pressure, C_{satd}, are recorded in Table V. No adjustment for the effect of premelting has been applied to these data. The temperature increments used in the measurements were small enough that corrections for non-linear variation of C_{satd} with temperature were unnecessary. Generally, the precision of the results is within ±0.1%; and it is estimated that above 30°K., the accuracy uncertainty is not greater than 0.2%.

The heat capacity curve, C_{satd} *vs.* T, for solid pyridine is smooth and regular from 13 to 200°K. A very small "bump" was observed in the curve between 200 and 215°K. (about 20° below the melting point). When the sample was cooled rapidly from a point above 215°K., the "bump" was not detected. It is believed that this anomaly was due to melting of the eutectic between pyridine and an impurity, and that rapid cooling caused the eutectic mixture to supercool. The excess energy associated with the "bump" was only 1.3 cal. mole^{-1}. This amount of energy corresponds to about 0.06 mole % impurity if the heat of fusion of the eutectic mixture is assumed to be about 2000 cal. mole^{-1}. In Table V, the values indicated by asterisks define the anomalous "bump." These points were disregarded in drawing the smoothed heat-capacity curve of pyridine.

An empirical equation that represents the observed heat capacity data for liquid pyridine between 240 and 347°K. with an average deviation of 0.01% is

$$C_{satd}(\text{liq.}) = 33.633 - 9.1446 \times 10^{-2}T + 3.8478 \times 10^{-4}T^2 - 3.3430 \times 10^{-7}T^3, \text{ cal. deg.}^{-1}\text{ mole}^{-1} \quad (1)$$

The Heat of Fusion.—Two determinations were made of the heat of fusion. Measurements were made of the enthalpy change over a finite temperature interval that included the melting point. Subtraction of the energy absorbed non-isothermally by the crystals and liquid gave the latent heat of fusion, 1978.6 ± 0.6 cal. mole^{-1}; the indicated uncertainty is the deviation of the two results from the mean. Corrections for premelting were applied in calculating the heat of fusion. The energy associated with the anomaly at about 210°K. is included in the value given.

The Triple Point Temperature, Cryoscopic Constants and Purity of Sample.—For determination of the triple point temperature and purity of sample, a study of the melting temperature, T_{obsd}, as a function of fraction of total sample melted, F, was made by the procedure outlined in an earlier publication.[18] The results are summarized in Table VI. Values of T_{obsd} were plotted as a function of $1/F$. The triple point temperature, $T_{T.P.} = 231.49 \pm 0.05$°K., was obtained by linear extrapolation to zero value of $1/F$. If the impurities present form ideal solutions in the liquid phase and are insoluble in the solid phase, the relation between mole fraction of total impurity, N^*_2, and melting point depression, $\Delta T = T_{T.P.} - T_{obsd}$, is[19]

$$-\ln(1 - N_2) = A\Delta T(1 + B\Delta T + \ldots..) \quad (2)$$

where $N_2 = N^*_2/F$. The cryoscopic constants, $A = \Delta H_{fusion}/RT^2_{T.P.} = 0.01858$ deg.$^{-1}$ and $B = 1/T_{T.P.} -$

(10) J. P. McCullough, H. L. Finke, W. N. Hubbard, W. D. Good, R. E. Pennington, J. F. Messerly and Guy Waddington, THIS JOURNAL, **76**, 2661 (1954).

(11) The harmonic oscillator contributions to the thermodynamic functions were taken from H. L. Johnston, L. Savedoff and J. Belzer, "Contributions to the Thermodynamic Functions by a Planck–Einstein Oscillator in One Degree of Freedom," NAVEXOS P-646, Office of Naval Research, Department of the Navy, Washington, D. C., July, 1949. Anharmonicity contributions were computed from the tables of R. E. Pennington and K. A. Kobe, *J. Chem. Phys.*, **22**, 1442 (1954).

(12) D. D. Wagman, J. E. Kilpatrick, W. J. Taylor, K. S. Pitzer and F. D. Rossini, *J. Research Natl. Bur. Standards*, **34**, 143 (1945).

(13) Edward Wichers, THIS JOURNAL, **74**, 2447 (1952).

(14) F. D. Rossini, F. T. Gucker, Jr., H. L. Johnston, L. Pauling and G. W. Vinal, *ibid.*, **74**, 2699 (1952).

(15) H. F. Stimson, *J. Research Natl. Bur. Standards*, **42**, 209 (1949).

(16) H. J. Hoge and F. G. Brickwedde, *ibid.*, **22**, 351 (1939).

(17) R. A. Ruehrwein and H. M. Huffman, THIS JOURNAL, **65**, 1620 (1943); H. M. Huffman, S. S. Todd and G. D. Oliver, *ibid.*, **71**, 584 (1949); D. W. Scott, D. R. Douslin, M. E. Gross, G. D. Oliver, and H. M. Huffman, *ibid.*, **74**, 883 (1952); H. M. Huffman, *Chem. Revs.*, **40**, 1 (1947).

(18) S. S. Todd, G. D. Oliver and H. M. Huffman, THIS JOURNAL, **69**, 1519 (1947).

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$\Delta C_{fusion}/2\Delta H_{fusion}$ = 0.00255 deg.$^{-1}$ were evaluated from the values for $T_{T.P.}$ and ΔH_{fusion} and from ΔC_{fusion} = 6.99 cal. deg.$^{-1}$ mole^{-1} (Table VII). Application of eq. 2 in its simplified form (for $N^*_2 << 1$), $N^*_2 = AF\Delta T$, yielded a value of 0.08 mole % for the indicated concentration of impurity in the Standard Sample of pyridine.

TABLE V

THE MOLAL HEAT CAPACITY OF PYRIDINE IN CAL. DEG.$^{-1}$

T, °K.[a]	ΔT[b]	C_{satd}[c]	T, °K.[a]	ΔT[b]	C_{satd}[c]
	Crystals		169.31	6.005	16.396
13.08	1.311	1.063	172.38	7.155	16.606
13.61	1.270	1.204	172.49	6.402	16.624
14.37	1.283	1.359	173.90	5.889	16.728
14.97	1.381	1.454	174.19	5.895	16.752
15.84	1.675	1.646	178.13	11.633	17.049
16.25	1.193	1.722	179.26	7.146	17.107
17.46	1.586	1.999	179.44	6.969	17.150
17.67	1.662	2.041	179.72	5.767	17.154
19.23	1.948	2.406	180.58	6.905	17.250
19.43	1.901	2.448	186.32	6.792	17.707
21.26	2.126	2.888	187.39	6.728	17.807
21.42	2.089	2.930	189.24	6.714	17.945
23.42	2.211	3.410	193.02	6.622	18.276
23.55	2.183	3.446	193.43	6.630	18.327
25.78	2.508	3.975	193.48	6.527	18.310
25.88	2.489	3.998	194.02	6.561	18.369
28.53	2.820	4.610	195.86	6.536	18.558
28.61	3.166	4.625	198.37	3.269	18.756
31.74	3.595	5.306	199.54	6.452	18.881
35.36	3.663	6.049	199.97	6.456	18.958
39.20	4.025	6.738	200.49	6.388	19.006
43.54	4.652	7.429	200.75	3.276	18.995
48.14	4.549	8.060	201.61	3.223	19.081
53.18	5.545	8.669	204.00	3.234	19.294
54.23	3.647	8.784	204.80	3.183	19.368
58.52	5.128	9.228	205.88	6.256	19.636*
58.63	5.148	9.243	206.33	6.286	19.597
64.01	5.607	9.739	206.84	4.180	19.549
70.06	6.509	10.203	207.20	3.194	19.609
76.40	6.173	10.646	207.28	7.210	19.821*
82.91	6.857	11.093	207.93	3.118	19.883*
85.74	4.830	11.279	210.75	3.938	19.938
89.62	6.568	11.515	211.98	6.121	20.151
90.50	4.681	11.568	212.16	5.388	20.183
95.57	5.465	11.839	212.53	6.117	20.299*
101.39	6.192	12.156	212.55	7.108	20.311*
107.41	5.853	12.499	213.43	6.099	20.389*
111.70	4.261	12.735	215.70	6.014	20.605
113.19	5.701	12.823	217.99	5.939	20.943
117.78	7.905	13.086	218.70	4.954	21.076
119.37	6.600	13.175	219.42	5.885	21.320
125.29	7.112	13.527	223.53	4.747	22.278
125.93	6.476	13.560	223.74	5.613	22.545[d]
132.30	6.910	13.954			
132.32	6.314	13.940		Liquid	
138.56	6.160	14.329			
138.91	6.319	14.346	239.70	4.616	29.213
144.89	6.516	14.727	245.82	7.638	29.431
145.61	7.076	14.769	254.41	9.564	29.765
151.57	6.844	15.161	263.90	9.445	30.159
152.58	6.888	15.227	273.75	10.256	30.575
158.32	6.672	15.613	283.92	10.116	31.040
159.38	6.716	15.693	293.96	9.974	31.521
161.87	6.152	15.861	303.85	9.841	31.997
163.24	6.142	15.957	307.16	8.668	32.159
165.75	6.112	16.106	316.61	10.254	32.641
166.02	6.555	16.158	326.79	10.102	33.177
167.60	7.294	16.265	336.81	9.954	33.712
167.95	6.018	16.292	346.69	9.809	34.246

[a] T is the mean temperature of each heat capacity measurement. [b] ΔT is the temperature increment used in each heat capacity measurement. [c] C_{satd} is the heat capacity of the condensed phase under its own vapor pressure. [d] The data below the melting point have *not* been corrected for the effect of premelting caused by impurities.

TABLE VI

PYRIDINE: MELTING POINT SUMMARY

Melted, %	1/F	T, °K. Obsd.	T, °K. Graph.[b]
11.56	8.648	231.1659	231.13
25.66	3.897	231.3397	231.330
49.99	2.000	231.4076	231.4086
70.08[a]	1.427[a]	231.4310[a]	231.4310
90.18[a]	1.109[a]	231.4440[a]	231.4440
100.00	1.000		231.4485
Pure	0.0		231.489[c]

[a] A straight line through these points was extrapolated to $1/F = 0$ to obtain the triple-point temperature, $T_{T.P.}$ [b] Temperatures read from the straight line of footnote *a*; deviations from T_{obsd} indicate slight departure from assumed conditions. [c] Triple-point temperature.

Biddescombe, Coulson, Handley and Herington[2c] report a value for t_f°, the freezing point in air at 1 atm., that is 0.12° higher than the triple-point temperature found in this investigation. However, recent unpublished studies by these authors[20] on a purer sample of pyridine gave a value of t_f° that is 0.10° lower than their reported value, in better consistency with the results of this work.

The Thermodynamic Properties in the Solid and Liquid States.—Values of the free energy function, heat content function, heat content, entropy and heat capacity at selected temperatures between 10 and 350°K. were computed from the low-temperature calorimetric data for pyridine. The values at 10°K. were calculated from a Debye function for 4 degrees of freedom with θ = 107.40°; these parameters were evaluated from the heat capacity data between 13 and 22°K. The thermodynamic properties above 10°K. were computed from the values of the heat of fusion and triple-point temperature, and from increments computed by numerical integration of values of C_{satd} read from a large scale plot of the data in Table V. The results are given in Table VII. Corrections for the effect of premelting have been applied to the "smoothed" data recorded in Table VII.

The results in Table VII agree with those of Parks, Todd and Moore[2d] within the 1% accuracy uncertainty of the earlier data. The results of Pearce and Bakke[2e] seem to be in error.

The Vapor Pressure.—The vapor pressure of pyridine at temperatures between 67 and 153° was measured with an improved version of the twin ebulliometer system described in an earlier publication.[21] Observations were made of the boiling and condensation temperatures of pyridine and water as the two compounds boiled simultaneously at a common pressure. The pressures corresponding to the observed boiling points of the water were obtained from the data of Osborne, Stimson and Ginnings.[22] The results are presented in Table VIII. The difference between the boiling and condensation temperatures of the sample was observed to be 0.004° or less; this observation indicates that the material was essentially free of impurities of different volatility. The constants in an Antoine equation

$$\log_{10} p \text{ (mm.)} = 7.04162 - 1374.103/(t + 215.014) \quad (3a)$$

were obtained from the data in Table VIII by a least squares treatment.[23] Also, to provide a more accurate means of

(20) Communicated by Dr. J. D. Cox, Chemical Research Laboratory, Teddington, Middlesex, England (1955–1956).

(21) Guy Waddington, J. W. Knowlton, D. W. Scott, G. D. Oliver, S. S. Todd, W. N. Hubbard, J. C. Smith and H. M. Huffman, THIS JOURNAL, 71, 797 (1949).

(22) N. S. Osborne, H. F. Stimson and D. C. Ginnings, *J. Research Natl. Bur. Standards*, 23, 261 (1939).

(23) C. B. Willingham, W. J. Taylor, J. M. Pignocco and F. D. Rossini, *J. Research Natl. Bur. Standards*, 35, 219 (1945).

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TABLE VII

MOLAL THERMODYNAMIC PROPERTIES OF PYRIDINE IN THE SOLID AND LIQUID STATES[a]

T, °K.	$-(F_{satd}-H°_0)/T$, cal. deg.$^{-1}$	$(H_{satd}-H°_0)/T$, cal. deg.$^{-1}$	$H_{satd}-H°_0$, cal.	S_{satd}, cal. deg.$^{-1}$	C_{satd}, cal. deg.$^{-1}$
		Crystals			
10	0.042	0.124	1.243	0.166	0.491
15	.137	.393	5.895	.530	1.439
20	.303	.798	15.961	1.101	2.588
25	.531	1.276	31.89	1.807	3.789
30	.809	1.792	53.75	2.601	4.937
35	1.125	2.316	81.07	3.441	5.977
40	1.468	2.831	113.24	4.299	6.874
45	1.830	3.324	149.58	5.154	7.638
50	2.205	3.789	189.45	5.994	8.294
60	2.972	4.634	278.01	7.606	9.377
70	3.743	5.373	376.1	9.116	10.199
80	4.504	6.020	481.5	10.524	10.895
90	5.247	6.598	593.8	11.845	11.538
100	5.970	7.119	711.9	13.089	12.080
110	6.670	7.596	835.5	14.266	12.640
120	7.350	8.040	964.7	15.390	13.212
130	8.011	8.460	1099.8	16.471	13.802
140	8.652	8.864	1240.9	17.516	14.420
150	9.278	9.255	1388.2	18.533	15.059
160	9.887	9.639	1542.1	19.526	15.728
170	10.483	10.018	1703.0	20.501	16.440
180	11.066	10.395	1871.1	21.461	17.193
190	11.639	10.774	2047.1	22.413	18.022
200	12.201	11.158	2231.5	23.359	18.876
210	12.754	11.547	2424.7	24.301	19.773
220	13.300	11.943	2627.3	25.243	20.755
230	13.841	12.348	2840.1	26.189	21.797
231.49	13.920	12.410	2872.7	26.330	21.958
		Liquid			
231.49	13.920	20.957	4851	34.87	28.950
240	14.68	21.245	5098	35.92	29.228
250	15.55	21.571	5392	37.12	29.588
260	16.40	21.887	5690	38.29	29.995
270	17.24	22.195	5992	39.43	30.41
273.16	17.49	22.291	6089	39.79	30.54
280	18.05	22.497	6299	40.55	30.85
290	18.84	22.793	6610	41.64	31.33
298.16	19.48	23.032	6867	42.52	31.72
300	19.62	23.086	6925	42.71	31.81
310	20.38	23.375	7246	43.76	32.30
320	21.13	23.662	7571	44.79	32.81
330	21.86	23.948	7902	45.81	33.34
340	22.58	24.232	8238	46.81	33.88
350	23.29	24.516	8580	47.80	34.43

[a] The values tabulated are the free energy function, heat content function, heat content, entropy and heat capacity of the condensed phases at saturation pressure.

extrapolation to temperatures beyond the range of the experiments, the following Cox equation[24] was derived

$$\log_{10}P\ (\text{atm.}) = A(1 - 388.394/T) \qquad (3b)$$
$$\log_{10}A = 0.858631 - 6.7114 \times 10^{-4}T + 6.0722 \times 10^{-7}T^2$$

In these equations, t is in °C. and T is in °K. Comparisons of the observed and calculated vapor pressures for both the Antoine and Cox equations are given in Table VIII. The normal boiling point of pyridine, calculated from either equation, is 115.23° (388.39°K.).

The results in Table VIII are in good agreement with those of Herington and Martin.[20] In the range of temperature of the experimental data, values of the boiling point differ by 0.02° or less.

(24) E. R. Cox, *Ind. Eng. Chem.*, **28**, 613 (1936).

TABLE VIII

THE VAPOR PRESSURE OF PYRIDINE

Boiling point, °C. Water	Boiling point, °C. Pyridine	p(obsd.),[a] mm.	p(obsd.) − p(calcd.) Eq. 3a	p(obsd.) − p(calcd.) Eq. 3b
60.000	67.299	149.41	+0.02	+0.02
65	73.154	187.57	− .02	− .01
70	79.045	233.72	− .02	− .01
75	84.974	289.13	.00	+ .01
80	90.946	355.22	.00	.00
85	96.958	433.56	.00	− .01
90	103.008	525.86	+ .03	+ .01
95	109.101	633.99	+ .02	− .01
100	115.234	760.00	+ .02	.00
105	121.408	906.06	+ .01	.00
110	127.622	1074.6	.00	+ .1
115	133.878	1268.0	− .1	.00
120	140.174	1489.1	− .1	.00
125	146.509	1740.8	.0	.00
130	152.886	2026.0	.0	− .1

[a] From vapor pressure data for water given in ref. 22.

The Heat of Vaporization.—The heat of vaporization and vapor heat capacity of pyridine were measured in the flow calorimeter system described in previous publications.[25] The modified apparatus and procedure of ref. 25b were used. The results of measurements of the heat of vaporization at boiling points corresponding to 1/4, 1/2 and 1 atm. pressure are summarized in Table IX. The estimated accuracy uncertainty of the values of the heat of vaporization reported in Table IX is ±0.1%. The following empirical equation was derived for interpolation in the temperature range of the measurements (346 to 388°K.)

$$\Delta Hv = 13077 - 10.201T - 4.7941 \times 10^{-3}T^2, \text{ cal. mole}^{-1} \qquad (4)$$

The standard heat of vaporization at 298.16°K. was calculated by three methods: (1) from eq. 3b, 4 and 6 (given in the following section) and the relationship, $\Delta Hv° = \Delta Hv - BRT/V + (dB/dT)RT^2/V$; (2) from the Clapeyron equation with the aid of eq. 3b and 6; and (3) from a thermodynamic network that used the experimental value of S_{satd} (Table VII), the calculated value of $S°$ (Table IV) and eq. 3b. The results are 9612, 9599 and 9606 cal. mole^{-1}, respectively, and the average value, 9606 ± 7 cal. mole^{-1}, was selected as $\Delta Hv°_{298.16}$.

TABLE IX

THE MOLAL HEAT OF VAPORIZATION AND SECOND VIRIAL COEFFICIENT OF PYRIDINE

T, °K.	P, atm.	ΔHv(obsd.), cal.	B, cc. Obsd.	B, cc. Calcd.[a]
346.65	0.250	8965 ± 1[b]	−1292	−1326
366.11	0.500	8700 ± 2	−1157	−1147
388.40	1.000	8392 ± 4	− 990	− 990

[a] Calculated by use of eq. 6. [b] Maximum deviation from the mean of 3 to 5 determinations.

The Vapor Heat Capacity and the Effect of Gas Imperfection.—The vapor heat capacity of pyridine was measured at two or more pressures at each of five temperatures between 374 and 500°K. The results are summarized in Table X.

To correlate the thermal data, an equation of state for pyridine was obtained from data for the vapor pressure, heat of vaporization and vapor heat capacity. "Observed" values of the second virial coefficient, B, in the equation of state, $PV = RT(1 + B/V)$, were computed by use of the exact Clapeyron equation. Values of d^2B/dT^2 were determined from the thermodynamic relationship, $(\partial^2 V/\partial T^2)_P = -(1/T)(\partial C_p/\partial P)_T$, in terms of which the variation

(25) (a) Guy Waddington, S. S. Todd and H. M. Huffman, THIS JOURNAL, **69**, 22 (1947); (b) J. P. McCullough, D. W. Scott, R. E. Pennington, I. A. Hossenlopp and Guy Waddington, *ibid.*, **76**, 4791 (1954).

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TABLE X

THE MOLAL VAPOR HEAT CAPACITY OF PYRIDINE IN CAL. DEG.$^{-1}$

T, °K.	374.20	397.20	420.20	450.20	500.20
C_p(1.00 atm.)		25.877	27.110	28.753	31.336
C_p(0.50 atm.)	24.199	25.540			
C_p(0.25 atm.)	23.991	25.390	26.761	28.512	31.170
C_p°(obsd.)	23.79	25.23	26.65	28.43	31.12
$-T(d^2B/dT^2)$,[a] obsd.	0.79	0.60	0.44	0.30	0.21
$-T(d^2B/dT^2)$,[a] calcd.[b]	.80	.59	.45	.33	.20

[a] $-T(d^2B/dT^2) = \lim_{p\to 0}(\partial C_p/\partial P)_T$; units are cal. deg.$^{-1}$ mole^{-1} atm.$^{-1}$. [b] Calculated by use of eqs. 5 and 6.

of vapor heat capacity with the pressure is represented, with slight approximations,[25b] by

$$C_p = C_p^\circ - T\left(\frac{d^2B}{dT^2}\right)P + 2\left(\frac{B}{R}\right)\left(\frac{d^2B}{dT^2}\right)\left(1 - \frac{3BP}{RT}\right)P^2 \quad (5)$$

The value of the last term in eq. 5 (0.04 cal. deg.$^{-1}$ mole^{-1} or less) was estimated for each experimental point and subtracted from C_p(obsd.). The adjusted values of C_p at each temperature were plotted against P. The intercept and slope of the resulting straight lines were taken as C_p°(obsd.) and $\lim_{p\to 0}(\partial C_p/\partial P)_T = -T(d^2B/dT^2)$(obsd.), respectively. Constants in the following empirical equation for B were evaluated from the values of B(obsd.) and (d^2B/dT^2)(obsd.).

$$B = -15 - 84.5\exp(950/T), \text{ cc. mole}^{-1} \text{ (346–500°K.)} \quad (6)$$

Iteration using eq. 6 with eq. 5 and the experimental data produced no change in the correlation. The values of C_p° (obsd.) so determined are given in Table X. Observed values of B and $T(d^2B/dT^2)$ are compared in Tables IX and X with values calculated by using eq. 6.

The accuracy uncertainty of the values of C_p° (obsd.) listed in Table X should not exceed 0.2%. The following empirical equation represents these data within ±0.07% from 374 to 500°K.

$$C_p^\circ = -8.262 + 10.608\times 10^{-2}T - 5.4662\times 10^{-5}T^2, \text{ cal. deg.}^{-1}\text{ mole}^{-1} \quad (7)$$

Gas density measurements on pyridine were recently made at the Chemical Research Laboratories, Teddington, England.[20] Values of B calculated from an equation representing these data are −1258, −1126 and −993 cc. mole^{-1} at 346.65, 366.11 and 388.40°K. (the temperatures at which data were obtained in this Laboratory). These values of B are in excellent agreement with those listed in Table IX.

The Entropy in the Ideal Gaseous State.—The experimental and derived data given in the foregoing sections were used in computing "observed" values of the entropy in the ideal gaseous state at one atmosphere pressure. These calculations are summarized in Table XI.

TABLE XI

THE MOLAL ENTROPY OF PYRIDINE IN CAL. DEG.$^{-1}$

0–10°K.	Debye extrapolation	0.166
10–231.49°	Crystals, $\int C_{satd}\, d\ln T$	26.164
231.49°	Fusion, 1978.6/231.49	8.547
231.49–298.16°	Liquid, $\int C_{satd}\, d\ln T$	7.639
S_{satd}(liq.), 298.16°K. [±0.09][a]		42.52

T, °K.	346.65	366.11	388.40
S_{satd}(liq.)	47.48[b]	49.38[c]	51.50[c]
$\Delta Hv/T$[d]	25.86	23.76	21.61
S(ideal) − S(real)[e]	0.06	0.10	0.16
$R\ln P$[f]	−2.75	−1.38	0.00
S°(obsd.)[±0.15][a]	70.65	71.86	73.27

[a] Estimated accuracy uncertainty. [b] Interpolated in Table VII. [c] Extrapolation by use of eq. 1. [d] Entropy of vaporization; from data in Table IX. [e] Entropy of gas imperfection; calculated by use of eq. 6. [f] Entropy of compression; calculated with the aid of eq. 3b.

The Heat of Formation and Related Properties.—The heat of combustion of pyridine was determined by precise combustion calorimetric experiments, details of which will appear as part of another publication.[26] From this study, the heat of formation of liquid pyridine, $\Delta Hf°_{298.16}$ (liq.), was found to be 23.89 kcal. mole^{-1}. Addition of the standard heat of vaporization, 9.606 kcal. mole^{-1}, given in a preceding section, yields the heat of formation of pyridine in the ideal gaseous state, 33.50 kcal. mole^{-1}, as presented in Table I.

The value of S_{satd} (liq.) from Table VII and values of the entropy of C(graphite),[12] H_2(g)[12] and N_2(g)[12] were used in computing values of the entropy, free energy and logarithm of the equilibrium constant of formation of liquid pyridine according to the reaction

$$5C(\text{graphite}) + 5/2H_2(g) + 1/2N_2(g) \longrightarrow C_5H_5N(l)$$

$\Delta Hf°_{298.16}$ = 23.89 kcal. mole^{-1}; $\Delta Sf°_{298.16}$ = −65.20 cal. deg.$^{-1}$ mole^{-1}*; $\Delta Ff°_{298.16}$ = 43.33 kcal. mole^{-1}; $\log_{10}Kf$ = −31.76

NOTE ADDED IN PROOF.—Dr. Kun Li of Jones and Laughlin Steel Corporation, Pittsburgh, Pa., recently has published a paper [*J. Phys. Chem.*, **61**, 782 (1957)] in which the earlier thermodynamic data for pyridine are correlated and extended. With the exception of the heat of formation and vapor pressure data (refs. 2b and 2c of this paper), the accuracy of the experimental data used by Li is significantly lower than that of the data given in this paper. Those thermodynamic properties derived from the less accurate experimental data are also subject to greater uncertainty than the corresponding values listed in this paper.

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(26) W. N. Hubbard, F. R. Frow and Guy Waddington, to be published.

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Spectrophotometric Studies of Uranyl-Urea, -Thiourea and -Guanidine Systems in Absolute Ethyl Alcohol[1]

BY PHILIP S. GENTILE AND LAWRENCE H. TALLEY

RECEIVED APRIL 26, 1957

Analysis of absorption spectra and continuous variation studies have been employed to determine the stoichiometry of complexes present in uranyl-urea, -thiourea and -guanidine systems in absolute ethyl alcohol. Evidence is presented to show that only one complex is formed with each of the ligands. The urea and thiourea complexes were found to exist in a 1:2 (uranium/organic base) mole ratio. However, the guanidine complex exhibited a stoichiometry of 1:1. In addition, isolation of the compound $UO_2(NO_3)_2 \cdot [CO(NH_2)_2]_2$ from alcoholic solution supports the interpretation of the spectral measurements made with the urea system.

It had previously been reported[2] that no evidence of compound formation was observed at room temperature when attempts were made to prepare coordination compounds of uranyl nitrate with various organic ligands in alcoholic solutions. The complexing agents cited were urea, thiourea, guanidine, nitrilotriacetic acid and ethylenediaminetetraacetic acid. In the course of some studies conducted in our laboratories, evidence was obtained for uranyl compound formation with urea, thiourea and guanidine, a summary of which is presented in this paper.

Experimental

Materials.—Uranyl nitrate dihydrate was obtained by vacuum drying the hexahydrate (Baker and Adamson, A.C.S.) over sulfuric acid. The urea (American Cyanamid Company), thiourea (Eastman Kodak Company), guanidine (Eastman Kodak Company) and the absolute alcohol (U. S. Industrial Chemical Company, Reagent Grade, U. S. P.) were used without further purification.

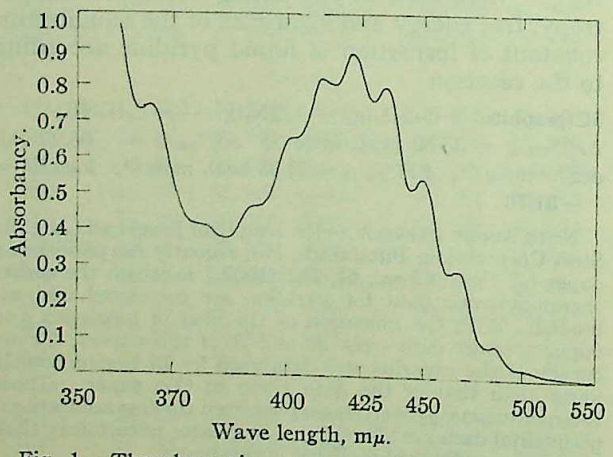

Fig. 1.—The absorption spectrum of a 0.076 *M* uranyl nitrate dihydrate solution in absolute ethyl alcohol. The absorption curves for 0.076 *M* solutions of uranyl-urea and thiourea are so similar that major differences are not detectable throughout the range of 420–600 mμ. Except for minor shifts in some spectral bands, the uranyl-guanidine curve was similar to that shown above.

Analysis.—Urea was determined according to the method of Gertner and Inkovik.[3] The uranium was assayed by ignition to uranouranic oxide (U_3O_8).

Procedure.—In applying Job's[4] technique of continuous variation, 0.076 *M* solutions of uranyl nitrate dihydrate, urea, thiourea and guanidine were prepared and arbitrarily allowed to stand 24 hours in the dark prior to making measurements. The instability of the solutions toward light necessitated this precaution.

Initial spectral transmission curves were obtained with a model DK-2 Beckman spectrophotometer while subsequent studies were made with a model DU Beckman spectrophotometer using Corex cells of 10 mm. light path.

Diureadioxouranium(VI) Nitrate.—To 60 ml. of a 4 *M* alcoholic solution of uranyl nitrate dihydrate, urea (19.7 g.) was added in small increments. A finely divided yellow precipitate was obtained which was filtered and air-dried. This compound melted at 203–205° and was extremely water-soluble.

Anal. Calcd. for $UO_2(NO_3)_2 \cdot [CO(NH_2)_2]_2$: U, 46.30; N, 16.34; urea, 23.36. Found: U, 46.07; N, 15.83; urea, 22.51.

In an analogous manner, the addition of thiourea to an alcoholic solution of uranyl nitrate dihydrate resulted in the formation of a deep red-colored solution showing a reaction had taken place. However, all efforts to isolate a uranyl–thiourea complex were unsuccessful.

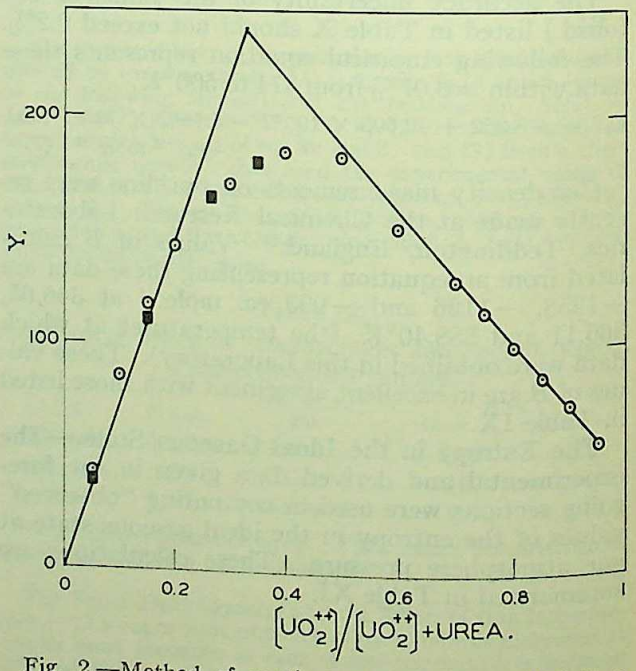

Fig. 2.—Method of continuous variation applied to a uranyl nitrate–urea system. The concentrations (UO_2^{++} + urea) were 0.076 *M* for each solution. The value *Y* represents the difference between the absorbancy of the complex mixture and that of uranium if no reaction had occurred. The solid squares represent solutions of diureadioxouranium(VI) nitrate in molarities equivalent to that of the corresponding uranium concentration used for continuous variation studies. Since these points are coincident with the curve obtained, it provides further supporting evidence for the existence of an MR_2 complex in alcoholic solutions.

(1) This paper is based on work performed for the Atomic Energy Commission by the National Lead Company of Ohio at Cincinnati, Ohio.

(2) G. W. Watt and A. R. Machel, THIS JOURNAL, **72**, 2801 (1950).

(3) A. Gertner and H. Z. Inkovik, *Anal. Chem.*, **142**, 36 (1954).

(4) P. Job, *Compt. rend.*, **184**, 204 (1927).

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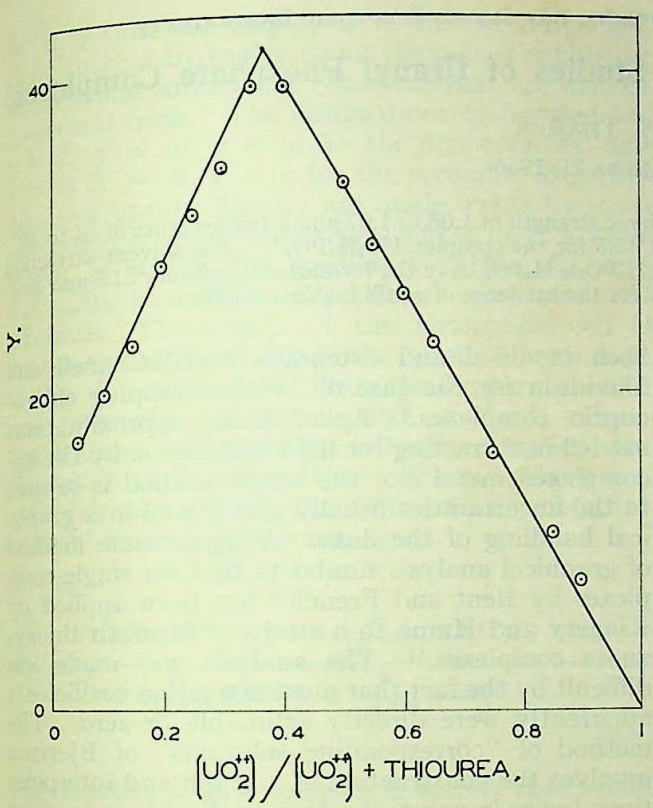

Fig. 3.—Uranyl complex with thiourea.

Solutions of guanidine and uranyl nitrate retained the characteristic yellow color of uranyl compounds and the isolation of a complex was not realized.

Results and Discussion

For the low concentration employed (0.076 *M*) at maximum absorbancy, all the solutions displayed the typical yellow coloration of uranyl compounds. The absorption curves were so similar that *major* differences in the spectral bands were not detectable throughout the range of 420–600 mμ (Fig. 1). It is not surprising, therefore, that Watt and Machel,[2] employing 0.057 *M* solutions, reported no evidence for compound formation in these systems. However, at high concentrations, unlike the urea and guanidine systems, the uranyl-thiourea solution is deep red in color indicating major changes in the spectral curves. Unfortunately, these curves could not be obtained readily with available facilities due to high absorbancy in this concentration region.

For the urea and thiourea system, the differences in spectral bands as compared to uranyl nitrate are so slight as to be virtually undetectable. The presence of new chemical species was indicated by abnormal increases in the absorbancy which were unattributable to the uranyl ion concentration present.

For the guanidine system, the 356 mμ band vanished and the 366, 368 and 488 mμ bands of uranyl nitrate shifted slightly to 364, 464 and 480 mμ. The 480 mμ band also was characterized by a relatively large increase in extinction coefficient. In the region of 370–465 mμ, there was virtually no change in the spectral bands.

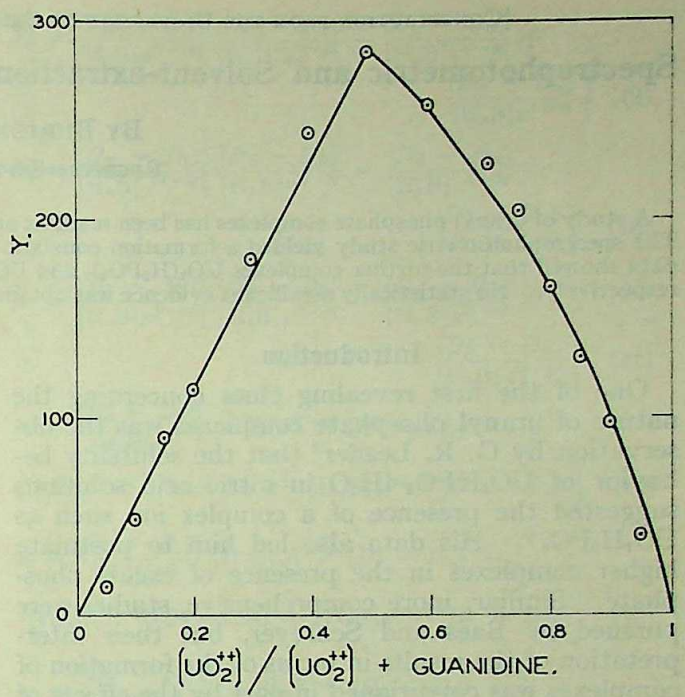

Fig. 4.—Uranyl complex with guanidine.

Continuous variation data for uranyl-urea mixtures were examined at 423, 435 and 467 mμ. As seen in Fig. 2, the experimental data show the presence of a uranyl-urea complex with a 1:2 mole ratio as indicated by a maximum at 0.33. The broad maxima are characteristic of compounds that display appreciable dissociation. Isolation of the compound $UO_2(NO_3)_2 \cdot [CO(NH_2)_2]_2$ and subsequent absorption studies in solution (Fig. 2) provides supporting evidence for the interpretation of the spectral measurements.

Uranyl-thiourea mixtures examined at 412, 423 and 435 mμ (Fig. 3) indicate the presence of a complex with a uranyl/thiourea mole ratio of 1:2. As in the case of urea, it is very unlikely that other complexes exist in solution. The absence of major differences in the spectral bands, as compared to uranyl nitrate, indicates that if other complexes are present, it would be difficult to detect them in the concentration range utilized (0.076 *M*).

For the uranyl-guanidine system (Fig. 4), there is evidence to support the presence of only one complex, namely, a coördination compound with a 1:1 mole ratio. Spectral measurements were made at 402, 423 and 450 mμ.

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[CONTRIBUTION FROM THE UNIVERSITY OF CALIFORNIA, LOS ALAMOS SCIENTIFIC LABORATORY]

Spectrophotometric and Solvent-extraction Studies of Uranyl Phosphate Complexes[1]

BY BURTON J. THAMER

RECEIVED SEPTEMBER 21, 1956

A study of uranyl phosphate complexes has been made at an ionic strength of 1.06 to 1.07 and a temperature of 24 to 25°. The spectrophotometric study yielded a formation constant of 15.5 for the complex $UO_2H_2PO_4^+$. The solvent-extraction data showed that the further complexes $UO_2(H_2PO_4)_2$ and $UO_2(H_2PO_4)_2 \cdot H_3PO_4$ have the formation constants 21.8 and 10.2, respectively. No statistically significant evidence was obtained for the existence of a still higher complex.

Introduction

One of the first revealing clues concerning the nature of uranyl phosphate complexes was the observation by G. R. Leader[2] that the solubility behavior of $UO_2HPO_4 \cdot 4H_2O$ in nitric acid solutions suggested the presence of a complex ion such as $UO_2H_2PO_4^+$. His data also led him to postulate higher complexes in the presence of excess phosphate. Similar, more comprehensive, studies were pursued by Baes and Schreyer, but their interpretation of the results in terms of the formation of complexes was conditioned in part by the effects of inconstant ionic strength.[3,4] Findings from the original spectrophotometric study of the first complex,[5] which they and J. M. Lesser had made, recently have been revised to take into account the effect of the second complex.[6] These results as well as those of this article will be discussed in some detail later.

1. Spectrophotometric Studies.—Spectrophotometry is one of the more experimentally suitable techniques with which to study complex ions of uranium. The ease and rigor with which spectrophotometric data on complex ions have been interpreted have depended largely upon the complexity of the system and the degree of overlap of the ranges of stability of the complex ions. In his study of chromate–phosphate complexes, Holloway was able to separate largely the two operative equilibria, and thus simplify the problem, by altering the *p*H.[7] The method was based on successive approximations. The slope-intercept method of Benesi and Hildebrand[8] for a single complex has been modified and extended by McConnell and Davidson for the case of two overlapping chlorocupric complexes.[9] Apart from approximations needed in correcting for light absorption by the uncomplexed metal ion, the latter method is subject to the uncertainties usually introduced in a graphical handling of the data. A logarithmic method of graphical analysis similar to that for single complexes by Bent and French[10] has been applied by Kingery and Hume to a study of bismuth thiocyanate complexes.[11] The analysis was made less difficult by the fact that most extinction coefficients apparently were directly estimable or zero. The method of "corresponding solutions" of Bjerrum involves the construction of a graph and interpolations between points.[12] It is applicable to systems of strong complexes. All but the last of the above methods that are applicable in the formation of two complex ions become appreciably less accurate or more time consuming if the two complexes have overlapping ranges of stability. The following algebraic treatment is rigorously applicable to the case of two complexes no matter what their degree of overlap. (Even if appreciable amounts of other complexes are present, a proper use of the data will yield better information concerning one of the two principal complexes than would be obtained otherwise.) A minimum amount of data is required. No extinction coefficients need be directly estimated. The method is most suitable for systems of other than strong complexes. As in all of the above methods except that of Bjerrum, the concentration of unbound complexing agent must be calculated with corrections for its equilibrium as an acid or base and for what is bound in complexes, the latter possibly requiring a few successive approximations. In the present application no more than 20% of the complexing agent was bound to the uranium in any solution.

This treatment is designed for the case of a light-absorbing species A (UO_2^{++}) forming two complexes with a non-light-absorbing, *s*-basic acid H_sB (H_3PO_4).

$$A + XH_sB = AH_{sX-x}B_X + xH^+ \qquad (1)$$

$$k_y = \frac{[AH_{sX-x}B_X][H^+]^x}{[A][H_sB]^X} \qquad (2)$$

The equilibria are expressed in terms of undissociated acid as the complexing agent because this is its predominant form at the acidities (0.5 and 1.0

(1) Work done under the auspices of the Atomic Energy Commission. Based on the report of the same title, LA-1996, February 23, 1956, available from the Office of Technical Services, Department of Commerce.

(2) G. R. Leader, University of Chicago Metallurgical Laboratory Report CN-2195, December 26, 1944.

(3) J. M. Schreyer and C. F. Baes, Jr., "The Chemistry of Uranium (VI) Orthophosphate Solutions: Part II, The Solubility of Uranium (VI) Orthophosphates in Phosphoric Acid Solutions," Oak Ridge National Laboratory Report ORNL-1578, June 30, 1953.

(4) C. F. Baes, Jr., and J. M. Schreyer, "The Chemistry of Uranium(VI) Orthophosphate Solutions: Part III, The Solubility Behavior of $UO_2HPO_4 \cdot 4H_2O$ in Perchloric Acid Solutions," Oak Ridge National Laboratory Report ORNL-1579, July 1, 1953; J. M. Schreyer and C. F. Baes, Jr., *J. Phys. Chem.*, **59**, 1179 (1955).

(5) C. F. Baes, Jr., J. M. Schreyer, and J. M. Lesser, "The Chemistry of Uranium(VI) Orthophosphate Solutions: Part I, A Spectrophotometric Investigation of Uranyl Phosphate Complex Formation in Perchloric Acid Solution," Oak Ridge National Laboratory Report AECD-3596, October 20, 1953.

(6) C. F. Baes, Jr., paper entitled "A Spectrophotometric Investigation of Uranyl Phosphate Complex Formation in Perchloric Acid Solution" presented at the Nuclear Engineering and Science Congress, Cleveland, Ohio, December 12–16, 1955; *J. Phys. Chem.*, **60**, 878 (1956).

(7) F. Holloway, THIS JOURNAL, **74**, 224 (1952).

(8) H. A. Benesi and J. H. Hildebrand, *ibid.*, **71**, 2703 (1949).

(9) H. McConnell and N. Davidson, *ibid.*, **72**, 3164 (1950).

(10) H. E. Bent and C. L. French, *ibid.*, **63**, 568 (1941).

(11) W. D. Kingery and D. N. Hume, *ibid.*, **71**, 2393 (1949).

(12) J. Bjerrum, *Kgl. Danske Videnskab. Selskab., Mat.-fys. Medd.*, **21**, No. 4, 28 (1946).

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M H^+) that are employed in this investigation. Ionic charges are neglected for the sake of simplicity in these and subsequent equations that are written in general form. The designations to be used are $y = 1$, $X = M$, $x = m$ for the first complex, and $y = 2$, $X = N$, $x = n$ for the second. Measurements of optical density are made *versus* the concentration of the complexing agent H_sB at a wave length at which the species A, $AH_{sM-m}B_M$ and $AH_{sN-n}B_N$ have markedly different absorption coefficients. The length of the absorption cell is kept constant, as is also c, the total concentration of A in all forms. In addition the temperature and ionic strength are maintained at fixed values. Under these conditions the following equation, analogous to that derived by Holloway,[7] relates the optical density D to D_1, the optical density obtained in the absence of complexing agent.

$$D - D_1 = \frac{\frac{k_1}{[H^+]^m}[H_sB]^M (LcE_2 - D_1) + \frac{k_2}{[H^+]^n}[H_sB]^N(D_3 - D_1)}{1 + \frac{k_1}{[H^+]^m}[H_sB]^M + \frac{k_2}{[H^+]^n}[H_sB]^N} \quad (3)$$

The quantity LcE_2 is the optical density that would be obtained if $AH_{sM-m}B_M = c$, and D_3 is that corresponding to $AH_{sN-n}B_N = c$. Neither LcE_2 nor D_3 need be directly measured.

A rearrangement of equation 3 gives the following for each i-th solution

$$\Phi_i(D_i - D_1)[k_1] + (D_i - D_1)[k_2] - [k_2(D_3 - D_1)] - \Phi_i[k_1(LcE_2 - D_1)] = -\theta_i\Phi_i(D_i - D_1) \quad (4)$$

where

$$\theta_i = \frac{[H^+]_i^m}{[H_sB]_i^M} \text{ and } \Phi_i = \frac{[H^+]_i^{n-m}}{[H_sB]_i^{N-M}} \quad (5)$$

A knowledge of the values of m and n is not required at this point. Leaving m and n unspecified, all other quantities in equation 4 are directly measurable except those that are enclosed in brackets. The four constants within brackets can be evaluated in terms of m and n by the determinantal solution of four equations of the form of equation 4. Hence measurements on four aqueous solutions having different phosphate concentrations and designated as α, β, γ and δ provide the following for k_1 and k_2

$$\frac{k_1}{[H^+]^m} = \frac{\left(\frac{\lambda_1}{[H_sB]_\alpha^M} - \frac{\lambda_2}{[H_sB]_\beta^M} + \frac{\lambda_3}{[H_sB]_\gamma^M} - \frac{\lambda_4}{[H_sB]_\delta^M}\right)}{\lambda_4 - \lambda_3 + \lambda_2 - \lambda_1} \quad (6)$$

$$\frac{k_2}{[H^+]^n} = \left(\frac{1}{[H_sB]_\alpha[H_sB]_\beta[H_sB]_\gamma[H_sB]_\delta}\right)^{N-M} \times \left(\frac{\lambda_5 - \lambda_6 + \lambda_7 - \lambda_8}{\lambda_4 - \lambda_3 + \lambda_2 - \lambda_1}\right) \quad (7)$$

where it is assumed that the hydrogen ion concentration is the same among these four solutions, and

$$\lambda_1 = \frac{(D_\alpha - D_1)}{[H_sB]_\alpha^{N-M}}\left[\frac{(D_\delta - D_\gamma)}{[H_sB]_\beta^{N-M}} - \frac{(D_\delta - D_\beta)}{[H_sB]_\gamma^{N-M}} + \frac{(D_\gamma - D_\beta)}{[H_sB]_\delta^{N-M}}\right] \quad (8)$$

$$\lambda_2 = \frac{(D_\beta - D_1)}{[H_sB]_\beta^{N-M}}\left[\frac{(D_\delta - D_\gamma)}{[H_sB]_\alpha^{N-M}} - \frac{(D_\delta - D_\alpha)}{[H_sB]_\gamma^{N-M}} + \frac{(D_\gamma - D_\alpha)}{[H_sB]_\delta^{N-M}}\right] \quad (9)$$

$$\lambda_3 = \frac{(D_\gamma - D_1)}{[H_sB]_\gamma^{N-M}}\left[\frac{(D_\delta - D_\beta)}{[H_sB]_\alpha^{N-M}} - \frac{(D_\delta - D_\alpha)}{[H_sB]_\beta^{N-M}} + \frac{(D_\beta - D_\alpha)}{[H_sB]_\delta^{N-M}}\right] \quad (10)$$

$$\lambda_4 = \frac{(D_\delta - D_1)}{[H_sB]_\delta^{N-M}}\left[\frac{(D_\gamma - D_\beta)}{[H_sB]_\alpha^{N-M}} - \frac{(D_\gamma - D_\alpha)}{[H_sB]_\beta^{N-M}} + \frac{(D_\beta - D_\alpha)}{[H_sB]_\gamma^{N-M}}\right] \quad (11)$$

$$\lambda_5 = \frac{(D_\alpha - D_1)}{[H_sB]_\alpha^M}\left[[H_sB]_\beta^{N-M}(D_\delta - D_\gamma) - [H_sB]_\gamma^{N-M}(D_\delta - D_\beta) + [H_sB]_\delta^{N-M}(D_\gamma - D_\beta)\right] \quad (12)$$

$$\lambda_6 = \frac{(D_\beta - D_1)}{[H_sB]_\beta^M}\left[[H_sB]_\alpha^{N-M}(D_\delta - D_\gamma) - [H_sB]_\gamma^{N-M}(D_\delta - D_\alpha) + [H_sB]_\delta^{N-M}(D_\gamma - D_\alpha)\right] \quad (13)$$

$$\lambda_7 = \frac{(D_\gamma - D_1)}{[H_sB]_\gamma^M}\left[[H_sB]_\alpha^{N-M}(D_\delta - D_\beta) - [H_sB]_\beta^{N-M}(D_\delta - D_\alpha) + [H_sB]_\delta^{N-M}(D_\beta - D_\alpha)\right] \quad (14)$$

$$\lambda_8 = \frac{(D_\delta - D_1)}{[H_sB]_\delta^M}\left[[H_sB]_\alpha^{N-M}(D_\gamma - D_\beta) - [H_sB]_\beta^{N-M}(D_\gamma - D_\alpha) + [H_sB]_\gamma^{N-M}(D_\beta - D_\alpha)\right] \quad (15)$$

A combination of four aqueous solutions will give values for $k_1/[H^+]^m$ and $k_2/[H^+]^n$ that are the same within experimental error as those from another combination of four aqueous solutions at the same hydrogen ion concentration only if the correct values for M and N have been used.

It should be noted that in equations 6 to 15 the only spectrophotometric quantities required are *differences* in optical densities. Hence one need not measure directly the optical density D_1, for example, but can obtain instead all of the necessary spectrophotometric data by measuring each of the four solutions *versus* the solution with pure A in it to give the quantities $D_\alpha - D_1$, $D_\beta - D_1$, $D_\gamma - D_1$ and $D_\delta - D_1$. This use of the technique of differential spectrophotometry should also give improved accuracy.[13]

All of the spectrophotometric data were obtained with a Beckman Model DU spectrophotometer. The cell compartment was thermostated at 25.0 ± 0.1° and the solutions were left in a 25.0 ± 0.1° constant-temperature bath for at least 10 hours before measurement. Solutions of hexavalent uranium are known to re-emit absorbed light in the form of fluorescent light with a wave length of 490 mμ and higher.[14,15] Since such fluorescence could have destroyed the Beer's law relation implicit in equation 3, all uranium solutions were measured with a light filter in the light path between the sample compartment and the phototube compartment. The wave lengths at which optical density measurements were made were below 400 mμ. Hence the filter that was used was a Corning No. 5970 Color Filter, which cut out light above 425 mμ.

(13) For example, see R. Bastian, R. Weberling and F. Palilla, *Anal. Chem.*, **22**, 160 (1950).

(14) S. I. Weissman and R. B. Duffield, "Estimation of Small Quantities of Uranium in Thorium," Los Alamos Scientific Laboratory Report LA-15, July 26, 1943.

(15) C. J. Rodden and J. C. Warf, Part 1, Ch. 1, p. 131, in C. J. Rodden, ed., "Analytical Chemistry of the Manhattan Project," McGraw-Hill Book Co., Inc., New York, N. Y., 1950.

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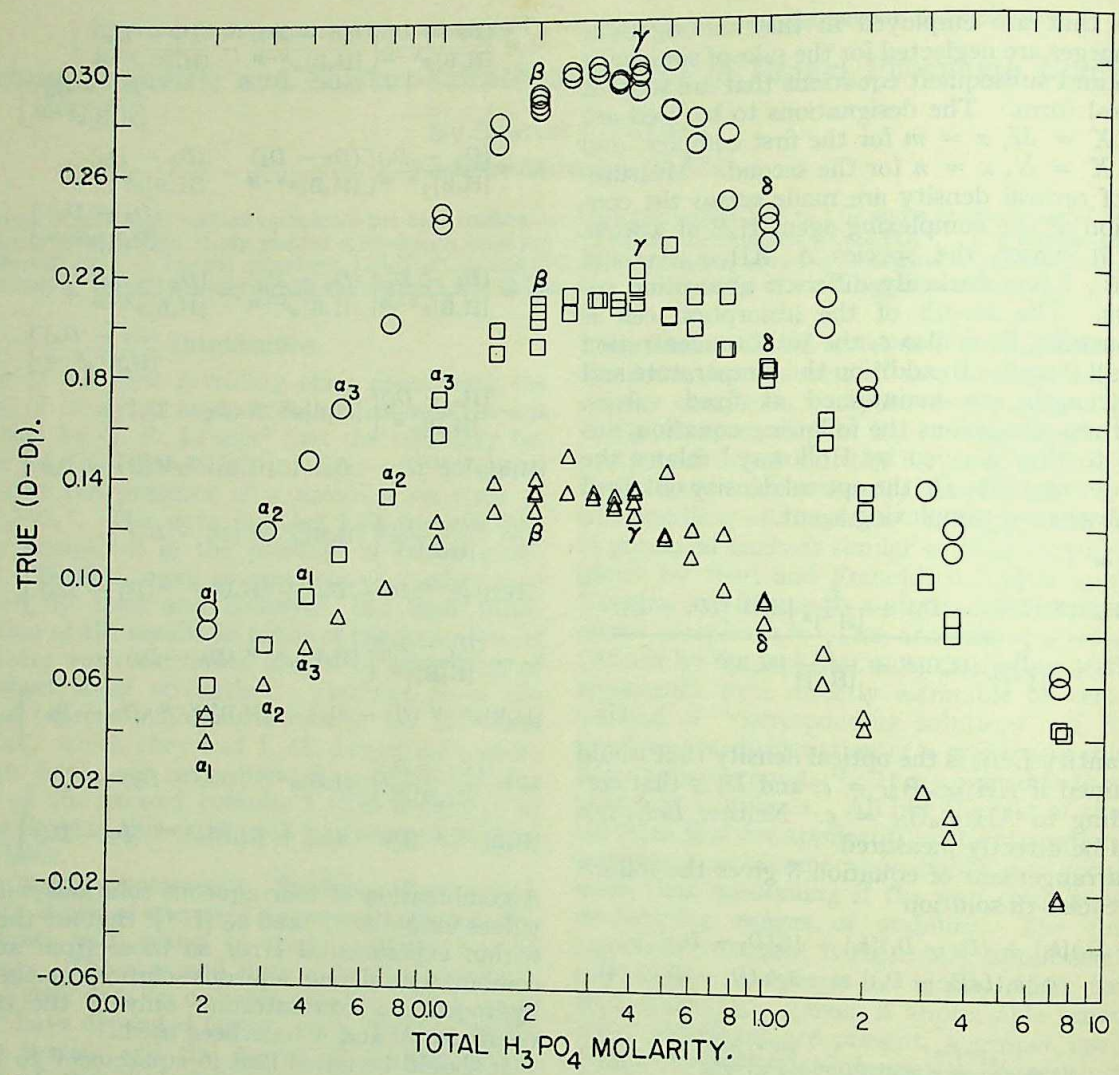

Fig. 1.—Spectrophotometric data at three wave lengths in $UO_2(ClO_4)_2$–H_3PO_4 solutions at 1.004 M H^+ and an ionic strength of 1.06: ○, at 393 mμ; □, at 388 mμ; △, at 383 mμ.

Four different wave lengths were found at which UO_2^{++} and the first two complexes had absorption coefficients favorable to the study of these two complexes. The four different wave lengths—393, 388, 383 and 376 mμ—were located in a region where the extinction coefficients varied rapidly with wave length. The solutions were measured in matched 10.00-cm. silica absorption cells and the appropriate blank corrections always were made. Exactly the same slit width was reproduced for each measurement at a given wave length. The band width was about 4 mμ. It was found that Beer's law was obeyed in the absence or presence of phosphoric acid. The fact that Beer's law was obeyed in 3.7 M phosphoric acid indicated that no significant amounts of polynuclear complexes were formed in the more concentrated phosphoric acid solutions. The concentration of uranium used in the subsequent spectrophotometric measurements was 0.01885 M, in the mid-section of the plots of Beer's law.

All of the spectrophotometric and solvent-extraction studies of the complex-ion equilibria were made in $HClO_4$–$NaClO_4$ solutions having a calculated ionic strength of 1.06 or 1.07. The contribution to the ionic strength of the 0.01885 M $UO_2(ClO_4)_2$ used in the spectrophotometric measurements was assumed to be $3 \times 0.01885 = 0.057$, but in many solutions the actual contribution to the ionic strength probably was as much as 0.019 less than that because of the effect of phosphate complexing.

The contribution to the ionic strength and to the hydrogen-ion concentration that was made by the dissociation of the phosphoric acid was calculated from a value of $k_{1a} = 0.019 \pm 0.001$ for the first concentration dissociation constant for this acid. This figure was determined at an ionic strength of 1.07 in $NaClO_4$ solutions having no uranium. The method was that of v. Halban and Brüll,[16] in which, for the present application, $HClO_4$ was the source of the known hydrogen-ion concentration and the indicator was thymolsulfonphthalein at a chemically negligible concentration. This value of k_{1a} agrees well with a value of 0.020 (30°, μ = 1.0 to 1.1) by Cher and Davidson[17] and a value of 0.021 (*ca.* 25°, μ = *ca.* 1) estimated by Baes, Jr.[6] (The second and third dissociations of phosphoric acid were ignored because their effect on the complex ion equilibria was negligible.)

The spectrophotometric data on the complexes were obtained at two different values of the hydrogen-ion concentration. Figure 1 represents the data at 1.004 M hydrogen ion and an ionic strength of 1.06. Similar data also were obtained with 0.510 M hydrogen ion and an ionic strength of 1.07. The values of "true $(D - D_1)$" were obtained by measuring the solution with phosphoric acid *versus* a solution having the same uranium concentration, hydrogen-ion molarity and ionic strength, but no phosphoric acid. The blank corrections were determined and applied for each solution. The values of corrected or true H_3PO_4 molarity were consistent within ±3% in every case with the final constants for the complexes as summarized at the end of the paper.

The data at the higher acidity were examined in order to determine M of equations 1 and 2 by plotting log $(D - D_1)$ *versus* log (true H_3PO_4 molarity) in a manner similar to that of Bent and French.[10] The slope was found to be +0.82 at about 0.020 M true H_3PO_4 molarity. This H_3PO_4 concen-

(16) H. v. Halban and J. Brüll, *Helv. Chim. Acta*, **27**, 1719 (1944).
(17) M. Cher and N. Davidson, THIS JOURNAL, **77**, 793 (1955).

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tration is a little too high to allow more than an approximate identification of M with the slope. A better approximation is to take $M = +0.82\ (1 + k_1[H_3PO_4]^M/[H^+]^m)$. Anticipating the values of $k_1 = 15.5$, $M = 1$ and $m = 1$, one calculates $M = 1.07$ which is 1 within experimental error. Hence a value of unity was taken for M. The data at both acidities were tested for the most consistent value for N by a method derived from a treatment for dibasic acids.[18] The best value by far for N was 2. However, the resulting values for $k_2/[H^+]^n$ varied considerably more than the values for $k_1/[H^+]^m$, thus indicating the probable presence of a still higher complex.

Because of the presence of the third complex it was decided not to estimate values of $k_2/[H^+]^n$ from the spectrophotometric data. Only values of $k_1/[H^+]^m$ were calculated by the method of equations 6 to 15, which automatically corrected for the presence of the second complex. Rules of thumb concerning the optimum spectrophotometric relations as summarized in an analogous treatment of dibasic acids[19] were modified to minimize the effect of the third complex. The data that were used were confined to solutions for which it was later estimated that the one with the highest phosphoric acid concentration (solution δ) had about 21% of the uranium in the form of the third complex. (The resulting percentage of error produced in $k_1/[H^+]^m$ should be much smaller than this, however.) Figure 1 and Table I indicate the points that were used at 1.004 M H^+. Likewise, Table II shows the data that were used at 0.510 M H^+. Equations 6, 8, 9, 10 and 11 were used in calculating the values of $k_1/[H^+]^m$ given in the last column of Tables I and II. The constancy within experimental error of these values within each table further confirms that $M = 1$ and $N = 2$. The average value of $k_1/[H^+]^m$ obtained from Table I is $k_1/1.004^m = 15.9 \pm 1.9$.

TABLE I

CALCULATION OF $k_1/[H^+]^m$ AT 1.004 M H^+ FROM EQUATION 6 ($\mu = 1.06$, $[H_3PO_4]_\beta = 0.180$ M, $[H_3PO_4]_\gamma = 0.373$ M, $[H_3PO_4]_\delta = 0.956$ M)

Wave length, mμ	$[H_3PO_4]_\alpha$, M	$D_\alpha - D_1$	$D_\beta - D_1$ (av)	$D_\gamma - D_1$ (av)	$D_\delta - D_1$ (av)	$\frac{k_1}{[H^+]^m}$
393.0	0.0159	0.084(av)	0.2884	0.2981	0.2388	15.3
393.0	.0242	.1195	.2884	.2981	.2388	16.6
393.0	.0415	.168	.2884	.2981	.2388	16.3
388.0	.0328	.094	.2026	.2155	.1823	13.4
388.0	.0592	.1335	.2026	.2155	.1823	12.7
388.0	.0866	.1648(av)	.2026	.2155	.1823	16.1
383.0	.0159	.0415(av)	.1341	.1321	.0893	16.1
383.0	.0242	.059	.1341	.1321	.0893	17.7
383.0	.0328	.0735	.1341	.1321	.0893	19.1

Similarly, the average and standard deviation obtained from Table II is $k_1/0.510^m = 28.2 \pm 5.2$. Solving for the value of m one obtains $m = 0.85 \pm 0.32$. In view of the magnitude of the standard deviation, there is little justification for assuming m to be other than unity. Hence the value of m is taken to be exactly 1. Use of $m = 1$ gives $k_1 = 16.0 \pm 1.9$ and $k_1 = 14.4 \pm 2.7$, respectively, the grand mean of which is $k_1 = 15.5 \pm 1.6$.

TABLE II

CALCULATION OF $k_1/[H^+]^m$ AT 0.510 M H^+ FROM EQUATION 6 ($\mu = 1.07$, $[H_3PO_4]_\beta = 0.0819$ M, $[H_3PO_4]_\gamma = 0.1185$ M, $[H_3PO_4]_\delta = 0.4114$ M)

Wave length, mμ	$[H_3PO_4]_\alpha$, M	$D_\alpha - D_1$	$D_\beta - D_1$ (av)	$D_\gamma - D_1$ (av)	$D_\delta - D_1$ (av)	$\frac{k_1}{[H^+]^m}$
393.0	0.0138	0.1275	0.3093	0.3298	0.3108	25.9
393.0	.0215	.174	.3093	.3298	.3108	26.9
393.0	.0296	.2145	.3093	.3298	.3108	31.4
388.0	.0138	.089	.2253	.2445	.2378	24.2
388.0	.0215	.1215	.2253	.2445	.2378	24.6
388.0	.0379	.165(av)	.2253	.2445	.2378	21.3
383.0	.0138	.0675	.1535	.1618	.1388	29.6
383.0	.0215	.0905	.1535	.1618	.1388	30.4
383.0	.0296	.112	.1535	.1618	.1388	39.7

(18) B. J. Thamer and A. F. Voigt, *J. Phys. Chem.*, **56**, 225 (1952).
(19) B. J. Thamer, *ibid.*, **59**, 450 (1955).

It might be mentioned that in principle one could rigorously extend the method of this section as embodied in equations 4 to 15 to the case of the formation of three complexes instead of two. However, the solution of the sixth-order determinants that would be involved is thought to necessitate such a prohibitive amount of work as to be impractical.

2. Solvent-extraction Studies.—Although the spectrophotometric data had allowed an evaluation of the formula and stability of the first complex, they had not done so reliably for the second complex, and they had only shown the probable existence of a third complex species. However, experiments with solvent extraction were found to yield data that more readily delineated the nature of the second and third complexes.

The equilibria are expressed in terms of equations 1 and 2 with $y = 1$, $X = M = 1$, $x = m = 1$ and $k_1 = 15.5$ for the first complex; $y = 2$, $X = N$, $x = n$ for the second; and $y = 3$, $X = P$, $x = p$ for the third. The algebraic handling of Leden's method[20] by Sullivan and Hindman[21] can be extended to allow the implicit evaluation of the extraction equilibrium constant k, as well as the determination of k_2 and k_3 by means of the equations

$$k_2 = \frac{\left(1 - \frac{f_\alpha}{f_r} - \mu_\alpha k_1\right)\pi_\beta - \left(1 - \frac{f_\beta}{f_r} - \mu_\beta k_1\right)\pi_\alpha}{\nu_\alpha\pi_\beta - \nu_\beta\pi_\alpha} \quad (16)$$

$$k_3 = \frac{\left(1 - \frac{f_\beta}{f_r} - \mu_\beta k_1\right)\nu_\alpha - \left(1 - \frac{f_\alpha}{f_r} - \mu_\alpha k_1\right)\nu_\beta}{\nu_\alpha\pi_\beta - \nu_\beta\pi_\alpha} \quad (17)$$

where

$$\mu_i,\ \nu_i \text{ or } \pi_i = \frac{f_i[H_sB]_i^X}{f_r[H^+]_i^x} - \frac{[H_sB]_r^X}{[H^+]_i^x} \quad (18)$$

and $X = M, x = m$ for μ; $X = N, x = n$ for ν; and $X = P$, $x = p$ for π. The quantities f_α, f_β and f_r represent the fractions of aqueous uranium that are complexed at three different complexing agent concentrations none of which is zero. The quantities f_α/f_r and f_β/f_r are determined experimentally. The determination of N and P rests upon the fact that at the same acidity various pairs of solutions serving as α and β will give values of k_2 and k_3 that are constant within experimental error only if the right values have been chosen for N and P. Similarly, the obtaining of the same values of k_2 and k_3 at different acidities gives evidence of the proper choice for n and p.

Dibutyl phosphate dissolved in kerosene was used as the extracting agent. A purified grade of dibutyl phosphate, obtained from the Victor Chemical Works, was used without further purification. A sample of it was titrated with sodium hydroxide to determine its dibutyl phosphate content and the content of the likely contaminant monobutyl phosphate.[22] Its composition by weight corresponded to 96.0% dibutyl phosphate, 0.35% monobutyl phosphate and 3.65% of non-acidic material. This small amount of monobutyl phosphate would not appreciably extract uranium[23] nor

(20) I. Leden, *Z. physik. Chem.*, **A188**, 160 (1941).
(21) J. C. Sullivan and J. C. Hindman, THIS JOURNAL, **74**, 6091 (1952).
(22) R. M. Wagner, "The Hydrolysis Products of Tributyl Phosphate and Their Effect on the Tributyl Phosphate Process for Uranium Recovery," Hanford Works Report HW-19959, April 15, 1951.
(23) D. C. Stewart and T. E. Hicks, "Alkyl Phosphoric Acid Extractions," University of California Radiation Laboratory Report UCRL-861, August 9, 1950.

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would it form a precipitate with it.[22] If the non-acidic material were tributyl phosphate, this component by itself should have no extracting action because no nitrate was present in these solvent-extraction experiments.[24] In any case the non-acidic material was considered to act only as a diluent. All concentrations reported herein for dibutyl phosphate have been corrected for these impurities. Kerosene was used as the organic solvent because it gave good phase separations. The dibutyl phosphate solutions always were prepared from the same stock of kerosene.

Studies by Wagner[22] have indicated that with 0.005 to 0.01 *M* dibutyl phosphate in a paraffinic hydrocarbon mixture (AMSCO 125-90 W) the extraction equilibrium conforms to the equation

$$UO_2^{++}(aq) + 2HD(org) = UO_2D_2(org) + 2H^+(aq) \quad (19)$$

$$k = \frac{(U)}{[UO_2^{++}]} \times \frac{[H^+]^2}{(HD)^2} \quad (20)$$

where (HD) is the molarity of free dibutyl phosphate in the organic phase and (U) is the molarity of UO_2D_2 in the organic phase. Equations 19 and 20 also have been verified for extractions with di-(2-ethylhexyl)-phosphoric acid in *n*-hexane over the range of 10^{-5} to 0.2 *M* initial uranium, 0.001 to 2 *M* extractant, and 0.1 to 2 *M* perchloric acid in the aqueous phase.[25] However, some results obtained by Stewart and Hicks[23] have indicated that with 0.004 to 0.015 *M* dibutyl phosphate in *n*-hexane and an aqueous phase containing 0.58 or 1.98 *M* HNO_3, the extraction coefficient varies as the third power of the concentration of free dibutyl phosphate. Studies by Burger[26] have indicated that appreciable dimerization of dibutyl phosphate might take place in the organic phase. The data of Table III were obtained in order to determine what dibutyl phosphate dependence was operative under the experimental conditions of this investigation. Since the total phosphoric acid molarity is the same for each solution, so also is the fraction of aqueous uranium that is uncomplexed. Under these conditions the slope of the log-log plot of the fourth *versus* the third column should be equal to the number of dibutyl phosphate molecules reacting with each uranyl ion in equation 19. The slope of the least-squares straight line drawn through these points is 1.99, *i.e.*, a value of 2 within experimental error. Hence these data indicate that equations 19 and 20 as written are the correct relations. (The values calculated for the third column of Table III were calculated on the assumption of two dibutyl phosphate groups per uranium atom in the extracted species.

TABLE III

THE DIBUTYL PHOSPHATE DEPENDENCE OF THE URANIUM EXTRACTION COEFFICIENT E AT 1.004 *M* TOTAL H_3PO_4

$V_{aq}/V_{org} = 1$, 0.510 *M* H^+

Initial (HD)	(U) at equilibrium	(HD) at equilibrium	E
0.0817	0.00733	0.0592	1.64
.0817	.00719	.0594	1.62
.1441	.01035	.1090	6.51
.192	.01682	.1399	8.29

However, the value of this assumed figure would influence the slope only slightly.) If the non-acidic impurity in the dibutyl phosphate were tributyl phosphate, the molarity of the latter would be 3% of the initial dibutyl phosphate molarity. Although the data of Table III provide support for the use of equations 19 and 20, it is possible that this small amount of tributyl phosphate might exert some synergistic influence on the extraction such as it has been found to do with di-(2-ethylhexyl)-phosphoric acid.[25] Of the data to be presented shortly in Table IV, the equilibration that would be affected the most by such an effect would be the one with a total phosphate molarity of 3.76, because the uranium loading in the organic phase would be the least in that equilibration. That equilibration was repeated in a separate experiment with the organic phase containing an amount of added Eastman tributyl phosphate equal to 3% of the dibutyl phosphate molarity. Thus this equilibration involved twice the tributyl phosphate concentration that those of Table IV might have. The extraction coefficient in this equilibration was 4% less than that of the otherwise identical one in Table IV. The difference probably was within experimental error and, in any event, no increased synergistic effect was observed. Hence, it is concluded that no such measurable effect is operative in the equilibrations presented in Table IV. The hydrogen-ion dependence as given in equations 19 and 20 receives approximate corroboration in the acid range 0.5 to 1.0 *M* H^+ of the present experiments from data obtained by Stewart and Hicks[23] with dibutyl phosphate dissolved in dibutyl ether.

TABLE IV

THE SOLVENT EXTRACTION OF URANIUM AT VARIOUS PHOSPHORIC ACID CONCENTRATIONS

H^+, *M*	Total phosphate, *M*	True $[H_3PO_4]$	(U)	E	V_{aq}/V_{org}	(HD) from eq. 21	$f/f_{.35}$ from eq. 22
0.510	0.3514	0.323	0.01035	8.70	1	0.0539	0.989
.510	.3514	.323	.01037	8.85	1	.0538	1.010
.510	.6024	.562	.00912	3.82	1	.0560	.402
.510	1.004	.947	.00733	1.64	1	.0592	.1546
.510	1.004	.947	.00719	1.62	1	.0594	.1516
.510	1.505	1.427	.00520	0.713	1.167	.0617	.0618
.510	2.545	2.427	.00247	.269	1	.0678	.01933
.510	2.545	2.427	.00228	.263	1	.0681	.01873
1.036	2.545	2.473	.00224	.240	1	.0684	.0699
1.036	2.545	2.473	.00220	.232	1	.0685	.0673
0.510	3.76	3.597	.000931	.0897	1	.0705	.00596

If one equilibrates V_{org} milliliters of organic phase containing originally a dibutyl phosphate molarity of $(HD)_{in}$ with V_{aq} milliliters of aqueous phase containing uranium, the following relation holds at equilibrium

$$(HD) = \frac{(HD)_{in} - 2(U)}{1 + \frac{1}{k_{HD}}\left(1 + \frac{k_a}{[H^+]}\right)\frac{V_{aq}}{V_{org}}} \quad (21)$$

where k_{HD}, the distribution coefficient for undissociated dibutyl phosphate, has been determined to be 8.0 ± 0.4, and k_a, the aqueous ionization constant for dibutyl phosphate, is estimated to be 0.031 by means of Wagner's data[22] and the Debye–Hückel equation. Equation 21 is used in all of the solvent-extraction equilibrations reported here for calculating the molarity of free dibutyl phosphate in the organic phase at equilibrium. The equation

$$\frac{f_i}{f_r} = \left(\frac{[H^+]_i}{[H^+]_r}\right)^2\left(\frac{(HD)_r}{(HD)_i}\right)^2\left(\frac{E_i}{E_r}\right) \quad (22)$$

relates the desired quantity f_i/f_r for an i-th solution to the uranium extraction coefficients, E_i and E_r, of the i-th solution and the r-th, or reference, solution, respectively. In the present application the reference solution is the average of the two at the lowest complexing agent concentration in Table IV. The r-th solution had as its principal uranium species the first complex, the stability of which was known from the spectrophotometric studies. Thus the r-th solution, in effect, represents the evaluation of k in equation 20. This experimental arrangement allowed all extraction coefficients to be within a factor of about 10 of unity in order to minimize errors due to imperfect phase separations, and it allowed (HD) of Table IV to be within 13% of a constant value in order to minimize errors due to any slight deviation from equation 19.

The solvent-extraction equilibrations were conducted in separatory funnels shaken at maximum pitch on a Burrell Model BB Wrist-Action Shaker. The temperature was 24.0 ± 0.5°. The shaking time was 1 hour, which was proven by tests to give complete equilibration. At the end of this period the separatory funnels were allowed to stand for one more hour in order to allow complete phase separation before the phases were analyzed. Observations under a strong light at this time showed the aqueous phase to be completely free of suspended material, but the organic phase sometimes had a fine mist of aqueous droplets in it. Tests indicated that although longer standing caused the mist to

(24) R. L. Moore, "Mechanism of Extraction of Uranium by Tributyl Phosphate," Atomic Energy Commission Report AECD-3196, June 11, 1951.

(25) K. B. Brown, *et al.*, "Narrative Status Report, Raw Materials Chemistry Section," Oak Ridge National Laboratory Report ORNL-2002, November 11, 1955.

(26) L. L. Burger, "Partition of Dibutyl Phosphate," General Electric Company Report HW-33682, November 8, 1954.

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disperse, the analyses of the two phases remained unchanged. The data have been summarized in Table IV. The initial concentration of uranium in the aqueous phase was 0.0115 M. The initial concentration of dibutyl phosphate in the organic phase was 0.0817 M. If the equilibrated phases were allowed to stand several hours before analysis, a pale yellow precipitate would form. The precipitate may have been the uranyl dibutyl phosphate salt, judging from solubility figures that have been given for it by Wagner.[22] However, the data of Table IV were obtained in the absence of any precipitate, and presumably they should be explainable within the scope of equilibria that have already been formulated. The uranium concentration in the aqueous phase was determined by analyzing an aliquot by the procedure of Schreyer and Baes,[27] using smaller quantities of reagents and applying an indicator correction. The uranium concentration in the organic phase was determined on a 20-ml. aliquot by diluting it fourfold with kerosene, re-extracting with three successive 20-ml. portions of 1:3 85% H_3PO_4, and then using the same analytical procedure. Experiments indicated that the re-extraction procedure was quantitative. The values of true $[H_3PO_4]$ given in Table IV were calculated from the values of total phosphate molarity as in the spectrophotometric studies. They are consistent within ±1% with the final constants for the complexes as summarized at the end of the paper.

The values of $f/f_{0.35}$ in the last column of Table IV have been plotted *versus* phosphate molarity in Fig. 2. The values $N = 2$, $n = 2$, $P = 3$, $p = 2$ have been assumed in calculating the results given in Table V, which includes cal-

TABLE V

CALCULATIONS OF k_2 AND k_3 FROM DATA AT 0.510 M H^+ BASED ON THE ASSUMPTION $N = 2$, $n = 2$, $P = 3$, $p = 2$

Point α		Point β			
True $[H_3PO_4]\alpha$	$\frac{f\alpha}{f_{0.35}}$	True $[H_3PO_4]\beta$	$\frac{f\beta}{f_{0.35}}$	k_2 from eq. 16	k_3 from eq. 17
0.562	0.402	1.427	0.0618	22.3	11.1
.562	.402	2.427	.01933	25.7	9.0
.562	.402	2.427	.01873	24.4	9.8
.562	.402	3.597	.00596	19.2	13.0
.947	.1531(av)	2.427	.01933	22.6	9.2
.947	.1531(av)	2.427	.01873	20.3	9.9
.947	.1531(av)	3.597	.00596	13.3	12.3
				$k_2 =$	$k_3 =$
				21.1 ± 3.8	10.6 ± 1.4

culations from all of the data at 0.510 M H^+. The standard deviations given for k_2 and k_3 at the bottom of the table indicate good consistency among the assumed values of $N = 2$, $P = 3$, and the experimental data. The same type of calculation has been repeated in Table VI, with the same

TABLE VI

CALCULATIONS OF k_2 AND k_3 WITH POINT α AT 0.510 M H^+ AND POINT β AT 1.036 M H^+ BASED ON THE ASSUMPTION $N = 2$, $n = 2$, $P = 3$, $p = 2$

Point α		Point β			
True $[H_3PO_4]\alpha$	$\frac{f\alpha}{f_{0.35}}$	True $[H_3PO_4]\beta$	$\frac{f\beta}{f_{0.35}}$	k_2 from eq. 16	k_3 from eq. 17
0.562	0.402	2.473	0.0699	24.8	9.6
.562	.402	2.473	.0673	23.2	10.6
.947	.1531(av)	2.473	.0699	21.3	9.6
.947	.1531(av)	2.473	.0673	18.7	10.5
				$k_2 =$	$k_3 =$
				22.0 ± 2.3	10.1 ± 0.5

assumptions but with point β at 1.036 M H^+. The results confirm that, in equations 1 and 2, $N = 2$, $n = 2$ for the second complex and $P = 3$, $p = 2$ for the third. In Tables V and VI all available combinations of points were used for α and β except those involving adjacent points, *i.e.*, those immediately to the left and right of one another in Fig. 2.

(27) J. M. Schreyer and C. F. Baes, Jr., "The Volumetric Determination of Uranium (VI) in Phosphate Solutions," Oak Ridge National Laboratory Report ORNL-1292, May 4, 1952; *Anal. Chem.*, **25**, 644 (1953).

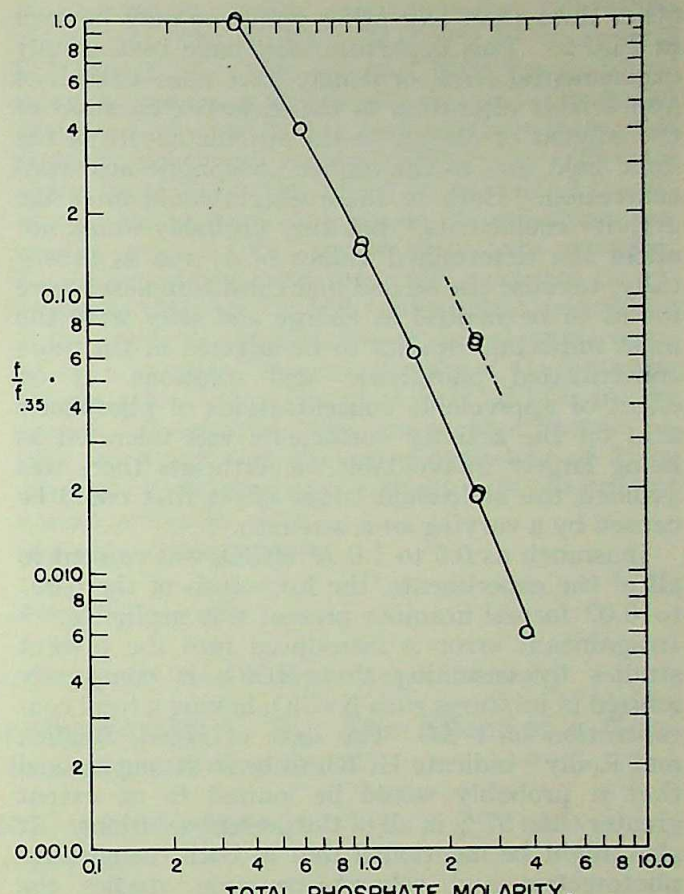

Fig. 2.—Values of $f/f_{0.35}$ *vs.* total phosphate molarity from Table IV and curves calculated from the three complex ion equilibria: solid curve, 0.510 M H^+; dotted curve, 1.036 M H^+.

Such combinations were omitted in order to keep the effect of experimental error to a minimum. The grand means of the results of Tables V and VI give $k_2 = 21.8 \pm 2.0$ and $k_3 = 10.2 \pm 0.5$ for these equilibria in equations 1 and 2. The curves that have been drawn in Fig. 2 have been calculated with the aid of these values.

Other assumed combinations of n and p fit the data much more poorly. An extension of the method of equations 16, 17 and 18 can be used to include a 1:4 uranyl phosphate complex. Since the value of k_4 thus found is 1 ± 2, it is concluded that no fourth complex is present.

Discussion

It is thought that nearly the best experimentally feasible conditions were obtained for the attainment of constancy of activity coefficients and concentration constants. Biedermann and Sillén have obtained evidence in $HClO_4$–$NaClO_4$ solutions of ionic strength 3 tending to indicate that the activity coefficients of cations remain constant from 0.0 M to at least 0.6 M $HClO_4$.[28] It has been assumed that a constancy of activity coefficients held for cations and neutral species in the present experiments. Appreciable concentrations of phosphoric acid had to be used in studying the uranyl phosphate complexes. The value of k_1 was determined entirely from points of 1 M H_3PO_4 or less. Most of the data used in calculating the values of k_2 and k_3 were obtained at phosphoric acid concentrations of 2.5 M or less. The one exception, the point at 3.76 M H_3PO_4, was used in less than 20% of these calculations. It departed more from the

(28) G. Biedermann and L. Sillén, *Arkiv Kemi*, **5**, 425 (1953); *C. A.* **47**, 10388 (1953).

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other data than any other point, as may be seen in Fig. 2. This departure may have been simply experimental error, or it may have been a result of appreciable alteration in the dielectric constant of the solvent or change in the specific nature of the ionic field due to the higher phosphoric acid concentration. Both of these effects could alter the activity coefficients,[29] but they probably would not affect the determined values of k_2 and k_3 drastically, because the second and third complexes were found to be neutral in charge and they were the most important species to be affected in the more concentrated phosphoric acid solutions. If an effect of appreciable concentrations of phosphoric acid on the activity coefficients was tolerated as being largely unavoidable, nevertheless there was avoided the additional larger effect that could be caused by a varying ionic strength.

Inasmuch as 0.5 to 1.0 M $HClO_4$ was present in all of the experiments, the hydrolysis of the 0.001 to 0.02 formal uranium present was negligible.[30,31] Insignificant error is introduced into the present studies by assuming that $HClO_4$ is completely ionized in mixtures with $NaClO_4$ having a total concentration of 1 M. The data of Hood, Redlich and Reilly[32] indicate $HClO_4$ to be so strong an acid that it probably would be ionized to an extent greater than 97% in all of the present solutions. It also might be mentioned that in both the spectrophotometric and solvent-extraction studies the acid liberated by the formation of the uranyl phosphate complexes was considered not to alter appreciably the hydrogen-ion concentration of the solution. The maximum variation in the hydrogen ion so liberated was 0.027 M in the spectrophotometric data that were used. However, the resultant effect was negligible in the calculations pertaining to the first complex. The maximum variation of the concentration of hydrogen ion liberated in the solvent-extraction experiments was only 0.006 M; the effect probably was less than experimental error.

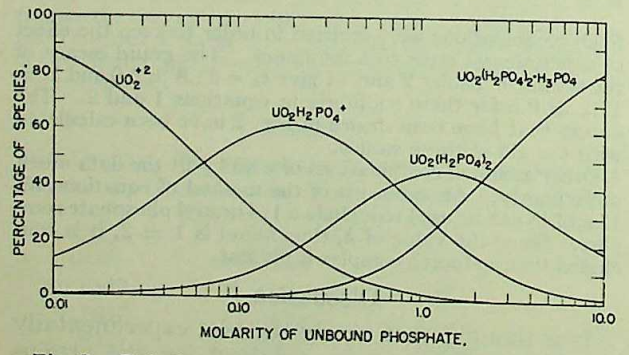
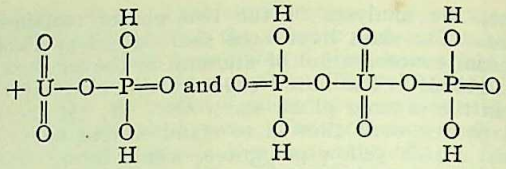


Fig. 3.—Relative amounts of species as a function of unbound phosphate concentration; 1.00 M H^+; μ = 1.06 to 1.07.

The structure of the first two complexes (exclusive of hydration) could be represented by



where the double bonds would be understood to have some ionic character. The third complex might owe its existence to hydrogen bonding as in one of the following structures or a combination of the two:

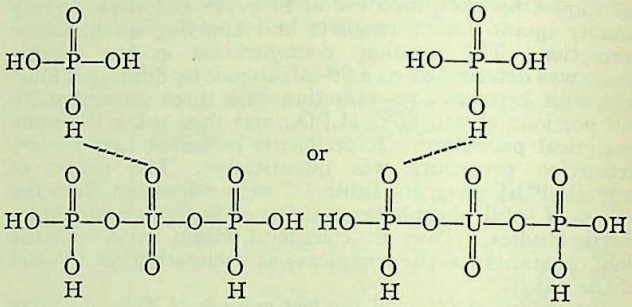


Figure 3 shows the percentage of each uranium species that is calculated from the above results to be present at any phosphoric acid concentration. It may be noted that the results recently obtained by Baes from spectrophotometric measurements in 1 M $HClO_4$ agree substantially with the above conclusions concerning the first and second complexes.[6] His formation quotient for the first complex would appear to be reliable, but the value for the second would be less so because the use of as much as 0.6 M H_3PO_4 would introduce appreciable amounts of a third complex, as may be seen from Fig. 3. His repetition of the spectrophotometric measurements with 0.1 M $HClO_4$–0.9 M $NaClO_4$ led him to consider the first complex to be a mixture of $UO_2H_2PO_4^+$ and $UO_2H_3PO_4^{++}$ and the second complex to be a mixture of $UO_2(H_2PO_4)_2$ and $UO_2(H_2PO_4)(H_3PO_4)^+$. Although the results of the present spectrophotometric study could have been interpreted in terms of the presence of a small amount of $UO_2H_3PO_4^{++}$ along with $UO_2H_2PO_4^+$, there was no statistical justification for doing so. It is thought that the solvent-extraction data at 2.545 M total phosphate, together with the other values in Table IV, provide striking evidence that the 1:2 and 1:3 uranyl phosphate complexes have the same charge as the uranium species that is extracted into the organic phase, *i.e.*, zero. Hence the species $UO_2(H_2PO_4)(H_3PO_4)^+$ must have been present to a much smaller extent than $UO_2(H_2PO_4)_2$ in the 0.5 to 1.0 M hydrogen-ion concentration of these experiments. It is evident that the conclusions based on the measurements of Baes in 0.1 M $HClO_4$–0.9 $NaClO_4$ might differ significantly from those of the present data in 0.5 M $HClO_4$–0.5 M $NaClO_4$, although there is good agreement at 1 M $HClO_4$. It is possible that the differences might have been caused by the existence of different activity coefficients in 0.5 and 0.9 M $NaClO_4$, even though the ionic strength was the same. The variation in activity coefficients from those in 1 M $HClO_4$ probably would be less in the present measurements than in Baes's spectrophotometric study. For example, this generalization would be

(29) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd edition, Reinhold Publ. Corp., New York, N. Y., 1950, pp. 397–401.
(30) S. Ahrland, *et al.*, *Acta Chem. Scand.*, **8**, 1907 (1954).
(31) J. Sutton, *J. Chem. Soc.*, S275 (1949).
(32) G. C. Hood, O. Redlich and C. A. Reilly, *J. Chem. Phys.*, **22**, No. 12, 2067 (1954).

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expected to hold for $\gamma_{\pm}$ of perchloric acid itself, judging from a study of activity coefficients in analogous 1 M chloride solutions.[33] Also, the corrections due to ionized phosphoric acid would be less at the higher acidity. Nevertheless an elucidation of the charges on the complex ions would require less accuracy from Baes's values for the formation constants.

The data of Schreyer and Baes on the solubility of uranyl phosphates in phosphoric acid[3,4,34] can be interpreted in terms of a 1:3 uranyl phosphate complex in addition to the lower complexes.[4,6] However, the interpretation of such data is futile whenever charged complexes are concerned unless a constant ionic strength is maintained. An interesting, possibly anomalous, phenomenon is the solubility behavior in phosphoric acid at 6.1 M H_3PO_4, the transition point between $UO_2HPO_4 \cdot 4H_2O$ and $UO_2(H_2PO_4)_2 \cdot 3H_2O$.[3,34] If a neutral 1:3 uranyl phosphate complex were the principal dissolved species at that point, the solubility would be expected to continue to increase there instead of sharply decreasing, as it actually does. The reversed solubility trend might be explained by assuming the average complex to be a polynuclear species, *e.g.*, a 3:5 uranyl phosphate complex. However, evidence confuting the existence of appreciable amounts of such polynuclear complexes at the uranium concentration of the present investigation is supplied by conformance of the uranium solutions to Beer's law at 3.7 M H_3PO_4 in the present investigation, the spectrophotometric results of Baes,[6] and the incompatibility of large amounts of polynuclear complexes with the present solvent-extraction data.

Los Alamos, New Mexico

(33) H. S. Harned, This Journal, **48**, 326 (1926).
(34) J. M. Schreyer and C. F. Baes, Jr., *ibid.*, **76**, 354 (1954).

[Communication No. 1893 from the Kodak Research Laboratories, Eastman Kodak Company]

The Mechanism of Dye Formation in Color Photography. V. The Effect of a Non-ionic Surfactant on the Ionization of Couplers[1]

By L. K. J. Tong and M. Carolyn Glesmann

Received April 2, 1957

The effect of a non-ionic surfactant on the apparent ionization constant of phenolic and naphtholic hydrogen has been measured by a photometric method. The data have been interpreted by assuming a different solubilization of the acid and salt forms of these compounds. The solubilization constants, defined as distribution coefficients between the micelle and the aqueous phase, were found to be very similar to the corresponding distribution coefficients between *n*-octanol and water. The solubilized salts appear to be completely dissociated.

The dyes in many color photographic systems are products of the oxidative condensation of a developing agent, usually N,N-disubstituted-*p*-phenylenediamines and a coupler, a compound with an active coupling site. In the Kodacolor and Kodak Ektacolor systems, water-insoluble couplers are incorporated in a highly dispersed organic phase, in the aqueous gelatin medium of the photographic emulsion; and the developing agent is supplied to the film from a high-*p*H-bath during processing. The couplers, on contact with the alkaline developer solution, form salts, which presumably are oriented in high concentration at the very large interface. This reaction is probably rapid and reversible; therefore, equilibrium is likely to be established before an appreciable fraction of the coupler reacts with the oxidized developer to form dye.

Dye formation may take place both in the organic phase and at the interface. The relative importance of both sites for color formation depends on many factors, and it was one of our primary objectives in this work to investigate these factors. In this paper and in the next (Part VI) emphasis is placed on the phenomena at the interface. Systems containing micelle-forming colloids are convenient for such studies because of their large surface-to-volume ratio. The colloid used for this investigation was Triton X-100. This material, supplied by Rohm and Haas, is the condensation product of diisobutylphenol and ethylene oxide. From its origin and molecular weight the following formula has been derived

in which n has an average of 9.5 units. This surfactant was chosen because its properties as a micelle-forming agent are well known from the investigations of Marsden, Gonick and McBain.[2]

The equilibria of the molecular species involved in dye formation and their distribution are discussed in the present paper, thus laying the foundation for a study of the dye formation in the subsequent communication.

II. Experimental Method and Treatment of Data

The behavior of couplers in the presence of Triton X-100 was studied by means of light absorption and *p*H measurements of coupler solutions containing different concentrations of this colloid. Most of the experiments were carried out with solutions of constant ionic strength (μ = 0.43 to 0.45) and constant potassium ion concentration (0.25 M). Therefore, in the following equations, the equilibrium constants are expressed in terms of concentrations, and are equal to the products of the thermodynamic constants and of the activity co-

(1) For Parts III and IV, see L. K. J. Tong and M. Carolyn Glesmann, This Journal, **79**, 583 (1957).
(2) (a) S. S. Marsden and J. W. McBain, *J. Phys. Chem.*, **52**, 110 (1948); (b) E. Gonick and J. W. McBain, This Journal, **69**, 334 (1947).

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efficients which are assumed to be constant. The concentrations of the substances in the micelles are defined as the amounts of substance solubilized divided by the volume of the micelles. This volume is assumed to be the volume of Triton X-100 added in making up the solution less the volume at the critical micelle concentration (CMC), since this amount of Triton does not contribute to the micelles.

In accordance with Reich's[3] argument, it is further assumed that the volume of the individual micelles is approximately independent of the Triton X-100 concentration; therefore, the total interface is also approximately proportional to the micellar volume, and the following conclusions are equally valid, whether solubilization takes place in the interior of the micelles or at their periphery (adsorption). Let

$(HC)_m$ = concn. of the coupler acid in the micellar region
$(HC)_a$ = concn. of the coupler acid in the aq. region
$(C^-)_m$ = concn. of the coupler ion in the micellar region
$(C^-)_a$ = concn. of the coupler ion in the aq. region

The coupler dissociates in the aqueous region, according to eq. 1

$$K_0 = \frac{(C^-)_a\, 10^{-p\mathrm{H}}}{(HC)_a} \qquad (1)$$

The distribution of substances by solubilization is assumed to be governed by laws analogous to those on which distribution between bulk phases depends. This principle has been discussed by McBain and Hutchinson.[4] We, therefore, set

$$\alpha = \frac{(HC)_m}{(HC)_a} \qquad (2a)$$

and

$$\beta = \frac{(C^-)_m}{(C^-)_a} \qquad (2b)$$

For constant (K^+), β should be constant whether the salt is solubilized as (1) dissociated ions with the counterions in the outer layer of the electrical double layer or (2) as ion-pairs in the inner layer. For variable (K^+), however, β should remain constant under situation 1, but should vary in proportion to (K^+) under situation 2. The results in Table V show that β is independent of (K^+), and, therefore, situation 1 is indicated.

Let $\overline{(C^-)}$ and $\overline{(HC)}$ be the over-all concentrations of the salt and acid, defining

$$\overline{(C^-)} = \frac{v_a(C^-)_a + v_m(C^-)_m}{v_a + v_m} \qquad (3)$$

$$\overline{(HC)} = \frac{v_a(HC)_a + v_m(HC)_m}{v_a + v_m} \qquad (4)$$

where v_a = volume of the aqueous region and v_m = volume of the micellar region. Let

$$V_m = \frac{v_m}{v_m + v_a} \qquad (5)$$

and

$$V_a = \frac{v_a}{v_m + v_a} \cong 1 \text{ since } v_m << v_a \qquad (6)$$

The eq. 2 to 6 lead to

$$\overline{(C^-)} = (C^-)_a(1 + \beta V_m) \qquad (7)$$

$$\overline{(HC)} = (HC)_a(1 + \alpha V_m) \qquad (8)$$

Let us define

$$K = \frac{\overline{(C^-)}\, 10^{-p\mathrm{H}}}{(HC)} \qquad (9)$$

Combining eq. 1, 7, 8 and 9, we have

$$\frac{K}{K_0} = \frac{(1 + \beta V_m)}{(1 + \alpha V_m)} \qquad (10)$$

For analytical purposes, eq. 10 can be rearranged into a more useful form

$$\left(1 - \frac{K}{K_0}\right)\frac{1}{V_m} = \alpha\frac{K}{K_0} - \beta \qquad (11)$$

By the use of eq. 11, α and β can be obtained graphically by plotting the left-hand side of the equation *vs.* K/K_0, the two constants α and β are equal to the slope and the negative intercept of the straight line, respectively.

Evaluation of K, as just defined, was made from photometric and pH measurements. The molar extinction coefficients for each of the molecular species, C^- or HC, may be different, depending on whether the respective species is present in the aqueous region or in the micellar region. Although changes in pH will shift the equilibrium between the molecular species, the distribution coefficient of each of the species between the two regions is assumed not affected. Therefore, as long as V_m is kept constant, it is only necessary to find a wave length where the molar extinction coefficients for the salt and acid forms are sufficiently different in order to measure the ratio $\overline{(C^-)}/\overline{(HC)}$.

To determine K, we set

$$K = \frac{(D - D_a)}{(D_b - D)}\, 10^{-p\mathrm{H}} \qquad (12)$$

where, at a given wave length and with a constant total coupler concentration, D_a is the optical density in an acid solution; D_b is the optical density in a strong basic solution; and D is the optical density in buffers at intermediate and known pH values.

III. Results and Discussion

The effect of colloids on dissociation constants of acid indicators has been studied in recent years by Hartley,[5] by Hartley and Roe,[6] by Krishnappa, Doss and Rao,[7] and by Hiskey and Downey.[8] All these investigators, however, used ionic colloids. This introduces complications owing to (1) superimposing the effect of complex formation between the indicator and molecularly dispersed colloids on that of solubilization by the micelles and (2) high zeta-potentials causing a large and uncertain concentration of H^+ near the surface of the micelle.[6] Krishnappa, Doss and Rao interpreted their data entirely on the basis of molecular complexes, confining their results to concentrations below the CMC, but, judging from their data, some of the concentrations reported may have exceeded that limit. In our work, complex formation between colloids and substrates would introduce additional complications in the interpretation of the coupling rate obtained in the presence of the col-

(3) I. Reich, *J. Phys. Chem.*, **60**, 257 (1956).
(4) M. E. L. McBain and E. Hutchinson, "Solubilization and Related Phenomena," Academic Press, Inc., New York, N. Y., 1955, p. 139.
(5) G. S. Hartley, *Trans. Faraday Soc.*, **30**, 444 (1934).
(6) G. S. Hartley and J. W. Roe, *ibid.*, **36**, 101 (1940).
(7) T. Krishnappa, K. S. Doss and B. S. Rao, *Proc. Indian Acad. Sci.*, **23**, 47 (1946).
(8) C. F. Hiskey and T. A. Downey, *J. Phys. Chem.*, **58**, 835 (1954).

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TABLE I

DEPENDENCE OF DENSITY OF α-NAPHTHOL SOLUTIONS ON *p*H

A. No Triton X-100 (K^+) = 0.25 *M*			B. 0.25% Triton X-100 (K^+) = 0.25 *M*			C. 1% Triton X-100 (K^+) = 1.00 *M*		
*p*H	D_{332}	*p*K	*p*H	D_{332}	*p*K	*p*H	D_{332}	*p*K
12	1.565		12	1.55		12	1.480	
6	0.028		6	0.093		6.5	0.113	
8.69	.357	9.26	9.51	.491	9.93	9.30	.206	10.44
8.89	.481	9.26	9.72	.661	9.92	9.68	.320	10.43
9.13	.709	9.23	9.90	.822	9.90	10.00	.490	10.42
9.19	.769	9.23	10.11	.995	9.90	10.27	.66	10.45
9.41	.942	9.24	10.29	1.120	9.90	10.61	.95	10.41
9.50	.99	9.28	10.42	1.208	9.94	11.13	1.276	10.36
9.72	1.151	9.29				11.34	1.365	10.30

loids. To minimize these complications, a non-ionic colloid, Triton X-100, was used.

A. Determination of *K*.—Table I shows three examples of α-naphthol measured in solution of different concentration of Triton X-100 as well as at different (K^+) values in order to illustrate the determination of *K* from photometric and *p*H measurements. For each set of determinations, the average error of *p*K calculated by eq. 12 is ± 0.02 unit for measurements within a *p*H range not greater than 0.5 unit from the average *p*K. In taking the average, more weight was given to the experiments at a *p*H very close to the *p*K of the coupler, because the accuracy of these data is the highest in this region. The average values of *p*K are listed in Table II. It is evident that *K* is practically independent of potassium ion concentration and ionic strength within the experimental range indicated.

TABLE II

VARIATION OF *p*K WITH TRITON X-100 CONCENTRATION

	(K^+) = 0.125 *M* Triton X-100 (vol. %)	*p*K	(K^+) = 0.25 *M* Triton X-100 (vol. %)	*p*K	(K^+) = 1.00 *M* Triton X-100 (vol. %)	*p*K
α-Naphthol	0	9.25	0	9.25	0	9.22
	0.15	9.77	0	9.26	0.20	9.94
	.20	9.88	0.15	9.73	1.0	10.44
	.30	9.98	.20	9.83	2.0	10.61
	.40	10.14	.25	9.93		
	1.00	10.42	.25	9.92		
			.40	10.10		
			.50	10.20		
			.50	10.11		
			1.00	10.42		
4-Cl-1-naphthol	0	8.69	0	8.64	0	8.61
	2.00	10.01	0	8.67	2.00	10.02
			0	8.70		
			0 Av.	8.67		
			0.0825	9.53		
			.0888	9.58		
			.100	9.59		
			.100	9.62		
			.100	9.58		
			.125	9.66		
			.125	9.67		
			.125	9.62		
			.150	9.71		
			.150	9.72		
			.200	9.77		
			.250	9.80		
			.300	9.78		
			.400	9.85		
			.500	9.81		
			.500	9.83		
6-Nitro-1-naphthol	0	8.53	0	8.47	0	8.44
	0.25	9.32	0.25	9.35	0.25	9.33
	.50	9.48	.50	9.49	.25	9.39
	1.00	9.62	2.00	9.63	.50	9.51
	2.00	9.64			1.00	9.59
					2.00	9.64
2,4-Dichloro-1-naphthol	0	7.13	0	7.13	0	6.98
	1.00	8.07	1.0	8.08	1.0	8.00
2-Butyramido-5-methylphenol			0	9.28		
			0.25	9.36		
			.30	9.34		
			.40	9.38		
			.50	9.42		
			.50	9.39		
			.75	9.49		
			1.00	9.52		
			1.50	9.62		
			2.00	9.68		
			3.00	9.77		
			5.00	9.88		
2-Benzamido-5-methylphenol			0.25	9.44		
			.50	9.63		
			.75	9.73		
			1.00	9.78		
			2.00	9.96		
(2-Disulfobenzamido)-5-methylphenol			0	9.23		
			0.50	9.34		
			0.75	9.38		
			1.00	9.41		
			1.50	9.48		
			2.00	9.55		
			3.00	9.63		
			5.00	9.74		
2-(2-Furamido)-5-methylphenol	0	8.97	0	8.94	0	8.92
	0.25	9.21	0.15	9.11	0.25	9.25
	1.00	9.54	.20	9.14	1.00	9.63
	2.00	9.71	.25	9.23	2.00	9.76
			.25	9.17		
			.30	9.24		
			.50	9.36		
			1.00	9.52		
			2.00	9.74		

B. Determination of the Distribution Constants for Acid, α and Ion β.—The constants α and β were obtained graphically according to eq. 11. Data for various couplers are plotted in Figs. 1 and 2. Apparently, they are satisfactorily repre-

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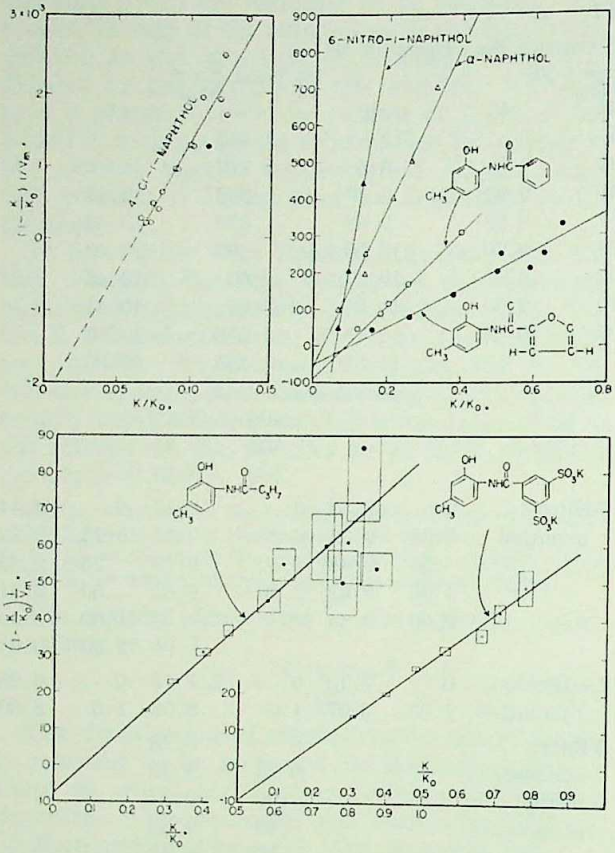

Figs. 1 and 2.—Graphical determination of the distribution constants α and β, according to equation 11.

sented by straight lines as required by the equation. It should be pointed out that accuracy is low at low V_m and/or high K/K_0. At low V_m, the uncertainty is caused mainly by the error inherent in obtaining a small difference from two relatively large quantities, one of them being the CMC of Triton X-100, 0.054 volume %.[9,10]

At high ratios of K/K_0, the factor $(1 - K/K_0)$ becomes uncertain. In Fig. 2, the rectangles represent the magnitude of error caused by ± 0.02 unit in pK (curve on the left) and ±0.01 unit in pK (curve on the right). The lines were drawn within these limits.

C. Distribution of Couplers between *n*-Octanol and Aqueous Buffers.—In this treatment, α and β were postulated as distribution constants of the acid and salt, respectively, between the micellar and the aqueous regions. Comparison of these constants with the distribution constants in organic solvents having properties similar to those of Triton may show the nature of solubilization. The couplers were distributed between the *n*-octanol and aqueous buffers, and the distribution constants, ϕ_{HC}, for the coupler acid are listed in Table III.

Unfortunately, accurate distribution constants of the salts ϕ_{C^-} could not be obtained for most of the couplers for the following reason. In order to determine the distribution constants, the total coupler concentration in each phase is measured and the distribution ratio, R, is expressed as

$$R = \frac{(HC)_S + (C^-)_S}{(HC)_a + (C^-)_a}$$

where the subscripts S and a indicate organic solvent or aqueous phase, respectively. At high pH, $(HC)_a$ can be neglected in comparison with $(C^-)_a$ and the expression becomes

$$R = \frac{(H^+)\phi_{HC}}{K_0} + \phi_{C^-} \qquad (13)$$

Since ϕ_{C^-} is calculated from eq. 13 as a difference between two experimentally determined quantities, its error will be large if its magnitude is relatively small.

TABLE III

DISTRIBUTION OF COUPLERS BETWEEN *n*-OCTYL ALCOHOL AND pH 6.5 BUFFER

Coupler	V_{aq}, cc.	V_{alc}, cc.	(Coupler)aq, $M \times 10^4$	(Coupler)alc, $M \times 10^4$	$\phi_{HC} \times 10^{-3}$
α-Naphthol	250	25	0.556	690	1.24
	250	25	.270	330	1.22
4-Cl-1-naphthol	250	25	.0445	564	12.7
	250	25	.0224	276	12.3
2,4-Dichloro-1-naphthol	500	50	.033	1880	57
6-Nitro-1-naphthol	250	25	.26	845	3.25
	250	25	.139	412	2.97
2-(2-Furamido)-5-methylphenol	500	10	.053	36.9	0.69
2-Butyramido-5-methylphenol	300	10	.112	19.7	.18
2-Benzamido-5-methylphenol	500	10	.254	29.8	1.2
2-(3,5-Disulfobenzamido)-5-methylphenol	25	100	2.0	Est. .04	< .00002

Preliminary experiments indicated that, for most couplers, $R \cong \phi_{HC}(H^+)/K_0$. Table IV shows the distribution of 2,4-dichloro-1-naphthol be-

TABLE IV

DISTRIBUTION OF 2,4-DICHLORO-1-NAPHTHOL BETWEEN *n*-OCTYL ALCOHOL AND pH 12 BUFFER, (K^+) VARIED

V_{alc} = 50 ml., V_{aq} = 150 ml.

	Coupler initially in alcohol phase			Coupler initially in aqueous phase		
(K^+), M	(Coupler)aq, $M \times 10^4$	(Coupler)alc, $M \times 10^4$	R	(Coupler)aq, $M \times 10^4$	(Coupler)alc, $M \times 10^4$	R
0.125	2.20	8.4	3.82	1.62	6.36	3.93
.25	1.49	10.5	7.05	1.12	7.86	7.02
.50	0.913	12.3	13.5	0.692	9.15	13.2
1.00	.537	13.4	25.0	.409	9.99	24.4

tween *n*-octanol and a strongly alkaline solution. The value of R was found to depend upon the (K^+) and the data can be represented by $R = 0.8 + 25(K^+)_a$. The last term of this expression, ϕ_{C^-}, is proportional to (K^+) because both ions of the salt are extracted together into the bulk organic phase; therefore, $(K^+C^-)_S/(K^+)_a(C^-)_a = 25$. The value 0.8 in the equation agrees with the calculated value of the first term on the right-hand side of eq. 13.

(9) S. S. Marsden and J. W. McBain, *J. Phys. Chem.*, **52**, 110 (1948).
(10) E. Gonick and J. W. McBain, THIS JOURNAL, **69**, 334 (1947).

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D. Comparison of the Micellar Distribution Constants α, β and the Bulk Distribution Constants ϕ_{HC}.—The constants α, β and ϕ_{HC} are summarized in Table V. The data show that the constants α and β or the ratio β/α for a given coupler do not vary over an eightfold change of (K^+), but Table IV shows that ϕ_{C^-} is directly proportional to (K^+). This is taken to mean that, in the presence of Triton, the salt is solubilized as dissociated ions (in contrast to ion-pairs) with the counterions in the double layer. The (K^+) in the double layer is proportional to that in the bulk of the aqueous phase, and in solutions of high buffer salt concentration they are nearly equal. Therefore, the effect of (K^+) variation on the activity of the salt in the two regions is also nearly equal. The solubilization of the salts may be regarded as the formation of mixed micelles with the coupler ions hydrated at the surface.

TABLE V

SUMMARY OF CONSTANTS α, β AND ϕ_{HC}

$(K^+) = 0.25\ M$, $\mu = 0.43$–0.45, unless otherwise noted

Couplers	$\alpha \times 10^{-3}$	$\beta \times 10^{-3}$	$\phi_{HC} \times 10^{-3}$	β/α	$\frac{\phi_{HC}}{\alpha}$
α-Naphthol	2.2	0.06	1.2	0.027	0.55
	2.4[a]	.06[a]			
	2.5[b]	.05[b]			
4-Cl-1-naphthol	37.0	2.4	12.0	0.065	.32
				.048[a]	
				.039[b]	
2,4-Dichloro-1-naphthol			57.0	.13	..
				.13[a]	
				.10[b]	
6-Nitro-1-naphthol	6.2	0.38	3.0	.061	.48
	4.5[a]	.30[a]			
	6.0[b]	.35[b]			
2-(2-Furamido)-5-methylphenol	0.50	.05	0.69	.10	1.4
	.48[a]	.04[a]			
	.68[b]	.05[b]			
2-Butyramido-5-methylphenol	.095	.008	0.18	.08	1.9
2-Benzamido-5-methylphenol	1.0	.09	1.2	.09	1.2
2-(3,5-Disulfobenzamido)-5-methylphenol	0.070	.009	$<2 \times 10^{-5}$	.13	$<3 \times 10^{-4}$

[a] $(K^+) = 0.125\ M$. [b] $(K^+) = 1.00\ M$.

All the couplers, with the exception of 2-(3,5-disulfobenzamido)-5-methylphenol, have values of ϕ_{HC} very nearly equal to their α values, as shown by the α/ϕ_{HC} ratios given in the last column of Table V. The similarity holds over a wide range of values of either term. One may surmise from these data that the solubilized non-ionized acids are located in the interior of the micelles where the environment is similar to the bulk of the octanol. The disulfo compound, however, exhibits a very small ϕ_{HC}/α. This may be explained by a large free energy of hydration of the ionized sulfonate groups, which inhibits extraction into the interior of the alcohol, but does not inhibit solubilization where the hydrated ions may be oriented at the surface of the micelle.

As pointed out by Hiskey and Downey,[8] the shift in the apparent pK can be interpreted equally well by either solubilization or complex formation. In the experiments described by Hiskey and Downey, the complex was isolated, and, in the experiments of Krishnappa, Doss and Rao,[7] the surfactant concentrations were low, probably below the CMC. Therefore, the results of both investigations were justifiably interpreted with complex formation. In our case, however, the concept of differential solubilization is preferable because a non-ionic colloid is used at concentrations above the CMC. As further evidence of the similarity of the two interpretations, it is noteworthy that the equation derived by Krishnappa, Doss and Rao expressing the change in pH as the same form as eq. 10 expressing the change in pK.

IV. Experimental

A. Ionization.—Solutions of the couplers in Triton and phosphate buffer ranged in concentration from 10^{-4} to $7.5 \times 10^{-4}\ M$. Solutions with a $(K^+) = 0.25\ M$ and lower were prepared by mixing and diluting stock solutions of 0.0833 M potassium phosphate (tribasic) containing Triton and 0.25 M potassium phosphate (monobasic) containing Triton. Solutions with $(K^+) = 1.0\ M$ were prepared by adding potassium chloride to the same stock solutions.

The densities of the solutions were measured in a Beckman model DU spectrophotometer in the region between 300 and 350 mμ, with the exception of 6-nitro-1-naphthol solutions, which were measured at 520 mμ. The pH of the solutions was measured with a Beckman Model G pH meter. The solutions were kept in a thermostat at 25° and the absorption cell was surrounded by a jacket through which 25° water was circulated.

B. Distribution.—To obtain ϕ_{HC}, the couplers were distributed between n-octyl alcohol and pH 6.5 phosphate buffer, with (K^+) equal to 0.25 M and ionic strength equal to 0.375. With α-naphthol, 4-chloro-1-naphthol and 6-nitro-1-naphthol, weighed amounts of the coupler were dissolved in n-octyl alcohol and shaken with the buffer. After clarification by centrifuging, the coupler in the aqueous solution was analyzed by measuring the density of the butyl acetate extract of the dyes formed by coupling with excess 4-amino-2-methyl-N-diethylaniline at pH 8. The distributions were measured at two different coupler concentrations.

The phenolic-type couplers were first dissolved in the aqueous pH 6.5 buffer and then shaken with the alcohol. The coupler in the aqueous phase was analyzed before and after distribution by the procedure just described.

The 2-(3,5-disulfobenzamido)-5-methylphenol showed an apparent increase in coupler concentration in the aqueous phase after distribution, which was attributed to the extraction of water into the alcohol. A maximum value for the distribution coefficient was estimated after correction for volume change.

Experimental details of the distribution of the acid form of the couplers appear in Table III.

The distribution of 2,4-dichloro-1-naphthol salt (pH 12) was found to be dependent on the potassium ion concentration. In this experiment, a weighed amount of the coupler was dissolved in $^1/_{12}\ M$ potassium phosphate (tribasic). After the solution of potassium phosphate (tribasic) was diluted with water or mixed with KCl solution to give the desired (K^+), it was shaken with n-octyl alcohol. The coupler in the aqueous phase, after distribution, was analyzed by measuring the optical density of the butyl acetate extract of the dye formed by coupling with excess 4-amino-N-diethylaniline at pH 6.5. The distributions at each level of (K^+) were repeated with the coupler initially in the alcohol phase. For details, see Table IV.

C. Materials.—**Inorganic salts** used in preparing the buffers were reagent grade K_3PO_4, KH_2PO_4 and KCl.

The ***n*-octyl alcohol** used in the distribution experiments was Eastman White Label Grade.

The ***n*-butyl acetate** was Eastman Special Grade.

Triton X-100 was purchased from Rohm and Haas Company. The molecular weight and composition of this material have been determined and found to be in reasonable agreement with the information furnished by the manufacturer.

The **α-naphthol** was Eastman White Label Grade, further purified by sublimation, followed by recrystallization from cyclohexane, m.p. 97–98°.

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The **2,4-dichloro-1-naphthol** was Eastman White Label Grade, recrystallized from methanol; m.p. 106–107°.

The **6-nitro-1-naphthol**, m.p. 178–180°, was prepared and purified in accordance with the procedure of Hodgson and Turner.[11]

The **4-chloro-1-naphthol**, m.p. 119–120°, was prepared by the method of Kast.[12]

The following compounds were prepared by C. R. Barr, of these Laboratories, using as starting materials commercially available Eastman White Label Grade chemicals. The final products are all crystalline and in acid form except 2-(3,5-disulfobenzamido)-5-methylphenol, which is a dipotassium salt.

2-Benzamido-5-methylphenol.—To a solution of 12.3 g. (0.1 mole) of 2-amino-5-methylphenol[13] and 26 g. (0.2 mole) of quinoline in 150 ml. of dioxane was added, with stirring, at 25°, 15.5 g. (0.1 mole) of benzoyl chloride in 30 ml. of dioxane. The temperature rose rapidly to 40°. The reaction mixture was stirred at room temperature for one hour and then was poured into two liters of 5% hydrochloric acid. The solid product was collected by filtration, dried and recrystallized from ten parts of toluene, giving 15 g. (68%); m.p. 168–169°. *Anal.* Calcd. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.7; N, 6.2. Found: C, 74.3; H, 5.8; N, 6.4.

2-Butyramido-5-methylphenol.—Prepared as described in the preceding section, this material (10 g., 52%) melted at 114–115° after crystallization from ligroin. *Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8; N, 7.3. Found: C, 68.8; H, 7.9; N, 7.4.

2-(2-Furamido)-5-methylphenol.—Prepared similarly to the preceding compound, this material gave a yield of 10 g. (46%); m.p. 167–168°. *Anal.* Calcd. for $C_{12}H_{11}NO_3$: C, 66.4; H, 5.1; N, 6.5. Found: C, 66.8; H, 5.4; N, 6.6.

2-(3,5-Disulfobenzamido)-5-methylphenol Potassium Salt.—To a solution of 18.5 g. (0.15 mole) of 2-amino-5-methylphenol and 15 g. (0.18 mole) of sodium acetate in 300 ml. of 90% acetic acid, 50 g. (0.15 mole) of 3,5-dichlorosulfonylbenzoyl chloride was added, with stirring, at 30°. The temperature rose rapidly to 37°. The reaction mixture was stirred at room temperature for 5 hr. and diluted with 300 ml. of water. The solid was collected, dried and recrystallized from 26 parts of xylene, giving 44 g. (70%) of **2-(3,5-dichlorosulfonylbenzamido)-5-methylphenol**, melting at 173–174°. *Anal.* Calcd. for $C_{14}H_{11}Cl_2NO_6S_2$: N, 3.3. Found: N, 3.2.

To a refluxing solution of 28 g. (0.066 mole) of the dichlorosulfonyl compound in 140 ml. of methyl alcohol, 100 ml. of water was added. The resultant clear solution was heated at reflux for one-half hour and then concentrated to dryness under reduced pressure. The residue was dissolved in 80 ml. of water, and a solution of 13.8 g. (0.066 mole) of barium chloride in 40 ml. of water was added. The mixture was left standing at room temperature overnight, **the barium salt of 2-(3,5-disulfobenzamido)-5-methylphenol** separating in the form of fine, white needles; yield 20 g. (58%). *Anal.* Calcd. for $C_{14}H_{11}NO_8S_2Ba$: C, 32.2; H, 2.1; N, 2.7. Found: C, 32.4; H, 2.5; N, 2.6.

The barium salt (19.9 g., 0.038 mole) was dissolved in 150 ml. of hot water and converted to the potassium salt by the addition of 6.6 g. (0.038 mole) of potassium sulfate in 50 ml. of water. The barium sulfate was collected, and the filtrate was concentrated under reduced pressure. The residue was washed with 50 ml. of methyl alcohol and dried. Crystallization from 30 parts of glacial acetic acid gave 12 g. (68%) of the **dipotassium salt of 2-(3,5-disulfobenzamido)-5-methylphenol**. *Anal.* Calcd. for $C_{14}H_{11}NO_8S_2K_2$: C, 36.3; H, 2.4; N, 3.0. Found: C, 36.1; H, 2.7; N, 2.8.

ROCHESTER, NEW YORK

(11) H. Hodgson and H. Turner, *J. Chem. Soc.*, 9 (1944).

(12) H. Kast, *Ber.*, **44**, 1337 (1911).

(13) M. C. Sannie and M. H. Lapin, *Bull. soc. chim. France*, 322 (1950).

[COMMUNICATION NO. 1894 FROM THE KODAK RESEARCH LABORATORIES, EASTMAN KODAK COMPANY]

The Mechanism of Dye Formation in Color Photography. VI. The Effect of a Non-ionic Surfactant on the Rate of Coupling

BY L. K. J. TONG AND M. CAROLYN GLESMANN

RECEIVED APRIL 2, 1957

The kinetics of coupling in the presence of a non-ionic surfactant between phenols (and naphthols) and quinonediimines formed by oxidation of disubstituted-*p*-phenylenediamine have been resolved in terms of simultaneous reactions in the micellar and in the aqueous regions. Both reactions involve the ionized form of the coupler exclusively. A method has been devised for calculating the amount of the reaction in each region.

Introduction

In the preceding paper,[1] the distribution constants α and β were calculated for both the acid and the salt forms of the couplers between aqueous and micellar regions in colloid solutions. The effect of this partition on the rate of coupling with the oxidized developing agent will be discussed in the present paper. The data are interpreted on the assumption that (1) simultaneous and independent reactions occur in the micellar and in the aqueous regions, and (2) the rate in each region is proportional to the product of reactant concentrations determined from the constants α and β.

The symbols have the same meaning as those in Part V of this series.

Since the quinonediimine T^+ is predominantly an hydrophilic cation, it is not solubilized to any great extent in the interior of the micelle; but if the electrical double layer is regarded as part of the micelle, then we can write

$$\gamma = \frac{(T^+)_m}{(T^+)_a} \qquad (1)$$

and

$$(\overline{T^+}) = (1 + \gamma V_m)(T^+)_a \qquad (2)$$

Since the addition of Triton will not, however, remove more than a very small fraction of T^+ from the aqueous region, we can set $(\overline{T^+}) \doteq (T^+)_a$. This assumption is justified by the absence of a measurable influence of Triton X-100 on the rate of deamination of T^+ (see under Results and Discussion).

The coupling rates were measured for the overall solution and the rate constants were therefore calculated in terms of the total concentrations

$$\frac{d(\overline{dye})}{dt} = k[(\overline{C^-}) + (\overline{HC})](\overline{T^+}) \qquad (3)$$

(1) For Part V, see L. K. J. Tong and M. Carolyn Glesmann, THIS JOURNAL, **79**, 4305 (1957).

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To resolve the observed rate into its components, we assume

$$(v_m + v_a)\frac{d(\overline{dye})}{dt} = v_a k_a (T^+)_a (C^-)_a + v_m k_{1,m} (T^+)_m (C^-)_m + v_m k_{2,m} (T^+)_m (HC)_m \quad (4)$$

The terms on the right-hand side of equation 4 express, respectively, the coupling rate of: (1) the coupler ion in the aqueous region, (2) the coupler ion in the micellar region, and (3) the non-ionized coupler acid in the micellar region. The term expressing the coupling rate of the coupler acid in the aqueous phase has been omitted from the equation because from the earlier work[2] it is known to be negligible.

Equation 4 holds equally well whether the reaction takes place in the interior or at the surface of the micelle; for, as long as the size of individual micelles remains constant, the extents of the two regions are proportional to each other. Combining equations 1 to 4 with those in Part V, we have

$$k[1 + 10^{(pK - pH)}] = \frac{k_a + k_{1,m}\gamma\beta V_m}{(1 + \beta V_m)} + \frac{k_{2,m}\gamma\alpha V_m(\overline{HC})}{(1 + \alpha V_m)(\overline{C^-})} \quad (5)$$

If, for a given V_m, the second term on the right of equation 5 is zero, the product, $k[1 + 10^{pK - pH}]$, will be independent of pH and will be the specific rate constant based on the total coupler ion concentration. Conversely, if the variation of k with pH can be predicted on the basis of $(\overline{C^-})$ alone, then the second term on the right of equation 5 and also the final term of equation 4 are negligible.

The fractional part of the reaction which takes place in each region can be calculated more conveniently from equation 6, which can be obtained from the earlier equations.

$$k\left[\left(\frac{\alpha(H^+)}{K_0} + \beta\right)V_m\right] = k_a + \left[k_{1,m}\beta + k_{2,m}\frac{\alpha(H^+)}{K_0}\right]\gamma V_m \quad (6)$$

using 10^{-pH} as (H^+).

Experimental

Coupling rates were determined by steady-state flow methods, either using direct analysis of the end product or comparison with a competing reaction of known kinetics, as described previously.[2] Unless otherwise stated, the method used in the present experiments is the "continuous method," in which the extent of the reaction is measured by the optical density of the dye solution as it passes through the absorption cell at the end of the flow system. All reactions were carried out at 25°.

The solutions were made up as described[2] except that Triton X-100 was added to the alkaline coupler solution. Therefore, the reaction mixtures have, as before, the ionic strength $\mu = 0.375$ M, and $(K^+) = 0.19$ to 0.25 M.

The molar extinction coefficients of the dyes involving 4-chloro-1-naphthol were obtained from solutions of the purified dyes. In the case of 2-(disulfobenzamido)-5-methylphenol, the molar extinction coefficient of the dye was obtained from the product of the coupling reaction with excess coupler.

All dye solutions containing Triton X-100 were found to obey Beer's law within the dye-concentration range of the experiments. The molar extinction coefficients were independent of the Triton X-100 concentration. The solutions of 2-(disulfobenzamido)-5-methylphenol dye in the absence of Triton X-100 did not obey Beer's law. In this case, the dye concentrations in the reaction mixtures were obtained from empirical calibration curves, using solutions of the same pH and ionic strength.

Materials.—The developing agents and couplers used in these experiments were prepared and purified as described in earlier papers of this series. The 4-amino-N,N-diethyl-3-methylaniline hydrochloride[3] is the same sample used in Part III of this series.[2] The 4-amino-3-methyl-N-ethyl-N-(β-methylsulfonamidoethyl)-aniline sulfate[4] is the same sample as in Part III of this series. The 4-chloro-1-naphthol is the same sample as in Part V of this series, m.p. 119–120°.[5] The 2-(3,5-disulfobenzamido)-5-methylphenol (dipotassium salt) is the same sample as in Part V of this series.

Results and Discussion

The addition of Triton X-100 does not alter the characteristics of the coupling reactions. Second-order rate plots produced in most cases smooth curves with constant slopes which could be extrapolated through the origin. Second-order rate constants k were calculated according to equation 3, using the total concentrations of the coupler and quinonediimine. Table IA shows that k is

TABLE I

COUPLING RATE BETWEEN 4-CHLORO-1-NAPHTHOL AND 3-METHYL-4-AMINO-N,N-DIETHYLANILINE

A. pH 11.03 ± 0.02; initial concn. of reactants varied

0.25% Triton X-100	3-Methyl-4-amino-N,N-diethylaniline $(A)_0 \times 10^4$, M	Ferricyanide 2 $(B)_0 \times 10^4$, M	4-Chloro-1-naphthol $(C)_0 \times 10^4$, M	$k \times 10^{-4}$, M l./mole sec.
	2.50	5.00	2.50	9.72
	2.50	2.50	2.50	9.57
	1.25	1.25	2.50	9.22
	5.00	2.50	2.50	9.71
	5.00	5.00	2.50	9.16
	10.00	2.50	2.50	9.50
	2.50	2.50	5.00	9.40
	2.50	2.50	1.25	8.75
			Av.	9.38 ± 0.22
2.0% Triton X-100	2.50	2.50	2.50	5.0
	5.00	5.00	2.50	5.0
	5.00	5.00	5.00	5.1

B. Initial concn. of reactants constant

$(A)_0 = 2.5 \times 10^{-4}$ M, $(B)_0 = 2.5 \times 10^{-4}$ M, $(C)_0 = 2.5 \times 10^{-4}$ M, Triton X-100 varied

Triton X-100 (vol. %)	$k \times 10^{-4}$ (l./mole sec.) pH 11.13	pH 8.71
0.15	10.4	0.99
.20	9.8	.85
.25	9.4	..
.30	8.6	.68
.40	7.5	.57
.50	7.0	.55
1.00	6.0	.43
1.50	5.4	.40
2.00	5.2	..
2.50	..	.41

(2) L. K. J. Tong and M. Carolyn Glesmann, (Part III), THIS JOURNAL, **79**, 583 (1957).

(3) (a) J. E. Lu Valle, D. B. Glass and A. Weissberger, *ibid.*, **70**, 2223 (1948); (b) R. L. Bent, J. C. Dessloch, F. C. Duennebier, D. W Fassett, D. B. Glass, T. H. James, D. B. Julian, W. R. Ruby, J. M. Snell, J. H. Sterner, J. R. Thirtle, P. W. Vittum and A. Weissberger, *ibid.*, **73**, 3100 (1951).

(4) A. Weissberger, Eastman Kodak Co., U. S. Patent 2,193,015 (1940).

(5) H. Kast, *Ber.*, **44**, 1897 (1911).

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unaffected by variation of the initial concentration of the reactants, by excess ferricyanide, $(B)_0 > (A)_0$, or by excess developing agent, $(A)_0 > (B)_0$. The last two facts have been pointed out in an earlier paper as evidence against mechanisms involving semiquinone in the rate expression. The independence of k on $(C)_0$ indicates that the rate of diffusion of quinonediimine to the micelle is not a controlling factor.

At constant Triton X-100 concentration, the rate constants k are proportional to the over-all degree of ionization calculated from K (see Table II, Part V). In Fig. 1, k was calculated as a function

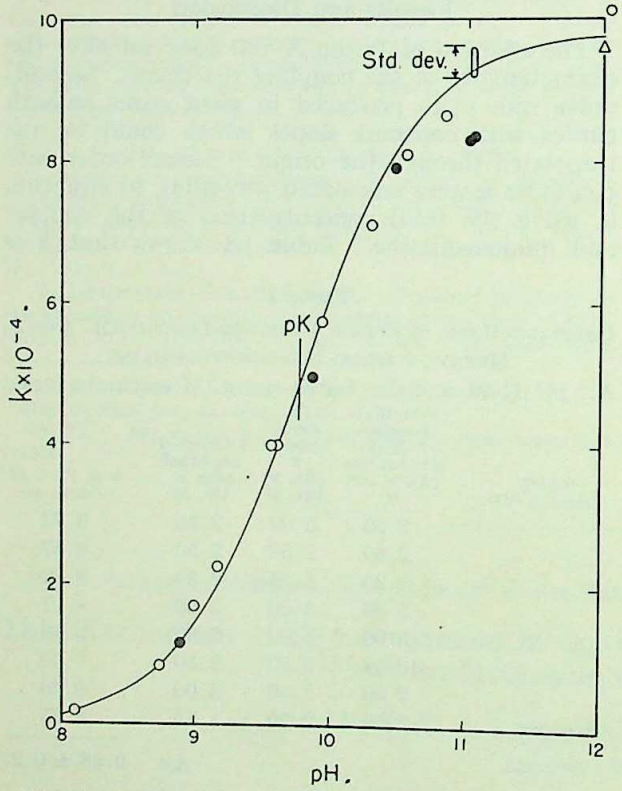
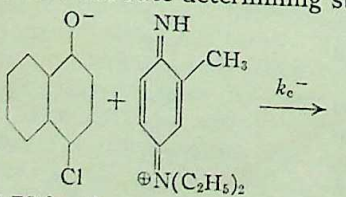


Fig. 1.—Rate of coupling between 4-chloro-1-naphthol and 3-methyl-4-amino-N,N-diethylaniline; Triton X-100 concentration = 0.25 (vol. %); curve calcd; experimental methods: O, continuous; △, competitive; ●, chemical stop.

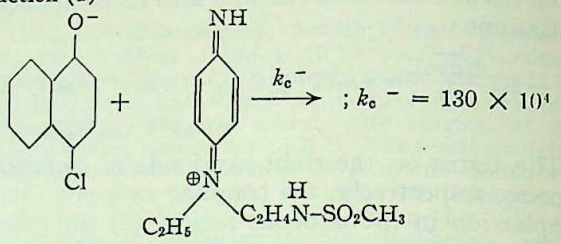
of pH for the reaction between 4-chloro-1-naphthol and 3-methyl-4-amino-N,N-diethylaniline, it being assumed that the rate-determining step is



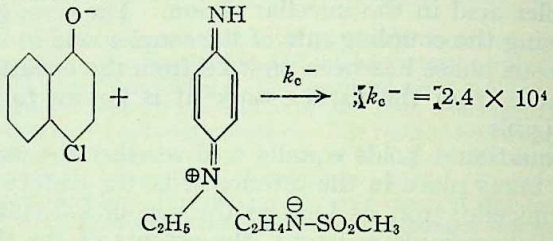
with $pK = 9.78$ for the coupler, and $k_c^- = 9.80 \times 10^4$, the specific rate constant of the ion. In Fig. 2, the rates for the reaction between 4-chloro-1-naphthol and 4-amino-3-methyl-N-ethyl-N-(β-methylsulfoamidoethyl)-aniline have been resolved into the rates of the two reactions: one involving the cation and the other involving the zwitterion of the quinonediimine in the rate-determining step.

In the experimental range of pH, reaction 1 is predominant; the sharp peak in Fig. 2 is due to the

Reaction (1)



Reaction (2)



fact that the pK of the coupler (9.78) is very near the pK of the quinonediimine (9.56).[6]

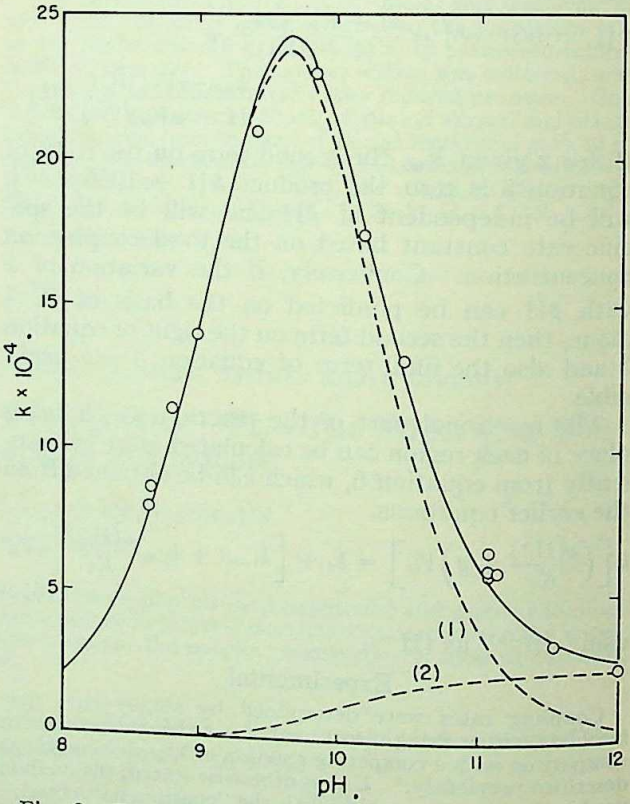
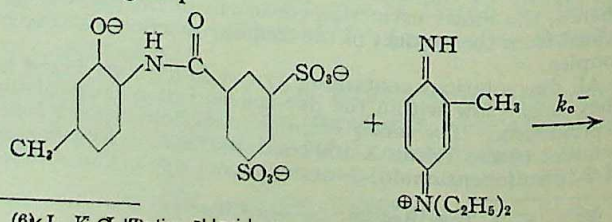


Fig. 2.—Rate of coupling between 4-chloro-1-naphthol and 4-amino-3-methyl-N-ethyl-N-(β-methylsulfoamidoethyl)-aniline. Triton X-100 concentration = 0.25%. Curve 1, coupler ion and the quinonediimine cation; curve 2, coupler ion and the quinonediimine zwitterion; continuous curve, curve 1 + curve 2.

In Fig. 3, log k was plotted *vs.* pH, and the curves were calculated for the reaction having the rate-determining step



(6) J. K. Cohen, *J. Phys. Chem.*, **58**, 1090 (1954).

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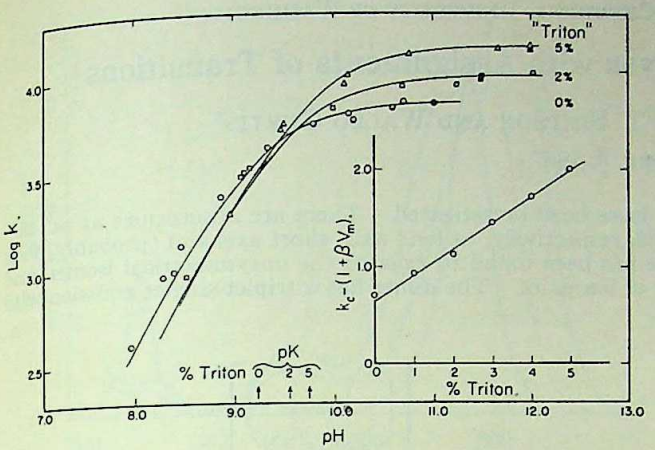

Fig. 3.—Rate of coupling between 5-methyl-2-(3,5-disulfobenzamido)-phenol and 3-methyl-4-amino-N,N-diethylaniline. Triton X-100 concentrations are indicated.

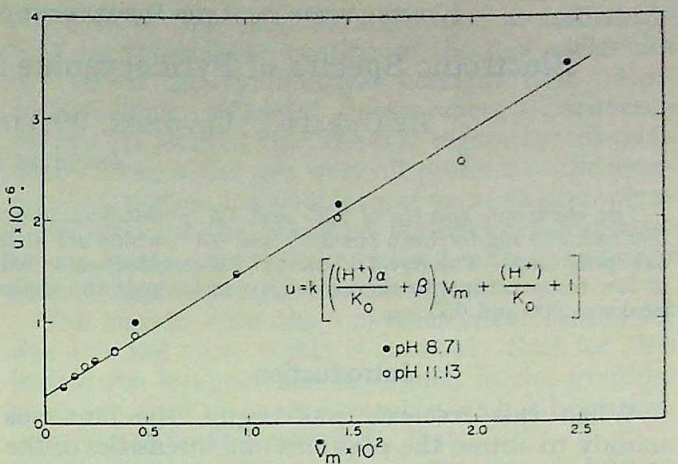

Fig. 4.—Effect of Triton X-100 on coupling rate between 4-chloro-1-naphthol and 3-methyl-4-amino-N,N-diethylaniline u (defined in figure) *vs.* V_m.

The values of log k_c^- (horizontal asymptotes) increase with Triton concentration, as shown.

The experimental points in Figs. 1 and 2 are in agreement with the calculated lines, within the accuracy of the *p*H measurements. In Fig. 3, the errors are slightly higher than can be expected from the error in *p*H. In the low *p*H region, however, the curves seem to deviate by a constant value in the log k scale. They show no tendency to approach a constant value of k, which would be expected if any of the rate terms containing (HC) were significant.

At constant *p*H, the rate constants vary with the Triton X-100 concentration, as shown by Table IB. These results were used to calculate the values of the left-hand side of equation 6. In Fig. 4, these data are plotted *vs.* V_m. Although the coupler is ionized only slightly at the lower *p*H values, and almost completely at the high *p*H values, the two sets of data, when plotted, lie practically on the same line. This again shows the insignificance of any term involving the un-ionized coupler in the rate expression. The extrapolated value at $V_m = 0$ is k_a, the rate constant in the aqueous region in equilibrium with the micelles. At any other value of V_m, the ratio $(\mu - k_a)/k_a$ represents the ratio of the reaction rate in the micelle to that in the aqueous region. From Fig. 4 it can be estimated that, in the presence of 2% Triton X-100, 90% of the coupling reaction takes place in the micelles. The effect of the molecularly dispersed Triton X-100 on the coupling rate could be observed by comparing k_a obtained by extrapolation with k measured directly in the absence of Triton; unfortunately, the latter cannot be obtained for the reaction shown in Fig. 4, owing to the precipitation of the dye. The reaction shown in Fig. 3, however, has been followed without Triton X-100. The insert in Fig. 3 shows a plot of equation 6, with k_c^- obtained at high *p*H. The point at zero Triton concentration obtained directly agrees well with k_a obtained by extrapolation; this shows that there is no measurable effect of the molecularly dispersed Triton X-100 on the coupling rate. The points at high *p*H in Fig. 3 were either obtained by the "continuous method," corrected for deamination in the calculation, or by the method of competing reactions described earlier, the rate of deamination being used as a standard. The rate of deamination has been found independently to be unaffected by Triton X-100, up to a concentration of 5%. The independence of deamination rate on Triton X-100 concentration indicates that very little quinonediimine has been removed from the aqueous phase by solubilization. This argument is valid except for the improbable situation where the deamination of the solubilized and the unsolubilized quinonediimine would have the same rate. This situation seems improbable, especially since we have found that the presence of an anionic surfactant, *e.g.*, (Duponol) where solubilization is likely to be high, lowers the deamination rate very markedly. The ratios $\gamma k_m/k_a$ for the reactions of 3-methyl-4-amino-N,N-diethylaniline with 4-chloro-1-naphthol, and with 2-(disulfobenzamido)-5-methylphenol are 0.30 and 4.1, respectively. The ratio probably depends on the orientation of the coupler ion in the micelle, which influences the availability of the reactive site of the solubilized coupler. Systematic studies with this point in mind may prove instructive both with respect to problems of solubilization and of reaction kinetics.

Acknowledgment.—The authors are indebted to Dr. A. Weissberger for his interest and encouragement in this research, and for his helpful discussions and suggestions in the preparation of this manuscript.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

Electronic Spectra of Pyridocyanine Dyes with Assignments of Transitions[1]

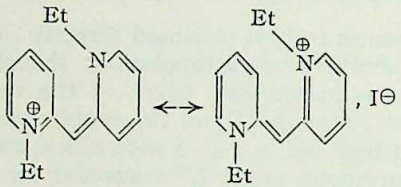
BY GERALD S. LEVINSON, WILLIAM T. SIMPSON AND WALDO CURTIS[2]

RECEIVED APRIL 3, 1957

The electronic spectra of 2,2′- and 4,4′-pyridocyanine dyes have been investigated. There are absorptions at *ca.* 490, 360 and 260 mμ for both the 2,2′- and 4,4′-, which are assigned, respectively, as long axis, short axis and (probably) long axis polarized. The dye 1,1′-diethyl-2,2′-pyridocyanine iodide has been found to exist as the unsymmetrical isomer, and at low temperatures to aggregate into an ion pair and a dimer of ion pairs. The dimer has a triplet-singlet emission with peaks at 600 and 650 mμ.

Introduction

When this research was begun, the aim was mainly to obtain the positions and intensities of the electronic transitions in the visible and quartz ultraviolet for the dye 1,1′-diethyl-2,2′-pyridocyanine iodide[3] (called dye I). (The Kekulé resonance in

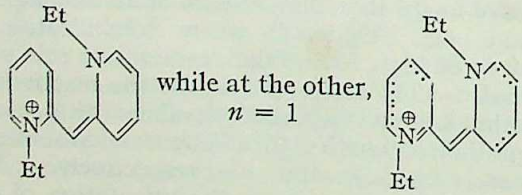


I

the pyridinium rings is not shown.) One reason for studying this dye was that it is but a single step up in complexity as compared with the family of straight chain dyes

$$R_2\overset{\oplus}{N}{=}CH{-}(CH{=}CH)_n{-}NR_2$$

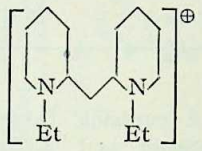
for which the wave length of absorption varies linearly with chain length. The step is significant because it no longer becomes possible to define a chain length. At one extreme, the effective chain length corresponds to $n = 5$



This means that empirical correlations between chain length and color are ruled out; some sort of interpretation guided by quantum theory is called for.

In the course of the investigation of dye I, it was found that certain chemical effects had to be understood before the spectroscopic investigation could be considered reasonably complete.[4]

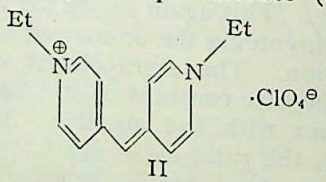
In the first place, it was found necessary to decide which of the plausible isomers was in preponderance, the one given above or the symmetrical one.



Second, it was found that aggregation, while not observed in dilute methanol solutions at room temperature, becomes very marked at liquid–nitrogen temperatures.

Isomerism.[5]—In the absorption spectrum of dye I there are strong peaks at 486 and 357 mμ (Fig. 1). It is believed these represent transitions to the first two singlet excited states. The polarization of the second transition (357 band) relative to the first was determined using the method of polarized fluorescence, and was found to be positive, though less so than the first transition. If the symmetrical isomer predominates, as was anticipated from a superficial consideration of steric hindrance, this positive polarization can only mean that the directions of oscillation of charge for the two transitions are intrinsically the same, and in all probability along the long axis. However, the theoretical treatments all favor having the first two transitions, respectively, long axis and short axis polarized.

Turning to the closely related substance 1,1′-diethyl-4,4′-pyridocyanine perchlorate[6] (dye II)



II

we again find two peaks in the absorption spectrum, one at 505 mμ and one at 372 mμ (Fig. 1), corresponding to those found for dye I at 486 and 357. This time the peak at 372 is markedly weaker than for dye I. There is only one isomer possible for dye II: it has to be symmetric. Although we tried and were unable to measure the polarization by fluorescence experiments, still the natural conclusion is that the 372 band of dye II represents a short axis polarized transition, because of its low intensity compared to the corresponding band of dye I. The band in dye I may be considered to have gained its strength (and positive polarization) through borrowing from the strong first band. This borrowing

(1) This research was supported in part by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under Contract No. AF 18(600)-375. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) Eastman Kodak Pre-doctoral Fellow, 1950–1951.

(3) The dye was synthesized by the method of L. G. S. Brooker and G. H. Keyes, THIS JOURNAL, **57**, 2490 (1935).

(4) In this connection, see S. E. Sheppard, *Revs. Mod. Phys.*, **14**, 303 (1942).

(5) Work on isomerism in cyanine dyes has been reported by G. Scheibe, *Z. Angew. Chem.*, **52**, 631 (1939); *Z. Elektrochem.*, **47**, 73 (1941); L. G. S. Brooker, F. L. White, R. H. Sprague, S. G. Dent, Jr., and G. Van Zandt, *Chem. Revs.*, **41**, 325 (1947), and L. G S. Brooker, F. L. White, D. W. Heseltine, G. H. Keyes, S. G. Dent, Jr., and E. Van Lare, *J. Phot. Sci.*, **1**, 173 (1953).

(6) We are indebted to Dr. L. G. S. Brooker of the Eastman Kodak Co. for sending us this dye.

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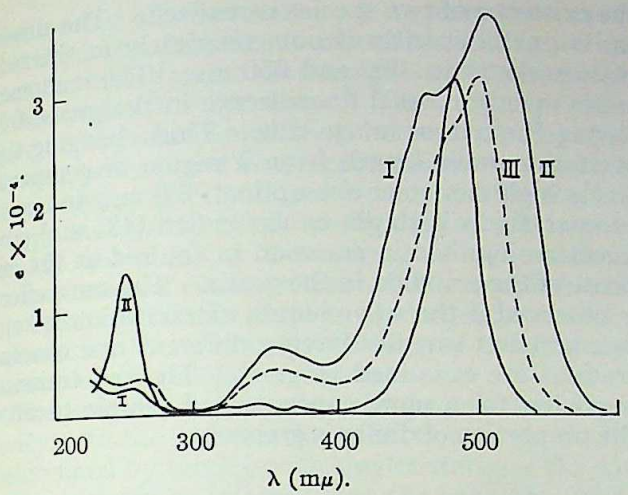
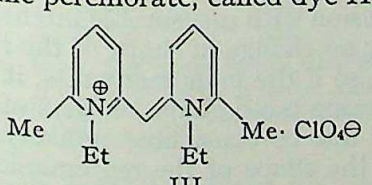


Fig. 1.—Room temperature absorptions of 2,2′-pyridocyanine (dye I), 4,4′-pyridocyanine (dye II), and crowded 2,2′-pyridocyanine (dye III) in methyl alcohol.

could only be induced by departure from symmetry. On this basis it is concluded that dye I exists as the unsymmetrical isomer.

The polarized fluorescence measurements on dye I, interpreted in conformity with our findings on aggregation at low temperatures (see below) might be explained another way, by assuming that the predominant monomeric species at low temperatures is an ion pair consisting of the symmetrical dye cation bonded unsymmetrically to the anion. The lack of symmetry would be considered as producing the borrowing referred to above. If this were the case, however, the room temperature absorptions in a region of concentration for which Beer's law is obeyed would show the 357 band as weak (as for dye II), and the band would strengthen markedly as ion pair formation develops on cooling. Effects of this nature were sought but not found. Thus the evidence favors our first conclusion, that for dye I the unsymmetrical isomer predominates.

In attempting to test this conclusion directly, we synthesized dyes designed to be forced sterically into the symmetrical configuration. The best example found was 1,1′-diethyl-6,6′-dimethyl-2,2′-pyridocyanine perchlorate, called dye III.[7]



III

The spectrum of this substance (Fig. 1) shows a considerable reduction in the height and area of the 357 band as compared with the corresponding band of dye I (the curve in Fig. 1 is dotted because the values on the ordinate are not quantitative. Instead, the height is made equal to that for dye I in the 486 region.). The reduction in the relative intensity of this band is interpreted as indicating that an appreciable fraction of the dye molecules is now in the symmetrical configuration. Notwithstanding, polarized fluorescence experiments on dye III showed that the 357 region is still positive. Even if the dye were all present as the symmetrical isomer, ion pair formation at the temperatures used for the polarized fluorescence measurements would have to be reckoned with as possibly influencing the polarization direction.

The reason why the unsymmetrical isomer of dye I is the more stable is probably that for this isomer the local permanent dipoles in the pyridine rings are lined up more favorably, as has been suggested to us by Professor J. R. Platt.

Aggregation.—Efforts to determine a unique emission spectrum of dye I were at first unsatisfactory, and the analysis of the difficulties led finally to the discovery that there were two separate species present, each with its own absorption and emission spectrum.

Absorption spectra at two initial concentrations of dye I at 77°K in a rigid glass[8] are shown in Fig. 2.

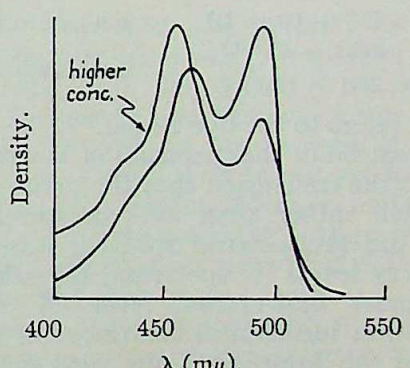


Fig. 2.—Absorption spectra at 77°K. of dye I taken at two different initial concentrations. Solvent is isopropyl alcohol–isopentane mixture.

The dependence on concentration shows aggregation. If pairs of curves such as those in Fig. 2 are worked up by scaling the ordinates to be the same at 495 mμ and subtracting, then a spectrum is obtained substantially like the one in Fig. 3 marked as belonging to species Y, where Y is the species which grows as the concentration is increased. This process is based on the assumption that Y does not absorb appreciably at 495, and the fact that pairs of curves corresponding to various concentrations all give the same curve for Y is taken as effectively proving the assumption. A curve for a second species, X, was not so easily found because there is no useful wave length where X does not absorb. However, the ratio of optical densities at 495 and 455 was plotted against the optical density at 495 as abscissa for various concentrations. The resulting curve was extrapolated to the value of the abscissa equal to zero, to determine the value of the ratio of infinite dilution. This gave the ratio of densities at 495 and 455 for the X component of the mixture. From this information together with the derived spectrum of Y, and using the absorption obtained with the least concentration of dye, a curve for pure X was constructed (Fig. 3).

The degree of polymerization could unequivocally be obtained from a typical law of mass action plot[9] if it were not for the fact that the solutions be-

(7) The method of reference 3 was used in the synthesis. The condensation was carried out between 2,6-lutidinium ethiodide and 2-methyl-6-iodopyridinium ethiodide in propyl alcohol with 2.1 moles of triethylamine. The iodopyridinium salt was prepared by heating 1 mole of 2-methyl-6-bromopyridine with 4 moles of ethyl iodide in a sealed tube at 100° for three days. The 2-methyl-6-bromopyridine was prepared by Mr. F. Bell under the supervision of Dr. A. G. Anderson.

(8) All rigid solutions used were made by dissolving the dye in a mixture of 3 parts of isopropyl alcohol and 7 parts of isopentane, by volume.

(9) The concentration of X can be determined from the composite spectrum at 495 mμ and the concentration of Y by subtraction. Beer's law is, of course, assumed for the components.

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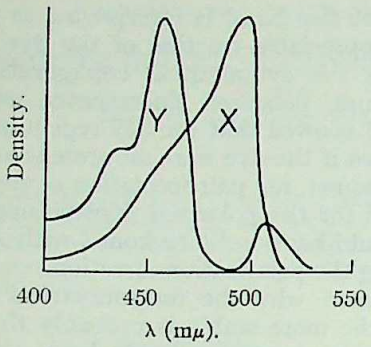

Fig. 3.—Absorptions derived from curves like those in Fig. 2, for species X and Y.

come rigid on approaching (but prior to) 77°K., where the absorption measurements are made. The actual result of a mass action study was to give an order of polymerization equal to the integer two within experimental error. The closeness to two is taken as indicating that the equilibria turned out to be all measured at the same effective temperature. The possible aggregation processes of order two are

$$\left.\begin{aligned} D^+ + I^- &= DI \\ 2D^+ &= D_2^{++} \\ 2DI &= (DI)_2 \end{aligned}\right\} \quad \begin{aligned} &\text{ion pair formation} \\ &\text{dimerization} \end{aligned}$$

where D^+ refers to the dye cation.

A comparison of the spectrum of Y with that for X leads to the conclusion that the process is one of dimerization rather than ion-pair formation, because of the symmetrical splitting into two separate energy levels (Y spectrum) on either side of the monomer first-excited level (X spectrum). The quantum mechanical treatment of this effect is given in the Appendix along with some further consideration of the experimental results.

The experiments have all been repeated using the dye perchlorate instead of the iodide. The half dimerization point is reached at a much lower concentration, and the split between the peaks (Y) is noticeably greater than for the iodide. This means that the anion must be involved in the dimer (and also rules out enhanced singlet-triplet absorption as an explanation of the first absorption). Moreover, since the order of polymerization is only two, the monomeric species (X) has to be the ion pair.

The driving force for the dimerization reaction is essentially the difference between two heats of ion-pair formation. The greater stability of the dimer is to be attributed to the fact that the resonance in the dye cation puts approximately one-half of a positive charge on each ring. By bringing two dye cations together to form a sandwich (see Fig. 7) an arrangement is obtained which allows each fully charged iodide anion to be adjacent to two half charges (one half for each dye cation). In contrast, for the monomeric ion pair the negative iodide can only be adjacent to a full positive charge by polarizing the dye, at the expense of the resonance stabilization of the ground state.

Emission Spectra.[10]—The pattern of the emission spectra is simple in its broad outlines, once the existence of two species is realized. The dimer emits predominantly if not completely in the red, with peaks at *ca.* 600 and 650 mμ. The monomer emits mainly normal fluorescence in the green, following the mirror image rule. Thus changing the excitation wave length from a region of comparatively high monomer absorption (470 mμ) to one of comparatively high dimer absorption (435 mμ) produces an increase in emission in the red at the expense of the emission in the green. The same effect is observed if the wave length of excitation is kept constant but samples having different dye concentrations are examined (Fig. 4). The red emission is greater for a more concentrated sample because the proportion of dimer is greater.

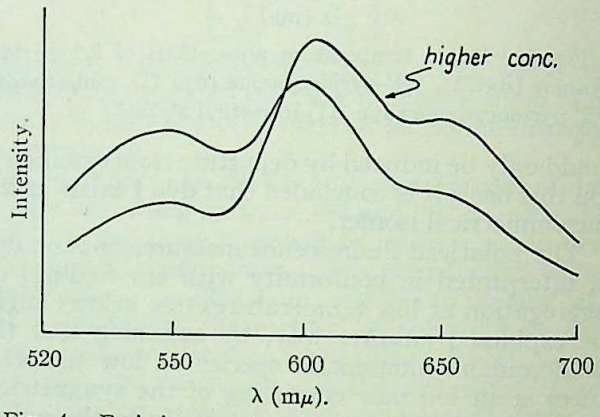

Fig. 4.—Emission spectra of dye I taken at two different initial concentrations (in isopropyl alcohol–isopentane glass at 77°K.).

Using a high concentration and keeping the excitation as much as possible in the dimer absorption region gives an emission spectrum which is approximately that for the pure dimer. From experiments of this type it was found that dimer emission in the green is at least an order of magnitude weaker than in the red.

To see whether or not there is any red emission from the monomer, measurements were carried out using very dilute solutions. However, the results are inconclusive because it was not found possible to lower the dimer concentration by dilution and still have a sufficient monomer concentration to give an emission with measurable intensity. There was little or no change in shape of the red emission on dilution, so if the monomer emits, it is with virtually the same band shape as that of the dimer. This would not be considered unlikely. The reason is that the shape of the red emission in simultaneous emission experiments is the same as that seen through a phosphoroscope (Fig. 5) so the emission is considered to be triplet-singlet. The dimer triplet-singlet emission spectrum would be expected to be virtually identical with the monomer spectrum because the resonance force coupling disappears after the inter-system crossing into the triplet state.

Examination of the emission curves for dilute solutions allows us to say that if the monomer phos-

(10) The spectra were obtained either photoelectrically or photographically. The exciting light was suitably modified using combinations of Corning filters, or a monochromator. Photoelectric detection was with a Photovolt Multiplier Photometer unit adopted to monitor the output of an infrared sensitive photomultiplier tube (Dumont Type K 1292). All spectra were recorded at 77°K. in the isopropyl alcohol, isopentane glass described above.

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phoresces at all, the intensity is no more than about one-third the fluorescent intensity. Thus we see that the inter-system crossing probability is considerably higher for the dimer. The crossing rate is governed by the competition between the intrinsic crossing process and fluorescent emission. Fluorescent emission for the dimer would be from the low energy state (510 band in Fig. 3), which is only weakly absorbing. The corresponding smallness in spontaneous emission probability coupled with the closeness of this state to the triplet state may account for the greater probability of crossing and hence phosphorescent emission.[11]

The emission in the red is always polarized negatively. If the polarization direction were simply determined by mixing with singlet states of the dye cation it could be inferred that the negative polarization would have to involve an out-of-plane singlet-singlet transition. The alternative is ruled out because the in-plane directions ($\parallel$ and $\perp$) are not strongly differentiated by the spin-orbit coupling, so the mixing would be with the closest levels, resulting in long-axis (hence positive) polarization. It was suggested by Dr. D. S. McClure that the existence of neighboring iodide ions might complicate this interpretation. What could be involved, say, is mixing with a charge-transfer transition polarized in the direction of a line joining iodide to nitrogen (see Fig. 7).

Energies, Intensities and Assignments.—The spectra of the 2,2′- and 4,4′-pyridocyanines in the visible and quartz ultraviolet are much alike (Fig. 1). In addition to the bands around 490 and 360, there is a band at about 260 mμ. Absorption is stronger in the 360 region than in the 260 region for the 2,2′-dye, though for the 4,4′-dye this order of intensity is reversed. The transition moment lengths are given in Table I together with the positions of the long wave length peaks.

TABLE I

TRANSITION MOMENT LENGTHS[a] AND LOCATION OF FIRST PEAKS FOR THE 2,2′- AND 4,4′-PYRIDOCYANINES[b]

2,2′ (Dye I)		4,4′ (Dye II)	
λ(mμ)	q(Å.)	λ(mμ)	q(Å.)
486	1.40	505	1.50
357	0.66	372	0.27
260	0.35	254	0.72

[a] Calculated from the areas using the formula $q^2 = -1.09 \times 10^{-19} \int \epsilon d \log \lambda$ (here q is in cm. and ϵ is the molar extinction coefficient). [b] The intensities for the 4,4′-dye were obtained by Mr. R. Lund.

The emission spectrum of dye I is typical in that there is fluorescence from the lowest energy excited singlet, represented by the 486 band in absorption; and, also, phosphorescence at longer wave lengths. The 0,0 value for the singlet-singlet transition is estimated to be $1.9_8 \times 10^4$ cm.$^{-1}$ and for the singlet-triplet, $1.7_2 \times 10^4$ cm.$^{-1}$.

The first singlet-singlet transition is assigned as long axis polarized from the observation that the transition moment length depends directly on the physical chain lengths of members of vinylogous series of cyanine dyes. The ion of dye II has a plane of symmetry perpendicular to the plane of the molecule, so the wave functions and in-plane transitions may be described by reference to the following simple character table .

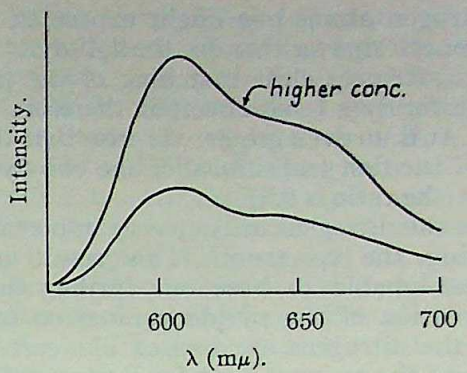

Fig. 5.—Phosphorescence emission spectra of dye I at two different initial concentrations (in isopropyl alcohol–isopentane glass at 77°K.).

	E	σ
A ($\perp$)	1	1
B ($\parallel$)	1	−1

The ground state is almost certainly totally symmetric so the long wave length transition described as "long axis" (and denoted as $\parallel$) is assigned as A → B. Because of the markedly lower intensity, which increases after an unsymmetrical perturbation, the next transition is presumed to be A → A($\perp$). The transition at 254 mμ is tentatively assigned as A → B because of the pattern of alternating intensity behavior for dyes II and III as compared with dye I (Fig. 1).

The point of view adopted with regard to dye I is that there is a close correspondence between its levels and the levels for dye II, and that as explained above the intensity changes are caused by the asymmetry (in the placement of the nitrogen atoms) considered as a perturbation. Thus the increase in the 357 region for dye I is attributed to mixing with the adjacent A → B transition at 486 and (with the above assignment) to a lesser extent with the one at 260. It is consistent with this interpretation that these essentially long axis transitions are reduced in intensity as compared to those in the symmetrical dye II. In fact, there seems to be something very close to conservation of intensity operative. The extra intensity in the 357 region for dye I is taken as $0.66^2 - 0.27^2$, the difference between the squares of the transition moment lengths. It is 0.36 Å.^{2}. This is balanced by the extra intensity in the 505 region for dye II, $1.50^2 - 1.40^2$ or 0.31 Å.^{2}.

Theoretical Interpretation.—Referring to the structural formula for the straight chain dyes in the Introduction, the 4,4′-dye has a chain length characterized by $n = 3$. Consistent with this it absorbs at around 500 mμ, in accord with our expectation based on counting 100 mμ for each pair of π electrons in conjugation. The second transition for a simple straight chain dye with $n = 3$ comes, however, at 305 mμ, compared with 372 mμ for the pyridocyanine. As noted in the Introduction, for the 2,2′-dye a chain length cannot be unambiguously selected, but considering the placement of

(11) We have learned from Professor M. Kasha that phosphorescence seems to predominate over fluorescence in a variety of cases where the concentration or other conditions are such as to favor aggregation.

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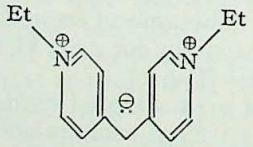
the nitrogen atoms one might expect an effective chain length shorter than for the 4,4′-dye.

The extremely close matching of the transition energies for dyes I and II comes, therefore, as a surprise. It is an even greater surprise that the intensities of the first transitions for the two dyes are so similar (the ratio is 0.87).

Thus the nitrogens are not very important in determining the spectrum. This result makes it seem reasonable to base our further theoretical consideration of the pyridocyanines on models in which the nitrogens are treated like carbons. At this point the avenues open for interpretation are a molecular orbital approach or an approach using valence bond structures. The most fruitful procedure for dealing with cyanine dye spectra appears to be to abandon the idea of finding a uniquely simple and effective scheme, and to use the various contemporary approximate theories in their full variety.[12] Such a procedure has been used throughout the course of the present research, but it would be impractical to go into too much detail here. Nonetheless, we shall go on to consider the pyridocyanines according to first an orbital and then a structures approach.

According to the Hückel theory, virtually the same pattern of orbital energies is obtained as for benzene; though there is an extra non-bonding orbital, and all the levels except the non-bonding one are doubled. The non-bonding orbital exists roughly speaking because of structures like



The energy level pattern is shown in Fig. 6. Symmetries of orbitals are given by lower case letters, and of states and configurations by capitals; in each case using species as shown in the character table in the last section.

The ground configuration has symmetry A and may be denoted by the product of species of the two highest energy electrons.

$$\ldots a^2$$

The first excited configuration is threefold degenerate

$$\ldots ab(B) \quad \ldots aa'(A) \quad \ldots ab'(B)$$

Allowing for the nitrogens by changing α's does split the degeneracy but gives the wrong result; namely, that for the 4,4′-dye the first transition would be $a^2 \rightarrow ab(\parallel)$, but for the 2,2′-dye it would be $a^2 \rightarrow aa'(\perp)$! This is analogous to the situation involving pyridine and benzene, where the degenerate configurations obtained on the assumption of an all-carbon model have to be allowed to interact first before the hetero atom is taken into account.

If we allow the configurations to interact here, we find the upper levels ordered

B, A, B

simply by virtue of the "repulsion" between the B configurations. The first transition is now given as A → B, in agreement with experiment, but only after going to a higher order of approximation. This may be compared with the situation encountered using structures, where resonance between structures must be considered before a reasonable description of the ground state emerges.

Using the Hückel theory before configurational interaction, we can calculate the center of gravity of the triad of absorptions, say, in terms of the center of gravity of the benzene tetrad (average absorption at 210 mμ). Using the orbital energies for the two cases, we find for the dye triad a wave length

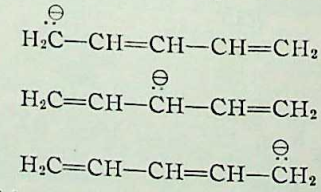
$$210 \text{ m}\mu \frac{2.133}{1.333} = 337 \text{ m}\mu$$

which agrees with what is observed (the average of the six transition energies listed in Table I corresponds to absorption at 346 mμ).

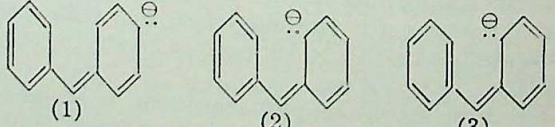
The transition moment length for one of the A → B transitions is 1.9 Å. and for the other, 0.4 Å. These values fit the values in Table I reasonably well when it is remembered that configuration interaction is involved. The transition moment length for the A → A (⊥) transition is calculated to be 0.6 Å., which is too high.

The A. O. coefficients squared in that b orbital which best characterizes the first B state (that is, with transition moment length 1.9 Å.) are larger at the 4,4′-positions than at the 2,2′-positions. Moreover, the non-bonding (a) orbital does not discriminate between the 2- or 4-positions. Thus putting in nitrogen atoms at the 4,4′-positions would, according to first-order perturbation theory, make the transition energy for the intense first transition somewhat smaller than for the 2,2′-dye, as observed.

If we want to emphasize calculating the position of the first transition, a method using structures proves to be more satisfactory. The basic interaction is considered to be very similar to what occurs in allyl anion, so that the straight chain dye with $n = 1$ would be treated using wave functions corresponding to the following three structures[13]



For the pyridocyanines there are a large number of interactions of allylic type, and there is the Kekulé interaction in the pyridinium rings as well. The allylic interaction is illustrated by the first two structures



The magnitude of the allylic interaction matrix element is taken so as to give correctly the color of the $n = 2$ dye (λ 409 mμ). Interaction between functions, illustrated by the second and third

(12) This is illustrated in the recent paper on dyes of J. R. Platt, *J. Chem. Phys.*, **25**, 80 (1956).

(13) The method is described by W. T. Simpson, THIS JOURNAL, **73**, 5350 (1951).

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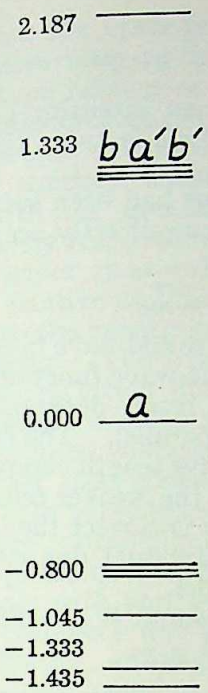

Fig. 6.—Diagram of energies of L.C.A.O: M.O.'s according to Hückel theory. Energies are in units of $|\gamma|$; and highest two levels (+4.000 and +5.076) have been omitted.

structures, is taken so as to put the $A_{1g} \rightarrow B_{2u}$ transition in benzene at 260 mμ. If the charge moves more than two carbon atoms the interaction is set equal to zero, as it is also when there are multiple interactions. In addition, the wave functions are assumed to be orthogonal. The upper corner of the secular equation for the pyridocyanine corresponding to the structures as numbered above would for example, be

	1	2	3
1	$-\lambda$	G	0
2	G	$-\lambda$	K
3	0	K	$-\lambda$

where G is the allyl anion resonance parameter and K is the Kekulé resonance parameter. The ratio $K/G = 0.787$.

The first few energies in units of G and the calculated absorption wave lengths are given in Table II where it will be seen that the calculated wave length of the first transition falls very nicely between the $n = 2$ and $n = 3$ dye colors, as observed.

TABLE II

TERM VALUES IN UNITS OF G AND POSITIONS OF THE PEAKS AS CALCULATED USING STRUCTURES

	Chain dyes			
	$n = 1$	$n = 2$	$n = 3$	Pyridocyanine
E_1	1.414	1.618	1.732	3.047
E_2	0	0.618	1.000	2.201
E_3	−1.414	−0.618	0	1.696[b]
$\lambda(E_2 - E_1)$, mμ	289	(409)	559	470
λ (obsd.)[a]	309	409	511	486–505
$\lambda(E_3 - E_1)$				330 (double)
λ (obsd.)				360 and 260

[a] W. T. Simpson, *J. Chem. Phys.*, 16, 1124 (1948). [b] Doubly degenerate.

The transition moment length for the first (A → B) transition is calculated to be 1.90 Å., the same as for the most intense transition in the first triad according to the Hückel theory. The third energy level obtained using structures is accidentally degenerate, with absorption at 330 mμ and species A and B. The transition moment lengths to these two states are, respectively, 0.25 Å. (short axis polarized) and 0.14 Å. (long axis polarized). The transition moment lengths agree with what is observed for the 4,4′-dye (Table I) if the absorption at 372 mμ is assigned as A → A, and if it is assumed that the actual absorptions at 254 and 505 correspond (after some mixing has taken place) to the first two A → B transitions calculated to come at 470 and 330.

Appendix

We shall start by reviewing the theory of the splitting of the monomer levels upon formation of the dimer.[14] It is assumed that the molecular planes of the dye cations are parallel in the dimer, forming a sandwich. One possible arrangement is as shown in Fig. 7.

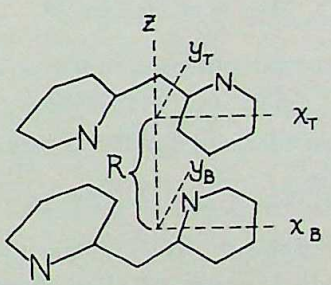

Fig. 7.—One of two possible structures for dimer of dye I. Location of each anion would be in a plane between the two dye cations, as close to a pair of nitrogen atoms as possible.

Neglecting interaction between the monomeric parts the electronic wave functions for the ground state and the (doubly degenerate) first-excited state would be in the form of products

$$\psi_T\psi_B$$

$$\psi_T\dagger\psi_B,\ \psi_T\psi_B\dagger$$

where T and B refer to "top" and "bottom" molecules, and the dagger denotes electronic excitation, in the present example corresponding to the 486 band of the monomer. The electrostatic interaction in the dipole approximation is the sum of the static coulomb energy, which can be disregarded, and the potential

$$V = (-2\Sigma z_T \Sigma z_B + \Sigma x_T \Sigma x_B + \Sigma y_T \Sigma y_B)e^2/R^3$$

Here, for example, Σz_T means a sum over the z components of the electrons in the top molecule, and x, y and z are referred to origins in the respective molecules, as shown in Fig. 7.

(14) An assumption necessary in order that the theory have the simple form outlined here is that the vibrational parts of the wave functions for the dimer excited states can be factored from the electronic parts, which leads to what is called strong coupling. The appropriateness of this assumption is judged by evaluating the terms in the coupling inequality (see W. T. Simpson and D. L. Peterson, *J. Chem. Phys.*, **25**, 588 (1957)). The monomer band width for the absorption at 486 mμ, $\Delta \approx 3000$ cm.$^{-1}$ while the splitting for the iodide is actually less, $2v \approx 2300$ cm.$^{-1}$; and for the perchlorate more, $2v \approx 4800$ cm.$^{-1}$. According to this the perchlorate dimer is in the strong coupling range $2v/\Delta > 1$, and the iodide is in the intermediate coupling range. The theory in this Appendix is a strong coupling theory, but it corresponds fairly well to the iodide.

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Only terms of the type

$$\int \psi_T^\dagger \psi_B V \psi_T \psi_B^\dagger d\tau_T d\tau_B$$

are considered important. That is, the permanent moments, like

$$e \int \psi_T \Sigma x_T \psi_T d\tau_T$$

are taken as zero. The first-order energy correction for the ground state is therefore zero. The correct wave functions for the degenerate manifold are

$$\psi_\pm = 2^{-1/2}(\psi_T^\dagger \psi_B \pm \psi_T \psi_B^\dagger)$$

The expectation value of V for these functions does not involve the term

$$-2\Sigma z_T z_B$$

because the transition moments for the monomeric component species are in-plane. What is left is actually the dot product of the respective transition moments, each referred to its own coördinate frame

$$W_\pm = \pm \vec{m}_T \cdot \vec{m}_B / R^3$$

where the x component, say, of $\vec{m}_T$ is

$$(m_T)_x = e \int \psi_T \Sigma x_T \psi_T^\dagger d\tau_T$$

The transition moment for the dimer absorption is

$$\vec{m}_\pm = e \int \psi_T \psi_B [\vec{i}(\Sigma x_T + \Sigma x_B) + \vec{j}(\Sigma y_T + \Sigma y_B)] \, 2^{-1/2}(\psi_T^\dagger \psi_B \pm \psi_T \psi_B^\dagger) d\tau_T d\tau_B = 2^{-1/2}(\vec{m}_T \pm \vec{m}_B)$$

To illustrate the use of these formulas, let us now assume that the nitrogen atoms in the molecules are in fact oriented as shown in Fig. 7. We would then have

$$\vec{m}_T = -\vec{m}_B$$

Substituting in the formula for the energy we find that the lower energy state is W_+

$$+ m_T \cdot (-m_T)/R^3$$

with the corresponding wave function ψ_+. The transition moment from the ground state (long wave length component of the doublet) is

$$2^{-1/2}(m_T + (-m_T)) = 0$$

The transition moment to the state with wave function ψ_-, and energy

$$W_- = + m_T^2/R^3$$

is $2^{-1/2}\ \vec{m}_T$, leading to an intensity proportional to the square, $2|m_T|^2$ which is twice the intensity for a single molecule.

Even if the orientations had been switched so as to put the nitrogen atoms directly on top of one another, giving

$$\vec{m}_T = \vec{m}_B$$

the same physical result would have been obtained, although the phases in the wave functions would be reversed. The physical result depends on having the transition moments parallel. The fact that experimentally the long wave length component (species Y in Fig. 3) is much the weaker tells us that if a sandwich configuration is correct then the transition moments of the individual dye cations must indeed be virtually parallel.

The dimer split is, of course, $W_- - W_+$ or

$$2|m_T|^2/R^3$$

From this we may obtain R by using $|m_T|$ from Table I and the observed splittings for iodide and perchlorate, respectively, 2300 and 4800 cm.$^{-1}$. This gives for the iodide R = 5.8 Å., and for the perchlorate R = 4.5 Å.

The dipole approximation introduces some error (It would give a calculated split which is too high by *ca.* 1/3. Thus we should use $\sim$4/3 the observed splits, which would reduce the calculated R by 10%.) Also, taking the splitting as the energy difference between the peaks results in uncertainty. Even so the values obtained are certainly reasonable. The usual distance between centers for un-charged aromatic systems on top of each other is 3.4 Å. Considering the fact that the dye cations are charged and that this charge cannot be neutralized perfectly by the anions, it seems as if the cations in the perchlorate dimer are virtually in contact. In the iodide it appears that the dye cations actually are separated to a degree by the iodide ions entering as "filling" to the sandwich. If the iodide ions were completely inside the sandwich, R would be 7.7 Å., based on an iodide ion diameter of 4.3 Å.

SEATTLE, WASHINGTON

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Chemorheological Study of Polyurethan Elastomers[1]

BY P. C. COLODNY[2] AND A. V. TOBOLSKY

RECEIVED APRIL 26, 1957

Two series of polyurethan elastomers were prepared which contained (a) predominantly urethan linkages and (b) equal numbers of urethan and substituted urea or biuret groups. The chemorheology of these samples was investigated by stress relaxation experiments. It was found that the urethan linkages underwent scission at a rate one-tenth that of the combined rate of the substituted urea and biuret groups.

Introduction

The chemorheology of polyurethan elastomers based on polyester and polyether chains has recently been investigated by Offenbach and Tobolsky.[3] Polyester rubbers cured with benzoyl peroxide had been studied previously.[4] From these works it was concluded that neither the scission of

(1) This article is based upon a dissertation submitted by Paul C. Colodny in partial fullfillment of the requirements for the degree of Doctor of Philosophy at Princeton University.

(2) Thiokol Chemical Corporation Fellow 1955–1957.

(3) J. A. Offenbach and A. V. Tobolsky, *J. Colloid Sci.*, **11**, 39 (1956).

(4) R. D. Andrews, Ph.D. Thesis, Princeton University, 1948.

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the ester nor the ether links along the chain contributed appreciably to the stress relaxation of the Vulcollan type rubbers or du Pont Adiprene B at elevated temperatures. The cause of the stress decay at constant elongation was attributed to the scission of urethan, substituted urea and biuret linkages with the urea and biuret groups being thought chiefly responsible.

In this paper clear evidence is presented that shows the relative stability of the urethan groups compared to the substituted urea linkages and the biuret linkages. The basis of this evidence rests with stress relaxation data of rubber samples so prepared from the same linear polyester that one class of specimens contains nearly all urethan links and the other class contains half urethan and the other half both substituted urea and biuret groups. The samples containing principally urethan linkages were prepared first by the direct reaction of the polyester with stoichiometric amounts of isocyanate. Sample I was prepared by the reaction of this polyester, an 80–20 mole % ethylene–propylene adipate, with an equivalent amount of 2,4-toluene diisocyanate. This gave a linear product that flowed at elevated temperature. Sample II was prepared by the reaction of the polyester with methyl triphenyl triisocyanate. Samples III and IV discussed below were prepared as follows. An isocyanate terminated polyester (A), commonly referred to as "prepolymer,"[5] was prepared by the addition of excess diisocyanate to the polyester. Sample III was formed by curing this prepolymer with 1,4-butanediol. A linear material similar to I was obtained which indicates that little or no cross-linking was introduced by allophanate formation. Sample IV was prepared by treating this same prepolymer with 1,2,6-hexanetriol. Sample V was prepared from prepolymer A by the addition of water to form a network containing substituted urea linkages and biuret cross linkages, the sum of these being equal to the number of urethan linkages.

$$\sim OH + OCN{-}R{-}NCO + HO\sim \longrightarrow \sim O{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}O\sim$$

$$HO\sim OH + 2OCN{-}R{-}NCO \longrightarrow OCN{-}R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}O \sim O{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}R{-}NCO$$

(A)

Another prepolymer (B) was prepared using another polyester, Thiokol ZL-219, and the same diisocyanate. Sample VI was prepared by curing this prepolymer with excess water. A substantial number of trisubstituted biuret linkages were also formed in V and VI by the reaction of free isocyanate with the urea hydrogen atoms as indicated by the network structure of the elastomer. The purpose of this duplication was to minimize the possibility of erroneous results due to catalytic effects from trace impurities.

$$OCN\sim NCO + 2H_2O \longrightarrow \sim \overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N} \sim \overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}\sim$$

(B)

$$\overset{\overset{H}{|}}{\sim N}{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}\sim + \sim NCO \longrightarrow \sim \overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}\sim$$

(VI)

Experimental

Material.—The polyester used was the Thiokol ZL-219 and an 80-20 mole % ethylene–propylene adipate. The Thiokol polyester had an acid no. of 2.4 and an isocyanate equiv. wt. of 1170 while the ethylene–propylene adipate had an acid no. of 3 and an isocyanate equiv. wt. of 1580. These were dried by heating for 4 hours at 120–130° while a stream of nitrogen was bubbled through the material. The triisocyanate used was Mobay Mondur TM consisting of a 20% solution of methyl triphenyl triisocyanate in CH_2Cl_2. The diisocyanate was du Pont Hylene T which analyzed for 95% 2,4-toluene diisocyanate. The diol and triol were highly purified 1,4-butanediol and 1,2,6-hexanetriol.

Preparation of Elastomers with Predominantly Urethan Linkages.—Sample I was prepared by the reaction of 50.0 g. (0.0316 isocyanate equiv. wt.) of the ethylene–propylene adipate with 2.75 g. (0.0316 equiv.) of 2,4-toluene diisocyanate in a mold at 70° for 4 hours. 131 g. (0.0826 isocyanate equiv. wt.) of the polyester was treated with 10.1 g. (0.0826 equiv.) of methyl triphenyl triisocyanate in CH_2Cl_2 solution for the preparation of II. The reaction was carried out in a sample mold placed in a vacuum oven at 75°. As the sample contained numerous bubbles due to the evaporation of the solvent it was passed through a rubber mill and pressed out at 150° for 30 min. at 20,000 p.s.i.

The prepolymer for III, IV and V was prepared by the addition of 49.5 g. (0.284 mole) of 2,4-toluene diisocyanate, a 10% excess, to 409.9 g. (0.258 isocyanate equiv. wt.) of ethylene–propylene adipate at room temperature and under an atmosphere of nitrogen. The mixture was allowed to react for 48 hours to give a prepolymer with an equiv. wt. of 1760. III was prepared by the reaction of 52.3 g. (0.0298 equiv.) of this prepolymer with 1.34 g. (0.0298 equiv.) of 1,4-butanediol while IV was formed from 51.5 g. (0.0294 equiv.) of prepolymer and 1.31 g. (0.0294 equiv.) of 1,2,6-hexanetriol. The conditions were the same as for I.

Preparation of Samples with Substituted Urea and Biuret Linkages.—Sample V was prepared by the reaction of 50.0 g. (0.0285 equiv.) of this same prepolymer and 1 g., fourfold excess, of water. A prepolymer prepared from 2400 g. (2.03 isocyanate equiv. wt.) of Thiokol Polyester ZL-219 and 394 g. (2.23 moles), a 10% excess, 2,4 toluene diisocyanate gave an equiv. wt. of 1230. 50.0 g. (0.0406 equiv.) of this was mixed with 1 g., also a fourfold excess, of water to give VI. These reactions were carried out at 75° and required 72 hours for completion.

Stress Relaxation Measurements.—All measurements were made on Firestone relaxometers[6] which had been modified for strip samples.[7] All samples were post cured for 1 week at 100° prior to physical study to ensure complete cure.

Results and Discussion

Stress relaxation studies were performed on these samples over a temperature range from 100 to 140° at 20% elongation. The data have been plotted as relative stress, f/f_0, as a function of logarithmic time. As it had been shown in previous studies that such relaxation curves are independent of elongation up to fairly large strains, elongation was not investigated as a variable. The reference stress, f_0, was determined by graphical interpolation for the time 0.01 hour. Duplicate determinations were completely superimposable.

The data for the cure of the ethylene–propylene adipate polyester with the triisocyanate are presented in Fig. 1. Figure 2 contains a comparison of the stress decay curves at 120°. It is apparent

(5) (a) E. Muller, *et al.*, *Rubber Chem. and Technol.*, **26**, 493 (1953); (b) O. Bayer, *et al.*, *ibid.*, **23**, 812 (1950).

(6) A. V. Tobolsky, I. B. Prettyman and J. H. Dillon, *J. Appl. Phys.*, **15**, 380 (1944).

(7) J. J. Coleman, Bachelor Thesis, Princeton University, 1955.

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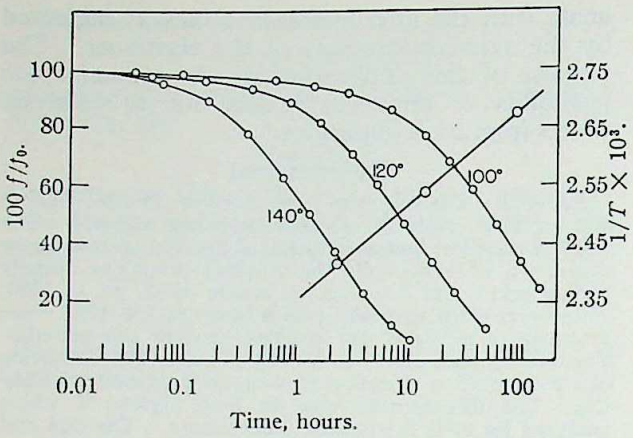

Fig. 1.—Stress relaxation of II.

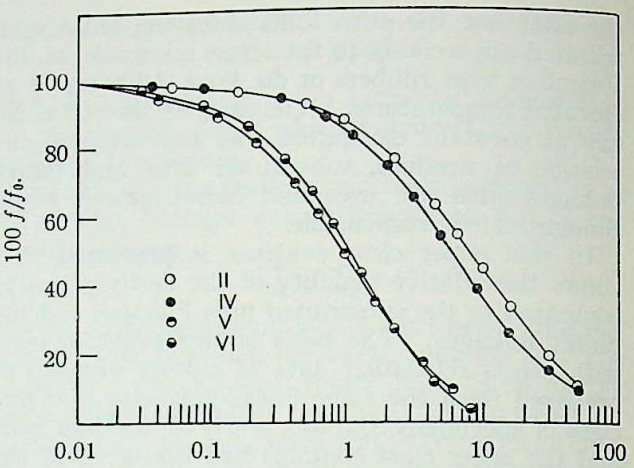

Fig. 2.—Stress relaxation at 120°.

that all samples approached zero stress asymptotically and underwent a major portion of decay within two decades of logarithmic time. Similar behavior had been observed for the polysulfide,[8] natural and silicone[9] rubbers and other polyurethans.[3] The cause for the stress decay in these materials has been attributed to chemical scission of network chains. Decay due to molecular flow has been shown to extend not over two but over many cycles of logarithmic time.

The stress at a time, t, is related to the number of effective network chains[10] by the equation

$$f = NkT\left(\alpha - \frac{1}{\alpha^2}\right)$$

where f is the stress based on the original cross section at relative length α and N is the number of network chains per cubic centimeter which have never been cut. The stress decay at constant strain and elevated temperature of these rubbers has been found to obey approximately the equation $f/f_0 = e - t/\tau$, where τ is the relaxation time of the sample at the specified temperature. The relaxation time, τ, is equal to the time required for the stress to decay to $1/e$ or 36.8% of its reference value. As τ may be considered to be the reciprocal of a chemical rate constant, it is possible to calculate an activation energy for the process from the slope of a plot of log τ *vs.* $1/T$. The relaxation times in hours and activation energies are listed in Table I. The values for samples I and III were approximately zero.

TABLE I

STRESS-RELAXATION TIME (HOURS)

Sample	τ100°	τ120°	τ140°	$E\ddagger$(kcal./mole)
II	87	14	2.3	27.7 ± 1.5
IV	66	9.7	1.6	28.4 ± 1.5
V	12.7	1.6	0.28	29.2 ± 1.0
VI	14	1.65	0.25	30.8 ± 2.0

Structure of Polymers.—Samples I, II, III and IV contain, besides the polyester backbone, predominantly urethan linkages prepared by the reaction of the hydroxyl terminals with isocyanate

$$2HO \sim OH + OCN{-}R{-}NCO \longrightarrow \sim O{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}O\sim$$

Small amounts of amide and substituted urea groups also are present due to the reaction of terminal carboxyl groups[11] with isocyanates resulting with the formation of a mixed anhydride which is followed by the loss of carbon dioxide. The mixed

$$R{-}NCO{-}R'{-}\overset{\overset{O}{\|}}{C}{-}OH \longrightarrow R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}O{-}\overset{\overset{O}{\|}}{C}{-}R' \longrightarrow R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}R' + CO_2$$

$$2R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}O{-}\overset{\overset{O}{\|}}{C}{-}R' \longrightarrow R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}O{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}R + R'C{-}O{-}C{-}R'$$

anhydride can also undergo a disproportionation into anhydrides of carboxylic and carbamic acids

$$R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}O{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}R \longrightarrow R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}R + CO_2$$

from which a disubstituted urea is formed upon the loss of carbon dioxide. More substituted urea linkages are formed by the reaction of isocyanate groups with traces of water.[12] Despite the anhydrous conditions of the preparation procedures it is likely that this reaction occurred to a small degree.

$$R{-}NCO + H_2O \longrightarrow R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}OH \longrightarrow R{-}NH_2 + CO_2$$

$$R{-}NH_2 + R{-}NCO \longrightarrow R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}R$$

From the zero relaxation time of sample I and III it can be concluded that the urethan hydrogen atom reacted with free isocyanate to a negligible

(8) (a) M. D. Stern and A. V. Tobolsky, *J. Chem. Phys.*, **14**, 93 (1946); (b) M. Mochulsky and A. V. Tobolsky, *Ind. Eng. Chem.*, **40**, 2155 (1948).

(9) D. H. Johnson, J. R. McLoughlin and A. V. Tobolsky, *J. Phys. Chem.*, **58**, 1073 (1954).

(10) H. Mark and A. V. Tobolsky, "Physical Chemistry of High Polymeric Systems," Interscience Publishers, New York, N. Y., 1950, pp. 348-357.

(11) C. Naegeli, *et al.*, *Helv. Chim. Acta*, **17**, 931 (1934); **18**, 142 (1935); **21**, 1100, 1127 (1938).

(12) S. Petersen, *Ann.*, **562**, 205 (1949).

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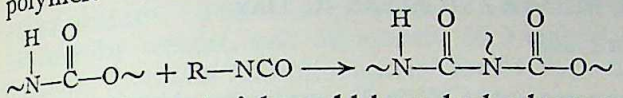
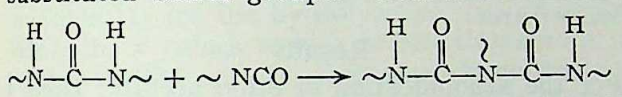
extent to form the allophanate.[13,14] This is particularly evident in III which contained a 10% excess of the diisocyanate in the preparation of the prepolymer. Even if this reaction occurred only



partially the material would have had a loose network structure with a measurable relaxation time instead of undergoing complete flow at the temperature of the relaxation studies. Such behavior is indicative of a linear polymer containing little or no crosslinking.

Samples V and VI were prepared by the addition of water to a prepolymer containing excess diisocyanate. In addition to the formation of disubstituted urea linkages a substantial amount of crosslinking occurred by the reaction of free isocyanate with the urea hydrogen atoms to form trisubstituted biuret groups. This is evidenced by



the stress relaxation data for these samples which indicate that the materials possess a network structure. Also, it has been found by chemical methods that this reaction proceeds at a rate comparable to that of water and isocyanate.[15] The structures of these samples are summarized in Table II.

TABLE II

ELASTOMER STRUCTURE

Sample	Linkages
I	Ester, urethan, no cross-linkages
II	Ester, urethan, triisocyanate cross-linkages
III	Ester, urethan, no cross-linkages
IV	Ester, urethan, triol cross-linkages
V	Ester, urethan, urea, biuret cross-linkages
VI	Ester, urethan, urea, biuret cross-linkages

Possible Sites of Chain Cleavage.—The possibility of ester–ester interchange may be ruled out as a major factor contributing to the stress decay on the basis of previous work involving benzoyl peroxide vulcanizates of the Paraplex type and succinic acid–propylene glycol[4] type originating from the Bell Telephone Laboratories. The relaxation times of these materials were at least ten times longer than those of the samples involved in this investigation. Also, polyurethans having polyester backbones gave comparable relaxation times to polyurethans having polyether backbones which also indicates that neither the ether nor the ester groups were responsible for the stress decay.

The thermal instability of urethans has long been known.[16] It has been shown that aromatic urethans dissociate[12] to isocyanates around 180°. More recently quantitative studies have been made of the kinetics of urethan dissociation[17] in a series of solvents. As the reaction rate was greatly affected by the solvent, little correlation can be made with the present investigation.

It is also well known that substituted ureas dissociate[16] to isocyanates and amines between 170–180°.[12] Kinetic studies[18] of these decompositions in several solvents indicate that the reaction proceeds at an appreciable rate at 150°.

It is obvious from Table I that the samples with predominantly urethane linkages, II and IV, have relaxation times five times greater than those with 50% urethan and 50% substituted urea and biuret groups, V and VI. If this is the effect on the relaxation rate of replacing one half the urethan groups with biurets and ureas, a sample containing all urea and biuret linkages would decay at a rate ten times that of II and IV. Since the relaxation time is inversely proportional to the rate constant for the chain scission reaction it appears that the rate constant for the dissociation of the urethan group is less than one-tenth that for the combined effect of the substituted urea and biuret groups under these experimental conditions. A more quantitative statement differentiating between the substituted urea linkages and the biuret cross linkages is not possible at this time.

Acknowledgment.—The authors wish to express their gratitude to the Thiokol Chemical Corporation for the coöperation extended to us which made this research possible.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Solvent Effects and Ester Interchange in Basic Hydrolysis of Esters

BY GEORGE A. GALLAGHER, JOHN G. MILLER AND ALLAN R. DAY

RECEIVED MARCH 1, 1957

The saponification of ethyl acetate and methyl acetate has been measured at 30° in dioxane–water mixtures containing additional solvents found earlier to facilitate ammonolysis and concurrent hydrolysis of these esters. The effect of these additional solvents in the highly basic solutions is different from that found for the ammoniacal solutions. Ester interchange was observed with methanol and ethylene glycol as additives. The alcohols as well as glycol and some lactamides decrease the velocity of the hydrolysis, probably by solvating the hydroxyl ion through hydrogen bonding, thereby decreasing its reactivity. The effect of acetone, which increases the rate of saponification, is probably due to solvation of the activated complex.

In studies of the effect of hydroxylated substances and especially substances containing the groupings O–C–C–O or O–C–C–N upon the rate of ammonolysis of methyl acetate, it has been observed that these substances also accelerated the concurrent hydrolysis of the ester.[1] To investigate separately the effect of these and other solvents upon the hydrolysis reaction alone, the present study deals with the saponification of esters in dioxane–water systems to which these solvents were added in partial replacement of the dioxane. Thus, the reference standard reaction system was 20 molar water in dioxane and at the start of reaction contained 0.048 *M* NaOH and 0.040 *M* ester. In the other systems, the added substances merely replaced some of the dioxane, the standard amounts of water, NaOH and ester remaining constant.

Experimental

Reagents.—Dioxane, methyl acetate, methyl alcohol, ethylene glycol, lactamide, N-methyllactamide and N,N-dimethyllactamide were purified as described previously.[1] The pinacol was Eastman Kodak white label material and was used without further purification; m.p. 42.5–43°.

Ethyl acetate was dried over anhydrous potassium carbonate and fractionally distilled through a 35 cm. packed column; b.p. 77.0°, $n^{25}D$ 1.3704. Acetone was purified by refluxing with addition of small quantities of solid potassium permanganate until a pink color persisted. It was then fractionally distilled; b.p. 56.1°, $n^{25}D$ 1.3567. Ethyl alcohol was dried by the method of Lund and Bjerrum[2] and was then distilled; b.p. 78.4°, $n^{25}D$ 1.3599.

Procedure.—A stock solution of 0.1 *N* NaOH in dioxane was made by weighing the calculated amount of carbonate-free 0.2 *N* NaOH into a 1-liter volumetric flask, followed by weighed addition of sufficient water to give a final water concentration of 40 molar. The flask was filled close to the mark with dioxane, thermostated for two hours at 30° and then filled to the mark with dioxane. This stock solution was stored in a paraffin-coated flask under nitrogen. New solutions were made every three weeks. Determinations of the normality of the solution at the beginning and end of the three-week period showed a variation of only one part per thousand.

Runs were made in the following typical way. A freshly-prepared dioxane solution of known added solvent concentration was added volumetrically in desired amount to a reaction flask, followed by the requisite amount of stock solution, also measured volumetrically. After mixing, the flask was thermostated for at least two hours and then brought to volume with dioxane. Reproducibility of NaOH concentration at this stage was shown to be within one part per thousand.

Next, the ester was weighed to the nearest 0.1 mg., in a 1-ml. glass-stoppered weighing bottle and added to the thermostated reaction flask. The empty weighing bottle was also dropped in to ensure complete transfer of ester. By this procedure, shaking could be started within one to two seconds after addition of ester. After shaking for 25 seconds, the flask was replaced in the thermostat. Ten-ml. aliquots were removed periodically and added to 25 ml. of chilled 0.025 *N* HCl to stop reaction. Back-titration was run with 0.025 *N* NaOH.

The thermostat was kept within ±0.01 of 30° in all runs. Frequent reference determinations (no solvent catalyst added) were run.

Results

For the saponification of ethyl acetate, Table I lists the results showing the effects of acetone, pinacol, and a group of substances found earlier[1] to facilitate the ammonolysis and concurrent hydrolysis of esters. The values for the water–dioxane systems at 2, 4 and 8 *M* additional water may be compared with the results of other workers.

TABLE I

THE EFFECT OF VARIOUS ADDED SUBSTANCES ON THE RATE OF HYDROLYSIS OF ETHYL ACETATE AT 30° IN 0.048 *M* NaOH IN DIOXANE CONTAINING 20 *M* H_2O[a]

Added substance	Concn., *M*	Rate constant[b] ($k \times 10^2$)	Mean error $\times 10^2$
Water[d]	..	6.98[c]	0.06
	0.12	6.98	.02
	.20	7.12	.03
	.40	7.19	.17
	2.00	7.93	.08
	4.00	8.12	.10
	8.00	8.93	.13
Ethanol	0.40	6.33	.05
	2.00	6.01	.01
	6.00	4.24	.03
	8.00	3.63	.01
Acetone	0.40	7.21	.05
	2.00	7.36	.08
	6.00	7.56	.06
Pinacol	0.20	6.97	.04
	1.00	6.80	.14
Lactamide	0.12	4.49	.03
N-Methyllactamide	0.12	4.54	.04
	.20	3.51	.07
	.40	2.39	.02
	.80	1.49	.01
N,N-Dimethyllactamide	.12	6.54	.11

[a] Initial ester concentration 0.04 *M* throughout. [b] The rate constant in the usual bimolecular rate expression, $dx/dt = k(a - x)(b - x)$, expressed in liter mole^{-1} sec. Except where otherwise noted, each k is the mean of the separate values obtained from six samples taken at 120 second intervals in a single run. [c] This is the grand mean for eight separate runs. [d] The concentrations listed for H_2O are, of course, the concentrations above 20 *M*.

(1) T. A. Koch, J. G. Miller and A. R. Day, THIS JOURNAL, **75**, 953 (1953); G. R. Wolf, J. G. Miller and A. R. Day, *ibid.*, **78**, 4372 (1956).

(2) H. Lund and J. Bjerrum, *Ber.*, **64B**, 210 (1931).

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The 2 and 8 *M* solutions correspond nearly to 60 and 50 volume % dioxane, concentrations at which Nair and Anantakrishnan[3] found k to be 7.44×10^{-2} and 8.58×10^{-2} l. mole^{-1} sec.$^{-1}$ at 30° for ethyl acetate. The 4 *M* system is about 57.5% dioxane by weight, and at exactly 57.9 weight % dioxane, Tommila and co-workers[4] found the value 8.16×10^{-2} l. mole^{-1} sec.$^{-1}$ at 30° for this ester. In the concentration range in which we have worked these and other workers have observed the same increase in rate with increase in amount of water.

The other results are not directly comparable to any other values in the literature for the reason that no one else has reported measurements of the hydrolysis of ethyl acetate in these ternary solvent mixtures.

Table II shows the behavior of the hydrolysis of ethyl acetate in water–methanol–dioxane and water–ethylene glycol–dioxane systems at 30°. Closely related to these data are the results shown in Table III for the hydrolysis of methyl acetate. While the k values were constant throughout any run for methyl acetate, they show large drifts upward for ethyl acetate in the presence of methanol and ethylene glycol. That these increases are due to ester interchange is apparent from the dependence of the change upon the amount of methanol or ethylene glycol present and of the near equality of the velocity constants of methyl acetate hydrolysis at 4 and 8 *M* methanol with the specific rates for ethyl acetate near the end of the runs in the presence of 4 and 8 *M* methanol. For ethyl acetate and NaOH concentrations nearly the same as ours, Tommila and co-workers[4] reported that a similar increase in k took place during reaction in methanol–water and ethylene glycol–water mixtures, this increase being ascribed to transesterification. These workers noted that when the solutions contained 70 weight % or more of methanol, k was almost constant, which they took to indicate that the conversion of ethyl acetate to methyl acetate is very rapid at that concentration. Our highest methanol concentration was only 27 weight %.

Extrapolation of the ethyl acetate rates to zero time, *i.e.*, to a condition of no transesterification, shows that the saponification of that ester is hindered by both methanol and ethylene glycol, the magnitude of the effect of methanol being nearly the same as that of ethanol. The results also agree with the finding of Tommila[4] that in aqueous systems the solvent effects of ethylene glycol and methanol were closely similar in depressing the alkaline hydrolysis of ethyl acetate. Figures 1 and 2 show the extrapolation of the ethylene glycol runs and the methanol runs at higher methanol concentrations. At the lowest concentrations

Table II

The Hydrolysis of Ethyl Acetate at 30° in 0.048 *M* NaOH in Dioxane Containing 20 *M* H_2O and Methanol or Ethylene Glycol[a]

Additional substance	Concn., *M*	$k \times 10^2$ for sample taken at time (in sec.) shown: 120	240	360	480	600	720
Methanol	0.20	7.40	7.45[b]	7.74	7.71	7.81	7.74
	0.40	7.54	..	8.13	8.13	8.12	8.40
	2.00	6.80	7.51	8.15	8.49	8.91	9.18
	4.00	5.19	5.95	6.43	6.58	7.05	7.34
	4.00	5.17	5.83	6.35	6.67	7.44	7.10
	8.00	3.26	3.41	3.70	3.81	3.93	4.05
Ethylene glycol	0.20	7.35	7.69	7.92	7.93	8.17	8.22
	1.00	5.92	6.65	7.31	7.56	7.95	7.83
	2.00	3.85	4.62	5.15	5.58	5.88	6.10

[a] Initial ester concentration 0.04 *M* throughout. [b] At 245 seconds.

Table III

The Effect of Addition of Water or Methanol on the Rate of Hydrolysis of Methyl Acetate at 30° in 0.048 *M* NaOH in Dioxane Containing 20 *M* H_2O[a]

Added substance	Concn., *M*	$k \times 10^2$	Mean error $\times 10^2$
Water	..	16.28	0.19
	0.40	16.18	.43
	2.00	16.92	.23
	6.00	16.99	.38
	8.00	17.22	.41
Methanol	..	16.27	.16
	0.40	15.25	.32
	2.00	10.94	.17
	4.00	7.39	.15
	6.00	5.50	.02
	8.00	4.22	.05

[a] The procedures, initial concentration of ester, and units of k were the same as for ethyl acetate, except that samples were taken at 90 instead of 120 second intervals.

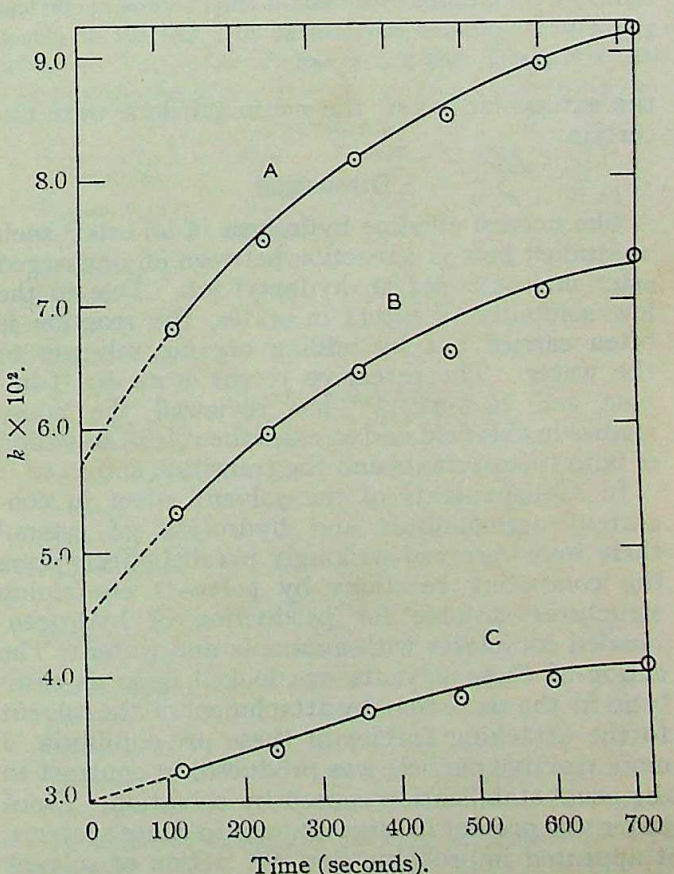

Fig. 1.—The extrapolation to zero time of the velocity constants for the alkaline hydrolysis of ethyl acetate in methanol–water–dioxane mixtures at 30°: (A) 2 *M* methanol; (B) 4 *M* methanol; (C) 8 *M* methanol.

(3) P. M. Nair and S. V. Anantakrishnan, *Proc. Indian Acad. Sci.*, **32A**, 187 (1952).
(4) E. Tommila, A. Koivisto, J. P. Lyrra, K. Antell and S. Heimo, *Ann. Acad. Sci. Fennicae*, [A] II, **47**, 3 (1952).

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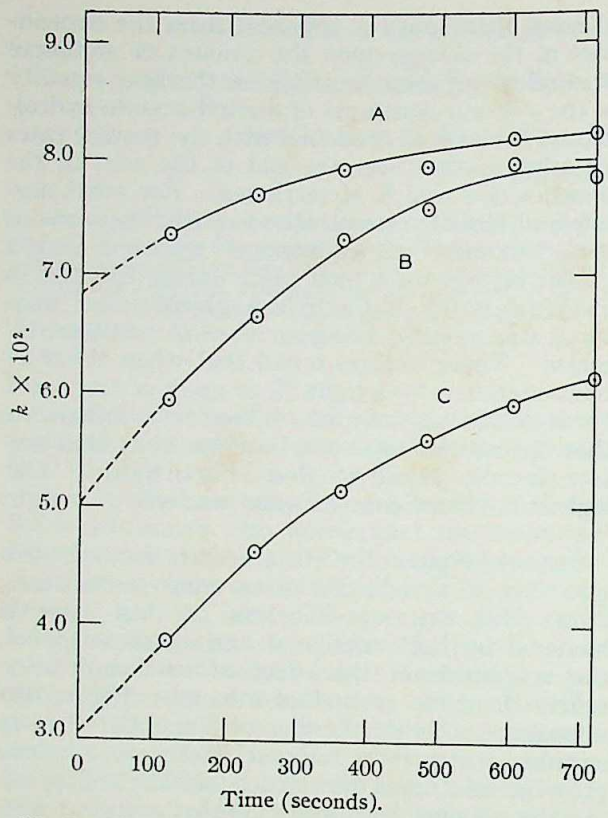


Fig. 2.—The extrapolation to zero time of the velocity constants for the alkaline hydrolysis of ethyl acetate in ethylene glycol–water–dioxane mixtures at 30°: (A) 0.2 *M* glycol; (B) 1 *M* glycol; (C) 2 *M* glycol.

the extrapolations of the methanol data were uncertain.

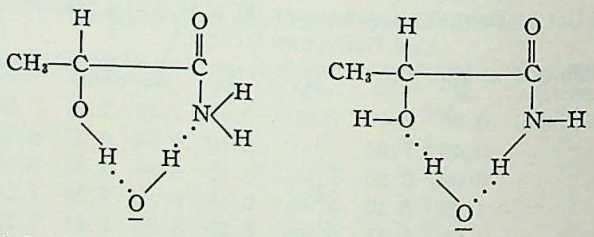
Discussion

The normal alkaline hydrolysis of an ester[5] such as studied here is a reaction between an uncharged ester molecule and an hydroxyl ion. Due to the low solubility of esters in water, the reaction is often carried out by adding organic solvents to the water. The extensive recent work by Tommila and co-workers[4,6] has reviewed the many studies in this field and stresses the role of solvation of both the reactants and the transition state.

In measurements of the solvent effect in concurrent ammonolysis and hydrolysis of esters,[1] there were observed strikingly parallel effects upon the competing reactions by solvents containing structures suitable for production of hydrogen-bonded complexes with ammonia and water. The action of these solvents was looked upon as catalytic in the sense that by attachment of the solvent to the attacking species in these pre-equilibria, a more reactive particle was produced, in contrast to the usual stabilization caused by solvation. Since water was present in large amount in those systems, it appeared improbable that the action of solvent was through complete removal of a proton from ammonia to form free amide ions as the principal attacking species in ammonolysis. It also appeared unlikely that the effect of the added solvent was exerted through transesterification, for the rate constants did not show strong drifts during progress of reaction. Indeed, direct tests showed that no appreciable ester interchange in the simple ammonolysis of esters is probable in ethylene glycol–water mixtures.[7] In anhydrous systems containing alcohols, the reaction of free amide ions and the role of ester interchange may be more important.[8–10]

It is now apparent that the simulated hydroxyl ions pictured for hydrolysis in the ammoniacal reaction systems are of small importance in competition with the hydroxyl ions in the more basic media. Indeed, the addition of alcohol at nearly constant water concentration causes a decrease in reactivity of the hydroxyl ions in the highly basic media. Since Tommila[4,6] has shown that the effect due to complete transfer of a proton from alcohol to the ion probably is not appreciable until alcohol concentrations much higher than those used here are reached, the decrease in rate may be due to solvation of the type R–O–H. . .$\bar{O}$H.

The lactamides exerted a strong effect in comparison with methanol or ethanol. Here, cyclic hydrogen bonded complexes of the types shown here for lactamide



might be operative. For N,N-dimethyllactamide, which showed relatively little activity, the second type would not exist and the first type might not form due to the bulk of the methyl groups attached to the nitrogen atom.

Pinacol would be expected to have small effect because of the steric hindrance and electron release effects of the methyl groups attached to the carbon atoms holding the hydroxyl groups. Kuhn[11] has suggested that in the presence of any given hydrogen acceptor, the hydrogen bond formed by various alcohols would be stronger the more acidic the alcohol. We note also that little ester exchange would be expected for this tertiary alcohol, as confirmed by the constancy of the velocity constants throughout the runs with pinacol.

Finally, we may inspect the effect of acetone. In binary mixtures with water, methanol and ethylene glycol always decrease the rate of basic hydrolysis of esters. On the other hand, addition of ethanol and other aliphatic alcohols, as well as acetone and dioxane, increases the reaction velocity at low temperatures and up to a mole fraction of

(5) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 752 ff.

(6) E. Tommila, *Suomen Kemistilehti*, **25B**, No. 9, 37 (1952); E. Tommila and S. Hietala, *Acta Chem. Scand.*, **8**, 257 (1954); E. Tommila and S. Maltamo, *Suomen Kemistilehti*, **28B**, No. 3, 73, 118 (1955).

(7) M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **71**, 1250 (1949).

(8) W. H. Watanabe and L. R. DeFonso, *ibid.*, **78**, 4542 (1956).

(9) R. Baltzly, I. M. Berger and A. A. Rothstein, *ibid.*, **72**, 4149 (1950).

(10) F. H. Wetzel, J. G. Miller and A. R. Day, *ibid.*, **75**, 1150 (1953).

(11) L. P. Kuhn, *ibid.*, **74**, 2492 (1952).

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less than 0.1 for the organic solvent. Tommila[4,6] has ascribed the increase in rate to the existence of both hydrophilic and hydrophobic groups in the activated complex. Because of the specific attractions of these groups, solvation of the complex should be greater in some mixtures of water and organic solvents than in water alone. The effects found for dioxane and acetone in binary mixtures with water were remarkable for their near equality,[4] and our results show that in the ternary solvent system dioxane–acetone–water these effects augment each other up to a mole fraction of acetone higher than 0.2.

PHILADELPHIA 4, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Photochemical Decomposition of Cyclohexanone, Cyclopentanone and Cyclobutanone[1]

BY F. E. BLACET AND ARNOLD MILLER

RECEIVED MARCH 2, 1957

Quantum yields of the photodecomposition products of these cycloketones have been determined in the ranges 3130–2537 Å. and 100–300°. Cyclohexanone principal products were carbon monoxide, cyclopentane and pentene-1; minor products were ethylene and propylene. At 2537 and 2654 Å. quantum yields were temperature independent. At 3130 Å. the yields of carbon monoxide, cyclopentane and pentene-1 increased with temperature. Cyclopentanone products were carbon monoxide, cyclobutane and ethylene. The yields were temperature dependent at 3130 Å., but independent at 2654 and 2537. Cyclobutanone products were carbon monoxide, cyclopropane, ethylene, propylene and presumably ketene. Yields were temperature independent at 3130 and 2654 Å. All the ketones gave some evidence of polymer formation and a polymerization quantum yield is given based on material balance. A general mechanism of photodecomposition has been proposed involving two primary chemical reactions, which accounts moderately well for all experimental results.

The photochemistry of cyclic ketones was initially investigated by Norrish and co-workers[2,3] and later by Benson and Kistiakowsky,[4] utilizing full radiation from mercury arcs. In this paper are given quantum yields obtained under controlled conditions of wave length and temperature for the vapor phase photolyses of cyclohexanone, cyclopentanone and cyclobutanone. Dunn and Kutschke[5] have published a few results obtained with cyclohexanone since the information given herein was reported originally.[1]

Experimental

Photolyses were performed in a 20-cm. cylindrical fused silica cell of 3 cm. diameter which could be maintained at desired temperatures. Monochromatic radiant energy obtained by the use of a quartz monochromator was measured with the aid of a phototube which had been calibrated at each wave length involved with a thermopile-galvanometer system. Photolysis products were identified and quantitatively analyzed by means of both mass spectrometric and microgas analytical techniques.

The cyclohexanone and cyclopentanone were prepared by drying and fractionating standard Eastman White Label material. Both the boiling points and refractive indices of the final products checked published values. Cyclobutanone was synthesized by the method of Roberts and Sauer.[6] The boiling point was 98.2° at 755 mm. and $n^{25}D$ was 1.4191. These values are to be compared to 98–100° and $n^{25}D$ 1.4189 reported by Roberts.

Absorption spectra of the three compounds determined in heptane solution, and determined also in the vapor phase for cyclohexanone and cyclopentanone, were in agreement with those reported previously.[4] The electronic absorption region of interest extends approximately from 2400 to 3400 Å. Cyclobutanone and cyclopentanone have several prominent absorption bands in this region, while the cyclohexanone spectrum has only a faint indication of structure.

Quantum yields obtained in the study of all three of the ketones are given in Table I. All values are averages based on duplicate runs at each temperature, except for one experiment shown for cyclobutanone in which water vapor was added to the reaction system. Mean deviations of quantum yields were from 4 to 7%. Exposure times averaged between three and four hours and at the several wave lengths absorbed intensity, I_a, varied between 1×10^{-8} and 1×10^{-9} Ein./l./sec. Where temperature ranges are indicated, quantum yields were found to be constant for runs

TABLE I

QUANTUM YIELDS OF PRODUCTS IN THE PHOTOLYSIS OF CYCLOHEXANONE, CYCLOPENTANONE AND CYCLOBUTANONE

Cyclohexanone				
Wave length, Å.	3130	3130	2654	2537
Temp., °C.	125	300	100–300	100–300
$\Phi_{\text{carbon monoxide}}$	0.22	0.91	0.78	0.81
Φ_{ethylene}	.02	.02	.02	.03
$\Phi_{\text{propylene}}$	.03	.03	.02	.02
$\Phi_{\text{cyclopentane}}$	.06	.31	.28	.21
$\Phi_{\text{pentene-1}}$	.12	.59	.45	.32
$\Phi_{\text{polymerization}}$	.01	− .02	.03	.25
Cyclopentanone				
Wave length, Å.	3130	3130	2654	2537
Temp., °C.	125	225	100–300	100–300
$\Phi_{\text{carbon monoxide}}$	0.33	0.42	0.61	0.74
Φ_{ethylene}	.15	.34	.25	.21
$\Phi_{\text{cyclobutane}}$	.26	.17	.27	.21
$\Phi_{\text{polymerization}}$	.01	.10	.21	.43
Cyclobutanone				
Wave length, Å.	3130	3130[a]	2654	
Temp., °C.	100–300	100	100–300	
$\Phi_{\text{carbon monoxide}}$	0.35	0.40	0.53	
Φ_{ethylene}	.51	.54	.53	
$\Phi_{\text{cyclopropane}}$	.13	.14	.17	
$\Phi_{\text{propylene}}$	.014	.014	.12	
$\Phi_{\text{polymerization}}$	.21	.25	.24	

[a] 70 mm. H_2O vapor and 136 mm. cyclobutanone in reaction cell.

(1) Presented before the Division of Physical and Inorganic Chemistry at the Chicago meeting of the American Chemical Society, September, 1953.
(2) M. Saltmarsh and R. G. W. Norrish, *J. Chem. Soc.*, 455 (1935).
(3) C. H. Bamford and R. G. W Norrish, *ibid.*, 1421 (1938).
(4) S. W. Benson and G. B. Kistiakowsky, THIS JOURNAL, **64**, 80 (1942).
(5) J. R. Dunn and K. O. Kutschke, *Can. J. Chem.*, **32**, 725 (1954).
(6) J. D. Roberts and C. W. Sauer, THIS JOURNAL, **71**, 3925 (1949).

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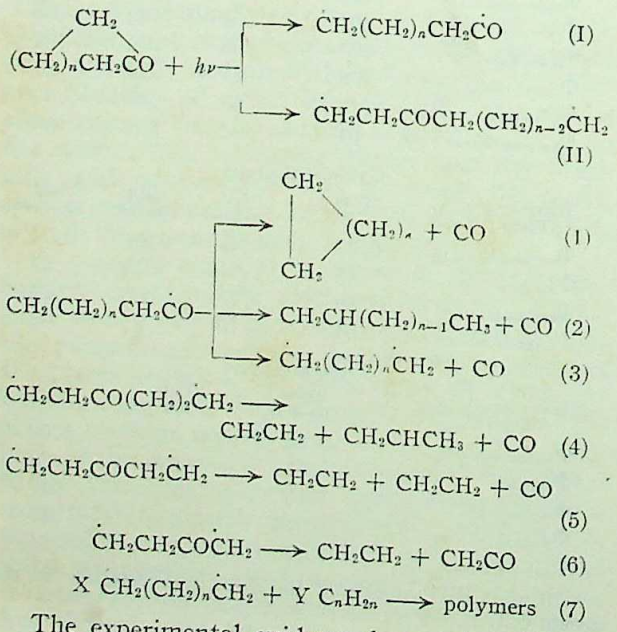
made at seventy-five degree intervals within the range. Pressures of the ketones in all runs were between 100 and 150 mm., measured at 125°. "$\Phi_{polymerization}$," in the table, is a function postulated to attain material balance and is considered to be a measure of polymer formation, giving rise to an equivalent amount of carbon monoxide without production of like amounts of low molecular weight hydrocarbons. A light yellow non-volatile residue became evident in the reaction cell after several runs, especially at the shorter wave lengths. Mass spectra of butanone photolysis products contained prominent 42 and 41 peaks which were attributed to ketene. Because of experimental difficulties, no other direct evidence was obtained for this compound.

Discussion

Often temperature independence of quantum yields signifies intramolecular rearrangement in the primary process followed by unimolecular dissociation. Free radical primary processes, on the other hand, often lead to quantum yields which are temperature dependent since secondary reactions involving a radical and a normal molecule may occur requiring an activation energy of several kilocalories per mole. In this study, each ketone, at two different wave lengths, gave quantum yields which are temperature independent over a two-hundred-degree range, thus indicating non-free radical primary processes. Opposed to this concept, cyclohexanone and cyclopentanone show temperature dependence at 3130 Å. and all the ketones gave some polymerization under all experimental conditions. These facts perhaps can best be explained by postulating as primary photochemical processes the formation of biradicals by opening the rings followed for the most part by rapid dissociation of these radicals in a variety of ways to give stable molecules. The general mechanisms may be the following in which, however, reactions 4, 5 and 6 deal with biradicals from specific ketones.



$$\text{(CH}_2\text{)}_n\text{CH}_2\text{CO} + h\nu \longrightarrow \begin{cases} \text{CH}_2(\text{CH}_2)_n\dot{\text{C}}\text{H}_2\dot{\text{C}}\text{O} & \text{(I)} \\ \dot{\text{C}}\text{H}_2\text{CH}_2\text{COCH}_2(\text{CH}_2)_{n-2}\dot{\text{C}}\text{H}_2 & \text{(II)} \end{cases}$$

$$\text{CH}_2(\text{CH}_2)_n\text{CH}_2\text{CO} \longrightarrow \begin{cases} \text{CH}_2 \\ \quad (\text{CH}_2)_n + \text{CO} & \text{(1)} \\ \text{CH}_2 \\ \text{CH}_2\text{CH}(\text{CH}_2)_{n-1}\text{CH}_3 + \text{CO} & \text{(2)} \\ \text{CH}_2(\text{CH}_2)_n\text{CH}_2 + \text{CO} & \text{(3)} \end{cases}$$

$$\text{CH}_2\text{CH}_2\text{CO}(\text{CH}_2)_2\text{CH}_2 \longrightarrow \text{CH}_2\text{CH}_2 + \text{CH}_2\text{CHCH}_3 + \text{CO} \quad (4)$$

$$\text{CH}_2\text{CH}_2\text{COCH}_2\text{CH}_2 \longrightarrow \text{CH}_2\text{CH}_2 + \text{CH}_2\text{CH}_2 + \text{CO} \quad (5)$$

$$\text{CH}_2\text{CH}_2\text{COCH}_2 \longrightarrow \text{CH}_2\text{CH}_2 + \text{CH}_2\text{CO} \quad (6)$$

$$\text{X CH}_2(\text{CH}_2)_n\text{CH}_2 + \text{Y C}_n\text{H}_{2n} \longrightarrow \text{polymers} \quad (7)$$

The experimental evidence leaves doubtful the number of primary processes. However, *a priori* reasoning has led the authors to postulate two which lead to chemical change: reaction I, in which an α-carbon is separated from the carbonyl carbon, and reaction II, in which the energy absorbed in the carbonyl group is perhaps transmitted both ways around the ring causing rupture at or near the opposite side. (I) is the logical precursor of reactions 1, 2 and 3 and (II) of (4), (5) or (6), depending on the particular ketone under investigation. In considering the mechanics of the processes, it is reasonable to assume the initial breaking of a single carbon–carbon bond followed by other reactions of the resulting biradicals. The constant ratios of (1) and (2), and presumably (3), over a wide temperature range indicates that the biradicals first produced in (I) rapidly rearrange and dissociate without environmental influence. Since only photons of equal energy were used in a given experiment, this implies that the state of a ketone molecule at the moment of light absorption determined which of the three secondary adjustments would take place. Why this should be is not evident. It is not clear, also, why the ratios of (I) and (II) for all three compounds remain constant, as determined by the quantum yields of the products, at each of two wave lengths over a two-hundred-degree temperature range.

Cyclohexanone.—It follows from the assumed mechanism that Φ_{CO} is a measure of the sum of primary quantum yields, ϕ_I and ϕ_{II}. Reaction (II) is followed by (4), perhaps so inevitably that they could be combined in one concerted process. Thus, the quantum yields of ethylene or propylene, which are equal under all conditions employed, are a measure of ϕ_{II}. Since ϕ_{II}, thus estimated, was always small, Φ_{CO} is an approximate measure of ϕ_I. At wave lengths 2537 and 2654 Å. this indicates about 20% of the absorbed energy was dispersed by photophysical means, *i.e.*, by fluorescence or by thermal deactivation, independent of temperature over the range 100–300°. At λ 3130 Å., however, ϕ_I increases from about 0.2 to 0.9 over the range 125–300°, indicating that at this wave length the quantum energy is near, and perhaps slightly less than the activation energy which is necessary to rupture the molecules by (I).

At λ 3130 and λ 2654, the sum of quantum yields of pentene-1, cyclopentane and ethylene (or propylene) is equal to Φ_{CO}. This is not so at λ 2537 and $\Phi_{polymerization}$, involving reactions 3 and 7, was devised to account for the difference. In reaction 7, C_nH_{2n} may represent other biradicals or, as photolysis proceeded, the olefin products also may have become involved. Perhaps the marked decrease in quantum yield of pentene-1 found at λ 2537 from that obtained at λ 2654 can be accounted for in this way.

Cyclopentanone.—For this compound also, Φ_{CO} is a measure of the sum of ϕ_I and ϕ_{II}, and the values indicate that from one-fourth to two-thirds of the absorbed energy was dissipated photophysically, depending on experimental conditions. Reaction (II) presumably was followed always by (5), thus $\frac{1}{2}\,\Phi_{ethylene}$ equalled ϕ_{II}. The absence of a butene among the reaction products shows that under no condition employed did reaction (2) occur and, therefore, from the mechanism, (I) could be followed only by (1) and (3). At λ 3130 and 125°, $\frac{1}{2}\,\Phi_{ethylene}$ plus $\Phi_{cyclobutane}$ equals Φ_{CO}, indicating that (3) was not occurring, and therefore $\Phi_{cyclobutane}$ was a measure of ϕ_I. At 225° and this

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wave length and at both λ 2654 and 2537 over the temperature range studied, this simple relationship no longer held, indicating that reaction 3, followed by (7), was taking place. The absence of butene among the photolysis products may be interpreted to mean that the free radical cyclization reaction has a substantially lower activation energy than the reaction involving a hydrogen shift to form an olefin. This is to be expected since considerable strain would be present in the transition state required to form butene.

Cyclobutanone.—The large amount of ethylene formed from cyclobutanone indicates that reaction 6, involving the production of ketene, is important. Because ethylene was produced in excess of carbon monoxide at λ 3130, it was suggested originally that ketene further decomposed. To evaluate this hypothesis, water vapor was added in one instance on the assumption that it would react with the ketene vapor to form acetic acid. Experimental difficulties left the test for acetic acid in doubt and it may or may not have been produced. However, it is apparent from the results given in Table I that the water had no important effect on quantum yields and it follows, also, that it did not trap the postulated biradicals. In view of the results later obtained at λ 2654, appreciable ketene decomposition does not appear to have occurred in any event.

The general mechanism postulated above applies to this cycloketone, also. Accepting this mechanism, Φ_{CO} is a measure of ϕ_I and $\Phi_{ethylene}$ is a measure of ϕ_{II}. ϕ_I plus ϕ_{II}, estimated in this way, is about 0.9 at λ 3130 and 1, within experimental errors, at λ 2654; thus, for this compound, photochemical conversion of absorbed energy is high. Polymerization, reaction 7, was important under all conditions in which this ketone was studied.

Los Angeles, Cal.

[Contribution from the Department of Chemistry, The University of Texas]

Kinetic Studies of Thiourea Derivatives. III. Trimethylthiourea and Tetramethylthiourea

By William H. R. Shaw and David G. Walker

Received March 20, 1957

Trimethylthiourea has been studied kinetically in aqueous solutions at elevated temperatures. This substance decomposes to form methylamine, dimethylamine and carbon oxysulfide as ultimate products in acid solutions. The decomposition is first-order and is uninfluenced by ionic strength in media of low *p*H. Rate constants at various temperatures and Arrhenius parameters are reported. Tetramethylthiourea also has been studied under similar conditions. This substance shows little or no tendency to react in neutral solutions. In acidic or basic media, however, hydrolysis is observed. The significance of these findings and their relevance to previous work is discussed.

Introduction

Thiourea,[1] methylthiourea[2] and the dimethylthioureas[3] have been studied previously in this Laboratory. Although some information on the chemistry of trimethylthiourea[4] and tetramethylthiourea[5] is available, no kinetic investigations with these compounds have been reported. The present work was, consequently, undertaken to secure rate data for these substances and to complete, thereby, our kinetic study of the methylated thioureas.

Experimental

Trimethylthiourea (1,1,3-trimethyl-2-thiourea) was prepared by the addition of dimethylamine to methyl isothiocyanate.[6] It was crystallized, m.p. 87° (lit.[4] 87°) twice from water solutions.

Anal. Calcd. for $C_4H_{10}N_2S$: C, 40.68; H, 8.54; N, 23.70. Found: C, 40.77; H, 8.50; N, 23.74.

Tetramethylthiourea (1,1,3,3-tetramethyl-2-thiourea) was prepared by heating bis-(dimethylthiocarbamyl) sulfide under air reflux for several hours,[7] followed by twice crystallizing the resulting mass from water. The product was then distilled at atmospheric pressure, b.p. 243° (lit.[8] 245°). Recrystallization from water gave the final product, m.p. 78° (lit.[8] 78°).

Anal. Calcd. for $C_5H_{12}N_2S$: C, 45.45; H, 9.14; N, 21.1. Found: C, 44.94; H, 8.68; N, 19.6.

The analytical methods for thiocyanate, ammonia, methylamine and dimethylamine have been described.[1-3] Total amine produced was also determined according to the following procedure. Reaction solutions of the thiourea under study were made 10 to 20 m*M* in standard acid, and the samples were then allowed to react until the total amine concentration was approximately 4 m*M*. The unreacted acid in the samples was subsequently determined by titration with standard NaOH (approximately 10 m*M*). During the titration the *p*H was read at convenient intervals and the end-point taken as the point when the change of *p*H with a small increment of standard basic solution was a maximum. Titration blanks were always run on aliquots of the unreacted experimental solutions. Results given by this method were compared with those obtained by our usual spectrophotometric techniques. Within the combined experimental uncertainties, the two methods gave identical results.

The procedures used in conducting the kinetic runs and the apparatus employed in this investigation have been described in previous work.[1-3]

Results

Reacted solutions of trimethylthiourea were found to contain methylamine, dimethylamine and carbon oxysulfide. The rates of formation of methylamine and dimethylamine were followed and the corresponding empirical first-order rate constants, k_3 and k_4, were calculated by the rate equation previously presented. Measurements were made with 0.015 *M* H_2SO_4 and 0.015 *M* HNO_3 solutions. These solutions also contained tri-

(1) W. H. R. Shaw and D. G. Walker, This Journal, **78**, 5769 (1956).
(2) W. H. R. Shaw and D. G. Walker, *ibid.*, **79**, 2681 (1957).
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(4) R. Singh, *J. Indian Chem. Soc.*, **33**, 610 (1956).
(5) M. Schenck, *Z. physiol. Chem.* (*Hoppe-Seyler's*), **77**, 370 (1912).
(6) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, New York, N. Y., 1955, pp. 599, 617.
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(8) M. Delépine, *Bull. soc. chim. France*, [4] **7**, 988 (1910).

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methylthiourea at concentrations ranging from 9.2 to 73.5 mM. In these acid media at 100° the following values were obtained for k_3 and k_4, respectively, $38.2 \pm 3.8 \times 10^{-7}$ and $37.2 \pm 2.2 \times 10^{-7}$ sec.$^{-1}$. Moreover results in acid solutions containing added sodium nitrate varying in concentration from 0.00 to 1.02 M demonstrated that the rate, under these conditions, was independent of ionic strength. Thus in acid media k_3 and k_4 are, within experimental error, equal and independent of average trimethylthiourea concentration, $\bar{u}$. No thiocyanate ion or ammonia could be detected in the reaction mixtures by our rather sensitive techniques. A first-order reaction producing methylamine and dimethylamine in equimolar amounts is clearly indicated.

The drastic dependence of k_4 on pH (Fig. 1) is quite different from the behavior of the analogous constant obtained with *unsym*-dimethylthiourea, but is very similar to the pH dependence of the k_3's obtained with methylthiourea and *sym*-dimethylthiourea.

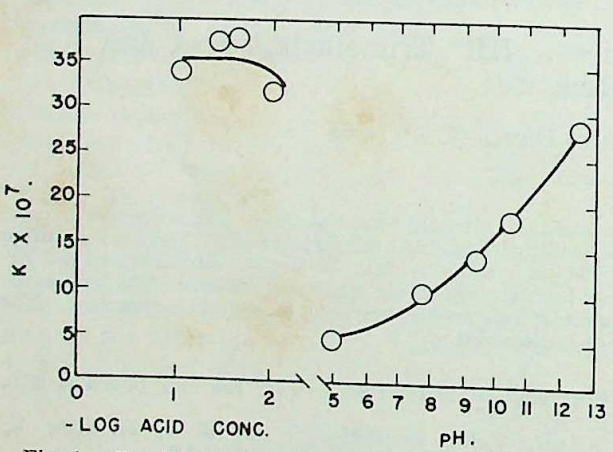


Fig. 1.—Empirical first-order rate constant (k_4) based on dimethylamine production as a function of acid concentration. Runs below pH 8 were made in HNO_3 solutions. Results recorded above pH 8 were obtained with 0.01 M borax buffers. An initial trimethylthiourea concentration of 50 mM was used with reaction times of 3.23 hr. on the basic side and 6.00 hr. in the low pH media.

A least squares analysis of data obtained spectrophotometrically at various temperatures in acid media (Table I) gave a frequency factor of 7.89×10^{14} sec.$^{-1}$ and an activation energy of 34.9 kcal. for k_4. A similar analysis applied to the data obtained by total amine analysis yielded a frequency factor of 4.98×10^{14} sec.$^{-1}$ and an activation energy of 34.4 kcal. The total amine analysis is somewhat more precise.[9]

Tetramethylthiourea was studied in various media at elevated temperature (Table II). In sharp contrast to the methylated thioureas containing a hydrogen bonded to nitrogen, this compound did not react extensively in neutral solution even at high temperatures and long reaction periods. Significant reaction in acidic and basic media did, however, occur producing dimethylamine and carbon oxysulfide. Ammonia, methylamine and thiocyanate ion were not detected in the reacted samples. Consequently since the slight reactivity of the compound was most probably due to hydrolysis and not to a simple decomposition no detailed quantitative studies were attempted.

(9) These parameters will reproduce the rate constants in Table I obtained by the titration method with a maximum deviation of 4%.

Table I

Rate Constants Obtained at Various Temperatures in Acid Solutions

Temp. ± 0.1°	$\bar{u}$[a]	t[b]	First-order rate constant,[c] sec.$^{-1} \times 10^7$ k_4
71.2	49.7	43.7	0.64
79.5	20.1	12.6	2.45[d]
80.0	49.5	21.4	2.38
90.0	49.0	11.0	8.10
90.0	99.9	6.15	9.83[d]
100.0	48.3	3.57	37.2
100.0	29.4	5.97	37.1[d]
109.6	8.91	5.85	120[d]
110.3	48.1	3.86	129
119.9	4.01	3.78	366[d]

[a] $\bar{u}$ is the average concentration of trimethylthiourea (mmoles/l.). [b] t is reaction time in hours. [c] The constant is based on the rate of dimethylamine production measured spectrophotometrically except values marked with superscript *d*. [d] These values were obtained by the titration method described in the Experimental section.

Table II

The Hydrolysis of Tetramethylthiourea

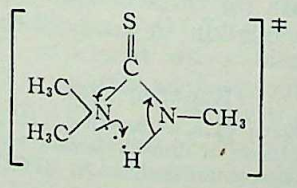
Medium	Time, hr.	Temp., °C.	Initial tetramethylthiourea, mM	Me_2NH[a] formed, mM
Water	123	110 ± 2	98.5	0.334
Water	18.5	150 ± 5	200	4.5
0.5 M HNO_3	25.5	110 ± 2	98.5	55.2
0.5 M NaOH	70	110 ± 2	98.5	137

[a] No NH_3, $MeNH_2$ or NCS^- could be detected in the reaction mixtures.

Discussion

All of the data obtained with trimethylthiourea can be rationalized by the reaction scheme

$(CH_3)_2N—CS—NH(CH_3) \rightleftharpoons$



(1)

$CH_3NCS + (CH_3)_2NH \longleftarrow$

$CH_3NCS + H_2O \longrightarrow CH_3NH_2 + COS$ (2)

Since reaction 2 is fast in acid solution, methylamine and dimethylamine should be produced in equimolar amounts. The stoichiometry (Results) is in accord with this reasoning since $k_3 = k_4$. As before the behavior of the empirical rate constant k_4 with increasing pH can be attributed to the occurrence of complicating reactions. With increasing pH the amines are no longer predominantly in the protonated form. Since the reverse of reaction 1 must take place through the unionized amine the reverse reaction will be more important at high pH. The other possible reaction

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$$CH_3NCS + CH_3NH_2 \longrightarrow (CH_3NH)_2CS \quad (3)$$

is also most probably involved.

The finding that tetramethylthiourea does not decompose establishes that a hydrogen atom bonded to nitrogen is necessary for decomposition to take place. It also provides additional strong support for the conclusion previously presented[3] that methyl groups do not migrate and that decomposition takes place by intramolecular hydrogen transfer and dissociation of the activated complex.

A more detailed theoretical interpretation of this and other data will be presented in the last paper of this series.

Acknowledgment.—The authors gratefully acknowledge the generous grant from the Research Corporation of New York that made this study possible. It is also a pleasure to express our thanks to the Humble Oil & Refining Company for the fellowship awarded to D.G.W.

AUSTIN 12, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KENTUCKY]

The Polarography of Quinoxaline[1]

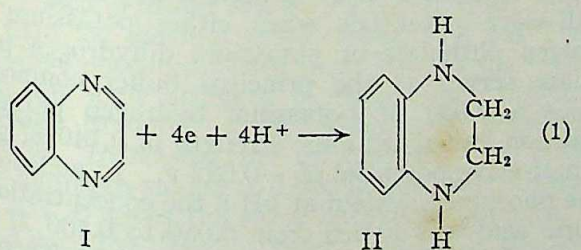
BY MURRAY P. STRIER AND J. C. CAVAGNOL[2]

RECEIVED APRIL 2, 1957

The reductions of quinoxaline at the dropping mercury electrode, conducted in buffered media in the *p*H range of 1 to 10, show well-defined, *p*H dependent waves. The influence of variations in buffer components, concentration and ionic strength on the nature of the waves have been investigated. The course of the reduction at all *p*H levels is not affected by changes in buffer components, buffer concentration or ionic strength. However, certain variations in half-wave potentials and diffusion current constants occur. Reduction to 1,4-dihydroquinoxaline is postulated for the whole *p*H range. From *p*H 1 to *p*H 2 reduction may proceed by a bimolecular, one-electron process that is not completely reversible. Reduction may also proceed by this process at *p*H 3 but this is apparently not true as the concentration of buffer components is increased. Over the *p*H range of 4 to 10 the simultaneous addition of two protons and two electrons is presumed to occur in an essentially reversible manner. Catalytic hydrogen waves are manifested following the formation of dihydroquinoxaline at *p*H's < 7 but are absent at higher *p*H's. At *p*H 7 the catalytic wave appears only at high buffer concentration.

Introduction

The polarography of quinoxaline (I) was undertaken in order to determine whether 1,2,3,4-tetrahydroquinoxaline (II) could be obtained by electrochemical methods. The over-all reduction is represented by



(1)

I II

The literature on polarography involving reduction at the dropping mercury electrode contains only two references to simple quinoxalines. Winkel and Proske[3] obtained a polarographic wave for 2,3-dimethylquinoxaline in 0.1 *M* ammonium chloride solution, but no analysis is given. Sartori and Furlani[4] studied the polarographic reduction of quinoxaline, its methiodide and its di-N-oxide. They found that quinoxaline gives a nearly reversible, 2-electron wave having an $E_{0.5}$ of -0.267 v. S.C.E. at *p*H 0 and 25°. Both prewaves and kinetic waves were found, in agreement with the present work. The formation of dihydroquinoxaline and the absence of the tetrahydro form were postulated. The roles of ionic strength and buffer composition were minimized, in contrast to the present paper.

Equation 1 demonstrates that *p*H is a critical factor in governing the reduction process. The need for employing buffered solutions having adequate ionic strength as supporting electrolytes has been stressed elsewhere.[5] Quinoxaline was studied systematically by varying buffer components, ionic strength, buffer concentration, *p*H and reductant concentration.

Experimental

Materials.—Quinoxaline was prepared by the method of Cavagnol and Wiselogle.[6] The product, resublimed prior to use was colorless and melted at 31.0–31.5°. It was used in the form of a 0.010 *M* stock solution stored under nitrogen in the dark. All supporting electrolyte components were C.P. grade and the suitability for polarographic work was established by blank runs.

Stock solutions of 0.110 *N* sodium hydroxide and 0.205 *N* hydrochloric acid were prepared and stored under nitrogen.

Apparatus.—A manual instrument of the type described by Kolthoff and Lingane[7] was used. Both the applied potential and the resulting current (as the potential across a 10,000-ohm precision resistor) were measured with a Leeds and Northrup student-type potentiometer. With this apparatus, solutions of 5.8×10^{-4} *M* cadmium sulfate in 0.100 *M* potassium chloride gave an $E_{0.5}$ value of -0.597 ± 0.001 v. *vs.* S.C.E. and an $I_d/Cm^{2/3}t^{1/6}$ value of 3.38 ± 0.02 at 25°.

All measurements were performed in a 100-ml. Berzelius

(1) Abstracted from a dissertation submitted to the Graduate School by Murray P. Strier in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Jan. 1952.

(2) Research Center, General Foods Corp., Tarrytown, N. Y.

(3) A. Winkel and G. Proske, *Ber.*, **69**, 1917 (1936).

(4) G. Sartori and C. Furlani, *Ann. chim.* (*Rome*), **45**, 251 (1955), *C. A.*, **49**, 15557b.

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beaker thermostated at 25 ± 0.05°. A saturated calomel electrode, stored permanently in the constant temperature bath, served as the reference electrode. This electrode was connected to the electrolysis cell by means of a saturated potassium chloride–agar bridge fitted with a sintered glass tip. Two capillaries, prepared from Corning marine barometer tubing, delivered mercury into distilled water at rates of 2.09 and 2.14 mg. sec.$^{-1}$. The height of the mercury column was fixed at 58.0 cm. for all measurements.

The *p*H measurements were made with a Beckman Model G *p*H meter and all resistances were measured with a Serfass Conductance Bridge, Model RC M15.

Procedure.—Preliminary experiments showed that the most suitable working range of the instrument was from 1 to 7 ma. Under these conditions the half-wave potentials were reproducible to ±2 mv. and the diffusion current constants varied less than ±1%.

The constituents of the Clark and Lubs buffer system were used in the *p*H range of 1 to 9. In order to study the effect of the reduction wave, it was necessary to employ other buffer systems. At *p*H 1 and *p*H 2 potassium hydrogen sulfate was substituted. Sodium hydrogen tartrate was used at *p*H 3 and the phosphate buffer system served well at *p*H 10. The concentrations of buffer salt (acid) were varied from 0.05 to 0.8 *M* with ionic strengths being 0.05 to 1.4 *M*.

Test solutions containing buffer components other than Clark and Lubs were prepared as follows. The appropriate solid buffer was weighed, dissolved in distilled water and standard acid or base added until the desired *p*H was reached. Sufficient potassium chloride or sodium chloride then was added to bring the ionic strength to the desired level. A final adjustment of *p*H was made by adding standard acid or base. Gelatin was added as maximum suppressor from a stock solution so that after dilution to volume (100 ml.), its concentration was 0.01%. Finally, quinoxaline stock solution was added to obtain the desired concentration without changing the *p*H.

Current and applied potential measurements were made in an atmosphere of purified nitrogen. After scanning the complete working range at 0.1 v. intervals and plotting the data, intermediate points were taken at 0.01 v. intervals. The mercury drop time was measured at 0.1 v. intervals over the significant portions of the wave. At the conclusion of each polarogram the cell resistance was determined to correct the half-wave potential for *iR* drop across the cell.

Results

In Table I are summarized the results obtained for the reduction of 4.5×10^{-4} *M* solutions of quinoxaline in two different buffer systems. The first buffer system employed is the Clark and Lubs buffers and will be designated henceforth as the "Low" buffers. The second buffer system, designated as the "High" buffers, is characterized by having a higher concentration of buffer components and ionic strength than the "Low" buffers at all *p*H's. The level of ionic strength for the "High" buffers is 0.6 *M* and the *p*H range covered is 1 to 10. The *p*H range covered with the "Low" buffers is 1 to 9.

Two major waves are obtained for quinoxaline over the *p*H range of 1 to 7. Only the first major wave is present at *p*H's > 7. The second major wave is not evident at *p*H 7 in the "Low" buffer and is measured with difficulty at this *p*H in the "High" buffer. The first major wave is partially differentiated into two equal segments at *p*H 1 and *p*H 2 in each buffer system but this is less distinct at *p*H 2. At *p*H 3 faint evidence of differentiation for the first major wave exists in the "Low" buffer but not in the "High" buffer. Some differentiation of the second major wave occurs in the "Low" buffers at *p*H 1 and *p*H 2, but this vanishes with increasing buffer concentration.

Generally, the concentration of quinoxaline was varied from 2.5×10^{-4} *M* to 7.0×10^{-4} *M* in both "Low" and "High" buffers. Also at each *p*H the effect of such variables as buffer constituents, concentrations and ionic strengths[8] on the nature of the polarographic waves, half-wave potentials and diffusion current constants were ascertained for 4.5×10^{-4} *M* solutions of quinoxaline. The results obtained can be given[9] briefly as follows:

A. First Major Wave.—At *p*H 1 the half-wave potential remains constant as the concentration of potassium hydrogen sulfate is varied from 0.400 to 0.800 *M* with an accompanying increase in ionic strength from 0.620 to 1.43 *M*. No uniform variations in half-wave potentials with increased buffer concentration and ionic strength can be discerned at *p*H 2. At *p*H 3 there is no apparent change in half-wave potential in going from 0.050 *M* potassium hydrogen phthalate buffer to 0.050 *M* sodium hydrogen tartrate buffer. Increasing the concentration of sodium hydrogen tartrate at this *p*H to 0.300 *M* leads to decreasingly negative half-wave potentials. Either increasing the ionic strength to 0.601 *M* by addition of neutral salt or increasing the concentration of sodium hydrogen tartrate to 0.400 *M* while maintaining the ionic strength constant at 0.601 *M* has no further influence on the half-wave potential. At *p*H 4 the half-wave potential varies from −0.488 to −0.480 v. as the concentration of potassium hydrogen phthalate increases from 0.050 to 0.250 *M* with the ionic strength increasing from 0.050 to 0.258 *M*. The half-wave potential then remains constant as the concentration of potassium hydrogen phthalate is increased to 0.450 *M*.

At each *p*H level in the range of 5 to 9 inclusive, there are only small changes in half-wave potentials with variations in any of the experimental conditions. At *p*H 6 there is little if any difference in half-wave potentials when either potassium hydrogen phthalate or potassium dihydrogen phosphate serves as the principal buffer component since a 0.050 *M* potassium hydrogen phthalate solution having an ionic strength of 0.140 *M* gives a half-wave potential of −0.622 v. In addition to the phosphate system at *p*H 8 the concentration of boric acid was varied from 0.050 to 0.400 *M* and the ionic strength ranged from 0.050 to 0.600 *M*. For the phosphate buffers at the same *p*H the concentration of potassium dihydrogen phosphate was varied from 0.050 to 0.300 *M* with accompanying variations in ionic strengths ranging from 0.144 to 1.014 *M*.

In studies conducted at *p*H 10 when the concentration of potassium dihydrogen phosphate is 0.050 *M*, increasing the ionic strength from 0.153 to 0.600 *M* renders the half-wave potential less negative by 0.018 v. Increasing the concentration of potassium dihydrogen phosphate to 0.320 *M* as the ionic strength is kept at 0.600 *M* and then increasing the ionic strength to 1.015 *M* have no further effect on the half-wave potentials.

Half-wave potentials are independent of con-

(8) With one exception, potassium chloride was employed in effecting increases in ionic strength in addition to the contribution made by buffer constituents. At *p*H 3 sodium chloride was used with sodium hydrogen tartrate buffer.

(9) In these discussions *p*H values are expressed as the nearest whole number to clarify the exposition. Precise values are given in Table I.

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TABLE I

POLAROGRAPHIC BEHAVIOR OF QUINOXALINE IN THE *p*H RANGE OF 1 TO 10

Buffer[a]	Concn., mmoles/l.	Electrolyte[b]	*p*H	Ionic strength	$E_{0.5}$ (S.C.E.) 1st wave	$E_{0.5}$ (S.C.E.) 2nd wave	$I_d/Cm^{2/3}t^{1/6}$ 1st wave	$I_d/Cm^{2/3}t^{1/6}$ 2nd wave
H	0.449	0.400 *M* $KHSO_4$	0.96	0.620	−0.254	−0.809	3.50	2.18
L	.446	.104 *N* HCl + 0.050 *N* KCl	1.00	.154	− .279	− .772	3.78	0.81
H	.449	.220 *M* $KHSO_4$ + 0.009 *N* KCl	2.05	.598	− .339	− .889	3.37	.90
L	.446	.013 *N* HCl + 0.050 *N* KCl	1.93	.063	− .342	− .865	3.82	.65
H	.449	.400 *M* NaHTr + 0.200 *N* NaCl	3.00	.601	− .401	− .936	3.24	1.13
L	.446	.050 *M* KHPh	2.92	.051	− .441	− .935	3.71	1.42
H	.446	.400 *M* KHPh + 0.200 *N* KCl	3.99	.647	− .481	− .981	2.90	1.20
L	.446	.050 *M* KHPh	4.00	.050	− .488	−1.011	3.63	1.28
H	.449	.285 *M* KHPh	4.99	.598	− .550	−1.044	3.22	0.93
L	.446	.050 *M* KHPh	4.99	.098	− .554	−1.053	3.64	.70
H	.448	.350 *M* KH_2PO_4 + 0.086 *N* KCl	6.00	.600	− .617	−1.092	3.46	.43
L	.447	.050 *M* KH_2PO_4	6.00	.062	− .616	−1.06[c]	3.54	.14
H	.448	.260 *M* KH_2PO_4	6.96	.606	− .675	−1.14[c]	3.36	.14
L	.447	.050 *M* KH_2PO_4	7.00	.110	− .676		3.69	
H	.449	.200 *M* KH_2PO_4 + 0.020 *N* KCl	7.98	.600	− .738		3.23	
L	.447	.050 *M* KH_2PO_4	8.00	.144	− .745		3.71	
H	.449	.440 *M* H_3BO_3 + 0.456 *N* KCl	8.62	.602	− .777		3.16	
L	.446	.050 *M* H_3BO_3 + 0.050 *N* KCl	9.00	.071	− .798		3.77	
H	.448	.180 *M* KH_2PO_4 + 0.038 *N* KCl	10.13	.600	− .863		3.55	

[a] L "Low" buffer; H "High" buffer. [b] Adjusted to final *p*H with sodium hydroxide or hydrochloric acid solution. Ph = phthalate, Tr = tartrate. [c] Too low to be measured more accurately.

centration in the *p*H range of 2 to 9. Variations of 5% are observed at *p*H 1 where differentiation into minor waves is more extensive.

The diffusion current constants for the first major waves have the same order of magnitude throughout the *p*H range of 1 to 10. However, their values tend to decrease with increasing buffer concentration and to a lesser extent with increasing ionic strength. Variations of quinoxaline concentration in both buffer systems give diffusion current constants having deviations of 2 to 8%.

B. Second Major Wave.—The trends are different than for the first major wave. At *p*H 1 the half-wave potential varies from −0.772 to −0.803 v. as the ionic strength of the "Low" buffer is increased to 0.617 *M* by addition of potassium chloride. Increasing the concentration of potassium hydrogen sulfate to 0.800 *M* and ionic strength to 1.434 *M* gives the same half-wave potential as found with the "High" buffer. At *p*H 2, the half-wave potentials become more negative with increasing ionic strength and buffer concentration. At *p*H 3, the half-wave potential remains essentially constant as the ionic strength in the "Low" buffer is increased to 0.606 *M* by addition of potassium chloride. Also, the change to the sodium hydrogen tartrate buffer does not affect the half-wave potential as the concentration of this salt is raised to 0.400 *M* and the ionic strength is increased to 0.601 *M*. At *p*H 4 the half-wave potential varies uniformly from −1.011 v. in the "Low" buffer to −0.982 v. in a buffer of 0.250 *M* potassium hydrogen phthalate and potassium chloride having an ionic strength of 0.368 *M*. Further increases in concentration of potassium hydrogen phthalate to 0.450 *M* and the ionic strength to 0.647 *M* do not affect half-wave potentials. At low *p*H the wave is too small to be evaluated accurately in the "Low" buffer. Increasing the buffer concentration to 0.350 *M* potassium dihydrogen phosphate affords a sufficiently high wave for quantitative evaluation. The half-wave potential varies uniformly from −1.079 to −1.101 v. as the concentration of potassium dihydrogen phosphate is increased from 0.350 to 0.600 *M*, and the ionic strength is increased from 0.600 to 1.000 *M* with potassium chloride.

Contrary to the trend noted for the first major wave, the half-wave potentials for the second major wave generally become more negative as the concentration of quinoxaline is increased in the "Low" and "High" buffers. Exceptions are noted at *p*H 1 in the two buffers, *p*H 2 in the "Low" buffer, *p*H 4 in the "High" buffer and possibly at *p*H 6 in the "Low" buffer. In these cases the trends are not uniform and in nearly each instance the size and form of these waves make their evaluations somewhat uncertain. In all cases polarograms were run at quinoxaline concentrations of 2.5×10^{-4} *M*, 4.5×10^{-4} *M* and 7.0×10^{-4} *M*.

The diffusion current constant for the second major wave generally appears to increase with increasing concentration of buffer components, with the influence of ionic strength not being too significant. At *p*H 3, the diffusion current constant is higher in the potassium hydrogen phthalate buffer than in the sodium hydrogen tartrate buffer. In the latter, the diffusion current constant fails to increase with buffer concentration. At *p*H 4 there are no significant increases in diffusion current constants with increasing buffer concentration.

In Fig. 1 is shown the variation in diffusion current constants with *p*H for the second major wave of 4.5×10^{-4} *M* solutions of quinoxaline in both systems of buffers. The heights of these waves are not only dependent upon *p*H but also upon buffer composition, as already noted.

The diffusion current constants for the second major wave tend to decrease with increasing concentration of quinoxaline both in the "Low" and "High" buffers. Furthermore, these values tend to have average deviations > ±5% in each buffer system at every *p*H level. It is evident that the

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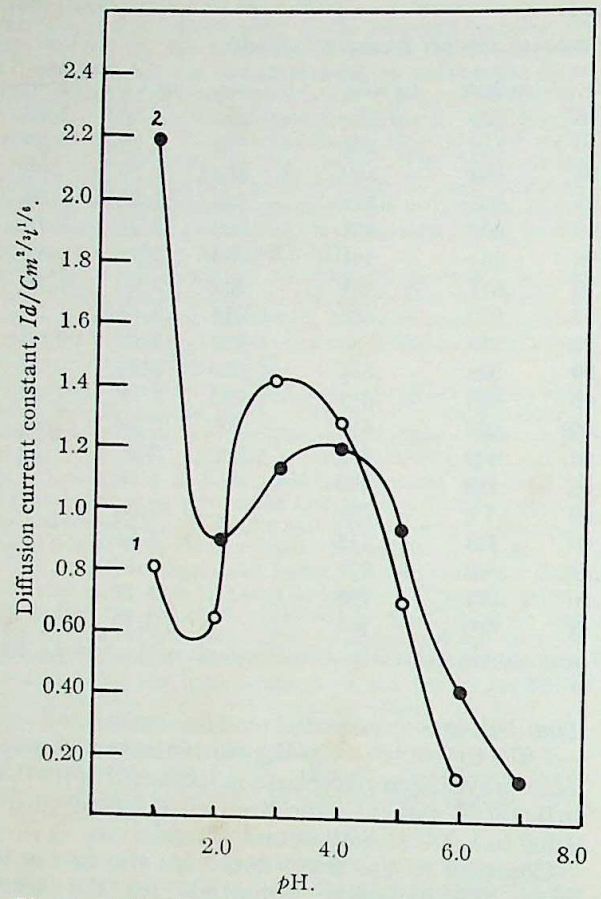


Fig. 1.—Diffusion current constants *vs.* *p*H for 4.5×10^{-4} *M* quinoxaline: 1, Clark and Lubs ("Low") buffers; 2, "High" buffers.

two major waves for quinoxaline represent decidedly different reduction processes.

Evaluation of *n* and Discussions

A. First Major Wave.—The significant aspects of this wave are (1) diffusion current constants have the same order of magnitude throughout the range of *p*H explored, indicating the same number of electrons involved in reduction, (2) diffusion current constants decrease somewhat with increasing buffer concentration and ionic strength at each *p*H, (3) except for the cases noted at *p*H 1 and *p*H 2, half-wave potentials are independent of the concentration of quinoxaline and (4) with certain exceptions noted at *p*H's 1, 2, 3 and 10 the half-wave potentials are independent of the nature of buffer components, concentration and ionic strength.

Efforts were made to evaluate *n* of this wave for 4.5×10^{-4} *M* quinoxaline solutions in the "Low" and "High" buffers by means of the Ilkovic equation

$$n = id/605D^{1/2}Cm^{2/3}t^{1/6} \qquad (2)$$

A value for *D* in the above equation was calculated from the Stokes–Einstein equation where the molar volume of 6-methylquinoxaline was employed. The density for 6-methylquinoxaline of 1.1125 at 25°, reported by Cavagnol and Wilson[10] was used to calculate the molar volume. The value of *D* obtained by this method is 6.55×10^{-6} cm.^{2} sec.$^{-1}$ at 25°. For 4.5×10^{-4} *M* solutions of quinoxaline in the "Low" buffers and in the "High" buffers the values of *n* varied from 1.9 to 2.5 with the average being 2.3.

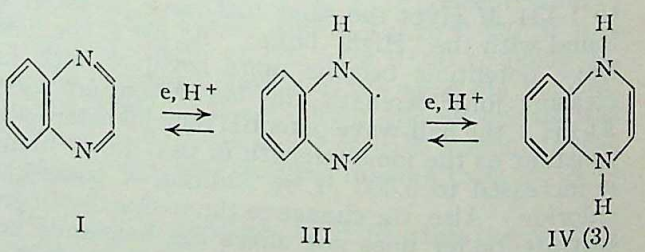
It is evident that the first major wave represents reduction involving two electrons. At *p*H's 1 and 2 wave differentiation into two equal portions signifies that reduction may proceed as a bimolecular reaction in two successive one-electron steps. It has been observed in our laboratory that the quinoxalinium ion behaves as a strong acid which makes it unlikely that the conjugate acid is being reduced. This condition may exist at *p*H 3 in the "Low" buffer but as an increase in buffer concentration appears to remove evidence of such differentiation completely then the wave differentiation may have been due to inadequate buffering. At higher *p*H's, reduction must proceed by the simultaneous addition of two electrons.

The equation of a reversible electrode process for an inorganic substance involving the addition of *n* electrons and *n* protons in a buffered solution indicates that the variation of half-wave potential with *p*H should be linear with the slope being −0.059. The plot of half-wave potential *versus* *p*H for 4.5×10^{-4} *M* solutions of quinoxaline in the "Low" buffers gives a straight line from *p*H 1 to *p*H 5 having a slope of 0.070. A straight line can be drawn from *p*H 4 to *p*H 9 having a slope of 0.063.

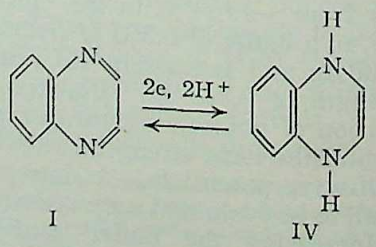
A similar plot for 4.5×10^{-4} solutions of quinoxaline in the "High" buffers gives a straight line from *p*H 1 to *p*H 10 having a slope of 0.063. Evidently, similar orders of reversibility are prevalent in the "Low" buffers and the "High" buffers. Reduction occurring at the low *p*H's is not as reversible as the reduction occurring at higher *p*H's.

On the basis of the analysis of results for the first major wave, the following mechanisms are proposed.

In the *p*H range of 1 to 2 inclusive, dihydroquinoxaline is formed by two consecutive single-electron steps



At *p*H's > 4 reduction follows the simultaneous two-electron process



(4)

At *p*H 3 reduction may proceed by either of the above processes.

(10) J. C. Cavagnol and G. Wilson, Jr., THIS JOURNAL, 72, 3752 (1950).

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It is postulated that 1,4-addition occurs in preference to 1,2-addition owing to the greater electronegativity of nitrogen. Also, it has been found in the polarographic reduction of other simple nitrogen-containing systems such as quinoline[11–13] and acridine[14] that reduction to the *dihydro* stage occurs at the 1,4-position.

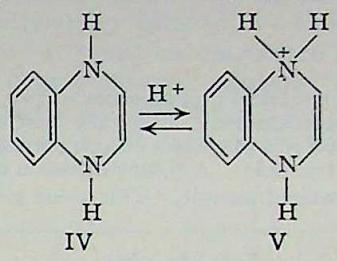
The tendency for nitrogen-containing heterocyclic systems to undergo reduction to the *dihydro* form by a semiquinone process in acid media and by a simultaneous two-electron process in alkaline media has been observed for 2-carboxyquinoline,[11] 8-carboxyquinoline,[12] 4-carboxyquinoline,[13] and methylpyridinium hydroxide.[15]

B. **Second Major Wave.**—The significant aspects of this wave are (1) it is present in acidic media but vanishes at *p*H's > 7, (2) the height increases with increasing concentration of acidic buffer component but not necessarily increasing ionic strength, except at *p*H 3 and *p*H 4. At *p*H 3 and *p*H 4 the diffusion current constants appear to be independent of concentration of potassium hydrogen phthalate and of ionic strength, (3) the variations in the diffusion current constants with quinoxaline concentration at each *p*H are greater than those of the first major wave. This suggests that the second major wave does not strictly follow the Ilkovic equation relating diffusion current and reductant concentration, (4) the half-wave potentials become more negative with increasing concentration of quinoxaline except for the results found in the "Low" buffers at *p*H 1, 2 and 6 where there are no uniform trends, (5) the half-wave potentials of this wave generally appear to be more sensitive to variations in buffer components, buffer concentration and ionic strength than those for the first major wave.

Kolthoff and Lingane[16] gave the relation describing the change of half-wave potential with change in acid concentration due to hydrogen discharge for a weak acid in an excess of indifferent supporting electrolyte as

$$\Delta E_{0.5}/\Delta \log [HA] \simeq -0.089 \text{ v.} \qquad (5)$$

where HA represents the weak acid. By taking $\Delta E_{0.5}/\Delta \log [HA]$ quotients from the results obtained in this investigation for the variation in half-wave potentials of the second major wave with quinoxaline concentration, an average value of −0.083 v. is obtained for quinoxaline in both buffers. On this basis it is postulated that the second major wave is hydrogen reduction catalyzed by the 1,4-dihydroquinoxalinium ion (V), *viz.*



IV V (6)

It is believed that the catalytic action is caused by the dissociation of V which is presumed to be a weak acid. According to Cavagnol and Wilson,[10] the first and second acid dissociation constants of 1,2,3,4-tetrahydroquinoxaline are 7.8×10^{-3} and 1.45×10^{-5}, respectively. Electronic considerations dictate that 1,2,3,4-tetrahydroquinoxaline is a weaker acid than 1,4-dihydroquinoxaline. Thus the proton leading to the catalytic wave comes from the monobasic acid.

The conclusion that the second major wave is due to hydrogen discharge catalyzed by the *dihydro* form of quinoxaline, is not unique for heterocyclic systems. Knobloch[17] observed that the reduction of nicotinamide proceeded to the dihydro stage which catalyzed the evolution of hydrogen in acid and neutral media. Catalytic hydrogen waves have been reported to follow the reduction of quinoline in weakly acidic media.[18] Kirkpatrick[19] found catalytic hydrogen waves for a number of alkaloids containing the indole structure as well as for quinine and quinidine. The failure to obtain tetrahydroquinoxaline in aqueous media at *p*H's > 7 where kinetic waves are absent must be due to the existence of the isolated double bond in the 2,3-position. Compounds containing a single ethylenic function are not ordinarily reduced at the dropping mercury electrode.[20]

Acknowledgment.—The authors wish to thank Dr. Clark E. Bricker of Princeton University for his helpful suggestions during the preparation of this manuscript.

MADISON, NEW JERSEY

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

Dynamic Electrical Birefringence Studies of Poly-γ-benzyl-L-glutamate[1]

BY IGNACIO TINOCO, JR.[2]

RECEIVED MARCH 20, 1957

The dynamic electrical birefringence of two samples of different molecular weight poly-γ-benzyl-L-glutamate in ethylene dichloride has been studied. A specific Kerr coefficient (B/c) of 0.057 cm.^{4}/volt g. for M_w = 84,000 and 0.31 cm.^{4}/volt g. for M_w = 350,000 was obtained. Both permanent and induced dipole moments contributed to the orientation of the molecules in the electric field. A rotary diffusion coefficient ($\Theta_{20,w}$) at infinite dilution of 9.8×10^2 sec.$^{-1}$ was obtained for the high molecular weight sample. This value gives a length of 2.7×10^3 Å. for a rigid rod or ellipsoid.

Introduction

Poly-γ-benzyl-L-glutamate (PBLG) should be an excellent model substance for dynamic electrical birefringence measurements. Doty, *et al.*,[3] have shown that in certain solvents this polypeptide exists in a wide range of molecular weights as unassociated rigid rods with the α-helix[4] configuration. Besides its known structure, PBLG has special advantages for electrical birefringence studies because it is soluble in non-conducting solvents and is uncharged. The interpretation of previous electrical birefringence experiments on charged molecules in water[5-9] is complicated by ion atmosphere[5,9] and proton migration[10-11] effects which are absent in these non-conducting systems. Furthermore, the polarizability ellipsoid of a helix must be a figure of revolution and the dipole moment must be along the symmetry axis (except for end effects). This simplifies the equations for the dynamic birefringence[11] to those given by Benoit.[6]

The orientation of a rigid molecule in a time dependent parallel electric field can be characterized by three parameters: the dipole moment μ, the polarizability α, and the rotary diffusion coefficient Θ. The decay of the orientation after application of a square electrical pulse gives a direct measure of Θ. Unlike the values obtained from hydrodynamic experiments such as flow birefringence[12] and viscosity,[13] this Θ does not depend upon explicit assumptions about the shape, for an asymmetric molecule. Values of the dipole moment μ and the electrical (α_E) and optical (α_0) polarizabilities cannot in general be separated, however, using only electrical birefringence measurements. Either the optical factor must be obtained from flow birefringence or depolarization of scattered light experiments, or dielectric dispersion measurements must be made to obtain μ and α_E.

In the present study the dynamic electrical birefringence of two PBLG samples of different molecular weight has been measured. A rotary diffusion coefficient for the high molecular weight sample was obtained, but the exact nature of the orienting electrical couple must await further information.

Experimental

The poly-γ-benzyl-L-glutamate was obtained through the courtesy of Dr. E. R. Blout and Dr. P. Doty. The two samples were: RK 1149-B with a weight average molecular weight (M_w) of 84,000 and RK 1263, M_w = 350,000. Ethylene dichloride (EDC), Union Carbide and Carbon technical grade, was dried with Drierite, then distilled through a 30 plate column at atmospheric pressure. The concentrations of the two stock solutions were determined by dry weight.

The electrical birefringence apparatus has been described before.[7,8] A Teflon cell was used, however, instead of the glass cell described previously. The cell, machined from Teflon rod, has threaded ends for standard polarimeter end plates. Gold electrodes, 0.079 × 0.476 × 8.86 cm., rest on the bottom of the cell and are held 0.249 cm. apart against the sides of the cell by Teflon spacers. Electrical connection to the electrodes is made by platinum wires. The volume of solution necessary to fill the cell is about 2.5 ml.

The performance of the apparatus was checked using nitrobenzene (J. T. Baker, purified grade). A Kerr coefficient ($B = \Delta n/\lambda E^2$) of 4.24×10^{-5} cm./volt^2 was obtained for nitrobenzene at the average effective wave length of 510 mμ. This is in satisfactory agreement with previously obtained values at 546 mμ after correction for the wave length difference. The instrumental relaxation time was also obtained from the nitrobenzene experiments; the molecular relaxation time is of course negligible. A value of 13.7 μsec., in excellent agreement with that obtained by Billick,[8] resulted.

All measurements were made at room temperature; an average value of 298°K. was used in calculations.

The methods for analyzing the primary data have been described previously.[7] It was not necessary to correct the observed rotary diffusion coefficient for the instrumental relaxation time as it was negligible compared to the relaxation time of the high molecular weight PBLG. To calculate the rotary diffusion coefficients for the molecules in water at 20°, the viscosity of the solvent (η = 0.0078 poise)[14] at 25° was used.

Results

The Kerr coefficients and rotary diffusion coefficients for solutions of PBLG in EDC are given in Table I; the Kerr coefficients are plotted *vs.* concentration in Fig. 1.

For the high molecular weight sample the birefringence was studied as a function of field strength

(1) This work was supported in part by the Office of Naval Research under Contract N7onr-28509.

(2) Public Health Service Fellow of the National Cancer Institute at Yale University.

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over the range 170–1200 practical[15] volts per cm. The Kerr coefficient was found to be independent of field strength. The number of measurements made at different voltages is given in parentheses to the right of the average value of the Kerr coefficient which is shown in the table.

The slopes of the plots in Fig. 1 give specific Kerr coefficients of $B/c = 0.31$ cm.^{4} volt^2 g. for $M_w = 350{,}000$ and $B/c = 0.057$ cm.^{4}/volt^2 g. for $M_w = 84{,}000$.

The curves for the rise of the birefringence of the high molecular weight sample on application of a rectangular electrical pulse were not symmetrical to the decay curves. The shape of the curves showed that both permanent and induced dipole orientation were important.

TABLE I

KERR COEFFICIENTS AND ROTARY DIFFUSION COEFFICIENTS FOR POLY-γ-BENZYL-L-GLUTAMATE

Mol. wt. = 350,000			Mol. wt. = 84,000	
Concn. (g./l.)	$B \times 10^4$ (cm./volt^2)	$\Theta_{20,w} \times 10^{-2}$ (sec.$^{-1}$)	Concn. (g./l.)	$B \times 10^4$ (cm./volt^2)
3.75	10.9(7)	2.8	14.80	9.2
1.35	4.2(10)	7.0	7.25	3.4
0.50	1.5(7)	8.2	2.05	1.1
0.15	0.52(4)	10.1	1.10	0.66
(0)		(9.8)		

Discussion

Kerr Coefficients.—The specific Kerr coefficient for a molecule with a polarizability ellipsoid of revolution and permanent dipole μ_1 along the symmetry axis is related to molecular parameters by the equation[11]

$$B/c = (2\pi/15n_0\rho\lambda_0)(g_1 - g_2)(p_1 + q)$$

The quantities n_0, ρ, λ_0 are the refractive index of the solvent, the density of the solute, and the vacuum wave length of the light, respectively. The anisotropy of the optical polarizability per unit volume of particle is $(g_1 - g_2)$. The electrical orientation parameters are $p_1 = (\mu_1/kT)^2$ and $q = v(g_1^0 - g_2^0)/kT$. The permanent dipole moment is μ_1, and the anisotropy of the electrical polarizability is $(g_1^0 - g_2^0)$.

Although the factors cannot be untangled from the Kerr data alone, we can deduce the following facts. From the definitions of the molecular parameters we see that for different length rods, *e.g.*, different molecular weights of PBLG: (1) $(g_1 - g_2)$ is independent of molecular weight for long rods, (2) p_1 is proportional to the square of the molecular weight, (3) q is proportional to the molecular weight. Therefore, for the two samples studied, if the permanent dipole is the principal orienting factor, then

$$(B/c)_{M_1}/(B/c)_{M_2} = 17.4$$

or, if the induced dipole is primarily responsible

$$(B/c)_{M_1}/(B/c)_{M_2} = 4.2.$$

Experimentally we find $(B/c)_{M_1}/(B/c)_{M_2} = 5.4$; thus indicating that, although both terms are effective, induced dipole orientation is the more important. For example, if we take $p_1 = q/2$ for the high molecular weight sample, $(B/c)_{M_1}/(B/c)_{M_2} = 5.6$.

The orienting torque acting on a rigid ellipsoid of revolution of dielectric constant ϵ in a solvent of dielectric constant ϵ_0 can be calculated from an equation derived by Maxwell.[6] Using this equation a value of q can be calculated for PBLG in EDC if the helices are approximated by ellipsoids of the same length and volume. This q is nearly independent of shape for axial ratios greater than 10, if ϵ is finite.

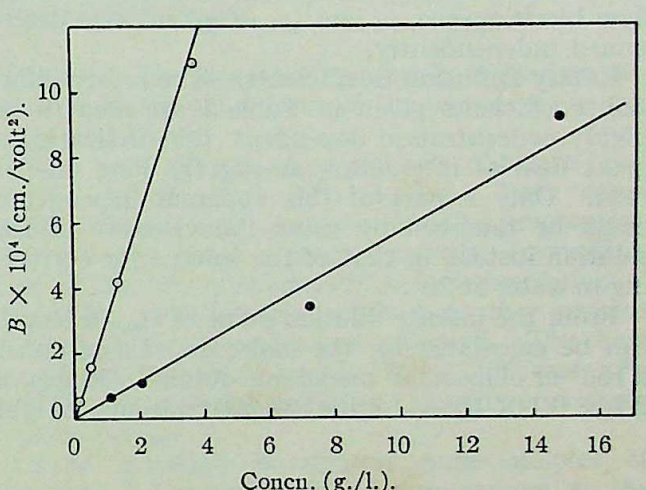

Fig. 1.—The Kerr coefficient of poly-γ-benzyl-L-glutamate in ethylene dichloride *vs.* concentration. The open circles are for $M_w = 350{,}000$; the closed circles are for $M_w = 84{,}000$.

For the calculation a dielectric constant of 2.5 for PBLG was used. This value is based on the assumption that the electrical polarizability of PBLG is completely electronic and thus ϵ is equal to the square of the refractive index obtained from Doty's (dn/dc) measurements.[3] The other parameters used were: $\epsilon_0 = 10.36$,[14] $\rho = 1.32$.[3] The shape of the rise of the birefringence curves and the molecular weight dependence of the Kerr coefficients were consistent with values of p_1 and q of the same order of magnitude for the high molecular weight sample; therefore, p_1 can be set equal to q, and the dipole moment μ_1 and optical factor $(g_1 - g_2)$ also can be estimated. For the calculation of $(g_1 - g_2)$ the following data were used: $n_0 = 1.443$,[14] $\lambda_0 = 510$ mμ. The values thus obtained for the 350,000 molecular weight sample were: $q = 4.1 \times 10^{-6}$ cm.^{3}/erg, $\mu_1 \cong 80$ debye, $(g_1 - g_2) \cong 8.9$. The value of $(g_1 - g_2)$ is very large compared to values found for many proteins in water solution.[16] Furthermore, a value of $\mu_1 = 7{,}200$ D would be estimated for a polyglycine α-helix of the same length.[17] Because of these discrepancies we should examine the assumptions in

(15) Unless designated otherwise voltages are given in practical volts (1 RSU = 300 practical volts).

(16) R. Cerf and H. A. Scheraga, *Chem. Revs.*, **51**, 185 (1952).

(17) Schellman[18] gives $\mu_1 \cong (7.2 + 4.5)n$ debye for a polyglycine α-helix where n is the degree of polymerization. The first term is the contribution to the dipole moment from a charged carboxyl group at one end of the molecule and a charged amino group at the other end. The second term is the contribution from each NH and C=O group in the helix. Obviously, only this second term is present for our system.

(18) J. A. Schellman, *Compt. rend. trav. Lab. Carlsberg, Serie chim.*, **29**, 254 (1955).

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our calculation. The critical assumption is that the electrical polarizability of PBLG is purely electronic, *i.e.*, $\epsilon = 2.5$. If instead we consider that the dipolar ester side chains can orient in the electric field and thus give rise to a very large atomic polarizability, the value of ϵ could be much larger than ϵ_0, the dielectric constant of the solvent. To calculate an upper limit for μ_1 we shall let $\epsilon \rightarrow \infty$. The value of q then approaches a limit depending on the axial ratio of the ellipsoid. For an axial ratio of 100, q becomes 1.9×10^{-2} cm.^{3}/erg, $\mu_1 \cong 5{,}400\,D$, $(g_1 - g_2) \cong 1.9 \times 10^{-3}$.

By measurements of dielectric dispersion and flow birefringence, μ_1 and $(g_1 - g_2)$ may be determined independently.

Rotary Diffusion Coefficients.—The rotary diffusion coefficients given in Table I are seen to be highly concentration dependent, thus indicating a great deal of interaction among the long dipolar rods. Only a part of this apparent dependence could be removed by using the viscosity of the solution instead of that of the solvent for correcting to water at 20°.

From the infinite dilution value of $\Theta_{20,w}$ a length can be calculated for the molecule. Using either a rod[9] or ellipsoidal[6] model one obtains a length of $2.7 \pm 0.1 \times 10^3$ Å. for the 350,000 molecular weight PBLG. This value may be compared with a light scattering length of about 2.0×10^3 Å. obtained by Doty, *et al.*,[3] and a calculated α-helix length of 2.4×10^3 Å. (length = 1.5 times degree of polymerization).[4] Doty's light scattering lengths agreed well with the α-helix configuration for the lower molecular weights; for the high molecular weight he attributed the disagreement to a slight flexibility in the longer rods. This flexibility might lower the rotational diffusion of the molecules and cause an apparent longer length. However, O'Konski[9] found a rotational diffusion length for tobacco mosaic virus significantly larger than electron microscope values, thus suggesting that rod-like models for these molecules may not be adequate.

Acknowledgments.—This work was done in Professor John D. Ferry's laboratory; we are very grateful to him for his hospitality and for his helpful suggestions. We also wish to thank Dr. E. R. Blout and Professor P. Doty for the samples of PBLG which made this work possible.

NOTE ADDED IN PROOF.—Professor Doty has kindly supplied a value of $(g_1 - g_2)$ for PBLG in EDC of 4.1×10^{-3} from flow birefringence experiments of J. T. Yang and P. Doty. If one assumes $p_1 = q$, this value leads to $\mu_1 = 3{,}900\,D$. for $M_w = 350{,}000$.

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ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION NO. 2190 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Coördination of Silver Ion with Unsaturated Compounds. IX. Solid Complexes of Silver Salts with Cyclohexene, α-Pinene and β-Pinene[1]

BY ALAN E. COMYNS[2] AND HOWARD J. LUCAS[3]

RECEIVED MARCH 6, 1957

Silver perchlorate with cyclohexene, α-pinene and β-pinene forms crystalline complexes which contain two molecules of hydrocarbon to one of silver perchlorate. Silver nitrate forms a similar complex with cyclohexene but none with the pinenes. By means of silver perchlorate the pinenes can be separated from each other, and both α-pinene and β-pinene can be obtained optically pure from optically impure specimens of the respective hydrocarbons.

The first complexes of silver salts with alkenes to be isolated[4] were those of silver nitrate with cyclopentadiene dimer and of silver perchlorate with biallyl and cyclopentadiene dimer. Many complexes of silver nitrate with cyclic olefins have since been prepared and have been used to purify and characterize the olefins.[5] The melting points of a number of olefin–silver nitrate complexes have been compared by Salomon,[6] and some unusual "liquid complexes" of silver nitrate with propene and 1-butene have been described.[7]

When silver perchlorate is added to cyclohexene, α-pinene and β-pinene finely divided solid compounds are formed in the ratio of one mole of silver perchlorate to two of the hydrocarbon. When the mixture of solid with excess of hydrocarbon (plus acetone in the case of cyclohexene) is cautiously warmed,[8] the solid dissolves and crystallizes on cooling. The cyclohexene complex was prepared for study by X-ray diffraction.[9]

The pinene complexes are of interest because they enable the two pinenes to be separated from each other and to be obtained optically pure. The separations are effected by mixing less than one mole of silver perchlorate with two moles of the pinene mixture, letting them react, removing uncomplexed pinene by high vacuum distillation and recovering pinene from the complex by the addition of water. The separations probably depend on differences in the solubilities of the complexes in the pinene mixtures.

The best sample of α-pinene[10] obtained had $[\alpha]^{25}D$ +52.4° and $n^{25}D$ 1.4632. Two other methods have been described for the preparation of "optically pure" α-pinene, namely, crystallization of the nitrosochloride[10a] and isomerization of "optically pure" β-pinene,[10b] but the present method is easier and more effective. The best sample of β-pinene[11] had $[\alpha]^{25}D$ −22.7° and $n^{25}D$ 1.4764; the rotation is higher than any previously reported value.

It is necessary to employ pure samples of pinenes. α-Pinene which had been exposed to the air for several days gave a sticky black mass with silver perchlorate. Negligible optical fractionation of α-pinene was obtained with a "practical" grade, although the complex was formed as usual.

Experimental

Materials.—Silver perchlorate (anhydrous) was used as purchased from G. F. Smith and Co. The cyclohexene had been prepared from cyclohexanol by Dr. N. Koenig in this Laboratory and had $n^{25}D$ 1.4441. The pinenes, prepared specially for this work by the Glidden Co. and stated to be of better than 99.9% purity, were stored before use under vacuum in sealed ampoules. α-Pinene[10] had $[\alpha]^{25}D$ +30.0° (in 1 dm. tube),[12] $n^{25}D$ 1.4631, and β-pinene[11] had $[\alpha]^{25}D$ −21.0°, $n^{25}D$ 1.4765.

Analyses.—Silver determinations on the cyclohexene complexes were by thiocyanate titration in the presence of the hydrocarbon; other analyses were by A. Elek, Los Angeles, Calif.

Preparation of Silver Perchlorate–Cyclohexene Complex.—An excess of cyclohexene, 12 ml., was added to crystalline silver perchlorate, 2.63 g. A rapid exothermic reaction occurred, and the silver perchlorate was converted into a voluminous white powder which was filtered off; yield 4.28 g.

Anal. Calcd. for $AgClO_4 \cdot 2C_6H_{10}$: C, 38.78; H, 5.42; Cl, 9.54; Ag, 29.03. Found: C, 38.91; H, 5.53; Cl, 9.77; Ag, 28.97, 28.93.

Crystallization of Silver Perchlorate–Cyclohexene Com-

(1) This research has been made possible by support extended to the California Institute of Technology by the Office of Naval Research under Contract Nonr-270(00).

(2) Arthur Amos Noyes Fellow, 1952–1953.

(3) To whom requests for reprints should be sent.

(4) S. Winstein and H. J. Lucas, THIS JOURNAL, **60**, 836 (1938).

(5) W. Reppe, O. Schlichting, K. Klager and T. Toepel, *Ann.*, **560**, 11 (1948); A. C. Cope and M. R. Kintner, THIS JOURNAL, **72**, 630 (1950); A. C. Cope, C. L. Stevens and F. A. Hochstein, *ibid.*, **72**, 2510 (1950); A. C. Cope and F. A. Hochstein, *ibid.*, **72**, 2515 (1950); A. C. Cope and H. C. Campbell, *ibid.*, **74**, 179 (1952); A. C. Cope and D. J. Marshall, *ibid.*, **75**, 3208 (1953); A. C. Cope, R. H. Pike and C. F. Spencer, *ibid.*, **75**, 3212 (1953); A. C. Cope, D. C. McLean and N. A. Nelson, *ibid.*, **77**, 1628 (1955); A. C. Cope and W. R. Moore, *ibid.*, **77**, 4939 (1955); A. C. Cope and C. L. Bumgardner, *ibid.*, **78**, 2812 (1956); C. Grundmann, G. Ottmann and G. Gollmer, *Ann.*, **582**, 178 (1953); W. O. Jones, *J. Chem. Soc.*, 2036 (1953); 312, 1808 (1954).

(6) G. Salomon in "Cationic Polymerisation and Related Complexes," P. H. Plesch, ed., Heffer, Cambridge, England, 1953, p. 62.

(7) A. W. Francis, THIS JOURNAL, **73**, 3709 (1951).

(8) Rapid or excessive heating could cause decomposition. A Dewar vessel containing liquid N_2 should be handy in order to freeze the mixture rapidly in case any darkening is observed.

(9) This investigation is being made in these laboratories by Albert E. Smith. The complexes of silver nitrate and silver perchlorate with cyclopentadiene dimer have been investigated similarly but with meager results; J. J. Arlen, private communication to G. Salomon and C. Konigsberger, *J. Polymer Sci.*, **2**, 535 (1947).

(10) Lit. rotations: (a) $[\alpha]^{20}D$ +51.14°, −51.28°; (b) $[\alpha]^{27}D$ −47.4°. (a) F. H. Thurber and R. C. Thielke, THIS JOURNAL, **53**, 1030 (1931); (b) R. N. Moore, C. Golumbic and G. S. Fisher, *ibid.*, **78**, 1173 (1956). Lit. $n^{25}D$: (c) 1.4631; (d) 1.4631–1.4632. (c) R. E. Fuguitt, W. D. Stallcup and J. E. Hawkins, *ibid.*, **64**, 2978 (1942); (d) J. E. Hawkins and G. E. Armstrong, *ibid.*, **76**, 3756 (1954).

(11) Lit. $[\alpha]^{25}D$: (a) −21.49°, (b) −18.54°, (c) −21.5°. (a) Ref. 10c; (b) ref. 10d; (c) G. Widmark, *Acta Chem. Scand.*, **9**, 938 (1955). Lit. $n^{25}D$: (d) 1.4768, (e) 1.4762. (d) Ref. 10c and 10d; (e) ref. 11c.

(12) Specific rotations were calculated from observed rotations using the densities of α-pinene and β-pinene, namely, d^{25}_4 0.8542 and 0.8666, respectively, given by Fuguitt, *et al.*[10c]

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plex.—Silver perchlorate, 4.05 g., was dissolved in a warm mixture of cyclohexene, 5 ml., with acetone, 5 ml., and the solution was cooled in ice. The complex crystallized in the form of rectangular plates, which were filtered off; yield 5.02 g.

Anal. Found: C, 37.97; H, 5.41; Cl, 9.66; Ag, 29.00, 28.93.

Recovery of Cyclohexene from Silver Perchlorate Complex.—The powdered complex, 3.64 g., was shaken with water, 15 ml., until all the solid had dissolved. The upper liquid layer, 1.6 ml., was separated, dried overnight with sodium and then distilled under vacuum; yield 1.21 g. (75%) of liquid having $n^{25}D$ 1.4438. The lower aqueous layer yielded only a trace of second liquid phase when treated with an excess of ammonium hydroxide.

Solubility of Silver Perchlorate Complex in Cyclohexene.—Silver perchlorate, *ca.* 0.2 g., contained in an ampoule fused to the vacuum system, was dried by pumping for 24 hr. with a mercury-vapor diffusion pump followed by a liquid-air trap. Cyclohexene, 25 ml., over sodium in a flask attached to the vacuum system, was distilled directly onto the silver perchlorate, and the ampoule was then sealed and removed from the apparatus. After having been shaken at 25.0° for 4 days, the ampoule was opened, and a 10-ml. portion of the clear supernatant liquid was withdrawn. This was evaporated. Titration of the silver in the residue against thiosulfate showed the solubility to be 0.003 g. of $AgClO_4$/100 ml. of solution. A similar experiment in which the silver perchlorate had been dried for only 4 hr. gave a solubility of 0.005 g./100 ml.

Preparation of Silver Perchlorate–α-Pinene Complex.—When silver perchlorate was left to stand with α-pinene at 25° for several hours, a voluminous white powder formed. It was not possible to obtain a solid of reproducible silver content by removing adhering liquid by high-vacuum distillation from room temperature to a trap cooled by liquid air. For the preparation of the crystalline complex, silver perchlorate, *ca.* 0.2 g., was left with α-pinene, 10 ml., at room temperature for 3 hr., and the mixture was then warmed[8] to dissolve the complex thus formed. Cooling to room temperature yielded small hexagonal plates; yield 0.1 g.

Anal. Calcd. for $AgClO_4 \cdot 2C_{10}H_{16}$: C, 50.06; H, 6.72; Cl, 7.39; Ag, 22.48. Found: C, 50.36; H, 6.72; Cl, 7.26; Ag, 22.64.

When these crystals were heated in a melting-point tube, they broke up into a liquid and a solid phase at 76 ± 1°, and on further heating this mixture blackened suddenly at 125°. Observation of these processes under a hot-stage microscope showed that at 74° the edges of the crystals started to become etched with the formation of liquid drops and that at 80° the crystalline form had been lost entirely. Again, further heating to 125° caused sudden blackening. When heated in a test-tube, the complex exploded mildly. The crystals were not stable in air at room temperature; a sample that had been kept for 3 days in the dark in a well-corked tube had become gray, and microscopic examination showed liquid drops to be present on the faces of the crystals. No attempt was made at storage in the absence of oxygen.

The crystalline complex was prepared in better yield by the use of acetone. Silver perchlorate, *ca.* 4 g., was dissolved in a mixture of α-pinene, 6 ml., and acetone, 1.4 ml., thereby forming a system of two liquid phases. Most of the acetone was removed by standing in a continuously evacuated desiccator. Filtration yielded crystals 2.3 g., m.p. 77–78°, dec. *ca.* 150°.

Anal. Found: Ag, 22.6, 22.9.

Preparation of Silver Perchlorate–β-Pinene Complex.—Silver perchlorate reacted rapidly with β-pinene at room temperature, the mixture becoming warm and much white powder being produced. As in the case of the α-pinene complex, a pure product could not be obtained using this procedure. The crystalline complex was obtained by allowing silver perchlorate, *ca.* 0.4 g., to stand with β-pinene, 10 ml., for 5 min., heating[8] to dissolve the complex so formed, cooling to room temperature and filtering; yield 0.4 g. of small rectangular plates, m.p. 108–109°. The molten complex underwent violent decomposition at 125°.

Anal. Found: C, 49.00; H, 6.56; Cl, 7.21; Ag, 22.40.

The same complex was obtained in better yield by the addition of acetone to the β-pinene. An excess of silver perchlorate was warmed with a mixture of β-pinene, 3.5 ml., having $[\alpha]^{25}D$ −20.6°, $n^{25}D$ 1.4763, and acetone, 0.5 ml., "reagent" grade. The liquid was decanted and allowed to cool slowly to 4°. Filtration yielded rectangular plates, 0.42 g., m.p. 107–109°, decomposing at 126°.

The crystalline complex, 0.32 g., was decomposed by water, 0.4 ml., the β-pinene phase was separated and dried with a small lump of calcium sulfate and then distilled in the vacuum system. The distillate, *ca.* 0.1 g., had $[\alpha]^{25}D$ −22.4°, $n^{25}D$ 1.4763.

Optically Pure α-Pinene from Optically Impure α-Pinene.—α-Pinene, 12.75 g., having $[\alpha]^{25}D$ +30.0°, $n^{25}D$ 1.4631, and crushed silver perchlorate, 4.83 g., were shaken together in a stoppered flask at 25° for 24 hr. Although less than half the α-pinene had reacted, the product was a semi-solid white mass. Unreacted α-pinene was removed from the mixture by high-vacuum distillation at room temperature into a receiver cooled in liquid air. Pinenes volatilize very slowly from their complexes with silver perchlorate under these conditions, and this quantity of unreacted α-pinene distilled completely in about 1 hr.[13] The distillate was dried over calcium sulfate (the trace of water present probably originated in the silver perchlorate), decanted and redistilled in the same apparatus under the same conditions: yield 6.08 g. (48%) of α-pinene, $[\alpha]^{25}D$ +16.2°, $n^{25}D$ 1.4630. The solid complex was decomposed by water, 10 ml., and the upper layer of α-pinene was separated. This was dried over calcium sulfate and distilled as before: yield 4.52 g. (36%), $[\alpha]^{25}D$ +50.7°, $n^{25}D$ 1.4630.

The sample of α-pinene obtained from the complex was fractionated again by the same procedure: 4.27 g. was shaken with silver perchlorate, 2.33 g., at 25° for 24 hr. In this experiment, however, little reaction occurred in this period, and the mixture was warmed in a water-bath at 95° for 0.5 min. to initiate the reaction. After a further 24 hr. little more reaction had occurred, so the mixture was warmed in a water-bath at 60° for several minutes, and then left to stand at 25° for a further 24 hr., by which time the mixture had become a semi-solid white mass. The products were separated, and the complex decomposed by water, 0.5 ml., as in the previous experiment. The unreacted α-pinene, 2.21 g. (52%), had $[\alpha]^{25}D$ +49.6°, $n^{25}D$ 1.4633; the α-pinene, 1.31 g. (30%), obtained from the solid complex had $[\alpha]^{25}D$ +52.4°, $n^{25}D$ 1.4632. The constancy of the refractive index throughout showed that no chemical change was taking place.

Optically Pure β-Pinene from Optically Impure β-Pinene.—β-Pinene, 8.59 g. having $[\alpha]^{25}D$ −21.0°, $n^{25}D$ 1.4765, reacted exothermally with silver perchlorate, 2.93 g., to produce a semi-solid white mass in several minutes; the mixture was then left at 25° for 18 hr. The product was treated in the same manner as the α-pinene complex. The unreacted β-pinene, 3.34 g. (39%), had $[\alpha]^{25}D$ −20.6°, $n^{25}D$ 1.4763. The β-pinene, 2.93 g. (34%), obtained by treating the solid complex with water, 10 ml., had $[\alpha]^{25}D$ −22.7°, $n^{25}D$ 1.4764.

Separation of α-Pinene from β-Pinene.[14]—The initial mixture was prepared by mixing α-pinene, 1.11 g., $\alpha^{25}D$ +44.7°, $n^{25}D$ 1.4632, with β-pinene, 1.13 g., $\alpha^{25}D$ −19.7°, $n^{25}D$ 1.4764. The mixture had $\alpha^{25}D$ +12.8°, $n^{25}D$ 1.4699. The percentage of α-pinene in this mixture, as calculated from the quantities taken, is 49.6. Assuming linear relations, the measured optical rotation of the mixture corresponds with that of a mixture containing 50.5% α-pinene, and the

(13) On one occasion an attempt was made to hurry this process by warming the reaction mixture in a water-bath at 90°; an explosion occurred which shattered the apparatus.

(14) Mixtures were analyzed by measurement of optical activity and refractive index, the results of these two methods agreeing within the limits of accuracy of the refractive index measurements. In this experiment the optical activities are expressed as measured rotations in a 1-dm. tube, the measured rotations of mixtures of α-pinene and β-pinene being approximately linear functions of relative concentration. The error involved in assuming refractive indices to be linear functions of concentration is only 1.5% at equal concentrations; the accuracy of our measurements did not warrant the more accurate treatment given by Fuguitt, *et al.*[10] Optically pure pinenes, prepared by the methods described in the preceding two sections, were employed in order to avoid simultaneous fractionation of optical isomers which would vitiate the simple optical method of analysis. Other experiments in which optically pure pinenes were not employed gave similar results, as shown by the refractive index method.

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refractive index corresponds with that of a mixture containing 51.1% α-pinene.

The mixture, 2.05 g., was treated with silver perchlorate, 0.75 g., and left to stand at 25° for 7 hr., when the products were separated by the method described above. The liquid, 1.00 g. (49%), distilled from the mixture had $\alpha^{25}D$ +30.7°, $n^{25}D$ 1.4662. These figures correspond with those of a mixture of α-pinene with β-pinene containing 78.3 and 78.2% α-pinene, respectively. The liquid, 0.60 g. (29%), obtained by treating the solid phase with water, 2 ml., had $\alpha^{25}D$ −14.7°, $n^{25}D$ 1.4756. These figures correspond with those of a mixture containing 92.2 and 93.1% β-pinene, respectively. The agreement between the two methods of analysis for both fractions confirms that no chemical change had occurred and that the recovered liquids consisted of only the mixed pinenes.

Behavior of α-Pinene and β-Pinene toward Aqueous Silver Perchlorate.—A solution of silver perchlorate, 6 g., in water, 5 ml., was shaken with β-pinene, 0.5 ml., for several minutes at 25°. The β-pinene was thereby completely converted to a white solid, which was not analyzed but was probably the same complex as that formed in the absence of water. An identical experiment in which α-pinene was substituted for the β-pinene did not produce any solid, the α-pinene remaining instead as a separate liquid phase. A further experiment, in which a mixture, 0.5 ml., of equal volumes of the two pinenes was taken, gave a mixture of solid and two liquid phases. This might be a promising method for the separation of α-pinene and β-pinene from each other.

Preparation of Silver Nitrate–Cyclohexene Complex.[15]—Silver nitrate, 3.6 g., was dissolved in a warm mixture of cyclohexene, 15 ml., and ethanol, 2 ml. At room temperature a system of two colorless phases was formed, and at 0° the lower phase gave a mass of needle-shaped crystals. Filtration at *ca.* 4° gave 4.6 g. of product, m.p. 24–32°.

Anal. Calcd. for $AgNO_3 \cdot 2C_6H_{10}$: Ag, 32.3. Found: Ag, 33.2, 33.3.

Pinenes and Silver Nitrate.—Attempts to obtain a solid complex were unsuccessful with pinene (practical) or pinene diluted with a solvent, for example, acetone, methanol or ethanol.

Miscellaneous Observations.—Silver perchlorate dissolves readily in 2-pentene, in 1-hexene and in 4-methyl-2-pentene to form systems consisting of two colorless liquid phases.[16] Crystals form when the 2-pentene system is cooled below room temperature. Silver nitrate dissolves to some extent in 2-pentene and in 4-methyl-2-pentene, but no second liquid phase results.

(15) The complex, but not its preparation, has previously been described by Salomon.[6]

(16) Francis[7] found that silver nitrate gave two liquid phases with propene and 1-butene but not with mixed pentenes.

PASADENA, CALIF.

[CONTRIBUTION NO. 2191 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Coördination of Silver Ion with Unsaturated Compounds. X. Complexes of Silver Perchlorate and Silver Nitrate with Alkynes[1]

BY ALAN E. COMYNS[2] AND HOWARD J. LUCAS[3]

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Systems of silver nitrate and silver perchlorate with 2-butyne, 2-pentyne and 3-hexyne have been studied. Solid complexes are formed, and their solubilities in the alkynes have been measured at 25°.

Previous investigations in this series[4,5] of the coordination[6] of alkynes with silver ion were devoted to measuring equilibrium constants in aqueous solution. We now report studies on systems formed in the absence of added solvent. As before, only dialkylacetylenes have been studied in order to obviate complications from the presence of acidic hydrogen atoms on 1-alkynes.

Silver perchlorate and silver nitrate differ markedly in their solubilities in the three alkynes, as shown in Table I. Except in the case of the silver perchlorate–2–butyne system, where a solid complex is rapidly and quantitatively formed, the solids in contact with the "saturated" solutions were mixtures of unreacted silver salt with solid complexes. This was due to the slowness with which solid complexes were formed, and in consequence the solubilities given in Table I are not true equilibrium values.

TABLE I

SOLUBILITIES OF $AgClO_4$ AND $AgNO_3$ COMPLEXES IN ALKYNES AT 25°

	2-Butyne	2-Pentyne	3-Hexyne
$AgClO_4$[a]	0.10	68	65
$AgClO_4$[b]	.10	211	185
$AgNO_3$[a]	.28	0.22	0.24

[a] Grams of $AgClO_4$ or $AgNO_3$ per 100 g. of solution. [b] Grams of $AgClO_4$ per 100 g. of solvent.

Silver Perchlorate Complexes.—The solubility of silver perchlorate in 2-pentyne and 3-hexyne is about two thousand times that in 2-butyne. This is probably a consequence of the symmetry of the 2-butyne molecule, which favors packing into a crystal lattice, rather than the formation of concentrated solutions. Similar behavior is found in related systems: thus silver perchlorate is insoluble in dioxane[7] but very soluble in tetrahydropyran[8] and is sparingly soluble in cyclohexene but very soluble in 1-hexene.[9] In each of these systems the solvents of more symmetrical structure readily form solid complexes with silver perchlorate but are poor solvents for these complexes.

The compositions of the "saturated" solutions of silver perchlorate in 2-pentyne and 3-hexyne at 25° correspond with molal ratios of alkyne to silver perchlorate of 1.4:1. Partial evaporation of the

(1) This research has been made possible by support extended the California Institute of Technology by the Office of Naval Research under Contract Nonr-270(00).

(2) Arthur Amos Noyes Fellow, 1952–1953.

(3) To whom requests for reprints should be sent.

(4) W. S. Dorsey and H. J. Lucas, THIS JOURNAL, **78**, 1665 (1956).

(5) G. K. Helmkamp, F. L. Carter and H. J. Lucas, *ibid.*, **79**, 1306 (1957).

(6) The reaction is considered to be complexing; J. G. Traynham and M. F. Sehnert, *ibid.*, **78**, 4024 (1956).

(7) A. E. Comyns and H. J. Lucas, *ibid.*, **76**, 1019 (1954).

(8) A. E. Comyns and H. J. Lucas, unpublished results.

(9) A. E. Comyns and H. J. Lucas, THIS JOURNAL, **79**, 4339 (1957).

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alkyne gives in each case a solid in which this ratio is approximately 1:3.

Solutions of 7.2 to 41% silver perchlorate in 2-pentyne (molal ratios of alkyne to silver perchlorate between 39:1 and 4.3:1) exist at 25° as two conjugate liquid phases of these compositions. Solutions containing less than 7.2% and between 41 and 68% of silver perchlorate in 2-pentyne consist of one liquid phase. The more concentrated solutions are viscous and become pale brown after standing for several days.

Solutions of silver perchlorate in alkynes silver-plate metallic copper, as do solutions of silver salts of fluoro acids in aromatic hydrocarbons.[10] Concentrated solutions in 2-pentyne and 3-hexyne explode on contact with mercury.

Vapor pressure data obtained on the system silver perchlorate–2-butyne, are plotted in Fig. 1. Systems containing 2-butyne in excess of the formula $AgClO_4 \cdot 3C_4H_6$ exert a pressure equal to that of 2-butyne (254 mm. at 0°), and those containing between 3 and 2.5 moles[11] of 2-butyne to 1 of silver perchlorate have a vapor pressure of 46 mm. at 0°.

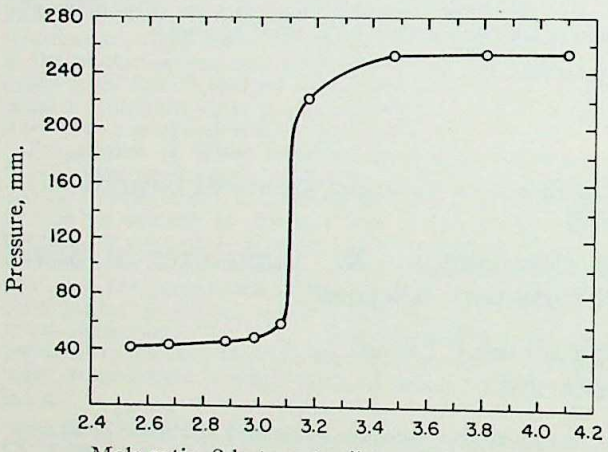

Fig. 1.—Vapor pressure of 2-butyne in the silver perchlorate–2-butyne system.

Silver Nitrate Complexes.—The solubility of silver nitrate is about the same in 2-butyne, 2-pentyne and 3-hexyne (Table I). 2-Pentyne reacts the most rapidly, for within a few minutes of adding powdered silver nitrate a fluffy white powdery complex is noticed. In the presence of a trace of moisture, introduced for example by working in an open test-tube, a second liquid phase forms, but even when the anhydrous reactants are heated to 90° in a sealed tube, no second liquid phase is observed. Evaporation of a saturated solution of silver nitrate gave a small amount of a flaky crystalline solid, $AgNO_3 \cdot 3C_5H_8$. This lost 2-pentyne rapidly on exposure to the atmosphere, and the resulting white powder had the approximate composition $AgNO_3 \cdot C_5H_8$.

When 2-butyne and 2-pentyne were shaken with silver nitrate at 25° for five days, some silver nitrate remained unchanged. 2-Butyne became yellow and a silver mirror was deposited on the walls of the vessel. When a mixture of 2-butyne and silver nitrate was warmed gently to 65°, the crystals of silver nitrate dissolved and a second, denser, initially yellow liquid phase appeared. This rapidly became dark brown and a silver mirror was deposited. Because of this side reaction, no satisfactory complex was isolated.

Powdered silver nitrate reacted quantitatively with 3-hexyne in 8 weeks to give the colorless crystalline complex, $AgNO_3 \cdot C_6H_{10}$.[12]

Experimental

Materials.—Silver perchlorate and silver nitrate were of reagent grade, the former from the G. F. Smith Co. The alkynes were all purchased from the Farchan Research Laboratories and purified by standing over sodium for 24 hr., followed by fractionation through a series of U-tubes in the vacuum system. The purified 2-butyne had v.p. 253 mm. at 0°, in agreement with that calculated from the formula given by Heisig and Davis.[13] The vapor density at 321 mm. and 24.5° was 2.46 g./l., which corresponds to a mol. wt. of 55.2 (calcd., 54.1). 2-Pentyne had d^{25}_4 0.705, $n^{25}D$ 1.4005. The vapor pressure of 2-pentyne was measured between −33° and +26° and obeyed the relation $\log_{10} P_{mm} = 8.067 - (1695/T_{abs})$. 3-Hexyne had $n^{25}D$ 1.4091.

Analyses.—The complexes of silver perchlorate with 2-butyne and of silver nitrate with 3-hexyne were analyzed by Dr. A. Elek. Other silver analyses were by thiocyanate titration using ferric alum indicator.

Solubility Measurements.—The solubility measurements for silver perchlorate in 2-pentyne and 3-hexyne are described in their respective sections below. The solubilities of silver perchlorate in 2-butyne and of silver nitrate in 2-butyne, 2-pentyne and 3-hexyne were measured by the following technique. A small quantity of the salt, contained in a glass ampoule fused to the vacuum system, was dried by pumping for at least 24 hr. with a mercury-vapor diffusion pump followed by a liquid-air trap. The alkyne, dried over sodium, was distilled directly into the ampoule which was then sealed off from the vacuum system and left to shake in a thermostat at 25.0° for several days. By this time the silver perchlorate with 2-butyne had been completely converted to a white powder: in the three silver nitrate systems the salt had been partially converted to solid complexes, which had the form of exceedingly thin, transparent flakes. Aliquots of the solutions were transferred to small flasks by pipets which had previously been warmed to 25°. The solutions were evaporated to dryness, and the residues were dissolved in 3 *N* nitric acid and titrated with 0.1 *N* potassium thiocyanate solution.

Silver Perchlorate–2-Butyne.—2-Butyne, 2.8 ml. at 0°, was distilled onto finely crystalline silver perchlorate, 0.90 g., contained in a graduated tube closed by a mercury float valve. In 15 minutes the solid, which had previously occupied 0.6 ml., had become transformed into a white, powdery mass which occupied 2.0 ml. An excess of liquid 2-butyne was present. The solid underwent no further volume change in 15 hr. All volatile constituents were then distilled from the mixture into a trap cooled in liquid air, 2 hr. being required. The distillate consisted of unchanged 2-butyne, 2.8 ml. at 0°, v.p. 254 mm. at 0°. The residual silver perchlorate, now in the form of a fine, white powder, occupied 1.8 ml.; it was completely soluble in water.

The complex was prepared on a sintered-glass disk fused into the middle of a centrifuge tube, the latter initially fused to the vacuum system. After the complex had formed on the disk, the contents of the tube were frozen, and the tube was sealed off from the vacuum system. The excess of liquid 2-butyne was then removed from the solid complex by centrifuging; by this means the solid was in

(10) D. W. A. Sharp and A. G. Sharpe, *J. Chem. Soc.*, 1858 (1956).

(11) Systems containing less butyne than this were not examined owing to the long time necessary for them to reach equilibrium. The experiment illustrated in Fig. 1 took ten weeks. For this reason it is not possible to deduce the nature of the second solid phase in equilibrium with the complex when less than 3 moles of 2-butyne is present. It may be silver perchlorate or another complex. Solid solutions are precluded by the shape of the vapor pressure curve.

(12) The formation of a solid complex of silver nitrate with 3-hexyne was first observed by F. L. Carter in these Laboratories.

(13) G. B. Heisig and H. M. Davis, THIS JOURNAL, 57, 339 (1935).

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contact with saturated 2-butyne vapor until finally it was removed and sealed in a small glass tube for analysis.

Anal. Calcd. for $AgClO_4 \cdot 3C_4H_6$: C, 39.0; H, 4.91; Cl, 9.59; Ag, 29.2. Found: C, 38.7; H, 5.02; Cl, 8.98; Ag, 29.4.

For the vapor pressure measurements, Fig. 1, silver perchlorate (1.049 g., 0.0051 mole) was contained in a small bulb which was maintained at 0° throughout the experiment. This bulb was connected to a manometer, and, *via* a mercury float valve, to a bulb of known volume, 147 ml., provided with a manometer of known volume per unit length. This larger bulb was in turn connected to the main line of the vacuum system by another mercury float valve. 2-Butyne (1.121 g., 0.0207 mole) was distilled onto the silver perchlorate, the valve was closed, and the mixture was left to equilibrate for 24 hr.; the vapor pressure remained at 254 mm., showing free liquid 2-butyne to have been present. Successive samples of 2-butyne vapor were removed from the small bulb, their masses being determined by measurement of the pressures exerted in the calibrated bulb. The pressures exerted by the complex were recorded as a function of time in order to find when equilibrium was established. Systems in the region of the inflection of the curve, Fig. 1, came to equilibrium in about 2 days, but the system of composition $AgClO_4 \cdot 2.6C_4H_8$ took approximately 30 days. At the conclusion of the experiment (after 10 weeks) the combined samples of removed vapors, 0.276 g., were shown to consist of pure 2-butyne (v.p. 254 mm. at 0°; v.d. 2.45 g./l.) and to account for 65% of the quantity expected on the basis of the separate pressure measurements. The remainder probably was lost through the stopcock grease of the storage flask during the experiment. At the conclusion of the experiment 1.0 ml. of water was admitted to the complex to release the remaining 2-butyne.[14] The liquids were distilled into a trap on the vacuum line and roughly fractionated by allowing the 2-butyne to distil out of the mixture into a second trap containing sodium. The 2-butyne, 0.451 g. (0.0083 mole), thus obtained had v.p. 254 mm. at 0°.

Silver Perchlorate–2-Pentyne.—Silver perchlorate, 4.75 g., and 2-pentyne, 17 ml., were shaken together in a stoppered test-tube in a thermostat at 25.0° for 24 hr. The solid dissolved, forming approximately equal volumes of two colorless liquid phases. The densities of the phases were determined using a pycnometer of 1.7-ml. volume. The concentrations of silver ion in the two phases were measured by shaking known weights with 3 *N* nitric acid and titrating with 0.1 *N* potassium thiocyanate. They are expressed as g. of $AgClO_4$ per 100 g. of solution. The upper phase had d^{25}_4 0.752; $AgClO_4$, 7.22, 7.24%. The lower phase had d^{25}_4 1.136; $AgClO_4$, 41.1, 41.2%.

The liquids remaining after the measurements had been made were treated with an excess of silver perchlorate, and the mixture was stirred intermittently at 25.0° during 48 hr., using a Trubore stirrer fitted in a test-tube. An orange, viscous solution was formed having d^{25}_4 1.748; $AgClO_4$, 67.8, 67.9%. The solid phase filtered from this solution appeared to contain unchanged silver perchlorate, contaminated with a small amount of a dark powder: analyses gave $AgClO_4$, 96.3, 95.7%. The viscous solution was evaporated under vacuum to approximately half-volume and the resulting white powder was filtered off.

Anal. Calcd. for $(AgClO_4)_3 \cdot C_5H_8$: Ag, 46.9. Found: Ag, 47.7, 46.4, 47.3.

Silver Perchlorate–3-Hexyne.—A mixture of silver perchlorate, 16.1 g., and 3-hexyne, 10 ml., was stirred intermittently for four days at 25.0° using the same apparatus as was used for the system with 2-pentyne. Here also a viscous, orange solution was formed. It had d^{25}_4 1.654; $AgClO_4$, 64.8, 64.9%. The solid phase which was filtered from this solution had a pale, creamy color and was more powdery than the silver perchlorate taken initially. Analyses gave $AgClO_4$, 95.9, 95.1%. Partial evaporation of the saturated solution yielded a cream-colored powder which was filtered off and freed from excess of 3-hexyne by exposure in the vacuum system for 4 min.

Anal. Calcd. for $(AgClO_4)_3 \cdot C_6H_{10}$: Ag, 46.0. Found: Ag, 45.6, 45.7.

(14) It was later found that distillation into a trap cooled in liquid air would have been more effective.

Silver Nitrate–2-Butyne.—The solid complex taken for analysis was that removed from a mixture which had been used for a solubility determination. This mixture had been shaken at 25° for 5 days and a pale yellow color had developed in the liquid phase. The solid phase, which was separated from this solution by centrifuging in a stoppered tube fitted with a sintered disk, contained small crystals of unchanged silver nitrate.

Anal. Found: Ag, 41.0, 40.5; ratios of $AgNO_3$ to C_4H_6 calcd. from these figures are 1 to 1.72 and 1.78, resp.

Silver Nitrate–2-Pentyne.—The solid phase formed during a solubility experiment was analyzed; the mixture had been shaken in a sealed tube at 25° for 4 days and had remained colorless.

Anal. Calcd. for $AgNO_3$: Ag, 63.5. Found: Ag, 64.0, 63.1.

The yield of crystals formed by evaporating a saturated solution of silver nitrate in 2-pentyne is very small. An apparatus, Fig. 2, was designed in order to repeat the process any desired number of times on the same mixture. Bulb A, 100 ml., contained silver nitrate. 2-Pentyne was distilled

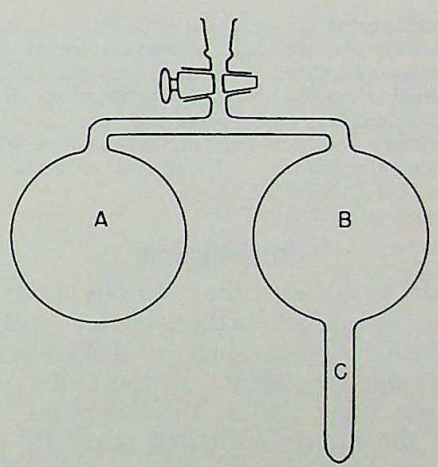

Fig. 2.—Apparatus for the preparation of the silver nitrate–2-pentyne complex.

onto it from the vacuum system, after which the stopcock was closed and the apparatus was detached from the system. The apparatus was shaken at room temperature for several hours for solution to occur, and then it was carefully tilted in order to decant the solution into bulb B, also 100 ml. With the apparatus in the vertical position again, bulb A was cooled by solid carbon dioxide thus causing 2-pentyne to distil back into bulb A and, by evaporation, to deposit crystals in bulb B which settled in tube C, 5 cm. × 1 cm. When all the 2-pentyne except that in tube C had distilled, bulb A was warmed to room temperature whereupon the whole process was repeated several times. When sufficient crystals had been formed, air was admitted through the stopcock and tube C was cut off. The contents were rapidly filtered and analyzed.

Anal. Calcd. for $AgNO_3 \cdot 3C_5H_8$: Ag, 28.8. Found: Ag, 30.66, 30.39; ratios of $AgNO_3$ to C_5H_8 calcd. from these figures are 1 to 2.67 and 2.72, resp.

The remainder of the crystals were left in a conical flask, 25 ml., open to the atmosphere, and the rate of loss in weight found, Table II.

TABLE II

CHANGE IN WEIGHT OF $AgNO_3 \cdot 3C_5H_8$ WHEN EXPOSED TO AIR

Time, min.	0	1	2	3	5	9	17	33	46	217
Weight, mg.	70	66	63	61	58	56	53	51	50	50

The very rapid initial loss shows that the samples which had been analyzed must have lost some 2-pentyne prior to analysis, and the initial composition was probably $AgNO_3 \cdot 3C_5H_8$. The powder which had come to constant weight in the atmosphere was analyzed

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Anal. Calcd. for $AgNO_3 \cdot C_5H_8$: Ag, 45.3. Found: Ag, 46.5.

Silver Nitrate–3-Hexyne.—A mixture of silver nitrate with an excess of 3-hexyne was prepared following the same technique as in the solubility experiments, and it was left to stand at room temperature for 8 weeks. The tube was then opened and the resulting crystalline mass was freed from liquid by centrifuging in a tube fitted with a sintered-glass disk.

Anal. Calcd. for $AgNO_3 \cdot C_6H_{10}$: C, 28.6; H, 4.00; N, 5.56; Ag, 42.8. Found: C, 28.4; H, 3.92; N, 5.47; Ag, 43.5.

This solid evolved 3-hexyne readily when warmed, and it burned with a smoky flame leaving a residue which contained free silver and also some water-soluble silver compound, presumably silver nitrate.

PASADENA, CALIF.

[CONTRIBUTION FROM THE LABORATORY OF POLYMER CHEMISTRY, TOKYO INSTITUTE OF TECHNOLOGY]

Structures of the Reaction Products of Tetraalkoxytitanium with Acetylacetone and Ethyl Acetoacetate

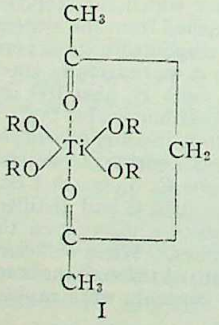
BY AKIO YAMAMOTO AND SHU KAMBARA

RECEIVED APRIL 1, 1957

The structures of the reaction products of a series of tetraalkoxytitaniums with acetylacetone and ethyl acetoacetate were studied by chemical and physical analysis of the isolated pure compounds. In contrast to the previously published paper, penta-coördinated titanium complexes (III and IV) with three alkoxy groups and one bidentate chelating group were obtained when equimolecular proportions of these chelating agents and tetraalkoxytitaniums were used. When two moles of the chelating agents were used per mole of tetraalkoxytitaniums, hexa-coördinated titanium complexes (V and VI) with two alkoxy and two chelating groups were formed. The compounds obtained were found to be present as monomers in dilute benzene solutions. Hydrolysis of dialkoxy-titanium-bis-(acetylacetonate) (V) gave a new type of titanium complex, $[TiO-(CH_3COCHCOCH_3)_2]_2$.

Introduction

Schmidt[1] has studied the reactions of tetraalkoxytitanium (tetraalkyl orthotitanate) with bidentate chelating agents such as diacetone alcohol, acetylacetone and ethyl acetoacetate with the aim of obtaining stable titanic esters. He has proposed the hexa-coördinated structure I for the reaction product of one mole of tetraalkoxytitanium with one mole of acetylacetone and structure II for the product of one mole of tetraalkoxytitanium with two moles of ethyl acetoacetate.



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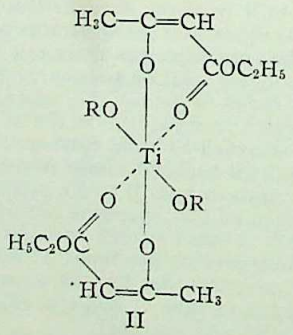


II

A similar study has been carried out cryoscopically by Reeves and Mazzeno,[2] recently. They have measured the freezing points of *t*-butyl alcohol solutions containing tetra-*t*-butoxytitanium (tetra-*t*-butyl titanate) and ethyl acetoacetate in various ratios and obtained evidence that tetra-*t*-butoxytitanium reacts with ethyl acetoacetate with the formation of 1:1 and 1:2 compounds.

The reaction products have been neither isolated as pure compounds nor analyzed in these two studies. The purpose of the present work was to determine the structures of the reaction products of a series of tetraalkoxytitaniums with bidentate ligands and also to study the physical and chemical properties of the titanium compounds having both alkoxy groups and chelate rings.

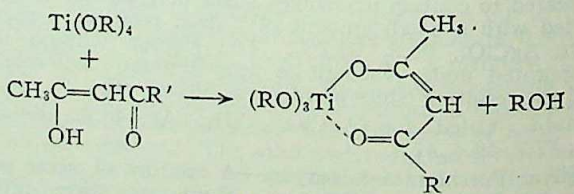
(1) F. Schmidt, *Angew. Chem.*, **64**, 536 (1952); German Patent 851,846.

(2) R. E. Reeves and L. W. Mazzeno, Jr., THIS JOURNAL, **76**, 2533 (1954).

Results and Discussions

(a) **Reaction of Tetraalkoxytitaniums with Acetylacetone and Ethyl Acetoacetate in a Molar Ratio 1:1.**—When one mole of acetylacetone was mixed with one mole of tetraalkoxytitaniums (tetraethoxy-, tetrapropoxy- and tetrabutoxy-titanium), crystalline or liquid complex products and one mole of alcohols (ethyl, propyl and butyl alcohol) were obtained. Physical constants and analytical data of the complexes obtained are summarized in Table I (nos. 1, 3 and 5.)

The results of the chemical analyses of the compounds formed lead to structure III, which is considered to be formed by an exchange reaction of an alkoxy group of each tetraalkoxytitanium with bidentate ligand.



III, $R' = CH_3$
IV, $R' = OC_2H_5$
$R = C_2H_5$, n-C_3H_7, n-C_4H_9.

A similar experiment on the reaction of tetraalkoxytitanium with ethyl acetoacetate indicated the formation of one mole of trialkoxy-titanium-(ethyl acetoacetate) (IV) (nos. 2, 4 and 6 in Table I) and one mole of alcohols.

These results disagree with Schmidt's proposal for the hexa-coördinated structure I with four alkoxy groups and one chelating group in keto-form bound to central titanium. In order to confirm the structures III and IV, infrared absorption spec-

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TABLE I

REACTION PRODUCTS IN 1:1 MOLAR RATIO

No.	Formula	Appearance	M.p., °C.	Analyses, % Calcd. Ti	C	H	Found Ti	C	H
1	$(EtO)_3Ti(acac)$[a]	Colorless prisms	59–65[b]	17.0	46.8	7.86	16.9	45.6	7.72
2	$(EtO)_3Ti(etac)$[a]	Colorless prisms	89–92[b]	15.3	46.2	7.75	15.3	45.6	7.42
3	$(PrO)_3Ti(acac)$	Light yell. liquid		14.8	51.9	8.70	14.3	51.4	8.86
4	$(PrO)_3Ti(etac)$	Colorless prisms	38–42[b]	13.5	50.9	8.54	13.6	50.0	8.83
5	$(BuO)_3Ti(acac)$	Light yell. liquid		13.1	55.3	10.1	12.9	54.2	8.92
6	$(BuO)_3Ti(etac)$	Light yell. liquid		12.1	54.5	9.16	12.2	54.9	8.30

[a] (acac) and (etac) represent chelated acetylacetone and ethyl acetoacetate groups, respectively. [b] Considerable difficulties were encountered in obtaining sharp melting points on account of the hygroscopic nature of the compounds. Crystals were introduced into a capillary in a dry-box and the melting points were measured after sealing the capillary tube.

TABLE II

REACTION PRODUCTS IN 1:2 MOLAR RATIO

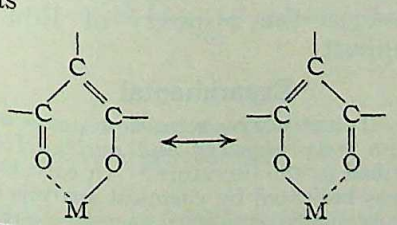
No.	Formula	Appearance	M.p., °C.	d^{25}_4	$n^{25}D$	Analyses, % Calcd. Ti	C	H	Found Ti	C	H
1	$(EtO)_2Ti(acac)_2$[a]	Colorless prisms	48–52			14.3	50.0	7.19	14.2	49.7	7.20
2	$(EtO)_2Ti(etac)_2$	Colorless prisms	40–45			12.1	48.5	7.12	12.1	48.3	7.05
3	$(PrO)_2Ti(acac)_2$	Light yell. liquid		1.125	1.554	13.1	52.8	7.74	13.1	51.8	7.62
4	$(PrO)_2Ti(etac)_2$	Light yell. liquid		1.117	1.526	11.3	50.9	7.60	11.2	51.4	7.23
5	$(BuO)_2Ti(acac)_2$	Light yell. liquid		1.089	1.542	12.2	55.0	8.21	12.1	53.9	9.39
6	$(BuO)_2Ti(etac)_2$	Light yell. liquid		1.090	1.519	10.6	53.1	8.03	10.6	51.8	8.09

[a] See references, Table I.

tra of the products were observed. The results are shown in Fig. 1.

The infrared absorption spectrum of tetrabutoxytitanium (Fig. 1-A) has strong absorption bands at 1080 and 1120 cm.$^{-1}$. Tributoxytitanium-(acetylacetonate) (III) (Fig. 1-B) also has two strong bands at exactly the same positions. The positions of these two peaks agree well with the positions of C–O stretching bands of aliphatic ethers at 1050 and 1150 cm.$^{-1}$. No band was found in the same range of the spectrum of the hydrolysis product of dialkoxy-titanium-bis-(acetylacetonate) (Fig. 1-D), which was prepared by hydrolysis of alkoxy groups of dialkoxytitanium-bis-(acetylacetonate) as is described later. These facts prove that the strong bands are due to C–O stretching vibrations of alkoxy groups bound to a titanium atom.

The spectrum of III (Fig. 1-B) indicates two strong bands at 1376 and 1577 cm.$^{-1}$ with nearly equal intensity and a strong band at 1523 cm.$^{-1}$. On the other hand, there is no band observed in the region of unperturbed carbonyl vibrations between 1700 and 1750 cm.$^{-1}$. These results agree well with the results of Lecomte[3] and Bellamy, *et al.*,[4] who have observed two strong bands of nearly equal intensity near 1560 cm.$^{-1}$ and between 1310 and 1410 cm.$^{-1}$ in the spectra of various metal chelate compounds of acetylacetone. They have assigned these bands to the assymmetric and symmetric vibrations of two CO links in the resonating structure as



(3) J. Lecomte, *Disc. Faraday Soc.*, **9**, 125 (1950).
(4) L. J. Bellamy and L. Beecher, *J. Chem. Soc.*, 4489 (1954).

The other strong band in the region between 1500 and 1534 cm.$^{-1}$ has been assigned by Lecomte to the vibration of perturbed C=C bonds of the enolic form.

The absorption spectrum of tributoxy-titanium-(ethyl acetoacetate) (IV) (Fig. 1-C) is similar to that of tributoxytitanium-(acetylacetonate) (III) (Fig. 1-B), except that the band at 1577 cm.$^{-1}$ of acetylacetone chelate is shifted to higher frequency, 1628 cm.$^{-1}$, in the spectrum of ethyl acetoacetate chelate. The shift is considered to indicate an influence of the substitution of the ethoxy group in place of the methyl group of acetylacetone. The electron-attracting tendency of the ethoxy group may interfere with the resonance.

Titanium exhibits an apparent coördination number of five in these complexes with three alkoxy groups and one bidentate ligand. However, there exist the alternative possibilities that the compounds may actually be di- or trititanium compounds having the favored coördination number of six. The values of molecular weight determined cryoscopically in benzene solutions are shown in Table III. The observed values roughly correspond to monomer in the molality range between 0.01 and 0.04 mole per 1000 g. of solvent and tend to increase with the solute concentration, suggesting that association might occur to some extent.

(b) Reaction of Tetraalkoxytitaniums with Acetylacetone and Ethyl Acetoacetate in a Molar Ratio 1:2.—In case of the reaction of the series of tetraalkoxytitaniums with acetylacetone or ethyl acetoacetate in a molar ratio 1:2, crystalline or liquid complex products and two moles of alcohols were formed. Physical constants and analytical data of the complexes formed are listed in Table II, and the molecular weights are summarized in Table III (nos. 1′ to 4′).

From these results, the reaction is considered to proceed according to the following equation in agreement with Schmidt's proposal, forming hexa-

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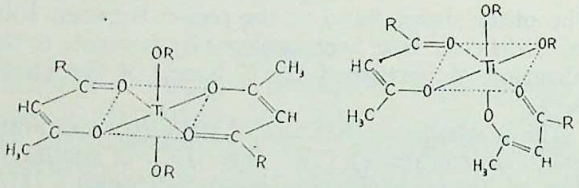
TABLE III

RESULTS OF MOLECULAR WEIGHT DETERMINATION

No.	Formula	Mole/kg. of solvent	ΔT, °C.	Molecular weight Found	Calcd.
1	$(EtO)_3Ti(acac)$	0.0396	0.179	310	282.2
		.151	.502	430	
2	$(EtO)_3Ti(etac)$	.0348	.179	310	312.2
3	$(PrO)_3Ti(acac)$	.0371	.181	335	324.3
		.0623	.236	440	
		.0887	.306	475	
4	$(PrO)_3Ti(etac)$	.0190	.092	375	354.3
5	$(BuO)_3Ti(acac)$	.0198	.100	370	366.3
1′	$(EtO)_2Ti(acac)_2$	0.0195	0.119	280	336.2
2′	$(EtO)_2Ti(etac)_2$	.0119	.065	370	396.3
3′	$(PrO)_2Ti(acac)_2$	.0533	.290	340	364.3
4′	$(PrO)_2Ti(etac)_2$	.0448	.253	385	424.4
		.0604	.362	360	

coördinated dialkoxy-titanium-bis-(acetylacetonate) (Va or Vb) or dialkoxy-titanium-bis-(ethyl acetoacetate) (VIa or VIb).

$$Ti(OR)_4 + 2CH_3C(OH)=CHC(=O)R' \longrightarrow 2ROH +$$



(a) *trans* form
Va, R′ = CH_3
VIa, R′ = OC_2H_5

or

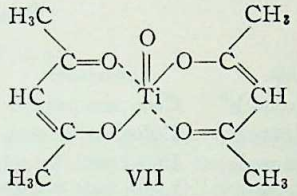
(b) *cis*, form
Vb, R′ = CH_3
VIb, R′ = OC_2H_5

Infrared spectra of these compounds are essentially the same as those of trialkoxy chelate compounds, indicating the presence of alkoxy and chelating groups.

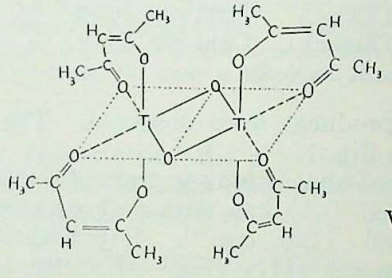
When more than two moles of the chelating agents were used per mole of tetraalkoxytitanium, the same compounds as structure V or VI were obtained. It seems, therefore, that no further substitution of the alkoxy groups with the chelating agents occurs under the condition employed.

Hydrolyses.—These complexes (III, IV and VI) with the alkoxy and the chelating groups, except dialkoxy-titanium-bis-(acetylacetonate)s (V), turn to gel-like substances, gradually in moist air and rapidly with the addition of water. The change may be ascribed to the hydrolysis of unstable alkoxy groups and subsequent condensation with the formation of polymeric substances with Ti–O–Ti bonds.

In the cases of diethoxy-, dipropoxy- and dibutoxy-titanium-bis-(acetylacetonate)s, on the other hand, pale yellow needles were produced by addition of water. The crystals were stable in the organic solvents from which the compound was recrystallized. When the solvents were removed, the crystals readily lost their crystalline form.[5] The infrared spectrum of the hydrolysis product of V, shown in Fig. 1-D, indicates the complete absence of the absorption bands due to alkoxy groups in the region between 1080 and 1150 cm.$^{-1}$. The other bands due to the chelate rings, near 1370, 1520 and 1570 cm.$^{-1}$, are essentially the same as the bands of dialkoxy-titanium-bis-(acetylacetonate) (V). This fact together with the results of the chemical analyses leads to the formula $Ti(CH_3COCHCOCH_3)_2$. Two structures can be considered for this formula, namely, (a) titanyl structure VII and (b) cyclic polymer structure, in which titanium achieves a coördination number of six by the sharing of the oxygen atom between titanium atoms.



VII



VIII

Molecular weight determination in benzene solution gave a value of 490, suggesting the dimeric structure VIII, the theoretical value for the monomer being 262.

Photochemical Reaction.—The color of titanium acetylacetonates (III, V and VIII) in hermetically sealed glass cells turns to blue when irradiated with a high-pressure mercury lamp or with sunlight. The change in color occurs rapidly in the absence of air, and the development of the blue color is retarded by the air in the cell. When the compounds are exposed to the open air, the blue color disappears rapidly. The blue color could be due to trivalent titanium which is produced by the fission of the Ti–O bond with the action of light. The trivalent titanium thus formed would be oxidized to quadrivalent titanium by oxygen when exposed to the open air. The further investigation of the photochemical reaction will clarify the detailed mechanisms of this reaction.

Acknowledgment.—The authors would like to express their sincere thanks to Professor K. Kojima for the infrared spectra and to Professor Y. Inamura for visible and ultraviolet spectra, and to Mr. Y. Takahashi for his assistance. The authors are indebted to the Ministry of Education for financial support.

Experimental

Materials.—Tetraethoxy-, tetra-*n*-propoxy- and tetra-*n*-butoxytitanium were prepared and purified following the method described in the literature.[6] In each case satisfactory purity was indicated by chemical analysis of the compound. Commercially available acetylacetone and ethyl acetoacetate were purified by fractional distillation and the

(5) Similar behavior has been observed by Jones, Pfeiffer and Werner in cases of vanadyl and platinum complexes with acetylacetone and salicylaldehyde diimine; M. M. Jones, THIS JOURNAL, 76, 5975 (1954); Pfeiffer, *et al.*, *J. prakt. Chem. N. F.*, 149, 217 (1937); A. Werner, *et al.*, *Ber.*, 34, 2584 (1901).

(6) J. Nelles, German Patent 720,080; U. S. Patent, 2,187,821.

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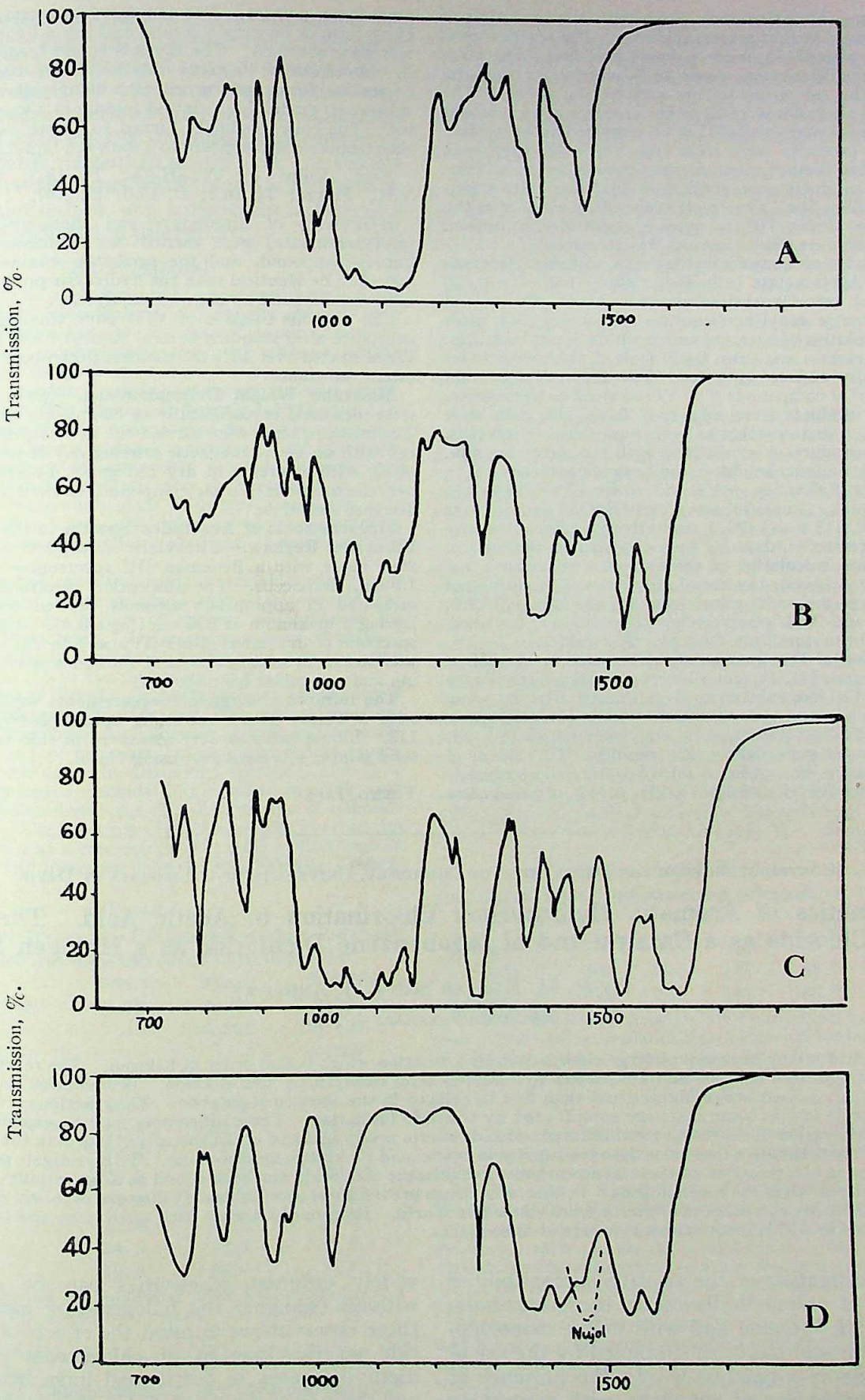

Fig. 1.—Infrared absorption spectra: 1-A, $Ti(OC_4H_9)_4$; 1-B, tributoxy-titanium-(acetylacetonate) (III); 1-C, tributoxy-titanium-(ethylacetoacetate) (IV); 1-D, hydrolysis product of dibutoxy-titanium-bis-(acetylacetonate).

fractions of b.p. 139–140° (760 mm.) and 94–95° (40 mm.), respectively, were used; $n^{25}D$ for acetylacetone, 1.4480; $n^{25}D$ for ethyl acetoacetate, 1.4169.

General Synthetic Procedures. (a) Reaction of Tetraalkoxytitaniums with Acetylacetone and Ethyl Acetoacetate in a Molar Ratio 1:1.—To 0.010 mole of tetraalkoxytitanium (tetraethoxy-, tetrapropoxy- and tetrabutoxy-titanium) was added 0.010 mole of acetylacetone or ethyl

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acetoacetate. Reaction took place with the evolution of heat and ended within several minutes. The reaction mixture was fractionated under reduced pressure. The volatile liquid distillates were shown to be alcohols by measurements of the refractive indices and boiling points. The quantity of alcohol was 0.010 mole. An equivalent amount (0.010 mole) of compounds III or IV remained as the residue. When the products were solid (see Table I), they were purified using diethyl ether or petroleum ether as solvent. The liquid products were distilled at 10^{-4} mm. with a pot-still or "falling-film" type molecular still, maintaining the temperature under 70° to prevent heat decomposition. These products are soluble in most organic solvents.

(b) **Reaction of Tetraalkoxytitaniums with Acetylacetone and Ethyl Acetoacetate in a Molar Ratio 1:2.**—To 0.010 mole of each tetraalkoxytitanium was added 0.020 mole of acetylacetone or ethyl acetoacetate. Reaction took place with the evolution of heat and ended within several minutes. From the reaction mixtures, 0.020 mole of alcohols were removed under reduced pressure. The theoretical amount (0.010 mole) of compounds V or VI remained as the residue. When the products were solid (see Table II), they were purified using diethyl ether or petroleum ether as solvents. The liquid products were distilled with the molecular still. These compounds are soluble in most organic solvents.

Molecular Refraction.—*MR* values for $(PrO)_2Ti(acac)_2$, $(PrO)_2Ti(etac)_2$, $(BuO)_2Ti(acac)_2$ and $(BuO)_2Ti(etac)_2$ were 103.8, 116.6, 113.4 and 125.9, respectively. Since there are no atomic refraction data for hexa-coördinated titanium in the literature, calculation of the molecular refractions was impossible. Instead, the atomic refraction was calculated from observed molecular refractions, and the values of 19.9, 20.1, 20.2 and 20.2, respectively, were obtained for hexa-coördinated titanium from these four *MR* values.

Hydrolyses of the Compounds and Isolation of VIII.—The compounds III, IV and VI were hydrolyzed readily by moisture. Gel-like substances were formed after standing several hours in moist air or instantly by addition of water. In case of dialkoxytitanium-bis-(acetylacetonate)s (V), addition of water gave light-yellow needles. To 1.62 g. of $(BuO)_2Ti(acac)_2$ was added 5 ml. of water. The crystals obtained were filtered and dried to give 0.74 g. of pale-yellow amorphous powder. The powder was recrystallized from chloroform or benzene solution, and again light yellow crystals were obtained. The crystals (plate form) were stable in chloroform or benzene solutions, but they lost their crystalline form and turned to a light yellow amorphous substance, gradually in air and rapidly in a vacuum desiccator. The color gradually turned to brown over 200° and the compound decomposed to a dark-red liquid at 235°.

Anal. Calcd. for $TiC_{10}H_{14}O_5$: Ti, 18.3; C, 45.9; H, 5.38. Found: Ti, 18.2; C, 45.6; H, 5.57.

Hydrolyses of dipropoxy- and diethoxy-titanium-bis-(acetylacetonate) were carried out analogously with the butoxy-compound, and the products obtained were confirmed to be identical with the hydrolysis product of the dibutoxy-compound by chemical analyses.

The aqueous solution of VIII gave transparent gel-like substance after standing several days at room temperature. When heated over 40°, the solution decomposed to an opalescent substance.

Molecular Weight Determinations.—Molecular weights were measured cryoscopically in completely dried benzene. The measurements were carried out in a shielded cryoscopic cell with an electromagnetic stirring device after exclusion of air with a stream of dry nitrogen. Freezing points of benzene solutions of some compounds showed a tendency to decrease with time.

Measurements of Absorption Spectra in the Visible and Ultraviolet Regions.—Ultraviolet absorption measurements were made with a Beckman DU spectrophotometer using 1.0-cm. silica cells. The absorption spectra of III and V measured in appropriate alcohols showed similar curves having a maximum at 325 mμ (log ε 3.5). The absorption spectrum of irradiated $(BuO)_2Ti(acac)_2$ in the visible region was measured in *n*-hexane and showed a maximum at 600 mμ and a shoulder near 650 mμ.

The infrared absorption measurements were carried out with a Perkin–Elmer recording spectrophotometer model 112. Liquid samples were measured in thin films and the solid sample was measured using Nujol.

TOKYO, JAPAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT DAVIS]

The Kinetics of Aromatic Hydrocarbon Chlorination in Acetic Acid. The Use of Zinc Chloride as a Catalyst and of Iodobenzene Dichloride as a Halogen Source

BY R. M. KEEFER AND L. J. ANDREWS

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In acetic acid methylbenzenes undergo chlorination by a reaction which is first order in halogen. The reactions are not inhibited by hydrogen chloride and are subject to relatively mild catalysis by zinc chloride. Bromination and iodination reactions in this solvent are of higher order than first in halogen in the absence of catalyst. The reactions are accelerated by zinc chloride and in some cases are complicated by trihalide formation. These differences may be explained in part through consideration of the relative stabilities of trihalide ions in acetic acid and of the role of acetic acid in the substitution reaction. Polymethylbenzenes chlorinate too rapidly in acetic acid for kinetic measurement. To investigate possible steric complications in the reactions of these hydrocarbons, iodobenzene dichloride has been tested as a potentially less reactive chlorinating agent than the free halogens. In this sense it has proved to be unsuitable. It dissociates slowly and comes to equilibrium with its components in dilute solutions in acetic acid. Its rate of reaction with mesitylene and pentamethylbenzene in acetic acid is identical with its rate of dissociation.

The investigation of the relative susceptibilities of a series of polymethylbenzenes to nuclear halogenation with bromine and with iodine monochloride in acetic acid has been simplified by the use of zinc chloride as a catalyst.[1,2] In the presence of this salt the orders of reactions with respect to these halogens reduce to unity and the kinetic complication of trihalide formation[2] is eliminated. In addition, by varying the catalyst concentration, relative halogenation rates for hydrocarbons of widely different reactivities can be established without changing the halogenating agent. With these observations in mind the effects of zinc chloride on the kinetics of chlorination of various methylbenzenes in acetic acid have been studied, and the results are presented in this paper.

One of the original objectives of this investigation was to determine whether the methyl group steric effect, which so markedly influences the susceptibility of polymethylbenzenes to bromination or iodination,[1,2] is less apparent in chlorination reactions. However, the higher molecular weight hydrocarbons, even in the absence of catalyst, react

(1) L. J. Andrews and R. M. Keefer, THIS JOURNAL, **78**, 4549 (1956).

(2) R. M. Keefer and L. J. Andrews, *ibid.*, **78**, 5623 (1956).

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too rapidly with chlorine for kinetic measurement. The possibility, therefore, has been considered that iodobenzene dichloride might serve as a less reactive chlorinating agent for use in a comparative rate study of the more reactive hydrocarbons. Although in this sense iodobenzene dichloride has proved to be an unsuitable reagent in acetic acid, the results of kinetic investigations concerning its function in aromatic chlorination are sufficiently interesting that they are included in this report.

Experimental

Materials.—The procedures used in preparing pure acetic acid, the aromatic hydrocarbons and dry zinc chloride have been described previously.[3,4] Eastman Organic Chemicals cyclohexene and iodobenzene were used without further treatment except for distillation of the latter.

Solutions of chlorine in acetic acid were prepared by passing cylinder gas (Ohio Chemical) directly into the solvent. Halogen analyses of the solutions were made iodometrically. In determining the extinction coefficients of chlorine solutions, the spectrum measurements were made first, and samples for iodometric analysis were then removed by pipet directly from the ground glass stoppered absorption cells to avoid volatility losses. Solutions of hydrogen chloride in acetic acid were prepared and analyzed as described elsewhere.[2]

Iodobenzene dichloride was made in small lots which were used immediately. The standard synthetic method[5] was used with the substitution of carbon tetrachloride for chloroform as the solvent. Iodometric analyses of weighed samples of the fresh product in acetic acid solution were generally within 1% of the theoretical value.

The Spectrum of Chlorine in Acetic Acid and in Solutions Containing Hydrogen Chloride and Zinc Chloride.—Contrary to what was found for solutions of hydrogen bromide and bromine[1] and of hydrogen chloride and iodine monochloride[2] in acetic acid, the ultraviolet spectra (Table I) of solutions of hydrogen chloride and chlorine in acetic acid do not offer positive evidence of the formation of trihalide ion (or HCl_3). The spectrum of a chlorine solution containing zinc chloride, at a concentration typical of that used in the rate runs, and hydrogen chloride is included in Table I.

TABLE I

THE EFFECT OF HYDROGEN CHLORIDE AND ZINC CHLORIDE ON THE SPECTRUM OF CHLORINE IN ACETIC ACID[a]

	Soln. I	Soln. II	Soln. III
$Cl_2 \times 10^3$, M	9.75	9.75	9.75
HCl, M	..	0.112	0.112
$ZnCl_2$, M	..	...	0.200
λ, mμ	ε	ε	ε
300	40.4	42.2	44.0
310	61.6	62.6	64.8
320	74.6	75.6	77.7
330	76.0	76.6	77.9
340	66.5	66.5	68.7
350	50.5	51.0	53.2
360	34.5	35.3	37.2
380	12.9	13.9	15.3

[a] The ε values are the molecular extinction coefficients of chlorine.

It is apparent that the salt also has no marked effect on the halogen spectrum.

The Rates of Chlorinations of the Hydrocarbons.—A single batch of purified acetic acid was used in carrying out the kinetic experiments. Stock solutions of the hydrocarbons and of zinc chloride in acetic acid were prepared from weighed samples of the reagents. Known volumes of these and of stock solutions of chlorine and hydrogen chloride were mixed at the temperature of the rate measurement. Samples of these mixtures, in silica absorption cells (10 cm., 2 cm. or 1 cm., depending on the initial concentration of chlorine), were placed in the housing of the Beckman spectrophotometer. Details concerning temperature control are given elsewhere.[2]

The changes in chlorine concentration were followed, generally to more than 75% of completion, by measuring optical densities of the rate samples (against an acetic acid blank) at a fixed wave length in the 340–370 mμ region. The wave lengths were chosen to provide initial readings, somewhere between 1.0–0.4. The data were, in certain cases, corrected for slight absorption by zinc chloride in the solutions.

The optical densities of dilute solutions of chlorine in acetic acid were observed to change negligibly during the time interval of even the longest rate runs. In other words errors resulting from the volatilization of chlorine were negligible.

The Dissociation of Iodobenzene Dichloride in Acetic Acid.—Qualitative experiments showed that the absorption in the near ultraviolet region of freshly prepared solutions of iodobenzene and chlorine in acetic acid were found to increase slowly with time. These changes were attributed to slow equilibration between iodobenzene dichloride and its components in acetic acid. It was found that the spectrum of an acetic acid solution which was 5.55×10^{-4} M in iodobenzene dichloride and 0.0989 M in iodobenzene did not change with time. The increases in absorption of solutions of chlorine and iodobenzene occurred more rapidly as the iodobenzene concentrations of the media were raised.

The optical density readings at equilibrium for two solutions, initially 2.39×10^{-3} M in chlorine and 0.164 and 0.0164 M in iodobenzene, were (after correction for the absorption of iodobenzene) nearly the same. It was assumed, therefore, that in acetic acid solutions in which the free iodobenzene concentration is of the order of 0.1 M, the conversion of chlorine to dichloride is essentially complete.

Extinction coefficients for iodobenzene dichloride over a short wave length range were calculated from equilibrium optical density readings of two of the solutions described above. These are recorded in Table II. Details of further experiments to determine the forward and reverse rate constants for dissociation of iodobenzene dichloride are included with the results.

TABLE II

THE SPECTRUM OF IODOBENZENE DICHLORIDE IN ACETIC ACID[a]

λ, mμ	350	360	370	380	390
ε of soln. I[b]	309	233	147	85.6	...
ε of soln. II[c]	312	224	144	86.0	45.6

[a] Based on optical densities after attainment of equilibrium. The optical densities were corrected for iodobenzene absorption. [b] Soln. I was originally 5.55×10^{-4} M in $C_6H_5ICl_2$ and 0.0989 M in C_6H_5I. [c] Soln. II was originally 2.39×10^{-3} M in Cl_2 and 0.164 M in C_6H_5I.

The Kinetics of Reaction of Iodobenzene Dichloride with Mesitylene and Pentamethylbenzene.—All rate measurements were carried out spectrophotometrically using 1-cm. absorption cells and an acetic acid blank. The changes in optical density with time recorded during a run were corrected for any small absorption which was observed at infinite reaction time.

Several hours prior to starting rate runs, a stock acetic acid solution of chlorine containing more than an equivalent amount of iodobenzene was prepared. The rate samples were prepared by mixing known volumes of this solution with known volumes of solutions of the hydrocarbon and, in some cases, of iodobenzene. A single batch of purified acetic acid was used in studying both kinetics of dissociation of iodobenzene dichloride and of chlorinations with iodobenzene dichloride.

The Product of Reaction of Pentamethylbenzene with Iodobenzene Dichloride in Acetic Acid.—To a freshly prepared solution of 0.65 g. (0.0024 mole) of iodobenzene dichloride in 80 ml. of acetic acid was added 0.300 g. (0.00202 mole) of pentamethylbenzene. This solution was allowed to

(3) N. Ogimachi, L. J. Andrews and R. M. Keefer, THIS JOURNAL, 77, 4202 (1955).

(4) R. M. Keefer, A. Ottenberg and L. J. Andrews, *ibid.*, **78**, 255 (1956).

(5) H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N.Y., p. 482.

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stand in the dark overnight. It was then poured into 250 ml. of water. The slightly gummy precipitated solid, after washing with water and air drying, weighed 0.250 g. This material was recrystallized from ethanol to provide 90 mg. of fine white crystals of m.p. 153–155° (reported[6] m.p. for 6-chloro-1,2,3,4,5-pentamethylbenzene, 155°). The yield, based on crude product, was 67%. The purified product gave no precipitate when it was boiled with alcoholic silver nitrate.

Results

Zinc Chloride Catalyzed Chlorination.—The results of earlier investigations indicate that chlorination of methylbenzenes in acetic acid leads to high yields of nuclear substituted products[7] by processes which appear, on the basis of rather limited experimental detail, to be first order in hydrocarbon and in halogen.[8–10]

To assess the effects of zinc chloride on the chlorination rates of several methylbenzenes a more detailed investigation of the kinetics of the uncatalyzed reactions has now been conducted. In agreement with de la Mare and Robertson[9] these new data have been found to conform to the rate law

$$-d(Cl_2)/dt = k(ArH)(Cl_2) \qquad (1)$$

Retardation of the reactions through the accumulation of hydrogen chloride in the medium has not been encountered with any of the hydrocarbons under investigation, and this observation is in accord with the negative spectrophotometric evidence (see Experimental section) for interaction between hydrogen chloride and chlorine in acetic acid solution. Actually for several runs with *p*-xylene in which excesses of hydrogen chloride (as compared to chlorine) were added to the reaction mixtures, a slight enhancement in rates was observed, as was reported previously by de la Mare and Robertson.[9] For those runs in which the initial *p*-xylene to chlorine ratio was large the initial phase of the reaction was abnormally fast, probably because of a trace of *m*-xylene impurity in the hydrocarbon sample.

Table III summarizes the results of the runs, both at 25.2 and 45.3°, on the several hydrocarbons under investigation. Where the variation in hydrocarbon concentration was small, values of k(ArH) were calculated from the slopes of plots of logarithms of the measured optical densities (see Experimental section) *vs.* time. In general the fit of the data to linear plots was excellent except as noted for *p*-xylene. For the few runs in which the hydrocarbon concentration dropped appreciably as reaction occurred, k values were evaluated graphically by the usual procedure for bimolecular reactions.[11]

(6) A. Tohl, *Ber.*, **25**, 1524 (1892).

(7) G. Illuminati and G. Marino, THIS JOURNAL, **78**, 4975 (1956).

(8) K. Lauer and R. Oda, *Ber.*, **69**, 1061 (1936).

(9) P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.*, 279 (1943).

(10) Chlorinations of phenolic ethers and of anilides in acetic acid have been shown to be second order over-all; see, for example, A. E. Bradfield and B. Jones, *J. Chem. Soc.*, 3073 (1928); B. Jones, *ibid.*, 418, 676 (1942).

(11) The relative values found for k at 25.2° for toluene, *p*-xylene and *o*-xylene are in the ratio 1/6.7/10. These values compare favorably with those (1/6.3/13.4) calculated from the times of 20% reaction at 24° in 99% acetic acid reported by de la Mare and Robertson[9] for reaction mixtures containing equal concentrations of chlorine and hydrocarbon. The rate constants at 25.2° reported in Table III for toluene, and the xylenes are about 1.3 times as large as those which can be estimated from the results reported by de la Mare and Robertson for 24°.

TABLE III

CHLORINATION RATE CONSTANTS AT 25.2°

$(ArH)_i$, mole/l.	$10^3 \times (Cl_2)_i$, moles/l.	$10^3 \times k$, sec.$^{-1}$ mole^{-1} l.	$(ArH)_i$, mole/l.	$10^3 \times (Cl_2)_i$, moles/l.	$10^3 \times k$, sec.$^{-1}$ mole^{-1} l.
Benzene			Toluene		
0.800	11.6	0.0069	0.400	27.0	0.60
			.400	14.4	.60
o-Xylene			.400	6.8	.61
			.200	6.7–7.1	.74[a]
0.402	7.4	8.3	.196	6.6	3.11[b]
0.201	7.4	7.5	.100	7.1	0.71
p-Xylene			*m*-Xylene		
0.194	30.8	3.56	0.0218	1.65	336
.194	15.4	3.50	.0218	0.85	336
.194	7.7	4.5[d]	.0109	0.85	338[c]
.198	8.6	4.6[e]			
.198	8.6	5.2[f]	Durene		
.097	7.7	4.3	0.00188	1.78	4640
.049	7.7	3.9	0.00188	0.90	3740

[a] Average of two runs of which values of 10^3k were 0.73 and 0.745. [b] Temperature for this run was 45.3°. [c] Average of two runs of which values of 10^3k were 335 and 341. [d] Average of two runs of which values of 10^3k were 4.5 and 4.5. [e] The initial concentration of HCl in the reaction mixture was 0.0112 *M*. [f] The initial concentration of HCl in the reaction mixture was 0.112 *M*.

As zinc chloride is added to the reaction medium, an acceleration of the aromatic hydrocarbon chlorination rate is observed. Equation 2 has been used in interpreting rate runs in the presence of this salt.

$$-d(Cl_2)/dt = k'(ArH)(Cl_2) = [k + k_c(ZnCl_2)][(ArH)(Cl_2)] \qquad (2)$$

Rate constants, k', have been determined for individual runs in the same way as were the constants, k, for the uncatalyzed reaction. These values and the k_c values for the third-order catalytic reactions at 25.2 and 45.3° of the several aromatic hydrocarbons which have been investigated are given in Table IV. Average values of k from Table III have been used in calculating the k_c values.

From the results reported in Tables III and IV it is clear that there are several marked differences in the kinetics of reaction of aromatic hydrocarbons with chlorine and with bromine or iodine monochloride in acetic acid. In discussing these differences the generalized mechanism for aromatic halogenation[1,2,12,13] in solvents of low polarity, which is given in equations 3–5, is useful.

$$ArH + X_2 \rightleftharpoons ArH\cdot X_2 \qquad (3)$$

$$ArH\cdot X_2 + E \longrightarrow ArH\cdot X^+ + EX^- \qquad (4)$$

$$ArHX^+ \longrightarrow ArX + H^+ \qquad (5)$$

Equation 4, in which the halogen–halogen bond of an aromatic–halogen π-complex is severed by attack of an electrophilic reagent, E, represents the rate-determining step.

In the absence of a catalyst the solvent alone may function as the reagent E, in which case the reaction should show first-order dependence on halogen. The reactions of toluene and *p*-xylene with iodine monochloride in trifluoroacetic acid behave kineti-

(12) R. M. Keefer, A. Ottenberg and L. J. Andrews, THIS JOURNAL, **78**, 255 (1956).

(13) K. L. Nelson, *J. Org. Chem.*, **21**, 145 (1956).

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cally in this way.[14] In acetic acid the uncatalyzed iodination reactions are second order in iodine monochloride,[2] and bromination reactions are second order in halogen, although a small contribution from a first-order process may be detected at low bromine concentrations.[12] Apparently in these cases a second halogen molecule serves as the electrophilic reagent. The superiority of trifluoroacetic acid as compared to acetic acid in promoting halogenation by the first-order process has been ascribed to the importance of proton sharing by the solvent when it participates in the abstraction of halide ion from the complex in the rate determining step.[14]

TABLE IV

RATE CONSTANTS FOR THE ZINC CHLORIDE CATALYZED REACTION AT 25.2°

$(ArH)_i$, mole/l.	$10^3 \times (Cl_2)_i$, moles/l.	$(ZnCl_2)$, mole/l.	$10^3 k'$, sec.$^{-1}$ mole^{-1} l.	$10^3 k_c$, sec.$^{-1}$ mole^{-2} l.^{2}
		Benzene		
0.400	14.0	0.400	0.072	0.16
		Toluene		
0.400	14.4	0.400	8.4	19.5
.400	30.2	.200	3.52	14.6
.400	14.4	.200	3.52	14.6
.400	7.5	.200	3.35	13.7
.400	14.4	.100	1.80	12.0
.200	7.5	.200	3.48	13.9
.100	6.8–7.5	.200	3.57	14.3[a]
.098	6.6	.196	14.9	60.2[b]
		o-Xylene		
0.402	7.4	0.200	33.1	128
0.402	7.4	0.100	19.7	122
		m-Xylene		
0.0109	0.79	0.103	632	2860
0.00109	0.66	0.207	920	2820
		p-Xylene		
0.198	8.0	0.200	24.0	102
.198	8.0	.100	12.7	92
.198	8.0	.050	8.0	91
.198	8.6	.200	34.4	146[c]
		Durene		
0.00188	0.78	0.103	4660	[d]

[a] Average of two runs of which values of $10^3 k'$ were 3.52 and 3.61. [b] Temperature for this run was 45.3°. [c] The initial concentration of HCl in the reaction mixture was 0.112 *M*. [d] The k_c value for durene is not reported since the k value required for its calculation is somewhat uncertain (see Table III). The error resulting from this uncertainty might have been minimized were not durene too reactive to permit the determination of k' values at zinc chloride concentrations higher than 0.1 *M*.

In chlorination reactions in acetic acid the solvent again appears to serve satisfactorily as the reagent E. The likelihood that a second molecule of chlorine should fill this role seems minimal since, unlike iodine monochloride, chlorine shows no tendency to coördinate with chloride ion in acetic acid. Actually the rate of first-order bromination of mesitylene in acetic acid is relatively slow,[12] but the hydrocarbon chlorinates virtually instantaneously in this medium even at low (0.01 *M* or less) initial reactant concentrations.

The rate superiority of chlorine over bromine and iodine monochloride in the first order (in halogen) substitution reactions may be explained in part by consideration of the solvation energies of the halogens. Acetic acid functions as a donor in interacting with iodine monochloride and with bromine.[15] The extent of this interaction is smaller for bromine than for iodine monochloride and must be even smaller[16] in solutions of chlorine in acetic acid, and the solvation energies for the halogens probably fall off in this same order.[2] In forming a complex with the aromatic hydrocarbon (equation 3) the halogen must undergo some desolvation, and the desolvation energy must make a direct contribution (smaller for chlorine than for the heavier halogens) to the activation energy of the substitution reaction.

It appears, furthermore, that acetic acid is considerably more effective in the transition state of the chlorination reaction as a solvating agent for halide ion which is separating from the aromatic–halogen complex than it is in bromination and iodination reactions. Zinc chloride has a relatively small influence on the kinetics of hydrocarbon chlorination. At concentration levels of zinc chloride at which bromination and iodination reactions are first order with respect to the two reactants and to the catalyst,[1,2] a significant fraction of the chlorination reaction still appears to take place by a catalyst-independent process. Whereas the ratio of k_c/k values for the chlorination reactions studied in this investigation range from 23 for benzene to 8 for *m*-xylene, the corresponding ratio of rate constants[1,4] for mesitylene bromination by reactions which are first order in halogen is of the order of magnitude of 3×10^5.

A comparison of the activation energies for the halogenation reactions also indicates that the influence of zinc chloride is small in chlorinations. For mesitylene bromination the activation energy for the first-order (in bromine) uncatalyzed reaction[4] is 15 kcal./mole and that for the reaction in the presence of zinc chloride[1] is only 7 kcal./mole. Activation energies for the zinc chloride catalyzed iodination reaction of several aromatic hydrocarbons[2] range around 17 kcal./mole, and those for uncatalyzed first-order reactions in iodine monochloride, if measurable, would probably be much higher. The corresponding activation energies for the uncatalyzed and catalyzed chlorination of toluene (calculated from the k and k_c values at 25.2 and 45.3° given in Tables III and IV) are both 13.4 kcal./mole. In view of the identity of these two experimental values, one is inclined to wonder whether the favorable influence of zinc chloride on the chlorination rate might better be classified as a salt effect rather than as true catalysis. It is evident from previous studies of the influences of zinc chloride on the rates of hydrocarbon bromination and iodination reactions that catalytic and environmental effects of this salt cannot be measured separately.

(14) L. J. Andrews and R. M. Keefer THIS JOURNAL, **79**, 1412 (1957).

(15) R. E. Buckles and J. F. Mills, *ibid.*, **75**, 552 (1953).

(16) L. J. Andrews and R. M. Keefer *ibid.*, **73**, 462 (1951).

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The Relative Halogenation Rates of the Methylbenzenes.—As noted in the introduction, the results of the earlier investigations of the kinetics of zinc chloride catalyzed halogenations indicate that the reactions of highly methylated benzenes are subject to marked steric retardation.[1,2] The steric problem seems to be much more pronounced in iodination than in bromination reactions. Presumably the attack of chlorine on the aromatic nucleus should be less subject to hindrance than that of the larger halogens. The present results provide limited information on this point.

Partial rate factors for halogenation at positions *ortho*, *meta* and *para* to methyl groups relative to that at one position in benzene[17] have been calculated from the chlorination rate constants at 25.2° for benzene, toluene and *o*- and *p*-xylene. For the uncatalyzed reaction they are $o_f = 95$, $m_f = 7.9$ and $p_f = 304$; and for the catalyzed reaction they are $o_f = 130$, $m_f = 6.4$ and $p_f = 235$. These values for the catalyzed reaction may be used to predict a reactivity ratio of 1.3×10^4 for *m*-xylene and benzene as compared with an experimental value of 1.7×10^4. The partial rate factors for the uncatalyzed reaction lead to predicted *m*-xylene/benzene and durene/benzene rate ratios of 1.1×10^4 and 1.9×10^5, respectively. The experimental values are 4.8×10^4 and 5.7×10^5, respectively. In situations in which extreme steric hindrance to halogenation appears to exist, observed polymethylbenzene reactivities are considerably less than those predicted from the partial rate factors.[1,2] In other words, the available data suggest that methylbenzene chlorinations are not unusually sensitive to the methyl group steric effect.

Reactions with Iodobenzene Dichloride.—An attempt has been made to determine the rate constant, k, for chlorination of the higher molecular weight methylbenzenes through inclusion of iodobenzene in the reaction mixtures. If an equilibrium were established rapidly and reversibly with respect to formation of iodobenzene dichloride, one might, by adjustment of the iodobenzene concentration, lower the concentration of free chlorine sufficiently to permit rate measurements on the more reactive hydrocarbons.

Investigation has shown, however, that while an equilibrium is indeed established between iodobenzene dichloride and its components in acetic acid solution, the equilibration process is relatively slow. When mesitylene or pentamethylbenzene are chlorinated in solutions containing iodobenzene, the chlorination rate is independent of the aromatic hydrocarbon and iodobenzene concentrations and is controlled by the rate of decomposition of iodobenzene dichloride into its components (see equations 6 and 7).

$$C_6H_5ICl_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C_6H_5I + Cl_2$$

$$k_1/k_2 = K = \frac{(C_6H_5I)(Cl_2)}{(C_6H_5ICl_2)} \qquad (6)$$

$$ArH + Cl_2 \xrightarrow{k_3} ArCl + HCl \qquad (7)$$

In other words, for the reactions of pentamethylbenzene and mesitylene the condition that $k_3(ArH) >> k_2(C_6H_5I)$ must hold.

In Table V rate constants k_1 for the reactions of these two hydrocarbons with iodobenzene in acetic acid are summarized. These were calculated on the assumption that the rate law for chlorination is

$$-d(ArH)/dt = -d(C_6H_5ICl_2)/dt = k_1(C_6H_5ICl_2) \qquad (8)$$

TABLE V

RATE CONSTANTS AT 25.2° FOR CHLORINATION BY $C_6H_5ICl_2$

$(ArH)_i$, mole/l.	$10^3 \times (Cl_2)_i$, moles/l.	$10^3 \times (\varphi I)_i$, moles/l.	$10^3 k_1$, sec.$^{-1}$	$(ArH)_i$, mole/l.	$10^3 \times (Cl_2)_i$, moles/l.	$10^3 \times (\varphi I)_i$, moles/l.	$10^3 k_1$, sec.$^{-1}$
Mesitylene				Pentamethylbenzene			
0.400	4.6	25.7	0.145	0.100	5.4	25.7	0.177
.100	18.8	18.8	.246[a]	.0100	11.1	11.9	.226
.100	9.2	31.6	.234	.0102	9.9	11.9	.277
.100	4.6	45.5	.184	.0100	9.7	11.6	2.38[b]
.100	4.6	25.7	.184	.0100	5.4	25.7	0.207
.100	2.3	22.8	.184	.0100	5.4	5.9	.212
.010	5.5	25.7	.199	.0102	4.9	5.9	.227
				.0100	4.8	5.8	2.02[b]
Cyclohexene				.0100	2.77	2.97	0.206
0.102	18.8	18.8	0.232[a]				

[a] Crystalline $C_6H_5ICl_2$ was used in preparing rate samples. [b] Temperature for these two runs was 45.6°. Rate constants for these two runs and for the runs just above them in the table were used in calculating the reported activation energy. These runs were all made on the same day using the same batches of stock solutions.

As the disappearance of iodobenzene dichloride was followed spectrophotometrically (see Experimental section), k_1 values for each run were actually determined from the slopes of linear plots of the logarithms of measured optical densities *versus* time. The reactions were in general followed to at least 74% completion.

In most cases the initial iodobenzene dichloride concentrations of the reaction mixtures were established through dilution of relatively concentrated solutions of iodobenzene and chlorine in acetic acid, which had been prepared sufficiently well in advance so that the chlorine was largely converted to the dichloride. When solid iodobenzene dichloride itself was used as the dihalide source, the rate samples were made up using freshly prepared solutions of the solid in acetic acid. In all reported runs, therefore, the initial iodobenzene dichloride concentrations are approximated by the values of $(Cl_2)_i$ given in Table V. It may be assumed that any free chlorine initially present in the reaction mixtures disappeared immediately by reaction with the aromatic hydrocarbon.

The rate constants for runs of widely varying concentrations of the various reactants are all of the order of magnitude of 0.2×10^{-3} sec.$^{-1}$ at 25.2° for both pentamethylbenzene and mesitylene and are in close agreement with the rate constant measured for one run in which the aromatic hydrocarbon was replaced by cyclohexene, a substance which consumes free chlorine rapidly.

The constant k_1 was evaluated independently by studying the rate of equilibration of iodobenzene dichloride with its components in acetic acid. Solutions of the solid dichloride in acetic acid were prepared and standardized iodometrically. The changes in optical density of these solutions at an

(17) J. E. Condon, THIS JOURNAL, **70**, 1963 (1948).

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appropriate wave length in the 340–380 mμ region were followed to the time of equilibration. The concentrations of free chlorine and of iodobenzene dichloride throughout the runs were calculated from measured optical densities using the extinction coefficients given in Tables I and II.

The equilibrium constants, $K = k_1/k_2$, for each run were calculated from equilibrium readings. The individual rate constants for the forward and reverse reaction are also related by differential equation 9.

$$-d(C_6H_5ICl_2)/dt = k_1(C_6H_5ICl_2) - k_2(C_6H_5I)(Cl_2) \quad (9)$$

A useful integrated form of equation 9 is given in equation 10, in which $a = (C_6H_5ICl_2)_i$, $b = -2(C_6H_5ICl_2)_i - K$ and $A = (C_6H_5ICl_2)$. The

$$\ln \frac{2A + b - \sqrt{b^2 - 4a}}{2A + b + \sqrt{b^2 - 4a}} - \ln \frac{2a + b - \sqrt{b^2 - 4a}}{2a + b + \sqrt{b^2 - 4a}} = k_2 t \sqrt{b^2 - 4a} \quad (10)$$

constants k_2 were determined from the slopes of the linear plots of the left-hand term of equation 10 *vs.* time. The results of these runs are summarized in Table VI, in which the values of k_1 and K for the several runs at 25.2 and 45.6° are listed along with equilibrium values of the optical densities of the reaction mixtures.

Table VI

Rate Constants and Equilibrium Constants for the Decomposition of Iodobenzene Dichloride

$10^3 \times (C_6H_5ICl_2)$, moles/l.	λ,[a] mμ	d_{eq}	$10^3 k_1$, sec.$^{-1}$	$10^3 K$,[b] moles/l.	t, °C.
13.7	380	0.900	...	1.47	25.2
2.73	340	.340	0.139	1.54	25.2
1.37	360	.134	0.148	1.44	25.2
2.75	360	.254	1.24	4.3	45.6
1.37	360	.100	1.30	4.3	45.6

[a] Wave length at which runs were made; 1-cm. absorption cells and an acetic blank were used. [b] Value of $\Delta H^0 = 9.9$ kcal./mole is calculated from average K values at the two temperatures.

One run also was made at 25.2° in which the change in optical density at 380 mμ of an acetic acid solution originally 2.97×10^{-3} M in iodobenzene and 3.23×10^{-3} M in chlorine was followed to the equilibrium point. An equilibrium constant ($K = 2.0 \times 10^{-3}$ mole/l.), calculated from the equilibrium data for this run, compares favorably with an average value of 1.5×10^{-3} mole/l. for the runs reported in Table VI. Rate constants for this run were evaluated graphically according to equation 10 with, in this case, $a = (C_6H_5I)_i(Cl_2)_i$ and $b = -(C_6H_5I)_i - (Cl_2)_i - K$. The resultant k_1 value, 0.16×10^{-3} sec.$^{-1}$, was also in good agreement with the values listed in Table VI.

Although the values of k_1 reported in Table V are on the average somewhat higher than those in Table VI, the agreement is sufficiently good to support the proposed mechanism for the aromatic chlorinations by iodobenzene dichloride. It is particularly gratifying that the activation energy calculated from rate constants k_1 for the reaction of pentamethylbenzene with iodobenzene at 25.2 and 45.6° ($E_a = 20.1$ kcal./mole) is almost identical with that calculated from the averages of rate constants for the dissociation of iodobenzene dichloride which are given in Table VI ($E_a = 20.2$ kcal./mole.)

A few qualitative tests were made to determine the behavior of iodobenzene dichloride in non-polar solvents. Dilute solutions of the dihalide in benzene and in carbon tetrachloride showed no changes in spectra over a several-hour period, an indication that dissociation to form the component materials did not occur. Similarly the ultraviolet spectrum of a benzene solution of the dichloride which contained an excess of cyclohexene remained invariant for several hours, and then the dichloride suddenly disappeared completely from the solution.

The reaction which occurred may well have been radical induced. Certainly, further work on the function of the dihalide as a halogen source in non-polar media is required to rationalize the results of earlier investigators.[18–20]

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

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Davis, California

[Contribution from Loyola University of Los Angeles]

Nature of Aliphatic C-Nitroso Compounds. I. Study of the Rate of Dissociation of the Aliphatic C-Nitroso Dimer in Various Solvents

By Joseph R. Schwartz

Received March 27, 1957

The rate of dissociation of two aliphatic nitroso dimers, $(CH_3)_2C(NO)CH_2R$, with R = CH_3 and R = OAc in a series of solvents at several temperatures is reported. From the activation parameters, it is concluded that the inductive effect is mainly responsible for rate trends and solvent effects observed.

Introduction

It has been known for some time that many aliphatic C-nitroso compounds exist in the solid state as dimers and, when dissolved in various solvents, dissociate into blue monomers at a measurable slow rate.[1,2] Crystal studies on the dimer show that the N–N distance is between the single- and

(1) Bamberger and Seligmann, *Ber.*, **36**, 692 (1903).
(2) N. V. Sidgwick, "Organic Chemistry of Nitrogen Compounds," Oxford University Press, London, 1942, p. 204.

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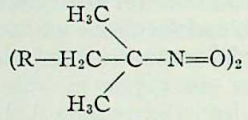
double-bonded values.[3] Recent spectral evidence on some substituted aromatic C-nitroso compounds has yielded information on the effect of substitution on the monomer–dimer equilibrium in the dissolved state and in the solid state. The ground and excited electronic states for both the monomer and dimer were identified from absorption spectra.[4]

It is of interest to determine more specifically the nature of the bonding forces in the dimer and to gain further insight into the rate of monomer formation. Reported herein is a preliminary investigation of these questions. The rate of monomer formation of the tertiary aliphatic nitroso compounds in a series of solvents of varying dielectric



I, R = CH_3COO-

II, R = H_3C-

constant and hydrogen bonding ability and at various temperatures has been measured.

Experimental

Preparations. I. 2-Methyl-2-nitroso-1-acetoxy-propane.—One hundred and seven grams of 2-methyl-2-nitro-1-propanol (Matheson, Coleman and Bell P1242), m.p. 93–95°, was added to 98 g. of acetic anhydride and the mixture was refluxed for 0.5 hr. One hundred and forty-eight grams of the acetate (81% yield, b.p. 125–127° (30 mm.)) was reduced with 130 g. of zinc dust added portionwise to the acetate in 500 ml. of water containing 200 g. of ammonium chloride. The reduction mixture was cooled, filtered free of solids and 93 g. of potassium dichromate in 200 ml. of 2 *N* sulfuric acid was added, whereupon oxidation of the hydroxylamine to the nitroso compound occurred,[5] as indicated by the presence of the blue color of the I monomer. The solution was extracted with two 250-ml. portions of ether. The ether layer was washed several times with water and dried over anhyd. sodium sulfate. The ether was removed with aspirator vacuum at room temperature. The nitroso acetate I was recrystallized twice from 60–90° boiling range petroleum ether: m.p. 67–69°. *Anal.* Calcd. for $C_6H_{11}NO_3$: C, 49.63; H, 7.64. Found: C, 49.32; H, 7.48. The absorption maximum at 674 mμ, $\epsilon(C_6H_6)$ = 13.9, of the monomer was used to follow the rate of dissociation, since the dimer does not absorb at this wave length.

II. 2-Ethyl-2-nitrosopropane.—*t*-Amylurea (Matheson, Coleman and Bell P5547) was hydrolyzed in diethylene glycol with sodium hydroxide,[6] and the *t*-amylamine so obtained was oxidized to the nitro compound following the directions of Kornblum and Clutter.[7] The nitro compound was reduced to the hydroxylamine and oxidized to the nitroso compound II, using the procedure described under the preparation of I above. Due to the great volatility of the nitroso compound, the ether solution extract of I was evaporated slowly at room temperature under a 20-plate column. A blue-white residue remained. This (approx. 1 g.) was taken up in 8 ml. of isopentane and cooled to −80°, whereupon a white solid precipitated out in a few seconds. This was filtered off and air-dried. Recrystallization from the same solvent yielded a material of m.p. 50.3–51.2°; Bamberger and Seligmann[1] report 50.0–50.5°. In no case was better than 10% yield obtained. Note: several attempts to prepare these aliphatic nitroso compounds in any recoverable yield by method of Bamberger and Seligmann[1] were unsuccessful for 2-methyl-2-nitrosopropane and 2-methyl-2-acetonyl-nitrosopropane (oxidation of the corresponding amine with Caro acid). The absorption maximum at 680 mμ, $\epsilon(C_6H_6)$ 20.4, of the monomer was used to follow the rate of dissociation since here, also, the dimer does not absorb at this wave length.

Measurement of the Dissociation Rate.—A Beckman DU model spectrophotometer was fitted with a special water-tight, pitch-lined compartment, having soft glass windows, so as to function as part of the instrument, and constant temperature water was circulated through this compartment. The temperature was maintained constant to within a variation of 0.01°. Samples of solvent of approximately 3 ml. each were placed in 3 test-tubes, tightly stoppered and allowed to thermally equilibrate. Approximately a 10-mg. sample of the finely powdered nitroso compound was added to the first test-tube, the tube then being stoppered, covered with a cloth to insulate thermally and shaken violently to dissolve the nitroso compound rapidly and transferred to a 1.00-cm. path length Corex cell already in the compartment and at thermal equilibrium. The cell was stoppered. The $t = 0$ for the dissociation was taken as 1 second after the solid was added to the tube, it having previously been determined that approximately this time was necessary for solution of the substance. In exactly the same manner, the other two cells were filled at exactly 1-minute intervals, with successively increasing sample sizes to furnish multiplicate determinations.

The reaction showed good first-order behavior, within experimental error. The reaction was followed for 2 half-lives or more, except where indicated in parentheses in the figures for the rate constants in Tables I and II. Attempts to follow the reaction in acetic acid were unsuccessful, because no clear first-order plot was obtained: the earlier part of the run was first-order, followed by a break in slope and a curving off from linearity. Redetermination of several of the rate constants on other occasions under the same conditions gave the reproducibility indicated in the table; k and the activation parameters were calculated from the data: k by the least squares method, ΔH^* by the Arrhenius plot of log k *vs.* $1/T$, and ΔS^* fron the Eyring absolute rate equation, using k at a given T and ΔH^*.

TABLE I

RATE OF DISSOCIATION OF 2-METHYL-2-NITROSO-1-ACETOXY-PROPANE DIMER

Solvent		k_1, sec.$^{-1}$ 12.88	18.00	25.00
$C_6H_5NO_2$	(36.1)[a]		0.048	0.149
MeOH	(33.1)		.0425	.099
$AcCH_3$	(21.4)		.054	.145
$AcOC_2H_5$	(5.0)		.069	.188
$CHCl_3$	(5.0)	0.0153	.032	.087
C_6H_6	(3.1)		.081	.234

[a] Dielectric constant of solvent at 20; source "Internatl. Critical Tables."

TABLE II

RATE OF DISSOCIATION OF 2-ETHYL-2-NITROSOPROPANE DIMER

In acetone +5% water, k_1 = 0.0046 min.$^{-1}$ at 12.88.

Solvent		k_1, sec.$^{-1}$ 12.88	18.00	25.00
$C_6H_5NO_2$	(36.1)[a]		0.0195	0.0463
MeOH	(33.1)	0.0048(50%)[b]	.0088	.025
$AcCH_3$	(21.4)	.0094		.053
$AcOC_2H_5$	(5.0)	.0112	.0233	.0609
$CHCl_3$	(5.0)	.0048[c]	.0050	.0156
C_6H_6	(3.1)	.0122	.026	.072

[a] Dielectric constant of solvent at 20°; source "Internatl. Critical Tables." [b] Extent of reaction followed: where not indicated, this is 75% or more. [c] This reaction was run at 12.80°.

These nitroso compounds in ether solution gradually decolorized upon standing in direct sunlight, in agreement with the observation of Bamberger and Seligmann.[1] Their further observation that freshly dissolved dimer dissociates more slowly if first exposed to light is under study at the present time. Because of these facts, the nitroso solid compounds were stored in the refrigerator, and the solutions were not exposed to strong light at the beginning of the

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(4) K. Nakamoto and R. E. Rundle, THIS JOURNAL, **78**, 1113 (1956).

(5) P. Tarte, *Bull. soc. chim. Belge*, **63**, 525 (1954).

(6) *Org. Syntheses*, **29**, 21 (1949).

(7) N. Kornblum and R. J. Clutter, THIS JOURNAL, **76**, 4404 (1954).

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runs. The solutions at final equilibrium (dissociation equilibrium) obeyed Beer's law if the solutions were kept more dilute than optical density corresponding to 1.5 units. In all cases under study the optical density was less than 1.5 units for the infinity value.

Results

In Tables I and II are reproduced the results of this investigation at 12.88°, 18.00° and 25.00°, respectively, in the solvents nitrobenzene, acetone, methanol, ethyl acetate, chloroform and benzene. The solvents used in this investigation were reagent grade quality and were used as obtained from J. T. Baker Chemical Co.

TABLE III

ACTIVATION PARAMETERS FOR DISSOCIATION OF I AND II

Solvent	H, kcal./mole	S, e.u.	Solvent	H, kcal./mole	S, e.u.
Compound I			Compound II		
$C_6H_5NO_2$	28.1	32.1	$C_6H_5NO_2$	13.4	10.0
MeOH	20.9	7.6	MeOH	23.2	13.3
$AcCH_3$	21.4	9.4	$AcCH_3$	27.5	28.8
$AcOC_2H_5$	28.2	33.1	$AcOC_2H_5$	25.2	21.3
$CHCl_3$	24.2	18.0	$CHCl_3$	18.6	15.5
C_6H_6	23.5	17.2	C_6H_6	24.9	20.6

Discussion

It may be noted that there is definitely smaller entropy of activation for I in the polar solvents methanol and acetone, indicating that solvent is effectively associated with the bond about to break in the dissociation. Nitrobenzene seems to be particularly effective in assisting the bond to break in the case of II. It may be noted that the solvents have been ordered according to decreasing dielectric constant. No trend seems evident here. Figure 1 shows that for I, ΔH^* is a good linear function of ΔS^*, but this relationship shows a good deal of scatter for II. Figure 2 shows the plot of k_1 for I *vs.* k_1 for II at 25° in various solvents and indicates a fairly linear relationship, with slope = 0.270 ± 0.116 (95% confidence interval), for the straight line through the origin. The line was made to pass through the origin, since, if the Eyring equation is assumed to hold

$$k_1 = \frac{kT}{h} \exp(-\Delta F^*/RT), \text{ then}$$

$$k_1(\mathrm{I})/k_1(\mathrm{II}) = \exp(-\Delta\Delta F^*/RT)$$

which means that the k_1's are linear functions of one another at a given temperature and that the intercept is 0. On the basis of this line, r, the coefficient of correlation = 0.575, and $\Delta\Delta F^*$ was calculated from the mean slope to be 0.78 kcal./mole. Thus, in all the solvents studied, ΔF^* for I is greater by this amount than ΔF^* for II. This is taken to mean that less organized-energy is needed in the dimer to break the N–N bond in dissociating partially to the transition state and that this must be mainly related to the inductive pull of electrons in the acetoxy group, and perhaps it may be stated that this inductive pull contributes a definite amount of energy to the organized states (organized along the direction in which the bond breaks).

If there were any steric effects involving solvents, then some of the solvents might be expected to deviate from this line markedly. Since no strong deviation is observed, it suggests that no steric effects seem to enter the picture. Preliminary work is in

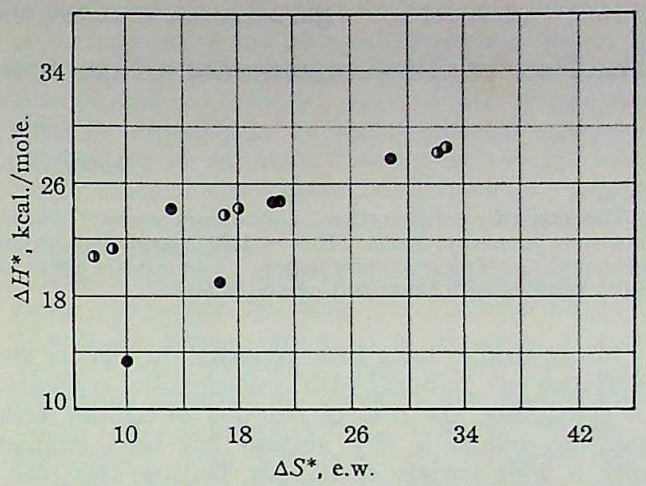

Fig. 1.—Correlation of ΔH^* and ΔS^*: ◐, I; ●, II.

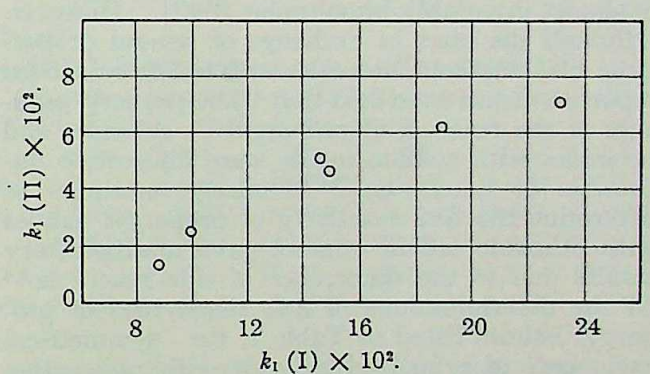

Fig. 2.—Correlation of k_1 of I with k_1 of II in various solvents, at 25.00°.

progress to determine the extent of this factor using R = *t*-butyl.

Nakamoto and Rundle[4] suggest that electron-donating groups stabilize the monomer of aromatic nitroso compounds through a resonance mechanism. In the two compounds studied here, only inductive effects are possible between the substituent and the reaction center and, since no equilibrium constants were determined, it can only be concluded that electronegative groups would make the unshared pair of electrons on the nitrogen atom less available for dimer formation, and hence there might be a contribution from this source to lower the activation energy for monomer formation. The fact that N–N–O compounds do not dimerize, however, is in keeping with these ideas, since nitrogen is quite strongly electronegative and probably would keep the unshared pair on the nitroso-nitrogen unavailable for dimer-bonding.

In a preliminary experiment the rate of dissociation of the pseudonitrole, $(CH_3)_2(NO)(NO_2)$, and nitrosobenzene in benzene were found to be too rapid to measure. This probably indicates that the N–N dimer bond is quite weak. It is a well known fact that negative substituents decrease the stability of these dimers. For example, $(CH_3)_2$-$CCl(NO)$[5] and $(CF_3)_2C(F)(NO)$[6] are both known only as the blue monomer.

Acknowledgment.—The author is much indebted to Research Corporation for the grant-in-aid which made this research possible.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Rate of Quaternization of a Piperazine by Some Propargylic and Allylic Bromides[1]

BY M. HARFENIST

RECEIVED JANUARY 28, 1957

The rate of quaternization of a tertiary amine, 1-carbethoxy-4-methylpiperazine, with allyl bromide ($10k$ = 2.25 l./mole-min.), methyl iodide ($10k$ = 1.22), propargyl bromide ($10k$ = 0.892) and 1-bromo-2-heptyne ($10k$ = 3.50) was measured in acetone–water solution. The order of these rate constants is somewhat different from that reported for other SN2 reactions with these and related halides.

Many studies have been reported on relative reactivities of halides with nucleophilic reagents. In particular, the rate of reaction of halides with metallic iodides in dry acetone has been studied with a wide variety of halides, because this reaction is normally relatively free of side reactions and is almost invariably bimolecular (SN2). However, although the rates of exchange of several propargylic chlorides and bromides with iodide have been reported, it has been said that "The primary products of the reaction of propargyl. . . chlorides and bromides with sodium iodide were difficult or impossible to determine."[2] Similarly, attempts to determine the SN2 reactivity of propargyl halides with ethoxide ion in ethanol gave unsatisfactory results due to the occurrence of side reactions.[3,4] Of the determinations of SN2 reactivities of propargyl halides listed in Table I, the "symmetrical exchange" of propargyl chloride with radioactive chloride in acetone seems most likely to be free of side reactions.

TABLE I

RATES OF SOME BIMOLECULAR REACTIONS OF ALLYL AND PROPARGYL HALIDES

Halide	k, l./mole-min.
A. With inorganic iodide in acetone at 25°[a]	
$CH_2{=}CHCH_2Cl$	0.0111[2]
$CH_2{=}CHCH_2Br$	7.30[b]
$CH{\equiv}CCH_2Cl$	0.0181[2,3,a,d]
$CH{\equiv}CCH_2Br$	10.2[2]
$CH_3C{\equiv}CCH_2Cl$	0.0273[3,d,a]
$C_4H_9C{\equiv}CCH_2Br$	4.150[b]
$(CH_3)_3CC{\equiv}CCH_2Br$	5.270[b]
$C_6H_5C{\equiv}CCH_2Cl$	0.111[c,d]
B. With lithium chloride in acetone at 44.6°[4]	
$CH_2{=}CHCH_2Cl$	0.00352
$CH{\equiv}CCH_2Cl$	0.00394

[a] Recalculated to 25° where indicated, using the formula: $\log \frac{k_2}{k_1} = 4000\left(\frac{1}{T_1} - \frac{1}{T_2}\right)$ [J. B. Conant, W. R. Kirner and R. E. Hussey, THIS JOURNAL, 47, 488 (1925)]. [b] P. D. Bartlett and L. J. Rosen, *ibid.*, 64, 543 (1942). [c] M. J. Murray, *ibid.*, 60, 2662 (1938). [d] Multiplied by 2.303 since $\log_{10}$ appears to have been used.

The author had occasion to quaternize 1-carbethoxy-4-methylpiperazine with a variety of halides.[5] In the course of these syntheses it was observed that the rates of the reactions with the propargylic halides appeared to be in a somewhat different order from those anticipated from the previous work. Since substantially quantitative yields of pure quaternary salts were readily obtained from these reactions, it was felt that a more precise determination of the rate constants of some representative quaternizations would be of value. Rates were therefore determined for the reaction of 1-carbethoxy-4-methylpiperazine with propargyl bromide, allyl bromide, 1-bromo-2-heptyne and with methyl iodide. The last might serve as a reference halide to allow the data reported here to be used to anticipate results with other amines for which methyl iodide quaternization rates are known. The solvent used was a mixture of equal volumes of acetone and water ("50% acetone") which was found to dissolve the reactants and the products.

Experimental

Materials.—Allyl bromide (Matheson–Coleman and Bell), propargyl bromide (General Aniline and Film Corp.), and methyl iodide (R.S.A. Corp.) were distilled within one week of each use, retaining an arbitary center cut, and were stored in the dark.[6] The 1-bromo-2-heptyne[7a,b] made from hept-2-yne-1-ol (Farchan Research Laboratories) was redistilled *in vacuo* within two days of each use, since it darkened quite rapidly. This bromoheptyne gave 101% of the theoretical amount of halide after hydrolysis with excess of hot alcoholic sodium hydroxide. The 1-carbethoxy-4-methylpiperazine was an arbitrary center cut of material[8] with acceptable values for the boiling point, made from hydrochloride of proper m.p.

Method.—Rates were measured by adding an equimolar amount of the halide to a solution of the amine in "50% acetone"[9] contained in a glass-stoppered 250-ml. volumetric flask thermostated at 25 ± 0.15°. Approximately 12 millimoles of each reagent was normally taken, although only

TABLE II

REACTION OF 1-BROMO-2-HEPTYNE WITH 1-CARBETHOXY-4-METHYLPIPERAZINE IN "50% ACETONE"

Initial wt. amine = 974.5 mg. (5.662 millimoles); initial wt. of halide = 990.8 mg. (5.659 millimoles); volume = 250.0 ml.; T = 25.0°; slope found: 7.98 × 10^{-3}; k = 3.52 × 10^{-1} l. moles^{-1} min.$^{-1}$

Time, min.	10	60	114	174	244
Ml. Ag^+ (0.1000 N)	0.400	0.800	1.200	1.500	1.800
Ml. SCN^- (0.0110 N)	2.010	.585	1.070	1.720	2.950
Millimoles Br^-/l.	1.79	7.366	10.82	13.11	14.75
$A - X$ (millimoles/l.)	20.85	15.27	11.82	9.53	7.49
$X/A - X$	0.086	0.483	0.916	1.376	1.970

(1) This is paper No. 12 on unsymmetrical piperazines from these laboratories. For the previous paper see M. Harfenist and E. Magnien, THIS JOURNAL, 79, 2215 (1957).

(2) T. L. Jacobs and W. F. Brill, *ibid.*, 75, 1314 (1953).

(3) L. F. Hatch and V. Chiola, *ibid.*, 73, 360 (1951).

(4) C. A. Vernon, *J. Chem. Soc.*, 4462 (1954).

(5) M. Harfenist, THIS JOURNAL, 79, 2211 (1957).

(6) (a) A single run with slightly discolored propargyl bromide which had been stored for 6 months and not distilled just before use gave a normal rate of quaternization; (b) propargyl bromide: b.p. 82–83°, $n^{24.5}$D 1.4910; allyl bromide: b.p. 68–69°, $n^{26.8}$D 1.4640.

(7) (a) M. S. Newman and J. H. Wotiz, THIS JOURNAL, 71, 1292 (1949); (b) b.p. 83.3–85° (22 mm.), $n^{23.5}$D 1.4884.

(8) L. P. Albro, R. Baltzly and A. P. Phillips, *J. Org. Chem.*, 14, 771 (1949).

(9) The "50% acetone" was made of equal volumes of acetone and water and was therefore 44.1% acetone by weight.

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5.66 millimoles of each component could be used in the reactions of 1-bromo-2-heptyne in "50% acetone," because of the low solubility of this halide. At measured intervals 10.0-ml. aliquots were pipetted from the reaction flasks into 20 ml. of 0.5 *N* aqueous nitric acid, treated with a slight excess of standard 0.1 *N* silver nitrate, 2 ml. of nitrobenzene was added, and the excess of Ag^+ was back-titrated with thiocyanate. Preliminary experiments proved that no detectable change in titer was found in aliquots titrated after 0.5 hour as compared with aliquots titrated immediately.[10]

The results of the titrations were converted to rate constants by plotting $X/A - X$ *vs.* t, where X was the amount of halide ion produced in t minutes, and A was the initial amount of alkyl halide and amine in moles/l. The slopes of the resulting straight lines were equal to Ak. The reactions were followed to 50–70% of completion. Five points were taken for each of the duplicate runs with the bromoheptyne in "50% acetone," and 8–11 points for each of the other runs. All constants reported were determined at least in duplicate.

The results of typical runs with the two acetylenic halides are given in Tables II and III.

of hydroxyl ion with allyl and propargyl chlorides in aqueous ethanol,[4] although the variation of the rate constant for the allyl chloride with concentration of base in Vernon's work makes precise comparison impossible. It was separately shown in preliminary experiments that the sum of the halide ion produced by solvolysis and by the Sn2 reaction with hydroxyl ion was too small to account for the results reported here.[13]

The increase in rate of quaternization in going from propargyl bromide to 1-bromo-2-heptyne (Table IV, lines 3 and 4) is in the same direction as the results reported (Table I, lines 3 and 5) for propargyl chloride *vs.* 1-chloro-2-butyne with iodide. The opposite order, however, would be anticipated from the propargyl bromide results (Table I, lines 4, 6 and 7). The increase in rate

Table III

Reaction of Propargyl Bromide with 1-Carbethoxy-4-methylpiperazine in "50% Acetone"

Initial wt. amine = 2.1062 mg. (12.23 millimoles); initial wt. of halide = 1.4552 mg. (12.24 millimoles); volume = 250.0 ml.; T = 24.90°; slope found: 4.43×10^{-3}; $k = 9.07 \times 10^{-2}$ l moles^{-1} min.$^{-1}$

Time, min.	2	14	60	90	122	162	200	261	325	394
Ml. Ag^+ (0.1000 *N*)	0.300	0.400	2.350	3.000	3.000	3.000	3.000	3.500	4.000	4.000
Ml. SCN^- (0.1100 *N*)	0.227	0.100	1.158	1.440	1.178	0.897	0.650	0.784	0.987	0.805
Millimoles Br^-/l.	.50	2.90	10.76	14.06	17.04	20.13	22.85	26.38	29.14	31.14
$A - X$, millimoles/l.	48.44	46.04	38.18	34.88	31.90	28.81	26.09	22.56	19.80	17.80
$X/A - X$	0.013	0.0630	0.2820	0.4067	0.5341	0.6995	0.8763	1.161	1.472	1.749

Results and Discussion

The rate constants found in this work are given in Table IV.

Table IV

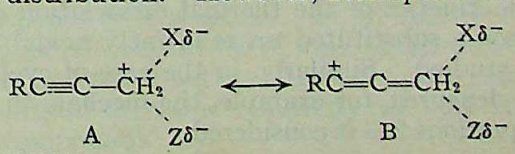
Rate Constants for Quaternization of Halides with 1-Carbethoxy-4-methylpiperazine at 25°

Halide	Solvent	$10k$, l./mole-min.	No. of determ.	Relative k CH_3I = 1
CH_3I	"50% acetone"[9]	1.22 ± 0.02	2	1
$CH_2{=}CHCH_2Br$	"50% acetone"[9]	2.25 ± .03	2	1.84
$CH{\equiv}CCH_2Br$	"50% acetone"[9]	0.892 ± 0.007	4[11]	0.73
$C_4H_9C{\equiv}CCH_2Br$	"50% acetone"[9]	3.50 ± .02	2	2.86
$C_4H_9C{\equiv}CCH_2Br$	"75% acetone"[12]	1.59 ± .02	2	

The rate of quaternization is seen to be 2.5 times as fast for allyl bromide as for propargyl bromide. Comparison of this result with those summarized in Table I shows that our results are in opposite order to those found with the halide interchange reactions of either iodide or of radiochloride. However, the same order of reactivity appears to occur in the initial rate constants for the Sn2 reactions constant obtained for the iodide reaction on going from the 3-*n*-butyl- to the 3-*t*-butyl-substituted propargyl bromide (Table I, lines 6 and 7) shows an activating influence of additional alkyl groups, as would be expected from our results and from those based on the chlorides with iodide in acetone.

The high Sn2 reactivity of propargyl halides is not readily understood. It is commonly explained in terms of a contribution toward lowered energy of the transition state by a resonance form (illustrated for attack by nucleophile Z^-), by analogy with similar explanations for allylic systems (*cf.* ref. 4). Contribution of a resonance form resembling B to the structure of the propargyl halides has been used to explain the C–halogen distances determined by electron diffraction for those compounds.[14] An increased stabilization of B by electron feed-in when R = alkyl as compared to B when R = H might lead to the increase in rate found going from the propargyl bromide to the heptynyl bromide quaternization.

The structure B seems to have an unlikely electronic distribution. However, attempts were made



(10) Two adsorption indicators were tried unsuccessfully in an attempt to use direct titration with silver nitrate solution. Phenosafranin gave a poor end-point, as it frequently does with bromides, and eosin could not be used because the halide production was not "frozen" adequately by acetic acid solutions. Conductimetric measurement [*cf.* R. W. D. Preston and H. O. Jones, *J. Chem. Soc.*, **101**, 1930 (1912); R. P. Larsen and C. A. Kraus, *Proc. Nat. Acad. Sci.*, **40**, 70 (1954)] gave rate constants higher than were obtained titrimetrically, which increased with time. It is presumed that this was due to an increase in the relative contribution of the unimolecular solvolysis with lowered concentration of amine and halide. A disproportionately large effect of the hydrogen ion produced by the solvolysis on the conductivity of the solution would be expected.

(11) One of these, run in the presence of an equivalent of potassium nitrate to test for interference due to salt effect of the quaternary salt formed by the reaction under study, gave $k = 0.891 \times 10^{-2}$, in excellent agreement with the others.

(12) Three volumes of acetone to one of water; therefore, 70.3% by wt. of acetone.

(13) Neither propargyl bromide, 1-bromo-2-heptyne nor methyl iodide gave appreciable amounts of halide after 200 minutes in "50% acetone" containing an equimolar amount of disodium phosphate [pK_a for the conjugate acid, $H_2PO_4^-$ = 7.12; pK_a for the conjugate acid of 1-carbethoxy-4-methylpiperazine = 7.31—*cf.* M. Harfenist, This Journal, **76**, 4991 (1954)]. Only 7% of the amount of bromide produced by the Sn2 reaction in that time (70% completion) was produced in 200 minutes under those conditions by allyl bromide.

(14) L. Pauling, W. Gordy and J. H. Saylor, This Journal, **64**, 1753 (1942). However, see L. F. Hatch and D. J. Mangold, *ibid.*, **77**, 176 (1955), and reference 2.

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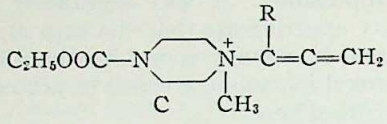
to detect any allene C which might have been produced by attack of the nucleophilic amine at the positive carbon of resonance form "B." The quaternary salt from propargyl bromide gave the



theoretical titer of acetylenic hydrogen by silver ion titration, and so appears free of detectable allene C, R = H. The hept-2-ynyl quaternary salt which might contain C, R = C_4H_9, showed no infrared absorption in the 5 μ region characteristic of allenic absorption (0.1 mm. thickness, 5% in $CHCl_3$). Surprisingly, for a compound with a "buried" acetylenic group,[15] this latter quaternary salt showed moderately intense acetylenic absorption at 4.41 μ.

It is, of course, possible to reconcile non-detection of allenes with existence of the allenic resonance form B. It would seem wiser, however, to tentatively explain the high SN2 reactivity of propargylic halides as due to the great polarizability of the triple bond,[16] and the increase in rate when R = alkyl by an increase in electron availability leading to a further increase in polarizability. This of course does not explain the electron-withdrawing properties of the propargyl group which are shown, for example, by the low basicity of propargylamines,[17] and the high acidity of α,β-acetylenic acids.[18]

The rate of quaternization with methyl iodide as compared with allyl bromide reported here seems reasonable. The most nearly comparable experiments[18] are the quaternizations of dimethylaniline by allyl *iodide* (k = 1.08) and methyl iodide (k = 0.143) in ethanol solution. If it is assumed that the rate of reaction of allyl bromide is slower than that of the iodide by a factor of about 6–7,[19] these constants would be in reasonable agreement with the ratio of rates reported here. Although the ratio of the results of Preston and Jones for triisoamylamine and the same halides differs from what would be expected from the work reported here, their methyl iodide results with this amine are also out of line with the rest of their own data.[20]

Acknowledgment.—The author acknowledges helpful discussions with Dr. R. Baltzly. The infrared absorption curve was run by Mr. J. E. Murphy of The Analytical Research Laboratory, Burroughs Wellcome & Co.

(15) J. H. Wotiz and F. A. Miller, THIS JOURNAL, **71**, 3441 (1949).
(16) *Cf.* J. K. Kochi and G. S. Hammond, *ibid.*, **75**, 3452 (1953).
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(20) N. Menschutkin, *Z. physik. Chem.*, **5**, 589 (1890).

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE TOKYO INSTITUTE OF TECHNOLOGY]

On the Thermal Dissociation of Organic Compounds. XIII. The Effect of Ring Size on the Rate of the Thermal Dissociation of Cyclopolymethyleneureas

BY SHOICHIRO OZAKI, TERUAKI MUKAIYAMA[1] AND KEIKICHI UNO

RECEIVED DECEMBER 7, 1956

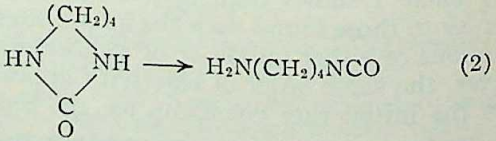
On heating, cyclic ureas dissociate into ω-aminoalkyl isocyanates with opening of the ring. The rate constants of the thermal dissociation of eight cyclic ureas in fatty acid were determined. The rates increase in the order 5-, 6- < 15- < 17- < 13- < 11- < 7- < 8-membered ring ureas. The relation between ring size and reactivity in this dissociation is discussed.

Introduction

It already has been shown that, on heating, ureas dissociate into isocyanates and amines.

$$RHN{-}CO{-}NHR \rightleftharpoons R{-}NCO + H_2N{-}R \quad (1)$$

The kinetics of the thermal dissociation of urea and some substituted ureas in fatty acids[2-6] have been studied. Similarly, in the case of cyclotetramethyleneurea, for example, the mechanism shown by equations 2–4 is considered.



$$H_2N(CH_2)_4NCO + 2ClCH_2COOH \longrightarrow ClCH_2CONH(CH_2)_4NHCOOCOCH_2Cl \quad (3)$$

$$ClCH_2CONH(CH_2)_4NHCOOCOCH_2Cl \longrightarrow ClCH_2CONH(CH_2)_4NHCOCH_2Cl + CO_2 \quad (4)$$

The reaction in chloroacetic acid can be followed by measuring the rate of evolution of carbon dioxide[5] (eq. 4), as reaction 2 is rate-determining.

In the present work, the kinetics of the thermal dissociation of eight cyclopolymethyleneureas in chloroacetic acid were studied, and the relation between ring size and the reactivity of the cyclic ureas was obtained.

Ring ureas were synthesized from polymethylene diisocyanate and water *via* equations 6 and 7.

(1) Department of Physics and Chemistry, Gakushuin University, Mejiro, Tokyo.
(2) T. Hoshino, T. Mukaiyama and H. Hoshino, THIS JOURNAL, **74**, 3097 (1952).
(3) T. Hoshino, T. Mukaiyama and H. Hoshino, *Bull. Chem. Soc. Japan*, **25**, 392 (1952).
(4) T. Mukaiyama and T. Matsunaga, THIS JOURNAL, **75**, 6209 (1953).
(5) T. Mukaiyama, S. Ozaki and T. Hoshino, *Bull. Chem. Soc. Japan*, **27**, 578 (1954).
(6) T. Mukaiyama, S. Ozaki and Y. Kobayashi, *ibid.*, **29**, 51 (1956).

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$$OCN(CH_2)_{n-3}NCO + H_2O \longrightarrow H_2N(CH_2)_{n-3}NCO + CO_2 \quad (6)$$

$$H_2N(CH_2)_{n-3}NCO \longrightarrow \text{cyclic urea} \quad (7)$$

Experimental

Procedure.—The procedures for measuring the rates of dissociation of ureas in fatty acid[2,3,5] have been described previously. On plotting the logarithm of volume of carbon dioxide, ΔY, evolved at regular intervals of time, a straight line was obtained. This indicates a first-order reaction rate. The rate constant is given by the gradient of such a plot.[7]

Preparation of Materials.—Cylic ureas were synthesized[8] from the corresponding diisocyanates and water by methods a and b.

(a) **Without Using a High Dilution Technique. Cyclotetramethyleneurea (I).**—To a solution of 120 ml. of acetone and 120 ml. of water was added dropwise the mixture of 5.4 g. of tetramethylene diisocyanate and 40 ml. of acetone in a period of 3 hr. under refluxing. After another 30 minutes the reaction mixture was cooled and polytetramethyleneurea precipitated was filtered off. The filtrate was evaporated to about 20 ml., then the precipitate which deposited was separated. Recrystallization from acetone yielded 2.8 g. (64%) of I, as colorless crystals, melting at 172–173°.

(b) **Using a High Dilution Technique. Cycloöctamethyleneurea (II).**—To a solution of 900 ml. of acetone and 900 ml. of water was added, in the rate of a drop in 10 seconds, the mixture of 3.2 g. of octamethylene diisocyanate and 70 ml. of acetone in a period of 17 hr. using a Hunsdiecker apparatus.[9] After another 30 minutes, the solution was evaporated to about 900 ml., the poly-octamethyleneurea precipitated was filtered off and again evaporated to about 10 ml. and the precipitate was collected. Recrystallization from acetone yielded 0.5 g. (18.1%) of II as colorless crystals melting at 159–160°. The melting point, synthetic method, yield of cyclic ureas and boiling point for the corresponding diisocyanate are listed in Table I.

TABLE I

Methylene-ureas	Ring number	M.p., °C.	Synthetic method	Yield, (%)	B.p. °C. (corresponding diisocyanate)	Mm.
Cyclo-di-	5	129	a	35	85–86	76
Cyclo-tri-	6	258	b	60	98	26
Cyclo-tetra-	7	172–173	a	64	93	7
Cyclo-penta-	8	238	b	22	128–130	19
Cyclo-hexa-	9		b	0	139	18
Cyclo-hepta-	10		b	0	103–104	6
Cyclo-octa-	11	159	b	18	150	10
Cyclo-deca-	13	190–191	b	49	132	0.45
Cyclo-dodeca-	15	201–202	b	41	168–169	3
Cyclo-tetradeca-	17	195–196	b	36	171	0.45

Solvent.—Chloroacetic acid was distilled thrice, b.p. 185–186°.

Identification of Reaction Product.—N,N′-Diphenylacetyltetramethylenediamine was produced by heating cyclotetramethyleneurea in phenylacetic acid for 6 hr. at 170°. It was obtained as an ether-insoluble product, m.p. 176–177°, recrystallized from acetone.

Anal. Calcd. for $C_{20}H_{24}O_2N_2$: C, 74.44; H, 7.43; N, 8.63. Found: C, 74.01; H, 7.44; N, 8.44.

The rate constants of the thermal dissociation of cyclic ureas were determined under the following condition: the ratio of ureas to solvents was 1 mole:100 moles. The kinetic results are summarized in Table II and Fig. 1.

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(8) More details about the synthesis of these ureas have been submitted to the *J. Chem. Soc. Japan*, Pure Chemistry Section by Y. Iwakura and K. Uno.

(9) H. Hunsdiecker and H. Erlbach, *Chem. Ber.*, **80**, 137 (1947).

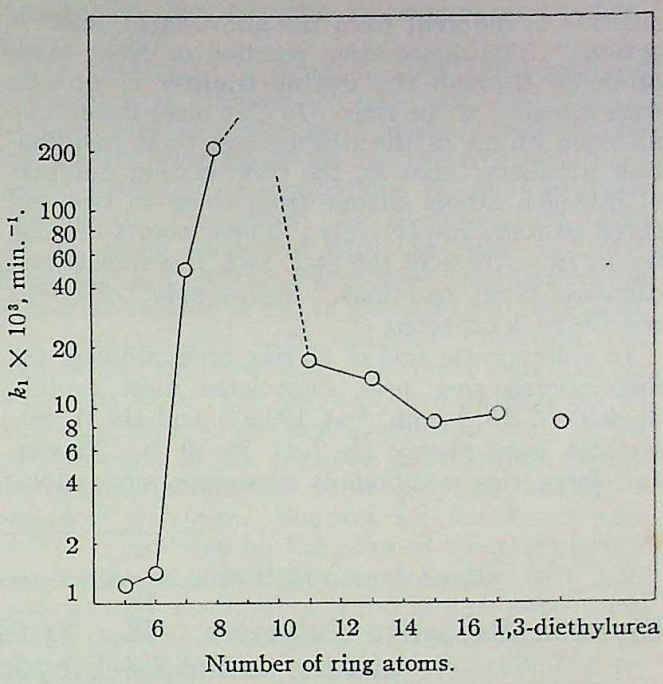

Fig. 1.—Relation between ring size and reactivity on the thermal dissociation of cyclopolymethyleneurea in chloroacetic acid: the plot of k_1 (at 139.5°) against ring number.

TABLE II

SUMMARY OF THE RATE DATA FOR THE THERMAL DISSOCIATION OF CYCLOPOLYMETHYLENEUREA IN CHLOROACETIC ACID AT 139.5°

Ring number	Rate constant $k_1 \times 10^3$, min.$^{-1}$	Relative rate
5	1.21	1
6	1.47	1.2
7	50.3	41.5
8	210	174
11	17	14
13	14.1	12
15	8.36	6.9
17	9.55	7.9
1,3-Diethylurea	8.51	7.0

Result and Discussion

It is commonly known that the reactivity of cyclic compounds depends on their ring sizes. On this matter, many[10] available kinetic results have been reported for common ring and several[11–14] for medium and large ring compounds. The SN1, SN2 and free radical type reactions proceed rapidly in 5- and 7-membered ring compounds and slowly in 6-membered compounds. 5- and 7-membered ring compounds react slower than 6- in the carbonyl-type reaction. In all reaction types mentioned above, the large ring compounds have medium reactivity between these two extremes and have almost the same reactivity as that of open chain compounds.

In the dissociation of ureas, the reaction mech-

(10) For instance (a) H. C. Brown, J. H. Brewster and H. Shechter, THIS JOURNAL, **76**, 467 (1954); (b) H. C. Brown, R. S. Fletcher and R. B. Johanesen, *ibid.*, **73**, 212 (1951).

(11) V. Prelog and M. Kobelt, *Helv. Chim. Acta*, **32**, 1187 (1949).

(12) H. C. Brown and M. Borkowski, THIS JOURNAL, **74**, 1894 (1952).

(13) K. Ziegler and H. Froitzheim-Kuehlhorn, *Ann.*, **589**, 159 (1954).

(14) C. G. Overberger, H. Biletch, A. B. Finestone, J. Lilker and J. [illegible] 2078 (1953).

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anism[5,6] is different from the above-mentioned reactions. The dissociation reaction of cyclic ureas proceeds through the double transfer of protons with opening of the ring. In this mechanism, two nitrogen atoms in the ring change their coördination numbers; that is, the coördination numbers of nitrogen atoms change from three to two and three to four, respectively. These points are different from those of the SN1, SN2, free radical and carbonyl-type reactions. Accordingly, different reactivity is expected.

In chloroacetic acid of all ring ureas studied, the 8-membered ring urea dissociates most rapidly (k_1 210 × 10^{-3} min.$^{-1}$ at 139.5°) and the 5- dissociates most slowly (k_1 1.21 × 10^{-3}). Eleven- and large ring compounds dissociate moderately. Comparing the results with those of other ring compounds reported, they generally resemble the reactivity of SN1, SN2 and radical-type reactions.[14] Accordingly, the reactivity of ring ureas is in inverse relation with that of carbonyl-type reactions.[11] A characteristic result obtained in the present experiment is that 5- and 6- ring ureas have similar reactivity, which has not been observed in other reaction types.

Acknowledgments.—The authors wish to express their hearty thanks to Prof. T. Hoshino for his helpful advice and encouragement throughout the course of this work and to Dr. H. C. Brown for his helpful discussion and to Mr. K. Teranishi for his help in the synthesis of ring ureas.

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[CONTRIBUTION NO. 1383 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Electron Exchange Polymers. IX. Synthesis of Polymers of 2,5-Dihydroxyphenylalanine and of 3,4-Dihydroxyphenylalanine (DOPA)[1]

BY H. JAMES HARWOOD[2] AND HAROLD G. CASSIDY

RECEIVED JANUARY 23, 1957

Methods are given for the preparation by the N-carboxyl anhydride technique of high molecular weight polypeptides of 2,5-dihydroxyphenylalanine and 3,4-dihydroxyphenylalanine and of copolymers of each with L-glutamic acid. The methods include those for the preparation of the appropriate monomers in which the phenolic hydroxyls of the dihydroxyphenylalanines are protected by acetyl groups. These syntheses now make available new electron exchange polymers that are also polypeptides.

In the first paper of this series,[3] the possible usefulness of electron exchange polymers of suitable composition and structure as models for certain biological systems was suggested. It seemed desirable to investigate this possibility. The postulate on which this work was based is that a reactive group when incorporated in a polymeric structure will show one or more properties different in kind or different in quantity from those of the "same" group in the molecularly dispersed monomeric state. A number of investigations have been carried out effectively from this point of view. For example, the investigations of Haskell and Hammett[4] and the further investigations of Hammett and co-workers[5] fall in this category. These investigators compared the catalytic behavior of hydrochloric acid and the acid forms of cation exchangers toward the hydrolysis of esters. They found differences in rate and specificity effects. As another example from a growing literature, Morawetz and Zimmering[6] found that solvolysis of the ester group in acrylic acid–*p*-nitrophenyl methacrylate copolymers seemed to proceed by a mechanism different from that of the solvolysis of the ester group in the monomeric model *p*-nitrophenyl trimethylacetate. As a third example, Lautsch and his co-workers[7] have carried out extensive investigations of the changes in spectra, in catalytic properties and in oxidation–reduction potential that occur when a porphyrin group is incorporated into a large molecule. We have set out to examine the properties of hydroquinone and catechol groups when present as side-chains to a polypeptide structure, thus supplementing our earlier work.[8]

This paper reports the first steps in this investigation: the synthesis of polymers of 2,5-dihydroxyphenylalanine and 3,4-dihydroxyphenylalanine and copolymers of these two amino acids with L-glutamic acid by the N-carboxyl anhydride technique. Our synthesis is patterned after the polytyrosine synthesis reported by Schlögl, Wessely and Wawersich[9] and the polyserine synthesis reported by Frankel, Cordova and Breuer.[10]

2,5-Dihydroxyphenylalanine, (I), was treated

(1) Abstracted from the Dissertation submitted by H. James Harwood to the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Union Carbide and Carbon Corp. Fellow in Organic Chemistry, 1954–1955; Procter and Gamble Co., Summer Fellow, 1955. This work was supported for several months by a research grant G 3207 (C2) from the National Institutes of Health, Public Health Service, and by a grant from the Research Corporation.

(3) H. G. Cassidy, THIS JOURNAL, **71**, 402 (1949).

(4) V. C. Haskell and L. P. Hammett, *ibid.*, **71**, 1284 (1949).

(5) S. A. Bernhard and L. P. Hammett, *ibid.*, **75**, 1798, 5834 (1953); S. A. Bernhard, E. Garfield and L. P. Hammett, *ibid.*, **76**, 991 (1954); P. Riesz and L. P. Hammett, *ibid.*, **76**, 992 (1954).

(6) H. Morawetz and P. E. Zimmering, *J. Phys. Chem.*, **58**, 753 (1954).

(7) For bibliography see W. Lautsch, W. Broser, W. Biedermann and H. Gnichtel, *J. Polymer Sci.*, **17**, 479 (1955). W. Lautsch, W. Broser, E. Höfling, H. Gnichtel, E. Schröder, R. Kruger, J. Woldt, G. Schulz, R. Wiechert, W. Bandel, G. Kurth, H.-J. Kraege, W. Gehrmann, K. Prater, G. Parsiegla, R. Pasedag and W. Hunger, *Kolloid Z.*, **144**, 82 (1955).

(8) For references, see L. Luttinger and H. G. Cassidy, *J. Polymer Sci.*, **20**, 417 (1956); **22**, 271 (1956); and M. Ezrin and H. G. Cassidy, THIS JOURNAL, **78**, 2525 (1956).

(9) K. Schlögl, F. Wessely and E. Wawersich, *Monatsh.*, **84**, 705 (1953).

(10) M. Frankel, S. Cordova and M. Breuer, *J. Chem. Soc.*, 1991 (1953); M. Frankel, M. Breuer and S. Cordova, *Experientia*, **8**, 299

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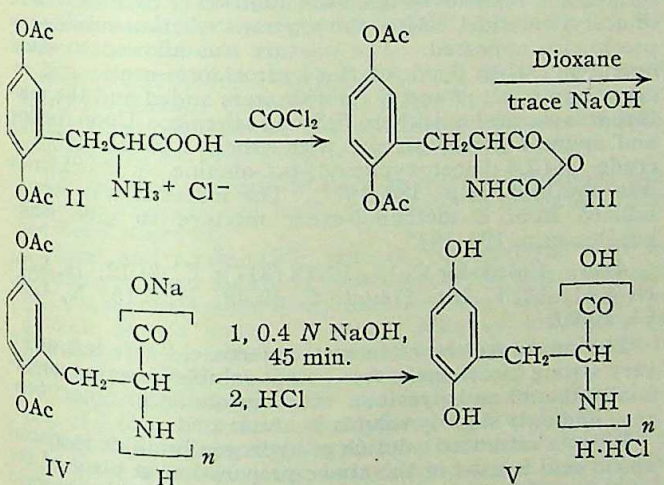
with acetyl chloride in the presence of glacial acetic acid saturated with hydrogen chloride, according to the procedure described by Bretschneider and Biemann[11] for the synthesis of O-acetyltyrosine hydrochloride, to form 2,5-diacetoxyphenylalanine hydrochloride (II). II was suspended in dioxane and treated with phosgene to form the desired monomer, 4-(2,5-diacetoxybenzyl)-2,5-oxazolidine dione (III). Polymerizations to IV were carried out in dioxane solution by initiation with 0.005 mole of sodium hydroxide in methanol per mole of monomer. Acetyl groups were cleaved by alkaline treatment in an inert atmosphere to give V. This method appears to be superior to that employing Overell and Petrow's hydrobromic–acetic acid reagent[12]; see Experimental.

Poly-DOPA was prepared through a synthetic sequence similar to I to V, except that it was more convenient to isolate the 3,4-diacetoxyphenylalanine as the hydrobromide than as the hydrochloride. The latter was characterized, but the former was used in the synthesis.

Copolymers were prepared by copolymerizing the above-described monomers with the N-carboxyl anhydride of γ-benzyl glutamate. Protecting groups were removed stepwise from the copolymers by first cleaving the benzyl esters with a saturated solution of hydrobromic acid in acetic acid, then completing the removal of acetyl groups in a separate step by alkaline treatment.



Katchalski and Sela[13] reported a polytyrosine synthesis which has advantages in the step where protective groups are removed. We found that the tricarbobenzoxy derivatives, intermediates in this synthesis, were inconvenient to work with. The tricarbobenzoxy derivative of 2,5-dihydroxyphenylalanine (N-benzyloxycarbonyl-β-(2,5-dibenzyloxycarbonyloxyphenyl)-D,L-alanine) was prepared and purified. A tricarbobenzoxy derivative of 3,4-dihydroxyphenylalanine could not be prepared, though a tricarbomethoxy derivative, m.p. 127°, was prepared in a small-scale run and characterized on the basis of its infrared spectrum. Attempts to repeat this synthesis failed to yield crystalline material. Apparently similar difficulty of this kind was encountered by O'Neill, Veitch and Wagner-Jauregg[14] in their attempts to prepare simple peptides of DOPA.

The molecular weights of the unhydrolyzed polymers were checked by end-group titrations.[15] Number average molecular weights between 5,000 and 10,000 were observed by this method. Intrinsic viscosity determinations of unhydrolyzed copolymers, determined in dichloroacetic acid (DCA), when compared with the data of Doty, Bradbury and Holtzer,[16] indicated weight average molecular weights in the range of 34,000 to 45,000. The unexpectedly large difference between the number and weight average molecular weights suggests that either the polymer preparations are of wide molecular weight distributions or that partial saponification of the phenolic ester groups during the polymerization led to a polymer having a branched structure. Support for the latter possibility is provided by the color of the polymerization mixtures (see Experimental), the fact that more amino[17] than carboxyl end groups were found in the polymer, the difficulty of titrating the dihydroxyphenylalanine monomers with alkaline reagents[15] and the known ready hydrolysis of acetylated phenolic groups in similar types of compounds.[18]

The intrinsic viscosity values observed for the simple polymers appear to be in better agreement with the number average molecular weights estimated from end-group titration results, although an exact assignment of weight average molecular weight values to these polymers cannot be made at present.

The difference in polydispersity between the simple polymers and the copolymers might suggest that the latter are polyblends; mixtures of relatively low molecular weight (5–6,000) polydiacetoxyphenylalanine and high molecular weight poly-γ-L-benzyl glutamate (*ca.* 50,000). Against this supposition is the observation that the hydrolyzed copolymers are completely soluble at *p*H 7.3, while poly-3,4-dihydroxyphenylalanine is insoluble at this *p*H. The differences in phenolic ionization behavior observed for the simple polymers and the copolymers is of interest in this connection, and we hope to report on this subsequently.

Methods for preparing these substances are presented because of the increasing interest in the catalytic and reagent properties of quinones. They provide reagents which are readily removable from a reaction mixture by precipitation or dialysis and which, like other oxidation–reduction polymers based on quinones,[3] contribute to or remove from the reaction only electrons and protons. Investi-

(11) H. Bretschneider and K. Biemann, *Monatsh.*, **81**, 647 (1950).
(12) B. G. Overell and V. Petrow, *J. Chem. Soc.*, 232 (1955).
(13) E. Katchalski and M. Sela, THIS JOURNAL, **75**, 5381 (1953).
(14) J. J. O'Neill, F. P. Veitch and T. Wagner-Jauregg, Abstract of paper 151, presented before the Division of Organic Chemistry, 126th Meeting, A.C.S., New York, September, 1954.
(15) M. Sela and A. Berger, THIS JOURNAL, **77**, 1893 (1955); A. Berger, M. Sela and E. Katchalski, *Anal. Chem.*, **25**, 1554 (1953).
(16) P. Doty, J. H. Bradbury and A. M. Holtzer, THIS JOURNAL, **78**, 947 (1956). The comparison is believed to be justified since copolymer contained about 90% of γ-benzyl glutamate.
(17) These values have been corrected for the amount of NaOH initiator added to the polymerization mixtures. The –COONa end-group on the polymers formed as a result of the initiation step would be counted as amine end-groups if this correction were not made. We thank Mr. R. D. Lundberg for calling this to our attention.
(18) C. R. Harington and S. S. Randall, *Biochem. J.*, **25**, 1028 (1931).

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gation of the reagent and catalytic properties of these substances is being continued.

Experimental

N-Benzyloxycarbonyl-β-(2,5-dibenzyloxycarbonyloxyphenyl)-D,L-alanine.—An ice-cold solution of 4.01 g. of 2,5-dihydroxyphenylalanine[19] in 38 ml. of 0.74 *N* sodium hydroxide was treated slowly under nitrogen, with rapid stirring, with 12.2 g. of 93.5% benzyl chloroformate and 15.0 ml. of cold 4 *N* sodium hydroxide added simultaneously. The mixture became turbid and a heavy oily substance deposited upon the sides of the flask. Ether, 10 ml., was then added to help disperse the mixture. Stirring was continued for 2.5 hr., and the reaction mixture was diluted with ether. Three fractions were obtained: aqueous and ether phases, and the insoluble sodium salt of the tricarbobenzoxy derivative. The aqueous and sodium salt layers were acidified with 4 *N* HCl to congo red. The ether layer was extracted further with 5% sodium bicarbonate solution. The aqueous and sodium salt layers were again separated from the ether and acidified with 4 *N* hydrochloric acid. The aqueous and sodium salt layers could be made miscible if the mixture was diluted with distilled water. After several days in the refrigerator, the oily product solidified as a light brown mass. The material was filtered and washed with distilled water. The yield was 9.6 g. (78%).

The material is very difficult to purify. Repeated recrystallization from a dilute solution in 30% acetic acid led to 2.0 g. of small, white needles, m.p. 126.7–127.8°.

Anal. Calcd. for $C_{33}H_{23}O_{10}N$ (600): C, 66.09; H, 4.86; N, 2.34; neut. equiv., 600. Found: C, 65.95; H, 4.98; N, 2.30; neut. equiv., 600.6, 596.1.

Crystalline material may be obtained if the gummy mass which is often obtained from either the reaction mixture or the purification process is partially dissolved in ether. Some crystalline material is usually left undissolved. The ether solution on standing usually begins to deposit crystalline material after several days. The crystals thus obtained are cubic, and the substance melts at 169–170°. The cubic crystals are not appreciably soluble in chloroform whereas those in the needle form, melting at 127–8°, are readily soluble. Both types of crystals show almost identical infrared spectra in Nujol mulls. The soluble form, in chloroform solution, showed ester absorption at 5.68 μ and carboxyl absorption at 5.82 μ.

Regeneration of 2,5-Dihydroxyphenylalanine.—Purified tricarbobenzoxy derivative, 72.9 mg., was dissolved in 2 ml. of glacial acetic acid, and 3.7 ml. of a 50% solution (by weight) of hydrogen bromide in glacial acetic acid was added. After an hour, the solution was swamped with ether and the crystalline 2,5-dihydroxyphenylalanine hydrobromide was isolated. The yield was 30.7 mg. (91%), m.p. 272–273° dec. The infrared spectrum in Nujol was identical with that of an authentic sample of 2,5-dihydroxyphenylalanine hydrobromide prepared directly from the pure amino acid and the hydrobromic–acetic acid reagent, m.p. 274.5–275° dec.

β-(2,5-Diacetoxyphenyl)-D,L-alanine Hydrochloride.—Five grams of β-(2,5-dihydroxyphenyl)-D,L-alanine was added to 30 ml. of glacial acetic acid, previously saturated with dry hydrogen chloride. The amino acid dissolved and after a short time its salt settled out. Acetyl chloride, 25 ml., was added either to the solution or the suspension, and the mixture was allowed to stand overnight at room temperature, whereupon 30 ml. of the hydrochloric–acetic acid reagent and 30 ml. of acetyl chloride were added and the reaction mixture heated quickly to 75° with stirring. The mixture was allowed to cool and was then swamped with anhydrous ether. The crude β-(2,5-diacetoxyphenyl)-D,L-alanine hydrochloride after several hours quickly solidified, and was collected, washed with ether and allowed to dry in air. The yield was 5.3 g. (66%), m.p. 158–159°.

For analysis the sample was recrystallized from a methanol–ether mixture, giving colorless needles, m.p. 154–155° (after drying in the Abderhalden apparatus, m.p. 160–161°).

Anal. Calcd. for $C_{12}H_{16}O_6NCl$ (317.7): C, 49.12; H, 5.09; N, 4.41; Cl, 11.16. Found: C, 48.68; H, 5.74; N, 4.75; Cl, 10.81.

(19) H. B. Gillespie, *Biochem. Prep.*, **3**, 79 (1953).

The compound in a Nujol mull showed ester absorption in the infrared region at 5.65 μ and carboxyl absorption at 5.72 μ.

The compound is soluble in water, pyridine, methanol and is insoluble in chloroform, benzene and ether. It gives negative tests with ferric chloride, Millon reagent and iodine in potassium iodide.

4-(2,5-Diacetoxybenzyl)-2,5-oxazolidine Dione.—Phosgene was slowly bubbled into a rapidly stirred suspension of 4.8 g. of β-(2,5-diacetoxyphenyl)-D,L-alanine hydrochloride in 50 ml. of dry purified dioxane, maintained between 40 and 60°. After about 2 or 3 hr. all of the salt had dissolved and the flask was flushed with dry nitrogen for 0.5 hr. to remove unreacted phosgene. The dioxane was then removed by distillation *in vacuo* leaving a colorless sirup, which was dissolved in 50 ml. of ethyl acetate, and the ethyl acetate was removed by distillation *in vacuo*. This process was repeated and the sirupy residue was taken up in a small amount of ethyl acetate. The crude anhydride was precipitated from solution by the addition of a large excess of ligroin. The oily residue which deposited usually solidified upon standing for several hours; yield was 3.4 g. (73.5%).

Several recrystallizations from ethyl acetate–petroleum ether mixtures yielded 2.8 g. of nearly colorless needles, m.p. 132.3–134.0°. The material showed a negative ferric chloride test. It is soluble in chloroform, ethyl acetate, dioxane and methanol and is insoluble in petroleum ether. The compound showed ester absorption in the infrared region: at 5.65 μ and anhydride absorption at 5.35 and 5.57 μ.

Anal. Calcd. for $C_{14}H_{13}O_7N$ (307): C, 54.73; H, 4.26; N, 4.55; acetyl, 28.01. Found: C, 54.94; H, 4.49; N, 4.53; acetyl, 28.23, 28.62.

β-(3,4-Diacetoxyphenyl)-D,L-alanine Hydrochloride.—One gram of 3,4-dihydroxyphenylalanine (Eastman No. 4915) was dissolved in 6 ml. of glacial acetic acid saturated with hydrogen chloride; 5 ml of acetyl chloride was then added carefully with swirling. A gummy precipitate formed and redissolved upon the addition of each increment of acetyl chloride. After the vigorous reaction subsided, a precipitate appeared. The mixture was allowed to stand overnight, when 6 ml. of the hydrochloric–acetic acid reagent and 5 ml. of acetyl chloride were added and the mixture was warmed quickly to 70° with stirring. Upon cooling and swamping the mixture with ether, 1.06 g. (66%) of crude β-(3,4-diacetoxyphenyl)-D,L-alanine hydrochloride was obtained, m.p. 186–187°. The material was recrystallized from a methanol–ether mixture to give white needles, m.p. 193–194°.

Anal. Calcd. for $C_{13}H_{16}O_6NCl$ (317): C, 49.12; H, 5.09; N, 4.41; Cl, 11.16. Found: C, 49.48; H, 5.15; N, 4.36; Cl, 10.90.

The substance shows a negative ferric chloride test and a very strong bicarbonate test. It is soluble in water, methanol, ethanol and pyridine. It is insoluble in ether, benzene and only slightly soluble in acetic acid.

When a saturated solution of hydrogen bromide in glacial acetic acid is used in the above preparation in place of the hydrogen chloride–acetic acid reagent, a quantitative yield of the corresponding hydrobromide is obtained. The hydrobromide was used in further synthetic work but was not characterized since it was probably contaminated with the corresponding hydrochloride.

Both materials showed similar infrared spectra in Nujol mulls. Peaks occurring at 5.65 μ (phenolic ester) and 5.76 μ (carboxyl) were observed.

4-(3,4-Diacetoxybenzyl)-oxazolidine-2,5-dione.—Finely ground β-(3,4-diacetoxyphenyl)-D,L-alanine hydrobromide, 4.5 g., was mixed with 100 ml. of purified dioxane, and phosgene was bubbled slowly into the rapidly stirred suspension kept at 50–70° until all of the amino acid salt went into solution. This required 3 to 4 hr. The red solution was heated for 0.5 hr. longer and was then flushed with dry nitrogen for 1 hr. to displace unreacted phosgene. The solution was then concentrated to a viscous sirup under nitrogen *in vacuo* (40–60°). The sirup was taken up in ethyl acetate and precipitated by adding petroleum ether slowly. Scratching and allowing the mixture to stand for several hours usually led to the solidification of the crude anhydride. In some cases it was necessary to repeat the above process before solid material was obtained.

Several recrystallizations from ethyl acetate–petroleum ether mixtures at room temperature led to 2.90 g. (75%) of

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pure 4-(3,4-diacetoxybenzyl)-oxazolidine-2,5-dione as granular colorless crystals, m.p. 116–117° (swelling in sealed tube).

Anal. Calcd. for $C_{14}H_{13}NO_7$ (307.3): C, 55.06; H, 4.45; N, 4.52; acetyl, 28.01. Found: C, 54.73; H, 4.26; N, 4.55; acetyl, 28.13.

When 50.1 mg. of the material was heated slowly to 135° at 0.1 mm., it lost 7.3 mg. of CO_2. The calculated value for the weight loss during thermal polymerization was 7.2 mg. The material is soluble in ethyl acetate, hot benzene, ether, chloroform and dioxane. It is insoluble in petroleum ether and water. The compound shows infrared absorption in the carbonyl region at 5.31 and 5.55 mμ. Apparently ester and anhydride bands overlap at 5.55 μ for this compound.

When β-(3,4-diacetoxyphenyl)-D,L-alanine hydrochloride is used as the starting material in this preparation, identical material is obtained in 72% yield.

Poly-β-(2,5-diacetoxyphenyl)-D,L-alanine.—A solution of 2.75 g. of 4-(2,5-diacetoxybenzyl)-oxazolidine-2,5-dione in 35 ml. of purified dioxane was mixed with a solution of 0.45 ml. of 0.14 *N* sodium hydroxide in absolute methanol dissolved in 35 ml. of purified dioxane.

The mixture, on standing for one week, became light yellow in color. It was concentrated to one third its volume under reduced pressure at 40–50°. The polymer was then precipitated from solution by the addition of petroleum ether. The yellow sticky polymer was then taken up in ethyl acetate and reprecipitated by the addition of petroleum ether. The polymer was now cream in color and was no longer sticky. It was dissolved in a mixture of 125 ml. of redistilled benzene and 40 ml. of dioxane. The solution was filtered and freeze dried, yielding 2.23 g. (91%) of poly-2,5-diacetoxyphenylalanine.

The polymer thus obtained was fluffy and very friable but became very hard and dense during storage. Material which was convenient to work with was obtained by dissolving the polymer in glacial acetic acid and freeze-drying this solution. The light yellow powder thus obtained was dried *in vacuo* over sodium hydroxide to remove the last traces of acetic acid.

Anal. Calcd. for $(C_{13}H_{13}O_5N)_n$: C, 59.31; H, 4.98; N, 5.32. Found: C, 58.97; H, 5.18; N, 5.07; amino end-group titrations showed the polymer to have a number average mol. wt. of 11,000; [η] in DCA at 25°, 0.08.

The polymer appears to be somewhat hygroscopic, particularly when the last traces of dioxane or acetic acid have not been removed.

Biuret and picric acid[20] tests on this material were inconclusive due to the ready hydrolysis of the acetoxy groups and the accompanying discoloration of the liberated hydroquinone groups under the strong alkaline conditions required for these tests. The ninhydrin test, in contrast to most polypeptides, appeared to be negative.

The polymer showed ester absorption in the infrared region at 5.68 μ, and amide absorption at 6.00 and 6.46 μ.

Poly-β-(3,4-diacetoxyphenyl)-D,L-alanine.—A solution of 3.80 g. of 4-(3,4-diacetoxybenzyl)-oxazolidine-2,5-dione in 75 ml. of purified dioxane was mixed with a solution of 0.35 ml. of 0.186 *N* sodium hydroxide in anhydrous methanol dissolved in 50 ml. of dioxane. The mixture became light yellow overnight and was allowed to stand four days.

The polymerization solution was then filtered and concentrated to one-third its volume under nitrogen *in vacuo* (40–60°). The crude caramel-colored sticky polymer was obtained by precipitating it from solution by the addition of petroleum ether. A small amount of starting material (10–20 mg.) was isolated from the supernatant which was decanted from this precipitated polymer. This indicates that a somewhat longer polymerization time would perhaps have been advisable.

The crude polymer dissolved in ethyl acetate was treated with Norite and filtered. The polymer was then reprecipitated by adding petroleum ether. The light, cream-colored powder that separated from solution was then partially dissolved in fresh ethyl acetate, and enough petroleum ether was added to make the resulting solution contain 15% petroleum ether. The polymer was now dissolved in purified glacial acetic acid and freeze dried. The yield of poly-β-(3,4-diacetoxyphenyl)-D,L-alanine was 2.30 g. (67.4%). The polymer was obtained as a faintly yellow powder which did not appear to be hygroscopic, in contrast to the behavior of its 2,5-isomer.

The material showed a negative picric acid test. Heating the polymer with a ninhydrin solution caused the polymer to become blue in color, leaving a colorless solution. The biuret test was inconclusive, the catechol groups liberated in the alkaline solution apparently reduced the cupric reagent. The polymer showed ester absorption in the infrared region at 3.65 μ and monosubstituted amide absorption at 5.99 and 6.48 μ.

Anal. Calcd. for $(C_{13}H_{13}O_5N)_n$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.22; H, 5.17; N, 5.44; end amino titration showed the polymer to have a mol. wt. of 7000; [η] in DCA, 0.10

Poly-[90% γ-benzyl L-glutamate; 10%-β-(2,5-diacetoxyphenyl)-D,L-alanine].—A solution of 3.29 g. of benzyl L-4-β-(2,5-diketoöxazolidinyl)-propionate[21] (γ-benzyl N-carboxyl-L-glutamate anhydride) and 0.429 g. of 4-(2,5-diacetoxybenzyl)-oxazolidine 2,5-dione in 50 ml. of purified dioxane was diluted with 75 ml. of dioxane to which 0.69 ml. of 0.1 *N* sodium hydroxide in methanol had been added.

The polymerization mixture was allowed to stand for two weeks. Most of the dioxane was then removed by distillation under reduced pressure (40–60°) and the sirupy residue was treated with petroleum ether to precipitate the sticky, faintly green polymer. The material was then dissolved in ethyl acetate and partially reprecipitated by the addition of petroleum ether. The powdery precipitate was then dissolved in redistilled benzene to form a very viscous solution. This solution was treated with Norite, filtered and freeze-dried yielding 2.50 g. of the white spongy copolymer.

Anal. Calcd. for $[(C_{12}H_{13}O_3N)_9(C_{13}H_{13}O_5N)]_n$: C, 64.7; H, 5.80; N, 6.23. Found: C, 63.95; H, 5.86; N, 5.08; end carboxyl and amino group determinations gave number average mol. wts. of 7,500 and 5–6,000, respectively; [η] in DCA at 25°, 0.28 corresponding to a weight average mol. wt. of 34,000; $[\alpha]^{25}D$ +15.0 (*c* 5.62 mg./ml. in dioxane).

The material gave a negative picric test, appeared to give a negative ninhydrin test and showed a strongly positive biuret test only after being precipitated from dichloroacetic acid solution with water.

Poly-[90% γ-benzyl L-glutamate; 10% β-(3,4-diacetoxyphenyl)-D,L-alanine].—A solution of 4.50 g. of benzyl L-4-β-(2,5-diketoöxazolidinyl)-propionate[21] and 0.595 g. of 4-(3,4-diacetoxybenzyl)-oxazolidine 2,5-dione in 75 ml. of purified dioxane was mixed with a solution of 0.95 ml. of 0.1 *N* sodium hydroxide in anhydrous methanol dissolved in 100 ml. of purified dioxane. The solution became light pink immediately and became faintly blue in a few minutes. After several hours it developed a greenish cast. After three weeks the polymerization mixture was concentrated to one-half its volume under reduced pressure (50–60°). The crude polymer was precipitated as a very pale yellow sticky solid by the addition of petroleum ether.

The mixture was allowed to stand overnight and the supernatant liquid was decanted. The polymer was then taken up in ethyl acetate, treated with Norite and filtered. The polymer was then partially reprecipitated by the addition of petroleum ether. It was obtained as a colorless powder which when filtered was difficult to separate cleanly from filter paper. The polymer was then taken up in redistilled benzene and the resulting very viscous solution was filtered and freeze-dried.

The material was obtained as a white spongy mass which became easily charged when rubbed with glass. The yield was 2.8 g. (66%).

Anal. Calcd. for $[(C_{12}H_{13}O_3N)_9(C_{13}H_{13}O_5N)]_n$: C, 64.7; H, 5.79; N, 6.23. Found: C, 63.85; H, 5.76; N, 5.35; end carboxyl and amino group titrations showed the polymer to have number average mol. wts. of 8,900 and 5,500, respectively; [η] in DCA at 25°, 0.33 corresponding to a weight average mol. wt. of 45,000; $[\alpha]^{25}D$ +13.2 (*c* 7.04 mg./ml. in dioxane); $[\alpha]^{20}D$ +18.1 (*c* 32.0 mg./ml. in ethyl acetate).

The material showed a negative picric acid test. After being precipitated from dichloroacetic acid with water, the polymer gives a strongly positive biuret test. When the

(20) E. Abderhalden and E. Komm, *Z. physiol. Chem.*, **139**, 181 (1924).

(21) W. E. Hanby, S. G. Waley and J. Watson, *J. Chem. Soc.*, 3239 (1950).

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polymer is boiled with ninhydrin, the polymer becomes blue in color but the solution remains colorless. The polymer showed ester absorption in the infrared region at 5.78 μ and monosubstituted amide absorption at 6.06 and 6.47 μ.

Poly-β-(2,5-dihydroxyphenyl)-D,L-alanine.—Poly-β-(2,5-diacetoxyphenyl)-D,L-alanine, 285 mg., was mixed with 25 ml. of 0.4 *N* sodium hydroxide in a nitrogen atmosphere. After 0.5 hr. the polymer had completely dissolved. The solution was allowed to stand 45 minutes longer and was then acidified with 1 ml. of concd. hydrochloric acid. The resulting light yellow solution was deionized by passage through a 20-g. Amberlite 1R-100 column. The polymer was isolated by freeze-drying. To ensure complete removal of inorganic material, the freeze-dried product was dissolved in distilled water and the resulting solution was passed through a fresh Amberlite 1R-100 column. The polymer was again isolated by freeze-drying. The polymer was dried 12 hr. at 80° (0.1 mm.) over sodium hydroxide for analysis.[22] The polymer is very hygroscopic and must be stored in a desiccator.

Anal. Calcd. for $(C_9H_9O_3N)_n$: C, 60.33; H, 5.06; N, 7.82. Found: C, 53.87; H, 4.01; N, 5.27; acetyl, 11.13.[23]

Poly-β-(3,4-dihydroxyphenyl)-D,L-alanine (Poly-DOPA).—Five hundred mg. of poly-β-(3,4-diacetoxyphenyl)-D,L-alanine was covered with 35 ml. of 0.4 *N* sodium hydroxide. During this time the flask was flushed out with a stream of nitrogen to prevent oxygen from reacting with the liberated hydroquinone groups. The polymer was difficult to wet but went into solution in a period of 0.5 hr. The light brown solution was allowed to stand 45 minutes longer and was then filtered and acidified with concentrated hydrochloric acid. The precipitated polymer was centrifuged and washed five times with distilled water. The polymer was almost white in color at this stage. A small amount of sticky material was taken up in absolute ethanol and reprecipitated by the addition of water. The material thus obtained was fine and powdery. The polymer was then dried over sodium hydroxide at 0.1 mm. and 80° for 12 hr. The yield was 142 mg. (48%).

Anal.[22] Calcd. for $(C_9H_9O_3N)_{20}$: C, 60.33; H, 5.06; N, 7.82; NH_2, 0.45. Found: C, 59.22; H, 5.30; N, 5.80; NH_2, 0.56; acetyl, 1.65.

The material is not appreciably soluble in water in contrast to its 2,5-isomer and does not appear to be hygroscopic. The material showed a negative picric acid test and an inconclusive biuret test similar to its parent acetylated derivative. One of the reviewers kindly pointed out that comparison of the ratio of found N (5.80) to found NH_2 (0.56) with that calculated for the assumed degree of polymerization suggests that some degradation had occurred during deacetylation.

Poly-[90% L-glutamic acid; 10% β-(2,5-dihydroxyphenyl)-D,L-alanine].—Poly-[90% L-γ-benzyl glutamate; 10%-β-(2,5-diacetoxyphenyl)-D,L-alanine], 336 mg., was mixed with 10 ml. of a freshly saturated (50% by weight) solution of anhydrous hydrogen bromide in purified glacial acetic acid. The polymer swelled and went almost completely into solution during the first hour the mixture was allowed to stand. One hour later solid material had begun to separate from solution again. The mixture was allowed to stand overnight in a calcium chloride-dried atmosphere. The next day the mixture was swamped with ether and centrifuged. The precipitate was washed with ether and the mixture was centrifuged. This process was repeated six or more times until the ether washings showed a negative test for acid.

The swollen gelatinous polymer was then dried to a white amorphous powder and dried in the Abderhalden apparatus at 80° and 0.1 mm. over sodium hydroxide to remove the last traces of acetic acid, ether and hydrogen bromide. It is important that hydrogen bromide be completely removed before the polymer is exposed to the atmosphere, otherwise colored material will be produced. The yield was 189 mg. (94.6%).

Anal.[22] Calcd. for $[(C_5H_7O_3N)_9(C_9H_9O_3N)]_n$: C, 48.3; H, 5.4; N, 10.4. Found: C, 48.00; H, 5.33; N, 9.43; acetyl, 2.50.

The material gave a positive biuret test. Hydrolysis could be completed by allowing the polymer to stand for 1 hr. in 0.2 *N* sodium hydroxide, whereupon its acetyl content fell to 0.92%.

Poly-[90%-L-glutamic acid; 10%-β-(3,4-dihydroxyphenyl)-D,L-alanine].—One gram of poly-[90% γ-benzyl-L-glutamate; 10% β-(3,4-diacetoxyphenyl)-D,L-alanine] was suspended in 5 ml. of purified glacial acetic acid, and the suspension was warmed to 45°; 25 ml. of a freshly prepared, saturated (50% by weight) solution of anhydrous hydrogen bromide in purified glacial acetic acid was then added and the mixture was allowed to stand in a calcium chloride dried atmosphere. After the first hour nearly all had gone into solution and approximately 1 hr. later white material began to separate from solution. After 18 hr. the mixture was swamped with ether and centrifuged. The supernatant liquid was decanted, the polymer was washed with fresh ether and the mixture was again centrifuged. This process was repeated five or six times until the ether washings showed a negative test for acid.

The swollen gelatinous polymer was then dried in the Abderhalden apparatus over sodium hydroxide at 80° and 0.1 mm. to ensure removal of the last traces of acetic acid, hydrogen bromide and ether. The yield of white powdery material was 540 mg. (90%). The material is slightly hygroscopic and was stored in a desiccator.

Anal. Calcd. for $[(C_5H_7O_3N)_9(C_9H_9O_3N)]_n$: C, 48.3; H, 5.4; N, 10.4. Found: C, 47.99; H, 5.26; N, 8.88; acetyl 1.09; $[\alpha]^{25}D$ −68.5° (*c* 5.522 mg./ml. in *p*H 7.3 phosphate buffer); $[\alpha]^{29}D$ −60.4° (*c* 4.70 mg./ml. in *p*H 7.3 phosphate buffer).

The material showed a negative picric acid test, an apparent negative ninhydrin test and a very strong biuret test. The infrared spectrum of this polymer in a Nujol mull was difficult to interpret because the bands were very broad and diffuse. Carboxylic acid (5 80 μ) and monosubstituted amide (6.05) and 6.53 μ) bands were observed, however.

A sample of the product of the hydrobromic–acetic hydrolysis, 176 mg., was mixed under nitrogen with 10 ml. of 0.35 *N* sodium hydroxide, and the solution was allowed to stand 1 hr. at room temperature. The solution was then acidified with 4 *N* hydrochloric acid, and the precipitate that formed was centrifuged and washed with distilled water until the washings were neutral. The gelatinous precipitate was dried at 80° and 0.1 mm. over sodium hydroxide pellets for 16 hr.; yield 138 mg. The polymer treated in this way analyzed for 4.46% "acetyl."[22,23] Resuspended in distilled water and washed six to eight times with fresh portions of distilled water, and dried as above, the polymer analyzed for 0.0% acetyl.

It was difficult to remove acetyl completely from the acetylated polymers. The hydrobromic acid–acetic acid

TABLE I

SUMMARY OF ACETYL ANALYSES[23]

Hydrolysis conditions	Acetyl, % 2,5-Series	Acetyl, % 3,4-Series
Pure polymers		
a, 50% HBr–HOAc overnight at RT[a]	...	1.55
b, 0.2 *N* NaOH, 1 hr. under N_2 at RT	...	13.9
c, 0.4 *N* NaOH, 1 hr. under N_2 at RT	11.3	1.65
d, 0.2 *N* NaOH, 1 hr. under N_2 at RT followed by 0.4 *N* NaOH, 1 hr. under N_2	0.0	...
Copolymers (γ-benzyl glutamate)		
a, 50% HBr–HOAc overnight at RT	2.50	1.09
b, 50% HBr–HOAc overnight at RT followed by 0.2 *N* NaOH, 1 hr. under N_2 at RT	0.92	...
c, 50% HBr–HOAc overnight at RT followed by 0.4 *N* NaOH, 1 hr. under N_2 at RT	...	4.46
d, Above product rewashed with distilled water	...	0.0

[a] RT is room temperature.

(22) The hydrolyzed polymers, in general, were difficult to purify and gave poor analytical results, it being difficult to remove inorganic material and to dry them.

(23) Experimental "acetyl" values tend to be high due to some hydrochloric acid (bound by end amino groups) in the distillate.

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reagent of Overell and Petrow[12] was fairly effective. There was some indication that more vigorous conditions were required for the 2,5-series than the 3,4-series. The polymers prepared by this method of deacetylation analyzed poorly for carbon, hydrogen and nitrogen. A summary of results is given in Table I.

Acknowledgments.—We are indebted to Drs. Alfred M. Holtzer and E. Peter Geiduschek for furnishing the apparatus and solvents used in the viscosity studies and for helpful suggestions.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

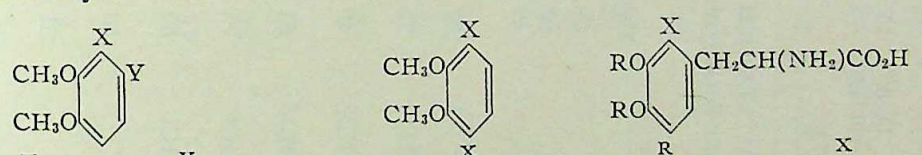
2-Substituted Derivatives of 3,4-Dihydroxyphenylalanine

BY CARL KAISER[1] AND ALFRED BURGER

RECEIVED MARCH 6, 1957

Because 2-methyl- and 2-chloro-3,4-dihydroxyphenylalanine inhibited the multiplication of influenza virus in the allantoic fluid of the chick embryo, the following additional 2-substituted derivatives of DOPA and their dimethyl ethers have been synthesized for biological screening: 2-bromo-, 2-fluoro-, 2-ethyl- and 2-nitro-DOPA. In addition, the synthesis of β-(2-methyl-3,4-dihydroxyphenyl)-N-methyl-α-alanine and β-(2-chloro-3,4-dihydroxyphenyl)-β-alanine has been performed.

3,4-Dihydroxyphenylalanine (DOPA) is the substrate of several enzyme systems such as dopa oxidase and dopa decarboxylase which convert it to melanins[2] and to 3,4-dihydroxyphenethylamine and norepinephrine.[3,4] These reactions play an important role in animal and plant metabolism and have been studied extensively *in vitro* and *in vivo*. Interference with these reactions should prevent the accumulation of the respective reaction products in certain pathogenic conditions and for this purpose inhibitors for dopa decarboxylase have been sought repeatedly.[5-10] When 2-methyl-3,4-dihydroxyphenylalanine[11,12] became available, it was included in a series of some two hundred compounds in tests for dopa decarboxylase inhibition *in vitro*, and the same substance and its 2-chloro analog[11] were screened for anti-phenylalanine behavior in various biological systems. Since several analogs of amino acids had been found to possess antiviral activity,[13,14] it seemed desirable to test the effect of both compounds against influenza virus. In the course of these experiments it was observed that both compounds inhibited the multiplication of the PR-8 strain of influenza virus in the allantoic fluid of the chick embryo.[15] Although in rats infected with the virus these two compounds were inactive, additional 2-substituted derivatives of 3,4-dihydroxyphenylalanine were prepared with the hope of overcoming this obstacle.



X	Y
Br	CH_2Cl (II)
F	CH_2Cl (VII)
C_2H_5	CH_2Cl* (XX)
NO_2	CH_2Cl (XI)
Br	$CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ (III)
F	$CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ (VIII)
C_2H_5	$CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$* (XXI)
NO_2	$CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ (XII)

X
Br (I)
F (VI)
C_2H_5 (XIX)

R	X
CH_3	Br (IV)
CH_3	F (IX)
CH_3	C_2H_5* (XXII)
CH_3	NO_2 (XIII)
CH_3	CH_3 (XXVI)
H	Br (V)
H	F (X)
H	C_2H_5* (XXIII)
H	NO_2 (XIV)

* The position of this group has not been confirmed conclusively.

Fig. 1.

For the synthesis of 2-bromo-3,4-dihydroxyphenylalanine, 3-bromoveratrole (I)[16] was chloromethylated to 2-bromoveratryl chloride (II); this was condensed with diethyl acetamidomalonate to give III which was hydrolyzed to β-(2-bromo-3,4-dimethoxyphenyl)-α-alanine (IV) with hydrochloric acid. β-(2-Bromo-3,4-dihydroxyphenyl)-α-alanine (V) was obtained by ether cleavage with 47% hydriodic acid. By an analogous sequence (VI → VII → VIII → X) 3-fluoroveratrole (VI)[17] was transformed into β-(2-fluoro-3,4-dihydroxy-

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TABLE I

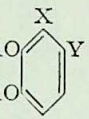
INFRARED SPECTRA OF DIMETHOXY-SUBSTITUTED BENZOIC ACIDS[a]

Dimethoxybenzoic acid derivative	Wave length, microns																	
2(?)-Ethyl-3,4-	9.13	9.33	9.48	9.78	10.16		10.84		11.67	11.95	12.10	12.61	12.75	13.06	13.26		14.35	
2-Methyl-3,4-	9.23		9.54		9.96	10.56	10.90		11.74	11.93	12.16		12.75	13.02	13.33		14.35	
2-Fluoro-3,4-	9.14			9.72		10.43	10.79	11.25			12.16		12.80	13.06		13.51	14.19	15.09
2-Bromo-3,4-				9.72			10.94			11.97	12.27		12.80	13.06				15.07
5-Methyl-3,4-	9.11		9.50		10.04		10.79	11.35	11.65				12.84	13.03	13.34		14.03	
2,3-	9.18		9.50		9.97	10.30	10.68	11.15			12.20	12.42		13.19		13.68		15.45

[a] Perkin–Elmer model 21 infrared spectrophotometer, potassium bromide pellets.

TABLE II

DESCRIPTIVE AND ANALYTICAL DATA



Compound	R	X	Y	Yield, %	M.p., °C.	Solvent of crystln.	Composition	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2-Bromoveratryl chloride	CH_3	Br	CH_2Cl[a]	78	37.5–39	EtOH	$C_9H_{10}BrClO_2$	40.71	3.79	40.82	4.09
2-Fluoroveratryl chloride	CH_3	F	CH_2Cl	68	50.5–51.5	MeOH	$C_9H_{10}ClFO_2$	52.82	4.93	53.37	4.74
2-Ethylveratryl chloride	CH_3	C_2H_5	CH_2Cl	16	36–37.5	Ligroin	$C_{11}H_{15}ClO_2$	61.54	7.04	61.93	7.04
Diethyl acetamido-(2-bromo-3,4-dimethoxybenzyl)-malonate	CH_3	Br	$CH_2C(NHAc)(CO_2C_2H_5)_2$	86	139.5–141	$(i\text{-Pr})_2O$[b]	$C_{18}H_{24}BrNO_7$	48.44	5.42	48.31	5.25
Diethyl acetamido-(2-fluoro-3,4-dimethoxybenzyl)-malonate	CH_3	F	$CH_2C(NHAc)(CO_2C_2H_5)_2$	75	93–95	EtOH–H_2O	$C_{18}H_{24}FNO_7$	56.10	6.27	56.40	6.22
Diethyl acetamido-(2-ethyl-3,4-dimethoxybenzyl)-malonate	CH_3	C_2H_5	$CH_2C(NHAc)(CO_2C_2H_5)_2$	40	86–88	EtOH–H_2O	$C_{20}H_{27}NO_7$	60.74	7.39	60.45	7.22
Diethyl acetamido-(2-nitro-3,4-dimethoxybenzyl)-malonate	CH_3	NO_2	$CH_2C(NHAc)(CO_2C_2H_5)_2$[c]	64	144–146	EtOH	$C_{18}H_{24}N_2O_9$	52.42	5.87	52.61	5.68
β-(2-Bromo-3,4-dimethoxyphenyl)-α-alanine·HCl	CH_3	Br	$CH_2CH(NH_2)CO_2H$		237.5–239 d.	[d]	$C_{11}H_{14}BrNO_4$	43.44	4.64	43.31	4.68
	CH_3	Br	$CH_2CH(NH_2)CO_2H\cdot HCl$	73	258–259 d.	EtOH–Et_2O	$C_{11}H_{15}BrClNO_4$	38.79	4.44	38.76	4.58
β-(2-Fluoro-3,4-dimethoxyphenyl)-α-alanine·HCl	CH_3	F	$CH_2CH(NH_2)CO_2H$		219 d.	[d]	$C_{11}H_{14}FNO_4$	54.32	5.80	54.39	6.16
	CH_3	F	$CH_2CH(NH_2)CO_2H\cdot HCl$	69	209–211 d.	EtOH–Et_2O	$C_{11}H_{15}ClFNO_4$	47.23	5.41	47.31	5.19
β-(2-Ethyl-3,4-dimethoxyphenyl)-α-alanine	CH_3	C_2H_5	$CH_2CH(NH_2)CO_2H$	50	255.5–256.5 d.	[d]	$C_{13}H_{19}NO_4$	61.64	7.56	61.04	7.69
β-(2-Nitro-3,4-dimethoxyphenyl)-α-alanine	CH_3	NO_2	$CH_2CH(NH_2)CO_2H$[e]	81	218 d.	[d]	$C_{11}H_{14}N_2O_6$	48.89	5.22	48.58	4.96
β-(2-Methyl-3,4-dimethoxyphenyl)-α-alanine·HCl	CH_3	CH_3	$CH_2CH(NH_2)CO_2H$		247 d.	[d]	$C_{12}H_{17}NO_4$	60.23	7.16	60.13	7.21
	CH_3	CH_3	$CH_2CH(NH_2)CO_2H\cdot HCl$	37	243–245 d.	EtOH–Et_2O	$C_{12}H_{18}ClNO_4$	52.26	6.57	51.78	6.67
β-(2-Fluoro-3,4-dihydroxyphenyl)-α-alanine·HBr	H	F	$CH_2CH(NH_2)CO_2H$		282–283 d.	H_2O[f]	$C_9H_{10}FNO_4$	50.23	4.68	49.97	4.60
	H	F	$CH_2CH(NH_2)CO_2H\cdot HBr$	93	187–190 d.	$(i\text{-Pr})_2O$–*i*-PrOH	$C_9H_{11}BrFNO_4$	36.50	3.75	36.69	4.15
β-(2-Bromo-3,4-dihydroxyphenyl)-α-alanine	H	Br	$CH_2CH(NH_2)CO_2H$	39	205 d.	H_2O[f]	$C_9H_{10}BrNO_4$	39.15	3.65	39.56	4.19
β-(2-Ethyl-3,4-dihydroxyphenyl)-α-alanine	H	C_2H_5	$CH_2CH(NH_2)CO_2H$	26	196–198 d.	H_2O[f]	$C_{11}H_{15}NO_4$	58.66	6.71	57.79	6.92

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β-(2-Nitro-3,4-dihydroxyphenyl)-α-alanine	H	NO_2	$CH_2CH(NH_2)CO_2H$[e]	67	182–185 d.	H_2O[f]	$C_9H_{10}N_2O_6 \cdot H_2O$	41.54	4.65	41.46	4.49
2-Ethylveratric acid	CH_3	C_2H_5	CO_2H		152–154	EtOH–H_2O	$C_{11}H_{14}O_4$	62.84	6.71	62.57	6.55
2-Fluoroveratric acid	CH_3	F	CO_2H	74	188–190	MeOH–H_2O	$C_9H_9FO_4$	54.01	4.53	53.94	4.36
2,3-Dimethoxy-6-carbomethoxybenzenediazonium fluoborate	CH_3	N_2BF_4	CO_2CH_3[c]	78	167.5–169 d.	Me_2CO–Et_2O	$C_{10}H_{11}BF_4N_2O_4$	38.74	3.58	38.30	3.60
Methyl 2-fluoroveratrate	CH_3	F	CO_2CH_3	9	80–81.5	EtOH–H_2O	$C_{10}H_{11}FO_4$	56.07	5.17	55.99	5.18
2-Ethylveratraldehyde semicarbazone	CH_3	C_2H_5	$CH{=}NNHCONH_2$		191–193	EtOH	$C_{12}H_{17}N_3O_3$	57.35	6.82	57.26	6.37
2-Ethylveratraldoxime	CH_3	C_2H_5	$CH{=}NOH$		89–90	EtOH–H_2O	$C_{11}H_{15}NO_3$	63.14	7.23	62.94	6.72
4-(2-Ethyl-3,4-dimethoxybenzal)-2-phenyl-5-oxazolone	CH_3	C_2H_5	Azl[g,h]	41	157.5–158.5	EtOH	$C_{20}H_{18}NO_4$	71.20	5.68	71.40	5.84
4-(2-Nitro-3,4-dimethoxybenzal)-2-phenyl-5-oxazolone	CH_3	NO_2	Azl[g,h]	37	168.5–170	AcOH	$C_{18}H_{14}N_2O_6$	61.01	3.98	61.32	4.26
4-(2-Bromo-3-acetoxy-4-methoxybenzal)-2-phenyl-5-oxazolone	3-CH_3CO 4-CH_3	Br	Azl[e,h]	67	178–179	C_6H_6	$C_{19}H_{14}BrNO_5$	54.82	3.39	54.85	3.13
α-Benzamido-2-ethyl-3,4-dimethoxycinnamic acid	CH_3	C_2H_5	$CH{=}C(NHBz)CO_2H$	95	162–163.5	EtOH–H_2O	$C_{20}H_{21}NO_5$	67.59	5.95	67.79	6.03
α-Benzamido-2-nitro-3,4-dimethoxycinnamic acid	CH_3	NO_2	$CH{=}C(NHBz)CO_2H$[i]	91	212–213.5	EtOH–H_2O	$C_{18}H_{16}N_2O_7$	58.06	4.33	58.25	3.97
α-Benzamido-2-bromo-3-hydroxy-4-methoxycinnamic acid	3-H 4-CH_3	Br	$CH{=}C(NHBz)CO_2H$	83	119–121	EtOH–H_2O	$C_{17}H_{14}BrNO_5$	52.06	3.60	52.17	3.71
α-Benzamido-2-ethyl-3,4-dimethoxyphenylpropionic acid	CH_3	C_2H_5	$CH_2CH(NHBz)CO_2H$	98	75–76	EtOH–H_2O	$C_{20}H_{23}NO_5 \cdot C_2H_6O$	65.49	7.25	65.58	7.63
6-Chloro-3,4-dimethoxycinnamic acid	CH_3	Cl	$CH{=}CHCO_2H$	65	220–222	EtOH	$C_{11}H_{11}ClO_4$	54.44	4.57	54.76	4.62
β-(2-Chloro-3,4-dimethoxyphenyl)-β-alanine	CH_3	Cl	$CH(NH_2)CH_2CO_2H$	37	240–241 d.	[d]	$C_{11}H_{14}ClNO_4$	50.87	5.43	50.44	5.19
β-(2-Chloro-3,4-dihydroxyphenyl)-β-alanine	H	Cl	$CH(NH_2)CH_2CO_2H$	90	163–164 d.[j]	[d]	$C_9H_{10}ClNO_4 \cdot H_2O$	43.29	4.85	43.16	5.08
Methyl β-(2-methyl-3,4-dimethoxyphenyl)-α-aminopropionate hydrochloride	CH_3	CH_3	$CH_2CH(NH_2)CO_2CH_3 \cdot HCl$[k]	95	176–177	EtOH–Et_2O	$C_{13}H_{20}ClNO_4$	53.89	6.95	53.55	6.81
β-(2-Methyl-3,4-dimethoxyphenyl)-N-*p*-tosyl-α-alanine	CH_3	CH_3	$CH_2CH(NH\text{-}p\text{-}Ts)CO_2H$[l,m]	91	171–172.5	EtOH–H_2O	$C_{19}H_{23}NO_6S$	58.00	5.89	58.15	5.89
β-(2-Methyl-3,4-dimethoxyphenyl)-N-*p*-tosyl-N-methyl-α-alanine	CH_3	CH_3	$CH_2CH[N(CH_3)(p\text{-}Ts)]CO_2H$	63	154–155.5	AcOEt–Ligroin	$C_{20}H_{25}NO_6S$	58.95	6.18	59.02	6.17
β-(2-Methyl-3,4-dihydroxyphenyl)-N-methyl-α-alanine	H	CH_3	$CH_2CH(NHCH_3)CO_2H$	27	303–304 d.	[d]	$C_{11}H_{15}NO_4$	58.65	6.71	58.39	6.65

[a] All compounds are colorless crystalline solids unless otherwise noted. [b] Also crystallized from aqueous ethanol producing a dimorph, m.p. 90–91°. Found: C, 48.18; H, 5.24. [c] Turned pink on standing. [d] Purified by reprecipitation from 10% hydrochloric acid. [e] Bright yellow prisms. [f] Containing a small amount of sulfur dioxide. [g] Fine yellow needles. [h] The 4-methylidene-2-phenyl-5-oxazolone group, $-CH{=}C(-N{=}C(C_6H_5)-O-)-C{=}O$, has been abbreviated as Azl. [i] Pale yellow crystals. [j] After drying over phosphorus pentoxide for two days. [k] Prepared by Fischer esterification from the amino acid. [l] Tan crystals. [m] *p*-Ts represents the *p*-toluenesulfonyl group.

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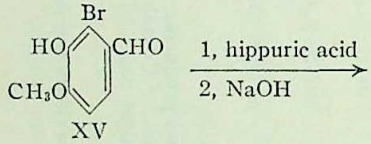
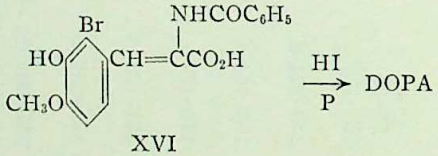
phenyl)-α-alanine (X); here, isolation of the intermediate dimethoxy derivative IX was possible but not necessary. This held also for the similar series of steps from 2-nitroveratryl chloride (XI)[18] to β-(2-nitro-3,4-dihydroxyphenyl)-α-alanine (XIV).

The position of the chloromethyl group in II was proved by oxidation to 2-bromoveratric acid.[16] In an analogous manner, 2-fluoroveratryl chloride (VII) was oxidized to 2-fluoroveratric acid. The identity of this acid was established by a Schiemann synthesis from methyl 2-aminoveratrate.[19]

An attempt was made to synthesize β-(2-bromo-3,4-dihydroxyphenyl)-α-alanine (IV) by a shorter route starting from the readily accessible 2-bromoisovanillin (XV).[20] The acetoxy-azlactone from this aldehyde was hydrolyzed to α-benzamido-2-bromo-3-hydroxy-4-methoxycinnamic acid (XVI) but this compound was debrominated to DOPA on heating with hydriodic acid and phosphorus.

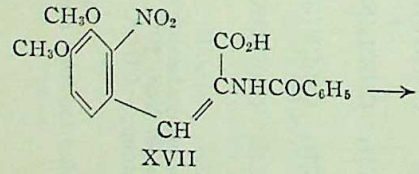


XV

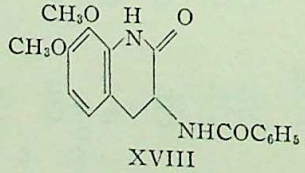


XVI

α-Benzamido-2-nitro-3,4-dimethoxycinnamic acid (XVII) was prepared from 2-nitroveratraldehyde[21] in a similar way and was hydrogenated in the presence of Adams catalyst in the hope of securing the corresponding saturated 2-amino derivative. While this compound was undoubtedly formed, it lactamized spontaneously to 3-benzamido-7,8-dimethoxy-3,4-dihydro-2-quinolone (XVIII).



XVII

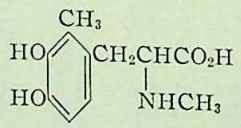


XVIII

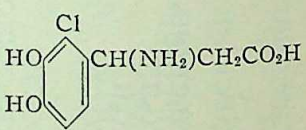
The yields in the preparation of the ethyl substituted malonate ester XXI from 3-ethylveratrole (XIX) were so low that a different route to β-(ethyldihydroxyphenyl)-α-alanine (XXIII) was chosen. 3-Ethylveratrole,[22] obtained by the Huang-Minlon modification of the Wolff–Kishner method[23] from 2,3-dimethoxyacetophenone, was subjected to a Gattermann aldehyde synthesis with hydrogen cyanide; the position of the formyl group in the resulting ethyldimethoxybenzaldehyde could not be proved conclusively since oxidation with potassium permanganate or chromic acid only led to an ethyldimethoxybenzoic acid which decomposed on continued oxidation. The same acid was obtained from the oxidation of the chloromethylation product of 3-ethylveratrole. Since the chloromethylation of 3-methyl-, 3-chloro-, 3-bromo- and 3-fluoroveratrole introduced the chloromethyl group *ortho* to the 3-substituent, a similar orientation could be expected for the chloromethylation of 3-ethylveratrole. In support of this assumption the infrared spectra of pertinent dimethoxybenzoic acids are listed in Table I. It may be significant that 2-methylveratric acid and our ethyldimethoxybenzoic acid differ from 5-methylveratric acid in their absorption characteristics at 11.0–12.3 μ. The aldehyde and chloromethyl derivatives obtained from 3-ethylveratrole are tentatively assigned the structures 2-ethylveratraldehyde and 2-ethylveratryl chloride (XX), respectively.

2-Ethylveratraldehyde gave β-(2-ethyl-3,4-dimethoxyphenyl)-α-alanine (XXII) by an azlactone synthesis followed by hydrolysis, saturation of the side chain and removal of the benzoyl group. The ether groups of XXII were cleaved with hydriodic acid (XXIII).

In order to study the effect of various structural alterations in the amino group of antiviral 2-substituted derivatives of 3,4-dihydroxyphenylalanine, β-(2-methyl-3,4-dihydroxyphenyl)-N-methyl-α-alanine (XXIV) and β-(2-chloro-3,4-dihydroxyphenyl)-β-alanine (XXV) have been synthesized. Diethyl acetamido-(2-methyl-3,4-dimethoxybenzyl)-malonate[11] was hydrolyzed and decarboxylated, the amino acid XXVI was tosylated and the N-



XXIV



XXV

tosyl derivative treated with dimethyl sulfate. Scission of the methoxyl groups and the N-tosyl linkage furnished XXIV. The chloro derivative XXV was prepared by subjecting 2-chloroveratraldehyde[11] to a Perkin reaction, treating the resulting 2-chloro-3,4-dimethoxycinnamic acid with hydroxylamine and cleaving the methoxyl groups.

β-(2-Fluoro-3,4-dihydroxyphenyl)-α-alanine had activity against influenza virus similar to β-(2-methyl-3,4-dihydroxyphenyl)-α-alanine. 2-Bromo-, 2-fluoro-, 2-ethyl- and 2-nitro-DOPA and their dimethyl ethers were screened for bacteriostatic, antifungal and antiviral activity. In chick embryo protection tests, using the PR-8 strain of the influenza virus, XXII and XXVI possessed slight activity. β-(2-Chloro-3,4-dihydroxyphenyl)-β-alanine (XXV), in concentrations of 1:500, inhibited the growth of *Histoplasma capsulatum* and *Micrococcus pyogenes*, as well as *Diplococcus pneumoniae*, and provided slight protection in mice infected with this organism.[15]

(18) K. H. Slotta and F. Lauerson, *J. prakt. Chem.*, **139**, 220 (1934).
(19) W. M. Rodionow and A. M. Fedorowa, *Bull. soc. chim.*, **6**, 478 (1939).
(20) H. Pauly, *Ber.*, **48**, 2013 (1915).
(21) R. Pschorr and C. Sumuleanu, *ibid.*, **32**, 3407 (1899).
(22) W. Mosimann and J. Tambor, *ibid.*, **49**, 1262 (1916).
(23) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

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Experimental[24]

General Directions. (a) Chloromethylation of Veratrole Derivatives (II, VII, XX).—A solution of 0.25 mole of the 3-substituted veratrole derivative and 0.50 mole of monochloromethyl ether in 175 ml. of glacial acetic acid was stirred and warmed. Reaction times and temperatures were as follows: for 3-bromoveratrole,[16] 24 hr., 50–55°; for 3-ethylveratrole,[22] 8 hr., 30°; and for 3-fluoroveratrole,[17] 24 hr., 60°. The mixture was poured into 750 ml. of ice-water and the colorless solid recrystallized.

(b) (1) Structural Proof of Chloromethylveratrole Derivatives.—A solution of 1.5 g. of the chloromethyl derivative and 3.0 g. of potassium permanganate in 50 ml. of water and 1.0 ml. of 25% sodium hydroxide solution was refluxed for 1 hr., filtered from manganese dioxide and acidified. The precipitated benzoic acid derivatives were recrystallized. 2-Bromo-[16] and 2 fluoroveratric acid were identified by mixture melting points with samples prepared by unequivocal routes.

(2) 2-Fluoroveratric Acid.—An ice-cold stirred suspension of 23.7 g. of methyl 2-aminoveratrate[19] and fluoboric acid, prepared by saturating 60 ml. of 48% hydrofluoric acid with boric acid at 10°, was diazotized with 30 ml. of a 33% aqueous solution of sodium nitrite. The yellow diazonium fluoborate was filtered and recrystallized. For data, see Table II. Thirteen grams of the salt was decomposed by heating at 170° for 2 hr., the black tarry residue was distilled under reduced pressure and recrystallized.

A mixture melting point of the resulting methyl 2-fluoroveratrate with a sample obtained by diazomethane methylation of 2-fluoroveratric acid from the oxidation of 2-fluoroveratryl chloride showed no depression.

Saponification of 0.1 g. of methyl 2-fluoroveratrate with 0.5 ml. of a hot 10% sodium hydroxide solution yielded, upon acidification, 70 mg. (74.5%) of 2-fluoroveratric acid, m.p. 188–190°. A mixture melting point of this substance and of the acid procured by oxidation of 2-fluoroveratryl chloride remained undepressed.

(c) Diethyl Arylacetamidomalonates (III, VIII, XII, XXI).—To 250 ml. of an absolute ethanolic solution of 0.13 mole of sodium ethoxide were added 0.13 mole of diethyl acetamidomalonate and 0.13 mole of the 2-substituted chloromethylveratrole, and the mixture was stirred and refluxed for 8 hr. The precipitated sodium chloride was filtered, the filtrate concentrated under reduced pressure and the residue recrystallized.

(d) β-(2-Substituted-dimethoxyphenyl)-α-alanine Derivatives (IV, IX, XIII, XXII, XXVI).—To a solution of 2.0 g. of the respective diethyl arylacetamidomalonate in 5 ml. of glacial acetic acid was added 8 ml. of 37% hydrochloric acid, and the mixture was heated at 95° for 6 hr. The solvents were distilled under reduced pressure, the crystalline hydrochloride was triturated with dry acetone and recrystallized.

The free phenylalanine derivatives were prepared by buffering the aqueous solutions of the hydrochlorides with potassium carbonate to *p*H 5–6 and purifying by reprecipitation from dilute hydrochloric acid solution with the same reagent.

(e) Nuclear 2-Substituted Derivatives of DOPA.—(1) A solution of 8.5 g. of the diethyl malonate derivatives (VIII, XII) in 40 ml. of redistilled 47% hydrobromic acid was refluxed for 7 hr. while hydrogen was bubbled through, concentrated under reduced pressure at 90° and the residual hydrobromide was recrystallized. The amino acid was liberated by adjusting the concentrated aqueous solution of the pure salt to *p*H 5–6 with sodium acetate with the help of a trace of sodium hydrosulfite. The material crystallized on cooling.

(2) Solutions of 6.4 g. of the dimethoxyphenylalanine derivatives (IV, XXII) in 60 ml. of 47% hydriodic acid were refluxed for 7 hr., concentrated as above, and the amorphous residue was adjusted to *p*H 5–6 with a saturated solution of sodium acetate. The amino acids crystallized on prolonged standing.

(f) Azlactones.—Starting with 2-bromoisovanillin,[20] 2-nitroveratraldehyde[21] and 2-ethylveratraldehyde, respectively, a mixture of 0.08 mole of the aldehyde, 0.09 mole of hippuric acid and 0.09 mole of anhydrous sodium acetate and 35 ml. of acetic anhydride was heated at 95° for 3 hr. The mixture solidified; it was diluted with 100 ml. of absolute ethanol, cooled to 0° and the crystalline deposit was filtered and washed with water.

(g) Hydrolysis of Azlactones.—The azlactones were refluxed with 30 volumes of a 1% sodium hydroxide solution in 50% aqueous ethanol for 10 minutes, the mixture was filtered and the filtrate acidified with 10% hydrochloric acid. The precipitated oils crystallized on standing.

Reductive Cleavage of α-Benzamido-2-bromo-3-hydroxy-4-methoxycinnamic Acid.—To an ice-cold mixture of 35 ml. of acetic anhydride and 35 ml. of 57% hydriodic acid was added 3.5 g. of red phosphorus and 6.5 g. of the acid XVI, and the mixture was refluxed for 3 hr. After filtering from phosphorus and extraction with ether, the solution was evaporated to dryness under reduced pressure, the residue was taken up in 10 ml. of water and buffered to *p*H 5–6 with sodium acetate. After standing for several days, 2.5 g. (77%) of crystals deposited which were recrystallized from water, m.p. 280° dec. The compound contained no halogen and did not depress the melting point of β-(3,4-dihydroxyphenyl)-α-alanine.

2-Ethylveratraldehyde.—3-Ethylveratrole[22] (30 g.) was dropped with stirring into a suspension of 29.8 g. of powdered aluminum chloride in 21 ml. of benzene at 0°, and then an anhydrous solution of 18.6 g. of hydrogen cyanide in 25 ml. of benzene was added. A slow stream of anhydrous hydrogen chloride was passed through at 28–30° for 8 hr., and the dark red mixture was poured onto a mixture of 106 ml. of 37% hydrochloric acid and 250 g. of crushed ice. Excess hydrogen cyanide was boiled out, the cooled mixture was extracted with ether, the ether extract was dried and distilled. The aldehyde was a straw-colored oil, b.p. 145–148° (5 mm.), yield 24.8 g. (70.5%). It was converted to the **oxime** and **semicarbazone** (Table II).

Oxidation of the aldehyde with alkaline potassium permanganate or chromic acid yielded the same ethyldimethoxybenzoic acid, m.p. 152–154°, which also resulted from the oxidation of ethyldimethoxybenzyl chloride (XX).

α-Benzamido-2-ethyl-3,4-dimethoxyphenylpropionic Acid.—A solution of 1.0 g. of α-benzamido-2-ethyl-3,4-dimethoxycinnamic acid in 50 ml. of absolute ethanol containing 0.1 g. of Adams catalyst was hydrogenated under 3 atm. of pressure at 25° for 48 hr. and worked up as usual. The oily residue of the evaporated solution crystallized on standing. The yield was quantitative.

The benzamido group was hydrolyzed with a 5:8 mixture of glacial acetic acid and 37% hydrochloric acid as described under the general directions (d) above.

3-Benzamido-7,8-dimethoxy-3,4-dihydro-2-quinolone (XVIII).—A solution of 13.0 g. of α-benzamido-2-nitro-3,4-dimethoxycinnamic acid in 100 ml. of absolute ethanol was hydrogenated in the presence of 0.25 g. of platinum oxide at a pressure of 3 atmospheres for 24 hr. and worked up. The filtered solution deposited 4.5 g. (39%) of a colorless product on cooling, m.p. 223.5–226° after recrystallization from ethanol. The substance was insoluble in dilute acid and base.

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56. Found: C, 66.42; H, 6.23.

2-Chloro-3,4-dimethoxycinnamic Acid.—A mixture of 20.6 g. of 2-chloroveratraldehyde,[11] 10 g. of anhydrous sodium acetate and 20 ml. of acetic anhydride was heated at 170–180° for 8 hr., allowed to cool and diluted with 100 ml. of water. The solid precipitate was filtered and recrystallized.

β-(2-Chloro-3,4-dimethoxyphenyl)-β-alanine.—To a hot solution of 6.8 g. of sodium ethoxide in 80 ml. of ethanol was added a hot solution of 6.95 g. of hydroxylamine hydrochloride in 5 ml. of water. The mixture was cooled rapidly and the precipitated sodium chloride was filtered. To the filtrate was added 12.1 g. of 2-chloro-3,4-dimethoxycinnamic acid and the mixture heated on a steam-bath for 24 hr. After cooling, the crystalline product was filtered.

β-(2-Chloro-3,4-dihydroxyphenyl)-β-alanine (XXV).—A mixture of 1 g. of β-(2-chloro-3,4-dimethoxyphenyl)-β-alanine and 10 ml. of 57% hydriodic acid was refluxed for 5 hr., evaporated to dryness under reduced pressure and the residue was taken up in 5 ml. of water. Colorless crystals formed when the *p*H was adjusted to 6 with sodium acetate. They were filtered, washed with water, acetone and ether.

β-(2-Methyl-3,4-dimethoxyphenyl)-N-*p*-tosyl-α-alanine.—A mixture of 17 g. of β-(2-methyl-3,4-dimethoxyphenyl)-

(24) All melting points are corrected. Microanalyses by Miss Barbara J. Williamson.

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α-alanine (XXVI), 17 g. of *p*-toluenesulfonyl chloride and 170 ml. of 4% sodium hydroxide solution was shaken for 24 hr. The reddish-black solution was filtered and acidified with 10% hydrochloric acid. The gummy precipitate solidified when the mixture was heated on a steam-bath for 30 minutes and was filtered.

β-(2-Methyl-3,4-dimethoxyphenyl)-N-methyl-N-*p*-tosyl-α-alanine.—To a stirred solution of 19.6 g. of β-(2-methyl-3,4-dimethoxyphenyl)-N-*p*-tosyl-α-alanine in 100 ml. of 10% sodium hydroxide solution was added 20 ml. of dimethyl sulfate, at room temperature. After 10 minutes, the mixture was made alkaline by adding 10% sodium hydroxide solution, diluted with 2 l. of water and heated on a steam-bath until solution was complete. After treatment with Darco the solution was acidified with dilute hydrochloric acid. The gummy solid became crystalline after standing for several hours.

β-(2-Methyl-3,4-dihydroxyphenyl)-N-methyl-α-alanine (XXIV).—A mixture of 2 g. of β-(2-methyl-3,4-dimethoxyphenyl)-N-methyl-N-*p*-tosyl-α-alanine and 17 ml. of 57% hydriodic acid was heated under reflux for 4 hr. The dark brown reaction mixture was concentrated under reduced pressure, the residue suspended in 20 ml. of water and extracted continuously with ether for 5 days. The clear aqueous layer was separated and concentrated to dryness under reduced pressure. When the residue was dissolved in 4 ml. of water and adjusted to *p*H 5–6, colorless crystals appeared.

5-Methylveratric Acid.—5-Methylvanillin[25] was methylated with dimethyl sulfate and 10% sodium hydroxide solution, as described for an analogous case,[26] and the crude oily 5-methylveratraldehyde was oxidized with alkaline potassium permanganate solution under the conditions used in the oxidation of 2-methylveratryl chloride.[11] Recrystallization from 50% aqueous ethanol gave colorless needles, m.p. 146–148°.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 60.87; H, 5.91.

(25) J. Koetschet and P. Koetschet, *Helv. Chim. Acta*, **13**, 476 (1930).

(26) H. Decker and O. Koch, *Ber.*, **40**, 4794 (1907).

CHARLOTTESVILLE, VIRGINIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

The $BF_3 \cdot N_2O_3$ Complex. Its Use in Diazotization and Nitration[1]

BY G. BRYANT BACHMAN AND TAKEO HOKAMA

RECEIVED JANUARY 2, 1957

Boron trifluoride reacts with nitrogen trioxide to form a stable, white, solid complex, $BF_3 \cdot N_2O_3$. Physical and chemical properties suggest that the structure is best represented as $(F_3B \leftarrow NO_2)^-(NO)^+$. The complex is a weak nitrating agent but a powerful diazotizing agent in the aromatic series.

It was reported recently that boron trifluoride forms a 1:1 addition complex with dinitrogen tetroxide[2] which is an excellent nitrating agent. It has now been found that boron trifluoride also forms a similar complex with dinitrogen trioxide. The combining ratio was determined gravimetrically to be 1:1. The complex is a white, stable solid, insoluble in all solvents with which it does not react, including alkanes, nitroalkanes and polychlorinated alkanes. It sublimes at room temperatures and does not melt in a sealed tube below 300°. Above this temperature, the very dark color of the dissociation products (especially NO_2) prevents observation of the remaining solid. These properties suggest that the complex is ionic in character and is formed as illustrated in equation 1 or 2

$$F_3B + ON\dot{:}NO_2 \longrightarrow \underset{A}{(F_3B \leftarrow NO_2)^-(NO)^+} \quad (1)$$

$$F_3B + O_2N\dot{:}NO \longrightarrow \underset{B}{(F_3B \leftarrow NO)^-(NO_2)^+} \quad (2)$$

That the preferred one of the above two formulations is A is probable on the basis of the chemical properties described below.

The $BF_3 \cdot N_2O_3$ complex reacts rapidly with substances with which BF_3 and N_2O_3 react separately, including water, alcohols, ethers, ketones, carboxylic acids, amines and pyridine. However, under rather vigorous conditions it will introduce an NO_2 group into aromatic nuclei. If benzene is refluxed over the complex in a glass fiber thimble in a Soxhlet extractor for 42 hr., a 5–6% yield of nitrobenzene is obtained. Under the same conditions, toluene yields a red-black tar, but in the solvent nitroethane at 60–65° for 3 days, toluene gives a 56% yield of *o*-nitrotoluene. Other nitration results are shown in Table I. It will be noted that the complex produces a different ratio of isomers than is reported for nitric acid nitrations of toluene, 1-nitronaphthalene and chlorobenzene. This apparently is the result of its mild nitrating action since the isomer distribution obtained represents increased amounts of the principal isomer produced in nitric acid nitrations. Powerful reagents favor a more nearly statistical distribution of isomers in aromatic substitution.

The nitrating action of the complex suggests structure B but does not preclude structure A since it has been shown by Ingold[3] that primary attack by a nitrosonium ion is probably a factor in the nitration of *p*-nitrophenol and *p*-chloroanisole. Furthermore it has been shown that nitrogen trioxide produces nitrosonium cations in the presence of another strong acid, namely, sulfuric acid.[4,5] In addition there remains the possibility that oxidation by air occurs during the nitration and converts the nitroso product to a nitro product or converts the complex $BF_3 \cdot N_2O_3$ to $BF_3 \cdot N_2O_4$ a known nitrating agent.[2] To test this, naphthalene was nitrated at 25° in three different ways: under air, under nitrogen, and with oxygen bubbling through the mixture. The second of these produced a low yield (14%) of 1-nitronaphthalene and

(1) From the M.S. Thesis of Takeo Hokama, Purdue University, January, 1956.

(2) G. B. Bachman, H. Feuer, B. R. Bluestein and C. M. Vogt, THIS JOURNAL, **77**, 6188 (1955).

(3) C. K. Ingold, C. A. Bunton, E. D. Hughes, D. I. H. Jacobs, M. H. Jones, G. J. Minkoff and R. I. Reed, *J. Chem. Soc.*, 2628 (1950).

(4) C. K. Ingold and E. D. Hughes, *et al.*, *ibid.*, 2504 (1950).

(5) J. G. D. Couldard and D. J. Millen, *ibid.*, 2620 (1950).

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TABLE I

NITRATIONS WITH $BF_3N_2O_3$

Substance	Products	Yields,[e] %	Time, hr.	Temp., °C.	Solvent
Benzene	Nitrobenzene	5	42	45	None
Toluene[a]	*o*-Nitrotoluene	56	72	60–65	Nitroethane
	p-Nitrotoluene	1			
	2,4-Dinitrotoluene	3			
o-Nitrotoluene[b]	2,4-Dinitrotoluene	40	12	85–90	Nitroethane
Naphthalene (air)	1-Nitronaphthalene	67	24	25	2-Nitropropane
Naphthalene (oxygen)	1-Nitronaphthalene	62	24	25	2-Nitropropane
	Dinitronaphthalene	13			
Naphthalene (nitrogen)	1-Nitronaphthalene	14	24	25	2-Nitropropane
1-Nitronaphthalene[c]	1,5-Dinitronaphthalene	14	24	60–70	Nitroethane
	1,8-Dinitronaphthalene	36			
Chlorobenzene[d]	2-Nitrochlorobenzene	12	24	85–95	Nitroethane
	4-Nitrochlorobenzene	50			
Cyclohexane	No reaction	..	4	*ca.* 80	Nitroethane

[a] An *ortho–para* ratio of 60:40 in the mononitration of toluene with mixed acids has been reported by A. F. Holleman, J. Vermeulen and W. J. deMooy, *Rec. trav. chim.*, **33**, 1 (1914). [b] In the nitration of *o*-nitrotoluene with mixed acids, a 91% yield of dinitrotoluene with a 66:34 ratio of 2,4- to 2,6-dinitrotoluene was obtained by W. H. Gibson, R. Deuckham and R. Fairbairns, *J. Chem. Soc.*, 121, 270 (1922). [c] A 1:2 ratio of 1,5- and 1,8-dinitronaphthalene was obtained in the nitration of 1-nitronaphthalene with mixed acids by H. H. Hodgson and J. S. Whitehurst, *J. Chem. Soc.*, 202 (1945). [d] An *ortho–para* ratio of 30:70 in the nearly quantitative mononitration of chlorobenzene by mixed acids was obtained by A. F. Holleman and B. R. deBruyn, *Rec. trav. chim.*, 19, 189 (1900). [e] No attempt was made to determine isomer distributions by highly refined techniques, such as infrared analyses. The results are believed, however, to be accurate enough to indicate marked differences between the nitrating actions of the complex and nitric acid.

much tar. The first and third produced good yields of 1-nitronaphthalene (>60%). The oxygen experiment also gave a considerable amount (13%) of mixed dinitronaphthalenes. We conclude that the nitrating action of the complex is negligible in the absence of oxidizing agents such as air or pure oxygen, and that the structure B for the complex is therefore unlikely.

The $BF_3 \cdot N_2O_3$ complex is a powerful diazotizing agent in inert (non-aqueous) solvents and will convert weak aromatic amines such as 2,4-dinitroaniline into diazonium salts in a few minutes at room temperatures or below. The diazonium salts formed are generally insoluble in the reaction medium and may be isolated readily in a pure, stable form by filtration. If heated, these salts decompose to form fluoro derivatives of the starting aromatic nucleus (Schiemann reaction). Thus, fluorobenzene is prepared readily in 56% yield by diazotizing aniline with the complex in nitrobenzene and then raising the temperature gradually to about 85° when nitrogen is smoothly evolved and fluorobenzene distills.

Another reaction which can be accomplished satisfactorily in non-aqueous solvents is the Gomberg–Bachmann reaction.[6] Thus, if the diazotization is carried out in benzene solution and then sodium acetate is added, nitrogen is evolved and the corresponding biphenyl derivative is formed. The yields of 2,4-dinitrobiphenyl and 4-chlorobiphenyl by this method were better than those reported by Hey.[7]

Alternatively, the isolated diazonium salt may be coupled with phenols or otherwise treated in aqueous solution in the customary manner. Table II shows some of the results obtained with a series of aromatic amines, most of which were selected because of their weak basicity and corresponding troublesomeness in ordinary diazotization procedures. It will be noted that the results were uniformly excellent except for the tetrazotizations of the *p*-phenylenediamines. Apparently the complex is not effective in preventing coupling between the diazotized intermediates and the unreacted diamine.

A study of the nitrosating action of the complex was made with diethyl malonate at −40° in nitroethane. A 39% yield of diethyl oximinomalonate and a 28% yield of diethyl mesoxalate were obtained, results which are comparable to those resulting by the action of N_2O_3 alone on diethyl malonate.[8] Ethyl propionate did not react with the complex in 12 hr. at its reflux temperature.

An addition reaction was attempted with the complex and cyclohexene in chloroform of 0°. A thick dark oil was obtained which decomposed on attempted vacuum distillation. Steam distillation produced very little volatile material and a non-volatile tar. The isolation procedures[9] used successfully in working up the reaction products of cyclohexene and N_2O_4 failed to yield identifiable products in this case.

Conclusions.—The complex $BF_3 \cdot N_2O_3$ is prepared readily and serves as a useful reagent in mild nitrations of aromatic compounds. It produces the usual isomers in different ratios than are normally obtained with nitric acid and absorbs oxygen (from the air) in the process. The complex is a powerful nitrosating agent and is especially useful and convenient in diazotizing weakly basic aromatic amines in non-aqueous solvents and in preparing pure, dry, stabilized diazonium salts. Decomposition of these diazonium salts by heat leads to the corresponding fluoro compounds

(6) M. Gomberg and W. E. Bachmann, THIS JOURNAL, **46**, 3339 (1924).

(7) D. H. Hey, J. W. Haworth and J. Elks, *J. Chem. Soc.*, 1284 (1940); D. H. Hey, H. France and I. M. Heilbron, *ibid.*, 369 (1940).

(8) V. Cerchez and R. Locquin, *Bull. soc. chim. France*, [4] **47**, 1279 (1930).

(9) H. Baldock, N. Levy and C. W. Scaife, *J. Chem. Soc.*, 2627 (1949).

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TABLE II

DIAZOTIZATION WITH $BF_3 \cdot N_2O_3$

Aromatic amine	Reactant	Product	M.p., °C.	Yield, % Present	Yield, % Lit.
Aniline	Heat	Fluorobenzene		56	Quant.[a]
	2-Naphthol	Azo dye	133–134	85	Quant.[b]
4-Chloroaniline	Benzene + Na acetate	4-Chlorobiphenyl	76–77	47	40[c]
4-Nitroaniline	Heat	4-Nitrofluorobenzene	26–27	43.5	50–60[d]
sym-Tribromoaniline	2-Naphthol	Azo dye	173–174	98	Quant.[e]
2,6-Dibromo-4-nitroaniline	2-Naphthol	Azo dye	222–223	98	Quant.[f]
2,4-Dinitroaniline	2-Naphthol, benzene + Na acetate	Azo dye	305–306	98	Quant.[f]
		2,4-Dinitrobiphenyl	109–110	25	10[c]
2,4-Dinitro-1-naphthylamine	KI	Iodide	182–183	80	60–85[g]
Picramide	No reaction	...	.....	...	Quant.[f]
2-Nitro-*p*-phenylenediamine	KI	Diiodide	108–110	Trace	.....[f]
p-Phenylenediamine	KI	Diiodide	127–128	Trace	Quant.[f]

[a] G. Balz and G. Schiemann, *Ber.*, **60**, 1186 (1927). [b] C. Liebermann, *ibid.*, **16**, 2860 (1883). [c] *Cf.* reference 7. [d] G. Schiemann and R. Pillarsky, *Ber.*, **62**, 3035 (1929). [e] K. J. P. Orton, *J. Chem. Soc.*, **83**, 808 (1903). [f] H. A. J. Schoutissen, THIS JOURNAL, **55**, 4531 (1933). [g] H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 1620 (1933).

(Schiemann reaction). Isolation by filtration and reaction in aqueous media leads to the usual replacement reactions.

Experimental

Preparation of $BF_3 \cdot N_2O_3$.—Dry nitroethane (300 ml.) was placed in a 3-necked flask fitted with a stirrer, a reflux condenser having a calcium chloride drying tube at the top and a gas inlet tube extending below the surface of the liquid. The flask and contents were cooled to −20° with a Dry Ice–trichloroethylene bath and previously collected, dry, liquid nitrogen tetroxide,[2] 23 g. (0.5 mole), was added. Then dry nitric oxide gas was bubbled slowly into the solution while the bath temperature was lowered quickly to −70°. A low temperature is used to minimize the dissociation of N_2O_3 and to avoid the formation of $BF_3 \cdot 2NO_2$. Abel and Proisl[10] report that N_2O_3 is 90% dissociated at 25°, while Berl and Winnacker[11] report that it is not over 6% dissociated at −50°. Good cooling is essential since the complex formation is exothermic. When brown fumes began to be emitted from the condenser as a result of unabsorbed nitric oxide being oxidized to nitrogen dioxide by the air, the nitric oxide flow was stopped and a dry, gaseous, flow of boron trifluoride was started. This was continued until the blue color of the dinitrogen trioxide disappeared and white fumes of boron trifluoride appeared at the end of the condenser. The flask now contained a suspension of the white, solid complex in nitroethane. It could be used as such or the complex could be filtered off under anhydrous conditions, washed with an inert solvent and stored in stoppered bottles or suspended in another inert liquid medium.

In a series of five experiments, the combining mole ratios by weight of the reactants were determined in the absence of solvents. The results are shown in Table III. In order

TABLE III

COMPOSITION OF THE COMPLEX BY COMBINING WEIGHTS

Expt.	Dinitrogen trioxide Gram	Dinitrogen trioxide Mmoles	Boron trifluoride Gram	Boron trifluoride Mmoles	Mole ratio N_2O_3/BF_3
1	0.3785	4.98	0.3302	4.87	1.02
2	.2567	3.37	.2306	3.40	0.99
3	.1837	2.42	.1650	2.43	0.99
4	.2014	2.68	.1803	2.66	0.99
5	.3432	4.51	.3016	4.51	1.00
Av.	.2727	3.59	.2415	3.57	1.00

to be sure that the complex was not a mixture of the two complexes, $BF_3 \cdot 2NO$ and $BF_3 \cdot 2NO_2$, an attempt was made to form a complex between boron trifluoride and nitric oxide alone but without success. Furthermore no gas, including nitric oxide, was evolved during the addition of the boron trifluoride. Any evolution of nitric oxide would have led to the formation of $BF_3 \cdot 2NO_2$. Hence it may be concluded that the reactants combine in a 1:1 ratio and that the correct formula for the complex is $BF_3 \cdot N_2O_3$.

Nitration Procedure.—The complex was prepared in one of the lower nitroalkanes, and the material to be nitrated was added in about an equimolar amount. The temperature of mixing was adjusted to the expected reactivity of the aromatic compound, being about 0° for a substance such as naphthalene and room temperature for a substance such as *o*-nitrotoluene. The reaction mixture was allowed to stand or, if reaction was slow, it was heated until the insoluble complex disappeared. Boron trifluoride and oxides of nitrogen were evolved during the reaction. Eventually, the mixture was cooled, poured into water, the organic layer separated, dried and distilled or steam distilled. In some cases (*e.g.*, dinitronaphthalene), the product separated as a solid during the reaction. In such cases the solid was filtered off, washed with water and recrystallized.

The isomeric ratio of dinitronaphthalenes (1,5- and 1,8-) formed was determined by the method of Hodgson and Walker.[12] The ratio for the nitrochlorobenzenes and the nitrotoluenes (*o*- and *p*-) was determined by separating the isomers in part by distillation and in part by recrystallization from alcohol.

Diazotization Procedure.—The aromatic amine was added with stirring to a suspension of a 10% molar excess of the complex in dry chloroform at 0–5°. After 30 minutes, 20 ml. of ether was added to destroy the excess complex. The precipitated diazonium salt was filtered off and used as such.

Thermal Decomposition of Diazonium Salts.—The diazonium salt of aniline was prepared as described above except that the solvent was nitrobenzene instead of chloroform. After diazotization was complete the temperature was raised until nitrogen evolution began and fluorobenzene distilled; yield 56%, b.p. 84–85°.

The diazonium salt of *p*-nitroaniline was prepared in chloroform, isolated by filtration and decomposed by heating in the absence of solvent. The yield of *p*-nitrofluorobenzene was 43%, m.p. 26–27°, b.p. 203–205°.

p-Nitroaniline was diazotized in dibutyl phthalate, and the diazonium salt was decomposed by heating. The *p*-nitrofluorobenzene distilled from the reaction mixture amounted to a 5% yield.

Coupling Procedure.—The isolated diazonium salt was added with stirring to a solution of 2-naphthol in 10% sodium hydroxide. The precipitated azo dye was filtered off, washed with water and dried and recrystallized.

Replacement Reactions. (a) **In Aqueous Solvent.**—The isolated diazonium salt was added to a solution of potassium iodide in 50% phosphoric acid and allowed to stand overnight to obtain the corresponding iodide. (b) **In Non-aqueous Solvents (Gomberg–Bachmann Reaction).**—The diazonium salt was prepared in benzene, and 10% molar excess of sodium acetate and 2 ml. of acetic anhydride were added. The reaction mixture was heated with stirring until the evolution of nitrogen ceased and the benzene solution

(10) E. Abel and J. Proisl, *Z. Elektrochem.*, **35**, 712 (1929).

(11) E. Berl and K. Winnacker, *Z. anorg. Chem.*, **212**, 123 (1933).

(12) H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 1346 (1933).

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was filtered. The solid obtained by removal of the benzene was purified according to the methods utilized in the literature references (*cf.* Table II).

Nitrosation Procedure.—Diethyl malonate, 55.0 g. (0.32 mole), was added dropwise at −40° to a suspension of 72.0 g. (0.45 mole) of complex in 300 ml. of nitroethane in a 500-ml. flask equipped with a dropping funnel, stirrer and reflux condenser. After 45 minutes the blue-colored mixture was allowed to warm to room temperature whereupon an exothermic reaction occurred which required cooling to maintain the temperature below 35°. When the reaction subsided, the mixture was washed with 5% sodium carbonate solution and water, dried and distilled. There were obtained: (a) diethyl mesoxalate, 11 g. (28%), b.p. 95–115° (18 mm.), hydrate m.p. 56°; (b) diethyl oximinomalonate, 25 g. (39%), b.p. 170–180° (18 mm.).

A 90% yield of diethyl mesoxalate was obtained by Curtiss[13] using gaseous N_2O_3 on diethyl malonate in the absence of solvent while Cerchez[6] reported a 50–90% yield of diethyl oximinomalonate using N_2O_3 and sodium ethoxide.

Dimethylaniline, 1.2 g., dissolved in 30 ml. of nitroethane, was added to a suspension of complex in nitroethane at 0–2°. The nitroethane was boiled off after washing with 5% sodium carbonate solution giving 1.5 g. of *p*-nitrosodimethylaniline, m.p. 84°.

(13) R. S. Curtiss, *Am. Chem. J.*, **35**, 482 (1906).

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

Triphenylsilyl Phenyl Ketone

BY A. G. BROOK

RECEIVED APRIL 1, 1957

Triphenylsilyl phenyl ketone, the first reported α-silyl ketone, has been prepared. Although not susceptible to thermal rearrangement, it is readily decomposed by base to triphenylsilanol and benzaldehyde. It reacts abnormally with phenylmagnesium bromide and phenyllithium.

The abnormal behavior of substituents (especially halogen) attached to carbon alpha to a silicon atom has been referred to as the "α-silicon effect."[1,2] It is also apparent that functional groups located alpha to a silicon atom display unusual reactivity: the susceptibility of α-silanecarboxylic acids and their esters both to thermal rearrangement and to base-catalyzed decomposition have been reported recently from this Laboratory.[2] It seemed of interest to see whether this enhanced reactivity was present in other α-silylcarbonyl compounds, to which end the ketone, triphenylsilyl phenyl ketone, has been prepared. No α-silyl ketones have previously been reported in the literature, although indirect evidence for the formation of an α-silylaldehyde has been reported.[3]

Triphenylsilyl phenyl ketone was best prepared from triphenylbenzylsilane. Neither permanganate oxidation nor chromic acid oxidation yielded the desired compound, probably because of its instability, and only triphenylsilanol was isolated. Treatment with two equivalents of N-bromsuccinimide led to triphenylsilyl-α,α-dibromobenzylsilane. This compound was converted readily with silver acetate in an acetone–ethanol–water medium to the yellow ketone, m.p. 102–104°, in good yield. A phenylhydrazone derivative was prepared; attempts to prepare the oxime led to the formation of triphenylsilanol and benzaldehyde.

The ketone was also prepared, but in poor yield, by treatment of benzoyl chloride with an ethereal suspension of triphenylsilylpotassium: attempts to prepare it from triphenylsilane and benzoyl chloride using pyridine, aluminum chloride or boron fluoride as catalysts failed, and only tars or starting materials were isolated.

(1) F. C. Whitmore and L. H. Sommer, THIS JOURNAL, **68**, 481 (1946).

(2) A. G. Brook and H. Gilman, *ibid.*, **77**, 2322, 4827 (1955); A. G. Brook and R. J. Mauris, *ibid.*, **79**, 971 (1957).

(3) L. H. Sommer, D. L. Bailey, G. M. Goldberg, C. E. Buck, T. S. Bye, F. J. Evans and F. C. Whitmore, *ibid.*, **76**, 1613 (1954).

That the ketone is colored is of interest since organosilicon compounds are generally colorless, a fact generally attributed to the failure of silicon to participate significantly in resonance hybridization.[4] In the present case the color is even more unusual since the carbon analog, β-benzopinacolone, is colorless. The infrared spectrum of the ketone shows apparently normal absorption for the benzoyl group at about 1575 and 1610 cm.$^{-1}$.

The ketone does not rearrange thermally. When heated to 250°, it was recovered almost quantitatively, and when heated to 365°, although some decomposition occurred, no carbon monoxide was eliminated, and 70% of the material was recovered unchanged. However, the compound is extremely labile in basic medium. If a dilute ethanol solution is treated at room temperature with a few drops of aqueous alkali, the yellow color disappears in a few minutes and triphenylsilanol and benzaldehyde are formed. The same reaction occurs when the compound is chromatographed on activated alumina, although it may be recovered by elution from acid-washed alumina. This decomposition is evidently analogous to the base-catalyzed decomposition of triphenylsilanecarboxylic acid and its esters.

$$Ph_3SiCOPh \xrightarrow{OH^-} Ph_3Si(OH)—CO—Ph \xrightarrow{HOH} Ph_3SiOH + PhCHO + OH^-$$

When triphenylsilyl phenyl ketone was treated with phenylmagnesium bromide, the expected product of addition to the carbonyl group, triphenylsilyldiphenylcarbinol, was not isolated. Instead, the only product isolated was tetraphenylsilane (5%), other than some recovered ketone and triphenylsilanol, presumably formed by decomposition of the ketone when the reaction mixture

(4) For a summary of pertinent evidence and references see H. Gilman and G. E. Dunn, *Chem. Revs.*, **52**, 77 (1953).

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was hydrolyzed. The same product was isolated in 10% yield when phenyllithium was used. This product was probably formed by nucleophilic attack on silicon by the organometallic reagent analogously to the reaction described above, although, as will be shown in a forthcoming publication, the addition product triphenylsilyldiphenylcarbinol is itself decomposed by phenyllithium forming tetraphenylsilane in high yield.

$$Ph_3SiCOPh + PhLi \longrightarrow Ph_3-\overset{\curvearrowright}{Si}-COPh \longrightarrow \begin{matrix} \\ \vdots \\ Ph^- \ Li^+ \end{matrix}$$

$$Ph_4Si + \text{fragments}$$

From this and related work it seems probable that all α-silylcarbonyl compounds will be susceptible to base-catalyzed hydrolysis in which the silicon–carbonyl bond is broken.

Experimental[5]

Triphenyl-α,α-dibromobenzylsilane.—To 4.85 g. (0.0138 mole) of triphenylbenzylsilane[6] in 50 ml. of carbon tetrachloride was added 5.3 g. (0.030 mole) of N-bromosuccinimide. The mixture was refluxed for 18 hr., cooled and 3.05 g. (110%) of crude succinimide, m.p. 117–122°, was filtered off. The filtrate was evaporated to dryness under reduced pressure and the gummy solid recrystallized from ethyl acetate to yield 4.85 g. (70%) of crude white triphenyl-α,α-dibromobenzylsilane, m.p. 112–116°. One additional crystallization raised the melting point to 119–120°.

Anal. Calcd. for $C_{25}H_{20}SiBr_2$: Si, 5.51; Br, 31.5. Found: Si, 5.53; Br (as AgBr), 31.7.

Triphenylsilyl Phenyl Ketone. A. From Triphenyl-α,α-dibromobenzylsilane.—A mixture of 3.0 g. (0.059 mole) of triphenyl-α,α-dibromobenzylsilane and 2.0 g. (0.12 mole) of silver acetate in 40 ml. of ethanol, 15 ml. of water and 30 ml. of acetone was stirred at room temperature for 15 hr. The purplish-gray precipitate was filtered off and washed with acetone to yield 2.31 g. (103%) of silver bromide. The combined filtrates were evaporated to dryness under reduced pressure at room temperature to yield 1.99 g. of yellow powder, m.p. 90–99°. This was twice recrystallized from absolute ethanol to yield 1.67 g. (78%) of yellow needles, m.p. 102–103°.

Anal. Calcd. for $C_{25}H_{20}OSi$: C, 82.4; H, 5.53; Si, 7.70. Found: C, 82.7; H, 5.50; Si, 7.63.

When silver nitrate was used to remove the bromine, the same compound was obtained, but considerable decomposition occurred as indicated by the formation of triphenylsilanol and benzaldehyde (see below).

B. **From Triphenylsilylpotassium and Benzoyl Chloride.**[7]—To a solution of 2.81 g. (0.02 mole) of benzoyl chloride in 50 ml. of dry ether at 0° was added over an hour a suspension of 0.02 mole of amalgamated triphenylsilylpotassium in 100 ml. of ether. The green suspension was stirred for 14 hr. and then was hydrolyzed with water. Insoluble hexaphenyldisilane, m.p. 353–355°, weighing 1.66 g. (33%) was filtered off and identified by mixed melting point with an authentic specimen.

The ether layer, dried over sodium sulfate, was concentrated and then distilled under reduced pressure (1 mm.). There was isolated 0.13 g. (6%) of benzoyl chloride and 0.90 g. of a yellow solid boiling at 130–170°. Several recrystallizations from carbon tetrachloride and petroleum ether (b.p. 60–70°) yielded 0.28 g. (4%) of triphenylsilyl phenyl ketone, m.p. 102–104°, whose identity was confirmed by a mixed melting point with the material described above.

A phenylhydrazone derivative was prepared by refluxing a mixture of 0.5 g. (0.00137 mole) of the ketone in 8 ml. of ethanol with 0.18 g. of phenylhydrazine and 5 drops of glacial acetic acid for 5 minutes. During this time the yellow color of the original solution faded. On cooling white crystals were deposited which on recrystallization from 1:1 benzene–ethanol yielded 0.35 g. (56%) of almost colorless crystals, m.p. 150–151.5°.

Anal. Calcd. for $C_{31}H_{26}N_2Si$: C, 82.0; H, 5.78; N, 6.17. Found: C, 82.1; H, 5.77; N, 6.33.

Attempts to prepare the oxime by treatment of the ketone with hydroxylamine hydrochloride and pyridine in ethanol–water caused rapid fading of the yellow color. The odor of benzaldehyde was noticeable and a small amount of triphenylsilanol, m.p. 150–151°, was the only product isolated.

Attempted Thermal Rearrangement of Triphenylsilyl Phenyl Ketone.—A 0.5-g. sample of the ketone was heated in a small test-tube to 250° and held at this temperature for 5 minutes. No carbon monoxide[8] was evolved, but a faint odor of benzaldehyde was detected. After cooling the yellow solid melted at 100–102°, and one recrystallization from absolute ethanol gave 0.42 g. (84%) of ketone which melted at 102–103°.

When a 0.1-g. sample was heated at 365° for 10 minutes, no carbon monoxide was evolved, but a strong odor of benzaldehyde was observed and the color of the liquid darkened. The crude material melted at 88–93°, but one recrystallization from ethanol yielded 0.07 g. (70%) of ketone, m.p. 101–102°, identified by mixed melting point with an authentic specimen.

Reaction of Triphenylsilyl Phenyl Ketone with Alkali.—When 0.5 g. (0.00137 mole) of the ketone, dissolved in acetone (or ethanol), was treated with a few drops of 10% aqueous sodium hydroxide at room temperature, the yellow color rapidly faded (2–5 minutes). The odor of benzaldehyde was noticeable. When the solution was drowned in water, a white precipitate formed. After recrystallization from petroleum ether (b.p. 90–100°), this 0.34 g. (89%) of triphenylsilanol melted at 150–152°, and a mixed melting point with an authentic sample was not depressed.

To isolate the benzaldehyde, a hydrolyzed ethanol solution of the ketone was drowned in water and extracted 3 times with ether. The ether solution was treated with 1 ml. of phenylhydrazine, several drops of glacial acetic acid and 10 ml. of ethanol. The solution was boiled to remove the ether and then cooled. Fractional crystallization of the reaction mixture yielded a total of 0.23 g. (85%) of crude benzaldehyde phenylhydrazone, which after recrystallization from ethanol yielded 0.19 g. (70%) of pale yellow needles, m.p. 154–156°, which were identified by mixed melting point with an authentic specimen, m.p. 156–157°. In addition, 0.03 g. (8%) of triphenylsilanol, m.p. 150–152°, was isolated.

Reaction of Triphenylsilyl Phenyl Ketone with Phenylmagnesium Bromide and Phenyllithium.—When 2.0 g. (0.0055 mole) of triphenylsilyl phenyl ketone in 45 ml. of ether was treated with 2.5 ml. of 2.16 *N* phenylmagnesium bromide (0.0055 mole) no apparent change occurred until after 1 hr. when a white precipitate formed. The mixture was stirred for 18 hr. but still gave a positive Color Test I.[9] It was then hydrolyzed with water and acid. The yellow ether layer was worked up yielding a yellow oil which eventually partially crystallized. Recrystallization from benzene gave 0.1 g. (5%) of tetraphenylsilane, m.p. 233–235°, identified by mixed melting point. The residual oil was chromatographed on acid-washed alumina, eluting with petroleum ether (b.p. 60–70°), and although some decomposition occurred as evidenced by the loss of color, 0.18 g. (9%) of the ketone, m.p. 102–104°, was eventually isolated. Finally 0.23 g. (15%) of triphenylsilanol, m.p. 150–152°, was isolated and identified by mixed melting point.

When 2.0 g. (0.0055 mole) of the ketone in 30 ml. of dry ether was treated with 15 ml. of 0.5 *N* phenyllithium (0.0075 mole), the first few drops added caused a color change to orange and then to orange-red. A white solid then precipitated. The mixture was refluxed for 8 hr. at which time a positive Color Test I was obtained. The reaction mixture was poured into cold dilute acid. The only products isolated were 0.64 g. (42%) of crude triphenylsilanol, m.p. 135–145°, which was recrystallized from petroleum ether (b.p. 90–100°) to yield 0.32 g. (21%) of triphenylsilanol,

(5) Reactions involving organometallic reagents were carried out in a dry, oxygen-free nitrogen atmosphere.

(6) H. Gilman, A. G. Brook and L. S. Miller, THIS JOURNAL, **75**, 3757 (1953).

(7) This run was carried out by Saul Wolfe in this Laboratory.

(8) R. Nowicki, *Chem. Ztg.*, **35**, 1120 (1911).

(9) H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).

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m.p. 149–151°, and 0.28 g. (15%) of crude tetraphenylsilane, m.p. 193–208°, which after recrystallization from benzene gave 0.18 g. (10%) of pure tetraphenylsilane, m.p. 230–232°, all products identified by mixed melting point.

Acknowledgment.—The author is indebted to N. Wolfish and M. Gold for technical assistance, to Dr. Henry Gilman and the Institute for Atomic Research, Iowa State College, for the infrared spectrum and to the National Research Council of Canada for a grant supporting this research.

TORONTO, CANADA

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

10-(3-Dimethylaminopropyl)-2-(Trifluoromethyl)-phenothiazine Hydrochloride (VESPRIN[1]) and Related Compounds. I

BY HARRY L. YALE, FRANCIS SOWINSKI AND JACK BERNSTEIN

RECEIVED MARCH 18, 1957

The thionation of 3-(trifluoromethyl)-diphenylamine has yielded 2- and 4-(trifluoromethyl)-phenothiazine. These two nuclei have been allowed to react with various dialkylaminoalkyl chlorides in the presence of sodamide to give 10-dialkylaminoalkyl-2- and 4-(trifluoromethyl)-phenothiazine. Hydrogen peroxide has converted these compounds to various oxygenated derivatives. An improved procedure is described for the preparation of 3-(trifluoromethyl)-phenothiazine. Since this nucleus did not react with dimethylaminopropyl chloride in the presence of sodamide, an indirect procedure was used to prepare the 10-(3-dimethylaminopropyl) derivative.

We have for several years been interested in variously substituted phenothiazine derivatives[2] and wish now to report on a series of 10-dialkylaminoalkyl-2-, -3- and -4-(trifluoromethyl)-phenothiazines and their oxygenated derivatives. Several of these compounds have shown good specificity and high potency as ataractic agents in laboratory animals[3] and are now undergoing clinical evaluation.

The thionation of 3-(trifluoromethyl)-diphenylamine should lead to the formation of both 2-(trifluoromethyl)-phenothiazine and 4-(trifluoromethyl)-phenothiazine. From such a reaction, however, Smith[4] isolated only one (trifluoromethyl)-phenothiazine. This compound showed a deep band in the infrared at 12.17 μ, an absorption band not seen in the spectrum of phenothiazine itself. Since the infrared spectra of asymmetrical trisubstituted benzenes show a characteristic deep band in the region 12.0–12.5 μ while vicinal trisubstituted benzenes show a characteristic deep band in the region 12.5–13.15 μ, Smith concluded that his product was 2-(trifluoromethyl)-phenothiazine. This method of differentiating isomers in monosubstituted phenothiazines received additional support in the observation of Roe and Little[5] that 3-(trifluoromethyl)-phenothiazine, prepared by an unambiguous synthesis, showed a deep band in the infrared at 12.2 μ.

The work of Charpentier[6] has demonstrated that the thionation of 3-substituted diphenylamines, *e.g.*, 3-methyldiphenylamine, leads to 2- and 4-substituted phenothiazines; the less soluble, higher melting isomer (m.p. 187–188°) when heated with copper bronze gave 2-methylcarbazole, while the more soluble, lower melting isomer (m.p. 114–115°) gave 4-methylcarbazole.

We have re-examined the thionation of 3-(trifluoromethyl)-diphenylamine, and have isolated both 2-(trifluoromethyl)-phenothiazine, m.p. 188–189°, in 45% yield, and the hitherto unreported 4-(trifluoromethyl)-phenothiazine, m.p. 72–73° in 32% yield. It is of interest that the latter isomer showed a strong band at 12.7 μ, as anticipated, since it corresponds to a *vicinal* substituted benzene.

3-(Trifluoromethyl)-phenothiazine was prepared in one step in 52% yield by Roe and Little[5] *via* the Smiles rearrangement of 2-formamido-2′-nitro-4′-(trifluoromethyl)-diphenyl sulfide. Based on our own experience, we prefer the two step modification of the Smiles rearrangement, which employed the *2-acetamido derivative* and which gave a 91% yield over-all.

The reactions of 2- and 4-(trifluoromethyl)-phenothiazine with various dialkylaminoethyl chlorides and dialkylaminopropyl chlorides in toluene or xylene, in the presence of sodamide, gave the desired 10-substituted derivatives in good yields. The reaction of 3-(trifluoromethyl)-phenothiazine with dimethylaminopropyl chloride under the same conditions was unsuccessful. Instead of the usual dark brown colored reaction mixtures, deep violet colored solutions were obtained, which, even after prolonged reflux periods, when cooled and hydrolyzed with water became colorless and when worked up in the usual manner yielded only unreacted 3-(trifluoromethyl)-phenothiazine. It became necessary to use the indirect procedure outlined below which gave the desired product.

2-(Trifluoromethyl)-10-phenothiazinepropionitrile[7] and lithium aluminum hydride gave 10-(3-aminopropyl)-2-(trifluoromethyl)-phenothiazine.

The preparation of 10-(4-dimethylaminobutyl)-2-(trifluoromethyl)-phenothiazine followed the sequence of reactions shown below, employing 4-

(1) VESPRIN is a trademark of the Olin Mathieson Chemical Corporation.

(2) H. L. Yale, THIS JOURNAL, **77**, 2270 (1955).

(3) The tranquilizing activity of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine hydrochloride was reported by J. C. Burke, H. L. Yale, G. L. Hassert and J. P. High and by J. J. Piala, J. P. High, K. Greenspan and J. C. Burke at the 1956 Meeting of The American Society for Pharmacology and Experimental Therapeutics at French Lick Springs, Indiana, November 8–10, 1956.

(4) N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).

(5) A. Roe and W. F. Little, *ibid.*, **20**, 1577 (1955), have discussed the infrared spectra of this compound as well as a number of other fluorine substituted phenothiazines.

(6) P. Charpentier, P. Gailliot, R. Jacob, J. Gaudechon and J. Buisso, *Compt. rend.*, **235**, 59 (1952).

(7) N. L. Smith, *J. Org. Chem.*, **16**, 415 (1951).

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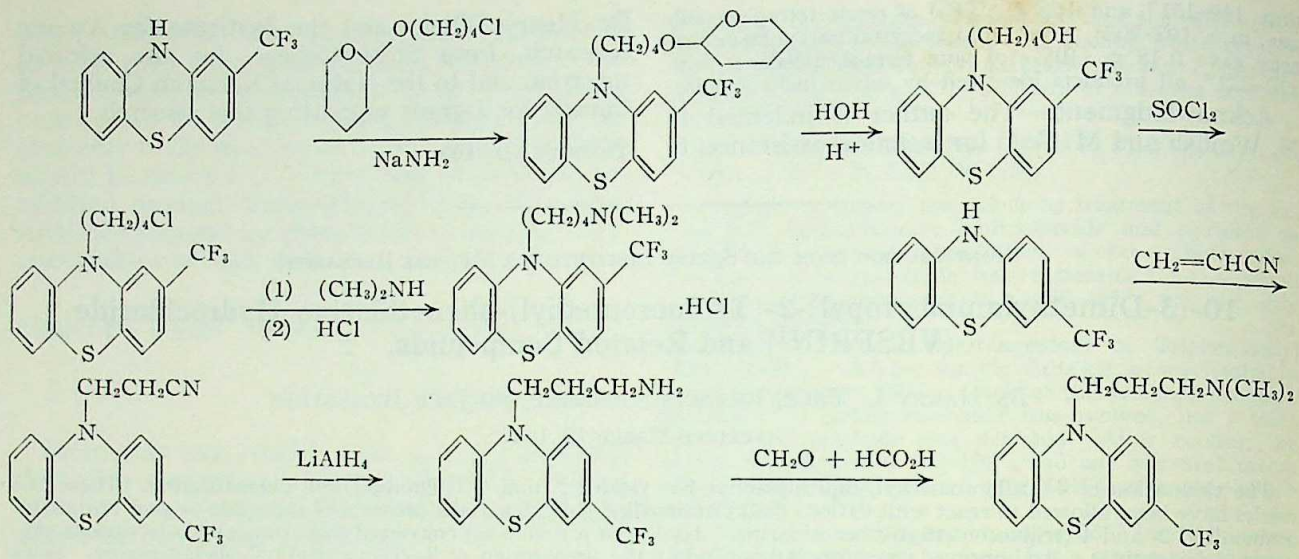

chlorobutyl-2-tetrahydropyranyl ether as the side chain precursor; several of the intermediates were high boiling viscous oils which were difficult to obtain analytically pure, although the final product, as the hydrochloride, was easily purified.[8] It was observed that during the reaction of thionyl chloride with 10-(4-hydroxybutyl)-2-(trifluoromethyl)-phenothiazine some cleavage to 2-(trifluoromethyl)-phenothiazine occurred. This is not surprising since Charpentier[9] found that 10-(2-dimethylaminopropyl)-phenothiazine and boiling 48% hydrobromic acid readily gave phenothiazine and 2-dimethylaminopropyl bromide, hydrobromide.

These 10-dialkylaminoalkyl-2- and 4-(trifluoromethyl)-phenothiazines were obtained as viscous

TABLE I

10-DIALKYLAMINOALKYL-2-(TRIFLUOROMETHYL)-PHENOTHIAZINES AND THEIR DERIVATIVES

Side chain	Mol. formula	Yield, %	Boiling point °C.	Mm.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Base										
$-(CH_2)_3NH_2$	$C_{16}H_{15}F_3N_2S$	42	176–178	0.6			4.31[a]			4.30[a]
$-(CH_2)_2N(CH_3)_2$	$C_{17}H_{17}F_3N_2S$	84	[b]							
$-(CH_2)_3N(CH_3)_2$	$C_{18}H_{19}F_3N_2S$	93	162–164	.4			7.94			8.16
$-CH_2CH(CH_3)N(CH_3)_2$[c]	$C_{18}H_{19}F_3N_2S$	20	166–169	.3			7.94			8.00
$-(CH_2)_4N(CH_3)_2$	$C_{19}H_{21}F_3N_2S$	82	[b]							
$-(CH_2)_2N(C_2H_5)_2$	$C_{19}H_{21}F_3N_2S$	56	171–173	.5	62.27	5.78		62.16	5.80	
$-(CH_2)_3N(C_2H_5)_2$	$C_{20}H_{23}F_3N_2S$	73	167–170	.4	63.16	6.09		63.18	6.13	
$-(CH_2)_3-N<\begin{matrix}CH_2-CH_2\\ \vert\quad\vert\\ CH_2-CH_2\end{matrix}$	$C_{20}H_{21}F_3N_2S$	100	[b]		63.46	5.59		63.92	5.70	
Salts										
Mol. formula			M.p., °C.							
$C_{16}H_{15}F_3N_2S\cdot HCl$[d]		48	161–162		53.25	4.47	7.76	53.13	4.70	7.82
$C_{17}H_{17}F_3N_2S\cdot HCl$[e]		70	245–246		54.76	4.32	7.51	54.83	4.68	7.39
$C_{18}H_{19}F_3N_2S\cdot HCl$[e,f]		61	173–174		55.59	5.18	7.20	55.53	5.33	7.14
$C_{18}H_{19}F_3N_2S\cdot HCl$[g]		41	224–225 dec.		55.59	5.18	7.20	55.53	5.36	7.38
$C_{19}H_{21}F_3N_2S\cdot HCl$[h]		48	153–154		56.64	5.50	6.95	56.89	5.42	6.89
$C_{19}H_{21}F_3N_2S\cdot HCl$[i]		74	160–162		56.64	5.50	6.95	56.36	5.58	6.91
$C_{20}H_{23}F_3N_2S\cdot HCl$[e]		79	163–165		57.62	5.56	6.72	57.44	5.94	7.07
$C_{20}H_{23}F_3N_2S\cdot C_2H_2O_4$[j]		100	192–194 dec.				5.96			5.96
$C_{20}H_{21}F_3N_2S\cdot HCl$[k]		32	173–174		57.89	5.34	6.75	58.15	5.35	6.75

[a] Titratable N with $HClO_4$ in glacial acetic acid. [b] Base was not distilled but converted directly to hydrochloride. [c] The 2-dimethylaminopropyl side chain is tentatively assigned to this compound by analogy with similar compounds prepared by P. Charpentier, *et al.*, *Compt. rend.*, **225**, 306 (1947); **232**, 415 (1951), by the reaction of phenothiazine with 1-dimethylamino-2-chloropropane. As shown by Charpentier and also by N. D. Edge and W. R. Wragg, *J. Pharm. Pharmacol.*, **5**, 279 (1953), this reaction leads to two isomers. The isomer formed in the larger quantity has the 2-dimethylaminopropyl side chain and can be separated from the isomeric product with the 2-dimethylamino-1-methylethyl side chain by fractional crystallization of their hydrochlorides. The less soluble hydrochloride has the 2-dimethylaminopropyl side chain. [d] Recrystallized successively from dry chlorobenzene and from absolute isopropyl alcohol. [e] Recrystallized from dry chlorobenzene. [f] Recrystallized from acetonitrile. [g] Recrystallized from absolute ethanol–ether. [h] Recrystallized from dry toluene. [i] Recrystallized from dry benzene. [j] Recrystallized from water. [k] Recrystallized from dry xylene.

(8) This procedure is very briefly outlined in U. S. Patent 2,645,640 (July 14, 1953) as the method used to prepare 2-chloro-10-(4-dimethylaminobutyl) phenothiazine.

(9) P. Charpentier, P. Gailliot and J. Gaudechon, *Compt. rend.*, **232**, 2232 (1951).

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TABLE II

10-DIALKYLAMINOALKYL-3-(TRIFLUOROMETHYL)-PHENOTHIAZINES AND THEIR DERIVATIVES

Side chain	Mol. formula	Yield, %	Boiling point °C.	Mm.	Analyses, % Calcd. C	H	N	Found C	H	N
Base										
$-(CH_2)_3NH_2$	$C_{16}H_{15}F_3N_2S$	33	175–178	0.5			4.31[a]			4.64
$-(CH_2)_3N(CH_3)_2$	$C_{18}H_{19}F_3N_2S$	35	168–171	.3	61.34	5.43		62.11	5.41	
Salts										
Mol. formula			M.p., °C.							
$C_{18}H_{19}F_3N_2S·HCl$[b]		66	140–141		55.59	5.18	7.20	55.68	5.35	7.32

[a] Titratable N with $HClO_4$ in glacial acetic acid. [b] Recrystallized from dry toluene.

TABLE III

10-DIALKYLAMINOALKYL-4-(TRIFLUOROMETHYL)-PHENOTHIAZINES AND THEIR DERIVATIVES

Side chain	Mol. formula	Yield, %	Boiling point °C.	Mm.	Analyses, % Calcd. C	H	N	Found C	H	N
Base										
$-(CH_2)_3N(CH_3)_2$	$C_{18}H_{19}F_3N_2S$	79	169–172	0.3	61.34	5.43		61.27	5.16	
$CH_2CH(CH_3)N(CH_3)_2$	$C_{18}H_{19}F_3N_2S$	77	172–175	.4	61.34	5.43		62.38	5.37	
$-(CH_2)_3-N<$ (CH2—CH2 / CH2—CH2)	$C_{20}H_{21}F_3N_2S$	41	176–179	.3	63.46	5.59		63.81	5.63	
Salts										
Mol. formula			M.p., °C.							
$C_{18}H_{19}F_3N_2S·HCl$[a]		61	146–147		55.59	5.18	7.20	55.53	5.10	7.41
$C_{18}H_{19}F_3N_2S·HCl$[b]		78	196–197		55.59	5.18	7.20	55.58	5.09	6.93
$C_{20}H_{21}F_3N_2S·HCl$[c]		35	148–149		57.89	5.34	6.75	57.99	5.36	6.98

[a] Recrystallized from dry chlorobenzene–ether. [b] Recrystallized from dry chlorobenzene. [c] Recrystallized from dry acetone.

liquids which could be distilled *in vacuo* without decomposition; they formed crystalline hydrochlorides and acid oxalates. Their properties along with analytical data are summarized in Tables I, II and III.

It was of interest that 10-dimethylaminopropyl-2-(trifluoromethyl)-phenothiazine hydrochloride showed a deep band at 12.2 μ, 10-dimethylaminopropyl-3-(trifluoromethyl)-phenothiazine hydrochloride a deep band at 12.3 μ and 10-dimethylaminopropyl-4-(trifluoromethyl)-phenothiazine a deep band at 12.6 μ.

The 10-dialkylaminoalkyl-2- and 4-(trifluoromethyl)-phenothiazines were converted to the **5-oxide derivatives** by refluxing the oxalate in ethanol with one molar equivalent of 30% hydrogen peroxide. The N,5-dioxides were obtained by refluxing the base in ethanol with two molar equivalents of 30% hydrogen peroxide. To prepare the 5,5-dioxides, the 2- and 4-(trifluoromethyl)-phenothiazines were first converted to the **10-acetyl derivatives** and the latter in glacial acetic acid were oxidized with an excess of 30% hydrogen peroxide; during the latter step, as was observed previously,[2] deacetylation also occurred and the product obtained was 2- or 4-(trifluoromethyl)-phenothiazine-5,5-dioxide. These 5,5-dioxides, either because of their insolubility or lack of reactivity under the usual condensation conditions, gave low yields of the 10-3-dimethylaminopropyl derivatives.

In the ultraviolet, 10-dimethylaminopropyl-2-(trifluoromethyl)-phenothiazine hydrochloride showed two maxima at 255 and 305 mμ ($E^{1\%}_{1cm}$ 700, 90); four maxima, however, were shown by the corresponding 5-oxide, 235, 278, 302 and 348 mμ ($E^{1\%}_{1cm}$ 608, 256, 177, 116) and the corresponding N,5-dioxide 233, 274, 303 and 348 mμ ($E^{1\%}_{1cm}$ 548, 257, 173, 119); in the infrared, the latter two compounds showed deep bands at 9.8 μ, which is attributed to the S → O group.

The pertinent data on the oxygenated 10-dialkylaminoalkyl-(trifluoromethyl)-phenothiazines are summarized in Table IV.

Acknowledgment.—The microanalyses were carried out by Mr. Joseph F. Alicino and his associates. The infrared and ultraviolet spectra were determined by Dr. Nettie Coy and her associates.

Experimental Part

All melting and boiling point temperatures are uncorrected.

2- and 4-(Trifluoromethyl)-phenothiazines.—A mixture of 506 g. (2.14 moles) of 3-(trifluoromethyl)-diphenylamine, 134 g. (4.18 moles) of sulfur and 12.9 g. of iodine were fused at 150–160° for 3.5 hr. and the hot melt poured into 3.5 l. of warm toluene. The toluene solution was heated to boiling, treated with Hyflo and filtered hot. The filtrate was cooled to −5° and filtered to give 216 g. of 2-(trifluoromethyl)-phenothiazine, m.p. 183–185; concentration of the mother liquors by one-half and cooling gave an additional 45 g. of product. The over-all yield was 261 g. (45%). The filtrate from the second crop was freed of toluene and the residue distilled. The viscous distillate, b.p. 172–175° (0.5 mm.), solidified on cooling. It was recrystallized from ligroin to give 185 g. (32% yield) of 4-(trifluoromethyl)-phenothiazine, m.p. 72–73°.

Anal. Calcd. for $C_{13}H_8F_3NS$: C, 58.41; H, 3.01. Found: C, 58.84; H, 3.08.

10-(3-Dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine Hydrochloride.—The following description represents a typical preparation. A mixture of 26.7 g. (0.1 mole) of 2-(trifluoromethyl)-phenothiazine, 4.7 g. (0.12 mole) of sodamide, 14.6 g. (0.12 mole) of 3-dimethylaminopropyl chloride and 500 ml. of dry xylene was stirred and refluxed 17 hr. and the hot solution filtered. The filtrate

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TABLE IV

OXYGENATED 10-DIALKYLAMINOALKYL-(TRIFLUOROMETHYL)-PHENOTHIAZINES AND THEIR DERIVATIVES

Side chain	Position of CF_3	Position of O	Mol. formula	Yield, %	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$-(CH_2)_3N(CH_3)_2$	2	5	$C_{18}H_{19}F_3N_2OS\cdot C_2H_2O_4$[a,b]	85	213–215	52.39	4.62	6.11	52.78	4.57	6.15
$-(CH_2)_3N(CH_3)_2$	2	N,5	$C_{18}H_{19}F_3N_2O_2S\cdot 3H_2O$[c]	68	135–137	49.30	5.75	6.39	49.04	5.74	6.74
$-(CH_2)_3N(CH_3)_2$	4	5	$C_{18}H_{19}F_3N_2OS\cdot HCl\cdot H_2O$[d]	36	150–152 d.	51.11	5.24	6.62	51.32	5.08	6.43
$-(CH_2)_3N(C_2H_5)_2$	2	5	$C_{20}H_{23}F_3N_2OS\cdot C_2H_2O_4$[e,f]	36	229–230 d.			5.76			5.73
$-(CH_2)_3N(C_2H_5)_2$	2	N,5	$C_{20}H_{23}F_3N_2O_2S\cdot HCl$[g]	48	182–184 d.	53.50	5.17	6.24	53.79	4.99	6.21
$-(CH_2)_3N(CH_3)_2$	4	5,5	$C_{18}H_{19}F_3N_2O_2S\cdot HCl$[h,i]	5	240–241	51.36	4.79	6.65	51.68	4.68	6.72

[a] Recrystallized from 95% ethanol. [b] Free base, m.p. 99–100°. *Anal.* Calcd.: C, 58.68; H, 5.20. Found: C, 58.40; H, 5.25. Hydrochloride, m.p. 209–210°. *Anal.* Calcd.: C, 53.39; H, 4.98; N, 6.92. Found: C, 53.53; H, 5.06; N, 6.87. [c] Recrystallized from methyl ethyl ketone. [d] Recrystallized from isopropyl alcohol–ether. [e] Recrystallized from butanol. [f] Free base, m.p. 125–127°. *Anal.* Calcd.: C, 60.58; H, 5.85; N, 7.07. Found: C, 61.01; H, 5.73; N, 7.10. [g] Recrystallized from glacial acetic acid–ether. [h] Recrystallized from acetonitrile and ether. [i] Free base, m.p. 164–165°. *Anal.* Calcd.: C, 56.38; H, 4.99. Found: C, 56.57; H, 4.88.

was concentrated *in vacuo*, the residue was taken up in 400 ml. of ether and the ether solution was extracted with 200, 100 and 100 ml. of 5% hydrochloric acid. The hydrochloric acid extracts were washed with ether, made strongly alkaline with 40% aqueous sodium hydroxide and the base extracted with ether; the ether extracts were dried, concentrated and distilled to give 30 g. (85% yield) of product, b.p. 176° (0.7 mm.), $n^{23}D$ 1.5780.

The above distilled base in 300 ml. of dry ether was cooled and treated with a slight excess of ethereal HCl. The precipitated **hydrochloride** was filtered and dried; it weighed 34.0 g., m.p. 165–168° dec. A recrystallization from xylene gave 26.5 g. (69% yield) of product, m.p. 172–174° dec.

10-(3-Dimethylaminopropyl)-3-(trifluoromethyl)-phenothiazine Hydrochloride. 2-[2-Nitro-4-(trifluoromethyl)-phenylthio]-acetanilide.—A mixture of 23.7 g. (0.075 mole) of 2-[2-nitro-4-(trifluoromethyl)-phenylthio]-aniline, 35 ml. of acetic anhydride and 2.5 ml. of pyridine was heated on the steam-bath for 1.5 hr. and then concentrated *in vacuo* to a small volume. The product which crystallized on cooling was filtered, washed consecutively with water, 5% aqueous sodium bicarbonate and water and dried to give 24.9 g. (93% yield) of the **acetanilide**, m.p. 148–149°. An analytical sample, from isopropyl alcohol, melted at 148–149°.

Anal. Calcd. for $C_{15}H_{11}F_3N_2O_3S$: C, 50.55; H, 3.08. Found: C, 50.88; H, 3.11.

To a nitrogen diffused solution of 22 g. (0.33 mole) of 85% potassium hydroxide in 375 ml. of 95% ethanol was added 3.0 l. of acetone, the mixture was stirred and again diffused with nitrogen, 119.5 g. (0.33 mole of the **acetanilide** was added and the mixture distilled rapidly from the steam-bath. The residual material was treated with 1.8 l. of ether and 275 ml. of water, the ether layer was separated, washed with saturated sodium chloride solution, dried and concentrated. The **10-acetyl-3-(trifluoromethyl)-phenothiazine** was isolated as a viscous *gum*. This gum was dissolved in a mixture of 250 ml. of 95% ethanol and 50 ml. of concentrated hydrochloric acid and the solution refluxed for 2 hr. The cooled mixture was filtered to give 80 g. of **3-(trifluoromethyl)-phenothiazine**, m.p. 213–215° (lit.[5] m.p. 217–218°). The filtrate when concentrated to dryness gave 6 g. of additional material, m.p. 214–216°. The combined yield was 86 g. (96%). A mixture of 46.8 g. (0.175 mole) of 3-(trifluoromethyl)-phenothiazine, 125 ml. of acrylonitrile and 2 ml. of 40% Triton B was warmed to initiate reaction and then refluxed for 1 hr. The solution was concentrated to a small volume, cooled and the solid filtered. The crude product was recrystallized from acetone to give 34.7 g. (62% yield) of 3-(trifluoromethyl)-10-phenothiazinepropionitrile, m.p. 110–111°.[10]

Anal. Calcd. for $C_{16}H_{11}F_3N_2S$: N, 8.74. Found: N, 9.10.

To an ice-cooled slurry of 6.4 g. (0.17 mole) of lithium aluminum hydride in 500 ml. of anhydrous ether, with stirring, was added, in portions, 27.3 g. (0.085 mole) of 3-(trifluoromethyl)-10-phenothiazinepropionitrile. Subsequently, the mixture was refluxed and stirred for 1 hr., cooled and decomposed by the addition of 25 ml. of water and 10 ml. of 20% aqueous sodium hydroxide. The ether solution was separated, dried, concentrated and distilled to give 9.3 g. (33% yield) of **10-(3-aminopropyl)-3-(trifluoromethyl)-phenothiazine**. To the **3-aminopropyl derivative**, 9.2 g. (0.028 mole) in 14.7 g. (0.28 mole) of formic acid, was added 7 g. (0.086 mole) of 37% formalin and the mixture heated in an oil-bath at 90–100° for 8 hr. The mixture was cooled, filtered and the filtrate treated with 30.4 ml. of 0.955 *N* aqueous hydrochloric acid. The mixture was concentrated to dryness *in vacuo*, the residue was dissolved in 100 ml. of water and then made alkaline with an excess of 20% aqueous sodium hydroxide. **The base** was isolated, distilled and converted to the hydrochloride in the manner described above.

10-(4-Dimethylaminobutyl)-2-(trifluoromethyl)-phenothiazine Hydrochloride. 10-[4′-(2″-Tetrahydropyranoloxy)-1′-butyl]-2-(trifluoromethyl)-phenothiazine.—A mixture of 66.8 g. (0.25 mole) of 2-(trifluoromethyl)-phenothiazine, 11.7 g. (0.30 mole) of sodamide and 750 ml. of dry xylene were refluxed for 2 hr. The reaction mixture was cooled, and a solution of 58.6 g. (0.30 mole) of 2-tetrahydropyranyl-4-chlorobutyl ether[8] in 250 ml. of dry xylene was added dropwise. The mixture was then refluxed for 3.5 hr., filtered hot and the xylene removed *in vacuo*. The residue was extracted with 500 ml. of ether, the filtered ether extracts were concentrated and the residue distilled to give 97.8 g. (96% yield) of crude product, b.p. 200–202° (0.2 mm.). *Anal.* Calcd. for $C_{22}H_{24}F_3NOS$: C, 64.84; H, 5.93. Found: C, 62.44; H, 5.67. **10-(4-Hydroxybutyl)-2-(trifluoromethyl)-phenothiazine.**—A solution of 97.8 g. (0.24 mole) of the **pyranyl derivative**, 25 ml. of concentrated hydrochloric acid and 1 l. of 75% ethanol was refluxed for 1 hr. The alcohol was then distilled from the steam-bath and the residue extracted with ether. The dried ether extracts were concentrated and distilled to give 64.8 g. (79% yield) of product, b.p. 178–181° (0.3 mm.). *Anal.* Calcd. for $C_{17}H_{16}F_3NOS$: C, 60.10; H, 4.75. Found: C, 60.93; H, 4.93. **10-(4-Chlorobutyl)-2-(trifluoromethyl)-phenothiazine.** To a refluxing solution of 9.8 g. (0.03 mole) of 10-(4-hydroxybutyl)-2-(trifluoromethyl)-phenothiazine in 65 ml. of dry benzene was added dropwise 3.6 g. (0.03 mole) of thionyl chloride. The mixture was then refluxed for 1 hr. and poured into 50 ml. of ice-water. The mixture was treated with an excess of solid sodium bicarbonate, the organic layer was separated and the aqueous layer extracted with ether. The combined dried extracts were then concentrated and the residue distilled to give 6.6 g. of crude product, b.p. 182–185° (0.7 mm.), which was contaminated with some (2-trifluoromethyl)-phenothiazine. This crude distillate was dissolved in 25 ml. of boiling hexane and the solution cooled; the (2-trifluoromethyl)-phenothiazine was filtered off. Concentration of the filtrate gave 5.2 g. (48% yield) of crude product suitable for the next step.

Anal. Calcd. for $C_{17}H_{15}ClF_3NS$: Cl, 9.90. Found: Cl, 7.69.

10-(4-Dimethylaminobutyl)-2-(trifluoromethyl)-phenothiazine Hydrochloride.—A solution of 5.0 g. of crude 10-(4-chlorobutyl)-2-(trifluoromethyl)-phenothiazine in 10 ml. of anhydrous dimethylamine was kept in a sealed tube for seven days at room temperature. The tube was opened, the excess dimethylamine allowed to evaporate and the pasty residue dissolved in 50 ml. of 10% hydrochloric acid. This

(10) This cyanoethylation procedure has been used by Smith, ref. 7, in the reaction between 2-(trifluoromethyl)-phenothiazine and acrylonitrile.

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acid solution was extracted with three 50-ml. portions of ether, treated with an excess of 20% potassium hydroxide and the liberated base extracted with ether. Concentration of the ether extracts gave 4.2 g. (82% yield) of **base** as a viscous oil. The oil, in ether, was converted to the hydrochloride in the usual manner.

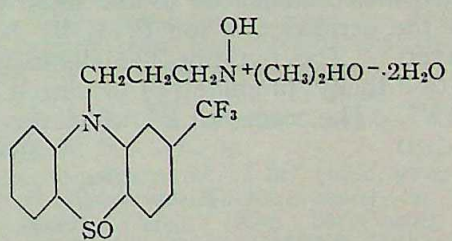
10-(3-Diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine 5-Oxide. 10-(3-Diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine Oxalate.—To 11.4 g. (0.03 mole) of 10-(3-diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine in 100 ml. of 95% ethanol was added a solution of 2.7 g. (0.03 mole) of anhydrous oxalic acid in 10 ml. of 95% ethanol; the oxalate separated directly and was filtered to give 14.1 g. (100% yield) of product, m.p. 192–194° dec., unchanged by recrystallization from water. This product, in a mixture of 250 ml. of 95% ethanol and 100 ml. of water, was treated with 3.4 ml. of 30% hydrogen peroxide and the solution refluxed for 17 hr. The mixture was concentrated *in vacuo* to give a quantitative yield of the **oxalate of the 5-oxide**, m.p. 229–230° dec. The m.p. was unaffected by a recrystallization from *n*-butyl alcohol. This latter product was decomposed with warm 10% aqueous sodium hydroxide and the **base** extracted with chloroform. The chloroform extracts were concentrated to dryness and the crystalline residue recrystallized from Skellysolve E to give **10-(3-diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine 5-oxide.**

10-(3-Diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine N,5-Dioxide Hydrochloride.—A solution of 11.4 g. (0.03 mole) of 10-(3-diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine, 100 ml. of 95% ethanol and 6.8 ml. of 30% hydrogen peroxide was refluxed for 17 hr. and then concentrated to dryness. The residual oil crystallized. The crude **base** could be recrystallized from ethyl acetate or methyl ethyl ketone–hexane and formed colorless crystals, m.p. 136–138° dec. On standing, however, the crystals changed to a deep yellow color; satisfactory analytical data could not be obtained. The crude base was dissolved in 200 ml. of boiling methyl ethyl ketone, the solution was cooled and treated with an excess of ethereal HCl; the salt which separated was filtered and recrystallized from a mixture of glacial acetic acid–dry ether to give the product.

10-(3-Dimethylaminopropyl)-4-(trifluoromethyl)-phenothiazine 5,5-Dioxide Hydrochloride.—A mixture of 40 g. (0.15 mole) of 4-(trifluoromethyl)-phenothiazine 75 ml. of acetic anhydride and 4 ml. of pyridine was refluxed for 4 hr. and then concentrated to dryness. The residual solid was washed with hexane to give 45.9 g. (quantitative yield) of crude 10-acetyl-4-(trifluoromethyl)-phenothiazine, m.p. 135–137°. An analytical sample was recrystallized from isopropyl alcohol and melted at 140–141°. *Anal.* Calcd. for $C_{15}H_{10}F_3NOS$: C, 58.24; H, 3.23. Found: C, 57.81; H, 3.27. **The acetyl derivative**, 30.3 g. (0.098 mole), 33.3 g. of 30% hydrogen peroxide, 225 ml. of glacial acetic acid and 25 ml. of acetic anhydride were refluxed for 4 hr. and the mixture cooled. The solid which separated was filtered; it weighed 19.7 g., m.p. 273–274°. A recrystallization from aqueous Cellosolve raised the m.p. to 275–276°. As noted previously, deacetylation had occurred during the oxidation so that the product obtained was **4-(trifluoromethyl)-phenothiazine 5,5-dioxide.** The yield was 68%. *Anal.* Calcd. for $C_{13}H_8F_3NO_2S$: C, 52.17; H, 2.69. Found: C, 52.06; H, 2.86. The condensation between 14.1 g. (0.047 mole) of 4-(trifluoromethyl)-phenothiazine 5,5-dioxide, 0.1 mole of 3-dimethylaminopropyl chloride and 2.7 g. (0.07 mole) of sodamide in 250 ml. of xylene was carried out under the usual conditions. The reaction mixture was filtered hot and the filtrate concentrated to dryness. The residue, 1.7 g., m.p. 159–160°, was recrystallized from toluene to give 1.4 g. (8% yield) of **10-(3-dimethylaminopropyl)-4-(trifluoromethyl)-phenothiazine 5,5-dioxide**, m.p. 164–165°. To 1.3 g. of the **5,5-dioxide** in 25 ml. of warm toluene was added slowly with stirring a slight excess of ethereal hydrogen chloride. The solid which separated, m.p. 233–235°, was recrystallized from acetonitrile–ether to give 1 g. (70% yield) of **10-(3-dimethylaminopropyl)-4-(trifluoromethyl)-phenothiazine 5,5-dioxide hydrochloride**, m.p. 240–241°.

10-(3-Dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine 5-Oxide, Hydrochloride.—To a solution of 9.7 g. (0.036 mole) of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine in 25 ml. of acetonitrile was added 3.28 g. (0.036 mole) of oxalic acid in 10 ml. of acetonitrile. **The oxalate** separated directly and was filtered; the crude product, m.p. 193–195° dec., was recrystallized from acetonitrile to give 6 g. (49% yield) of pure product, m.p. 196–197° dec. A solution of 6 g. of the **oxalate**, 150 ml. of absolute ethanol and 1.6 g. of 30% hydrogen peroxide when refluxed for only 1 hr. began to deposit a crystalline product; after 5 hr. of refluxing, heating was interrupted and the mixture was cooled and filtered to give 5.5 g. (88% yield) of the **oxalate of the 5-oxide derivative**, m.p. 213–215° dec.; a recrystallization from 95% ethanol did not affect the m.p. The oxalate was decomposed with warm 5% aqueous sodium hydroxide, the liberated base extracted with ether, the ether solution was dried and treated with an excess of ethereal hydrogen chloride. The hydrochloride which separated was filtered and recrystallized from chlorobenzene to give 2.5 g. (55% yield) of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine 5-oxide hydrochloride, m.p. 203–205°.

10-(3-Dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine N,5-Dioxide Trihydrate.—A mixture of 15.4 g. (0.044 mole) of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine, 150 ml. of 95% ethanol and 10 ml. of 30% hydrogen peroxide was refluxed for 24 hr. and concentrated on the steam-bath. The residual oil crystallized partially when kept in the cold. A wash with 50 ml. of dry ether removed the oily by-product and left behind a nicely crystalline material. After recrystallization from methyl ethyl ketone, the product sintered at 80° and melted with decomposition at 135–137°. An analytical sample when pistol-dried at 58° lost considerable weight; the dried sample thus obtained was very hygroscopic in air, forming a trihydrate. Since the product is 2% soluble in water at room temperature, it is suggested that the hydrated compound probably has the structure



2-(Trifluoromethyl)-phenothiazine 5,5-Dioxide.—A mixture of 13.4 g. (0.05 mole) of 2-(trifluoromethyl)-phenothiazine, 25 ml. of acetyl chloride and 50 ml. of acetic anhydride was refluxed for 4 hr. and then concentrated *in vacuo* on the steam-bath. To the viscous residue was added 50 ml. of glacial acetic acid and 17 ml. of 30% hydrogen peroxide. The mixture was gradually heated to the boiling point at which temperature a vigorous exothermic reaction occurred. The source of heat was removed until the reaction subsided after which the mixture was refluxed for 4 hr. During this time a crystalline solid began to separate. The mixture was cooled and filtered to give 13.5 g. (90% yield) of product, m.p. 265–267°. On recrystallization from 95% ethanol, the product melted at 268–270°. Again, deacetylation has occurred during the oxidation.

Anal. Calcd. for $C_{13}H_8F_3NO_2S$: C, 52.19; H, 2.70. Found: C, 52.22; H, 2.87.

NEW BRUNSWICK, N. J.

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[CONTRIBUTION FROM THE LABORATORY OF APPLIED ORGANIC CHEMISTRY, RESEARCH COUNCIL OF ISRAEL]

Synthesis of Thieno[b]quinolizinium Salts

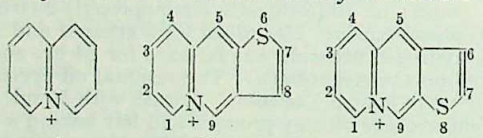
BY M. NEEMAN,[1] E. KRAKAUER AND Y. SHORR

RECEIVED JANUARY 28, 1957

3-Thenyl bromide and pyridine-2-aldehyde reacted to form a quaternary salt, which was cyclodehydrated in boiling hydrobromic acid. The structure of the product, thieno[2,3-b]quinolizinium bromide, was established by desulfurization–reduction with Raney nickel to 3-ethylquinolizidine hydrobromide, which was converted into its known picrate. An analogous synthesis starting from 2-thenyl chloride and pyridine-2-aldehyde yielded a small amount of product to which the structure of thieno[3,2-b]quinolizinium bromide is assigned. The linear thieno- and benzoquinolizinium ions show ultraviolet spectra of considerable similarity.

The synthesis of the quinolizinium ion I is of recent date.[2,3] A number of benzologs of the quinolizinium ion have been reported.[4–6]

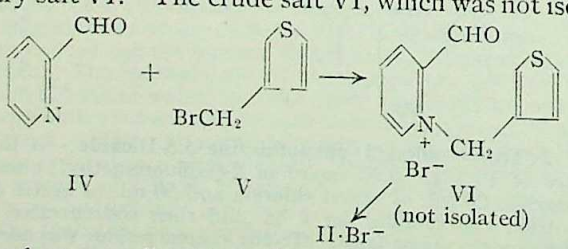
The present study was undertaken to prepare heterocyclic ions of a new type, in which the quinolizinium ion is condensed with a thieno ring (thienologs of quinolizinium). The synthesis of the two linear thieno[b]quinolizinium ions (II) and (III) was attempted first, as it was expected that the two linear isomers would be accessible by cyclodehydration of more readily available inter-



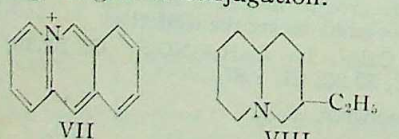
I II III

mediates than would be required for the synthesis of any of the six possible angular isomers, or of the third linear isomer, thieno[3,4-b]quinolizinium ion.

The synthesis of the thieno[2,3-b]quinolizinium ion was effected in good over-all yield (72%) by a reaction sequence analogous to the reported synthesis of the acridizinium ion (VII) by Bradsher and Beavers.[5] The pyridine-2-aldehyde (IV) reacted with 3-thenyl bromide (V) to form a quaternary salt VI. The crude salt VI, which was not isolated, was cyclized in boiling aqueous hydrobromic acid to thieno[2,3-b]quinolizinium bromide (II·Br⁻). The product had an ultraviolet absorption spectrum (Table I) which was closely related to that of the acridizinium ion (VII).[5] The new heterocyclic ion II showed a spectrum which indicated a high degree of conjugation.



IV V VI (not isolated) II·Br⁻



VII VIII

(1) Department of Chemistry, University of Wisconsin, Madison, Wisconsin (on leave of absence from the Technion Israel Institute of Technology, Haifa).

(2) V. Boekelheide and W. G. Gall, THIS JOURNAL, **76**, 1832 (1954).

(3) V. Boekelheide and J. M. Ross, *ibid.*, **77**, 5691 (1955).

(4) C. K. Bradsher and L. E. Beavers, *ibid.*, **77**, 453 (1955).

(5) C. K. Bradsher and L. E. Beavers, *ibid.*, **77**, 4812 (1955).

(6) C. K. Bradsher and L. E. Beavers, *ibid.*, **78**, 2515 (1956).

TABLE I

ULTRAVIOLET ABSORPTION CHARACTERISTICS OF LINEAR BENZO- AND THIENO-QUINOLIZINIUM IONS (IN ETHANOL)

Acridizinium perchlorate[5] (VII·ClO₄⁻)		Thieno[2,3-b]quinolizinium bromide (II·Br⁻)		Thieno[3,2-b]quinolizinium bromide (III·Br⁻)	
λ_{max}, mμ	log ϵ_{mol}	λ_{max}, mμ	log ϵ_{mol}	λ_{max}, mμ	log ϵ_{mol}
242	4.68	247	4.61	247	4.57
		350 (sh)	4.08	353	3.87
361	3.99	362	4.36		
379.5	4.01				
				387	4.11
399	3.93				

The structure of II was established by desulfurization–reduction of its bromide with Raney nickel to a sulfur-free hydrobromide (VIII·HBr), which was converted into a picrate. The latter was proved to be 3-ethylquinolizidine picrate (VIII·picrate)[7] by comparison of infrared spectra and melting points with an authentic sample kindly supplied by Dr. Boekelheide. Apparently the same racemate was obtained by both routes. The ultraviolet and infrared spectra of VIII·HBr support this structure. Hence, the formally possible isomeric structure of thieno[3,4-b]quinolizinium ion is excluded for the product of the cyclodehydration. This result is in accord with the known higher electron density at the α-position relative to that at the β-position of thiophene.[8] Accordingly, the electrophilic cyclizing attack at the α-position of thiophene in VI was favored.

The reaction of 2-thenyl chloride with pyridine-2-aldehyde was considerably slower than the corresponding quaternization with 3-thenyl bromide. The glassy reaction product gave an intractable black residue after attempted cyclization with boiling 48% hydrobromic acid. A crystalline reaction product could be isolated in 4% yield by alumina chromatography. It afforded analytical values in accord with the formulation of a thienoquinolizinium bromide. The product showed spectral characteristics of pronounced similarity to those of the acridizinium ion and of the isomeric II·Br⁻ (Table I). Salts of the two ions also showed comparable, though distinct, properties. The structure of thieno[3,2-b]quinolizinium bromide (III·Br⁻) is assigned tentatively to the second cyclodehydration product pending its conversion into a compound of established structure.

Biological Activity.—Thieno[2,3-b]quinolizinium bromide was tested for curariform activity. It showed no effect by itself, but it was observed to

(7) V. Boekelheide and S. Rothchild, *ibid.*, **71**, 879 (1949).

(8) Cf. J. de Heer, *ibid.*, **76**, 4802 (1954).

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potentiate the effect of succinylcholine when tested on the sciatic nerve in male cats.

Acknowledgment.—Thanks are due to Dr. F. Bergmann for biological tests.

Experimental

3-Thenyl bromide (V) was prepared by the method of Campaigne and LeSuer.[9]

Thieno[2,3-b]quinolizinium Bromide (II·Br⁻).—The method of Bradsher and Beavers[5] was used. Pyridine-2-aldehyde (7.35 g.) and 3-thenyl bromide (12.1 g.) were mixed and kept at 25–30° for 12 days. The reaction mixture formed a dark reddish-brown glass-like mass. On the ninth day about 1 ml. of a light yellow liquid was decanted. The mass was washed with ether and taken up in 48% aqueous hydrobromic acid (110 ml.) with gentle heating. The resulting solution was left overnight. A small amount of a dark impurity was filtered off. The dark red-brown solution was refluxed for 20 hr. The hydrobromic acid was distilled off at 20 mm. pressure. The black solid residue was taken up in hot water (130 ml.), boiled with charcoal (0.15 g.) and filtered. Dark-colored crystals were deposited from the solution on standing overnight in the refrigerator, which were filtered off and washed with ice-water. The yield was 12.1 g., m.p. 226–228°. The mother liquor was concentrated to a small volume at 20 mm. giving 1 g. of the product with the same m.p. The total yield was 72%. Recrystallization from ethanol (charcoal) yielded light brown needles, 10.5 g., m.p. 227–228°. The product was subjected to alumina chromatography (ethanol as solvent and eluent), yielding long glistening lemon-yellow needles, m.p. 227–228° (hot-stage).

Anal. Calcd. for $C_{11}H_8NSBr$: C, 49.64; H, 3.03; N, 5.26. Found: C, 49.39; H, 3.07; N, 4.96, 5.18.

The infrared spectrum of II·Br⁻ (solid, potassium bromide pellet) showed the following bands (cm.$^{-1}$): 3400-(strong); 3050(s); 2924; 2850; 2359(weak); 1616(s); 1500(w); 1475; 1460(s); 1430(w); 1385(s); 1312(s); 1293; 1247(w); 1174(w); 1167(w); 1152; 1130; 1033; 952(w); 910(w); 870(s); 830(w); 799(w); 765–760(s); 674–670; 664(w).

The picrate was precipitated from an ethanolic solution of the bromide and was crystallized twice from nitromethane. It was obtained as felted yellow needles, m.p. 213–214° (hot-stage).

Anal. Calcd. for $C_{17}H_{10}O_7N_4S$: C, 49.28; H, 2.43; N, 13.52; S, 7.74. Found: C, 49.64; H, 2.49; N, 13.63; S, 7.48.

3-Ethylquinolizidine Hydrobromide (VIII·HBr).—Thieno-(2,3-b)quinolizinium bromide (II·Br⁻) (1.06 g., 0.004 mole) and Raney nickel W-2[10] (12 g.) in ethanol (50 ml.) were refluxed for 2 hr. Fresh Raney nickel (4 g.) and ethanol (100 ml.) were added, and hydrogen was introduced (in a Parr apparatus) for 3 hr. at 2 atm. and 25°. The catalyst was filtered off, washed with ethanol and finally extracted with ethanol in a Soxhlet extractor. The combined ethanol extracts gave on evaporation a sticky brown product, which yielded 0.13 g. (13%) of a crystalline product, m.p. 184°, from butyl acetate. Recrystallization from this solvent gave a product of m.p. 190–191.5° (0.07 g.).

Anal. Calcd. for $C_{11}H_{22}NBr$: C, 53.22; H, 8.94; N, 5.64. Found: C, 52.97; H, 8.87; N, 5.44.

3-Ethylquinolizidine hydrobromide (VIII·HBr) showed very weak absorption in the ultraviolet above 215 mμ. The infrared spectrum (solid, potassium bromide pellet) showed no evidence of unsaturation. The following bands were observed (cm.$^{-1}$): 3425; 2941(strong); 2700–2674(s); 2577-(s); 2551(s); 2359(weak); 1650(w); 1460(s); 1342; 1174–1168; 1053-1048; 1032; 1010-1006(w); 995; 970-(w); 945(w); 920(w).

3-Ethylquinolizidine Picrate (VIII·Picrate).—The hydrobromide VIII·HBr was dissolved in ethanol and treated with ethanolic picric acid solution under reflux for 10 minutes. The picrate was deposited in clusters of lemon yellow needles, m.p. 156–157.5°.

The m.p. was undepressed by an authentic specimen of 3-ethylquinolizidine picrate of Boekelheide and Rothchild.[7] The infrared spectra of both specimens were superposable and showed the following bands (cm.$^{-1}$; solid, potassium bromide pellet): 3440(weak); 3070(w); 2950(strong); 2750(s); 2600; 1625–1610(s); 1565–1560(s); 1515(s); 1506(s); 1472(s); 1462(shoulder); 1430(s); 1362(s); 1340–1316(s); 1265(s); 1207(w); 1160; 1078; 1052; 996(w); 972-(w); 943(shoulder); 936; 917(w); 907; 787; 744; 723-(shoulder); 708(s); 678(w); 667(w).

Thieno(3,2-b)quinolizinium Bromide (III·Br⁻).—Pyridine-2-aldehyde (23.5 g.) and 2-thenyl chloride[11] (29.1 g.) were kept for eight weeks at 20–30° in a stoppered flask in the dark. Most of the reaction mixture turned into a dark brown-red glassy mass. A small amount of dark brown-red viscous supernatant liquid was decanted, and the glassy solid was left under the same conditions for a further period of four weeks. Hydrobromic acid (100 ml., 48%) was added. The glassy solid dissolved overnight, leaving a slight black residue, which was filtered off. The acid solution was refluxed for 19 hr. and filtered. The hydrobromic acid was removed at 20 mm., leaving a black residue. The latter was extracted with hot water, leaving a considerable part undissolved. The aqueous extract was evaporated to dryness at 20 mm., and the black residue was extracted with ethanol, leaving a considerable part undissolved. The ethanolic extract was passed through a column of alumina, which was subsequently eluted with ethanol, from which dark greenish needles were deposited on concentration, m.p. 216° (2.7 g.). After five crystallizations from ethanol, light yellow needles of m.p. 216–217° (hot-stage) were obtained.

Anal. Calcd. for $C_{11}H_8NSBr$: C, 49.64; H, 3.03; N, 5.26; Br, 30.03; S, 12.05. Found: C, 49.66; H, 3.16; N, 5.37; Br, 30.33; S, 11.94.

The infrared spectrum of III·Br⁻ (solid, potassium bromide pellet) showed the following bands (cm.$^{-1}$): 3472-(strong), 3068(s); 2941; 2874; 2370(weak); 1626(s); 1582(w); 1560(w); 1479(w); 1447(s); 1412(s); 1380(s); 1360, 1340; 1300(s); 1260(w); 1217(w); 1160(s); 1097-(w); 1029; 948(w); 893–890; 865(s); 830(w); 804; 788; 755(s); 680(s).

The picrate (III· picrate) was precipitated from an ethanolic solution of the bromide III·Br⁻ and crystallized from nitromethane as fine felted light yellow needles, m.p. 210.5–211°.

Anal. Calcd. for $C_{17}H_{10}O_7N_4S$: C, 49.28; H, 2.43; N, 13.52. Found: C, 49.97; H, 2.51; N, 13.00.

JERUSALEM, ISRAEL

(9) E. Campaigne and W. M. LeSuer, THIS JOURNAL, **70**, 1555 (1948).

(10) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.

(11) K. B. Wiberg and H. F. McShane, *ibid.*, p. 157.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUQUESNE UNIVERSITY]

Derivatives of 1-Thia-4,5-diazacyclohepta-2,4,6-triene. III. Isomeric Dibenzo-1-thia-4,5-diazacyclohepta-2,4,6-triene-1,1-dioxides and Dibenzo-1-thia-4,5-diazacyclohepta-2,4,6-triene-1,1,4-trioxides

BY H. HARRY SZMANT AND YUAN-LANG CHOW[1]

RECEIVED JUNE 8, 1956

The isolation of three isomers of the previously described heterocyclic system containing either the azo or the azoxy function is described. Isomerization, oxidation and reduction experiments, as well as physical properties are utilized in the provisional assignment of conformations to the three isomers in each series. While two of each group of three isomers seem to be chair and boat conformations of the heterocyclic ring, the third isomer appears to be a novel seven-membered puckered ring in which a *trans* azo or azoxy group is part of the ring.

Repetition of the previously described[2] oxidation of di-(*o*-aminophenyl) sulfone by means of phenyliodoso acetate gave in addition to the already reported dibenzo-1-thia-4,5-diazacyclohepta-2,4,6-triene-1,1-dioxide (I) of melting point 170–171°,[3] another compound melting at 130°. This material was shown to be an isomer of I by analysis and by thermal conversion to the higher melting solid, and the two compounds are herewith designated IA and IB, respectively. As previously reported,[2] the oxidation of IA by peracetic acid gave dibenzo-1-thia-4,5-diazacyclohepta-2,4,6-triene-1,1,4-trioxide (II) of melting point 251–252°, and analogous oxidation of IB gave a mixture of the already known azoxy compound and an isomeric azoxy compound of melting point 239°. These two azoxy compounds are herewith designated IIA and IIB, respectively, and as in the case of IA and IB, the new isomer (IIB) could be isomerized thermally (and also photochemically) to IIA.

It was of interest to confirm the existence of the two isomeric compounds I by the reduction of the azoxy function of II to the azo function in I. To our surprise, the reduction of either IIA or IIB by means of lithium aluminum hydride or zinc in acetic acid gave neither IA or IB but rather a third isomer of I, a solid of melting point 193°, which is herewith designated as IC. The fact that IC is related structurally to IA was established by successful photochemical isomerization of IC to IA. The same isomerization could be accomplished by dissolving IC in cold sulfuric acid and precipitating IA upon dilution of the solution with ice. The oxidation of IC by means of peracetic acid gave IIA just as did the oxidation of IA.

The existence of three isomers of I implied the possible existence of three isomers of II, and the third isomer of II of melting point 250–251° (IIC) was indeed isolated when dibenzo-1-thia-4,5-diazacyclohepta-2,6-diene was subjected to oxidation with peracetic acid. While IIB and IIC have almost identical melting points they differ in several respects. Thus while IIA is a yellow solid which melts without decomposition, IIC is a white solid which undergoes complete decomposition upon melting. IIC is isomerized to IIA when heated in acetic acid solution and reduction of IIC by means of lithium aluminum hydride gives IC.

The above mentioned results prove the existence of three isomers in the azo series I and also in the azoxy series II. Assuming a non-planar structure of the heterocyclic ring in I and II, there can be visualized two isomers in which the heterocyclic ring assumes either a chair or a boat conformation. This hypothesis still does not account for the existence of the third pair of isomers. We wish to suggest at this time that the third pair of isomers represents a puckered, seven-membered ring in which the azo function exists in the *trans* form. Evidence in support of this suggestion is cited below. The three suggested conformations in the azo series I are represented schematically in Fig. 1.

Assuming the correctness of the proposed conformational differences between IA,B,C and IIA,B,C, our efforts were next directed toward the assignment of specific conformations to the individual isomers.

Examination of the ultraviolet spectra of IA,-B, C(Fig. 2) revealed a distinct feature differentiating IC from IA and IB. The 430 mμ band, the well recognized[4] R-band of azo compounds, was abnormally weak in IC (ε 14) while it was of normal intensity in IA and IB (ε 380–595). Since in negatively substituted azo compounds the intensity of the R band is generally higher in the *cis* isomer, the weak R band in IC favors the assignment of the *trans* azo structure to this isomer. Supporting this assignment is the above mentioned facile isomerization of IC to IA by ultraviolet light or by acid catalysis. In the course of both kinds of treatments the temporary breaking of the nitrogen–nitrogen double bond would permit the rearrangement to the *cis* azo structure which would be expected to be the more stable structure in a cyclic azo compound. Further support of the *trans* azo assignment to IC is the fact that the reduction of all three isomers of II gave exclusively this particular isomer. Badger[5] has shown that the reduction of both *cis*- and *trans*-azoxybenzene gives the *trans* azo system and explains these results in terms of the preferential *trans* elimination of water from the intermediate dihydroazoxy structure. The same explanation may account for the formation of IC from IIA,B,C on reduction with lithium aluminum hydride or zinc, even though IC is readily isomerized to IA.

(1) From the Ph.D. thesis of Y.L.C.

(2) H. H. Szmant and R. L. Lapinski, THIS JOURNAL, 78, 458 (1956).

(3) Extensive purification raised the melting point to 171°.

(4) R. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold, London, 1954.

(5) G. M. Badger, R. G. Buttery and G. E. Lewis, *J. Chem. Soc.*, 2143 (1953).

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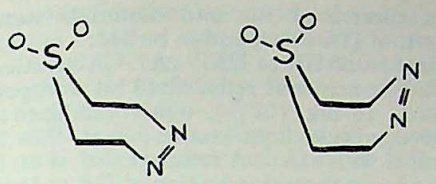
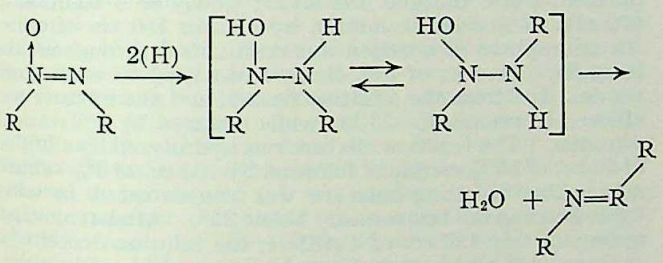


Fig. 1.—Conformations of I. Heavy lines indicate fusion of benzene rings.

The assignment of the conformations to IA and IB is more difficult in the absence of additional physical data,[6] but provisionally the higher melting and more stable isomer IA is assigned the *cis* azo chair structure. In this connection it was found that IB was oxidized 13 times faster than IA by perbenzoic acid. Badger[5] has shown that the greater rate of oxidation of *cis*-azobenzene as compared to *trans*-azobenzene (50–80 fold difference) can be accounted for by considering the greater electron-availability in the *cis* azo linkage. In the case of IA and IB, both compounds are assumed to be *cis* azo structures and apparently the electron-withdrawing sulfone group is more effective in the chair structure.



The comparison of the behavior of the isomeric II compounds at their respective melting points reveals that IIA is the most stable compound since it is the only isomer which does not decompose. It is of interest that IIB decomposes violently with evolution of brown gas, while IIC decomposes to a tar without noticeable gas evolution. The relative stability of IIA suggests that it may have the *cis*-azoxy chair configuration. The oxidation of IA to IIA was reported in the preceding publication[2] and the formation of a mixture of IIA and IIB by peracetic acid oxidation of IB was mentioned above. These results indicate that IA and IIA are configurationally related, and the fact that IB isomerizes to IA upon heating explains why the oxidation of IB gives some IIA in addition to IIB. A mixture of IIA and IIB was also obtained when di-(*o*-aminophenyl) sulfone was oxidized by peracetic acid. The conclusion that IB and IIB are configurationally related also is supported by the selective oxidation of IB to IIB by perbenzoic acid. The success of the last mentioned experiment is in line with the experiences of Badger[5] who demonstrated that perbenzoic acid oxidizes *cis*-azobenzene without isomerization while peracetic acid also brings about isomerization.

In an attempt to bring about a controlled reduction of the azoxy to the azo linkage, IIB was treated with deactivated nickel (see Experimental) but in place of the expected IB the only product which could be isolated from this reaction was II-A. Since this experiment was performed without application of heat it demonstrates the relatively greater stability of IIA.

(6) The measurement of the dipole moments of the compounds under discussion is planned for the near future.

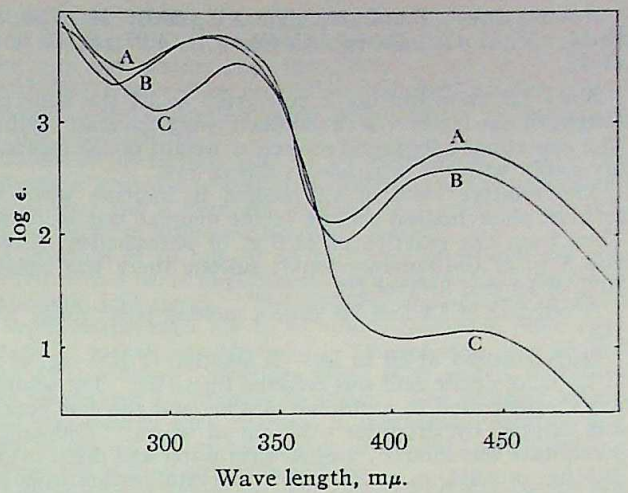


Fig. 2.—Ultraviolet spectra of IA (curve A), IB (curve B), and III (curve C).

The assignment of the chair and boat conformations to IIA and IIB, respectively, leaves the *trans*-azoxy conformation for the IIC isomer. It was hoped to confirm this assignment by the perbenzoic acid oxidation of IC to IIC but unfortunately the oxidation of IC gave exclusively IIA. When the kinetics of this reaction was examined it was found that IC is subject to a very rapid isomerization to IA with the loss of one equivalent of perbenzoic acid. The isomerized product could be isolated when the oxidation was stopped at that point, and when the oxidation was allowed to continue it proceeded at a rate essentially equal to that of IA. The mechanism of isomerization of IC to IA with loss of perbenzoic acid is not understood at this time and is subject to additional study.

The successful isomerization of IC to IA by concentrated sulfuric acid prompted the examination of possible isomerization of IIC under the same conditions. Neither IIC nor the other two azoxy compounds were found to be isomerized when dissolved in concentrated sulfuric acid in the cold and were recovered when the solutions were poured on ice. The failure of IIC to be isomerized can be ascribed to the protonation of the azoxy group at the oxygen atom without disturbing the nitrogen–nitrogen double bond.

Experimental[7]

Preparation and Isolation of IA and IB.—A mixture of 5 g. (0.02 mole) of di-(*o*-aminophenyl) sulfone, 5.8 g. (0.02 mole) of phenyliodoso acetate and 500 cc. of dry toluene was allowed to stand at room temperature for 5 days. A brown precipitate, 0.8 g., was filtered, washed with hot toluene and discarded since it did not melt at 350°. The filtrate and washings were concentrated *in vacuo* and the residue was crystallized from methanol to give 2.2 g. of dark red crystals, m.p. 164–169°; yield 42%. Three crystallizations from isopropyl alcohol gave orange crystals, m.p. 174°, which did not depress the m.p. of the previously reported[2] IA. Concentration of the filtrates yielded 2.1 g. (40%) of dark orange crystals, m.p. 125–130°, which were purified to constant m.p. 130.5–131.5° by crystallization from methanol. Chromatography of this material (IB) on alumina gave only one band.

(7) All melting points are uncorrected. Microanalyses by Drs. Strauss and Weiler, Oxford, England, and by Dr. Bernhardt, Mülheim, Germany.

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Anal. Calcd. for $C_{12}H_8O_2N_2S$: C, 59.0; H, 3.30; S, 13.11; N, 11.47. Found: C, 59.4; H, 4.07; S, 13.3; N, 11.40.

Since IB upon heating is converted to IA the molecular weight of the latter was determined using the Rast method. The experimentally found molecular weight of 233 compares favorably with the calculated value of 244.

The relative yield of IA seemed to increase when the ratio of phenyliodoso acetate to the diamine was increased. Thus from the reaction of 15.0 g. of phenyliodoso acetate and 8 g. of di-(*o*-aminophenyl) sulfone there was isolated 70% of IA and 21% of IB.

A mixture of IA and IB gave a melting point range 129–148°.

Isomerization of IB to IA.—A solution of 300 mg. of IB in 12 cc. of acetic acid was refluxed for 13 hr. The solution was concentrated to a volume of 4 cc. and the cold residue was diluted by dropwise addition of water. The orange precipitate was filtered, washed with water and dried to give 210 mg. of solid, m.p. 169–173°. Crystallization from isopropyl alcohol gave orange crystals, m.p. 173–174°, which did not depress the m.p. of IA.

Attempts to effect isomerization of IB by irradiation with ultraviolet light were unsuccessful. Also attempted isomerizations of IA by either thermal or photochemical means failed.

IA and IB were recovered in nearly quantitative yields when solutions in cold concd. sulfuric acid were poured on ice.

Oxidation of IB.—Ten cc. of 40% peracetic acid was added over a period of 30 minutes to a solution of 1 g. of IB in 35 cc. of acetic acid. The mixture was stirred and cooled by means of an ice-bath during the addition, and then was allowed to stand at room temperature for 15 hr. Faintly yellow needles precipitated from the solution and they were filtered, washed with methanol and dried to give 850 mg. (80%) of solid, m.p. 212–218° dec. The filtrate was poured on ice and gave an additional 210 mg. of the same solid. The combined crystals were purified by dissolving in a minimum volume of hot dioxane, addition of approximately 100 cc. of water, and slow cooling. The resulting product gave a constant m.p. 243–245° dec. Admixture with IIA gave m.p. 244–251°, and admixture with IIB gave m.p. 242–244°. A portion of the product on heating in glacial acetic acid for 14 hr. was converted quantitatively to IIA, m.p. and mixture m.p. 250–251°.

Oxidation of IB with 30% hydrogen peroxide in refluxing acetone gave the same results, but oxidation of IB with peracetic acid in refluxing acid gave directly a quantitative yield of IIA, m.p. and mixture m.p. 251–252°.

Oxidation of IA to IIA.—A solution of 50 mg. of IA in 10 cc. of hot acetic acid was treated with 1 cc. of 40% peracetic acid. The solution was refluxed for 10 hr. and then poured on ice to give greenish-yellow needles, m.p. 247–249°. Crystallization from acetic acid gave pure IIA, m.p. and mixture m.p. 251–252°.

Preparation of IIA and IIB.—A solution of 2.5 g. of di-(*o*-aminophenyl)sulfone in 35 cc. of acetic acid and 10 cc. of benzene was cooled below 10° and stirred while a solution of 10 cc. of 40% peracetic acid in 50 cc. of acetic acid was added dropwise over 40 hr. The colorless solution turned brown. Mechanical stirring was extended for another 24 hr. at room temperature. The reaction mixture on cooling in an ice-bath deposited dark needles which were filtered, washed with methanol and water. The solid, 2.1 g., m.p. 235–241° dec., was fractionally crystallized from acetone. The first fraction, 1.8 g. (69%), consisted of white needles, m.p. 235° dec., while the second fraction, 0.3 g., consisted of yellow-green needles, m.p. 235–245°. The first fraction was crystallized repeatedly from acetone and gave white needles of constant m.p. 239° (violent decomposition with evolution of brown gas). This material is considered to be IIB.

Anal. Calcd. for $C_{12}H_8O_3N_2S$: S, 12.31; N, 10.8; mol. wt., 260. Found: S, 11.95; N, 10.8; mol. wt. (Rast), 247.

The mother liquor was poured into water and gave 0.5 g. of green-yellow needles, m.p. 238–245°. This material was combined with the second fraction from the above crystallization and the solids (30%) were treated with charcoal in acetic acid solution. The purified product, m.p. 251–252°, did not depress the m.p. of IIA and the ultraviolet spectra of the two materials were identical. The mol. wt. of IIA was found to be 244.

Isomerization of IIB to IIA. (A).—A solution of 15 mg. of IIB in acetic acid was refluxed 48 hr. and poured on ice. The product, 13 mg. (87%), was crystallized from acetic acid to give green-yellow needles, m.p. 250–251°, which were identical with IIA. A reflux period of 30 hr. was also sufficient to cause the isomerization of IIB to IIA. When in addition to acetic acid there was present also a small amount of hydrochloric acid (1 cc. of concd. hydrochloric acid in 20 cc. of acetic acid), the yield of IIA was only 60% and an unidentified brown gelatinous precipitate was produced.

(B).—A solution of 50 mg. of IIB in 50 cc. of acetic acid was irradiated for 3 days in a quartz vessel by means of an ultraviolet lamp. The solution turned brown and when poured on ice there was obtained 42 mg. (84%) of solid, m.p. 241–244°. A charcoal treatment in acetic acid and an additional crystallization from the same solvent gave pure IIA, m.p. and mixture m.p. 251–252°.

(C).—A solution of 130 mg. of IIB in 180 cc. of toluene was added to two scoops of deactivated Raney nickel[8] covered by toluene. The mixture changed from the original slight yellow color to a green-yellow color upon shaking, and after 5 hr. it was filtered and the solvent was evaporated *in vacuo*. The residual solid, 100 mg. (78%), m.p. 237–239°, was recrystallized from methanol to give pure IIA, m.p. and mixture m.p. 251–252°.

Reduction of IIA and IIB to IC. (A) Lithium Aluminum Hydride.—A suspension of 350 mg. of IIA in 80 cc. of purified, warm dioxane was added slowly to a solution of 470 mg. of lithium aluminum hydride in 180 cc. of ether. An atmosphere of nitrogen was maintained throughout the reaction. Ten cc. of hot dioxane was used to wash down residual IIA from the addition funnel, and the mixture was allowed to remain for 25 hr. while agitated by a stream of nitrogen. The reaction mixture was hydrolyzed by addition of 50 cc. of 50% methanol followed by 100 cc. of 3% sulfuric acid. The resulting mixture was concentrated *in vacuo* while keeping the temperature below 35°. After removal of approximately 120 cc. of distillate, the solution deposited a yellow solid which was filtered and washed with water. The product, 270 mg., m.p. 183–187°, was crystallized from isopropyl alcohol to give IC, yellow needles, m.p. 194–196°.

Anal. Calcd. for $C_{12}H_8O_2N_2S$: C, 59.00; H, 3.30; N, 11.47; S, 13.11; mol. wt., 244. Found: C, 58.82; H, 3.80; N, 11.35; S, 13.00; mol. wt. (Rast), 244.

Using the same procedure the reduction of IIB gave 83% of IC, m.p. and mixture m.p. 194–196°. In another experiment in which the amount of dilute sulfuric acid was in excess of the amount required to neutralize the reaction mixture and the temperature during the distillation was raised to 100°, IA was obtained instead of IC. IA was identified by m.p. and mixture m.p. with authentic IA.

(B) **Zinc Dust.**—A solution of 100 mg. of IIA in 15 cc. of acetic acid was warmed on a hot plate while 1 g. of zinc dust was added in small portions. The mixture was filtered after 20 minutes and the solid was washed with 3-cc. portions of boiling acetic acid. The combined filtrate and washings were poured into a large volume of water and a solid was collected. The crude product was charcoaled and crystallized from methanol to give 60 mg. (64%) of yellow needles, m.p. 185–190°. Additional crystallization gave m.p. and mixture m.p. 194–196°.

The same procedure was applied to 150 mg. of IIB and gave 100 mg. (79%) of IC.

Isomerization of IC to IA.—A solution of 30 mg. of IC in 30 cc. of ethanol was irradiated in a quartz vessel for one week by means of an ultraviolet lamp. The solution was poured on ice and the resulting solid, 28 mg. (94%), m.p. 169–172°, was recrystallized from ethanol to give pure IA, m.p. and mixture m.p. 173–174°.

The same reaction was followed spectrophotometrically using a 1.134×10^{-3} *M* solution of IC and determining the ϵ at 430 mμ. The initial value of ϵ agreed with that reported for IC and upon irradiation, the ϵ gradually approached the value of 550.

The isomerization of IC to IA also could be achieved by refluxing an ethanolic solution for 40 hr. However, the product was isolated in a yield of only 65–75%.

(8) H. Hauptmann and B. Wladislaw, THIS JOURNAL, **72**, 707

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IC, 20 mg., was dissolved in cold concd. sulfuric acid and the resulting red solution was immediately poured on ice. There was isolated 17 mg. (85%) of crude IA, m.p. 157–167°, which upon crystallization from ethanol gave m.p. and mixture m.p. 173–174°.

Oxidation of IC to IIA.—A solution of 50 mg. of IC in 10 cc. of acetic acid was warmed with 2 cc. of 40% peracetic acid and the temperature was raised gradually to reflux. The color was observed to change from yellow to dark orange and finally to green-yellow. After a reflux period of 2 hr. the solution was diluted with an equal volume of water and gave 40 mg. (78%) of solid, m.p. 245–250°. One crystallization from acetic acid gave pure IIA, m.p. and mixture m.p. 250–252°.

A solution of 50 mg. of IC in 5 cc. of acetic acid was treated dropwise with 5% solution of potassium permanganate in acetone. The addition was continued until the pink color persisted and then an additional 2-cc. volume of oxidizing solution was added. The mixture was warmed for two hours and allowed to stand until a crystalline precipitate began to appear. The mixture was then diluted with an equal volume of water and was filtered. The solid was extracted with isopropyl alcohol and the filtrate yielded upon concentration 20 mg. of solid, m.p. 250–252°. The product did not depress the m.p. of authentic IIA. The filtrate was poured into a large volume of water and the orange precipitate was crystallized to give IA, m.p. and mixture m.p. 173.5–174°.[9]

Preparation of Dibenzo-1-thia-4,5-diazacyclohepta-2,6-diene.—Di-(*o*-nitrophenyl) sulfide, 15 g., in 700 cc. of hot isopropyl alcohol was diluted with an equal volume of water and 42 g. of sodium acetate was dissolved in the mixture. The vigorously stirred solution was treated with 30 g. of zinc dust while a nitrogen atmosphere was maintained in the flask. The temperature was gradually raised to reflux (30 minutes) and maintained at reflux for 10 minutes. The reaction mixture was filtered rapidly and the filtrate was collected in a preheated 2-l. suction flask. Without changing the container the filtrate was concentrated by application of vacuum and 350–400 cc. of solvent was removed in this fashion. During all these operations care was taken to prevent excessive contact of the solution with air since the latter caused discoloration and separation of solid. The concentrated solution was diluted with water to a volume of 2 l. and, after refrigeration, there was isolated 8.5 g. (75%) of white crystals, m.p. 121° (with evolution of gas). Attempted crystallizations from alcohol caused discoloration of the product and in view of the failure to obtain satisfactory analysis of the previously prepared[10] cyclic hydrazo compounds the material from this experiment was used immediately for the preparation of IIC.

Preparation of IIC.—The hydrazo compound from the preceding experiment, 8.5 g., was dissolved in 30 cc. of acetic acid and the resulting solution was stirred and treated dropwise with a solution of 10 cc. of 40% peracetic acid in 100 cc. of acetic acid. An additional 20 cc. of 40% peracetic acid was added after 5 hr. When a white solid began to precipitate the mixture was first heated for 30 minutes on a hot plate, cooled and then filtered. The white solid was washed with methanol to give 7.0 g. (72%) of product, m.p. 243–247° dec. Crystallization from acetic acid raised the m.p. to 250–251° dec.

Anal. Calcd. for $C_{12}H_8O_3N_2S$: C, 55.38; H, 3.09; S, 12.31; N, 10.88; mol. wt., 260. Found: C, 55.13; H, 3.03; S, 12.28; N, 10.91; mol. wt. (Rast), 257.

Isomerization of IIC to IIA.—A solution of 50 mg. of IIC in 100 cc. of acetic acid was refluxed for 100 hr., treated with charcoal, filtered and cooled to give 35 mg. (70%) of green-yellow needles, m.p. 251–252° (no decomposition!). This material did not express the m.p. of IIA.

Neither irradiation by ultraviolet light nor dissolution in concentrated sulfuric acid were effective in the isomerization of IIC.

Reduction of IIC to IC. (A) Lithium Aluminum Hydride.—The procedure described for the reduction of IIA and IIB gave 390 mg. (92.5%) of crude IC, m.p. 190–192°, from 450 mg. IIC. A single crystallization from ethanol gave m.p. and mixture m.p. 194–196°.

(B) Zinc Dust.—The procedure described for the reduction of IIA and IIB was applied to 600 mg. of IIC and gave 490 mg. (87%) of IC.

Oxidation of IA, IB and IC by Perbenzoic Acid.—The perbenzoic acid was prepared as described in the literature[11] except that the chloroform solution was washed with 1% sodium bisulfite before washing with water.

A solution of 70 mg. of IA in 20 cc. of chloroform was treated with 3 cc. of chloroform containing 0.1807 mmole of perbenzoic acid per cc. The solution was allowed to stand at room temperature for 48 hr. and a change in color from orange to yellow was observed. The solution was washed with 10% sodium hydroxide, twice with water, and then was evaporated to dryness *in vacuo*. The residual yellow solid was treated with charcoal in methanolic solution and gave 70 mg. of yellow solid, m.p. 246–249°, which did not depress the m.p. of authentic IIA.

Application of the same procedure to 76 mg. of IB and 5 cc. of perbenzoic acid solution of the same concentration gave 65 mg. (80%) of crude product, m.p. 225–235° dec. Crystallization from methanol gave white needles, m.p. 239° (violent dec.), which did not depress the m.p. of authentic IIB.

A solution of 66 mg. (0.2712 mmole) of IC in 20 cc. of chloroform was mixed with 4 cc. of chloroform containing a total of 0.386 mmole of perbenzoic acid. The color of the solution changed instantly from yellow to dark orange and immediate iodimetric titration of an aliquot showed the loss of 0.27 mmole of perbenzoic acid. The solution was shaken with 10% sodium hydroxide 15 minutes after mixing, and the washed chloroform layer was evaporated to give 66 mg. of product which was obtained as orange cubes from methanol, m.p. 173–174°. This material did not depress the m.p. of IA.

In another experiment in which IC was allowed to react at room temperature with 2.5 equivalents of perbenzoic acid there was isolated after 50 hr. a quantitative yield of IIA.

Kinetics of the Oxidation of IA, IB and IC by Perbenzoic Acid. General Procedure.[5]—An accurately weighed sample of I was dissolved in reagent grade chloroform and the solution was thermostated at 25.0 ± 0.1° in a 25-cc. volumetric flask coated with black enamel. A stock solution of freshly prepared perbenzoic acid in chloroform (approximately 0.20 mmole perbenzoic acid per cc.) was also thermostated. The time at which one-half of the perbenzoic acid solution was added to the solution of I was taken as zero time, and the mixture was rapidly diluted to the 25 cc. mark and shaken. Approximately 1.5 equivalents of perbenzoic acid were used in each oxidation of I. The first aliquot was titrated as promptly as possible upon mixing and subsequent aliquots were titrated at suitable intervals. The initial concentration of perbenzoic acid was determined by extrapolation. A sample of perbenzoic acid solution of equal concentration was kept side by side with the kinetic sample and the autodecomposition of perbenzoic acid was also followed by iodimetric titration in order to correct the observed loss of perbenzoic acid in the kinetic experiments. The reactions were followed for at least 50% oxidation of I and second-order rate constants were calculated.

Oxidation of IA.—The solution contained 0.4725 mmole of IA and 0.5862 mmole of perbenzoic acid. Aliquots of 2.0 cc. were titrated with 0.00493 *N* sodium thiosulfate.

Time, min.	Titer, cc. Oxid.	Control	$k \times 10^2$ ./mole min.
0	19.00	19.05	..
4.1	18.98	19.05	..
100	18.10	19.05	2.73
215	17.69	19.05	1.91
480	15.80	17.85	2.18
632	14.47	16.91	2.09
1112	12.32	15.70	1.99
1360	11.19	15.41	2.57
1807	10.47	14.82	2.23

Av. $k \times 10^2 = 2.2 \pm 0.3$ l./mole min.

(9) The permanganate oxidation of IC is apparently accompanied by isomerization of IC to IA, and the latter is then oxidized to IIA. The isomerization of IC to IA by means of permanganate (without oxidation) was demonstrated in an independent experiment and is subject to additional study.

(10) H. H. Szmant and R. L. Lapinski, THIS JOURNAL, **75**, 6338 (1953).

(11) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 778.

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Oxidation of IB.—The solution contained 0.1600 mmole of IB and 0.1875 mmole of perbenzoic acid. The average rate constant was found to be 0.29 ± 0.03 l./mole-min.

Oxidation of IC.—The solution contained 0.4355 mmole of IC and 0.9035 mmole of perbenzoic acid. After an almost instantaneous loss of one equivalent of perbenzoic acid the rate of oxidation approached that of the rate of oxidation of IA, and during the interval of 400–800 minutes the rate of oxidation coincided with the rate reported above for IC.

Ultraviolet Spectra.—The ultraviolet spectra were determined in 95% ethanol by means of a Beckman DU spectrophotometer. The absorption curves are reproduced in Fig. 2.

PITTSBURGH 19, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

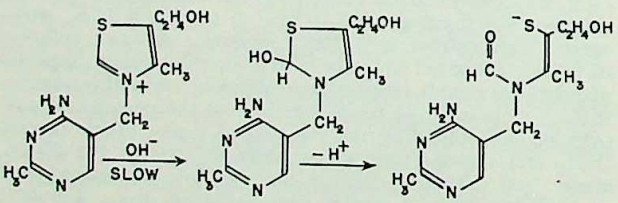
Structures of Thiamine in Basic Solution[1]

BY GEORGE D. MAIER AND DAVID E. METZLER

RECEIVED MARCH 29, 1957

Thiamine in basic solution is instantly converted to a yellow form which fades within a few minutes in water but which persists for several hours in methanol. The *p*H dependence of the zero-time concentration of this yellow form indicates that it arises by the simultaneous loss of two protons from the neutral form of thiamine with an apparent average pK value of 11.6 at 19°. In methanol the two dissociation steps are distinct and an intermediate can be detected. This intermediate non-ionic form of thiamine has been isolated as a white crystalline solid. It apparently arises through the intramolecular addition of the amino group of thiamine to the thiazolium ring with loss of one proton; opening of the thiazole ring and loss of a second proton produce the yellow form. The *p*H dependence indicates that fading of the yellow color results from formation of the pseudo-base and open-ring thiol forms. The possible biochemical significance of these unstable forms of thiamine is considered.

Thiamine (I) reacts slowly with hydroxyl ions to form a pseudo-base II and a thiol form III in which the thiazole ring has been opened.[2–4] In addition, it has been known for many years that thiamine in alkaline solutions develops a transient yellow color.[5,6] We have investigated this latter phenomenon in the belief that it might shed some light on the mechanism of the catalytic action of this vitamin.



I II III

Pseudo-Base and Colorless Thiol Forms.—Figure 1, curve A shows the ultraviolet absorption spectrum of the neutral form of thiamine (I) and (curve B) that of thiamine at *p*H 10.4, 90 minutes after its addition to this basic buffer. The latter represents the spectrum of the thiol, III, which forms slowly over a period of about an hour at this *p*H. An identical spectrum is observed for the crystalline sodium salt of III[6] dissolved in 0.02 *N* KOH. (Addition of base to simpler thiazolium salts such as 3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium chloride causes very similar absorbancy increases at all wave lengths.)

The two reactions by which the neutral form of thiamine is converted to the thiol form III can be regarded as formally equivalent to the stepwise dissociation of a diprotic acid with characteristic acid dissociation constants which can be measured titrimetrically. Williams and Ruehle[2] have reported the apparent pK_{av} (average of the apparent pK's for the two steps) of 9.0, and Watanabe and Asahi,[4] of 9.33 at 25°. We have estimated pK_{av} spectrophotometrically as 9.3 for thiamine and 10.3 for the simpler 3,4-dimethyl-5-(2-hydroxyethyl)- and 3-benzyl-4-methyl-5-(2-hydroxyethyl)-thiazolium salts.

The Yellow Form of Thiamine.—The addition of thiamine to solutions of *p*H 11 and above leads to the instantaneous production of a yellow color, which fades rapidly in aqueous media,[5] but which is clearly visible, depending on the basicity, for an hour or more in methanol. Figure 1C shows the spectrum of thiamine in 0.1 *N* NaOH extrapolated to zero time (see Experimental) and Fig. 4A the spectrum in methanolic KOH. Since these spectra are not further changed at higher base concentrations, we believe that they represent a single substance. No other forms of thiamine absorb light above 325 mμ; hence we have used the absorbancy at 349 mμ to measure the concentration of this yellow form in mixtures. In water the yellow form decays within several minutes to a substance having a spectrum identical to that of the thiol form III (Fig. 1B). A similar but much slower decay occurs in methanol. The change leading to color formation appears to be completely and rapidly reversible as indicated by the quenching of the yellow color and the immediate appearance of the spectrum of thiamine hydrochloride upon addition of hydrochloric acid to a solution containing the yellow form. The yellow color can then be regenerated quantitatively (97% or more of the original amount) by addition of more base.[5]

Figure 2 shows the increase in zero time absorbancy at 349 mμ with increasing *p*H of an aqueous

(1) This study was supported in part by the National Science Foundation. Journal Paper No. J-3174 of the Iowa Agricultural Experiment Station, Ames, Iowa, Project No. 1259.

(2) R. R. Williams and A. E. Ruehle, THIS JOURNAL, **57**, 1856 (1935).

(3) H. T. Clarke and S. Gurin, *ibid.*, **57**, 1876 (1935).

(4) A. Watanabe and Y. Asahi, *J. Pharm. Soc. Japan*, **75**, 1046 (1955).

(5) R. A. Peters and J. H. L. Philpot, *Proc. Roy. Soc.* (*London*), **B113**, 48 (1933).

(6) O. Zima and R. R. Williams, *Ber.*, **73**, 941 (1940).

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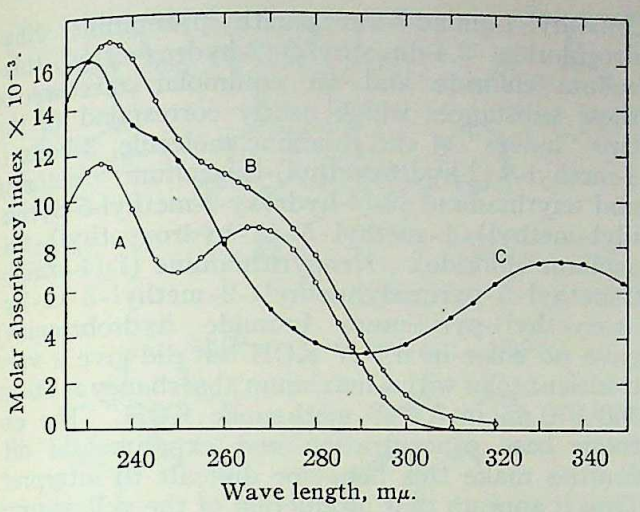

Fig. 1.—Spectra of thiamine in aqueous solutions: A, thiamine at *p*H 6.8, phosphate buffer; B, thiamine in *p*H 10.4 piperidine buffer after standing 90 minutes, or in 0.02 *N* KOH after standing 30 minutes, and white sodium salt of thiamine in 0.02 *N* KOH; C, thiamine in 0.1 *N* NaOH at time of mixing (from extrapolation).

solution of thiamine. The curve is an S-shaped "titration curve" similar to that ordinarily observed when a spectral change results from the dissociation of an acidic group. Curve A (Fig. 2) has been constructed to pass through the experimentally observed mid-point at *p*H 11.6 and to approach the limiting absorbancies at the high and low *p*H ends; it has the shape theoretically expected for the dissociation of a monoprotic acid or a diprotic acid in which $K_1 >> K_2$. However, the experimental points do not fit this curve, but do fit curve B which has a mid-point slope of twice that of curve A and which represents the theoretical shape expected for a diprotic acid in which the two protons dissociate simultaneously with no detectable amount of an intermediate singly dissociated form ($K_1 << K_2$) and $pK_{av} = {}^1/_2(pK_1 + pK_2) = 11.6$ (the apparent pK_{av} for an ionic strength of 0.2) at 19°. This unusual type of behavior is known for several compounds reported by Schwarzenbach[7] and for benzothiazole methiodide.[8] It is evident from the shapes of the published titration curves that the conversion of thiamine to the colorless thiol form III is also a reaction of this type. In thiamine solutions the pseudo-base form II is never present in amounts great enough to affect the shape of titration curves,[2,4] nor can II be detected through oxidation to the thiazolone.[9]

From the foregoing results we conclude that the yellow form arises from neutral thiamine by a reaction involving the removal of *two* protons. Zima and Williams in 1940 isolated a crystalline yellow sodium salt of thiamine by treatment of thiamine hydrochloride in ethanol with three moles of sodium ethoxide.[6] We have prepared this salt and find its spectrum and fading behavior in methanol and water to be identical to those of the yellow form described here.

(7) G. S. Schwarzenbach, *Helv. Chim. Acta*, **26**, 418 (1943); G. S. Schwarzenbach and R. Sulzberger, *ibid.*, **26**, 453 (1943).
(8) W. H. Mills, L. M. Clark and J. A. Aeschlimann, *J. Chem. Soc.*, **123**, 2353 (1923).
(9) P. Sykes and A. R. Todd, *ibid.*, 534 (1951).

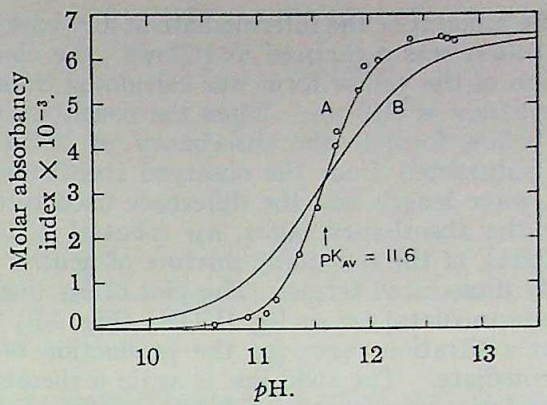

Fig. 2.—Absorbancy of thiamine at 349 mμ *versus* *p*H. Data are extrapolated back to the time of mixing. The lines are theoretical curves constructed for: A, a monoprotic acid; B, a diprotic acid with no detectable singly dissociated intermediate.

The Intermediate between the Neutral and Yellow Forms.—The development of the yellow color in methanol shows a fundamental difference from that in water. In Fig. 3A the absorbancy at 349 mμ is plotted against the logarithm of the excess, unreacted KOH concentration. The solid line is a curve of the theoretical shape for a monoprotic acid and in this case fits the experimental points well. This suggests that in methanol a more normal situation prevails in which $K_1 > K_2$ and that at intermediate basicities the thiamine should exist largely in the form of a singly dissociated intermediate. The spectra of the yellow and neutral forms exhibit points of equal absorbancy at 263 and 290 mμ. The absorbancies of thiamine in methanolic KOH of basicities intermediate to those in which either the neutral and yellow forms predominate were measured at these wave lengths. The presence of an intermediate was clearly indicated at 290 mμ by a marked increase in absorbancy (to an a_M of 5.55×10^3 at log [KOH] = −2.86) and subsequent decrease at higher base concentrations, and at 263 mμ by a lower absorbancy at intermediate base concentrations. (Similar measurements in *water* at 289 mμ indicate that no more than 5% of the intermediate is ever present, that amount being present at *p*H 11.6.)

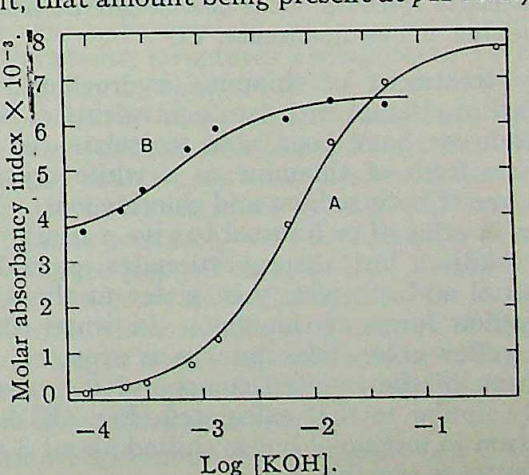

Fig. 3.—Ultraviolet absorbancy of thiamine *versus* concentration of methanolic KOH: A, molar absorbancy index at 349 mμ; B, molar absorbancy index of the intermediate plus free base forms at 290.3 mμ (see text). The lines are theoretical curves for dissociation of monoprotic acids.

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The amount of the intermediate at any base concentration was computed as follows: the concentration of the yellow form was calculated from the absorbancy at 349 mμ. Then the contribution of the yellow form to the absorbancy at 290.3 mμ was subtracted from the observed absorbancy at that wave length and the difference used to compute the absorbancy index, a_M (neutral + intermediate), of the remaining mixture of neutral plus singly dissociated forms. The plot of a_M (neutral + intermediate) *versus* log [KOH] (Fig. 3B) is in effect a titration curve for the production of the intermediate. The solid line is again a theoretical curve for a monoprotic acid with a mid-point at log [KOH] = −3.2. From Fig. 3A, the mid-point of the second dissociation step is estimated as log [KOH] = −2.15 and it follows that K_1 is about 16 times K_2. These constants are sufficiently far apart that the lower points in Fig. 3A should deviate from the constructed curve by only a few per cent. From the spectrum of a solution of log [KOH] = −3.1 in which 58% of the thiamine exists as the intermediate, the spectrum of the intermediate was computed (by subtracting the absorbancy of the neutral and yellow forms at each wave length) Fig. 4B shows the spectrum of the intermediate form in methanol.

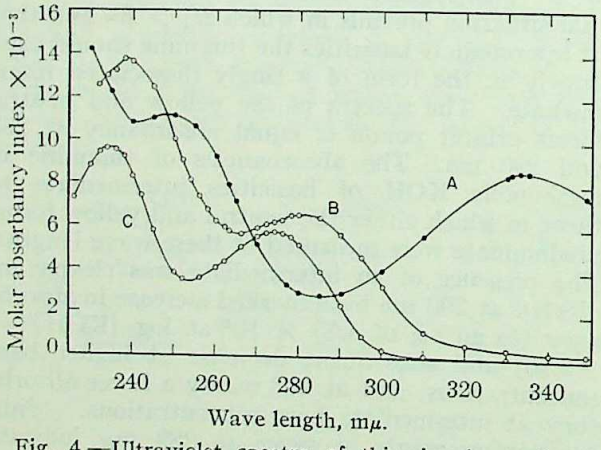

Fig. 4.—Ultraviolet spectra of thiamine in methanol: A, thiamine, 1 *N* KOH, 1–6 minutes after addition of KOH; B, calculated spectrum of the intermediate tricyclic form; C, spectrum of dihydrothiamine, VI.

By treatment of thiamine hydrochloride suspended in ethanol with two equivalents of sodium ethoxide we have been able to isolate the intermediate form of thiamine as a white crystalline solid free of both sodium and chloride ions. It dissolves in ethanol or butanol to give a nearly colorless solution but disproportionates partially in methanol and completely in water to the neutral and yellow forms of thiamine. In water the intense yellow color fades quickly as expected. The spectrum of the isolated compound in butanol is closely similar to that calculated (Fig. 4B) for the spectrum in methanol but is shifted about 3 mμ to shorter wave lengths.

The Structures of the Yellow and Intermediate Forms.—The following compounds which are structurally related to thiamine do not undergo spectral changes in 0.1 or 5.4 *N* methanolic KOH corresponding to those observed with thiamine: 2-methyl-4-amino-5-aminomethylpyrimidine dihydrochloride, 3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium chloride and an equimolar mixture of these substances which nearly correspond to the two "halves" of the thiamine molecule, 3-benzyl-4-methyl-5-(2-hydroxyethyl)-thiazolium chloride and oxythiamine (3-(4-hydroxy-2-methyl-5-pyrimidyl-methyl)-4-methyl-5-(2-hydroxyethyl)-thiazolium chloride). Neopyrithiamine (1-(4-amino-2-methyl-5-pyrimidylmethyl)-2-methyl-3-(2-hydroxyethyl)-pyridinium bromide hydrobromide) gave no color in 0.1 *N* KOH but did give a very transient color with a maximum absorbancy at about 360–370 mμ in 5.4 *N* methanolic KOH. The extreme base concentration and experimental difficulties make this behavior difficult to interpret. Thus it appears that production of the yellow form requires the presence of the primary amino group on the pyrimidine ring and the presence of the thiazolium ring in the same molecule.

We propose that the amino group of thiamine adds, with simultaneous loss of a proton, to the thiazolium ring to yield the intermediate, tricyclic, dihydrothiachromine form IV in a manner analogous to the addition of a hydroxyl ion to form the pseudo-base II. The intramolecular nature of the reaction with the amino group helps to explain its rapidity as compared to the reaction of a hydroxyl group. The ionization of IV with an opening of the thiazole ring leads to the yellow thiol form V. This structure for the yellow form was proposed by Zima and Williams[6] for their isolated compound and is supported by their analyses.

Additional support for the tricyclic structure IV for the intermediate comes from a comparison with the spectra of other aminopyrimidines. The absorption band of the intermediate near 280 mμ is shifted about 10 mμ to a longer wave length than that of the corresponding pyrimidine absorption band of dihydrothiamine (VI, Fig. 4C). Similarly, Brown and Short[10] have shown that methylation of 4-aminopyrimidines leads to bathochromic shifts of 8–9 mμ. However, IV absorbs more strongly around 240 mμ than does dihydrothiamine. It is quite possible that in IV the carbon–sulfur bond which breaks to yield V is already weakened and that this polarization of the molecule results in a higher absorption around 240 mμ, similar to that observed with the thiol form III (Fig. 1B).

The tricyclic form, IV, is closely related to thiochrome (VII) and in alcoholic solutions is gradually oxidized by air to VII as evidenced by the development of an intense blue fluorescence.[11]

(10) D. J. Brown and L. N. Short, *J. Chem. Soc.*, 334 (1953).

(11) Thiamine is oxidized readily to thiochrome by alkaline ferricyanide [G. Barger, F. Bergel and A. R. Todd, *Ber.*, **68**, 2257 (1935)]. However, we find that if the thiamine stands in base long enough for the yellow form to disappear before addition of the ferricyanide, no thiochrome is formed, nor is thiochrome formed from the white sodium salt of the thiol III (except for a trace which arises from the small amount of yellow form V in equilibrium with III. See the succeeding section of this paper for a discussion of this equilibrium). The thiol III apparently is oxidized to thiamine disulfide instead of thiochrome. On the other hand, the yellow sodium salt of V and the tricyclic form IV are oxidized readily to thiochrome by alkaline ferricyanide in accord with Syke's and Todd's view (reference 9) that V is the precursor of thiochrome.

Structure IV has also been suggested as an intermediate in the de-

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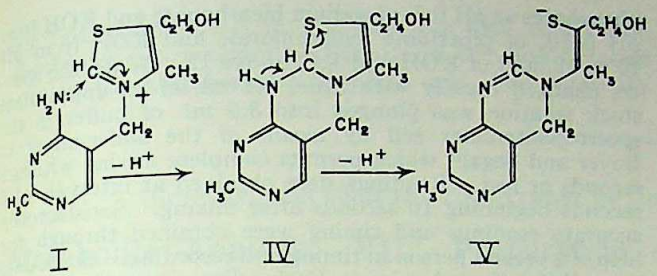
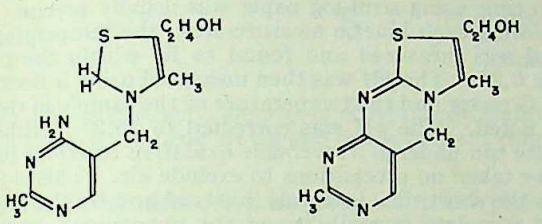
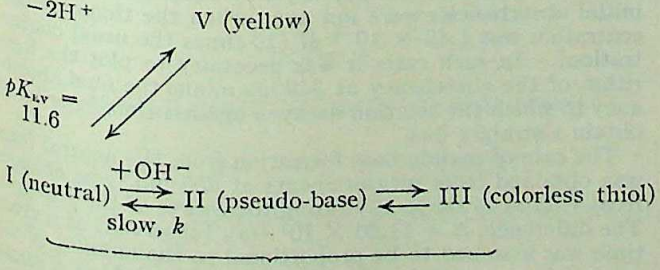


I IV V



VI VII

The Kinetics of Decay of the Yellow Color.—The yellow color decays in aqueous solutions at all *p*H values, with a half-life of less than one minute at 19° in some cases. By plunging a portion of thiamine into an alkaline buffer in a spectrophotometer cell and measuring the absorbancy at 349 mμ as a function of time, we were able to determine the rates of decay with satisfactory accuracy. At all *p*H values this decay was accurately first order with respect to the yellow form. First-order rate constants were calculated, and their logarithms are plotted against *p*H in Fig. 5. The yellow form does not exist to an appreciable extent below a *p*H of about 10.6; hence, no points could be obtained at lower *p*H values. However, the rate of reaction of thiamine with hydroxyl ion to form the colorless thiol form III could be measured in the *p*H range 10 to 10.8 by following the increase in absorbancy at 255 mμ. Again the rate was first order, this time with respect to the neutral form of thiamine. Rate data for this second reaction are also plotted against *p*H in Fig. 5. The points fall on the *same* hyperbola-like curve that describes the *p*H dependence of the rate of fading of the yellow color suggesting that the fading is caused by the *slow* reaction of hydroxyl ion with the neutral form I which is in a *rapid* equilibrium with the yellow form V. The final product is the more stable colorless thiol form III. From the pK_{av} values of 11.6 for the conversion to the yellow form



V and of 9.3 for conversion to the thiol form III, it follows that at equilibrium, the ratio of the colorless thiol form to the yellow form should be 200

composition of thiamine disulfide (ref. 9) and as a product of the reduction of thiochrome by hydrosulfite [R. Kuhn and H. Vetter, *Ber.*, **68**, 2375 (1935)].

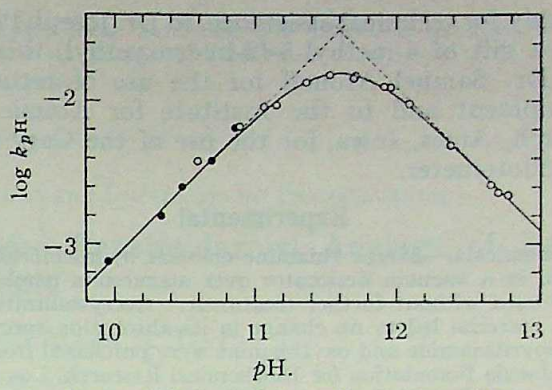


Fig. 5.—Rates of fading of the yellow color: ○, apparent first-order rate constants for the disappearance of the yellow form of thiamine in buffers of 0.2 ionic strength; ●, apparent first-order rate constants for conversion of neutral thiamine to the thiol form. The line represents the theoretical *p*H dependence (see text).

and the disappearance of the yellow color will be almost complete.

This scheme leads to the prediction that the apparent first-order rate constants k_{pH} for the fading of the yellow color and for reaction of the neutral form to give the thiol form should have the *p*H dependence

$$\log k_{pH} = \log kK_w - pH - \log (K_{av}^2 + [H^+]^2)$$

where k is the *second-order* rate constant for the reaction of the neutral form of thiamine with hydroxyl ion; K_w is the ion-product of water, and K_{av} is the average of K_1 and K_2 for the dissociation of thiamine to form the yellow compound V. The solid line in Fig. 5 is a theoretical curve constructed to fit the foregoing equation using values of log $kK_w = -13.1$ moles liter^{-1} sec.$^{-1}$ and $pK_{av} = 11.6$ at 19.2°. The excellent fit of the experimental points to this theoretical curve provides additional support for the assumption of a two-proton dissociation of thiamine to form the yellow substance.

Significance with Respect to Enzymic Catalysis.—The mechanism of the catalytic action of thiamine is still uncertain although Breslow[12] has recently presented a plausible new theory. Consideration should also be given to the possibility that at some stage in the reaction sequence by which thiamine functions, structures analogous to IV or V occur. It may be objected that a *p*Kav of 11.6 for the formation of these structures is too high to permit their function in a biological system. However, a prior reaction with a substrate such as pyruvate might decrease *p*Kav greatly. If an intermediate analogous to V were formed after reaction with pyruvate (*e.g.*, as visualized by Breslow[12]) its decarboxylation would be assisted by the conjugation with the electron-accepting centers of the pyrimidine ring in a manner quite similar to that suggested in the decarboxylation of α-amino acids by vitamin B_6-containing enzymes.[13,14]

Acknowledgments.—We gratefully acknowledge our thanks to Marcella Vermeersch and to Frances

(12) Ronald Breslow, THIS JOURNAL, **79**, 1762 (1957).

(13) A. E. Braunstein and M. M. Shemyakin, *Biokhimia*, **18**, 393 (1953).

(14) D. E. Metzler, M. Ikawa and E. E. Snell, THIS JOURNAL, **76**, 648 (1954).

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Roddy for technical assistance, to Dr. Joseph Picken for a gift of 4-methyl-5-(2-hydroxyethyl)-thiazole, to Dr. Samuel Aronoff for the use of recording equipment and to the Institute for Atomic Research, Ames, Iowa, for the use of the Cary spectrophotometer.

Experimental

Chemicals.—Merck thiamine chloride hydrochloride was dried in a vacuum desiccator over magnesium perchlorate and used without further treatment. Recrystallization of this material led to no change in its absorption spectrum. Neopyrithiamine and oxythiamine were purchased from the California Foundation for Biochemical Research, Los Angeles, and 2-methyl-4-amino-5-(2-aminomethyl)-pyrimidine from Nutritional Biochemicals Corp., Cleveland. 3,4-Dimethyl-5-(2-hydroxyethyl)-thiazolium chloride was prepared from du Pont 4-methyl-5-(2-hydroxyethyl)-thiazole and methyl iodide.[15] Eight g. of the resulting methiodide was dissolved in water and shaken for 1 hour with an excess of freshly precipitated silver chloride. The precipitated silver iodide was filtered off and the solution was concentrated in vacuum to a thick sirup. This was dissolved in 20 ml. of absolute alcohol, 15 ml. of ether was added and the methochloride was allowed to crystallize, then recrystallized from alcohol and ether; m.p. 136–138°. *Anal.* Calcd. for $C_7H_{12}ONSCl$: C, 43.4; H, 6.25; Cl, 18.3. Found: C, 43.4; H, 6.2; Cl, 18.4. 3-Benzyl-4-methyl-5-(2-hydroxyethyl)-thiazolium chloride was prepared by the procedure of Livermore and Sealock[16]; m.p. 145–147°.

Dihydrothiamine was prepared by reduction of thiamine with trimethoxyborohydride according to the procedure of Bonvicino.[17]

The white sodium salt of the thiol form of thiamine (III), the yellow sodium salt of thiamine and thiamine monochloride were prepared according to the procedures of Zima and Williams.[6]

Reagent grade (Baker) absolute methanol was employed. Moisture was carefully excluded.

The Tricyclic (Dihydrothiachromine) Form of Thiamine.—Five grams (0.015 mole) of thiamine chloride hydrochloride was suspended in 20 ml. of cold absolute alcohol and 0.03 mole of sodium ethoxide in cold ethanol of total volume 12 ml. was added with stirring. The sodium chloride was quickly filtered off by suction on a sintered glass filter and the filtrate was allowed to stand for about 3 hours in the cold. The white crystalline solid was collected on a buchner funnel. Moisture was carefully excluded through use of a rubber dam to prevent yellowing of the product. After washing with cold alcohol and peroxide-free ether the compound was dried *in vacuo* at room temperature; yield 1.1 g., m.p. 128–129° dec. *Anal.* Calcd. for $C_{12}H_{16}ON_4S$: C, 54.5; H, 6.1; N, 21.2; neut. equiv., 264. Found: C, 54.6; H. 6.2; N, 21.3; neut. equiv., 267; molecular wt. by comparison of spectrum in 0.1 *N* HCl with that of thiamine hydrochloride, 267.

Spectral Measurements.—A Beckman DU spectrophotometer with the cell compartment thermostated at 25° in most cases and at 19.2° in some experiments was used for quantitative spectral measurements. A Cary model 12 recording spectrophotometer was employed for preliminary evaluation of spectra.

Spectra usually were measured on 1.42×10^{-4} *M* solutions of the thiazolium compounds prepared by dilution of a stock solution. Spectra in methanol were obtained by adding an aliquot of the stock solution to methanolic KOH of appropriate concentration, mixing and reading the spectrum within 5 minutes for qualitative studies and within 2–3 minutes for quantitative measurements. The absorbancy of the yellow form decreased by 1–3% during the first 6 minutes after mixing.

Spectra in aqueous solutions were measured in buffers, usually of 0.2 ionic strength and consisting of potassium phosphates at *p*H 6.8, of sodium bicarbonate and KOH from *p*H 9–10, of piperidine hydrochloride and KOH from *p*H 10 to 12, and of KOH and KCl above 12. When the spectra changed rapidly with time, 0.1 ml. of an appropriate stock solution was plunged into 3.0 ml. of buffer in the spectrophotometer cell by means of the adder-mixer of Boyer and Segal[18] which permits complete mixing within 2 seconds or less. Readings were obtained at intervals of 5 seconds beginning 10 seconds after mixing. Satisfactorily accurate readings and timing were obtained through the help of a second person in timing and recording. Some data were also collected using a Varian linear recorder to plot transmittancy *versus* time. Extrapolation of absorbancies to zero time using semi-log paper was usually precise.

Following each kinetic measurement, the temperature in the cell was measured and found to lie within the limits 19.2 ± 0.2°. The *p*H was then measured using a Beckman model G meter and the temperature of the sample in the *p*H meter noted. The *p*H was corrected to 19.2°. Although thiamine can undergo irreversible oxidative reactions in air, we have taken no precautions to exclude air. This is justified by the short time intervals involved and by the demonstrated complete reversibility of the phenomena described here when the elapsed time was kept small. It appears that in most cases, only a few per cent. of irreversible decomposition occurs in the spectrophotometer cell in periods up to two hours.

Calculations.—The methanolic KOH solutions were standardized and the basicity of the final diluted solutions expressed as the logarithm of the excess KOH concentration. When the KOH concentration was low, the amount of KOH which had reacted with the thiamine was subtracted from the total amount added to give the excess. From the spectrum the amounts of yellow form, intermediate and free base present were computed and the correction was made on the assumption that 3, 2 and 1 equivalents of base, respectively, were consumed in the production of these forms from the hydrochloride. Satisfactory accuracy in the log [KOH] values was obtainable except below log [KOH] = −4.

The curve in Fig. 3B which shows the molar absorbancy index, a_M for the neutral plus intermediate forms in methanol was computed using the following data. From Fig. 3A the limiting value for a_M at 349 mμ was taken as 7.75×10^3 and assumed to represent a_M for the yellow form (the corresponding a_M in aqueous solution is 6.52×10^3). Within experimental error, the same molar absorbancy indices were obtained for the yellow sodium salt described by Zima and Williams.[6] At 290.3 mμ the a_M for the yellow form is 3.38×10^3.

First-order rate constants for the fading of the yellow color in aqueous solutions were computed by plotting the logarithm of the absorbancy at 349 mμ against time and measuring the slope. A linear relationship was observed (except in samples of low initial absorbancies) as might be expected when the absorbancy falls to zero at equilibrium. Actually a_M did not fall to zero, but from initial values as high as 6.5×10^3 to 0.02 to 0.1 $\times 10^3$. a_M would be expected to decrease to 0.03×10^3 representing the 0.5% of yellow form still present at equilibrium. The presence of impurities and slow side reactions and the difficulty of measuring very low absorbancies accurately may account for the variation in these values. In some samples, at the lower *p*H values, only a small amount of yellow color was present and initial absorbancies were low even when the thiamine concentration was 1.42×10^{-3} *M* (10 times the usual concentration). In such cases it was necessary to plot the logarithm of the absorbancy at 349 mμ minus the final absorbancy to which the solution decayed against time in order to obtain a straight line.

The rate of pseudo-base formation from the neutral form was obtained from measurements at 255 mμ. a_M changes from 7.36 to 11.66×10^3 during the course of the reaction. The difference, $\Delta = 11.66 \times 10^3 - a_M$ (observed) at a given time was assumed to be proportional to the amount of the neutral form remaining at that time. Plots of log Δ *versus* time were linear and permitted calculation of the rate constants.

Estimates of the pK_{av} for conversion to the thiol form were also obtained from data at 255 mμ for thiamine and two sim-

(15) E. R. Buchman, R. R. Williams and J. C. Keresztesy, THIS JOURNAL, **57**, 1849 (1935).

(16) A. H. Livermore and R. R. Sealock, *J. Biol. Chem.*, **167**, 699 (1947).

(17) G. E. Bonvicino, Ph.D. Thesis, Fordham University, 1952; see also P. Karrer and H. Krishna, *Helv. Chim. Acta*, **35**, 555 (1952).

(18) P. D. Boyer and H. L. Segal in "A Symposium on the Mechanism of Enzyme Action," W. D. McElroy and B. Glass, Eds., Johns Hopkins Press, Baltimore, Md., 1954, p. 523.

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pler thiazolium salts. In this case the final equilibrium absorbancy was measured. Because of the slow reaction rates in the neighborhood of pK_{av}, and slow secondary reactions, these particular pK estimates have an uncertainty of as much as ±0.2 unit.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Metabolite Analogs. VII. Preparation of Some Benzimidazolyl Analogs of Ethyl Pteroylglutamate

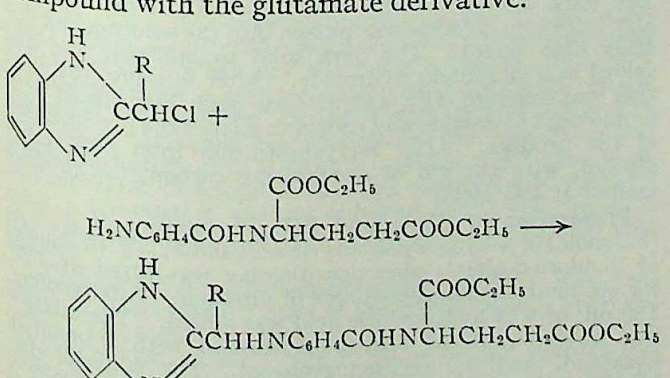
BY W. RAYMOND SIEGART AND ALLAN R. DAY

RECEIVED JANUARY 15, 1957

Some benzimidazolyl analogs of ethyl pteroylglutamate have been prepared. Substituents have been placed on the carbon atom of the methylene bridge and in the benzene ring of the benzimidazole.

Two benzimidazolyl analogs of pteroylglutamic acid have been reported previously, N-{4-[(2-benzimidazolyl)-methylamino]-benzoyl}-glutamic acid[1] and N{4-[(5-chloro-2-benzimidazolyl)-methylamino]-benzoyl}-glutamic acid. The first compound was reported to retain a certain degree of growth-promoting activity[1a] and also to be a weak growth antagonist.[1b] The 5-chloro compound was reported to be a stronger growth antagonist than the unsubstituted analog.[1b] It seemed to be desirable to extend this work, in several ways, in order to determine the possibility of obtaining strong anti-folic activity in this type of compound. In the present investigation, benzimidazolyl analogs of folic acid have been synthesized containing not only substituents in the benzene ring but also on the carbon atom of the methylene bridge. Substituents have been placed on the methylene bridge when there were no substituents on the ring and when there were substituents on the benzene ring. The choice of substituents in the benzene ring was influenced by the work of Hoover and Day.[2]

The syntheses of the benzimidazolyl analogs of pteroylglutamic acid involved four steps: (1) preparation of diethyl *p*-aminobenzoylglutamate; (2) preparation of 2-hydroxyalkylbenzimidazoles; (3) preparation of 2-chloroalkylbenzimidazoles; and (4) finally, the condensation of the chloroalkyl compound with the glutamate derivative.



p-Nitrobenzoylglutamic acid was prepared by a modified Schotten–Baumann procedure from *p*-nitrobenzoyl chloride and glutamic acid. The nitro group was reduced by catalytic hydrogenation over palladium and the corresponding aminobenzoylglutamic acid converted to its diethyl ester. Preliminary work had shown that the final products, the benzimidazolyl analogs of folic acid, were most readily isolated and purified in the form of their ethyl esters.

The 2-hydroxyalkylbenzimidazoles were prepared from the appropriate hydroxy acid and *o*-phenylenediamine by the Phillips method[3] or by fusing the reactants together. The hydroxy compounds were then converted to the corresponding chloro compounds by treatment with thionyl chloride.

In order to reduce side reactions to a minimum, the hydrochlorides of the chloro compounds were used for condensation with diethyl *p*-aminobenzoylglutamate. The condensations were carried out in dioxane solution in the presence of two equivalents of triethylamine. The main side-reaction which occurred to a greater or less extent, depending on the nature of the chloro compound, was self condensation. It had been shown earlier[4] that the 2α-chloroalkylbenzimidazoles do not always undergo normal anionic replacement reactions. They show a marked tendency to undergo self-condensation to form tetracyclic compounds. For example, 2-chloromethylbenzimidazole readily forms dibenzimidazo[1,2,-a,1′,2′,-d]piperazine. On several occasions during the course of the present work, high melting, crystalline compounds were isolated whose analyses indicated that they were tetracyclic. No attempt was made to purify these secondary products. Gummy materials also were separated from the reactions of the 2α-chloroalkylbenzimidazoles with ethyl *p*-aminobenzoylglutamate. They were assumed to be linear polymers formed from self-condensation of the chloro compounds.

For testing purposes, two benzimidazolyl analogs of the ethyl ester of pteroic acid were prepared also. They were prepared by condensing the chloroalkyl benzimidazoles with ethyl *p*-aminobenzoate.

All of the final products are being tested for physiological activity. The test results will be published elsewhere.

(1) (a) P. C. Edwards, D. Starling, A. M. Mattocks and H. E. Skipper, *Science*, **107**, 119 (1948); (b) F. E. King, R. M. Acheson, and P. C. Spensley, *Nature*, **162**, 153 (1948); *J. Chem. Soc.*, 1401 (1949).

(2) J. R. E. Hoover and A. R. Day, THIS JOURNAL, **77**, 4324 (1955); **77**, 5652 (1955); Progress Report, July 1955–January 1956, U.S.P.H.S. Grant C-2189, University of Pennsylvania.

(3) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(4) H. Skolnik, J. G. Miller and A. R. Day, THIS JOURNAL, **65**, 1854 (1943).

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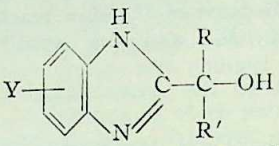
TABLE I

2-HYDROXYALKYLBENZIMIDAZOLES



Compound	R	R′	Y	Yield, %	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Found C	Found H	Found N	Found Cl
I[a]	CH_3	H	H	77	178.5–179.5								
II[b]	CH_3	CH_3	H	60	227.5–228.5								
III[a]	C_6H_5	H	H	30	202–203								
IV[c]	CH_3	H	5-Chloro	48	178–179	54.96	4.62	14.25	18.03	54.68	4.75	14.09	17.82
V[d]	CH_3	CH_3	5-Chloro	15	250–251	57.01	5.27	13.30	16.82	57.00	5.35	13.39	16.82
VI[d]	C_6H_5	H	5-Chloro	15	189–190.5	64.99	4.29	10.83	13.70	64.84	4.08	10.77	13.59
VII[e]	H	H	5-Nitro	52	196–198	49.74	3.63	21.75		49.70	3.86	21.69	
VIII[e]	CH_3	H	5-Nitro	33	204–205	52.17	4.39	20.29		52.35	4.57	20.35	
IX[e]	CH_3	CH_3	5-Nitro	21	219–221	54.29	5.02	18.99		54.27	4.95	18.89	
X[e]	H	H	4-Nitro 6-Chloro	20	213–215	42.21	2.65	18.47	15.57	42.27	2.47	18.29	15.42
XI[c]	CH_3	H	4-Nitro 6-Chloro	4	156–157	44.73	3.34	17.39	14.67	44.87	3.40	17.14	14.68
XII[d]	CH_3	CH_3	4-Nitro 6-Chloro	6	170–171.5	46.97	3.91	16.43	13.89	46.76	3.71	16.47	14.01
XIII[f]	H	H	5-Methyl	78	202–203								
XIV[c]	CH_3	H	5-Methyl	42	183–184	68.15	6.88	15.90		68.13	6.99	15.78	
XV[d]	CH_3	CH_3	5-Methyl	16	244–245	69.43	7.43	14.73		69.25	7.24	14.64	
XVI[d]	H	H	4-Amino 6-Chloro	53	224–225	48.61	4.09	21.27	17.94	48.45	4.29	21.15	17.76

[a] Ref. 3. [b] Ref. 4. [c] Recryst. from 33% ethanol. [d] Recryst. from 50% ethanol. [e] Recryst. from 95% ethanol. [f] P. Mamalis, V. Petrow and B. Sturgen, *J. Chem. Soc.*, 1600 (1950).

Experimental

p-**Nitrobenzoylglutamic Acid.**—A solution of 47 g. (0.25 mole) of *p*-nitrobenzoyl chloride in 170 ml. of benzene was added slowly, with stirring and cooling, to a solution of 29.4 g. (0.2 mole) of glutamic acid and 32 g. (0.8 mole) of sodium hydroxide in 170 ml. of water. After the completion of the reaction, the aqueous layer was separated and adjusted to a *p*H of 4 to 5 with concentrated hydrochloric acid and the *p*-nitrobenzoic acid removed by filtration. The filtrate was adjusted to a *p*H of 1 and cooled overnight. The precipitated *p*-nitrobenzoylglutamic acid was removed and recrystallized from hot water; yields 75–80%, m.p. 112.5–113.5°.

p-**Aminobenzoylglutamic Acid.**—The amino compound was obtained by hydrogenation of the nitro derivative over palladium-in-ethanol solution. The crude product was recrystallized from hot water with the aid of decolorizing carbon; yield 75%, m.p. 172–173°.

Diethyl *p*-**Aminobenzoylglutamate.**—This ester was prepared by the method of Waller, *et al.*[5]; yield 70%, m.p. 143–144°.

Preparation of 2-Hydroxyalkylbenzimidazoles.—These compounds were prepared from the corresponding *o*-phenylenediamines and α-hydroxy acids. The following were made by the Phillips method[3]: 2-(1-hydroxyethyl)-benzimidazole (I), 2-(1-hydroxyisopropyl)-benzimidazole (II), 2-(1-hydroxybenzyl)-benzimidazole (III), 2-(1-hydroxyethyl)-5-chlorobenzimidazole (IV), 2-(1-hydroxyisopropyl)-5-chlorobenzimidazole (V), 2-hydroxymethyl-5-nitrobenzimidazole (VII), 2-(1-hydroxyethyl)-5-nitrobenzimidazole (VIII), 2-(1-hydroxyisopropyl)-5-nitrobenzimidazole (IX), 2-hydroxymethyl-4-nitro-6-chlorobenzimidazole (X), 2-(1-hydroxyethyl)-4-nitro-6-chlorobenzimidazole (XI), 2-hydroxymethyl-5-methylbenzimidazole (XIII), 2-(1-hydroxyethyl)-5-methylbenzimidazole (XIV), 2-(1-hydroxyisopropyl)-5-methylbenzimidazole (XV), and 2-hydroxymethyl-4-amino-6-chlorobenzimidazole (XVI).

The Phillips method did not give good yields in all cases. In the preparation of IV and VIII, after the refluxing period was completed, the solution was adjusted to a *p*H of 5. The aqueous layer was decanted from a dark oil that had formed and the solution adjusted to *p*H 8 to precipitate the benzimidazole product. The procedure was least efficient for the preparation of X, XI and XII. In these cases, after the refluxing period, the mixture was cooled and the solid removed by filtration. After washing with water, the solid was treated with 2 *N* sodium hydroxide solution and filtered. The filtrate was acidified with hydrochloric acid, neutralized with ammonium hydroxide, cooled and the solid removed. The first filtrate was made 2 *N* with sodium hydroxide and filtered. The filtrate was acidified with hydrochloric acid, neutralized with ammonium hydroxide, cooled and the precipitate removed. The two precipitates were combined and recrystallized from alcohol.

The following compounds were prepared by fusing the diamine and hydroxy acid: 2-(1-hydroxybenzyl)-5-chlorobenzimidazole (VI) and 2-(1-hydroxyisopropyl)-4-nitro-6-chlorobenzimidazole (XII).

Preparation of VI.—4-Chloro-*o*-phenylenediamine (14.25 g., 0.1 mole) was added to 13.6 g. (0.1 mole) of molten mandelic acid (125°). The reaction mixture was maintained at 125° in an atmosphere of nitrogen for two hours. The dark gummy residue was dissolved in dry ethanol. Dry hydrogen chloride was passed into the solution and dry ether then added. The dark solid so obtained was dissolved in 2 *N* sodium hydroxide. After filtering, the solution was acidified with hydrochloric acid, neutralized with ammonium hydroxide and cooled to hasten the precipitation of the product. After recrystallization from 50% ethyl alcohol, with the aid of decolorizing carbon, the product melted at 189–190.5°.

Preparation of Compound XII.—A mixture of 20.8 g. (0.2 mole) of-α-hydroxyisobutyric acid and 37.5 g. (0.2 mole) of 5-chloro-3-nitro-*o*-phenylenediamine was fused at 110° for six hours in an atmosphere of nitrogen. After cooling, 150 ml. of 4 *N* hydrochloric acid was added. The mixture was filtered and the filtrate neutralized with ammonium hydroxide and the product removed. The material that was insoluble in the hydrochloric acid was treated with 2 *N* sodium hydroxide and filtered. The filtrate was acidified with hydrochloric acid, neutralized with ammonium hydroxide, cooled and the product removed by filtration. The two products were combined and recrystallized from 50% ethyl alcohol with the aid of decolorizing carbon. Yellow needles were obtained.

Preparation of 2-Chloroalkylbenzimidazoles.—Many difficulties were encountered in attempting to convert the hydroxy compounds to the corresponding chloro compounds.

(5) C. W. Waller, *et al.*, THIS JOURNAL, 70, 19 (1948).

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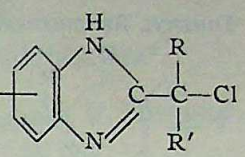
TABLE II

2-CHLOROALKYLBENZIMIDAZOLES



Compound	R	R′	Y	Yield, %	M.p., °C.	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl
XVII[b]	CH_3	H	H	95[a]									
XVIII[b]	CH_3	CH_3	H	95[a]									
XIX	C_6H_5	H	H	28	164–168 d.	69.28	4.57	11.55	14.60	69.47	4.62	11.65	14.45
XX	CH_3	H	5-Chloro	12	128–130	50.23	3.72	13.02	33.02	50.47	3.75	12.87	32.84
XXI[b]	CH_3	CH_3	5-Chloro	47	123–125 d.	45.22	4.18	10.55	40.04	43.46	4.5–4.6	10–10.6	37–39
XXII	H	H	5-Nitro	23	184–185	45.40	2.86	19.86	16.75	45.39	3.08	19.87	16.55
XXIII[b]	CH_3	H	5-Nitro	25–40	[c]								
XXIV[b]	CH_3	CH_3	5-Nitro	35–40	[d]								
XXV[c]	CH_3	H	5-Methyl	50–60	[e]								
XXVI[b]	CH_3	CH_3	5-Methyl	76	[e]								

[a] Yield as hydrochloride. [b] This compound was not obtained analytically pure, but was used successfully to make the folic acid analog. [c] Gummy solid. [d] No definite m.p.; starts to decompose at 130°. [e] Starts to decompose at 45–50°.

The free bases of the 2-chloroalkylbenzimidazoles are very reactive and tend to self-condense. In four cases the pure free bases could not be obtained although the crude free bases were used successfully to make the folic acid analogs. In most cases the hydrochlorides of the 2-chloroalkyl compounds could be isolated in better yields than the free bases and they appeared to be considerably more stable.

2-(1-Chloroethyl)-benzimidazole (XVII) and 2-(1-chloroisopropyl)-benzimidazole (XVIII) were obtained as their hydrochlorides by heating the hydrochlorides of I and II, respectively, in chloroform solution for 2–3 hours with thionyl chloride.[4] After cooling, dry ether was added to precipitate the hydrochlorides. The products were thoroughly washed with ether and dried.

The hydrochloride of 2-(1-chlorobenzyl)-benzimidazole (XIX) was prepared in a similar way in 50–60% yields. The free base was obtained by dissolving the hydrochloride in the least amount of water. This solution was cooled and slowly neutralized with sodium bicarbonate solution. The crude free base was removed, washed with ice-water and dried *in vacuo*. It was recrystallized by dropping the compound into boiling acetone, decanting the acetone from a heavy red oil and cooling. White needles were obtained.

The hydrochloride of 2-(1-chloroethyl)-5-chlorobenzimidazole (XX) was prepared from 2-(1-hydroxyethyl)-5-chlorobenzimidazole hydrochloride as described above, yields 60–70%. The dry, crude free base obtained from the hydrochloride was recrystallized by adding it to boiling benzene. The benzene was decanted from a dark oil which formed and cooled. White needles were obtained.

Difficulties were encountered in preparing the hydrochloride of 2-(1-chloroisopropyl)-5-chlorobenzimidazole (XXI) from 2-(1-hydroxyisopropyl)-5-chlorobenzimidazole hydrochloride. When dry ether was added to precipitate the hydrochloride, a gummy material was obtained. It was converted to a solid by stirring it with several portions of dry ether. Attempts to recrystallize the solid from dry alcohol and ether gave a gummy material which once more was converted to a solid by treating several times with dry ether. Although it was not obtained analytically pure, it was used successfully for the preparation of the folic acid analog.

2-Chloromethyl-5-nitrobenzimidazole (XXII) was prepared by dissolving 0.1 mole of the corresponding hydroxymethyl compound in 250 ml. of boiling dioxane. The solution was cooled to 60° and 30 ml. of thionyl chloride was added with stirring. The reaction was exothermic and no further heat was applied. After the temperature dropped to room temperature, dry ether was added to complete the precipitation of the hydrochloride. After removing the hydrochloride, washing with dry ether and drying, it was dissolved in cold water. This solution was slowly neutralized with sodium bicarbonate solution. The product was removed by filtration, washed with water and dried. It was purified by dropping it into boiling benzene and filtering to remove insoluble material. On cooling slowly an oil was first separated. The benzene was decanted and further cooled to give the product (white needles).

2-(1-Chloroethyl)-5-nitrobenzimidazole (XXIII) was prepared from 0.15 mole of the hydroxyethyl compound and 80 ml. of thionyl chloride. The solution was refluxed for 1.5 hours. The free base was obtained from this solution by the same procedure used for XXII. The product could not be obtained in pure form but it formed the expected analog with diethyl *p*-aminobenzoylglutamate. The following is a typical analysis. *Anal.* Calcd. for $C_9H_8O_2N_3Cl$: C, 47.90; H, 3.58; N, 18.63; Cl, 15.71. Found: C, 49.45; H, 3.64; N, 17.60; Cl, 14.44.

2-(1-Chloroisopropyl)-5-nitrobenzimidazole (XXIV) was prepared from 2-(1-hydroxyisopropyl)-5-nitrobenzimidazole in the same manner as XXIII. The final crystallization was made from a solution containing equal amounts of benzene and petroleum ether. The analytical data were similar to those noted above but the product was used successfully to prepare the desired analog.

2-(1-Chloroethyl)-5-methylbenzimidazole hydrochloride (XXV) was prepared from the corresponding hydroxyethyl compound by the method used for the preparation of XVII. The free base could not be obtained and even the hydrochloride could not be obtained analytically pure. The latter was obtained as an oil from dry ethanol and ether. The oil was extracted several times with dry ether and placed in a vacuum desiccator over calcium chloride until solidification was complete; yields 50–63%. A typical analysis: *Anal.* Calcd. for $C_{10}H_{12}N_2Cl_2$: C, 51.96; H, 5.24; N, 12.12; Cl, 30.67. Found: C, 50.19; H, 5.71; N, 11.99; Cl, 27.43.

2-(1-Chloroisopropyl)-5-methylbenzimidazole (XXVI) was prepared from 2-(1-hydroxyisopropyl)-5-methylbenzimidazole by the same procedure used for XXV. Similar to XXV, it could not be obtained analytically pure, but was used successfully for the preparation of the corresponding folic acid analog.

Preparation of Benzimidazolyl Analogs of Diethyl *p*-Aminobenzoylglutamate. Diethyl N-{4-[1-(2-Benzimidazolyl)-ethylamino]-benzoyl}-glutamate (XXVII).—2-(1-Chloroethyl)-benzimidazole hydrochloride (54.25 g., 0.25 mole), 80 g. (0.25 mole) of diethyl *p*-aminobenzoylglutamate and 200 ml. of dry dioxane were placed in a flask. Triethylamine (50.5 g., 0.5 mole) was added and the solution refluxed for 10 hours. After standing overnight, the precipitated triethylamine hydrochloride was removed. It was washed with water and the water-insoluble residue was dried. The product was extracted with benzene and then recrystallized from alcohol–water.

Diethyl N-{4-[1-(2-Benzimidazolyl)-isopropylamino]-benzoyl}-glutamate (XXVIII).—The procedure for XXVII was used here also. In these preparations an additional small amount of product could be obtained by concentrating the original filtrate. The oil so obtained was extracted with benzene leaving a small amount of solid product.

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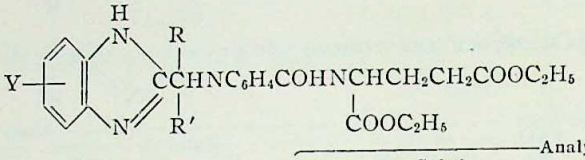
TABLE III

DIETHYL BENZIMIDAZOLYL *p*-AMINOBENZOYLGLUTAMATES



Compound	Substituents R	R′	Y	Yield, %	M.p., °C.	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl
XXVII	CH_3	H	H	23	197–198	64.35	6.49	12.01		64.45	6.45	12.03	
XXVIII	CH_3	CH_3	H	24	178–180	65.07	6.72	11.66		65.23	6.67	11.70	
XXIX	C_6H_5	H	H	41	168–170	68.17	6.11	10.60		68.38	6.02	10.51	
XXX	CH_3	H	5-Chloro	18	90–91	59.93	5.85	11.16	7.08	59.96	5.75	10.93	7.27
XXXI	CH_3	CH_3	5-Chloro	32	157–159	60.65	6.08	10.88	6.86	60.78	6.25	10.89	6.94
XXXII	H	H	5-Nitro	12	184–185	57.93	5.48	14.08		57.78	5.46	14.00	
XXXIII	CH_3	H	5-Nitro	11	107–110	58.69	5.73	13.69		58.50	5.54	13.87	
XXXIV	CH_3	CH_3	5-Nitro	14	195–197	59.46	5.96	13.33		59.45	5.91	13.47	
XXXV	CH_3	H	5-Methyl	11	161.5–162.5	64.97	6.72	11.66		64.91	6.61	11.73	
XXXVI	CH_3	CH_3	5-Methyl	15	108–110	65.55	6.94	11.33		65.39	6.93	11.38	

Diethyl N-{4-[1-(2-Benzimidazolyl)-benzylamino]-benzoyl}-glutamate (XXIX).—In this preparation the free base 2-(1-chlorobenzyl)-benzimidazole was used in place of the hydrochloride and only one equivalent of triethylamine was added. Otherwise the procedure for XXVII was followed.

Diethyl N-{4-[1-(5-Chloro-2-benzimidazolyl)-ethylamino]-benzoyl}-glutamate (XXX).—The procedure for the preparation of XXVII was used in this case. To obtain the product the filtrate from the triethylamine hydrochloride was evaporated under reduced pressure and the resulting oil allowed to stand overnight under benzene to produce a solid material which was recrystallized from benzene to give a product with one molecule of benzene; m.p. 103–105°.

Anal. Calcd. for $C_{31}H_{35}O_5N_4Cl$: C, 64.29; H, 6.10; N, 9.68; Cl, 6.12. Found: C, 63.98; H, 6.13; N, 9.69; Cl, 6.22.

Several recrystallizations from carbon tetrachloride gave a pure product free of benzene; yield 18%.

Diethyl N-{4-[1-(5-Chloro-2-benzimidazolyl)-isopropyl-amino]-benzoyl}-glutamate (XXXI).—The method used for preparing XXVII was employed here also. The product was obtained from the filtrate, after removing the triethylamine hydrochloride, in the same manner that XXIX was isolated. In this case the pure, unsolvated product was obtained by recrystallization from benzene.

Diethyl N-{4-[1-(5-Nitro-2-benzimidazolyl)-methyl-amino]-benzoyl}-glutamate (XXXII).—This compound was prepared by the method used for compound XXVII except that the product was isolated from the filtrate from the triethylamine hydrochloride by evaporation under reduced pressure. The oily product so obtained was extracted with hot benzene. On cooling to room temperature some diethyl *p*-aminobenzoylglutamate separated and was removed. The analog XXXII was obtained by evaporation of the benzene filtrate under reduced pressure. It was recrystallized from 50% alcohol–water.

Diethyl N-{4-[1-(5-Nitro-2-benzimidazolyl)-ethylamino]-benzoyl}-glutamate (XXXIII).—It was prepared by the method used for XXXI from 2-(1-chloroethyl)-5-nitrobenzimidazole hydrochloride and diethyl *p*-aminobenzoylglutamate with the following modifications: (a) the triethylamine in an equal volume of dioxane was added over a period of one hour to the reaction mixture at 60°; and (b) the resulting mixture was held at 60° for 8 hours with continual stirring.

Diethyl N-{4-[1-(5-Nitro-2-benzimidazolyl)-isopropyl-amino]-benzoyl}-glutamate (XXXIV) and diethyl N-{4-[1-(5-methyl-2-benzimidazoyl)-ethylamino]-benzoyl}-glutamate (XXXV) were prepared by the method used for XXX. In these cases, however, the products were recrystallized from alcohol–water.

Diethyl N-{4-[1-(5-Methyl-2-benzimidazolyl)-isopropyl-amino]-benzoyl}-glutamate (XXXVI).—The procedure used for the preparation of XXX was used here also. In this case the final purification was accomplished by recrystallization from carbon tetrachloride.

Preparation of Benzimidazolyl Analogs of the Ethyl Ester of Pteroic Acid. Ethyl 4-[1-(2-Benzimidazolyl)-ethylamino]-benzoate.—2-(1-Chloroethyl)-benzimidazole hydrochloride (39.4 g., 0.18 mole), 29.7 g. (0.18 mole) of ethyl *p*-aminobenzoate and 125 ml. of dry dioxane were placed in a flask and 36.36 g. (0.36 mole) of triethylamine added. The solution was refluxed for 8 hours, cooled and the precipitate removed. After thorough extraction with water, the residue was recrystallized from alcohol–water; yield 34%, m.p. 213–215°.

Anal. Calcd. for $C_{18}H_{19}O_2N_3$: C, 69.88; H, 6.20; N, 13.59. Found: C, 70.08; H, 6.34; N, 13.72.

Ethyl 4-[1-(5-Chloro-2-benzimidazolyl)-ethylamino]-benzoate.—This compound was prepared from 2-(1-chloroethyl)-5-chlorobenzimidazole by the above procedure. The product was purified by recrystallization from benzene; yield 14%, m.p. 191–193°.

Anal. Calcd. for $C_{18}H_{18}O_2N_3Cl$: C, 62.87; H, 5.29; N, 12.22; Cl, 10.31. Found: C, 62.61; H, 5.37; N, 12.08; Cl, 10.27.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

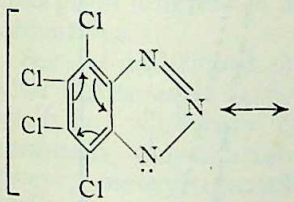
Halogenated Benzotriazoles[1]

BY RICHARD H. WILEY AND KARL F. HUSSUNG

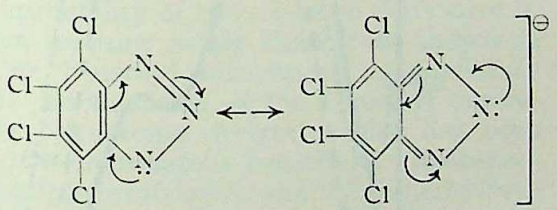
RECEIVED FEBRUARY 23, 1957

4,7- and 5,6-dichlorobenzotriazole add to conjugated systems to give 2- and 1-substituted derivatives, respectively. This establishes with more certainty the previously postulated steric effect in which 4,7-substituents direct this type of addition to the 2-position. Tetrabromobenzotriazole and 5-methyl-4,6,7-trichlorobenzotriazole also give 2-substituted conjugate addition products. The halogenation of 2-methyl-4-nitro-, 4-nitro- and 2,5-dimethylbenzotriazoles gives the 4,5,6,7-tetrachloro derivative with replacement of the bz substituent by chlorine. Some previously undescribed compounds including several tetrachlorobenzotriazole derivatives, 4-iodobenzotriazole and 2-methyl-5-nitrobenzotriazole have been prepared and characterized. Nitration of 2-methylbenzotriazole gives the 5-nitro derivative whose structure has been established by comparison with 2-methyl-4-nitrobenzotriazole, the structure of which has been established by its chlorination to 2-methyl-4,5,6,7-tetrachlorobenzotriazole.

In previous papers in this series,[2-4] we have described the structural problems which result from the possibility for 1- and 2-isomerism in the products of the conjugate addition of azoles to unsaturated systems. One of the unusual observations in these studies was that 4,5,6,7-tetrachlorobenzotriazole adds to conjugated unsaturated systems to give 2-substituted derivatives whereas benzotriazole itself gives only 1-substituted derivatives. The absence of any obvious electronic factor attributable to the chlorine substituents, which can result in the exclusive participation of



Ia

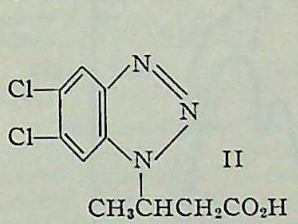


Ib Ic

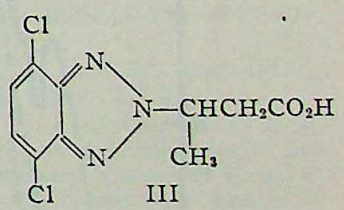
resonance structure Ic in the addition reaction, suggests that a steric factor is primarily responsible. In order to evaluate this factor in more detail the 4,7- and 5,6-dichlorobenzotriazoles, their 1- and 2-methyl derivatives and their conjugate addition products have been prepared and characterized. A variety of additional types of substituted benzotriazoles, including tetrabromobenzotriazole, have been prepared and the chlorination and bromination processes have been further characterized. The results of these studies will be discussed in this paper.

5,6-Dichlorobenzotriazole was prepared from *o*-dichlorobenzene *via* 4,5-dichloro-1,2-dinitrobenzene[5] which was reduced to the diamine and cyclized to the triazole in 50% yield. 4,7-Dichlorobenzotriazole was prepared from 2,5-dichloroaniline. The acylated aniline was nitrated and converted to 2,5-dichloro-6-nitroaniline.[6] This was reduced to 3,6-dichloro-*o*-phenylenediamine[7] which was diazotized to give the triazole in 81% yield. The 1- and 2-methyl derivatives of each were separated by recrystallization from dilute sulfuric acid in which the less basic 2-methyl derivatives are less soluble. The absorption data for the 1- and 2-methyl derivatives of 5,6-dichlorobenzotriazole show maxima at 272 and 295 and at 293 mμ, respectively. The absorption data for the 1- and 2-methyl derivatives of 4,7-dichlorobenzotriazole show the same general pattern but with more structure. The principal maxima occur at 272 and 294 and at 285 mμ, respectively, with several additional slightly less intense maxima. The complete data are given in Figs. 1 and 2.

Addition reactions with crotonic acid gave β-1′-(5′,6′-dichlorobenzotriazolyl)-butyric acid (II) and



II



III

β-2′-(4′,7′-dichlorobenzotriazolyl)-butyric acid (III). β-Phenyl-β-2′-(4′,7′-dichlorobenzotriazolyl)-propiophenone was obtained from benzalacetophenone and 4,7-dichlorobenzotriazole. The absorption maxima, summarized in Figs. 1 and 2, are consistent with these structural assignments. Both of the 2-substituted derivatives show single maxima at 286 mμ, and the 1-substituted derivative shows double maxima at 274 and 296 mμ. These data establish that the presence of the chlorine atoms in the 4,7-positions is sufficient to cause the addition reaction to take place in the 2-position and that the 5,6-chlorine substituents do not interfere with addition at the 1-position. In the absence of additional data relating this orientation to the inductive effect of the chlorine or to contributions from resonance structures related to the electron release characteristics of the chlorine, the orientation to the 2-position is assigned to a type

(1) The authors gratefully acknowledge a grant from Eli Lilly and Co. in partial support of this research.
(2) Richard H. Wiley, Karl F. Hussung and James Moffat, THIS JOURNAL, **77**, 5105 (1955).
(3) Richard H. Wiley, N. R. Smith, D. M. Johnson and James Moffat, *ibid.*, **77**, 2572 (1955).
(4) Richard H. Wiley, N. R. Smith, D. M. Johnson and James Moffat, *ibid.*, **76**, 4933 (1954).
(5) J. J. Blanksma, *Rec. trav. chim.*, **21**, 419 (1902).
(6) F. Beilstein and A. Kurbatow, *Ann.*, **196**, 215 (1879).
(7) E. Noelting and E. Kopp, *Ber.*, **38**, 3515 (1905).

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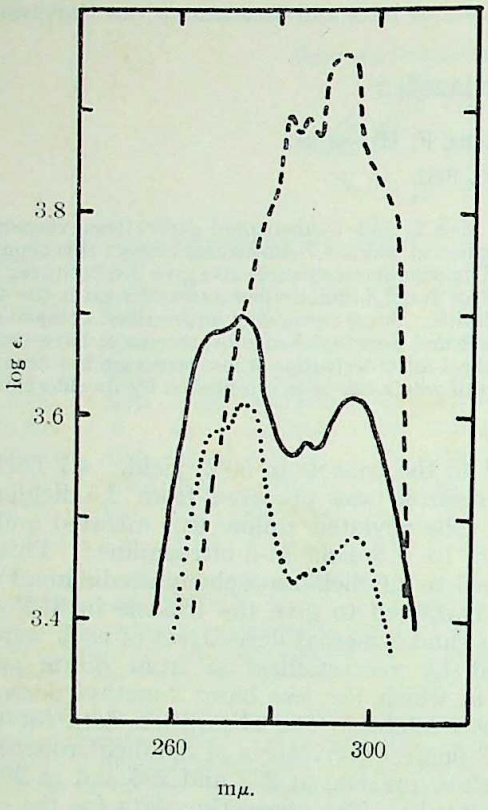

Fig. 1.—Ultraviolet absorption curves for 1-methyl-5,6-dichlorobenzotriazole (———); 2-methyl-5,6-dichlorobenzotriazole (– – – –); β-1′-(5′,6′-dichlorobenzotriazolyl)-butyric acid (. . . .).

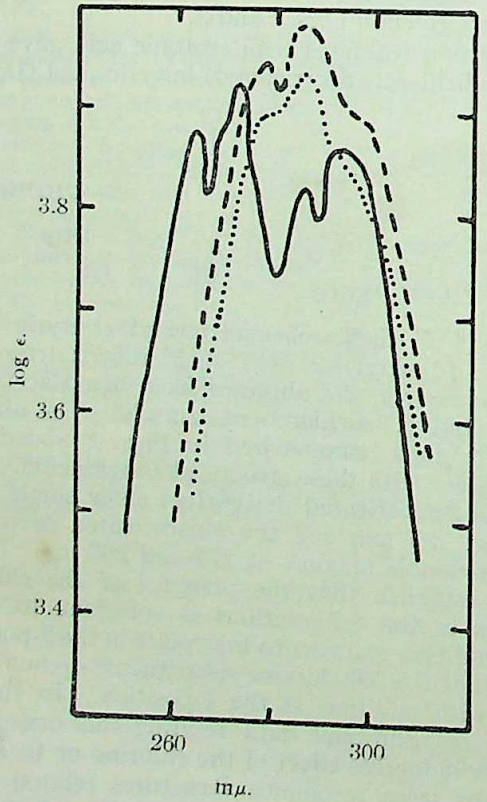

Fig. 2.—Ultraviolet absorption curves for 1-methyl-4,7-dichlorobenzotriazole (———); 2-methyl-4,7-dichlorobenzotriazole (– – – –); β-2′-(4′,7′-dichlorobenzotriazolyl)-butyric acid (. . . .).

of steric hindrance presumably characteristic of these and related systems.

The addition products obtained from tetrabromobenzotriazole are also of the 2-substituted type. Tetrabromobenzotriazole has been obtained in 54% yield from benzotriazole, bromine and concd. nitric acid. 5-Chloro-4,6,7-tribromobenzotriazole has been obtained similarly from 5-chlorobenzotriazole in 56% yields. The 1- and 2-methyl and ethyl derivatives of tetrabromobenzotriazole have been prepared by bromination of 1- and 2-alkylbenzotriazoles. The absorption data show maxima for the 1-alkyl derivatives at 278–289 and 308 mμ. The 2-alkyl derivatives show a single principal maximum at 306 mμ. The introduction of four bromo groups has produced very little, if any, bathochromic shift in these maxima as compared to the tetrachloro analog. The adduct from benzalacetophenone, β-phenyl-β-2′-(4′,5′,6′,7′-tetrabromobenzotriazolyl)-propiophenone, shows a single maximum in the 300–308 mμ range characteristic of the 2-substituted benzotriazoles. The data are given in Figure 3.

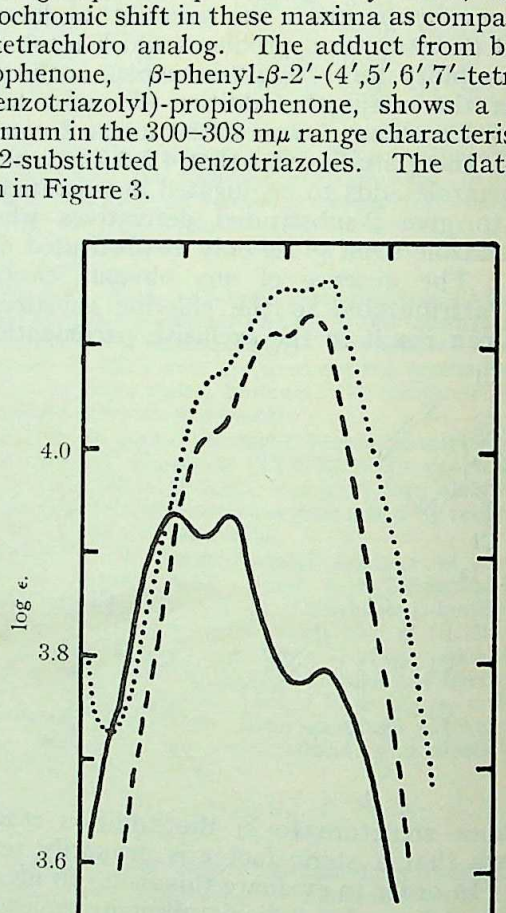

Fig. 3.—Ultraviolet absorption curves for 1-ethyl-4,5,6,7-tetrabromobenzotriazole (———); 2-ethyl-4,5,6,7-tetrabromobenzotriazole (– – – –); β-phenyl-β-2′-(4′,5′,6′,7′-tetrabromobenzotriazolyl)-propiophenone (. . . .).

Addition products obtained from 5-methyl-4,6,7-trichlorobenzotriazole[8] are also of the 2-substituted type. Chlorination of 5-methylbenzotriazole gives the trichloro derivative. Adducts from benzalacetophenone, acrylamide and acrylonitrile show single maxima in the 295–300 mμ range characteristic of the 2-substituted derivatives.

In the course of these studies several previously

(8) T. Zincke and H. Lawson, *Ann.*, **249**, 370 (1888).

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undescribed derivatives of benzotriazole have been obtained. These include the methiodide and dimethochloride of 2-(2-dimethylaminoethyl)-tetrachlorobenzotriazole, 1-dimethylamino-4,5,6,7-tetrachlorobenzotriazole, β-2′-(tetrachlorobenzotriazolyl)-butyramide, β-1′-(benzotriazolyl)-butyramide and the 1- and 2-ethyl derivatives of tetrachlorobenzotriazole. 4-Iodobenzotriazole has been prepared from 4-nitrobenzotriazole[9] by reduction and replacement of the amino group. 1-Methyl-6-chlorobenzotriazole has been prepared from 4-chloro-1,2-dinitrobenzene[10] *via* 5-chloro-2-nitro-N-methylaniline,[11] reduction to the diamine and cyclization with nitrous acid. Bromination gave the tribromo derivative.

Some new observations about substitution reactions in the benzotriazole series are available. The nitration of 2-methylbenzotriazole has been shown to give 2-methyl-5-nitrobenzotriazole, m.p. 150–152°. This structure is established by comparison with 2-methyl-4-nitrobenzotriazole, m.p. 183–184°. The latter was obtained by methylation of the known 4-nitrobenzotriazole. The structure of the 4-nitro compound as that of a 2-methyl derivative is established by the fact that it gives 2-methyl-4,5,6,7-tetrachlorobenzotriazole on chlorination. The presence of the nitro group obscures the usual absorption differences between the 1- and 2-methyl derivatives.

Several additional observations about the character of the aqua regia chlorinations are also now available. Contrary to our previous report[2] the persistent chlorination of 1-methylbenzotriazole gives 1-methyltetrachlorobenzotriazole. Apparently, the incomplete chlorination results from an increased insolubility of the trichloro derivative in the reaction mixture rather than from the steric effect of the 1-methyl substituent as previously postulated. Bromination of the 1-methyl derivative to the tetrabromo derivative also has been achieved. On chlorination 2-methyl-4-nitrobenzotriazole, 4-nitrobenzotriazole and 2,5-dimethylbenzotriazole are converted to tetrachlorobenzotriazoles. In these systems the bz (but not the 2) substituents are replaced by chlorine. 2,5-Dimethylbenzotriazole was prepared by alkylation and separated by precipitation of the ether-insoluble hydrochlorides of the 1-methyl analogs.

These observations establish two new factors about the substitution reactions of benzotriazoles: (1) substitution takes place at the 5-position in the 2-substituted types and (2) replacement of nitro and methyl by chloro takes place during chlorination.

Experimental[12]

5,6-Dichlorobenzotriazole.—To a solution of 16.3 g. (0.069 mole) of 4,5-dichloro-1,2-dinitrobenzene[5] in 75 ml. of concd. hydrochloric acid was added 93.5 g. (0.414 mole) of stannous chloride dissolved in 300 ml. of concd. hydrochloric acid. The resulting solution was heated with stirring until all the dinitrobenzene was reacted as indicated by the disappearance of an orange color. The solution was cooled, filtered and the resulting product washed with concd. hydrochloric acid. The dihydrochloride of the diamine thus obtained was dissolved in water, cooled to 0° and treated with 4.75 g. (0.069 mole) of sodium nitrite in 15 ml. of water. The solid product was filtered, washed with water, recrystallized from ethanol–water and dried to give 6.5 g. (50%) of crude product. Two recrystallizations from nitromethane and one from ethyl acetate gave an analytical sample, m.p. 264–266°; λ_{max}, 265 (s = shoulder) (log ε 3.50), 270(3.53), 286(s)(3.61), 292(3.67).

Anal. Calcd. for $C_6H_3N_3Cl_2$: N, 22.35; neut. equiv., 188.0. Found: N, 22.42; neut. equiv., 188.3.

2-Methyl-5,6-dichlorobenzotriazole.—To a solution of 3.7 g. (0.02 mole) of 5,6-dichlorobenzotriazole in 100 ml. of 1 *N* sodium hydroxide was added 2.5 g. (0.02 mole) of dimethyl sulfate dropwise over a period of 10 minutes. The resulting mixture was heated on a steam-bath for 1 hr. The solid product which separated on cooling was collected on a filter, washed with water and dried to give 2.0 g. of a crude mixture of 1- and 2-methyl derivatives. Two recrystallizations from dilute sulfuric acid gave 0.75 g. (18%) of reasonably pure 2-methyl derivative. Two additional recrystallizations from methanol gave an analytical sample, m.p. 186–188°; λ_{max}, 282(3.89), 286(3.89), 293(3.95), 300(s)(3.84).

Anal. Calcd. for $C_7H_5N_3Cl_2$: N, 20.80. Found: N, 20.65.

1-Methyl-5,6-dichlorobenzotriazole.—The sulfuric acid filtrates from the recrystallization of the above mixture of 1- and 2-methyl-5,6-dichlorobenzotriazole were diluted with water to precipitate 1.25 g. (31%) of reasonably pure 1-methyl derivative. Three additional recrystallizations from nitromethane gave an analytical sample, m.p. 210–212°; λ_{max}, 268(s)(3.68), 272(3.70), 286(s)(3.57), 295 (3.62).

Anal. Calcd. for $C_7H_5N_3Cl_2$: N, 20.80. Found: N, 20.60.

β-1′-(5′,6′-Dichlorobenzotriazolyl)-butyric Acid (II).—A mixture of 1.5 g. (0.08 mole) of 5,6-dichlorobenzotriazole, 0.86 g. (0.01 mole) of crotonic acid and 20 drops of pyridine was heated for 15 hr. at 100°. The reaction mixture was poured into 100 ml. of 1.0 *N* hydrochloric acid to precipitate the crude product which was filtered, dried and washed with 100 ml. of ether to give 1.4 g. (64%) of the product. Three recrystallizations from acetic acid–water gave an analytical sample, m.p. 174–175°; λ_{max}, 268(s)(3.57), 274(3.61), 290(s)(3.45), 296(3.48).

Anal. Calcd. for $C_{10}H_9N_3Cl_2O_2$: N, 15.33; neut. equiv., 274.1. Found: N, 15.60; neut. equiv., 271.2.

4,7-Dichlorobenzotriazole.—To a solution of 25.91 g. (0.1465 mole) of 3,6-dichloro-*o*-phenylenediamine[6,7] dissolved in 245 ml. of glacial acetic acid was added 45 ml. of water. The resulting solution was cooled to 5° and 11.03 g. (0.16 mole) of sodium nitrite dissolved in 20 ml. of water was added with stirring. The precipitate from the reaction mixture was filtered, dried and recrystallized from dilute ethanol to give 22.4 g. (81%) of crude product. Three recrystallizations from nitromethane gave an analytical sample, m.p. 275–277°; λ_{max}, 264(3.82), 270(3.85), 285(3.81), 292(s)(3.79).

Anal. Calcd. for $C_6H_3N_3Cl_2$: N, 22.35; neut. equiv., 188.0. Found: N, 22.07; neut. equiv., 188.9.

2-Methyl-4,7-dichlorobenzotriazole.—To a solution of 5.64 g. (0.03 mole) of 4,7-dichlorobenzotriazole in 200 ml. of 0.5 *N* sodium hydroxide was added 3.8 g. (0.03 mole) of dimethyl sulfate dropwise with stirring over a period of 10 minutes. The resulting mixture was heated on a steam-bath for 1 hr. After cooling, the precipitated product was collected on a filter, washed with water and dried to give 3.3 g. of a crude mixture of 1- and 2-methyl derivatives. Two recrystallizations from dilute sulfuric acid gave 1.05 g. (17%) of reasonably pure 2-methyl derivative. Four additional recrystallizations from methanol gave an analytical sample, m.p. 174–176°; λ_{max}, 278(3.95), 285(3.98), 292(3.92), 296(s)(3.89).

Anal. Calcd. for $C_7H_5N_3Cl_2$: C, 41.61; H, 2.50; N, 20.80. Found: C, 41.58; H, 2.51; N, 20.30.

1-Methyl-4,7-dichlorobenzotriazole.—The sulfuric acid filtrates from the recrystallization of the above mixture of 1- and 2-methyl-4,7-dichlorobenzotriazole were diluted

(9) K. Fries, H. Güterbach and H. Kuhn, *Ann.*, **511**, 213 (1934).
(10) A. Laubenheimer, *Ber.*, **9**, 760 (1876).
(11) M. H. Behrens, *Rec. trav. chim.*, **21**, 276 (1902).
(12) Melting points uncorrected. Analyses by Micro Tech Laboratories, Skokie, Ill.

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with water to precipitate 2.25 g. (37%) of reasonably pure 1-methyl derivative. Four additional recrystallizations from carbon tetrachloride gave an analytical sample, m.p. 150–152°; λ_{max}, 264(3.88), 272(3.93), 286(3.82), 294(3.86).

Anal. Calcd. for $C_7H_5N_3Cl_2$: N, 20.80. Found: N, 20.60.

β-2′-(4′,7′-Dichlorobenzotriazolyl)-butyric Acid (III).—A mixture of 3.76 g. (0.02 mole) of 4,7-dichlorobenzotriazole, 1.72 g. (0.02 mole) of crotonic acid and 5 ml. of pyridine was heated for 14 hr. at 80°. The reaction mixture was poured into 300 ml. of 0.5 *N* hydrochloric acid to precipitate 2.5 g. (45%) of the crude product. Three recrystallizations from acetic acid–water gave an analytical sample, m.p. 158–160°; λ_{max}, 280(s)(3.90), 286(3.94), 292(s)(3.86), 295(s)(3.84).

Anal. Calcd. for $C_{10}H_9N_3Cl_2O_2$: N, 15.33; neut. equiv., 274.1. Found: N, 15.18; neut. equiv., 278.8.

β-Phenyl-β-2′-(4′,7′-dichlorobenzotriazolyl)-propiophenone.—To a melt of 1.88 g. (0.01 mole) of 4,7-dichlorobenzotriazole and 2.08 g. (0.01 mole) of benzalacetophenone was added 4 drops of benzyltrimethylammonium hydroxide solution. The mixture was heated for 3 hr. at 80°, cooled and dissolved in 50 ml. of ether. Addition of petroleum ether precipitated 2.65 g. (67%) of the crude product. Three recrystallizations from ethanol gave an analytical sample, m.p. 150–151°; λ_{max}, 280(s)(3.97), 286(4.03), 298(s)(3.83).

Anal. Calcd. for $C_{21}H_{15}N_3Cl_2O$: N, 10.60. Found: N, 10.75.

4,5,6,7-Tetrabromobenzotriazole.—A solution of 11.9 g. (0.10 mole) of benzotriazole and 72.0 g. (0.45 mole) of bromine in 150 ml. of concd. nitric acid was heated for 30 hr. under reflux. The crystalline product was collected on a filter, washed and dried to give 23.5 g. (54%) of the crude product. Several recrystallizations from acetic acid gave the pure product, m.p. 262–266°; λ_{max}, 278(4.01), 285(4.03), 300(3.94).

Anal. Calcd. for $C_6HN_3Br_4$: N, 9.67; neut. equiv., 434.8. Found: N, 9.89; neut. equiv., 434.5.

5-Chloro-4,6,7-tribromobenzotriazole.—A solution of 4.6 g. (0.03 mole) of 5-chlorobenzotriazole and 21.0 g. (0.13 mole) of bromine in 60 ml. of concd. nitric acid was heated for 22 hr. under reflux. The crystalline product was collected on a filter, washed and dried to give 6.60 g. (56%) of the crude product. Several recrystallizations from methanol gave the pure product, m.p. 249–251°; λ_{max}, 277(s)(3.93), 285(3.98), 302(3.91).

Anal. Calcd. for $C_6HN_3ClBr_3$: N, 10.77; neut. equiv., 390.3. Found: N, 11.00; neut. equiv., 398.0.

1-Methyl-4,5,6,7-tetrabromobenzotriazole.—A solution of 1.33 g. (0.01 mole) of 1-methylbenzotriazole and 7.00 g. (0.044 mole) of bromine in 25 ml. of concd. nitric acid was heated for 24 hr. under reflux. The crystalline product was collected on a filter, washed and dried to give 2.20 g. (48%) of the crude 1-methyl derivative. Several recrystallizations from nitromethane gave the pure product, m.p. 225–226°; λ_{max}, 278(3.96), 289(3.95), 308(3.80).

Anal. Calcd. for $C_7H_3N_3Br_4$: N, 9.36. Found: N, 9.35.

2-Methyl-4,5,6,7-tetrabromobenzotriazole.—A solution of 1.33 g. (0.01 mole) of 2-methylbenzotriazole and 7.00 g. (0.044 mole) of bromine in 25 ml. of concd. nitric acid was heated for 8 hr. under reflux. The crystalline product was collected on a filter, washed and dried to give 3.0 g. (67%) of the crude 2-methyl derivative. Several recrystallizations from nitromethane gave the pure product, m.p. 250–253°; λ_{max}, 285(s)(3.99), 294(4.10), 299(4.10), 306(4.12).

Anal. Calcd. for $C_7H_3N_3Br_4$: C, 18.73; H, 0.67; Br, 71.23. Found: C, 19.12; H, 0.79; Br, 70.83.

1-Ethyl-4,5,6,7-tetrabromobenzotriazole.—A solution of 3.0 g. (0.02 mole) of 1-ethylbenzotriazole and 14.0 g. (0.088 mole) of bromine in 75 ml. of concd. nitric acid was heated for 24 hr. under reflux. The crystalline product was collected on a filter, washed and dried to give 6.3 g. (68%) of the crude 1-ethyl derivative. Several recrystallizations from ethyl acetate gave the pure product, m.p. 150–152°; λ_{max}, 278(3.94), 290(3.94), 308(3.79).

Anal. Calcd. for $C_8H_5N_3Br_4$: N, 9.08; Br, 69.07. Found: N, 9.00; Br, 69.05.

2-Ethyl-4,5,6,7-tetrabromobenzotriazole.—A solution of 3.0 g. (0.02 mole) of 2-ethylbenzotriazole and 14.0 g. (0.088 mole) of bromine in 75 ml. of concd. nitric acid was heated for 18 hr. under reflux. The crystalline product was collected on a filter, washed and dried to give 1.60 g. (21%) of the crude 2-ethyl derivative. Several recrystallizations from ethyl acetate gave the pure product, m.p. 167–170°; λ_{max}, 285(s)(4.01), 298(4.11), 305(4.13).

Anal. Calcd. for $C_8H_5N_3Br_4$: N, 9.08; Br, 69.07. Found: N, 9.26; Br, 68.85.

1-Methyl-6-chloro-4,5,7-tribromobenzotriazole.—A solution of 0.70 g. (0.0042 mole) of 1-methyl-6-chlorobenzotriazole and 4.00 g. (0.025 mole) of bromine in 25 ml. of concd. nitric acid was heated for 24 hr. under reflux. The crystalline product was collected on a filter, washed and dried. There was obtained 1.20 g. (71%) of the crude 1-methyl derivative. Several recrystallizations from nitromethane gave the pure product, m.p. 213–214.5°; λ_{max}, 277(3.88), 287(3.92), 307(3.78).

Anal. Calcd. for $C_7H_3N_3ClBr_3$: N, 10.39. Found: N, 10.35.

β-Phenyl-β-2′-(4′,5′,6′,7′-tetrabromobenzotriazolyl)-propiophenone.—To a melt of 4.35 g. (0.01 mole) of tetrabromobenzotriazole and 2.08 g. (0.01 mole) of benzalacetophenone was added 10 drops of benzyltrimethylammonium hydroxide solution. The mixture was heated 20 hr. at 80°. Dilution of the cooled reaction mixture with ether precipitated 3.6 g. of crude product. This product was extracted with carbon tetrachloride to separate the insoluble, unreacted tetrabromobenzotriazole. Evaporation of the filtrate gave 2.9 g. (45%) of the crude addition product. Several recrystallizations from nitromethane gave the pure product, m.p. 195–198°; λ_{max}, 287(s)(4.11), 300(4.20), 308(4.20).

Anal. Calcd. for $C_{21}H_{13}N_3Br_4O$: C, 39.22; H, 2.04; Br, 49.71. Found: C, 39.29; H, 2.00; Br, 49.62.

β-Phenyl-β-2′-(4′,6′,7′-trichloro-5′-methylbenzotriazolyl)-propiophenone.—To a melt of 2.36 g. (0.01 mole) of 4,6,7-trichloro-5-methylbenzotriazole[8] and 2.08 g. (0.01 mole) of benzalacetophenone was added 5 drops of benzyltrimethylammonium hydroxide. The mixture was heated 15 hr. at 80°. Dilution of the cooled reaction mixture with ether precipitated 2.3 g. (52%) of crude product. Three recrystallizations from nitromethane gave the pure product, m.p. 173–175°; λ_{max}, 285(s)(4.14), 290(s)(4.17), 294(4.20), 298(4.20).

Anal. Calcd. for $C_{22}H_{17}N_3Cl_3O$: N, 9.43. Found: N, 9.68.

β-2′-(4′,6′,7′-Trichloro-5′-methylbenzotriazolyl)-propionamide.—To a melt of 2.36 g. (0.01 mole) of 4,6,7-trichloro-5-methylbenzotriazole and 0.71 g. (0.01 mole) of acrylamide was added 5 drops of benzyltrimethylammonium hydroxide. The mixture was heated for 15 hr. at 80°. Dilution of the cooled reaction mixture with ether precipitated 2.6 g. (85%) of the crude product. Three recrystallizations from ethyl acetate gave the pure product, m.p. 259–260°; λ_{max}, 280(4.01), 290(4.12), 294(4.11), 298(4.13).

Anal. Calcd. for $C_{10}H_9N_4Cl_3O$: N, 18.22. Found: N, 17.97.

β-2′-(4′,6′,7′-Trichloro-5′-methylbenzotriazolyl)-propionitrile.—A mixture of 2.36 g. (0.01 mole) of 4,6,7-trichloro-5-methylbenzotriazole, 5 ml. of acrylonitrile and 5 drops of benzyltrimethylammonium hydroxide was heated 18 hr. at 80°. Dilution of the cooled reaction with ether precipitated 0.7 g. (24%) of crude product. Three recrystallizations from methanol gave the pure product, m.p. 189–190°; λ_{max}, 280(4.05), 290(4.17), 294(4.14), 298(4.16).

Anal. Calcd. for $C_{10}H_7N_4Cl_3O$: N, 19.35. Found: N, 19.54.

2-Dimethylaminoethyl-4,5,6,7-tetrachlorobenzotriazole Methiodide.—To a solution of 2.8 g. (0.0085 mole) of 2-dimethylaminoethyl-4,5,6,7-tetrachlorobenzotriazole in 175 ml. of acetone was added 4.0 g. (0.03 mole) of methyl iodide. The precipitate was collected on a filter and dried to give 3.2 g. (80%) of the crude product. Several recrystallizations from ethanol gave the pure product, m.p. 249–250° dec.; λ_{max}, 294(4.09), 304(4.10).

Anal. Calcd. for $C_{11}H_{13}N_4Cl_4I$: N, 11.92. Found: N, 11.92.

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2-Dimethylaminoethyl-4,5,6,7-tetrachlorobenzotriazole Dimethochloride.—To a solution of 3.28 g. (0.01 mole) of 2-dimethylaminoethyl-4,5,6,7-tetrachlorobenzotriazole in 75 ml. of methanol was added 1.26 g. (0.01 mole) of dimethyl sulfate. The resulting solution was then evaporated to dryness and the crude salt redissolved in a mixture of 50 ml. of water and 10 ml. of concd. hydrochloric acid. After heating to boiling, 2.44 g. (0.01 mole) of barium chloride dihydrate was added. After boiling several minutes, the hot solution was filtered to remove the barium sulfate. The filtrate was cooled and the precipitate collected on a filter, washed, dried and extracted with 100 ml. of ethanol. The filtered ethanol solution was evaporated to precipitate 3.4 g. (79%) of the crude product. Several recrystallizations from nitromethane gave the pure product, m.p. 236–237°; λ_{max}, 294(4.13), 300(4.13), 306(4.12).

Anal. Calcd. for $C_{12}H_{16}N_4Cl_6$: C, 33.59; H, 3.76. Found: C, 33.80; H, 3.77.

1-Dimethylaminoethyl-4,5,6,7-tetrachlorobenzotriazole.—To 21 g. (0.082 mole) of 4,5,6,7-tetrachlorobenzotriazole dissolved in 500 ml. of 0.5 *N* potassium hydroxide was added 11.7 g. (0.082 mole) of dimethylaminoethyl chloride hydrochloride. The resulting solution was heated for 30 minutes on a steam-bath. The oil which separated solidified on cooling. The product was collected on a filter, dried and taken up in ether. Evaporation to dryness gave 3.5 g. (13%) of the crude product. Several recrystallizations from ethanol gave an analytical sample, m.p. 93–95°; λ_{max}, 276(3.90), 283(3.92), 305(3.73).

Anal. Calcd. for $C_{10}H_{10}N_4Cl_4$: N, 17.08; Found: N, 17.16.

β-2′-(4′,5′,6′,7′-Tetrachlorobenzotriazolyl)-butyramide.—To 10 ml. of thionyl chloride was added in small portions 1.7 g. (0.005 mole) of β-2′-(4′,5′,6′,7′-tetrachlorobenzotriazolyl)-butyric acid. After solution was complete, the thionyl chloride was removed on a steam-bath. The remaining solution was added dropwise with stirring to 20 ml. of cold concd. ammonium hydroxide to precipitate 1.6 g. (95%) of crude product. Several recrystallizations from nitromethane gave the pure product, m.p. 228–229°; λ_{max}, 294(4.09), 302(4.08).

Anal. Calcd. for $C_{10}H_8N_4Cl_4O$: N, 16.38; Cl, 41.47. Found: N, 16.51; Cl, 41.50.

1-Ethyl-4,5,6,7-tetrachlorobenzotriazole.—A solution of 1.5 g. (0.01 mole) of 1-ethylbenzotriazole in 300 ml. of concd. hydrochloric acid and 100 ml. of concd. nitric acid was heated for 52 hr. under reflux. The solution was cooled and the crystalline product collected on a filter, washed and dried to give 2.3 g. (81%) of the crude product. Several recrystallizations from methanol gave the pure product, m.p. 114–117°; λ_{max}, 276(s)(3.86), 283(3.89), 304(3.71).

Anal. Calcd. for $C_8H_5N_3Cl_4$: N, 14.75; Cl, 49.77. Found: N, 14.77; Cl, 49.82.

2-Ethyl-4,5,6,7-tetrachlorobenzotriazole.—A solution of 1.5 g. (0.01 mole) of 2-ethylbenzotriazole in 300 ml. of concd. hydrochloric acid and 100 ml. of concd. nitric acid was heated for 50 hr. under reflux. The solution was cooled and the crystalline product collected on a filter, washed and dried to give 1.8 g. (63%) of the crude product. Several recrystallizations from methanol gave the pure product, m.p. 160–163°; λ_{max}, 294(4.11), 300(4.10).

Anal. Calcd. for $C_8H_5N_3Cl_4$: N, 14.75; Cl, 49.77. Found: N, 14.55; Cl, 49.80.

4-Iodobenzotriazole.—To 13.5 g. (0.06 mole) of stannous chloride in 50 ml. of concd. hydrochloric acid was added in small portions a mixture of 3.28 g. (0.02 mole) of 4-nitrobenzotriazole in 20 ml. of concd. hydrochloric acid. The resulting solution was heated to boiling and allowed to cool. The chlorostannate, which crystallized on cooling, was collected on a filter and washed with concd. hydrochloric acid. The crystalline product was dissolved in water and hydrogen sulfide bubbled through until no more precipitation of tin sulfides was evident. The tin sulfides were removed by filtration and the filtrate made strongly acidic by the addition of 50% sulfuric. The solution was cooled to 0°, and sodium nitrite was added until a slight excess existed. The clear solution was then poured into 300 ml. of ice-water, and an excess of potassium iodide in water was added slowly with stirring. The free iodine which formed was reduced with sodium sulfite, and 10 g. of sodium acetate was added. The solution was then neutralized to a *p*H 3 with 6 *N* sodium hydroxide and extracted with three 300-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and evaporated to give 0.8 g. (16.3%) of crude product. Several recrystallizations from water gave the pure product, m.p. 216–218°; λ_{max}, 264 (3.95), 272(3.95), 286(3.90), 290(3.88).

Anal. Calcd. for $C_6H_4N_3I$: N, 17.15. Found: N, 17.20.

1-Methyl-6-chlorobenzotriazole.—A solution of 15.5 g. (0.083 mole) of 2-nitro-5-chloro-N-methylaniline[10,11] in 20 ml. of concd. hydrochloric acid was added in small portions to 56.4 g. (0.25 mole) of stannous chloride dissolved in 150 ml. of concd. hydrochloric acid. This solution was poured into 500 ml. of water and made distinctly basic by the addition of aqueous potassium hydroxide. The resulting solution was extracted with three 100-ml. portions of ether. The combined ether extracts were then extracted with three 100-ml. portions of 1 *N* hydrochloric acid. The aqueous extracts were combined, chilled to 10° and treated with 6.35 g. (0.092 mole) of sodium nitrite. The dark colored solution was made distinctly basic and extracted with three 100-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate, the ether removed on a steam-bath and the product fractionated. There was obtained 4.0 g. (29%) of the crude 1-methyl derivative, b.p. 165° (25 mm.). Two recrystallizations of the solidified liquid from carbon tetrachloride gave the pure product, m.p. 121–123°; λ_{max}, 270(3.83), 282(3.77).

Anal. Calcd. for $C_7H_6N_3Cl$: N, 25.07. Found: N, 24.82.

2-Methyl-4-nitrobenzotriazole.—A solution of diazomethane in ether was added to 1.64 g. (0.01 mole) of 4-nitrobenzotriazole dissolved in 75 ml. of ether until a light yellow color persisted. Evaporation of the ether gave 1.7 g. (95.5%) of crude product. One recrystallization from dilute ethanol and two recrystallizations from ethyl acetate gave an analytical sample, m.p. 183–184° (light yellow needles).

Anal. Calcd. for $C_7H_6N_4O_2$: N, 31.45. Found: N, 31.52.

2-Methyl-5-nitrobenzotriazole.—A solution of 4.0 g. (0.03 mole) of 2-methylbenzotriazole in 40 ml. of water and 20 ml. of concd. nitric acid was heated for 60 hr. under reflux. The solution was cooled and the pale yellow crystalline product collected on a filter, washed and dried. There was obtained 1.7 g. (32%) of the crude product. Several recrystallizations from ethanol gave the pure product, m.p. 150–152°.

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.40; N, 31.45. Found: C, 47.31; H, 3.17; N, 31.21.

2-Methyl-4,5,6,7-tetrachlorobenzotriazole from 2-Methyl-4-nitrobenzotriazole.—A solution of 0.18 g. (0.001 mole) of 2-methyl-4-nitrobenzotriazole in 39 ml. of concd. hydrochloric acid and 13 ml. of concd. nitric acid was heated under reflux for three days. The solution was cooled and diluted with water to precipitate 0.06 g. (22%) of the crude 2-methyl derivative, m.p. 179–182°. The product was recrystallized from methanol to give white needles, m.p. 182–184°. A mixed melting point with an authentic sample of 2-methyl-4,5,6,7-tetrachlorobenzotriazole showed no depression while the melting point of a mixture of the product with a pure sample of starting material was 148–157°.

1-Methyl-4,5,6,7-tetrachlorobenzotriazole by Chlorination of 1-Methylbenzotriazole.—A solution of 3.0 g. (0.0225 mole) of 1-methylbenzotriazole in 300 ml. of concd. hydrochloric acid and 100 ml. of concd. nitric acid was heated under reflux. The solid which had precipitated after 1 hr. heating was redissolved by the addition of 300 ml. of concd. nitric acid. This mixture was then refluxed for 72 hr. The solution was cooled and diluted with water to precipitate 3.5 g. (57%) of the crude product. Several recrystallizations from carbon tetrachloride gave the pure product, m.p. 193–196°. On admixture this material does not depress the m.p. of an authentic sample of 1-methyl-4,5,6,7-tetrachlorobenzotriazole.

4,5,6,7-Tetrachlorobenzotriazole from 4-Nitrobenzotriazole.—A solution of 1.2 g. (0.0075 mole) of 4-nitrobenzo-

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triazole in 300 ml. of concd. hydrochloric acid and 150 ml. of concd. nitric acid was heated for one week under reflux. The solution was cooled and the crystalline product collected on a filter, washed and dried to give 1.2 g. (62%) of crude product. Recrystallization from nitromethane gave the pure product, m.p. 256–260°. On admixture this material does not depress the m.p. of an authentic sample of 4,5,6,7-tetrachlorobenzotriazole.

2-Methyl-4,5,6,7-tetrachlorobenzotriazole from 2,5-Dimethylbenzotriazole.—A solution of 1.5 g. (0.01 mole) of 2,5-dimethylbenzotriazole in 80 ml. of concd. hydrochloric acid and 80 ml. of concd. nitric acid was heated under reflux for 10 hr. The solution was cooled and the crystalline product collected on a filter, washed and dried. Three recrystallizations of this solid from methanol gave the pure product, m.p. 181–183°. On admixture this product does not depress the m.p. of an authentic sample of 2-methyl-4,5,6,7-tetrachlorobenzotriazole.

2,5-Dimethylbenzotriazole.—A solution of diazomethane in ether was added slowly to 13.3 g. (0.1 mole) of 5-methylbenzotriazole dissolved in ether until a slight yellow color persisted. The resulting solution was refluxed until the slight excess of diazomethane was removed and dried over anhydrous sodium sulfate. Dry hydrogen chloride was then bubbled through the ethereal solution. The precipitated hydrochlorides were removed by filtration. Evaporation of the ethereal solution gave 8.8 g. (60%) of crude product. Fractionation gave an analytical sample, b.p. 117° (12 mm.); λ_{max}, 276(s)(4.12), 284(4.14), 288(4.11).

Anal. Calcd. for $C_8H_9N_3$: N, 28.55. Found: N, 28.72.

β-1′-(Benzotriazolyl)-butyramide.—To 1.0 g. (0.005 mole) of β-1′-(benzotriazolyl)-butyric acid was added 4.0 ml. of thionyl chloride. After solution was complete, the mixture was added dropwise with stirring to 15 ml. of cold concd. ammonium hydroxide. The product was collected on a filter, washed with water and dried to give 0.3 g. which was 30% of the theoretical amount. Several recrystallizations from water gave an analytical sample, m.p. 104–105°; λ_{max}, 256(3.80), 262(3.80), 280(3.61).

Anal. Calcd. for $C_{10}H_{12}N_4O$: N, 27.44. Found: N, 27.42.

Ultraviolet Absorption Data.—Ultraviolet absorption measurements were made with a Beckman DU photoelectric spectrophotometer with 1.00-cm. silica cells and a hydrogen discharge lamp as the light source. The measurements were made in methanol solution. The data are recorded in the preceding Experimental sections as wave lengths at which maxima or shoulders(s) occur with the corresponding log ε in parentheses.

LOUISVILLE, KENTUCKY

[CONTRIBUTION OF THE SCHOOL OF SCIENCE, BRANDEIS UNIVERSITY]

Preparation and Decomposition of a Cyclic Azo Compound. 3,6-Diphenyl-3,4,5,6-Tetrahydropyridazine

BY SAUL G. COHEN, SHU-HSI HSIAO,[1a] EUGENE SAKLAD AND CHI HUA WANG[1b]

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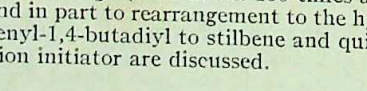
The azo compound I was prepared by addition of diethyl azodicarboxylate to 1,4-diphenylbutadiene-1,3, hydrogenation, hydrolysis, decarboxylation and autoxidation; λ_{max} 387 mμ, log ε 2.89, displaced from 345 mμ of *trans*-aliphatic azo compounds. Compound I decomposes in hydrocarbon solvents, including solutions containing styrene, with essentially quantitative yield of nitrogen, and about 100 times as fast at 80° as acyclic analogs. Solid I, heated at about 125°, led in part to styrene and in part to rearrangement to the hydrazone tautomer. Attempts to obtain products of addition of the biradical 1,4-diphenyl-1,4-butadiyl to stilbene and quinone failed. The mode of decomposition of I and its possible activity as a polymerization initiator are discussed.

As part of our study of the chemistry of azo compounds[2] we undertook to prepare 3,6-diphenyl-3,4,5,6-tetrahydropyridazine (I) and by its decomposition, the biradical 1,4-diphenyl-1,4-butadiyl (II), $C_6H_5\dot{C}HCH_2CH_2\dot{C}HC_6H_5$. Compound I, because of its cyclohexene type structure would be a *cis*-azo compound, while acyclic aliphatic azo compound are normally *trans*, and it seemed of interest to compare its physical properties, its ease of decomposition and its products of decomposition with those of the closely related *trans*-acyclic compounds,[3] 1-azo-bis-1-phenylethane or 1-azo-bis-1-phenylpropane, $C_6H_5-\underset{\displaystyle R}{\underset{|}{CH}}-N=N-\underset{\displaystyle R}{\underset{|}{CH}}C_6H_5$ (III), R = CH_3 or C_2H_5. The 1,4-biradical II, which might



I

be formed, would be of interest both for a study of its chemistry as such and because it is identical with the product of "tail-to-tail" reaction of two molecules of styrene which had once been proposed as the active intermediate in the initiation of the thermal polymerization of styrene,[4] but which is no longer supported.[5]

Preparation of Compound I.—The preparation of the azo compound I has been reported[6] by (1) condensation of two molecules of α-chloroacetophenone semicarbazone to a compound which appears to be 2-carbamyl-3,4,5-trihydro-3,6-diphenylpyridazine (a) followed by (2) treatment with sodium ethoxide at 160°. The product was converted to 3,6-diphenylpyridazine by treatment with bromine water and was assigned structure I. We repeated this preparation and found that the compound had an absorption maximum at 292 mμ, log ε 4.19, which has been characteristic of the hydrazones tautomeric with the acyclic azo compounds in this work,[2a,7] and end absorption in the near ultraviolet but no maximum in the range of 300–400 mμ which would be characteristic of the azo compound.[3] This, coupled with the strongly

(1) (a) This paper is derived in part from a thesis submitted by Shu-hsi Hsiao in partial fulfillment of the degree of Master of Arts in Chemistry, Brandeis University. (b) For preliminary report see C. H. Wang, S. Hsiao, E. Saklad and S. G. Cohen, THIS JOURNAL, **79**, 2661 (1957).

(2) (a) S. G. Cohen and C. H. Wang, *ibid.*, **77**, 2457 (1955); (b) **77**, 3628 (1955).

(3) S. G. Cohen, S. J. Groszos and D. B. Sparrow, *ibid.*, **72**, 3947 (1950).

(4) F. R. Mayo, *ibid.*, **65**, 2324 (1943).

(5) F. R. Mayo, *ibid.*, **75**, 6133 (1953).

(6) A. P. J. Hoogeveen and C. V. van Hoogstraten, *Rec. trav. chim.*, **52**, 378 (1933).

(7) C. Fodor and P. Szinai, *Ber.*, **76B**, 334 (1943).

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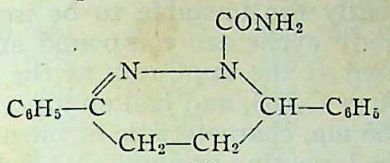
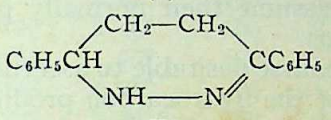
ionizing conditions of preparation, which would favor tautomerism, and the high thermal stability of the material, lead us to assign to it the tautomeric structure IV, m.p. 157–159°.



(a)

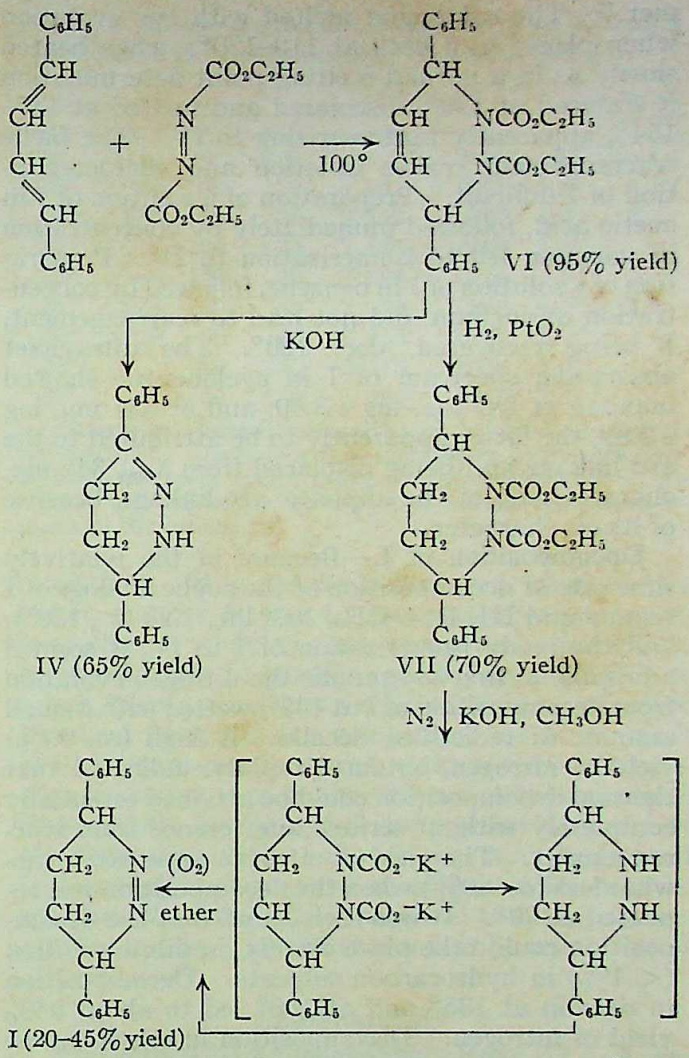


IV

Compounds of type III have been prepared by conversion of the relevant ketone C_6H_5COR to the azine, hydrogenation to the hydrazine and oxidation to the azo compound.[3] However, the reactions of γ-diketones necessary for the formation of cyclic azo compounds related to I do not proceed this simply. The reactions of 1,2-dibenzoylethane[8] and acetonylacetone[9,10] with hydrazine do not lead to isolation of the pure azine, *i.e.*, the 4,5-dihydropyridazine, but to a mixture from which the disproportionation products, the pyridazine and the tetrahydropyridazine, each substituted at the 3- and 6-positions, may be obtained. Again the conditions of formation of the tetrahydro compound would indicate that the one from dibenzoylethane is probably the more stable tautomer IV. In our work treatment of 1,2-dibenzoylethane with hydrazine led to a mixture V which was apparently not readily separated into its components. Attempted hydrogenation to the hexahydropyridazine over platinum oxide in ethanol containing hydrogen chloride led to the hydrazone IV in about 50% yield, while when the reaction was attempted in acetic acid, 3,6-diphenylpyridazine was obtained, also in about 50% yield. While we cannot rule out that these products were formed by disproportionation of the dihydro compound in the presence of the hydrogenation catalyst, they may well have comprised the crude reaction product V. Attempted reduction of the hydrazone IV or the mixture V with lithium aluminum hydride was not successful, although some of the azo compound I may have been present in the product from V. It seemed likely that more vigorous reduction, as with zinc and hydrochloric acid, would lead to cleavage of the nitrogen–nitrogen bond.[11]

The azo compound I was prepared by: (a) Diels–Alder addition of diethyl azo-dicarboxylate to 1,4-diphenylbutadiene, forming the adduct[12] VI, (b) hydrogenation[12] of the carbon–carbon double bond in VI, leading to VII, followed by (c) saponification of the hydrogenated adduct, decarboxylation and, apparently, autoxidation in ether solution to form I (Chart 1). Saponification of the adduct VI in methanol led, as reported,[12] to the tautomeric product IV instead of to the $\Delta^{4,5}$-

CHART 1



compound. While hydrogenation of VI did not, in our experiment, lead to a product of quite as sharp a melting point as reported, elementary analysis was satisfactory. Attempted acid hydrolysis of both the adduct VI and the hydrogenated adduct VII led to recovery of the respective starting materials. Alkaline hydrolysis of the hydrogenated adduct, compound VII, in glycol in the presence of air was reported[12] to lead to the tautomeric product of oxidation IV, while saponification in the absence of air led to impure hexahydrodiphenylpyridazine.[12]

In our work, alkaline hydrolysis of VII in glycol under nitrogen followed by attempted precipitation of the hydrochloride of the hexahydro compound from the ether extract of the saponification product led to the hydrazone IV. Observation of some crystals, which decomposed at 110° with gas evolution, in a portion of the product which had not been treated with hydrogen chloride led to successful synthesis of I. The hydrolysis of VII was carried out by treatment with potassium hydroxide in refluxing methanol under nitrogen, decarboxylation apparently occurring concomitantly. The solution was diluted with water and extracted with ether, either with or without prior neutralization with hydrochloric acid. Concentration of the dried ether solution led to the azo compound I, autoxidation of the hydrazo compound apparently taking place at this stage, since autoxidation during

(8) C. Paal and E. Dencks, THIS JOURNAL, **36**, 491 (1903).
(9) E. E. Blaise, *Compt. rend.*, **170**, 1324 (1920).
(10) C. G. Overberger, N. R. Byrd and R. R. Mesrobian, THIS JOURNAL, **78**, 1961 (1956).
(11) O. Diels and K. Alder, *Ann.*, **450**, 237 (1926).
(12) K. Alder and H. Niklas, *ibid.*, **585**, 81 (1954).

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the hydrolysis would lead to the hydrazone tautomer.[12] The compound melted with gas evolution when placed in a bath at 110–120°; when heated slowly as in a normal melting point determination it sintered at 120°, discolored and melted at 147–154°, apparently tautomerizing to IV. The facile rearrangement makes isolation and characterization of I difficult. Preparation of a solution of I in acetic acid, followed immediately by concentration in vacuum, led to isomerization to IV. Preparation of a solution of I in benzene, followed by concentration in vacuum, did not lead to rearrangement, I being recovered, dec. 120°. The ultraviolet absorption spectrum of I in cyclohexane showed maxima at 287 mμ, log ε 3.49, and at 387 mμ, log ε 2.89, the latter apparently to be attributed to the azo linkage and being displaced from λ_{max} 345 mμ, characteristic of the aliphatic azo linkage, because of its *cis* character.

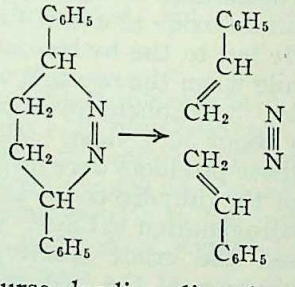
Decomposition of I.—Because of the relatively slow rate of decomposition of the acylic analogs of I (compound III, R = CH_3, half-life, 1.25 hr., 110°), and the ready isomerization of I to IV, it seemed advisable at first to examine the nitrogen evolution from decomposition of I at 135°, wetted with a small amount of redistilled decalin. A high (*ca.* 90%) yield of nitrogen, obtained rapidly, indicated that thermal decomposition could be attained essentially completely without serious interference from rearrangement. The yield of nitrogen appeared somewhat less (*ca.* 80%) when the decomposition was repeated at 90°. It was then found that the decomposition could take place cleanly, in dilute solution (< 1%) in hydrocarbon solvents. Decomposition in decalin at 135° and at 100° led to about 95% yield of nitrogen. Decomposition in ethylbenzene that had not been freshly distilled led to low, non-reproducible yields, rearrangement presumably taking place; distillation of the ethylbenzene led to high yields of nitrogen at 100°.

Since we would wish to examine compound I as an initiator of polymerization and as a source of the biradical II, a possible intermediate in the thermal polymerization of styrene, the decomposition of compound I in 3.46 moles/l. styrene in ethylbenzene was examined briefly. Nitrogen evolution was rapid and essentially quantitative both at 100 and at 80°. The data on evolution of nitrogen are summarized in Table I.

Observations made during the measurements of the evolution of nitrogen indicate that decomposition was essentially complete in about 20 minutes at 100° and that the half-life at 80° was about 20 minutes. In contrast, the half-life for decomposition of the acyclic analog $C_6H_5CH(CH_3)N{=}NCH(CH_3)C_6H_5$ (III) is about 4 hr.[3] at 100°. It may be estimated that the first-order rate constant for decomposition of I at 80° is about 6×10^{-4} sec.$^{-1}$, while that for III is about two orders of magnitude less, 4.5×10^{-6}. Apparently the *cis*-azo structure of I (possibly aided by another factor to be discussed below) leads to increased ease of decomposition, in addition to the shift in absorption maximum noted above. It will be of interest to examine the kinetics of decomposition of cyclic azo compounds of this type. Extreme instability had been reported[13] for a seven-membered cyclic azo compound, but subsequent work[14] assigned a different structure to the material. The six-membered cyclic analog of azo-bis-isobutyronitrile was apparently too unstable to be isolated.[10] A 24-membered[15] cyclic azo compound analogous to I decomposed at the same rate as the acyclic analog III (R = C_2H_5), and had an absorption maximum at 355 mμ, characteristic of the acyclic compounds; the large ring presumably allowed the azo linkages to assume their normally preferred *trans* configurations.

It was of course desirable to ascertain, if possible, the nature of the hydrocarbon products of decomposition. A sample of the azo compound I (0.053 g.) was decomposed in the solid state under nitrogen, and the residue was worked up. The rearranged product IV was obtained in 30% yield, and it appears likely and not unreasonable that the isomerization occurs to a greater extent under these conditions than in dilute solution in hydrocarbon solvents. The odor of styrene was detected readily immediately after the decomposition, and treatment of the filtrate, after removal of IV, with bromine in acetic acid led to styrene dibromide in 7% yield (based on non-rearranged I). Since this product was isolated in only 17% yield in a control experiment carried out under similar conditions, it may be that half of the azo compound which decomposes is converted to styrene. The styrene may be formed (a) in a second reaction from the biradical II or (b) directly from decomposition of the azo compound into three fragments

$$C_6H_5\dot{C}HCH_2CH_2\dot{C}HC_6H_5 \longrightarrow 2C_6H_5CH{=}CH_2 \quad \text{(a)}$$



(b)

The latter course, leading directly to three molecules and no radicals, might well contribute to the observed enhanced ease of decomposition of I. The rupture of the three bonds in process b need not be completely symmetrical, the two carbon–nitrogen bonds being more completely broken in the transition state than the carbon–carbon bond and the transition state possibly having characteristics of the transition state of both processes a and b. This would contribute to increased ease of decomposition and allow both styrene and products of the biradical to be observed.

Attempts were made to find evidence for the formation of the biradical II by carrying out the decomposition of I in the presence of unsaturated material that might react with II. In the presence of stilbene we failed to isolate the possible six-membered cyclic adduct, recovering part of the

(13) C. G. Overberger, P. T. Huang and T. B. Gibb, THIS JOURNAL, **75**, 2082 (1953).

(14) C. G. Overberger and B. S. Marks, *ibid.*, **77**, 4097 (1955).

(15) C. G. Overberger and M. Lapkin, *ibid.*, **77**, 4651 (1955).

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TABLE I

THERMAL DECOMPOSITION OF COMPOUND I
EVOLUTION OF NITROGEN

Expt.	Cmpd. I, g.	Solvent, g.	T, °C.	N_2 Ml.	N_2 Yield, %
1	0.0331	0.050[a]	135	3.10	90
2	.0422	.060[a]	136	4.32	99
10	.0194	.050[a]	110	1.80	90
11	.0203	.040[a]	90	1.60	80
12	.0228	2.78[a]	135	2.60	108
15	.0170	2.37[a]	135	1.70	95
16	.0199	2.16[a]	100	2.00	96
17	.0165	1.90[a]	100	1.70	96
20	.0148	1.74[b]	100	1.29	82
21	.0298	2.76[b]	100	0.50	16
22	.0173	1.65[c]	100	1.60	89
27	.0264	2.52[c]	100	2.85	103
33	.0215	2.09[c]	100	2.20	99
23	.0140	1.57[d]	100	1.40	96
24	.0210	2.21[d]	100	2.13	97
29	.0253	1.97[d]	100	2.58	98
31	.0211	2.07[d]	100	2.20	100
34	.0207	2.23[d]	80	2.22	103
36	.0223	2.12[d]	80	2.25	97

[a] Decalin. [b] Ethylbenzene (not distilled). [c] Ethylbenzene (distilled). [d] 3.46 moles/l. styrene in ethylbenzene.

stilbene. In the presence of quinone the possible derivative of naphthohydroquinone was not found. In addition to recovered quinone and quinhydrone, a small amount of the rearrangement product IV and a considerable quantity (47% yield) of the product of dehydrogenation of I or IV, 3,6-diphenylpyridazine, were obtained.

In order to obtain preliminary information about the efficacy of this potential biradical source as a polymerization initiator, the styrene–ethylbenzene solutions in which the azo compound had been decomposed in the nitrogen evolution experiments were examined for polymer contents and compared with blank solutions treated in the same way in the absence of compound I. The data are summarized in Table II. In experiments carried out at 100° (expts. 23, 24, 25, 26), the polymer was precipitated in methanol; an undesirably high yield of polymer was found in the blank run in the absence of azo compound I. After correction for this, it appeared that about 4 molecules of styrene had been polymerized per molecule of I originally present. In experiments carried out at 80° (expts. 34, 35, 36, 37), the volatile components were removed in vacuum until the residue was brought to constant weight; satisfactory low yields were obtained in the absence of I and the small corrections were made. It appeared that about 8 molecules of styrene were rendered non-volatile per molecule of I originally present. Such a number has significance for comparison with other initiators only if (a) the rate of decomposition of the azo compound and (b) the fraction which is converted to radicals (as distinguished from styrene molecules) are known. Using the approximate rate constant, given before, and making the necessary corrections for concentration and temperature, we estimate[16] that benzoyl peroxide would polymerize about 70 molecules of styrene per molecule of peroxide under similar

(16) S. G. Cohen, THIS JOURNAL, 67, 17 (1945).

TABLE II

THERMAL DECOMPOSITION OF COMPOUND I IN 3.46 M./L. STYRENE IN ETHYLBENZENE. POLYMER CONTENT

Exp. no.	Cmpd. I, m./l.	T, °C.	Time, min.	Sample, g.	Polymer g.	Polymer %	Mole polymd. per mole cmpd. I
23[a]	0.033	100	30	1.461	0.0351	5.8	4.3
24[a]	.035	100	30	2.112	.0427	4.9	3.1
25[a]	...	100	30	2.658	.0199	1.8	
26[a]	...	100	30	2.089	.0145	1.7	
34[b]	.034	80	150	2.128	.0842	8.7[c]	8.6
36[b]	.039	80	150	2.015	.0897	9.7[c]	8.5
35[b]	...	80	150	2.115	.0026	0.3	
37[b]	...	80	150	1.952	.0011	0.1	

[a] Sample was diluted with methanol and insoluble portion was weighed. [b] Sample was evaporated to constant weight in vacuum, room temperature. [c] Correction applied, assuming half the hydrocarbon part of the azo compound remains in the residue.

conditions. It is not clear, however, whether this larger number is due to the peroxide leading to long chains, while the azo compound through its biradical leads to smaller cyclic products,[5,17,18] or arises from a comparatively low yield of effective biradical from the azo compound, the larger part of it decomposing to styrene—the reverse of a possible initiating step in the thermal polymerization. Study of the kinetics of decomposition of I and of the properties of the polymer that may be formed in low yield are required to give indication as to whether the biradical II may lead to high polymer and be involved in the thermal polymerization of styrene.

Experimental[19]

3,6-Diphenyl-2,3,4,5-tetrahydropyridazine (IV). A.—α-Chloroacetophenone, 15.5 g. (0.1 mole), in 125 ml. of ethanol was treated with 11 g. (0.1 mole) of semicarbazide hydrochloride in 12.5 ml. of water at 40° with gradual addition of 8.5 g. (0.1 mole) of sodium bicarbonate. The mixture was boiled and cooled, and the product was collected, washed with ethanol and dried; α-chloroacetophenone semicarbazone 12.5 g. (0.059 mole), 59% yield, m.p. 151–152°, reported[20] 156°. The semicarbazone, 12.5 g., was heated under reflux for 1.2 hr. with 11 g. (0.13 mole) of sodium bicarbonate in 200 ml. of 1:1 ethanol–water. The product was collected and dried; 7.3 g. (0.026 mole), 44% yield, m.p. 213–216°, 218.5–220° after two crystallizations from benzene, reported[6] 221°. *Anal.* Calcd. for $C_{17}H_{17}ON_3$: C, 73.10; H, 6.13; N, 15.04. Found: C, 72.87; H, 5.85; N, 14.78. The product above, 2 g. (0.0072 mole), was heated for 6 hr. at 160° in a solution of 6 g. of sodium in 120 ml. of ethylene glycol and cooled. The product IV was collected and crystallized from ethanol, 1.6 g. (0.0068 mole), 94% yield, m.p. 157–159°, reported[6] 159°. No gas was evolved when it was heated to 300°. The absorption spectrum was determined in chloroform in a Beckman DU spectrophotometer and showed a small minimum at 245 mμ, log ε 3.68, a maximum at 292 mμ, log ε 4.19, which fell off rapidly to log ε 1.20 at 365 mμ and more slowly to log ε 0.45 at 400 mμ.

B.—Succinyl chloride, 20 g. (0.13 mole), in 56 ml. of thiophene-free benzene was added at room temperature over a period of 2 hr. with stirring to 25 g. (0.19 mole) of aluminum chloride in 200 ml. of benzene. The mixture was treated with ice and 20 ml. of concentrated hydrochloric

(17) D. H. Johnson and A. V. Tobolsky, *ibid.*, **74**, 938 (1952); K. E. Russell and A. V. Tobolsky, *ibid.*, **75**, 5052 (1953).

(18) B. H. Zimm and J. K. Bragg, *J. Polymer Sci.*, **9**, 476 (1952).

(19) Melting points are uncorrected. Elementary microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology.

(20) G. Kliegler, *Monatsh.*, **31**, 108 (1910).

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acid. The benzene solution was concentrated and the precipitate was washed and crystallized from ethanol, 1,2-dibenzoylethane, 5.0 g. (0.021 mole), 16% yield, m.p. 144–145°, reported[21] 144–145°. 1,2-Dibenzoylethane, 5 g. (0.021 mole), was dissolved in 30 ml. of ethanol and treated with 2 g. of hydrazine hydrate. A white solid V was obtained, 4.8 g., 96% yield, m.p. 140–210°. Attempted crystallization from ethanol did not lead to pure compounds.

A solution of 3 g. of the mixture V in 200 ml. of ethanol was treated with 5 ml. of ethanol saturated with hydrogen chloride, then with hydrogen over platinum oxide at 50° for 2.5 hr., filtered and cooled. Compound IV crystallized out, 0.650 g., m.p. 144–152°, 155–157°, after recrystallization from alcohol, alone and when mixed with the product from procedure A, above. The original filtrate was made alkaline, leading to an additional 1.1 g. of crude IV, m.p. 140–155°, 155–157° after several recrystallizations. The ultraviolet absorption spectrum was identical with that described in A, above.

C.—The adduct of diethyl azo-dicarboxylate and 1,4-diphenylbutadiene, compound VI below, 1 g. (0.0026 mole), was boiled in 3 ml. of 40% potassium hydroxide in methanol for 1 hr. under nitrogen. The solution was cooled, diluted with 2 ml. of water and acidified with concentrated hydrochloric acid. A solid separated, was collected, washed with water and crystallized from methanol; 0.4 g., 64% yield, m.p. 156–158°, mixed m.p. with IV, 157–159°.

3,6-Diphenylpyridazine. A.—A solution of 1.0 g. of mixture V in 10 ml. of acetic acid was treated with hydrogen over platinum oxide at 30 p.s.i. for 2 hr., filtered and concentrated in vacuum, leading to 3,6-diphenylpyridazine, 0.50 g., 50% yield, m.p. 207–219°, crystallized from ethanol, m.p. 219–220°, reported[12] m.p. 222°.

B.—A solution of IV, 0.384 g. (1.62 mmoles), in 30 ml. of acetone was treated with 6 drops of 30% hydrogen peroxide at room temperature for 16 hr. and concentrated. The residue was crystallized from ethanol, leading to 3,6-diphenylpyridazine, 0.155 g., 40% yield, m.p. and mixed m.p. 218–220°.

Attempted Reductions with Lithium Aluminum Hydride.—A: Treatment of the mixture V, 2 g., with 1.1 g. of $LiAlH_4$ in 50 ml. of ether under reflux for 6 hr. led to material melting 155–180°, 1.6 g. B: Treatment of 4.8 g. of mixture V with 1 g. of $LiAlH_4$ in di-*n*-butyl ether at 80° for 13 hr. led to 2.5 g. of material melting at 95–110°, 116–120° dec. after crystallization from methanol–water in Dry Ice. C: Treatment of the hydrazone IV, 0.5 g., with 0.1 g. of $LiAlH_4$ in 50 ml. of di-*n*-butyl ether at 80° for 13 hr. led to recovered IV, 0.3 g. D: Treatment of the hydrazone IV, 0.350 g., with 0.150 g. of $LiAlH_4$ in 30 ml. of di-*n*-butyl ether under reflux for 5 hr. led to recovered IV, 0.120 g.

1,2-Dicarboethoxy-3,6-diphenyl-1,2,3,6-tetrahydropyridazine (VI).—A: 1,4-Diphenylbutadiene[22] was prepared by condensation of phenylacetic acid (150 g., 1.10 moles) and cinnamaldehyde (169 g., 1.28 moles) in acetic anhydride (155 ml.) in the presence of lead oxide (122 g.) at 145°; 50 g., 22% yield, m.p. 152–153°, from benzene–ethanol, reported[22] 152.5–153.5°. B: Diethyl 1,2-hydrazinedicarboxylate[23] was prepared from reaction of hydrazine hydrate (78.2 g.) with ethyl chlorocarbonate (108 g., 1.00 mole) in ethanol at 0°; 47.5 g. (0.27 mole), 54% yield, m.p. 132–133° from water, reported[23] 130°. C: Diethyl azo-dicarboxylate[24] was prepared by treatment of a solution of 20 g. (0.11 mole) of diethyl 1,2-hydrazinedicarboxylate in 24 ml. of concentrated nitric acid with 4.8 ml. of fuming nitric acid at 0° for 1.5 hr. The mixture was poured into ice-water, extracted with ether, washed with sodium bicarbonate, dried and distilled; 8.3 g. (0.048 mole), 42% yield, b.p. 106–108° (13 mm.), reported[24] 106° (13 mm.). D: 1,2-Dicarboethoxy-3,6-diphenyl-1,2,3,6-tetrahydropyridazine (VI) was prepared by reaction of 9.0 g. (0.05 mole) of diethyl azodicarboxylate with 9 g. (0.044 mole) of 1,4-diphenylbutadiene in 10 ml. of toluene on the steam-bath for 3 hr. The toluene was removed in vacuum and the adduct VI was crystallized from ethyl acetate; 15.8 g., 95% yield, m.p. 134–136°, reported[12] 132°. *Anal.* Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.44; H, 6.36. Found: C, 69.13; H, 6.42.

3,4,5,6-Tetrahydro-3,6-diphenylpyridazine (I). A.—The adduct VI, 5 g. (0.013 mole), was hydrogenated in 300 ml. of acetic acid over platinum oxide at 30 p.s.i. The solution was filtered and concentrated and the residue was crystallized from ethanol, 3.5 g., 70% yield, m.p. 85–87°, solid persisting to 95°, reported[12] 87°. Recrystallization from ethanol did not affect the melting range. *Anal.* Calcd. for $C_{22}H_{26}N_2O_4$: C, 69.06; H, 6.85. Found: C, 69.22; H, 6.96. Treatment of the hydrogenated adduct VII above with concentrated hydrochloric acid in methanol under reflux for 1 hr. led to recovery of VII. The adduct VI was also unaffected under these conditions.

B (1): A solution of 1.0 g. (2.6 mmoles) of VII and 1.5 g. of potassium hydroxide in 5 ml. of ethylene glycol was boiled under nitrogen for 2 hr., cooled, diluted with 25 ml. of water and extracted with peroxide-free ether. The solution was dried over magnesium sulfate and treated with dry hydrogen chloride. An oil precipitated, at first white, then turning orange, crystallization of which from ethanol and water and from ethyl acetate led to the hydrazone IV, m.p. 156–158°. Some crystals were observed in the magnesium sulfate; the latter was dissolved in water, the crystals were collected and dried, dec. 110° with gas evolution when heated rapidly, sintered 98°, melting over a range to 145° when heated slowly. (2). A second saponification was carried out in the same way. The dried ether extract was concentrated and cooled leading to long flat crystals, 0.284 g. (1.25 mmoles), 48% yield, decomposing with gas evolution at 110°. (3): Saponification of 1.0 g. of VII by 2 g. of potassium hydroxide in 5 ml. of boiling methanol was carried out similarly. The dried ether extract was concentrated and crystals were obtained and dried in a desiccator; 0.15 g. (0.64 mmole), 25% yield, dec. 110°. (4): The hydrogenated adduct VII, 1.0 g. (2.6 mmoles), was boiled for 1 hr. under nitrogen in a solution of 2.0 g. of potassium hydroxide in 5 ml. of methanol, cooled in ice, diluted with 10 ml. of water, brought to *p*H 8 with 6 *N* hydrochloric acid and extracted with ether. The ether solution was dried over magnesium sulfate, concentrated and refrigerated. Elongated plate-like crystals formed, 0.135 g., 22% yield, decomposing with gas evolution when placed in a bath at 120°. *Anal.* Calcd. for $C_{16}H_{16}N_2$: C, 81.30; H, 6.82; N, 11.85. Found: C, 81.48; H, 6.92; N, 11.75. In other runs yields varied from 20 to 45%. The ultraviolet absorption spectrum in cyclohexane showed maxima at 287 mμ, log ε 3.49, and at 387 mμ, log ε 2.89.

Rearrangement of I.—A small quantity of the azo compound I was dissolved in acetic acid and the solution was immediately evaporated to dryness in vacuum at room temperature, leading to the hydrazone IV, m.p. and mixed m.p. 155–158°.

Decomposition of I. A. Nitrogen Evolution.—The azo compound I was dissolved in a small quantity of redistilled solvent in a test-tube connected to a thermostated gas buret, the system (including the solution) was swept with oxygen-free nitrogen and leveled, the test-tube was heated at 135° or 110° for 0.5 hr. or at 100 or 90° for 1 hr. or at 80° for 2.5 hr. and brought back to the thermostat temperature (30°) and the evolved gas was measured. The interim readings were observed at the reaction temperature. The volumes measured were small and the accuracy was probably about ±5%. The data are summarized in Table I.

B. Products of Decomposition.—(1): Compound I, 0.053 g. (0.225 mmole), in a tared centrifuge-tube under nitrogen, was heated at 110° for a few minutes, then placed in an oil-bath at 125° for 5 minutes, strong nitrogen evolution ensuing and droplets condensing on the walls of the tube. The tube was opened and the odor of styrene was detected; the tube was swept again with nitrogen, stoppered and reweighed, loss of 0.008 g. being observed. The residue (solidified) was treated with 3 ml. of 95% ethanol, leading to compound IV, 0.016 g., 30% yield, m.p. 156–158°, mixed m.p. 157–158°. The filtrate was treated with 4% bromine in acetic acid until a pale yellow color persisted, diluted with 1 ml. of water and cooled, leading to styrene dibromide, m.p. and mixed m.p. 68–70°, 0.006 g. (0.023 mmole), 7% yield. Styrene, 0.100 g. (1 mmole), was dissolved in 3 ml. of ethanol and brominated as described above, [illegible] styrene dibromide, m.p. 68–70°, 0.044

(21) S. Kapf and C. Paal, *Ber.*, **21**, 3056 (1888).

(22) B. B. Corson, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 229–230.

(23) U. Sachsse, *Ber.*, **27**, 773 (1894).

(24) O. Diels and P. Fritzsche, *ibid.*, **44**, 3018 (1911).

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g. (0.17 mmole), 17% yield, reported[25] 72–73°. The infrared spectra of the two samples were identical, showing a strong carbon–bromine bond at 695 cm.$^{-1}$.

(2) A solution of compound I, 0.050 g. (0.212 mmole), and stilbene, 0.036 g. (0.212 mmole), in 1 ml. of ethylbenzene (b.p. 134–134.5°) was heated in vacuum at 100° for 50 minutes, concentrated to dryness in vacuum and treated with methanol. Stilbene was recovered; 0.014 g., 39% yield, m.p. and mixed m.p. 123–125°. The residue was an oil.

(3) A solution of I, 0.061 g. (0.26 mmole), and freshly sublimed quinone, m.p. 114–115°, 0.221 g. (2.0 mmoles), in 6 ml. of benzene was heated under nitrogen at 90° (bath temperature) for 42 hr. The solution was concentrated and sublimed in vacuum leading to recovery of quinone and separation of some black solid, 0.020 g. melting unsharply above 160°, presumably quinhydrone. The black residue, 0.145 g., was heated with a little ethanol, leading to compound IV, 0.003 g., 5% yield, m.p. and mixed m.p. 155–157°. The residue was chromatographed on alumina, leading to 3,6-diphenylpyridazine, 0.028 g., 47% yield, m.p. and mixed m.p. 219–220°

(25) R. Fittig and E. Erdmann, *Ann.*, **216**, 194 (1883).

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WALTHAM, MASS.

[CONTRIBUTION NO. 403 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO.]

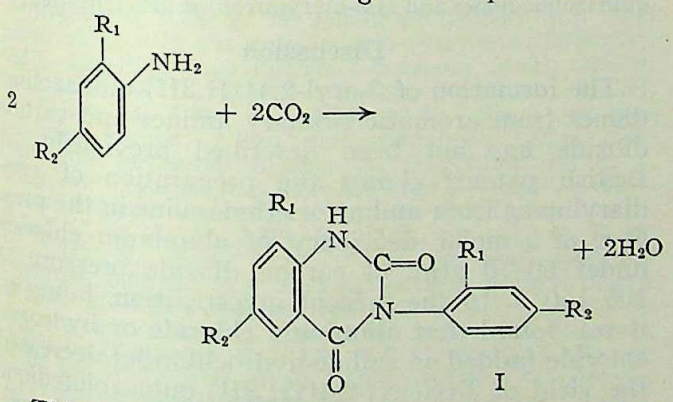
Quinazolinediones from Aromatic Amines and Carbon Dioxide

BY T. L. CAIRNS, D. D. COFFMAN AND W. W. GILBERT

RECEIVED FEBRUARY 12, 1957

The reaction of carbon dioxide with certain primary aromatic amines at 8500 atm. and 200–250° has given high conversions to 3-aryl-2,4(1H,3H)-quinazolinediones (I). A sharp pressure threshold for the reaction was found at about 3300 atm.; the quinazolinediones were not formed at lower pressures, while conversions increased to 65–70% at the highest temperatures and pressures investigated.

Previous communications[1] from this Laboratory have described investigations of the effects of pressures of 6000 to 8500 atm. on chemical reactions. This paper reports a new reaction, the high pressure synthesis of 3-aryl-2,4(1H,3H)-quinazolinediones (I) from certain primary aromatic amines and carbon dioxide according to the equation[2]



This unusual transformation has been examined in terms of the effects of temperature, pressure, solvents, catalysts and substituents. Conversions of aniline to 3-phenyl-2,4(1H,3H)-quinazolinedione (I, $R_1 = R_2 = H$) as high as 70% were obtained at temperatures above 200° at 8500 atm., but the conversion fell to zero at 150°. A sharp pressure threshold for the reaction was found at about 3300 atm. The quinazolinedione was not formed at lower pressures, and the conversion increased rapidly with increased pressures above the threshold value. The reaction occurred in the presence of either alkaline or acidic catalysts, but with acidic catalysts the yield of quinazolinedione was decreased by formation of unidentified by-products. In the uncatalyzed reaction, formation of the corresponding *sym*-diarylurea was the chief competing reaction.

Quinazolinediones were also obtained from *o*-toluidine (15% conversion, $R_1 = CH_3$, $R_2 = H$) and from *p*-toluidine (50% conversion, $R_1 = H$, $R_2 = CH_3$). Quinazolinediones were not identified among the reaction products when the aromatic amine contained nitro, halogen or hydroxyl substituents or when the amine was α- or β-naphthylamine.

Primary aromatic diamines have given complex intractable products with carbon dioxide under these conditions. These products may have been low molecular weight polymeric quinazolinediones or polymeric ureas.

Experimental

Aniline and CO_2.—Aniline (4.08 g.) and carbon dioxide (2.39 g.) were charged into a stainless steel cylinder fitted with a movable piston.[3] In some runs a small quantity of nitrogen (*ca.* 0.3 g.) was used to ensure return of the piston to its original position when the external pressure on it was released at the end of the experiment. The cylinder was placed in a Bridgman-type pressure apparatus,[4] and its contents were subjected to an initial pressure of 8500 atm. at room temperature. The entire high-pressure system was then heated to 200°. After 14 hr. the apparatus was cooled to room temperature. The final pressure was about 7900 atm. The pressure was released and the cylinder removed and vented. The reaction product was washed from the vessel with ether and collected on a filter to give 3.37 g. of crude solid, m.p. 267–268°. It was purified by recrystallization from a mixture of ethanol and benzene or by sublimation under reduced pressure to give white crystals, m.p. 275–280°.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.57; H, 4.23; N, 11.76. Found: C, 70.76; H, 4.43; N, 11.60, 11.65.

The product was identified as 3-phenyl-2,4-(1H,3H)-quinazolinedione by hydrolysis to aniline and anthranilic

(1) (a) T. L. Cairns, G. L. Evans, A. W. Larchar and B. C. McKusick, THIS JOURNAL, **74**, 3982 (1952); (b) T. L. Cairns, A. W. Larchar and B. C. McKusick, *ibid.*, **74**, 5633 (1952); (c) *J. Org. Chem.*, **17**, 1497 (1952); (d) **18**, 748 (1953); (e) T. L. Cairns, D. D. Coffman, Richard Cramer, A. W. Larchar and B. C. McKusick, THIS JOURNAL, **76**, 3024 (1954).

(2) W. W. Gilbert, U. S. Patent 2,680,741, June 8, 1954.

(3) *Cf.* reference 1a, p. 3986; 1d, p. 749.

(4) P. W. Bridgman, "The Physics of High Pressure," G. Bell and Sons, London, 1949, pp. 80–89.

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acid and by comparison of its m.p., mixed m.p., infrared spectrum and X-ray diffraction pattern with authentic material prepared by cyclization of the N-phenylurea of anthranilic acid.[5]

TABLE I

REACTION OF ANILINE WITH CARBON DIOXIDE: EFFECT OF TEMPERATURE, PRESSURE AND CATALYSTS ON SYNTHESIS OF 3-PHENYL-2,4(1H,3H)-QUINAZOLINEDIONE

Reactions of possible intermediates

Charge, g.	Conditions[a]	Quinazolinedione, g.
Aniline, 4.08 CO_2, 2.39	200° 8500–7900	3.37
Aniline, 71.5 CO_2	250°[b] 3000	0[c]
Aniline, 71.5 CO_2	320°[d] 3000	0[e]
Aniline, 4.03 CO_2, 1.75	250° 1500–1150	0[f]
Aniline, 4.23 CO_2, 2.52; N_2, 0.32	250° 3300–2600	0.05[g]
Aniline, 4.00 CO_2, 2.14	250° 4300–3600	0.74
Aniline, 1.05 CO_2, 1.79	250° 5300	0.05
Aniline, 4.33 CO_2, 3.65; N_2, 0.20	250° 6000–5600	1.68[h]
Aniline, 4.00 CO_2, 2.56	150° 8500–7700	0[f]
Aniline, 4.16 CO_2, 3.97	200° 8500–8100	2.51
Aniline, 2.02 CO_2, 2.07; H_2O, 4.00	100° 8500–7900	0[f]
Aniline, 4.06; H_2O, 0.75 CO_2, 3.27; Na_2CO_3, 1.00	250° 8500–7700	3.72
Aniline, 3.14; $AlCl_3$, 1.00 CO_2, 4.00; N_2, 0.24	200° 8500–7700	1.55[i]
Aniline, 2.00; $AlCl_3$, 3.00 CO_2, 3.06; N_2, 0.40	250° 8500–7100	0.05[j]
Aniline, 2.09; CO_2, 3.07 Aniline·HCl, 2.00; N_2, 0.28	250° 7300–3200[k]	0.16[l]
Aniline, 1.86; CO_2, 4.02 Aniline·HCl, 2.00; N_2, 0.19	150° 8500–7900	0[m]
Aniline, 2.07; CO_2, 2.95 Aniline·HCl, 2.00; N_2, 0.33	200° 8500–7900	0.67[n]
Aniline, 4.10; CO_2, 2.63 Concd. HCl, 0.02; N_2, 0.39	250° 8500–7900	2.15
Aniline, 4.11; CO_2, 2.56 Powd. NaOH, 0.50; N_2, 0.30	200° 8500–7700	1.62
Aniline, 4.06; CO_2, 3.48 K_2CO_3, 0.50; N_2, 0.30	150° 8500–7300	0[h]
Aniline, 4.25; N_2, 0.23 CO_2, 3.73 Phenyldimethylphosphine, 0.10	250° 8500–7900	2.25[h]
Aniline, 3.99; N_2, 0.23 CO_2, 4.14 Phenyldimethylphosphine, 0.10	150° 8500–7900	0[o]
sym-Diphenylurea, 2.00 CO_2, 2.82; N_2, 0.15 Ether, 2.56	250° 8500–7900	0
sym-Diphenylurea, 3.00 CO_2, 3.61; N_2, 0.35 Triethylamine, 0.56	200° 8500–6600	0.15[p]
Anthranilic acid, 3.04 Ether, 4.98	250° 8500–8900	0.02[q]
Anthranilic acid, 3.26 CO_2, 3.20; N_2, 0.46	250° 8500–8100	1.67[f,p]
Phenyl isocyanate, 10.54	250° 8500–7100	0[r]

[a] Reaction time 12–15 hr. unless otherwise specified. Pressures are initial and final pressures in atm. [b] Reaction time, 3 hr. [c] Small amount of *sym*-diphenylurea formed. [d] Reaction time, 2 hr. [e] *sym*-Diphenylurea, 0.16 g. [f] No *sym*-diphenylurea detected. [g] *sym*-Diphenylurea, 0.12 g. [h] *sym*-Diphenylurea, 0.02 g. [i] Neutral fraction, 0.43 g., m.p. 43–47°. [j] Neutral fraction, 0.32 g., m.p. 36–41°. [k] Slow leak in reactor. [l] Neutral fraction, 1.20 g., m.p. 44–46°. [m] Neutral fraction, 0.10 g., m.p. 50–53°. [n] Neutral fraction, 0.85 g., m.p. 30–40°. [o] *sym*-Diphenylurea, 0.29 g. [p] Some aniline recovered. [q] CO_2 formed. [r] Quantitative conversion to triphenyl isocyanurate.

In most of this work the crude reaction product was purified by suspension in ether and extraction first with 2 *N* hydrochloric acid and then with 5% sodium hydroxide solution. The 3-aryl-2,4-(1H,3H)-quinazolinediones were recovered by saturating the sodium hydroxide solution with carbon dioxide. The small neutral fraction which was sparingly soluble in ether was recrystallized from ethanol to give the *sym*-diarylurea. From aniline and carbon dioxide this urea was *sym*-diphenylurea, long white needles, m.p. 244–246°. The mixed m.p. with authentic *sym*-diphenylurea, m.p. 245–247°, was not depressed.

Examples in the table illustrate the effects of temperature, pressure, solvents, catalysts and substituents on the reactions of representative primary aromatic amines with carbon dioxide. The relative proportions of 3-aryl-2,4-(1H,3H)-quinazolinediones and *sym*-diarylureas are also indicated.[6,7,8]

Discussion

The formation of 3-aryl-2,4(1H,3H)-quinazolinediones from aromatic primary amines and carbon dioxide has not been described previously. A British patent[9] claims the preparation of *sym*-diarylureas from aniline or ethylaniline in the presence of a molar deficiency of aluminum chloride under 50–70 atm. of carbon dioxide pressure at 105–150°. In the present investigation, however, it was found that aluminum chloride or hydrogen chloride (added as aniline hydrochloride) decreased the yield of 3-phenyl-2,4(1H,3H)-quinazolinedione without giving isolable quantities of *sym*-diphenylurea. This effect was accompanied by an increased formation of unidentified, low-melting, neutral, ether-soluble side-reaction products.

It does not appear that *sym*-diphenylurea was formed first and that subsequently it underwent reaction with more carbon dioxide to give the quinazolinedione. However, the experiments to demonstrate this point are not unequivocal, since phenomena involving contact of carbon dioxide with massive crystals of *sym*-diphenylurea *vs.*

(5) C. Paal, *Ber.*, **27**, 977 (1894).

(6) A. F. Kizber and A. J. Glagoleva, *Doklady Akad. Nauk, S.S.S.R.*, **83**, 89 (1952); *C. A.*, **47**, 4343 (1953). The m.p. of 3-*p*-tolyl-6-methyl-2,4(1H, 3H)-quinazolinedione was reported to be 285–286° and that of 3-(1-naphthyl)benzo[h]quinazoline-2,4(1H,3H)-dione to be 333–334°.

(7) G. V. Jadhav, *J. Indian Chem. Soc.*, **10**, 391 (1933), reported *sym*-di-α-naphthylurea, m.p. 296°, and *sym*-di-β-naphthylurea, m.p. 310°.

(8) P. Pierron, *Ann. chim. phys.*, [8] **15**, 194 (1908), reported benzimidazolone platelets, m.p. 310° (sublimes above 270°).

(9) G. T. Morgan and D. D. Pratt, British Patent 353,464 (to Imperial Chemical Industries, Ltd.), July 20, 1931.

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TABLE II

REACTIONS OF OTHER AROMATIC PRIMARY AMINES WITH CARBON DIOXIDE

Reaction temperature 250° unless otherwise specified; reaction time 12–14 hr.

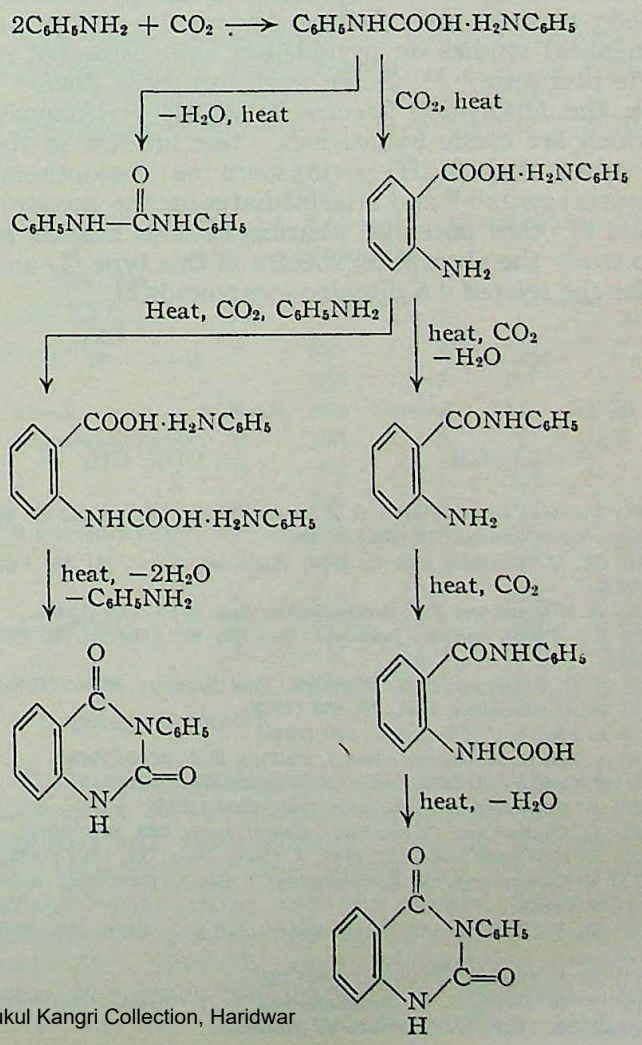
Charge, g.	Pressure, atm.	Quinazolinedione, g.
o-Toluidine, 3.96 CO_2, 2.88	7500–7100	Some[a]
o-Toluidine, 4.00 CO_2, 3.33; N_2, 0.36	8500–7900	0.76[b]
p-Toluidine, 3.73 CO_2, 2.92; N_2, 0.78	8500–7900	2.33
p-Toluidine, 8.00[c] CO_2, 8.03; N_2, 0.35	8500–7700	5.09[d,e]
2,6-Dimethylaniline, 3.82 CO_2, 4.34; N_2, 0.27	8500–7500	0[f]
α-Naphthylamine, 3.00 CO_2, 3.03; Ether, 2.16; N_2, 0.14	8500–8300[g]	..[h]
α-Naphthylamine, 3.00 CO_2, 4.48; N_2, 0.13	8500–8300	..
β-Naphthylamine, 2.00 CO_2, 2.26; Ether, 2.53; N_2, 0.18	8500–8100	0[i]
p-Phenylenediamine, 3.05 CO_2, 4.69; N_2, 0.13	8300–8100	..[k]
2,4-Diaminotoluene, 2.80 CO_2, 3.16; N_2, 0.53	8500–8100	..[l]
o-Phenylenediamine, 3.03 CO_2, 4.89; N_2, 0.28	8500–7300	..[m]
Benzidine, 2.95 CO_2, 4.39; N_2, 0.19	8100–7300	..[n]

[a] Recovered 0.46 g. of *sym*-di-*o*-tolylurea, m.p. and mixed m.p. with authentic *sym*-di-*o*-tolylurea, 257–258°. [b] M.p. 224–225° from methanol–benzene. *Anal.* Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.18; H, 5.30; N, 10.52. Found: C, 72.30; H, 5.48; N, 10.57, 10.53. Some *sym*-di-*o*-tolylurea formed. [c] Two runs combined. [d] M.p. 288–290° from methanol–benzene. A. F. Kizber and A. J. Glagoleva[6] reported m.p. 285–286° for 3-*p*-tolyl-6-methyl-2,4(1H,3H)-quinazolinedione. *Anal.* Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.18; H, 5.30; N, 10.52. Found: C, 71.89; H, 5.37; N, 10.44, 10.47. [e] Also recovered *sym*-di-*p*-tolylurea, 0.05 g., m.p. and mixed m.p. with authentic sample, 271–272°. [f] Recovered 1.41 g. of *sym*-di-2,6-dimethylphenylurea, m.p. above 325° (sublimation). *Anal.* Calcd. for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.46; H, 7.65; N, 10.42, 10.38. [g] 200°. [h] Recovered 1.71 g. of di-α-naphthylurea, m.p. 310–312°. *Anal.* Calcd. for $C_{21}H_{16}N_2O$: C, 80.74; H, 5.16; N, 8.97. Found: C, 80.97; H, 5.85; N, 8.94, 8.96. G. V. Jadhav[7] reported *sym*-di-α-naphthylurea, m.p. 296°. [i] An alkali-soluble solid, m.p. 345° (0.68 g. from methanol–benzene), that was precipitated from alkaline solutions by carbon dioxide, gave no satisfactory analytical results for a quinazolinedione. 3-(1-Naphthyl)-benzo[h]quinazoline-2,4(1H,3H)-dione, m.p. 333–334°, was reported by A. F. Kizber and A. J. Glagoleva.[6] [j] Recovered 0.30 g. of di-β-naphthylamine and 0.17 g. of *sym*-di-β-naphthylurea, m.p. 310–315°.[7] *Anal.* Calcd. for $C_{21}H_{16}N_2O$: C, 80.74; H, 5.16; N, 8.97. Found: C, 80.37; H, 5.18; N, 9.75, 9.76. [k] Recovered 3.52 g. of black solid, m.p. above 350°. Intractable solid Soxhlet extracted with ether without appreciable weight loss. *Anal.* Calcd. for $(C_8H_4N_2O_2)_x$ (polymeric quinazolinedione): C, 60.00; H, 2.51; N, 17.51. Found: C, 60.51; H, 4.44; N, 17.57, 17.49. [l] Recovered 3.17 g. of brown solid which darkened at 240–250°. Intractable solid Soxhlet extracted with ether. *Anal.* Calcd. for $(C_9H_6N_2O_2)_x$ (polymeric quinazolinedione): C, 62.07; H, 3.47; N, 16.09. Found: C, 61.60; H, 4.96; N, 15.53, 15.60. [m] Recovered 1.27 g. of cyclic urea benzimidazolone, m.p. 320°. P. Pierron[8] reported benzimidazolone, m.p. 310°. *Anal.* Calcd. for $C_7H_6N_2O$: C, 62.67; H, 4.51; N, 20.89. Found: C, 62.36; H, 4.57; N, 20.59, 20.64. [n] Recovered 2.96 g. of gray solid. Soxhlet extraction with ether, methanol, acetone and dimethylformamide gave no appreciable loss in weight of solid. *Anal.* Calcd. for $(C_{13}H_{10}N_2O)_x$ (polymeric urea): C, 74.27; H, 4.80; N, 13.33. Found: C, 73.10; H, 4.95; N, 13.54, 13.63.

finely divided urea crystals formed *in situ* from aniline and carbon dioxide might lead to entirely different rates of reaction. In the presence of a small amount of triethylamine to give a basic environment, *sym*-diphenylurea did give a detectable quantity of the quinazolinedione, but the reaction was complicated by gross amounts of unidentified by-products.

Recent work by Kizber and Glagoleva[6] indicated that *sym*-diphenylurea when heated with potassium carbonate for 5 hr. at 250–260° under 50–55 atm. carbon dioxide pressure underwent modest conversions to *p*-aminobenzoic acid, anthranilic acid and 3-phenyl-2,4(1H,3H)-quinazolinedione. Further the potassium salt of anthranilic acid was converted to the quinazolinedione by heating in a sealed tube at 230–240° for 8 hr. *sym*-Diphenylurea was also cleaved by potassium carbonate and carbon dioxide in 8 hr. at 160–170°, giving 80–85% of the potassium salt of phenylcarbamic acid. The latter on heating above 180° in carbon dioxide was converted to potassium salts of *p*-aminobenzoic and anthranilic acids.

Conditions in the present reaction system do not favor the formation of phenyl isocyanate, which, incidentally, at 250° and 8500 atm. was quantitatively trimerized to triphenyl isocyanurate, m.p.



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265–270°.[10] The aniline salt of phenylcarbamic acid, $C_6H_5NHCOOH \cdot H_2NC_6H_5$, might be stable even in the presence of water under carbon dioxide pressure. This salt might be capable of rearranging under the combined agencies of heat and carbon dioxide pressure to give the aniline salt of anthranilic acid in analogy to the reported results with the potassium salt. This mechanism appears consistent with the observed lower conversions in the presence of aluminum chloride and aniline hydrochloride. Other possible intermediates in the transformation to the quinazolinedione are indicated in the diagram.

(10) N. W. Hofmann, *Ber.*, **18**, 764 (1885). Triphenyl isocyanurate, m.p. 275°, was prepared by heating phenyl isocyanate (5 moles) with potassium acetate (1 mole) at 100°.

Acknowledgments.—The authors are pleased to acknowledge the assistance given by Dr. N. E. Searle who supplied known samples of *sym*-di-*o*-tolyl- and di-*p*-tolylurea. We would like to thank Drs. W. W. Prichard, E. L. Jenner, J. R. Roland and A. L. Barney, and Messrs. A. W. Larchar, H. S. Young and P. J. Rennolds for stimulating discussions and helpful suggestions.

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

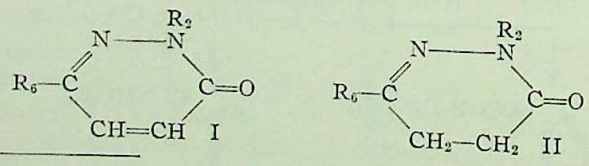
Absorption Spectra of Heterocyclic Compounds. VII.[1] Some 3(2H)-Pyridazones

BY EDGAR A. STECK AND FREDERICK C. NACHOD

RECEIVED MARCH 2, 1957

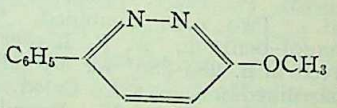
The absorption spectra of a series of 3-pyridazones have been reported and interpreted.

Pyridazine derivatives may be considered to contain a potential hydrazine unit in the 1,2-diazine ring and hence are not readily obtainable from biochemical transformations involving nitrogen. In fact, this ring system has not been found to occur in natural products, a sharp distinction from the other diazines. This heterocyclic type has not been investigated as thoroughly as the pyrimidines and pyrazines, and relatively few reports of physicochemical studies on pyridazines have appeared in the literature.[2–14] Some work has been done[3,9,13] on the absorption spectra of 3(2H)-pyridazones, which are cyclic hydrazones. Our interest in the 6-substituted 3(2H)-pyridazones as chemotherapeutic agents[15,16] and intermediates for the preparation of other potential pharmaceuticals has led us to study the absorption spectra of this type (I) and also the related 4,5-dihydro compounds II.



I II

The range of structures which may be chosen for 3(2H)-pyridazones and related dihydro compounds is limited sharply by the non-equivalence of the two formulas possible for pyridazine.[5,7] Thus, comparison of the absorption spectra of 6-phenyl-3(2H)-pyridazone (I, R_2 = H, R_6 = C_6H_5) with those of 2-methyl-6-phenyl-3-pyridazone (I, R_2 = CH_3; R_6 = C_6H_5) and 3-methoxy-6-phenylpyridazine (III) clearly substantiates the formulation of the first-mentioned compound as (I). The spectra of the three compounds in 95% ethanol are shown in Fig. 1.



III

Absorption spectra of 6-(2-thienyl)-3(2H)-pyridazone and the related 4,5-dihydro compound in 95% ethanol, 0.01 *N* sodium hydroxide and 0.01 *N* hydrochloride are presented in Fig. 2. 4,5-Dihydro-6-(2-thienyl)-3(2H)-pyridazone shows little difference in pattern of spectra in the three solvents. While the spectra of 6-(2-thienyl)-3(2H)-pyridazone in ethanol and acid are identical, the absorption in basic solutions is more closely related in effect to those obtained with the dihydro compound. This indicates that the sodium enolate, which may be formed through keto–enol tautomerism in this type of the pyridazone, is more or less closely related to the dihydropyridazone (*cf.* ref. 13). However, the behavior in neutral or acid solution shows that 6-(2-thienyl)-3(2H)-pyridazone may not exist in keto form (in those solvents) as evident by comparison of Fig. 2 with Fig. 1.

In Table I, the comparison of spectral absorption of 6-substituted 3(2H)-pyridazones in neutral, alkali and acid solutions is presented. A chlorine in the *p*-position of the phenyl group produced a slight batho- and hyperchromic effect, this being more pronounced when ethanol was the solvent. This behavior is not unexpected, nor was a similar shift in the case of the 6-(2-thienyl)-3(2)-pyridazone

(1) Previous contribution: E. A. Steck, F. C. Nachod and G. W. Ewing, THIS JOURNAL, **71**, 2334 (1949).
(2) M. G. Korshun and C. Roll, *Bull. soc. chim.*, [4] **39**, 1223 (1926).
(3) D. Biquard and P. Grammaticakis, *ibid.*, [5] **7**, 766 (1940).
(4) W. Hückel and W. Jahnentz, *Ber.*, **74**, 652 (1941); **75**, 1438 (1942).
(5) R. C. Evans and F. Y. Wiselogle, THIS JOURNAL, **67**, 60 (1945).
(6) W. C. Schneider, *ibid.*, **70**, 627 (1948).
(7) A. Macoll, *J. Chem. Soc.*, 670 (1946).
(8) A. Albert, R. Goldacre and J. Phillips, *ibid.*, 2240 (1948).
(9) H. Gregory, J. Hills and L. F. Wiggins, *ibid.*, 1248 (1949).
(10) S. Dixon and L. F. Wiggins, *ibid.*, 3236 (1950).
(11) O. Chalvet and C. Sandorfy, *Compt. rend.*, **228**, 566 (1949).
(12) F. Halverson and R. C. Hirt, *J. Chem. Phys.*, **17**, 1165 (1949).
(13) K. Eichenberger, R. Rometsch and J. Druey, *Helv. Chim. Acta*, **37**, 1298 (1954).
(14) R. H. Horning and E. D. Amstutz, *J. Org. Chem.*, **20**, 1069 (1955).
(15) E. A. Steck, U. S. Patent 2,624,730.
(16) E. A. Steck, R. P. Brundage and L. T. Fletcher, (a) THIS JOURNAL, **75**, 1117 (1953); (b) to be published.

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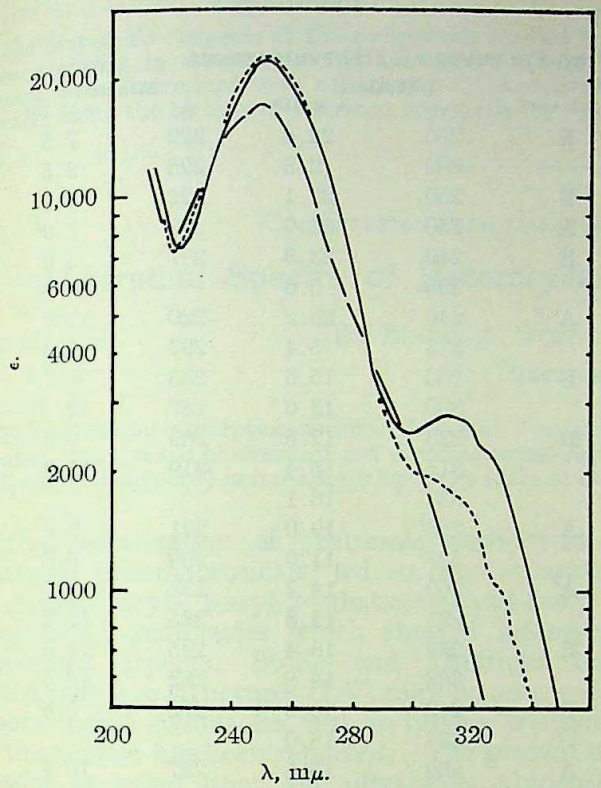

Fig. 1.—Absorption spectra in 95% ethanol of: - - - - -, 6-phenyl-3(2H)-pyridazone; — —, 3-methoxy-6-phenylpyridazine; ——, 2-methyl-6-phenyl-3(2H)-pyridazone.

and its bromo derivative (*cf.* ref. 17). In the substitution of the nucleophilic nitro group in the *m*-position, there is less effect than noted with the *p*-halogen type, and a slight hypochromic shift results (*cf.* ref. 17).

Table II summarizes significant aspects of the

TABLE I

ABSORPTION SPECTRA OF 6-SUBSTITUTED-3(2H)-PYRIDAZONES

6-Substituted-3-(2H)-pyridazone	Solvent[a]	Maxima[b] λ	Maxima[b] ε × 10³	Minima[b] λ	Minima[b] ε × 10³	Inflection[b] λ	Inflection[b] ε × 10³
6-Phenyl	E	253	22.0	220	8.3	300	2.0
	B	265	17.0	225	11.3	300	4.3
	A	249	23.0	221	7.2	295	2.2
6-(4-Chlorophenyl)	E	257	27.5	226	8.7	300	2.5
	B	265	20.0	232	9.9	305	5.7
	A	255	27.1	224	7.5	295	3.0
6-(3-Nitrophenyl)	E	250	23.5	217	13.2		
	B	265	22.5	241	12.3		
	A	245	24.5	217	13.6		
6-(2-Thienyl)	E	270	16.0	232	3.9		
	B	293	13.5	235	5.1	270	10.0
	A	268	15.8	230	4.1		
6-(5-Bromo-2-thienyl)	E	318	16.9	235	3.7		
	B	318	17.6	238	4.0		
	A	319	16.2	235	3.5		

[a] Legend: E, ethanol; B, 0.01 *N* NaOH; A, 0.01 *N* HCl. [b] Wave length in mμ; ε × 10³, extinction values.

absorption spectra of 6-substituted 4,5-dihydro-3(2H)-pyridazones obtained in ethanolic, basic and acidic solutions. The general interrelationships in these cases were of the same character as observed for the 6-substituted 3(2H)-pyridazones.

(17) E. A. Steck, G. W. Ewing and F. C. Nachod, THIS JOURNAL, 71, 238 (1949).

It may be noted that the dihydro compounds exhibit bathochromic and hypsochromic displacement with respect to the related 3(2H)-pyridazones. This is a consequence of the fact that a greater number of contributors may be formulated for the dihydro type which contain conjugation permissible for such a system having non-equivalence of structural forms.

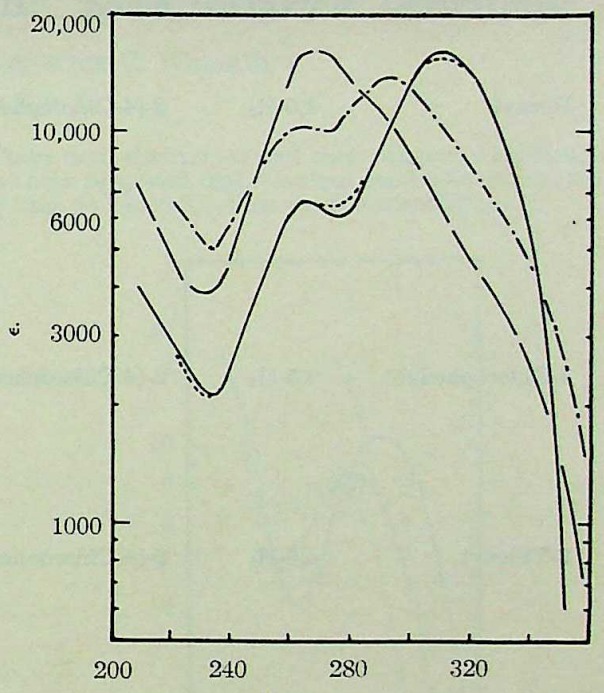

Fig. 2.—Absorption spectra of 6-(2-thienyl)-4,5-dihydro-3-(2H)-pyridazone: —, in 95% ethanol; - - - -, in 0.01 *N* NCl and 0.01 *N* NaOH; 6-(2-thienyl)-3(2H)-pyridazone; — —, in 95% ethanol and 0.01 *N* NCl; —·—·—, in 0.01 *N* NaOH.

TABLE II

ABSORPTION SPECTRA OF 6-SUBSTITUTED-4,5-DIHYDRO-3-(2H)-PYRIDAZONES

6 Substituted-4,5-dihydro-3(2H)-pyridazone	Solvent[a]	Maxima[b] λ	Maxima[b] ε × 10³	Minima[b] λ	Minima[b] ε × 10³
6-Phenyl	E	285	16.1	236	2.2
	B	280	16.8	232	2.3
	A	280	16.0	232	2.3
6-(4-Chlorophenyl)	E	290	19.0	240	2.6
	B	285	19.2	235	2.7
	A	285	19.2	235	2.9
6-(3-Nitrophenyl)	E	274	18.8	236	7.3
	B	274	20.4	232	6.4
	A	274	20.6	234	6.6
6-(2-Thienyl)	E	310	15.5	235	2.2
	B	311	15.1	235	2.3
	A	311	15.4	235	2.1

[a,b] Legend as in Table I.

Table III contains information on the salient features of the absorption spectra of certain 2,6-disubstituted 3-pyridazones. Among the simpler representatives of the group, *viz.*, 2-methyl-6-phenyl-3-pyridazone and the related 2-(4-chlorophenyl) compound, the spectra in ethanol (in particular) show the expected patterns resulting from increased conjugation. A maximum was found in the short-wave range when alcoholic

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TABLE III

ABSORPTION SPECTRA OF VARIOUS 6-SUBSTITUTED POLYHYDRO-3(2H)-PYRIDAZONES

6-Substituent	Polyhydro	Other substituent	Solvent[a]	Maxima[b] λ	Maxima[b] ε × 10³	Minima[b] λ	Minima[b] ε × 10³
Phenyl		2-Methyl	E	250	22.4	222	7.5
				309	2.8	298	2.5
			B	250	22.1	222	8.1
			A	250	22.0	222	7.9[f]
Phenyl		2-(4-Chlorophenyl)	E	240	23.8	297	2.9
				335	5.6		
			A[c,d]	240	23.2	220	11.6
				333	5.4	297	2.6
Phenyl	4,5-H_2	2-(4-Chlorophenyl)	E	260	15.6	233	8.7
				300	13.0	287	12.4
			B	236	12.5	269	5.5
				315	15.4	319	15.0
				333	16.1		
			A	255[e]	19.0	231	6.9
				287	11.0	260	9.8
			A[c]	260	14.7	233	7.2
				295	12.8	285	12.2
4-Chlorophenyl	4,5-H_2	2-(4-Chlorophenyl)	E	259	16.4	235	11.0
				303	15.8	282	13.5
			B	242	16.0	272	5.8[g]
				338	18.0		
			A	259	15.5	237	10.4
				303	15.5	280	13.2
2-Thienyl	4,5-H_2	2-(4-Chlorophenyl)	E	260	14.7	232	6.1
				322	15.0	290	7.6
			B	254	16.2	283	5.2[h]
				352	17.5		
			A	259	11.4	233	6.0
				317	15.3	284	7.1

[a,b] Legend as in Table I. [c] Alcoholic acid. [d] Not soluble in aqueous or alcoholic alkali. [e] Flat maximum. [f] Inflection at 300 mμ (3.0). [g] Inflection at 313 mμ (15.4). [h] Inflection at 310 mμ (9.7).

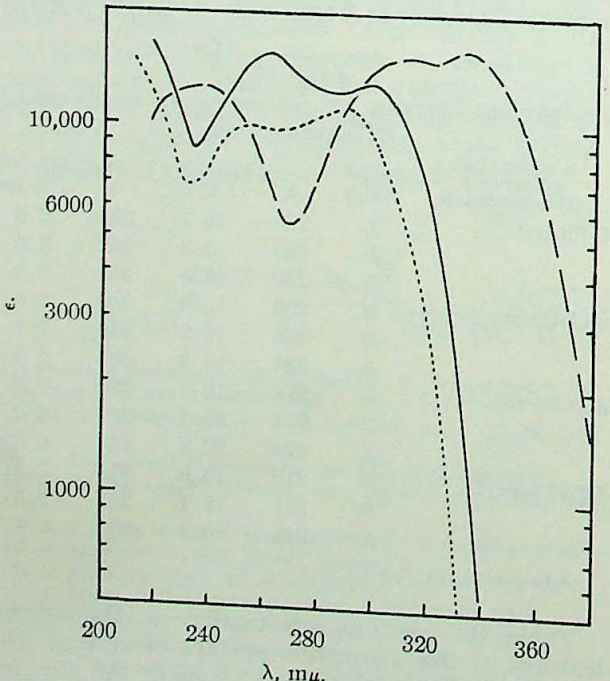
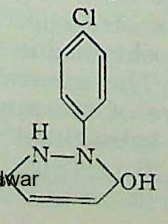


Fig. 3.—Absorption spectra of 2-(4-chlorophenyl)-4,5-dihydro-6-phenyl-3(2)-pyridazone; —, in 95% ethanol; - - - -, 0.01 *N* HCl; — —, 0.01 *N* NaOH.

hydrochloric acid was used to dissolve 2-(4-chlorophenyl)-6-phenyl-3-pyridazone. The effect of varying the 6-substituent of 2-(4-chlorophenyl)-4,5-dihydro-3-pyridazones also was studied, with the substituent involved being a phenyl, a 4-chlorophenyl or a 2-thienyl group. Figure 3 gives detailed information on 2-(4-chlorophenyl)-4,5-dihydro-6-phenyl-3-pyridazone, with the spectra run in ethanol, base and acid. In the case of the 6-phenyl compound, it is to be noted that a marked bathochromic shift occurred when 0.01 *N* sodium hydroxide was used as solvent rather than ethanol or 0.01 *N* hydrochloric acid. This alteration is obviously a result of an increase in conjugation, possibly through formation of IV (as sodium salt). The presence of a 4-chlorophenyl or a 2-thienyl group in position 6 of the 2-(4-chlorophenyl)-4,5-dihydro-3-pyridazones did not lead to such definite spectral evidence. In each of these latter cases, there is an inflection in the region in which a bifurcation was found for the 6-phenyl compound (*cf.* Fig. 3). It is to be noted that the dihydro-3-pyridazones bearing a substituent in position 2 follow the general aspects found in 3(2H)-pyridazones, with the additional expected complexity.



IV

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Experimental

The preparative aspects of the compounds studied have been reported in detail.[15,16] The ultraviolet absorption spectra were determined with a Beckman DU spectrophotometer using the technique described previously.[18]

Acknowledgment.—The assistance of Mrs. M. Becker is gratefully acknowledged.

(18) G. W. Ewing and E. A. Steck, THIS JOURNAL, 68, 3181 (1946).

RENSSELAER, NEW YORK

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

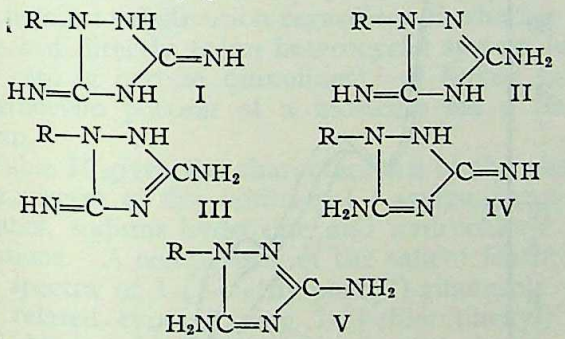
Absorption Spectra of Heterocycles. VIII.[1] Some Guanazole Derivatives

BY EDGAR A. STECK AND FREDERICK C. NACHOD

RECEIVED MARCH 9, 1957

The ultraviolet absorption spectra of several 1-arylguanazoles have been determined and their relation with structure treated. As a result of chemical and physical considerations, it has been suggested that 1-arylguanazoles be formulated as 3(5)-amino-1-aryl-5(3)-imino-1,2,4-triazolones (III) or (IV) rather than as 1-aryl-3,5-diimino-1,2,4-triazolidines (I).

The investigation of guanazole derivatives as potential pharmaceuticals[2] led to the preparation of certain 1-aryl-, 1-aryl-2-substituted and 1-aryl-3-substituted guanazoles which showed interesting structural aspects. Stollé and Dietrich[3] have noted that five structures (I-V) may be assigned to 1-substituted guanazoles, but no further treatment of this matter has been reported. The present discussion is based upon the ultraviolet absorption spectra of the 1-arylguanazoles and derivatives.



The reaction of arylhydrazines with cyanoguanidine might result in the formation of 1-arylguanazoles having several possible structures, as indicated by formulas I-V. These types represent the relationship of these 1,2,4-triazoles with guanidines and biguanides where arrangement of the atoms may be considered as being formed of two amidine groups. In these electrically neutral structures it is seen readily that the greatest degree of conjugation is present in V; forms III and IV show less conjugation, and no conjugation occurs in I and II. A study was made of the various proton donor and acceptor forms possible for those 1,2,4-triazole derivatives known as guanazoles; a summary of these considerations is shown in Table I. The contribution of the non-conjugated forms exceeds those of either conjugated type; this is in harmony with the experimental findings.

In Fig. 1 are shown the spectra of 1-phenylguanazole in acid, base and ethanol. For purposes of comparison, the spectrum of biphenyl in hexane[4] is also included since, as will be seen later in the case of 1-(4-xenyl)-guanazole (Fig. 3), there is a typical super-position of the component spectra in the solvent studied. It may be noted that the highest maximum in the spectrum of 1-phenylguanazole is attained in alcoholic solution. There is a related shift in the spectrum to longer wave lengths in neutral solution, whereas the spectra in solutions of both high and low *p*H are found to

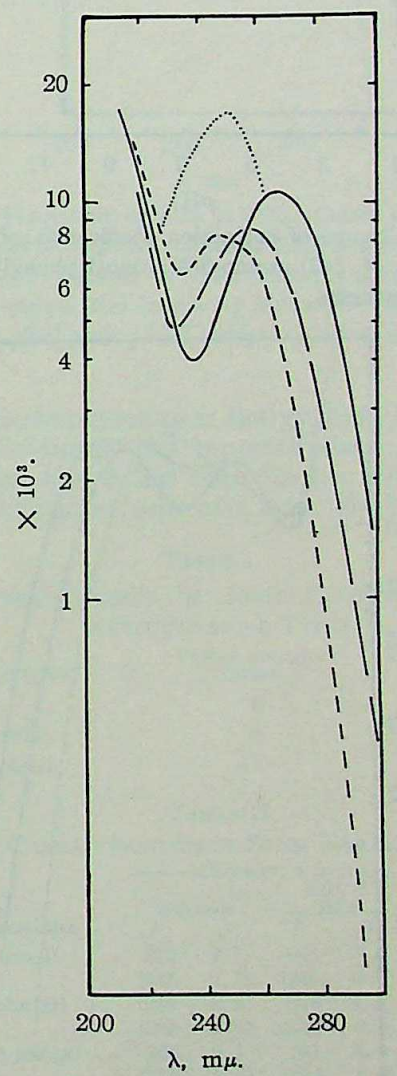


Fig. 1.—Absorption spectra of 5(3)-amino-3(5)-imino-1-phenyl-1,2,4-triazolone in: —, 95% ethanol; - - - , 0.01 *N* HCl; — —, 0.01 *N* NaOH; and . . . .biphenyl in *n*-hexane.

(1) Previous contributions, E. A. Steck and F. C. Nachod, THIS JOURNAL, 79, 4408 (1957).
(2) E. A. Steck, R. P. Brundage and L. T. Fletcher, to be published.
(3) R. Stollé and W. Dietrich, *J. prakt. Chem.*, [2] 139, 193 (1934).
(4) M. T. O'Shaughnessy and W. H. Rodebush, THIS JOURNAL, 62, 2096 (1940).

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occur at shorter wave lengths. This, too, is in agreement with our above-noted considerations. To test the idea further, it was decided to determine the influence of *p*H upon the extinction coefficients in the spectrum of 1-phenylguanazole. Figure 2 shows the results of spectral studies made with a number of buffer solutions. This demonstrates clearly that a maximum in conjugation, as may be attributable to forms III-V, results at neutral *p*H

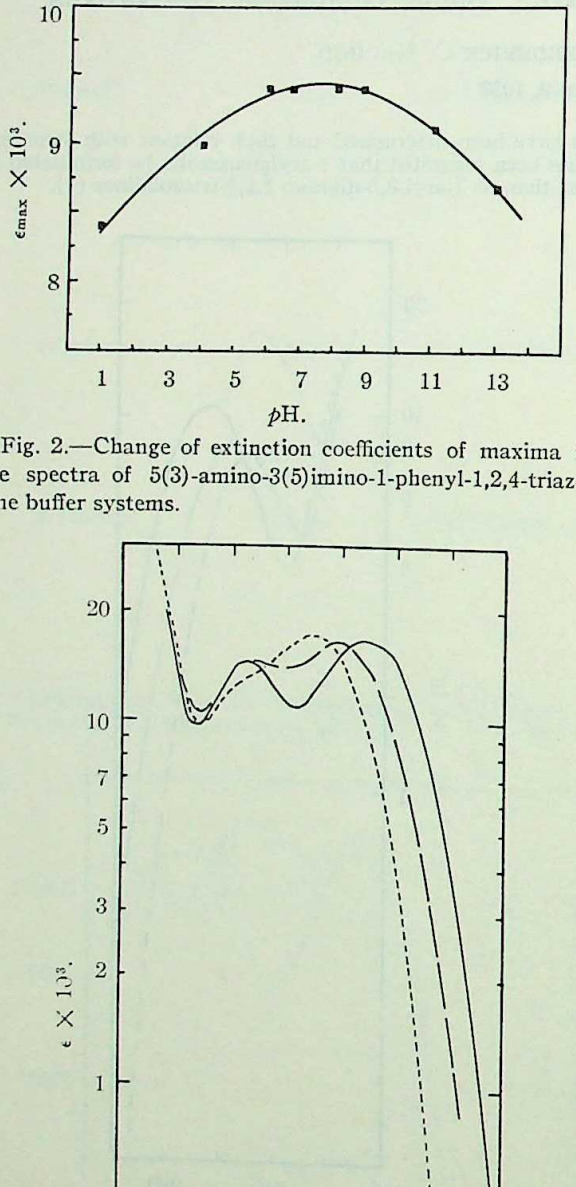

Fig. 2.—Change of extinction coefficients of maxima in the spectra of 5(3)-amino-3(5)imino-1-phenyl-1,2,4-triazolone buffer systems.

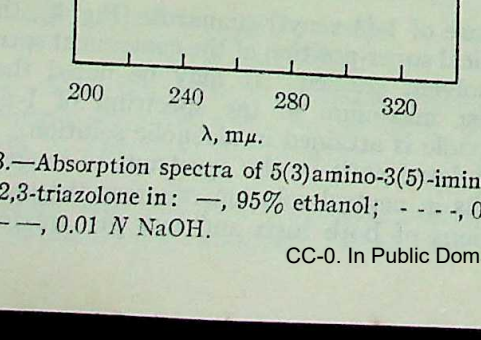

Fig. 3.—Absorption spectra of 5(3)amino-3(5)-imino-1-*p*-xenyl-1,2,3-triazolone in: —, 95% ethanol; - - - -, 0.01 *N* HCl; — —, 0.01 *N* NaOH.

range. Moreover, it should be noted that the hyperchromic effect in ethanolic solution (Fig. 1) is to be ascribed to an additional solvent effect.

The spectra for 1-(4-xenyl)-guanazole in ethanol, acid and base are shown in Fig. 3. There are two maxima in the spectral curves determined with use of solutions in sodium hydroxide and ethanol; the relative positions of the curves are in the expected order and magnitude. In acid solution the maximum obtained for 1-(4-xenyl)-guanazole is to be seen to occur at the same wave length as for biphenyl in hexane solution[4] (Fig. 1), namely, 248 mμ. A characteristic curve with a single maximum is the result of the influence of the non-conjugated aromatic and heterocyclic contributors in 1-(4-xenyl)-guanazole.

Figure 4 shows the spectra for 1-(2-naphthyl)-guanazole in the three customary solvents. The pattern of these data obtained in acidic, basic and neutral solutions reflects the individual contributions of the aromatic and heterocyclic moieties in-

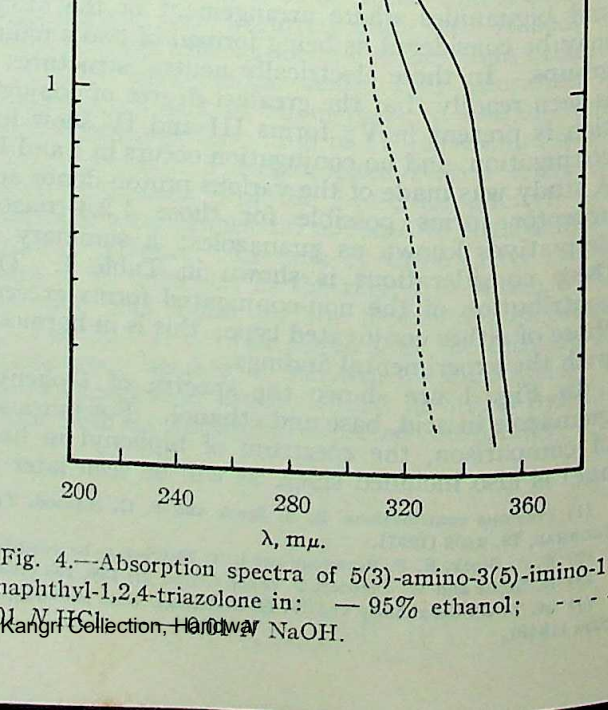

Fig. 4.—Absorption spectra of 5(3)-amino-3(5)-imino-1-β-naphthyl-1,2,4-triazolone in: — 95% ethanol; - - - - 0.01 *N* HCl; — — 0.01 *N* NaOH.

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volved. The maxima contributed by the 1,2,4-triazole nucleus appear again in the 260 mμ region for the three solvents, while the naphthalenic substituent shows its strong and characteristic absorption in the 220 mμ region (for a comparison with the spectra of 2-naphthol and 2-naphthylamine, *cf.* refs. 5 and 6). In the case of the absorption spectrum obtained when ethanol was the solvent, there is to be seen the expected bathochromic shift with relation to the other two solvents. It is also to be noted that the characteristic triplet was maintained in the spectrum of 1-(2-naphthyl)-guanazole in alcohol but was nearly obliterated in acidic and alkaline solvents, only a memory of it remaining in the respective inflection points.

The influence of a para-halogen substituent upon the absorption spectrum of 1-phenylguanazole is indicated in Fig. 5. The expected batho- and hyperchromic shifts upon transition from the fluoro to the iodo grouping is indeed realized. It should be noted, however, that there is little change in character from 1-(4-chlorophenyl)-guanazole to the related bromo compound. The development of an additional maximum in the short wave region first appears in 1-(4-bromophenyl)-guanazole and is again evidenced with a concomitant bathochromic shift in the case of the spectrum of the iodo compound. These effects appear to be caused by the halogen substitution regardless of whether it is attached directly to an heterocyclic system (as in the case of certain quinolines),[7] or linked to the heterocyclic portion of a molecule *via* a phenyl group.

Table II gives the characteristics of the absorption spectra of five additional 1-arylguanazoles in ethanol, sodium hydroxide and hydrochloric acid solutions. A comparison of the salient features of the spectra of 1-(4-methylphenyl)-guanazole with the related types having 1-(3-chlorophenyl) and 1-(3-chloro-4-methylphenyl) groups shows that substitution of position 3 by a chloro group has less influence upon the spectrum of 1-(3-chloro-4-methylphenyl)-guanazole than does the 4-methyl group. This is presumably due to the interaction of position and inductive effects.[8] Also given in Table II are characteristic portions of the spectra of 1-[4-(4′-methylphenoxy)-phenyl]-guanazole and 1-[4-(4′-methylphenylthio)-phenyl]-guanazole, which may likewise be compared with 1-(4-methylphenyl)-guanazole. The interposition of the phenoxy group between the methyl and phenyl radicals results only in an intensification but not a shift in the respective spectra of 1-[4-(4′-methylphenoxy)-phenyl]-guanazole from those of the related 1-(4-methylphenyl) compound. However, the replacement of the oxygen by the heavier sulfur atom in 1-[4-(4′-methylphenylthio)-phenyl]-guanazole not only leads to further intensification but also to a bathochromic shift of *ca.* 21–25 mμ. This is to be expected, as the sulfur atom has a

(5) G. W. Ewing and E. A. Steck, THIS JOURNAL, **68**, 2164 (1946).
(6) E. A. Steck and G. W. Ewing, *ibid.*, **70**, 3397 (1948).
(7) E. A. Steck, G. W. Ewing and F. C. Nachod, *ibid.*, **70**, 3410 (1948).
(8) A. E. Remick, "Electronic Interpretations of Organic Chemistry," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 52, *et seq.*

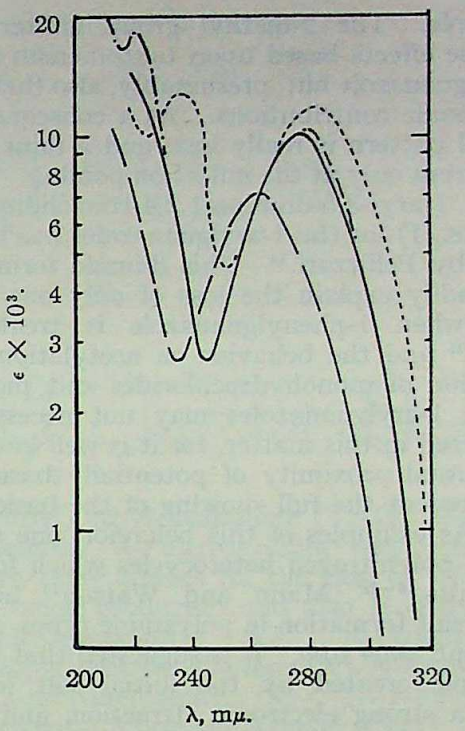

Fig. 5.—Absorption spectra in 95% ethanol of: —, 5(3)-amino-3(5)-imino-1-*p*-chlorophenyl-1,2,4-triazolone; — —, 5(3)-amino-3(5)-imino-1-*p*-fluorophenyl-1,2,4-triazolone; —·—, 5(3)-amino-3(5)-imino-1-*p*-bromophenyl-1,2,4-triazolone; - - - -, 5(3)-amino-3(5)-imino-1-*p*-iodophenyl-1,2,4-triazolone.

higher inherent resonance energy than the oxygen atom. McMurry[9] has reported data relating to this matter, and it has been further substantiated by several authors (*inter alia*, refs. 10–13).

TABLE I

CONTRIBUTORY EFFECTS OF IONIC CONFIGURATIONS IN 1-ARYLGUANAZOLE TYPES

Type of conjugation	Proton acceptor forms	Proton donor forms
Endocyclic	6	2
Endo-exo cyclic	6	3
Non-conjugated	11	7

TABLE II

SPECTRAL CHARACTERISTICS OF SOME 1-ARYLGUANAZOLES

	Maxima[a]; λ in mμ, ε × 10⁻³					
	Ethanol		0.01 *N* HCl		0.01 *N* NaOH	
1-Arylguanazoles	λ	ε	λ	ε	λ	ε
1-(3-Chlorophenyl)	272	7.7	256	5.5	266	6.2
	(246	2.7)	(240	3.8)	(240	3.2)
1-(4-Methylphenyl)	267	9.1	248	7.8	256	8.0
	(239	3.4)	(256	6.0)	(232	4.4)
1-(3-Chloro-4-methylphenyl)	268	9.4	251	6.9	259	7.8
	(242	3.2)	(239	5.0)	(236	4.0)
1-[4-(4′-Methylphenoxy)-phenyl]	267	12.8[b]	248	12.2[b]	256	11.1[b]
	(245	8.5)	(240	12.0)	(243	10.2)
1-[4-(4′-Methylphenylthio)-phenyl]	288	16.1[b]	273	14.3[b]	280	14.8[b]
	(240	7.7)	(239	7.7)	(238	8.1)

[a] Values for minima are given in parentheses. [b] Flat maximum.

Table III shows a comparison of the spectra of 1-phenylguanazole with that of 2-methyl-1-phenyl-

(9) H. L. McMurry, *J. Chem. Phys.*, **9**, 241 (1941).
(10) R. N. Jones, THIS JOURNAL, **67**, 2127 (1945).
(11) R. O. Clinton and C. M. Suter, *ibid.*, **70**, 491 (1948).
(12) E. A. Fehnel and M. Carmack, *ibid.*, **71**, 84, 2889 (1949).
(13) R. B. Hannan, J. H. Lieblich and A. G. Renfrew, *ibid.*, **71**, 2732 (1949).

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guanazole. The 2-methyl group obliterates not only the effects based upon tautomerism in the 1-phenylguanazole but, presumably, also that of some of the ionic contributions. As a consequence, the original pattern is really lost, and a faint memory is apparent only at the inflection points.

The 1-aryl-3,5-diimino-1,2,4-triazolidine structure (*i.e.*, I) for the 1-arylguanazoles has been preferred by Pellizzari.[14] This diimino formula does not readily explain the loss of only one nitrogen atom when 1-phenylguanazole is treated with caustic[15] and the behavior on acetylation.[15] The formation of monohydrochlorides and picrates[14,15] by the 1-arylguanazoles may not necessarily be considered in this matter, for it is well known that the mutual proximity of potentially basic groups may prevent the full showing of the basic properties. As examples of this behavior, one may cite certain polynitrogen heterocycles which form only monosalts.[16–18] Mann and Watson[19] have discussed salt formation in polyamine types, and they comment, *inter alia*, "it is suggested that the positive pole created by the initial salt formation exerts a strong electronic attraction, and this attraction, relayed by the inductive or mesomeric effect, may virtually immobilize the lone pair of electrons on a neighboring nitrogen atom and so deactivate this atom." Evidence here presented renders it desirable that the 1-substituted guanazoles should be considered to have the amino-imino structures indicated as III or IV rather than as diimino compounds as I. It does not appear to be possible to exclude the possibility of structure V, use of which has been made in the formulation of the products obtained from 1-phenylguanazole and isothiocyanates.[20]

(14) G. Pellizzari, *Gazz. chim. ital.*, **21**, II, 14 (1891); **24**, I, 481 (1894).
(15) G. Pellizzari and C. Roncagliolo, *ibid.*, **31**, I, 477 (1901).
(16) C. Stoehr, *J. prakt. Chem.*, [2] **51**, 456, 462 (1895).
(17) O. Hinsberg, *Ann.*, **237**, 335 (1887); **292**, 245 (1896).
(18) S. Gabriel and J. Colman, *Ber.*, **37**, 3651 (1904).
(19) F. G. Mann and J. Watson, *J. Org. Chem.*, **13**, 502 (1948).

TABLE III
SPECTRAL CHARACTERISTICS OF SOME GUANAZOLE DERIVATIVES

Guanazole derivatives	Maxima[a]; λ in mμ, ε × 10³ — Ethanol λ	ε	0.01 *N* HCl λ	ε	0.01 *N* NaOH λ	ε
1-Phenyl	266	10.6	250	8.4	254	8.9
	(238	4.0)	(237	6.6)	(232	5.1)
2-Methyl-1-phenyl	216	30.0	224	19.7	220	22.1[b]
	245	7.0[b]	(218	18.1)	260	6.1[b]

[a] Values for minima given in parentheses. [b] Inflection point.

Experimental

1-Arylguanazoles.—All guanazoles were prepared as described in another publication.[2]

Absorption Spectra.—The spectrophotometric studies were all carried out with a Beckman quartz spectrophotometer, model DU, serial no. D-377. The method and solvents used have been described in other contributions from these laboratories.[5,6]

Acknowledgments.—To Dr. E. J. Lawson we owe much for his helpful counsel and patience in discussions concerning the potential ionic configurations in 1-arylguanazoles. A considerable portion of the spectrophotometric studies have been due to the efforts of Mrs. M. Becker and Mr. M. Priznar.

(20) E. Fromm and R. Kapeller-Adler, *Ann.*, **467**, 248, 267 (1928).

RENSSELAER, N. Y.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some 9-Amino-3-nitroacridine Derivatives

BY EDGAR A. STECK, JOHANNES S. BUCK[1] AND LYNN T. FLETCHER

RECEIVED MARCH 9, 1957

A series of 9-amino-3-nitroacridine types bearing hydroxylated side-chains was prepared for investigation as potential chemotherapeutic agents. In most cases, the 6,7-positions of the acridine nucleus were substituted, as by dimethoxy, methylenedioxy and ethylenedioxy groups; two derivatives of 9-amino-7-butoxy-3-nitroacridine also were made.

It appears that the investigation of 9-amino-3-nitroacridine derivatives has been largely neglected because little antimalarial activity has been found in this type[2]; the most interesting property in the group lies in their activity against microörganisms, which is even exhibited by 9-amino-3-nitroacridine itself.[3–6a] 9-(3-Diethylamino-2-hydroxypropylamino)-6,7-dimethoxy-3-nitroacridine (I), also known as Nitroakridine 3582 (Hoeschst) and 3043B for Entozon (Entozon is a mixture of I with 6,9-diamino-2-ethoxyacridine, Rivanol, and urea), and its salts have been the most carefully studied of the 9-amino-3-nitroacridines.[1,6–11] It has been claimed that this compound, and certain salts and combinations containing it, possess activity against

(1) Deceased.
(2) H. Mauss, *Medizin und Chemie*, **IV**, 60 (1942).
(3) A. Albert, S. D. Rubbo, R. J. Goldacre, M. E. Davey and J. D. Stone, *Brit. J. Exptl. Pathol.*, **26**, 160 (1945).
(4) A. Albert and R. J. Goldacre, *J. Chem. Soc.*, 706 (1956).
(5) J. E. Smadel, J. C. Snyder, E. B. Jackson, P. J. Fox and H. L. Hamilton, *J. Immunol.*, **57**, 155 (1947).
(6) (a) M. D. Eaton, A. van Allen and A. Wiener, *Proc. Soc. Exptl. Biol. Med.*, **66**, 141 (1947); (b) M. D. Eaton, F. S. Cheever and C. G. Levenson, *J. Immunol.*, **66**, 464 (1951).
(7) C. S. Miller and C. A. Wagner, *J. Org. Chem.*, **13**, 891 (1948).
(8) British Intelligence Objectives Subcommittee (BIOS), Final Report 766, Items 22 and 24, London, England, 1946. Report by T. Dewing, W. J. C. Dyke, C. C. Green, Hindley, Hoblyn, G. E. H. Skrimshire and Wilkinson, p 11.
(9) M. Bockmühl and A. Pehrle. U. S. Patent 2,040,070; German Patent 608,668.
(10) P. E. C. Goissedet and R. L. Depois, U. S. Patent 2,092,114.
(11) K. Streitwolf and H. Oesterlin, German Patents, 613,349; 618,567.

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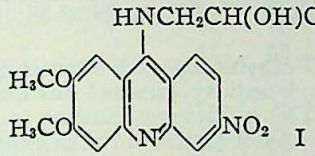
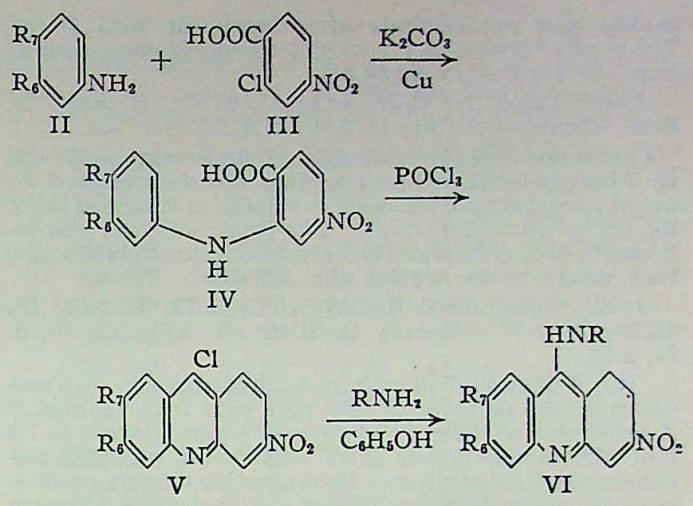
bacteria,[9–12] rickettsia,[5,13–15] viruses,[6,16–20] trichomonads[21] and babesiidae.[9] While certain antibiotics have ranges of activity which include those mentioned, this investigation was begun before such were well studied and was particularly concerned with those bearing an hydroxylated basic chain attached to position 9 of a 3-nitroacridine nucleus with at least one alkoxy group in position 6 or 7 or with a methylenedioxy- or ethylenedioxy group bridging positions 6 and 7.



I

The synthesis of the 9-chloro-3-nitroacridines required for reaction with the various amines was accomplished by the Ullmann reaction[22] as modified by Leśniański.[23,24] In this procedure, the intermediate N-arylanthranilic acids (*e.g.*, IV) prepared from an aniline (II) and a 2-halobenzoic acid (*e.g.*, III) undergo cyclization to the 9-chloroacridine (*e.g.*, V) by the action of phosphorus oxychloride. In the reactions of 2-chloro-4-nitrobenzoic acid with 3,4-dimethoxyaniline, 3,4-methylenedioxyaniline and 3,4-ethylenedioxyaniline, methanol or ethanol were satisfactory solvents, but with 4-butoxyaniline it was necessary to use pentanol (*cf.* refs. 25–27). The purified N-arylanthranilic acids were all cyclized without difficulty by use of phosphorus oxychloride in toluene.

The reaction of the 9-chloro-3-nitroacridines (V) with aliphatic amino compounds bearing hydroxyl groups, in phenol as a solvent (*cf.* refs. 27, 28), was exothermic but readily controlled; this produced the type VI of which I is an example. 7-Butoxy-9-chloro-3-nitroacridine, 9-chloro-6,7-methylenedioxy-3-nitroacridine and 9-chloro-6,7-ethylenedioxy-3-nitroacridine were caused to react with 3-diethylamino-2-hydroxypropylamine (VII) and N-(2-



hydroxyethyl) ethylenediamine (VIII). 9-Chloro-6,7-dimethoxy-3-nitroacridine was caused to react with these amines (in the case of VII, compound I being produced) and also N-(2-hydroxypropyl)-ethylenediamine (IX), N-(2-hydroxy-2-methylpropyl)-ethylenediamine (X), N-(2-hydroxyethyl)-1,3-propanediamine (XI), N-(2-hydroxy-2-methylpropyl)-1,3-propanediamine (XII) and N-(2-hydroxyethyl)-1,7-heptanediamine (XIII). The compounds produced by use of the amine VII were, ordinarily, the most difficult to purify. Since the hydrochlorides of the 9-amino-3-nitroacridines (Table I) lost hydrogen chloride readily upon drying at elevated temperatures, it was advisable to dry the products at room temperature. Several of the compounds thus obtained were hydrated. It was of interest that, while several of the intermediates did not give concordant values for nitrogen by the Dumas method,[29] most of the final products offered little difficulty.

The testing of the compounds herein described will be reported subsequently by other members of this Institute.

Experimental[30]

A. 9-Chloro-3-nitroacridines. I. 7-Butoxy-9-chloro-3-nitroacridine.—4-Butoxynitrobenzene was obtained in 68.5% yield by the action of butyl bromide upon potassium 4-nitrophenolate in butanol.[31] Use of butyl iodide gave yields of 54–58%.[32] The reduction of the nitro compound to 4-butoxyaniline in methanol with Raney nickel catalyst (25°, 80 atm.) gave a conversion of 92.5%; b.p. 95–98° (1 mm.).

Thirty-three grams (0.2 mole) of 4-butoxyaniline, 35.3 g. (0.26 mole) of powdered, anhydrous potassium carbonate, 36.3 g. (0.18 mole) of 2-chloro-4-nitrobenzoic acid[33] and 0.5 g. of copper powder in 150 cc. of pentanol were stirred and refluxed for 5 hr. The excess amine and solvent were steam distilled, the residues diluted to 500 cc. with water, boiled with Darco G-60 and filtered. Acidification of the cooled filtrates gave 56.0 g. (85% yield) of crude greenish product, m.p. 170–174°. To obtain pure N-(4′-butoxyphenyl)-4-nitroanthranilic acid from the crude, it was necessary to crystallize from 85% ethanol, dissolve the greenish solid in

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(13) Office of Publication Board (O.P.B.), Dept. of Commerce, Washington, D. C., 1945. (a) V. Conquest, E. C. Kleiderer, J. B. Rice and J. H. Williams, Report 4, p. 15. (b) H. M. Horack, P. J. Leaper, J. E. Smadel, L. M. White and E. H. Volwiler, Report 241, p. 5. (c) E. C. Kleiderer, J. B. Rice, V. Conquest and J. H. Williams, Report 981, p. 19.
(14) G. Holler, *Med. Klinik*, **40**, 374(1944).
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(21) B. B. Morgan, L. Lombard and A. E. Pierce, *Proc. Soc. Exptl. Biol. Med.*, **70**, 243 (1946).
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(25) F. Mietzsch and H. Mauss, German Patents 553,072, 565,411 (1932); U. S. Patent 2,113,357 (1938).
(26) O. J. Magidson and A. M. Grigorowski, *Ber.*, **66B**, 866 (1933).
(27) O. J. Magidson and A. M. Grigorowski, *ibid.*, **69B**, 396 (1936).
(28) H. Jensch and O. Eisleb, U. S. Patent 1,962,277.

(29) Satisfactory nitro nitrogen values were obtained in such cases by use of the method described by S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York 16, N. Y., 1949. p. 82.
(30) All melting points recorded were corrected, whereas boiling points were not.
(31) J. G. McNally and J. B. Dickey, British Patent 585,940.
(32) G. O. Gutekunst and H. LeB. Gray, THIS JOURNAL, **44**, 1742 (1922).
(33) All of this acid was crystallized from water (charcoal) before use and melted no lower than 137–138° (E. Wenis and T. S. Gardner *J. Am. Pharm. Assn., Sci. Ed.*, **38**, 9 (1949) reported m.p. 139–140°).

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caustic and re-precipitate after treatment with Darco. The product crystallized from 80% ethanol as orange blades, m.p. 197.3–197.8°, yield 64.5%.

Anal. Calcd. for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.81; H, 5.60; N, 8.27.

Cyclization of N-(4′-butoxyphenyl)-4-nitroanthranilic acid to 7-butoxy-9-chloro-3-nitroacridine was accomplished by use of phosphorus oxychloride in toluene as described below for the 6,7-dimethoxy type. The pure compound was obtained in 69% yield after three crystallizations from heptane; long, golden-brown needles, m.p. 159–160°.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.51; Cl, 10.72; N, 8.47. Found: C, 61.60; H, 4.51; Cl, 10.79; N, 8.52.

II. **9-Chloro-6,7-dimethoxy-3-nitroacridine.**[34]—4-Nitroveratrole was prepared in 75% pure yield from veratrole.[35] A suspension of 450 g. (2.46 mole) of 4-nitroveratrole in 1.4 l. of ethanol was reduced at 25° and 50 atm. with 10% palladium–charcoal catalyst. The reduction mixture containing 4-aminoveratrole was filtered and kept under nitrogen. A mixture of 337 g. (2.44 moles) of anhydrous potassium carbonate, 492 g. (2.66 moles) of 2-chloro-4-nitrobenzoic acid and 0.5 l. of water at 60° was prepared, then the solution of 4-aminoveratrole, 25 g. of copper powder and 25 g. of Filter-cel were added. The mixture was stirred vigorously and the alcohol removed until the still temperature reached 92°, then refluxed for 5 hr. The solids which were collected were extracted with 2 l. of boiling water after mixing with 25 g. of Darco G-60 and 50 g. of Filter-cel; the filter-cake was re-extracted with the boiling liquors, then chilled. The potassium salt of N-(3,4-dimethoxyphenyl)-4-nitroanthranilic acid was collected from the extracts (357 g.) and the liquors concentrated. A total yield of 392 g. (45%) of the salt was obtained; acid isolated from the salt melted at 221–223.5°.

A mixture of 356.3 g. (1.0 mole) of potassium N-(3,4-dimethoxyphenyl)-4-nitroanthranilate and 3.5 l. of toluene was stirred while *ca.* 0.5 l. of distillate was collected to ensure anhydrous conditions before the addition of 220 cc. (368 g., 2.4 moles) of phosphorus oxychloride during 15 minutes. The well-stirred mixture was refluxed for 3 hr. and then 0.5 l. of distillate removed *in vacuo*. Cooling of the residue gave the phosphorus salt of 9-chloro-6,7-dimethoxy-3-nitroacridine, which was collected, then washed with toluene and ether. The complex was decomposed by gradually adding it to a well-stirred mixture of 310 cc. of 35% sodium hydroxide solution, 1300 cc. of water and 1300 g. of ice and stirring for 2 or 3 hr. at 0°. A brownish product resulted; this was washed free of alkali, air-dried and washed with benzene. The 9-chloro-6,7-dimethoxy-3-nitroacridine was boiled with 4 l. of ethylene dichloride for 2 hr., cooled and the light yellow product dried. A yield of 230 g. (72%) resulted, m.p. 246–248° dec.

III. **9-Chloro-6,7-methylenedioxy-3-nitroacridine.**—A portion of the required 3,4-methylenedioxyaniline was obtained in 88% yield, b.p. 85–86° (1 mm.) (m.p. 44.5–45.5°), from the reduction of 3,4-methylenedioxynitrobenzene in methanol with Adams catalyst at 3 atm. hydrogen pressure. The nitro compound was a by-product from the preparation of 6-nitropiperonal[36] or made from 1,2-methylenedioxybenzene[37] by nitration.[38] Some had been prepared earlier by a Hofmann degradation of piperonylamide.[39]

The reaction of 3,4-methylenedioxyaniline, 2-chloro-4-nitrobenzoic acid and potassium carbonate in the presence of copper powder and Filter-cel was carried out after the method described for 4-aminoveratrole. A 91% yield of crude N-(3,4-methylenedioxyphenyl)-4-nitroanthranilic acid (m.p. *ca.* 210°) was collected; two crystallizations from 60% methanol (charcoal) gave a 60% yield of pure compound. The beautiful garnet plates melted at 246–247°.

Anal. Calcd. for $C_{14}H_{10}N_2O_6$: C, 55.63; H, 3.34; N, 9.27. Found: C, 55.52; H, 3.36; N, 9.40.

Conversion of the above acid to 9-chloro-6,7-methylenedioxy-3-nitroacridine followed the same pattern as the related types. The crude material was crystallized from chlorobenzene to give the desired compound as fluffy yellow needles, m.p. >300°, in a purified yield of 63%.

Anal. Calcd. for $C_{14}H_7ClN_2O_4$: C, 55.55; H, 2.33; Cl, 11.71; N,[29] 4.63. Found: C, 55.51; H, 2.33; Cl, 11.82; N,[29] 4.57.

IV. **9-Chloro-6,7-ethylenedioxy-3-nitroacridine.**—1,4-Benzodioxane (1,2-ethylenedioxybenzene) was made by the method of Ghosh.[40] The nitration according to the directions of Vorländer[41] was not particularly satisfactory, but the modification of Heertjes, *et al.*,[42] readily gave 80% yields of pure 4-nitro-1,2-ethylenedioxybenzene even with large batches.

The reduction of pure 4-nitro-1,2-ethylenedioxybenzene with Adams catalyst at 40° and 3 atm. was run in methanol. The filtered reduction liquors were employed in the same manner as described above for the 3,4-dimethoxyaniline; N-(3,4-ethylenedioxyphenyl)-4-nitroanthranilic acid was isolated in 69% yield (after one crystallization from dilute ethanol with use of Darco G-60; m.p. *ca.* 235°). Further crystallization gave the pure compound in the form of golden needles, m.p. 249–250.5°.

Anal. Calcd. for $C_{15}H_{12}N_2O_6$: C, 56.96; H, 3.83; N,[29] 4.43. Found: C, 57.23; H, 3.53; N,[29] 4.32.

Interaction of the anthranilic acid type with phosphorus oxychloride in toluene was accomplished in the usual manner. The 9-chloro-6,7-ethylenedioxy-3-nitroacridine isolated after one crystallization from xylene melted *ca.* 285° (86.5% yield). Further crystallization from chlorobenzene (followed by extraction with boiling ether to remove the adhering solvent) produced the pure compound; orange microcrystals, m.p. 298.7–299.5° (76% yield from the acid).

Anal. Calcd. for $C_{15}H_9ClN_2O_4$: C, 56.88; H, 2.87; Cl, 11.19; N,[29] 4.43. Found: C, 56.96; H, 2.92; Cl, 11.23; N,[29] 4.23.

B. **Side-Chains. 3-Diethylamino-2-hydroxypropylamine (VII) and N-(2-hydroxyethyl)-ethylenediamine (VIII)** were redistilled commercial products.

N-(2-Hydroxypropyl)-ethylenediamine (IX), b.p. 88–91° (3 mm.), $n^{25}D$ 1.4744, was obtained in 48% yield from ethylenediamine and propylene oxide.[43] The by-product, N,N′-bis-(2-hydroxypropyl)-ethylenediamine, was isolated in 21.5% yield; shimmering white platelets from ethanol, m.p. 147–147.5°.

Anal. Calcd. for $C_8H_{20}N_2O_2$: C, 54.51; H, 11.44; N, 15.90. Found: C, 54.80; H, 11.41; N, 15.88.

N-(2-Hydroxy-2-methylpropyl)-ethylenediamine (X), b.p. 89–93° (2 mm.), $n^{25}D$ 1.4670, was prepared (58.5% yield) from ethylenediamine and isobutylene oxide.[43] N,N′-Bis-(2-hydroxy-2-methylpropyl)-ethylenediamine was also formed (22.5% yield); it crystallized from hexane as white blades, m.p. 69.5–70°.

Anal. Calcd. for $C_{10}H_{24}N_2O_2$: C, 58.79; H, 11.84; N, 13.72. Found: C, 58.74; H, 11.12; N, 13.60.

N-(2-Hydroxyethyl)-1,3-propanediamine (XI) resulted when 2-(2-hydroxyethyl)-propionitrile was catalytically reduced in ammoniacal ethanol[44,45]; b.p. 105–107° (1 mm.), $n^{25}D$ 1.4837.

N-(2-Hydroxy-2-methylpropyl)-1,3-propanediamine (XII) was obtained by catalytic reduction of the related propionitrile in ammoniacal ethanol[46]; b.p. 102–106° (4 mm.), $n^{25}D$ 1.4672.

(34) This procedure was devised by Dr. B. F. Tullar of the Development Laboratories of this Institute during 1945. It was partly based upon experiments of Drs. C. E. Kwartler, W. Boehme and E. A. Steck. The over-all yield obtained from veratrole and 2-chloro-4-nitrobenzoic acid was uniformly about 24%, while the procedure of Miller and Wagner[7] would produce 9-chloro-6,7-dimethoxy-3-nitroacridine in *ca.* 13% yield.

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TABLE I

9-AMINO-3-NITROACRIDINE HYDROCHLORIDES

R_6	R_7	R_9[a]	Yield, %	Appearance[b]	M.p., °C.[c]	Analyses, % Calcd. N	Calcd. Cl	Found N	Found Cl
H	O(*n*-C_4H_9)	VII	58.5	Scarlet microcrystals	182–184[d]	10.72	13.57	10.58[e]	13.30[e]
		VIII	76	Orange platelets	290–292	11.89	15.04	11.86[f]	15.00[f]
OCH_3	OCH_3	VIII	71	Scarlet needles	240–243	11.96	15.14	11.74[g,h]	15.22[g,h]
		IX	78.5	Orange microcrystals	250–251	11.84	14.98	11.99	14.80
		X	70	Orange needlets	253–257	11.29	14.29	11.19[i]	14.39[i]
		XI	68	Brick red microcrystals	228–228.5	11.00	13.92	11.00[j]	13.88[j]
		XII	73	Brick red needlets	235–235.5	11.17	14.14	11.01	14.19
		XIII	65.5	Scarlet microcrystals	238–239	10.58	13.39	10.48	13.46
$-OCH_2O-$		VII	62	Bright orange prisms	251–251.5	11.54	14.61	11.32[k,l]	14.62[k]
		VIII	72.5	Orange microcrystals	>300[m]	12.38	15.67	12.42[n]	15.38[n]
$-OCH_2CH_2O-$		VIII	50	Garnet needlets	236–238	12.25	15.51	12.24	15.45
		VII	74	Russet microcrystals	198–199	10.83	13.70	10.68[o]	13.87[o]

[a] Code as given in text. [b] Method of purification as detailed for compound I except in cases of those bearing side-chain (VII), which have been noted in the Experimental. [c] Melting with decomposition unless otherwise stated. It was advisable to immerse the sample in bath at a temperature *ca.* 20° below the m.p. and heat rapidly to obtain reproducible values. [d] No decomposition. This compound was investigated as a trypanocide by R. Schnitzer and W. Silberstein [*Z. Hyg. Infektionskrankh.*, **109**, 519 (1929)], but no constants were given. [e] Hemihydrate. *Anal.* Calcd. for $C_{24}H_{32}N_4O_4 \cdot 2HCl \cdot 0.5 H_2O$: H_2O, 1.72. Found: H_2O, 1.57. [f] Dry basis; sample contained 0.61% water. [g] Hemihydrate. *Anal.* Calcd. for $C_{19}H_{22}N_4O_5 \cdot 2HCl \cdot 0.5H_2O$: H_2O, 1.92. Found: H_2O, 2.04. [h] Anhydrous material was obtained by prolonged drying at 100° (0.5 mm.) and replacing lost HCl by action of an absolute ether solution of hydrogen chloride. The product was washed with 5:1 ether–ethanol and dried; scarlet microcrystals resulted, m.p. 260–263°. *Anal.* Calcd. for $C_{19}H_{22}N_4O_5 \cdot 2HCl$: N, 12.20; Cl. 15.44. Found: N, 12.43; Cl, 15.42. [i] Hemihydrate. *Anal.* Calcd. for $C_{21}H_{26}N_4O_5 \cdot 2HCl \cdot 0.5H_2O$: H_2O, 1.81. Found: H_2O, 1.82. [j] Dihydrate. *Anal.* Calcd. for $C_{20}H_{24}N_4O_4 \cdot 2HCl \cdot 2H_2O$: H_2O, 7.07. Found: H_2O, 6.90. [k] Dry basis; sample contained 1.23% water. [l] Dumas determination made with use of copper(II) acetate after method of D. F. Hayman and S. Adler, *Ind. Eng. Chem., Anal. Ed.*, 9, 197 (1937). [m] Chars at *ca.* 250°. [n] Hemihydrate. *Anal.* Calcd for $C_{18}H_{18}N_4O_5 \cdot 2HCl \cdot 0.5H_2O$: H_2O, 1.99. Found: H_2O, 1.89. [o] Monohydrate. *Anal.* Calcd. for $C_{22}H_{26}N_4O_5 \cdot 2HCl \cdot H_2O$: H_2O, 3.48. Found: H_2O, 3.15.

N-(2-Hydroxyethyl)-1,7-heptanediamine (XIII).—Pimelonitrile[47] was reduced in 10% ammoniacal ethanol with Raney nickel catalyst at 60 atm. and 90°. An 88% yield of 1,7-heptanediamine was collected at 52–54° (1 mm.); this compound was prepared[48] earlier by sodium–ethanol reduction of pimelonitrile.

A solution of 33.3 g. (0.26 mole) of 1,7-heptanediamine in 100 cc. 90% methanol was stirred at 0° in a flask equipped with condenser through which brine was circulated at −10°. To this there was added 12 cc. (10.6 g., 0.24 mole) of liquefied ethylene oxide contained in a jacketed dropping funnel having brine circulated through the jacket. When addition had been completed (*ca.* 0.5 hour), the reaction mixture was allowed to warm to room temperature, and reaction caused the temperature to rise to 40°. The mixture was stirred for 3 hr., then refluxed for 1 hr. before fractionation. A yield of 20.9 g. (47%) of N-(2-hydroxyethyl)-1,7-heptanediamine (XIII) was collected at 164–168° (1 mm.), $n^{25}D$ 1.4751.

Anal. Calcd. for $C_9H_{22}N_2O$: N, 16.08. Found: N, 16.10.

C. 9-Amino-3-nitroacridines.—The 9-amino-3-nitroacridine derivatives which were prepared by the reaction of the appropriate 9-chloro-3-nitroacridine and amine in phenol melt have been presented with pertinent data in Table I. Indication of the procedure employed is given in the preparation of 9-(3-diethylamino-2-hydroxypropylamino)-6,7-dimethoxy-3-nitroacridine, for this is somewhat different in certain respects from those published.[7,8]

I. 9-(3-Diethylamino-2-hydroxypropylamino)-6,7-dimethoxy-3-nitroacridine Dihydrochloride.—A melt comprised of 440 g. of phenol and 220 g. (0.69 mole) of 8-chloro-6,7-dimethoxy-3-nitroacridine was stirred under reflux at 70°. The heat was removed and 123 g. (0.84 mole) of 3-diethylamino-2-hydroxypropylamine was added at such a rate that the temperature did not exceed 95°. At the end of the addition, heating was resumed for 1 hr.; the mixture was cooled to 40° and poured into a well-stirred solution of 120 cc. of concd. hydrochloric acid in 4 l. of acetone at 20°, then stirred for an hour or two. A brick-red hydrochloride resulted and was leached well with acetone to remove phenol. The crude product was dissolved in 1 l. of water at 70–75° and charcoaled. The filtrates were at 40–45° when 350 cc. of concd. hydrochloric acid was added and thereafter cooled very slowly, then collected, slurried the product with acetone, washed with acetone and ether. This scarlet dihydrochloride was dried *in vacuo* below 50° to avoid loss of HCl; m.p. 223–225° dec. The product weighed up to 250 g. and contained some 5–9.5% moisture; the yield, on the dry basis, was 56–65%. Miller and Wagner[7] have reported a product containing 6.8% water; Hurst[19] employed a sample containing *ca.* 8% moisture.[49]

In the case of most compounds listed in Table I, the method detailed for the preparation and purification of 9-(3-diethylamino-2-hydroxypropylamino)-6,7-dimethoxy-3-nitroacridine dihydrochloride was that followed. However, in the case of the types bearing the 3-diethylamino-2-hydroxypropylamine chain (VII), variations were desirable. In most cases the phenol melt was quenched in acetone–40% ethanolic hydrogen chloride mixture, and the crude products crystallized from ethanol–ether. A pure sample of 9-(3-diethylamino-2-hydroxypropylamino)-6,7-methylenedioxy-3-nitroacridine dihydrochloride was most readily obtained by merely extracting the crude with boiling ethanol and drying the residue. The products were, ordinarily, dried *in vacuo* over phosphoric anhydride, sodium hydroxide pellets and wax. Use of high temperatures for drying led to considerable loss of hydrogen chloride, which was sometimes difficult to replace. All determinations of water content were done by the Karl Fischer method.

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(49) The authors wish to express their appreciation to Dr. P. Gaubert and Dr. E. W. Hurst of Imperial Chemical Industries, Ltd., for their friendly communications concerning these and related matters.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, HOKKAIDO UNIVERSITY]

The Ultraviolet Absorption Spectra of Stereoisomeric 1,2,3,4,9,10,4a,9a-Octahydroacridines and Related Compounds[1]

BY TADASHI MASAMUNE

RECEIVED JANUARY 21, 1957

The near ultraviolet absorption spectra of *cis*- and *trans*-1,2,3,4,9,10,4a,9a-octahydroacridines and related stereoisomeric bases were measured in isoöctane, ether and alcohol. The absorption maximum of each *cis* isomer was situated at a longer wave length than that of the corresponding *trans* isomer in isoöctane and in ether; this shift was especially remarkable in alcohol. The solvent effect of alcohol on simple derivatives of aniline was examined and was found to be mainly attributable to the formation of hydrogen bonding between amine and alcohol, which depended upon the strength of the basicity and upon their steric configuration. This explanation was applied to the absorption spectra of four pairs of stereoisomeric tricyclic bases with success, it being emphasized that the formation of hydrogen bonding may be strongly influenced by the geometry of the bases. The ultraviolet absorption spectra of these bases were furthermore examined in 0.1 *N* hydrochloric acid and a characteristic peak was found to exist near 320 mμ.

Introduction

During the course of an investigation of the dehydrogenation of hydrogenated acridines,[2] it became desirable to study their ultraviolet absorption spectra in order to identify small amounts of dehydrogenated products. It was found that the absorption maximum of *cis*-1,2,3,4,9,10,4a,9a-octahydroacridine was situated at a longer wave length than that of the corresponding *trans*-base in alcohol. In the present work, the absorption spectra of those compounds were measured in isoöctane or in ether. The difference of absorption spectra of the stereoisomers in alcohol is believed principally due to the difference in solvation.

There are available many reports on the relation between geometrical form and absorption spectra of organic compounds.[3] However, no attention has been paid to the problem of whether or not the solvent effect on absorption spectra is affected by a difference in the molecular configuration of the solute. In the present article it will be shown that such a solvent effect does exist. For example, *trans*-tetrahydro-2,3-trimethylenequinoline exhibits a distinct blue shift in alcohol,[4] while the corresponding *cis* isomer shows a red shift in the same medium. A similar difference in solvation was observed in several other cases such as isomers of octahydroacridine and related compounds.

Experiments and Results

Materials.—The following stereoisomeric tricyclic bases were prepared by procedures described in the literature. Solid compounds were recrystallized to constant melting point from the solvents indicated and liquids were freshly redistilled before use: *cis*-hexahydrocarbazole,[5] m.p. 98–99° (alcohol); *trans*-hexahydrocarbazole,[5] m.p. 128–130° (alcohol); *cis*-octahydroacridine,[6] m.p. 71–72° (benzine); *trans*-octahydroacridine, m.p. 80–81° (petroleum ether); *cis*-tetrahydro-2,3-trimethylenequinoline,[7] oil, benzoyl derivative, m.p. 159–160° (acetone); *trans*-tetrahydro-2,3-trimethylenequinoline,[8] m.p. 66–68° (petroleum ether); *cis*-tetrahydro-2,3-pentamethylenequinoline,[8] oil, benzoyl derivative, m.p. 145–146° (alcohol); *trans*-tetrahydro-2,3-pentamethylenequinoline,[8] m.p. 59–60° (petroleum ether).

Ultraviolet absorption measurements were made using a Beckman quartz spectrophotometer, model DU; the following four solvents were used: ethanol, ether, isoöctane (dried over phosphorus pentoxide) and 0.1 *N* hydrochloric acid. The spectrum was examined at 0.5 mμ intervals near maximum and at 3 mμ intervals in another region of 215 to 350 mμ.

Basicity measurements were carried out at 15° according to the method of Thomson[9]: that is, because of the low solubility of the bases in water, solutions in 50% aqueous ethyl alcohol were used, and in view of uncertainty as to the value of K_w in those alcoholic solutions, the result was expressed as pK_a for the conjugated acids (calculated by means of the simple Henderson equation $pK_a = pH + \log(\text{salt})/(\text{base})$. Solutions were prepared as follows: in "50% alcohol" by dissolving *a* g. of the base in rather less than 10 cc. of ethanol, adding *b* cc. of 0.113 *N* aqueous

a	pH	*b*	pK_a
Tetrahydroquinoline			
0.0276	4.60	1.05	4.72
.0272	4.60	1.05	4.73
.0311	4.70	1.05	4.71
.0385	4.80	1.05	4.65
		Mean	4.70
trans-Tetrahydro-2,3-trimethylenequinoline			
0.0285	4.17	1.00	4.50
.0400	4.45	1.00	4.43
		Mean	4.47
trans-Octahydroacridine			
0.0278	3.95	1.00	4.45
.0339	4.16	1.00	4.38
.0458	4.40	1.00	4.33
		Mean	4.39
trans-Tetrahydro-2,3-pentamethylenequinoline			
0.0299	4.06	1.05	4.64
.0403	4.46	1.05	4.62
		Mean	4.63
trans-Hexahydrocarbazole			
0.0325	4.18	1.25	4.66
.0290	4.39	1.00	4.70
.0351	4.50	1.00	4.60
		Mean	4.66
Dihydroindole			
0.0204	4.58	1.05	4.92
.0231	4.68	1.05	4.88
		Mean	4.90
cis-Tetrahydro-2,3-trimethylenequinoline			
0.0344	4.32	1.00	4.44
.0288	4.06	1.00	4.39
.0421	4.58	1.00	4.52
		Mean	4.45
cis-Octahydroacridine			
0.0528	4.19	1.00	4.02
.0352	3.94	1.00	4.12
.0318	3.86	1.00	4.09
.0317	3.83	1.00	4.06
		Mean	4.08
cis-Tetrahydro-2,3-pentamethylenequinoline			
0.0323	4.11	1.05	4.55
.0401	4.27	1.05	4.47
		Mean	4.51
cis-Hexahydrocarbazole			
0.0380	4.63	1.25	4.97
.0290	4.21	1.25	4.93
.0318	4.63	1.00	4.83
.0264	4.51	1.00	4.96
.0298	4.59	1.05	4.93
		Mean	4.92

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TABLE I

NEAR ULTRAVIOLET ABSORPTION SPECTRA OF CYCLIC BASES IN VARIOUS SOLVENTS

Compound	Absorption maximum (mμ) and intensity (ε)[a] Isoöctane	Ether	Alcohol	$\Delta\lambda_{eth}$	$\Delta\lambda_{alc}$	$\Delta\lambda_{sol}$	$\Delta\lambda_{iso}$
Dihydroindole	298 (2500)	302 (2610)	290.5 (2300)	4.0	−7.5	−11.5	
Tetrahydroquinoline	301 (2350)	303.5 (2650)	300 (2120)	2.5	−1.0	−3.5	
trans-Tetrahydro-2,3-trimethylenequinoline	298.5 (2320)	300 (2420)	295.5 (1980)	1.5	−3.0	−4.5	−8.5
cis-Tetrahydro-2,3-trimethylenequinoline	300 (2800)	303.5 (2380)	304 (1750)	3.5	4.0	−0.5	
trans-Octahydroacridine	300.5 (2050)	302.5 (2910)	300.5 (2100)	2.0	0.0	−2.0	−3.5
cis-Octahydroacridine	302 (2650)	304.5 (3580)	304 (2300)	2.5	2.0	−0.5	
trans-Tetrahydro-2,3-pentamethylenequinoline	301.5 (2460)	303 (2460)	300.5 (2170)	1.5	−1.0	−2.5	−3.5
cis-Tetrahydro-2,3-pentamethylenequinoline	303 (4540)	304 (2390)	304 (2690)	1.0	1.0	0.0	
trans-Hexahydrocarbazole	292.5 (2700)	293 (2920)	286.5 (1930)	0.5	−6.0	−6.5	−7.5
cis-Hexahydrocarbazole	295.5 (2970)	297.5 (3000)	293 (2200)	2.0	−2.5	−4.5	

[a] The figures in parentheses refer to molecular extinction coefficients.

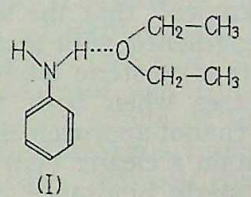
hydrochloric acid, then adding (12.5 − *a*) cc. of distilled water and making the volume up to 25 cc. with ethanol in a standard flask.

Results.—The values of λ_{max}, $\Delta\lambda_{ether}$ or $\Delta\lambda_{alc}$ (displacement of the λ_{max} in alcohol or ether relative to that in isoöctane) and $\Delta\lambda_{iso}$ (difference of λ_{max} between *cis* and *trans* isomers) of the near ultraviolet absorption spectra (Doub's "secondary" band)[10] of all the compounds included in this study are shown in Table I with data of their ϵ_{max}. The λ_{max} was estimated with reference to the intensity of absorption maximum, as λ_{max} was most easily measured and most often recorded to evaluate the solvent effect, which will be discussed in the following section. On the other hand, the values of λ_{max} and ϵ_{max} of absorption spectra of those bases in 0.1 *N* hydrochloric acid are given in Table III with basicity.

Discussion

The experimental results given in Table I may be summarized under the following two points. (1) The near ultraviolet absorption band of each *cis* compound of four pairs of stereoisomeric tricyclic bases was situated at a longer wave length than that of the corresponding *trans* compound. This red shift of the absorption maximum of each *cis* compound was observed in isoöctane and in ether; the effect was especially remarkable in alcohol. (2) In either *cis* or *trans* compounds, the absorption curve of each base in ether was found to be displaced always toward the visible side in isoöctane ($\Delta\lambda_{ether}$ positive). On the other hand, anomalous displacements were found in alcohol. In the case of *trans* isomers the absorption maximum shifted toward the shorter wave length ($\Delta\lambda_{alc}$ negative) or remained unchanged, while in the *cis* isomers the shift occurred toward the longer wave length side ($\Delta\lambda_{alc}$ positive), the only exception being *cis* hexahydrocarbazole. It is to be noted, however, that the blue shift of the *cis* compound of the latter was much less pronounced than that of the *trans* isomer.

The Solvent Effect on Near Ultraviolet Absorption Spectra.—Several papers,[11-13] have recently appeared in which solvent effects on organic spectra are correlated with various properties of the solute and the solvent. For example, Coggeshall and Lang[14] in dealing with the spectra of phenols have discussed effects due to the dipole–dipole interaction, to hydrogen bonding and to the polarization effect between solvent and solute. From among the above three effects Nagakura and Baba[15] directed special attention to the hydrogen bonding in explaining the shift of near ultraviolet absorption spectra of aniline in solutions. They observed that the solvent effect of ether upon the spectra was unusually large when compared with that in hexane. Their explanation of this abnormal behavior is as follows: On the formation of hydrogen bonds[16] shown in diagram (I), semi-ionic structures with the positive charge at the N atom come to have extra energies of stabilization.[17,18] Consequently the degree of electron migration from the N atom to the benzene ring increases, producing an abnormal red shift.



(I)

The red shifts of absorption ($\Delta\lambda_{ether}$ positive) in ether of all compounds examined in the present work (see Tables I and II) are found to be essentially the same as the results of Nagakura and Baba. This suggests that the observed shifts[19] for these compounds are due to the hydrogen bonding between the H atom of the imino group of the solute and the O atom of the solvent.

The spectroscopic behavior in alcohol is different from that in ether. In contrast to ethereal solutions, two types of hydrogen bonds are believed to be formed between amine and alcohol. One is formed between the H atom of the imino group and the O atom of alcohol, while the other is

(10) L. Doub and J. M. Vandenbelt, THIS JOURNAL, **69**, 2714 (1947).

(11) N. S. Bayliss and E. G. McRae, *J. Phys. Chem.*, **58**, 1002, 1006 (1954).

(12) L. G. S. Brooker, G. H. Keyes, R. G. Sprague, R. H. Van Dyke, E. Van Lare, G. Van Zandt and F. L. White, THIS JOURNAL, **73**, 5332 (1951); L. G. S. Brooker, G. H. Keyes and D. W. Heseltine, *ibid.*, **73**, 5350 (1951).

(13) H. E. Ungnade, *ibid.*, **75**, 432 (1953).

(14) N. D. Coggeshall and E. M. Lang, *ibid.*, **70**, 3283 (1948).

(15) S. Nagakura and H. Baba, *ibid.*, **74**, 5693 (1952).

(16) M. Tsuboi, *J. Chem. Soc. Japan*, **72**, 146 (1951); H. Tsubomura, *ibid.*, **73**, 841, 926 (1952).

(17) F. A. Matsen, THIS JOURNAL, **72**, 5243 (1950); C. Curran and G. K. Estok, *ibid.*, **72**, 4575 (1950). See also H. Baba, *Monogr. Res. Inst. Appl. Elec. Hokkaido Univ.*, **4**, 61 (1954).

(18) B. M. Wepster, *Rec. trav. chim.*, **72**, 661 (1953).

(19) Spectral shifts are measured by taking dilute solution of isoöctane as the standard. No association of the solute appears to play an important role, since extremely diluted solution with 0.0001 *M* of the solute was employed in the present work.

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TABLE II

NEAR ULTRAVIOLET ABSORPTION SPECTRA OF SIMPLE DERIVATIVES OF ANILINE IN VARIOUS SOLVENTS

Compound	Absorption maxima in solvent (mμ) Isoöctane	Ether	$\Delta\lambda_{eth}$	Alcohol	$\Delta\lambda_{alc}$	$\Delta\lambda_{sol}$	Basicity pK_a[a]
	287.5						
Aniline	284	290	—	286	—	−4.0	4.62
o-Toluidine	285	289	4.0	285.5	0.5	−3.5	4.39
m-Toluidine	288	292	4.0	287.5	−0.5	−4.5	4.69
p-Toluidine	294	296	2.0	290.5	−3.5	−5.5	5.12
3,4-Dimethylaniline	292	296	4.0	287	−5.0	−9.0	[b]
Methylaniline	294.5	297	2.5	295.5	1.0	−1.5	4.85
Ethylaniline	294.5	296	1.5	295.5	1.0	−0.5	5.11
Dimethylaniline	297.5	298.5	1.0	297.5	0	−1.0	5.06
o-Methyldimethylaniline	No max.	No max.	—	No max.	—	—	5.86

[a] These values were measured at 25° in aqueous solution by N. F. Hall and M. R. Sprinkle, THIS JOURNAL, 54, 3469 (1932). [b] This value has never been measured, but the base is easily supposed to be stronger in basicity than *p*-toluidine on the basis of induction and resonance.

between the N atom of amine and the H atom of hydroxyl group. Solvent effects associated with the former are expected to produce the shift toward red the same way as in ethereal solutions. The situation becomes just the opposite in the latter case. With the formation of the latter type of hydrogen bond, the lone-pair electrons at the nitrogen atom will become displaced toward the hydrogen atom of alcohol. This displacement would increase the effective electron affinity of the nitrogen atom. Consequently, the magnitude of electron migration from the nitrogen atom into the benzene ring decreases, thus resulting in the blue shift of absorption maximum.

There are available several examples[20] which show the displacement of absorption spectra due to the hydrogen bonding of the latter type. Furthermore, it is known[21] that the solvent effect of this type is strengthened with increasing basicity of amines, if there is no steric hindrance; that is, excepting the cases when both the amino and hydroxyl groups cannot approach each other.

In order to obtain a clearer view on the relation of basicity and steric hindrance, the near ultraviolet absorption spectra of various simple derivatives of aniline were measured in isoöctane and in alcohol. The results obtained are given in Table II together with data on their basicity. In aromatic primary amines, which were supposed not to suffer from the steric hindrance, the degree of the displacement toward shorter wave lengths became greater with increasing basicity. This tendency will be seen at a glance at the values of $\Delta\lambda_{alc}$ or more clearly at those of $\Delta\lambda_{sol}$. Contrary to the above, the shifts toward the visible are produced in secondary amines. Moreover, no change of absorption maxima of tertiary amines occurs with variation of solvent ($\Delta\lambda_{alc}$ null).

The striking differences observed between the primary and tertiary (or secondary) amines might be explained as follows. The energy of the hydrogen bond is markedly less than the usual bond energy. Consequently, the existence of methyl groups on the N atom more strongly inhibits the formation of hydrogen bond with the use of the nitrogen atom concerned.

(20) G. J. Brealey and M. Kasha, THIS JOURNAL, 77, 4462 (1955); T. Kubota, *J. Pharm. Soc. Japan*, 74, 831 (1954).
(21) M. Tsuboi, *J. Japan. Chem.*, 7, 611 (1953).

Further support of the above view may be found in the behavior of methylaniline, dihydroindole and tetrahydroquinoline given in Tables I and II. The blue shift of the absorption maximum in alcohol relative to that in isoöctane increases in the order of methylaniline, tetrahydroquinoline and dihydroindole. This order agrees with the order of decrease in steric hindrance of methylene groups. As was elaborated by Arnold[22] and others[23] the methylene group in five-membered ring offers less steric hindrance than that in a six-membered ring, while the latter offers less than that in an aliphatic normal chain.

The Influence of Conformation of Tricyclic Bases on their Near Ultraviolet Absorption Spectra.—Attempts were made to consider conformations of four pairs of stereoisomeric tricyclic bases and to explain why the near ultraviolet absorption spectrum of the *cis* compound should produce a smaller blue shift in alcohol as compared with that in isoöctane than that of the corresponding *trans* isomer ($\Delta\lambda_{alc}$ of *cis*-base − $\Delta\lambda_{alc}$ of *trans*-base, positive). A glance at the results given in Table I and the strength of basicity given in Table II will show for these displacements that there is no relationship with the strength of basicity. These shifts, therefore, have to be interpreted from the viewpoint of stereochemistry. As an example, the conformations of octahydroacridine will be discussed in the following.

Conformations of Octahydroacridine.—Tetrahydroquinoline is regarded as an analog of tetralin with substitution of nitrogen for carbon at position 1 and consequently with only slight distortion of the ring. Arguments similar to those given in the case of tetralin by Barton[24] and others[25] may, therefore, be applicable to derivatives of tetrahydroquinoline. Since 1,2,3,4,9,10,4a,9a-octahydroacridine is regarded as a 2,3-tetramethylene derivative of tetrahydroquinoline, its *trans* isomer may be assigned a conformation with the tetra-

(22) R. T. Arnold and P. N. Craig, THIS JOURNAL, 72, 2728 (1950); R. T. Arnold and J. Richter, *ibid.*, 70, 3505 (1948); R. T. Arnold and P. N. Craig, *ibid.*, 70, 2791 (1948); R. T. Arnold and E. Rondestvedt, *ibid.*, 68, 2176 (1946); 67, 1265 (1945).
(23) R. Adams and D. C. Blomstrom, *ibid.*, 75, 2375 (1955); M. Orchin and C. Golumbic, *ibid.*, 71, 4151 (1951).
(24) D. H. R. Barton, R. C. Cookson, W. Klyne and C. W. Shoppee, *Chemistry & Industry*, 21 (1954).
(25) E. J. Corey and R. A. Sneen, THIS JOURNAL, 77, 2505 (1955).

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methylene group equatorial in positions 2 and 3 of tetrahydroquinoline. A conformation with both the substituents axial can be excluded by steric considerations. There may, moreover, be considered two conformations concerning the nitrogen atom, as represented in diagrams II and III, respectively, one having the lone-pair electrons in the quasi-axial position and the other in quasi-equatorial. In contrast to piperidine analogs in which the latter is considered to exist predominantly,[26] it is assumed that tetrahydroquinoline has another conformation (the former type) with the lone-pair electrons in quasi-axial position. There is an evidence for the above assumption: on account of the overlap between the π-orbits of the benzene ring and the p-orbital of the nitrogen atom, the structure with the electrons in quasi-axial position should be stabilized. Further support may be found in the existence of the "secondary" absorption band of octahydroacridine and other aromatic amines treated in this study, in the decrease in basicity as compared with aliphatic amines, and in also several chemical reactions.[27]

Two conformations are possible for *cis*-octahydroacridine, as shown in diagrams IV and V, since those having the lone-pair electrons in quasi-axial position are excluded from consideration. In conformation IV, the methylene group at C_3 exists in an axial position and that at C_2 in equatorial one, whereas in V their positions are reversed.

In the former, the tetramethylene group produces steric compression over the p-orbital of a nitrogen atom whereas in the latter, the substituent shields the quasi-axial hydrogen atom at C_4. Little attention has been directed to steric influence due to the lone-pair electrons. This appears to be less than the steric hindrance caused by the hydrogen atom. By the above reason conformation IV may be inferred to be more predominant than the latter. On the basis of these likely assumptions it seems reasonable to assign conformations II and IV for *trans*- and *cis*-octahydroacridines,[28] respectively. Similar interpretation may be developed to assign conformations for *trans* and *cis* isomers of tetrahydro-2,3-trimethylenequinoline and of tetrahydro-2,3-pentamethylenequinoline.

The Difference $\Delta\lambda_{sol}$.—In order to account for the solvent effect in alcohol more definitely, the concept $\Delta\lambda_{sol}$ will be proposed, being defined as $\Delta\lambda_{alc} - \Delta\lambda_{ether}$. Since the size of the ether molecule is almost the same as that of the alcohol molecule, the value of $\Delta\lambda_{ether}$ is considered to indicate the solvent effect afforded only by hydrogen bonding between the H atom of the imino group and the O atom of the alcohol. Consequently, the term $\Delta\lambda_{sol}$ displays the solvent effect resulting from only hydrogen bonding between the N atom of the amine and the H atom of the alcohol. Examination of Table I shows that the term $\Delta\lambda_{sol}$ was particularly small in each of three *cis* derivatives of tetrahydroquinoline. This means that no hydrogen bonding is formed between the N atom of amine and the H atom of alcohol. The conformations of these *cis* isomers suggested in the previous paragraph are in good agreement with these facts: tri-, tetra- or pentamethylene substituent dominates so much space over the p-orbital of the nitrogen atom that the polymethylene groups will obstruct the proximity of ethanol molecules and will thus block the formation of hydrogen bonding.

On the other hand, the three *trans* isomers are supposed to suffer steric hindrance to only a slight degree in the formation of hydrogen bonding between the N atom of the amine and the H atom of the alcohol, as shown by negative values of the term $\Delta\lambda_{sol}$ given in Table I. It is to be noted that the value of $\Delta\lambda_{sol}$ in *trans*-tetrahydro-2,3-trimethylenequinoline (-4.5 mμ) was smaller than that in the other two *trans* isomers (-2.0 and -2.5 mμ), being consistent with the observation[22] by Arnold and his associates as mentioned above.

Conformations of hexahydrocarbazole will be discussed next. As it is well known that cyclohexane fused with a five-membered ring consists mainly of the chair form,[29] conformation VI will be suitable to be assigned for *trans*-hexahydrocarbazole and VII or VIII for the *cis* isomer, each corresponding to those, II, V and IV, of octahydroacridine. The conformation VI is formed when each of two equatorial hydrogen atoms on the two adjacent carbon atoms of cyclohexane is substituted by amino and phenyl radical of aniline, respectively. In conformation VII, the *cis* isomer has a configuration with the amino and phenyl radicals in the equatorial and axial position of adjacent carbon atoms of cyclohexane, respectively, whereas in conformation VIII they are in axial and equatorial position, respectively. Similar argument to that described in the case of *cis*-octahydroacridine cannot be applied to the stability between conformations VII and VIII. However, it will be reasonable to consider that *cis*-hexahydrocarbazole consists chiefly of conformation VII, because the p-orbital of nitrogen atom is screened with the tetramethylene group in conformation VIII but, on the contrary, conformation VII hardly suffers steric hindrance as is also true in the case of the *trans* isomer. Examination of Table I indicates that the value of $\Delta\lambda_{sol}$ of *cis*-hexahydrocarbazole was not very different from that of the *trans* isomer, as expected from a consideration as above outlined.

The Difference $\Delta\lambda_{ether}$.—In addition to the term of $\Delta\lambda_{sol}$, the values of $\Delta\lambda_{ether}$ must, therefore, be discussed in order to elucidate the difference of absorption maxima of the *cis* and *trans* isomers of tricyclic bases in alcohol, and the following will be proposed as an explanation. The positive values of $\Delta\lambda_{ether}$ are due mainly to the formation of hydrogen bonding between the H atom of the imine and the O atom of the ether. It seems to require a carbon atom at the β-position in relation to the nitrogen atom (called β-carbon) or a hydrogen atom attached to the carbon (called β-hydrogen) to display a serious steric influence on the proximity

(26) D. H. R. Barton, *Quart. Revs.*, **10**, 73 (1956).
(27) J. Hartwell and A. W. Schrecker, THIS JOURNAL, **73**, 2909 (1951).
(28) This argument does not exclude the existence of structures other than II and IV, which possibly exist at room temperature. But it is assumed that these structures, II and IV, are more important than others for the analysis of absorption spectra.
(29) E. L. Eliel and C. Pillar, THIS JOURNAL, **77**, 3600 (1955).

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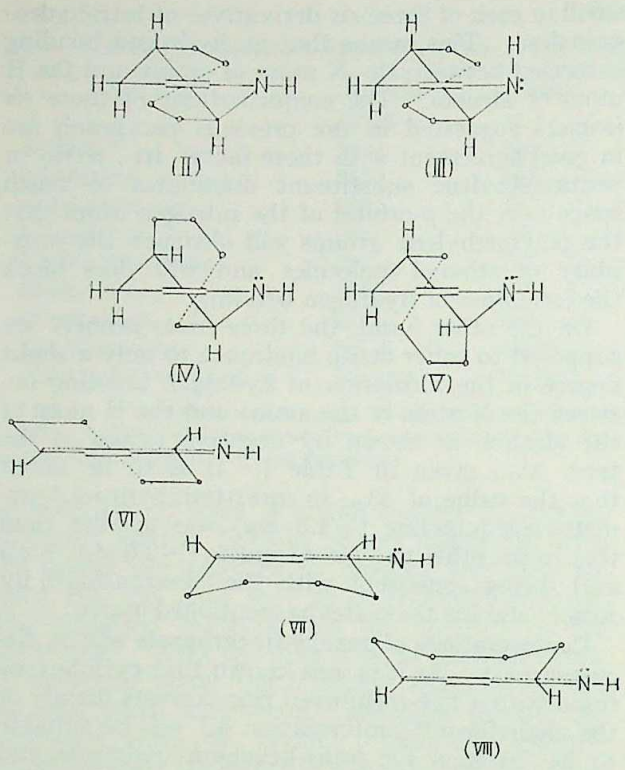

of the ether molecule. In each of conformations II and IV of *cis*- and *trans*-octahydroacridines, a quasi-equatorial hydrogen atom of an imino group runs almost parallel to the equatorial β-hydrogen atom, and those atoms with the nitrogen atom and β-carbon atom lie approximately coplanar with the benzene ring. The latter steric relation was extended to both *cis* and *trans* isomers of tetrahydro-2,3-pentamethylenequinoline with slight change due to transformation from a six-membered ring to a seven-membered ring. Therefore, in each of the two pairs both the *cis* and *trans* isomers are able to form the hydrogen bonding with ether molecule to the same degree, and as the result the difference of $\Delta\lambda_{ether}$ between isomers is supposed to be almost nothing.

On the other hand, the position is different in the other two pairs of stereoisomers where a five-membered ring combines with a six-membered ring. While the above-mentioned relation comes to each of two *trans*-isomers of those bases, each of two *cis*-isomers behaves differently: that is, each β-carbon atom, and more important each β-hydrogen atom, is forced out of coplanarity with tetrahydroquinoline or dihydroindole, because each atom of a five-membered ring is coplanar. As a result, it would be expected that the approach of an ether molecule toward the hydrogen atom of imino group is easier in each *cis* isomer, and the value of ($\Delta\lambda_{ether}$ of *cis* isomer $-$ $\Delta\lambda_{ether}$ of *trans* isomer) is expected to be positive. The values of $\Delta\lambda_{ether}$ given in Table I were found to fit in with these considerations.

One might conclude that the experimental results given in Table I are in good agreement qualitatively with what might be expected from both the conformational analysis for tricyclic bases and the inferences on the solvent effect of alcohol developed by division into terms of $\Delta\lambda_{ether}$ and of $\Delta\lambda_{sol}$. This inference of the solvation of alcohol may be extended with some reason to simple derivatives of aniline included in Table II; it may be pointed that the effect caused by the hydrogen bonding between the N atom of the aromatic amine and the H atom of the alcohol is large and depends remarkably on steric hindrance as well as on strength of basicity; however, on the contrary, that between the amino H and the alcohol O is comparatively small and is probably influenced only by steric hindrance and not by basicity.

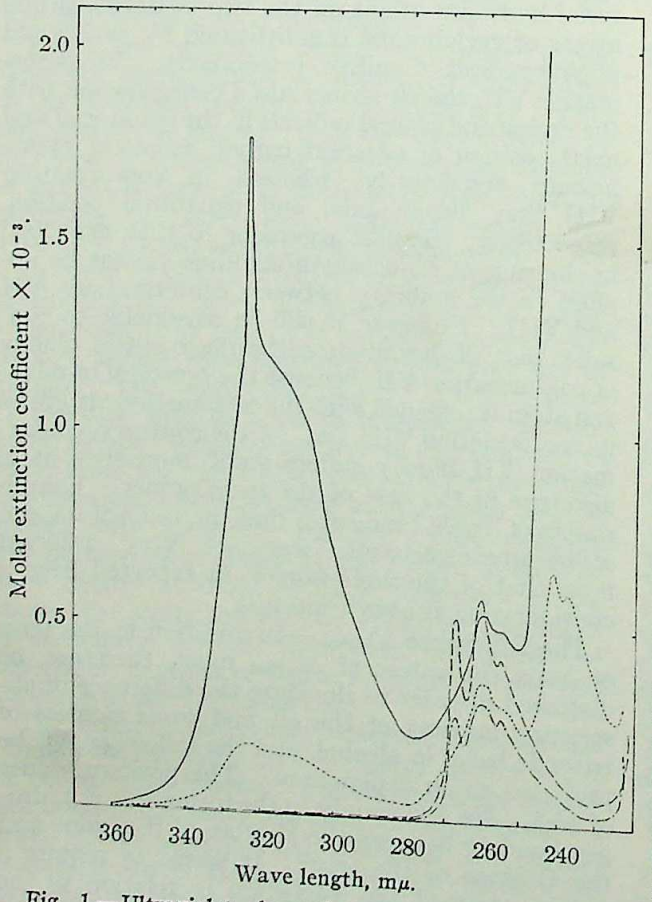

Fig. 1.—Ultraviolet absorption spectra of tricyclic bases in 0.1 *N* hydrochloric acid, concn. $M \times 10^{-3}$: ———, *cis*-hexahydrocarbazole; —·—·—, *trans*-hexahydrocarbazole; - - - - -, *cis*-octahydroacridine; ———, *trans*-octahydroacridine.

Ultraviolet Absorption Spectra of Tricyclic Bases in 0.1 *N* Hydrochloric Acid and their Basicity.—It is well known that the absorption spectra of derivatives of aniline in acidic solution agree closely with the spectrum of benzene.[30] This rule was recognized in stereoisomeric hexahydrocarbazoles in this study. But absorption spectra of the other three pairs of stereoisomers of tricyclic bases exhibited characteristic peaks at longer wave lengths (near 320 mμ), as shown in Fig. 1 and in Table III. Especially, *trans*-octahydroacridine displayed an absorption peak with extraordinary strong intensity in this region. While a rational explanation could not be offered for these phenomena, which probably result from distortion of the benzene ring by ring formation of substituents, attention should be drawn to the association of intensity of those

(30) A. Corbellini, *J. Chem. Phys.*, **7**, 984 (1939).

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TABLE III

NEAR ULTRAVIOLET ABSORPTION SPECTRA OF TRICYCLIC BASES IN 0.1 *N* HYDROCHLORIC ACID

Compound	Absorption maxima (mμ) and intensity (ε)[a]				Basicity,[b] pK_a
trans-Tetrahydro-2,3-trimethylenequinoline	324 (57)	267 (268)	260 (572)	244 (269)	4.47
cis-Tetrahydro-2,3-trimethylenequinoline	324 (266)	266 (267)	259 (310)	243 (850)	4.45
trans-Octahydroacridine	324 (1760)		261 (536)	242 (3000)	4.39
cis-Octahydroacridine	324 (176)		261 (360)	242 (650)	4.08
trans-Tetrahydro-2,3-pentamethylenequinoline	321 (920)		260 (380)	241 (2690)	4.63
cis-Tetrahydro-2,3-pentamethylenequinoline	321 (260)		261 (355)	242 (1080)	4.51
trans-Hexahydrocarbazole		268 (276)	261 (310)	256 (265)	4.66
cis-Hexahydrocarbazole		268 (522)	261 (576)	256 (419)	4.92

[a] The figures in parentheses refer to molecular extinction coefficient. [b] The basicity was measured at 15° in 50% aqueous alcohol.

absorption spectra with basicity. In each of four pairs cited in Table III, absorption maxima agree within the limit of 1 mμ, but those intensities were different among stereoisomers. Each of the bases possessing absorption bands of higher intensities was found to be a stronger base than the corresponding isomer. This correlation might be assumed because the strength of basicity of aromatic amines is closely associated with the resonance state of benzene, but no generalization would be safe from the few examples treated in this study. The problem will be kept under further investigation.

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SAPPORO, JAPAN

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, IOWA STATE COLLEGE]

The Preparation and Dichromate Oxidation of Certain 6-Substituted Phenanthridines

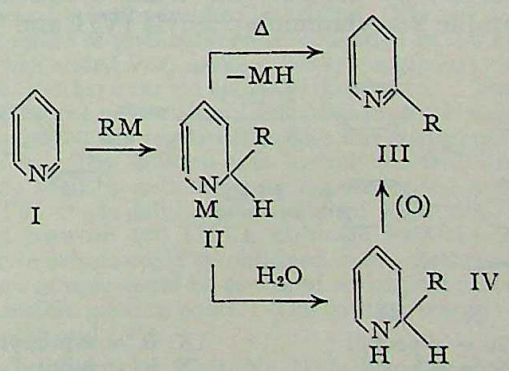
BY HENRY GILMAN AND JOHN EISCH

RECEIVED MARCH 7, 1957

The preparation of 6-substituted phenanthridines and their 5,6-dihydro derivatives by the organometallic alkylation of phenanthridine has been examined. It was found that not only do organolithium compounds (*n*-butyl- and *o*-tolyllithium) attack phenanthridine readily, but active Grignard reagents such as benzylmagnesium chloride can also add to the azomethine linkage. Finally, even ordinary Grignard reagents such as *n*-propylmagnesium bromide alkylate this heterocycle if the reaction time is protracted.

The dichromate oxidation of 6-*n*-propyl- and 6-*n*-butylphenanthridines gave, in addition to phenanthridinone, the corresponding 6-acylphenanthridines. This reaction is suggested not only to be diagnostic for 6-alkylphenanthridines but also to be a preparative method for 6-acylphenanthridines.

Although the aza-aromatic heterocycles previously studied, pyridine, quinoline and isoquinoline, are readily alkylated by organolithium compounds,[1] they react with organomagnesium compounds only with difficulty.[2] To obtain even mediocre yields, workers have resorted to such stringent reaction conditions as autoclave technique, higher-boiling solvents or dioxane media. The course of the reaction, however, seems quite analogous for organolithium and organomagnesium compounds, *i.e.*, addition of RM (M = Li, MgX) to the nitrogen heterocycle in a 1,2- or 1,4-manner. The interaction of pyridine (I) and an organometallic compound (RM) may be viewed as typical[3]



The resulting adduct II may either split out MH to give III thermally, or the dihydro compound IV obtained upon hydrolysis may be dehydrogenated.

Recent investigations have demonstrated that dibenzopyridines such as phenanthridine exhibit a high order of reactivity toward allylmagnesium

(1) K. Ziegler and H. Zeiser, *Ann.*, **485**, 174 (1931).

(2) For a general review of the interaction of Grignard reagents with aza-aromatic heterocycles, see M. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice–Hall, Inc., New York, N. Y., 1954, p. 1257 *et seq.*

(3) The predominating isomer from the reaction between pyridine and organolithium compounds is the 2-isomer, whereas the action of benzylmagnesium chloride leads in small yield to a 4:1 mixture of 4- benzyl- and 2-benzylpyridines (R. A. Benkeser and D. Holton, THIS JOURNAL, **73**, 5861 (1951)). With allylmagnesium bromide the main product has been shown to be 4-allylpyridine; smaller amounts of 2-allylpyridine which may have been formed could not be isolated (ref. 4).

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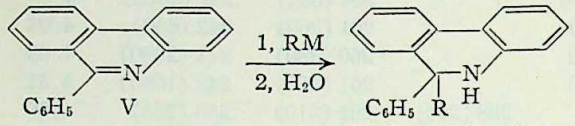
bromide in ether, in comparison to that of benzopyridines or pyridine itself.[4] Moreover, phenanthridine gives high yields of 6-arylphenanthridines with organolithium compounds,[5] and even 6-phenylphenanthridine (V) can add phenyllithium[5] or allylmagnesium bromide to give VI.[6]



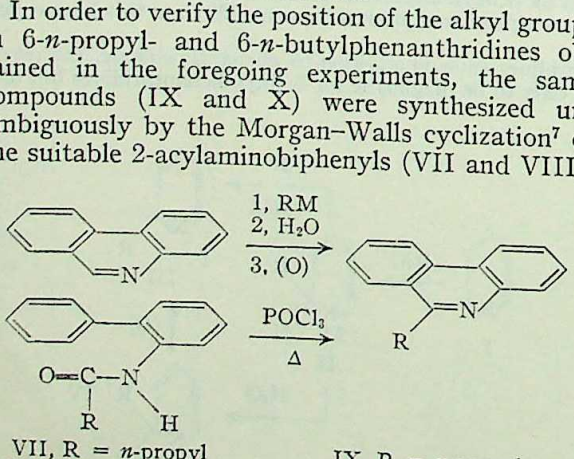
VI, R = C_3H_5, C_6H_5

In the present study it was of interest to learn whether this enhanced reactivity of phenanthridine would be reflected in its behavior toward ordinary Grignard reagents and whether organometallic alkylation was feasible for the synthesis of 6-substituted phenanthridines of various types.

Although Ziegler and Zeiser[1] have reported that *n*-butyllithium adds readily to various nitrogen bases, this reaction has not been reported for phenanthridine. Indeed, it was found that phenanthridine was immediately alkylated at −50° to give 6-*n*-butylphenanthridine in essentially quantitative yield. It may be noted that 6-*n*-butylphenanthridine could not be freed entirely of its dihydro form, as is indicated by the NH band in its infrared spectrum and the orange-yellow cast of its picrate.

A second illustration of phenanthridine's superior reactivity is its behavior with *n*-propylmagnesium bromide in ether. By prolonging the reaction time, but without use of customary "forcing" conditions, an 84% yield of 6-*n*-propylphenanthridine was secured. The excellent yield with this ordinary Grignard reagent suggests that in certain cases the organomagnesium compound may replace the organolithium compound when the latter is difficultly accessible.

In order to verify the position of the alkyl groups in 6-*n*-propyl- and 6-*n*-butylphenanthridines obtained in the foregoing experiments, the same compounds (IX and X) were synthesized unambiguously by the Morgan–Walls cyclization[7] of the suitable 2-acylaminobiphenyls (VII and VIII).



VII, R = *n*-propyl
VIII, R = *n*-butyl

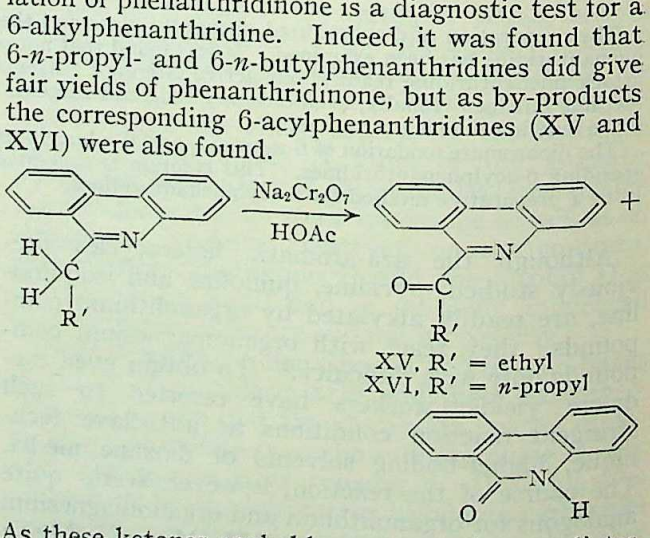
IX, R = *n*-propyl
X, R = *n*-butyl

Third, a more reactive, allylic Grignard reagent such as benzylmagnesium chloride, analogous to allylmagnesium bromide,[4] attacked phenanthridine readily to give the 6-benzyl-5,6-dihydro derivative XI in 78% yield. Since the product was not amenable to purification by crystallization, it was identified by dichromate oxidation to the known 6-benzoylphenanthridine (XII) in high yield.

Finally, a somewhat hindered aryllithium system, such as *o*-tolyllithium, added readily to the azomethine linkage in phenanthridine. Also quite significant is the fact that here the dihydro derivative XIII could be isolated as a moderately stable solid. It could be dehydrogenated smoothly by palladium in boiling mesitylene to the 6-*o*-tolyl derivative XIV which was isolated as a low melting picrate.

The above illustrated Morgan–Walls cyclization[7] of 2-acylaminobiphenyls has represented, since its introduction in 1931, the most general method for preparing 6-substituted phenanthridines. However, the use of organolithium compounds or organomagnesium reagents (when the latter are more accessible) on phenanthridine offers an attractive alternative, especially since newer methods have made phenanthridine more available in organic synthesis.[8] In addition, organometallic alkylation may be the preferred method when 6-substituted-5,6-dihydrophenanthridines themselves are desired. The latter are of interest for their potential physiological activity.[9]

The dichromate oxidation of 6-methylphenanthridines first carried out by Walls[10] led to excellent yields of phenanthridinones. The pre ent authors examined the behavior of 6-*n*-propyl- and 6-*n*-butylphenanthridines toward sodium dichromate in glacial acetic acid to learn if the formation of phenanthridinones was general for 6-alkylphenanthridines. As phenanthridine itself was essentially unaffected by the dichromate oxidation procedure, it could then be concluded that the isolation of phenanthridinone is a diagnostic test for a 6-alkylphenanthridine. Indeed, it was found that 6-*n*-propyl- and 6-*n*-butylphenanthridines did give fair yields of phenanthridinone, but as by-products the corresponding 6-acylphenanthridines (XV and XVI) were also found.



XV, R′ = ethyl
XVI, R′ = *n*-propyl

As these ketones probably represent intermediates in oxidizing 6-alkylphenanthridines to phenanthridinones, it is feasible to prepare 6-acylphenanthridines in this way by employing milder conditions. As has been mentioned previously, the impure 6-benzyl-5,6-dihydrophenanthridine was

(4) H. Gilman, J. Eisch and T. Soddy, THIS JOURNAL, **79**, 1245 (1957).
(5) H. Gilman and R. D. Nelson, *ibid.*, **70**, 3316 (1948).
(6) H. Gilman and J. Eisch, *ibid.*, **79**, 2150 (1957).
(7) G. T. Morgan and L. P. Walls, *J. Chem. Soc.*, 2447 (1931).
(8) (a) D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 717 (1953); (b) E. C. Taylor, Jr., and N. W. Kalenda, THIS JOURNAL, **76**, 1699 (1954); (c) E. C. Taylor, Jr., and A. E. Martin, *ibid.*, **74**, 6295 (1952).
(9) (a) A. G. Caldwell, F. C. Copp and L. P. Walls, *J. Chem. Soc.*, 2698 (1950); (b) J. Finkelstein and S. Linder, THIS JOURNAL, **72**, 3282 (1950); (c) C. P. Huttrer, *ibid.*, **71**, 4147 (1949).
(10) L. P. Walls, *J. Chem. Soc.*, 1405 (1935).

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transformed by this method to 6-benzoylphenanthridine in 72% yield.

Experimental

The melting points were determined on an electrically heated copper block and are corrected. All operations involved in the preparation and reaction of organometallic compounds were conducted under an atmosphere of dry, oxygen-free nitrogen.

6-*n*-Butylphenanthridine (X). Method A. From 2-Valeraminobiphenyl (VIII) and Phosphorus Oxychloride.[7]—A 500-ml., round-bottomed flask was equipped with an air condenser bearing a calcium chloride tube and the latter tube connected to a hydrogen chloride gas trap. The reaction flask was charged with 25.5 g. (0.10 mole) of 2-valeraminobiphenyl and 42 g. (0.27 mole) of phosphorus oxychloride, and this solution was heated cautiously until coloration appeared and gas evolution began. The heating was then discontinued and the reaction allowed to proceed spontaneously. When the vigorous reaction subsided, the solution was heated at the reflux temperature for 2 hr. The excess phosphorus oxychloride was removed at reduced pressure, and the residue extracted portionwise with 200 ml. of hot 6 *N* hydrochloric acid. After filtration through glass wool, the extracts were treated with excess sodium hydroxide. The liberated base was taken up in an ether–benzene mixture and dried with anhydrous sodium sulfate. After removal of the solvent the 6-*n*-butylphenanthridine distilled at 182–184° (4.0 mm.), 14.0 g. (60%). It was a pale yellow, viscous liquid, $n^{20}D$ 1.6369.

Anal. Calcd. for $C_{17}H_{17}N$: N, 5.96. Found: N, 6.06.

The picrate recrystallized from a dioxane–ethanol pair as fine, yellow needles, m.p. 195.5–197°.

Anal. Calcd. for $C_{23}H_{20}N_4O_7$: N, 12.06. Found: N, 12.11.

Method B. From Phenanthridine and *n*-Butyllithium.—In a 500-ml., three-necked flask fitted with a sealed stirrer, addition funnel and low-temperature thermometer and flushed with nitrogen, 20.0 g. (0.112 mole) of phenanthridine was suspended in 200 ml. of dry ether. After the contents of the flask were cooled to −45° by means of an acetone–Dry Ice-bath, 0.11 mole of freshly prepared *n*-butyllithium[11] in 120 ml. of ether was added to the stirred suspension during 20 minutes. The temperature was then lowered to −50° and held there for 15 minutes, during which time the reaction mixture formed a fluorescent green solution. Thereupon the solution was poured rapidly onto a slurry of Dry Ice in dry ether. After the mixture had warmed up to room temperature, it was extracted with 200 ml. of 5% potassium hydroxide solution. Separation and careful acidification of the aqueous layer gave no precipitated acid.

The ethereal layer of the carbonated mixture was dried over anhydrous sodium sulfate, filtered and the solvent removed. The residual orange liquid was heated with 30 ml. of nitrobenzene for 20 minutes to oxidize the dihydro derivative. After the nitrobenzene was distilled under water-pump vacuum, the residue was distilled at the oil-pump. The main fraction of pale orange liquid (23.7 g., 90%) boiled at 177–178° (3.4 mm.). That some dihydro form was still present was indicated by an N–H band at 3.0 μ in the infrared spectra and by the formation of an orange picrate. The product was redistilled through a short column, and a pale yellow liquid was obtained at 184° (4.0 mm.). The melting point of the picrate prepared from this fraction agreed well with that of the picrate prepared in method A, but still had an orange-yellow cast. A mixture melting point of the picrates was not depressed. The infrared spectra of the two preparations also were almost superimposable, except for the presence of an N–H band in the preparation from method B.

6-*n*-Propylphenanthridine (IX). Method A. From 2-Butyraminobiphenyl (VII) and Phosphorus Oxychloride.[7]—Analogous to the procedure detailed in method A above for the preparation of 6-*n*-butylphenanthridine, 23.9 g. (0.10 mole) of 2-butyraminobiphenyl and 38 g. (0.25 mole) of phosphorus oxychloride reacted to give, upon work-up, 16.0 g. (73%) of pale yellow 6-*n*-propylphenanthridine, b.p. 164–166° (2.0 mm.), $n^{20}D$ 1.6552.

Anal. Calcd. for $C_{16}H_{15}N$: N, 6.33. Found: N, 6.69.

The picrate formed fine, bright yellow needles from a dioxane–ethanol pair, m.p. 196–197.5°.

Anal. Calcd. for $C_{22}H_{18}N_4O_7$: N, 12.44. Found: N, 12.23.

Method B. From Phenanthridine and *n*-Propylmagnesium Bromide.—In a 500-ml., three-necked flask equipped with a sealed stirrer, addition funnel and reflux condenser were placed 21.1 g. (0.117 mole) of phenanthridine and 150 ml. of dry ether. Then 0.247 mole of *n*-propylmagnesium bromide in 120 ml. of ether was introduced, and the resulting yellow suspension stirred at the reflux temperature for 100 hr., during which time most of the solid dissolved to form a dark solution. The reaction mixture was hydrolyzed with ammonium chloride solution and the separated organic layer dried with anhydrous sodium sulfate. After filtration and distillation of the ether, the residual oil was heated with 30 ml. of nitrobenzene for 0.5 hr. The nitrobenzene was distilled at the water-pump and the remaining orange oil fractionated under reduced pressure. The main fraction consisted of 18.4 g. of yellow liquid, b.p. 163–164° (1.9 mm.), $n^{20}D$ 1.6525. Redistillation of the forerun gave an additional 3.4 g. of product for a total crude yield of 84%. The picrate prepared from this crude product melted at 194–195°. Admixed with the 6-*n*-propylphenanthridine picrate prepared in method A, the mixture melted at 194–197°. Moreover, the infrared spectra of this product and its picrate were almost superimposable with those of 6-*n*-propylphenanthridine and its picrate (method A), respectively.

2-Butyraminobiphenyl (VII).—A 500-ml., round-bottomed flask was equipped with a short air condenser which in turn bore a bent tube leading to a receiver. The reaction flask was charged with 33.9 g. (0.20 mole) of 2-aminobiphenyl, 35.4 g. (0.40 mole) of butyric acid and 0.1 g. of zinc dust. The contents were so heated during a 6 hr. period that a mixture of water and butyric acid slowly distilled into the receiver. Thereupon the warm mixture was poured into ice and the solidified product filtered off. After recrystallization from dilute ethanol, 38.2 g. (80%) of white product was obtained, m.p. 83–85°. The analytical sample was obtained from petroleum ether (b.p. 60–70°) as long, white needles, m.p. 86–86.5°.

Anal. Calcd. for $C_{16}H_{17}NO$: N, 5.87. Found: N, 5.80.

2-Valeraminobiphenyl (VIII).—By extension of the above procedure for 2-butyraminobiphenyl, 2-valeraminobiphenyl was prepared from 33.9 g. (0.20 mole) of 2-aminobiphenyl, 40.9 g. (0.40 mole) of valeric acid and 0.1 g. of zinc dust by an 8 hr. heating period. Recrystallization of the crude solid from dilute ethanol gave 41.8 g. (82%) of white product, m.p. 68–70°. The analytical sample consisted of long, white needles obtained from petroleum ether, m.p. 73–74.5°.

Anal. Calcd. for $C_{17}H_{19}NO$: N, 5.53. Found: N, 5.41.

6-Benzyl-5,6-dihydrophenanthridine (XI).—To 32.3 g. (0.180 mole) of phenanthridine suspended in 100 ml. of dry ether was added 0.26 mole of benzylmagnesium chloride in 190 ml. of ether over the course of 30 minutes. The initially formed bright yellow slurry slowly changed to a dark green solution when the reaction mixture was stirred under reflux for 24 hr. The solution was hydrolyzed with ammonium chloride solution and the resulting suspended solid filtered off. The crude white solid weighed 38.2 g. (78%) and melted between 130–133°. Although well-formed glistening white prisms could be obtained from an ethanol–benzene pair, no sample could be procured which had a consistently reproducible melting point. The melting points ranged between 125 and 134°.

Anal. Calcd. for $C_{20}H_{17}N$: N, 5.17. Found: N, 5.41.

The infrared spectrum had a pronounced N–H band at 3.05 μ. That the product was actually 6-benzyl-5,6-dihydrophenanthridine in intimate mixture with perhaps 6-benzylphenanthridine and some starting material was demonstrated by oxidation to the known 6-benzoylphenanthridine in high yield.

6-Benzoylphenanthridine (XII).—In 100 ml. of warm glacial acetic acid were dissolved 6.8 g. (0.025 mole) of impure 6-benzyl-5,6-dihydrophenanthridine melting over the range 129–133°. In the course of 20 minutes, 14.3 g. (0.047 mole) of solid sodium dichromate was introduced. The resulting green solution was refluxed for 90 minutes and then poured

(11) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, THIS JOURNAL, 71, 1499 (1949).

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into water. Cooling and filtration gave 7.0 g. (99%) of pale yellow solid, melting over the range 140–147°. From ethanol 5.1 g. (72%) of white solid melting at 150–152° was obtained. Another crystallization yielded white plates, m.p. 152–154°. The product gave a positive test for the carbonyl group with 2,4-dinitrophenylhydrazine and exhibited an intense infrared band at 6.0 μ. Ritchie reports that 6-benzoylphenanthridine melts at 152°.[12]

6-*o*-Tolyl-5,6-dihydrophenanthridine (XIII).—To 30.0 g. (0.168 mole) of phenanthridine suspended in 200 ml. of dry ether was added 0.196 mole of *o*-tolyllithium in 180 ml. of ether during 50 minutes. (The *o*-tolyllithium was previously prepared from 3.3 g., 0.50 g. atom, of lithium wire and 39.3 g., 0.230 mole, of *o*-bromotoluene in 88% yield.) The reaction mixture was stirred at room temperature for 7 hr. and the resulting green solution subsequently hydrolyzed. The suspended solid upon filtration and drying melted over the range 134–138° and weighed 9.3 g. The ethereal layer upon evaporation yielded an additional 26.7 g. of product of the same melting range. One recrystallization from an ethanol–benzene pair gave 31.5 g. (64%) of slightly tan crystals, m.p. 140–141°. The presence of a dihydro grouping was indicated by the blue fluorescence of an alcoholic solution.[9a] The analytical sample consisted of cream-colored crystals, m.p. 140.5–141.5°, which became light brown when left in the air.

Anal. Calcd. for $C_{20}H_{17}N$: N, 5.17. Found: N, 5.14.

6-*o*-Tolylphenanthridine Picrate (XIV).—The product obtained in the preceding experiment was dehydrogenated catalytically. One gram (0.0073 mole) of 6-*o*-tolyl-5,6-dihydrophenanthridine, 100 mg. of palladium-on-Darco (5% palladium) and 5 ml. of mesitylene were refluxed for 1 hr. while a rapid stream of nitrogen was swept through the reaction vessel. At the end of this time, the initial blue fluorescence of the solution had disappeared. The reaction mixture was filtered and the catalyst washed with 10 ml. of ether. The mesitylene was distilled from the filtrate, leaving an oily yellow residue. Since only an oil was obtained from 95% ethanol, the base was converted to the picrate, a crystalline yellow solid melting at 165–167°, 1.6 g. (87%). 6-*o*-Tolylphenanthridine picrate formed bright yellow prisms from 95% ethanol, m.p. 167.5–168.0°.

Anal. Calcd. for $C_{26}H_{18}N_4O_7$: N, 11.24. Found: N, 11.41.

Oxidation of 6-*n*-Butylphenanthridine.[10]—In a 250-ml., three-necked flask fitted with a condenser, stirrer and solids funnel were placed 7.8 g. (0.033 mole) of 6-*n*-butylphenanthridine and 100 ml. of glacial acetic acid. While the solution was held at incipient reflux, 14.3 g. (0.047 mole) of sodium dichromate was introduced portionwise during 75 minutes. The orange solution turned dark green during the following 2-hr. reflux period. The solution was poured into water and the precipitated tan solid was collected. When dry, the solid was extracted with two 100-ml. portions of ether. The residual tan solid weighed 2.3 g. (36%) and melted over the range 289–292°. A mixed melting point determination with an authentic specimen showed this product to be phenanthridinone.

Removal of solvent from the ether extracts left 4.0 g. (49%) of a dark yellow solid melting over the range 85–95°. Recrystallizations from 95% ethanol (Norit A) gave silky, white needles, m.p. 108–109°. This solid proved to be 6-butyrylphenanthridine (XVI) as its infrared spectrum showed an intense carbonyl band at 5.95 μ. Moreover, it formed derivatives with 2,4-dinitrophenylhydrazine and with picric acid.

Anal. Calcd. for $C_{17}H_{15}NO$: N, 5.62. Found: N, 5.52.

The 2,4-dinitrophenylhydrazone was prepared in the conventional manner. Successive recrystallizations from an ethanol–ethyl acetate pair and then a chloroform–ethanol pair gave light orange, matted needles, m.p. 158.5–161°.

Anal. Calcd. for $C_{23}H_{19}N_5O_4$: C, 64.32; H, 4.46. Found: C, 64.30; H, 4.61.

The picrate crystallized from a dioxane–95% ethanol pair as stout, yellow needles, m.p. 198–199°.

Anal. Calcd. for $C_{23}H_{18}N_4O_8$: N, 11.71. Found: N, 11.62.

Oxidation of 6-*n*-Propylphenanthridine.[10]—In a manner similar to the preceding experiment 7.3 g. (0.033 mole) of 6-*n*-propylphenanthridine in 100 ml. of glacial acetic acid was heated for 3 hr. with 14.3 g. (0.047 mole) of sodium dichromate. Dilution of the reaction mixture with water and extraction of the collected solid with ether gave a 3.4-g. (53%) residue of phenanthridinone, m.p. 292–293°.

Evaporation of the ether extracts gave 2.3 g. (30%) of impure 6-propionylphenanthridine (XV) melting from 53–57°. Recrystallizations from 95% ethanol gave white needles melting from 73–76°. This sample showed a pronounced carbonyl band at 5.9 μ in its infrared spectrum. Further purification was carried out by preparing the 2,4-dinitrophenylhydrazone. By recrystallization from a chloroform–ethanol pair this derivative formed compact orange prisms, m.p. 225.5–227.5°.

Anal. Calcd. for $C_{22}H_{17}N_5O_4$: C, 63.85; H, 4.12. Found: C, 63.61; H, 4.26.

The picrate was obtained as chartreuse-colored needles from a dioxane–ethanol pair, m.p. 195.5–197°.

Anal. Calcd. for $C_{22}H_{16}N_4O_8$: N, 12.08. Found: N, 12.34.

Attempted Oxidation of Phenanthridine.—Phenanthridine (6.6 g., 0.033 mole) was heated with 14.3 g. (0.047 mole) of sodium dichromate in 100 ml. of glacial acetic acid for 24 hr. The red solution darkened somewhat during this time. The cooled solution was poured into water and the precipitated orange solid was collected and dried. Probably this was the dichromate salt of phenanthridine, for treatment with sodium hydroxide solution regenerated phenanthridine, 6.8 g., melting from 106–111°. When heated with 50 ml. of dilute hydrochloric acid, the phenanthridine dissolved almost completely, leaving only 0.1 g. of residue.

Acknowledgments.—The authors are grateful to Dr. V. A. Fassel and Mr. R. McCord of the Institute for Atomic Research for the infrared determinations. Also, it is a pleasure to acknowledge that this work was supported in part by the United States Atomic Energy Commission under Contract No. AT(11-1)-59.

AMES, IOWA

(12) E. Ritchie, *J. Proc. Roy. Soc. N. S. Wales*, **78**, 134 (1945) [*C. A.*, **40**, 876 (1946)].

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MASSACHUSETTS]

Oxidative Reactions of Hydrazines. IV. Elimination of Nitrogen from 1,1-Disubstituted-2-arenesulfonhydrazides[1-4]

BY LOUIS A. CARPINO

RECEIVED MARCH 28, 1957

Alkaline degradation of 1,1-dibenzyl-2-benzenesulfonhydrazides leads to the formation of bibenzyls. The reaction is represented as proceeding through an intermediate formed by α-elimination of the elements of benzenesulfinic acid. A new method of introducing the very conveniently removed carbo-*t*-butoxy group is described involving acylation by *t*-butyl azidoformate.

Generally, the oxidation of 1,1-disubstituted hydrazines leads to the formation of the corresponding tetrazenes (eq. 1).[5] However, in several cases,

$$R_2NNH_2 \xrightarrow{[O]} R_2NN{=}NNR_2 \qquad (1)$$

as yet relatively unexplored, other products have been obtained. Oxidation of 1,1-dibenzylhydrazine with mercuric oxide was first noted by Busch and Weiss[6] to yield bibenzyl, and recently Overberger and Marks achieved the same result using bromine in ethanol or *t*-butyl hypochlorite as oxidizing agents. Busch and Lang[7] studied the mercuric oxide oxidation of numerous 1-aryl-1-benzylhydrazines and obtained either the tetrazenes or substituted benzaldehyde arylhydrazones. Kenner and Knight[8] postulated that the Busch–Weiss reaction involved the formation of the intermediate Ia which subsequently underwent decomposition

$$(C_6H_5CH_2)_2NNH_2 \xrightarrow{[O]} \underset{\text{Ia}}{[(C_6H_5CH_2)_2\dot{N}{-}\ddot{N}:} \longleftrightarrow$$

$$\underset{\text{Ib}}{(C_6H_5CH_2)_2\overset{+}{N}{=}\ddot{\overset{-}{N}}:]} \longrightarrow C_6H_5CH_2CH_2C_6H_5 + N_2 \qquad (2)$$

to bibenzyl (eq. 2). Intermediates such as I[9] are clearly analogous to the aliphatic diazo compounds except that they lack the resonance stabilization possible with the latter. The present study is designed to obtain evidence relative to the postulation of Kenner and Knight. In view of the analogy between the postulated intermediates such as I and aliphatic diazo compounds it would appear that many of the syntheses of the latter could be modified to provide new routes to bibenzyls and to shed more light on this novel and potentially useful reaction. The first such process to be examined was that of Bamford and Stevens[10] who found that phenyldiazomethane was obtained by treatment of the benzenesulfonhydrazone of benzaldehyde with alkali (eq. 3, Z = CH). As an α-elimination[11] of the elements of benzenesulfinic acid this reaction is related to the conversion of the corresponding triazene to the azide[12] (eq. 3, Z = N). These results suggested that alkaline degradation of 1,1-dibenzyl-2-benzenesulfonhydrazide should yield bibenzyl if the postulation of Kenner and Knight is correct (eq. 4). This reaction did, in fact, yield bibenzyl in 85% yield suggesting that the same intermediates might intervene in the two cases.[13]

$$C_6H_5Z{=}NNHSO_2C_6H_5 \xrightarrow{OH^-} \underset{Z = N, CH}{C_6H_5Z{=}\overset{+}{N}{=}\overset{-}{N}} \qquad (3)$$

$$(C_6H_5CH_2)_2NNHSO_2C_6H_5 \xrightarrow{OH^-} (C_6H_5CH_2)_2\overset{-}{N}NSO_2C_6H_5 \longrightarrow$$

$$\underset{+\ -}{[(C_6H_5CH_2)_2N{=}N]} \longrightarrow C_6H_5CH_2CH_2C_6H_5 \qquad (4)$$

(1) This work was supported in part (see Experimental section) by the following organizations: (a) Research Corporation, New York, N. Y.; (b) the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract number 18(603)-114; (c) The Office of Ordnance Research, United States Army, under contract number DA-19-059-ORD-2468.

(2) Paper III, L. A. Carpino, *Chemistry & Industry*, 172 (1957).

(3) Paper II, L. A. Carpino, THIS JOURNAL, **79**, 98 (1957).

(4) Presented at the 130th National Meeting of the American Chemical Society, Sept. 18, 1956, Atlantic City, N. J. (Abstracts, p. 18-O).

(5) See C. G. Overberger and B. S. Marks, THIS JOURNAL, **77**, 4104 (1955).

(6) M. Busch and B. Weiss, *Ber.*, **33**, 270 (1900). A preliminary account of an investigation of the scope of the Busch–Weiss reaction has been given by R. L. Hinman and K. L. Hamm, Abstracts of the 130th National Meeting of the American Chemical Society, Sept. 18, 1956, p. 17-O. The reaction has seen only limited use as a preparative method [see J. Kenner and J. Wilson, *J. Chem. Soc.*, 1108 (1927), and F. G. Mann, I. T. Miller and B. B. Smith, *ibid.*, 1130 (1953)].

(7) M. Busch and K. Lang, *J. prakt. Chem.*, [2] **144**, 291 (1936). References to other anomalous results are given by Overberger and Marks.[5]

(8) J. Kenner and E. C. Knight, *Ber.*, **69**, 341 (1936).

(9) The name *azamine* has been suggested for the parent substance, $H_2N^+{=}N^-$ (ref. 4 and reference cited therein). Recently W. R. McBride and H. W. Kruse [THIS JOURNAL, **79**, 572 (1957)] have presented evidence for the existence of stable azaminiun salts, $[R_2N{=}NH]X$, obtained through the oxidation of 1,1-disubstituted hydrazines.

(10) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4335 (1952).

(11) Most α-eliminations yield unstable substances which either react with the environment or achieve stabilization by rearrangement. For leading references to such postulated cases of α-elimination see S. J. Cristol and R. F. Helmreich, THIS JOURNAL, **77**, 5034 (1955); J. Hine, *ibid.*, **72**, 2438 (1950); R. L. Letsinger and D. F. Pollart, *ibid.*, **78**, 6079 (1956). While α-elimination of the elements of benzenesulfinic acid is rare the corresponding β-elimination is relatively common. For examples see O. Piloty, *Ber.*, **29**, 1565 (1896); A. Hantzsch and R. Glogauer, *ibid.*, **30**, 2555 (1897); E. L. Holmes and C. K. Ingold, *J. Chem. Soc.*, 1305 (1926); A. Michael and A. M. Comey, *Am. Chem. J*, **5**, 116 (1883). When there is a choice between α- or β-elimination of HX from alkyl halides, reaction rarely, if ever, goes by the former route. The possibility exists that this preference may be reversed in the sulfonhydrazide series due to the acidity of the α-hydrogen and the presence of an unshared electron pair on the atom beta to the leaving group. The implications of this possibility are being pursued further. There does not appear to be any evidence as to whether labile 3-ring intermediates (gamma elimination) intervene in the formation of the diazo and azido groups by reactions such as 3. The diazo and azido groups are known to be linear (see K. Clusius and H. Hürzeler, *Helv. Chim. Acta*, **37**, 383 (1954), and earlier work by these authors and others).

(12) A. Key and P. K. Dutt, *J. Chem. Soc.*, 2053 (1928).

(13) Alkaline degradation of 1-phenyl-2-benzenesulfonhydrazide has been postulated [M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Woolf, *J. Chem. Soc.*, 2093 (1948)] to involve β-elimination to yield phenyldiimide ($C_6H_5N{=}NH$) which subsequently decomposes to benzene and nitrogen. The results reported in the present paper suggest that α-elimination with the formation of the azamine ($C_6H_5\overset{+}{N}H{=}\overset{-}{N}$) may represent a second possibility

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TABLE I

1,1-DIBENZYL-2-ARENESULFONHYDRAZIDES,[a,b,d] p-$RC_6H_4SO_2NHN(CH_2C_6H_4R')_2$

R	R	M.p., °C.	Yield,[c] %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
F	H	115–117	57 (92)	$C_{20}H_{19}O_2N_2SF$	64.84	65.19	5.17	5.34
Br	H	128–129 dec.	68 (82)	$C_{20}H_{19}O_2N_2SBr$	55.68	55.65	4.44	4.48
CH_3O	H	123–125	27 (57)	$C_{21}H_{22}O_3N_2S$	65.94	66.21	5.80	5.60
H	p-NO_2	160–162 dec.	56 (69)	$C_{20}H_{18}O_6N_4S$	54.29	54.23	4.10	4.13
CH_3	o-Br	124.5–126.5	53 (83)	$C_{21}H_{20}N_2SO_2Br_2$	48.10	48.22	3.85	3.61

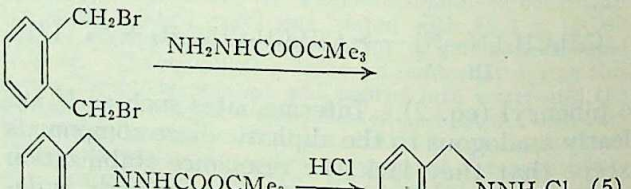
[a] Nitromethane was used as recrystallization solvent for all of the hydrazides. [b] 1,1-Bis-(o-bromobenzyl)-hydrazine was prepared by the method of Kenner and Wilson, ref. 6. [c] Yield of crude product is given in parentheses. [d] Alkaline degradation of the sulfohydrazides appeared to proceed equally as well with 5% as with 20% aqueous alkali. With the p-bromo and p-methoxy derivatives use of the more concentrated alkali caused separation of a solid, presumably the sodium sulfinate, which hindered further reaction.

Nitrogen elimination and coupling of benzyl groups also proceeds readily with the sulfonyl derivatives of 1,1-bis-(p-nitrobenzyl)- and 1,1-bis-(o-bromobenzyl)-hydrazine. By utilizing the cyclic hydrazide, 1-p-toluenesulfonamido-2,7-dihydro-3,4,5,7-dibenzazepine, 9,10-dihydrophenanthrene may be obtained in 95% yield (final step).[14] The synthetic usefulness of this reaction has been reported previously.[2] As yet no non-benzyl 1,1-disubstituted hydrazines have been found to undergo the reaction.

A brief study has been made of the effect of substitution in the benzenesulfonyl moiety on the decomposition–rearrangement since ease of loss of the benzenesulfinate anion might be expected to parallel the acidity of the corresponding sulfinic acid.[15,16] No gross differences were observed in the decomposition when 1,1-dibenzyl-2-p-bromo-, p-fluoro- or p-methoxybenzenesulfonhydrazides were compared with the unsubstituted compound. However, a marked effect was observed in the case of the o- and p-nitrobenzenesulfonhydrazides. When the reaction between p-nitrobenzenesulfonyl chloride and 1,1-bis-(p-nitrobenzyl)-hydrazine was carried out at ice-bath temperatures an unstable solid was obtained which decomposed with gaseous evolution on repeated crystallization yielding 4,4′-dinitrobibenzyl. A nitro-substituted hydrazide was isolated in a state of analytical purity by reaction of o-nitrobenzenesulfonyl chloride with 1,1-dibenzylhydrazine. Addition of either p- or o-nitrobenzenesulfonyl chloride to 1,1-dibenzylhydrazine at room temperature in the presence of triethylamine resulted in immediate gas evolution and direct formation of bibenzyl (55 and 16.5%, respectively).

Trichloromethanesulfonyl chloride similarly converted, 1,1-bis-(p-nitrobenzyl)-hydrazine directly to the bibenzyl (25–35% yield) and operation at low temperatures did not serve to yield an intermediate hydrazide.[17] For general synthetic work the p-toluenesulfonyl derivatives are preferred since these usually crystallize more readily than the benzenesulfonyl compounds.

The 1,1-disubstituted hydrazines have in general been prepared by alkylation of hydrazine or substituted hydrazines. Because of the possibility of polysubstitution, it has been found convenient in some cases to employ t-butyl carbazate in place of hydrazine. For example, N-t-butyloxycarbonyl-aminodihydroisoindole was prepared readily from α,α'-dibromo-o-xylene and t-butyl carbazate in 57% yield (eq. 5) whereas N-aminodihydroisoindole could not be isolated from the reaction of the dibromide and hydrazine hydrate or free hydrazine although a variety of experimental procedures were examined; resins appeared to be formed. Removal of the carbo-t-butoxy group occurred in a few minutes when the carbazate was added to concentrated hydrochloric acid. The use of the t-butyl compound proved decidedly superior to the use of benzyl carbazate,[18] both from the point of view of the initial condensation and the subsequent cleavage to the N-amino compound.[19]



(5)

which should be considered. Work is underway by which we hope to distinguish between these two processes. It also has been suggested [F. Raschig, *Z. angew. Chem.*, **23**, 972 (1910)] that benzenesulfonhydrazide itself undergoes β-elimination of benzenesulfinic acid under alkaline conditions yielding diimide which then undergoes decomposition to equimolar amounts of nitrogen and hydrogen.

A variety of other reactions have been postulated to yield diimide as an intermediate followed by subsequent decomposition to (a) nitrogen and hydrazine and (b) ammonia and hydrazoic acid [A. Angeli and Z. Jolles, *Ber.*, **62**, 2099 (1929); F. O. Rice and M. Freamo, THIS JOURNAL, **73**, 5529 (1951), **75**, 548 (1953); R. E. Kirk and A. W. Browne, *ibid.*, **50**, 337 (1928); J. Thiele, *Ann.*, **271**, 127 (1892)]. Conclusive evidence for the occurrence of diimide in any of these reactions is not available and the contradictory results suggest that other intermediates may be involved.

(14) Reference 2; experimental details are included in the present paper.

(15) Hydrazides which have been prepared but are not covered in the Experimental section are listed in Table I. The method of preparation followed that given for 1,1-dibenzyl-2-benzenesulfonhydrazide.

(16) The acidity constants of only a few benzenesulfinic acids have been determined. The unsubstituted compound has an ionization constant of approximately 3×10^{-2} [R. R. Coats and D. T. Gibson, *J. Chem. Soc.*, 442 (1940)].

(17) This reaction may proceed not through the hydrazide but rather by virtue of the oxidizing properties associated with "positive halogen" compounds. According to M. Battegay and W. Kern [*Bull. soc. chim. France*, **41**, 34 (1927)] this chloride acts as an oxidizing agent even toward ammonia and other amines. Recently trifluoromethanesulfonyl chloride has been prepared and found to react normally with amines [T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 173 (1956); R. N. Haszeldine and J. M. Kidd, *ibid.*, 2901 (1955); 4228 (1954)]. This compound was not available at the time of our work although trifluoromethanesulfonhydrazides would be of considerable interest since the corresponding sulfinic acid would undoubtedly be comparable to a mineral acid in strength.

(18) See the Experimental section.

(19) Mercuric oxide oxidation of N-aminodihydroisoindole as well as alkaline degradation of the corresponding p-toluenesulfonhydrazide will be the subject of a future communication.

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In this and the previous paper[3] the very conveniently removed carbo-*t*-butoxy group[20] has been introduced indirectly by means of isocyanate or carbazate reactions. However, it was recorded[3] that *t*-butyl hydrazodiformate could be obtained through use of a crude sample of *t*-butyl azidoformate.[21] In view of the relative instability of *t*-butyl chloroformate and the lack of knowledge concerning the acylating power of azidoformates, representative amino compounds have been treated with the azide, which has now been obtained pure by vacuum distillation. The azide reacts readily with aqueous ammonia, hydrazine, phenylhydrazine, *t*-butyl carbazate and benzylamine yielding the expected carbamates. The reaction with aniline is more sluggish, requiring about two weeks standing in pyridine in order to give a 50–60% conversion to the carbanilate. These results suggest that the azide will be generally useful for the acylation of amino derivatives which are at least as basic as aniline. Attempted acylation of acetamide under the conditions described for aniline gave no isolable acylation product. We have not examined the acylation products of amino acids or their esters although these probably would be useful in peptide synthesis. No studies in these areas are contemplated.

$$Me_3COCON_3 \xrightarrow{RNH_2} RNHCOOCMe_3$$

Experimental[22,23]

1,1-Dibenzyl-2-benzenesulfonhydrazide.[1a]—A solution of 10.6 g. of 1,1-dibenzylhydrazine in 40 ml. of dimethylformamide and 6.95 ml. of triethylamine was cooled in an ice-bath and treated dropwise with 6.4 ml. of benzenesulfonyl chloride. After the mixture had stood for 15–20 min. it was diluted with water and acidified with hydrochloric acid. The oil which separated solidified in a few minutes and was dried prior to recrystallization from nitromethane which gave 13.2 g. (75%) of small yellowish needles, m.p. 138–140° dec. For analysis, see ref. 2.

An attempt to prepare this compound by the action of benzyl chloride on benzenesulfonhydrazide in the presence of triethylamine in hot dimethylformamide gave an alkali-stable solid which was recrystallized from nitromethane, m.p. 149–150.5°. This appeared to be benzyl phenyl sulfone (lit.[24] m.p. 148°) as would be expected if the unsubstituted hydrazine were first converted to the triethylamine salt of benzenesulfinic acid. The yield was 70–80%.

Anal. Calcd. for $C_{13}H_{12}SO_2$: C, 67.24; H, 5.18. Found: C, 67.40; H, 4.98.

Alkaline Decomposition of 1,1-Dibenzyl-2-benzenesulfonhydrazide.[1a]—A solution of 25 ml. of 20% sodium hydroxide was warmed to 70–80° and 5 g. of 1,1-dibenzyl-2-benzenesulfonhydrazide was added in 2–3 portions. When the evolution of nitrogen slowed down the mixture was warmed to 90° for a few minutes until the evolution stopped. The mixture was diluted with 75 ml. of water and cooled whereupon the oil solidified and was filtered and recrystallized from methanol which yielded 2.2 g. (85%) of tiny white crystals, m.p. 51–52.5°. A second recrystallization from ethanol raised the melting point to 51.5–53.5°. A mixed melting point with an authentic sample of bibenzyl showed no depression. The 1,3,5-trinitrobenzene complex melted at 100–102° (lit.[25] m.p. 102°). From the aqueous alkaline filtrate after filtration of the bibenzyl there was isolated a crystalline white solid, m.p. 80–83° (lit.[26] m.p. of benzenesulfinic acid 85°).

1,1-Dibenzyl-2-*o*-nitrobenzenesulfonhydrazide.[1a]—A solution of 2.21 g. of 1,1-dibenzylhydrazine in 10 ml. of dimethylformamide and 1.39 ml. of triethylamine was cooled in an ice-bath and a similarly cooled solution of 2.22 g. of *o*-nitrobenzenesulfonyl chloride[27] in 2.5 ml. of dimethylformamide was added dropwise. After allowing the mixture to stand for four hours, 50 ml. of water was added and the resulting mixture stored in an ice-box for five days whereupon partial solidification occurred and was completed by trituration with ethanol. Recrystallization from methanol yielded 2.2 g. (55.4%) of yellow solid which softened at 88° and melted at 91–92° dec. After three further recrystallizations from methanol the powder softened at 92° and had m.p. 95–97° dec.

Anal. Calcd. for $C_{20}H_{19}N_3O_4S$: C, 60.44; H, 4.82. Found: C, 60.30; H, 4.99.

The hydrazide evolved gas on contact with aqueous sodium hydroxide at room temperature or by heating alone in solvents such as dimethylformamide. A similar reaction was run with *p*-nitrobenzenesulfonyl chloride but the crude hydrazide (m.p. 88–92° dec.) was decomposed on attempted recrystallization from methyl ethyl ketone.

1,1-Bis-(*p*-nitrobenzyl)-hydrazine.[1a]—A modification of the method of Busch and Weiss[6] was used. A solution of 35 g. of α-chloro-*p*-nitrotoluene and 4.6 g. of 64% hydrazine in 250 ml. of warm ethanol was treated all at once with 37.8 ml. of triethylamine. A solid began to precipitate after two hours and was filtered after two days standing. The crude product amounted to 20 g. (66.3%), m.p. 115–117°. Recrystallization from nitromethane gave 12 g. (39.8%) of tiny bright yellow crystals, m.p. 135–137° (lit.[6] m.p. 137–138°).

Thermal Decomposition of 1,1-Bis-(*p*-nitrobenzyl)-2-methanesulfonhydrazide.[1a]—The hydrazide (crude, 79.5%, m.p. 139–149°) was prepared as given for the dibenzyl compound and recrystallized from nitromethane which gave tiny yellow crystals, m.p. 154–155° dec., yield 58%.

Anal. Calcd. for $C_{15}H_{16}N_4SO_6$: C, 47.36; H, 4.24. Found: C, 47.48; H, 4.46.

Heating of this hydrazide for 1–2 min. at 145–150° in ethylene glycol gave 4,4′-dinitrobibenzyl (70%), m.p. 182–184° (lit.[6] m.p. 179°). Treatment of the corresponding benzenesulfonhydrazide with 20% aqueous sodium hydroxide gave only 40% of the bibenzyl, possibly because of decomposition due to the nitro groups.

Reaction between 1,1-Dibenzylhydrazine and *p*-Nitrobenzenesulfonyl Chloride.[1a]—A solution of 2.12 g. of 1,1-dibenzylhydrazine in 10 ml. of dimethylformamide and 2.8 ml. of triethylamine was treated over a period of 3–4 minutes with 2.2 g. of *p*-nitrobenzenesulfonyl chloride (Eastman Kodak Co.) while allowing the reaction mixture to warm up spontaneously. The mixture was then held at a temperature just below its boiling point for 5 minutes, diluted with 250 ml. of water, acidified with phosphoric acid and steam-distilled. The yield of bibenzyl collected in 1 liter of distillate was 1.0 g. (54.9%), m.p. 50–51°. The same procedure applied to *o*-nitrobenzenesulfonyl chloride gave only 16.5% of bibenzyl.

(20) Observations to be published shortly in coöperation with Mr. Paul J. Crowley indicate that a wide spectrum of protective groups of the carboalkoxy and thiocarboalkoxy types is available which can be cleaved selectively under anhydrous conditions by acids of varying strengths.

(21) Repetition of the acylation of *t*-butyl carbazate using a distilled sample of the azide led to the isolation (80%) of a white solid, m.p. 124.5–125.5° (see Experimental section), which had the correct analysis for the expected hydrazo compound. The compound previously obtained, m.p. 103–105°, which also gave a correct analysis, has not been obtained since. The compound, m.p. 124.5–125.5°, was characterized by N-bromosuccinimide oxidation to the azo derivative and reconversion of the latter by reduction with hydrazine to the hydrazide. Unfortunately at the time of preparation of the compound m.p. 124.5–125.5°, none of the lower melting substance was available for direct comparison although it was noted that an attempt to oxidize the compound m.p. 103–105°, by exactly the same procedure used for the higher melting compound was not successful.

(22) All boiling and melting points are uncorrected.

(23) Analyses are by Geller Laboratories, Hackensack, N. J., and Drs. Weiler and Strauss, Oxford, England.

(24) E. Knoevenagel, *Ber.*, **21**, 1349 (1888).

(25) J. J. Sudborough, *J. Chem. Soc.*, **109**, 1344 (1916).

(26) S. Krishna and H. Singh, THIS JOURNAL, **50**, 792 (1928).

(27) H. E. Fierz, E. Schlitter and H. Waldman, *Helv. Chim. Acta*, **12**, 663 (1929).

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Preparation of N-(*t*-Butyloxycarbonylamino)-dihydroisoindole.[1b]—A solution of 39.6 g. of *o*-xylylene dibromide[28] and 19.8 g. of *t*-butyl carbazate in 100 ml. of dimethylformamide was warmed to 50° and 41.7 ml. of triethylamine was added during 5–8 minutes while maintaining the temperature at 50–60° by slight tap-water cooling, if necessary. After complete addition the mixture was allowed to stand at room temperature for three hours and diluted with water to a final volume of 400 ml. After standing for one hour the amorphous white solid was filtered and on air-drying amounted to 31 g. (88.5%), m.p. 103–113° (previous softening at 98°). Recrystallization from the minimum amount of nitromethane gave 20 g. (56.9%) of tiny crystals, m.p. 115.5–117.5° (very slight previous softening at 110°). The analytical sample (from nitromethane) melted at 119–120°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74. Found: C, 66.35; H, 7.77.

Preparation of N-Aminodihydroisoindole Hydrochloride.[1b]—At room temperature 4.6 g. of N-(*t*-butyloxycarbonylamino)-dihydroisoindole was added during 1–2 minutes to 6 ml. of concentrated hydrochloric acid (d. 1.18). After standing for one hour the mixture, from which the crystalline hydrochloride had begun to separate, was evaporated with a water aspirator (17 mm.) from a water-bath (65–70°) until the residue was dry (1.5–2 hours). The crystalline hydrochloride (3.32 g., 62.6%, m.p. 150–180°) was washed onto a funnel with ether and recrystallized twice by solution in the minimum amount of hot ethanol followed by precipitation with ether: I, amount 2.77 g. (52.3%), m.p. 185–195° after previous softening at 160°; II, amount 2.55 g. (48%), m.p. 203–205.5° (lit.[29] m.p. 190–194°). The benzal derivative melted at 129.5–131° (lit.[29] m.p. 127–129°).

N-Benzyloxycarbonylaminodihydroisoindole.[1b]—This compound was obtained as indicated above for the corresponding *t*-butyl derivative by substituting benzyl carbazate[30] for *t*-butyl carbazate except that after addition of the triethylamine the mixture was heated for two hours on a steam-bath prior to precipitation with water. The product, which was difficult to purify, was recrystallized from dimethylformamide and then nitromethane, yield 31%, m.p. 134–135°.

Anal. Calcd. for $C_{16}H_{16}O_2N_2$: C, 71.62; H, 6.01. Found: C, 71.52; H, 5.84.

Cleavage by means of hydrogen bromide in nitromethane gave a tacky brown solid which was not easily purified although it gave a benzal derivative, m.p. 129.5–131°.

N-*p*-Toluenesulfonamidodihydroisoindole.[1b]—A solution of 1.35 g. of the hydrochloride of N-aminodihydroisoindole in 5 ml. of warm dimethylformamide was treated with 1.4 ml. of triethylamine and the resulting mixture cooled in an ice-bath and treated during 1–2 minutes with 0.95 g. of *p*-toluenesulfonyl chloride. After 15 minutes standing in the ice-bath, dilution with water gave a tan-colored solid which was recrystallized at once by solution in hot acetone and precipitation with water. The yield was 1.3 g. (67%), m.p. 130–132° dec. (previous darkening at 126°). A second recrystallization in the same way gave 0.9 g. (46.4%) of yellow crystals, m.p. 135–136° dec. The analytical sample, m.p. 136–138° dec., was recrystallized from acetone. Recrystallization from higher-boiling solvents caused considerable decomposition.

Anal. Calcd. for $C_{15}H_{16}N_2SO_2$: C, 62.47; H, 5.59. Found: C, 62.50; H, 5.54.

1-Amino-2,7-dihydro-3,4,5,7-dibenzazepine Hydrochloride.[1b]—*o*-Bitolyl was prepared and converted to *o,o'*-bis-(bromomethyl)-biphenyl according to the procedures of Wenner.[31] The *m*-tolidine used was a commercial sample[32] of a salt having "54% contained amine." A warm solution (50–60°) of 4.15 g. of *o,o'*-bis-(bromomethyl)-biphenyl and 1.61 g. of *t*-butyl carbazate in 10 ml. of dimethylformamide was treated slowly (2–3 minutes) with 3.42 ml. of triethylamine. After standing for 3–4 hours the solution was diluted with water and the oily semi-solid extracted with methylene chloride. Removal of solvent from the dried ($MgSO_4$) solution by means of a water aspirator yielded an oil which would not crystallize and was cleaved by addition of 10 ml. of concd. hydrochloric acid. The remainder of the procedure followed that given for the corresponding dihydroisoindole. The crude hydrochloride, after one precipitation from ethanol by means of ether, amounted to 1.8 g. (60%), m.p. 213–220° A second precipitation gave 1.5 g. (50%), m.p. 226–228°. The analytical sample[2] was recrystallized from nitromethane–ethanol (1:1), m.p. 230–231°.

1-*p*-Toluenesulfonamido-2,7-dihydro-3,4,5,7-dibenzazepine.[1b]—This derivative was prepared as indicated for the corresponding dihydroisoindole compound. The yield of pure hydrazide, m.p. 149.5–151.5° dec., recrystallized from ethanol–nitromethane (2:1), was 50%. For analysis, see ref. 2.

9,10-Dihydrophenanthrene.[1b]—The azepine described directly above was decomposed as given for the 1,1-dibenzyl compound. The crude product (m.p. 33–35°, 94.5%) was recrystallized from methanol, yield 67.5%, m.p. 34.5–35.5° (lit.[33] m.p. 34.5–35°).

***t*-Butyl Azidoformate.**[1c]—*t*-Butyl phenyl carbonate was prepared as indicated previously[3] except that tap-water cooling of the reaction mixture was dispensed with, the acid chloride being added at a rate such that the temperature remained between 38–41°. *t*-Butyl carbazate was prepared in the manner previously reported[3] although the yield was 89–94% rather than 68.3% as previously indicated. Conversion of the carbazate to the azide followed the earlier method except that the water-washed, $NaHCO_3$-washed ether extracts were dried (magnesium sulfate) and the solvent removed from a water-bath at 40–45° with a water aspirator pressure of 140–150° mm. The azide was then distilled by raising the bath temperature to 90° and lowering the pressure to 70 mm. where the azide collected as a water-white liquid, b.p. 73–74° (70 mm.), yield 80%.[34]

Anal.[35] Calcd. for $C_5H_9N_3O_2$: C, 41.95; H, 6.34. Found: C, 41.90; H, 6.29.

***t*-Butyl 2-Phenylcarbazate.**[1c]—A mixture of 2.86 g. of *t*-butyl azidoformate, 2.16 g. of phenylhydrazine, 2.78 ml. of triethylamine and 5 ml. of water was placed on a continuous shaking machine for 40 hours. Filtration gave 3.2 g. (80.4%) of yellow-orange solid which was washed with water and air-dried, m.p. 85–91°. Recrystallization from ligroin (60–90°) gave 2.75 g. (69.1%) of cream-colored crystals, m.p. 91–93°. The analytical sample, recrystallized from the same solvent, melted at 92–93.5°.

Anal. Calcd. for $C_{11}H_{16}O_2N_2$: C, 63.44; H, 7.75. Found: C, 63.56; H, 7.56.

Other Acylations Using *t*-Butyl Azidoformate.[1c]—*t*-Butyl 2-phenylcarbazate also was prepared by allowing a solution of the reactants in methylene chloride to stand overnight, although the product was less easily purified (yield 40–50%). *t*-Butyl carbamate[36] was prepared by allowing the azide to stand in contact with concd. aqueous ammonia for 16 hours with occasional shaking. The yield was 80%, m.p. 108–109.5° (1:1, 60–90° ligroin–benzene). Hydrazine (64%) converted the azide back to *t*-butyl carbazate with spontaneous warming (yield 83.3%). Acylation of benzylamine occurred with spontaneous warming when 2.86 g. of the azide, 4.28 g. of the amine and 5 ml. of pyridine were mixed and allowed to stand overnight. Precipitation with water gave 3.8 g. (91.8%) of white solid, m.p. 54–57°. Recrystallization from ligroin (b.p. 60–90°) gave 3.5 g. (84.6%) of ***t*-butyl N-benzylcarbamate**, m.p. 57–58°.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27. Found: C, 69.30; H, 8.20.

Acylation of aniline by means of the azide was more difficult to achieve than that of more basic amino compounds. The method used for the acylation of phenylhydrazine gave

(28) A. C. Cope and S. W. Fenton, THIS JOURNAL, **73**, 1668 (1951).
(29) K. Frankel, *Ber.*, **33**, 2808 (1900).
(30) N. Rabjohn, THIS JOURNAL, **70**, 240 (1948).
(31) W. Wenner, *J. Org. Chem.*, **17**, 523 (1952).
(32) We wish to acknowledge a generous gift of this material from the Carwin Co., North Haven, Conn.
(33) G. Schroeter, H. Muller and J. Y. S. Huang, *Ber.*, **62**, 649 (1929).
(34) The azide should be handled with adequate ventilation. Careless handling of the azide was always accompanied by development of a painful throbbing headache which, however, disappeared within several hours. In large doses the azide also affects the nasal passages in a manner similar to the action of the common cold.
(35) Prepared by Mr. C. A. Giza.
(36) A. R. Choppin and J. W. Rogers, THIS JOURNAL, **70**, 2967 (1948).

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only a trace of *t*-butyl carbanilate, m.p. 135–137°. By allowing equimolar amounts of the azide and aniline to stand in pyridine solution for two weeks followed by precipitation with water, a 50–60% yield, m.p. 135–137°, was obtained (lit.[36] m.p. 136.3–136.5).

t-Butyl Hydrazodiformate[1c,21]—A solution of 2.86 g. of distilled *t*-butyl azidoformate, 2.64 g. of *t*-butyl carbazate in 6 ml. of pyridine was allowed to stand for one week (if allowed to stand for two weeks the yield was only 3–5% greater) and then diluted with 75 ml. of water. The snow-white solid which precipitated amounted to 3.7 g. (80.1%), m.p. 124–126°. The analytical sample was recrystallized from ligroin (60–90°)–benzene (1:1) as tiny needles, m.p. 124–125.5°.

Anal. Calcd. for $C_{10}H_{20}O_4N_2$: C, 51.71; H, 8.70. Found: C, 52.00; H, 8.77.

AMHERST, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Mechanism of Trimethylene Oxide Formation from 3-Chloropropyl Acetate

BY DONALD C. DITTMER, WALTER R. HERTLER AND HERBERT WINICOV

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Evidence has been obtained that the better yields of trimethylene oxide from 3-chloropropyl acetate than from 3-chloropropanol may be caused by a protective effect of the acetate group and not by a fundamentally different mechanism. Oxide prepared from carbonyl O^{18}-labeled ester contained no excess O^{18}; this result rules out any mechanism for trimethylene oxide formation in which the two acetate oxygens are equivalent. Trimethylsilyl 3-chloropropyl ether gave as high a yield of oxide as the acetate, and 3-chloropropyl thiolacetate gave only trimethylene sulfide.

Yields of trimethylene oxide obtained by treatment of 3-chloropropyl acetate with strong base have been reported to be much greater than yields from 3-chloropropanol.[1] A similar result has been reported for the preparation of ethylene oxide from 2-chloroethyl acetate.[2]

$$ROCH_2CH_2CH_2Cl \xrightarrow{OH^\ominus} \begin{matrix} CH_2 & CH_2 \\ | & | \\ CH_2 & O \end{matrix} \qquad (1)$$

R = H–, CH_3CO–

Since in the concentrated base used the acetate presumably would be hydrolyzed to the same chlorohydrin anion, $^\ominus OCH_2CH_2CH_2Cl$, as the one formed from 3-chloropropanol, the yields of trimethylene oxide, if they proceeded from this alkoxide, would not be expected to be as different as they are between acetate and chlorohydrin.

To explain the disparity in yields between chlorohydrin and chloroacetate, a protective effect of the acetate group or a different mechanism may be invoked. The chloroacetate may yield the chlorohydrin anion at a slower rate than it is produced from the chlorohydrin. Since the concentration of alkoxide from chloroacetate at any time would be smaller than from chlorohydrin, conditions might be more favorable for intramolecular cyclization than for intermolecular reaction which would produce a polymeric ether. In other types of ring closure, high dilution of the reactants is necessary to prevent intermolecular reactions since the extent of intermolecular reaction depends on the concentration of the reactants while that of the intramolecular reaction does not.[3]

$$^\ominus OCH_2CH_2CH_2Cl \longrightarrow (OCH_2CH_2CH_2)_x \qquad (2)$$

Indeed, a linear polymeric ether, $(C_3H_6O)_x$, has been isolated as a by-product in the preparation of trimethylene oxide from 3-chloropropanol.[4] Excellent yields (70–80%) of 3,3-dichloromethyloxetane have been reported from trichloropentaerythritol and potassium hydroxide.[5] Here, the intermolecular reaction involves a displacement reaction on a neopentyl-type system which would be expected to be very slow.

$$(ClCH_2)_3CCH_2OH \xrightarrow{OH^\ominus} \begin{matrix} (CH_2Cl)_2 & \\ | & \\ C & CH_2 \\ | & | \\ CH_2 & O \end{matrix} \qquad (3)$$

70–80%

Other side products from 3-chloropropanol were said to be allyl alcohol and allyl chloride.[1a] It is not expected that acetylation of the hydroxyl group would have much effect on these olefin-producing side reactions.

If the production of trimethylene oxide from 3-chloropropyl acetate involved a different mechanism other than the straightforward intramolecular displacement of chloride ion by the alkoxide part of the molecule,[6] higher yields of oxide might be expected if the free energy of activation for the new mechanism were less than that for the old

$$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2CH_2Cl \xrightarrow{OH^\ominus} CH_3\overset{O^\ominus}{\overset{|}{C}}OCH_2CH_2CH_2Cl$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OH$$

$$\xrightarrow{OH^\ominus} \xrightarrow{-Cl^\ominus} CH_3C\begin{matrix} O-CH_2 \\ O-CH_2 \end{matrix}CH_2 \quad (I) \xrightarrow{OH^\ominus} CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2CH_2O^\ominus \qquad (4)$$

$$\xrightarrow{-CH_3COO^\ominus} \begin{matrix} CH_2 & CH_2 \\ | & | \\ O & CH_2 \end{matrix}$$

(1) (a) C. G. Derick and D. W. Bissell, THIS JOURNAL, **38**, 2478 (1916); (b) C. R. Noller, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 835.

(2) E. Demole, *Ann.*, **173**, 125 (1874).

(3) P. Ruggli, *ibid.*, **392**, 92 (1912); G. M. Bennett, *Trans. Faraday Soc.*, **37**, 794 (1941); K. Ziegler, H. Eberle and H. Ohlinger, *Ann.*, **504**, 94 (1933).

(4) M. Reboul, *Ann. chim.*, [5] **14**, 497 (1878).

(5) F. Govaert and M. Beyaert, *Natuur. Tijdschr.*, **22**, 73 (1940); *C. A.*, **37**, 3054 (1943).

(6) S. Winstein and H. J. Lucas, THIS JOURNAL, **61**, 1576 (1939).

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mechanism, thereby reducing the importance of side reactions. A possibility exists that the carbonyl group of the ester could displace chloride ion to give an intermediate, I, which decomposes to trimethylene oxide.

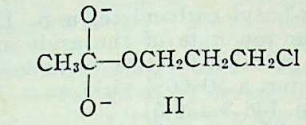
The attack by hydroxide ion on the carbonyl carbon may be concerted with the displacement of chloride ion by the carbonyl oxygen, intermediate I being formed directly. The intermediate I might go to trimethylene oxide by a concerted elimination of acetate with ring closure.

The displacement of chloride ion by the oxygen anion derived from a carbonyl group has an analogy in the Darzens glycidic ester reaction.[7] Participation of acetate carbonyl in displacements of neighboring groups is well known.[8] A displacement of bromide ion by an ester carbonyl oxygen has been suggested to occur in the pyrolysis of γ-bromoesters.[9] A cyclic *ortho* ester analogous to I has been prepared from the monotrichloroacetate of ethylene glycol,[10] and a similar *ortho* ester has been suggested as an intermediate in the preparation of *trans*-2-chlorocyclohexanol from *cis*-1,2-diacetoxycyclohexane.[11] The reaction of the acetate of 3-bromo-2,2-dimethyl-1-propanol with potassium iodide in acetone is 38 times faster than the reaction of neopentyl bromide which indicates a participation by the acetoxy group.[12]

Results

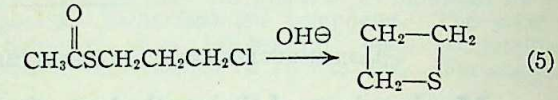
The possibility of a different mechanism of trimethylene oxide formation from 3-chloropropyl acetate was investigated by preparing the oxide from carbonyl O^{18}-labeled 3-chloropropyl acetate which was made by hydrolysis of 3-chloropropyl iminoacetate with H_2O^{18}. If the reaction scheme 4 were correct, excess O^{18} should appear in the trimethylene oxide since in I the two oxygens are equivalent. No excess O^{18} was found in the trimethylene oxide. This result is apparent in Table II in the Experimental section.

Some loss of O^{18} from the ester might occur by the scheme proposed by Bender for ester hydrolysis.[13] The concentration of base used by Bender was 0.001–0.007 *M* while the concentration of base used in the preparation of trimethylene oxide was approximately 200 *M*. The formation of the conjugate acid of the ester-hydroxide ion adduct, $CH_3C(OH)_2OR$, as proposed by Bender would seem to be rather unlikely in such strong base, although the formation of the dianion II is a possibility. Nevertheless, if the dianion were formed, at least 25% of the O^{18} in the original ester should be found in the trimethylene oxide if the latter were formed as shown in equation 4.



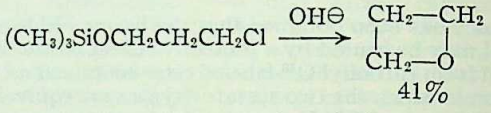
II

Only trimethylene sulfide could be isolated from the reaction of 3-chloropropyl thiolacetate with base. Trimethylene sulfide has been prepared in the same way by Bordwell and Hewett.[14]



(5)

Trimethylsilyl 3-chloropropyl ether on treatment with potassium hydroxide gave a yield of trimethylene oxide comparable to the yields from 3-chloropropyl acetate.



41%

Attempts to prepare trimethylene oxide from 3-hydroxypropyl acetate, 3-hydroxypropyl chloroacetate, 3-hydroxypropyl trichloroacetate and 3-hydroxypropyl *p*-toluenesulfonate were not successful.

Trimethylene oxide could be prepared in 24% yield from 3-chloropropyl chloroacetate and potassium hydroxide, but 3-chloropropyl trifluoroacetate and 3-chloropropyl trichloroacetate gave no oxide.

Discussion

The lack of evidence for participation of the ester carbonyl group of 3-chloropropyl acetate in the formation of trimethylene oxide seems to show that the effect of acetylation of chlorohydrins in improving yields of cyclic oxides is not to change the basic mechanism but possibly to minimize side reactions such as the intermolecular Williamson ether synthesis illustrated by equation 2. The fact that the trimethylsilyl ether of 3-chloropropanol gives about the same yield of trimethylene oxide as does the acetate implies that there is nothing special about the function of acetate.

With the silyl ether as with the acetate, the reaction with hydroxide to produce the chlorohydrin anion is slow in comparison with the abstraction of a proton from the chlorohydrin. This slow hydrolysis in both cases decreases the concentration of the anion so that, by this "dilution" effect, the cyclization to trimethylene oxide is favored at the expense of the intermolecular reaction.

Where the intermolecular reaction is hindered as in the reaction of trichloropentaerythritol with base, higher yields of oxide are observed.[5] However, a substituted chlorohydrin also may have a lower free energy of activation for ring closure than its unhindered analog.[15] Steric hindrance in intramolecular reactions has been said to be less than for intermolecular reactions.[16]

(7) M. S. Newman and J. B. Magerlein, "Organic Reactions," Vol. V, John Wiley and Sons, Inc. New York, N. Y., 1949, p. 413; M. Ballester and P. D. Bartlett, THIS JOURNAL, **75**, 2042 (1953).

(8) S. Winstein, H. V. Hess and R. E. Buckles, *ibid.*, **64**, 2780, 2787 (1942); S. Winstein and R. E. Buckles, *ibid.*, **65**, 613 (1943).

(9) J. Weinstock, *ibid.*, **78**, 4967 (1956).

(10) H. Meerwein and H. Sönke, *J. prakt. Chem.*, **137**, 295 (1933); H. Meerwein and H. Sönke, *Ber.*, **64**, 2375 (1931).

(11) R. Boschan and S. Winstein, THIS JOURNAL, **78**, 4921 (1956).

(12) C. R. Lindegren and S. Winstein, Abstracts of Papers, 123rd Meeting of the American Chemical Society, Los Angeles, Calif., March, 1953, p. 30M.

(13) M. L. Bender, THIS JOURNAL, **73**, 1626 (1951).

(14) F. G. Bordwell and W. A. Hewett, Abstracts of Papers, 126th Meeting of the American Chemical Society, New York, N. Y., September, 1954, p. 6-O.

(15) A. Streitwieser, Jr., *Chem. Revs.*, **56**, 683 (1956); E. Eliel in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 117–119.

(16) G. Baddeley, *Ann. Repts. on Prog. Chem., (Chem. Soc. London)*, **52**, 149 (1955).

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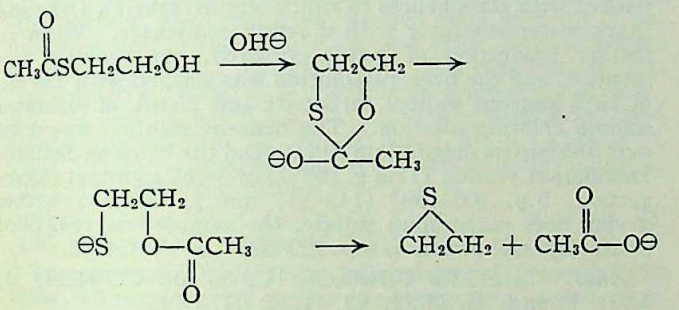
Another explanation for the higher yields from 3-chloropropyl acetate and from 3-chloropropyl trimethylsilyl ether is that the attack by hydroxide ion on the carbonyl carbon or on silicon is concerted with ring closure, there being no intermediates involved.

The synthesis of trimethylene sulfide in 24% yield from 3-chloropropyl thiolacetate and the absence of detectable trimethylene oxide did not necessarily rule out a cyclic intermediate, since in the intermediate it might be expected that the carbon–sulfur bond would break preferentially to the carbon–oxygen bond. Ethylene sulfide is prepared in 25% yield from the S-acetate of 2-mercaptoethanol by treatment with base.[17] The analogy to equation 4 is apparent.



Mono-*p*-toluenesulfonates of 1,2-glycols give good yields of epoxides on treatment with base.[18] Our finding that the mono-*p*-toluenesulfonate of 1,3-propanediol gave no trimethylene oxide on treatment with potassium hydroxide agrees with an earlier result.[19]

The failure of monoesters of trimethylene glycol to give trimethylene oxide does not necessarily rule out the mechanism of equation 4 since intermediate I could conceivably go directly to trimethylene oxide by a concerted process. The use of sodium to produce the alkoxides was not very satisfactory since there was evidence of reduction of the ester group.

Experimental

3-Chloropropanol was prepared according to Marvel and Calvery.[20]

3-Chloropropyl Iminoacetate Hydrochloride.—The procedure was based on that by McElvain and Schroeder.[21]

To a mixture of 94.5 g. (1.0 mole) of 3-chloropropanol, 42.2 g. (1.0 mole) of acetonitrile (Eastman Kodak Co. practical grade, redistilled and dried over Drierite) in 50 ml. of anhydrous ether and 5 ml. of reagent-grade chloroform, was added about 40 g. (1.1 moles) of anhydrous hydrogen chloride gas. The reaction mixture was placed in a refrigerator for 12 hr. after which a layer of about 25 ml. of anhydrous ether was placed carefully on top of the viscous solution. The iminoacetate hydrochloride precipitated after 2 to 4 more days in the refrigerator. The crystals were filtered rapidly by reduced pressure and dried in a desiccator over Drierite, potassium hydroxide and paraffin chips. The yield was 158 g. (0.9 mole, 90%), m.p. 75–77° dec. Infrared analysis (potassium bromide disk) showed characteristic bands at 1558 and 1635 cm.$^{-1}$. Ionic chloride was determined by the Volhard method.

Anal. Calcd. for $C_5H_{11}Cl_2NO$: ionic Cl, 20.64. Found: ionic Cl, 20.54.

3-Chloropropyl Acetate (Carbonyl-O^{18}-labeled).—The 3-chloropropyl iminoacetate hydrochloride (120 g., 0.7 mole) was dissolved in 25 g. (1.4 moles) of water containing greater than 1.4% O^{18} (Stuart Oxygen Co., 211 Bay St., San Francisco, Cal.). Heat was evolved and ammonium chloride precipitated. The flask was cooled under a cold water tap until heat was no longer evolved and then was warmed under a hot water tap for 15 to 20 minutes and allowed to stand for 4 hr. at room temperature. About 100 ml. of ether was added and the ammonium chloride removed by filtration and washed several times with ether. The combined ether solutions were dried over anhydrous magnesium sulfate for 24 hr. After the removal of the magnesium sulfate, the ether was evaporated and the crude 3-chloropropyl acetate was distilled through a 25-cm. column packed with glass helices to give 85.4 g. (0.62 mole, 88%) of the carbonyl-O^{18}-labeled ester.

The unlabeled ester was prepared in a similar manner except that ordinary water was used. It also was prepared from 3-chloropropanol and acetyl chloride.

Trimethylene Oxide.—The procedure of Noller was followed,[1b] in which the O^{18}-labeled 3-chloropropyl acetate was treated with hot potassium hydroxide. The trimethylene oxide was distilled as it was formed and was collected in a flask equipped with a Dry Ice condenser. The crude oxide was dried over potassium hydroxide and distilled through a small column to give 10 g. (38%) of material, b.p. 47–48°, $n^{25}D$ 1.3906. The oxide was dried over sodium metal and redistilled after removal of the sodium. Two fractional distillations of the oxide directly from sodium metal were carried out, followed by a final distillation, b.p. 47.0–47.2°, $n^{25}D$ 1.3896.

Unlabeled trimethylene oxide was prepared in a similar manner from unlabeled 3-chloropropyl acetate.

Mass Spectrometric Analyses.—Mass spectra of the labeled and unlabeled 3-chloropropyl acetates and samples of trimethylene oxide prepared from each were taken on a Consolidated model 21-101 (modified) mass spectrometer at an ionizing current of 10 amperes and an ionizing voltage of 70. Table I gives the abridged mass spectra of the labeled and unlabeled acetates and Table II of the trimethylene oxide from the respective acetates.

TABLE I

MASS SPECTRA OF CARBONYL-O^{18}-LABELED 3-CHLOROPROPYL ACETATE AND UNLABELED 3-CHLOROPROPYL ACETATE

Mass	Relative intensity[a] Unlabeled	Labeled	Probable fragment
61	100.0	100.0	$CH_3C(OH)_2^+$
63	3.0	4.3	$CH_3C(O^{18}H)OH^+$
73	48.8	48.0	$CH_3COOCH_2^+$
75	1.6	2.2	$CH_3CO^{18}OCH_2^+$
87	6.0	5.8	$CH_3COOCH_2CH_2^+$
89	0.07	0.14	$CH_3CO^{18}OCH_2CH_2^+$
93	12.2	12.2	$Cl^{35}CH_2CH_2CH_2O^+$
95	3.8	3.8	$Cl^{37}CH_2CH_2CH_2O^+$
	Normalized on Basis of Mass 93		
87	49.4	49.1	
88	2.3	2.3	
89	0.74	0.97	
90	0.08	0.11	
93	100.0	100.0	
95	32.5	32.7	
101	29.6	29.1	$CH_3COOCH_2CH_2CH_2^+$
103	0.26	0.45	$CH_2CO^{18}OCH_2CH_2CH_2^+$

[a] Normalized to intensity 100 for abundant peaks (61 and 93).

Estimation of Enrichment of Labeled 3-Chloropropyl Acetate.—The method is similar to that used by Long and Pritchard for propylene and isobutylene glycols.[22] They

(17) J. S. Harding, L. W. C. Miles and L. N. Owen, *Chemistry & Industry*, 887 (1951); L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 817 (1952); J. S. Harding and L. N. Owen, *ibid.*, 1528 (1954).

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(19) D. D. Reynolds and W. O. Kenyon, THIS JOURNAL, **72**, 1593 (1950).

(20) C. S. Marvel and H. O. Calvery, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 533.

(21) S. M. McElvain and J. P. Schroeder, THIS JOURNAL, **71**, 40 (1949).

(22) F. A. Long and J. G. Pritchard, *ibid.*, **78**, 2663 (1956).

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TABLE II

MASS SPECTRA OF TRIMETHYLENE OXIDE PREPARED FROM LABELED AND UNLABELED 3-CHLOROPROPYL ACETATES

Mass	Relative intensity[a] From unlabeled ester	From labeled ester	Probable fragment
42	2.4	2.4	$CH_2CH_2CH_2^+$
43	1.3	1.3	
52	0.25	0.24	
53	0.97	0.95	
55	1.3	1.3	
56	1.7	1.7	
57	17.6	17.6	$CH_2{=}CHCH_2O^+$
58	100.0	100.0	$CH_2CH_2CH_2O^+$
59	3.5	3.4	
60	0.26	0.26	$CH_2CH_2CH_2O^{18+}$

[a] Reference *a*, Table I.

were careful to use in their calculations only those peaks for which only one fragment could be written for the O^{16}-containing isotope and for which only the enriched species of the same fragment was possible for a mass number two units higher. Since the natural O^{18}/O^{16} ratio is 0.002 (0.2%) for a fragment containing only one oxygen, the ratio of the relative intensity of the mass number two units higher to the relative intensity of the mass number for this fragment should be 0.002. For a fragment containing two oxygen atoms the ratio would be 0.004, and for a fragment containing two oxygen atoms one of which is enriched to 1.4% in O^{18}, the ratio would be 0.016.

Since none of the presumed oxygen-containing fragments gave a ratio of 0.002 or 0.004 (with the exception of mass 103) but gave higher values, it is likely that these peaks are contaminated with other unknown fragments. If a constant amount of contamination by an unknown fragment or fragments is assumed in the peaks of mass $M + 2$, a rough estimate of the enrichment can be made as follows: Let

h = peak height of mass M for unenriched cmpd. due to single fragment
h' = peak height of mass M for enriched cmpd. due to a single fragment
h_2 = peak height of mass $M + 2$ for unenriched compound
h_2' = peak height of mass $M + 2$ for enriched compound
x = height of peak due to O^{18} fragment in h_2
x' = height of peak due to O^{18} fragment in h_2'
y = peak height due to unknown fragment (or combn. of fragments) in h_2
y' = peak height due to unknown fragment (or combn. of fragments) in h_2'

Consider a peak for which a fragment containing two oxygens can be written. Then

$$x + y = h_2$$
$$x' + y' = h_2'$$
$$y'/y = h'/h$$

Assume $x/h = 0.004$ and $x = 0.004h$

$$y = h_2 - 0.004h$$
$$y' = (h'/h)(h_2 - 0.004h)$$
$$x' = h_2' - ((h'/h)(h_2 - 0.004h))$$

Therefore, the O^{18}/O^{16} ratio is $x'/h' = h_2'/h' - h_2/h + 0.004$

This derivation is not completely satisfactory because it assumes that the mass peak heights of the fragments which contain O^{16} (unenriched) are uncontaminated by any other fragment. However, it seems likely that most of the height of the peak may be accounted for by the O^{16}-containing fragment. The results are given in Table III.

It seems likely that the enriched 3-chloropropyl acetate actually contains about 1.6 to 1.7% O^{18} which is the value to be expected from acetate prepared from water containing in excess of 1.4 atom per cent. O^{18}. The method of preparation of the enriched acetate is such that acetate should have the same enrichment in its carbonyl oxygen as the water used.

It is interesting to observe that the 93/95 ratio for 3-chloropropyl acetate is close to the natural ratio of 3 for Cl^{35}/Cl^{37}.

TABLE III

MASS RATIOS AND CALCULATED PERCENTAGE ENRICHMENT OF O^{18} IN 3-CHLOROPROPYL ACETATE

Mass ratios	O^{16} Acetate	O^{18} Acetate	Difference in ratios	Atom % O^{18}
63/61	0.030	0.043	0.013	1.7
75/73	.033	.046	.013	1.7
89/87	.012	.025	.013	1.7
	.014	.026	.012	1.6
	.015	.020	.005	0.9
103/101	.009	.015	.006	1.0
	.006	.018	.012	1.6
	.007	.014	.007	1.1

3-Chloropropyl Chloroacetate.—Chloroacetic acid (118.1 g., 1.25 moles), 3-chloropropanol (94.5 g., 1.0 mole), *p*-toluenesulfonic acid (1 g.) and 150 ml. of benzene were refluxed in a 500-ml. flask equipped with a 25-cm. column packed with glass helices to which was attached a Dean and Stark water-separator with a reflux condenser. When no further separation of water occurred, the reaction was stopped, and the benzene solution was washed with 120 ml. of 10% aqueous sodium carbonate and 25 ml. of saturated sodium chloride solution. The benzene solution was dried over anhydrous magnesium sulfate and the benzene distilled. Distillation yielded 117.8 g. (69%) of 3-chloropropyl chloroacetate, b.p. 166–169° (142–147 mm.). After a further drying over magnesium sulfate, the sample was redistilled at atmospheric pressure, b.p. 222–223°, $n^{25.4}D$ 1.4595.

Anal. Calcd. for $C_5H_8O_2Cl_2$: C, 35.10; Cl, 41.17; H, 4.71. Found: C, 35.22; Cl, 41.36; H, 4.74.

3-Chloropropyl trichloroacetate was prepared by the procedure used for 3-chloropropyl chloroacetate. The 3-chloropropyl trichloroacetate distilled at 69–70° (0.9 mm.), $n^{22.5}D$ 1.4773, $n^{20}D$ 1.4784 (lit.[23] b.p. 107° (8 mm.), 97.0–97.7 (3 mm.); $n^{15}D$ 1.4830, $n^{20}D$ 1.47985).

3-Chloropropyl Trifluoroacetate.—A variation of a general method of Burgoyne and Condon was used.[24] Trifluoroacetic acid (40 g., 0.36 mole), 3-chloropropanol (25.6 g., 0.27 mole) and chloroform (50 ml.) were distilled from a 250-ml. flask fitted with an addition funnel and a 25-cm. column packed with glass helices. The distillate was placed in an addition funnel where the aqueous layer was separated from the chloroform layer. The chloroform was allowed to run back into the distilling flask. In this way 30 g. (62%) of 3-chloropropyl trifluoroacetate was obtained, b.p. 143–144°, $n^{24}D$ 1.3700, $n^{25}D$ 1.3698. The ester was insoluble in water but soluble in chloroform, carbon tetrachloride and carbon disulfide. A further distillation gave a sample, b.p. 143.5–144.2°, $n^{25}D$ 1.3694, d^{20}_4 1.349. Infrared absorption spectra showed bands at 1786, 1400, 1347, 1225 and 1146–1170 cm.$^{-1}$. A yield of 82% was obtained by using doubled amounts of starting materials.

Anal. Calcd. for $C_5H_6O_2ClF_3$: C, 31.49; H, 3.15. Found: C, 31.60; H, 3.31.

Preparation of Trimethylene Oxide from 3-Chloropropyl Esters.—The procedure used for the preparation of trimethylene oxide from 3-chloropropyl acetate was followed.[1b]

Potassium hydroxide (90.6 g.), 3-chloropropyl chloroacetate (92.2 g., 0.54 mole) and water (8 ml.) were allowed to react. Trimethylene oxide (7.6 g., 24.3%) was obtained, b.p. 46–48°, $n^{26}D$ 1.3885. A higher boiling fraction (99°) gave a positive test with ceric nitrate reagent.[25] It may have been allyl alcohol.

When 3-chloropropyl trifluoroacetate was used, the temperature of the reaction mixture rose rapidly to 200°. No trimethylene oxide was isolated. The residue gave a positive ceric nitrate test.[25]

The reaction of 3-chloropropyl trichloroacetate with potassium hydroxide gave chloroform but no trimethylene oxide. The residue gave a positive ceric nitrate test.[25]

(23) C. W. Gayler and H. M. Waddle, THIS JOURNAL, **63**, 3358 (1941); M. H. Palomaa, E. J. Salmi and R. Korte, *Ber.*, **72**, 790 (1939).

(24) E. E. Burgoyne and F. E. Condon, THIS JOURNAL, **72**, 3276 (1950).

(25) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 90.

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3-Chloropropyl Trimethylsilyl Ether.—The procedure of Sprung and Nelson was followed.[26] Commercial grade trimethylchlorosilane (kindly donated by the General Electric Company) was purified by precipitation of excess hydrogen chloride with pyridine and distillation of the chlorosilane through a 25-cm. column packed with glass helices. This procedure was repeated, and the chlorosilane was stored with a small amount of pyridine.

Dry pyridine (55.0 g., 0.7 mole, Mallinckrodt reagent grade), 3-chloropropanol (57.5 g., 0.6 mole, dried over Drierite) were placed in a dry, 3-necked 500-ml. flask provided with a mechanical stirrer, thermometer and condenser. The flask was cooled to 10° in an ice-bath. Purified trimethylchlorosilane (74.5 g., 0.68 mole) was added slowly from a dropping funnel on top of the condenser while the reaction mixture was being stirred. The funnel was provided with a calcium chloride drying tube. After the addition, the stirrer was removed, and the reaction mixture was refluxed 15 minutes. Dilute hydrochloric acid was added to neutralize the excess pyridine, and the solution was extracted three times with one-half its volume of ether. The ether extracts were combined, washed twice with 0.1 *N* hydrochloric acid, twice with water and dried over anhydrous magnesium sulfate. After the ether was removed, distillation gave 56 g. (56%) of 3-chloropropyl trimethylsilyl ether, b.p. 141–146.5°, $n^{23.5}$D 1.4170. A further distillation gave a purer product, b.p. 53° (17–20 mm.), $n^{28.1}$D 1.4148, $d^{28.7}_4$ 0.931. Infrared analysis showed characteristic bands at 1253, 1176, 1105 and 846 cm.$^{-1}$.

Anal. Calcd. for $C_6H_{15}OClSi$: C, 43.17; H, 9.07; Cl, 21.27. Found: C, 43.32; H, 9.21; Cl, 21.47.

Trimethylene Oxide from 3-Chloropropyl Trimethylsilyl Ether.—The procedure used in the preparation of trimethylene oxide from 3-chloropropyl acetate was followed.[1b] The distillate from the reaction mixture containing trimethylene oxide and probably water, trimethylsilanol and hexamethyl disiloxane was dried over potassium hydroxide and distilled through a Vigreux column. The first fraction (to 61°) gave 9.5 g. of impure trimethylene oxide. This fraction was dried over sodium and distilled, after removal of the sodium, to give 7 g. (41%) of trimethylene oxide. A third fractionation gave 6 g. (35%) of the oxide which was distilled directly from sodium, b.p. 47–49°, n^{23}D 1.3910.

3-Hydroxypropyl acetate was prepared at first by the method of Bogert and Slocum from acetyl chloride and trimethylene glycol.[27] Distillation gave a fraction, b.p. 206–209°, n^{25}D 1.4191 (lit.[27] b.p. 202–203°).

Another preparation was from 95 g. (1.58 moles) of glacial acetic acid, 114 g. (1.5 moles) of trimethylene glycol (redistilled), 115 ml. of chloroform and 1 ml. of concentrated sulfuric acid which was refluxed, and the water was removed by a Dean and Stark separator. When 30 ml. of water and acetic acid had been separated, a third of the chloroform was distilled and the reaction mixture washed with a small amount of sodium bicarbonate solution. The mixture was distilled through a 25-cm. column packed with glass helices, and two fractions were collected: 24.2 g., b.p. 136–140° (95 mm.), and 72.8 g., b.p. 110–115° (25 mm.), n^{25}D 1.4175, d^{25}_4 1.026

A third preparation of 3-hydroxypropyl acetate was tried using an adaptation of the method of Meerwein and Sönke for preparing glycol monoesters.[10] Trimethylene glycol (76.1 g., 1 mole) was dissolved in 100 ml. of dioxane in a 500-ml. flask cooled in an ice-bath. Acetyl chloride (78.5 g., 1 mole) was added dropwise with stirring, and the mixture was refluxed for 2 hr. The dioxane was distilled at atmospheric pressure, and the residue was distilled under reduced pressure to give 63.8 g. (54%) of product, b.p. 105–115° (31 mm.), n^{24}D 1.4210.

3-Hydroxypropyl Chloroacetate.—Chloroacetyl chloride (103.7 g., 0.92 mole) in 20 ml. of dioxane was added to trimethylene glycol (68.5 g., 0.9 mole) in 80 ml. of dioxane in a 500-ml. flask immersed in an ice-bath. The mixture was refluxed for 3 hr., and, after removal of the dioxane and distillation through a 25-cm. column packed with glass helices, gave 46.8 g. (33.5%) of product, b.p. 95–112° (1.3–1.7 mm.), n^{23}D 1.4591.

3-Hydroxypropyl trichloroacetate was prepared by the method of Meerwein and Sönke[10] from trichloroacetyl chloride and trimethylene glycol. The trichloroacetyl chloride was prepared from trichloroacetic acid and phosphorus trichloride. The hydroxyester distilled at 98–115° (0.9–1.5 mm.), $n^{25.5}$D 1.4680.

3-Hydroxypropyl *p*-Toluenesulfonate.—Trimethylene glycol (128.2 g., 1.69 moles) was added to a stirred mixture of *p*-toluenesulfonyl chloride (160.5 g., 0.84 mole) in pyridine (133 g., 1.69 moles) in a 500-ml. flask immersed in a Dry Ice–acetone-bath. The addition was as fast as possible without causing a great rise in temperature. The reaction mixture was allowed to reach room temperature, and stirring was continued for 0.5 hr. The pyridine hydrochloride was removed by filtration, and the filtrate was poured into water to give an oil which was separated, washed with water, dilute hydrochloric acid and water again. The oil was dried over anhydrous magnesium sulfate. Distillation of the ester (74.2 g., 32%) at 1 mm. resulted in decomposition. Crystals of trimethylene glycol di-*p*-toluenesulfonate separated from the oil after standing, m.p. 92–93° (lit.[28] m.p. 93–94°).

Attempted Preparation of Trimethylene Oxide from Monoesters of Trimethylene Glycol.—No trimethylene oxide was obtained from 3-hydroxypropyl *p*-toluenesulfonate or 3-hydroxypropyl acetate on treatment with potassium hydroxide in the usual way[1b] or from 3-hydroxypropyl acetate, 3-hydroxypropyl chloroacetate, 3-hydroxypropyl trichloroacetate and 3-hydroxypropyl *p*-toluenesulfonate on treatment with sodium metal which was used in order to produce the alkoxide.

3-Chloropropyl thiolacetate was prepared by the method of Sjöberg[29] from allyl chloride and thiolacetic acid. The thiolester was obtained in 71% yield, b.p. 93–96° (20 mm.), n^{27}D 1.4910 (lit.[29] b.p. 83–84° (10 mm.), n^{20}D 1.4954).

Trimethylene Sulfide.—3-Chloropropyl thiolacetate (119 g., 0.78 mole) was added gradually to potassium hydroxide (131 g., 2.34 moles) and water (12 ml.) in the apparatus used for the preparation of trimethylene oxide.[1b] The temperature of the reaction mixture varied from 150 to 170°. The product which distilled from the reaction mixture at 77° was dried over Drierite and redistilled through a 25-cm. column packed with glass helices to give trimethylene sulfide (13.8 g., 23.8%), b.p. 94–94.5°, n^{25}D 1.5027. It was characterized as the dimethyl sulfonium iodide, m.p. 97–98°.[30] The infrared spectrum of the sample was identical with that obtained by other workers.[31] No trimethylene oxide could be isolated from the reaction.

Acknowledgments.—We wish to thank Dr. C. B. Euston, J. Sager and J. Bates and the Polychemical Department of E. I. du Pont de Nemours for the mass spectrometric analyses.

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(27) M. T. Bogert and E. M. Slocum, THIS JOURNAL, **46**, 763 (1924).
(28) G. A. C. Gough and H. King, *J. Chem. Soc.*, 2426 (1928).
(29) B. Sjöberg, *Ber.*, **74B**, 64 (1941).
(30) G. M. Bennett and A. L. Hock, *J. Chem. Soc.*, 2496 (1927).
(31) D. W. Scott, H. L. Finke, W. N. Hubbard, J. P. McCullough, C. Katz, M. E. Gross, J. F. Messerly, R. E. Pennington and G. Waddington, THIS JOURNAL, **75**, 2795 (1953).

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[CONTRIBUTION FROM THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Rearrangement of Ketones in Acid Media[1]

BY HARRY D. ZOOK, WARREN E. SMITH AND JANICE L. GREENE

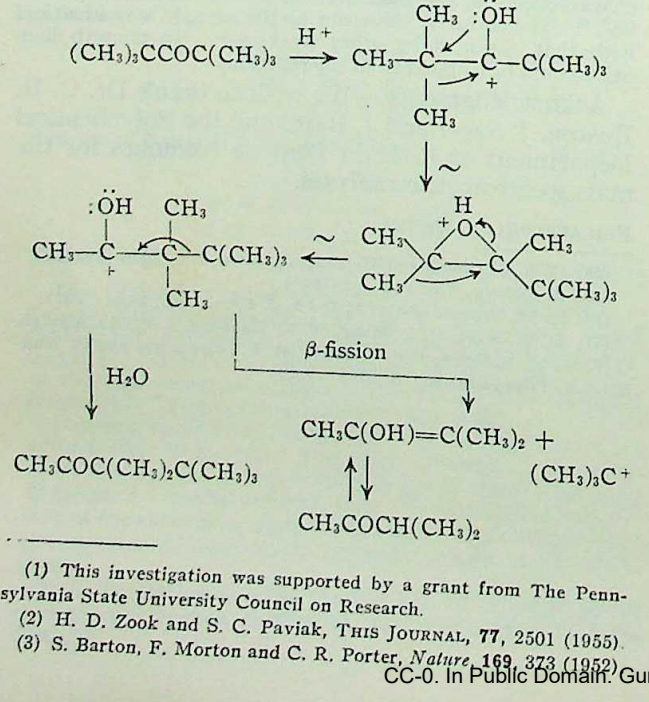
RECEIVED FEBRUARY 22, 1957

Ketones with two alkyl or two phenyl groups in the α-position rearrange to isomeric ketones in 83–97% sulfuric acid. A single product or an equilibrium mixture of a single product and the original ketone is obtained. The positions of the equilibria are qualitatively in accord with resonance and hyperconjugation theories. Methyl pentamethylethyl ketone, the initial product from the rearrangement of hexamethylacetone, undergoes β-fission to methyl isopropyl ketone. The rearrangements and cleavage have been studied kinetically.

In connection with a study of the Schmidt reaction, it was shown that ethyl *t*-butyl ketone undergoes molecular rearrangement to methyl *t*-amyl ketone in concentrated sulfuric acid.[2] The rearrangement is analogous to that reported previously for hexamethylacetone.[3] This paper describes the behavior of nine ketones in 83–97% sulfuric acid.

The rearrangement of hexamethylacetone is most interesting. When equal weights of this ketone and 97% sulfuric acid were heated for six hours at 75°, approximately half of the ketone was converted to methyl pentamethylethyl ketone. However, methyl isopropyl ketone also was identified as a product of the reaction. Similar results were obtained at 30°, where the rate of rearrangement was found to increase as the ratio of sulfuric acid to ketone was increased. Finally, eight experiments were carried out at 30.0° with 0.14 *M* solutions of hexamethylacetone in several concentrations of aqueous sulfuric acid. Aliquots were quenched in ice and extracted with carbon tetrachloride. The three ketones were determined quantitatively by infrared analysis.

The disappearance of hexamethylacetone followed a first-order rate law with a half-life varying from 40 min. in 96% sulfuric acid to 176 min. in 83.6% acid (Fig. 1). Methyl isopropyl ketone was formed at the expense of the rearranged product, methyl pentamethylethyl ketone, by a consecutive first-order reaction, the half-life of which was four to eight times greater than that for the initial rearrangement.



The over-all process of rearrangement and cleavage is most simply represented by two concerted nucleophilic substitutions involving the protonated ketone and protonated oxide followed by a β-fission of protonated methyl pentamethylethyl ketone.

Rearrangement of the *t*-butyl group rather than a methyl group in the protonated oxide would give the same product.

The rates of the two consecutive reactions do not vary in the same manner with the concentration of sulfuric acid. Therefore, the maximum concentration of methyl pentamethylethyl ketone and the relative time at which this maximum is reached are functions of the acid concentration (Fig. 2). The rates of cleavage of pure methyl pentamethylethyl ketone measured independently at several concentrations of sulfuric acid were in excellent agreement with those calculated from the rearrangement data by the equation for two consecutive first-order reactions (Table I). Only methyl pentamethylethyl ketone exhibited the cleavage reaction. In this instance, the cleaved group is stabilized by multiple hyperconjugation. The

TABLE I

REARRANGEMENT AND FISSION OF KETONES RCOR′

R	R′	H_2SO_4, %	A_0[a]	k[b]	k'[c]
$(CH_3)_3C-$	$(CH_3)_3C-$	96.1	0.13	28.8	
		95.7	.145	27.5	
		95.4	.145	27.5	
		93.7	.14	27.3	6.5[d]
		93.2	.13	26.6	6.0[d]
		87.2	.13	15.8	1.9[d]
		86.8	.135	15.5	
		83.6	.13	6.6	0 8[d]
$(CH_3)_3C-$	$(CH_3)_2CH-$	95.5	.15	2.2	
		94.2	.15	1.8	
		91.8	.15	1.7	
$(CH_3)_3C-$	CH_3CH_2-	93.0	.17	1.6	
$(CH_3)_2CC(CH_3)_2$ |	CH_3-	93.2	.064		6.0
		93.2	.046		5.8
		87.2	.058		2.1
		83.6	.058		0.7
$(CH_3)_2CHC(CH_3)_2-$	CH_3-	94.2		0.3[e]	
$C_2H_5C(CH_3)_2$	CH_3-	93.2	.16	0.3	
$(C_6H_5)_3C-$	CH_3-	96.7	.0073	>700	
$(CH_3)_2CH-$	$(CH_3)_2CH-$	95.5		0.00	
$(C_6H_5)_2CCH_3$ |	C_6H_5-	95.5	.0075	0.00	

[a] Initial concentration of ketone in moles/liter. [b] First order rate constant for rearrangement at 30.0° in sec.$^{-1}$ × 10^5. [c] First-order rate constant for cleavage at 30.0° in sec.$^{-1}$ × 10^5. [d] Cleavage of methyl pentamethylethyl ketone calculated from the equation of two successive first-order reactions. [e] Calculated from the rate of approach of pentamethylacetone to equilibrium and the equilibrium constant.

(1) This investigation was supported by a grant from The Pennsylvania State University Council on Research.

(2) H. D. Zook and S. C. Paviak, THIS JOURNAL, 77, 2501 (1955).

(3) S. Barton, F. Morton and C. R. Porter, *Nature*, 169, 373 (1952).

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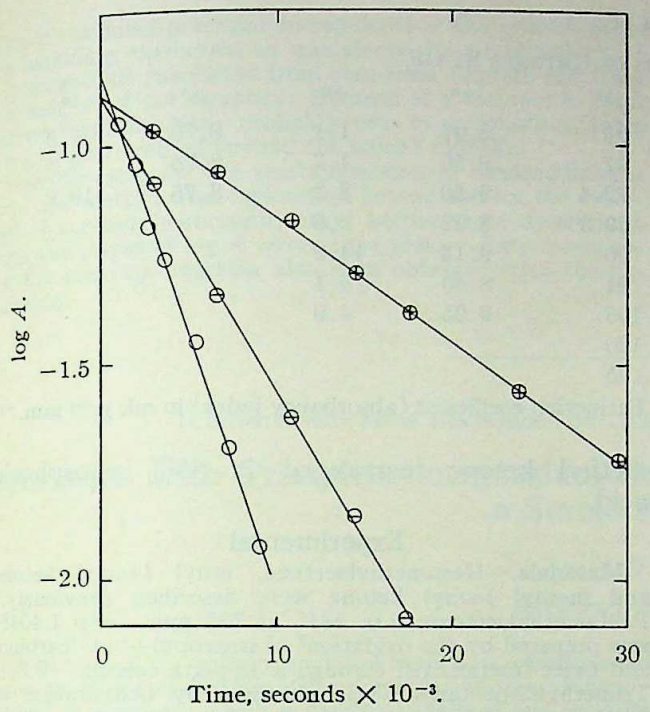

Fig. 1.—Rearrangement of hexamethylacetone; log A *vs.* time: ○, 93.7% sulfuric acid; ⊖, 87.2% sulfuric acid; ⊕, 83.6% sulfuric acid.

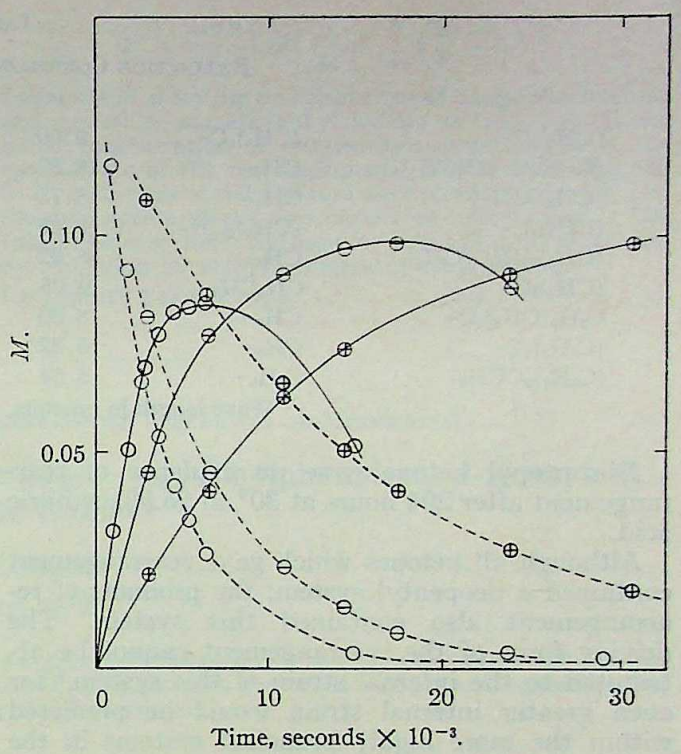

Fig. 2.—Formation and cleavage of methyl pentamethylethyl ketone. Molar concentration of ketone *vs.* time. Solid lines represent methyl pentamethylethyl ketone, broken lines show the corresponding concentrations of hexamethylacetone: ○, 95.7% sulfuric acid; ⊖, 87.2% sulfuric acid; ⊕, 83.6% sulfuric acid.

β-fission of this ketone is analogous to similar β-elimination of relatively stable groups during the dehydration of alcohols[4] and glycols[5] and accompanying the Schmidt and similar rearrangements.[2]

Effect of Structure on Equilibria.—Several rearrangements of pentamethylacetone in 92–96% sulfuric acid led to an equilibrium mixture containing 86.1 mole % 3,3,4-trimethyl-2-pentanone and 13.9 mole % pentamethylacetone corresponding to an equilibrium constant of 6.2 for the reaction

$$(CH_3)_3CCOCH(CH_3)_2 \underset{k_{-1}}{\overset{k}{\rightleftharpoons}} (CH_3)_2CHC(CH_3)_2COCH_3$$

Specific rates of approach to equilibrium were obtained from plots of log $A_0 - A_e/A - A_e$ *versus* time, where A_0, A_e and A are initial, equilibrium and instantaneous concentrations of ketone, respectively (Fig. 3). The constants obtained from the slopes of these lines are equal to the sum of the specific rates for the forward and reverse reactions. From these and the fact that $k_1/k_{-1} = 6.2$, specific rates for the forward and reverse reactions were evaluated. These values are in agreement with specific rates obtained from plots of log A *versus* time over the first 20% of the reaction.

Similarly, rearrangement of ethyl *t*-butyl ketone in 93% sulfuric acid gave a mixture of methyl *t*-amyl ketone and ethyl *t*-butyl ketone corresponding to an equilibrium constant of 5. The equilibrium then was approached by rearrangement of methyl *t*-amyl ketone. After 127 hr., a mixture containing 15.3 mole % ethyl *t*-butyl ketone and corresponding to a constant of 5.5 was obtained.

(4) F. C. Whitmore and E. E. Stahly, THIS JOURNAL, **55**, 4153 (1933); F. C. Whitmore, *Chem. Eng. News*, **26**, 671 (1948).

(5) L. Schmerling, B. S. Friedman and V. N. Ipatieff, THIS JOURNAL, **62**, 2446 (1940); Kalischev, *J. Russ. Phys. Chem. Soc.*, **46**, 427 (1914).

An equilibrium constant for the conversion of hexamethylacetone to methyl pentamethylethyl ketone could not be determined because of the fission of the latter compound. However, the equilibrium is extremely far to the right. No hexamethylacetone could be detected during the cleavage reactions of pure methyl pentamethylethyl ketone.

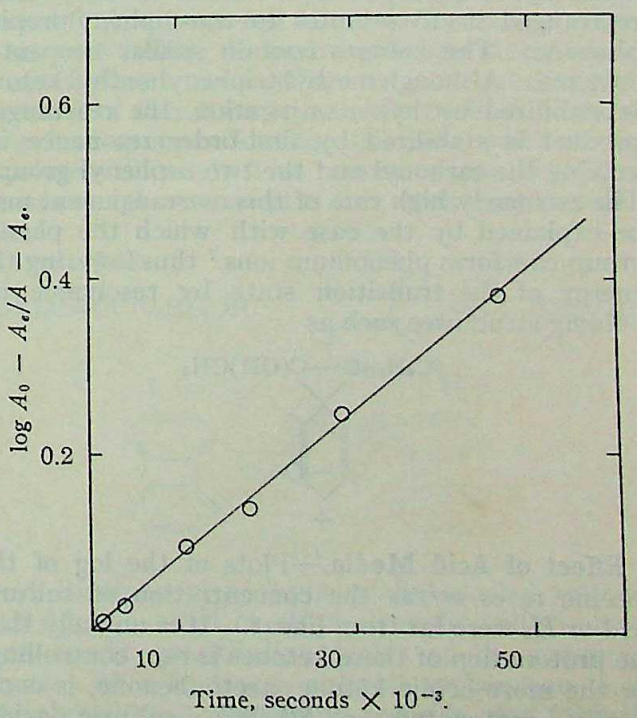

Fig. 3.—Rate of approach of pentamethylacetone to equilibrium; log $A_0 - A_e/A - A_e$ *vs.* time

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TABLE II

EXTINCTION COEFFICIENTS OF KETONES RCOR′

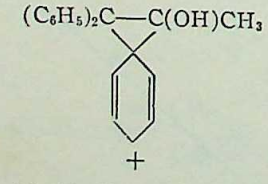
R	R′	λ^a	k^b	λ^a	k^b	λ^a	k^b
$(CH_3)_3C-$	$(CH_3)_3C-$	9.50	95	8.97	1.1	8.75	1.3
$(CH_3)_3C—C(CH_3)_2$	CH_3-	8.97	97	9.50	1.7	8.75	9.5
$(CH_3)_2CH-$ |	CH_3-	8.75	72.4	9.50	3.2	8.75	19.8
$(CH_3)_3C-$	$(CH_3)_2CH-$	9.15	29.3	8.92	2.5		
$(CH_3)_2CHC(CH_3)_2$	CH_3-	8.92	90	9.15	14.9		
$(CH_3)_3C-$ |	CH_3CH_2-	9.05	91	8.80	5.1		
$C_2H_5(CH_3)_2C-$	CH_3-	8.80	103	9.05	4.9		
$(C_6H_5)_3C-$	CH_3-	5.82	120				
$(C_6H_5)_2CCH_3$	C_6H_5-	5.94	105				
|							

[a] Wave length in microns. [b] Extinction coefficient (absorbancy index) in ml. g.$^{-1}$ mm.$^{-1}$.

Diisopropyl ketone gave no evidence of rearrangement after 294 hours at 30° in 95.5% sulfuric acid.

Although all ketones which gave rearrangement contained a neopentyl system, the products of rearrangement also contained this system. The driving force of the rearrangement cannot be attributed to the internal strain of this system,[6] for even greater internal strain would be predicted within the more highly branched systems in the products. The series in which the hydrogen atoms of pinacolone are progressively substituted by methyl groups is of interest. Protonated hexamethylacetone is not stabilized by resonance, whereas three contributing hyperconjugation structures are involved in the protonated rearranged product. Pentamethylacetone and methyl *t*-butyl ketone have one and two α-hydrogen atoms, respectively, which results in a corresponding decrease in the extent of the rearrangement equilibria.

Methyl triphenylmethyl ketone is completely rearranged in 15 minutes to α,α-diphenylpropiophenone. The ketones contain similar neopentyl systems. Although methyl triphenylmethyl ketone is stabilized by hyperconjugation, the rearranged product is stabilized by first-order resonance involving the carbonyl and the two α-phenyl groups. The extremely high rate of this rearrangement may be explained by the ease with which the phenyl group can form phenonium ions,[7] thus lowering the energy of the transition state by resonance involving structures such as



Effect of Acid Media.—Plots of the log of the specific rates *versus* the concentration of sulfuric acid or H_0 were far from linear. It is unlikely that the protonation of these ketones is rate controlling, for the more acidic ketone, acetophenone, is completely protonated in 80–96% sulfuric acid.[8] Neither hexamethylacetone nor methyl triphenylmethyl ketone rearranged in 85% phosphoric acid.

Experimental

Materials.—Hexamethylacetone, ethyl *t*-butyl ketone and methyl *t*-amyl ketone were described previously.[2] Pentamethylacetone, b.p. 131° at 725 mm., $n^{25}D$ 1.4046, was prepared by the oxidation[9] of isopropyl-*t*-butylcarbinol and twice fractionated through a 12-plate column. 3,3,4-Trimethyl-2-pentanone was obtained by dehydration of 2,3,4-trimethyl-2,3-pentanediol.[10] The material used in this study, b.p. 149° at 735 mm., $n^{24.8}D$ 1.4209–1.4210, was obtained by refractionation of a sample prepared in this Laboratory by C. R. Enyeart. Sulfuric acid solutions were prepared by diluting Baker Analyzed Reagent with distilled water. Concentrations were determined by dilution and titration with standard base. Carbon tetrachloride was fractionated through a 35-plate column to remove carbon disulfide.

Methyl Pentamethylethyl Ketone (3,3,4,4-Tetramethyl-2-pentanone).—To 1 l. of 88% sulfuric acid at 27° was added 20.5 g., 25 ml., of hexamethylacetone. The mixture was shaken, allowed to stand 4 hr. at 30° and poured onto 5 l. of crushed ice. The ketone was extracted into three 50-ml. portions of carbon tetrachloride and steam distilled along with the solvent to remove traces of sulfuric acid. Fractional distillation through a 12-plate column gave 13.1 g. (64%) of methyl pentamethylethyl ketone, b.p. 164–167°, m.p. 54–60°, containing 15% of hexamethylacetone (infrared). Two additional refractionations were required to give material boiling at 165° at 728 mm., m.p. 61–63°, free of hexamethylacetone. Purification probably would have been easier had the reaction been allowed to continue for 8 hr. Then the main impurity would have been the lower-boiling methyl isopropyl ketone.

Kinetic Studies.—A standard procedure was used for most of the experiments. Sulfuric acid (200.0 ml.) was measured at 30.0° and cooled to 27° in a 250-ml. volumetric flask. After addition of 5.00 ml. of ketone, the mixture was shaken and held at 30.0 ± 0.05° in a constant-temperature bath. Eight 25.0-ml. aliquots were removed at suitable intervals, quenched in 125 ml. of crushed ice and extracted with carbon tetrachloride in 10-ml., 10-ml. and 5-ml. portions. The first 20 ml. of extract was washed with 10 ml. of distilled water and the last 5 ml. used to wash the water layer. The extract was made up to 25.0 ml. and dried with 1 g. of Drierite. A 1:1 dilution of this solution in a 0.52-mm. cell was suitable for infrared analysis. A Perkin-Elmer model 21 spectrophotometer was employed. Analyses were made by determination of a base line with solvent in two matched cells, then by substitution of the solution for the solvent in one cell. Absorbance was measured at frequencies characteristic of each ketone present, and concentrations were determined by solution of simultaneous equations. Extinction coefficients were obtained from the slopes of absorbance curves determined from four or five concentrations of each pure ketone (Table II). Known mixtures of ketones were analyzed to a precision of ±5%.

(6) *Cf.* H. C. Brown and R. S. Fletcher, THIS JOURNAL, **71**, 1845 (1949).

(7) D. J. Cram, *ibid.*, **71**, 3863, 3875, 3883 (1949).

(8) L. A. Flexser, L. P. Hammett and A. Dingwall, *ibid.*, **57**, 2103 (1935).

(9) L. T. Sandborn, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 340.

(10) R. Locquin and L. Leers, *Bull. soc. chim. France*, **39**, 433 (1926); C. R. Enyeart, Ph.D. Thesis, The Pennsylvania State University, 1942.

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This is the same precision encountered in the over-all process including extraction as was shown by a comparison of concentrations calculated from zero-time aliquots and from the weights of the samples. Because of a decrease in total ketone concentration, probably due to sulfonation, rates were not determined beyond the second half-life.

Specific rates for the rearrangements of hexamethylacetone and methyl triphenylmethyl ketone and for the cleavage of methyl pentamethylethyl ketone were determined from the slopes of log *A versus* time plots. Rate constants for the cleavage reaction also were obtained from the expression

$$k' = \frac{-2.3}{t} \log \left[\frac{A}{A_0} - \frac{B}{A_0}\left(\frac{k'}{k} - 1\right) \right]$$

where A and B are the concentrations of hexamethylacetone and methyl pentamethylethyl ketone at time t, A_0 is the initial concentration of hexamethylacetone and k is the specific rate of the rearrangement. Values were assigned to k', both sides of the equation were plotted against k' and the intersection of the two curves was determined. The values of k' were fairly constant for points near the maximum concentration of methyl pentamethylethyl ketone.

UNIVERSITY PARK, PENNA.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Syntheses with Triarylvinylmagnesium Bromides. α,γ-Bisdiphenylene-β-phenylallyl, a Stable Free Radical

BY C. F. KOELSCH

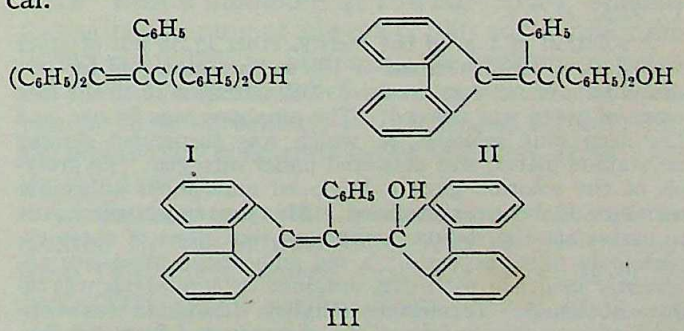
RECEIVED[1] APRIL 10, 1957

Unlike α,α,β,γ,γ-pentaphenylallyl alcohol, α,γ-bisdiphenylene-β-phenylallyl alcohol can be converted into a chloride because its geometry hinders it from cyclization to an indene. The chloride has been converted into the corresponding free radical, a substance which is highly dissociated and remarkably stable to oxygen.

Ziegler's[2] tetraphenylallyl radical, $(C_6H_5)_2C{=}CH{-}C(C_6H_5)_2$, and its substituted derivatives are particularly remarkable in that although they contain only two aryl groups on the methane carbon atom, molecular weight determinations show them to be largely monomolecular. Their deep colors in solution or in the solid state, and their sensitivity toward oxygen also attest their high degree of dissociation. This degree of dissociation, so much exceeding that of triphenylmethyl, was explained by Ziegler on the ground that as 1,1-diphenylethylene is more unsaturated than benzene, diphenylvinyl has a larger "valence requirement" than phenyl.

The completely phenylated allyl radical, pentaphenylallyl, as yet unknown, is of interest because of the intermediate position of the constituent triphenylvinyl group between tetraphenylethylene, whose double bond does not add bromine, and 1,1-diphenylethylene, which adds bromine readily.

A previous paper[3] described the difficulties which were encountered when an attempt was made to synthesize the pentaphenylallyl radical and suggested a means for avoiding these. When pentaphenylallyl alcohol (I) is treated with any acidic reagent, a necessary step in its conversion into a radical, it loses water to form 1,1,2,3-tetraphenylindene. α,α,β-Triphenyl-γ-diphenyleneallyl alcohol (II) is unable to lose water directly, but acidic reagents cause it to undergo an allylic rearrangement followed by the formation of 1-diphenylene-2,3-diphenylindene. α,γ-Bisdiphenylene-β-phenylallyl alcohol (III) is hindered in indene formation, since no matter whether the hydroxyl group is on carbon 1 or 3 the same steric effect tends to prevent the approach of this atom to an *ortho* position of a diphenylene group. Linkage of these positions is therefore difficult.[4] The present paper describes the successful conversion of this alcohol into a radical.



α,γ-Bisdiphenylene-β-phenylallyl alcohol treated with dilute methyl or ethyl alcoholic sulfuric acid gave nearly quantitative yields of the expected ethers. With hydrogen chloride in benzene, α,γ-bisdiphenylene-β-phenylallyl chloride was formed.

The ethers were of no value in the preparation of the radical. When they were treated with sodium amalgam in ether, they yielded deep blue solutions, believed to contain the expected sodio deriva-

(1) The experimental work in the present paper was done in the Converse Memorial Laboratory of Harvard University in 1931–1932, when the author was a National Research Council fellow. A paper describing the work was submitted to THIS JOURNAL June 9, 1932, but it was not accepted for publication. The referee held that the properties of the chief compound, α,γ-bisdiphenylene-β-phenylallyl, could not be those of a radical.

Recent quantum mechanical calculations by M. M. Kreevoy (to be published in *J. Chem. Phys.*), however, now indicate that a radical of the structure named would be unusually resonance-stabilized, and that the properties reported for the substance in question would be not at all inconsistent with the structure claimed. A study of the thermodynamics of addition of sodium to the substance [N. B. Keevil, THIS JOURNAL **59**, 2104 (1937)] hinted that the compound might be unusually stable as a radical. And finally, recent studies by J. E. Wertz and J. L. Vivo, using electron spin resonance methods (briefly reported in OSR Technical Note 55-203, May 1955, p. 133, and to be published in detail in *J. Chem. Phys.*) indicate that the substance is highly dissociated, has an unusually narrow line-width, and is very stable. A sample kept in air 23 years is unchanged in appearance and shows a high free-radical content.

Because the structure originally suggested appears to be confirmed, and because many requests for samples and preparational details are being received, it appears desirable to publish the work now. In the interest of historical accuracy, the only important changes in the original paper are the additions of footnotes 5, 6 and 8.

(2) K. Ziegler and C. Ochs, *Ber.*, **55**, 2257 (1922); K. Ziegler, *Ann.*, **434**, 34 (1923).

(3) C. F. Koelsch, THIS JOURNAL, **54**, 3384 (1932).

(4) C. F. Koelsch, *ibid.*, **54**, 4744 (1932).

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tive. But this sodio derivative did not react with tetramethylethylene dibromide. Its ether solution was not decolorized until a considerable amount of alcohol was added. When 40% sodium amalgam was used to cleave the ethers, the blue solutions first formed became red on continued shaking and then contained trisodium compound, whose hydrolysis gave α,γ-bisdiphenylene-β-phenylpropane.[5]

α,γ-Bisdiphenylene-β-phenylallyl chloride reacted with mercury to form the radical, α,γ-bisdiphenylene-β-phenylallyl. The molecular weight of this radical in boiling benzene indicated that it was largely dimolecular (α = 5.6%), and this was also evidenced by its great resistance to atmospheric oxidation.[6] The radical could be recovered in part unchanged after oxygen has been passed through its solution in boiling benzene for six hours. Bromine cleaved the radical slowly, but the reaction was complicated by partial formation of unworkable substitution products. It is difficult, however, to reconcile the behavior of the substance toward sodium with a low degree of dissociation; it is cleaved immediately by even 1% amalgam. Also the deep color of the substance, green in the solid state and red in solution, appears to be much too intense to be caused only by the fulvene groups present in a dimer.

In order to be able to ascribe the anomalous behavior of α,γ-bisdiphenylene-β-phenylallyl to the presence of the diphenylene groups or to the fifth (β) aryl group, it is planned to investigate tetraarylallyl radicals containing two diphenylene groups.[7]

Experimental

α,γ-Bisdiphenylene-β-phenylallyl Methyl Ether.—A solution of 6 g. of α,γ-bisdiphenylene-β-phenylallyl alcohol[4] in 360 ml. of hot methanol was cooled rapidly and mixed with 5 ml. of concd. sulfuric acid in 20 ml. of methanol. After ten hours, the product was removed by filtration and washed with methanol containing ammonia. Recrystallization from benzene–ligroin gave 5.7 g. of pale yellow prisms, m.p. 184–186°.

Anal. Calcd. for $C_{34}H_{24}O$: C, 91.1; H, 5.3. Found: C, 91.1; H, 5.5.

The ethyl ether had m.p. 187–190°.

Anal. Calcd. for $C_{35}H_{26}O$: C, 90.8; H, 5.6. Found: C, 90.5; H, 5.7.

A solution of 1 g. of the methyl ether in 35 ml. of ether was shaken with an excess of 1% sodium amalgam for several hours, or with an excess of 40% amalgam until the first tinge of green was noticed. The amalgam was frozen, and the deep blue solution, in which was suspended shining crystalline plates, was decanted under nitrogen. Hydrolysis of the solution gave a brick-red amorphous substance which could not be crystallized. Many attempts were made to carbonate the sodium compound, but none of these experiments were successful; a red amorphous substance apparently identical with that obtained by hydrolysis was always obtained. Tetramethylethylene dibromide was without action on the monosodium compound. Phenyl isocyanate reacted, as did benzyl chloride, but no crystalline products could be obtained.

When the methyl ether was shaken in ether with an excess of 40% sodium amalgam for about one hour the color changed from blue to green and finally to deep red-brown. Kept for several days this solution deposited dichromate-colored prisms of presumably a trisodium compound. Carbon dioxide, phenyl isocyanate and benzyl chloride gave no crystalline products. Tetramethylethylene dibromide reacted, giving deep blue solution of the monosodium compound, hydrolyzed to the red amorphous substance. Hydrolysis of the trisodium compound gave *α,γ-bisdiphenylene-β-phenylpropane* (0.6 g. from 1 g. of the methyl ether), colorless needles from acetic acid, m.p. 236–237°. The hydrocarbon was not changed when treated with an excess of sodium in boiling amyl alcohol.

Anal. Calcd. for $C_{33}H_{24}$: C, 94.3; H, 5.7. Found: C, 94.5; H, 5.7.

α,γ-Bisdiphenylene-β-phenylallyl Chloride.—A solution of 16 g. of α,γ-bisdiphenylene-β-phenylallyl alcohol in the minimum amount of hot dry benzene was cooled to 15°, a few grams of powdered calcium chloride was added, and a current of dry hydrogen chloride was led in for one hour. The mixture was filtered and distilled to a small volume under reduced pressure at a temperature not higher than 30°. The addition of ligroin caused a rapid separation of the chloride, pure enough for use directly. Recrystallization from benzene–ligroin gave bright yellow prisms that darkened at 125° and melted with blackening and gas evolution at 145–155°.

Anal. Calcd. for $C_{33}H_{21}Cl$: C, 87.7; H, 4.6; Cl, 7.8. Found: C, 88.1; H, 4.6; Cl, 7.8.

When boiled with methyl or ethyl alcohol, the chloride gave the corresponding ethers in quantitative yield. When treated with sodium in boiling ethanol, it yielded a deep blue solution, not decolorized by excess sodium; diluted with water, this solution lost its color ahd deposited a red amorphous substance. A benzene solution of the chloride gave a deep violet color with aluminum chloride.

α,γ-Bisdiphenylene-β-phenylallyl.—A suspension of 12 g. of α,γ-bisdiphenylene-β-phenylallyl chloride in 200 ml. of dry ether was shaken with 50 g. of mercury for 12 hours. The solid was then removed, washed with ether, and extracted repeatedly with hot benzene. Cooling the combined extracts gave 4.5 g. of the radical, and from the combined ether and benzene mother liquors there was obtained an additional 1.3 g. At first these operations were carried out under nitrogen, but the inert atmosphere was later found to be unnecessary.

From benzene the radical crystallized in beautiful diamond-shaped plates, green by reflected light and red-brown by transmitted light, m.p. 222–224°. These crystals contain one molecule of benzene which is given off completely only when the compound is heated at 100° for two hours under reduced pressure.

Anal. Calcd. for $C_{33}H_{21} + C_6H_6$: C, 94.6; H, 5.4; C_6H_6, 15.8. Found (sample dried at 25° under reduced pressure): C, 94.3; H, 5.5; C_6H_6 (loss at 100°), 16.5. Calcd. for $C_{33}H_{21}$: C, 94.9; H, 5.1. Found (sample dried at 100° under reduced pressure): C, 94.5; H, 5.0.

From acetic acid the radical crystallized in brown needles, m.p. 188–191°, that contained no solvent.[8]

Anal. Calcd. for $C_{33}H_{21}$: C, 94.9; H, 5.1. Found: C, 94.8; H, 5.1.

Molecular Weight (ebullioscopic).—Benzene, 19.9; $C_{33}H_{21} + C_6H_5$, 0.2782, 0.4139, 0.6277, 0.6962; Δt, 0.038, 0.056, 0.093, 0.103: M, 818, 827, 756, 757; mean, 790. Calcd. for $C_{66}H_{42}$: M, 834; α = 5.6%.

Reactions of the Radical.—The red-brown solution of the radical in acetone became deep blue when a piece of solid potassium hydroxide was added; this color was discharged by water.

A 1% ether solution of the radical became blue immediately on shaking with 1% sodium amalgam. With 40% amalgam, the solution became blue and finally red-brown, and then on hydrolysis gave α,γ-bisdiphenylene-β-phenylpropane in nearly quantitative yield. The same hydrocar-

(5) A hydrocarbon tentatively given this structure was synthesized in a different way by L. A. Pinck and G. E. Hilbert (THIS JOURNAL, 68, 2014 (1946)]. Repetition of their synthesis gave the product described by them and found to be identical with the substance described here (mixed m.p. and infrared spectrum), confirming the structure assigned.

(6) In view of the recent more accurate data from E. S. R. measurements (footnote 1) it is now felt that the original molecular weight determinations were in error. Resistance to oxygen is ascribed to unusual resonance stabilization of the radical.

(7) Early experiments in this direction were unsuccessful, but it now appears feasible to try again using a synthetic method discovered recently by S. Wawzonek and E. Dufek (THIS JOURNAL, 78, 3530 (1956)).

(8) The appearance of this solvent-free material was unchanged after 23 years, but unlike the solvated radical, E.S.R. measurements by Professor Wertz showed that the old sample had lost its free radical

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bon was obtained by reduction of the radical with sodium and boiling amyl alcohol.

An excess of a carbon tetrachloride solution of chlorine decolorized the radical after 30 minutes; hydrogen chloride was evolved and no crystalline product could be isolated. When the radical (0.5 g.) in 20 ml. of carbon tetrachloride was mixed with 0.2 g. of bromine and allowed to stand for 12 hours, the color became noticeably lighter. Distillation of the solvent at room temperature left a brown gum which was partly dissolved by 35 ml. of boiling alcohol. Cooling this solution gave 0.15 g. of α,γ-bisdiphenylene-β-phenylallyl ethyl ether.

A solution of 0.4 g. of the radical in 25 ml. of benzene was boiled for 6 hours while a stream of oxygen was passed through. The solution was then distilled to a small volume and cooled, giving 0.1 g. of unchanged radical. No other crystalline substance could be isolated.

A hot solution of 0.5 g. of the radical in 25 ml. of acetic acid was treated with 1 g. of chromic acid in a little water. After the vigorous reaction was over the solution was boiled for five minutes. There was obtained 0.1 g. of benzoic acid and 0.3 g. of steam distilled fluorenone.

MINNEAPOLIS, MINNESOTA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

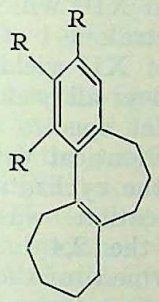
The Cyclodehydration of 2-(γ-Phenylpropyl)-cycloheptanone[1,2]

BY C. DAVID GUTSCHE, N. N. SAHA[3] AND HERBERT E. JOHNSON

RECEIVED DECEMBER 26, 1956

The cyclodehydration of 2-(γ-phenylpropyl)-cycloheptanone has been found to give, instead of the expected olefin Ia, a mixture containing 1-cyclohexyltetralin, 2-cyclohexyltetralin, 1-cyclohexylnaphthalene, 2-cyclohexylnaphthalene and other unidentified products. These materials were characterized by isolation from the cyclization mixture followed by comparison with authentic samples, the syntheses for which are described.

The work described in this communication had its inception in an attempt to synthesize octahydrodemethoxydeoxydeacetamidocolchicine (Ib)[4] by cyclization of 2-[(γ-3′,4′ 5′-trimethoxyphenyl)-propyl]-cycloheptanone (IVb). The reaction, however, did not take the desired course. In the hope of elucidating the actual events, the same reaction with the un-methoxylated analog IVa was investigated in considerable detail.



Ia, R = H
Ib, R = OCH_3

The ketones IVa and IVb were prepared in 60 and 68% over-all yield, respectively, from the corresponding γ-arylbutylamines IIa and IIb by cathylation to IIIa and IIIb followed by nitrosation and treatment with cyclohexanone under the usual ring-enlargement conditions.[5] In view of the known efficacy of polyphosphoric acid as a cyclizing agent for systems containing methoxyl groups,[6] this was the reagent of choice in the case of IVb and, for comparative purposes, in the case of IVa also. In both instances, somewhat more strenuous conditions than are usually employed were necessary to effect complete disappearance of the ketone, and it is this fact which may be responsible for the wayward course of the cyclization. Ketone IVb required contact with polyphosphoric acid at 125° for 30 minutes; ketone IVa required contact with polyphosphoric acid at 100° for 24 hr. or 200° for 2.5 hr. In each case a volatile fraction (30–45%) was obtained which boiled in the range expected for the cyclodehydration product. It is these materials, principally that derived from IVa, which is the subject of this discussion.

The cyclization product from IVb consisted of an oil possessing an analysis in approximate agreement with a $C_{19}H_{26}O_3$ formula (although a methoxyl determination indicated some demethylation). The ultraviolet spectrum, however, showed strong absorption bands at 235 mμ 41,500) and 278 mμ (5000) with a minimum at 254 mμ (3580), whereas Ib has a maximum at 254 mμ (7760) and a minimum at 243 mμ (6030).[4] Similarly, the cyclization product from IVa consisted of an oil possessing an analysis in close agreement with a $C_{16}H_{20}$ formula but an ultraviolet spectrum quite different from that expected for Ia.[7]

Cyclization into the benzene nucleus was indicated by the infrared spectrum of the product from IVa which showed a pattern of bands in the 1650–2000 $cm.^{-1}$ region characteristic of 1,2-disubstituted benzenes.[8] The virtual absence of an olefinic linkage in the product was indicated by the

(1) This work was supported, in part, by: (a) a grant-in-aid from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council, and (b) a grant-in-aid from the National Science Foundation.

(2) A preliminary account of this work was presented at the 126th Meeting of the American Chemical Society, New York, N. Y., 1954, Abstracts, p. 33-O.

(3) Postdoctoral research associate, 1955–1956.

(4) H. Rapoport, A. R. Williams, J. E. Campion and D. E. Pack, THIS JOURNAL, **76**, 3693 (1954).

(5) C. D. Gutsche, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 364.

(6) *Cf.* for example, A. Koebner and R. Robinson, *J. Chem. Soc.*, 1994 (1938); W. E. Bachmann and W. J. Horton, THIS JOURNAL, **69**, 58 (1947); R. C. Gilmore and W. J. Horton, *ibid.*, **73**, 1411 (1951); J. Koo, *ibid.*, **75**, 1891 (1953).

(7) Compounds containing a double bond in conjugation with a phenyl group ordinarily have an absorption maximum in the 245–265 mμ region. Thus, styrene has a maximum at 245 mμ (16,000)—M. Pestemer and L. Willigut, *Monatsh.*, **66**, 119 (1935); 2-phenylcyclohexene has a maximum at 247 mμ (12,000)—A. C. Cope, F. S. Fawcett and G. Munn, THIS JOURNAL, **72**, 3399 (1950); 1,2-dihydronaphthalene has a maximum at 262 mμ (10,000)—R. A. Morton and A. J. A. de Gouveia, *J. Chem. Soc.*, 916 (1934). The cyclization product from IVa has maxima at 218 mμ (13,800), 224 mμ (30,000), 268 mμ (1820) and 274 mμ (1900).

(8) C. W. Young, R. B. DuVall and N. Wright, *Anal. Chem.*, **23**, 709 (1951).

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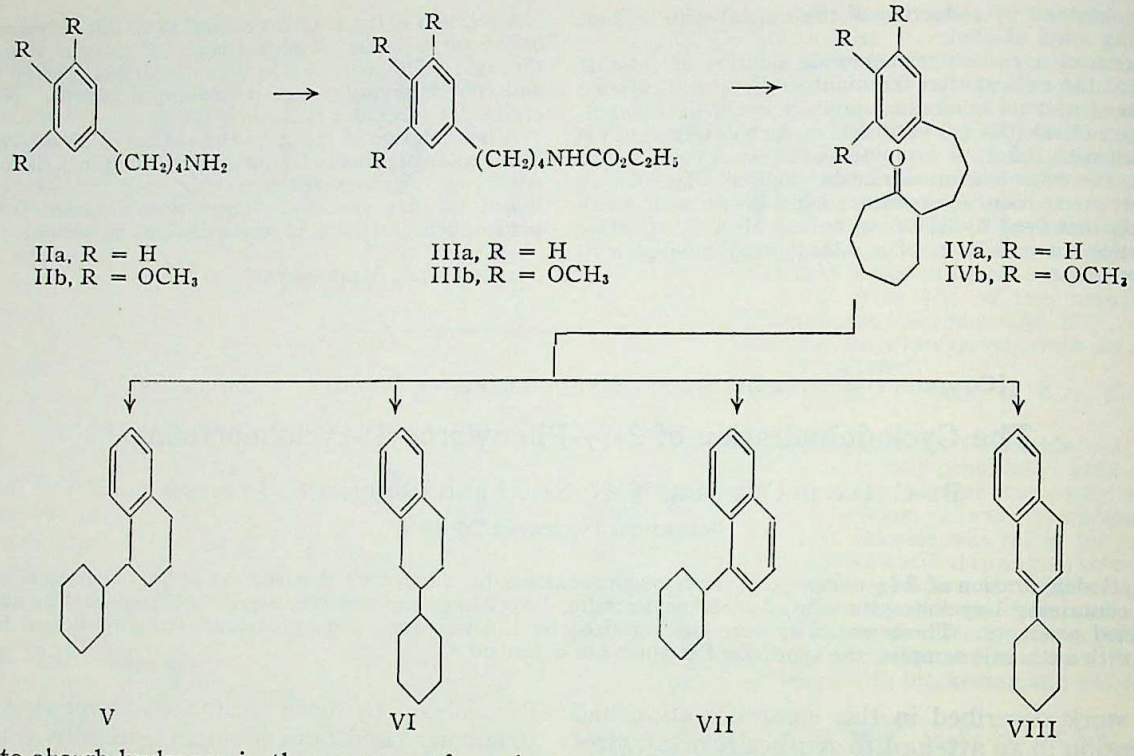

failure to absorb hydrogen in the presence of a palladium catalyst and by the failure to react with potassium permanganate, nitrosyl chloride, ozone or perbenzoic acid.[9] At first, these facts were difficult to reconcile with a $C_{16}H_{20}$ formula. It was eventually ascertained, however that the cyclization product is not a single entity but a mixture of at least five compounds including 1-cyclohexyltetralin (V), 2-cyclohexyltetralin (VI), 1-cyclohexylnaphthalene (VII) and 2-cyclohexylnaphthalene (VIII).[10] The evidence for this conclusion is detailed in the following section.

Identification of 1-Cyclohexyltetralin (V).—When the cyclization product from IVa was fractionated, either by distillation through a spinning band column or by chromatography on alumina, a lower-boiling, less strongly adsorbed material was obtained which had an analysis in close agreement with a $C_{16}H_{22}$ formula. The infrared spectrum of this compound was characteristic of a 1,2-disubstituted benzene derivative,[8] and the ultraviolet spectrum showed only the bands characteristic of the phenyl nucleus. When dehydrogenated with 10% palladium-on-charcoal, 1-phenylnaphthalene was produced, suggesting that the $C_{16}H_{22}$ compound is 1-cyclohexyltetralin. However, since migration of phenyl groups between the 1- and 2-positions of naphthalene is known to occur[11] and since even more drastic events are known to take place under conditions of dehydrogenation,[12] a more secure identification was sought through comparison with the product from an unequivocal synthesis of 1-cyclohexyltetralin. Hexahydrobenzophenone (IX) was subjected to a Reformatsky reaction with ethyl α-bromoacetate, and the resulting hydroxy ester was dehydrated, hydrolyzed and reduced to the acid X. An Arndt–Eistert sequence applied to X yielded XI[13] which was then cyclized to 4-cyclohexyltetralone-1 (XII). Removal of the keto group of XII yielded 1-cyclohexyltetralin (V) in 41% over-all yield from IX. The infrared and ultraviolet spectra of the authentic sample of V were identical with those of the sample obtained from the cyclization product of IVa. Further identification was obtained through a comparison of the 2,4-dinitrophenylhydrazones (two isomers formed) of the acetyl derivative of authentic V and that derived from IVa.

Identification of 2-Cyclohexyltetralin (VI).—When the cyclization product from IVa was fractionated by chromatography on alumina, a material was obtained in exceedingly small amount which had an infrared spectrum different from that of 1-cyclohexyltetralin and almost identical with that of 2-cyclohexyltetralin (VI). An authentic sample of VI was prepared from cyclohexylsuccinic anhydride by condensation with benzene followed by reduction to XIX and XVI, cyclization to 2-cyclohexyltetralone-1 (XIX) and 3-cyclohexyltetralone-1 (XVII) and reduction to 2-cyclohexyltetralin (VI). The structural assignment of XIX and XVI is based on the premise that mono-alkyl-substituted succinic anhydrides usually react with benzene to yield the α-alkyl-β-benzoylpropionic

(9) Ozone and perbenzoic acid, however, were not completely without action. Ozonolysis produced a very small amount of carbonyl-containing material, and perbenzoic acid oxidation showed a 25% consumption of oxidant in 24 hr. and another 25% in 14 days.

(10) In addition to these four compounds, an unidentified solid was isolated in small quantity. It had an analysis compatible with a $C_{16}H_{16}$ formula and an ultraviolet spectrum very similar to that of a naphthalene but shifted somewhat to the visible. Dehydrogenation yielded a hydrocarbon with a $C_{16}H_{12}$ or a $C_{16}H_{10}$ formula.

(11) F. Mayer and R. Schiffner. *Ber.*, **67**, 67 (1934).

(12) P. A. Plattner in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, pp. 36–51.

(13) An alternate synthesis of XI from IX was attempted *via* the Stobbe condensation. Difficulties were encountered, however, (*cf.* Experimental section) and the route was abandoned. Also attempted was the condensation of cyclohexylmagnesium bromide and α-tetralone as reported by J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 1434 (1936). 1-Cyclohexyl-3,4-dihydronaphthalene was formed in low yield (Cook and Lawrence do not report a yield) and was contaminated with difficultly separable starting ketone.

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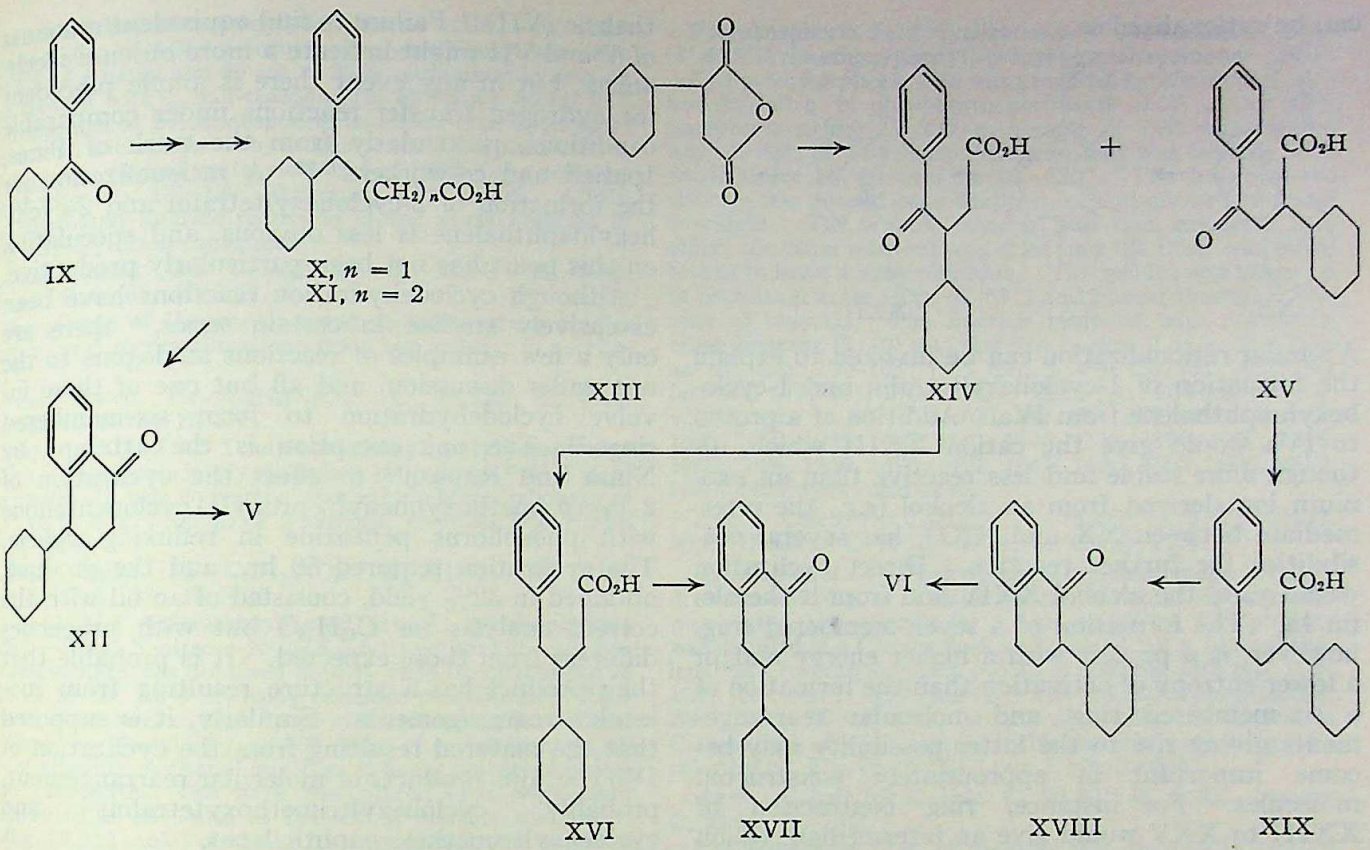


acid in larger amount.[14] Thus, the higher-melting product from XIII and benzene, obtained in 73% yield, is assigned structure XV; the lower-melting product, obtained in 13% yield, is assigned structure XIV. 2-Cyclohexyltetralin, like the 1-isomer, forms two 2,4-dinitrophenylhydrazones of the acetyl derivative.

Identification of 1-Cyclohexylnaphthalene (VII).—From one of the middle fractions obtained from the distillation of the product from IVa 1-cyclohexylnaphthalene (VII) could be isolated *via* the picrate. Authentic VII was prepared by controlled dehydrogenation of 1-cyclohexyltetralin.

Identification of 2-Cyclohexylnaphthalene (VIII). When the cyclization product from IVa was fractionated, either by distillation through a spinning band column or by chromatography on alumina, a higher-boiling, more strongly adsorbed material was obtained which had an analysis in close agreement with a $C_{16}H_{18}$ formula. The ultraviolet spectrum of this fraction was identical with that of authentic VIII, it formed a trinitrobenzene complex which gave no depression in m.p. when admixed with the trinitrobenzene complex of authentic VIII, and it could be dehydrogenated to 2-phenylnaphthalene. Authentic VIII was prepared by reduction of 2-cyclohexenylnaphthalene, obtained from 2-naphthylmagnesium bromide and cyclohexanone.[15]

No accurate quantitative data as to the relative amounts of V, VI, VII and VIII present in the mixture were obtained. However, on the basis of the ultraviolet spectrum of the crude material, the yields of dehydrogenation products and the yields from chromatographic separation, it appears that the mixture contains *ca.* 65% of V, 25% of VIII and 10% of VI, VII and unidentified products.[16]

(14) E. Berliner, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 242.

(15) F. Bergmann and E. Bergmann, THIS JOURNAL, **62**, 1699 (1940).

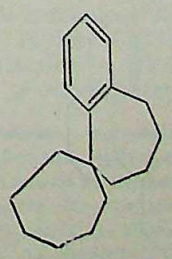
Discussion of Results

The rearrangement of alicyclic rings under the influence of various catalysts is a well-known and extensively-studied phenomenon. For instance, Pines, *et al.*,[17] have found that cycloheptanol reacts with benzene under the influence of aluminum chloride or sulfuric acid to give a mixture containing appreciable amounts of methylphenylcyclohexanes. In the course of the present work an intramolecular counterpart to this reaction was discovered when it was found that the alcohol XX yields 1-cyclohexyltetralin (V) under the influence of Friedel–Crafts catalysts.[18] This conversion

(16) These figures apply only to the volatile portion of the product (30–45%). The non-volatile portion has not been investigated.

(17) H. Pines, A. Edeleanu and V. N. Ipatieff, THIS JOURNAL, **67**, 2193 (1945).

(18) The product from XX contains other materials in addition to V, possibly the spiran A which, on the basis of other published data (*cf.* R. O. Roblin, D. Davidson and M. T. Bogert, *ibid.*, **57**, 151 (1935); R. A. Barnes, *ibid.*, **76**, 3004 (1953)) would be expected to be the major product. On the basis of the infrared and ultraviolet spectra of the product and on the basis of its dehydrogenation products, 2-cyclohexyltetralin does not appear to be present.



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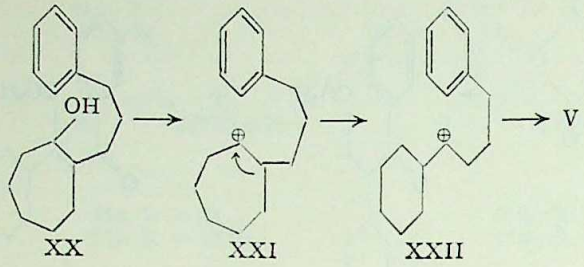
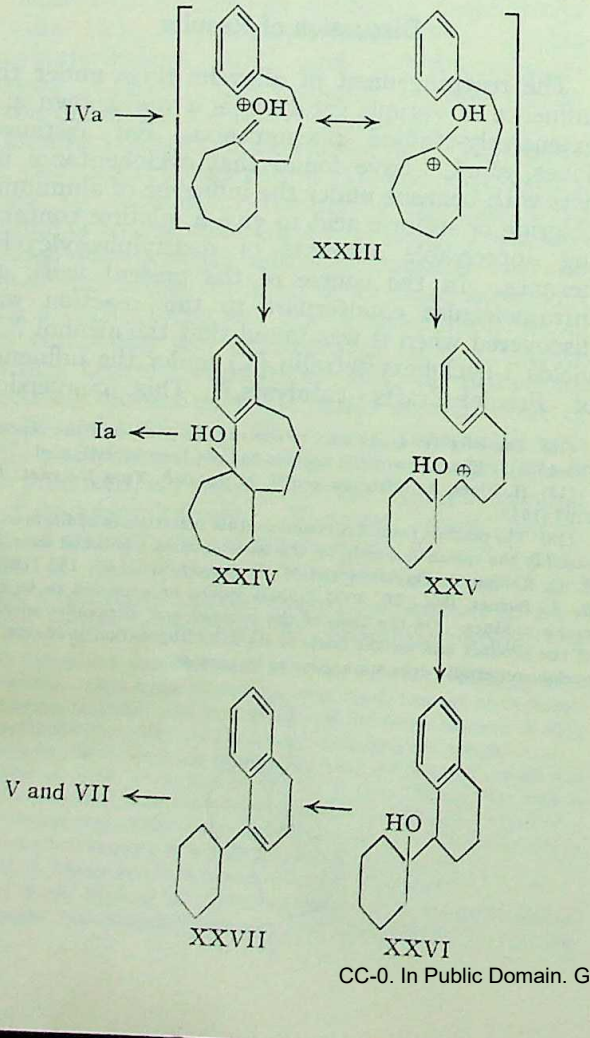
can be rationalized as



A similar rationalization can be invoked to explain the formation of 1-cyclohexyltetralin and 1-cyclohexylnaphthalene from IVa. Addition of a proton to IVa would give the cation XXIII which, although more stable and less reactive than an oxonium ion derived from an alcohol (*e.g.*, the intermediate between XX and XXI), has several possibilities for further reaction. Direct cyclization would yield the alcohol XXIV and from it the olefin Ia. The formation of a seven-membered ring, however, is a process with a higher energy and/or a lower entropy of activation than the formation of a six-membered ring, and molecular rearrangements giving rise to the latter possibility may become important in appropriately constructed molecules. For instance, ring contraction of XXIII to XXV would give an intermediate which could cyclize to the hydroxytetralin (XXVI). Loss of water and bond migration could then yield 1-cyclohexyl-3,4-dihydronaphthalene (XXVII) which, through disproportionation, would lead to 1-cyclohexyltetralin (V) and 1-cyclohexylnaphthalene (VII). Failure to find equivalent amounts of V and VII might indicate a more obscure mechanism, but in any event there is ample precedent for hydrogen transfer reactions under comparable conditions, particularly from the work of Pines, Ipatieff and co-workers.[19,20] A rationalization for the formation of 2-cyclohexyltetralin and 2-cyclohexylnaphthalene is less obvious, and speculation on this point has not been particularly productive.



Although cyclodehydration reactions have been extensively studied in certain series,[21] there are only a few examples of reactions analogous to the one under discussion, and all but one of these involve cyclodehydration to form six-membered rings.[22] The one exception is the attempt by Nunn and Rapson[23] to effect the cyclization of 2-[γ-(*p*-methoxyphenyl)-propyl]-cyclopentanone with phosphorus pentoxide in refluxing xylene. The cyclization required 50 hr., and the product, obtained in 32% yield, consisted of an oil with the correct analysis for $C_{15}H_{18}O$ but with properties different from those expected. It is probable that their product has a structure resulting from molecular rearrangements. Similarly, it is supposed that the material resulting from the cyclization of IVb contains products of molecular rearrangement, probably cyclohexyltrimethoxytetralins and cyclohexyltrimethoxynaphthalenes.

Experimental[24-26]

2-Arylcycloalkanones (IV). γ-(3,4,5-Trimethoxyphenyl)-butyronitrile.—Following a previously described procedure[27] a mixture of 53.0 g. (0.217 mole) of 1-chloro-3-(3′,4′,5′-trimethoxyphenyl)-propane (b.p. 135–144° (0.5 mm.); $n^{25}D$ 1.5305), 31.8 g. (0.49 mole) of potassium cyanide, 1.5 g. of potassium iodide, 210 ml. of 95% ethanol and 80 ml. of water was refluxed for 14 hr. The reaction mixture was then concentrated to half of its original volume, poured into 400 ml. of water and worked up in the usual fashion to yield 45.0 g. (88%) of a colorless liquid with b.p. 150–160° (mainly 156°) at 0.4 mm., $n^{25}D$ 1.5263. A middle cut was taken for analysis.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.75; H. 7.31.

(19) C. Mentzer and Dat Xuong, *Bull. soc. chim. France*, 885 (1947), found that anisole and cyclohexanone react in the presence of aluminum chloride to give a mixture of *p*-methoxyphenylcyclohexene and *p*-methoxyphenylcyclohexane, the latter apparently predominating. R. F. Evans and J. C. Smith, *J. Chem. Soc.*, 798 (1954), have described a reaction in which a compound of the dihydronaphthalene type undergoes disproportionation in the presence of polyphosphoric acid.

(20) H. Pines, A. Weizmann and V. N. Ipatieff, THIS JOURNAL, **70**, 3589 (1948); V. N. Ipatieff, H. Pines and R. C. Olberg, *ibid.*, **70**, 2123 (1948); R. C. Olberg and V. N. Ipatieff, *ibid.*, **74**, 4872 (1952).

(21) *Cf.* C. K. Bradsher, *Chem. Revs.*, **38**, 447 (1938) for a review of cyclodehydration reactions leading to aromatic systems. *Cf.* E. C. Horning and J. Koo, THIS JOURNAL, **73**, 5830 (1951), for a recent and typical example of the Bougault type of cyclodehydration (J. Bougault, *Compt. rend.*, **159**, 745 (1915)).

(22) H. France, S. H. Tucker and J. Forrest, *J. Chem. Soc.*, 7 (1945); J. Colonge and F. Collomb, *Bull. soc. chim. France*, 285 (1951).

(23) J. R. Nunn and W. S. Rapson, *J. Chem. Soc.*, 1051 (1951).

(24) All melting points are corrected; all boiling points are uncorrected.

(25) The microanalyses were performed by Mrs. Charlotte Thompson, Washington University, and by Drs. Weiler and Strauss, Oxford, England.

(26) The ultraviolet spectra were determined with a Beckman model DU spectrophotometer and a Cary recording spectrophotometer; the infrared spectra were determined with a Perkin–Elmer model 21 spectrophotometer.

(27) H. Rapoport and J. E. Campion, THIS JOURNAL, **73**, 2239 (1951).

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δ-(3,4,5-Trimethoxyphenyl)-butylamine (IIb).—A solution of 45.0 g. of γ-(3,4,5-trimethoxyphenyl)-butyronitrile in 250 ml. of ethanol and 60 ml. of 28% ammonium hydroxide was treated with 3 half-teaspoonsful of Raney nickel and hydrogenated at 2.5 atmospheres in a Parr-type apparatus. After 5 hr. the uptake of hydrogen ceased, and the reaction mixture was worked up to yield 38.5 g. (84%) of a colorless liquid with b.p. 137–139° (0.3 mm.), $n^{25}D$ 1.5292. A lithium aluminum hydride reduction of the nitrile resulted in only a 51% yield of the amine.

Anal. Calcd. for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85. Found: C, 65.65; H, 8.79.

The picrate of IIc was obtained as yellow-green needles after several recrystallizations from hot water; m.p. 172–173°.

Anal. Calcd. for $C_{19}H_{24}N_4O_{10}$: C, 48.72; H, 5.16. Found: C, 48.76; H, 5.11.

Ethyl N-[δ-(3,4,5-Trimethoxyphenyl)-butyl]-carbamate (IIIb).—Using previously described procedures,[28] 51.6 g. of the amine IIb was converted with ethyl chlorocarbonate at 0–5° to 67.0 g. (100%) of a viscous, colorless liquid with $n^{25}D$ 1.5150.

Anal. Calcd. for $C_{16}H_{25}NO_5$: C, 61.61; H, 8.09. Found: C, 61.73; H, 8.28.

2-[γ-(3′,4′,5′-Trimethoxyphenyl)-propyl]-cycloheptanone (IVb).—Ethyl N-nitroso-N-[δ-(3,4,5-trimethoxyphenyl)-butyl]-carbamate was obtained in 98% yield by nitrosation of IIIb at 15–20° for 6 hr. using standard procedures.[29] In a 500-ml. three-necked flask fitted with a dropping funnel and a stirrer was placed 30 g. (0.306 mole) of cyclohexanone, 80 ml. of absolute methanol and 5 g. of finely powdered potassium carbonate. The flask was placed in a water-bath maintained at 25°, and to the stirred mixture was added 67.0 g. (0.212 mole) of the nitroso compound over a period of 45 minutes. The yellowish mixture was allowed to stand at room temperature for 4 hr. and was then filtered. The filtrate was evaporated by heating under reduced pressure, and the residue was distilled to give 41.6 g. (62%) of a yellow liquid with b.p. 190–220° (0.5–1.5 mm.). Redistillation gave 36.0 g. (54%) of almost colorless product, b.p. 172–175° (0.2 mm.), $n^{25}D$ 1.5286.

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.05; H, 8.59.

The 2,4-dinitrophenylhydrazone of IVb was obtained as dull red needles from petroleum ether (b.p. 63–69°), m.p. 140–141°.

Anal. Calcd. for $C_{25}H_{32}N_4O_7$: C, 59.99; H, 6.44. Found: C, 60.13; H, 6.45.

Ethyl N-(δ-Phenylbutyl)-carbamate (IIIa).—Using previously described procedures, 49.0 g. of δ-phenylbutylamine (IIIa) (prepared by catalytic reduction of γ-phenylbutyronitrile) was converted to 66.3 g. (91%) of IIIa, obtained as a colorless liquid, b.p. 120–122° (0.2 mm.), n_D^{25} 1.5060.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65. Found: C, 70.34; H, 8.81.

2-(γ-Phenylpropyl)-cycloheptanone (IVa).—Ethyl N-nitroso-N-(δ-phenylbutyl)-carbamate was obtained in 100% yield by nitrosation of IIIa at 18–25° for 5.5 hr. using standard procedures. A 73.0-g. sample of the nitroso compound was treated with 40 g. of cyclohexanone, 100 ml. of methanol and 10 g. of potassium carbonate as described above to yield 50.6 g. (74.5%) of a colorless liquid with b.p. 124–125°(0.3 mm.), $n^{25}D$ 1.5212.

Anal. Calcd. for $C_{16}H_{22}O$: C, 83.43, H, 9.63; N, 0.00. Found: C, 83.64; H, 9.63; N, 0.00.

The 2,4-dinitrophenylhydrazone of IVa was obtained as bright orange needles from ethanol; m.p. 120–121°.

Anal. Calcd. for $C_{22}H_{26}N_4O_4$: C, 64.37; H, 6.39. Found: C, 64.65; H, 6.18.

Redistillation of the forerun obtained in the preparation of IVa gave a colorless liquid with b.p. 55°(0.3 mm.), $n^{25}D$ 1.4917. This material appears to be **ethyl δ-phenylbutyl ether.**

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.92; H, 9.82.

(28) W. W. Hartman and M. R. Brethen, *Org. Syntheses*, **12**, 38 (1932).

(29) W. W. Hartman and R. Phillips, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 464.

Polyphosphoric Acid Cyclizations. Cyclization of 2-[γ-(3′,4′,5′-Trimethoxyphenyl)-propyl]-cycloheptanone (IVb).—The polyphosphoric acid was prepared by dissolving, with heating, 40 g. of phosphorus pentoxide in 25 ml. of 85% phosphoric acid.[6] A 2.00-g. sample of IVb was treated with 30 ml. of polyphosphoric acid and was heated, with swirling, for 30 minutes at 120–130°. The brownish-red mixture was poured onto chopped ice and allowed to stand overnight. The organic material was then extracted into ether, the ether solution was dried and the ether was evaporated to leave a yellow residue. The residue was taken up in petroleum ether (b.p. 63–69°) and passed through a column of alumina. The fraction removed with petroleum ether–benzene (1:10) was distilled to give 0.56 g. (30%) of an oil, b.p. 160–163° (0.1 mm.), $n^{25}D$ 1.5713; λ_{max}^{EtOH} mμ (ε): 235 (37,700), 278 (5350); λ_{min}^{EtOH} (ε): 254 mμ (3280); $\tilde{\gamma}_{max}^{liquid}$ in cm.$^{-1}$: 707, 738, 760, 782, 838, 878, 922, 943, 969, 1003, 1042, 1065, 1097, 1121, 1146, 1158, 1190, 1227, 1248, 1280, 1324, 1350, 1390, 1421, 1445, 1490, 1602, 2630, 2810, 2880, 3460(weak) and 4300.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67; CH_3O, 30.7. Found: C, 76.75; H, 8.85; CH_3O, 25.3.

Cyclization of 2-(γ-Phenylpropyl)-cycloheptanone (IVa).—A mixture of 75 g. of IVa and 900 ml. of polyphosphoric acid was heated with stirring for 2.5 hr. at 200°. The product was distilled in a Claisen flask and yielded 1.8 g. of naphthalene[30] as a forerun and 31 g. (45%) of material with b.p. 109–126° (0.4 mm.); λ_{max}^{EtOH} mμ (ε): 218 (13,800), 224 (30,000), 268 (1820), 274 (1900). A second distillation through a Claisen flask of a 4-g. sample of this material gave 2.6 g. of a colorless oil, b.p. 96–98° (0.2 mm.), $n^{25}D$ 1.5548.

Anal. Calcd. for $C_{16}H_{20}$: C, 90.50; H, 9.50. Found: C, 90.61; H, 9.82.

The remaining 27 g. of material was distilled through a Piros–Glover spinning band column, and 25 fractions were collected at arbitrary intervals. These could be roughly classified into four groups: (a) fractions 5–10 containing 7.5 g. with b.p. 104–108° (0.7 mm.), $n^{25}D$ 1.5490–1.5510; (b) fractions 17–20 containing 4.2 g. with b.p. 115–117° (0.8 mm.), $n^{25}D$ 1.5600–1.5810; (c) fractions 23–24 containing 2.9 g. with b.p. 124–126° (0.8 mm.), $n^{25}D$ 1.5970–1.5980; (d) fraction 25 containing 2.3 g. with b.p. 127–128° (0.3 mm.), $n^{25}D$ 1.6215. Further information on these fractions is given in succeeding sections of the Experimental section.

From another comparable experiment, a 3.91-g. sample of once-distilled material was subjected to chromatographic separation on a column 2 cm. × 30 cm. containing 173 g. of alumina (Fisher adsorption grade). The column was eluted with petroleum ether (b.p. 63–69°), and 45 fractions of 15 ml. each were collected. These could be classified into three groups: (a) fractions 8–18 containing 2.80 g., $n^{25}D$ 1.5490; (b) fraction 20 containing 0.03 g.; (c) fractions 27–45 containing 0.37 g., $n^{25}D$ 1.5980.

Cyclization also could be effected by heating for longer periods at 100°. A reaction carried out at 100° for 2.5 hr. showed *ca.* 80% of unreacted IVa; after 10 hr., *ca.* 30% of unreacted IVa remained; after 24 hr., *ca.* 5% of unreacted IVa remained. The infrared spectrum of the material obtained from the 24-hr. run at 100° was identical in every respect with that of the material obtained from a 2.5 hr. run at 200°, and it is presumed that the products are very similar in nature. The identification of V, VI, VII and VIII as described below involved material obtained from the 200° runs. In a number of instances, however, similar experiments with similar results were performed on material from 100° runs

1-Cyclohexyltetralin (V). (A) Synthesis from Hexahydrobenzophenone *via* Reformatsky and Arndt–Eistert Sequence.—Ethyl β-hydroxy-β-phenyl-β-cyclohexylpropionate was prepared by the reaction of 28 g. (0.148 mole) of hexahydrobenzophenone[31] with a total of 37 g. (0.22 mole) of ethyl α-bromoacetate and 14.6 g. (0.22 gram atom) of zinc according to previously described methods.[32] The product consisted of 38 g. (93%) of solid material, m.p. 55–56.5°,

(30) The genesis of naphthalene is uncertain, but it is believed to arise through cyclization of ethyl δ-phenylbutyl ether, a probable contaminant of IVa, to tetralin followed by dehydrogenation.

(31) V. Meyer and W. Scharvin, *Ber.*, **30**, 1940 (1897).

(32) *Cf.*, for example, J. W. Cook, C. L. Hewett and C. A. Lawrence, *J. Chem. Soc.*, 71 (1936); C. D. Gutsche, THIS JOURNAL, **73**, 786 (1951).

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from which an analytical sample was obtained as colorless needles by recrystallization from ethanol; m.p. 57–57.5°.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.22; H, 8.56.

The hydroxy ester was dehydrated by the thionyl chloride–pyridine method[32] to yield a mobile, yellow oil with b.p. 155–158° (0.9 mm.). Reduction with hydrogen at two atmospheres of pressure in the presence of 10% palladium-on-charcoal catalyst followed by saponification by refluxing for 7 hr. with 30% aqueous potassium hydroxide produced **β-phenyl-β-cyclohexylpropionic acid** (X) in 80% over-all yield from the hydroxy ester, m.p. 96–98°. An analytical sample was obtained as fine needles by two recrystallizations from aqueous ethanol; m.p. 99–100°.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.20; H, 8.55.

γ-Phenyl-γ-cyclohexylbutyric acid (XI) was obtained from X by application of the Arndt–Eistert sequence. A 10.0-g. sample of X was converted to the acid chloride with an excess of purified[33] thionyl chloride. The crude acid chloride was then treated at 0° over a period of 25 minutes with 300 ml. of ether containing diazomethane from 31 g. of nitrosomethylurea. After the reaction mixture had stood at 0° for an additional hour, the volatile materials were removed under vacuum, and the residue was dissolved in methanol and decomposed by the method of Newman and Beal,[34] 95% of the theoretical amount of nitrogen being evolved. The resulting methyl ester was saponified by 2.5 hr. of refluxing with 50 ml. of 45% aqueous potassium hydroxide and 50 ml. of ethanol and yielded 9.3 g. (88%) of a solid with m.p. 56–78°. Two recrystallizations from petroleum ether (b.p. 63–69°) gave 7.5 g. (71%) of colorless, short, thick needles, m.p. 101–102°.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.05; H, 8.98.

4-Cyclohexyl-3,4-dihydronaphthalenone (XII) was obtained in 85% yield by cyclization of XI with anhydrous hydrogen fluoride; b.p. 128–130° (0.06 mm.). For analysis, a portion of this material was redistilled and a center cut taken; $n^{25}D$ 1.5640, $\tilde{\nu}_{max}^{liquid}$ 1684 cm.$^{-1}$ (benzoyl).

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.60; H, 8.79.

A 2,4-dinitrophenylhydrazone of XII was obtained as fine, deep red needles after two recrystallizations from ethyl acetate; m.p. 234–234.5° dec.

Anal. Calcd. for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92. Found: C, 64.80; H, 5.77.

An 8.64-g. sample of XII was dissolved in 170 ml. of ethyl acetate, treated with 3 g. of 10% palladium-on-charcoal and 12 drops of 70% perchloric acid[35] and subjected to hydrogenation at two atmospheres pressure. After 30 minutes the theoretical amount of hydrogen for complete reduction of the carbonyl group had been absorbed. The product, **1-cyclohexyltetralin** (V), consisted of 7.4 g. (91%) of a colorless oil with b.p. 101–102° (0.1 mm.). A middle fraction taken for analysis had n_D^{25} 1.5464; λ_{max}^{EtOH} mμ (ε); 212.5(8305), 266.5 (488), 274 (479); $\tilde{\nu}_{max}^{liquid}$ in cm.$^{-1}$ *736, 753, 761, 802,* 841, 851, 867, *891, 942,* 967, 1035, 1118, 1130, 1156, 1215, *1240, 1265, 1280, 1325, 1347, 1451, 1492,* 1585, *1608,* 1690, *2860, 2920, 3035.*[36]

Anal. Calcd. for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.94; H, 10.19.

(B) Attempted Synthesis from Hexahydrobenzophenone *via* Stobbe Method.—An 18.8-g. (0.1 mole) sample of hexahydrobenzophenone was condensed with 73 g. (0.5 mole) of dimethyl succinate in the presence of 400 ml. of *t*-butyl alcohol containing 16.8 g. (0.43 g. atom) of dissolved potassium according to the method described for the Stobbe condensation with benzophenone.[37] The crude product consisted of 31 g. (102%) of a solid with m.p. 104–111°. After a number of recrystallizations of a portion of this material from petroleum ether (b.p. 63–69°)–benzene, a sample of feathery needles was obtained, m.p. 120–121°, which is presumed to be **β-carbomethoxy-γ-phenyl-γ-cyclohexylvinylacetic acid** or a bond isomer thereof.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.18; H, 7.29.

Attempted decarboxylation of the half-ester by refluxing with acetic acid–48% hydrobromic acid–water[38] gave a mixture from which no pure compound could be isolated. However, when the crude material was subjected to treatment with phosphorus and hydrogen iodide, a solid could be separated which has an analysis and a spectrum in accord with **γ-phenyl-γ-cyclohexylparaconic acid.** After recrystallization from aqueous methanol, this material was obtained as prismatic needles, m.p. 182–182.5°; $\tilde{\nu}_{max}^{CHCl_3}$ in cm.$^{-1}$ 1718 (carboxyl), 1766 (γ-lactone).

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.91; H, 6.98.

Saponification of the Stobbe half-ester gave **β-carboxy-γ-phenyl-γ-cyclohexylvinylacetic acid,** m.p. 152–153°, in 94% yield. An analytical sample was prepared by further recrystallization from petroleum ether (b.p. 63–69°)–ethyl acetate and was obtained in the form of small pellets, m.p. 153–154°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.81; H, 7.28.

Attempted decarboxylation of the dibasic acid by heating for 1 hr. at 160–180° over potassium bisulfate yielded 73% of a compound which, on the basis of the analysis and infrared spectrum, is presumed to be **α-(β-phenyl-β-cyclohexyl)-methylenesuccinic anhydride,** m.p. 123–126°. Further purification by recrystallization from methanol yielded diamond-shaped plates, m.p. 130–130.5°, $\tilde{\nu}_{max}^{CHCl}$ 1780 and 1840 cm.$^{-1}$ (anhydride).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.58; H, 7.30.

(C) Isolation from Cyclization Product of IVa.—Fraction 8 from the fractional distillation of the cyclization product from IVa (*cf.* above), b.p. 108° (0.7 mm.), $n^{25}D$ 1.5495, possessed an infrared spectrum identical in every detail with that given above for authentic 1-cyclohexyltetralin except for an additional weak band at 696 cm.$^{-1}$. This band, which is strong in the earlier fractions of the distillation, is probably due to slight contamination from these materials. Similarly, fraction 13 from the chromatographic separation of the cyclization product from IVa (*cf.* above) possessed an infrared spectrum identical with that of authentic 1-cyclohexyltetralin.

Anal. Calcd. for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: Fraction 8 from distillation: C, 89.94; H, 10.19. Fraction 13 from chromatography: C, 89.55; H, 10.05.

(D) Synthesis from 2-(γ-Phenylpropyl)-cycloheptanol (XXI).—The reduction of the ketone IVa to the alcohol XXI was accomplished in 89% yield with lithium aluminum hydride in ether solution. The **2-(γ-phenylpropyl)-cycloheptanol** was obtained as a colorless oil, b.p. 132–134° (0.3 mm.), $n^{25}D$ 1.5272.

Anal. Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 83.14; H, 10.61.

A solution of 2.71 g. (0.012 mole) of XXI in 20 ml. of carbon disulfide was cooled to 10° and treated with 2.00 g. (0.015 mole) of anhydrous aluminum chloride. The reaction mixture was allowed to warm to room temperature whereupon hydrogen chloride was evolved. After the evolution of gas had ceased, the mixture was gently boiled for a few minutes and then poured onto ice and sulfuric acid. The product, isolated in the usual manner, consisted of 1.91 g. (76%) of a colorless liquid, b.p. 109–110° (0.4 mm.), $n^{25}D$ 1.5460; λ_{max}^{EtOH} mμ (ε): 210 (8700), 266 (850), 274 (725); $\tilde{\nu}_{max}^{liquid}$ in cm.$^{-1}$: *696, 737, 753, 762, 802,* 842, 851, 867, *891, 942, 971, 989,* 1020–1040 (broad), 1118, 1127, 1158, 1218, *1238, 1266, 1280, 1324, 1347, 1450, 1491,* 1581, *1605,* 1690, 1702, 1800, 1910, 1940, 2650, *2840, 2900, 3010* and *3020.*[36]

Anal. Calcd. for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.44; H, 10.39.

That the product resulting from the cyclization of XXI contains 1-cyclohexyltetralin is indicated by the infrared

(33) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., Boston, Mass., 1941, p. 381.

(34) M. S. Newman and P. F. Beal, THIS JOURNAL, **72**, 5163 (1950).

(35) K. W. Rosenmund and E. Karg, *Ber.*, **75**, 1850 (1942).

(36) The absorption bands which are italicized are strong and/or well-defined.

(37) W. S. Johnson and G. H. Daub, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 1.

(38) W. S. Johnson, J. W. Petersen and W. P. Schneider, THIS JOURNAL, **69**, 74 (1947).

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spectrum and, more conclusively, by the formation of solid derivatives identical with those from authentic V (*cf.* below). Other compounds must also be present, however, as suggested by certain bands (*e.g.*, 696, 971 and 989 cm.$^{-1}$) in the infrared spectrum which are not present in the spectrum of pure V.

(E) **Acetyl Derivatives of 1-Cyclohexyltetralin.**—Acetylation of a sample of authentic 1-cyclohexyltetralin with acetyl chloride and aluminum chloride in carbon disulfide yielded 100% of a pale yellow oil. This was treated with 2,4-dinitrophenylhydrazine to yield a solid which could be separated, by fractional crystallization from ethanol–ethyl acetate, into two compounds: (a) yellow, micro-crystalline material with m.p. 239–240°; *Anal.* Calcd. for $C_{24}H_{28}N_4O_4$: C, 66.03; H, 6.47. Found: C, 66.04; H, 6.16. (b) An orange-red micro-crystalline material with m.p. 177–178°. *Anal.* Calcd. for $C_{24}H_{28}N_4O_4$: C, 66.03; H, 6.47. Found: C, 65.99; H, 6.29.

In similar fashion, fraction 8 from distillation and fraction 13 from chromatography (from the cyclization product of IVa) were acetylated and converted to a 2,4-dinitrophenylhydrazone mixture from which in each case two compounds, identical with those described above, were isolated.

Also, the product resulting from the cyclization of 2-(γ-phenylpropyl)-cycloheptanol (XXI) yielded the same two 2,4-dinitrophenylhydrazone derivatives, although in somewhat lower yield, when subjected to this treatment.

2-Cyclohexyltetralin. (A) Synthesis from Cyclohexylsuccinic Anhydride.—β-Carbethoxy-β-cyclohexenylpropionic acid was prepared from cyclohexanone and diethyl succinate according to the method of Johnson, *et al.*[39] The half-ester was hydrogenated in the presence of 10% palladium-on-charcoal catalyst, saponified to cyclohexylsuccinic acid and converted, with acetic anhydride, to cyclohexylsuccinic anhydride, m.p. 35–36°. To a stirred solution of 8.84 g. (0.048 mole) of the anhydride in 35 ml. of dry, thiophene-free benzene cooled to 5–10°, 13.08 g. (0.098 mole) of anhydrous aluminum chloride was added slowly. The reaction mixture was allowed to stand for 16 hr. at room temperature, then heated for 2 hr. at 60–70° and finally worked up in the usual fashion to yield 12 g. (95%) of crude product, m.p. 110–120°. Two recrystallizations from benzene–hexane yielded 9.20 g. (73%) of colorless, fine needles, m.p. 125–126°, presumed to be **α-cyclohexyl-β-benzoylpropionic acid (XV)**.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.26; H, 7.81.

Concentration of the mother liquors from the recrystallizations followed by two further recrystallizations from benzene–hexane yielded 1.61 g. (13%) of colorless needles, m.p. 99–100°, presumed to be **β-cyclohexyl-β-benzoylpropionic acid (XIV)**.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.92; H, 7.67.

A 5.0-g. sample of the higher-melting keto acid was reduced by the Huang-Minlon modification of the Wolff–Kishner method[40] to give 3.2 g. (68%) of **α-cyclohexyl-γ-phenylbutyric acid (XIX)**, with b.p. 174–175° (0.15 mm.), m.p. 59–60°.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.88; H, 9.01.

2-Cyclohexyl-3,4-dihydronaphthalenone (XVIII) was obtained when a 4.5-g. sample of XIX was treated with 150 ml. of anhydrous hydrogen fluoride, allowed to stand for 6 hr. and worked up in the usual fashion to yield 3.44 g. (83%) of pale yellow liquid with b.p. 140° (0.13 mm.), $n^{25}D$ 1.5547, $\bar{\nu}_{max}^{liquid}$ 1685 cm.$^{-1}$ (benzoyl).

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.10; H, 8.84.

The 2,4-dinitrophenylhydrazone of XVIII was obtained, after two recrystallizations from ethanol–ethyl acetate, as orange-red needles, m.p. 231–231.5°.

Anal. Calcd. for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92. Found: C, 64.71; H, 5.96.

The 2,4-dinitrophenylhydrazone of 3-cyclohexyl-3,4-dihydronaphthalenone (XVII) was obtained by reducing the lower-melting keto acid XIV to β-cyclohexyl-γ-phenylbutyric acid (XVI) followed by cyclization to the ketone XVII and derivatization with 2,4-dinitrophenylhydrazine. The pure material was obtained as bright orange, very small needles after two recrystallizations from ethanol–ethyl acetate; m.p. 235–236° dec.

Anal. Calcd. for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92. Found: C, 65.06; H, 6.16.

2-Cyclohexyltetralin (VI) was obtained in 80% yield by hydrogenolysis of XVIII in the presence of 10% palladium-on-charcoal in an ethyl acetate solution containing perchloric acid. It consisted of a colorless, mobile liquid with b.p. 132–134° (0.6 mm.), $n^{25}D$ 1.5413; λ_{max}^{EtOH} mμ (ε): 210 (8280), 266.5 (613), 273.5 (710); $\bar{\nu}_{max}^{liquid}$ in cm.$^{-1}$: *739*, 810, 840, 886, 910, *942*, 968, 1034, 1096, 1185, 1249, *1346*, 1370, *1432*, *1448*, *1494*, *1583*, 1678, *2850* and *2912*.[36]

Anal. Calcd. for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.39; H, 10.13.

(B) Isolation from Cyclization Product from IVa.—Fraction 20 from the chromatographic separation of the cyclization product from IVa (*cf.* above) showed an infrared spectrum almost identical with that of authentic 2-cyclohexyltetralin. The infrared spectrum of 1-cyclohexyltetralin contains more bands than that of 2-cyclohexyltetralin and includes all of those present in the former compound. Only two of these show any noticeable shift (736 and 891 cm.$^{-1}$ in 1-cyclohexyltetralin, 739 and 886 cm.$^{-1}$ in 2-cyclohexyltetralin). Concurrent spectral determinations charted on the same graph, however, show quite clearly the difference between V and VI and support the identity of fraction 20 with VI.

(C) Acetyl Derivatives of 2-Cyclohexyltetralin.—Acetylation of a sample of authentic 2-cyclohexyltetralin with acetyl chloride and aluminum chloride in carbon disulfide yielded a liquid which was then treated with 2,4-dinitrophenylhydrazine. The resulting solid was recrystallized from ethanol–ethyl acetate and yielded two compounds: (a) dark yellow, microcrystalline material with m.p. 247–248°. *Anal.* Calcd. for $C_{24}H_{28}N_4O_4$: C, 66.03; H, 6.47. Found: C, 66.03; H, 6.18. (b) yellow, micro-crystalline material with m.p. 187–188°.

Anal. Calcd. for $C_{24}H_{28}N_4O_4$: C, 66.03; H, 6.47. Found: C, 66.02; H, 6.53. Mixed m.p.'s of these derivatives with the corresponding ones from 1-cyclohexyltetralin showed marked depressions. Insufficient VI was available from fraction 20 of the chromatographic separation to allow identification through the acetyl derivative.

1-Cyclohexylnaphthalene (VII). (A) Synthesis from 1-Cyclohexyltetralin.—A 1.0-g. sample of 1-cyclohexyltetralin was heated for 5 hr. at 235–258° with 0.7 g. of 5% palladium-on-charcoal. The crude product was chromatographed on 40 g. of alumina using petroleum ether (b.p. 63–69°) as the elutrient, and 0.25 g. of VII was obtained, $n^{25}D$ 1.6005; λ_{max}^{EtOH} mμ (ε): 225 (80,050), 273 (6170), 283 (7285), 294 (5120), 313.5 (387) [reported[41] λ_{max} mμ (ε): 225 (31,500), 274 (4000), 283 (4800), 294 (3300), 314 (320)]; $\bar{\nu}_{max}^{liquid}$ in cm.$^{-1}$: 699, *729*, 741, *775*, *788*, *795*, *842*, *856*, *887*, *898*, 947 965, *989*, 1015, *1028*, *1090*, 1130, 1142, *1168*, *1232*, *1263*, 1300, 1325, *1350*, *1400*, *1453*, *1516*, *1606*, *2867*, *2930* and *3080*.[36]

Anal. Calcd. for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.34; H, 8.68.

A picrate of VII with m.p. 126–127° (reported[42] 122–123.5°) and a trinitrobenzene complex with m.p. 118–119° (reported[42] 116.5–117.5°) could be prepared.

(B) Isolation from Cyclization Product of IVa.—Inspection of the infrared spectra of distillation fractions 18–22 indicated that 1-cyclohexylnaphthalene was present (based particularly on the bands at 775, 795, 887, 947, 1263 and 1400 cm.$^{-1}$ which are prominent in VII but weak or absent in VIII) although contaminated with other materials. When a 2.25-g. sample comparable to fraction 18 of the distillation, b.p. 115–117° (0.7 mm.), $n^{25}D$ 1.5870, was treated with an alcoholic solution of picric acid, 1.47 g. of an orange picrate, m.p. 112–115°, precipitated. Several recrystallizations of this material from methanol saturated with picric acid yielded 0.37 g. of orange needles, m.p. 124–125°, which

(39) W. S. Johnson, C. E. Davis, R. H. Hunt and G. Stork, THIS JOURNAL, **70**, 3021 (1948).

(40) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(41) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951.

(42) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 1431 (1936).

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showed no depression in m.p. when admixed with the picrate of authentic VII. The picrate was decomposed by dissolving in benzene and passing through a column of alumina. The resulting product was an oil (λ_{max}^{EtOH} mμ (ε): 225 (78,000), 273 (5800), 283 (6800) 294 (4550), 313.5 (398)) which was converted to a trinitrobenzene complex, m.p. 118–119°, which showed no depression in m.p. when admixed with the same derivative of authentic VII.

2-Cyclohexylnaphthalene (VIII). (A) Synthesis from 2-Naphthylmagnesium Bromide.—A stirred mixture of 6.79 g. (0.033 mole) of 2-bromonaphthalene, 1.59 g. (0.066 g. atom) of magnesium and 50 ml. of dry ether was treated over a period of 30 minutes with a solution of 3.58 g. (0.033 mole) of ethyl bromide in 15 ml. of ether. After an additional 3 hr. of stirring, the reaction mixture was cooled and treated with a solution of 6.44 g. (0.066 mole) of cyclohexanone in 25 ml. of ether. After refluxing the reaction mixture for 3.5 hr. and allowing it to stand at room temperature overnight, the product was isolated in the usual fashion. The crude material was slowly distilled from 3 g. of fused potassium bisulfate in a Claisen flask to yield 4.0 g. (59%) of 2-cyclohexenylnaphthalene, b.p. 135° (0.06 mm.), m.p. 55–57°. One recrystallization from methanol yielded colorless needles, m.p. 60–60.5° (reported[44] 61–62°). Reduction of the olefin with hydrogen in the presence of 10% palladium-on-charcoal yielded 89% of 2-cyclohexylnaphthalene as a colorless, mobile liquid, b.p. 150–152° (0.65 mm.), $n^{25}D$ 1.5955; λ_{max}^{EtOH} mμ (ε): 225 (114,000), 268 (4700), 275 (5050), 285 (3400), 304 (475), 310 (280) 319 (430); $\tilde{\nu}_{max}^{liquid}$ in cm.$^{-1}$: *745*, 768, 786, *815*, *852*, *883*, 920, *954*, *1018*, *1127*, 1142, 1155, 1203, *1270*, *1352*, 1380, *1451*, *1510*, *1610*, *1640*, *2867*, *2934*, and *3067*.[36]

Anal. Calcd. for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.48; H, 8.87.

A trinitrobenzene complex of VIII was obtained as feathery, yellow needles after several recrystallizations from methanol; m.p. 122–123°.

Anal. Calcd. for $C_{22}H_{21}N_3O_6$: C, 62.40; H, 5.00. Found: C, 62.55; H, 4.86.

A picrate with m.p. 98–103° which could not be further purified could be prepared from VIII.

(B) Isolation from Cyclization Product of IVa.—Fraction 24 from the distillation (*cf.* above) and fractions 27–45 from the chromatographic separation (*cf.* above) had infrared spectra very close to that of authentic 2-cyclohexylnaphthalene.

Anal. Calcd. for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: Fraction 24 from distillation: C, 91.28; H, 8.90. Fraction 27–45 from chromatography: C, 91.31; H, 8.44.

When a 0.35-g. sample of distillation fraction 24 was treated with an alcoholic solution of trinitrobenzene, 0.26 g. of bright yellow needles, m.p. 116–120°, precipitated. Several recrystallizations from methanol produced feathery yellow needles, m.p. 122–123°, which showed no depression in m.p. when admixed with the trinitrobenzene complex of authentic VIII.

Unidentified Product.—A 1.70-g. sample of fraction 25 from the distillation of the cyclization product of IVa, b.p. 127–128° (0.3 mm.), was treated with an alcoholic solution of trinitrobenzene. The precipitate, consisting of 1.61 g. of bright orange needles with m.p. 100–114°, was recrystallized from methanol to give 1.0 g. of dull orange needles, m.p. 115–119°. This material was dissolved in petroleum ether (b.p. 63–69°), passed through a column of alumina and 0.46 g. of an oil collected, $n^{32}D$ 1.6255. Upon standing, the oil partially solidified and was thereupon pressed on a porous plate to yield 0.21 g. of material with m.p. 78–84°. Recrystallization from methanol yielded glistening plates, m.p. 91–92°; λ_{max}^{EtOH} (ε): 230 (55,000), 235 (79,000), 285 (6300), 295 (6600), 314 (3800), 328 (3800).

Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.01; H, 7.66.

Dehydrogenation Experiments. (A) Dehydrogenation of 1-Cyclohexyltetralin (V).—The low temperature dehydrogenation of V to give cyclohexylnaphthalene is described above. A more strenuous dehydrogenation was carried out by mixing 1.0 g. of V with 0.3 g. of 10% palladium-on-charcoal catalyst and heating at 235–310° for 10.5 hr. The product consisted of 0.6 g. of a colorless liquid with a slight bluish fluorescence, b.p. 140–143° (0.4 mm.), $n^{25}D$ 1.6598; λ_{max}^{EtOH} mμ (ε): 225 (55,600), 240 (6530), 282.5 (8230), 287.5 (9515), 341.5 (186) [reported[43] λ_{max}^{EtOH} mμ (ε): 226 (62,000), 282 (11,000), 288 (11,000)].

(B) Dehydrogenation of 2-Cyclohexyltetralin (VI).—A mixture of 0.5 g. of 2-cyclohexyltetralin and 0.2 g. of 10% palladium-on-charcoal was heated for 3 hr. at 260–330°. The product consisted of 0.3 g. of solid, m.p. 95–99°, from which pure 2-phenylnaphthalene could be obtained after two recrystallizations from ethanol; m.p. 102–103° (reported[43] 102–103°); λ_{max}^{EtOH} mμ (ε): 212 (36,000), 250 (63,000), 285 (11,000) [reported[43] λ_{max}^{EtOH} mμ (ε): 251 (63,000), 269 (12,500), 288 12,500)].

(C) Dehydrogenation of Cyclization Product of IVa.—A 2.67-g. sample of cyclization product, b.p. 109–126° (0.4 mm.), was treated with 1.0 g. of 5% palladium-on-charcoal catalyst and heated for 2.5 hr. at 390°. The product consisted of 2.00 g. of a red oil from which 1.30 g. of 1-cyclohexylnaphthalene and 0.50 g. of 2-phenylnaphthalene could be separated by chromatography on alumina.

(D) Dehydrogenation of Chromatographic Fractions from Cyclization Product of IVa.—A 0.5-g. sample of chromatographic fractions 8–18 (*cf.* above) dehydrogenated in the presence of 0.35 g. of 5% palladium-on-charcoal at 245–300° for 22 hr. yielded a mixture of 1-cyclohexylnaphthalene and 1-phenylnaphthalene and 4% of 2-phenylnaphthalene, separated by chromatography on alumina. Although the 2-phenylnaphthalene may have arisen by rearrangement during the dehydrogenation, it is thought more probable that it was formed from the small amount of 2-cyclohexyltetralin probably present in chromatographic fractions 8–18. A 0.2-g. sample of chromatographic fractions 27–45 (*cf.* above) dehydrogenated in the presence of 0.1 g. of 10% palladium-on-charcoal at 300–350° for 3.5 hr. yielded 60% of 2-phenylnaphthalene.

(E) Dehydrogenation of Distillation Fractions from Cyclization Product of IVa.—A 0.83-g. sample of distillation fraction 9, b.p. 107–108° (0.7 mm.) (*cf.* above), was dehydrogenated in the presence of 0.2 g. of 5% palladium-on-charcoal at 290° for 2.5 hr. and yielded 2-cyclohexylnaphthalene, isolated as the picrate in 27% yield. A 0.96-g. sample of distillation fraction 24, b.p. 125–126° (0.8 mm.), (*cf.* above) was dehydrogenated in the presence of 0.2 g. of 5% palladium-on-charcoal at 360° for 3 hr. and yielded 90% of 2-phenylnaphthalene.

(F) Dehydrogenation of Cyclization Product of XXI.—A 0.44-g. sample of the cyclization product of XXI was treated with 0.20 g. of 5% palladium-on-charcoal and heated for 3 hr. at 390°. The product consisted of 0.38 g. of a greenish-yellow oil with λ_{max}^{EtOH} mμ (ε): 225 (55,000), 285 (8100) and λ_{min}^{EtOH} 250 mμ. This is very similar to the ultraviolet spectrum of 1-phenylnaphthalene and different from that of 2-phenylnaphthalene which has a maximum at 250 mμ (63,000).

(G) Dehydrogenation of Unidentified Product.—A 40-mg. sample of the unidentified product obtained from the cyclization of IVa (*cf.* above) was treated with 20 mg. of 10% palladium-on-charcoal and heated for 3 hr. at 260–300°. The solid product was recrystallized from ethanol to give colorless plates: m.p. 107–108°; λ_{max}^{EtOH} mμ (ε): 212 (26,000), 224 (16,000), 250 (47,000), 257 (58,000), 280 (10,400), 291 (10,500), 303 (13,700), 321 (890), 336 (1600).

Anal. Calcd. for $C_{16}H_{12}$: C, 94.08, H, 5.92. For $C_{16}H_{10}$: C, 95.02, H, 4.98. Found: C, 94.74; H, 6.24.

A trinitrobenzene complex of the dehydrogenation product was obtained after recrystallization from ethanol, as yellow feathery needles, m.p. 168–169°.

Anal. Calcd. for $C_{22}H_{15}N_3O_6$: C, 63.31; H, 3.62. For $C_{22}H_{13}N_3O_6$: C, 63.61; H, 3.15. Found: C, 63.81; H, 3.48.

ST. LOUIS, MO.

(43) L. F. Fieser and E. B. Hershberg, THIS JOURNAL, **60**, 940 (1938).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

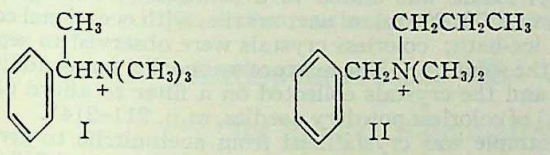
A Novel Ring Enlargement Involving the *ortho* Substitution Rearrangement by Means of Sodium Amide in Liquid Ammonia[1]

BY DANIEL LEDNICER AND CHARLES R. HAUSER

RECEIVED MARCH 28, 1957

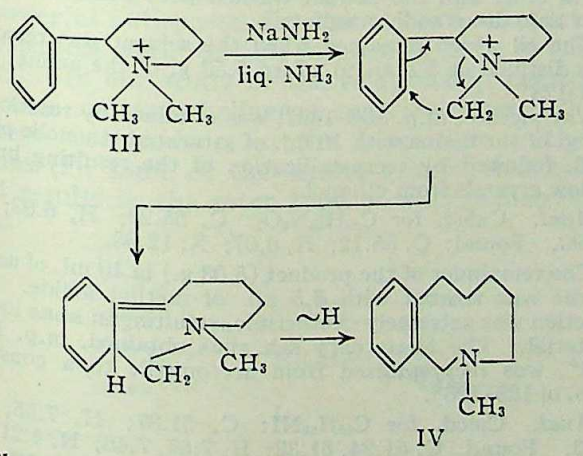
The *ortho* substitution rearrangement was realized with the 1,1-dimethyl-2-phenylpiperidinium ion, the piperidine ring of which underwent ring enlargement to form a new nine-membered nitrogen-containing ring system. The structure of the product was established by independent synthesis. The success of the rearrangement appears to be dependent on a favorable conformation of the molecule, in which a methyl group is near to the *o*-position of the aromatic ring, since similar open-chain quaternary ammonium ions exhibit considerable β-elimination.

The *ortho* substitution rearrangement by means of sodium amide in liquid ammonia has been especially characteristic of benzyl-type quaternary ammonium ions having no β-hydrogen such as the benzyltrimethylammonium ion.[2] The rearrangement has been realized, however, in fairly good yields with quaternary ions I and II which do have β-hydrogens.[3] For example, the former ion underwent the rearrangement to 2-ethylbenzyldimethylamine in 42% yield. This reaction was accompanied by β-elimination to give styrene in 14% yield as well as some dimerization and trimerization.



I II

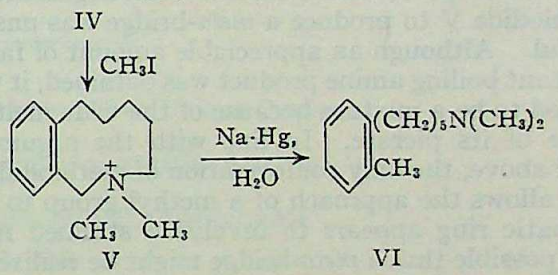
Since the quaternary ion III has some of the structural features of both I and II, it might be expected to undergo the rearrangement to some extent involving the novel ring enlargement shown below. Actually this reaction was realized in 83% yield to form tertiary amine IV, which has a new nine-membered nitrogen-containing ring system. No appreciable β-elimination was observed.



III IV

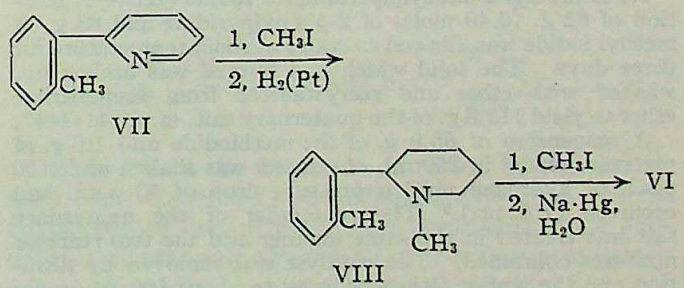
The starting quaternary ion III (as iodide) was prepared by the hydrogenation of the methiodide of 2-phenylpyridine followed by treatment with methyl iodide. This is a modification of the route described in the literature[4] in which 2-phenylpyridinium chloride was hydrogenated, the product then methylated and finally quaternized.

The reaction of III with sodium amide in liquid ammonia was carried out in the usual manner. The colorless amine product boiled over a narrow range. On exhaustive oxidation with permanganate, *o*-phthalic acid was obtained in 55% yield, showing that the rearrangement had indeed involved substitution into an *o*-position of the aromatic ring. That ring enlargement had occurred to form amine IV was established by an Emde reduction of the methiodide of the product V which gave amine VI in 80% yield.



V VI

The structure of the latter amine VI was confirmed by an independent synthesis from 2-*o*-tolylpyridine (VII),[5] the structure of which seems well established.



VII VIII

Each of four steps of this independent synthesis appears unequivocal. Thus, the hydrogenation of the methiodide should not be expected to cause structural changes, while the Emde reduction is known to cleave only benzyl-type quaternary salts. The over-all yield from VII to VI was 54%.

It was shown, incidentally, that the product from the *ortho* substitution rearrangement of quaternary ion III was not tertiary amine VIII[6] which is isomeric with tertiary amine IV. Thus, the methiodides of these two amines not only melted seventeen degrees apart, but a considerable depression of the melting points was observed on mixing the two

(1) Supported by the Office of Ordnance Research, U. S. Army.
(2) S. W. Kantor and C. R. Hauser, THIS JOURNAL, **73**, 4122 (1951).
(3) C. R. Hauser and A. J. Weinheimer, *ibid.*, **76**, 1264 (1954).
(4) R. A. Robinson, *J. Org. Chem.*, **16**, 1911 (1951).

(5) We are indebted to Dr. C. K. Bradsher and Mr. Kenneth B. Moser for a generous sample of this compound which was prepared from *o*-tolyllithium and pyridine, by the method for the preparation of 2-phenylpyridine; J. C. W. Evans and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 517.

(6) This product might have arisen by the migration of a methyl group from nitrogen to the ring by a mechanism that has earlier been discarded; see ref. 2.

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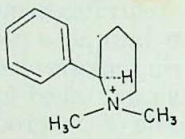
derivatives. Moreover, the two amines showed different infrared absorption bands in the 10–15 μ region.

The fact that quaternary ion III underwent the *ortho* substitution rearrangement unaccompanied by an appreciable amount of β-elimination may be due in part to the closeness of the methyl groups to the aromatic ring as indicated in IX. All conformations of the molecule have at least one of the methyl groups in a favorable position for the attack of its carbanion on the ring. On the other hand, the quaternary ions I and II have conformations which appear to place the methyl groups in less favorable positions for rearrangement; hence, even though they have fewer β-hydrogens than quaternary ion III, they exhibit relatively more β-elimination.



IX

An attempt to effect further rearrangement of methiodide V to produce a *meta*-bridge was unsuccessful. Although an appreciable amount of fairly constant boiling amine product was obtained, it was judged to be a mixture because of the wide melting range of its picrate. In line with the argument cited above, the only conformation of methiodide V that allows the approach of a methyl group to the aromatic ring appears to involve a strained ring. It is possible that a *meta*-bridge might be realized if a larger nitrogen-containing ring were employed. Studies along these lines are now being carried out.

Experimental[7]

1,1-Dimethyl-2-phenylpiperidinium Iodide (III).—A solution of 62 g. (0.40 mole) of 2-phenylpyridine and 88 g. of methyl iodide was allowed to stand at room temperature for three days. The solid which had formed was broken up, washed with ether and recrystallized from acetonitrile–ether to yield 113.8 g. of the quaternary salt, m.p. 141–144°.

A suspension of 56.9 g. of the methiodide and 1.0 g. of platinum oxide[8] in 250 ml. of ethanol was shaken under 50 p.s.i. of hydrogen until a pressure drop of 40 p.s.i. had occurred (1.5 hr.).[9] The remainder of the quaternary salt was treated in the same manner and the two reaction mixtures combined. The catalyst was removed by filtration and the amber filtrate reduced to about 100 ml. under vacuum. The residual oil was taken up in water and the solution saturated with sodium bicarbonate. The alkaline suspension was then extracted with ether and the organic layer dried over sodium sulfate. The yellow oil which remained behind when the solvent was removed *in vacuo* was distilled to afford 41.8 g. of 1-methyl-2-phenylpiperidine, b.p. 103–109° at 9 mm.

The solid which came out when a solution of the tertiary amine in 100 ml. of acetonitrile was treated with methyl iodide (65 g.) followed by ether was recrystallized from acetonitrile–ether to yield 74.1 g. (68% from 2-phenylpyridine) of III, m.p. 178–179.5°, lit.[4] 180°.

Rearrangement of III to IV.—Over a period of 10 minutes 74.1 g. (0.234 mole) of the solid methiodide III was added to 0.46 mole of sodium amide (from 10.6 g. of sodium metal) in 900 ml. of liquid ammonia. The light orange-tan suspension was stirred for an additional hour and then neutralized with 23 g. of solid ammonium chloride. The residue which remained after the ammonia had evaporated was washed thoroughly with about 1 l. of ether; these extracts were washed with water and dried over anhydrous sodium sulfate. The light yellow oil which remained after the ether was removed afforded 38.5 g. (83%) of IV, b.p. 104–106° at 4 mm.

The analytical sample, n^{24}D 1.5380, distilled at 95.5° at 3 mm.

Anal. Calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.67; H, 9.92; N, 7.33.

The picrate of IV was formed from 0.5 g. of the amine and 10 ml. of saturated ethanolic picric acid and recrystallized to a constant m.p. of 169–170°.

Anal. Calcd. for $C_{19}H_{22}N_4O_7$: C, 54.54; H, 5.31; N, 13.38. Found: C, 54.61; H, 5.20; N, 13.35.

Exhaustive Oxidation of IV.—The tertiary amine IV (2.5 g., 0.013 mole) was added to a solution of 0.5 g. of potassium hydroxide and 6.25 g. of potassium permanganate in 100 ml. of water. The suspension was brought to reflux and, over a period of 48 hr., an additional 18.75 g. of permanganate was added in portions. The cooled suspension was filtered and reduced in volume to 30 ml. This solution was cooled in ice, saturated with hydrogen chloride and extracted with 120 ml. of ether. The solid which remained (1.2 g., 55%) on removing the ether was recrystallized from water. The m.p. of this acid, 216° dec., was not depressed by admixture with *o*-phthalic acid. The infrared spectrum of the oxidation product was superposable on that of an authentic sample of the dibasic acid.

Reaction of Amine IV with Methyl Iodide.—Forty ml. of methyl iodide was added to a solution of 38.5 g. (0.205 mole) of IV in 200 ml. of acetonitrile, with occasional cooling in an ice-bath; colorless crystals were observed to separate from the solution. The mixture was cooled for an additional hour and the crystals collected on a filter to afford 65.0 g. (96%) of colorless powdery needles, m.p. 211–214°.

A sample was crystallized from acetonitrile to give the analytical sample as heavy colorless prisms, m.p. 223–225°.

Anal. Calcd. for $C_{14}H_{22}NI$: C, 50.76; H, 6.70; N, 4.23. Found: C, 50.68; H, 6.58; N, 4.31.

Emde Reduction of the Methiodide V to VI.—Over a period of 50 minutes 276 g. of 5% sodium amalgam was added to a hot stirred solution of 10.5 g. (0.034 mole) of the quaternary salt in 200 ml. of water. The mixture was then heated (with stirring) on a steam-bath for 24 hr. The oily layer which separated when the reaction cooled was taken up in ether and the extract washed with water and dried over anhydrous sodium sulfate.

The oil which remained when the solvent was removed was distilled at 5 mm. to afford 5.53 g. of the amine, b.p. 126–128°.

The picrate, m.p. 108–109°, was obtained by reaction of 0.5 g. of the amine with 10 ml. of saturated ethanolic picric acid, followed by recrystallization of the resulting bright yellow crystals from ethanol.

Anal. Calcd. for $C_{20}H_{26}N_4O_7$: C, 55.29; H, 6.03; N, 12.90. Found: C, 55.12; H, 6.07; N, 12.93.

The remainder of the product (5.03 g.) in 10 ml. of acetonitrile was treated with 6.5 ml. of methyl iodide. The reaction was extremely exothermic, resulting in some loss of material. The quaternary salt thus obtained, m.p. 124–126°, was recrystallized from acetonitrile to a constant m.p. of 125–126°.

Anal. Calcd. for $C_{15}H_{26}NI$: C, 51.87; H, 7.55; N, 4.03. Found: C, 51.24, 51.33; H, 7.57, 7.46; N, 4.21.

Independent Synthesis of the Tertiary Amine VI. 1-Methyl-2-*o*-tolylpyridinium Iodide.—Thirty grams (0.21 mole) of methyl iodide was added to 20 g. (0.12 mole) of 2-*o*-tolylpyridine in an ice-cooled flask. The orange solid thus obtained was dissolved in chloroform and treated with activated charcoal. Yellow to orange crystals came out on the addition of ether. The yield of methiodide, m.p. 182–187°, was 34.7 g. (94%). This material was used in the next step without further purification.

A sample, m.p. 199–200°, was obtained by repeated recrystallization from acetonitrile–ether.

Anal. Calcd. for $C_{13}H_{14}NI$: C, 50.18; H, 4.53; N, 4.55. Found: C, 50.14; H, 4.56; N, 4.55.

1-Methyl-2-*o*-tolylpiperidine (VIII).—A suspension of 34.2 g. (0.109 mole) of the above methiodide and 0.5 g. of

(7) Boiling points are uncorrected; melting points are recorded as obtained on a Fisher–Johns melting point block. The microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

(8) American Platinum Works, Newark, N. J.

(9) In a preliminary run it was noted that if the reaction is not stopped when one equivalent of hydrogen has been taken up, considerable overreduction probably in the form of ring cleavage occurs.

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platinum oxide in 200 ml. of ethanol was shaken under 60 p.s.i. of hydrogen. The pressure drop was less than 1 p.s.i.; 3.5 hours after an additional 0.5 g. of catalyst had been added, the theoretical amount (23 p.s.i.) of hydrogen had been taken up. The reaction was worked up in the same manner as described for the reduction of 1-methyl-2-phenylpyridinium iodide. Distillation of the residual oil afforded 15.6 g. (75%) of yellow liquid, b.p. 103–105° at 4.5 mm. This was redistilled through a short Vigreux column to yield 14.8 g. of yellowish oil, $n^{24}D$ 1.5280, b.p. 98–99° at 3.5 mm.

Anal. Calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.30; H, 9.93; N, 7.29.

1,1-Dimethyl-2-*o*-tolylpiperidinium iodide was obtained as colorless fine crystals, m.p. 190–195°, from the reaction of 10.0 g. (0.053 mole) of the tertiary amine in 25 ml. of acetonitrile with 15 ml. of methyl iodide. The yield was 17.4 g. (99%).

A sample of this quaternary salt was recrystallized from acetonitrile–ether to a constant melting point of 206–208°. The mixed melting point of this with the methiodide V (223–225°) was 179–185°.

Anal. Calcd. for $C_{14}H_{22}NI$: C, 50.78; H, 6.70; N, 4.23. Found: C, 50.65; H, 6.72; N, 4.24.

1-Dimethylamino-5-*o*-tolylpentane (VI).—To a well-stirred hot solution of 16.4 g. (0.050 mole) of the above methiodide in 300 ml. of water there was added over 1 hr. 400 g. of 5% sodium amalgam. After an additional 26 hr. heating on steam, the reaction mixture was worked up as in the Emde reduction described above to afford 7.80 g. (77%) of the tertiary amine, b.p. 122–125° at 4.8 mm.

The picrate, m.p. 108–109°, and the methiodide, m.p. 125–126°, were prepared in the same manner as described above. A mixed m.p. of each of these derivatives with those of the amine obtained by reduction of V failed to show any depression.

Attempted Rearrangement of V.—The methiodide (20 g., 0.0605 mole) was added to 0.122 mole of sodium amide (from 2.8 g. of sodium metal) in 200 ml. of liquid ammonia. After 40 minutes stirring, the reaction was neutralized with 12 g. of solid ammonium chloride. The oil which was obtained when the reaction mixture was worked up in the usual manner was distilled through a short Vigreux column. At 2 mm., 2.72 g. of colorless liquid, b.p. 96–100°, was obtained; this was followed by 1.0 g., b.p. 100–110°; the residue (5.07 g.) had not yet come over when the bath temperature was 250°. The first fraction formed a picrate of m.p. 110–165°, which could not be recrystallized readily.

Substantially the same result was obtained with a reaction time of 5 hr. In this case, however, some ether-insoluble, rubber gum was obtained as well.

DURHAM, NORTH CAROLINA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

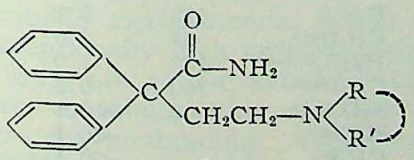
Antispasmodics. X. α,α-Diphenyl-γ-amino Amides[1]

BY ROBERT BRUCE MOFFETT AND BROOKE D. ASPERGREN

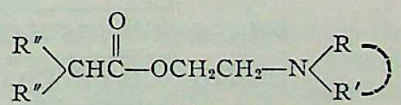
RECEIVED MARCH 25, 1957

A number of α,α-diphenyl-γ-amino amides, their salts and intermediate nitriles have been prepared and tested for anticholinergic activity. In several cases the same tertiary amino groups that previously gave highly active anticholinergics in the ester series also gave very active compounds when introduced into the γ-position of these amides. The effects of substitution or replacement of one of the phenyl groups and of branching the alkyl chain were also explored.

The reports of Bockmühl and Ehrhart[2] in which certain α,α-diphenylamino amides were shown to be powerful antispasmodic agents have stimulated considerable work[3] on this interesting type of compound. In our study of the relationship between structure and anticholinergic activity it seemed of interest to introduce, in the γ-position of these amides (I), some of the amino groups that gave good results in the ester type of anticholinergics[4] (II).



I



II

Table I lists the compounds tested in this study with their toxicities and antispasmodic and gastric antisecretory activities. For comparison the activities of atropine, Pamine,[5] and a few previously reported amides have also been included.

It would hardly be expected that any correlation would exist between the anticholinergic activity and the type of amino groups in molecules so fundamentally different, and indeed no *close* correlation was found. For example, esters containing dimethylamino and piperidyl groupings have not been very effective, whereas at least one amide with each of these groupings has been outstanding enough to market.[6] On the other hand, some pyrrolidine-containing amides are no better than the corresponding pyrrolidine-containing esters. However, the methyl-substituted pyrrolidine-containing esters III, IV and V had atropine indexes (in Thiry-vella dogs) of 2, 1 and 1, and antisecretory ED_{50}'s of 0.4, 0.5 and 0.1, respectively, while the

(1) Presented in part before the Division of Medicinal Chemistry, A.C.S., at Miami, Florida, April, 1957, abstracts p. 19-N.

(2) M. Bockmühl and G. Ehrhart, German Patent 731,560 (1943); *Ann.*, **561**, 52 (1948).

(3) (a) J. B. Hoekstra and H. L. Dickison, *J. Pharmacol. Exptl. Therap.*, **98**, 14 (1950); R. J. Cozort, *ibid.*, **100**, 325 (1950). (b) O. Schaumann and E. Lindner, *Arch. Exper. Path. Pharmacol.*, **214**, 93 (1951). (c) L. C. Cheney, W. B. Wheatley, M. E. Speeter, W. M. Byrd, W. E. Fitzgibbon, W. F. Minor and S. B. Binkley, *J. Org. Chem.*, **17**, 770 (1952); W. B. Wheatley, *ibid.*, **19**, 434 (1954); W. B. Wheatley, W. F. Minor, W. M. Byrd, W. E. Fitzgibbon, M. E. Speeter, L. C. Cheney and S. B. Binkley, *ibid.*, **19**, 794 (1954). (d) P. Janssen, D. Zivkovic, P. Demoen, D. K. deJongh and E. G. von Proosdij-Hartzema, *Arch. intern. pharmacodynamie*, **103**, 82 (1955).

(4) R. B. Moffett, B. D. Aspergren and F. E. Visscher, THIS JOURNAL, **77**, 1565 (1955), and preceding papers.

(5) Pamine Bromide is the Upjohn brand of scopolamine methyl bromide.

(6) α,α-Diphenyl-γ-dimethylaminovaleramide hydrogen sulfate is being marketed by Bristol Laboratories as Centrine; α,α-diphenyl-γ-piperidylbutyramide methobromide is marketed by Farbwerke Hoechst as Resantin.

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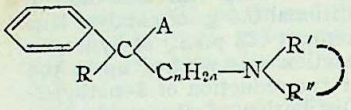
TABLE I

PHARMACOLOGICAL ACTIVITIES



No. of base	R	$-C_nH_{2n}-N\begin{matrix}R'\\R''\end{matrix}$	A	Salt	Toxicity LD_{50} (mg./kg.)[a]	Anti-spasmodic activity At. I.[b]	Anti-secretory activity ED_{50} (mg./kg.)[c]
1	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	H_2SO_4[d]	233	<0.1	0.5
1	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br[d]	167	1.0	0.3
2	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2$	$-C\equiv N$	HCl	..	<0.1	$\ll$1.0
3	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2$	$-CONH_2$	HCl	200	0.1	0.2
3	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	167	3.5	0.08
4	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-C\equiv N$	HCl	200	<0.1	$\ll$1.0
5	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	$^1/_2H_2SO_4$	200	0.1	0.4
5	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	77	4.0	0.003
5	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	$\rightarrow$ O	533	0.2	1.0
6	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CHCH_3$	$-C\equiv N$	HCl	167	<0.05	<1.0
7	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CHCH_3$	$-CONH_2$	HCl	167	<0.1	0.2
7	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CHCH_3$	$-CONH_2$	CH_3Br	77	3.0	0.1
8	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	$-C\equiv N$	HCl	..	...	...
9	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	$-CONH_2$	HCl	..	<0.1	...
9	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	$-CONH_2$	CH_3Br	167	5.0	0.2
10	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	$-C\equiv N$	CH_3Br[e]	65	0.5	0.1–1.0
11	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	$-CONH_2$	HCl[2]	167	1.0	0.1–0.2
11	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br[e]	100	2.0	0.1
11	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	$-CONH_2$	$\rightarrow$ O	767	0.3	1.0
12	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2CH_2$	$-CONH_2$	HCl[f]	167	0.5	0.2
12	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br[f]	77	3.0	0.2
13	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2CHCH_3$	$-C\equiv N$	Base[g]	..	...	...
14	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2CHCH_3$	$-CONH_2$	HCl	65	<0.2	<1.0
14	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2CHCH_3$	$-CONH_2$	CH_3Br	200	1.0	0.2
15	C_6H_5	$-CH_2CH_2-N[CH(CH_3)_2]_2$	$-CONH_2$	H_2SO_4	133	0.1	2.0
15	C_6H_5	$-CH_2CH_2-N[CH(CH_3)_2]_2$	$-CONH_2$	CH_3Br[3d]	65	3.0	0.1
16	C_6H_5	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CONH_2$	H_2SO_4[3a,3c,8]	133	1.0	0.5
16	C_6H_5	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CONH_2$	CH_3I[3a,3c]	150	0.5	5.0
17	C_6H_5	$-CH(CH_3)CH_2-N(CH_3)_2$	$-CONH_2$	$\rightarrow$O·HBr	1000	<0.1	>1.0
17	C_6H_5	$-CH(CH_3)CH_2-N(CH_3)_2$	$-CONH_2$	HCl[3c]	..	<0.1	>1.0
18	C_6H_5	$-CH_2C(CH_3)_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	..	<0.1	$\gg$1.0
18	C_6H_5	$-CH_2C(CH_3)_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	HCl	175	<0.1	0.5
19	C_6H_5	$-CH_2CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	100	3.0	0.1
20	C_6H_5	$-CH_2CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-C\equiv N$	HCl	..	...	...
20	C_6H_5	$-CH_2CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	HCl	200	0.12	>1.0
21	C_6H_5	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	$-CONH_2$	CH_3Br	65	1.0	$\gg$1.0
21	C_6H_5	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	$-CONH_2$	HCl	200	0.1	...
22	C_6H_5	$-CH_2CH_2-N(CH_2)_3C(CH_2)_4CH_2$	$-CONH_2$	CH_3Br	65	0.75	1.0
22	C_6H_5	$-CH_2CH_2-N(CH_2)_3C(CH_2)_4CH_2$	$-CONH_2$	HCl[h]	77	<0.1	...
23	m-ClC_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br[h]	167	0.5	...
			$-C\equiv N$	Base	..	...	...

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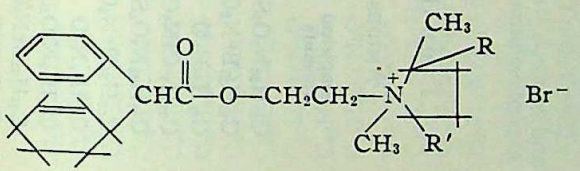
TABLE I (*Continued*)

No. of Base	R	$-C_{n2n}-N\langle R'/R''\rangle$	A	Salt	Toxicity LD_{50} (mg./kg.)[a]	Anti-spasmodic activity At. I.[b]	Anti-secretory activity ED_{50} (mg./kg.)[c]
24	*m*-ClC_6H_4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	HCl	100	<0.1	...
24	*m*-ClC_6H_4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	65	3.0	...
25	*p*-ClC_6H_4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	HCl	167	<0.1	...
25	*p*-ClC_6H_4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	..	2.0	...
26	$-CH(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	HCl	200	<0.1	≫0.1
26	$-CH(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	53	0.2	>0.1
27	$-CH(CH_3)_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	$-C\equiv N$	HCl	..	<0.1	≫0.1
28	$-CH(CH_3)_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	$-CONH_2$	HCl	200	<0.1	>0.1
28	$-CH(CH_3)_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	$-CONH_2$	CH_3Br	77	0.5	>0.1
29	Atropine			$^1/_2H_2SO_4$	150	1.0	0.07
30	Scopolamine			CH_3Br[b]	150	6.0	0.003

[a] The compounds were administered to mice intraperitoneally. The values are approximations with an accuracy of about +100% to −50%. [b] The antispasmodic activity was determined in Thiry-Vella dogs [O. H. Plant, *J. Pharmacol. Exp. Therap.*, 16, 311 (1921)]. The results are expressed as the ratio of the activity to that of atropine sulfate (Atropine Index). [c] The gastric antisecretory activity was determined in pyrolic ligration rats [F. E. Visscher, P. H. Seay, A. P. Tazelaar, Jr., W. Veldkamp and M. J. VanderBrook, *J. Pharmacol. Exp. Therap.*, 110, 188 (1954)]. It is expressed as the effective dose necessary to reduce the gastric secretion by approximately 50%. [d] The corresponding free base, methiodide, and ethosulfate have been reported previously.[3c] [e] This compound was reported by us before the Division of Medicinal Chemistry, A.C.S., at Los Angeles, California, March, 1953. [f] The corresponding free base and methyl *p*-toluenesulfonate quaternary salt have been reported.[3c] [g] Preparation by a different method reported by D. J. Dupré, J. Elks, B. A. Hems, K. N. Speyer and R. M. Evans, *J. Chem. Soc.*, 506 (1949). [h] Preparation reported in paper IX of this series, THIS JOURNAL, 79, 3186 (1957).

corresponding amides had atropine indexes of 3.5, 4 and 3 and ED_{50}'s of 0.08, 0.003 and 0.1. Another grouping occurring in active compounds in both series was the diisopropylamino group. An



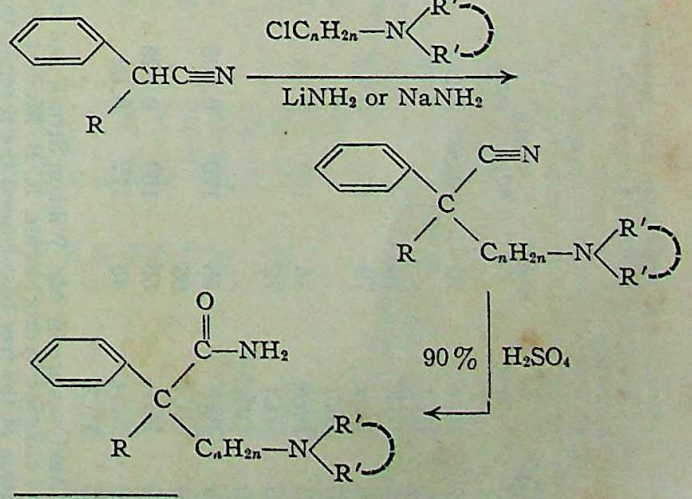
III, R and R′ = H
IV, R = CH_3, R′ = H
V, R = H, R′ = CH_3

ester containing this group, 2-(diisopropylamino)-ethyl-9-xanthine carboxylate methobromide is on the market[7] and the corresponding amide (No. 15 (CH_3Br), Table I) has been extensively studied by Dr. Paul Janssen and associates.[3d] One compound, α,α-diphenyl-γ-(2,2,4-trimethyl-1-pyrrolidyl)-butyramide methobromide (Table I, no. 9) showed exceptionally high antispasmodic activity but only moderate gastric antisecretory activity. The esters containing this trimethylpyrrolidyl group[4] were not outstanding. Therefore, whereas broadly speaking, a surprising number of groups previously found in active esters are also present in our most active amides, considerable variation is apparent between parallel members of the two classes. In addition, it is clear that ED_{50}'s do not go hand-in-hand with atropine indexes.

The amide series (Table I) has been extended by the preparation of a few compounds in which one of the phenyl groups is replaced by an isopropyl group. These were found to be less active than the corresponding diphenyl amides. Substitution of a chlorine atom in the *meta* or *para* positions of one of the phenyl rings tended to decrease the anticholinergic activity. Compounds with the amino group on the δ-carbon atom had very little activity. α,α-Diphenyl-γ-amino amides with a methyl group on the γ-carbon atom are well known.[3a,b,c] Aminopentamide[8] (Table I, no. 16) is of this type. In one case in which two methyl groups were substituted on the γ-carbon atom, the product (Table I, no. 18, MeBr) was considerably more active than the corresponding compound with no methyls on the γ-carbon.

In general, the quaternary salts (methobromides) were more active both as antispasmodics and as antisecretories than the corresponding tertiary amine salts. Aminopentamide[9] is an exception, being more active than its methiodide.[3a] The amine oxides of a few of these amino amides were prepared. They were considerably less toxic than the parent amines but also less active.

A number of the intermediate nitriles were also tested but were found to be much less active as anticholinergics than the corresponding amides.



(7) Probanthine, G. D. Searle and Company.

(8) Centrine, Bristol Laboratories, Inc.

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TABLE II

INTERMEDIATE NITRILES

No. of base (Table I)	Salt or base	Yield, %	B.p. °C.	B.p. Mm.	$n^{25}D$	M.p., °C.	Empirical formula	Carbon Calcd.	Carbon Found[a]	Hydrogen Calcd.	Hydrogen Found[a]	Nitrogen Calcd.	Nitrogen Found[a]	Halogen Calcd.	Halogen Found[a]
2	Base	70	173	0.2	1.5600	.....	$C_{21}H_{24}N_2$	82.85	82.68	7.95	7.76	9.24	9.39	.....	.....
2	HCl	..	..	...	....	189–191[b]	$C_{21}H_{25}ClN_2$	73.99	73.64	7.39	7.26	8.22	8.40	Cl, 10.40	Cl, 10.31
4	HCl[c]	76	..	...	....	209–211	$C_{22}H_{27}ClN_2$	74.45	74.70	7.67	7.98	7.89	8.09	Cl, 9.99	Cl, 9.69
6	Base[d]	79	170	0.12	1.5538	.....	$C_{22}H_{26}N_2$	82.97	82.82	8.23	8.00	8.79	8.99	.....	.....
6	HCl	..	..	...	....	177–179[b]	$C_{22}H_{27}ClN_2$	74.45	74.37	7.67	7.68	7.89	7.67	Cl, 9.99	Cl, 9.99
8	Base	35	150	0.05	1.5473	.....	$C_{23}H_{28}N_2$	83.08	81.99	8.49	8.85	8.43	8.91	.....	.....
8	HCl	72[e]	..	...	....	188–190	$C_{23}H_{29}ClN_2$	74.87	73.90	7.92	7.60	7.59	7.54	Cl, 9.61	Cl, 9.36
10	CH_3Br[f]	..	..	...	....	205.5–207.5	$C_{22}H_{27}BrN_2$	...	...	...	..	7.02	6.95	Br, 20.01	Br, 20.43
13	Base[g]	58	170	0.005	1.5568	.....	$C_{23}H_{28}N_2$	83.08	82.70	8.48	8.50	8.43	8.70	.....	.....
19	HCl[h]	68	..	...	....	157–158	$C_{21}H_{25}ClN_2$	73.99	74.01	7.39	7.69	8.22	8.07	Cl, 10.40	Cl, 9.76
22	Base	56	160	0.025	1.5619	... ..	$C_{22}H_{25}ClN_2$	74.87	74.75	7.14	6.95	7.94	7.99	Cl, 10.05	Cl, 10.23
26	Base[i]	45	112	0.02	1.5002	.....	$C_{17}H_{26}N_2$	79.01	78.73	10.14	9.70	10.84	11.22	.....	.....
26	HCl	..	..	...	....	167–169[j]	$C_{17}H_{27}ClN_2$	69.24	68.98	9.23	9.04	9.50	9.70	Cl, 12.02	Cl, 11.94

[a] Analyses are by Mr. William Struck and staff of our Analytical Chemistry Laboratory. [b] Crystallized from isopropyl alcohol. [c] Prepared from 2-(2,2-dimethyl-1-pyrrolidyl)-ethyl chloride hydrochloride, R. B. Moffett, J. L. White, B. D. Aspergren and F. E. Visscher, THIS JOURNAL, **77**, 1565 (1955). The addition of hydrochloric acid to the toluene solution of the free base caused the precipitation of the hydrochloride. It was collected, dried and recrystallized from a mixture of ethanol and methyl ethyl ketone. [d] This was prepared from 2-(2,5-dimethyl-1-pyrrolidyl)-ethyl chloride hydrochloride, W. B. Reid, J. B. Wright, H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **70**, 3100 (1948). [e] Yield based on the reaction of diphenylacetonitrile without isolation of the free base. A sample was recrystallized from ethyl acetate. [f] This methobromide was prepared from the known base[2] by Mr. John L. White in these laboratories. It was recrystallized from methanol plus methyl ethyl ketone. [g] This was prepared from 2-(2,6-dimethyl-1-piperidyl)-ethyl chloride hydrochloride, J. W. Cusic and R. A. Robinson, *J. Org. Chem.*, **16**, 1921 (1951). (See Table I, footnote *g*.) [h] The addition of hydrochloric acid to the toluene solution of the crude free base caused the precipitation of the hydrochloride. It was collected, dried and recrystallized from methyl ethyl ketone. [i] Prepared from α-phenyl-β-methylbutyronitrile (Table III, footnote *k*) by the general procedure described in the Experimental part except sodium amide was used in place of lithium amide. [j] Recrystallized from ethanol plus ethyl acetate.

TABLE III

AMIDES

No. of base (Table I)	Salt or base	Yield, %	M.p., °C.[a]	Crystallizing solvent	Empirical formula	Carbon Calcd.	Carbon Found[b]	Hydrogen Calcd.	Hydrogen Found[b]	Nitrogen Calcd.	Nitrogen Found[b]	Other element Calcd.	Other element Found[b]
1	H_2SO_4	77	115–118	MeEtCO	$C_{20}H_{26}N_2O_5S$	59.09	59.09	6.45	6.34	6.89	7.12	S, 7.89	S, 7.60
1	CH_3Br	75	228–230	MeOH + *i*-PrOH	$C_{21}H_{27}BrN_2O$	62.52	62.95	6.75	6.77	6.95	7.52	Br, 19.81	Br, 19.90
3	Base	74	142–144	*i*-PrOH	$C_{21}H_{26}H_2O$	78.22	78.60	8.13	8.08	8.69	9.10	.....	.....
3	HCl	..	207–209	MeEtCO	$C_{21}H_{27}ClN_2O$	70.27	70.56	7.58	7.67	7.87	7.92	Cl, 9.88	Cl, 9.72
3	H_2SO_4	..	185–187	EtOH	$C_{21}H_{28}N_2O_6S_{1/2}$	59.97	60.43	6.71	6.73	6.66	6.84	S, 7.62	S, 7.87
3	CH_3Br	98	231–233	MeOH + *i*-PrOH	$C_{22}H_{29}BrN_2O$	63.30	63.36	7.00	7.08	6.71	6.90	Br, 19.15	Br, 19.27
5	Base[c]	72	164–165	*i*-PrOH	$C_{22}H_{28}N_2O$	78.53	78.35	8.39	8.06	8.33	8.21	.....	.....
5	$^1/_2H_2SO_4$	83	173–174	EtOH + MeEtCO	$C_{22}H_{29}N_2O_3S$	68.54	67.84	7.58	7.77	7.27	7.24	S, 4.16	S, 4.22
5	CH_3Br	87	231–233	EtOH	$C_{23}H_{31}BrN_2O$	64.03	64.12	7.24	7.18	6.50	6.57	Br, 18.52	Br, 18.45
5	→ O	33	146.5–148	*i*-PrOH + MeEtCO + Et_2O	$C_{22}H_{28}N_2O_2$	74.96	74.44	8.01	8.06	7.95	7.89	.....	.....
7	Base	66	129–131	*i*-PrOH + H_2O	$C_{22}H_{28}N_2O$	78.53	78.65	8.39	8.43	8.33	8.34	.....	.....

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7	*HCl*	..	*222–224*	*EtOH + EtOAc*	$C_{22}H_{28}ClN_2O$	70.85	70.73	7.84	7.71	7.51	7.76	Cl, 9.51	Cl, 9.12
7	CH_3Br	95	231–235	EtOH + EtOAc + MeEtCO	$C_{23}H_{31}BrN_2O$	64.03	64.36	7.24	7.09	6.50	6.59	Br, 18.52	Br, 18.28
9	Base	82	124–126	*i*-PrOH + H_2O	$C_{23}H_{30}N_2O$	78.81	78.77	8.63	8.39	8.00	8.29	.....	.....
9	HCl	..	221–223	EtOH + MeEtCO	$C_{23}H_{31}ClN_2O$	71.38	70.87	8.08	7.99	7.24	7.17	Cl, 9.16	Cl, 9.36
9	CH_3Br	96	225–226	Benzene	$C_{24}H_{33}BrN_2O$	64.71	64.73	7.46	7.76	6.29	6.13	Br, 17.94	Br, 17.50
11	CH_3Br[d]	87	216–216.5	*i*-PrOH + EtOAc	$C_{22}H_{29}BrN_2O$	63.29	63.33	7.00	6.85	..	..	Br, 19.15	Br, 19.14
11	→ O	98	167.5–168.5	Me_2CO	$C_{21}H_{28}N_2O_2$	74.52	74.44	7.74	7.56	8.30	8.16	.....	.....
12	HCl[c]	55	208–210	EtOH + MeEtCO	$C_{22}H_{28}ClN_2O$	70.85	70.86	7.84	7.74	7.51	7.69	Cl, 9.51	Cl, 9.37
12	CH_3Br[c]	95	209–210	Benzene	$C_{23}H_{31}BrN_2O$	64.02	63.73	7.24	7.07	6.49	6.46	Br, 18.52	Br, 18,27
14	HCl[e]	..	225–227	MeEtCO	$C_{23}H_{31}ClN_2O$	71.38	71.23	8.08	8.26	7.24	7.16	Cl, 9.16	Cl, 8.87
14	CH_3Br	93[e]	224–225	*i*-PrOH	$C_{24}H_{33}BrN_2O$	64.71	64.62	7.47	7.36	6.29	6.60	Br, 17.94	Br, 17.52
15	H_2SO_4[c]	..	178–180	*i*-PrOH + Et_2O	$C_{22}H_{32}N_2O_5S$	60.52	60.56	7.39	7.43	6.42	6.70	S, 7.35	S, 7.45
16	→ O	75	152–154	*i*-PrOH + H_2O	$C_{19}H_{24}N_2O_2 \cdot H_2O$	69.06	68.39	7.93	7.76	8.48	8.56	.....	.....
16	→ O·HBr	83	156–158.5	MeEtCO + EtOAc	$C_{19}H_{25}BrN_2O_2$	58.02	57.74	6.41	6.52	7.12	6.89	Br, 19.45	Br, 21.05
17	CH_3Br[f]	78	194–186	MeOH + *i*-PrOH	$C_{20}H_{27}BrN_2O \cdot H_2O$[g]	58.68	59.32	7.14	7.07	6.84	6.83	Br, 19.52	Br, 19.47
18	HCl[h]	40	220–224	MeOH + *i*-PrOH	$C_{22}H_{29}ClN_2O$	70.85	71.62	7.84	7.70	7.51	7.59	Cl, 9.51	Cl, 9.65
18	CH_3Br	55	167–168	EtOH	$C_{23}H_{31}BrN_2O$	64.03	63.87	7.24	7.24	6.49	6.24	Br, 18.52	Br, 18.73
20	Base	75	125–127	*i*-PrOH	$C_{21}H_{26}N_2O$	78.22	78.55	8.13	8.12	8.69	8.37	.....	.....
20	HCl	100	217–219	EtOH + MeEtCO	$C_{21}H_{27}ClN_2O$	70.27	70.62	7.58	7.59	7.81	7.57	Cl, 9.88	Cl, 9.59
20	CH_3Br	100	215–218	MeEtCO	$C_{22}H_{29}BrN_2O$	63.30	63.66	7.00	7.04	6.71	6.70	Br, 19.15	Br, 18.77
21	HCl[i,e]	73	210–211	*i*-PrOH	$C_{21}H_{29}ClN_2O$	69.88	69.44	8.10	8.18	7.76	7.99	Cl, 9.82	Cl, 9.63
21	CH_3Br	87[e]	187–189	MeEtCO	$C_{22}H_{31}BrN_2O$	63.00	63.34	7.45	7.10	6.68	6.45	Br, 19.06	Br, 18.98
23	Base	54	156–157.5	EtOH	$C_{22}H_{27}ClN_2O$	71.23	70.99	7.34	7.31	7.55	7.65	Cl, 9.56	Cl, 9.56
23	HCl	83	218–220	MeOH + *i*-PrOH	$C_{22}H_{28}Cl_2N_2O$	64.86	65.06	6.93	6.89	6.88	6.82	Cl, 17.41	Cl, 17.03
23	CH_3Br	83	226–228	EtOH	$C_{23}H_{30}BrClN_2O$	59.29	59.31	6.49	6.70	6.01	5.78	Br, 17.16	Br, 17.31
24	Base[j]	68	140–142	EtOH	$C_{22}H_{27}ClN_2O$	71.23	71.36	7.34	8.22	7.55	7.54	Cl, 9.56	Cl, 9.64
24	HCl	79	216–218	EtOH + EtAOc	$C_{22}H_{28}Cl_2N_2O$	64.86	64.72	6.93	6.61	6.88	6.73	Cl, 17.41	Cl, 17.54
24	CH_3Br	60	226–228	MeEtCO	$C_{23}H_{30}BrClN_2O$	59.29	59.55	6.49	6.36	6.01	5.88	Br, 17.06	Br, 17.08
25	HCl[k]	..	226–228	*i*-PrOH	$C_{19}H_{31}Cl_2NO$	67.33	67.03	9.22	8.91	8.27	8.29	Cl, 10.46	Cl, 10.25
25	CH_3Br[e]	82	178–180	MeEtCO	$C_{20}H_{33}BrN_2O$	60.44	61.02	8.37	8.24	7.05	6.84	Br, 20.11	Br, 19.67
27	HCl	..	174–176	EtOH + MeEtCO	$C_{17}H_{29}ClN_2O$	65.25	65.26	9.33	9.19	8.95	8.77	Cl, 11.33	Cl, 11.45
27	CH_3Br	..	164–166	EtOH + EtOAc	$C_{18}H_{31}BrN_2O$	58.41	58.40	8.20	8.56	7.54	7.30	Br, 21.52	Br, 21.20

[a] Melting points are uncorrected. [b] See Table II, footnote *a*. [c] The free base and several quaternary salts of this amide have been reported by Janssen, *et al.*[3d] [d] Some samples of this compound which crystallized from the reaction mixture (tetrahydrofuran) had a melting point of 177.5–178.5°. These had the correct analysis (Found: Br, 19.23) and the same infrared spectrum in chloroform solution although different in a mull. The two forms must therefore be dimorphic. See Table I, footnote *e*. [e] The free base could not be obtained crystalline. The hydrochloride was prepared from the crude free base. The yield for the methobromide is based on the pure hydrochloride from which it was prepared. [f] The free base is reported by Cheney, *et al.*[3o] [g] Water determination by the Karl Fischer method indicated approximately one molecule of water of crystallization. [h] The intermediate nitrile was distilled, b.p. 174° (0.03 mm.), but was not obtained in analytical purity. The yield is the over-all yield from diphenylacetonitrile. [i] Prepared from the corresponding nitrile, D. J. Dupre, J. Elks, B. A. Hems, K. N. Speyer and R. M. Evans, *J. Chem. Soc.*, 500 (1949). [j] The intermediate α-(*p*-chlorophenyl)-α-phenyl-γ-(2,2-dimethyl-1-pyrrolidyl)-butyronitrile was prepared from α-(*p*-chlorophenyl)-α-phenylacetonitrile [M. E. Speeter, L. C. Cheney and S. B. Binkley, THIS JOURNAL, 72, 1659 (1950)] in 55% yield, b.p. 170° (0.1 mm.), but not obtained in analytical purity. [k] The intermediate α-phenyl-α-isopropyl-γ-(2,2-dimethyl-1-pyrrolidyl)-butyronitrile was prepared from α-phenyl-β-methylbutryonitrile (D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 252) in 44% yield by the general procedure described in the Experimental Part, except sodium amide was used in place of lithium amide. The yield was 44%, b.p. 120° (0.015 mm.). It was not obtained in analytical purity but was hydrolyzed to the amide and converted to the hydrochloride.

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Except as noted in the experimental part or in the tables, the amides were prepared by alkylating the appropriate disubstituted nitrile with the requisite amino alkyl halide and hydrolyzing with 90% sulfuric acid. An example is given in the Experimental part.

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Experimental

Unless otherwise indicated all the nitriles, amides and their salts were prepared essentially as described in the following examples.

α,α-Diphenyl-γ-(2-methyl-1-pyrrolidyl)-butyronitrile.—To a suspension of 13.8 g. (0.6 mole) of lithium amide in 900 ml. of dry toluene, was added slowly with stirring 96.62 g. (0.5 mole) of diphenylacetonitrile. The mixture was heated and stirred under reflux for four hours. A solution of 2-(2-methyl-1-pyrrolidyl)-ethyl chloride was prepared by adding an excess of 40% aqueous sodium hydroxide to 92.1 g. (0.5 mole) of the corresponding hydrochloride[9] and extracting with 500 ml. of toluene in several portions. The toluene solution was dried over potassium carbonate and slowly added to the hot suspension of the lithium derivative of diphenylacetonitrile. After heating under reflux with stirring for 18 hours the mixture was cooled and 300 ml. of water was cautiously added. The toluene layer was extracted with dilute hydrochloric acid, and this aqueous acid solution was washed with ether and made basic with 20% sodium hydroxide solution. The free base was extracted with several portions of benzene which were washed with water and dried over sodium sulfate. After removal of the solvent the product was distilled under reduced pressure giving 107 g. (70.3%) of nearly colorless oil; b.p. 173–175° (0.2 mm.).

Hydrochloride.—A sample of the above nitrile in ethyl acetate was acidified with ethanolic hydrogen chloride. The product was recrystallized from isopropyl alcohol giving white crystals, m.p. 189–192°.

α,α-Diphenyl-γ-(2-methyl-1-pyrrolidyl)-butyramide.—A mixture of 126 ml. of concentrated sulfuric acid, 12.6 ml. of water and 67 g. (0.22 mole) of the above nitrile free base[10] was heated with stirring on a steam-bath for four hours. The mixture was cooled, poured onto ice and made strongly basic with ammonium hydroxide. The product separated as a gum which crystallized on standing. It was collected, dried and recrystallized from 400 ml. of isopropyl alcohol giving 52.2 g. (74%) of white crystals, m.p. 142–144°.

Hydrochloride.—A sample of the above amide in ethyl acetate was acidified with ethanolic hydrogen chloride. The resulting gum was recrystallized from methyl ethyl ketone; m.p. 207–209°.

Acid Sulfate.—A sample of the above amide free base in methanol was treated with one molar equivalent of concentrated sulfuric acid. The acid sulfate was precipitated by the addition of absolute ether and was recrystallized from ethanol; m.p. 185–187°.

Methobromide.—A large excess of cold methyl bromide was added to a cold solution of 20 g. (0.062 mole) of the above amide free base in 100 ml. of benzene.[11] The flask (round) was tightly stoppered, and allowed to stand at room temperature for three days. The product was collected giving 25.5 g. (98.5%) of crystals, m.p. 230–233°. This was recrystallized from a mixture of methyl and isopropyl alcohols giving 22.8 g. of white crystals, m.p. 231–233°.

α,α-Diphenyl-γ-(1-piperidyl)-butyramide N-Oxide.—To a suspension of 19.7 g. (0.061 mole) of α,α-diphenyl-γ-(1-piperidyl)-butyramide[2] in about 1 l. of methanol was added 35 ml. of 30% hydrogen peroxide. The mixture was shaken for three days during which time the solid dissolved. The excess hydrogen peroxide was decomposed by adding an aqueous slurry of platinum-on-charcoal and shaking for five hours. The solution was filtered and distilled below 50° under reduced pressure. The residue was dissolved in boiling ethyl acetate and on cooling an oil separated which soon crystallized. The crystalline solid was collected and air dried; weight 22 g., m.p. 70–75°. This appears to be a hydrate containing about 1.5 molecules of water.

Anal. Calcd. for $C_{21}H_{26}N_2O_2 \cdot 1\frac{1}{2}H_2O$: C, 69.0; H, 8.00; N, 7.67; H_2O, 7.40. Found: C, 68.94, 69.95; H, 8.18, 7.82; N, 7.61; H_2O, 8.88 by Karl Fischer method.[12]

A sample of this hydrate was mixed with 75 ml. of boiling acetone. Most of it dissolved and then immediately began to precipitate as a white crystalline solid. After boiling a few minutes and cooling the anhydrous material was obtained, m.p. 167.5–168.5°.

α,α-Diphenyl-γ-(dimethylamino)-valeramide N-Oxide Hydrate.—This was prepared by a procedure similar to the above from 14.8 g. (0.05 mole) of the corresponding free base[3c] and 10 ml. of 30% hydrogen peroxide in 190 ml. of methanol. The product was crystallized from 80% aqueous isopropyl alcohol and appears to contain approximately one molecule of water as a hydrate.

Hydrobromide.—To a solution of 11.2 g. (0.04 mole) of the above free base in 50 ml. of methanol was added 4 ml. (0.041 mole) of 48% hydrobromic acid. The solution was distilled nearly to dryness below 40° under reduced pressure. The resulting sirup was dissolved in 25 ml. of methyl ethyl ketone and diluted to turbidity at the b.p. with ethyl acetate. After cooling in the refrigerator the crystals were collected and dried for a short time in a vacuum desiccator. Too much drying causes the material to turn red; yield 10.94 g. (82.5%). It appears to contain a small amount (about 1/4 molecule) of water of crystallization.

2-(2,2,4-Trimethyl-1-pyrrolidyl)-ethyl Chloride Hydrochloride.—Hydrogen chloride gas was passed into a solution of 42 g. (0.267 mole) of 2-(2,2,4-trimethyl-1-pyrrolidyl)-ethanol[13] in 200 ml. of benzene, with stirring and cooling by an ice-bath, until it tested strongly acid. While still cooled by the ice-bath, 24.5 g. (0.4 mole) of thionyl chloride was added dropwise with stirring. The solution was then gently heated under reflux for two hours during which sulfur dioxide and hydrogen chloride were evolved. About 50 ml. of solvent was removed by distillation and the mixture was cooled. The crystalline product was collected and washed with absolute ether; yield 55.3 g. (98%), m.p. 162–165°. Recrystallization from isopropyl alcohol raised the melting point to 164–166°.

Anal. Calcd. for $C_9H_{19}Cl_2N$: C, 50.95; H, 9.03; Cl, 33.42; N, 6.60. Found: C, 51.29; H, 9.19; Cl, 33.22; N, 6.96.

2-Methyl-2-(1-pyrrolidyl)-propyl Chloride Hydrochloride.—This was prepared by a procedure similar to the above from 104 g. (0.728 mole) of 2-methyl-2-(1-pyrrolidyl)-propanol,[14] 65 ml. of thionyl chloride and 500 ml. of benzene. The product was recrystallized from a mixture of ethanol and ethyl acetate; yield 138 g. (96%), m.p. 145–147°.

Anal. Calcd. for $C_8H_{17}Cl_2N$: C, 48.49; H, 8.65; N, 7.07; Cl, 35.79. Found: C, 48.79; H, 8.74; N, 6.78; Cl, 35.58.

3-(1-Pyrrolidyl)-propyl Chloride Hydrochloride.—This was prepared by a similar procedure from 200 g. (1.55 moles) of 3-(1-pyrrolidyl)-propanol,[15] 135 ml. of thionyl chloride and 1 l. of benzene. The product was recrystallized from a mixture of isopropyl alcohol and ethyl acetate; yield 250 g. (88%), m.p. 140–142°.

Anal. Calcd. for $C_7H_{15}Cl_2N$: C, 45.66; H, 8.21; Cl, 38.52; N, 7.61. Found: C, 46.13; H, 8.40; Cl, 38.87; N, 7.78.

(9) H. G. Kolloff, J. H. Hunter, E. H. Woodruff and R. B. Moffett, THIS JOURNAL, **71**, 3988 (1949).

(10) Hydrochlorides or other salts may be used equally well for this hydrolysis.

(11) In general methyl ethyl ketone was found to be a superior solvent for the preparation of quaternary salts.

(12) The Karl Fischer water determination tends to give high results with amine oxide hydrates probably due to reaction of the N-oxide with the reagent.

(13) R. B. Moffett and J. L. White, *J. Org. Chem.*, **17**, 407 (1952).

(14) R. B. Moffett, *ibid.*, **14**, 862 (1949).

(15) H. G. Kolloff, J. H. Hunter, E. H. Woodruff and R. B. Moffett, THIS JOURNAL, **70**, 3862 (1948).

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m-Chlorophenylphenylacetonitrile.—This was prepared essentially as described for diphenylacetonitrile[16] from 203.2 g. (2.0 moles) of *m*-chlorophenylacetonitrile, 110.3 ml. (2.2 moles) of bromine, 936 ml. of benzene and 267 g. (2.0 moles) of aluminum chloride. The product was distilled under reduced pressure, b.p. 145–148° (0.25 mm.), giving an oil which crystallized from 300 ml. of isopropyl alcohol, m.p. 50–52°; yield 230.3 g. (50.6%).

Anal. Calcd. for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43; N, 6.15; Cl, 15.57. Found: C, 73.95; H, 4.25; N, 6.09; Cl, 15.59.

KALAMAZOO, MICHIGAN

(16) C. M. Robb and E. M. Schultz, *Org. Syntheses*, **28**, 55 (1948).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

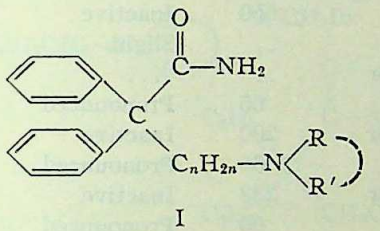
Antispasmodics. XI. α,α-Diphenyl-γ-amino-N-monosubstituted Amides[1]

BY ROBERT BRUCE MOFFETT, BROOKE D. ASPERGREN AND M. E. SPEETER

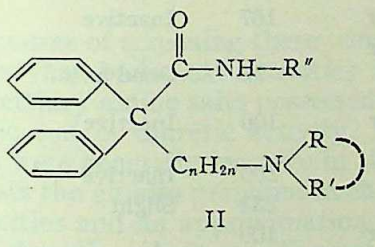
RECEIVED MARCH 25, 1957

Although α,α-diphenyl-γ-tertiaryamino amides (I) are well known as anticholinergics, no similar amides monosubstituted on the amide nitrogen (II) have been previously reported. A series of these have now been made but unexpectedly they have little if any anticholinergic properties. However, these tertiary amino amides were found to be powerful oxytocics and/or diuretics.

Amides of the general type I, unsubstituted on the amide nitrogen, are well known as anticholinergics.[2] In our study of the relationship of structure



I

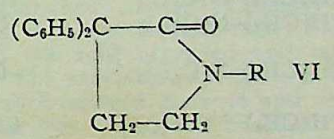


II

to anticholinergic activity it seemed desirable to prepare some amides substituted on the amide nitrogen. A search of the literature revealed that while many unsubstituted amides and a few disubstituted amides[3–5] of this type are known, none of the N-monosubstituted amides (II) have been reported.

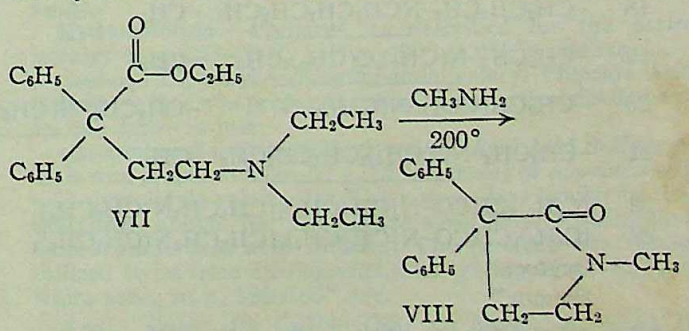
The simplest method for preparing these substituted amides would involve hydrolysis of the well known nitriles III, to the acids IV. These would then be converted to the acid chlorides V, and treated with the requisite primary amine.

This (method A) gave good results when $-C_nH_{2n}-$ was $-CH_2CH(CH_3)-$ or $-CH_2CH_2CH_2-$ but when $-C_nH_{2n}-$ was $-CH_2CH_2-$ or $-CH(CH_3)CH_2-$ the cyclization reaction to give 3,3-diphenylpyrrolidones (VI)[6,7] took precedence and little if any of the desired amides were obtained.



VI

Likewise when the ethyl ester VII was heated with methylamine under sufficiently vigorous conditions to cause reaction, the only product isolated was a pyrrolidone (VIII). It is interesting that in this case the substituent on the nitrogen was methyl rather than ethyl.



VII VIII

An attempt to alkylate a diphenyl-N-monosubstituted acetamide with an amino alkyl chloride gave only N-alkylation even when a hindered amide (isopropyl) was used.

The amides (II, $-C_nH_{2n}-$ = $-CH_2CH_2-$ or $-CH(CH_3)CH_2-$) could, however, be obtained readily (with one exception) by alkylating the correspond-

(1) Presented in part before the Division of Medicinal Chemistry, American Chemical Society, at Miami, Florida, April, 1957, Abstracts p. 19-N.

(2) Paper X of this series and references given therein, THIS JOURNAL, **79**, 4451 (1957).

(3) M. Bockmühl and G. Ehrhart, German Patent 731,560 (1943).

(4) L. C. Cheney, W. B. Wheatley, M. E. Speeter, W. M. Byrd, W. E. Fitzgibbon, W. F. Minor and S. B. Binkley, *J. Org. Chem.*, **17**, 770 (1952).

(5) P. Janssen, THIS JOURNAL, **78**, 3862 (1956).

(6) J. H. Gardner, N. R. Easton and J. R. Stevens, *ibid.*, **70**, 2906 (1948).

(7) R. L. Clarke, A. Mooradian, P. Lucas and T. J. Slauson, *ibid.*, **71**, 2821 (1949).

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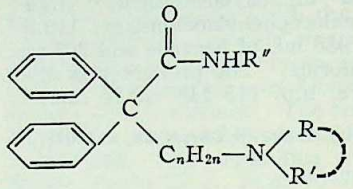
TABLE I

PHARMACOLOGICAL ACTIVITIES



No. of base	$-C_nH_{2n}-N$	R″	Salt	Toxicity LD_{50} (mg./kg.)[a]	Oxytocic activity[b] at 1 mg./kg.	Diuretic activity[c] at 10 mg./kg.
1	$-CH_2CH_2-N(CH_2CH_3)_2$	$-CH_3$	HCl	200	Pronounced	Good
1	$-CH_2CH_2-N(CH_2CH_3)_2$	$-CH_3$	CH_3Br	100	Inactive	...
2	$-CH_2CH_2-N[CH(CH_3)_2]_2$	$-CH_3$	HCl	65	Pronounced[d]	Excellent
3	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2$	$-CH_3$	HCl	200	Moderate	Inactive
4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CH_3$	HCl	167	Slight	Good
4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CH_3$	CH_3I	..	Inactive	...
5	$-CH(CH_3)CH_2-N(CH_3)_2$	$-CH_3$	HCl	..	Inactive	Mild
6	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_3$	HCl	65	Pronounced	Excellent
6	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_3$	CH_3Br	100	Inactive	Inactive
6	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_3$	→ O	>1000	Inactive	Good
7	(*d*)$-CH_2CH(CH_3)-N(CH_3)_2$[e]	$-CH_3$	HCl	77	Moderate	Excellent
7	(*d*)$-CH_2CH(CH_3)-N(CH_3)_2$[e]	$-CH_3$	CH_3Br	..	...	...
7	(*d*)$-CH_2CH(CH_3)-N(CH_3)_2$[e]	$-CH_3$	→ O	650	Inactive	Excellent
8	(*l*)$-CH_3CH(CH_3)-N(CH_3)_2$[f]	$-CH_3$	HCl	..	Slight	Good
8	(*l*)$-CH_2CH(CH_3)-N(CH_3)_2$[f]	$-CH_3$	CH_3Br	..	...	...
9	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH_3$	HCl	65	Pronounced	Excellent
9	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH_3$	CH_3Br	200	Inactive	Inactive
10	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH(CH_3)_2$	HC.	65	Pronounced	Excellent
10	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH(CH_3)_2$	CH_3Br	233	Inactive	Inactive
11	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH=CH_2$	HCl	65	Pronounced	Fair
11	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH=CH_2$	CH_3Br	167	Inactive	...
12	$-CH_2CH(CH_3)-N(CH_3)_2$	$-(CH_2)_3CH_3$	CH_3Br	..	...	...
13	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH(CH_2)_5$	HCl	77	Good at 0.5	Fair
13	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH(CH_2)_5$	CH_3Br	100	Inactive	...
14	$-CH_2CH(CH_3)-N(CH_3)_2$	C_6H_5	HCl	200	Inactive	Slight
15	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH_2OH$	HCl	233	Slight	Good
15	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH_2OH$	CH_3Br	100	...	...
16	$-CH_2CH(CH_3)-N(CH_3)_2$	$-NH_2$	Base[g]	86[h]	Inactive	Fair
17	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	$-CH_3$	HCl	233	Slight	Inactive
17	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	$-CH_3$	CH_2Br	65	Inactive	Inactive
18	$-CH_2CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CH_3$	HCl	200	Inactive	...
18	$-CH_2CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CH_3$	CH_3Br	65	Inactive	Inactive
19	$-CH_2CH_2-N(CH_2)_3C(CH_2)_4CH_2$	$-CH_3$	HCl[i]	100	Pronounced	Fair
20	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH_2-N(CH_2)_3CH_2$	2HCl	200	Inactive	Inactive
21	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$[j]	$-CH_3$	Base[k]	200	...	Fair
22	$(C_6H_5)_2CHCO-N[CH(CH_3)_2]CH_2CH_2N(CH_2CH_3)_2$		HCl	167	Pronounced	Mild
22	$(C_6H_5)_2CHCO-N[CH(CH_3)_2]CH_2CH_2N(CH_2CH_3)_2$		CH_3Br	65	Inactive	Inactive
	Oxytocin[l]		...	..	Pronounced	...
	Diamox[m]			1000	...	Excellent

[a] Administered to mice intraperitoneally. The values are approximations with an accuracy of about +100% to −50%. [b] Tested by intravenous administration in cats by a modification of the method of M. L. Clary, A. Cameron and B. N. Cramer, *Proc. Soc. Exp. Biol., Med.*, **77**, 778 (1951). [c] Administered orally to rats. [d] At 2 mg./kg. [e] This is the dextrorotating stereoisomer. [f] This is the levorotating stereoisomer. [g] Hydrazide. [h] This toxicity was by intravenous injection. [i] Preparation reported, THIS JOURNAL, **79**, 4451 (1957). [j] In this compound a *p*-chlorophenyl replaces one of the phenyl groups. [k] This base was dissolved in dilute hydrochloric acid and buffered to suitable *p*H for biological testing. [l] Oxytocic principle from the posterior lobe of the pituitary gland. It was given at 0.05 unit per kg. [m] The Lederle Laboratories brand of 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide.

ing unsubstituted amides with sodium amide and an alkyl halide (method B). Methyl bromide was used in this work. The one exception noted was the case where R and R′ were methyls. In this case the attack was on the amino nitrogen and the quaternary salt was the principal product.

These amides in the form of their hydrochlorides and also their methobromides were tested as anti-

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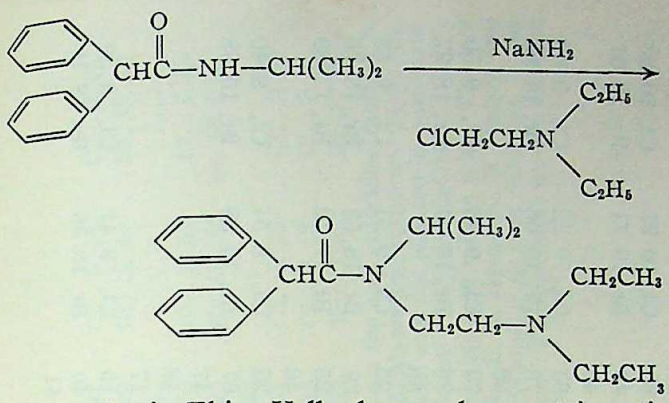
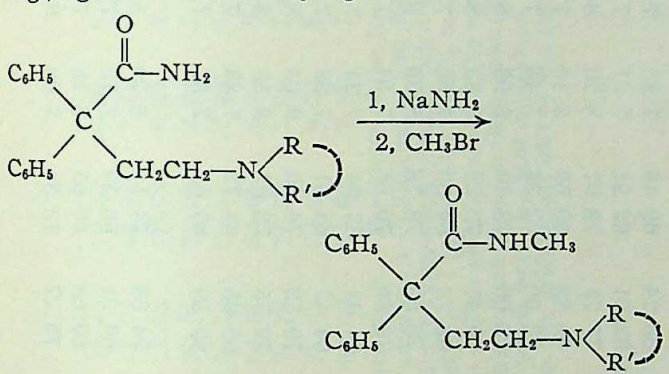


spasmodics in Thiry-Vella dogs and as gastric antisecretories in pyloric ligation rats. Surprisingly neither the tertiary amine nor quaternary salts showed any appreciable anticholinergic activity, being generally less than one-tenth as active as atropine sulfate as antispasmodic and inactive at 1 mg./kg. as antisecretory agents.



In the course of screening these compounds for a wide variety of biological activities it was found that the tertiary amine salts possessed a high order of oxytocic and/or diuretic activity. The quaternary salts were generally inactive in these respects. Table I lists the amides prepared in this study with their toxicities and an approximation of their oxytocic and diuretic activities. Several of these are considered to have sufficiently desirable properties to warrant clinical investigation.

Acknowledgments.—The authors are indebted to Dr. P. H. Seay, Mr. Wm. Veldkamp, Mr. O. F. Swoap, Mr. B. E. Graham and associates of our Department of Pharmacology for the pharmacological data. The authors also wish to express their appreciation to Dr. R. V. Heinzelman of our Department of Chemistry for guidance in this work.

Experimental

Method A (compounds no. 6–18 and 20 in Table II were made by this method).

α,α-Diphenyl-γ-dimethylamino-N-methylvaleramide.—To a cooled suspension of 207 g. (0.5 mole) of α,α-diphenyl-γ-dimethylaminovaleryl chloride acid sulfate[6] in 600 ml. of benzene was added slowly 78 g. of methylamine in 300 ml. of benzene with stirring. The mixture was allowed to warm to room temperature with stirring for 4 hours. It was then heated under reflux on a steam-bath for one-half hour. After cooling, the benzene solution was well washed with water and extracted with dilute hydrochloric acid. The acidic aqueous solution was made basic with sodium hydroxide and the free base was collected on a filter and dried. The product was recrystallized from isopropyl alcohol giving 138.5 g. (89.2%) of white crystals, m.p. 168–169°.

Hydrochloride.—To a warm solution of 62.1 g. (0.2 mole) of the above free base in 700 ml. of ethyl acetate was added a slight excess of ethanolic hydrogen chloride. On cooling, the hydrochloride crystallized giving 64.5 g. (93%) of white crystals, m.p. 217–219°.

Methobromide.—To a cold solution of 10 g. (0.032 mole) of the above free base in 100 ml. of benzene was added a large excess of cold methyl bromide. The flask was stoppered and allowed to stand at room temperature for 4 days. The product was collected on a filter, dried, m.p. 190–192°.

α,α-Diphenyl-γ-dimethylamino-N-methylvaleramide N′-Oxide.—A mixture of 31.0 g. (0.1 mole) of the above free base, 350 ml. of methanol and 25 ml. of 30% hydrogen peroxide was stirred rapidly at room temperature for 22 hours by which time all the solid had dissolved. After standing for 3 days the excess hydrogen peroxide was decomposed by adding a small amount of an aqueous slurry of platinum-on-charcoal and stirring for 5 hours. The solution was filtered through Supercel and distilled practically to dryness under reduced pressure below 50°. The crystalline residue was recrystallized from ethyl acetate giving white crystals, m.p. 141–144° after sintering at about 120°. This appeared to be a solvate which lost weight on drying at 50° (20 mm.) for 20 hours; yield 29.4 g. (90%); m.p. 147–148.5°.

***dextro*-α,α-Diphenyl-γ-dimethylaminovaleric Acid Acid Sulfate.**—A mixture of 138 g. (0.5 mole) of *dextro*-α,α,γ-dimethylaminovaleronitrile,[8] 175 ml. of concentrated sulfuric acid and 107 ml. of water was heated under reflux at 150° for 5 hours. After cooling it was poured onto ice and the white solid was collected on a filter. This was dissolved in 290 ml. of boiling absolute ethanol and diluted with an equal amount of ether. The product was collected and dried giving 322 g. (94%) of the acid sulfate salt; m.p. 195–198°; $[\alpha]^{22}D$ +74° (1.0% in methanol).

Free Basic Acid.—A sample of the above salt was dissolved in dilute sodium hydroxide and made just acid with acetic acid. The product was collected and dried; m.p. 219–221° dec.; $[\alpha]^{22}D$ +115° (1.0% in methanol).

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.79; N, 4.71. Found: C, 76.74; H, 7.70; N, 4.76.

***dextro*-α,α-Diphenyl-γ-dimethylaminovaleryl Chloride Acid Sulfate.**—A mixture of 105 g. (0.265 mole) of the above *dextro* acid sulfate salt, 120 ml. of thionyl chloride and 150 ml. of benzene was heated under reflux with stirring for 45 minutes. All the acid dissolved and later the product crystallized. The excess thionyl chloride was removed by distillation under reduced pressure and an additional 100 ml. of benzene was added and distilled. The crystalline product was collected, washed with benzene and absolute ether and dried in a vacuum desiccator; yield 104 g. (95%).

***levo*-α,α-Diphenyl-γ-dimethylaminovaleric Acid Acid Sulfate.**—This was prepared as described above for the *dextro* isomer; yield 81%; m.p. 195–198°, $[\alpha]^{22}D$ −76° (1.0% in methanol).

Free Basic Acid.—Prepared as described for the *dextro* isomer; m.p. 219–221° dec., $[\alpha]^{22}D$ −111° (1.0% in methanol).

Hydrochloride.—Prepared as described for the *dextro* isomer; m.p. 228–230°, $[\alpha]^{22}D$ −90° (1.0% in methanol).

***levo*-α,α-Diphenyl-γ-dimethylaminovaleryl Chloride Acid Sulfate.**—This was prepared in 96% yield as described above for the *dextro* isomer.

α,α-Diphenyl-γ-(1-pyrrolidyl)-valeric Acid Acid Sulfate.—This was prepared from 50 g. (0.146 mole) of α,α-diphenyl-γ-(1-pyrrolidyl)-valeronitrile[2] by a procedure similar to that described above for the *dextro*-α,α-diphenyl-γ-dimethylaminovaleric acid acid sulfate. The product was recrystallized twice from alcohol plus ether giving 50 g. (82%) of white solid, m.p. 180–185° dec.

Anal. Calcd. for $C_{21}H_{27}NO_6S$: C, 59.83; H, 6.45; N, 3.33; S, 7.61. Found: C, 60.16; H, 6.71; N, 3.50; S, 7.52.

β-Pyrrolidylethylamine.[9]—To 853 g. (12 moles) of dry pyrrolidine, in a 5-l. flask, was added slowly 499 g. (2.44 moles) of β-bromoethylamine hydrobromide with vigorous stirring and cooling by an ice-bath. The addition was carried out at such a rate that the temperature did not rise

(8) A. Pohland, F. J. Marshall and T. P. Carney, THIS JOURNAL, **71**, 460 (1949).

(9) This compound has been previously reported, J. J. van Alphen, *Rec. trav. chim.*, **58**, 1105 (1939), and R. H. Reitsema and J. H. Hunter, THIS JOURNAL, **70**, 4009 (1948), but the present method appears to be more convenient.

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— TABLE II

AMIDES

No. of base (Table I)	Salt (or base)	Yield, %[a]	M.p., °C.	Crystallizing solvent	Empirical formula	Carbon Calcd.	Carbon Found[b]	Hydrogen Calcd.	Hydrogen Found[b]	Nitrogen Calcd.	Nitrogen Found[b]	Other element Calcd.	Other element Found[b]
1	HCl	23[c]	185–187	EtOH	$C_{21}H_{29}ClN_2O$	69.88	69.72	8.10	7.81	7.76	7.61	Cl, 9.82	Cl, 9.81
1	CH_2Br	..	216–217	EtOH + EtOAc	$C_{22}H_{31}BrN_2O$	63.00	63.38	7.45	7.73	6.68	6.56	Br, 19.05	Br, 18.70
2	HCl	..	202–204	MeEtCO + Et_2O	$C_{23}H_{33}ClN_2O$	71.02	70.99	8.55	8.24	7.20	7.15	Cl, 9.12	Cl, 9.00
3	HCl	..	195–198	MeEtCO + EtOH	$C_{22}H_{29}ClN_2O$	70.85	70.70	7.84	7.61	7.51	7.49	Cl, 9.51	Cl, 9.61
4	HCl	73[c]	214–216	EtOAc	$C_{23}H_{31}ClN_2O$	71.38	71.38	8.08	8.35	7.24	7.13	Cl, 9.16	Cl, 9.30
4	CH_3I	98[d]	122–125	Benzene	$C_{24}H_{33}IN_2O$	58.53	58.89	6.75	7.18	5.69	5.69	I, 25.77	I, 23.83
5	HCl	64[c]	248–250	EtOH + EtOAc	$C_{20}H_{27}ClN_2O$	69.24	69.66	7.85	7.85	8.08	7.55	Cl, 10.22	Cl, 10.08
6	Base	89	168–169	*i*-PrOH	$C_{20}H_{26}N_2O$	77.38	77.71	8.44	8.46	9.03	9.22	.....	.....
6	HCl	93	217–219	EtOH + EtOAc	$C_{20}H_{27}ClN_2O$	69.24	69.17	7.85	7.59	8.08	8.31	Cl, 10.22	Cl, 10.10
6	CH_3Br	..	190–192	Benzene	$C_{21}H_{29}BrN_2O$	62.21	62.16	7.21	7.03	6.91	6.90	Br, 19.71	Br, 19.65
6	→ O	90	147–148.5	MeOH + EtOAc	$C_{20}H_{26}N_2O_2$	73.75	73.66	8.03	8.23	8.58	8.49	O, 9.80	O, 9.86
7	Base	89	114–116[e]	*i*-PrOH + H_2O	$C_{20}H_{26}N_2O$	77.38	77.26	8.44	8.13	9.03	9.21	.....	.....
7	HCl	95	223–224[f]	EtOH + EtOAc	$C_{20}H_{27}ClN_2O$	69.24	69.11	7.85	7.63	8.08	8.44	Cl, 10.22	Cl, 9.94
7	CH_3Br	96	184–186[g]	MeEtCO	$C_{21}H_{29}BrN_2O$	62.21	62.03	7.21	6.89	6.91	6.74	Br, 19.71	Br, 19.68
7	→ O	..	154–155	EtOAc	$C_{20}H_{26}N_2O_2$	73.75	73.57	8.03	7.72	8.58	8.56	.....	.....
8	Base	95	116–117[h]	*i*-PrOH + H_2O	$C_{20}H_{26}N_2O$	77.38	77.78	8.44	8.12	9.03	9.06	.....	.....
8	HCl	98	221–223[i]	EtOH + EtOAc	$C_{20}H_{27}ClN_2O$	69.24	69.49	7.85	7.71	8.08	7.89	Cl, 10.22	Cl, 10.22
8	CH_3Br	100	181–182[j]	MeEtCO	$C_{21}H_{29}BrN_2O$	62.21	62.21	7.21	7.56	6.91	6.43	Br, 19.71	Br, 19.91
9	Base	84	133–135	*i*-PrOH	$C_{20}H_{28}N_2O$	77.73	78.01	8.70	8.40	8.64	8.42	.....	.....
9	HCl	86	197–199	EtOH + EtOAc	$C_{21}H_{29}ClN_2O$	69.88	69.69	8.10	7.83	7.76	7.63	Cl, 9.82	Cl, 9.66
9	CH_3Br	98	176–178	*i*-PrOH	$C_{22}H_{31}BrN_2O$	63.00	62.86	7.45	7.16	6.68	6.78	Br, 19.06	Br, 18.83
10	Base	48	116–118	Cyclohexane	$C_{22}H_{30}N_2O$	78.06	78.16	8.93	8.89	8.28	8.29	.....	.....
10	HCl	90	216–218	EtOH + MeEtCO	$C_{22}H_{31}ClN_2O$	70.47	70.22	8.33	8.37	7.47	7.73	Cl, 9.46	Cl, 9.50
10	CH_3Br	..	155–158	EtOAc + Et_2O	$C_{23}H_{33}BrN_2O$	63.73	64.09	7.62	7.71	6.46	6.36	Br, 18.44	Br, 18.27
11	Base	84	99–101	*i*-PrOH + H_2O	$C_{22}H_{28}N_2O$	78.53	78.78	8.39	8.32	8.33	8.59	.....	.....
11	HCl	72	167–170	EtOH + EtOAc	$C_{22}H_{29}ClN_2O$	70.85	70.55	7.84	7.59	7.51	7.25	Cl, 9.51	Cl, 9.53
11	CH_3Br	98	167–169	*i*-PrOH	$C_{23}H_{31}BrN_2O$	64.03	63.94	7.24	7.18	6.50	6.29	Br, 18.53	Br, 18.76
12	CH_3Br	76[k]	175–177	EtOAc + Et_2O	$C_{24}H_{35}BrN_2O$	64.42	64.61	7.88	7.73	6.28	6.25	Br, 17.86	Br, 17.89
13	Base	..	94–97	*i*-PrOH + H_2O	$C_{25}H_{34}N_2O$	79.32	79.66	9.05	8.91	7.40	7.48	.....	.....
13	HCl	..	188–191	EtOAc	$C_{25}H_{35}ClN_2O$	72.35	72.07	8.50	8.64	6.75	6.22	Cl, 8.54	Cl, 8.40
13	CH_3Br	..	130–135	EtOAc + Et_2O	$C_{26}H_{37}BrN_2O$	65.95	66.73	7.88	7.98	5.92	5.67	Br, 16.88	Br, 16.38
14	Base	..	169–171	MeOH	$C_{25}H_{28}N_2O$	80.59	80.63	7.57	7.31	7.52	7.47	.....	.....
14	HCl	..	243–244.5	EtOH	$C_{25}H_{29}ClN_2O$	...	...	..	..	6.84	6.86	.....	.....
15	Base	77	149.5–151.5	Benzene + cyclohexane	$C_{21}H_{28}N_2O_2$	74.08	74.55	8.29	8.27	8.23	8.17	.....	.....
15	HCl	77	198–201	EtOH + EtOAc	$C_{20}H_{29}ClN_2O_2$	66.91	66.59	7.75	7.74	7.43	7.15	Cl, 9.41	Cl, 9.39
15	CH_3Br	94	170–171	*i*-PrOH + EtOAc	$C_{22}H_{31}BrN_2O_2$	60.68	60.63	7.18	7.00	6.44	6.40	Br, 18.36	Br, 18.19
16	Base	..	156–158	EtOAc	$C_{19}H_{25}N_3O$	73.27	73.34	8.09	8.01	13.49	13.51	.....	.....

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17	HCl[l]	68	178–180	EtOH + EtOAc	$C_{22}H_{31}ClN_2O$	70.47	8.33	8.43	7.47	6.97	Cl, 9.46
17	CH_3Br	65[d]	190–192	MeEtCO	$C_{25}H_{33}N_2O$	63.73	7.67	7.59	6.46	6.38	Br, 18.44
18	Base	63[m]	122–124	Cyclohexane	$C_{22}H_{28}N_2O$	78.53	8.39	8.25	8.33	8.51	.....
18	HCl	77	147–149	EtOH + MeEtCO	$C_{22}H_{29}ClN_2O$	70.85	7.84	7.72	7.51	7.79	Cl, 9.51
18	CH_3Br	98	238–240	MeEtCO	$C_{23}H_{31}BrN_2O$	64.03	7.24	7.12	6.49	6.55	Br, 18.52
20	2HCl	62	160–163	EtOH + EtOAc	$C_{25}H_{37}Cl_2N_3O$	64.37	8.00	8.19	9.01	9.12	.....
21	Base	26	121–123	Hexane	$C_{23}H_{29}ClN_2O$	71.76	7.59	7.68	7.28	7.51	Cl, 9.21
22	HCl	..	180–182	Dioxane	$C_{23}H_{33}ClN_2O$	71.02	8.52	8.43	7.20	7.35	Cl, 9.12
22	CH_3Br	..	161–163	MeEtCO	$C_{24}H_{35}BrN_2O$	64.42	7.88	7.92	6.26	6.55	Br, 17.86

[a] Unless otherwise indicated the yields of the salts are calculated from the corresponding free bases. The yields of the bases are calculated from the acid chlorides (method A, used for numbers 6 to 18 inclusive and for number 20) or the amides (method B, used for numbers 1 to 5 inclusive and for number 21). [b] Analyses and rotations are by Mr. William Struck and staff of our Analytical Chemistry Laboratory. [c] This yield is based on the corresponding unsubstituted amide. The free base was not isolated in pure form. [d] This yield is based on the corresponding purified hydrochloride. [e] $[\alpha]^{22}D$ +100° (1% in MeOH). [f] $[\alpha]^{22}D$ +66° (1.5% in MeOH). [g] $[\alpha]^{22}D$ +28° (1.5% in MeOH). [h] $[\alpha]^{22}D$ −98° (0.7% in MeOH). [i] $[\alpha]^{22}D$ −64° (0.7% in MeOH). [j] $[\alpha]^{22}D$ −29° (1.0% in MeOH). [k] This yield is based on the corresponding acid chloride acid sulfate salt. The free base was not isolated in pure form. [l] This was prepared from the acid sulfate of α,α-diphenyl-δ-diethylaminovaleric acid (D. J. Dupre, J. Elks, B. A. Hems, K. N. Speyer and R. M. Evans, *J. Chem. Soc.*, 500 (1949)) *via* the acid chloride, and free basic amide, neither of which were obtained crystalline. The procedure was similar to that described in the experimental section for the corresponding pyrrolidyl compounds. [m] This was prepared from the acid sulfate salt of the corresponding basic acid (Experimental section) *via* the acid chloride which, however, was not isolated.

above 10°. Most of the excess pyrrolidine was then distilled through an efficient column and recovered. To the residue was added with stirring 240 g. (6 moles) of sodium hydroxide in 240 ml. of water. The oil was decanted and dried over solid potassium hydroxide. The sodium bromide and potassium hydroxide residues were extracted with absolute ether which was added to the oil and dried over potassium carbonate. After filtration the solution was carefully distilled though an efficient column. The product distilled at 164–167° giving 220 g. (80%) of colorless liquid; $n^{25}D$ 1.4672.

α,α-Diphenyl-γ-dimethylamino-N-[2-(1-pyrrolidyl)-ethyl]-valeramide Dihydrochloride.—A solution of 70 g. (0.61 mole) of β-pyrrolidylethylamine in 250 ml. of benzene was cooled in an ice-bath and 82.8 g. (0.2 mole) of α,α-diphenyl-γ-dimethylaminovaleryl chloride acid sulfate[6] was added in small portions with stirring during one-half hour. After stirring for 2 hours at room temperature and 15 minutes under reflux the mixture was cooled and filtered. The filtrate was washed well with water and extracted with dilute hydrochloric acid. The aqueous acid solution was washed with ether and made basic with sodium hydroxide. The free base was extracted with benzene which was washed with water and the solvent was distilled.

The residual free base was dissolved in ethyl acetate and a slight excess of ethanolic hydrogen chloride was added. After cooling the product was collected giving 57.4 g. (62%) of white crystals, with the properties given in Table II.

Method B (compounds no. 1–5 and 21 in Table II were prepared by this method from amides previously described[2]).

α α-Diphenyl-γ-diethylamino-N-methylbutyramide Hydrochloride.—A mixture of 63.5 g. (0.205 mole) of α,α-diphenyl-γ-diethylaminobutyramide,[4] 8 g. (0.205 mole) of sodium amide and 500 ml. of dry toluene was heated under reflux for 2.5 hours. After cooling, a solution of 19.5 g. (0.205 mole) of methyl bromide in 100 ml. of dry toluene was added slowly. After stirring for 1 hour more water was added. The organic layer was extracted with dilute hydrochloric acid and this acid solution was again made basic with dilute sodium hydroxide. The free base was extracted with benzene and the solvent was distilled leaving 40 g. of yellow oil. This was dissolved in 400 ml. of methyl ethyl ketone and a slight excess of ethanolic hydrogen chloride was added. The hydrochloride separated as a white solid; m.p. 175–185°. This product contained a small amount of the hydrochloride of the starting material which was removed by repeated crystallizations from isopropyl or ethyl alcohol. The over-all yield was 23%. The infrared spectrum[10] indicated that this was monosubstituted amide essentially free from unsubstituted or disubstituted amides.

Reaction of Ethyl α,α-Diphenyl-γ-diethylaminobutyrate with Methylamine.—A solution of 25 g. (0.074 mole) of ethyl α,α-diphenyl-γ-diethylaminobutyrate[11] and 47.5 g. (1.53 moles) of methylamine in 75 ml. of ethylene glycol gave no reaction at room temperature or at 100°, but reacted when heated in an autoclave at 200° for 15 hours. On standing, crystals separated which were collected, washed with water and dried; m.p. 140–145°. After two recrystallizations from benzene–cyclohexane, it gave a product, m.p. 144–146°. This was found by mixed melting point and comparison of the infrared spectrum[10] with that of an authentic sample to be 1-methyl-3-diphenylpyrrolidone-2.[12]

α,α-Diphenyl-N-isopropylacetamide.—A mixture of 72.6 ml. (1.0 mole) of thionyl chloride, 106.1 g. (0.5 mole) of diphenylacetic acid and 100 ml. of benzene was heated under reflux for 45 minutes. The benzene and excess thionyl chloride were distilled under reduced pressure and 75 g. (1.26 moles) of isopropylamine in 200 ml. of dry benzene was added slowly with cooling. After stirring for 2 hours, the mixture was heated to the boiling point, filtered and cooled. The crystalline amide was collected and recrystallized from benzene giving 89 g. (70%) of white solid, m.p. 158–159°.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.59; H, 7.56; N, 5.53. Found: C, 80.89; H, 7.48; N, 5.81.

α,α-Diphenyl-N-isopropyl-N-(2-diethylaminoethyl)-acetamide Hydrochloride.—To a suspension of 12.5 g. (0.32 mole) of sodium amide in 700 ml. of dry toluene was added

(10) The infrared spectra are by Dr. James L. Johnson and associates of our Department of Physics.

(11) M. Bockmühl and G. Ehrhart, U. S. Patent 2,230,774 (1941).

(12) D. J. Dupre, J. Elks, B. A. Hens, K. N. Speyer and R. M. Evans, *J. Chem. Soc.*, 500 (1949).

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78.49 g. (0.31 mole) of α,α-diphenyl-N-isopropylacetamide and the mixture was heated under reflux with stirring for 3 hours. A solution of 44.7 g. (0.33 mole) of β-diethylaminoethyl chloride in 100 ml. of dry toluene was added slowly with stirring at reflux temperature and the heating was continued for 20 hours. The toluene solution was washed with water, and extracted with dilute hydrochloric acid. The aqueous solution was washed with toluene and made basic with sodium hydroxide. The free base was extracted with benzene which was washed with water, dried over sodium sulfate and the solvent distilled. A yellow oil remained which could not be crystallized.

The free base was dissolved in methyl ethyl ketone, acidified with a slight excess of ethanolic hydrogen chloride and evaporated. A gum was obtained which crystallized from dioxane giving white crystals, with the properties given in Table II.

Methobromide.—An aqueous solution of 10 g. of this hydrochloride was made basic with sodium hydroxide and extracted with benzene. A portion of the benzene was distilled to remove water and cooled. Then 30 g. of cold methyl bromide was added, the flask was stoppered, clamped and allowed to stand at room temperature for 3 days. Concentration of the solution caused an oil to separate which solidified on trituration with ether. It was recrystallized from ethyl acetate and a little ethanol giving crystals, m.p. 76–78°. Recrystallization of this material gave a different modification, m.p. 161–163°.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

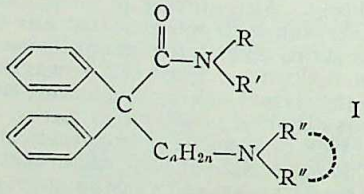
Antispasmodics. XII. α,α-Diphenyl-tertiaryamino-N,N-disubstituted Amides[1]

BY ROBERT BRUCE MOFFETT AND BROOKE D. ASPERGREN

RECEIVED MARCH 25, 1957

A series of α,α-diphenyl-γ-tertiaryamino-N,N-disubstituted amides (I, R and R′ = alkyl) have been prepared. In general they have been found to have little if any anticholinergic properties, but, like the monosubstituted amide series, the acid addition salts are oxytocics and/or diuretics.

Amides of the general type I (R and R′ = H), unsubstituted on the amide nitrogen, are well known as anticholinergics.[2]

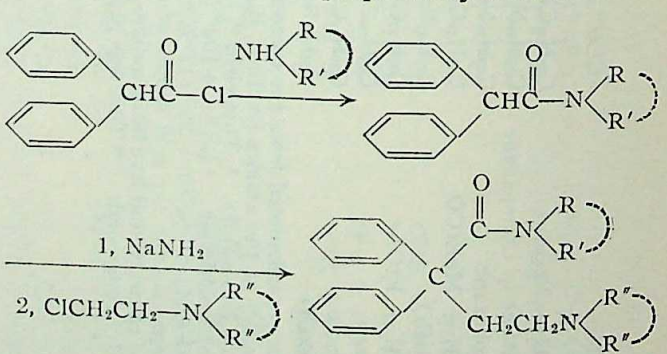


I

The preceding paper of this series[3] reported monosubstituted amides (I, R = H, R′ = alkyl). These were found to have little, if any, anticholinergic properties, but were powerful oxytocics and/or diuretics. It was therefore of interest to determine what type of activity would be shown by the disubstituted amides (I, R and R′ = alkyl). A very few of these disubstituted amides have been reported in the literature.[4–6] The first of these were reported in articles[4,5] dealing with antispasmodics but no pharmacology was given. Recently certain ones were reported to have high analgetic activity.[6]

A considerable number of these disubstituted amides have now been made and are listed in Table I. Like the monosubstituted amides[3] neither the hydrochlorides nor the methobromides had much antispasmodic activity in the Thiry-Vella dogs or gastric antisecretory activity in pyloric ligation rats but the hydrochlorides were generally oxytocics and/or diuretics.

In cases where $-C_nH_{2n}-$ (I) was $-CH_2CH(CH_3)-$ or $-CH_2CH_2CH_2-$ the dimethylamides (no. 15–18 in the table) were prepared from the corresponding acid chloride by a procedure essentially like procedure A described in the preceding paper[3] using dimethylamine in place of monomethylamine. When C_nH_{2n} = $-CH_2CH_2-$ or with large or hindered secondary amines pyrrolidones[7,8] were the chief products. Where $-C_nH_{2n}-$ was $-CH_2CH_2-$ the disubstituted amides were prepared by the method



This method is illustrated by an example in the Experimental part and the physical properties of the amides are listed in Table II (no. 1–14).

Acknowledgments.—The authors are indebted to Dr. P. H. Seay, Mr. Wm. Veldkamp, Mr. O. F. Swoap, Mr. B. E. Graham and associates of our Department of Pharmacology for the pharmacological data. The authors also wish to express their appreciation to Dr. R. V. Heinzelman of our Department of Chemistry for guidance in this work.

Experimental

α,α-Diphenyl-γ-(2,2-dimethyl-1-pyrrolidyl)-N,N-dimethylbutyramide.—A mixture of 54 g. (0.226 mole) of diphenyl-

(1) Presented in part before the Division of Medicinal Chemistry, A.C.S., at Miami, Florida, April, 1957, Abstracts, p. 19-N.

(2) R. B. Moffett and B. D. Aspergren, THIS JOURNAL, **79**, 4451 (1957), and references given therein.

(3) R. B. Moffett, B. D. Aspergren and M. E. Speeter, *ibid.*, **79**, 4457 (1957).

(4) M. Bockmühl and G. Ehrhart, German Patent 731,560 (1943).

(5) L. C. Cheney, W. B. Wheatley, M. E. Speeter, W. M. Byrd, W. E. Fitzgibbon, W. F. Minor and S. B. Binkley, *J. Org. Chem.*, **17**, 770 (1952).

(6) P. Janssen, THIS JOURNAL, **78**, 3862 (1956).

(7) J. H. Gardner, N. R. Easton and J. R. Stevens, *ibid.*, **70**, 2960 (1948).

(8) R. L. Clarke, A. Mooradian, P. Lucas and T. J. Slauson, *ibid.*, **71**, 2814 (1949).

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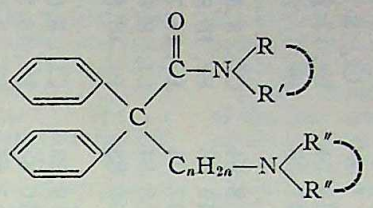
TABLE I



No. of base	$-N\begin{matrix}R\\R'\end{matrix}$	$-C_nH_{2n}-N\begin{matrix}R''\\R''\end{matrix}$	Salt	Toxicity LD_{50} (mg./kg.)[a]	Oxytocic activity at 1 mg./kg.[b]	Diuretic activity at 10 mg./kg.[c]
1	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_3)_2$	HCl	100	Inactive	Excellent
1	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_3)_2$	CH_3Br	65	Inactive	Inactive
2	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	HCl	65	Pronounced	Excellent
2	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	CH_3Br	77	Inactive	Inactive
3	$-N(CH_3)_2$	$-CH_2CH_2-N[CH(CH_3)_2]_2$	HCl	65	Pronounced	Good
3	$-N(CH_3)_2$	$-CH_2CH_2-N[CH(CH_3)_2]_2$	CH_3Br	200	Inactive	Inactive
4	$-N(CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2$	HCl	65	Slight	Inactive
4	$-N(CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2$	CH_3Br	65	Inactive	Inactive
5	$-N(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	HCl	65	Pronounced	Excellent
5	$-N(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	CH_3Br		Inactive	Inactive
5	$-N(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$\rightarrow O\cdot HBr$	200	Inactive	Fair
6	$-N(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	HCl	65		Fair
6	$-N(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	CH_3Br		Inactive	
7	$-N(CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	Base[d]	200	Inactive	Slight
7	$-N(CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	CH_3Br	65	Inactive	Inactive
8	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_2)_3C(CH_2)_4CH_2$	HBr[e,f]	65	Slight	Inactive
8	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_2)_3C(CH_2)_4CH_2$	CH_3Br[f]	167		
9	$-N(CH_2CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	HCl[3]		Slight	Good
9	$-N(CH_2CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	CH_3Br			
10	$-N[CH(CH_3)_2]_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	HCl	20	Slight	Good
10	$-N[CH(CH_3)_2]_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	$CH_3Br\cdot H_2O$		Slight	Inactive
11	$-N[CH(CH_3)_2]_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	HCl			Inactive
11	$-N[CH(CH_3)_2]_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	CH_3Br			
12	$-NCH_2CH_2CH_2CH_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	HCl	65	Moderate	Excellent
12	$-NCH_2CH_2CH_2CH_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	CH_3Br		Inactive	
13	$-NCH_2CH_2CH_2CH_2CH_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	HCl	65	Moderate	Inactive
13	$-NCH_2CH_2CH_2CH_2CH_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	CH_3Br	167	Inactive	Inactive
14	$-NCH_2CH_2CH_2CH_2CH_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	Base[d]	167	Inactive	Inactive
14	$-NCH_2CH_2CH_2CH_2CH_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	CH_3Br	77	Inactive	Inactive
15	$-N(CH_3)_2$	$(dl)-CH_2CH(CH_3)N(CH_3)_2$	HCl	65	Slight	Excellent
15	$-N(CH_3)_2$	$(dl)-CH_2CH(CH_3)N(CH_3)_2$	$CH_3Br\cdot H_2O$		Slight	
15	$-N(CH_3)_2$	$(dl)-CH_2CH(CH_3)N(CH_3)_2$	$\rightarrow O\cdot HBr$	233	Slight	Good
16	$-N(CH_3)_2$	$(d)-CH_2CH(CH_3)N(CH_3)_2$	HCl			Excellent
16	$-N(CH_3)_2$	$(d)-CH_2CH(CH_3)N(CH_3)_2$	CH_3Br			
17	$-N(CH_3)_2$	$(l)-CH_2CH(CH_3)N(CH_3)_2$	HCl			Excellent
17	$-N(CH_3)_2$	$(l)-CH_2CH(CH_3)N(CH_3)_2$	CH_3Br	65	Inactive	Inactive
18	$-N(CH_3)_2$	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	HCl	65	Slight	Inactive
18	$-N(CH_3)_2$	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	CH_3Br	30	Inactive	Inactive

[a] Administered to mice intraperitoneally. The values are approximations with an accuracy of about +100% to −50%. [b] Tested by intravenous administration in cats by a modification of the method of M. L. Clary, A. Cameron and B. N. Cramer, *Proc. Soc. Exp. Biol. Med.*, **77**, 778 (1951). [c] Administered orally to rats. [d] Previously reported.[5] This base was dissolved in dilute acid for testing. [e] Isolated as a solvate containing one molecule of acetone. [f] Preparation previously reported, R. B. Moffett, THIS JOURNAL, **79**, 4457 (1957).

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(Table I) No. of base	Salt or base	Yield, %[a]	M.p., °C.	Crystallizing solvent
1	Base	23	97–99	Hexane
1	HCl	89	228–230	*i*-PrOH + Et_2O
1	CH_3Br	69	225–227	*i*-PrOH + Et_2O
2	HCl	46[c]	184–186	Me_2CO
2	CH_3Br	82[d]	177–179	*i*-PrOH + Et_2O
3	Base	..	74–76	Pentane
3	HCl	64	205–207	EtOH + EtOAc
3	CH_3Br	79	188–190	MeEtCO
4	Base	66	142–144	*i*-PrOH
4	HCl	63	197–199	EtOH + MeEtCO
4	CH_3Br	80	190–192	EtOAc
5	Base	52	110–112	Hexane
5	HCl	..	205–207	EtOAc
5	CH_3Br	77	200–202	*i*-PrOH + Et_2O
5	→ O·HBr	13	158–162	*i*-PrOH
6	Base	46	102–104	Cyclohexane
6	HCl	55	218–220	EtOH + EtOAc
6	CH_3Br	86	195–197	MeEtCO
7	CH_3Br[f]	93	205–207	MeEtCO
9	HCl	..	172–174[g]	EtOAc
9	CH_3Br	40	123–125	EtOAc
10	Base	..	72–74	Pentane
10	HCl	55	211–213	MeEtCO
10	CH_3Br	81[h]	181–183	MeEtCO + Et_2O
11	HCl	51[i]	228–230	EtOAc
11	CH_3Br	86[c]	226–228	MeEtCO
12	HCl	..	212–214	MeEtCO
12	CH_3Br	..	174–176	Benzene
13	HCl	56[j]	225–227	EtOH + MeEt + CO
13	CH_3Br	75[d]	195–197	MeEtCO
14	CH_3Br[e]	82	202–204	EtOH + EtOAc
15	HCl	..	199–201	EtOAc
15	CH_3Br	..	161–163	EtOAc
15	→ O·HBr	69[d]	116–119	*i*-PrOH + Et_2O
16	HCl	52[l]	192–194[m]	EtOH + EtOAc
16	CH_3Br	49[l]	157–159[n]	EtOAc
17	HCl	58[l]	191–193[o]	EtOH + EtOAc
17	CH_3Br	54[l]	155–157[p]	MeEtCO
18	HCl	65[l]	155–158	*i*-PrOH + Et_2O
18	CH_3Br	73[d]	165–166	EtOH + EtOAc

Table II

Physical Properties

Empirical formula	Carbon Calcd.	Carbon Found[b]	Hydrogen Calcd.	Hydrogen Found[b]	Nitrogen Calcd.	Nitrogen Found[b]	Halogen Calcd.	Halogen Found[b]
$C_{20}H_{26}N_2O$	77.37	76.78	8.44	8.84	9.03	9.11	.....	.....
$C_{20}H_{27}ClN_2O$	69.24	69.08	7.85	7.88	8.08	7.95	Cl, 10.22	Cl, 10.21
$C_{20}H_{29}BrN_2O$	62.22	62.18	7.21	7.04	6.91	6.64	Br, 19.71	Br, 19.41
$C_{22}H_{31}ClN_2O$	70.47	70.42	8.33	8.45	7.47	7.33	Cl, 9.46	Cl, 9.44
$C_{22}H_{31}BrN_2O$	63.73	64.09	7.67	7.52	6.46	6.29	Br, 18.44	Br, 17.73
$C_{24}H_{34}N_2O$	78.72	79.09	9.36	9.26	7.65	7.75	.....	.....
$C_{24}H_{35}ClN_2O$	71.52	71.56	8.75	8.62	6.95	7.09	Cl, 8.80	Cl, 8.84
$C_{25}H_{37}BrN_2O$	65.06	65.09	8.08	8.11	6.07	6.00	Br, 17.32	Br, 17.43
$C_{22}H_{28}N_2O$	78.53	78.63	8.39	8.10	8.33	8.17	.....	.....
$C_{22}H_{29}ClN_2O$	70.85	71.07	7.84	7.57	7.51	7.49	Cl, 9.51	Cl, 9.63
$C_{23}H_{31}BrN_2O$	64.03	64.08	7.24	7.32	6.49	6.56	Br, 18.52	Br, 18.53
$C_{24}H_{32}N_2O$	79.07	79.04	8.85	8.96	7.68	7.71	.....	.....
$C_{24}H_{33}ClN_2O$	71.88	71.86	8.29	8.40	6.99	7.07	Cl, 8.84	Cl, 8.56
$C_{25}H_{35}BrN_2O\cdot H_2O$[e]	62.88	62.81	7.81	7.71	5.87	6.05	Br, 16.74	Br, 17.29
$C_{24}H_{32}BrN_2O_2$	62.60	62.84	7.01	7.19	6.09	6.42	Br, 17.36	Br, 17.27
$C_{25}H_{34}N_2O$	79.32	79.53	9.05	8.99	7.40	7.32	.....	.....
$C_{25}H_{35}ClN_2O$	72.35	71.89	8.50	8.48	6.75	6.65	Cl, 8.54	Cl, 8.51
$C_{26}H_{37}Br_2N_2O$	65.95	65.75	7.88	7.84	5.92	5.67	Br, 16.88	Br, 16.83
$C_{24}H_{33}BrN_2O$	64.71	64.66	7.47	7.35	6.29	6.13	Br, 17.94	Br, 17.70
$C_{25}H_{35}ClN_2O$	72.35	72.22	8.50	8.40	6.75	6.89	Cl, 8.54	Cl, 8.62
$C_{26}H_{37}BrN_2O$	65.95	66.09	7.88	7.89	5.92	5.61	Br, 16.88	Br, 16.81
$C_{26}H_{38}N_2O$	79.14	79.29	9.71	9.56	7.10	7.16	.....	.....
$C_{26}H_{39}ClN_2O$	72.44	72.08	9.12	8.78	6.50	6.37	Cl, 8.23	Cl, 8.09
$C_{27}H_{41}BrN_2O$	66.24	66.20	8.44	8.13	5.72	5.44	Br, 16.33	Br, 16.34
$C_{29}H_{43}ClN_2O\cdot H_2O$[e]	71.21	71.38	9.27	9.08	5.73	5.72	Cl, 7.25	Cl, 7.33
$C_{30}H_{45}BrN_2O$	68.03	68.21	8.56	8.65	5.29	5.30	Br, 15.09	Br, 14.95
$C_{24}H_{33}ClN_2O$	71.88	72.17	8.30	8.06	6.99	6.95	Cl, 8.84	Cl, 8.49
$C_{25}H_{35}BrN_2O\cdot H_2O$[e]	62.88	62.97	7.81	7.59	5.87	5.75	Br, 16.74	Br, 16.66
$C_{25}H_{35}ClN_2O$	72.35	72.69	8.50	8.42	6.75	7.09	Cl, 8.54	Cl, 8.39
$C_{26}H_{37}BrN_2O$	65.95	65.96	7.88	7.70	5.92	5.98	Br, 16.88	Br, 16.61
$C_{27}H_{39}Br_2N_2O$	66.79	66.98	7.68	7.43	5.77	5.81	Br, 16.46	Br, 16.37
$C_{21}H_{29}ClN_2O$	69.88	69.56	8.10	8.16	7.76	8.10	Cl, 9.82	Cl, 9.91
$C_{22}H_{31}BrN_2O\cdot H_2O$[d]	60.40	60.27	7.60	7.46	6.41	6.47	Br, 18.27	Br, 18.38
$C_{21}H_{29}BrN_2O_2$	59.85	56.66[k]	6.94	7.02	6.65	6.63	Br, 18.97	Br, 18.95
$C_{21}H_{29}ClN_2O$	69.88	69.85	8.10	8.37	7.76	7.45	Cl, 9.82	Cl, 9.84
$C_{22}H_{31}BrN_2O\cdot H_2O$[e]	60.40	59.80	7.60	8.17	6.41	6.57	Br, 18.27	Br, 18.35
$C_{21}H_{29}ClN_2O$	69.88	69.79	8.10	8.24	7.76	7.58	Cl, 9.82	Cl, 9.83
$C_{22}H_{31}BrN_2O$[q]	63.00	63.26	7.45	7.11	6.68	6.75	Br, 19.06	Br, 19.23
$C_{23}H_{33}ClN_2O$	71.02	70.72	8.55	8.48	7.20	7.29	Cl, 9.12	Cl, 9.18
$C_{24}H_{35}BrN_2O$	64.42	64.30	7.88	7.58	6.26	6.33	Br, 17.86	Br, 17.93

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[a] Unless otherwise noted the yields of the free bases are based on the diphenyl dialkylacetamide. The yields of the salts are based on the pure free bases. [b] Analyses and rotations are by Mr. William Struck and staff of our Analytical Chemistry Laboratory. Infrared spectra are by Dr. James L. Johnson and associates of our Department of Physics. [c] This yield is based on diphenyl-N,N-dimethylacetamide. The free basic amide was not isolated in pure form. [d] Yield based on pure hydrochloride. [e] The infrared spectrum[b] as well as the analysis indicates that this is a hydrate. [f] Prepared from the corresponding free base which has been previously reported.[5] [g] This salt has been reported by Bockmühl and Ehrhart[4] with m.p. 182–183°, but no analytical figures were given. It was prepared from diphenyl-N,N-diethylamide [N. Maxim, *Compt. rend.*, 182, 1393 (1926); *Ann. chim.*, 9, 55 (1928)]. [h] This compound was isolated as a hydrate, m.p. 129–132°. *Anal.* Calcd. for $C_{27}H_{41}BrN_2O \cdot H_2O$: N, 5.52; Br, 15.75. Found: N, 5.44; Br, 15.65. A sample was dried giving the properties listed in the table. The hydrate was used for pharmacological study. [i] The free base was not isolated. The hydrochloride crystallized from an aqueous acid solution on the addition of ether. [j] This yield is based on diphenylacetyl-1-piperidine.[5,9] The free basic amide was not isolated in pure form. [k] In spite of repeated attempts by two laboratories a satisfactory carbon analysis could not be obtained. The results ranged from 56.66 to 58.09. Good analyses for the other elements were obtained without difficulty. [l] Yield based on the α,α-diphenyl-γ or δ-*t*-aminovaleroyl chloride acid sulfate. The intermediate free basic amide was not isolated in pure form. [m] $[\alpha]^{23}D$ +59° (1% in CH_3OH). [n] $[\alpha]^{23}D$ +7° (1% in CH_3OH). [o] $[\alpha]^{23}D$ −63° (0.6% in CH_3OH). [p] $[\alpha]D$ −6° (1% in CH_3OH). [q] Isolated as a hydrate as shown by infrared[b] spectrum but after drying analyzed as anhydrous material.

N,N-dimethylacetamide,[5,9] 9.7 g. (0.25 mole) of sodium amide and 500 ml. of dry toluene was heated under reflux with stirring for 3 hours. To 44.8 g. (0.226 mole) of 2-(2,2-dimethyl-1-pyrrolidyl)-ethyl chloride hydrochloride[10] was added a slight excess of aqueous sodium hydroxide and the mixture was extracted with 300 ml. of toluene in several portions. The toluene solution was dried over potassium carbonate and slowly added to the above suspension of the sodium derivative. The mixture was heated under reflux with stirring for 2 hours, cooled, washed with water and extracted with dilute hydrochloric acid. The aqueous acid solution was made basic with dilute sodium hydroxide and the product was extracted with benzene. After removal of the solvent an oil was obtained which crystallized from pentane and was recrystallized from hexane giving white crystals having the properties given in Table II (no. 5, base).

Hydrochloride.—This was prepared by treating a sample of the free base in ethyl acetate with a slight excess of ethanolic hydrogen chloride. It was recrystallized from ethyl acetate, m.p. 206–207° (no. 5, HCl).

Methobromide.—To a cold solution of 10 g. (0.0322 mole) of the free base in 100 ml. of methyl ethyl ketone was added a large excess of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 2 days. The crystals which separated had the properties given in Table II (no. 5, CH_3Br).

N-Oxide Hydrobromide.—A solution of 14.6 g. (0.04 mole) of the above free base and 10 ml. of 30% hydrogen peroxide in 150 ml. of methanol was allowed to stand at room temperature for 2 days. The excess hydrogen peroxide was decomposed by adding a small amount of a slurry of platinum-on-charcoal and shaking for 2 hours. The solution was filtered and distilled to dryness under reduced pressure below 30°. The resulting gummy free base failed to crystallize. It was dissolved in acetone and made acidic with a slight excess of 48% hydrobromic acid, and diluted with ether. On standing, the gummy hydrobromide partly crystallized. This was rubbed with ethyl acetate giving a solid product. This was recrystallized from isopropyl alcohol giving light tan crystals having the properties given in Table II (no. 5 → O·HBr).

α,α-Diphenylacetyl-1-pyrrolidine.—A mixture of 106.1 g. (0.5 mole) of diphenylacetic acid, 73 ml. of thionyl chloride and 100 ml. of benzene was heated under reflux with stirring for 1 hour. The solvent and excess thionyl chloride were removed by distillation under reduced pressure and the crude acid chloride was diluted with 300 ml. of benzene. To this was added slowly with stirring a solution of 85.4 g. (1.2 moles) of dry pyrrolidine in 200 ml. of benzene. After standing at room temperature overnight or heating under reflux for 1 hour, the solution was washed with water. The benzene solution was concentrated by distillation, treated with decolorizing charcoal, and cooled. It crystallized giving 111 g. (84%) of white crystals, m.p. 163–165°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.66; H, 8.01; N, 5.38.

Diphenyl-N,N-diisopropylacetamide.—By a similar procedure this was prepared from diisopropylamine. It was recrystallized from *n*-pentane giving a 60% yield of amide, m.p. 53–55°.

Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.26; H, 8.59; N, 4.88.

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(9) V. G. Gokhale, N. L. Phalnikar and B. V. Bhide, *J. Univ. Bombay*, **16**, No. 5, 32–36 (1948); *C. A.*, **43**, 1144e (1949).

(10) R. B. Moffett, J. L. White, B. D. Aspergren and F. E. Visscher, THIS JOURNAL, **77**, 1565 (1955).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE A. M. TODD COMPANY]

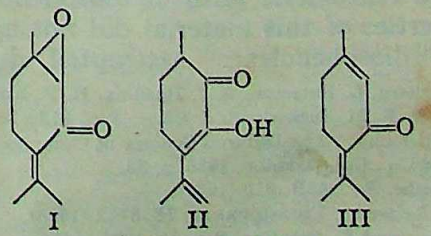
The Synthesis of Racemic Piperitenone Oxide and Diosphenolene

BY ROBERT H. REITSEMA[1]

RECEIVED OCTOBER 12, 1956

The enolic diketone, diosphenolene, separated from the oil of *Mentha rotundifolia* has been synthesized by three methods. Piperitenone has been converted to a monoepoxide and this with acid gave diosphenolene. Pulegone was a useful starting material for two other methods. The syntheses provide further evidence that the structure of diosphenolene is 3,8(9)-*p*-menthadiene-2-one as previously proposed.

Mentha rotundifolia is one of the more interesting mint species and its oil contains constituents which are quite different from most other mint oils. It has been shown that the major constituent is piperitenone oxide (1,2-epoxy-4(8)-*p*-menthene-3-one) (I).[2] Associated with this keto oxide in the oil and readily obtained from it in the laboratory is a new enolic ketone called diosphenolene for which the structure of 3-hydroxy-3,8(9)-*p*-menthadiene-2-one (II) was proposed.[2]



I II III

The evidence for the location of the double bond

(1) The Ohio Oil Company, Denver Research Center, Littleton, Colorado.

(2) R. H. Reitsema, THIS JOURNAL, **78**, 5022 (1956).

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in piperitenone oxide at the 4–8 position giving an isopropylidene group was from chemical and spectroscopic evidence. The structure given for diosphenolene required the shift of the double bond to the 8–9 position. This was postulated particularly on the basis of the ultraviolet absorption maximum at about 306 mμ as could be calculated for the system C=CC=C(OH)C=O. Additional evidence for the view that this tautomeric form is predominant is given by the infrared spectrum. Diosphenolene shows a strong absorption at 884 cm.$^{-1}$ in agreement with the assignment of this region to the isopropenyl group.[3] Absence of significant absorption at 825 cm.$^{-1}$ makes the isopropylidene structure unlikely. The absorption at 1604 cm.$^{-1}$ is in agreement with the conjugated C=C group.[4]

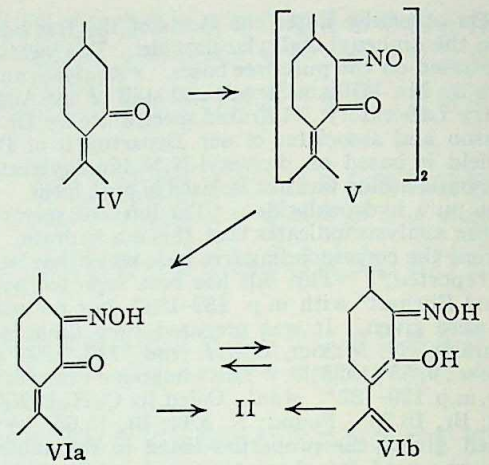
Piperitenone was treated with alkaline hydrogen peroxide by the general method of Treibs[5] to give a monoepoxide. Elementary analysis indicated the presence of a small amount of piperitenone in the product. The semicarbazone, prepared in aqueous suspension as for the active piperitenone oxide from *M. rotundifolia*, was identical to the *M. rotundifolia* ketone in respect to elementary analysis, ultraviolet absorption spectrum and in behavior in acid and base. The minor differences between the infrared spectra of the two appeared to be due to the necessary use of solid spectra.

The monoepoxide or its semicarbazone derivative could be converted to diosphenolene (II) readily by treatment with dilute acid. The product was identical in all respects to that obtained from piperitenone oxide obtained from *M. rotundifolia*. The reaction is analogous to the formation of diosphenol from piperitone oxide.[6]

Other syntheses of diosphenolene started with pulegone which is more readily available than piperitenone. Conversion of pulegone into diosphenolene by two independent paths was possible.

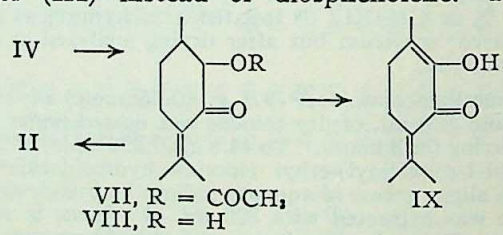
The formation of bis-nitrosopulegone (V) by treatment of pulegone with amyl nitrite and hydrochloric acid was reported by Bayer and Prentice.[7] This had been converted to an isonitrosopulegone with ammonia. Heating the isonitroso derivative VI with dilute acid had given a low yield of nitrogen containing material which was not characterized. It has now been found that the isonitroso derivative can be converted to diosphenolene by acid treatment as already used for syntheses of diosphenolene reported above. The product was identical to diosphenolene from other methods of synthesis.

A possible synthetic route to diosphenolene from pulegone was by selenium dioxide treatment as reported by Cauquil.[8] The product was reported to be a diketone to which the structure of 4(8)-*p*-menthene-2,3-dione was given. This was a possible tautomeric form of diosphenolene, but the properties of this material did not agree with those of diosphenolene. Attempted duplication



of the work gave a product in poor yield which was quite distinct from diosphenolene and in view of the other successful syntheses was not further studied.

The most useful synthesis of diosphenolene was a modification of the method used for the preparation of diosphenol from menthone.[9] Treatment of pulegone (IV) with mercuric acetate gave the desired 2-acetoxypulegone (VII). Hydrolysis and oxidation steps as with acetoxymenthone gave diosphenol (IX) instead of diosphenolene. It was



found that acetoxypulegone was saponified readily and in the presence of excess alkali rearrangement of the bonds gave diosphenol. The formation of diosphenol occurred in the presence of 8% potassium hydroxide under reflux very quickly, and somewhat more slowly with 4% potassium hydroxide at 52°. It was possible to avoid this reaction by use of 1% alkali at lower temperatures. The resulting 2-hydroxypulegone (VIII) was then oxidized in good yield to diosphenolene under milder conditions than used for hydroxymenthone. The product from this synthesis also was identical to authentic diosphenolene.

Thus, the synthesis used, involving the conversion of ketone derivatives of piperitenone and pulegone to diosphenolene, provides further evidence for the proposed structures.

Acknowledgment.—The technical assistance of Mr. Verners J. Varnis and encouragement of this work by the A. M. Todd Company is gratefully acknowledged.

Experimental[10]

Epoxidation of Piperitenone.—To 5.0 g. of piperitenone[11]

(3) D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.*, 915 (1950).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1956, p. 35.

(5) W. Treibs, *Ber.*, **66B**, 610 (1933).

(6) R. H. Reitsema, THIS JOURNAL, **78**, 3792 (1956).

(7) A. Bayer and K. Prentice, *Ber.*, **29**, 1078 (1896).

(8) G. Cauquil, *Compt. rend.*, **208**, 1156 (1939).

(9) A. K. Macbeth and W. G. P. Robertson, *J. Chem. Soc.*, 3512 (1953).

(10) Unbracketed α_D is used for observed rotations on homogeneous material taken without solvent at room temperature in a 1 decimeter tube. Ultraviolet absorptions were taken on a Model DU Beckman spectrophotometer in 95% ethanol. Infrared analyses by Anderson Physical Laboratories, Champaign, Illinois. Microanalysis by Clark Microanalytical Laboratory, Urbana, Illinois, and Microtech Laboratories, Skokie, Illinois.

(11) The sample of piperitenone was kindly provided by Dr. J. P. Guth of the Glidden Co., Jacksonville, Florida.

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(n^{20}D 1.5296; reported[12] 1.5294) in 20 ml. of isopropyl alcohol cooled to −9° there was added dropwise with stirring, at equal rates through two dropping funnels, 4 ml. of 30% aqueous hydrogen peroxide and 4.0 ml. of 10% potassium hydroxide. The temperature was maintained below −2° during the addition and the mixture was stirred at this temperature for an additional five hours. After standing overnight in a refrigerator, the slightly yellow solution was diluted with 70 ml. of water containing sodium chloride. The mixture was extracted with three 10-ml. portions of ether, the ether layers were combined, dried over magnesium sulfate and distilled. After removal of ether, two main fractions, distilling at 12 mm. pressure were obtained: (a) b.p. 149–154°, 2.5 g., n^{20}D 1.5056; and (b) b.p. 154–160°, 1.54 g., n^{20}D 1.4948. These were recombined and 3.24 g. was redistilled through a 10 cm. helices packed column at 2 mm. pressure giving: (1) b.p. 84–87°, 0.28 g., n^{20}D 1.5065, λ_{max}^{EtOH} 260 mμ (ε 6,950); (2) b.p. 87°, 1.28 g., n^{20}D 1.5043, λ_{max}^{alc} 260 mμ (ε 6,040); and (3) b.p. 87–88°, 0.42 g., n^{20}D 1.5048.

The elementary analysis of the fractions showed the presence of some unreacted piperitenone mixed with the major product, piperitenone oxide. Chromatography also showed the presence of a low concentration of piperitenone with the main constituent not distinguishable from naturally occurring piperitenone oxide. The infrared spectrum of the product fractions showed the presence of all peaks found in the piperitenone oxide separated from *M. rotundifolia*. Eight additional minor absorption points correlated with the major absorptions of piperitenone. Separation of the epoxide from the starting material contaminant by distillation was difficult because of the limited amount of starting material and the similarity in boiling points. Regeneration from derivatives was not possible due to sensitivity of the oxide to acids and bases.

The semicarbazone was prepared from the reaction product by vigorously stirring a suspension of 0.4 g. with 0.45 g. of sodium acetate and 0.6 g. of semicarbazide hydrochloride in 6.6 ml. of water for 4.5 hours at room temperature. The liquid was decanted from the waxy solid after cooling. The solid was washed with warm methanol and recrystallized from methanol giving 0.15 g. of a white granular product, m.p. 168–169°, λ_{max}^{EtOH} 274.5 mμ (ε 10,950). The melting point varied slightly under different conditions of recrystallization, drying and melting point determination and 170–171° was observed at times.

Anal. Calcd. for $C_{11}H_{17}O_2N_3$: C, 59.17; H, 7.68; N, 18.82. Found: C, 59.17; H, 7.67; N, 18.88.

The semicarbazone of *d*-piperitenone oxide from *M. rotundifolia* melted at 177.5–178° and had the same ultraviolet absorption as the synthetic material with λ_{max} 10,700 at 274.5 mμ.[2] As a result of the very low solubility of the semicarbazones in suitable solvents, the liquid phase infrared spectra were not obtained. The spectra of the solids run pelletized with KBr were slightly different in minor respects. It is known that differences in crystal structure can lead to some differences in infrared spectra.[13] Whether this slight variation is the result of different crystal structures of the racemic and active materials, of different forms of the semicarbazones being isolated, or, less likely, of diastereoisomerism was not determined. All other properties of the two series were identical.

3-Hydroxy-3,8(9)-*p*-menthadiene-2-one (Diosphenolene).—The synthetic piperitenone oxide (fraction 2 above) (0.5 g.) was added to 50 ml. of hot 10% sulfuric acid. Steam was passed into the mixture and 20 ml. of first fraction distillate and 35 ml. of second fraction distillate were collected. Both fractions gave very strong ferric chloride tests. Filtration of the first fraction after cooling gave white needles which were recrystallized from aqueous ethanol giving diosphenolene, m.p. 74–75°, λ_{max}^{alc} 306.5 mμ (ε 8,900), which showed no depression of melting point when mixed with material prepared by similar treatment of *M. rotundifolia* ketone.

Diosphenolene from Nitrosopulegone.—To a mixture of 50 g. of *d*-pulegone (n^{24}D 1.4861, α^{24}D 23.55°), 50 ml. of Skellysolve B, and 25 g. of amyl nitrite cooled in an ice-bath was added with stirring 13 drops of concentrated hydrochloric acid. The mixture became rather thick in ten minutes and was filtered. Repetition of the addition of acid to the cold filtrate gave three more crops of crystals which were washed with cold Skellysolve B. A total of 8.14 g. (15%) of air-dried crystals was obtained.

To 0.5 g. of the first crop covered with ether was added two drops of concentrated ammonia. This was allowed to stand until all was in solution and then 2 *N* sulfuric acid (about five drops) was added dropwise with stirring. The yellow crystals which appeared in the neutral mixture after separation and drying melted at 114.5–118°. Steam distillation of 0.32 g. of this crude product from 15 ml. of 10% sulfuric acid gave a few crystals in the condenser and white needles in the distillate upon cooling. These crystals gave a positive ferric chloride test and after recrystallization melted at 73–74° and failed to show depression in melting point when mixed with authentic diosphenolene. The ultraviolet absorption was in agreement with the previous spectrum of diosphenolene and showed a maximum absorption at 305 mμ (ε 9,200).

2-Acetoxy-4(8)-*p*-menthene-3-one (2-Acetoxypulegone).—A mixture of 85.5 g. of mercuric acetate and 41.0 g. of *d*-pulegone in 70 ml. of glacial acetic acid was stirred under gentle reflux for three hours. The liquid which had undergone numerous color changes was decanted from the layer of 47.7 g. of mercury into 800 ml. of water and extracted with three portions of ether. The organic layers were combined, washed twice with water, and dried over magnesium sulfate. Distillation after removal of ether and of acetic acid gave: 18.73 g. of recovered pulegone, b.p. 60–65° (3 mm.), n^{20}D 1.4863; 2.66 g. of an intermediate fraction, b.p. 75–92° (3 mm.), n^{20}D 1.4919; and 12.93 g. (44% of theoretical yield based upon recovered pulegone) of 2-acetoxypulegone, b.p. 96–98° (3 mm.), n^{20}D 1.4883. Redistillation of the main fraction through a short helices packed column gave a center cut, b.p. 102° (4 mm.), n^{22}D 1.4882, λ_{max}^{alc} 252 mμ (ε 6,010), α^{22}D −15.88.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.35; H, 8.33.

The yield was not maximum and some undecomposed organic mercury derivatives remained as shown by the appearance of some mercury during the distillation.

Diosphenol from Acetoxypulegone.—2-Acetoxypulegone (5.8 g.) was stirred under reflux for 30 minutes with 50 ml. of 8% aqueous potassium hydroxide solution. After cooling, the orange oil was extracted with ether, the ether extracts dried and ether removed under vacuum leaving 3.5 g. (72%) of an oily solid. Recrystallization of this from methanol gave diosphenol, m.p. 82.5–83°, λ_{max}^{alc} 272 mμ (ε 8,800), positive ferric chloride test, which showed no melting point depression when mixed with an authentic sample.

2-Hydroxypulegone.—To 7.7 g. (0.0385 equiv.) of 2-acetoxypulegone was added with stirring 0.16 *N* aqueous potassium hydroxide at such a rate as to maintain the *p*H of the mixture between 8 and 10. After the first half hour at 25° when 41 ml. was added, the temperature was raised to 40° with a water-bath. After six hours 241 ml. (calculated 240 ml.) had been added and the rate of consumption of alkali had decreased to a very small value. The mixture was cooled and extracted with ether. No solid could be separated from the aqueous solution by neutralization with dilute sulfuric acid. Evaporation of ether from the organic extract left 4.66 g. (72%) of yellow oil which was distilled giving 3.74 g., b.p. 73–78° (3 mm.), n^{23}D 1.5048, λ_{max}^{alc} 254 mμ (ε 5,670), αD −5.65°. The crude product itself corresponded rather closely to the calculated analysis and was not purified further.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.56. Found: C, 70.85; H, 9.50.

Diosphenolene from Hydroxypulegone.—A mixture of 3.4 g. of 2-hydroxypulegone, 12.5 g. of glacial acetic acid and 4.65 g. of bismuth oxide was stirred at 110° for 10 minutes. The liquid was decanted from the bismuth metal (about 2.5 g.) into 250 ml. of water and the ether extracts were washed with water to remove acetic acid. Addition of ether caused more white solid to precipitate. This was removed by filtration and the organic layer was separated from the filtrate. The aqueous layer was extracted twice more with ether and the combined organic layers were washed with water to remove acetic acid. After drying the ether solution, ether was removed under vacuum leaving 3.19 g. (94%) of a light orange oil which suddenly crystal-

(12) Y. R. Naves and G. Papazian, *Helv. Chim Acta*, **25**, 1023 (1942).

(13) H. Gilman, "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 139.

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lized to an oily solid. Recrystallization four times from methanol left 1.16 g. of white needles, m.p. 75–76°, λ_{max}^{alc} 304 mμ (ε 9,245). The material showed no mixed melting point depression with authentic diosphenolene prepared from piperitenone oxide. The ferric chloride test was very heavy dark green in color similar to the test with diosphenolene prepared in other ways.

KALAMAZOO, MICHIGAN

[JOINT CONTRIBUTION FROM THE INSTITUTO DE QUIMICA DE LA UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO AND THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Terpenoids. XXX.[1] The Structure of the Cactus Triterpene Chichipegenin

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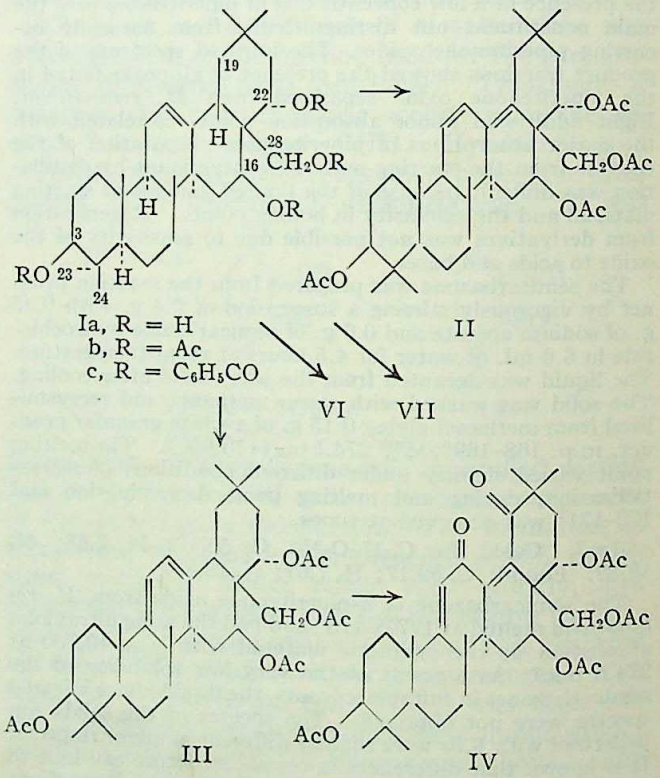
Chichipegenin—isolated from various *Myrtillocactus* species and from *Lemaireocereus chichipe*—has been converted *via* its 28-trityl ether VIa to longispinogenin (Va). Coupled with other degradation experiments, this leads to the conclusion that chichipegenin is Δ^{12}-oleanene-3β,16β,22α,28-tetrol (Ia), thus falling into the earlier established oxygenation pattern established for cactus triterpenes.

As pointed out recently,[4] the most characteristic triterpene of the genus *Myrtillocactus* of the *Cactaceae* family is a new tetrol, $C_{30}H_{50}O_4$. This substance has been named "chichipegenin" since it occurs also in large amounts in a single species of the genus *Lemaireocereus, L. chichipe*[5] (see Experimental section), and the taxonomic implications of this observation have already been commented upon.[4,6] We should now like to record the approach employed in the structure elucidation of this interesting triterpene.

Chichipegenin did not exhibit any infrared absorption in the carbonyl region but showed a strong band typical of one or more hydroxyl groups. Acetylation or benzoylation under mild conditions afforded the corresponding tetraacetate Ib and tetrabenzoate Ic, thus accounting for all four oxygen atoms. Furthermore, the ease of acylation indicated that these hydroxyl groups must either be primary and/or equatorially oriented secondary alcoholic functions. Since eventual correlation with a known triterpene was required for a definitive structure proof, it was important to establish to which broad class of triterpenes chichipegenin belonged. This was accomplished by examining the reactivity of chichipegenin tetraacetate toward selenium dioxide.

Oxidation in boiling acetic acid smoothly led to a diene, which on the basis of its characteristic triple ultraviolet absorption maxima[7] could be assigned the heteroannular $\Delta^{11,13(18)}$-formulation II, thus



showing that chichipegenin was a member of the β-amyrin class of triterpenes. In order to eliminate position 19 as the site of one of the hydroxyl groups, the further oxidation of this diene II with selenium dioxide to the well known $\Delta^{9(11),13(18)}$-diene-12,19-dione IV[8] was attempted, but no pure product could be isolated. Reaction of chichipegenin tetraacetate Ib with N-bromosuccinimide did not lead to the desired $\Delta^{9(11),12,18}$-triene[9] but rather to an impure bromine-containing product in accordance with earlier observations in the queretaroic acid series.[10] However, with a limited amount of N-bromosuccinimide, it was possible to isolate

(1) Paper XXIX, C. Djerassi and W. Rittel, THIS JOURNAL, **79**, 3528 (1957).

(2) Postdoctorate research fellow (1956–1957) at Wayne State University on funds supplied by the Division of Research Grants (grant No. RG-3863) of the National Institutes of Health, U. S. Public Health Service.

(3) Postdoctorate research fellow (1955) at Universidad Nacional Autonoma de Mexico under a grant from the Rockefeller Foundation.

(4) C. Djerassi, S. Burstein, H. Estrada, A. J. Lemin, A. E. Lippman, A. Manjarrez and H. G. Monsimer, THIS JOURNAL, **79**, 3525 (1957).

(5) N. L. Britton and J. N. Rose, "The Cactaceae," Vol. II, Carnegie Institution of Washington, Washington, D. C. 1920, p. 89. H. Bravo, "Las Cactaceas de Mexico," Imprenta Universitaria, Mexico, D. F., 1937, p. 258.

(6) C. Djerassi, 'Cactus Triterpenes' in "Festschrift Arthur Stoll," Birkhäuser, A. G., Basel, 1957, pp. 330–352.

(7) L. Ruzicka, G. Müller and H. Schellenberg, *Helv. Chim. Acta*, **22**, 767 (1939); D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.*, 257 (1951).

(8) A list of the various rings, C, D and E-substituted precursors leading to the same diene-dione (type IV) is given by D. H. R. Barton, N. J. Holness, K. H. Overton and W. J. Rosenfelder, *ibid.*, 3751 (1952), and by J. M. Beaton, J. D. Johnston, L. C. McKean and F. S. Spring, *ibid.*, 3660 (1953).

(9) *Cf.* L. Ruzicka, O. Jeger and J. Redel, *Helv. Chim. Acta*, **26**, 1235 (1943).

(10) C. Djerassi, J. A. Henry, A. J. Lemin, T. Rios and G. H. Thomas, THIS JOURNAL, **78**, 3783 (1956).

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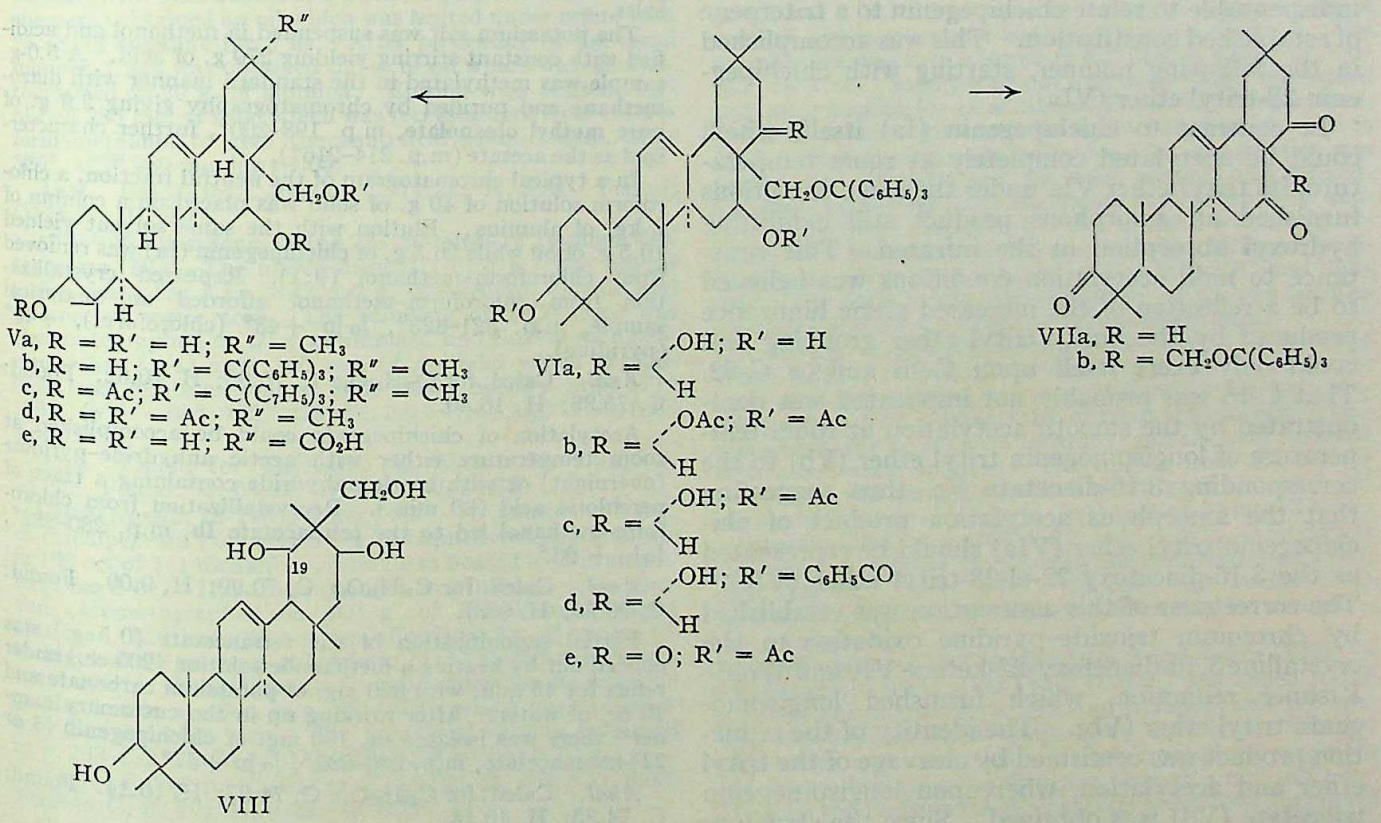
another diene, which must be the homoannular $\Delta^{9(11),12}$-diene III since it exhibited a single ultraviolet absorption maximum at 281 mμ. Selenium dioxide oxidation[8] of the latter (III) gave the required diene-dione IV, demonstrating that C-19 in chichipegenin must have been unsubstituted.

A close companion of chichipegenin in several *Myrtillocactus* species[4] is myrtillogenic acid (Ve),[11] and it seemed attractive to speculate that both triterpenes were oxygenated at identical carbon atoms.[12] This possibility was ruled out by the experimental observation[4] that lithium aluminum hydride reduction of myrtillogenic acid (Ve) produced a tetrol, different from chichipegenin. It was necessary, therefore, to remove one or more hydroxyl groups in chichipegenin in order to achieve a correlation with a known triterpene and attempts at selective manipulation of the hydroxyl groups were initiated.

Chichipegenin did not form an acetonide and assuming the existence of a 3β-hydroxyl group—found in all cactus triterpenes[6]—this observation excluded hydroxyl groups at C-23, C-24,[13] C-2 (β)[14] and presumably also C-1 (β). The presence of a 1,2-glycol moiety was eliminated by the observed stability of chichipegenin toward lead tetraacetate, but the presence of a 1,3-glycol grouping in other parts of the molecule still had to be considered since 16β,28-diols such as longispinogenin (Va) do not form acetonides.

As described in the Experimental portion of this paper, chichipegenin is accompanied in the cactus *L. chichipe* by oleanolic acid and by longispinogenin (Va). This suggested that one of the hydroxyl groups of chichipegenin might be located at C-28, and since a model experiment with longispinogenin (Va) demonstrated the ready formation of a 28-trityl ether Vb, chichipegenin was subjected to similar treatment with triphenylmethyl chloride. The resulting trityl ether VIa yielded a triacetate VIb when heated with acetic anhydride and a triketone VIIb upon oxidation with chromium trioxide–pyridine. This demonstrated the presence of one primary and three secondary hydroxyl groups in chichipegenin. Furthermore, the spectral properties of the triketo-trityl ether VIIb required the absence of an enolizable α- or β-diketone grouping. Detritylation of VIIb by boiling with alcoholic sulfuric acid led in poor yield to a nortriketone VIIa, which gave a strongly positive ferric chloride reaction and exhibited an ultraviolet absorption maximum (λ_{max}^{EtOH} 290 mμ, λ_{max}^{KOH} 309 mμ) consistent with the presence of a β-diketone function.[15] The identical nor-trione VIIa could also be obtained in one step by direct chromium trioxide–acetic acid oxidation of chichipegenin (Ia), thus requiring a triol moiety of type A in chichipegenin. The direct formation of the nor-trione VIIa (D) from the trityl ether VIIb (B) is due to retro-aldolization of the intermediate keto alcohol C and finds its exact counterpart in a similar reaction sequence described recently with the sesquiterpene iresin.[16]

Partial structure A can be incorporated into an



(11) C. Djerassi and H. G. Monsimer, THIS JOURNAL, **79**, 2901 (1957).

(12) A precedent being the co-occurrence of longispinogenin (Va) and the corresponding acid, cochalic acid, in the same cactus (see Table II in ref. 6).

(13) 3β,23- and 3β-24-acetonides can be formed readily (see J. L. Beton, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 2904 (1956)).

(14) The formation of a 2β,3β-acetonide has recently been demonstrated in the alfalfa sapogenin medicagenic acid (to be published).

(15) No good model appears to be available to predict the exact position of the ultraviolet absorption maximum of such a β-diketone (*cf.* E. R. Blout, V. W. Eager and D. C. Silverman, THIS JOURNAL, **68**, 566 (1946)).

(16) C. Djerassi, W. Rittel, A. L. Nussbaum, F. W. Donovan and J. Herrán, *ibid.*, **76**, 6410 (1954).

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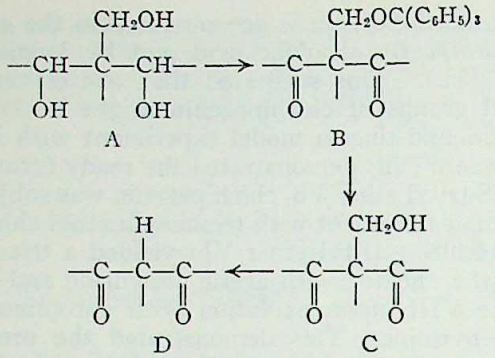

intact β-amyrin skeleton only in rings D and E leading to structure I or VIII. However, chichipegenin cannot have a hydroxyl group at C-19 (as in VIII) because of the ease of acetylation, the formation of a tetraacetoxy diene-dione IV and the lack of ultraviolet absorption typical of an α,β-unsaturated ketone[17] shown by the trityl ether trione VIIb in alkaline solution. The above analysis leaves I as the only structural alternative for chichipegenin, but since this is based on a process of elimination which in turn is predicated on a normal triterpene skeleton—so far unproved—it was indispensable to relate chichipegenin to a triterpene of established constitution. This was accomplished in the following manner, starting with chichipegenin 28-trityl ether (VIa).

In contrast to chichipegenin (Ia) itself, which could be acetylated completely at room temperature, its trityl ether VIa under the same conditions furnished an amorphous product still exhibiting hydroxyl absorption in the infrared. This resistance to mild acetylation conditions was believed to be a reflection of the increased steric hindrance produced by the bulky trityl ether grouping and could only exert itself upon C-16 and/or C-22. That C-16 was probably not implicated was demonstrated by the smooth acetylation at room temperature of longispinogenin trityl ether (Vb) to the corresponding 3,16-diacetate Vc, thus suggesting that the amorphous acetylation product of chichipegenin trityl ether (VIa) should be represented as the 3,16-diacetoxy-22-ol-28-trityl ether (VIc).[18] The correctness of this assumption was established by chromium trioxide–pyridine oxidation to the crystalline 3,16-diacetoxy-22-ketone VIe and Wolff–Kishner reduction, which furnished longispinogenin trityl ether (Vb). The identity of the reduction product was confirmed by cleavage of the trityl ether and acetylation, whereupon longispinogenin triacetate (Vd) was obtained. Since the structure and stereochemistry of longispinogenin (Va) has been proved rigorously,[19] chichipegenin can now be given the systematic name Δ^{12}-oleanene-3β,16β-22α,28-tetrol (Ia).[20] Attention already has been called earlier[6] to the fact that the sixteen triterpenes which have so far been isolated in our laboratories from giant cacti all fall into a restricted oxygenation pattern which involves only rings D and E aside from position C-3. The structure of chichipegenin further supports this "rule" which may be of some utility in narrowing down structural alternatives when working with unknown cactus triterpenes.

(17) If structure VIII were the correct expression for chichipegenin, then the triketo trityl ether VIIb would contain a 19-keto function, and such β,γ-unsaturated ketones are readily isomerized with base to the corresponding conjugated ketone (see P. Bilham, G. A. R. Kon and W. C. J. Ross, *J. Chem. Soc.*, 540 (1942); L. Ruzicka, A. Grob, R. Egli and O. Jeger, *Helv. Chim., Acta*, **26**, 1218 (1943)).

(18) Similarly, benzoylation of the trityl ether VIa yielded a 3,16-dibenzoate VId which could be crystallized.

(19) C. Djerassi, L. E. Geller and A. J. Lemin, *Chemistry & Industry*, 161 (1954); THIS JOURNAL, **76**, 4089 (1954).

(20) The equatorial (α) orientation is assigned to the 22-hydroxyl group because of its ease of acetylation and benzoylation.

Experimental[21]

Isolation of Triterpenes from *Lemaireocereus chichipe*.—The fresh cactus (106 kg.) collected near Tehuacán, Puebla, and identified by Dr. Helia Bravo of the Instituto de Biologia (Universidad Nacional Autonoma de Mexico), was cut into small portions and dried for 7 days at 35°. The ground, dried material (32 kg.) was continuously extracted with hot ethanol and the dry extract (9.5 kg.) was washed well with acetone and then ether, leaving 4.5 kg. of "glycosidic" fraction. A 2-kg. portion of it was heated under reflux for 2 hr. with 10 l. of methanol and 2 l. of concd. hydrochloric acid, concentrated to one-half of its volume and diluted with water. Filtration produced 720 g. of solid while basification of the filtrate with ammonia did not reveal the presence of any alkaloids. A chloroform solution of the solid was shaken repeatedly with aqueous potassium hydroxide solution furnishing approximately 400 g. of neutral material and 300 g. of insoluble potassium salts.

The potassium salt was suspended in methanol and acidified with constant stirring yielding 270 g. of acid. A 5.0-g. sample was methylated in the standard manner with diazomethane and purified by chromatography giving 2.6 g. of pure **methyl oleanolate**, m.p. 198–200°, further characterized as the acetate (m.p. 214–216°).

In a typical chromatogram of the neutral fraction, a chloroform solution of 40 g. of solid was placed on a column of 2 kg. of alumina. Elution with the same solvent yielded 10.5 g. of oil while 26.5 g. of **chichipegenin (Ia)** was removed from chloroform–methanol (9:1). Repeated crystallization from chloroform–methanol afforded an analytical sample, m.p. 321–323°, $[\alpha]_D$ +43° (chloroform), +40° (pyridine).

Anal. Calcd. for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. Found: C, 75.39; H, 10.40.

Acetylation of chichipegenin could be accomplished at room temperature either with acetic anhydride–pyridine (overnight) or with acetic anhydride containing a trace of perchloric acid (30 min.). Recrystallization from chloroform–methanol led to the **tetraacetate Ib**, m.p. 280–282°, $[\alpha]_D$ + 26°.

Anal. Calcd. for $C_{38}H_{58}O_8$: C, 70.99; H, 9.09. Found: C, 70.96; H, 9.23.

Partial saponification of the tetraacetate (0.5 g.) was carried out by heating a methanolic solution (200 cc.) under reflux for 45 min. with 800 mg. of potassium carbonate and 10 cc. of water. After working up in the customary manner[22] there was isolated *ca.* 100 mg. of **chichipegenin (3 or 22)-monoacetate**, m.p. 280–282°, $[\alpha]_D$ +57°.

Anal. Calcd. for $C_{32}H_{52}O_5$: C, 74.37; H, 10.14. Found: C, 74.35; H, 10.14.

Benzoylation of chichipegenin (benzoyl chloride–pyridine, 14 hr., 23°) followed by chromatography and recrystallization from ether–methanol yielded the **tetrabenzoate Ic**, m.p. 245–247°, $[\alpha]_D$ +62°.

Anal. Calcd. for $C_{58}H_{66}O_8$: C, 78.32; H, 7.65. Found: C, 78.20; H, 7.47.

(21) All melting points were determined on the Kofler block. Unless noted otherwise, rotations were measured in 1-dcm. tubes in chloroform solution. Infrared spectra were obtained in part with a Perkin–Elmer (Instituto de Quimica) and in part with a Baird (Wayne State University) double beam spectrophotometer. The microanalyses were carried out by Geller Laboratories (Hackensack, N. J.), Dr. Franz Pascher (Bonn, Germany) and Dr. Alfred Bernhardt (Mülheim, Germany).

(22) C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins and F. Walls, THIS JOURNAL, **76**, 2969 (1954).

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Similar treatment of the monoacetate led to **chichipegenin tribenzoate monoacetate**, m.p. 221–223°, $[\alpha]D$ +50°.

Anal. Calcd. for $C_{53}H_{64}O_8$: C, 76.76; H, 7.78. Found: C, 76.95; H, 7.70.

The ether and acetone washings of the "glycosidic" fraction were combined and evaporated to dryness (4.1 kg.) yielding an oily, dark colored mass. A 290-g. portion was dissolved in 200 cc. of dioxane and heated under reflux for 6 hr. with 200 g. of potassium hydroxide dissolved in 2 l. of methanol. After concentrating and diluting with water, the mixture was extracted continuously with ether. Concentration of the washed and dried ether solution gave 77 g. of **longispinogenin (Va)**, m.p. 249–252°, $[\alpha]D$ +57°, tetraacetate, m.p. 219–222°, $[\alpha]D$ +76°.

$\Delta^{11,13(18)}$-Oleadiene-3β,16β,22α,28-tetrol Tetraacetate (II).—A solution of 200 mg. of chichipegenin tetraacetate (Ib) in 25 cc. of glacial acetic acid was heated under reflux for 3 hr. with 200 mg. of freshly sublimed selenium dioxide. After working up in the usual way including chromatography and recrystallization from chloroform–methanol, there was obtained 102 mg. of the diene II, m.p. 192–193.5°, $[\alpha]D$ −114°; λ_{max}^{EtOH} 242, 250 and 260 mμ; log ϵ 4.43, 4.56 and 4.35.

Anal. Calcd. for $C_{38}H_{56}O_8$: C, 71.22; H, 8.81. Found: C, 71.58; H, 9.09.

$\Delta^{9(11),12}$-Oleadiene-3β,16β,22α,28-tetrol Tetraacetate (III).—A mixture of 2.0 g. of chichipegenin tetraacetate (Ib), 1.2 g. of N-bromosuccinimide and 100 cc. of carbon tetrachloride was heated under reflux for 2 hr. After filtering, washing with bicarbonate and water, drying and evaporating, there was obtained an oil which was heated under reflux with 25 cc. of collidine for 3 hr. After processing in the usual manner, there was obtained 0.5 g. of oil which was chromatographed on 20 g. of alumina. Elution with benzene furnished 285 mg. of solid which was recrystallized from chloroform–methanol to give the analytical sample, m.p. 323–325°, λ_{max}^{EtOH} 280 mμ, log ϵ 4.05.

Anal. Calcd. for $C_{38}H_{56}O_8$: C, 71.22; H, 8.81. Found: C, 71.77; H, 9.12.

$\Delta^{9(11),13(18)}$-Oleadiene-3β,16β,22α,28-tetrol-12,19-dione Tetraacetate (IV).—The above diene III (1.0 g.) was heated under reflux for 5 hr. with 1.0 g. of selenium dioxide and 200 cc. of acetic acid. The resulting oil (800 mg.) was chromatographed on 50 g. of alumina, and elution with benzene–ether (1:1) gave 100 mg. of material which crystallized from dilute acetone as light yellow needles, m.p. 171–173°, $[\alpha]D$ −69°, λ_{max}^{EtOH} 278 mμ, log ϵ 4.15; λ_{max}^{Nujol} 5.75, 6.05 and 6.20 μ.

Anal. Calcd. for $C_{38}H_{52}O_{10}$: C, 68.24; H, 7.84; O, 23.92. Found: C, 68.02; H, 7.87; O, 24.35.

Chichipegenin 28-Trityl Ether (VIa).—A solution of 2.0 g. of chichipegenin (Ia) and 6.0 g. of triphenylmethyl chloride in 160 cc. of 1:1 dioxane–pyridine was heated on the steam-bath for 8 hr. The crude product was isolated with ether and chromatographed on 400 g. of Merck acid-washed alumina. Elution with benzene afforded 4.2 g. of triphenylcarbinol while benzene–chloroform (1:1) eluted the desired trityl ether. Crystallization from benzene–hexane gave 2.3 g. of colorless needles, m.p. 261–270°, which were satisfactory for the next step. The analytical sample exhibited m.p. 263–272°, $[\alpha]D$ +70°, $\lambda_{max}^{CHCl_3}$ 6.22(w) and 6.70(m) μ.

Anal. Calcd. for $C_{49}H_{64}O_4$: C, 82.08; H, 9.00; O, 8.93. Found: C, 82.20; H, 9.16; O, 8.29.

Complete acetylation could be accomplished by heating a mixture of 300 mg. of the trityl ether, 15 cc. of pyridine and 15 cc. of acetic anhydride for 4 hr. on the steam-bath. Dilution with water and filtration yielded a solid which was chromatographed on 30 g. of Merck acid-washed alumina and eluted with benzene. Recrystallization from ethanol led to 200 mg. of the **triacetoxy trityl ether (VIb)**, m.p. 252–256°, $[\alpha]D$ +70°, no infrared hydroxyl absorption.

Anal. Calcd. for $C_{55}H_{70}O_7$: C, 78.34; H, 8.37; O, 13.28. Found: C, 78.48; H, 8.29; O, 12.85.

Δ^{12}-Oleanene-3β,16β,28-triol-22-one 3,16-Diacetate 28-Trityl Ether (VIe).—A solution of 1.5 g. of chichipegenin in 100 cc. of pyridine and 50 cc. of acetic anhydride was left at room temperature for 15 hr.[23] After diluting with water, the amorphous precipitate ($\lambda_{max}^{CHCl_3}$ 2.80 and 5.75 μ) was collected, and since it could not be crystallized, even after chromatography, it was oxidized directly with 1 g. of chromium trioxide in 30 cc. of pyridine for 20 hr. at room temperature. The product (62% over-all yield) was isolated with ether and crystallized from methanol; m.p. 287–290°, $[\alpha]D$ −44°; $\lambda_{max}^{CHCl_3}$ 5.77(broad), 6.20(v.w.), 6.68(m) and 7.95(s).

Anal. Calcd. for $C_{53}H_{66}O_6$: C, 79.64; H, 8.33; O, 12.01. Found: C, 79.66; H, 8.76; O, 11.46.

Longispinogenin 28-Trityl Ether (Vb). (a) **From Longispinogenin (Va).**—Longispinogenin (Va) (3.0 g.), triphenylmethyl chloride (10.0 g.) and 1:1 dioxane–pyridine (240 cc.) were heated on the steam-bath for 8 hr. Chromatography on 550 g. of Merck acid-washed alumina yielded 8 g. of triphenylcarbinol (benzene), 2.3 g. of the desired trityl ether (benzene–ether 3:1) and 0.7 g. of unchanged longispinogenin (chloroform–methanol 9:1). Crystallization from benzene–hexane afforded colorless needles of the dimorphic trityl ether, m.p. 208–210° and 268–280°, $[\alpha]D$ +35°.

Anal. Calcd. for $C_{49}H_{64}O_3$: C, 83.95; H, 9.20; O, 6.85. Found: C, 84.38; H, 9.32; O, 6.25.

Acetylation with acetic anhydride–pyridine at room temperature overnight yielded the **diacetoxy trityl ether (Vc)**, m.p. 209–211° and 227–232°, $[\alpha]D$ +69°.

Anal. Calcd. for $C_{53}H_{68}O_5$: C, 81.09; H, 8.74; O, 10.20. Found: C, 81.05; H, 8.72; O, 9.83.

(b) **By Wolff–Kishner Reduction of VIe.**—A mixture of 1.0 g. of the 22-keto trityl ether VIe, 100 cc. of diethylene glycol and 6 cc. of hydrazine hydrate was heated to reflux until all of the triterpene had dissolved (*ca.* 5 min.). The temperature was then allowed to fall and was kept at 110–130° for 1 hr. Solid potassium hydroxide (5 g.) was added and, after keeping for an additional hr. at that temperature, distillation was commenced until the temperature rose to 215°. After heating under reflux for 5 hr., the solution was poured into ice-water and the solid product was filtered. Chromatography on 50 g. of alumina and elution with benzene–ether (4:1) provided 400 mg. of solid which was recrystallized from benzene–hexane to yield needles of longispinogenin trityl ether (Vb) with m.p. 208–210° and 268–280°, $[\alpha]D$ +33°. The infrared spectra of the two samples (prepared according to (a) and (b)) were identical.

A 300-mg. sample of longispinogenin trityl ether from the Wolff–Kishner reduction was dissolved in 25 cc. of chloroform, and the solution was saturated with hydrogen chloride gas for 1.5 hr. After 20 hr. at room temperature, water was added, the layers were separated and the acid removed with bicarbonate solution. The residue from the chloroform layer was chromatographed on 15 g. of alumina, and elution with ether–chloroform (3:1) yielded 74 mg. of longispinogenin (Va), m.p. 253–256°, $[\alpha]D$ +57°. Acetylation at room temperature gave longispinogenin triacetate (Vd), m.p. 226–228°, $[\alpha]D$ +72°. Identity was confirmed in each case by mixture melting point determination and infrared comparison.

Δ^{12}-Oleanene-3,16,22-trione-28-ol Trityl Ether (VIIb).—Chichipegenin trityl ether (VIa) (0.6 g.) was added to 0.6 g. of chromium trioxide in 25 cc. of pyridine, and the mixture was kept at room temperature overnight. Dilution with water and extraction with ether produced emulsions which were broken up by filtration through a mat of Celite. The solid residue from the ether extract was chromatographed on 30 g. of Merck acid-washed alumina, and elution with benzene–ether (20:1) led to 300 mg. of the triketone. The analytical sample crystallized from benzene–hexane as colorless needles, m.p. 292–295°, $[\alpha]D$ −53°, λ_{max}^{KBr} 5.80(s), 6.2(w) and 6.68(m) μ. The substance gave no color with ferric chloride and exhibited no high ultraviolet absorption maximum in alcoholic alkali.[17]

Anal. Calcd. for $C_{49}H_{58}O_4$: C, 82.78; H, 8.22; O, 9.00. Found: C, 82.45; H, 8.02; O, 9.39.

28-Nor-Δ^{12}-Oleanene-3,16,22-trione (VIIa). (a) **From Chichipegenin (Ia).**—Chichipegenin (1.0 g.) was dissolved in 200 cc. of acetic acid, and a solution of 1.0 g. of chromium trioxide in 10 cc. of 90% acetic acid was added. After standing overnight, water was added, the product was extracted with ether and washed with 3% potassium hydroxide to leave 340 mg. of neutral oil. Crystallization from methanol afforded 90 mg. of yellowish needles, m.p. 253–257°, $[\alpha]D$ −45°, λ_{max}^{EtOH} 290 mμ, log ϵ 4.10; λ_{max}^{KOH} 309 mμ,

(23) When the reaction was performed with benzoyl chloride in pyridine, there was obtained after recrystallization from ethanol the 3,16-dibenzoate VId, m.p. 196–198.5°, $[\alpha]D$ +77°. *Anal.* Calcd. for $C_{44}H_{72}O_6$: C, 81.76; H, 7.85. Found: C, 82.09; H, 7.90.

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log ϵ 4.65; $\lambda_{max}^{CHCl_3}$ 5.83, 6.09 and 6.21 (shoulder) μ. The substance gave a red color with ferric chloride.

Anal. Calcd. for $C_{29}H_{42}O_3$: C, 79.40; H, 9.65; O, 10.94. Found: C, 78.97; H, 9.27; O, 11.10.

(b) From the Trityl Ether VIIb.—When 1.0 g. of the trityl ether VIIb was heated under reflux for 8 hr. with 50 cc. of ethanol and 0.5 cc. of sulfuric acid and then cooled, there separated approximately 50 mg. of crystals. These were filtered and recrystallized from methanol whereupon they exhibited m.p. 248–251°, undepressed upon admixture with a sample prepared according to (a). The ultraviolet absorption spectrum and the red color with ferric chloride supported the identification of this substance.

Anal. Calcd. for $C_{29}H_{42}O_3$: C, 79.40; H, 9.65. Found: C, 79.41; H, 9.53.

DETROIT, MICHIGAN
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[CONTRIBUTION FROM THE LABORATORIES OF THE SCHERING CORPORATION]

Long-acting Testosterone Esters. Some Considerations on their Biological Utilization[1]

BY DAVID GOULD, LAWRENCE FINCKENOR, E. B. HERSHBERG, JAMES CASSIDY AND PRESTON L. PERLMAN

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A series of testosterone 17-esters was prepared to find those with the best activity and duration. Several potent derivatives were found, including the entire family of aryloxyalkanoates. Injections of these esters in rodents are shown to be efficient and enduring sources of testosterone.

Since testosterone was established as the true androgenic hormone,[2] attempts have been made to potentiate its effect and prevent its rapid metabolic destruction.[3] The program reported here was carried out with this aim, and led to many esters considerably more valuable in potentiating the androgenic effect than testosterone propionate,[4] as well as a group of esters which are outstanding in the assays used with respect to intensity and duration of androgenic action. The results are given in Tables I-IV.

The acids corresponding to the esters, if they were not available commercially, were prepared by methods reported in the literature, mainly from "Beilstein: Handbuch der Organischen Chemie." The acid chlorides were made using thionyl chloride and generally isolated by vacuum distillation, though the residues were used when distillation caused decomposition. Although some of the acid chlorides had not been known previously, they are not reported here, since they were not characterized and analyzed. All of the esters were made according to the standard procedure given below, in which chilling was found to be essential for the ready preparation of pure products. In the case of oily esters, chromatography gave materials with the correct analyses.

The intensity and duration of androgenic action were tested in mice and rats, giving results which are shown qualitatively in the tables according to their relation to the action of testosterone propionate (TP). The effects were measured by weighing the seminal vesicles of castrated animals at various times after subcutaneous injection of the ester. We have considered that compounds effecting a maximum seminal vesicle weight less than $1/2$ of that due to TP are not of interest and such are rated "0." Conversely, compounds with maxima several times that of TP generally last correspondingly longer before falling below our cut-off point.

The original hypothesis on which this study was based stemmed from the maximal activity of the lowest melting members of the straight chain acid series of esters, *e.g.*, heptanoate and nonanoate.[4,5] This suggested that the more oil-soluble esters are most useful; therefore, a group of esters of branched chain acids was prepared (see Table I). The results show that, while none surpasses the heptanoate and nonanoate, several esters containing four to eleven carbons approached them in activity. The variation of the activity from good to poor of intermediate-length esters, all of them low melting solids or oils readily soluble in hydrocarbon solvents, shows the invalidity of the hypothesis. For example, the decreased activity of the 3,3-dimethylpentanoate compared to the 3-methylpentanoate is in disagreement.

It is, however, possible to make some generalizations. (1) All of the esters with dialkyl-substituted chains have poor activity. (2) The 2-alkyl-substituted esters (except isobutyrate) have a low order of activity. These statements suggest that steric hindrance plays an important role in decreasing the activity. Thus, fatty acids, such as trimethylacetic and diethylacetic, which are known to esterify at less than one-tenth the rate of acetic, and, therefore, also to hydrolyze with difficulty, due to hindrance caused by branching,[6] form testosterone esters whose intensity is so reduced that they are therapeutically useless.

Since no trend or advance in activity is observable in the fatty acid series, other types were prepared (Tables II-IV), especially a group of substituted cyclohexane-carboxylic acid esters (Table

(1) Presented in part before the Medicinal and Biological Chemistry Section of the Delaware Valley Regional Meeting of the American Chemical Society, Philadelphia, February 16, 1956.

(2) K. David, E. Dingemanse, J. Freud and R. Laqueur, *Z. physiol. Chem.*, **233**, 281 (1935); A. Butenandt and G. Hanisch, *Ber.*, **68**, 1859 (1935); L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935).

(3) *Inter alia*, T. F. Gallagher, D. K. Fukushima, M. C. Barry and K. Dobriner, in: "Recent Progress in Hormone Research," Vol. VI, Academic Press, New York, N. Y., 1951, p. 131; L. T. Samuels and C. D. West, in: "Vitamins and Hormones," Vol. X, Academic Press, New York, N. Y., 1952, p. 251.

(4) K. Miescher, A. Wettstein and E. Tschopp, *Biochem. J.*, **30**, 1977 (1936); K. Miescher, H. Kägi, C. Scholz, A. Wettstein and E. Tschopp, *Biochem. Z.*, **294**, 39 (1937); L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **19**, 1141 (1936).

(5) K. Junkmann, *Arch. exper. Path. Pharmakol.*, **215**, 85 (1952).

(6) K. L. Loening, A. B. Garrett and M. S. Newman, THIS JOURNAL, **74**, 3929 (1952).

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TABLE I

BRANCHED FATTY ACID ESTERS OF TESTOSTERONE

Ester Stem	Substituent	M.p., °C.	$[\alpha]^{25}D^{g}$	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Duration[f]	Method[f]	Intensity[f]
Propionic	2-Methyl[a]	133–135	+71.0°	(Lit.[b] m.p. 134–136°)				2,3,2	A,B,C	2,3,3
Propionic	2,2-Dimethyl[a]	156–158	77.3	(Lit.[c] m.p. 157–158°)				0,0	A,C	0,0
				[α]D 88 (Chlf.)						
Butyric	2-Methyl	135–137	74.8	77.37	9.74	77.21	9.49	2,2,3	A,B,C	1,1/2,3
Butyric	3-Methyl[a]	136–138	80.9	(Lit.[b] m.p. 138–140°)				2	A	2
Butyric	2-Ethyl	129–130	78.3	77.67	9.91	77.50	10.10	2,0	A,C	1,0
Butyric	2-Isopropyl	121–123	79.1	77.95	10.07	78.04	9.96	1,0	A,C	1/2,0
Pentanoic	2-Methyl	81–84	80.1	77.67	9.91	77.91	10.14	3	A	1
Pentanoic	3-Methyl	70–71.5	82.7	77.67	9.91	77.35	9.87	3,2,2	A,B,C	3,2,2
Pentanoic	4-Methyl	82–84.5	82.3	77.67	9.91	77.81	9.63	4	A	3
Pentanoic	3,3-Dimethyl	Oil	72.4	77.95	10.07	78.20	9.71	1	A	1/2
Pentanoic	3-Isopropyl-4-methyl	Oil	70.3	78.45	10.35	78.55	10.15	2	A	1
Hexanoic	3-Methyl	45–46.8	79.2	77.95	10.07	77.79	10.25	3	A	3
Hexanoic	5-Methyl	57–59	79.6	77.95	10.07	77.84	10.05	3	A	3
Hexanoic	2-Ethyl	89–90	75.0	78.21	10.21	78.38	10.18	3	A	1/2
Hexanoic	2-Isopropyl	Oil	66.7	78.45	10.35	78.12	10.71	0,0	A,B	0,0
Hexanoic	3,5,5-Trimethyl	57–60	70.9	78.45	10.35	78.20	10.58	0	A	0
Heptanoic[a]		Oil	75.3	(Lit.[d] m.p. 36–37.5°)				3,3	A,B	3,3
				[α] 78 (diox.)						
Heptanoic[a]	6-Methyl	Oil	66.9	78.21	10.21	78.21	10.23	3[e]	A	3
Octanoic[a]		44–45.2	73.9	(Lit.[d] m.p. 47–48°)				2[e]	A	1/2
				[α]D +76						
Octanoic[a]	2-Methyl	Oil	63.5	78.45	10.35	78.22	10.53	3	A	1
Nonanoic		49–51	75.5	78.45	10.35	78.35	10.59	3,3	A,B	3,3
Nonanoic	3-Methyl	Oil	67.8	78.68	10.48	78.33	10.57	2,2	A,B	1/2,3
Decanoic[a]		54–56	70.7	(Lit.[b] m.p. 55–57°)				2	A	1
Undecenoic		61–62.5	71.8	78.90	10.59	79.31	10.75	2,4,3	A,B,C	1/2,3,2
10-Undecenoic		52–54	72.3	79.24	10.20	79.03	10.02	4,4	A,B	2
Hexadecanoic[a]		72–73	72.4	(Lit.[b] m.p. 72–74°)				0	A	0

[a] Included for comparison. Analyses satisfactory. [b] L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, 19, 1141 (1936). [c] P. Wieland, J. Heer, J. Schmidlin and K. Miescher, *ibid.*, 34, 354 (1950). [d] Footnote 5. [e] Extrapolated value. [f] The different procedures were: A, 2.5 mg. of ester in oil in mice; B, 7.5 mg. of ester in oil in rats; C, 7.5 mg. of ester in aqueous suspension in rats. Duration of effect is rated as follows: 0 = no effect. (Seminal vesicle weighs less than 1/2 of the TP maximum); 1 = *ca.* that of TP (2–2.5 weeks in mice; 3–4 weeks in rats). 2 = 1–2 × TP; 3 = 2–4 × TP; 4 = 4–6 × TP. Intensity is rated on seminal vesicle weights as follows: 0 = <1/2 TP maximum; 1/2 = 1/2–1 × TP; 1 = TP (55–75 mg. in mice; 200–250 mg. in rats); 2 = 1–1 1/2 × TP; 3 = 1 1/2–2 × TP; 4 = >2 × TP. [g] Rotations in dioxane.

TABLE II

SUBSTITUTED CYCLOHEXANECARBOXYLATES OF TESTOSTERONE

Ester	M.p., °C.	$[\alpha]^{25}D^{a}$	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Duration[c]	Method[c]	Intensity[c]
Cyclohexanecarboxylate	125.4–127.2	+86.1°	(Lit.[b] m.p. 126–127°;				3,3,3	A,B,C	1,2,1
			[α]D +88 (Chlf.)						
2-Methylcyclohexanecarboxylate	134–136	80.5	78.59	9.77	78.60	9.67	3,0,2	A,B,C	1/2,0,1
3-Methylcyclohexanecarboxylate	120–124	80.5	78.59	9.77	78.31	10.05	3,3,3	A,B,C	3,2,2
4-Methylcyclohexanecarboxylate	163–165.1	78.4	78.59	9.77	78.64	9.94	4,3,3	A,B,C	3,3,3
4-Ethylcyclohexanecarboxylate	138.4–140.5	77.3	78.82	9.92	78.72	9.78	3	A	3
4-Propylcyclohexanecarboxylate	139.5–141.6	75.7	79.04	10.06	78.76	10.11	3	A	2
4-Isopropylcyclohexanecarboxylate	141.5–142.5	81.8	79.04	10.06	78.89	10.20	3	A	2
3,3,5-Trimethylcyclohexanecarboxylate	135–136	78.7	79.04	10.06	79.14	10.14	2,0	A,C	1/2,0

[a] Rotations in dioxane. [b] G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, 72, 4077 (1950). [c] See footnote *f*, Table I.

II). Although these acids may be considered as disubstituted acetic acids, the ring ties the alkyl groups back so that hindrance is lessened, except in the case of the 2-methyl and trimethyl derivatives. The 3- and 4-alkylcyclohexane carboxylates generally have intensity about equal to the best fatty acid esters, but the peak activity is maintained better so that the duration of effective action is longer. Extension of the chain to the methylcyclohexylacetates decreases the potency and duration (Table IV). Further extension of the chain to phenyl or cycloalkyl propionates, butyrates, etc., gives esters of varying intensity and with duration similar to the heptanoate, with the exception of the 4-cyclohexylhexanoate whose activity curve climbs only slowly but is maintained high for an exceptionally long period of 14–18 weeks in rats (Table IV). The phenylacetate, 3-phenylpropionate and 3-cyclopentylpropionate which are given here for comparison have intensity and duration in oil similar to the heptanoate. Inexplicably, the 3-cyclopentylpropionate is, as an aqueous suspen-

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TABLE III

17-ARYLOXYALKANOATES OF TESTOSTERONE

Ester	M.p., °C.	$[\alpha]^{25}D$[a]	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Duration[b]	Method[b]	Intensity[b]
Phenoxyacetic	173–174.8	+81.8°	76.74	8.11	76.60	8.33	3,3,3	A,B,C	3,3,4
2-Chlorophenoxyacetic	165–165.9	78.9	70.96 (Cl, 7.72)	7.28	70.70 (Cl, 7.22)	7.15	3[d],4	A,C	2,3
4-Chlorophenoxyacetic	178–180.2	75.3	70.96 (Cl, 7.72)	7.28	71.22 (Cl, 6.95)	7.48	4,3	A,C	4,2
4-Bromophenoxyacetic	174–175	66.8	64.67 (Br, 15.94)	6.63	64.84 (Br, 16.08)	6.93	3,4	A,C	3,3
2,4-Dichlorophenoxyacetic	118–120	74.7	65.98 (Cl, 14.43)	6.56	66.24 (Cl, 14.62)	6.77	3,3,3	A,B,C	3,3,4
2,4,5-Trichlorophenoxyacetic	157–158.4	59.7	61.66 (Cl, 20.23)	5.94	61.44 (Cl, 20.43)	6.10	4,3.3	A,B,C	3,3,3
2,4,6-Triiodophenoxyacetic	251–254	54.0	40.52 (I, 47.58)	3.90	40.77 (I, 48.36)	4.00	..	....	..
4-Methoxyphenoxyacetic	176–178	71.9	74.30	8.02	74.02	8.28	3,3	A,C	3,4
4-Methylphenoxyacetic	183.5–187	73.4	77.03	8.31	76.82	8.42	3	A	3
4-*t*-Butylphenoxyacetic	156.8–158.2	69.4	77.78	8.85	77.76	9.03	4,4,4	A,B,C	3,3,4
(−)-2-Phenoxypropionic[c]	164.5–166	49.4	77.03	8.31	76.83	8.41	3[d],2[d]	A,C	2,2
(+)-2-Phenoxypropionic[c]	126.4–129.8	90.7	77.03	8.31	76.88	8.55	3[d],3	A,C	2,3

[a] Rotations in dioxane. [b] See footnote *f*, Table I. [c] Resolved by crystallization of the mixed esters of the racemic acid. [d] Extrapolated value.

TABLE IV

MISCELLANEOUS ESTERS OF TESTOSTERONE

Ester	M.p., °C.	$[\alpha]^{25}D$[i]	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Duration[h]	Method[h]	Intensity[h]
3-Ethoxypropionate[a]	51–52	+75.7°	(Lit.[b] m.p. 53–55°) $[\alpha]^{29}D$ 74.7 (EtOH)				1	A	1
3-(*n*-Butoxy)-butyrate	Oil	65.5	75.31	9.83	75.24	9.83	3,2	A,B	2,1
2-Furoate[a,d]	227–230	149.5	(Lit.[b] m.p. 221°) $[\alpha]^{27}D$ 170.5 (Chlf.)				3[e]	A	2
2-Chlorobenzoate	213–214.9	114.5	73.13	7.32	73.04	7.23	0	A	0
4-Chlorobenzoate	257–261	117.9	73.13 (Cl, 8.30)	7.32	73.31 (Cl, 8.35)	7.33	0	A	0
4-Ethoxybenzoate	163.2–164.2	148.2	77.03	8.31	77.21	8.45	3,2	A,C	2,2
3,4-Dimethoxybenzoate	147.5–149.0	155.0	74.30	8.02	74.29	8.19	1	A	1/2
p-Toluate	219–221.1	144.2	79.76	8.43	79.66	8.25	2	A	1
Phenylacetate[a]	126.5–127.5	80.0	(Lit.[c] m.p. 129–131°)				3,3	A,C	2,3
Cyclohexylacetate[a,d]	86.5–88.5	78.6	78.59	9.77	78.42	9.79	3	A	1
3-Methylcyclohexylacetate	Oil	68.7	78.82	9.92	78.60	10.05	2[e]	A	1
4-Methylcyclohexylacetate	Oil	68.6	78.82	9.92	78.85	10.11	2[e]	A	1
3-Cyclopentylpropionate[a]	104–105	78.2	(Lit.[d] m.p. 101–102°) $[\alpha]_D$ 87, 76.4[g] (Chlf.)				3,3,1	A,B,C	3,3,1
3-Cyclohexylpropionate[a,d]	74.5–76	74.9	78.82	9.92	78.75	10.26	3	A	3
3-Phenylpropionate[a]	113–114.5	86.8	(Lit.[f] m.p. 114.5–115.5°) $[\alpha]_D$ 85 to 91°				3[e],3	A,B	3,3
trans-Cinnamate	238.5–239.5	156.8	80.34	8.19	80.63	8.36	2	A	2
2-Phenylbutyrate	133–134	66.7	80.14	8.81	80.34	9.04	0	A	0
4-Phenylbutyrate	Oil	68.0	80.14	8.81	79.99	8.77	3,2	A,B	3,2
4-Cyclohexylhexanoate	Oil	68.1	79.44	10.32	79.66	10.57	3,4	A,B	3,4
1-Naphthylacetate	170–172	68.9	81.54	7.95	81.68	8.16	1	A	1
Diphenylacetate[a,d]	128.5–129.5	86.4	82.12	7.94	81.92	7.87	0	A	0

[a] Included for comparison. Analyses satisfactory. [b] A. Mooradian, C. Cavallito, A. Bergman, E. Lawson and C. Suter, THIS JOURNAL, 71, 3372 (1949). [c] See Note 4. [d] A. C. Ott, M. H. Kuizenga, S. C. Lyster and B. A. Johnson, *J. Clin. Endoc. and Metabol.*, 12, 15 (1952). [e] Extrapolated value. [f] Data from Dr. Eugene Shapiro, Organon Laboratories. [g] A. C. Ott, U. S. Patent 2,566,358. [h] See footnote *f*, Table I. [i] Rotations in dioxane.

sion, only equal to testosterone propionate in intensity and duration. Variation between activity of preparations in aqueous and oily vehicles and between mice and rats are observed in a few other cases, but generally only small differences exist and agreement is relatively good between the alternate procedures used here.

Further study beyond the series of alkylcyclohexane-carboxylates led to a new family of esters, the phenoxyalkanoates, having surprisingly enhanced intensity and duration[7] (Table III). The

(7) A preliminary announcement by D. Gould, L. Finckenor, P. Perlman, J. Cassidy, S. Margolin, M. T. Spoerlein and E. B. Hershberg appeared in *Chemistry & Industry*, 1424 (1955).

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4-chlorophenoxyacetate (in oil in mice) has given a maximum peak of over twice that of the propionate, which has not been observed with any other ester, and has, along with the 4-*t*-butylphenoxyacetate, lasted 16 weeks while the previously outstanding esters drop off at 8 weeks. In rats in aqueous suspension, the phenoxyacetate and the 4-*t*-butylphenoxyacetate have given maxima as high as three times that of the propionate and twice that of previously known esters, and the 4-*t*-butylphenoxyacetate has shown a useful level of activity for over 120 days.[8] Variations in substituents do not have the severe effects on activity seen in other families of esters. For example, even when the molecular weight is increased as in the 2,4,5-trichlorophenoxyacetate, activity is not lost. It is also of interest that the isomeric pair of 2-phenoxypropionates did not differ greatly, the observed variation probably being related to the solubilities.

In view of the consistently useful esters in this family, a more fundamental basis than solubility or hydrolytic rate might be suspected. The thought occurs that the phenoxyalkanoic acids are plant growth regulators[9] as are phenylacetic, phenylpropionic, and other unsaturated ring-substituted fatty acids. The anabolic activity of testosterone and the superior effect of these particular esters suggests the intriguing possibility that there may be a basic similarity in the biochemical mechanisms of control of growth in plants and animals.[1,7,10]

The potentiation of androgenic activity of these esters is seen more clearly in comparison with normal effects from endogenous testosterone. While no experiments have been designed for the purpose of determining these values for mice and rats, it is possible to obtain useful estimates of minima. Castrated rats are stated to be maintained properly on: 3×1 mg. TP/wk.,[11] 0.5–1.4 mg. T/day,[12] 1–2 mg. of androsterone/day[13] (equivalent to 0.1–0.2 mg. T/day),[14] 2×0.3 mg. T/day,[15] and 0.1–0.5 mg. TP/day.[16] Castrated mice are reported to be maintained by 65 γ TP/day.[17] Urinary ketosteroids in rats are stated to be: 0.15 mg./day[11]; 0.2–0.5 mg./day[14,18]; in mice, 0.5–1.9 mg./month.[19] Since steroidal metabolites in rodents are only found to the extent of $^1/_4$–$^1/_8$ of the injected testosterone,[20] the endogenous production of C-19 steroids may be calculated to be at least 8 mg./wk. in rats and 4 mg./month in mice. Although the ratio of testicular to adrenal orgin is not known for rodents, it is probably high,[21] and it is not unreasonable to assume from these figures and the maintenance doses that minimal figures for the endogenous production of testosterone at 1 mg./wk. in rats and 1 mg./mo. in mice. The latter figure is supported by Chai's estimate of 1.95 mg./mo. in mice.[17]

Using these figures, maintenance with endogenous testosterone in mice requires 4 mg. in 16 weeks while only 2.5 mg. of testosterone 4-chlorophenoxyacetate lasted for that period; and in rats, maintenance was observed with 7.5 mg. of the 4-*t*-butylphenoxyacetate for 17 weeks, a period requiring 17 mg. of endogenous testosterone. The high efficacy of these derivatives implies that they protect the testosterone from metabolism until it reaches the site of action. In any case, it would appear that these esters supply the hormone in a manner at least as efficient and perhaps more so than the intact testis.

Acknowledgment.—We are indebted to Walter Pummer, Eric Jorgensen and Gerold Krakower for aid in the preparation of some esters. We are especially indebted for the biological testing in rats to Dr. Solomon Margolin presently of Wallace Laboratories, New Brunswick, N. J.

Experimental[22]

Preparation of Acid Chlorides.—In a dry system, 100 g. of the acid was dissolved in 400 cc. of benzene and some benzene was distilled off to remove water. To this was slowly added 300 cc. of thionyl chloride, and the mixture was refluxed 12–16 hr.

The benzene and excess thionyl chloride were distilled off at atmospheric pressure in a dry system. If it was necessary to remove the last traces of thionyl chloride, another 100 cc. of benzene was distilled off. Finally, the pressure was reduced to 5–20 mm. and the acid chloride was distilled. Some high boiling acid chlorides were used without distillation.

General Procedure for Preparation of Testosterone Esters.—Five g. of testosterone was dissolved in 50 ml. of dry distilled pyridine. The solution was chilled to 0–10° in an ice-bath and 5 g. (or 1.25 equiv.) of acid chloride was added dropwise with good stirring. Stirring was continued for 12–15 hr. at room temperatures.

The mixture was poured with good stirring into a mixture of 400 g. of ice and 100 ml. of concd. sulfuric acid. If a precipitate was obtained, the product was filtered off, washed with 10% sodium carbonate and water (until neutral) and air-dried. The crude was then crystallized from methanol or methanol–benzene.

If the product did not solidify in the ice mixture, it was extracted several times with benzene and the benzene solution was washed with 10% sodium carbonate to remove the excess acid, with water until neutral, and dried over magnesium sulfate. The solution was evaporated, and the residue crystallized from methanol. If crystallization was not possible, the residue was chromatographed from hexane on alumina, removing oily impurities in the hexane eluates. Elution was continued with 1:1 hexane–benzene and with benzene to obtain the last of the ester. Ether eluted any unchanged testosterone. On standing or trituration with methanol, the benzene-containing fractions usually solidified. In any case, these fractions analyzed correctly, after sufficient drying *in vacuo*.

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(8) The last measurement still showed seminal vesicle weights greater than the TP maximum. It can be presumed that effective activity could be observed for a considerably longer duration.

(9) *Inter alia*, *cf.*, Å. Jönsson, *Acta Chem. Scand.*, **7**, 596 (1953).

(10) *Cf.*, I. A. Mirsky, D. Diengott and G. Perisutti, *Endocrinology*, **59**, 715 (1956).

(11) Unpublished data, these laboratories.

(12) V. Korenchevsky, M. Dennison and J. Brovsin, *Biochem. J.*, **30**, 558 (1936).

(13) C. R. Moore and D. Price, *ibid.*, **31**, 313 (1937).

(14) R. I. Dorfman and R. A. Shipley, in: "Androgens," John Wiley and Sons, Inc., New York, N. Y., 1956.

(15) J. S. Davis, R. K. Meyer and W. H. McShan, *Endocrinology*, **44**, 1 (1949).

(16) M. E. Simpson and H. M. Evans, *ibid.*, **38**, 281 (1946).

(17) C. K. Chai, *Am. J. Physiology*, **186**, 463 (1956).

(18) P. Koets, *J. Clin. Endocrinology*, **9**, 278 (1950).

(19) D. A. Karnofsky, I. T. Nathanson and J. C. Aub, *Cancer Research*, **4**, 772 (1944).

(20) M. C. Barry, M. L. Eidinoff, K. Dobriner and T. F. Gallagher, *Endocrinology*, **50**, 587 (1952).

(21) 1:1 or greater in man, *cf.* D. K. Fukushima, K. Dobriner and T. F. Gallagher, *J. Biol. Chem.*, **206**, 845, 863 (1954).

(22) All m.p.'s are corrected. Analyses and rotations were obtained by the Microanalytical Department of these laboratories.

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[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, MERCK & CO., INC.]

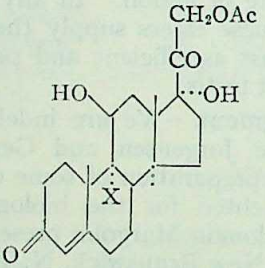
Transannular Hydrogen Transfer in the Steroid Series[1]

BY N. L. WENDLER, R. P. GRABER, C. S. SNODDY, JR., AND F. W. BOLLINGER

RECEIVED DECEMBER 10, 1956

The chemical transformations bearing on the transannular hydrogen transfer–rearrangement of 9β,11β-oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate (II) are described.

The acid-catalyzed scission of the epoxide function in 9β,11β-oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate (II) has been found to be directionally dependent on the nature of the acid catalyst employed. Whereas hydrogen halides and dilute mineral acids evoke normal scission to give the respective halohydrins (I, X = halogen)[2] and glycol (I, X = OH),[1,3] concentrated acids produce predominantly rearrangement of a duodirectional



I, X = halogen, OH

character. In the latter case the course of rearrangement is directed to a minor extent to give the corresponding 11-ketone, whereas the major product appearing results as a consequence of "2,6"-transannular migration of hydrogen.[4] Treatment of 9β,11β-oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate (II) in chloroform solution at 0° with 60% perchloric acid caused the development of a red coloration with the steroid partitioning itself nearly completely in the aqueous phase. Subsequent isolation of the reaction product yielded 10–15% of cortisone acetate[5] together with 65% of an isomeric compound[6] formed as the major product.[7] The homoallylic character of this isomeric substance was suggested by the observation that its 11-mesylate derivative underwent acidolysis to a significant extent with configurational retention to give the corresponding ester derivative in a manner reminiscent of the *i*-steroid phenomenon.[8] This substance, as will be borne out by the chemistry subsequently to be discussed, proved to be 17α-hydroxy-Δ⁸⁽¹⁴⁾-dehydrocorticosterone 21-acetate (III), a structure hardly to have been anticipated on the basis of classical theoretical considerations.

In establishing the structure of III, it was subjected *inter alia* to oxidation with chromic acid in pyridine,[9] to give what subsequently proved to be the Δ⁴,⁸⁽¹⁴⁾-dienedione IV. This substance on treatment with sodium methoxide was readily isomerized to the completely conjugated Δ⁴,⁸⁽⁹⁾-dienedione V. The latter compound was found to be identical with material obtained from 9-bromocortisone acetate (VII) by dehydrobromination of the latter with refluxing pyridine.[10] On the other hand, elimination of the elements of hydrogen bromide from VII with lithium chloride in dimethylformamide[11] afforded the 14β-isomer VI also obtained from the Δ⁴,⁸⁽⁹⁾-dienedione V by isomerization with hydrogen chloride in chloroform. The 14β-isomer VI, unlike its epimer V, afforded a 17-acetate derivative on acetylation with acetic anhydride in pyridine at room temperature for 7 days or 6 hours at 100°. Model inspection suggests a greater degree of steric accessibility of the 17α-OH in the 14β-iso (*cis* C/D) series, a consequence of the orientational change of the 17α-OH from pseudo-axial to pseudo-equatorial.

Since the Δ⁴,⁸⁽⁹⁾-dienedione V exhibited a somewhat unusual ultraviolet absorption for this structure with a low band position at 236.5 mμ as well as

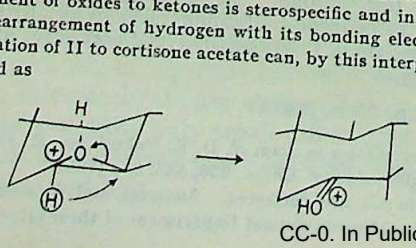
(1) For preliminary accounts of this work see: R. P. Graber, C. S. Snoddy, Jr., and N. L. Wendler, *Chemistry & Industry*, 57 (1956); N. L. Wendler, R. P. Graber and F. W. Bollinger, *ibid.*, 1312 (1956).

(2) (a) J. Fried and E. Sabo, THIS JOURNAL, **75**, 2273 (1953); (b) **76**, 1455 (1954).

(3) R. Littell and S. Bernstein, *ibid.*, **78**, 984 (1956).

(4) Meerwein with extraordinary insight first proposed 2,6-migration of hydrogen in 1924 to account for certain transformations in the camphane series. [See H. Meerwein and R. Wortmann, *Ann.*, **435**, 190 (1924); H. Meerwein and F. Montfort, *ibid.*, **435**, 207 (1924).] Recent corroboration for this transfer theory in the bicyclo[2,2,1]-heptane series has been provided by S. Beckmann and R. Bamberger, *ibid.*, **574**, 65 (1951); **580**, 198 (1953). See also J. D. Roberts and J. A. Yancey, THIS JOURNAL, **75**, 3165 (1953); W. R. Vaughan and R. Perry, Jr., *ibid.*, **75**, 3168 (1953). See also footnotes 29 and 30.

(5) The work of (a) K. Heusler and A. Wettstein (*Helv. Chim. Acta*, **36**, 399 (1953)) and (b) P. Bladon, H. B. Henbest, E. R. H. Jones, B. I. Lowell, G. W. Wood, G. F. Woods, J. Elks, R. M. Evans, D. E. Hathway, J. F. Oughton and G. H. Thomas (*J. Chem. Soc.*, 2921 (1953)) has provided unique and compelling evidence that the mechanism of rearrangement of oxides to ketones is sterospecific and involves a 1,2-Wagner rearrangement of hydrogen with its bonding electrons. The transformation of II to cortisone acetate can, by this interpretation, be represented as



(6) Fried and Sabo, ref. 2a, have described a substance of unknown constitution arising in *ca.* 10% yield from the reaction of hydrogen fluoride on II and possessing characteristics essentially the same as the perchloric acid product herein described. Fried and Sabo, however, established that this substance possessed a new epoxidizable double bond and an easily acylable hydroxyl group. See also ref. 17. In the meantime J. Fried and E. F. Sabo [THIS JOURNAL, **79**, 1130 (1957)] have published details of their findings regarding this substance.

(7) There was also formed *ca.* 10% of I (X = OH) in this reaction.

(8) See, for example, *Ann. Repts. Chem. Soc.*, **44**, 172 (1947).

(9) Method of G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(10) Attempted dehydrobromination of VII with collidine resulted in reductive loss of bromine to give cortisone acetate in a manner reminiscent of the behavior of 2-bromocholestanone (see Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, p. 263). On the other hand, the collidine-dehydrobromination of 3β-acetoxy-9α-bromoergostane-11-one yields the corresponding Δ⁸-11-ketone (see ref. 15).

(11) Methodology in Hardwar, THIS JOURNAL, **75**, 4432 (1953).

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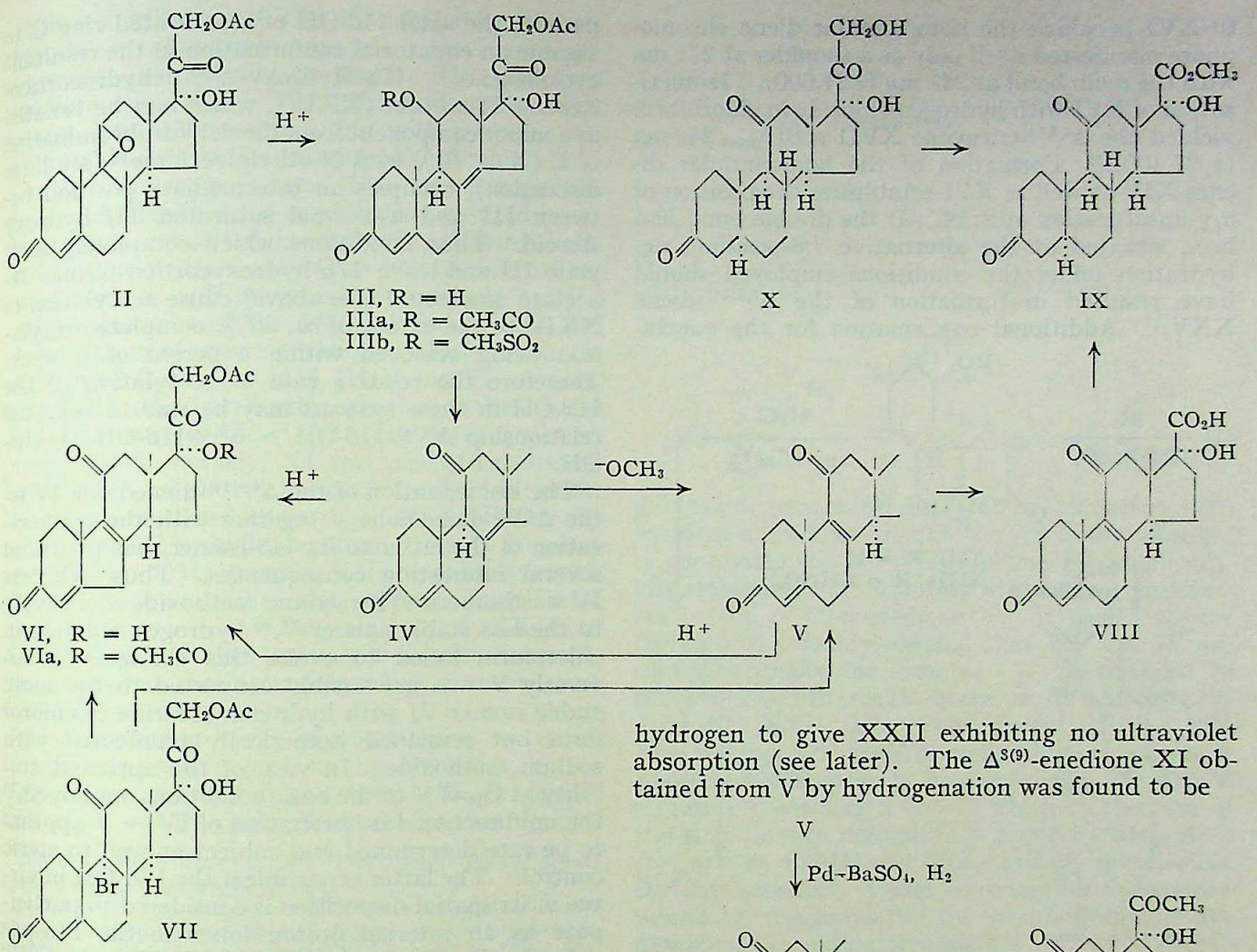
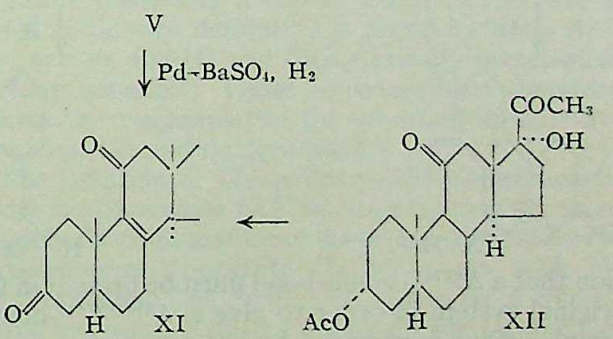


low intensity (ϵ 17,700),[12] it was considered advisable under the circumstances to secure this structure against the possibility that skeletal alteration had supravened. It was also desired to provide unequivocal confirmation for the configuration at C_{14}. Consequently the $\Delta^{4,8(9)}$-dienedione V was hydrolyzed and cleaved with periodic acid to afford the intermediate dienic acid VIII; subsequent reduction of VIII with lithium in liquid ammonia[13] followed by methylation with diazomethane and reoxidation with chromic acid gave the known methyl 17α-hydroxy-3,11-diketoallo-etianate (IX).[14] The latter compound was compared with an authentic sample prepared from allodihydrocortisone (X) by successive periodate cleavage and esterification. Additional corroboration for structure V which also served to resolve the feature of its unique ultraviolet absorption was provided by hydrogenation of the Δ^4-double bond of V to give the $\Delta^{8(9)}$-enedione XI which now exhibited the expected absorption for this system with λ_{max} 256 mμ (8,175). In contrast to V, IV absorbed 1 mole of hydrogen to give XXII exhibiting no ultraviolet absorption (see later). The $\Delta^{8(9)}$-enedione XI obtained from V by hydrogenation was found to be



identical with material isolated as an intermediate by-product from the conversion of pregnane-3α-17α-diol-11,20-dione 3-acetate (XII) to cortisone by a sequence in which bromination–dehydrobromination at C_9 occurred.[15] The identity of XI obtained by these two methods secures additionally the directional course of hydrogenation of V as giving the normal A/B-ring system (5β-H).

At this juncture it has been established that the major rearrangement product III possesses a normal steroid skeleton with unsaturation situated β,γ with respect to the 11-oxygen function. The exact assignment of the β,γ-double bond to the $\Delta^{8(14)}$-position was made possible in the following manner: III was hydrogenated to its 4,5-dihydro derivative XIII and the latter was dehydrated in the form of its 11-mesylate derivative by refluxing pyridine to provide the $\Delta^{9(11),8(14)}$-homoannular diene XIV with λ_{max} 271 mμ (ϵ, 4,600). Isomerization of XIV with hydrogen chloride in chloroform produced the $\Delta^{8,14}$-heteroannular diene XV, λ_{max} 246 mμ (ϵ, 21,500). In a similar manner III itself was converted

(12) This absorption approximates that for a lone Δ^4-3-ketone. C. Djerassi, A. J. Lemin, G. Rosenkranz and F. Sondheimer [J. *Chem. Soc.*, 2346 (1954)] report for 22a-spirosta-4,8-diene-3,11-dione an ultraviolet absorption spectrum with λ_{max} 236–242 mμ (ϵ, 20,800).

(13) The reduction of $\Delta^{(8)9}$-11-ketones with lithium in liquid ammonia has been shown in other series to proceed without involvement of C_{14} (E. Schoenewaldt, L. Turnbull, E. M. Chamberlin, D. Reinhold, A. E. Erickson, W. V. Ruyle, J. M. Chemerda and M. Tishler, THIS JOURNAL, **74**, 2696 (1952); F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952)); see also ref. 5.

(14) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **25**, 988 (1942).

(15) Observations by Dr. G. Hazen and Dr. G. Krsek of these laboratories to be published elsewhere. Also see H. B. Henbest, E. H. R. Jones, A. A. Wagland and T. I. Wrigley, *J. Chem. Soc.*, 2477 (1955).

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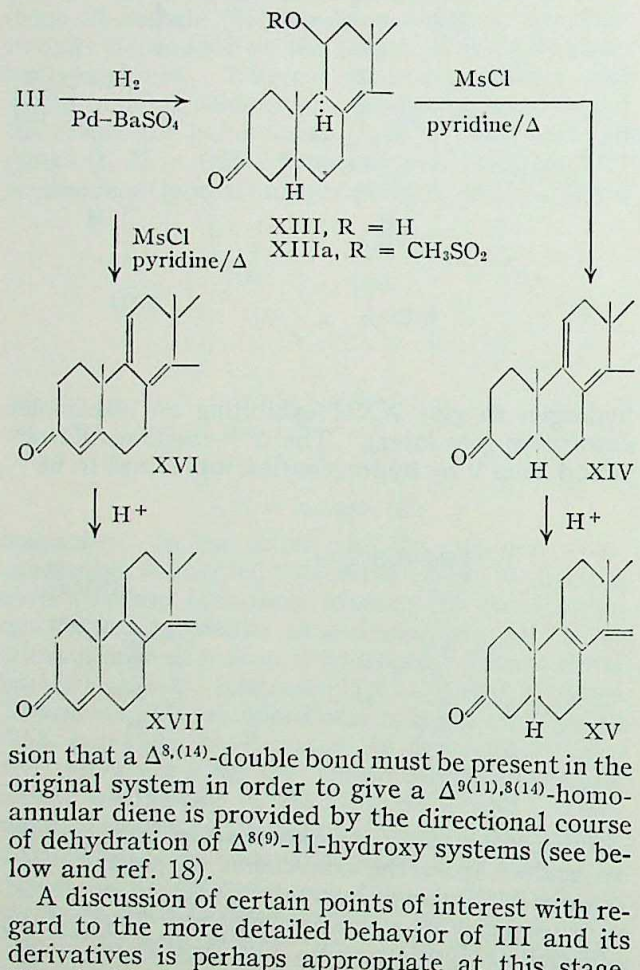
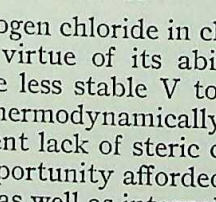
to XVI in which the homoannular diene chromophore manifested itself only as a shoulder at 271 mμ with the main band at 241 mμ (ε 21,600). Isomerization of XVI with hydrogen chloride in chloroform yielded the $\Delta^{4,8,14}$-trieneone XVII with λ_{max} 242 mμ (ε 37,400).[16] Formation of the homoannular dienes XIV as well as XVI establishes the position of β,γ-unsaturation at 8:14. If the double bond had been situated at the alternative 7,8-position, dehydration under the conditions employed should have resulted in formation of the $\Delta^{7,9(11)}$-diene XXV.[17] Additional confirmation for the conclu-



sion that a $\Delta^{8,(14)}$-double bond must be present in the original system in order to give a $\Delta^{9(11),8(14)}$-homoannular diene is provided by the directional course of dehydration of $\Delta^{8(9)}$-11-hydroxy systems (see below and ref. 18).

A discussion of certain points of interest with regard to the more detailed behavior of III and its derivatives is perhaps appropriate at this stage. The double bond at 8:14 appears to decrease the hindrance generally associated with 11β-hydroxyl groups thereby permitting III to be acetylated at room temperature with acetic anhydride in pyridine,[17] conditions which leave an 11β-OH in a saturated normal steroid system unaffected. This fact becomes additionally apparent when it is considered that the introduction of the 8:14 double bond permits the axial 11β-OH of a saturated ring C to assume an equatorial conformation in the resultant cyclohexene. 17α-Hydroxy-$\Delta^{8(9)}$-dehydrocorticosterone 21-acetate (XXIV), which can be isolated as a minor component from the dehydrobromination of I, (X = Br), with N-ethylpiperidine[19] (see later discussion), occupies an intermediate position between III and a normal saturated 11β-hydroxy steroid. Thus, conditions which completely acetylate III and leave 17α-hydroxycorticosterone 21-acetate unaffected (see above) cause acetylation of XXIV to the extent of *ca.* 30%, complete acetylation being achieved within a period of a week. Therefore the relative ease of acetylation of the 11β-OH in these systems may be said to bear the relationship $\Delta^{8(14)}$-11β-OH > $\Delta^{8(9)}$-11β-OH > 11β-OH.

The isomerization of the $\Delta^{4,8(14)}$-dienedione IV to the $\Delta^{4,8(9)}$-dienedione V together with the epimerization of the latter to its 14β-isomer, has produced several interesting consequences. Thus, whereas IV was isomerized by sodium methoxide exclusively to the less stable epimer V,[20] hydrogen chloride in chloroform failed to evoke this change.[21] Conversely V was irreversibly converted to the more stable isomer VI with hydrogen chloride in chloroform but remained isomerically unaffected with sodium methoxide. In view of the apparent stability at C_{14} of V to the basic conditions employed,[20] the unidirectional isomerization of IV → V appears to be rate determined and subject as well to steric control. The latter is possible if the 17α-OH in virtue of its spatial disposition is considered to participate as an internal proton-donor to the 14α-position in the manner depicted by XVIII. Isomeri-



XVIII

zation with hydrogen chloride in chloroform, on the other hand, by virtue of its ability to effect the conversion of the less stable V to the more stable VI should be a thermodynamically controlled process. The apparent lack of steric control at C_{14} follows from the opportunity afforded to exchange the C_{14}-H externally as well as internally.[22,23]

(16) B. M. Bloom, E. J. Agnello and G. D. Laubach, [*Experientia*, **12**, 27 (1956)] have recently reported the formation of this compound from the treatment of 14α,15α-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate with *p*-toluenesulfonic acid in refluxing benzene. These authors report a molecular extinction of 28,600 at 240 mμ which is considerably lower than that observed by us.

(17) III is readily acylated under room temperature conditions.[6] Since it has been shown (ref. 5b) that $\Delta^{7(8)}$-11β-hydroxysteroids are *not* acetylated under these conditions, this constitutes further evidence excluding the $\Delta^{7(8)}$-position of the double bond in III. It has also been pointed out by Fried and Sabo (ref. 2) that the by-product which they obtained from II with hydrogen fluoride (see ref. 6) could not possess a $\Delta^{(7)}$-double bond for reasons of molecular rotation deviation.

(18) R. F. Hirschmann, C. S. Snoddy, Jr., and N. L. Wendler, THIS JOURNAL, **75**, 3252 (1953).

(19) The conditions employed by Fried and Sabo (ref. 2) for the conversion of I (X = Br) to the 9β,11β-oxide (II), namely, potassium acetate in refluxing ethanol, also give detectable amounts of XXIV as evidenced by paper strip analysis.

(20) Because of the lability of the cortical side chain to alkali [see N. L. Wendler and R. P. Graber, *Chemistry & Industry*, 549 (1956)] the conditions of sodium methoxide isomerization were limited to room temperature treatment for 10 minutes. In view thereof, the conclusions based on the results of these conditions are necessarily limited to them.

(21) IV was isomerized to VI, however, when heated at 100° for 2 hours in dimethylformamide containing hydrogen bromide (see footnote 22).

(22) The conversion of V → VI with hydrogen chloride in chloroform at 0° occurred to the extent of about 60% in 1 hour and was essentially complete after 18 hours. Complete isomerization of V → VI was also achieved with dimethylformamide containing one equivalent of hydrogen bromide for 2 hours at 100°.

(23) Certain analogies to this isomerization are afforded by observations concerned with the neopinone–codeinone change; see H. Conroy, THIS JOURNAL, **77**, 5760 (1955).

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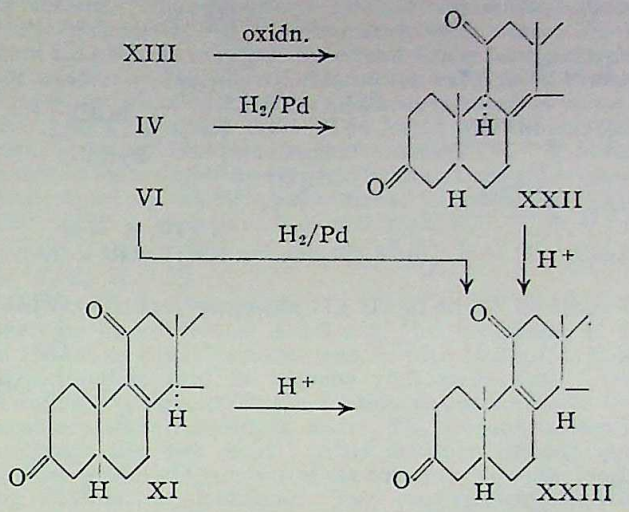
The isomerization of V → VI induced by lithium chloride in dimethylformamide containing one equivalent of pyridine hydrobromide (compare transformation VII → VI) was found not to occur to any detectable extent either with pyridine hydrobromide in pyridine or with lithium chloride in dimethylformamide alone. The interesting consequence arises that the combination-induced isomerization is concerted in nature[24] requiring both protonation of the C_{11}-C=O as well as assisted removal of the $C_{14\alpha}$-H by dimethylformamide.[25]

Hydrogenation of the Δ^4-double bond in all the systems possessing unsaturation in the functionally substituted C ring (*i.e.*, III, IV, V and VI) was observed to proceed predominantly to give the normal A/B ring system (5β-H).[5,26] The hydrogenation product of V, namely, XI was related as already mentioned (see above) to the natural 5β-H series. XI in turn was acid-isomerized to XXIII, also obtained from VI by hydrogenation. The hydrogenation product of III, namely, XIII on oxidation with chromic acid gave XXII also produced from IV by hydrogenation. The isomerization of XXII to XXIII with hydrogen bromide in dimethylformamide completed the interrelationship of the various 4,5β-dihydro derivatives.

The remaining point of constitution requiring clarification with regard to the immediate structures under consideration concerns the configuration at C_9. It was pointed out earlier that the major rearrangement product III on oxidation with pyridine–chromium trioxide for 18 hours afforded in good yield the $\Delta^{4,8(14)}$-dienedione IV which rapidly isomerized (10 minutes) with sodium methoxide to the $\Delta^{4,8(9)}$-dienedione V; it would appear therefore reasonably assured that III and IV are configurationally the same at C_9. In contrast to the $\Delta^{4,8(14)}$-dienedione IV, however, its 4,5β-dihydro derivative XXII, failed to isomerize: $\Delta^{8(14)} \rightarrow \Delta^{8(9)}$ with sodium methoxide or on an alumina column.[5b] These results appear to be consistent only with a structure possessing a $C_9\alpha$-H which in the case of the 4,5β-dihydro derivative is caged by a *cis* A/B ring system (5β-H) and thus sterically inaccessible to base attack.[27] These considerations therefore permit the assignment of the 9α-orientation of hydrogen to III and its derivatives.

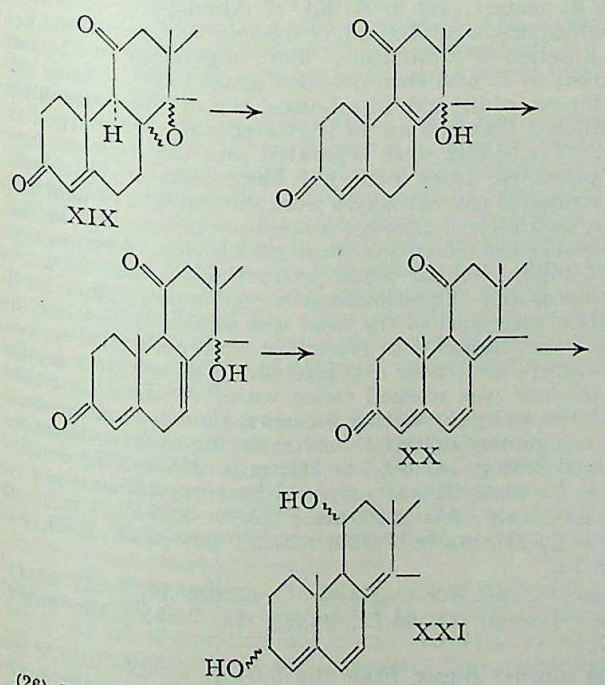


The isolation of 17α-hydroxy-$\Delta^{8(9)}$-dehydrocorticosterone 21-acetate (XXIV) as a by-product from the dehydrobromination of 9α-bromo-17α-hydroxycorticosterone 21-acetate (I, X = Br) with N-ethylpiperidine (see earlier) proved to be of considerable importance in its bearing on the mechanism of the rearrangement of II → III. The constitution of XXIV was established by oxidation with manganese dioxide to give the $\Delta^{4,8(9)}$-dienedione V as well as dehydration with mesyl chloride in pyridine to afford $\Delta^{4,7,9(11)}$-pregnatriene-17α,21-diol-3,20-dione 21-acetate (XXV). Of singular significance was the finding that XXIV on treatment with 60% perchloric acid was converted exclusively to the heteroannular $\Delta^{8,14}$-diene XVII thereby ruling it out as a possible intermediate in the conversion of II → III. In the same connection neither 9α,17α-dihydroxycorticosterone 21-acetate (I, X = OH)[1,3] nor 9α,11α-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate[2] were appreciably affected by the acidic conditions employed for the conversion of II → III. These systems, it will be noted, are sterically ideal when compared with II for the intervention of a classical 1,2-Wagner shift of the 8β-H, and when extrapolated would lead to the 9β-H-epimer of III.

In the light of the foregoing observations, it may be concluded with reasonable certainty that the acid-catalyzed transformation of II → III proceeds from within a protonated species (*e.g.*,

(24) C. G. Swain. *Record of Chem. Prog.*, Kresge–Hooker Science Library, Wayne Univ., **12**, 21 (1951).

(25) A further base-induced transformation which sensibly involves at an intermediate phase an $\alpha\beta \rightarrow \beta\gamma$ change is concerned with the extremely insoluble 8,14-oxido derivative XIX formed from IV on treatment with perbenzoic acid. Treatment of XIX with sodium methoxide caused elimination of the epoxide function with formation of the $\Delta^{4,6,8(14)}$-trienedione XX, λ_{max} 337 mμ (ϵ 25,800). Structure XX was substantiated by lithium aluminum hydride reduction to give a product (XXI) exhibiting characteristic ultraviolet absorption for the $\Delta^{4,6,8(14)}$-triene chromophore at 285 mμ (ϵ 19,150) [*cf.* L. Dorfmann, *Chem. Revs.*, **53**, 47 (1953)]. The sequence involved in the formation of XX may reasonably be represented as



(26) It is noteworthy that in the sapogenin series, A. J. Lemin and C. Djerassi (THIS JOURNAL, **76**, 5672 (1954)) found the $\Delta^{4,8(9)}$-dienone system hydrogenated to give mainly the 4,5β-dihydro derivative.

(27) The steric accessibility of a 9β-H to base attack should not be adversely affected by hydrogenation of the Δ^4-double bond (see ref. 5b).

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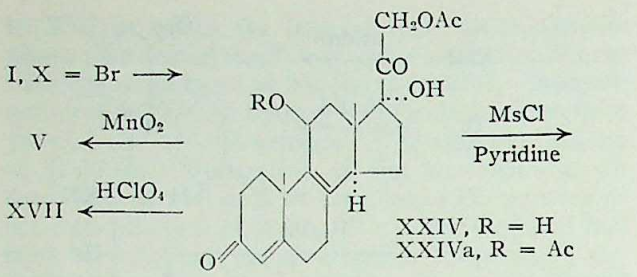

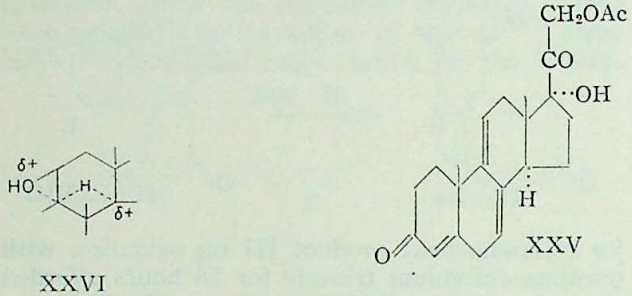

XXVI)[28] by way of transannular migration of hydrogen with its bonding pair from $C_{14\alpha} \rightarrow C_{9\alpha}$ with attending extrusion of the $C_8\beta$-H. Moreover, since hydrogen transfer of this type should proceed with steric control,[4,29] it follows that the stereochemistry of the product II becomes defined as formulated.[30]

Experimental[31]

Δ^4-Pregnene-9α,11β,17α,21-tetrol-3,20-dione 21-Acetate (I, R = OH).—A suspension of 4.025 g. (10.0 millimoles) of the oxide II in 66.7 ml. of purified dioxane and 33.3 ml. of 2.0 *N* aqueous perchloric acid was stirred at 25°. After a period of 1.5 hours, the solid had dissolved and the solution was light yellow. After a period of 3 days, the bright yellow solution was diluted with 200 ml. of saturated salt solution and extracted with 3 portions of ethyl acetate. The combined extracts were washed with water and 5% aqueous sodium bicarbonate until free of acid and finally with water and saturated salt solution. The washed extracts were dried by filtration through anhydrous magnesium sulfate and the solvents removed *in vacuo* to give 3.95 g. of a partly crystalline yellow residue. Crystallization from acetone–chloroform gave 2.50 g. (65%) of needles, m.p. 224–230° dec. An additional crystallization from acetone afforded 1.575 g. (41.6%) of **Δ^4-pregnene-9α,11β,17α,21-tetrol-3,20-dione**, m.p. 239–246.5° dec. A sample prepared for analysis by recrystallization from the same solvent was obtained as prisms, m.p. 243–249° dec., $[\alpha]^{26}D$ +152° (1.1, acetone), λ_{max} 242 mμ (ϵ 15,600); $\lambda\lambda^{Nujol}_{max}$ 2.9–3.0, 5.84 and 6.1 μ.

Anal. Calcd. for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.61; H, 7.90.

The mother liquor of the 2.50-g. sample above was treated with 8 ml. of pyridine and 8 ml. of acetic anhydride at 25° overnight. A small amount of crystalline solid which had separated was removed by filtration, washed several times with ether and dried, weight 0.109 g., m.p. 219–234°. This material was shown by paper-strip analysis to be a mixture of unidentified materials. The pyridine–acetic anhydride–ether filtrate was concentrated *in vacuo* to an oil. Water (50 ml.) was added to the concentrate and the oil extracted with 3 portions of ethyl acetate. The combined extracts were washed successively with water, 1 *N* hydrochloric acid, sodium bicarbonate solution and finally with water and saturated salt solution. The washed extracts were dried over magnesium sulfate and the solvent removed *in vacuo* to give 1.64 g. of a yellow-brown amorphous residue which was shown by paper-strip analysis to be substantially pure I (R = OH). Crystallization from acetone–ether afforded 0.84 g. (20%) of buff-colored prisms, m.p. 210–216°, undepressed on admixture with a sample prepared from the tetroldione by acetylation as described above. A sample prepared for analysis by recrystallization from acetone–ether was obtained as colorless needles, m.p. 212–214.5°, λ_{max} 242 mμ (ϵ 15,570); $\lambda\lambda^{Nujol}_{max}$ 2.92, 5.79–5.82, 6.1–6.15; $\lambda\lambda^{CHCl_3}_{max}$ 5.75(sh), 5.79, 6.0 and 6.15 μ. It was observed that several samples partly crystallized as prisms during melting, then finally melted at *ca.* 223°.

Anal. Calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.43; H, 7.51.

Δ^4-Pregnene-9α,17α,21-triol-3,11,20-trione 21-Acetate.—To a solution of 61.3 mg. (0.613 millimole) of chromium trioxide in 2 drops of water and 4.9 ml. of glacial acetic acid was added 386.2 mg. (0.92 millimole) of I (R = OH). The solid dissolved immediately and after 12 minutes the reaction mixture was diluted with 25 ml. of water. Extraction with 3 portions of ethyl acetate followed by the usual washing with water, sodium bicarbonate, etc., gave, after removal of the solvent, 358 mg. (93%) of a crystalline residue, m.p. 228.5–235°. Recrystallization from acetone–ether gave 241 mg. of needles, m.p. 236–242°. An additional recrystallization raised the m.p. to 237–243.5°, λ_{max} 238 mμ (ϵ 15,620); $\lambda\lambda^{Nujol}_{max}$ 2.96, 5.71, 5.75, 5.83, 6.0 and 6.16 μ; $\lambda\lambda^{CHCl_3}_{max}$, 5.7(sh), 5.79, 5.99 and 6.15 μ.

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.14; H, 7.02.

$\Delta^{4,8(14)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 21-Acetate (III). (17α-Hydroxy-$\Delta^{8(14)}$-dehydrocorticosterone 21-Acetate.)—To a stirred, ice-cold solution of 8.05 g. (20.0 millimoles) of 9β,11β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (II) in 80 ml. of ethanol-free chloroform was added dropwise 20.0 ml. of ice-cold 60% perchloric acid over a period of 2 minutes. The temperature of the mixture rose to 7° and then dropped again to 0°. After stirring for an additional 15 minutes, the orange-red solution was diluted with 200 ml. of ice-water which discharged the color. The layers were separated and the aqueous layer was extracted twice with 2:1 chloroform–ethyl acetate. The combined solvent layers were washed free of acid with water, and filtered through anhydrous magnesium sulfate. Removal of the solvents *in vacuo* gave 8.70 g. of yellow crystalline solid. To the crude product was added 35 ml. of chloroform and the suspension heated under reflux for 10 minutes; only part of the solid was soluble. The hot suspension was diluted with 175 ml. of benzene, cooled to room temperature for 1 hour and filtered. The colorless crystalline product was washed twice with 1:1 chloroform–benzene followed by three ether washes to remove small amounts of brown gummy material. After drying *in vacuo* there was obtained 3.84 g. (47.6%) of III, m.p. 246.5–257° dec. A sample for analysis was prepared by recrystallization from methanol, m.p. 255–260° dec., $[\alpha]^{25}D$ +293° (1.0, acetic acid), λ_{max} 240 mμ (ϵ 17,200); $\lambda\lambda^{Nujol}_{max}$ 2.93, 3.02, 5.75, 5.81 and 6.1 μ.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; acetyl, 10.69. Found: C, 68.22, 68.53; H, 7.35, 7.13; acetyl, 11.47.

The mother liquor from the 3.84-g. sample above was taken to dryness *in vacuo*, wt. 4.77 g. Paper chromatographic analysis of this material showed it to contain additional amounts of III together with cortisone acetate and a

(28) The dotted lines in this formulation are intended to represent partial bond character with the steric connotations:

$$O\overset{\beta}{\cdots}C_9\overset{\alpha}{\cdots}H\overset{\alpha}{\cdots}C_{14}$$

(29) In recent years the occurrence of transannular hydrogen transfer in medium sized rings has been dramatically demonstrated. In this regard see: A. C. Cope, S. W. Fenton and C. F. Spenser, THIS JOURNAL, **74**, 5884 (1952); V. Prelog and K. Schenker, *Helv. Chim. Acta*, **35**, 2044 (1952); V. Prelog, K. Schenker and W. Küng, *ibid.*, **36**, 471 (1953); V. Prelog, H. J. Urech, A. A. Bothner-By and J. Würsch, *ibid.*, **38**, 1095 (1955); V. Prelog and V. Boarland, *ibid.*, **38**, 1776 (1955); V. Prelog and W. Küng, *ibid.*, **39**, 1394 (1956); A. C. Cope, T. A. Liss and C. W. Wood, *Chemistry & Industry*, 823 (1956).

(30) This instance of transannular-hydrogen transfer in an unbridged 6-membered ring system is unique in several respects: (1) transannular transfer occurs in a system wherein the centers involved are of fixed stereochemistry; (2) proton extrusion takes place as the ultimate step and (3) the product of this transfer reaction is the major one. Recenty A. C. Cope, H. E. Johnson and J. S. Stephenson (THIS JOURNAL, **78**, 5599 (1956)) have demonstrated transannular hydrogen transfer in the cyclohexane series in the performic acid-hydroxylation of cyclohexene.

(31) Unless otherwise indicated, the m.p.'s were taken on a micro-block and are not corrected; the samples were placed on the block at *ca.* 25° below the m.p. The rotations were observed in chloroform and the ultraviolet spectra in methanol.

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substantial amount of a more polar material. The amorphous yellow-brown mother liquor material was treated with 30 ml. of pyridine and 15 ml. of acetic anhydride and stirred at 25° overnight. At the end of this time a small amount of crystalline solid was present which was removed by filtration and washed 3 times with ether, wt. 0.394 g., m.p. 223–228°. The ether and excess reagents were removed *in vacuo* to give a partly crystalline residue which was treated with 20 ml. of ether and filtered to give an additional 0.409 g. of crystalline solid, m.p. 229–238°, undepressed on admixture with the sample above and with cortisone acetate.

The filtrate was diluted with 50 ml. of ethyl acetate and 50 ml. of water, the mixture shaken vigorously, separated and the aqueous layer extracted twice more with ethyl acetate. The combined extracts were washed successively with 1 *N* hydrochloric acid, water, 5% aqueous sodium bicarbonate, water and finally with saturated salt solution. The washed extracts were filtered through anhydrous magnesium sulfate and the solvents removed *in vacuo* to give 4.12 g. of amorphous solid. The latter was dissolved in benzene and chromatographed over 206 g. of neutral alumina. After development with benzene and 10% chloroform–benzene, the first fraction eluted (25% chloroform–benzene) weighed 0.155 g. and gave 46.5 mg. of an unidentified material as prisms, m.p. 202.5–207°. The succeeding 7 fractions (50% chloroform–benzene and chloroform) were examined by paper-strip analysis and found to contain diacetate IIIa (see below), in an amount estimated to be 1.57 g., thus raising the total amount of III formed in the perchloric acid reaction to 65.2%. Cortisone acetate was also present in fractions 4–8 and was estimated to amount to 0.316 g. Crystals were obtained from fractions 4–6 by crystallization from acetone–ether, total weight 0.230 g., each sample of which did not depress the m.p. of cortisone acetate. The latter 0.230-g. sample was combined with the two samples isolated above (weights 0.394 and 0.409 g.) and recrystallized from acetone to give 0.708 g. (8.8%) of needles, m.p. 230–233°, undepressed on admixture with cortisone acetate and identified by paper-strip comparison and infrared spectra.

Finally, the column was eluted with acetone and 25% methanol–acetone to yield 3 fractions, total weight 0.920 g. (10.9%), which crystallized on seeding with Δ^4-pregnene-9α,11β,17α,21-tetrol-3,20-dione 21-acetate (I, X = OH). The latter were combined and recrystallized from acetone–ether to give 0.598 g. (7.1%) of prisms, m.p. 215–218.5°, undepressed on admixture with authentic material and further identified by infrared comparison. Thus, the amounts of the three major products formed can be estimated as follows: III together with IIIa, 65.2%; cortisone acetate, 13.9%; (I, X = OH), 10.9%.

Treatment of 9α,11α-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate with 60% perchloric acid as described above for the 9β,11β-oxide resulted in the recovery of unchanged starting material.

A sample of III was treated with 0.5 *N* perchloric acid in aqueous dioxane at 25° for 8 days in an effort to prepare the 21-alcohol. The product could not be crystallized but on acetylation with acetic anhydride and pyridine at 25° afforded the diacetate IIIa (see below). Hydrolysis of III with sodium methoxide in methanol–tetrahydrofuran by the procedure used in the hydrolysis of the dienedione V (see below) also gave only amorphous material. Again acetylation produced the diacetate IIIa (see below). In both experiments above, paper chromatographic examination of the total re-acetylated material showed it to be substantially pure diacetate.

Osmylation of III resulted in the recovery of starting material as the only recognizable crystalline entity. Likewise selective dehydrogenation of III with selenium dioxide in aqueous ethanol according to the procedure of Callow[32] for the oxidation of $\Delta^{8(14)}$-steroid olefins to $\Delta^{8,8(14)}$-dienes produced no change in the ultraviolet spectrum and the material was recovered unchanged.

$\Delta^{4,8(14)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 11β,21-Diacetate (IIIa).—A solution of 1.61 g. (4.0 millimoles) of III in 10 ml. of pyridine and 10 ml. of acetic anhydride was allowed to stand at 25° for 18 hours. The excess reagents were removed *in vacuo* and the oily residue was dissolved in chloroform. The chloroform solution was washed successively with water, 1.0 *N* hydrochloric acid, water, 5% sodium bicarbonate solution, water and finally with saturated salt solution. The washed chloroform was filtered through anhydrous magnesium sulfate and concentrated *in vacuo* to give 1.98 g. of crude IIIa. The latter was substantially pure by paper chromatographic examination. A sample prepared for analysis by recrystallization from ether–petroleum ether (b.p. 30–60°) was obtained as prisms, m.p. 210–215°, $\lambda\lambda_{max}^{Nujol}$ 3.05, 5.74, 5.81 and 6.16(sh) μ.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.57; H, 7.27. Found: C, 67.52; H, 7.32.

8ξ,14ξ-Oxido-Δ^4-pregnene-11β,17α,21-triol-3,20-dione 21-Acetate.—A solution of 402.5 mg. (1.0 millimole) of III in 150 ml. of chloroform was treated with 14.3 ml. of 0.350 *M* perbenzoic acid in benzene (5.0 millimoles). After standing overnight at 0°, the solution was washed with 10% aqueous sodium thiosulfate, water, 5% aqueous sodium bicarbonate and with water. After filtration through magnesium sulfate and removal of the solvents, a residue weighing 480 mg. was obtained. Two recrystallizations from acetone–Skellysolve B gave 192 mg. of the oxide,[2b] m.p. 203–206° dec., λ_{max} 242 mμ (ϵ 14,000); $\lambda\lambda_{max}^{Nujol}$ 2.96, 3.01, 5.75, 5.78 and 6.05–6.1 μ.

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.90; H, 7.24.

$\Delta^{4,8(14)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 11β-Mesylate-21-acetate (IIIb).—To a solution of 1.0 g. of III in 8 ml. of pyridine cooled to 0° was added dropwise with cooling 0.75 ml. of methanesulfonyl chloride. The mixture was allowed to stand at 0–5° for 18 hours. To the mixture was added 10 g. of ice and after 15 minutes the product was extracted with ether. The ether extract was washed successively with dilute aqueous hydrochloric acid, potassium bicarbonate solution and water, dried over anhydrous magnesium sulfate and concentrated to dryness *in vacuo*. After crystallization from ether the product amounted to 1.1 g. (92%), m.p. 145–147° dec. (reported[2b] m.p. 151–152° dec.).

Acidolysis of IIIb.—A solution of 750 mg. of IIIb in 5 ml. of propionic acid was treated with 750 mg. of potassium bicarbonate and heated in a nitrogen atmosphere at 100° for 1 hour. The reaction mixture was evaporated *in vacuo* and water added to precipitate the product. The latter was isolated by ether extraction and the ether extract washed free of acid, dried and concentrated. The residue obtained after concentration was chromatographed on neutral alumina to yield a small amount of $\Delta^{4,8(14)}$-pregnadiene-11β,17α,21-triol-3,20-dione 11-propionate-21-acetate, m.p. 250–255°; the latter was identical by mixed m.p. and infrared comparison with an authentic sample prepared by propionylation of II with propionic anhydride in pyridine.[2b]

Similar treatment of IIIb with sodium acetate in acetic acid afforded a product containing IIIa by paper chromatography. A considerable amount of XVI and/or XVII appears to accompany the acidolysis reactions.

$\Delta^{4,8(14)}$-Pregnadiene-17α,21-diol-3,11,20-trione 21-Acetate (IV). ($\Delta^{8(14)}$-Dehydrocortisone Acetate).—To a solution of 402.5 mg. (1.0 millimole) of $\Delta^{4,8(14)}$-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (III) in 4 ml. of pyridine was added a solution of 333 mg. (3.33 millimoles) of chromium trioxide in 0.33 ml. of water and 1.0 ml. of pyridine. The mixture was allowed to stand at 25° overnight and then diluted with 30 ml. of water and 20 ml. of ethyl acetate. A brown insoluble solid was removed by filtration through Celite and the residue washed thoroughly with water and ethyl acetate. The layers of the filtrate were separated and the aqueous layer extracted twice with ethyl acetate. The combined ethyl acetate layers were washed successively with dilute hydrochloric acid, water and saturated salt solution, and filtered through anhydrous magnesium sulfate. After removal of the solvent, 365 mg. (91.1%) of nearly colorless crystalline solid was obtained. Two recrystallizations from acetone–Skellysolve B afforded 172 mg. (42.9%) of prismatic needles, m.p. 225–229° dec., $[\alpha]^{25}D$ +449° (0.95), λ_{max} 239 mμ (ϵ 15,650); $\lambda\lambda_{max}^{Nujol}$ 3.1, 5.75, 5.80, 5.89, 6.02 and 6.15 μ; $\lambda\lambda_{max}^{CHCl_3}$ 3.00–3.05, 5.75 (sh), 5.80, 5.90, 6.02 and 6.15 μ.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.21; H, 7.22.

In another run, 8.05 g. (20.0 millimoles) of III was

(32) R. K. Callow, *J. Chem. Soc.*, 462 (1936).

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oxidized exactly as described above to give 7.57 g. (94.6%) of crude IV; one recrystallization from ethyl acetate gave 5.79 g. (72.4%) of pure IV, m.p. 227–231°, λ_{max} 238 mμ (ε 16,350).

An attempt to hydrolyze the dienedione IV to its **21-alcohol** by treatment with 0.50 *N* perchloric acid in aqueous dioxane at 25° for 8 days gave only amorphous material which, however, on reacetylation with pyridine and acetic anhydride afforded the original 21-acetate.

Treatment of IV with selenium dioxide[32] produced no change in the ultraviolet spectrum and the material was recovered unchanged.

The epimerization of Δ^7-11-ketones with a 9β-hydrogen to the natural 9α-configuration has been reported by Bladon, *et al.*[5b]; the procedure involves treatment with a specially prepared alumina. A sample of IV was adsorbed on this alumina, allowed to stand at 25° for 18 hours, and then eluted. The material was recovered unchanged.

Attempts to isomerize the $\Delta^{4,8(14)}$-dienedione IV to a $\Delta^{4,8(9)}$-dienedione (V or VI) with either (a) lithium chloride in dimethylformamide at 100° for two hours, or (b) hydrogen chloride in ethanol-free chloroform at 0° for one hour failed. In the latter case, the product was contaminated by a chlorine-containing impurity, which, however, was converted to the original dienedione IV by short treatment with refluxing pyridine.

$\Delta^{4,8(14)}$-Pregnadiene-17α,21-diol-3,11,20-trione 17α,21-Diacetate.—A 235-mg. (0.587 millimole) sample of IV in 8.0 ml. of glacial acetic acid and 3.0 ml. of acetic anhydride was treated with 235 mg. of *p*-toluenesulfonic acid monohydrate and the resulting yellow solution stored at 25° overnight. Addition of 50 g. of ice caused the separation of a yellow-brown oil which was extracted with four portions of chloroform. The combined extracts were washed four times with water, once with 5% aqueous sodium bicarbonate, again with water and finally with saturated salt solution. After filtration through anhydrous magnesium sulfate and removal of the solvent an amorphous residue was obtained. One crystallization from acetone–ether gave 169 mg. (65%) of needles, m.p. 212–214°, λ_{max} 238 mμ (ε 15,100); $\lambda\lambda_{max}$ 5.70, 5.75, 5.86, 5.97 and 6.10 μ (no hydroxyl bands in the 3.0 μ region were observed).

Anal. Calcd. for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83; acetyl, 19.45. Found: C, 67.67; H, 6.82; acetyl, 20.8.

A solution of 114.6 mg. (0.25 millimole) of the diacetate above in 3.0 ml. of chloroform was treated with 1.96 ml. of 0.383 *M* perbenzoic acid in benzene (0.75 millimole) and the mixture stored at 0° overnight. The mixture was then extracted twice with 10% sodium thiosulfate solution, washed twice with water, once with 5% sodium bicarbonate solution, again with water and finally with saturated salt solution. Filtration through anhydrous magnesium sulfate and removal of the solvents *in vacuo* gave a colorless crystalline residue, weight 125 mg. One recrystallization from acetone–ether afforded 92.9 mg. (81%) of **8ξ,14ξ-oxido-Δ^4-pregnene-17α,21-diol-3,11,20-trione 17α,21-diacetate** as needles, m.p. 209–211°, depressed on admixture with the starting diacetate, λ_{max} 238 mμ (ε 16,600); $\lambda\lambda_{max}^{Nujol}$ 5.7, 5.75, 5.85, 5.99 and 6.15 μ (no hydroxyl bands in the 3.0 μ region were observed).

Anal. Calcd. for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60. Found: C, 65.59, 65.46; H, 6.43, 6.51.

$\Delta^{4,8(9)}$-Pregnadiene-17α,21-diol-3,11,20-trione 21-Acetate (V). ($\Delta^{8(9)}$-Dehydrocortisone Acetate). (A). By Pyridine Dehydrobromination of 9α-Bromo-Δ^4-pregnene-17α,21-diol-3,11,20-trione 21-Acetate (VII).—The pyridine dehydrobromination of 9α-bromocortisone acetate (VII)[2] was carried out as follows. A solution of 2.41 g. (5.0 millimoles) of VII in 36 ml. of dry purified pyridine was heated under reflux for one hour in an atmosphere of nitrogen. The yellow solution was then concentrated *in vacuo* to give a yellow crystalline residue which was dissolved in 50 ml. of ethyl acetate and 50 ml. of water. The layers were separated and the water layer extracted with two 50-ml. portions of ethyl acetate. The yellow extracts were combined and washed twice with 1.25 *N* hydrochloric acid, with water, with 5% aqueous sodium bicarbonate, again with water and finally with saturated salt solution. The solution was filtered through anhydrous magnesium sulfate and concentrated to dryness *in vacuo* to give 2.01 g. (100%) of yellow crystals, m.p. 233–241° dec. Paper chromatographic analysis of this crude material showed only one spot. Recrystallization from acetone afforded 1.395 g. (69.7%) of yellow prisms, m.p. 241–248° dec. One additional recrystallization did not raise the m.p.; the m.p. (cap.) was 249–250° dec., $[\alpha]^{25}D$ +422° (1.05), λ_{max} 236.5 mμ (ε 17,700); $\lambda\lambda_{max}^{Nujol}$ 2.99, 5.72, 5.80, 6.04 and 6.24 μ.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.04; H, 6.75.

The corresponding **21-alcohol** derived from V was prepared by two methods as follows: (a) **By Sodium Methoxide Hydrolysis.**—A 200.5-mg. (0.5 millimole) sample of V in 20 ml. of tetrahydrofuran and 8 ml. of methanol was placed under nitrogen and 0.54 ml. of 0.97 *N* sodium methoxide in methanol (0.525 millimole) added. The mixture was stirred for 10 minutes at 25° and neutralized with a slight excess of glacial acetic acid. The solvents were removed *in vacuo* and the residue dissolved in 25 ml. of water and 25 ml. of ethyl acetate. The layers were separated and the aqueous layer re-extracted with two portions of ethyl acetate. The combined extracts were washed with water, 5% aqueous sodium bicarbonate solution, water and with saturated salt solution, filtered through magnesium sulfate and taken to dryness *in vacuo* to give 170 mg. (95%) of a partly crystalline yellow residue. One crystallization from acetone–ether gave 63 mg. of bright yellow prisms, m.p. 239–243° dec. A sample recrystallized for analysis melted (cap.) at 249–252° dec., λ_{max} 237 mμ (ε 17,900); $\lambda\lambda_{max}^{Nujol}$ 3.0, 5.87, 6.01–6.08 and 6.25 μ.

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.16; H, 7.18.

A small sample of the material, m.p. 239–243°, was acetylated with acetic anhydride and pyridine and the product shown by paper strip, mixed m.p., and infrared comparison to be authentic V.

(b) **By Potassium Bicarbonate Hydrolysis.**—A suspension of 1.20 g. (3.0 millimoles) of V in 36 ml. of methanol was heated to reflux in an atmosphere of nitrogen; 9 ml. of 1.0 *M* aqueous potassium bicarbonate (9.0 millimoles) was then added. The solid dissolved in one minute and the light reddish-brown solution was refluxed for 5 minutes. The reaction mixture was neutralized with 0.9 ml. of glacial acetic acid and the methanol removed *in vacuo*. The solid which separated was extracted with 1:1 ethyl acetate–chloroform and the extracts washed with water, 5% aqueous sodium bicarbonate, water and saturated salt solution. After drying by filtration through magnesium sulfate, the solvents were removed *in vacuo* to give 1.04 g. (96.7%) of yellow crystals. Two recrystallizations from acetone afforded material, m.p. 240.5–252° dec., identical by infrared comparison with material prepared by sodium methoxide hydrolysis.

(B) **By Alkaline Isomerization of the $\Delta^{4,8(14)}$-Dienedione IV.**—A solution of 2.00 g. (5.0 millimoles) of the dienedione IV in 300 ml. of tetrahydrofuran and 50 ml. of methanol was placed under a nitrogen atmosphere and 16.62 ml. of 0.376 *N* sodium methoxide in methanol (6.25 millimoles) was added with stirring at 23°. After 10 minutes, 0.50 ml. of glacial acetic acid was added to neutralize the solution and the reaction mixture was concentrated *in vacuo* to a yellow gum. The residue was dissolved in 100 ml. of water and 250 ml. of ethyl acetate, the mixture shaken and separated, and the aqueous layer extracted twice with ethyl acetate. The combined extracts were washed with water, 5% aqueous sodium bicarbonate, water and saturated salt solution, filtered through anhydrous magnesium sulfate and the solvents removed *in vacuo* to give a pale yellow foam, weight 1.835 g. A 10-mg. sample of the product was reacetylated with pyridine and acetic anhydride for one-half hour at 65°. Paper-strip analysis of this material showed it to consist mainly of two components, one with an R_f value the same as the starting dienedione IV and the other with an R_f value the same as the isomeric dienedione V. The remainder of the product was crystallized from acetone to give 293 mg. (16.5%) of yellow prisms, m.p. 235–245° dec., undepressed on admixture with the 21-alcohol of V prepared above. The infrared spectra of the two samples were identical. In another run, a product, m.p. 225–230° dec., was obtained in the same manner. A sample of this material on acetylation with pyridine and acetic anhydride gave, after one recrystallization, material of m.p. 227.5–236° dec., undepressed on admixture with V and identical in the

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infrared; this acetylated material depressed the m.p. of the starting dienedione acetate IV.

The mother liquor of the 293-mg. sample above was acetylated in the usual manner and 250 mg. of this material separated by chromatography on Whatman No. 4 paper. Additional V was isolated from the more polar spot and IV was obtained from the less polar spot, m.p. 218.5–227°, identical by mixed m.p. and infrared with the starting material IV.

(C) By Oxidation of XXIV.—To a solution of 100 mg. (0.248 millimole) of $\Delta^{4,8(9)}$-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (XXIV) in 10 ml. of chloroform was added 1.0 g. (11.5 millimoles) of manganese dioxide.[33] The mixture was stirred for 22 hours at room temperature (22°), filtered, the residue washed with chloroform and the filtrate concentrated to yield 79.7 mg. of crude material. This mixture was chromatographed on Whatman No. 4 paper to yield 16 mg. (16%) of unoxidized starting material and 23 mg. (27%, based on starting material consumed) of crude $\Delta^{4,8(9)}$-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (V). The crude material was crystallized twice from acetone–hexane to yield 10.9 mg. (13%, based on starting material consumed) of product, m.p. 232–239° dec., identical with previously obtained material by mixed m.p., infrared spectral comparison and paper strip comparison.

Several experiments carried out on the dienedione V are worthy of mention. In an early attempt to ascertain the disposition of double bonds in V, a sample was reduced with lithium aluminum hydride to give an oily mixture of products which had only end absorption in the ultraviolet. Treatment of a sample of V with selenium dioxide in aqueous alcohol gave only unchanged starting material.[32] Two unsuccessful attempts to isomerize V to the epimeric dienedione VI were carried out (compare below). A solution of V in 60% aqueous perchloric acid was held at 25° and sampled at intervals. Even after 23 hours, no VI could be detected by paper-strip analysis although considerable hydrolysis of the 21-acetate function had occurred and a small amount of an unknown by-product formed. Finally, treatment of V with lithium chloride in dimethylformamide at 100° under nitrogen for 23 hours gave only unchanged starting material by m.p., infrared, and paper-strip analysis.

$\Delta^{4,8(9)}$-17α-Hydroxy-3,11-diketoetiadienic Acid (VIII).—A mixture of 358.5 mg. (1.0 millimole) of the 21-alcohol of V and 250.8 mg. (1.1 millimoles) of periodic acid dihydrate in 50 ml. of tetrahydrofuran and 12 ml. of water was allowed to stand at 25° overnight. Removal of the tetrahydrofuran *in vacuo* caused the separation of a yellow oil which was extracted with three portions of ethyl acetate. The combined extracts were washed twice with water and once with saturated salt solution, filtered through anhydrous magnesium sulfate and concentrated *in vacuo* to give a yellow crystalline residue, weight 365 mg. Recrystallization from acetone gave 216 mg. of the etio-acid VIII, m.p. 228–232° dec. A sample prepared for analysis by recrystallization from acetone–ether had the m.p. (cap.) 238.5–240.5° dec., λ_{max} 235 mμ (ϵ 18,300); $\lambda\lambda_{max}^{Nujol}$ 2.92–3.05, 5.75, 6.0–6.12 and 6.27 μ.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.41; H, 7.23.

Methyl 17α-Hydroxy-3,11-diketoalloetianate (IX).—To the deep blue solution obtained from 113 mg. (16.3 millimoles) of lithium dissolved in 50–60 ml. of liquid ammonia was added with stirring a solution of 172.6 mg. (0.5 millimole) of the etio-acid VIII in 18 ml. of dry tetrahydrofuran. After 10–15 minutes, the solution was no longer blue. Therefore, an additional 104 mg. (15.0 millimoles) of lithium was added. Again, after 1 hour, a third portion of lithium was introduced, 115 mg. (16.6 millimoles). After a total time of 5 hours, the deep blue solution was treated with portions of solid ammonium chloride and the resulting nearly colorless solution allowed to evaporate until the ammonia had disappeared. Water was added to the remaining solution and the tetrahydrofuran removed *in vacuo*. The aqueous solution was acidified with 6 *N* hydrochloric acid and the organic material extracted with five portions of ethyl acetate. After washing the combined extracts with water, they were extracted with five portions of 5% aqueous sodium bicarbonate. Acidification of the combined bicarbonate extracts and extraction with ethyl acetate gave 160 mg. of light brown amorphous solid which showed no maxima in the ultraviolet.

The crude reduced acid was dissolved in 5 ml. of methanol and 20 ml. of ether and treated with an excess of ethereal diazomethane. Removal of the solvents gave 170 mg. of crude methyl ester which was dissolved in 5 ml. of glacial acetic acid and treated with 93 mg. (0.93 millimole) of chromium trioxide in 5 drops of water and 6.0 ml. of acetic acid. After standing at 25° for three hours, the acetic acid was removed *in vacuo*. To the residue was added 75 ml. of water and the reoxidized ester extracted with 3 portions of ethyl acetate. The combined extracts were washed with water, 5% aqueous sodium bicarbonate, water and with saturated salt solution, then dried by filtration through anhydrous magnesium sulfate and the solvent removed *in vacuo* to give 110 mg. of a colorless oil. One recrystallization from acetone gave 33 mg. of plates, m.p. 199–215°, undepressed on admixture with a sample of authentic IX, m.p. 198–208°. An additional recrystallization gave 13 mg., m.p. 212.5–226.5°, which by paper-strip comparison consisted of IX together with a small amount of a second more polar material. Therefore, the combined mother liquors were concentrated to dryness and chromatographed over 4.75 g. of neutral alumina. The fractions eluted with benzene and 10% chloroform–benzene were combined, wt. 45.2 mg., and recrystallized to give 23 mg., m.p. 199–211°.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.65; H, 8.73.

This material was identical by mixed m.p., infrared and paper-strip comparison with authentic IX prepared from allopregnane-17α,21-diol-3,11,20-trione[34] by successive periodic acid cleavage followed by esterification with diazomethane.

It was ascertained independently that Δ^4-17α-hydroxy-3,11-diketoetienic acid, the acid obtained from cortisone on periodic acid cleavage, on reduction with lithium and ammonia as described above, followed by esterification with diazomethane and reoxidation with chromium trioxide lead mainly to the same alloester IX.

$\Delta^{4,8(9)}$-14-Isopregnadiene-17α,21-diol-3,11,20-trione 21-Acetate (VI). (A) By Lithium Chloride–Dimethylformamide Dehydrobromination of 9α-Bromo-Δ^4-pregnene-17α,-21-diol-3,11,20-trione 21-Acetate (VII).—A mixture containing 7.23 g. (15.0 millimoles) of the bromoketone VII and 7.5 g. (0.177 mole) of lithium chloride in 75 ml. of dimethylformamide was heated for 2 hours at 100° in an atmosphere of nitrogen. The solution was then cooled to 60° and 225 ml. of water added in portions. After cooling at 0° for two hours, the suspension was filtered, the crystalline residue washed thoroughly with water and dried *in vacuo*, weight 5.47 g. (91%), m.p. 186–193°. This material was shown to be essentially pure VI by paper strip analysis. One recrystallization from ethyl acetate gave 4.65 g. (77%), m.p. 193–196°, identical in all respects to material prepared by acid isomerization of V (see below). A sample prepared for analysis had the m.p. 195–198°, $[\alpha]^{25}D$ +348° (0.87), λ_{max} 237.5 mμ (ϵ 19,700); $\lambda\lambda_{max}^{CHCl_3}$ 2.92–2.98, 5.71, 5.79, 5.99 and 6.17 μ.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.20; H, 7.25.

(B) By Isomerization of the Dienedione V. (a) *Via* Hydrogen Chloride in Chloroform.—Dry hydrogen chloride was passed into an ice-cold solution of 2.00 g. (5.0 millimoles) of V in 150 ml. of ethanol-free chloroform. Within 5 minutes, the solution was orange-red in color and a red oil had separated. The introduction of hydrogen chloride was continued for 1 hour. Addition of 100 ml. of water discharged the red color and the oil redissolved to give a yellow chloroform layer which was separated and washed free of acid with three portions of water. Filtration through anhydrous magnesium sulfate and removal of the solvent gave a partly crystalline pale yellow residue, wt. 2.10 g.; paper-strip analysis indicated this to be a mixture of V and VI in the ratio of *ca.* 40:60. This material was chromatographed over 210 g. of neutral alumina. The fractions eluted with 25% chloroform–benzene and 35% chloroform–

(33) Manganese dioxide prepared according to the procedure of M. Harfenist, A. Bavley and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

(34) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **25**, 988 (1942)

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benzene and which were mainly VI by paper-strip analysis were combined, wt. 515 mg., and recrystallized. After removal of a small first crop, wt. 87 mg., which was mainly V, the mother liquor on concentration afforded 286 mg. (14.3%) of VI, m.p. 186–194°, undepressed on admixture with material prepared in (A) above, and identical by paper-strip comparison and infrared.

The experiment above was repeated using 40.0 mg. (0.10 millimole) of V in 4.0 ml. of ethanol-free chloroform. After passing in hydrogen chloride for 1 hour, the solution and oil were stored at 0° for 18 hours and then worked up as described above. The crude product was shown to be essentially pure VI by paper strip analysis and on recrystallization afforded 25.1 mg. (62.8%) of crystals, m.p. 188.5–193°, identical to that prepared in (A) above by mixed m.p., paper-strip and infrared comparison.

(b) *Via* **Lithium Chloride–Dimethylformamide–Hydrogen Bromide.**—A mixture of 50.0 mg. (0.125 millimole) of V and 53.0 mg. (1.25 millimoles) of lithium chloride in 0.625 ml. of 0.20 *N* hydrogen bromide (0.125 millimole) in dimethylformamide was heated for 2 hours in an atmosphere of nitrogen. Addition of 6.0 ml. of water and saturation with sodium chloride caused the separation of crystals which were removed by filtration, washed thoroughly with water and dried *in vacuo* to give 45.3 mg. (90.6%) of needles, m.p. 180–191°, undepressed on admixture with material prepared by hydrogen chloride isomerization of V. The identity was confirmed by paper-strip and infrared comparison.

(c) *Via* **Lithium Chloride–Dimethylformamide–Pyridine Hydrobromide.**—A solution of 200 mg. (0.50 millimole) of V, 64 mg. (1.50 millimoles) of lithium chloride and 80 mg. (0.5 millimole) of pyridine hydrobromide in 5.0 ml. of dimethylformamide was heated for 2 hours at 100° under nitrogen. The mixture was cooled to 25° and 5.0 ml. of water added. The crystalline solid which separated was removed by filtration, washed three times with water and dried *in vacuo* to give 80 mg. of crude V, m.p., 225–235°, identified by paper-strip comparison. Recrystallization gave 32 mg., m.p. 229–235° dec. Addition of 50 ml. of saturated salt solution to the aqueous dimethylformamide filtrate above caused the separation of an additional 105 mg. of crystals, m.p. 177–193°, identified as substantially pure VI by paper-strip comparison. Recrystallization afforded 67.5 mg. of pure VI, m.p. 193–197°, undepressed on admixture with material prepared *via* hydrogen chloride isomerization and identified by paper-strip comparison.

(C) By Isomerization of the Dienedione IV with Lithium Chloride–Dimethylformamide–Hydrogen Bromide.—A solution of 100 mg. (0.25 millimole) of the dienedione IV in 0.51 ml. of dimethylformamide containing 100 mg. of lithium chloride (0.236 millimole) was treated with 1.0 ml. of 0.337 *N* hydrogen bromide (0.337 millimole) in dimethylformamide and heated on a steam-bath for 1 hour. The reaction mixture was diluted with water to afford 70–75 mg. of crystalline $\Delta^{4,8}$-dienedione VI which after recrystallization (Norite) from acetone–ether melted at 191–192.5° and was not depressed on admixture with authentic material. The infrared spectra of the two samples were essentially the same.

$\Delta^{4,8(9)}$-14-Isopregnadiene-17α,21-diol-3,11,20-trione 17α,21-Diacetate (VIa).—The 17α,21-diacetate VIa was prepared by treatment of 100 mg. of VI with 3 ml. each of pyridine and acetic anhydride for 7 days at 25°. The excess reagents were then removed *in vacuo* at 25° and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with water, 1.25 *N* hydrochloric acid, water, 5% aqueous sodium bicarbonate, water and saturated salt solution and dried by filtration through anhydrous magnesium sulfate. Removal of the solvent *in vacuo* gave an amorphous residue, weight 115 mg., which was estimated to contain *ca.* 95% of the 17α,21-diacetate by paper-strip analysis. Separation of the diacetate from unchanged VI was carried out by chromatography on Whatman No. 4 paper. Elution of the diacetate band gave 106 mg. of oily residue which on crystallization from acetone–ether afforded 72.5 mg. of VIa as needles, m.p. 183–185°, $[\alpha]^{25}D$ +275° (0.965), λ_{max} 237.5 mμ (ϵ 19,900); $\lambda\lambda_{max}^{Nujol}$ 5.74, 5.80, 6.04 and 6.30 μ (no hydroxyl bands observed).

Anal. Calcd. for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83. Found: C, 67.87; H, 6.47.

The 21-alcohol derived from VI was prepared by treatment of VI with (a) sodium methoxide in methanolic tetrahydrofuran or (b) potassium bicarbonate in aqueous methanol as described above for the 21-alcohol of the dienedione V. The material could not be crystallized, but reacetylation of small samples followed by paper-strip analysis indicated that no other structural change had occurred. The corresponding etio-acid **$\Delta^{4,8(9)}$-17α-hydroxy-3,11-diketo-14-isoetiadienic acid** was prepared by periodic acid oxidation of the amorphous 21-alcohol as described above. The m.p. after recrystallization from acetone–ether was 235.5–239° dec., λ_{max} 241 mμ (ϵ 19,350); $\lambda\lambda_{max}^{Nujol}$ 2.82–3.0, 5.79 and 6.0–6.2 μ. The m.p. was depressed on admixture with the epimeric acid VIII.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.68; H, 6.99.

Several attempts to back-isomerize VI at C_{14} were unsuccessful, thus: (1) Treatment of VI with anhydrous hydrogen chloride in ethanol-free chloroform at 0° for 1 hour gave back unchanged starting material, identified by mixed m.p. and by paper-strip comparison with authentic material, and (2) heating VI at 100° for 1 hour in pyridine in the presence of pyridine hydrobromide gave only unchanged VI identified as above.

$\Delta^{8(9)}$-Pregnene-17α,21-diol-3,11,20-trione 21-Acetate (XI).—A solution of 200 mg. (0.5 millimole) of the yellow dienedione V in 15 ml. of methanol was stirred in an atmosphere of hydrogen in the presence of 50 mg. of 5% palladium-on-barium sulfate. In about 0.5 hour, 12.3 ml. of hydrogen had been absorbed and the uptake ceased. The colorless solution was filtered and the methanol removed *in vacuo* to give 203 mg. of crude XI, m.p. 207–213°. One recrystallization raised the m.p. to 212–216°, $[\alpha]^{25}D$ + 157° (0.78),[35] λ_{max} 256 mμ (ϵ 8,175); $\lambda\lambda_{max}^{CHCl_3}$ 2.85–2.92, 5.72(sh), 5.79, 5.85, 6.01 and 6.21 μ.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.69; H, 7.29.

The m.p. of the material above was not depressed when mixed with $\Delta^{8(9)}$-pregnene-17α,21-diol-3,11,20-trione 21-acetate, m.p. 210–216°, isolated as a by-product in the conversion of pregnane-3α,17α-diol-11,20-dione to cortisone acetate[15]; the infrared spectra were identical.

A sample of XI on base hydrolysis and reacetylation resulted in recovery of XI unchanged.

$\Delta^{8(14)}$-Pregnene-11β,17α,21-triol-3,20-dione 21-Acetate (XIII).—A slurry consisting of 3.62 g. of $\Delta^{4,8(14)}$-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (III), 2.5 g. of 5% palladium-on-barium sulfate and 130 ml. of methanol was purged with hydrogen and hydrogenated with magnetic stirring at atmospheric pressure. The steroid dissolved during the hydrogenation. The uptake of hydrogen amounted to 103% of the theoretical amount of 1 mole per mole of steroid. The mixture was filtered, the filtrate evaporated to dryness *in vacuo* and the crystalline material dried for 1 hr. at 100° and 0.1 mm. The product, m.p. 188–199°, was obtained in quantitative yield. Three crystallizations from acetone–hexane yielded material, m.p. 195–197°, $[\alpha]^{25}D$ +165° (1.0), no maximum in the ultraviolet; $\lambda\lambda_{max}^{CHCl_3}$ 2.8, 2.92, 5.75(sh), 5.80 and 5.87 μ.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.16; H, 7.88.

Attempted hydrogenation of XIII over platinum-in-methanol and over platinum-in-acetic acid resulted in no further hydrogen uptake. Reduction of XIII with lithium aluminum hydride followed by attempted oxidation with selenium dioxide[31] produced no change in the ultraviolet spectrum.

$\Delta^{8(14)}$-Pregnene-11β,17α,21-triol-3,20-dione 11β-Mesylate 21-Acetate (XIIIa).—To a solution of 0.404 g. (1.0 millimole) of $\Delta^{8(14)}$-pregnene-11β,17α,21-triol-3,20-dione 21-acetate (XIII) in 5 ml. of pyridine cooled to 0° was added dropwise with cooling 1.0 ml. of methanesulfonyl chloride (13 millimoles). The mixture was allowed to stand at 0° for 24 hours. To the mixture was added 10 g. of ice and

(35) On several occasions the hydrogenation product exhibited unusual behavior. Paper-strip analysis indicated a less polar constituent as the major product separable by chromatography on neutral alumina, having a m.p. 173–177° and infrared ($CHCl_3$) and ultraviolet the same as XI with slightly lower extinction. This compound changed on standing in the solid state to the more polar XI, m.p. 212–216°. This behavior might be interpreted as the consequence of a boat ⇄ chair conformational transition induced by lattice forces.

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after 15 minutes the product was extracted with ethyl acetate. The ethyl acetate extract was washed successively with water, 1.6% phosphoric acid, 5% sodium bicarbonate solution, water, dried over magnesium sulfate and concentrated to dryness *in vacuo*. The residue was crystallized from acetone–hexane to yield 0.255 g. (53%) of XIIIa, m.p. 142–144° dec., $[\alpha]^{25}D$ +131.5° (1.0).

Anal. Calcd. for $C_{24}H_{34}O_8S$: C, 59.71; H, 7.10; S, 6.64. Found: C, 59.76; H, 6.82; S, 6.72.

$\Delta^{8(14),9(11)}$-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate (XIV).—A solution of 100 mg. (0.208 millimole) of $\Delta^{8(14)}$-pregnene-11β,17α,21-triol-3,20-dione 11-mesylate-21-acetate (XIIIa) in 1.0 ml. of pyridine was refluxed for 2 hours. After addition of 10 ml. of water the mixture was extracted with three 10-ml. portions of ethyl acetate. The combined ethyl acetate extracts were washed with water, 1.6% phosphoric acid, 5% sodium bicarbonate solution, water and saturated salt solution, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was treated with decolorizing charcoal and crystallized from acetone–hexane, m.p. 180–185°, $[\alpha]^{24}D$ +79° (1.0), λ_{max} 271 mμ (ϵ 4,600); $\lambda\lambda_{max}^{Nujol}$ 2.91, 5.73, 5.80, 5.85 and 5.91 μ.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.22; H, 7.88.

Reduction of XIV with lithium aluminum hydride gave an amorphous product, λ_{max} 271 mμ (ϵ 4,210).

$\Delta^{8(14)}$-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate (XV).—A solution of 150 mg. (0.39 millimole) of $\Delta^{8(14),9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (XIV) in 10 ml. of chloroform was treated with gaseous hydrogen chloride at 0° for 1 hour. The mixture was evaporated to dryness, treated with decolorizing charcoal and crystallized from acetone–hexane, m.p. 210–214°, $[\alpha]^{23}D$ −26.2° (1.0), λ_{max} 246 mμ (ϵ 21,500); $\lambda\lambda_{max}^{Nujol}$ 2.9, 5.75(sh), 5.79, 5.87, 6.11 and 6.20 μ.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.46; H, 7.55.

$\Delta^{4,8(14),9(11)}$-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate (XVI).—By a method analogous to the preparation of XIV from XIIIa, $\Delta^{4,8(14)9,(11)}$-pregnatriene-17α,21-diol-3,-20-dione 21-acetate (XVI) was obtained from $\Delta^{4,8(14)}$-pregnadiene-11β,17α,21-triol-3,20-dione 11β-mesylate 21-acetate (IIIb). The product was obtained as needles from acetone, m.p. 182–186°, $[\alpha]^{24}D$ +120° (1.0), λ_{max} 241 mμ (ϵ 21,600), 270 mμ(sh) (ϵ 4,700); $\lambda\lambda_{max}^{CHCl_3}$ 2.85–2.90, 5.73, 5.78, 6.00 and 6.15 μ.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.88; H, 7.30. Found: C, 71.66; H, 7.11.

$\Delta^{4,8,(14)}$-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate (XVII). (A).—By treatment with gaseous hydrogen chloride in chloroform as previously described for conversion of XIV to XV, $\Delta^{4,8(14),9(11)}$-pregnatriene-17α,21-diol-3,20-dione 21-acetate (XVI) was converted to $\Delta^{4,8(9),14}$-pregnatriene-17α,21-diol-3,20-dione 21-acetate, m.p. 188–192°, $[\alpha]^{24}D$ +143°, λ_{max} 242 mμ (ϵ 37,400); $\lambda\lambda_{max}^{CHCl_3}$ 2.90–2.95, 5.73(sh), 5.78, 6.00 and 6.1(sh) μ.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.88; H, 7.30. Found: C, 71.64; H, 7.56.

(B).—The method which employed 60% perchloric acid for conversion of II to III converted 17α-hydroxy-$\Delta^{8(9)}$-dehydrocorticosterone 21-acetate (XXIV) exclusively to $\Delta^{4,8(9),14}$-pregnatriene-17α,21-diol-3,20-dione 21-acetate (XVII) identical with material of method A by mixed m.p. and by ultraviolet spectrum.

8ξ,14ξ-Oxido-Δ^4-pregnene-17α,21-diol-3,11,20-trione 21-Acetate (XIX). (A) By Perbenzoic Acid Oxidation of the Dienedione IV.—A solution of 801 mg. (2.0 millimoles) of the dienedione IV in 20 ml. of chloroform was treated with 17.25 ml. of 0.348 *M* perbenzoic acid in benzene (6.0 millimoles) and the mixture stored overnight at 0°. During this time rosettes of needles had separated and were removed by filtration and washed once with ether, once with 10% aqueous sodium thiosulfate, three times with water, three times with ether and dried *in vacuo*, wt. 756.4 mg. (90.8%), m.p. 247.5–260° dec. Extraction of the filtrate and washings was effected with ethyl acetate, the extracts were washed with water, aqueous sodium thiosulfate and aqueous sodium bicarbonate in the usual manner, and afforded an additional 115 mg. of crude product. Recrystallization of this latter sample from methanol gave 39.4 mg. (4.6%), m.p. 249–262° dec. A sample prepared for analysis by recrystallization from acetone–methanol had the m.p. 245–250° dec. (the m.p. of this oxide was dependent on the state of subdivision and the rate of heating), λ_{max} 238 mμ (ϵ 14,600); $\lambda\lambda_{max}^{Nujol}$ 2.9, 5.74, 5.80, 5.90 and 6.04 μ.

Anal. Calcd. for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78; acetyl, 10.30. Found: C, 66.10; H, 6.59; acetyl, 9.72.

(B) Pyridine–Chromium Trioxide Oxidation of 8ξ,14ξ-Oxido-Δ^4-pregnene-11β,17α,21-triol-3,20-dione 21-Acetate.—Oxidation of 126 mg. (0.30 millimole) of the oxide of III, m.p. 203–206° dec., with chromium trioxide in pyridine (see oxidation of III to IV) afforded, after one crystallization from acetone, 88 mg. of XIX, m.p. 242–254° dec., undepressed on admixture with material prepared in (A) above. The infrared spectra were identical.

The 21-alcohol of the oxide XIX was prepared as follows: a 208.2-mg. (0.50 millimole) sample of XIX in 75 ml. of dioxane was mixed with 25.0 ml. of 2.0 *N* aqueous perchloric acid and the mixture stored at 25° for 6 days; 200 ml. of saturated salt solution was added and the organic material extracted with three portions of ethyl acetate. The combined extracts were washed with water until neutral, then with saturated salt solution, filtered through anhydrous magnesium sulfate and the solvents removed to give a granular crystalline residue, weight 180 mg., m.p. 210–225° dec. Recrystallization twice from acetone–ether afforded 92.5 mg. of micro-needles, m.p. 222–226° dec., λ_{max} 240 mμ (ϵ 12,700); $\lambda\lambda_{max}^{Nujol}$ 2.78, 3.04, 5.83, 5.89 and 6.07 μ; $\lambda\lambda_{max}^{CHCl_3}$ 5.84, 5.99 and 6.1 μ.

Anal. Calcd. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.59; H, 6.80.

In order to prove that no changes other than hydrolysis had occurred, a 30-mg. sample of the 21-alcohol was acetylated with acetic anhydride and pyridine at 25°. Within 10 minutes the solution had deposited crystalline material. After standing overnight at 25°, ice and water were added and the excess acetic anhydride decomposed. Filtration gave 31 mg. of XIX, m.p. 252–260° dec., undepressed on admixture with authentic material. Comparison of the infrared spectra confirmed the identity.

A number of unsuccessful experiments were performed in an effort to transform the oxide XIX into other products. These are briefly as follows: (1) an attempt to epimerize XIX at C-9 on special alumina[5b] gave unchanged starting material; (2) treatment with excess ozone in ethyl acetate at −80° gave 25% of unchanged XIX and an amorphous mixture of unidentified products; (3) subjection of a sample of XIX to the action of osmium tetroxide in pyridine–benzene gave 62% recovery of starting material with no other products isolated; (4) on treatment with periodic acid in dilute aqueous dioxane, XIX was recovered unchanged; and (5) heating a sample of XIX with lithium chloride in dimethylformamide for two hours at 100° again gave unchanged starting material. Under more strongly acidic conditions, however, the oxide XIX was not recovered, but no pure products could be isolated. The acidic conditions employed were as follows: (1) acetic acid, acetic anhydride and *p*-toluenesulfonic acid at 25° overnight; (2) treatment of a chloroform solution of XIX with 60% aqueous perchloric acid at 0° for 15 minutes; and (3) the action of dry hydrogen chloride in chloroform at 0° for one hour.

$\Delta^{4,6,8(14)}$-Pregnatriene-17α,21-diol-3,11,20-trione (XX).[25]—A suspension of 521 mg. (1.25 millimoles) of the oxide XIX in a mixture of 75 ml. of tetrahydrofuran and 25 ml. of methanol was placed under a nitrogen atmosphere and 4.16 ml. of 0.376 *N* sodium methoxide in methanol (1.56 millimoles) added with stirring. After 7 minutes, the solid had dissolved to give a pale purple-yellow solution and after 8 minutes, the reaction was quenched by the addition of 0.20 ml. of glacial acetic acid. The solvents were removed *in vacuo* at 25° and the sirupy residue taken up in ethyl acetate. After washing the solution with water, 5% aqueous sodium bicarbonate solution, water and saturated salt solution, it was filtered through anhydrous magnesium sulfate and the ethyl acetate removed *in vacuo* to give a yellow amorphous solid, weight 445 mg., $\lambda\lambda_{max}$ 237 mμ, $E_{1\,cm.}^{1\%}$ 279 and 336 mμ, $E_{1\,cm.}^{1\%}$ 270. Two crystallizations from acetone afforded 89.5 mg. (19%) of XX, m.p. 225–235° dec., λ_{max} 337 mμ (ϵ 25,800); $\lambda\lambda_{max}^{Nujol}$ 3.0, 5.82, 6.1 and 6.26 μ; $\lambda\lambda_{max}^{CHCl_3}$ 3.0, 5.82, 6.02 and 6.23 μ.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.49; H, 7.04.

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A sample of the trienedione XX prepared above was acetylated with acetic anhydride and pyridine at 25° overnight. Isolation in the usual manner gave the 21-acetate of XX, m.p. 218–225° dec., λ_{max} 334 mμ (ε 27,500), $\lambda\lambda_{max}^{CHCl_3}$ 3.0, 5.72(sh), 5.79, 6.01 and 6.22 μ; $\lambda\lambda_{max}^{Nujol}$ 2.95, 5.74, 5.80, 5.85, 6.0 and 6.23 μ.

Anal. Calcd. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.06; H, 6.83.

The disposition of double bonds in the trienedione XX was ascertained by reduction with lithium aluminum hydride. A 40-mg. (0.122 millimole) sample of XX in 10 ml. of tetrahydrofuran was added over 20 minutes to a stirred solution of 106 mg. (2.8 millimoles) of lithium aluminum hydride in 10 ml. of tetrahydrofuran. The addition was carried out in an atmosphere of nitrogen. After heating under reflux for 1.5 hours, the reaction was worked up by adding ethyl acetate, saturated aqueous sodium sulfate and anhydrous magnesium sulfate. Filtration and removal of the solvents afforded a gummy residue. This was dissolved in ethyl acetate, the solution washed twice with water, once with saturated salt solution, dried, filtered and the solvent removed *in vacuo* to give 20.9 mg. of amorphous solid XXI, λ_{max} 284.5 mμ (ε 19,150).

Hydrogenation of 132 mg. (0.37 millimole) of XX over 50 mg. of palladium-on-barium sulfate in 10 ml. of methanol also was carried out. The absorption of hydrogen continued at a steady rate until 18.4 ml. had been consumed (0.74 millimole or 2 moles/mole). The solution was filtered and the methanol removed *in vacuo*. Acetylation with acetic anhydride in pyridine at 60–70° for one hour followed by isolation in the usual manner gave 160 mg. of amorphous solid exhibiting only end absorption in the ultraviolet. This product was chromatographed on neutral alumina and the fractions eluted with 20 and 30% chloroform in benzene were combined, weight 104 mg. Two crystallizations, from ether–Skellysolve B and then from acetone–ether, gave 14.5 mg. of crystals, m.p. 193–203° with previous softening; $\lambda\lambda_{max}^{CHCl_3}$ 2.76, 2.84–2.97, 5.72(sh), 5.79(sh) and 5.83 μ. A mixture with the $\Delta^{8(14)}$-enedione XXII was depressed.

$\Delta^{8(14)}$-Pregnene-17α,21-diol-3,11,20-trione 21-Acetate (XXII). (A) By Hydrogenation of IV.—A solution of 400.5 mg. (1.0 millimole) of the dienedione IV in 20 ml. of methanol was stirred in a hydrogen atmosphere at 25° and atmospheric pressure in the presence of 100 mg. of 5% palladium-on-barium sulfate. In 1.5 hours, the absorption of hydrogen ceased, 23.2 ml. having been taken up. The solution was filtered and the solvent removed *in vacuo* to give an amorphous residue. This material exhibited only end absorption in the ultraviolet. One recrystallization from ethyl acetate afforded 330 mg. of XXII, m.p. 196–198.5°, $\lambda\lambda_{max}^{Nujol}$ 2.85, 5.73, 5.79 and 5.86 μ; $[\alpha]^{25}D$ +306 (0.8). This material was identical by mixed m.p. and infrared spectrum with material prepared by oxidation of XIII (see below).

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.37; H, 7.37.

A 100-mg. (0.25 millimole) sample of XXII in 2.5 ml. of tetrahydrofuran and 1.5 ml. of methanol was placed under a nitrogen atmosphere and treated with 4.64 ml. of 0.118 *N* sodium methoxide in methanol (1.10 millimoles). The amber solution was held at 23° for 1 hour, then neutralized with 0.2 ml. of glacial acetic acid. The residue on concentration to dryness *in vacuo* was treated with 1.0 ml. of acetic anhydride and 2.0 ml. of pyridine and allowed to stand overnight at room temperature (23°). After concentration to dryness *in vacuo* 101 mg. of yellow crystalline material was obtained. Paper chromatographic analysis and the infrared spectrum showed the material to be essentially unchanged. One recrystallization from ethyl acetate–ether yielded colorless needles which did not depress the m.p. of starting material.

A sample of XXII was dissolved in chloroform and gaseous hydrogen chloride was bubbled through the solution for 1 hour at room temperature. The product after concentration to dryness showed an ultraviolet spectrum unchanged from that of starting material.

A sample of XXII together with 3 equivalents of lithium chloride were dissolved in dimethylformamide. The mixture was heated on the steam-bath under nitrogen for 2 hours, then cooled to room temperature, diluted with water and saturated salt solution and the product obtained by filtration. The product, m.p. 188–191°, did not depress the m.p. of starting material. The ultraviolet spectra of the product and the starting material were identical.

(B) By Oxidation of XIII.—To a solution at 0° consisting of 0.404 g. (1.0 millimole) of $\Delta^{8(14)}$-pregnene-11β,17α,21-triol-3,20-dione 21-acetate (XIII) in 4 ml. of pyridine was added dropwise with cooling 0.333 g. of chromium trioxide (3.33 millimoles) dissolved in 0.33 ml. of water and 0.50 ml. of pyridine. The mixture was allowed to stand for 18 hours at room temperature. After dilution with 80 ml. of water and 20 ml. of ethyl acetate the mixture was filtered. The residue was washed with ethyl acetate and the aqueous phase extracted with ethyl acetate. The ethyl acetate phase was washed successively with water, 0.5 *N* phosphoric acid and water, then filtered through anhydrous magnesium sulfate. The crude product after concentration *in vacuo* amounted to 0.361 g. (90%). Two recrystallizations from ethyl acetate–ether yielded a product identical with that of method A by m.p. 194–198°, mixed m.p., infrared spectrum and paper-strip comparison.

$\Delta^{8(9)}$-14-Isopregnene-17α,21-diol-3,11,20-trione 21-Acetate (XXIII). (A) By Hydrogenation of the Dienedione VI.—A solution of 800 mg. (2.0 millimoles) of VI in 40 ml. of methanol was hydrogenated as described above in the presence of 100 mg. of 5% palladium-on-barium sulfate. The absorption of hydrogen ceased in *ca.* 15 minutes, 49 ml. having been taken up. After filtration to remove the catalyst, the solvent was removed *in vacuo* to yield a colorless crystalline residue, weight 815 mg., m.p. 177–181°. One recrystallization from ethyl acetate–ether gave 750 mg. (93%) of XXIII, m.p. 178–181°, λ_{max} 248 mμ (ε 8,450), $\lambda\lambda_{max}^{CHCl_3}$ 2.85, 2.95, 5.73, 5.79, 5.83, 6.0 and 6.18 μ.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.56; H, 7.49.

(B) By Isomerization of the Enedione XI.—Treatment of 100 mg. of XI with anhydrous hydrogen chloride in ethanol-free chloroform at 0° for one hour as described above for the conversion of V to VI gave 97 mg. of crude product, m.p. 161–190°. Crystallization from ethyl acetate–ether gave 30 mg., m.p. 198–208°, which on recrystallization had the m.p. 206–213°, undepressed on admixture with the starting enedione XI. The mother liquor of the 30 mg. sample on concentration and seeding with XXIII prepared by hydrogenation afforded 17 mg. of crystals, m.p. 174–180°, undepressed on admixture with authentic XXIII and possessing an identical infrared spectrum.

A sample of the low-melting, less polar form of XI[24] described above gave essentially the same results on isomerization with hydrogen chloride in chloroform.

The enedione XXIII was stable to the action of hydrogen chloride in chloroform at 0° for one hour, the conditions under which it is formed from XI.

(C) By Isomerization of the Enedione XXII.—Isomerization of XXII with hydrogen bromide–lithium chloride–dimethylformamide exactly as described above for the conversion of IV to VI (method C) gave on dilution with water essentially pure XXIII, m.p. 176–178°, λ_{max} 248 μ (ε 8,400). The m.p. was undepressed on admixture with material prepared by hydrogenation and the infrared spectra were identical. The above isomerization occurred also when the lithium chloride was omitted.

$\Delta^{4,8(9)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 21-Acetate (17α-Hydroxy-$\Delta^{8(9)}$-dehydrocorticosterone 21-Acetate) (XXIV).—A solution consisting of 62.0 g. (0.128 mole) of 9α-bromo-17α-hydroxycorticosterone 21-acetate (I, X = Br) and 400 ml. of tetrahydrofuran was added to 400 ml. of N-ethylpiperidine and the mixture refluxed for 7.5 hours. The mixture was concentrated *in vacuo* to about 450 ml., filtered and the precipitate washed with three 50-ml. portions of distillate. The precipitate was then washed with water until free of bromide ion; the water washes were caught separately and discarded. The residue amounting to 39.0 g. (75.5%) was chiefly 9β,11β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (II), as determined by m.p., mixed m.p. and paper-strip analysis.

The filtrate upon concentration to dryness *in vacuo* yielded 16.74 g. of a steroid mixture. Of this mixture, a 5.00-g. aliquot was chromatographed on neutral alumina. Fractions were eluted with mixtures of benzene and chloroform and the composition of these determined by paper chromatography. $\Delta^{4,8(9)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (XXIV) shows an R_f of 0.09 (benzene–formamide–Eluting system, cortisone 21-acetate and 9β,-

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11β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (II) show R_f 0.33 and 0.50, respectively. Fractions amounting to 2.04 g., rich in product were rechromatographed on neutral alumina to yield 0.667 g. of purified compound, m.p. 195–215° dec. Treatment with decolorizing charcoal and three crystallizations from acetone–hexane yielded analytical material, m.p. 213–216° dec., $[\alpha]^{24}D$ +219° (1.0), λ_{max} 238 mμ (ϵ 16,400); $\lambda\lambda_{max}^{Nujol}$ 2.82, 2.89, 5.81, 6.00 and 6.19 μ.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.69; H, 7.51. Found: C, 68.65; H, 7.58.

$\Delta^{4,8(9)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 11β,21-Diacetate (XXIVa).—A solution consisting of 102.5 mg. (0.255 millimole) of $\Delta^{4,8(9)}$-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (XXIV), 1 ml. of pyridine and 1 ml. (10.6 millimoles) of acetic anhydride was allowed to stand for 1 week at room temperature (24°). The mixture was diluted with 20 ml. of water, filtered and the residue washed with water. The precipitate amounting to 81.5 mg. (71.4%) was recrystallized from acetone–hexane to yield 65.4 mg. (57.3%) of product, m.p. 201–204°, $[\alpha]^{25}D$ +224° (1.0), λ_{max} 237 mμ (ϵ 16,000); $\lambda\lambda_{max}^{Nujol}$ 2.96, 5.79, 5.97 and 6.13 μ.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.52; H, 7.51.

$\Delta^{4,7,9(11)}$-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate (XXV).—To a solution of 304 mg. (0.756 millimole) of 17α-hydroxy-$\Delta^{8(9)}$-dehydrocorticosterone 21-acetate (XXIV) and 3.75 ml. of pyridine cooled to 0° was added dropwise with cooling 0.75 ml. (10 millimoles) of methanesulfonyl chloride. The mixture was allowed to stand at 0° for 24 hours. To the mixture was added 10 g. of ice and after 15 minutes the product was extracted with ethyl acetate. Concentration of the washed, dried extract yielded 189 mg. (64.9%) of crude triene. The crude material was treated with decolorizing charcoal and crystallized twice from acetone–hexane to yield 85 mg. (29%) of pale yellow needles, m.p. 199–203°, $[\alpha]^{27}D$ +236° (1.0); $\lambda\lambda_{max}$ 242.5 mμ (ϵ 26,200), 237.5(sh) and 250(sh) mμ (ϵ 24,900 and 22,100), $\lambda\lambda_{max}^{CHCl_3}$ 2.9, 5.74(sh), 5.78, 6.0 and 6.12 μ.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.53; H, 7.31.

Reduction of XXV with lithium aluminum hydride in tetrahydrofuran yielded an amorphous product; $\lambda\lambda_{max}$ 237, 244 mμ (ϵ 7,780, 8,510), 251(sh) mμ (ϵ 6,130).

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RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

Synthetic Studies in Resin Acids. II[1]

BY USHARANJAN GHATAK, NARENDRA NATH SAHA[2] AND PHANINDRA CHANDRA DUTTA[3]

RECEIVED FEBRUARY 18, 1957

The conversion of $>C{=}O$ to $>C<^{CH_3}_{CO_2H}$ has been studied for the case of cyclohexanone and 10-methyldecalone. Two successful methods were achieved for cyclohexanone and one of these was also effective for the decalone system. The second procedure, involving action of methylmagnesium iodide on ethyl 10-methyldecalidene-1-cyanoacetate, failed because reduction rather than addition occurred. The significance of the above syntheses for the preparation of diterpenoid resin acids is noted.

In the synthesis of compounds related to diterpenoid resin acids, the conversion of the tricyclic ketones[1,4] to the corresponding *gem*-methylcarboxylic acids, is of considerable importance. The purpose of the present investigation was to seek suitable means for this conversion, using cyclohexanone and 10-methyldecalone as model compounds. In this communication the essential steps for two procedures, which were successful for the synthesis of 1-methyl-1-carboxy-cyclohexane VII are described. A recent publication,[5] which appeared subsequent to our preliminary communication[6] embodying these methods, has also supported these results.

In procedure I, ethyl cyclohexane-1-carbethoxy-1-acetate obtained from the dicyano-ester[7] was the starting material. The silver salt of the monoester IV afforded the bromoester V on treatment with bromine. Hunsdiecker degradation promised to be a useful route to rather inaccessible bromides of the neopentyl type and hence it has been utilized successfully to build up the quaternary methyl group. The bromide V on reduction with zinc and acetic acid yielded VI, from which VII was obtained on alkaline hydrolysis. VII was further characterized by conversion to its amide.[8] In procedure II, VIII was obtained through the conjugate addition[9] of methyl Grignard reagent to III in the presence of cuprous iodide.[10] The controlled hydrolysis of VIII and pyrolysis of the acidic product yielded the nitrile IX. Attempts at acidic or alkaline hydrolysis of the nitrile were unsuccessful. The nitrile IX was then allowed to react with phenylmagnesium bromide leading to X, which on further reaction with the same reagent gave a mixture of the corresponding carbinol and the dehydrated product. This mixture was directly oxidized to VII.

With the idea that these two procedures in the case of unsymmetrical ketones should lead to dif-

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(2) Post-doctoral Fellow, Department of Chemistry, University of Southern California.

(3) Communications regarding this paper may be sent to this author.

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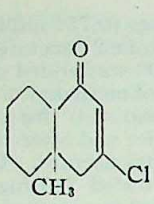
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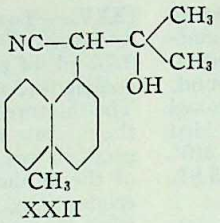
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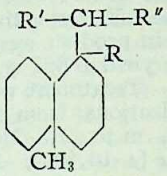
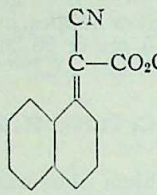

XIV, R = R′ = CN; R″ = $CO_2C_2H_5$
XV, R = CO_2H; R″ = H; R′ = CO_2H
XVI, R = CO_2CH_3; R″ = H, R′ = CO_2H
XVII, R = CO_2CH_3; R″ = H, R′ = Br
XVIII, R = CO_2CH_3; R′ = R″ = H
XIX, R = H, R′ = CN; R″ = CO_2CH_3
XX, R = R′ = H; R″ = CN
XXI, R = R′ = H; R″ = COC_6H_5
XXIII, R = H, R′ = CN; R″ = $CO_2C_2H_5$
XXX, R = R′ = H; R″ = CO_2CH_3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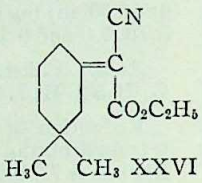
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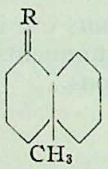
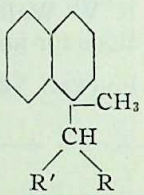
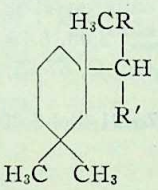
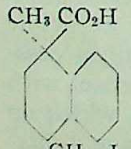

XI, R = O

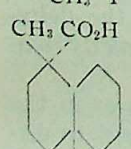
XIII, R = $=C<^{CN}_{CO_2C_2H_5}$

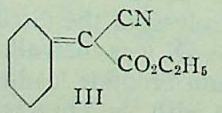

XXV, R = CN; R′ = $CO_2C_2H_5$ XXVIII, R = H; R′ = $COCH_3$


XXVII, R = CN; R′ = $CO_2C_2H_5$
XXIX, R = H; R′ = $COCH_3$

ferent epimers[11] and also for the reasons stated before,[1b] 10-methyldecalone (XI) was selected as the second starting ketone. In this case the stereochemistry of the final products, which were expected to result by the above routes, was of special interest in connection with the synthesis of the natural resin-acids, represented by abietic acid and podocarpic acid or their congeners. It was believed that the conjugate addition to the unsaturated cyano-ester XIII, of ions or components of Grignard complex probably through ions and/or radicals,[12] might be markedly influenced stereochemically[13] by the presence of the angular methyl group (*e.g.*, in XI). The degree of stereospecificity may not be the same in both cases and one of the reasons might be that the general pattern of homolytic reactions is singularly free from powerful electrostatic forces, which operate in ionic reactions in addition to steric factors. The first of the above routes proved successful and led to 1,10-dimethyldecalin-1-carboxylic acid, the stereochemistry of which may be either as shown in I or II.


I


II


III

IV, R = CH_2CO_2H; R′ = $CO_2C_2H_5$
V, R = CH_2Br; R′ = $CO_2C_2H_5$
VI, R = CH_3; R′ = $CO_2C_2H_5$
VII, R = CH_3; R′ = CO_2H
VIII, R = CH_3; R′ = $CH(CN)CO_2C_2H_5$
IX, R = CH_3; R′ = CH_2CN
X, R = CH_3; R′ = $CH_2CO{\cdot}C_6H_5$

From consideration of the steric courses of reactions and results in a closely related work,[14] it can be concluded with confidence that the product obtained is II. That the synthetic acid did not belong to the podocarpic acid series (*e.g.*, I) was also apparent from the comparatively less drastic conditions,[15] that were required for the isolation of the acid II.

The ketone XI was obtained from 10-methyldecalin-1,3-dione.[16] This was converted to the chloro-ketone XII which in its turn was reduced catalytically with or without the addition of pyridine. The formation of the isomeric 3-ketone appeared less likely from steric considerations, and structure XI was confirmed through the isolation of 1-methylnaphthalene by action of methylmagnesium iodide and subsequent dehydrogenation. The desired ketone XI condensed[17] with ethyl cyanoacetate to afford XIII. The dicyano-ester XIV was obtained in an excellent yield by addition of hydrocyanic acid[18] to XIII. The dibasic acid XV was isolated in a highly crystalline form and the partial hydrolysis of the diester led to the half-ester XVI. Hunsdiecker degradation of the latter yielded XVII, which was reduced to XVIII. Finally acid II was obtained by hydrolyzing the ester with methanolic potassium hydroxide.

During the course of this investigation, the remote possibility of the formation of XXX in place of XVIII was considered and discarded on the basis of hydrolytic experiments. Attempts at hydrolysis under mild conditions led to the re-

(11) N. N. Saha, Thesis, 1953, Calcutta University.

(12) M. S. Kharasch and O. Reinmuth, "Grignard Reaction of Non-metallic Substances," Constable & Co., London, 1954, Chapter V.

(13) (a) D. H. Hey, *J. Chem. Soc.*, 1974 (1952); (b) H. Heusser, P. Th. Herzig, A. Fürst and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

(14) N. N. Saha, B. K. Ganguli and P. C. Dutta, *Chemistry & Industry*, 412 (1956).

(15) (a) I. R. Sherwood and W. F. Short, *J. Chem. Soc.*, 1006 (1938); (b) W. P. Campbell and D. Todd, THIS JOURNAL, **64**, 928 (1942).

(16) C. R. Clemo and H. G. Dickenson, *J. Chem. Soc.*, 735 (1935).

(17) E. J. Cragoe, C. M. Robb and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950).

(18) F. Ingold, W. Hanhart, *J. Chem. Soc.*, **121**, 2223 (1922).

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covery of the ester thereby ruling out the structure XXX.

In the second route which was expected to lead to acid I, reaction of XIII with methylmagnesium iodide in the presence of cuprous iodide did not proceed as anticipated on the basis of reaction in the cyclohexane series; the product isolated was a complex mixture as revealed by infrared studies and was characterized by a strong hydroxyl band (3 μ) and a doublet (7.25 and 7.3μ) of a *gem*-dimethyl group. The neutral material was subjected to controlled alkaline hydrolysis. The acid from the base-soluble portion, was decarboxylated and the nitrile so obtained was converted into the corresponding phenyl ketone. The analytical values of it and of the related dinitrophenylhydrazone indicated that the ketone should be represented by XXI. This was further confirmed by the mixed melting point determination of this derivative, prepared from an authentic sample of the ketone XXI (*vide infra*). It is now apparent that the major product of the Grignard reaction is XXIII, resulting from the reduction of the double bond. Consequently XX represents the structure of the nitrile. This observation parallels action of Grignard reagents on azo-compounds[19] or hindered ketones.[20] There are recorded[21] some cases of reduction of alkalidene cyano-acetates with Grignard reagents from higher aliphatic as well as aromatic halides. In the original reaction mixture some amount of the compound XXII, quite analogous to that isolated in the case of the tricyclic ketone,[14] was most probably present but the isolation of the same or of the corresponding dehydration product in a pure state could not be accomplished.

To prepare an authentic dinitrophenylhydrazone of XXI, the unsaturated cyano-ester XIII was reduced with aluminum amalgam to XXIII which through the same series of reactions as described before, yielded the corresponding ketone. Fractional crystallization of the dinitrophenylhydrazones revealed that this ketone was a mixture of stereoisomers, one of which was identical with the ketone XXI described above.

Finally to trace the origin of this abnormal type of reaction induced by the Grignard reagent and to evaluate the steric effect of the angular methyl group, α-decalone was converted to XXIV, which led to the normal addition product XXV and the corresponding ketone XXVIII in good yields. Similarly XXVI from 3,3-dimethylcyclohexanone behaved in a normal way leading to XXVII, which yielded XXIX. In both cases the ketones were characterized through well-defined semicarbazones.

Evidently the powerful non-bonded interaction between the angular methyl group and the axially oriented intermediate complex,[22] incorporating the cyanoacetic ester residue in the normal addition product, was responsible for this abnormal reaction-path, indicating once more the importance of steric factors in the abnormalities of Grignard reactions.

Acknowledgments.—We are indebted to Prof. Norman Kharasch, Department of Chemistry, University of Southern California, for kindly reading this manuscript. Our grateful thanks are also due to Dr. R. Schwyzer, Basle, Switzerland, and to Mrs. Chhabi Dutta, University College of Science, Calcutta, for micro-analyses.

Experimental[23]

Ethyl 1-Bromomethylcyclohexane-1-carboxylate (V).—Ethyl cyclohexane-1-carbethoxy-1-acetate (15 g., 0.062 mole) was hydrolyzed with a solution of potassium hydroxide (4.5 g., 0.08 mole), water (4.5 ml.) and ethanol (81 ml.). The crude half-ester (11.1 g.) in alcohol (20 ml.) was neutralized (phenolphthalein) with 1 *N* sodium hydroxide solution and converted into the silver salt. It was dried at 50–60° and finally under vacuum at 110° for 15 hours. The salt (11 g.) was suspended in dry carbon tetrachloride (50 ml.) and gradually treated with a solution of bromine (2 ml.) in the same solvent (10 ml.) at the reflux temperature. Silver bromide was collected and the carbon tetrachloride layer was washed with 5% sodium carbonate solution. Distillation afforded 6.9 g. (43%), b.p. 105–107° (4 mm.).

Anal. Calcd. for $C_{10}H_{17}O_2Br$: C, 48.2; H, 6.8. Found: C, 48.2; H, 6.8.

Ethyl 1-Methylcyclohexane-1-carboxylate (VI).—A mixture of the bromide (3.75 g., 0.0145 mole), zinc dust (7.2 g., 0.11 g. atom) and glacial acetic acid (24 ml.) was refluxed for 8 hours. The reaction mixture was poured into water, neutralized with sodium carbonate and finally extracted with ether. The pleasant-smelling ester, 1.5 g. (61%), distilled at 62–63° (4 mm.).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.6; H, 10.6. Found: C, 70.3; H, 10.5.

On hydrolysis with methanolic potassium hydroxide (20%), the free acid was obtained; m.p. 36° (lit.[6] 38°). The corresponding amide melted at 67–68° (lit.[6] 68–69°).

Ethyl 1-Methylcyclohexylcyanacetate (VIII).—To the Grignard reagent prepared from magnesium (3.7 g., 0.152 g. atom), methyl iodide (27.7 g., 0.195 mole) in ether (60 ml.) cuprous iodide (1 g., 0.0026 mole) was added, followed by the slow addition of the unsaturated cyano-ester (25 g., 0.129 mole) in ether (50 ml.). On refluxing for 2 hours the reaction mixture was worked up and purified by treating with a solution of sodium cyanide (7.2 g.) in aqueous alcoholic solution. The colorless ester, 19.6 g. (72.7%), boiled at 157° (12 mm.), $n^{35}D$ 1.4613.

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.9; H, 9.1. Found: C, 69.3; H, 9.4.

Methylcyclohexylacetonitrile (IX).—The cyano-ester VIII (15 g., 0.071 mole) was hydrolyzed with a solution of potassium hydroxide (5.25 g., 0.093 mole) in water (3.7 ml.) and ethanol (120 ml.). The acidic product (10 g.) was decarboxylated at 200° for a half-hour and the nitrile was obtained as a colorless mobile liquid; 5 g. (51.4%), b.p. 80° (3 mm.).

Anal. Calcd. for $C_9H_{15}N$: C, 78.8; H, 10.9. Found: C, 79.1; H, 10.8.

ω-(Methylcyclohexyl)-acetophenone (X).—To a solution of phenylmagnesium bromide, from magnesium (5.2 g., 0.219 mole) and bromobenzene (34 g., 0.216 mole), in ether (100 ml.) was added the nitrile (14.7 g., 0.107 mole) in ether (20 ml.). The reaction mixture was refluxed for one hour and after removal of most of the ether, it was again heated on the water-bath for another hour. On decomposition of the complex the ketone was isolated as a pale-yellow mobile liquid, b.p. 150–155° (6 mm.), 21.3 g. (92.2%).

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.3; H, 9.2. Found: C, 83.1; H, 9.05.

The 2,4-dinitrophenylhydrazone crystallized as orange needles from ethyl acetate, m.p. 215°.

Anal. Calcd. for $C_{21}H_{24}N_4O_4$: C, 63.6; H, 6.0. Found: C, 63.3; H, 5.8.

Methylcyclohexylcarboxylic Acid (VII).—The above ketone (15 g., 0.069 mole) was again treated with the Grignard reagent from magnesium (3.3 g., 0.136 mole) and bromobenzene (21.67 g., 0.138 mole) in the usual way. A

(19) H. Franzen and W. Deibel, *Ber.*, **38**, 2716 (1905).
(20) C. G. Swain and H. B. Boyles, THIS JOURNAL, **73**, 870 (1951).
(21) F. S. Prout, *ibid.*, **74**, 5915 (1952), and subsequent publications.
(22) H. J. Shine, *J. Chem. Soc.*, 8 (1951).

(23) All boiling points and melting points are uncorrected.

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viscous liquid (14 g.) was finally obtained, b.p. 197–200° (2 mm.).

Anal. Calcd. for $C_{21}H_{26}O$: C, 85.7; H, 8.8. Calcd. for $C_{21}H_{24}$: C, 91.3; H, 8.7. Found: C, 89.3; H, 8.2.

The above compound (10 g.) was oxidized with chromic anhydride (9 g.) in water (6 ml.) and acetic acid (56 ml.) at room temperature and finally on the boiling water-bath for 2 hours. The reaction mixture was subjected to steam distillation and from the distillate the cyclohexane acid, m.p. 36°, was isolated. The amide melted at 66–67° alone or mixed with the previous sample.

1-Keto-3-chloro-10-methyl-Δ^2-octalin (XII).—10-Methyldecalin-1,3-dione was prepared from 2-methylacetylcyclohexene[24] with a slight modification. The diketone (27 g., 0.15 mole) in chloroform (50 ml.) was refluxed on the water-bath for 3 hours with phosphorus trichloride (7.5 g., 0.055 mole). The solvent was distilled off under reduced pressure. It was cooled and treated with an excess of ice-cold water. The ethereal extract was washed with cold sodium hydroxide solution (2%). On removal of the solvent, the residue distilled at 126–128° (6 mm.) as a colorless liquid; 17 g. (57.1%).

Anal. Calcd. for $C_{11}H_{15}OCl$: C, 66.4; H, 7.5. Found: C, 66.4; H, 7.5.

1-Keto-10-methyldecalin (XI).—The enol-chloride (14.2 g.) in ethanol (40 ml.) was hydrogenated with palladium–carbon (2 g., 5%) at room temperature. The hydrogenated product was worked up and the ketone, 10 g. (84%), boiled at 130–132° (12 mm.) as a sweet-smelling colorless liquid.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.5; H, 10.8. Found: C, 79.4; H, 10.8.

The semicarbazone was obtained in a quantitative yield, m.p. 204–205°, and crystallized from dilute ethanol in shining flakes, m.p. 206–207°.

Anal. Calcd. for $C_{12}H_{21}N_3O$: N, 18.8. Found: N, 18.8.

1-Methylnaphthalene.—The ketone (3 g., 0.018 mole) was allowed to react with methylmagnesium iodide, prepared from magnesium (2.4 g., 0.098 g. atom). The carbinol was dehydrated by distillation (85 mm.) in the presence of a crystal of iodine. The hydrocarbon (2.4 g.) distilled at 140–142° (85 mm.). To a solution of the hydrocarbon (1.4 g.) in carbon tetrachloride (6 ml.) was added bromine (1.4 g.). The residue, on removal of the solvent, was mixed with collidine (4 ml.) and refluxed for 15 minutes in an atmosphere of nitrogen. The reaction mixture was poured into ice-cold 6 *N* hydrochloric acid and extracted with ether. The diene (0.4 g., b.p. 130–140° (85 mm.)), was dehydrogenated in a sealed tube at 300–325° for 50 hours with selenium (1.6 g.). The hydrocarbon was purified by distillation over sodium and converted into a picrate. On crystallization from ethanol, this melted at 139–140° (lit.[25] 140–141°) alone or mixed with an authentic sample.

Ethyl 10-Methyldecalidene-1-cyanoacetate (XIII).—The ketone XI (2.5 g., 0.015 mole) was condensed with ethyl cyanoacetate (3.4 g., 0.03 mole) in benzene (6 ml.) and acetic acid (1.5 ml.) in the presence of ammonium acetate (0.4 g. added in 4 lots) by refluxing for 36 hours in a flask fitted with a constant water-separator. The product was extracted with benzene and thoroughly washed with water. On removal of the solvent and low boiling products, the unsaturated ester, 2.6 g. (66.4%), was collected at 175–180° (4 mm.).

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.5; H, 8.8. Found: C, 73.5; H, 8.4.

Ethyl 10-Methyldecalin-1-cyano-1-cyanoacetate (XIV).—To a cold solution of the unsaturated ester XIII (8.5 g., 0.033 mole) in ethanol (130 ml.) was added sodium cyanide (4.8 g., 0.098 mole), dissolved in the minimum quantity of water and subsequently diluted with ethanol (30 ml.). The temperature of the reaction mixture was raised to 38° whereupon the solution turned pale red. It was cooled and acidified with concentrated hydrochloric acid (5.4 ml.). On allowing the solution to stand for one hour at room temperature, it was poured into an excess of ice-cold dilute hydrochloric acid. The chloroform extract afforded a thick yellowish liquid, 8 g. (85.4%) at 180–185° (0.3 mm.).

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.8; H, 8.3. Found: C, 70.8; H, 8.2.

10-Methyldecalin-1-succinic Acid (XV).—A solution of the dicyano-ester XIV (10 g., 0.035 mole) in acetic acid (20 ml.) was treated with a mixture of concentrated sulfuric acid (20 ml.) and water (20 ml.) and the mixture was refluxed slowly on an oil-bath for 25 hours. The mixture was cooled and diluted with ice-cold water (40 ml.). A crystalline solid separated out. The solid was filtered and washed with petroleum ether (b.p. 40–60°) to remove the adhering oil. A white crystalline solid (3.8 g.) was obtained, m.p. 173–174°. The filtrate was diluted with an excess of water and extracted with ether. The ethereal layer was mixed with petroleum ether washings. The crude mixture (4 g.), left after the removal of the solvents, was again hydrolyzed as before. On working up the reaction mixture a colored solid was obtained and this on crystallization from ethyl acetate–acetic acid after boiling with charcoal, yielded a further lot of the crystalline acid (0.6 g., m.p. 172–174°). The total yield was 4.4 g. (50%). This was recrystallized from acetic acid containing a little water and it melted at 175°.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.1; H, 8.6. Found: C, 65.9; H, 8.5.

The acid (2.5 g.) in methanol (25 ml.) was esterified with an excess of an ethereal solution of diazomethane. After removal of the solvent, the residue afforded a colorless liquid, 2.55 g. (92%), boiling at 147° (0.15 mm.).

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.1; H, 9.2. Found: C, 68.5; H, 9.2.

10-Methyldecalin-1-carbomethoxy-1-acetic Acid (XVI).—To a solution of the diester (2.3 g.) in methanol (13 ml.) was added a solution of potassium hydroxide (0.6 g.) in water (1 ml.). The solution was allowed to stand at room temperature for 3 hours and finally refluxed for 3 hours on the water-bath. The reaction mixture was cooled and excess alkali neutralized with acetic acid. After removal of methanol under suction, the residue was diluted with water and extracted with ether to remove neutral materials. The alkaline solution was acidified whereupon a crystalline solid, 1.8 g. (82.3%), separated out. This on crystallization from ethyl acetate separated as shining needles and melted at 161–162°.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.2; H, 8.9. Found: C, 67.4; H, 9.0.

Methyl 10-Methyl-1-bromomethyldecalin-1-carboxylate (XVII).—The half-ester (1.3 g.) in methanol (50 ml.) was neutralized with 1 *N* sodium hydroxide solution. A little more than the calculated quantity of silver nitrate solution was added with stirring and the white silver-salt precipitated out. The mixture was filtered and the precipitate was thoroughly washed with water and finally dried at 110–120° for 15 hours in vacuum. The silver salt (1.8 g.) was suspended in carbon tetrachloride (35 ml.) and treated with a solution of bromine (0.92 g.) in the same solvent (5 ml.) and worked up as before. The bromo-ester, 1.25 g. (85%), boiled at 135–140° (0.2 mm.).

Anal. Calcd. for $C_{14}H_{23}O_2Br$: C, 55.4; H, 7.5. Found: C, 55.2; H, 7.6.

Methyl 1,10-Dimethyldecalin-1-carboxylate (XVIII).—A mixture of the bromo-ester (1.0 g.), zinc dust (2.0 g.) and acetic acid (17 ml.) was refluxed for 15 hours. The reaction was poured into water while hot and thoroughly extracted with ether. It afforded 0.35 g. (47.4%) which boiled at 120–122° (4 mm.).

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 75.0; H, 10.7. Found: C, 75.1; H, 10.7.

1,10-Dimethyldecalin-1-carboxylic Acid (II).—The ester (*ca.* 0.25 g.), recovered from an unsuccessful attempt at hydrolysis with 10% methanolic potassium hydroxide, was again refluxed for 32 hours with potassium hydroxide (1.5 g.) in methanol (5 ml.). The reaction mixture was diluted with water, and methanol was removed by passing in steam. The alkaline solution was extracted with ether to remove any neutral matter. On acidification with cold hydrochloric acid, it afforded a crystalline acid (*ca.* 0.1 g.). On crystallization from aqueous acetone it afforded small cubes, m.p. 120°.

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.2; H, 10.4. Found:

(24) N. C. Deno and H. Chafetz, THIS JOURNAL, **74**, 3940 (1952).

(25) G. Darzens and M. Moureu, *Compt. rend.*, **133**, 748 (1920).

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Methyl 10-Methyldecalin-1-cyanoacetate (XIX).—To the Grignard reagent prepared from magnesium (4.7 g., 0.193 g. atom) and methyl iodide (12.5 ml., 0.201 mole) in ether (50 ml.), pure benzene (70 ml.) was added. To the hot solution, left after removal of ether from the water-bath, was added cuprous iodide (1.0 g.). The reagent was cooled in ice and the unsaturated cyano-ester XIII (11.8 g., 0.045 mole) in benzene (10 ml.) was added dropwise. The mixture was allowed to stand in an ice-bath for 30 minutes and finally refluxed for 2 hours. The complex was decomposed and the benzene layer was washed with water and 2% sodium bisulfite solution. On removal of the solvent, the residue was dissolved in alcohol (50 ml.) and purified by treatment with a solution of sodium cyanide (5 g.) in aqueous alcoholic solution. On working up the reaction mixture in the usual way, the product (8.5 g.) distilled at 120–170° (1.5 mm.). A high-boiling residue remained in the distillation flask. The distillate (8.5 g.) was hydrolyzed with a solution of potassium hydroxide (12.5 g.) in methanol (125 ml.) at room temperature for 6 hours and on reflux for one hour. On acidification, methanol was distilled off and a neutral material, 3.5 g. (31.1%), was isolated boiling at 135–145° (4 mm.). On acidification of the alkaline extract the cyano-acid (3.5 g.) was re-esterified with an excess of diazomethane. The cyano-ester, 3 g. (26.6%), boiled at 155–160° (1 mm.).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.2; H, 9.2. $C_{16}H_{25}NO_2$: C, 73.0; H, 9.5. Found: C, 72.1; H, 9.0.

The neutral fraction on redistillation boiled at 138–140° (4 mm.).

Anal. Calcd. for $C_{16}H_{27}NO$: C, 77.1; H, 10.8. $C_{17}H_{29}NO$: C, 77.5; H, 11.0. Found: C, 76.7; H, 10.4.

In the infrared, the compound was characterized by strong bands at 3 μ (OH), 4.4 μ (CN) and a doublet at 7.25 and 7.3 μ (*gem*-dimethyl group). There was no absorption in the carbonyl or in the double-bond region.

Three grams of this product was mixed with *phosphorus pentoxide* (4.8 g.) under benzene (20 ml.) and the mixture was refluxed for 2 hours on the water-bath. A yellowish liquid (2 g.) was obtained boiling at 120–125° (3 mm.); λ_{max}^{alc} 220 mμ, log ϵ 3.8.

Anal. Calcd. for $C_{16}H_{25}N$: C, 83.1; H, 10.8; N, 6.0. $C_{17}H_{27}N$: C, 83.2; H, 11.0; N, 5.7. Found: C, 83.3, 82.9; H, 10.7, 10.7; N, 5.8.

10-Methyldecalin-1-acetonitrile (XX).—The cyano-acid (1.5 g.) was heated in an oil-bath at 200–205° for a half-hour until the evolution of carbon dioxide was over. A mobile liquid, 0.7 g. (57.6%), distilled at 128–130° (6 mm.).

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.7; H, 10.9. $C_{14}H_{23}N$: C, 81.9; H, 11.2. Found: C, 82.1; H, 10.5.

ω-(10-Methyldecalin-1)-acetophenone (XXI).—Phenylmagnesium bromide from magnesium (0.88 g., 0.0362 mole) and bromobenzene (5.7 g., 0.0363 mole) was diluted with benzene (15 ml.). On distilling off most of ether a solution of the nitrile (2.4 g., 0.0125 mole) in benzene (10 ml.) was added and the mixture was refluxed for 4 hours. The phenyl ketone, 2.8 g. (83%), was obtained, b.p. 165–170° (0.7 mm.). It formed a **2,4-dinitrophenylhydrazone**, which on crystallization from ethyl acetate afforded orange shining flakes, m.p. 207°.

Anal. Calcd. for $C_{25}H_{30}N_4O_4$: C, 66.6; H, 6.6; O, 14.2. $C_{26}H_{32}N_4O_4$: C, 67.2; H, 6.9; O, 13.8. Found: C, 66.7, 66.6; H, 6.5, 6.3; O, 14.5, 14.4.

The ketone was regenerated from this derivative on treatment with stannous chloride in aqueous acetone.[26]

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.4; H, 9.6. $C_{20}H_{28}O$: C, 84.5; H, 9.8. Found: C, 84.2; H, 9.9.

Ethyl 10-Methyldecalin-1-cyanoacetate (XXIII).—To aluminum amalgam (5.0 g.) under moist ether (300 ml.) was added the unsaturated cyano-ester XIII (5.0 g.). The mixture was allowed to stand for 48 hours with occasional addition of water (5 ml., total 20 ml.). During this period, almost all the aluminum foil had disappeared. The ethereal layer was decanted off. The sludge was dissolved in ice-cold hydrochloric acid and the turbid solution was again extracted with ether. The combined ethereal extracts were worked up and the saturated ester, 4.4 g. (87.3%), was obtained boiling at 147–148° (0.3 mm.).

Anal. Calcd. for $C_{16}H_{28}NO_2$: C, 73.0; H, 9.5. Found: C, 73.2; H, 9.5.

The cyano-acid (2.8 g.) obtained from the alkaline hydrolysis of the cyano-ester XXIII (4 g.) afforded on pyrolysis the nitrile, 1.8 g. (79.4%), b.p. 130° (7 mm.).

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.7; H, 10.9. Found: C, 81.9; H, 10.9.

The nitrile (1.0 g.) yielded the phenyl ketone (1.1 g.), b.p. 150–160° (0.5 mm.). **The 2,4-dinitrophenylhydrazone** melted at 160–165°, which on repeated crystallization from ethyl acetate furnished shining orange flakes, m.p. 205–206°, alone or mixed with sample described before.

Anal. Calcd. for $C_{25}H_{30}N_4O_4$: C, 66.6; H, 6.6. Found: C, 67.0; H, 6.6.

Ethyl 3,3-Dimethylcyclohexylidenecyanoacetate (XXVI).—3,3-Dimethylcyclohexanone[27] (24 g., 0.190 mole) was condensed with ethyl cyanoacetate (46 g., 0.407 mole) as before. The product, 26 g. (62%), was collected at 130–132° (4 mm.).

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.6. Found: C, 70.4; H, 8.9.

Ethyl 1,3,3-Trimethylcyclohexylcyanoacetate (XXVII).—Methylmagnesium iodide from magnesium (4.8 g., 0.197 g. atom) was added to the above ester (11.0 g., 0.049 mole) in the presence of cuprous iodide (1.0 g.) as a catalyst and the expected cyano-ester, 7.5 g. (64.6%), boiled at 138–140° (6 mm.).

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.9; H, 9.7. $C_{13}H_{21}NO_2$: C, 69.9; H, 9.4. Found: C, 71.1; H, 10.0.

(1,3,3-Trimethylcyclohexyl)-acetone (XXIX).—The nitrile (1.7 g., 0.0103 mole) from hydrolysis and decarboxylation of the above cyano-ester (5.0 g.) was converted into methyl ketone by allowing it to react with methylmagnesium iodide from magnesium (0.7 g., 0.0288 g. atom) and methyl iodide (5 g., 0.0352 mole). The ketone (1.3 g., 69.4%) was obtained as a sweet-smelling liquid boiling at 96° (6 mm.).

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.1; H, 12.0. $C_{11}H_{20}O$: C, 78.5; H, 11.9. Found: C, 78.7; H, 12.0.

The semicarbazone was obtained as silky white needles after recrystallization from dilute ethanol; m.p. 165–166°.

Anal. Calcd. for $C_{13}H_{25}N_3O$: C, 65.2; H, 10.4; N, 17.5. $C_{12}H_{23}N_3O$: C, 64.0; H, 10.2; N, 18.6. Found: C, 65.5; H, 10.2; N, 17.7.

Ethyl Decalidene-1-cyanoacetate (XXIV).—α-Decalone (15 g., 0.099 mole) was condensed with ethyl cyanoacetate (20 g., 0.177 mole) under identical conditions and the unsaturated ester, 17 g. (69.7%), was obtained, b.p. 170–172° (4 mm.).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.8; H, 8.5. Found: C, 72.7; H, 8.5.

Ethyl 1-Methyldecalin-1-cyanoacetate (XXV).—Methylmagnesium iodide from magnesium (4.4 g., 0.181 g. atom) was added in the usual way to the above unsaturated cyano-ester (11.4 g., 0.046 mole). The purified product afforded a colorless mobile liquid; 6.5 g. (53.7%), b.p. 150–152° (0.6 mm.).

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 73.0; H, 9.5. $C_{15}H_{23}NO_2$: C, 72.3; H, 9.2. Found: C, 72.9; H, 9.8.

1-Methyldecalylacetone (XXVIII).—The nitrile (1.3 g.) obtained through controlled hydrolysis and decarboxylation of the ester XXV was converted to the methyl ketone, 1 g. (70.6%), as before, b.p. 100–105° (3 mm.).

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.7; H, 11.5. Found: C, 80.9; H, 11.4.

The semicarbazone, was obtained as shining needles after recrystallization from ethanol, m.p. 183–184°.

Anal. Calcd. for $C_{15}H_{27}N_3O$: C, 67.92; H, 10.2. Found: C, 67.98; H, 10.28.

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[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

The Constitution of a Wheat Starch Dextrin[1]

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An "acid converted" wheat starch dextrin of the "canary" type was investigated to determine the structural transformations brought about by the process of dextrinization. The dextrin was subjected to periodate and methylation studies. It is shown that dextrinization of starch involves transglycosidation and the development of a more highly branched structure.

Pyro-dextrins, the gum-like substances extensively used in the adhesives industry, are prepared by pyrolysis of native starches with or without acids under a wide variety of conditions. Although various theories have been advanced,[2-6] little precise information is available concerning the mechanism of the reaction and the structural changes that occur during the dextrinization of starch.

In a previous paper[7] periodate oxidation studies on an "acid-converted" corn starch dextrin showed that the amount (5%) of D-glucose stable to periodate oxidation is greater than in the parent native starch. The methylation results showed[7] (a) that while the hydrolyzate of methylated amylopectin contains 2,3,4,6-tetra-, 2,3,6-tri- and 2,3-di-*O*-methyl-D-glucose and (b) while the hydrolysate of methylated amylose contains 2,3,4,6-tetra- and 2,3,6-tri-*O*-methyl-D-glucose, the hydrolysate from the methylated corn starch dextrin contained ten different methyl derivatives of D-glucose, namely: 2,3,4,6-tetra-, 2,3,6-tri-, 2,3,4-tri-, 2,4,6-tri-, 2,3-di-, 2,6-di-, 3,6-di-, 2-, 3- and 6-*O*-methyl-D-glucose. Although the dextrin was prepared from the native starch, consisting of amylopectin and amylose, the nature and amounts of these ten cleavage fragments seemed to warrant the tentative conclusion that dextrinization not only involves a reduction in the molecular weight of the starch, a fact long recognized from physico-chemical studies, but that in addition, considerable transglycosidation occurs with the production of a highly branched structure.

This paper is concerned with the structural changes that take place when wheat starch is dextrinized in the presence of an acid catalyst, as revealed by methylation and periodate oxidation studies. Investigations into the dextrinization of amylose and of amylopectin are now being carried out, and they will form the subject of later communications.

The wheat starch dextrin was fractionated from aqueous solution with ethanol (Table I) and the major fraction (no. 10) purified by acetylation (Table II).

A sample of the purified dextrin, regenerated from the acetate, was subjected to periodate oxidation (Table III), sodium borohydride reduction and acid hydrolysis.[8] The periodate oxidation studies indicated that the molecule had an average repeating unit of 8 anhydroglucose residues. Since wheat starch, which is a mixture of the linear and branched chain components, has an average repeating unit of 20–25 glucose residues,[9a] it is apparent that a profound change in structure takes place during the dextrinization process. This value of 8 for the average repeating unit of the dextrin agrees reasonably well with the value of 9.5 from the analysis of the acid hydrolysis products of the dextrin polyalcohol which showed that for every molar proportion of glycerol there were 7.5 molar proportions of erythritol and 1 molar proportion of glucose.

In addition, since the wheat starch dextrin contains approximately 10% glucose that is immune to periodate cleavage, it is clear that new linkages must be produced during dextrinization (the original starch has not been investigated, but by analogy with other starches the amount of glucose stable to periodate is probably no more than 0.5%).[8,10]

Treatment of the dextrin first with methyl sulfate and then with silver oxide and methyl iodide furnished the methylated dextrin, which was found to be essentially homogeneous. After methanolysis of the methylated dextrin, followed by acid hydrolysis, the mixture of methylated sugars was separated by partition chromatography on a cellulose–hydrocellulose column[11] using butanone:water azeotrope[12] as the irrigating solvent and the components identified by preparing suitable crystalline compounds (Table IV).

The hydrolyzate from the methylated wheat starch dextrin was found to consist of 2,3,4,6-tetra- (12.2%), 2,3,6-tri- (74.8%), 2,3-di- (3.9%), 2,6-di- (7.9%), 2- (0.9%) and 3-*O*-methyl-D-glucose (0.3%). Since the dextrin was made from native starch, extensive structural deduction cannot be made, but it is apparent, however, from the percentage (12.2) of 2,3,4,6-tetra-*O*-methyl-D-glucose, that the dextrin must be much more highly branched than the parent wheat starch. It is noticeable that the amounts of tetra- and di-*O*-methylglucose are approximately the same, a result required by the general structural concept that the

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number of terminal, non-reducing ends should be the same as the number of branches in the molecular complex. Since the tetra-*O*-methyl-D-glucose arises from those glucose units which give rise to formic acid upon periodate oxidation, it is of interest to note that the average repeating unit (8) from periodate oxidation studies agrees with the value (8.3) from methylation studies.

The characterization of 2,6-di-*O*-methyl-D-glucose in relatively large amounts (7.9%) reveals the fundamental difference in structure between the dextrin and the parent starch since the methylated starch does not give rise to appreciable amounts of 2,6-di-*O*-methyl-D-glucose.[9a,c,9b,9c] This finding also shows that the dextrinization process not only causes degradation of the starch molecule but that it must also involve the generation of new 1,3-glycosidic linkages. The same phenomenon was observed in the previous studies on the "acid converted" corn starch dextrin.[7] The presence of these 1,3-linkages in the dextrin is also supported by the fact that the parent dextrin contains approximately 10% glucose that is immune to periodate oxidation.

Although the fraction of the wheat starch dextrin subjected to study comprised only 37% of the original dextrin, it seems likely that the same general transformations during dextrinization would be revealed by studies of the other dextrin fractions; the correctness of this view will form the subject of a later investigation.

From the above results, therefore, it seems reasonable to deduce that the physical properties of the dextrins, especially their adhesive, gum-like properties and solubility characteristics, must be attributed, at least in part, to the fact that the dextrins have a highly branched structure, the building units of which are mutually joined by a wide variety of glycosidic bonds.

Experimental

The partition chromatographic analyses were carried out with solvent A, butan-1-ol:ethanol:water (4:1:5),[13] solvent B, butanone:water azeotrope[12] or solvent C, propan-1-ol:water azeotrope.[14] The spray reagent used for the development of color with glucose methyl ethers was *p*-anisidine:trichloroacetic acid:water (1:5:250).[15] Unless stated otherwise all concentrations were carried out *in vacuo* at a bath temperature of 45–50°.

Preparation of the Wheat Starch Dextrin.—Commercial wheat starch was heated for 3 hr. at 120° and then for 5 hr. at 140° in the presence of 2 *N* hydrochloric acid added previously as a spray with mixing. The amount of 2 *N* acid used per gram of starch corresponded to that required to give a *p*H of 3 when added to a mixture of starch (1 part) and water (2 parts); this was predetermined in a separate experiment. The "canary" dextrin so obtained had a slight yellow color, and 95% of it was soluble in water.

Fractional Precipitation of the Wheat Starch Dextrin.—The dextrin (50 g. as prepared and without pre-drying) was dissolved in water (200 ml.) and fractionally precipitated by the addition of increasing amounts of ethanol. Each fraction was redissolved in water and the solution poured with stirring into an excess of ethanol. The white amorphous precipitate was removed by centrifugation and washed successively with ethanol, ethyl ether and light petroleum ether and then dried *in vacuo* at 50°. The results of this fractionation are recorded in Table I.

Table I

Fractional Precipitation of Dextrin from Aqueous Solution with Ethanol

Fraction no.	1	2	3	4	5	6	7	8	9	10	11	12
Wt., g.	1.5	2.4	2.2	2.6	0.6	1.0	0.4	1.7	7.1	18.5	2.1	5.8
Total ethanol added, ml.	7	17	37	52	72	92	112	137	157	207	257	307
Color with iodine[a]	P	P	P	P-L	P-L	P-L	P-L	L	L	L	L-R	R
$[\alpha]^{25}D$ (H_2O), *c* 1)	+175°	+153°	+153°	+154°	+155°	+158°	+162°	+160°	+156°	+130°	+122°	+121°

[a] P = Purple; L = Lavender; R = Red-brown.

Acetylation of Starch Dextrin.—A solution of the dextrin (17.6 g., fraction 10, Table I) in formamide (100 ml.) was slowly added, with stirring during 3 hr., to a mixture of pyridine (100 ml.) and acetic anhydride (100 ml.) cooled in an ice-bath.[16] After standing for 10 hr. at room temperature the reaction mixture was poured, with stirring, into 8–10 volumes of ice-water to precipitate the acetate. The white amorphous precipitate was filtered, washed successively with absolute ethanol, ether and petroleum ether and dried *in vacuo*. The acetylated dextrin (yield 24 g.) showed $[\alpha]^{25}D$ +158° in chloroform (*c* 0.6). After reacetylation with 5 parts of pyridine–acetic anhydride (1:1) for 3 hr. at 55°, the dextrin acetate (23.5 g.) showed $[\alpha]^{25}D$ +155° in chloroform (*c* 0.6).

The acetyl value was determined by dissolving a sample of the acetylated material in a small volume of acetone, adding an excess of 0.1 *N* NaOH and warming for 2 hr. at 50°. After cooling, the excess alkali was back titrated with 0.1 *N* sulfuric acid; a blank was carried out at the same time (Found: Ac, 44.7%).

The acetylated dextrin (18.5 g.) was fractionally precipitated from chloroform solution by adding increasing quantities of petroleum ether in the usual manner. The results are given in Table II.

Table II

Fractional Precipitation of Dextrin Acetate

Fraction no.	1	2	3	4	5	6
Total petr. ether added, ml.	10	35	55	75	115	145
Wt., g.	9.2	1.5	2.0	2.4	2.3	0.4
$[\alpha]^{25}D$ ($CHCl_3$, *c* 1)	+158°	+156°	+157°	+151°	+166°	...

Fractions 1, 2 and 3, being essentially the same, were combined and used for the experiments which follow.

Deacetylation of Dextrin Acetate.—A solution of the acetate (3 g.) in 10% (w./w.) aqueous potassium hydroxide (10 ml.) and acetone (15 ml.) was stirred for 1 hr. at room temperature and for 0.5 hr. at 50°. The solution was cooled, neutralized with acetic acid and poured into ethanol. The dextrin precipitate was collected (centrifuge), redissolved in water, reprecipitated with ethanol as before and finally dried *in vacuo* at 45°, giving a white amorphous powder which had $[\alpha]^{24}D$ +132° in water (*c* 0.6).

Periodate Oxidation of Wheat Starch Dextrin.—The dextrin fraction (0.9 g.) was oxidized with 0.1 *N* sodium periodate (100 ml.) at 5° in the dark and aliquots of the reaction solution periodically withdrawn in order to follow

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the rate of periodate consumption and formic acid production in the usual way.[17] Blank experiments were conducted at the same time. The results are summarized in Table III.

TABLE III

PERIODATE OXIDATION OF STARCH DEXTRIN

Reacn. time, hr.	$[\alpha]^{25}D$	Mols. of anhydrohexose per mol. of formic acid produced	Mols. of periodate consumed per mol. anhydrohexose unit
0.08	+77°	25.9	0.66
52	+19	12.7	1.01
138	+19	9.0	1.06
213	+18	7.9	1.06

Reduction of the Periodate Oxidized Dextrin with Sodium Borohydride.—The periodate oxidation reaction mixture was treated with barium chloride solution to precipitate the iodate and excess periodate and the solution centrifuged. Four times the theoretical amount of sodium borohydride was then added to the supernatant solution at room temperature to reduce the dextrin polyaldehyde. The solution was agitated periodically for 3 hr., after which time the evolution of hydrogen ceased and the reduced polysaccharide slowly precipitated from the solution. The precipitated dextrin polyalcohol was removed from the solution, washed with cold ethanol, redissolved in water and reprecipitated with alcohol. The material was then acidified with acetic acid and evaporated to dryness to decompose the residual borohydride. Methanolic hydrogen chloride (30 ml. of 1%) was added, and after shaking for 5 minutes the solution was evaporated *in vacuo* at 40° (bath temperature) to remove borate.[18] The residue was retreated with 1% methanolic hydrogen chloride to ensure complete removal of borates. The dextrin polyalcohol was hydrolyzed by treatment with 0.5 *N* HCl at room temperature for 2 hr. with constant stirring followed by warming at 50° for 1 hr.

The hydrolysis solution was neutralized with $BaCO_3$, filtered and passed through Amberlite IR-120 cation and then through Duolite A_4 anion exchange resin to remove inorganic ions, and evaporated to a sirup. The hydrolyzate showed $[\alpha]^{25}D$ +8.5° in water (*c* 2.7).

Determination of Glucose, Erythritol and Glycerol in the Dextrin Polyalcohol.—A small portion of the sirupy hydrolysate of the dextrin polyalcohol was placed on Whatman No. 1 filter paper and developed with solvent C. Glucose, erythritol and glycerol were located in the boundaries of the paper and the three compounds were then quantitatively separated and eluted from the paper with a known volume of water.[19]

The quantitative determination of glucose was carried out colorimetrically with the phenol–sulfuric acid reagent,[20] and chromotropic acid was used for the quantitative determination of glycerol and erythritol.[21,22]

The molar ratios of glucose:erythritol:glycerol in the hydrolysate of the dextrin polyalcohol was found to be 1.0: 7.5:1.0, respectively.

Methylation of Dextrin Acetate.—Wheat dextrin acetate (8.5 g.) was dissolved in acetone (190 ml.) and methylated with methyl sulfate (90 ml.) and sodium hydroxide (250 ml. of 30%) according to the method of Haworth.[23] The reaction was completed by heating for 0.5 hr. on the boiling water-bath when the methylated dextrin separated readily from the reaction mixture. This precipitate was washed by decantation with boiling water to remove salts and then dissolved in acetone in preparation for the next methylation. The mother liquor was extracted with chloroform and the combined extracts dried (Na_2SO_4) and concentrated. The residue was dissolved in acetone and added to the acetone solution of that portion of the dextrin that precipitated from the reaction mixture. Three additional methylations were applied as above, and the product was isolated each time by heating the reaction mixture (chloroform extraction was not necessary).

The methylated dextrin was subjected to three treatments with Purdie reagents using silver oxide (6 g.) and methyl iodide (30 ml.), the reaction mixture being refluxed for 18 hr. After recovering the excess of the methyl iodide, the product was isolated by extraction with acetone, traces of silver iodide being removed by centrifugation. Evaporation gave the methylated dextrin as a brown sirup (4.20 g.).

Fractional Precipitation of Methylated Dextrin.—The methylated dextrin (4.10 g.) was dissolved in acetone (40 ml.) and fractionally precipitated by adding petroleum ether in the usual way. Examination of the five fractions obtained in this manner showed that the product was essentially homogeneous; $[\alpha]D$ +182° in chloroform (*c* 1). Found: OMe, 43.5.

Methanolysis of Methylated Dextrin.—The methylated dextrin (3.30 g.) from a composite of fractions 2, 3 and 4 above was refluxed for 10 hr. with 2.5% methanolic hydrogen chloride. After 3 hr. the rotation of the solution became constant, $[\alpha]^{24}D$ +85° in methanol (*c* 3).

The solution was neutralized (Ag_2CO_3), filtered and the clear yellow solution evaporated with a current of air to avoid possible loss of the methyl 2,3,4,6-tetra-*O*-methyl-D-glucoside. Any residual solvent was removed *in vacuo* at 40°.

Separation of the Cleavage Products of the Methylated Dextrin.—The methyl glycosides (3.42 g.) were heated at 98° with *N* H_2SO_4 (40 ml.) for 19 hr. The solution became cloudy upon adding the acid, and the initial rotation could not be determined, but after 1 hr. it showed $[\alpha]^{25}D$ +49.5° and did not appear to change thereafter. The solution was neutralized ($BaCO_3$), filtered and the residue washed with water. The filtrate and washings were combined and extracted twice with chloroform. The sirup (1.75 g.) from the combined chloroform extracts and that (1.43 g.) from the aqueous layer were separately subjected to partition chromatography on a cellulose–hydrocellulose column using solvent B, the fractions being collected in test-tubes using an automatic fraction collector, during a period of 120 hr.[11]

The methylated sugars were isolated by concentrating the appropriate fractions and provisionally identified by paper chromatography using solvents A, B and C in the usual way. Results of the column chromatography are recorded in Table IV.

TABLE IV

COLUMN CHROMATOGRAPHY OF THE HYDROLYSATE OF METHYLATED STARCH DEXTRIN

Component	Identity of *o*-methyl-D-glucose	*Rf*[a]	Wt., g.	Ratio (approx.) Mole	Ratio (approx.) %
1	2,3,4,6-Tetra-	0.82	0.373	31.5	12.2
2	2,3,6-Tri-	.51	2.290	208	74.8
3	2,3-Di-	.18	0.119	11.5	3.9
4	2,6-Di-	.15	.240	23	7.9
5	2-	.042	.029	3	0.9
6	3-	.062	.010	1	0.3
		Total	3.061[b]		

[a] By paper chromatography with solvent B. [b] Recovery = 96%.

Identification of Cleavage Products of Methylated Dextrin. 1. 2,3,4,6-Tetra-*O*-methyl-D-glucose.—Component 1 (Table IV, 0.373 g.) crystallized spontaneously upon removal of the solvent and after recrystallization from ethyl ether gave 2,3,4,6-tetra-*O*-methyl-α-D-glucose, m.p. 89°, mixed m.p. 88–89°, $[\alpha]^{24}D$ +81.5° equilibrium value in water (*c* 5); lit.[24] m.p. 88–89°, $[\alpha]D$ +83.3° in water. To a solution of the tetra-*O*-methyl-D-glucose (20.7 mg.) in dry pyridine (2 ml.), was added *p*-nitrobenzoyl chloride (48.3 mg.). The mixture was heated at 80–85° (bath temperature) for 40 min. After cooling, a few drops of water was added to the reaction mixture which was then poured into a cold, saturated, sodium bicarbonate solution (10 ml.). Extraction of the product with chloroform and crystallization from aqueous methanol gave the mono-*p*-nitrobenzoate of

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2,3,4,6-tetra-*O*-methyl-D-glucose, m.p. and mixed m.p. 101–102°; lit.[25] m.p. 102°.

2. **2,3,6-Tri-*O*-methyl-D-glucose.**—Component 2 (Table IV, 2.29 g.) crystallized spontaneously and after recrystallization from ethyl ether, gave 2,3,6-tri-*O*-methyl-D-glucose, m.p. and mixed m.p. 112–115°, $[\alpha]^{24}D$ +62° equilibrium value in water (*c* 1); lit.[26] m.p. 121–123°, $[\alpha]D$ +70.5° equilibrium value in water. Treatment of the trimethyl sugar with *p*-nitrobenzoyl chloride in the usual way[27] gave the 1,4-di-*p*-nitrobenzoate of 2,3,6-tri-*O*-methyl-D-glucose, m.p. and mixed m.p. 190–191°, $[\alpha]^{24}D$ −32° in chloroform (*c* 2); lit.[27] m.p. 189–190°, $[\alpha]D$ −33° in chloroform.

3. **2,3-Di-*O*-methyl-D-glucose.**—Component 3 (Table IV, 0.119 g.) crystallized spontaneously from ethyl ether and methanol, giving 2,3-di-*O*-methyl-D-glucose, m.p. and mixed m.p. 85–86°, $[\alpha]^{24}D$ +49° in methanol (*c* 4); lit.[28] m.p. 85–87°, $[\alpha]D$ +48.3° in acetone. Treatment with aniline gave the characteristic N-phenyl-D-glucopyranosylamine 2,3-dimethyl ether, m.p. and mixed m.p. 134°, $[\alpha]^{22}D$ −83° in chloroform (*c* 4) (after recrystallization from ethyl acetate); lit.[29] m.p. 134°.

4. **2,6-Di-*O*-methyl-D-glucose.**—Component 4 (Table IV, 0.240 g.), a sirup, showed $[\alpha]^{24}D$ +63° equilibrium value in water (*c* 5); lit.[30,31] $[\alpha]D$ +63.3° in water. Chromatographic analysis using solvents A and B indicated that it was 2,6-di-*O*-methyl-D-glucose. Treatment with *p*-phenylazobenzoyl chloride in pyridine gave the 1,3,4-triazobenzoate of 2,6-di-*O*-methyl-D-glucose, m.p. and mixed m.p. 202–206° (after recrystallization from ethyl acetate–petroleum ether), $[\alpha]^{23}D$ −260° in chloroform (*c* 0.1); lit.[31] m.p. 205–207°, $[\alpha]_{6252}$ −275° in chloroform.

5. **2-*O*-Methyl-D-glucose.**—Component 5 (Table IV, 0.029 g.) crystallized spontaneously and afforded 2-*O*-methyl-D-glucose, m.p. and mixed m.p. 157–158°, $[\alpha]^{24}D$ +65° equilibrium value in water (*c* 1) (after recrystallization from ethanol); lit.[32–34] m.p. 157–158°, $[\alpha]$ +66° equilibrium value in water.

6. **3-*O*-Methyl-D-glucose.**—Component 6 (Table IV, 0.01 g.) crystallized spontaneously from ethanol and appeared to be essentially pure 3-*O*-methyl-α-D-glucose, m.p. and mixed m.p. 157–158°, $[\alpha]^{24}D$ +56° equilibrium value in water (*c* 1); lit.[23,35] m.p. 161°, $[\alpha]D$ +55.5° equilibrium value in water.

In addition to the six components identified above, column chromatography of the hydrolysate of the methylated dextrin yielded 10 mg. of material whose R_f value, 0.062, corresponded to D-glucose. However, the substance failed to crystallize, and since its rotation, $[\alpha]^{24}D$ +17° in water (*c* 0.2), showed that only one-third of it could be D-glucose, it was not examined further.

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ST. PAUL, MINNESOTA

[CONTRIBUTION FROM PULP MILLS RESEARCH AND THE DEPARTMENTS OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF WASHINGTON]

Lignin. VIII. Molecular Weights of Lignin Sulfonates during Delignification by Bisulfite–Sulfurous Acid Solutions

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The average molecular weight has been estimated of the sodium lignin sulfonates dissolved from hemlock, spruce and maple woods into bisulfite–sulfurous acid solutions after several periods of treatment at elevated temperatures. With the gymnosperm woods, it is found that lower molecular weight lignin sulfonates are obtained first, and then as the time of treatment is extended, the average molecular weight of the dissolved lignin sulfonates increases to a maximum, decreases to a minimum and finally begins to rise again. These changes are attributed to the effects of the following three processes which are thought to be proceeding simultaneously but at different rates: hydrolysis of hydrolyzable bonds in the lignin polymer, polycondensation of some lignin molecules with others and diffusion of soluble lignin sulfonates from the wood tissue into solution. With maple wood, the molecular weights of the dissolved lignin sulfonates obtained are about constant and strikingly smaller than those observed for the gymnosperm lignins].

Introduction

In prior reports from this Laboratory, diffusion[2a] and light scattering[2b] methods have been described for the estimation of the average molecular weights of lignin sulfonate preparations. Fractionation of such preparations followed by estimation of the molecular weights of the lignin sulfonates in the resultant fractions has provided information concerning the distribution in lignin sulfonate molecular weights.[2c] Since these distributions were found to be somewhat different for several preparations examined, the present research was undertaken to obtain more knowledge concerning the average molecular weights and the distribution in molecular weights of lignin sulfonates which exist at various stages of delignification of wood by use of bisulfite–sulfurous acid solutions.

Experimental

A description previously has been given[2b] of the preparation of the Western Hemlock wood meal (*Tsuga heterophylla;* 10 to 30 mesh; ethanol–benzene and hot water extracted; 6.14% H_2O and 5.15% OCH_3) used for the experiments. Delignifications were carried out by sealing into a Pyrex tube 1.00 or 4.50 g. of wood meal with ten times its weight of an aqueous solution which contained 50 g. of SO_2/liter and 9.67 g. of Na_2O/liter for series I, and 90 g. of SO_2/liter and 9.67 g. of Na_2O/liter for series II. Each bomb was placed in a steel tube which was closed, fastened to a "Ferris" wheel in an oil-bath at 135° (±0.1°) and rotated

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TABLE I

DELIGNIFICATION OF HEMLOCK WOOD WITH SODIUM BISULFITE–SULFUROUS ACID SOLUTIONS (4% "FREE" SO_2)

Reaction time, hr.	Wood residue: Yield, %	Wood residue: OCH_3, %	Wood residue: Delig.,[a] %	Solutions: pH[b]	Solutions: $\lambda_{min.}$,[d] Å.	Solutions: A_{2800}	Solutions: $A_{2800}/A_{min.}$	Solutions: A_{2800}/A_{3100}	Solutions: D_A, $10^7 \times$ cm.^{2} sec.$^{-1}$	Solutions: Estim. mol. wt.
0.5	86.5	4.75	20.3	..	2580	83	1.67	4.72	25.9	3,000
1.0A	76.7	4.64	30.8	5.76	2600	137	1.50	4.39	23.4	4,200
1.0B	76.6	..	..	..	2600	138	1.53	4.16	..	....
3.0A	56.0	2.28	75.2	5.45	2600	342	1.47	3.75	15.8	11,000
3.0B	53.0	..	..	..	2600	386	1.44	3.68	..	....
6.0A	45.5	..	..	..	2600	477	1.49	3.82	16.9	10,000
6.0B	45.8	0.49	95.7	5.86[c]	2605	475	1.48	3.57	16.8	10,000
9.0	44.2	0.22	98.1	4.22[c]	2605	508	1.49	3.64	18.1	9.000
12.0A	41.9	0.11	99.1	1.98	2620	570	1.35	3.05	21.3	5,500
12.0B	42.1	..	..	..	2620	555	1.36	3.26	..	....
15.0A	40.0	0.08	99.4	1.80[c]	2620	626	1.29	2.54	22.2	5,000
15.0B	41.5	..	..	1.80	2620	625	1.29	2.67	21.3	5,500
20.0	40.1	0.075	99.4	1.70	2625	760	1.18	2.22	20.3	6,500

[a] Delignification percentage = 100 − (% OCH_3)(% yield of wood residue)/(5.15). [b] Recorded pH values are those found for a tenfold diluted and steam-stripped solution. [c] Sulfate in samples 6.0B, 9.0 and 15.0A was 0.0, 0.28 and 1.92 g. of SO_3/liter, respectively. [d] λ_{min} = wave length of minimum ultraviolet absorption near 2600 Å.

TABLE II

DELIGNIFICATION OF HEMLOCK WITH SODIUM BISULFITE–SULFUROUS ACID SOLUTIONS (8% "FREE" SO_2)

Reaction time, hr.	Wood residue: Yield, %	Wood residue: OCH_3, %	Wood residue: Delignif.,[a] %	Solutions: pH[a]	Solutions: $\lambda_{min.}$,[a] Å.	Solutions: A_{2800}	Solutions: $A_{2800}/A_{min.}$	Solutions: A_{2800}/A_{3100}	Solutions: D_A, $10^7 \times$ cm.^{2} sec.$^{-1}$	Solutions: Estim. mol. wt.
0.5A	76.7	..	..	5.91	2585	140	1.51	4.00	21.1	5,700
0.5B	74.7	..	..	..	2590	142	1.55	4.27	22.1	5,000
1	63.5	3.44	57.5	5.64	2600	256	1.48	3.68	17.9	9,200
2	49.6	1.08	90.4	5.92	2600	461	1.46	3.64	17.0	10,000
3A	44.7	0.56	95.1	5.82[b]	2600	471	1.48	3.66	16.0	11,000
3B	44.5	..	..	..	2600	489	1.49	3.62	15.4	12,000
4.5	43.5	..	98.7	5.54	2610	510	1.48	3.59	..	....
6	44.3	0.15	99.5	2.84	2610	520	1.50	3.53	19.1	7,700
9	40.5	0.067	99.6	1.84	2615	594	1.32	2.90	22.5	4,700
10	40.4	..	..	..	2620	650	1.26	2.58	22.5	4,700
12	39.2	..	..	1.53[b]	2625	700	1.18	2.33	22.9	4,500
15A	39.5	0.035	99.7	1.62	2650	837	1.10	2.01	18.2	9,000
15B	36.3	..	..	..	2650	840	1.09	2.01	18.2	9,000
17	34.7	..	..	1.35	2650	866	1.07	1.91	17.7	9,500
18	33.8	..	..	1.39	2650	878	1.05	1.92	18.7	8,200

[a] Same as footnotes *a*, *b* and *d* for Table I. [b] Sulfate in samples 3A and 12 was 0.34 and 1.89 g. SO_3/liter, respectively.

at 25 r.p.m. for the desired time. The bombs were cooled, opened and the contents were filtered. The wood residues were washed with distilled water, dried overnight at 60° and 1 mm. pressure, then weighed and analyzed. The filtrates and washings were combined, diluted with distilled water to about 100 times the original wood weight, then stored at 3° after adding a few drops of toluene to prevent or minimize microörganism action (Tables I and II).

For the experiments with spruce (*Picea sitchensis*) and maple (*Acer saccharum*), small air-dry wood blocks obtained from Professor H. D. Erickson of the College of Forestry of this University were reduced to a fine meal by use of a cross cut saw. Delignifications were conducted using solutions containing 41.2 g. of SO_2/liter and 10.2 g. of Na_2O/liter at 135° (±0.1°) for various periods of time (Table III).

One sample of the hemlock lignin sulfonates was fractionated. Preliminary to this fractionation, toluene was evaporated from an aliquot of the solution containing the lignin sulfonates, and metal cations were then removed using a Dowex 50 resin column. The solution was then extracted five times with ether to remove such non-lignin substances as conidendrin and furfural which absorb ultraviolet radiation, and residual ether and sulfurous acid were removed under vacuum. Usually the solution was neutralized to pH 5, vacuum evaporated to 50 ml., then concentrated to 10 ml. or less in a vacuum desiccator over $CaCl_2$.

For fractionation, a 7-ml. aliquot was weighed exactly and added to a culture tube (1.5″ × 7″) containing 300 mg. % of crystalline NaCl. To secure the first fraction, at 25 ± 0.1°, 133 ml. of dry ethanol was added dropwise with vigorous stirring which was continued for an additional five minutes. The contents were then transferred to a centrifuge bottle and centrifuged for about five minutes after which the clear solution was poured off, vacuum evaporated at 50° with periodic additions of distilled water to complete ethanol removal and then made to 50 ml. with distilled water and designated as fraction A. Precipitate in the culture tube was then dissolved in 10 ml. of 0.5 *N* NaCl and combined with that in the centrifuge bottle, and the fractionation of this solution was then continued in general as already described with appropriate ethanol additions, and the results as well as final alcohol concentrations are given in Table IV.

Analyses for methoxyl were conducted by the Zeisel method. Ultraviolet absorbances were determined from 2500 to 3100 Å. at 50-Å. intervals on aliquots of lignin sulfonate solutions from which sulfur dioxide had been removed and after dilution such that absorbance was not more than about 0.80. Lignin sulfonate concentrations were estimated for the experiments with spruce and maple from measurements of absorption at 2800 Å. Two absorptivity ratios, A_{2800} Å./$A_{min.}$ and A_{2800}Å./A_{3100} Å., were calculated. The acidity of some of the samples weas measured after expelling sulfur dioxide and diluting ten times. Sulfate in certain samples was determined by a conductometric method.[3]

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TABLE III

ESTIMATED MOLECULAR WEIGHTS OF SPRUCE AND MAPLE LIGNIN SULFONATES DURING DELIGNIFICATION

Delignif. time, hr.	Lignin dissolved,[a] % A[c]	B[c]	Est. $D_A \times 10^7$, cm.²/sec. A	B	Est. NaLS mol. wt.[b] A	B
			Spruce (*Picea sitchensis*)			
0.5	19	20	..	28.8	....	2300
1.0	31	27	26.8	23.5	2800	4200
2.0	53	43	20.0	22.4	5900	4800
4.0	80	78	14.2	15.8	14,000	11,000
6.0	91	91	13.9	16.5	14,000	11,000
8.0	100	97	18.3	20.6	8,800	6,200
			Maple (*Acer saccharum*)			
0.5	18	15	35.7	39.9	1200	800
1.0	27	26	38.0	34.5	1000	1300
2.0	48	53	38.1	32.3	1000	1600
4.0	73	79	33.1	29.5	1500	2100
6.0	87	87	41.4	34.5	700	1300
8.0	97	98	38.2	31.6	1000	1700

[a] Estimated from the absorbance of the lignin sulfonate solutions for 2800 Å radiation. [b] Diffusion coefficients are D_A averages for solutes absorbing 2800 Å. radiation. Molecular weights have been estimated from D_A using a previously reported correlation.[2b] [c] A and B designate results of duplicate experiments.

Discussion

The degrees to which lignins were removed from hemlock wood by treatment with sodium bisulfite–sulfurous acid solutions have been estimated from determinations of methoxyl in the original wood and in the wood residues (Tables I and II) assuming that the methoxyl content of lignin or lignin sulfonates is approximately constant. As shown in Fig. 1, delignification of hemlock is nearly completed after about 8 hr. treatment at 135° where the solution contains about 4.0% "free" SO_2 or after about 3 hr. with 8.0% "free" SO_2.

The several hemlock lignin sulfonate solutions obtained were diluted appropriately, absorbances for 2800 Å. radiation were measured and the absorbances were calculated back to the uniform basis of the undiluted reaction mixture. These absorbances are plotted in Fig. 2 against the degree of delignification estimated from methoxyl. An apparently linear relationship is obtained up to about 90 or 95% delignification indicating that, within this range, the absorptivities of lignin sulfonates on a methoxyl basis are approximately constant and thus that the degree of delignification can be estimated from measurements of ultraviolet absorbance.

TABLE IV

ESTIMATED DISTRIBUTIONS IN MOLECULAR WEIGHTS OF CERTAIN HEMLOCK LIGNIN SULFONATES (8% "FREE" SO_2)

Sample fraction[a]	0.5B Σw_i,[b] %	D_A[c]	Estim. mol. wt.	3.0B Σw_i,[b] %	D_A[b]	Estim. mol. wt.	10.0 Σw_i,[b] %	D_A[c]	Estim. mol. st.	15.0B Σw_i,[b] %	D_A[c]	Estim. mol. wt.
A	31.4	31.9	1,600	15.6	41.3	800	17.1	41.9	730	14.3	39.1	900
B	45.8	27.4	2,600	31.2	25.3	3,300	33.2	29.4	2,100	27.1	31.7	1,700
C	54.3	23.8	4,000	41.4	19.8	7,000	44.7	25.2	3,300	35.8	27.8	2,500
D	69.4	21.4	5,500	61.1	17.3	10,000	68.3	16.8	10,000	51.7	18.7	8,200
E	81.6	15.7	12,000	82.7	10.9	22,000	83.6	13.5	15,000	64.5	16.9	10,000
F	88.0	11.8	19,000	92.3	7.8	40,000	89.0	11.4	20,000	70.9	12.5	17,000
G	91.8	10.6	23,000	98.8	4.4	100.000	93.3	9.5	28,000	82.4	11.4	20,000
H	96.9	10.5	23,000	99.3	..	....	95.8	12.4	17,000	100.6	10.9	22,000
$(\Sigma w_i D_i^{-0.5})^{-2}$	..	21.3[d]	5,600[e]	..	14.9[d]	13,000[e]	..	19.9[d]	7,000[e]	...	17.9[d]	9,300[e]
Unfractd.	..	22.1	5,000	..	15.4	12,000	..	22.5	4,700	...	17.7	9,500

[a] For fractions A, B, C, D, E, F and G final ethanol concentrations were 95, 90, 85, 80, 76, 73 and 70% by volume, respectively. H designates the material insoluble in 70% ethanol. [b] Weight percentages of lignin sulfonates in fractions were estimated from absorbances observed at 2800 Å. [c] Units of D_A are $10^7 \times$ cm.²/sec. [d] Average D_A for unfractionated samples estimated from values found for fractions. [e] Average molecular weight for unfractionated sample estimated from average D_A calculated from values found for fractions.

Diffusion coefficients,[2a] "D_A," of the sodium lignin sulfonates of Tables I and II were measured by a solution-to-gel method at 25° in 0.02 *M* NaCl after the samples had been de-ashed, extracted with ether, neutralized and then evacuated; the samples of Table III were prepared for diffusion by pulling air through the solutions for at least 24 hr.: for Table IV, diffusions were carried out on the final fractionated samples after ethanol removal. Molecular weights were estimated from diffusion coefficients using a previously developed correlation.[2b]

The relationship between the average diffusion coefficient, D_A, and the diffusion coefficient for an individual molecular species, D_i, is

$$\frac{1}{D_A^{0.5}} = \Sigma_{(wi}\left(\frac{1}{D_i^{0.5}}\right)$$

where w_i = weight fraction of i-th species. The approximate relation between D_i and the molecular weight, M_i, is

$$D_i \cong \frac{b}{M_i^{1/a}}$$

where b and a are constants. Thus the particular average molecular weight, M_A, obtained in the present work is, approximately

$$M_A = [\Sigma(w_i)(M_i)^{0.5a}]\ 2/a \cong [\Sigma(w_i)(M_i)^{1.5}]^{0.67}$$

since $a \cong 3$.

On this basis lignin removals from spruce and maple woods were also estimated (Table III) and the rates of delignification found (Fig. 1) are roughly as expected for the concentration of about 3.1% "free" SO_2 which was used in the delignification solution.

The yield of hemlock wood residue decreases and approaches a limiting asymptotic value as delignification proceeds. However, when delignification is almost completed and this limiting value is nearly reached, the percentage of wood residue begins to decline again and continues to decline at a somewhat increased rate (Fig. 1). This increased degradation and solution of the carbohydrate residue is caused by a large increase in the acidity of the delignification solution as reflected in the *p*H values given in Tables I and II. The increase in acidity is in turn caused at least largely by formation of sulfate which is shown by analyses to be present at a much higher concentration after the acidity increase than before. Corresponding with this in-

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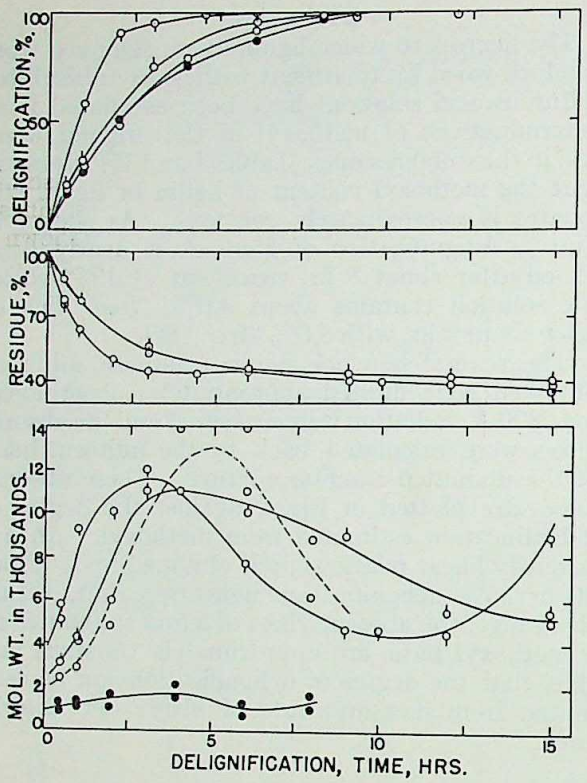

Fig. 1.—Percentage delignification and wood residue and average molecular weights of dissolved lignin sulfonates after various times of delignification with sodium bisulfite–sulfurous acid solutions: O, spruce, 3.1% "free" SO_2; ♂, hemlock, 4.0% "free" SO_2; ♀, hemlock, 8.0% "free" SO_2; ●, maple, 3.1% "free" SO_2.

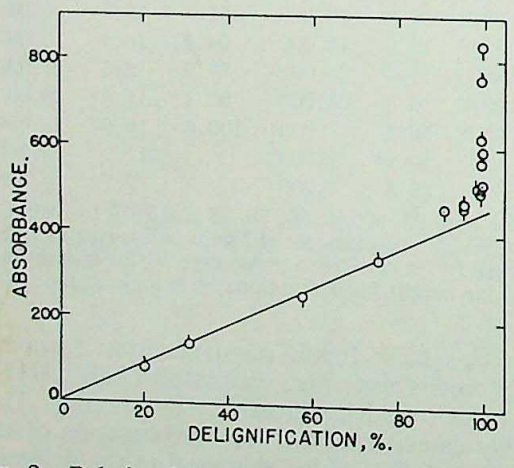

Fig. 2.—Relation between percentage delignification of hemlock and solution absorbance at 2800 Å.: ♂, 4.0% "free" SO_2; ♀, 8.0% "free" SO_2.

creased acidity is a substantial increase in absorbance (Fig. 2) which may arise from lignin hydrolysis or condensation reactions or formation of such sugar derivatives as furfural and hydroxymethylfurfural which absorb ultraviolet radiation.[4]

Examination of the ultraviolet absorption spectra of the several solutions showed that the usual spectra[2] was obtained for the samples up to about 90% delignification. The wave length of the minimum absorption was about 2580 Å. in the first samples obtained and this shifted to longer wave lengths as delignification proceeded. The absorptivity ratios, $A_{2800\ Å.}/A_{2600\ Å.}$ and $A_{2800\ Å.}/A_{3100\ Å.}$, were largest in the first samples obtained and decreased and became nearly constant as treating time was extended toward completion of delignification, thus indicating an increase in molecular weight in view of prior work.[2c] However, after the solutions underwent the substantial increase in acidity, the values for the ratios again decreased.

The average molecular weights of the dissolved lignin sulfonates in the several solutions were estimated from diffusion coefficients, and the results are given in Tables I–III and are graphed in Fig. 1. With hemlock and spruce woods, it is found that the molecular weights of the lignin sulfonates first obtained are about 2000–4000. As delignification proceeds, the molecular weight increases and reaches a maximum value in the range of about 11,000 when the delignification has been nearly completed. Continuation of treatment brings about a decrease in molecular weight to a minimum value of about 5000 and thereafter an increase is again observed. Similar trends were observed at concentrations of 40, 50 and 90 g. total SO_2/liter, although the changes occurred more rapidly in the solutions of higher acidity.

With maple wood, the molecular weight of the lignin sulfonates is found to be strikingly smaller, *i.e.*, of the order of 1000–1500. These values remain nearly constant as the time of treating is increased. In prior work in this Laboratory by Dr. J. C. Aggarwala similar low average molecular weights have been indicated for the lignin sulfonates from a bamboo (*Dendrocalamus strictus*), since it was found[5] that only some 15% of the original methoxyl remains associated with the non-dialyzable bamboo lignin sulfonates, whereas around 50% of the methoxyl in gymnosperm lignin sulfonates is usually non-dialyzable.

The lignin sulfonate samples obtained in one set of experiments with hemlock wood were fractionated by a "reprecipitation" method and the results are summarized in Table IV and Fig. 3. The lignin sulfonates obtained after 0.5 hr. reaction time, which comprise about one-quarter of the total lignins, are found to be distributed predom-

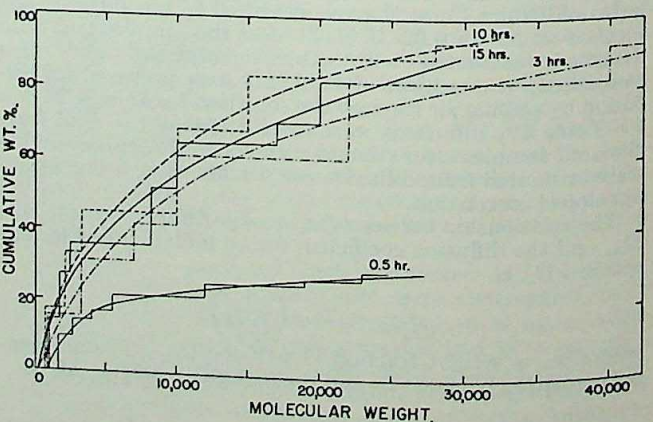

Fig. 3.—Estimated distribution in molecular weights of dissolved hemlock lignin sulfonates after various times of treatment.

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inantly in the molecular weight range of about 500 to 10,000. However after 3 hr. when the delignification has been nearly completed, the molecular weights are found to range on up to around 100,000. Longer reaction time to a total of 10 hr. brings about a general shift in the cumulative distribution curve into a substantially lower range of molecular weights while still further treatment again shifts the curve but this time into a higher range of molecular weights.

These results, together with others previously obtained here and in other laboratories, are believed to provide additional evidence in support of the following concepts: (a) that lignins are branched chain polymers existing in woody tissue at least mostly as relatively large molecules, probably combined with each other and/or with carbohydrates to make three dimensional networks; (b) that the bonds between the lignin structural units are of at least two types, one relatively easily hydrolyzable in acidic aqueous solution and the other not; (c) that for removal of lignin from wood into acidic aqueous solution, hydrolysis of some linkages between structural units must occur to set free segments or "ζ-lignins" from the presumed proto lignin polymer and also these segments must have already been sulfonated or must become sulfonated to the degree necessary to permit them to dissolve in water; (d) that lower molecular weight lignins are first removed during delignification because the distribution of hydrolyzable and of hydrolyzed linkages may be approximately random, and the smaller ζ-lignins diffuse out from the wood residue into solution more rapidly than the larger fragments which are removed later with the result that the average molecular weight increases as delignification proceeds; (e) that acidic hydrolysis of the ζ-lignin sulfonates continues even after they have become dissolved in the aqueous medium so that although the average molecular weight observed for dissolved lignin sulfonates reaches a maximum at about the time that the delignification is completed, thereafter the molecular weight decreases as hydrolysis proceeds, (f) that the average molecular weight of the lignin sulfonates finally reaches a minimum value at which presumably all of the hydrolyzable linkages have been hydrolyzed to provide an "ω-lignin"; and (g) that an increase may then become evident in the average molecular weights of the lignins as a result of progress of irreversible condensation reactions, perhaps of the phenol-carbonyl type, which have presumably continued throughout the delignification process and can finally bring about condensation of the lignin sulfonates to a water-insoluble state.

Additional research is in progress toward the development of a quantitative formulation of these relationships.

SEATTLE, WASHINGTON

[CONTRIBUTION FROM PULP MILLS RESEARCH, DEPARTMENTS OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF WASHINGTON]

Lignin. IX. Molecular Weights of Lignin Sulfonates as Influenced by Certain Acidic Conditions

BY VINCENT F. FELICETTA AND JOSEPH L. MCCARTHY

RECEIVED SEPTEMBER 17, 1956

Lignin has been removed incrementally by treating hemlock wood in five steps with sodium bisulfite–sulfurous acid solutions of progressively increasing acidity. Low molecular weight lignins were removed first, and the later removed lignins were found generally to be of progressively increasing molecular weight. The lignin sulfonates in each increment were hydrolyzed in bisulfite–sulfurous acid solutions and a substantial decrease in molecular weights occurred. Generally similar results were obtained when purified non-dialyzable lignin sulfonates were hydrolyzed in acidic bisulfite–sulfurous acid solutions and also in hydrochloric acid solutions. Hydrolysis proceeds only to a limiting degree and condensation seems to occur simultaneously but more slowly. The new end groups may be carbonyl and phenolic hydroxyl.

Introduction

Many studies have been made of the removal of lignin from woody tissue,[1] and evidence has recently been submitted[2] indicating that as lignin is removed from gymnosperm woods using bisulfite–sulfurous acid solutions, relatively low molecular weight lignin sulfonates are first obtained in solution. Then, as the time of treatment is extended, the average molecular weight of the dissolved lignin sulfonates increases to a maximum, decreases to a minimum and finally begins to rise again. These changes are attributed to the effects of the following three processes which are thought to proceed simultaneously but at different rates: hydrolysis of hydrolyzable bonds in the lignin polymer, polycondensation of some lignin molecules with others and diffusion of soluble lignin sulfonates from the woody tissue into solution.

However, the usual delignification procedure which was used in our prior study comprised the heating of wood with aqueous bisulfite–sulfurous acid solutions in a closed autoclave or bomb. Under these batch conditions, the lignin sulfonates dissolved early in the period of reaction remain exposed to an acidic environment at elevated temperature for the remaining reaction time. In this situation hydrolysis and polycondensation reactions may be important. Thus the now-reported investigation was carried out using an "incremental" delignification method designed to minimize progress of these reactions during delignification. Experiments also have been conducted to establish

(1) F. E. Brauns, "The Chemistry of Lignin," Academic Press, Inc., New York, N. Y., 1952.

(2) E. Nokihara, M. J. Tuttle, V. F. Felicetta and J. L. McCarthy, THIS JOURNAL, 79, 4495 (1957).

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a basis for a study of the hydrolysis and polycondensation reactions in homogeneous solution.

Experimental

Incremental Delignification of Hemlock Wood.—Hemlock wood meal was prepared by passing hemlock wood shavings through a hammer mill. The resulting wood meal was exhaustively extracted with 2:1 ethanol–benzene followed by hot water and then air-dried and sieved to remove fines leaving a wood meal of mesh size 35 to 65. Analysis of this wood meal gave a methoxyl content of 4.62% OCH_3 on air-dried wood of 9.25% H_2O. Air-dried wood meal (12.8 g.) was used for the first delignification step, and each succeeding delignification was conducted on the wood residue from the preceding step. Delignification was carried out in sealed glass bombs at 130 ± 0.5° for 15 hr. except for the first step where an additional 2 hr. was used to slowly bring the temperature to 130°. The treating solution was prepared by passage of sulfur dioxide into an aqueous sodium hydroxide solution until the desired composition was attained as shown in Table I. The bombs were tumbled at about 25 r.p.m. in a stirred thermostated oil-bath.

Table I

Incremental Delignification[a] of Hemlock Wood

Characteristic	Treatment[b] or incremental sample number I	II	III	IV	V
Wood residue					
Weight, %	...	82.1	72.9	61.1	51.5
S, %	1.08	1.15	1.09	0.67	0.25
OCH_3, %	3.76	3.85	2.81	1.40	0.40
Delignfcn., % OCH_3 basis	(26.7)	36.3	55.6	81.3	95.5
Solution product					
*p*H	4.8	4.8	3.4	2.5	2.1
D_A $10^7 \times$ cm.^{2} sec.$^{-1}$	25.5	20.1	14.9	9.5	12.1
Mol. wt.	3400	6600	14,500	30,000	20,500
Solution after hydrolysis[a]					
D_A, $10^7 \times$ cm.^{2} sec.$^{-1}$	30.9	22.5	19.5	17.2	15.8
Mol. wt.	1900	4800	7200	10500	13000

[a] Conditions for the delignification and hydrolysis reactions are given in the Experimental part. [b] Treatments to secure samples I, II, III, IV and V were conducted using aqueous solutions containing the following proportions of "free" and "combined" SO_2: 2.5, 2.5; 2.5, 2.5; 2.6, 2.4; 2.75, 2.25; and 3.25 and 1.75 g. of SO_2/liter, respectively.

After each delignification step the wood residue was separated from the solution product by filtration, washed thoroughly with water, air-dried and weighed and then subjected to the next delignification step. A portion of each wood residue was set aside for sulfur and methoxyl and moisture analyses which were carried out by previously described methods.[3] Solutions obtained from each step were analyzed for methoxyl and characterized by measurement of diffusion coefficient, D_A.[4] Molecular weights were estimated from the diffusion coefficients[5] and are average values, M_A, related to the molecular weights of the individual species, M_i, by the approximate expression

$$M_A = [\Sigma(w_i)(M_i)^{0.5a}]^{2/a} \cong [\Sigma(w_i)(M_i)^{1.5}]^{0.67}$$

where w_i = weight fraction of i-th species, and since $a \cong 3$.

Hydrolyses of the lignin sulfonates were conducted at 130° for 15 hr. in glass bombs. For sample I the hydrolyzing medium was adjusted to 2.25% "combined" SO_2 and 2.89% "free" SO_2 whereas for samples II, III, IV and V the composition was 1.75% "combined" SO_2 and 3.25% "free" SO_2. Diffusion coefficients of the lignin sulfonates were also measured after hydrolysis.

Sulfonation of Lignin Sulfonates.—The non-dialyzable lignin sulfonates used in this investigation were secured by continuous exhaustive dialysis of an industrial sulfite spent liquor made from a mixture of about 85% western hemlock and 15% white fir woods. Determinations of total sulfur, methoxyl, strong and weak acids, and diffusion coefficient on the sodium salt of the non-dialyzable lignin sulfonates were conducted. The treating solution was prepared by passing sulfur dioxide into cold water and then adding solid sodium bisulfite to attain the desired composition. Thirty cc. of the non-dialyzable sodium lignin sulfonate solution was combined with 45 cc. of the concentrated resulfonation solution to give a final combined "SO_2" content of 0.75% and free "SO_2" content of 4.7% and sodium lignin sulfonate concentration of 37.4 g./l. Reactions were conducted in sealed glass tubes with rotation at 25 r.p.m. in an oil-bath at 130 ± 0.5° for varying periods of time as shown in Table II. A separate sample was used for each reaction period.

The products from the reaction were prepared for analysis by the following sequence of steps: (a) filtration to remove free sulfur, (b) de-ashing and steam-distilling to remove sulfur dioxide and convert sulfates to sulfuric acid, (c) preparation of barium salts by slow addition of barium carbonate with stirring, (d) centrifuging to remove barium sulfate and excess barium carbonate and finally, (e) exhaustive dialysis through a Visking cellophane membrane tubing against distilled water.

Measurements for total solids and diffusion coefficient were made on each product before and after dialysis. Determinations of sulfur, methoxyl and strong and weak acids were conducted on the solutions after dialysis. Determination of strong and weak acids was conducted by titrating the free acids with standard 0.1 *N* carbonate-free NaOH and following the progress of neutralization with a Leeds and Northrup glass electrode *p*H electrometer.

Hydrolysis of Lignin Sulfonates.—Acidic hydrolysis was conducted on two non-dialyzable lignin sulfonate preparations, A and B, obtained by exhaustive dialysis of gymnosperm spent sulfite liquors obtained from two different industrial sources. Reactions were carried out in sealed glass tubes in 0.01 *N* HCl solutions using several conditions of time, temperature and sodium lignin sulfonate concentra-

Table II

Homogeneous Sulfonation of Lignin Sulfonates

Characteristic	Sulfonation time in hours or sample number 0	1	2	4	8	24	48
Solution product							
$D_A \times 10^7$, cm.^{2}/sec.	7.5	9.2	12.5	13.5	13.9	16.5	15.2
Mol. wt.	44,000	25,000	19,500	17,000	16,000	12,000	14,000
Soln. after dialysis							
Wt. loss, %	~0	14	9	15	10	18	15
S, %	6.25	5.53	5.81	5.95	6.30	6.99	8.16
OCH_3, %	11.56	10.3	10.4	10.2	10.3	9.7	10.1
Strong acids, meq./g.	2.02	1.50	1.50	1.54	1.83	1.85	2.06
Weak acids, meq./g.	0.13	0.36	0.41	0.54	0.33	0.79	0.61
D_A, $10^7 \times$ cm.^{2} sec.$^{-1}$	7.5	.....	9.4	9.5	9.9	11.1	14.0
Mol. wt.	44,000	.....	31,000	30,000	28,000	23,000	16,000

(3) Q. P. Peniston and J. L. McCarthy, This Journal, **70**, 1324 (1948).

(4) V. F. Felicetta, A. E. Markham, Q. P. Peniston and J. L. McCarthy, *ibid.*, **71**, 2879 (1949).

(5) (a) J. Moacanin, V. F. Felicetta, W. Haller and J. L. McCarthy, *ibid.*, **77**, 3470 (1955), and (b) V. F. Felicetta, A. Ahola and J. L. McCarthy, *ibid.*, **78**, 1849 (1956).

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tion as shown in Table III. Diffusion coefficients of the hydrolyzed mixture were determined and molecular weights were estimated from the diffusion coefficients.

TABLE III

HOMOGENEOUS HYDROLYSIS OF LIGNIN SULFONATES

Hydrolysis time, hr.	$D_A \times 10^7$, cm.²/sec.	Mol. wt.	Hydrolysis time, hr.	$D_A \times 10^7$, cm.²/sec.	Mol. wt.
(A: 40 g./l.; 131°)[a]			(A: 0.4 g./l.; 147°)		
0	7.4	45,000	0.17	9.6	30,000
1	9.9	28,000	.33	11.7	21,000
2	10.6	25,000	.67	14.2	15,500
4	11.7	21,000	1.50	14.7	14,500
8	13.4	17,000	3.00	15.4	13,500
(A: 40 g./l.; 146°)			(B: 40 g./l.; 146°)		
1	12.1	20,500	0.0	7.7	42,000
2	13.4	17,500	.25	8.8	34,000
4	13.5	17,000	.5	10.1	27,000
8	13.5	17,000	1.0	12.4	20,000
			2.0	13.3	17,000
(A: 4 g./l.; 145°)			4.0	13.9	16,500
0.17	14.3	26,500	8.0	14.0	16,000
0.5	14.4	15,500			
1.0	15.4	13,500			
2.0	15.4	13,500			
8.0	15.4	13,500			

[a] Hydrolysis reactions were conducted in 0.01 *N* HCl aqueous solutions at the indicated temperatures and sodium lignin sulfonate concentrations with preparation A or B. For Fig. 2, the samples are designated as, for example, A-40–131, which signifies preparation A treated at 40 g./liter and at 131°, etc.

Discussion

Hemlock wood has been delignified by successive treatments with five aqueous sodium bisulfite–sulfurous acid solutions of increasing acidity, *i.e.*, at *p*H 4.8, 4.8, 3.40, 2.51 and 2.09, respectively. After each treatment the solution was removed and the wood residue retreated with a fresh increment of bisulfite–sulfurous acid solution, and this procedure is somewhat similar to one followed by Freudenberg, Lautsch and Piazolo.[6]

Results of analyses of the several wood residues and solutions (Table I) show that about one-third of the lignin, as indicated by methoxyl groupings, can be removed from wood under weakly acidic conditions as previously observed by Abrahamson Lindgren and Hagglund.[7] Increasingly acidic solutions are required to remove the remaining lignin. The lignin sulfonates obtained in the first increment are found to be of relatively low average molecular weight, about 3000 as estimated by a diffusion method[4] calibrated by light scattering observations.[5a] The lignin sulfonates obtained in later increments proved to be of increasingly high average molecular weight up to about 30,000 for IV, but yet only about 20,000 for V.

Since it was thought that the disorderly molecular weight of V might have arisen as a result of progress of more extensive hydrolysis of lignin molecules in this increment compared with the others, further heating of each of the lignin sulfonate solutions in a more acidic environment was carried out. The average molecular weights of the lignin sulfonates were again estimated. They were now found to have decreased substantially as represented in Fig. 1 and, moreover, to increase progressively from the first to the last extracted increment.

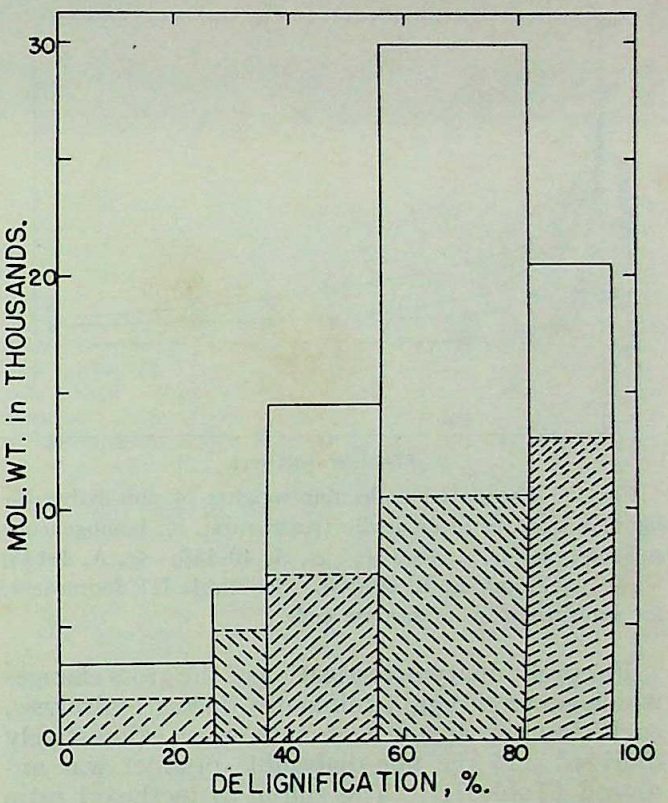

Fig. 1.—Estimated molecular weight of lignin sulfonates from incremental delignification and after hydrolysis (cross-hatched).

The weighted average molecular weight for the five lignin sulfonate preparations after hydrolysis, *i.e.*, for nearly the total lignin of the wood, is about 6000. After making allowances for the influences of the differences in types of molecular weight averages and also for the proportions of the total lignin examined, this value is believed to be in approximate agreement with a limiting value of about 3500 found by Gralen[8] and with the value of 3900 given by Loughborough and Stamm[9] and with quite a number of other average molecular weights of lignin preparations which have been reported in the literature.[1] However the molecular weights of these lignins are considerably higher than the values of around 1000 found in this Laboratory for the lignin sulfonates from maple wood,[2] and this difference may prove to be a characteristic distinction between gymnosperm and angiosperm lignins.

To observe the hydrolysis of lignin sulfonates in homogeneous aqueous solution in the substantial absence of sugars and other non-lignin substances, a non-dialyzable lignin sulfonate preparation was dissolved in sodium bisulfite–sulfurous acid solution adjusted to about *p*H 2 and then heated at 130° for various periods of time up to 48 hr. Average

(6) K. Freudenberg, W. Lautsch and P. Piazolo, *Cellulosechem.*, **22**, 97 (1944).

(7) B. Abrahamson, B. Lindgren and E. Hagglund, *Svensk Papperstidn.*, **51**, 471 (1948).

(8) N. Gralen, *J. Colloid Sci.*, **1**, 453 (1946).

(9) D. L. Loughborough and A. J. Stamm, *J. Phys. Chem.*, **40**, 1113 (1936); **45**, 1137 (1941).

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molecular weights were estimated and were found to decrease progressively and to approach a limiting value of about 12,000 (Table II and Fig. 2). Lignins which have been hydrolyzed to this apparently limiting degree may be conveniently designated as "ω-lignins."

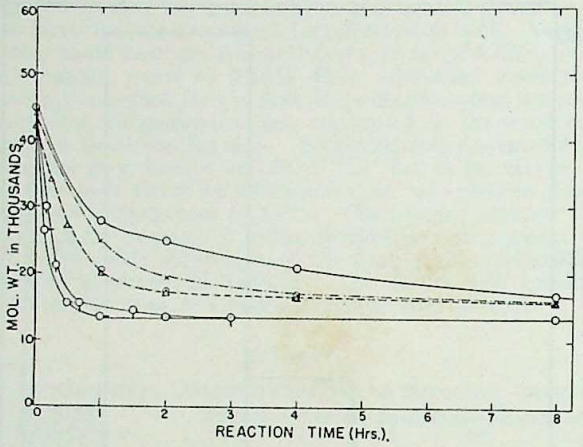

Fig. 2.—Estimated molecular weights of non-dialyzable lignin sulfonates after acidic treatments: ×, homogeneous sulfonation; O, A, 40–131; ♁, A, 40–146; ⊶, A, 4–145; ♀, 0.4–147; and △, B, 40–146. See Table III, footnote *a*, for interpretation of sample code.

For preliminary investigation of the gross changes which occur in lignin sulfonates during hydrolysis, each treated lignin sulfonate was exhaustively dialyzed and the non-dialyzable product was analyzed (Table II). The sulfur to methoxyl ratio increases from the initial value of 0.52 to a final value of 0.78 after 48 hr. Judging from the values found for "strong acid" groups, this increase occurs mostly as the result of increased sulfonation. The "weak acid" groups increase three- to sixfold, apparently because of formation of carboxylic or phenolic hydroxyl groups. From the estimated weight of the lignin sulfonates which passed through the membrane during dialysis, together with the average diffusion coefficients of the treated lignin sulfonates before and after dialysis, it is evident that the average molecular weights of these sulfonates which passed through the dialysis membrane must be small.

Preliminary hydrolysis experiments were also conducted under several conditions with aqueous solutions of hydrochloric acid, and average molecular weights and some other characteristics of the products were estimated (Table III and Fig. 3). With increasing reaction time, a decrease in average molecular weight is again found to occur and a limiting value is approached. For non-dialyzable lignin sulfonate preparations from two different sources, hydrolyses conducted at relatively high concentration (40 g./liter) gave rise to ω-lignin sulfonates with molecular weights in the range of 17,000 while hydrolyses at lower concentrations (4 and 0.4 g./liter) yielded products of substantially lower molecular weight, presumably because polycondensation reactions were minimized by dilution. An approximate fit to the present results can be obtained by assuming that the rate of hydrolysis is proportional to the concentration of unhydrolyzed hydrolyzable bonds. On this basis, values for reaction rate constants can be computed from the present data and correlated. However, for a serious treatment of the kinetics of the hydrolysis and condensation reactions of the lignin polymer, molecular weight distributions need to be known after various times of reactions under several different conditions. In this Laboratory such data are now being assembled and studied to provide a basis for a detailed statistical kinetic formulation.

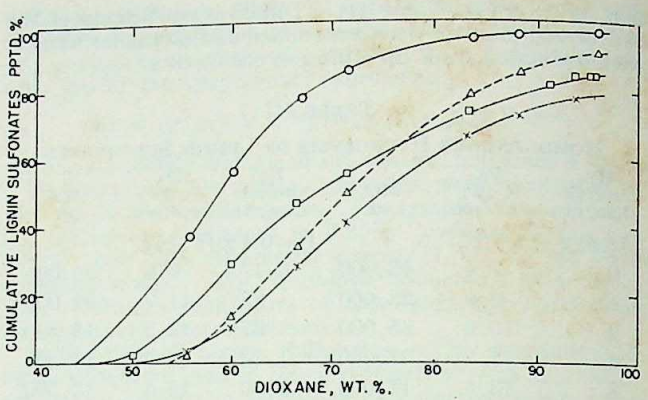

Fig. 3.—Precipitability of barium lignin sulfonate preparations in dioxane–water mixtures: whole sulfite spent liquor, □; dialyzable lignin sulfonate, ×; non-dialyzable lignin sulfonate, O; hydrolyzed lignin sulfonate (sample B, 40–146, 8 hr.), △.

The ultraviolet spectra of non-dialyzable lignin sulfonate preparation A and of its 8-hr. hydrolysis product (expt. A, 40–146) were ascertained. The spectra were very similar except that for the hydrolyzed sample the absorption minimum at about 2600 Å. was less pronounced and its absorptivity at 2800 Å. had increased by about 15%. For preparation B hydrolysis for 4 and 8 hr. (expt. B, 40–146) brought about increases of 70 and 86%, respectively, in the reducing substances calculated as glucose compared with the unhydrolyzed material. These changes may indicate formation of carbonyl end-groups as a result of the hydrolysis reaction, and the nature of the end-groups formed is now under study.

A non-dialyzable ω-lignin sulfonate (expt. B, 40–146, 8 hr.) was converted to a barium salt, dioxane was added in various proportions to aqueous solutions of the salt and the percentages of lignin precipitated were determined. Precipitation occurs over quite a wide range of dioxane concentrations (Fig. 3) which suggests that the preparation is rather polydisperse. Similar measurements were carried out with a non-dialyzable lignin sulfonate preparation which had not been hydrolyzed, and its precipitation at lower ranges of dioxane concentration may be a manifestation of the lower solubility of higher molecular weight lignin sulfonates in a less polar solvent medium. This interpretation is supported by the observation that precipitation of the relatively low molecular weight lignin sulfonates which had passed through a cellophane dialysis membrane took place only at the higher dioxane concentrations while the total lignin sulfonates in whole sulfite spent liquor were precipitated at intermediate concentrations of dioxane.

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[CONTRIBUTION FROM THE UNIVERSITY OF FLORIDA AND ORLANDO RESEARCH, INC.]

Isolation of a Cell-free Enzyme System from *Acetobacter xylinum* Capable of Cellulose Synthesis

BY GLENN A. GREATHOUSE

RECEIVED NOVEMBER 5, 1956

A cell-free enzyme system was isolated from the cellulose forming bacterium, *Acetobacter xylinum*. Cellulose-C^{14} was produced by this enzyme system from D-glucose-1-C^{14} and the position of the C^{14}-label determined in the D-glucose resulting from the hydrolysis of the cellulose formed. Ninety-six per cent. of the label was found to be in position one of the cellulose molecule.

Introduction

Previous publications[1-5] have been concerned with the biosynthesis of cellulose-C^{14} by *Acetobacter xylinum* from specifically C^{14}-labeled hexoses and trioses. We now report studies on the isolation of a cell-free enzyme or enzymes from the bacterium capable of synthesizing radioactive cellulose from D-glucose-1-C^{14}. Analyses reported include the distribution of the C^{14}-label in the purified D-glucose from the hydrolyzed enzyme cellulose-C^{14}.

Muhlethaler[6] by means of electron microscopic studies of *A. xylinum* presents evidence that the formation of cellulose by this bacterium probably does not take place within the cell or from its surface, but rather at some distance from the organism. This suggests that cellulose results from a possible enzymatically induced polymerization of the embedding slime that can accordingly be thought of as a kind of cellulose-precursor.

Schramm, Gromet and Hestrin[7,8] state that glucose, gluconate, dihydroxyacetone and glycerol in the presence of oxygen were rapidly converted to cellulose by the dry cell preparation of *A. xylinum*. They also state since aldolase was present in the cell extract, elongation and cleavage of the sugar carbon chain could have occurred by an action of this enzyme.

As far as we know this report describes the first experimental proof that a cell-free enzyme system capable of polymerization of hexose to cellulose has been studied.

Experimental

Culture Conditions.—The bacterium, *Acetobacter xylinum*, was grown on the following medium: 20 g. of yeast extract (Difco),[9] 10 g. of D-glucose, 1 g. of KH_2PO_4 and 10 ml. of ethyl alcohol per liter. This medium had a *p*H of 5.88. The inoculum was 1 ml. of a 24-hour liquid culture. The cultures were incubated for 48 hours at 30°. By this time membrane formation was evident.

Methods of Preparing Cell-free Enzymes from *A. xylinum*.—Muhlethaler's[6] study indicated that this organism produced cellulose by means of extracellular enzymes. It is realized that bacteria cells are particularly difficult to disrupt as well as produce cell-free enzyme systems. Thus, the degree of disruption was assessed by high power microscopic examination of stained preparations and making viable count to determine whether the enzyme product was cell-free. In addition, controls were made for each experiment and were left to incubate for 7 days and then examined microscopically for whole or living cells. In no case were cells found using the adopted method described. Hugo[8] discusses methods of preparing cell-free enzymes from microörganisms. The suggested methods of Hugo were evaluated and the one producing satisfactory results as to enzyme activity and being cell-free was selected.

The first experiments were performed utilizing a combination of standard methods for extracellular enzyme isolation. Later experiments used methods of disruption with abrasive particles, crushing without the use of abrasives, disintegration by agitation with small particles, disintegration by alternate freezing and thawing and by chemicals (surface active, dehydrating, etc.). An activity capable of producing cellulose in 15 to 18% yields from D-glucose was obtained with each of the methods studied at an optimum *p*H of 8.5. Consequently, the following method was adopted for this study. The contents (250 ml.) of ten flasks were poured into a chilled Waring Blendor vessel, and the blender was run for 15–30 seconds in order to break up completely the existing membranes. The crushed material (0.5 to 1 g. solids) was centrifuged at 3000 r.p.m. for 5 minutes to remove large particles and any abrasive material. The supernatant fluid was lyophilized. The resulting material was a light brown, hygroscopic powder. The freeze-drying required between 4 and 6 hours. The total solids were ether extracted to remove fats, etc., and then ground with 200-mesh powdered glass. The crude enzyme material was kept cold (−5 to 0°) until used in the experiments 1–2 hours later.

A 10% "enzyme" solution of the dry extracted material was made. Two and one-half ml. of this solution was added to 25 ml. of previously sterilized liquid medium consisting of 1% glucose, 2% yeast extract, 0.1% KH_2PO_4, and 0.5% ethyl alcohol plus 0.1% adenosine triphosphate (ATP). The enzyme system was incubated at 30°. The enzymatically synthesized cellulose was formed within 2–4 hours and no contamination occurred. A small quantity of ether was added to the surface of the cultures to delay or prevent possible contamination.

Preliminary experiments were conducted toward purification of the crude enzyme system. Of the purification methods tried, the glycerol (75%) extraction procedure gave the most promising results. Further research is required on this phase of the study.

Results and Discussion

The effect of varying *p*H values on the extent of cellulose produced by the cell-free enzyme systems is shown in Table I.

These data indicate the optimum *p*H for the enzyme systems is 8.5 to 9.0. Consequently all enzyme systems were adjusted to a *p*H of 8.5 for further studies.

Preliminary experiments indicated that the addition of adenosine triphosphate (ATP) to the other medium ingredients increased the cellulose yield. Thus experiments were designed to evaluate this factor. These data are presented in Table II.

(1) F. W. Minor, G. A. Greathouse, H. G. Shirk, A. M. Schwartz and M. Harris, THIS JOURNAL, **76**, 1658 (1954).

(2) F. W. Minor, G. A. Greathouse, H. G. Shirk, A. M. Schwartz and M. Harris, *ibid.*, **76**, 5052 (1954).

(3) G. A. Greathouse, H. G. Shirk and F. W. Minor, *ibid.*, **76**, 5157 (1954).

(4) F. W. Minor, G. A. Greathouse and H. G. Shirk, *ibid.*, **77**, 1244 (1955).

(5) G. A. Greathouse, *Science*, **117**, 553 (1953).

(6) K. Muhlethaler, *Biochim. et Biophys. Acta*, **3**, 527 (1949).

(7) M. Schramm, Z. Gromet and S. Hestrin, *Bull. Res. Council of Israel*, **5A**, No. 1, 99 (1955).

(8) W. B. Hugo, *Bacteriol. Rev.*, **18**, 87 (1954).

(9) No satisfactory synthetic medium has been developed for the production of cellulose by *A. xylinum*, therefore, the utilization of yeast extract in the culture and enzyme medium.

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TABLE I

OPTIMUM *p*H OF ENZYME SYSTEMS CAPABLE OF CELLULOSE FORMATION

*p*H	Cellulose yield, mg.	*p*H	Cellulose yield, mg.
5.0	0.40	8.0	34.30
5.5	0.82	8.5	48.04
6.0	4.71	9.0	47.35
6.5	12.34	9.5	32.50
7.0	19.85	10.0	0.25
7.5	25.22		

TABLE II

THE EFFECT OF ADDING ADENOSINE TRIPHOSPHATE TO THE MEDIUM ON CELLULOSE YIELD (30°, *p*H 8.5)

Amount of ATP added, g.	Cellulose yield, mg.	Amount of ATP added, g.	Cellulose yield, mg.
0	0.2	0.10	43.4
0.02	10.5	.20	45.1
.04	18.7	.40	44.8

Practically no cellulose was produced by this enzyme system without the addition of ATP. The yield was increased to 40 to 45 mg. by the addition of 0.1 to 0.4 g. of ATP. The energy for this possible direct polymerization of the glucose or glucose phosphate to cellulose by the cell-free enzyme system is likely phosphorylation, high energy phosphate bonds of ATP.

Production of Cellulose-C^{14} by the Isolated Cell-free Enzyme System.—The crude enzyme preparation was added to the medium containing D-glucose-1-C^{14} (50 microcuries) and 0.1% ATP along with the standard D-glucose, and other medium ingredients after adjusting to a *p*H of 8.5. Cellulose was produced as before, purified and the radioactivity determined. The yield based on the D-glucose-1-C^{14} was approximately 15%.

The cellulose was hydrolyzed and the resultant labeled D-glucose purified and crystallized. Paper chromatographic analysis of the cellulose hydrolyzate showed only one radioactive spot, being an R_f value identical with that of a D-glucose reference shot. An aniline hydrogen phthalate spray revealed only the same spot. The hydrolyzates were mixed with unlabeled D-glucose and purified by crystallization, to give D-glucose-C^{14} with the specific activity of 1.665 mc./m*M*. A 50-mg. sample of this radioactive glucose was oxidized by oxygen in aqueous potassium hydroxide to remove carbon 1.[10] The resulting potassium D-arabonate was separated and recrystallized and the percentage of C^{14}-activity determined. Calculations showed that 96.7% of the label was in the original position 1. Consequently, no other carbon positions were analyzed.

The radioactivity of the D-glucose was obtained with an α-β-γ proportional counter Model PC-1 and checked with a Vibrating Reed Electrometer. The proportional counter is a "P-gas (90% argon, 10% methane) windowless type counter." The geometry for small samples is 2π and the efficiency of a thin sample is 50% with this counter. Necessary precautions were taken to assure a precision of about 1% of the observed count rate. Counts were made of thin samples of $BaCO_3$ and D-glucose and the results were corrected in the standard way for the effects of background count, geometry and self-absorption.

The samples counted using the Vibrating Reed Electrometer were first combusted by the Van Slyke method and the CO_2 was collected in ionization chambers. The activity of the sample was then determined by the rate at which the condenser was charged or millivolts per second drift rate. The difference between this drift rate and the normal background of the reed gives the measure of the activity of the combusted sample. For this vibrating reed 0.1270 mv./sec. equalled one disintegration per second.

These data are most interesting, since they constitute strong evidence that glucose-1-C^{14} was synthesized to cellulose directly by the cell-free enzyme system.

Acknowledgment.—The author wishes to express his gratitude to the Office of Scientific Research of the Air Research Development Command, U. S. Air Force, for supporting the research, and to Wm. Borysewich, Jr., for his assistance with the radioactive analysis.

GAINESVILLE, FLA.

(10) H. L. Frush and H. S. Isbell, *J. Research Natl. Bur. Standards*, **51**, 167 (1953).

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[CONTRIBUTION FROM THE UNIVERSITY OF FLORIDA AND ORLANDO RESEARCH, INC.]

Biosynthesis of C^{14}-Labeled Cellulose by *Acetobacter xylinum*. IV. From D-Glucose-1-C^{14}, D-Glucose-6-C^{14} and Glycerol-1,3-C^{14}

BY GLENN A. GREATHOUSE[1]

RECEIVED NOVEMBER 5, 1956

The distribution of C^{14} in the D-glucose from the bacterial cellulose hydrolyzate produced from D-glucose-1-C^{14}, added 24 hours after inoculation as compared with that added initially was 10–12% higher in the original position 1. The hydrolyzate of cellulose-C^{14} produced from D-glucose-6-C^{14} indicated that approximately 82% of the label was in the original position 6 and had 9% in position 1, with smaller quantities in positions 2, 3, 4 and 5. The distribution of C^{14} in the D-glucose units of cellulose produced from glycerol-1,3-C^{14} was approximately 12% position 1; 4% position 2; 22% position 3; 29% position 4; 3% position 5; and 30% position 6.

Introduction

Preceding publications[2–5] have been made on the incorporation of labeled sugars into cellulose. Both *Acetobacter xylinum*[2–4] and wheat plants[6] appear to incorporate D-glucose directly. However, some of the original hexose units are cleaved prior to cellulose formation.

It would assist in determining the mechanism of cellulose formation, if the percentage of label could be changed in the original position by adding the labeled hexose after the growth of the bacteria had progressed and enzyme formed. Such experiments utilizing D-glucose-1-C^{14} are reported herein, along with the new data on the incorporation of D-glucose-6-C^{14} and glycerol-1,3-C^{14} into cellulose.

Procedures

Culture Conditions.—The culture conditions were identical with those described in the preceding paper of this series, unless designated as different.[4]

Counting Apparatus.—Counting rates were calculated from the results of counts obtained with an α-β-γ proportional counter Model PC-1 and in certain instances with a Vibrating Reed Electrometer. The proportional counter is a "P-gas (90% argon, 10% methane) windowless type counter." The geometry for small samples is 2π and the efficiency of a thin sample is 50% with this counter. Necessary precautions were taken to assure a precision of about 1% of the observed count rate. Counts were made of thin samples, as $BaCO_3$, glucose, etc. and the results were corrected in the standard way for the effects of background count, geometry and self-absorption.

The samples counted using the vibrating reed electrometer were first combusted by the Van Slyke method and the CO_2 was collected in ionization chambers. The activity of the sample was then determined by the rate at which the condenser was charged or millivolts per second drift rate. The difference between this drift rate and the normal background of the reed gives the measure of the activity of the combusted sample. For this vibrating reed 0.1270 mv./sec. equaled one disintegration per second.

Radioactivity Determinations of the Culture Products.—The procedure for the determination of C^{14} content in the CO_2, the C^{14} remaining in the culture media and the C^{14} activity of the cellulose were the same as those previously described.[2a]

Purification of the Cellulose Hydrolyzate D-Glucose.—The D-glucose-C^{14} resulting from the cellulose-C^{14} was purified by the method of Whistler and Durso[7] and by several recrystallizations before assay for C^{14}.

Methods Used for Location of C^{14} in Cellulose.—The distribution of C^{14} within the D-glucose units in the cellulose was determined by analysis of the D-glucose obtained by hydrolysis of the cellulose-C^{14}. Carrier D-glucose was added to the hydrolyzate to obtain the desired specific activity and increase the amount of C^{14}-glucose.

The activity at carbon 1 was obtained by the Frush and Isbell method.[8] Positions 2 and 3 were obtained by using the potassium D-arabonate from carbon 1-analysis and preparing its benzimidazole according to the method of Moore and Link.[9]

Carbon atoms 2 and 3 of D-glucose were then degraded stepwise by a method described by Roseman[10] by formation of benzimidazole carboxylic acid and carbon atom 2 by the benzimidazole. Position 2 was counted directly and position 3 was determined by difference of 2 and 3.

Activity at positions 4 and 5 were by difference of positions 1, 2, 3 and 6 or as described in previous publication.[2a]

Carbon atom 6 was made by the method of Reeves,[11] which involves oxidation with periodic acid of the C_6-carbon to CH_2O and its conversion to the dimedone derivative. Counts were made of this derivative, plated on aluminum pans from aqueous methanol or pyridine solutions.

Results

Cellulose-C^{14} Produced from D-Glucose-1-C^{14} Added Initially and 24 Hours after Inoculation.—The weight yields, as carbon content and the percentage of C^{14}-label in each of purified cellulose and carbon dioxide, are indicated in Table I. The table shows also, for comparison, the carbon and percentage of label in the D-glucose-1-C^{14} and ethanol that was supplied.

TABLE I

SUBSTRATES, YIELD OF PRODUCTS AND C^{14}-LABEL DISTRIBUTION

	A. When D-glucose-1-C^{14} was added initially		B. D-glucose-1-C^{14} added 24 hr. after inoculation	
	Wt., mg. C	Label C^{14}, %	Wt., mg. C	Label C^{14}, %
Substrates				
D-Glucose-1-C^{14}	80.5	100	80.5	100
Ethanol	79.3	None	79.3	None
Products				
Carbon dioxide	88.2	30.5[a]	92.4[a]	24.5[a]
Cellulose	26.2	28.7[a]	28.4[a]	33.6[a]

[a] These data were secured from three separate experiments and analyses. There was little variation in the three individual sets of data.

(1) The author wishes to thank the office of Scientific Research of the Air Research Development Command, U. S. Air Force, for supporting this study under Contracts AF-18 (600) 1126, University of Florida and AF 18 (600) 1389, Orlando Research, Inc.

(2) (a) F. W. Minor, G. A. Greathouse, H. G. Shirk, A. M. Schwartz and Milton Harris, THIS JOURNAL, **76**, 1658 (1954); (b) **76**, 5052 (1954).

(3) G. A. Greathouse, H. G. Shirk and F. W. Minor, *ibid.*, **76**, 5157 (1954).

(4) F. W. Minor, G. A. Greathouse and H. G. Shirk, *ibid.*, **77**, 1244 (1955).

(5) G. A. Greathouse, *Science*, **117**, 553 (1953).

(6) S. A. Brown and A. C. Neisch, *Can. J. Biochem. Physiol.*, **32**, 170 (1954).

(7) R. L. Whistler and D. F. Durso, THIS JOURNAL, **72**, 677 (1950).

(8) H. L. Frush and H. S. Isbell, *J. Research Natl. Bur. Standards*, **51**, 167 (1953).

(9) S. Moore and K. P. Link, *J. Biol. Chem.*, **133**, 293 (1940).

(10) S. Roseman, THIS JOURNAL, **75**, 3854 (1953).

(11) R. E. Reeves, *ibid.*, **63**, 1476 (1941).

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The original percentage activity per 1 mg. of D-glucose (100/80.5) is 1.24. The percentage activity per 1 mg. for the resultant cellulose when D-glucose-1-C^{14} was added initially (28.7/26.2) is 1.10; when D-glucose-1-C^{14} was added 24 hours after inoculation (33.6/28.4) is 1.18. Thus the activity was slightly lower than the original D-glucose-1-C^{14}.

The label in the cellulose-C^{14} was distributed over the six positions in the glucose units as shown in Table II. These experiments were performed at the same time and under identical conditions except the time of adding the D-glucose-1-C^{14}.

TABLE II

LOCATION OF LABEL IN D-GLUCOSE FROM BACTERIAL CELLULOSE

Structure position	D-Glucose-1-C^{14} Added 0 hr.	D-Glucose-1-C^{14} Added 24 hr. later
1	62.5	79.1
2	1.6	0.4
3	19.2	11.0
4	15.4	8.0
5	0.9	0.4
6	0.4	1.1
	100	100

Cellulose-C^{14} Produced by D-Glucose-6-C^{14}.—Radioactive cellulose was produced from D-glucose-6-C^{14} by use of *A. xylinum*. The procedure was similar to that described for the other labeled sugar and cellulose formation. The results of these experiments are summarized in Tables III and IV.

TABLE III

SUBSTRATES, YIELD OF PRODUCTS AND C^{14}-LABEL DISTRIBUTION

	Wt., mg. C	Label C^{14}, %
Substrates		
D-Glucose-6-C^{14}	80.5	100
Ethanol	79.3	None
Products		
Carbon dioxide	111.0	28.9
Cellulose	32.6	23.8

TABLE IV

LOCATION OF LABEL IN GLUCOSE FROM BACTERIAL CELLULOSE—FROM D-GLUCOSE-6-C^{14}

Structure position	%	Structure position	%
1	9.3	4	3.5
2	1.7	5	
3	3.9	6	81.6

The major portion (81.6%) of the label was located at position 6, corresponding to its position in the labeled substrate. Position 1 contained 9.3% and the remaining 9% was distributed at positions 3, 4 and 5 and 2 in descending order.

Cellulose-C^{14} Produced by Glycerol-1,3-C^{14}.—Cellulose-C^{14} was produced by *A. xylinum* using glycerol-1,3-C^{14} as the sole carbon label source. The procedures and analyses were the same as for the previously described radioactive sugar studies. These data are presented in Tables V and VI.

TABLE V

SUBSTRATES, YIELD OF PRODUCTS AND C^{14} LABEL DISTRIBUTION

	Wt., Mg. C	Label C^{14}, %
Substrates		
Glycerol-1,3-C^{14}	98.0	100
Ethanol	79.3	None
Products		
Carbon dioxide	87.4	6.1
Cellulose	11.8	5.7

TABLE VI

LOCATION OF LABEL IN GLUCOSE FROM BACTERIAL CELLULOSE FROM GLYCEROL-1,3-C^{14}

Structure position	%	Structure position	%
1	12.7	4	28.9
2	3.7	5	3.0
3	21.7	6	30.0

Smaller quantities of C^{14} were found in the CO_2 and cellulose with glycerol-1,3-C^{14} as the label source than with glucose-C^{14} during the 7 day incubation period. Most of the 87.4 mg. carbon as CO_2 must have come from the oxidation of the ethanol. The liquid products of the cultures contained a large portion of the label. *A. xylinum* is required to form cellulose from trioses in this case and it may be the time required for the bacteria or its enzyme system to produce sizable quantities of cellulose intermediate (hexoses, hexose phosphates, etc.) exceeds the 7-day period of the experiments. Experiments (to be reported elsewhere) concerned with the isolation of the cellulose intermediates between glycerol-1,3-C^{14} and cellulose formation bear out this reasoning.

The label in the cellulose was distributed over the six positions in the glucose units, with the smaller quantities being in position 2 and 5.

Discussion

This paper presents data for the first time on the biosynthesis of cellulose-C^{14} from D-glucose-1-C^{14} added 24 hours after inoculation as compared with that added initially. The delayed addition of D-glucose-1-C^{14} produced a 10–12% higher concentration of the label in the original position 1. These data indicate that polymerization of the D-glucose, as such, without prior cleavage is favored by adding the radioactive sugar after the bacteria have initiated growth. No previous data have been reported on the biosynthesis of cellulose-C^{14}, and the position of label, utilizing D-glucose-6-C^{14} or glycerol-1,3-C^{14}. The hydrolyzate of cellulose-C^{14} from D-glucose-6-C^{14} showed that approximately 82% of the label was in the original position 6. When glycerol-1,3-C^{14} was the sole carbon source, the label was 12% position 1, 4% position 2, 22% position 3, 29% position 4, 3% position 5 and 30% position 6.

In every case of cellulose biosynthesis studied, some of the original hexose units are cleaved prior to cellulose formation. The concentration of the label in the original position depends on which of

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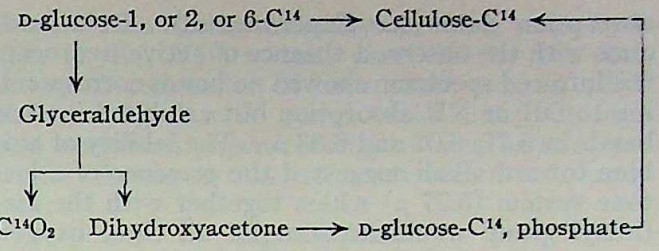
the six carbon atoms is labeled and on the time of adding the radioactive sugar. Thus, the mechanisms of cellulose polymerization is complex. At least two major mechanisms appear from these studies, (1) direct polymerization, possibly involving phosphorylation and (2) cleavage of the hexose and resynthesis of hexose phosphates from trioses such as glycerol. Hexose phosphates[12] have been isolated and identified as intermediates in the biosynthesis of cellulose from D-glucose, thus the reason for suggesting these products as possible energy sources in the major mechanism of polymerization.

To summarize the research, a schematic representation of the processes of cellulose formation may be shown as



A cell-free enzyme system has been isolated from *A. xylinum* capable of producing cellulose-C^{14}.[13] D-Glucose-1-C^{14} was polymerized to cellulose and the hydrolyzate (D-glucose) analyzed. Ninety-six per cent. of the label was found in position one of the cellulose molecule.

(12) Unpublished data.

(13) G. A. Greathouse, THIS JOURNAL, **79**, 4503 (1957).

GAINESVILLE, FLA.

[JOINT CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY AND THE INSTITUTO DE QUIMICA AGRICOLA, MINISTERIO DA AGRICULTURA, RIO DE JANEIRO]

The Chemistry of Rosewood. Isolation and Structure of Anibine and 4-Methoxyparacotoin[1]

BY WALTER B. MORS,[2a,3] OTTO RICHARD GOTTLIEB[2b,3] AND CARL DJERASSI

RECEIVED APRIL 12, 1957

From the wood of the South American rosewood trees (genus *Aniba*) there has been isolated a new alkaloid, $C_{11}H_9NO_3$, which has been named anibine. By various degradations, in particular by alkaline cleavage, it was shown that anibine is 4-methoxy-6-(3′-pyridyl)-α-pyrone (IV). A neutral companion substance of anibine, when subjected to similar reactions, was proved to be 4-methoxy-6-piperonyl-α-pyrone (X) (4-methoxyparacotoin) and attention is called to the structural similarity with the constituents of the closely related *Coto* barks.

The South American rosewood trees belong to the *Lauraceae* family, and the derived essential oil has long been an article of commerce.[4] The botanical identification has been confusing, and the trees were once believed to belong to the genus *Ocotea*.[5] It is now accepted that the *bois de rose* from French Guiana and adjacent areas is *Aniba rosaeodora* Ducke and the Brazilian *páu rosa* from the lower Amazon basin *Aniba Duckei* Kostermans (*A. rosaeodora* var. *amazonica* Ducke).[6,7] The main constituent of the rosewood essential oil is linalool, but a ready differentiation of the two species is even possible on chemical grounds since the essential oil from French Guiana is strongly levorotatory while the Brazilian one is only slightly so or even dextrorotatory.[4]

Aside from the essential oil, no chemical work seems to have been done with these plants, and a detailed examination of the composition of these *Aniba* species was undertaken by one of us (O.R.G.) The Brazilian *Aniba Duckei* Kostermans represented commercial material from Manaus (State of Amazonas) while a sample of *Aniba rosaeodora* Ducke came from an isolated tree from the region of the Amaparí river (Territory of Amapá, Brazil).[8] A number of products were isolated, and the present paper is concerned with the alkaloid and one of the neutral constituents, which were found in both *Aniba* species.

Extraction of the rosewood sawdust with benzene followed by removal of basic material with hydrochloric acid and basification yielded a single, crystalline alkaloid, m.p. 179–180°, in *ca.* 2.6% yield. Its empirical formula, $C_{11}H_9NO_3$, immediately indicated that it must differ considerably from the few alkaloids (isoquinoline types) hitherto encountered among the *Lauraceae*,[5,9] and we have named the substance "anibine." Functional group analysis demonstrated the presence of one methoxyl group and the absence of N-methyl or C-methyl groups. Anibine contained no active hydrogen atom and was optically inactive over the range 700–400 mμ. The alkaloid, though forming a crystalline methiodide, hydrochloride and picrate, was weakly basic and in fact could be removed from hydrochloric acid solution by continuous extraction with chloroform. The nitrogen atom was, therefore, assumed to be part of a heterocyclic ring which was not inconsistent with the ultraviolet

(1) This article should be considered paper XVIII in the Wayne series "Alkaloid Studies"; for preceding article see THIS JOURNAL, **79**, 2203 (1957).

(2) (a) Rockefeller Foundation Fellow at Wayne State University, 1956–1957. (b) Acknowledgment is due to the Conselho Nacional de Pesquisas, Brazil, for financial aid.

(3) Instituto de Quimica Agricola, Rio de Janeiro, Brazil.

(4) E. Guenther, "The Essential Oils," Vol. IV, Van Nostrand Co., Inc., New York, N. Y., 1950, p. 191.

(5) See C. Wehmer, "Die Pflanzenstoffe," Vol. I, Gustav Fischer, Jena, 1929, pp. 364–365. References to earlier chemical investigations of the *Lauraceae* can be found on pp. 350–373.

(6) A. Ducke, *Arq. Jard. Bot. Rio de Janeiro*, **5**, 109 (1930).

(7) A. J. G. H. Kostermans, *Rec. trav. bot. neerl.*, **35**, 68 (1938).

(8) The botanical identification was carried out by Dr. Arthur de Miranda Bastos (Botanical Garden, Rio de Janeiro) and confirmed by the rotation ($[\alpha]_D$ −16°) of its essential oil.

(9) See T. A. Henry, "The Plant Alkaloids," Blakiston, Philadelphia, 1948, p. 310.

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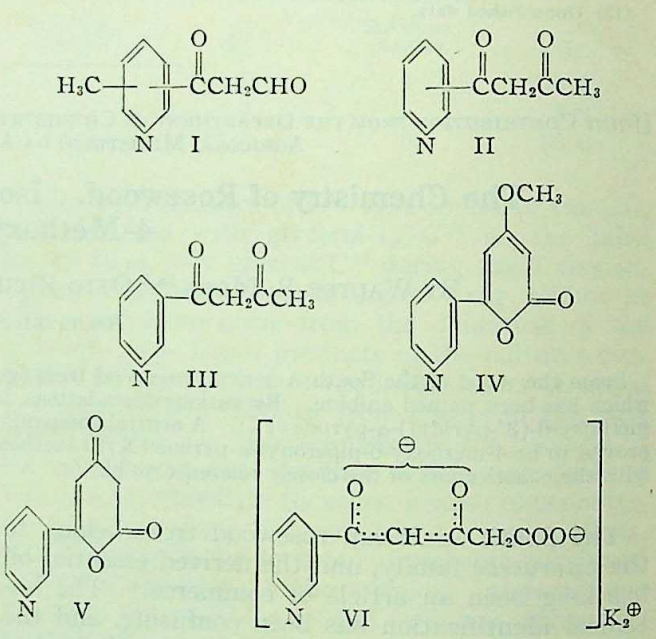
absorption data (see Experimental). In accordance with the observed absence of active hydrogen, the infrared spectrum showed no bands corresponding to OH or NH absorption but exhibited intense bands at 5.77, 6.02 and 6.33 μ. The lability of anibine toward alkali suggested the presence of a lactone system (5.77 μ) which together with the methoxyl group would account for all three oxygen atoms. The 6.02 μ band could be assigned to an enol ether and this was proved subsequently to be correct. Catalytic hydrogenation (platinum oxide in acetic acid) resulted in the uptake of 6 moles of hydrogen which indicated that hydrogenolysis must have occurred,[10] although no pure product could be isolated.

An ethanolic alkaline solution of anibine turns yellow immediately, but the spectrum (λ_{max}^{KOH} 252, 282 and 381 mμ) changes upon long standing (λ_{max}^{KOH} 334 mμ), and the color is virtually discharged. When this reaction was carried out on a preparative scale, there was isolated an insoluble dipotassium salt ($C_{10}H_7K_2NO_4 \cdot H_2O$), which in contrast to anibine itself did not contain any methoxyl group. Acidification of an aqueous solution of the potassium salt resulted in decarboxylation—indicating the presence of a β-keto acid—and the isolation of an amphoteric crystalline solid, $C_9H_9NO_2$. The latter also could be obtained in somewhat poorer yield by boiling anibine with acid. The absence of a methoxyl group already was noted in the potassium salt precursor, but it was now observed that the cleavage product contained one C-methyl group, which was not present in the parent alkaloid. Consequently, this new C-methyl group must represent the point of attachment of the potential carboxyl group of anibine which was lost by decarboxylation during the acid and alkaline cleavage reactions.

The infrared spectrum of the $C_9H_9NO_2$ cleavage product was very instructive since it showed no definite OH absorption or significant carbonyl absorption below 6 μ. Rather, it exhibited a broad band in the 6.2 μ region typical of carboxylate or enolate anions, and the above-mentioned chemical and analytical data were only compatible with the latter. Catalytic hydrogenation resulted in the uptake of 5 moles of hydrogen, and since only 6 units of unsaturation are permissible in $C_9H_9NO_2$, the substance can only contain one ring, from which it follows that the tertiary nitrogen atom in a heterocyclic ring present in anibine must be represented by a pyridine ring. A $C_9H_9NO_2$ formulation containing one C-methyl group, a pyridine ring and a β-diketone enolate moiety can only be incorporated in partial formulas I or II. Of these, the former is rather unlikely since model Kuhn–Roth oxidations with various methylated pyridines showed that virtually no acetic acid was produced while the cleavage product yielded slightly over 100% of volatile acid. All three possible isomers of II have been described in the literature, and it was shown by direct comparison with a synthetic specimen that the $C_9H_9NO_2$ cleavage product of anibine was identical with the known[11] 1-(3′-pyridyl)-butane-1,3-dione (β-acetoacetylpyridine)-(III).[12]

With this information at hand, anibine can only be represented by 4-methoxy-6-(3′-pyridyl)-α-pyrone (VI). As stated above, the absence of a C-methyl group in anibine requires that the carboxyl group of the lactone be attached to the end of the side chain of III. Since anibine clearly did not contain a β-lactone ring, lactonization must have involved the oxygen atom at the δ-position, leading to structure V. Anibine, however, contains one methoxyl group which can only be incorporated into V as an enol ether grouping, thus resulting in expression IV for anibine,[13] which appears to be the first alkaloid containing an α-pyrone ring.



Crystallization of the neutral benzene-soluble fraction of rosewood furnished a colorless solid, m.p. 221–224°, possessing the empirical formula $C_{13}H_{10}O_5$. The substance possessed one methoxyl and no C-methyl group, exhibited no hydroxyl absorption but showed general spectral similarities to anibine. When boiled with alkali, there was isolated piperonylic acid and 3,4-methylenedioxyacetophenone (VII). On the other hand, when the reaction was conducted at room temperature with ethanolic potassium hydroxide as was the case with anibine (IV), there was isolated an insoluble potassium salt. Acidification led to an unstable β-keto acid, m.p. 125–130°, shown to have structure VIII, since it was decarboxylated readily upon heating or attempted recrystallization to the previously unknown 1-piperonyl-butane-1,3-dione (IX). This compound was identified by comparison with a synthetic specimen prepared from methyl piperonylate and acetone. By employing precisely the same arguments outlined above for ani-

(10) The empirical formula of anibine permits eight double bonds or rings. The presence of a lactone ring and of a heterocyclic ring in the parent alkaloid would allow only for the uptake of 5 moles of hydrogen unless hydrogenolysis occurred as well.

(11) A. Ferenczy, *Monatsh.*, **18**, 673 (1897).

(12) Subsequently, nicotinic acid was isolated in poor yield in one alkaline cleavage reaction and by nitric acid oxidation of anibine.

(13) The loss of the methoxyl group in the alkaline cleavage presumably involves addition of hydroxide ion at the β-position followed by reverse Michael condensation with expulsion of methoxide. The initial product ($C_{10}H_7K_2NO_4 \cdot H_2O$), isolated in the alkaline cleavage of anibine, should then be represented by the hydrate of VI.

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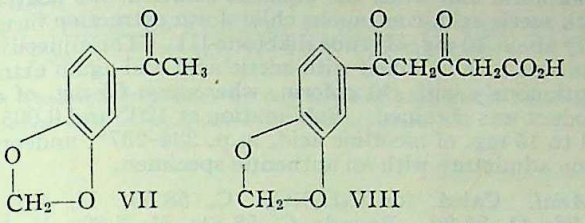
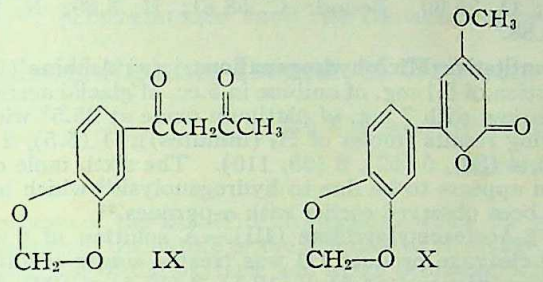
bine, the neutral product can only be 4-methoxy-6-piperonyl-α-pyrone (X).

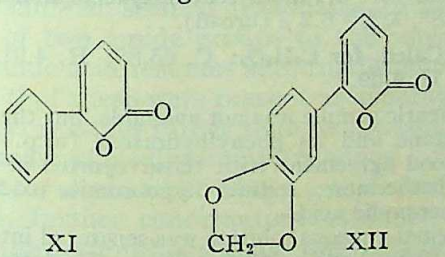


VII VIII



IX X

Aside from the steroidal toad poisons and squill glycosides,[14] α-pyrones are quite rare in nature.[15] It is interesting to note that the only two closely related naturally occurring α-pyrones, phenylcoumalin (6-phenyl-α-pyrone) (XI) and paracotoin (6-piperonyl-α-pyrone) (XII), are found in *Coto* and *Paracoto* bark.[16] Although it was known that the Bolivian *Coto* bark was derived from a tree belonging to the *Lauraceae*, all of the early medicinal and chemical work[17] was carried out when the taxonomic problem was still very confused.[18] Only the comparatively recent botanical revision of the *Lauraceae*[7] has resulted in the classification of *Coto* as *Aniba coto* (Rusby) Kostermans (syn. *Nectandra coto* Rusby) and of *Paracoto* as *Aniba pseudo-coto* (Rusby) Kostermans (syn. *Ocotea*[19] *pseudo-coto* Rusby). The striking chemical relationship between these four, naturally-occurring α-pyrones (IV, X, XI, XII) is thus paralleled by the close botanical connection of their plant sources, all of them belonging to the genus *Aniba*, and would suggest a common biogenetic origin. Synthetic experiments relating to these structures are now in progress.

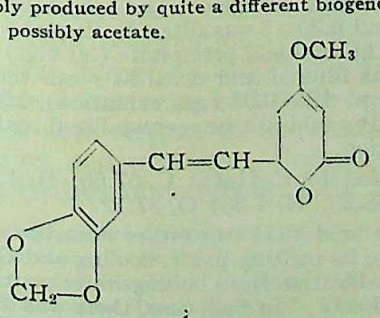


XI XII

(14) See C. Tamm in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. XIII, Springer, Vienna, 1956.

(15) See J. Fried in R. C. Elderfield's "Heterocyclic Compounds," Vol. I, John Wiley and Sons, New York, N. Y., 1950, pp. 354–370.

(16) Methysticin (i) and other 6-substituted-4-methoxy-5,6-dihydro-α-pyrones (*cf.* W. Borsche, C. H. Meyer and W. Peitzsch, *Ber.*, **60**, 2113 (1927)) isolated from *Piper methysticum* Forst. (fam. *Piperaceae*) are probably produced by quite a different biogenetic route from piperic acid and possibly acetate.



i

(17) A complete review of the chemical and biological work is given by Messner, *Pharm. Zentr.*, **67**, 625, 680, 696 (1926).

(18) *Cf.* H. H. Rusby, *J. Amer. Pharm. Assoc.*, **11**, 775 (1922); C. W. Maplethorpe, *Pharm. J.*, **110**, 238 (1923).

(19) It should be noted that rosewood itself was once assumed to belong to this genus (see ref. 5).

Experimental[20]

Extraction Procedure.—The rosewood[21] was reduced to sawdust and then extracted exhaustively with benzene in a Soxhlet apparatus. After concentration, the basic fraction was removed with dilute hydrochloric acid and the latter made alkaline with ammonia. Crude anibine (IV) was filtered and additional quantities could be recovered by chloroform extraction to raise the yield to 2.6%.

The benzene solution was next extracted several times with 3% sodium hydroxide solution, washed with water until neutral, dried and evaporated to yield a solid residue mixed with essential oil from which it could be separated by direct filtration. The solid (*ca.* 2%) was best purified by chromatography in order to remove an orange-colored contaminant and afforded 1.2% of 4-methoxyparacotoin (X).

Anibine (IV).—Crystallization from 95% ethanol and sublimation at 130° and 0.003 mm. provided colorless crystals, m.p. 179–180°, which showed no perceptible rotation in methanol solution (*c* 0.1) over the range 700–400 mμ and did not give any color with alcoholic ferric chloride solution. The infrared bands (Nujol or chloroform solution) were found at 5.77, 6.02 and 6.33 μ (no OH or NH absorption) and are thus somewhat shifted from those reported for steroidal bufadienolides.[22] The ultraviolet spectral data are listed in Table I.

TABLE I

Solvent	Max. mμ (log ε)	Shoulder mμ (log ε)	Min. mμ (log ε)
EtOH	228.5(4.32), 315(4.09)	254(3.70)	269(3.67)
1 *N* HCl–EtOH	227.5(4.22), 322(3.95)	254(3.71)	278(3.42)
1 *N* KOH–EtOH (immediate)	253(3.84), 282(3.72), 381(4.16)		275(3.71), 300(3.65)
1 *N* KOH–EtOH (after 1 week)	334(3.36)		293(2.96)

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89; O, 23.62; OCH_3, 15.27; mol. wt., 203. Found: C, 64.91; H, 4.56; N, 6.90; O, 23.31; OCH_3, 14.80; active H, 0.00; C–CH_3, 0.20; Rast mol. wt., 216.

The yellow **picrate** was prepared in ethanol solution and was recrystallized from the same solvent; m.p. 199–201°.

Anal. Calcd. for $C_{17}H_{12}N_4O_{10}$: C, 47.23; H, 2.80; N, 12.96. Found: C, 47.73; H, 2.50; N, 12.98.

Anibine hydrochloride was prepared by passing hydrogen chloride gas through an ethereal solution of anibine and recrystallizing from absolute ethanol. The decomposition point varied greatly m.p. 179–209° (dec. Kofler), 205–230° (dec. sealed capill.). As indicated in the Discussion, anibine can be removed in *ca.* 80% yield from aqueous hydrochloric acid by continuous extraction (14 hr.) with chloroform.

Anal. Calcd. for $C_{11}H_{10}ClNO_3$: C, 55.12; H, 4.21; Cl, 14.81; N, 5.84. Found: C, 54.87; H, 4.23; Cl, 14.34; N, 5.68.

The pale yellow **methiodide** was formed when a methanolic solution of anibine was left at room temperature overnight with an excess of methyl iodide. The precipitate was recrystallized once from methanol and dried *in vacuo* at room temperature; m.p. 233–236° dec.

Anal. Calcd. for $C_{12}H_{12}INO_3$: C, 41.75; H, 3.51; N, 4.06; O, 13.91; I, 36.77. Found: C, 41.88; H, 3.55; N, 3.95; O, 13.87; I, 36.85.

(20) All melting points were determined on the Kofler block. We are indebted to Mrs. Dolores Phillips for the spectral measurements and to Dr. A. Bernhardt (Mülheim, Germany) and Mr. Joseph F. Alicino (Metuchen, N. J.) for the microanalyses.

(21) The composition of both rosewood samples (*Aniba Duckei* and *A. rosaeodora*) in terms of their main constituents was qualitatively identical, but the yields recorded are for a sample of commercial *A. Duckei* from Manaus, Amazonas.

(22) N. Jones and W. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

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Acid Cleavage of Anibine (IV).—A solution of 200 mg. of anibine in 50 cc. of 5% hydrochloric acid was heated under reflux for 6 hr. in a stream of nitrogen, decarboxylation occurring during this process as evidenced by the precipitation of barium carbonate (88% yield) in a barium hydroxide trap. The solution was cooled, extracted continuously with chloroform for 17 hr., and the chloroform layer was washed with water, dried and evaporated. The residual semi-solid (55 mg.) was crystallized from petroleum ether and then sublimed at 80° and 0.005 mm.; m.p. 84–86°, red color with ferric chloride, $\lambda_{max}^{CHCl_3}$ broad band at 6.1–6.25 μ and small band at 5.80 μ. The ultraviolt absorption data are listed in Table II.

TABLE II

Solvent	Max., mμ (log ϵ)	Min., mμ (log ϵ)
EtOH	236(3.88), 309(4.15)	256(3.57)
1 *N* HCl–EtOH	251.5(3.83), 315(4.07)	236(3.73), 268(3.69)
1 *N* KOH–EtOH	245(3.79), 330(4.17)	275(3.47)

Identity with a synthetic specimen[11] of β-acetoacetylpyridine (III) was established by mixture melting point determination and infrared spectral comparison.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58; O, 19.61; C–CH_3, 9.20; active H, 0.61; mol. wt., 163. Found: C, 66.32; H, 5.42; N, 8.66; O, 20.22; OCH_3, 0.00; C–CH_3,[23] 9.42, 9.64; active H, 0.69; neut. equiv. (perchloric acid titration), 162.

Alkaline Cleavage of Anibine.—A solution of 200 mg. of anibine dissolved in 40–50 cc. of 1 *N* ethanolic potassium hydroxide was kept at 20° in an atmosphere of nitrogen. After 2–3 hr. crystals started to appear and these were filtered after 15 hr. and washed well with absolute ethanol; yield 163 mg., m.p. 240–250° dec. This virtually colorless potassium salt (VI) was insoluble in organic solvents, highly soluble in water and gave a red color with ferric chloride solution. The analysis as well as the infrared spectrum (λ_{max}^{Nujol} 3.03, 6.08, 6.18 and 6.29 μ) indicated the presence of water, but this could not be removed even on attempted azeotropic distillation with toluene.

Anal. Calcd. for $C_{10}H_7K_2NO_4 \cdot H_2O$: C, 39.85; H, 3.01; N, 4.65; K, 26.54. Found: C, 39.96; H, 2.91; N, 4.39; K, 25.79; OCH_3, 0.00.

The potassium salt VI could be transformed into the corresponding silver salt by dissolving in water and adding 5% aqueous silver nitrate solution. The pale yellowish precipitate was dried in a desiccator before analysis.

Anal. Calcd. for $C_{10}H_7Ag_2NO_4 \cdot H_2O$: C, 27.36; H, 2.07; N, 3.19; Ag, 49.15. Found: C, 26.94; H, 1.85; N, 2.97; Ag, 50.33.

A solution of 511 mg. of the potassium salt VI in 50 cc. of water was acidified with a few drops of hydrochloric acid and then extracted continuously with chloroform for 30 hr. The extraction was accompanied by decarboxylation as demonstrated by the formation of barium carbonate in a barium hydroxide trap attached to the extraction apparatus. The chloroform solution was dried, evaporated to dryness and the crystalline residue was sublimed at 80° and 0.005 mm. to yield 316 mg. of pure β-acetoacetylpyridine (III), m.p. 84–86°. This is the preferred procedure since the over-all yield based on anibine is 50%. The cleavage product readily forms a 2:1 adduct with silver nitrate in water solution.

Anal. Calcd. for $C_{18}H_{18}N_2O_4 \cdot AgNO_3$: C, 43.57; H, 3.66; N, 8.46; Ag, 21.74. Found: C, 43.35; H, 3.32; N, 8.72; Ag, 21.73.

Isolation of Nicotinic Acid from Cleavage of Anibine (IV).—In one experiment, the ethanolic potassium hydroxide solution of 150 mg. of anibine was left for only 1 hr., most of the ethanol was removed at room temperature *in vacuo* and water was added. Nothing could be extracted by means of chloroform and when the aqueous solution was neutralized with acetic acid, continuous chloroform extraction furnished only about 10 mg. of crude diketone III. The aqueous solution was then acidified with acetic acid and again extracted continuously with chloroform, whereupon 65 mg. of crude product was obtained. Sublimation at 120° and 0.005 mm. led to 15 mg. of nicotinic acid, m.p. 234–237°, undepressed upon admixture with an authentic specimen.

Anal. Calcd. for $C_6H_5NO_2$: C, 58.53; H, 4.09; N, 11.38; O, 25.99. Found: C, 58.81; H, 3.89; N, 11.40; O, 25.88.

Quantitative Microhydrogenations. (a) **Anibine (IV).**—A solution of 6.1 mg. of anibine in 5 cc. of glacial acetic acid was shaken with 7 mg. of platinum oxide at 25.5° with the following results (moles of H_2 (minutes)): 1 (5.5), 2 (14), 3 (25), 4 (39), 5 (52), 6 (65, 110). The sixth mole of hydrogen appears to be due to hydrogenolysis[10] which has already been observed earlier with α-pyrones.[24]

(b) β-Acetoacetylpyridine (III).—A solution of 6.9 mg. of the cleavage product III was treated under exactly the same conditions: 1 (4.5), 2 (10.5), 3 (17.5), 4 (29), 5 (78, 94).

4-Methoxyparacotoin (4-Methoxy-6-piperonyl-α-pyrone) (X).—The crude product was purified by chromatography on alumina deactivated with 3% of 10% acetic acid and eluted with benzene. Recrystallization from ethanol yielded the analytical sample as colorless needles, m.p. 222–224°, $[\alpha]D \pm 0°$ ($CHCl_3$); λ_{max}^{Nujol} 5.75, 6.04, 6.12 and 6.38 μ; λ_{max}^{EtOH} 336 mμ (log ϵ 3.98), λ_{min}^{EtOH} 272 mμ (log ϵ 3.44).

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.41; H, 4.09; O, 32.49; OCH_3, 12.59. Found: C, 63.30; H, 4.07; O, 32.68; OCH_3, 12.73; C–CH_3, 0.00.

Alkaline Cleavage of 4-Methoxyparacotoin (X). (a) **With Boiling Alkali.**—A solution of 201 mg. of 4-methoxyparacotoin (X) was heated under reflux for 3 hr. with 20 cc. of 0.5 *N* ethanolic potassium hydroxide. After dilution with water, the neutral material was extracted continuously with chloroform yielding 93 mg. of cream colored solid, m.p. 53–80°.

Recrystallization from water gave 45 mg. of small, colorless needles of **3,4-methylenedioxyacetophenone (VII)**, m.p. 87–88°, $\lambda_{max}^{CHCl_3}$ 6.2 μ (broad).

Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 66.35; H, 4.59.

An authentic sample was not available, but the constants of the ketone and its phenylhydrazone (m.p. 112–114°) were in good agreement with those reported in the literature.[25] Furthermore, sodium hypobromite oxidation furnished piperonylic acid.

The original aqueous solution was separated into phenolic (less than 10 mg.) and acidic fractions. The latter (34 mg.) represented a yellowish solid which crystallized from ethanol as colorless needles, m.p. 231–233°, undepressed upon admixture with an authentic sample of **piperonylic acid** (m.p. 231–233°).

(b) **At Room Temperature.**—A solution of 100 mg. of 4-methoxyparacotoin (X) was left at room temperature in 50 cc. of 1 *N* ethanolic potassium hydroxide solution for 24 hr. in a current nitrogen. The potassium salt (59 mg., λ_{max}^{Nujol} 3.15 and 6.30 μ) was filtered, dissolved in water and acidified. The colorless precipitate (30 mg.) of the **β-keto acid VIII** was filtered and dried at room temperature for analysis; m.p. 125–130° (gas evolution), λ_{max}^{Nujol} 5.82, 6.08 and 6.2 μ. It could not be recrystallized without effecting decarboxylation.

Anal. Calcd. for $C_{12}H_{10}O_6$: C, 57.60; H, 4.03; O, 38.37. Found: C, 58.23; H, 4.30; O, 37.12.

The β-keto acid VIII was either decarboxylated by first heating above its melting point, cooling and then subliming or by recrystallization from boiling water containing a small amount of ethanol. In each case, there was obtained colorless crystals of **1-piperonyl-butane-1,3-dione (IX)**, m.p. 91–

(23) On the other hand, Mr. Alcino reported that under the same conditions of the Kuhn–Roth oxidation, α-, β- and γ-picoline as well as 2,6-lutidine yielded no titratable acetic acid. Up to 90% of acetic acid could be obtained when the pyridine ring was activated (*e.g.*, 2-amino-4-methylpyridine, pyridoxine).

(24) See A. Stoll, A. Hofmann and H. Helfenstein, *Helv. Chim. Acta*, **18**, 644 (1935); J. Fried and R. C. Elderfield, *J. Org. Chem.*, **6**, 566 (1941).

(25) G. Ciamician and P. Silber, *Ber.*, **24**, 2989 (1891), report m.p. 88° for the ketone and m.p. 114° for its phenylhydrazone.

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92°; $\lambda_{max}^{CHCl_3}$ 5.80 (small) and broad, strong band at 6.2 μ; λ_{max}^{EtOH} 238.5 and 335 mμ, log ϵ 4.02 and 4.29; λ_{max}^{EtOH} 253 mμ, log ϵ 3.64.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89; C-CH_3, 7.29. Found: C, 63.60; H, 4.82; C-CH_3, 8.13.[26]

(26) The high value may be due to small amounts of piperonylic acid carried over in the Kuhn–Roth determination.

The substance proved to be identical by mixture melting point determination and infrared comparison with a synthetic specimen (m.p. 92–93°) prepared by condensation of methyl piperonylate and acetone in ether solution in the presence of sodium.

DETROIT, MICHIGAN
RIO DE JANEIRO, BRAZIL

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

The Isoglutamine Isomer of Oxytocin: Its Synthesis and Comparison with Oxytocin[1]

BY CHARLOTTE RESSLER AND VINCENT DU VIGNEAUD

RECEIVED FEBRUARY 27, 1957

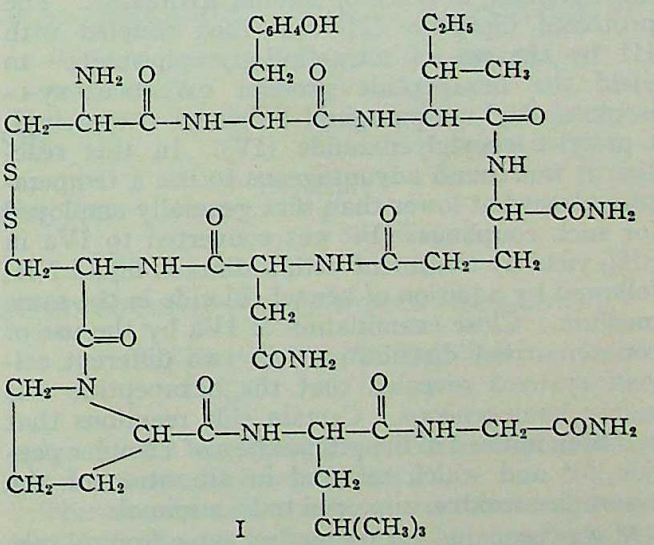
Synthesis of the isomer of oxytocin in which the glutamine residue has been substituted by isoglutamine is described. The change in the nature of the glutamic acid linkage with the consequent ring enlargement was found to result in virtually complete loss of the oxytocic and avian depressor activities of oxytocin. The *isoglutamine-oxytocin* differed from oxytocin also in some of its physical properties and exhibited a striking difference in optical rotation. However, several of the other properties of the two polypeptides were found to be indistinguishable.

The structure of oxytocin, the chief oxytocic principle of the posterior pituitary gland, has been established through its synthesis[2,3] as an octapeptide composed of a 20-membered cyclic disulfide ring branched by a tripeptide side chain, namely, the cyclic disulfide of L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide.

It may be recalled that this synthesis was based on structural studies[4] in this Laboratory on natural oxytocin and, in addition, on certain assumptions regarding the position of two amide groups and the nature of the linkages of the aspartic acid and glutamic acid residues. In proposing the structure for oxytocin[4,5] it seemed reasonable to assign the position of two amide groups to the aspartic acid and glutamic acid residues and, furthermore, it was assumed that these were present as asparaginyl and glutaminyl residues rather than as the isomeric isoasparaginyl and isoglutaminyl residues. After this structure for oxytocin had been established through synthesis, further confirmatory evidence with respect to the assumptions made was obtained by the demonstration of the presence of glutamine and asparagine in enzymatic hydrolysates of oxytocin and vasopressin.[6]

It was of considerable interest to determine whether oxytocin could be distinguished from the octapeptides isomeric with it with respect to the glutamine and/or asparagine residues. Such isomers would allow observations on the effect of a small structural change on the physical and chemical properties of oxytocin, and these results might be of interest with respect to the characterization of polypeptides and proteins. Comparison of the biological activities of oxytocin with those of its isoglutamine and/or isoasparagine isomer would provide, in addition, information bearing on the relationship of structure to the biological activities of the oxytocic hormone.

These considerations have led us to undertake the synthesis of the isoglutamine isomer of oxytocin. In this polypeptide an isoglutamine residue replaces the glutamine residue of oxytocin. It may be noted that the ring moiety of this isomer is larger by two methylene units than that present in oxytocin, and thus, *isoglutamine-oxytocin* (I) possesses a 22-membered ring.



I

The synthesis of isoglutamine-oxytocin was approached *via* the nonapeptide intermediate N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-isoglutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (VI), which corresponds in structure to the key intermediate used in the synthesis of oxytocin, with isoglutamine replacing the glutamine of the oxytocin intermediate. In the synthesis of oxytocin, suitable reduction of the nonapeptide intermediate followed by oxidation led to the desired 20-membered cyclic disulfide hormone. The projected synthesis of isoglutamine-oxytocin through a similar route, *i.e.*, by oxidation of the appropriate sulfhydryl nonapeptide, involved the as-

(1) This work was supported in part by a grant (H-1675) from the National Heart Institute, Public Health Service.

(2) V. du Vigneaud, C. Ressler, J. M. Swan, C. W. Roberts, P. G. Katsoyannis and S. Gordon, THIS JOURNAL, **75**, 4879 (1953).

(3) V. du Vigneaud, C. Ressler, J. M. Swan, C. W. Roberts and P. G. Katsoyannis, *ibid.*, **76**, 3115 (1954).

(4) V. du Vigneaud, C. Ressler and S. Trippett, *J. Biol. Chem.*, **205**, 949 (1953).

(5) H. Tuppy, *Biochim. Biophys. Acta*, **11**, 449 (1953).

(6) H. C. Lawler, S. P. Taylor, A. M. Swan and V. du Vigneaud, *Proc. Soc. Exper. Biol. Med.*, **87**, 550 (1954).

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sumption that ring closure to a 22-membered cyclic disulfide could be effected. Actually, the synthesis of the appropriate sulfhydryl nonapeptide afforded an excellent opportunity to determine whether oxidation would lead to a 22-membered cyclic disulfide. If closure to a ring of this size could not be effected, a larger disulfide ring might well be formed or a polymer might result. It was therefore vital, after oxidation of the isoglutamine sulfhydryl nonapeptide and isolation of the corresponding disulfide, to determine the molecular weight of the compound.

The synthetic reactions leading to isoglutamine-oxytocin are summarized in the accompanying diagram. Throughout the synthetic work described, the carbobenzoxy group was used to protect the amino group,[7] and the benzyl group served to protect the sulfhydryl group. The protective groups were removed by reductions with sodium in liquid ammonia.[8]

The preparation of VI was accomplished by coupling N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucine (V) with the hexapeptide amide L-isoglutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (IVa), which had been prepared in turn from the coupling product of carbobenzoxy-L-isoglutaminyl-L-asparagine (II) and S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (III).[9]

Carbobenzoxy-L-isoglutaminyl-L-asparagine (II) was prepared by the condensation of carbobenzoxy-L-isoglutamine with asparagine in aqueous solution by means of the mixed anhydride procedure with isobutyl chlorocarbonate,[10] modified by the use of triethylamine in place of sodium hydroxide. The protected dipeptide (II) was then coupled with III by the use of tetraethyl pyrophosphite[11] to yield the hexapeptide product carbobenzoxy-L-isoglutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (IV). In this reaction it was found advantageous to use a temperature somewhat lower than that generally employed for such couplings. IV was converted to IVa in 81% yield by treatment with sodium in liquid NH_3 followed by addition of benzyl chloride in the same medium. Close examination of IVa by the use of countercurrent distribution[12] in two different solvent systems revealed that the hexapeptide was highly homogeneous. Certain side reactions that had been noticed in the preparation of a similar peptide,[13,14] and which resulted in alteration of the asparagine residue, appeared to be minimal.

V was prepared *via* its methyl ester from N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosine and methyl L-isoleucinate by the N,N′-dicyclohexylcarbodiimide method.[15] Although some of the physical constants of both the ester and acid V differed from the values in the literature for these compounds obtained through several other methods, application here of one of the reported procedures[16] led to material which, after further purification, agreed closely in melting point and rotation with the methyl ester of V obtained here through the carbodiimide method.

V was coupled with IVa in aqueous tetrahydrofuran by the use of N,N′-dicyclohexylcarbodiimide and yielded the protected nonapeptide VI in 64% yield. All the protecting groups were then removed from VI by treatment with sodium in liquid NH_3, and the resulting material was oxidized to the disulfide form by aeration in aqueous solution at *p*H 6.9.

The final product was isolated by countercurrent distribution in 0.05% acetic acid–*sec*-butyl alcohol (K = 0.37) followed by distribution in 0.01 M NH_3–*sec*-butyl alcohol (K = 1.8). Only one product was found in contrast to the situation with the earlier syntheses of two other related polypeptides, namely oxytocin[3] and the cyclic disulfide of L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinamide.[13,14] Data obtained from the final distribution of the isoglutamine polypeptide indicated that the material possessed a high degree of purity.

That the compound actually possessed the desired monomeric octapeptide structure was shown by the value obtained for the molecular weight, which was within the expected range.

Isoglutamine-oxytocin was tested for some of the physiological activities associated with oxytocin. Oxytocic activity was measured on the isolated rat uterus according to the method of Burn[17] and the avian blood pressure effect was determined in the anaesthetized chicken by the method of Coon.[18] The U. S. P. Standard posterior lobe powder served as reference. Since it was desired to test the polypeptide also in its reduced form, a solution of the peptide was also assayed in the chicken soon after reduction without subsequent aeration. In addition, the reduction product was tested in the presence of added cysteine. The isoglutamine polypeptide was found to be essentially inert, any activity, if present, existing below the limits of detection of the assay procedures. Similar results were obtained with the reduced preparations. Based on the amounts of compound tested, the oxytocic activity was estimated to be below 0.01 unit per mg., and the avian vasodepressor activity below 0.05 unit per mg. In view of the high potencies of these biological effects in oxytocin (500 units per mg.) and the great sensitivity of the assay procedures,[19] the virtual absence of these activities in isoglutamine-oxytocin is striking and emphasizes the very high degree of biological specificity associated with those structural aspects of the oxytocic hormone under consideration. Fur-

(7) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).
(8) R. H. Sifferd and V. du Vigneaud, *J. Biol. Chem.*, **108**, 753 (1935).
(9) C. Ressler and V. du Vigneaud, THIS JOURNAL, **76**, 3107 (1954).
(10) J. R. Vaughan, Jr., *ibid.*, **73**, 3547 (1951).
(11) G. W. Anderson, J. Blodinger and A. D. Welcher, *ibid.*, **74**, 5309 (1952).
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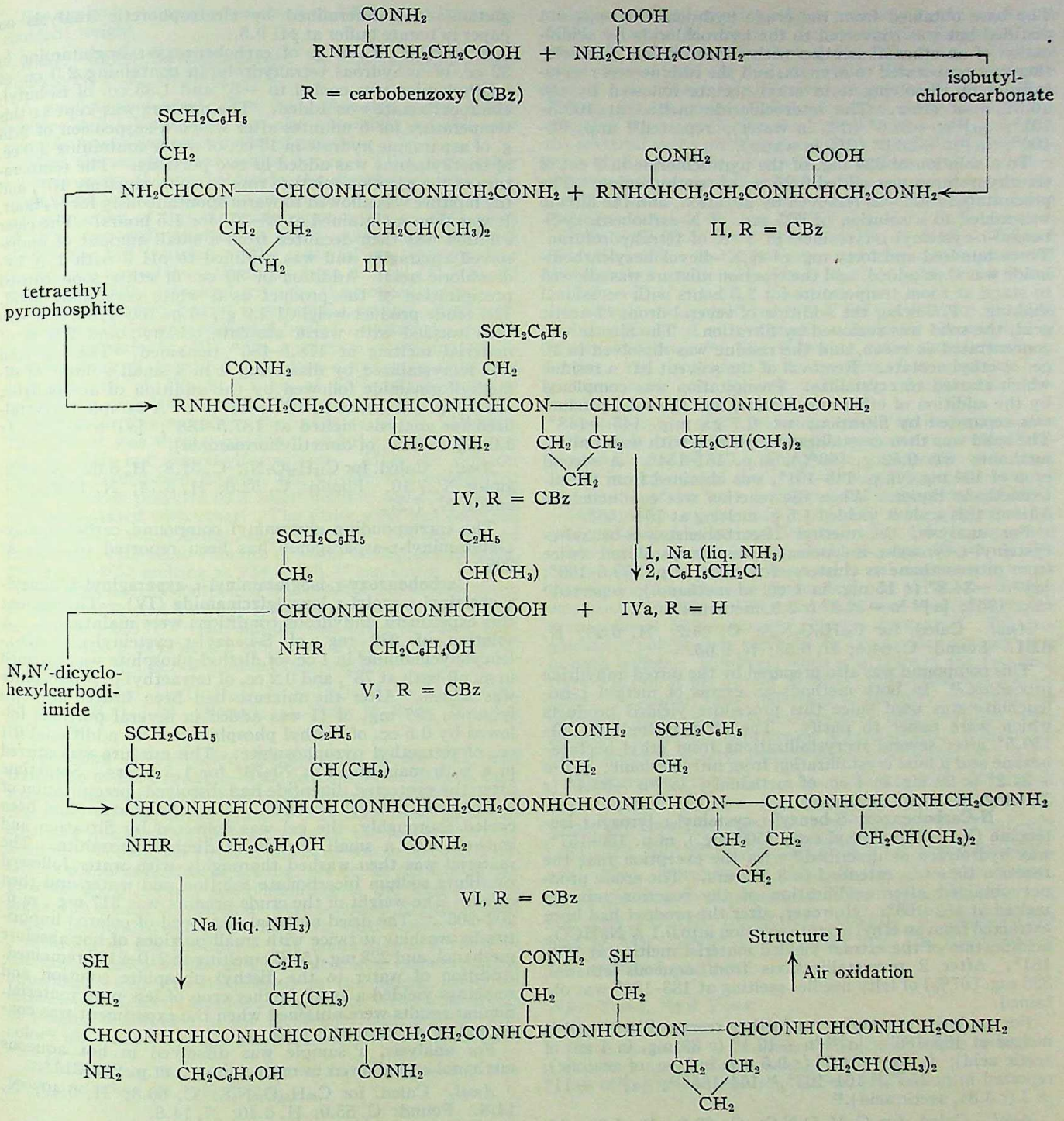

thermore, no pressor activity was detected when measured in the rat.[20]

The isoglutamine octapeptide was found to have the expected amino acid composition. Its distribution coefficient was essentially the same as that of oxytocin in the acetic acid–*sec*-butyl alcohol system, but in the ammonia–*sec*-butyl alcohol system the coefficient was somewhat higher than that of oxytocin. The physical constant that was found to differ most strikingly from oxytocin was the optical rotation. The specific rotation in water of the acetate of isoglutamine-oxytocin was approximately 59 degrees higher than that of oxytocin, as given in the Experimental section. No differences were detected in the infrared patterns of isoglutamine-oxytocin and oxytocin. Only small differences were observed when the two polypeptides were subjected to electrophoresis on paper at both *p*H 5.5 and *p*H 9.5.

These comparative data on oxytocin and its isoglutamine isomer demonstrate that small changes in the structure of a polypeptide of this degree of complexity may indeed be reflected in some of the properties. Thus, oxytocin and its isoglutamine isomer can be differentiated readily on the basis of certain differences in physical behavior as well as in biological properties, although a few of the properties of these two polypeptides are indistinguishable.

Experimental[21]

Methyl N-Carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucinate.—Methyl L-isoleucinate hydrochloride was prepared as described[16] with the following modification.

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(21) The reported melting points are corrected, capillary melting points.

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The base obtained from the crude hydrochloride was not distilled but was converted to the hydrochloride by acidification of an ethereal solution with concd. HCl. The solution was evaporated to dryness, and the residue was recrystallized by dissolving it in ethyl acetate followed by the addition of ether. The hydrochloride melted at 100.5–101°; $[\alpha]^{23}D$ +26.6° (2% in water); reported[22] m.p. 98–100°; $[\alpha]^{21}D$ +26.6° (2% in water).

To a solution of 324 mg. of the hydrochloride in 2 cc. of tetrahydrofuran was added 0.25 cc. of triethylamine. The precipitated solid was removed by filtration, and the filtrate was added to a solution of 625 mg. of N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosine[23] in 3 cc. of tetrahydrofuran. Three hundred and forty mg. of N,N′-dicyclohexylcarbodiimide was then added, and the reaction mixture was allowed to stand at room temperature for 2.5 hours with occasional shaking. Following the addition of several drops of acetic acid, the solid was removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was dissolved in 10 cc. of ethyl acetate. Removal of the solvent left a residue which started to crystallize. Precipitation was completed by the addition of ether and hexane, and the solid product was separated by filtration; wt. 0.7 g., m.p. 145.5–148°. The solid was then crystallized by stirring with warm nitromethane; wt. 0.52 g. (66%), m.p. 151–154°. A second crop of 104 mg., m.p. 146–151°, was obtained from the nitromethane liquor. When the reaction was conducted on 3 times this scale it yielded 1.5 g. melting at 154–156°.

For analysis, the methyl N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucinate was recrystallized twice from nitromethane as clusters of needles, m.p. 159.5–160°; $[\alpha]^{23}D$ −34.8° (*c* 15 mg. in 1 cc. of methanol); reported[16] m.p. 135°; $[\alpha]^{19.5}D$ −32.3° (*c* 2.9, methanol).

Anal. Calcd. for $C_{34}H_{41}O_7N_3S$: C, 64.2; H, 6.50; N, 6.61. Found: C, 64.4; H, 6.59; N, 6.65.

This compound was also prepared by the mixed anhydride procedure.[16] In both methods an excess of methyl L-isoleucinate was used since this procedure yielded products which were easier to purify. The ester melted at 159–159.5° after several recrystallizations from ethyl acetate–hexane and a final crystallization from nitromethane; $[\alpha]^{24}D$ −34.2° (*c* 29 mg. in 1 cc. of methanol); $[\alpha]^{24}D$ −34.7° (*c* 13.6 mg. in 1 cc. of methanol).

N-Carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucine (V).—The methyl ester (500 mg.), m.p. 156–157°, was hydrolyzed as described[16] with the exception that the reaction time was extended to 3.5 hours. The crude product obtained after acidification of the reaction mixture melted at 162–166°. However, after the product had been extracted from an ethyl acetate solution into 0.1 *N* $NaHCO_3$, acidification of the extract yielded material melting at 179–181°. After 2 recrystallizations from aqueous ethanol, 326 mg. (67%) of felty needles melting at 183–184° was obtained.

For analysis, a sample was further recrystallized, and it melted at 185–186°; $[\alpha]^{23.5}D$ −10.1° (*c* 39 mg. in 1 cc. of acetic acid); $[\alpha]^{23}D$ −31.2° (*c* 9.5 mg. in 1 cc. of acetone); reported m.p. 155°,[16] 161–163°,[24] 164–165°[25]; $[\alpha]^{23}D$ −11° ± 1 (*c* 3.84, acetic acid).[25]

Anal. Calcd. for $C_{33}H_{39}O_7N_3S$: C, 63.8; H, 6.32; N, 6.76. Found: C, 63.7; H, 6.51; N, 6.75.

Carbobenzoxy-L-isoglutaminyl-L-asparagine (II).—Carbobenzoxy-L-isoglutamine was prepared according to Bergmann and Zervas[7] by the addition of carbobenzoxy-L-glutamic acid anhydride[26] to a cooled solution of ammonia in chloroform. It was recrystallized from acetone–petroleum ether followed by ethanol–petroleum ether, after which the melting point was 172.5–173.5°; reported[7] m.p. 175°. A sample treated at room temperature with 1 *N* HBr in acetic acid for 2 hr. to remove the carbobenzoxy group was free of glutamine as determined by electrophoretic analysis on paper in borate buffer at *p*H 9.5.

A solution of 4.0 g. of carbobenzoxy-L-isoglutamine in 32 cc. of anhydrous tetrahydrofuran containing 2.0 cc. of triethylamine was cooled to −5° and 1.83 cc. of isobutylchlorocarbonate was added. The mixture was kept at this temperature for 5 minutes after which a suspension of 2.14 g. of asparagine hydrate in 16 cc. of water containing 2.0 cc. of triethylamine was added in two portions. The temperature of the reaction mixture rose to approximately 10°, and the mixture was allowed to warm spontaneously for ½ hour. It was then maintained at 25–30° for 1.5 hours. The clear solution was then decanted from a small amount of undissolved asparagine and was acidified to *p*H 3 with 1 *N* hydrochloric acid. Addition of 50 cc. of ether soon caused precipitation of the product as a white crystalline solid. The crude product weighed 2.9 g., m.p. 166–170°. It was then washed with warm absolute ethanol, and 2.6 g. of material melting at 178.5–180° remained. The material was recrystallized by dissolving it in a small volume of dimethylformamide followed by the addition of acetonitrile; wt. 2.3 g. (41%), m.p. 186.5–187.5°. A sample recrystallized for analysis melted at 187.5–188°; $[\alpha]^{21}D$ +7.28° (*c* 3.0 mg. in 1 cc. of dimethylformamide).

Anal. Calcd. for $C_{17}H_{22}O_7N_4$: C, 51.8; H, 5.62; N, 14.2; amide N, 7.10. Found: C, 52.0; H, 5.74; N, 14.3, 13.9; amide N, 7.27.

The corresponding glutaminyl compound carbobenzoxy-L-glutaminyl-L-asparagine[27] has been reported to melt at 206°.

Carbobenzoxy-L-isoglutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (IV).—Throughout this experiment anhydrous conditions were maintained. A solution of 239 mg. of S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide[9] in 1 cc. of diethyl phosphite was warmed in an oil-bath at 78°, and 0.2 cc. of tetraethyl pyrophosphite was added. After the mixture had been heated for two minutes, 197 mg. of II was added in several portions followed by 0.5 cc. of diethyl phosphite and an additional 0.1 cc. of tetraethyl pyrophosphite. The mixture was stirred in a bath maintained at 70–72° for 1.5 hours. Sometime after the protected dipeptide had dissolved, precipitation of the product as a gel occurred. After the mixture had been cooled thoroughly, the gel was collected by filtration and washed with a small portion of diethyl phosphite. The material was then washed thoroughly with water followed by dilute sodium bicarbonate solution and water and then dried. The weight of the crude product was 317 mg., m.p. 202–206°. The dried material was freed of colored impurities by washing it twice with small portions of hot absolute methanol, and 228 mg. (54%) melting at 210–213° remained. Addition of water to the diethyl phosphite solution and washings yielded a small further crop of less pure material. Similar results were obtained when the experiment was conducted on six times this scale.

For analysis, a sample was dissolved in hot aqueous methanol and allowed to reprecipitate; m.p. 212–214°.

Anal. Calcd. for $C_{40}H_{55}O_{10}N_9S$: C, 56.3; H, 6.49; N, 14.8. Found: C, 55.9; H, 6.40; N, 14.8.

L-Isoglutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (IVa).—A solution of 200 mg. of the protected hexapeptide amide IV in 50 cc. of liquid ammonia was treated at −40° under anhydrous conditions with sodium until a deep blue color lasting approximately 30 seconds was obtained. A solution of 34 mg. of benzyl chloride in toluene was added, and the mixture was stirred for 1 hour, after which 146 mg. of ammonium chloride was added, and the ammonia was removed *in vacuo*. The water-soluble residue was extracted with ether and the insoluble portion was distributed for 105 transfers in the system 0.01 *M* NH_3–*sec*-butyl alcohol. The distribution of material was followed by determining the absorption in the ultraviolet at 260 mμ and the copper-Folin color[28] at 700 mμ. One main band, with a partition coefficient of 1.3, was obtained which agreed rather well with the theoretical curve. Concentration and lyophilization of the contents of the appropriate tubes yielded 114 mg. (68%).

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For analysis, a sample was dried at 100° and 0.1 mm. to constant weight.

Anal. Calcd. for $C_{32}H_{49}O_8N_9S$: N, 17.5; amide N, 5.84. Found: N, 17.2; amide N, 5.60.

A small second band (K = 0.11) that was copper-Folin-positive and UV-negative was also obtained, and this presumably contained unbenzylated peptide.

When the reaction was carried out on a 2.0-g. scale using a 2 mole excess of benzyl chloride, the distribution yielded a single band with a total yield of 1.6 g. A portion of a large center fraction of this material, representing an 81% yield of IVa, was redistributed in 0.5% acetic acid–*sec*-butyl alcohol for 177 transfers. The material was recovered as the acetate almost quantitatively from a band (K = 0.34) which essentially coincided with the theoretical curve.

Carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-isoglutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (VI).—To a solution of 240 mg. of N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucine and 250 mg. of IVa in 1.5 cc. of 75% tetrahydrofuran at +5° was added 90 mg. of N,N′-dicyclohexylcarbodiimide. The mixture was stored in the refrigerator for 19 hours. The solvent was then evaporated, and the residue was extracted with hot dimethylformamide. After the extracts had been cooled and filtered, the filtrate was evaporated under reduced pressure to a small volume and the product was precipitated with ether. The white solid was collected by filtration; wt. 400 mg., m.p. 229–231°. When washed three times with small volumes of warm methanol and dried, 296 mg. (64%) melting at 234.5–236.5° remained.

For analysis, the compound was dissolved in several drops of cold formic acid and was reprecipitated with cold water, m.p. 234.5–236.5°. The sample was dried at room temperature for 2 days at 0.2 mm. over P_2O_5, $[\alpha]^{21.7}D$ −44.1° (*c* 9.99 mg. in 1 cc. of dimethylformamide).

Anal. Calcd. for $C_{65}H_{86}O_{14}N_{12}S_2 \cdot H_2O$: C, 58.2; H, 6.62; N, 12.5; H_2O, 1.36. Found: C, 58.0; H, 6.58; N, 12.4; H_2O, 1.80.

Reduction of Protected Nonapeptide Amide (VI) and Oxidation of the Product.—Two batches VI of 200 mg. each were reduced with sodium in liquid ammonia and treated as described for the preparation of oxytocin from its corresponding nonapeptide derivative[3] with the following modifications. The dried reduced material was aerated in solution at a concentration of 0.4 mg. per cc. at *p*H 6.9 for approximately 3 hours. After standing in the ice-box overnight, the combined solutions were adjusted to *p*H 3.5 and were concentrated and lyophilized to a white powder.

Isolation of the Product.—The material was divided in the first 5 tubes of the all-glass automatic countercurrent apparatus[29] and was distributed in the system *sec*-butyl alcohol–0.05% acetic acid for 592 transfers. Determinations of weight, absorption in the ultraviolet, and copper-Folin color[28] all defined a single band traveling with a K of 0.37, which was irregularly shaped due probably to the emulsions which occurred in this area during the distribution. The material was then redistributed for 197 transfers in *sec*-butyl alcohol–0.01 M NH_3 in which the K was approximately 1.8. Spectrophotometric analysis at 275 mμ and at 700 mμ for the copper-Folin color, and comparison of the resulting curves with the theoretical curve indicated that the material had a purity estimated as over 90%. The contents of the peak were removed in fractions, and these were concentrated to a small volume. The solutions were acidified with acetic acid and finally were dried by lyophilization yielding a total of 152 mg. (50%) of a white fluffy powder; $[\alpha]^{21.5}D$ +33.0° (*c* 0.55, water), $[\alpha]^{24}D$ +24.2° (*c* 0.54, 1 N acetic acid). In comparison, oxytocin acetate possessed the negative rotations $[\alpha]^{22}D$ −26.2° (*c* 0.53, water)[3] and $[\alpha]^{22.5}D$ −23.1° (*c* 0.51, 1 N acetic acid).

A sample was hydrolyzed in 6 N HCl at 120° for 14 hours and was analyzed on the starch column by the method of Moore and Stein.[30] The following ratios were obtained: leucine, 1.0; isoleucine, 1.0; tyrosine, 0.9; proline, 0.9; glutamic acid, 1.0; aspartic acid, 1.1; glycine, 1.0; ammonia, 3.1; and cystine, 0.8.

Determination of the molecular weight of the isoglutamine polypeptide by the thermoelectric osmometer method[31] indicated a value of 852. This result corresponds with what would be expected of the cyclic octapeptide represented by Structure I, which has a calculated molecular weight of 1007.

Isoglutamine-oxytocin and oxytocin were applied separately to a doubled strip of Whatman No. 1 filter paper and subjected to electrophoretic analysis using 300 v. at 5°. Acetate buffer at *p*H 5.5 was used in one experiment which was run for 11 hours, and glycine buffer at *p*H 9.5 for 8 hours was used in another. The materials were stained with the brom phenol blue–mercuric chloride reagent.[32] The isoglutamine polypeptide traveled slightly faster than oxytocin in both buffers. However, when a mixture of the two peptides was run at *p*H 5.5 for 19 hours, separation was incomplete. A similar, small difference in mobility on paper was obtained when isoglutamine-oxytocin and oxytocin were subjected to chromatography on Whatman No. 1 filter paper for 16 hours in *n*-butyl alcohol–acetic acid–water (5:1:5).

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NEW YORK, NEW YORK

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

Synthetic Studies on Arginine-vasopressin: Condensation of S-Benzyl-N-carbobenzoxy-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine and its O-Tosyl Derivative with S-Benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide[1]

BY PANAYOTIS G. KATSOYANNIS, DUANE T. GISH[2] AND VINCENT DU VIGNEAUD

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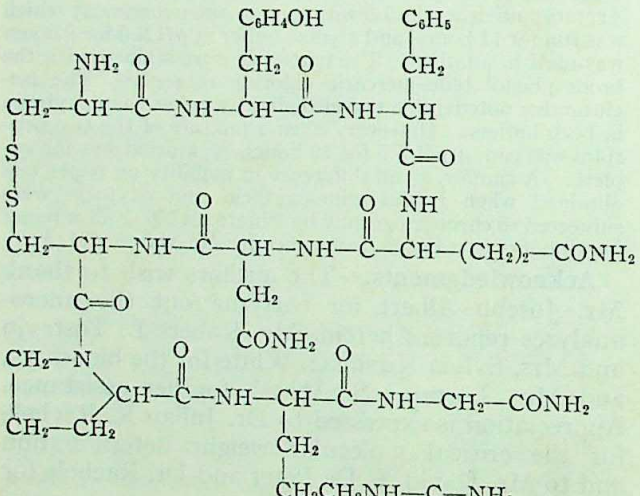
Two synthetic routes to arginine-vasopressin were investigated. The first approach involved the coupling of S-benzyl-N-carbobenzoxy-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine with S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide monohydrobromide. Treatment of the product with sodium in liquid ammonia and subsequent oxidation of the sulfhydryl nonapeptide gave a biologically active product. Partial purification resulted in a product with a specific activity of 175 pressor units/mg. The synthetic product possessed biological properties associated with natural arginine-vasopressin and also many physical and chemical properties of the natural hormone. The second approach involved the coupling of S-benzyl-N-carbobenzoxy-L-cysteinyl-O-tosyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine with S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide monohydrobromide, routes to these intermediates differing from those used for the first approach. The resultant active product, after partial purification, assayed 220 pressor units/mg.

The isolation[3,4] in highly purified form of arginine-vasopressin, the pressor and antidiuretic hormone of the posterior pituitary gland of beef, followed by degradation studies[5-7] led to the postulation of structure I.[7,8] Synthetic studies were then undertaken. The ultimate objective of these synthetic studies was the preparation of a compound with the sequence L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-arginylglycinamide, the sulfhydryl and free amino groups of which were covered by protective groups which could be removed by treatment with sodium in liquid ammonia. It was expected that subsequent oxidation of this compound by aeration in aqueous solution would lead to a product of structure I. This is analogous to the work on synthetic oxytocin.[9]



I

The first approach undertaken in this endeavor[10] was the coupling of the pentapeptide, S-benzyl-N-carbobenzoxy-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine,[11] with the monohydrobromide of S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide,[12] by the tetraethyl pyrophosphite procedure.[13] The resultant crude product was isolated and treated with sodium in liquid ammonia. A dilute acetic acid solution of the reduction product was adjusted to *p*H 6.7 and aerated. Concentration on the flash evaporator[14] and lyophilization of the solutions from several runs gave material which on assay[15] showed a total of 58,000 units of pressor activity. After countercurrent distribution of this material in the solvent system 2-butanol–0.06 *M* *p*-toluenesulfonic acid, 520 mg. of a product with pressor activity of about 80 units/mg. was obtained. This material was purified further by electrophoresis at *p*H 4.0 in a pyridine–acetate buffer with a cellulose block[16] as the supporting medium. From the peak segments a solution was obtained which, after concentration and lyophilization, yielded a powder weighing 70 mg. which had a specific activity of about 175 pressor units/mg.

The distribution constant of this active material in 2-butanol–0.06 *M* *p*-toluenesulfonic acid (K = 0.84) was the same, within the limits of experimental duplication, as that for a highly purified sample of natural arginine-vasopressin[17] (K = 0.87). When equal quantities of the synthetic and natural products were mixed and chromatographed on an Amberlite IRC-50 (XE-64) ion-exchange column, a single peak was obtained. A com-

(1) This work was supported by a grant (H-1675) from the National Heart Institute, Public Health Service, and a grant from the Lederle Laboratories Division, American Cyanamid Co., for which we wish to express our appreciation.

(2) Lilly Postdoctoral Fellow in the Natural Sciences, administered by the National Research Council, 1953–1955.

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(17) Specific activity, 425 units/mg., prepared in this Laboratory by D. W. Wilson (see ref. 29).

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parison of the behavior of the natural and synthetic preparations on a partition column of Hyflo Super-Cel also showed that the synthetic pressor activity occupied the same position in the chromatogram as did the natural hormone.[18] When the synthetic and natural products were spotted separately on a single strip of paper and subjected to electrophoresis at *p*H 4.0 in a pyridine–acetate buffer the two spots were indistinguishable with relation to mobility, size and shape and both spots consisted of material of uniform mobility under these conditions.

In addition to the assays against the United States Pharmacopeia Standard Posterior Pituitary Powder for pressor activity, the product was assayed for antidiuretic and avian vasodepressor activities. The ratios between pressor, antidiuretic[19] and avian vasodepressor[20] activities were the same as those found for natural arginine-vasopressin (1:1:0.15).

It was obvious, however, due to the low specific activity, that our synthetic preparation was not homogeneous. It was also apparent, assuming that the active material represented arginine-vasopressin, that the chemical structure of the contaminant differed from that of the natural hormone in such a subtle way that its behavior in countercurrent distribution, ion-exchange and partition chromatography and electrophoresis, under the experimental conditions used, was identical to that of the active material. An amino acid analysis of a hydrolysate by starch column chromatography[21] showed the presence of the expected amino acids in approximately the calculated ratio. However, it was noted that the cystine peak had a larger spread than usually found and in one chromatogram it appeared that a second peak had actually started to separate from the cystine peak. This indicated the possible presence of another amino acid, such as a dibasic amino acid, which might appear at this point on the chromatogram. The identity of this ninhydrin-positive material was not established.

Several possibilities of the cause of the difficulty were considered. Among those initially considered were the possibilities of racemization, instability of one of the intermediates, structural changes during treatment with sodium in liquid ammonia of the protected nonapeptide and subsequent oxidation of the reduction product, and inactivation of the active material once it had been formed. The latter is known to take place in the case of the natural hormone[22] and a steady loss in total activity is incurred during handling of this unstable hormone. Any of the possibilities outlined above could lead to slight structural changes which, while altering only slightly the physical and chemical properties of the desired material, might lead to complete loss of biological activity. Rendering the problem yet more difficult was the sparing solubility in almost all solvents of the crude protected nonapeptide and the tendency of this mixture to form a gel in aqueous solvents. This fact caused the failure of attempts to purify this crude product before conversion of the nonapeptide to the active hormone.

Although at this time the root of the difficulty had not yet become apparent, a second approach to the synthesis of arginine-vasopressin was undertaken which we hoped might render the intermediates more stable and alter their solubility. O-Tosyl-N-carbobenzoxy-L-tyrosine was coupled by the mixed anhydride procedure,[23] with isobutyl chlorocarbonate in tetrahydrofuran solution, to L-phenylalanyl-L-glutaminyl-L-asparagine[24] in aqueous solution containing an equivalent of triethylamine. Conversion of the O-tosyl-N-carbobenzoxy-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine to O-tosyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine by treatment with HBr in acetic acid[25] and coupling of this tetrapeptide with S-benzyl-N-carbobenzoxy-L-cysteine by the mixed anhydride procedure, as described for the preparation of the tetrapeptide, gave S-benzyl-N-carbobenzoxy-L-cysteinyl-O-tosyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine.

S-Benzyl-N-carbobenzoxy-L-cysteinyl-L-prolyl-L-arginylglycinamide hydrobromide was prepared by a procedure analogous to that used for the preparation of the *p*-nitrobenzyloxycarbonyl derivative.[12] Treatment with sodium in liquid ammonia, rebenzylation and purification of the product by countercurrent distribution gave S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide dihydrohalide.[26] The tetrapeptide was then converted to the monohydrohalide and coupled with S-benzyl-N-carbobenzoxy-L-cysteinyl-O-tosyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine by the tetraethyl pyrophosphite method. The unreacted tetrapeptide was removed from the crude product by trituration with water. Treatment of the resulting product with sodium in liquid ammonia, followed by aeration in aqueous solution, gave 57,000 units of pressor activity. The solvent was removed by concentration and lyophilization and most of the inorganic salts were removed by an extraction procedure. The crude peptide material, which assayed 41,000 units, was distributed in the system 2-butanol–0.1% acetic acid. The material recovered from the active peak weighed 400 mg. and assayed 70 units/mg. Electrophoresis of 195 mg. of this material on a cellulose block at *p*H 4.0 in a pyridine–acetate buffer gave, as the most active fraction, 63 mg. of material which assayed 150 units/mg. This active material was then redistributed in the system 2-butanol–0.1% acetic acid. The most active fraction recovered was 23 mg. of a product which had a specific pressor activity of 220 units/mg.

It seemed to us that the activity obtained repre-

(18) P. G. Condliffe, *J. Biol. Chem.*, **216**, 455 (1955).

(19) The antidiuretic assays utilizing the hydrated normal dog were carried out by Professor H. B. Van Dyke, Dr. K. Adamsons, Jr., and Dr. S. L. Engel, to whom we express our appreciation.

(20) J. M. Coon, *Arch. Intern. pharmacodynamie*, **62**, 79 (1939).

(21) S. Moore and W. H. Stein, *J. Biol. Chem.*, **178**, 53 (1949).

(22) This has been the experience of the authors as well as that of others (refs. 3 and 5).

(23) J. R. Vaughan, Jr., and J. A. Eichler, THIS JOURNAL, **75**, 5556 (1953).

(24) E. A. Popenoe and V. du Vigneaud, *ibid.*, **76**, 4751 (1954).

(25) G. W. Anderson, J. Blodinger and A. D. Welcher, *ibid.*, **74**, 5309 (1952); D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952); I. Schumann and R. A. Boissonnas, *Helv. Chim. Acta*, **35**, 2237 (1952).

(26) This product would be expected to be a mixture of the hydrobromide and hydroiodide salts.

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sents unquestionably arginine-vasopressin because of all the biological and physical properties encountered with it. In view of the data on the authenticity of the protected pentapeptides and the tetrapeptide, it appeared that something had occurred during the condensation between the protected pentapeptides and the tetrapeptide yielding a by-product or by-products which we were unable to separate from arginine-vasopressin by the techniques available. Therefore, reactions leading to the formation of the peptide bond through the carboxyl group of asparagine have been subjected to closer scrutiny. As reported recently, evidence has now been derived that in the formation of asparaginyl peptides a mixture of products is obtained.[27] Means of avoiding the formation of by-products have been investigated and these results will be reported subsequently.

Experimental[28]

Coupling of S-Benzyl-N-carbobenzoxy-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine with S-Benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide Monohydrobromide and Conversion of the Product to Active Material.—S-Benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide dihydrobromide[12] was dissolved in about 4 parts of dimethylformamide and about a 10% excess of triethylamine was added with stirring. Chloroform was then added, dropwise at first, to redissolve the precipitate of triethylamine hydrobromide and to precipitate the tetrapeptide monohydrobromide as a semi-solid. The monohydrobromide was collected by filtration, washed with chloroform and then redissolved in dimethylformamide. Two or three drops of triethylamine was added and the material was again precipitated with chloroform, washed, and dried *in vacuo* over P_2O_5 and NaOH. The yield of the monohydrobromide was nearly quantitative.

In a typical experiment, S-benzyl-N-carbobenzoxy-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine[11] (114 mg., 0.16 millimole), S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide monohydrobromide (75 mg., 0.13 millimole), tetraethyl pyrophosphite[13] (0.09 g., 0.35 millimole) and diethyl phosphite (0.45 ml.) were heated at about 95° for 50 minutes. Ether was added to the cooled reaction mixture to precipitate the crude product which was collected by filtration, washed with ether and dried over P_2O_5 *in vacuo*. The crude product was treated with sodium in liquid ammonia.[9] The residue, after evaporation of the ammonia, was dissolved in 200 ml. of 0.1% acetic acid, the *p*H was adjusted to 6.7 with NH_4OH and the solution was aerated with a slow stream of air for one hour. Solutions from a number of runs were combined and a total activity of 66,000 pressor units[29] was obtained. The solution was concentrated in the rotary evaporator[14] (bath temperature 25°) and lyophilized to give about 4 g. of a mixture of peptide material and inorganic salt which assayed 58,000 units of pressor activity. This material was subjected to countercurrent distribution in the solvent system 2-butanol–0.06 *M* *p*-toluenesulfonic acid. The material was placed in the first 5 tubes of the all-glass countercurrent distribution machine.[30] The distribution was followed by developing the Folin color[31] and the Sakaguchi color,[32] and by pressor assays, on aliquots of selected tubes. After 690 transfers the solvent from the tubes containing the active peak was pooled and the two phases separated. The organic phase was extracted several times with water and the aqueous extract was combined with the aqueous phase. This solution was passed through a column of Amberlite IR-45 in the acetate form to remove the *p*-toluenesulfonic acid. The solution, which assayed 45,000 pressor units, was concentrated on the rotary evaporator and lyophilized to yield a powder, wt. 520 mg.

Electrophoresis on a Cellulose-supported Medium.—Essentially the procedure described by Kunkel[16] was followed. The supporting medium was a cellulose product, Solka-Floc, of Brown Co. of New York. The buffer used was a pyridine–acetic acid buffer of *p*H 4.0 prepared by diluting 24 ml. of pyridine and 91 ml. of acetic acid to 4 liters with distilled water. The above partially purified material (490 mg.) was dissolved in 3 ml. of the buffer and placed on the block along with two 0.25-ml. washes. The electrophoresis was carried out for 40 hours at 5° with a potential gradient of 9 volts/cm. The Folin color was developed on aliquots of the solutions from the various segments and pressor assays were obtained. The solutions from the three segments which exhibited the highest activity was lyophilized to give about 70 mg. of a powder which assayed 175 units/mg. of pressor activity. When a sample of this material was dissolved and the solution assayed for pressor, antidiuretic[19] and avian vasodepressor[20] activities, the ratio found was 1:1:0.15, the ratio found for natural arginine-vasopressin.[4]

Ion-exchange Chromatography.—The procedure described by Taylor,[33] which employed the resin Amberlite IRC-50 (XE-64) and a 0.2 *M* sodium phosphate buffer of *p*H 6.95, was followed. The preparation of the resin and operation of the column was carried out according to the procedures of Hirs, Moore and Stein[34] and Tallan and Stein.[35] One mg. each of the synthetic product and natural arginine-vasopressin[17] were mixed and chromatographed. A single peak was obtained and there was no evidence of any separation whatever.

Paper Electrophoresis.—The buffer used was the *p*H 4.0 pyridine–acetic acid buffer already described. Solutions of the synthetic product and of natural arginine-vasopressin[17] (0.1 ml. of a solution containing about 0.85 mg./ml.) were spotted, side by side, on Whatman No. 1 paper previously wet with the buffer, and the electrophoresis was carried out, with glass plates as described by Kunkel and Tiselius,[36] for 18 hours with a potential gradient of 9 volts/cm. and at a temperature of 5°. The material was stained on the paper with brom phenol blue as described by Durrum.[37] The spots were identical in appearance, each containing material of uniform mobility in this buffer, and the mobility of the synthetic product was the same as that of natural arginine-vasopressin.

Amino Acid Analysis.—Amino acid analysis by the starch column chromatographic method of Moore and Stein[21] of the synthetic material after hydrolysis showed the following molar ratios: phenylalanine, 1.2; tyrosine, 1.2; proline, 0.8; glutamic acid, 1.3; aspartic acid, 0.85; glycine, 1.0; ammonia, 3.7; arginine, 1.1; cystine, 0.85; unknown, 0.5.[38] The value for ammonia was somewhat high but is uncorrected for the liberation of ammonia due to the destruction of amino acids. In the example cited, sufficient separation of the unidentified peak, which emerged just following cystine, was obtained to permit its approximate quantification. In other chromatograms only partial separation of these two peaks was obtained.

O-Tosyl-L-tyrosine.[39]—To a solution of 18 g. (0.1 mole) of L-tyrosine in 200 ml. (0.2 mole) of *N* NaOH was added a solution of 12.5 g. (0.05 mole) of $CuSO_4 \cdot 5H_2O$ in 50 ml. of water. The mixture was stirred until solution was complete and then was added a solution of 19 g. (0.1 mole) of *p*-toluenesulfonyl chloride in 40 ml. of ether. The reaction mixture was shaken for 3.5 hours and the precipitated copper complex was isolated by filtration, washed with water and finally dissolved in 200 ml. of concd. HCl. After several

(27) D. T. Gish, P. G. Katsoyannis, G. P. Hess and R. J. Stedman, THIS JOURNAL, **78**, 5954 (1956).

(28) Corrected capillary melting points are reported.

(29) At the time the assays recorded in this paper were performed, a value of 0.47 unit/mg. was assigned to the United States Pharmacopeia Posterior Pituitary Standard Powder. A value of 0.40 unit/mg. has now been assigned to this standard.

(30) L. C. Craig, W. Hausmann, E. H. Ahrens, Jr., and E. J. Harfenist, *Anal. Chem.*, **23**, 1236 (1951).

(31) O. H. Lowry, N. J. Rosebrough, A. L. Farr and R. J. Randall, *J. Biol. Chem.*, **193**, 265 (1951).

(32) A. A. Albanese and J. E. Frankston, *ibid.*, **159**, 185 (1945).

(33) S. P. Taylor, Jr., *Proc. Soc. Exptl. Biol. Med.*, **85**, 226 (1954).

(34) C. H. W. Hirs, S. Moore and W. H. Stein, *J. Biol. Chem.*, **200**, 493 (1953).

(35) H. H. Tallan and W. H. Stein, *ibid.*, **200**, 507 (1953).

(36) H. G. Kunkel and A. Tiselius, *J. Gen. Physiol.*, **35**, 89 (1951).

(37) E. L. Durrum, THIS JOURNAL, **72**, 2943 (1950).

(38) It might be noted that there is a possibility that this unidentified peak might represent the presence of α,γ-diaminobutyric acid (see C. Ressler, *ibid.*, **78**, 5956 (1956)).

(39) The authors are indebted to Dr. F. H. C. Stewart for the description of the preparation of this compound.

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hours cooling the precipitated crystalline hydrochloride of the product was collected by filtration, dissolved in 1 l. of water and the *p*H of the solution was adjusted to 6 with NH_4OH. After cooling, the precipitated crystalline product was filtered, washed with water and dried, wt. 15 g. Recrystallization from 1.5 l. of boiling water gave 12.5 g. (37%) m.p. 215–217°, $[\alpha]^{22}D$ +9.0° (*c* 3.0, *N* HCl); reported in literature[40] m.p. 213–214° uncor. and $[\alpha]^{20}D$ +9.5° (*c* 3.16, *N* HCl).

O-Tosyl-N-carbobenzoxy-L-tyrosine.—A mixture of 3.35 g. (0.01 mole) of O-tosyl-L-tyrosine, 10 ml. of *N* NaOH, 15 ml. of *N* Na_2CO_3 and 80 ml. of *N* $NaHCO_3$ (*p*H 9) was warmed for a few minutes and then cooled to 0°. To this suspension 2 g. (0.016 mole) of carbobenzoxy chloride was added in portions over a period of one hour with vigorous stirring and cooling. After the final addition the reaction mixture was stirred for a further 30 minutes, acidified with HCl and stirred for 15 minutes. The precipitated product was isolated by filtration, washed with water and dried. For purification it was dissolved in ethyl acetate and precipitated with hexane; wt. 3.8 g. (83%), m.p. 124–126°, $[\alpha]^{25}D$ −27° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{24}H_{23}O_7NS$: C, 61.4; H, 4.93; N, 2.98. Found: C, 61.3; H, 4.97; N, 3.05.

O-Tosyl-L-tyrosine from HBr–Acetic Acid Cleavage of N-Carbobenzoxy-O-tosyl-L-tyrosine.—Tosyl-N-carbobenzoxy-L-tyrosine (0.7 g., 0.0015 mole) was suspended in 15 ml. of acetic acid saturated with HBr and the mixture was allowed to stand at 25° for one hour with occasional stirring. The solution was concentrated *in vacuo* to dryness, the residue was mixed with 50 ml. of water and the *p*H of the mixture was adjusted to 6.0 with NH_4OH. The precipitated crystalline O-tosyl-L-tyrosine was filtered off, washed with water and dried; wt. 0.45 g. (90%), m.p. 214–216°.

O-Tosyl-N-carbobenzoxy-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine.—A solution of 1.88 g. (0.004 mole) of O-tosyl-N-carbobenzoxy-L-tyrosine and 0.4 g. (0.004 mole) of triethylamine in 12 ml. of tetrahydrofuran was cooled to −10° and 0.55 g. (0.004 mole) of isobutyl chlorocarbonate was added with stirring. After 10 minutes at −10° a cooled solution of 1.7 g. (5% excess) of L-phenylalanyl-L-glutaminyl-L-asparagine[24] and 0.43 g. of triethylamine in 9 ml. of water was added. The mixture was then allowed to come to room temperature over a period of 25 minutes and the triethylamine salt of the tetrapeptide was precipitated with ether. The product was then collected by filtration, washed with ether, suspended in 100 ml. of water and acidified with HCl. The tetrapeptide thus obtained was separated by filtration, washed with water, dried and triturated with ethyl acetate; wt. 2.7 g. (78.7%), m.p. 214–216°. A sample for analysis was precipitated from 50% acetic acid; m.p. 218–220°, $[\alpha]^{25}D$ −16.6° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{42}H_{46}O_{12}N_6S$: N, 9.78; S, 3.73. Found: N, 9.62; S, 3.62.

S-Benzyl-N-carbobenzoxy-L-cysteinyl-O-tosyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine.—O-Tosyl-N-carbobenzoxy-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine (2.55 g.) was suspended in 50 ml. of 2 *N* HBr in acetic acid and the mixture was allowed to stand at 25° for one hour. The hydrobromide of the O-tosyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine was precipitated from the reaction mixture with ether, collected by filtration, washed with ether and reprecipitated twice from methanol–ether; wt. 1.92 g. (82%). The product (2.4 millimoles) was dissolved in 5 ml. of water plus 4.8 ml. (4.8 millimoles) of *N* NaOH and the mixture was cooled and added to the anhydride of S-benzyl-N-carbobenzoxy-L-cysteine and isobutylcarbonic acid, prepared according to the procedure described in the preceding section from 7.6 g. (2.34 millimoles) of S-benzyl-N-carbobenzoxy-L-cysteine[41] in 12 ml. of tetrahydrofuran, 0.24 g. (2.34 millimoles) of triethylamine and 0.32 g. (2.34 millimoles) of isobutyl chlorocarbonate. The sodium salt of the pentapeptide was precipitated from the reaction mixture with ether, separated by filtration, suspended in 200 ml. of water and acidified with HCl. The precipitated S-benzyl-N-carbobenzoxy-L-cysteinyl-O-tosyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine was filtered off, washed with water, dried and triturated with ethyl acetate; wt. 1.92 g. (83%), m.p. 214–216°. For analysis a sample was precipitated from 70% acetic acid; m.p. 217–219°, $[\alpha]^{25}D$ −33.5° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{52}H_{57}O_{13}N_7S_2$: C, 59.3; H, 5.46; N, 9.31. Found: C, 59.2; H, 5.56; N, 9.16.

S-Benzyl-N-carbobenzoxy-L-cysteinyl-L-prolyl-L-arginylglycinamide Hydrobromide.—S-Benzyl-N-carbobenzoxy-L-cysteinyl-L-proline was prepared through the methyl ester as described for the *p*-nitrobenzyloxycarbonyl derivative.[12] The yields of the methyl ester and of the saponification product, neither of which could be crystallized, were 70 and 85%, respectively. The protected dipeptide (2.92 g., 0.0066 mole), L-arginylglycinamide monohydrobromide[12] (1.86 g., 0.003 mole), tetraethyl pyrophosphite (3.10 g., 0.006 mole) and diethyl phosphite (10 ml.) were heated at 100° for 30 minutes. The reaction mixture was cooled and the product, along with unreacted L-arginylglycinamide, was precipitated with ethyl acetate. The material was collected by filtration, washed with ethyl acetate and dried over P_2O_5 and NaOH. This crude product was purified by countercurrent distribution in the solvent system 2 butanol–1% acetic acid; 120 transfers were sufficient to separate the tetrapeptide (K = 1.2) from the dipeptide (K = 0.23). The Sakaguchi color reaction was used for the preparation of the distribution curve. The solvent from the tubes containing the tetrapeptide was concentrated and lyophilized to give 3.0 g. (68%) of an hygroscopic amorphous powder.

S-Benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide Dihydrohalide.[26]—S-Benzyl-N-carbobenzoxy-L-cysteinyl-L-prolyl-L-arginylglycinamide hydrobromide (2.87 g., 0.0039 mole) was treated with sodium (0.47 g.) in liquid ammonia (300 ml.). The sodium was added in small pieces until a permanent blue color persisted. Ammonium chloride was then added in an amount just sufficient to discharge the blue color, and benzyl chloride (0.5 ml., 10% excess) was added and the mixture was stirred for 30 minutes. Ammonium chloride (1.09 g.) was then added and the ammonia was allowed to evaporate and the last traces then removed *in vacuo*. The residue was extracted with 30 ml. of glacial acetic acid in 3 portions, the solution filtered, and the product was precipitated by addition of 400 ml. of ether. This material was reprecipitated from 70 ml. of acetic acid with ether. The amorphous peptide material was collected, washed with ether and dried *in vacuo* over P_2O_5 and NaOH. This material was purified by countercurrent distribution in the solvent system 2-butanol–0.1% acetic acid, 520 transfers being sufficient for the separation of the tetrapeptide (K = 0.18)[42] from a small peak which possessed a very low distribution constant. The Folin color reaction was used for preparation of the distribution curve. Concentration and lyophilization of the solvent from the tubes containing the tetrapeptide gave 1.9 g. (82%) of an amorphous hygroscopic powder. An analysis of this material indicated that it was a mixture of the hydrochloride and hydrobromide salt, that is, part of the acid bound was HBr and part was HCl. This fact rendered it difficult to interpret the analytical results, but the behavior of this tetrapeptide in countercurrent distribution indicated it to consist of a single component.

Preparation and Isolation of Active Material.—The coupling of the pentapeptide S-benzyl-N-carbobenzoxy-L-cysteinyl-O-tosyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine with the tetrapeptide S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide monohydrohalide by the tetraethyl pyrophosphite method was carried out as described above for the coupling without the presence of the O-tosyl group. In a typical experiment 1.05 g. (1 millimole) of pentapeptide, 0.56 g. (0.93 millimole) of tetrapeptide monohydrohalide, 4 ml. of diethyl phosphite and 0.56 g. (2.2 millimoles) of tetraethyl pyrophosphite was used. The reaction product was precipitated with water, filtered off and again triturated with water to remove the unreacted tetrapeptide, and dried. The treatment with sodium in liquid ammonia of this material and subsequent oxidation, in the manner described above, gave a solution which possessed an activity of 22,000 pressor units when assayed in the rat.[15] Solution from a number of runs with a total activity of 57,000 pressor units were combined, concentrated on the rotary evaporator and lyophilized to give about 6 g. of a mixture of peptide material and inorganic salt. This mixture was extracted with 50 ml. of glacial acetic acid, the

(40) E. L. Jackson, THIS JOURNAL, **74**, 837 (1952).

(41) C. R. Harington and T. H. Mead, *Biochem. J.*, **30**, 1598 (1936).

(42) This distribution constant is almost identical with that reported by Cole, Gish, and du Vigneaud (see ref. 12).

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solution was filtered and the peptide material was precipitated with 200 ml. of absolute, peroxide-free ether and collected immediately by filtration before crystallization of sodium acetate hydrate occurred. The peptide material thus obtained weighed 1.95 g. and had a specific activity of 21 pressor units/mg. For purification this material was placed in the first 8 tubes of the all-glass automatic countercurrent distribution apparatus and distributed in the system 2-butanol–0.1% acetic acid for 1100 transfers. The activity was concentrated in a single peak. The solvent from the tubes containing the active peak was pooled and the solution, which assayed 28,000 pressor units, was concentrated and lyophilized to give 400 mg. of a product which had a specific activity of about 70 units/mg. A portion of this material (195 mg.) was subjected to electrophoresis on a cellulose block at *p*H 4.0 in a pyridine–acetate buffer and yielded, as the most active fraction, 63 mg. of material which assayed 150 units/mg. This material was redistributed in the system 2-butanol–0.1% acetic acid for 2000 transfers to give as the most active fraction 23 mg. of a product which possessed a specific activity of 220 units/mg.

NEW YORK 21, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE KON. NED. GIST- EN SPIRITUSFABRIEK]

Bottromycin. I. A New Sulfur-containing Antibiotic

BY J. M. WAISVISZ, M. G. VAN DER HOEVEN, J. VAN PEPPEN AND W. C. M. ZWENNIS

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A new antibiotic bottromycin[1] has been isolated from fermentation broth by solvent extraction and purified either by chromatography on Florisil or by means of its salts with organic acids. On the basis of analysis of bottromycin and its crystalline derivatives, the antibiotic has been assigned an empirical formula $C_{38}H_{57-61}N_7O_{7-8}S$.

The antibiotic activity present in the fermentation broths of a soil actinomycete *Streptomyces bottropensis*[2] was found to be extractable at neutral or alkaline *p*H by a variety of organic solvents, such as diethyl ether, ethyl acetate and butyl acetate and at acid *p*H by chloroform.

Paper chromatographic methods gave evidence that two antibiotic substances were present in the culture broth, one of which was present in only minor quantities. This one was discarded during the isolation of bottromycin.

The main antibiotic was extracted from the filtered culture broth with butyl acetate. The extracts were concentrated to a small volume by distillation of the azeotropic mixture and thereafter re-extracted with phosphate buffer at *p*H 2. When the aqueous layer was adjusted to *p*H 9 with dilute sodium hydroxide, the crude bottromycin precipitated as an amorphous white product. This crude antibiotic produced a red color with concentrated mineral acids. The crude product was purified by chromatography on Florisil or by precipitation from its solutions in ether or butyl acetate with organic acids, such as salicylic, acetylsalicylic, *p*-aminosalicylic, 3,5-dinitrosalicylic, 3,5-dibromosalicylic, 3,5-dibromo-4-aminosalicylic, benzoic, *p*-aminobenzoic, 3,5-dinitrobenzoic, acetic, phenylacetic, picric, anthranilic acids and benzylpenicillin. Several of the amorphous salts thus obtained could be crystallized from ethyl acetate.

The water-soluble phosphate as well as the relatively insoluble sulfate and hydrochloride also have been prepared. The free bottromycin base could be obtained from its salts by suspending these salts in water–diethyl ether, adjusting the *p*H with dilute sodium hydroxide to 9 followed by repeated extraction of the alkaline water layer with ether. Evaporation of the dried ether extracts yielded the antibiotic as a glittering white amorphous powder. The purified product, thus obtained, no longer produces a red color with concentrated mineral acids.

As to whether bottromycin is a chemically pure entity the following comments may be made. When highly purified bottromycin preparations derived from different production batches were compared, identical elementary analyses were always obtained. Also, the biological activities per mg. bottromycin, determined microbiologically, were identical and the value obtained could not be increased by further purification.

On the other hand some of these seemingly pure products gave a definite red coloration when treated with concentrated sulfuric acid whereas others did not. Such batches, after further purification, usually yielded products which no longer gave a positive test.

The molecular weight determined by the isothermic distillation method[3] was found to be about 743 ± 36. On the basis of analyses of bottromycin as well as of its crystalline salts, the antibiotic has been assigned the empirical formula $C_{38}H_{57-61}N_7O_{7-8}S$. The antibiotic is a very weak base (pK'_a = *ca.* 6.5); it is readily soluble in most organic solvents but is virtually insoluble in hexane, cyclohexane and petroleum ether. In ice-water it is more soluble (2.3 mg./ml.) than in water of about 30° (1.3 mg./ml.). The compound is optically active, $[\alpha]^{25}D$ −14.2° (*c* 0.5, in 96% ethanol).

Bottromycin is not adsorbed on alumina or cellulose but is completely adsorbed on activated carbon from which it can be recovered in part (*ca.* 65%) by elution with acetone containing 3% concentrated hydrochloric acid. "Magnesol" also adsorbs the antibiotic. In this case it can be eluted with benzene containing 5% of methyl alcohol.

Amorphous bottromycin or its crystalline salts are fully stable when stored for several months in the refrigerator. Aqueous solutions of the new antibiotic at *p*H 7 show no loss in microbiological activity after 8 days at 0°. However, a solution at *p*H 2 loses 50% of its activity when exposed for 1.5 hours at 100°. Alkaline solutions of *p*H 9 are completely inactivated when kept for the same

(1) Bottromycin is the generic name given to an antibiotic isolated from a culture of *Streptomyces bottropensis* n.sp.

(2) Dutch patent no. 79,749 (16-10-1955); Belgian patent no. 537,

(3) E. J. Clark, *Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941).

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period of time at 100°. When dissolved in organic solvents bottromycin is relatively stable even at elevated temperatures.

The ultraviolet absorption spectrum of the free base in 96% ethanol solution shows a strong absorption peak at 203 mμ and a weak shoulder at 240 mμ.

The infrared spectrum (KBr) shows bands at: 3.01 μ (3322 cm.$^{-1}$), 3.23 (3086), 3.31 (3021), 5.73 (1745), 5.90 (1695), 6.05 (1653), 6.48 (1543), 6.68 (1497), 7.32 (1366), 7.65 (1307), 7.94 (1295), 8.53 (1172), 8.74 (1144), 8.93 (1120), 9.23 (1083), 9.45 (1058), 10.01 (999), 10.28 (973), 11.07 (903), 11.75 (851) and 13.17 μ (760 cm.$^{-1}$).

Further studies on the degradation and structure of bottromycin will be reported in two other papers.[4,5]

Experimental

Isolation of Crude Bottromycin.—The filtrate from 3000 l. of bottromycin fermentation broth (9000 γ/l.) was extracted in a Podbielniak extractor with 4,100 l. of butyl acetate. After azeotropic concentration of this extract to 16 l. (1.35 g./l.), the concentrate was washed three times with 5 l. of 5% sodium bicarbonate solution and two times with 5 l. of distilled water. The antibiotic was then re-extracted from the butyl acetate with 5 l. of phosphate buffer of *p*H 2. The aqueous extract was then washed with ether to remove dissolved butyl acetate. After evaporation of dissolved ether the crude bottromycin could be precipitated from the aqueous extract by adjusting the *p*H to 9, with 4 *N* sodium hydroxide. The amorphous white product was filtered and dried *in vacuo* (17.4 g.); yield 64.5%. Microbiological assays were carried out by a plate assay method using *B. subtilis* (A.T.C.C. 6633) as test organism.

Purification of Bottromycin. (a) By Florisil Chromatography.—Commercial Florisil was purified by suspending in 4 *N* hydrochloric acid. After 24 hours the adsorbent was filtered and washed with distilled water until free of acid and then air dried. A solution of crude bottromycin (144 g.) in chloroform (800 ml.) was added to a column previously packed with purified Florisil (1500 g.) in chloroform (column-size: 950/63 mm.). The column was developed by gravity with chloroform containing 7.5% of ethyl alcohol. Fractions of 1.5 l. (1), 1.8 l. (2), 200 ml. (3), 100 ml. (4), 100 ml. (5), 1 l. (6), 60 ml. (7), 660 ml. (8), and finally 3 l. (9) were collected. To each fraction was added an equal volume of 0.1 *N* sulfuric acid after which the organic solvent was removed by evaporation under reduced pressure. Bottromycin was precipitated as an amorphous white product from the various aqueous solutions by adjusting the *p*H to 9 with 4 *N* sodium hydroxide. Fractions 5 and 6 both yielded pure bottromycin (3.6 and 48.5 g.). On addition of concentrated mineral acids no red color appeared. Fractions 4, 7 and 8 and 9 on the other hand, yielded impure products, namely, 2.1, 4.7, 24 and 6.5 g. (red color with mineral acids). However, pure bottromycin could be isolated from these fractions by subjecting them to a second chromatographic procedure.

(b) By Means of its Salts with Organic Acids.—The crude antibiotic (26.8 g.) was dissolved in 1 l. of phosphate buffer *p*H 2. To this solution was added 3 l. of ether whereupon the *p*H was adjusted to 9 with 4 *N* sodium hydroxide. The alkaline aqueous layer was extracted repeatedly with ether. The combined ether extracts (6.7 l.) were dried with anhydrous sodium sulfate and after filtration were concentrated to a volume of 3 l.

Under vigorous stirring a solution of 25 g. of salicylic acid in 150 ml. of ether was added. The salicylate of bottromycin precipitated at once as an amorphous yellowish powder. After storing for three hours in the refrigerator the product was filtered and dried in the desiccator (21.35 g.). This product still gave a red color upon addition of concentrated mineral acids.

A suspension of the crude salicylate was stirred in cold ethyl acetate (100 ml.). After filtration, the washed product was recrystallized from ethyl acetate (150 ml.) to yield 15.05 g. of crystalline bottromycin salicylate; m.p. 161–162° dec. This product gave no red color upon addition of concentrated mineral acids.

Anal. Calcd. for $C_{38}H_{60}N_7O_7S \cdot C_7H_6O_3$: C, 60.27; H, 7.37; N, 10.94; S, 3.57. Found: C, 59.95; H, 7.30; N, 11.17; S, 3.49.

Recovery of Free Bottromycin Base.—The crystalline salicylate (10.05 g.) was dissolved in acetone (220 ml.). To this solution was added successively distilled water (650 ml.), ether (400 ml.) and 1 *N* sodium hydroxide (10 ml.). After shaking, followed by addition of solid sodium chloride in order to break emulsions, the ether layer was separated whereupon the alkaline water layer again was extracted with two 400-ml. portions of ether.

The combined ether extracts were dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure to a volume of 150 ml., then allowed to evaporate to dryness at room temperature. Glittering white amorphous bottromycin was obtained (8.20 g.); yield 96.5%. The substance melted at 143–147° dec.

Anal. Calcd. for $C_{38}H_{59}N_7O_8S$: C, 58.99; H, 7.63; N, 12.68; S, 4.14. Found: C, 58.94; H, 7.78; N, 12.53; S, 3.88.

Salts of Bottromycin. (1) The *p*-Aminosalicylate.—The *p*-aminosalicylate of bottromycin was prepared by the same method as described for the salicylate. It may be recrystallized from ethyl or butyl acetate. The crystalline salt had a m.p. of 175–180° dec.

Anal. Calcd. for $C_{38}H_{57}N_7O_7S \cdot C_7H_7NO_3$: C, 59.47; H, 7.05; N, 12.33; S, 3.52. Found: C, 59.77; H, 7.11; N, 12.25; S, 3.64.

(2) The Benzylpenicillinate.—Benzylpenicillin sodium salt (712 mg.) was dissolved in a few ml. of distilled water. Butyl acetate (10 ml.) was added followed by 2 *N* phosphoric acid (4 ml.). After shaking, the organic layer was separated, washed twice with water and dried over anhydrous sodium sulfate. After filtration, a solution of purified bottromycin (1.48 g.) in butyl acetate (4 ml.) was added.

The white precipitate formed was filtered off, washed with ether and dried. The crude amorphous penicillinate was dissolved in 50 ml. of cold ethyl acetate, filtered, then concentrated, at 10° under reduced pressure, to a small volume. The penicillinate crystallized after remaining in the refrigerator; 1.57 g. of the pure penicillinate was obtained, m.p. 157–159° dec.

Anal. Calcd. for $C_{38}H_{58}N_7O_8S \cdot C_{16}H_{18}N_2O_4S$: C, 58.59; H, 6.87; N, 11.39; S, 5.79. Found: C, 59.05; H, 6.95; N, 11.26; S, 5.72.

(3) The Sulfate.—Bottromycin (1.48 g.) was dissolved in butyl acetate (4 ml.). To this solution was added ether (40 ml.) and a few drops of concentrated sulfuric acid.

The sulfate, which precipitated at once, was filtered. The hygroscopic salt was dissolved in 20 ml. of alcohol, the solution was filtered and the salt was precipitated by the addition of ether. This purification procedure was repeated and yielded 1.02 g. of amorphous bottromycin sulfate, m.p. 189–196° dec. The product is readily soluble in water.

Anal. Calcd. for $C_{38}H_{60}N_7O_7S \cdot 2H_2O_4S \cdot 3H_2O$: C, 45.23; H, 6.95; N, 9.72; S, 9.53. Found: C, 45.22; H, 6.96; N, 9.60; S, 9.60.

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(5) J. M. Waisvisz, M. G. van der Hoeven and B. te Nijenhuis, *ibid.*, **79**, 4524 (1957).

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Bottromycin. II. Preliminary Degradation Studies

BY J. M. WAISVISZ, M. G. VAN DER HOEVEN, J. F. HÖLSCHER AND B. TE NIJENHUIS

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Bottromycin, $C_{38}H_{57-61}N_7O_{7-8}S$, is cleaved by vigorous acid hydrolysis into six ninhydrin-positive substances, two of which have been identified as glycine and valine. Two of the four unidentified fragments have been isolated and shown to have the formulas $C_6H_8N_2O_2S$ and $C_{10}H_{13}NO_2$. Acetylation of the antibiotic yielded two crystalline ninhydrin-negative compounds $C_{19}H_{23}N_3O_4S$ and probably $C_{21}H_{34}N_4O_4$.

In a previous publication Waisvisz and coworkers[1] have reported the isolation, purification and some of the properties of a new sulfur-containing antibiotic, bottromycin.

Analyses and molecular weight determinations[1] indicated a probable molecular formula for bottromycin as $C_{38}H_{57-61}N_7O_{7-8}S$.

Although bottromycin gives a negative ninhydrin test, a Van Slyke nitrogen test indicates the presence of one primary amino group.

Ready decolorization of bromine suggests the unsaturated character of the antibiotic. A Friederich N-alkyl determination and an acetyl determination on the intact antibiotic proved that no such groups are present. The reaction of Kuhn-Roth revealed the presence of two or three C-methyl groups. A Zeisel determination indicated the presence of one methoxyl group.

Desulfurization of the antibiotic with Raney nickel and precipitation of the reaction product with salicylic acid yielded an amorphous sulfur-free degradation product.

Refluxing a solution of bottromycin in 20% aqueous or alcoholic potassium hydroxide resulted in extensive degradation and only tarry or oily products could be isolated.

Hydrolysis of the antibiotic with concentrated hydrochloric acid at 110° for 72 hours yielded a hydrolyzate containing several compounds which gave a positive ninhydrin reaction.

By paper chromatographic methods we were able to demonstrate the presence of seven ninhydrin-positive compounds in this hydrolyzate (compounds no. I/VII, numbers according to the position of the fragments on paper chromatograms).

CHART I

Bottromycin, $C_{38}H_{57-61}N_7O_{7-8}S$

Vigorous acid hydrolysis | "Acetylation"

7 ninhydrin-positive reacting compd.		$C_{19}H_{23}N_3O_4S$ (VIII)	$C_{21}H_{34}N_4O_4$? (IX)
Glycine	(I)	↓ vigorous acid hydrolysis	↓ vigorous acid hydrolysis
Degradation product of III	(II)		
$C_6H_8N_2O_2S$	(III)	$C_6H_8N_2O_2S$ (III)	Glycine (I)
Unidentified	(IV)	$C_{10}H_{13}NO_2$ (VII)	Unidentified (IV)
Valine	(V)		Valine (V)
Unidentified	(VI)		Unidentified (VI)
$C_{10}H_{13}NO_2$	(VII)		

No. I, V, VI and VII developed a purple color on spraying with ninhydrin, II and IV produced faint yellow colors, whereas III showed a brown spot turning purple on exposure to daylight. Up to the present two compounds (I and V) have been identified as glycine (I) and valine (V).

Fractionation of the acid hydrolyzate on an Amberlite IR-4B resin column resulted in the isolation of VII as a pure crystalline compound (m.p. 176–177°) and the isolation of an unidentified ninhydrin-negative substance (m.p. 218° after sublimation). Compound VII crystallizes from 96% alcohol as a monohydrate. Molecular weight determination by the method of Rast indicated that this compound has a molecular weight of about 187. It is optically active. On the basis of analysis of VII and its dinitrophenyl, acetyl- and tosyl-derivatives we have assigned to it the empirical formula $C_{10}H_{13}NO_2$.

Acetylation of bottromycin with boiling acetic anhydride yielded, in addition to tarry and amorphous products, two crystalline degradation products VIII and IX. Compound VIII, recrystallized from ethyl acetate, diisopropyl ether or benzene, contains sulfur and melts at 215–216° (after sublimation). The molecular weight of VIII, determined in camphor, is approximately 408 ± 20. Analysis disclosed that this ninhydrin-negative product has the molecular formula $C_{19}H_{23}N_3O_4S$. According to group analyses, compound VIII contains one acetyl-, one methoxyl- and also one C-methyl group. Kunz-hydrolysis[2] of VIII showed that one molecule utilizes one molecule of sodium hydroxide under the conditions of the reaction, which means that one group of the molecule is subjected to saponification.

By paper chromatographic methods it was shown that mild hydrolysis of compound VIII produced three ninhydrin-positive compounds, namely, the above-mentioned III and VII, and in addition a product with a rather high R_f-value (VIIIa). VIIIa which could be isolated from the hydrolyzate and recrystallized from alcohol or water. The melting point of this sulfur-containing degradation product was 203–206°. Analyses indicated a probable molecular formula $C_{16}H_{19}N_3O_3S.{}^1/_2H_2O$. The same product (VIIIa) could be isolated from a mild acid hydrolyzate of the antibiotic.

Vigorous hydrolysis (72 hours with concentrated hydrochloric acid at 110°) of VIII or VIIIa yielded mainly the two products III and VII. Both products were isolated from these hydrolyzates either by fractional crystallization of their hydrochlorides or by

(1) J. M. Waisvisz, *et al.*, THIS JOURNAL, 79, 4520 (1957).

(2) A. Kunz and C. S. Hudson, *ibid.*, **48**, 1982 (1926); M. L. Wolfrom, M. Konigsberg and S. Stolzberg, *ibid.*, **58**, 490 (1936).

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column chromatography on Amberlite IR-4B. III, recrystallized from alcohol, melts at 197.5–201.5° dec. and has the molecular formula $C_6H_8N_2O_2S$. A mono-dinitrophenyl derivative of III was prepared.

A third unidentified product (IIIa), which showed a salmon-pink spot on the paper chromatograms, was isolated from the above-mentioned hydrolyzates as its crystalline hydrochloride. Continued vigorous acid hydrolysis of IIIa yielded III. The other crystalline product IX obtained by acetylation of the antibiotic with boiling acetic anhydride could be recrystallized from ethyl acetate and melted at 165–170°. This ninhydrin-negative compound contained no sulfur. Its composition is best represented by the formula $C_{21}H_{34}N_4O_4$.

A Friederich determination on IX disclosed the presence of one or two N-alkyl groups. However, the same determination on bottromycin failed to demonstrate the presence of N-alkyl groups in the intact antibiotic.

A Kuhn-Roth determination showed the presence of two C-methyl groups. Vigorous hydrolysis of IX with concentrated hydrochloric acid yielded a hydrolyzate which contained the ninhydrin-positive reacting compounds I (= glycine), IV, V (= valine) and VI. A crystalline mixture of the four substances was isolated. Further work on the purification and structure of these compounds will be reported later.

It has been found that alkaline hydrolysis or oxidation of III results in the formation of II, in other words, II is a degradation product of III.

Taking into account the above-mentioned facts, it seems likely that bottromycin has a peptide-like structure.

Experimental

Acid Hydrolysis of Bottromycin.—Purified bottromycin (2 g.) was heated for 72 hr. in a Carius tube with concentrated hydrochloric acid (10 ml.) at 100–110°. Paper chromatograms (run in butanol–acetic acid–water 100:12:100) showed the presence of seven ninhydrin-positive compounds in this hydrolyzate.

Fractionation of the Acid Hydrolyzate of Bottromycin on an Amberlite IR-4B Resin Column (Isolation of VII).—The acid hydrolyzate was evaporated *in vacuo* and redissolved in water (50 ml.). This solution was added to an Amberlite IR-4B (OH-form) resin column (310 × 28 mm.). The column was at first developed by gravity with distilled water (205 fractions of 12.5 ml. were collected) followed by 0.5 *N* hydrochloric acid (65 fractions of 12.5 ml. and one of 600 ml.). Although the paper chromatograms (run in butanol–acetic acid–water 100:12:100) disclosed that a poor elution and separation had been achieved, nevertheless we could isolate by freeze-drying (1) from the water fractions (no. 1/10) an amorphous ninhydrin-negative compound. This product was crystallized from ethyl acetate–acetone and melted at 218° (after sublimation in needles at 184°).

(2) The water fractions (no. 33/60) contained, according to the paper chromatograms, a single ninhydrin-positive compound VII. After freeze-drying and several recrystallizations from alcohol we obtained 18 mg. of pure VII melting at 176–177°. The mother liquors yielded another 11 mg. (m.p. 173°) of the same compound. The hydrochloric acid fractions contained the impure III together with VI.

Anal. Calcd. for $C_{10}H_{13}NO_2 \cdot H_2O$: C, 60.91; H, 7.61; N, 7.11. Found: C, 60.91; H, 7.64; N, 7.17.

Acetylation of Bottromycin (Isolation of VIII and IX).—A solution of bottromycin (50 g.) in acetic anhydride (500 ml.) was heated for 3 hours on a steam-bath. The solution was then concentrated *in vacuo* to a small volume (100 ml.) and cooled in the refrigerator, whereupon spontaneous crystallization took place. The snow-white crystals were filtered off, washed with acetic anhydride (20 ml.) and dried. The crude product (14.2 g.) was recrystallized from ethyl acetate (800 ml.) and yielded VIII (11.4 g.) melting at 215–216° (after sublimation in needles).

From the recrystallization mother liquor we isolated another crop of VIII (2.3 g.) melting at 209–211°.

Anal. Calcd. for $C_{19}H_{23}N_3O_4S$: C, 58.61; H, 5.91; N, 10.80; S, 8.23; CH_3CO, 11.05; OCH_3, 7.97; mol. wt., 392. Found: C, 58.52; H, 6.05; N, 10.62; S, 8.29; CH_3CO, 11.57; OCH_3, 8.14; mol. wt. (Rast), 408.

The reaction mother liquor was evaporated to dryness and the tarry residue dissolved in acetone (20 ml.). Crystallization occurred very slowly. After one week the crystals were collected, washed with a small quantity of cold acetone and dried.

Recrystallization from ethyl acetate (100 ml.) yielded 3.8 g. of IX melting at 165–170°.

Anal. Calcd. for $C_{12}H_{34}N_4O_4$: C, 62.04; H, 8.43; N, 13.78. Found: C, 61.86; H, 8.35; N, 13.67.

Hydrolysis of VIII with 6 *N* Hydrochloric Acid. a. Isolation of VIIIa.—Compound VIII (120 mg.) was dissolved in 6 *N* (11 ml.) hydrochloric acid and heated on a steam-bath for 4.5 hours. The hydrolyzate was evaporated to dryness, redissolved in water and concentrated. Finally the concentrate was dissolved in water (2 ml.) and extracted several times with a 5% solution of methyldioctylamine in chloroform until the *p*H of the water layer was about 6. The remaining water layer was evaporated to dryness and the solid residue recrystallized from ethanol (1 ml.). VIIIa (21 mg.), m.p. at 203–206°, was obtained.

Anal. Calcd. for $C_{16}H_{19}N_3O_3S \cdot 1/2H_2O$: C, 56.11; H, 5.85; N, 12.28; S, 9.38. Found: C, 55.89; H, 5.87; N, 12.03; S, 9.72.

Hydrolysis of VIII with Concentrated Hydrochloric Acid. a. Isolation of III and VII by Fractionation on an Amberlite IR-4B Resin Column.—Compound VIII (3.21 g.) was heated with concentrated hydrochloric acid (16 ml.) in a Carius tube at 110° for 72 hours. Paper chromatograms (run in butanol–acetic acid–water 100:12:100) showed that mainly two ninhydrin-positive compounds III and VII were present in this hydrolyzate. The acid solution was evaporated to dryness, dissolved in water (50 ml.) and added to a previously packed IR-4B (OH-form) resin column (430 × 42 mm.). The column was successively developed with water (135 fractions of 50 ml. and one of 300 ml.) and 0.5 *N* hydrochloric acid (17 fractions of 50 ml., one of 850 ml. and 3 fractions of 100 ml.). According to the paper chromatograms the water fractions 1–24 contained mainly compound III, the fractions 25–110 contained substance VII, whereas the hydrochloric acid fractions contained both III and VII. After evaporation and several recrystallizations from alcohol, the water fractions 1–24 yielded 68 mg. of III melting at 197–201.5°. From the water fractions 25–100 we obtained by evaporation and recrystallization from alcohol 500 mg. of VII melting at 176–177°.

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.86; H, 4.66; N, 16.28; S, 18.60. Found: C, 41.86; H, 4.71; N, 15.91; S, 17.95.

b. Isolation of the Hydrochlorides of III and VII by Fractional Crystallization.—Compound VIII (10 g.) was heated with concentrated hydrochloric acid (50 ml.) in a Carius tube at 110° for 72 hr. The hydrolyzate crystallized when stored in the refrigerator. The white crystals were collected, washed with two small portions of cold concentrated hydrochloric acid, and dried to yield 2.88 g. of solid K_1. The mother and wash liquors were combined and concentrated *in vacuo* to half their volume. A second crop of crystals (1.15 g.) K_2 was isolated. After concentration of the filtrate to a still smaller volume another 0.5 g. of solid product K_3 was obtained.

The remaining mother liquor was evaporated to dryness and the resulting brown gum was dissolved in a small quantity of cold alcohol. Spontaneous crystallization set in. After storing in the ice-box for a few hours, the yellowish product was collected, washed with two small portions of cold alcohol and dried to give K_4 (4.1 g.), as a crystalline solid.

Paper chromatographic methods showed that K_1 and K_2 were both the pure hydrochloride of VII, $[\alpha]^{25}D$ −10.6 (*c*

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5%, water). K_3 was a mixture of III and VII, whereas K_4 proved to be the pure hydrochloride of III.

Preparation of Derivatives of III and VII. a. The 2,4-Dinitrophenyl Derivative of III.—According to the method of Sanger[3] the dinitrophenyl derivative of III was prepared by treating the hydrochloride of III (239 mg.) with 2,4-dinitrofluorobenzene (0.56 ml.). After three recrystallizations from 60% methyl alcohol, the yellow, acicular crystalline derivative (223 mg.) was obtained, m.p. 148–151°.

Anal. Calcd. for $C_{12}H_{10}N_4O_6S$: C, 42.61; H, 2.98; N, 16.57; S, 9.46. Found: C, 42.47; H, 2.91; N, 16.49; S, 9.34.

b. The 2,4-dinitrophenyl derivative of VII was prepared from the hydrochloride (283 mg.) and 2,4-dinitrofluorobenzene (0.28 ml.). After three recrystallizations from 60% methanol we obtained the yellow derivative (254 mg.), m.p. 175–179°.

Anal. Calcd. for $C_{16}H_{15}N_3O_6$: C, 55.65; H, 4.38; N, 12.17. Found: C, 55.62; H, 4.37; N, 12.27.

c. The Tosyl Derivative of VII.—The hydrochloride of VII (500 mg.) was dissolved in 1 *N* sodium hydroxide (10 ml.). A solution of *p*-toluenesulfonyl chloride (1 g.) in ether (12.5 ml.) was added and the mixture was shaken mechanically for 4 hr. The ether layer was discarded and the water layer acidified with 4 *N* hydrochloric acid. A white precipitate formed, which was recrystallized several times from 60% alcohol. The acicular, white crystals (414 mg.) melted at 169–171°.

Anal. Calcd. for $C_{17}H_{19}NO_4S$: C, 61.25; H, 5.75; N, 4.20; S, 9.60. Found: C, 61.23; H, 5.79; N, 4.25; S, 9.73.

d. The Acetyl Derivative of VII.—A solution of the hydrochloride of VII (5 g.) in 1 *N* sodium hydroxide (50 ml.) was cooled in an ice-bath. Acetic anhydride (3 ml.) and 1 *N* sodium hydroxide (25 ml.) were added simultaneously and gradually under stirring over a period of 15 minutes. The mixture was stirred for an additional 30 minutes, whereupon another portion of acetic anhydride (3 ml.) and sodium hydroxide (65 ml.) were added in 13 minutes. After another 30 minutes the solution was filtered, acidified with concentrated hydrochloric acid and cooled; the precipitated solid was filtered off, washed with water and dried.

The product was recrystallized from 20% alcohol. A white, acetyl derivative (3.4 g.), m.p. 177–185°, $[\alpha]^{25}D$ +35.0° (*c* 2%, 96% ethyl alcohol), was obtained.

(3) F. Sanger, *Biochem. J.*, **39**, 507 (1945).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.79; N, 6.33. Found: C, 64.84; H, 6.79; N, 6.42.

Kunz-hydrolysis of VIII.—Compound VIII (197.9 mg.) was dissolved in purified acetone (25 ml.). To this solution was added 0.1011 *N* sodium hydroxide (25 ml.). After 2.5 hours in the refrigerator, titration with 0.0906 *N* hydrochloric acid showed that 0.98 milliequivalent of alkali had been consumed per milliequivalent of VIII.

Identification of Valine and Glycine in the Acid Hydrolyzate of Bottromycin by Means of Paper Chromatography.—A hydrolyzate of bottromycin with concentrated hydrochloric acid (72 hr. hydrolysis) was compared with known amino acids by means of paper chromatographic methods. The one-dimensional descending method was used (Whatman no. 1 paper). The following eluent systems were used: *n*-propanol–water (70:30), *n*-propanol–water–diethylamine (85:15:3), *n*-butanol–acetic acid–water (100:12:100), isobutyl alcohol–formic acid–water (70:15:13), phenol–water–NH_3–NaCN, pyridine–isoamyl alcohol–water (35:35:30). In all six systems spots I and V coincided with the spots of glycine and valine, respectively. Identity was demonstrated also as follows. The hydrolyzate was evaporated to dryness under vacuum and treated with 2,4-dinitrofluorobenzene, according to the method of Levy.[4] This yielded a mixture of dinitrophenyl derivatives. By paper chromatographic technique this mixture was compared with the dinitrophenyl derivatives of glycine and valine. The following systems were used: 1, the Blackburn system[5] (phthalate buffered paper strips of *p*H 6.0 and as eluent: (a) phthalate buffer–saturated *n*-propanol–petroleum ether 3:7); (b) phthalate buffer saturated amyl alcohol; 2, the Biserte system[6] (toluene–pyridine–ethylene chlorhydrin–0.8 *N* ammonia, 5:1:3:3). In all cases the spots of dinitrophenylvaline and dinitrophenylglycine coincided with two spots of dinitrophenyl derivatives obtained with bottromycin hydrolyzate.

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(5) S. Blackburn and A. G. Lowther, *Biochem. J.*, **48**, 126 (1951).
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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE KON. NED. GIST-EN SPIRITUSFABRIEK]

The Structure of the Sulfur-containing Moiety of Bottromycin

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The degradation of the antibiotic bottromycin by means of boiling acetic anhydride yielded two crystalline acetyl products $C_{19}H_{23}N_3O_4S$ and probably $C_{21}H_{34}N_4O_4$. The sulfur-containing moiety proved to be the methyl ester of a N-acetyl dipeptide. The two components of this peptide are two new naturally occurring amino acids, α-amino-β-phenylbutyric acid and β-(2-thiazole)-β-alanine.

Previously[1] it was reported that treatment of bottromycin with boiling acetic anhydride yields two crystalline acetyl-degradation products: $C_{19}H_{23}N_3O_4S$ (VIII) and a compound with the probable formula $C_{21}H_{34}N_4O_4$ (IX).

This paper deals with the elucidation of the structure of the sulfur-containing moiety. It has already[1] been reported that VIII contains one acetyl, one methoxyl and, in addition, one C-methyl group. Furthermore on Kunz hydrolysis one group of the molecule is split off, whereas mild acid hydrolysis yields a crystalline substance $C_{16}H_{19}N_3O_3S$ (VIIIa). Finally, vigorous hydrolysis of VIII or VIIIa yields two ninhydrin-positive compounds $C_{10}H_{13}NO_2$ (VII) and $C_6H_8N_2O_2S$ (III).

The ultraviolet spectrum of VII showed the typical absorption maxima of the phenyl nucleus (252.5–258 and 264 mμ).

By paper electrophoretic methods it could be demonstrated that VII has basic properties whereas the hydroxamic acid test[2] proved that, in addition, a carboxyl group was present in the molecule.

(1) J. M. Waisvisz, *et al.*, THIS JOURNAL, **79**, 4522 (1957).
(2) F. Feigl, "Qualitative Analysis by Spot Tests," 2nd ed., Elsevier Publishing Co., Houston, 1939, p. 204.

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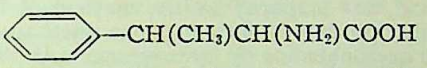
The fact that crystalline acetyl, 2,4-dinitrophenyl and tosyl derivatives of VII[1] could be prepared indicated the presence of an amino grouping. Potentiometric titrations suggested the presence of an amino acid grouping.

Oxidation of VII with potassium permanganate at room temperature yields acetophenone, which was isolated and identified as its *p*-nitrophenyl- and 2,4-dinitrophenylhydrazones. This indicated a branched side chain and proved the presence of the expected phenyl nucleus. Ultraviolet spectra of VII at alkaline and acid *p*H indicated that no dissociable grouping was attached to the phenyl nucleus.

Decarboxylation and deamination of VII with ninhydrin according to the method of Van Slyke[3] yielded hydratropic aldehyde which was isolated and identified as its 2,4-dinitrophenylhydrazone.

All these data left open only this possibility



VII, α-amino-β-phenylbutyric acid

Apart from the question of the optical activity the validity of these structural deductions was confirmed by synthesis of this amino acid according to E. Fischer.[4] Fischer reported the synthesis of α-amino-γ-phenylbutyric acid, but because of the work of F. Knoop,[4] later agreed[4] that the substance was not the γ-isomer but in fact was α-amino-β-phenylbutyric acid. Although two isomers are possible, DL- and DL-allo, synthetic α-amino-β-phenylbutyric acid proved to be identical with the natural product isolated from bottromycin in respect to analyses, melting range, mixed melting range, melting and mixed melting ranges of the tosyl-, acetyl- and dinitrophenyl derivatives, R_f values on paper chromatograms, ultraviolet and infrared spectra.

The other ninhydrin-positive, optically inactive hydrolytic degradation product of VIII is $C_6H_8N_2O_2S$ (III). This water-soluble compound also is unsaturated. Its ultraviolet spectrum showed maxima at 210 and 242.5 mμ. Paper electrophoretic methods demonstrated the acid properties of III. The presence of a single amino group was shown by the facts that it was possible to prepare only a mono-dinitrophenyl derivative, and that the hydrochloride salt, isolated from an acid hydrolysate, proved to be a monohydrochloride.[1]

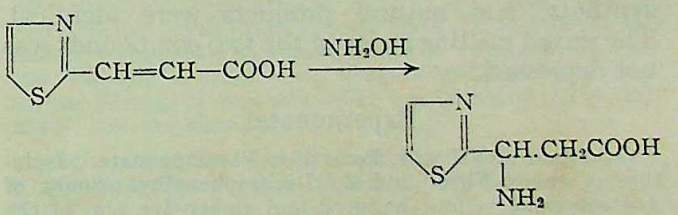
These facts suggested the presence of a heterocyclic nucleus containing sulfur and nitrogen in III. This supposition was supported by the infrared spectrum.

A literature study revealed that R. G. Jones, *et al.*,[5] synthesized a compound which has the same molecular formula and melting point as III, namely, 2-thiazolealanine. A comparative study of the two compounds revealed that they are very similar but not identical. For instance, the mixed melting point had a depression of 5°.

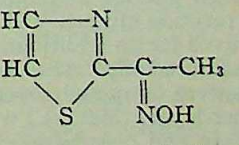
Paper chromatographic methods showed that in one of the four development solvents employed there was a slight difference in R_f value and that the spot produced by compound III turned from brown to purple on exposure to daylight, whereas the spot of 2-thiazolealanine remained brown.

There were only minor differences in the ultraviolet and infrared spectra of the two compounds, the latter indicating that III possibly could have a β-amino acid structure. Paper electrophoresis, on the other hand, showed marked differences: at *p*H 8.5 compound III moved in the direction of the anode, whereas 2-thiazolealanine did not move at all. There was also a marked difference in the melting points of the dinitrophenyl derivatives, that of III melting at 148–151° dec. and that of 2-thiazolealanine at 203.5–210° dec.

Paper chromatographic studies using the method of Crumpler[6] with the aid of copper carbonate were indecisive. Desulfurization of III with Raney nickel catalyst proved unsatisfactory. Oxidation with potassium permanganate, however, yielded a crystalline compound $C_4H_4N_2OS$. This compound proved to be 2-thiazolecarbonamide.[7] This established the presence of a thiazole nucleus substituted in the 2-position. This fact and the infrared spectrum indicated III to be β-(2-thiazole)-β-alanine. We succeeded in synthesizing this compound by the following route. 2-Methylthiazole,[8] prepared from chloroacetaldehyde and thioacetamide,[9] was converted to β-2-thiazoleacrylic acid by the method of Jones, *et al*.[8,10] Condensation with hydroxylamine gave β-(2-thiazole)-β-alanine, m.p. 199–202° dec.



A by-product (m.p. 163–165.5°) was also obtained. It is thought to be methyl 2-thiazolyl ketoxime



Apart from the question of the optical activity the synthetic β-amino acid (m.p. 199–202° dec.) was identical with the natural product as is evidenced by analysis, identical melting points and mixed melting point, identical melting points and mixed melting point of the dinitrophenyl derivatives, same ultraviolet and infrared spectra, same

(3) D. D. Van Slyke, R. T. Dillon, D. A. MacFadyen and P. Hamilton, *J. Biol. Chem.*, **141**, 627 (1941); A. I. Virtanen, T. Laine and T. Toivonen, *Z. physiol. Chem.*, **266**, 198 (1940).

(4) E. Fischer and W. Schmitz, *Ber.*, **39**, 351, 2208 (1906); E. Fischer, *ibid.*, **37**, 3063 (1904); F. Knoop and H. Hoessli, *ibid.*, **39**, 1477 (1906).

(5) R. G. Jones, E. C. Kornfeld and K. C. MacLaughlin, THIS JOURNAL, **72**, 4526 (1950).

(6) H. R. Crumpler and C. E. Dent, *Nature*, **164**, 441 (1949).

(7) H. Erlenmeyer, R. Marbet and H. Schenkel, *Helv. Chim. Acta*, **28**, 924 (1945).

(8) H. Erlenmeyer, O. Weber, P. Schmidt, G. Küng, C. Zinsstag and B. Prijs, *Helv. Chim. Acta*, **31**, 1156 (1948).

(9) A. Hantzsch, *Ann.*, **250**, 271 (1889).

(10) R. G. Jones, E. C. Kornfeld and K. C. MacLaughlin, THIS JOURNAL, **72**, 4528 (1950).

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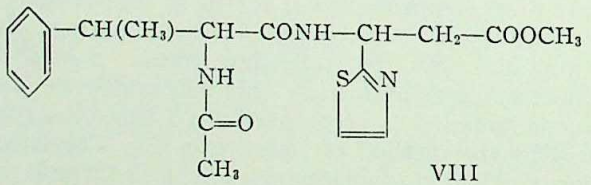
R_f values on paper chromatograms, and identical behavior on paper electrophoresis.

The structure elucidation of the two amino acids III and VII being completed, there remained the question of the structure of the acetyl degradation compound of bottromycin, $C_{19}H_{23}N_3O_4S$ (VIII) from which these two amino acids were derived. Group analyses showed that VIII contained one acetyl and one methoxyl group.[1] Since neither of the two degradation products of VIII possessed a hydroxyl group, it is very likely that the acetyl group was linked to a nitrogen atom and that the methoxyl group possibly was a methyl ester grouping. The last supposition was supported by Kunz hydrolysis of VIII and by the fact that we were able to prepare a benzylamide derivative of the acetyl compound by reaction with benzylamine.

By lithium aluminum hydride reduction of VIII and acid hydrolysis of the reaction product followed by paper chromatographic study of the products formed we could establish that β-(2-thiazole)-β-alanine was the C-terminal amino acid. By synthesis of the dipeptide from the natural N-acetyl-α-amino-β-phenylbutyric acid[1] and β-(2-thiazole)-β-alanine methyl ester, by the method of Sheehan,[11] we could prove that apart from the question of the optical activity the structure of the acetyl degradation product VIII is



VIII

Analyses, ultraviolet and infrared spectra of the synthetic and natural products were identical. The mixed melting range of the two compounds was not depressed.

Experimental

Oxidation of VII with Potassium Permanganate. Isolation of the *p*-Nitro- and 2,4-Dinitrophenylhydrazones of Acetophenone.—Four hundred and eighty-five mg. of the hydrochloride of VII was dissolved in 27.5 ml. of water. To this solution was added gradually with stirring and external cooling a solution of 553 mg. of potassium permanganate in 27.5 ml. of water, the addition being completed in 55 minutes. After stirring at room temperature for another 50 min. the reaction mixture was heated to a temperature of 50° and stirred for an additional 30 min. The manganese dioxide was filtered off, washed with hot water and the combined filtrates were extracted several times with ether. The combined ether layers (300 ml.) were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residual oily product (67 mg.) was dissolved in 1 ml. of ethanol and heated on a steam-bath for five minutes with 1 ml. of a solution of *p*-nitrophenylhydrazine (1 g. of *p*-nitrophenylhydrazine dissolved in 2 ml. of 4 *N* hydrochloric acid and 10 ml. of water). After cooling, the orange-colored derivative was filtered off, washed with water and dried. Fifty-one and a half mg. of the *p*-nitrophenylhydrazone was obtained (m.p. 160–178°). After two recrystallizations from 70% ethanol the derivative melted at 177–184° (with sublimation).

The mixed melting point with synthetic material was not depressed. The ultraviolet spectra of both compounds were identical.

Repetition with 485 mg. of VII gave a similar oily product. After heating with 5 ml. of a solution of 2,4-dinitrophenylhydrazine (according to Shriner and Fuson[12]) an orange-colored 2,4-dinitrophenylhydrazone was obtained. Recrystallized twice from ethanol 56 mg. of pure product was obtained which had a m.p. of 243–246° (with sublimation), undepressed on mixture with an authentic sample. The ultraviolet spectra of both compounds were also identical.

Decarboxylation and Deamination of VII with Ninhydrin. Isolation of Hydratropicaldehyde 2,4-Dinitrophenylhydrazone.—To a solution of 234 mg. of the hydrochloride of VII 42 g. of sodium chloride and 28 g. of primary potassium phosphate in 280 ml. of water was added 56 ml. of a 1% ninhydrin solution in water. Over a period of 30 minutes the reaction mixture was heated to its boiling point, then steam distilled. To the distillate (80 ml.) was added 10 ml. of a 2,4-dinitrophenylhydrazine solution and the solution was heated briefly on a steam-bath. After cooling the yellow crystals were collected, washed with water and recrystallized from 4 ml. of ethanol. Recrystallized once more 25 mg. of pure 2,4-dinitrophenylhydrazone (m.p. 133–136°) was obtained, not depressed on mixture with an authentic sample. The ultraviolet spectra of both products also proved to be identical.

The Synthesis of α-Amino-β-phenylbutyric Acid.—This α-amino acid was prepared by the method of E. Fischer.[4] The starting product, 1-bromo-1-phenylethane, was prepared from acetophenone by hydrogenation.[13] This yielded phenylmethylcarbinol, which was brominated according to the method of J. B. Conant, *et al.*[14] The amino acid obtained was recrystallized from water as a monohydrate and melted at 162–166°. After drying *in vacuo* for four hours at 110° the product had lost its water content and melted at 234° dec.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.00; H, 7.24; N, 7.75.

Preparation of Derivatives of α-Amino-β-phenylbutyric Acid. a.—The 2,4-dinitrophenyl derivative was prepared from 239 mg. of its monohydrate and 0.28 ml. of 2,4-dinitrofluorobenzene according to the method of Sanger.[15] After two recrystallizations from 68% methanol it showed a melting range of 185–213° dec.

b.—**The tosyl derivative** of synthetic α-amino-β-phenylbutyric acid was prepared according to the method described in the previous paper.[1] The product melted at 147–152.5°.

c.—**The acetyl derivative** of the synthetic α-amino-β-phenylbutyric acid was prepared according to the method described in the previous paper.[1] The derivative melted at 185–190°.

Oxidation of III with Potassium Permanganate. Isolation of 2-Thiazole-carbonamide.—Four hundred and ninety-one mg. of the hydrochloride of III was dissolved in 27.5 ml. of water. The *p*H of the solution was adjusted to 8 by addition of concentrated sodium hydroxide solution. Gradually with stirring and external cooling (with running water) a solution of 1.24 g. of potassium permanganate in 40 ml. of water was added over a period of 45 min. The reaction mixture was heated to 50° and stirred for an additional 15 min. After cooling the manganese dioxide was filtered off, washed with hot water and the combined filtrates extracted continually with ether. The ether extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residual crystalline product (122 mg.) melting at 116–118° was recrystallized from 75 ml. of heptane; obtained, 95 mg. of the acicular crystalline product, melting at 117–118°. A molecular weight determination (Rast-camphor) gave a value of approximately 124.

Anal. Calcd. for $C_4H_4N_2OS$: C, 37.51; H, 3.15; N, 21.87; S, 25.00. Found: C, 37.61; H, 3.13; N, 21.66; S, 27.39.

Synthesis of β-(2-Thiazole)-β-alanine.—Chloroacetaldehyde was prepared by direct chlorination of paraldehyde according to the method of H. Guinot[16] (yield 46%). Thio-

(11) J. C. Sheehan and G. P. Hess, THIS JOURNAL, 77, 1067 (1955).

(12) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 174.

(13) H. Adkins and R. Connor, THIS JOURNAL, **53**, 1093 (1931).

(14) J. B. Conant and A. H. Blatt, *ibid.*, **50**, 554 (1928).

(15) F. Sanger, *Biochem. J.*, **39**, 507 (1945).

(16) H. Guinot and J. Tabuteau, *Compt. rend.*, **231**, 234 (1950).

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acetamide was obtained by treating acetamide with phosphorus pentasulfide[9] (average yield 30%). 2-Methylthiazole was prepared from above-mentioned components by the method of Erlenmeyer[8] (average yield 45%). 2-(β-Oxy-γ-trichloro)-*n*-propylthiazole and 2-thiazoleacrylic acid were prepared from 2-methylthiazole and trichloroacetaldehyde by the method of Jones.[10] Yields obtained were in agreement with those given by the authors. β-(2-Thiazole)-β-alanine was prepared as follows: 0.46 g. of sodium was dissolved in 16 ml. of absolute ethanol. To this solution was added a hot solution of 1.39 g. of hydroxylamine hydrochloride in 1 ml. of water. After cooling in an ice-bath the precipitated sodium chloride was filtered with suction and the filtercake washed with three portions of 1 ml. each of absolute ethanol. To the combined filtrates was added under shaking 1.55 g. of 2-thiazoleacrylic acid. The solution obtained was heated under reflux for 9 hours on a steam-bath, followed by an additional 14 hours at room temperature. On concentration *in vacuo* to a small volume crystallization occurred. The crystals were collected, washed with small quantities of alcohol and hexane, respectively; obtained, 600 mg. of a cream-colored product (m.p. 195–200°). After recrystallization from 280 ml. of 96% ethyl alcohol 475 mg. of the acicular crystalline compound was isolated (m.p. 199–202° dec.).

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.86; H, 4.68; N, 16.28; S, 18.59. Found: C, 41.73; H, 4.68; N, 16.12; S, 18.60.

A second crop of crystals (155 mg.) was obtained from the mother liquors by concentration. The melting point of this fraction was 155–162° (under sublimation). After recrystallization from water 80 mg. of a white product was isolated melting at 163–165.5°. Supposedly this compound is methyl 2-thiazolyl ketoxime.

Anal. Calcd. for $C_5H_6N_2OS$: C, 42.25; H, 4.26; N, 19.71; S, 22.52. Found: C, 42.24; H, 4.30; N, 19.58; S, 22.56.

The Dinitrophenyl Derivative of β-(2-Thiazole)-β-alanine.—Similarly as described for this derivative of III[1] we prepared the 2,4-dinitrophenyl-β-(2-thiazole)-β-alanine from 260 mg. of synthetic β-amino acid and 0.84 mg. of 2,4-dinitrofluorobenzene. After two recrystallizations from 60% methanol 300 mg. of a yellow derivative was obtained. The melting point was 148–151°.

Anal. Calcd. for $C_{12}H_{10}N_4O_6S$: C, 42.61; H, 2.98; N, 16.57; S, 9.46. Found: C, 42.51; H, 3.06; N, 16.44; S, 9.52.

Synthesis of the Benzylamide of VIII.—A hundred and ninety-nine mg. of VIII was dissolved in 1 ml. of benzylamine on a steam-bath. After an additional 18 hr. at room temperature crystallization occurred. The reaction mixture was heated for another 2 hr. under reflux on a steam-bath and stored for an additional 24 hr. at room temperature. To the crystalline mass was added a mixture of 10 ml. of ethyl acetate and 2 ml. of alcohol, whereupon the suspension was heated to the boiling point, then filtered with suction while still hot; obtained, 117 mg. of a white solid of melting point 286° (dec. after sublimation). After recrystallization from 200 ml. of ethanol 80 mg. of the crystalline compound was isolated. The melting point was 290–291° (dec. under sublimation).

Anal. Calcd. for $C_{25}H_{28}N_4O_3S$: C, 64.64; H, 6.08; N, 12.06; S, 6.89. Found: C, 64.36; H, 6.13; N, 12.14; S, 7.41.

Lithium Aluminum Hydride Reduction of VIII.—A finely divided suspension of 97 mg. of lithium aluminum hydride in 25 ml. of dry ether was treated with 66 mg. of VIII introduced by extraction (7 hours) from an extraction thimble. After the thimble was removed the heating was continued for another 30 min. and the reaction mixture thereafter kept at room temperature for 16 hours. The excess of lithium aluminum hydride was destroyed by careful addition of 1 ml. of water. The precipitated hydroxides were filtered off and extracted several times with small portions of boiling alcohol. The combined ethereal alcoholic filtrates were evaporated to dryness and the residual oily product was hydrolyzed in a Carius tube for 72 hr. with 2 ml. of concentrated hydrochloric acid at 100–110°. Paper chromatograms run in butanol–acetic acid–water (100:12:100) showed that only the unchanged VII was present in this hydrolyzate, while the spot due to III was no longer observed.

Methyl Ester of III.—Two grams of the hydrochloride of III was suspended in 75 ml. of absolute methanol. The suspension was saturated with a stream of dry hydrogen chloride whereupon the compound dissolved. The reaction mixture was heated under reflux for 2.5 hours, then kept for 15 hours in the refrigerator. After evaporation to dryness the residual crystalline mass was dissolved in 10 ml. of ice-water, the solution adjusted to a *p*H of 8.5 by careful addition of a saturated solution of potassium carbonate and extracted several times with ether (180 ml.). The combined extracts were dried over anhydrous sodium sulfate, filtered, then evaporated to dryness; obtained, 1.27 g. yellow colored, oily methyl ester of III.

Synthesis of VIII.—One and a half g. of the methyl ester of III, 1.89 g. of the N-acetyl compound of VII[1] and 2.05 g. dicyclohexyl carbodiimide[17] were suspended in 25 ml. of purified tetrahydrofuran. The reaction mixture was shaken occasionally and kept at room temperature for 4 hr. The precipitate (1.9 g., dicyclohexyl carbamide) was removed by filtration and washed with a small quantity of tetrahydrofuran. After addition of a few drops of glacial acetic acid the filtrates were evaporated *in vacuo*, and the tarry residue dissolved in 25 ml. of boiling ethyl acetate. This solution was decolorized with active carbon. After cooling another crop (129 mg.) of dicyclohexyl carbamide was obtained. This was removed by filtration. The filtrate was extracted with three portions of 5 ml. each of 1 *N* hydrochloric acid. The *p*H of the combined extracts was adjusted to 5 by addition of a few drops of 33% potassium hydroxide solution. The resulting solution was re-extracted twice with 10-ml. portions of ethyl acetate. The extracts were dried and concentrated *in vacuo* to a small volume. After cooling crystallization took place. The product was filtered with suction and dried (96 mg.). The melting point was 195–202°. After two recrystallizations from ethyl acetate 34 mg. of synthetic VIII was obtained (m.p. 202–208.5° with sublimation).

Anal. Calcd. for $C_{19}H_{23}N_3O_4S$: C, 58.61; H, 5.91; N, 10.80; S, 8.23. Found: C, 58.65; H, 5.85; N, 10.63; S, 8.13.

Acknowledgments.—The authors wish to thank Mr. P. J. Hubers and Mr. M. Van Leeuwen for microanalyses, Miss V. Roest and Dr. L. M. Rientsma for infrared absorption determinations, and Professor W. Berends of Delft for many helpful discussions. We are also indebted to the Eli Lilly Research Labs. for a gift of 2- and 4-thiazolealanine, and to Mr. A. K. J. Mulder for the synthesis of α-amino-β-phenylbutyric acid.

DELFT, HOLLAND

(17) E. Schmidt, F. Hitzler and E. Lahde, *Ber.*, **71**, 1938 (1938).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Cross-linking of Gelatin Using a Water-soluble Carbodiimide

BY JOHN C. SHEEHAN AND JOSEPH J. HLAVKA[1]

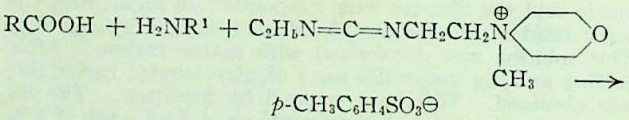
RECEIVED MARCH 30, 1957

Treatment of an aqueous gelatin solution with a water-soluble carbodiimide (III) resulted in very rapid gelation, shown to be due to amide bond formation.

Recently[2] we reported that water-soluble carbodiimides may be used to form peptide bonds in fully aqueous solution. It is of obvious interest to study the effect of these unusual reagents on proteins.

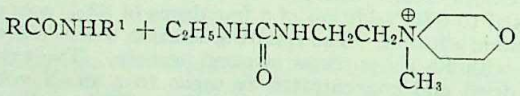
Gelatin may be regarded as a partially degraded protein, being derived from collagen by acidic or basic hydrolysis. In addition to amino and carboxy terminal groups, the peptides possess side-chains, some of which end in carboxy groups (due principally to glutamic and aspartic acid residues) and others bear free amino functions (accounted for chiefly by lysine).

We have found that treatment of an aqueous solution of gelatin with a water-soluble carbodiimide [1-ethyl-3-(2-morpholinyl-(4)-ethyl)-carbodiimide metho-*p*-toluenesulfonate (III)] results in very rapid (30 seconds) gelation, presumably due to cross-linking by amide bond formation.



p-$CH_3C_6H_4SO_3\ominus$

III



p-$CH_3C_6H_4SO_3\ominus$

IV

Previously, known methods for denaturing, insolubilizing, hardening or tanning protein-type materials with chemical agents, such as aldehydes (formaldehyde or glyoxal) or metallic ions (chrome-alum), are slower acting, leave a residue in the treated material, and operate by complex and poorly understood mechanisms. The carbodiimides II and III are especially useful for amide and peptide bond formation in high yield,[2] by virtue of their accessibility from commercially available intermediates and favorable physical properties.

The normal gelation of gelatin is considered generally to involve hydrogen bond formation through amide groups.[3] It is of interest to demonstrate that the carbodiimide reagent is operating by a different mechanism, namely, formation of new amide bonds. The following experiments convincingly demonstrate this latter mechanism.

Gelatin will not gel in a 2 *M* urea solution at 25° (considered to be due to efficiency of urea in the disruption of hydrogen bonds), but the addition of III causes immediate gelation. Benzoyl gelatin,[4] which contains essentially no free amino groups, gels reversibly as a 5% solution in 10–15 minutes at 25° with or without added III.

Treatment of gelatin with a high ratio (equal weight dry basis) of water-soluble carbodiimide leads to very rapid gelation, but after 10–16 hours storage at 25°, the mixture liquefied. However, if the gelled solution of gelatin and carbodiimide is heated immediately on a steam-cone for 10 minutes, the mixture remains solid at the elevated temperature and on storage for five days at 25°.

At ratios of 10–25% by weight of carbodiimide to a 5% gelatin solution, the rate of gelation is less. The melting point of the treated gelatin is increased to 50–90° and no liquefaction was observed on storage.

In a separate experiment a 5% gelatin solution was freeze-dried immediately after gelation with a nearly equal weight of III. The resulting powder was washed free of water-soluble components and divided into three portions. The first portion (a control) was suspended in water corresponding to a 5% solution and stored three days at 25°, but the mixture did not become homogeneous. A second portion, suspended in water containing the urea IV, likewise did not dissolve on storage. The third portion, treated with an additional quantity of III, did dissolve on storage, thereby establishing excess III as the factor producing liquefaction.

On storing the gelatin–carbodiimide mixture, the rate of disappearance of carboxyl groups (Sörensen titration[5]) paralleled the loss of free amino functions (Van Slyke determination), further evidence that amide bond formation was taking place. Immediately after gelation the carboxy value dropped to 25% of the original gelatin figure and after reliquefaction only 10% of the amino and carboxyl groups remained. Liquefaction is considered to be associated with phase-separation, and the phenomenon is being investigated further.

Experimental[6]

1-Ethyl-3-(2-morpholinyl-(4)-ethyl)-thiourea (I).—To a solution of 10 g. (0.077 mole) of N-(2-aminoethyl)-morpholine in 100 ml. of ether was added slowly 6.7 g. (0.077 mole) of ethyl isothiocyanate. After ebullition had ceased, the reaction solution was stored overnight at 0°. The crystalline product I amounted to 14.0 g. (84%), m.p. 94–96°.

Anal. Calcd. for $C_9H_{19}N_3OS$: C, 49.75; H, 8.81; N, 19.34. Found: C, 49.80; H, 8.83; N, 19.35.

1-Ethyl-3-(2-morpholinyl-(4)-ethyl)-carbodiimide (II).—A solution of 5.0 g. (0.023 mole) of 1-ethyl-3-(2-morpholinyl-(4)-ethyl)-thiourea in 100 ml. of dry acetone was stirred at room temperature with 7.0 g. of mercuric oxide (Merck Yellow) for 5 hours. The precipitated mercuric sulfide was

(1) Aided by a Fellowship from the National Institutes of Health.

(2) J. C. Sheehan and J. J. Hlavka, *J. Org. Chem.*, **21**, 439 (1956).

(3) C. Robinson and M. Bott, *Nature*, **168**, 325 (1951).

(4) A sample of benzoyl gelatin, prepared by Schotten–Baumann benzoylation of gelatin, was furnished by Dr. E. R. Blout, Polaroid Corporation, Cambridge, Mass.

(5) G. Wilson, "Laboratory Manual of Physiological Chemistry," The Williams and Wilkins Co., Baltimore, Md., 1952, p. 72.

(6) All melting points are uncorrected. We wish to thank Dr. S. M. Nagy and associates for the microanalytical data.

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removed by filtration and the filtrate was again stirred 12 hours with 7.0 g. of mercuric oxide. After filtration the acetone was distilled under reduced pressure and the residue was purified by distillation at 80° (0.05 mm.), yield 3.5 g. (76%).

Anal. Calcd. for $C_9H_{17}N_3O$: C, 58.98; H, 9.35; N, 22.93. Found: C, 59.11; H, 9.34; N, 23.10.

1-Ethyl-3-(2-morpholinyl-(4)-ethyl)-carbodiimide Metho-*p*-toluenesulfonate (III).—A mixture of 2.0 g. (0.011 mole) of methyl *p*-toluenesulfonate and 2.0 g. (0.11 mole) of carbodiimide II was heated on a steam-bath for 10 minutes. On trituration with benzene the mixture crystallized; 3.6 g. (90%), m.p. 86–88°. Recrystallization from an acetone–benzene mixture raised the m.p. to 91–93°.

Anal. Calcd. for $C_{17}H_{27}N_3O_4S$: C, 55.27; H, 7.37; N, 11.38. Found: C, 55.41; H, 7.50; N, 11.50.

Reaction of Gelatin[7] with an Excess of 1-Ethyl-3-(2-morpholinyl-(4)-ethyl)-carbodiimide Metho-*p*-toluenesulfonate (III). Experiment 1.—To a solution of 2.0 g. of gelatin[7] in 25.0 ml. of water was added 1.5 g. of III. The solution gelled almost immediately (30 seconds), but liquefied on storage at room temperature for 16 hours. The resulting solution was dialyzed (using $^8/_{32}''$ cellulose casing) for 4 days. The solution was freeze-dried to a white powder; weight 2.0 g. A Sorensen titration[5] on 0.4 g. required 0.25 ml. of 0.103 *N* sodium hydroxide. An untreated gelatin sample (0.4 g.) required 2.6 ml. A Van Slyke analysis yielded 0.19% nitrogen, while untreated gelatin yielded 0.64% nitrogen.

Experiment 2.—A solution of gelatin in 50.0 ml. of water was gelled with 2.25 g. of carbodiimide III. The gel was immediately freeze-dried, followed by trituration with 500 ml. of water. The resulting material after drying weighed 3.0 g. The wash water on evaporation yielded 2.3 g. of urea IV.

A 0.5-g. sample of the above-treated gelatin was dissolved in 20 ml. of a 50% calcium chloride solution by heating on a steam-bath for 1 hour. A Sorensen titration[5] required 0.65 ml. of 0.103 *N* sodium hydroxide.

When 0.1 g. of the gelatin prepared above was suspended in 2.0 ml. of water containing 75 mg. of urea IV, no liquefaction occurred even after 9 days. If, however, carbodiimide was substituted for IV, liquefaction occurred.

When conductometric amino titrations[8] were carried out on the gelatins prepared in both runs 1 and 2, a decrease in amino content as compared to untreated gelatin was observed.

Experiment 3.—A solution of 0.2 g. of gelatin, 0.45 g. of urea and 0.15 g. of carbodiimide III in 4.0 ml. of water gelled after 20 seconds. On storage overnight the reaction mixture liquefied.

Reaction of Carbodiimide III and Benzoyl Gelatin.[4]—To a solution of 0.1 g. of benzoyl gelatin[4] in 2 ml. of water was added 0.1 g. of III. On stirring no sudden gelation occurred as with the control gelatin.

(7) The gelatin was obtained from the Atlantic Gelatin Co., Division of General Foods, Lot #6200-X.

(8) S. Ellis and J. Parkhurst, *Biochem. J.*, **52**, 350 (1952).

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Biogenesis of Nicotine. III. Further Observations on the Incorporation of Ornithine into the Pyrrolidine Ring[1]

BY EDWARD LEETE AND KENNETH J. SIEGFRIED

RECEIVED MARCH 6, 1957

Radioactive nicotine was isolated from two groups of *Nicotiana tabacum* plants, which were harvested one and three weeks after the administration of equal counts of ornithine-2-C^{14}. The nicotine from the two experiments had almost the same specific activity, indicating that little or no metabolic breakdown of nicotine had occurred during the last two weeks of the second experiment. The nicotine from both experiments was degraded unambiguously and all the activity in the alkaloid was shown to be equally divided between the two α-carbons of the pyrrolidine ring.

Introduction

It has been shown that radioactive nicotine is obtained when ornithine-2-C^{14} is fed intact *N. tabacum*[1a] or *N. rustica*[2] plants, or to sterile roots[3] of the former species. Degradation of the radioactive nicotine[1a,2] indicated that half the activity was located on C-2 of the nicotine molecule I. This result could be explained by postulating that ornithine was metabolized to a symmetrical compound before incorporation into nicotine. In the biogenetic scheme suggested by the author,[1b] the mesomeric anion of Δ^1-pyrroline functioned as the symmetrical intermediate. Putrescine (1,4-diaminobutane) is another plausible intermediate, which would result from ornithine on decarboxylation. However the feeding of radioactive putrescine to *Datura stramonium* plants did not yield radioactive hyoscyamine,[4] whereas radioactive ornithine was incorporated into the pyrrolidine ring of the hyoscyamine.[5] Furthermore in other biological systems the pyrrolidine ring has been shown to arise from ornithine *via* glutamic-γ-aldehyde, putrescine not being an intermediate.[6]

It was considered of interest to investigate changes in the activity of the nicotine after feeding ornithine-2-C^{14} for varying lengths of time. In the present work radioactive ornithine was administered to two groups of *N. tabacum* plants growing in inorganic nutrient solution. The first group was harvested after 7 days and the second after 21 days. The degradative steps which were used to locate the positions of activity in the radioactive nicotine are shown in Fig. 1. Treatment of nicotine with hydrogen iodide yielded methyl iodide which was absorbed in triethylamine affording methyltriethylammonium iodide (II). Oxidation of nicotine with concentrated nitric acid yielded

(1) Parts I and II of this series are considered to be: (a) E. Leete, *Chemistry & Industry*, 537 (1955), and (b) E. Leete, THIS JOURNAL, **78**, 3520 (1956), respectively. This work has been supported in part by a grant from the Research Corporation, New York.

(2) L. J. Dewey, R. U. Byerrum and C. D. Ball, *Biochim. Biophys. Acta*, **18**, 141 (1955).

(3) R. F. Dawson, private communication.

(4) D. G. M. Diaper, S. Kirkwood and L. Marion, *Can. J. Chem.*, **29**, 964 (1951).

(5) (a) E. Leete, L. Marion and I. D. Spenser, *ibid.*, **32**, 1116 (1954); (b) *Nature*, **174**, 650 (1954).

(6) M. R. Stetten in "Amino Acid Metabolism," edited by W. D. McElroy and H. B. Glass, John Hopkins Press, Baltimore, Md., 1955, pp. 277–290.

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nicotinic acid (III) and 3-nitro-5-(3′-pyridyl)-pyrazole (V). This pyrazole derivative was first isolated by Gough and King[7] who suggested that it was 4-nitro-5-(3′-pyridyl)-pyrazole. The assigned position of the nitro group was shown to be incorrect by Lund[8] and shown to be actually on the 3-position by Clemo and Holmes.[9] The mechanism of the formation of the pyrazole is being inves-

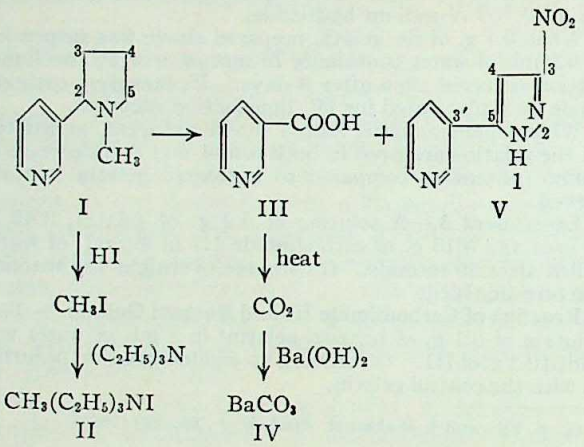

Fig. 1.—Degradation of radioactive nicotine.

tigated. It is only obtained in about 5% yield from nicotine, but it is separated readily from nicotinic acid by adjustment of the *p*H of the oxidation mixture. The pyrazole derivative contains all the carbons of nicotine except C-5 and the N-methyl group. The nicotinic acid was decarboxylated in boiling quinoline, the evolved carbon dioxide being absorbed in barium hydroxide.

Experimental[10]

Administration of the Ornithine-2-C^{14} to the Tobacco Plants and Isolation of the Nicotine.—The *N. tabacum* (variety Turkish Samsun) was grown as previously described[1b] in soil and then in inorganic nutrient. When they were about 4 months old, eight healthy plants (about 30 inches tall) were selected and ornithine-2-C^{14} monohydrochloride[11] (490 mg.) with an activity of 7.56×10^7 c.p.m./m*M*[12] (total activity, 2.22×10^8) was divided equally between their nutrient solutions. After 7 days four of the plants were harvested. The method of isolation of the nicotine was identical with that used for the isolation of anabasine from *N. glauca*,[1b] and was less tedious than the method previously used. In brief, the method involved digestion of the fresh macerated plant with chloroform and aqueous ammonia. The chloroform was extracted with 2 *N* sulfuric acid, which was then made basic with ammonia and again extracted with chloroform yielding crude nicotine after drying and evaporation. The crude alkaloid[13] was distilled *in vacuo* and converted to the diperchlorate. After 21 days the other four plants were harvested and the nicotine similarly isolated. Activity and weights of plant material from the two experiments are shown in Table I.

TABLE I

TOTAL ACTIVITIES IN C.P.M.

	7 day	21 day
Fresh wt. of plants at time of harvesting, g.	810	860
Dried wt. of plant after extraction with $CHCl_3$ and NH_3, g.	41	51
Wt. of distilled nicotine, mg.	96	115
Activity of:		
Chloroform extract	1.0×10^6	1.1×10^6
Ammoniacal sap	1.5×10^6	0.8×10^6
Dried residue[14]	7.1×10^6	4.2×10^6
Crude nicotine (not distilled)	0.6×10^6	0.7×10^6

Degradation of the Nicotine. (a) Activity in the N-Methyl Group.—About 70 mg. of the undiluted nicotine diperchlorate was dissolved in water, made alkaline with sodium hydroxide and the solution extracted with ether. The dried ether solution water evaporated and the residue distilled *in vacuo* (120° (0.01 mm.)). The distilled nicotine was demethylated according to the procedure of Brown and Byerrum.[15]

(b) Oxidation with Nitric Acid.—The active nicotine diperchlorate (100 mg.) was diluted with inactive perchlorate (1.900 g.) and recrystallized from ethanol. Diluted nicotine diperchlorate (1.50 g.) was dissolved in 20 ml. of concentrated nitric acid and heated at 100° for 18 hours. The solution was then evaporated to dryness *in vacuo* and the residue redissolved in 10 ml. of water. The pale yellow solution was brought to *p*H 5 by the addition of 10% sodium hydroxide. At this *p*H a yellow crystalline precipitate of 3-nitro-5-(3′-pyridyl)-pyrazole (V) (32.6 mg., 4.1%) separated out. It was sublimed (200° (0.001 mm.)) and recrystallized from glacial acetic yielding long colorless needles, m.p. 277–278°.

Anal. Calcd. for $C_8H_6N_4O_2$: C, 50.53; H, 3.18. Found: C, 50.76; H, 2.98.

The filtrate obtained after removal of the pyrazole derivative contained nicotinic acid which was isolated as its cupric salt and degraded as previously described.[1b] The activities of nicotine and its degradation products from the two feeding experiments are shown in Table II. The activities are for carrier free material.

TABLE II

	Specific activities (c.p.m./m*M*) 7 day expt.	21 day expt.
Ornithine-2-C^{14} fed	7.56×10^7	7.56×10^7
Nicotine diperchlorate	9.0×10^5	8.4×10^5
Nicotine dipicrate	8.9×10^5	8.2×10^5
3-Nitro-5-(3′-pyridyl)-pyrazole (V)	4.6×10^5	4.4×10^5
Nicotinic acid (III)	4.3×10^5	4.1×10^5
Nicotinic acid hydrochloride	4.4×10^5	4.0×10^5
Methyltriethylammonium iodide (II)	0	0
Barium carbonate (IV)	4.2×10^5	3.9×10^5

Discussion

An examination of Table I shows that the loss of activity from the plants was surprisingly large. Thus after 7 days only 9% (9.6×10^6 c.p.m.) of the radioactive carbon administered in the form of ornithine remained in the plant. After 21 days the activity in the plant had been reduced to 5% (6.1×10^6). The radioactive carbon was presumably ex-

(7) G. A. C. Gough and H. King, *J. Chem. Soc.*, 2968 (1931).

(8) H. Lund, *ibid.*, 686 (1933).

(9) G. R. Clemo and T. Holmes, *ibid.*, 1739 (1934).

(10) All melting points are corrected and analyses were performed by Miss Heather King of this department.

(11) The ornithine-2-C^{14} was synthesized from ethyl acetamidocyanoacetate-2-C^{14} (purchased from Tracerlab, Inc., Boston, Mass.) by the method of M. Fields, D. E. Walz and S. Rothchild, THIS JOURNAL, **73**, 1000 (1951).

(12) All counts were determined using a windowless G. M. counter (Nuclear Instrument and Chemical Co. Model D-46-A) using "Q gas" as the quenching gas. Determinations of activity were carried out in duplicate, making corrections for the geometry of the instrument and self absorption. The preparation of the samples was standardized and results reproducible to 5% were obtained.

(13) Paper chromatography of the crude alkaloid did not indicate the presence of any alkaloids other than nicotine.

(14) Activity in the residual plant material was determined by the method of D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, 509 (1940).

(15) S. S. Brown and R. U. Byerrum, THIS JOURNAL, **74**, 1523 (1952).

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pired as carbon dioxide since the activity of the nutrient solution was negligible. Although the total activity of the plants in the 21 day experiment was less than in the 7 day experiment, the activity of the crude alkaloid fraction had increased slightly.

It is considered that there was an initial rapid uptake of radioactive ornithine which was incorporated into proteins and a certain fraction into nicotine. Inactive ornithine was then synthesized by normal routes from inactive precursors. This inactive ornithine apparently exchanged with combined radioactive ornithine in proteins or other non-alkaloid plant components reducing the activity in the residual plant material. Some of the released radioactive ornithine would be incorporated into nicotine and some would be oxidized to carbon dioxide which on expiration would reduce the over-all activity in the plant. Since the nicotine fraction had a slightly higher activity after 21 days it appears that nicotine does not re-enter the general metabolic pool of the plant once it has been formed. Work is proceeding to see whether the nicotine remains indefinitely in the plant without undergoing metabolic change.

The activities of nicotine and its degradation products in the two experiments are almost identical and they can be discussed together. No activity was found in the N-methyl group. This result is in agreement with that previously obtained.[1a] Dewey, *et al.*,[2] detected a small amount of activity in the N-methyl group after feeding ornithine-2-C^{14} to tobacco plants. The plants used by these workers were younger than ours and possibly had not as large a photosynthetic capacity. Thus the plants were possibly deficient in carbon and would utilize some of the breakdown products of ornithine for the synthesis of N-methyl groups, albeit inefficiently. Our plants were grown in a strong draught, expired radioactive carbon dioxide being rapidly swept away. It has been reported[16] that excised tobacco leaves utilize carbon dioxide for the synthesis of the N-methyl group of nicotine.

The activity of the barium carbonate represents the activity of C-2 of nicotine. Since the activity of the nicotinic acid and its hydrochloride are almost identical with this, there must be negligible activity in the pyridine ring. Since no activity was found in the N-methyl group, the difference in the activity of the nicotine and the pyrazole (V) represents the activity of C-5. The difference in the activity of the pyrazole and nicotinic acid represents the activity of C-3 and C-4. This is negligible, thus all the activity in the nicotine is located on C-2 and C-5 and is equally divided between them. This confirms our previous hypothesis[1a] that ornithine is metabolized to a symmetrical four carbon compound before incorporation into the nicotine molecule.

Acknowledgment.—The authors are indebted to Dr. S. G. Wildman and Dr. A. Lang of the Department of Botany of this University for help in the cultivation of the tobacco plants.

(16) A. M. Kuzin and V. I. Merenova, *Doklady Akad. Nauk. SSSR.*, **85**, 393 (1952).

LOS ANGELES 24, CAL.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE]

The Veratrum Alkaloids. XLI.[1] The Position of the Second Hydroxyl in Rubijervine and the Identity of Certain Dehydrogenation Products

BY S. WILLIAM PELLETIER AND DAVID M. LOCKE

RECEIVED MARCH 22, 1957

The second hydroxyl of rubijervine is shown to be at position 12 by infrared and optical rotatory dispersion studies on rubijervone-12. Reduction of this ketone with sodium-in-propanol gives 12-epirubijervine (IIIa), showing that the 12-hydroxyl in rubijervine (Ia) is axial. Molecular rotation data for rubijervine and 12-epirubijervine derivatives are also in agreement with assignment of the 12α- and 12β-configurations, respectively, to these compounds. The hydrocarbon $C_{18}H_{16}$ from the dehydrogenation of rubijervine is shown to be 1′-methyl-1,2-cyclopentenophenanthrene (VIII). The phenol $C_{18}H_{16}O$ obtained in the same dehydrogenation has been converted to 1′-methyl-1,2-cyclopentenophenanthrene (VIII) by reduction of its diethyl phosphate ester with sodium in liquid ammonia. Its infrared spectrum leads to the conclusion that it is 1′-methyl-1,2-cyclopentenophenanthrol-3 (X).

The various species of *Veratrum* elaborate a series of complex alkaloids, some of which have found use in combatting hypertensive disorders. The alkaloids fall into two broad classes.[2,3] The first includes a series of highly oxygenated alkamines of the formula $C_{27}H_{43}NO_{7-9}$, which occur in nature as esters of relatively simple organic acids. The second comprises a group of C_{27}-bases of low oxygen content which occur free or as glycosides. Rubijervine,[3,4] an example of the latter class, was first discovered by Wright and Luff[5] in *Veratrum album*[6] and has since been found in *Veratrum viride*.[7,8] Studies by Jacobs and Craig showed this alkaloid to have the molecular formula $C_{27}H_{43}NO_2$[9] and to be a hexacyclic tertiary steroidal base containing a 3β-hydroxy-Δ^5-stenol system and a second hydroxy

(1) A preliminary account of a portion of this work is outlined in Paper XL, D. M. Locke and S. W. Pelletier, *Chemistry & Industry*, 1049 (1956).

(2) V. Prelog and O. Jeger, in "The Alkaloids, Chemistry and Physiology," edited by R. H. F. Manske and H. L. Holmes, Vol. III, Academic Press, Inc., New York, N. Y., 1953, p. 270.

(3) J. McKenna, *Quart. Revs.*, **7**, 231 (1953).

(4) Reference 2, pp. 277–280.

(5) C. R. A. Wright and A. P. Luff, *J. Chem. Soc.*, **35**, 405, 421 (1879).

(6) G. Salzberger, *Arch. Pharm.*, **228**, 462 (1890).

(7) E. J. Seiferle, I. B. Johns and C. H. Richardson, *J. Econ. Entomol.*, **35**, 35 (1942).

(8) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **160**, 555 (1945).

(9) W. A. Jacobs and L. C. Craig, *ibid.*, **148**, 41 (1943).

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group.[10] Dehydrogenation of rubijervine with selenium afforded 2-ethyl-5-methylpyridine and a methylcyclopentenophenanthrene[9] and a phenanthrol, $C_{18}H_{16}O$,[9,11] both of uncertain identity. Rubijervine was subsequently shown to be a hydroxysolanidine by Sato and Jacobs who oxidized rubijervine monobenzoate to a ketone which was reduced by the Wolff–Kishner method to solanidine.[11] These workers also reduced diketodihydrorubijervine to solanidan-3β-ol. An assignment of the second hydroxyl group of rubijervine was made on the basis of the following argument. Since it is this hydroxyl which appears in the $C_{18}H_{16}O$ phenanthrol (no phenol was isolated from solanidine under the same conditions),[12] its position is thereby restricted to the A, B or C ring. The available data exclude all of these positions except carbon-12. Thus, rubijervine is stable to periodate; dihydrorubijervine gives a diketone which is stable to alkali, forms a disemicarbazone, fails to form a pyridazine with hydrazine and shows no interaction of the chromophores in the ultraviolet; rubijervone-12 shows no α,β-unsaturation in the ultraviolet.[11] In addition, the molecular rotation difference between diketodihydrorubijervine and solanidan-3-one is in agreement with that recorded for a 12-keto steroid.[13] The second hydroxyl in rubijervine was tentatively assigned the α-configuration by Sato and Jacobs[11] who noted that the molecular rotation difference between dihydrorubijervine and solanidan-3β-ol is comparable to that recorded for a 12α-hydroxy steroid.[13]

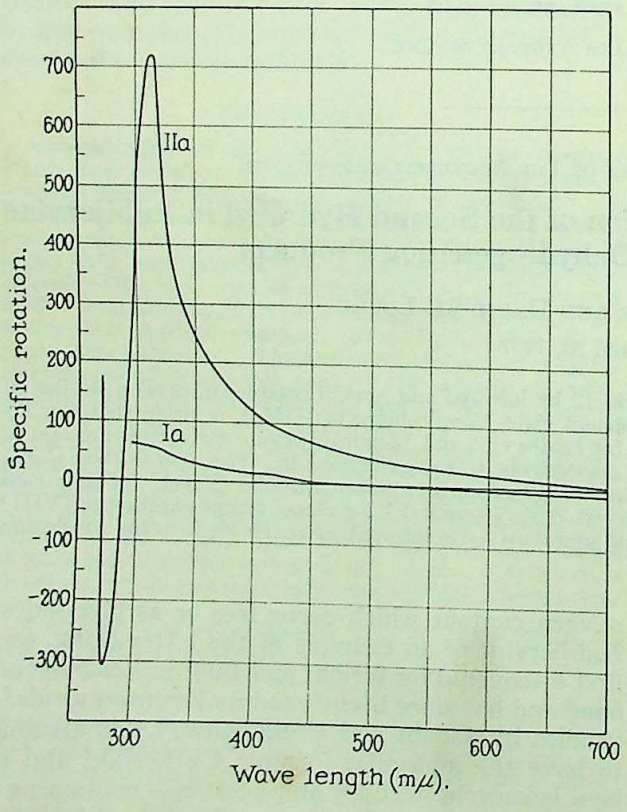

Fig. 1.—Rotatory dispersion curves[16] of: rubijervine (Ia) and rubijervone-12 (IIa) in dioxane.

Data have now been accumulated which demonstrate that rubijervine is indeed Δ^5-solanidene-3β,12α-diol. It is the purpose of this paper to present the details of this work and to discuss the identity of the hydrocarbon $C_{18}H_{16}$[9] and phenol $C_{18}H_{16}O$[9,11] obtained from the dehydrogenation of rubijervine.

The structure proposed requires that rubijervone-12 benzoate (IIb), produced by chromic acid oxidation of rubijervine 3-benzoate (Ib), should show absorption in the infrared for an unconjugated ketone in a six-membered ring. This compound shows, in fact, only single carbonyl absorption at 1708 cm.$^{-1}$, due to both the benzoyl and the keto groups.[14] Its hydrolysis product, rubijervone-12 (IIa), shows carbonyl absorption at 1706 cm.$^{-1}$.[15] More striking confirmation of the position of this carbonyl function is available from a comparison of the optical rotatory dispersion curves of rubijervine and rubijervone-12 (IIa) (Fig. 1),[16] which were determined in the laboratory of Professor Carl Djerassi. The curve of the ketone with a "maximum" of 720° at 313 mμ may be compared with those of a series of 12-keto bile acids which show "maxima" of 772–887° at 305–307 mμ[17] and with those of 12-ketosapogenins which show "maxima" of 424°, 783° and 802° at 312.5–315 mμ.[18] In the case of the bile acids the maxima are more positive than for rubijervone-12 because of the higher background rotation of the bile acid system. The curve is perfectly compatible with that expected for a 12-ketone, while an 11-ketone may be definitely excluded.

The configuration of the second hydroxyl in rubijervine was established by two lines of evidence, the first chemical and the second based on molecular rotation differences.

Thus, reduction of rubijervone-12 (IIa) by sodium-in-alcohol (a reaction which is known to be the equivalent of equilibration[19]) should in theory produce the epimer with a 12-equatorial hydroxyl,[20] *viz.*, Δ^5-solanidene-3β,12β-diol (IIIa). In practise, this reaction afforded in 79% yield, not rubijervine (see Fig. 2 for infrared spectra), but an isomer of m.p. 231–233°, $[\alpha]^{27}D$ −18°. The benzoate of the above ketone, Δ^5-solanidene-3β-ol-12-one benzoate (IIb), was similarly reduced to the same isomer IIIa. Catalytic reduction of IIIa over plat-

(10) W. A. Jacobs and L. C. Craig, (a) *J. Biol. Chem.*, **152**, 641 (1944); (b) **159**, 617 (1945).

(11) Y. Sato and W. A. Jacobs, *ibid.*, **179**, 623 (1949).

(12) L. C. Craig and W. A. Jacobs, *ibid.*, **149**, 451 (1943).

(13) D. H. R. Barton and W. Klyne, *Chemistry & Industry*, 755 (1948).

(14) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 114, 152.

(15) It should be noted that even if the position of the hydroxy is not restricted to the A, B or C ring, the 15-position is excluded by the infrared data. In addition, the 26-position is excluded since oxidation at this position should produce a lactam and not a ketone. It seems unlikely that a hydroxyl group would occur on the 23- or 24-position because of the isolation from the dehydrogenation mixture of 2-ethyl-5-methylpyridine and the failure to isolate a hydroxypyridine. Both jervine and veratramine contain oxygen functions at carbon-24 and give rise to hydroxypyridines on dehydrogenation. By this alternative argument, all positions in the D, E and F rings may be excluded as possible locations for the hydroxyl.

(16) We wish to express our grateful appreciation to Professor Carl Djerassi for supplying the rotatory dispersion curves presented in this paper and also for his advice in interpreting them.

(17) C. Djerassi and W. Closson, THIS JOURNAL, **78**, 3761 (1956).

(18) C. Djerassi and R. Ehrlich, *ibid.*, **78**, 440 (1956).

(19) M. G. Vavon, *Bull. soc. chim. France*, Ser. 4, **49**, 937 (1931); W. Hückel, *Ann.*, **523**, 1 (1936).

(20) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

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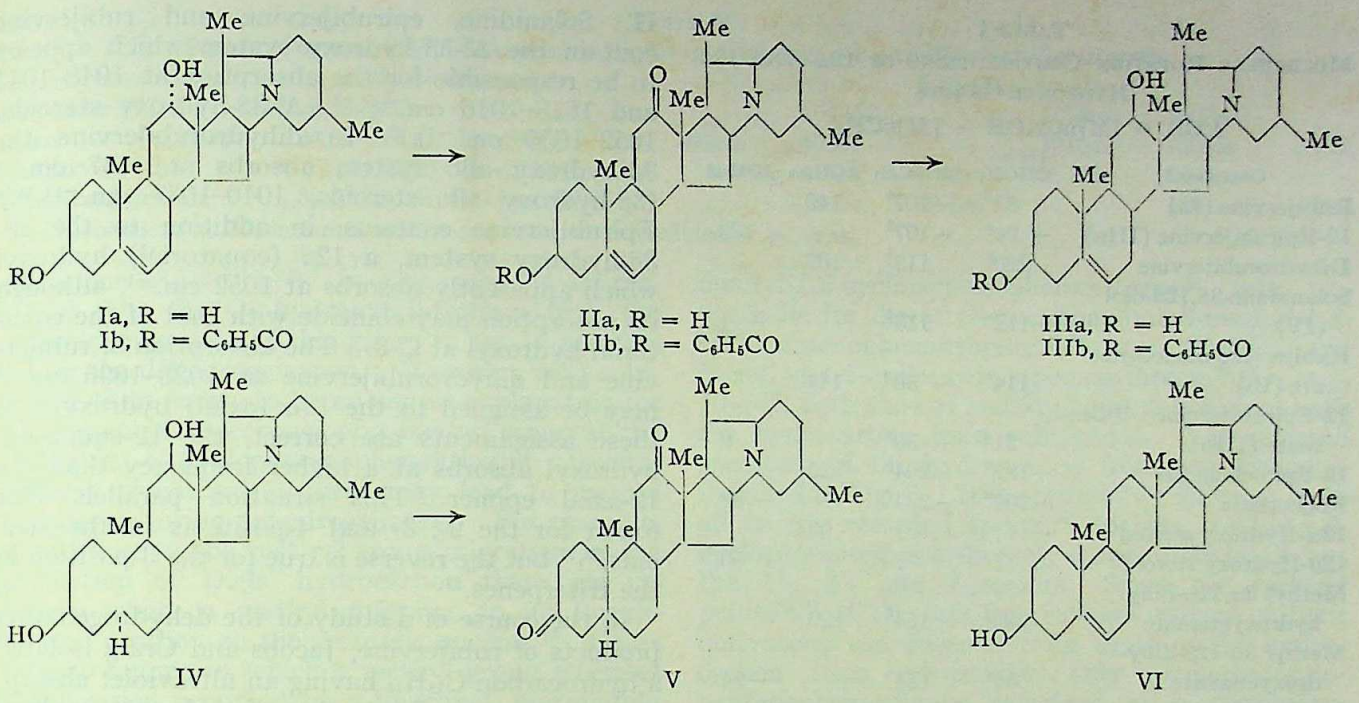

Ia, R = H
Ib, R = C_6H_5CO

IIa, R = H
IIb, R = C_6H_5CO

IIIa, R = H
IIIb, R = C_6H_5CO

IV V VI

inum oxide gave in 84% yield a dihydro compound, solanidane-3β-12β-diol (IV), m.p. 220–221°, $[\alpha]^{26}D$ 27°, different from dihydrorubijervine, but furnishing on oxidation with chromic acid the known diketodihydrorubijervine (V).[11] This series of reactions (together with those reported below) demonstrates that the product of sodium-in-alcohol is in fact 12-epirubijervine (IIIa) and possesses a hydroxyl with the 12β-configuration (equatorial).

lated in small yield rubijervine monobenzoate (Ib) and in slightly greater yield its 12-epimer, 12-epirubijervine 3-benzoate (IIIb), m.p. 230.5–231.5°, $[\alpha]^{26}D$ −4°. The structure of the latter was shown by its hydrolysis to 12-epirubijervine (IIIa).

It has been pointed out that the molecular rotation difference between dihydrorubijervine and solanidane-3β-ol is close to that recorded for a

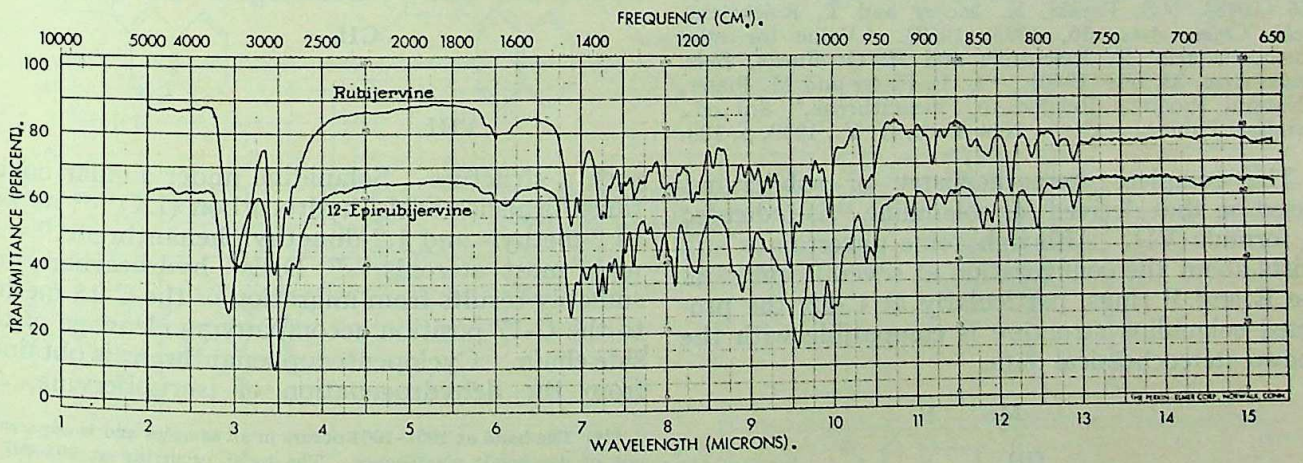

Fig. 2.—Infrared absorption spectra in KBr.

It is a general rule that lithium aluminum hydride or sodium borohydride reduces a highly hindered ketone to an axial hydroxyl and an unhindered ketone to an equatorial hydroxyl.[20,21] The 12-position in steroids is a moderately hindered one, and it is therefore not surprising that rockogenin, a 12-ketosapogenin, gives on lithium aluminum hydride reduction a mixture of epimeric 12-diols.[22] In agreement with these results, sodium borohydride reduction of rubijervone-12 benzoate (IIb) produced a mixture of epimers from which was isolated in small yield rubijervine monobenzoate (Ib) and in slightly greater yield its 12-epimer, 12-epirubijervine 3-benzoate (IIIb), m.p. 230.5–231.5°, $[\alpha]^{26}D$ −4°. The structure of the latter was shown by its hydrolysis to 12-epirubijervine (IIIa).

It has been pointed out that the molecular rotation difference between dihydrorubijervine and solanidane-3β-ol is close to that recorded for a 12α-hydroxy steroid. With a series of rubijervine derivatives which are epimeric at C-12 now available, the molecular rotation differences of both configurations may be compared with those of related compounds whose configuration at carbon-12 is known. In Table I are included a series of rubijervine and 12-epirubijervine derivatives together with appropriate steroids, sapogenins and bile acids. It will be noted that in a given epimeric pair, the molecular rotation difference for the 12α-epimer is always more strongly positive than for the 12β-isomer. Thus the molecular rotation differences support the assignment of the 12α-configuration to compounds of the rubijervine series and the 12β configuration to those of the 12-epirubijervine series.

(21) W. G. Dauben, G. J. Fonken and D. S. Noyce, THIS JOURNAL, **78**, 2579 (1956); W. G. Dauben, E. J. Blanz, Jr., J. Jiu and R. A. Micheli, *ibid.*, **78**, 3752 (1956); D. J. Cram and F. A. Abd Elhafez, *ibid.*, **74**, 5828 (1952).

(22) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, *ibid.*, **76**, 4013 (1954).

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TABLE I

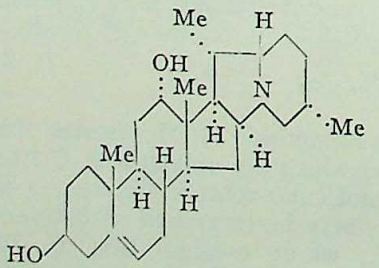
MOLECULAR ROTATION CONTRIBUTIONS OF 12α- AND 12β-HYDROXYL GROUPS

$\Delta OH = [M]_D CHOH - [M]_D CH_2$

Compound	$[M]_D$-CHOH	$[M]_D CH_2$	$\Delta OH_{12\alpha}$	$\Delta OH_{12\beta}$
Rubijervine (Ia)	33[a]	−107[b]	140	
12-Epirubijervine (IIIa)	− 74[a]	−107[b]		33
Dihydrorubijervine	220[c]	113[b]	107	
Solanidane-3β,12β-diol (IV)	112[a]	113[b]		− 1
Rubijervine monobenzoate (Ib)	114[a]	− 30[a]	144	
12-Epirubijervine 3-benzoate (IIIb)	− 21[a]	− 30[a]		9
12-Epirockogenin	−182[d]	−204[e]	22	
Rockogenin	−292[d]	−204[e]		−88
12α-Hydroxy steroid[f]	....	....	93	
12β-Hydroxy steroid[f]	....	....		50
Methyl 3α,12α-dihydroxyetianate	283[g]	154[h]	129	
Methyl 3α-12β-dihydroxyetianate	60[g]	154[h]		−94
3α,12α-Dihydroxycholanic acid	208[i]	120[i]	88	
3α,12β-Dihydroxycholanic acid	149[i]	120[i]		29

[a] Reported in this paper. [b] V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **27**, 390 (1944). [c] Y. Sato and W. A. Jacobs, *J. Biol. Chem.*, 179, 623 (1949). [d] R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, THIS JOURNAL, **76**, 4013 (1954). [e] L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 3rd ed., 1949, p. 591. [f] D. H. R. Barton and W. Klyne, *Chemistry & Industry*, 755 (1948). [g] S. Pataki, K. Meyer and T. Reichstein, *Helv. Chim. Acta*, **36**, 1295 (1953). [h] Value for etiolithocholic acid, T. Reichstein and H. G. Fuchs, *Helv. Chim. Acta*, **23**, 658 (1940). [i] L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 108.

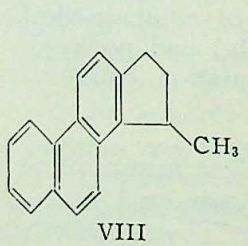
The complete stereochemistry of rubijervine, based on that derived for solanidine,[23] is indicated in formula VII. Although some uncertainty still exists about the configuration at several centers in the E and F rings, particularly at C-22, the proposed solanidine structure is compatible with the known stereochemical data.



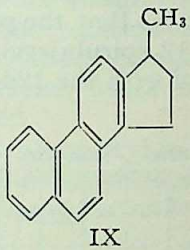
VII, rubijervine

Since the configurations of the hydroxyls in rubijervine and its derivatives now appear well established, it is interesting to consider the assignment of infrared absorption bands in the C–O stretching region to the different types of hydroxyls. The appropriate bands are given in Table II. Solanidine, epirubijervine and rubijervine contain the Δ^5-3β-hydroxy system which appears to be responsible for the absorption at 1048–1047 and 1018–1016 cm.$^{-1}$ [24] (Δ^5-3β-hydroxy steroids, 1052–1050 cm.$^{-1}$).[25] In dihydrorubijervine the 3β-hydroxy allo system absorbs at 1037 cm.$^{-1}$ (3β-hydroxy allo steroids, 1040–1037 cm.$^{-1}$).[25,26] Epirubijervine contains, in addition to the Δ^5-3β-hydroxy system, a 12β (equatorial) hydroxyl which apparently absorbs at 1052 cm.$^{-1}$, although its absorption may coincide with that of the equatorial hydroxyl at C-3. The absorption of rubijervine and dihydrorubijervine at 1028–1026 cm.$^{-1}$ may be assigned to the 12α (axial) hydroxyl. If these assignments are correct, the 12-equatorial hydroxyl absorbs at a higher frequency than the 12-axial epimer. This situation parallels that found for the 2-, 3- and 4-positions in the steroids,[25,27] but the reverse is true for the 3-position in the triterpenes.[28]

In the course of a study of the dehydrogenation products of rubijervine, Jacobs and Craig isolated a hydrocarbon $C_{18}H_{16}$ having an ultraviolet absorption spectrum similar to that of cyclopentenophenanthrene.[9] Its melting point and that of its TNB adduct were very close to the corresponding constants reported for 1′-methyl-1,2-cyclopentenophenanthrene.[29] It is difficult to rationalize the formation from rubijervine of a hydrocarbon of



VIII



IX

such a structure. Solanidine under similar conditions furnishes Diels' hydrocarbon (IX)[12,30] as well as 2-methyl- and 1,2-dimethylphenanthrene.[12] As with most steroids,[31,32] Diels' hydrocarbon presumably results from migration of the C-18 methyl to the C-17 position accompanying cleavage of the side chain. Cyclopentenophenanthrene is obtained from the dehydrogenation of isorubijervine, Δ^5-

(23) (a) Y. Sato and H. G. Latham, Jr., *Chemistry & Industry*, 444 (1955); (b) THIS JOURNAL, **78**, 3146 (1956).

(24) The band at 1001–1004 occurs in all samples and is apparently not of diagnostic significance. The band occurring at 995–997 in epirubijervine and dihydorubijervine cannot be assigned readily.

(25) A. R. H. Cole, R. N. Jones and K. Dobriner, THIS JOURNAL, **74**, 5571 (1952); W. G. Dauben, E. Hoerger and N. K. Freeman, *ibid.*, **74**, 5206 (1952).

(26) H. Rosenkrantz and L. Zablow, *ibid.*, **75**, 903 (1953).

(27) R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *ibid.*, **73**, 3215 (1951); A. Fürst, H. H. Kuhn, R. Scotoni, Jr., and Hs. H. Günthard, *Helv. Chim. Acta*, **35**, 951 (1952); A. R. H. Cole, *J. Chem. Soc.*, 4969 (1952).

(28) I. L. Allsop, A. R. H. Cole, D. E. White and R. L. S. Willix, *ibid.*, 4868 (1956).

(29) L. Ruzicka, L. Ehmann, M. W. Goldberg and H. Hösli, *Helv. Chim. Acta*, **16**, 833 (1933).

(30) H. Rochelmeyer, *Arch. Pharm.*, **274**, 543 (1936); A. Soltys and K. Wallenfels, *Ber.*, **69**, 811 (1936).

(31) P. A. Plattner, "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 48.

(32) J. W. Cook, *Chemistry & Industry*, **13**, 176 (1935); E. Bergmann, *ibid.*, **13**, 175 (1935); O. Rosenheim and H. King, *ibid.*, **11**, 299 (1933); A. Cohen, J. W. Cook and C. L. Hewett, *J. Chem. Soc.* 445 (1939).

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TABLE II

POSITION OF THE C–OH STRETCHING BANDS OF RUBIJERVINE AND RELATED COMPOUNDS

Compound	Substitution type	Frequency,[a] cm.$^{-1}$					
Solanidine (VI)	Δ^5,3β-OH(e)		1047s		1018m	1003w	
Epirubijervine (IIIa)	Δ^5,3β-OH(e); 12β-OH(e)	1052m	1047s		1018m	1004m	997m
Rubijervine (Ia)	Δ^5,3β-OH(e); 12α-OH(a)		1048s	1028m	1016m	1003m	
Dihydrorubijervine	5α-H,3β-OH(e); 12α-OH(a)		1037s	1026m		1001m	995m

[a] 5% solutions in CS_2 in 2-mm. cell; s = strong, m = medium, w = weak.

solanidene-3β,18-diol.[10b] In this case, it is presumed that the C_{18}-hydroxyl interferes with the expected migration of this group to the 17-position during the dehydrogenation. However, with rubijervine there seems to be no simple explanation for the presumed appearance of a methyl group at the 1′-position of cyclopentenophenanthrene. Several different structural features may lead to methyl migrations during dehydrogenation. For example, in addition to the methyl group migration in the production of Diels' hydrocarbon there are instances where a methyl migrates to an unsubstituted position on the aromatic nucleus.[33] Cases are also known in which a methyl group migrates to a position occupied by a hydroxyl, presumably by a retropinacol rearrangement, prior to the dehydrogenation proper.[34] The unique feature of the dehydrogenation of rubijervine is the apparent methyl migration to an unsubstituted methylene on the non-aromatic portion of the molecule, two carbon atoms removed from its original site.

These considerations seemed to warrant a further study of the identity of this hydrocarbon. Accordingly, a sample of the hydrocarbon from the original dehydrogenation,[9] which was placed at our disposal by Drs. Jacobs and Craig, was purified by repeated chromatography and crystallization to give material melting at 78–80° cor. and with an ultraviolet absorption spectrum almost identical with Diels' hydrocarbon[35] IX and with cyclopentenophenanthrene.[36] A new analysis confirmed its formula as $C_{18}H_{16}$. Synthetic 1′-methyl-1,2-cyclopentenophenanthrene[29] was unavailable for direct comparison, but 3-methyl-1,2-cyclopentenophenanthrene,[37,38] m.p. 86–87°, and 5-methyl-1,2-cyclopentenophenanthrene,[38,39] m.p. 75–76°, both showed melting point depressions with the hydrocarbon from rubijervine. The infrared spectrum of the hydrocarbon from rubijervine is included in Fig. 3. It is appreciably different from all of the recorded spectra[40] for the methyl-1,2-cyclopentenophenanthrenes, which include all but the 1′-, 2′- and 7-isomers. Since the melting points[29,41] of the last two isomers and/or of their derivatives are different from those of the hydrocarbon from rubijervine, only 1′-methylcyclopentenophenanthrene remained as a possibility. Accordingly, the synthesis of this compound by the method of Ruzicka, *et al.*,[29] was repeated (with minor modification)[42] to give material of m.p. 79–81°, mixture m.p. with the hydrocarbon from rubijervine, 78–80°. The ultraviolet and infrared absorption spectra (Fig. 3) of the latter were identical with those of the synthetic sample. In addition, the picrates and trinitrobenzene adducts of each hydrocarbon showed no melting point depression on admixture. Thus, the identity of the $C_{18}H_{16}$ hydrocarbon from rubijervine with 1′-methyl-

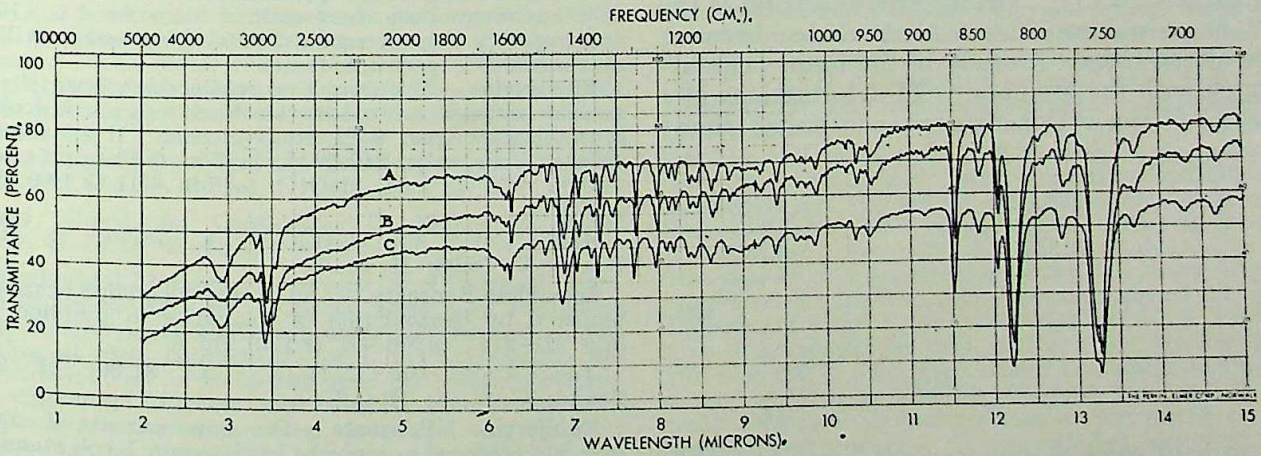

Fig. 3.—Infrared absorption spectra of 1′-methyl-1,2-cyclopentenophenanthrene in KBr: A, from dehydrogenation of rubijervine; B, from reduction of $C_{18}H_{16}O$ phenol; C, synthetic.

(33) R. D. Haworth, C. R. Mavin and G. Sheldrick, *J. Chem. Soc.*, 454 (1934).

(34) L. Ruzicka, M. W. Goldberg and K. Hofmann, *Helv. Chim. Acta*, **20**, 325 (1937); L. Ruzicka, H. Schellenberg and M. W. Goldberg, *ibid.*, **20**, 791 (1937).

(35) S. H. Harper, G. A. R. Kon and F. C. J. Ruzicka, *J. Chem. Soc.*, 124 (1934).

(36) W. V. Mayneord and E. M. F. Roe, *Proc. Roy. Soc. (London)*, Ser. A, **152**, 299 (1935).

(37) A. Butenandt, H. Dannenberg and D. von Dresler, *Z. Naturforsch.*, **1**, 151 (1946); B. Riegel, S. Siegel and D. Kritchevsky, THIS JOURNAL, **70**, 2950 (1948).

(38) We wish to thank Professor Butenandt for samples of 3-methyl- and 5-methylcyclopentenophenanthrene and Dr. Riegel for a sample of 3-methyl-cyclopentenophenanthrene and its TNB and TNF derivatives.

(39) A. Butenandt, H. Dannenberg, E. Bieneck and W. Steidle, *Z. Naturforsch.*, **5b**, 405 (1950).

(40) H. Dannenberg, U. Schiedt and W. Steidle, *ibid.*, **8b**, 269 (1953).

(41) A. Butenandt, H. Dannenberg and D. von Dresler, *ibid.*, **1**, 227 (1946).

(42) The required 2-(1-naphthyl)-ethanol was prepared in 76% yield by reduction of 1-naphthylacetic acid with lithium aluminum hydride.

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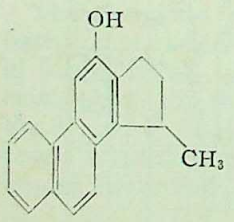
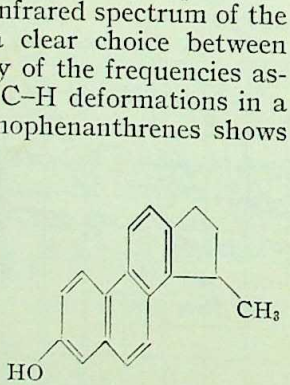
1,2-cyclopentenophenanthrene is established.

A related question concerns the formation of the phenanthrol $C_{18}H_{16}O$, m.p. 136–138°, obtained in the same dehydrogenation.[9] In order to provide more information concerning this phenol, which was kindly supplied by Drs. Jacobs and Craig, several attempts were made to convert it to the corresponding hydrocarbon by heating with zinc dust. At temperatures high enough to effect reduction, rearrangement occurred since only a high melting hydrocarbon fraction could be obtained which had the ultraviolet spectrum of chrysene. Recently Kenner and Williams[43] have reported a mild method for the conversion of phenols to aromatic hydrocarbons, which involves reduction of the aryl diethyl phosphate with sodium in liquid ammonia. Since the method had been tested only with benzene and naphthalene derivatives, its application to phenols of higher molecular weight was first explored by reduction of 3-phenanthrol,[44] chosen as a suitable model for the phenol from rubijervine. The reduction proceeded smoothly to give phenanthrene in 30% yield. Reduction of the phenol from rubijervine by this method gave in 36% yield, 1′-methyl-1,2-cyclopentenophenanthrene, identified by mixture melting point, infrared (Fig. 3) and ultraviolet absorption spectra. The hydroxyl of this phenol has been assumed (*vide supra*) to be derived from the second hydroxyl (position-12) of rubijervine. If so, the phenol can be assigned the structure 1′-methyl-1,2-cyclopentenophenanthrol-3 (X). If, however, the hydroxyl is derived from the 3-hydroxyl of rubijervine, the structure should be 1′-methyl-1,2-cyclopentenophenanthrol-7 (XI). The infrared spectrum of the $C_{18}H_{16}O$ phenol provides a clear choice between these alternatives. A study of the frequencies associated with the aromatic C–H deformations in a series of fifteen cyclopentenophenanthrenes shows



X



XI

that without exception compounds having four adjacent ring hydrogens (*i.e.*, an unsubstituted A-ring) show strong absorption at 741–762 cm.$^{-1}$ [40]. The only other situation which causes strong absorption in this region is the presence of three adjacent ring hydrogens,[45] and these occur in neither X nor XI. Since the phenol from rubijervine shows strong absorption at 748 cm.$^{-1}$ [46] it appears that the A-ring is unsubstituted and that the phenol therefore has structure X. Regardless of the precise structure of the phenol, the fact that it is a derivative of 1′-methylcyclopentenophenanthrene demonstrates that the methyl group is able to migrate without prior, or simultaneous, loss of the hydroxyl from the molecule. On the other hand, the hydroxyl seems to be implicated in this migration in some fashion since solanidine (VI), in which this hydroxyl is absent, gives Diels' hydrocarbon. Thus the precise mode of formation of the dehydrogenation products from rubijervine remains to be explained.

Acknowledgment.—We wish to express our appreciation to The Lilly Research Laboratories, Eli Lilly and Co., for a generous grant in support of this work. We also wish to thank Dr. Walter A. Jacobs who kindly read the manuscript and who placed his collection of samples at our disposal. Analyses are by Mr. D. Rigakos of this Laboratory. The technical assistance of Miss Vera Bohan is gratefully acknowledged.

Experimental

General Experimental Procedures.—Boiling points are uncorrected. Melting points are corrected and were taken on a hot-stage equipped with a polarizer. Finely powdered samples were placed on the stage about 15° below the melting point and the temperature raised rapidly to within 5° of the melting point. The temperature was then raised 2°/min.

Petroleum ether refers to a light petroleum fraction of b.p. 30–60°. Ligroin refers to a light petroleum fraction of b.p. 60–70°.

The removal of solvents *in vacuo* was accomplished with a rotating flash evaporator at about 15 mm. and with a heating bath operated usually at about 35–40°.

Infrared spectra were determined from 2 to 15 μ without compensation on a Perkin–Elmer model 21 double beam spectrometer with sodium chloride optics, set at resolution 927, response 2, gain 6, suppression 2 and a scanning speed of 0.3 μ/minute on a chart scale of 5 cm. for 1 μ. Ultraviolet spectra were determined in 95% ethanol on a Beckman model DU spectrophotometer.

Rubijervine.—The sample of rubijervine[9,47] used for the transformations reported in this work was purified by recrystallization from 95% ethyl alcohol. It consisted of colorless rods, m.p. 242–244°, $[\alpha]^{27.5}D$ +8° (*c* 0.54, chf.) $[\alpha]^{27.5}D$ +20° (*c* 1.04, MeOH), $[\alpha]^{27.5}D$ +11 (*c* 1.00, dioxane).[48]

Anal. Calcd. for $C_{27}H_{43}O_2N$: C, 78.40; H, 10.48. Found: C, 78.08; H, 10.23.

Solanidine Benzoate.—A sample of solanidine benzoate,[49] prepared by benzoylation of solanidine in pyridine, had m.p. 213–214°, $[\alpha]^{27}D$ −6° (*c* 1.40, chf.).

Anal. Calcd. for $C_{34}H_{47}O_2N$: C, 81.39; H, 9.44. Found: C, 81.44; H, 9.27.

Rubijervine 3-Benzoate.—The monobenzoate of rubijervine was prepared as reported by Sato and Jacobs[11] and was isolated directly from the reaction mixture by crystallization from benzene without recourse to chromatography. Colorless prisms were obtained, m.p. 256–259°, $[\alpha]^{28}D$ +22° (*c* 1.60, chf.).

Anal. Calcd. for $C_{34}H_{47}O_3N$: C, 78.87; H, 9.15. Found: C, 78.94; H, 8.97.

Rubijervone-12 Benzoate.—Oxidation of rubijervine monobenzoate according to the directions of Sato and Jacobs[11] gave rubijervone-12 benzoate, m.p. 227–231°, with a prior change in crystalline form at *ca.* 210°. A double melting point is reported, 214–216°, 233–234°. This compound showed in the infrared (Nujol) a single peak in the carbonyl region at 1708 cm.$^{-1}$.

(43) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955).

(44) We wish to thank Professor L. F. Fieser for a generous sample of 3-phenanthrol.

(45) This type of substitution is characterized by an additional absorption band at 786–792. The phenol from rubijervine shows no absorption in this region.

(46) *Cf.* the spectrum of 1,-methylcyclopentenophenanthrene which has a strong band at 754 cm.$^{-1}$ (KBr).

(47) The authors wish to thank Dr. A. Stoll of Sandoz for placing at their disposal a generous sample of rubijervine.

(48) *Cf.* Fig. 1. The values obtained for $[\alpha]D$ (dioxane) in Prof. Djerassi's rotatory dispersion studies were −4° (*c* 0.05) and −7° (*c* 0.095). The accuracy at the sodium D-line is rather poor, due to the dilute solutions used.

(49) E. Berger and R. Wagner, *Ber.*, **66**, 1093 (1933).

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Rubijervone-12.—Hydrolysis of rubijervone-12 benzoate gave material melting at 229.5–232°. In our hands the sample prepared by Sato and Jacobs[11] melted at 226–228° (reported[11] m.p. 236–238° (uncor.)). A mixture of these two samples showed intermediate melting. The infrared spectrum (Nujol) of this compound shows hydroxyl absorption at 3185 cm.$^{-1}$ and carbonyl absorption at 1706 cm.$^{-1}$.

12-Epirubijervine. A. From Rubijervone-12.—A solution of 352 mg. of rubijervone-12 in 20 ml. of refluxing *n*-propyl alcohol was saturated slowly with small pieces of sodium over a period of several hours. After cooling to room temperature, the mixture was treated with several drops of ethyl alcohol and evaporated to dryness *in vacuo*. The residue was taken up in benzene and water. The aqueous layer was extracted with benzene, and the combined benzene extracts were washed with a small amount of water, which gave rise to an emulsion. Filtration of the mixture gave a crystalline solid, m.p. 226–228°. The benzene layer was evaporated to dryness *in vacuo* giving further crystalline material melting at 224–228°, showing partial melting at 208°. The former gave on recrystallization from benzene 123 mg. of large rods converted above 160° to tiny needles, m.p. 230–231°. The latter gave 155 mg. of material showing the same prior change in crystalline form and a final melting point of 224–228°.

An analytical sample was prepared by two recrystallizations from acetone, m.p. 231–233°, $[\alpha]^{27}D$ −18° (*c* 1.07, chf.). The infrared absorption spectrum is included in Fig. 2.

Anal. Calcd. for $C_{27}H_{43}O_2N$: C, 78.40; H, 10.48. Found: C, 78.46; H, 10.56.

B. From Rubijervone-12 Benzoate.—A solution of 90 mg. of rubijervone-12 benzoate in 5 ml. of refluxing *n*-propyl alcohol was saturated with sodium and worked up as above (without emulsion formation) to give 87 mg. of crude product, m.p. 226–229°, with the same preliminary change in crystalline form as noted above. Recrystallization from acetone gave needles, m.p. 232–234°. A mixture of this sample with an authentic sample of rubijervine (m.p. 240–242°) melted at 222–229°.

Solanidane-3β,12β-diol.—A solution of 55 mg. of 12-epirubijervine in methanol containing a small amount of acetic acid was treated with hydrogen in the presence of 28 mg. of platinum oxide. In 1 hr. one mole of hydrogen was consumed. The catalyst was then removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from ether to give 46 mg. of needles, m.p. 218–220°. An analytical sample prepared by several recrystallizations from acetone–ligroin melted at 220–221°, $[\alpha]^{26}D$ +27 (*c* 1.45, chf.).

Anal. Calcd. for $C_{27}H_{45}O_2N$: C, 78.02; H, 10.91. Found: C, 78.13; H, 11.17.

Solanidane-3,12-dione.—To a solution of 12 mg. of solanidane-3β,12β-diol in 2 ml. of glacial acetic acid was added 5 mg. of chromic oxide in 1 ml. of 90% acetic acid. After standing at room temperature for 1 hr., the solution was poured into 25 ml. of water and extracted with chloroform. The chloroform extracts were washed successively with sodium bicarbonate and water, dried and evaporated to dryness *in vacuo* to give 5 mg. of plates, m.p. 237–239°, undepressed on admixture with an authentic sample.[11]

Sodium Borohydride Reduction of Rubijervone-12 Benzoate. 12-Epirubijervine 3-Benzoate.—To a solution of 54 mg. of rubijervone-12 benzoate in 50 cc. of ether–methanol (60/40) was added 167 mg. of sodium borohydride. After standing at room temperature for 3 hr., the solution was evaporated to dryness *in vacuo*. The residue was taken up in chloroform and water, and the aqueous layer was extracted with chloroform. Concentration of the chloroform extracts gave 54 mg. of crude material, m.p. 215–230° (softens *ca.* 205°).

A partial fractional crystallization of this material furnished two fractions, one of m.p. 252–254° and the other with m.p. 220–222°. From the former was isolated by chromatography over alumina and recrystallization from benzene 4 mg. of crystals, m.p. 255–259°, undepressed on admixture with an authentic sample of rubijervine benzoate.

The 220–222° fraction on chromatography over alumina and subsequent recrystallization from ligroin furnished 16.5 mg. of tiny, fine needles of 12-epirubijervine 3-benzoate, m.p. 230.5–231.5°, $[\alpha]^{26}D$ −4° (*c* 0.83, chf.).

Anal. Calcd. for $C_{34}H_{45}O_3N$: C, 79.18; H, 8.80. Found: C, 79.10; H, 9.07.

Hydrolysis of 12-Epirubijervine 3-Benzoate.—A solution of 5 mg. of 12-epirubijervine 3-benzoate in 3 ml. of 1% methanolic potassium hydroxide was refluxed on the steam-bath for 0.5 hr. The solution was then evaporated to dryness *in vacuo* and taken up in chloroform and water. The chloroform layer was washed with water, dried and evaporated to dryness *in vacuo*. The residue was crystallized from acetone to give 3 mg. of long rods, m.p. 234–236°. A mixture with 12-epirubijervine (m.p. 231–233°) melted at 232–235°.

1′-Methyl-1,2-cyclopentenophenanthrene. A. From Rubijervine.—The original sample of the hydrocarbon obtained by Jacobs and Craig[9] from the selenium dehydrogenation of rubijervine was subjected to repeated chromatography over alumina and recrystallization from petroleum ether at 5°. This procedure gave material melting at 78–80° with an ultraviolet absorption spectrum almost identical with Diels' hydrocarbon[35] and with cyclopentenophenanthrene.[36] Its infrared spectrum showed aromatic C–H bands at 868, 830, 819, 758 sh. and 754 cm.$^{-1}$ (Fig. 3).

Anal. Calcd. for $C_{15}H_{16}$: C, 93.06; H, 6.94. Found: C, 92.88; H, 6.80.

The melting point of this material was strongly depressed on admixture with samples of 3-methyl-1,2-cyclopentenophenanthrene[37,38] and 5-methyl-1,2-cyclopentenophenanthrene.[38,39] It was not depressed on admixture with 1′-methyl-1,2-cyclopentenophenanthrene as prepared below. The infrared (Fig. 3) and ultraviolet spectra of the hydrocarbon from rubijervine were identical with those of 1′-methyl-1,2-cyclopentenophenanthrene.

A picrate of this hydrocarbon prepared in methanol melted at 130.5–131.5° (reported 131–132°).[9] A mixture melting point with a sample of the picrate from synthetic 1′-methyl-1,2-cyclopentenophenanthrene (described below) was not depressed.

A TNB of the hydrocarbon from rubijervine prepared in methanol melted at 143–143.5° (reported[9] 144–145°). A mixture melting point with authentic 1′-methyl-1,2-cyclopentenophenanthrene TNB was not depressed.

B. Synthetic.—The synthesis of **2-(1-naphthyl)-ethanol** was accomplished by lithium aluminum hydride reduction of 1-naphthylacetic acid. Reduction of 25 g. of acid for 1 hr. in boiling ether with 5.1 g. of lithium aluminum hydride gave 17.5 g. of 2-(1-naphthyl)-ethanol, m.p. 59–61° (reported 62°).[50] This alcohol was converted to **2-(1-naphthyl)-ethyl bromide**, b.p. 130–135° at *ca.* 0.3 mm., reported[51] b.p. 145–148° at 0.3 mm., in 88% yield by the method of Haworth and Mavin.[51] **Ethyl 5-methylcyclopentanone-2-carboxylate** was synthesized according to the directions of Cornubert and Borrel[52] giving material boiling at 114–119° at *ca.* 14 mm., reported[53] b.p. 105° at 12 mm. The condensation of β-(1-naphthyl)-ethyl bromide with ethyl 5-methylcyclopentanone-2-carboxylate was carried out by the directions of Kon[54] to give the β-keto ester, b.p. 195–208° at *ca.* 1 mm. (reported[54] b.p. 227° at 4 mm.) in 56% yield. This material (8.3 g.) was cyclized and aromatized by the method of Ruzicka, Ehmann, Goldberg and Hösli.[29] The product was isolated from the reaction mixture by chromatography over alumina. Elution with light petroleum gave a first fraction of 2.5 g. of a colorless oil with a blue fluorescence, which partially crystallized on standing. Further elution with the same solvent gave 2.0 g. of faintly yellow oil with a blue fluorescence, which crystallized completely on standing, m.p. 72–76°. Recrystallization of this latter material from ethanol gave 1.5 g. of material of m.p. 78–80°. Further recrystallization raised the melting point to 79–81° (reported[29] m.p. 76–77°).

A picrate of this hydrocarbon was prepared in methanol, m.p. 131–132°. *Anal.* Calcd. for $C_{18}H_{16}C_6H_3N_3O_7$: C, 62.47; H, 4.15. Found: C, 62.78; H, 4.04.

The TNB derivative prepared in methanol melted at 143–144° (reported 143–144°). *Anal.* Calcd. for $C_{18}H_{16}$-$C_6H_3N_3O_6$: C, 64.71; H, 4.30. Found: C, 64.86; H, 4.23.

(50) V. Grignard, *Compt. rend.*, **141**, 44 (1905).

(51) R. D. Haworth and C. R. Mavin, *J. Chem. Soc.*, 1012 (1933).

(52) R. Cornubert and C. Borrel, *Bull. soc. chim. France*, Ser. 4, **47**, 301 (1930).

(53) L. Bouveault and R. Locquin, *Compt. rend.*, **146**, 138 (1908).

(54) G. Kon, *J. Chem. Soc.*, 1081 (1933).

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The Phenol $C_{18}H_{16}O$ from Dehydrogenation of Rubijervine.—A sample of the material obtained by Jacobs and Craig[9] was used without further purification for the experiments reported in this paper. In our hands it melted at 130–132° (reported[9] m.p. 136–138°). Its infrared spectrum (KBr) was characterized by bands at 3240 cm.$^{-1}$ (OH stretching) and 859, 853, 844, 827, 817, 755sh. and 748 cm.$^{-1}$ (aromatic C–H).

Reduction of the Phenol $C_{18}H_{16}O$ with Zinc Dust.—A mixture of 55 mg. of the phenol and 2.1 g. of zinc dust was heated in a sealed tube at 350–360° for 2 hr. After cooling to room temperature, the tube was opened and the contents were extracted repeatedly with benzene. On evaporation to dryness *in vacuo*, the benzene solution gave 39 mg. of a dark brown gum. This material was chromatographed over alumina giving 8 mg. of brown oil on elution with benzene and an additional 30 mg. of brown oil on elution with ether and methanol. The former resisted attempts at further purification and the latter furnished, on rechromatography and recrystallization (Norit) from ether, colorless needles, m.p. 133–134°, undepressed on admixture with starting material.

A mixture of 51 mg. of the phenol and 1.0 g. of zinc dust was heated at 400 ± 10° for 6 hr. to give 18 mg. of crude product which on chromatography over alumina gave on elution with benzene 11.5 mg. of an amorphous colorless glass. This material was crystallized from ethanol to give irregular crystals subliming above 220°, with a melting point *ca.* 242–248°, much dependent on the rate of heating. The melting point of a mixture of this material and a sample of chrysene (m.p. 256–258°) was 252–256°. The ultraviolet absorption spectrum was identical with that reported for chrysene[55] within experimental error.

Reduction of 3-Phenanthrol to Phenanthrene *via* Its Diethyl Phosphate Ester.[43]—Solutions containing 0.28 mmole of diethyl phosphite[56] and of triethylamine in carbon tetrachloride were prepared. A 52-mg. (0.26 mmole) sample of 3-phenanthrol[44] was dissolved in a 1-ml. aliquot of the diethyl phosphite solution, and this solution was cooled in an ice-bath. A 1-ml. aliquot of the triethylamine solution was then added, and the solution was allowed to stand at room temperature overnight. An additional 10 ml. of carbon tetrachloride was added, and the solution was washed with dilute hydrochloric acid and cold dilute sodium hydroxide (four times) and finally water. The organic layer was evaporated to dryness *in vacuo* giving 67 mg. of light brown oil. This material was taken up in a minimum of ether and cooled in a Dry Ice–Cellosolve-bath. A large excess of liquid ammonia was then run in until only one liquid phase was present and a solid had separated. The solution was then removed from the bath, and when it had reached the boiling temperature of the liquid ammonia several drops of ether were added to bring the solid into solution. Small pieces of sodium were added until a permanent blue color developed. Several drops of alcohol were added, and the solution was allowed to evaporate overnight. The residue was taken up in ether, washed with sodium bicarbonate, sodium hydroxide and finally water and then dried and evaporated to dryness *in vacuo* to give 27 mg. of nearly colorless oil. This was chromatographed over alumina to give 14.5 mg. of white crystals, m.p. 83–91°. Recrystallization from ethanol gave colorless scales 95–98°, undepressed when mixed with authentic phenanthrene. The infrared absorption spectrum of this material in KBr was identical with that of an authentic sample.

Reduction of the Phenol $C_{18}H_{16}O$ *via* Its Diethyl Phosphate Ester.—A sample of 45 mg. of the phenol from the dehydrogenation of rubijervine was converted to its diethyl phosphate ester (54 mg.) by the above procedure. Reduction was accomplished as above, 11 mg. (2 moles) of sodium being added without a permanent blue color developing. The reaction mixture was worked up as before giving 28 mg. of crude petroleum ether-soluble product. This material on chromatography over alumina furnished 15 mg. of white crystals, m.p. 75.5–78.5°. Rechromatography and recrystallization from ethanol gave crystals of m.p. 79–81°, undepressed on admixture with authentic 1′-methyl-1,2-cyclopentenophenanthrene. The infrared (Fig. 3) and ultraviolet absorption spectra of this material are identical with those of 1′-methyl-1,2-cyclopentenophenanthrene.

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(55) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, Fig. 447.

(56) H. McCombie, B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 380 (1945).

[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Preparation and Properties of the Isomeric Forms of Cystine and S-Benzylpenicillamine

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Racemization of bis-(acetyl)-L-cystine in glacial acetic solution was achieved readily through the action of acetic anhydride at room temperature, and the epimeric mixture of optically inactive bis-(acetyl)-cystine so derived isolated in high yield. The asymmetric hydrolytic action of the L-directed renal acylase I upon this latter derivative, at *p*H 7.5 and 37°, resulted in a mixture of free L-cystine, monoacetyl-*meso*-cystine (acetyl moiety at D-position), and bis-(acetyl)-D-cystine. The marked insolubility of the former compound permitted its direct isolation from the enzymic digest by filtration, while the two latter compounds were acid hydrolyzed to *meso*-cystine and D-cystine, respectively, after their separation and isolation from the filtrate on a Dowex-50 column in the acid phase. Specific rotation values were −211 and +208° (1% in *N* HCl) for the L- and D-enantiomorphs, respectively, whereas the *meso*-cystine was completely devoid of detectable optical activity. In addition, a resolution of S-benzyl-DL-penicillamine was effected *via* the hydrolytic action of hog kidney amidase on the amide derivative at *p*H 8.0. Subsequent separation of the liberated S-benzyl-L-penicillamine from the unhydrolyzed S-benzyl-D-penicillamine amide on an Amberlite XE-64 column, followed by acid hydrolysis of the latter compound, ultimately yielded the pure enantiomorphs with specific rotation values of +91.3 and −90.6° (1% in *N* HCl) for the L- and D-forms, respectively. Infrared spectra for each of the stereoisomeric forms of cystine, in addition to data on the susceptibility of these compounds or certain of their selected derivatives to the enzymic action of L- and D-amino acid oxidase and hog renal acylase I, are presented.

Cystine is a symmetrical diaminodicarboxylic acid which, although hitherto found in nature only as the L-form, may in fact exist as two racemic modifications, one an internally compensated *meso*-form, and the other a mixture of externally compensated isomerides. Since L-cystine may be relatively inexpensively isolated from acid hydrolysates of certain natural materials, *e.g.*, hair or wool, such source has provided the major supply of commercially available cystine. However, the drastic hydrolytic conditions employed in its manufacture might also lead to rather extensive racemization, and commercial samples of "L-cystine" whose specific rotation values differ by as much as thirty or forty degrees from the generally accepted value of −212° (in *N* HCl) have not been uncommon. With the view in mind that certain biochemical studies demand not only L-cystine, but also the D-

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and *meso*-forms, in a high degree of stereochemical purity, the preparation of these isomers *via* the general enzymic resolution procedures developed in this Laboratory[1] is here presented. In addition, an enzymic resolution procedure for preparing the optical antipodes of S-benzylpenicillamine is also described.

Results and Discussion

Racemization and Resolution of Cystine.—The preparation of inactive cystine by Mörner,[2] in 1899, subsequently led to a series of investigations[3–5] concerned with the question of its stereochemical identity. Such question was resolved when du Vigneaud, in collaboration with Hollander[4] and Loring,[5] demonstrated that the racemization of L-cystine, upon boiling for five days in hydrochloric acid, led to an epimeric mixture of DL- and *meso*-cystine. Separation of the *meso*- from the DL-form could be effected through a series of fractional crystallizations of the hydrochloride salts. Treatment of the bis-(acetyl) derivative of the epimeric mixture with brucine resulted in a separation of the alkaloid salt of bis-(acetyl)-D-cystine, which, after some twelve crystallizations, yielded D-cystine with $[\alpha]_D^{20}$ +212° (in HCl).[4] Preparation of D-cystine with $[\alpha]_D^{26}$ +208° could be achieved, in addition, from the insoluble salt which arose from the treatment of bis-(formyl)-DL-cystine with strychnine.[6] Alternative preparations of D-cystine with $[\alpha]_D^{20}$ +224°[7] and +221.2°[8,9] (in HCl) resulted from the debenzylation of S-benzyl-D-cysteine with the sodium–liquid ammonia procedure, followed by oxidation of the D-cysteine so liberated.[10]

The direct resolution of DL-cystine was handicapped by virtue of the prolonged refluxing (5 days) of L-cystine with concentrated HCl required for its conversion to the epimeric starting material, as well as by the tedious fractional crystallizations necessitated for the separation of the DL- and the *meso*-forms.[5] A search for methods whereby these difficulties could be obviated was therefore undertaken. The former difficulty was resolved with the observation that the action of a glacial acetic acid–acetic anhydride mixture[11] on bis-(acetyl)-L-cystine, at room temperature, readily proceeded with the formation of an epimeric mixture of bis-(acetyl)-DL- and *meso*-cystine, which could be isolated in high yield (84% of theory).[12] With an eye toward the previous success achieved in the separation of the D-, L- and *meso*-forms of α,ϵ-diaminopimelic acid *via* the asymmetric enzymic hydrolysis of a mixture of their amide derivatives,[13] it appeared particularly tempting to subject the epimeric mixture of acetylcystine to an analogous scheme. Such scheme, if successful, would lead to an easily separable mixture of L-cystine, bis-(acetyl)-D-cystine and monoacetyl-*meso*-cystine (acetyl moiety at the D-position). Although a previous report from this Laboratory[9] had indicated that the N-acylated cystines were highly resistant to the hydrolytic action of hog renal acylase I, under the conditions given, re-investigation of the hydrolytic reaction with varying concentrations of enzyme revealed that it could be induced to proceed at a rate which was of sufficiently large magnitude to make the resolution of inactive bis-(acetyl)-cystine practicable.

Racemization of bis-(acetyl)-L-cystine was effected upon treatment of a glacial acetic acid solution thereof with an excess of acetic anhydride at room temperature. The course of the racemization was followed polarimetrically. As is revealed in Fig. 1, a plot of observed rotation *vs.* time

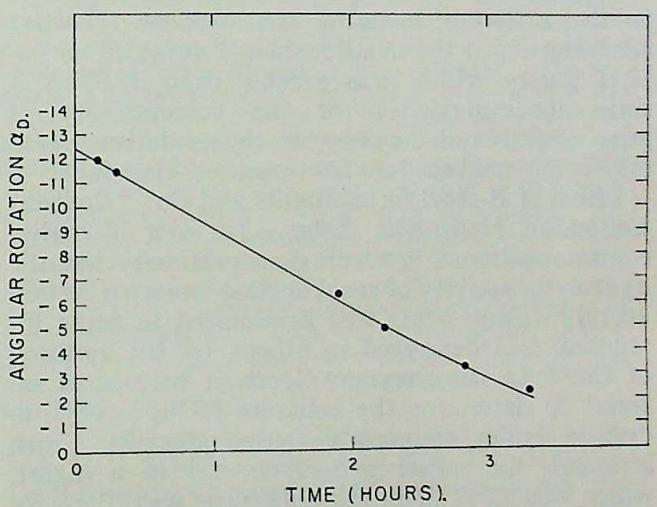

Fig. 1.—Change in optical rotation, with time, of a solution of 20 g. of bis-(acetyl)-L-cystine in 150 ml. of glacial acetic acid upon the addition of 12 moles of acetic anhydride at room temperature (about 27°). A 2 dm. tube was employed.

revealed a linear relationship over approximately the first three hours, during which time the observed rotation fell to about 25% of its initial value. In order to ensure complete optical inactivation, the reaction mixture was permitted to stand for some 16 hours prior to the isolation of the epimeric substance. No detectable desulfuration of the cystine residue was apparent during the entire course of the reaction under the conditions employed herein.

(1) J. P. Greenstein, *Adv. Protein Chem.*, **9**, 122 (1954); J. P. Greenstein, S. M. Birnbaum and M. C. Otey, *J. Biol. Chem.*, **204**, 307 (1953).

(2) K. A. H. Mörner, *Z. physiol. Chem.*, **28**, 595 (1899).

(3) W. F. Hoffman and R. A. Gortner, THIS JOURNAL, **44**, 341 (1922); R. A. Gortner and W. F. Hoffman, *J. Biol. Chem.*, **72**, 433 (1927).

(4) L. Hollander and V. du Vigneaud, *ibid.*, **94**, 243 (1931–1932).

(5) H. S. Loring and V. du Vigneaud, *ibid.*, **102**, 287 (1933).

(6) V. du Vigneaud, R. Dorfmann and H. S. Loring, *ibid.*, **98**, 577 (1932).

(7) J. L. Wood and V. du Vigneaud, *ibid.*, **130**, 109 (1939).

(8) L. Levintow, V. E. Price, and J. P. Greenstein, *ibid.*, **184**, 55 (1950).

(9) S. M. Birnbaum and J. P. Greenstein, *Arch. Biochem. Biophys.*, **39**, 108 (1952).

(10) The S-benzyl-D-cysteine here employed was secured from the resolution of formyl-S-benzyl-DL-cysteine with brucine,[7] and from the asymmetric enzymic hydrolyses of S-benzyl-DL-cysteine amide[8] and acetyl-S-benzyl-DL-cysteine[9] with hog kidney amidase and acylase I, respectively.

(11) M. Bergmann and L. Zervas, *Biochem. Z.*, **203**, 280 (1928).

(12) The racemization of bis-(acetyl)-L-cystine with acetic anhydride in an aqueous medium at 37° was previously reported (V. du Vigneaud and C. E. Meyer, *J. Biol. Chem.*, **98**, 295 (1932)). However, an appreciable degree of desulfuration was noted by these investigators during the course of the reaction.

(13) E. Work, S. M. Birnbaum, M. Winitz and J. P. Greenstein, THIS JOURNAL, **77**, 1916 (1955); R. Wade, S. M. Birnbaum, M. Winitz, R. J. Koegel and J. P. Greenstein, *ibid.*, **79**, 648 (1957).

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The bis-(acetyl) derivative of inactive cystine was subjected to the asymmetric hydrolytic action of the L-directed renal acylase I. Description of the preparation of this enzyme from hog kidney homogenates has appeared elsewhere.[14] Digestion of a 0.1 *M* solution of the epimeric substrate with the lyophilized enzyme, at *p*H 7.5, was effected at 37°. An initial rate of hydrolysis, as measured by the Van Slyke manometric ninhydrin-CO_2 procedure, was 10 micromoles per hr. per mg. of protein nitrogen. Upon completion of the reaction, the liberated L-cystine, by virtue of its extreme insolubility, could be isolated directly from the enzymic digest by simple filtration. The mixture of bis-(acetyl)-D-cystine and monoacetyl-*meso*-cystine, which remained in the filtrate, could ultimately be separated upon passage through a Dowex-50 column in the acid phase. Acid hydrolysis of each of the latter two compounds subsequently yielded pure D- and *meso*-cystine, respectively, which could be crystallized from water through the hydrochloride salts.[15] Optical rotation values for the enantiomorphic D- and L-forms were equal and opposite within the limits of experimental error, while the *meso*-form was devoid of any detectable optical activity, an indication of its freedom from optical contamination. The D-cystine, when subjected to the action of L-amino acid oxidase (*Crotalus adamanteus*) in the usual fashion,[16] revealed an optical purity which was greater than 99.9%. A time–rate comparison of the susceptibility of *meso*-cystine and L-cystine to the oxidative action of L-amino acid oxidase has appeared elsewhere.[17,18]

Effect of N-Acyl Substituents and Co^{++} Concentration on Hydrolytic Rates.—In view of earlier communications[19,20] which demonstrated that the hydrolytic activity of renal acylase I toward certain acetyl-L-amino acids was accelerated in some instances, and depressed in others, by the addition of Co^{++} to the enzymic digest, it became of interest to determine the behavior of bis-(acetyl)-L-cystine under comparable circumstances. Thus, although the initial hydrolytic rate of a digest, which was 0.017 *M* in this substrate, was 10 micromoles per hr. per mg. of protein nitrogen, such rate was progressively increased to a value of 19.6 at a Co^{++} concentration of 10^{-3} *M*. An even greater increase in activation was shown with bis-(chloroacetyl)-L-cystine, with the rate of hydrolysis in the presence of a 10^{-3} *M* concentration of Co^{++} increasing some 186% over the digest devoid of added cobalt. Such results indicated that the degree of activation of acylase I by Co^{++}, in addition to being dependent upon the nature of the amino acid residue, as hitherto observed,[20] was also highly dependent upon the nature of the N-acyl substituent. Substantiation of this latter view was obtained with digests containing acetyl-L-alanine and D-chloropropionyl-L-alanine[21] as substrates, with a 10^{-3} *M* Co^{++} concentration leading to a 60% activation in the former instance and a 147% activation in the latter. The results secured with various levels of Co^{++} are revealed in Table I.

TABLE I

EFFECT OF Co^{++} ON THE SUSCEPTIBILITY OF N-ACYLAMINO ACIDS TO THE HYDROLYTIC ACTION OF RENAL ACYLASE I

Substrate	Rate[a] without added Co^{++}	Increase in rate on addn. of Co^{++} at concn., % 1×10^{-4} *M*	1×10^{-3} *M*	1×10^{-2} *M*	4×10^{-2} *M*
Bis-(acetyl)-L-cystine	10.2	+ 14	+ 96	+81	−75
Bis-(chloroacetyl)-L-cystine	36.6	+109	+186	+87	−59
D-Chloropropionyl-L-alanine	32.3	+ 63	+147	+80	−61
Acetyl-L-alanine	5800	+ 12	+ 60	+25	− 9

[a] Rates expressed as micromoles of substrate hydrolyzed per hr. per mg. of protein N in the reaction mixture at *p*H 7.0 and 37°; substrate at 0.017 *M* concentration; hydrolysis figures taken within 30% of complete cleavage so as to approximate a zero order reaction.

It should perhaps be noted, in addition, that preliminary studies on the hydrolytic susceptibility of various acylated cystines to acylase I indicated that while the monocarbobenzoxy derivative of L-cystine[22,23] was completely resistant to enzymic cleavage, the bis-(chloroacetyl) and bis-(glycyl) derivatives were hydrolyzed at rates of 37 and 60 micromoles per hr. per mg. of protein nitrogen, respectively. This finding was of interest in the light of previous data[19] that, with the exception of the tryptophan and tyrosine derivatives, the acylase I induced hydrolysis of a given chloroacetyl-L-amino acid generally proceeded at a greater rate than that of the corresponding glycyl-L-amino acid. The anomalous behavior of the part of the tyrosine and tryptophan derivatives was attributed to the presence of one or more as yet unidentified highly specific acylases in hog kidney. On the basis of the data here obtained, the association of the hydrolytic activity toward the acylated cystines with an unidentified acylase is likewise suggested.[24]

(14) S. M. Birnbaum, L. Levintow, R. B. Kingsley and J. P. Greenstein, *J. Biol. Chem.*, **194**, 455 (1952).

(15) E. Fischer and K. Raske, *Ber.*, **41** 893 (1908).

(16) A. Meister, L. Levintow, R. B. Kingsley and J. P. Greenstein, *J. Biol. Chem.*, **192**, 535 (1951).

(17) N. Izumiya and J. P. Greenstein, *Arch. Biochem. Biophys.*, **52**, 203 (1954).

(18) The initial rates of oxidation for L- and *meso*-cystine by L-amino acid oxidase (*Crotalus adamanteus*) here observed were 59 and 28 micromoles of oxygen consumed per hr. per mg. of protein nitrogen, respectively. The former value is in full accord with that previously observed,[17] while the latter, although still considerably less than that of L-cystine, is somewhat larger than the value recorded earlier.[17]

(19) K. R. Rao, S. M. Birnbaum, R. B Kingsley and J. P. Greenstein, *J. Biol. Chem.*, **198**, 507 (1952).

(20) R. Marshall, S. M. Birnbaum and J. P. Greenstein, THIS JOURNAL, **78**, 4636 (1956).

(21) S.-C. J. Fu, S. M. Birnbaum and J. P. Greenstein, *ibid.*, **76**, 6054 (1954).

(22) Carbobenzoxy-*cyclo*-L-cystinyl was also resistant to enzymic cleavage. The only carbobenzoxy-amino acid which has thus far proved susceptible to hydrolysis by acylase I was the L-glutamic acid derivative (L. Levintow, J. P. Greenstein and R. B. Kingsley, *Arch. Biochem. Biophys.*, **31**, 77 (1951)).

(23) Preparation of this derivative was effected by the treatment of a several-fold excess of L-cystine with carbobenzoxy chloride under Schotten–Baumann conditions. Removal of the excess L-cystine was achieved by adjustment of the *p*H to 6, followed by filtration. Subsequent adjustment of the *p*H of the filtrate to 3.2 led to the precipitation of the desired monocarbobenzoxy derivative which, upon being copiously washed with ethanol, was freed from any contaminating dicarbobenzoxy derivative. The compound should prove of value for the synthesis of unsymmetrical cystine peptides.

(24) The peptidase action of an 87% glycerol extract of hog intestinal mucosa has been earlier employed to cleave L-cystinylglycine and L-cystinylbisglycine, the cystine thus liberated isolated in pure, crystalline form (J. P. Greenstein, *J. Biol. Chem.*, **124**, 255 (1938)).

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Resolution of S-Benzylpenicillamine.—The synthetic work related to penicillin during the early 1940's stimulated considerable interest in the general preparation and chemistry of the penicillamines. Resolution of DL-penicillamine was generally effected *via* the action of alkaloids on N-formyl-DL-penicillamine,[25] N-formylisopropylidene-DL-penicillamine[25] and various derivatives of S-benzylpenicillamine.[25,26] Application of the general enzymic procedures developed in this Laboratory to the resolution of DL-penicillamine assumed especial interest in view of the previous behavior exhibited toward hydrolytic enzymes by derivatives of the structurally related *t*-leucine. Thus, although the complete resistance of chloroacetyl-DL-*t*-leucine to the hydrolytic action of renal acylase I could be conceivably attributed to the high degree of steric hindrance arising from complete substitution about the β-carbon atom of the substrate, no such absolute resistance was encountered upon subjecting *t*-leucine amide to the hydrolytic action of hog kidney amidase.[27] That the same general pattern was followed for the N-acetyl derivatives of S-benzyl- and S-methylpenicillamine was indicated by the inability of renal acylase I to effect their cleavage. However, the ability of the L-directed hog kidney amidase[28] to induce an asymmetric cleavage of S-benzyl-DL-penicillamine amide, albeit slow, nonetheless made an enzymic resolution feasible here.

The S-benzyl-DL-penicillamine amide employed in the present investigation was prepared by the conversion of carbobenzoxy-S-benzyl-DL-penicillamine to the corresponding amide derivative, *via* the mixed carbonic–carboxylic anhydride procedure,[29] followed by decarbobenzoxylation of this latter compound with hydrogen bromide in glacial acetic acid.[30] Asymmetric cleavage of the amide with a hog kidney amidase preparation[28] proceeded at a rate of 5 micromoles per hr. per mg. protein nitrogen at *p*H 8.0, 38°, and a substrate concentration of 0.01 to 0.02 *M*. Isolation of the liberated S-benzyl-L-penicillamine and S-benzyl-D-penicillamine amide was achieved through the utilization of an Amberlite XE-64 resin in the acid phase.[31] It is especially noteworthy that the steric hindrance imposed by the groups about the β-carbon atom presumably made the D-amide extremely resistant to acid hydrolysis, for less than 10% cleavage occurred upon refluxing the compound with ten volumes of 2 *N* HCl for 2 hr.[32] Conversion of the D-amide to S-benzyl-D-penicillamine was achieved upon its treatment with 5 *N* HCl, under reflux, for some 6 hr. An $[\alpha]^{24}D$ −90.6° (1% in *N* HCl) was revealed for the D-amino acid so procured, a value which was equal and opposite, within the limits of experimental error, to the $[\alpha]^{24}D$ +91.3° (1% in *N* HCl) secured for the L-antipode. Unfortunately, the complete resistance of these enantiomers to D-amino acid oxidase and L-amino acid oxidase (*Crotalus adamanteus*), respectively, did not permit measurements of their optical purity.[16]

Infrared Spectra.—The absorption spectra of L-cystine and of such peptides as cyclo-L-cystinyl and of L-cystinyl-L-cystine have been described.[33] L-Cystine and D-cystine were mixed in equal amounts and the mixture recrystallized as described above. The solid state spectrum in the infrared region of the resulting DL-cystine was found to be identical with that of L-cystine which in turn is identical with that of D-cystine The spectra of *meso*-cystine was found to be almost indistinguishable from that of L-, D- or DL-cystine.

Experimental

I. Resolution and Derivatives of Cystine. Monocarbobenzoxy-L-cystine.—One hundred grams (0.42 mole) of L-cystine was dissolved in 1 l. of cold 1.65 *N* NaOH. The solution was placed in an ice-bath and 25 ml. of carbobenzoxy chloride added thereto over a period of 1 hr. with vigorous stirring. After an additional 20 min., the reaction mixture was carefully adjusted to *p*H 6 with 6 *N* HCl and the stirring and cooling continued for 20 min. longer. The precipitate of excess L-cystine was filtered over suction and washed with 100 ml. of water. The combined filtrate and washings were adjusted to exactly *p*H 3.2 with 6 *N* HCl and, after cooling at 4° for several hours, was filtered and washed copiously with alcohol, then ether. A yield of 37.5 g. of pure monocarbobenzoxy-L-cystine was so secured. Recrystallization could be effected by suspending the material in 1 l. of water, bringing the *p*H to 6.5 by the addition of 2 *N* NaOH with stirring to effect solution filtering off any undissolved material, and then adjusting the *p*H downward to 3.2 by the addition of 6 *N* HCl. After cooling, the precipitate was filtered, and washed successively with a little cold water, ethanol and ether; $[\alpha]^{23}D$ −126° (1% in 5 *N* HCl) and −120° (1% in 1 *N* NaOH).

Anal. Calcd. for $C_{14}H_{18}O_6N_2S_2$: C, 44.9; H, 4.8; N, 7.5; S, 17.1. Found: C, 44.6; H, 4.9; N, 7.4; S, 16.7.

Carbobenzoxycyclo-L-cystinyl.—This compound was prepared by the carbobenzoxylation of cyclo-L-cystinyl[34] according to the usual Schotten–Baumann procedure. The precipitate secured after acidification of the reaction mixture was recrystallized from ethyl acetate–petroleum ether; dec. p. 170–172° with preshrinking at 141°, $[\alpha]^{24}D$ −52.5° (1% in methanol).

Anal. Calcd. for $C_{14}H_{16}O_5N_2S_2$: C, 47.2; H, 4.5; N, 7.9; S, 18.0. Found: C, 47.6; H, 4.8; N, 7.6; S, 17.6.

Bis-(glycyl)-L-cystine.—Preparation of this compound has been reported by several investigators.[35–38] The material here employed was prepared by amination of the precursor bis-(chloroacetyl)-L-cystine[39] according to a modification of the procedure of Abderhalden and Wybert[35]; $[\alpha]^{23}D$ −118° (1% in water) for the monohydrate, and −114° (1% in *N* HCl).

Bis-(acetyl)-L-cystine.—To a solution of 24.0 g. of L-cystine in 100 ml. of ice-cold 2 *N* NaOH were added alter-

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(26) L. H. Werner, A. Wettstein and K. Miescher, *Helv. Chim. Acta*, **30**, 432 (1947).

(27) N. Izumiya, S.-C. J. Fu, S. M. Birnbaum and J. P. Greenstein, *J. Biol. Chem.*, **205**, 221 (1953).

(28) D. Hamer and J. P. Greenstein, *ibid.*, **193**, 8 (1951); S. M. Birnbaum in "Methods in Enzymology," Vol. II, Academic Press, Inc., New York, N. Y., 1955, p. 397.

(29) J. R. Vaughan and R. Osata, THIS JOURNAL, **74**, 676 (1952); R. A. Boissonas, *Helv. Chim. Acta*, **34**, 874 (1951); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951).

(30) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

(31) *Cf.* C. G. Baker and H. A. Sober, THIS JOURNAL, **75**, 4058 (1953).

(32) Determinations with a 0.03 *M* solution of S-benzyl-DL-penicillamine amide in 5 *N* HCl revealed that after reflux periods of 1, 1.5 2.5 and 4.8 hours, the degree of hydrolysis was 19, 34, 70 and 100%, respectively.

(33) R. J. Koegel, J. P. Greenstein, M. Winitz, S. M. Birnbaum and R. A. McCallum, THIS JOURNAL, **77**, 5708 (1955); M. C. Otey and J. P. Greenstein, *Arch. Biochem. Biophys.*, **53**, 501 (1954).

(34) R. Wade, M. Winitz and J. P. Greenstein, THIS JOURNAL, **78**, 373 (1956).

(35) E. Abderhalden and E. Wybert, *Ber.*, **49**, 2449, 2838 (1916).

(36) E. Fischer and U. Suzuki, *ibid.*, **37**, 4575 (1904).

(37) N. W. Pirie, *Biochem. J.*, **25**, 614 (1931).

(38) J. P. Greenstein, *J. Biol. Chem.*, **128**, 241 (1939).

(39) E. Fischer and O. Gerngross, *Ber.*, **42**, 1485 (1909).

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nately, and in small portions, 500 ml. of 2 *N* NaOH and 50 ml. of acetic anhydride, with vigorous cooling and shaking. The reaction mixture was shaken for an additional 30 min. and then acidified to congo red with 6 *N* HCl. The mixture was exhaustively extracted with ethyl acetate and the combined ethyl acetate fractions dried over anhydrous sodium sulfate and concentrated to dryness. The residual oil was taken up in hot acetone and a white solid precipitated upon the addition of petroleum ether. This was filtered off, again dissolved in hot acetone, filtered and the solution permitted to stand for 2 hr. at 10°. Microscopic examination revealed white, prism-shaped crystals which were highly hygroscopic upon exposure to air. The bis-(acetyl)-L-cystine was therefore separated from the acetone supernatant by centrifugation and subsequent decantation, and immediately placed in a vacuum desiccator where the residual solvent was removed. After drying over phosphorus pentoxide at 80° for some 12 hr., the compound appeared no longer hygroscopic; yield 19 g., m.p. 121–122°, $[\alpha]^{23}D$ −118° (1% in water). This compound was previously prepared[4] as a non-crystalline solid for which no physical constants were given, and as a white solid with m.p. 120° (J. P. Greenstein and F. M. Leuthardt, *Archiv. Biochem.*, 18, 377 (1948)).

Anal. Calcd. for $C_{10}H_{16}O_6N_2S_2$: C, 37.0; H, 4.9; N, 8.6; S, 19.8. Found: C, 37.1; H, 5.1; N, 8.6; S, 19.5.

Racemization of Bis-(acetyl)-L-cystine.—To a solution of 20 g. of bis-(acetyl)-L-cystine in 150 ml. of glacial acetic acid, at room temperature (*ca.* 27°), was added 30 ml. of acetic anhydride. A very small quantity of crystalline material appeared within a few minutes but did not change noticeably in amount during the next 16 hours. An aliquot of the solution was removed and its change in optical rotation followed polarimetrically. A plot of the optical rotation value *versus* time is given in Fig. 1. After some 16 hr., the optically inactive solution was filtered and the filtrate evaporated to dryness under a jet of air. A white, sticky residue remained which began to crystallize upon rubbing under ether and which appeared to be completely crystalline after standing for two days in the cold. Since the material was highly hygroscopic, it was separated from the ethereal layer by centrifugation and decantation, and then immediately placed in a vacuum desiccator where the residual ether was drawn off. After drying over potassium hydroxide *in vacuo*, the yield of the epimeric mixture of bis-(acetyl)-cystine was 16.8 g. (84%), dec. point 78°, $[\alpha]^{23}D$ 0° (in water). The compound exhibited a slight hygroscopicity and was analyzed after drying *in vacuo* at 60°.

Anal. Calcd. for $C_{10}H_{16}O_6N_2S_2$: C, 37.0; H, 4.9; N, 8.6. Found: C, 37.2; H, 5.2; N, 8.2.

One gram of the epimeric mixture was hydrolyzed by refluxing with 100 ml. of 2 *N* HCl for 2 hr. The solution was concentrated to dryness *in vacuo* at 37°, and the evaporation repeated several times subsequent to the addition of water. The residue was taken up in water, the solution filtered, and the *p*H adjusted to 5.5 with aqueous ammonia. After standing for several hours in the cold, the optically inactive cystine was recovered by filtration over suction; yield 0.43 g. (58%), $[\alpha]^{23}D$ 0° (1% in 1 *N* HCl).

Anal. Calcd. for $C_6H_{12}O_4N_2S_2$: C, 30.0; H, 5.0; N, 11.7; S, 26.7. Found: C, 29.9; H, 5.0; N, 11.6; S, 26.5.

Enzymic Resolution.—A solution of 9.72 g. (0.03 mole) of optically inactive bis-(acetyl)-cystine in 150 ml. of water was prepared, the *p*H adjusted to 7.5 with 2 *N* NaOH, and the volume brought to 300 ml. with distilled water. After the addition of 1 g. of hog renal acylase I powder,[14] the digest was incubated at 37° for some 16 hr., at which point the degree of hydrolysis, as measured by the van Slyke manometric-CO_2 procedure,[40] had proceeded to only 18.5% of theory. The *p*H of the digest was adjusted to 7.5 and an additional 8 g. of "crude" acylase I[41] was added. After some 24 hr., a 50% hydrolysis of the total substrate was indicated. This value remained unchanged upon the further addition of 1 g. of crude acylase I and subsequent incubation for an additional 16 hr. The hydrolysate was then adjusted to *p*H 5.5 with glacial acetic acid and concentrated to 100 ml. *in vacuo* at 35–40° in the presence of capryl alcohol to eliminate foaming. The concentrate was warmed over the steam-bath for some 10 min. (to denature the protein), allowed to stand in the cold overnight, and the precipitate of L-cystine plus coagulated protein filtered and washed with 100 ml. of cold water. The combined filtrate and washings, which contained both the bis-(acetyl)-D-cystine and monoacetyl-*meso*-cystine, was concentrated to about 50 ml. *in vacuo* at 40°, and the concentrate then run onto a Dowex 50-X[4] column (30 × 2.5 cm.) in the acid phase which had been previously washed with water. Fractions were collected in 30–35-ml. cuts, with water as the eluent, and the presence of bis-(acetyl)-D-cystine was indicated in tubes 2 to 16 by the drop in *p*H of the eluate. The column was further eluted with 1 l. of water, which was discarded, and then with 1 *N* HCl, which was collected in 30–35-ml. cuts and examined for the presence of monoacetyl-*meso*-cystine with ninhydrin as the indicator. All "positive" fractions were combined.

L-Cystine.—The combined precipitate of L-cystine and denatured protein, secured above, was extracted twice with 250-ml. portions of warm (70°) 1 *N* HCl, the extracts treated with Norite, filtered and the filtrate adjusted to *p*H 5.5 with aqueous ammonia. After standing for 6 hr. in the cold, the L-cystine was filtered, washed with water and recrystallized from water *via* the hydrochloride derivative according to the procedure of Fischer and Raske.[15] An over-all yield of 0.8 g. of L-cystine was obtained, $[\alpha]^{23}D$ −211° (1% in *N* HCl).

Anal. Calcd. for $C_6H_{12}O_4N_2S_2$: C, 30.0; H, 5.0; N, 11.7; S, 26.7. Found: C, 29.9; H, 5.3; N, 11.7; S, 26.5.

D-Cystine.—The combined eluates of tubes 2 to 16, secured above, were concentrated to dryness *in vacuo* and the residual oil was dissolved in 100 ml. of 2 *N* HCl. After refluxing for 2 hr., the hydrolysate was decolorized with Norite and the *p*H brought to 5.5 with aqueous ammonia. The precipitated D-cystine was recrystallized in the same manner employed for the L-antipode; yield 0.95 g., $[\alpha]^{23}D$ +208° (1% in *N* HCl).

Anal. Found: C, 30.1; H, 5.1; N, 11.6; S, 26.5.

Mesocystine.—The combined 1 *N* HCl eluates, secured above, were concentrated to dryness and the residual monoacetyl-*meso*-cystine taken up in 100 ml. of 2 *N* HCl and refluxed for 2 hr. Recovery of the *meso*-cystine from the acid hydrolysate, as well as its recrystallization, was effected as given for the D-stereoisomer; yield 0.8 g., $[\alpha]^{23}D$ 0° (1% in *N* HCl).

Anal. Found: C, 29.8; H, 5.0; N, 11.7; S, 26.5.

II. Resolution, Derivatives and Analogs of S-Benzyl-penicillamine. N-Acetyl-S-benzyl-DL-penicillamine.—To a solution of 19.1 g. (0.1 mole) of acetyl-DL-penicillamine[25] in 500 ml. of liquid ammonia was added small pieces of sodium metal, with stirring, until a slight excess was present (as indicated by a permanent light blue color). S-Benzylation[42] was effected by the dropwise addition of benzyl chloride until the blue color just disappeared, and then the further dropwise addition of an additional 12.7 ml. (0.11 mole) of benzyl chloride. The mixture was stirred for 3 hr. after the addition was complete, the liquid ammonia then allowed to evaporate spontaneously, and the resulting residue extracted into water. Following filtration of a slight amount of insoluble residue, the *p*H of the solution was adjusted to 1.7 with 6 *N* HCl and the mixture extracted exhaustively with ethyl acetate. The ethyl acetate extracts were pooled, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated to dryness. After recrystallization of the crystalline residue from 50% ethanol, a yield of 21.9 g. (78%) of N-acetyl-S-benzyl-DL-penicillamine was secured, m.p. 174°.

Anal. Calcd. for $C_{14}H_{19}O_3NS$: C, 59.8; H, 6.8; N, 5.0; S, 11.4. Found: C, 60.0; H, 6.9; N, 5.0; S, 11.4.

N-Acetyl-S-methyl-DL-penicillamine.—This compound was prepared in the same general manner as employed for the S-benzyl analog through the use of methyl iodide *in lieu* of benzyl chloride.[43] A 76% yield of the desired product

(40) Although the precipitation of free L-cystine accompanied the hydrolysis, a representative aliquot could be removed successfully from the well-shaken reaction mixture and the degree of hydrolysis measured with a high degree of precision.

(41) This acylase I preparation has not been carried as far as the acetone fractionation step, but rather is a lyophilized powder of a dialysate prepared just subsequent to the ammonium sulfate precipitation stage (*cf.* ref. 14).

(42) *Cf.* V. du Vigneaud, L. F. Audrieth and H. S. Loring, THIS JOURNAL, **52**, 4500 (1930).

(43) *Cf.* V. du Vigneaud, H. M. Dyer and J. Harmon, *J. Biol. Chem.*, **101**, 719 (1933); J. E. Wilson and V. du Vigneaud, *ibid.*, **184**, 63 (1939).

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was secured after recrystallization from water; m.p. 196–197°.

Anal. Calcd. for $C_8H_{15}O_3NS$: C, 46.8; H, 7.3; N, 6.8; S, 15.6. Found: C, 46.7; H, 7.2; N, 6.7; S, 15.6.

N-Carbobenzoxy-S-methyl-DL-penicillamine.—N-Acetyl-S-methyl-DL-penicillamine was hydrolyzed to S-methyl-DL-penicillamine upon refluxing with 2 *N* HCl (10 ml. per g. of acetyl derivative) for 2 hr. After evaporation of the hydrolysate to dryness *in vacuo*, the residue was extracted into water, the *p*H adjusted to *p*H 5.5 with aqueous ammonia, and the resulting crystals of S-methyl-DL-penicillamine filtered, washed with water, and finally recrystallized from water. This compound has been previously prepared[43] *via* methylation of penicillamine with methyl iodide in the sodium–liquid ammonia system.

Anal. Calcd. for $C_6H_{13}O_2NS$: C, 44.2; H, 8.0; N, 8.6; S, 19.6. Found: C, 44.1; H, 8.0; N, 8.2; S, 19.4.

Preparation of the carbobenzoxy derivative was effected in a manner comparable to that given below for the S-benzyl analog. A 67% yield was obtained after recrystallization from benzene–petroleum ether; m.p. 89°.

Anal. Calcd. for $C_{14}H_{19}O_4NS$: C, 56.6; H, 6.5; N, 4.7; S, 10.8. Found: C, 57.0; H, 6.5; N, 4.6; S, 10.3.

N-Carbobenzoxy-S-benzyl-DL-penicillamine.—A solution of 105.5 g. of S-benzyl-DL-penicillamine in 450 ml. of 1 *N* NaOH was cooled to about 5° and a total of 95.4 ml. of carbobenzoxy chloride and 650 ml. of 1 *N* NaOH added alternately thereto, in small portions, with vigorous shaking and cooling. Separation of an oil was noted at this stage. The reaction mixture was shaken for an additional 2 hr. in the cold and then acidified to *p*H 1.7 with 6 *N* HCl. An oil was precipitated which was taken up in half-saturated sodium bicarbonate solution, filtered, and reprecipitated with 6 *N* HCl. Although an oil was initially formed, crystallization soon commenced. The crystals were dissolved in ethyl acetate and the solution dried with anhydrous sodium sulfate, filtered and concentrated to dryness in a stream of dry air. An oil was secured which readily crystallized upon rubbing with water; yield 99 g., m.p. 81°.

Anal. Calcd. for $C_{20}H_{23}O_4NS$: C, 64.3; H, 6.2; N, 3.8; S, 8.6. Found: C, 64.0; H, 6.2; N, 3.7; S, 8.4.

N-Carbobenzoxy-S-benzyl-DL-penicillamine Amide.—A solution of 98.5 g. of carbobenzoxy-S-benzyl-DL-penicillamine and 37.1 ml. of triethylamine in 1.5 l. of dry dioxane was cooled to 10°, and 35.2 ml. of isobutyl chloroformate added thereto. The reaction mixture was maintained at 10° for 1 hr., with occasional shaking, and 34.4 ml. of concentrated aqueous ammonia then added. As no carbon dioxide was evolved at this temperature, the mixture was warmed to 80° over a steam-bath and was maintained at this temperature for 10–15 minutes, during which time vigorous gas evolution was observed. An additional 34.4 ml. of concentrated ammonia was then added, the mixture allowed to stand at room temperature overnight, the precipitate of triethylamine hydrochloride removed by filtration, and the filtrate concentrated to dryness *in vacuo*. The residue was dissolved in chloroform and the chloroform layer washed successively with half-saturated sodium bicarbonate, water, 1 *N* HCl and water. The chloroform layer was evaporated to dryness *in vacuo*, benzene added, and the evaporation repeated. Crystallization of the residue was effected from ether–petroleum ether. Since the precipitate was slightly colored, it was taken up in ethyl acetate, the solution decolorized with Norite, dried over anhydrous sodium sulfate, and evaporated to dryness. The white crystals were recrystallized from absolute ethanol; yield 63.5 g. (65%), m.p. 123–124°.

Anal. Calcd. for $C_{20}H_{25}O_3N_2S$: C, 64.3; H, 6.7; N, 7.5; S, 8.6. Found: C, 64.2; H, 6.6; N, 7.4; S, 8.4.

S-Benzyl-DL-pencillamine Amide Hydrobromide.—Decarbobenzoxylation of carbobenzoxy-S-benzyl-DL-penicillamine amide was effected according to the general procedure of Ben-Ishai and Berger.[30] A stream of dry hydrogen bromide was passed through a solution of 60 g. of the carbobenzoxy-amide in 1 l. of glacial acetic acid to saturation, the temperature being maintained below 35°. After 0.5 hr. at room temperature, the mixture was concentrated to 500 ml. and 3 l. of dry ether added thereto. After standing overnight in the cold, the mixture was filtered and the precipitate washed with ether, dried *in vacuo* over potassium hydroxide and recrystallized from 95% ethanol; yield 44 g. (86%), m.p. 227–228°.

Anal. Calcd. for $C_{12}H_{25}ON_2SBr$: C, 45.1; H, 6.0; N, 8.8; S, 10.0; Br, 25.0. Found: C, 45.0; H, 6.0; N, 8.6; S, 9.7; Br, 25.0.

Enzymic Resolution.—The *p*H of a solution of 4 g. of S-benzyl-DL-penicillamine amide hydrobromide and 50 mg. of $MnCl_2 \cdot 4H_2O$, in water, was adjusted to 8.0 with 2 *N* LiOH; 30 ml. of a hog kidney amidase[44] solution containing 5 mg. of nitrogen per ml. was added thereto, and the final volume diluted to 250 ml. The mixture was subsequently digested at 38° for 18 hr., at which point the manometric ninhydrin-CO_2 procedure revealed 50% hydrolysis of the total substrate. No change in the degree of hydrolysis was revealed upon digestion for an additional 24 hr. after the addition of 7 ml. more of amidase solution. The digest was adjusted to *p*H 5.2 with glacial acetic acid, deproteinized by filtration in the presence of Norite, the precipitate washed with water and the filtrate and washings combined. Since the precipitate contained some adsorbed substrate, this was extracted twice with hot methanol, filtered, the filtrate evaporated to dryness *in vacuo* at 35° and the resulting residue taken up in the pooled aqueous filtrate. This latter was concentrated to about 250 ml. *in vacuo* and the concentrate run onto an Amberlite XE-64 column (28 × 2.5 cm.) in the acid phase. With water as the eluent, fractions were collected every 8 ml. and examined for ninhydrin-positive material. The presence of S-benzyl-L-penicillamine in tubes 10 to 170 was so indicated. After emergence of the L-amino acid, the column was washed with 2 l. of distilled water and the S-benzyl-D-penicillamine amide then eluted with 0.3 *N* HCl (fractions tested for ninhydrin positive material, as previously).

S-Benzyl-L-penicillamine.—The combined eluate of tubes 10 to 170 was concentrated to dryness *in vacuo* at 40°. The residue was dissolved in 1 *N* HCl and the *p*H brought to 5.5 with aqueous ammonia. A crystalline precipitate of S-benzyl-L-penicillamine was so obtained in 96% yield. Recrystallization was effected from water; $[\alpha]^{24}D$ +87.5° (1% in NaOH) and $[\alpha]^{24}D$ +91.3° (1% in *N* HCl).

Anal. Calcd. for $C_{12}H_{17}O_2NS$: C, 60.3; H, 7.1; N, 5.9; S, 13.4. Found: C, 60.2; H, 7.3; N, 5.8; S, 13.1.

S-Benzyl-D-penicillamine Amide Hydrochloride.—The 0.3 *N* HCl eluate from the column, which contained the D-amide, was brought to *p*H 4.5 with silver carbonate and filtered. Adsorbed material on the silver chloride precipitate was eluted off with hot methanol, the methanol extracts filtered, concentrated to dryness and the residue taken up in the aqueous filtrate. Hydrogen sulfide was passed through the latter to remove silver ions, the suspension filtered, and the filtrate concentrated to dryness *in vacuo*. The residue was dissolved in approximately 100 ml. of methanol, the solution filtered, the filtrate concentrated to dryness, and the residue crystallized from 80% ethanol to yield S-benzyl-D-penicillamine amide hydrochloride. This material contained approximately one molecule of water of crystallization which could be removed upon drying *in vacuo* at 80°; yield 1.4 g. (81%) of anhydrous product, m.p. 182–183°, $[\alpha]^{24}D$ −73.0 (1% in ethanol).

Anal. Calcd. for $C_{12}H_{19}ON_2SCl$: C, 52.4; H, 6.9; N, 10.2; S, 11.7; Cl, 12.9. Found: C, 52.4; H, 7.0; N, 10.0; S, 12.0; Cl, 13.0.

S-Benzyl-D-penicillamine.—A solution of 0.7 g. of S-benzyl-D-penicillamine amide hydrochloride in 20 ml. of 5 *N* HCl was refluxed for 6 hr. and the hydrolysate then concentrated to dryness *in vacuo* at 38°. After the addition of a little water, the evaporation was repeated. The residue was dissolved in a few ml. of water and the *p*H adjusted to 5.5 with 2 *N* LiOH. The D-isomer, which crystallized out on standing, was filtered, washed with water and dried; yield 0.58 g. Recrystallization was effected from water; $[\alpha]^{24}D$ −90.6 (1% in 1 *N* HCl).

(44) The amidase preparation employed was prepared as described previously,[28] but without prior adsorption on calcium phosphate gel. Its rate of hydrolysis toward L-leucine amide, under the same conditions as utilized for the S-benzylpenicillamine amide, was 2880 μmoles

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Anal. Calcd. for $C_{12}H_{17}O_2NS$: C, 60.3; H, 7.1; N, 5.9; S, 13.4. Found: C, 60.1; H, 7.0; N, 5.8; S, 13.2.

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BETHESDA, MD.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Synthesis of Ethyl β,β-Diethoxyalanyl-L-cysteinate Hydrochloride[1]

BY HOMER ADKINS[2] AND BURRIS D. TIFFANY[3]

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Ethyl β,β-diethoxyalanyl-L-cysteinate hydrochloride (XIX) has been synthesized through the coupling of N-carbobenzoxy-β,β-diethoxyalanine azide (XI) with S-benzyl-L-cysteine, followed by selective removal of the protecting N-carbobenzoxy and S-benzyl groups by mild reduction. The azide XI was prepared by the carbobenzoxylation of ethyl β,β-diethoxyalanate (IV) followed by conversion of the ester IX to the hydrazide X and then to the azide. The primary coupling product, N-carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteine (XIV) and (XV), was separated into its component D,L- and L,L-diastereoisomers by fractional crystallization of its methyl esters and sodium salts. D,L-N-Carbobenzoxy-β,β-diethoxyalanylglycine (XII) resulted from a preliminary investigation of the synthetic route using glycine. An attempt to couple the unprotected β,β-diethoxyalanine azide (VI) with glycine yielded 3-diethoxymethyl-2,5-piperazinedione (VIII).

In connection with a study of the structure of benzylpenicillin,[4] it was of interest to synthesize the stereoisomeric ester hydrochlorides (I) of β,β-diethoxyalanylpenicillamine, a dipeptide incorporating certain structural features known to be present in benzylpenicillin itself.

$$(CH_3CH_2O)_2CHCHCONHCHCO_2CH_2CH_3 \qquad \begin{matrix} \text{I, R} = CH_3 \\ \text{II, R} = H \end{matrix}$$
$$\qquad\qquad\quad H_2N{\cdot}HCl \qquad\quad CR_2SH$$

This paper describes the synthesis of one of the stereoisomers of the lower homolog, ethyl β,β-diethoxyalanyl-L-cysteinate hydrochloride (II), derived from L-cysteine, as a model for the synthesis of the dipeptide ester hydrochlorides I, which require the less available penicillamine.

The first approach studied was the azide coupling of β,β-diethoxyalanine (III) with ethyl glycinate. The latter amino acid was employed in developing the method to avoid difficulties due to the sensitive sulfhydryl group and the complications of diastereoisomeric dipeptides.

Ethyl β,β-diethoxyalanate (IV), prepared from ethyl glycinate,[5] was converted to the hydrazide V in good yield, using anhydrous hydrazine. The hydrazide was surprisingly stable, considering the functional groups present, and could be distilled at reduced pressure without change.

We were encouraged by the unusual stability of the hydrazide to attempt direct conversion to the azide VI and coupling with glycine without protecting the amino group. When this unconventional series of reactions was tried, the product, obtained in 10% yield, was not the dipeptide ester VII, however, but a white water-soluble solid which gave correct carbon and hydrogen values for 3-diethoxymethyl-2,5-piperazinedione (VIII) *i.e.*, the compound to be expected upon cyclization of the coupled product VII. The failure, therefore, appeared not to be in the coupling, although of low yield, but rather in preventing the subsequent cyclization. Herein is implied the existence of a moderately stable aliphatic primary amino acid azide, which seems to be unprecedented.[6]

For a successful coupling procedure we turned to Bergmann's method for protection of the amino group. Carbobenzoxylation of ethyl β,β-diethoxyalanate (IV) was accomplished in 81% yield, and the resulting ethyl N-carbobenzoxy-β,β-diethoxyalanate (IX) was converted readily to the hydrazide X with 85% hydrazine hydrate in ethanol. Before treatment with nitrous acid this acetal-containing hydrazide was tested for stability in aqueous acid. It could be dissolved in three equivalents of cold 1 *N* hydrochloric acid and largely recovered unchanged upon neutralization of the acid. The azide XI was prepared from the hydrazide using nitrous acid and coupled with glycine in potassium carbonate solution, giving N-carbobenzoxy-β,β-diethoxyalanylglycine (XII) as a white crystalline solid in good yield. The crystalline methyl ester XIII was prepared readily from the acid upon treatment with diazomethane.

Having demonstrated that the acetal system would survive in the coupling reaction, attention was next turned to the dipeptide containing the L-cysteine residue. The sensitive sulfhydryl group was protected with a benzyl group as described by Wood and du Vigneaud.[7] When the coupling procedure was carried out with S-benzyl-L-cysteine, the product, obtained in 80% yield, was a solid with a broad melting range and presumably was a mixture of the D,L- and L,L-diastereoisomers of the dipeptide XIV and XV.

For separation of the diastereoisomers the mixture of acids was converted to the methyl esters

(1) From a thesis submitted by Burris D. Tiffany to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1949.

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(4) *Cf.* H. Adkins, R. M. Ross and D. C. Schroeder, THIS JOURNAL, **72**, 5401 (1950).

(5) "The Chemistry of Penicillin," Clarke, Johnson and Robinson, Editors, Princeton University Press, Princeton, N. J., 1949, p. 1125.

(6) *Cf.* P. A. S. Smith's review of the Curtius reaction in "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 353.

(7) J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, **130**, 110 (1939).

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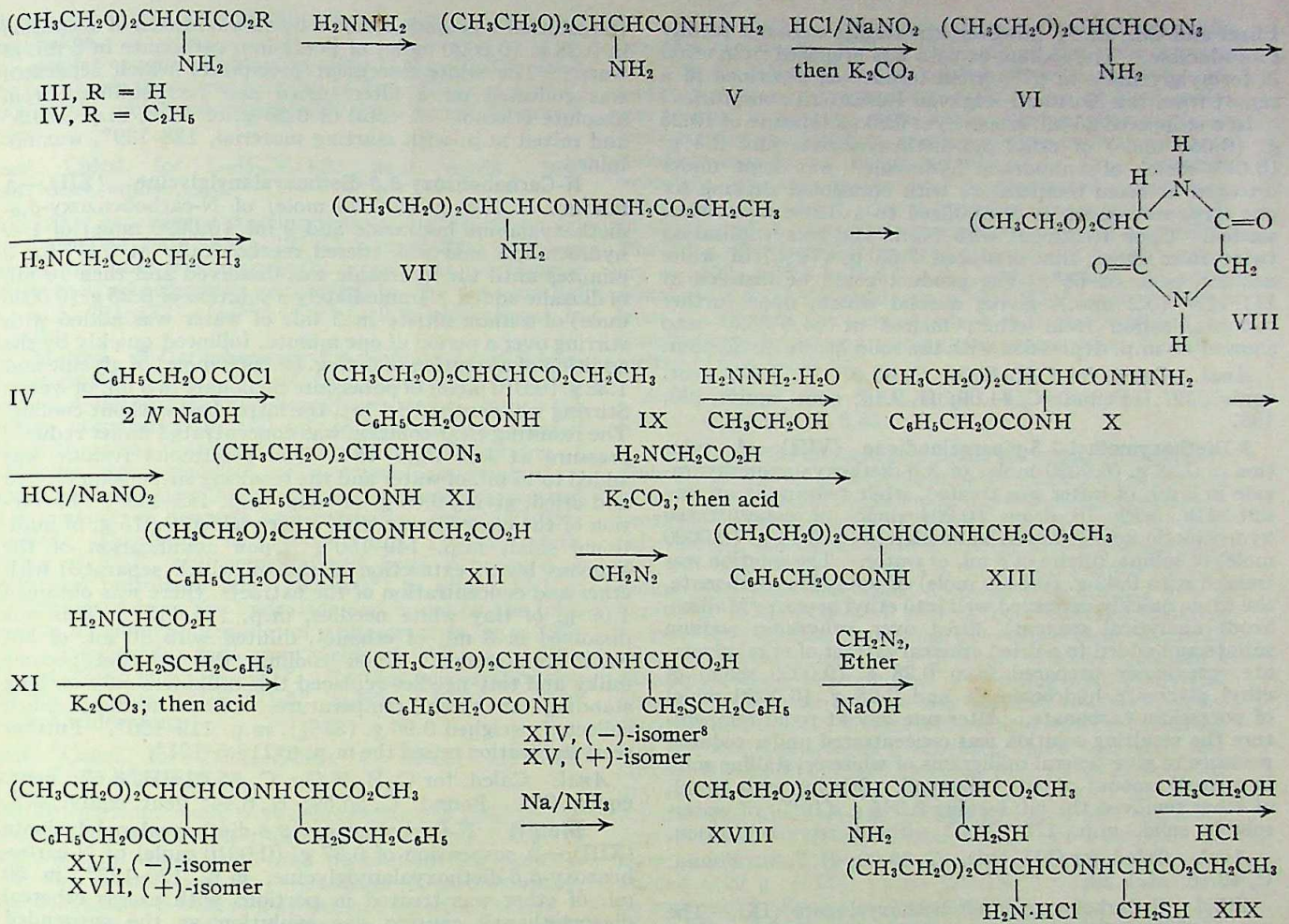

XVI and XVII with diazomethane, and recrystallized from a mixture of benzene and petroleum ether in which the dextrorotatory ester was the less soluble. Material of good quality was obtained in 25% over-all yield from the hydrazide (based on the total amount of all isomers expected). Hydrolysis of the ester to the free acid apparently was accompanied by some decomposition or partial racemization, since material of sharp melting point could not be obtained. Attempts to separate the isomers by fractional recrystallization of the acids instead of the esters was not promising.

The levorotatory form of the dipeptide XIV was obtained by hydrolysis of the residual methyl esters from which the dextrorotatory ester had been crystallized, extraction of the *sodium salts* into chloroform and fractional recrystallization of these salts from absolute ethanol. The alkali salts of these isomeric acids showed a remarkable solubility in chloroform, being much more soluble in this solvent than in water. Furthermore, the sodium salt of the levorotatory form, which was isolated in a fairly pure state, had a surprisingly low melting point, 169–173°. The levorotatory free acid XIV was prepared from a dilute aqueous solution of the salt by treatment with dilute acid and was recrystallized from chloroform. Reaction with diazomethane converted it to the crystalline methyl ester (XVI).

Both protecting groups in the dipeptides, the N-carbobenzoxy and the S-benzyl groups, were removed simultaneously upon reduction with sodium in liquid ammonia. The process was successful however, only when applied to the methyl ester and not with the free acid as suggested by the literature.[9] Hopkins mercuric sulfate reagent, which usually is successful for separation of cysteine-containing peptides, failed to precipitate the product in either case here. The product from reduction of the dextro methyl ester was a crystalline solid but apparently a mixture. By means of an ester interchange in ethanolic hydrogen chloride, however, it was converted to a homogeneous product consisting of the ethyl ester hydrochloride, ethyl β,β-diethoxyalanyl-L-cysteinate hydrochloride (XIX), a sensitive white crystalline solid. A test with sodium nitroprusside reagent verified the presence of the sulfhydryl group and a Zeisel determination indicated the presence of three ethoxyl groups. The free amino group was evidenced by the formation of a hydrochloride.

Acknowledgment.—We wish to express our appreciation to Dr. A. L. Wilds for advice concerning the preparation of the manuscript.

Experimental[10]

β,β-Diethoxyalanine Hydrazide (V).—Ethyl β,β-diethoxyalanate (IV) required in this preparation was prepared from sodium ethyl α-N-formylamino-β-hydroxyacrylate in 30% yield by a procedure described in a report from Charles

(8) In these compounds (+) and (−) are used to designate an observed rotation with no implication regarding actual configurations. Small capital D and L are employed as usual to designate known configurations.

(9) C. R. Harington and R. V. P. Rivers, *Biochem. J.*, **38**, 417 (1944).

(10) All melting points are corrected. Microanalyses were carried out by Richard Hunt and Edward Shiner and by the Clark Microanalytical Laboratory, Urbana, Ill.

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Pfizer and Co., Inc.[5]; however, the results were not readily reproducible. The sodium enolate was prepared from ethyl N-formylglycinate in 97% yield (crude) as described in a report from the Northern Regional Research Laboratories.[5]

In a stoppered 25-ml. erlenmeyer flask, a mixture of 10.25 g. (0.050 mole) of ethyl β,β-diethoxyalanate and 2.4 g. (0.075 mole) of anhydrous hydrazine[11] was kept under nitrogen at room temperature with occasional shaking for one day, whereupon it crystallized to a dense mass when seeded. Upon treatment with Norit and recrystallization twice from ether, this produced 7.55 g. (79%) of white needles, m.p. 63–65°. The product could be distilled at 111–112° (0.2 mm.), giving a solid which, upon further recrystallization from ether, melted at 64.5–65.5° and showed no m.p. depression with the solid before distillation.

Anal. Calcd. for $C_7H_{17}N_3O_3$: C, 43.97; H, 8.96; neut. equiv., 191. Found: C, 44.09; H, 9.16; neut. equiv., 190, 193.

3-Diethoxymethyl-2,5-piperazinedione (VIII).—A solution of 0.38 g. (0.0020 mole) of β,β-diethoxyalanine hydrazide in 5 ml. of water was treated, while swirling in an ice–salt-bath, with 10 drops (0.004 mole) of concentrated hydrochloric acid followed immediately by 0.14 g. (0.0020 mole) of sodium nitrite in 3 ml. of water. The solution was treated with 0.42 g. (0.0030 mole) of potassium carbonate, the azide quickly extracted well into ethyl acetate (Mallinckrodt analytical reagent), dried over anhydrous sodium sulfate and added to a dried ethereal extract of ethyl glycinate, previously prepared from 0.28 g. (0.0020 mole) of ethyl glycinate hydrochloride and 0.28 g. (0.0020 mole) of potassium carbonate. After one day at room temperature the resulting solution was concentrated under reduced pressure to give several milligrams of white crystalline solid in a small amount of pale yellow oil. Stirring with 50 ml. of ether removed the oil, leaving 0.045 g. (10%) of water-soluble solid, m.p. 176–177.5° without recrystallization.

Anal. Calcd. for $C_9H_{16}N_2O_4$: C, 50.00; H, 7.40. Found: C, 49.76; H, 7.29.

Ethyl N-Carbobenzoxy-β,β-diethoxyalanate (IX).—The preparation of this compound by procedures differing from the one given below has been described previously.[12] In a 250-ml. three-necked flask equipped with a mechanical stirrer and two dropping funnels was placed 23.3 g. (0.100 mole) of ethyl β,β-diethoxyalanate, rinsing in with 23 ml. of water. This was stirred and cooled in an ice–salt-bath while 20.0 g. (0.115 mole) of carbobenzoxy chloride[13] and 60 ml. of 2 *N* sodium hydroxide were added simultaneously during 25 minutes causing an orange oil to separate. After an additional 15 minutes of cooling and stirring, the mixture was extracted with three 100-ml. portions of ether and these washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure. Distillation of the resulting 29.4 g. of brown oil produced 27.4 g. (81%) of a pale yellow viscous oil, b.p. 164–168° (0.2 mm.), $n^{25}D$ 1.4903.

N-Carbobenzoxy-β,β-diethoxyalanine Hydrazide (X).—In a 125-ml. erlenmeyer flask 27.35 g. (0.080 mole) of ethyl N-carbobenzoxy-β,β-diethoxyalanate, 12 ml. of 85% hydrazine hydrate and 25 ml. of absolute ethanol were shaken until homogeneous and kept at room temperature for 20 hr. The crystals which formed were collected, rinsed with 20 ml. of 50–50 ethanol–ether and dried, giving 16.5 g. of solid, m.p. 139.5–140.5°. The filtrate yielded an additional 6.0 g., m.p. 139.5–140.5°, and 0.6 g., m.p. 134–136°, for a total of 23.1 g. (89%). A sample was recrystallized from ethanol–ether for analysis, m.p. 139.5–140.5°.

Anal. Calcd. for $C_{15}H_{23}N_3O_5$: C, 55.33; H, 7.13. Found: C, 55.47; H, 7.03.

Stability of N-Carbobenzoxy-β,β-diethoxyalanine Hydrazide (X) toward 1 *N* Hydrochloric Acid.—In 3 ml. of 1 *N* hydrochloric acid[14] at 0–5° was dissolved 0.34 g. (0.0010 mole) of N-carbobenzoxy-β,β-diethoxyalanine hydrazide, m.p. 139.5–140.5°. After 5 minutes at this temperature the solution was made alkaline by slow addition of a solution of 0.28 g. (0.0020 mole) of potassium carbonate in 3 ml. of water. The white flocculent precipitate which separated was collected on a filter, dried and recrystallized from absolute ethanol. A total of 0.25 g. of solid, m.p. 139.5° and mixed m.p. with starting material, 138–139°, was obtained.

N-Carbobenzoxy-β,β-diethoxyalanylglycine (XII).—A mixture of 1.00 g. (0.0030 mole) of N-carbobenzoxy-β,β-diethoxyalanine hydrazide and 9 ml. (0.0090 mole) of 1 *N* hydrochloric acid was stirred mechanically at 0–5° for 3 minutes until the hydrazide was dissolved and then 10 ml. of dioxane added. Immediately a solution of 0.25 g. (0.0036 mole) of sodium nitrite in 3 ml. of water was added with stirring over a period of one minute, followed quickly by the addition of a solution of 0.45 g. (0.0060 mole) of glycine and 1.38 g. (0.010 mole) of potassium carbonate in 5 ml. of water. Stirring was continued 1 hr., the latter half without cooling. The resulting clear solution was concentrated under reduced pressure at less than 45°. The gelatinous residue was added to 15 ml. of water and the resulting suspension filtered and dried, giving 0.05 g. of solid, m.p. 142–148°. Extraction of the clear filtrate with ether yielded 0.015 g. of additional solid, m.p. 149–150°. Upon acidification of the aqueous layer, extraction of the oil which separated with ether and concentration of the extracts, there was obtained 1.09 g. of tiny white needles, m.p. 111–115°. This was dissolved in 3 ml. of ethanol, diluted with 20 ml. of hot water and seeded. Upon cooling, the solution became milky and tiny needles replaced this milkiness only on long standing at room temperature. The needles, when collected, weighed 0.96 g. (83%), m.p. 119–120°. Further recrystallization raised the m.p. to 119.5–121°.

Anal. Calcd. for $C_{17}H_{24}N_2O_7$: C, 55.43; H, 6.57; neut. equiv., 368. Found: C, 55.59; H, 6.44; neut. equiv., 378.

Methyl N-Carbobenzoxy-β,β-diethoxyalanylglycinate (XIII).—A suspension of 0.37 g. (0.0010 mole) of N-carbobenzoxy-β,β-diethoxyalanylglycine, m.p. 120–122°, in 50 ml. of ether was treated in portions with excess ethereal diazomethane[15] causing gas evolution as the suspended solid dissolved. After 20 minutes at room temperature the solution was concentrated to 2 ml., and the rosettes which then slowly formed were collected and dried, giving 0.35 g. (92%) of white crystals, m.p. 94–96°. A sample was recrystallized from ether–petroleum ether (40–60°), m.p. 94.5–96°.

Anal. Calcd. for $C_{17}H_{24}N_2O_7$: C, 56.54; H, 6.85. Found: C, 56.83; H, 7.09.

N-Carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteine (XIV and XV).—A mixture of 26.1 g. (0.080 mole) of N-carbobenzoxy-β,β-diethoxyalanine hydrazide, 240 ml. (0.240 mole) of 1 *N* hydrochloric acid and 240 ml. of dioxane was stirred mechanically at 0°, whereupon the hydrazide dissolved rapidly. After 10 minutes a solution of 6.6 g. (0.096 mole) of sodium nitrite in 72 ml. of water was added with continued stirring at 0° during one minute causing a cloudiness. Immediately, a previously prepared solution of 21.1 g. (0.100 mole) of S-benzyl-L-cysteine[7] and 41.5 g. (0.300 mole) of potassium carbonate in 120 ml. of water was added over about 4 minutes at 0–5°. The resulting oily suspension was stirred with cooling for 30 minutes and without cooling for another 60 minutes, whereupon it became an essentially clear yellow solution which was then concentrated under reduced pressure to a thick white paste of tiny needles. These were suspended in 700 ml. of water and stirred with 150 ml. of chloroform into which they were quickly extracted.[16] Without separating the layers, the mixture was acidified to congo red with about 160 ml. of 3 *N* hydrochloric acid and the extraction of the resulting free organic acid completed with two additional 120-ml. portions of chloroform. The combined extract was washed with two 100-ml. portions of water, dried over sodium sulfate, filtered and concentrated under reduced pressure on the steam-bath. The clear red residue (40 g.) crystallized from a mixture of 75 ml. of benzene and 110 ml. of petroleum ether (60–68°) only as a gelatinous precipitate which was

(11) L. I. Smith and K. L. Howard, *Organic Syntheses*, **24**, 53 (1944).

(12) Reference 5, p. 518.

(13) H. E. Carter, R. L. Frank and H. W. Johnson, *Org. Syntheses*, **23**, 13 (1943).

(14) It was found that in all cases three equivalents of strong acid was required to effect complete solution of this hydrazide.

(15) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 166, note 3.

(16) It should be noted here that the sodium and potassium salts of the product were more soluble in chloroform than in water even though this would not be expected.

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used directly in the preparation of the methyl ester described below.

In a similar experiment starting with 11.3 g. (0.035 mole) of the hydrazide there was isolated 14.1 g. (80%) of a solid, m.p. 95–109°, which was presumably a mixture of diastereoisomers.

Anal. Calcd. for $C_{25}H_{32}N_2O_7S$: neut. equiv., 504. Found: neut. equiv., 513.

In another experiment starting with 32.5 g. (0.100 mole) of the hydrazide, only 15.9 g. (31%) of crystalline solid was obtained, but this was apparently largely the (+)-isomer since it was subsequently converted to the (+)-methyl ester, m.p. 131–132°, $[\alpha]^{27}D$ 17.8° (*c* 2.8, chloroform) in 82% yield.

(+)-Methyl N-Carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteinate[8] (XVII).—A solution of the crude N-carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteine from the preceding preparation in 150 ml. of benzene was treated slowly with excess diazomethane in ether while stirring at 5°, causing the separation of a crystalline precipitate. This was collected after 20 hr. at room temperature, washed with a mixture of benzene and petroleum ether (40–60°) and dried. The 24 g. of crystals, m.p. 116–120° with softening at 110°, was recrystallized from a mixture of benzene and petroleum ether (90–100°) to afford 10.1 g. (25% calculated from the hydrazide and based on the total amount of all isomers possible) of white crystals, m.p. 130–131.5°. Two similar runs gave yields of 26%, m.p. 131–132°, and 27%, m.p. 130–131°. Further recrystallization raised the m.p. to 131.0–131.5°, $[\alpha]^{27}D$ +17.8°, +17.9° (*c* 2.8, 1.8, chloroform).

Anal. Calcd. for $C_{26}H_{34}N_2O_7S$: C, 60.23; H, 6.61. Found: C, 60.25; H, 6.44.

The filtrates from above were concentrated to yield 11.7 g. of crystals, m.p. 109–112°, $[\alpha]^{27}D$ −9.7°, and 1.8 g. of amorphous solid which were used without further purification in the preparation of (−)-sodium N-carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteinate described below.

(−)-Sodium N-Carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteinate.—The 11.7 g. of solid, m.p. 109–112°, and 1.8 g. of amorphous methyl N-carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteinate from the preceding preparation were dissolved in 40 ml. of dioxane with slight warming, cooled to room temperature and treated with 8 ml. of 5 *N* sodium hydroxide. After 50 minutes with occasional shaking at room temperature, the two-phase system was diluted with 400 ml. of water, causing first a clear solution and then an oily suspension. This was extracted well with chloroform (in which sodium N-carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteinate is quite soluble) and the combined extract washed with two 20-ml. portions of water, dried over sodium sulfate, filtered and concentrated to a viscous yellow sirup. The latter crystallized from 40 ml. of absolute ethanol at room temperature upon seeding and then diluting with 30 ml. of petroleum ether (60–68°) when rosettes began to grow. After two days the crystals were collected, rinsed with a mixture of ethanol and petroleum ether (40–60°) and dried, affording 2.0 g., m.p. 169–173°, $[\alpha]^{25}D$ −18.6° (*c* 1.7, chloroform). From the concentrated filtrate was obtained 1.7 g. of fluffy needles, m.p. 167–171°, and from the original aqueous layer an additional 1.5 g., m.p. 165–170°.

(−)-N-Carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteine (XIV).—Several samples of (−)-sodium N-carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteinate representing material melting in the range of 165–175° were combined (2.7 g., 0.0051 mole) and dissolved in 75 ml. of water by warming. The gelatinous precipitate which resisted solution was removed by filtration and the clear solution acidified by dropwise addition of 6 *N* hydrochloric acid producing an oily suspension which coagulated and solidified overnight. The solid was collected, pressed on the filter, dissolved in chloroform, dried over sodium sulfate and concentrated to an almost colorless sirup which changed to a suspension of fine white crystals when ether was added. Upon isolating a small portion (155 mg.) of these crystals, triturating them with ether, collecting and drying, they melted at 126.0–126.5°, $[\alpha]^{29}D$ −13.5° (*c* 1.6, chloroform).

Anal. Calcd. for $C_{25}H_{32}N_2O_7S$: C, 59.53; H, 6.38. Found: C, 59.46; H, 6.51.

(−)-Methyl N-Carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteinate (XVI).—The bulk of the ether suspension of (−)-N-carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteine from the preceding preparation (0.0048 mole) was treated in portions with excess ethereal diazomethane while cooling and swirling, resulting in gas evolution but no visible change in the suspended material. After standing overnight the suspension was concentrated, petroleum ether (40–60°) added, the suspension concentrated again to 40 ml. and the fine white precipitate collected and dried. The 2.1 g. (84%) of solid melted at 114.5–116° with softening at 112°, $[\alpha]^{27}D$ −16.9° (*c* 2.1, chloroform). An additional 0.10 g. (88% total), m.p. 111–114°, was obtained from the filtrate. A sample which was recrystallized by dissolving in ether and adding petroleum ether (40–60°) melted at 116.0–116.5°.

Anal. Calcd. for $C_{26}H_{34}N_2O_7S$: C, 60.23; H, 6.61. Found: C, 60.49; H, 6.65.

(+)-N-Carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteine (XV).—In a 25-ml. erlenmeyer flask 0.52 g. (0.0010 mole) of (+)-methyl N-carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteinate, m.p. 131–132°, $[\alpha]^{27}D$ 17.8° (*c* 2.8, chloroform), was dissolved with stirring and slight warming in 3 ml. of dioxane. Then 1.5 ml. (0.0015 mole) of 1 *N* sodium hydroxide was added dropwise with stirring over a period of 5 minutes and stirring continued 45 minutes longer, the solution becoming essentially clear after 15 minutes. Gradual dilution with 20 ml. of water produced a cloudiness which was removed by treating with Norit and filtering. The clear solution was acidified to congo red by dropwise addition of 1 *N* hydrochloric acid with rapid stirring and the white gelatinous precipitate which separated was stirred 45 minutes, filtered, washed with water and sucked dry on the filter affording 0.45 g. (89%), m.p. 118–122°. Another run in which the precipitated acid was extracted into chloroform, dried, concentrated and recrystallized from a mixture of benzene and petroleum ether (60–68°) yielded 0.29 g. (57%), m.p. 129–133°, which could not be improved by further recrystallization.

(+)-Ethyl β,β-Diethoxyalanyl-L-cysteinate Hydrochloride (XIX).—In a 250-ml. three-necked flask equipped with a mechanical stirrer, drying tube containing soda-lime and nitrogen inlet was placed 40 ml. of liquid ammonia and 1.04 g. (0.0020 mole) of (+)-methyl N-carbobenzoxy-β,β-diethoxyalanyl-S-benzyl-L-cysteinate, m.p. 130–131.5°, and a pinch of iron rust added. While the suspension was stirred, 0.18 g. (0.008 mole) of sodium was added in 0.02-g. pieces during two minutes, the characteristic blue color disappearing almost immediately after each addition until the reduction was complete, whereupon the color persisted. (During this process the original white suspension first dissolved completely and then a new white suspension formed.) Almost immediately, 0.70 g. (0.005 mole) of ammonium sulfate was added, whereupon the color gradually disappeared. The ammonia was evaporated under a stream of nitrogen during 1 hr., the white residue treated with 2 ml. of water and the gray solution neutralized to Alkacid test paper with 42 drops of 6 *N* sulfuric acid which produced a short-lived gas evolution and a strong odor of hydrogen sulfide at each addition. While the neutral solution was stirred, it was treated slowly with 25 ml. of absolute ethanol, causing the separation of a white granular precipitate which was removed by filtration and discarded. The clear colorless filtrate was concentrated under reduced pressure below 40° to a yellow sirup (which always crystallized spontaneously in later runs). It was dissolved in 30 ml. of absolute ethanol, this saturated with anhydrous hydrogen chloride while cooling and after 2 hr. at room temperature concentrated under reduced pressure. Fresh solvent was added and this also removed, leaving an orange moist cake of crystals which was triturated with 1.5 ml. of methyl ethyl ketone. The solid was collected on a filter stick, rinsed with 1 ml. of methyl ethyl ketone, then with ether and dried under diminished pressure at 70°. The almost white crystalline product weighed 249 mg., m.p. 168–170° (micro block), $[\alpha]^{29}D$ +25.5° (*c* 0.64, chloroform).

Anal. Calcd. for $C_{12}H_{25}N_2O_5SCl$: C, 41.80; H, 7.28; alkoxyl (calcd. as 3 ethoxyl), 39.25. Found: C, 42.17; H, 7.01; alkoxyl (ethoxyl), 39.58.

A sample of the product dissolved in 10% sodium hydroxide and treated with aqueous sodium nitroprusside

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solution gave a deep red color indicating the presence of a sulfhydryl group.

Hopkins reagent was of no value in isolating this product. When added to an acidified aqueous solution of the residue after the liquid ammonia was removed, it sometimes caused a yellow color but gave no precipitate. The final crystalline hydrochloride also failed to give a precipitate with this reagent.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Studies on the Occurrence and Structure of Acetylandromedol (Andromedotoxin)

BY W. H. TALLENT, MARY L. RIETHOF AND E. C. HORNING

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A procedure for the detection of acetylandromedol in plant extracts was developed through use of paper electrophoresis with borate buffer solutions. Positive results were found for some but not all species of *Kalmia, Leucothoe, Lyonia, Pernettya, Pieris* and *Rhododendron*. A particularly good source was found in *K. angustifolia* var. *caroliniana*. New evidence indicated that the empirical formula for andromedol is $C_{20}H_{34}O_6$, and that acetylandromedol, grayanotoxin I and rhodotoxin are identical and have the formula $C_{22}H_{36}O_7$.

The reported toxicity to stock of *Andromeda, Kalmia, Leucothoe* and *Lyonia* species indicates that a number of plants of the *Ericaceae* in addition to those of the genus *Rhododendron* contain physiologically active compounds. Acetylandromedol,[1] isolated[2] from leaves of *Rhododendron maximum*, was found to be a potent hypotensive agent,[3] and in order to determine if commonly occurring species of these genera contained acetylandromedol or related substances a survey was made of a number of plants of the *Ericaceae* with reported or potential physiological activity. These included *Andromeda japonica* from which Eykman[4] isolated in 1882 a crude toxic substance to which the name asebotoxin was given, and *Rhododendron luteum*, reported by Xenophon to be the source of a poisonous honey given to Grecian soldiers in an early campaign in Asia Minor. It was necessary to develop a method for the identification of acetylandromedol in plant samples, and this work is described in Part I together with the results of a limited survey made for ten genera in the *Ericaceae*.

Part II describes further chemical studies on acetylandromedol.

I. Plant Studies

Acetylandromedol is known to contain a 1,2-glycol structure.[2] This suggested the possibility of utilizing paper electrophoresis with a borate electrolyte for the separation and identification of plant components in the acetylandromedol fraction. The rate of migration of a borate diol complex during paper electrophoresis depends on the borate–diol equilibrium and upon the absorption characteristics of the complex with regard to cellulose. In dilute borate solutions a 2:1 diol–borate complex may be formed in addition to a 1:1 complex, and this effect usually can be recognized by studying the effect of borate concentration changes. The 2:1 diol–borate complex is the stronger acid of the two.[5]

It was found that acetylandromedol migrated toward the anode on paper electrophoresis with sodium tetraborate solutions. The vanillin–perchloric acid spray of Godin[6] was an excellent visualizing reagent. With 0.05 *M* sodium tetraborate concentration, a single migrating species was observed (curve B, Fig. 1), and with 0.01 *M* electrolyte concentration two ionic species were observed (1a and 1b in curve D, Fig. 1). The principal species under the latter conditions was assumed to be the expected 1:1 borate–diol complex. The secondary species with higher mobility occurring in very dilute borate solution was assumed to be the 2:1 complex. An alternate but less likely explanation for the two ionic species is that they represent borate complexes with two different pairs of hydroxyl groups of acetylandromedol.[5a,5e]

When this procedure was used with crude acetylandromedol fractions from *Rhododendron maximum* leaves, the characteristic behavior of acetylandromedol with different borate concentrations was exhibited (curves A and C in Fig. 1), and compounds responsible for two additional colored areas (marked 2 and 3 in curves A and C) were indicated by the spray reagent. The recognition of these and other compounds in successive runs was aided materially by the strong and distinctive colors produced by the Godin reagent.

This procedure was applied to a number of plant specimens from the U. S., Cuba and Costa Rica. Figure 2 shows examples of the results obtained after electrophoresis. Data taken from such electrophoretograms are summarized in Table I. The presence of acetylandromedol was checked, where it occurred, in two concentrations of sodium tetraborate electrolyte (0.01 and 0.05 *M*) in order to confirm the characteristic equilibrium behavior.

(1) This is proposed in Part II as a change in name from andromedotoxin.

(2) H. B. Wood, V. L. Stromberg, J. C. Keresztesy and E. C. Horning, THIS JOURNAL, **76**, 5689 (1954).

(3) N. C. Moran, P. E. Dresel, M. E. Perkins and A. P. Richardson, *J. Pharmacol. Exp. Therap.*, **110**, 415 (1954); N. C. Moran, M. E. Perkins and A. P. Richardson, *ibid.*, **111**, 454 (1954). In normal dogs, intravenous administration of 5–10 mcg./kg. led to 20–40% lowering of blood pressure. Levels required for hypotensive action in humans were slightly higher.

(4) J. F. Eykman, *Rec. trav. chim.*, **1**, 225 (1882).

(5) Details on the effect of borate concentration and other factors on borate–diol complex formation are given in (a) H. S. Isbell, J. F. Brewster, N. B. Holt and H. L. Frust, *J. Research Nat. Bur. Standards*, **40**, 129 (1948); (b) J. Boeseken, *Advances in Carbohydrate Chem.*, **4**, 189 (1949); (c) C. A. Zittle, *Advances in Enzymology*, **12**, 493 (1951); R. Consden and W. M. Stanier, *Nature*, **169**, 783 (1952), and (e) D. J. Bell and D. H. Northcote, *Chemistry & Industry*, 1328 (1954).

(6) P. Godin, *Nature*, **174**, 134 (1954).

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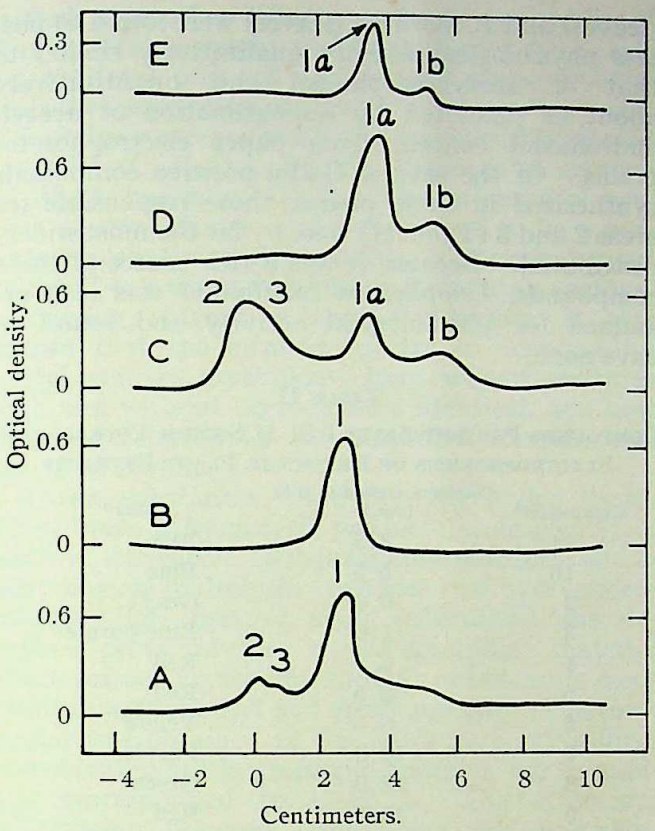

Fig. 1.—Densitometer tracings of paper electrophoretograms obtained with 0.05 *M* sodium tetraborate solution for crude *Rhododendron maximum* extract (curve A) and acetylandromedol (curve B) and of paper electrophoretograms obtained with 0.01 *M* sodium tetraborate solution for crude *Rhododendron maximum* extract (curve C) and acetylandromedol (curve D). Grayanotoxin I from *Leucothoe grayana*[11] was used for curve E with 0.01 *M* sodium tetraborate solution. The times were 4 hours for A and B, and 6 hours for C, D and E. A vanillin–perchloric acid spray was used as a visualizing reagent. Colors are noted in Table II.

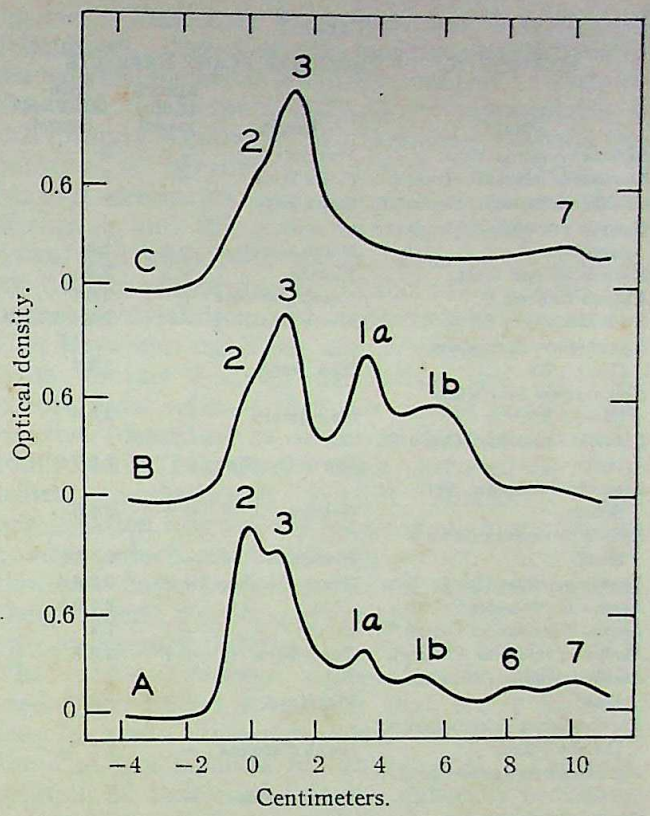

Fig. 2.—Densitometric tracings of paper electrophoretograms obtained with 0.01 *M* sodium tetraborate solution (6 hours) for extracts of *R. japonicum* (curve A), *K. angustifolia* (curve B) and *Leucothoe axillaris* (curve C). A vanillin–perchloric acid spray was used as a visualizing reagent.[6] Colors are in Table II. Bioassays for hypotensive activity were negative for the sample used for C, while a low order of activity was found for A. The plant used for B contained the highest amount of acetylandromedol of all of those investigated.

It was not possible to secure quantitative data relating to acetylandromedol, but by working with selected quantities of the extracts and by estimating the intensity of color it was found that some degree of differentiation could be made between plants containing much acetylandromedol and those containing little. This is indicated by the ratings of + to +++ in Table I. The highest concentration observed for acetylandromedol was in *K. angustifolia* var. *caroliniana*, and in separate isolation experiments (on a large scale) it was found that the yield of acetylandromedol from fresh leaves of this plant was about 0.06–0.09%.[7]

Rhododendron species showed a considerable variation in their acetylandromedol content; *R. calendulaceum*, *R. canadense* and *R. canescens* gave completely negative results. *R. luteum*, believed to be the source of the poisonous *Rhododendron* honey mentioned by Xenophon and Dioscorides, contained acetylandromedol. It was not possible to examine the flowers of this species, but flowers of *R. catawbiense* contained more acetylandromedol than the leaves. Two common species of the genus *Kalmia* were examined. *K. latifolia* ("mountain laurel"), although reported to be toxic to stock, contained far less acetylandromedol than *K. angustifolia* ("sheep-kill"). *Lyonia* and *Leucothoe* species are also regarded generally as being poisonous to stock, and *Leucothoe editorum* was found to contain acetylandromedol in a quantity comparable to *R. maximum* and *R. luteum*. *Lyonia* species contained little (*L. mariana*) or no acetylandromedol.

There has been uncertainty about the identity or non-identity of the substances described by Eykman[4] (asebotoxin, from *A. japonica*), de Zaayer[8] (andromedotoxin, m.p. 228–229°, from *Andromeda* species), Hardikar[9] (andromedotoxin, m.p. 258°, from an unidentified *Rhododendron* species), Makino[10] (rhodotoxin, m.p. 245°, from *R. hymenanthes*), Takemoto[11] (grayanotoxin I, m.p. 259–260°, from *L. grayana*) and acetylandromedol from *R. maximum*[2] and *K. angustifolia*. Through the courtesy of Dr. Takemoto, samples were exchanged and compared. The infrared spectra of all samples were identical[11] (rhodotoxin from *R. metternichii*, grayanotoxin I, and acetylandromedol). The borate electrophoresis behavior

(7) Yields from *R. maximum* collected in North Carolina averaged about 0.008%. This was estimated as a ++ concentration.

(8) H. G. de Zaayer and P. C. Plugge, *Arch. ges. Physiol.*, **40**, 480 (1886–1887).

(9) S. W. Hardikar, *J. Pharmacol. Exptl. Therap.*, **20**, 17 (1922).

(10) M. Makino, Okayama-Igakki-Zasshi, **39**, 2099 (1927); **40**, 138 (1928); [*C. A.*, **23**, 1691, 3027 (1929)].

(11) T. Takemoto, Y. Nishimoto, H. Meguri and K. Katayama, *J. Pharm. Soc. Japan*, **75**, 1441 (1955), and ref. 15.

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TABLE I

EXAMINATION OF ERICACEAE PLANT EXTRACTS

Plant[a]	Origin	Acetylandromedol	Unidentified[b] compd.
Befaria racemosa Vent.	Florida	–	2
Gaultheria donnellii Sleumer	Costa Rica	–	2
Gaultheria donnellii Sleumer[c]	Costa Rica	–	2
Kalmia angustifolia L. (var. *caroliniana*)	North Carolina	+++	2,3
Kalmia hirsuta Walt.	Florida	–	2,3
Kalmia latifolia L.	North Carolina	+	2,3,6
Kalmia latifolia L.[c]	North Carolina	–	2,3,4,5,7,8,9
Leiophyllum buxifolium (Berg.) Ell.	New Jersey	–	2,3,7
Leiophyllum buxifolium (Berg.) Ell.[c]	New Jersey	–	2,3,4
Leucothoe axillaris (Lam.) D. Don	North Carolina	–	2,3,7,8
Leucothoe editorum Fern. et Schub.	Georgia	++	2,3,8
Lyonia ferruginea (Walt.) Nutt.	Florida	–	2,5,10
Lyonia mariana (L.) D. Don	North Carolina	+	2,3,4,6
Lyonia myrtilloides Griseb.	Cuba	–	2,3,6,8
Lyonia myrtilloides Griseb.[d]	Cuba	–	2,3
Pernettya coriaceae Klotzsch	Costa Rica	++	2,3,7
Pieris japonica (Thunb.) D. Don[e]	Maryland	+++	2,3,7
Rhododendron calendulaceum (Michx.) Torr.	South Carolina	–	2
Rhododendron canadense (L.) Torr.	Pennsylvania	–	2
Rhododendron canescens (Michx.) Sweet	North Carolina	–	2,4
Rhododendron catawbiense Michx.	North Carolina	++	2,3,5,6
Rhododendron catawbiense Michx.[c]	Maryland	+++	2,3
Rhododendron japonicum (Gray) Suringar	Maryland	+	2,3,6,7
Rhododendron luteum Sweet	Maryland	++	2,3,7,8,9
Rhododendron ponticum L.	Maryland	++	2,3
Rhododendron maximum L.	North Carolina	++	2,3
Vaccinium consanguineum Klotzsch	Costa Rica	–	2,3,10
Vaccinium myrsinites Lam.	Florida	–	2

[a] Leaves or leaves and stems were used unless otherwise specified. [b] See Table II for additional data. [c] Flowers. [d] Bark. [e] *Andromeda japonica*.

for grayanotoxin I was identical with that observed for acetylandromedol (curve E, Fig. 1). The paper electrophoresis patterns for extracts of *A. japonica* also showed areas 1 and 1a and 1b, and it therefore seems likely that all of these descriptions relate to the same compound.

In carrying out this work, it was evident that certain reservations were required. Experiments with different species showed that a number of compounds giving positive color reactions were always present in the crude fractions (Tables I and II). One or more of these compounds, or possibly other substances which did not give a Godin color, might well exhibit physiological activity similar to that of acetylandromedol. In order to examine this possibility, several fractions from plants reported to be toxic and found to contain several Godin-positive compounds but little or no acetylandromedol were compared with fractions from *K. angustifolia* with regard to their physiological activity. These fractions included extracts of *L. axillaris* (leaves), *L. myrtilloides* (leaves) and *K. latifolia* (flowers), and in these cases it was found that the physiological activity was negligible. Extracts from *R. japonicum* (leaves), *R. latifolia* (leaves) and *L. mariana* (leaves) were found to possess physiological activity qualitatively similar to that of acetylandromedol and quantitatively about as predicted by approximation of acetylandromedol content from paper electrophoretograms. Of the several Godin-positive compounds synthesized in these plants, those responsible for areas 2 and 3 (Table II) were by far the most widely distributed. Because it was a rich source of these compounds, *Leiophyllum buxifolium* was also examined for physiological activity and found to have none.

TABLE II

COMPOUNDS PRESENT AFTER 0.01 *M* SODIUM TETRABORATE ELECTROPHORESIS OF ERICACEAE PLANT EXTRACTS

Compound[a]	Distance moved in 6 hr. (cm.)[b]	Color[c]
1a	3.5	Blue
1b	5.5	Blue
2	0.0	Gray
3	1.0	Blue-purple
4	3.5	Red
5	6.5	Red
6	8.5	Yellow
7	10.0	Purple
8	12.0	Green
9	13.5	Red
10	14.0	Blue

[a] Diol complexes 1a and 1b are derived from acetylandromedol (see Fig. 1). [b] Conditions: 7.5 volts per cm., 1–2 ma., 6 hours, corrected for electroendosmosis. [c] After spraying with vanillin–perchloric acid reagent.[6]

These results do not exclude the possibility that a second compound with the same characteristics as acetylandromedol may exist, but the chemical and bioassay data obtained up to the present time point to the identification of a common substance as the principal physiologically active agent of the Ericaceae.[12] The compounds responsible for colored areas described here as 2 and 3 are widely distributed through the family, but their presence or absence has no apparent relationship to the acetylandromedol content of the plant.

II. Chemical Studies

The presence of physiologically active materials in *Rhododendron*, *Kalmia*, *Pieris* (*Andromeda*) and *Leucothoe* species has been confirmed in every laboratory that has studied the problem, but there has been no general agreement on the physical properties and empirical formulas of the agent or agents responsible for the activity. (The two most recent formulas are $C_{19}H_{30}O_6$ and $C_{22}H_{36}O_7$.) The work in the previous section points to the occurrence of a common substance throughout these plants, and it is proposed that this be named acetylandromedol.[13]

Acetylandromedol (from *R. maximum*) was sub-

(12) Investigations of grayanotoxins I, II and III (see Part II) point to three substances with physiological activity. The Japanese workers used a fresh-water fish for their work; the activity described in this paper relates only to hypotensive action studied in anesthetized dogs. There is a possibility that andromedol (grayanotoxin III) accompanied acetylandromedol in crude fractions, but we have not observed this compound in our isolation work up to the present time.

(13) It is desirable to use a name which reflects the functional groups of the molecule and which permits a systematic naming of derivatives. The parent polyhydroxy compound has been named andromedol, following the plant first used by Eykman[4] and de Zaayer and Plugge.[5]

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mitted to another laboratory for X-ray studies.[14] The molecular weight was found to be 410.2, calculated from unit cell and density measurements, with the assumption of four molecules per unit cell. This value corresponded to the previously suggested formula[2] ($C_{19}H_{30}O_6$) and the elements of acetone ($C_{22}H_{36}O_7$ has m.w. 412.5). The presence of acetone of crystallization was considered to be a possible explanation for this result; the crystals used in the X-ray work were obtained from an acetone-containing solvent mixture. However, it was known that the infrared spectra of acetylandromedol samples crystallized from solvent mixtures with and without acetone were identical, and new evidence relating to the empirical formula was therefore sought.

Three substances were brought under study. These were a hydrolysis product (andromedol), a benzoyl derivative (tribenzoylandromedol), and a dehydration–hydrolysis product (anhydroandromedol). The first of these substances was described previously[2] as a non-crystalline material which formed crystalline adducts of indefinite composition with methyl and ethyl acetate. The compound was obtained in this work as a crystalline, non-solvated but hygroscopic material, whose analysis corresponded to $C_{20}H_{34}O_6$. The structural relationship between andromedol and acetylandromedol is the same as that between grayanotoxin III and grayanotoxin I[15] (to which the formula $C_{22}H_{36}O_7$ was assigned), and andromedol and grayanotoxin III should therefore be identical. A more direct comparison is not possible since grayanotoxin III has been described only as a solvated material with one-half molecule of water or ethyl acetate.[15] We have not observed this compound as a component of *Rhododendron* or *Kalmia* species, but it may be present in low concentration in these plants.

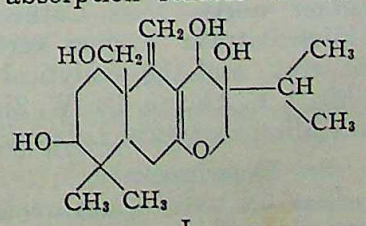
Miyajima and Takei[15] also described anhydrograyanotoxin III as a compound obtainable from both grayanotoxin III and grayanotoxin I. In our work, acetylandromedol was subjected to acid treatment in aqueous solution, and from the mixture of products there was isolated by countercurrent distribution a crystalline substance of formula $C_{20}H_{32}O_5$. The melting point (and empirical formula) is in agreement with that given by Miyajima and Takei[15] for anhydrograyanotoxin III. Additional points of comparison are lacking. It is likely that these compounds are identical, but melting points in this series are not a reliable index of identity.

The calculated and found C, H analytical values for acetylandromedol, rhodotoxin and grayanotoxin I reported in this and other papers[2,9–11,15] do not distinguish between the formulas $C_{19}H_{30}O_6$ and $C_{22}H_{36}O_7$ (different acetyl analyses have been reported; these may have been due to analytical difficulties). However, the reported derivatives of the isolated materials should be subject to correlation with the formula $C_{20}H_{34}O_6$ for andromedol, if this formula is correct. We therefore reviewed the question of benzoyl and acetyl derivatives. A benzoyl derivative was prepared from acetylandromedol, and this compound was found by analytical and ultraviolet spectra data to correspond to tribenzoylandromedol (Table III). The tribenzoylacetylandromedol (tribenzoylgrayanotoxin I) of Miyajima and Takei and of Yamashita[15] represents another benzoyl derivative, and the analytical data indicate that our earlier benzoyl derivative (described as dibenzoylandromedotoxin[2]), confirmed by Takemoto[11] was a methanol solvate of tribenzoylandromedol. Further studies of the benzoylation reaction are required to determine the point at which ester exchange occurs. Acetyl derivatives have been reported in several papers; these include diacetylandromedol (Table III) and two apparently different tetraacetyl derivatives.[15] The carbon–hydrogen values for diacetylandromedol correspond so closely that either formula may be used; the acetyl values, however, point to the $C_{20}H_{34}O_6$ formula for andromedol. The acetylation of andromedol to the naturally occurring acetylandromedol has not been accomplished, and a triacetylandromedol is not known.

A remaining problem concerns the structure of isopropylideneanhydroandromedotoxin,[2] which should now correspond, on the basis of its infrared spectrum, to an isopropylideneanhydroacetylandromedol with one double bond. The reaction leading to this compound is under investigation.

Table III contains newly determined analytical data for acetylandromedol and a number of derived compounds. These data, with the comparisons made as a consequence of Takemoto's recent reisolation of grayanotoxin I and rhodotoxin mentioned in Part I and the molecular weight determination for acetylandromedol,[14] indicate that the correct formula for andromedol is $C_{20}H_{34}O_6$ and that the acetyl derivatives, grayanotoxin I, rhodotoxin and acetylandromedol, are identical.

Recent work on grayanotoxin II has resulted in a structural proposal (I).[16] It seems reasonable to accept a close structural relationship between acetylandromedol and a second polycyclic polyhydroxy compound isolated from *L. grayana*, but our observations do not particularly support structure I as a basic system subject to elaboration for acetylandromedol. Anhydroandromedol and andromedol were examined for evidence of unsaturation by ultraviolet absorption studies to 195 mμ. Both



I

(14) We are indebted to Dr. Ray Pepinsky, Pennsylvania State University, for cell measurements and the molecular weight determination.

(15) S. Miyajima and S. Takei, *J. Agr. Chem. Soc. Japan*, **10**, 1093 (1934); **12**, 497 (1936) [*C. A.*, **29**, 1133 (1935); **30**, 6747 (1936)]. Grayanotoxin I was first described by O. Kubo, *Arch. Exptl. Pathol. Pharmakol.*, **67**, 111 (1912) (as $C_9H_{14}O_3$) and was later studied by M. Yamashita, *Sci. Repts. Tohoku Imp. Univ.*, **31**, 537 (1932) [*Chem. Zentr.*, **104**, [I] 1793 (1933); *C. A.*, **27**, 989 (1933)], *J. Chem. Soc. Japan*, **53**, 664 (1932) [*C. A.*, **27**, 303 (1933)].

(16) M. Nakajima and I. Iwasa, *Botyu Kagaku*, **13**, 11 (1949) [*C. A.*, **44**, 1090 (1950)]; **16**, 28, 32 (1931) [*C. A.*, **46**, 3986, 3987 (1952)]; M. Nakajima and S. Miyajima, *ibid.*, **15**, 28, 30 (1950) [*C. A.*, **44**, 7301 (1950)].

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TABLE III

ANALYTICAL DATA FOR ACETYLANDROMEDOL AND RELATED COMPOUNDS

Compound	Empirical formula	Calcd C	Calcd H	Calcd O	Calcd Acetyl	Found[a,b] C	Found[a,b] H	Found[a,b] O	Found[a,b] Acetyl
Andromedol	$C_{17}H_{28}O_5$	65.36	9.03	..	...	64.81, 64.93	9.11, 9.23	.....	...
	$C_{20}H_{34}O_6$	64.84	9.25	..	...				
Acetylandromedol	$C_{19}H_{30}O_6$	64.38	8.53	27.1	12.14	63.96, 64.04	8.82, 8.86	26.8, 26.9	10.66
	$C_{22}H_{36}O_7$	64.05	8.80	27.2	10.43				
Diacetylandromedol	$C_{21}H_{32}O_7$	63.61	8.14	28.3	21.71	63.55, 63.45	8.61, 8.53	28.1, 27.8	18.38
	$C_{24}H_{38}O_8$	63.41	8.43	28.2	18.94				
Tribenzoylandromedol	$C_{38}H_{40}O_8$	73.06	6.45	..	...	72.45, 72.57	6.64, 6.85	.....	None
	$C_{41}H_{46}O_9$	72.12	6.79	..	...				
Anhydroandromedol	$C_{17}H_{26}O_4$	69.36	8.90	21.7	...	68.33, 68.19	9.17, 9.15	22.8, 22.8	...
	$C_{20}H_{32}O_5$	68.15	9.15	22.7	...				

[a] Carbon, hydrogen and acetyl determinations by Mr. J. F. Alicino, Metuchen, N. J. [b] Direct oxygen determinations by Dr. W. Zimmermann, Melbourne, Australia.

substances showed no ultraviolet absorption. Anhydroandromedol was unaffected by bromine and by hydrogenation conditions, and this may be taken to indicate an ether bridge possibly similar to that found for some steroids. If the empirical formula $C_{20}H_{34}O_6$ for andromedol is correct, a tetracyclic system must be allocated to the parent compound. One of the hydroxyl groups of the 1,2-diol structure evidently is involved in ether formation in anhydroandromedol, since the anhydro-compound does not form a borate–diol complex.

Terminal methyl determinations were made for andromedol, acetylandromedol and anhydroandromedol. These indicate that two or three methyl groups may be tentatively assigned to andromedol. We suspect that andromedol may be a hexahydroxy compound; positive evidence bearing on this point is an active hydrogen determination on anhydroandromedol (four active hydrogens were indicated). In the absence of additional supporting evidence this should not be taken as a definitive structural assignment. There is no strong evidence for the nature of the ring system of andromedol, but the cell measurements for crystalline acetylandromedol suggest that a steroid-like skeleton is possible. The most attractive part of this hypothesis lies in the possibility that suitably substituted steroids may have a direct effect on blood pressure control centers.

Oxidation and dehydrogenation experiments present additional possibilities for further study, and this approach is under investigation.

Acknowledgments.—We are indebted to the Section of Plant Introduction, Agricultural Research Service, U. S. Department of Agriculture, for the collection and identification of plant materials, and to Dr. N. C. Moran for the pharmacological data. Mr. D. L. Rogerson carried out the plant extraction work; Miss Catherine Monaghan and Miss Patricia Wagner performed the spectroscopic work, and the analytical data were supplied by Mr. J. F. Alicino, Dr. W. Zimmermann and the Clark Microanalytical Laboratories.

Experimental[17]

Plant Extractions.—A 500-g. sample of undried plant material was ground in a Wiley mill and suspended in 5 l. of water. The *p*H was adjusted to 7.0–7.5 with barium hydroxide, and the suspension was heated to 90–100° for 1 hour with efficient stirring. It was filtered (Supercel pad) and the filter cake was washed well with hot water. The combined filtrates were concentrated (reduced pressure) to 500 ml.; the *p*H was adjusted to 7.0–7.5 and 4.5 l. of ethanol was added. A precipitate was removed by filtration and washed with alcohol. The filtrate and washes were combined and concentrated to 300 ml. (reduced pressure). The solution was adjusted to *p*H 6.5 and filtered. The filter cake was washed with water, and the solution was concentrated to 300 ml. and continuously extracted with chloroform for 24 hours. The solvent was removed from the organic extract *in vacuo*, and the residue was examined for the presence of acetylandromedol and related compounds by paper electrophoresis.

After the observation was made that *K. angustifolia* was a particularly rich source of acetylandromedol, several large-scale isolation experiments were carried out according to the published procedure.[2] One run, on a 100 lb. scale, gave 28.6 g. of acetylandromedol. The yields were in the range 0.06–0.09% (about ten times that observed for *R. maximum*).

Paper Electrophoresis.—Strips of Whatman #1 paper 42 cm. long and 26.5 cm. wide were used. For solid samples, solutions containing 10 mg. per ml. in ethanol or chloroform were employed. Approximately 0.02 ml. of the solution was applied to the paper. For crude plant extracts, 0.06 ml. of solutions containing 25 mg. per ml. in chloroform or ethanol was used. The mixtures or compounds were spotted at 4 cm. intervals along a center line parallel to the short edge of the paper. The strip was supported at the center line by a glass rod, and the ends dipped about 1 cm. into electrode compartments containing sodium tetraborate solution. The entire system was enclosed in a Lucite box. The strip was allowed to wet by a capillary action, and the separation was carried out at 300 v. (a gradient of 7.5 v. per cm.). This resulted in a current of 1–2 ma. when 0.01 *M* sodium tetraborate was used and 5–6 ma. when the buffer concentration was 0.05 *M*. The time for electrophoresis was 6 hours for a 0.01 *M* buffer and 4 hours for a 0.05 *M* buffer. Acetylandromedol and related compounds were detected by spraying the air-dried strip with a solution prepared just before use by mixing equal volumes of solutions of 3% perchloric acid in ethyl alcohol and 1% vanillin in ethyl alcohol.[6] Electroendosmosis was determined by spotting urea (0.02 ml. of a water solution containing 10 mg./ml.) on the strip and determining its position after electrophoresis by cutting the appropriate part of the strip and spraying it with a 0.5% solution of *p*-dimethylaminobenzaldehyde in 1.0 *N* hydrochloric acid. A yellow spot resulted, the center of which represented "0 cm. moved" for all curves and data reported in this paper.

Optical density measurements were made with a Photo-

(17) All melting points were taken on a Kofler stage. Optical rotations were determined with a Rudolph photoelectric-matching polarimeter. Ultraviolet spectra were taken with Cary Recording Spectrophotometers (Models 11 and 14). Infrared spectra were taken with a Perkin–Elmer Model 21 instrument. Infrared spectra of all new compounds described here have been deposited as Document No. 5130 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting $1.25 for photoprints, or $1.25 for 35 mm. microfilm, by check or money order payable in advance to Chief, Photoduplication Service, Library of Congress. Other spectra are available through a previous paper.[2]

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volt Electronic Densitometer, Model 525. A tungsten light source (no filter) was used, and the sensitivity dial was at 2.

Comparison of Samples.—A sample of grayanotoxin I[18] (identical with rhodotoxin), was compared with acetylandromedol samples from *R. maximum* and *K. angustifolia*. The infrared spectra of all of these materials were identical. The behavior on electrophoresis, including the borate concentration effect, was identical for all samples. Curve E, Fig. 1, shows the characteristic result found with 0.01 *M* buffer solution for the grayanotoxin I sample.

Physiological Activity.—The hypotensive action of crude plant extracts and related materials was determined as described elsewhere.[3]

Acetylandromedol.—The molecular weight of acetylandromedol was determined by measurements of the crystal density and unit cell dimensions.[14] Assuming four molecules per unit cell, the value was 410.2 (calcd. for $C_{22}H_{36}O_7$, 412.5; for $C_{19}H_{30}O_6$, 354.4).

A C-methyl determination showed the presence of at least three such groups (one must be allocated to the acetyl group).

Anal. Calcd. for $C_{22}H_{36}O_7$: C-CH_3, 10.93 (for three). Found: C-CH_3, 9.16, 9.19.

Additional analytical data are in Table III. The sample used for these analyses was prepared for clinical studies; the isolation followed our earlier work.[2]

Diacetylandromedol.—Newly determined analytical data are in Table III. The sample was from a previous preparation.[2]

Tribenzoylandromedol.—Benzoyl chloride (15 ml.) was added to a previously chilled (0°) solution of 500 mg. of acetylandromedol in 60 ml. of pyridine. After 12 hours at 0°, the mixture was added to stirred iced 10% sodium carbonate solution. The suspension was stirred for 1 hour, and the product was extracted with chloroform. The chloroform solution was washed (sodium bicarbonate solution and water), and the solvent was removed under reduced pressure. After trituration of the residue with benzene–hexane, 433 mg. remained; this was crystallized from benzene–methanol to give 295 mg. of colorless crystalline solid, m.p. 213–216°. Recrystallization from chloroform–benzene gave a sample melting at 217–219°, and this was not changed by further recrystallization from methanol–chloroform, chloroform–benzene, methanol–benzene, and ethyl acetate–benzene.

Optical rotation values were found to be $[\alpha]^{24}_{589}$ + 85.5, $[\alpha]^{24}_{436}$ +200.0 (*c* 0.93, chloroform).

Analytical data are in Table III.

The ultraviolet spectrum of this substance in ethanol was qualitatively similar to that of ethyl benzoate. The maxima for the two spectra were at 230 and 228 mμ, respectively. The ϵ_{max} values were 3.71×10^4 and 1.22×10^4. The ϵ_{max} value for the andromedol derivative is therefore in close agreement with that expected for three benzoyl groups (calcd. value 3.66×10^4), and since the acetyl analysis showed no acetyl groups, the structure assigned to this compound is that of tribenzoylandromedol.

The infrared spectrum was similar to that of our previous benzoyl derivative (reported m.p. 226.5–227.5°) except for differences in bands at 9.70 and 9.80 μ. Three carbonyl bands were found at 5.80, 5.85 and 5.90 μ, and a sharp hydroxyl band at 2.80 μ. Since the earlier sample was used for analytical purposes, it was not possible to obtain mixed m.p. or additional analytical data on the original sample. It should be pointed out that the material described previously as "dibenzoylandromedotoxin" was prepared by benzoylation in pyridine at steam-bath temperature, and it was recrystallized for analysis from methanol–benzene. The analytical data and the great similarity in infrared spectra with that from the compound prepared at 0° suggest that the earlier product was a methanol solvate of tribenzoylandromedol (*Anal.* Calcd. for $C_{42}H_{50}O_{10}$: C, 70.57; H, 7.05. Found[2]: C, 70.27; H, 6.78). The occurrence of solvates in this series is not uncommon. The analytical sample for the new benzoyl derivative was recrystallized from chloroform–benzene immediately before analysis and solvation is not indicated. It is not possible to define the relationship of this tribenzoyl derivative to the "tribenzoylgrayanotoxin I" (tribenzoylacetylandromedol) of Yamashita,[15] except that the analytical data point to solvation as a possible explanation. The experimental conditions described here were chosen to allow the use of a large excess of benzoyl chloride, but to avoid ester exchange or dehydration effects which might result from heating the reaction mixture. Since ester exchange occurred in this case at 0°, it is likely that it also occurred in cases where reaction mixtures were heated.

Andromedol.—A solution of 3.0 g. of acetylandromedol in water (135 ml.) and ethanol (30 ml.) containing 15 g. of sodium hydroxide was heated under reflux for 7 hours. The alkali was removed with Amberlite IRC-50 (H+) resin, and the product was extracted with chloroform (continuous extraction). The chloroform solution was reduced to a small volume, and a crystalline material separated slowly. This product, m.p. 224–227° dec., was hygroscopic and could not be recrystallized in satisfactory form.

The infrared spectrum showed no carbonyl band. A strong, broad band at 2.90 μ indicated a hydroxyl group or groups.

Optical rotations were found to be $[\alpha]^{26}_{589}$ −16.7, $[\alpha]^{26}_{436}$ −29.6 (*c* 0.96, ethanol).

Analytical data are in Table III. A C-methyl determination showed at least two such groups.

Anal. Calcd. for $C_{20}H_{34}O_6$: C-CH_3, 8.12 (for two). Found: C-CH_3, 8.10, 8.18.

This compound was water-soluble, and its ultraviolet absorption properties were measured in water solution to 195 mμ. No absorption of any kind was found; this suggests that unsaturation was not present.

When examined by paper electrophoresis with a borate electrolyte, andromedol was found to migrate very much like acetylandromedol. The behavior was similar with different borate concentrations, indicating that the stereochemical relationships of the hydroxyl groups involved in the borate complexes were essentially the same for the two compounds. The Godin color was blue, and sufficiently similar to that from acetylandromedol to make differentiation difficult.

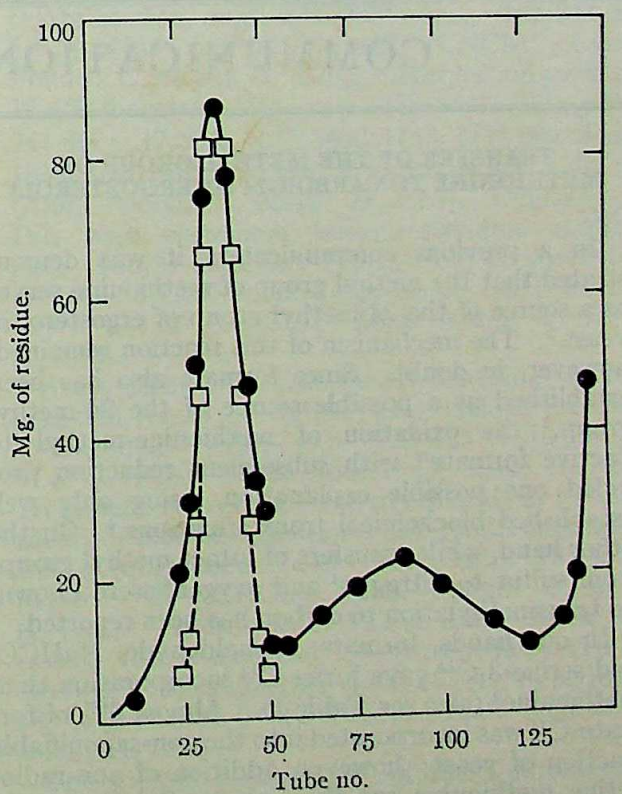

Fig. 3.—Countercurrent distribution of reaction products from treatment of acetylandromedol with acid. The solvent system used was prepared by mixing equal volumes of cyclohexane, ethyl acetate, ethanol and water. The operation was carried out with a 50 tube, 100 ml. per phase apparatus. Tubes 50 to 149 in the figure represent withdrawal fractions of top phase. The closed circles represent experimental points, and the calculated values for the theoretical curve are shown as open squares.

(18) We are indebted to Dr. Takemoto for this sample.

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The physiological activity is under study. Preliminary work indicates that the compound has some degree of hypotensive action, and comparison studies are in progress with andromedol, acetylandromedol and the crystalline adduct of andromedol and ethyl acetate.

Andromedol has not been observed in isolation studies with *R. maximum* and *K. angustifolia* var. *caroliniana*, but it might have been present in low concentration in these plants. It has been reported to be present, along with grayanotoxin I (acetylandromedol) in extracts from *L. grayana*.[15]

Anhydroandromedol.—A solution of acetylandromedol (12.5 g.) in 2.5 l. of water containing 7.5 ml. of concd. sulfuric acid was heated under reflux for 4 hr. The dark mixture was neutralized with sodium hydroxide and filtered to remove polymerized material. The filtrate was extracted with chloroform; the chloroform was removed under reduced pressure to yield 3.8 g. of dark, amorphous material. The usual chromatographic methods (alumina, silica) failed to yield a pure substance. Preliminary small-scale studies indicated that purification by countercurrent distribution might be successful. With a solvent system containing equal parts of water, ethanol, ethyl acetate and cyclohexane (this mixture gives two phases of about equal volume) a separation of components was effected. The separation was carried out with 3.6 g., in a 50-tube apparatus with 100 ml. per phase capacity, and with an arrangement for collecting withdrawal fractions of top phase.

The shape of the major band with a peak concentration in tube 37 was compared with a theoretical curve; Fig. 3 shows the experimental and theoretical values. The close correspondence provides evidence for the purity and homogeneity of this product. The contents of tubes 30 to 45 were combined to yield 1.1 g. of crystalline material, m.p. 223–226° after recrystallization from benzene–ethyl acetate.

The infrared spectrum (Nujol) of this compound showed a broad hydroxy band (2.80 μ) but no evidence of a carbonyl group or unsaturation. The ultraviolet absorption was examined to 195 mμ in water solution, but no evidence of unsaturation was found. The compound did not decolorize bromine in chloroform solution, and an ethanol solution did not absorb hydrogen in the presence of a 10% Pd–C catalyst (the compound was recovered unchanged).

The optical rotation was found to be $[\alpha]^{25}_{589}$ −9.3, $[\alpha]^{25}_{436}$ −15.2 (*c* 0.76, ethanol).

When subjected to electrophoresis on paper with a borate solution, the substance gave a purple Godin color and had a mobility of zero. It displayed no physiological activity.

In addition to the analytical data in Table III, the compound was examined for C–CH_3 and active hydrogen.

Anal. Calcd. for $C_{20}H_{32}O_5$: C–CH_3, 8.53 (for two), 12.80 (for three); active H, 0.86 (for three), 1.14 (for four). Found: C–CH_3, 9.84; active H, 1.04.

The broad band with maximum at tube 90 (Fig. 3) was not characteristic of a pure substance; when material from this tube was examined through paper electrophoresis with a borate solution, two compounds were indicated. Both gave purple Godin colors; one was uncharged and the other moved slightly toward the anode. The mixture showed ultraviolet absorption in ethanol solution (λ_{max} 248 mμ) and therefore consisted in part of an unsaturated compound. Tubes 60 to 110 were combined and attempts to separate the components were not successful.

Tubes 125 to 149 contained dark material which was not investigated.

BETHESDA 14, MD.

COMMUNICATIONS TO THE EDITOR

TRANSFER OF THE METHYL GROUP OF METHIONINE TO CARBON-24 OF ERGOSTEROL[1]

Sir:

In a previous communication it was demonstrated that the methyl group of methionine serves as a source of the 24-methyl group of ergosterol in yeast.[2] The mechanism of this reaction remained, however, in doubt. Since formate also has been established as a possible source of the 24-methyl group,[3] the oxidation of methionine-methyl to "active formate" with subsequent reduction provided one possible explanation, using only well established biochemical transformations.[4] On the other hand, while transfers of intact methyl groups from sulfur to nitrogen[4] and oxygen[5] were known, no transmethylation to carbon has been reported.

In our hands, formate, formaldehyde, $NaHCO_3$ and serine-3-C^{14} gave lower C^{14} incorporation than methionine[2] (also see Table I). Almost 6% of formate-C^{14} was incorporated into the non-saponifiable fraction of yeast; however, addition of non-radioactive methionine cut the formate-C^{14} incorporation to 0.3%. Under similar conditions, 24.8% of methionine-methyl-C^{14} was incorporated and addition of non-radioactive formate did not affect this incorporation significantly. Addition of homocysteine, which reacts with formate to give methionine,[6] doubled the yields from formate-C^{14}. Folic acid, which is essential in *de novo* methyl synthesis, further increased the yield. On the other hand, aminopterin, a folic acid antagonist, decreased the formate-C^{14} incorporation to 2.3%. While formate itself had only a slight effect on the incorporation of methionine-methyl-C^{14}, formate and homocysteine cut this incorporation sharply. Aminopterin, which prevents the condensation of formate and homocysteine, counteracted the formate homocysteine effect. In the absence of exogeneous formic acid, aminopterin increased the yields from methionine-methyl-C^{14}, probably by preventing partial oxidation of the S-methyl groups.

Serine-3-C^{14} was 50% as efficient as methionine but twice as efficient as formate as the source of C-28 of ergosterol. Non-radioactive serine raised the yield of C-28 from methionine, possibly by acting as an acceptor of the homocysteine moiety, left after the methyl transfer from methionine to ergosterol. The cystathionine thus formed has been shown to be biologically inactive.[6,7]

When doubly labeled methionine, made by mixing methionine-methyl-C^{14} with methionine-

(1) This work was supported by the U. S. Public Health Service, Grant C321, The Jane Coffin Childs Memorial Fund, and an institutional grant from the American Cancer Society.

(2) G. J. Alexander, A. M. Gold and E. Schwenk, THIS JOURNAL, **79**, 2967 (1957).

(3) H. Danielson and K. Bloch, *ibid.*, **79**, 500 (1957).

(4) G. Ehrensvard, *Ann. Rev. Biochem.*, **24**, 275 (1955).

(5) C. S. Sato, R. U. Byerrum and C. D. Ball, *J. Biol. Chem.*, **224**, 717 (1957).

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(7) V. M. Dixon, H. L. Fritton and J. Awapara, *Arch. Biochem. Biophys.* **67**, 404 (1957).

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TABLE I

FORMATE-C^{14}, METHIONINE-METHYL-C^{14} AND SERINE-3-C^{14} AS C-24 METHYL DONORS[a]

Source of C^{14}	Non-radioactive additions	Non-saponifiable fraction Mg.	S. A. $\times 10^{-3}$	Total counts $\times 10^{-3}$	Yield, %
HCOOH	...	3.7	2.3	8.6	6
HCOOH	Homocysteine[b]	3.5	4.3	15.2	10
HCOOH	Homocysteine, folic acid	4.0	6.4	25.7	17
HCOOH	Homocysteine, aminopterin	4.2	0.8	3.5	2
HCOOH	Methionine	3.8	0.1	0.4	0.3
Methionine	...	3.9	9.5	37.2	25
Methionine	Formate	5.2	6.1	31.5	22
Methionine	Formate, homocysteine	3.3	2.5	8.5	6
Methionine	Formate, homocysteine, aminopterin	3.7	6.2	20.3	14
Methionine	Aminopterin	1.9	34.4	65.4	44
Methionine	Serine	3.6	28.4	102.1	68
Serine	...	3.5	4.7	16.6	11

[a] Each flask contained 4 ml. of homogenate made from 1 g. of dry yeast, 2×10^{-4} *M* ATP and 0.5 μc. of C^{14} (1 mc./mmole). [b] Additions per flask (where indicated): homocysteine, 5 mg.; folic acid, 1 mg.; aminopterin, 2 mg.; methionine, 15 mg.; HCOONa, 5 mg.; serine, 15 mg.

TABLE II

TRITIUM:CARBON^{14} RATIOS IN METHIONINE AND ERGOSTEROL

Each experiment consisted of 5 flasks, each containing 4 ml. of yeast extract, 5 mg. of serine, 2 mg. of aminopterin, 1 mg. of ATP, and 0.175 mg. of doubly labeled methionine. Incubation time was 48 hr.; radioactivities were determined on a Packard Tri-Carb Scintillation Counter. The values given are the averages of four samples.

Expt.	T:C^{14} Ratio Methionine	Ergosterol
1	1.12 ± 0.06	0.97 ± 0.06
2	1.12 ± 0.06	1.02 ± 0.02

methyl-T, was incubated with yeast homogenates and the resulting ergosterol rigorously purified, the T:C^{14} ratios of the substrate and product showed that all three hydrogen atoms of the methyl group of methionine are transferred to ergosterol. Were the methyl group oxidized to the level of formaldehyde, one third of the tritium would be lost, and the T:C^{14} ratio in ergosterol (Table II) would have been 67%. Since the ratio is 86–91%, at least some methyl groups of methionine must have been transferred intact to the carbon 24 of the sterol.

WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY
SHREWSBURY, MASS. GEORGE J. ALEXANDER
ERWIN SCHWENK

RECEIVED JULY 2, 1957

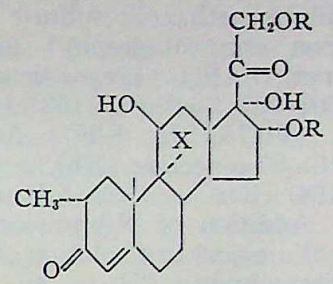
16-HYDROXYLATED STEROIDS. V.[1] THE SYNTHESIS OF THE 16α-HYDROXY DERIVATIVES OF 2α-METHYL-STEROIDS

Sir:

In view of our previous Communication[1] concerning the ability of the 16α-hydroxyl group to abolish the sodium retaining property of a steroid without destroying its glucocorticoid activity, we have investigated the effect of 16α-hydroxylation on the activities of 2α-methyl steroids.[2]

Hydrolysis of 21-acetoxy-3,20-bis-ethylenedioxy-5-pregnene-11β,16α,17α-triol (I)[3] in dilute acetic acid afforded 21-acetoxy-20-ethylenedioxy-11β,16α,-17α-triol-4-pregnen-3-one (II), m.p. 262–263°, $[\alpha]^{25}D$ + 85° ($CHCl_3$); (*Anal.* Found: C, 64.77; H, 8.03). Treatment of compound II with ethyl oxalate and sodium methoxide in *t*-butyl alcohol formed the sodium enolate of 20-ethylenedioxy-2-ethoxyoxalyl- 11β,16α,17α,21 -tetrahydroxy-4-pregnen-3-one (III) as a pale yellow amorphous solid. Methylation of III with methyl iodide and potassium carbonate in acetone followed by removal of the ethoxyoxalyl group by sodium methoxide in methanol gave a glass. After removal of the 20-ketal group with dilute ethanolic sulfuric acid, partition chromatography[4] yielded 11β,16α,17α,21-tetrahydroxy- 2α -methyl- 4 -pregnene- 3,20 -dione (IVa) apparently with one molecule of acetone of crystallization, m.p. 201–203°, $\lambda_{max.}$ 240–241 mμ (ϵ 16,600),[5] $[\alpha]^{25}D$ + 145° ($CHCl_3$); (*Anal.* Found: C, 65.59; H, 8.39). Acetylation gave the 16α,21-diacetate IVb, m.p. 253–254°, $\lambda_{max.}$ 240–241 mμ (ϵ 17,500), $\upsilon_{max.}^{KBr}$ 3450, 1743, 1726 (shoulder), 1654, 1620 and 1238 cm.$^{-1}$, $[\alpha]^{25}D$ + 92° ($CHCl_3$); (*Anal.* Found: C, 65.43; H, 7.75). Oxidation of IVb with chromium trioxide–pyridine reagent[6] gave 16α,21-diacetoxy-17α-hydroxy-2α-methyl-4-pregnene-3,11,20-trione (V), m.p. 240.5–241.5°, $[\alpha]^{25}D$ + 129° ($CHCl_3$); (*Anal.* Found: C, 65.49; H, 7.30).

IVa, X = H, R = H
IVb, X = H, R = Ac
XIIIa, X = F, R = H
XIIIb, X = F, R = Ac



Acetylation of 3,20-bis-ethylenedioxy-5-pregnene-11β,16α,17α,21-tetrol (VIa)[7] yielded the 16α,-21-diacetate (VIb), m.p. 129–135°,[8] $[\alpha]^{25}D$ − 61.5° ($CHCl_3$); (*Anal.* Found: C, 62.49; H, 7.81). Treatment with phosphorus oxychloride in pyridine afforded 3,20-bis-ethylene-dioxy-16α,21-diacetoxy-5,9(11)-pregnadien-17α-ol (VII), m.p. 221–224°, $[\alpha]^{25}D$ − 48° ($CHCl_3$); (*Anal.* Found: C, 65.52; H, 7.67). Hydrolysis of VII in dilute acetic acid gave 16α,21-diacetoxy-20-ethylenedioxy-17α-hydroxy-4,9(11)-pregnadien-3-one (VIII), m.p. 184.5–186°, $[\alpha]^{25}D$ ± 0° ($CHCl_3$); (*Anal.* Found: C, 66.63; H, 7.65).

The sodium enolate (IX) of the 2-ethoxyoxalyl

(1) Paper IV, S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and C. H. Hunter, THIS JOURNAL, 78, 5693 (1956).

(2) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *ibid.*, 77, 6401 (1955).

(3) W. S. Allen and S. Bernstein, *ibid.*, 78, 3223 (1956).

(4) R. Littell and S. Bernstein, *ibid.*, 78, 984 (1956).

(5) The ultraviolet spectra were determined in absolute alcohol solutions.

(6) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, 75, 422 (1953).

(7) W. S. Allen and S. Bernstein, *ibid.*, 78, 1909 (1956).

(8) This compound seemed to be solvated and could not be brought to a better melt or analytical value.

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derivative of VIII (free steroid) was obtained as an amorphous solid in the manner described above. Treatment with methyl iodide and potassium carbonate in acetone followed by reaction with sodium methoxide in methanol and finally hydrolysis in dilute methanolic sulfuric acid yielded after partition chromatography[4] 16α,17α,21-trihydroxy-2α-methyl-4,9(11)-pregnadiene-3-20-dione, (Xa), m.p. 203–207, $[\alpha]^{25}D$ + 103° ($CHCl_3$); (*Anal.* Found: C, 70.75; H, 8.29). Acetylation afforded the 16α,21-diacetate (Xb), m.p. 221.5–224°, $[\alpha]^{25}D$ + 104° ($CHCl_3$); (*Anal.* Found: C, 68.10; H, 7.53).

Addition of N-bromoacetamide and 10% perchloric acid to a solution of Xb in dioxane gave the bromohydrin XI as an amorphous solid, m.p. 131–134° which could not be purified. Treatment of XI with potassium acetate in acetone furnished the 9β,11β-epoxide XII, m.p. 222–223°, $[\alpha]^{25}D$ − 34° ($CHCl_3$); (*Anal.* Found: C, 65.57; H, 7.49). Hydrofluoric acid converted XII to 16α,21-diacetoxy- 9α -fluoro -11β,17α- dihydroxy- 2α -methyl-4-pregnene-3,20-dione (XIIIb), m.p. 140–200°[8], λ_{max} 237–238 mμ (ϵ 16,300), ν_{max}^{KBr} 3420, 1740, 1732, 1725, 1660, 1627 (shoulder) and 1235 cm^{-1}; (*Anal.* F, 3.87. Found: F, 4.29). The corresponding 16α,21-diol XIIIa formed from XIIIb by potassium hydroxide hydrolysis melted at 231–234° d., λ_{max} 237–238 mμ (ϵ 15,100), ν_{max}^{KBr} 3450, 1720, 1660, and 1635 $cm.^{-1}$, $[\alpha]^{25}D$ + 115° (pyridine); (*Anal.* Found: C, 64.30; H, 7.66; F, 4.57).

Bio-assays.[9]—Preliminary assay (rat liver glycogen procedure) of 11β,16α,17α,21-tetrahydroxy-2α-methyl-4-pregnene-3,20-dione (IVa) indicated definite activity (less than that of hydrocortisone); the 16α,21-diacetate IVb and the 16α,21-diacetoxy-11-one V were inactive. In the same assay, 9α-fluoro - 11β,16α,17α,21 - tetrahydroxy - 2α - methyl-4-pregnene-3,20-dione (XIIIa), and its diacetate XIIIb were found to be at least two times as active as hydrocortisone.

In the rate electrolyte (sodium retention) assay, IVa, IVb and V were inactive. The 9α-fluoro-compounds XIIIa and XIIIb exhibited minor activity (much less than that of desoxycorticosterone).

(9) The assays were done by L. Bortle, E. Heyder, J. Perrine, E. Ross, and I. Ringler (Experimental Therapeutics Research Section of these Laboratories).

SEYMOUR BERNSTEIN
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RECEIVED JULY 2, 1957

STEROIDS. LXXXIX.[1] 19-NORDIHYDROTESTOSTERONE DERIVATIVES. A POTENT CLASS OF ANTI-ESTROGENIC COMPOUNDS.

Sir:

Following Birch's[2] synthesis of 19-nortestosterone (Ia) in 1949 a number of 19-nor analogs of the steroid hormones and metabolites have been prepared[3a–h] and many of these substances exhibited unusual biological activity.

We now wish to describe the synthesis of a new series of biologically active 19-nor compounds, namely, the 4,5-dihydroallo derivatives of nortestosterone and 17α-alkyl substituted nortestosterones as well as the corresponding 3β,17β-diols.

While catalytic hydrogenation of Ia, Ib and Ic led to mixtures of the rings A/B *cis* and *trans* compounds, it was found that reduction of the unsaturated ketones in ether–dioxane solution with lithium in liquid ammonia[4] followed by ammonium chloride decomposition, furnished in excellent yield the dihydroallo derivatives: 19-norandrostan-17β-ol-3-one (IIa) (m.p. 130–132°, $[\alpha]D$ + 60°.[5] Found for $C_{18}H_{28}O_2$: C, 78.34; H, 9.94); 17α-methyl-19-norandrostan-17β-ol-3-one (IIb) (m.p. 145–146°, $[\alpha]D$ +35°. Found for $C_{19}H_{30}O_2$: C, 78.49; H, 10.40); and 17α-ethyl-19-norandrostan-17β-ol-3-one (IIc) (m.p. 212–213°, $[\alpha]D$ +33°. Found for $C_{20}H_{32}O_2$: C, 78.47; H, 10.49). Reduction of the 17-vinyl (Id) and the 17-ethynyl (Ie) compounds by this technique resulted in saturation of the 4,5-double bonds only, furnishing, respectively, 17α-vinyl-19-norandrostan-17β-ol-3-one (IId) (m.p. 192–193°, $[\alpha]D$ +47°. Found for $C_{20}H_{30}O_2$: C, 79.18; H, 10.05) and 17α-ethynyl-19-norandrostan-17β-ol-3-one (IIe) (m.p. 222–223°, $[\alpha]D$ +6°. Found for $C_{20}H_{28}O_2$: C, 80.30; H, 9.52). That the unsaturated side-chains had withstood the reduction conditions was demonstrated conclusively by the conversion of IIe to IId by partial hydrogenation (palladium on calcium carbonate–pyridine) and the derivation of IIc from either IId or IIe by reduction over palladium–carbon in methanol solution. The A/B allo configuration for compounds II which could be predicted on thermodynamic grounds,[6] is firmly established by the rotatory dispersion curves[7] of these dihydro compounds, the curves being virtually identical with that of androstan-17β-ol-3-one.

Treatment of IIa through IIe with sodium borohydride in aqueous dioxane gave the corresponding 19-norandrostan-3β,17β-diols: IIIa (m.p. 168–170°, $[\alpha]D$ +37°. Found for $C_{18}H_{30}O_2 \cdot 2C_3H_6O$: C, 72.88; H, 10.94); IIIb (m.p. 174–176°, $[\alpha]D$ ±0°. Found for $C_{19}H_{32}O_2.2C_3H_6O$: C, 73.76; H, 11.12); IIIc (m.p. 181–183°, $[\alpha]D$ +2°. Found for $C_{20}H_{34}O_2$: C, 78.20; H, 11.03[8]); IIId (m.p. 167–169°, $[\alpha]D$ +9°. Found for $C_{20}H_{32}O_2$: C,

(1) Paper LXXXVIII, J. Romo, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **79**, in press. (1957).

(2) A. J. Birch, *J. Chem. Soc.*, 367 (1950).

(3) (a) L. Miramontes, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3540 (1951); **75**, 4440 (1953); (b) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, *ibid.*, **75**, 4117 (1953); (c) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5366 (1953); (d) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954); (e) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *ibid.*, **76**, 6210 (1954); (f) B. J. Magerlein and J. A. Hogg, *ibid.*, **79**, 1508 (1957); (g) F. B. Colton, L. N. Nysted, B. Riegel and A. L. Raymond, *ibid.*, **79**, 1123 (1957); (h) F. B. Colton, U. S Patent 2,725,389 (1955).

(4) *Cf.* F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 2695 (1952).

(5) All melting points are uncorrected and rotations were determined at 20° in chloroform. Thanks are due Mr. E. Denot for his able technical assistance and to Mr. E. Avila for rotations and spectra.

(6) See D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954), and references cited therein.

(7) We are grateful to Professor C. Djerassi, Wayne State University, for the determination and comparison of rotatory dispersions.

(8) Analytical sample sublimed in high vacuum.

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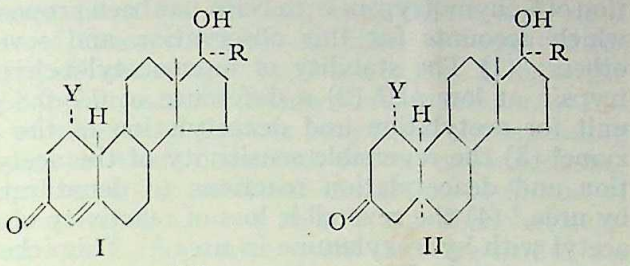
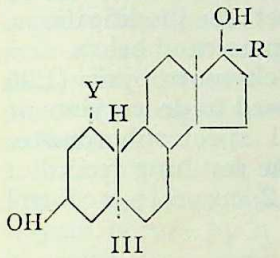
78.63; H, 10.71[8]); IIIe (m.p. 192–193°, $[\alpha]_D$ −15°. Found for $C_{20}H_{30}O_2$: C, 79.63; H, 9.84[8]).



I II



III

a, Y = H, R = H
b, Y = H, R = Me
c, Y = H, R = Et
d, Y = H, R = —CH=CH$_2$
e, Y = H, R = —C≡CH
f, Y = Me, R = H

Similarly, 1α-methyl-19-nortestosterone (If)[9] was converted to the allo[7] compound, 1α-methyl-19-norandrostan-17β-ol-3-one (IIf) (m.p. 186–188°, $[\alpha]_D$ +46°. Found for $C_{19}H_{30}O_2$: C, 78.78; H, 9.94) and to the 3β,17β-diol (IIIf) (m.p. 204–206°, $[\alpha]_D$ +51°. Found for $C_{19}H_{32}O_2$: C, 77.55; H, 10.84).

This series of nordihydrotestosterone derivatives (II) and the diols (III) are potent anti-estrogens as measured by inhibition of the uterotrophic activity of estrone in the immature mouse.[10] Nordihydrotestosterone (IIa) exhibits about 8× the activity of 19-nortestosterone (Ia) in this assay (subcutaneous route) while the 17-alkyl compounds (*e.g.* IIb) are highly active by the oral as well as subcutaneous route. Clinical evaluation of some of these compounds in certain types of hormone dependent tumors has been initiated.

(9) H. J. Ringold, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 2477 (1956). For assignment of the 1α-configuration, see C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6377 (1956).

(10) Bioassays carried out at the Worcester Foundation for Experimental Biology under the direction of one of the authors (R. I. D.).

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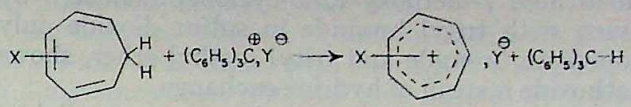
RECEIVED JUNE 13, 1957

SYNTHESIS OF TROPENIUM (CYCLOHEPTATRIENYLIUM) SALTS BY HYDRIDE EXCHANGE[1]

Sir:

The previously reported[2] novel method of synthesis of tropenium[3] perchlorate by hydride abstraction from cycloheptatriene by trityl perchlorate in acetonitrile has been found to be versatile and adaptable to the preparation of a number of tropenium salts containing various anions and/or nuclear substituents, some previously unknown or unavailable by other methods.



Hydride exchange reactions between cycloheptatrienes and trityl salts occur rapidly and quantitatively only in solvents which effect dissociation of these salts. In consonance with conductivity studies, trityl halides function satisfactorily as hydride abstractors in liquid sulfur dioxide but trityl perchlorate or fluoborate gives equally good results in acetonitrile or sulfur dioxide. Most tropenium salts may be prepared by the following general procedure (all reactants and conditions anhydrous): equivalent quantities of trityl salt and the cycloheptatriene[4] in acetonitrile (minimum amount) at room temperature or sulfur dioxide (30–50 ml./g. triene) at −20° or lower are allowed to react for a few minutes, all solvent then evaporated (acetonitrile *in vacuo;* sulfur dioxide by warming, finally *in vacuo*), triphenylmethane removed by trituration and extraction with ether from the tropenium salt product; pure perchlorate and fluoborate salts obtained by recrystallization from acetonitrile–ethyl acetate, halide salts by sublimation at 80–100° (1 mm.); yields of crude salts almost quantitative, of pure salts 60–90%. Tropenium salts prepared (λ_{max} and ϵ_{max} in concd. sulfuric acid): (i) X = H, Y = ClO_4,[2] white, m.p. >300°, 217 mμ (41,000) and 273.5 mμ (4350)(ii, iii, iv, v show same spectrum), 44.03% C, 3.71% H; (ii) X = H, Y = BF_4,[5c] white, m.p. dec. slowly above 210°, 47.17% C, 3.59% H; (iii) X = H, Y = Cl,[5] white, 66.61% C, 5.56% H; (iv) X = H, Y = Br,[2,5] yellow, m.p. 203°; (v) X = H, Y = I,[5] red, m.p. 127°, readily transformed into tropenium triiodide, deep red-black, m.p. 127°, 292 mμ (39,800) and 361 mμ (22,100) in acetonitrile, 18.06% C, 1.51% H; (vi) X = Cl, Y = ClO_4, white, m.p. 164°, 237 mμ (29,800) and 310 mμ (8220), 37.37%, C 2.77% H, converted to tropone by water or ethanol[5b] (analogous preparation of bromide or iodide salts gives mixed halotropenium halides due to halogen interchange); (vii) X = Br, Y = ClO_4, white, m.p. 149.5°, 247 mμ (22,750) and 323 mμ (8900), 31.27% C, 1.89% H, converted to tropone by water or ethanol[5b]; (viii) X = MeO, Y = ClO_4, white, m.p. 107°, 234 mμ (32,100) and 315 mμ (10,050), 43.38% C, 4.34% H (similarly prepared bromide or iodide salts yield tropone and methyl bromide or iodide on warming); (ix) X = Me, Y = ClO_4,[5c] white, m.p. 109°, 226 mμ (37,100) and 288 mμ (3500), 46.89% C, 4.73% H (yellow bromide salt preparable in sulfur dioxide at −70° but decomposes on warming). Perchlorate and fluoborate salts, due to greater stability and non-hygroscopicity, are easier to handle than chloride (very hy-

(1) Supported in part by the Office of Ordnance Research, U. S. Army, Contracts DA-04-200-ORD-235 and 601.

(2) H. J. Dauben, Jr., and D. L. Pearson, Abstracts, 126th Meeting, American Chemical Society, New York, N. Y., Sept. 13, 1954, p. 18-O.

(3) Tropenium seems preferable to tropylium as the name for the $C_7H_7^{\oplus}$ ion because of its representation of all structural features of the ion and its consistency with benzenium, azulenium, etc., names for related carbonium ions.

(4) Substituted cycloheptatrienes prepared by the method of W. v. E. Doering and L. H. Knox, THIS JOURNAL, **75**, 297 (1953).

(5) Previously reported by: (a) Doering and Knox, *ibid.*, **76**, 3203 (1954); (b) W. v. E. Doering and H. Krauch, *Angew. Chem.*, **68**, 661 (1956); (c) M. J. S. Dewar and R. Pettit, *J. Chem. Soc.*, 2021, 2026 (1956); the color, stability and spectrum reported for their methyltropenium bromide monohydrate are inconsistent with this structural assignment.

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groscopic), bromide (hygroscopic) or iodide (non-hygroscopic but unstable) salts. The allylically substituted 7-methoxy-1,3,5-cycloheptatriene,[5a] by giving with trityl bromide in sulfur dioxide only tropenium bromide and trityl methyl ether, shows methoxide instead of hydride exchange.

With more complete spectral data now available, it is evident that both predicted bands (4.33 ev, weak; 6.37 ev, intense)[6] for tropenium ion agree reasonably well with observed values (4.54 ev, 4350; 5.73 ev, 41,000). Results to date indicate that substituent effects on both $^1E_{1u}$ and $^1E_{3u}$ bands of substituted tropenium ions are in accord with those on $^1E_{1u}$[7] and $^1B_{1u}$, but not $^1B_{2u}$, bands of monosubstituted benzenes and are interpretable in terms of highly polar excited states for the ions.

Additional hydride exchange studies on tropenium and other systems for preparative and theoretical purposes are in progress.

(6) J. N. Murrell and H. C. Longuet-Higgins, *J. Chem. Phys.*, **23**, 2347 (1955).

(7) H. B. Klevens and J. R. Platt, Technical Report, Part 1, 1953–4, Laboratory of Molecular Structure and Spectra, University of Chicago, p. 145.

(8) (a) National Science Foundation Predoctoral Fellow, 1956–7; (b) Allied Chemical and Dye Co. Fellow, 1953–4.

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RECEIVED JULY 3, 1957

AN INTERMEDIATE IN THE DEACETYLATION OF MONO-ACETYL-δ-CHYMOTRYPSIN HAVING THE PROPERTIES OF ACETYL-IMIDAZOLYL[1]

Sir:

In a previous communication,[2] evidence was presented which indicated that upon acetylation of δ-chymotrypsin by *p*-nitrophenylacetate, there was no detectable change in the spectral characteristics of the enzyme in the region of 245 mμ. This region was studied carefully since a postulated intermediate in the reaction, acetyl-imidazolyl-,[3,4] possesses a characteristic absorption maximum at this wave length.[4] Recently, a mechanism of reaction of δ-chymotrypsin with NPA has been proposed[5] which accounts for this observation and several others: (1) The stability of monoacetyl-δ-chymotrypsin at low *p*H[6] (2) a difference of 0.7–0.8 *pK* unit for acetylation and deacetylation of the enzyme[6] (3) the reversible sensitivity of the acetylation and deacetylation reactions to denaturation by urea,[2] (4) the reversible loss of reactivity of the acetyl with hydroxylamine in urea.[2] This scheme is presented in Fig. 1 with certain modifications, the evidence for which will be presented below.

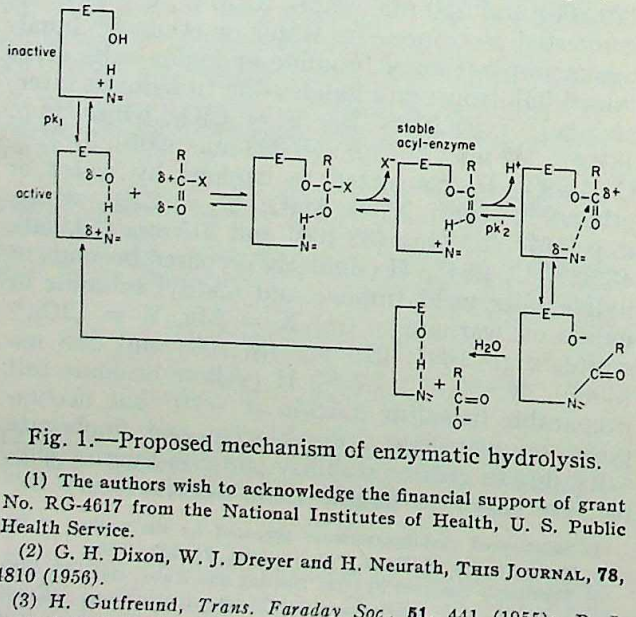

Fig. 1.—Proposed mechanism of enzymatic hydrolysis.

A solution of monoacetyl-δ-chymotropysin (1.95 mgm./ml.) at *p*H 3.5 was allowed to deacetylate at *p*H 9.0 in a Beckman DK-1 spectrophotometer which was set at 245 mμ. The resulting record of ΔE_{245} with time is seen in Fig. 2, curve 1; a control of non-acetylated δ-chymotrypsin is seen in curve 2. Curve 2 was also followed when a portion of the acetyl-δ-chymotrypsin was allowed to deacetylate at *p*H 7.2 for 15 minutes at room temperature and then adjusted to *p*H 3.5 with acid before the reaction.

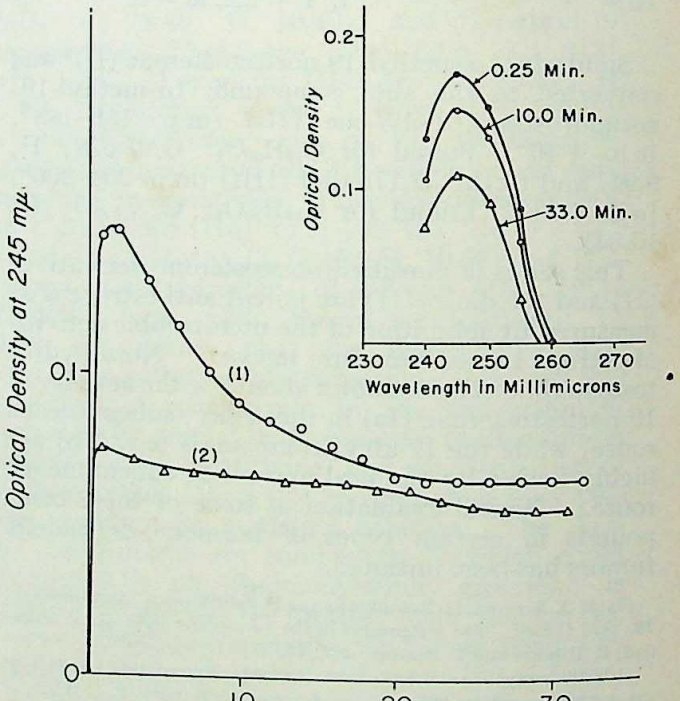

Fig. 2.—Both sample and reference cuvettes in a Beckman DK-1 spectrophotometer contained 3.0 ml. of the same solution of acetyl-δ-chymotrypsin[7] at *p*H 3.5; the temperature was 10.0 ± 0.2°. The *p*H of the sample was raised to 8.9 ± 0.1 by adding a small aliquot of a triethylammonium-ammonium acetate buffer on a plunger type rapid mixer.

It is clear that only in the case of acetyl-δ-chymotrypsin is there the rapid formation of a species absorbing at 245 mμ which decreases slowly in concentration with time. The control curve indicates that part of the initial increase at 245 mμ is due to a non-specific, *p*H dependent, spectral change in the enzyme.

(1) The authors wish to acknowledge the financial support of grant No. RG-4617 from the National Institutes of Health, U. S. Public Health Service.

(2) G. H. Dixon, W. J. Dreyer and H. Neurath, THIS JOURNAL, **78**, 4810 (1956).

(3) H. Gutfreund, *Trans. Faraday Soc.*, **51**, 441 (1955); B. J. Jandorf, H. O. Michel, N. K. Schaffer, R. Egan and W. H. Summerson, *Faraday Soc. Discussions*, **20**, 134 (1955).

(4) E. Stadtman in "Mechanism of Enzyme Action," Johns Hopkins Press, Baltimore, Md., 1954, p. 581.

(5) L. W. Cunningham, *Science*, in press.

(6) G. H. Dixon and H. Neurath, *Fed. Proc.*, **16**, 173 (1957); G. H. Dixon and H. Neurath, *J. Biol. Chem.*, **223**, 1049 (1957).

(7) A. K. Balls and H. N. Wood, *J. Biol. Chem.* **219**, 245(1956).

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When deacetylation was allowed to occur at the same *p*H but at 5.0 ± 0.2° and the spectrum was scanned from 270–230 mμ both before and, at a series of times, after the addition of base, the resulting difference spectra (inset to Fig. 2) show the rapid appearance of a peak with its maximum at 245 mμ which slowly declines with time, corresponding closely to that described for acetyl-imidazole.[4] According to the published extinction coefficient of this compound[4] ($\epsilon = 3 \times 10^3$), the observed maximum increase and subsequent decrease at 245 mμ is equivalent to 0.41–0.42 mole acetylimidazole per mole of reactive acetyl in the enzyme. Similar results were obtained in glycine buffer, but in phosphate the magnitude of the change at 245 mμ was reduced.

It is postulated, therefore, that as indicated in Fig. 1, the deacetylation of mono-acetyl-δ-chymotrypsin occurs by a rapid intramolecular transfer of acetyl- from serine hydroxyl to imidazolyl- followed by a slower hydrolysis of acetyl-imidazolyl-. The first order rate constant for the disappearance of the E_{245} compound corresponds closely with that observed for the rate of deacetylation of δ-chymotrypsin as measured by the reappearance of enzyme activity,[6] which in turn corresponds to the rate of base catalyzed hydrolysis of acetyl-imidazole in a model system.[8]

(8) M. L. Bender and B. W. Turnquest, THIS JOURNAL, **79**, 1656 (1957).

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RECEIVED JUNE 6, 1957

SYNTHESIS OF POTENTIAL ANTICANCER AGENTS. X. 2-FLUOROADENOSINE[1]

Sir:

Recently the biological activity of three fluoro derivatives of naturally occurring pyrimidines has been reported.[2]

Of these three fluoropyrimidines, 5-fluorouracil and 5-fluoroörotic acid have shown appreciable tumor-inhibitory activity against a variety of rat and mouse tumors[2a] and 5-fluorouracil was selected for clinical trials.[2b] The biological activity of the fluoropyrimidines increased our interest in the preparation of fluoropurines and their ribosides, especially fluoro derivatives of naturally occurring purines. Although Bendich, Giner-Sorolla and Fox were unable to prepare 6-fluoropurine from adenine by the Schiemann reaction,[3] Weisbach successfully prepared 2-fluoropyrimidine from 2-aminopyrimidine by this method.[4] The success of the latter reaction led us to attempt the preparation of 2-fluoroadenosine from 2,6-diaminopurine riboside by diazotization in fluoboric acid.

An aqueous solution of sodium nitrite (360 mg. in 2.4 ml.) was added with stirring to a solution of 2,6-diaminopurine riboside[5] (846 mg.) in 48% fluoboric acid (9.6 ml.) at −10°. The solution was stirred at −10° to 0° for 15 minutes, cooled to −20° and neutralized with 50% sodium hydroxide solution. The water was removed *in vacuo* and the residue chromatographed on a Celite column using water-saturated butanol. The crude 2-fluoroadenosine obtained (149 mg.) was recrystallized from absolute ethanol and dried *in vacuo* over P_2O_5 at 70° for several hours: yield, 75 mg. (8.7%), dec. at 200°; $(\alpha)^{26}D$ −60.3 ± 11.1 (0.127% in ethanol); $\lambda_{max}^{pH\ 1}$ 260.5 mμ (a_M 13,700); $\lambda_{max}^{pH\ 7}$ 260.5 mμ (a_M 14,300); $\lambda_{max}^{pH\ 13}$ 260.5 (a_M 14,800). *Anal.* Calcd. for $C_{10}H_{12}FN_5O_4 \cdot {}^1/_4C_2H_5OH$: C, 42.45; H, 4.60; N, 23.60. Found: C, 42.34; H, 4.93; N, 23.40. A qualitative test for fluorine was positive. The ratio of the R_f values of 2-fluoroadenosine and adenine in butanol–water on a descending paper chromatogram (Watman No. 1) was 0.9.

2-Fluoropurine was prepared in the same manner from 2-aminopurine[6] (850 mg.): yield, 254 mg. (41%) dec. at 216°; $\lambda_{max}^{pH\ 1}$ 264 mμ (a_M 8,300) $\lambda_{max}^{pH\ 7}$ 266.5 mμ (a_M 8,400), $\lambda_{max}^{pH\ 13}$ 272 mμ (a_M 8,800). *Anal.* Calcd. for $C_5H_3FN_4$: C, 43.48; H, 2.20; N, 40.60. Found: C, 43.52; H, 2.01; N, 40.37. A qualitative test for fluorine was positive.

In preliminary tests 2-fluoroadenosine inhibits the growth of Human Epidermoid Carcinoma (HE 2) at 10^{-8} g./ml. Five times this concentration is required to inhibit monkey kidney cells. Azaserine and 6-diazo-5-oxo-L-norleucine inhibit the growth of these tissues at 10^{-7} g./ml.

The preparation of other 2-fluoropurines is now under way in this laboratory.

(5) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 1650 (1951).
(6) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).
(7) Affiliated with Sloan–Kettering Institute.

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THE SYNTHESIS OF 5-FLUOROPYRIMIDINES

Sir:

We wish to report the synthesis of a new class of compounds, some of which were designed to function as nucleic acid antagonists, by substituting fluorine for hydrogen in naturally occurring pyrimidines.

The 5-fluoropyrimidines (III) were obtained from pseudourea and pseudothiourea salts (I) and α-fluoro-β-keto ester enolates (II) by adaptation of the Wheeler synthesis.[1]

Crystalline IIa was prepared by the addition at 0° of 2.4 moles of methyl formate and 1.2 moles of ethyl fluoroacetate (IV) to 1.2 moles of potassium ethoxide in 800 ml. of toluene and letting the mix-

(1) This work was supported by funds from the C. F. Kettering Foundation. Part IX, John A. Montgomery and Carroll Temple, Jr., THIS JOURNAL, in press.
(2) (a) C. Heidelberger, D. Morren, L. Griesbach, B. J. Montag, R. Duschinsky, E. Pleven and R. Schnitzer, *Proc. Am. Ass. Cancer Research*, **2**, 212 (1957); (b) F. A. McIver, A. R. Curreri, O. O. Meyer, R. F. Schilling and H. Waisman, *ibid.*, **2**, 230 (1957); (c) C. Heidelberger, L. Bosch, N. K. Chaudhuri and P. B. Danneberg, *Federation Proc.*, **16**, 194 (1957); (d) J. M. Scheiner, E. Kostelak and R. Duschinsky, *ibid.*, **16**, 242 (1957); (e) T. Wong and W. M. Benson, *ibid.*, **16**, 348 (1957).
(3) A. Bendich, A. Giner-Sorolla and J. J. Fox, "The Chemistry and Biology of Purines" (A Ciba Foundation Symposium), J. and A. Churchill Ltd., London, England, 1957, p. 7.
(4) D. E. Weisbach, M. S. Thesis, University of North Caroline 1954.
(1) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **29**, 478 (1903); A. Dornow, F. Boberg and L. Schürer, *Arch. Pharm.*, **286**, 494 (1953).

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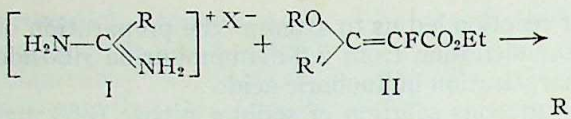
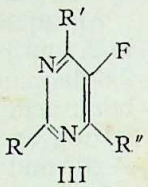


I II



III

I	a	b	c	II	a	b	c	d
R =	SEt	OMe	SMe	R =	K	Na	K	H
X =	Br	Cl	$^1/_2SO_4$	R′ =	H	H	CO_2Et	CH_2F

III	a	b	c	d	e	f	g	h	i	j	k	l
R =	SEt	OH	OMe	SMe	SH	SEt	SEt	OH	SEt	OH	SMe	OH
R′ =	OH	OH	OH	OH	OH	Cl	NH_2	NH_2	OH	OH	OH	OH
R″ =	H	H	H	H	H	H	H	H	CO_2Et	CO_2H	CH_2F	CH_2Cl

ture stand at 25° for 16 hours.[2] After IIa was refluxed for 2 hours with 0.6 moles of Ia and 0.6 moles of sodium methoxide in 1440 ml. of ethanol, evaporation, extraction with water and acidification gave IIIa (24% yield from IV), m.p. 192–193° dec. (recrystallized from ethyl acetate) (Calcd. for $C_6H_7FN_2OS$: C, 41.38; H, 4.05; F, 10.91. Found: C, 41.45; H, 4.25; F, 11.48.) Hydrochloric acid hydrolysis[1] of IIIa afforded 72% of 5-fluorouracil (IIIb), m.p. 282–283° dec., $\lambda_{max}^{0.1N\ HCl}$ 265–266 mμ (ε 7070)[3] (Calcd. for $C_4H_3FN_2O_2$: C, 36.93; H, 2.32; F, 14.61. Found: C, 37.07; H, 2.30; F, 14.69). Similarly Ib and IIa gave IIIc, m.p. 206–207° dec. (Calcd. for $C_5H_5FN_2O_2$: C, 41.67; H, 3.50; OCH_3, 21.63; F, 13.18. Found: C, 42.01; H, 3.87; OCH_3, 21.70; F, 13.51). This was hydrolyzed to yield IIIb. Hydrogenation of IIIb (1 mole hydrogen) with palladium charcoal in 2 moles of sodium hydroxide yielded 80% of uracil, whereas rhodium catalyst[4] in acetic acid produced a mixture from which 6.5% of 5-fluorodihydrouracil, m.p. 237–238° dec. (Calcd. for $C_4H_5FN_2O_2$: C, 36.37; H, 3.82; F, 14.38. Found: C, 36.32; H, 3.43; F, 14.59) was isolated by cellulose powder chromatography.[5] Condensation of Ic and IIa gave IIId, m.p. 241–243° dec. (Calcd. for $C_5H_5FN_2OS$: C, 37.49; H, 3.15; N, 17.49. Found: C, 37.98; H, 3.44; N, 17.52) which on demethylation[6] afforded 49% of IIIe, m.p. 227–229° dec. (Calcd. for $C_4H_3FN_2OS$: C, 32.87; H, 2.07; F, 13.00; Found: C, 33.45; H, 2.36; F, 12.78). Chlorination[7] of IIIa produced oily IIIf, which by autoclaving (12 hours, 100°) with liquid ammonia gave IIIg, m.p. 94°, in 88% over-all yield (Calcd. for $C_6H_8FSN_3$: C, 41.60; H, 4.66; N, 24.26. Found: C, 41.43; H, 4.73; N, 23.96). Hydrobromic acid hydrolysis of IIIg afforded 52% of 5-fluorocytosine (IIIh), m.p. 295–297° dec., $\lambda_{max}^{0.1N\ HCl}$ 285 mμ (ε 8900) (Calcd. for $C_4H_4FN_3O$: C, 37.21; H, 3.12; F, 14.72. Found: C, 36.92; H, 3.07; F, 14.47).

Diethyl oxalate (2 moles), potassium ethoxide and IV gave IIc[8] (Calcd. for $C_8H_{10}FKO_5$: C, 39.34; H, 4.12; K, 16.01; F, 7.78. Found: C, 39.03; H, 4.34; K, 16.48; F, 7.59). Condensation (as described for IIa) of Ia and IIc yielded, after processing IIIi (23% from IV), m.p. 168–169° dec. (Calcd. for $C_9H_{11}FN_2O_3S$: C, 43.89; H, 4.50. Found: C, 43.96; H, 4.61). Hydrochloric acid hydrolysis of IIIi yielded 88% of 5-fluoroörotic acid monohydrate (IIIj) m.p. 255° dec., $\lambda_{max}^{0.1N\ HCl}$ 284–285 mμ (ε 7100)[3] (Calcd. for $C_5H_3FN_2O_4,H_2O$: C, 31.26; H, 3.13; F, 9.89. Found: C, 31.36; H, 2.95; F, 10.11), which on refluxing in Dowtherm yielded 86% of IIIb.[9] Condensation of Ic and IId[10] (2 moles sodium methoxide) gave IIIk m.p. 221–222° dec. which was impure, due to partial loss of side chain fluorine (Calcd. for $C_6H_6F_2N_2OS$: C, 37.49; H, 3.15; F, 19.77. Found C, 37.68; H, 2.79; F, 13.01). This upon refluxing with hydrochloric acid yielded III (40% over-all yield from IId) m.p. 240–241° dec. (Calcd. for $C_5H_4ClFN_2O_2$: C, 33.63; H, 2.26; Cl, 19.86; F, 10.64. Found: 34.03; H, 2.11; Cl, 19.47; F, 10.64).

5-Fluorouracil and 5-fluoroörotic acid have profound activity[11] against bacteria *in vitro* and against several transplanted tumors in animals. The former is under clinical investigation in neoplastic diseases.

We are indebted to Mrs. Ellen Chiamulera for technical assistance and to Dr. Al Steyermark for the microanalyses.

(2) The compound is impure and unstable; it should be used without undue delay in the next step. In a similar run with sodium ethoxide the obtained IIb was converted by treatment with ethanolic hydrochloric acid at 25° into ethyl fluoromalonaldehydate diethyl acetal (9.3% from IV), b.p. 115–118° (24 mm.), $n^{25}D$ 1.4041. (Calcd. for $C_9H_{17}FO_4$: C, 51.91; H, 8.23; F, 9.12; OC_2H_5, 64.92. Found: C, 52.19; H, 8.38; F, 9.02; OC_2H_5, 64.55.)

(3) Data supplied by Dr. A. Motchane.

(4) W. E. Cohn and D. G. Doherty, THIS JOURNAL, **78**, 2803 (1956).

(5) The upper phase of a mixture of ethyl acetate, water, formic acid (60:35:5) was used as eluant. *Cf.* K. Fink, R. E. Cline, R. B. Henderson and R. M. Fink, *J. Biol. Chem.*, **221**, 430 (1956). The collaboration of Mr. W. E. Oberhansli in the chromatographic work is gratefully acknowledged.

(6) H. W. Barrett, I. Goodman and K. Dittmer, THIS JOURNAL, **70**, 1755 (1948).

(7) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **29**, 196 (1903).

(8) *Cf.* I. Blank, J. Mager and E. D. Bergmann, *J. Chem. Soc.*, 2192 (1955).

(9) This method produced 2-C^{14} labeled IIIb from Ia via IIIj.

(10) E. T. McBee, O. R. Pierce, H. W. Kilbourne and E. R. Wilson, THIS JOURNAL, **75**, 3152 (1953).

(11) C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven and J. Scheiner, *Nature*, **179**, 663 (1957).

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RECEIVED JULY 1, 1957

SOME SELECTIVE REACTIONS OF THE SILICON-HYDROGEN GROUP WITH ORGANOMETALLIC COMPOUNDS

Sir:

We are reporting a series of reactions which readily make available the synthesis of a wide variety of organosilicon compounds, particularly those of an unsymmetrical nature. The introduction of the various R groups can be effected stepwise by the proper choice of solvent and organometallic compound. The synthesis is particularly appropriate for the preparation of low-melting organosilicon compounds of the type R_4Si where all of the R groups can be different.

Previous reports have shown that organolith-

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ium compounds react with the silicon–hydrogen group in diethyl ether to give tetrasubstituted products. Triethylsilane[1a,b] has been found to react with methyl-, *n*-propyl-, *n*-butyl- and phenyllithium to give the respective tetrasubstituted organosilicon compounds. Triphenylsilane[2] also has been found to react similarly.

Nebergall[3] has shown that phenylsilane reacts with an excess of phenyllithium and ethyllithium in diethyl ether to give tetraphenylsilane and triethylphenylsilane, respectively. That the solvent plays an important role in the reaction was demonstrated when excess ethyllithium was treated with phenylsilane in petroleum ether. The product from this reaction was diethylphenylsilane. Nebergall reported that no reaction occurred between phenylsilane and a large excess of phenylmagnesium bromide in diethyl ether.

Triphenylsilane[2] has been found to be unreactive toward phenylmagnesium bromide in ether, refluxing xylene, and a mixture of ether and dioxane. West and Rochow[4] have reported that di-*n*-butylsilane does not react with ethylmagnesium bromide in a mixture of ether and toluene at 100°.

One of the steps in the cleavage[5] of symmetrical diphenyldisiloxane with Grignard reagents in diethyl ether has been shown to lead to alkylation of the silicon–hydrogen group.

We have found that triphenylsilane, diphenylsilane, and phenylsilane will react with Grignard reagents in tetrahydrofuran (THF). Triphenylsilane reacted with phenylmagnesium bromide, after 24 hours of refluxing in THF, to give a 14% yield of tetraphenylsilane which was identified by infrared spectrum and by mixed melting point with an authentic sample. Triphenylsilane also gave allyltriphenylsilane in a 53% yield when treated for 24 hours with allylmagnesium chloride[6] in refluxing THF.

Diphenylsilane when allowed to react with excess phenylmagnesium bromide for a period of two days in refluxing THF gave a 79% yield of triphenylsilane. Diphenylsilane also reacted with excess *n*-butylmagnesium bromide under similar conditions to give a 72% yield of *n*-butyldiphenylsilane, b.p. 110–112° (1 mm.), $n^{20}D$ 1.5541, d^{20}_4 0.9604. *Anal.* Calcd. for $C_{16}H_{21}Si$: Si, 11.68; MR, 80.17. Found: Si, 11.53, 11.52; MR, 80.24. Refluxing a solution of diphenylsilane with an excess of phenylmagnesium bromide in diethyl ether gave a 31% yield of triphenylsilane.

Phenylsilane after reaction with one equivalent of phenylmagnesium bromide in THF at room temperature for 6.5 hours gave a 66% yield of diphenylsilane; while the same reaction, when carried out in diethyl ether at room temperature for 24 hours, gave a 52% yield of diphenylsilane. Likewise, phenylsilane reacted with one equivalent of *n*-dodecylmagnesium bromide in THF to give a 78% yield of *n*-dodecylphenylsilane, b.p. 130–131° (0.6 mm.), $n^{20}D$ 1.4480, d^{20}_4 0.8629. *Anal.* Calcd. for $C_{18}H_{32}Si$: Si, 10.16; *MR*, 92.29. Found: Si, 10.13, 9.99; *MR*, 92.41.

n-Dodecylphenylsilane, prepared as previously stated, reacted with one equivalent of benzylmagnesium chloride, after refluxing for 18 hours in THF, to give a 63% yield of benzyl-*n*-dodecylphenylsilane, b.p. 180–183° (0.12 mm.), $n^{20}D$ 1.5233, d^{20}_4 0.9209. *Anal.* Calcd. for $C_{25}H_{38}Si$: Si, 7.66; MR, 121.05. Found: Si, 7.59, 7.62; MR, 121.68.

Related reactions, with a variety of RM compounds, are in progress with other combinations having one or more hydrogens attached to various metals and metalloids. Some dialkylsilanes appear to behave differently than the diarylsilanes.

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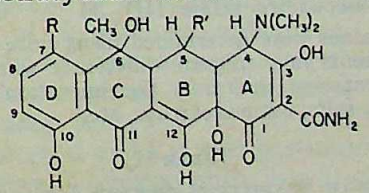
RECEIVED JULY 1, 1957

(1) (a) H. Gilman and S. P. Massie, Jr., THIS JOURNAL, **68**, 1128 (1946); (b) R. N. Meals, *ibid.*, **68**, 1880 (1946).
(2) H. Gilman and H. W. Melvin, Jr., *ibid.*, **71**, 4050 (1949).
(3) W. H. Nebergall, *ibid.*, **72**, 4702 (1950).
(4) R. West and E. G. Rochow, *J. Org. Chem.*, **18**, 302 (1953).
(5) M. C. Harvey, W. H. Nebergall and J. S. Peake, THIS JOURNAL, **79**, 1437 (1957).
(6) Unpublished studies of Theodore Soddy in this Laboratory have indicated that triphenylsilane will not react with allylmagnesium chloride in diethyl ether.

A NEW FAMILY OF ANTIBIOTICS: THE DEMETHYLTETRACYCLINES

Sir:

Among the most useful of the broad-spectrum antibiotics is a small group of substances derived from perhydronaphthacene and called the tetracyclines. Tetracycline, 7-chlorotetracycline, and 5-hydroxytetracycline[1] are used in therapy.



	R	R'
Tetracycline	H	H
7-Chlorotetracycline	Cl	H
5-Hydroxytetracycline	H	OH

We now wish to describe four members of a new family of compounds closely related to the previously known tetracyclines. On the basis of physical and chemical properties presented here and on the basis of degradation studies presented in the accompanying papers, it has been established that these four new compounds are 6-demethyltetracycline (I), 7-chloro-6-demethyltetracycline (II), 6-demethyl-4-*epi*-tetracycline (III), and 7-chloro-6-demethyl-4-*epi*-tetracycline (IV). 6-Demethyltetracycline hydrochloride hemihydrate: $[\alpha]^{25}D$ −259° (0.5% in 0.1 *N* H_2SO_4); m.p., dec. 203–209°; *Anal.* Calcd. for $C_{21}H_{24}N_2ClO_{8.5}$: C, 53.00; H, 5.08; N, 5.89; Cl, 7.45; O, 28.58; H_2O, 1.89. Found: C, 52.52; H, 5.34; N, 6.05;

(1) The trademarks of the American Cyanamid Company for tetracycline and 7-chlorotetracycline are Achromycin and Aureomycin, respectively. The trademarks of Chas. Pfizer and Co., Inc., for tetracycline and 5-hydroxytetracycline are Tetracyn and Terramycin, respectively.

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Cl, 7.51; O, 28.58 (diff.); H_2O, 1.96. 7-Chloro-6-demethyltetracycline sesquihydrate: $[\alpha]^{25}D$ −258° (0.5% in 0.1 *N* H_2SO_4); m.p., dec. 174–178°; *Anal.* Calcd. for $C_{21}H_{24}N_2ClO_{9.5}$: C, 51.27; H, 4.92; N, 5.70; Cl, 7.21; O, 30.90; H_2O, 5.49. Found: C, 51.13; H, 4.93; N, 6.00; Cl, 7.39; O, 30.55 (diff.); H_2O, 4.45. 6-Demethyl-4-*epi*-tetracycline hydrochloride: $[\alpha]^{25}D$ −335° (0.5% in 0.1 *N* H_2SO_4); m.p., dec. 225–230°; *Anal.* Calcd. for $C_{21}H_{23}N_2ClO_8$: C, 54.02; H, 4.97; N, 6.00; Cl, 7.61; O, 27.42. Found: C, 54.56; H, 5.19; N, 6.07; Cl, 7.67; O, 26.51 (diff.). 7-Chloro-6-demethyl-4-*epi*-tetracycline hydrochloride: $[\alpha]^{25}D$ −323° (0.5% in 0.1 *N* H_2SO_4); m.p., dec. 214–216°; *Anal.* Calcd. for $C_{21}H_{22}N_2Cl_2O_8$: C, 50.31; H, 4.42; N, 5.59; Cl, 14.15; O, 25.53. Found: C, 50.38; H, 4.81; N, 5.28; Cl, 14.21; O, 25.32 (diff.).

TABLE I

R_f VALUES IN PAPER CHROMATOGRAPHIC SYSTEMS[a]

	0.3*M* sodium phosphate/ *n*-butanol (*p*H 3.0)	Mac-Ilvaine's buffer/ ethyl acetate (*p*H 4.7)	0.3*N* H_3PO_4, 0.1% CCl_3COOH 9:1 $CHCl_3$ —*n*-BuOH (*p*H 1.9)
7-Chlorotetracycline	0.59	0.78	0.61
7-Chloro-4-*epi*-tetracycline	.59	.28	.33
7-Bromotetracycline	.59	.78	.61
7-Bromo-4-*epi*-tetracycline	.59	.28	.33
7-Chloro-6-demethyltetracycline (II)	.47	.70	.39
7-Chloro-6-demethyl-4-*epi*-tetracycline (IV)	.47	.26	.20
5-Hydroxytetracycline	.37	.60	.23
5-Hydroxy-4-*epi*-tetracycline	.37	.03	.11
Tetracycline	.37	.46	.20
4-*epi*-Tetracycline	.37	.15	.12
6-Demethyltetracycline (I)	.30	.27	.22
6-Demethyl-4-*epi*-tetracycline (III)	.30	.09	.10

[a] These values were determined using pure components. The components may migrate differently when present in crude fermentation mixtures, the migration rates being influenced by salts, natural carriers, etc.

TABLE II

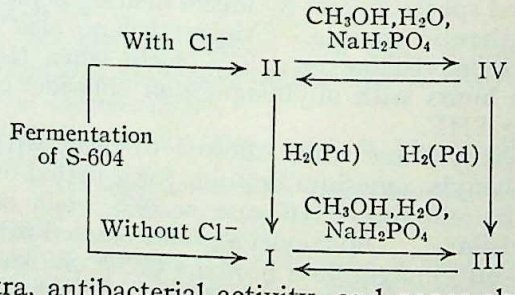
COMPARISONS OF STABILITIES TOWARD ACID AND BASE AND OF *in Vitro* ANTIBACTERIAL ACTIVITIES

	Half destruction time (min.) in: 1.0 *N* H_2SO_4 at 100°	0.1 *N* NaOH at 100°	% of *in vitro* antibact-activ. of 7-chlorotetracycline against *S. aureus* (turbidimetric meas.)
7-Chloro-6-demethyltetracycline (II)	445	40	75
7-Chlorotetracycline	2.1	<0.3	100
7-Chloro-6-demethyl-4-*epi*-tetracycline (IV)	322	35.6	7
7-Chloro-4-*epi*-tetracycline	5.8	<0.6	4.2
6-Demethyltetracycline (I)	24.8	31.5	24
Tetracycline	1.0	6.8	25
6-Demethyl-4-*epi*-tetracycline (III)	25.8	46	3
4-*epi*-Tetracycline	0.9	7.2	1.6
5-Hydroxytetracycline	4.5	2.2	24
5-Hydroxy-4-*epi*-tetracycline	2.6	3.3	1.1

Additional constants obtained on II hydrochloride were: Calcd.: N-methyl, for one dimethylamino group, 6.0; O-methyl, 0; O, 25.54. Found: N-methyl, 7.4; O-methyl, 0; O, 26.2 (Unterzaucher).

Compounds I and II are produced by a mutant of *Streptomyces aureofaciens* Duggar, coded as Mutant S-604 and derived ultimately from the original 7-chlorotetracycline-producing *S. aureofaciens* A-377 soil isolate of Duggar. Compounds III and IV are derived from I and II, respectively, by a process analogous to that used in the conversion of the previously known tetracyclines to their epimers.[2] Differentiation of these new compounds from each other and from the previously known tetracyclines can be accomplished by paper chromatography (Table I). The ultraviolet absorption spectra of these new compounds are essentially unchanged from those of their previously known 6-methyl analogs. A striking feature of all four new compounds is their great resistance to degradation by acid or by alkali. Comparisons are given in Table II. Relative *in vitro* antibacterial activities against *Staphylococcus aureus* are presented in Table II.[3]

The inter-relationships of these 6-demethyltetracyclines are established by the following observations. Catalytic hydrogenation (palladium on charcoal, 1.1 atm. of hydrogen) of II yields I and of IV yields III. Chloride-containing fermentations produce predominantly II; chloride-free fermentations produce I.[4] I and III are reversibly interconvertible under epimerizing conditions and II and IV behave analogously. Assignment of configuration at C.4, relative to the tetracyclines, was made on the basis of ultraviolet and infrared



spectra, antibacterial activity, and paper chromatographic behavior.

The great resistance of these new compounds to degradation by acid or by alkali was interpreted as meaning that the common difference between the new compounds and the previously known tetracyclines lay in Ring C, since degradation by acid and degradation by alkali both involve initially Ring C.[5,6,7,8] The ultraviolet absorption spectra,

(2) A. P. Doerschuk, B. A. Bitler and J. R. D. McCormick, THIS JOURNAL, **77**, 4687 (1955).

(3) This brings to three the number of positions in the tetracycline molecule at which a simple change of substituents has been possible without an appreciable reduction of the *in vitro* antibacterial activity against *S. aureus* from that of tetracycline: C.5, H to OH; C.6, CH_3 to H; C.7, H to Cl or Br. Other simple changes, such as 2-carboxamido to 2-cyano or inversion of C.4 configuration, diminish this activity by twenty-fold or greater.

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(7) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna,

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which are essentially superimposable on those of the corresponding 6-methylated tetracyclines, showed that the Rings B–C–D chromophore was not changed,[7,8] leaving carbons 5a and 6 as possible points of difference.

R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **75**, 5455 (1953).

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RECEIVED AUGUST 1, 1957

DEMETHYLTETRACYCLINES. STRUCTURE STUDIES

Sir:

The isolation and characterization of a new series of highly active tetracycline antibiotics has been reported recently.[1] In this communication degradation studies are presented showing that the parent compound of this series is 6-demethyltetracycline.[2]

In a preliminary experiment 7-chloro-6-demethyltetracycline (I) was distilled with a highly active zinc dust[3] giving naphthacene ($\lambda_{max.}^{CHCl_3}$, 420 mμ, 446 mμ, 477 mμ). Under the same conditions chlorotetracycline gave a distillate whose ultraviolet spectrum [$\lambda_{max.}^{CHCl_3}$, 425 mμ (broad), 452 mμ (broad), 476 mμ, 485 mμ] was indicative of a mixture of naphthacene and 5-methylnaphthacene. These data coupled with the analytical results[1] indicating that these new antibiotics had one less carbon atom than the known tetracyclines[4] suggested that the C.6 methyl group of the tetracycline nucleus was missing in the new series. This was confirmed immediately by numerous Kuhn–Roth determinations on I and related compounds, all of which gave zero values. In this determination the familar tetracyclines all gave appreciable C-methyl values.[4b,5]

That the structure of I was the same as chlorotetracycline in all other respects[6] was shown by several reactions. Heating in concentrated hydrochloric acid aromatized the C ring of I giving an anhydro compound (II) in good yield, $[\alpha]^{25}D$ +105° (0.467% in methyl cellosolve); m.p. 205–210° (dec.), (*Anal.* Calcd. for $C_{21}H_{19}N_2O_7Cl$: C, 56.44; H, 4.29; N, 6.27; Cl, 7.94. Found: C, 56.39; H, 4.60; N, 5.83; Cl, 7.81; *C-methyl, 0.0*). This was considered to be good evidence for an hydroxyl group on C.6 and a hydrogen atom on C.5a. The ultraviolet absorption spectrum of II [$\lambda_{max.}^{0.1\,N\,HCl}$, 223 mμ (ε 30,200), 272 mμ (ε 52,500), 430 mμ (ε 8,050)] was quite similar to the known anhydrotetracyclines[7] but exhibited a hypsochromic shift characteristic of an aromatic compound having one less alkyl substituent.[8] The acid stability of II eliminated the possibility of C.5 bearing an hydroxyl group.[4b]

That I and the known tetracyclines have the same A ring, was shown by oxidation of I in *N* NaOH with oxygen to give dimethylamine and 3,4 - dihydroxy - 2,5 - dioxocyclopentane - 1 - carboxamide[9a] (III) identical with the compound obtained similarly from tetracycline and chlorotetracycline.[7b] From the same reaction was obtained a new compound (IV), $[\alpha]^{25}D$ +2.5° (2.00%, methanol), m.p. 194–195° (*Anal.* Calcd. for $C_{13}H_{11}O_7Cl$: C, 49.62; H, 3.52; Cl, 11.27. Found: C, 49.88; H, 3.80; Cl, 11.26; *C-methyl, 0.0*). On treatment of IV with diazomethane, a methoxydimethyl ester (V) was formed, m.p. 119.5–120.5° (*Anal.* Calcd. for $C_{16}H_{17}O_7Cl$: C, 53.86; H, 4.80; Cl, 9.94; CH_3O, 26.10. Found: C, 53.59; H, 5.08; Cl, 10.12; CH_3O, 26.66). Compound V was hydrolyzed to a methoxydiacid (VI), m.p. 210–217° (*Anal.* Calcd. for $C_{14}H_{13}O_7Cl$: C, 51.15; H, 3.98; Cl, 10.79. Found: C, 50.82; H, 4.09; Cl, 10.9) which was converted to a methoxy anhydride (VII), m.p. 242.5–243° (*Anal.* Calcd. for $C_{14}H_{11}O_6Cl$: C, 54.12; H, 3.57; Cl, 11.41. Found: C, 54.16; H, 3.82; Cl, 11.56). The infrared absorption spectrum of this latter compound had bands typical of a glutaric anhydride. Compounds IV–VII had ultraviolet and infrared absorption spectra characteristic of phthalides. Since acid permanganate oxidation of IV gave tricarballylic acid[9b] in good yield, it was postulated that IV is β-(4-chloro-7-hydroxyphthalide-3)-glutaric acid, corresponding to the 3-methyl compound[9] obtained in similar fashion from chlorotetracycline[7b] thus indicating that the B rings of both compounds must be the same. With the isolation of dimethylamine, III and IV the 21 carbons and 2 nitrogens in I were accounted for.

Proof that the D rings of I and of chlorotetracycline were the same and also confirmation of the tertiary nature of C.6 in I was obtained by a series of reactions used in a degradation of chlorotetracycline.[4a] Reduction of I with zinc dust and acetic acid yielded a dedimethylaminodeoxy compound (VIII), m.p. 212–217° (dec.) (*Anal.* Calcd. for $C_{19}H_{16}O_7NCl$: C, 56.23; H, 3.97; N, 3.45; Cl, 8.74. Found: C, 56.20; H, 3.66; N, 3.80; Cl,

(1) J. R. D. McCormick, N. O. Sjolander, U. Hirsch, E. R. Jensen and A. P. Doerschuk, THIS JOURNAL, **79**, 4561 (1957).

(2) The experiments reported herein were carried out on 7-chloro-6-demethyltetracycline. Its relationship to the parent compound and also to the 4-*epi*-isomers has been established in reference 1.

(3) (a) F. Kögl and W. B. Deijs, *Ann.*, **515**, 19 (1935). (b) We are indebted to Dr. J. B. Patrick for recommending this preparation.

(4) (a) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **76**, 3568 (1954); (b) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **75**, 5455 (1953); (c) J. H. Boothe, J. Morton, II, J. P. Petisi, R. G. Wilkinson and J. H. Williams, *ibid.*, **75**, 4621 (1953).

(5) Unreported analyses from These Laboratories; for example, chlorotetracycline hydrochloride ($C_{22}H_{24}N_2O_8Cl_2$): Calcd. for 1 C-methyl, 2.92; Found: 1.93, 1.81, 1.91.

(6) The configurations about the five asymmetric centers in I and chlorotetracycline have not been related. However, it seems probable that they are the same in view of the high antibiotic activity of I and the strict configurational requirements for activity already demonstrated. *Cf.* A. P. Doerschuk, B. A. Bitler and J. R. D. McCormick, THIS JOURNAL, **77**, 4687 (1955), and footnote 3 of reference 1.

(7) (a) C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, W. J. Stein, C. F. Wolf and J. H. Williams, *ibid.*, **74**, 4981 (1952). (b) J. H. Boothe, J. Morton, II, J. P. Petisi, R. G. Wilkinson, and J. H. Williams, "Antibiotics Annual 1953–1954," Welch and Martí-Ibañez, Medical Encyclopedia, Inc., New York, N. Y., p. 46.

(8) F. Korte, *Angew. Chem.*, **63**, 375 (1951).

(9) (a) C. W. Waller, B. L. Hutchings, C. F. Wolf, R. W. Broschard, A. A. Goldman and J. H. Williams, THIS JOURNAL, **74**, 4978 (1952); (b) B. L. Hutchings, C. W. Waller, S. Gordon, R. W. Broschard, C. F. Wolf, A. A. Goldman, and J. H. Williams, *ibid.*, **74**, 3710 (1952).

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8.87), which was isomerized with alkali. The resulting iso-compound, without purification, was pyrolyzed giving a small yield of 4-chloro-7-hydroxyphthalide, m.p. 155–157°, which was identified by comparison with a known sample prepared by an unambiguous synthesis reported by Boothe, *et al.*, in an accompanying communication.[10]

(10) J. H. Boothe, A. Green, J. P. Petisi, R. G. Wilkinson and C. W. Waller, THIS JOURNAL, **79**, 4564 (1957).

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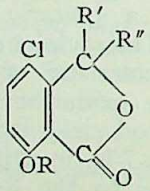
RECEIVED AUGUST 1, 1957

DEMETHYLTETRACYCLINES. SYNTHESIS OF A DEGRADATION PRODUCT

Sir:

In an accompanying communication[1] there is described a new series of antibiotics closely related to the tetracyclines, both in antibacterial activity and in structure. In a second accompanying communication[2] evidence has been presented that these new antibiotics differ from the parent compounds only in that they lack a methyl group at the 6-position of the tetracycline nucleus.

We now wish to report the synthesis of a degradation product which proves that the arrangement of substituents in the D ring and in portions of the C ring of demethylchlorotetracycline is the same as in chlorotetracycline except for the C-6 methyl group. This compound is 4-chloro-7-hydroxyphthalide (R = R′ = R″ = H) which is analogous to 4-chloro-7-hydroxy-3-methylphthalide (R = R′ = H, R″ = CH_3), obtained by the same degradative route from chlorotetracycline.[3]



The starting point for the synthesis is 4-chloro-3-hydroxy-7-methoxy-3-methylphthalide (R = R′ = CH_3, R″ = OH) whose synthesis has already been reported from this laboratory.[4] This compound was oxidized with potassium permanganate in 0.5 *N* sodium hydroxide at 90° for one hour to yield the 4-chloro-3-hydroxy-7-methoxyphthalide-3-carboxylic acid (R = CH_3, R′ = OH, R″ = COOH) in 67% yield. This compound has been isolated as a degradation product of chlorotetracycline and was named there as the tautomeric keto-acid, 6-chloro-3-methoxyphthalonic acid.[5] The reduction of this compound with sodium borohydride in *N* sodium hydroxide yielded 4-chloro-7-methoxyphthalide-3-carboxylic acid (R = CH_3, R′ = H, R″ = COOH) in 90% yield; m.p. 175–176° with effervescence; $\lambda_{max}^{0.1\,N\,HCl}$ 216 mμ (ε 32,200); 240 mμ (ε 8,240); 313 mμ (ε 5,220). $\lambda_{max}^{0.1\,N\,NaOH}$ (after standing one hour)[6] 214 mμ (ε 31,500); 285 mμ (ε 2,190).

Anal. Calcd. for $C_{10}H_7O_5Cl$: C, 49.5; H, 2.9; Cl, 14.6. Found: C, 49.5; H, 3.2; Cl, 14.8.

The phthalidecarboxylic acid was then decarboxylated by heating 5–10 minutes just above its melting point to yield 4-chloro-7-methoxy-phthalide (R = CH_3, R′ = R″ = H) which was sublimed at 175° (760 mm.); yield, 70%; m.p. 167–168° $\lambda_{max}^{0.1\,N\,HCl}$ 215 mμ (ε 37,300); 236 mμ (ε 8,830); 308 mμ (ε 4,560); $\lambda_{max}^{0.1\,N\,NaOH}$ (after standing one hour)[6] 286 mμ (ε 2,190).

Anal. Calcd. for $C_9H_7O_3Cl$: C, 54.4; H, 3.6; Cl, 17.9. Found: C, 54.8; H, 3.7; Cl, 17.7.

The methyl ether was cleaved by refluxing in 48% hydrobromic acid for 2.5 hours. The product, 4-chloro-7-hydroxyphthalide (R = R′ = R″ = H), crystallized from the hydrobromic acid on cooling in 70% yield and was then sublimed at 100° (15–20 mm.). The m.p. was 158–159° and there was no depression upon admixture with the degradation product.[2] The ultraviolet and infrared spectra were identical; $\lambda_{max}^{0.1\,N\,HCl}$ 235 mμ (ε 8,400); 308 mμ (ε 4,150); $\lambda_{max}^{0.1\,N\,NaOH}$ 254 mμ (ε 8,400); 343 mμ (ε 6,180).

Anal. Calcd. for $C_8H_5O_3Cl$: C, 52.1; H, 2.7; Cl, 19.2. Found: C, 52.2; H, 3.2; Cl, 19.0.

(1) J. R. D. McCormick, N. O. Sjolander, U. Hirsch, E. R. Jensen and A. P. Doerschuk, THIS JOURNAL, **79**, 4561 (1957).

(2) J. S. Webb, R. W. Broschard, D. B. Cosulich, W. J. Stein, and C. F. Wolf, *ibid.*, **79**, 4563 (1957).

(3) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **76**, 3568 (1954).

(4) J. H. Boothe, S. Kushner, J. P. Petisi and J. H. Williams, *ibid.*, **75**, 3261 (1953).

(5) B. L. Hutchings, C. W. Waller, S. Gordon, R. W. Broschard, C. F. Wolf, A. A. Goldman and J. H. Williams, *ibid.*, **74**, 3710 (1952). For a discussion of and references to this type of tautomerism see ref. 4.

(6) Upon standing in 0.1 *N* sodium hydroxide for an hour or less the long wave length absorption maximum undergoes a hypsochromic shift which is reversible by acidification. This is assumed to be attributable to the opening and closing of the lactone ring and will be dealt with in more detail in a subsequent publication.

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RECEIVED AUGUST 1, 1957

α,α′-DIGLYCEROPHOSPHATE IN PLANTS

Sir:

We have observed a P^{32}-labeled compound in hydrolysates of *Scendesmus* phosphatides which contained more than a third of the lipid phosphorus. The same phosphate ester also possessed as much as 90% of the alcohol-soluble non-lipid phosphorus of *Scenedesmus* cultured at low light intensity in media containing P^{32}. The cellular concentration of the ester, calculated from its P^{32} activity and the nutrient specific activity, was as high as 10^{-3} *M*. The same compound in lower concentrations occurred in the only two species of higher plants (clover) tested. It was isolated by chromatography on Whatman No. 1 paper with R_f = 0.36 in phenol–water and R_f = 0.11 in butanol–propionic acid–water.[1] These R_f values correspond to those recorded by Dawson[2] for an unknown in rat liver extracts.

(1) A. A. Benson, J. A. Bassham, M. Calvin, T. C. Goodale, V. A. Haas and W. Stepka, THIS JOURNAL, **72**, 1710 (1950).

(2) R. M. Dawson, *Biochim. et Biophys. Acta*, **14**, 374 (1954).

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The ester was half hydrolyzed during two minutes at 100° in 1.0 *N* nitric acid to give only one P^{32}-labeled product which was identified as glycerophosphate by paper chromatography and electrophoresis. The unknown was anionic in the *p*H range 2–12 and readily separable from the known glycerophosphoryl esters of the phospholipids.

Scenedesmus-C^{14} was cultured and the unknown was isolated and identified with the P^{32}-labeled compound. Acid hydrolysis produced equal activities of glycerophosphate and glycerol which was identified by its R_f values and by quantitative periodate oxidation to formaldehyde and formate. Periodate oxidation of the ester indicated an α,α'-structure. Synthetic α,α'-diglycerophosphate[3] was prepared and found inseparable from the radioactive unknown by paper chromatography and electrophoresis. Its identical hydrolysis rate was determined by neutron activation chromatography of the products.

Tetraacetyl bis-(L-α-glyceryl) phosphates have been synthesized by Baer.[4] Polyglycerophosphate structures in several lipids have been reported[5,6,7] but diglycerophosphate has not been identified previously. Its symmetry, simplicity and acid lability to give the usual products of lipid hydrolysis apparently have postponed its identification as a metabolite. Its occurrence in the glyceryl phosphatides will be reported.

We are indebted to Dr. R. J. Suhadolnik for invaluable assistance in the early stages of the identification. This work was supported by the National Science Foundation, the Atomic Energy Commission and the Pennsylvania Agricultural Experiment Station.

(3) E. Fischer and E. Pfähler, *Ber.*, **53**, 1606 (1920).
(4) E. Baer, *J. Biol. Chem.*, **198**, 853 (1952).
(5) M. C. Pangborn, *ibid.*, **168**, 351 (1947).
(6) J. M. McKibbin and W. E. Taylor, *ibid.*, **198**, 853 (1952).
(7) P. Fleury, *Bull. Soc. Chim. Biol.*, **30**, 521 (1948).

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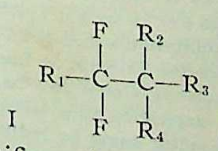
RECEIVED JULY 3, 1957

NUCLEAR MAGNETIC RESONANCE SPECTRA. HINDERED ROTATION AND MOLECULAR ASYMMETRY[1]

Sir:

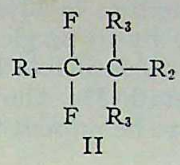
The elegant and unequivocal demonstration of non-equivalent fluorine atoms in certain *gem*-difluoro compounds of type I with the aid of their nuclear magnetic resonance spectra has been interpreted as indicating restricted rotation about the central C–C bond of I.[2]



I

	R_1	R_2	R_3	R_4
Ia	Br	H	Cl	Br
Ib	Br	F	Cl	Br
Ic	Br	H	Br	C_6H_5
Id	Cl	H	Cl	C_6H_5

Significantly, spectra for the "freely rotating" substances with "equivalent" *gem*-fluorines were not produced at temperatures up to 200°.[2] This behavior suggested to us the possibility that aliphatic compounds of type II might be resolvable into reasonably stable optical antipodes at room temperature since the barriers for rotation about the central C–C bond of II a-c should be substantially greater than for Ia-d.

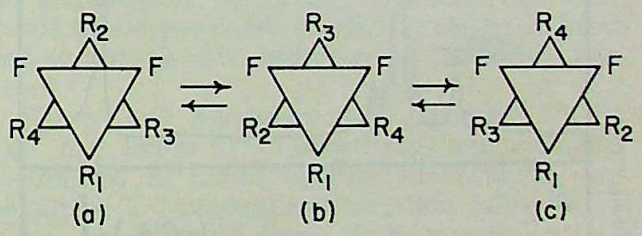


II

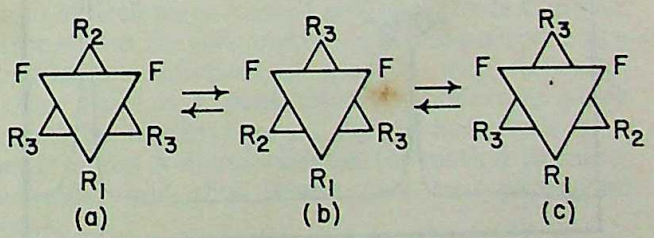
	R_1	R_2	R_3
IIa	Br	F	Br
IIb	Br	Br	Cl
IIc	Br	C_6H_5	Br

This expectation was not realized. The nuclear magnetic resonance spectra of IIa-c showed *equivalent gem*-fluorines down to −30°. Thus IIa shows doublet CF_2 and triplet CF absorptions separated by 440 c.p.s. with J equal to 18–19 c.p.s. The results indicate that there is rapid rotation at room temperature about the central C–C bond in IIa-c and, by inference, in Ia-d also.[3]

The solution to the apparent paradox is that the chemical shift between *gem*-groups as in compounds like I is not necessarily averaged by rapid rotation *unless the residence times of the molecule in each of the various rotational conformations (III) are equal.* The *gem*-group does not have equivalent atoms in any of the configurations IIIa, b or c. Therefore



III



IV

unless the residence times in each configuration are equal, the chemical shift difference between the *gem*-fluorines will not average out in the general case.[4] Since the relative residence times will be temperature dependent, the apparent degree of non-equivalence of the fluorines will vary with temperature as is observed.[2]

With more symmetrical compounds like II, rapid rotation at > −30° will average the chemical shifts of the *gem*-difluorines since the residence times (and populations) for the two configurations with non-equivalent fluorines (IVb,c) must be

(1) Supported in part by the Office of Naval Research.
(2) J. J. Drysdale and W. D. Phillips, THIS JOURNAL, **79**, 319 (1957).
(3) Drs. W. D. Phillips and J. J. Drysdale have informed us that they have independently made similar observations on fluorine compounds of related structure.
(4) In some situations, the spin–spin coupling between the non-equivalent fluorines, or other similarly located atoms, may be so large as to swamp out the chemical shift and give to all intents and purposes a single resonance line.

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equal since they are optical antipodes. IVa may have a very different residence time but has equivalent fluorines. At low temperatures in CS_2 solution, IIb and IIc show evidence of slow rotation about the C–C bond.[3] Thus at −80°, IIb appears to "freeze" to about a 1.4:1 mixture (analysis by line heights) of IVa (identifiable by its single resonance) and the *d,l*-pair IVb,c (identifiable by its quartet of resonance lines). With IIc, the rotational isomer IVa appears only to be present to the extent of about 10% at −80°.

Similar observations have been made for proton spectra of a few[4] compounds similar to I and II with $-CH_2-$ in place of $-CF_2-$. Compounds related to I like methyl 2,3-dibromo-2-methylpropanoate show "abnormal" spin–spin splittings for the $-CH_2-$ absorptions while those related to II like 1,2-dibromo-2-methylpropane give normal patterns; *cf.* Fig. 1. With substances like these, rotation about the C–C single bonds are unquestionably rapid.

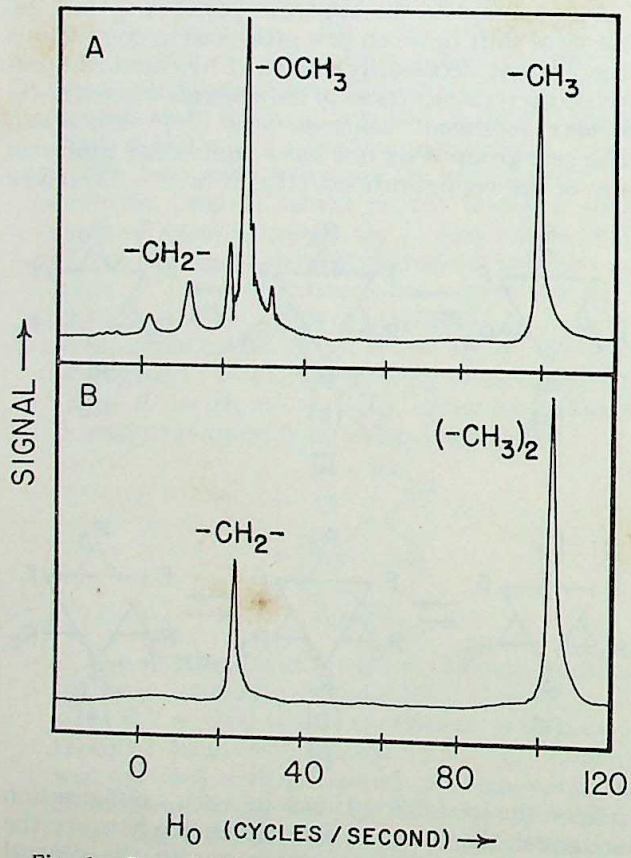

Fig. 1.—Pure liquid n.m.r. spectra of A, methyl 2,3-dibromo-2-methylpropanoate (J for coupling between *gem*-hydrogens at 3-position ~10–11 c.p.s.); B, 1,2-dibromo-2-methylpropane, taken with Varian Associates High Resolution Nuclear Magnetic Resonance Spectrometer, 12-in. magnet equipped with Super Stabilizer and at room temperature and 40 mc. Zero of reference scale was water absorption.

The importance of these observations is several fold. First, they establish beyond doubt that the residence times and populations for the various possible rotational configurations of compounds like I are not equal; second, with the aid of the reasoning used previously,[2] it becomes possible in principle to estimate, and perhaps determine, the population of the several configurations even though these are being rapidly interconverted. Third, populations of configurations may be measured directly for favorable cases by "freezing in" at low temperatures. Finally, a new and extraordinarily simple means is provided for possible detection of a carbon attached to a group without a plane of symmetry by observation of nuclear magnetic resonance spin–spin couplings without recourse to resolution into optical antipodes.[5]

(5) The method does not strictly provide a means for locating asymmetric atoms. Thus, 2-methyl-2-nitropropanediol shows nonequivalent methylene hydrogens although it is not capable of resolution into optical antipodes. However, each of the methylenes is attached to a group which has no plane of symmetry.

(6) Arthur Amos Noyes Fellow, 1956–1957.

Contribution No. 2211
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P. Madhavan Nair[6]
John D. Roberts

Received June 10, 1957

NEW LINES IN THE X-RAY DIFFRACTION PATTERN OF ORTHORHOMBIC SULFUR. "AMORPHOUS" (μ)-SULFUR

Sir:

In connection with another problem[1] we had occasion to purify some sulfur by a recommended[2–4] method.[5] On comparing the X-ray diffraction pattern with the ASTM card file[6] for orthorhombic sulfur, we were surprised to find several extra lines in our diffraction pattern.[7] Since different radiation sources were used[8] one might expect differences in relative intensity values but not in the number and positions of diffraction peaks. We found later that the sulfur we purified was not completely soluble in carbon disulfide and thus considered the possibility that the new lines we observed might be due to the presence of this insoluble sulfur.[9] Thus we determined the diffraction pattern

(1) A. G. Pinkus and J. S. Kim, *Can. J. Chem.*, accepted for publication, 1957.

(2) "Gmelin's Handbuch der anorganischen Chemie," System-Nummer 9, Schwefel, Teil A, Lieferung 3, 8 Auflage, Verlag Chemie, G.m.b.H., Weinheim/Bergstrasse, 1953, pp. 511, 512.

(3) "IUPAC Münster Colloquium on Silicon-Sulphur-Phosphates," Verlag Chemie, G.m.b.H., Weinheim/Bergstrasse, 1955, p. 82.

(4) W. N. Tuller, ed., "The Sulphur Data Book," McGraw-Hill Book Co., New York, N. Y., 1954, p. 12.

(5) R. F. Bacon and R. Fanelli, *Ind. Eng. Chem.*, **34**, 1043 (1942).

(6) ASTM X-Ray Powder Data File, Special Technical Publication No. 48-F, 1957.

(7) Our data have been deposited with Dr. G. W. Brindley, Editor, "ASTM X-Ray Powder Data File," College of Mineral Industries, Pennsylvania State University, University Park, Pa., and list the d values and intensities of reflection.

(8) The ASTM samples were run with MoKα radiation and film whereas we used Cu Kα radiation and a recording North American Philips X-ray diffractometer.

(9) The insoluble sulfur as determined by repeated extraction with carbon disulfide until there was no further loss in weight (within 0.2 mg.) was 3.25%. This is close to the equilibrium value of 3.75% at 121° listed in J. W. Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. X, Longmans, Green and Co., New York, N. Y., 1930, p. 47. Following a suggestion in a letter from Dr. Fanelli that the amount of insoluble sulfur could be reduced by heating at 125° overnight followed by slow cooling, the amount of insoluble sulfur was reduced to 2.49% after one such treatment using a ten-hour cooling period (heating mantle control). After the work in this paper was completed, a paper appeared (N. H. Hartshorne and M. Thackray, *J. Chem. Soc.*, 2122 (1957)) in which the amount of insoluble sulfur was reduced by "annealing at 100° for two days" (see also Kang Mo reference on this point).

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of sample of insoluble sulfur prepared according to the method in ref. 9. This diffraction pattern[7] was remarkably similar to that of orthorhombic sulfur. It is clear that this insoluble sulfur must have a crystalline structure. Since the line widths were comparable in the two cases, we conclude that the crystal size must be similar (since the half-width of the peak is proportional to particle size). This insoluble sulfur is commonly referred to as amorphous sulfur[10] or μ-sulfur and is thought to consist of long-chain polymers having molecular weights ranging from 18,000 to 73,000.[11] The only differences we have been able to observe between the diffraction patterns of the insoluble sulfur and orthorhombic sulfur are (1) differences in the relative intensities of several of the lines[7] and (2) the insoluble sulfur and the orthorhombic sulfur show a few lines not present in each others pattern; for example, lines at 2.99 Å. (insoluble) and 2.62 Å. (orthorhombic). The significance of these small differences is not clear at present. It is of course possible for polymeric materials to be in a crystalline form; however, one might expect a greater difference in the diffraction patterns of polymeric μ-sulfur and orthorhombic sulfur.

It is interesting that Das in a recent summary of his work[12] (some of it unpublished) has found an orthorhombic X-ray powder diagram for milk of sulfur (which has commonly been described as an amorphous modification) and also the same for colloidal sulfur prepared by the reaction of sulfur dioxide and hydrogen sulfide. In view of our findings and those of Das, it would seem advisable to discontinue the use of the term "amorphous" sulfur for these crystalline forms. The insoluble sulfur in the present paper could more aptly be referred to simply as "insoluble sulfur" or μ-sulfur.

The X-ray diffraction patterns were obtained on a North American Philips X-ray diffractometer using a rotating sample holder of the type previously described.[13] This sample holder minimizes the possibility of orientation effects in powdered samples and thus makes it possible to obtain a more complete and accurate diffraction pattern.

The authors express their appreciation to the Texas Gulf Sulphur Co., Newgulf, Texas, for a fellowship to J. S. K. under which this work was done; to Dr. R. Fanelli of the Texas Gulf Sulphur Co., New York, for helpful information; and to Baroid Division, National Lead Co., Houston, Texas, for the use of the X-ray diffractometer.

(10) Ref. 1, pp. 522, 574, 576; ref. 2, pp. 81, 83; ref. 3, pp. 4, 5, 7, 8; ref. 6, pp. 30, 32, 46; "Facts About Sulfur," Texas Gulf Sulphur Co., New York, N. Y., 1953, p. 19.

(11) H. Specker, *Z. anorg. allgem. Chem.*, **261**, 116 (1950).

(12) S. R. Das in ref. 3, p. 103.

(13) J. L. McAtee, Jr., *Am. Mineralogist*, **41**, 942 (1956).

(14) Baroid Division.

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RECEIVED JULY 16, 1957

CHEMISTRY OF THE NEOMYCINS. I. A PARTIAL STRUCTURE FOR NEOBIOSAMINES B AND C[1]

Sir:

Though the isomeric antibiotics neomycins B and C have been investigated extensively and widely employed clinically (as a mixture of the two isomers),[2] the structures of these compounds thus far have resisted complete elucidation. We wish to report here evidence that the neobiosamine[3] portion of both neomycins B and C consists of a diaminohexosido-pentose. In an accompanying Communication it is shown that the same pentose, D-ribose, is found in both isomers.[4]

Methanolysis of neomycin C gave neamine[2b] and methyl neobiosaminide C,[3] the latter, crude product, was carefully chromatographed and isolated as a mixture of its anomeric α- and β-glycosides [*Anal.* Calcd. for $C_{11}H_{21}N_2O_7(OCH_3)$: C, 44.44; H, 7.46; N, 8.64. Found: C, 44.60; H, 7.72; N, 8.55] and characterized as its derivative, methyl N,N′-dibenzoylneobiosaminide C, m.p. 250–252° [*Anal.* Calcd. for $C_{11}H_{19}N_2O_7(OCH_3)(COC_6H_5)_2$: C, 58.63; H, 6.00; N, 5.27. Found: C, 58.52; H, 5.77; N, 5.01]. These analytical values are in excellent agreement with the formulation of neobiosamine C as $C_{11}H_{22}N_2O_8$, a disaccharide composed of diaminohexose and pentose moieties, but do not support the formula $C_{11}H_{22}N_2O_7$, which would be a disaccharide containing desoxydiaminohexose and pentose moieties, as previously proposed.[3]

The α- and β-anomers were separated ($[\alpha]^{25}D$ 113° and $[\alpha]^{25}D$ 61°, respectively) and each was hydrolyzed in dilute hydrochloric acid to neobiosamine C (identical mutarotation value, $[\alpha]^{25}D$ 104°), which gave a single strong papergram spot [R_f 0.227 (TBAW)],[5] both reducing and ninhydrin-positive. The formation of a single compound from hydrolysis of methyl neobiosaminide C argues strongly for the formulation of neobiosamine C as a diaminohexosido-pentose, cleaved with difficulty, rather than as a pentosido-diaminohexose, which would be readily cleaved during hydrolysis to a pentose and a diaminohexose (or methyl diaminohexoside) and thus would give two papergram spots.

Similar arguments obtain for neobiosamine B. Both α- and β-anomers ($[\alpha]^{25}D$ 13° and $[\alpha]^{25}D$ −17°, respectively) of methyl neobiosaminide B [*Anal.* Calcd. for $C_{11}H_{21}N_2O_7(OCH_3)\cdot H_2O$: C, 42.10; H, 7.66; N, 8.19. Found: C, 41.82; H, 7.42; N, 7.95] are hydrolyzed to constant rotation ($[\alpha]^{25}D$ + 33°) and a single strong papergram spot [R_f 0.251 (TBAW)]; thus neobiosamine B also may be formulated as $C_{11}H_{22}N_2O_8$, a diaminohexosido-pentose.

(1) Presented in part at the XVIth International Congress of Pure and Applied Chemistry, Paris, July 18 to 24, 1957.

(2) For recent reviews, *cf.* (a) J. H. Ford, M. E. Bergy, A. A. Brooks, E. R. Garrett, J. Alberti, J. R. Dyer and H. E. Carter, THIS JOURNAL, **77**, 5311 (1955); (b) J. R. Dyer, Ph.D. Dissertation, University of Illinois, June, 1954; (c) S. A. Waksman, "Neomycin," Rutgers University Press, New Brunswick, N. J., 1953.

(3) J. D. Dutcher, N. Hosansky, M. N. Douin and O. Wintersteiner, THIS JOURNAL, **73**, 1384 (1951).

(4) K. L. Rinehart, Jr., P. W. K. Woo and A. D. Argoudelis, *ibid.*, **79**, 4568 (1957).

(5) TBAW is *tert*-butyl alcohol:acetic acid:water, 2:2:1.

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In the accompanying Communication[4] the pentose moiety is shown to be the same for both neobiosamines B and C. The disaccharides presumably differ then in their diaminohexose moieties and may be assigned the partial formula Ia, and methyl neobiosaminides B and C, Ib. Since neomycins B and C both contain neamine they may be formulated as Ic.

$$\underset{\text{Pentose}}{R—O—C_5H_6O(OH)_2—O—}\underset{\text{Diaminohexose (B or C)}}{C_6H_7O(OH)_2(NH_2)_2}$$

Ia, b, c

Ia, R = H
Ib, R = CH_3
Ic, R = $C_{12}H_{25}N_4O_5$ (neamine)

We wish to express our appreciation to the Public Health Service for a research grant (No. E-1278) in support of this work, and to the Upjohn Company for the generous gift of neomycin samples.

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RECEIVED JUNE 24, 1957

CHEMISTRY OF THE NEOMYCINS. II. THE PENTOSE MOIETY

Sir:

In the preceding Communication[1] it was shown that the neobiosamine portion of both neomycin B and neomycin C consists of a diaminohexosidopentose. We present here evidence that the pentose moiety in both neobiosamines B and C is D-ribose.

Methyl N,N′-dibenzoylneobiosaminide-C[1] was hydrolyzed with dilute aqueous hydrochloric acid at reflux to give a mixture of products. Purification by partial precipitation, ion exchange resins and chromatography gave a neutral, salt-free carbohydrate fraction, which was shown by color tests, papergrams and rotation to be D-ribose. The compound is an aldopentose[2] since its papergram gives an orange-brown color when developed with *p*-dimethylaminoaniline and trichloroacetic acid[5] and a red color when developed with aniline acid phthalate,[6] but no gray-green color (indicative of a ketopentose and found in model papergrams of ribulose and xylulose) when developed with orcinol and trichloroacetic acid.[7] In simultaneous papergrams (at least two chromatograms in each solvent system) with the four aldopentoses and two ketopentoses, the material was shown to give R_f values quite close to those of ribose, but very different from those of the other aldopentoses and the ketopentoses [ribose, R_f 0.553 (TBAW), 0.630 (PhNC), 0.368 (BAW); hydrolysate pentose, R_f 0.547 (TBAW), 0.630 (PhNC), 0.364 (BAW)].[8] The observed rotation of solutions of the pentose is negative, establishing the compound as D-ribose, rather than the L-isomer, which would give positive rotations.

The pentose obtained from hydrolysis of methyl N,N′-dibenzoylneobiosaminide B also has been shown to be D-ribose by a precisely analogous procedure, involving papergram color tests, R_f values, mutarotation data and osazone form. The R_f values are: ribose, 0.596 (TBAW), 0.308 (BAW); hydrolysate pentose, 0.598 (TBAW), 0.309 (BAW).[9] The mutarotation value of the isolated pentose was −17.1°, that of D-ribose, determined simultaneously, −17.6°. The moss-like crystal form of the osazone of the hydrolysate pentose, m.p. 158°, was the same as that of ribosazone, m.p. 159–162°, very different from the needles of xylosazone, m.p. 162–164°.[10]

Since the pentose from both neobiosamines is D-ribose and neomycins B and C both contain neamine,[3] the formulas of neobiosamines B and C, of methyl neobiosaminides B and C, and of neomycins B and C may be represented by Ia, Ib and Ic, respectively. The difference between the isomeric antibiotics presumably lies in the diaminohexose moieties. The structures of the diaminohexoses, their position of linkage to ribose, the position of ribose attachment to neamine and questions of pyranose *vs.* furanose ring structure will, it is hoped, be the subjects of future publications.

$$\underset{\text{D-Ribose}}{R—O—C_5H_6(OH)_2—O—}\underset{\text{Diaminohexose (B or C)}}{C_6H_7O(OH)_2(NH_2)_2}$$

Ia, b, c

Ia, R = H; Ib, R = CH_3; Ic, R = $C_{12}H_{25}N_4O_5$ (neamine)

We wish to express our appreciation to the Public Health Service for a research grant (No. E-1278) in support of this work, and to the Upjohn Company for the generous gift of neomycin samples. We also wish to thank Professor W. A. Wood for helpful advice and suggestions.

(1) K. L. Rinehart, Jr., P. W. K. Woo, A. D. Argoudelis and A. M. Giesbrecht, THIS JOURNAL, **79**, 4567 (1957).

(2) The presence of a pentose was demonstrated earlier since more vigorous acid hydrolysis of methyl neobiosaminide has been shown to give furfural,[3] and is the basis of a chemical assay for neomycin.[4]

(3) J. D. Dutcher, N. Hosansky, M. N. Donin and O. Wintersteiner THIS JOURNAL, **73**, 1384 (1951).

(4) J. D. Dutcher, N. Hosansky and J. H. Sherman, *Antibiotics and Chemotheraphy*, **3**, 534 (1953).

(5) R. B. Koch, W. F. Geddes and F. Smith, *Cereal Chem.*, **28**, 424 (1951).

(6) S. M. Partridge, *Nature*, **164**, 443 (1949).

(7) A. Bevenue and K. T. Williams, *Arch. Biochem. and Biophys.*, **34**, 225 (1951).

(8) TBAW is *tert*-butyl alcohol:acetic acid:water, 2:2:1; PhNC is phenol + 1% ammonia + hydrogen cyanide (trace); BAW is *n*-butyl alcohol:acetic acid:water:4:1:5.

(9) Slight variations in absolute values between these R_f's and those above are due to operator and room temperature differences. Each series is, however, self-consistent and values within a series were obtained in a single chromatogram.

(10) W. Z. Hassid and R. M. McCready, *Ind. Eng. Chem., Anal. Ed.*, **14**, 683 (1942).

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RECEIVED JUNE 24, 1957

EVIDENCE FOR THE HYDROGEN DICHLORIDE ANION: THE COMPOUND $CsHCl_2$

Sir:

The hydrogen bonded HF_2^- anion,[1] and its crystalline salts with heavy alkali metal cations,[2]

(1) E. F. Westrum, Jr., and K. S. Pitzer, THIS JOURNAL, **71**, 1940 (1949); S. W. Peterson and H. A. Levy, *J. Chem. Phys.*, **20**, 204 (1952).

(2) L. Helmholz and M. T. Rogers, THIS JOURNAL, **61**, 2590 (1939); M. T. Rogers and L. Helmholz, *ibid.*, **62**, 1533 (1940); R. V. Winsor and C. H. Cady, *ibid.*, **70**, 1500 (1948); R. Kruh, K. Fuwa, and T. E. McIver, *ibid.*, **78**, 4256 (1956).

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are well known. Chlorine is known to form hydrogen bonds under favorable circumstances,[3] but chlorine compounds analogous to the alkali metal bifluorides have not been reported. We now wish to report the compound CsCl·HCl, obtained by simply passing hydrogen chloride into rather concentrated aqueous cesium chloride solutions.

In a typical run 2 g. of cesium chloride was dissolved in 1.5 ml. of water and hydrogen chloride was bubbled through the solution with intermittent cooling. As the solution approached saturation with respect to hydrogen chloride, about 1 g. of the new compound was precipitated as colorless to pale yellow anisotropic needles. The solid lost hydrogen chloride and reverted to isotropic cesium chloride when attempts were made to dry it in air or *in vacuo*; but the compound could be obtained with only slight loss of hydrogen chloride when drying was carried out at 30° in a stream of hydrogen chloride. Several samples dried in this way gave ratios Cs:H:Cl varying from 1:0.7:1.4 to 1:1.0:2.0.

Examined in their mother liquors under the polarizing microscope, the crystals were observed[4] to be perfect orthorhombic prisms, with $2V \sim 70°$, moderately high birefringence, and positive optic sign. As the HCl concentration in the system decreased with time, the needles were transformed first into an anisotropic polycrystalline phase, and eventually into isotropic CsCl.

Cesium appears to be unique among the alkali metals in its tendency to form an "acid chloride." Attempts to prepare similar compounds of rubidium and potassium so far have led only to the normal chlorides. We wish to advance the hypothesis that the new cesium compound contains HCl_2^- anions with a hydrogen-bonded structure (Cl—H· · ·Cl$^-$) analogous to that of the HF_2^- ion; and further, that the HCl_2^- ion forms isolable crystalline salts only with very large cations. Other compounds which may contain the HCl_2^- anion are the "dihydrochlorides" by pyridine and other tertiary amines,[5] and the remarkably stable siliconium chloride–hydrogen chloride salts.[6] Structural studies on $CsHCl_2$ are in progress.

(3) K. Nakamoto, M. Margoshes and R. E. Rundle, THIS JOURNAL, **77**, 6480 (1955); L. R. Zumwalt and R. M. Badger, *J. Chem. Phys.*, **7**, 87 (1939); THIS JOURNAL, **62**, 305 (1940).

(4) Preliminary crystallographic examination was carried out with the help of Mr. Terence Patrick of the Department of Geology, University of Wisconsin.

(5) F. Kaufler and E. Kunz, *Ber.*, **42**, 385, 2482 (1909); F. Ephraim, *ibid.*, **47**, 1828 (1914).

(6) W. Dilthey, *Ber.*, **36**, 923 (1903); *Ann.*, **344**, 304 (1906); R. Riley, R. West and W. Erby, unpublished work.

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RECEIVED JULY 8, 1957

THE DEGRADATION OF LEUCINE-DERIVED CAROTENES

Sir:

In previous papers on the incorporation of labeled leucine into carotene by *Phycomyces blakesleeanus*, we have shown that only the 4-C of leucine is incorporated in sufficient quantity to permit its occurrence in each isoprene unit.[1] Incorporation of the 1-C is insignificant, and for the 3-C and 2-C atoms it is too low to account for the increased synthesis of β-carotene in the presence of leucine,[2] so that the selective use of an intact residual C_5 decarboxylated fragment of leucine becomes untenable.

We have therefore located some of the labeled leucine carbons in the carotene molecule in an attempt to explain the unique role of the 4-C atom.

The labeled carotene specimens, each *ca.* 3.5 mg., diluted with carrier to 19 to 32 mg. were insufficient for a complete analysis such as Grob and Bütler[3] performed. They were sufficient for recovery of the acetic acid obtained by chromic acid oxidation,[4] 6 moles of which are yielded per mole of carotene. The carboxyl groups are derived from the 5,5, 9,9, 13, and 13 carbons, and the methyl groups from corresponding side chains.

The acetic acid was decarboxylated in the Schmidt reaction to give CO_2 and methylamine. The CO_2 was converted to $BaCO_3$ and counted. The methylamine, crystallized as the hydrochloride, was burned and the CO_2 handled in the same way.

The *dl*-leucine labeled in positions 2, 3 and 4 and the β-carotene were prepared as described previously.[1,2] At the temperature of boiling water, we oxidized[5] about 20 mg of β-carotene, from which 3.5 to 5.3 mg. is radioactive.

The acetic acid obtained by four successive distillations was titrated by NaOH, 0.1 *N*. The yield of acetic acid varied from 75 to 85%. The calculated quantities of NaN_3 and H_2SO_4 were added to the CH_3COONa, obtained by evaporation of the solution (42 mg. NaN_3 and 0.9 ml. H_2SO_4 for 40 mg. CH_3COONa).[6] The liberated CO_2 was collected as $BaCO_3$. Then the methylamine was distilled into concd. HCl, crystallized as hydrochloride and burned; the CO_2 was collected as $BaCO_3$. The results are tabulated:

Leucine[a]	Total carotene, mg.	Radioactive carotene, mg.	CO_2 c.p.m.[b] per mg. $BaCO_3$	CH_3NH_2·HCl, c.p.m.[b] per mg. $BaCO_3$
4C	20.1	3.5	298 ± 11.0	4.2 ± 1.1
2C	20.2	3.5	53 ± 7.6	1.6 ± 0.8
3C	32.4	3.5	1.8 ± 0.4	10.1 ± 2.7
3C	19.6	5.3	2.0 ± 0.6	7.2 ± 1.3

[a] The counts added to the media differed in each case. [b] The standard deviation was computed to include self-absorption, weighing and counting errors.

The radioactivity of the 4-C is concentrated in the carboxyl group. Thus, the 4-C of leucine is located in positions 5,5, 9,9, 13 and 13 of the carotene molecule.

This strongly suggests that leucine provides an iso C_3 fragment in which the 4-C is centrally located. The distribution for the 2-C of leucine is the same as for the 4-C. Therefore we may assume that a C_2 fragment, also provided by leucine, can

(1) H. Yokoyama, *et al.*, THIS JOURNAL, **79**, 2029 (1957)
(2) C. O. Chichester, *et al.*, *J. Biol. Chem.*, **214**, 515 (1955).
(3) E. C. Grob and R. Bütler, *Helv. Chim. Acta*, **39**, 1975 (1956).
(4) E. C. Grob and R. Bütler, *ibid.*, **37**, 1908 (1954).
(5) P. Karrer and A. Helfenstein, *ibid.*, **13**, 1084 (1930).
(6) C. Schuerch and E. H. Huntress, THIS JOURNAL, **71**, 2233 (1949).

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be incorporated, though to a lesser extent than the C_3 fragment since the total incorporation of activity from the 2-C of leucine is limited.[2] This is explicable by dilution from a C_2 metabolic pool.

By contrast, the 3-C is found primarily in the methyl of the acetic acid. This does not rule out the possibility that this carbon may also be found elsewhere in the chain, and several choices still exist as to the pathway followed, which we hope to evaluate when warranted by additional data.

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BOOK REVIEWS

Actions Chimiques et Biologiques des Radiations. Deuxième Serie. I. Les Effets Chimiques Produits par les Rayons Ionisants en Phase Gazeuse. By W. MUND. **II. Phénomènes de Luminescence Provoqués par les Rayonnements de Grande Énergie.** By M. AGENO. **III. Introduction a la Dosimétrie des Radiations.** By N. MILLER. Edited by M. Haïssinsky. Masson et Cie. Éditeurs, 120, boulevard Saint-Germain, Paris-6e, France. 1956. vi + 224 pp. 16.5 × 24.5 cm. Price, Broché, 2.800 fr.; Cartonné toile, 3.400 fr.

This second collection of works consists of related sections on the chemical and physical aspects of ionizing radiations. This series, supplementing the first,[1] deals with the radiation chemistry of gases, with luminescence phenomena and with the dosimetry of ionizing radiations. Each section is written in French by an authority in the field.

The calculation of energy loss by α-particles in gases, the chemical action of low energy electrons and the ionization potentials of simple gases are basic topics treated by Dr. Mund in Part I. Negative ion formation and the methods for differentiating between free radicals and ions in the primary process are also briefly discussed. Mechanisms and some experimental data are given for the radiolysis of inorganic gases such as ammonia, hydrazine, hydrogen sulfide, the halogen acids, ozone, the nitrogen and carbon oxides, and of several organic vapors. Special attention is devoted to the hydrogen–deuterium exchange reaction. Emphasis throughout this section is on the extensive works of Mund and his collaborators. Reaction mechanisms are discussed in terms of free radical reactions and, unfortunately, no assessment is made of the possible contributions of molecule–ion reactions in gas phase radiation chemistry.

Dr. Ageno, in part II, succinctly summarizes the physical aspects of luminescence and compares the effects obtained by ultraviolet light and ionizing radiations. This section of the book is complete and the material is presented in logical order. All phases of luminescence phenomena from the experimental methods, luminescent yields of a large number of substances to the mechanism are covered. Progress in this field is very rapid. As a result, some recent data are missing and some of the older data on mean lives of organic scintillators (Table VI, p. 120) require revision.

Introduction to the Dosimetry of Radiations is an excellent, concise treatment of the physical and chemical methods of dosimetry by Dr. N. Miller in Part III. No attempt is made to describe radiotherapy dosimetry nor the instruments used in dosimetry. The dissipation of energy in matter by charged particles, by electromagnetic radiation and by ionization in gases is outlined. The chapter on relative methods consists of a discussion of several aqueous, organic and luminescent glass dosimeters and of their relative merits. The absolute methods of dosimetry such as calorimetry, charge collection, nuclear reactions in solution and ionization are more completely explained. Useful conversion factors and the oxidation yields of ferrous sulfate for different kinds of radiations are given in the Appendix.

Chemists, physicists, biologists and radiologists interested in the chemical and physical actions of ionizing radiations will welcome this volume, since material particularly applicable to dosimetry by ionization, scintillation and chemical methods is presented. An English edition will find wide appeal.

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Nouveau Traité de Chimie Minérale. Edited by PAUL PASCAL, Membre de l'Institut, Professeur honoraire a la Sorbonne. Volume X. **Azote—Phosphore.** By R. DUBRISAY and P. PASCAL. Masson et Cie. Éditeurs, Libraires de l'Académie de Médecine, 120 Boulevard Saint-Germain, Paris 6, France. 1956. xxxix + 963 pp. 18 × 25.5 cm. Price, Broché 6.600 fr., Cartonné toile 7.500 fr.

This volume (No. X) is the second to appear of the nineteen volumes projected for the complete treatise. A look around a library's reference shelves discloses that the nitrogen-phosphorus sections of the other large handbooks are now from twenty to thirty years old, which should assure the present treatise a warm welcome. In harmony with the general plan of the treatise, it has been necessary to compress the industrial aspects of the writing in order to make room for the host of new physico-chemical results and interpretations which have developed during the last half-century. A special aid to French readers is afforded by the List of Libraries both Parisian and Provincial (100 in all) in which the relevant Journals may be found, with an indication in each case of the extent to which the available files are complete. Bibliographic references are grouped by tens under general subjects at the end of each section of the book, and most of them purport to cover the literature up to the summer of 1955. At the bottom of each page of text is a reminder of the page where the relevant bibliography can be found. A variety of checks in matters of detail, including comparison with the necessarily much briefer treatments in Yost and Russell's Systematic Inorganic Chemistry (Prentice–Hall, Inc., New York, 1944) indicate that the present volume is in all ways a worthy example of this type of writing —so enormously time-consuming and difficult, and yet so necessary to the progress of science. The material on nitrogen, prepared by the Editor, occupies about 700 pages, while M. Dubrisay has contributed about 215 pages on Phosphorus. In the final chapter (18 pages), M. Pascal returns with a treatment of the organophosphorus compounds. Indexes and other matters bring the total to 963 pages. Printing and make-up are excellent and clear, and the few errors mostly involve minor misreadings of foreign terms in the bibliographies. American users familiar with French will find this a much handier and more selective source of information than Gmelin, though perhaps not quite so complete, when sections of equal date are compared.

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(1) E. J. Hart, THIS JOURNAL, 78, 2916 (1956).

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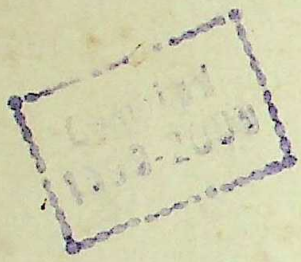

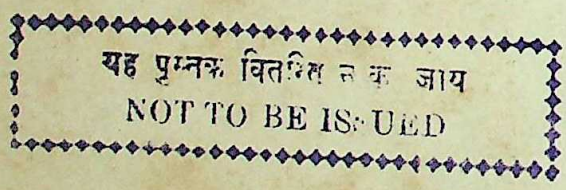

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